Common scaffolds for the enantioselective synthesis of marine, plant, and amphibian *cis*-decahydroquinoline alkaloids

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Programa de Doctorat:

Química Orgànica Experimental i Industrial

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Memòria presentada per Alexandre Miguel Gregório Pinto per optar al títol de Doctor per la Universitat de Barcelona

Dirigida per:

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Dra. Rosa Griera Farrés

Alexandre Miguel Gregório Pinto

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Dissemination of the work

Publications

1) **Stereoselective synthesis of (−)-lepadins A−C**. Amat, M.; Pinto, A.; Griera, R.; Bosch, J., *Chem. Commun.* **2013**, *49*, 11032-11034.

2) **Enantioselective synthesis of lepadins A–D from a phenylglycinol-derived hydroquinoline lactam**. Amat, M.; Pinto, A.; Griera, R.; Bosch, J., *Chem.Eur. J.* **2015**, *21*, 12804-21808 (selected as a *Hot-Paper* by the editorial board).

3) **Access to enantiopure 5-, 7-, and 5,7-substituted *cis*-decahydroquinolines: enantioselective synthesis of (−)-cermizine B**. Pinto, A.; Griera, R.; Molins, E.; Fernández, I.; Bosch, J.; Amat, M. *Org. Lett*. **2017**, *19*, 1714-1717.

4) **Enantioselective total synthesis of (+)-gephyrotoxin 287C**. Piccichè, M.; Pinto, A.; Griera, R.; Bosch, J.; Amat, M. *Org. Lett*. submitted**.**

5) **Polar-radical crossover in ynamides chemistry: a hydrative aminoxylation reaction**. Pinto, A.; Kaiser, D.; Maryasin, B.; González, L.; Maulide, N. *Angew. Chem. Int. Ed.* submitted (work not presented in this thesis).

Conferences

Oral Communication
Amat M., Griera R., Pinto A., Fabregat R., Bosch J.
Enantionselective Synthesis of Decahydroquinoline Alkaloids.
Organic-Medicinal Chemistry Workshop, Lisbon (Portugal), **June-2012**.

Poster (winner of a poster award sponsored by the Real Sociedad Española de Química)
Amat M., Pinto A., Griera R., Bosch J.
Enantioselective synthesis of cis-decahydroquinolines. Model studies on the synthesis of lepadins Alkaloids.
6th Spanish-Portuguese-Japanese Organic Chemistry Symposium, Lisbon (Portugal), **July-2012**.

Poster (winner of a poster award, sponsored by Sigma-Aldrich)
Amat M., Pinto A., Griera R., Bosch J.
Enantiopure cis-decahydroquinolines. Enantioselective synthesis of Lepadins A and B.
VI Mediterranean Organic Chemistry Meeting-REQOMED, Granada (Spain), June-2013.

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Enantionselective total synthesis of lepadin Alkaloids.
10th Spanish-Italian Symposium on Organic Chemistry (SISOC-X), Florence (Italy), **July-2014**.

Poster (winner of a poster award, sponsored by EJOC)
Pinto A., Amat M., Griera R., Bosch J.
Enantioselective total synthesis of (-)-lepadin A-C and (+)-lepadin D.
XXXV Bienal de la Real Sociedad Española de Quimica, A Coruña (Spain), **July-2015**.

Flash and Poster
Pinto A., Amat M., Griera R., Bosch J.
Enantioselective total synthesis of (-)-lepadin A-C and (+)-lepadin D.
XII Simposio de Investigadores Jóvenes Químicos RSEQ-Sigma Aldrich, Barcelona (Spain), **Nov-2015**.

Oral Communication
Pinto A., Amat M., Griera R., Bosch J.
Enantioselective total synthesis of marine alkaloid: lepadins.
9a Trobada de Joves Investigadors dels Països Catalans, Perpignan (France), **February-2016**.

Poster (winner of best poster award)
Pinto A., Griera R., Bosch J., Amat M.
Enantioselective total synthesis of marine alkaloid: lepadins.
COST meeting CM1407, Madrid (Spain), April-2016.

Flash and Poster
Pinto A., Piccichè, M., Griera R., Bosch J., Amat M.
Synthetic studies towards the enantioselective total synthesis of tricyclic decahydroquinoline Alkaloids.
XXVI Biennial Meeting in Organic Chemistry, Huelva (Spain), **June-2016**.

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Enantiopure Tricyclic Lactams for the Total Synthesis of Decahydroquinoline Alkaloids.
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Poster and oral communication (Award for best poster presentation sponsored by Elsevier)
Pinto A., Piccichè, M., Griera R., Bosch J. and Amat M.
Enantioselective Total Synthesis of Decahydroquinoline Alkaloids.
Ischia Advanced School of Organic Chemistry (IASOC-2016), Ischia (Italy), **September-2016**.

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Enantioselective Total Synthesis of Complex Decahydroquinoline Alkaloids.
XXXVI Reunión Bienal de la Real Sociedad Española de Química, Sitges (Spain), **June-2017**.

Research Internships

During this PhD thesis, a short-term research internship, from March 2017 to June 2017, was carried out in the group of Prof. Dr. Nuno Maulide at the University of Vienna. The project was focused on the metal-free radical hydrative aminoxylation of ynamides.

Table of contents

Abbreviations and Acronyms

In this manuscript, the abbreviations and acronyms used follow the recommendations found in the on-line "Guidelines for authors" *J. Org. Chem.* **2006**, *71*, 1A - 11A.

Chapter 1 – Introduction and Objectives

1. Introduction

Natural products have played a key role in the development of humankind since the beginning of civilization and allowed us to achieve great progress as a species. For instance, many consider the discovery of penicillin, an antibiotic natural product, a cornerstone in human history, which marked a new era of evolution for humankind. Diseases that killed thousands of human beings became non-lethal over-night.[1]

These secondary metabolites of living organisms suffer evolutive pressure towards their biological targets since their hosts depend on them to thrive under Nature's harsh law of survival of the fittest. This selective pressure contributes to the fact that natural products usually display optimal selectivity and binding ability to their biological targets. Hence they can be used as privileged scaffolds in drug discovery.[2] In fact, 40% of the New Chemical Entities reported between 1981 and 2014 are natural products or derivatives and if we look to particular diseases, 64% of the anticancer drugs and 75% of antibiotics developed in this same period were derived from natural products (Figure 1.1).[3]

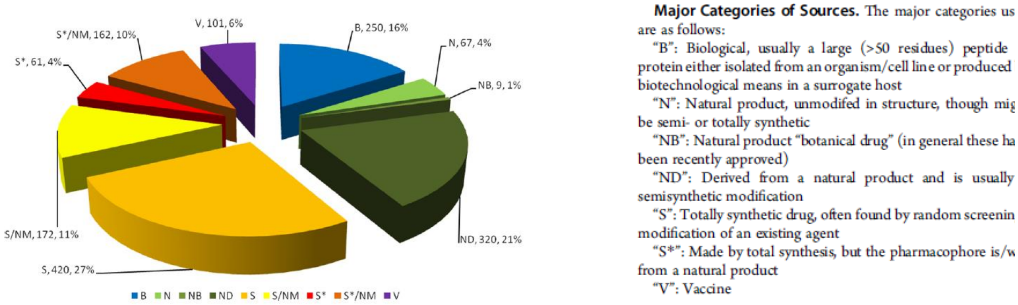

Figure 1.1. Sources of pharmaceuticals from 1981-2014.[3]

Their importance has driven science further, particularly organic chemistry, since man's desire to mimic or even surpass Nature's abilities allowed the emergence of organic chemistry as a discipline. The discovery and isolation of evermore complex and biologically relevant natural products pushed and continues to push the boundaries of knowledge and synthetic methods available to organic chemists. Moreover, this necessity to continuously improve and reinvent organic chemistry to meet these challenges led to paradigm shifts and new lines of thought within the field.[4] One may think of Corey's retrosynthetic analysis[5a] as one of these landmarks.[5b]

[1] Aldridge, S.; Parascandola, J.; Sturchio, J. L. in *The Discovery and Development of Penicillin 1928-1945*: *An International Historic Chemical Landmark*; American Chemical Society and Royal Society of Chemistry: Washington, D.C 1999.
[2] (a) Firn, R. D.; Jones, C. G. *Nat. Prod. Rep.* **2003**, *20*, 382-391. (b) Bon, R. S.; Waldmann, H. *Acc. Chem. Res.* **2010**, *43*, 1103-1114. (c) Trauner, D. *Nat. Prod. Rep.* **2014**, *31*, 411-413.
[3] Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2016**, *79*, 629-661.
[4] (a) Hoffmann, R. W. *Angew. Chem. Int. Ed.* **2013**, *52*, 123-130. (b) Nicolaou, K. C. *Angew. Chem. Int. Ed.* **2013**, *52*, 131-146.
[5] (a) Corey, E. J. Cheng, X.-M. in *The Logic of Chemical Synthesis*; John Wiley and Sons: New York 1989. (b) Nicolaou, K. C. *PNAS* **2004**, *101*, 11928.

This evolution can be easily observed in the field of total synthesis, where in the beginning it was all about target conquest, since the main goal was to artificially synthesize the natural product to elucidate its structure. With time and with the technological advances in spectroscopy, the structure elucidation became a secondary objective and the main goal shifted to the execution of a synthetic strategy with a given number of key steps and reactions that would ultimately lead to the total synthesis of a given product. This is perfectly exemplified by Woodward's synthesis of quinine[6a] and his historic synthesis of cobalamin, commonly known as vitamin B12 (Figure 1.2).[6b]

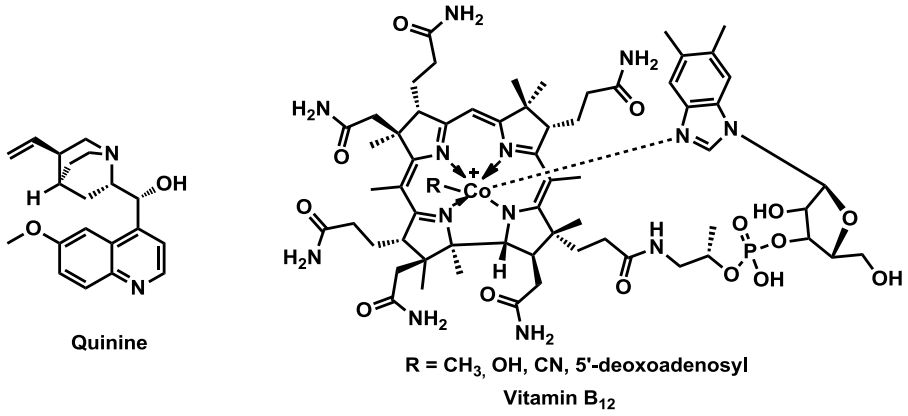

Figure 1.2. Woodward's breakthrough examples.

With all the scientific and methodological breakthroughs driven by the synthesis of more and more complex molecules, the paradigm began to change again, because synthetic chemists were now able to synthesize very complex molecules in high efficiency. Take for instance the classic example of strychnine, where the first enantioselective synthesis by Woodward in 1954[7a] took 29 steps in 0.0002% overall yield, compared to MacMillan's 2011 synthesis[7b] in 12 steps and 7% overall yield (Figure 1.3).[7c]

Figure 1.3. Strychnine – a synthetic milestone.

This resulted in a shift towards the synthesis of biologically relevant targets that can hypothetically have a societal impact, and of course, the synthesis of these natural products must convey all the previous *rules* of a well-designed synthetic plan that can deliver the final product in the most efficient manner possible. Perhaps the best example

[6] (a) Woodward, R. B.; Doering, W. E. *J. Am. Chem. Soc.* **1944**, *66*, 849-849. (b) Woodward, R. B. *Pure Appl. Chem.* **1973**, *33*, 145-178.
[7] (a) Woodward, R. B.; Cava, M. P.; Ollis, W.D.; Hunger, A.; Daeniker, H.U.; Schenker, K. *J. Am. Chem. Soc.* **1954**, *76*, 4749-4751. (b) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183-188. (c) Cannon, J. S.; Overman, L. *Angew. Chem. Int. Ed.* **2012**, *51*, 4288-4311.

of such important biologically active compounds are taxane diterpenes, namely Paclitaxel (Taxol®) which has spurred several total syntheses and many formal syntheses due to its medical importance and low availability in Nature (Figure 1.4).[8]

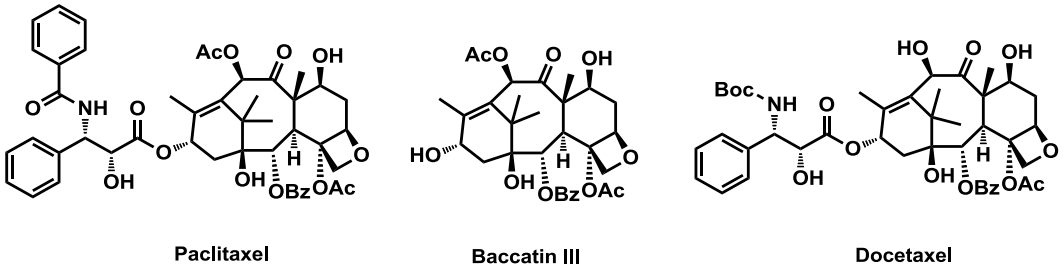

Figure 1.4. Taxane diterpenes.

Currently, the art of total synthesis is continuing to evolve with the emergence of the interrelated concepts of collective total synthesis[7b] or divergent oriented total synthesis.[4a,9a] This idea was first proposed by Dale L. Boger in 1984, and according to his own words "requires that an identical intermediate (preferably an advanced intermediate) be converted, separately, to at least two members of the class of compound".[9b] This poses an interesting challenge because when designing such a synthesis one needs an advanced intermediate that can provide two or more natural products of related families or natural product-like compounds, which can be of great importance for drug discovery.[4a,9a]

1.1. Alkaloids – privileged targets for total synthesis

Alkaloids are structurally diverse, and according to their biosynthetic origin they can be classified as true alkaloids, protoalkaloids and pseudoalkaloids. The first two are derived from amino acids, and true alkaloids, such as cocaine, have a heterocyclic ring with the nitrogen deriving from the amino acid, whereas in protoalkaloids the nitrogen atom is not incorporated in a heterocycle, like in dopamine. Pseudoalkaloids, such as caffeine, are not derived from amino acids.[10]

Undeniably, there is not a group of natural products as known and studied as the alkaloids. These naturally occurring compounds are the most useful and, at the same time, dangerous compounds found in Nature (Figure 1.5).

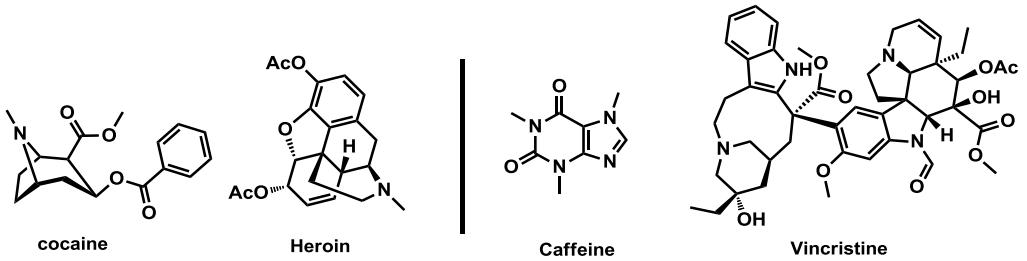

Figure 1.5. Alkaloid dichotomy.

[8] Urabe, D.; Asaba, T.; Inoue, M. *Chem. Rev.* **2015**, *115,* 9207-9231 and references therein.
[9] (a) Shimokawa, J. *Tet. Lett.* **2014**, *55*, 6156-6162. (b) Boger, D. L.; Brotherton, C. E. *J. Org. Chem.* **1984**, *49*, 4050-4055.
[10] Aniszewski, T. in *Alkaloids – Secrets of Life*; Elsevier B. V: Amsterdam 2007.

Due to their interesting biological properties and their structural complexity, alkaloids have been the target of intense study, either towards their synthesis and structural elucidation or for the preparation of derivatives that could be useful for biomedical applications. One needs only to think about some of the most notoriously harmful or potentially harmful and almost immediately, heroin, cocaine or strychnine come to mind. On the other hand, many cannot imagine life without a daily morning dose of caffeine to jump-start the brain or the *vinca* alkaloids that brought new hope for cancer therapy.

Although alkaloids are structurally diverse, as it can be seen in Figure 1.5, a quite common motif is a six-membered nitrogen-containing ring which can be the core unit or incorporated into more complex polycyclic structures, as in vincristine. Of all the systems bearing a six-membered nitrogen-containing ring, decahydroquinoline (DHQ) and derived alkaloids remain attractive targets for synthesis. Their biological properties are intertwined with their conformational equilibria, especially for the *cis* isomer, which is affected by several factors such as pH or ring substitution, leading to an increased flexibility of this system. Therefore, methodologies for the synthesis of decahydroquinoline alkaloids that could provide different substitution patterns around the ring are still very attractive in organic synthesis.

1.2. Decahydroquinoline alkaloids

Due to the vast structural variety and complexity of alkaloids, the decahydroquinoline system can be present in a wide array of very complex molecules, such as complanadine A. Therefore, for the purpose of the present work only alkaloids where the DHQ ring is the most predominant feature, as in (+)-pumiliotoxin C (*cis*-**195A**), will be discussed (Figure 1.6).

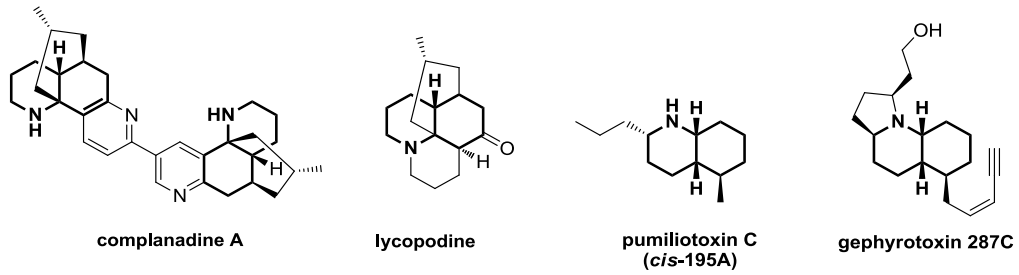

Figure 1.6. The decahydroquinoline moiety in various alkaloids.

1.2.1. Structural properties

The main feature of the decahydroquinoline alkaloids, as the name indicates, is the decahydroquinoline ring, which adopts a twin-chair conformation and it can have a *cis* or *trans* ring fusion. It should be noted that the *trans* isomer is conformationally stable, while the *cis* isomer can exist in a conformational equilibrium (Figure 1.7).

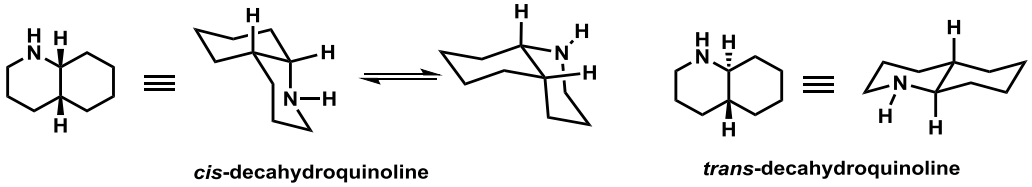

Figure 1.7. Decahydroquinoline isomers.

Both *cis* and *trans* isomers in both isomeric forms have been found in DHQ alkaloids, increasing the structural diversity considerably.

The substitution pattern along the DHQ ring is very diverse and specific patterns can be distinguished depending on the origin of these alkaloids, so they are classified according to their isolation source. There is, however an unusual feature, regarding the sources of DHQ alkaloids, which is that unlike most alkaloids the most abundant sources are animals instead of plants.
Accordingly, they can be divided into three main categories:

- Amphibian alkaloids
- Marine alkaloids
- Plant alkaloids

Given the interesting structural features and biological properties of each of these categories, they deserve to be discussed separately.

1.2.2. Amphibian alkaloids

1.2.2.1. Structure and isolation

Amphibians have proved to be a rich source of alkaloids with more than 800 compounds being isolated,[11] more than 50 of which are DHQ alkaloids. These were isolated from the skin extracts of several genera and families of amphibians: Melanophryniscus (Bufonidae)[12] from South America; Pseudophryne (Myobatrachidae)[13] from Australia; Dendrobates, Epipedobates and Phyllobates (Dendrobatidae)[14] native to Central America; and Mantella (Mantellidae)[15] from Madagascar.

Oophaga pumilio, formerly known as *Dendrobates pumilio*, a small poisonous frog native to Central America, provided the first decahydroquinoline alkaloid, pumiliotoxin C, in

[11] Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556-1575.
[12] (a) Daly, J. W.; Highet, R. J.; Myers, C. W. *Toxicon* **1984**, *22*, 905-919. (b) Garraffo, H. M.; Spande, T. F.; Daly, J. W.; Baldessari, A.; Gros, E. G. *J. Nat. Prod.* **1993**, *56*, 357-373.
[13] Daly, J. W.; Garraffo, H. M.; Pannell, L. K.; Spande, T. F. *J. Nat. Prod.* **1990**, *53*, 407-421.
[14] (a) Tokuyama, T.; Nishimori, N.; Karle, I. L.; Edwards, M. W.; Daly, J. W. *Tetrahedron* **1986**, *42*, 3453-3460. (b) Daly, J. W.; Myers, C. W.; Whittaker, N. *Toxicon* **1987**, *25*, 1023-1095. (c) Tokuyama, T.; Tsujita, T.; Shimanda, A.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *Tetrahedron* **1991**, *47*, 5401-5414. (d) Saporito, R. A.; Donnelly, M. A.; Jain, P.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *Toxicon* **2007**, *50*, 757-778.
[15] (a) Garraffo, H. M.; Caceres, J.; Daly, J. W.; Spande, T. F.; Andriamaharavo, N. R.; Andriantsiferana, M. *J. Nat. Prod.* **1993**, *56*, 1016-1038. (b) Daly, J. W.; Andriamaharavo, N. R.; Andriantsiferana, M.; Myers, C. W. *Am. Mus. Novitates* **1996**, *3177*, 1-34.

1969. Its absolute configuration and structure were determined by X-ray in the very same paper.[16] This alkaloid was isolated by John Daly and co-workers along with two other alkaloids, pumiliotoxin A and B (Figure 1.8).

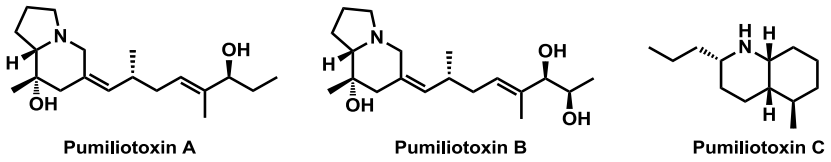

Figure 1.8. Pumiliotoxins isolated by Daly in 1969.

The structural differences between pumiliotoxin C and the other pumiliotoxins (indolizidine alkaloids) are quite evident, the former being much less toxic. To avoid confusion, a nomenclature for these alkaloids was established, dividing them into four stereochemical categories followed by the molecular weight (Figure 1.9), and the correct name for pumiliotoxin C is now decahydroquinoline *cis*-**195A**.[11]

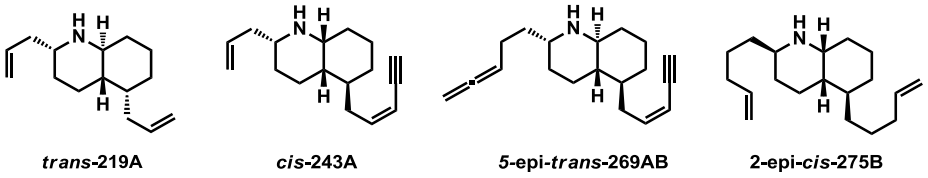

Figure 1.9. Stereochemical classification of *Dendrobatidae* alkaloids.

A key feature of the DHQ alkaloids isolated from *Dendrobatidae* frogs is that they are all substituted at the C-2 and C-5 positions; therefore, they are often referred to as 2,5-disubstituted decahydroquinolines. To a lesser extent, some members have a hydroxy group, which can be either on the ring (at C-6 usually) or the side-chains.

More recently, in 2009, an unprecedented finding was made, from the skin extracts of *Ameerega picta* collected in Bolivia, with the unexpected isolation of *N*-Me DHQ alkaloids (Figure 1.10).[17]

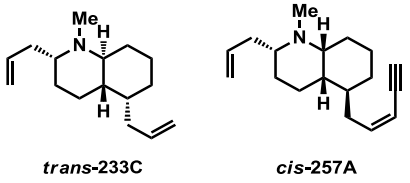

Figure 1.10. Novel *N*-Me DHQ alkaloids.

[16] Daly, J. W.; Tokuyama, T.; Habermehl, G.; Karle, I. L.; Witkop, B. *Liebig's Ann. Chem.* **1969**, *729*, 198-204.
[17] Daly, J. W.; Ware, N.; Saporito, R. A.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2009**, *72*, 1110-1114.

Another relevant group of amphibian DHQ alkaloids are gephyrotoxins, in that there are only two known alkaloids of this family, displaying a complex structure with a *cis*-DHQ moiety imbued with a pyrrolidine ring (Figure 1.11).[18]

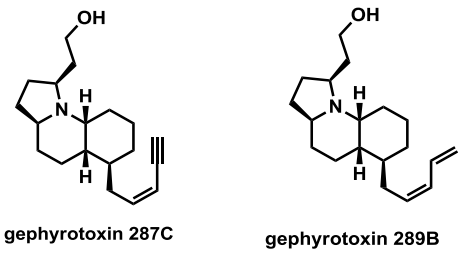

Figure 1.11. Gephyrotoxin class of amphibian alkaloids.

These alkaloids are characterized by a pyrrolidine ring fused at the N-1/C-2 positions of the *cis*-DHQ core and by the unsaturated five-carbon side-chain at C-5. Due to their relevance to the present thesis, gephyrotoxins will be discussed in more detail in chapter 4.

A particular aspect of the amphibian alkaloids is that they do not seem to be produced by the frogs themselves, being instead the result of a dietary uptake. This observation was supported by the fact that similar alkaloids as the ones found in amphibian skin extracts have been isolated from their prey, ants and mites. Subsequent studies showed that frogs raised in captivity did not possess these compounds.[19] Moreover, the type of alkaloids detected vary with the frog species, the geographic distribution, and even the gender of the frog. Various authors propose that the sequestration of these toxic alkaloids by the frogs grants an evolutionary advantage by inhibiting predation on them, increasing their chances of survival in the wild.

1.2.2.2. Biological properties

This family of amphibian alkaloids are not as toxic and poisonous as other families, like true pumiliotoxins (indolizidines), but have been shown to exhibit interesting properties that could be explored for therapeutical purposes. Some alkaloids seem to elicit a local anaesthetic effect, by inhibiting Na^+ and K^+ transport across the cell membranes,[20] while others could be useful for several neurological disorders such as nicotine addiction, epilepsy, Parkinson's or Alzheimer's diseases due to their reversal blockage of the neuronal nicotinic acetylcholine receptors (nAChRs).[19b,21]

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[18] Daly, J. W.; Witkop, B.; Tokuyama, T.; Nishikawa, T.; Karle, I. L. *Helv. Chim. Acta* **1977**, *60*, 1128-1140.

[19] (a) Daly, J.W. *Proc. Natl. Acad. Sci.* **1995**, *92*, 9-13. (b) Spande, T. F.; Jain, P.; Garraffo, H. M.; Pannell, L. K.; Yeh, H. J. C.; Daly, J. W.; Fukimoto, S.; Imamura, K.; Tokuyama, T.; Torres, J. A.; Snelling, R. R. Jones, T. H. *J. Nat. Prod.* **1999**, *62*, 5-21. (c) Hantak, M. M.; Grant, T.; Reinsch, S.; Meginnity, D.; Loring, M.; Toyooka, N.; Saporito, R. A. *J. Chem. Ecol.* **2013**, *39*, 1400-1406. (d) McGugan, J. R.; Byrd, G. D.; Roland, A. B.; Caty, S. N.; Kabir, N.; Tapia, E. E.; Trauger, S. A.; Coloma, L. A. *J. Chem. Ecol.* **2016**, *42*, 537-551.

[20] (a) Warnick, J. E.; Jessup, P. J.; Overman, L. E.; Eldefrawi, M. E.; Nimit, Y.; Daly, J. W.; Albuquerque, E. X. *Mol. Pharmacol.* **1982**, *22*, 565-573. (b) Daly, J. W. *Braz. J. Med. Biol. Res.* **1995**, *28*, 1033-1042.

[21] (a) Aronstam, R. S.; Daly, J. W.; Spande, T. F.; Narayanan, T. K.; Albuquerque, E. X. *Neurochem. Res.* **1986**, *11*, 1227-1240. (b) Daly, J. W.; Nishizawa, Y.; Edwards, M. W.; Waters, J. A.; Aronstam, R.

1.2.3. Marine alkaloids

1.2.3.1. Structure and isolation

The marine environment still remains one of the most promising sources to isolate natural products, because of its sheer size and the variety of both fauna and flora. However, it remains rather unexplored, probably due to the difficulties associated with the collection and handling of specimens. Therefore, the first example of a decahydroquinoline alkaloid isolated from a sea source was not reported until 1991 by Steffan.[22] This alkaloid was lepadin A, and led to the establishment of the lepadin alkaloids, after isolation of other related compounds (Figure1.12).[23]

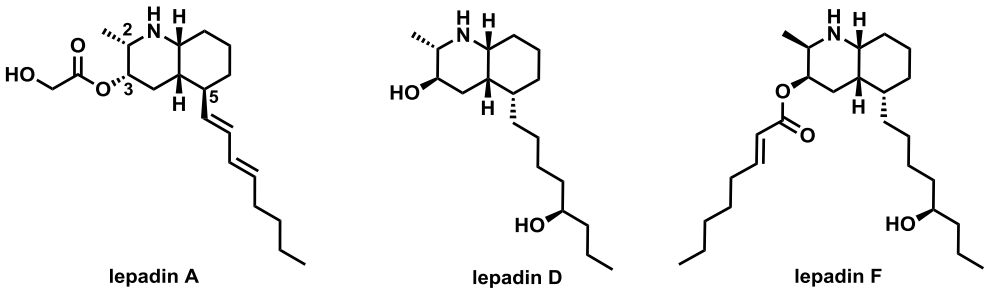


Figure 1.12. The lepadin alkaloids.

These alkaloids were mainly isolated from a tunicate, the ascidian *Clavelina lepadiformis*, hence the name lepadins, and from other tunicates from different regions of the world, although predominantly from the Great Barrier Reef in Australia.[22]

Structurally, they all have a 2,3,5-trisubstituted DHQ core, where unlike the amphibian alkaloids the ring fusion is always *cis*. Additionally, the substituent at C-5 is always an eight-carbon chain that varies in the degree of oxidation and saturation among the different alkaloids. Given the importance of the lepadin alkaloids in the context of this thesis, they will be discussed in more depth in chapter 2.

Interestingly, these alkaloids have also been isolated from the natural predator of these tunicates, the flatworm *Prostheceraeus villatus*¸ lending strength to the hypothesis that the predator sequesters secondary metabolites from its prey to gain an evolutive advantage and deter predation on itself.[18b,22b,c]

Another group of marine alkaloids bearing a DHQ moiety display an azatricyclic system, where the DHQ ring is fused to either a pyrrolidine or piperidine ring at N1/C-8a. Two main families of alkaloids can be established, namely the cylindricines and the lepadiformines.

S. *Neurochem. Res.* **1991**, *16*, 489-500. (c) Daly, J. W.; Nishizawa, Y.; Padgett, W. L.; Tokuyama, T.; McCloskey, P. J.; Waykole, L.; Aronstam, R. S.; *Neurochem. Res.* **1991**, *16*, 1207-1212.

[22] Steffan, B. *Tetrahedron*, **1991**, *47*, 8729-8732.

[23] (a) Kubanek, J.; Williams, D.; Dilip de Silva, E.; Allen, T.; Andersen, R. J. *Tet. Lett.* **1995**, *36*, 6189-6192. (b) Davis, R.; Carroll, A.; Quinn, R. *J. Nat. Prod.* **2002**, *65*, 454-457. (c) Wright, A.; Goclic, E.; König, G.; Kaminsky, R. *J. Med. Chem.* **2002**, *45*, 3067-3075.

To date, eleven cylindricines, A–K, have been isolated from the tunicate *Clavelina cylindrica*, related to *Clavelina lepadiformis*, which provided lepadins. This tunicate is native to the warm waters off the coast of Tasmania, and cylindricines were isolated by Blackman between 1993–1995.[24] These alkaloids are all *cis*-decahydroquinolines, and their main difference from lepadiformines is that they have an additional oxygenated function on the DHQ nucleus, usually at C-4 (Figure 1.13).

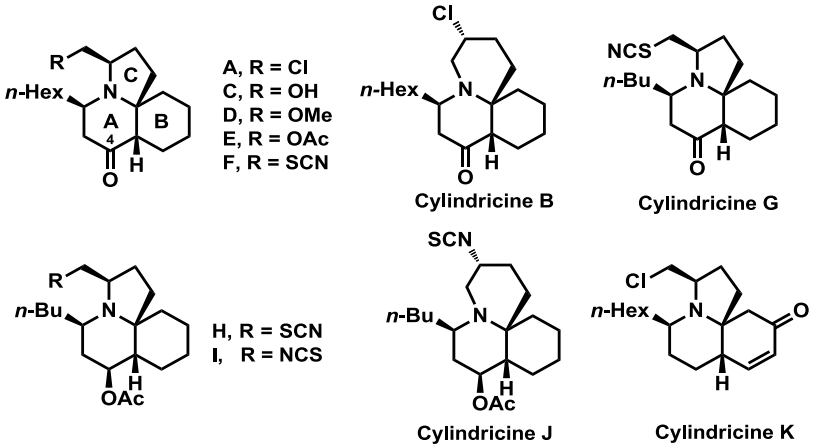


Figure 1.13. Cylindricine alkaloids.

It is easily observable that only cylindricine K varies considerably, since it has an enone moiety at the B ring. All the remaining cylindricines have the oxygenated group at C-4 either as a free hydroxy, acetoxy or a ketone function. The C ring can be either a pyrrolidine or a piperidine ring. It is noteworthy that cylindricine A upon being kept on solution could be interconverted to cylindricine B by ring expansion.[23a]

The lepadiformines are a relative small group of alkaloids, which include the related alkaloids fasicularin and polycytorols. The first member to be isolated was lepadiformine A in 1994 by Biard and co-workers,[25] followed by lepadiformines B and C in 2006 (Figure 1.14).[24b] These alkaloids were isolated from *Clavelina lepadiformis*, the same tunicate that afforded the lepadin alkaloids, although these specimens were collected off the coast of Tunisia.

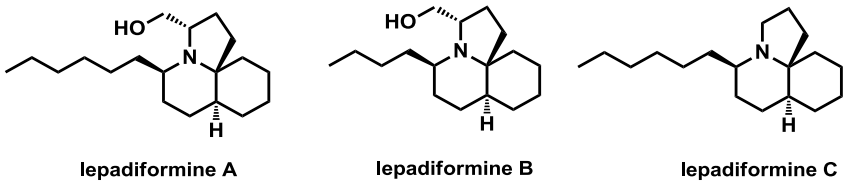


Figure 1.14. Lepadiformine alkaloids.

[24] (a) Blackman, A.; Li, C. *Tetrahedron*, **1993**, *49*, 8645-8656. (b) Li, C.; Blackman, A. *Aust. J. Chem.* **1994**, *47*, 1355-1361. (c) Li, C.; Blackman, A. *Aust. J. Chem.* **1995**, *48*, 955-965.
[25] (a) Biard, J. F.; Guyot, S.; Roussakis, C.; Verbist, J. F.; Vercauteren, J.; Weber, J. F.; Boukef, K. *Tetrahedron Lett.* **1994**, *35*, 2691-2694. (b) Sauviat, M. P.; Vercauteren, J.; Grimaud, N.; Jugé, M.; Nabil, M.; Petit, J. Y.; Biard, J. F. *J. Nat. Prod.* **2006**, *69*, 558-532.

Lepadiformine A is a good example of how even nowadays total synthesis is important for the determination of the isolated structure of a natural compound, because the reported structure for lepadiformine A was misassigned, since a *cis* stereochemistry was proposed for the ring fusion, and subsequent intensive synthetic studies showed that it was *trans*.[26]

The remaining members of this azatricyclic family, fasicularin and polycytorols, are structurally related to the lepadiformines (Figure 1.15).

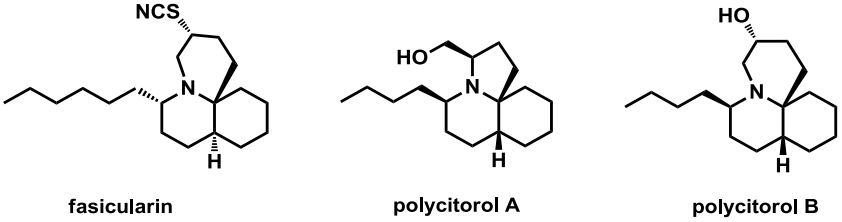


Figure 1.15. Other alkaloids of the lepadiformine family.

Polycitorols are a fairly unknown group of alkaloids, isolated in 2005 from an ascidian, off the coast of Flores, Indonesia.[27] Despite efforts towards the total synthesis of these alkaloids, it was not possible to confirm their originally reported structure, since the spectroscopic data for the synthetic polycitorols did not match those reported for the isolated compound. Therefore, their structure is still an open topic for research.[28]

On the other hand, fasicularin was isolated in 1997 from the tunicate *Nephteis fasicularis* collected in Micronesia by a group from the SmithKline Beecham, now Glaxo SmithKline pharmaceutical company, and has been the subject of active research due to its interesting biological properties.[29]

One can expect that in the near future, it will be possible to isolate even more DHQ alkaloids from the marine environment, with advances in collection and conservation techniques. Moreover, surveys of different geographic areas might lead to the isolation of different structures from related species, as seen for lepadins and lepadiformines for instance.

1.2.3.2. Biological properties

Biological activities have been reported only for fasicularin and lepadiformines A-C. Fasicularin displays selective activity in yeasts where the DNA-repair machinery was impaired. So it could be useful as an adjuvant in cancer therapy by increasing the effectiveness of DNA-damaging drugs. Additionally, it displayed cytotoxic activity against VERO cells and induced DNA damage by alkylation.[28,30]

[26] Weinreb, S. *Chem. Rev.* **2006**, *106*, 2531-2549.
[27] Issa, H. H.; Tanaka, J.; Rachmat, R.; Setiawan, A.; Trianto, A.; Higa, T. *Mar. Drugs,* **2005** *3*, 78-83.
[28] In, J.; Lee, S.; Kwon, Y.; Kim, S. *Chem. Eur. J.* **2014**, *20*, 17433-17442.
[29] Patil, A. D.; Freyer, A. J.; Reichwein, R.; Carte, B.; Killmer, L. B.; Faucette, L.; Johnson, R. K. *Tetrahedron Lett.* **1997**, *38*, 363-364.
[30] Dutta, S.; Abe, H.; Aoyagi, S.; Kibayashi, C.; Gates, K. S. *J. Am. Chem. Soc.* **2005**, *127*, 15004-15005.

On the other hand, lepadiformines showed cardiovascular activity by inducing bradycardia, with a subsequent drop of blood pressure, and antiarrhythmic properties by blocking the cardiac muscle K_{ir} channel.[25b,31] Besides the cardiovascular effects, lepadiformine A has shown moderate cytotoxic activity against nasopharynx carcinoma and non-small-cell lung carcinoma cell lines.[25a]

1.2.4. Plant alkaloids

1.2.4.1. *Lycopodium* alkaloids

Alkaloids isolated from the *Lycopodium* species are structurally diverse and can be divided into four main categories (Figure 1.16).[32]

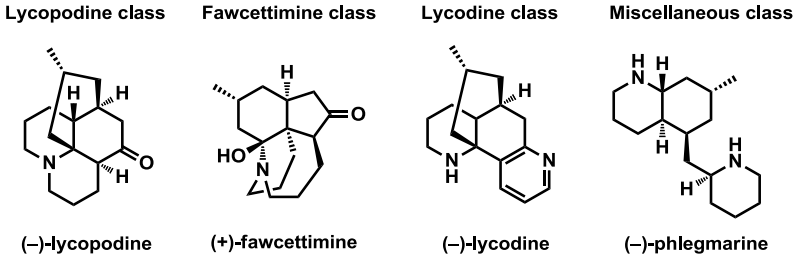


Figure 1.16. Classification of *Lycopodium* alkaloids.

For the context of this work, as previously commented, only the alkaloids where the DHQ core is the key feature will be discussed, and among the *Lycopodium* alkaloids only the miscellaneous class. This class arose due to the isolation of alkaloids that did not fit any of the previous classes. Therefore there is an important structural diversity amongst their members. For the sake of clarity, the DHQ alkaloids belonging to this group will be named as phlegmarine alkaloids.

1.2.4.1.1. Phlegmarine alkaloids – structure and isolation

The phlegmarine alkaloids are characterized by a 5,7-disubstituted DHQ moiety, which can be either *cis* or *trans*, and a $C_{16}N_2$ skeleton.[33a] They can be divided into four subclasses A-D, depending on the stereochemical relationship between the ring-fusion carbons, C-4a and C-8a, with C-7 (Figure 1.17).[33b]

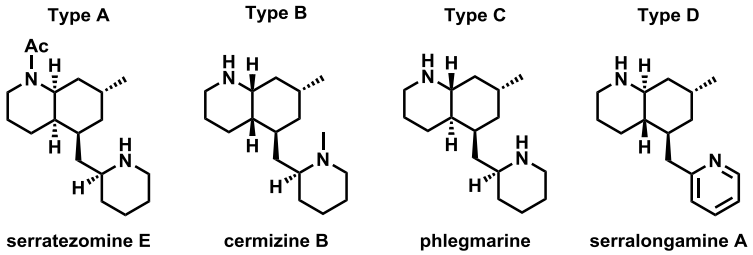


Figure 1.17. Sub-classification of phlegmarine alkaloids.

[31] Jugé, M.; Grimaud, N.; Biard, J.-F.; Sauviat, M.-P.; Nabil, M.; Verbist, J.-F.; Petit, J.-Y. *Toxicon.* **2001**, *39*, 1231-1237.
[32] Ayer W. A.; Trifonov L. S. in *The Alkaloids: Chemistry and Pharmacology*; Cordell G. A., Brossi A., Eds.; Vol. 45, Academic Press: 1994; pp. 233–266.
[33] (a) Siengalewicz, P.; Mulzer, J.; Rinner, U. In The *Alkaloids*, Vol. *72*; Knölker, H.-J., Elsevier: San Diego, 2013; p 1. (b) Saborit, G.; Bosch, C.; Parella, T.; Bradshaw, B.; Bonjoch, J. *J. Org. Chem.* **2016**, *81*, 2629-2634

To date, sixteen members of the phlegmarine alkaloids have been isolated, and they all have a piperidine or pyridine ring as a substituent at C-5. Additionally, the nitrogen atom of the piperidine moiety can be oxidized as the corresponding nitrone. The DHQ nitrogen can be either free, methylated, acylated or oxidized as the *N*-oxide. By far the largest group is Type C, with nine isolated alkaloids, where the ring fusion is *trans* and the C-7 methyl group is *cis* with respect to C-4a.

The prototype compound of phlegmarines is, as the name denotes, phlegmarine, which was isolated in 1978 by Braekman from the plant extracts of *Lycopodium clavatum* variant *borbonicum* collected in Zaire.[34] Interestingly, more than twenty years passed until the isolation of other phlegmarine-type alkaloids was reported in the literature, with the isolation of huperzine J, K and L from *Huperzia serrata*,[35] harvested in China. After 2000, there was a marked increase in the reports of isolation of these alkaloids, with the remaining members being isolated from *Lycopodium serratum* and *Huperzia serrata*, and the last alkaloid reported was N_{α}-methylphlegmarine-N_{β}-oxide, recently isolated from *Phlegmariurus phlegmaria*.[36] Interestingly, all plants were collected in China.

Up until 2004, of the nearly 1000 known *Lycopodium* species, only around 50 had been studied, which leaves a huge margin for the discovery of more alkaloids of this group with potentially important biological applications and novel structures.[37]

1.2.4.1.2. Biological properties

Despite the use of *Lycopodium* species in traditional Chinese medicine for several centuries, there is little information about the biological properties of the phlegmarine alkaloids. Moreover, the low natural abundance of these alkaloids, together with the very slow grow process of the plants and their unique habitat, makes synthetic methods for these compounds of utmost importance to study in depth their properties and use them as potential lead compounds.

Phlegmarine alkaloids, however, are expected to have biological properties similar to other *Lycopodium* alkaloids and could be useful for Alzheimer's disease and myasthenia gravis.[33a,38]

[34] Nyembo, L.; Goffin, A.; Hootelé, C.; Braekman, J.-C. *Can. J. Chem.* **1978**, *56*, 851-865.
[35] Gao, W.; Li, Y.; Jiang, S.; Zhu, D. *Planta Med.* **2000**, *66*, 664-667.
[36] (a) Morita, H.; Hirasawa, Y.; Shinzato, T.; Kobayashi, J. *Tetrahedron* **2004**, *60*, 7015-7023. (b) Katakawa, K.; Kitajima, M.; Yamaguchi, K.; Takayama, H. *Heterocycles* **2006**, *69*, 223-229. (c) Gao, W.-Y.; Li, Y.-M.; Jiang, S.-H.; Zhu, D.-Y. *Helv. Chim. Acta* **2008**, *91*, 1031-1035. (d) Kubota, T.; Yahata, H.; Yamamoto, S.; Hayashi, S.; Shibata, T.; Kobayashi, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3577-3580. (e) Jian, W.-P.; Ishiuchi, K.; Wu, J.-B.; Kitanaka, S. *Heterocycles* **2014**, *89*, 747-752. (f) Wang, Z.; Wu, J.; Zhao, N.; Yang, Y.; Chen, Y. *Nat. Prod. Res.* **2016**, *30*, 241-245.
[37] Ma, X.; Gang, D. R. *Nat. Prod. Rep.* **2004**, *21*, 752-772.
[38] Xu, J.; Lacoske, M. H.; Theodorakis, E. A. *Angew. Chem. Int. Ed.* **2014**, *53*, 956-987.

1.2.4.2. *Myrioneuron* alkaloids – structure and isolation

This family of alkaloids was described quite recently, beginning with the isolation of myrioxazins A and B in 2002 by Bodo and co-workers.[39] Since then, many more alkaloids have been discovered and now this group has around twenty known compounds (Figure 1.18). [40]

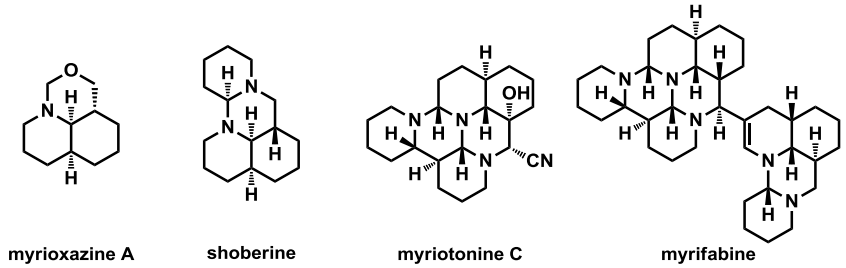


Figure 1.18. *Myrioneuron* alkaloids.

This group of alkaloids are named after the genus of the plants from which they were isolated, *Myrioneuron*, belonging to the *Rubiaceae* family of plants that are known for providing interesting bioactive alkaloids, such as caffeine and quinine.[39] Thus far, *Myrioneuron* alkaloids have been isolated from *Myrioneuron nutans*, *Myrioneuron faberi*, *Myrioneuron tokensis*, and *Myrioneuron effusum*. These small bushes are native to Asia, and were harvested in Vietnam and China.[40] As can be seen in Figure 1.18, these alkaloids vary greatly in terms of their complexity and, recently, polycyclic systems such as myriotonine C and myrifabine have been isolated.

All members of *Myrioneuron* alkaloids have a polycyclic structure, which is usually centred on a decahydroquinoline core. Given the context of this work, the structures of members of this family bearing a DHQ moiety as the main feature are shown in Figure 1.19.

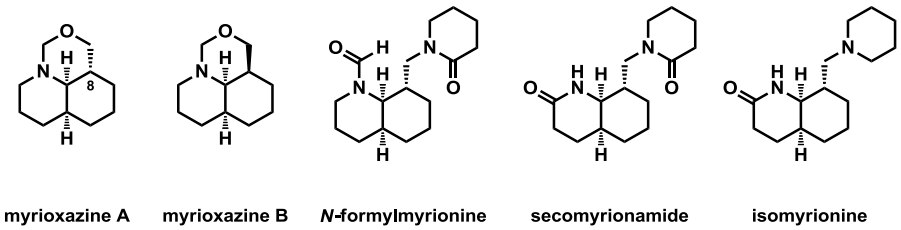


Figure 1.19. *Myrioneuron* alkaloids with a DHQ ring as the key feature.

[39] Pham, V. C.; Jossang, A.; Chiaroni, A.; Sévenet, T.; Bodo, B. *Tetrahedron Lett.* **2002**, *43*, 7565-7568.
[40] (a) Pham, V. C.; Jossang, A.; Grellier, P.; Sévenet, T.; Nguyen V. H.; Bodo, B. *Tetrahedron,* **2007**, *63*, 11244-11249. (b) Pham, V. C.; Jossang, A.; Grellier, P.; Sévenet, T.; Nguyen V. H.; Bodo, B. *J. Org. Chem.* **2007**, *72*, 9826-9829. (c) Pham, V. C.; Jossang, A.; Grellier, P.; Sévenet, T.; Nguyen V. H.; Bodo, B. *J. Org. Chem.* **2008**, *73*, 7565-7573. (d) Pham, V. C.; Jossang, A.; Sévenet, T.; Nguyen, V. H.; Bodo, B. *E. J. Org. Chem.* **2009**, 1412-1416. (e) Huang, S.-D.; Zhang, Y.; Cao, M.-M.; Di, Y.-T.; Tang, G.-H.; Peng, Z.-G.; Jiang, J.-D.; He, H.P.; Hao, X.-J. *Org. Lett.* **2013**, *15*, 590-593. (f) Cao, M.-M.; Huang, S.-D.; Di, Y.-T.; Yuan, C.-M.; Zuo, G.-Y.; Gu, Y.-C.; Hao, X.-J. *Org. Lett.* **2014**, *16*, 528-531. (g) Cao, M.-M.; Zhang, Y.; Huang, S.-D.; Di, Y.-T.; Peng, Z.-G.; Jiang, J.-D.; Yuan, C.-M.; Chen, D.-Z.; Li, S, -L.; He, H.-P.; Hao, X.-J. *J. Nat. Prod.* **2015**, *78*, 2609-2616. (h) Li, X.-H.; Zhang, Y.; Zhang, J.-H.; Li, X.-N.; Cao, M.-M.; Di, Y.-T.; Peng, Z.-G.; Jiang, J.-D.; Hao, X.-J. *J. Nat. Prod.* **2016**, *79*, 1203-1207. (i) Cao, M.-M.; Zhang, Y.; Huang, S.-D.; Peng, Z.-G.; Jiang, J.-D.; Hao, X.-J. *Tetrahedron Lett.* **2016**, *57*, 4021-4023. (j) Cao, M.-M.; Zhang, Y.; Huang, S.-D.; Peng, Z.-G.; Jiang, J.-D.; Hao, X.-J. *Tetrahedron Lett.* **2016**, *57*, 5632-5635. (k) Cao, M.-M.; Zhang, Y.; Peng, Z.-G.; Jiang, J.-D.; Gao, Y.-J.; Hao, X.-J. *RCS Adv.* **2016**, *6*, 10180-10184. (l) Zhang, J.-H.; Guo, J.-J.; Yuan, Y.-X.; Fu, Y.-H.; Gu, Y.-C.; Zhang, Y.; Chen, D.-Z.; Li, S.-L.; Di, Y.-T.; Hao, X.-J. *Fitoterapia* **2016**, *112*, 217-221.

For all compounds, the ring fusion is *cis* and they all have a substituent at the C-8 position, which in most cases has a *cis* relationship with the hydrogens at the ring-fusion. A structural feature of these alkaloids is that they are tricyclic, the extra ring being either an appendage at C-8 or fused with the *N* atom of the DHQ moiety to form a 1,3-morpholine ring.

1.2.4.2.1. Biological properties

Myrioneuron alkaloids display weak inhibition of KB cell proliferation, but their main feature, is their potent anti-malarial activity, which might originate from a different mode of action than the one that causes cytotoxicity.[41]
Recently, compounds from this family are gaining notoriety for their anti-viral activity, especially against Hepatitis C virus, and for their anti-microbial properties.[40e-l]

To date, only a small fraction of these plant species has been studied, therefore one can expect further reports on novel alkaloids from these sources with novel or improved biological activities.

1.3. Synthetic Background

Considering the relevance of DHQ alkaloids and their biological properties, it becomes apparent that synthetic methodologies that can provide access to differently substituted decahydroquinolines in an enantioselective/stereoselective fashion are worth pursuing. Moreover, the synthesis of DHQ alkaloids is of utmost importance given that the minute amounts in which they are isolated from natural sources hamper their biological studies.

Our research group has accumulated over the years a long-standing experience in the use of chiral oxazolopiperidone lactams as versatile building blocks for the preparation of a wide variety of natural products and biologically active compounds containing the piperidine ring (Figure 1.20).[42]

[41] Gravel, E.; Poupon, E. *Nat. Prod. Rep.* **2010**, *27*, 32-56.
[42] (a) Ballette, R.; Pérez, M.; Proto, S.; Amat, M.; Bosch, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 6202-6205. (b) Guignard, G.; Llor, N.; Molins, E.; Bosch, J.; Amat, M. *Org. Lett.* **2016**, *18*, 1788-1791. (c) Amat, M.; Griera, R.; Fabregat, R.; Bosch, J. *Tetrahedron Asymmetry* **2008**, *19*, 1233-1236. (d) Amat, M.; Llor, N.; Hidalgo, J.; Escolano, C.; Bosch, J. *J. Org. Chem.* **2003**, *68*, 1919-1928.

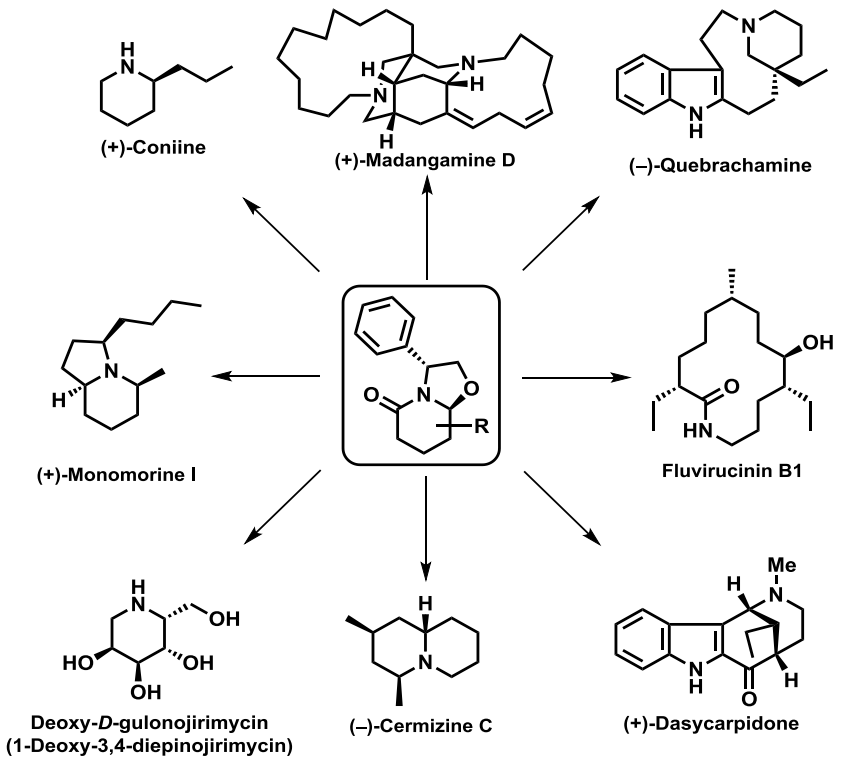


Figure 1.20. Oxazolopiperidones as building blocks for the enantioselective synthesis of piperidine-containing molecules.

These bicyclic lactams are the result of a cyclocondensation reaction between an oxo ester or oxo acid and a suitable chiral amino alcohol, typically (*R*)-phenylglycinol. Bicyclic lactams were pioneered by A.I. Meyers, who used these building blocks for the preparation of cycloalkenones and carboxylic acids bearing quaternary stereocenters.[43]

As a natural evolution of the previous developed synthetic methodology, research within the group began to target the construction of polycyclic chiral lactams as valuable building blocks for the synthesis of complex alkaloids. This resulted in the development of methodology whereby using (*S*)-tryptophanol or (*S*)-(3,4-dimethoxyphenyl) alaninol it was possible to access indole or benzo[*a*]quinolizidine alkaloids. More importantly, the chiral inductor employed, besides being the source of chirality, is incorporated into the final product (Figure 1.21).[44]

[43] For reviews see: (a) Romo, D.; Meyers, A. I. *Tetrahedron*, **1991**, *47*, 9503-9569. (b) Meyers, A. I.; Brengel, G. P. *Chem. Commun.* **1997**, 1-8. (c) Groaning, M. D.; Meyers, A. I. *Tetrahedron*, **2000**, *56*, 9843-9873.

[44] (a) Amat, M.; Santos, M. M. M.; Bassas, O.; Llor, N.; Escolano, C.; Goméz-Esqué, A.; Molins, E.; Allin, S. M.; McKee, V.; Bosch, J. *J. Org. Chem.* **2007**, *72*, 5193-5201. (b) Amat, M.; Santos, M. M. M.; Goméz, A. M..; Kokic, D.; Molins, E.; Bosch, J. *Org. Lett.* **2007**, *9*, 2907-2910. (c) Amat, M.; Goméz-Esqué, A.; Escolano, C.; Santos, M. M. M.; Molins, E.; Bosch, J. *J. Org. Chem.* **2009**, *74*, 1205-1211. (d) Amat, M.; Arioli, F.; Pérez, M.; Molins, E.; Bosch, J. *Org Lett.* **2013**, *13*, 2470-2473. (f) Amat, M.; Ramos, C.; Pérez, M.; Molins, E.; Florindo, P.; Santos, M. M. M.; Bosch, J. *Chem. Commun.* **2013**, *49*, 1954-1956.

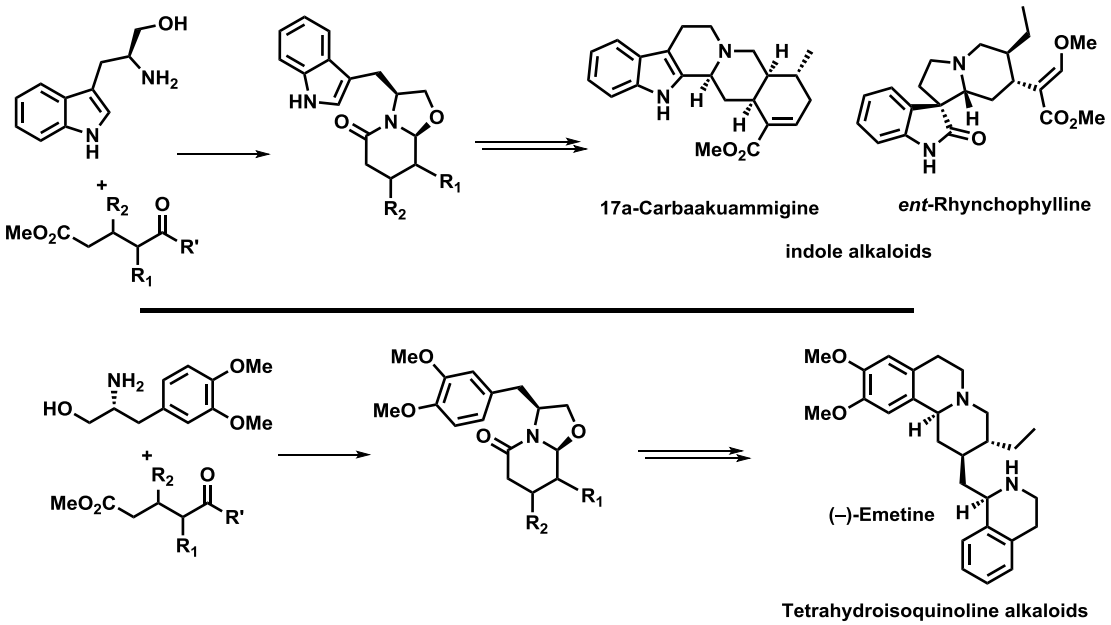


Figure 1.21. Chiral lactams for the enantioselective synthesis of polycyclic alkaloids.

1.3.1. Chiral tricyclic lactams as versatile scaffolds for alkaloid synthesis – Preparation of enantiopure 5-substituted *cis*-decahydroquinolines

The efforts towards the expansion of the methodology to more challenging targets, such as decahydroquinoline alkaloids, were carried out during the PhD thesis of Robert Fabregat. [45a] These initial studies resulted in the discovery that the cyclocondensation of (*R*)-phenylglycinol with 2-substituted-6-oxocyclohexenepropionate derivatives leads to a chiral tricyclic lactam, where a decahydroquinoline moiety is immediately recognized (Figure 1.22).

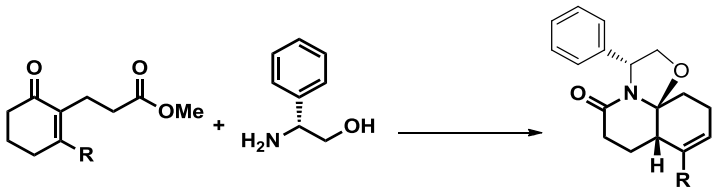
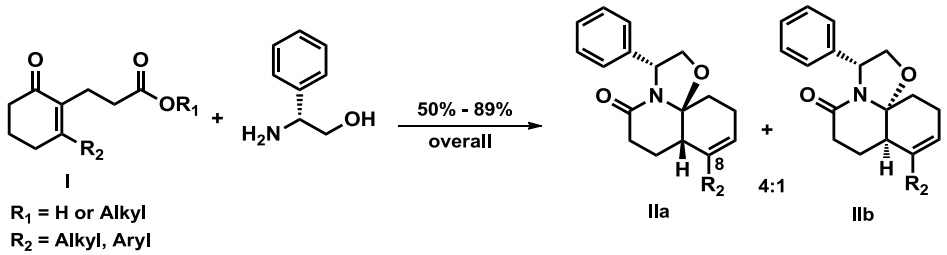


Figure 1.22. Chiral tricyclic lactams as precursors for decahydroquinolines.

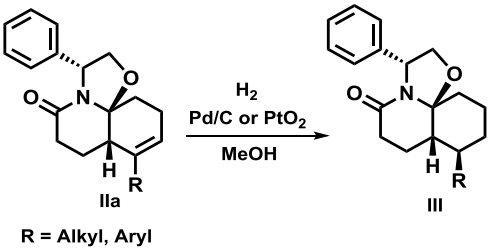
The reaction proved to be quite general, tolerating different substituents on the cyclohexenone moiety and could be performed with both the ester and the carboxylic acid derivatives of the propionate chain. All products were obtained as 4:1 mixtures of *cis* isomers favouring lactams **IIa**. (Scheme 1.1).[45]

[45] (a) Fabregat, R. PhD thesis, Barcelona **2009**. (b) Amat, M.; Fabregat, R.; Griera, R.; Bosch, J. *J. Org. Chem.* **2009**, *74*, 1794-1797. (c) Amat, M.; Fabregat, R.; Griera, R.; Florindo, P.; Molins, E.; Bosch, J. *J. Org. Chem.* **2010**, *75*, 3797-3805.



Scheme 1.1. Chiral tricyclic lactams as precursors for decahydroquinolines.

These tricyclic lactams are structurally rigid and could be hydrogenated with high to complete stereoselectivity depending on the metal catalyst used (Scheme 1.2).[45]



Scheme 1.2. Stereoselective hydrogenation of 8-substituted tricyclic lactams.

To take advantage of this highly efficient and stereoselective protocol to prepare tricyclic lactams with well-defined stereocenters at C-8 (C-5 decahydroquinoline numbering), the methodology was used to prepare 5-substituted *cis*-decahydroquinolines after stereoselective removal of the chiral inductor (Figure 1.23).

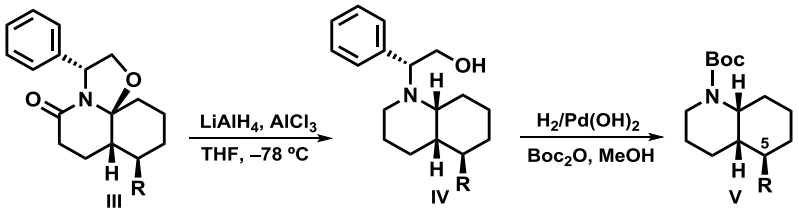


Figure 1.23. Synthesis of 5-subsituted *cis*-DHQ.

The developed methodology allowed the rapid, efficient and highly stereoselective synthesis of 5-alkyl *cis*-DHQ, and was later applied to the total synthesis of 2,5-disubstituted decahydroquinoline alkaloids, known as *Dendrobatidae* alkaloids, by accomplishing the total synthesis of *cis*-195A (pumiliotoxin C) and the C-2 epimer of its enantiomer (Figure 1.24).[46]

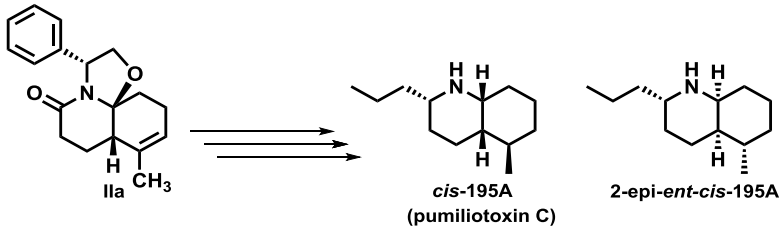


Figure 1.24. Total synthesis of 2,5-disubstituted decahydroquinoline alkaloids.

[46] Amat, M.; Fabregat, R.; Griera, R.; Molins, E.; Bosch, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 3348-3351.

1.3.2. Chiral tricyclic lactams as versatile scaffolds for alkaloid synthesis – Preparation of enantiopure 6-, 8-substituted and 6,8-di-substituted *cis*-decahydroquinolines

In recent years, the group was able to take the methodology even further and access 6-substituted *cis*-DHQ systems (Figure 1.25).[47] In these examples, the starting cyclohexenones are chiral, unlike in the previous case, and were used as racemates. This was not relevant, because a C−C double bond migration occurs during the cyclocondensation reaction. Although, the subsequent catalytic hydrogenation process was not completely stereoselective, given the position of the alkyl substituent, compounds **VIII** were obtained with very high diastereoselectivities (d.r. ≥85:15).

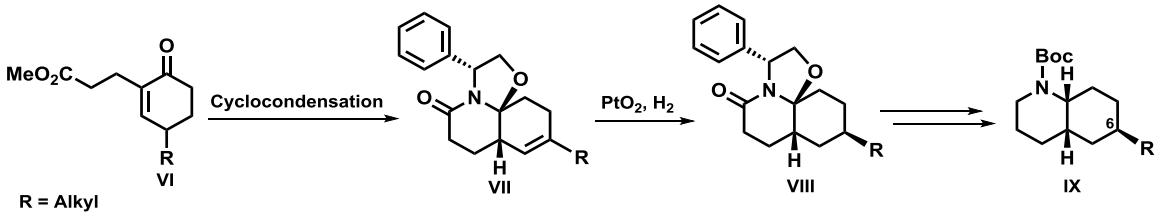


Figure 1.25. Access to 6-alkyl decahydroquinoline systems.

To further test this methodology, studies were carried out to assess the effects of having two propionate side-chains and a substituent at C-4 position of the cyclohexanone ring. This gave access to 6,8-disubstituted *cis*-DHQs (Figure 1.26).[48]

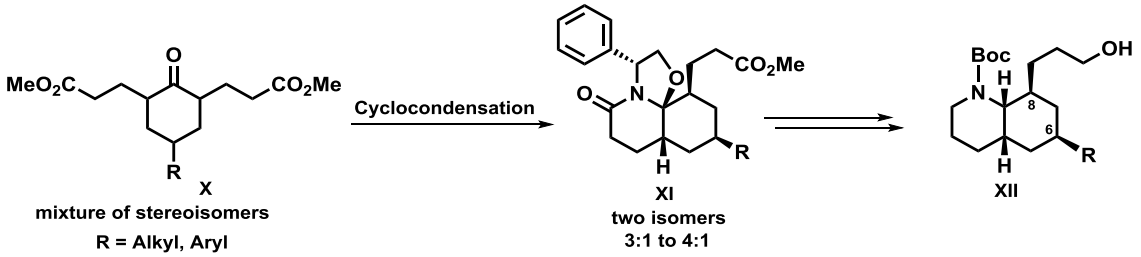


Figure 1.26. Access to 6,8-disubstituted *cis*-decahydroquinolines.

Even though the diastereoisomeric ratios might seem unimpressive, it should be noted that of the sixteen possible stereoisomers that could be expected, only two of them are formed in a *ratio* of about 4:1, which is a remarkable feat.

Additionally, if the cyclohexanone was not substituted at the C-4 position, the developed methodology allowed the preparation of 8-substuted *cis*-DHQ (Figure 1.27).

[47] (a) Navío, L. PhD thesis, Barcelona **2011**. (b) Amat, M.; Navío, L.; Llor, N.; Molins, E.; Bosch, J. *Org. Lett.* **2012**, *14*, 210-213.
[48] Amat, M.; Ghirardi, E.; Navío, L.; Griera, R.; Llor, N.; Molins, E.; Bosch, J. *Chem. Eur. J.* **2013**, *19*, 16044-16049.

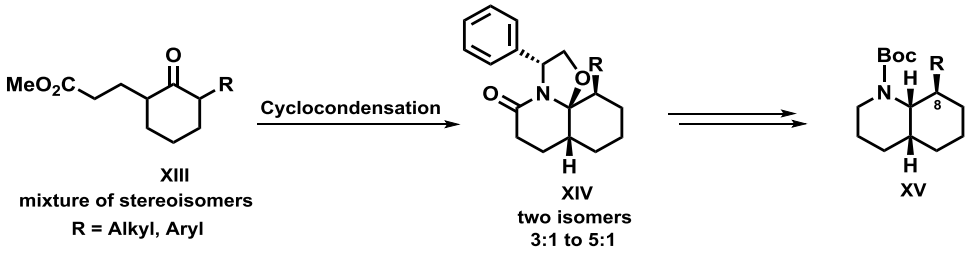


Figure 1.27. Preparation of 8-substituted *cis*-decahydroquinolines.

It should be noted that for both the 8-substituted and 6-,8-disubstituted *cis*-DHQ series the diastereoisomeric ratios of the cyclocondensation reaction could be improved if (1*S*,2*R*)-*cis*-1-amino-2-indanol was used as the chiral inductor. Ultimately, these results led to the formal synthesis of several *Myrioneuron* alkaloids, through the very short and efficient preparation of a known common precursor (Figure 1.28).[48]

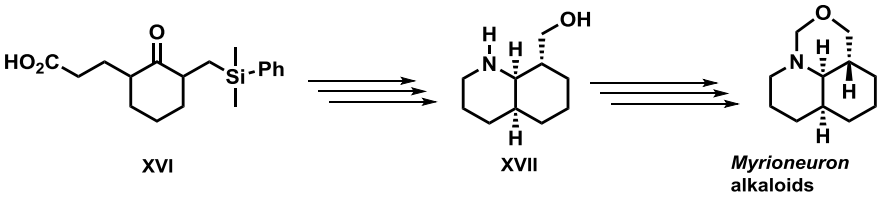


Figure 1.28. 8-substituted *cis*-DHQ for the synthesis of *Myrioneuron* alkaloids.

The commented synthetic precedents clearly show that phenylglycinol-derived chiral tricyclic lactams are versatile building blocks for the total synthesis of differently substituted *cis*-decahydroquinoline systems, and are suitable scaffolds for the synthesis of diversely functionalized DHQ alkaloids.

1.4. Objectives

Taking into consideration the group experience in the preparation of substituted *cis*-decahydroquinolines, successfully used in the synthesis of amphibian alkaloids, this PhD thesis is focused on the further development of the methodology to target more complex *cis*-DHQ alkaloids. To this end, it was decided to target the following alkaloids for synthesis:

Marine sources – lepadins;

Plant sources – cermizine B;

Amphibian sources – gephyrotoxin 287C.

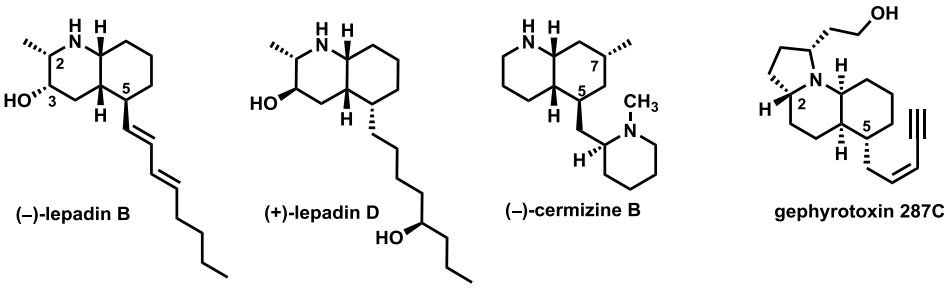


Figure 1.29. *cis*-DHQ alkaloids targeted for total synthesis.

To address the synthesis of these alkaloids, it was necessary to study the following:

1. The functionalization of the C-2 and C-3 positions for lepadins and C-2 for gephyrotoxin.
2. The introduction of an eight-carbon chain at the C-5 position for the lepadin alkaloids.
3. The introduction of a piperidine ring at the C-5 substituent for cermizine B;
4. The cyclocondensation reaction to introduce a substituent at the C-7 position for cermizine B.
5. The stereoselective removal of the phenylethanol moiety of the chiral inductor to obtain a *cis*-DHQs.

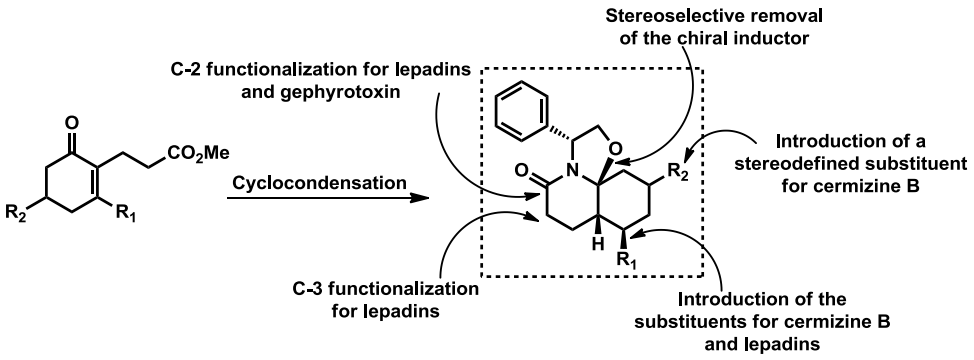


Figure 1.30. Synthetic transformations to study.

Chapter 2 – The Lepadin alkaloids

2. Lepadin alkaloids

The lepadin alkaloids are a small group of *cis*-decahydroquinoline (*cis*-DHQ) alkaloids, comprising eight members, which have been isolated (along with other metabolites) from different, although related, marine organisms found in opposite regions of the world, the North Sea[22,23a] and the Great Barrier Reef.[23b,c]

2.1. Isolation

The first member of this family and, therefore, the first marine decahydroquinoline alkaloid, to be isolated, was (–)-lepadin A by Steffan[22] in 1991. The source was a colonial ascidian, *Clavelina lepadiformis*, which lives in light-exposed rocks or submarine soil between 4 to 25 m depths. The specimens were collected near the German island of Helgoland, in the North Sea.[22]

Lepadins B and C were the next members to be isolated, 4 years later, alongside lepadin A, from the flatworm *Prostheceraeus villatus,* which was found preying on *C. lepadiformis* (which was also collected) by Andersen and co-workers.[23a] The specimens again originated from the cold waters of the North Sea, off the coast of Bergen in Norway at a depth of 3 to 20 m.

More than ten years after the isolation of the first lepadin, Wright and co-workers[22c] disclosed the isolation of four more members, lepadins D-F, from a new species of ascidian belonging to the *Didemnum* genus, native to the tropical waters of the Stanley Reef in the Great Barrier Reef. These alkaloids were discovered due to the authors' efforts to isolate biologically active compounds from different members of the *Didemnum* genus, which had previously afforded several different natural products with very interesting biological properties.[23b]

In that same year, 2001, Carrol and co-workers[23b] isolated the last two members of the lepadin family known to date, lepadin G and H, along with lepadin F. These alkaloids were isolated from *Aplidium tabascum*, a colonial ascidian, collected off Gannet Bay, Swains Reef in the Great Barrier Reef.

2.2. Structural features

All the members of the lepadin family, possess a 2,3,5-trisubstituted *cis*-decahydroquinoline moiety as the core. They all have a methyl group at C-2, an oxygenated group at C-3, which can be either a hydroxy or acyloxy function, and finally a functionalized eight carbon side-chain at C-5, which varies in the degree of saturation and oxygenation. All lepadins reported to date are optically active and can be divided into three different groups according to their relative stereochemistry between the C-2, C-3 and C-5 substituents (Figure 2.1).

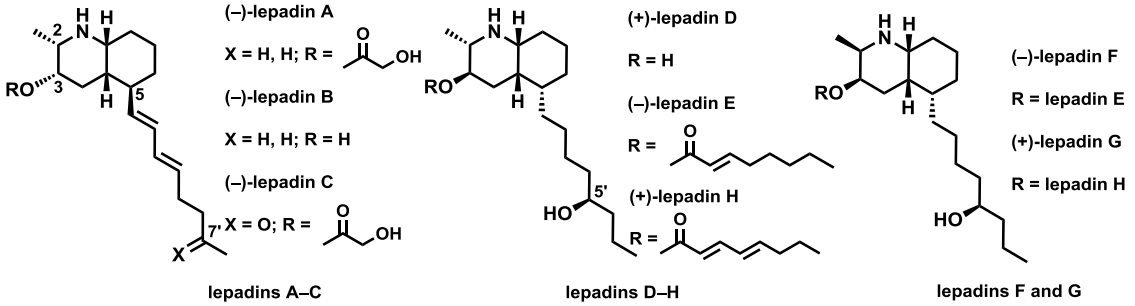


Figure 2.1. Lepadin alkaloids.

The first group comprises lepadins A–C, which from a stereochemical standpoint display a *cis* relationship between the C-2 and C-3 substituents, with these being *trans* with respect to the C-5 carbon side-chain. The C-3 hydroxy group is either free, as in (–)-lepadin B, or acylated with glycolic acid, as in (–)-lepadins A and C. Regarding the eight-carbon side-chain at C-5, all three members have a (*E*,*E*)-conjugated diene between the C-1' and C-4' positions. Additionally, (–)-lepadin C has a ketone function at the C-7' position of the C-5 side-chain.

In the second group of lepadins, (+)-lepadin D, (–)-lepadin E and (+)-lepadin H, the relative disposition between the C-2 and C-3 substituents is *trans*, and the C-2/C-5 relationship is *cis*. As in the previous family, the C-3 hydroxy group can be either free, as in (+)-lepadin D, or acylated with a mono or double unsaturated eight carbon chain, as in (–)-lepadin E and (+)-lepadin H, respectively. Contrary to lepadins A–C, the carbon side-chain at C-5 is fully saturated and only exhibits a single stereodefined hydroxy function at C-5'.

The last group of lepadin alkaloids has two members, (–)-lepadin F and (+)-lepadin G, which have a C-2/C-3 *cis* relationship, as in the first group. These stereocenters are also *trans* with respect to the C-5 substituent, albeit with the opposite configuration. Finally, the carbon side-chain at C-5 and the acyloxy substituents at C-3 are identical to those of the lepadins D–H family.

2.2.1. Conformational equilibria

The relative stereochemistry of the substituents on the *cis*-DHQ nucleus is of key importance with respect to the most stable conformation.

In later computational and NMR studies performed by Carrol and co-workers[23b] it was reported that for lepadin A, the methyl and C-5 chain are equatorial, in the favoured conformation, whereas the acylated hydroxy substituent at C-3 is axial. For lepadin G, the favoured conformation displays the C-2, C-3, and C-5 substituents in an equatorial disposition. Accordingly, these conformations can be extrapolated to their respective groups (Figure 2.2).

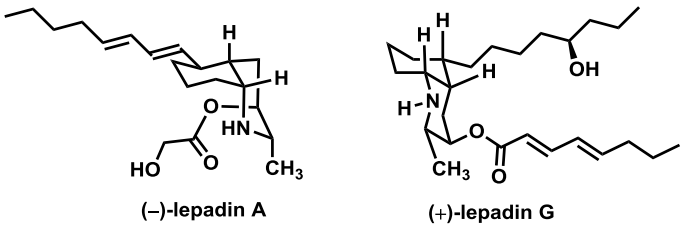


Figure 2.2. Favoured conformations for the lepadin alkaloids.

2.3. Biological properties

The structural differences between the different lepadin alkaloids have a strong effect on their biological properties of these alkaloids, which deserves some comments.

Regarding the first family, lepadins A and B display significant *in vitro* cytotoxic activity against murine leukemia P388 (ED_{50} 1.2 and 2.7 μg/mL), human breast cancer MCF7 (ED_{50} 2.3 and 17 μg/mL), human glioblastoma/astrocytoma U373 (ED_{50} 3.7 and 10 μg/mL), human ovarian carcinoma HEY (ED_{50} 2.6 and 15 μg/mL), human colon LOVO (ED_{50} 1.1 and 7.5 μg/mL) and human lung A549 (ED_{50} 0.84 and 5.2 μg/mL).[23a] Of the assayed compounds, lepadin A proved to be the most active, while lepadin C was completely inactive, therefore showing that the presence of the ketone group at the C-7' position of the C-5 side-chain completely eliminates the cytotoxic activity of these compounds.

In another assay it was shown that lepadin B is a reversible non-competitive blocker of the neuronal nicotinic acetylcholine receptors (nAChRs), with an IC_{50} of 0.9 μM for α4β2 and 0.7 μM for α7.[49] The inhibition of these receptors can be useful for the treatment of Parkinson's disease, Alzheimer's disease, nicotine addiction and epilepsy, among other neurological disorders. In the same study, the authors postulate that the 3-hydroxy piperidine moiety plays a significant role in the activity, since the related piperidine alkaloid (+)-prosafrinine (which has a methyl substituent at C-2 and a hydroxy group at C-3, with both having the same absolute stereochemistry as lepadin B) displayed a similar activity. The 2,5-disubstituted decahydroquinoline moiety also appears to play a

[49] Tsuneki, H.; You, Y.; Toyooka, N.; Sasaoka, T.; Nemoto, H.; Dani, J.A.; Kimura, I. *Biol. Pharm. Bull.* **2005**, *28*, 611-614.

decisive role, because several decahydroquinoline alkaloids with this pattern of substitution, such as the amphibian alkaloids, possess non-competitive blockage activity of the muscle-type nAChRs at the neuromuscular junction and ganglionic-type nAChRs in PC12 cells.[50]

An important consideration regarding the biological activity of lepadin B is that the dose required to cause the cytotoxic effects is much higher (30 to 60 fold higher) than the dose required to elicit the nAChR effects. As a consequence, this alkaloid can be useful as a lead compound for drug discovery of these type of blockers.

For the remaining families, only lepadins D, E and F have been biologically tested, since both lepadin G and H were isolated as unstable compounds in very minute amounts (21 mg and 4.5 mg, respectively).[23c] Their biological activity is quite different from that of the other lepadin alkaloids, since they are not cytotoxic and display instead anti-parasitic properties against *Plasmodium falciparum* K1 strain [(IC_{50} μg/mL = 6.1 (lepadin D), 0.4 (lepadin E) and 0.2 (lepadin F)], NF54 strain [(IC_{50} μg/mL = 10.0 (lepadin D), 0.9 (lepadin E) and 0.3 (lepadin F)], *Trypanosoma cruzi* [(IC_{50} μg/mL = 37.2 (lepadin D), 2.2 (lepadin E) and 2.6 (lepadin F)] and *Trypanosoma rhodesiense* [(IC_{50} μg/mL = 5.6 (lepadin D), 0.38 (lepadin E) and 0.23 (lepadin F)].[23c] Of the assayed compounds, lepadin F was the most active, and lepadin D the least. This indicates that the stereochemistry of the C-2 methyl substituent plays an important role, as does as the presence of an acyloxy substituent at C-3, since both lepadin E and F were highly active.

2.4. Synthesis of lepadin alkaloids

Due to the diverse and interesting biological activities as well as the uncommon 2,3,5-trisubstituted *cis*-DHQ system of lepadin alkaloids, several research groups have developed strategies towards the synthesis of these alkaloids. Given that our group is focused on the total synthesis of enantiopure alkaloids, only enantioselective approaches reported previously will be discussed, emphasizing the key synthetic steps, such as the assembly of the *cis*-DHQ system, the introduction of the substituents onto the decahydroquinoline core and, when relevant, the elaboration of the eight-length carbon chain at C-5.

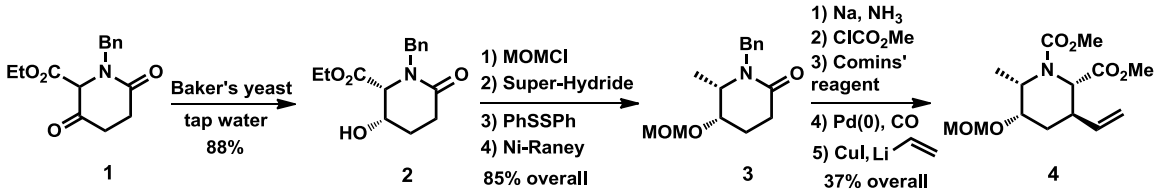
2.4.1. Total synthesis of (–)-lepadin B by Toyooka

Toyooka and co-workers were the pioneers in the field, landing the first enantioselective total synthesis of (–)-lepadin B in 1999.[50] This approach was based on the enzymatic reduction of racemic piperidone **1** to provide the enantiopure 3-hydroxy piperidone **2**. This strategy had been previously applied by the authors in the synthesis of several alkaloids.[51]

[50] (a) Toyooka, N.; Okumura, M.; Takahata, H. *J. Org. Chem.* **1999**, *64*, 2182-2183. (b) Toyooka, N.; Okumura, M.; Takahata, H.; Nemoto, H. *Tetrahedron.* **1999**, *55*, 10673-10684.

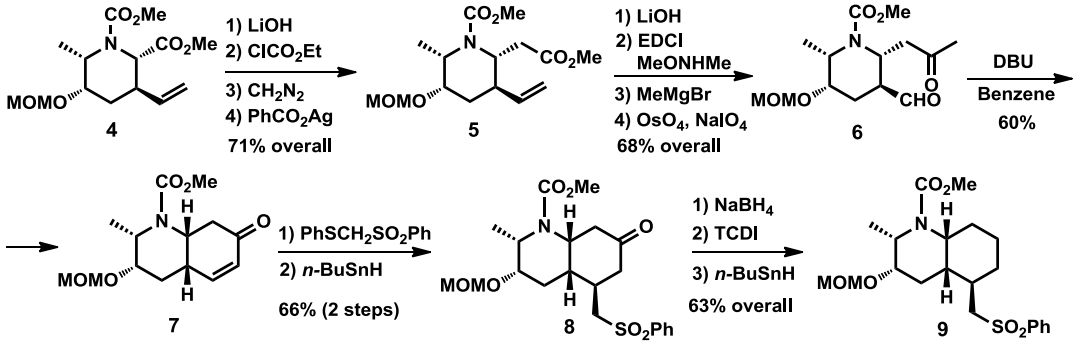
[51] a) Toyooka, N.; Fukutome, A.; Nemoto, H.; Daly, J. W.; Spande, T. F.; Garraffo, H. M.; Kaneko, T. *Org. Lett.* **2002**, *4*, 1715-1717. b) Toyooka, N.; Okumura, M.; Nemoto, H. *J. Org. Chem.* **2002**, *67*, 6078-6081.

Compound **2** has the correct stereochemistry at the C-2 and C-3 positions. However, to obtain the methyl substituent at C-2 from the ester precursor the authors needed four additional steps, which involved the MOM-protection of the 3-hydroxy group, reduction of the ester moiety, conversion of the corresponding primary alcohol to a thio-ether and subsequent hydrogenolysis of the thio-ether gave compound **3** (Scheme 2.1).



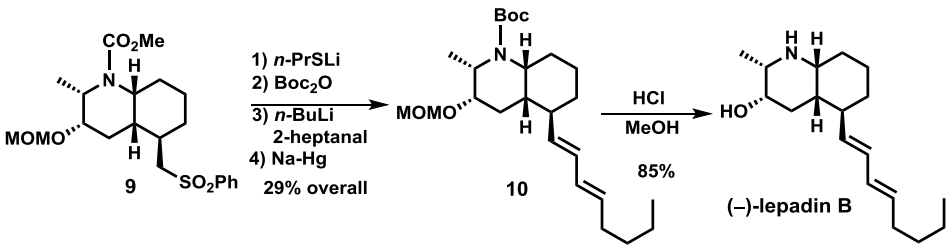
Scheme 2.1. Toyooka's first steps for the synthesis of (–)-lepadin B.

After achieving the required substituents at C-2 and C-3 with the desired stereochemistry, the *cis*-DHQ core was assembled by an intramolecular aldol cyclization. The preparation of the aldol cyclization precursor **6** required eight synthetic steps and a one-carbon homologation of the ester substituent through the Arndt-Eistert protocol. After saponification of the ester **5**, the carboxylic acid was converted to a Weinreb amide, which reacted with the Grignard reagent to afford methyl ketone **6**. The necessary aldehyde moiety, required for the intramolecular cyclization was installed *via* a dihydroxylation-oxidation sequence. Treatment of keto-aldehyde **6** with DBU brought about both the envisioned intramolecular aldol-cyclization and the epimerization of the stereocentre α to the aldehyde, affording the *cis*-DHQ derivative **7** (Scheme 2.2).



Scheme 2.2. Assembly of the *cis*-DHQ moiety.

The enone moiety in **7** was used to introduce the C-5 substituent by means of a conjugate addition, with a low selectivity (2:1) towards the desired stereoisomer. After removal of the phenylthio group, sulfone **8** was obtained.



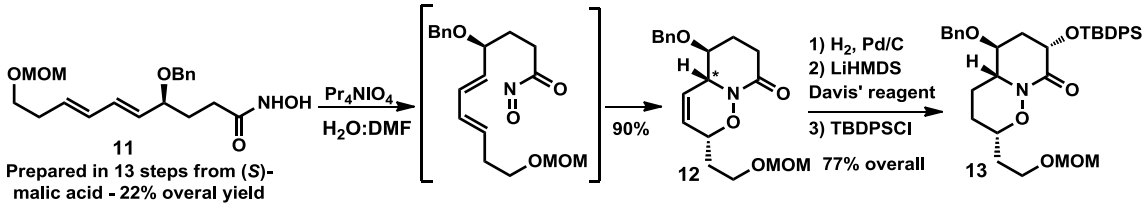
Scheme 2.3. Toyooka's synthesis of (–)-lepadin B.

The octadienyl moiety at C-5 was introduced by a Julia olefination with a suitable aldehyde, taking advantage of the sulfone functionality in **9**. After desulfonylation and final deprotection, (–)-lepadin B was obtained in 0.85% overall yield, with a total of 27 synthetic steps, allowing the confirmation of the assigned stereochemistry in the isolation report.

2.4.2. Kibayashi's approach to lepadins A–C

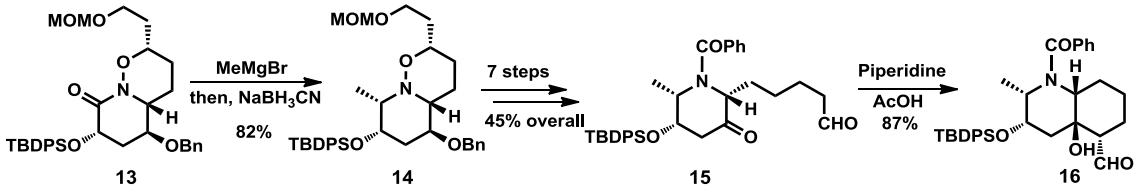
One year after the first synthesis of (–)-lepadin B, the Kibayashi group reported their efforts towards the synthesis of this alkaloid[52], and shortly afterwards the total synthesis of the first group of lepadins, lepadins A–C.[53]

Their strategy was based on an intramolecular acylnitroso Diels-Alder reaction, which they had previously employed on the total synthesis of various natural products.[54] This approach required the synthesis of the linear precursor **11** from (*S*)-malic acid, the source of chirality, in 13 steps. Hydroxamic acid **11** was oxidized, affording lactam **12** with a 6.6:1 selectivity (Scheme 2.4).



Scheme 2.4. Kibayashi's synthesis of lepadins A–C.

Lactam **12** was then used to introduce the C-3 hydroxy group by means of the Davis methodology, with good diastereoselectivity (17:1) and very high yield, under optimized conditions. Taking advantage of the lactam moiety in **13**, the stereocontrolled introduction of the methyl substituent was carried out with complete stereoselectivity, by a process previously developed by the authors, involving a tandem Grignard reaction-reduction (Scheme 2.5).[55]

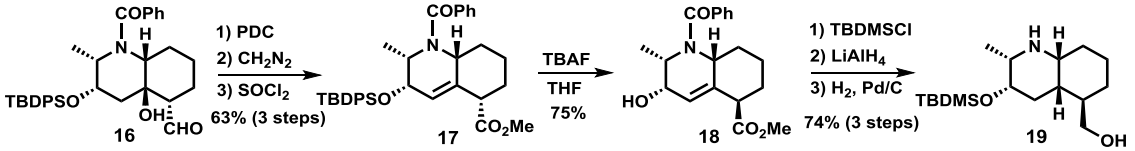


Scheme 2.5. Kibayashi's construction of the *cis*-DHQ ring.

[52] Ozawa, T.; Aoyagi, S.; Kibayashi, C. *Org. Lett.* **2000**, *2*, 2955-2958.
[53] Ozawa, T.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **2001**, *2*, 3338-3347.
[54] (a) Naruse, M.; Aoyagi, S.; Kibayashi, C. *Tet. Lett.* **1994**, *35*, 9213-9216. (b) Naruse, M.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1994**, *59*, 1358-1364.
[55] Iida, H.; Watanabe, Y.; Kibayashi, C. *J. Am. Chem. Soc.* **1985**, *107*, 5534-5535.

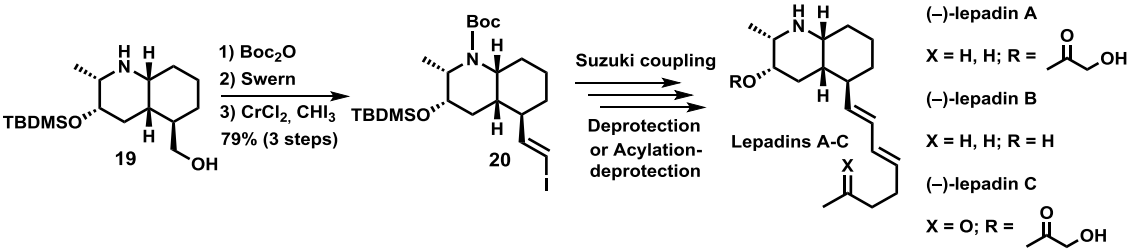
With the successful synthesis of compound **14**, possessing the methyl and hydroxy substituents with the required stereochemistry, the authors focused their efforts on the assembly of the *cis*-DHQ nucleus.

Kibayashi's approach was similar to Toyooka's, since it relied on the intramolecular aldol cyclization of a keto-aldehyde, **15**, leading to hydroxy-aldehyde **16**. However, compound **16** represented a synthetic problem, because the authors were not able to perform the dehydration of the hydroxy group directly from **16**. Additionally, the C-5 stereocentre had the incorrect stereochemistry. To overcome these problems, the authors needed four steps to correct the stereochemistry at C-5, *via* epimerization of ester **17** by treatment with TBAF. Three additional steps were needed to set the *cis* ring junction through a hydroxy group-directed catalytic hydrogenation (Scheme 2.6).



Scheme 2.6. Installing the required stereochemistry at C-4a and C-5.

Compound **19** was elaborated into vinyl iodide **20**, which was used as a common intermediate for the synthesis of lepadins A-C. The introduction of the remaining fragment of the carbon side-chain was performed *via* a Suzuki cross-coupling reaction with suitable boronic acids. For lepadins A and C, the introduction of the glycolic ester at C-3 was also needed and it was performed by esterification with a TIPS-protected glycolic acid derivative (Scheme 2.7).



Scheme 2.7. Kibayashi's endgame synthesis of lepadins A–C.

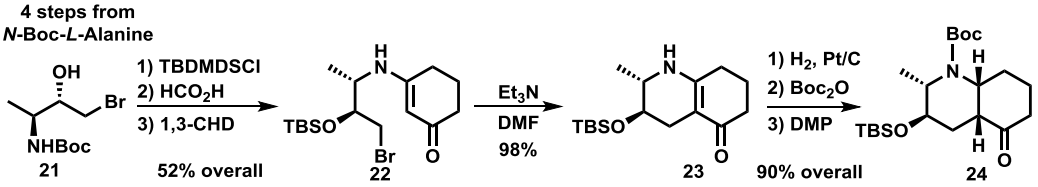
After the final deprotection step, Kibayashi and co-workers completed the synthesis of (–)-lepadin B in 33 steps with 1.3% overall yield, (–)-lepadin A in 35 steps with 1.4% overall yield, and finally, the total synthesis of (–)-lepadin C in 36 steps with 1.0% overall yield.

2.4.3. Ma's unified approach to lepadin alkaloids

The Ma group developed a concise approach to the first two groups of these alkaloids, first reporting the total synthesis of lepadins B, D, E and H, and two years later their complete efforts, spanning lepadins A-E and H.[56]

[56] (a) Pu, X.; Ma, D. *Angew. Chem. Int. Ed.* **2004**, *43*, 4222-4225. (b) Pu, X.; Ma, D. *J. Org. Chem.* **2006**, *71*, 6562-6572.

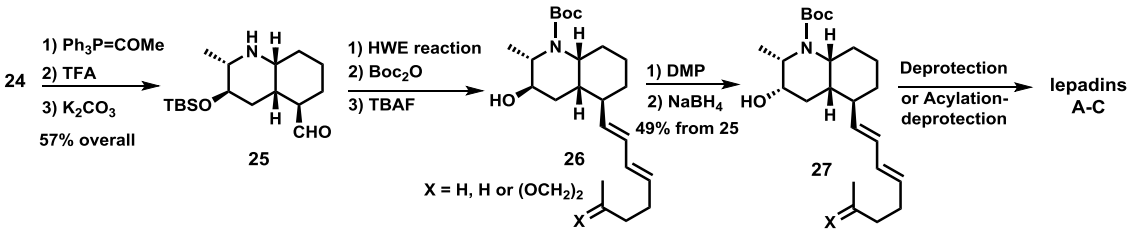
The approach devised by the Ma group was quite ingenious, since their starting material, *L*-alanine derivative **21**, already incorporated the C-2 and C-3 substituents with the correct stereochemistry for lepadins D-E and H. In order to develop a unified synthetic plan, Ma and co-workers envisioned a common synthetic precursor, such as **24**, that would allow the synthesis of both groups of lepadin alkaloids (Scheme 2.8).



Scheme 2.8. Ma's synthesis of a common synthetic intermediate.

The synthesis of the common precursor **24**, outlined in the above scheme, began with the formation of 1,3-cyclohexanedione enamine **22**. After alkylative cyclization, the DHQ core was formed. To achieve the desired *cis* relationship, a catalytic hydrogenation of **23** was performed. However, this also caused the reduction of the ketone moiety, and an additional oxidation step was necessary to obtain compound **24**.

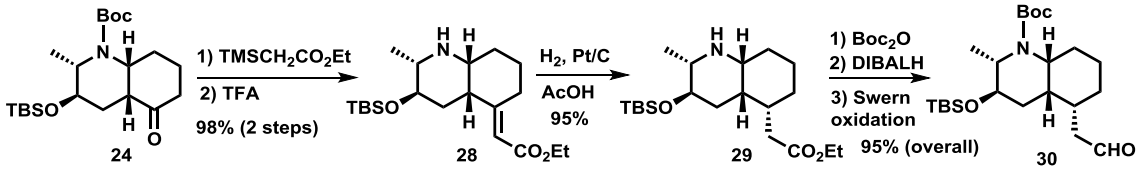
To introduce the carbon chain at C-5, compound **24** was elaborated into aldehyde **25**, where to get the desired configuration at C-5, the Boc group had to be removed. A Horner-Wadsworth-Emmons olefination with the suitable phosphonate partners afforded **26**, after protection-deprotection steps (Scheme 2.9).



Scheme 2.9. Ma's synthesis of lepadins A–C.

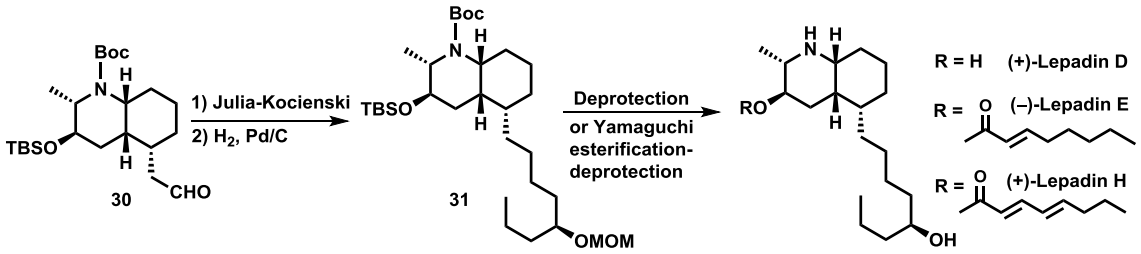
After the incorporation of the octadienyl C-5 substituent, before accomplishing the total synthesis of the first group of lepadins from **26**, inversion of the stereochemistry at the C-3 position was required. To this end, a two-step oxidation-reduction sequence was carried out, successfully achieving **27** with the necessary stereochemistry. A final deprotection afforded (–)-lepadin B in 8% overall yield over 16 steps. (–)-Lepadins A and C, which needed an additional acylation step, were obtained in 7.5% and 11% overall yield, respectively, over 17 steps.

To prepare other members of the lepadin family from the same intermediate **24**, the Ma group needed to introduce the C-5 chain with a different relative configuration. The authors proposed that the catalytic hydrogenation of an exocyclic C–C double bond at that position would be successful. Compound **24** was then subjected to a Peterson olefination to introduce the α,β-unsaturated ester present in **28**, and a catalytic hydrogenation afforded the desired stereochemistry for the synthesis of lepadins D–H (Scheme 2.10).



Scheme 2.10. Inversion of the stereochemistry at C-5.

Having achieved the correct stereochemistry at C-5, the side-chain was elongated by the Julia-Kocienski protocol. The stereochemistry of the C-5' hydroxy group of lepadins D, E and H was unknown at the time, and the authors were able to easily synthesize both enantiomers of the required sulfone partners used in the Julia-Kocienski coupling by modulating the Sharpless asymmetric epoxidation conditions required in their preparation. In doing way, the Ma group were able to synthesise both possible diastereoisomers at C-5' for each alkaloid. For lepadins E and H, the acyloxy chains at C-3 were introduced *via* the Yamaguchi esterification protocol (Scheme 2.11).



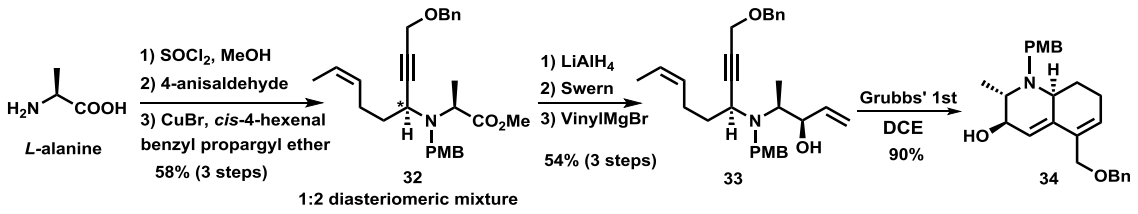
Scheme 2.11. Ma's approach to lepadins D, E and H.

With these efforts the Ma group was able to establish the stereochemistry of the natural compounds, and synthesize (+)-lepadin D in 24% overall yield in 16 steps, (–)-lepadin E and (+)-lepadin H in 19% and 16% overall yields, respectively, in 19 steps.

2.4.4. Total synthesis of *ent*-lepadins F and G by Blechert

After the aforementioned studies, the only members that still resisted total synthesis were lepadins F and G. To fill this gap, the group of Blechert in Germany reported in 2007 the total synthesis of the enantiomers of lepadins F and G. Blechert introduced an organometallic approach for the construction of the decahydroquinoline moiety of lepadins, since the key reaction step is a tandem ene-yne-ene ring-closing metathesis of compound **33**.[57] The metathesis precursor **33** was synthesized from *L*-alanine, which would allow the incorporation of the C-2 and C-3 substituents on the building block (Scheme 2.12).

[57] Niethe, A.; Fischer, D.; Blechert, S. *J. Org. Chem.* **2007**, *73*, 3088-3093.

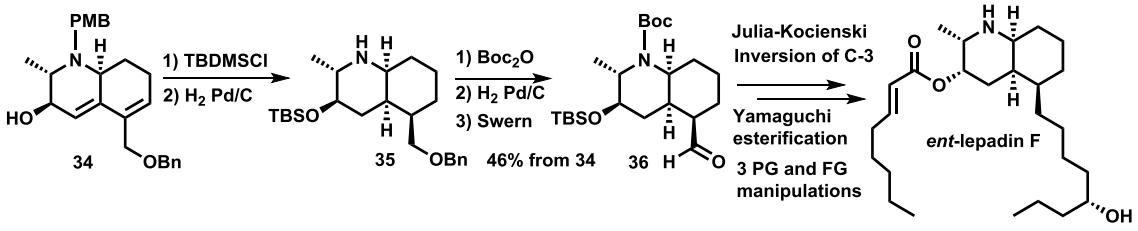


Scheme 2.12. Blechert's tandem RCM strategy.

Compound **32** was obtained after condensation of the intermediate PMB-protected alanine methyl ester and 4-hexenal, followed by the copper-catalysed propargylation of the resulting imine. It should be noted that when chiral ligands were used for the copper-catalysed process a 1:8 ratio was obtained, favouring diastereoisomer **32**. However, it was decided to obviate the use of chiral ligands and obtain an epimeric mixture of compound **32**, performing the chromatographic separation of both diastereoisomers. The authors argued that the other diastereoisomer would allow them to target lepadins A-C, although to date their efforts towards the synthesis of these alkaloids have not been reported. After subjecting compound **33** to optimized RCM conditions, the DHQ derivative **34** was obtained in excellent yield.

It is noteworthy that Blechert and co-workers relied on very subtle substrate features, since they argue that to achieve the desired DHQ product, the terminal olefin in **33** must be the first to undergo RCM, instead of the double substituted alkene. This regioselectivity was further enhanced by the coordinative ability of the free hydroxy group in the vicinity of the terminal double bond.

By installing a bulky protecting group on the hydroxy substituent of **34**, it was possible to control the catalytic hydrogenation process, and compound **35** was obtained as a single isomer, with the desired *cis*-DHQ configuration (Scheme 2.13).



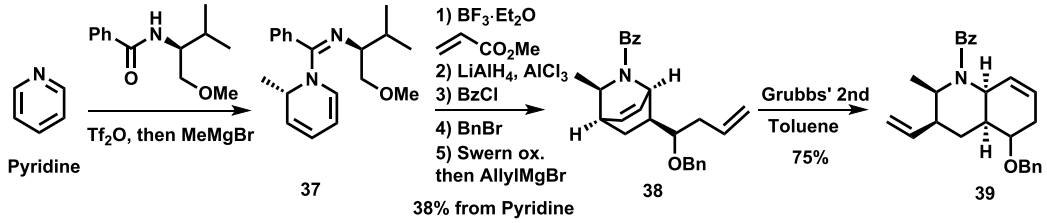
Scheme 2.13. Blechert's endgame synthetic steps.

Aldehyde **36** was used to introduce the eight-carbon side-chain at C-5 *via* a Julia-Kocienski olefination. In order to accomplish the synthesis of *ent*-lepadins F and G, the stereochemistry at C-3 had to be corrected, which was achieved using the same oxidation-reduction approach as Ma. Finally, Yamaguchi conditions to introduce the ester groups and deprotection afforded *ent*-lepadin F and ent-lepadin G in 5.3% overall yield over 17 steps.

2.4.5. Charette's total synthesis of *ent*-lepadin B

A year later, in 2008, after the tandem RCM strategy reported by Blechert, another lepadin synthesis based on this powerful reaction was reported by the Charette group.[58a]

Charette's synthesis began by the assembly of the desired metathesis precursor in a five-step sequence, where the methyl substituent was introduced by using the chiral auxiliary-based pyridine dearomatization methodology previously developed by the authors, affording **37**.[58b] This compound was then elaborated into precursor **38**, which underwent the ring-closing/ring-opening metathesis sequence, elegantly affording *cis*-DHQ **39** (Scheme 2.14).

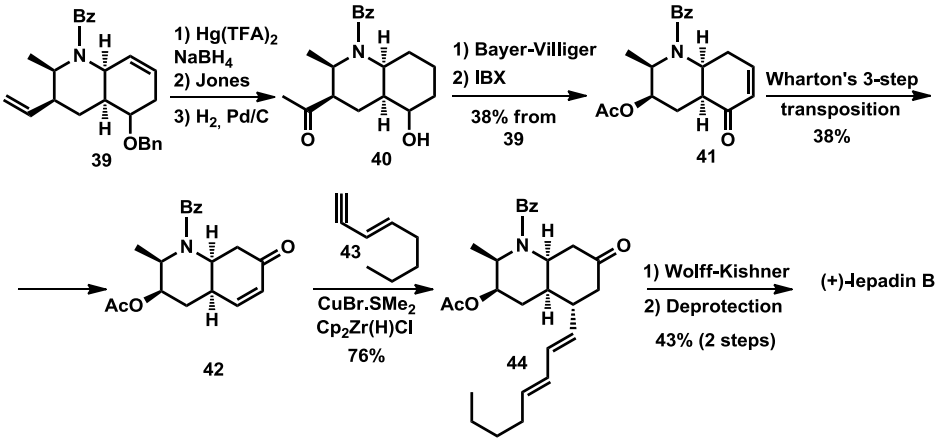


Scheme 2.14. Charette's RC-ROM approach to the *cis*-DHQ core.

The authors went to considerable lengths to demonstrate that the reaction leading to **39** followed a RCM-ROM-CM pathway and not an alternative route, ROM-RCM, by preparing several metathesis substrates.[58a]

Compound **39** had the C-2 and C-3 substituents with the correct *cis* relationship, although lacking the C-3 hydroxy group, which led to a considerable amount of work for the conversion of **39** into *ent*-lepadin B.

To introduce the required hydroxy group at C-3, the vinyl substituent was converted to a ketone **40**, which underwent a stereospecific Bayer-Villiger oxidation to give enone **41** after an IBX-mediated oxidation (Scheme 2.15).



Scheme 2.15. *ent*-lepadin B synthesis by Charette.

[58] (a) Barbe, G.; Charette, A. *J. Am. Chem. Soc.* **2008**, *130*, 13873-13875. (b) Charette, A.; Grenon, M.; Pourashraf, M.; Martel, J. *J. Am. Chem. Soc.* **2001**, *123*, 11829-11830.

To introduce the C-5 side-chain, the authors envisioned a Cu-catalysed conjugated addition of the zirconium species derived from alkyne **43** to a suitable enone. However, compound **41** had the enone at the wrong positions and had to be transposed with a three-step procedure. With the correct enone **42** in hand, the conjugated addition was carried out, affording compound **44** as a single diastereoisomer (Scheme 2.15).

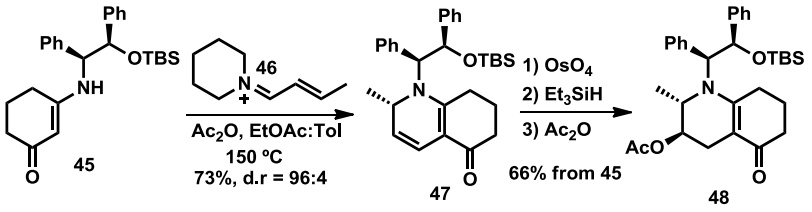
To complete the total synthesis of *ent*-lepadin B, the residual ketone group had to be removed, which was achieved with a Wolff-Kishner reduction. A final deprotection afforded *ent*-lepadin B in 18 steps and 1.4% overall yield. Overall, Charette's approach was very elegant for the assembly of the *cis*-DHQ moiety but fairly inefficient for the introduction of the remaining substituents onto the core.

2.4.6. Hsung's synthesis of (+)-lepadins F and G

The last synthetic reports found in the literature towards the total synthesis of lepadin alkaloids before our own were carried out by Richard Hsung's group.[59]

First they accomplished the total synthesis of (+)-lepadin F and then, to elucidate the stereochemistry at C-5', the authors went on to synthesize both possible C-5' diastereoisomers for (+)-lepadins F and G. This last report, together with the previous synthetic efforts, allowed the unambiguous assignment of the absolute stereochemistry for all lepadin alkaloids.

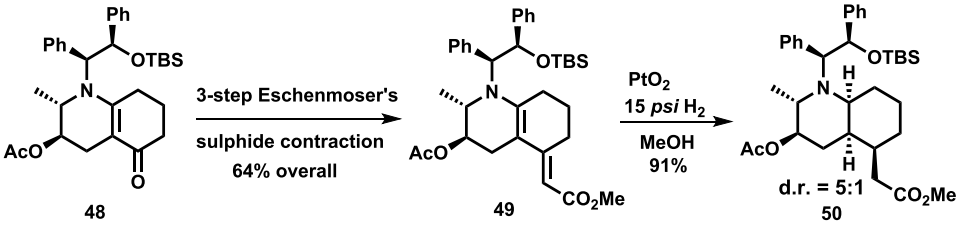
The Hsung group's contribution was their aza-[3+3] annulation between enamide **45** and the iminium ion **36**, which afforded hexahydroquinolone **47** in an excellent diastereoisomeric ratio. To install the hydroxy moiety a two-step protocol involving Os-promoted dihydroxylation and reductive C-4 hydroxy removal, was carried out, affording, after acetylation, enone **48** (Scheme 2.16).



Scheme 2.16. Hsung's initial synthetic sequence.

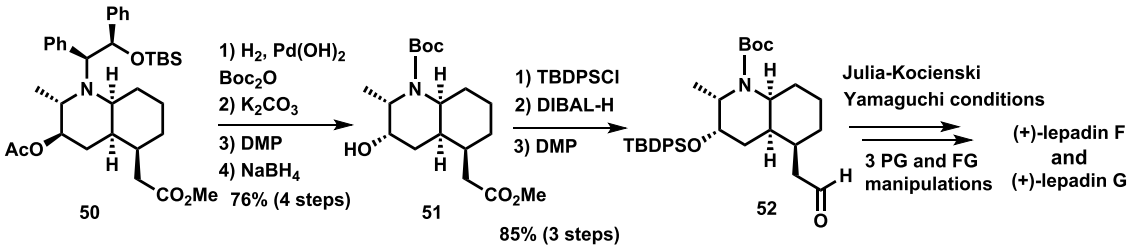
At this stage, the authors had successfully introduced the required substituents at C-2 and C-3, and focused their efforts on establishing the *cis* ring fusion and introducing the C-5 substituent. To this end, compound **48** was converted to unsaturated ester **49** by means of the Eschenmoser's sulphide contraction (Scheme 2.17).

[59] (a) Li, G.; Hsung, P.; Slafer, B.; Sagamanova, I. *Org. Lett.* **2008**, *10*, 4991-4994. (b) Li, G.; Hsung, P. *Org. Lett.* **2009**, *11*, 4616-4619.



Scheme 2.17. Introduction of the C-5 substituent.

With compound **49** in hand, inspired by Ma's approach, the authors thought that catalytic hydrogenation would bring about the *cis* ring fusion and the desired stereochemistry at C-5 to be defined. Indeed, after subjecting compound **49** to optimized hydrogenation conditions, the desired compound **50** was obtained in good overall yield and diastereoselectivity (Scheme 2.17).



Scheme 2.18. Hsung's end-game synthesis.

To complete the total synthesis of (+)-lepadins F and G, the inversion of the stereochemistry at C-3 was required. This was achieved by the two-step oxidation reduction sequence reported by Ma, the elongation of C-5, by means of a Julia-Kocienski olefination, and the esterification of the C-3 hydroxy group. Hsung and co-workers were able to synthesise (+)-lepadin F and (+)-lepadin G in 20 synthetic steps in 14% and 8.6% overall yields, respectively.

2.5. Objectives

The good results obtained in previous studies on the use of chiral tricyclic lactams derived from (*R*)-phenylglycinol in the synthesis of amphibian *cis*-decahydroquinoline alkaloids (pumiliotoxin C) prompted us to expand the methodology to target more complex natural products. Specifically, lepadins A-D were chosen because of their relevant and diverse biological activities. Moreover, we believed that our methodology could provide a competitive alternative to the total syntheses described before.

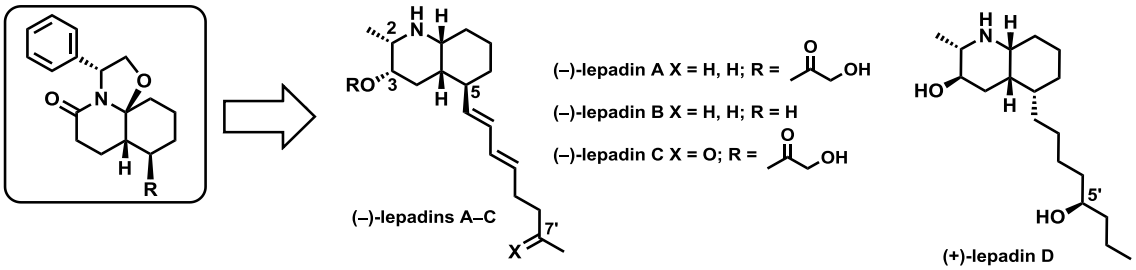


Figure 2.3. Chiral tricyclic lactams for the synthesis of lepadin alkaloids.

To meet the objective of the enantioselective total synthesis of lepadins A–D, starting from a chiral tricyclic lactam, three main synthetic transformations had to be studied:

1. The removal of the phenylethanol moiety of the chiral inductor.
2. The stereoselective introduction of the C-2 methyl substituent and C-3 hydroxy group.
3. The stereoselective elongation of the substituent for the introduction of a functionalized eight-carbon side-chain at C-5.

2.6. Synthetic strategy

In order to access the target alkaloids, a synthetic plan was devised. Starting from a suitable hydroxymethyl substituted unsaturated keto ester **A**, the cyclocondensation reaction with (*R*)-phenylglycinol, followed by catalytic hydrogenation, would give access to the enantiomeric scaffold **B** with the correct stereochemistry at C-5 (lepadin numbering) for the synthesis of lepadins A-C (Figure 2.4).

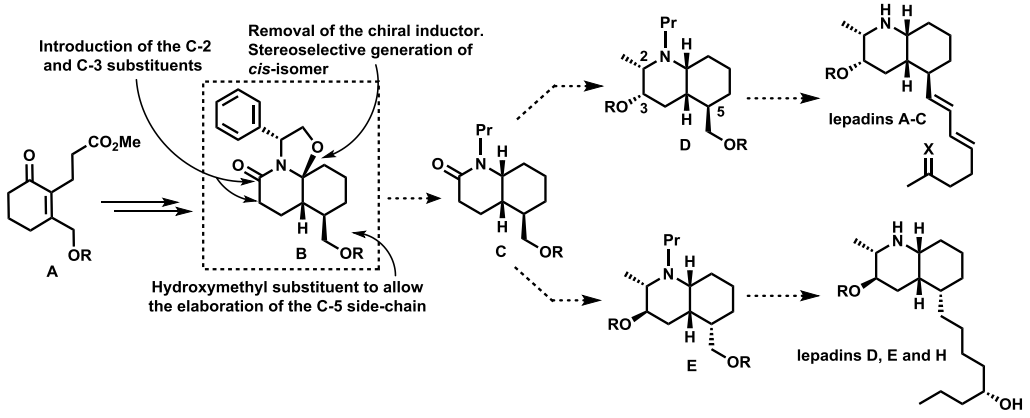


Figure 2.4. Synthetic strategy for lepadin alkaloids.

Compound **B** would be elaborated into advanced synthetic intermediates **D** and **E** for the synthesis of lepadins A–C and lepadins D, E and H, respectively. In order to obtain these intermediates, we would take advantage of the amide function to stereoselectively introduce both the C-2 and C-3 substituents.

Finally, the functionalized carbon side-chain at C-5 would be elongated by using the hydroxymethyl moiety as a synthetic handle for olefination or cross-coupling reactions. It is worth mentioning that from intermediate **C**, the synthesis of lepadins D, E and H additionally requires the inversion of the configuration of the C-5 stereocenter.

2.7. Total synthesis of lepadin alkaloids

2.7.1. Preparation of the keto-ester precursor A.

To begin with, a suitable tricyclic lactam bearing a functionality that would allow us to elongate or introduce the side-chain at C-5 was needed. To this end, we decided to prepare cyclohexenone **A**, with a hydroxymethyl function as a substituent at C-3. This functionality would allow in subsequent steps, the introduction of the C-5 carbon side-chain and, at the same time, could be used to correct the stereochemistry at C-5 as needed for the synthesis of lepadin D (Figure 2.5).

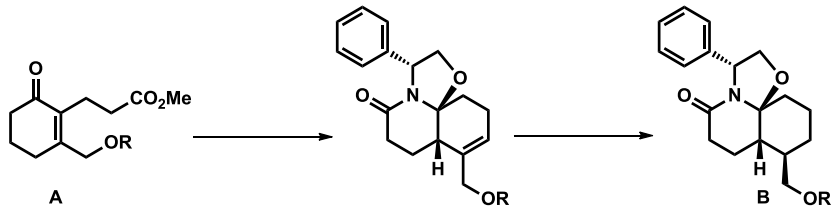


Figure 2.5. Strategy to introduce the hydroxymethyl substituent.

2.7.1.1. Introduction of the hydroxymethyl substituent.

To incorporate the hydroxymethyl substituent we decided to perform a Suzuki-Miyaura cross-coupling using an organotrifluoroborate potassium salt and the known vinyl bromide **1**, previously prepared in our group (Figure 2.6).[45a]

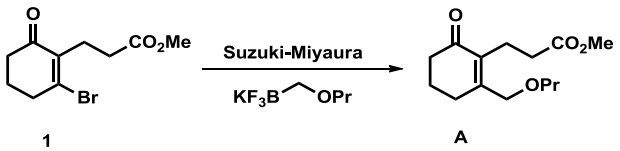


Figure 2.6. Preparation of keto-ester **A**.

This choice was made on the basis that there are few examples in the literature for the introduction of a functionalized single carbon unit, and even fewer that would be compatible with our keto-ester substrate. Moreover, Molander reagents can be easily prepared in large quantities, purified by simple crystallization, and are bench-stable almost indefinitely.

Over the course of their research, Gary Molander and his group developed several reagents of this type,[60a] but one in particular caught our attention, the alkoxymethyltrifluoroborates.[61] This set of boron reagents would allow us to introduce a suitably protected hydroxymethyl group, but the biggest advantage is their superior performance in the cross-coupling of sp^3 carbons, outperforming their boronic acid counterparts.[60]

The Suzuki-Miyaura reaction involves an initial oxidative addition followed by a transmetallation step, in which the active species is not the potassium trifluoroborate salt, but the corresponding boronic acid formed by hydrolysis of the former in the reaction media. This is the reason why almost all protocols involving these boron derivatives need H_2O as a co-solvent. After the transmetallation step, a reductive elimination occurs, delivering the coupled product and regenerating the active Pd(0) catalyst (Figure 2.7).

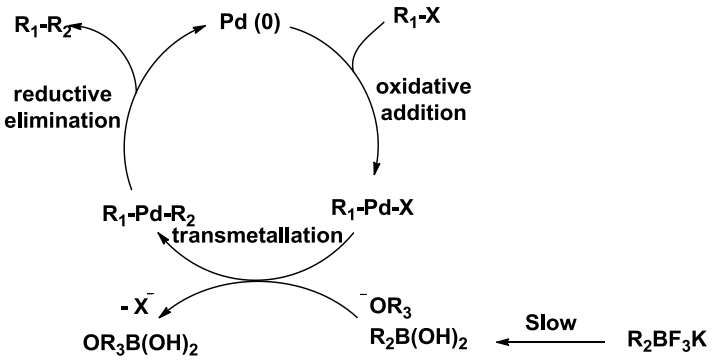
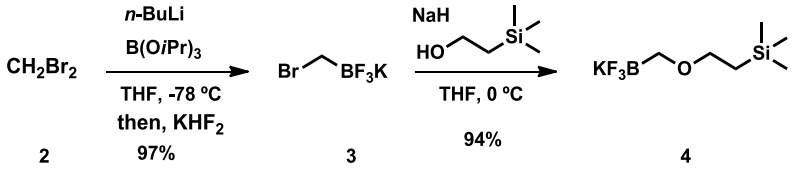


Figure 2.7. Suzuki-Miyaura cross-coupling reaction mechanism with potassium organotrifluoroborates.

Thus, the superior performance of organotrifluoroborate salts is not due to an inherent higher reactivity, residing instead in the slow liberation of the boronic acid. As a result, fewer side products are formed in comparison with their boronic ester/acid counterparts, since these salts are less susceptible to protodeboronation. Moreover, the formation of homo-coupling products is supressed, given the small amounts of boronic acid available to react at any given time during the reaction.

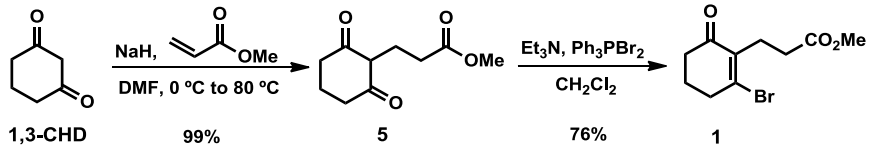
This is of particular importance in slow transmetallation systems such as the ones involving sp^3 carbons. Thus, with a suitable catalytic system that promotes a fast reductive elimination process, the competing ß-hydride elimination can be overcome, therefore avoiding the products resulting from this side-reaction. All of these factors taken together account for the higher yields and cleaner reactions usually observed when organotrifluoroborate salts are empoyed.[61] The required potassium organotrifluoroborate reagent was easily prepared in very high yield on a multi-gram scale (≥ 30g) following the literature conditions depicted in Scheme 2.19.[62]

[60] (a) Molander, G.; Canturk, B. *Angew. Chem. Int. Ed.* **2009**, *48*, 9240-9261. (b) Lennox, A.J.J.; Lloyd-Jones, G.C. *Chem. Soc. Rev.* **2014**, *43*, 412-443.
[61] Molander, G.; Canturk, B. *Org. Lett.*, **2008**, *10*, 2135-2138.



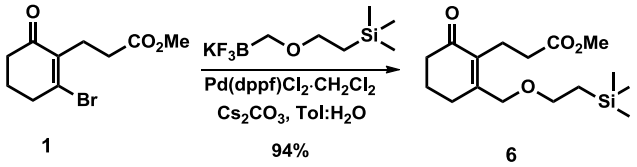
Scheme 2.19. Preparation of the potassium organotrifluoroborate.

Having secured the required coupling partner, the next step was the Suzuki-Miyaura cross-coupling reaction with the previously reported vinyl bromide **1**. It should be mentioned that the corresponding triflate was also used to screen the reaction, affording similar results. However, due to the difficulties in reproducibility of the large scale preparation of this triflate derivative, we decided to continue our synthesis with the vinyl bromide **1**. Compound **1** is easily accessible on a multi-gram scale through the synthetic sequence shown below (Scheme 2.20).



Scheme 2.20. Synthesis of the vinyl bromide **1**.

With both Suzuki-Miyaura coupling partners prepared in ample amounts, it was time to attempt the coupling reaction. The reaction was surprisingly easy to optimize, since the literature conditions[62] immediately afforded a 60% yield of the desired compound **6** and with a simple tweak, running the reaction at 100 °C instead of the 90 °C in the original report, the coupling product **6** was obtained in 94% yield (Scheme 2.21). Moreover, the reaction could be performed on a multi-gram scale with comparable yield.



Scheme 2.21. Suzuki-Miyaura cross coupling reaction to afford **6**.

2.7.1.2. The cyclocondensation reaction

Our group has previously reported[45a] that the cyclocondensation reaction between C-3 substituted cyclohexenone-propionate derivatives and (*R*)-phenylglycinol stereoselectively led to a chiral tricyclic lactam. This allowed the rapid preparation of an enantiopure chiral scaffold with well-defined stereocentres of predictable configuration. It should be noted that minor amounts of another diastereoisomer **IIb** with the opposite *cis* stereochemistry were also detected, usually in a 4:1 proportion favouring the major

[62] Molander, G. A.; Ham, J.; Seapy, D. G. *Tetrahedron*, **2007**, *63*, 768-775.

isomer **IIa** (Figure 2.8). More importantly, the *trans* isomers have never been detected as products of this reaction.

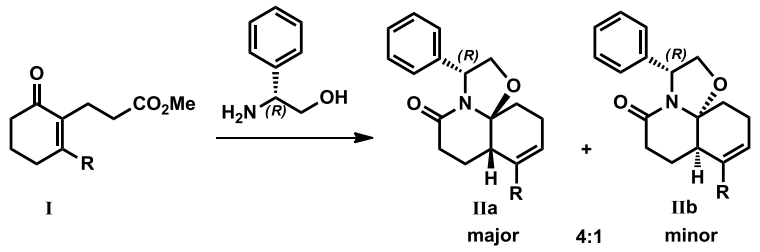


Figure 2.8. Cyclocondensation reaction with (*R*)-phenylglycinol.

The reaction proved to be quite general, tolerating different C-3 substituents, which did not have an effect on the reaction diastereoselectivity, affording a variety of chiral tricyclic lactams in good yields. These tricyclic lactams proved to be valuable chiral scaffolds, since after catalytic hydrogenation it was possible to define a new stereocenter at the C-8 position, with complete stereocontrol and predictable configuration (Figure 2.9).

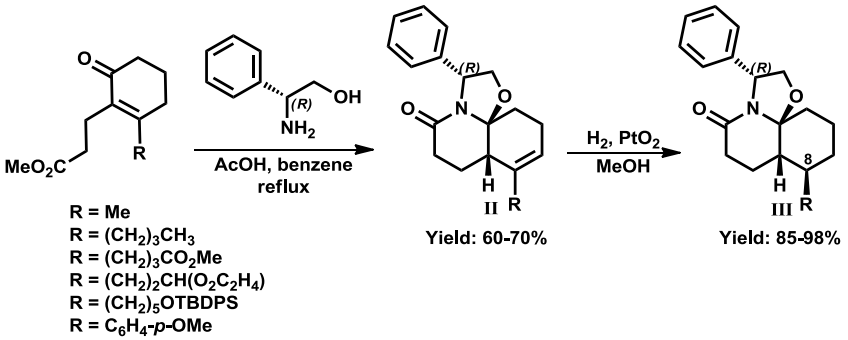


Figure 2.9. Cyclocondensation reaction scope.

After removal of the chiral inductor, these lactams were elaborated into enantiopure 5-alkyl *cis*-decahydroquinolines. The results obtained in the preparation of 5-substituted *cis*-DHQ structures in such an efficient and stereocontrolled manner stimulated synthetic studies that culminated in the enantioselective total synthesis of *cis*-**195A**, commonly known as pumiliotoxin C (Figure 2.10).

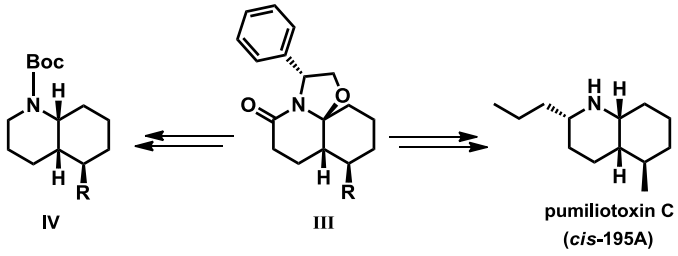


Figure 2.10. Chiral tricyclic lactams for the enantioselective synthesis of alkaloids.

The formation of tricyclic lactam **IIa** can be rationalized as depicted in Figure 2.11. It should be noted that a C−C double bond migration must occur and that four diastereoisomers can be formed for oxazolidine **I** (Figure 2.11).

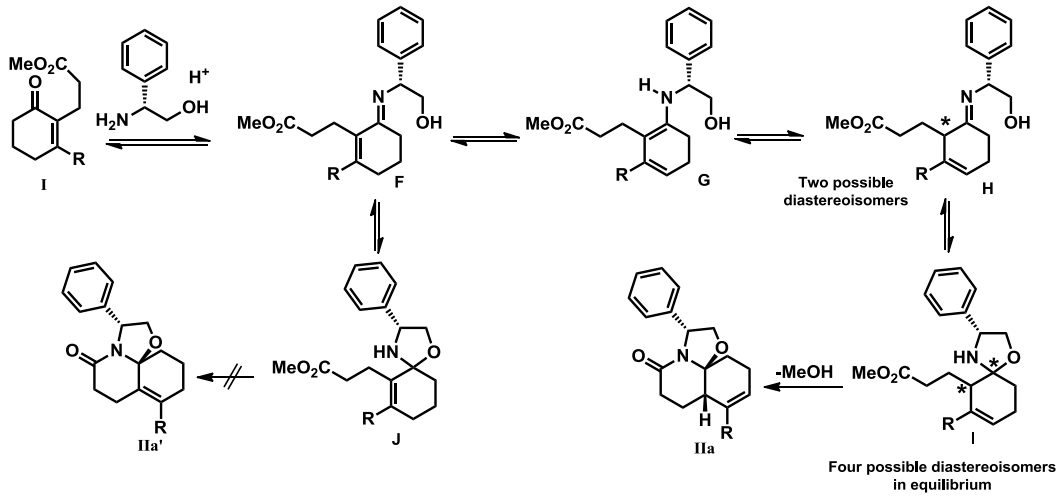


Figure 2.11. Proposed mechanism for the cyclocondensation reaction.

The proposed mechanism considers that first, under acid catalysis, formation of enimine **F** occurs by condensation of the amine moiety of the amino-alcohol with the ketone function of the cyclohexenone. At this point, **F** can evolve into dienamine **G** or, if the hydroxy group attacks the imine carbon of **F,** to an oxazolidine, **J**, which after irreversible lactamization would afford a tricyclic lactam such as **IIa'**. This compound would have a high annular tension, given the position of the C−C double bond on a bridgehead carbon in an already highly rigid tricyclic system, due to the presence of the amide bond. This is probably the main reason why the formation of **IIa'** has not been detected thus far. From dienamine **G**, however, the reaction pathway seems more feasible since after equilibration to an imine such as **H** by protonation of the ß position, oxazolidine ring formation can occur, affording **I**. This intermediate, where four possible diastereoisomers can exist undergoes the final irreversible lactamization step to afford the major product **IIa**, after loss of methanol. The formation of **IIa** is the driving force of the cyclocondensation process, displacing all the reaction equilibria to afford the kinetic product of the lactamization process. To account for the formation of **IIa** as the major isomer, we must look at the intermediate oxazolidines **int-I1** and **int-I2** and consider their reactive conformations (Figure 2.12).

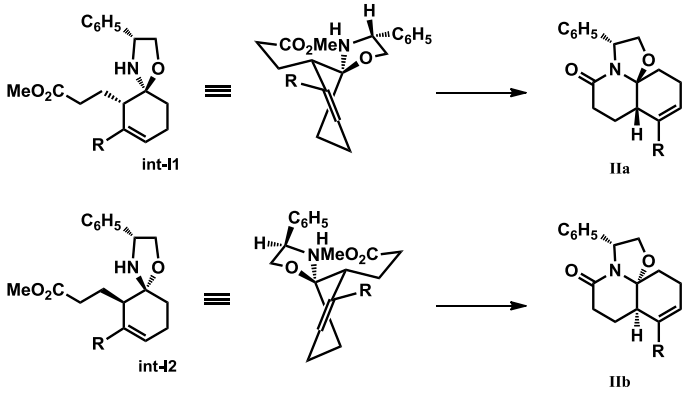
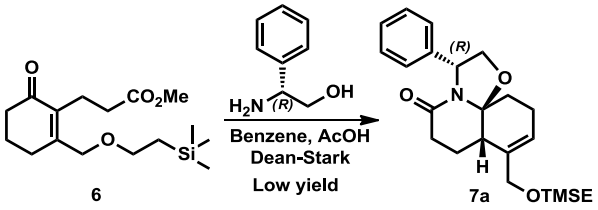


Figure 2.12. Conformations of intermediates **int-I1** and **int-I2**.

In both cases, the final lactamization occurs through a chair-like transition state, where in the case of **int-I1** the propionate side chain approaches from the opposite face with respect to the phenyl group of the chiral inductor position to avoid repulsive interactions. For **int-I2**, however, the transition state would involve a propionate side-chain approaching from the same face of the phenyl group, where the steric encumbrance of the aromatic ring would disfavour the attack. This slows down the lactamization step, hence the formation of isomer **IIb** as the minor diastereoisomer.

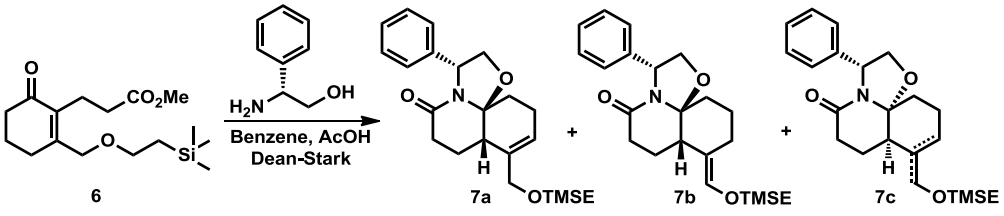
The absence of isomers with a *trans* fusion between the two six-membered rings can be rationalised considering that a conformationally rigid *trans*-decaline-like system in a tricyclic amide would be highly strained.

Taking into account all our previous experience we proceeded to perform the cyclocondensation reaction between (*R*)-phenylglycinol and the synthesised keto-ester **6**. Surprisingly, the first experiments proved to be quite challenging since, although full conversion was achieved, the isolated yield of compound **7a** was low. Moreover in no case was a pure sample of **7a** obtained, because purification of the crude reaction mixture proved troublesome (Scheme 2.22).



Scheme 2.22. Cyclocondensation reaction to afford the chiral building block.

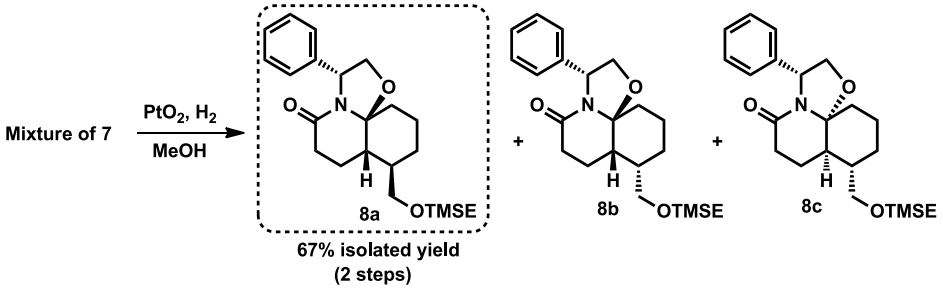
To obtain an insight into what was occurring, the ^{13}C-NMR spectra for each set of flash chromatography fractions was carefully analysed, and we noticed that two isomeric olefins had been formed. Comparison with previous ^{13}C-NMR data from similar compounds led us to hypothesise that during the cyclocondensation reaction, in addition to the formation of the endocyclic alkene, the exocyclic isomer had also been obtained (Scheme 2.23).



Scheme 2.23. Alkene isomers formed during the cyclocondensation reaction.

This was somewhat surprising, since it had not been detected in any of the previous examples reported by our group. However, it should also be taken into account that none of the said previous examples had a heteroatom, just one carbon away from the migration center. We reasoned that the presence of the oxygen facilitated the formation of these enol ethers.

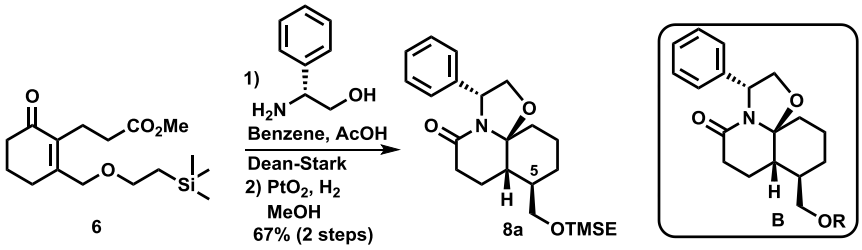
Given that our objective, besides the construction of the tricyclic lactam, was to hydrogenate the C−C double bond to define the C-5 stereocenter for the target alkaloids, we decided to perform the subsequent catalytic hydrogenation on the crude mixture (Scheme 2.24).



Scheme 2.24. Catalytic hydrogenation of tricyclic lactam.

Satisfyingly, the desired isomer **8a** was isolated in good yield after two synthetic steps from cyclohexenone **6**. Minor amounts of other isomers were also detected.

Compound **8a**, bearing a hydroxymethyl function at C-5 (decahydroquinoline numbering) and three well-defined stereocentres, constitutes our targeted synthetic intermediate **B** (Scheme 2.25).



Scheme 2.25. Synthesis of chiral tricyclic lactam **B**.

With the successful preparation of compound **8a**, we decided to continue our studies for the remaining necessary transformations.

2.7.2. Model studies

To carry out these studies, given the time and resources invested in the preparation of the valuable compound **8a**, it was deemed more reasonable to use a model compound. We chose a chiral tricyclic lactam previously reported by our group with a stereodefined C-5 methyl substituent (DHQ numbering), given its easy, cheap and fast preparation (Figure 2.13).[45b]

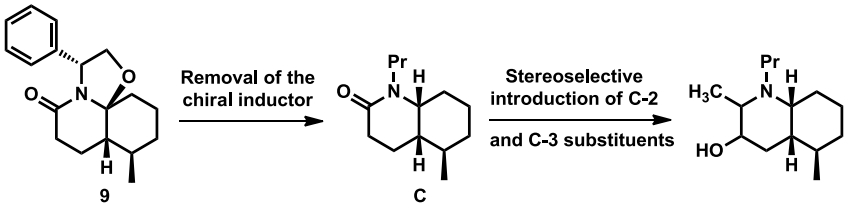


Figure 2.13. Model compound for the synthetic transformations.

Our main studies with compound **9** were focused on the stereoselective removal of the chiral inductor to afford *cis*-decahydroquinoline **C** and then the stereoselective introduction of the C-2 and C-3 substituents onto the DHQ core.

2.7.2.1. Removal of the phenylethanol moiety of the chiral inductor

Our group had previous experience in two procedures for the reductive cleavage of the C−O bond of the oxazolidine ring: the chemoselective reduction mediated either by a silane and a Lewis acid (**Route A**) or by aluminium hydride, AlH_3 (**Route B**), which also provokes the reduction of the carbonyl lactam (Figure 2.14).

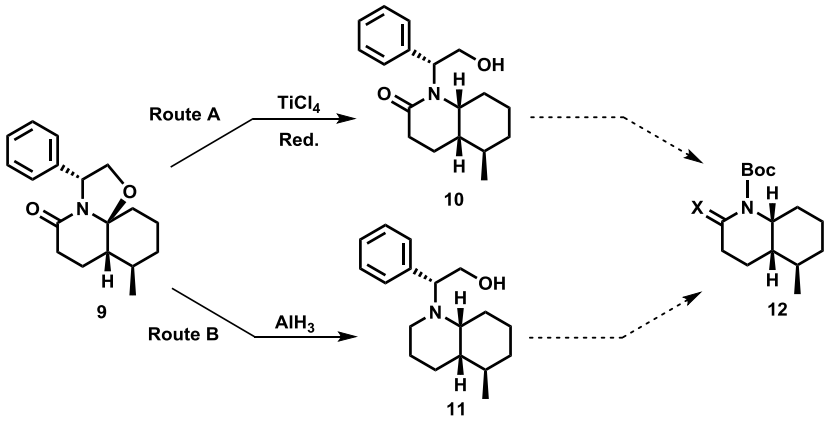


Figure 2.14. Alternative paths for the stereoselective removal of the chiral inductor.

Route A seemed more attractive because it would maintain the amide moiety intact, although this methodology had never been applied to this type of chiral tricyclic lactams. **Route A** would involve three synthetic steps to reach the target compound **12** (Figure 2.15).

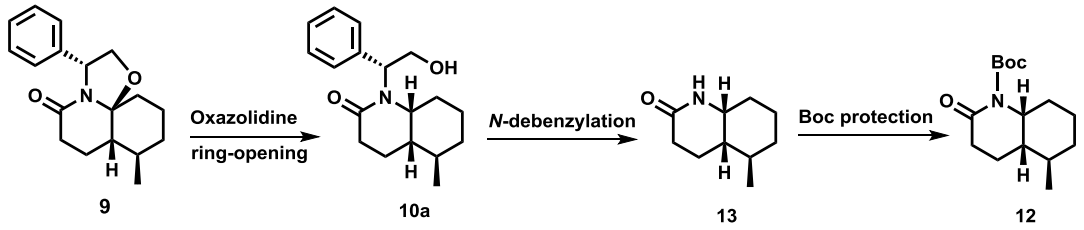
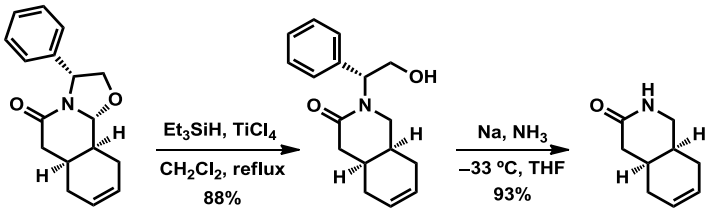


Figure 2.15. Synthetic outline for **Route A**.

In research on various bicyclic and tricyclic chiral lactams, our group has amassed considerable experience on the removal of the chiral inductor by reductive oxazolidine ring opening mediated by $TiCl_4$ and Et_3SiH, followed by Birch conditions to afford the secondary amide (Scheme 2.26).



Scheme 2.26. Previous results within our group.

The reaction is thought to proceed by the weakening of the C–O bond of the oxazolidine, promoted by the coordination of the Lewis acid, $TiCl_4$. This coordination leads to the formation of an acyliminium ion, which is subsequently reduced by the hydride source, in this case Et_3SiH.[63]

When the angular position of the amino-alcohol-derived lactams is substituted, a new stereogenic centre is generated. Meyers observed that in pyrrolidinone systems the reaction took place with retention of configuration and came up with a rationalisation for the excellent diastereoselectivities obtained (Figure 2.16).[63a]

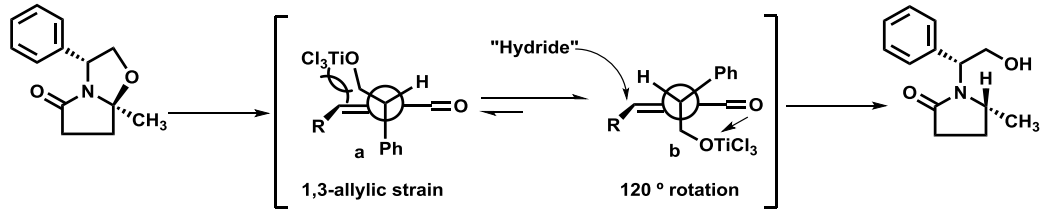


Figure 2.16. Meyers' rationale for the stereochemistry retention.

The hydride attack occurs from conformation **b**, avoiding the 1,3-allylic interaction present in **a** that is additionally stabilised by the chelation between the titanium moiety and the amide carbonyl.[63] We believed we could replicate these observations in our chiral tricyclic lactam system (Figure 2.17).

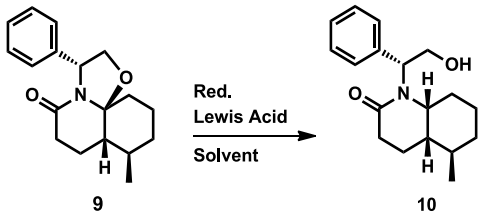
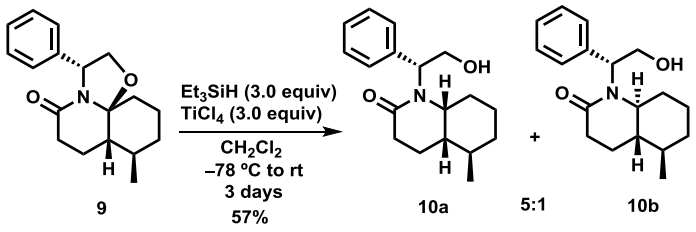


Figure 2.17. Reductive oxazolidine ring-opening of tricyclic lactams.

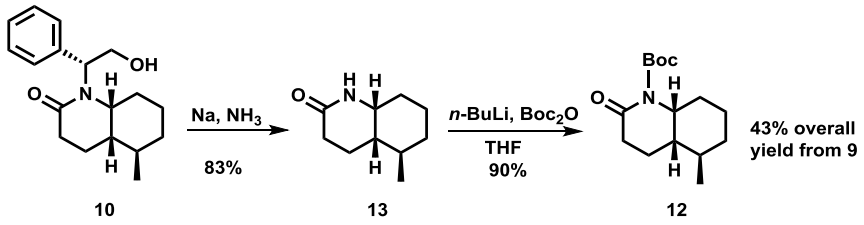
[63] (a) Burgess, L. E.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 1656-1662. (b) Meyers, A. I.; Tschantz, M. A.; Brengel, G. P. *J. Org. Chem.* **1995**, *60*, 4359-4362.

A round of experiments was conducted, to explore this possibility, varying the temperature (−78 ºC to reflux), inverse addition of the reactants, reaction times (short (minutes) to long (several hours or days)), solvent (CH_2Cl_2 or THF), and stoichiometry of the reagents. The best conditions found are shown in the scheme below (Scheme 2.27).



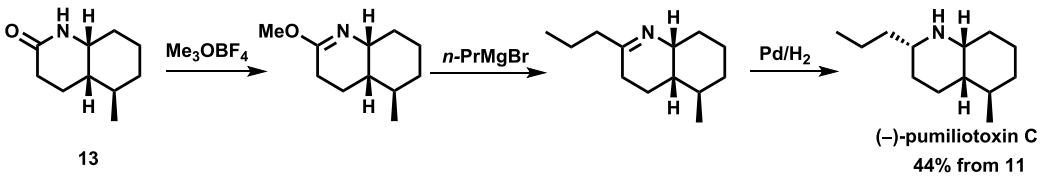
Scheme 2.27. Best conditions for the reductive oxazolidine ring-opening.

Unfortunately, although it was always possible to recover unreacted **9**, the yield could not be improved beyond 57%, even after prolonged reaction times and the use of super-stoichiometric amounts of Lewis acid and silane. Disregarding the moderate yield, the biggest setback was the fact that the reaction was not completely stereoselective, always affording a 5:1 mixture of *cis* and *trans* isomers, which could not be separated by flash chromatography. To access compound **12**, the *N*-debenzylation and Boc protection were carried out in good yields following conventional transformations. After subjecting benzyl amide **10** to Birch conditions followed by *N*-Boc protection, compound **12** was obtained in very high yield (Scheme 2.28).



Scheme 2.28. Synthesis of model DHQ **12** by **Route A**.

It should be mentioned that compound **13** constitutes a formal total synthesis of (–)-pumiliotoxin C, since with three more steps from this compound, Oppolzer completed the synthesis of this alkaloid (Scheme 2.29).[64]



Scheme 2.29. Oppolzer's total synthesis of *cis*-195 from **13**.

[64] Oppolzer, W.; Fehr, C.; Warneke, J. *Helv. Chim. Acta* **1977**, *60*, 48-58.

Given the lack of selectivity for the oxazolidine ring opening, we decided to explore the alternative **Route B** using $Et_3SiH/TiCl_4$. This would require an additional oxidation step (Figure 2.18).

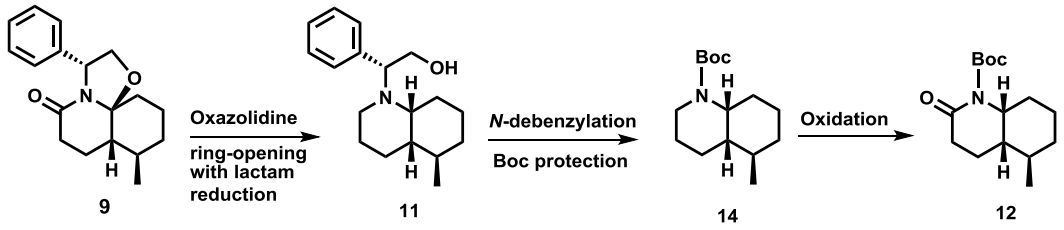


Figure 2.18. Synthetic outline for **Route B**.

For this synthetic route, we knew from previous studies that the *N*-debenzylation step could be performed one-pot with the Boc protection protocol. This meant that **Route B** would have the same number of synthetic steps as **Route A**, and the deciding factors would be the stereoselectivity of the oxazolidine ring-opening and the overall yield of **12**.

The AlH_3-promoted oxazolidine ring-opening had previously applied in chiral tricyclic lactams, such as **9**, in the context of synthetic studies on the preparation of 5-alkyl *cis* – DHQ.[45] This methodology afforded excellent diastereoselectivities and good yields of the corresponding tertiary amines.

This transformation occurs with retention of configuration. The reagent, AlH_3, serves as both the Lewis acid, which by coordination with the oxygen atom of the oxazolidine generates an incipient acyliminium salt, and the reducing agent. The coordination leads to a hydride delivery occurring from the same face as the leaving O atom (Figure 2.19).[63a]

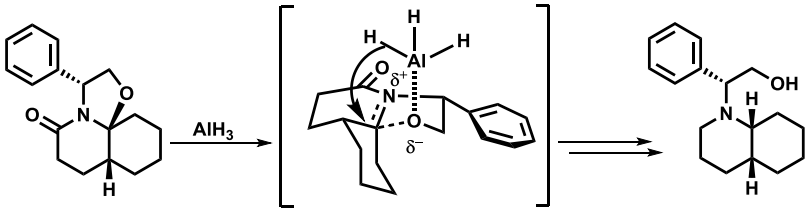
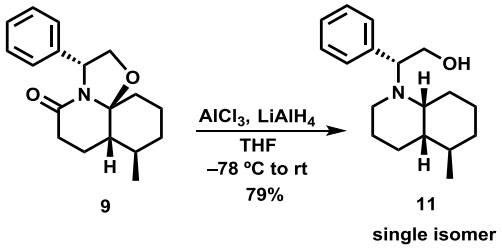


Figure 2.19. Mechanism of the oxazolidine ring-opening by AlH_3.

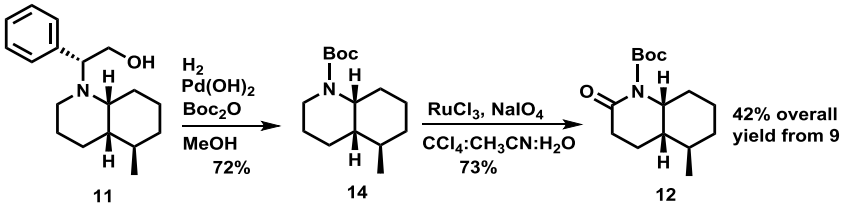
Considering the previous results reported by our group, we were confident of obtaining a good result and, indeed, after performing the oxazolidine ring-opening under aluminium hydride conditions, a single isomer **11** was obtained in high yield (Scheme 2.30).



Scheme 2.30. Oxazolidine ring-opening with AlH_3.

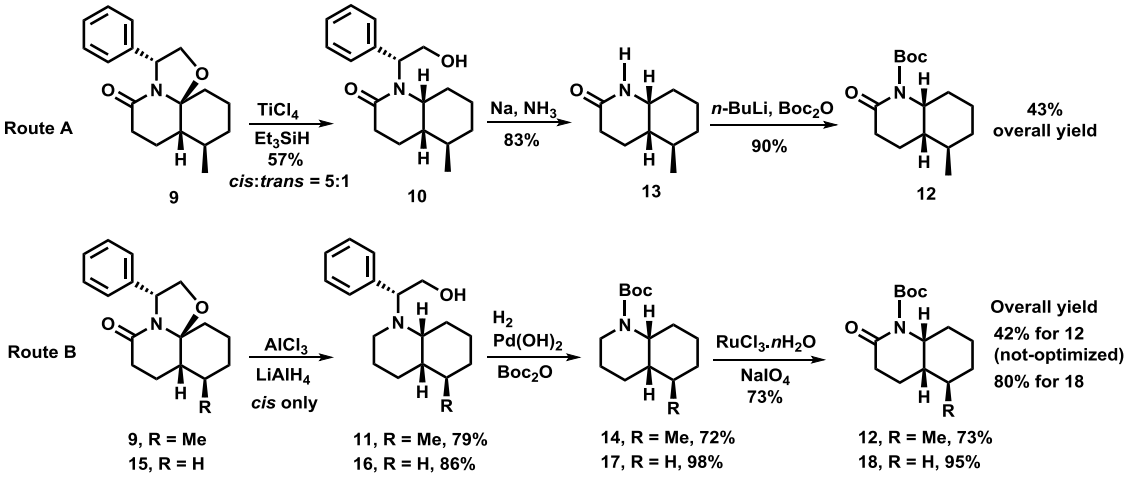
From a stereochemical standpoint, this outcome represented a clear improvement, on our previous results and thus encouraged by it, we went ahead with **Route B**.

The one-pot debenzylation was carried out under Boc protection conditions, affording the known *cis*-DHQ **14** in good yield. To prepare compound **12**, the amide moiety had to be re-introduced, given its collateral reduction during oxazolidine opening. In order to perform the oxidation, we chose the ruthenium tetroxide protocol, which smoothly afforded compound **12** in good yield (Scheme 2.31).[65]



Scheme 2.31. Preparation of **12** with **Route B**.

At this point, it was possible to draw a comparison between both synthetic routes. Moreover, in parallel experiments, an additional compound **18**, lacking a C-5 substituent, was prepared from known intermediates **15-17**, which provided additional data for **Route B** (Scheme 2.32).



Scheme 2.32. Comparison between both synthetic routes.

Given the high overall yield of the model derivative **18** through **Route B** and that the synthetic sequence towards **12** through **Route A** could not be further optimized, it was decided to proceed, with the synthesis by the former.

[65] Moriyama, K.; Sakai, H.; Kawabata, T. *Org. Lett.* **2008**, *10*, 3883-3886.

2.7.2.2. Stereoselective functionalization of C-2 and C-3

Having selected a synthetic protocol to perform the removal of the phenylethanol moiety in a stereoselective and efficient manner, we focused our attention on the introduction of the C-2 methyl and C-3 hydroxy substituents (Figure 2.20).

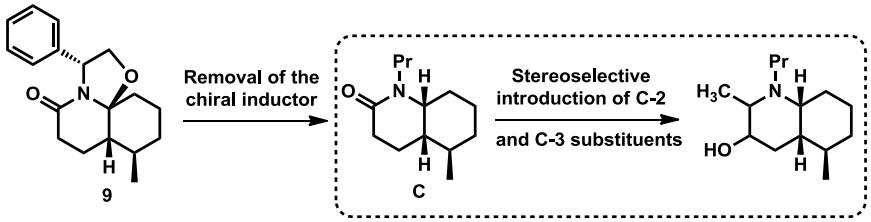


Figure 2.20. Model studies – next steps.

To accomplish the introduction of these two substituents, it was envisioned that if we could convert the lactam moiety in **12** to the corresponding vinyl triflate, it would then be possible to perform the required synthetic manipulations. After introduction of the C-2 methyl substituent and taking advantage of the resulting enecarbamate, a hydroboration-oxidation reaction could be used to introduce the C-3 hydroxy moiety (Figure 2.21). It was expected that substrate *bias* would generate the desired stereochemistry for **21**.

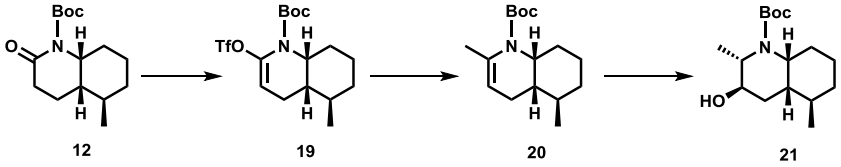
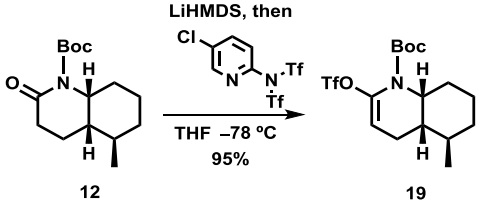


Figure 2.21. Introduction of the C-2 and C-3 substituents.

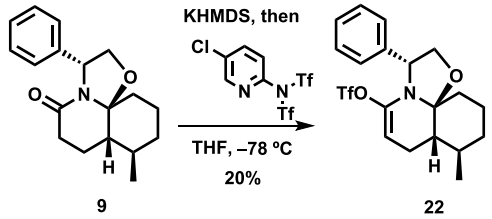
To prepare **19** we chose the Comins' protocol, making use of the higher reactivity of its *N*-(5-chloro-2-pyridyl)-triflimide with respect to the aniline counterpart developed by McMurry. With this reagent, the electron deficient aromatic ring facilitates the nucleophilic attack on the triflimide moiety by withdrawing electron density. Additionally, chelation effects between the generated metallo-enolate and the pyridine nitrogen and triflate groups also aid in the higher reactivity profile of this reagent.[66a] Using the Comins' reagent, under Dake conditions,[66b] it was possible to obtain vinyl triflate **19** in nearly quantitative yield (Scheme 2.33).



Scheme 2.33. Preparation of vinyl triflate **51**.

[66] (a) Comins, D.L.; Dehghani, A. *Tet. Lett.* **1992**, *33*, 6299-6302. (b) Easton, L. P.; Dake, G. *Can. J. Chem.* **2004**, *82*, 139-144.

This excellent result prompted us to explore the possibility of preparing the vinyl triflate of compound **9**. Given the aforementioned conformational rigidity of the tricyclic system, one could expect a higher stereocontrol in the introduction of the C-2 and C-3 substituents. However, after several assays we could not improve the yield above 20%, recovering unreacted **9** in the process (Scheme 2.34).



Scheme 2.34. Attempt to prepare the vinyl triflate of **22**.

Although initially we attempted a Suzuki-Miyaura cross-coupling using methyl boronic acid without success, the introduction of the methyl substituent on vinyl triflate **19** was achieved *via* coupling with methyllithium in the presence of a copper salt.[67] All attempts to isolate the resulting enecarbamate **20** proved unsuccessful or low-yielding since we found that upon chromatographic purification it decomposed to the corresponding ring-opened product **23** (Figure 2.22).

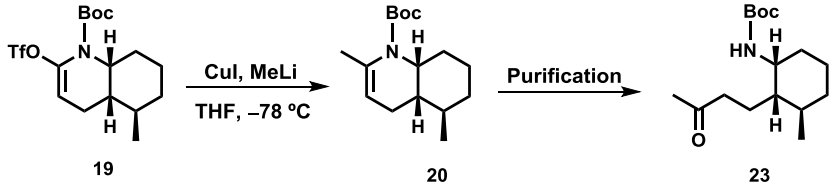
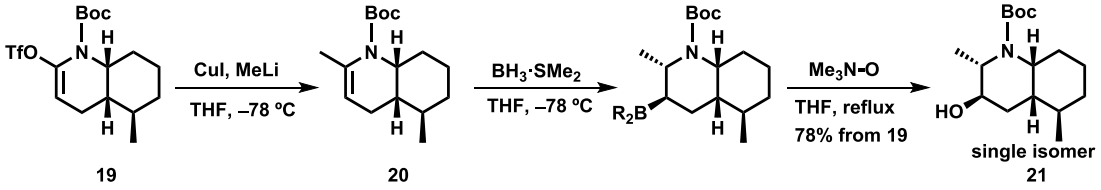


Figure 2.22. Introduction of the methyl group.

The instability of such enecarbamates was noted before by Occhiato and co-workers in their studies of cross-coupling reactions with related vinyl triflates derived from lactams.[68] Given the instability of **20** and that the crude ^{1}H-NMR of this transformation was exceptionally clean, showing complete conversion, it was decided to use the crude compound and perform the subsequent hydroboration-oxidation protocol to introduce the hydroxy group.

A brief screening of reaction conditions was performed, namely borane reagents, and we found that $BH_3 \cdot SMe_2$ was the best, while sterically encumbered boranes such as 9-BBN, thexyl or disiamylborane proved unreactive towards our substrate. After oxidation with trimethylamine *N*-oxide,[69] compound **21** was obtained as a single diastereoisomer in excellent overall yield (Scheme 2.35).

[67] Tsushima, K.; Hirade, T.; Hasegawa, H.; Murai, A. *Chem. Lett.* **1995**, 801-202.
[68] Occhiato, E.; Trabocchi, A.; Guarna, A. *J. Org. Chem.* **2001**, *66*, 2459-2465.
[69] Le Corre, L.; Kizirian, J.-C.; Levraud, C.; Boucher, J.-L.; Bonnet, V.; Dhimane, H. *Org. Biomol. Chem.* **2008**, *6*, 3388-3398.



Scheme 2.35. Stereoselective introduction of C-2 and C-3 substituents.

The obtention of **21** as a single isomer can be rationalised by considering that enecarbamate **20**, in order to avoid 1,3-allylic strain caused by the Boc substituent, adopts a conformation where the bond between C-8 and C-8a is axial, and that the borane reagent approaches the double bond from the most accessible face (Figure 2.23).

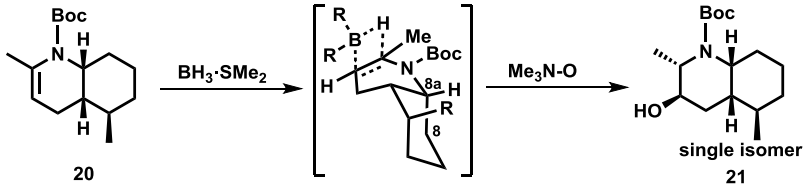


Figure 2.23. Stereoselectivity of the hydroboration reaction.

It should be noted that the obtained stereoisomer **21** has the correct stereochemistry at C-2 and C-3 for the lepadins D–E and H, whereas the C-3 stereocentre has the opposite configuration with respect to lepadins A–C.

With these results we accomplished our second objective, being able to stereoselectively introduce the C-2 methyl and C-3 hydroxy substituents.

2.7.3. Total synthesis of lepadins A–C

2.7.3.1. Assembly of the 5-subsituted *cis*-DHQ core

Having succesfully accomplished all the required synthetic model studies, we felt confident in applying the developed methodology to our chiral scaffold **8a** to advance our synthetic efforts towards lepadins A–C (Figure 2.24).

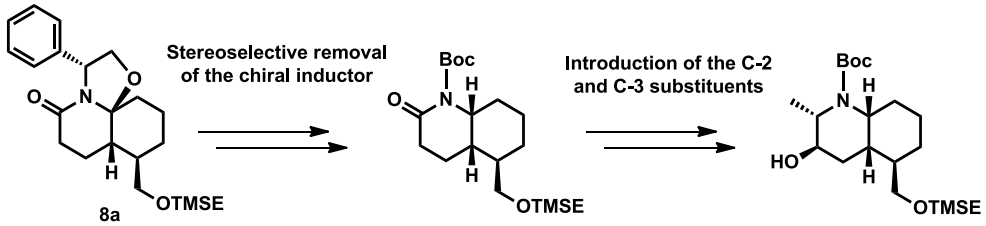
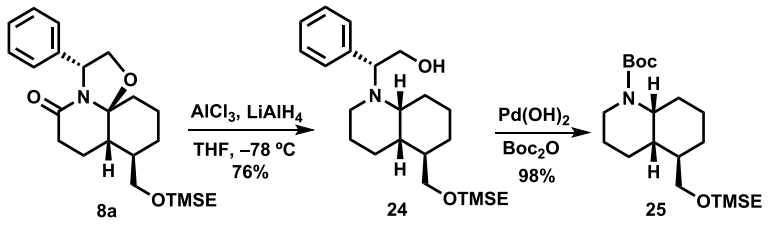


Figure 2.24. Application of the model studies to chiral lactam **8a**.

We began by performing the removal of the phenylethanol moiety by the two-step sequence developed previously (Scheme 2.36).

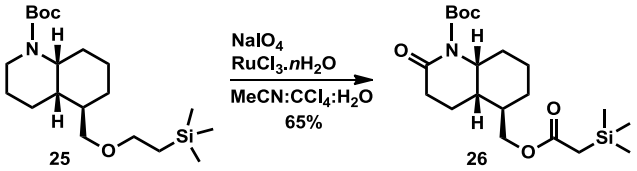


Scheme 2.36. Stereoselective removal of the chiral inductor.

Starting from lactam **8a**, the developed protocol afforded **25**, with the desired *cis*-DHQ ring fusion, in very high yield and complete stereoselectivity, establishing three of the five final stereocentres early on in the synthesis towards lepadins A–C.

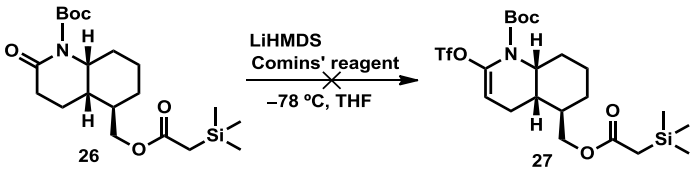
2.7.3.2. Introduction of the C-2 and C-3 substituents

The next step was to re-introduce the lactam carbonyl moiety by applying the RuO_4 oxidation protocol to compound **25**. However, we were wary of a possible issue, because having three methylene groups adjacent to a heteroatom could be problematic when using such a strong oxidant. The RuO_4-mediated oxidation of ethers to the corresponding esters is a known reaction,[70] although all oxidations with this reagent are highly dependent on the solvent systems used. When the oxidation protocol was applied to **25**, the double oxidized **26** was the only product of the reaction (Scheme 2.37).



Scheme 2.37. Bis-oxidation of **25**.

Nevertheless, we decided to attempt the selective formation of the vinyl triflate of the lactam moiety in **26**, knowing beforehand that it would be very difficult to differentiate between the methylene groups alpha to the lactam and to the ester group. We performed the previously optimized protocol, using a stoichiometric amount of base to generate the enolate. Unfortunately, this led only to decomposition and untreatable reaction mixtures (Scheme 2.38), so we had to re-consider our options and search for alternatives.



Scheme 2.38. Attempt to prepare the vinyl triflate of **26**.

[70] Naota, T.; Takaya, H.; Murahashi, S.-I. *Chem. Rev.* **1998**, *98*, 2599-2660.

The easiest way to adjust the synthesis was to change the protecting group of the hydroxymethyl function, although this could not be performed with the trifluoroborate coupling partner. Molander noted the impossibility of preparing reagents with a silyl protecting group such as **4**, from the corresponding silanol, due to the stabilizing effect of the silicon atom on the formed anion, hence the absence of reaction with **3** (Figure 2.25).[62] Other derivatives with different protecting groups incorporated, such as a PMB ether, would not have been stable under the required catalytic hydrogenation conditions of the synthetic route.

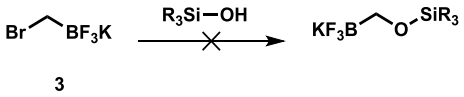
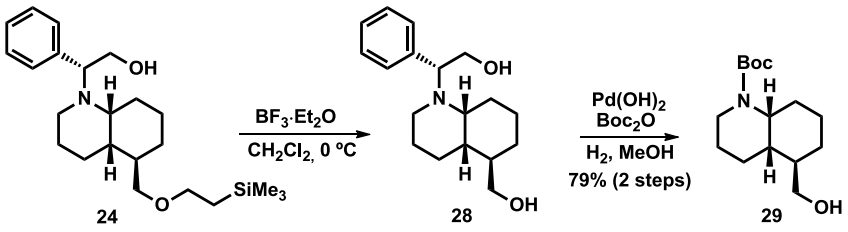


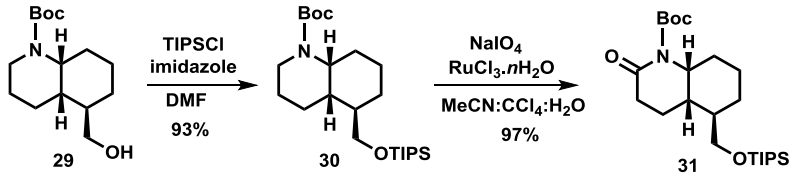
Figure 2.25. Silanols do not undergo alkylation with **3**.

We then decided to change the protecting group before the debenzylation step, because the conditions to perform the deprotection of the 2-trimethylsilylethyl protecting group, $BF_3 \cdot Et_2O$ in CH_2Cl_2 or CsF in DMF >210 ºC, would be incompatible with the Boc group.[71] Thus, deprotection of compound **24** by treatment with $BF_3.Et_2O$,[72] followed by debenzylation and *N*-Boc protection under standard conditions, afforded **29** in high overall yield (Scheme 2.39).



Scheme 2.39. Protecting group switch.

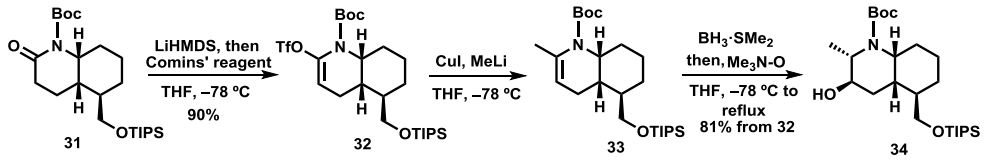
Compound **29** was then reprotected as the TIPS derivative **30** before the oxidation step. At this point, we were fairly confident that the bis-oxidized product would not be formed, since in the first assay the C-1' position was kept intact, probably due to steric factors. Indeed, oxidation of **30** afforded our desired lactam in excellent yield with no detection of over-oxidation products (Scheme 2.40).



Scheme 2.40. Introduction of the lactam moiety.

[71] Wuts, P. G.M.; Greene, T. W. in *Greene's Protective Groups in Organic Synthesis*; John-Wiley and Sons: Hoboken, New Jersey 2007; p 81.
[72] Jansson, K.; Frejd, T.; Kihlberg, J.; Magnusson, G. *Tetrahedron Lett.* **1986**, *27,* 753-756.

With lactam **31** in hand, we proceeded to apply the protocol developed with the model compound for the introduction of the C-2 and C-3 substituents (Scheme 2.41).



Scheme 2.41. Stereoselective introduction of the C-2 and C-3 substituents.

As in the model studies, the intermediate enecarbamate **33** proved unstable to purification, so the hydroboration-oxidation sequence was performed on the crude compound, affording **34** in excellent overall yield and as a single isomer.

Thus, despite having been forced to change the protecting group, we had developed an efficient protocol to access an advanced intermediate with all the necessary substituents incorporated onto the *cis*-DHQ core, and complete stereoselectivity.

Compound **34** represents our envisioned common advanced intermediate for the synthesis of lepadin alkaloids, since correcting the stereochemistry at C-3 would give us access to lepadins A–C and, on the other hand, by inverting the stereocentre at C-5 would lead to lepadins D, E and H (Figure 2.26).

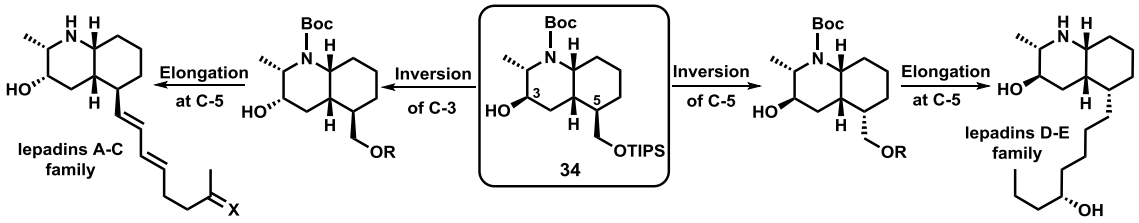
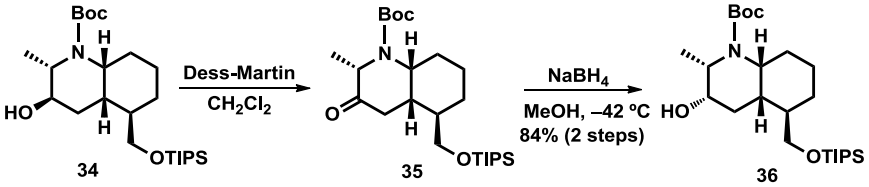


Figure 2.26. Common intermediate for both families of lepadin alkaloids.

2.7.3.3. Correction of the stereochemistry at C-3 – Synthesis of lepadins A–C

Having achieved a common intermediate, we focused on the inversion of C-3 and the elongation of the C-5 chain. For the first transformation, we decided to follow Ma's two-step sequence to ensure the correct stereochemistry (Scheme 2.42).



Scheme 2.42. Correction of the stereochemistry at C-3.

The reduction of ketone **35** took place from the less hindered side of the carbonyl group, opposite to the CH_3 substituent. Therefore, both substituents were now *cis* as required (Figure 2.27).

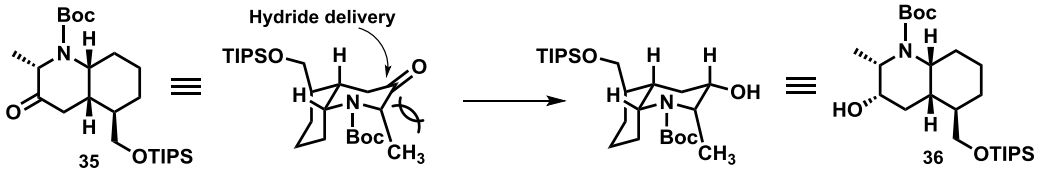
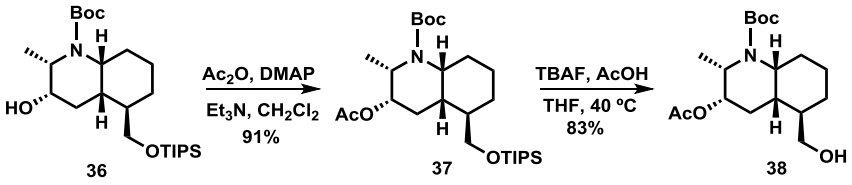


Figure 2.27. Correction of the stereochemistry at C-3.

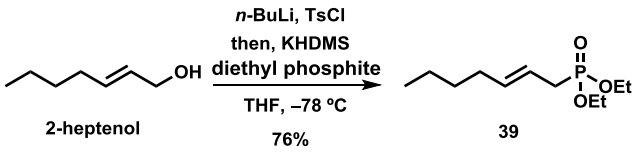
2.7.3.4. Introduction of the functionalized eight-carbon side-chain

To introduce the functionalised carbon at C-5, for lepadins A–C, we focused our efforts on the introduction of the functionalized carbon side-chain at C-5, we would need an aldehyde at C-5 for the olefination reaction. Therefore, compound **36** was elaborated into alcohol **38**, after protection of the secondary hydroxy group as an acetate derivative and deprotection of the silyl group in very good overall yield. The secondary hydroxy group had to be protected in order to avoid oxidation during the conversion of the primary alcohol to an aldehyde (Scheme 2.43).



Scheme 2.43. Elaboration of the C-5 side chain.

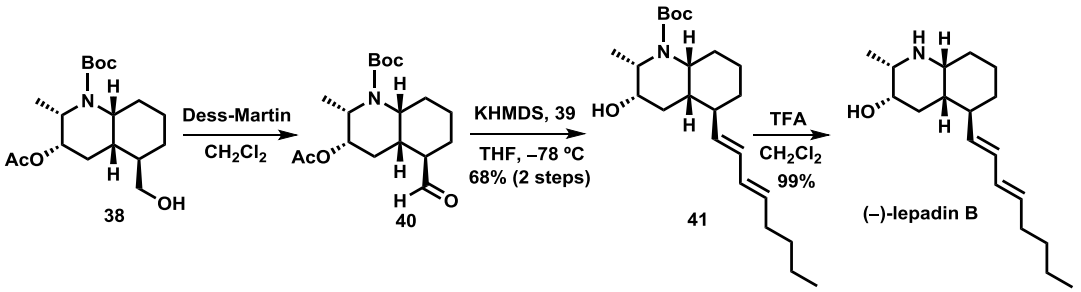
With an efficient synthetic procedure for the immediate precursor of the aldehyde partner **38**, we turned to the introduction of the carbon side-chain at C-5 by means of a Horner-Wadsworth-Emmons (HWE) reaction. For lepadins A and B, the phosphonate partner **39** for this olefination was easily prepared from 2-heptenol, *via* an Arbuzov-type reaction (Scheme 2.44).



Scheme 2.44. Synthesis of the phosphonate chain for lepadins A and B.

With a method for the preparation of phosphonate **39**, the synthetic route was resumed and compound **38** was converted to the corresponding aldehyde **40** by oxidation with Dess-Martin periodinane. We were concerned about the possible epimerization of the stereocenter adjacent to the aldehyde, so we decided to perform the oxidation

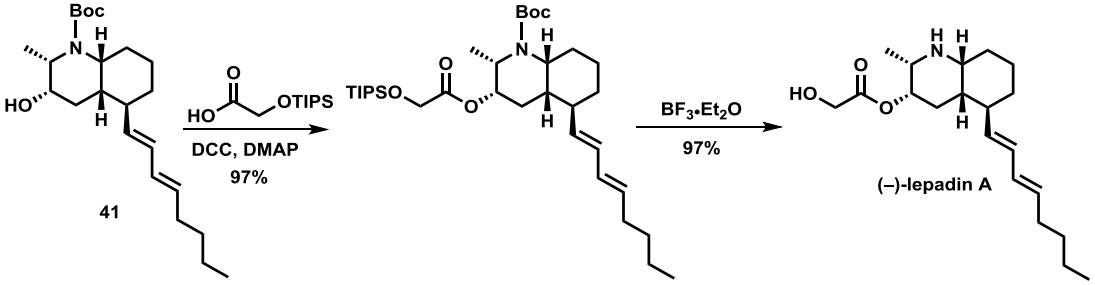
immediately prior to the olefination reaction and use compound **40** without chromatographic purification (Scheme 2.45).



Scheme 2.45. Enantioselective total synthesis of (–)-lepadin A (formal) and B.

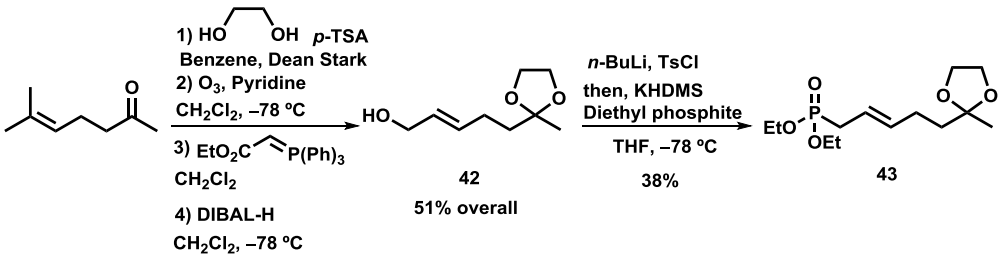
To our delight, after subjecting aldehyde **40** to the HWE-olefination conditions, diene **41** was obtained as the single (*E*,*E*)-isomer in good overall yield, with the added bonus of the deprotection of the acetate group under these reaction conditions. Treatment of **41** with TFA to perform the final deprotection step afforded (–)-lepadin B in nearly quantitative yield.

The synthesis of diene **41** constitutes a formal total synthesis of lepadin A, given that it intercepts Kibayashi's synthetic intermediate that provided (–)-lepadin A, after an additional two synthetic steps (Scheme 2.46).[54]



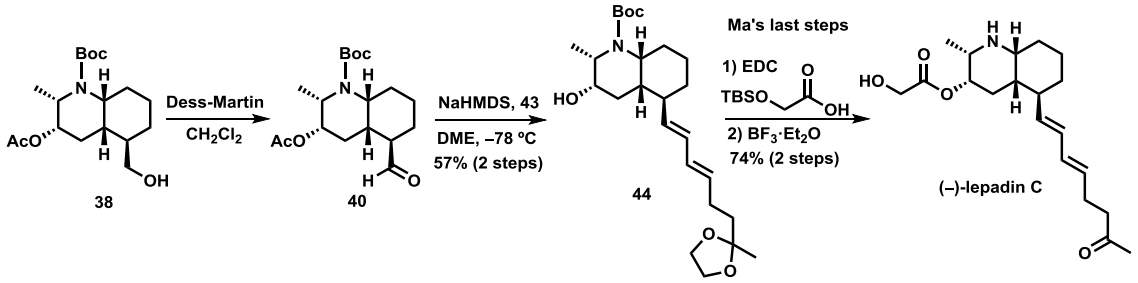
Scheme 2.46. Remaining steps by Kibayashi to synthesize (−)-lepadin A from **41**.

The synthesis of the side-chain required for the synthesis of (−)-lepadin C was a bit more challenging, since we needed a precursor for the carbonyl group at C-7'. The synthetic scheme is shown below and the commercially available methyl ketone was converted to **42** in moderate yield through a ketalization, ozonolysis, and olefination sequence. The unsaturated ester was then reduced to the allylic alcohol **42**, and following the above Arbuzov-like reaction, phosphonate **43** was obtained in moderate yield (Scheme 2.47).



Scheme 2.47. Synthesis of the phosphonate partner for lepadin C.

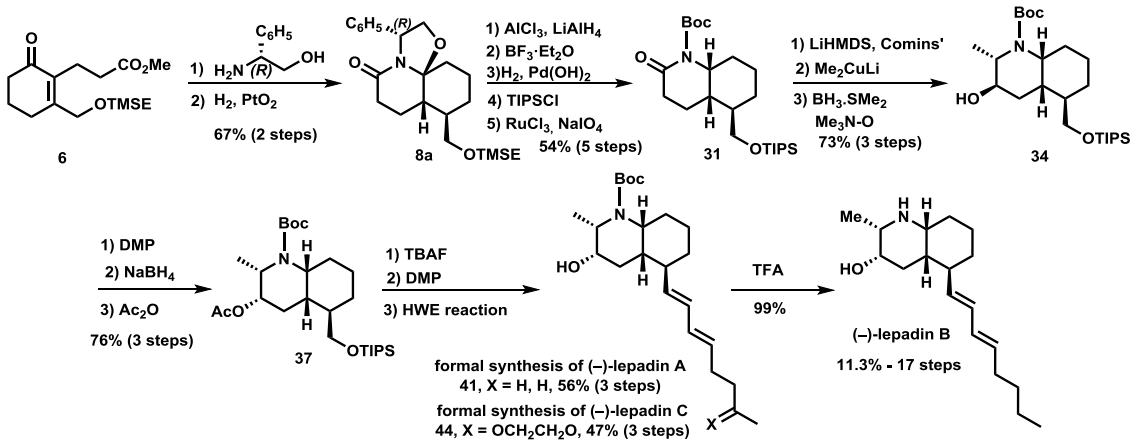
To accomplish the formal total synthesis of (–)-lepadin C, aldehyde **40** was reacted with phosphonate **43**, affording **44** in moderate overall yield (Scheme 2.48).



Scheme 2.48. Formal total synthesis of (–)-lepadin C.

As for lepadins A and B, only the (*E,E*)-isomer was detected, and deprotection of the acetate group occurred. The reaction conditions, however, had to be optimized by changing the base and the solvent to obtain a good yield of **44**. The synthesis of **44** constitutes the formal total synthesis of (–)-lepadin C, intercepting one of the final Ma's synthetic intermediates, needing only two additional steps to achieve the final alkaloid.[57]

Overall, we were able to accomplish the total synthesis of (–)-lepadin B in 11.3% overall yield over 17 synthetic steps (*vs* Ma's 8.4% overall yield, 16 steps), the formal synthesis of (–)-lepadin A in 11% yield (*vs* Kibayashi's intermediate 1.51%, 34 steps), and (–)-lepadin C with 9.6% overall yield (*vs* Ma's intermediate 14.6%, 16 steps) over 16 synthetic steps. With these results, the objective of developing a competitive synthetic strategy for these alkaloids was achieved, particularly in the case of (–)-lepadin B where we were able to accomplish the most efficient enantioselective total synthesis reported to date (Scheme 2.49).[73]



Scheme 2.49. Total synthesis of (–)-lepadins A–C.

[73] Amat, M.; Pinto, A.; Griera, R.; Bosch. J. *Chem. Commun.* **2013**, *49*, 11032-11034.

2.7.4. Total synthesis of (+)-lepadin D

Having accomplished the total synthesis of lepadins A–C, we directed our efforts towards (+)-lepadin D. In order to achieve this goal, starting from **34**, we needed to invert the stereochemistry of C-5 (Figure 2.28).

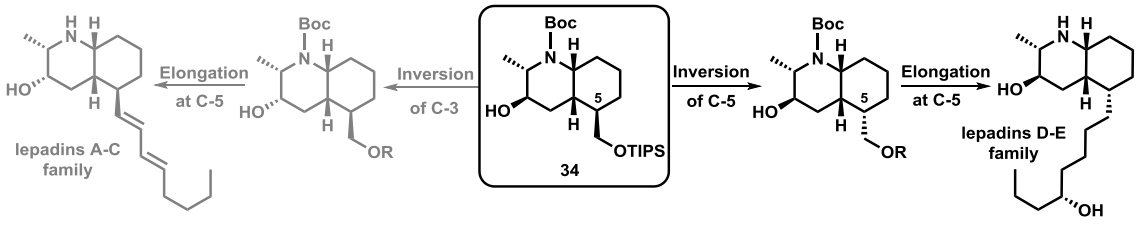


Figure 2.28. Key transformations for the lepadin D family.

2.7.4.1. Inversion of the stereochemistry at C-5

For the inversion of the configuration at the C-5 stereogenic centre of *cis*-decahydroquinoline **34**, we considered the results previously reported by D. Ma on closely related compounds.[57] For instance, selective hydrolysis of the enol ether depicted in Figure 2.29, followed by isomerization of the resulting aldehyde under basic conditions, afforded a mixture of both possible diastereomers **a** and **b** in low selectivity. However, removal of the Boc protecting group and subsequent isomerization led to **c** as a single isomer.

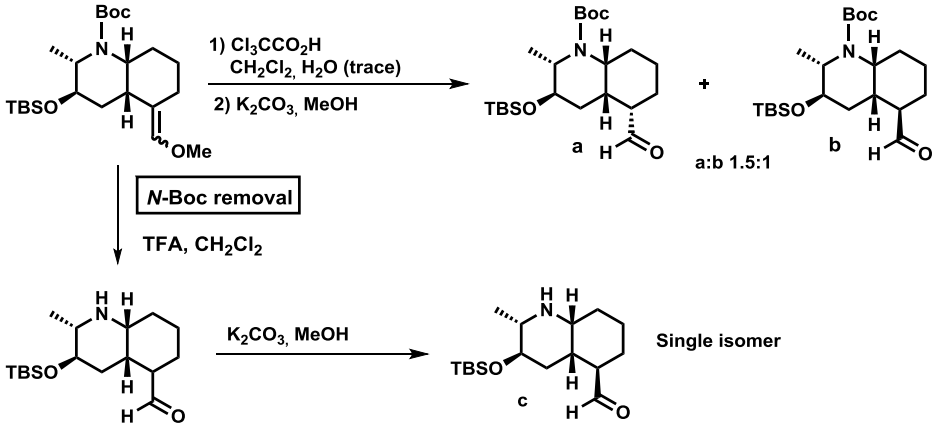


Figure 2.29. Ma's studies on the C-5 stereocenter manipulation.

This behaviour can be rationalized by considering that in the *N*-Boc derivative the *cis*-decahydroquinoline system adopts a conformation in which the methyl and the C-8/C-8a bond are axial, in order to avoid allylic $A^{1,3}$ interactions with the *N*-carbamate substituent. In this situation, in the equilibrium, both epimers **M** and **N** are in a nearly equimolecular ratio. However, removal of the N-Boc protecting group provokes a conformational change in the bicyclic *cis*-decahydroquinoline. The strong interactions of the axial aldehyde in isomer **P** shift the equilibrium in favour of the isomer **O**, in which the aldehyde is equatorially located (Figure 2.30).

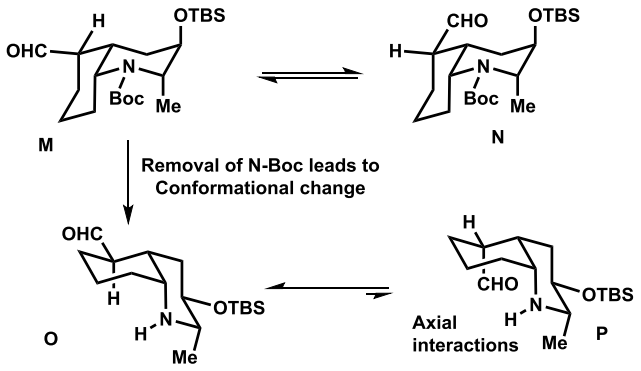


Figure 2.30. Boc-removal conformational changes.

Thus, considering these precedents for the inversion of the configuration of the C-5 stereocenter of **34**, a strategy based on the deprotection of the hydroxymethyl substituent, followed by oxidation and isomerisation, was not expected to render the desired isomer.

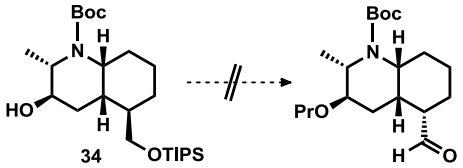


Figure 2.31. Oxidation-isomerization approach.

The same author, Ma, in the context of the synthesis of lepadins D, E and H, describes that the catalytic hydrogenation of the exocyclic C=C double bond at the 5-position of the *N*-Boc-protected *cis*-decahydroquinoline depicted in Figure 2.32 takes place in moderate stereoselectivity. However, the corresponding secondary amine undergoes catalytic hydrogenation in a highly stereoselective manner (> 95% de).[57]

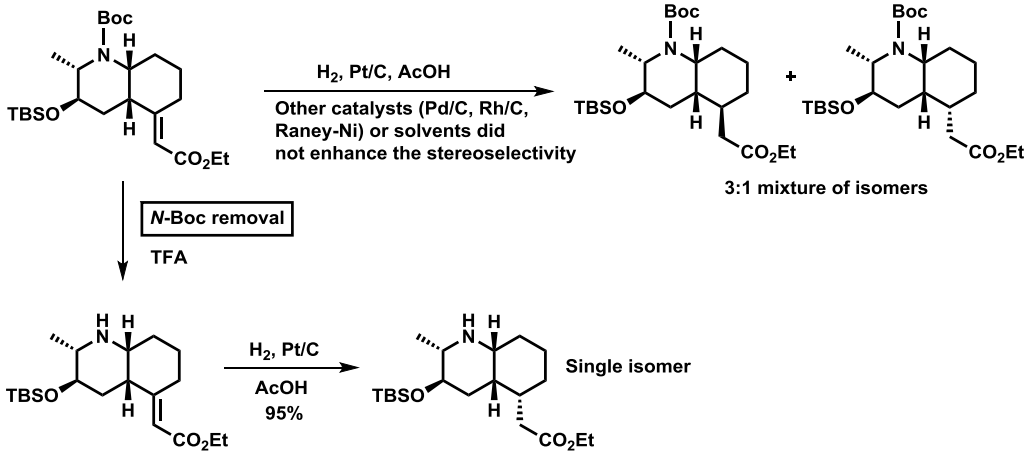


Figure 2.32. Ma's inversion of stereochemistry at C-5.

The different stereochemical outcome in the uptake of molecular hydrogen of both derivatives might be rationalized by considering that for the *N*-Boc-substituted derivative the preferred conformer might be **Q** and that the steric hindrance for both diastereotopic faces of the olefin moiety might be similar, and thereby a mixture of both

diastereoisomers is observed. In contrast, the steric hindrance of the *Re* face of the olefin moiety in the more stable conformation **R** of the *N*-unsubstituted compound is larger than that of the *Si* face. Thus, exclusive formation of one isomer was observed (Figure 2.33).

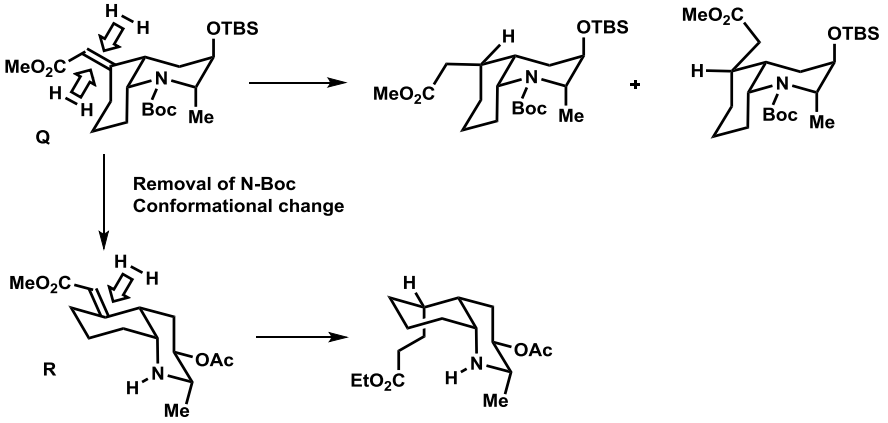


Figure 2.33. Favoured conformations for the C-5 olefin hydrogenation.

2.7.4.1.1. Inversion of the configuration of the C-5 stereogenic centre from 34 -. first approach

Taking into account the above precedents, it was envisioned that we could follow a similar strategy by converting our advanced intermediate **34** to the corresponding vinyl triflate. This would allow us to take advantage of a *B*-alkyl Suzuki-Miyaura reaction to incorporate the functionalized side-chain at C-5. The catalytic hydrogenation of the exocyclic-double bond on a *N*-unsubstituted derivative should afford the corresponding 5-alkyl substituted *cis*-decahydroquinoline with the correct stereochemistry for the synthesis of (+)-lepadin D (Figure 2.34).

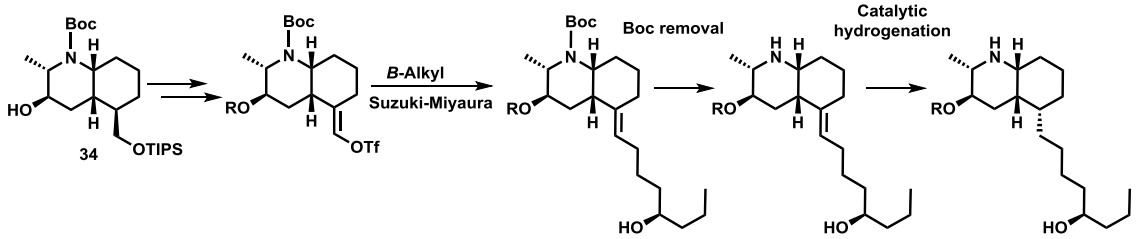
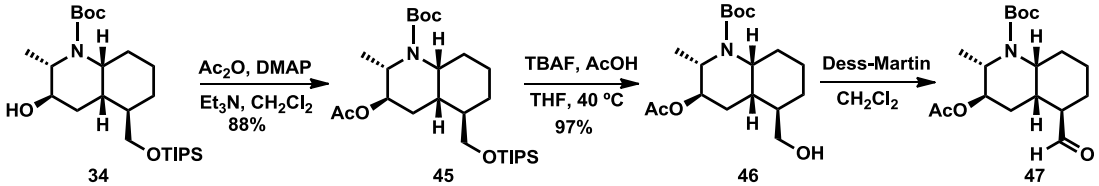


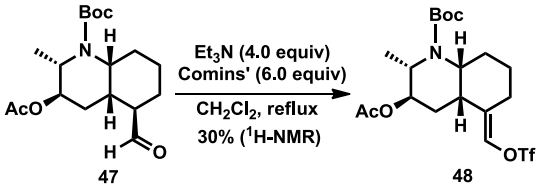
Figure 2.34. Synthetic strategy for lepadin D family.

This plan seemed robust and efficient, so we began by advancing our intermediate **34** to the primary alcohol **46** precursor of aldehyde **47**, as in the synthesis of lepadins A–C described in section 2.7.3.4 (Scheme 2.50).



Scheme 2.50. Initial approach to the lepadin D synthesis.

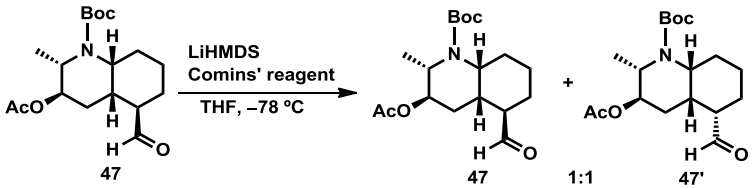
Overall, compound **47** was obtained with very high yield and we now attempted the formation of the vinyl triflate (Scheme 2.51).



Scheme 2.51. Attempts to prepare the vinyl triflate.

To our dismay, all efforts to convert aldehyde **47** into the vinyl triflate **48** met with failure or low yields. We attempted the classical protocol of treating the aldehyde with a non-nucleophilic encumbered base, such as 2,4,6-tri-*tert*-butylpyridine, in the presence of triflic anhydride in refluxing 1,2-dichloroethane or dichloromethane. However, the best results were obtained with an excess of Et_3N (4.0 equiv) and Comins' reagent (6.0 equiv) in refluxing dichloromethane, with a yield of only 30% (as determined by ^{1}H-NMR), which could not be further improved.

It is worth mentioning that when the reaction was attempted using LiHMDS in the presence of Comins' reagent, instead of the desired compound **48**, an isomerization of the C-5 stereocenter (1:1) was observed (Scheme 2.52).



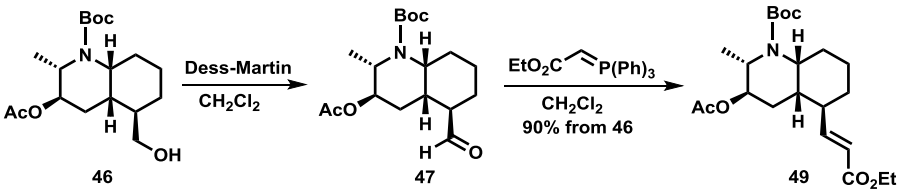
Scheme 2.52. Attempts to prepare the vinyl triflate leading to isomerization.

2.7.4.1.2. Inversion of the stereochemistry at C-5 from 34 – Second approach

After the disappointing results of the vinyl triflate route, we had to find an alternative that would allow us to install an exocyclic double bond from aldehyde **47**, and focused on the deconjugation of α,ß-unsaturated carbonyl groups. This type of transformation is usually achieved by photochemical protocols, although one report in the literature caught our eye, in which Paquette and co-workers treated an α,ß-unsaturated ester of a cyclohexane with base at low temperature, followed by protonation, which afforded the ß,γ-derivative.[74]

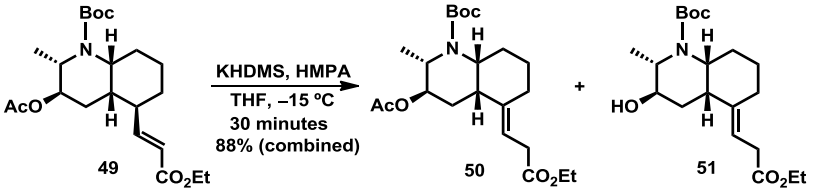
Inspired by this result, and hoping to find a viable solution to our problem, we converted aldehyde **47** to the unsaturated ester **49** in excellent overall yield and with only minor traces (as detected by ^{1}H-NMR) of the *Z*-isomer (Scheme 2.53).

[74] Paquette, L. A.; Tae, J.; Hickey, E. R.; Trego, W. E.; Rogers, R. D. *J. Org. Chem.* **2000**, *65*, 9160-9171.



Scheme 2.53 Preparation of the α,ß-unsaturated ester **49**.

Although conceptually simple, the isomerization of an α,ß-unsaturated ester to the corresponding ß,γ-isomer was not straightforward. Beforehand, we were aware that the reaction time had to be carefully monitored since if the reaction was allowed to run for too long, we would obtain the thermodynamic product, the α,ß-unsaturated compound. The deconjugative protonation[75] of conjugate enolate anions in steroid enones was the subject of intensive studies in the 1960's–70's by various groups.[76] It was established that anions of conjugated carbonyl compounds under kinetic control allow the protonation or alkylation at the α position, with subsequent isomerization of the C–C double bond to afford the ß,γ-unsaturated carbonyl compound.[76,77] Other studies also showed that if the carbanion is generated in a γ,γ-dialkyl substituted system, the ß,γ-unsaturated isomer is favoured,[78] which was the case for our molecule **49**. After careful optimization, we found the best conditions, depicted in Scheme 2.54.

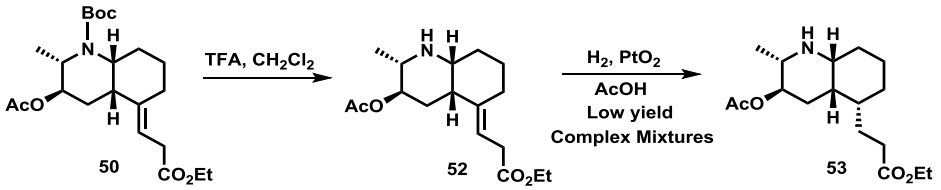


Scheme 2.54. 1st generation deconjugation approach to C-5 inversion.

The overall yield was very good but, as previously observed for the olefination protocol, the acetate group proved labile under the reaction conditions, and different proportions of **50**:**51** were obtained depending on the amount of base (2:1 at best). Attempts to optimize the reaction conditions could not avoid the partial removal of the acetate group.

Nonetheless we used compound **50** to evaluate if Ma's approach would work on our substrate. Although the molecule was fairly similar, we were unsure if the extra carbon at C-5 would decrease the reported stereoselectivity, since our chain had more degrees of freedom (Scheme 2.55).

[75] Kende, A. S.; Toder, B. H. *J. Org. Chem.* **1982**, *47*, 163-167
[76] (a) Birch, A. J. *J. Chem. Soc.* **1950**, 2325-2326. (b) House, H. O. in *Modern Synthetic Reactions*, W. A. Benjamin: Menlo Park, 2nd Edition, 1972, Chapter 9 (and references therein).
[77] For aldehydes see: de Graaf, S. A. G.; Oosterhoff, P. E. R.; van der Gen, A. *Tet. Lett.* **1974**, 1653-1656. Carboxylic acids: (a) Pfeffer, P. E.; Silbert, L. S. *J. Org. Chem.* **1971**, *36*, 3290-3293. (b) Pfeffer, P. E.; Silbert, L. S.; Kinsel, E. *Tet. Lett.* **1973**, 1163-1166. Esters: (a)Rathke, M. W.; Sullivan, D. *Tet. Lett.* **1972**, 4249-4252. (b) Koyama, H.; Kogure, K.; Mori, K.; Matsui, M. *Agr. Biol. Chem.* **1972**, *36*, 793-797. (c) Krebs, E.-P. *Hel. Chim. Acta*, **1981**, *64*, 1023-1025.
[78] Hubert, A. J.; Reimlinger, H. *Synthesis*, **1969**, 97-112 (and references therein).



Scheme 2.55. 1st generation approach to C-5 inversion.

In our hands this approach proved quite troublesome. The desired compound **53** was obtained in very low yields and as a complex mixture of products. A mass-spectra analysis of the reaction mixture revealed the presence of *N*-Me, *N*-formyl, the desired product, among other by-products (Figure 2.35).

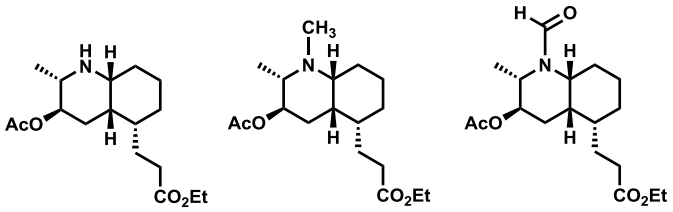
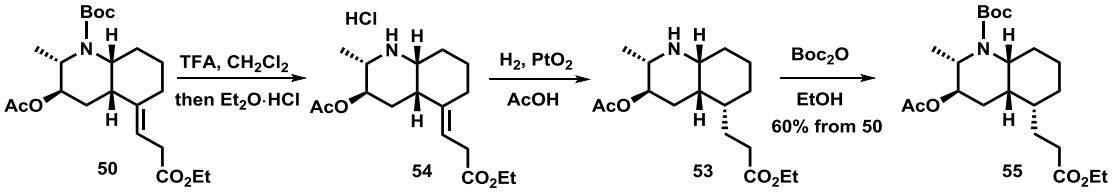


Figure 2.35. Main products of the hydrogenation procedure.

The obtention of the *N*-Me and *N*-formyl was surprising, to say the least, because although this type of reactivity is known to occur in some systems, the conditions usually required to achieve this transformation are quite demanding, with elaborated catalysts, high temperatures and pressure of H_2 and CO_2.[79] Moreover, the only possible source of CO_2 in the reaction media would derive from an improper degassing of the reaction vessel.

In the end, we decided to fully block the nitrogen atom as its HCl salt, even though the reaction solvent was acetic acid, which should have protonated the secondary amine. With this change, we overcame this bizarre problem and managed to obtain compound **55** as a single isomer, after *N*-Boc protection (Scheme 2.56).



Scheme 2.56. Inversion of the C-5 stereocenter.

The success of the stereoinversion was determined by comparison of the ^{13}C-NMR of **55** with that of its C-5 epimer **56** obtained by catalytic hydrogenation of **49**. We observed a

[79] (a) Li, Y.; Sorribes, I.; Yan, T.; Junge, K.; Beller, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 12156-12160. (b) Du, X.-L.; Tang, G.; Bao, H.-L.; Jiang, Z.; Zhong, X.-H.; Su, D. S.; Wang, J.-Q. *ChemSusChem* **2015**, *8*, 3489-3496.

pronounced γ-gauche effect, where C-4 suffered a shielding effect of ≈7 ppm, 18.3 ppm for **55** *versus* 25.6 ppm for **56** (Figure 2.36).

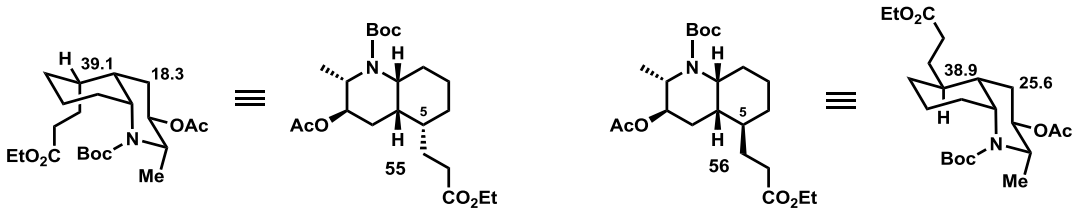


Figure 2.36. Most relevant ^{13}C signals of both C-5 isomers.

2.7.4.1.3. Optimization of the synthetic sequence

The excellent results observed in the inversion of the configuration at C-5 from alcohol **34** through a sequence involving a Wittig reaction on aldehyde **47**, deconjugation of the resulting unsaturated ester **49**, and stereoselective catalytic hydrogenation of the *N*-Boc unprotected derivative **54**, prompted us to optimize the sequence, particularly the deconjugation step in which mixtures of acetate **50** and alcohol **51** were obtained.

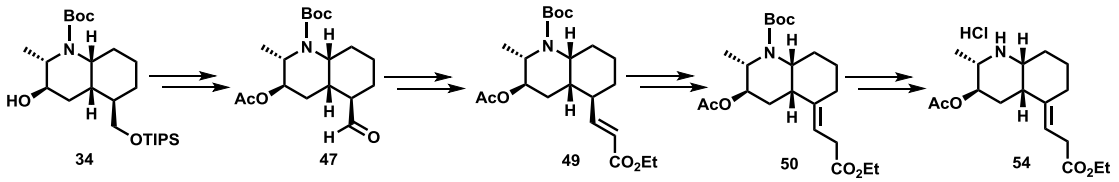


Figure 2.37. Synthetic sequence to be optimized.

Given the problems we had with the acetate protecting group during the deconjugation procedure, affording a mixture of protected and unprotected products, we attempted to change to a silyl group, such as TIPS or TBDPS derivatives of **34**. However, with these compounds, we observed significantly inferior results in terms of chemical yield (Figure 2.38).

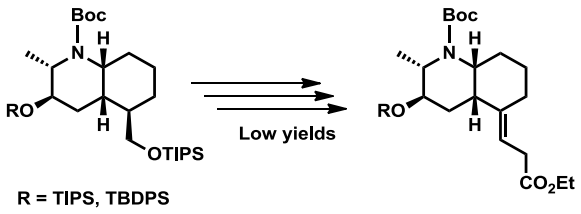


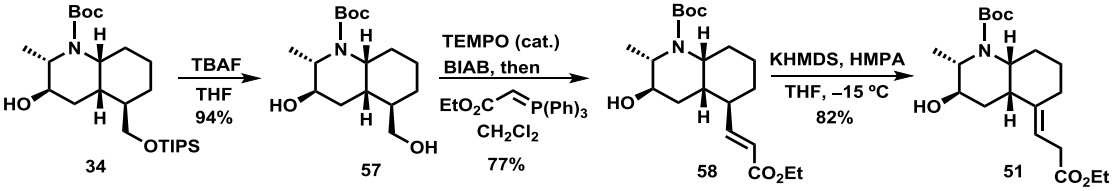
Figure 2.38. Other protecting groups assayed.

We then considered the possibility of developing the synthetic sequence without a protecting group of the secondary alcohol. We reasoned that chemoselective manipulations could be carried out taking advantage of the higher reactivity of the primary alcohol with respect to the secondary hydroxy group.

Deprotection of **34** afforded diol **57** in excellent yield. Here we introduced a small change since when performing the oxidation with even a stoichiometric quantity of Dess-Martin

periodinane, besides the desired aldehyde, the ketone was also formed. To overcome this inconvenience, a TEMPO-mediated oxidation was carried out, since this reagent is more selective for primary alcohols. Moreover, the subsequent olefination of the aldehyde could be performed in a one-pot operation, avoiding an additional synthetic step.

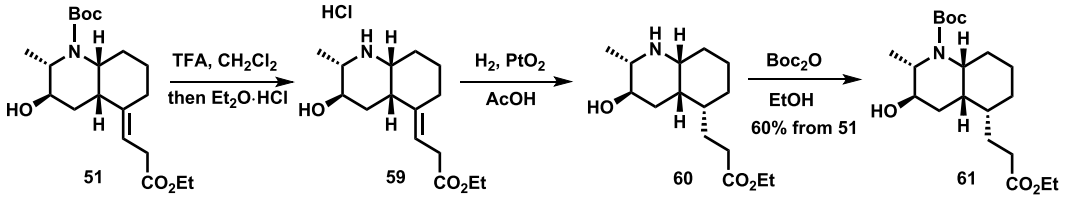
The subsequent deconjugation protocol of **58** took place in excellent yield, providing compound **51** (Scheme 2.57).



Scheme 2.57. 2nd generation approach to C-5 inversion.

As depicted in Scheme 2.57, the synthetic route to compound **51** was very efficient and the removal of the secondary hydroxy protecting group improved our overall approach. Having secured **51** with a reliable route, we focused on the hydrogenation and further elongation of C-5.

To this end, the *N*-unprotected compound **59** was subjected to the hydrogenation protocol and subsequent nitrogen protection, affording the desired compound **61** as a single isomer in good overall yield (Scheme 2.58).



Scheme 2.58. Inversion of C-5 stereochemistry.

With a satisfactory solution to our synthetic detour, it was time to tackle the side-chain elongation.

2.7.4.2. Introduction of the C-5 side chain

For the synthesis of (+)-lepadin D from **61**, we needed to incorporate a five-carbon chain bearing the C-5' hydroxy group. This could be achieved by transformation of the ester moiety into a sulfone and taking advantage of the acidity of the adjacent methylene group to generate an α-sulfonyl carbanion. Ring-opening of an appropriate enantiopure epoxide would set up the desired eight carbon chain. This strategy, however, would require the protection of the secondary hydroxy group (Figure 2.39).

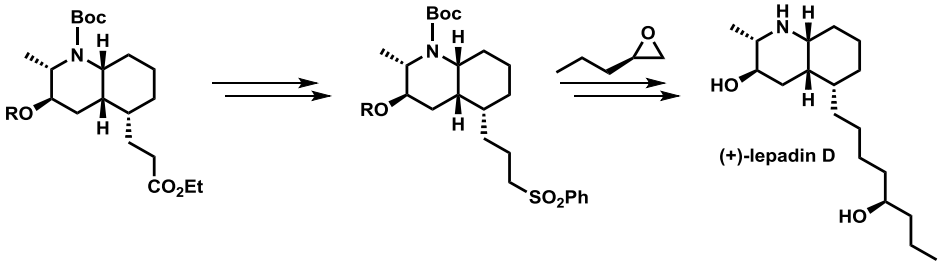
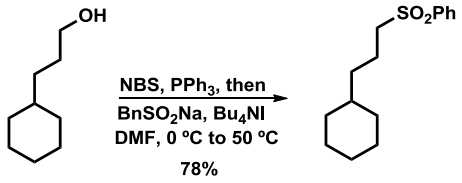


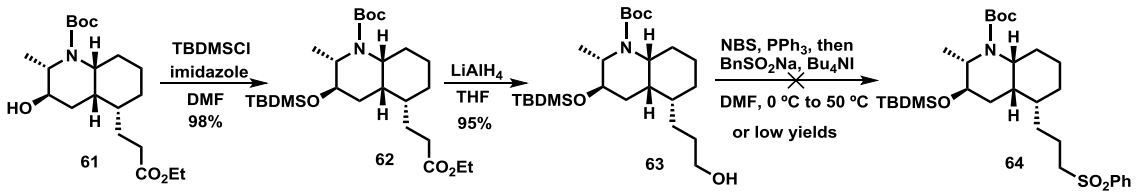
Figure 2.39. Strategy for the elongation of the C-5 side-chain.

A report in the literature[80] caught our attention, in which a one-pot procedure starting from a primary alcohol allowed the introduction of the sulfone moiety. This protocol was based on an Appel-type reaction, where treatment of the alcohol with NBS and PPh_3 affords the corresponding bromide, which is displaced by sodium benzenesulfinate in the presence of a catalytic amount of sodium iodide or tetrabutylammonium iodide to afford the corresponding aryl sulfone. This protocol was tested on a model compound with satisfactory yields (Scheme 2.59).



Scheme 2.59. Model studies to introduce the sulfone moiety.

Using this approach, we performed the protection of the alcohol **61**, in nearly quantitative yield, followed by the ester reduction to the corresponding primary alcohol **63** (Scheme 2.60).



Scheme 2.60. Initial attempt to introduce the sulfone moiety.

Unfortunately, all attempts to carry out the transformation of **63** to **64** in one-pot conditions were not suitable for our molecule. We observed the formation of several side-products, which originated from competing side reactions, such as the cleavage of the silyl group due to the formation of HI in the reaction medium (Figure 2.40).

[80] Murakami, T.; Furusawa, K. *Synthesis* **2002**, 479-482.

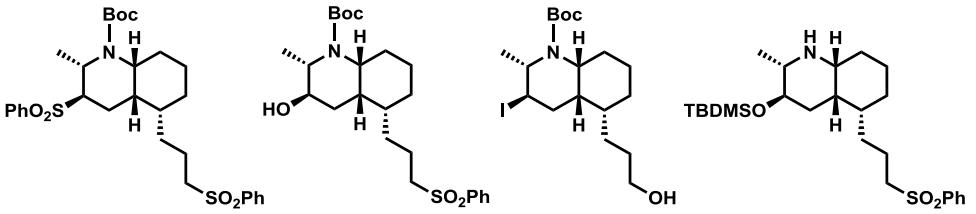
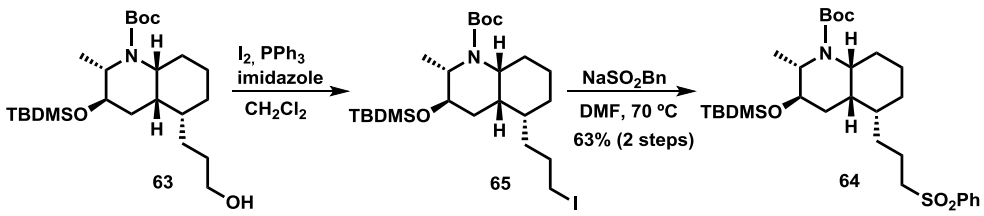


Figure 2.40. By-products detected with the one-pot sulfonylation.

With the myriad of sub-products obtained, we decided to go for a two-step buffered sequence to avoid the hydroxy deprotection and subsequent side-product formation.

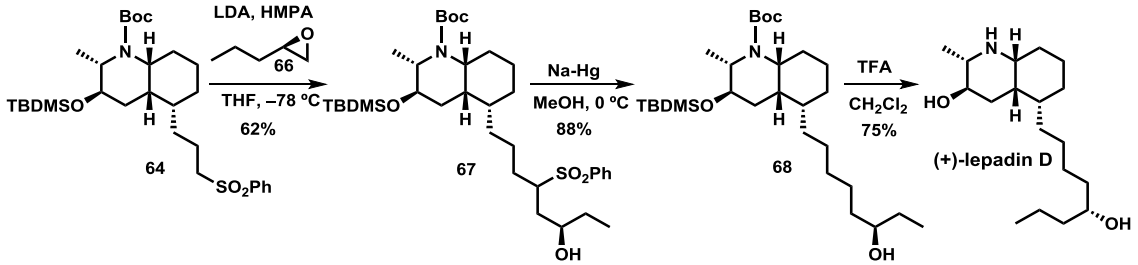
We turned our attention to carbohydrate chemistry and found a report in which, the authors obtained a clean conversion of the hydroxy group to the corresponding iodide without functional group intolerance by using an excess of imidazole, which acts as a HI scavenger.[81] With this modification, we were able to obtain the desired iodide **65**, which was then transformed to sulfone **64** by reaction with sodium benzenesulfinate (Scheme 2.61).



Scheme 2.61. Introduction of the sulfone moiety.

With the necessary sulfone **64** in hand, we were very close to accomplishing the enantioselective total synthesis of (+)-lepadin D. Therefore, we generated the carbanion of **64** by treatment with LDA in the presence of HMPA at low temperature, followed by addition of the enantiopure epoxide **66**, previously prepared according to the literature.[82] In this way, compound **67** was obtained as an inconsequential mixture of stereoisomers. Other conditions (bases: *n*-BuLi, LiHMDS; and solvents: Et_2O and DME) were attempted but the combination of LDA-HMPA was ideal.

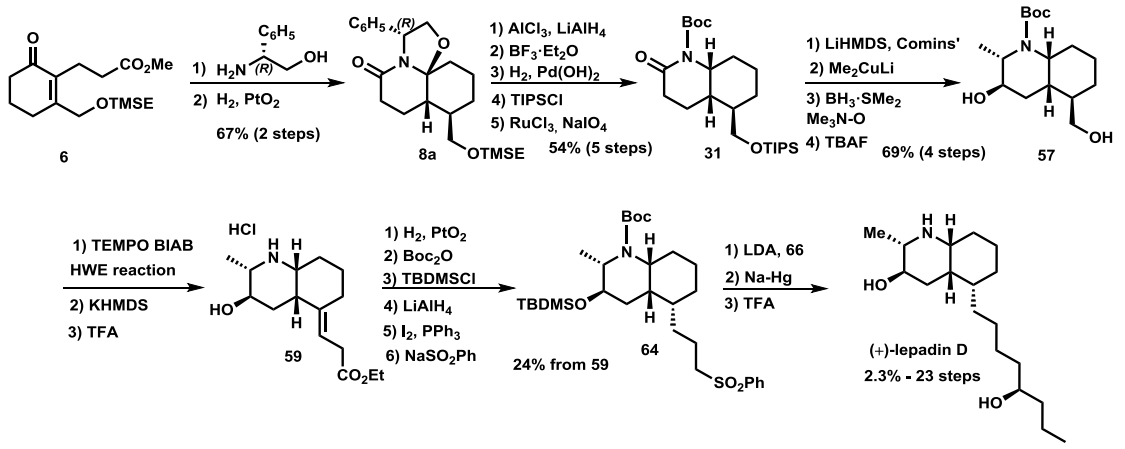
Final removal of the sulfone group using standard Na-Hg, and of the protecting groups by treatment of TFA afforded (+)-lepadin D (Scheme 2.62).



Scheme 2.62. Total synthesis of (+)-lepadin D.

[81] Garegg, P.; Samuelsson, B. *J. Chem. Soc. Perk. Trans. 1*, **1980**, 2866-2869.
[82] Masuo, R.; Ohmori, K.; Hinterman, L.; Yoshida, S.; Suzuki, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 3462-3465.

Overall, the enantioselective total synthesis of (+)-lepadin D was accomplished in 2.3% overall yield over 23 synthetic steps (Scheme 2.63).[83]



Scheme 2.63. Overall enantioselective total synthesis of (+)-lepadin D.

2.9. Conclusions

We have thus accomplished the enantioselective total synthesis of (–)-lepadin B and (+)-lepadin D, as well as the formal synthesis of (–)-lepadins A and C. With these results the proposed objectives for this part of the PhD thesis were fully accomplished.

The results also highlight that the developed methodology provides a robust, useful and unified synthetic approach to these alkaloids, in some examples, namely (–)-lepadin B, outperforming all the approaches reported to date. Moreover, the methodology provides several key synthetic points that could provide access to derivatives of these natural compounds, which constitutes an added value of this work.

[83] Amat, M.; Pinto, A.; Griera, R.; Bosch, J. *Chem. Eur. J.* **2015**, *21*, 12804-12808.

Chapter 3 – *Lycopodium* alkaloids

3. *Lycopodium* alkaloids

The *Lycopodium* genus of clubmosses comprises a vast number of species, nearly 1000, which are widely distributed in temperate to tropical climates. These plants can be especially found in coniferous forests, mountain areas and marshlands. The different species of *Lycopodium* plants are characterized by being flowerless, terrestrial or they can be found growing on other plants or trees. They have small leaves, resembling needles or spikes, which cover the stem and branches.[33a,37]

Lycopodium alkaloids can be grouped in four main classes, each of them named after a prototype alkaloid of that category (Figure 3.1).[32,33a,37]

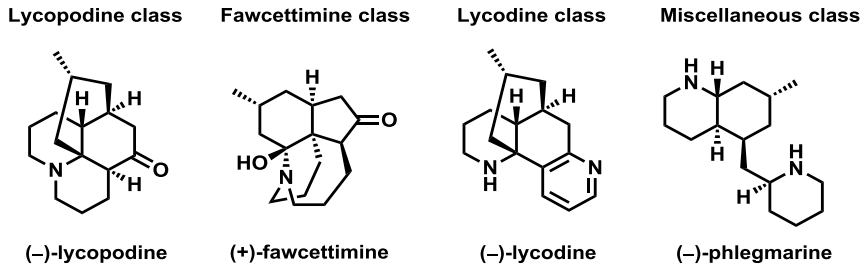


Figure 3.1. The four classes of *Lycopodium* alkaloids.

The first member of the *Lycopodium* alkaloids to be isolated was (–)-lycopodine by Bödeker in 1881[84] and today more than 300 compounds have been isolated belonging to this family. Of the four classes of *Lycopodium* alkaloids, the miscellaneous class is the most heterogeneous of them all, because this category was created to accommodate the isolated alkaloids that did not fit any of the previous three categories. This causes a great structural variety within this category (Figure 3.2).[33a]

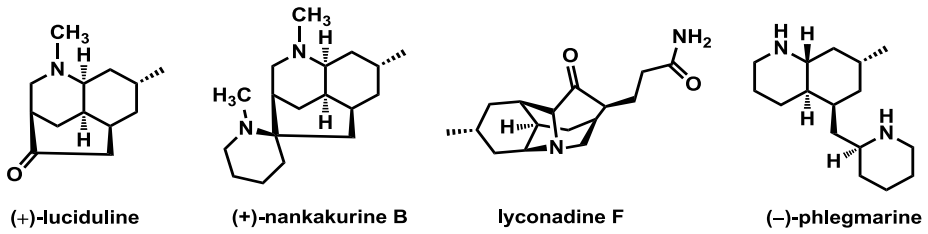


Figure 3.2. Structural variety within the miscellaneous class.

As can be observed in Figure 3.2, the decahydroquinoline moiety is the main structural feature of the phlegmarine subclass of alkaloids. For this reason we focused our attention on the use of chiral tricyclic lactams as enantiomeric scaffolds for the synthesis of this class of natural products.

[84] Bödeker, K. *Justus Liebigs Ann. Chem*. **1881**, *208*, 363.

3.1. Phlegmarine alkaloids – isolation

To date, fifteen phlegmarine-type alkaloids have been isolated. The prototype compound of phlegmarines is, as the name denotes, phlegmarine, which was isolated in 1978 by Braekman from the plant extracts of *Lycopodium clavatum* variant *borbonicum* collected in Zaire.[85] It was isolated along with its *N*-methyl and *N*-acetyl derivatives (Figure 3.3).

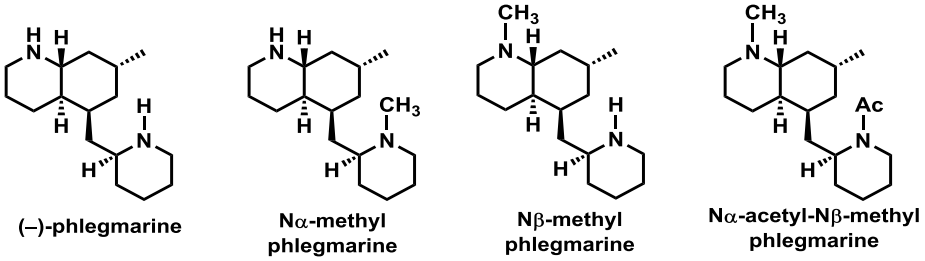


Figure 3.3. First phlegmarine alkaloids to be isolated.

More than twenty years went by before the isolation of huperzines J, K and L from *Huperzia serrata*, collected in China, was reported in the literature in 2000.[86] It should be noted that the *Huperzia* genus used to be included in the *Lycopodium* genus, hence the inclusion of *Huperzia* alkaloids in the same family as *Lycopodium*, but later it was recognised as a different one. Other alkaloids from *Huperzia* species were isolated in 2008, namely huperzine N and huperzine M. It should be noted that huperzine M was wrongly identified and later synthetic studies showed it to be lycoposerramine Y. These compounds were isolated from specimens collected in China as well (Figure 3.4).[87]

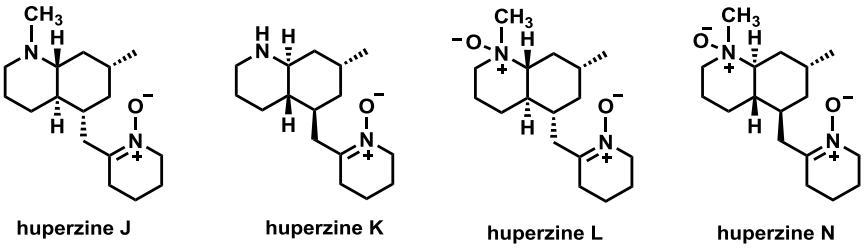


Figure 3.4. Alkaloids isolated from *Huperzia* specimens.

In 2004, from specimens collected in Okinawa in Japan, Kobayashi and co-workers isolated two novel *cis*-DHQ *Lycopodium* alkaloids, cermizine A and B, from *Lycopodium cernuum* (Figure 3.5).

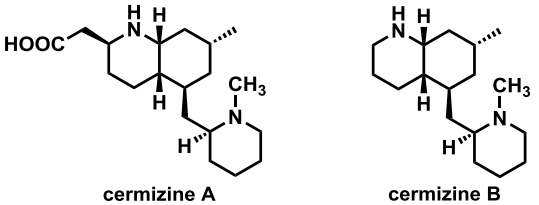


Figure 3.5. *cis*-DHQ alkaloids from *Lycopodium cernuum*.

[85] Nyembo, L.; Goffin, A.; Hootelé, C.; Braekman, J.-C. *Can. J. Chem.* **1978**, *56*, 851-865.
[86] Gao, W.; Li, Y.; Jiang, S.; Zhu, D. *Planta Med.* **2000**, *66*, 664-667.
[87] It should be noted that the original isolation paper reported incorrect structures for huperzine K and N.

A couple of years later, in 2006, another Japanese research group reported the isolation of lycoposerramine X, Y and Z. These compounds were isolated from *Lycopodium serratum*, collected in China, hence the name lycoposerramine, (Figure 3.6).

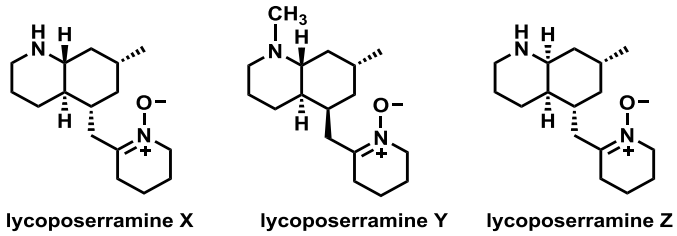


Figure 3.6. Lycoposeramines X–Z.

The last phlegmarine alkaloids to be isolated were serratezomine E in 2009, by Kobayashi and co-workers, and serralongamine A in 2014 by the Chen group. Both alkaloids were isolated from *Lycopodium serratum* specimens, although from different geographical origins, Japan (serratezomine E) and Taiwan (serralongamine A) (Figure 3.7).

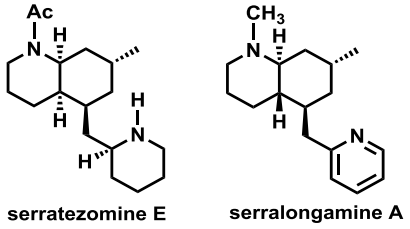


Figure 3.7. Last phlegmarine-type alkaloids to be isolated

It is worth mentioning that almost 1000 species of *Lycopodium* clubmosses exist and that up to 2004, only about 50 had been investigated. This means that it is very likely that in a near future the phlegmarine subclass of alkaloids will gain new members.[37]

3.2. Phlegmarine alkaloids –structural features

The phlegmarine subclass of alkaloids is characterized by a 5,7-disubstituted DHQ moiety, which can be either *cis* or *trans*, and a $C_{16}N_2$ skeleton.[33a] They all have a piperidine or pyridine ring substituent at C-5. Additionally, the nitrogen atom of the piperidine moiety can be oxidized as the corresponding nitrone. Structurally, the phlegmarine alkaloids can be divided into four subclasses A-D, depending on the stereochemical relationship between the ring-fusion carbons, C-4a and C-8a, with C-7 (Figure 3.8).[33b]

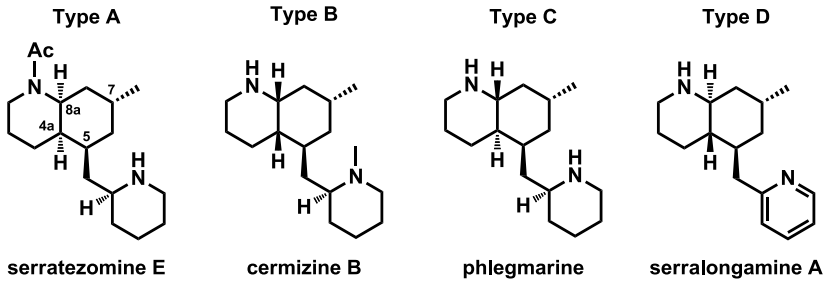


Figure 3.8. Structural classification of phlegmarine alkaloids.

Additionally, the use of α and ß notation has been proposed, depending on the orientation of the C-5 substituent. In the context of this work, only *cis*-DHQ alkaloids, type A and B, are of interest and their respective members are shown in Figure 3.9.[88]

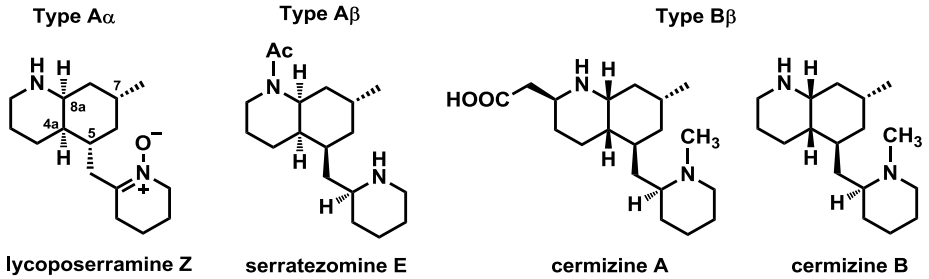


Figure 3.9. Type A and B phlegmarine alkaloids.

As can be seen, type A compounds have a *cis* ring fusion and an H-7/H-8a *trans* relationship. Additionally, for lycoposerramine Z, the H-4a/H-5 is *trans*, whereas in serratezomine E is *cis*. Of the four members of type A–B, lycoposerramine Z is the only one to have the nitrogen of the C-5 piperidine ring oxidized to the corresponding nitrone.

For type B compounds, both the ring fusion and the H-7/H-8a relationship are *cis*. Moreover, although originally compounds with an H-4a/H-5 *trans* relative stereochemistry were reported, later synthetic studies showed this to be incorrect.[89]

[88] Luque, C. PhD thesis, Barcelona **2014**.
[89] Huperzine N and huperzine M were originally assigned to have a type Bα, although later synthetic studies led to the revision of their structure (see reference 91c).

3.3. Biogenetic relevance

Even though the phlegmarine alkaloids constitute a very small group and at first glance might seem an unimportant group, the prototype compound phlegmarine is thought to be the biogenetic precursor of all *Lycopodium* alkaloids (Figure 3.10).

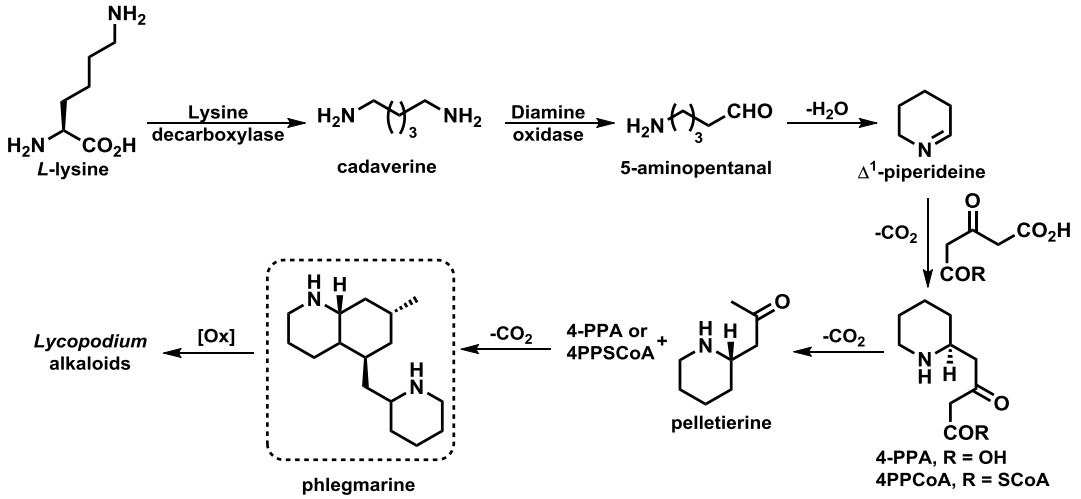


Figure 3.10. Proposed biosynthetic pathway for *Lycopodium* alkaloids.

The proposed biosynthetic route starts with the decarboxylation of *L*-lysine, catalysed by a lysine decarboxylase, to afford cadaverine. Cadaverine is then oxidized by a diamine oxidase to afford the intermediate 5-aminopentanal, which undergoes intramolecular imine formation, affording Δ^1-piperideine. Through a sequence of decarboxylative reactions catalyzed by unknown enzymes, pelletierine, the first general *Lycopodium* alkaloids precursor, is formed. Finally, coupling of pelletierine with 4-PPA or 4-PPSCoAaffords phlegmarine after loss of carbon dioxide. The phlegmarine framework is then the precursor of all other *Lycopodium* alkaloid classes, by subsequent oxidative reactions and *N*-methylations.[33a,37]

3.4. Biological properties

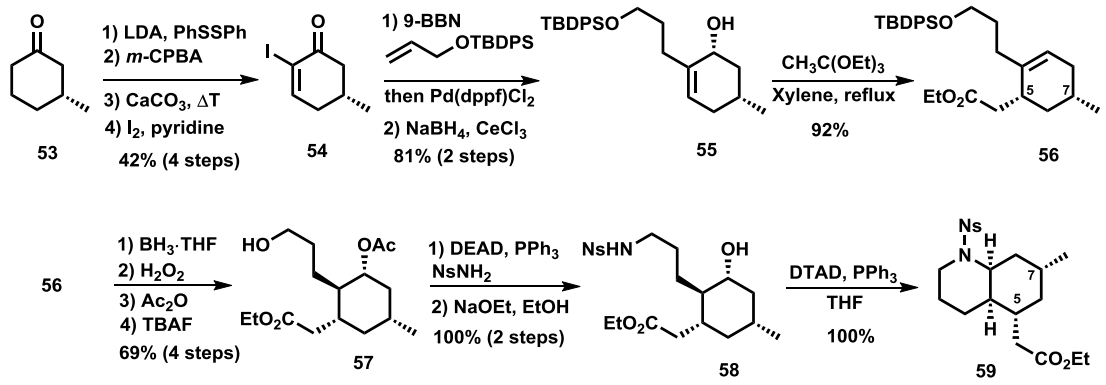
To date, despite the use of *Lycopodium* species in traditional Chinese medicine for several centuries, there is no information about the biological activity of phlegmarine alkaloids. The biological studies have been hampered by the low natural abundance of these alkaloids as well as the very slow growth of these plants and their unique habitat. Phlegmarine alkaloids, however, are expected to have biological properties similar to other *Lycopodium* alkaloids and could be useful for Alzheimer's disease and myasthenia gravis.[33a] These issues make the development of efficient and versatile methods for the synthesis of these alkaloids an area of interest.

3.5. Previous synthesis of phlegmarine alkaloids

The synthesis of phlegmarine alkaloids has been an active research subject and various groups have reported their efforts towards their synthesis. As previously mentioned, for this work only alkaloids of type A and B will be discussed and only enantioselective total synthesis will be commented.

3.5.1. Takayama's synthesis of lycoposerramine Z

The group of Takayama reported the first synthesis of lycoposerramine Z in 2009, along with lycoposerramine X.[90a] The author's approach was based on the chiral pool, starting from the commercially available enantiopure (*R*)-3-methylcyclohexanone, **53**. This compound possesses the C-7 methyl substituent with the correct stereochemistry and had been previously used by the author in the synthesis of related alkaloids (Scheme 3.1).[90b]



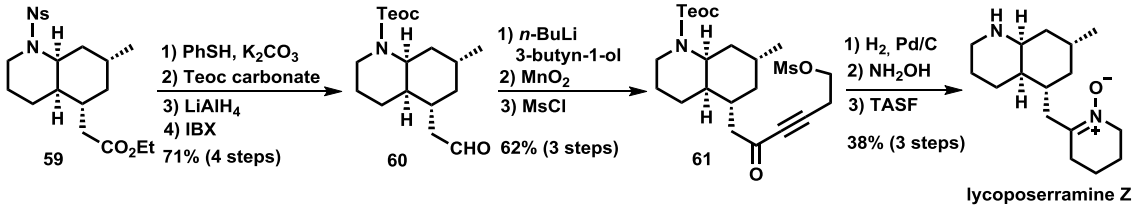
Scheme 3.1. Takayama's assembly of the 5,7-disubstituted *cis*-DHQ.

The synthesis began by the conversion of compound **53** to the corresponding iodo-enone **54** *via* a 4-step sequence previously developed by the authors.[90b] Compound **54** was then subjected to a *B*-alkyl Suzuki-Miyaura cross-coupling to introduce the fragment that would be later used to assemble the *cis*-DHQ. Allylic alcohol **55** was obtained after Luche reduction of the enone moiety and exposed to Johnson-Claisen rearrangement conditions to afford **56** in excellent yield. With this sequence the authors introduced a substituent at C-5, with the correct stereochemistry, for its subsequent elaboration. Trisubstituted cyclohexene **56** was subjected to a hydroboration-oxidation sequence to re-introduce the hydroxy group in good *d.r.* (82%) and, after protection-deprotection steps, **57** was obtained.

A Mitsunobu reaction followed by solvolysis of the secondary alcohol afforded the *N*-protected amino-alcohol **58**. This compound underwent an intramolecular cyclization, under Mitsunobu conditions, affording **59**, bearing the *cis*-DHQ nucleus with the correct stereochemistry at C-5 and C-7. Having assembled the core of lycoposerramine Z,

[90] (a) Tanaka, T.; Kogure, N.; Kitajima, M.; Takayama, H. *J. Org. Chem.* **2009**, *74*, 8675-8680. (b) Shigeyama, T.; Katakawa, K.; Kogure, N.; Kitajima, M.; Takayama, H. *Org. Lett.* **2007**, *9*, 4069-4072.

Takayama and co-workers focused on the elaboration of the piperidine ring, a feat that would require several synthetic steps (Scheme 3.2)



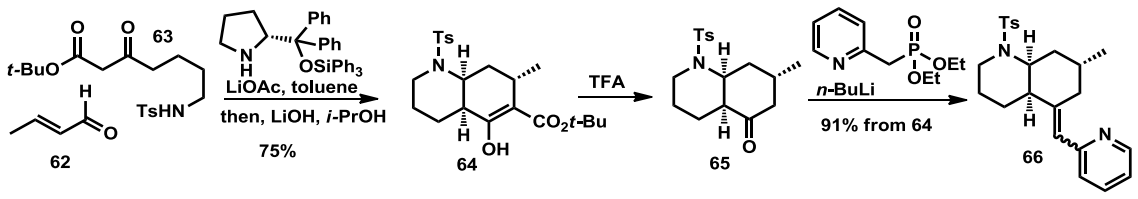
Scheme 3.2. First total synthesis of lycoposerramine Z.

Ester **59** was converted to aldehyde **60** by a four-step sequence that did not involve C–C bond formation reactions. Compound **60** was then propargylated, followed by oxidation of the secondary hydroxy group and mesylation of the primary alcohol, affording **61**. The alkyne moiety in **61** was hydrogenated and, after treatment with hydroxylamine, the cyclic nitrone was introduced. A final deprotection afforded lycoposerramine Z in 3.6% overall yield, over 25 steps from **53**.

It should be noted that the authors in their original report did the step-counting and overall yield from the non-acylated compound **57**, which according to the same authors results in 15 steps in 15.4% overall yield. However the preparation of that specific starting material is very heavy in terms of both synthetic steps, it takes 10 steps, which is a considerable amount of work and almost as long as the actual total synthesis.

3.5.2. Bonjoch's unified approach to type A and B phlegmarine alkaloids

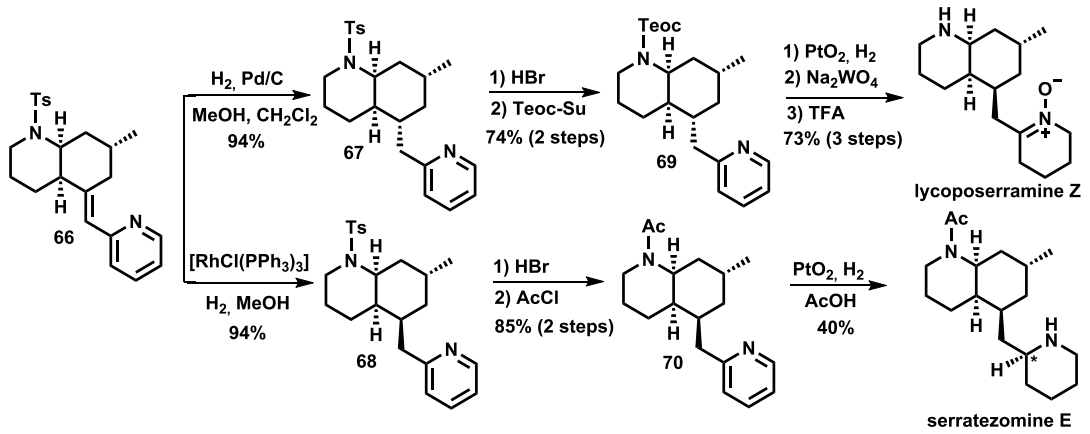
Bonjoch's research group have been very active in this field in the last four years.[91] Their unified approach to the enantioselective total syntheses of type A and B phlegmarine alkaloids was based on an organocatalytic one-pot Robinson annulation/aza-Michael cyclization to construct the *cis*-DHQ **64**. This transformation was carried out in the presence of Hayashi's catalyst starting from keto-ester **63** and crotonaldehyde **62**. A final decarboxylation afforded compound **65**, which can be seen as the common intermediate. Ketone **65** was then subjected to HWE-olefination with the suitable pyridyl phosphonate, leading to the vinyl pyridine **66** as a mixture of *E*:*Z* isomers (Scheme 3.3).



Scheme 3.3. Assembly of the 5,7-disubstituted *cis*-DHQ moiety by Bonjoch.

[91] (a) Bradshaw, B.; Luque-Corredera, C.; Bonjoch, J. *Org. Lett.* **2013**, *15*, 326-329. (b) Bradshaw, B.; Luque-Corredera, C.; Bonjoch, J. *Chem. Commun.* **2014**, *50*, 7099-7102. (c) Bosch, C.; Fiser, B.; Gómez-Bengoa, E.; Bradshaw, B.; Bonjoch, J. *Org. Lett.* **2015**, *17*, 5084-5087.

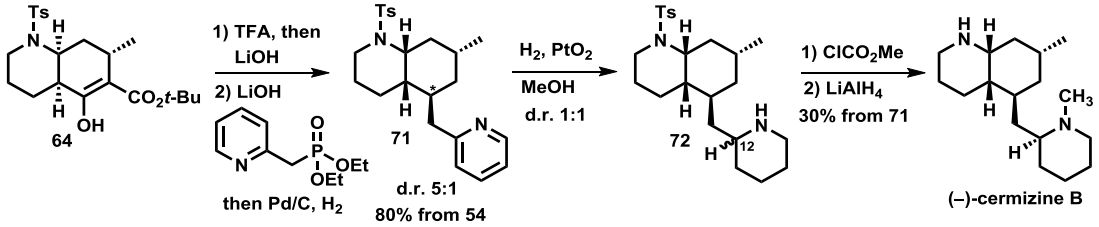
By changing the hydrogenation catalyst, Bonjoch and co-workers managed to effect a remarkable diastereodivergent hydrogenation of the C−C double bond. The authors reasoned that Wilkinson's catalyst might coordinate to the pyridine ring inducing the observed stereoselectivity (Scheme 3.4).



Scheme 3.4. Bonjoch's total syntheses of lycoposerramine Z and serratezomine E.

From the hydrogenated compounds **67** and **68**, modification of the protecting groups followed by hydrogenation of the pyridine ring afforded serratezomine E (from **68**). To complete the synthesis of lycoposerramine Z an additional oxidation to the nitrone and deprotection of nitrogen were required. It should be noted that the hydrogenation of the pyridine moiety afforded an epimeric mixture at the newly created stereocentre, hence the considerably lower yield in the transformation of **70** to serratezomine E. With these efforts the total synthesis of lycoposerramine Z was achieved in 35% overall yield over nine synthetic steps. Regarding serratezomine E, a seven-step sequence afforded the target alkaloid in 21% overall yield.

To synthesize cermizine B from the same precursor **64**, an inversion of the stereochemistry of the ring fusion was required. To this end, treatment of crude **64** with TFA to perform the decarboxylation, followed by treatment with LiOH to induce a retro aza-Michael reaction with subsequent partial ring closure, was carried out (Scheme 3.5).



Scheme 3.5. Bonjoch's total synthesis of (−)-cermizine B.

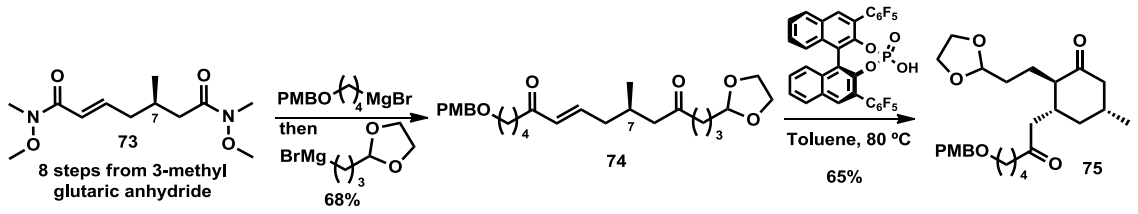
It should be noted that to achieve complete ring closure with the desired stereochemistry, an olefination reaction was required to displace the Michael-retro-Michael equilibrium. Hydrogenation of the pyridine ring was performed with Adams' catalyst, affording **72** as the expected epimeric mixture at C-12. With compound **72** in hand, the piperidine ring

was acylated, and a final reduction with $LiAlH_4$ brought about the removal of the tosyl protecting group and the reduction of the piperidine carbamate to the required methyl substituent. This allowed the authors to synthesize (–)-cermizine B in 20% overall yield and eight synthetic steps.

The above approach provides a fast and short synthesis of these alkaloids, although lacking stereoselectivity in the introduction of the C-12 stereocenter.

3.5.3. Yang-Yao synthesis of lycoposerramine Z

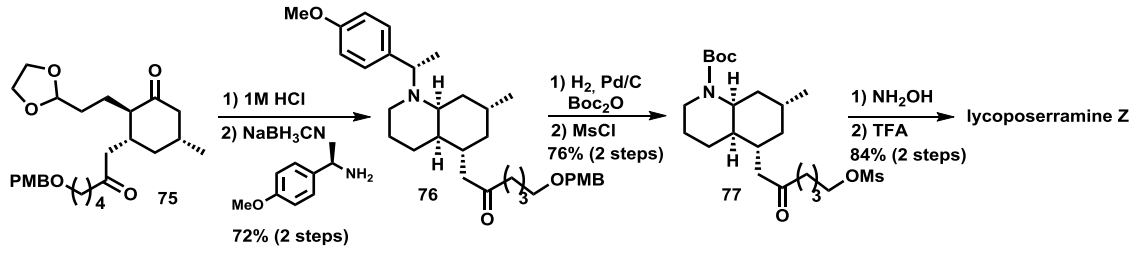
The last efforts in this field were recently reported by the Yang-Yao group from China.[92] These authors' strategy was based on the elaboration of a chiral bis-Weinreb amide **73**, prepared by desymmetrisation of 3-methyl glutaric anhydride. This desymmetrisation introduced early on in the synthesis the required stereochemistry of the C-7 methyl substituent (DHQ numbering). Two consecutive regioselective Grignard additions afforded enone **74** (Scheme 3.6).



Scheme 3.6. Intramolecular Michael-cyclization leading to ketone **75**.

Under optimized conditions, **74** underwent intramolecular Michael cyclization in the presence of a chiral phosphoric acid, leading to cyclohexanone **75** in good yield and nearly complete diastereoselectivity.

The *cis*-DHQ ring **76** was elaborated, after acetal deprotection, *via* a reductive amination between the aldehyde and ketone groups and a chiral benzylamine. Debenzylation of both the nitrogen atom, with subsequent Boc protection, and the PMB-protected hydroxy group afforded ketone **77**, after mesylation of the hydroxy group (Scheme 3.7).



Scheme 3.7. Yang-Yao synthesis of lycoposerramine Z.

[92] Zhang, L.- D.; Zhong, L.-R.; Xi, J.; Yang, X.-L.; Yao, Z.-J. *J. Org. Chem.* **2016**, *81*, 1899-1904.

The two last steps were identical to those of Takayama's synthesis, the cyclic nitrone was generated by treatment with hydroxylamine and a final deprotection with TFA afforded lycoposerramine Z in 20% overall yield over eight synthetic steps from **73**.

3.6. Objectives

After the success achieved in the synthesis of lepadins, we focused our attention on *Lycopodium* alkaloids. Their low natural availability along with their structural features prompted us to undertake this new task.

To achieve the synthesis of phlegmarine-type *Lycopodium* alkaloids from chiral lactams some challenges needed to be addressed, namely:

1. The introduction of the methyl substituent at C-7.
2. Control of the stereochemistry at C-5.
3. Introduction of a suitable substituent at C-5 to elaborate the piperidine ring.

Two synthetic approaches were considered starting from chiral bicyclic lactams as enantiomeric scaffolds.

In the first one, an unsaturated phenylglycinol-derived lactam, prepared from an achiral oxo-ester, would be used and the C-7 methyl substituent would be introduced by previous functionalization of the allylic position.

In the second approach, the C-7 methyl group would be already incorporated in the starting oxo-ester, which would be prepared from a compound of the chiral pool with the appropriate absolute configuration.

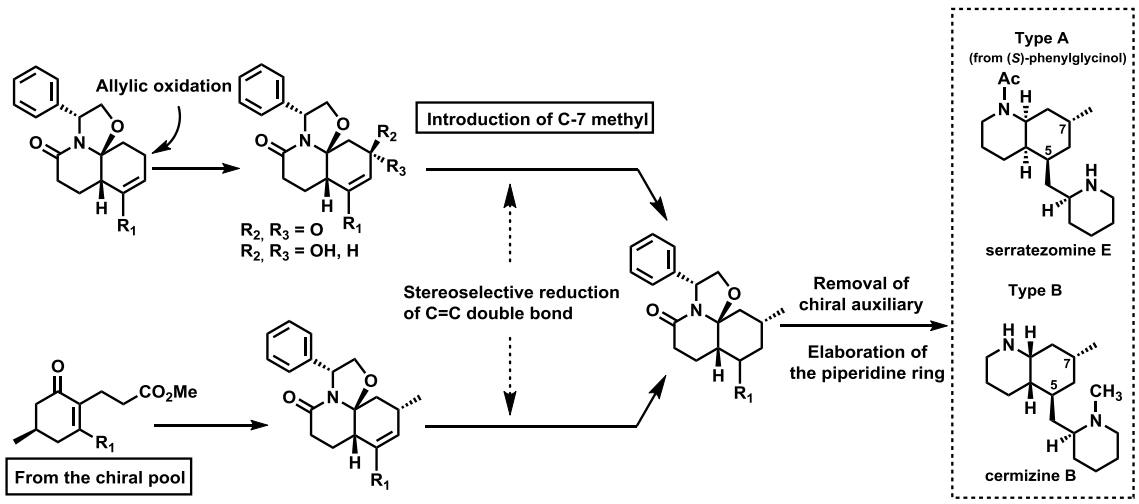


Figure 3.11. Synthetic approaches to phlegmarine alkaloids.

3.7. Synthetic strategy for the phlegmarine alkaloids

3.7.1. First approach. Allylic oxidation of unsaturated tricyclic lactams

The elaboration of a suitable precursor (**D**) for the synthesis of phlegmarine-type alkaloids from chiral unsaturated lactams can be approached from an unsubstituted lactam derivative (**A**) by allylic oxidation of the methylene, followed by a stereoselective conjugate addition for the introduction of the C-5 substituent (DHQ numbering). Alternatively, compound **C** can be obtained from a substituted lactam **B** by chemoselective allylic oxidation of the endocyclic methylene, followed by stereoselective reduction of the carbon-carbon double bond of the enone. Finally, the carbonyl group would be used for the introduction of the C-7 methyl either by methylenation and stereoselective hydrogenation or by stereoselective reduction and nucleophilic displacement of a sulfonate of the resulting alcohol (Figure 3.12).

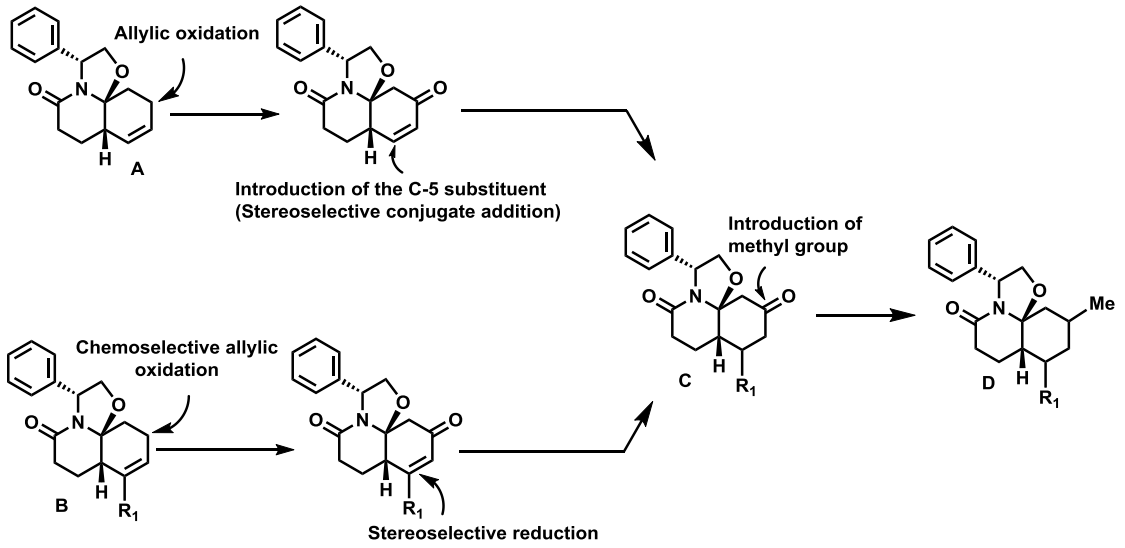


Figure 3.12. First generation approach to phlegmarine alkaloids.

We expected that both routes, from **A** or **B**, would be complementary in terms of the stereochemical outcome between C-4a and C-5, to provide access to type **A** and **B** phlegmarine alkaloids.

3.7.1.1. Preparation of the non-substituted chiral scaffold

To begin our studies, it was necessary to prepare the suitable unsaturated tricyclic lactam and introduce the hydroxy or the ketone moieties on the carbocyclic ring of our chiral scaffold. The latter transformations would be achieved by allylic oxidation of position C-7 (DHQ numbering) as depicted in Figure 3.13.

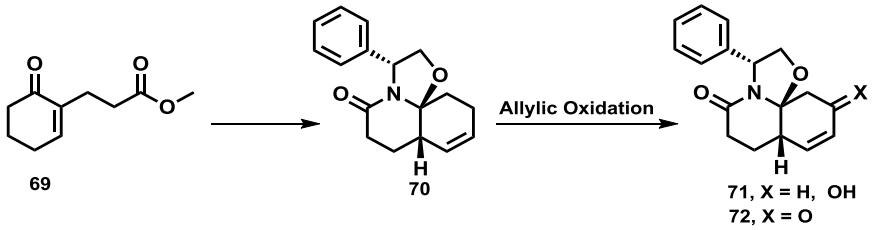
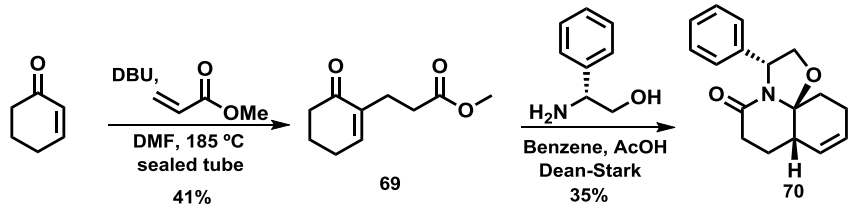


Figure 3.13. Preparation of the chiral scaffold.

We began by synthesizing the required unsaturated keto-ester **69**, previously prepared in our group[45a] from commercially available starting materials in moderate yield (Scheme 3.8). With compound **69** in hand, we performed the cyclocondensation reaction under standard conditions to afford our unsaturated chiral scaffold **70**. To our surprise, the cyclocondensation reaction led to consistently low yields of unsaturated lactam **70**, even though the TLC showed complete conversion and a clean reaction, further supported by the ^{1}H-NMR spectra of the crude reaction mixture. Attempts to improve the yield, by changing the solvent (toluene), acid (AcOH, *p*-TsOH) and heat source (MW irradiation) met with failure. Additionally, changes to the purification procedure, such as a different chromatography support such as Al_2O_3, or the addition of AcOH or Et_3N to the solvent system, had no effect (Scheme 3.8).



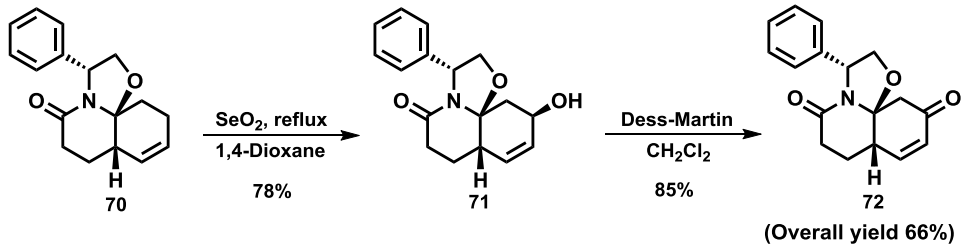
Scheme 3.8. Synthesis of unsaturated chiral tricyclic lactam **70**.

Undoubtedly, this was a setback, but we thought that if the allylic oxidation went well and the conjugate addition could introduce the substituent with good stereocontrol, it was worth taking the risk.

3.7.1.2. Allylic oxidation of lactam 70 and conjugate addition.

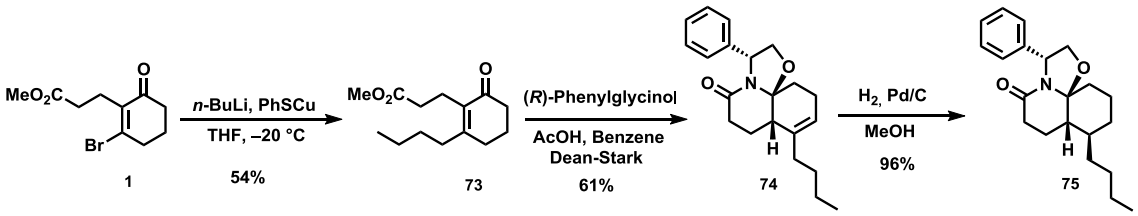
The allylic oxidation of **70** was carried out by the classical procedure mediated by SeO_2. This reagent is the most commonly used for this type of reactions, affording the corresponding allylic alcohol in good yields, even in complex structures (Scheme 3.9).[93] Subjecting unsaturated lactam **70** to the standard conditions smoothly provided allylic alcohol **71** in good yield and as a single diastereoisomer, which was important for subsequent studies on the introduction of the methyl group. Having obtained **71** in good yield we proceeded to oxidize the allylic alcohol to the corresponding enone, in order to attempt the conjugate addition reaction. Oxidation with Dess-Martin periodinane afforded enone **72** in high overall yield (Scheme 3.9).

[93] Nakamura, A.; Nakada, M. *Synthesis* **2013**, 1421-1451.



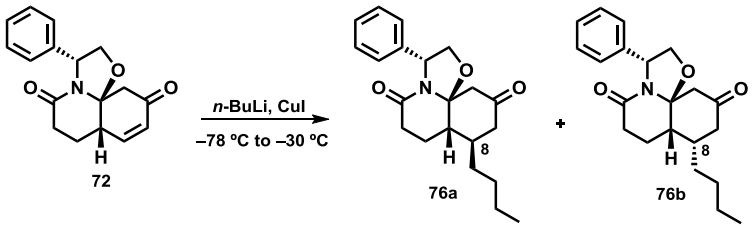
Scheme 3.9. Allylic oxidation and enone formation from **70**.

To prove the feasibility of the the conjugate addition reaction and easily analyse its stereochemical outcome, we decided to introduce a *n*-butyl substituent because a related compound of known configuration (**75**) had been previously prepared in the group (Scheme 3.10).



Scheme 3.10. Preparation of known chiral tricyclic lactam **75**.

The corresponding Gillman reagent required for the conjugate addition reaction was easily prepared from *n*-BuLi and a copper halide. Bearing this in mind we attempted the conjugate addition reaction. The conjugate addition proceeded smoothly in CH_2Cl_2, as the solvent, to afford ketone **76a** in high yield as a single diastereoisomer. It should be noted however, that CH_2Cl_2 is not a typical solvent for this reaction. Indeed, we initially used ethereal solvents, THF and Et_2O, but surprisingly they afforded a 1:1 mixture of diastereoisomers **76a** and **76b** (as determined by NMR of the crude mixture). Adding $BF_3 \cdot Et_2O$ or changing the Cu source ($CuBr \cdot SMe_2$, CuCN) had no influence on the stereochemical outcome of the reaction (Scheme 3.11).[94]

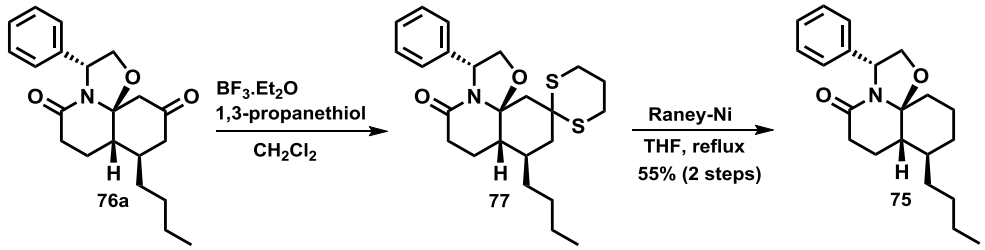


Solvent	dr (76a:76b)	Yield
CH_2Cl_2	100:0	83%
Et_2O	50:50	73%
THF	50:50	70%

Scheme 3.11. Conjugate addition to enone **72**.

[94] Schlosser, M. in *Organometallics in Synthesis – A Manual*; Chapter 4; John Wiley and Sons: Chichester 1994.

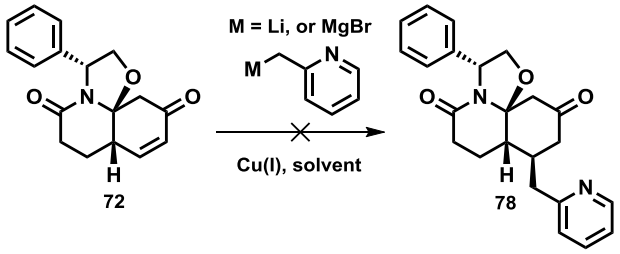
With this excellent result in hand, we needed to confirm the stereochemistry obtained at the C-5 centre (DHQ numbering). To do this, the ketone moiety in **76a** was converted to thioketal **78**, which was removed *via* a Mozingo reduction to give **75** (Scheme 3.12).



Scheme 3.12. Determination of the C-5 stereochemistry.

Comparison of the ^{1}H and ^{13}C-NMR data of the compound thus obtained, with those of the known compound **75** obtained as depicted is Scheme 3.10 confirmed the absolute configuration of the new stereocenter generated in the reaction.

With the synthesis of phlegmarine-type alkaloids in mind, we decided to explore the conjugate addition of a stabilized anion, such as that derived from 2-methylpyridine, to enone **72**. This would allow the incorporation of a moiety that is an immediate precursor of the 2-piperidylmethyl moiety present in these natural products (Scheme 3.13).



Scheme 3.13. Attempts to introduce the 2- pyridilmethyl moiety.

Unfortunately, after extensive screening of solvents (THF, Et_2O, DME, and CH_2Cl_2), Cu sources (CuI, $CuBr \cdot SMe_2$, and CuCN), additives ($BF_3 \cdot Et_2O$, TMSCl), and generation of either the lithiated or Grignard reagent of picoline, the desired compound **78** was never detected. The system proved unreactive, or 1,2-addition occurred.

3.7.1.3. Allylic oxidation of C-8 substituted tricyclic lactams

In order to expand the synthetic potential of the procedure for the synthesis of phlegmarine-type alkaloids of types A and B, we decided to explore an alternative for the stereoselective preparation of isomers with an opposite configuration at C-8 with respect to the major isomer **76a** obtained in the above conjugate addition reaction. This alternative involved the preparation of an enone derived from a chiral tricyclic lactam, with a substituent already incorporated at C-8 and a subsequent stereoselective conjugate reduction of the carbon-carbon double bond of the enone (Figure 3.14).

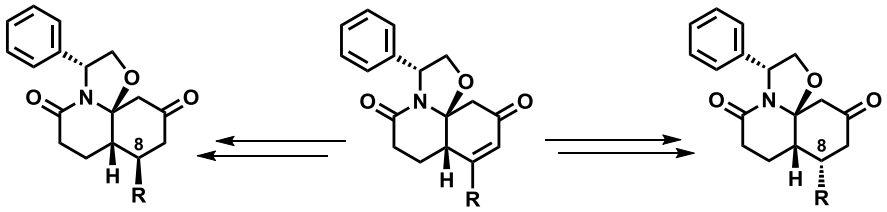


Figure 3.14. Stereoselective reduction of unsaturated chiral tricyclic lactams.

To explore this alternative, it was first required to perform a selective allylic oxidation of the endocyclic methylene group of C-8 substituted lactams such as **74** or **79**, which were prepared in good overall yields following the procedure previously reported by our group (Figure 3.15).[45a]

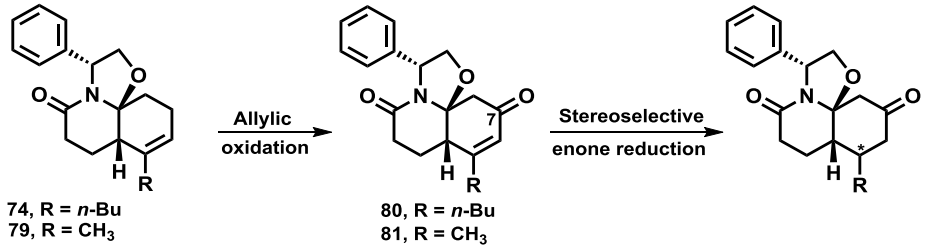
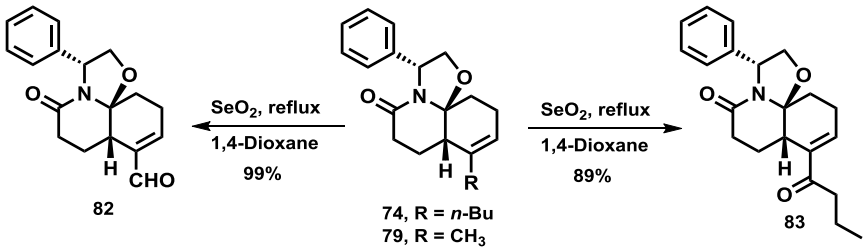


Figure 3.15. Model lactams for allylic oxidation.

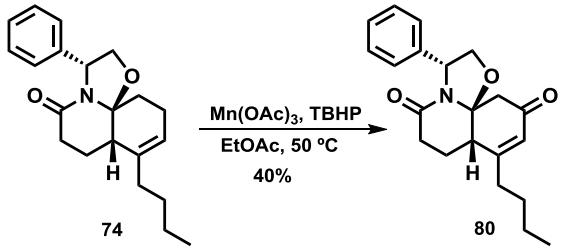
When lactam **79** was subjected to oxidation with SeO_2,[95] under the same conditions used for the oxidation of the unsubstituted chiral tricyclic lactam **70**, aldehyde **82**, resulting from the selective allylic oxidation of the methyl instead of the methylene group, was obtained in almost quantitative yield. Moreover, when lactam **74** was subjected to the same conditions, compound **83**, resulting from the oxidation of the exocyclic methylene group, was obtained exclusively and once again in very high yield. This high regioselectivity was somewhat surprising, given that the preferred site of oxidation is the endocyclic position. However, it is known that if there are steric factors involved, the allylic oxidation can occur in the exocyclic methyl group and this seems to be case for our lactams **74** and **79** (Scheme 3.14).[96]



Scheme 3.14. Allylic oxidation using SeO_2.

[95] Nishimata, T.; Sato, Y.; Mori, M. *J. Org. Chem.* **2004**, *69*, 1837-1843.
[96] Jorgensen, L.; McKerrall, S. J.; Kuttruff, C. A.; Ungeheuer, F.; Felding, J.; Baran, P. S. *Science* **2013**, *341*, 878-882.

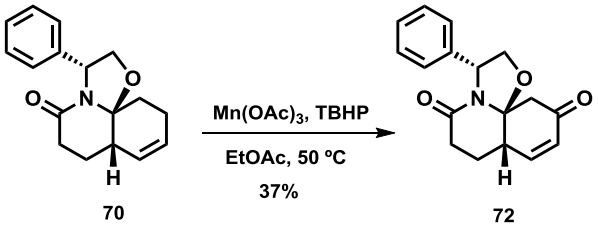
With these interesting but undesired results, we decided to change the allylic oxidation conditions, and attempted the oxidation of **74** with catalytic $Mn(OAc)_3$ and TBHP as the co-oxidant (Scheme 3.15).[97]



Scheme 3.15. Allylic oxidation of **74** catalyzed by $Mn(OAc)_3$.

These reaction conditions provided the desired endocyclic enone **80**, although in only moderate yield. Attempts were made to optimize the reaction, but it proved to be impossible to improve the yield beyond 40%. Other metals were screened to perform the required oxidation (CrO_3 with 3,4-DMP, $Pd(OAc)_2$), but the results were similar or there was no conversion.

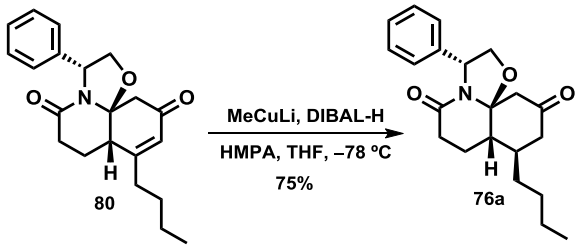
It is worth mentioning that the oxidation of **70** under the same reaction conditions provided enone **72** in 37% yield (Scheme 3.16), which does not improve the two-step procedure described in Scheme 3.9.



Scheme 3.16. Allylic oxidation of **70** catalyzed by $Mn(OAc)_3$.

Despite the above disappointing results, we decided to study the stereochemical outcome of the selective conjugate reduction of enone **80** with a copper hydride species generated with diisobutylaluminum hydride (DIBAL-H) in the presence of HMPA.[98] Although the reduction took place in good yield and selectivity, surprisingly, the reduction occurred with opposite facial selectivity with respect to the conjugate addition of organocopper reagents to enone **72** in CH_2Cl_2 (Scheme 3.11) and, consequently, provided the same stereoisomer **76a** (Scheme 3.17).

[97] Shing, T. K. M.; Yeung, Y. Y. *Angew. Chem. Int. Ed.* **2005**, *44*, 7891-7894
[98] Tsuda, T.; Hayashi, T.; Satomi, H.; Kawamoto, T.; Saegusa, T. *J. Org. Chem.* **1986**, *51*, 537-540.



Scheme 3.17. Conjugate reduction of enone **80**.

The low yields observed in the preparation of unsaturated lactam **70** (35%) or in the allylic oxidation leading to **80** (40%) led us to discard the above procedures for the synthesis of phlegmarine-type alkaloids and focus our efforts in the chiral pool approach.

3.7.2. Chiral pool strategy

This strategy required the selection of an appropriate compound from the chiral pool that incorporates the methyl substituent with the correct stereochemistry. Additionally, it should be versatile enough to allow the preparation of a functionalized keto-ester for the cyclocondensation reaction (Figure 3.16).

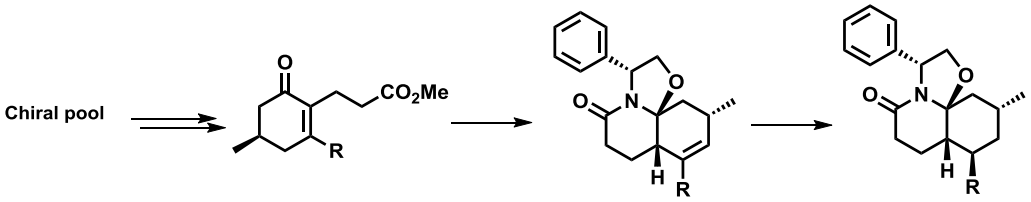
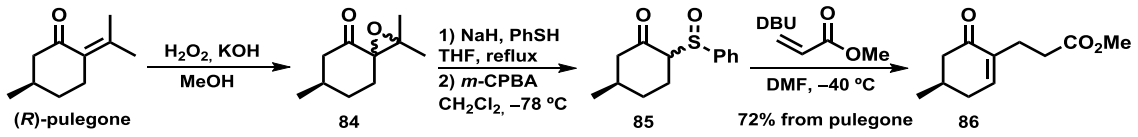


Figure 3.16. Second synthetic approach to phlegmarine alkaloids.

3.7.2.1. Preparation of the keto-ester bearing a stereodefined methyl substituent

Given that the chiral pool compound had to possess a methyl substituent with the (*R*) configuration, we selected (*R*)-pulegone, which is cheap and commercially available in enantiopure form in large quantities. Additionally, it has been used in several total syntheses of complex alkaloids, showcasing its versatility.[99] We began by converting (*R*)-pulegone to α,ß-unsaturated ketone **86** in very high yield, following literature procedures (Scheme 3.18).[100]



Scheme 3.18. Preparation of the chiral keto-ester **86**.

[99] For selected recent examples: (a) Samame, R. A.; Owens, C. M.; Rychnovsky, S. D. *Chem. Sci.* **2016**, *7*, 188-190. (b) Lee, A. S.; Liau, B. B.; Shair, M. D. *J. Am. Chem. Soc.* **2014**, *136*, 13442-13452. (c) Lin, K.-W.; Ananthan, B.; Tseng, S.-F.; Yan, T.-H. *Org. Lett.* **2015**, *7*, 3938-3940.

[100] Caine, D.; Procter, K.; Cassell, R. A. *J. Org. Chem.* **1984**, *49*, 2647-2648. (b) Mutti, S.; Daubié, C.; Decalogne, F.; Fournier, R.; Rossi, P. *Tetrahedron Lett.* **1996**, *37*, 3125-3128. (c) Kozak, J. A.; Dake, G. R. *Angew. Chem. Int. Ed.* **2008**, *47*, 4221-4223.

The required substituent would be introduced by means of the Saegusa-Ito protocol,[101] in which the enolate generated after the 1,4-addition of the copper reagent is trapped as its silyl enol ether derivative. As in the Wacker oxidation, exposure to a Pd source, usually $Pd(OAc)_2$ in stoichiometric amount, results in the release of the silyl group and formation of an oxo-allylpalladium complex. After ß-hydride elimination, and subsequent reductive elimination the desired enone is obtained.

Ideally, following the same principle as for the above allylic oxidation strategy, the desired substituent to introduce would be 2-pyridylmethyl (Figure 3.17).

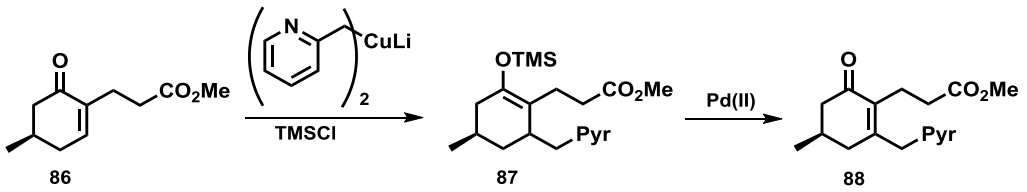
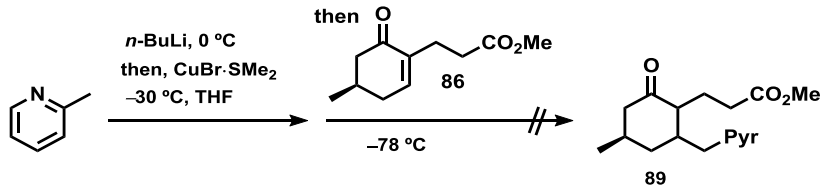


Figure 3.17. Saegusa-Ito protocol.

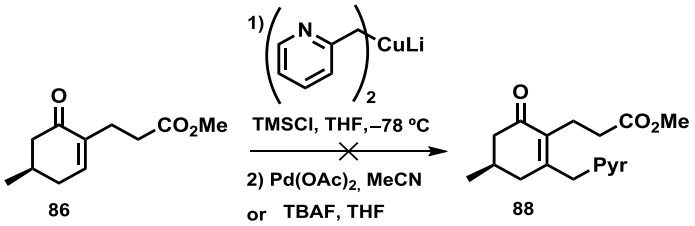
In the literature, there are scarce examples of the selective 1,4-addition of picoline-derived anions to enones.[102] Nonetheless, Taber and co-workers[102b] reported a procedure that allows this transformation from cyclic enones in high yields and regioselectivity. Unfortunately, under Taber's conditions a complex mixture of products was obtained and the target compound **89** was not identified (Scheme 3.19). We explored a range of reaction conditions by changing the Cu source (CuI, CuCN, CuCN · 2LiCl) or running the reaction at different temperatures, and even preparing the Grignard reagent of picoline, but all these efforts were to no avail.



Scheme 3.19. Attempted 1,4-addition of picoline under Taber's conditions.

As a last resort, the full Saegusa-Ito protocol was attempted (Scheme 3.20). However, in no case was compound **88** detected in the reaction mixture, and the results were even worse when the crude mixture was directly carried to the oxidation with $Pd(OAc)_2$, probably because the pyridine moiety coordinates with Pd and completely shuts down the reaction.

[101] Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011-1013. (b) Porth, S.; Bats, J. W.; Trauner, D.; Giester, G.; Mulzer, J. *Angew. Chem. Int. Ed.* **1999**, *38*, 2015-2016.
[102] (a) DeLorbe, J. E.; Lotz, M. D.; Martin, S. F. *Org. Lett.* **2010**, *12*, 1576-1579. (b) Taber, D. F.; Guo, P.; Pirnot, M. T. *J. Org. Chem.* **2010**, *75*, 5737-5739 and references therein.



Scheme 3.20. Saegusa-Ito protocol.

At this point it was necessary to revisit our strategy and try to introduce another kind of substituent that would allow the construction of the piperidine ring in a fast and efficient manner.

Heathcock, in the 1980's, studied the stereoselectivity of the conjugate addition of allylsilanes and allylcuprates to methyl-substituted cyclic enones.[103] In these studies he noted a remarkable facial selectivity of the 1,4-addition process, where for 5-methyl cyclohexenones, such as **88**, the *trans* isomer was the main isomer formed in the reaction, with only traces of the *cis*.

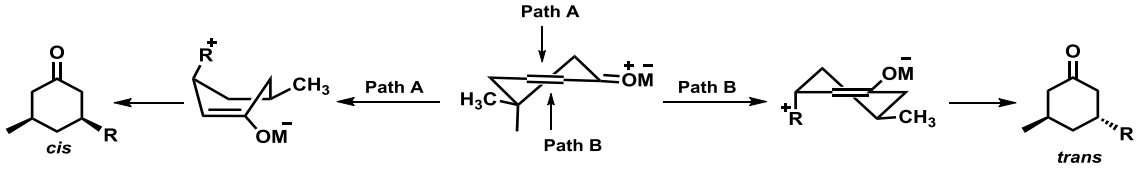
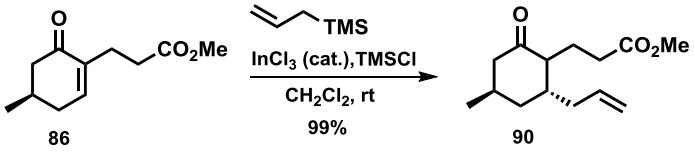


Figure 3.18. Possible pathways in the conjugate addition to 5-methyl cyclohexenone.

The addition occurs under stereoelectronic control and path **B**, leading to the *trans* isomer, is favoured over path **A**, since the latter path involves a highly unstable boat-like transition state (Figure 3.18). Of particular interest was the observation that if the reaction is performed with an allylsilane, known as the Hosomi-Sakurai allylation,[104] the preference for the *trans* product is nearly perfect, while the allylcuprate reagent generates slightly higher amounts of the *cis* product. A quick literature survey led us to select the indium-catalysed protocol (Scheme 3.21).[105] This procedure, which requires very mild reaction conditions, afforded a nearly quantitative yield of **90** as a mixture of C-2 epimers but with complete stereoselectivity in the formation of the C3-C5 *trans* isomer.



Scheme 3.21. Indium-catalyzed Hisomi-Sakurai allylation of **86**.

[103] Blumenkopf, T. A.; Heathcock, C. H. *J. Am. Chem. Soc.* **1983**, *105*, 2354-2358.
[104] Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673-1675.
[105] Lee, P. H.; Lee, K.; Sung, S.-Y.; Chang, S. *J. Org. Chem.* **2001**, *66*, 8646-8649.

It should be noted that the classical Sakurai allylation conditions (stoichiometric $TiCl_4$ and AllylTMS in CH_2Cl_2 at −78 ºC)[104] also afforded compound **90** in very high yield (85%) but were experimentally more cumbersome to carry out.

3.7.2.2. Total synthesis of (−)-cermizine B

3.7.2.2.1. Preparation of the chiral tricyclic lactam scaffold

Having secured an efficient synthetic route to prepare a suitably functionalized keto-ester **90**, we drew a synthetic plan (Figure 3.19) for the synthesis of *Lycopodium* alkaloids of type B, such as (−)-cermizine B, based on the expected generation of lactam **91** by the procedure we have extensively studied in our group.

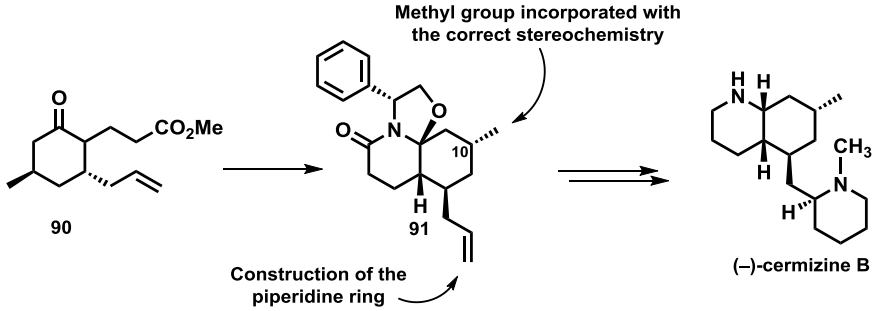
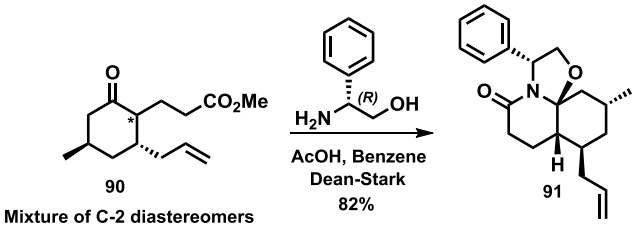


Figure 3.19. Synthetic strategy for the synthesis of (−)-cermizine B.

Compound **91**, already incorporates the methyl substituent at C-10 (C-7 DHQ numbering) with the correct stereochemistry. Additionally, the allyl moiety is a suitable functionalization to elaborate the piperidine ring at C-8 (C-5 DHQ numbering) in subsequent steps.

Having solved our initial synthetic problems and with the possibility of taking our methodology one-step further, we began by performing the cyclocondensation reaction between keto-ester **90** and (*R*)-phenylglycinol (Scheme 3.22).



Scheme 3.22. Cyclocondensation reaction of **90** with (*R*)-phenylglycinol.

We were very pleased to find that the cyclocondensation reaction of the C-2 diastereomeric mixture of keto-ester **90** with (*R*)-phenylglycinol took place in a diastereoconvergent manner affording chiral lactam **91** in excellent yield and as a single diastereoisomer. This represented the first example of a cyclocondensation from a cyclohexanone-derived keto-ester partner with two substituents on the carbocyclic ring and two stereocentres of well-defined configuration.

The absolute configuration of lactam **91** was unambiguously determined by X-ray crystallography, since enantiopure (*R*)-phenylglycinol was used as the chirality source (Figure 3.20).

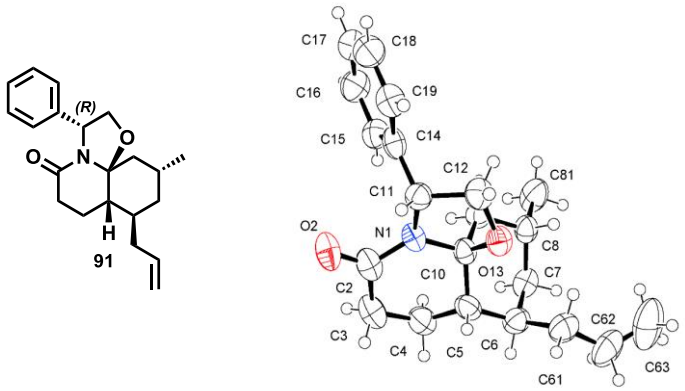


Figure 3.20. X-ray crystal structure of compound **91**.

These structural features clearly had an influence on the stereoselectivity of the reaction and deserve some comment (Figure 3.21).

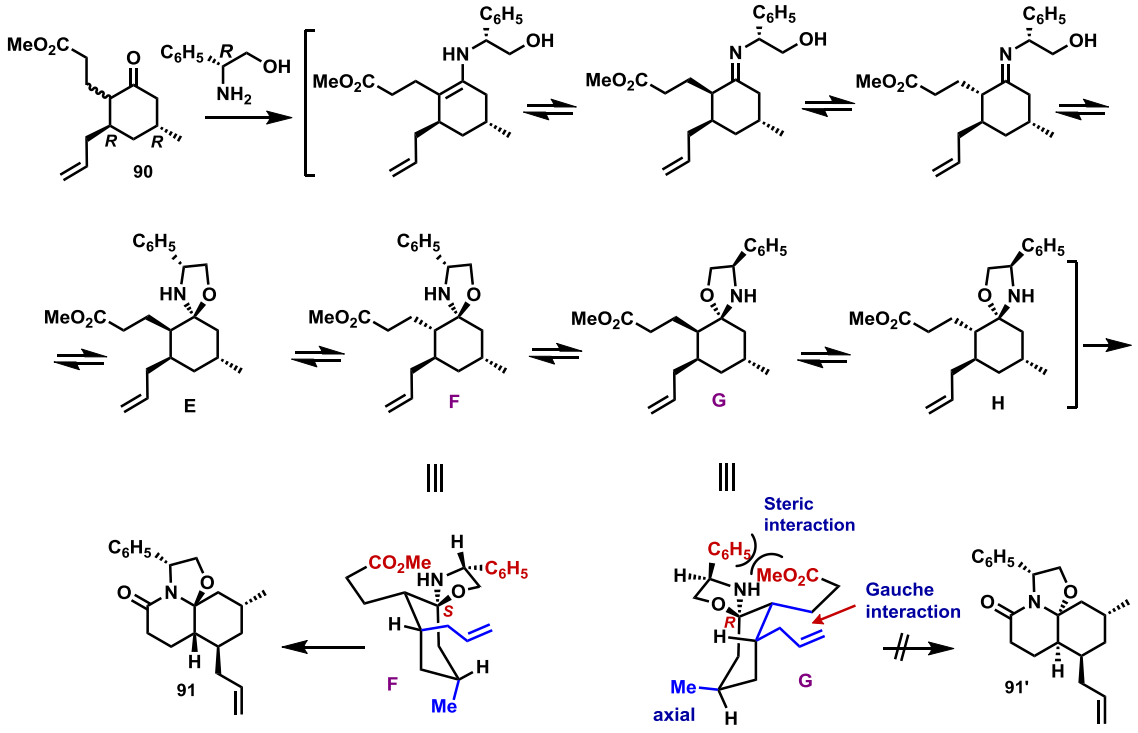


Figure 3.21. Intermediate oxazolidines from **90** and (*R*)-phenylglycinol.

The stereochemical outcome of the above reaction can be rationalized by considering that the reaction of (*R*)-phenylglycinol with ketone **90** affords a mixture of diastereomeric oxazolidines (**E**-**H**), which are in equilibrium through the corresponding imines-enamines. Oxazolidines **E** and **H** do not undergo lactamization since they would afford highly strained tricyclic lactams, in which the fusion between the two six membered rings would be *trans*. The lactamization step takes place faster from isomer **F** which, in the reactive conformation, the carboxylate approaches the nitrogen atom from the less hindered face of the oxazolodine ring, opposite to the phenyl substituent, and the methyl

group is equatorial. However, from isomer **G**, the carboxylate would lactamize from the most hindered face, the methyl substituent is axial, and there is a *gauche* effect between the equatorial allyl group and the propionate chain.

3.7.2.2.2. Construction of the C-5 piperidine substituent

With the assembly of our chiral scaffold it was now time to focus on the elaboration of the C-5 piperidine ring. Given the remote location of this substituent, it was anticipated that to induce a substrate control in the stereoselective generation of the stereocenter at the 2-position of the piperidine ring would be difficult. Therefore, we thought of using aldehyde **92** as a way to introduce the required chiral centre of the piperidine ring by means of a stereoselective allylation. The piperidine ring could be constructed later on in the synthesis *via* a ring-closing metathesis reaction (RCM) (Figure 3.22).

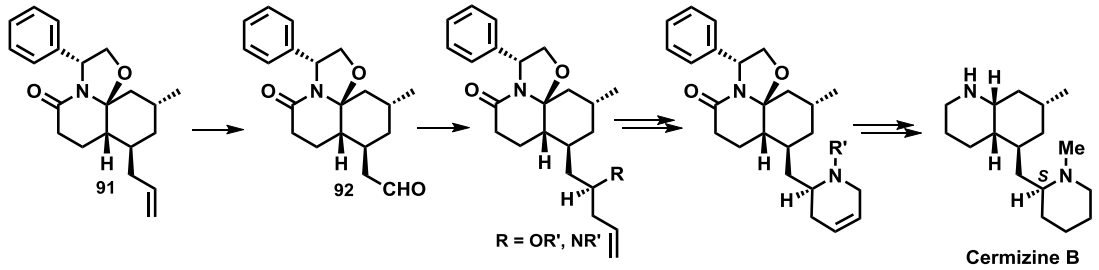
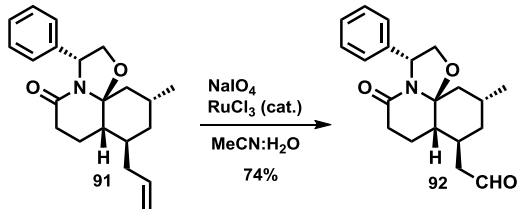


Figure 3.22. Synthetic plan to elaborate the piperidine ring.

Having devised a sound synthetic approach for the elaboration of the piperidine ring, we proceeded to perform the oxidative cleavage of the C-C double bond. Although the obvious choice would be a reductive ozonolysis, the good results observed previously (section 2.7.2.1) with RuO_4 oxidations, along with its operational simplicity prompted us to explore this alternative oxidant.[70,106] Using the literature[107] procedure, aldehyde **92** was obtained from alkene **91** in high yield, with a straightforward and easy protocol (Scheme 3.23).



Scheme 3.23. Oxidative cleavage of **91**.

With the desired compound in hand, we then focused on the stereoselective introduction of the allyl moiety. To do this we had two main options (Figure 3.23).

[106] Gore, E. S. *Platin. Met. Rev.* **1983**, *27*, 111-125
[107] Yang, D; Zhang, C. *J. Org. Chem*. **2001**, *66*, 4814-4818

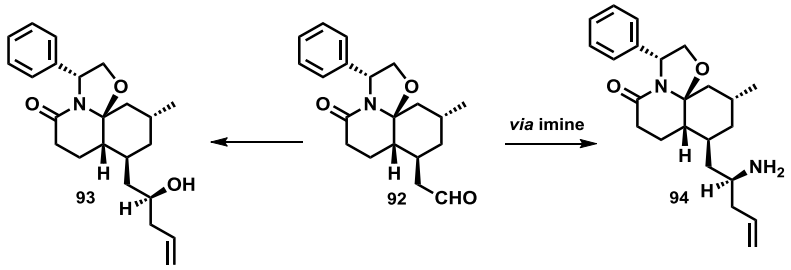


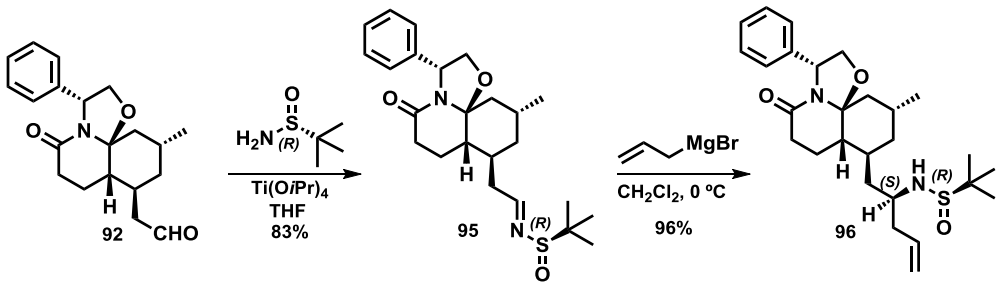
Figure 3.23. Synthetic plan to elaborate the piperidine ring.

The first option would be the direct allylation of aldehyde **92**. There are several methodologies available in the literature to enantioselectively and/or stereoselectively perform the allylation of aldehydes. Classical examples are Brown's[108a] or Roush's[108b] allylations and more modern Leighton's[108c] or Krische's[108d] allylation protocols. However, this route means that we would end-up with a secondary alcohol in the molecule, which we would then need to convert to the corresponding amine, and of course this would imply additional synthetic steps.

The other option would be the conversion of the aldehyde to the corresponding imine and then to perform the allylation reaction. Similarly, to the allylation of aldehydes, there are various procedures to perform this reaction, catalysed by metals (Pd, Ir, Rh)[109a] or by taking advantage of a chiral substituent on the imine to direct the allylation process.[109b]

After careful consideration, we decided to go on with the second option, using a chiral imine, namely Ellman's *tert*-butyl sulfinyl imine. This decision was made taking into account that this procedure is very general and affords consistent results with predictable stereochemical outcomes, without the need of complex catalysts or elaborated substituents on the nitrogen atom. Moreover, the introduction of this moiety is very mild and straightforward, by means of a simple Lewis acid mediated condensation of the sulfinamide reagent and the corresponding aldehyde or ketone group.

Having selected this route, we then prepared the chiral imine and performed the allylation (Scheme 3.24).



Scheme 3.24. Imine formation and allylation.

[108] (a) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293-294. (b) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339-6348. (c) Kubota, K.; Leighton, J. L. *Angew. Chem. Int. Ed.* **2003**, *42*, 946-948. (d) Kim, I.; Ngai, M.-Y.; Krische M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6340-6341

[109] (a) Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2011**, *111*, 7774-7854. (b) Robak, M., T.; Herbage, M., A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600-3740.

Following a slightly modified protocol for the sulfinyl imine preparation[110] [the usual Lewis acid is $Ti(OEt)_4$], compound **95** was obtained in very high yield under mild conditions. The subsequent allylation of aldimine **95** with the corresponding Grignard reagent afforded homo-allylic sulfinyl amine **96** in excellent yield and as a single diastereoisomer. To account for the high diastereoselectivities observed, Ellman proposed a mechanistic model, *via* a closed 6-membered ring transition state (Figure 3.24).[110b]

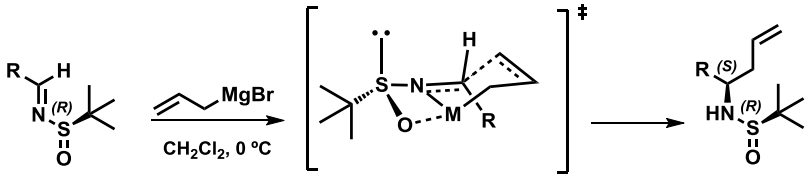
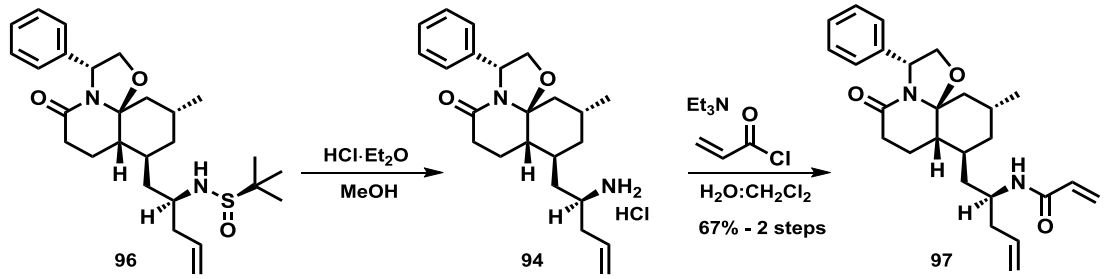


Figure 3.24. Mechanistic model proposed by Ellman.

This model allows the prediction of the stereoselectivity of the addition process in almost all situations. It is characterized by the bulky *tert*-butyl group occupying the less hindered equatorial position and therefore all additions occur from the *si*-face of the imine nitrogen. Additionally, the sulfinyl oxygen and the imine nitrogen are coordinated to the Mg atom. It is hypothesised that this coordination of the nitrogen to the Mg atom could activate the imine and could help justify the higher yields and diastereoselectivities of allyl Grignard reagents with respect to other Grignards.[109b,110b] It should be noted that if the formation of the closed 6-membered ring transition state is disrupted by coordinating solvents, such as Et_2O or THF, the diastereoselectivity of the reaction drops considerably, hence the preference for non-coordinating solvents like CH_2Cl_2 or toluene for these reactions.[110b]

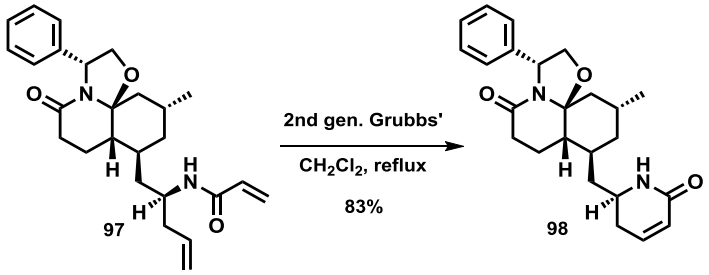
With the preparation of **96** in excellent overall yield and diastereoselectivity we focused on the elaboration of this compound to a precursor for the RCM reaction. To this end, the *tert*-butylsulfinyl group was readily removed, by methanolysis, and the resulting amine hydrochloride **94** was acylated with acryloyl chloride in the presence of trimethylamine to give the metathesis precursor **97** in good yield (Scheme 3.25).



Scheme 3.25. Synthesis of the RCM precursor.

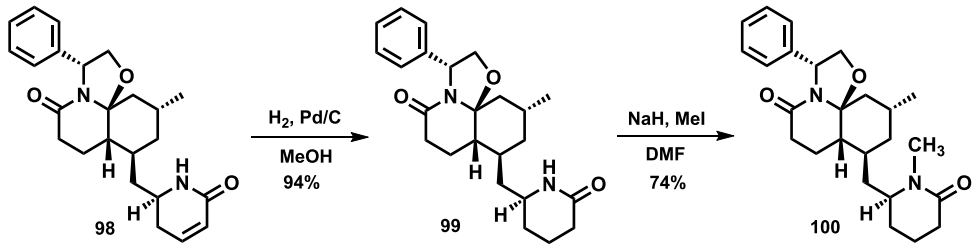
[110] (a) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem*. **1999**, *64*, 1278-1284. (b) Cogan, D., A.; Liu, G.; Ellman, J. A. *Tetrahedron* **1999**, *55*, 8883-8904.

We were fairly confident that the RCM of **97** would be an easy transformation, given that the formation of 6-membered ring is highly favoured and there are many examples in the literature (Scheme 3.26).[111]



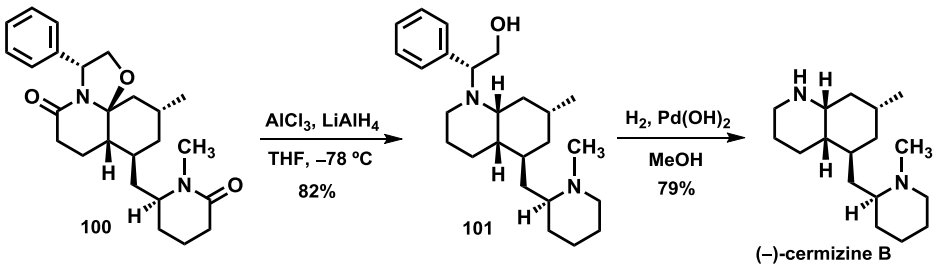
Scheme 3.26. RCM reaction to assemble the piperidine ring.

Subjecting **97** to standard RCM conditions afforded **98**, in very high yield under very mild conditions, and allowed us to assemble the piperidine moiety with complete stereoselectivity. At this point we were nearing the total synthesis of (–)-cermizine B and to achieve our goal we needed only to methylate the nitrogen atom, reduce the unsaturated lactam and remove the chiral auxiliary from **98** (Scheme 3.27).



Scheme 3.27. Catalytic hydrogenation and methylation of **98**.

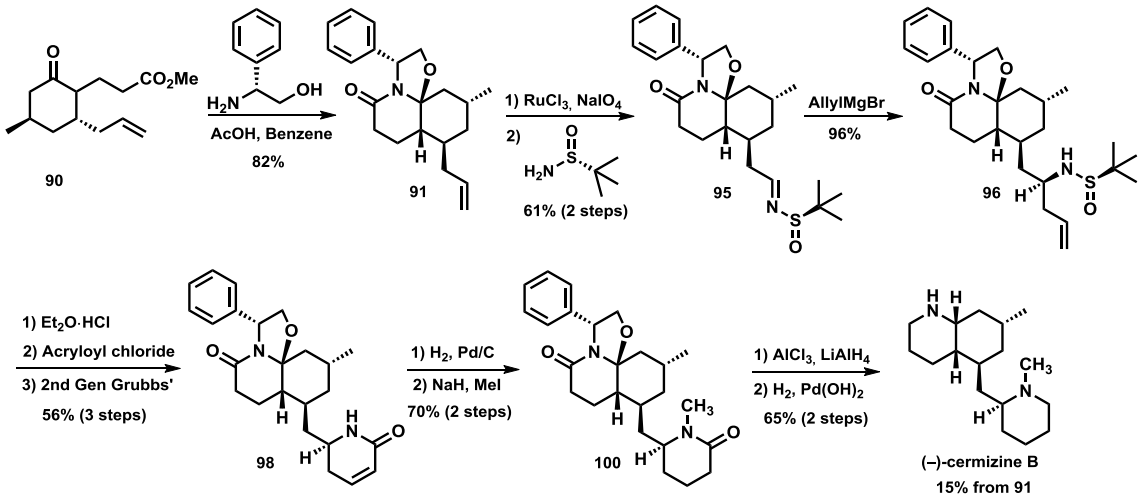
As expected, the hydrogenation of C-C double bond proceeded smoothly and in excellent yield, affording secondary amide **99**, which after methylation under standard conditions afforded **100** in high overall yield. Having prepared **100** the remaining steps were the alane mediated reduction of the lactam carbonyls with stereoselective oxazolidine ring opening to install the *cis*-DHQ ring fusion and *N*-debenzylation, following our previously developed protocol (Scheme 3.28).



Scheme 3.28. Total synthesis of (–)-cermizine B.

[111] (a) Grubbs, R. H. in *Handbook of Metathesis - Volume 2*; Wiley-VCH: Germany 2003. (b) Nicolaou, K. C.; Bulger, P. C.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4490-4527.

We were very pleased to find that reduction with AlH_3 afforded **101** as a single *cis* diastereoisomer in high yield, which was *N*-debenzylated to give (–)-cermizine B. Thus, a protecting-group-free total synthesis of this natural product has been accomplished in 10 steps, from our chiral scaffold **91**, in 15% overall yield (Scheme 3.29).[112]



Scheme 3.98. Overview of the total synthesis of (–)-cermizine B.

3.7.2.3. Studies for type A phlegmarine alkaloids

Taking into consideration the excellent previous results that allowed us to complete the enantioselective total synthesis of type B phlegmarine alkaloid (–)-cermizine B, we then focused our efforts in type A compounds. We reasoned that by changing the chiral inductor phenylglycinol to the (*S*) enantiomer it would be possible to access type A phlegmarine alkaloids, for instance serratazomine E, which differ in the relative configuration of the stereocenters at the carbon fusion positions (Figure 3.25).

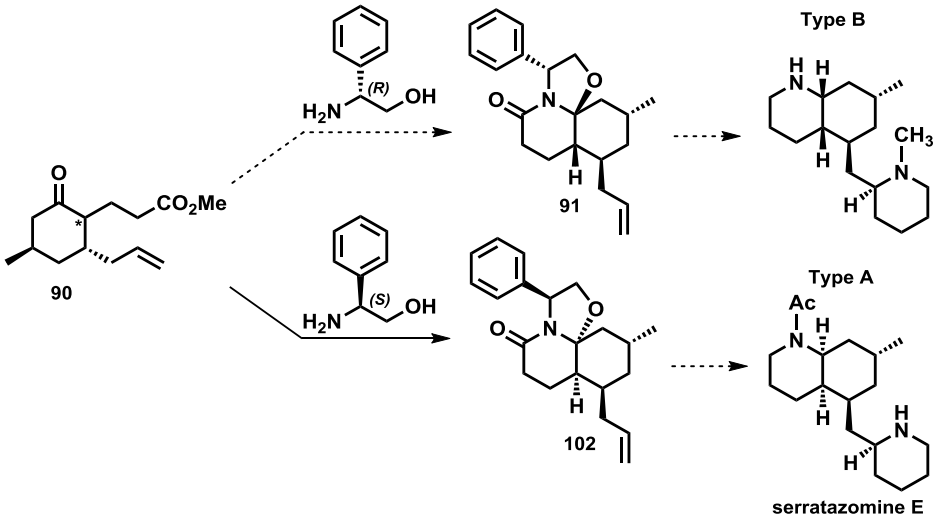
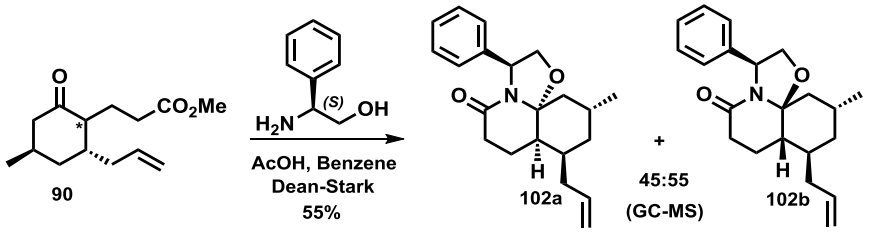


Figure 3.25. Access to type A phlegmarine alkaloids.

[112] Pinto, A.; Griera, R.; Mollins, E.; Fernández, I.; Bosch, J.; Amat, M. *Org. Lett.* **2017**, *19*, 1714-1717.

The possibility of developing a collective total synthesis of *Lycopodium* alkaloids led us to immediately perform the cyclocondensation reaction of keto-ester **90** with (*S*)-phenylglycinol (Scheme 3.30).



Scheme 3.30. Cyclocondensation reaction of **90** with (*S*)-phenylglycinol.

In an unforeseen turn of events, the cyclocondensation of **90** with (*S*)-phenylglycinol, afforded a nearly equimolecular mixture of diastereoisomer **102a** and **102b**, slightly favouring the latter, which *a priori* was the disfavoured isomer.

This result was quite surprising, given that the stereoselective formation of isomer **102b** would imply that the irreversible lactamization step occurred from isomer **I**, in which the approach of the carboxylate to the nitrogen atom takes place from the most hindered face, next to the phenyl substituent (Figure 3.26). However, as it can be observed in Figure 3.25, in isomer **H** the methyl substituent is axial and, although the allyl is equatorial, a destabilising *gauche* interaction between the propionate chain and the allyl occurs.

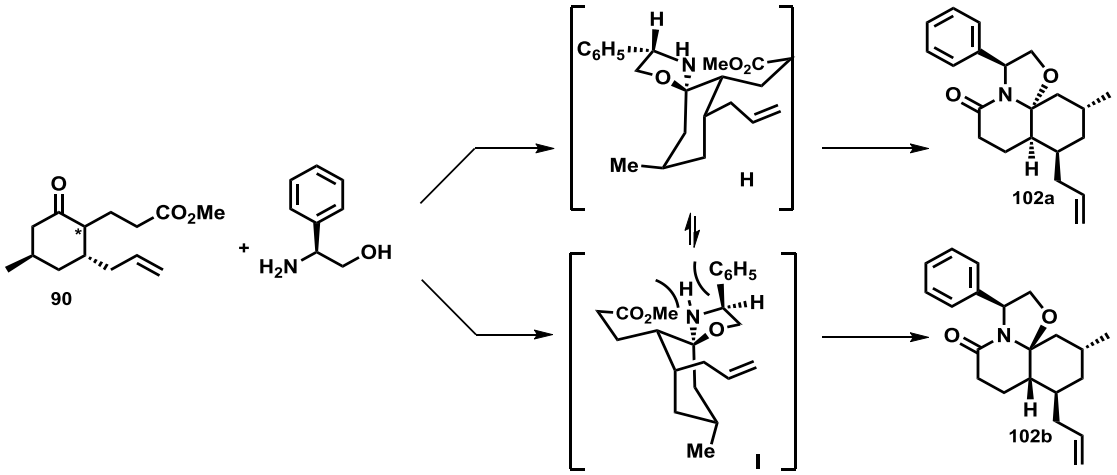


Figure 3.26. Oxazolidines for the irreversible lactamization with (*S*)-phenylglycinol.

To better understand this result and in order to gain insight into the factors governing the cyclocondensation process it was decided to carry out a series of control experiments.

3.7.2.3.1 Cyclocondensation reaction mechanistic studies

The devised control experiments were designed in order to evaluate which substitution pattern was most influential. This meant that it was needed the preparation of C-3 and C-5 substituted keto-esters of known configuration at these chiral centres. Moreover, each substrate would be tested with both enantiomers of phenylglycinol. Additionally, to ascertain the influence of the phenyl substituent of the chiral inductor in the cyclocondensation with keto-ester **90**, we thought of performing the reaction with the achiral 2-aminoethanol (Figure 3.27).

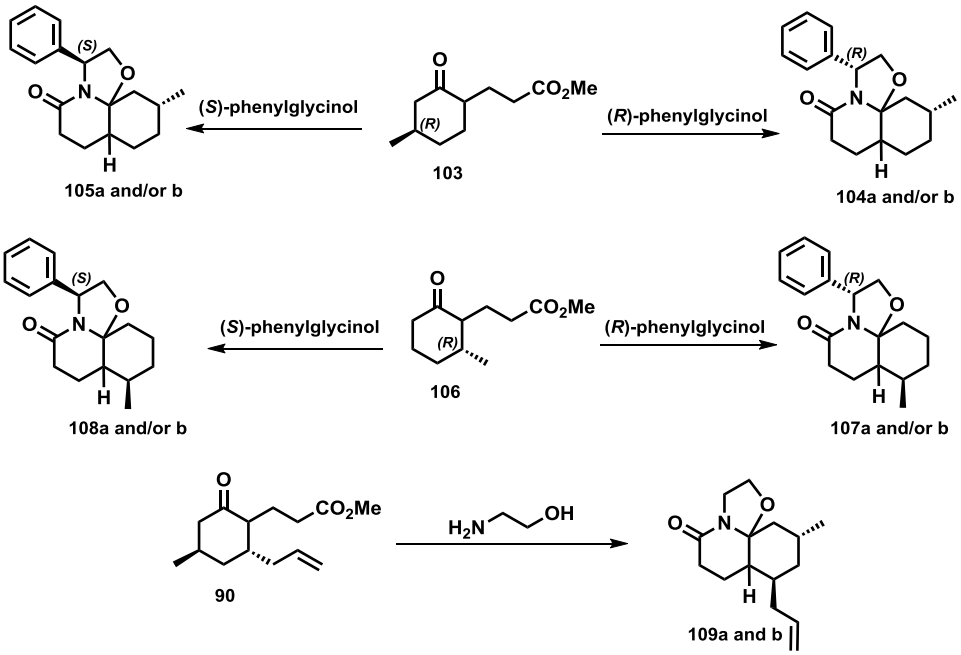
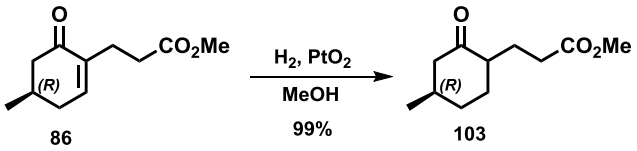


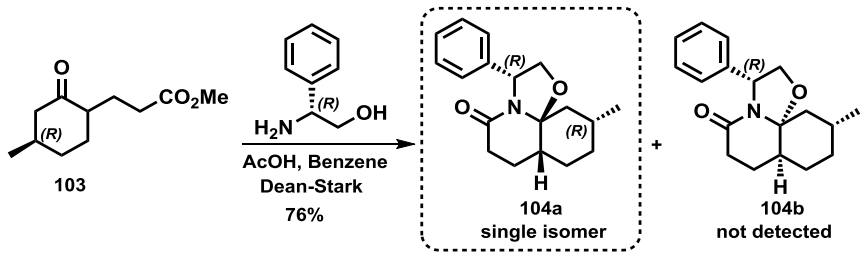
Figure 3.27. Cyclocondensation studies to carry out.

We decided to start with compound **103** which could be easily prepared from **86**. As expected, catalytic hydrogenation of **86** proceeded smoothly to provide **103** in nearly quantitative yield as a mixture (1:1) of diastereoisomers at C-2 (Scheme 3.31).



Scheme 3.31. Preparation of compound **103**.

With **103** in hand it was time to perform the cyclocondensation reaction. Following the same trend as for keto-ester **90**, the cyclocondensation reaction between **103** and (*R*)-phenylglycinol, afforded the expected isomer **104a** as the single product of the reaction (Scheme 3.32).



Scheme 3.32. Cyclocondensation assay of **103** with (*R*)-phenyglycinol.

The isomeric oxazolidines that would lead to both products, before the final lactamization step, are drawn in Figure 3.28 to aid in the interpretation of this result.

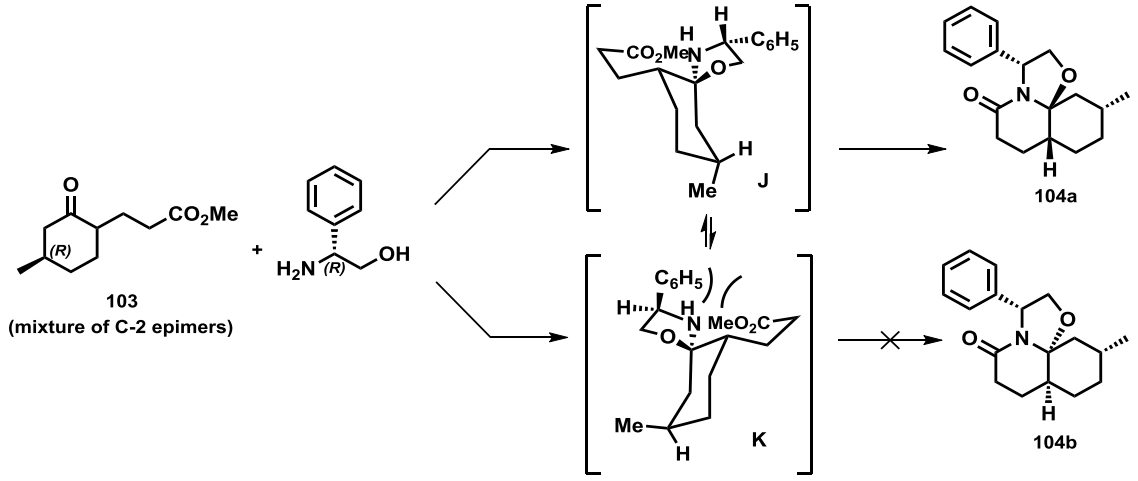
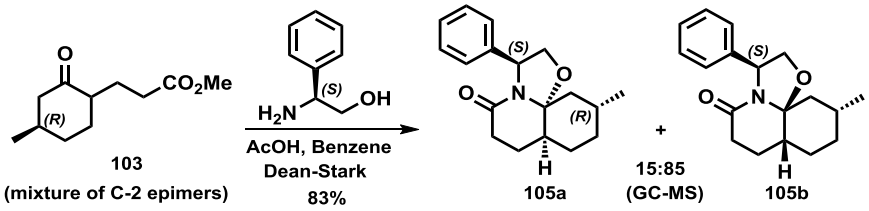


Figure 3.28. Oxazolidines leading to **104a** and **104b**.

As can observed in Figure 3.27, in the isomeric oxazolidine **J**, leading to isomer **104a**, the configuration at C-2 of the oxazolidine ring allows the lactamization to take place from the less hindered face and, on the other and, the methyl substituent is equatorial. Since the dynamic equilibration of isomeric oxazolidines takes place faster than the lactamization step, isomer **104a** is formed as the major isomer in excellent stereoselectivity.

With these first observations we focused on the cyclocondensation reaction between **103** and (*S*)-phenyglycinol (Scheme 3.33).



Scheme 3.33. Cyclocondensation assay of **103** with (*S*)-phenyglycinol.

Once again the cyclocondensation reaction of (*S*)-phenyglycinol with oxo-ester **103** afforded unexpected results. In this case the outcome of the reaction was even more dramatic, since compound **105b** should have been the minor isomer in the absence of the methyl group. This led us to consider the intermediate oxazolidines that would lead to both products (Figure 3.29).

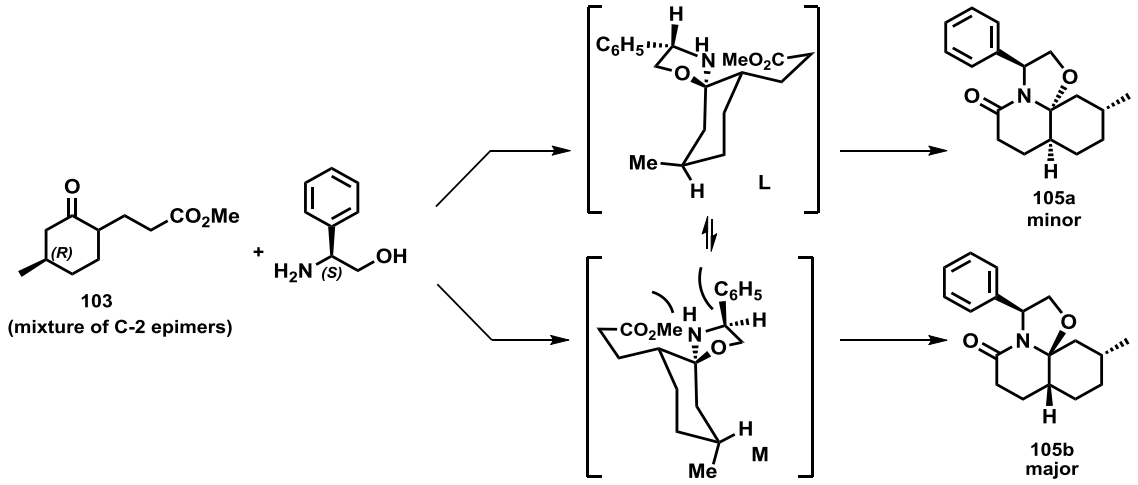
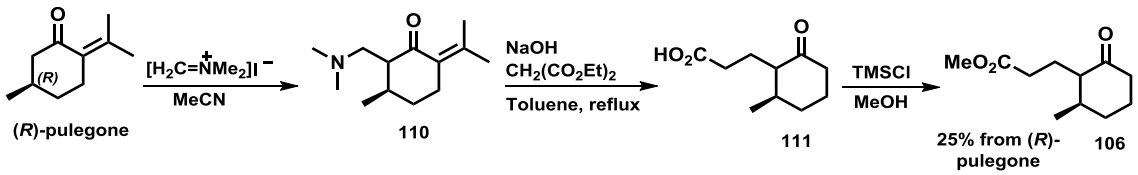


Figure 3.29. Oxazolidines leading to **105a** and **105b**.

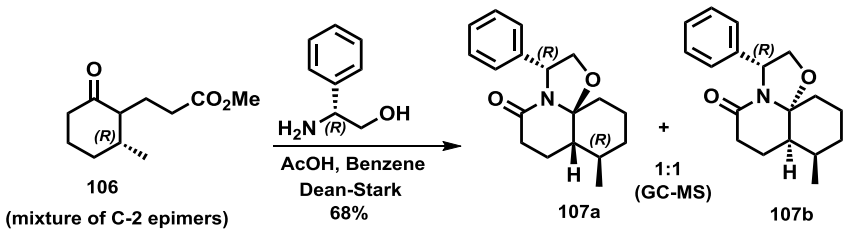
For intermediate oxazolidine **L** even though there is no steric clash between the phenyl group and the propionate chain, the methyl group is axial, and this leads to **105a** being the minor isomer. On the other hand for oxazolidine **M**, leading to the major isomer **105b**, the methyl substituent is equatorial. Both set of experiments, with both enantiomers of the chiral inductor, lead us to draw the conclusion that a substituent in an equatorial disposition at C-5 overcomes the steric repulsions between the phenyl group of the chiral inductor and the carboxylate.

Intrigued by these results, we proceeded to prepare keto-ester **106**. To this end (*R*)-pulegone was allowed to react with the Eschenmoser's iminium salt to give **110**, which by treatment with diethyl malonate under basic conditions afforded oxo-axid **111**. Compound **106** could be prepared in moderate yield (as a 2:1 mixture of C-2 epimers) over three synthetic steps, in sufficient amount to perform our cyclocondensation studies (Scheme 3.34).



Scheme 3.34. Preparation of keto-ester **106**.

With **108** in hand we first performed the cyclocondensation with (*R*)-phenylglycinol (Scheme 3.35) which afforded a 1:1 mixture of isomers **107a** and **107b**, where **107a** should have been the major isomer in the absence of the methyl group.



Scheme 3.35. Cyclocondensation of **106** with (*R*)-phenylglycinol.

To better understand this result, it is required to consider the intermediate oxazolidines as for the previous assays (Figure 3.30).

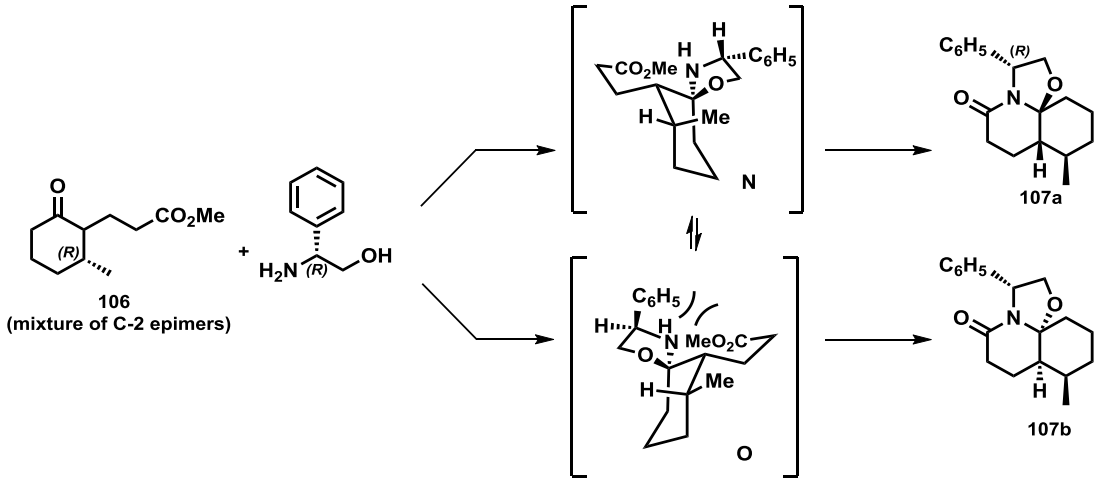
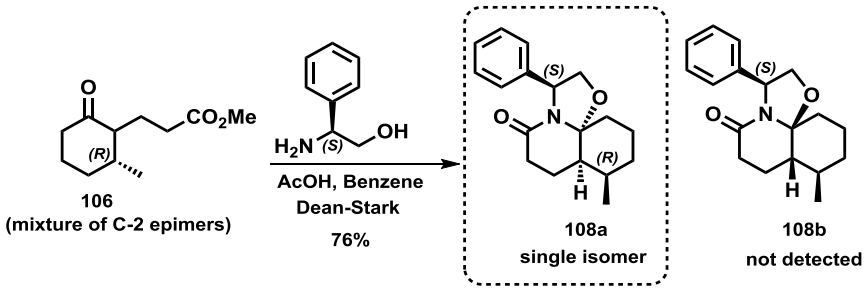


Figure 3.30. Oxazolidines leading to **107a** and **107b**.

Considering the preliminary conclusions drawn from the previous series of assays, the presence of a substituent in an axial disposition seems to be a relevant factor during the lactamization process. For oxazolidine **N** the methyl substituent is axial although the approach of the carboxylate to the nitrogen is less hindered than in the isomeric oxazolidine **O**. However, in this oxazolidine, although the methyl group is equatorial there are gauche interactions with the propionate chain.

A last essay was performed, the reaction of **106** with (*S*)-phenyglycinol which afforded a single isomer **108a** of the resulting tricyclic lactam (Scheme 3.36).



Scheme 3.36. Cyclocondensation of **106** with (*S*)-phenylglycinol.

To rationalize this result and to be able to draw a comparison, one must again consider the intermediate oxazolidines that lead to each of the possible isomers (Figure 3.31).

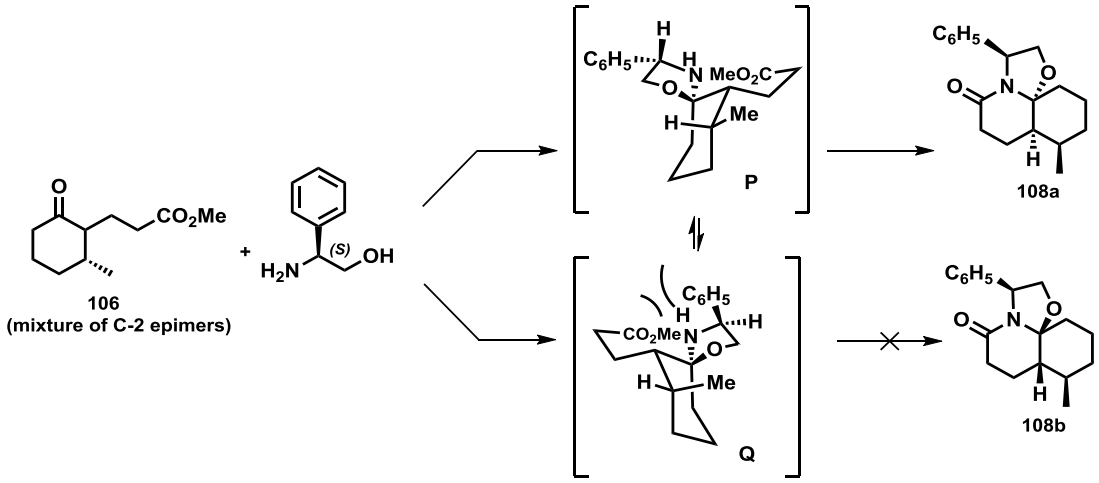
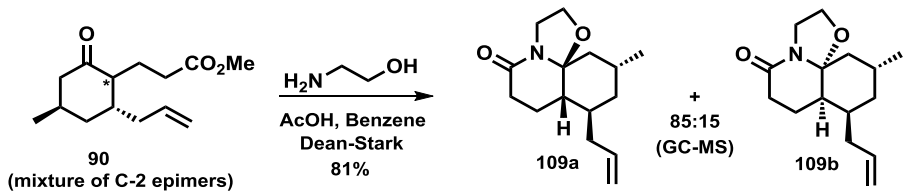


Figure 3.31. Intermediate oxazolidines leading to **108a** and **108b**.

Looking at the above figure, and bearing in mind the previous assays, now it seems straightforward to determine why **108a** is the sole product of this reaction. It is easily observable that oxazolidine **Q** has both hindering factors, the axial substituent plus the repulsive interactions between the propionate and the aromatic ring. Meanwhile, in oxazolidine **P** only gauche interactions of the equatorial methyl substituent are observed.

Finally, in order to investigate the influence of the chiral inductor (*R*)- or (*S*)-phenylglycinol in the stereochemical outcome of the reaction, compound **90** was subjected to the cyclocondensation with 2-aminoethanol (Scheme 3.37).



Scheme 3.37. Cyclocondensation reaction of **92** with 2-aminoethanol.

The reaction took place in good stereoselectivity affording an 85:15 mixture of isomers **109a** and **109b**. Thus, the presence of a phenyl in (*R*)-phenylglycinol has a positive influence in the stereoselectivity of the cyclocondensation reaction of this chiral inductor and keto-ester **90**.

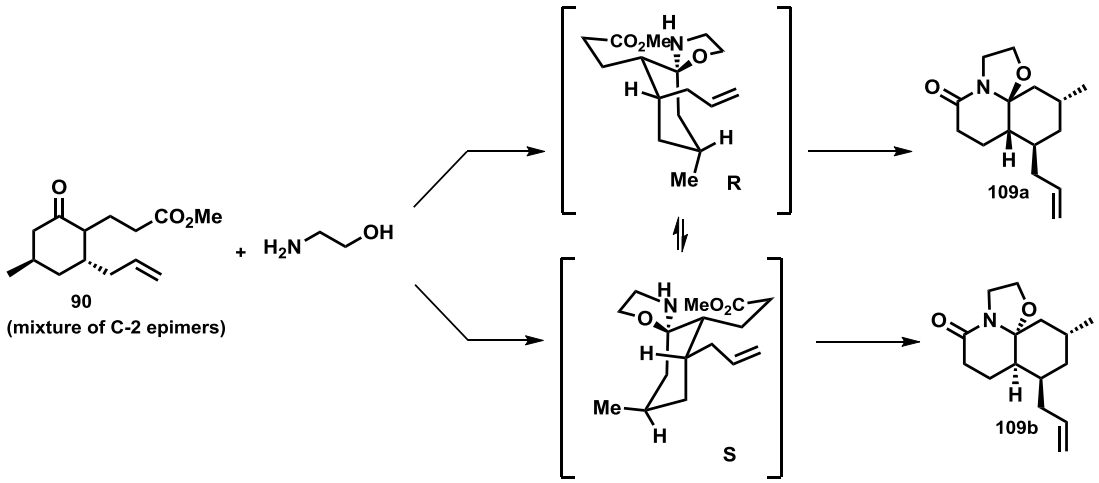


Figure 3.32. Intermediate oxazolidines leading to **109a** and **109b**.

From the above Figure 3.32 it is possible to draw a more general observation which is: even though both intermediate oxazolidines **R** and **S** have a substituent in axial position (the allyl group for **R** and the methyl for **S**) there is an additional subtle interaction. For intermediate **S**, there is a *gauche* destabilizing effect between the allyl substituent and the propionate chain, rendering it disfavoured.

As a summary of the all the above observations it can be said that the stereochemistry of the cyclocondensation reaction is influenced by an intricate balance of factors, such as:

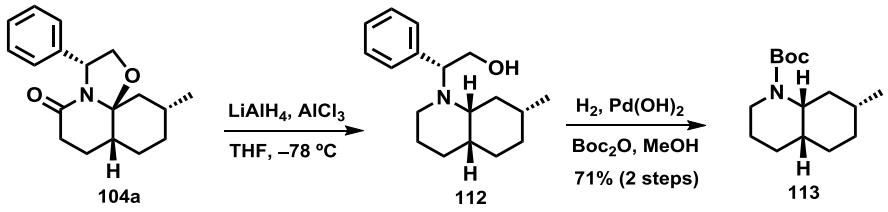
- The approach of the ester group to the nitrogen atom of the oxazolidine ring, either from the same or from the opposite face of the phenyl moiety of the chiral inductor;
- The presence of an axial substituent on the cyclohexane ring;
- *Gauche* interactions between the C-10 (C-5 DHQ numbering) substituent and the propionate side-chain.

Even though these cyclocondensation assays led to some unexpected results, the information they provided will surely be useful for further synthetic endeavours. Additionally, the gathered information allows a better understanding of the underlying factors governing the stereochemical outcome of the cyclocondensation reaction.[112]

3.7.2.4. Preparation of C-5 and C-7 substituted decahydroquinolines

The excellent results observed in the stereoselective formation of tricyclic lactams **104a** and **108a** prompted us to carry out their conversion into the corresponding C-5 and C-7 methyl-substituted *cis*-decahydroquinolines.

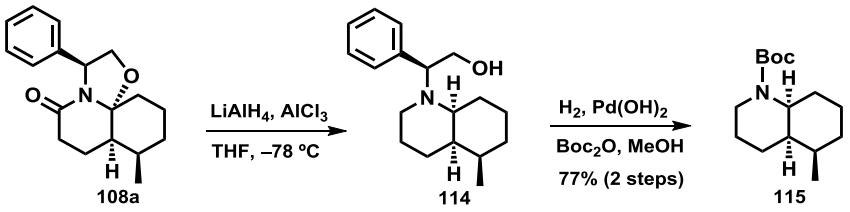
With this idea in mind, **104a** was subjected to the procedure previously described in section **2.7.2.1** of the present Thesis, reduction with AlH_3 followed by debenzylation with *in situ N*-Boc protection (Scheme 3.38).



Scheme 3.38. Preparation of C-7 substituted *cis*-DHQ.

Compound **113** was obtained in 71% overall yield as a single isomer. It should be highlighted that this is the first enantiopure C-7 substituted *cis*-decahydroquinoline prepared in our group from a chiral tricyclic lactam.

Following the same procedure, compound **115** was obtained in very high yield as a single stereoisomer (Scheme 3.39).



Scheme 3.39. Preparation of C-5 substituted *cis*-DHQ.

These results are preliminary and currently studies in our group are being carried out to widen the preparation of these type of C-5 and C-7 substituted *cis*-DHQ.

3.8. Conclusions

This project culminated in a short protecting-group-free enantioselective total synthesis of (–)-cermizine B with complete stereocontrol over the newly formed chiral centres. It also set the stage for the expansion of the methodology to C-7 substituted *cis*-DHQ and to the preparation of C-5 derivatives with the opposite stereochemistry previously reported by our group. Additionally, the investigation of unexpected results of the cyclocondensation reaction led to a better understanding of the structural factors and interactions governing this transformation.

Chapter 4 – Amphibian alkaloids

4. Gephyrotoxin alkaloids

The gephyrotoxin family of alkaloids is one of the four classes of tricyclic amphibian alkaloids, which have very distinct and interesting structures, leading to a variety of biological activities.[11a] It should be noted that, as for many other amphibian alkaloids, the original source of some the above classes of alkaloids is not clear. As an example, coccinellines, which were first isolated from coccinellid beetles, hence their name, were later found in the skin extracts of a frog, *Dendrobates auratus*, native of Panama (Figure 4.1).[11a]

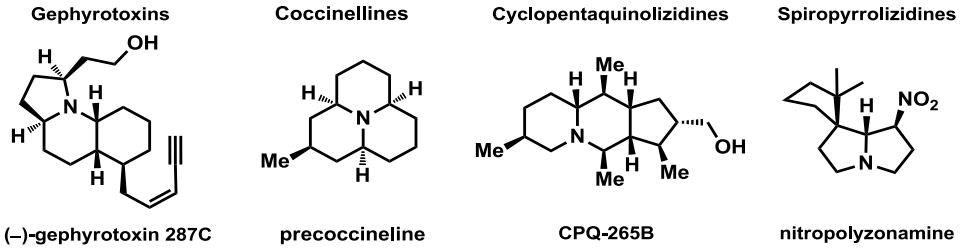


Figure 4.1. The four classes of tricyclic amphibian alkaloids.

Only gephyrotoxins have the *cis*-decahydroquinoline core as the main feature, therefore they will be discussed below in more depth.

4.1. Structure and Isolation

Gephyrotoxins (GTX) are an extremely rare family of alkaloids, with only two members isolated so far (Figure 4.2).

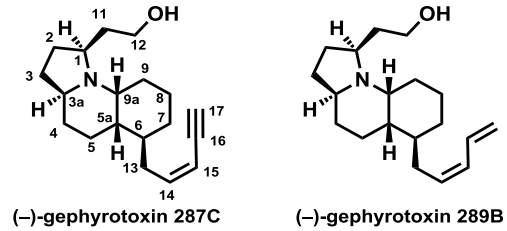


Figure 4.2. The gephyrotoxin alkaloids.

These alkaloids have only been isolated from the skin extracts of *Oophaga histrionica,*[113] a species of frogs native to Colombia with a highly variable alkaloid profile within its population. In addition to the problem of source variability, it took 1100 skin samples to isolate only 50 mg (approx.) of GTX-**287C** with minor amounts of its **289B** congener.[114] Gephyrotoxins were the least abundant compounds from these extracts, where the major alkaloids were histrionicotoxins (HTX). It should be noted that in the original report the structure remained undisclosed, and given that GTX-**287C** had a fragmentation profile

[113] This species used to be taxonomically known as *Dendrobates histrionicus*, but a major taxonomical revision led to a re-classification of several species.
[114] Tokuyama, T.; Uenoyama, K.; Brown, G.; Daly, J. W.; Witkop, B. *Helv. Chim. Acta* **1974**, *57*, 2597-2604.

similar to histrionicotoxin (HTX) it was named HTX-D. A few years later, in 1977, a crystalline sample was obtained, allowing and the X-ray structural elucidation of gephyrotoxin **287C** (Figure 4.3).[115]

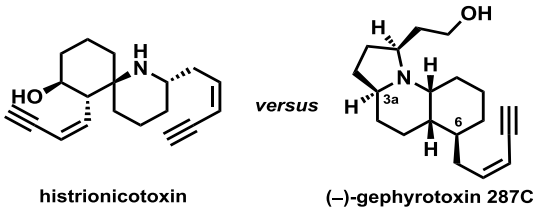


Figure 4.3. Initial structural ambiguity for gephyrotoxin **287C**.

To further illustrate the extreme scarcity of these alkaloids it must be mentioned that for the above study, from 3200 frog skins, only 15 mg of GTX-**287C** and 1 mg of GTX-**289B** were obtained.[115]

Structurally, as can be seen in Figure 4.2, gephyrotoxins are tricyclic alkaloids characterized by a *cis*-decahydroquinoline core fused with a pyrrolidine ring between C-2 (DHQ numbering) and the nitrogen atom. Additionally, the *cis*-DHQ core displays a five-carbon side chain at C-5 bearing a *cis*-enyne moiety in GTX-**287C** and a *cis*-diene in GTX-**289B**. The pyrrolidine ring is substituted with a hydroxyethyl moiety α to the nitrogen atom. As can be seen, the stereochemistry of both the C-2 and C-5 stereocenters (C-3a and C-6 systematic numbering) is *trans* with respect to the ring fusion. It has been proposed that gephyrotoxins might arise from the intramolecular cyclization of 2,5-disubstituted *cis*-DHQs such as *cis*-**219A** or *cis*-**243A** (Figure 4.4).[116]

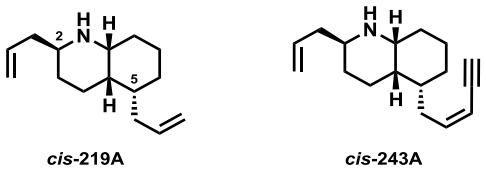


Figure 4.4. Possible precursors for gephyrotoxins.

Given the various structural motifs of gephyrotoxins also present in other classes of amphibian alkaloids (the DHQ core, the indolizidine ring, and the enyne moiety), these compounds were named gephyrotoxins, since *gephyros* means bridge in Greek, and therefore gephyrotoxins "bridge together" several families of alkaloids.

Regarding the naturally occurring configuration of GTX-**287C**, it is worth mentioning that there have been some doubts about the natural enantiomer of this compound. This issue derives from two conflicting data. In the 1977 paper[115] reporting the structural elucidation of GTX-**287C**, although the X-ray crystal structure of the hydrobromide salt

[115] Daly, J. W.; Witkop, B. *Helv. Chim. Acta* **1977**, *60*, 1128-1140.
[116] Daly, J. W.; Garraffo, H. M.; Spande, T. F. in *The Alkaloids*, Cordell, G. A., Ed.; Academic Press: New York, 1993; vol. 43, Chapter 3, 186-288.

was provided, allowing the determination of the absolute and relative stereochemistry (1*S*, 3a*S*, 5a*S*, 6*S*(*Z*), 9a*R*, 10*R*), an optical rotation value was not reported.

Some years later, in the first enantioselective total synthesis of this alkaloid, by Kishi and co-workers,[117] the authors aimed for the synthesis of the reported crystal structure. Starting from an enantiopure material, *L*-pyroglutamic acid, bearing the final 1*S* chiral stereocenter, the authors prepared synthetic GTX-**287C**, which showed a dextrorotatory value ($[\alpha]^{25}_D$ = +50.0º, 1.0, EtOH). Kishi and co-workers then asked for an authentic sample of gephyrotoxin **287C** from the isolation authors, John Daly's group, and measured the rotation value, which surprisingly had the same absolute value but with an opposite sign ($[\alpha]^{25}_D$ = –51.5º, 1.0, EtOH). This result led to the proposal that the natural structure for the alkaloid should be revised to the corresponding enantiomer (Figure 4.5).

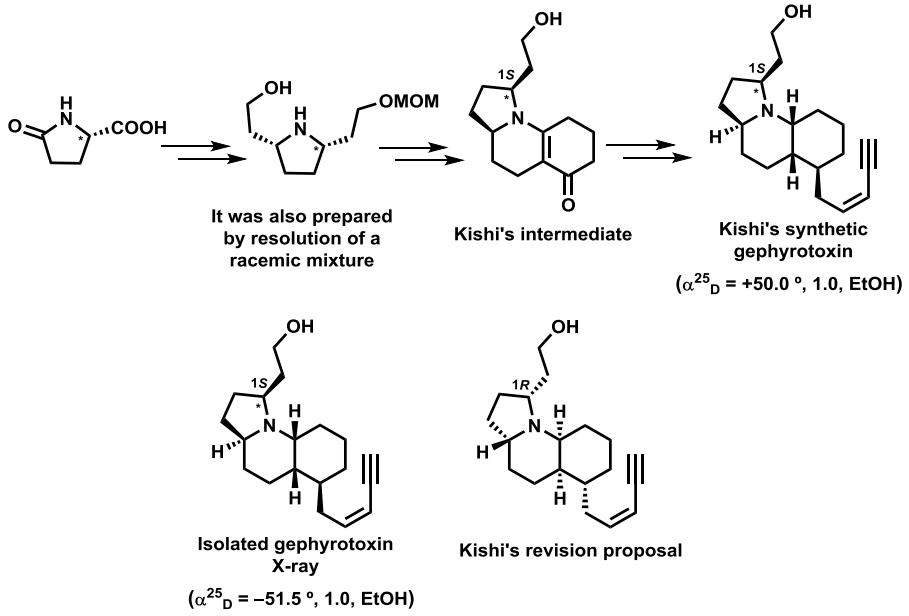


Figure 4.5. Kishi's structural revision proposal.

Nevertheless, it should be pointed out that Smith and co-workers have recently reported an enantioselective synthesis of (−)-gephyrotoxin **287C**[118] starting from *L*-pyroglutaminol, which predetermines the 1*S* final chiral center, as the chirality source, and obtained a levorotatory value for the alkaloid ($[\alpha]^{25}_D$ = − 52.3º, 1.0, EtOH). The 1*S* configuration of (−)-gephyrotoxin **287C** was again confirmed by X-ray analysis, thus supporting the claims in the original isolation paper. Moreover, subsequent studies from the Nemoto group, with their enantioselective total synthesis of (+)-gephyrotoxin **287C**,[119] lends strength to the absolute configuration proposed by Smith and Daly.

[117] Fujimoto, R.; Kishi, Y. *Tetrahedron Lett.* **1981**, *22*, 4197-4198.
[118] Chu, S.; Wallace, S.; Smith, M. D. *Angew. Chem. Int. Ed.* **2014**, *53*, 13826-13829.
[119] Nemoto, T.; Yamaguchi, M.; Kakugawa, K, Harada, S.; Hamada, Y. *Adv. Synth. Catal.* **2015**, *357*, 2547-2555.

4.2. Biological properties

A vast amount of amphibian alkaloids are poisonous, eliciting complex effects on the nervous system. Gephyrotoxins are not an exception, although as noted by Daly the term toxin is unfortunate given the relative non-toxicity of these compounds. Gephyrotoxins are moderate blockers of nicotinic acetylcholine receptor channels, GTX-**289B** being slightly more active.[120] Additionally, it was shown that GTX-**287C** causes complex effects in the neuromuscular junctions in a guinea-pig model.[6] The relative non-toxicity of these compounds, together with their biological activities, makes them attractive lead compounds for neurological diseases, such as Parkinson's disease, or as anaesthetics.

4.3. Previous synthesis of gephyrotoxins alkaloids

Due to the scarcity of gephyrotoxins in nature and their interesting biological properties, several groups have tackled their synthesis. However, almost all synthetic efforts have targeted a formal synthesis or the racemate.[121] As in the previous sections, only enantioselective total syntheses will be discussed, and to date these have only been reported for GTX-**287C**.

4.3.1. Total synthesis of gephyrotoxin 287C by Kishi

The first enantioselective total synthesis of gephyrotoxin **287C** was accomplished by Kishi and co-workers in 1981.[117] This synthesis was an expansion of Kishi's previous total synthesis of the racemic alkaloid.[121a] It should be noted that no reaction yields were provided. Kishi's approach relied on the use of commercially available *L*-pyroglutamic acid **78** as the source of chirality.

The synthesis began by converting the carboxylic acid in **78** to a nitrile, introducing an additional carbon in a three-step sequence. The lactam in **79** was converted into the corresponding thiolactam, which underwent an Eschenmoser's sulphide contraction to afford, after hydrogenation of the resulting vinyl ester, pyrrolidine **80** as a 2.3:1 mixture of *cis*:*trans* isomers, of which only the *cis* isomer was further advanced. Compound **80** was elaborated into the mono-protected diol **82** using a series of non-C–C bond formation reactions, *via* urethane **81** (Scheme 4.1).

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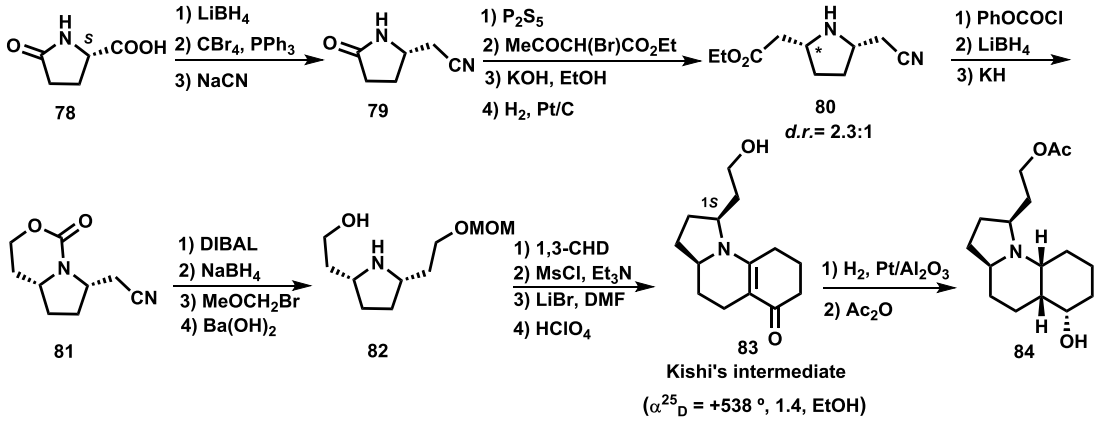
[120] (a) Souccar, C.; Varanda, W. A.; Daly, J. W.; Albuquerque, E. X. *Molec. Pharmacol.* **1984**, *25*, 384-394. (b) Souccar, C.; Varanda, W. A.; Daly, J. W.; Albuquerque, E. X. *Molec. Pharmacol.* **1984**, *25*, 395-400. (c) Aronstam, R. S.; Daly, J. W.; Spande, T. F.; Narayanan, T. K.; Albuquerque, E. X. *Neurochem. Res.* **1986**, *11*, 1227-1240.

[121] Racemic: (a) Fujimoto, R.; Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7154-7156. (b) Hart, D. J.; Kanai, K.-i. *J. Am. Chem. Soc.* **1983**, *105*, 1255-1263. (c) Overman, L. E.; Lesuisse, D.; Hashimoto, M. *J. Am. Chem. Soc.* **1983**, *105*, 5373-5379. (d) Shirokane, K.; Wada, T.; Yoritate, M.; Minamikawa, R.; Takayama, N.; Sato, T.; Chida, N. *Angew. Chem. Int. Ed.* **2014**, *53*, 512-516. (e) Shirokane, K.; Tanaka, Y.; Yoritate, M.; Minamikawa, R.; Takayama, N.; Sato, T.; Chida, N. *Bull. Chem. Soc. Jpn.* **2015**, *88*, 522-537. Formal: (e) Hart, D. J. *J. Org. Chem.* **1981**, *46*, 3576-3578. (f) Ito, Y.; Nakatsuka, M.; Saegusa, T. *Tetrahedron Lett.* **1983**, *24*, 2881-2884. (g) Pearson, W. H.; Fang, W-k. *J. Org. Chem.* **2000**, *65*, 7158-7174. (h) Wei, L.-L.; Hsung, R. P.; Sklenicka, H. M.; Gerasyuto, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 1516-1518. (i) Santarem, M.; Vanucci-Bacqué, C.; Lhommet, G. *J. Org. Chem.* **2008**, *73*, 6466-6469. (j) Miao, L.; Shu, H.; Noble, A. R.; Fournet, S. P.; Stevens, E. D.; Trudell, M. L. *ARKIVOC* **2010**, *iv*, 6-14. (k) Pichette, S.; Winter, D. K.; Lessard, J.; Spino, C. *J. Org. Chem.* **2013**, *78*, 12532-12544. (l) Yang, Z-P.; Wu, Q.-F.; Shao, W.; You, S.-L. *J. Am. Chem. Soc.* **2015**, *137*, 15899-15906.

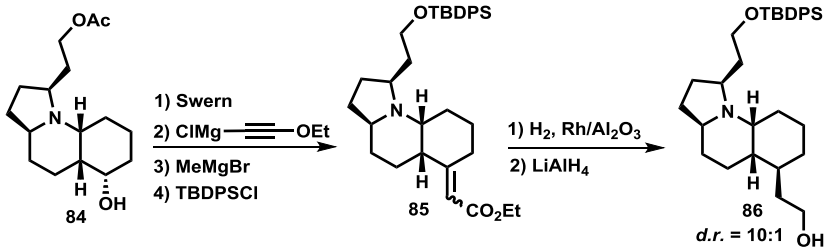


Scheme 4.1. Assembly of the tricyclic core by Kishi's group.

Formation of the enamine of **82** with 1,3-cyclohexanedione, followed by conversion of the unprotected hydroxy group to a leaving group and intramolecular alkylative cyclization afforded the so-called Kishi's intermediate **83**. Subsequently, this intermediate has been targeted for several enantioselective formal syntheses of GTX-**287C**,[121e-l] and its 1*S* configuration was confirmed by X-ray structural analysis.[121j]

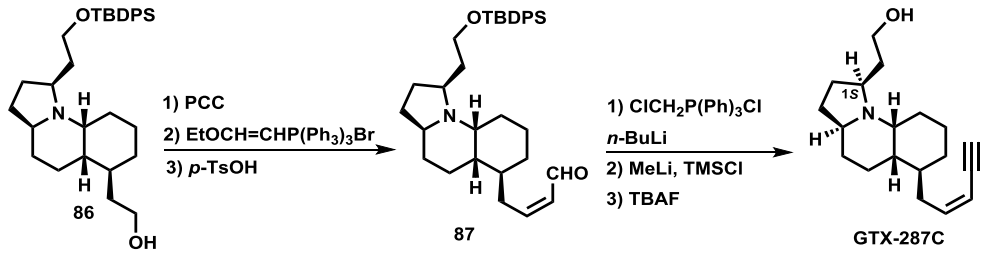
With compound **83** in hand, the presence of the free hydroxy group was crucial to direct the hydrogenation process of the enone, in order to obtain the desired *cis* configuration. Catalytic hydrogenation followed by acetylation of the primary alcohol led to the tricyclic alcohol *cis*-DHQ **84**.

The authors then focused on the introduction of the lateral chain on the carbocyclic ring. To achieve the desired stereochemistry at the DHQ C-5 position and a suitable function to incorporate the enyne moiety, alcohol **84** was oxidized to a ketone, which was reacted with a Grignard reagent to afford, after protecting group changes, unsaturated ester **85**. After considerable optimization efforts, the authors found that hydrogenation of **85** in the presence of Rh/Al_2O_3, followed by ester reduction, afforded compound **86** in a high diastereomeric ratio. It should be noted that a sterically encumbering protecting group on the hydroxy group was required to achieve good levels of selectivity (Scheme 4.2).



Scheme 4.2. Achieving the stereochemistry at C-5.

Having introduced a functionalized substituent at the C-5 position of the DHQ system with the desired stereochemistry, Kishi's group was almost at the end of the synthesis. Alcohol **86** was converted to enal **87** in a three-step sequence. Compound **87** was unstable and was immediately subjected to Corey's two-step methodology to prepare *cis*-enynes from *cis*-enals (a modification of the Corey-Fuchs reaction). A final deprotection afforded gephyrotoxin **287C** (Scheme 4.3).

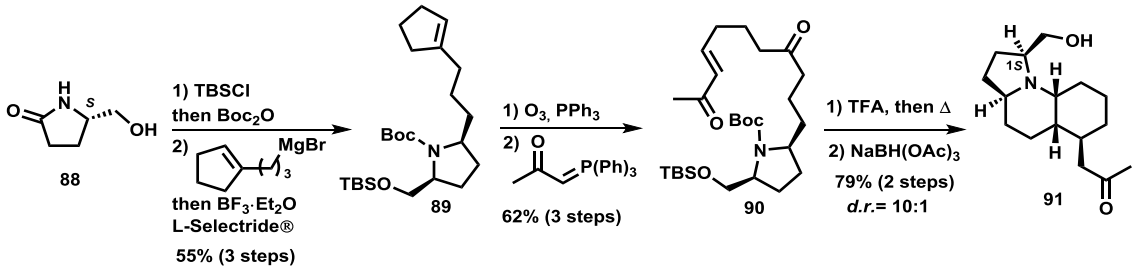


Scheme 4.3. Kishi's first enantioselective total synthesis of GTX-**287C**.

Kishi's approach afforded GTX-**287C** in 32 synthetic steps from (*L*)-pyroglutamic acid. The stereogenic center in the starting material secures the absolute (*S*) configuration of the C-1 position of the synthesized gephyrotoxin. However, the authors reported a sign of the optical rotation ($[\alpha]^{25}_{D}$ = +50.0°, 1.0, EtOH) contrary to that of the isolated gephyrotoxin, whose absolute configuration had been determined to be 1*S*, 3a*S*, 5a*S*, 6*S*(*Z*), 9a*R*, 10*R*, by X-ray crystallographic analysis.
Unfortunately, the publication does not allow an overall yield to be determined to evaluate the efficiency of the synthesis. Moreover, with the lack of experimental information in the original report, it would be very difficult to reproduce the original synthesis.

4.3.2. Total synthesis of (–)-gephyrotoxin 287C by Smith

It took more than 30 years until another enantioselective total synthesis of gephyrotoxin was reported by the Smith group in 2014.[118] The key feature of this approach was a cascade reaction, a trademark of the author's research group, to assemble the tricyclic nucleus of the alkaloid. Similarly to Kishi's approach, the synthesis began with (*L*)-pyroglutaminol **88** as the source of chirality, which determines the (*S*) configuration of the C-1 position of the tricyclic natural product (Scheme 4.4).

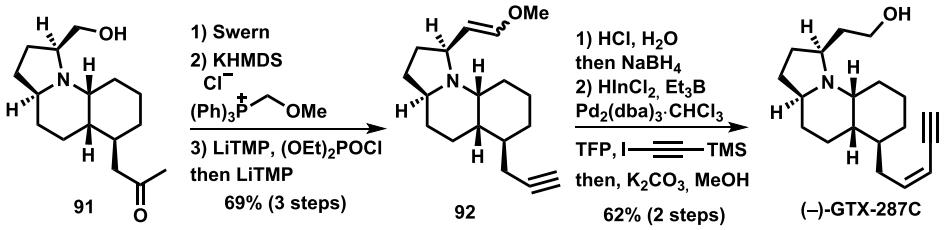


Scheme 4.4. Cascade assembly of the tricyclic core.

After protection of the alcohol and the nitrogen in **88**, the intermediate compound was reacted with a cyclopentenyl-containing Grignard reagent, followed by *in situ* reduction of the resulting *N*-acyliminium ion with L-Selectride® in the presence of $BF_3 \cdot Et_2O$. This transformation afforded pyrrolidine **89** as a single *cis* isomer. Taking advantage of the cyclopentene ring in **89** as a masked dicarbonyl moiety, an ozonolysis followed by olefination of the pending aldehyde led to the cascade cyclization precursor **90**. Treatment of compound **90** with TFA brought about the bis-deprotection and elicited the condensation between the pyrrolidine nitrogen and the ketone moiety, followed by an intramolecular Michael-addition of the resulting enamine to the enone function.

Intramolecular hydride delivery oriented by the free hydroxymethyl function afforded tricycle **91** in high overall yield and excellent diastereoselectivity.

Having assembled the GTX core, the authors focused their efforts on the introduction of the *cis*-enyne moiety and the one-carbon homologation of the hydroxymethyl side-chain (Scheme 4.5).



Scheme 4.5. Smith's final steps towards (–)-GTX-**287C**.

Oxidation of the hydroxy group to the corresponding aldehyde, followed by a Wittig reaction, introduced the C-1 enol ether moiety. Kinetic deprotonation of the ketone function, with subsequent enolate trapping and elimination, afforded alkyne **92**. Hydrolysis of the enol ether, followed by reduction of the resulting aldehyde, led to the hydroxyethyl appendage of the pyrrolidine ring. Sonogashira cross-coupling of the preformed organoindium species, taking advantage of the alkyne moiety in **92**, followed by deprotection, afforded (–)-GTX-**287C**. The absolute configuration of (−)-GTX-**287C**, in accordance with that reported for the natural (−)-GTX-**287C**, was unambiguously confirmed by the X-ray crystallographic analysis.

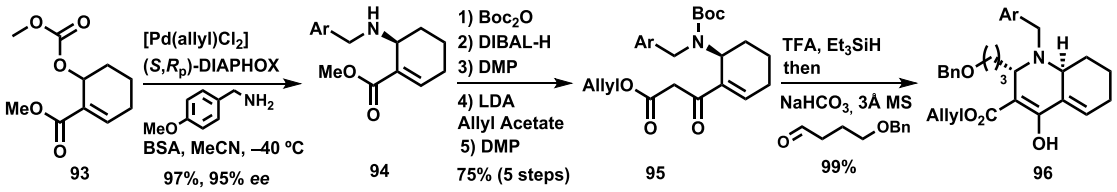
To date, Smith's group's enantioselective synthesis is the most efficient and shortest route to prepare this alkaloid, in nine synthetic steps and 14% overall yield. The only drawback of this synthesis is, as the authors note, the necessity to perform an inefficient one-carbon homologation to introduce the required hydroxyethyl moiety on the pyrrolidine ring.

4.3.3. The Nemoto-Hamada total synthesis of (+)-gephyrotoxin 287C

The last synthetic efforts towards enantiopure gephyrotoxins, before our own, were reported by Nemoto and Hamada from Japan in 2015.[119] The authors' strategy was based on a Pd-catalyzed allylic asymmetric amination, a variant of the Tsuji-Trost reaction, to generate the first stereocenter. This methodology had been previously developed and applied by the authors for the enantioselective total synthesis of other decahydroquinoline alkaloids.[122]

The synthesis began with the allylic asymmetric amination of carbonate **93**, under the conditions developed by the group, to afford chiral cyclic allyl amine **94**. This compound was then elaborated, *via* a five-step sequence, into dicarbonylic compound **95**, which was envisioned as the precursor for the intramolecular Mannich cyclization (Scheme 4.6).

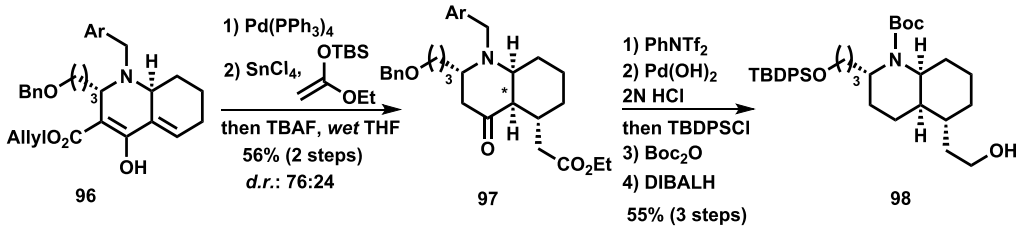
[122] Kakugawa, K.; Nemoto, T.; Kohno, Y.; Hamada, Y. *Synthesis*, **2011**, 2540-2548.



Scheme 4.6. Assembly of the functionalized DHQ core by Hamada.

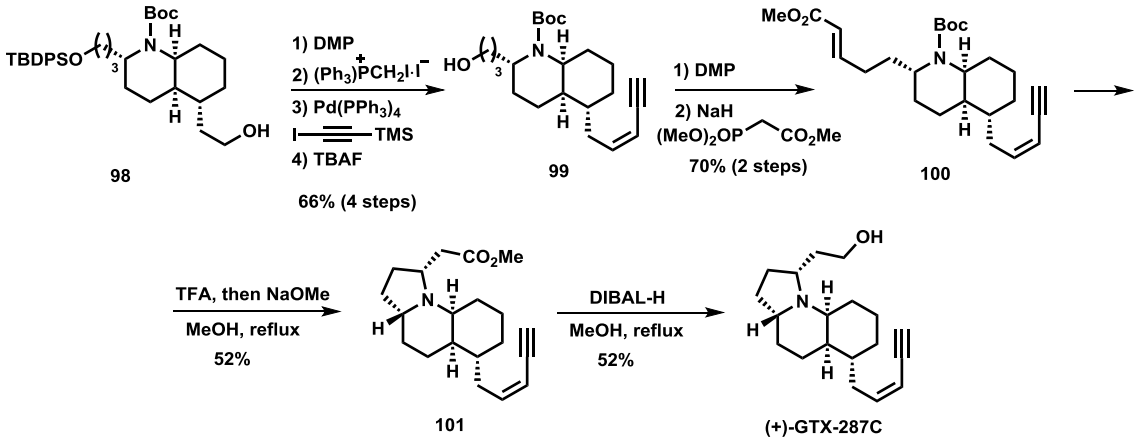
Deprotection of the Boc group, followed by condensation with the suitable aldehyde, brought about the diastereoselective Mannich cyclisation in quantitative yield and near perfect stereoselectivity, affording DHQ **96**.

Treatment of the allylic ester **96** with a Pd catalyst, followed by decarboxylation of the resulting β-keto-acid, afforded an enone, which was subjected to a diastereoselective conjugate addition with an appropriate ketene silyl acetal. A subsequent stereoselective protonation of the resulting enolate in *wet* THF afforded *cis*-DHQ **97** as the major isomer. At this point, the authors focused their efforts on the manipulation of the DHQ core for the elaboration of the C-2 and C-5 substituents. To this end, the ketone moiety in **97** was converted to the corresponding vinyl triflate and removed in the presence of Pearlman's catalyst, which also brought about the debenzylation of the nitrogen and the oxygen atoms. Protecting group introduction, and reduction of the ester to the alcohol, afforded intermediate **98** (Scheme 4.7).



Scheme 4.7. Establishment of the *cis* ring-fusion stereochemistry and the C-5 substituent.

The hydroxy group in **98** was oxidized to an aldehyde, which was subjected to the Stork-Zhao protocol to introduce the required *Z*-iodo alkene. A subsequent Sonogashira-coupling followed by desilylation afforded compound **99** in good overall yield. From compound **99** the authors needed to assemble the pyrrolidine ring to complete the total synthesis. To this end, the primary hydroxy group was oxidized and the resulting aldehyde was subjected to a HWE-olefination, affording unsaturated ester **100**. After *N*-Boc deprotection, treatment with base accomplished the pyrrolidine ring-closure, by an *aza*-Michael cyclization, leading to the cyclized product **101** in moderate yield. A final reduction of the ester moiety afforded (+)-GTX-**287C** in 20 steps and 3.2% overall yield (Scheme 4.8).



Scheme 4.8. Nemoto-Hamada's final steps for (+)-gephyrotoxin **287C**.

4.4. Objectives

Due to the interest of our research group in the synthesis of *cis*-decahydroquinoline alkaloids isolated from amphibian sources, and given their deceptively simple 2,5-disubstitution pattern and biological potential, we decided to develop our own enantioselective synthesis of gephyrotoxin **287C**. With the experience acquired in previous work[45,46] and the success of the lepadin alkaloid syntheses, we were confident of achieving a good result. Additionally, to provide access to various 2,5-disubstituted *cis*-DHQ alkaloids, we planned to study the control of the stereochemistry of the C-2 substituent to increase the scope of the methodology (Figure 4.6).

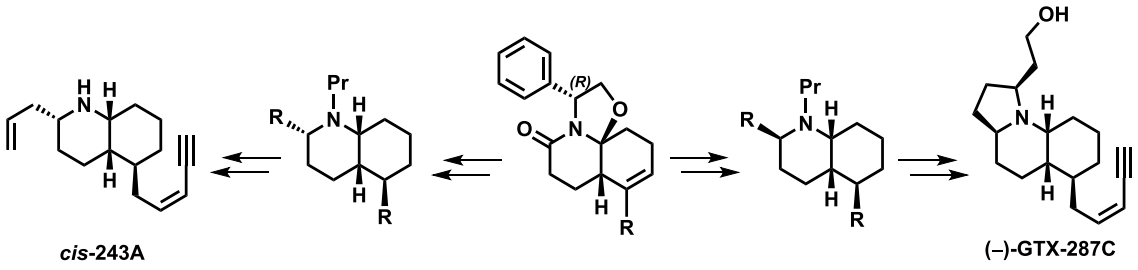


Figure 4.6. Stereodivergent access to amphibian alkaloids.

To achieve our goals, we needed to study:

1. The control of the stereochemistry at C-2.
2. The introduction of the enyne moiety with *Z*-selectivity.
3. The stereoselective ring-closure of the pyrrolidine ring.

4.5. Synthetic strategy

Our synthetic strategy was based on the successful previous studies developed for the synthesis of lepadins, where we performed the stereoselective removal of the chiral inductor and the introduction of substituents at the DHQ C-2 position taking advantage of the lactam moiety, leading to a 2-substituted *cis*-octahydroquinolines **I**. Reduction of the C−C double bond of enecarbamate **I**, either under stereoelectronic control, *via* an *N*-acyl iminium intermediate, or under kinetic control, by catalytic hydrogenation, would open diastereodivergent routes to H-2/H-8a *cis* or *trans* isomers. Additionally, a suitable functionalized two-carbon side chain at C-5 had to be incorporated to allow the introduction of the enyne moiety. (Figure 4.7).

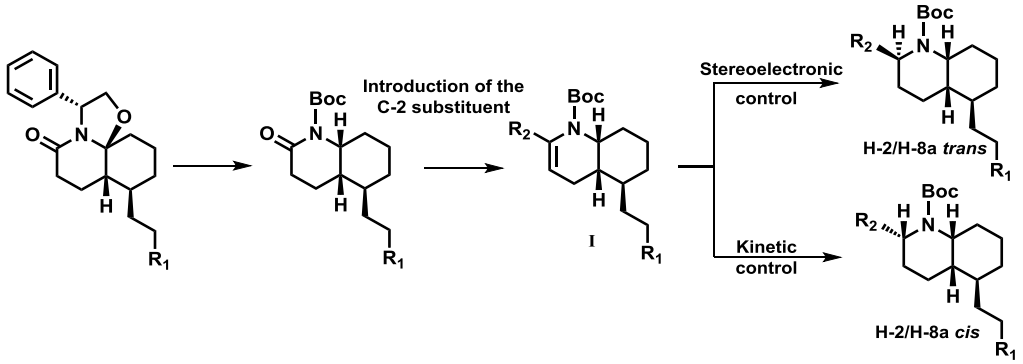
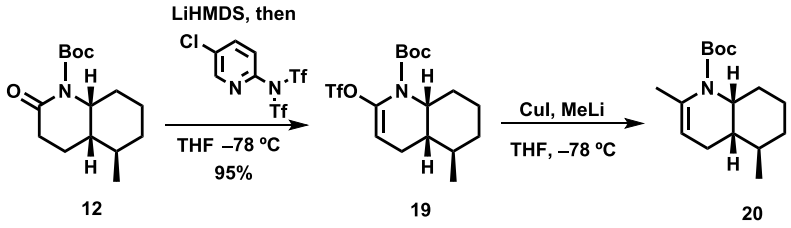


Figure 4.7. Synthetic strategy for 2,5-disubstituted *cis*-DHQ alkaloids.

4.6. Model studies to control the stereochemistry at C-2

Building on the model studies developed for the lepadin alkaloids, we decided to use the same synthetic sequence to convert compound **12** to **20** and attempt different protocols to reduce the C−C double bond (Scheme 4.9).



Scheme 4.9. Preparation of model enecarbamate **20**.

As depicted in Figure 4.7, we planned to use subtle substrate effects to achieve either a *trans* or *cis* H-2/H-8a relationship. To obtain the *trans* relationship, we would rely on the generation of an *N*-acyl iminium ion species by treatment with a strong acid, and its subsequent reduction with a hydride source. The presence of the Boc group exerts a strong effect on the C-8/C-8a bond, forcing an axial disposition of this sigma bond, strongly displacing the conformational equilibrium towards conformation **K**. Thus, the hydride transfer would occur under stereoelectronic control, from the bottom *face* of **K**,

via a chair-like transition state. An alternative attack from the top *face* would proceed *via* a disfavoured boat-like transition state (Figure 4.8).[123]

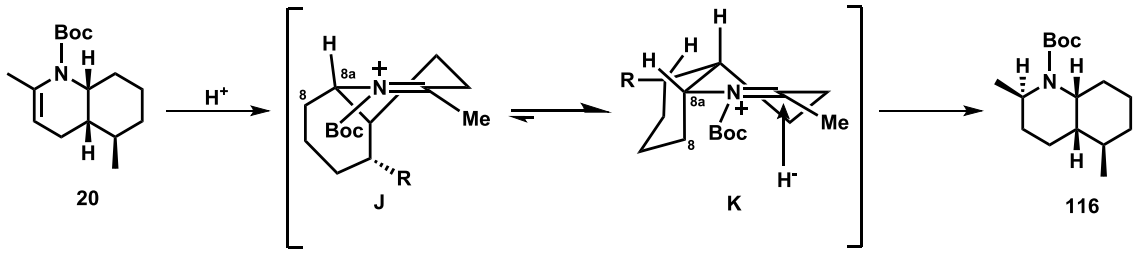
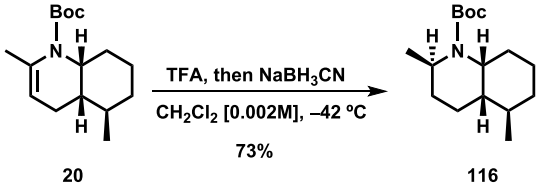


Figure 4.8. Conformational constraints for the *N*-acyl iminium ion reduction.

With this idea in mind, compound **20** was treated with TFA under high dilution conditions in CH_2Cl_2, and then with $NaBH_3CN$ at low temperature.[124] We were very pleased to find that under these conditions compound **116** was obtained in high yield as a single diastereoisomer. 1D and 2D NOESY experiments confirmed the obtained stereochemistry. This result would allow us to prepare 2,5-disubstituted alkaloids with a *trans* H-2/H-8a relationship, such as (+)-gephyrotoxin **287C** (Scheme 4.10).



Scheme 4.10. *N*-acyl iminium ion reduction of **20**.

To gain access to the alternative *cis* H-2/H-8a stereochemical relationship, we thought of performing the catalytic hydrogenation of **20**. This would lead to the *cis* relative configuration since the hydrogenation would take place from the least hindered face of the double bond, *cis* with respect to the ring-fusion hydrogens of the DHQ moiety (Figure 4.9).

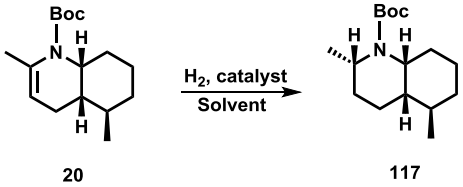


Figure 4.9. Expected catalytic hydrogenation of **20**.

A variety of metal catalysts (Pt/C, PtO_2, Pd/C, $Pd(OH)_2$, $Pd/BaSO_4$, Rh/C, Rh/Al_2O_3, $RhCl(PPh_3)_3$) and solvents (EtOAc, MeOH, *i*-PrOH) were screened, but unfortunately there was no reaction or decomposition to compound **23** occurred (Figure 4.10).

[123] (a) Deslongchamps, P. in *Stereoelectronic Effects in Organic Synthesis;* Pergamon Press: Exeter 1983. (b) Comins, D. L.; Weglarz, M. A. *J. Org. Chem.* **1991**, *56*, 2506-2512.
[124] Yu, S.; Pu, X.; Cheng, T.; Wang, R.; Ma, D. *Org. Lett.* **2006**, *8*, 3179-3182.

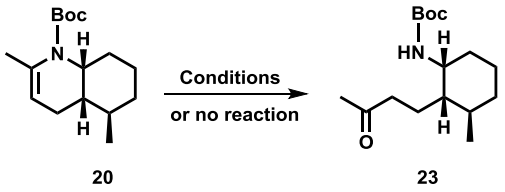


Figure 4.10. Unsuccessful hydrogenation of **20**.

This was quite disappointing for our plans, but with the successful preparation of **116**, we decided to pursue the synthesis of gephyrotoxin and put on hold our efforts to obtain the *cis* H-2/H-8a stereochemical relationship.

4.7. Total synthesis of (+)-gephyrotoxin 287C

To accomplish the enantioselective synthesis of our target molecule, we used the (*S*) enantiomer of phenylglycinol, which would lead to (+)-gephyrotoxin **287C**. To obtain the required tricyclic lactam, we would need to prepare a cyclohexenone-derived δ-keto-ester bearing a two-carbon chain, ideally a hydroxy group due to its versatility, that could be manipulated to introduce the enyne moiety. Regarding the elaboration of the pyrrolidine ring, we envisioned that an *aza*-Michael cyclization could be an efficient strategy, after introduction of the appropriate C-2 substituent with the required stereochemistry (Figure 4.11).

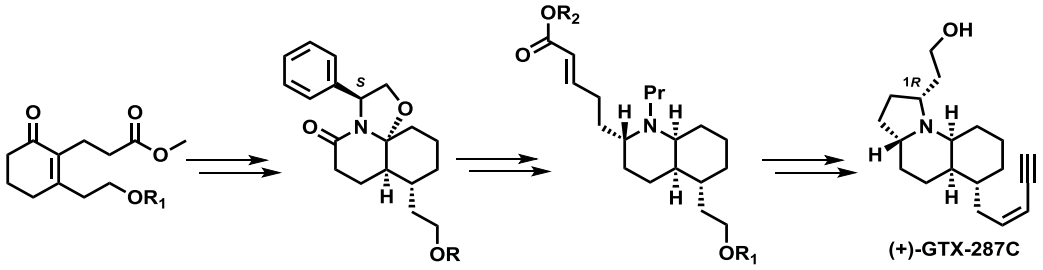
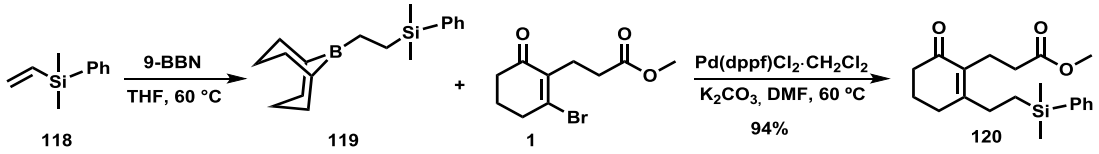


Figure 4.11. Synthetic strategy for (+)-gephyrotoxin **287C**.

4.7.1. Preparation of the chiral tricyclic lactam scaffold

This part of the PhD thesis was carried out in collaboration with Miriam Piccichè, a PhD student from our research group.

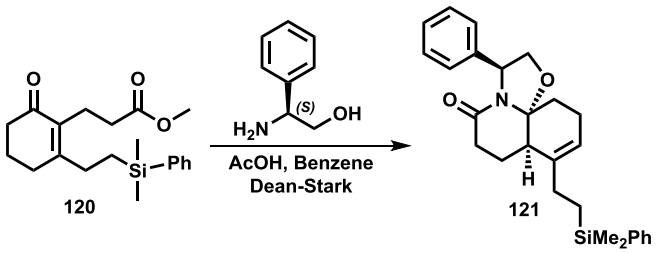
Our initial approach was to prepare a δ-keto-ester bearing a silyl moiety that could be further converted into the desired alcohol, avoiding redundant protecting-group chemistry. To this end, taking advantage of our bromo-enone derivative **1**, we performed a *B*-alkyl Suzuki-Miyaura cross-coupling with the commercially available vinyl silane **118** (Scheme 4.11).



Scheme 4.11. Preparation of keto-ester **120**.

The target compound **120** was obtained in high yield, taking advantage of the one-pot procedure previously optimised in our group,[45] by generating the alkyl borane **119,** followed by Suzuki coupling with the bromo-enone **1**.

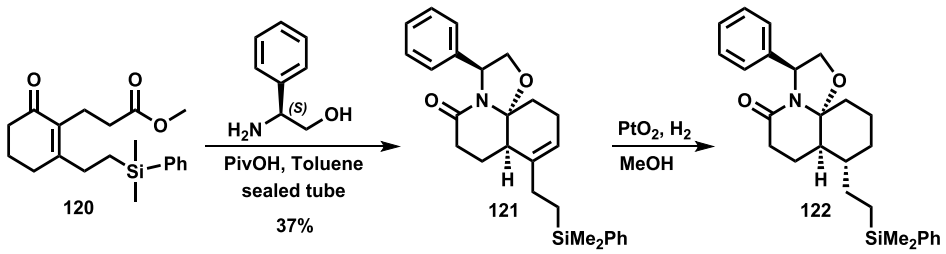
With compound **120** in hand, we performed the cyclocondensation reaction with (*S*)-phenylglycinol under the standard conditions (Scheme 4.12). However, conversion of **120** to our chiral scaffold **121** was very slow. Moreover, every 24h (*S*)-phenylglycinol had to be added to drive the reaction forward, and after 3 days the reaction mixture was a complex mixture of products.



Scheme 4.12. Cyclocondensation reaction between **120** and (*S*)-phenylglycinol.

We attempted to improve the cyclocondensation reaction by performing the following modifications: changing the solvent (from benzene to toluene); using the carboxylic acid derived from **120** as the substrate of the reaction; switching acetic acid to pivalic acid; using drying agents ($MgSO_4$, 4 Å molecular sieves); running the reaction in a sealed tube to increase the pressure. Most of these attempts did not lead to an improved result.

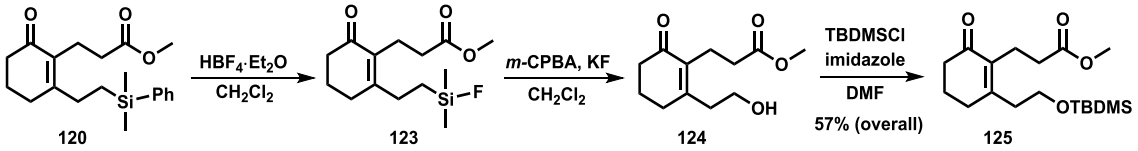
The only exception was when the reaction was performed in a sealed tube, the solvent was changed to toluene, and pivalic acid was used. Under these conditions, we observed a faster conversion and cleaner reaction, albeit with a significant mass loss after chromatographic separation. For this reason, we tried to directly hydrogenate the crude mixture to obtain **122** (Scheme 4.13).



Scheme 4.13. Attempts to synthesize **122**.

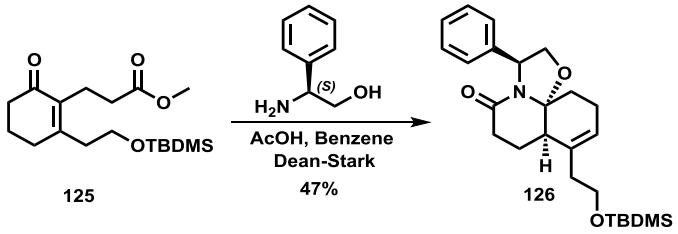
This proved also unsatisfactory since the hydrogenation was sluggish and we could not control the selective hydrogenation of the C−C double bond, always obtaining by-products resulting from the hydrogenation of the phenyl ring either from the chiral inductor or from the silane group.

Being unable to solve the above issues in an efficient manner, we decided to revise our strategy and perform the Tamao-Fleming oxidation[125] of the silane moiety in **120**, converting it to the corresponding alcohol. In this way, we believed that the problems found during the cyclocondensation reaction and the subsequent catalytic hydrogenation would be avoided. To this end, compound **120** was converted to the silyl fluoride **123**, which was subsequently oxidized to alcohol **124**. At this point, and considering the following synthetic steps, the hydroxy group was protected as the silyl ether **125**. Compound **125** was obtained in good overall yield after three steps, without requiring purification of the intermediates (Scheme 4.14).



Scheme 4.14. Oxidation of keto-ester **120**.

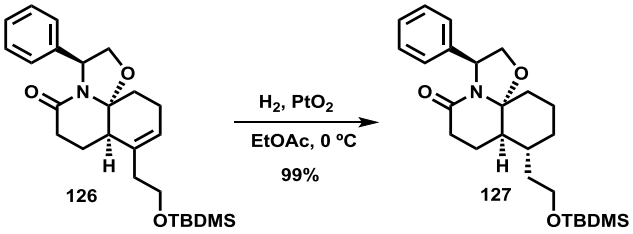
We then carried out the cyclocondensation reaction of **125** with (*S*)-phenylglycinol, which afforded unsaturated chiral lactam **126**. Several conditions were tried in order to optimize the reaction, and the best results are shown below. Even though the yield was moderate, we were able to prepare our chiral scaffold, avoiding the previously encountered issues (Scheme 4.15).



Scheme 4.15. Cyclocondensation reaction with (*S*)-phenylglycinol.

To introduce the C-8 (C-5 DHQ numbering) stereocenter, we then performed the catalytic hydrogenation reaction of compound **126**. The conditions shown in Scheme 4.16 were modified from the standard conditions previously used for the hydrogenation of compound **7** (section 2.7.1.2). These modifications, solvent (from MeOH to EtOAc) and temperature (from room temperature to 0 ºC), were introduced to control the reactivity of the Adam's catalyst because, under standard conditions, compounds resulting from the hydrogenation of the phenyl group and from the deprotection of the TBDMS group were detected in variable amounts. Nevertheless, with the modified hydrogenation protocol, compound **127** was obtained in nearly quantitative yield as a single C-8 stereoisomer (Scheme 4.16).

[125] Jones, G. R. *Tetrahedron* **1996**, *52*, 7599-7662.



Scheme 4.16. Catalytic hydrogenation of tricyclic lactam **127**.

4.7.2. Stereoselective removal of the chiral inductor and introduction of the C-2 substituent

With our chiral scaffold **127** in hand, we needed to stereoselectively introduce the C-2 substituent. To this end, we first had to stereoselectively remove the chiral inductor, using the procedure previously reported by our group,[45a] and secondly introduce the C-2 substituent following the vinyl triflate approach used for the introduction of the C-2 and C-3 substituents in the synthesis of lepadin alkaloids. The main difference was that we would take advantage of the enecarbamate generated after C-2 functionalization to define the stereochemistry at this position, based on our experience in the model studies described in section 4.6 (Figure 4.12).

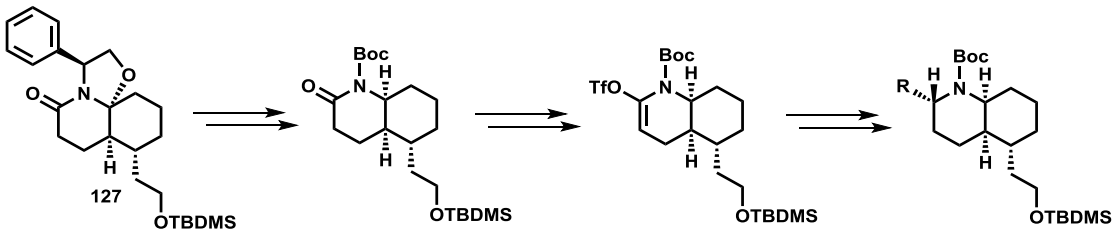
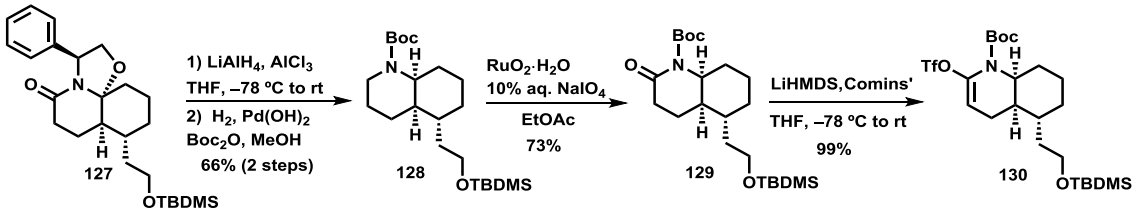


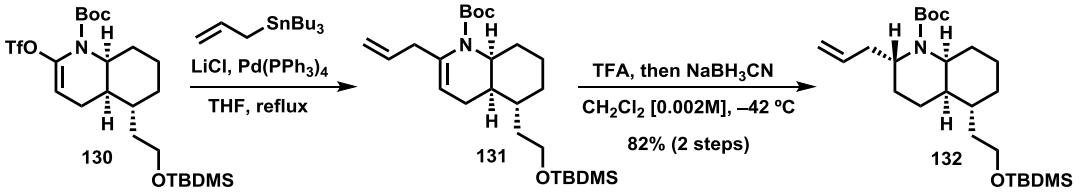
Figure 4.12. Elaboration of the enantiomeric scaffold **127**.

Treatment of compound **127** with alane, followed by *N*-debenzylation in the presence of Boc_2O, afforded decahydroquinoline **128** as a single *cis* isomer. Re-oxidation to the corresponding lactam **129** was carried out using a slight modification of the previously described RuO_4 oxidation. Under these conditions, compounds resulting from the oxidation of the silyl-ether moiety present in **128** were not observed. Finally, vinyl triflate **130** was prepared in virtually quantitative yield following the Comins' protocol we had optimized in the synthesis of lepadin alkaloids (Scheme 4.17).



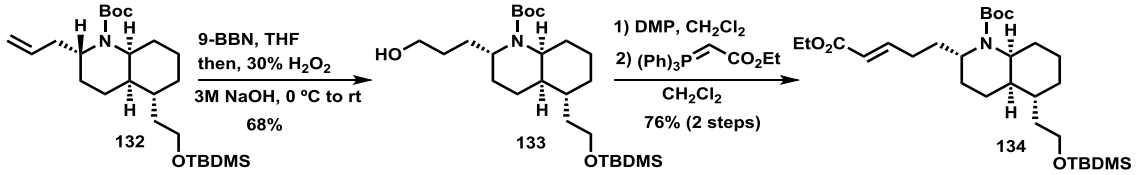
Scheme 4.17. Preparation of vinyl triflate **130**.

As shown in the previous scheme, the synthetic sequence leading to compound **130** was very efficient, so we then focused on the stereoselective introduction of a substituent at C-2. We knew beforehand that the most versatile method would be a Pd-catalyzed cross-coupling reaction and that a suitable moiety to further elaborate the C-2 substituent would be an allyl group. Therefore, we prepared compound **131** using allylstannane under the conditions reported by Stille.[126] Due to fears of instability of the enecarbamate moiety present in **131**, observed in previous experiments for the synthesis of lepadin alkaloids, we decided to subject this compound without purification to the *N*-acyl iminium ion reduction procedure developed for model compound **116** (Scheme 4.18).



Scheme 4.18. Stereoselective functionalization of C-2.

To our delight, compound **132** was obtained in high yield and, as expected, as a single diastereoisomer. With the successful preparation of **132**, we were closer to our target alkaloid, and decided to continue the elaboration of the C-2 side-chain. Therefore, taking advantage of the allyl group, compound **132** was converted to the α,ß-unsaturated ester **134** in good overall yield, over three synthetic steps involving the hydroboration-oxidation of the terminal olefin and an oxidation-olefination sequence (Scheme 4.19).



Scheme 4.19. Elaboration of the C-2 substituent.

Having introduced the required functionalization for the final installation of the pyrrolidine moiety, we focused on the C-5 side chain. The main challenge to address was the installation of a *Z*-enyne moiety. This could be accomplished either by a two-step procedure, a Stork-Zhao olefination followed by a Sonogashira coupling, or in a single step, using the Yamamoto-modified Peterson olefination.[127] The latter approach was highly attractive given that good levels of *Z*:*E* stereoselectivities can usually be achieved and, among all the previous syntheses of gephyrotoxins, only Overman has used a related reaction in his racemic synthesis.[120c]

[126] Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630-4632.
[127] (a) Yamakado, Y.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1981**, *103*, 5568-5570. (b) Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Org. Chem.* **1982**, *47*, 2225-2227. (c) Furuta, K.; Ishiguro, M.; Haruta, R.; Ikeda, N.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2768-2776.

4.7.3. Introduction of the C-5 *Z*-enyne moiety and *aza*-Michael cyclization – Total synthesis of (+)-gephyrotoxin 287C.

The Yamamoto-Peterson olefination is very similar to the Corey-Rücker reaction,[128] with the advantage of not requiring the use of HMPA as a co-solvent, and usually higher ratios of the *Z* isomer are obtained. This reaction consists in the low-temperature lithiation of a 1,3-bis(trialkylsilyl)propyne derivative to generate an allene, which is then trapped with a metal (Ti is preferred, since it affords higher diastereoselectivities). This allenic organometallic species is then reacted with an aldehyde (ketones are not reactive), leading to a ß-hydroxysilyl derivative that, similarly to the Peterson olefination, undergoes elimination to afford the ene-yne product (Figure 4.13).

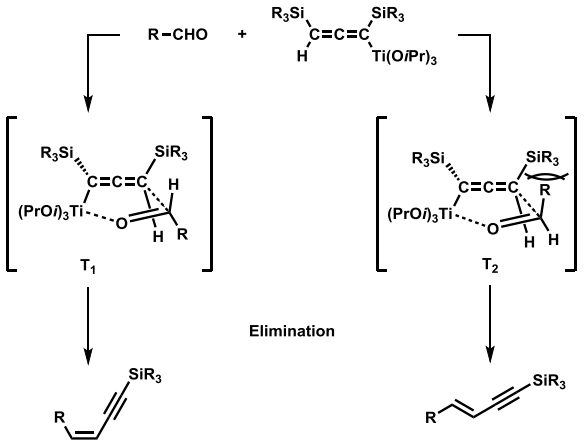
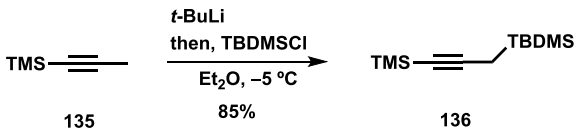


Figure 4.13. Mechanism of the Yamamoto-Peterson olefination.[127c]

As can be seen in Figure 4.13, transition state $\mathbf{T_2}$ is disfavoured because of the steric repulsion between the R and the silyl groups. This means that, in contrast to the classical Peterson olefination where the geometry of the double bond is determined by the *syn* or *anti* elimination of the ß-hydroxysilyl derivative, in the Yamamoto modification the final stereochemical outcome is mainly dictated by the diastereoselectivity of the initial attack of the titanium reagent on the aldehyde. This rationale can also explain why bulkier silyl groups on the carbon that adds to the carbonyl tend to afford higher selectivity for the *Z* isomer.

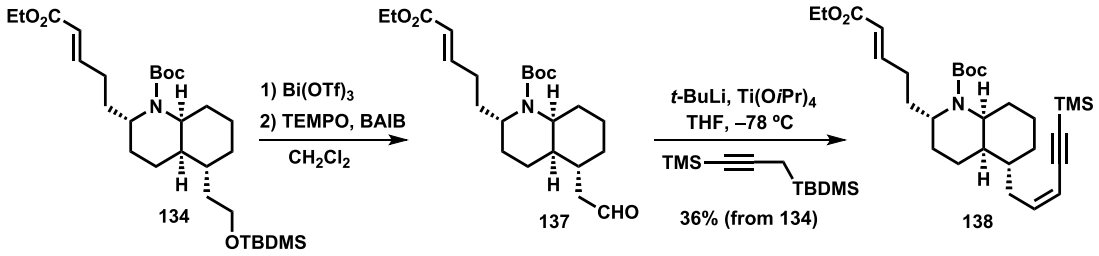
With this idea in mind, we prepared the known bulky 1,3-disilylpropyne derivative **139**, using the literature protocol (Scheme 4.20).[127a]



Scheme 4.20. Preparation of the bis(silyl) compound **136**.

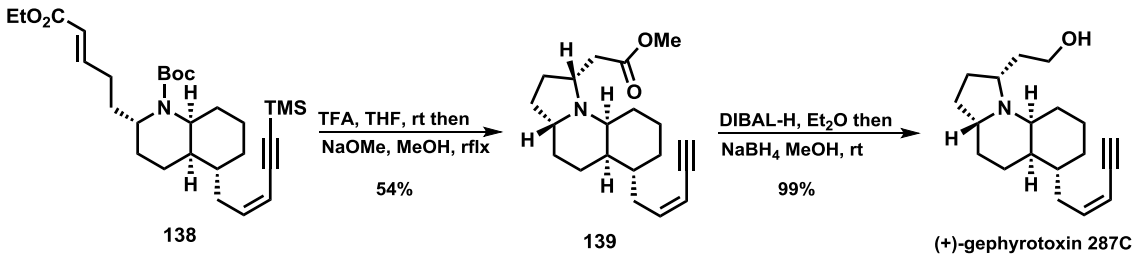
We then advanced compound **134** to the corresponding aldehyde **137** by performing the desilylation-oxidation sequence previously used in the synthesis of (+)-lepadin D and subjected this aldehyde to the Yamamoto-Peterson olefination (Scheme 4.21).

[128] Corey, E. J., Rücker, C. *Tetrahedron Lett.* **1982**, *23*, 719-722.



Scheme 4.21. Introduction of the *Z*-enyne moiety at C-5.

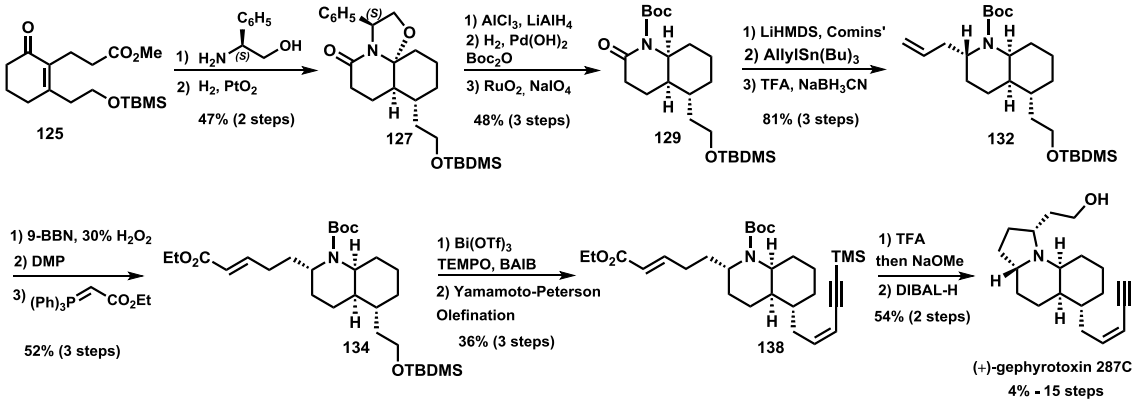
The required *Z*-enyne was introduced with complete *Z* selectivity, allowing the preparation of compound **138** with an average of 70% yield *per* step from **134**. At this point, we were close to achieving the total synthesis of (+)-gephyrotoxin **287C**, and to do this we followed the last steps of the Nemoto-Hamada synthesis (Scheme 4.22).[119]



Scheme 4.22. Total synthesis of (+)-gephyrotoxin **287C**.

Gratifyingly, treatment of **138** with TFA smoothly removed the Boc and TMS groups. A subsequent treatment of the crude reaction mixture with sodium methoxide brought about the desired *aza*-Michael cyclization, affording **139** in good overall yield. Finally, (+)-gephyrotoxin **287C** was obtained in virtually quantitative yield by reduction of the pending ester with DIBAL-H. Our synthetic gephyrotoxin showed a dextrorotatory optical rotation value ($[\alpha]^{23}_{D} = +49.0$, c 0.21, EtOH).

In summary, (+)-gephyrotoxin **287C** was synthesised in 14 steps and 4% overall yield from the chiral tricyclic lactam **127** as the starting enantiomeric scaffold (Scheme 4.23).



Scheme 4.23. Overall total synthesis of (+)-gephyrotoxin **287C**.

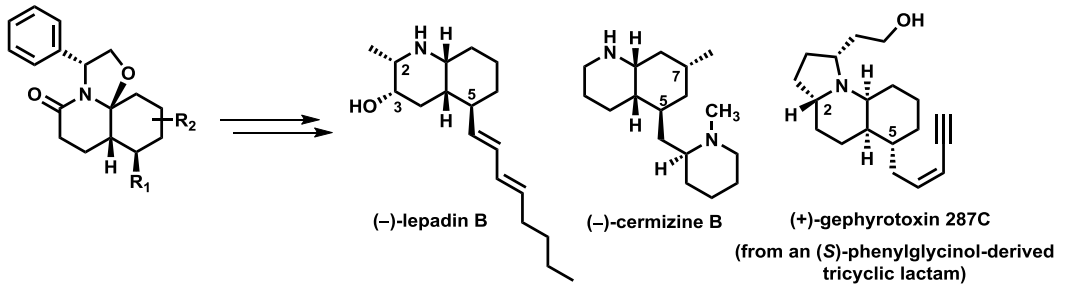
4.8. Conclusion

Accomplishing the total synthesis of (+)-gephyrotoxin **287C** highlights the synthetic usefulness of our chiral tricyclic lactams for the synthesis of *cis*-decahydroquinoline alkaloids. Our successful synthesis employing enantiopure scaffolds with well-defined stereocenters constitutes further proof for the initial X-ray structure proposed by Daly and co-workers for natural (−)-gephyrotoxin **287C**,[115] which was later supported by the synthetic efforts of the Smith group.[118]

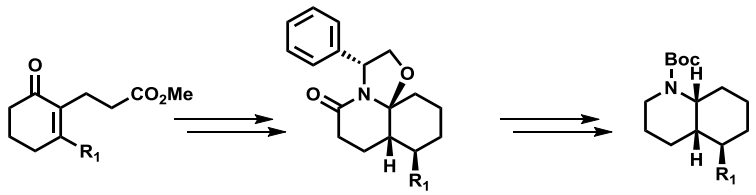
Additionally, in our studies we explored ways of controlling the stereochemistry at C-2, providing a good starting point to further expand the versatility of the developed methodology. Moreover, the proposed objectives of this final part of the thesis were fully accomplished.

Chapter 5 *– Conclusions*

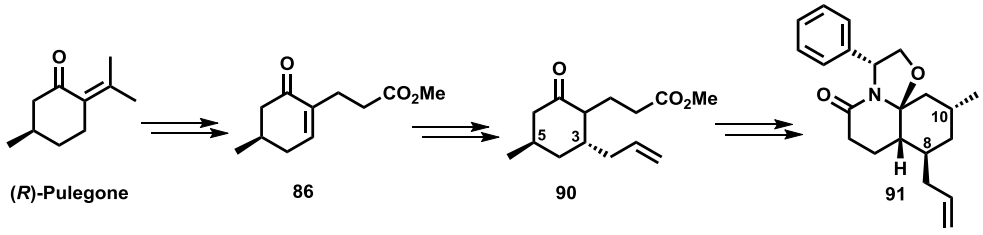
1. (*R*)- or (*S*)-phenylglycinol-derived hydroquinolone lactams are useful enantiopure scaffolds for the enantioselective synthesis of *cis*-decahydroquinoline alkaloids from marine sources (lepadins), plants ((−)-cermizine B), and amphibians ((+)-gephyrotoxin **287C**).



2. A straightforward procedure for the preparation of enantiopure *N*-Boc-5-substituted *cis*-decahydroquinolines with complete stereocontrol has been developed. It involves a stereoselective cyclocondensation reaction between (*R*)- or (*S*)-phenylgycinol and appropriately C-2 substituted 6-oxocyclohexenepropionate derivatives, followed by catalytic hydrogenation of the endocyclic C=C bond present in the resulting chiral tricyclic lactams, alane-mediated stereoselective removal of the chiral inductor and, finally, *N*-debenzylation in the presence of Boc_2O.

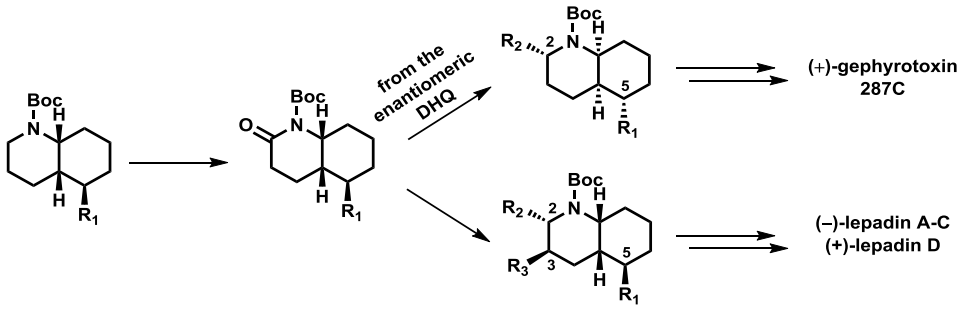


3. Starting from (*R*)-phenylgycinol and a *trans* 3,5-disubstituted 6-oxocyclohexanepropionate **90**, the above methodology can be extended to the enantioselective preparation of tricyclic lactams bearing stereodefined substituents at the C-8 (C-5 DHQ numbering) and C-10 (C-7 DHQ numbering) positions. The substituent at C-8 is introduced by a stereoselective substrate-controlled conjugate addition to unsaturated ester **86**, whereas the C-10 substituent derives from the chiral pool starting material.

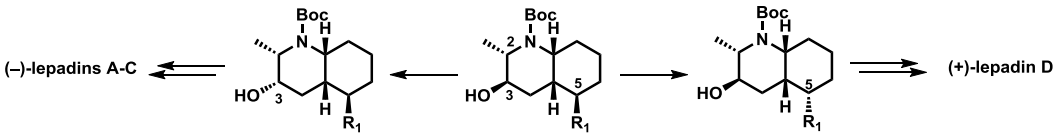


4. The functionalized C-8 substituent (C-5 DHQ numbering) of the tricyclic lactams allows the subsequent elongation/manipulation of the C-5 side-chain required for the successful total syntheses of lepadins A–D, (−)-cermizine B, and (+)-gephyrotoxin **287C**.

5. *N*-Boc-5-substituted *cis*-decahydroquinolines can be efficiently re-functionalised at the C-2 position by treatment with RuO_4, affording the corresponding lactams. This moiety was successfully used, *via* the intermediate vinyl triflate, for the stereoselective introduction of the C-2 substituent of (+)-gephyrotoxin **287C** and the C-2 and C-3 substituents of the lepadin alkaloids.



6. 2,3,5-trisubstituted-*N*-Boc-*cis*-decahydroquinolines provide a unified synthetic entry to the lepadin alkaloids. These compounds are versatile synthetic platforms, where correction of the C-3 stereochemistry allows access to (−)-lepadins A-C, whereas manipulation of the C-5 stereocenter leads to (+)-lepadin D.



7. A thorough study of the cyclocondensation reactions of (*R*)- and (*S*)-phenylglycinol, as well as 2-aminoethanol, with 3-, 5-, and 3,5-substituted 2-oxocyclohexanepropionate derivatives has provided a complete understanding of the factors influencing the stereochemical outcome of these reactions: a) the approach of the ester group to the nitrogen atom of the oxazolidine ring, either from the same or from the opposite face of the phenyl moiety of the chiral inductor; b) the presence of an axial substituent on the cyclohexane ring; and c) the *gauche* interactions between the C-10 (C-5 DHQ numbering) substituent and the propionate side-chain.

Chapter 6 – *Experimental Part*

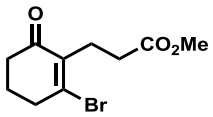
General Experimental Information

All air sensitive manipulations were carried out under a dry argon or nitrogen atmosphere, with dry freshly distilled solvents using standard procedures. Other solvents and reagents were purchased from Sigma-Aldrich, Alfa-Aesar or TCI, and were used without further purification. Drying of organic extracts during work-up of reactions was performed with $MgSO_4$ or Na_2SO_4. Evaporation of solven was accomplished with a rotatory evaporator. Thin-layer chromatography was performed on SiO_2 (silica gel 60 F_{254}), and the sports were located by UV, and either 1% $KMnO_4$ solution or 3% ethanolyc p-anysaldehyde. Chromatography refers to flash chromatography, and was carried out on SiO_2 (silica gel 60, 230-400 mesh).

NMR spectra were recorded at a 300, 400 MHz (^1H) and 75.4 or 100.6 MHz (^{13}C), and chemical shifts are reported in δ values, in parts per million (ppm) relative to Me_4Si (0 ppm) or relative to residual chloroform (7.26 ppm, 77.0 ppm), and methanol (3.31 ppm, 49.1 ppm) as internal standards, at 25 ºC. Data are reported in the following manner: chemical shift, multiplicity, coupling constant (*J*), in hertz (Hz), integrated intensity, and assignment (when possible). Assignments and stereochemical determinations are given only when they are derived from definitive two-dimensional NMR experiments (*g*-HSQC-COSY). IR spectra were performed in a spectrophotometer Nicolet Avatar 320 FT-IR, and only noteworthy IR absorptions (cm^{-1}) are listed. Optical rotations were measured in a Perkin-Elmer 241 polarimeter, using a Na lamp. $[\alpha]_D$ in 10^{-1} deg cm^2 g^{-1}. Melting points were determined in a capillary tube and are uncorrected.

High resolution mass spectra (HRMS) and elemental analyses were performed by the *Centres Científics i Tecnològics de la Universitat de Barcelona*.

X-ray analysis was performed using a diffractometer Enraf-Nonius CA D4, using graphite monochromatic radiation Mo Kα by Dr. Elies Molins group at the *Institut de Ciència de Materials de Barcelona* (ICMAB).



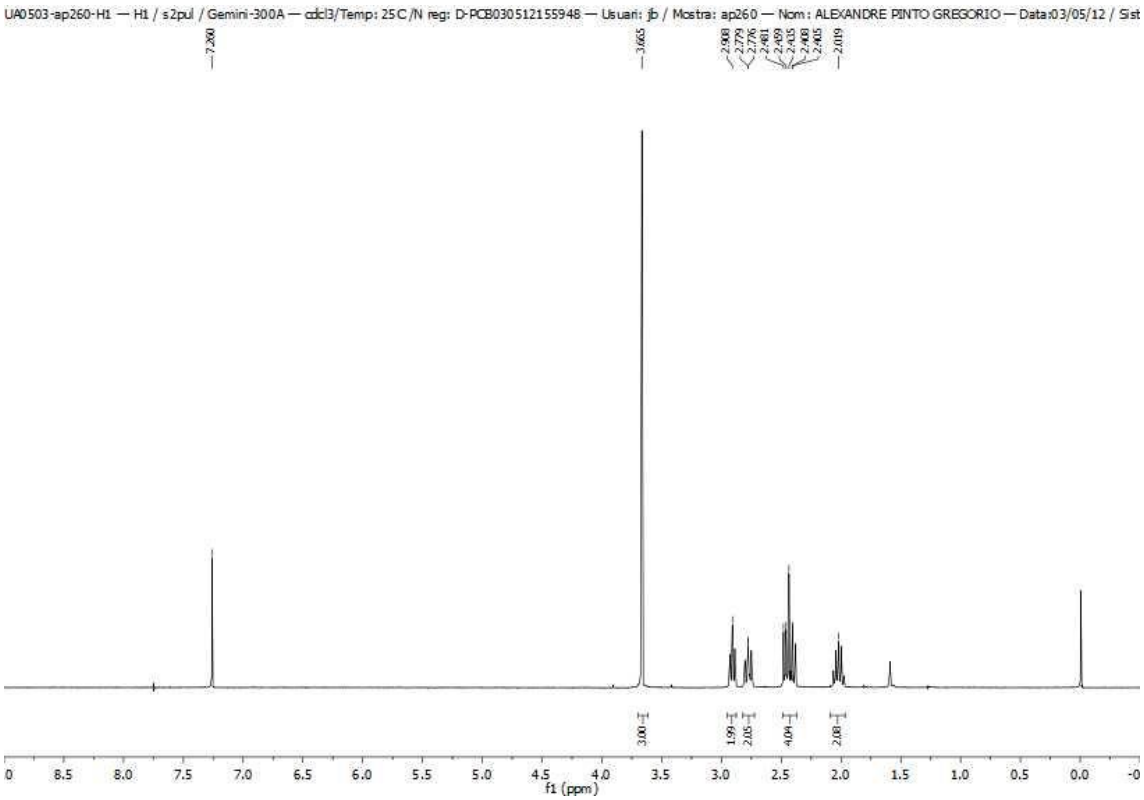
Methyl 2-Bromo-6-oxociclohexenpropionat (1)

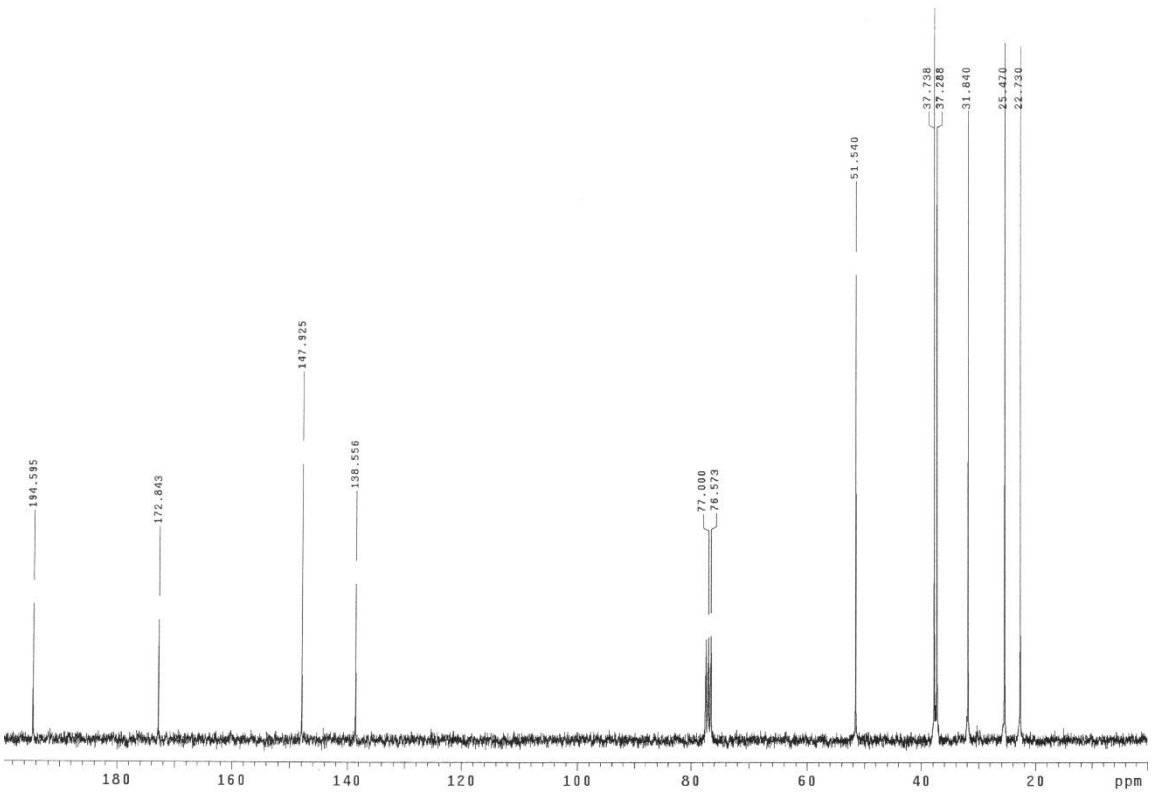
Et_3N (15.8 mL, 0.11 mol) and methyl 2,6-dioxocyclohexanepropionate **5** (20.5 g, 0.1 mol) were added to a solution of Ph_3PBr_2 (50 g, 0.11 mol) in CH_2Cl_2 (570 mL) at room temperature, and the mixture was stirred for 36 h. The solvent was evaporated and the obtained residue was chromatographed (9:1 hexane–EtOAc), affording compound **1** (20.4 g, 75%) as a yellowish oil.

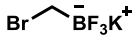
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.96-2.09 (m, 2H), 2.37-2.50 (m, 4H), 2.74-2.82 (m, 2H), 2.89-2.95 (m, 2H), 3.67 (s, 3H, CH_3).

^{13}C-NMR (75.4 MHz, $CDCl_3$) δ: 22.7 (CH_2), 25.5 (CH_2), 31.8 (CH_2), 37.3 (CH_2), 37.7 (CH_2), 51.5 (CH_3), 138.6 (C), 147.9 (C), 172.8 (COO), 194.6 (CO).

HRMS calcd for [$C_{10}H_{13}BrO_3 + Na^+$]: 282.995; found 282.994.


UA0503-ap260-H1 — H1 / s2pul / Gemini-300A — cdcl3/Temp: 25C /N reg: D-PCB030512155948 — Usuari: jb / Mostra: ap260 — Nom: ALEXANDRE PINTO GREGORIO — Data:03/05/12 / Sist
7.260
3.665
2.908
2.779
2.776
2.461
2.459
2.435
2.408
2.405
2.019
3.00
1.99
2.05
4.04
2.08
f1 (ppm)

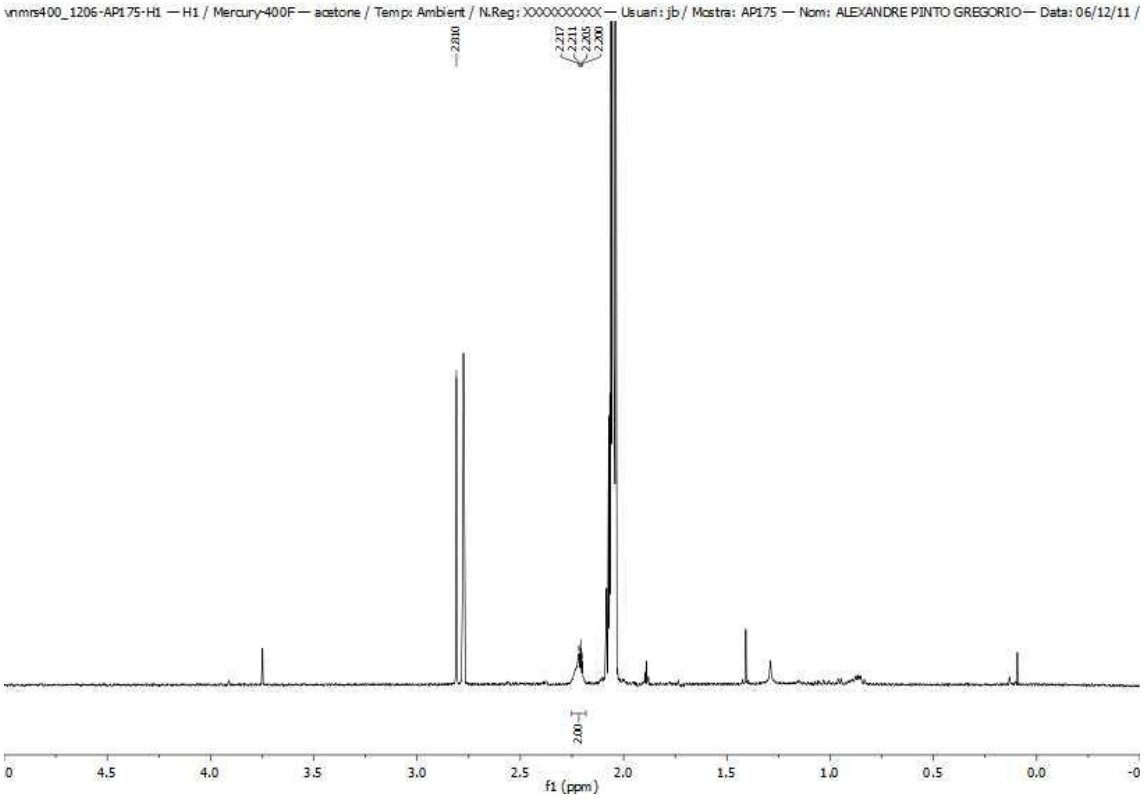

194.595
172.843
147.925
138.556
77.000
76.573
51.540
37.738
37.288
31.840
25.470
22.730
ppm

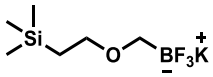


Potassium Bromomethyltrifluoroborate (3)

Triisopropylborate (61 mL, 0.264 mol) and CH_2Br_2 (19.1 mL, 0.274 mol) were added to a three-necked round bottom flask containing 400 mL of dry THF, at −78 ºC. *n*-BuLi (99.6 mL, 0.249 mol, 2.5 M in Hexane) was added dropwise *via* an addition funnel over 1h. After the addition of *n*-BuLi was complete, the reaction mixture was stirred at −78 ºC for 2.5h. Methanesulfonic acid (8.1 mL, 0.125 mol) was then added, and the reaction mixture was removed from the cooling bath and allowed to reach 0 ºC (aprox. 30 min). KHF_2 (58.35 g, 0.747 mol) was added in one portion to the mixture. Distilled H_2O (84 mL) was added dropwise *via* an addition funnel. After the addition of H_2O was complete, the mixture stirred for 30 min. The reaction mixture was then concentrated and the crude white residue was dried overnight *in vacuo* at 70 ºC. The crude solids were loaded onto Soxhlet cartridges and extracted continuously with HPLC-grade acetone overnight. The solvent was evaporated affording compound **3** (37.6 g, 75%) as a white solid.

^{1}H-NMR (400 MHz, d_6-Acetone) δ: 2.20-2.25 (m, 2H.)

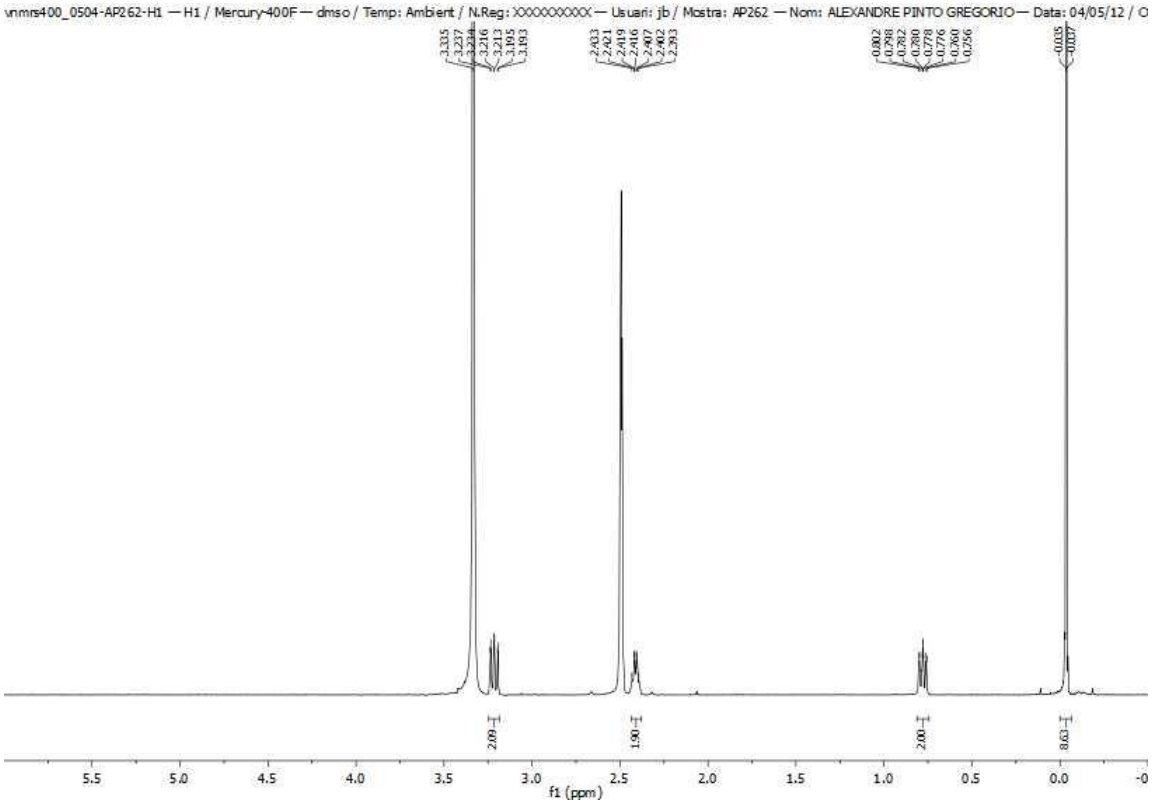

\nmrs400_1206-AP175-H1 — H1 / Mercury-400F — acetone / Temp: Ambient / N.Reg: XXXXXXXXX — Usuari: jb / Mostra: AP175 — Nom: ALEXANDRE PINTO GREGORIO — Data: 06/12/11 /
2.210
2.217
2.211
2.205
2.200
2.00
0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)

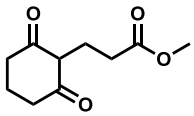


Potassium (2-Trimethylsilyl)ethoxy)methyltrifluoroborate (4)

Trimethylsilyl ethanol (5.0 mL, 0.035 mol) was added dropwise to a suspension of NaH (1.06 g, 0.042 mol) in dry THF (70 mL) at 0 ºC. The mixture stirred for 15 min at 0 ºC before being allowed to warm to room temperature. After 30 min, the mixture was cooled to 0 ºC and bromomethyltrifluoroborate (2.41 g, 0.012 mol) was added in one portion. The reaction mixture was allowed to warm to room temperature and stirred for 7h. After cooling to −20 ºC, the reaction was quenched with 4.5M aqueous KHF_2 until pH ≈ 6 and stirred for 30 min at room temperature. The crude mixture was concentrated and the residue was dried overnight in *vacuo* at 70 ºC. The crude solid was suspended in Et_2O, sonicated and filtered. The crude solids were loaded onto Soxhlet cartridges and extracted continuously with HPLC-grade acetonitrile overnight. The solvent was evaporated affording compound **3** (2.69 g, 94%) as a white solid.

^{1}H-NMR (400 MHz, DMSO-d_6) δ: −0.04 (br s, 9H), 0.76-0.80 (m, 2H), 2.39-2.43 (m, 2H), 3.19-3.24 (m, 2H).


vnmrs400_0504-AP262-H1 — H1 / Mercury-400F — dmso / Temp: Ambient / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP262 — Nom: ALEXANDRE PINTO GREGORIO — Data: 04/05/12 / O
3.335
3.237
3.224
3.216
3.213
3.195
3.193
2.433
2.421
2.419
2.416
2.407
2.402
2.393
0.802
0.798
0.782
0.780
0.778
0.776
0.760
0.756
0.035
0.017
2.09
1.90
2.00
8.63
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)



Methyl 2,6-dioxocyclohexanepropionate (5)

A solution of 1,3-cyclohexanedione (31 g, 0.268 mmol, 97%) in dry DMF (119 mL) was added to a suspension of NaH (6.77 g, 0.268 mmol, 95%) in dry DMF (150 mL) at 0 ºC. After 30 minutes at 0 ºC, methyl acrylate (29 mL, 0.322 mmol) and the mixture was heated to 80 ºC for 6h. The reaction mixture was cooled to room temperature, 2M HCl was added until pH = 1, and the crude mixture was extracted with EtOAc. The organic extracts were dried and concentrated to afford pure compound **5** (52.5 g, 99%) as a brown sticky solid.

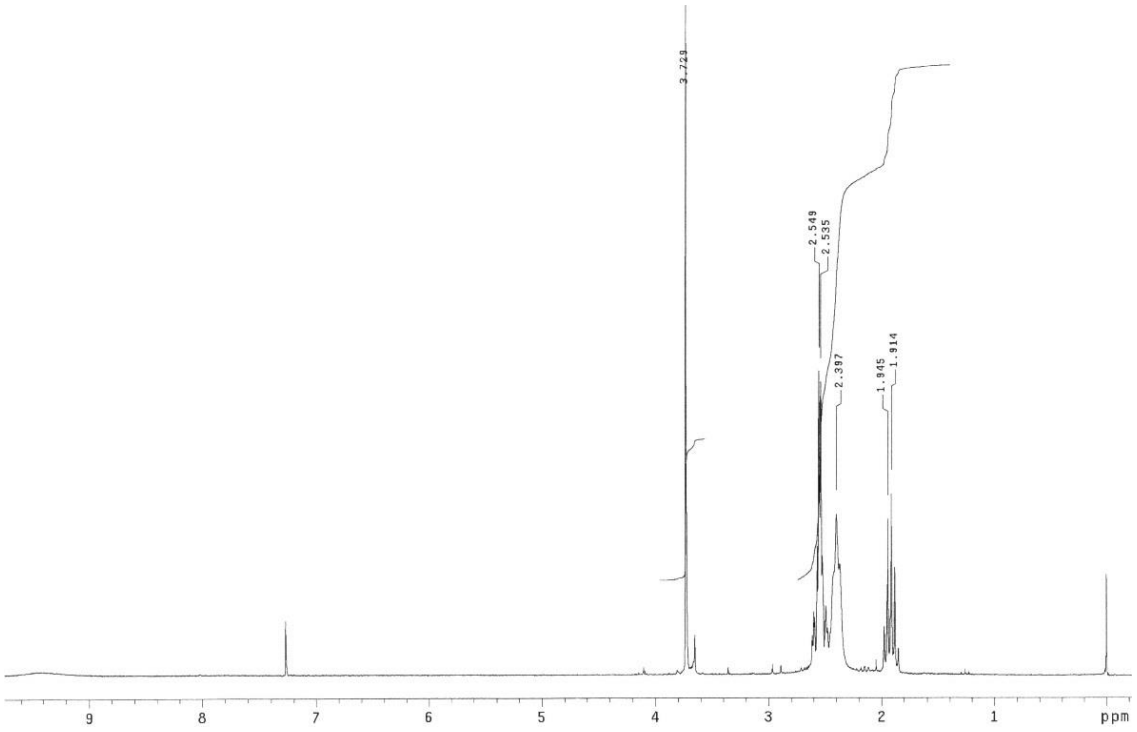
^{1}H-NMR (200 MHz, $CDCl_3$) *δ*: 1.88-1.93 (m, 2H), 2.38-2.60 (m, 9H), 3.73 (s, 3H, CH_3).

^{13}C-NMR (75.4 MHz, $CDCl_3$) *δ*: 16.7 (CH_2), 20.4 (CH_2), 32.7 (CH_2), 52.3 (CH), 114.3 (C), 177.9 (COO).

IR (NaCl): 1732, 1567 cm^{-1}.

HRMS calcd for [$C_{10}H_{14}O_4$ + H^+]: 198.0892 found 198.0894.

Melting point: 102−107 ºC.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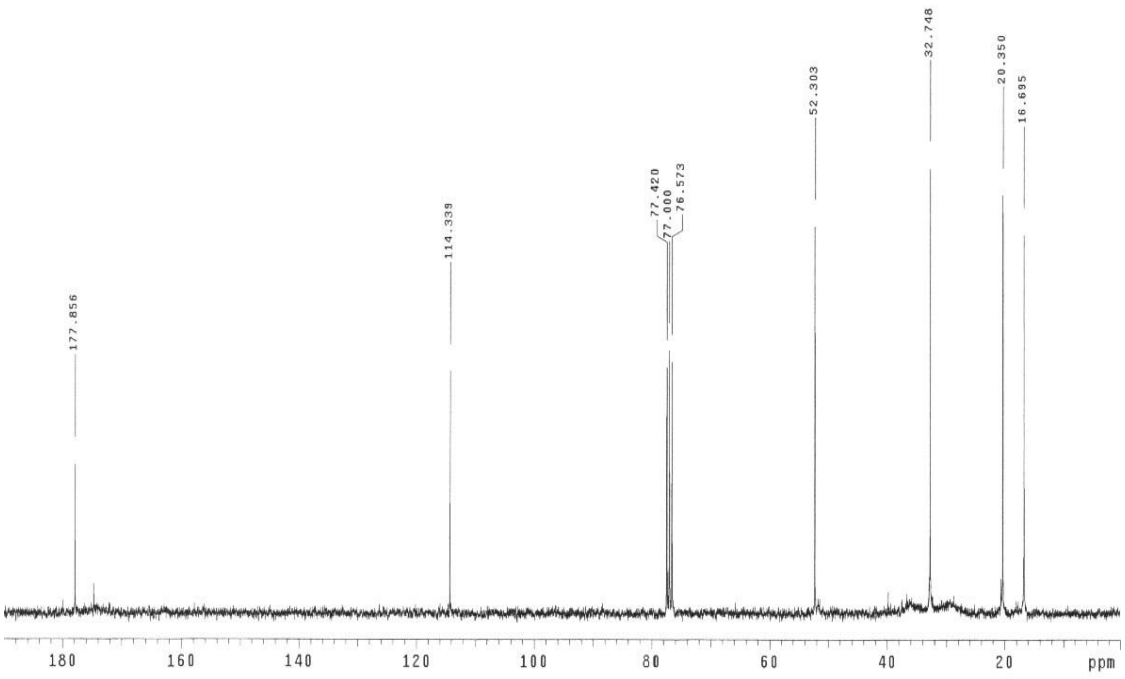
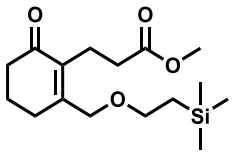
2.549
2.535
2.397
1.845
1.914
9
8
7
6
5
4
3
2
1
ppm


177.856
114.339
77.420
77.000
76.573
52.303
32.748
20.350
16.695
180
160
140
120
100
80
60
40
20
ppm



Methyl 6-oxo-2-[2-(trimethylsilyl)ethoxymethyl]cyclohexene-propionate (6)

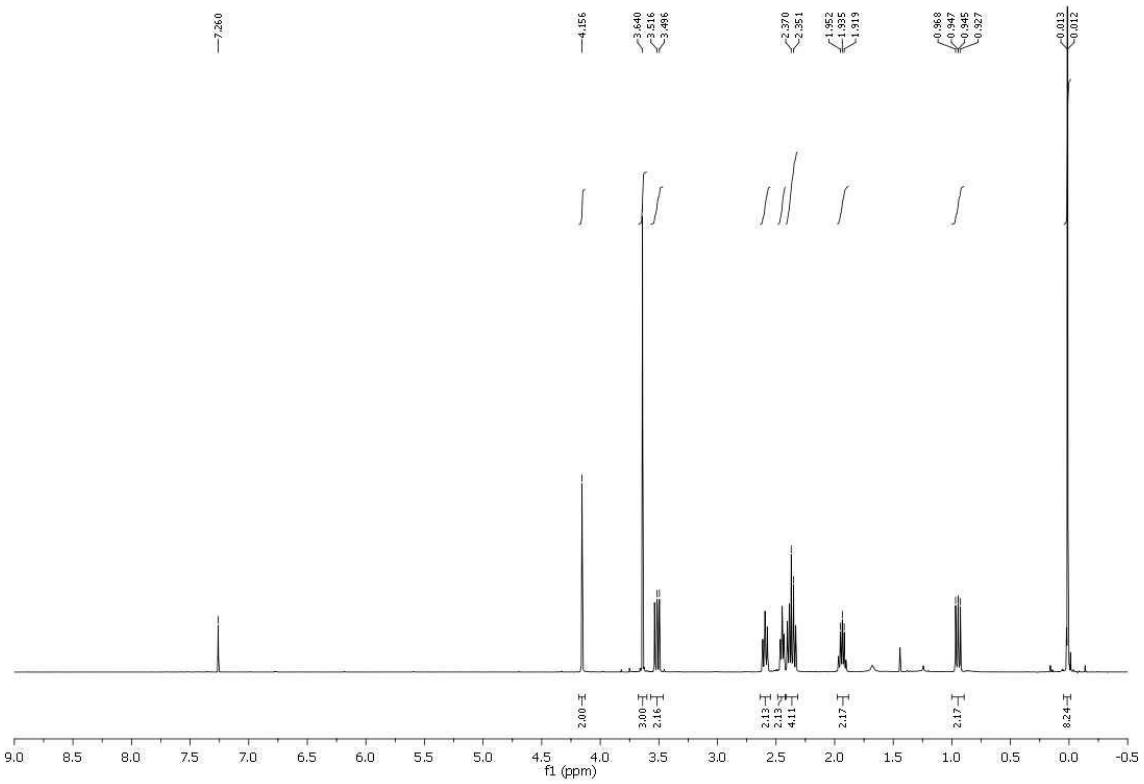
Degassed toluene (2.7 mL) and degassed H_2O (0.9 mL) were added *via* syringe to a sealed tube containing compound **1** (100 mg, 0.3 mmol), Cs_2CO_3 (296 mg, 0.9 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (24.6 mg, 0.03 mmol), and potassium trimethylsilylethoxymethyltrifluoroborate **4** (108 mg, 0.45 mmol), and the vessel was purged with nitrogen. The mixture was stirred at 100 ºC for 24 h. After cooling to room temperature, EtOAc was added, the resulting suspension was filtered over Celite®, and the filtrate was concentrated. Flash chromatography (7:3 hexane–EtOAc) afforded compound **6** (80 mg, 94%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.01 [s, 9H, $(CH_3)_3Si$], 0.93-0.97 (m, 2H, CH_2Si), 1.90-1.97 (m, 2H, CH_2), 2.33-2.40 (m, 4H, CH_2), 2.45 (t, J = 6.0 Hz, 2H, CH_2), 2.59 (t, J = 7.6 Hz, 2H), 3.49-3.54 (m, 2H, OCH_2), 3.64 (s, 3H, OCH_3), 4.16 (s, 2H, OCH_2).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: –1.39 ($3CH_3Si$), 18.2 (CH_2Si), 20.7 (CH_2), 22.2 (CH_2), 28.0 (CH_2), 33.3 (CH_2), 37.9 (CH_2), 51.5 (OCH_3), 68.5 (OCH_2), 69.9 (OCH_2), 134.3 (C=C), 156.0 (C=C), 173.5 (COO), 198.9 (CO).

IR (NaCl): 1739, 1670 cm^{-1}.

HRMS calcd for [$C_{16}H_{29}O_4Si + H^+$]: 313.183; found 313.1824.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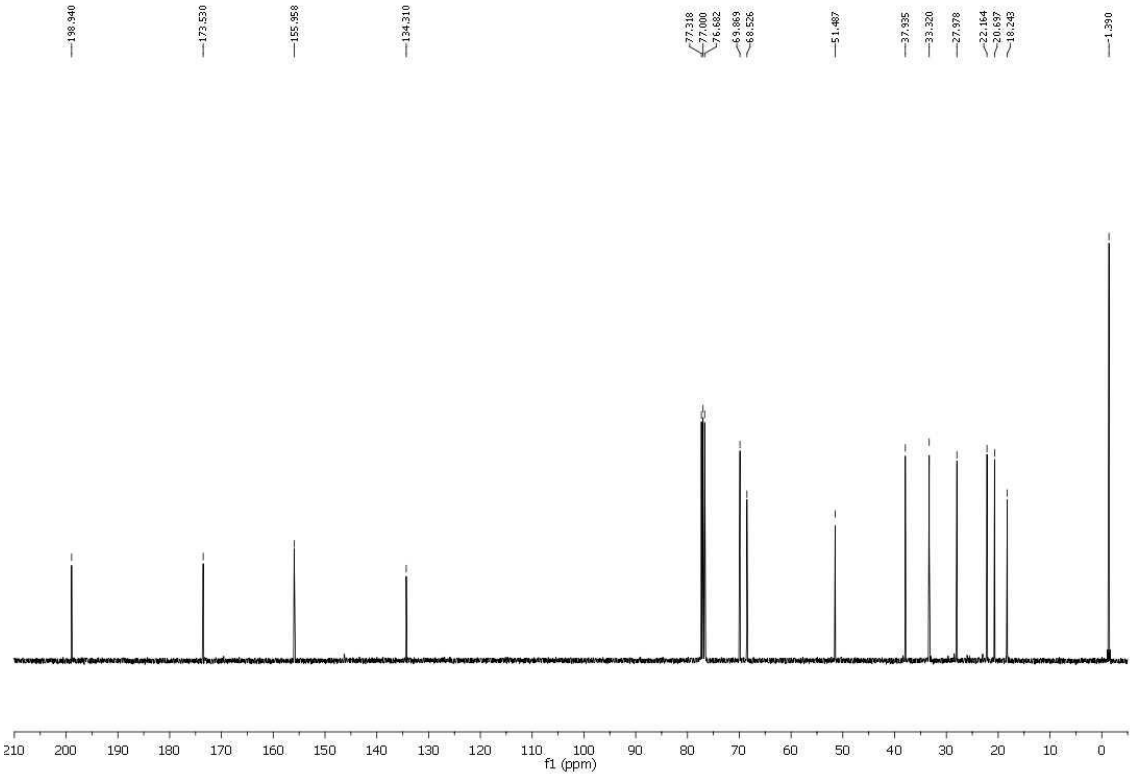
4.156
3.640
3.516
3.496
2.370
2.351
1.952
1.935
1.919
0.968
0.947
0.945
0.927
0.013
0.012
2.00
3.00
2.16
2.13
2.13
4.11
2.17
2.17
8.24
f1 (ppm)


198.940
173.530
155.958
134.310
77.318
77.000
76.682
69.869
68.526
51.487
37.935
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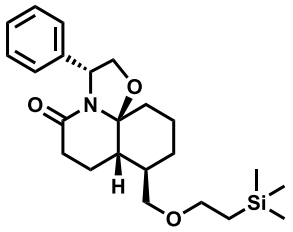
27.978
22.164
20.697
18.248
1.390
f1 (ppm)



(3*R*,7a*S*,8*R*,11a*S*)-5-Oxo-3-phenyl-8-{[2-trimethylsilyl)ethoxy]methyl}decahydrooxazolo [2,3-*j*]quinoline (8a)

Fisrt step: (*R*)-Phenylglycinol (878 mg, 6.4 mmol) was added to a solution of keto ester **6** (1.0 g, 3.2 mmol) and AcOH (370 µL, 6.4 mmol) in benzene (40 mL). The mixture was heated at reflux with azeotropic elimination of water by a Dean-Stark system. Additional 1.0 equiv of (*R*)-phenylglycinol and AcOH were added every 24 h to the reaction mixture, until all starting material was consumed. After 72 h, the mixture was cooled and concentrated, and the resulting oil was taken up in EtOAc. The organic solution was washed with saturated aqueous $NaHCO_3$ and brine, dried and concentrated.
Second step: A solution of the above residue in methanol (20 mL) containing Pt_2O (288 mg) was stirred under hydrogen at room temperature for 5 h. The catalyst was removed by filtration, and the solvent was evaporated. Flash chromatography (hexane to 6:4 hexane–EtOAc) afforded compound **8a** (860 mg, 67%) as a colorless oil.

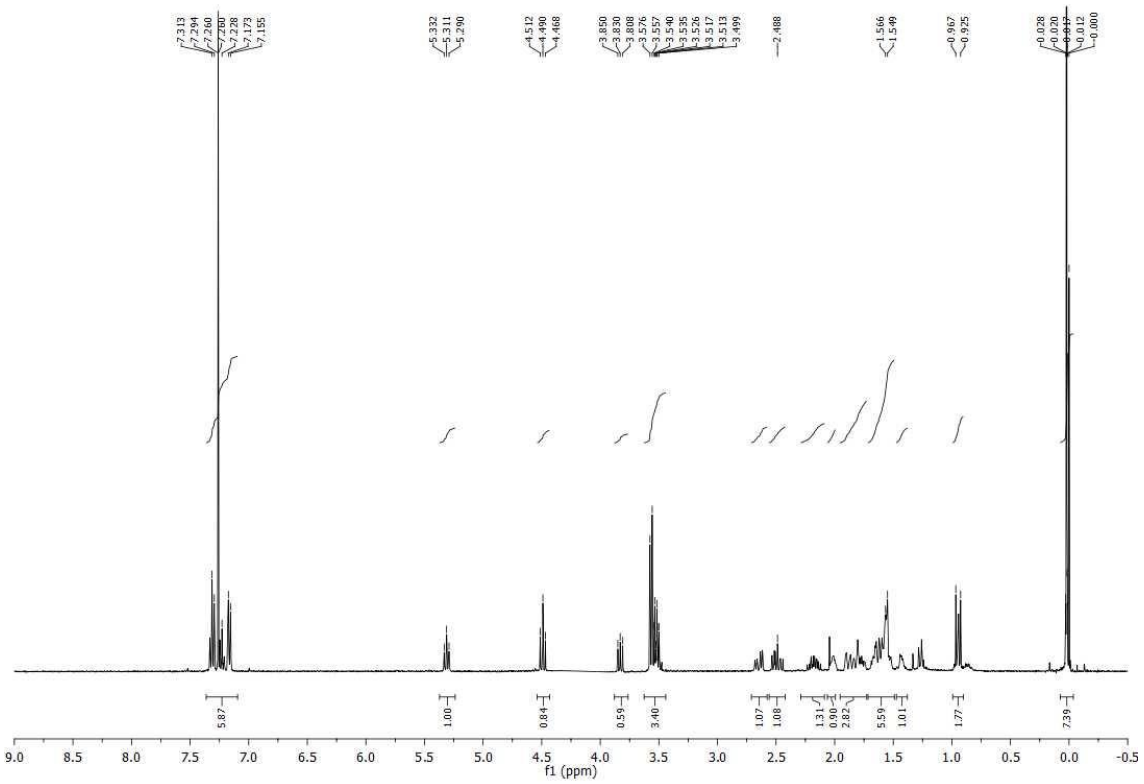
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.01 [s, 9H, $Si(CH_3)_3$], 0.94 (dd, J = 7.2, 2.4 Hz, 2H, CH_2Si), 1.39-1.44 (m, 1H, H-9), 1.52-1.70 (m, 4H, H-9, H-10, H-11), 1.72-1.93 (m, 3H, H-7, H-7a, H-11), 1.97-2.04 (m, 1H, H-8), 2.10-2.23 (m, 1H, H-7), 2.48 (ddd, J = 18.4, 10.8, 8.0 Hz, 1H, H-6), 2.64 (dd, J = 18.4, 6.8 Hz, 1H, H-6), 3.48-3.54 (m, 2H, OCH_2), 3.56 (d, J = 7.6 Hz, 2H, CH_2O), 3.82 (t, J = 8.4 Hz, 1H, H-2), 4.49 (t, J = 8.4 Hz, 1H, H-2), 5.31 (t, J = 8.4 Hz, 1H, H-3), 7.13-7.34 (m, 5H, Ar-H).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: –1.4, [$Si(CH_3)_3$], 18.2 (CH_2TMS), 18.2 (C-9), 21.8 (C-10), 24.2 (C-7), 30.3 (C-11), 31.0 (C-6), 40.0 (C-8), 40.8 (C-7a), 58.1 (C-3), 68.0 (OCH_2), 69.5 (C-2), 72.2 (CH_2O), 95.0 (C-11a), 125.3, 127.0 (C-*o, m*), 128.4 (C-*p*), 140.2 (C-*i*), 169.3 (C-5).

IR (NaCl): 1659, 1244 cm^{-1}.

HRMS calcd for [$C_{23}H_{35}NO_3Si$ + H^+]: 402.2459; found 402.2455.

$[\alpha]^{23}_D$ = – 65.1 (*c* 1.0, MeOH).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7.228
7.173
7.155
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5.311
5.290
4.512
4.490
4.468
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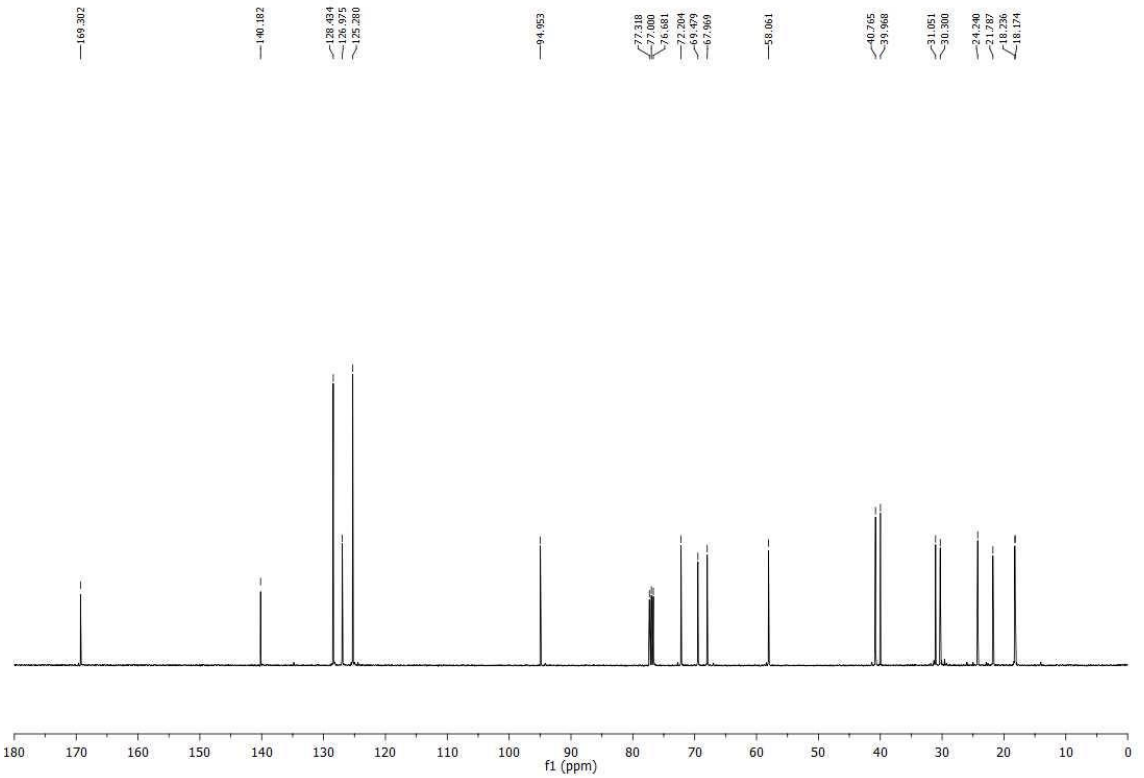
3.830
3.808
3.576
3.557
3.540
3.535
3.526
3.517
3.513
3.499
2.488
1.566
1.549
0.967
0.925
0.028
0.020
0.012
-0.000
5.87
1.00
0.84
0.59
3.40
1.07
1.08
1.31
0.90
2.82
5.59
1.01
1.77
7.39
f1 (ppm)


169.302
140.182
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126.975
125.280
94.953
77.318
77.000
76.681
72.204
69.479
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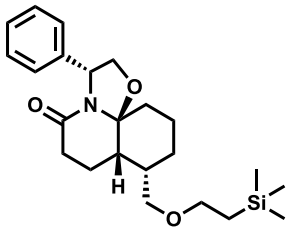
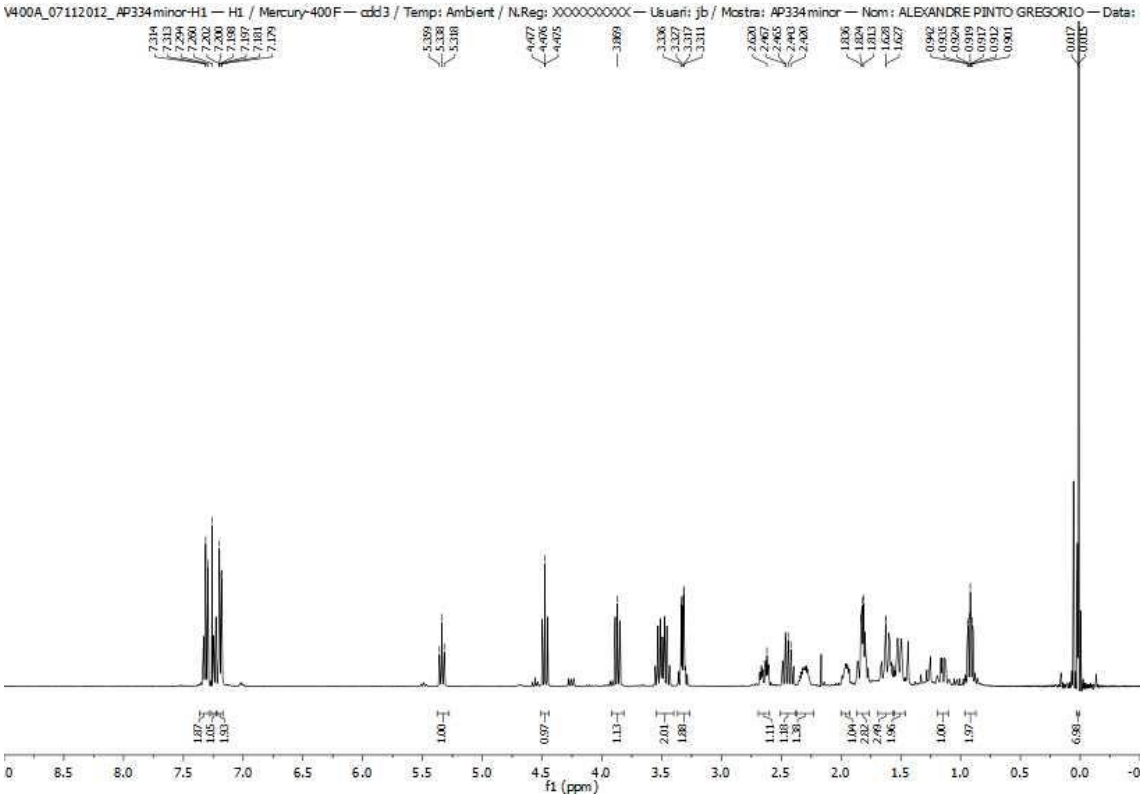
24.240
21.787
18.236
18.174
f1 (ppm)

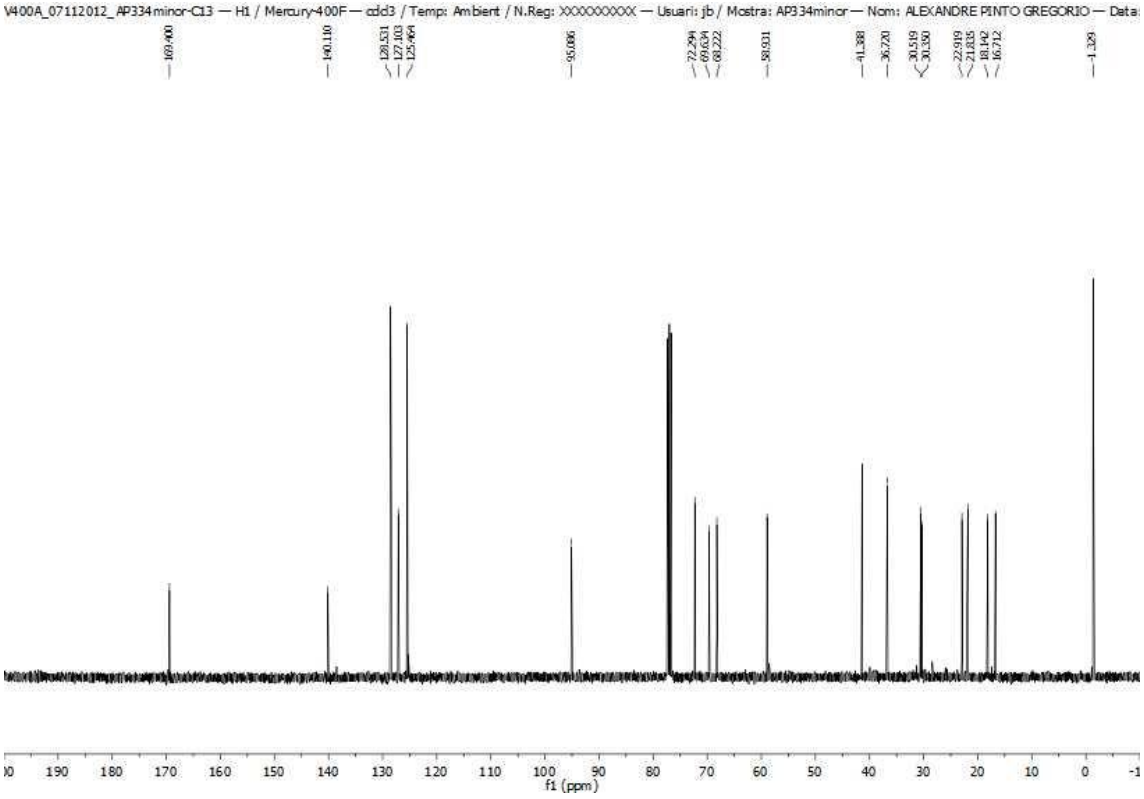


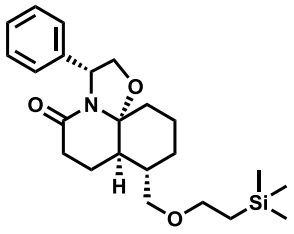
(3*R*,7a*S*,8*S*,11a*S*)-5-Oxo-3-phenyl-8-{[2-trimethylsilyl)ethoxy]methyl}decahydrooxazolo [2,3-*j*]quinoline (8b)

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.02 [s, 9H, $Si(CH_3)_3$], 0.90-0.94 (m, 2H, CH_2Si), 1.44 (dd, J = 12.8, 4.0 Hz, 1H), 1.49-1.53 (m, 2H), 1.57-1.67 (m, 3H), 1.77-1.84 (m, 2H), 1.86 (br s, 1H), 1.93-1.99 (m, 1H), 2.26-2.35 (m, 1H), 2.40-2.49 (m, 1H), 2.64 (dt, J = 18.0, 5.2 Hz, 1H, H-6), 3.29-3.36 (m, 2H, OCH_2), 3.43-3.55 (m, 2H, CH_2O), 3.87 (t, J = 8.6 Hz, 1H, H-2), 4.48 (t, J = 8.6 Hz, 1H, H-2), 5.34 (t, J = 8.6 Hz, 1H, H-3), 7.18-7.21 (m, 2H), 7.22-7.25 (m, 1H), 7.29-7.34 (m, 2H).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: –1.3, [$Si(CH_3)_3$], 16.7 (C-9), 18.1 (CH_2TMS), 21.8 (C-10), 22.9 (C-7), 30.4 (C-11), 30.5 (C-6), 36.7 (C-8), 41.4 (C-7a), 58.9 (C-3), 68.2 (OCH_2), 69.6 (C-2), 72.3 (CH_2O), 95.1 (C-11a), 125.5, 127.1 (C-*o, m*), 128.5 (C-*p*), 140.1 (C-*i*), 169.4 (C-5).


V400A_07112012_AP334minor-H1 — H1 / Mercury-400F — cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP334minor — Nom: ALEXANDRE PINTO GREGORIO — Data:
f1 (ppm)

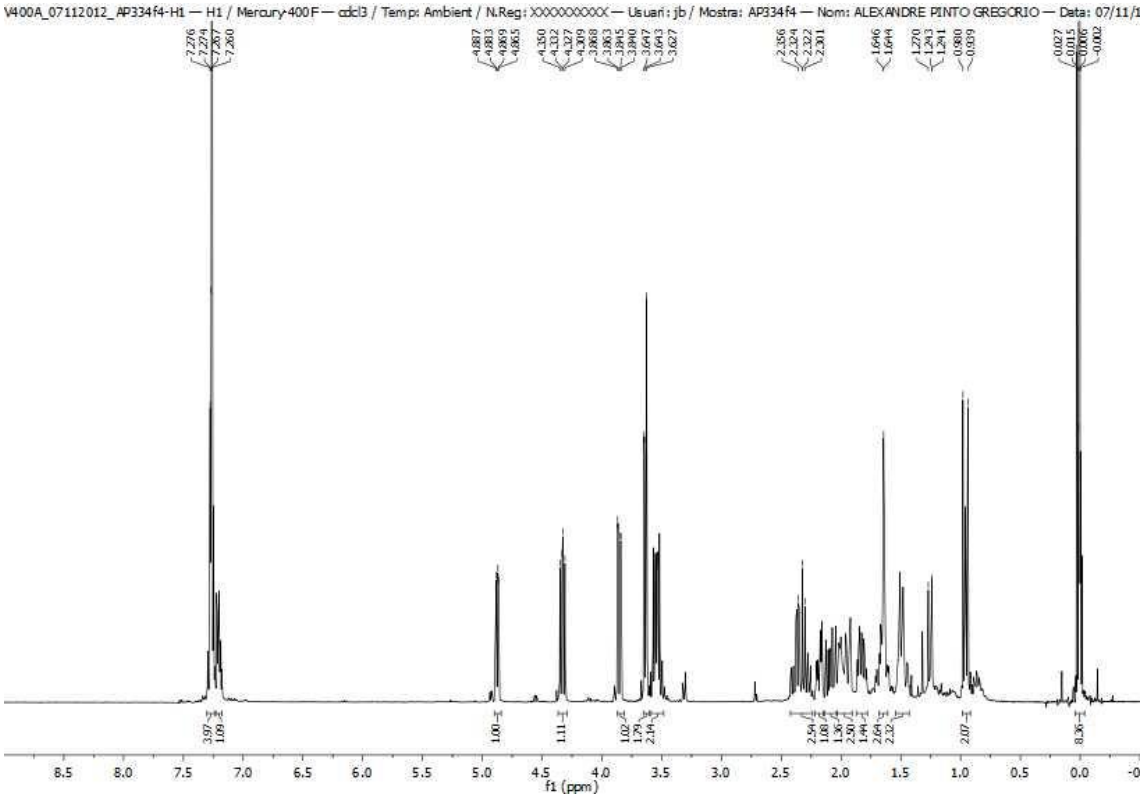

V400A_07112012_AP334minor-C13 — H1 / Mercury-400F — cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP334minor — Nom: ALEXANDRE PINTO GREGORIO — Data:
f1 (ppm)



(3*R*,7a*R*,8*R*,11a*R*)-5-Oxo-3-phenyl-8-{[2-trimethylsilyl)ethoxy]methyl}decahydrooxazolo [2,3-*j*]quinoline (8c)

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.01 [s, 9H, $Si(CH_3)_3$], 0.94-0.98 (m, 2H, CH_2Si), 1.44-1.52 (m, 2H), 1.60-1.68 (m, 3H), 1.79-1.86 (m, 2H), 1.92-2.04 (m, 3H), 2.05-2.13 (m, 1H), 2.18 (dd, J = 12.8, 5.2 Hz, 1H), 2.24-2.32 (m, 1H, H-6), 2.35-2.42 (m, 1H, H-6), 3.50-3.58 (m, 2H, OCH_2), 3.63-3.65 (m, 2H, CH_2O), 3.85 (dd, J = 9.2, 1.8 Hz, 1H, H-2), 4.33 (dd, J = 9.2, 3.2 Hz, 1H, H-2), 4.87 (dd, J = 7.2, 1.8 Hz, 1H, H-3), 7.18-7.24 (m, 1H, Ar-H); 7.25-7.30 (m, 4H, Ar-H).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: –1.4, [$Si(CH_3)_3$], 18.3 (CH_2TMS), 18.6 (C-9), 21.3 (C-10), 23.9 (C-7), 29.6 (C-11), 31.4 (C-6), 39.8 (C-8), 39.9 (C-7a), 58.8 (C-3), 68.1 (OCH_2), 70.8 (C-2), 72.4 (CH_2O), 94.5 (C-11a), 126.2 (C-H_{Ar}), 127.0 (C-H_{Ar}), 128.4 (C-H_{Ar}), 142.0 (C-*i*), 167.3 (C-5).


V400A_07112012_AP334f4-H1 — H1 / Mercury-400F — cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP334f4 — Nom: ALEXANDRE PINTO GREGORIO — Data: 07/11/1
7.276
7.274
7.267
7.260
4.887
4.883
4.869
4.865
4.350
4.332
4.327
4.309
3.868
3.863
3.845
3.840
3.647
3.643
3.627
2.356
2.324
2.322
2.301
1.646
1.644
1.270
1.243
1.241
0.980
0.939
0.027
0.015
0.006
-0.002
3.97
1.09
1.00
1.11
1.02
1.79
2.14
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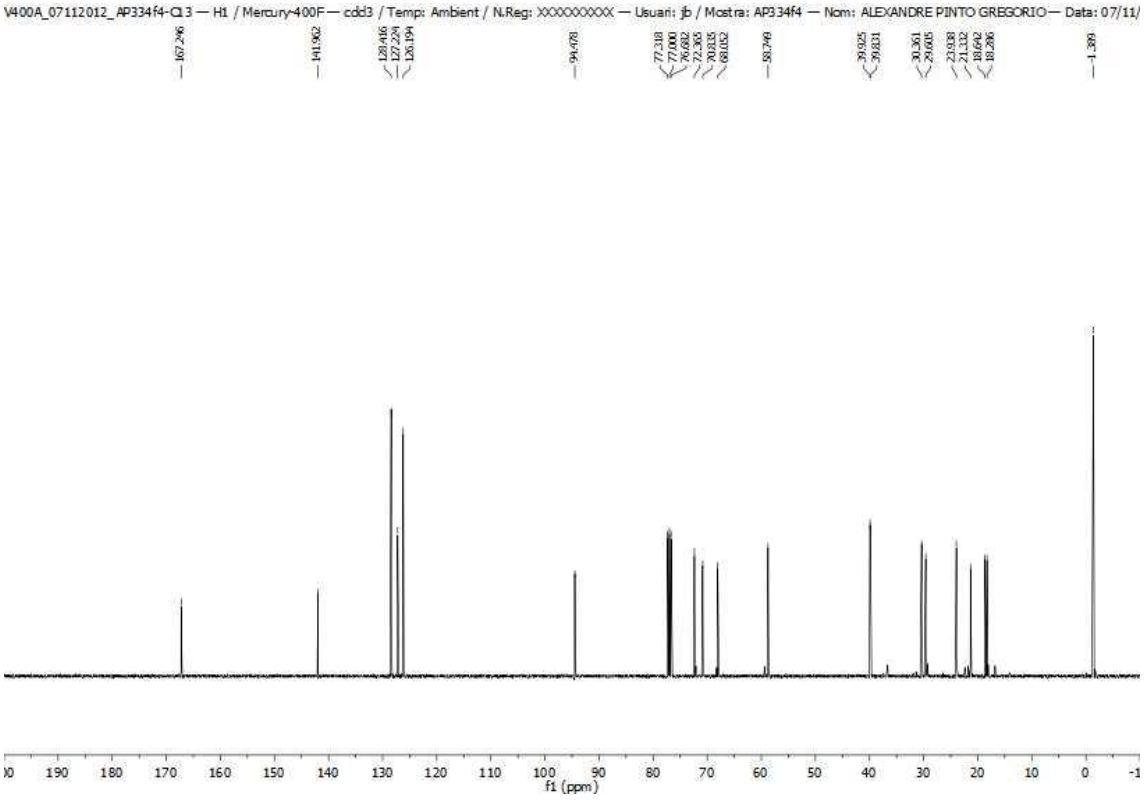
2.32
2.07
8.36
f1 (ppm)


V400A_07112012_AP334f4-C13 — H1 / Mercury-400F — cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP334f4 — Nom: ALEXANDRE PINTO GREGORIO — Data: 07/11/
167.246
141.962
128.416
127.224
126.194
94.478
77.318
77.000
76.682
72.305
70.835
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18.642
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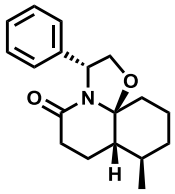
f1 (ppm)



(3*R*,7a*S*,8*R*,11a*S*)-8-Methyl-3-phenyloxodecahydrooxazolo [2,3-*j*]quinoline (9)

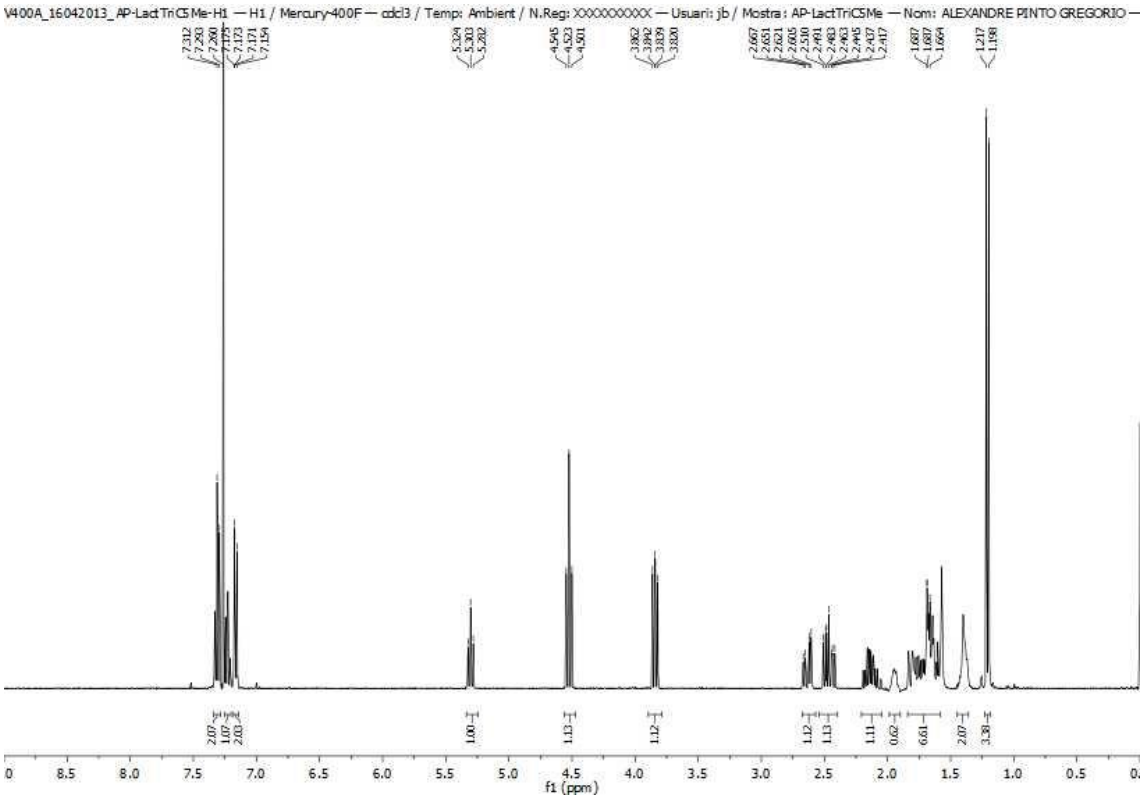
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.21 (d, J = 7.6 Hz, 3H, CH_3), 1.35-1.44 (m, 2H, H-10, H-11), 1.57-1.83 (m, 6H, H-7, H-7a, H-9, H-10, H-11), 1.90-1.98 (m, 1H, H-8), 2.08-2.19 (m, 1H, H-7), 2.46 (ddd, J = 18.4, 11.2, 7.6 Hz, 1H, H-6), 2.63 (dd, J = 18.4, 7.6 Hz, 1H, H-6), 3.84 (t, J = 8.4 Hz, 1H, H-2), 4.52 (t, J = 8.4 Hz, 1H, H-2), 5.30 (t, J = 8.4 Hz, 1H, H-3), 7.15-7.33 (m, 5H, H-Ar).

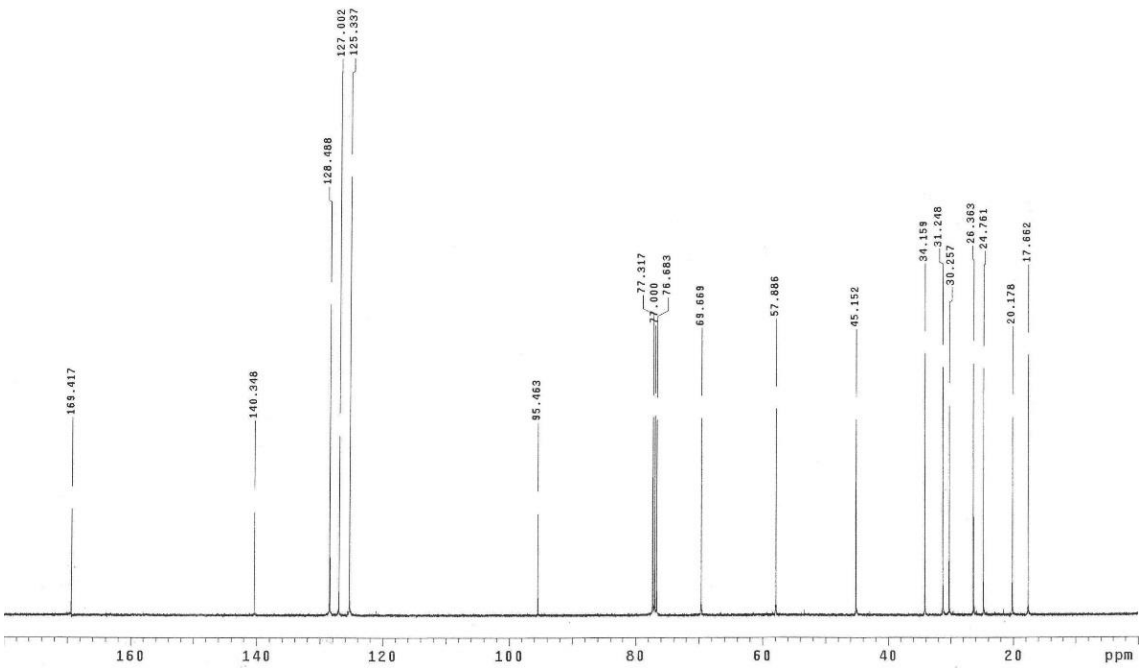
^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 17.7 (C-10), 20.2 (CH_3), 24.8 (C-7), 26.4 (C-11), 30.3 (C-9), 31.2 (C-6), 34.2 (C-8), 45.2 (C-7a), 57.9 (C-3), 69.7 (C-2), 95.5 (C-11a), 125.3 (CH-*o*), 127.0 (CH-*p*), 128.5 (CH-*m*), 140.3 (C-*i*), 169.4 (NCO).

IR (NaCl): 1654 cm^{-1}.

HRMS calcd for [$C_{18}H_{23}NO_2$ + H^+]: 286.1801; found 286.1802.

$[\alpha]^{23}_D$ = − 113.5 (c 1.0, MeOH).


V400A_16042013_AP-LactTriC5Me-H1 — H1 / Mercury-400F — cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP-LactTriC5Me — Nom: ALEXANDRE PINTO GREGORIO —
f1 (ppm)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140.348
128.488
127.002
125.337
95.463
77.317
77.000
76.683
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57.886
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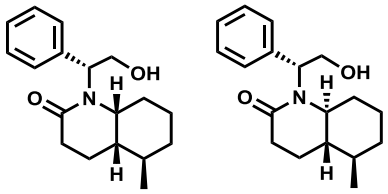
30.257
26.303
24.761
20.178
17.662
ppm



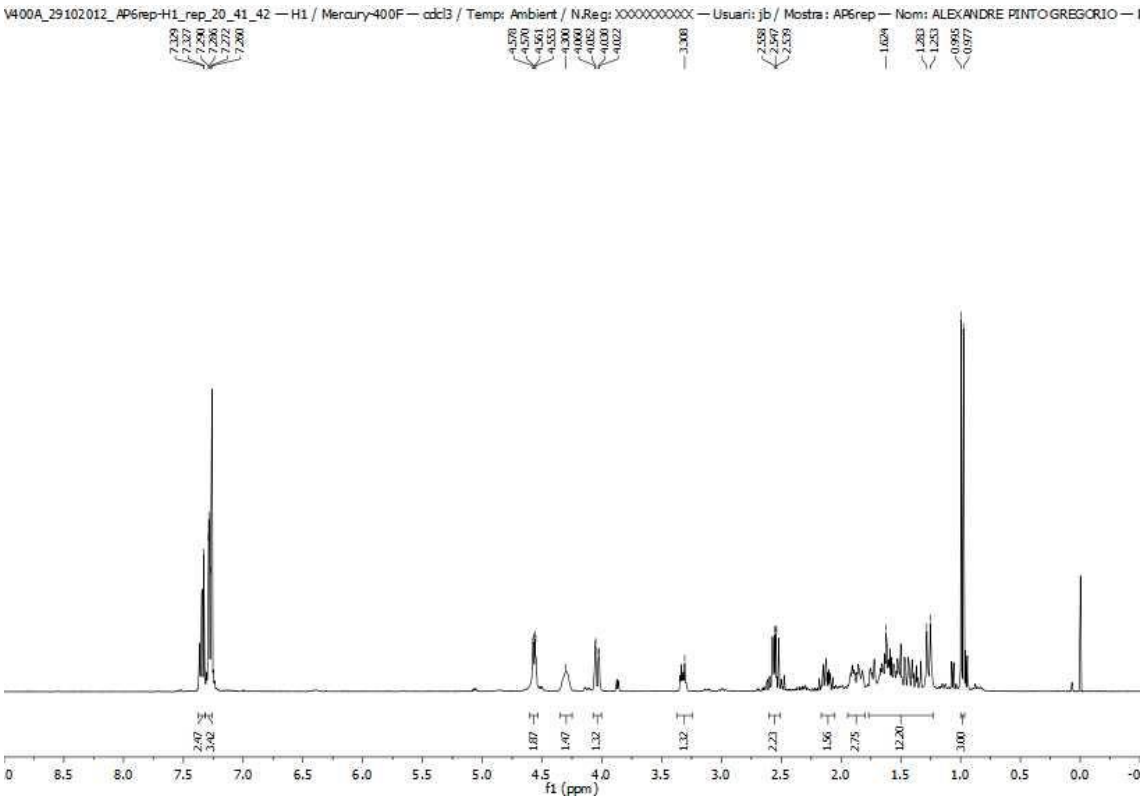
(4a*S*,5*R*,8a*R*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]--5-methyl-2-oxodecahydro-quinoline (10a)

$TiCl_4$ (2.106 mmol, 230 μL), was added to a 0.2 M solution of lactam **9** (0.702 mmol, 200 mg,) in dry DCM (4 mL) at −78ºC. The mixture was stirred at for 30 min. Et_3SiH (2.106 mmol, 340 μL) was added and the solution stirred for 45 min. The reaction mixture was allowed to warm to rt and stirred for an additional 72 h. The reaction was quenched with saturated $NaHCO_3$ and extracted with DCM. The combined organic extracts were washed with brine, dried with anhydrous $MgSO_4$, filtered and the solvent removed under reduced pressure. The residue was chromatographed (100% EtOAc) affording the desired compound **10a** and **10b** (116 mg, 57%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.99 (d, J = 7.6 Hz, 3H, CH_3), 1.23-1.79 (m, 11H, H-7, H-11), 1.81-1.94 (m, 2H, H-7a, H-8), 2.07-2.18 (m, 1H, H-7), 2.53-2.59 (m, 2H, H-6), 3.32 (dt, J = 11.2, 4.3 Hz, 1H, H-11a), 4.04 (dd, J = 11.6, 3 Hz, 1H, H-2), 4.26- 4.36 (m, 1H, H-2), 4.57 (dd, J = 6.4, 2.6 Hz, 1H, H-3), 7.26-7.30 (m, 3H, H-Ar), 7.32-7.35 (m, 3H, H-Ar).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 19.0 (CH_3), 19.7 (C-10), 22.5 (C-7), 26.1 (C-11), 28.1 (C-9), 32.0 (C-6), 33.2 (C-8), 40.1 (C-7a), 57.1 (C-11a), 64.8 (C-2), 66.6 (C-3), 127.2 (CH-*o*), 127.4 (CH-*p*), 128.6 (CH-*m*), 137.2 (Cq-Ar), 172.0 (NCO).

HRMS calcd for [$C_{18}H_{25}NO_2$ + H^+]: 288.1958, found 288.195.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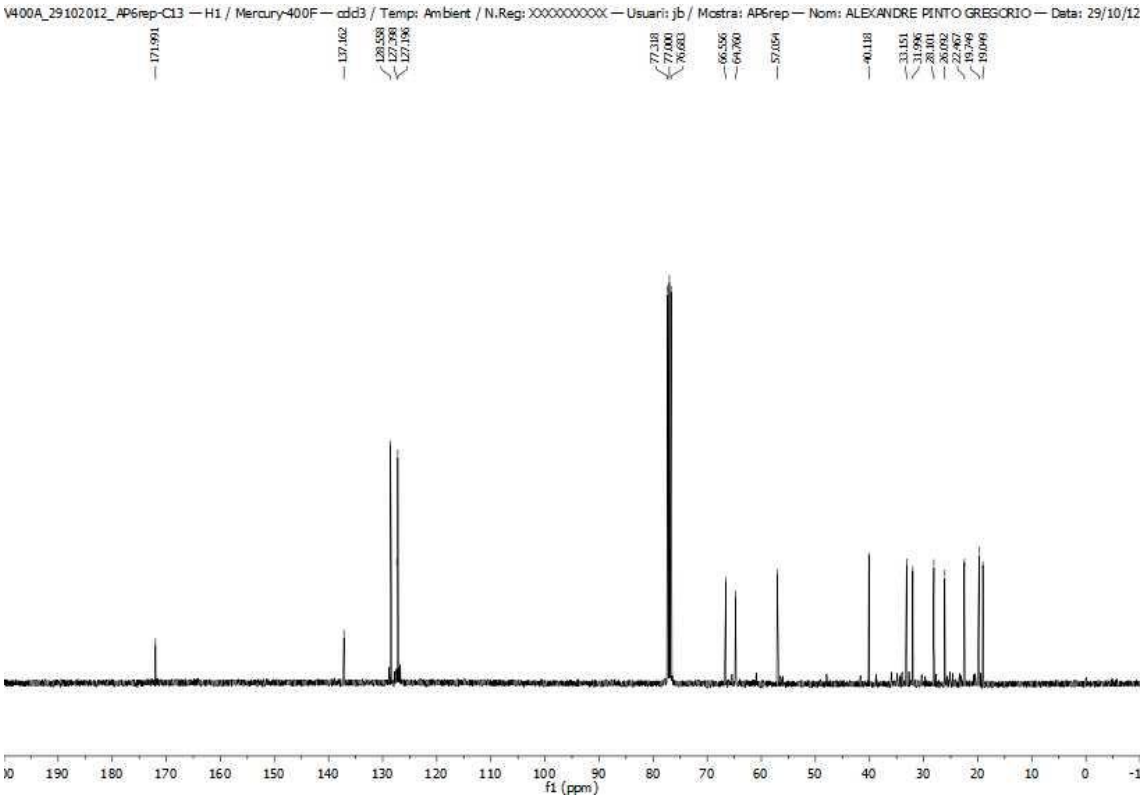
7.329
7.327
7.290
7.286
7.272
7.260
4.578
4.570
4.561
4.553
4.300
4.060
4.052
4.039
4.032
3.308
2.558
2.547
2.539
1.624
1.283
1.253
0.995
0.977
2.47
3.42
1.87
1.47
1.32
1.32
2.23
1.56
2.75
12.20
3.00
f1 (ppm)


V400A_29102012_AP6rep-C13 — H1 / Mercury-400F — cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP6rep — Nom: ALEXANDRE PINTO GREGORIO — Data: 29/10/12
171.991
137.162
128.588
127.398
127.196
77.318
77.000
76.683
66.556
64.760
57.054
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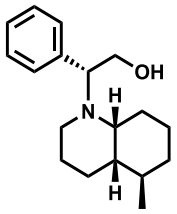
26.092
22.967
19.749
19.049
f1 (ppm)



(4a*S*,5*R*,8a*R*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-5-methyldecahydroquinoline (11)

$LiAlH_4$ (1.10 g, 28.93 mmol) was slowly added to a suspension of $AlCl_3$ (1.19 g, 8.94 mmol) in THF (94 mL) at 0 ºC. After the mixture was stirred at this temperature for 30 min and cooled to –78 ºC, a solution of lactam **9** (1.27g, 4.45 mmol) in THF (5 mL) was added dropwise. The stirring was continued at –78 ºC for 90 min and at room temperature for 3 h. Water was slowly added, the resulting mixture was filtered over Celite®, and the filtrate was washed with EtOAc. The organic extracts were dried and concentrated. Flash chromatography (hexane to 8:2 hexane–EtOAc) afforded **13** (960 mg, 79%) as a colorless oil.

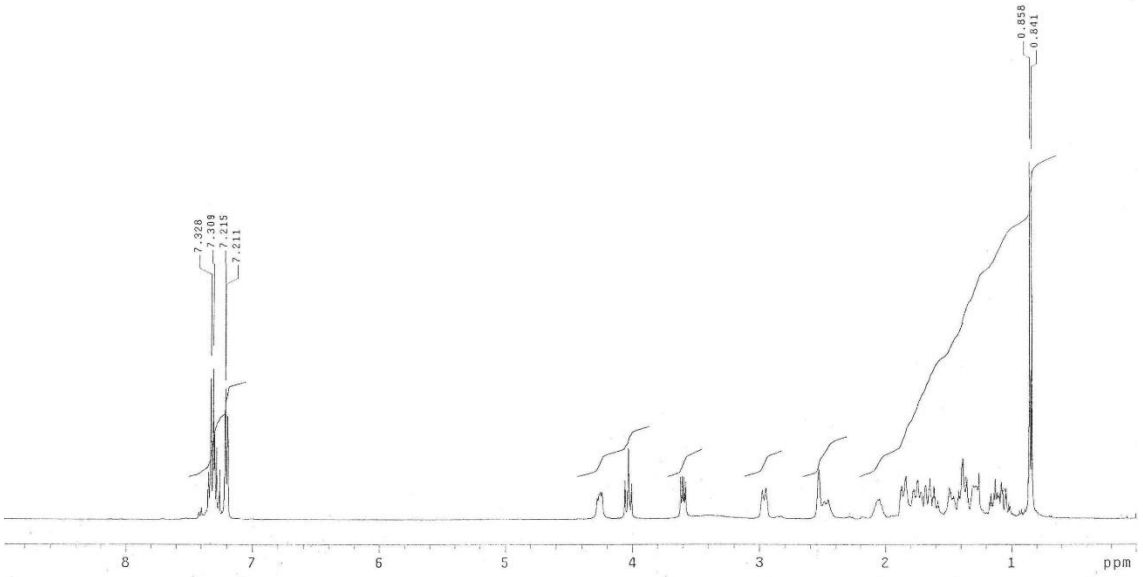
^{1}H-NMR (400 MHz; $CDCl_3$) δ: 0.85 (d, J = 6.8 Hz, 3 H, CH_3), 1.01-1.17 (m, 2 H, H-4, H-8), 1.25-1.30 (m, 2 H, H-4a, H-6), 1.34-1.50 (m, 2 H, H-3, H-7), 1.56-1.88 (m, 6 H, H-2, H-3, H-4, H-6, H-7, H-8), 2.04-2.08 (m, 1 H, H-5), 2.46-2.53 (m, 1 H, H-8a), 2.96 (d, J = 10.4 Hz, 1 H, H-2), 3.60 (dd, J = 10.4, 5.0 Hz, 1 H, H-2'), 4.03 (t, J = 10.4 Hz, 1 H, H-2'), 4.24-4.28 (m, 1 H, H-1'), 7.20-7.35 (m, 5 H, Ar-H).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 19.7 (CH_3), 20.6 (C-7), 21.6 (C-3), 27.0 (C-4), 28.7 (C-5), 29.2 (C-6), 35.4 (C-8), 44.4 (C-4a), 46.1 (C-2), 57.6 (C-8a), 59.9 (C-1' and C-2'), 127.5 (C-*o, m*), 128.1 (C-*p*), 128.9 (C-*o, m*), 135.9 (C-*i*).

IR (film): 3429 cm^{-1}.

HMRS calcd for [$C_{18}H_{27}NO + H^+$]: 274.2165, found: 274.2168.

$[\alpha]^{23}_D$ = − 41.4 (*c* 0.9, MeOH).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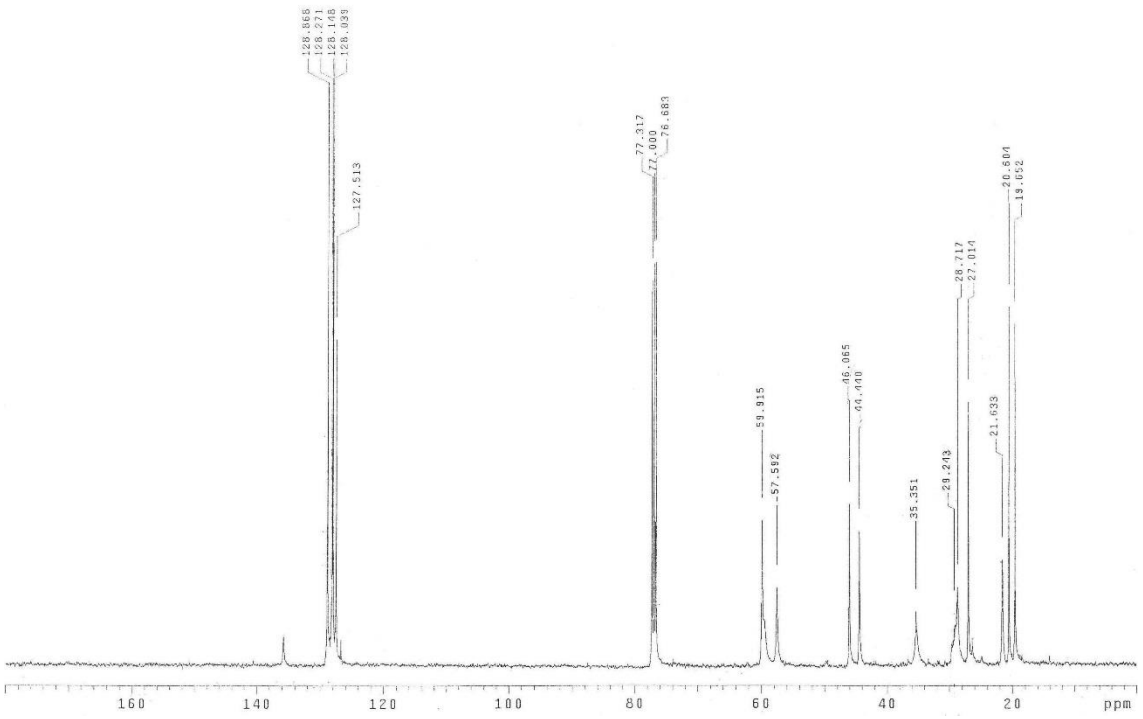
7.328
7.309
7.215
7.211
8
7
6
5
4
3
2
1
ppm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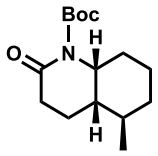
128.271
128.148
128.039
127.513
77.317
77.000
76.683
59.915
57.582
46.065
44.440
35.351
29.243
28.717
27.014
21.633
20.604
19.052
160
140
120
100
80
60
40
20
ppm



(4a*S*,5*R*,8a*R*)-1-(*tert*-Butoxycarbonyl)-5-methyl-2-oxodecahydroquinoline (12)

Method A: *n*-BuLi (680 µL, 1.09 mmol. 1.6M in Hexane) was added dropwise to a solution of compound **13** (173 mg, 1.03 mmol) in dry THF (12 mL) at −78 ºC. After 30 min, a solution of Boc_2O (340 mg, 1.55 mmol) in dry THF (3.1 mL) was added, and the mixture stirred for 1h 30 min at −78 ºC. Sat. aq. NH_4Cl was added and the crude mixture extracted with EtOAc. . The combined organic extracts were dried and concentrated. Flash chromatography (7:3 hexane–EtOAc) afforded **12** (250 mg, 90%) as a white solid.

Method B: $NaIO_4$ (1.79 g, 8.37 mmol) and $RuCl_3 \cdot nH_2O$ (17.4 mg, 0.08 mmol) were added to a heterogenous solution of **14** (212 mg, 0.84 mmol) in CCl_4–MeCN–H_2O (6 mL, 3:3:4) at 0 ºC. The mixture was stirred at 0 ºC for 5 min and at room temperature for 1 h. Then, EtOAc was added, the resulting mixture was filtered through Celite®, and the filtrate was concentrated. Flash chromatography (7:3 hexane–EtOAc) afforded **12** (164 mg, 73%) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.08 (d, J = 7.3 Hz, 3H, CH_3), 1.20-1.28 (m, 1H, H-7), 1.45-1.68 (m, 5H, H-4, H-6, H-7, H-8), 1.51 [s, 9H, $C(CH_3)_3$], 1.76-1.93 (m, 3H, H-4a, H-5, H-6), 2.05-2.17 (m, 1H, H-4), 2.39-2.59 (m, 2H, H-3), 4.13-4.21 (m, 1H, H-8a).

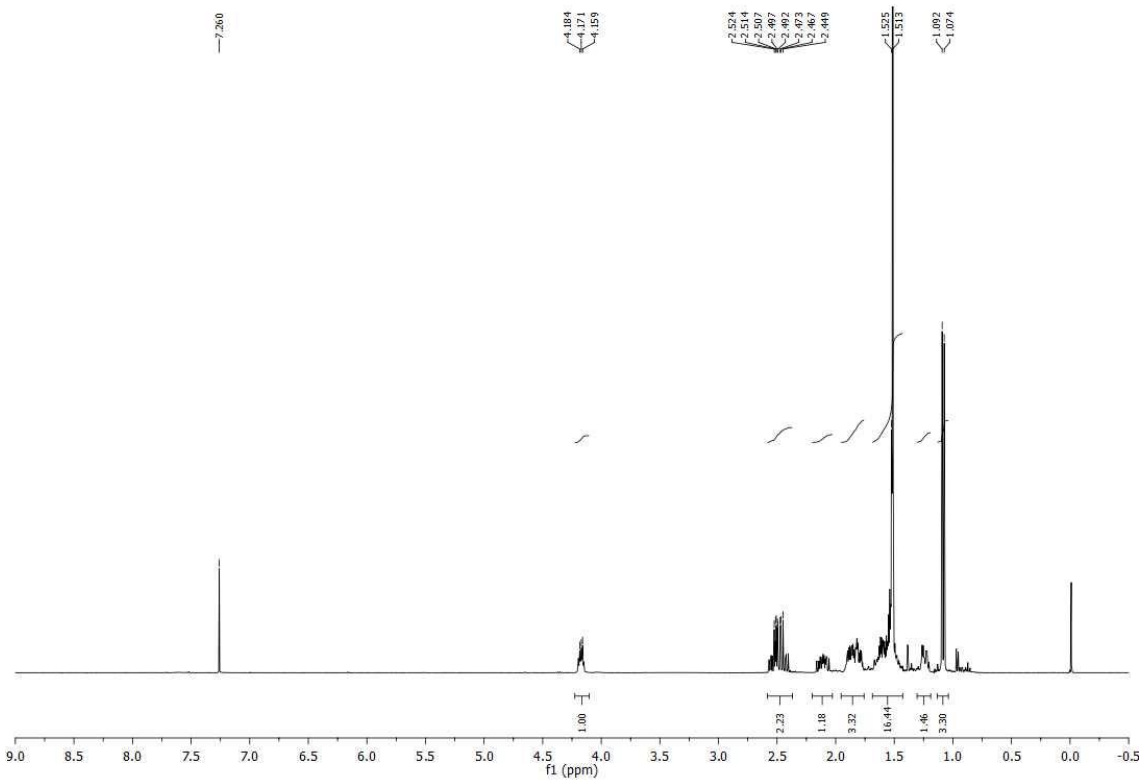
^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 19.0 (CH_3), 19.8 (C-7), 23.0 (C-4), 27.2 (C-7), 27.9 [(CH_3)$_3$C], 28.7 (C-6), 32.6 (C-5), 33.4 (C-3), 39.3 (C-4a), 54.6 (C-8a), 82.7 [(CH_3)$_3$*C*], 153.3 (CO), 171.4 (C-2).

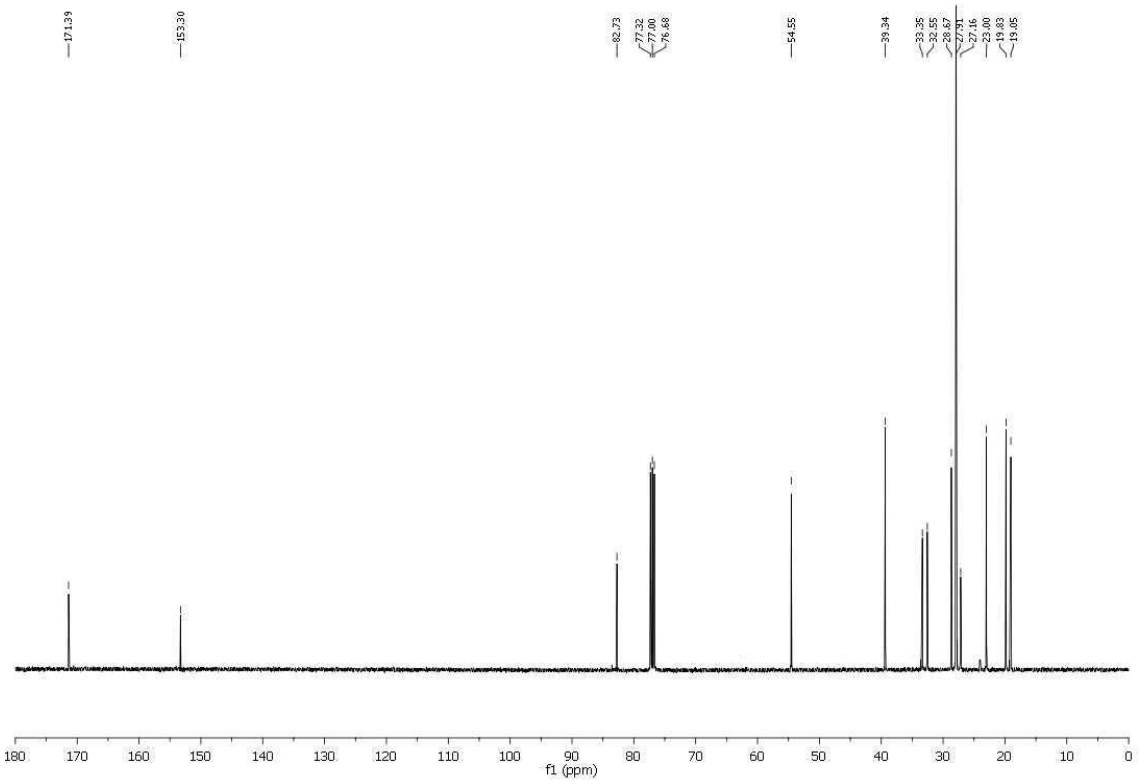
IR (film): 1765, 1712 cm^{-1}.

HRMS calcd for [$C_{15}H_{25}NO_3$ + Na^+]: 290.1727, found 290.1723.

$[\alpha]^{23}_D$ = – 23.92 (*c* 1.0, $CHCl_3$).

Melting point = 99–102 ºC.


7.260
4.184
4.171
4.159
2.524
2.514
2.507
2.497
2.492
2.473
2.467
2.449
1.525
1.513
1.092
1.074
1.00
2.23
1.18
3.32
16.44
1.46
3.30
f1 (ppm)


171.39
153.30
82.73
77.32
77.00
76.68
54.55
39.34
33.35
32.55
28.67
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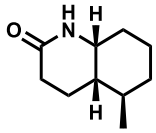
27.16
23.00
19.83
19.05
f1 (ppm)

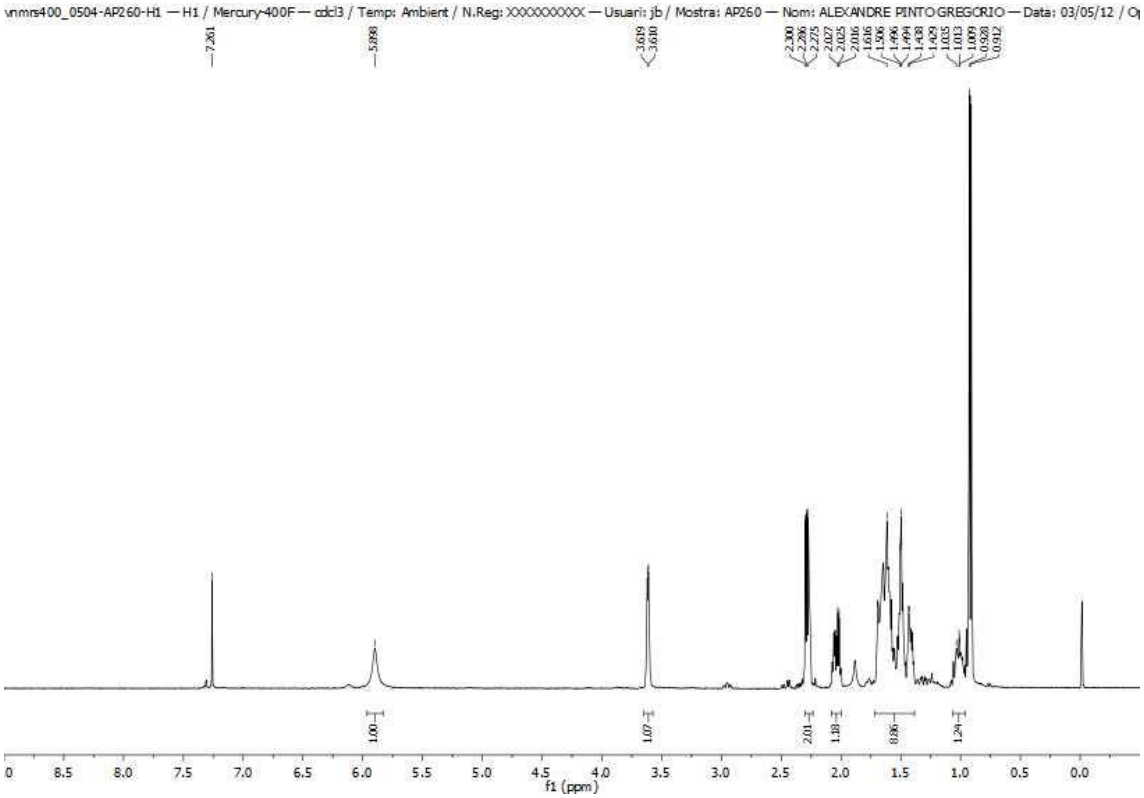


(4a*S*,5*R*,8a*R*)-5-Methyl-2-oxodecahydroquinoline (13)

Compound **10** (1.392 mmol, 400 mg) in THF (2 mL), were added dropwise to stirring solution of Na metal in liquid NH_3 (30 mL) at −78ºC. The reaction mixture was then warmed to −33ºC, and stirred for 15 min. The reaction was quenched with solid NH_4Cl, and continued stirring until all NH_3 evaporated. The residue was chromatographed (7:3 to 100, Hexane-EtOAc) affording a 5:1 mixture of the desired compound **11** and the *trans* isomer (202 mg, 87%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.93 (d, J = 6.4 Hz, 3H, CH_3), 0.99-1.09 (m, 1H), 1.39-1.71 (m, 8H), 2.00-2.10 (m, 1H), 2.26-2.32 (m, 2H), 3.59-3.64 (m, 1H, H-8a), 5.90 (bs, 1H, NH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 19.3 (CH_3), 20.0 (CH_2), 23.1 (CH_2), 27.3 (CH_2), 27.6 (CH), 31.8 (CH_2), 33.7 (CH_2), 39.7 (CH), 52.2 (CH), 172.9 (NCO).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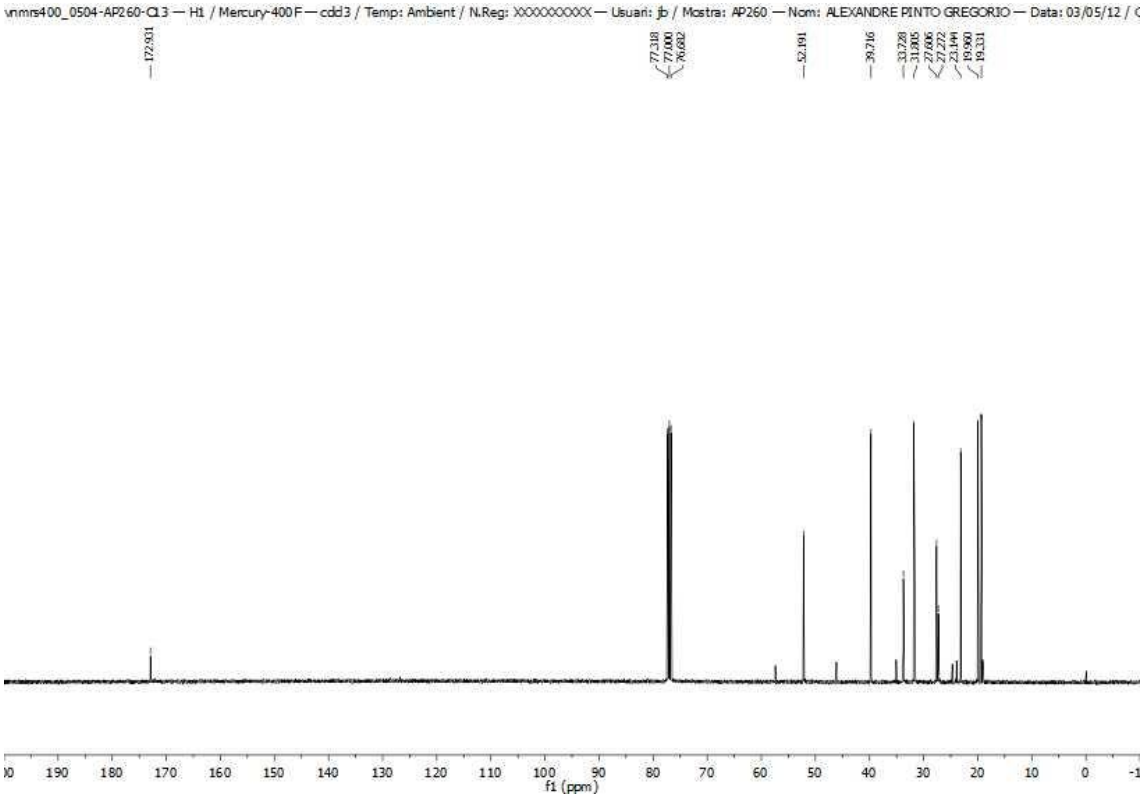
5.898
3.619
3.610
2.300
2.286
2.275
2.027
2.015
2.016
1.636
1.506
1.496
1.494
1.438
1.429
1.035
1.013
1.009
0.938
0.912
1.00
1.07
2.01
1.18
8.86
1.24
f1 (ppm)


\nmrs400_0504-AP260-CL3 — H1 / Mercury-400F — cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP260 — Nom: ALEXANDRE PINTO GREGORIO — Data: 03/05/12 / C
172.931
77.318
77.000
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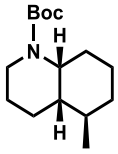
52.191
39.716
33.728
31.905
27.000
27.272
21.344
19.593
19.331
f1 (ppm)



(4a*S*,5*R*,8a*R*)-1-(*tert*-Butoxycarbonyl)-5-methyldecahydroquinoline (14)

A solution of **11** (960 mg, 3.52 mmol) and di-*tert*-butyl dicarbonate (1.0 g, 4.58 mmol) in MeOH (50 mL) containing 40% $Pd(OH)_2$ (380 mg) was stirred under hydrogen at room temperature for 24 h. The catalyst was removed by filtration, and the filtrate was concentrated. Flash chromatography (8:2 hexane–Et_2O) afforded **14** (640 mg, 72%) as an oil.

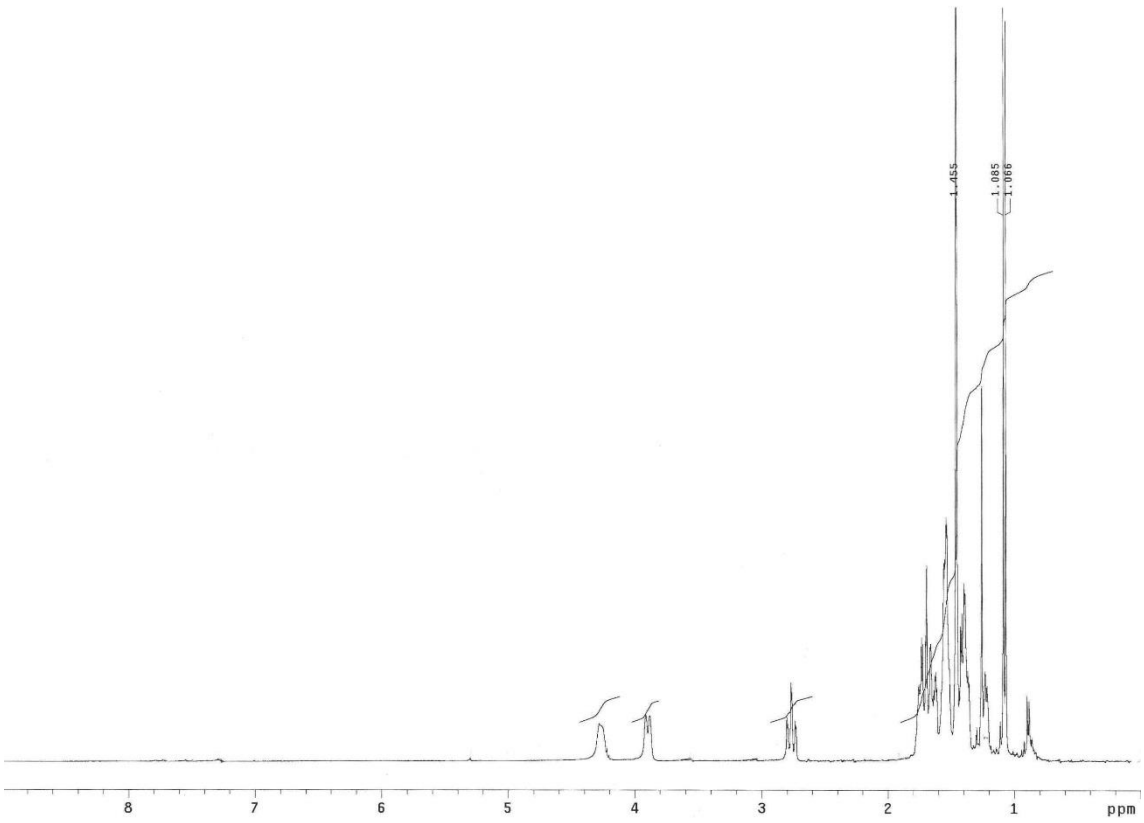
^{1}H-NMR (400 MHz; $CDCl_3$) δ: 1.76 (d, J = 7.6 Hz, 3H, CH_3), 1.19-1.26 (m, 1H, H-6), 1.34-1.43 (m, 3H, H-3, H-4, H-8), 1.45 [s, 9H, $C(CH_3)_3$], 1.51-1.58 (m, 4H, H-4a, H-6, H-7), 1.60-1.77 (m, 4H, H-3, H-4, H-5, H-8), 2.76 (td, J = 13.0, 2.8 Hz, 1H, H-2), 3.90 (d, J = 12.0 Hz, 1H, H-2), 4.23-4.30 (m, 1H, H-8a).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 19.0 (CH_3), 20.1 (C-7), 24.0 (C-4), 25.7 (C-8), 25.9 (C-3), 26.3 (C-6), 28.5 [(CH_3)$_3$C], 34.2 (C-5), 39.5 (C-2), 41.0 (C-4a), 49.5 (C-8a), 79.0 [(CH_3)$_3$*C*], 155.0 (NCOO).

IR (film): 1693 cm^{-1}.

HMRS calcd for [$C_{15}H_{27}NO_2$ + H^+]: 254.1958, found: 254.1970.

$[\alpha]^{22}_D$ = –37.3 (*c* 1.1, MeOH).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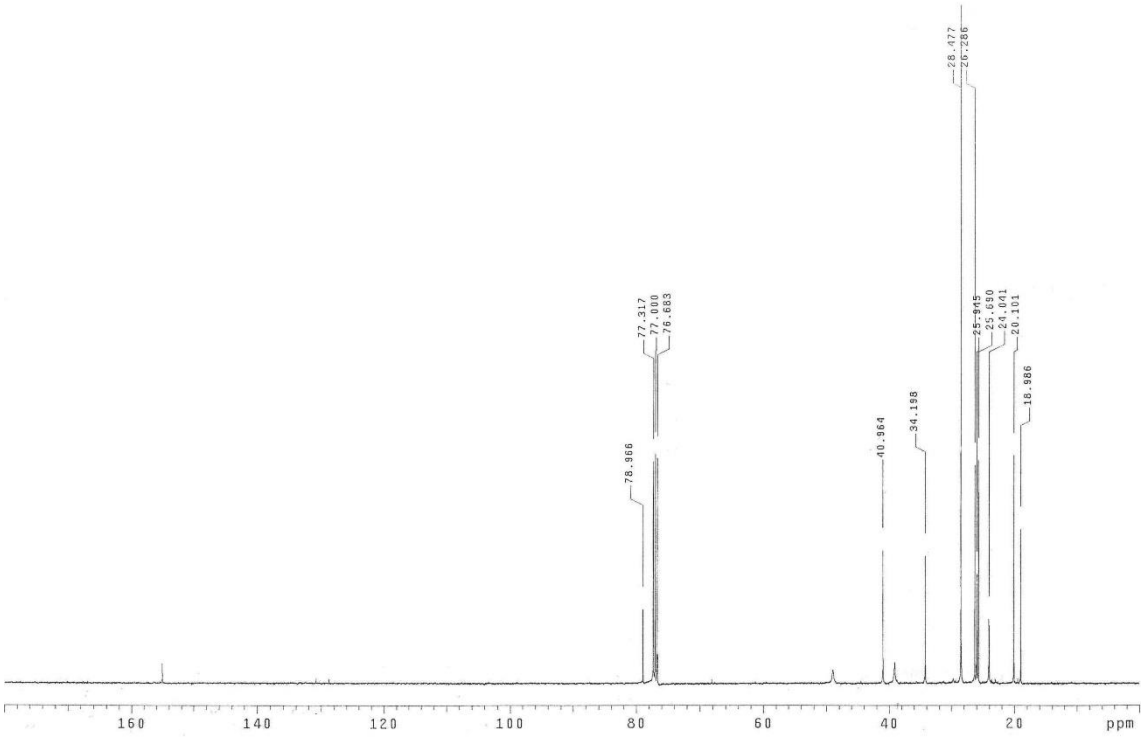
4
3
2
1
ppm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76.683
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25.690
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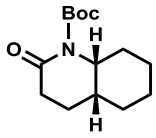
40
20
ppm



(4a*S*,8a*R*)-1-(*tert*-Butoxycarbonyl)-2-oxodecahydroquinoline (18)

$NaIO_4$ (644 mg, 3.01 mmol) and $RuCl_3 \cdot nH_2O$ (6.3 mg, 0.0301 mmol) were added to a heterogenous solution of **17** (72 mg, 0.301 mmol) in CCl_4–MeCN–H_2O (1.7 mL, 3:3:4) at 0 ºC. The mixture was stirred at 0 ºC for 5 min and at room temperature for 5 h. Then, EtOAc was added, the resulting mixture was filtered through Celite®, and the filtrate was concentrated. Flash chromatography (4:6 hexane–EtOAc) afforded **18** (72 mg, 95%) as a colorless oil.

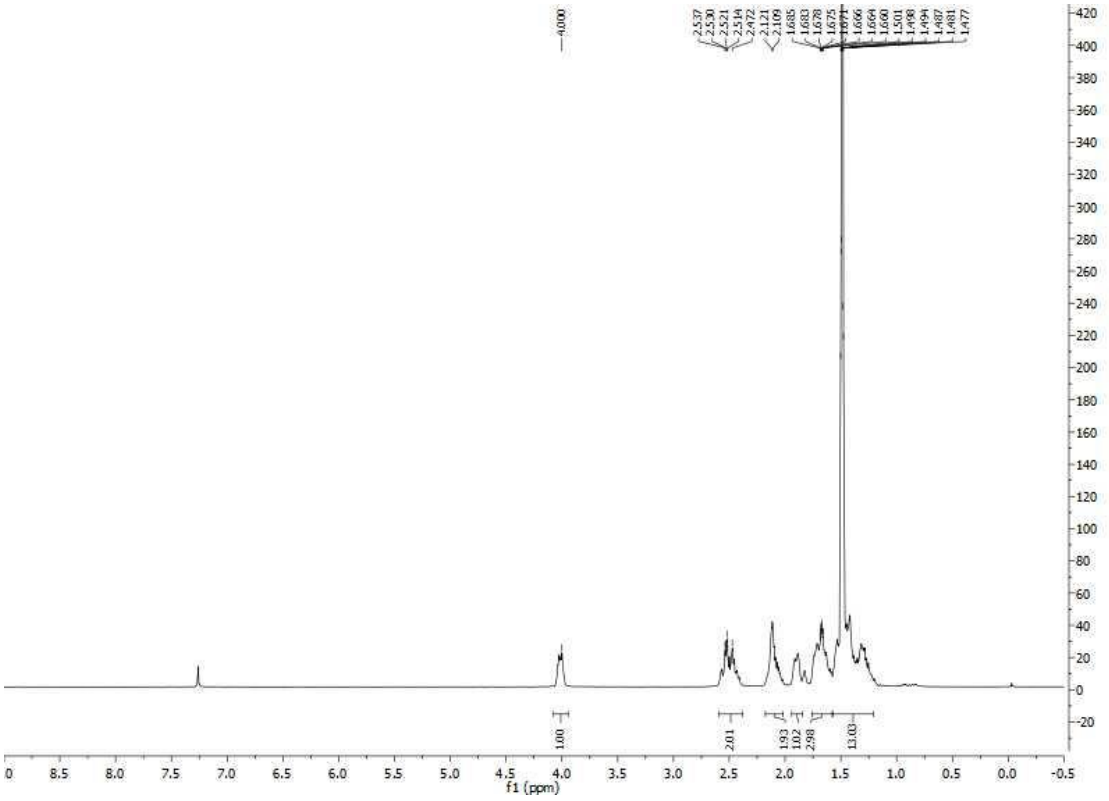
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.24-1.55 (m, 5H, H-4, H-5, H-7, H-8), 1.48 (br s, 9H, 3 CH_3), 1.58-1.74 (m, 3H, H-5, H-6), 1.87-1.92 (m, 1H, H-8), 2.02.-2.12 (m, 2H, H-4, H-4a), 2.41-2.58 (m, 2H, H-3), 3.99-4.04 (m, 1H, H-8a).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 20.0 (C-7), 21.3 (C-4), 25.1 (C-5), 27.9 [(*C*H_3)$_3$C], 28.2 (C-8), 30.3 (C-6), 33.3 (C-4a), 34.0 (C-3), 58.0 (C-8a), 82.6 [(CH_3)$_3$*C*], 152.8 (CO), 171.2 (C-2).

IR (film): 1765, 1712 cm^{-1}.

HRMS calcd for [$C_{14}H_{23}NO_3$ + Na^+]: 276.1570, found 276.1574.

$[\alpha]^{23}_D$ = + 2.19 (*c* 1.0, MeOH).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1.664
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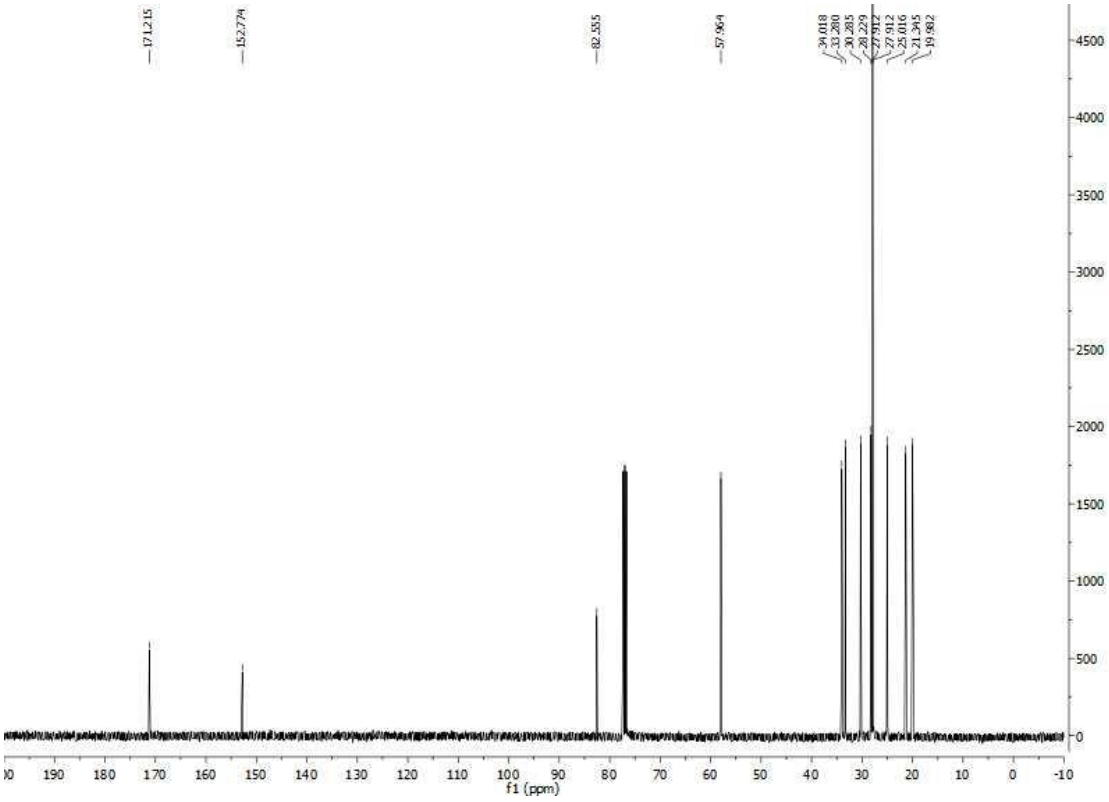
1.93
1.02
2.98
13.03
f1 (ppm)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34.018
33.280
30.285
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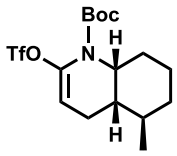
25.016
21.345
19.982
f1 (ppm)



(4a*S*,5*R*,8a*R*)-1-(*tert*-Butoxycarbonyl)-2-(trifluoromethylsulfonyloxy)-5-methyl-1,4,4a,5,6,7,8,8a-octahydroquinoline (19)

A solution of LiHMDS (1.7 mL of a 1 M solution in THF, 1.7 mmol) in THF (1.7 mL) was added to a solution of lactam **12** (300 mg, 1.12 mmol) in THF (3.8 mL) at –78 ºC, and the mixture was stirred at this temperature for 2 h. Then, a solution of Comins' reagent (880 mg, 2.24 mmol) in THF (3.7 mL) was added, and the reaction mixture was allowed to reach room temperature. After 1.5 h of stirring, the reaction was quenched by addition of 10% aqueous NaOH (6 mL), and the mixture was extracted with Et_2O. The combined organic extracts were dried and concentrated. Flash chromatography with SiO_2 previously deactivated with Et_3N (7:3 hexane–EtOAc) afforded the title vinyl triflate **19** (425 mg, 95%) as a white solid.

^{1}H-NMR (400 MHz; $CDCl_3$) δ: 1.12 (d, J = 7.2 Hz, 3H, CH_3), 1.22-1.29 (m, 2H, H-7), 1.49 [br s, 9H, $C(CH_3)_3$], 1.54-1.62 (m, 4H, H-6, H-8), 1.76-1.86 (m, 2H, H-4a, H-5), 2.21 (dt, J = 9.2, 3.6 Hz, 2H, H-4), 4.47 (dt, J = 12.4, 3.8 Hz, 1H, H-8a), 5.22 (t, J = 3.8 Hz, 1H, H-3).

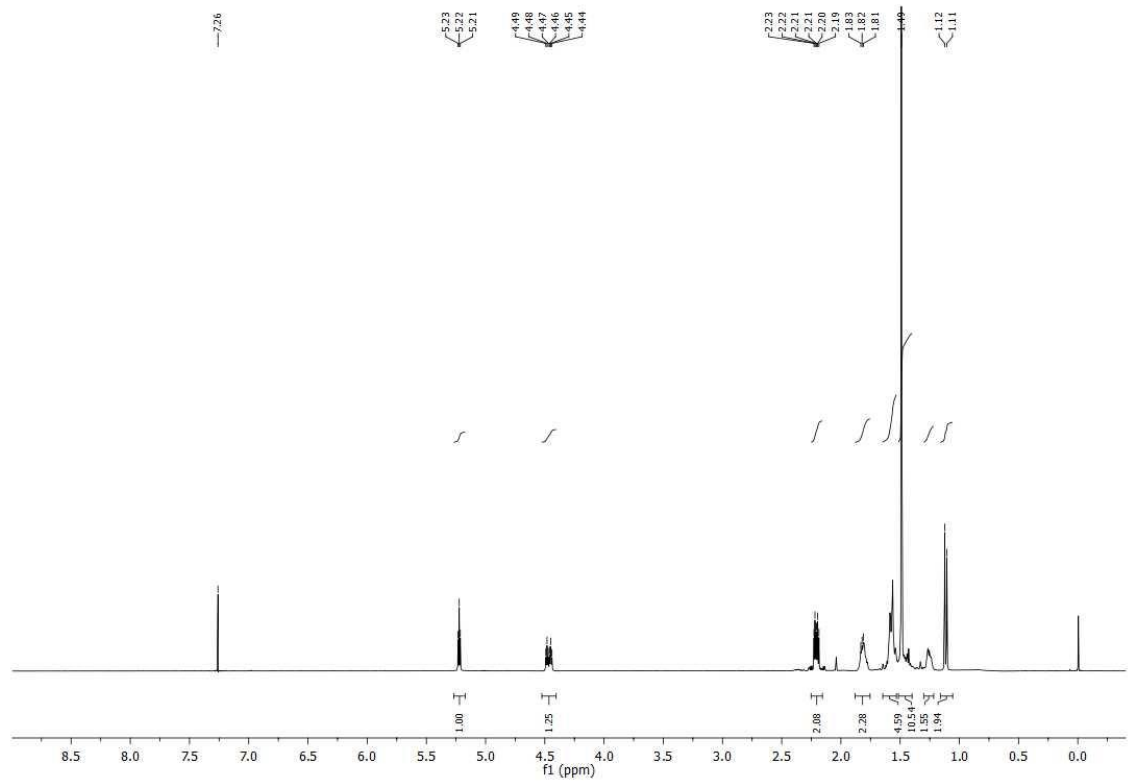
^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 18.8 (CH_3), 20.2 (C-6), 24.5 (C-8), 25.3, (C-4), 25.4 (C-7), 28.0 [(CH_3)$_3$C], 32.1 (C-5), 37.2 (C-4a), 52.3 (C-8a), 82.7 [(CH_3)$_3$C], 105.8 (C-3), 118.4 (CF_3), 138.5 (C-2), 152.6 (CO).

IR (film): 1675, 1168 cm^{-1}.

HRMS calcd for [$C_{16}H_{24}F_3NO_5S + Na^+$]: 422.1219, found 422.1222.

$[\alpha]^{23}_D$ = – 62.1 (c 1.0, $CHCl_3$).

Melting point: 52–55 ºC.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5.23
5.22
5.21
4.49
4.48
4.47
4.46
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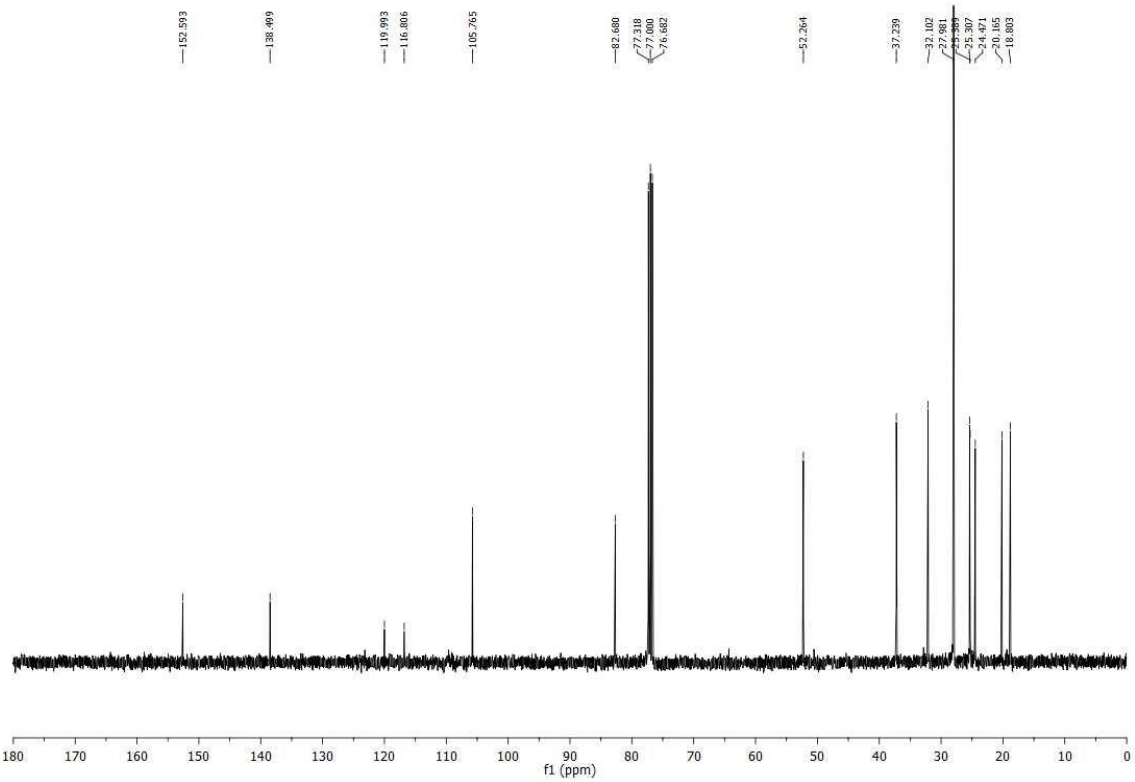
4.44
2.23
2.22
2.21
2.21
2.20
2.19
1.83
1.82
1.81
1.49
1.12
1.11
1.00
1.25
2.08
2.28
4.59
10.54
1.55
1.94
f1 (ppm)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77.000
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52.264
37.239
32.102
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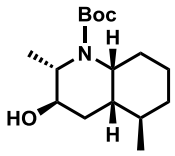
25.307
24.471
20.165
18.803
f1 (ppm)



(2*S*,3*R*,4a*S*,5*R*,8a*R*)-1-(*tert*-Butoxycarbonyl)-3-hydroxy-2,5-dimethyldecahydroquinoline (21)

First step: MeLi (1.56 mL, of a 1.6 M solution in Et_2O, 2.50 mmol) was added to a suspension of CuI (238 mg, 1.25 mmol) in THF (6.3 mL) at –20 ºC, and the mixture was stirred at this temperature for 30 min. After cooling to –78 ºC, the vinyl triflate **19** (100 mg, 0.25 mmol) in THF (1 mL) was added dropwise. Stirring was continued overnight, allowing the mixture to slowly reach room temperature. Hexane was added, and the resulting suspension was filtered over Celite®, which was then washed with EtOAc. The filtrates were concentrated, and the resulting residue was dissolved in Et_2O. The solution was filtered through 0.45 µm HPLC filters and concentrated to afford enecarbamate **20**, which was used without further purification in the next step.

Second step: $BH_3 \cdot SMe_2$ (1.25 mL of a 2.0 M solution in THF, 2.50 mmol) was added to a solution of the above crude in dry THF (23 mL) at –78 ºC. The mixture was stirred overnight and allowed to slowly warm to room temperature. Then, $Me_3NO \cdot 2H_2O$ (417 mg, 3.75 mmol) was added, and the mixture was heated at reflux for 45 min. After cooling to room temperature, the solution was concentrated, water was added, and the resulting mixture was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated. Flash chromatography (hexane to 8:2 hexane–EtOAc) afforded alcohol **21** (55 mg, 78%) as a white solid.

^{1}H-NMR (400 MHz; $CDCl_3$) δ: 1.10 (d, J = 7.6 Hz, 3 H, CH_3), 1.17 (3 H, d, J = 7.2 Hz, CH_3), 1.24-1.32 (2 H, m, H-7), 1.40-1.81 (7 H, m, H-3', H-4, H-5, H-6, H-8), 1.46 [9 H, s, $C(CH_3)_3$], 1.96-2.12 (2 H, m, H-4a, H-4), 3.81 (1 H, br s, H-3), 4.13 (1 H, q, J = 7.2 Hz, H-2), 4.21 (1 H, br s, H-8a).

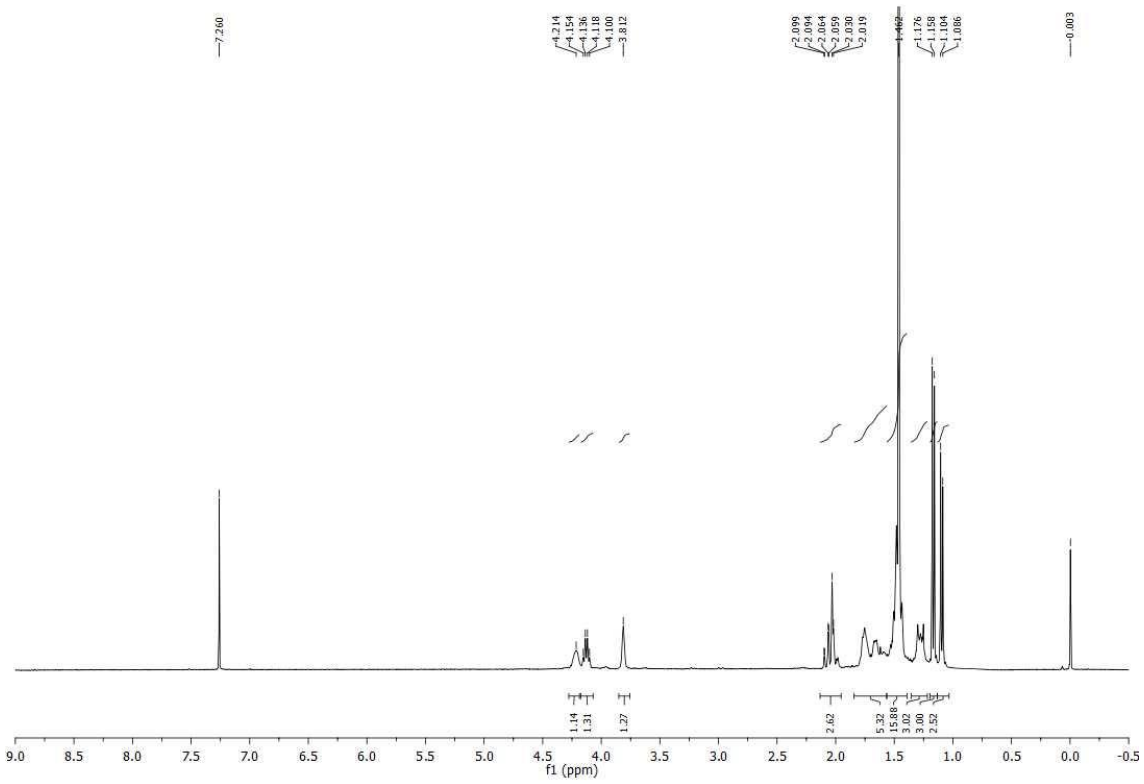
^{13}C-NMR (100.6 MHz; $CDCl_3$) δ: 19.4 (C-5), 20.1 (C-7), 20.3 (CH_3), 26.7, 28.1, 28.5 [(CH_3)$_3$C], 33.1, 33.7, 49.4 (C-8a), 53.5 (C-2), 69.5 (C-3), 79.4 [(CH_3)$_3$*C*], 155.8 (NCOO).

IR (film): 3430, 1682 cm^{-1}.

HRMS calcd for [$C_{16}H_{29}NO_3$ + H^+]: 284.2220, found 284.2214.

$[\alpha]^{23}_D$ = +7.96 (*c* 0.7, MeOH).

Melting point = 133−36 ºC.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4.136
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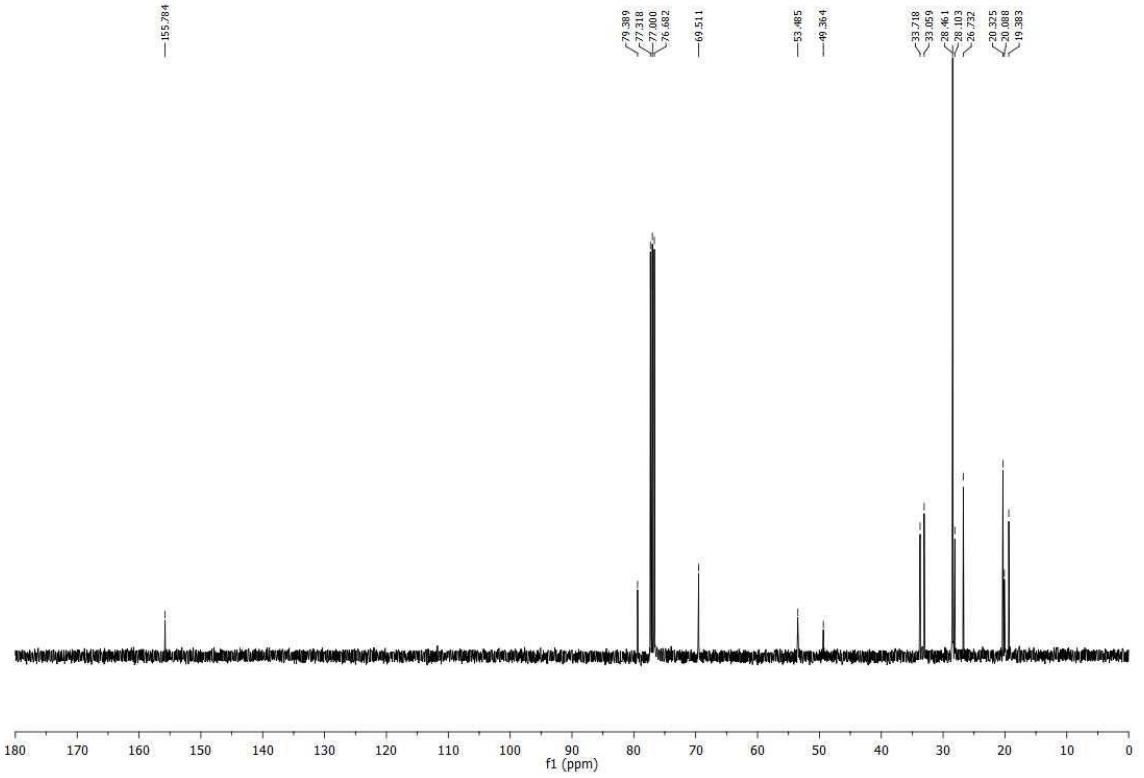
2.094
2.064
2.059
2.030
2.019
1.462
1.176
1.158
1.104
1.086
0.003
1.14
1.31
1.27
2.62
5.32
15.88
3.02
3.00
2.52
f1 (ppm)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77.000
76.682
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28.461
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20.325
20.088
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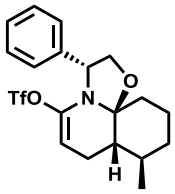
f1 (ppm)

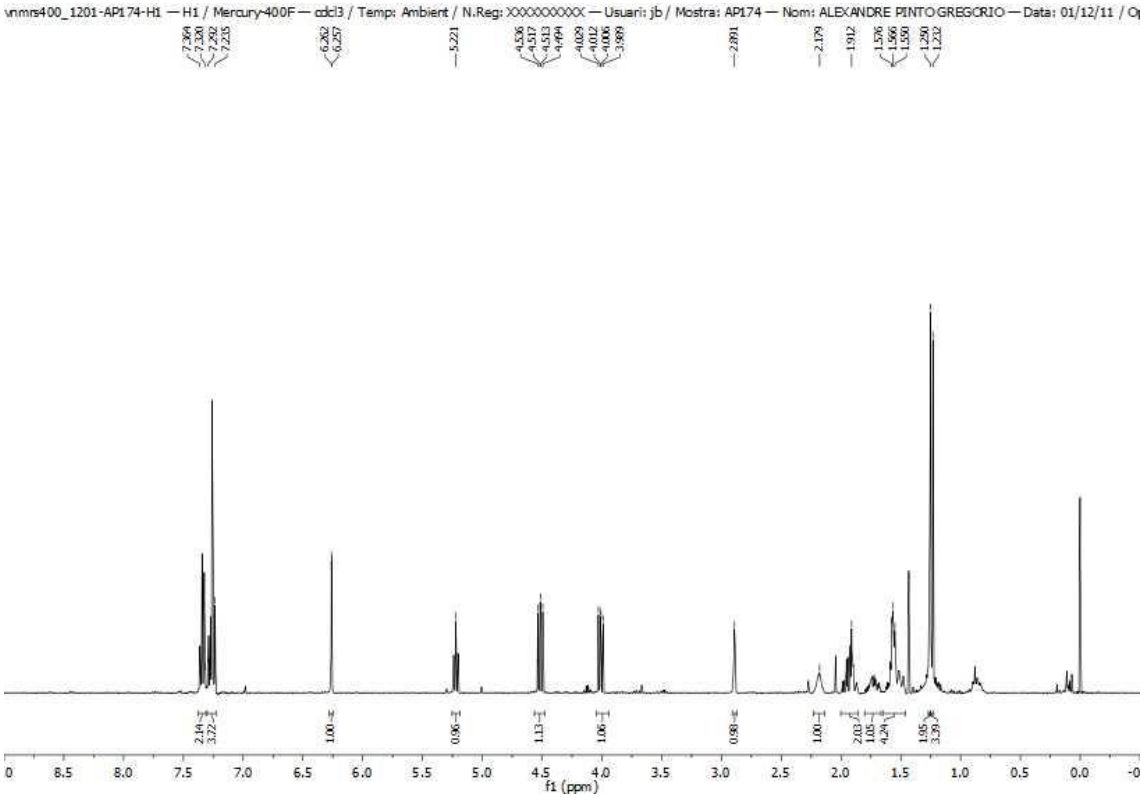


(3*R*,7a*S*,8*R*,11a*S*)-8-Methyl-3-phenyl-5-(trifluoromethylsulfonyloxy)-2,3,7,7a,8, 9,10,11-octahydrooxazolo [2,3-*j*]quinoline (22)

A solution of KHMDS (1.05 mL of a 0.51 M solution in Toluene, 0.525 mmol) in THF (1.05 mL) was added to a solution of lactam **9** (100 mg, 0.350 mmol) in THF (1.5 mL) at –78 ºC, and the mixture was stirred at this temperature for 2 h. Then, a solution of Comins' reagent (275 mg, 0.7 mmol) in THF (1.2 mL) was added, and the reaction mixture was allowed to reach room temperature. After 24 h of stirring, the reaction was quenched by addition of 10% aqueous NaOH (2 mL), and the mixture was extracted with Et_2O. The combined organic extracts were dried and concentrated. Flash chromatography with SiO_2 previously deactivated with Et_3N (7:3 hexane–EtOAc) afforded the vinyl triflate **22** (27 mg, 20%) as a colorless oil.

(400 MHz, $CDCl_3$, COSY, HETCOR) δ: 1.21-1.28 (m, 2H, H-9), 1.24 (d, J = 7.2 Hz, 3H, CH_3), 1.47-1.62 (m, 3H, H-10, H-11), 1.68-1.80 (m, 1H, H-11), 1.86-1.99 (m, 2H, H-7), 2.15-2.22 (m, 1H, H-8), 2.89 (s, 1H, H-7a), 4.01 (dd, J = 9.2, 3.2 Hz, 1H, H-2), 4.51 (dd, J = 9.2, 3.2 Hz, 1H, H-2), 5.22 (t, J = 7.2 Hz, 1H, H-3), 6.26 (d, J = 2.0 Hz, 1H, H-6), 7.24-7.29 (m, 3H), 7.32-7.36 (m, 2H).

^{13}C-NMR (100.6 MHz; $CDCl_3$) δ: 16.4 (CH_2), 19.0 (CH_3), 27.1 (CH_3), 31.1 (CH_3), 34.2 (C-8), 45.7 (C-7a), 58.9 (C-3), 72.3 (C-2), 95.4 (C-11a), 118.6 (q, J = 319 Hz, CF_3), 125.7 (C-*o*), 127.7 (C-*p*), 128.8 (C-*m*), 132.4 (C-6), 138.0 (C-5), 140.2 (Cq-Ar), 154.9 (C-5).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7.320
7.292
7.235
6.262
6.257
5.221
4.536
4.517
4.513
4.494
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4.012
4.006
3.989
2.891
2.179
1.912
1.576
1.566
1.550
1.290
1.232
2.14
3.22
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1.06
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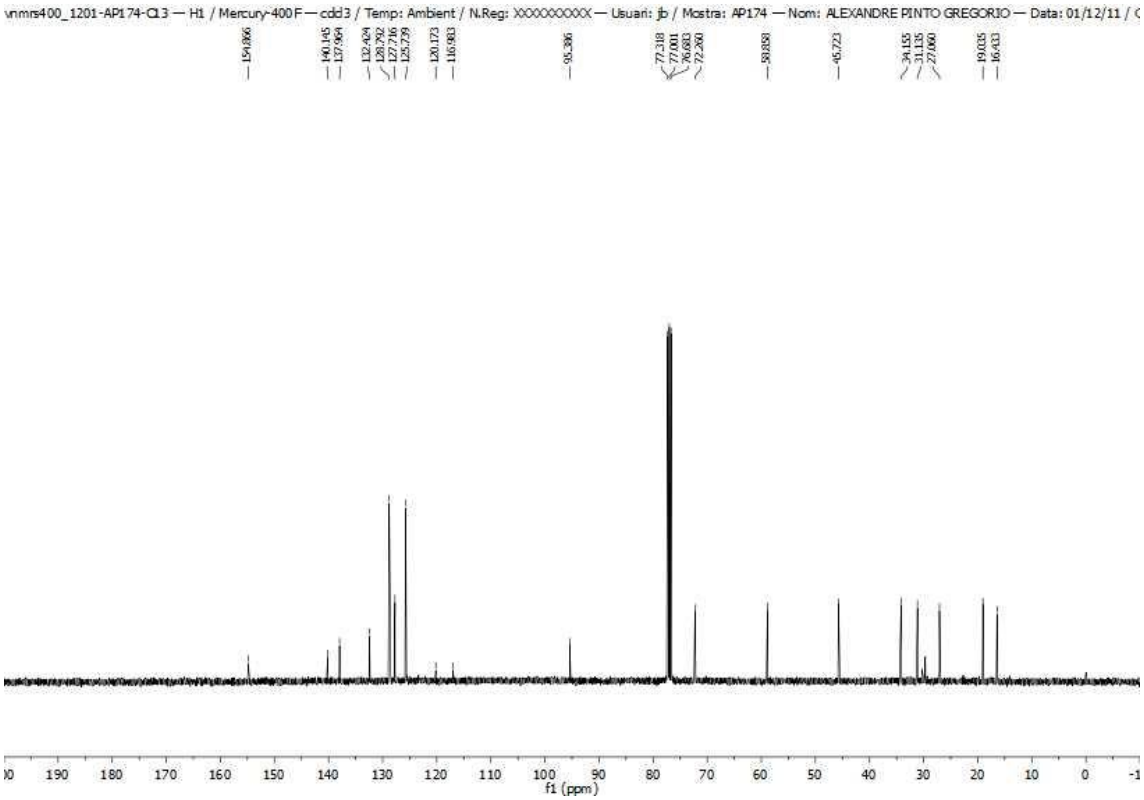
1.05
4.24
1.95
3.39
f1 (ppm)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140.145
137.964
132.434
130.792
127.716
125.739
120.173
116.983
95.386
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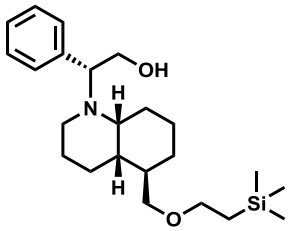
27.060
19.035
16.433
f1 (ppm)



(4a*S*,5*R*,8a*R*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-5-{[2-(trimethylsilyl)ethoxy] methyl} decahydroquinoline (24)

$LiAlH_4$ (844 mg, 22.23 mmol) was slowly added to a suspension of $AlCl_3$ (912 mg, 6.84 mmol) in THF (70 mL) at 0 ºC. After the mixture was stirred at this temperature for 30 min and cooled to –78 ºC, a solution of lactam **8a** (1.37 g, 3.42 mmol) in THF (5 mL) was added dropwise. The stirring was continued at –78 ºC for 90 min and at room temperature for 3 h. Water was slowly added, the resulting mixture was filtered over Celite®, and the filtrate was washed with EtOAc. The organic extracts were dried and concentrated. Flash chromatography (6:4 hexane–EtOAc) afforded the decahydroquinoline **24** (1.01 g, 76%) as a colorless oil.

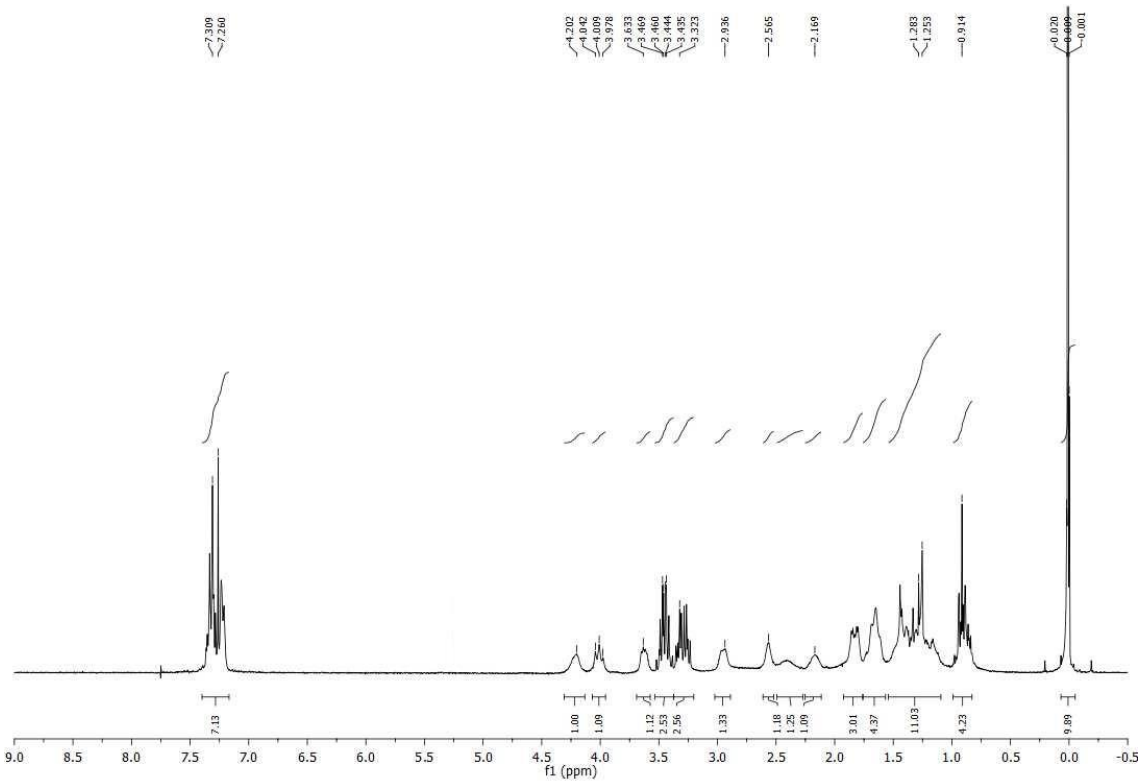
^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.01 [s, 9H, $Si(CH_3)_3$], 0.94 (dd, J = 7.2, 2.4 Hz, 2H, CH_2Si), 1.14-1.44 (m, 8H), 1.65-1.68 (m, 3H), 1.80-1.85 (m, 2H), 2.38 (br s, 1H), 2.40 (br s, 1H), 2.57 (br s, 1H), 2.93 (br s, 1H), 3.26 (dd, J = 8.8, 6.4 Hz, 1H, OCH_2), 3.32 (m, 1H, OCH_2), 3.63 (br s, 1H, CH_2O), 4.01 (br s, 1H), 4.21 (br s, 1H), 7.21-7.35 (m, 5H, Ar-H).

Several of the signals in the ^{13}C NMR spectrum at 25 ºC were broad and ill-defined, even not observed, thus indicating the existence of a slow conformational equilibrium. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: –1.3 [$Si(CH_3)_3$], 18.1 (CH_2), 20.4 (CH_2), 29.7 (CH_2), 30.9 (CH_2), 68.3 (OCH_2), 73.0 (CH_2O), 127.6 (C-*p*), 128.1 (C-*o, m*), 128.9 (C-*o, m*).

IR (NaCl): 3438, 1248 cm^{-1}.

HRMS calcd for [$C_{23}H_{39}NO_2Si + H^+$]: 390.2823; found 390.2817.

$[\alpha]^{23}_D$ = – 10.08 (*c* 1.25, MeOH).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2.565
2.169
1.283
1.253
0.914
0.020
0.000
-0.001
7.13
1.00
1.09
1.12
2.53
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1.18
1.25
1.00
3.01
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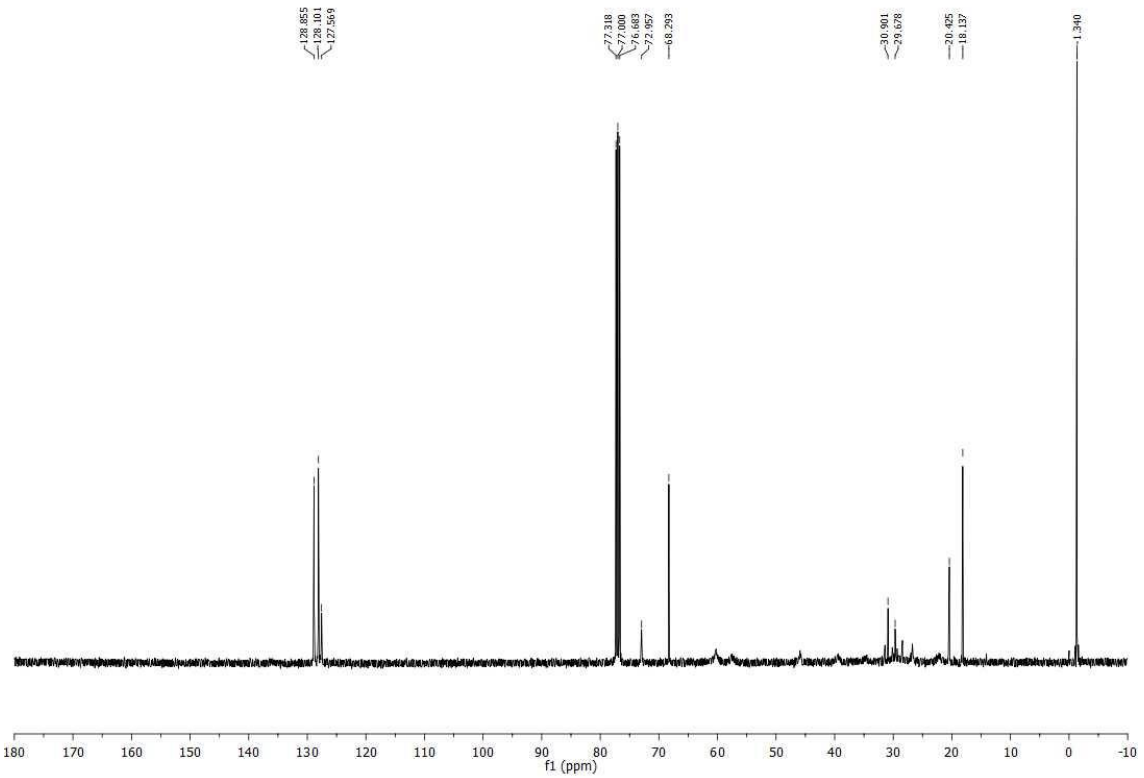
11.03
4.23
9.89
f1 (ppm)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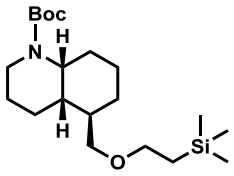
1.340
f1 (ppm)



(4a*S*,5*R*,8a*R*)-1-(*tert*-Butoxycarbonyl)-5{[2-(trimethylsilyl)ethoxy]methyl} decahydro- quinoline (25)

A solution of the amine **24** (130 mg, 0.33 mmol) and di-*tert*-butyl dicarbonate (102 mg, 0.47 mmol) in MeOH (7 mL) containing $Pd(OH)_2$ (52 mg) was stirred under hydrogen at room temperature for 24 h. The catalyst was removed by filtration, and the filtrate was concentrated. Flash chromatography (9:1 hexane–Et_2O) afforded **25** (120 mg, 98%) as a colorless oil:

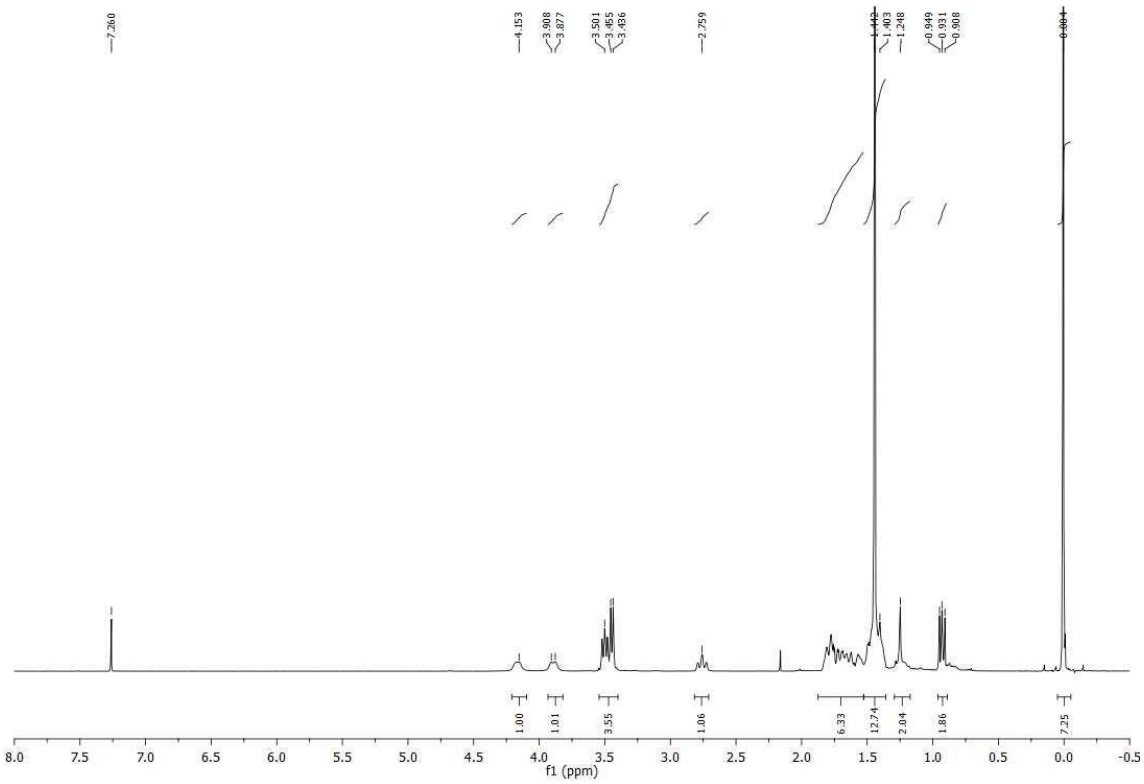
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.00 (s, 9H, $Si(CH_3)_3$), 0.93 (t, J = 8.2 Hz, 2H, CH_2Si), 1.16-1.31 (m, 2H, H-7), 1.34-1.84 (m, 10H, H-3, H-4, H-5, H-6, H-7, H-8), 1.44 [(s, 9H, $C(CH_3)_3$], 2.70-2.81 (m, 1H, H-2), 3.46-3.53 (m, 4H, OCH_2CH_2TMS), 3.90 (d, J = 11.6 Hz, 1H, H-2), 4.17 (d, J = 8.8 Hz, 1H, H-8a).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: –1.4 [$Si(CH_3)_3$], 18.1 (CH_2TMS), 21.0 (CH_2), 22.3 (CH_2), 23.8 (CH_2), 25.4 (CH_2), 25.9 (CH_2), 28.5 [$C(CH_3)_3$], 36.3 (C-4a), 39.1 (CH_2), 40.3 (C-5), 49.3 (C-8a), 68.1 (OCH_2), 71.8 (CH_2OTMSE), 79.0 [$C(CH_3)_3$], 155.0 (COO).

IR (NaCl): 1659, 1244 cm^{-1}.

HRMS calcd for [$C_{20}H_{39}NO_3Si + H^+$]: 370.2772; found 370.2772.

$[\alpha]^{23}_D$ = – 11.5 (*c* 1.0, $CHCl_3$).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0.931
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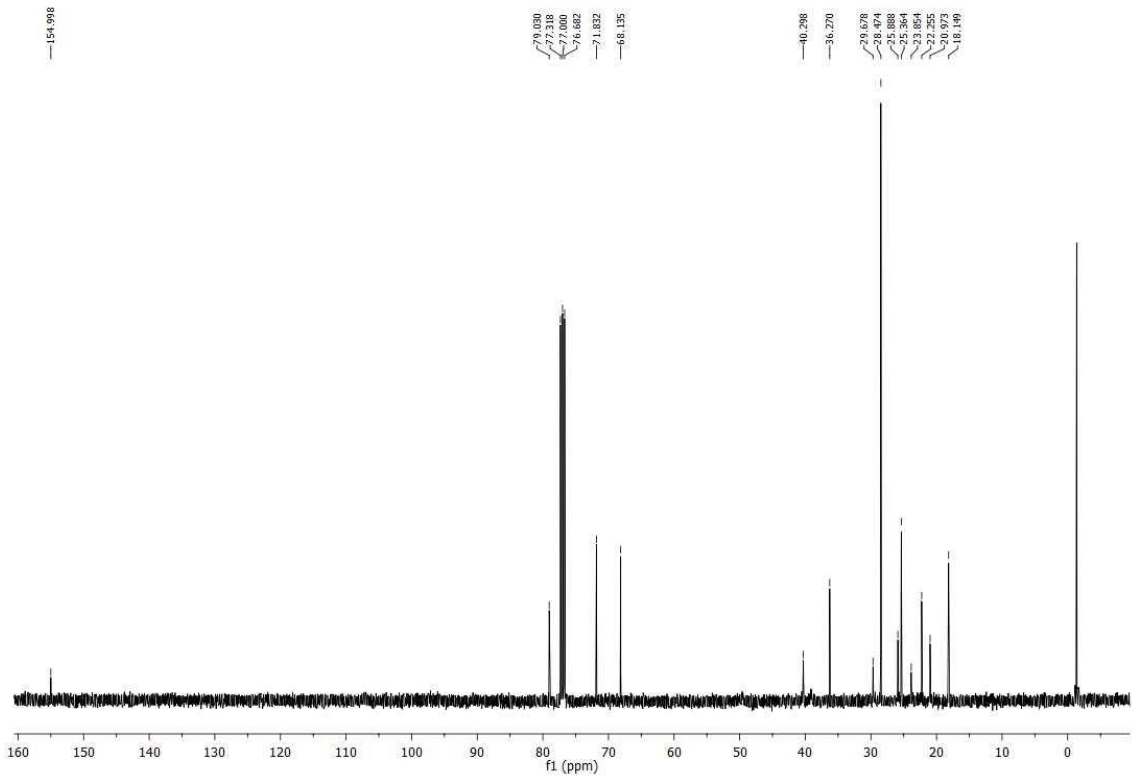
7.25
f1 (ppm)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22.255
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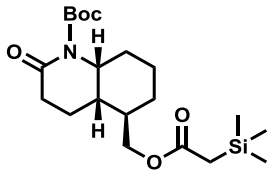
f1 (ppm)

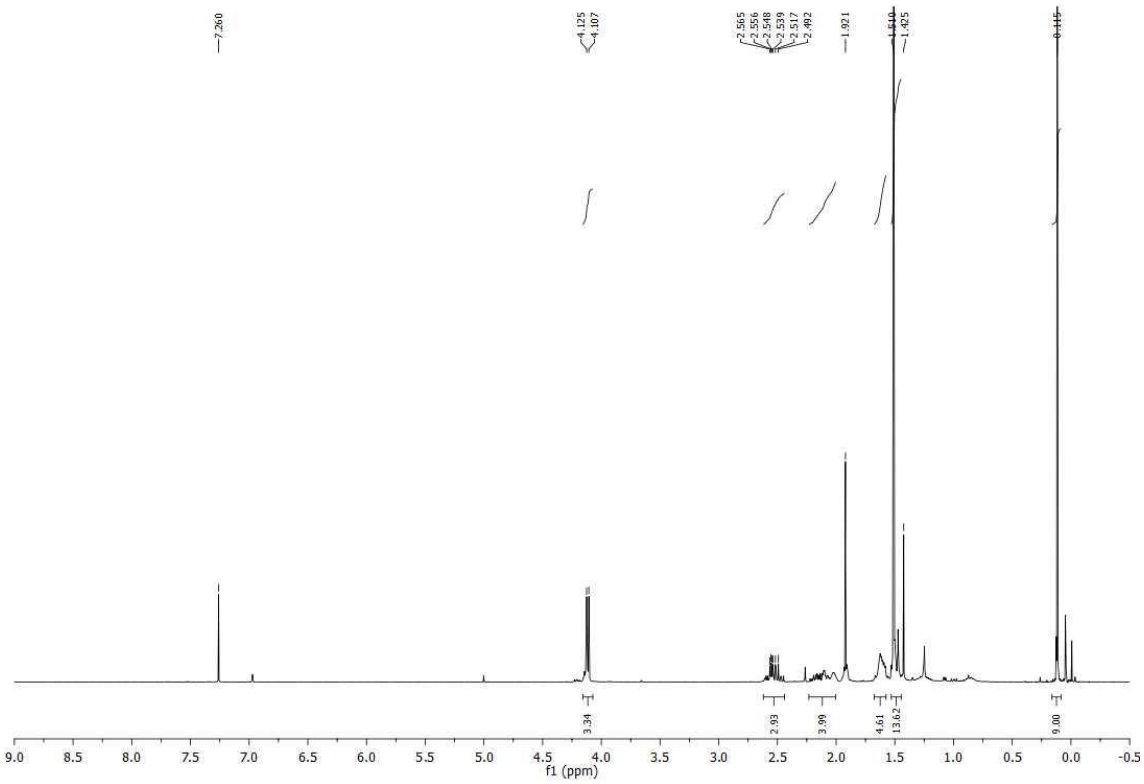


(4a*S*,5*R*,8a*R*)-1-(*tert*-Butoxycarbonyl)-5{[2-(trimethylsilyl)acetoxy]methyl} decahydroquinoline (26)

$NaIO_4$ (265 mg, 1.24 mmol) and $RuCl_3\,nH_2O$ (2.6 mg, 0.0124 mmol) were added to a heterogenous solution of **25** (46 mg, 0.124 mmol) in CCl_4–MeCN–H_2O (3 mL, 3:3:4) at 0 ºC. The mixture was stirred at 0 ºC for 5 min and at room temperature for 1 h. Then, EtOAc was added, the resulting mixture was filtered through Celite®, and the filtrate was concentrated. Flash chromatography (7.5:2.5 hexane–EtOAc) afforded **26** (32 mg, 65%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.10 (s, 9H), 1.42-1.68 (m, 8H), 1.51 [br s, 9H, $C(CH_3)_3$], 2.00-2.18 (m, 4H), 2.44-2.61 (m, 2H), 4.11 (d, J = 7.6 Hz, 3H).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 20.4 (CH_2), 22.4 (CH_2), 22.7 (CH_2), 26.9 (CH_2), 27.9 [$C(CH_3)_3$], 28.3 (CH_2), 33.6 (CH_2), 34.4 (CH), 38.0 (CH), 54.5 (CH), 65.0 (CH_2), 83.0 [$C(CH_3)_3$], 153.0 (COO), 171.0 (C-2), 172.9 (COO).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4.125
4.107
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2.556
2.548
2.539
2.517
2.492
1.921
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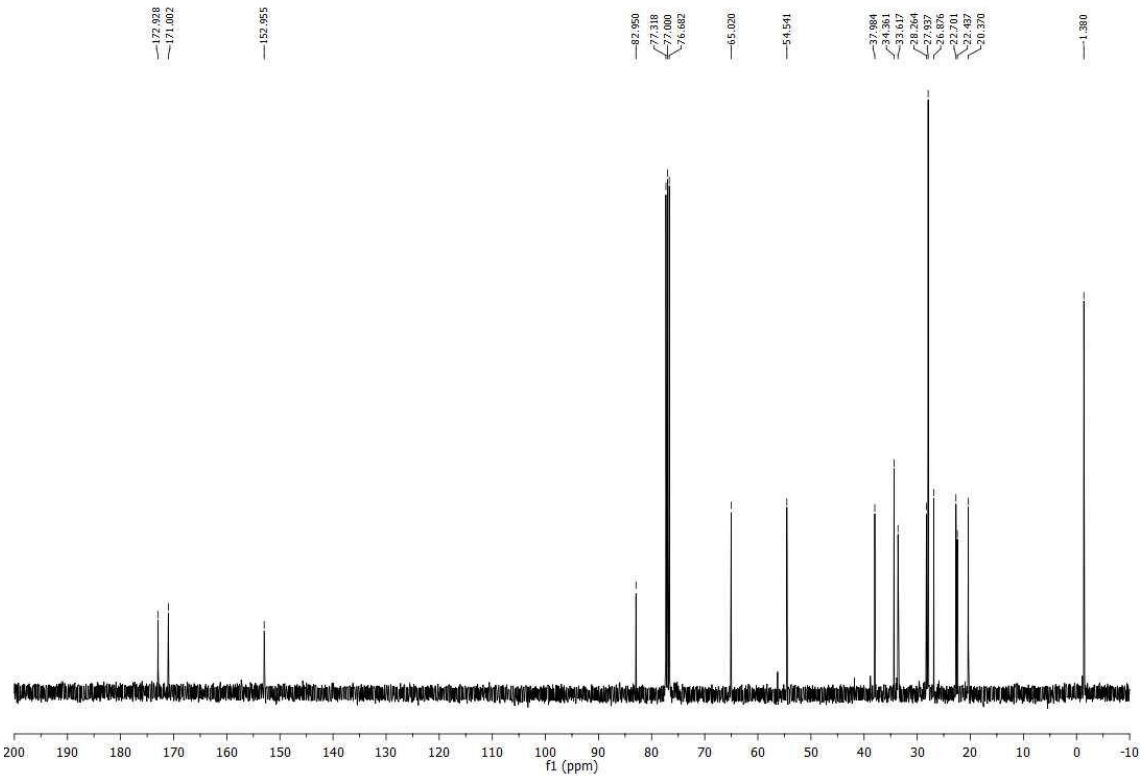
1.425
0.115
3.34
2.93
3.99
4.61
13.62
9.00
f1 (ppm)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77.000
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65.020
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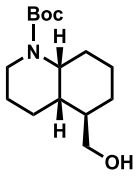
26.876
26.701
22.497
20.370
1.380
f1 (ppm)



(4a*S*,*5R*,8a*R*)-1-(*tert*-Butoxycarbonyl)-5-(hydroxymethyl)decahydroquinoline (29)

First step: $BF_3.Et_2O$ (970 μL, 7.85 mmol) was added to a solution of compound **24** (610 mg, 1.57 mmol) in CH_2Cl_2 (11 mL) at 0 ºC. The mixture was allowed to warm to room temperature and stirred for 2 h. Then, saturated aqueous $NaHCO_3$ was added, the phases were separated, and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried and concentrated to afford the desilylated product (445 mg, 99%) as a white foam.

Second step: A solution of the above crude alcohol (690 mg, 2.39 mmol) and di-*tert*-butyl dicarbonate (565 mg, 2.58 mmol) in MeOH (20 mL) was hydrogenated at room temperature for 20 h in the presence of 40% $Pd(OH)_2$ (290 mg). The catalyst was removed by filtration, and the solvent was evaporated. Flash chromatography (7:3 hexane–EtOAc) afforded the title alcohol **29** (510 mg, 79%) as a colorless oil.

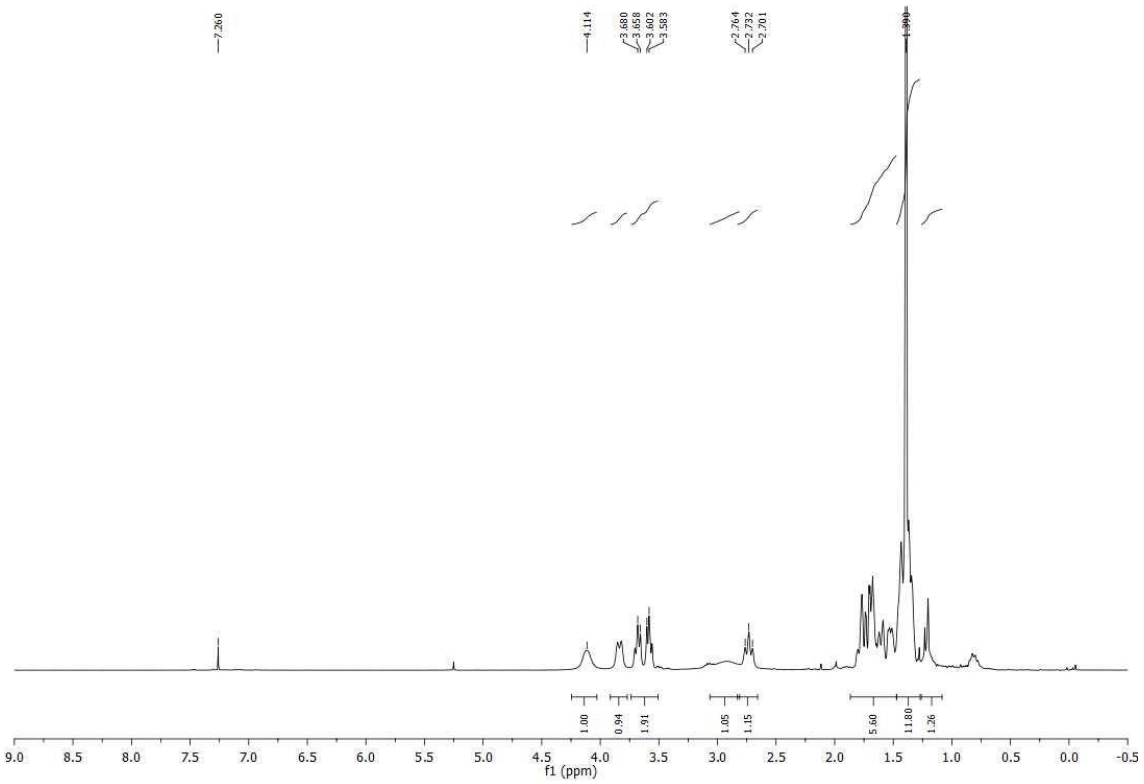
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.13-1.26 (m, 1H), 1.30-1.48 (m, 6H), 1.45 [s, 9H, $C(CH_3)_3$], 1.49-1.57 (m, 1H), 1.58-1.82 (m, 5H), 2.73 (d, J = 8.6 Hz, 1H, H-2), 3.58 (t, J = 9.2 Hz, 1H, CH_2OH), 3.68 (t, J = 9.2 Hz, 1H, CH_2OH), 3.84 (d, J = 8.4 Hz, 1H, H-2), 4.11 (br s, 1H, H-8a).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 20.8 (CH_2), 21.8 (CH_2), 23.8 (CH_2), 25.3 (CH_2), 25.9 (CH_2), 28.3 [(CH_3)$_3$C], 35.4 (C-4a), 39.1 (C-2), 42.6 (C-5), 63.5 (CH_2OH), 79.2 [(CH_3)$_3$*C*], 155.1 (NCOO).

IR (NaCl): 3435, 1693 cm^{-1}.

HRMS calcd for [$C_{15}H_{27}NO_3$ + H^+]: 270.2064; found 270.2061.

$[\alpha]^{23}_D$ = – 6.7 (*c* 1.0, $CHCl_3$).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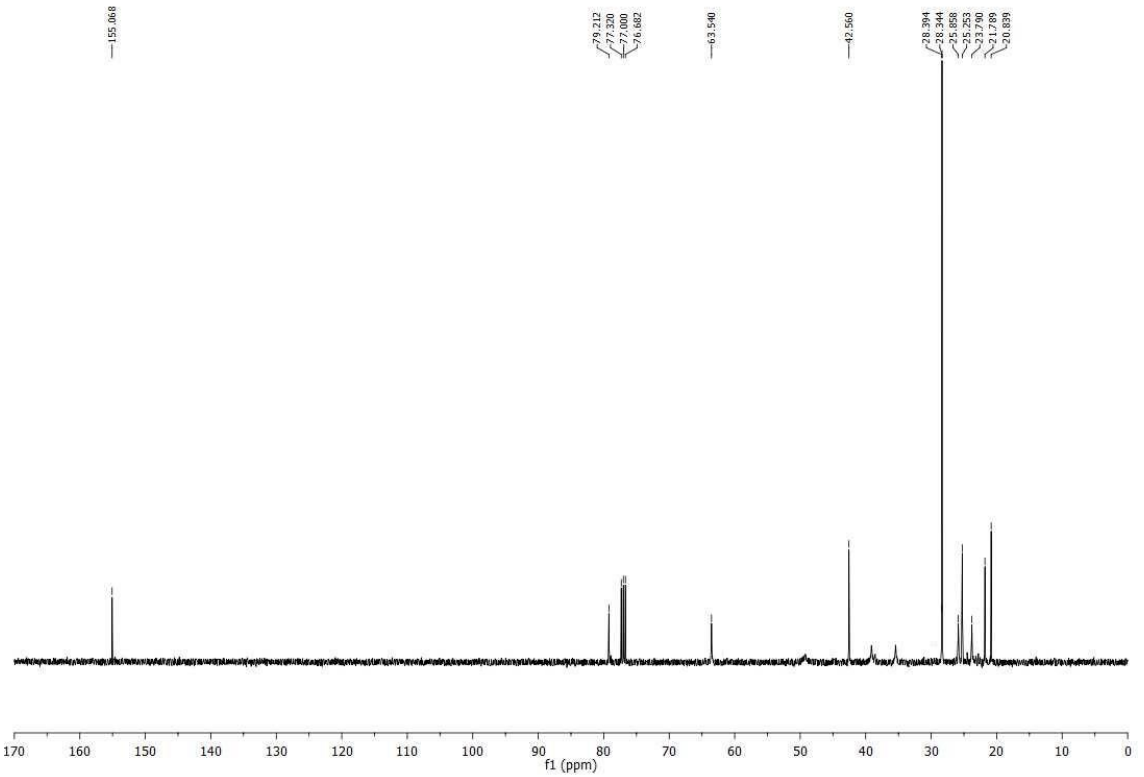
1.05
1.15
5.60
11.80
1.26
f1 (ppm)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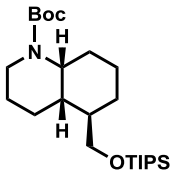
21.789
20.839
f1 (ppm)



(4a*S*,5*R*,8a*R*)-1-(*tert*-Butoxycarbonyl)-5-(triisopropylsilyloxymethyl) decahydroquinoline (30)

Imidazole (259 mg, 3.80 mmol) and TIPSCl (270 μL, 1.27 mmol) were added to a solution of alcohol **29** (170 mg, 0.63 mmol) in DMF (3.3 mL), and the mixture was stirred at room temperature overnight. Saturated aqueous $NaHCO_3$ was added, and the resulting mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried, and concentrated. Flash chromatography (9:1 hexane-EtOAc) afforded the TIPS derivative **30** (250 mg, 93%) as a colorless oil.

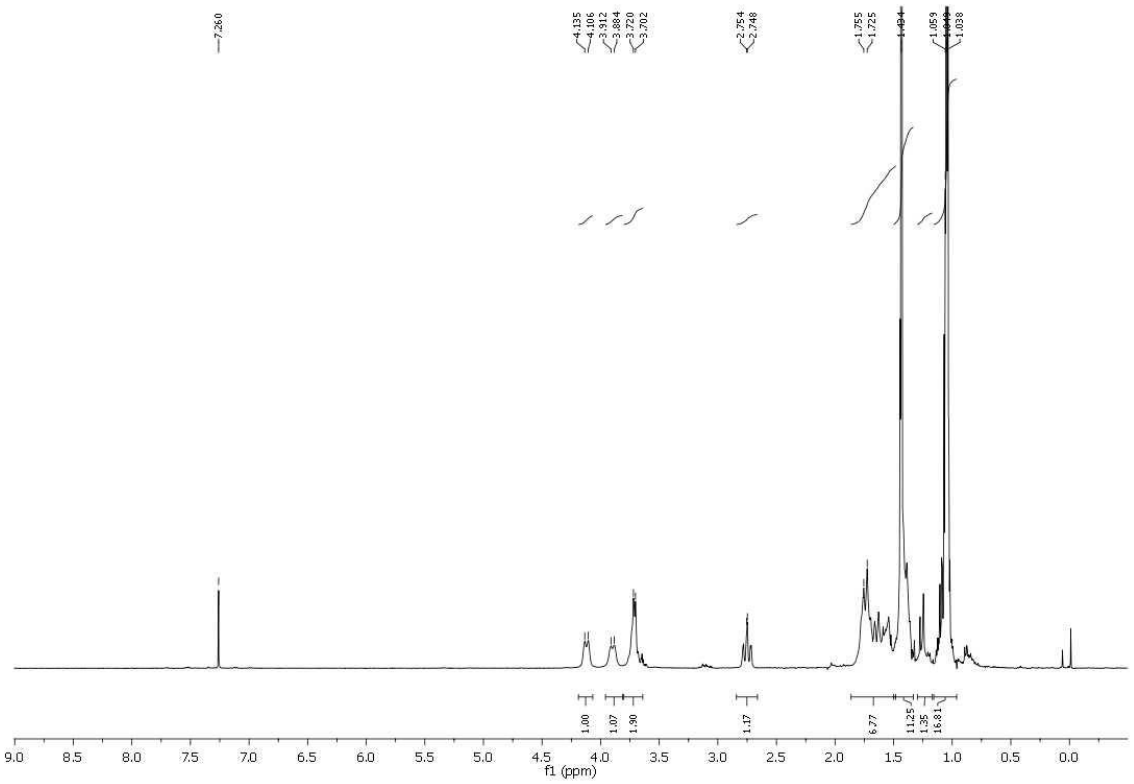
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.99-1.11 [m, 21H, Si(*i*Pr)$_3$], 1.34-1.83 (m, 9H, H-3, H-4, H-6, H-7, H-8), 1.43 [s, 9H, C(CH$_3$)$_3$], 1.83-1.92 (m, 3H, H-4a, H-5, H-8), 2.75 (td, J = 12.4, 2.8 Hz, 1H, H-2), 3.67-3.78 [m, 2H, C*H*$_2$OSi(*i*Pr)$_3$], 3.90 (d, J = 12.4 Hz, 1H, H-2), 4.12 (d, J = 12.4 Hz, 1H, H-8a).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 12.0 [(CH$_3$)$_2$*C*HSi], 18.0 [(*C*H$_3$)$_2$CHSi], 20.8 (CH$_2$), 21.5 (CH$_2$), 23.9 (CH$_2$), 25.5 (CH$_2$), 26.0 (CH$_2$), 28.4 [(*C*H$_3$)$_3$C], 35.9 (C-4a), 39.0 (C-2), 43.0 (C-5), 49.8 (C-8a), 64.4 [*C*H$_2$OSi(*i*Pr)$_3$], 79.0 [(CH$_3$)$_3$*C*], 155.0 (NCOO).

IR (NaCl): 1695 cm^{-1}.

HRMS calcd for [$C_{24}H_{47}NO_3Si$ + H$^+$]: 426.3398; found 426.3392.

$[\alpha]^{23}_D$ = + 3.24 (*c* 1.0, $CHCl_3$).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1.725
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6.77
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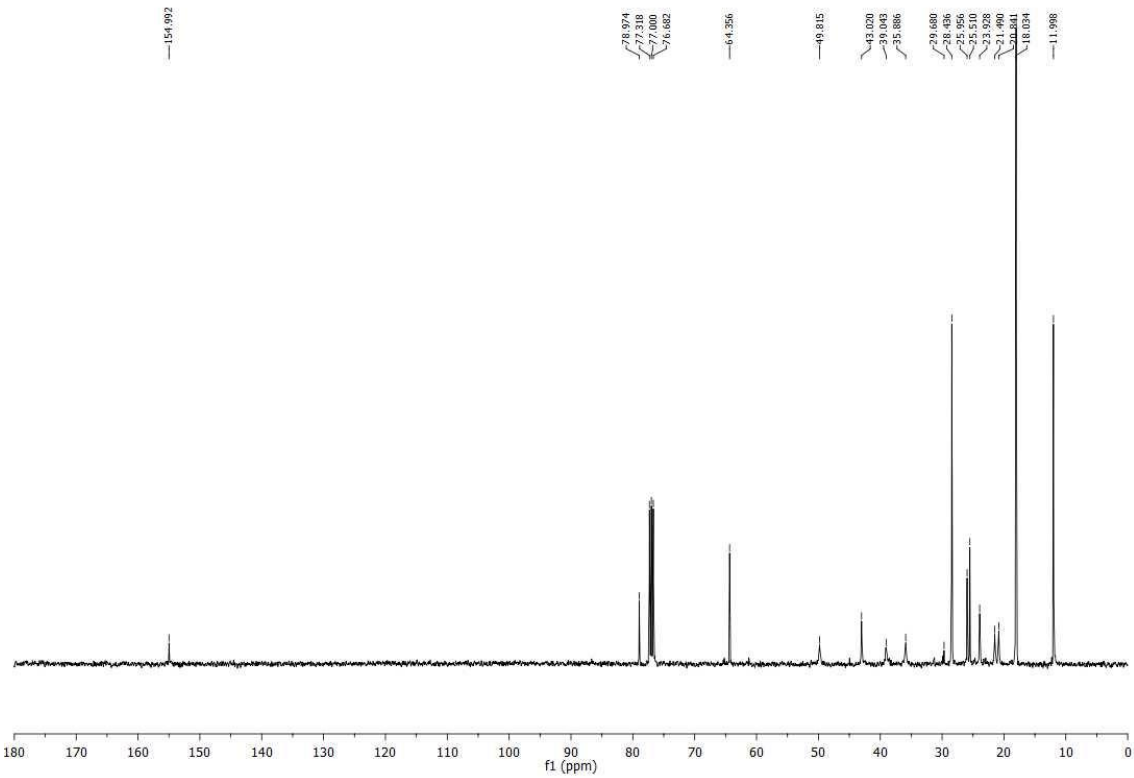
1.35
16.81
f1 (ppm)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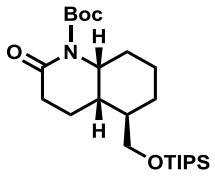
11.998
f1 (ppm)



(4a*S*,5*R*,8a*R*)-1-(*tert*-Butoxycarbonyl)-2-oxo-5-(triisopropylsilyloxymethyl) decahydroquinoline (31)

Operating as described in the oxidation of **12**, from decahydroquinoline **30** (200 mg, 0.47 mmol), $NaIO_4$ (1.81 g, 4.7 mmol), and $RuCl_3 \cdot nH_2O$ (9.7 mg, 0.05 mmol) in CCl_4–MeCN–H_2O (3:3:4, 6 mL), lactam **31** (200 mg, 97%) was obtained as a colorless oil after flash chromatography (9:1 hexane–EtOAc).

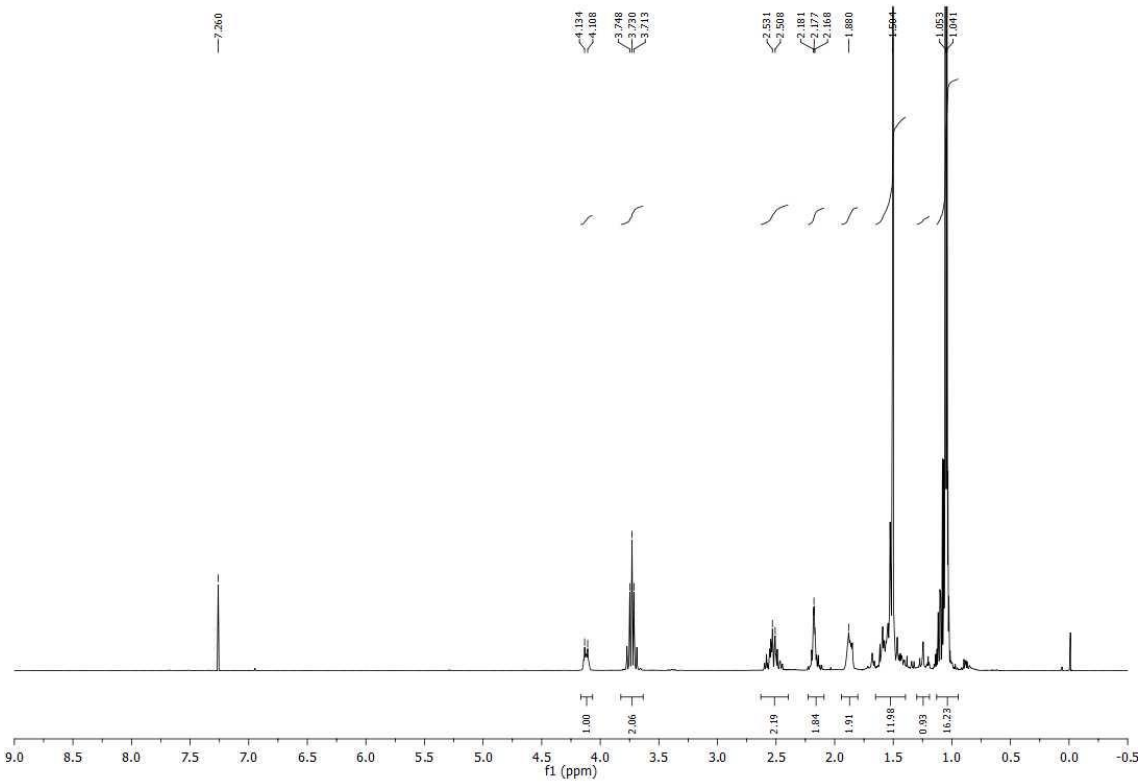
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.99-1.15 [m, 21H, Si(*i*Pr)$_3$], 1.42-1.62 (m, 6H, H-4, H-6, H-7, H-8), 1.50 [s, 9H, C(CH$_3$)$_3$], 1.83-1.92 (m, 2H, H-5, H-8), 2.12-2.24 (m, 2H, H-4, H-4a), 2.44-2.61 (m, 2H, H-3), 3.73 [td, J = 10.6, 7.2, 2.6 Hz, 2H, C*H*$_2$OSi(*i*Pr)$_3$], 4.13 (ddd, J = 10.0, 3.8 Hz, 1H, H-8a).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 11.9 [(CH$_3$)$_2$*C*HSi], 18.0 [(*C*H$_3$)$_2$CHSi], 20.7 (C-6), 22.4 (C-7), 22.9 (C-4), 27.9 [(*C*H$_3$)$_3$C], 28.4 (C-8), 33.8 (C-3), 33.9 (C-4a), 41.4 (C-5), 54.9 (C-8a), 64.5 [*C*H$_2$OSi(*i*Pr)$_3$], 82.7 [(CH$_3$)$_3$*C*], 153.1 (NCOO), 171.4 (C-2).

IR (NaCl): 1773, 1724, 1246 cm^{-1}.

HRMS calcd for [$C_{24}H_{45}NO_4Si$ – Boc + H^+]: 340.2666; found 340.2661.

$[\alpha]^{23}_D$ = – 3.95 (*c* 1.0, $CHCl_3$).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1.00
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11.98
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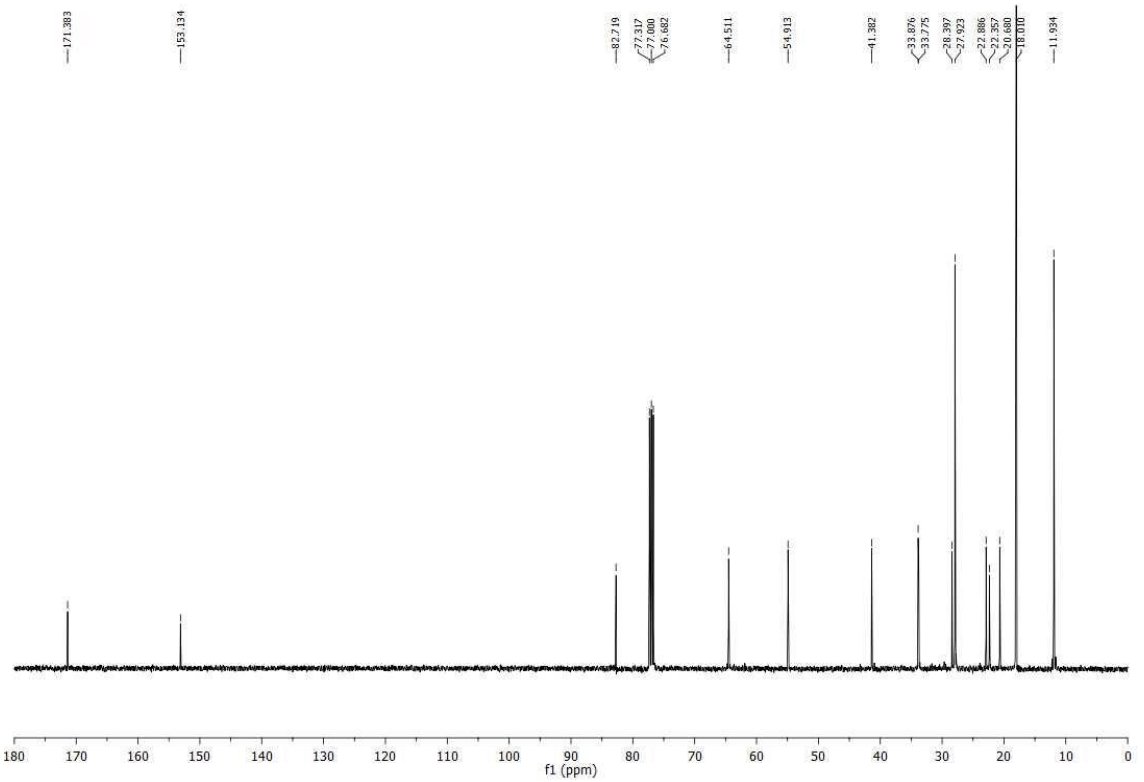
16.23
f1 (ppm)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33.775
28.397
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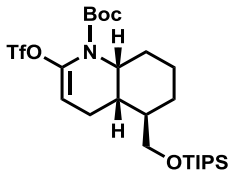
20.680
18.010
11.934
f1 (ppm)



(4a*S*,5*R*,8a*R*)-*1*-(*tert*-Butoxycarbonyl)-2-(trifluoromethylsulfonyloxy)-5-(triisopropylsilyl-oxymethyl)-1,4,4a,5,6,7,8,8a-octahydroquinoline (32)

A solution of LiHMDS (580 μL of a 1 M solution in THF, 0.58 mmol) in THF (1.7 mL) was added to a solution of lactam **31** (170 mg, 0.39 mmol) in THF (3.8 mL) at –78 ºC, and the mixture was stirred at this temperature for 2 h. Then, a solution of Comins' reagent (304 mg, 0.77 mmol) in THF (3.7 mL) was added, and the reaction mixture was allowed to reach room temperature. After 1.5 h of stirring, the reaction was quenched by addition of 10% aqueous NaOH (6 mL), and the mixture was extracted with Et_2O. The combined organic extracts were dried and concentrated. Flash chromatography (SiO_2 pre-treated with Et_3N; 9:1 hexane–EtOAc) afforded compound **32** (198 mg, 90%) as a yellowish oil.

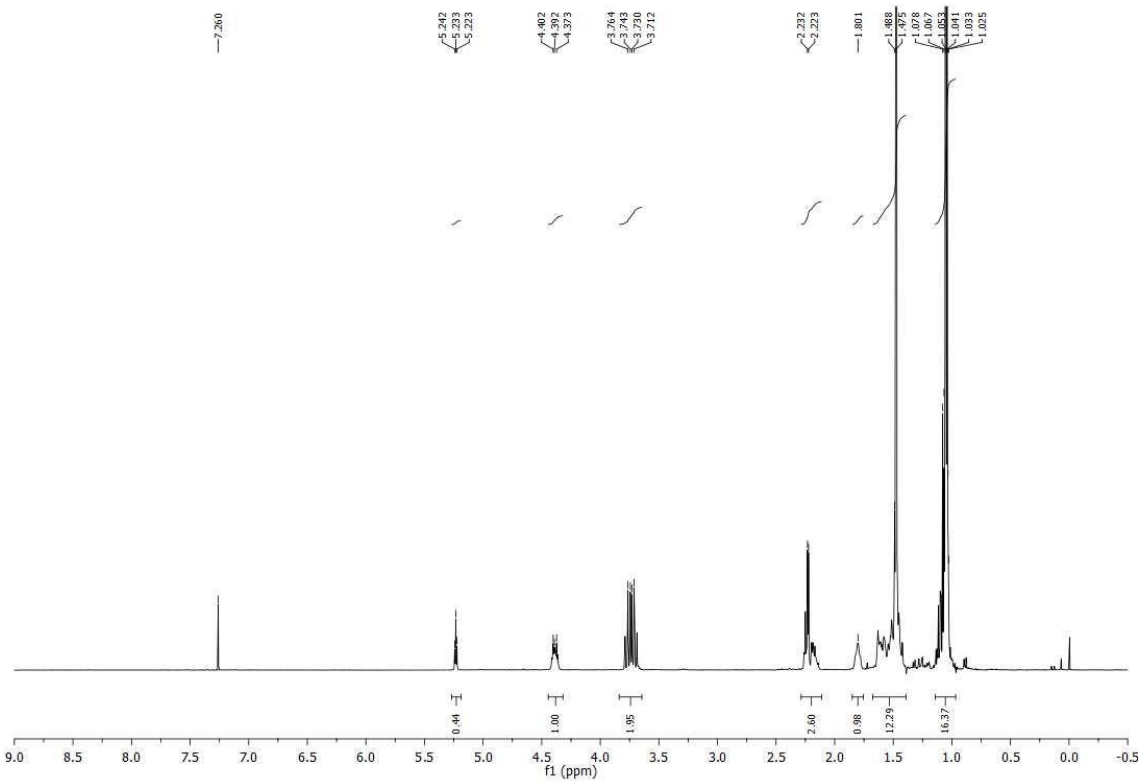
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.01-1.14 [m, 21H, Si(*i*Pr)$_3$], 1.41-1.66 [m, 6H, H-6, H-7, H-8], 1.47 [s, 9H, C(CH$_3$)$_3$], 1.77-1.84 (m, 1H, H-5), 2.14-2.20 (m, 1H, H-4a), 2.27-2.21 (m, 2H, H-4), 3.74 [td, J = 10.6, 7.4, 3.6 Hz, 2H, C*H*$_2$OSi(*i*Pr)$_3$], 4.39 (ddd, J = 11.6, 4.2 Hz, 1H, H-8a), 5.23 (t, J = 4.2 Hz, 1H, H-3).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 12.0 [(CH$_3$)$_2$*C*HSi], 18.0 [(*C*H$_3$)$_2$CHSi], 21.1 (CH_2), 21.2 (CH_2), 24.3 (CH_2), 25.2 (C-4), 27.9 [(*C*H$_3$)$_3$C], 31.8 (C-4a), 41.1 (C-5), 52.8 (C-8a), 64.1 [*C*H$_2$OSi(*i*Pr)$_3$], 82.6 [(CH$_3$)$_3$*C*], 105.6 (C-3), 118.4 (q, CF_3), 138.4 (C-2), 152.4 (NCOO).

IR (NaCl): 1724, 1688, 1137 cm^{-1}.

HRMS calcd for [$C_{25}H_{44}F_3NO_6SSi$ + NH_4^+]: 589.2943; found 589.2949.

$[\alpha]^{23}_D$ = – 30.32 (*c* 1.0, $CHCl_3$).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1.801
1.488
1.475
1.078
1.067
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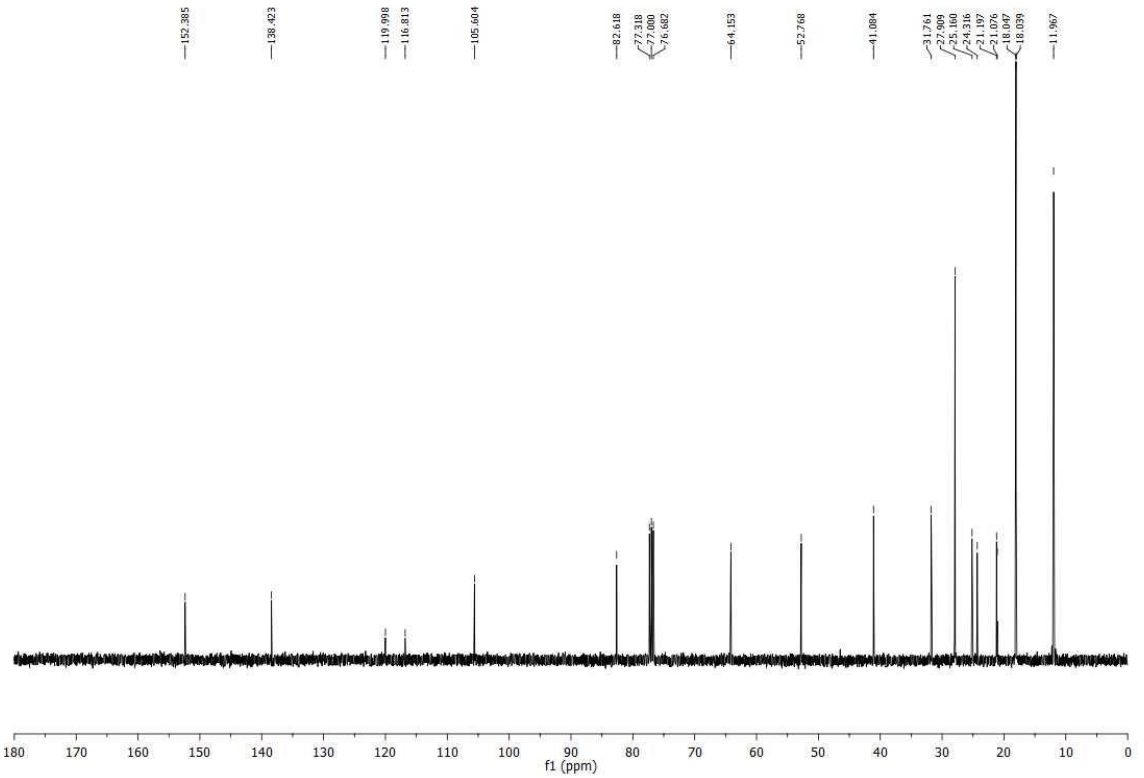
16.37
f1 (ppm)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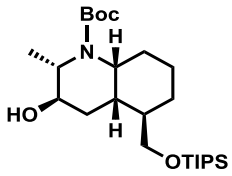
f1 (ppm)



(2*S*,3*R*,4a*S*,5*R*,8a*R*)-1-(*tert*-Butoxycarbonyl)-3-hydroxy-2-methyl-5-(triisopropylsilyl-oxymethyl)decahydroquinoline (34)

First step: Operating as in the preparation of **21**, from a solution of triflate **32** (770 mg, 1.35 mmol) in THF (6 mL), MeLi (8.44 mL, of a 1.6 M solution in Et_2O, 13.5 mmol), and CuI (1.29 g, 6.75 mmol) in THF (35 mL), enecarbamate **33** was obtained.

Second step: Operating as in the preparation of **21**, from a solution of the above crude **11** in THF (135 mL), $BH_3{\cdot}SMe_2$ (6.75 mL of a 2.0 M solution in THF, 13.5 mmol), and $Me_3NO{\cdot}2H_2O$ (2.25 g, 20.25 mmol), alcohol **34** (500 mg, 81%) was obtained as a yellowish oil after flash chromatography (9.5:0.5 CH_2Cl_2–MeOH).

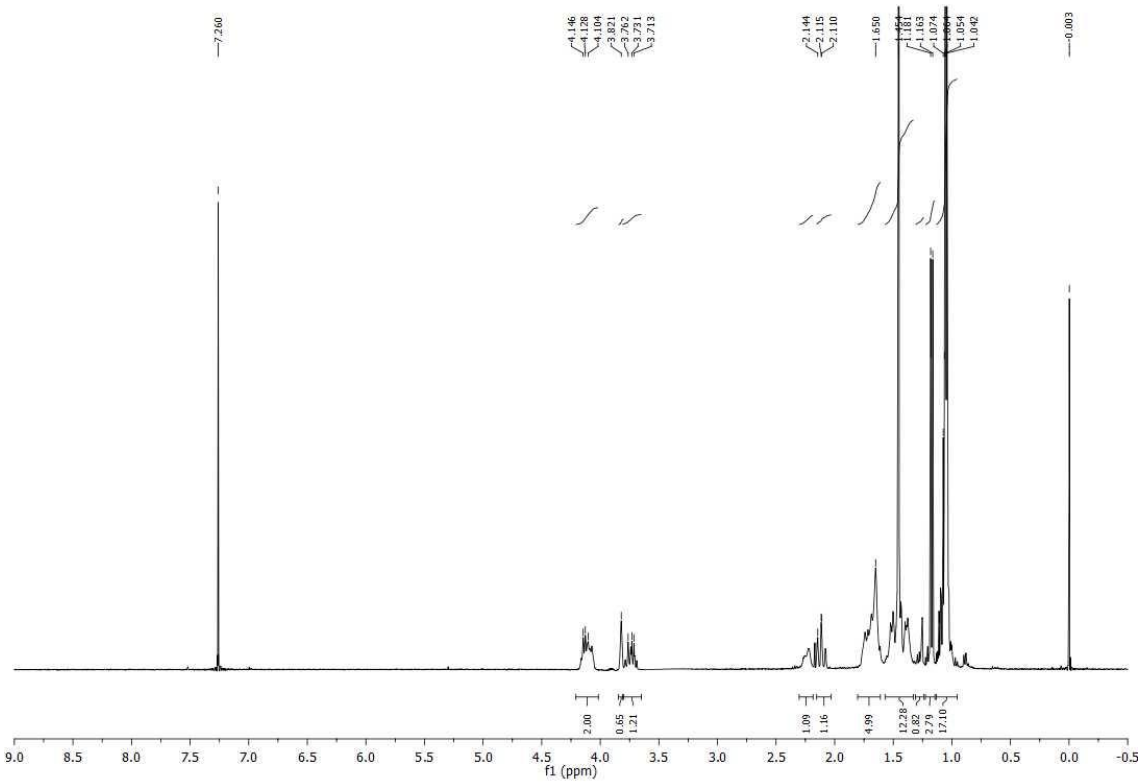
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.99-1.14 [m, 21H, Si(*i*Pr)$_3$], 1.15 (d, J = 13.2 Hz, 3H, CH_3), 1.34-1.79 (m, 8H, H-4, H-5, H-6, H-7, H-8), 1.45 [s, 9H, C(CH_3)$_3$], 1.77-1.84 (m, 1H, H-5), 2.06-2.16 (m, 1H, H-4), 2.20-2.27 (m, 1H, H-4a), 3.65-3.79 [m, 2H, CH_2OSi(*i*Pr)$_3$], 3.82 (br s, 1H, H-3), 4.04-4.19 (m, 2H, H-2, H-8a).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 12.0 [(CH_3)$_2$*C*HSi], 18.0 [(*C*H$_3$)$_2$CHSi], 20.0 (CH_3), 21.0 (CH_2), 21.7 (CH_2), 27.9 (2 carbons), 28.4 [(*C*H$_3$)$_3$C and CH_2], 42.4 (C-5), 50.2 (C-2), 53.4 (C-8a), 64.5 [*C*H$_2$O Si(*i*Pr)$_3$], 69.4 (C-3), 79.4 [(CH_3)$_3$*C*], 155.7 (NCOO).

IR (NaCl): 3432, 1687, 1662, 1245 cm^{-1}.

HRMS calculated for [$C_{25}H_{49}NO_4Si$ + H^+]: 456.3504; found 456.3497.

[α]$^{23}_D$ = + 19.45 (*c* 0.6, $CHCl_3$).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1.163
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1.054
1.042
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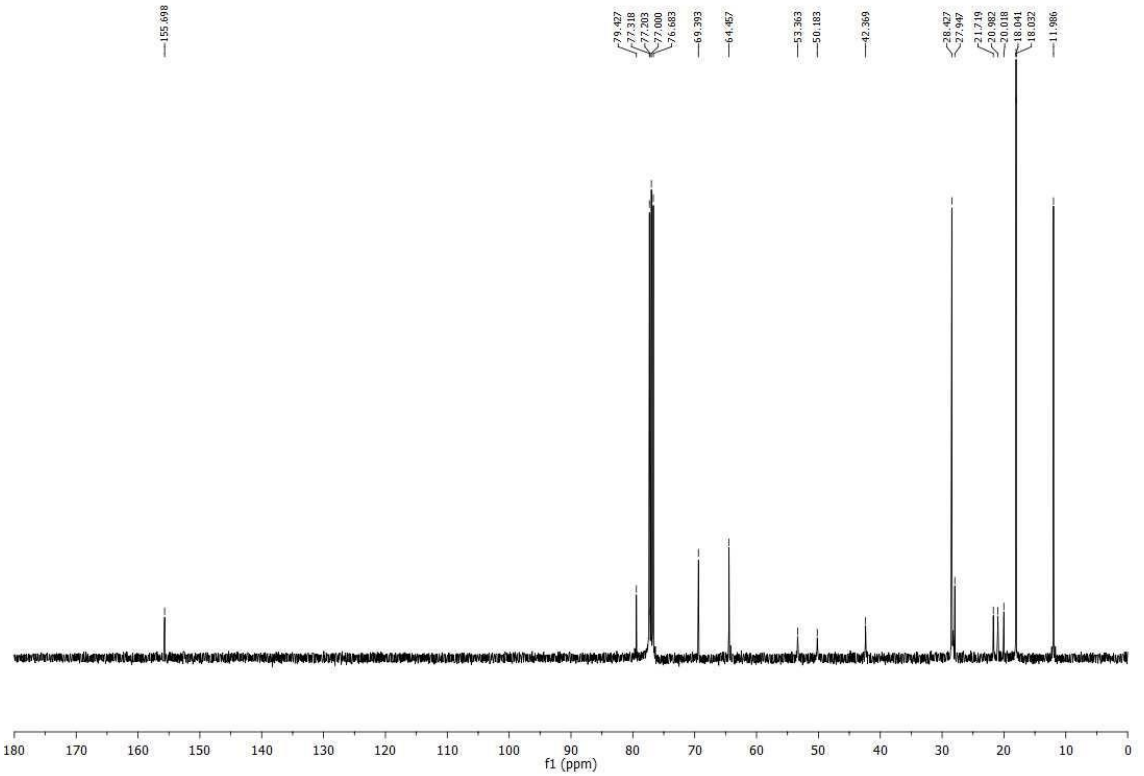
17.10
f1 (ppm)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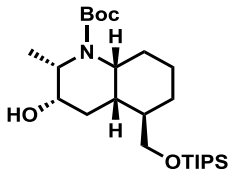
f1 (ppm)



(2*S*,3*S*,4a*S*,5*R*,8a*R*)-1-(*tert*-Butoxycarbonyl)-3-hydroxy-2-methyl-5-(triisopropylsilyloxy-methyl)decahydroquinoline (36)

Fisrt step: Dess-Martin periodinane (1.05 g, 2.48 mmol) was added to a solution of alcohol **34** (750 mg, 1.65 mmol) in CH_2Cl_2 (118 mL). The resulting white suspension was stirred at room temperature for 2.5 h. Then, the mixture was filtered through Celite® and the filtrate was concentrated.

Second step: $NaBH_4$ (250 mg, 6.6 mmol) was added to a solution of the above ketone **35** in MeOH (24 mL) at –55 ºC, and the mixture was stirred overnight at –40 ºC. Then, the mixture was filtered and the filtrate was concentrated. Flash chromatography (7:3 hexane–EtOAc) afforded alcohol **36** (630 mg, 84%) as a colorless oil.

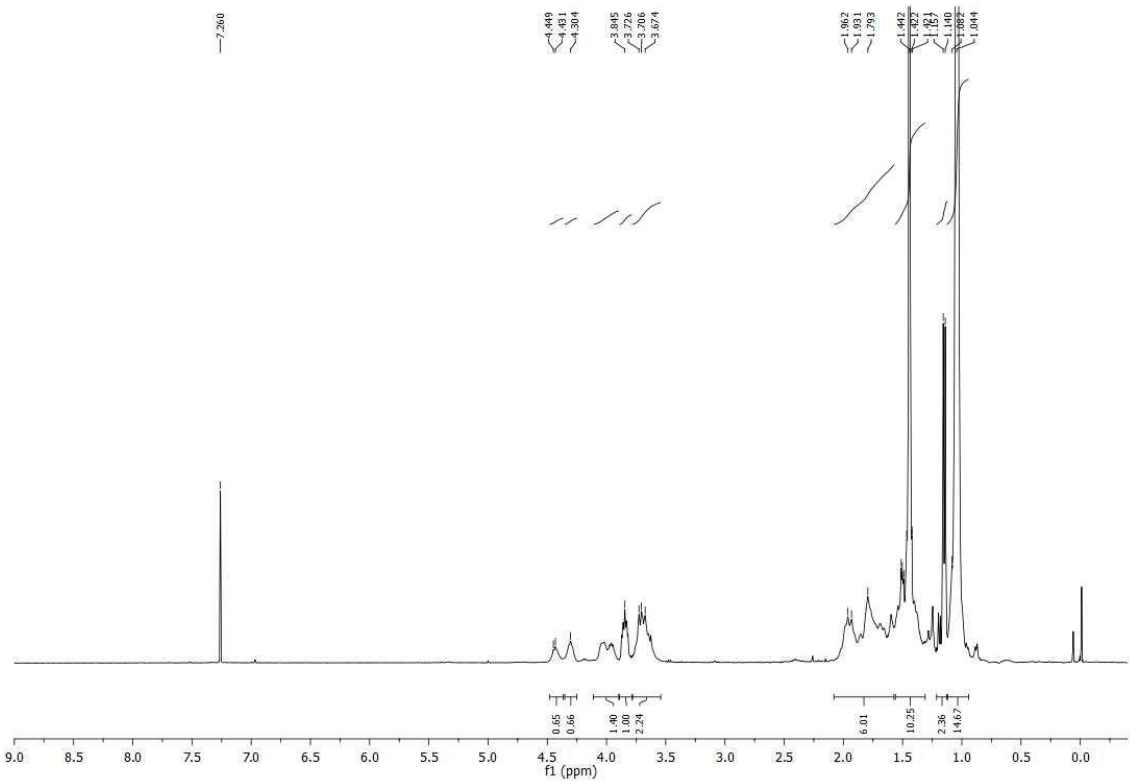
^{1}H-NMR (400 MHz, $CDCl_3$, amide rotamers) δ: 1.04 [br s, 21H, Si(*i*Pr)$_3$], 1.15 (d, J = 6.8 Hz, 3H,CH_3), 1.33-2.06 (m, 10H, H-4, H-5, H-6, H-7, H-8), 1.44 [s, 9H, C(CH_3)$_3$], 3.59 (m, 2H, CH_2OSi(*i*Pr)$_3$], 3.80-3.88 (m, 1H, H-3), 3.96 and 4.02 (br s, 1H, H-8a), 4.30 and 4.43 (br s,1H, H-2).

^{13}C-NMR (100.6 MHz, $CDCl_3$, amide rotamers) 12.0 [(CH_3)$_2$*C*HSi], 14.8 and 14.6 (1 carbon in 2:1 ratio, CH_3), 18.0 [(*C*H$_3$)$_2$CHSi], 21.6 and 21.0 (1 carbon in 2:1 ratio, CH_2), 22.7 and 22.1 (1 carbon in 2:1 ratio, CH_2), 28.4. [(*C*H$_3$)$_3$C], 28.8 and 28.2 (1 carbon in 2:1 ratio, CH_2), 30.1 and 29.7 (1 carbon in 2:1 ratio, C-4), 35.3 and 34.5 (1 carbon in 2:1 ratio, C-4a), 43.1 and 42.6 (1 carbon in 2:1 ratio, C-5), 49.9 and 49.3 (1 carbon in 2:1 ratio, C-8a), 50.7 and 50.0 (1 carbon in 2:1 ratio, C-2), 64.6 [*C*H$_2$OSi(*i*Pr)$_3$], 70.1 (C-3), 79.4 [(CH_3)$_3$*C*], 155.1 (NCOO).

IR (NaCl): 3432, 1665 cm^{-1}.

HRMS calcd for [$C_{25}H_{49}NO_4Si$ + H^+]: 456.3504; found 456.3497.

$[\alpha]^{23}_D$ = – 30.32 (*c* 1.0, $CHCl_3$).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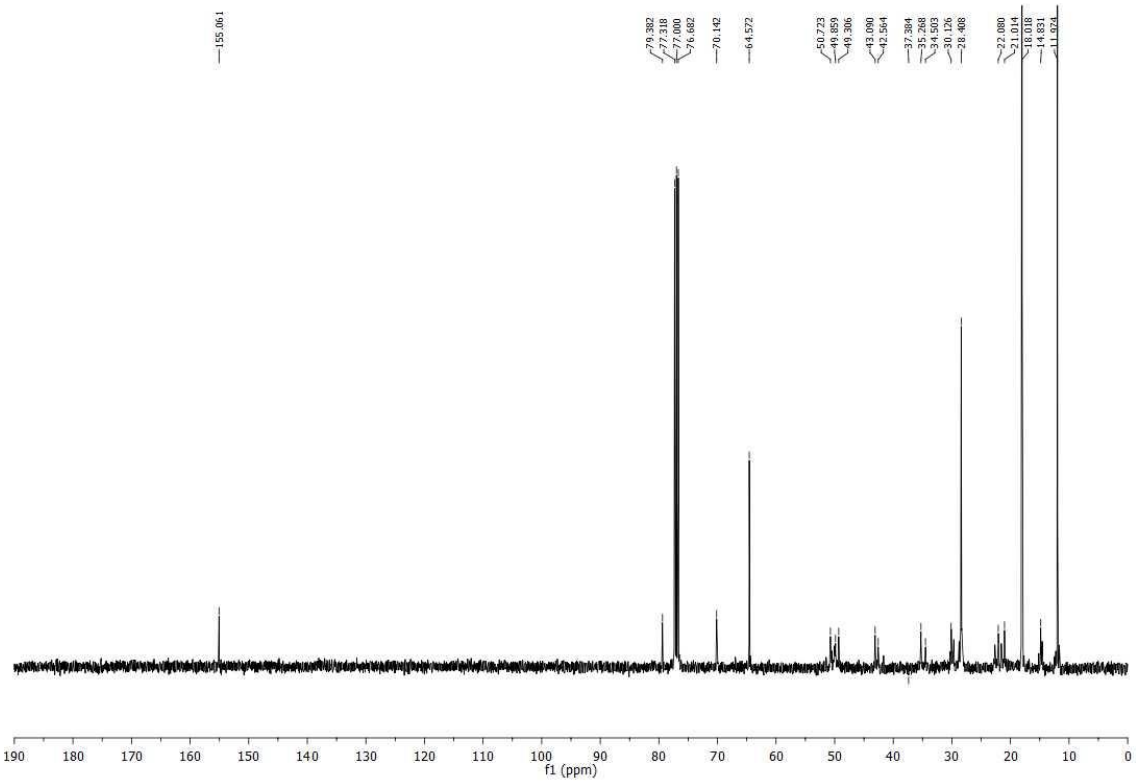
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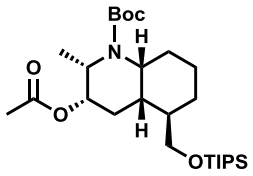


(2*S*,3*S*,4a*S*,5*R*,8a*R*)-3-Acetoxy-1-(*tert*-butoxycarbonyl)-2-methyl-5-(triisopropylsilyloxymethyl)decahydroquinoline (37)

Et_3N (620 μL, 4.44 mmol) and DMAP (18 mg, 0.15 mmol) were added to a solution of **36** (675 mg, 1.48 mmol) in CH_2Cl_2 (36 mL). The resulting solution was cooled to 0 ºC, Ac_2O (210 μL, 2.22 mmol) was added dropwise, and stirring was continued at room temperature for 3 h. The reaction mixture was diluted with CH_2Cl_2 and quenched with saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried, and concentrated. Flash chromatography (7:3 hexane–EtOAc) afforded the acetyl derivative **37** (670 mg, 91%) as a colorless oil.

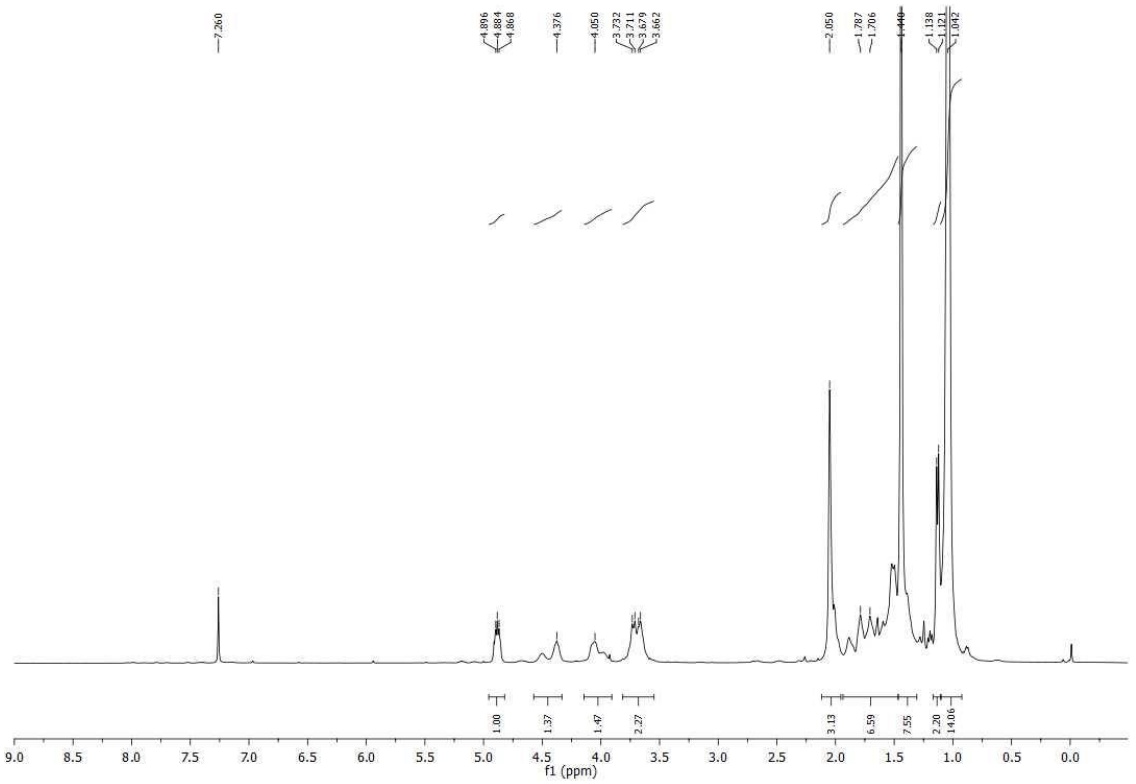
^{1}H-NMR (400 MHz, $CDCl_3$, amide rotamers) 0.91-1.11 [br s, 21H, Si(*i*Pr)$_3$], 1.13 (d, J = 6.8 Hz, 3H, CH_3), 1.30-1.94 (m, 10H, H-4, H-4a, H-5, H-6, H-7, H-8), 1.44 [s, 9H, C(CH$_3$)$_3$], 2.05 (s, 3H, CH_3CO_2), 3.61-3.78 [m, 2H, C*H*$_2$OSi(*i*Pr)$_3$], 4.0 and 4.05 (br s, 1H, H-8a), 4.38 and 4.50 (br s, 1H, H-2), 4.88 (ddd, J = 11.2, 4.6 Hz, 1H, H-3).

^{13}C-NMR (100.6 MHz, $CDCl_3$, amide rotamers) δ: 12.0 [(CH$_3$)$_2$*C*HSi], 15.4 and 15.7 (CH_3), 17.7 and 18.0 [(*C*H$_3$)$_2$CHSi], 20.9 and 21.4, 21.2 (CH_2), 21.8 (CH_2), 24.3 (CH_2), 25.2 (C-4), 26.5, 28.1 [(*C*H$_3$)$_3$C], 28.4 (CH_2), 35.0 (C-4a), 43.0 (C-5), 48.0 (C-2), 49.4 (C-8a), 64.4 [CH$_2$OSi(*i*Pr)$_3$], 71.9 (C-3), 79.7 [(CH$_3$)$_3$*C*], 154.8 (NCOO), 170.1 (COO).

IR (NaCl): 1740, 1687, 1238 cm^{-1}.

HRMS calcd for [$C_{27}H_{51}NO_5Si$ + H^+]: 498.3609; found 498.3611.

$[\alpha]^{23}_D$ = + 4.33 (*c* 2.0, $CHCl_3$).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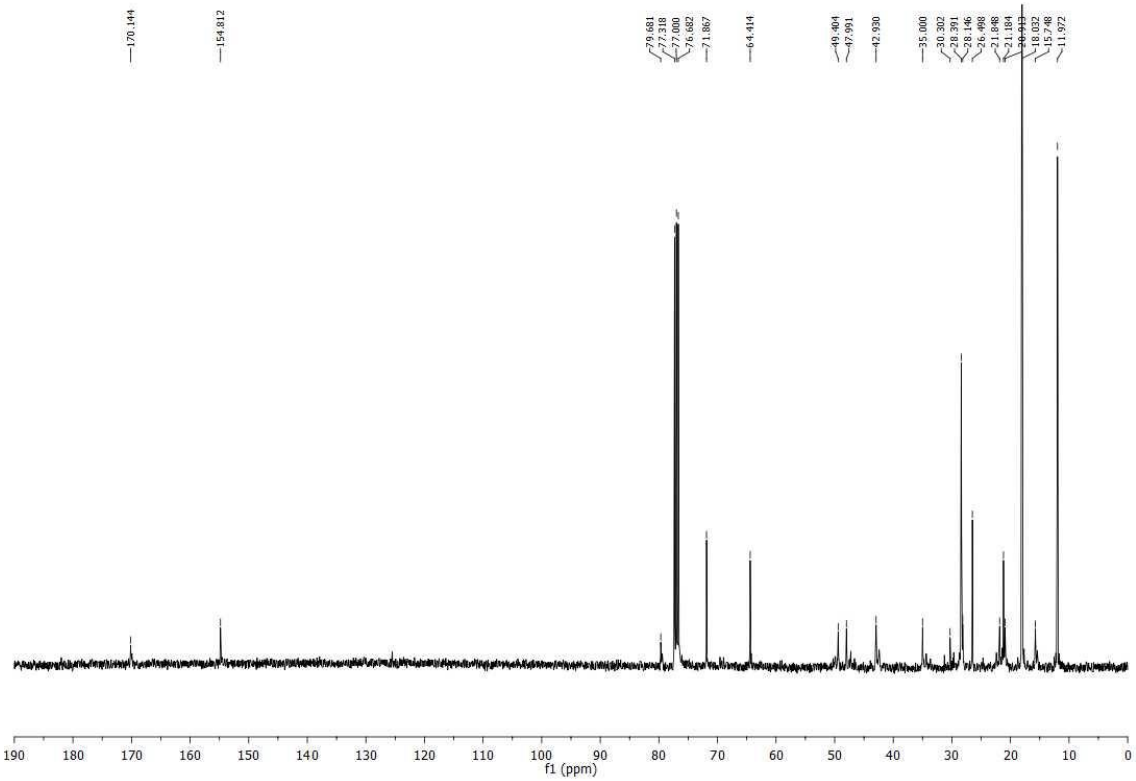
f1 (ppm)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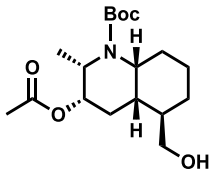
f1 (ppm)



(2*S*,3*S*,4a*S*,5*R*,8a*R*)-3-Acetoxy-1-(*tert*-butoxycarbonyl)-5-(hydroxymethyl)-2-methyl-decahydroquinoline (38)

TBAF (7.6 mL of a 1 M solution in THF, 7.6 mmol) and AcOH (440 μL, 7.6 mmol) were added to a solution of the acetate **37** (750 mg, 1.51 mmol) in THF (25 mL), and the mixture was stirred at 30-40 ºC for 24 h. The reaction was quenched with saturated aqueous NH_4Cl and the resulting mixture was extracted with Et_2O. The combined organic extracts were washed with brine, dried, and concentrated. Flash chromatography (7:3 to 1:1 hexane–EtOAc) afforded the title alcohol **38** (430 mg, 83%) as a yellowish oil.

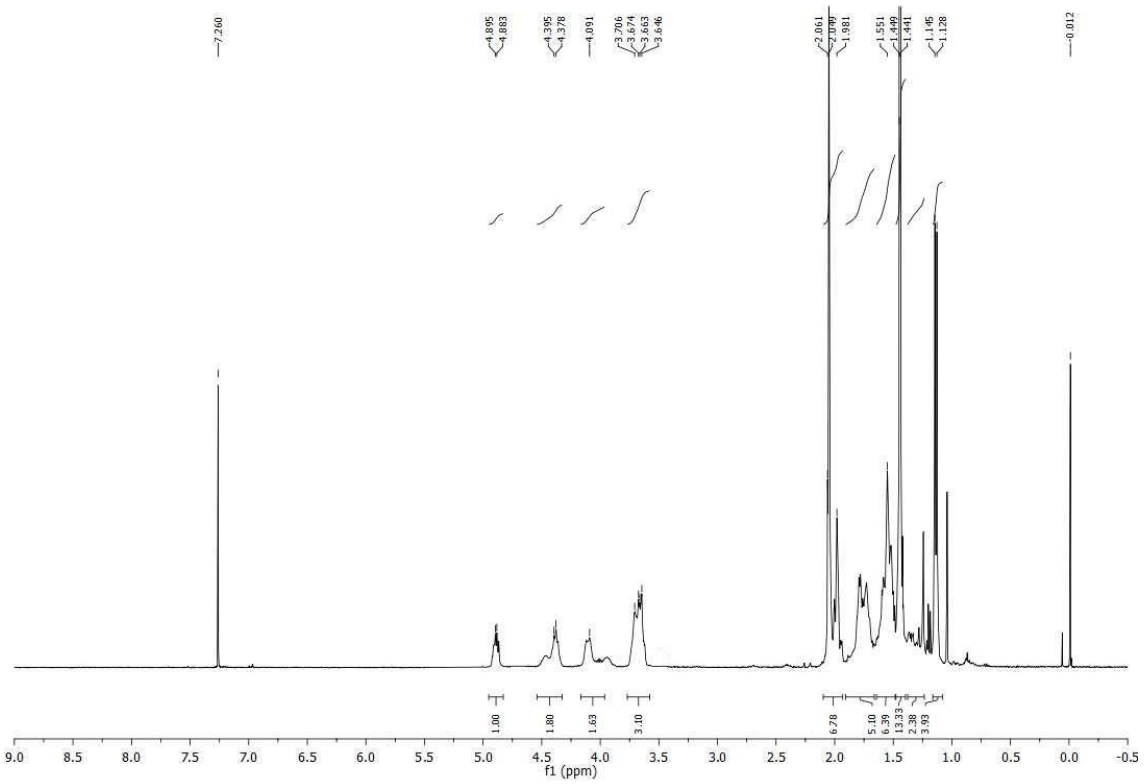
^{1}H-NMR (400 MHz, $CDCl_3$, amide rotamers) δ: 1.13 (d, *J* = 6.8 Hz, 3H, CH_3), 1.19-1.34 (m, 4H), 1.37-1.90 (m, 6H), 1.44 [s, 9H, $C(CH_3)_3$], 1.92-2.11 (m, 5H, CH_3, H-4, H-4a), 3.60-3.79 (m, 2H, CH_2OH), 4.11 (ddd, *J* = 10.8, 7.4, 3.0 Hz, 1H, H-8a), 4.37 and 4.47 (br s, 2:1 ratio, 1H, H-2) 4.84-4.95 (m, 1H, H-3).

^{13}C-NMR (100.6 MHz, $CDCl_3$, amide rotamers) *δ*: 15.8 (CH_3), 21.1 (2 carbons CH_2, CH_3COO), 22.4 (CH_2), 22.6 (CH_2), 26.4 (C-4), 28.0 and 28.4 [$(CH_3)_3C$], 31.6 (CH_2), 34.6 (C-4a), 42.6 (C-5), 48.0 (C-2), 49.0 (C-8a), 64.1 (CH_2OH), 71.7 (C-3), 79.8 [$(CH_3)_3C$], 154.9 (NCOO), 170.1 (COO).

IR (NaCl): 3309, 1740, 1683 cm^{-1}.

HRMS calcd for [$C_{18}H_{31}NO_5 + H^+$]: 342.2275; found 342.227.

$[\alpha]^{23}_D$ = + 7.17 (*c* 1.0, $CHCl_3$).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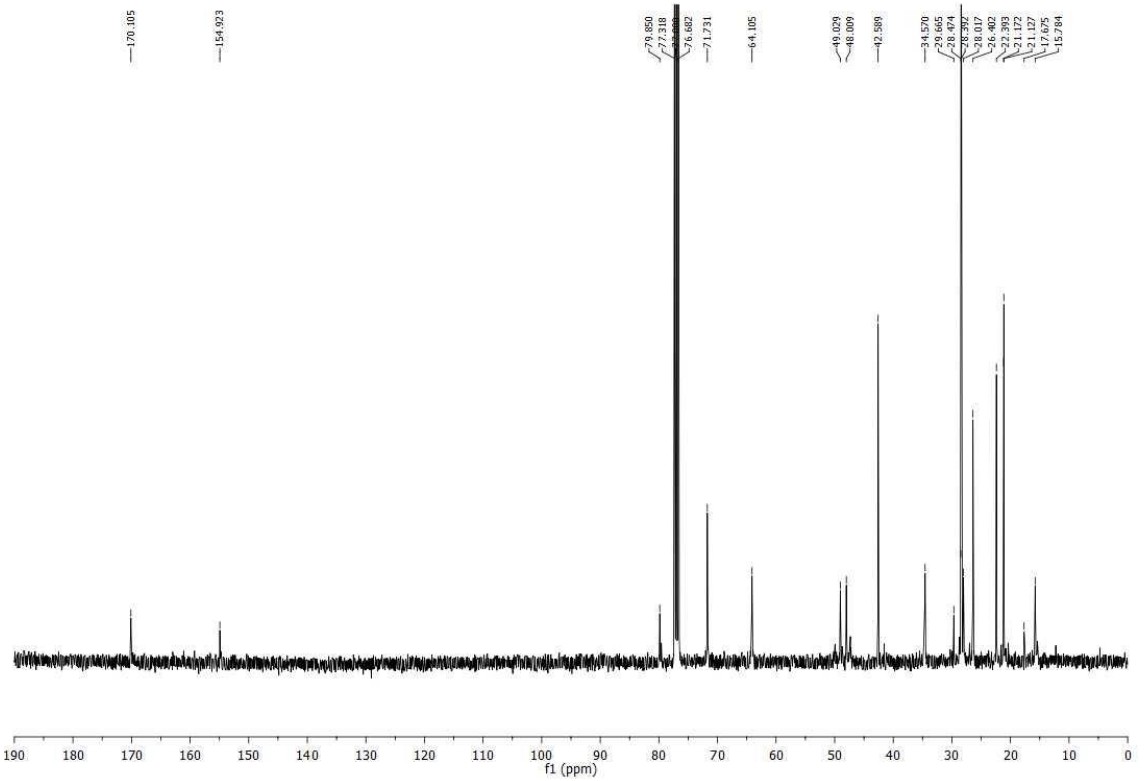
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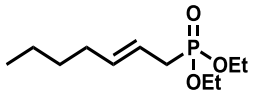
f1 (ppm)



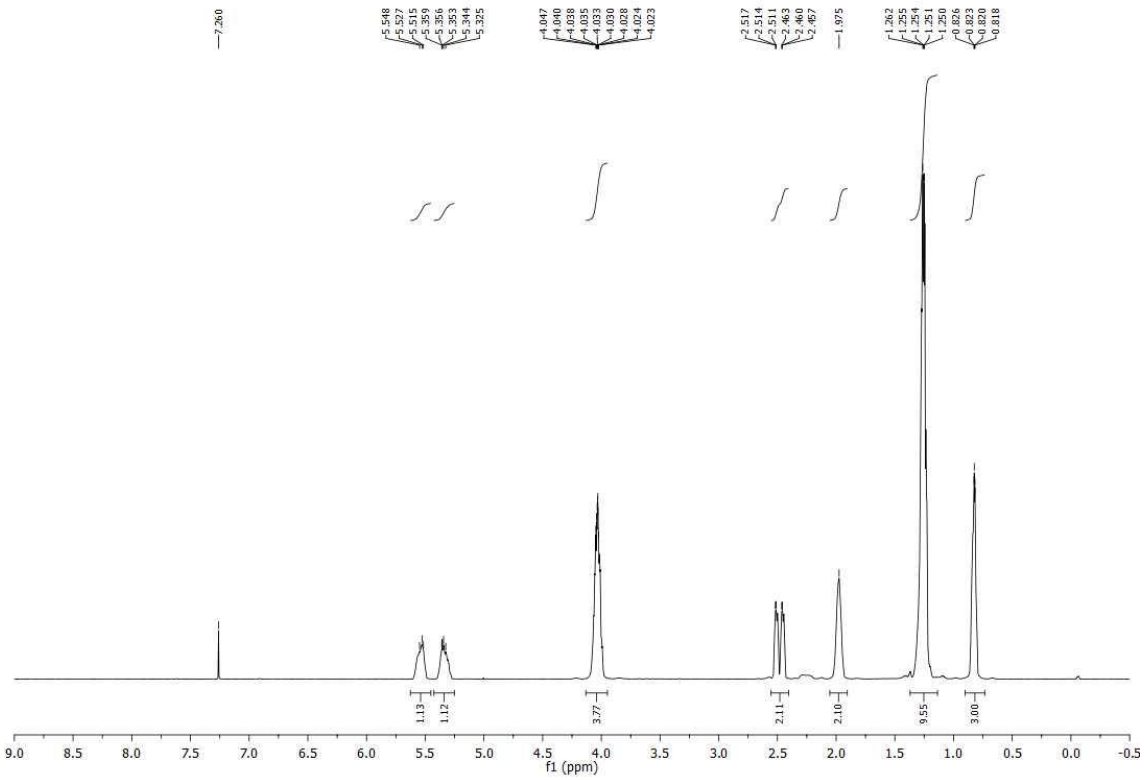
Diethyl (*E*)-hept-2-enylphosphonate (39)

n-BuLi (2.36 mL of a 2.5 M solution in hexane, 5.9 mmol) was added dropwise to a stirring solution of 2-heptenol (0.8 mL, 5.9 mmol) in THF (12 mL) at –78 ºC, and the resulting solution was stirred at this temperature for 10 min. Then, a solution of TsCl (1.24 g, 6.48 mmol) in THF (6 mL) was added dropwise, and the solution was stirred at –78 ºC for an additional hour. KHMDS (17.7 mL of a 0.5 M solution in toluene, 8.85 mmol) was added dropwise to a stirred solution of diethyl phosphite (1.25 mL, 9.72 mmol) in THF (12 mL), under an inert atmosphere at 0 ºC, and the solution was stirred for 30 minutes. The diethyl phosphite anion was transferred dropwise at –78 ºC *via* cannula to the above formed tosylate, and the mixture was allowed to slowly warm to room temperature and stirred overnight. Then, saturated aqueous NH_4Cl was added, the phases were separated, and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried and concentrated. Flash chromatography (95:5 to 85:15 hexane–acetone) afforded compound **39** (1.05 g, 76%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.82 (br s, 3H, CH_3), 1.23-1.27 (m, 10H), 1.97 (br s, 2H), 2.41-2.53 (m, 2H), 3.91-4.12 (m, 4H, OCH_2), 5.27-5.39 (m, 1H, CH), 5.46-5.61 (m, 1H, CH).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 13.7 (CH_3), 16.3 (CH_3, d, J = 6.2 Hz), 22.0 (CH_2), 29.6 (CH_2), 31.1 (CH_2, d, J = 14.0 Hz), 32.1 (CH_2, d, J = 2.3 Hz), 61.6 (CH_2, d, J = 6.9 Hz), 118.3 (CH, d, J = 11.0 Hz), 136.1 (CH, d, J = 14.0 Hz).

HRMS calcd for [$C_{11}H_{23}O_3P + H^+$]: 235.1458; found 235.1461.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2.511
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2.460
2.457
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1.255
1.254
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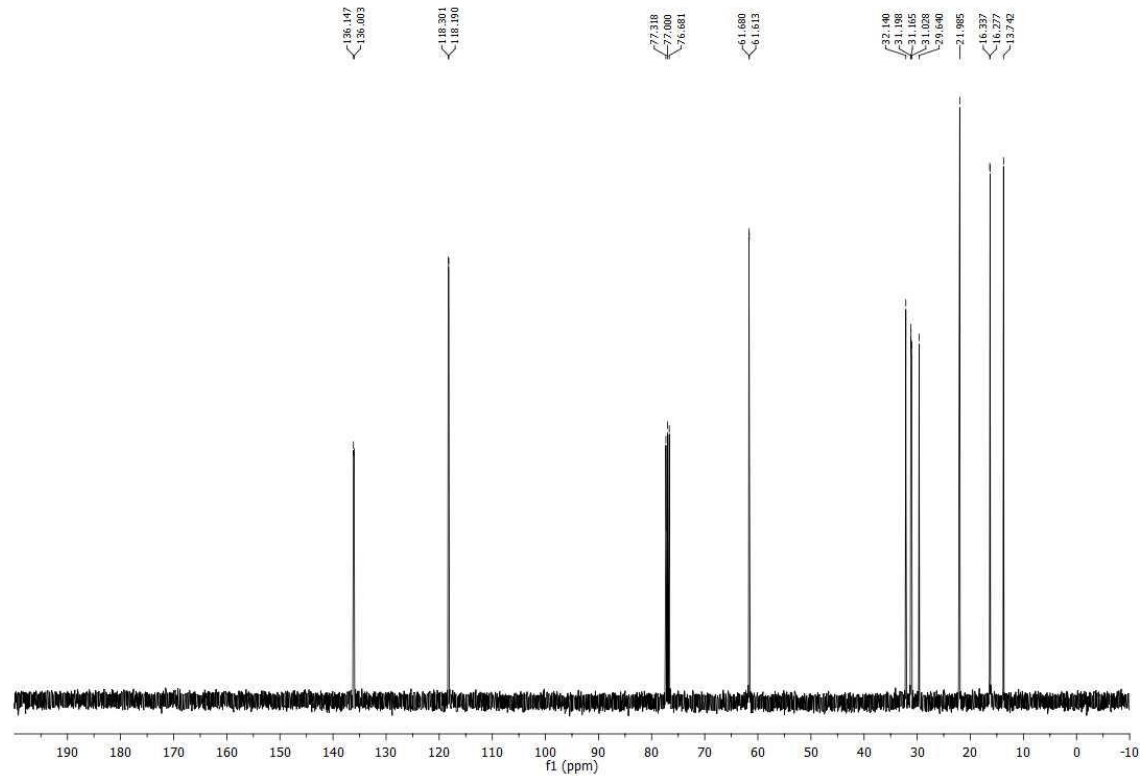
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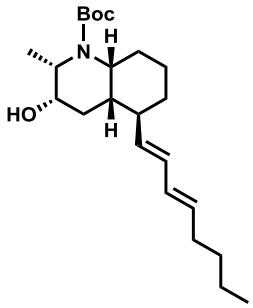


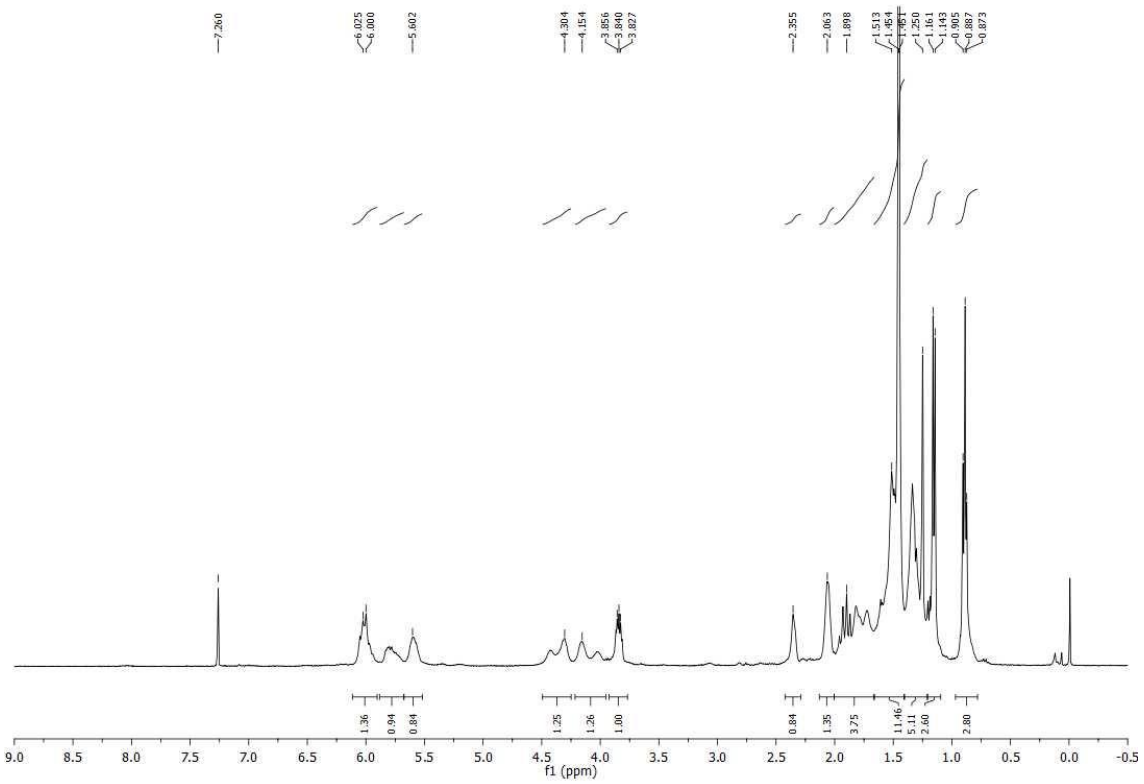
((2*S*,3*S*,4a*S*,5*S*,8a*R*)-1-(*tert*-Butoxycarbonyl)-3-hydroxy-2-methyl-5-[(1*E*,3*E*)-1,3-octadienyl]decahydroquinoline (41)

First Step: Dess-Martin periodinane (1.34 g, 3.15 mmol) was added to a solution of alcohol **38** (430 mg, 1.26 mmol) in CH_2Cl_2 (92 mL), and the mixture was stirred at room temperature for 3 h. Then, saturated aqueous $Na_2S_2O_3$ (20 mL) and saturated aqueous $NaHCO_3$ (20 mL) were added, and the resulting mixture was stirred for 1 h. The phases were separated, and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried and concentrated to afford crude aldehyde, which was used without further purification in the next step.
Second Step: KHMDS (570 μL of a 0.5 M solution in toluene, 0.28 mmol) was slowly added at –78 ºC to a solution of phosphonate **39** (67 mg, 0.24 mmol) in THF (1 mL). After the addition was complete, the solution was stirred for 30 min. Then, a solution of the crude aldehyde **40** (0.06 mmol) in THF (1 mL) was slowly added (10 min), and the resulting mixture was stirred at –78 ºC overnight. The mixture was slowly warmed to room temperature (5 h) and stirred at this temperature for an additional 30 min. Saturated aqueous NH_4Cl was added, and the resulting mixture was extracted with Et_2O. The organic extracts were dried and concentrated. Flash chromatography (9:1 to 7:3 hexane–EtOAc) afforded compound **41** (15 mg, 68%) as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$, amide rotamers) δ: 0.89 (t, J = 6.4 Hz, 3H, CH_3), 1.15 (d, J = 6.8 Hz, 3H, CH_3), 1.21-1.99 (m, 13H, H-4, H-4a, H-6, H-7, H-8, $2CH_2$), 1.45 [s, 9H, $C(CH_3)_3$], 2.06 (br s, 2H), 2.35 (br s, 1H, H-5), 3.77-3.90 (m, 1H, H-3), 4.02 and 4.16 (br s, 1H, 2:1 ratio, H-8a), 4.31 and 4.43 (br s, 1H, 2:1 ratio, H-2), 5.47-5.65 (m, 1H), 5.67-5.85 (m, 1H), 5.90-6.11 (m, 2H).

^{13}C NMR (100.6 MHz, $CDCl_3$, amide rotamers) δ: 13.9 (CH_3), 14.7 and 14.9 (1 carbon), 21.1, 22.2 (CH_2), 26.1, 28.0, 28.4 [(CH_3)$_3$C], 29.7 and 29.9 (1 carbon), 31.5 (CH_2), 32.3, 39.4 and 39.8 (1 carbon), 42.5 and 42.8 (1 carbon), 49.0, 50.0 and 50.8, (1 carbon), 70.1 (C-3), 79.5 [(CH_3)$_3$*C*], 130.2 (CH=), 130.3 (CH=), 133.4 (CH=), 134.7 (CH=), 155.1 (NCOO).

$[\alpha]^{23}_D = -$ 1.29 (*c* 1.0, $CHCl_3$).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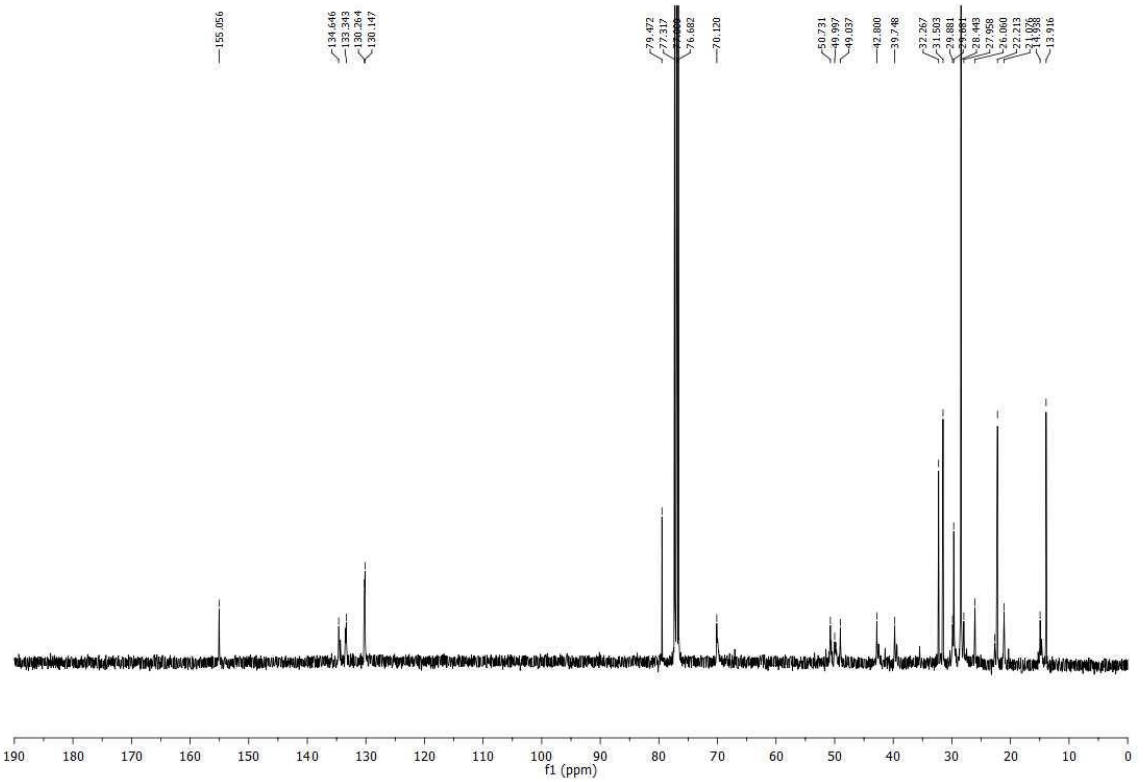
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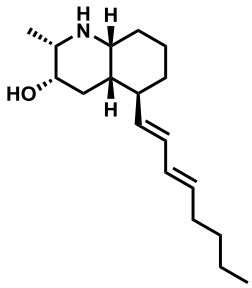


(–)-Lepadin B

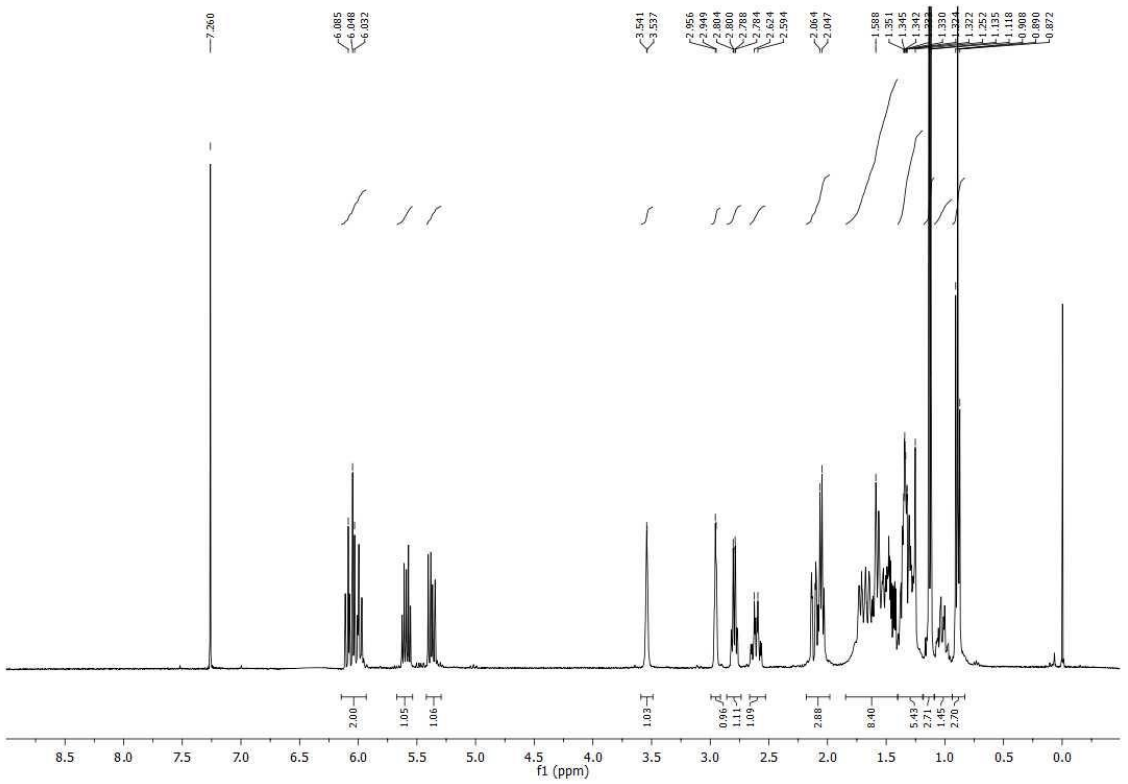
TFA (280 μL) was slowly added to a solution of compound **41** (24 mg, 0.06 mmol) in CH_2Cl_2 (2.8 mL) at 0 ºC, and the resulting solution was stirred at room temperature for 1 h. The mixture was concentrated, and the residue was taken up with $CHCl_3$ (11 mL). K_2CO_3 (224 mg) was added, and the resulting suspension was stirred at room temperature for 1 h. The mixture was filtered and concentrated to afford (–)-**lepadin B** (17.6 mg, 99%) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.89 (t, J = 7.2 Hz, 3H, CH_3), 1.13 (d, J = 6.8 Hz, 3H, CH_3), 1.24-1.78 (m, 12H, C-4, C-4a, C-6, C-7, C-8, CH_2), 2.05 (q, J = 6.8 Hz, 2H, CH_2), 2.12 (ddd, J = 14.4, 2.4 Hz, 1H, H-4) 2.61 (qd, J = 11.6, 3.8 Hz, 1H, H-5), 2.79 (qd, J = 5.1, 1.2 Hz, 1H, H-2), 2.96 (br s, 1H, H-8a), 3.54 (d, J = 1.6 Hz, 1H, H-3), 5.37 (dd, J = 8.8, 2.4 Hz, 1H), 5.59 (dt, J = 14.8, 6.8 Hz, 1H), 6.00 (dt, J = 14.8, 10.0 Hz, 1H), 6.08 (dd, J = 14.8, 10.0 Hz, 1H).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 13.9 (CH_3), 18.4 (CH_3), 20.8 (CH_2), 22.3 (CH_2), 31.5 (CH_2), 32.3 (CH_2), 33.0 (C-8), 34.1 (C-4), 34.2 (C-6), 38.7 (C-4a), 41.1 (C-5), 56.2 (C-8a), 56.7 (C-2), 68.8 (C-3), 130.3 (CH=), 130.9 (CH=), 132.8 (CH=), 137.1 (CH=).

HRMS calcd for $[C_{18}H_{31}NO + H]^+$: 278.2478; found 278.2473.

$[\alpha]^{23}_D = -74.8$ (c 0.55, MeOH).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2.064
2.047
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1.345
1.342
1.330
1.322
1.252
1.135
1.118
0.908
0.890
0.872
2.00
1.05
1.06
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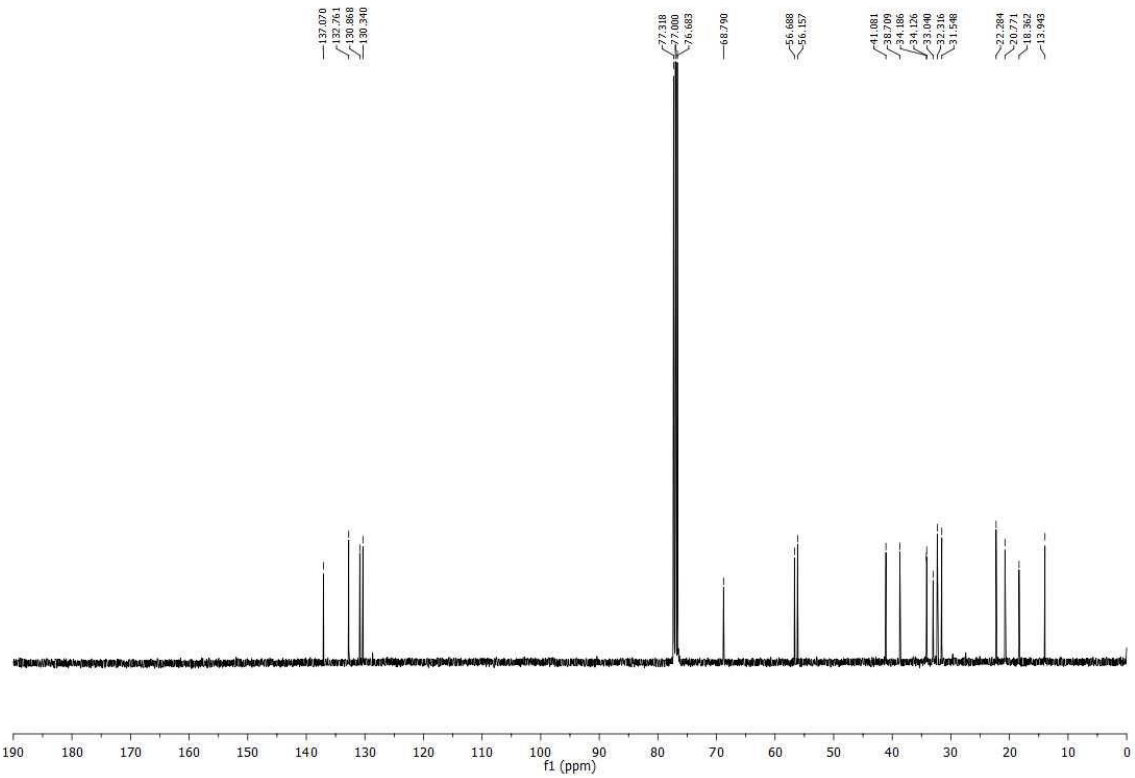
f1 (ppm)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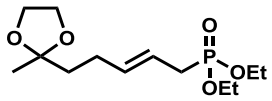
f1 (ppm)



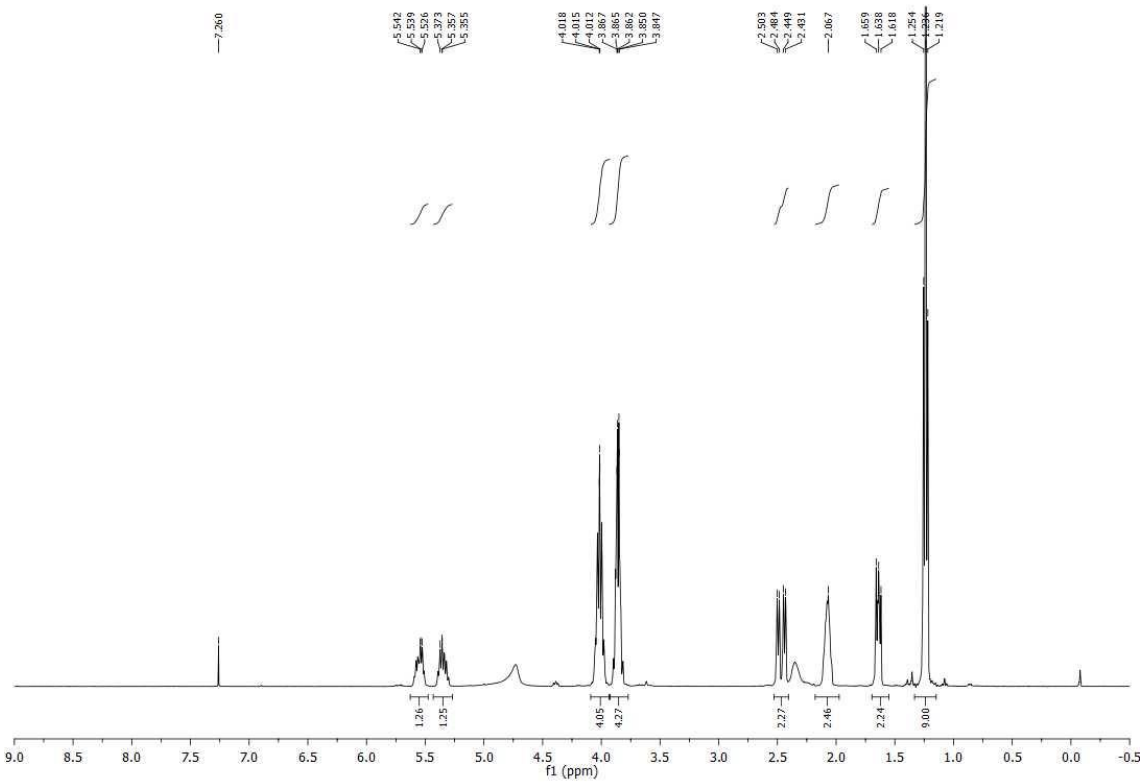
Diethyl (*E*)-6,6-(ethylenedioxy)hept-2-enylphosphonate (43)

Operating as described above for compound **39**, from *n*-BuLi (3.2 mL of a solution 2.5 M in hexane, 8.0 mmol), 6,6-(ethylenedioxy)-2-hexen-1-ol[129] (1.38 g, 8.0 mmol), TsCl (1.68 g, 8.81 mmol), KHMDS (24 mL of a 0.5 M solution in toluene, 12.0 mmol), and diethyl phosphite (1.7 mL, 15.4 mmol), compound **43** (890 mg, 38%) was obtained as a colorless oil after flash chromatography (7:3 hexane–EtOAc to EtOAc).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.18-1.30 (m, 9H, CH_3), 1.59-1.68 (m, 2H, CH_2), 2.07-2.08 (m, 2H, CH_2), 2.47 (dd d, J = 21.6, 7.2 Hz, 2H, CH_2), 3.79-3.91 (m, 4H, CH_2), 3.95-4.08 (m, 4H, CH_2), 5.29-5.41 (m, 1H, CH=), 5.49-5.60 (m, 1H, CH=).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 16.3 (CH_3, d, J = 6.2 Hz), 23.7 (CH_3), 27.0 (CH_2, d, J = 1.6 Hz), 29.5 (CH_2), 30.9 (CH_2), 38.3 (CH_2, d, J = 3.9 Hz), 61.7 (CH_2, d, J = 6.2 Hz), 64.5 (CH_2), 109.5 (Cq), 118.3 (CH=, d, J = 11.7 Hz), 135.4 (CH=, d, J = 14.8 Hz).

[129] H.-Y. Lee, W.-Y. Kim and S. Lee, *Tetrahedron Lett. 2007*, **48,** 1407.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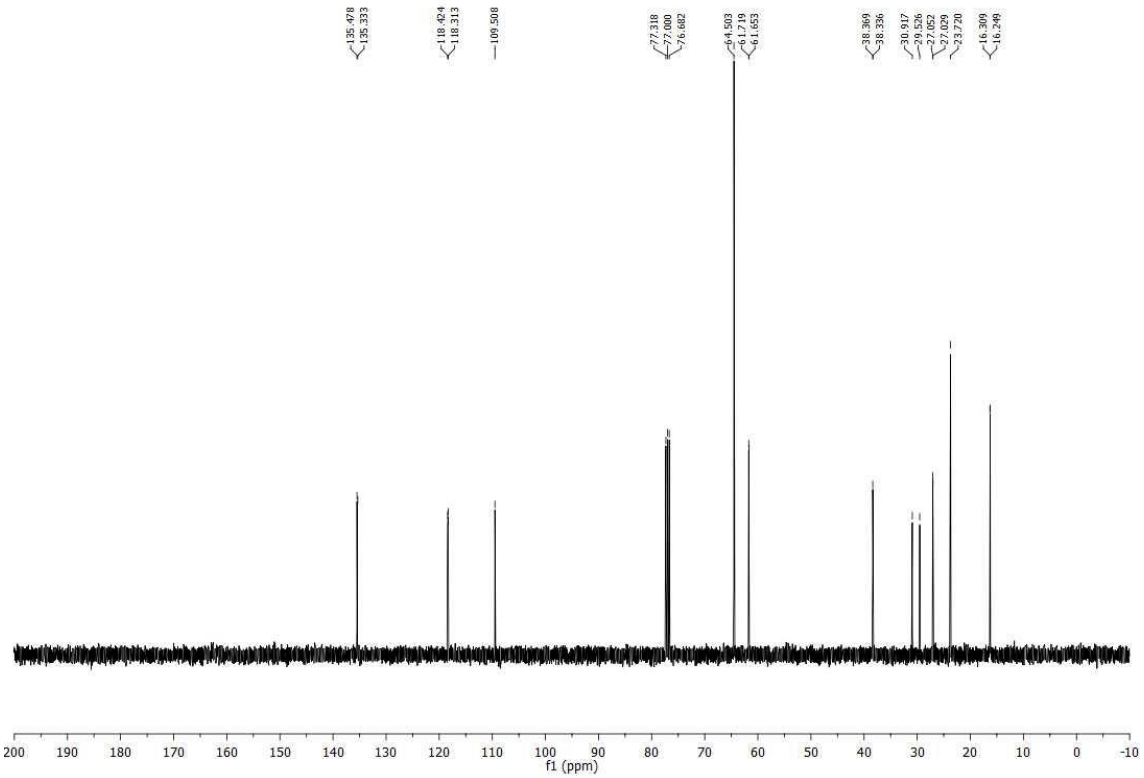
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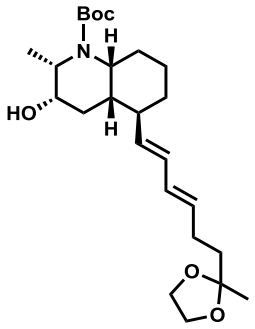
f1 (ppm)



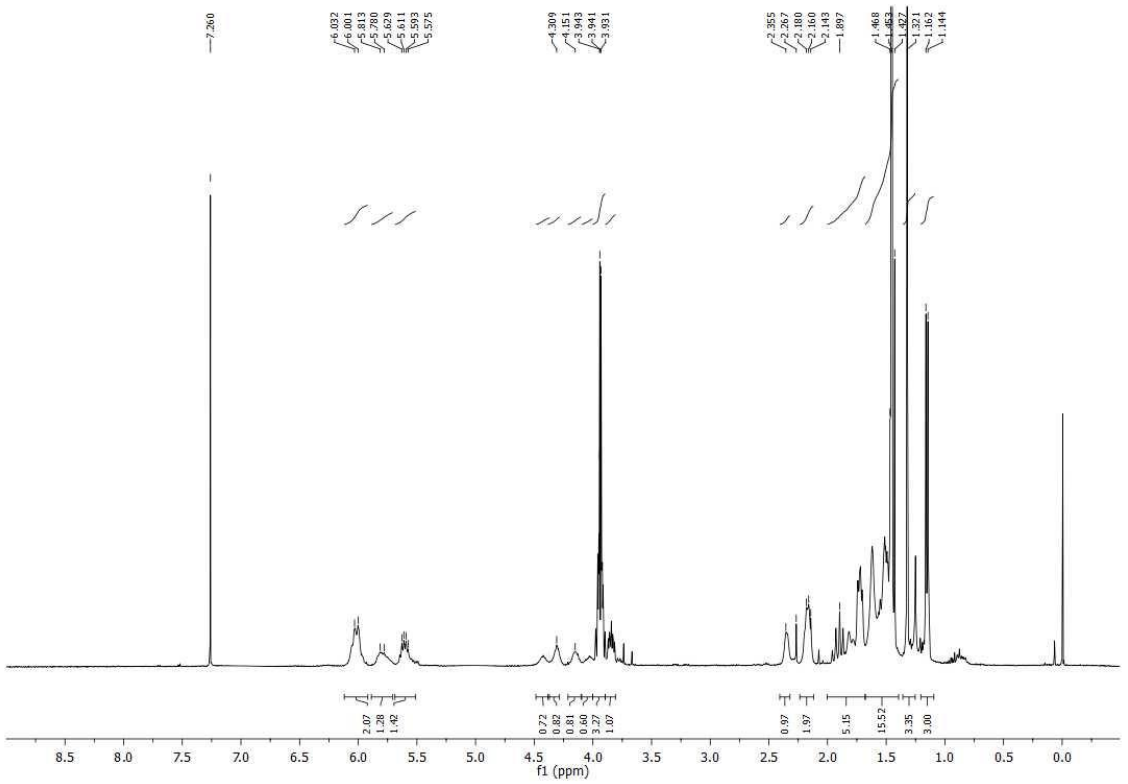
(2*S*,3*S*,4a*S*,5*S*,8a*R*)-1-(*tert*-Butoxycarbonyl)-5-[(1*E*,3*E*)-7,7-(ethylenedioxy)-1,3-octadienyl]-3-hydroxy-2-methyldecahydroquinoline (44)

NaHMDS (210 μL of a 1.0 M solution in THF, 0.21 mmol) was slowly added at –78 ºC to a solution of phosphonate **43** (62 mg, 0.21 mmol) in DME (1 mL). After the addition was complete, the solution was stirred for 1 h. Then, a solution of the crude aldehyde **40** (0.05 mmol) in DME (1 mL) was slowly added (10 min), and the resulting mixture was stirred at –78 ºC and slowly warmed to room temperature overnight. Saturated aqueous NH_4Cl was added, and the resulting mixture was extracted with EtOAc. The organic extracts were dried and concentrated. Flash chromatography (9:1 to 7:3 hexane–EtOAc) afforded compound **44** (13 mg, 57%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$, amide rotamers) δ: 1.15 (d, J = 7.2 Hz, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.40-1.97 (m, 13H), 1.45 (br s, 9H), 2.17 (br s, 2H), 2.35 (br s, 1H), 3.80-3.89 (m, 1H), 3.94 (dd like, J = 4.0 Hz, 4H), 4.03 and 4.15 (br s, 1H, 2:1 ratio), 4.31 and 4.43 (br s, 1H, 2:1 ratio), 5.50-5.65 (m, 1H), 5.70- 5.85 (m, 1H), 5.91-6.10 (m, 2H).

^{13}C-NMR (100.6 MHz, $CDCl_3$ amide rotamers) δ: 21.1 (CH_3), 23.9 (CH_3), 26.0 (CH_2), 27.2 (CH_2), 27.9 (CH_2), 28.4 ($3CH_3$-*t*Bu), 29.7 and 29.9 (1 carbon in 2:1 ratio), 38.6 (CH, 2 carbons), 39.4 and 39.7 (1 carbon in 2:1 ratio), 49.0 and 49.8 (1 carbon in 2:1 ratio), 50.0 and 50.7 (1 carbon in 2:1 ratio), 64.7 (OCH_2, 2 carbons), 70.1 (C-3), 79.5 (Cq-*t*Bu), 109.8 (Cq), 130.0 (CH=), 130.4 (CH=), 132.5 (CH=), 135.0 (CH=), 155.1 (COO).

$[\alpha]^{23}_D$ = – 2.2 (*c* 1.1, $CHCl_3$).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2.180
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1.468
1.463
1.427
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1.162
1.144
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1.28
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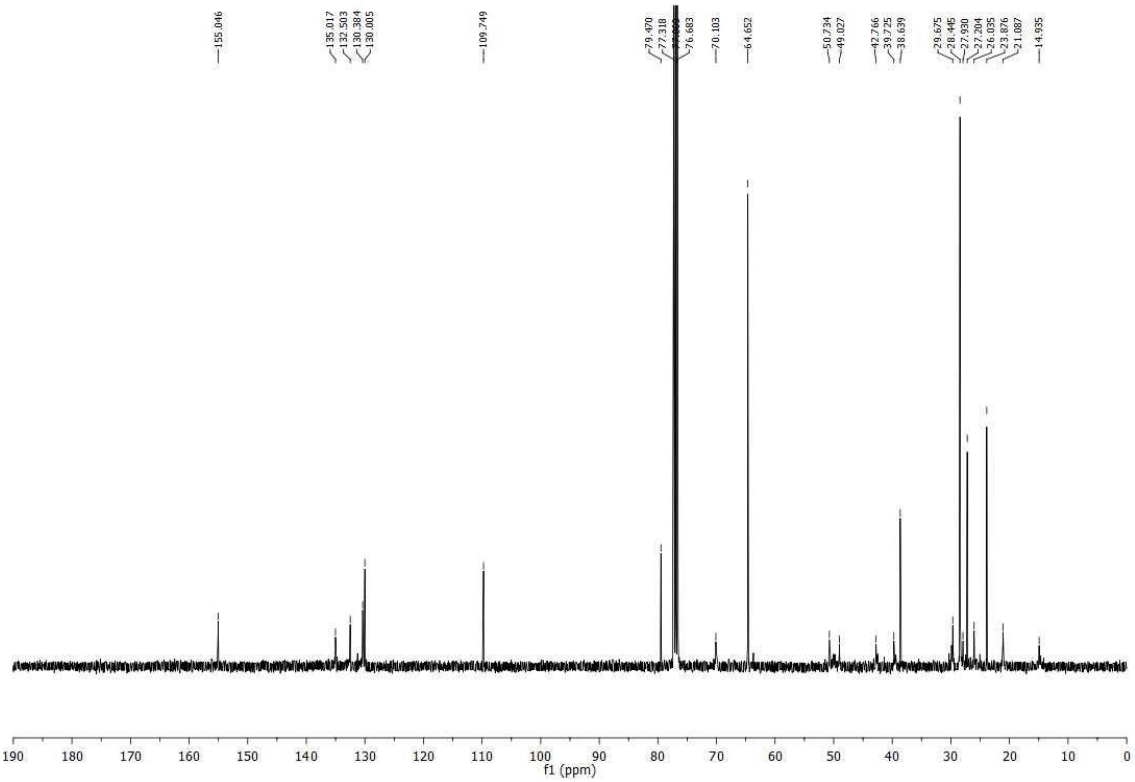
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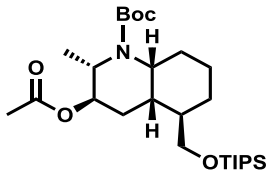


(2*S*,3*R*,4a*S*,5*R*,8a*R*)-3-Acetoxy-1-(*tert*-butoxycarbonyl)-2-methyl-5-(triisopropyl silyloxymethyl)decahydroquinoline (45)

Et_3N (410 μL, 2.96 mmol) and DMAP (12 mg, 0.01 mmol) were added to a solution of **34** (450 mg, 0.99 mmol) in CH_2Cl_2 (24 mL). The resulting solution was cooled to 0 ºC, Ac_2O (140 μL, 1.48 mmol) was added dropwise, and stirring was continued at room temperature for 5 h. The mixture was diluted with CH_2Cl_2 and quenched with saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried, and concentrated. Flash chromatography (9:1 hexane–acetone) afforded the acetyl derivative **45** (430 mg, 88%) as a colorless oil.

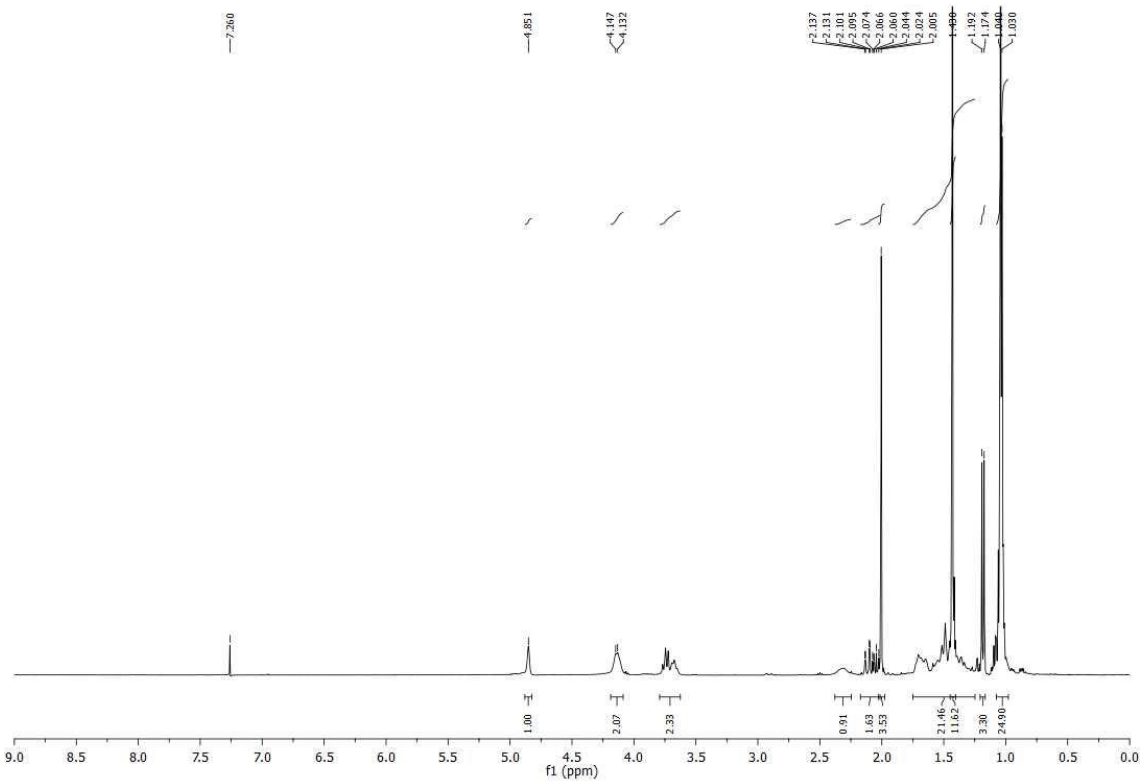
^{1}H-NMR (400 MHz, $CDCl_3$, amide rotamers) δ: 0.95-1.12 [m, 21H, Si(*i*Pr)$_3$], 1.18 (d, J = 7.6 Hz, 3H, CH_3), 1.24-1.74 (m, 6H, H-4, H-4a, H-5, H-6, H-7, H-8), 1.43 [s, 9H, C(CH_3)$_3$], 2.00 (s, 3H, CH_3COO), 2.02-2.15 (m, 2H), 2.31 (br s, 1H), 3.61-3.78 (m, 3H, CH_2OSi(*i*Pr)$_3$], 4.05-4.18 (m, 2H), 4.85 (s, 1H, H-3).

^{13}C-NMR (100.6 MHz, $CDCl_3$, amide rotamers) δ: 12.0 [(CH_3)$_2$*C*HSi], 18.0 [(*C*H$_3$)$_2$CHSi] 19.7 (C-4), 21.3 (CH_3), 21.8 (CH_2), 22.0 (CH_2), 25.4 (CH_2), 28.4 [C(*C*H$_3$)$_3$], 42.2 (C-5), 49.6 (C-2), 50.2 (C-8a), 64.4 [CH_2OSi(*i*Pr)$_3$], 71.7 (C-3), 79.3 [*C*(CH_3)$_3$], 155.2 (NCOO), 170.5 (COO).

IR (NaCl): 1734, 1691 cm^{-1}.

HRMS calcd for [$C_{27}H_{51}NO_5Si$ + H] $^+$: 498.3609; found 498.3601.

[α]$^{23}_D$ = + 15.4 (*c* 0.8, $CHCl_3$).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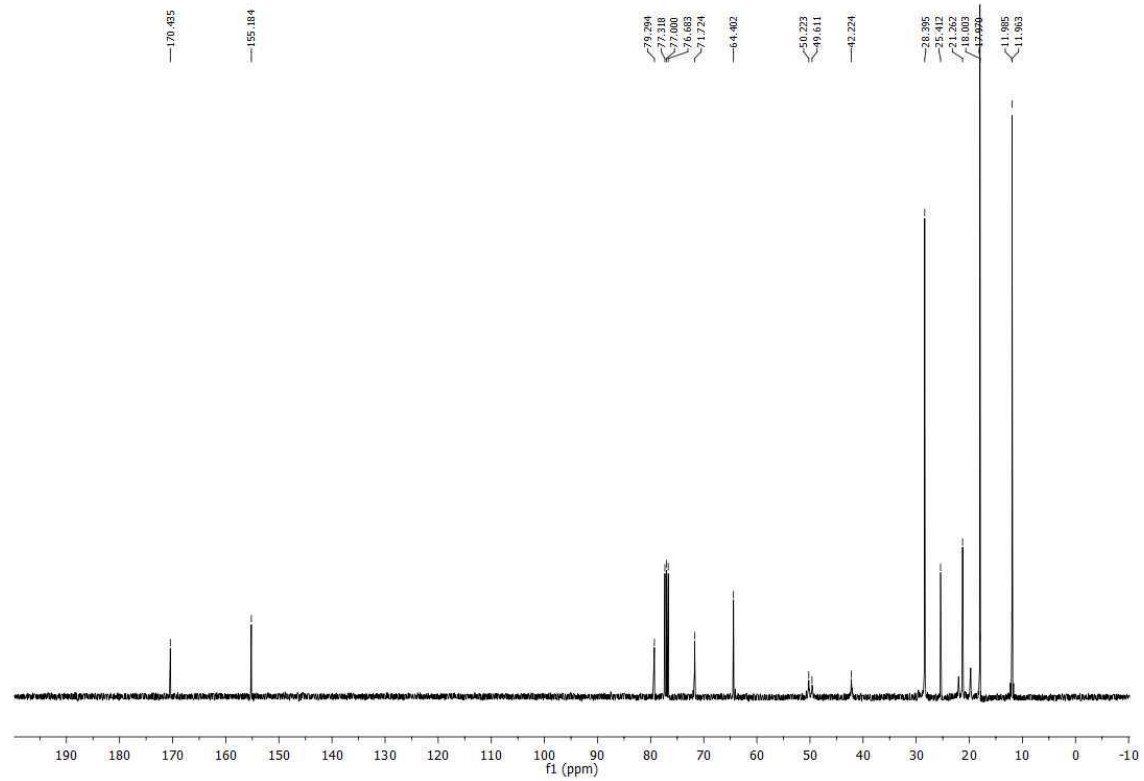
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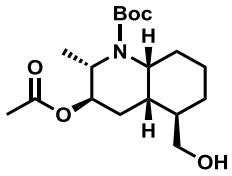
f1 (ppm)



(2*S*,3*R*,4a*S*,5*R*,8a*R*)-3-Acetoxy-1-(*tert*-butoxycarbonyl)-5-(hydroxymethyl)-2-methyldecahydroquinoline (46)

TBAF (4.4 mL of a 1M solution in THF, 4.4 mmol) and AcOH (100 μL, 1.73 mmol) were added to a solution of acetate **45** (430 mg, 0.86 mmol) in THF (14 mL), and the mixture was stirred at 30-40 ºC for 24 h. The reaction was quenched with saturated aqueous NH_4Cl, and the resulting mixture was extracted with Et_2O. The combined organic extracts were washed with brine, dried, and concentrated. Flash chromatography (4:6 to 3:7 hexane–EtOAc) afforded alcohol **46** (285 mg, 97%) as a yellowish oil.

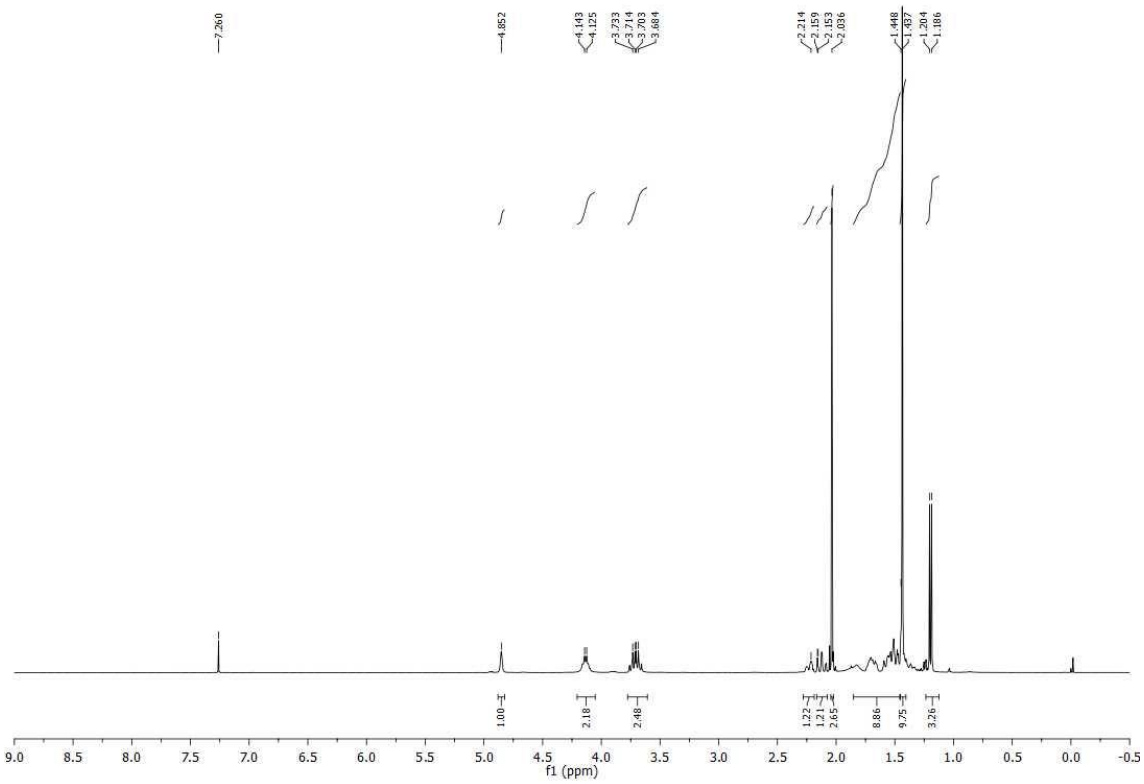
^{1}H-NMR (400 MHz, $CDCl_3$, amide rotamers) δ: 1.19 (d, J = 7.2 Hz, 3H, CH_3), 1.44 [s, 9H, [$C(CH_3)_3$], 1.46-1.83 (m, 8H), 2.04 (s, 3H, CH_3), 2.07-2.28 (m, 2H, H-4, H-4a), 3.60-3.78 (m, 2H, CH_2OH), 4.08-4.20 (m, 2H, H-2, H-8a) 4.85 (br s, 1H, H-3).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 19.8 (CH_3), 21.0 (CH_2), 21.4 (CH_3), 22.0 (CH_2), 25.4 (CH_2), 28.4 [C(CH_3)$_3$], 29.0 (C-4a), 42.1 (C-5), 49.4 (CH), 50.4 (CH), 64.1 (CH_2OH), 71.7 (C-3), 79.6 [$C(CH_3)_3$], 155.3 (NCOO), 170.5 (COO).

IR (NaCl): 3447, 1736, 1687 cm^{-1}.

HRMS calcd for [$C_{18}H_{31}NO_5$ + Na^+]: 364.2094; found 364.2106.

$[\alpha]^{23}_D$ = + 7.1 (*c* 1.65, $CHCl_3$).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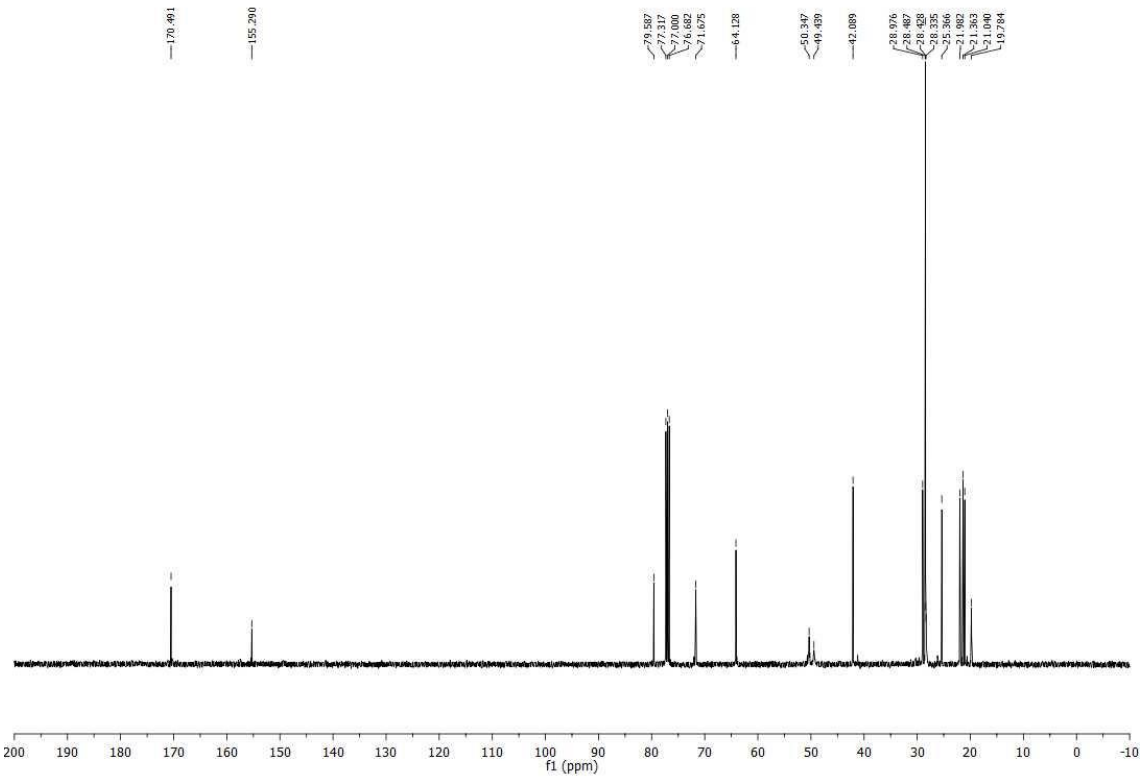
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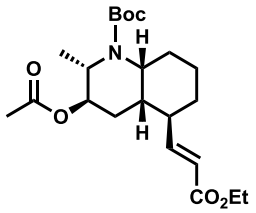


Ethyl(2*S*,3*R*,4a*S*,5*S*,8a*R*)-3-acetoxy-1-(*tert*-butoxycarbonyl)-2-methyl decahydroquinoline-5-(*E*)-propenoate (49)

First-step: Dess-Martin periodinane (372 mg, 0.88 mmol) was added to a solution of alcohol **46** (120 mg, 0.351 mmol) in CH_2Cl_2 (35 mL), and the mixture was stirred at room temperature for 2 h. Then, saturated aqueous $Na_2S_2O_3$ (20 mL) and saturated aqueous $NaHCO_3$ (20 mL) were added, and the resulting mixture was stirred for 1 h. The phases were separated, and the aqueous phase extracted with Et_2O. The combined organic extracts were dried and concentrated to afford crude aldehyde, which was used without further purification in the next step.

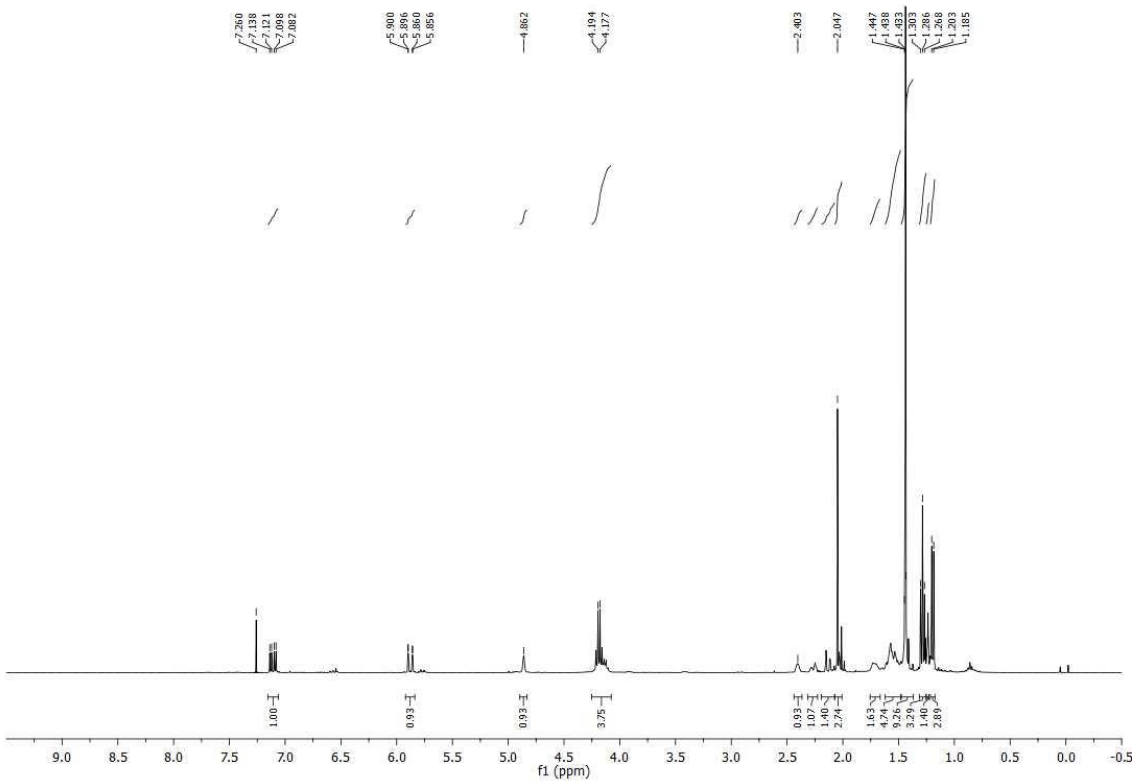
Second-step: (Ethoxycarbonylmethylene)triphenylphosphorane (135 mg, 0.39 mmol) was added to a stirred solution of the above crude in CH_2Cl_2 (2 mL), and the mixture was stirred at room temperature for 8 h. The solvent was evaporated. Flash chromatography (9:1 hexane–acetone) of the residue afforded compound **49** (130 mg, 90%) as a yellowish oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.19 (d, J = 7.6 Hz, 3H, CH_3), 1.28 (t, J = 7.2 Hz, 3H, CH_3), 1.41-1.45 (m, 2H), 1.44 [s, 9H, $C(CH_3)_3$], 1.48-1.61 (m, 4H), 1.63-1.74 (m, 1H), 2.05 (s, 3H, CH_3), 2.07-2.17 (m, 1H), 2.25 and 2.29 (br s, 1H), 2.40 (br s, 1H), 4.09-4.25 (m, 4H, H-2, H-8a, CH_2), 4.86 (s, 1H, H-3), 5.88 (dd, J = 15.8, 1.8 Hz, 1H, CH=), 7.11 (dd, J = 15.8, 6.8 Hz, 1H, CH=).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 14.1 (CH_3), 19.7 (CH_3), 21.2 (CH_3), 21.4 (CH_2), 24.8 (CH_2), 25.2 (CH_2), 28.4 [$C(CH_3)_3$], 28.5 (CH), 32.3 and 32.7 (CH), 41.7 (C-5), 49.3 (C-8a), 50.2 (C-2), 60.3 (OCH_2), 71.4 (C-3), 79.6 [$C(CH_3)_3$], 121.3 (CH=), 151.5 (CH=), 155.1 (NCOO), 166.6 (COO), 170.4 (COO).

IR (NaCl): 1734, 1720, 1688 cm^{-1}.

HRMS calcd for [$C_{22}H_{35}NO_6$ + H^+]: 410.2537; found 410.2531.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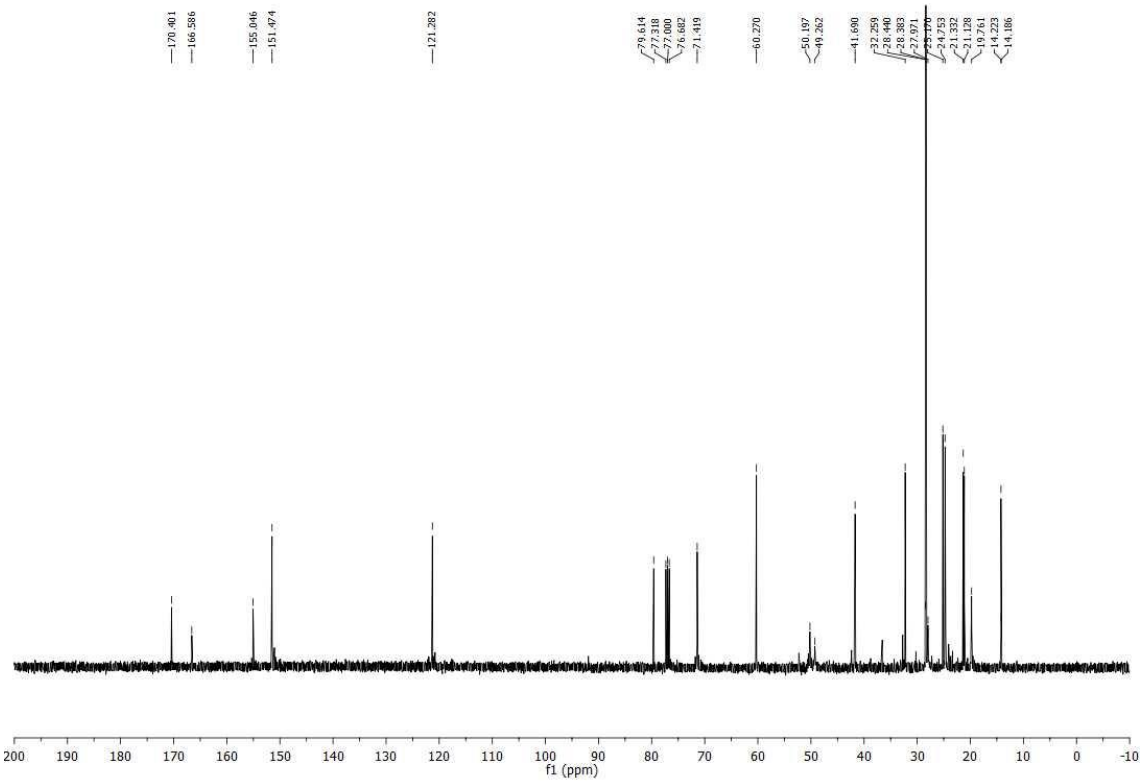
1.303
1.286
1.268
1.203
1.185
1.00
0.93
0.93
3.75
0.93
1.07
1.40
2.74
1.63
4.74
9.26
3.29
1.40
2.89
f1 (ppm)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41.690
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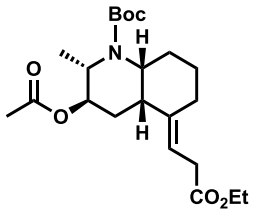
14.186
f1 (ppm)



Ethyl(2*S*,3*R*,4a*S*,8a*R*)-3-acetoxy-1-(*tert*-butoxycarbonyl)-2-methyldecahydro-quinoline-$\Delta^{5,\beta}$-propionate (50)

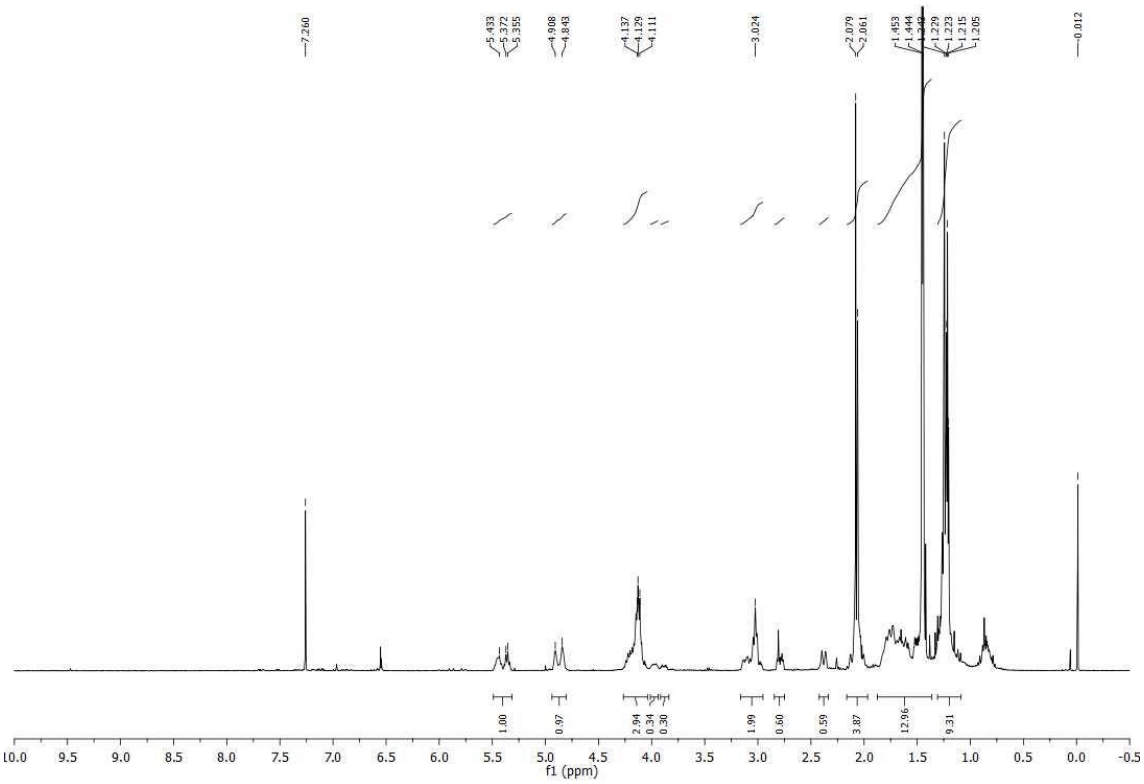
HMPA (270 μL) and KHMDS (440 μL of a 0.5 M solution in toluene, 0.22 mmol) were added to a solution of conjugated ester **49** (75 mg, 0.18 mmol) in THF (2 mL) at –78 ºC. The mixture was warmed to –15 ºC and stirred for 30 min. After cooling at –78 ºC, the reaction was quenched with saturated aqueous NH_4Cl (1 mL). The resulting mixture was stirred at room temperature for an additional 30 min, diluted with water, and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated. Flash chromatography (7:3 to 6:4 hexane–EtOAc) afforded compounds **50** (46 mg, 61%, higher *Rf*) as a colorless oil and **51** (20 mg, 27%, lower *Rf*) as a white residue.

^{1}H-NMR (400 MHz, $CDCl_3$, amide rotamers) δ: 1.15-1.33 (m, 8H), 1.36-1.86 (m, 5H), 1.44 [s, 9H, $C(CH_3)_3$], 2.06 and 2.08 (s, 3H, $COOCH_3$), 2.36 and 2.40 (br s, 1H), 2.73-2.82 (m, 1H), 2.95-3.19 (m, 2H), 4.09-4.22 (m, 4H), 4.84 and 4.91 (br s, 1H), 5.33-5.39 and 5.40-5.45 (m, 1H).

^{13}C-NMR (100.6 MHz, $CDCl_3$, amide rotamers) δ: 14.1 and 14.2 (CH_3), 19.4 and 19.8 (CH_3), 21.3 (CH_3), 24.1 and 24.3 (CH_2), 25.6 (CH_2), 28.4 [$C(CH_3)_3$], 29.4 and 29.7 (CH_2), 32.1 and 32.2 (CH_2), 32.7 (CH_2), 33.0 and 33.1 (CH_2), 39.5 (CH), 49.3 and 50.0 (CH), 53.2 and 53.6 (CH) 60.6 (CH_2) 70.9 and 71.2 (CH), 79.6 and 79.7 [$C(CH_3)_3$], 116.1 (CH), 143.1 and 143.3 (C), 155.1 and 155.2 (NCOO), 170.3 (COO), 171.9 and 172.1 (COO).

IR (NaCl): 1740, 1690 cm^{-1}.

HRMS calcd for [$C_{22}H_{35}NO_6 + H^+$]: 410.2537 found 410.2542.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5.433
5.372
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4.843
4.137
4.129
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3.024
2.079
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1.444
1.343
1.229
1.223
1.215
1.205
0.012
1.00
0.97
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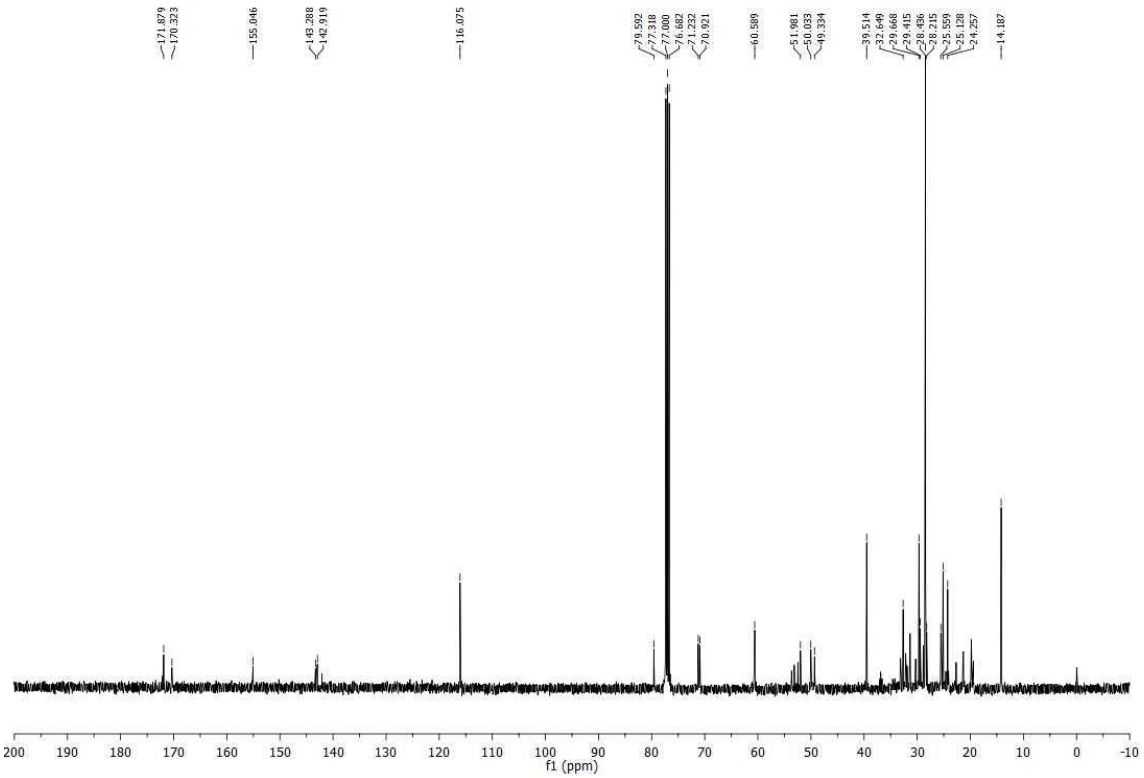
0.34
0.30
1.99
0.60
0.59
3.87
12.96
9.31
f1 (ppm)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77.000
76.682
71.232
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51.981
50.033
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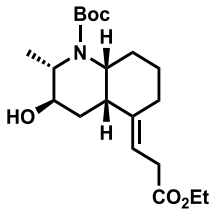
25.559
25.128
24.257
14.187
f1 (ppm)



Ethyl(2*S*,3*R*,4a*S*,8a*R*)-1-(*tert*-Butoxycarbonyl)-3-hydroxy-2-methyldeca-hydroquinoline-$\Delta^{5,\beta}$-propionate (51)

Method B: Operating as in the preparation of **50**, from a solution of the conjugated ester **58** (114 mg, 0.31 mmol) in THF (4 mL), HMPA (140 μL, 0.77 mmol), and KHMDS (1.43 mL of a 0.5 M solution in toluene, 0.71 mmol), compound **51** (93 mg, 82%) was obtained as a white residue after flash chromatography (9:1 hexane–EtOAc).

^{1}H-NMR (400 MHz, $CDCl_3$, amide rotamers) δ: 1.19 (d, J = 7.2 Hz, 3H, CH_3), 1.26 (t, J = 7.0 Hz, 4H, CH_3), 1.45 [s, 9H, $C(CH_3)_3$], 1.60-1.84 (m, 4H), 2.01-2.11 (m, 1H), 2.27 (br s, 1H), 2.38-2.41 (m, 1H), 2.55 (br s, 1H), 2.82-3.12 (m, 3H), 3.81-3.87 (m, 1H), 4.00 (br s, 1H), 4.09-4.24 (m, 3H) 5.35 and 5.47 (br s, 1H).

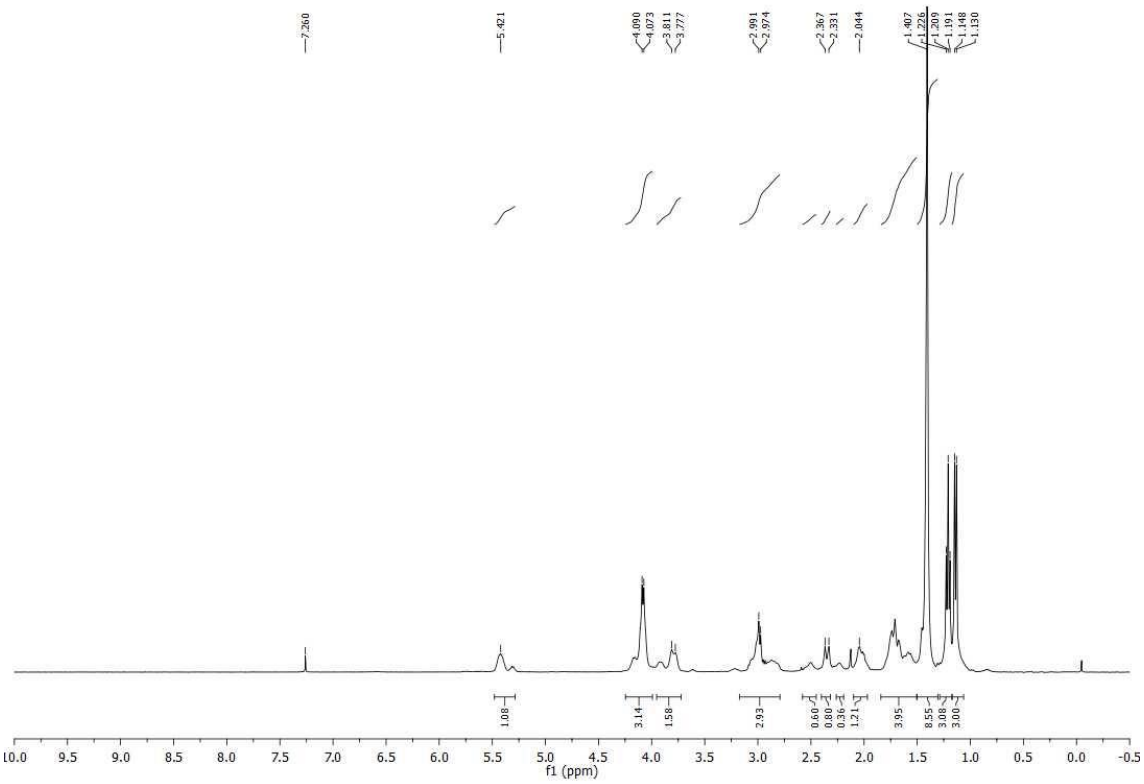
^{13}C-NMR (100.6 MHz, $CDCl_3$, amide rotamers) δ: 14.1 (CH_3), 19.6 and 20.1 (CH_3), 24.3 (CH_2), 25.1 (CH_2), 28.3 [$C(CH_3)_3$], 32.3 and 33.1 (CH_2), 38.4 (CH), 52.1 and 52.7 (CH), 52.7 and 53.8 (CH), 60.5 (CH_2), 68.6 and 68.7 (CH), 79.4 [$C(CH_3)_3$], 115.6 (CH=), 143.6 and 143.8 (C-5), 155.5 (NCOO) 172.0 (COO).

IR (NaCl): 3309, 1740, 1659 cm^{-1}.

HRMS calcd for [$C_{20}H_{33}NO_5$ + H^+]: 368.2431; found 368.2432.

$[\alpha]^{23}_{D}$ = + 15.1 (*c* 1.0, $CHCl_3$).

Melting point = 125−127 ºC.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1.226
1.209
1.191
1.148
1.130
1.08
3.14
1.58
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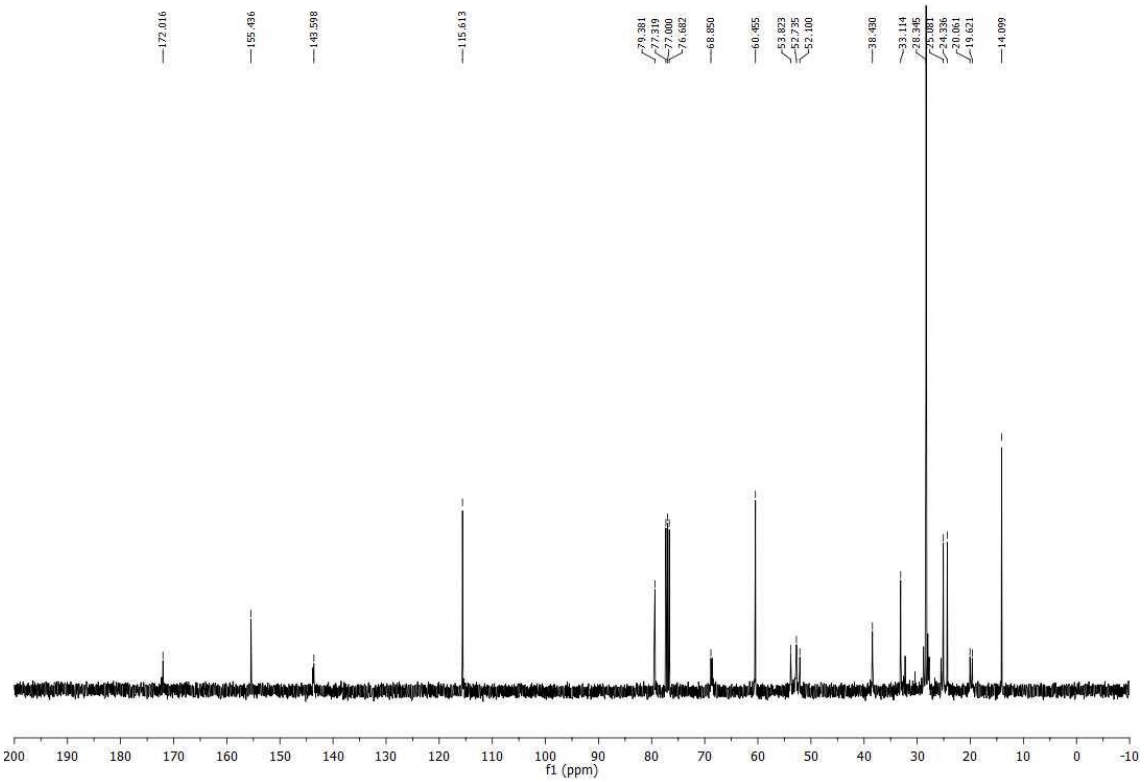
0.60
0.80
0.64
1.21
3.95
8.55
3.08
3.00
f1 (ppm)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60.455
53.823
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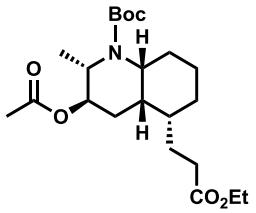
33.114
28.345
25.081
24.336
20.061
19.621
14.099
f1 (ppm)



Ethyl (2*S*,3*R*,4a*S*,5*R*,8a*R*)-3-acetoxy-1-(*tert*-butoxycarbonyl)-2-methyldeca-hydroquinoline-5-propionate (55)

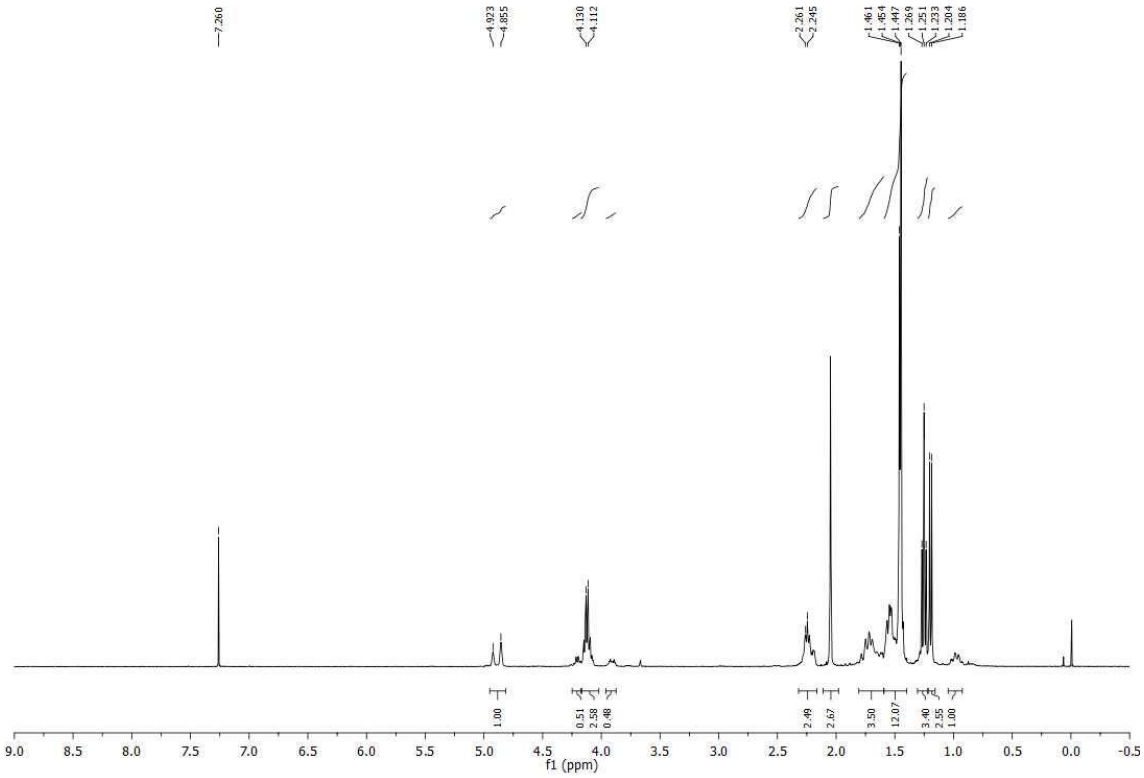
First-step: TFA (200 μL) was added to a solution of compound **50** (30 mg, 0.073 mmol) in CH_2Cl_2 (2 mL) at 0 ºC, and the resulting solution was stirred to room temperature for 2 h. Then, a few drops of NH_4OH were added and the mixture was diluted with CH_2Cl_2. The resulting solution was dried and concentrated to give a crude secondary amine.

Second-step: The above amine was taken up in 1 M HCl in Et_2O, and the solvent was removed in vacuum. The residue was dissolved in AcOH (5 mL), and PtO_2 (16.5 mg) was added to the solution. The resulting black slurry suspension was stirred under hydrogen at 50 ºC for 24 h. The catalyst was removed by filtration, and the solvent was evaporated.

Third-step: Boc_2O (32 mg, 0.146 mmol, 2.0 equiv) was added at room temperature to a stirred solution of the above hydrochloride in CH_2Cl_2 (4 mL) and Et_3N (31 μL, 0.22 mmol), and the mixture was stirred for 3 days. Water was added, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated. Flash chromatography (8:2 hexane–EtOAc) afforded compound **55** (18 mg, 60%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$, amide rotamers) δ: 0.90-1.04 (m, 1H, H-1'), 1.20 (d, J = 6.8 Hz, 3H, CH_3), 1.21-1.27 (m, 4H), 1.39-1.62 (m, 6H, H-4, H-5, H-8),1.45 [s, 9H, $C(CH_3)_3$], 1.66-1.80 (m, 3H, H-4, H-8), 2.05 (s, 3H, CH_3), 2.15-2.34 (m, 3H, H-2', H-4a), 3.88-3.96 (m, 0.5H, H-8a), 4.05-4.17 (m, 3H, OCH_2, H-2, H-8a), 4.18-4.24 (m, 0.5H, H-2), 4.86 and 4.92 (br s, 1H, H-3).

^{13}C-NMR (100.6 MHz, $CDCl_3$, amide rotamers) δ: 14.2 (CH_3), 18.3 (C-4), 19.6 and 20.0 (CH_3), 21.3 (CH_3), 25.2 and 25.3 (CH_2), 26.4 and 26.6 (CH_2), 27.7 (CH_2), 28.4 (CH_2), 28.5 [$C(CH_3)_3$], 31.8 (C-4a), 31.9 (C-2'), 39.1 (C-5), 50.0 and 50.7 (C-2), 53.0 and 54.2 (C-8a), 60.4 (CH_2), 71.2 and 71.5 (C-3), 79.6 [$C(CH_3)_3$], 155.4 (NCOO), 173.6 (COO).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1.233
1.204
1.186
1.00
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2.49
2.67
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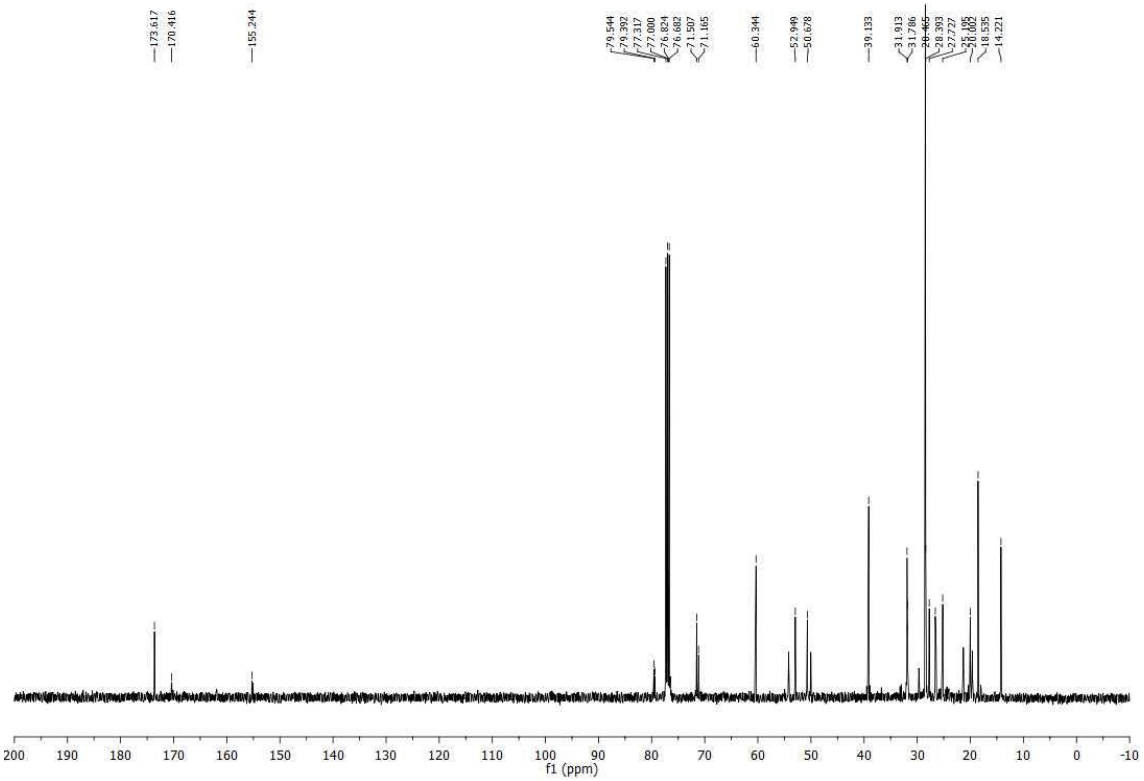
3.40
2.55
1.00
f1 (ppm)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50.678
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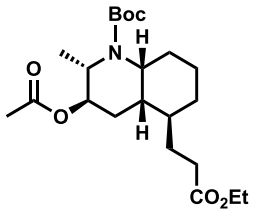
f1 (ppm)

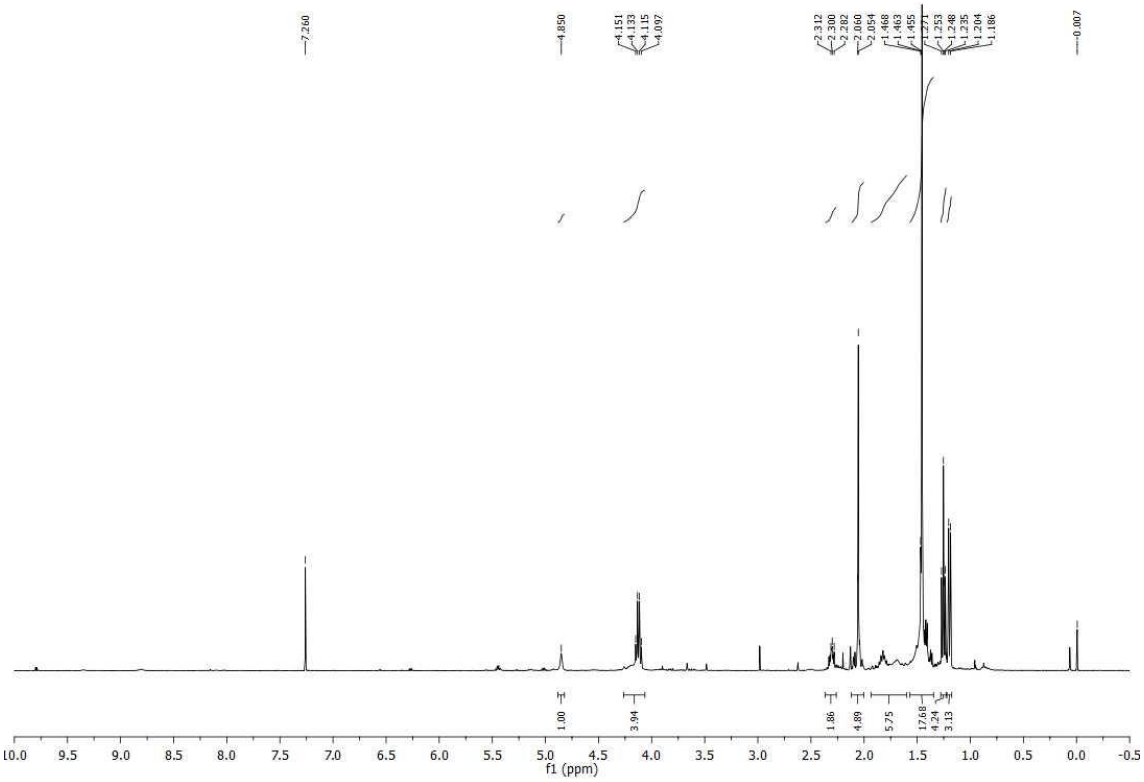


Ethyl (2*S*,3*R*,4a*S*,5*S*,8a*R*)-3-acetoxy-1-(*tert*-butoxycarbonyl)-2-methyldeca-hydroquinoline-5-propionate (56)

A solution of the Wittig adduct derived from **49** (10 mg, 0.02 mmol) in methanol (2 mL) containing Pt_2O (10 mg) was stirred under hydrogen at room temperature for 5 h. The catalyst was removed by filtration, and the solvent was evaporated. Flash chromatography (6:4 hexane–EtOAc) afforded compound **56** (10 mg, 99%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$, amide rotamers) δ: 1.19 (d, J = 6.8 Hz, 3H, CH_3), 1.23-1.27 (m, 4H), 1.34-1.56 (m, 5H, H-4, H-5, H-8), 1.45 [br s, 9H, $C(CH_3)_3$], 1.58-1.96 (m, 5H), 2.05 (s, 4H, H-4a, CH_3), 2.26-2.37 (m, 2H, H-2'), 4.08-4.29 (m, 4H, OCH_2, H-2, H-8a), 4.85 (br s, 1H, H-3).

^{13}C-NMR (100.6 MHz, $CDCl_3$, amide rotamers) δ: 14.2 (CH_3), 20.00 (CH_3), 21.4 (CH_3), 24.0 (CH_2), 25.6 (C-4), 27.7 (CH_2), 28.5 [$C(CH_3)_3$], 29.8 (C-1'), 32.6 (C-4a), 33.0 (C-2'), 38.9 (C-5), 49.1 (C-2), 50.4 (C-8a), 60.3 (CH_2), 71.8 (C-3), 79.6 [$C(CH_3)_3$], 155.3 (NCOO), 170.5 (COO), 173.7 (COO).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2.054
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1.465
1.277
1.253
1.248
1.235
1.204
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1.00
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1.86
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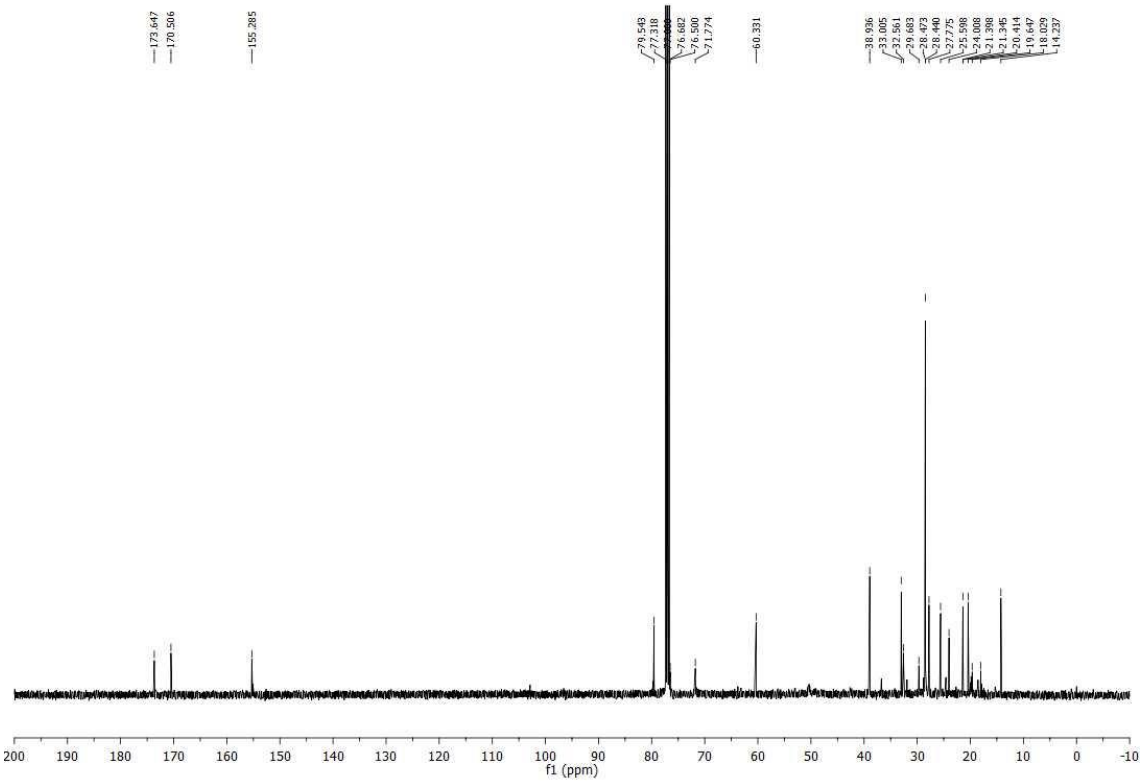
5.75
17.68
4.24
3.13
f1 (ppm)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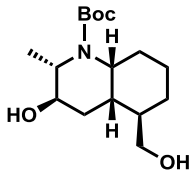
14.237
f1 (ppm)



(2*S*,3*R*,4a*S*,5*R*,8a*R*)-1-(*tert*-Butoxycarbonyl)-3-hydroxy-5-(hydroxymethyl)-2-methyldecahydroquinoline (57)

TBAF (2.3 mL of a 1 M solution in THF, 2.3 mmol) was added to a solution of **34** (212 mg, 0.46 mmol) in THF (6 mL), and the mixture was stirred at room temperature for 5 h. The reaction was quenched with saturated aqueous NH_4Cl, and the resulting mixture was extracted with EtOAc. The combined organic extracts were dried and concentrated. Flash chromatography (3:7 hexane–EtOAc) afforded diol **57** (130 mg, 94%) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$, amide rotamers) δ: 1.16 (d, J = 7.6 Hz, 3H, CH_3), 1.23-1.60 (m, 5H, H-4, H-6, H-7, H-8), 1.45 [s, 9H, $C(CH_3)_3$], 1.62-1.76 (m, 2H), 1.89 (br s, 1H, OH), 2.10 (td, J = 11.6, 2.4 Hz, 1H, H-4), 2.28-2.38 (m, 2H, H-4a), 2.52 (br s, 1H, OH), 3.61-3.67 (m, 1H, CH_2OH), 3.71-3.77 (m, 1H, CH_2OH), 3.82 (br s, 1H, H-3), 4.09-4.16 (m, 2H, H-2, H-8a).

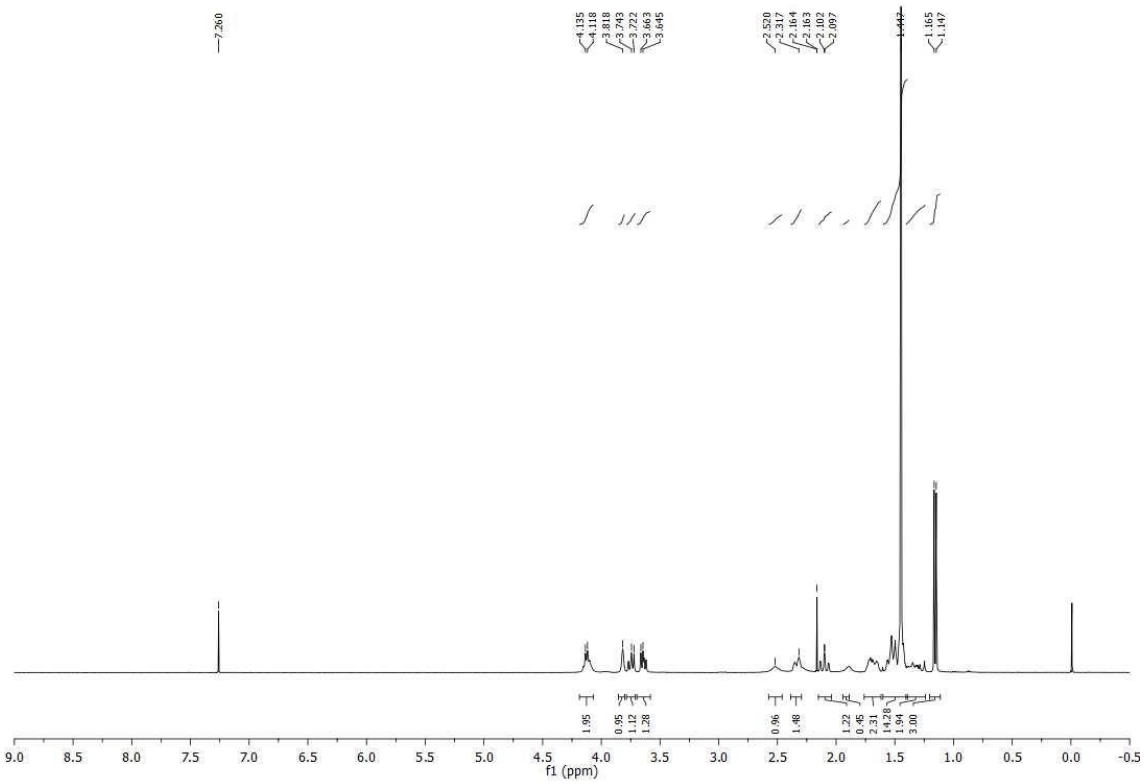
^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 20.0 (CH_3), 21.2 (CH_2), 22.4 (CH_2), 27.8 (C-4), 27.9 (C-4a), 28.4 [C(CH_3)$_3$], 28.5 (CH_2), 42.2 (C-5), 49.8 (C-2), 53.3 (C-8a), 64.3 (CH_2O), 69.3 (C-3), 79.6 [C(CH_3)$_3$], 155.8 (NCOO).

IR (NaCl) 3403, 1668 cm^{-1}.

HRMS calcd for [$C_{16}H_{29}NO_4$ + Na $^+$]: 322.1989; found 322.1986.

$[\alpha]^{23}_D$ = +19 (c 1.0, $CHCl_3$).

Melting point = 157−159 °C.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2.097
1.165
1.147
1.95
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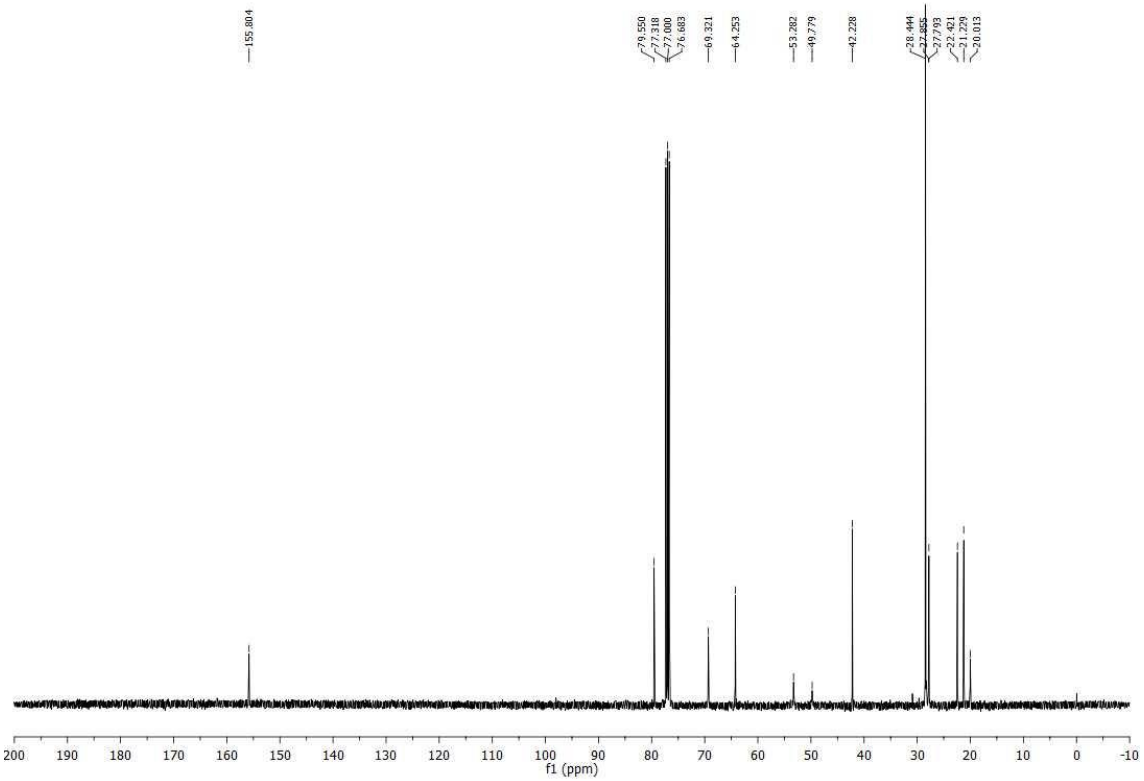
3.00
f1 (ppm)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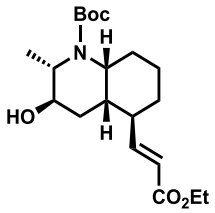
20.013
f1 (ppm)



Ethyl-(2*S*,3*R*,4a*S*,5*S*,8a*R*)-1-(*tert*-butoxycarbonyl)-3-hydroxy-2-methyl-decahydroquinoline-5-(*E*)-propenoate (58)

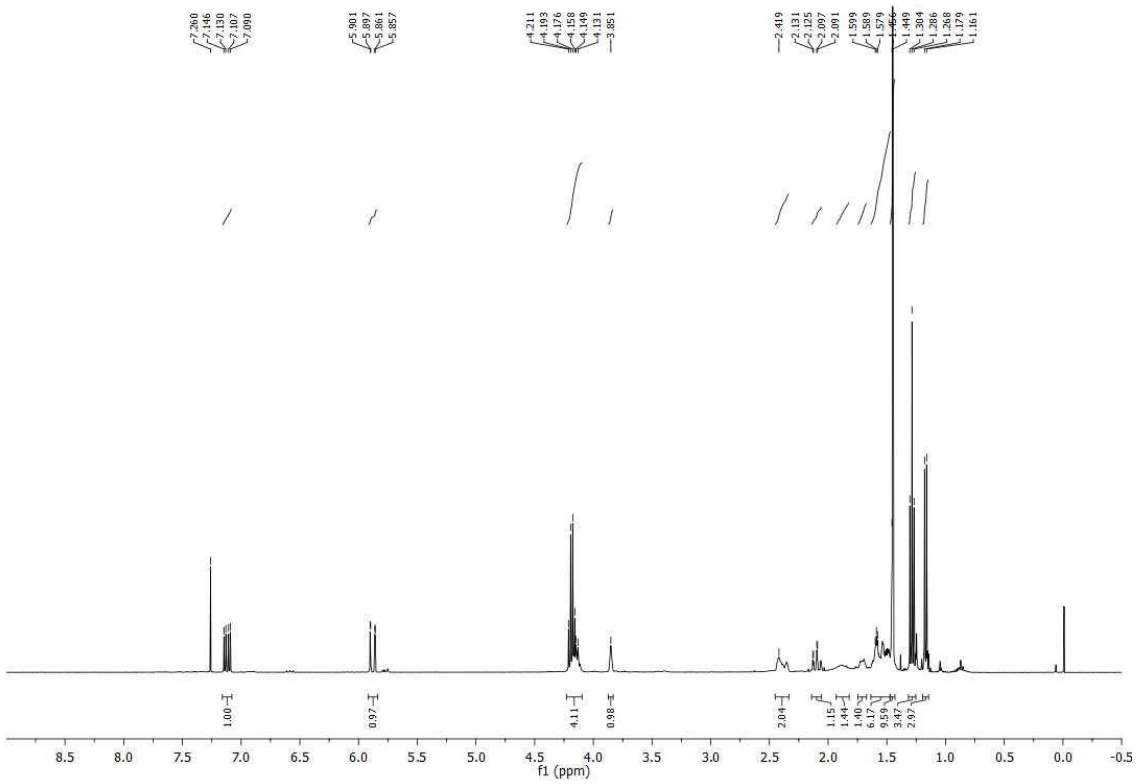
Bis(acetoxy)iodobenzene (435 mg, 1.35 mmol) and TEMPO (36 mg, 0.23 mmol) were added to a solution of the dihydroxy derivative **57** (350 mg, 1.20 mmol) in CH_2Cl_2–THF (2:1, 10 mL), and the resulting mixture was stirred at room temperature overnight. (Carboethoxymethylene)triphenylphosphorane (529 mg, 1.52 mmol) was added, and the mixture was stirred for 24 h. Then, the solvent was evaporated and the resulting residue was chromatographed (7:3 hexane–EtOAc) to afford compound **58** (331 mg, 77 %) as a yellowish oil.

^{1}H-NMR (400 MHz, $CDCl_3$, amide rotamers) δ: 1.17 (d, J = 7.6 Hz, 3H, CH_3), 1.29 (t, J = 7.4 Hz, 3H, CH_3), 1.41-1.63 (m, 5H), 1.45 [s, 9H, $C(CH_3)_3$], 1.69-1.74 (m, 2H), 1.89 (br s, 1H,), 2.09 (td, J = 14.0, 2.4 Hz, 1H), 2.35 (br s, 1H), 2.42 (br s, 1H), 3.85 (br s, 1H, H-3), 4.11-4.22 (m, 4 H, H-3, H-8a, CH_2), 5.87 (dd, J = 16.0, 2.0 Hz, 1H,), 7.12 (dd, J = 16.0, 6.8 Hz, 1H).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 14.3 (CH_3), 20.1 (CH_3), 21.2 (CH_2), 24.9 (CH_2), 27.6 (CH_2), 28.0 (CH_2), 28.4 [$C(CH_3)_3$], 31.5 (C-4a), 41.9 (C-5), 49.8 (C-8a), 53.3, (C-2), 60.3 (OCH_2), 69.2 (C-3), 79.7 [$C(CH_3)_3$], 121.3 (CH), 151.7 (CH), 155.6 (NCOO), 166.7 (COO).

IR (NaCl) 3452, 1721, 1663 cm^{-1}.

HRMS calcd for [$C_{20}H_{33}NO_5$ + Na^+]: 390.2251; found 390.2246.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4.131
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2.097
2.091
1.599
1.589
1.579
1.449
1.304
1.286
1.268
1.179
1.161
1.00
0.97
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0.98
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1.44
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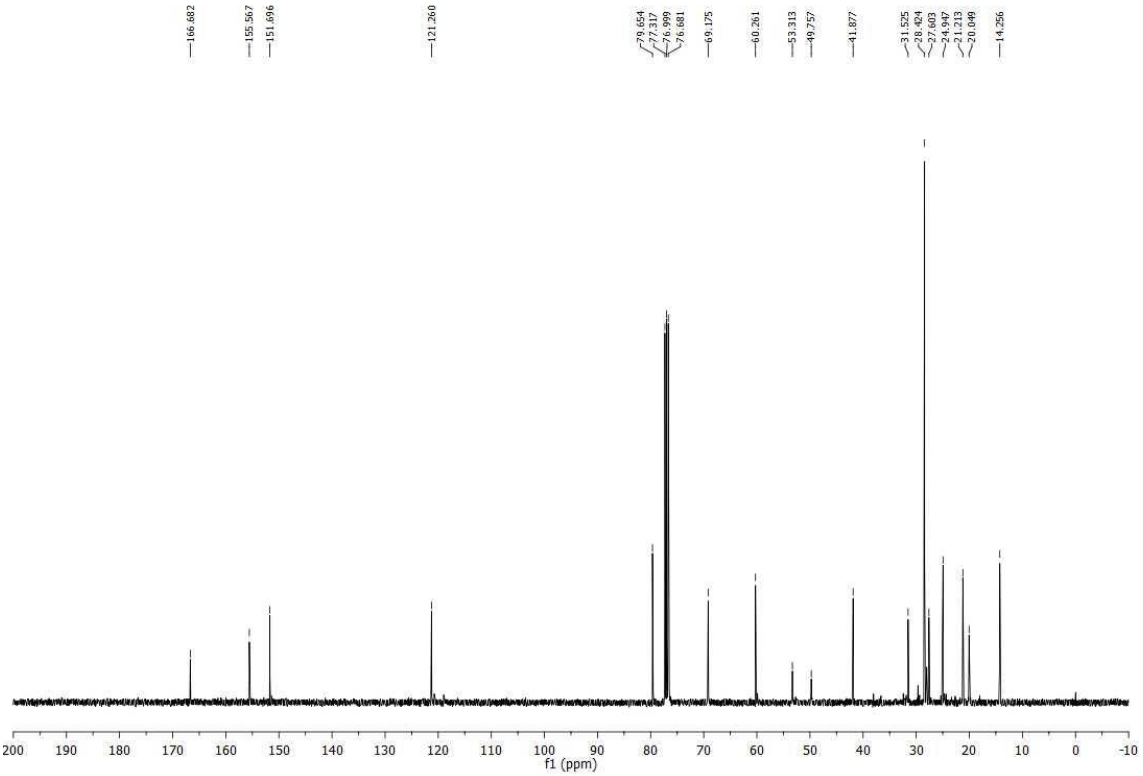
6.17
9.59
3.47
2.97
f1 (ppm)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76.681
69.175
60.261
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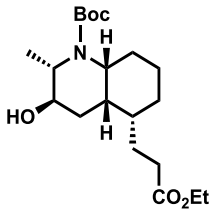
24.947
21.213
20.049
14.256
f1 (ppm)



Ethyl-(2*S*,3*R*,4a*S*,5*R*,8a*R*)-1-(*tert*-butoxycarbonyl)-3-hydroxy-2-methyldeca-hydroquinoline-5-propionate (61)

First-step: TFA (800 μL) was added to a solution of compound **51** (400 mg, 1.12 mmol) in CH_2Cl_2 (8 mL) at 0 ºC, and the resulting solution was stirred at room temperature for 2 h. Then, the solvent was evaporated, the residue was taken up in 10% aqueous NaOH, and the resulting solution was extracted with EtOAc. The combined organic extracts were dried and concentrated to give a crude secondary amine.

Second-Step: The above amine was taken up in 1 M HCl in Et_2O, and the solvent was removed in vacuum. The hydrochloride was dissolved in AcOH (15 mL), and PtO_2 (170 mg) was added to the solution. The black slurry suspension was stirred under hydrogen at 50 ºC for 24 h. The catalyst was removed by filtration, and the solvent was evaporated.

Third-Step: The hydrochloride was converted to the corresponding free base by addition of 10% aqueous NaOH, followed by extraction of the solution with EtOAc. The organic extracts were dried and concentrated. Boc_2O (368 mg, 1.68 mmol) was added to a solution of the resulting amine in EtOH (10 mL), and the mixture was stirred for 48 h. The solvent was evaporated, and the resulting residue was chromatographed (6:4 hexane–EtOAc) to afford compound **61** (245 mg, 60%) as a colorless oil.

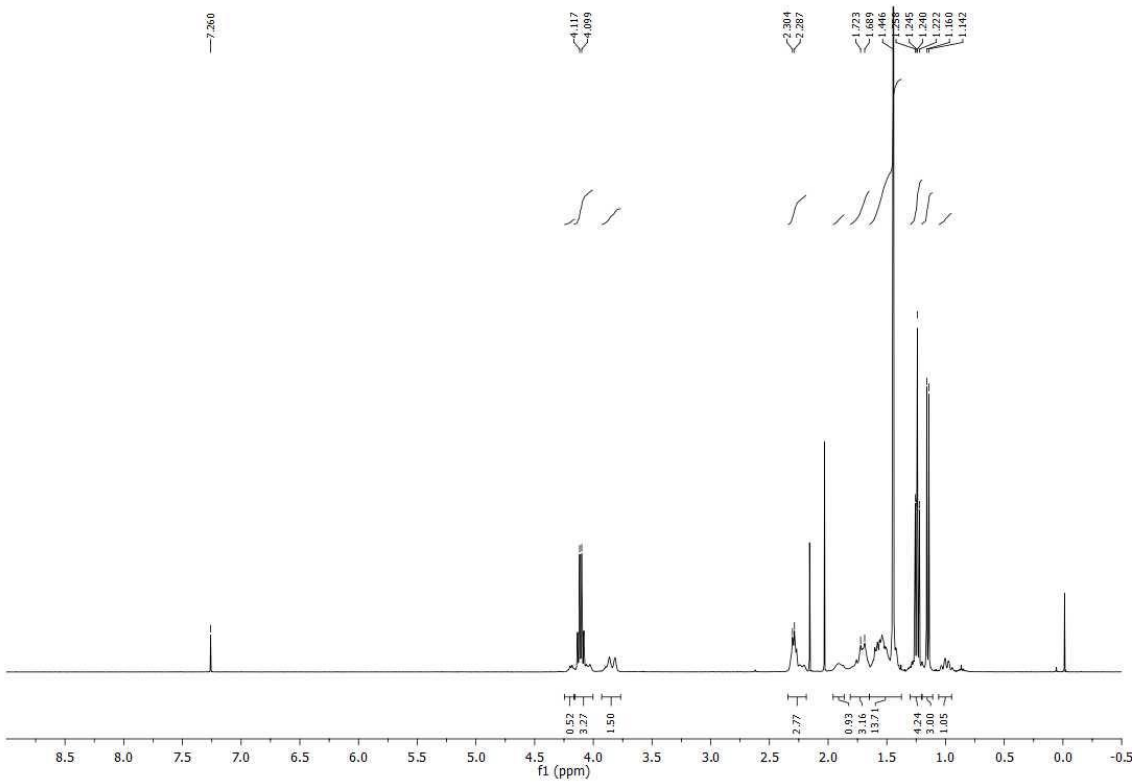
^{1}H-NMR (400 MHz, $CDCl_3$, amide rotamers) δ: 0.94-1.06 (m, 1H), 1.15 (d, J = 6.8 Hz, 3H, CH_3), 1.19-1.34 (m, 4H), 1.45 [s, 9H, $C(CH_3)_3$], 1.50-1.60 (m, 6H), 1.68-1.74 (m, 3H), 1.92 (br s, 1H), 2.18-2.36 (m, 3H, H-4, H-4a), 3.79-3.92 (br m, 1.5H, H-3, H-8a), 4.01-4.22 (m, 1.5H, H-2, H-8a), 4.11 (q, J = 7.2 Hz, 2H, CH_2).

^{13}C-NMR (100.6 MHz, $CDCl_3$, amide rotames) δ: 14.2 (CH_3), 19.7 and 20.3 (CH_3), 20.5 and 20.8 (CH_2), 25.2 and 25.4 (CH_2), 26.8 and 27.0 (CH_2), 27.6 (CH_2), 28.3 (CH_2), 28.4 [$C(CH_3)_3$], 30.8 and 30.9 (C-4a), 32.0 and 32.1 (CH_2), 39.5 and 39.6 (C-5), 53.3 and 53.7 (C-2), 53.0 and 54.5 (C-8a), 60.3 (OCH_2), 68.9 and 69.1 (C-3), 79.4 and 79.5 [$C(CH_3)_3$], 155.7 (NCOO), 171.1 and 173.9 (COO).

IR (NaCl): 3446, 1733, 1684 cm^{-1}.

HRMS calcd for [$C_{20}H_{35}NO_5$ + Na $^+$]: 392.2407; found 392.2408.

$[\alpha]^{23}_D$ = +5.8 (*c* 1.0, $CHCl_3$).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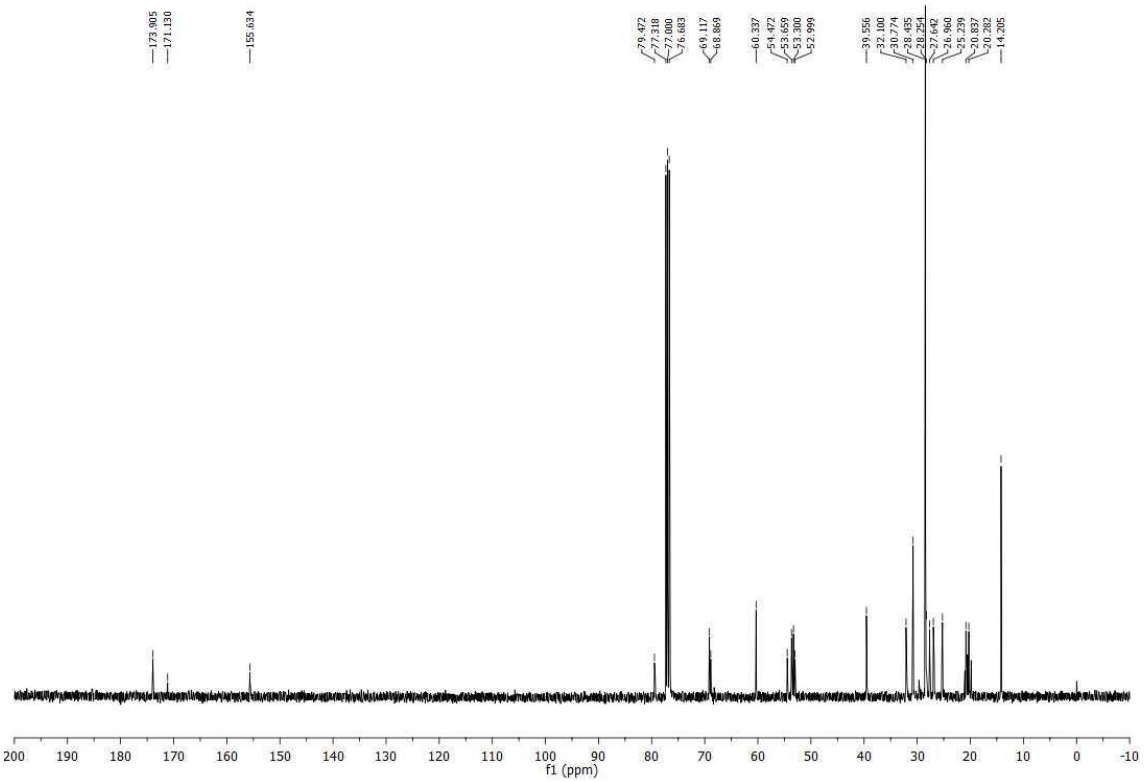
4.24
3.00
1.05
f1 (ppm)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69.117
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54.472
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52.999
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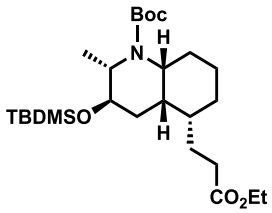
25.239
20.837
20.282
14.205
f1 (ppm)



Ethyl-(2*S*,3*R*,4a*S*,5*R*,8a*R*)-1-(*tert*-butoxycarbonyl)-3-(*tert*-butyldimethylsilyloxy)-2-methyldecahydroquinoline-5-propionate (62)

TBDMS-Cl (170 mg, 1.0 mmol) was added to a stirred solution of imidazole (105 mg, 1.494 mmol) and compound **61** (92 mg, 0.25 mmol) in DMF (0.9 mL). The resulting mixture was stirred at room temperature overnight. The reaction was quenched with water and the resulting mixture was extracted with EtOAc. The combined organic extracts were dried and concentrated. Flash chromatography (95:5 hexane–EtOAc) afforded the silyloxy derivative **62** (117 mg, 98%) as a colorless oil.

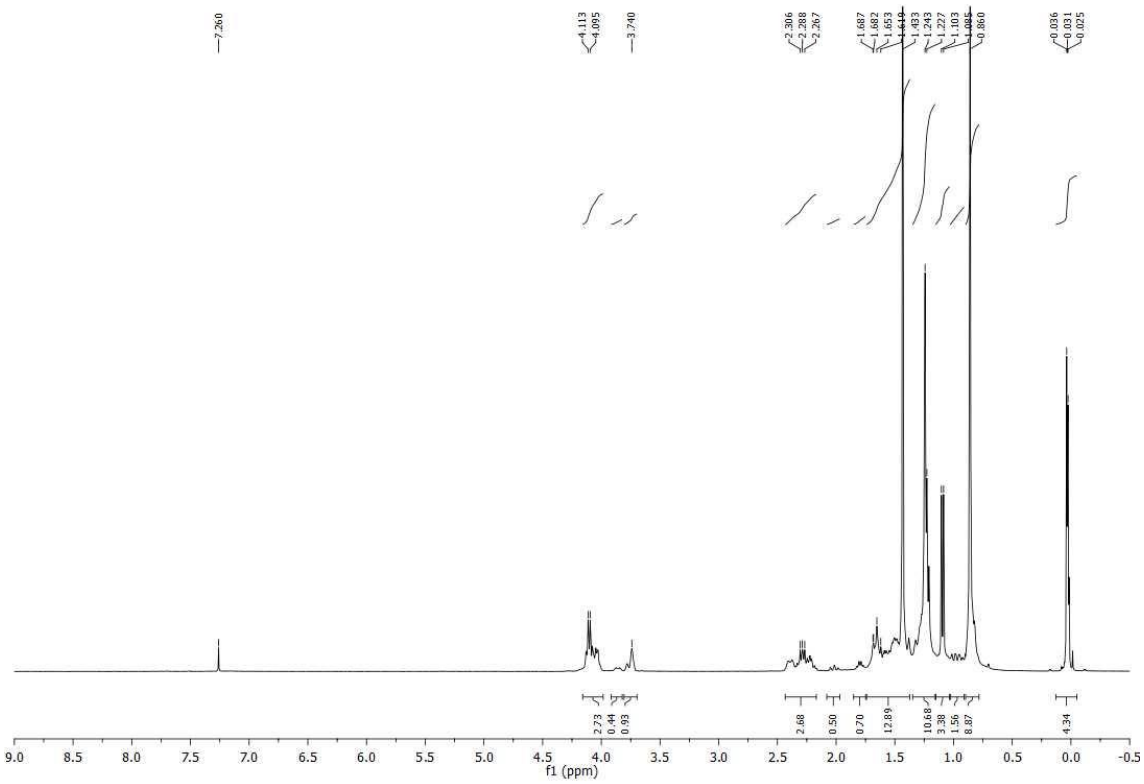
^{1}H-NMR (400 MHz, $CDCl_3$, amide rotamers) δ: 0.03 [s, 6H, $Si(CH_3)_2$], 0.86 [s, 9H, $SiC(CH_3)_3$], 0.94-1.06 (m, 1H, CH_2), 1.09 (d, J = 7.2 Hz, 3H, CH_3), 1.19-1.34 (m, 4H, CH_3), 1.37-1.71 (m, 9H, H-4, H-5, H-6, H-7, H-8), 1.43 [s, 9H, $C(CH_3)_3$], 1.75-1.83 (m, 1H), 1.96-2.06 (m, 1H), 2.16-2.41 (m, 3H, H-4, H-4a), 3.74 and 3.78 (br s, 1H, H-3), 3.82-4.14 (m, 0.5H, H-8a), 3.99-4.15 (m, 1.5H, H-2, H-8a).

^{13}C-NMR (100.6 MHz, $CDCl_3$, amide rotamers) δ: 14.1 and 14.2 (CH_3), 20.0 (CH_3), 21.3 (CH_2), 28.4 [$C(CH_3)_3$], 30.0 (CH), 38.9 (CH), 53.1 (CH), 53.7 (CH), 60.1 (CH_2), 69.5 (CH), 78.9 [$C(CH_3)_3$], 155.5 (NCOO), 173.9 (COO).

IR (NaCl): 1740, 1691 cm^{-1}.

HRMS calcd for [$C_{26}H_{49}NO_5Si + H^+$]: 484.3453; found 484.3461.

$[\alpha]^{23}_D = -3.46$ (c 1.0, $CHCl_3$).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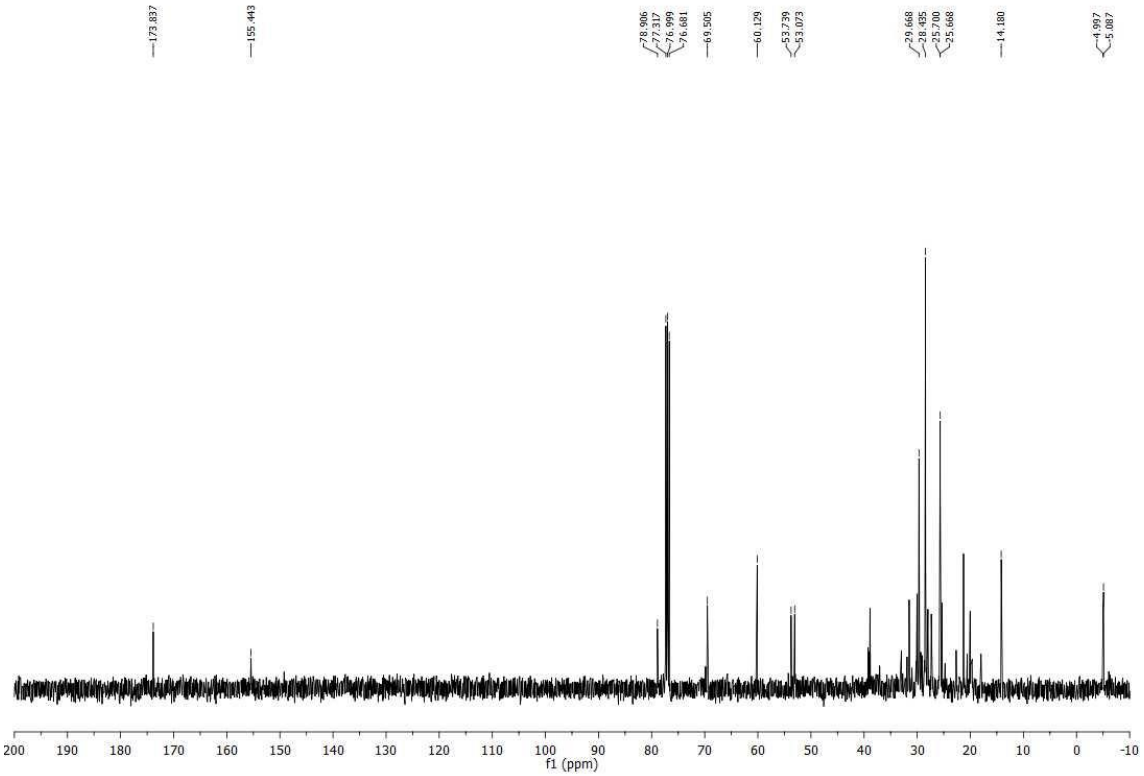
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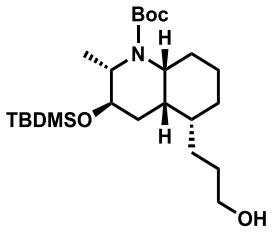
5.087
f1 (ppm)



(2*S*,3*R*,4a*S*,5*R*,8a*R*)-1-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldimethylsilyloxy)-5-(3-hydroxypropyl)-2-methyldecahydroquinoline (63)

$LiAlH_4$ (480 mg, 13.6 mmol) was added to a solution of ester **62** (115 mg, 0.24 mmol) in THF (4 mL) at 0 ºC. After the mixture was stirred at room temperature for 2 h, 10% aqueous NaOH was added, and the mixture was extracted with EtOAc. The combined organic extracts were dried and concentrated. Flash chromatography (85:15 hexane–EtOAc) afforded alcohol **63** (100 mg, 95%) as a colorless oil.

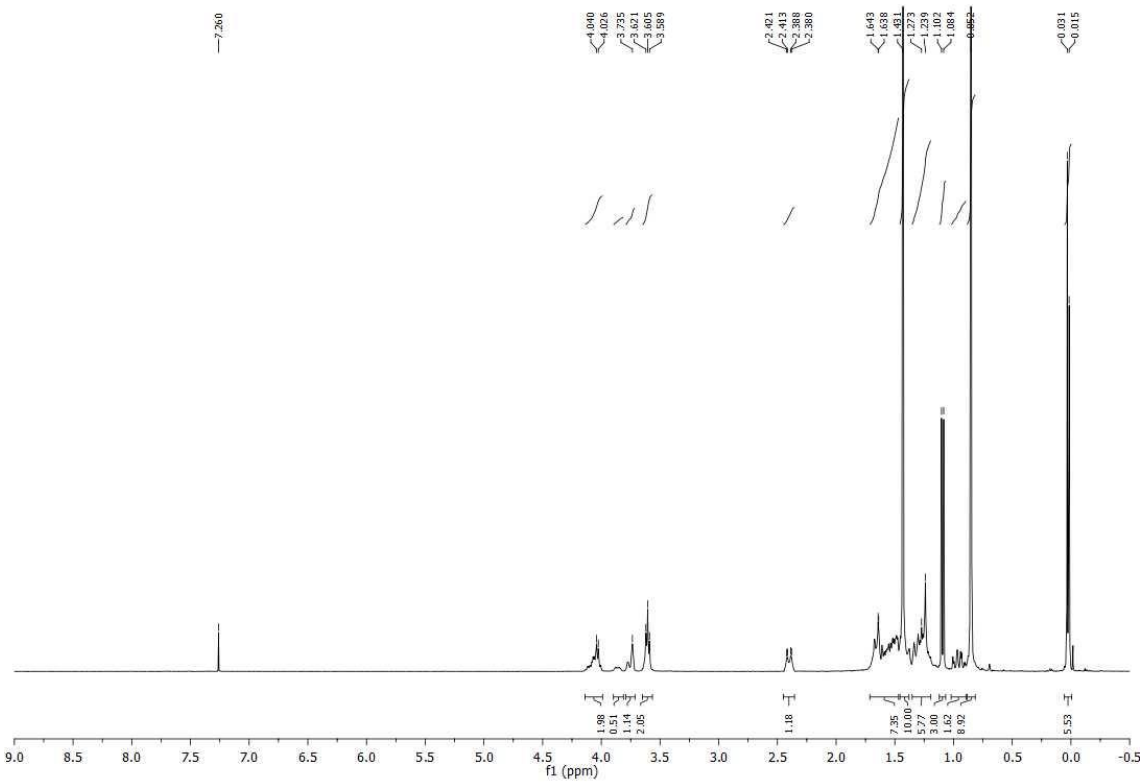
^{1}H-NMR (400 MHz, $CDCl_3$, amide rotamers) δ: 0.02 and 0.03 [s, 6H, $Si(CH_3)_2$], 0.85 [s, 9H, $SiC(CH_3)_3$], 0.90-1.04 (m, 1H, CH_2), 1.09 (d, J = 7.2 Hz, 3H, CH_3), 1.19-1.37 (m, 5H, H-6, H-7), 1.38-1.73 (m, 7H, H-4, H-5, H-8), 1.43 [s, 9H, $C(CH_3)_3$], 2.36-2.43 (m, 1H, H-4a), 3.61 (t, J = 6.4 Hz, 2H, CH_2OH), 3.74 and 3.77 (br s, 1H, H-3), 3.82-4.14 (m, 0.5H, H-8a), 3.99-4.16 (m, 1.5H,H-2, H-8a).

^{13}C-NMR (100.6 MHz, $CDCl_3$, amide rotamers) δ: –5.1 and –5.0 [$Si(CH_3)_2$], 19.7 and 20.1 (CH_3), 21.3 (CH_2), 25.5 (CH_2), 25.7 [$C(CH_3)_3$], 27.3 and 27.6 (C-6), 28.1 (CH_2) 28.4 and 28.7 [$C(CH_3)_3$], 29.2 and 29.3 (CH_2), 29.9 (CH_2), 30.3 and 30.6 (C-4a), 39.3 and 39.6 (C-5), 52.8 and 53.2 (C-2), 53.8 and 54.2 (C-8a), 63.1 (OCH_2), 69.6 (C-3), 78.9 [$C(CH_3)_3$], 155.5 (NCOO).

IR (NaCl): 3451, 1688, 1249 cm^{-1}.

HRMS calcd for [$C_{24}H_{47}NO_4Si$ + H^+]: 442.3347; found 442.3355.

$[\alpha]^{23}_D$ = – 7.39 (*c* 1.0, $CHCl_3$).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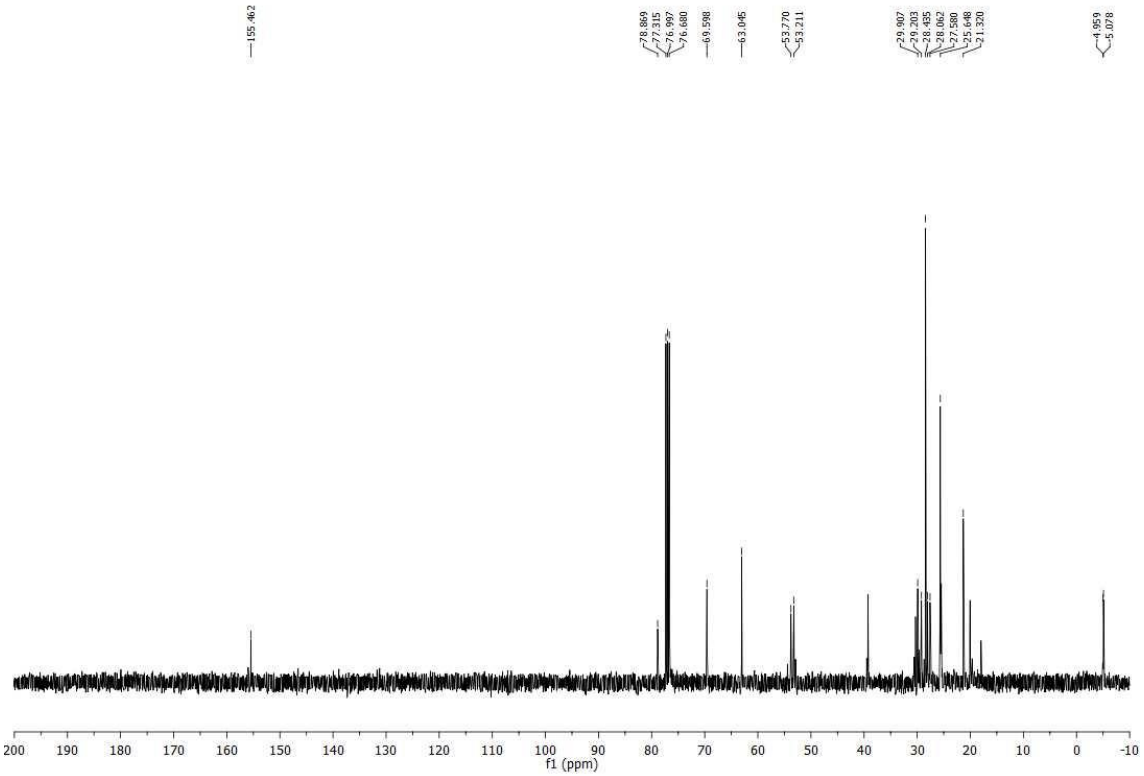
f1 (ppm)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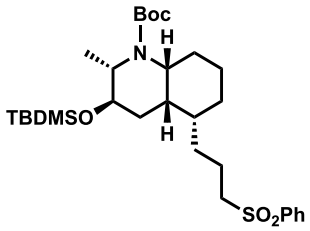
21.320
4.959
5.078
f1 (ppm)



(2*S*,3*R*,4a*S*,5*R*,8a*R*)-1-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldimethylsilyloxy)-2-methyl-5-[(3-(phenylsulfonyl)propyl)]decahydroquinoline (64)

First step: PPh_3 (136 mg, 0.52 mmol), imidazole (35 mg, 0.52 mmol), and iodine (87 mg, 0.34 mmol) were sequentially added at 0 ºC to a solution of alcohol **63** (76 mg, 0.17 mmol) in CH_2Cl_2 (2 mL), and the resulting mixture was stirred at room temperature overnight. The mixture was filtered through a short silica plug and washed with CH_2Cl_2, and the resulting solution was concentrated to give a crude iodo compound **65**.

Second step: $PhSO_2Na$ (57 mg, 0.34 mmol) was added to a solution of the above residue in DMF (600 μL), and the mixture was stirred at 70 ºC for 24 h. The solvent was evaporated, and the residue was chromatographed (95:5 hexane–EtOAc) to give compound **64** (60 mg, 63%) as a colorless oil.

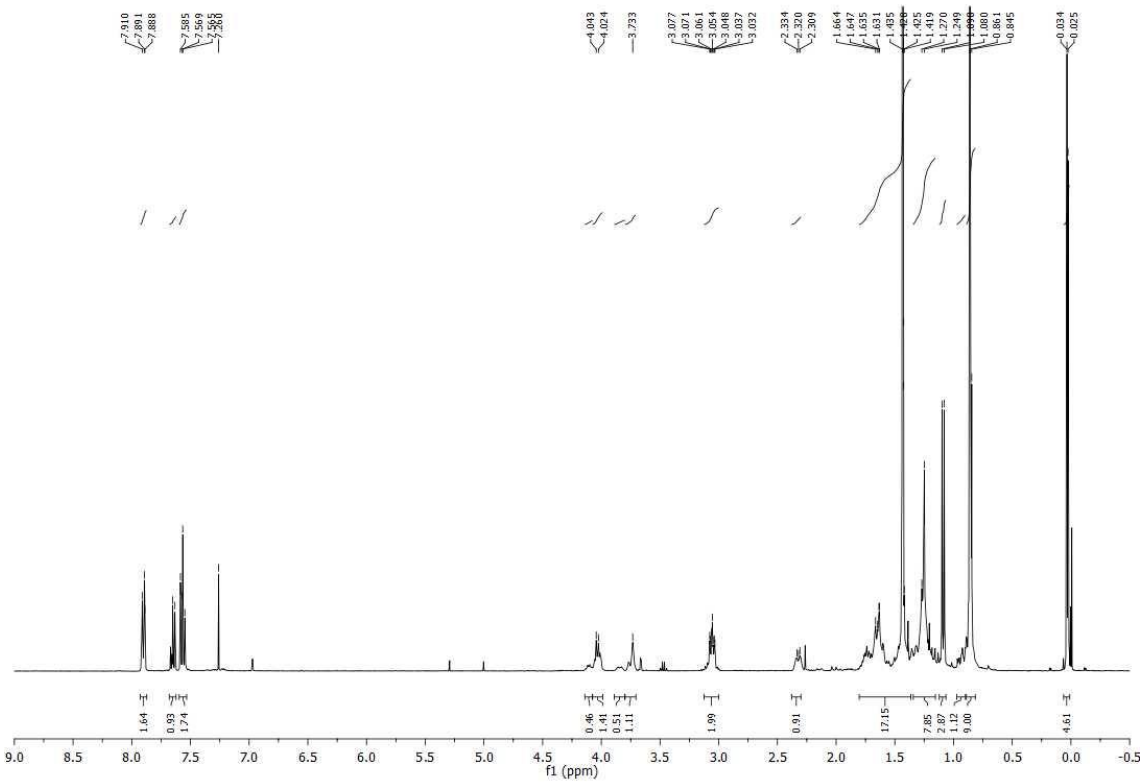
^{1}H-NMR (400 MHz, $CDCl_3$, amide rotamers) δ: 0.02 and 0.03 [s, 6H, $Si(CH_3)_2$], 0.85 [s, 9H, $SiC(CH_3)_3$], 0.87-0.99 (m, 1H), 1.09 (d, J = 7.6 Hz, 3H, CH_3), 1.16-1.34 (m, 6H, H-6, H-7), 1.36-1.82 (m, 6H, H-4, H-5, H-8), 1.43 [s, 9H, $C(CH_3)_3$], 2.25-2.36 (m, 1H, H-4a), 3.01-3.13 (m, 2H, CH_2SO_2Ph), 3.73 and 3.76 (br s, 1H, H-3), 3.80-3.89 (br m, 0.5H, H-8a), 3.99-4.16 (br m, 1.5H, H-2, H-8a), 7.53-7.58 (m, 2H, Ar-H), 7.61-7.70 (m, 1H, Ar-H), 7.90 (d, J = 7.6 Hz, 2H, Ar-H).

^{13}C-NMR (100.6 MHz, $CDCl_3$, amide rotamers) δ: –5.2 and –4.8 [$Si(CH_3)_2$], 20.0 and 20.2 (CH_3, CH_2), 21.5 (CH_2), 25.3 (CH_2), 26.7 and 27.0 (C-6), 27.9 (CH_2), 28.4 [$C(CH_3)_3$], 29.7 (CH_2), 30.3 (CH_2), 30.6 and 31.1 (C-4a), 32.0 and 32.2 (CH_2), 39.3 and 39.6 (C-5), 52.8 and 53.0 (C-2), 53.7 and 54.2 (C-8a), 56.4 (CH_2SO_2Ph), 69.4 (C-3), 79.0 [$C(CH_3)_3$], 128.0 (CH-Ar), 129.2 (CH-Ar), 133.6 (CH-Ar), 139.3 (Cq-Ar), 155.5 (NCOO).

IR (NaCl): 1682, 1321, 1246 cm^{-1}.

HRMS calcd for [$C_{30}H_{51}NO_5SSi + Na^+$]: 588.3149; found 588.3146.

$[\alpha]^{23}_D = -9.87$ (c 1.0, $CHCl_3$).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2.320
2.309
1.664
1.647
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1.435
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1.419
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1.249
1.080
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0.845
0.034
0.025
1.64
0.93
1.74
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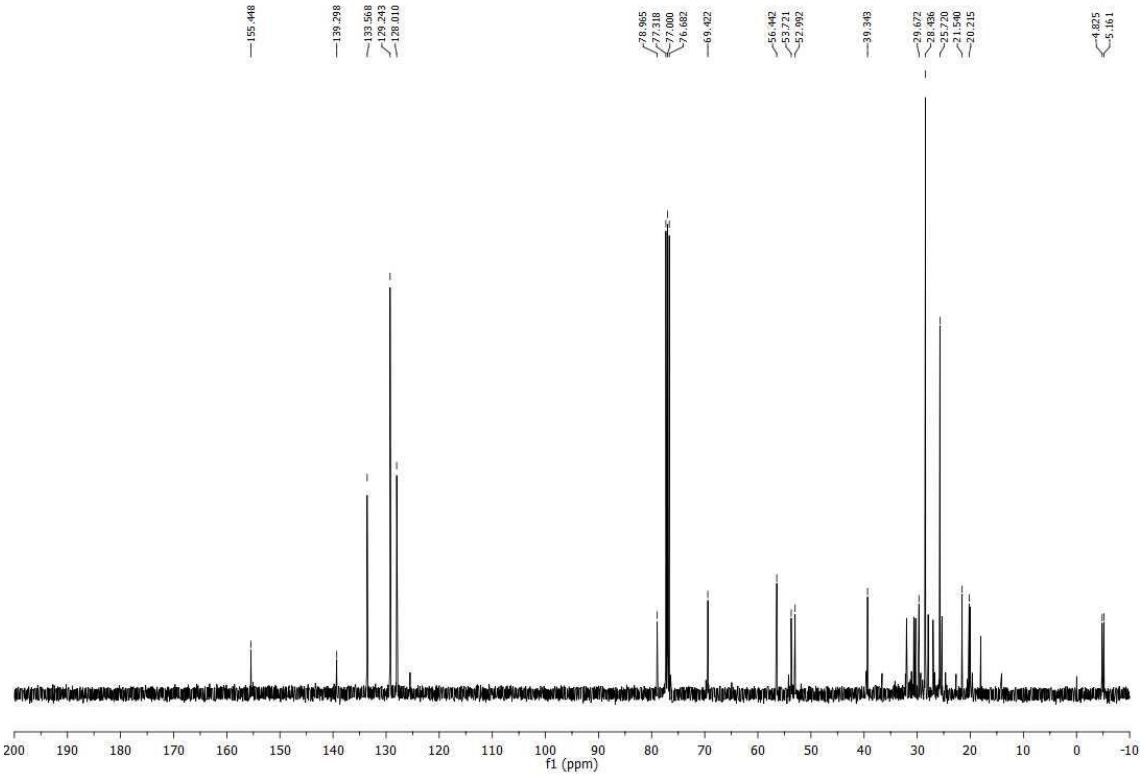
f1 (ppm)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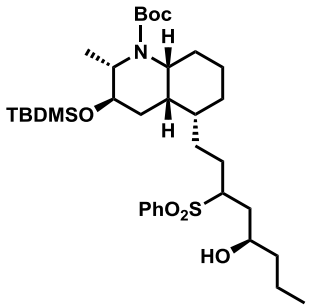
f1 (ppm)



(2*S*,3*R*,4a*S*,5*R*,8a*R*)-1-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldimethylsilyloxy)-5-[5(*R*)-hydroxy-3-(phenylsulfonyl)octyl]-2-methyldecahydroquinoline (67)

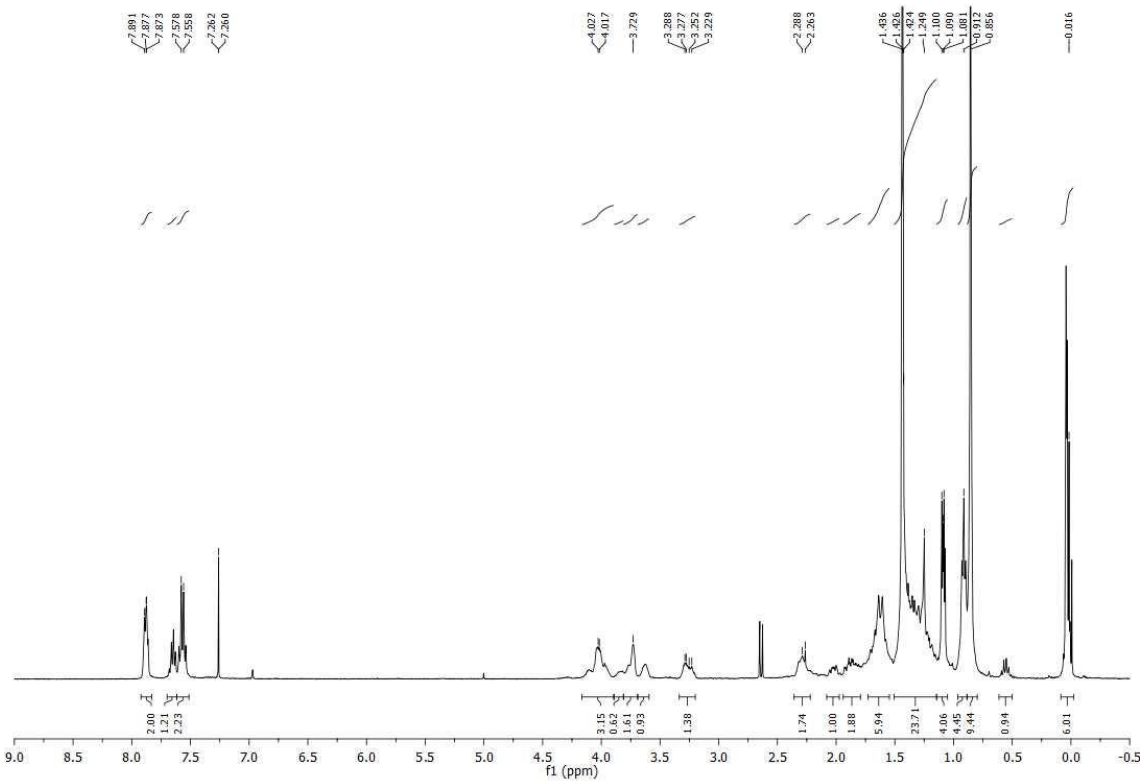
LDA (22 μL of a 2.0 M solution in THF/*n*-heptane/ethylbenzene, 0.054 mmol) was slowly added at –78 ºC to a solution of sulfone **64** (26 mg, 0.045 mmol) and HMPA (12 μL, 0.067 mmol) in THF (0.9 mL), and the resulting mixture was stirred at –78 ºC for 30 min. Then, a solution of (*R*)-propyloxirane in THF (390 μL, 0.09 mmol, 20 mg/mL) was added and the mixture was stirred for 1.5 h. The mixture was allowed to warm to room temperature and stirred overnight. Saturated aqueous NH_4Cl was added, the resulting mixture was diluted with CH_2Cl_2, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated. Flash chromatography (95:5 hexane–EtOAc) afforded compound **67** (18 mg, 62%) as a yellowish oil.

^{1}H-NMR (400 MHz, $CDCl_3$, amide rotamers) δ: –0.02-0.09 [m, 6H, 2(CH_3)], 0.51-0.61 (m, 1H), 0.80-0.99 [m, 12H, C(CH_3)$_3$, CH_3], 1.02-1.15 (m, 4H), 1.16-1.51 (m, 12H, H-6, H-7, H-4, H-5, H-8), 1.44 [s, 9H, C(CH_3)$_3$], 1.52-1.73 (br m, 4H), 1.76-1.94 (m, 1H), 1.96- 2.09 (m, 1H), 2.19 and 2.29 (br s, 1H, H-4a), 3.18-3.34 (m, 1H, $CHSO_2Ph$), 3.63 (br s, 0.5H, H-3), 3.69-3.79 (m, 1.5H, H-3, H-5', H-8a), 3.80-3.87 (br s, 0.5H, H-8a), 3.91-4.16 (br m, 1.5H, H-2, H-8a), 7.52-7.61 (m, 2H, Ar-H), 7.62-7.70 (m, 1H, Ar-H), 7.85-7.93 (m, 2H, Ar-H).

^{13}C-NMR (100.6 MHz, $CDCl_3$, amide rotamers) δ: –5.2 and –4.9 [Si(CH_3)$_2$], 14.0 [Si*C*(CH_3)$_3$], 14.0 (CH_3), 18.8 (CH_2), 19.9 and 20.0 (CH_3), 21.5 and 21.6 (CH_2), 25.4 (CH_2), 25.7 [C(*C*H_3)$_3$], 25.9 (CH_2), 26.8 (CH_2), 27.5 (CH_2), 27.9 (CH_2), 28.4 [C(*C*H_3)$_3$], 29.7 and 30.0 (CH_2), 30.3 (CH_2), 30.4 and 31.0 (C-4a), 35.3 (CH_2), 40.0 (C-5), 40.6 (CH_2), 53.0 (C-2), 53.7 and 54.1 (C-8a), 61.8 and 61.9 (C-3'), 68.5 and 68.8 (C-3), 69.5 and 69.4 (C-5'), 79.0 [*C*(CH_3)$_3$], 128.7 and 128.9 (CH-Ar), 129.1 and 129.2 (CH-Ar), 133.6 and 133.7 (CH-Ar), 138.0 and 138.1 (Cq-Ar), 155.5 (NCOO).

IR (NaCl): 3453, 1682, 1318, 1250 cm^{-1}.

HRMS calcd for [$C_{35}H_{61}NO_6SSi$ + H^+]: 652.4062; found 652.4073.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7.262
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3.277
3.252
3.229
2.288
2.263
1.436
1.426
1.424
1.249
1.100
1.090
1.081
0.912
0.856
0.016
2.00
1.21
2.23
3.15
0.62
1.61
0.93
1.38
1.74
1.00
1.88
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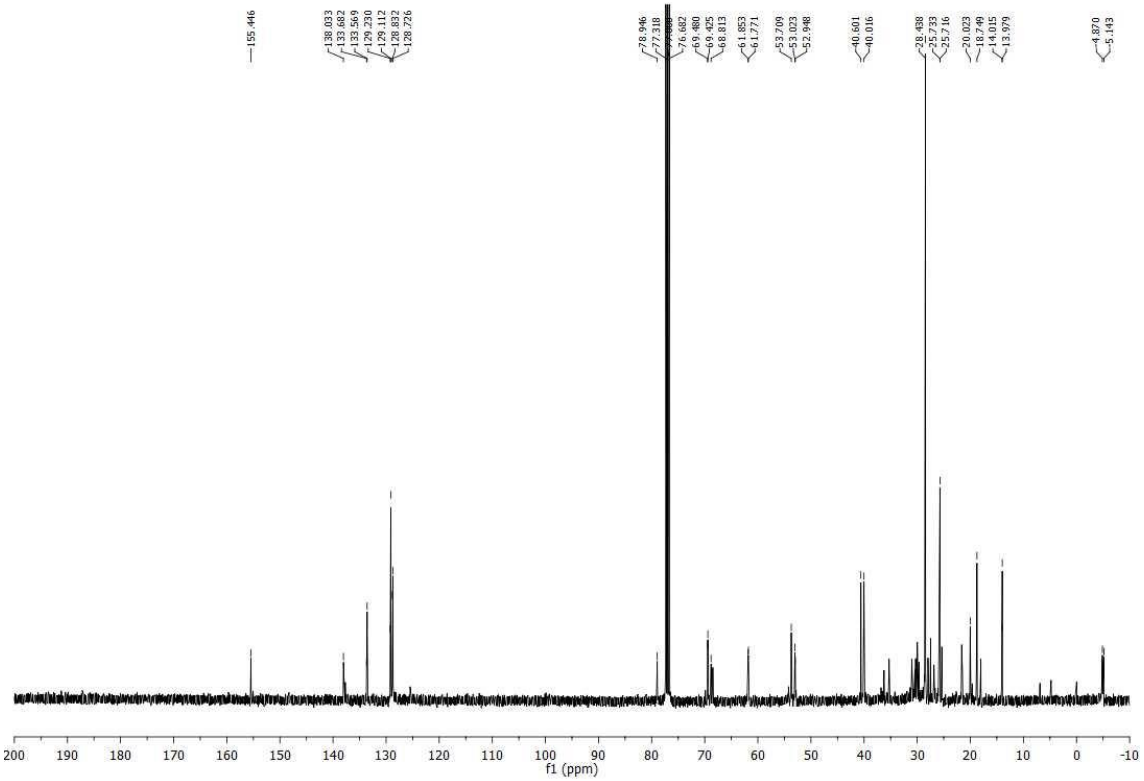
23.71
4.06
4.45
9.44
0.94
6.01
f1 (ppm)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133.569
129.230
129.112
128.832
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76.682
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69.425
68.813
61.853
61.771
53.709
53.023
52.948
40.601
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25.716
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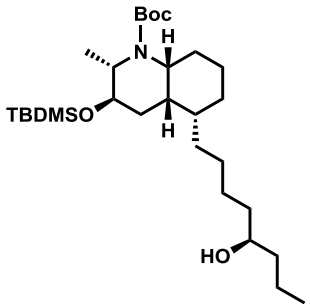
13.979
4.870
5.143
f1 (ppm)



(2*S*,3*R*,4a*S*,5*S*,8a*R*)-1-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldimethylsilyloxy)-5-[5(*R*)-hydroxyoctyl]-2-methyldecahydroquinoline (68)

Sodium amalgam (143 mg, 0.64 mmol) was added at 0 ºC to a solution of sulfone **67** (21 mg, 0.03 mmol) and $NaHPO_4$ (100 mg, 0.71 mmol) in MeOH (1 mL), and the resulting mixture was stirred at 0 ºC for 2 h and at room temperature for 4 h. Then, additional sodium amalgam (72 mg, 0.32 mmol) and $NaHPO_4$ (50 mg, 0.35 mmol) were added, and stirring was continued for 2 h. The mixture was filtered over Celite®, and the solvent evaporated under reduced pressure. The resulting residue was taken up with CH_2Cl_2, and saturated aqueous NH_4Cl was added. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated. Flash chromatography (9:1 cyclohexane–EtOAc) afforded the title compound **68** (14 mg, 88%) as a colorless oil.

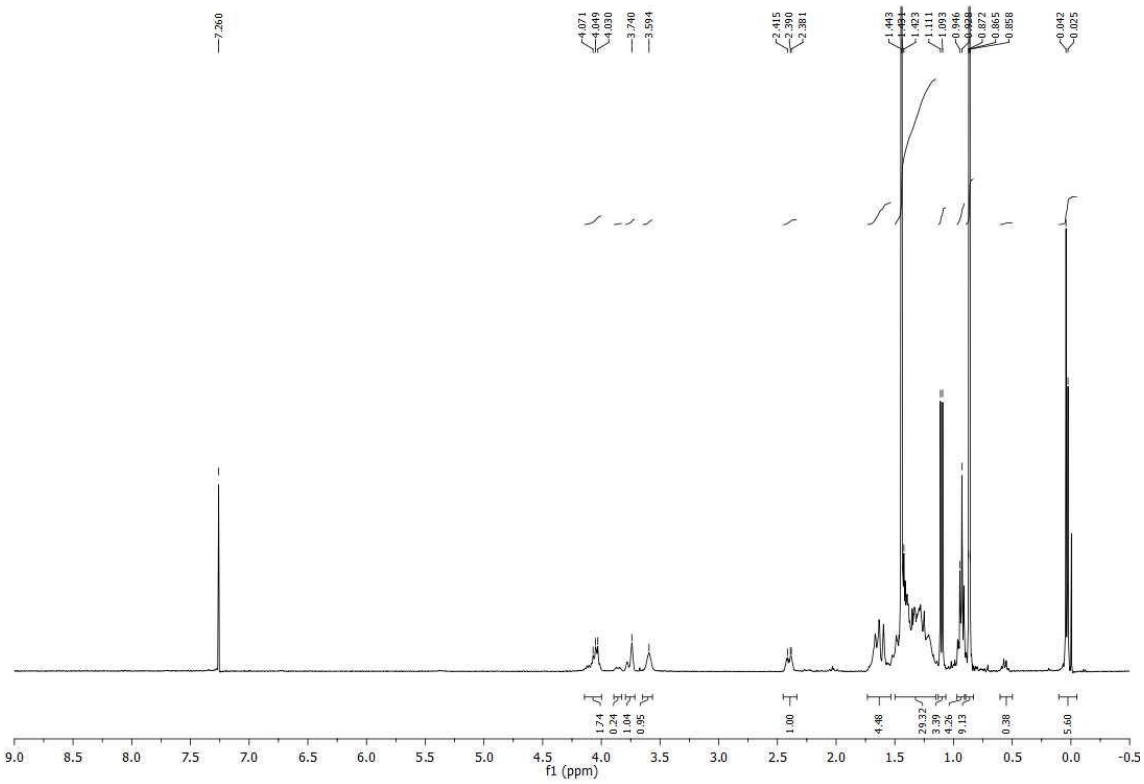
^{1}H-NMR (400 MHz, $CDCl_3$, amide rotamers) δ: 0.03 (br s, 3H, CH_3), 0.04 (br s, 3H, CH_3), 0.52-0.61 (m, 1H), 0.89 [s, 9H, $C(CH_3)_3$], 0.89- 0.99 (m, 4H), 1.10 (d, J = 6.8 Hz, 3H, CH_3), 1.17-1.51 (m, 16H, H-6, H-7, H-4, H-5, H-8), 1.44 [s, 9H, $C(CH_3)_3$], 1.55-1.72 (m, 4H, CH_2), 2.37-2.43 (m, 1H, H-4a), 3.59 (br s, 1H, H-5'), 3.74 and 3.78 (br s, 1H, H-3), 3.82-3.90 (m, 0.5H, H-8a), 4.00-4.12 (br m, 1.5H, H-2, H-8a).

^{13}C-NMR (100.6 MHz, $CDCl_3$, amide rotamers) δ: –5.1 and –5.0 [$Si(CH_3)_2$], 14.1 [$SiC(CH_3)_3$], 18.8 (CH_2), 20.1 (CH_3), 21.3 (CH_2), 25.7 (CH_2), 25.8 and 28.5 [$C(CH_3)_3$], 25.8 (CH_2), 26.6 and 26.9 (CH_2), 27.8 and 28.2 (CH_2), 30.3 (CH_2), 33.2 and 33.4 (C-4a), 37.5 (CH_2), 39.3 (C-5), 39.7 (CH_2), 53.0 and 53.3 (C-2), 53.8 and 54.5 (C-8a), 69.7 (C-3), 71.6 and 71.7 (C-5'), 78.8 [$C(CH_3)_3$], 155.2 and 155.5 (NCOO).

IR (NaCl): 3462, 1687, 1251 cm^{-1}.

HRMS calcd for [$C_{29}H_{57}NO_4Si$ + H^+]: 512.4130; found 512.4129.

$[\alpha]^{23}_D$ = – 6.6 (*c* 0.7, $CHCl_3$).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1.111
1.093
0.946
0.872
0.865
0.858
0.042
0.025
1.74
0.24
1.04
0.95
1.00
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29.32
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4.26
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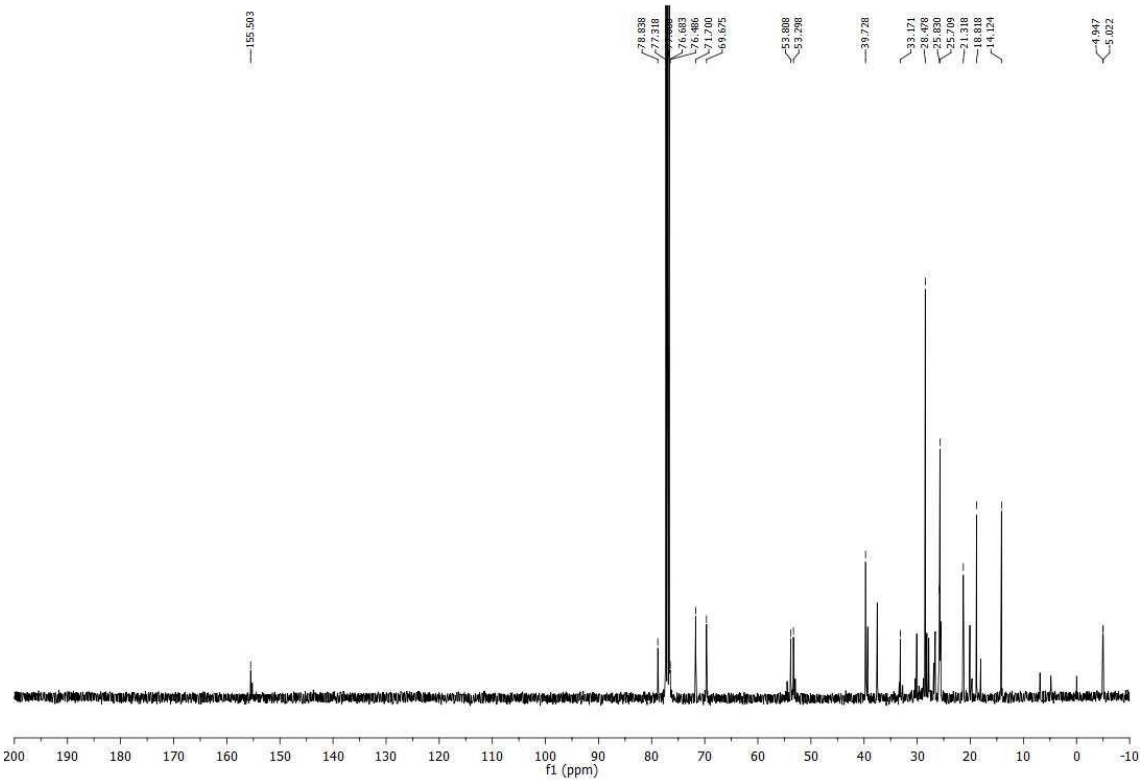
0.38
5.60
f1 (ppm)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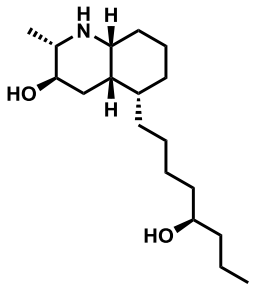
5.022
f1 (ppm)



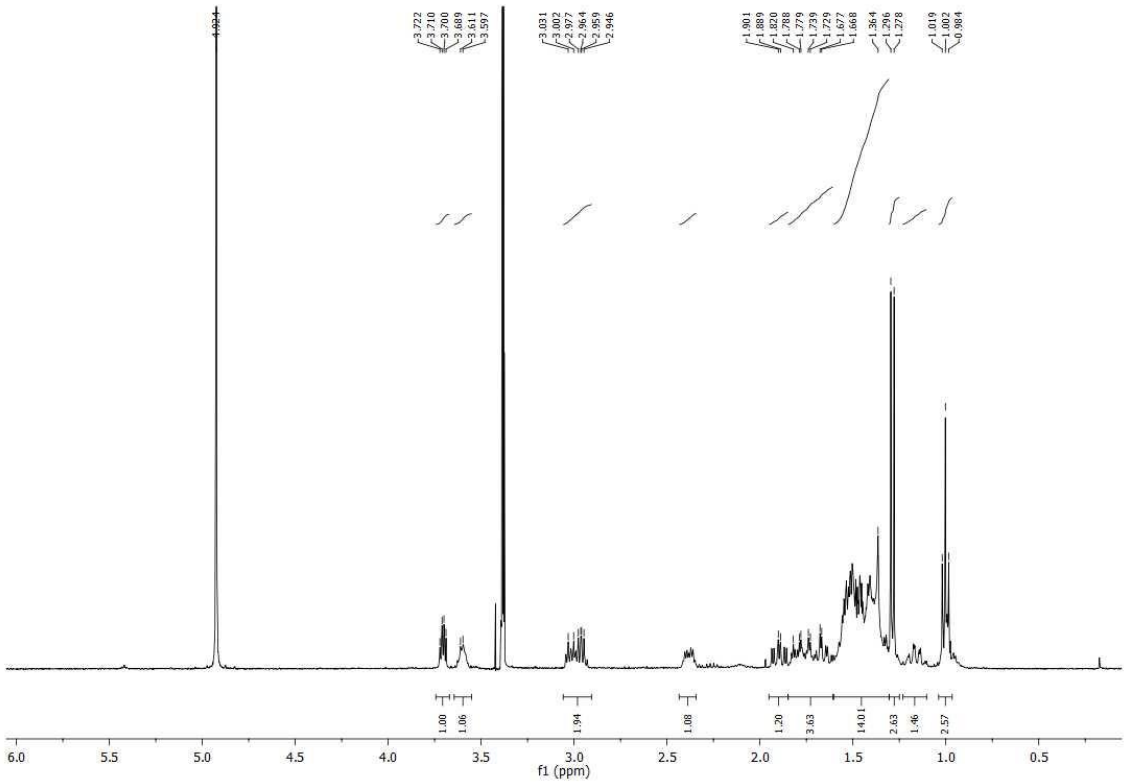
(+)-Lepadin D

TFA (500 μL) was added at 0 ºC to a solution of compound **68** (14 mg, 0.027 mmol) in CH_2Cl_2 (500 μL), and the resulting solution was allowed to warm to room temperature and stirred for 7 h. The solution was concentrated, and the resulting residue was dissolved in $CHCl_3$. Three pellets of NaOH were added, and the mixture was stirred for 2 h and filtered, and the solvent was evaporated. Flash chromatography (NH-SiO_2, AcOEt to 9:1 EtOAc–MeOH) afforded **(+)-lepadin D** (6 mg, 75%) as a colorless oil.

^{1}H-NMR (400 MHz, CD_3OD) δ: 1.00 (t, J = 7.0 Hz, 3H, CH_3), 1.12-1.21 (m, 1H), 1.29 (d, J = 6.8 Hz, 3H, CH_3), 1.31-1.59 (m, 14H), 1.60-1.83 (m, 5H), 1.87 (ddd, J = 14.0, 14.0, 4.8 Hz, 1H), 2.33-2.43 (m, 1H), 2.92-3.05 (m, 2H), 3.57-3.64 (m, 1H), 3.67-3.74 (m, 1H).

^{13}C-NMR (100.6 MHz, CD_3OD) δ: 14.5 (CH_3), 19.9 (CH_3), 19.9 (CH_2), 25.1 (CH_2), 25.6 (CH_2), 27.0 (CH_2), 28.3 (CH_2), 28.4 (CH_2), 30.7 (CH_2), 33.5 (CH), 34.4 (CH_2), 38.4 (CH_2), 40.4 (CH), 40.8 (CH_2), 53.9 (CH), 56.1 (CH), 71.5 (CH), 72.1 (CH).

$[\alpha]^{23}_D$ (HCl salt) = – 11.2 (c 0.375, MeOH).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1.06
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3.002
2.977
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2.946
1.94
1.08
1.901
1.889
1.820
1.788
1.779
1.739
1.729
1.677
1.668
1.364
1.296
1.278
1.20
3.63
14.01
2.63
1.46
1.019
1.002
0.984
2.57
6.0
5.5
5.0
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3.0
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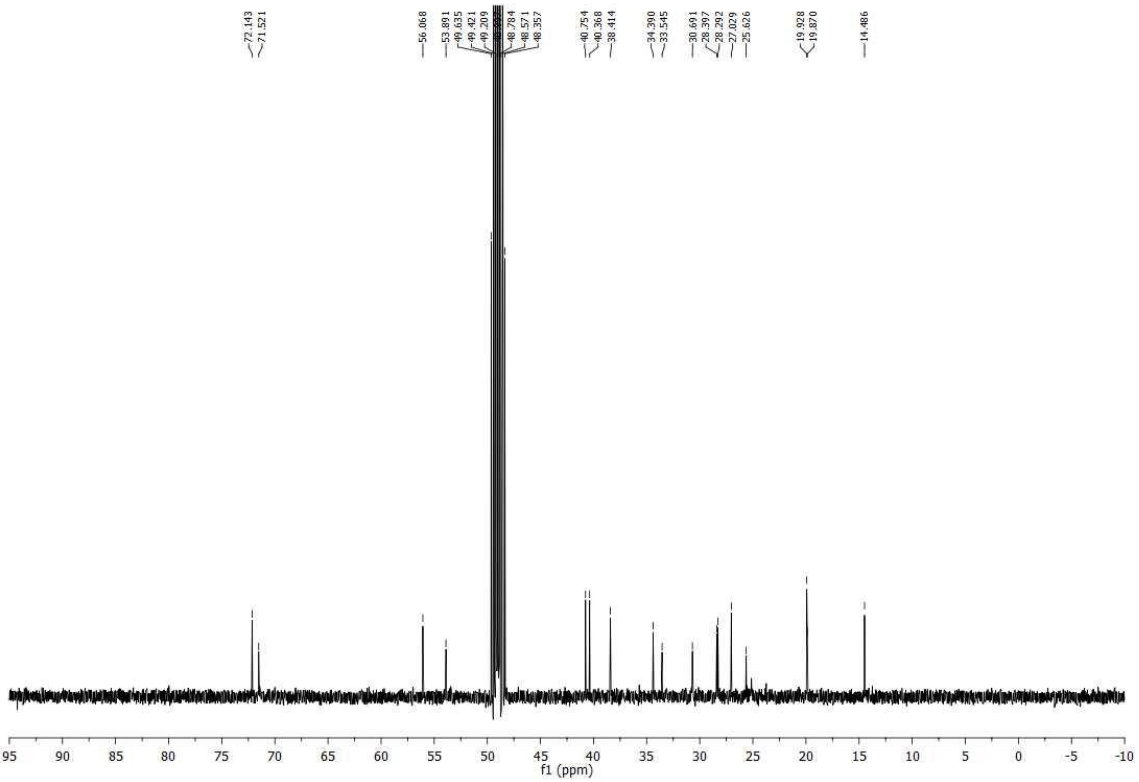
2.0
1.5
1.0
0.5
f1 (ppm)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48.357
40.754
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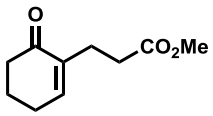
34.390
33.545
30.691
28.397
28.292
27.029
25.626
19.928
19.870
14.486
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
-10
f1 (ppm)



Methyl 6-oxocyclohexenepropionate (69)

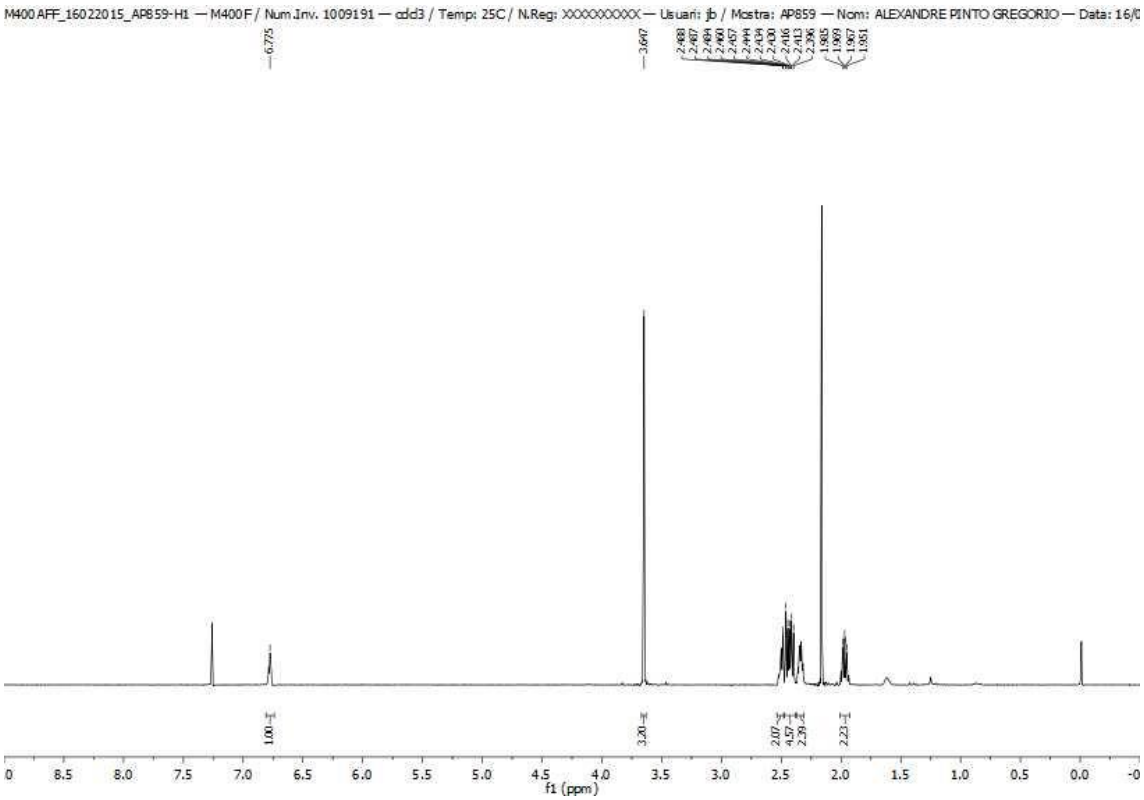
DBU (930 µL, 6.2 mmol) and methyl acrylate (3.63 mL, 40.3 mmol) were added to a sealed tube containing a solution [0.5M] of 2-cyclohexenone (3.0 mL, 31 mmol) in dry DMF (62 mL), at room temperature under an Argon atmosphere. The tube was sealed and the mixture heated to 185 ºC for 24h. After cooling to room temperature, the crude reaction mixture was poured into ice water and extracted with Et_2O. The combined organic extracts were washed with distilled H_2O and Brine. The organic extracts were, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Flash chromatography (hex: acetone, 8:2) afforded compound **69** (2.3 g, 41% yield) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.94-2.02 (m, 2H), 2.32-2.53 (m, 8H), 3.65 (s, 3H, CH_3O), 6.78 (t, J = 4.2 Hz, 1H, CH=).

^{13}C-NMR (75.4 MHz, $CDCl_3$) δ: 22.8 (CH_2), 25.3 (CH_2), 25.8 (CH_2), 32.8 (CH_2), 38.2 (CH_2), 51.3 (CH_3O), 137.8 (Cq), 146.1 (CH), 173.5 (COO), 198.2 (CO).

IR (NaCl): 1738, 1671 cm^{-1}.

HRMS calcd for [$C_{10}H_{14}O_3$ + Na $^+$]: 205.0835, found 205.0830.


M400AFF_16022015_AP859-H1 — M400F / Num.Inv. 1009191 — cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP859 — Nom: ALEXANDRE PINTO GREGORIO — Data: 16/0
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3.647
2.488
2.467
2.464
2.460
2.457
2.444
2.434
2.430
2.406
2.413
2.396
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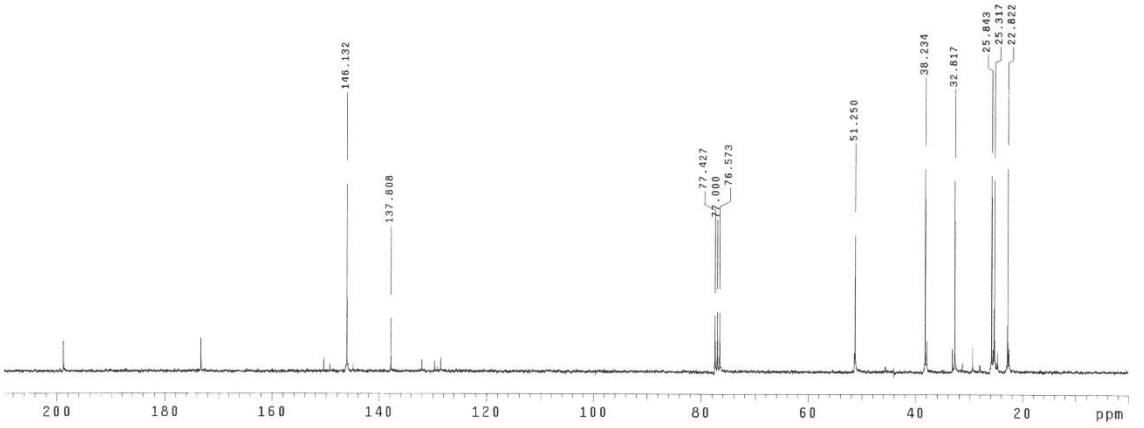
1.969
1.967
1.951
1.00
3.20
2.07
4.57
2.39
2.23
f1 (ppm)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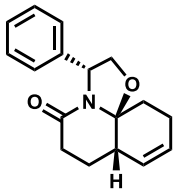
22.822
ppm



(3*R*,7a*S*,11a*S*)-5-oxo-3-phenyl-2,3,5,6,7,7a,10,11-octahydrooxazolo[2,3-*j*] quinoline (70)

(*R*)-Phenylglycinol (3.18 g, 23.16 mmol) was added to a solution of **69** (2.81 g, 15.44 mmol) and AcOH (1.32 mL, 23.16 mmol) in benzene (40 mL). The mixture was heated at reflux with azeotropic elimination of water by a Dean-Stark system. After 24 h, the mixture was cooled to room temperature and concentrated, and the resulting oil was taken up in EtOAc. The organic solution was washed with saturated aqueous $NaHCO_3$, 1M aqueous HCl and brine, dried and concentrated. Flash chromatography (from 85:15 to 65:35 hexane–EtOAc), afforded lactam **70** (1.42 g, 34% yield) as a white solid.

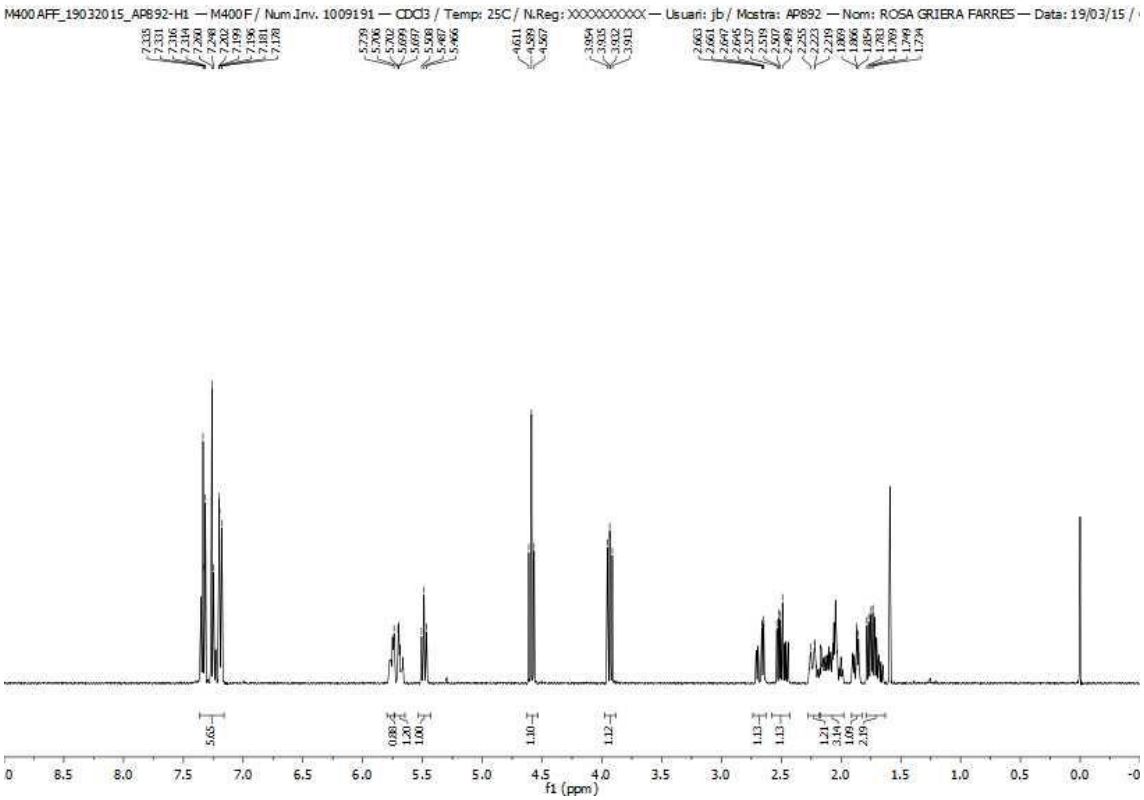
^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ: 1.62-1.79 (m, 2H, H-7), 1.87 (dd, J = 13,7, 5,6 Hz, 1H, H-11), 1.97-2.17 (m, 3H, H-10, H-11), 2.19-2.29 (m, 1H, H-7a), 2.42-2.54 (m, 1H, H-6), 2.67 (dd, J = 18.5, 6.2 Hz, 1H, H-6), 3.93 (dd, J = 8.8, 8.0Hz, 1H, H-2), 4.59 (t, J = 8.8Hz, 1H, H-2), 5.49 (t, J = 8,0 Hz, 1H, H-3), 5.65-5.71 (m, 1H, H-8), 5.72-5.78 (m, 1H, H-9), 7.17-7.36 (m, 5H, H-Ar).

^{13}C-NMR (75.4 MHz, $CDCl_3$) δ: 23.3 (C-10), 26.3 (C-7), 26.5 (C-11), 31.3 (C-6), 40.5 (C-7a), 58.3 (C-3), 69.4 (C-2), 94.0 (C-11a), 125.2 (CH-o), 126.5 (C-9), 127.0 (C-8), 127.1 (CH-*p*), 128.5 (CH-*m*), 140.4 (C-*i*), 169.9 (NCO).

IR (NaCl): 1652 cm^{-1}.

HRMS calcd for [$C_{17}H_{19}NO_3$ + H^+]: 270.1488, found 270.1498.

$[\alpha]^{23}_D$ = −75.2 (c 0.9, MeOH).


M400AFF_19032015_AP892-H1 — M400F / Num.Inv. 1009191 — CDCl3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP892 — Nom: ROSA GRIERA FARRES — Data: 19/03/15 /
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7.202
7.199
7.196
7.181
7.178
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5.706
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2.219
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1.854
1.783
1.769
1.749
1.724
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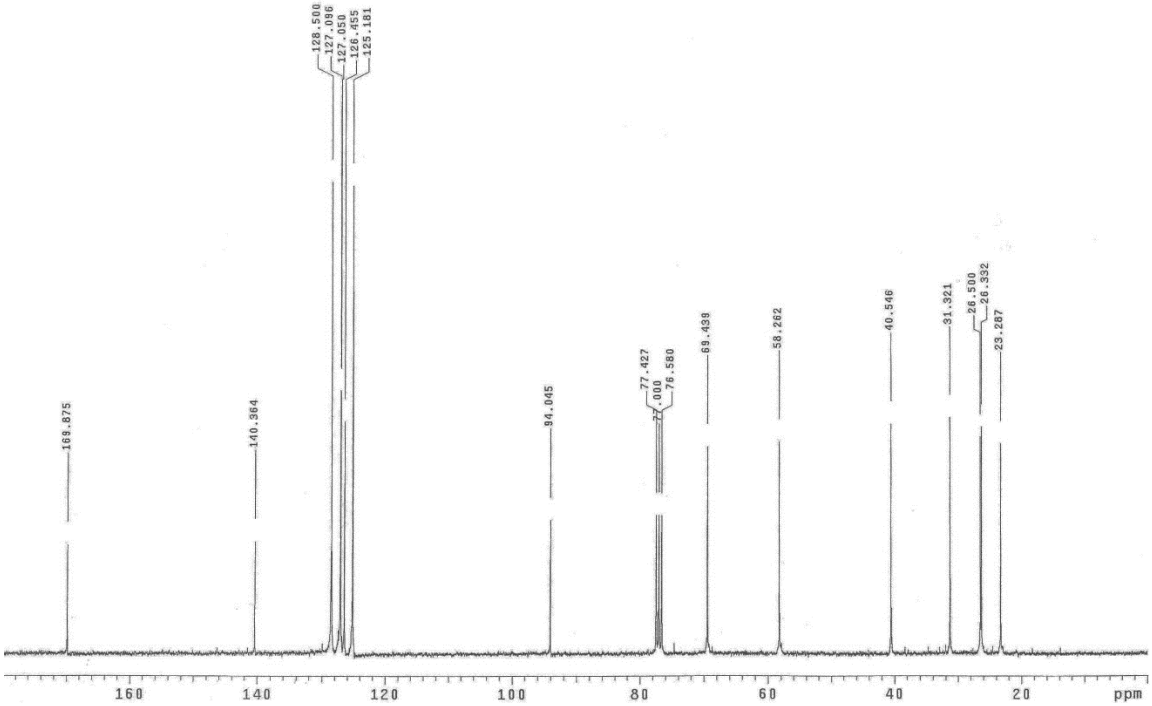
2.19
f1 (ppm)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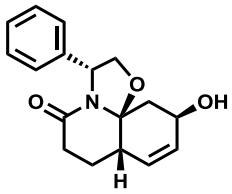


(3*R*,7a*S*,10*R*,11a*S*)-10-Hydroxy-5-oxo-3-phenyl-2,3,5,6,7,7a,10,11-octahydro oxazolo[2,3-*j*]quinoline (71)

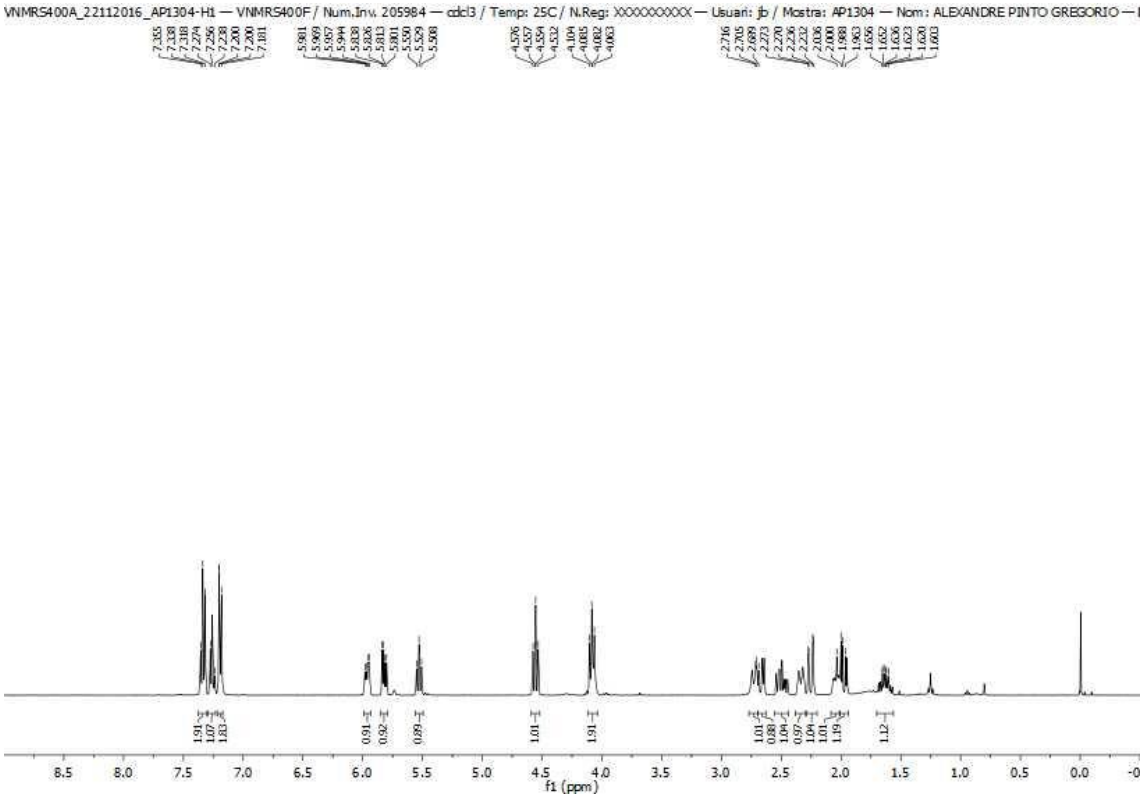
SeO_2 (1.08 g, 9.76 mmol) was added to a stirring solution of lactam **70** (610 mg, 2.27 mmol) in dry 1,4-dioxane (76 mL) at room temperature. The resulting suspension was heated at reflux for 24 h. The solvent was evaporated and the residue was taken up in EtOAc. The organic solution was washed with H_2O, dried and concentrated under reduced pressure. Flash chromatography (Hexane: EtOAc 2:8), afforded compound **71** (505 mg, 78 %) as a white residue.

^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ: 1.82-1.97 (m, 1H, H-7), 2.18-2.27 (m, 1H, H-7), 2.52-2.66 (m, 2H, H-7a, H-11), 2.72- 2.89 (m, 3H, H-6, H-11), 4.08 (t, J = 7.6 Hz, 2H, H-2, H-3), 4.55 (t, J = 7.6 Hz, 1H, H-2), 5.53 (t, J = 8.4 Hz, 1H, H-3), 5.82 (dd, J = 10, 4.8 Hz, 1H, H-9), 5.96 (dd, J = 9.6, 4.8 Hz, 1H, H-8), 7.16 (d, J = 7.6 Hz, 2H, H-Ar), 7.23-7.29 (m, 1H, H-Ar), 7.34 (m, 2H, H-Ar).

^{13}C-NMR (75.4 MHz, $CDCl_3$) δ: 24.7 (C-7), 31.1 (C-11), 34.2 (C-7a), 40.5 (C-6), 58.5 (C-3), 64.9 (C-10), 69.3 (C-2), 94.2 (C-11a), 125.3 (2CH-Ar), 127.3 (CH-Ar), 128.3 (C-9) 128.6 (2CH-Ar), 129.1 (C-8), 139.8 (C-Ar), 169.3 (NCO).

HRMS calcd for [$C_{17}H_{19}NO_3 + H^+$]: 286.1438, found 286.1438.

$[\alpha]^{23}_D = -26.8$ (c 1.2, $CHCl_3$).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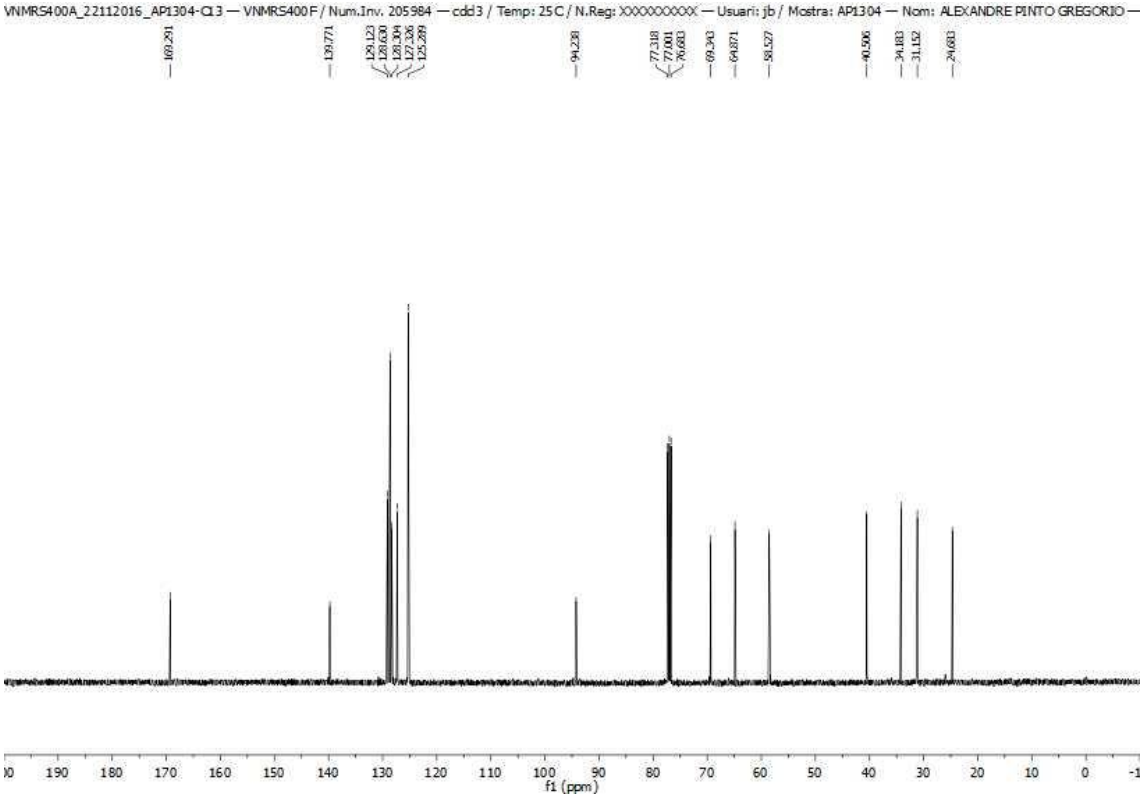
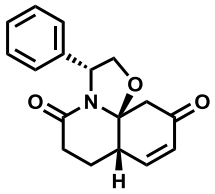
7.355
7.338
7.319
7.274
7.256
7.238
7.200
7.200
7.181
5.981
5.969
5.957
5.944
5.838
5.826
5.813
5.801
5.529
5.508
4.576
4.557
4.554
4.532
4.104
4.085
4.082
4.063
2.716
2.705
2.689
2.273
2.270
2.226
2.222
2.006
2.000
1.988
1.965
1.652
1.636
1.623
1.600
1.603
1.91
1.07
1.83
0.91
0.92
0.89
1.01
1.91
1.01
0.88
1.04
0.97
1.04
1.01
1.19
1.12
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


VNMRS400A_22112016_AP1304-C13 — VNMRS400F / Num.Inv. 205984 — cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP1304 — Nom: ALEXANDRE PINTO GREGORIO —
169.291
139.771
129.123
128.630
128.304
127.206
125.289
94.238
77.318
77.001
76.683
69.943
64.871
58.527
40.506
34.183
31.152
24.683
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



(3*R*,7a*S*, 11a*S*)- 5,10-Dioxo-3-phenyl-2,3,5,6,7,7a,10,11-octahydro oxazolo[2,3-*j*]quinoline (72)

Method A: Dess-Martin periodinane (1.97 g, 4.65 mmol) was added to a stirring solution of the crude **71** (500 mg) in dry CH_2Cl_2 (186 mL). The resulting suspension was stirred overnight at room temperature. Saturated aqueous $NaHCO_3$ (60 mL) and saturated aqueous $Na_2S_2O_3$ (60 mL) was added and the mixture was stirred 45 minutes. The layers were separated and the aqueous solution was further extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated under reduced pressure. Flash chromatography (3:7 hexane–EtOAc) afforded compound **72** (343 mg, 65% yield from **70**) as a white-yellow residue.

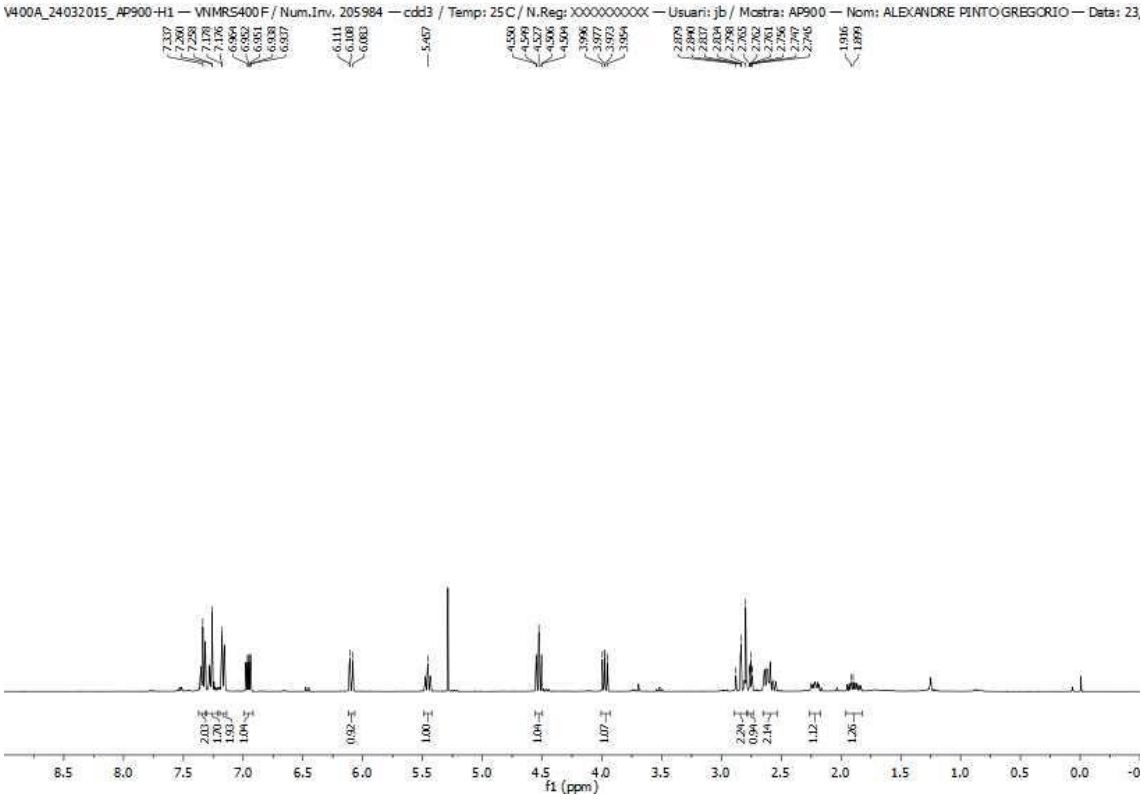
Method B: $Mn(OAc)_3$ (50 mg, 0.18 mmol) was added to a stirring solution of compound **70** (100 mg, 0.37 mmol), TBHP (340 μL of a solution 5.5 M in decane, 1.86 mmol) and 3Å molecular sieves (500 mg) in EtOAc (22 mL) under argon atmosphere. The resulting mixture was stirred for 40 h at 50 ºC. The crude mixture was filtered over Celite®, washed with EtOAc and the solvent was evaporated under reduced pressure. Flash chromatography (6:4, hexane–EtOAc), afforded compound **72** (20 mg, 37%) as a white-yellow residue.

^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ: 1.82-1.97 (m, 1H, H-7), 2.18-2.27 (m, 1H, H-7), 2.52-2.66 (m, 2H, H-7a, H-11), 2.72-2.89 (m, 3H, H-6, H-11), 3.98 (t, J = 8.2 Hz, 1H, H-2), 4.53 (t, J = 8.2 Hz, 1H, H-2), 5.46 (t, J = 8.2 Hz, 1H, H-3), 6.09 (d, J = 10.2 Hz, 1H, H-9), 6.95 (dd, J = 5.6, 10.2Hz, 1H, H-8), 7.16 (d, J = 7.4 Hz, 2H, H-Ar), 7.26 (t, J = 7.4 Hz, 1H, H-Ar), 7.34 (t, J = 7.4 Hz, 2H, H-Ar).

^{13}C-NMR (75.4 MHz, $CDCl_3$) δ: 23.7 (C-7), 31.0 (C-6), 41.6 (C-7a), 43.9 (C-11), 58.9 (C-3), 69.6 (C-2), 94.9 (C-11a), 125.3 (C-Ar), 127.6 (C-Ar), 128.3 (C-9) 128.8 (C-Ar), 139.1 (Cq-Ar), 148.0 (C-8), 168.6 (NCO), 194.8 (C=O).

HRMS calcd for [$C_{17}H_{17}NO_3$ + H^+]: 284.1281, found 284.1291.

$[\alpha]^{23}_D$ = – 119 (c 1.0, $CHCl_3$).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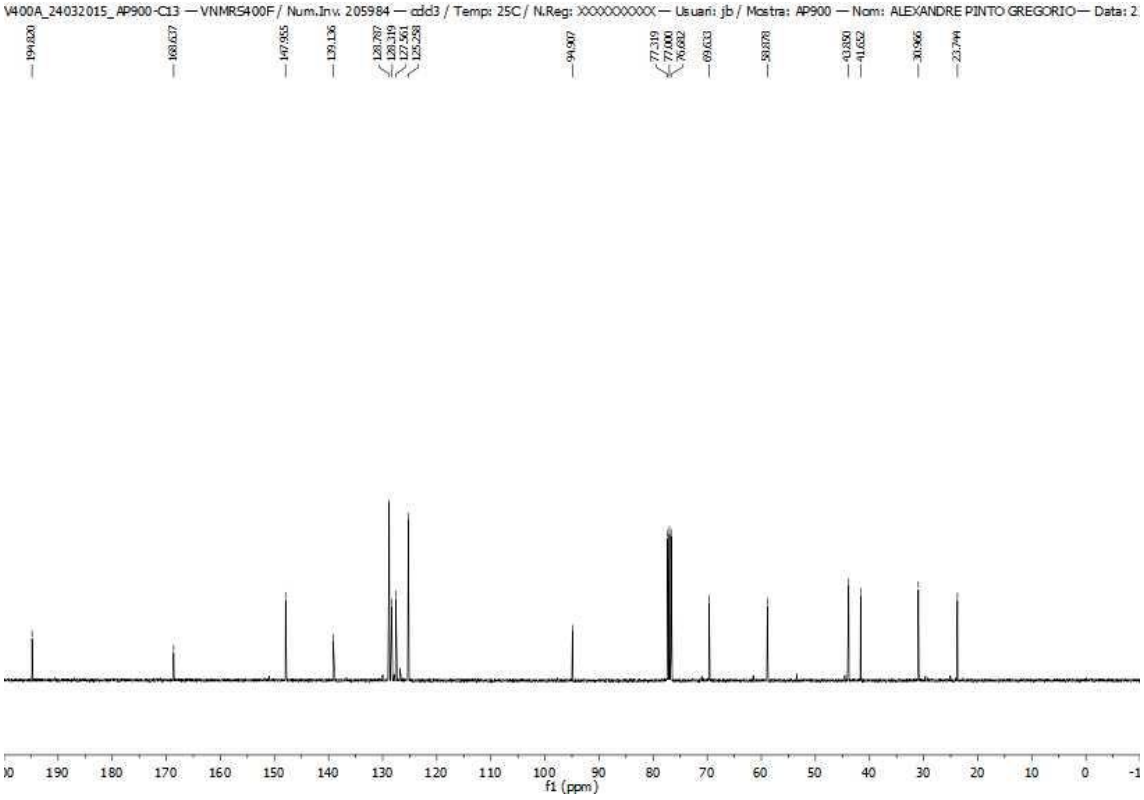
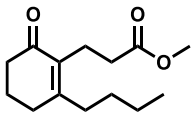
7.337
7.260
7.258
7.178
7.176
6.964
6.962
6.951
6.938
6.937
6.111
6.108
6.083
5.467
4.550
4.549
4.527
4.506
4.504
3.996
3.977
3.973
3.964
2.809
2.800
2.617
2.604
2.598
2.765
2.762
2.761
2.756
2.747
2.745
1.916
1.899
2.03
1.70
1.93
1.04
0.92
1.00
1.04
1.07
2.29
0.94
2.14
1.12
1.26
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


V400A_24032015_AP900-C13 — VNMRS400F / Num.Inv. 205984 — cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP900 — Nom: ALEXANDRE PINTO GREGORIO — Data: 2
194.820
168.637
147.955
139.136
128.787
128.319
127.501
125.258
94.907
77.319
77.000
76.682
69.633
58.078
43.850
41.652
30.866
23.744
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



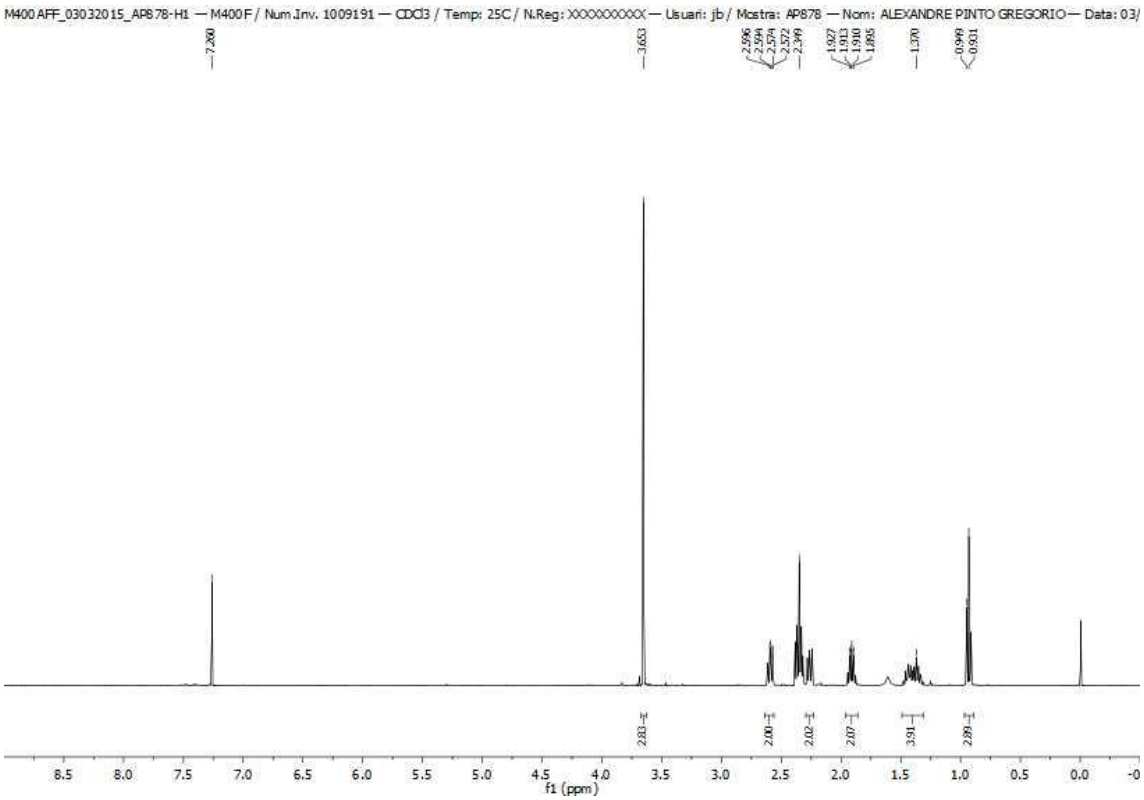
Methyl 2-butyl-6-oxocyclohexenepropionate (73)

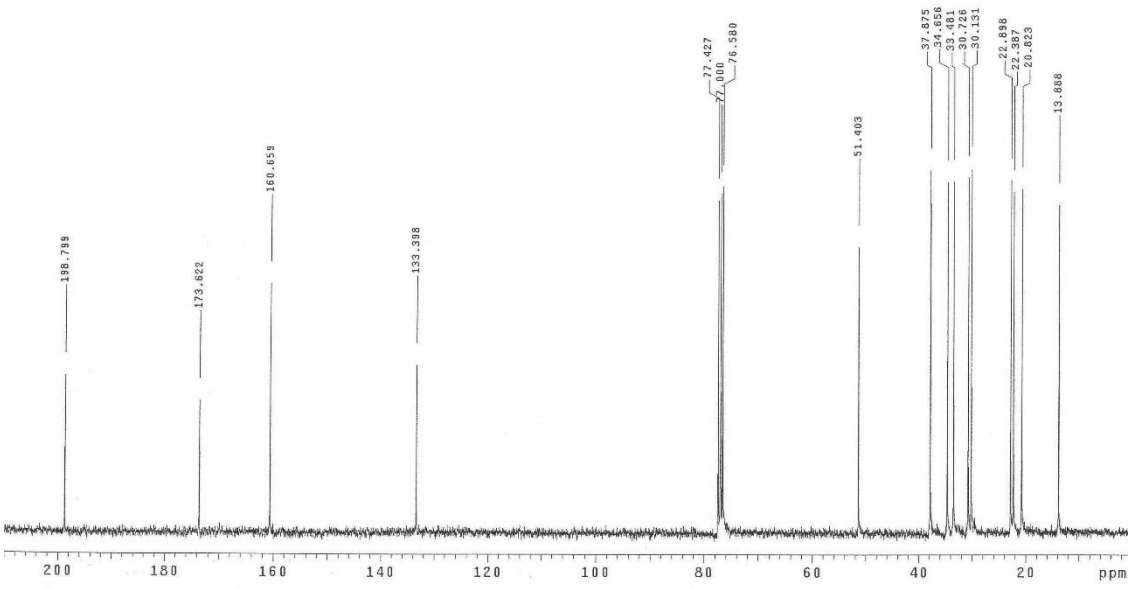
n-BuLi (2.16 mL, 1.6 M in hexane) was added to a suspension of C_6H_5SCu (597 mg, 3.45 mmol) in anhydrous THF (17 mL) at −20 ºC, and the mixture was stirred at this temperature for 15 min. After cooling at −78 ºC, bromo enone **1** (300 mg, 1.15 mmol) in anhydrous THF (5 mL) was added, and the mixture was allowed to reach 0 ºC, stirred for 2.5 h, and poured into saturated aqueous NH_4Cl. The aqueous layer was extracted with EtOAc, and the organic extracts were dried and concentrated. Flash chromatography (CH_2Cl_2) afforded **73** (148 mg, 54%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.92-0.96 (m, 3H), 1.35-1.44 (m, 4H), 1.90-1.93 (m, 2H), 2.24-2.39 (m, 8H), 2.57-2.59 (m, 2H), 3.65 (s, 3H).

^{13}C-NMR (75.4 MHz, $CDCl_3$) δ: 13.9 (CH_3), 20.8 (CH_2), 22.4 (CH_2), 22.9 (CH_2), 30.1 (CH_2), 30.7 (CH_2), 33.5 (CH_2), 34.7 (CH_2), 37.9 (CH_2), 51.4 (CH_3), 133.4 (C), 160.7 (C), 173.6 (C=O), 198.8 (C=O).

HMRS calcd for [$C_{14}H_{22}O_3 + H^+$]: 239.1641, found: 239.1637.


M400AFF_03032015_AP878-H1 — M400F / Num.Inv. 1009191 — CDCl3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP878 — Nom: ALEXANDRE PINTO GREGORIO — Data: 03/
7.260
3.653
2.596
2.594
2.576
2.572
2.399
1.927
1.913
1.900
1.885
1.370
0.949
0.931
3.83
2.00
2.02
2.07
3.91
2.89
f1 (ppm)


198.799
173.622
160.659
133.398
77.427
77.000
76.580
51.403
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34.656
33.481
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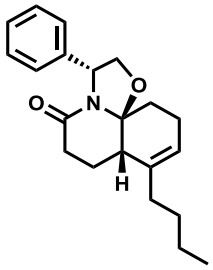
30.131
22.898
22.387
20.823
13.886
ppm



(3*R*,7a*S*,11a*S*)-8-Butyl-5-oxo-3-phenyl-2,3,5,6,7,7a,10,11-octahydrooxazolo[2,3-*j*]quinoline (74)

Operating as described for the preparation of **70**, from keto ester **73** (500 mg, 2.1 mmol), (*R*)-phenylglycinol (865 mg, 6.3 mmol), and acetic acid (360 μL, 6.3 mmol) in benzene (40 mL), lactam **74** (416 mg, 61%) was obtained after column chromatography (from 7:3 to 3:2 hexane-EtOAc).

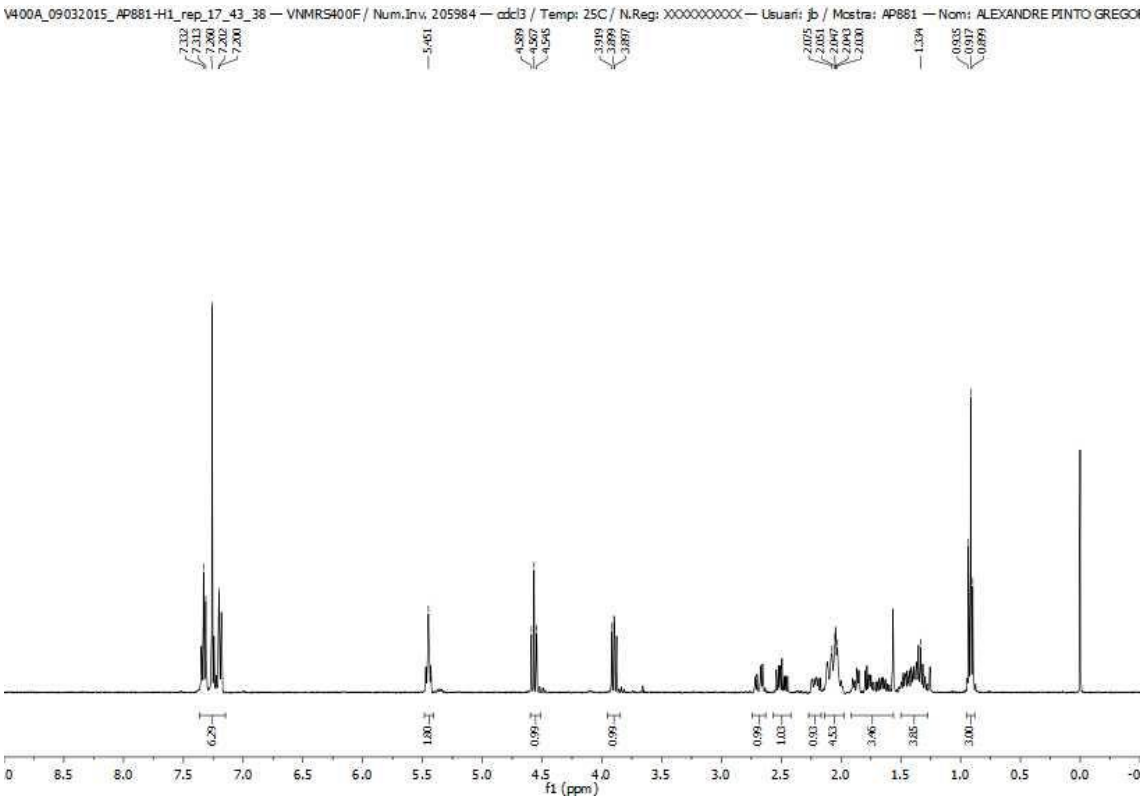
^{1}H-NMR (400 MHz, $CDCl_3$,) δ: 0.93 (t, 3H), 1.31-1.46 (m, 4H), 1.48-1.92 (m, 3H), 2.02-2.12 (m, 5H), 2.18-2.24 (m, 1H), 2.41-2.57 (m, 1H), 2.61-2.73 (m, 1H), 3.89 (t, J = 8.7 Hz, 1H), 4.57 (t, J = 8.7 Hz, 1H), 5.44-5.50 (m, 2H), 7.18-7.35 (m, 5H).

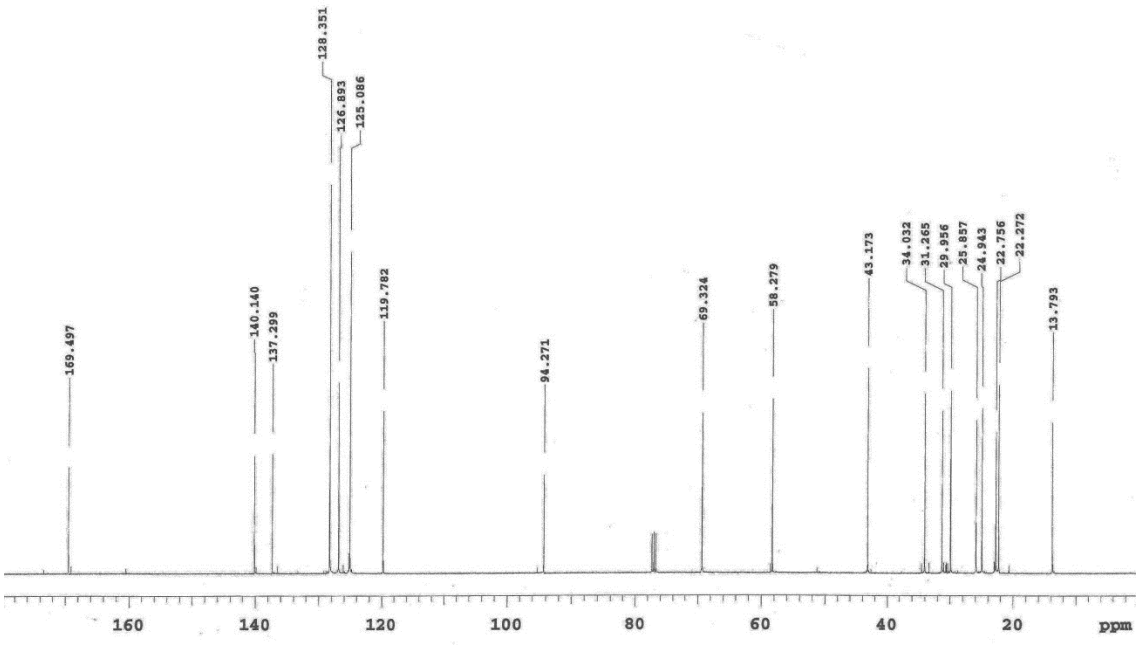
^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 13.8 (CH_3), 22.3 (CH_2), 22.8 (CH_2), 24.9 (CH_2), 25.9 (CH_2), 30.0 (CH_2), 31.3 (CH_2), 34.0 (CH_2), 43.2 (CH), 58.3 (CH), 69.3 (CH_2), 94.3 (C), 119.8 (CH), 125.1 (2CH), 126.9 (CH), 128.4 (2CH), 137.3 (C), 140.1 (C), 169.5 (C).

HRMS calcd for [$C_{21}H_{27}NO_2$ + H^+]: 326.2114, found: 326.2107.

$[\alpha]^{23}_D$ = – 87.5 (*c* 1.0, MeOH).

Melting point: 82–85 ºC.


f1 (ppm)


169.497
140.140
137.299
128.351
126.893
125.086
119.782
94.271
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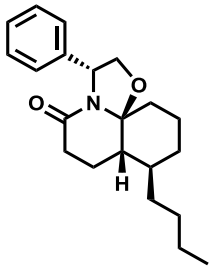
25.857
24.943
22.756
22.272
13.793
ppm



(3*R*,7a*S*,8*R*,11a*S*)-8-Butyl-5-oxo-3-phenyldecahydrooxazolo[2,3-*j*]quinoline (75)

Method A: A solution of compound **74** (300 mg, 0.92 mmol) in methanol (10 mL) containing Pd/C (120 mg, 40% weight) was stirred under hydrogen at room temperature for 17 h. The catalyst was removed by filtration over Celite®, and the solvent was evaporated, affording compound **75** (289 mg, 96%) as a white residue.

Method B: *1st step:* $BF_3 \cdot Et_2O$ (5 μL, 0.04 mmol) was added to a solution of compound **76a** (44 mg, 0.13 mmol) and 1,3-propanedithiol (20 μL, 0.194 mmol) in dry CH_2Cl_2 (2.0 mL), and the mixture stirred for 16h at room temperature. 2 M aqueous NaOH was added to quench the reaction, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed brine, dried and concentrated to afford crude dithiane, which was used without purification.
2nd step: Ni-Raney ® (200 mg, 10x weight) was added to a solution of the above crude in absolute EtOH (2.3 mL) and the slurry suspension heated to reflux for 23h. After cooling to room temperature, 5% aqueous HCl was added and the suspension filter over Celite ®. The solvent was evaporated and the residue was re-dissolved in 10% aqueous NaOH, and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated. Flash chromatography (6:4, hexane–EtOAc), afforded lactam **75** (24 mg, 55% overall yield) as white residue.

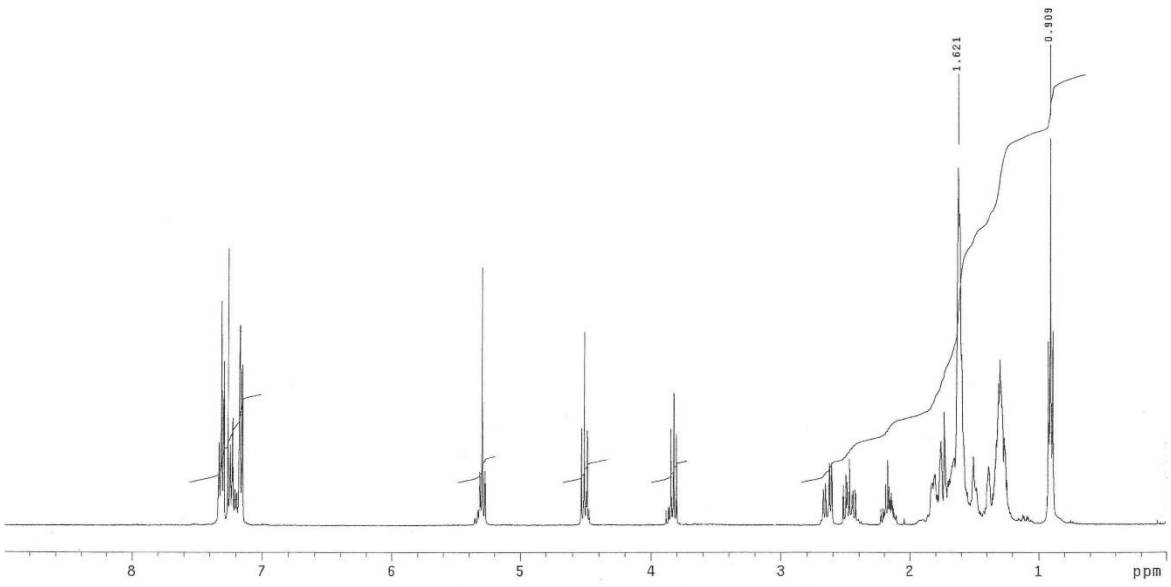
^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ: 0.91 (t, J = 6.8 Hz, 3H, H-4'), 1.24-1.84 (m, 15H), 2.11-2.23 (m, 1H), 2.47 (ddd, J = 18.5, 11.0, 7.2 Hz, 1H, H-6), 2.64 (dd, J = 18.5, 7.2 Hz, 1H, H-6), 3.83 (t, J = 8.4 Hz, 1H, H-2), 4.51 (t, J = 8.4 Hz, 1H, H-2), 5.30 (t, J = 8.4 Hz, 1H, H-3), 7.15-7.33 (m, 5H, H-Ar).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 14.2 (CH_3), 18.0 (C-10), 22.8 (C-7), 24.2 (C-11), 24.8 (C-7), 30.5 (C-9), 30.6 (CH_2), 31.3 (C-6), 32.9 (CH_2), 39.9 (C-8), 43.7 (C-7a), 58.0 (C-3), 69.6 (C-2), 95.5 (C-11a), 125.4 (CH-*o*), 127.0 (CH-*p*), 128.5 (CH-*m*), 140.3 (C-*i*), 169.5 (NCO).

Elemental analysis for [$C_{21}H_{29}NO_2$]: C: 77.03%, H: 8.93%, N: 4.28%, found C: 76.48%, H: 8.96%, N: 4.00%.

$[\alpha]^{23}_D = -77.1$ (c 1.1, MeOH).

Melting point: 83−86 ºC.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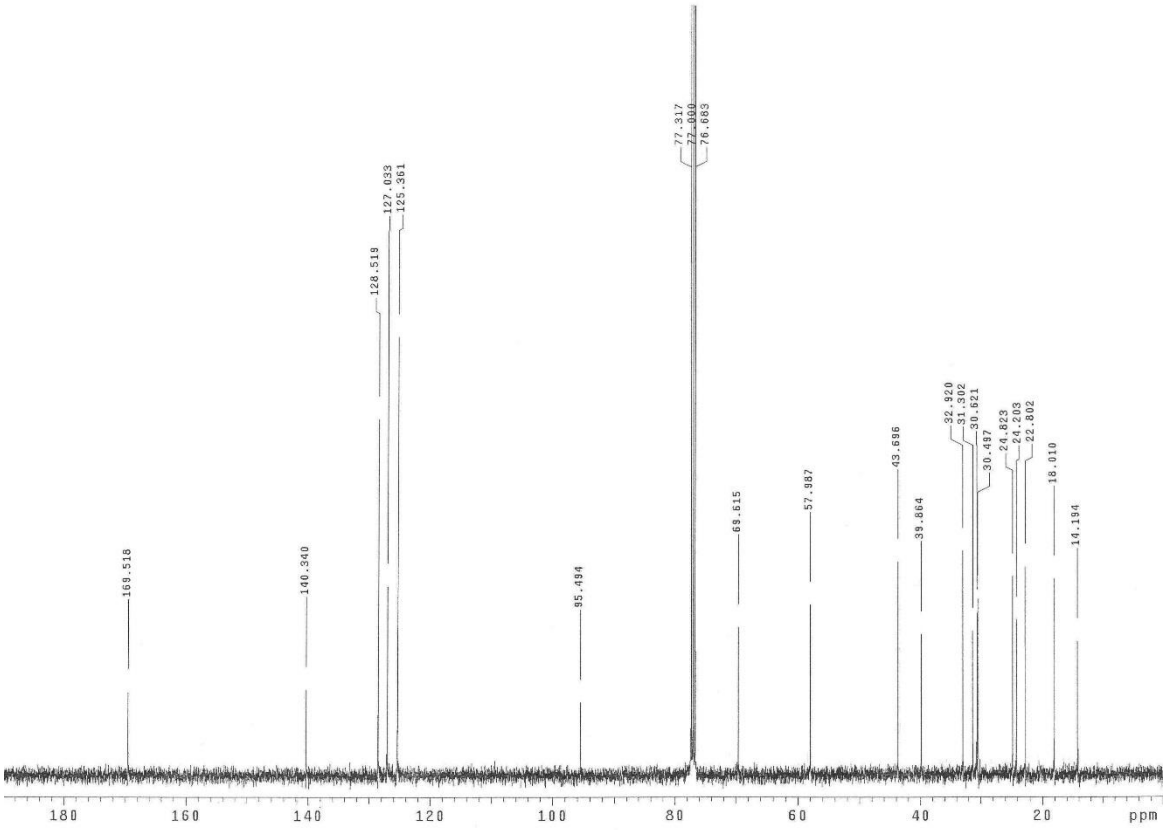
8
7
6
5
4
3
2
1
ppm


169.518
140.340
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127.033
125.361
95.494
77.317
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69.615
57.987
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32.920
31.302
30.621
30.497
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140
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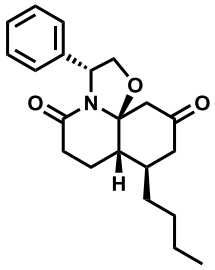
100
80
60
40
20
ppm



(3*R*,7a*S*,8*R*,11a*S*)-8-Butyl-5,10-dioxo-3-phenyldecahydrooxazolo[2,3-*j*]quinoline (76a)

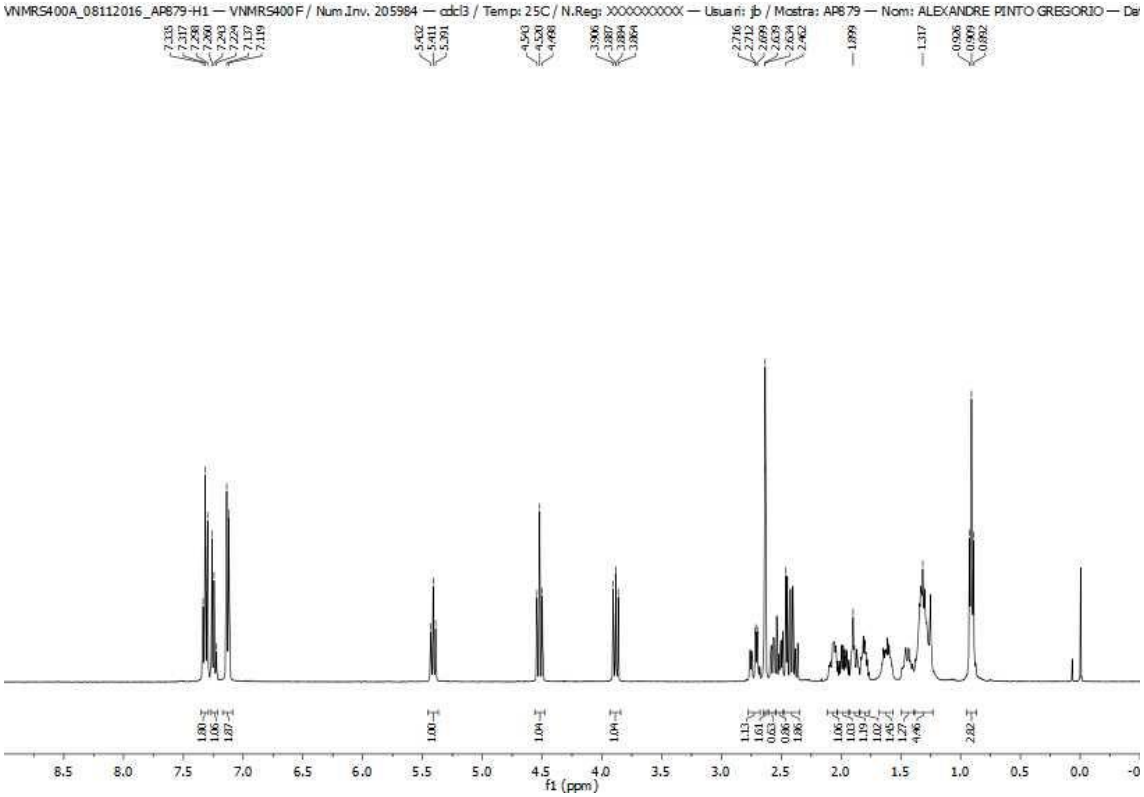
Method A: *n*-BuLi (560 µL of a solution 2.5 M in hexane, 1.41 mmol) was added dropwise to a suspension of CuI (135 mg, 0.71 mmol) in dry Et_2O (3.0 mL) at –20 ºC, under argon. After 30 minutes, the solvent was evaporated under a stream of argon. The obtained residue was dissolved with CH_2Cl_2 (5 mL) and the mixture was stirred for 10 min at –20 ºC. Compound **72** (40 mg, 0.14 mmol) in dry CH_2Cl_2 (1.0 mL) was added dropwise at –78 ºC. The resulting mixture was stirred at –78 ºC for 30 minutes and at –30 ºC for 3 h. Saturated aqueous NH_4Cl was added, the phases were separated and the aqueous phase was further extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. Flash chromatography (3:7 hexane−EtOAc) afforded compound **76a** (40 mg, 83%) as a yellowish oil.
Method B: MeLi (74 µL of a solution 1.6 M in Et_2O, 0.12 mmol) was added to a suspension of CuI (23 mg, 0.12 mmol) in dry THF (300 µL) at 0 ºC. The resulting yellow/brown suspension was cooled to –50 ºC and HMPA (60 µL, 20 % v/v) and DIBAL (240 µL of a solution 1 M in hexane, 0.24 mmol) were sequentially added. After 30 minutes, the mixture was cooled to –65 ºC and compound **80** (20 mg, 0.06 mmol) in THF (300 µL) was added dropwise. The reaction mixture was allowed to warm to – 50 ºC and stirring was continued for 2 h. 1 M aqueous HCl was added, the phases were separated and the aqueous phase was further extracted with CH_2Cl_2. The combined organic extracts were filtered over Celite® and the solvent evaporated. Flash chromatography (4:6 hexane−EtOAc) afforded compound **76a** (15 mg, 75 %) as a yellowish oil.

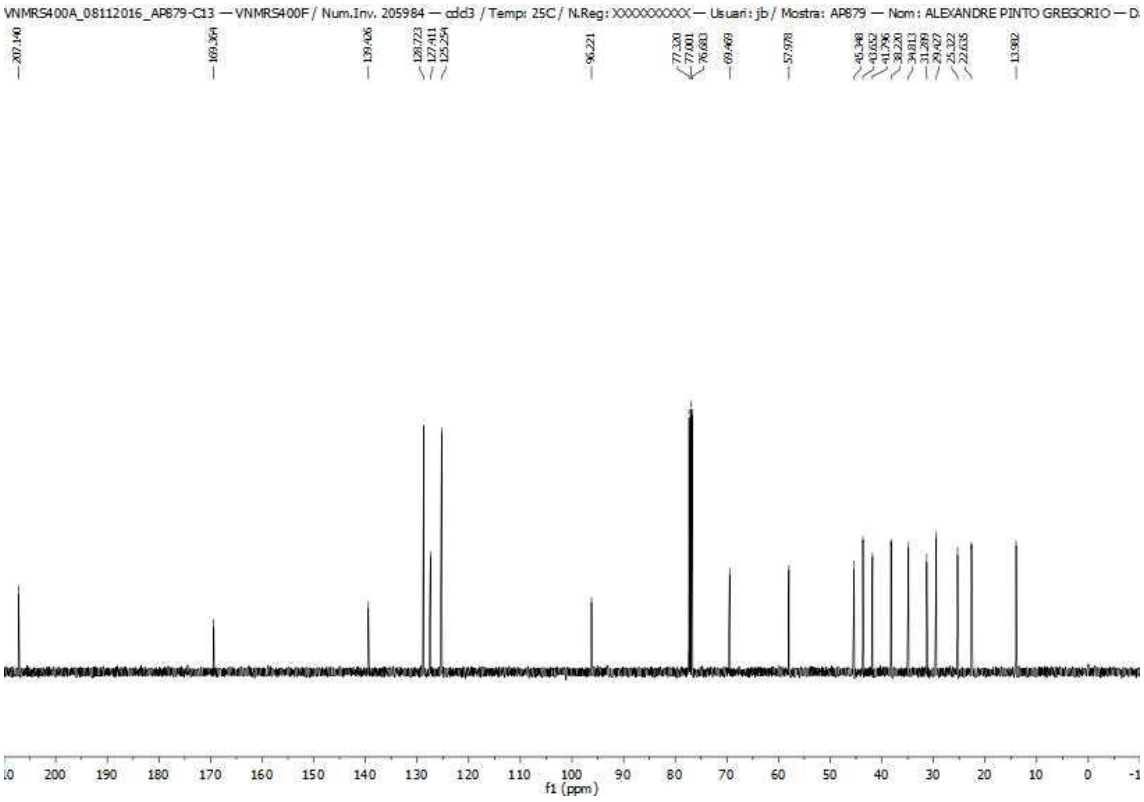
^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ: 0.91 (t, J = 6.8 Hz, 3H, CH_3), 1.25-1.37 (m, 4H, H-2', H-3'), 1.39-1.49 (m, 1H, H-1'), 1.57-1.66 (m, 1H, H-1'), 1.77-1.83 (m, 1H, H-8), 1.85-1.92 (m, 1H, H-7a), 1.93-2.01 (m, 1H, H-7), 2.03-2.11 (m, 1H, H-7), 2.42 (dd, J = 4.8, 16.0, Hz, 2H, H-9), 2.54 (ddd, J = 4.0, 10.8, 18.0 Hz, 1H, H-6), 2.64 (bs, 2H, H-11), 2.73 (dd, J = 4.0, 5.6 Hz, 1H, H-6), 3.94 (dd, J = 7.6, 8.8 Hz, 1H, H-2), 4.52 (t, J = 8.8 Hz, 1H, H-2), 5.41 (t, J = 8.2 Hz, 1H, H-3), 7.12 (d, J = 7.4 Hz, 2H, H-Ar), 7.24 (t, J = 7.4 Hz, 1H, H-Ar), 7.32 (t, J = 7.4 Hz, 2H, H-Ar).

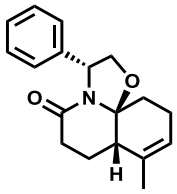
^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 14.0 (CH_3), 22.6 (C-3'), 25.3 (C-7), 29.4 (C-2'), 31.1 (C-6), 31.3 (C-1'), 38.2 (C-8), 41.8 (C-9), 43.7 (C-7a), 45.4 (C-11), 58.0 (C-3), 69.5 (C-2), 96.2 (C-11a), 125.3 (C-Ar), 127.4 (C-Ar), 128.7 (C-Ar), 139.4 (Cq-Ar), 169.4 (C-5), 207.1 (C-10).

HRMS calcd for [$C_{21}H_{22}NO_3$ + H^+]: 342.2064, found 342.2063.

$[\alpha]^{23}_D$ = – 80.1 (c 0.19, $CHCl_3$).


VNMRS400A_08112016_AP879-H1 — VNMRS400F / Num.Inv. 205984 — cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP879 — Nom: ALEXANDRE PINTO GREGORIO — Da
7.335
7.317
7.298
7.280
7.243
7.224
7.137
7.119
5.432
5.411
5.391
4.503
4.500
4.488
3.906
3.887
3.884
3.864
2.716
2.712
2.699
2.639
2.634
2.462
1.899
1.317
0.926
0.909
0.892
1.80
1.06
1.87
1.00
1.04
1.04
1.13
1.61
0.65
0.86
1.86
1.06
1.03
1.19
1.02
1.45
1.27
4.06
2.82
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


VNMRS400A_08112016_AP879-C13 — VNMRS400F / Num.Inv. 205984 — cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP879 — Nom: ALEXANDRE PINTO GREGORIO — D
207.140
169.364
139.406
128.723
127.411
125.254
96.221
77.320
77.001
76.683
69.469
57.978
45.248
43.652
41.396
36.233
34.011
31.289
29.427
25.322
22.635
13.982
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



(3*R*,7a*S*,11a*S*)-8-Methyl-5-oxo-3-phenyl-2,3,5,6,7,7a,10,11-octahydrooxazolo[2,3-*j*]quinoline (79)

Operating as described for the preparation of **70**, from methyl 2-methyl-6-oxocyclohexenepropionate (9.5 g, 48 mol), (*R*)-phenylglycinol (20 g, 145 mmol), and acetic acid (8.3 mL, 143 mmol) in benzene (750 mL), lactam **79** (9.6 g, 71%) was obtained after column chromatography (from 3:2 to 1:1 hexane−EtOAc).

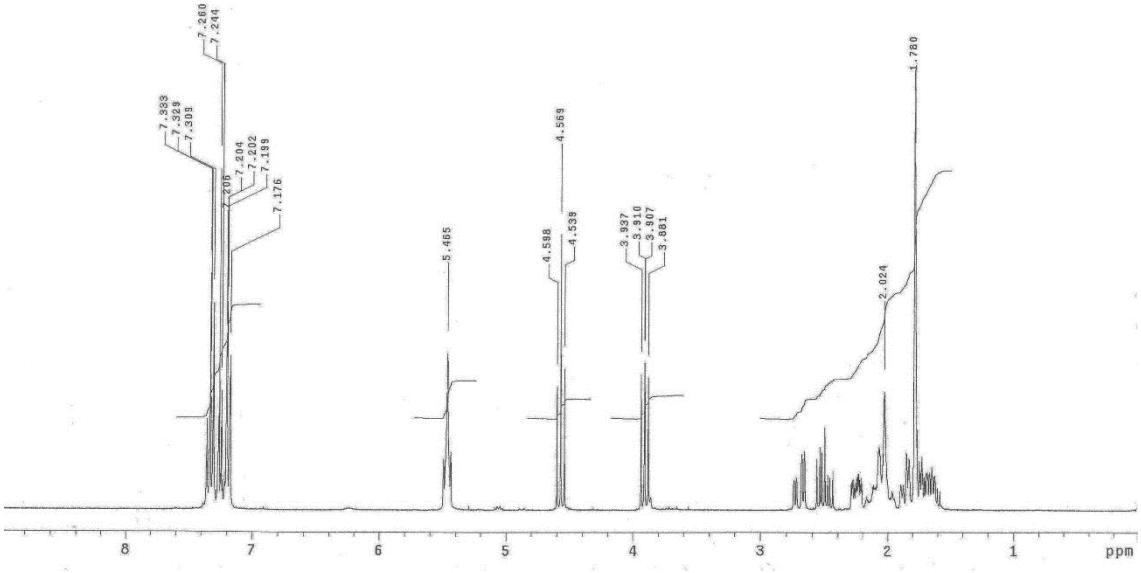
^{1}H-NMR (400 MHz, $CDCl_3$,) δ: 1.59-1.79 (m, 2H), 1.78 (s, 3H), 1.86 (dd, J = 13.2, 6.6 Hz, 1H), 1.96-2.13 (m, 3H), 2.20-2.29 (m, 1H), 2.44-2.56 (m, 1H), 2.70 (dd, J = 18.6, 6.0 Hz, 1H), 3.91 (t, J = 8.5 Hz, 1H), 4.57 (t, J = 8.5 Hz, 1H), 5.44-5.50 (m, 2H), 7.18-7.36 (m, 5H).

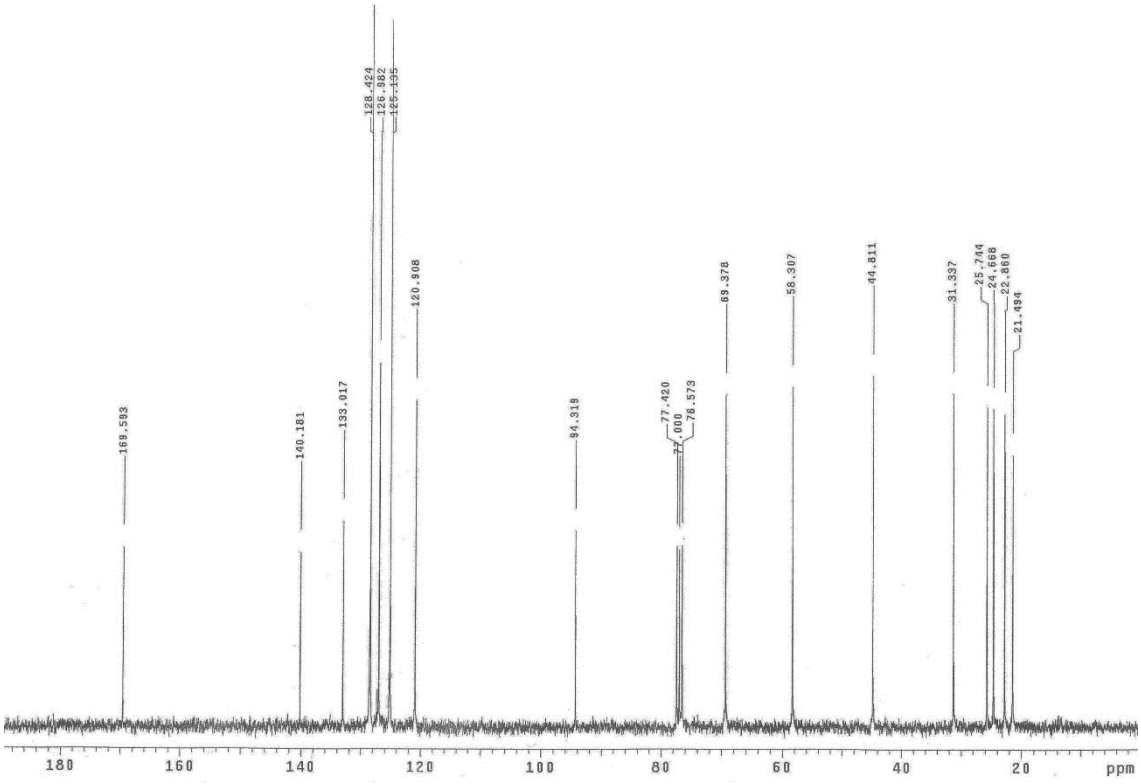
^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 21.5 (CH_3), 22.9 (CH_2), 24.7 (CH_2), 25.7 (CH_2), 31.3 (CH_2), 44.8 (CH), 58.3 (CH), 69.4 (CH_2), 94.3 (C), 120.9 (CH), 125.1 (2CH), 127.0 (CH), 128.4 (2CH), 133.0 (C), 140.2 (C*q*), 169.6 (NCO).

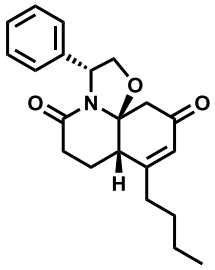
Elemental analysis for [$C_{18}H_{21}NO_2$]: C: 76.29%, H: 7.47%, N: 4.94%, found C: 76.60%, H: 7.52%, N: 4.92%.

$[\alpha]^{23}_{D}$ = – 102.6 (*c* 1,1, MeOH).

Melting point: 115−120 ºC.


7.260
7.244
7.383
7.329
7.309
7.204
7.202
7.199
7.176
5.465
4.569
4.588
4.539
3.937
3.910
3.907
3.881
2.024
1.780
8
7
6
5
4
3
2
1
ppm


169.593
140.181
133.017
128.424
126.382
120.908
84.318
77.420
77.000
76.573
69.378
58.307
44.811
31.337
25.744
24.668
22.860
21.494
180
160
140
120
100
80
60
40
20
ppm



(3*R*,7a*S*,11a*S*)-8-Butyl-5,10-dioxo-3-phenyl-2,3,5,6,7,7a,10,11-octahydrooxazolo[2,3-*j*]quinoline (80)

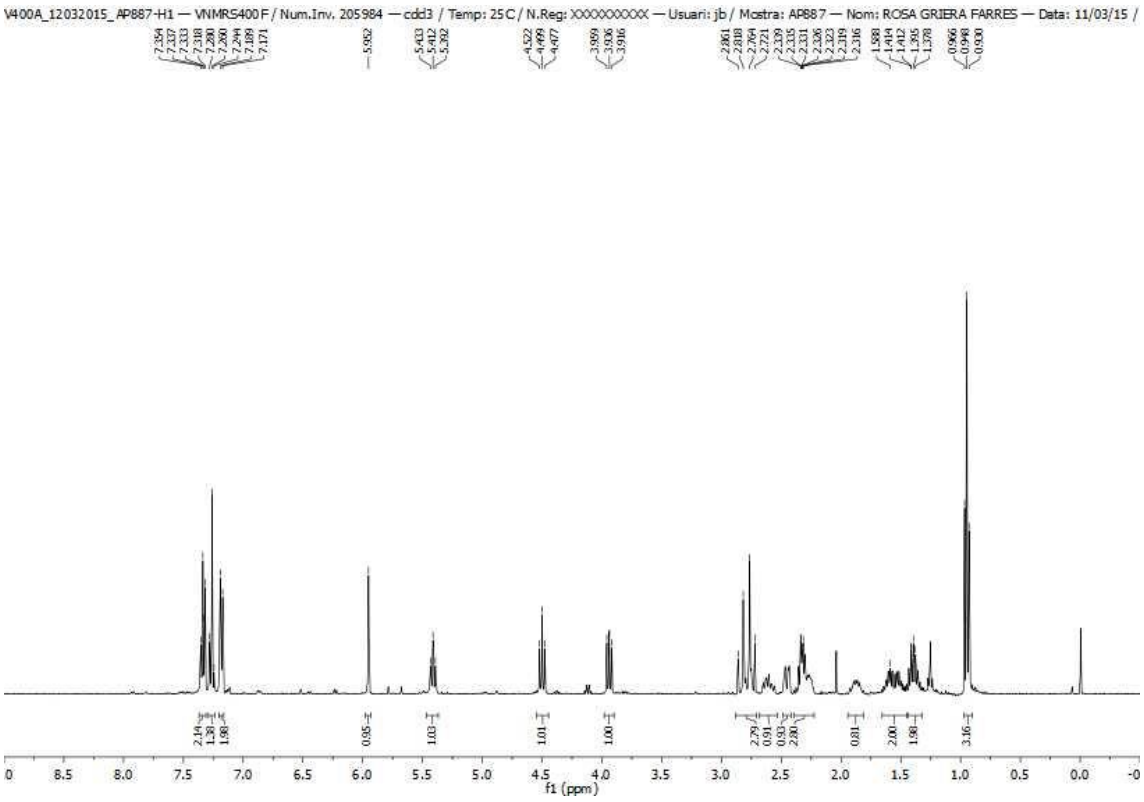
Operating as for the preparation of compound **72** *Method B* from lactam **74** (50 mg, 0.15 mmol), $Mn(OAc)_3$ (8.3 mg, 0.03 mmol), TBHP (140 μL, 5.5 M in decane, 0.77 mmol) and 3Å molecular sieves (180 mg) in EtOAc (9.0 mL), compound **80** (21 mg, 40%) was obtained as a colorless oil after flash chromatography (6:4, hexane−EtOAc).

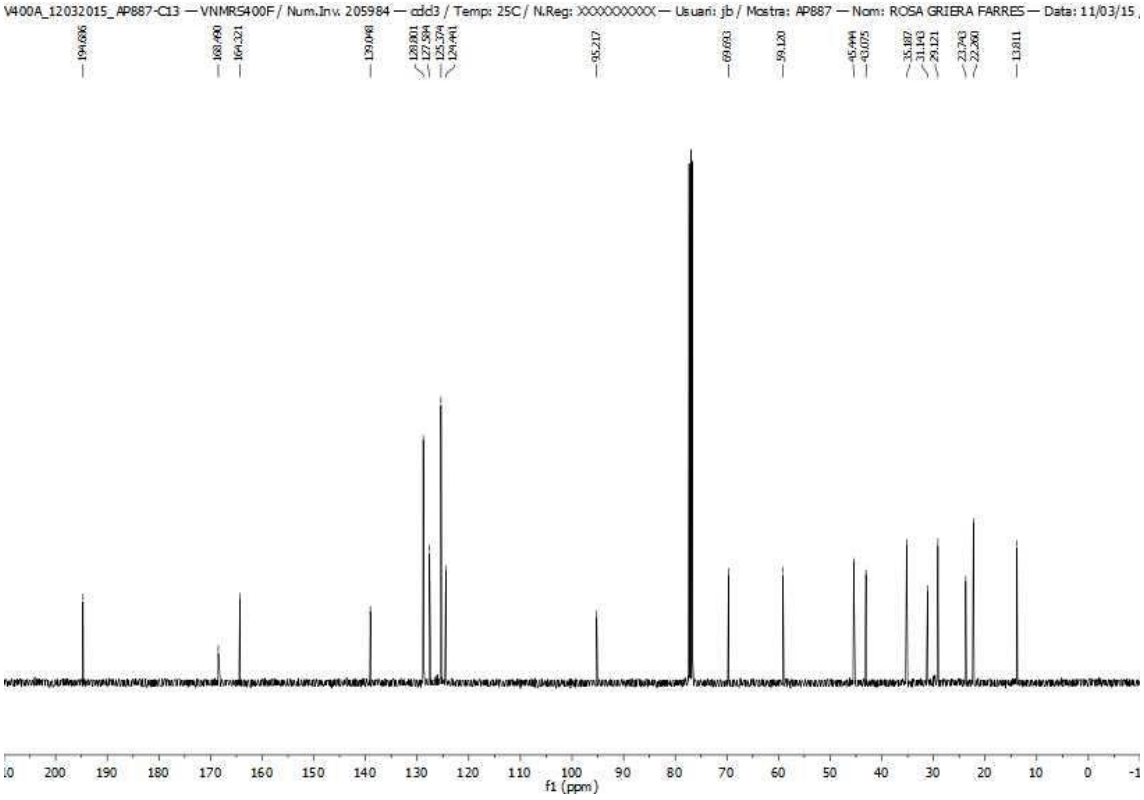
^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ: 0.95 (t, J = 7.4 Hz, 3H, CH_3), 1.34-1.43 (m, 2H, H-3'), 1.45-1.66(m, 2H, H-2'), 1.79-1.95 (m, 1H, H-1'), 2.21-2.40 (m, 3H, H-7, H-1'), 2.45 (dd, J = 3.6, 13.2 Hz, 1H, H-7a), 2.56-2.65 (m, 1H, H-6), 2.72-2.86 (m, 3H, H-6, H-11), 3.94 (t, J = 8.4 Hz, 1H, H-2), 4.50 (t, J = 8.4 Hz, 1H, H-2), 5.41 (t, J = 8.4 Hz, 1H, H-3), 5.95 (s, 1H, H-9), 7.18 (d, J = 7.4 Hz, 2H, H-Ar), 7.26 (t, J = 7.4 Hz, 1H, H-Ar), 7.34 (t, J = 7.4 Hz, 2H, H-Ar).

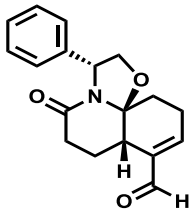
^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 13.8 (CH_3), 22.3 (C-3'), 23.7 (C-1'), 29.1 (C-2'), 31.1 (C-6), 35.2 (C-7), 43.1 (C-11), 45.4 (C-7a), 59.1 (C-3), 69.7 (C-2), 95.2 (C-11a), 124.5 (C-9), 125.4 (C-Ar), 127.6 (C-Ar), 128.8 (C-Ar), 139.1 (Cq-Ar), 164.3 (C-8), 168.5 (NCO), 194.7 (C=O).

HRMS calcd for [$C_{21}H_{25}NO_3$ + H^+]: 340.1907, found 340.1917.

$[\alpha]^{23}_D$ = – 97.1 (c 1.05, $CHCl_3$).


V400A_12032015_AP887-H1 — VNMRS400F / Num.Inv. 205984 — cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP887 — Nom: ROSA GRIERA FARRES — Data: 11/03/15 /
f1 (ppm)


V400A_12032015_AP887-C13 — VNMRS400F / Num.Inv. 205984 — cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP887 — Nom: ROSA GRIERA FARRES — Data: 11/03/15 ,
f1 (ppm)



(3*R*,7a*S*,11a*S*)-8-Formyl-5-oxo-3-phenyl-2,3,5,6,7,7a,10,11-octahydrooxazolo[2,3-*j*]quinolone (82)

Operating as for the preparation of compound **71**, from compound **79** (100 mg, 0.35 mmol), SeO_2 (169 mg, 1.52 mmol) in dry 1,4-dioxane (12 mL), crude aldehyde (105 mg, 99%) was obtained as a dark orange foam, after filtration over a short pad of silica.

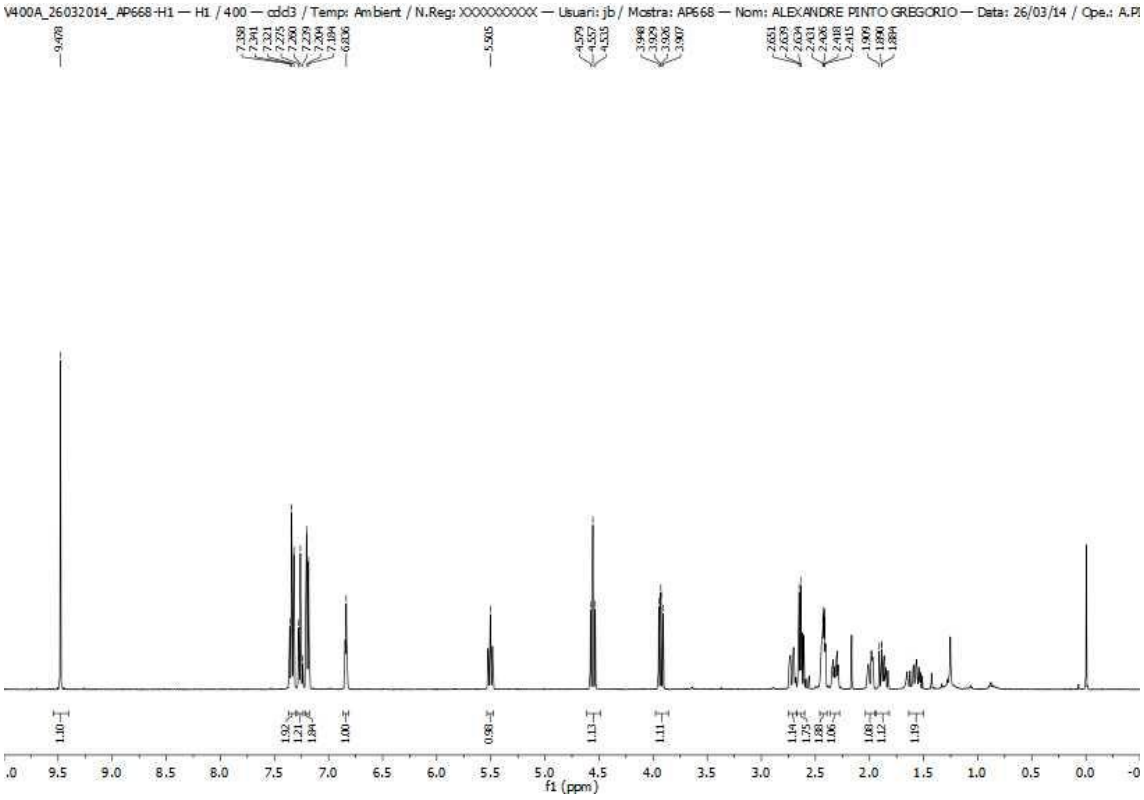
^{1}H-NMR (400MHz $CDCl_3$, COSY, HETCOR) δ: 1.59-1.62 (m, 1H, H-7), 1.80-1.92 (m, 1H, H-11), 1.94-2.04 (m, 1H, H-11), 2.25-2.36 (m, 1H, H-7), 2.39-2.47 (m, 2H, H-10), 2.55-2.59 (m, 2H, H-6), 2.69-2.75 (m, 1H, H-7a), 3.93 (t, J = 8.3 Hz, 1H, H-2), 4.56 (t, J = 8.3 Hz, 1H, H-2), 5.51 (t, J = 8.3 Hz, 1H, H-3), 6.84 (t, J = 3.6 Hz, 1H, H-9), 7.26 (t J = 7.2 Hz, 1H, Ar), 7.34 (t, J = 7.4 Hz, 2H, Ar), 9.48 (s, 1H, CHO).

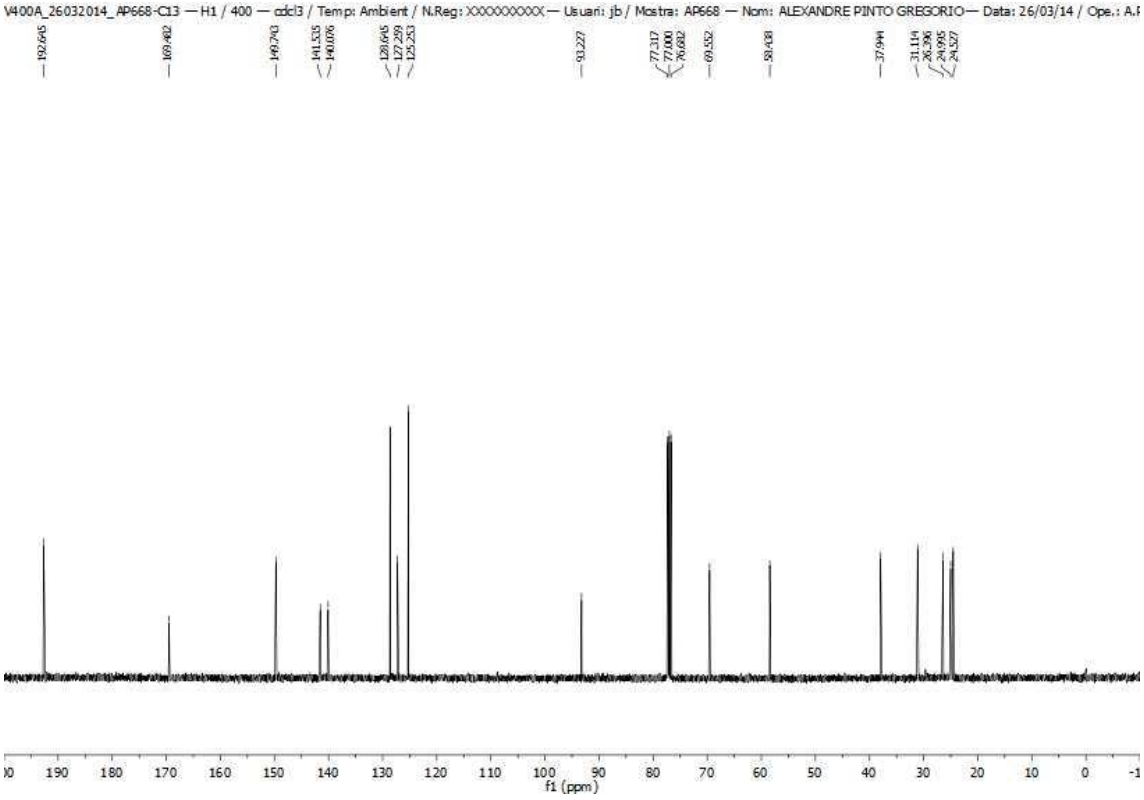
^{13}C-NMR (100.6MHz, $CDCl_3$) δ: 24.5 (C-10), 25.0 (C-7), 26.4 (C-11), 31.1 (C-6), 37.9 (C-7a), 58.4 (C-3), 69.6 (C-2), 92.2 (C-11a), 125.3 (C-Ar.), 127.3 (C-Ar.), 128.7 (C-Ar.), 140.1 (Cq-Ar.), 141.5 (C-8), 149.7 (C-9), 169.5 (C-5), 192.7 (CHO).

HRMS calcd for [$C_{18}H_{19}NO_3$ + H^+]: found 298.1438 found 298.1432.

$[\alpha]^{23}_D$ = – 128.7 (c 0.875, $CHCl_3$).

Melting point: 175−177 ºC.


V400A_26032014_AP668-H1 — H1 / 400 — cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP668 — Nom: ALEXANDRE PINTO GREGORIO — Data: 26/03/14 / Ope.: A.P
9.478
7.338
7.321
7.275
7.260
7.229
7.204
7.184
6.836
5.505
4.579
4.557
4.535
3.948
3.929
3.926
3.907
2.651
2.639
2.624
2.431
2.406
2.418
2.415
1.909
1.890
1.884
1.10
1.92
1.21
1.84
1.00
0.98
1.13
1.11
1.14
1.75
1.88
1.06
1.08
1.12
1.19
f1 (ppm)


V400A_26032014_AP668-C13 — H1 / 400 — cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP668 — Nom: ALEXANDRE PINTO GREGORIO — Data: 26/03/14 / Ope.: A.P
192.645
169.402
149.743
141.535
140.076
128.645
127.299
125.253
93.227
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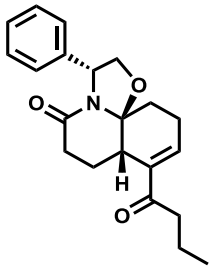
31.114
26.396
24.995
24.327
f1 (ppm)



(3*R*,7a*S*,11a*S*)-5-Oxo-8-(4-oxobutyl)-3-phenyl-2,3,5,6,7,7a,10,11-octahydrooxazolo[2,3-*j*]quinoline (83)

Operating as for the preparation of compound **71**, from compound **74** (50 mg, 0.15 mmol), SeO_2 (74 mg, 0.66 mmol) in dry 1,4-dioxane (5 mL), ketone **83** (47 mg, 89%) was obtained was obtained as an orange oil after flash chromatography (hexane: EtOAc 7:4) as a colorless oil.

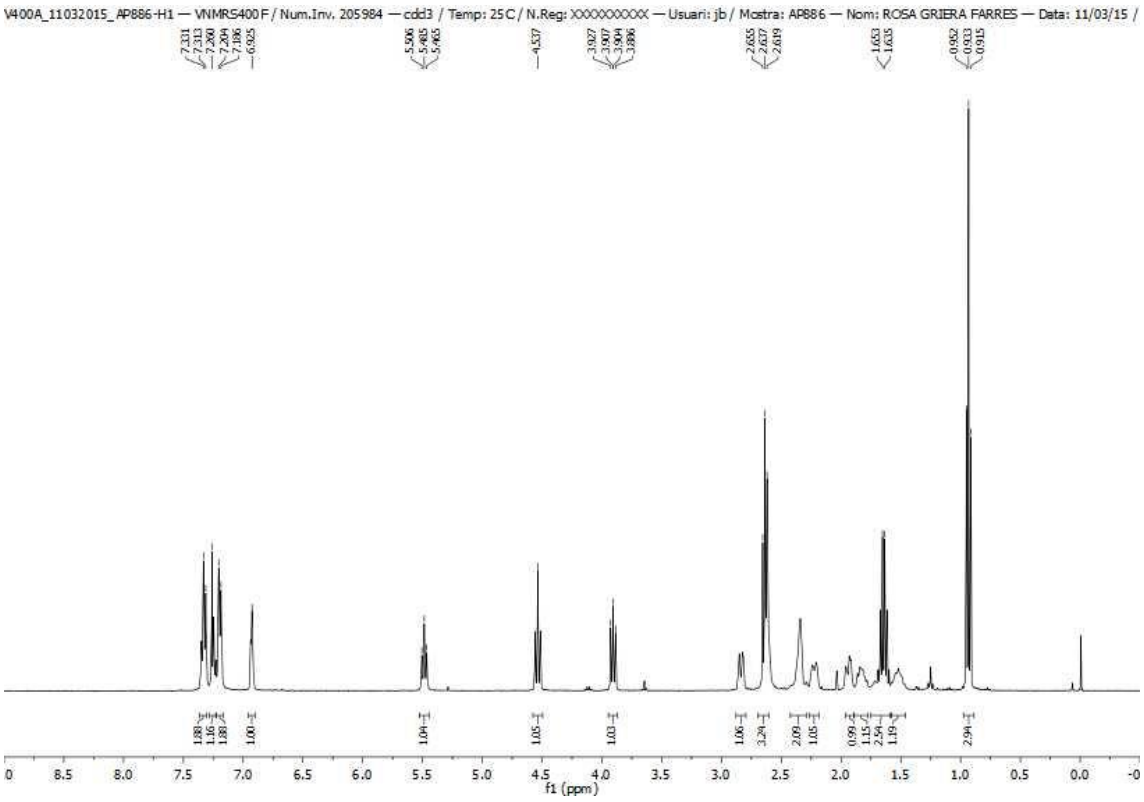
^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.93 (t, J = 7.4 Hz, 3H, CH_3), 1.47-1.58 (m, 1H, H-7), 1.59-1.74 (m, 2H, H-3'), 1.75-1.88 (m, 1H, H-11), 1.90-1.99 (m, 1H, H-11), 2.19-2.27 (m, 1H, H-7), 2.34 (bs, 2H, H-10), 2.57-2.69 (m, 4H, H-6, H-2'), 2.83 (d, J = 11.6 Hz, 1H, H-7a), 3.91 (t, J = 8.2 Hz, 1H, H-2), 4.54 (t, J = 8.2 Hz, 1H, H-2), 5.49 (t, J = 8.2 Hz, 1H, H-3), 6.93 (t, J = 3.4 Hz, 1H, H-9), 7.18 (d, J = 7.4 Hz, 2H, H-Ar), 7.25 (d, J = 5.2 Hz, 1H, Ar), 7.33 (t, J = 7.4 Hz, 2H, Ar).

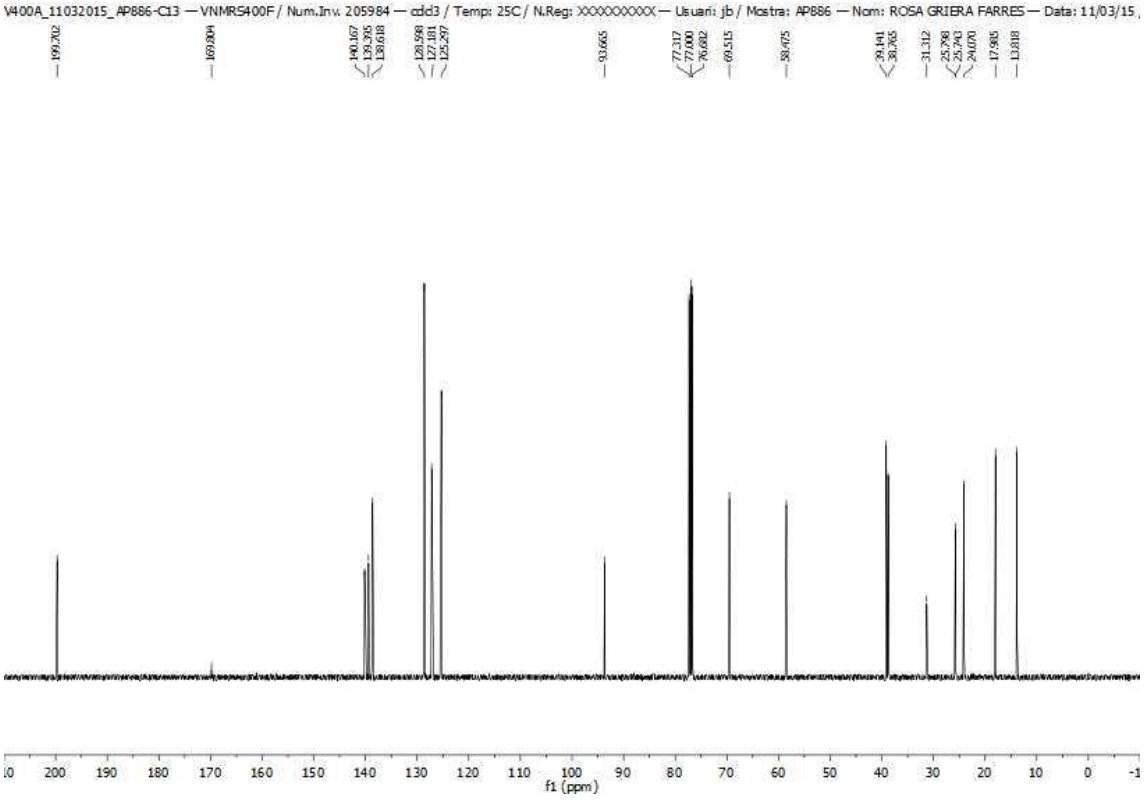
^{13}C-NMR (100.6MHz, $CDCl_3$) δ: 13.8 (CH_3), 18.0 (C-3'), 24.1 (C-10), 25.7 (C-11), 25.8 (C-7), 31.3 (C-6), 38.8 (C-7a), 39.1 (C-2'), 58.5 (C-3), 69.5 (C-2), 93.7 (C-11a), 125.3 (C-Ar), 127.2 (C-Ar), 128.6 (C-Ar), 138.6 (C-9) 139.4 (Cq-Ar), 140.2 (C-8), 169.8 (NCO), 199.7 (C=O).

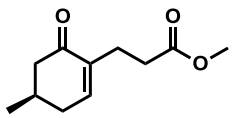
IR (NaCl): 1663 cm^{-1}.

HRMS calcd for [$C_{21}H_{25}NO_3$ + H^+]: 340.1907, found 340.1911.

$[\alpha]^{23}_D$= – 181.8 (c 1.1, $CHCl_3$).


V400A_11032015_AP886-H1 — VNMRS400F / Num.Inv. 205984 — cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP886 — Nom: ROSA GRIERA FARRES — Data: 11/03/15 /
7.331
7.311
7.260
7.209
7.186
6.925
5.506
5.485
5.465
4.537
3.927
3.907
3.904
3.886
2.655
2.637
2.619
1.653
1.635
0.952
0.933
0.915
1.81
1.16
1.88
1.00
1.04
1.05
1.03
1.06
3.24
2.09
1.05
0.99
1.15
2.54
1.19
2.94
f1 (ppm)


V400A_11032015_AP886-C13 — VNMRS400F / Num.Inv. 205984 — cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP886 — Nom: ROSA GRIERA FARRES — Data: 11/03/15 /
199.702
169.009
140.167
139.395
138.618
128.598
127.181
125.297
93.665
77.317
77.000
76.682
69.515
58.675
39.141
38.765
31.312
25.798
25.743
24.070
17.985
13.818
f1 (ppm)



Methyl (*R*)-4-methyl-6-oxocyclohexenepropionate (86)

1st step: 5 M aqueous KOH (12.5 mL) was slowly added to a stirring solution of (*R*)-pulegone (1.35 g, 8.71 mmol) and 30% H_2O_2 (12.5 mL) in MeOH (25 mL), at 0 ºC. After the addition of the KOH was completed, the reaction was stirred at room temperature for 4 h. The reaction mixture was poured into brine and extracted with Et_2O. The combined organic extracts were dried and concentrated, affording a colorless oil.

2nd step: PhSH (1.78 mL, 17.4 mmol) in dry THF (73 mL) was slowly added to a stirring suspension of NaH (440 mg, 17.4 mmol) in dry THF (29 mL), after the evolution of H_2 stopped, stirring was continued for 40 minutes at room temperature. The above crude in dry THF (58 mL) was then added *via* cannula and the resulting mixture was heated at reflux for 18 h. After cool to room temperature saturated aqueous NH_4Cl was added to quench the reaction, and the resulting mixture was stirred at this temperature for an additional 1 h. The phases were separated, and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and 5% aqueous NaOH, dried and concentrated to afford crude mixture of thioethers, which were used without further purification in the next step.

3rd step: *m*-CPBA (2.15 g, 9.58 mmol, 77%) in CH_2Cl_2 (50 mL) was added to a stirring solution of the above crude thioethers in CH_2Cl_2 (180 mL) at –78 ºC. After 5 h of stirring at –78 ºC saturated aqueous $NaHCO_3$ was added, the phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated aqueous $NaHCO_3$, and brine, dried and concentrated. The obtained mixture of sulfoxides was used without further purification.

4th step: DBU (1.43 mL, 9.57 mmol) in dry DMF (17 mL) and methyl acrylate (860 □L, 9.58 mmol) in dry DMF (17 mL) were sequentially added to a solution of the above sulfoxides in dry DMF (22 mL) at –40 ºC. The resulting mixture was allowed to slowly warm to room temperature and stirred overnight. Saturated aqueous NH_4Cl was added to quench the reaction, followed by dilution with Et_2O, the phases were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried and concentrated. Flash chromatography (6:4, hexane–EtOAc), afforded keto ester **86** (1.21 g, 71% overall yield) as a dark orange oil.

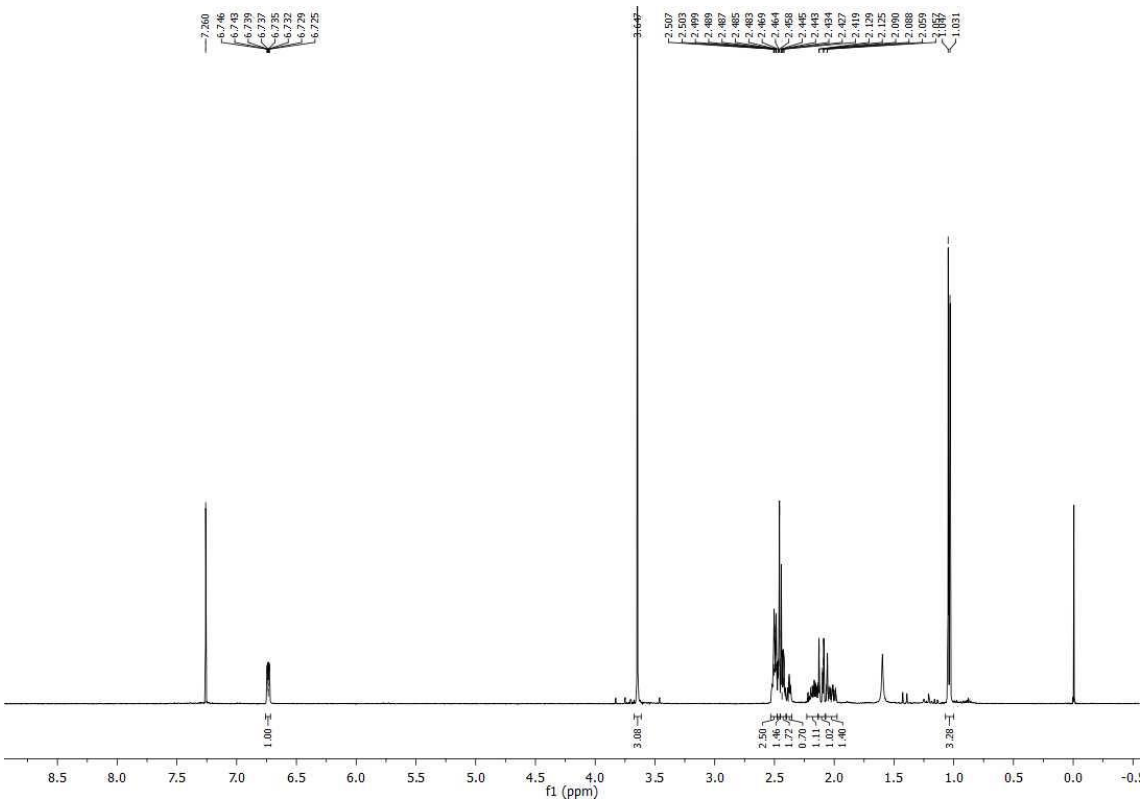
^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ 1.04 (d, J = 6.4 Hz, 3H, CH_3), 1.99-2.07 (m, 1H), 2.09-2.13 (m, 1H), 2.14-2.22 (m, 1H, H-5), 2.36-2.99 (m, 1H), 2.41-2.45 (m, 2H), 2.46-2.47 (m, 1H), 2.48-2.51 (m, 2H), 3.65 (s, 3H, OCH_3), 6.93 (ddd, J = 1.4, 2.6, 5.4 Hz, 1H, H-3).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ 21.1 (CH_3), 25.3 (CH_2), 30.5 (C-5), 33.0 (CH_2COO) 34.3 (C-4), 46.5 (C-6), 51.5 (OCH_3), 137.8 (C-2), 143.6 (C-3), 173.6 (COO), 199.3 (C=O).

IR (NaCl): 1736, 1668 cm^{-1}.

HRMS calcd for [$C_{11}H_{16}O_3$ + H^+]: 197.1172, found 197.1179.

$[\alpha]^{23}_{D}$ = – 50.3 (c 1.05, $CHCl_3$).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2.090
2.088
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2.057
1.047
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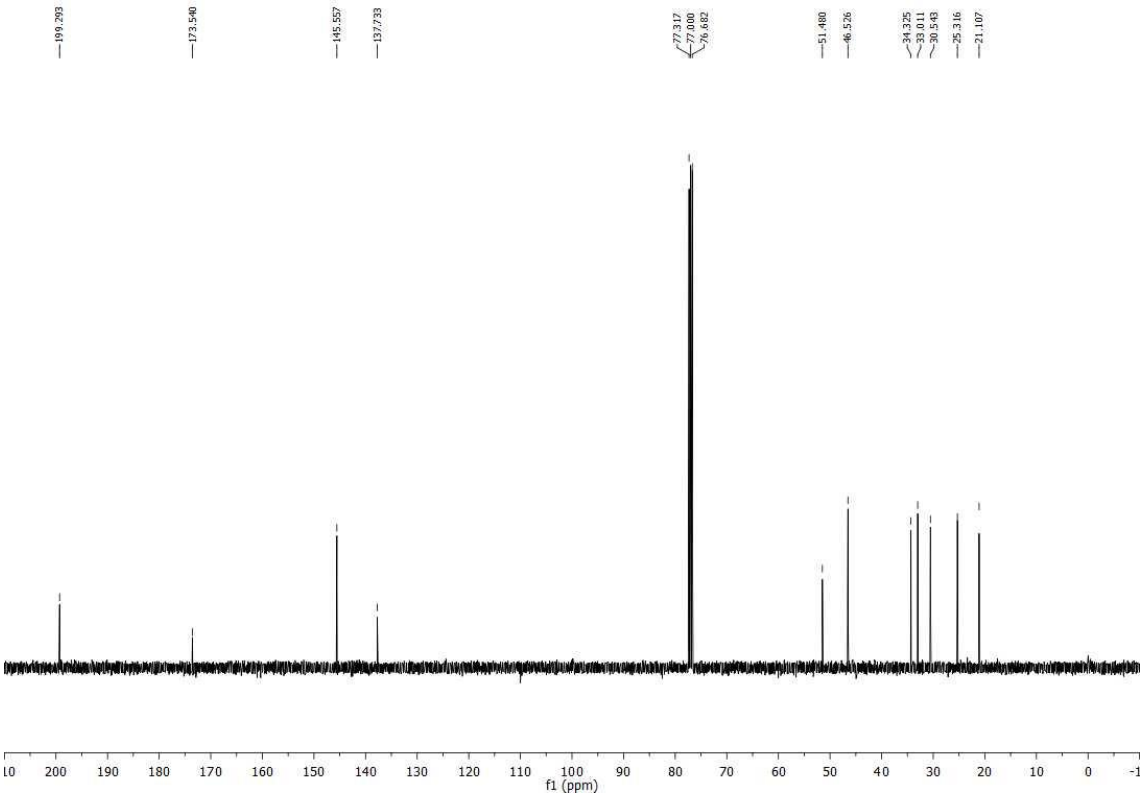
3.28
f1 (ppm)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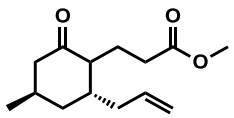
f1 (ppm)



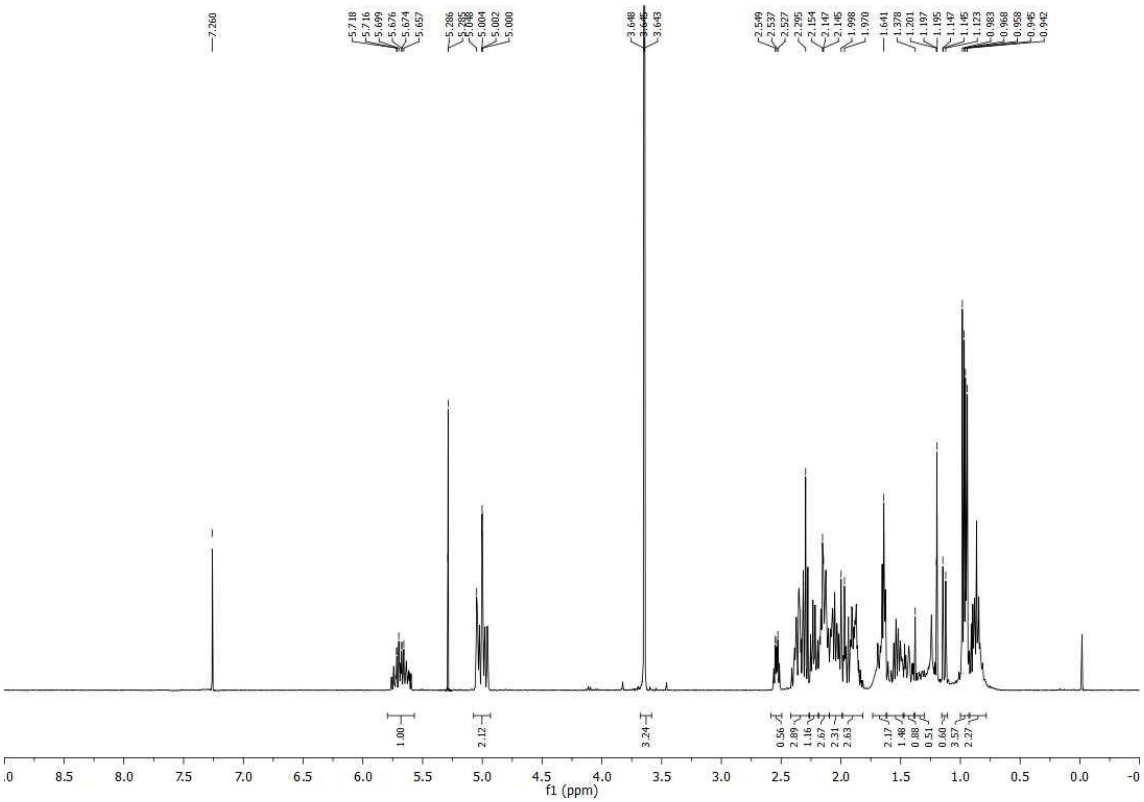
Methyl (2*R*,4*R*)-2-allyl-4-methyl-6-oxocyclohexenepropionate (90)

A solution of compound **86** (4.0 g, 20.4 mmol) in dry CH_2Cl_2 (8.0 mL), TMSCl (13 mL, 102 mmol) and AllylTMS (3.57 mL, 22.44 mmol) were added sequentially to a solution of $InCl_3$ (451 mg, 2.04 mmol) in dry CH_2Cl_2 (68 mL), and the resulting mixture was stirred at room temperature for 4 h. Saturated aqueous $NaHCO_3$ was added to quench the reaction, the phases were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated. Flash chromatography (96:4 hexane–EtOAc), afforded keto ester **90** (4.8 g, 99%; 1:1 mixture of diastereoisomers) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ: 0.84-0.91 (m, 2H), 0.95 and 0.97 (d, J = 6.4 Hz, 3H, CH_3), 1.12-1.15 (m, 1H), 1.82-1.98 (m, 2H), 2.00-2.09 (m, 2H), 2.10-2.18 (m, 3H), 2.19-2.25 (m, 1H), 2.28-2.41 (m, 3H), 2.51-2.56 (m, 1H), 3.65 (s, 3H), 4.94-5.06 (m, 2H), 5.58-5.77 (m, 1H).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 21.0 and 22.2 (CH_3), 21.9 (CH_2), 24.7 (CH_2), 29.4 and 29.6 (CH), 31.7 and 31.8 (CH_2), 32.0 (CH_2), 34.3 (CH_2), 36.6 (CH_2), 37.9 (CH_2), 40.4 (CH), 50.4 (CH_2), 51.5 and 51.6 (OCH_3), 53.7 (CH), 116.4 and 117.0 (CH_2), 136.3 and 135.7 (CH), 173.6 and 173.9 (COO), 211.8 and 213.5 (CO).

HRMS calcd for [$C_{14}H_{22}O_3$ + H^+]: 239.1642, found 239.1639.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2.549
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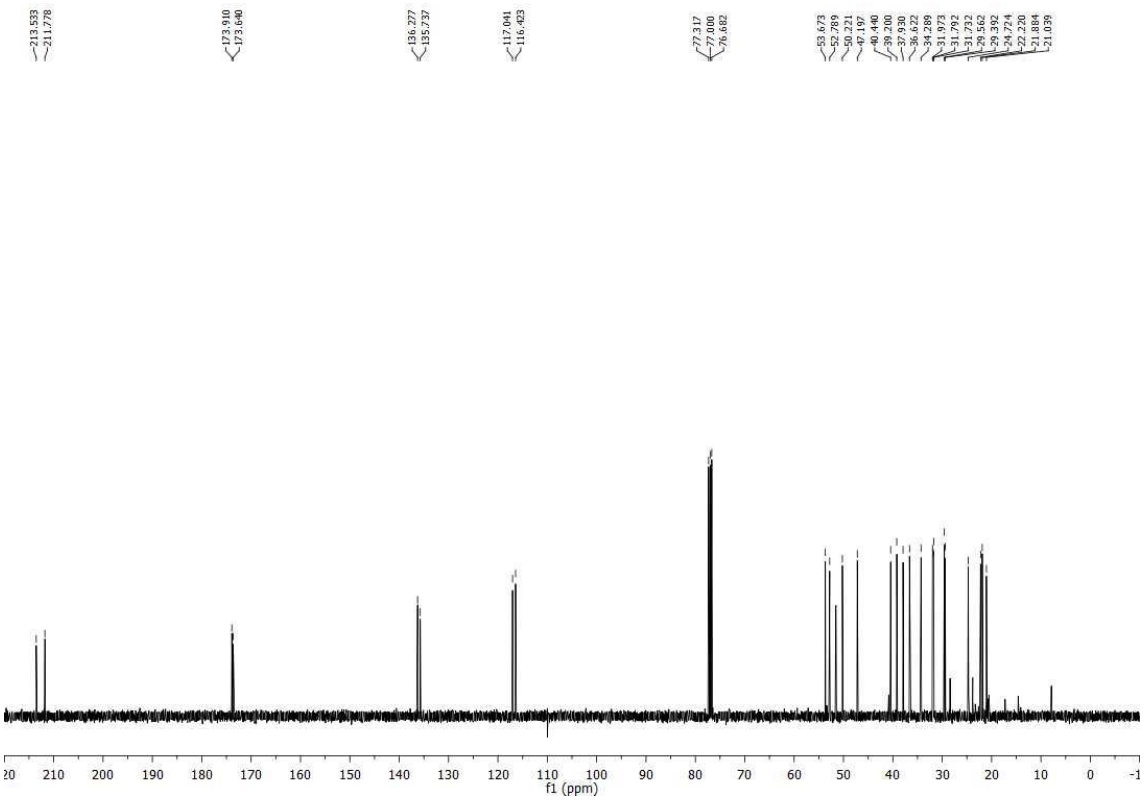
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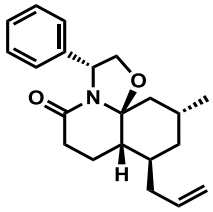
f1 (ppm)



(3*R*,7a*S*,8*R*,10*R*,11a*S*)-8-Allyl-10-methyl-5-oxo-3-phenylperhydrooxazolo[2,3-*j*]quinoline (91)

(*R*)-Phenylglycinol (390 mg, 2.84 mmol) was added to a solution of keto ester **90** (450 mg, 1.89 mmol) and AcOH (160 µL, 2.84 mmol) in benzene (15 mL). The mixture was heated at reflux with azeotropic elimination of water by a Dean-Stark system. After 24 h, the mixture was cooled to room temperature and concentrated, and the resulting oil was taken up in EtOAc. The organic solution was washed with saturated aqueous NaHCO3, 1 N aqueous HCl and brine, dried, and concentrated. Flash chromatography (4:6 hexane–EtOAc) afforded pure lactam **91** (503 mg, 82%) as a white/orange solid.

^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) *δ:* 0.85 (d, *J* = 6.8 Hz, 3H, CH_3), 1.24-1.36 (m, 2H, H-9, H-11), 1.50-1.54 (m, 1H, H-11), 1.66-1.83 (m, 5H, H-1', H-7, H-8, H-9, H-10), 2.04-2.17 (m, 1H, H-7), 2.30-2.36 (m, 1H, H-1'), 2.40-2.42 (m, 1H, H-11), 2.46 -2.52 (m, 1H, H-6) 2.58-2.66 (m, 1H, H-6), 3.84 (dd, *J* = 5.8, 9.0 Hz, 1H, H-2), 4.91 (t, *J* = 8.6 Hz, 1H, H-2), 5.00-5.10 (m, 2H, CH=C*H*2), 5.29 (t, *J* = 8.6 Hz, 1H, H-3), 5.70- 5.82 (m, 1H, C*H*=CH2), 7.15-7.19 (m, 2H, H-Ar), 7.20-7.26 (m, 1H, H-Ar), 7.29-7.35 (m, 2H, H-Ar).

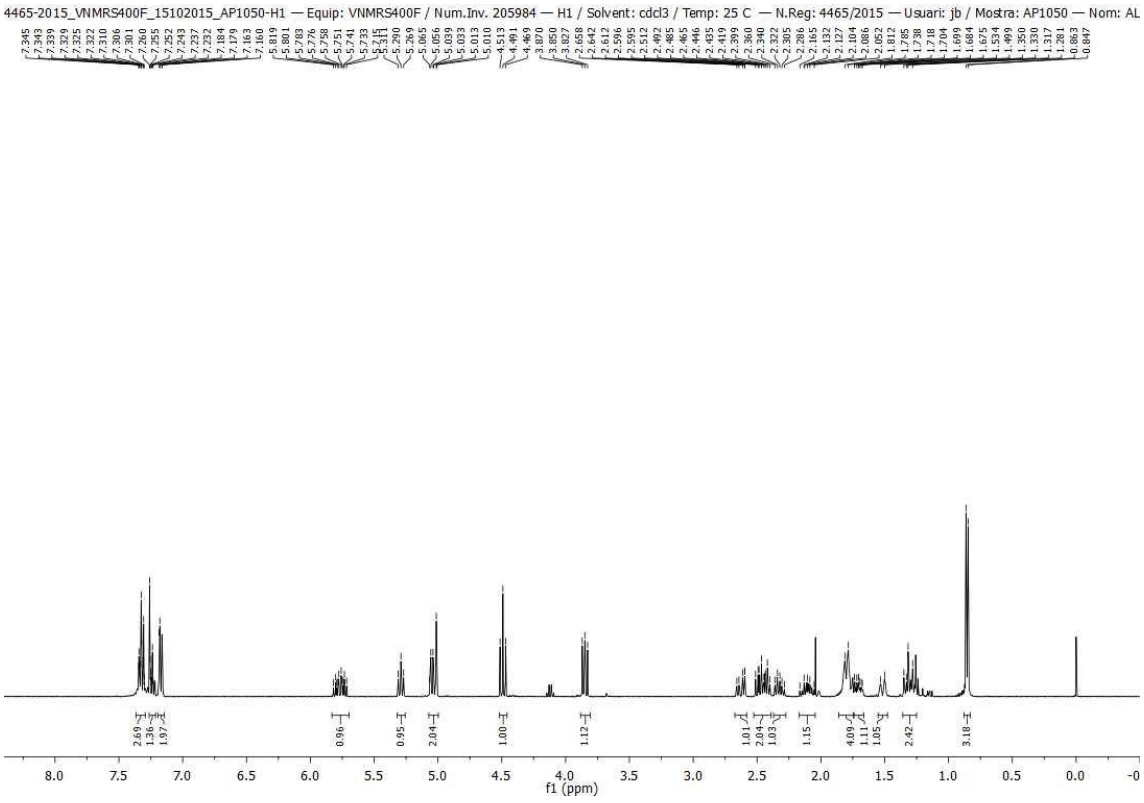
^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ:* 22.0 (CH_3), 24.2 (C-10), 24.6 (C-7), 31.1 (C-6), 33.1 (C-11), 38.3 (C-1'), 38.9 (C-9), 39.8 (C-8), 42.3 (C-7a), 58.2 (C-3), 69.6 (C-2), 96.0 (C-11a), 116.2 (C=*C*H_2), 125.4 (2C-H_{Ar}), 127.1 (C-H_{Ar}), 128.6 (2C-H_{Ar}), 138.2 (*C*H=C), 140.3 (Cq-Ar), 169.5 (NCO).

IR (film): 3068, 1657, 1453 cm^{-1}.

HRMS calcd for [$C_{21}H_{27}NO_2$ + H^+]: 326.2115, found 326.212.

$[\alpha]^{23}_D$ = – 72.9 (c 1.05, $CHCl_3$).

Melting point: 95–97 ºC.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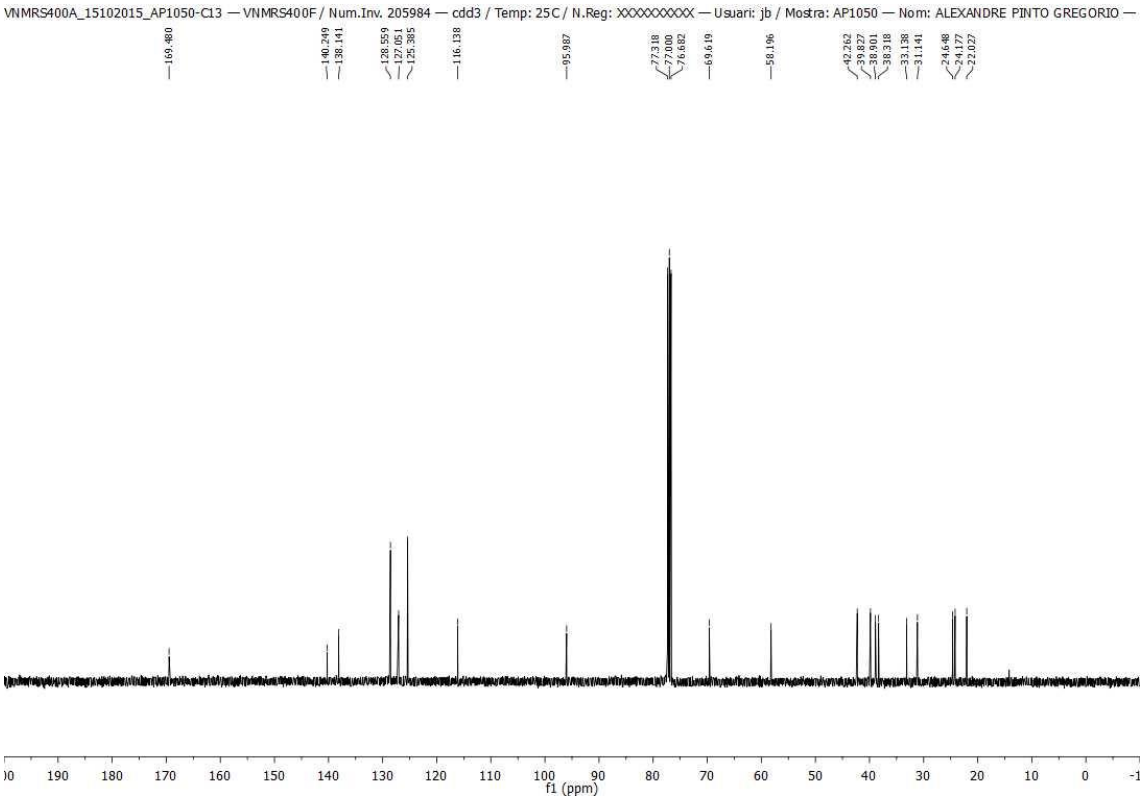
f1 (ppm)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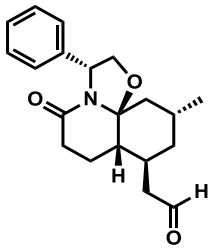
f1 (ppm)



(3*R*,7a*S*,8*S*,10*R*,11a*S*)-10-Methyl-5-oxo-8-(2-oxoethyl)-3-phenylperhydro-oxazolo[2,3-*j*]quinoline (92)

$RuCl_3.nH_2O$ in H_2O (1.54 mL, 0.054 mmol, 0.035 M stock solution) was added to a solution of lactam **91** (500 mg, 1.54 mmol) in MeCN (9.2 mL) under vigorous stirring. $NaIO_4$ (659 mg, 3.08 mmol) was then added in portions over 5 min, and the stirring was continued for 1 h 20 min. Saturated aqueous $Na_2S_2O_3$ was added, the resulting mixture was diluted with EtOAc, the phases were separated, and the aqueous solution was extracted with EtOAc. The combined organic extracts were dried and concentrated. Flash chromatography (4:6 hexane–EtOAc) afforded aldehyde **92** (370 mg, 74%) as a sticky white foam.

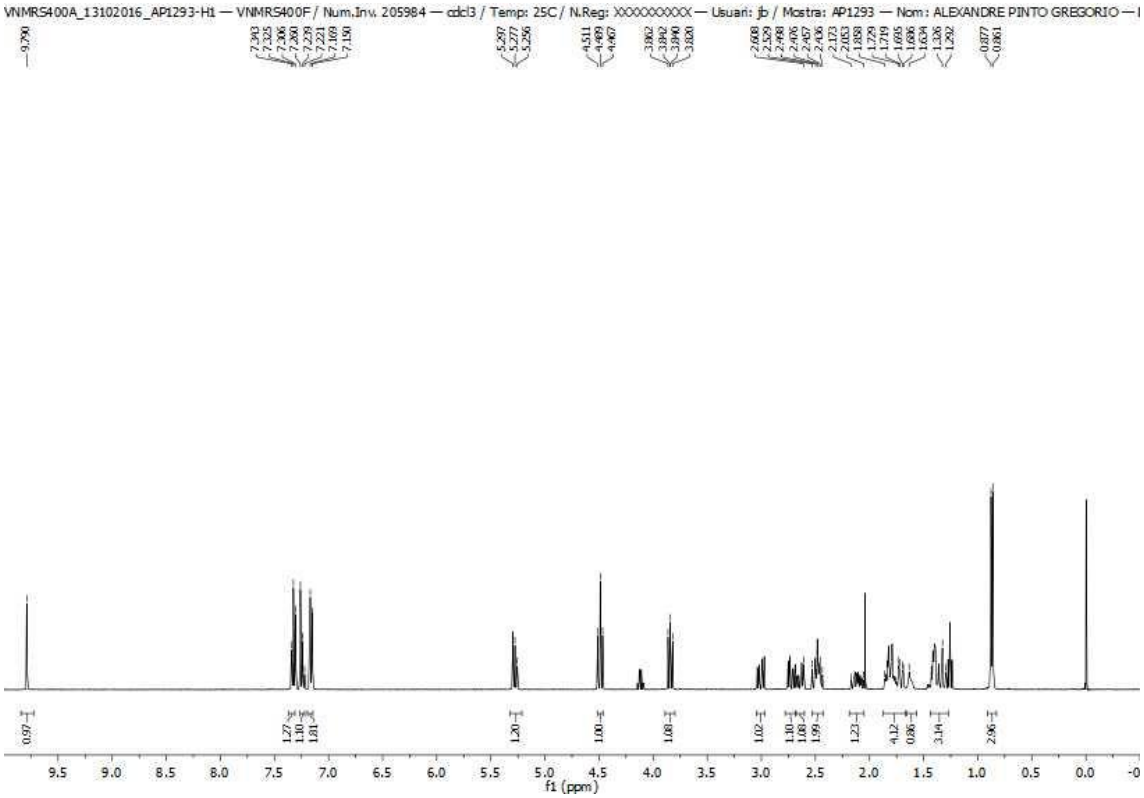
^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) *δ:* 0.87 (d, *J* = 6.4 Hz, 3H, CH_3), 1.29-1.43 (m, 3H, H-9, H-11), 1.69-1.73 (m, 1H, H-7a), 1.76-1.85 (m, 3H, H-7, H-9 H-10), 2.05-2.17 (m, 1H, H-7), 2.44-2.53 (m, 2H, H-6 and H-8), 2.61-2.68 (m, 1H, H-6), 2.72 (dd, *J* = 1.8, 7.2 Hz, 1H, H-1'), 3.01 (dd, *J* = 1.8, 7.2 Hz, 1H, H-1'), 3.84 (dd, *J* = 8.0, 8.4 Hz, 1H, H-2), 4.49 (t, *J* = 8.4 Hz, 1H, H-2), 5.28 (t, *J* = 8.4 Hz, 1H, H-3), 7.15-7.26 (m, 2H, H-Ar), 7.30-7.31 (m, 1H, H-Ar), 7.32-7.35 (m, 2H, H-Ar), 9.79 (s, 1H, CHO).

^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ:* 21.8 (CH_3), 24.1 (C-7), 24.4 (C-10), 31.0 (C-6), 33.2 (C-5), 33.6 (C-8), 38.6 (C-9), 42.9 (C-7a), 48.7 (C-1'), 58.3 (C-3), 69.7 (C-2), 95.6 (C-11a), 125.3 (2C-H_{Ar}), 127.1 (C-H_{Ar}), 128.6 (2C-H_{Ar}), 140.0 (Cq-Ar), 169.2 (NCO), 202.3 (CHO);

IR (film): 2947, 2717 and 1714, 1652 cm^{-1}.

HRMS calcd for [$C_{20}H_{25}NO_3$ + H^+]: 327.1834, found 328.1908.

$[\alpha]^{23}_D$ = – 57.5 (c 0.75, $CHCl_3$).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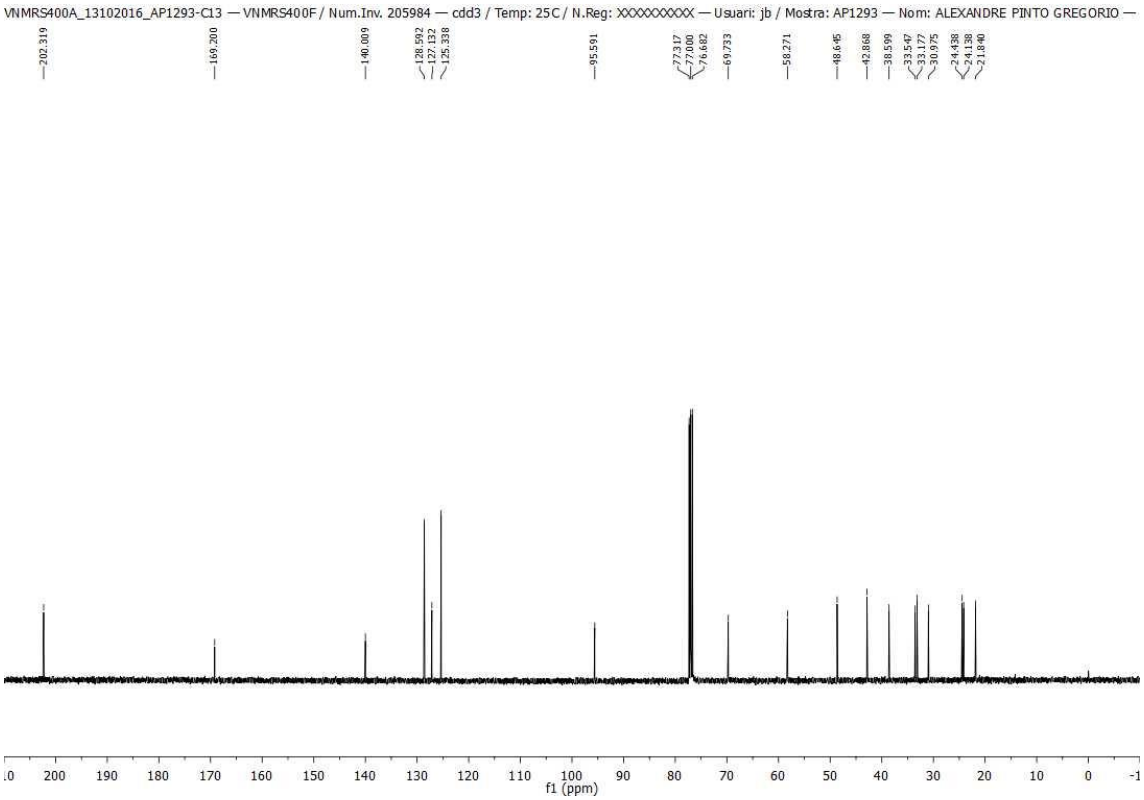
f1 (ppm)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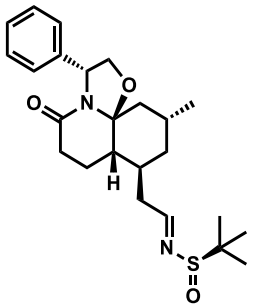


(3*R*,7a*S*,8*S*,10*R*,11a*S*)-8-[(*R*,*E*)-2-(*tert*-Butylsulfinylimino)ethyl]-10-methyl-5-oxo-3-phenylperhydrooxazolo[2,3-*j*]quinoline (95)

(R)-2-Methyl-2-propanesulfinamide (75 mg, 0.62 mmol) was added to a solution of the aldehyde **92** (184 mg, 0.56 mmol) and Ti(*i*OPr)$_4$ (330 µL, 1.12 mmol) in anhydrous THF (2.4 mL) under vigorous stirring. After 7 h at room temperature, brine was added under vigorous stirring, and the mixture was diluted with EtOAc. The suspension was filtered over Celite® and washed with EtOAc. The filtrate was dried and concentrated. Flash chromatography (4:6 hexane–EtOAc) afforded compound **95** (202 mg, 83%) as a sticky white foam.

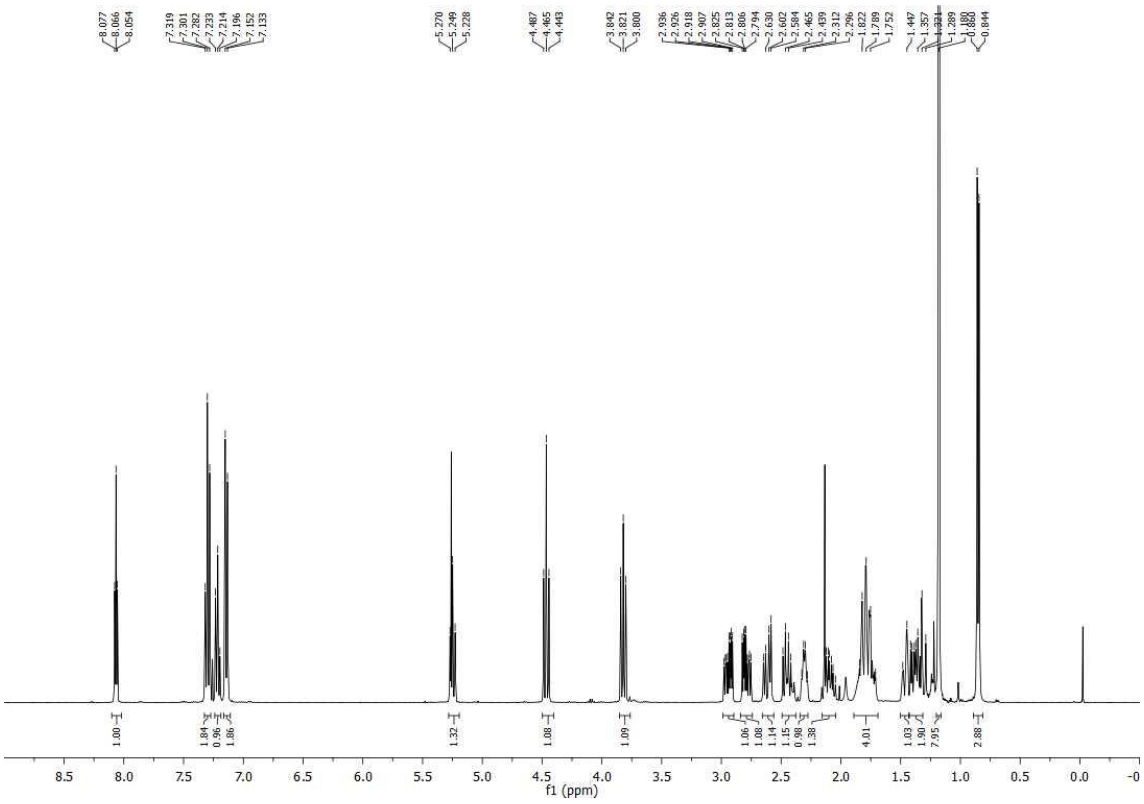
^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) *δ:* 0.85 (d, *J* = 6.8 Hz, 3H, CH3), 1.18 [br.s, 9H, C(C*H*3)], 1.33-1.42 (m, 2H, H-9, H-11), 1.44-1.49 (m, 1H, H-11), 1.71-1.85 (m, 4H, H-7, H-7a, H-9, H-10), 2.07-2.14 (m, 1H, H-7), 2.28 -2.33 (m, 1H, H-8), 2.39-2.49 (m, 1H. H-6), 2.62 (dd, *J* = 8.8, 18.4 Hz, 1H, H-6), 2.78 (ddd, *J* = 4.6, 7.6, 12.2 Hz, 1H, H-1'), 2.95 (ddd, *J* = 4.6, 7.6, 12.2 Hz, 1H, H-1'), 3.82 (dd, *J* = 0.8, 8.6 Hz, 1H, H-2), 4.47 (t, *J* = 8.6 Hz, 1H, H-2), 5.25 (t, *J* = 8.6 Hz, 1H, H-3), 7.14 (d, *J* = 7.6 Hz, 2H, H-Ar), 7.21 (t, *J* = 7.4 Hz 1H, H-Ar), 7.30 (t, *J* = 7.4 Hz, 2H, H-Ar), 8.07 (t, *J* = 4.6 Hz, H-2').

^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ:* 21.8 (CH3), 22.3 [C(*C*H3)], 24.2 (C-10 and C-7), 30.9 (C-6), 33.3 (C-11), 36.6 (C-8), 38.5 (C-9), 40.3 (C- 1'), 42.8 (C-7a), 56.6 [*C*(CH3)], 58.2 (C-3), 69.6 (C-2), 95.5 (C-11a), 125.2 (2C-H_{Ar}), 127.0 (C-H_{Ar}), 128.5 (2C-H_{Ar}), 139.9 (Cq-Ar), 169.0 (NCO), 169.2 (HC=NSO).

IR (NaCl): 1648, 1615, 1083 cm^{-1}.

HRMS calcd for [$C_{24}H_{34}N_2O_3S$ + H^+]: 431.2363, found 431.2364.

$[\alpha]^{23}_D$ = – 145 (c 0.535, $CHCl_3$).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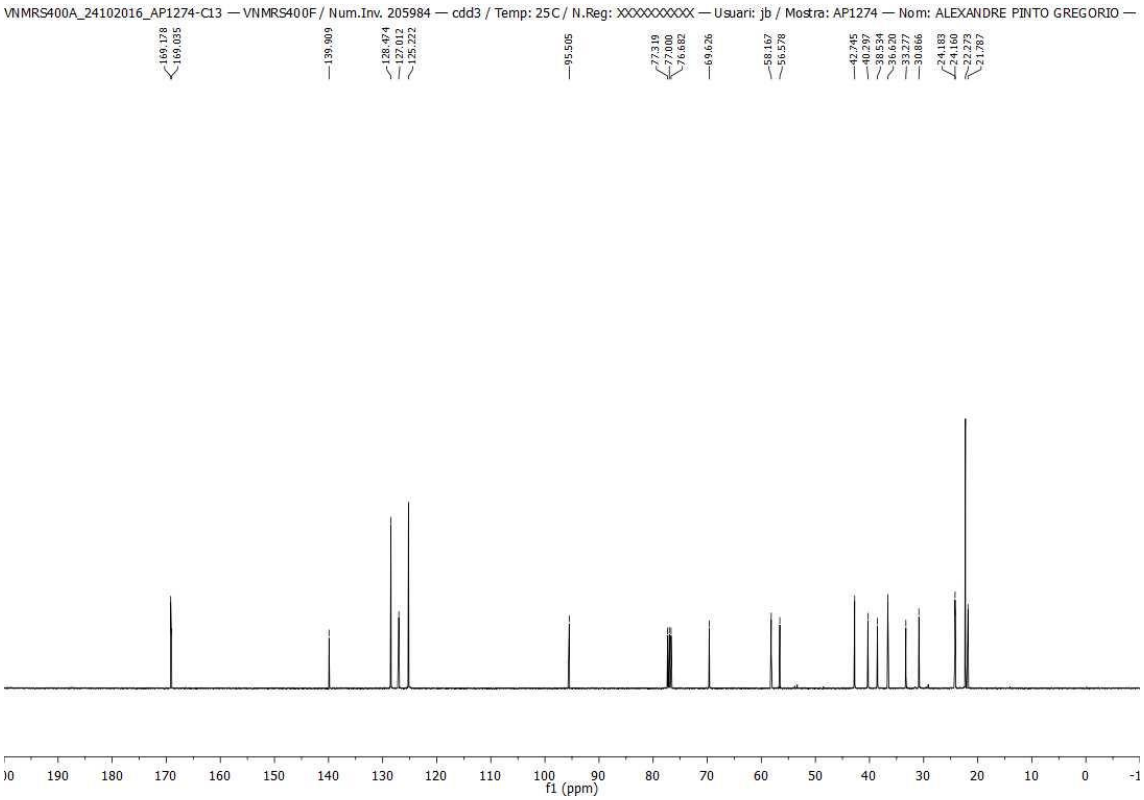
f1 (ppm)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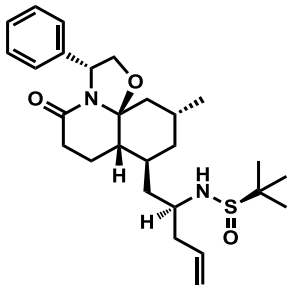
169.178
169.035
139.909
128.474
127.012
125.222
95.505
77.319
77.000
76.682
69.626
58.167
56.578
42.745
40.297
38.534
36.620
33.277
30.866
24.183
24.160
21.273
21.767
f1 (ppm)



(3*R*,7a*S*,8*S*,10*R*,11a*S*)-8-{(*S*)-2-[(*R*)-*tert*-Butylsulfinylamino]-pent-4-enyl}-10-methyl-5-oxo-3-phenylperhydrooxazolo[2,3-*j*]quinolone (96)

Allylmagnesium bromide (840 µL of a 1 M solution in Et_2O, 0.84 mmol) was slowly added to a stirring solution of *N*-sulfinyl imine **95** (180 mg, 0.42 mmol) in anhydrous CH_2Cl_2 (5.6 mL) at 0 ºC. After 2 h, saturated aqueous NH_4Cl was added, and the resulting mixture was diluted with EtOAc. The phases were separated, and the aqueous solution was extracted with EtOAc. The combined organic extracts were dried and concentrated. Flash chromatography (from CH_2Cl_2 to 9.85:0.15 CH_2Cl_2–MeOH) afforded sulfinamide **96** (190 mg, 96%) as a brown foam.

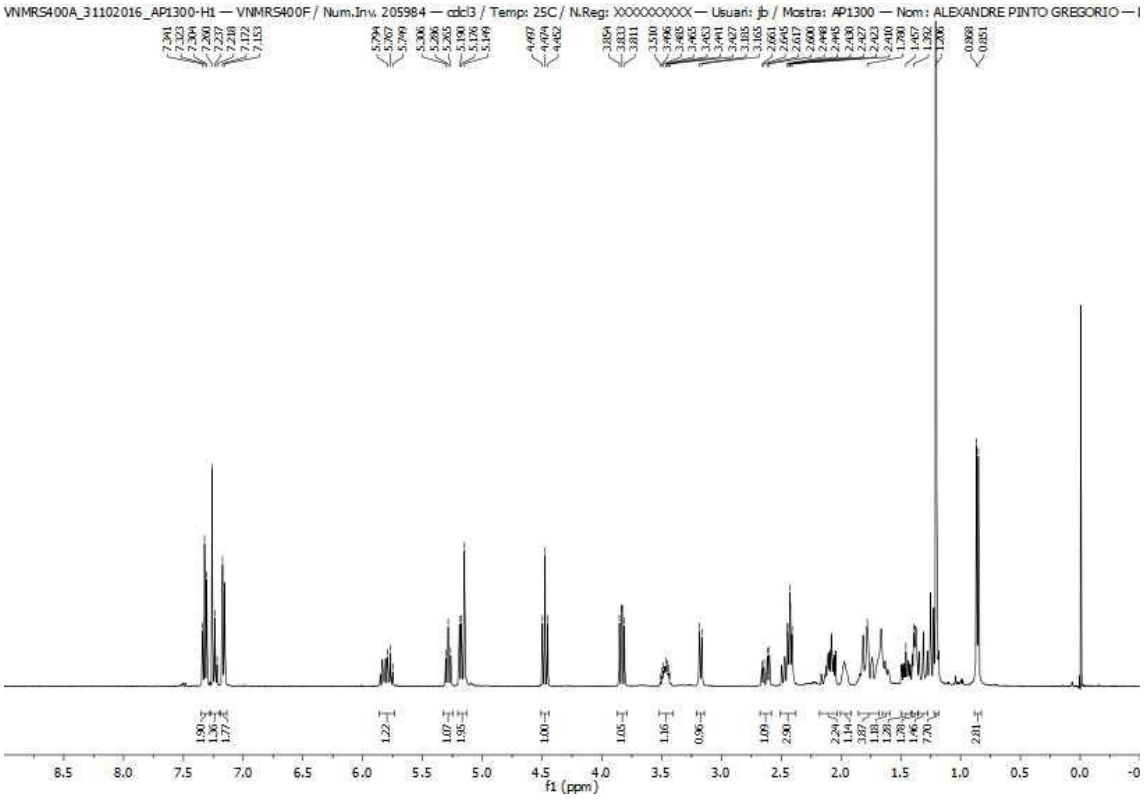
^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) *δ:* 0.86 (d, *J* = 6.4 Hz, 3H, CH_3), 1.21 [br.s, 9H, C(C*H*$_3$)], 1.28-1.35 (m, 2H, H-1'), 1.37-1.39 (m, 2H, H-1', H-11), 1.42-1.49 (m, 1H, H-9), 1.60-1.66 (m, 1H, H-7), 1.67-1.82 (m, 3H, H-1', H-8, H-10), 1.95-1.97 (m, 1H, H-7a), 2.01-2.17 (m, 2H, H-9, H-7), 2.40-2.50 (m, 3H, H-6, H-3'), 2.63 (dd, *J* = 7.6, 18.8 Hz, 1H, H-6), 3.18 (d, *J* = 8.0 Hz, 1H, NH), 3.43-3.51 (m, 1H, H-2'), 3.84 (dd, *J* = 8.2, 9.0 Hz, 1H, H-2), 4.47 (t, *J* = 9.0 Hz, 1H, H-2), 5.15-5.20 (m, 2H, H-5'), 5.29 (t, *J* = 8.2 Hz, 1H, H-3), 5.75-5.85 (m, 1H, H-4'), 7.15-7.26 (m, 2H, H-Ar), 7.29-7.31 (m, 1H, H-Ar), 7.32-7.34 (m, 2H, H-Ar).

^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ:* 22.0 (CH_3), 22.7 [C(*C*H$_3$)], 24.5 (C-7), 24.6 (C-10), 31.1 (C-6), 34.7 (C-11), 35.9 (C-8), 38.8 (C-1'), 39.3 (C-9), 41.0 (C-7a), 41.4 (C-3'), 54.0 (C-2'), 55.9 [*C*(CH$_3$)], 58.3 (C-3), 69.7 (C-2), 95.8 (C-11a), 119.0 (C-5'), 125.4 (2C-H$_{Ar}$), 127.1 (C-H$_{Ar}$), 128.6 (2C-H$_{Ar}$), 133.9 (C-4'), 140.1 (Cq-Ar), 169.3 (NCO).

HRMS calcd for [$C_{27}H_{41}N_2O_3S$ + H^+]: 473.2832, found 473.2839.

$[\alpha]^{23}_D$ = – 61.6 (c 0.67, $CHCl_3$).

Melting point: 129−131 ºC.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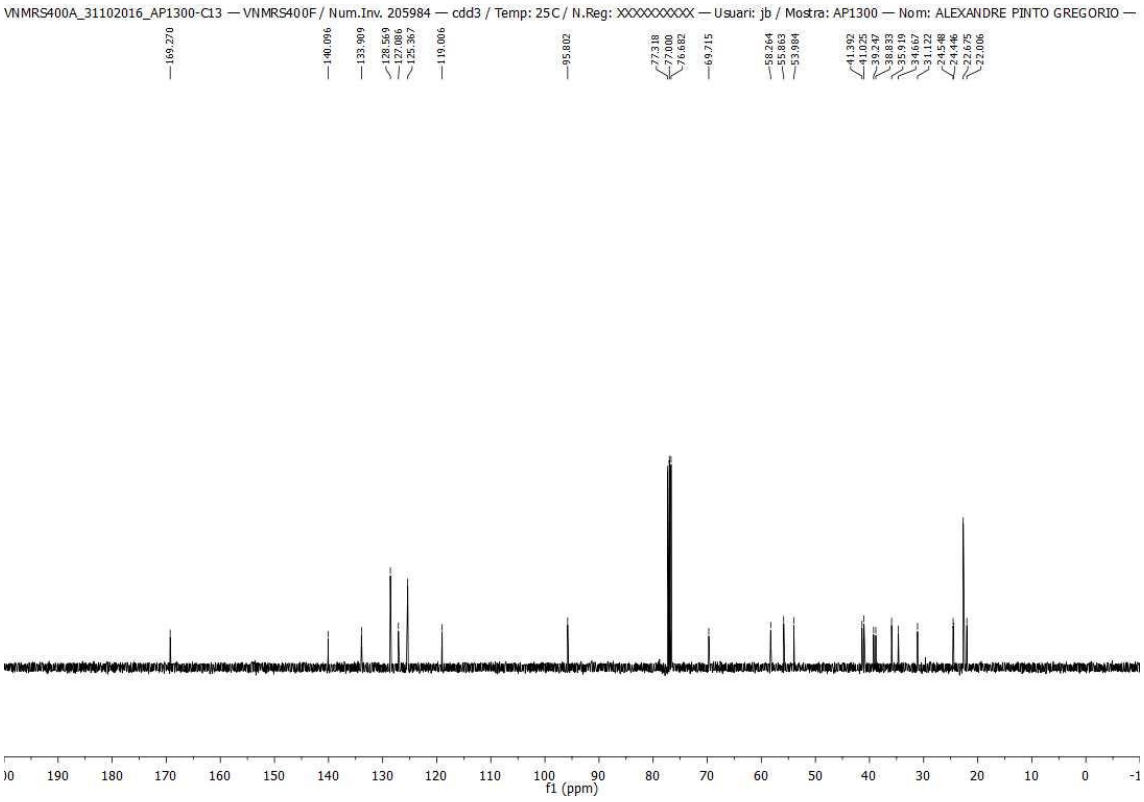
f1 (ppm)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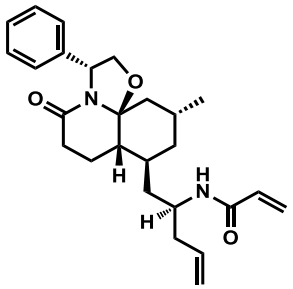
f1 (ppm)



(3*R*,7a*S*,8*S*,10*R*,11a*S*)-8-[(*S*)-2-(Acryloylamino)pent-4-enyl]-10-methyl-5-oxo-3-phenylperhydrooxazolo[2,3-*j*]quinoline (97)

First step: 1 M HCl in Et_2O (2.23 mL, 2.23 mmol) was slowly added to a stirred solution of sulfinamide **96** (420 mg, 0.89 mmol) in anhydrous MeOH (1.1 mL). After 1 h, the solvent was evaporated, and the resulting amine HCl salt was used without further purification in the next step.
Second step: Acryloyl chloride (1.13 mL, 14.2 mmol) was slowly added to a biphasic mixture of the above crude amine hydrochloride in H_2O–CH_2Cl_2 (17.8 mL, 1:1) and Et_3N (1.98 mL, 14.2 mmol) at 0 ºC. The mixture was stirred for 20 h at room temperature. Then, the mixture was diluted with $CHCl_3$, and the layers were separated. The aqueous solution was extracted with $CHCl_3$. The combined organic extracts were washed with brine, dried, and concentrated. Flash chromatography (from 4:6 to 3:7 hexane–EtOAc) afforded acrylamide **97** (250 mg, 67%) as a white foam.

^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) *δ:* 0.85 (d, *J* = 6.4 Hz, 3H, CH_3), 1.24-1.33 (m, 2H, H-1'), 1.39-1.51 (m, 2H, H-9), 1.65-1.71 (m, 1H, H-7), 1.77-1.82 (m, 3H, H-8, H-10, H-11), 1.86-1.91 (m, 1H, H-7a), 2.00-2.14 (m, 2H, H-7, H-11), 2.18-2.25 (m, 1H, H-3'), 2.30-2.37 (m, 1H, H-3'), 2.47-2.64 (m, 2H, H-6), 3.84 (dd, *J* = 8.0, 8.8 Hz, 1H, H-2), 4.18-4.27 (m, 1H, H-2'), 4.48 (t, *J* = 8.8 Hz, 1H, H-2), 5.07-5.11 (m, 2H, H-5'), 5.26-5.34 (m, 2H, H-3, NH), 5.63 (dd, *J* = 1.4, 10.2 Hz, 1H, C*H*$_2$=CHCO), 5.75-5.85 (m, 1H, H-4'), 6.05 (dd, *J* = 10.2, 17.0 Hz, 1H, CH_2=C*H*CO), 6.25 (dd, *J* = 1.4, 17.0 Hz, 1H, C*H*$_2$=CHCO), 7.15-7.24 (m, 2H, H-Ar), 7.25-7.30 (m, 1H, H-Ar), 7.31-7.34 (m, 2H, H-Ar).

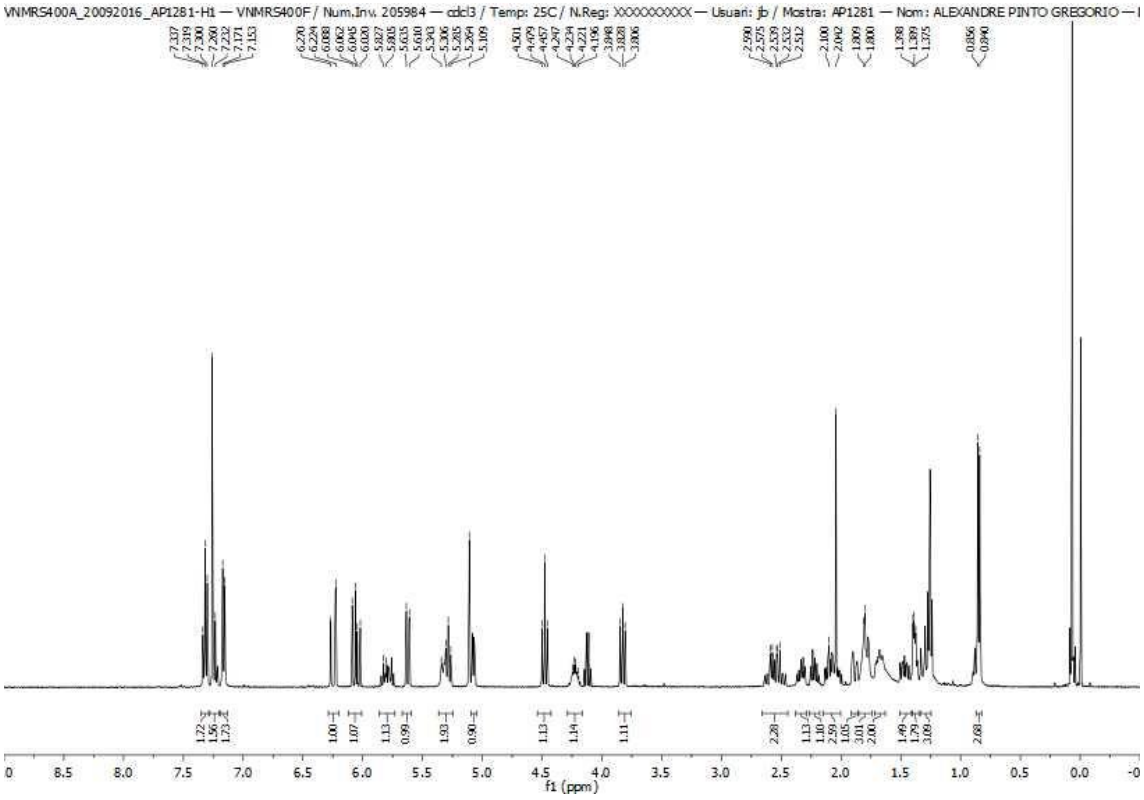
^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ:* 22.0 (CH_3), 24.6 (C-7 and C-10), 31.1 (C-6), 34.6 (C-9), 36.6 (C-8), 38.9 (C-1'), 39.1 (C-11), 39.6 (C-3'), 41.6 (C-7a), 47.0 (C-2'), 58.2 (C-3), 69.7 (C-2), 95.9 (C-11a), 118.0 (C-5'), 125.4 (2C-H_{Ar}),126.2 (*C*H_2=CHCO), 127.0 (C-H_{Ar}), 128.5 (2C-H_{Ar}), 131.0 (C-4'), 134.1 (CH_2=*C*HCO), 140.2 (Cq-Ar), 165.0 (NCO), 169.5 (NCO).

IR (NaCl): 1658, 1638, 1438 cm^{-1};

HRMS calcd for [$C_{26}H_{34}N_2O_3$ + H^+]: 423.2642, found 423.2646.

$[\alpha]^{23}_D$ = – 47.1 (c 0.5, $CHCl_3$).

Melting point: 156–159 ºC.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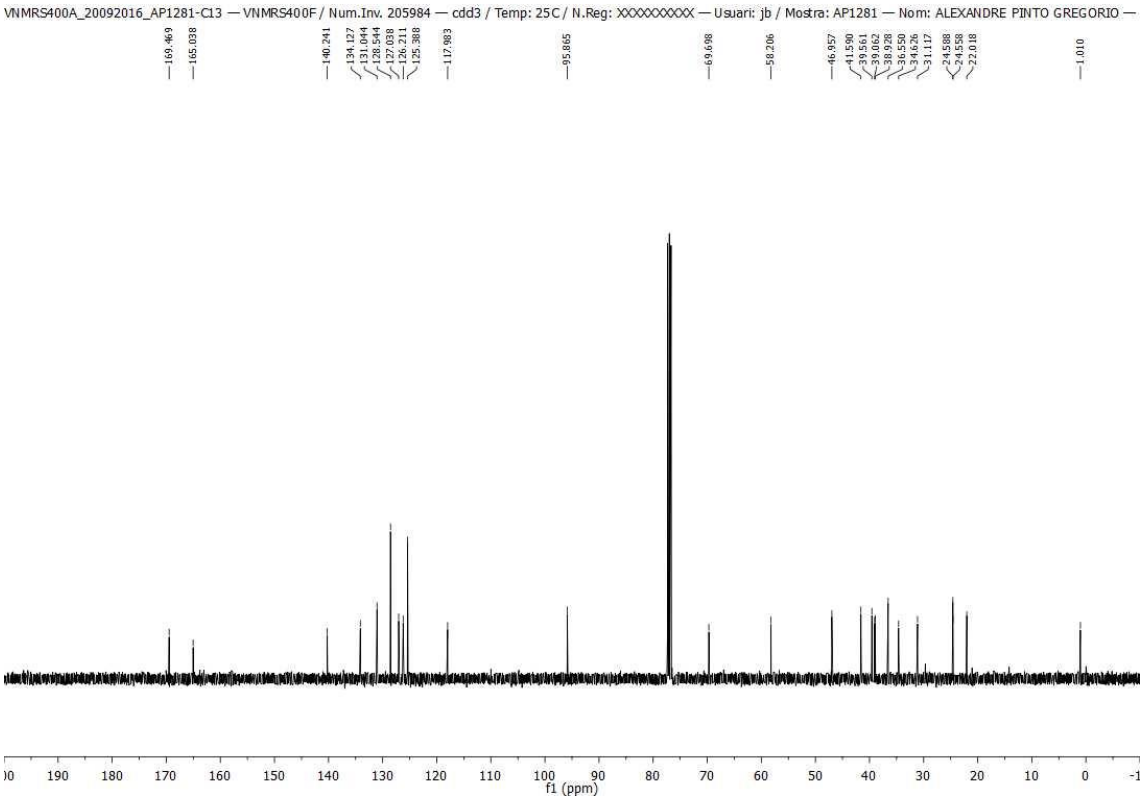
f1 (ppm)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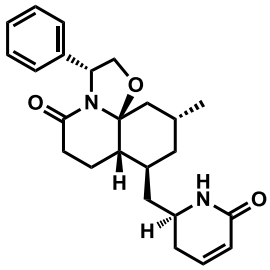
f1 (ppm)



(3*R*,7a*S*,8*S*,10*R*,11a*S*)-10-Methyl-8-{[(*S*)-6-oxo-1,2,3,6-tetrahydro-2-pyridyl] methyl}-5-oxo-3-phenylperhydrooxazolo[2,3-*j*]quinoline (98)

Second Generation Grubbs' catalyst (25 mg, 0.03 mmol) was added to a stirring solution of acrylamide **97** (245 mg, 0.58 mmol) in degassed anhydrous CH_2Cl_2 (19 mL). The resulting brown solution was stirred at reflux temperature for 4 h. After cooling to room temperature, the mixture was stirred for an additional hour exposed to air. The solvent was evaporated under reduced pressure. Flash chromatography (from EtOAc to 95:5 EtOAc–MeOH) afforded dihydropyridone **98** (191 mg, 83%) as a brown foam.

^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) *δ:* 0.87 (d, *J* = 6.4 Hz, 3H, CH_3), 1.25-1.47 (m, 3H, H-9, H-11), 1.70-1.77 (m, 3H, H-7, H-7a, H-11), 1.80-1.83 (m, 2H, H-1', H-10), 1.89 (br.s, 1H, H-8) 2.02-2.19 (m, 3H, H-1', H-7, H-7'), 2.36-2.53 (m, 2H, H-6, H-7'), 2.64 (dd, *J* = 7.2, 18.4 Hz, 1H, H-6), 3.68-3.75 (m, 1H, H-2'), 3.83 (t, *J* = 8.6 Hz, 1H, H-2), 4.49 (t, *J* = 8.6 Hz, 1H, H-3), 5.28 (t, *J* = 8.6 Hz, 1H, H-3), 5.63 (s, 1H, NH), 5.92 (dd, *J* = 1.8, 9.8 Hz, 1H, H-5'), 6.62 (ddd, *J* = 3.2, 5.4, 10.0 Hz, 1H, H-6'), 7.15 (t, *J* = 7.4 Hz, 2H, H-Ar), 7.24 (t, *J* = 7.4 Hz, 1H, H-Ar), 7.33 (t, *J* = 7.4 Hz, 2H, H-Ar).

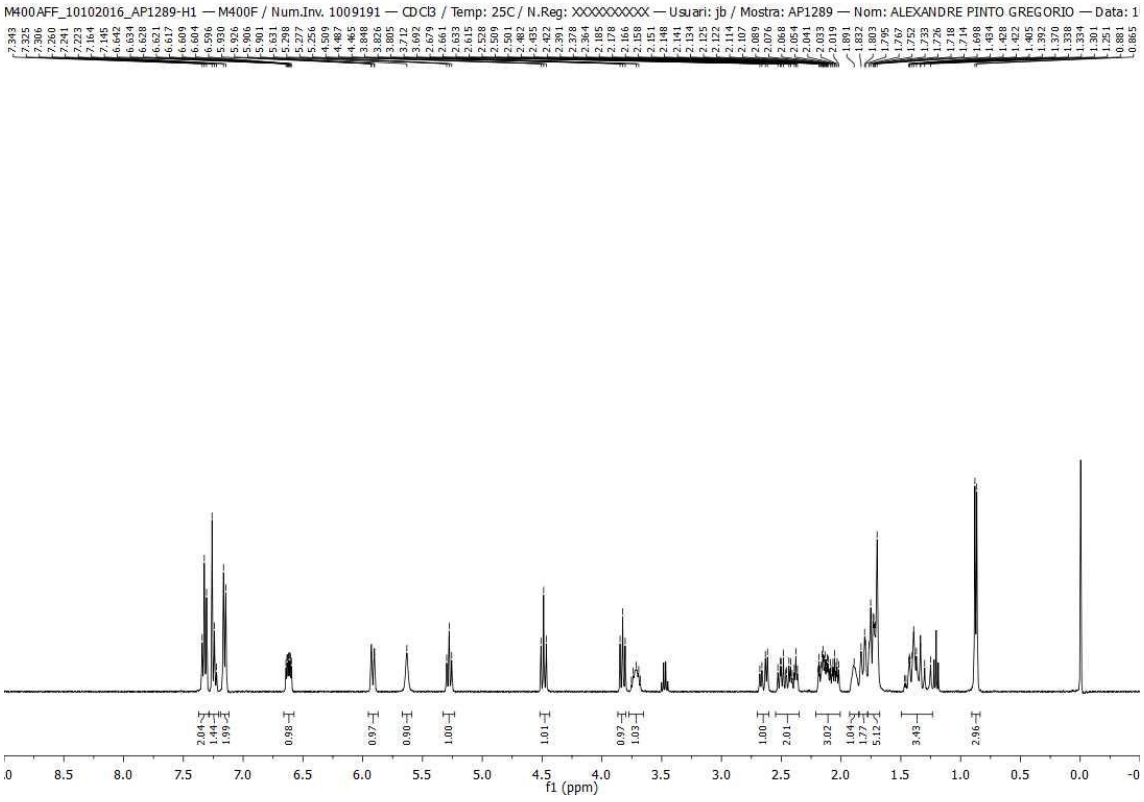
^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ:*21.9 (CH_3), 24.4 (C-10), 24.5 (C-7), 30.3 (C-7'), 31.1 (C-6), 34.1 (C-9), 35.7 (C-8), 38.8 (C-1'), 39.0 (C-11), 41.9 (C-7a), 49.1 (C-2'), 58.2 (C-3), 69.7 (C-2), 95.6 (C-11a), 124.6 (C-5'), 125.3 (2C-H_{Ar}), 127.2 (C-H_{Ar}), 128.6 (2C-H_{Ar}), 140.0 (Cq-Ar), 140.8 (C-6'), 166.3 (HNCO), 169.5 (C-5).

IR (NaCl): 1670, 1457 cm^{-1}.

HRMS calcd for [$C_{24}H_{30}N_2O_3$ + H^+]: 395.2329, found 395.2330.

$[\alpha]^{23}_D$ = – 63.3 (c 0.3, $CHCl_3$).

Melting point: 153−156 °C.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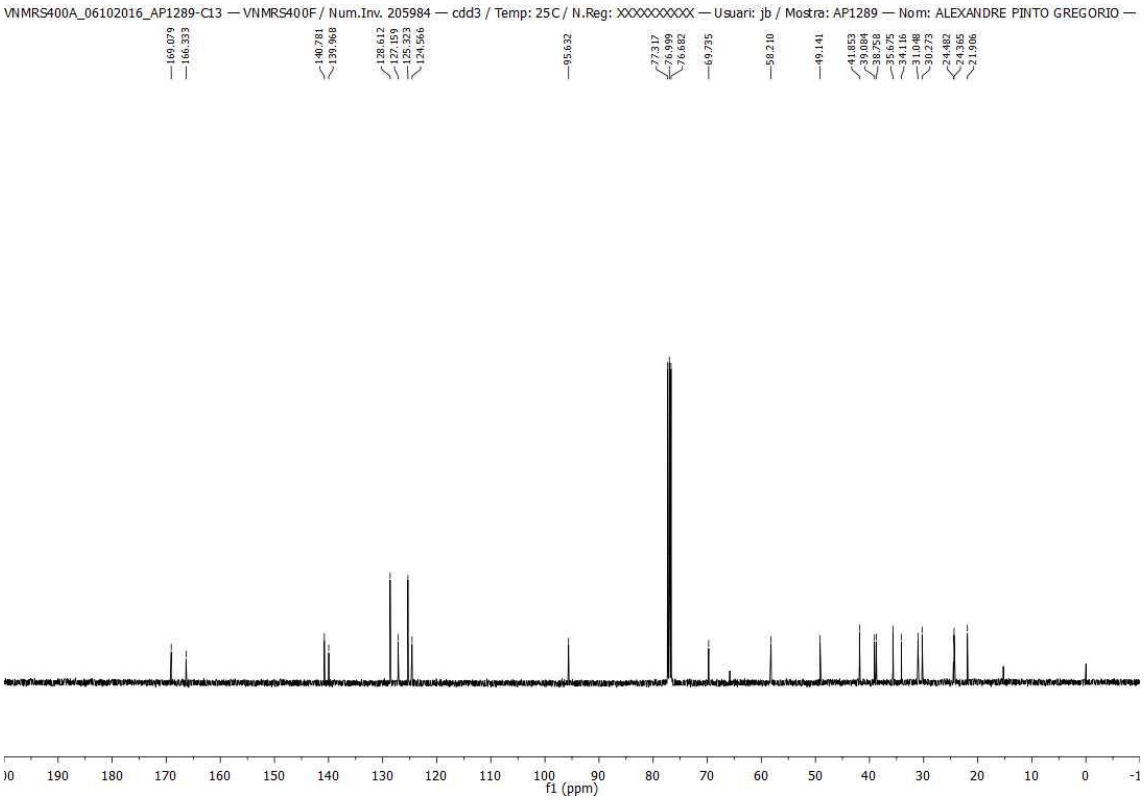
2.04
1.44
1.99
0.98
0.97
0.80
1.00
1.01
0.97
1.03
1.00
2.01
3.02
1.04
1.77
5.12
3.43
2.96
f1 (ppm)


VNMRS400A_06102016_AP1289-C13 — VNMRS400F / Num.Inv. 205984 — cdd3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP1289 — Nom: ALEXANDRE PINTO GREGORIO —
169.079
166.333
140.781
139.968
128.612
127.153
125.323
124.566
95.632
77.317
76.999
76.682
69.735
58.210
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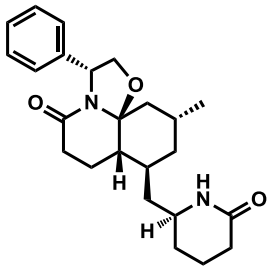
31.048
30.273
24.482
24.365
21.906
f1 (ppm)



(3*R*,7a*S*,8*S*,10*R*,11a*S*)-10-Methyl-8-{[(*S*)-6-oxo-2-piperidyl]methyl}-5-oxo-3-phenylperhydrooxazolo[2,3-*j*]quinoline (99)

A solution of dihydropyridone **98** (180 mg, 0.46 mmol) in MeOH (4 mL) containing Pd/C (36 mg, 10% Pd) was stirred under hydrogen at room temperature for 15 h. The catalyst was removed by filtration, and the solvent was evaporated affording piperidone **99** (170 mg, 94%) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) *δ:* 0.86 (d, *J* = 6.4 Hz, 3H, CH_3), 1.25-1.29 (br.d, 1H, H-11), 1.32-1.45 (m, 3H, H-6', H-9), 1.58-1.66 (m, 1H, H-1'), 1.68-1.77 (m, 3H, H-7, H-7a, H-7'), 1.78-1.83 (m, 2H, H-10, H-11), 1.86-1.93 (m, 3H, H-6', H-7', H-8), 1.95-2.02 (m, 1H, H-1'), 2.06-2.18 (m, 1H, H-7), 2.24-2.33 (m, 1H, H-5'), 2.36-2.42 (m, 1H, H-5'), 2.45-2.52 (m, 1H, H-6), 2.64 (dd, *J* = 7.0, 18.2 Hz, 1H, H-6), 3.43-3.50 (m, 1H, H-2'), 3.82 (dd, *J* = 8.2, 8.8 Hz, 1H, H-2), 4.48 (t, *J* = 8.8 Hz, 1H, H-2), 5.28 (t, *J* = 8.2 Hz, 1H, H-3), 5.91(s, 1H, NH), 7.14-7.17 (m, 2H, H-Ar), 7.22-7.26 (m, 1H, H-Ar), 7.20-7.34 (m, 2H, H-Ar).

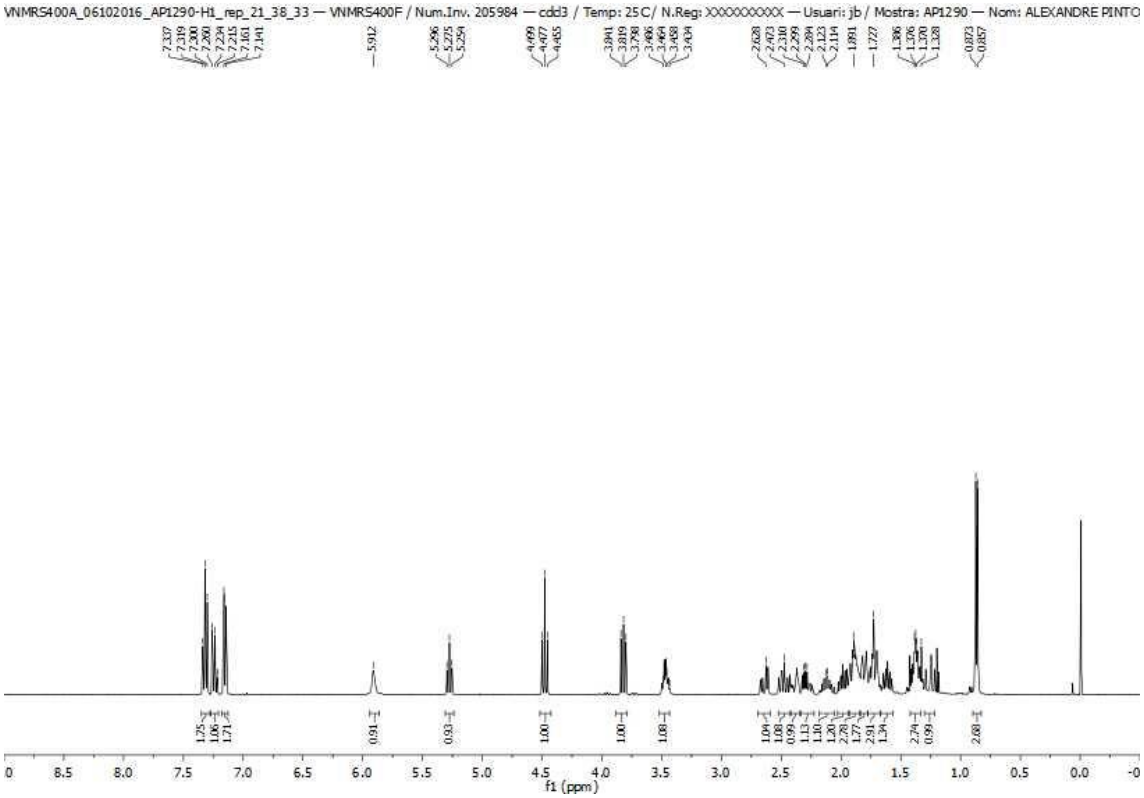
^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ:* 19.7 (C-7'), 21.9 (CH_3), 24.3 (C-10), 24.4 (C-7), 28.8 (C-6'), 31.1 (C-6), 31.3 (C-5'), 34.1 (C-9), 35.6 (C-8), 38.7 (C-11), 40.8 (C-1'), 42.0 (C-7a), 51.1 (C-2'), 58.2 (C-3), 69.7 (C-2), 95.6 (C-11a), 125.3 (2C-H_{Ar}), 127.1 (C-H_{Ar}), 128.6 (2C-H_{Ar}), 140.0 (Cq-Ar), 169.1 (C-5), 172.3 (NCO).

IR (NaCl): 1657 cm^{-1}.

HRMS calcd for [$C_{24}H_{32}N_2O_3$ + H+]: 397.2486, found 397.2491.

$[\alpha]^{23}_{D}$ = – 46.7 (c 0.28, $CHCl_3$).

Melting point: 170−172 ºC.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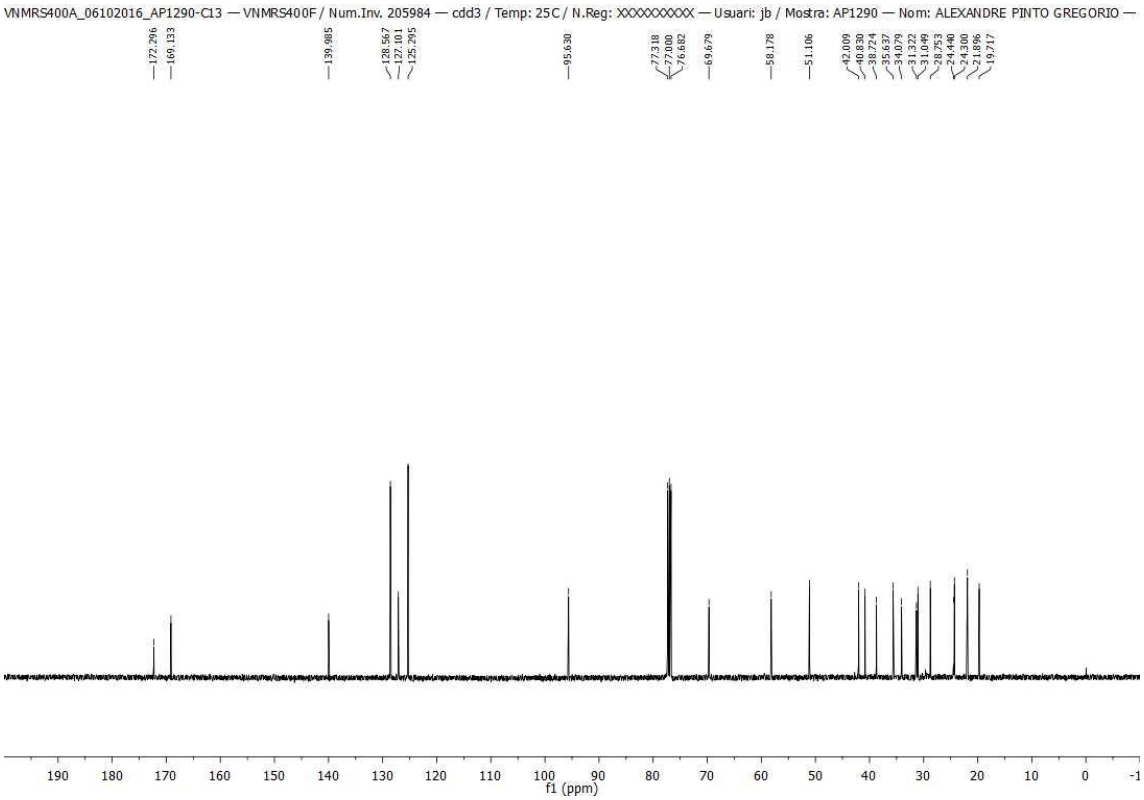
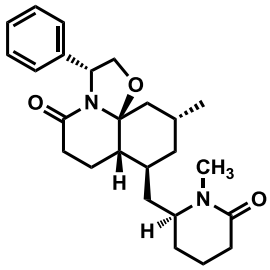
f1 (ppm)


VNMRS400A_06102016_AP1290-C13 — VNMRS400F / Num.Inv. 205984 — cdd3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP1290 — Nom: ALEXANDRE PINTO GREGORIO —
f1 (ppm)



(3*R*,7a*S*,8*S*,10*R*,11a*S*)-10-Methyl-8-{[(*S*)-1-methyl-6-oxo-2-piperidyl]methyl}-5-oxo-3-phenylperhydrooxazolo[2,3-*j*]quinoline (100)

NaH (13 mg, 0.51 mmol) was added to a solution of piperidone **99** (170 mg, 0.43 mmol) in anhydrous DMF (1.0 mL) at room temperature, and the mixture was stirred at this temperature for 1 h. Then, MeI (32 µL, 0.51 mmol) was added, and the stirring was continued at room temperature for 50 h. NaH (13 mg, 0.51 mmol) and MeI (32 µL, 0.51 mmol) were sequentially added, and the mixture was stirred for an additional 8 h. Saturated aqueous NH_4Cl was added, the resulting mixture was diluted with CH_2Cl_2, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried, and concentrated. Flash chromatography (from 3:7 to 2:8 hexane–acetone) afforded compound **100** (130 mg, 74%) as a yellowish oil.

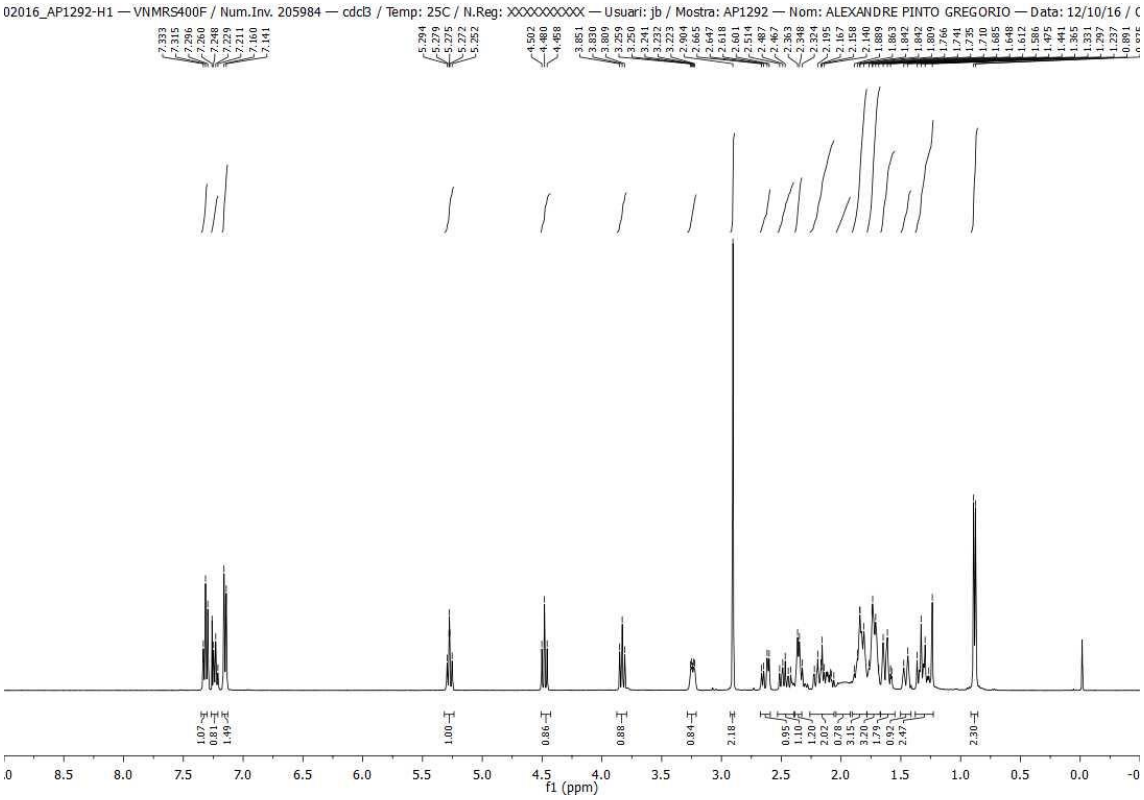
^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) *δ:* 0.88 (d, *J* = 6.4 Hz, 3H, CH_3), 1.24-1.33 (m, 2H, H-9, H-11), 1.44-1.48 (m, 1H, H-9), 1.58-1.65 (m, 2H, H-7, H-7a), 1.71-1.77 (m, 4H, H6', H-7'. H-8, H-10), 1.81-1.89 (m, 4H, H-6', H-7', H-10), 2.06-2.30 (m, 2H, H-1', H-7), 2.32-2.38 (m, 2H, H-5'), 2.42-2.51 (m, 1H, H-6), 2.63 (dd, *J* = 7.0, 18.6 Hz, 1H, H-6), 2.90 (s, 3H, NCH_3), 3.21-3.27(m, 1H, H-2'), 3.83 (d, *J* = 8.8 Hz, 1H, H-2), 4.48 (t, *J* = 8.8 Hz, 1H, H-2), 5.28 (t, *J* =8.8 Hz, 1H, H-3), 7.15 (d, *J* = 7.4 Hz, 2H, H-Ar), 7.23 (t, *J* = 7.4 Hz, 1H, H-Ar), 7.32 (t, *J* = 7.4 Hz, 2H, H-Ar).

^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ:* 17.2 (C-7'), 21.9 (CH_3), 24.1 (C-10), 24.5 (C-7), 26.0 (C-6'), 31.0 (C-6), 31.8 (C-5'), 32.1 (C-9), 33.7 (NCH_3), 36.2 (C-1'), 36.9 (C-8), 38.8 (C-11), 44.6 (C-7a), 57.6 (C-2'), 58.2 (C-3), 69.6 (C-2), 95.5 (C-11a), 125.3 (2C-H_{Ar}), 127.1 (C-H_{Ar}), 128.5 (2C-H_{Ar}), 139.9 (Cq-Ar), 169.1 (C-5), 170.1 (NCO);

IR (NaCl): 1633 cm^{-1}.

HRMS calcd for [$C_{25}H_{34}N_2O_3$ + H^+]: 411.2642, found 411.2644.

$[\alpha]^{23}_D$ = – 29.4 (c 2.345, $CHCl_3$).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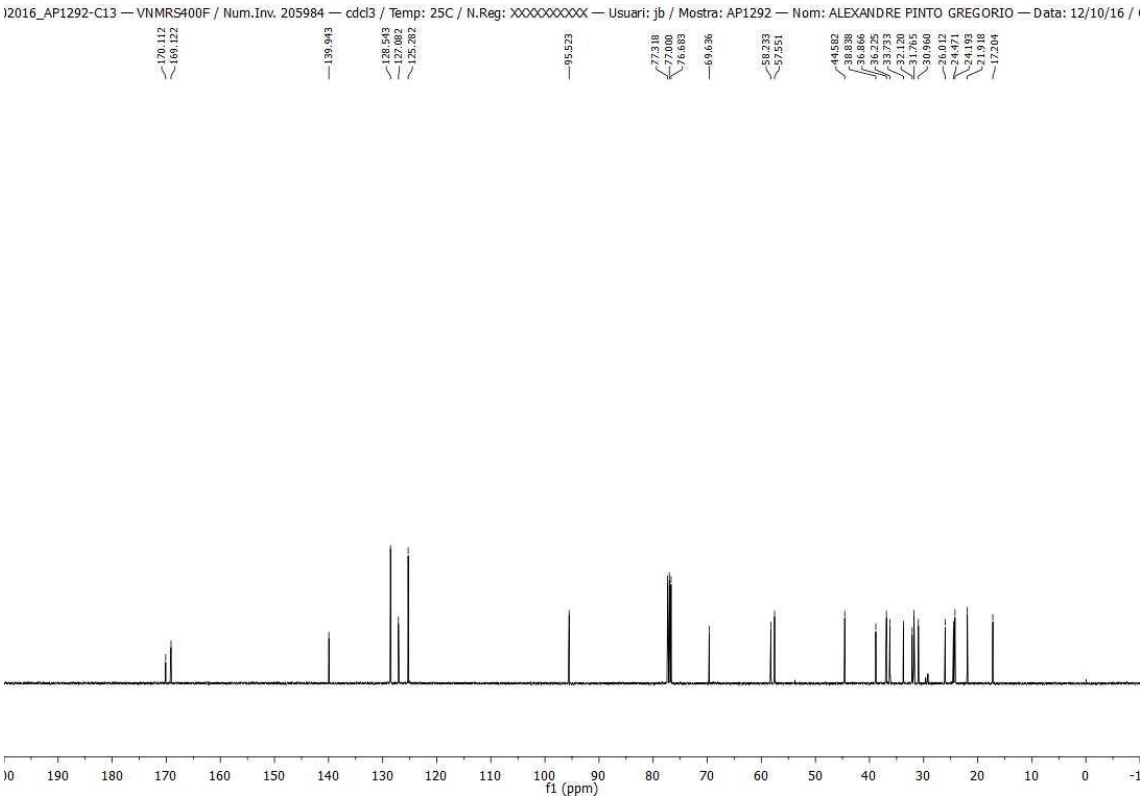
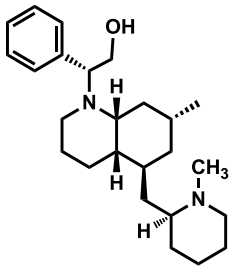
f1 (ppm)


2016_AP1292-C13 — VNMRS400F / Num.Inv. 205984 — cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP1292 — Nom: ALEXANDRE PINTO GREGORIO — Data: 12/10/16 /
f1 (ppm)



(4a*S*,5*S*,7*R*,8a*R*)-1-[(*R*)-2-Hydroxy-1-phenylethyl]-7-methyl-5-{[(*S*)-1-methyl-2-piperidyl]methyl}decahydroquinoline (101)

$LiAlH_4$ (2.06 mL of a 1 M solution in THF, 2.06 mmol) was added to a stirring solution of $AlCl_3$ (85 mg, 0.63 mmol) in anhydrous THF (12.7 mL) at 0 ºC. After 10 minutes, the mixture was allowed to warm to room temperature and stirred for an additional 30 minutes. The mixture was cooled to –78 ºC, and after 10 minutes a solution of **100** (130 mg, 0.32 mmol) in anhydrous THF (2.0 mL) was added. The stirring was continued at –78 °C for 90 min and at room temperature for 2 h. Water was slowly added, and the resulting mixture was diluted with EtOAc. The phases were separated, and the aqueous solution was extracted with EtOAc. The combined organic extracts were dried and concentrated. Flash chromatography (from CH_2Cl_2 to 8:2 CH_2Cl_2–MeOH) afforded *cis*-decahydroquinoline **101** (100 mg, 82%) as a colorless oil.

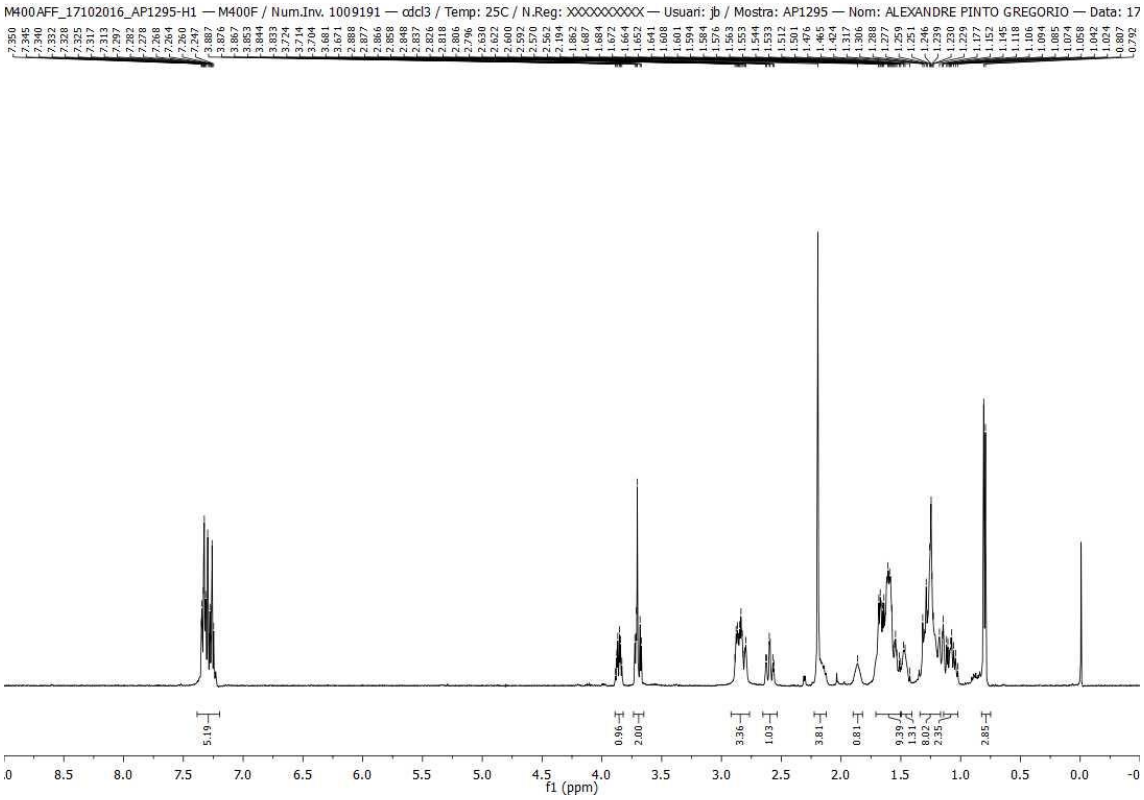
^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) *δ:* 0.80 (d, *J* = 6.0 Hz, 3H, CH_3), 1.02-1.12 (m, 3H), 1.15-1.35 (m, 8H, H-1', H-3, H-5'), 1.42-1.50 (m, 1H, H-5), 1.51-1.71 (m, 9H, H-3, H-4a, H-5', H-7), 1.86 (br.s, 1H, H-8a), 2.19 (s, 4H, H-4", NCH_3), 2.60 (td, *J* = 3.2, 12.0 Hz, 1H, H-2), 2.80-2.89 (m, 3H, H-2, H-2", H-4"), 3.67-3.72 (m, 2H, H-1', H-2'), 3.83-3.89 (m, 1H, H-2'), 7.25-7.35 (m, 5H, H-Ar).

^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ:* 22.8 (CH_3), 23.8 (C-3), 25.2 (C-5'), 25.4 (C-7), 25.8 (CH_2), 26.7 (CH), 28.2 (C-1"), 31.1 (CH_2), 33.5 (CH_2), 35.6 (CH_2), 37.3 (C-5), 40.3 (C-4a), 42.4 (NCH_3), 42.7 (C-2), 52.9 (C-2"), 56.6 (C-4"), 62.7 (C-8a), 63.3 (C-2'), 66.7 (C-1'), 127.4 (C-H_{Ar}), 128.2 (2C-H_{Ar}), 128.3 (2C-H_{Ar}), 140.7 (Cq-Ar).

IR (NaCl): 3370, 1022 cm^{-1}.

HRMS calcd for [$C_{25}H_{41}N_2O$ + H^+]: 385.3213, found 385.3203.

$[\alpha]^{23}_D$ = – 51.69 (c 1.415, $CHCl_3$).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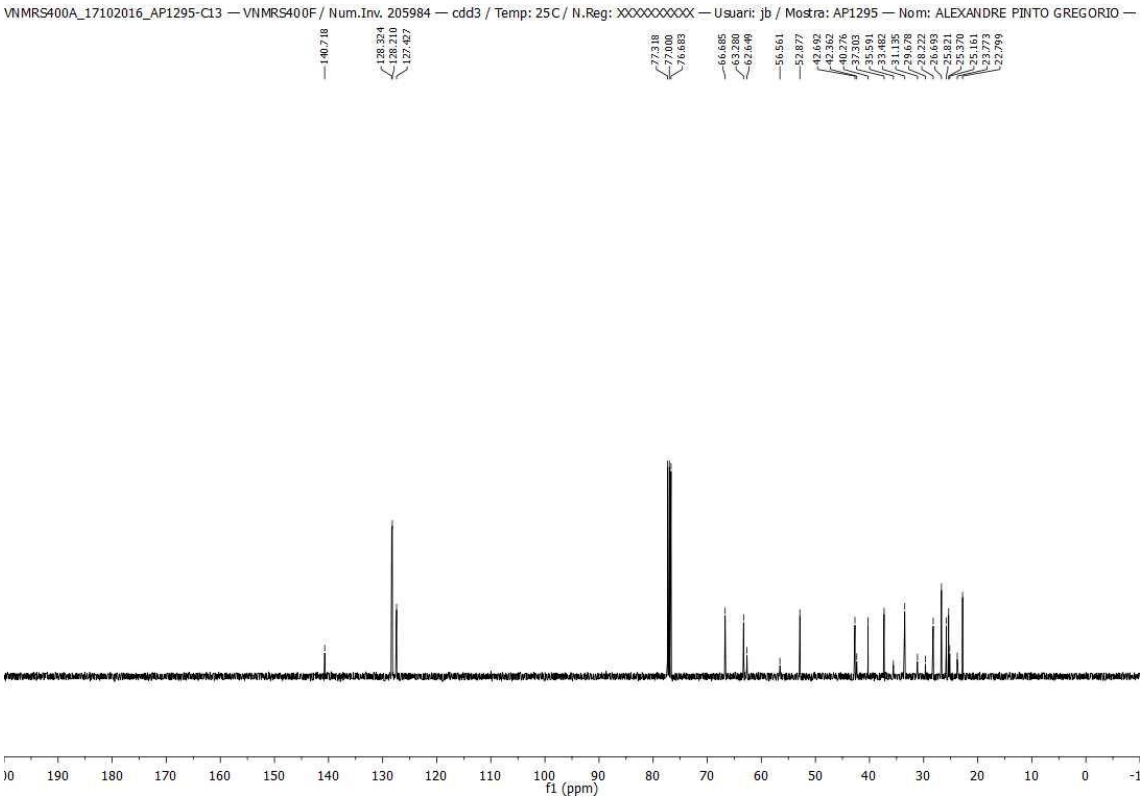
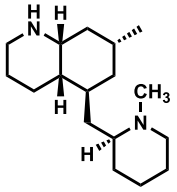
5.19
0.96
2.00
3.36
1.03
3.81
0.81
9.39
8.02
2.35
2.85
f1 (ppm)


VNMRS400A_17102016_AP1295-C13 — VNMRS400F / Num.Inv. 205984 — cdd3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP1295 — Nom: ALEXANDRE PINTO GREGORIO —
140.718
128.324
128.210
127.427
77.318
77.000
76.683
66.685
63.280
62.649
56.561
52.877
42.692
42.362
40.276
37.283
35.591
33.482
31.135
29.678
28.222
26.693
25.821
25.370
25.161
23.773
22.799
f1 (ppm)



(−)-Cermizine B

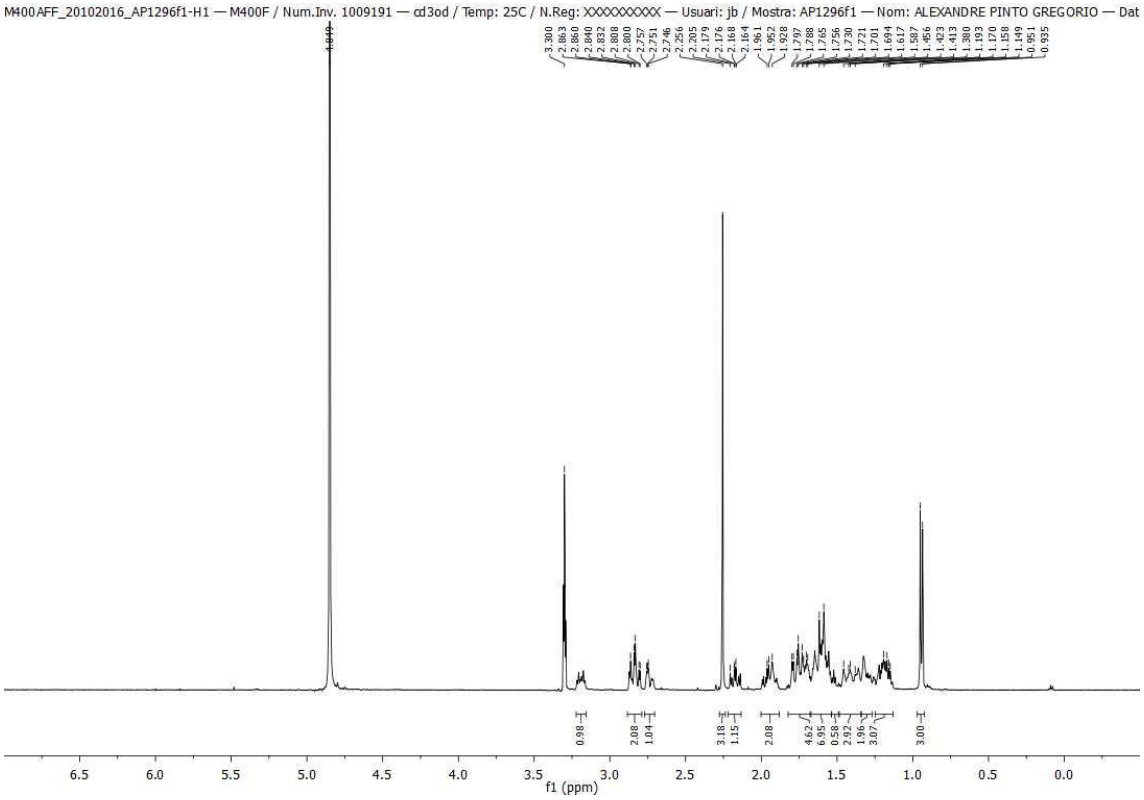
A suspension of **101** (53 mg, 0.14 mmol) in methanolic 1.25 M HCl (2.5 mL) containing $Pd(OH)_2$ (21.2 mg) was stirred under hydrogen at room temperature for 24 h. The catalyst was then removed by filtration over Celite ®, and washed with MeOH. The solvent was evaporated, and the residue was taken up in 2 M aqueous HCl and diluted with CH_2Cl_2. The layers were separated, and the aqueous phase was washed with CH_2Cl_2. The aqueous phase was then basified with solid KOH and extracted with EtOAc. The combined organic extracts were dried and concentrated. Flash chromatography (from 2:1 CH_2Cl_2–MeOH to 2:1:0.17 CH_2Cl_2–MeOH–NH_4OH) afforded **(−)-cermizine B** (29 mg, 79%) as a colorless oil.

^{1}H-NMR (400 MHz, CD_3OD, COSY, HETCOR) δ: 0.94 (d, J = 6.4 Hz, 3H, H-16), 1.14-1.25 (m, 3H), 1.26-1.38 (m, 4H), 1.39-1.48 (m, 2H), 1.51-1.67 (m, 6H), 1.68-1.83 (m, 4H), 1.88-1.99 (m, 2H, H-5, H-6), 2.17 (td, J = 4.2, 14.8 Hz, 2H, H-1) 2.26 (s, 3H, H-19), 2.71-2.76 (m, 1H, H-9), 2.83 (td, J = 3.0, 12.6 Hz, 2H, H-1, H-9), 3.19 (dt, J = 4.4, 12.0 Hz, 1H, H-13).

^{13}C.-NMR (100.6 MHz, CD_3OD) δ: 23.0 (C-16), 25.0 (C-3), 26.2 (C-2 and C-11), 27.0 (C-10), 28.0 (C-15), 31.9 (C-4), 33.7 (C-8), 34.2 (C-14), 36.9 (C-6), 38.5 (C-7), 40.4 (C-9), 41.7 (C-12), 43.0 (C-19), 51.9 (C-13), 57.9 (C-1), 63.9 (C-5).

HRMS calcd for [$C_{17}H_{33}N_2 + H^+$]: 265.2638, found 265.2638.

$[\alpha]^{23}_D = -16$ (c 0.29, MeOH).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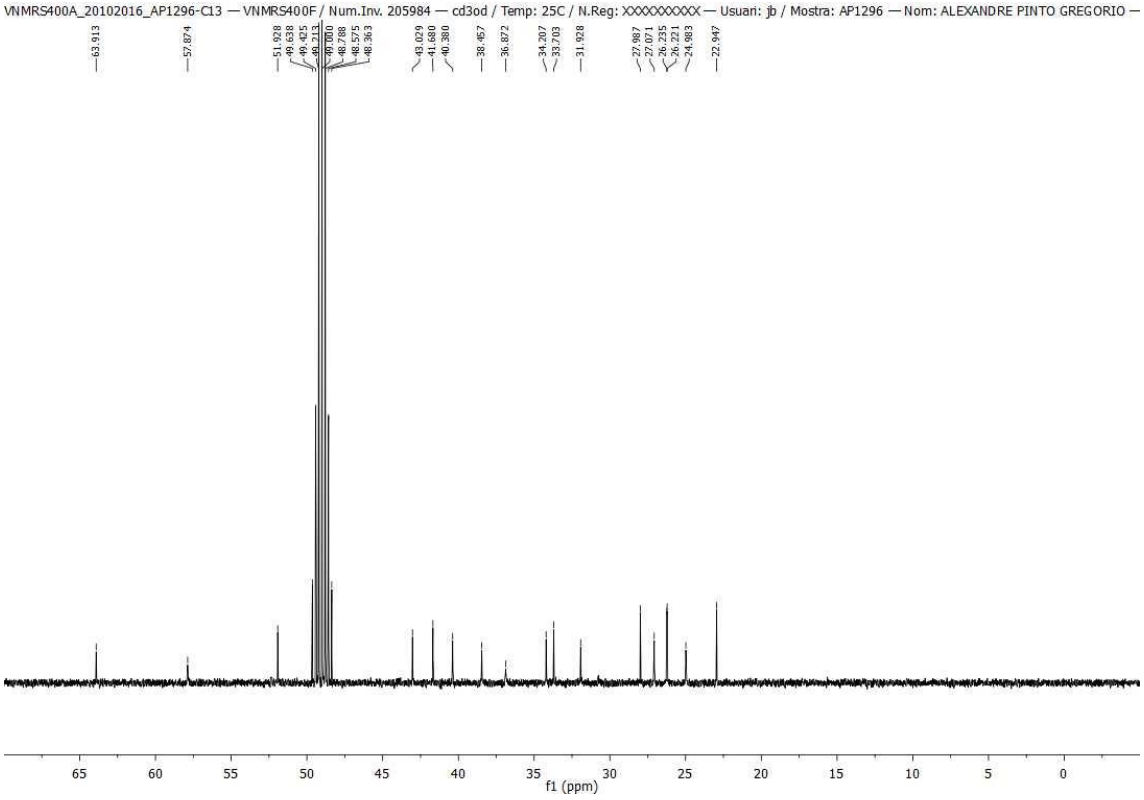
f1 (ppm)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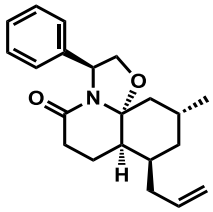
f1 (ppm)



(3*S*,7a*R*,8*R*,10*R*,11a*R*)-8-Allyl-10-methyl-5-oxo-3-phenylperhydrooxazolo[2,3-*j*]quinoline (102a)

Operating as described in the preparation of lactam **3**, from keto ester **90** (250 mg, 1.27 mmol), (*S*)-phenylglycinol (262 mg, 1.91 mmol), and AcOH (110 µL, 1.91 mmol) in benzene (8 mL), lactams **102a** (117 mg, 28%) and **102b** (112 mg, 27%) were obtained after flash chromatography (from 9:1 to 7:3 hexane: EtOAc) as yellowish residues. **102a** (higher *Rf*).

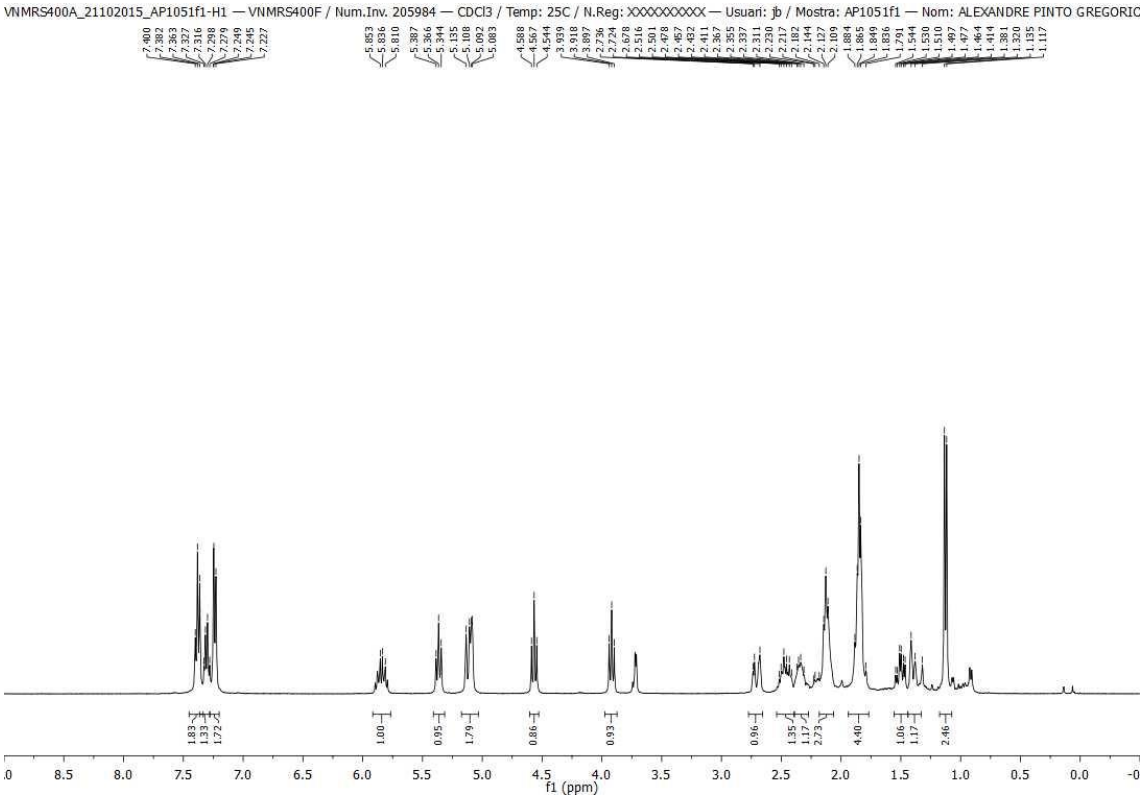
^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) *δ:* 1.13 (d, *J* = 7.6 Hz, 3H, CH_3), 1.32-1.41 (m, 1H, H-9), 1.50 (dt, *J* = 5.2, 13.2 Hz, 1H, H-9), 1.79-1.89 (m, 5H, H-7, H-7a, H-11), 2.11-2.23 (m, 3H,-10, H-1'), 2.30-2.35 (m, 1H, H-8), 2.43-2.53 (m, 1H, H-6), 2.66-2.74 (m, 1H, H-6), 3.92 (t, *J* = 8.6 Hz, 1H, H-2), 4.35 (t, *J* = 8.6 Hz, 1H, H-2), 5.07-5.14 (m, 2H, CH=CH_2), 5.37 (t, *J* = 8.6 Hz, 1H, H-3), 5.78-5.90 (m, 1H, C*H*=CH_2), 7.23 (d, *J* = 7.4 Hz, 2H, H-Ar), 7.28-7.33 (m, 1H, H-Ar), 7.38 (t, *J* = 7.4 Hz, 2H, H-Ar).

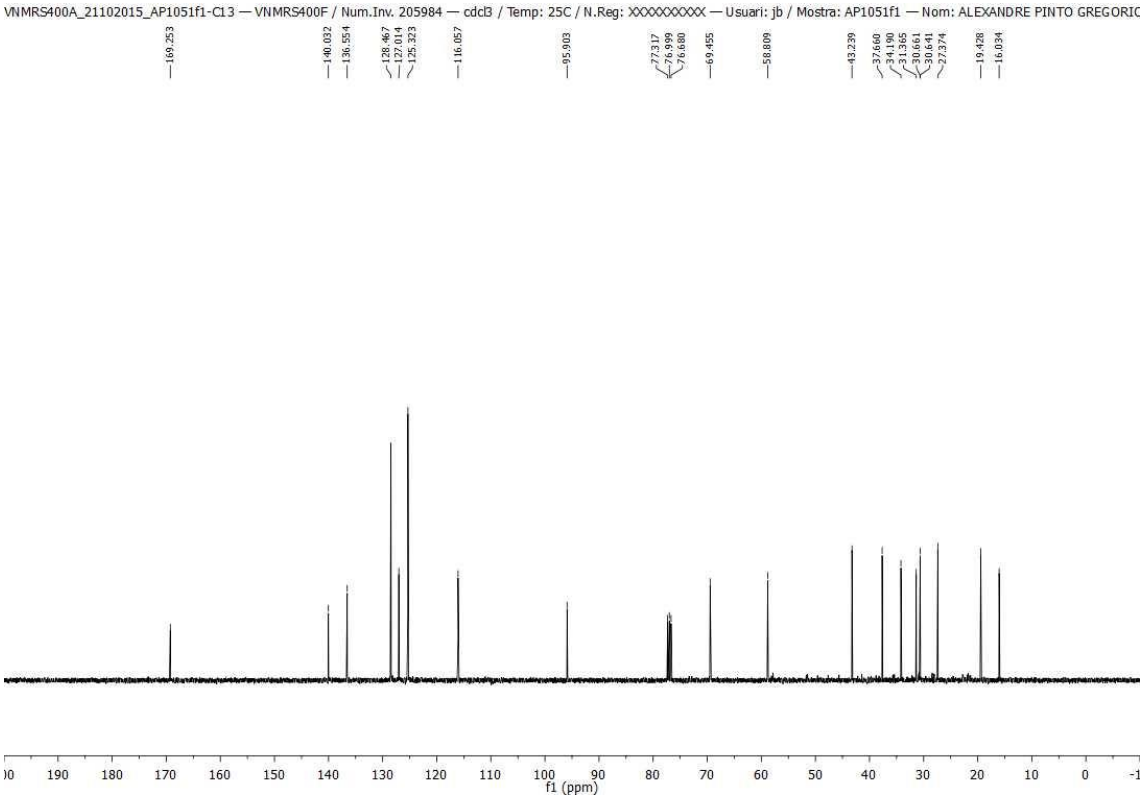
^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ:*16.0 (C-11), 19.4 (CH3), 27.4 (C-10), 30.6 (C-6), 30.7 (C-8), 31.4 (C-9), 34.2 (C-7), 37.7 (C-1'), 43.2 (C-7a), 58.8 (C-3), 69.5 (C-2), 95.9 (C-11a), 116.1 (C=*C*H_2), 125.3 (2C-H_{Ar}), 127.0 (C-H_{Ar}), 128.5 (2C-H_{Ar}), 136.6 (*C*H=C), 140.1 (Cq-Ar), 169.2 (C-5);

IR (NaCl): 1655, 1398 cm^{-1}.

HRMS calcd for [$C_{21}H_{27}NO_2$ + H^+]: 326.2115, found 326.2122.

$[\alpha]^{23}_D$ = + 79 (c 2.0, $CHCl_3$).


VNMRS400A_21102015_AP1051f1-H1 — VNMRS400F / Num.Inv. 205984 — CDCl3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP1051f1 — Nom: ALEXANDRE PINTO GREGORIC
7.400
7.382
7.363
7.327
7.316
7.300
7.279
7.249
7.245
7.227
5.853
5.836
5.810
5.387
5.366
5.344
5.135
5.108
5.092
5.083
4.588
4.567
4.544
3.939
3.918
3.897
2.736
2.724
2.678
2.516
2.501
2.478
2.467
2.432
2.411
2.387
2.355
2.327
2.311
2.230
2.217
2.182
2.144
2.127
2.109
1.884
1.865
1.849
1.836
1.791
1.544
1.530
1.510
1.497
1.477
1.464
1.414
1.381
1.320
1.135
1.117
1.83
1.33
1.72
1.00
0.95
1.79
0.86
0.93
0.96
1.35
1.17
2.73
4.40
1.06
1.17
2.46
f1 (ppm)


VNMRS400A_21102015_AP1051f1-C13 — VNMRS400F / Num.Inv. 205984 — cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP1051f1 — Nom: ALEXANDRE PINTO GREGORIC
169.253
140.032
136.554
128.467
127.014
125.323
116.057
95.903
77.317
76.999
76.680
69.455
58.809
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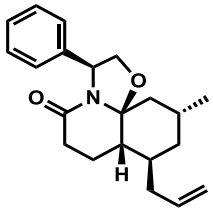
37.660
34.190
31.365
30.661
30.641
27.374
19.428
16.034
f1 (ppm)



(3*S*,7a*S*,8*R*,10*R*,11a*S*)-8-Allyl-10-methyl-5-oxo-3-phenylperhydrooxazolo[2,3-*j*]quinoline (102b)

(lower *Rf*)

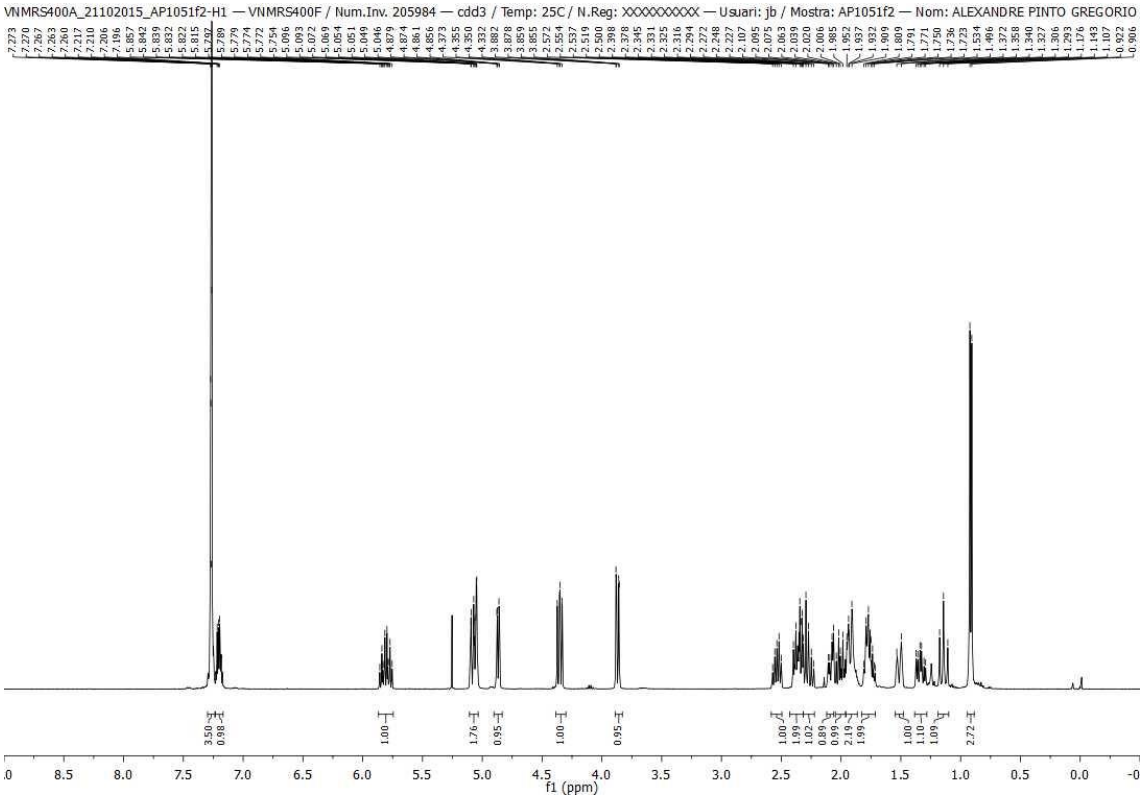
^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) *δ:* 0.91 (d, *J* = 6.0 Hz, 3H, CH_3), 1.15 (t, *J* = 13.8 Hz, 1H, H-11), 1.33 (dt, *J* = 4.8, 8.4 Hz, 1H, H-9), 1.49-1.53 (m, 1H, H-9), 1.71-1.81 (m, 2H, H-7, H-8), 1.87-1.96 (m, 2H, H-10. H-11), 1.97-2.03 (m, 1H, H-7), 2.05-2.12 (m, 1H, H-7a), 2.22-2.30 (m, 1H, H-1'), 2.32-2.40 (m, 2H, H-6, H-1'), 2.48-2.58 (m, 1H, H-1'), 3.86 (dd, *J* = 1.8, 7.2 Hz, 1H, H-2), 4.35 (dd, *J* =1.8, 7.2 Hz, 1H, H-2), 4.86 (dd, *J* = 1.8, 7.2 Hz, 1H, H-3), 5.04-5.10 (m, 2H, CH=C*H*$_2$), 5.80 (dddd, *J* = 7.2, 10.2, 14.4, 17.2 Hz 1H, C*H*=CH_2), 7.15-7.20 (m, 1H, H-Ar), 7.22-7.30 (m, 4H, H-Ar).

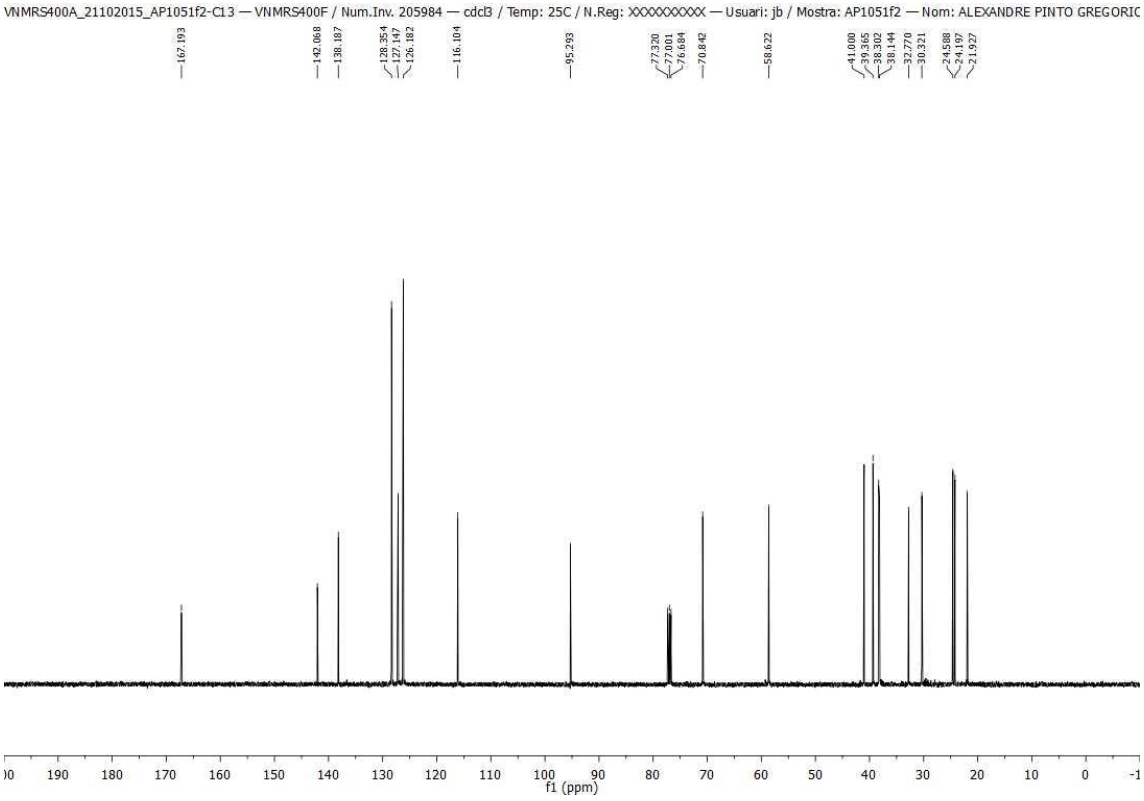
^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ:* 21.9 (CH_3), 24.2 (C-7), 24.6 (C-10), 30.3 (C-1'), 32.8 (C-9), 38.1 (C-11), 38.3 (C-6), 39.4 (C-8), 41.0 (C-7a), 58.6 (C-3), 70.8 (C-2), 95.3 (C-11a), 116.1 (C=*C*H_2), 126.2 (2C-H_{Ar}), 127.2 (C-H_{Ar}), 128.4 (2C-H_{Ar}), 138.2 (*C*H=C), 142.1 (Cq-Ar), 167.2 (NCO).

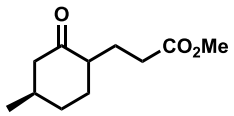
IR (NaCl): 1656, 1435 cm^{-1}.

HRMS calcd for [$C_{21}H_{27}NO_2$ + H^+]: 326.2115, found 326.2119.

$[\alpha]^{23}_{D}$ = – 44.5 (c 2.0, $CHCl_3$).


VNMRS400A_21102015_AP1051f2-H1 — VNMRS400F / Num.Inv. 205984 — cdd3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP1051f2 — Nom: ALEXANDRE PINTO GREGORIO
f1 (ppm)


VNMRS400A_21102015_AP1051f2-C13 — VNMRS400F / Num.Inv. 205984 — cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP1051f2 — Nom: ALEXANDRE PINTO GREGORIC
f1 (ppm)



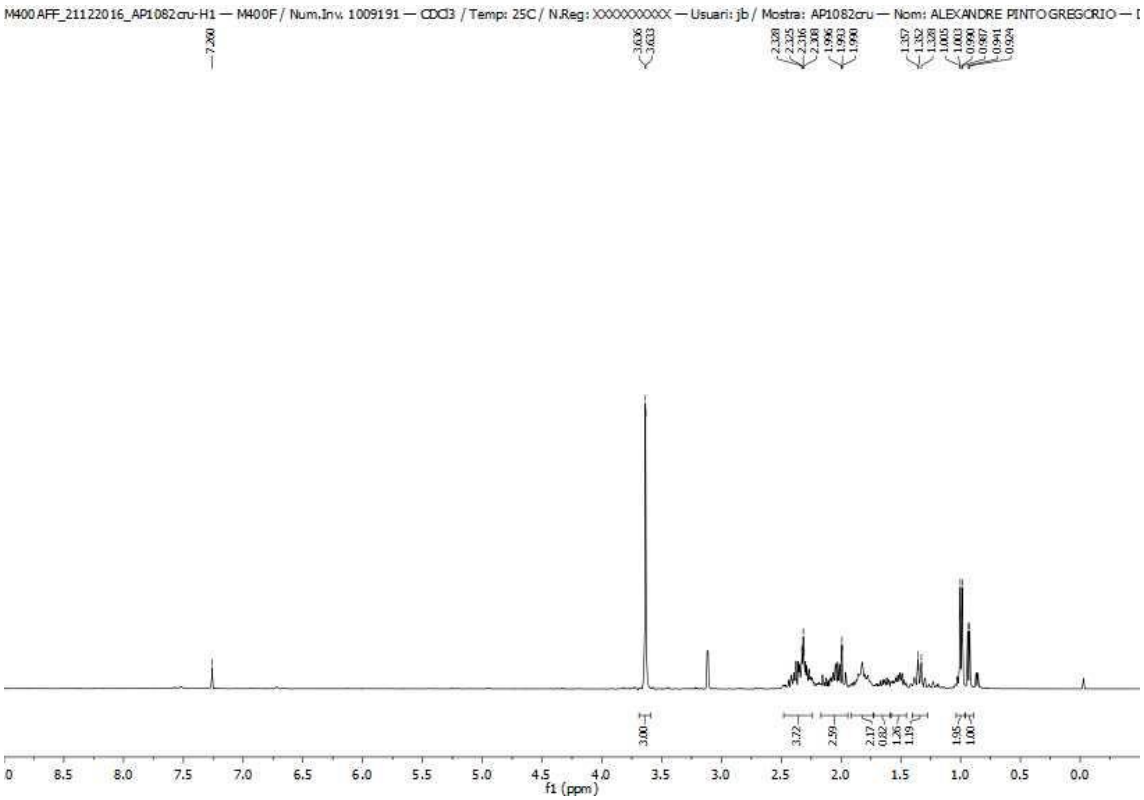
Methyl (*R*)-4-methyl-6-oxocyclohexanepropionate (103)

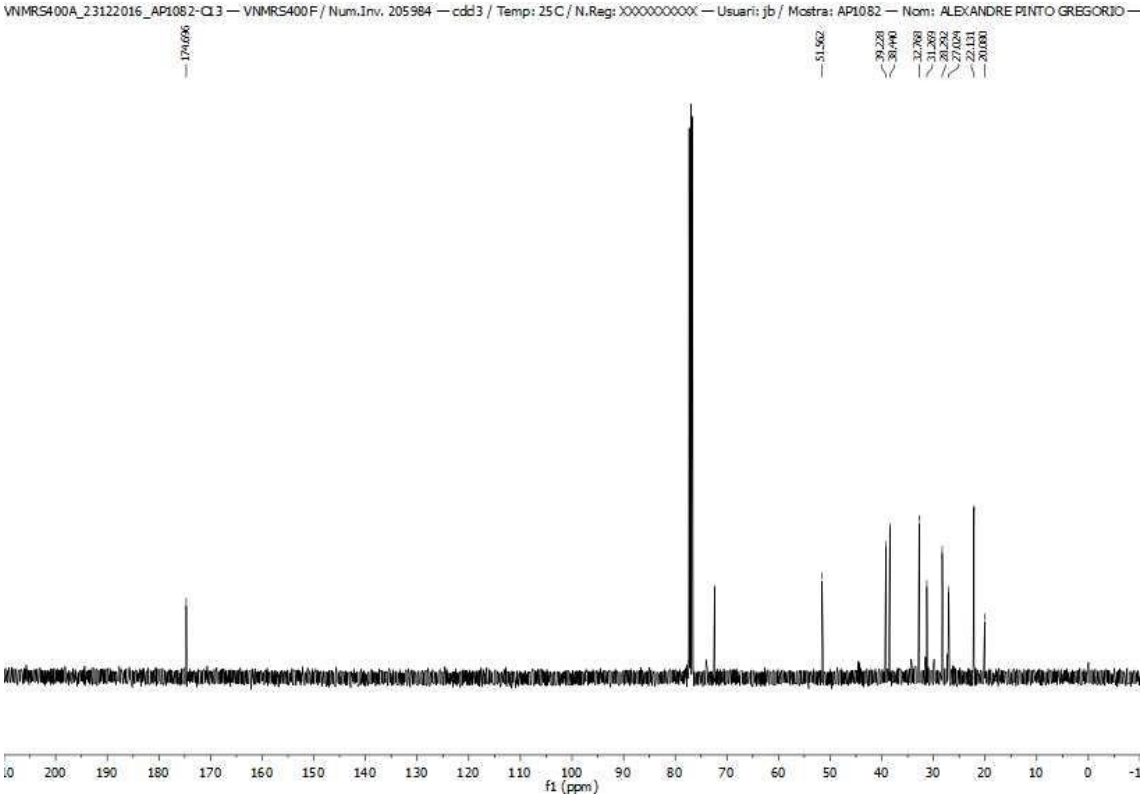
A solution of compound **86** (150 mg, 0.76 mmol) in MeOH (5.0 mL), containing PtO_2 (45 mg), was stirred under hydrogen at room temperature for 24 h. The catalyst was removed by filtration, and the solvent was evaporated affording **103** (147 mg, 97%) as a yellowish oil as a 2:1 mixture of isomers.

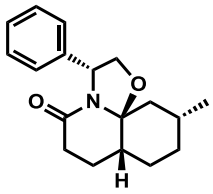
^{1}H-NMR (400 MHz, $CDCl_3$, major isomer) δ: 0.99 (d, J = 6.4 Hz, 3H, CH_3), 1.30-1.39 (m, 2H) 1.46-1.58 (m, 1H), 1.60-1.71 (m, 2H), 1.75-1.92 (m, 2H), 1.96-2.16 (m, 2H), 2.24-2.47 (m, 3H), 3.64 (s, 3H, OCH_3).

^{13}C-NMR (100.6 MHz, $CDCl_3$, major isomer) δ: 20.1 (CH_2), 22.1 (CH_3), 27.0 (CH_2), 28.3 (CH_2), 31.3 (CH), 32.8 (CH_2), 38.4 (CH_2), 39.3 (CH), 51.6 (CH_3), 174.7 (COO).

HRMS calcd for [$C_{11}H_{18}O_3 + H^+$]: 199.1329, found 199.1319.


M400AFF_21122016_AP1082cru-H1 — M400F / Num.Inv. 1009191 — CDCl3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP1082cru — Nom: ALEXANDRE PINTO GREGORIO — I
7.260
3.636
3.633
2.328
2.325
2.316
2.308
1.996
1.993
1.990
1.357
1.352
1.328
1.005
1.003
0.990
0.987
0.941
0.924
3.00
3.72
2.59
2.17
0.82
1.26
1.19
1.95
1.00
f1 (ppm)


VNMRS400A_23122016_AP1082-C13 — VNMRS400F / Num.Inv. 205984 — cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP1082 — Nom: ALEXANDRE PINTO GREGORIO —
174.696
51.562
39.228
38.440
32.769
31.369
28.292
27.024
22.131
20.100
f1 (ppm)



(3*R*,7a*R*,10*R*,11a*S*)-10-Methyl-5-oxo-3-phenylperhydrooxazolo[2,3-*j*]quinoline (104a)

Operating as described in the preparation of lactam **91**, from keto ester **103** (73 mg, 0.37 mmol), (*R*)-phenylglycinol (76 mg, 0.55 mmol), and AcOH (30 µL, 0.55 mmol) in benzene (5 mL), lactam **104a** (78 mg, 76%) was obtained after flash chromatography (7:3 hexane–EtOAc) as an orange oil.

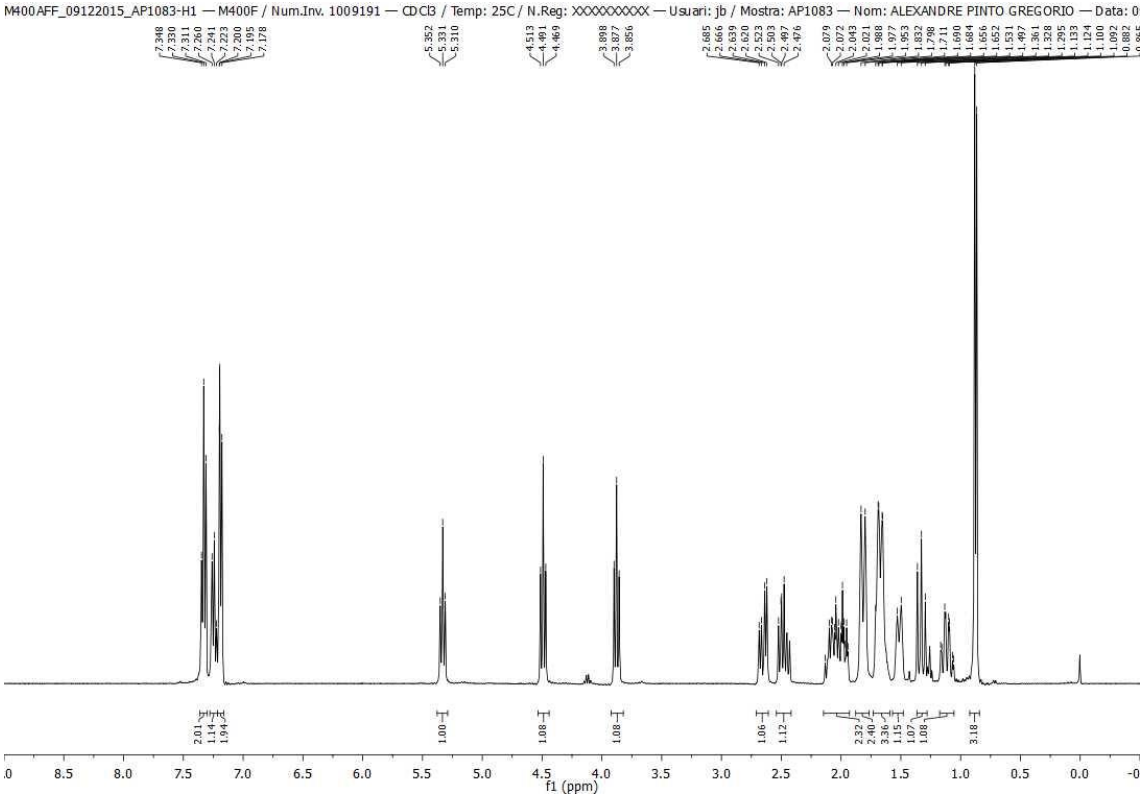
^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) *δ:* 0.87 (d, *J* = 6.8 Hz, 3H, CH_3), 1.11 (dt, *J* = 4.0, 13.6 Hz, 1H, H-9), 1.33 (t, *J* = 13.2 Hz, 1H, H-11), 1.51 (d, *J* = 13.4 Hz, 1H, H-9), 1.61-1.69 (m, 3H, H-7, H-8, H-10), 1.82 (d, *J* = 13.4 Hz, 2H, H-7a, H-11), 1.93-2.12 (m, 2H, H-7, H-8), 2.48 (ddd, *J* = 2.0, 7.6, 18.4 Hz, 1H, H-6), 2.65 (d, *J* = 7.6, 18.4 Hz, 1H, H-6), 3.88 (t, *J* = 8.6 Hz, 1H, H-2), 4.49 (t, *J* = 8.6 Hz, 1H, H-2), 5.33 (t, *J* = 8.6 Hz, 1H, H-3), 7.19 (d, *J* = 8.0 Hz, 2H, H-Ar), 7.23-7.26 (m, 1H, H-Ar), 7.33 (t, *J* = 7.4 Hz, 2H, H-Ar).

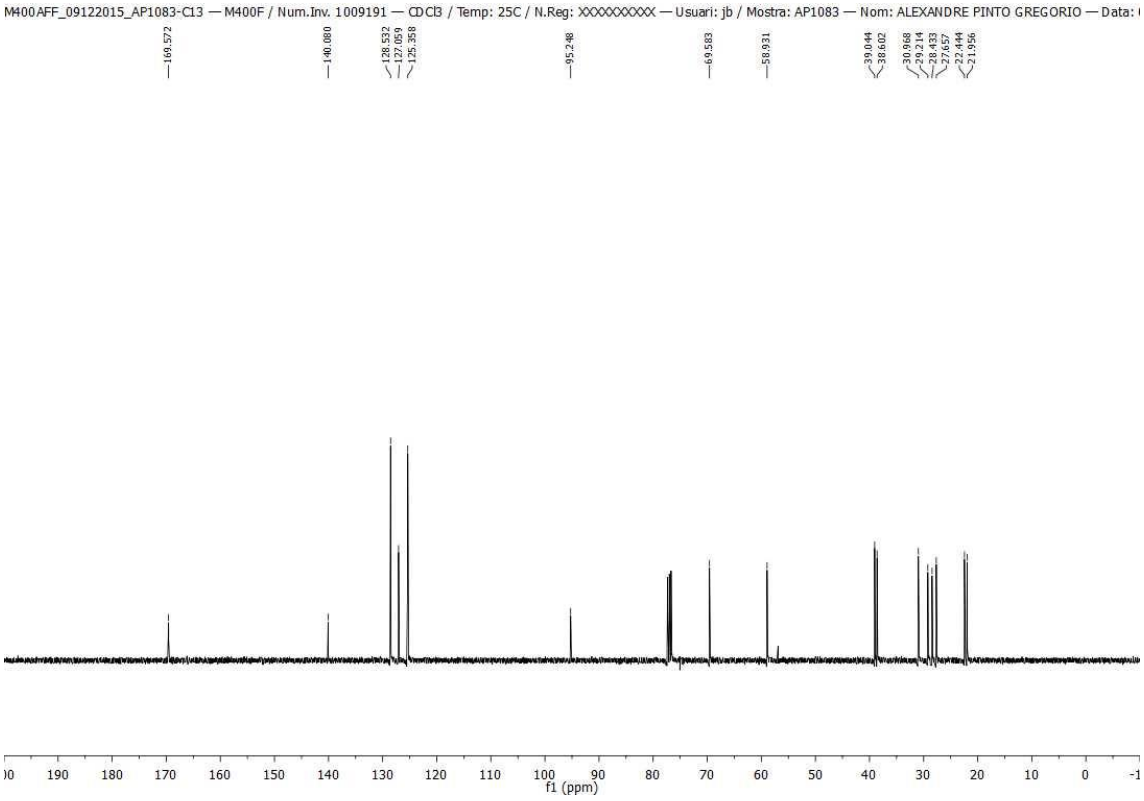
^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ:* 22.0 (CH_3), 22.4 (C-7), 27.7 (C-8), 28.4 (C-9), 29.2 (C-10), 31.0 (C-6), 38.6 (C-11), 39.0 (C-7a), 58.9 (C-3), 69.6 (C-2), 95.3 (C-11a), 125.4 (C-H_{Ar}), 127.1 (2C-H_{Ar}), 128.5 (C-H_{Ar}), 140.1 (Cq-Ar), 169.6 (NCO).

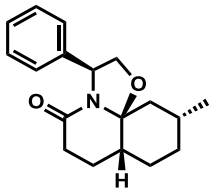
IR (NaCl): 1652 cm^{-1}.

HRMS calcd for [$C_{18}H_{23}NO_2$+ H^+]: 286.1802, found 286.1801.

$[\alpha]^{23}_{D}$ = – 104.3 (c 2.0, $CHCl_3$).


M400AFF_09122015_AP1083-H1 — M400F / Num.Inv. 1009191 — CDCl3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP1083 — Nom: ALEXANDRE PINTO GREGORIO — Data: 0
f1 (ppm)


M400AFF_09122015_AP1083-C13 — M400F / Num.Inv. 1009191 — CDCl3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP1083 — Nom: ALEXANDRE PINTO GREGORIO — Data:
f1 (ppm)



(3*S*,7a*S*,10*R*,11a*R*)-10-Methyl-5-oxo-3-phenylperhydrooxazolo[2,3-*j*]quinoline (105a) and (3*S*,7a*R*,10*R*,11a*S*)-10-methyl-5-oxo-3-phenylperhydrooxazolo[2,3-*j*]quinoline (105b)

Operating as described in the preparation of lactam **91**, from keto ester **103** (77 mg, 0.39 mmol), (*S*)-phenylglycinol (80 mg, 0.58 mmol), and AcOH (30 µL, 0.58 mmol) in benzene (5 mL), an inseparable mixture (15:85 by GC-MS) of lactams **105a** and **105b** (97 mg, 83%) was obtained after flash chromatography (7:3 hexane–EtOAc) as an orange oil. **105a** (data from the mixture).

^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) *δ:* 0.92 (d, *J* = 6.4 Hz, 3H, CH_3), 1.11-1.24 (m, 2H), 1.47-1.57 (m, 1H), 1.62-1.80 (m, 4H), 1.90-2.06 (m, 2H), 2.08-2.20 (m, 1H), 2.24-2.50 (m, 2H), 3.87 (dd, *J* = 1.8, 7.6 Hz, 1H, H-2), 4.39 (dd, *J* = 1.8, 7.6 Hz, 1H, H-2), 4.92 (dd, *J* = 1.8, 7.6 Hz, 1H, H-3), 7.16-7.31 (m, 5H, Ar).

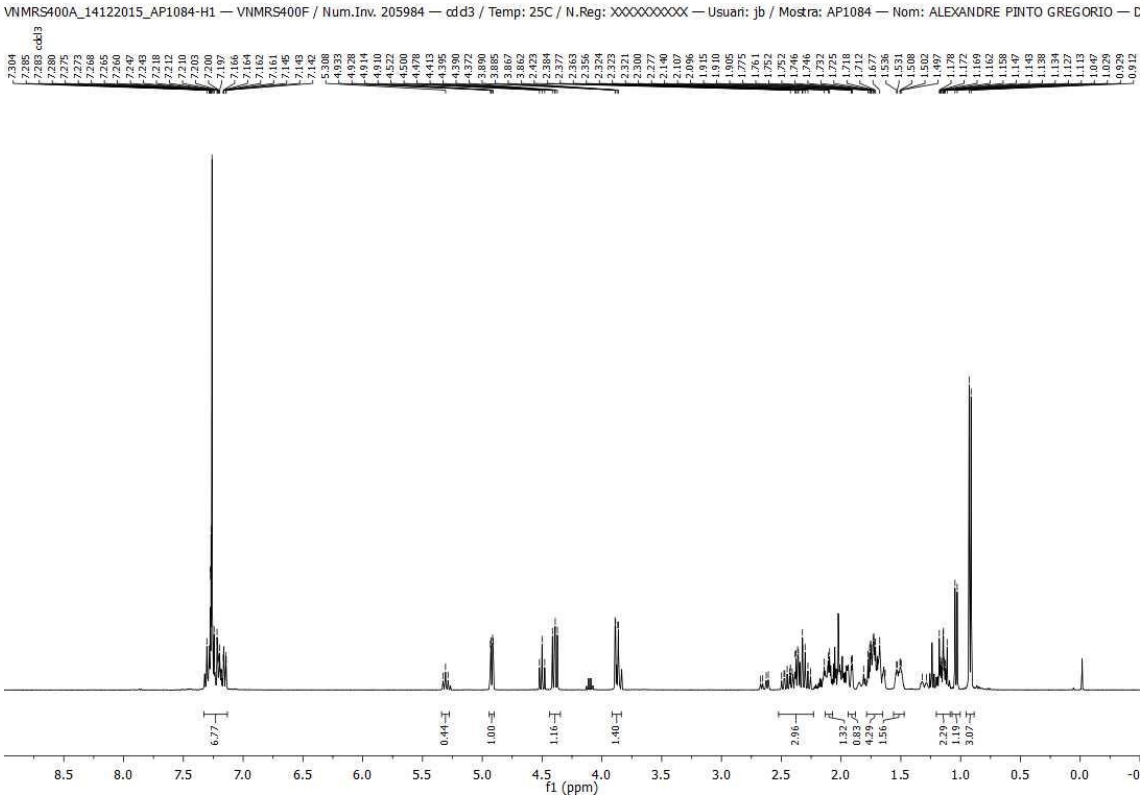
^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ:*21.9 (CH_3), 22.4 (CH_2), 27.5 (CH_2), 28.0 (CH_2), 29.7 (C-10), 34.4 (CH_2), 37.9 (CH_2 and C-7a), 59.3 (C-3), 71.0 (C-2), 94.6 (C-11a), 125.3 (C-H_{Ar}), 127.3 (C-H_{Ar}), 128.5 (C-H_{Ar}), 142.0 (Cq-Ar), 167.3 (NCO).

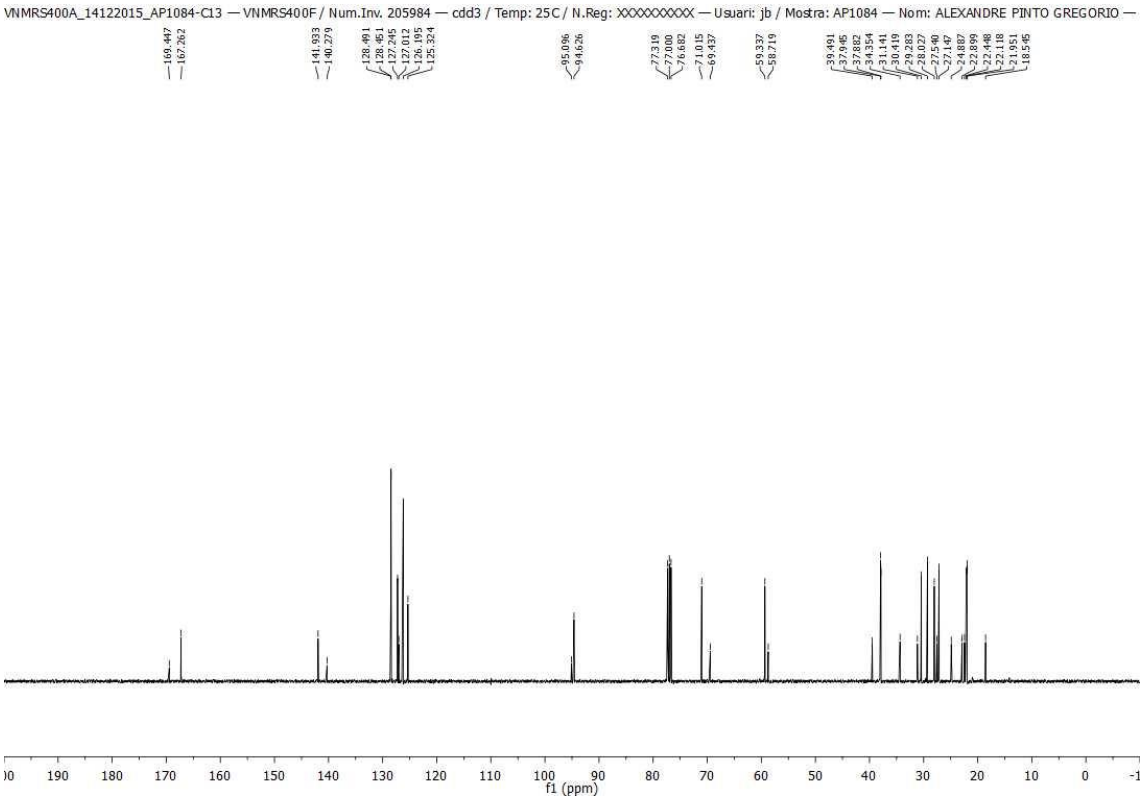
HRMS calcd for [$C_{18}H_{23}NO_2$+ H^+]: 286.1802, found 286.1798.

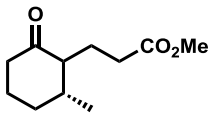
105b (selected data from the mixture):

^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) *δ:* 1.04 (d, *J* = 7.2 Hz, 3H, CH_3), 2.64 (dd, *J* = 6.8, 18.4 Hz, 1H, H-6), 4.50 (t, *J* = 8.4 Hz, 1H, H-2), 5.31 (t, *J* = 8.4 Hz, 1H, H-3).

^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ:* 18.6 (CH_3), 58.7 (C-3), 69.4 (C-2), 95.1 (C-11a), 169.5 (NCO).


VNMRS400A_14122015_AP1084-H1 — VNMRS400F / Num.Inv. 205984 — cdd3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP1084 — Nom: ALEXANDRE PINTO GREGORIO — D
f1 (ppm)


VNMRS400A_14122015_AP1084-C13 — VNMRS400F / Num.Inv. 205984 — cdd3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP1084 — Nom: ALEXANDRE PINTO GREGORIO —
f1 (ppm)



Methyl (2*R*)-2-methyl-6-oxocyclohexanepropionate (106)

First step: N,N-(dimethyl)methyliminium chloride (615 mg, 6.58 mmol) was added to a solution of (*R*)-pulegone (1 g, 6.58 mmol) in CH_3CN (6 mL) and the mixture was stirred at reflux temperature until the complete dissolution of the salt. After cooling to room temperature stirring was continued for 18 h. The solvent was evaporated affording an oil which was taken up in EtOAc. The resulting organic solution was extracted with 1N aqueous HCl and the aqueous extracts were basified by the addition of saturated aqueous $NaHCO_3$, and then extracted with AcOEt. The organic extracts were dried and concentrated to afford a crude amine which was used in the next step without further purification.

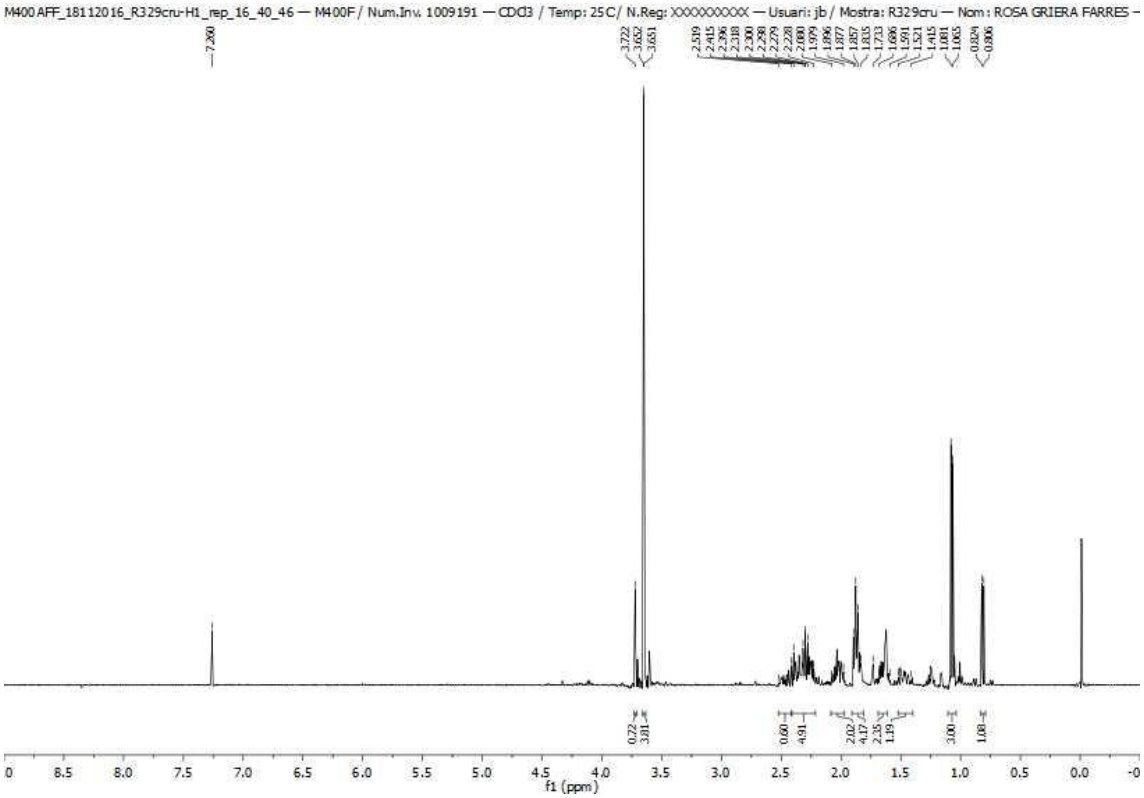
Second step: NaOH (104 mg, 2.6 mmol) and diethyl malonate (1.1 mL, 6.58 mmol) were added to a solution of the above amine in toluene (15 mL) and the mixture was heated at the reflux temperature for 24 h. Then, AcOH–HCl (2:1, 15 mL) was added to the mixture and the stirring was continued at the reflux temperature for 16 h. After cooling to room temperature, 1N aqueous NaOH was added (pH = 10-12) and the resulting biphasic mixture was extracted with EtOAc. 2N aqueous HCl was added to the aqueous phase (until pH = 2-3) and the organic residue was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated to afford a crude keto acid which was used in the next step without further purification.

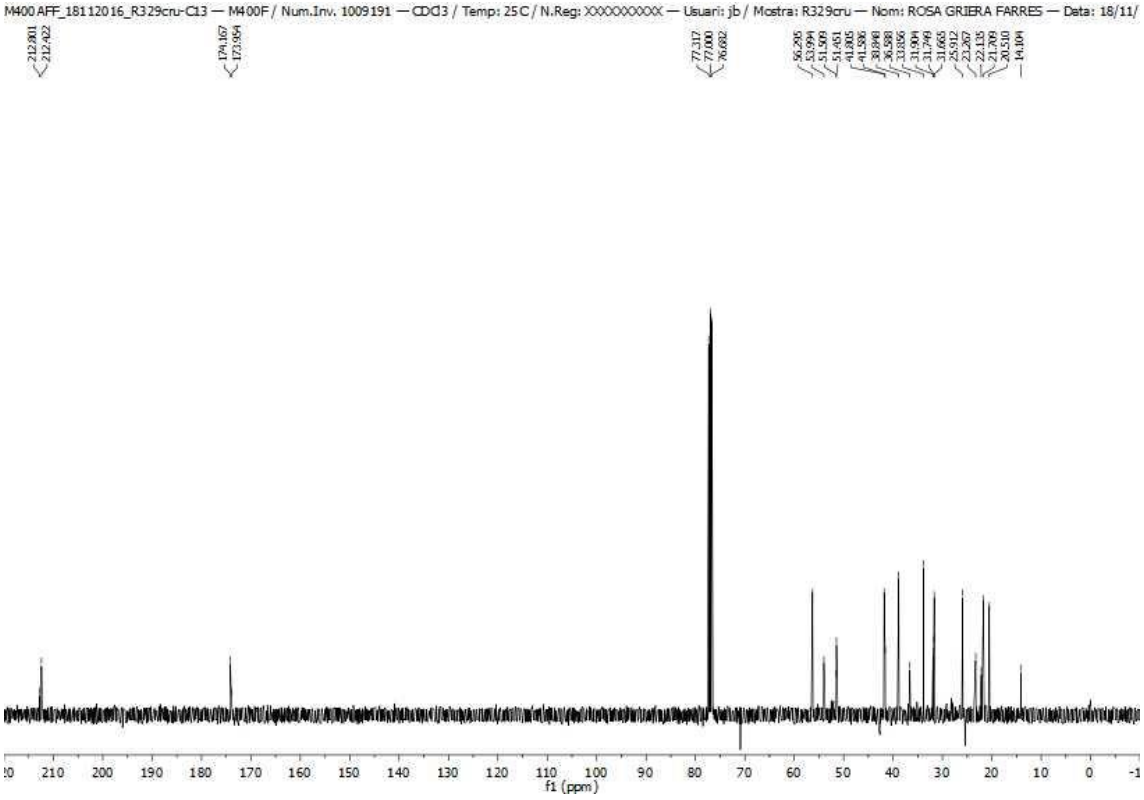
Third step: A solution of the above keto acid and TMSCl (3.6 mL 28 mmol) in MeOH (22 mL) was stirred at room temperature for 24 h. The solvent was evaporated affording an oil which was taken up in EtOAc. The organic solution was washed with saturated aqueous $NaHCO_3$, dried and concentrated affording keto ester **106** (326 mg, 25%, 5:1 *cis:trans* mixture).

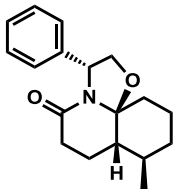
^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) *δ:* 0.81 and 1.07 (d, *J* = 7.2 and 6.4 Hz, 3H, CH_3), 1.42-1.52 (m, 1H), 1.59-1.69 (m, 2H), 1.84-1.90 (m, 4H), 1.98-2.08 (m, 2H), 2.23-2.40 (m, 5H), 2.42-2.52 (m, 1H), 3.65 and 3.72 (s, 3H, OCH_3).

^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ:*20.5 and 21.7 (CH_3), 22.1 and 23.3 (CH_2), 25.9 (CH_2), 31.7 (CH_2), 31.8 and 31.9 (CH_2), 33.9 and 36.6 (CH_2), 38.5 (CH), 41.6 and 41.8 (CH_2), 51.5 (OCH_3), 56.3 and 54.0 (CH), 174.0 and 174.2 (COO), 212.4 and 212.8 (CO).

HRMS calcd for [$C_{11}H_{18}O_3$ + H^+]: 199.1329, found 199.1328.


M400AFF_18112016_R329cru-H1_rep_16_40_46 — M400F / Num.Inv. 1009191 — CDCl3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: R329cru — Nom: ROSA GRIERA FARRES –
f1 (ppm)


M400AFF_18112016_R329cru-C13 — M400F / Num.Inv. 1009191 — CDCl3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: R329cru — Nom: ROSA GRIERA FARRES — Data: 18/11/
f1 (ppm)



(3*R*,7a*S*,8*R*,11a*S*)-8-Methyl-5-oxo-3-phenylperhydrooxazolo[2,3-*j*]quinoline (107a)

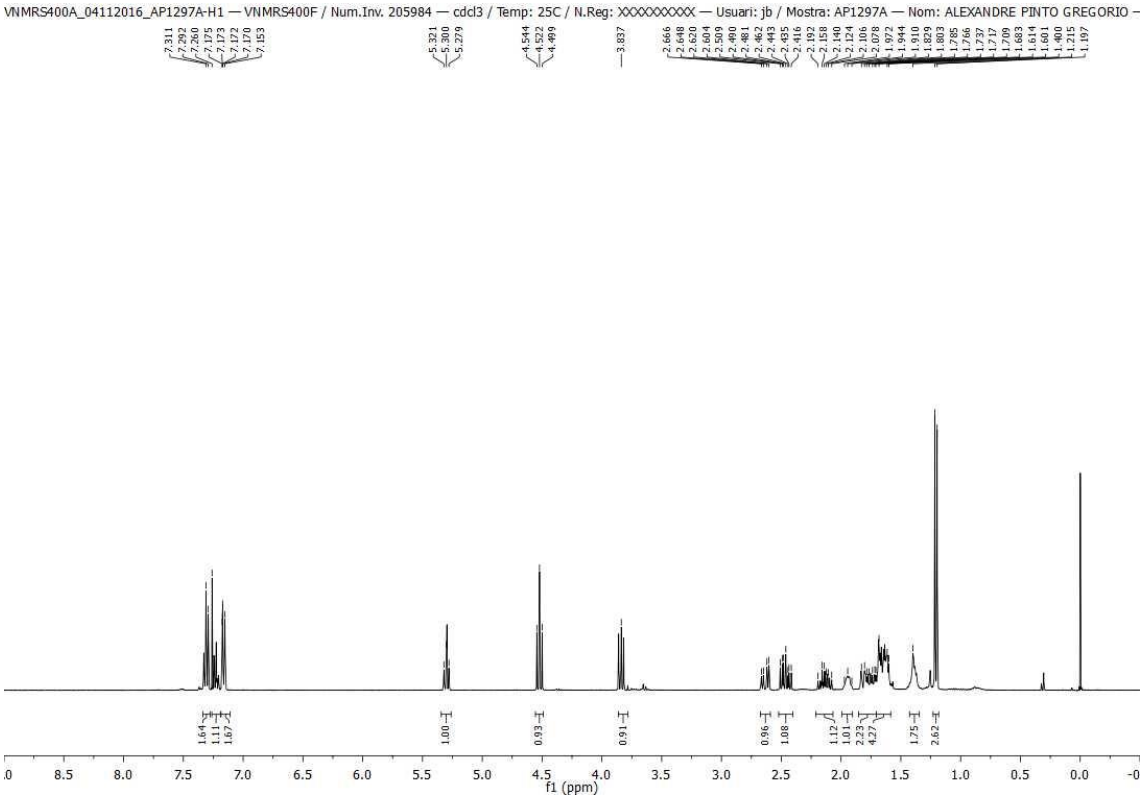
Operating as described in the preparation of lactam **91**, from keto ester **106** (72 mg, 0.36 mmol), (*R*)-phenylglycinol (75 mg, 0.54 mmol), and AcOH (30 µL, 0.58 mmol) in benzene (5 mL), lactams **107a** (34 mg, 33%) and **107b** (36 mg, 35%) were obtained after flash chromatography (from 7:3 to 4:6 hexane–EtOAc).

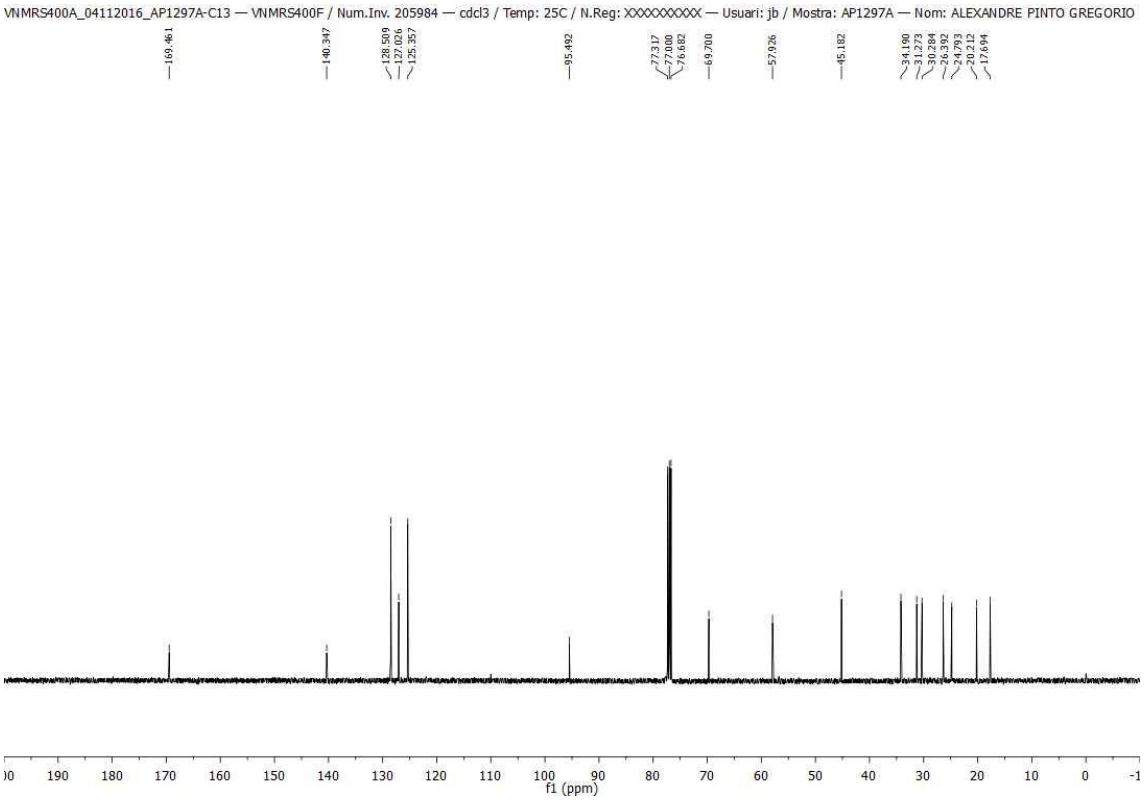
107a (higher *Rf*)

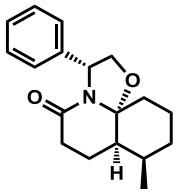
^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) *δ:* 1.21 (d, *J* = 7.2 Hz, 3H, CH_3), 1.35-1.43 (m, 2H), 1.58-1.71 (m, 4H), 1.72-1.83 (m, 2H), 1.91-1.97 (m, 1H), 2.46 (ddd, *J* = 7.4, 11.2, 18.4 Hz, 1H, H-6), 2.63 (dd, *J* = 7.4, 18.4 Hz, 1H, H-6) 3.84 (dd, *J* = 1.8, 7.6 Hz, 1H, H-2), 4.52 (t, *J* = 8.4 Hz, 1H, H-2), 5.30 (t, *J* = 8.4 Hz, 1H, H-3), 7.15-7.33 (m, 5H, H-Ar).

^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ:* 17.7 (C-10), 20.2 (CH_3), 24.8 (C-7), 26.4 (C-11), 30.3 (C-9), 31.3 (C-6), 34.2 (C-8), 45.2 (C-7a), 57.9 (C-3), 69.7 (C-2), 94.5 (C-11a), 125.4 (2C-H_{Ar}), 127.0 (C-H_{Ar}), 128.5 (2C-H_{Ar}), 140.4 (Cq-Ar), 169.5 (NCO).

$[\alpha]^{23}_{D}$ = – 103.8 (c 0.61, CH_3OH).


VNMRS400A_04112016_AP1297A-H1 — VNMRS400F / Num.Inv. 205984 — cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP1297A — Nom: ALEXANDRE PINTO GREGORIO –
7.311
7.292
7.280
7.175
7.173
7.172
7.170
7.153
5.321
5.300
5.279
4.544
4.522
4.499
3.837
2.666
2.648
2.620
2.604
2.509
2.490
2.481
2.462
2.443
2.435
2.416
2.192
2.158
2.140
2.124
2.106
2.078
1.972
1.944
1.910
1.829
1.803
1.785
1.766
1.737
1.717
1.709
1.683
1.614
1.601
1.400
1.215
1.197
1.64
1.11
1.67
1.00
0.93
0.91
0.96
1.08
1.12
1.01
2.23
4.27
1.75
2.62
f1 (ppm)


VNMRS400A_04112016_AP1297A-C13 — VNMRS400F / Num.Inv. 205984 — cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP1297A — Nom: ALEXANDRE PINTO GREGORIO
169.461
140.347
128.509
127.026
125.357
95.492
77.317
77.000
76.682
69.700
57.926
45.182
34.190
31.273
30.284
26.392
24.793
20.212
17.694
f1 (ppm)



(3*R*,7a*R*,8*R*,11a*R*)-8-Methyl-5-oxo-3-phenylperhydrooxazolo[2,3-*j*]quinoline (107b)

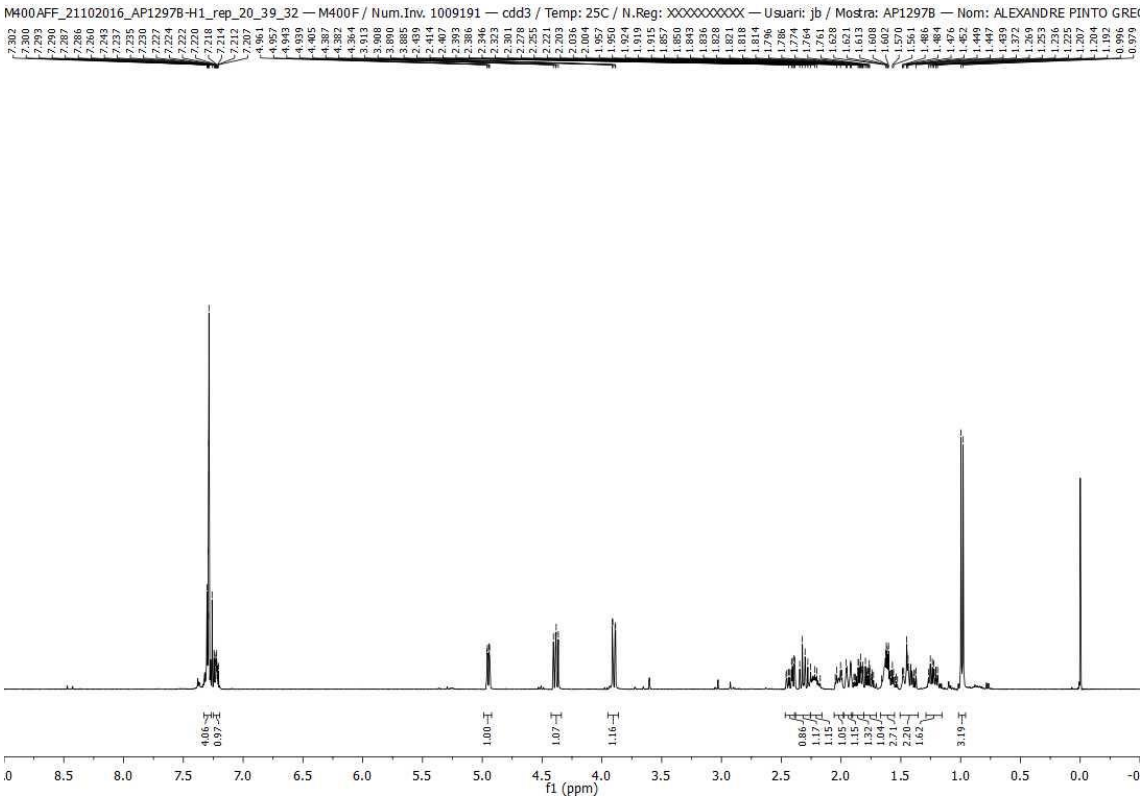
(lower *Rf*)

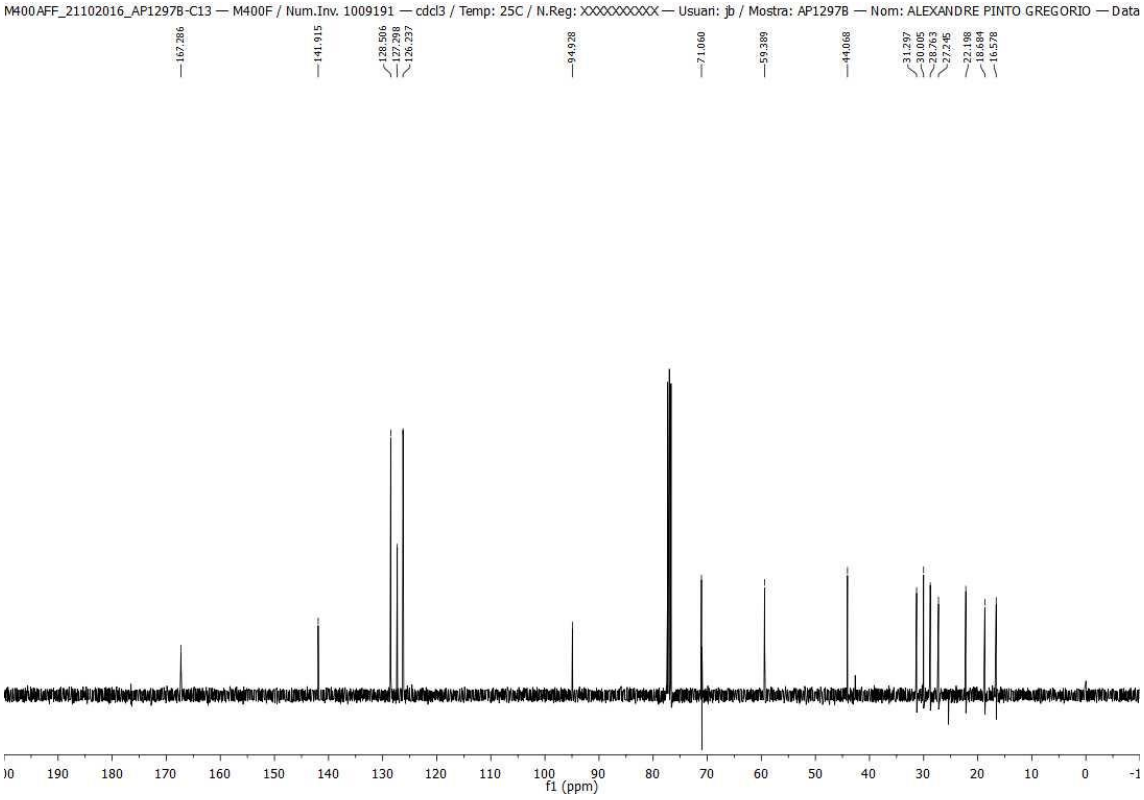
^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) *δ:* 0.99 (d, *J* = 6.8 Hz, 3H, CH_3), 1.19-1.27 (m, 1H, H-9), 1.37.1.49 (m, 2H, H-9, H-11), 1.53-1.64 (m, 2H, H-10), 1.73-1.80 (m, 1H, H-7), 1.81-1.89 (m, 1H, H-7), 1.92-1.96 (br.d, 1H, H-11), 1.99-2.05 (m, 1H, H-7a), 2.17-2.26 (m, 1H, H-8), 2.23-2.35 (m, 1H, H-6), 2.44 (dd, *J* = 2.8, 8.4 Hz, 1H, H-6), 3.90 (dd, *J* = 1.8, 9.2 Hz, 1H, H-2), 4.38 (dd, *J* = 7.2, 9.2 Hz, 1H, H-2), 4.95 (dd, *J* = 1.8, 7.2 Hz, 1H, H-3), 7.21-7.24 (m, 1H, H-Ar), 7.29-7.30 (m, 4H, H-Ar).

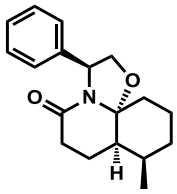
^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ:* 16.6 (C-7), 18.7 (CH_3), 22.2 (C-10), 27.3 (C-9), 28.8 (C-11), 30.0 (C-6), 31.3 (C-8), 44.1 (C-7a), 59.4 (C-3), 71.1 (C-2), 94.9 (C-11a), 126.2 (2C-H_{Ar}), 127.3 (C-H_{Ar}), 128.5 (2C-H_{Ar}), 142.0 (Cq-Ar), 167.3 (C-5).

HRMS calcd for [$C_{18}H_{23}NO_2$+ H^+]: 286.1802, found 286.1803.

$[\alpha]^{23}_{D}$ = – 92.8 (c 0.55, $CHCl_3$).


M400AFF_21102016_AP1297B-H1_rep_20_39_32 — M400F / Num.Inv. 1009191 — cdd3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP1297B — Nom: ALEXANDRE PINTO GRE
4.06
0.97
1.00
1.07
1.16
0.86
1.17
1.15
1.05
1.15
1.32
1.04
2.71
2.20
1.62
3.19
f1 (ppm)


M400AFF_21102016_AP1297B-C13 — M400F / Num.Inv. 1009191 — cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP1297B — Nom: ALEXANDRE PINTO GREGORIO — Data
167.286
141.915
128.506
127.298
126.237
94.928
71.060
59.389
44.068
31.297
30.005
28.763
27.245
22.198
18.684
16.578
f1 (ppm)



(3*S*,7a*R*,8*R*,11a*R*)-8-Methyl-5-oxo-3-phenylperhydrooxazolo[2,3-*j*]quinoline (108a)

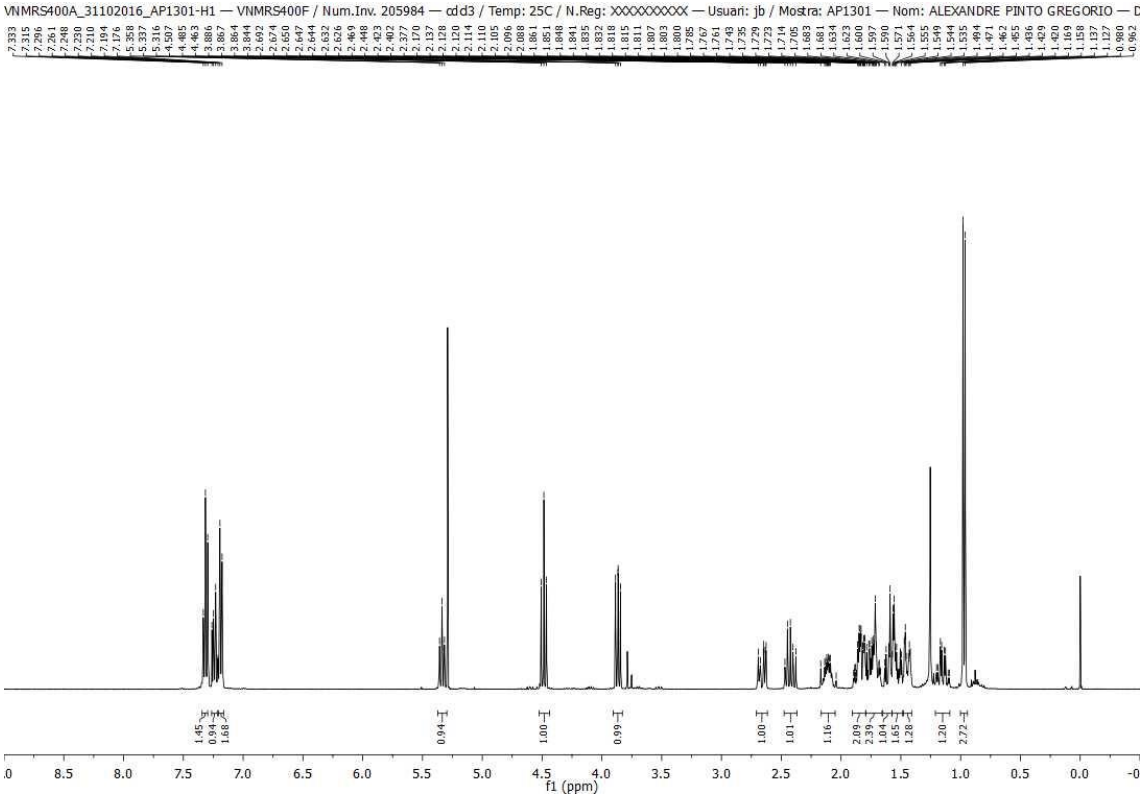
Operating as described in the preparation of lactam **91**, from keto ester **106** (100 mg, 0.5 mmol), (*S*)-phenylglycinol (104 mg, 0.76 mmol), and AcOH (45 µL, 0.76 mmol) in benzene (10 mL), lactam **108a** (110 mg, 76%) was obtained after flash chromatography (8:2 hexane–EtOAc).

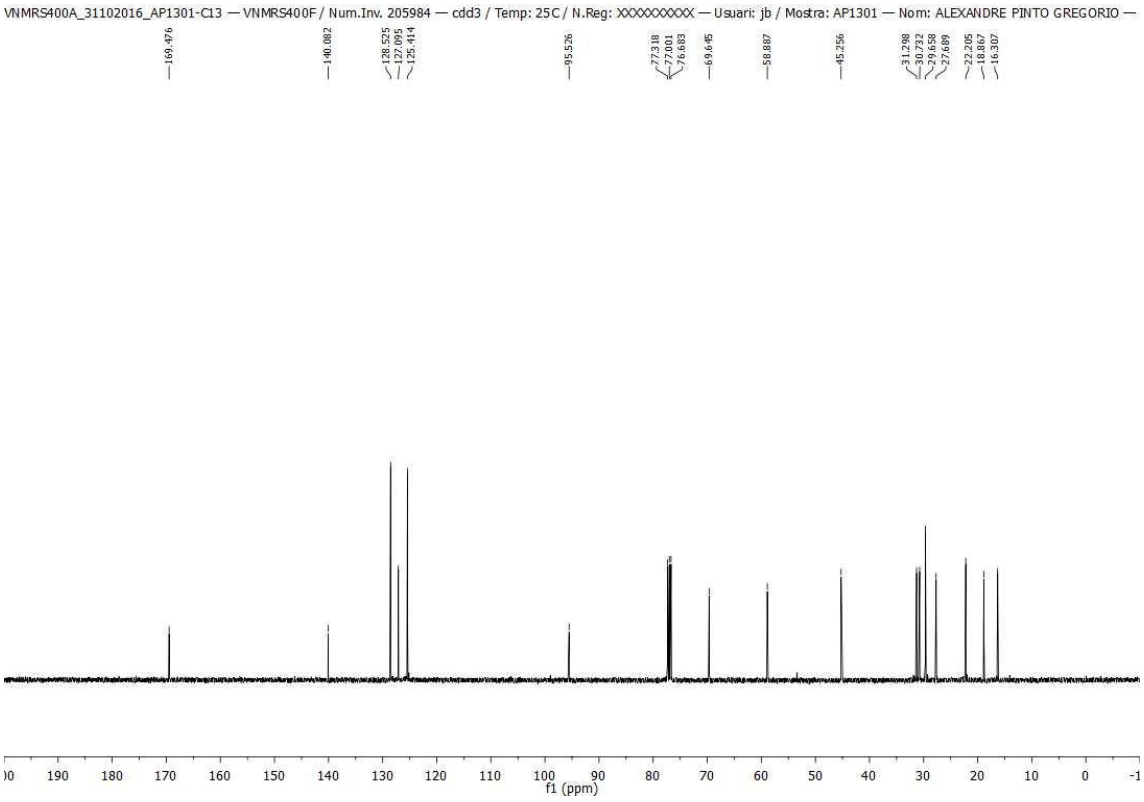
^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) *δ:* 0.97 (d, *J* = 7.2 Hz, 3H, CH_3), 1.15 (ddd, *J* = 3.6, 12.8, 16.8 Hz, 1H, H-9), 1.42-1.47 (m, 1H, H-9), 1.49-1.57 (m, 2H, H-10), 1.59-1.63 (m, 1H, H-11), 1.67-1.77 (m, 2H, H-7, H-7a), 1.79-1.90 (m, 2H, H-7, H-11), 2.04-2.17 (m, 1H, H-8), 2.38-2.47 (m, 1H, H-6), 2.63-2.70 (m, 1H, H-6), 3.86 (dd, *J* = 8.4, 8.8 Hz, 1H, H-2), 4.49 (t, *J* = 8.8 Hz, 1H, H-2), 5.34 (t, *J* = 8.4 Hz, 1H, H-3), 7.17-7.20 (m, 2H, H-Ar), 7.23-7.26 (m, 1H, H-Ar), 7.30-7.34 (m, 2H, H-Ar).

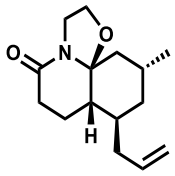
^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ:* 16.3 (C-7), 18.9 (CH_3), 22.2 (C-10), 27.8 (C-9), 29.7 (C-11), 30.7 (C-6), 31.3 (C-8), 45.3 (C-7a), 58.9 (C-3), 69.7 (C-2), 95.5 (C-11a), 125.4 (2C-H_{Ar}), 127.1 (C-H_{Ar}), 128.5 (2C-H_{Ar}), 140.1 (Cq-Ar), 169.5 (NCO).

HRMS calcd for [$C_{18}H_{23}NO_2$ + H^+]: 286.1802, found 286.1803.

$[\alpha]^{23}_{D}$ = + 105.5 (c 1.55, $CHCl_3$).


VNMRS400A_31102016_AP1301-H1 — VNMRS400F / Num.Inv. 205984 — cdd3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP1301 — Nom: ALEXANDRE PINTO GREGORIO — D
f1 (ppm)


VNMRS400A_31102016_AP1301-C13 — VNMRS400F / Num.Inv. 205984 — cdd3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP1301 — Nom: ALEXANDRE PINTO GREGORIO —
f1 (ppm)



(7a*R*,8*R*,10*R*,11a*R*)-8-Allyl-10-methyl-5-oxo-3-phenylperhydrooxazolo[2,3-*j*]quinolone (109a)

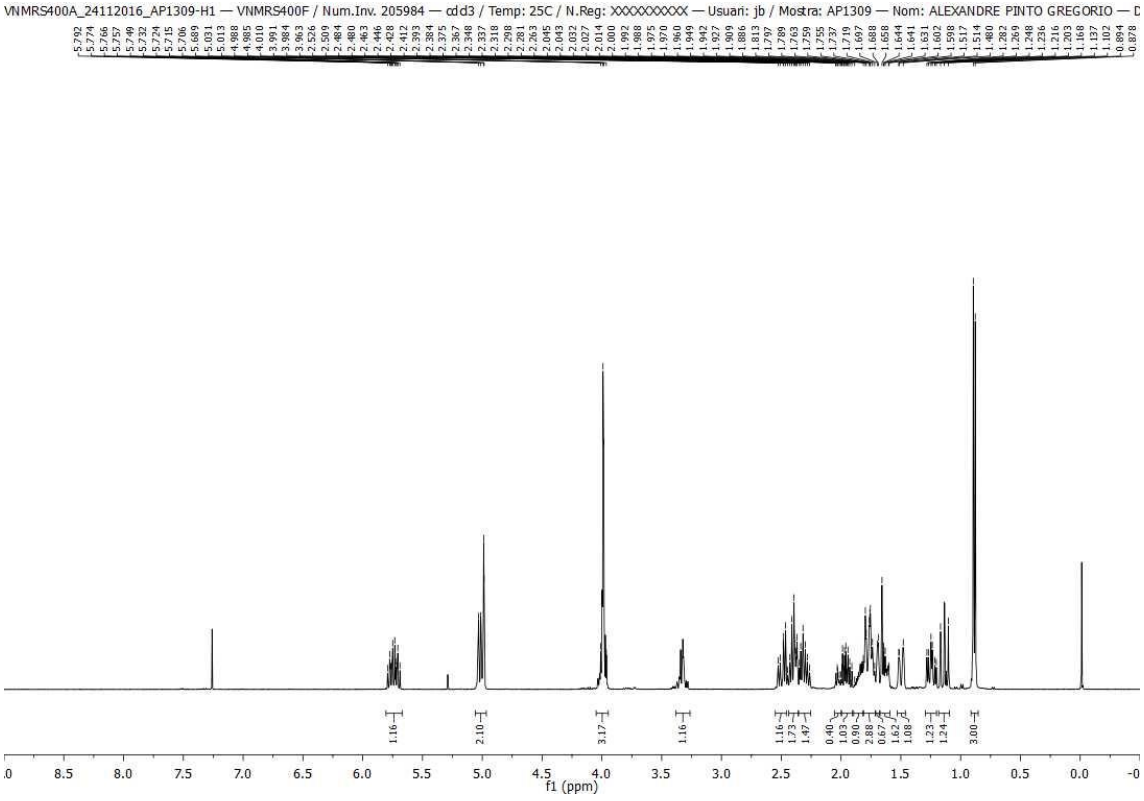
Operating as described in the preparation of lactam **91**, from keto ester **90** (322 mg, 1.35 mmol), 2-aminoethanol (120 µL, 2.03 mmol), and AcOH (120 µL, 2.03 mmol) in benzene (15 mL), lactams **109a** (258 mg, 76%) and **109b** (16 mg, 5%) were obtained after flash chromatography (2:8 hexane–EtOAc) as colorless oils. **109a** (higher *Rf*).

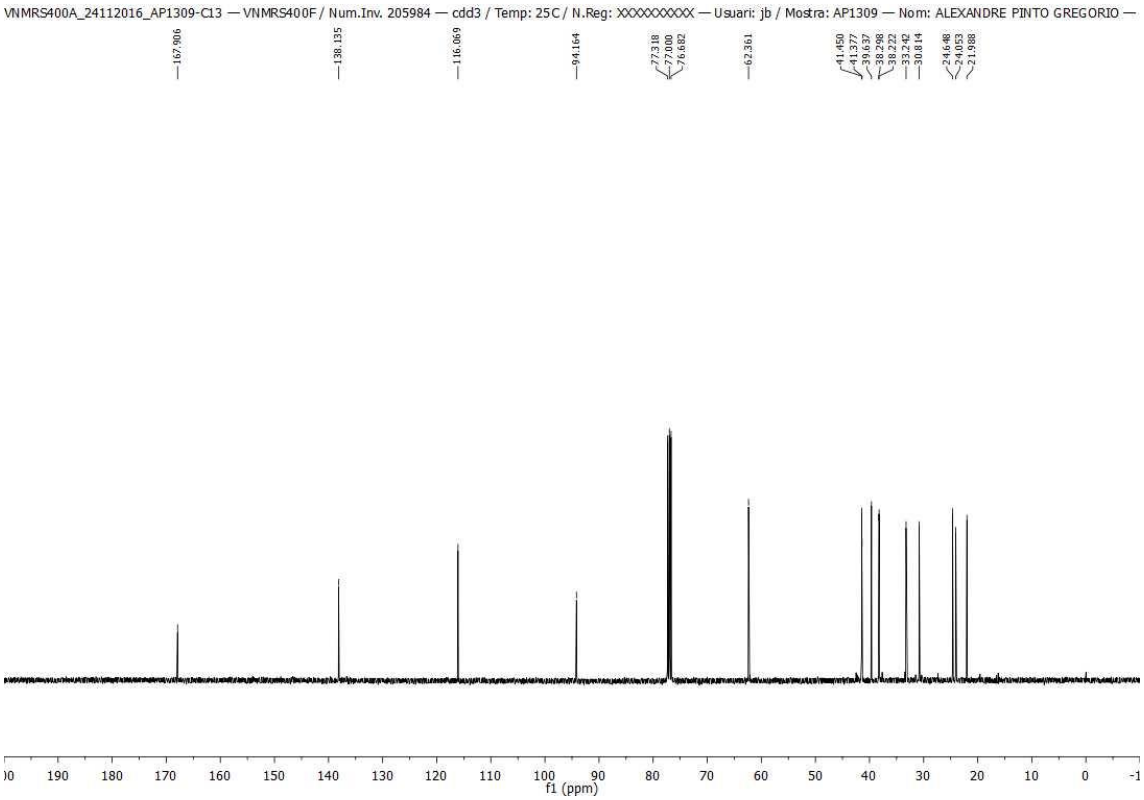
^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) *δ:* 0.88 (d, *J* = 6.4 Hz, 3H, CH_3), 1.14 (t, *J* = 13.2 Hz, 1H, H-11), 1.24 (dt, *J* = 5.2, 13.6 Hz, 1H, H-9), 1.48-1.52 (m, 1H, H-9), 1.60-1.66 (m, 2H, H-7, H-7a), 1.69-1.80 (m, 2H, H-8, H-11), 1.81-1.89-2.04 (m, 1H, H-10), 1.91-2.05 (m, 1H, H-7), 2.26-2.35 (m, 1H, H-6), 2.37-2.45 (m, 2H, H-6, H-1'), 2.50 (dd, *J* = 14.0, 18.0 Hz, 1H, H-1'), 3.31-3.34 (m, 1H, H-3), 3.96-4.01 (m, 3H, H-2, H-3), 4.98-5.04 (m, 2H, CH=CH_2), 5.80 (dddd, *J* = 7.2, 10.4, 14.0, 17.2 Hz 1H, C*H*=CH_2).

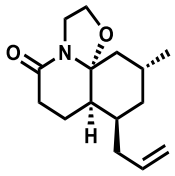
^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ:* 22.0 (CH_3), 24.1 (C-10), 24.5 (C-7), 30.8 (C-1'), 33.2 (C-9), 38.2 (C-11), 38.3 (C-6), 39.6 (C-8), 41.4 (C-7a), 41.5 (C-3), 60.4 (C-2), 94.2 (C-11a), 116.1 (C=*C*H_2), 138.1 (*C*H=C), 167.9 (NCO).

HRMS calcd for [$C_{15}H_{23}NO_2$ + H^+]: 250.1802, found 250.1801.

$[\alpha]^{23}_D$ = + 33.7 (c 0.87, $CHCl_3$).


VNMRS400A_24112016_AP1309-H1 — VNMRS400F / Num.Inv. 205984 — cdd3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP1309 — Nom: ALEXANDRE PINTO GREGORIO — D
f1 (ppm)


VNMRS400A_24112016_AP1309-C13 — VNMRS400F / Num.Inv. 205984 — cdd3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP1309 — Nom: ALEXANDRE PINTO GREGORIO —
f1 (ppm)



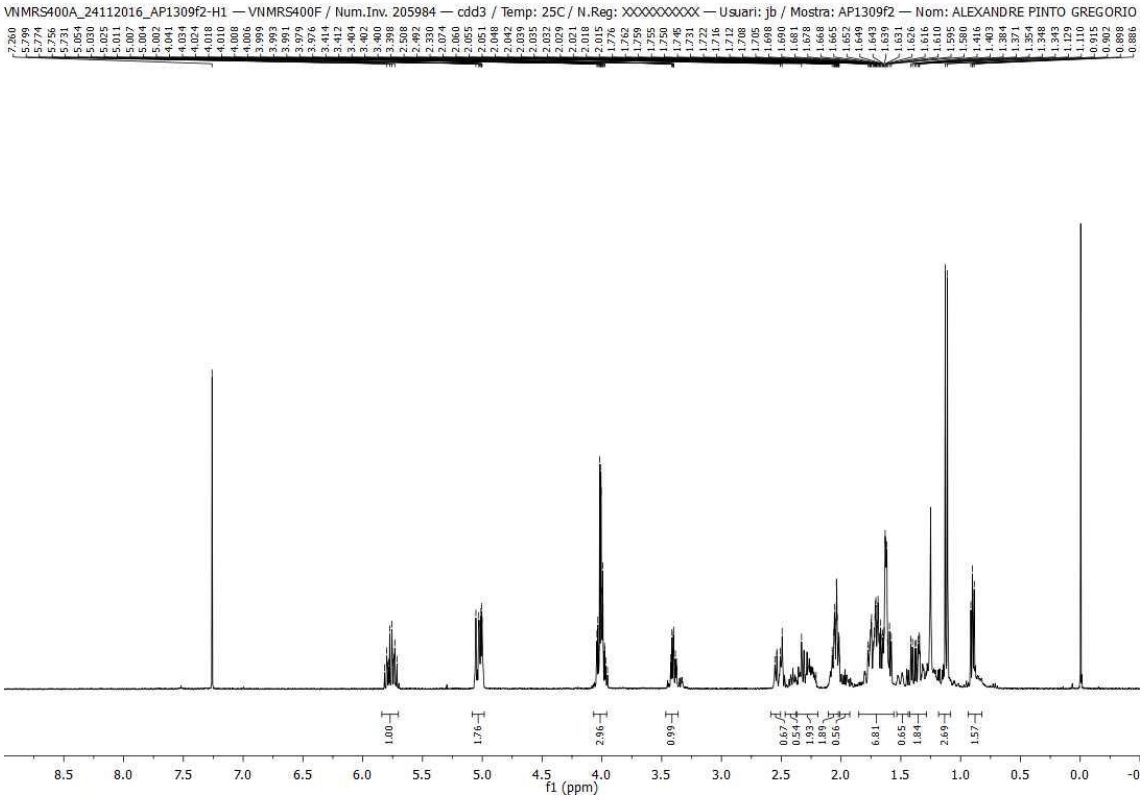
(7a*S*,8*R*,10*R*,11a*S*)-8-Allyl-10-methyl-5-oxo-3-phenylperhydrooxazolo[2,3-*j*]quinolone (109b)

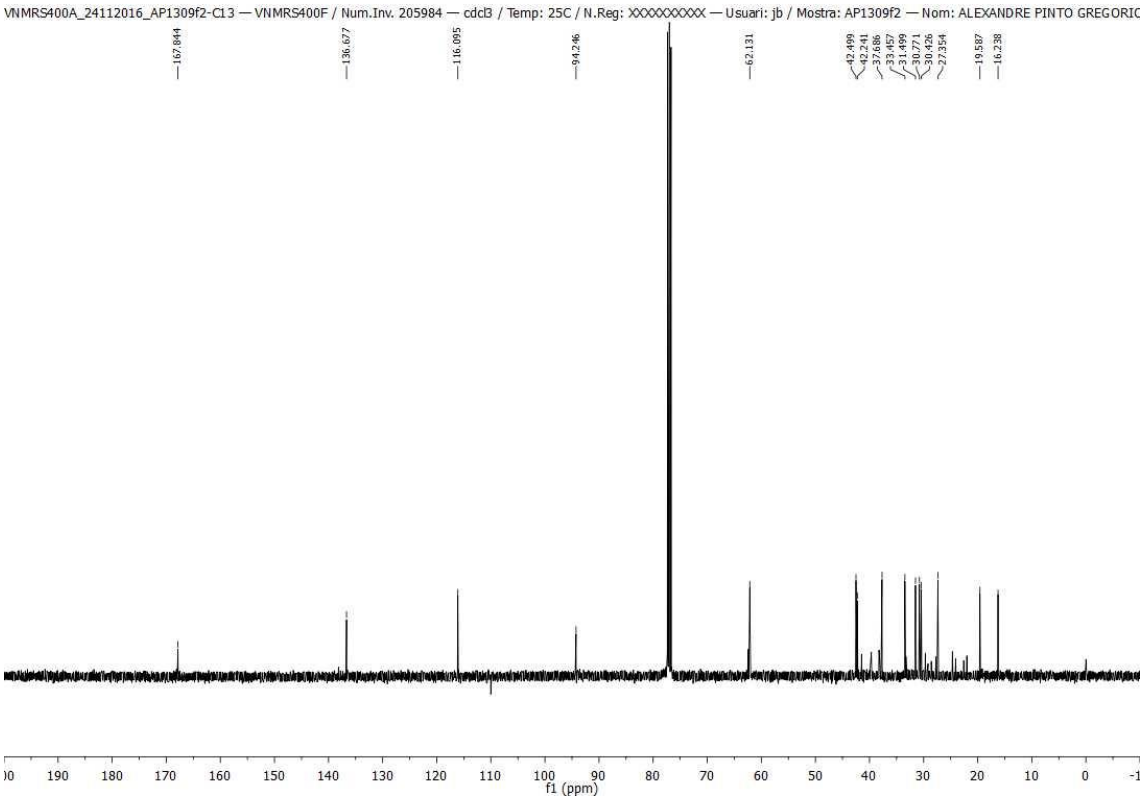
109b (data from a mixture containing minor amounts of **109a**).

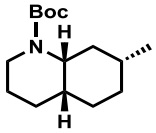
^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) *δ:* 1.12 (d, *J* = 7.6 Hz, 3H, CH_3), 1.14 (t, *J* = 13.2 Hz, 1H, H-11), 1.30-1.36 (m, 1H, H-9), 1.41 (dt, *J* = 5.2, 13 Hz, 1H, H-9), 1.58-1.78 (m, 5H, H-7, H-7a, H-11), 2.01-2.21 (m, 3H, H-1', H-10), 2.21-2.31 (m, 1H, H-8), 2.33-2.43 (m, 1H, H-6), 2.49-2.55 (m, 1H, H-6), 3.37-3.42 (m, 1H, H-3), 3.95-4.04 (m, 3H, H-2, H-3), 5.00-5.05 (m, 2H, CH=CH_2), 5.71-5.82 (m, 1H, C*H*=CH_2).

^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ:* 16.2 (C-11), 19.6 (CH_3), 27.4 (C10), 30.4 (C-6), 30.8 (C-8), 31.5 (C-9), 33.5 (C-7), 37.7 (C-1'), 42.2 (C-7a), 42.5 (C-3), 62.1 (C-2), 94.3 (C-11a), 116.1 (C=*C*H_2), 136.7 (*C*H=C), 167.8 (NCO).

HRMS calcd for [$C_{15}H_{23}NO_2$ + H^+]: 250.1802, found 250.1808.


VNMRS400A_24112016_AP1309f2-H1 — VNMRS400F / Num.Inv. 205984 — cdd3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP1309f2 — Nom: ALEXANDRE PINTO GREGORIO
1.00
1.76
2.96
0.99
0.67
0.54
1.93
1.89
0.56
6.81
0.65
1.84
2.69
1.57
f1 (ppm)


VNMRS400A_24112016_AP1309f2-C13 — VNMRS400F / Num.Inv. 205984 — cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: AP1309f2 — Nom: ALEXANDRE PINTO GREGORIC
167.844
136.677
116.095
94.246
62.131
42.499
42.241
37.686
33.457
31.499
30.771
30.426
27.354
19.587
16.238
f1 (ppm)



(4a*R*,7*R*,8a*R*)-1-(*tert*-Butoxycarbonyl)-7-methyldecahydroquinoline (113)

First step: $LiAlH_4$ (3.2 mL of a 1M solution in THF, 3.2 mmol) was added to a stirring solution of $AlCl_3$ (213 mg, 1.6 mmol) in anhydrous THF (20 mL) at 0 ºC. After 10 minutes, the mixture was allowed to warm to room temperature and stirred for an additional 30 minutes. The mixture was cooled to –78 ºC, and after 10 minutes a solution of lactam **104a** (140 mg, 0.49 mmol) in anhydrous THF (4.0 mL) was added. The stirring was continued at –78 °C for 90 min and at room temperature for 2 h. Water was slowly added, and the resulting mixture was diluted with EtOAc. The phases were separated and the aqueous solution was extracted with EtOAc. The combined organic extracts were dried and concentrated to afford crude *cis*-decahydroquinoline **112** as a yellow oil.

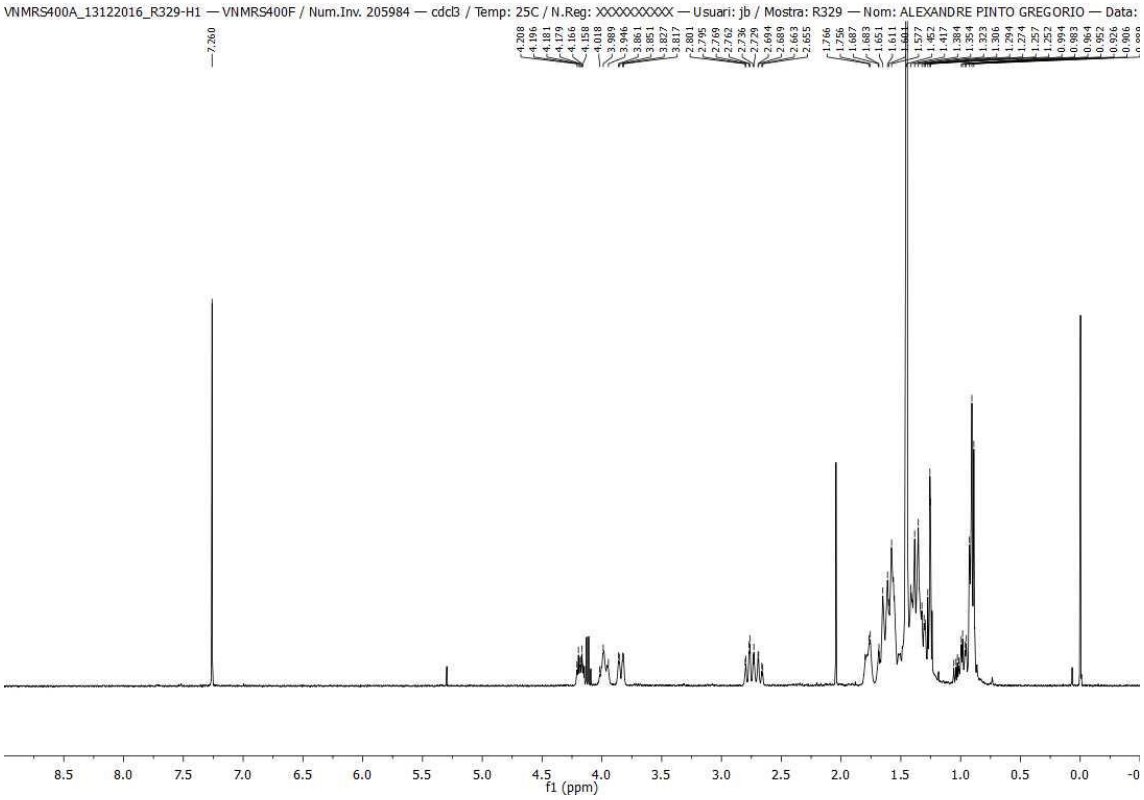
Second step: A solution of the above crude and Boc_2O (128 mg, 0.59 mmol) in CH_3OH (10 mL) containing $Pd(OH)_2$ (44 mg) was stirred under hydrogen at room temperature for 18 h. The catalyst was removed by filtration, and the filtrate was concentrated. Flash chromatography (from hexane to 9:1 hexane–EtOAc) afforded compound **113** (88 mg, 71%) as a colorless oil.

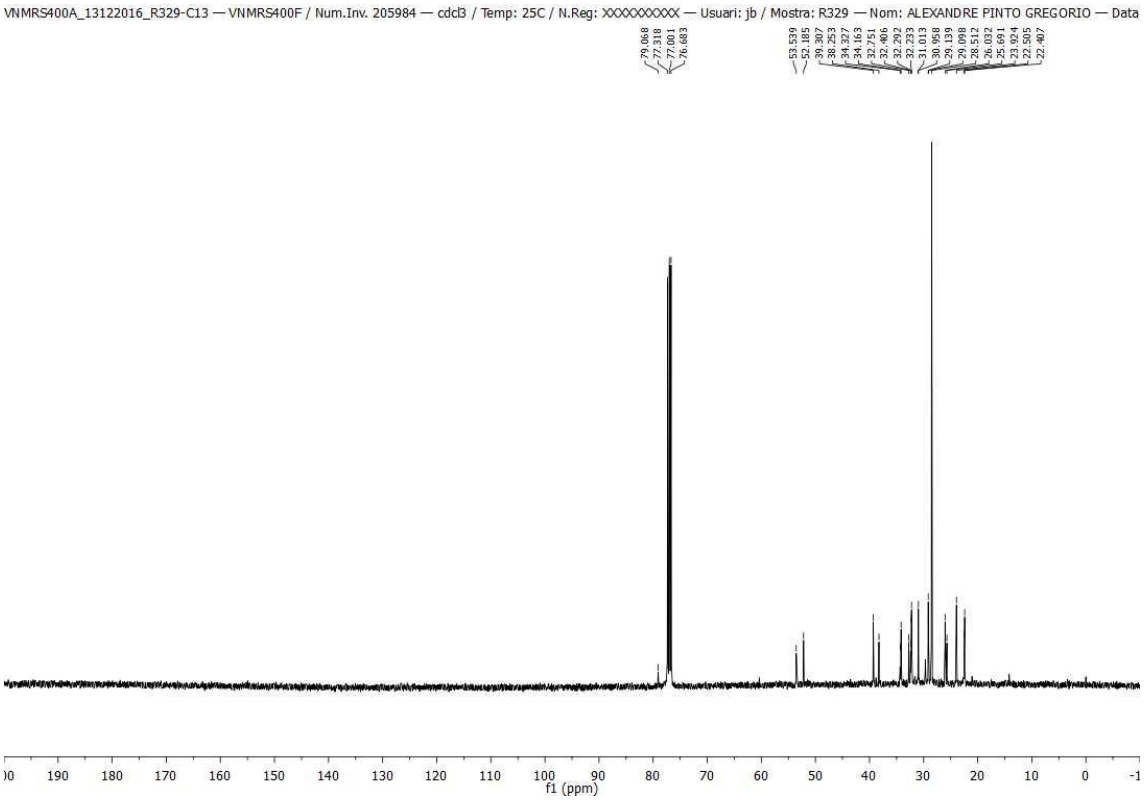
^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) *δ:* 0.89-0.93 (m, 3H, CH_3), 0.95-1.06 (m, 1H), 1.29-1.46 (m, 5H), 1.45 [br.s, 9H, C(C*H*$_3$)], 1.55-1.68 (m, 3H), 1.76-7.79 (m, 1H), 2.66-2.80 (m, 2H), 3.82-3.86 (m, 1H), 3.95-4.02 (m, 1H), 4.15-4.21 (m, 1H, H-8a).

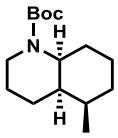
Several of the signals in the 13C NMR spectrum at 25 ºC were broad and ill-defined, even not observed, thus indicating the existence of a slow conformational equilibrium.
^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ:* 22.4 and 22.5 (CH_3), 23.9 (CH_2), 25.7 and 26.0 (CH_2), 28.5 [C(*C*H$_3$)], 29.1 (CH_2), 31.0 (CH_2), 32.2 and 32.3 (CH_2), 32.4 and 32.8 (CH_2), 34.2 and 34.3 (C-4a), 38.3 (CH_2), 39.3 (CH_2), 52.2 and 53.4 (C-8a), 79.1 [*C*(CH_3)].

HRMS calcd for [C15H27NO2 + H$^+$]: 254.2115, found 254.2112.

$[\alpha]^{23}{}_D$ = – 42.9 (c 0.41, CHCl3).


VNMRS400A_13122016_R329-H1 — VNMRS400F / Num.Inv. 205984 — cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: R329 — Nom: ALEXANDRE PINTO GREGORIO — Data:
7.260
4.208
4.196
4.181
4.179
4.166
4.158
4.018
3.989
3.946
3.861
3.851
3.827
3.817
2.801
2.795
2.768
2.762
2.736
2.729
2.694
2.689
2.663
2.655
1.766
1.756
1.687
1.683
1.651
1.611
1.601
1.577
1.462
1.417
1.384
1.354
1.333
1.306
1.294
1.274
1.257
1.252
0.994
0.983
0.964
0.952
0.926
0.906
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


VNMRS400A_13122016_R329-C13 — VNMRS400F / Num.Inv. 205984 — cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: R329 — Nom: ALEXANDRE PINTO GREGORIO — Data
79.068
77.318
77.001
76.683
53.539
52.185
39.307
38.253
34.327
34.163
32.751
32.406
32.303
32.233
31.013
30.958
29.139
29.098
28.512
26.032
25.691
23.924
22.505
22.407
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



(4a*R*,5*R*,8a*S*)-1-(*tert*-Butoxycarbonyl)-5-methyldecahydroquinoline (115)

First step: Operating as in the preparation of decahydroquinoline **113**, from $LiAlH_4$ (1.05 mL of a 1 M solution in THF, 1.05 mmol) and $AlCl_3$ (68 mg, 0.51 mmol) in anhydrous THF (6 mL) and a solution of lactam **108a** (45 mg, 0.16 mmol) in anhydrous THF (7 mL), a crude *cis*-decahydroquinoline **114** was obtained as a yellow oil.

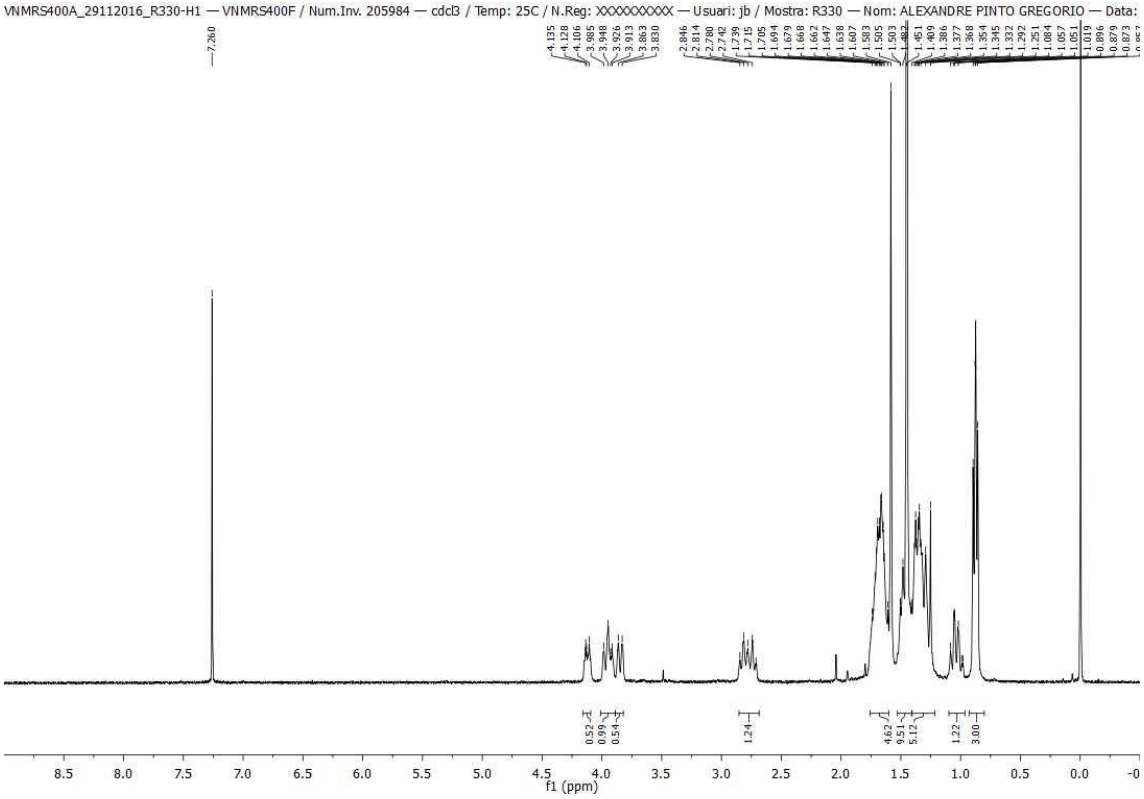
Second step: Operating as in the preparation of **113**, from the above crude, Boc_2O (41 mg, 0.19 mmol), and $Pd(OH)_2$ (14 mg) in MeOH (3 mL), *cis*-decahydroquinoline **115** (31 mg, 77%) was obtained as a colorless oil after flash chromatography (from hexane to 9:1 hexane–EtOAc).

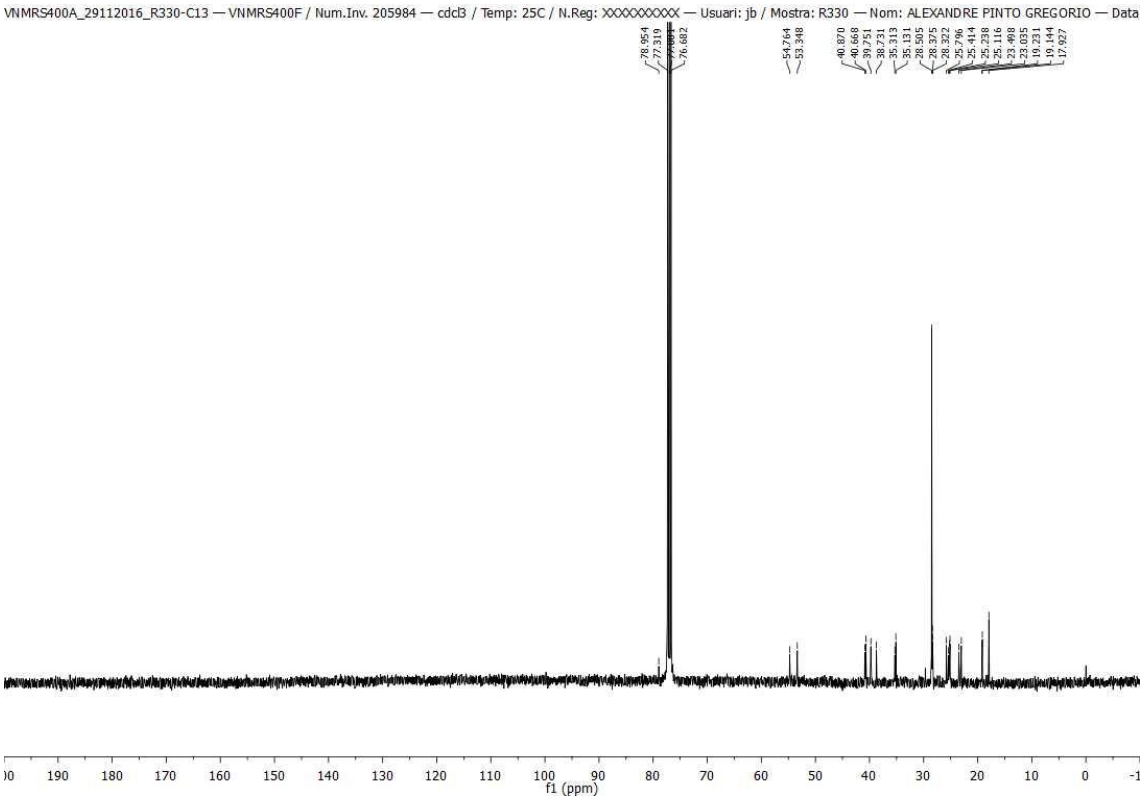
^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) *δ:* 0.86-0.90 (m, 3H, CH_3), 0.98-1.09 (m, 1H), 1.25-1.41 (m, 5H), 1.45 [br.s, 9H, C(C*H*$_3$)], 1.45-1.51 (m, 1H), 1.58-1.74 (m, 4H, H-4a, H-5), 2.71-2.85 (m, 1H), 3.83-3.86 (m, 1H), 3.91-3.99 (m, 1H), 4.11-4.14 (m, 1H, H-8a).

Several of the signals in the 13C NMR spectrum at 25 ºC were broad and ill-defined, even not observed, thus indicating the existence of a slow conformational equilibrium.
^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ:* 17.9 (CH_2), 19.1 and 19.2 (CH_3), 23.0 and 23.5 (CH_2), 25.1 and 25.2 (CH_2), 25.4 and 25.8 (CH_2), 28.4 and 28.3 (CH_2), 28.5 [C(*C*H_3)], 35.1 and 35.3 (CH), 38.7 and 39.8 (CH_2), 40.7 and 40.9 (CH), 53.4 and 54.8 (C-8a), 79.0 [*C*(CH_3)].

HRMS calcd for [$C_{15}H_{27}NO_2$ + H^+]: 254.2115, found 254.211.

$[\alpha]^{23}_D$ = + 28.8 (c 0.18, $CHCl_3$).


VNMRS400A_29112016_R330-H1 — VNMRS400F / Num.Inv. 205984 — cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: R330 — Nom: ALEXANDRE PINTO GREGORIO — Data:
7.260
4.135
4.128
4.106
3.985
3.948
3.926
3.913
3.863
3.830
2.846
2.814
2.780
2.742
1.739
1.715
1.705
1.694
1.679
1.668
1.647
1.647
1.638
1.607
1.583
1.505
1.503
1.482
1.461
1.409
1.386
1.377
1.368
1.354
1.345
1.332
1.292
1.251
1.084
1.057
1.051
1.019
0.896
0.879
0.873
0.52
0.99
0.54
1.24
4.62
9.51
5.12
1.22
3.00
f1 (ppm)


VNMRS400A_29112016_R330-C13 — VNMRS400F / Num.Inv. 205984 — cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX — Usuari: jb / Mostra: R330 — Nom: ALEXANDRE PINTO GREGORIO — Data
78.954
77.319
76.682
54.764
53.348
40.870
40.668
39.751
38.731
35.313
35.131
28.505
28.375
28.322
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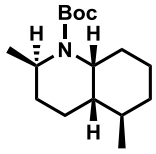
25.116
23.498
23.035
19.231
19.144
17.927
f1 (ppm)



(2*R*,,4a*S*,5*R*,8a*R*)-1-(*tert*-Butoxycarbonyl)-2,5-dimethyldecahydroquinoline (116)

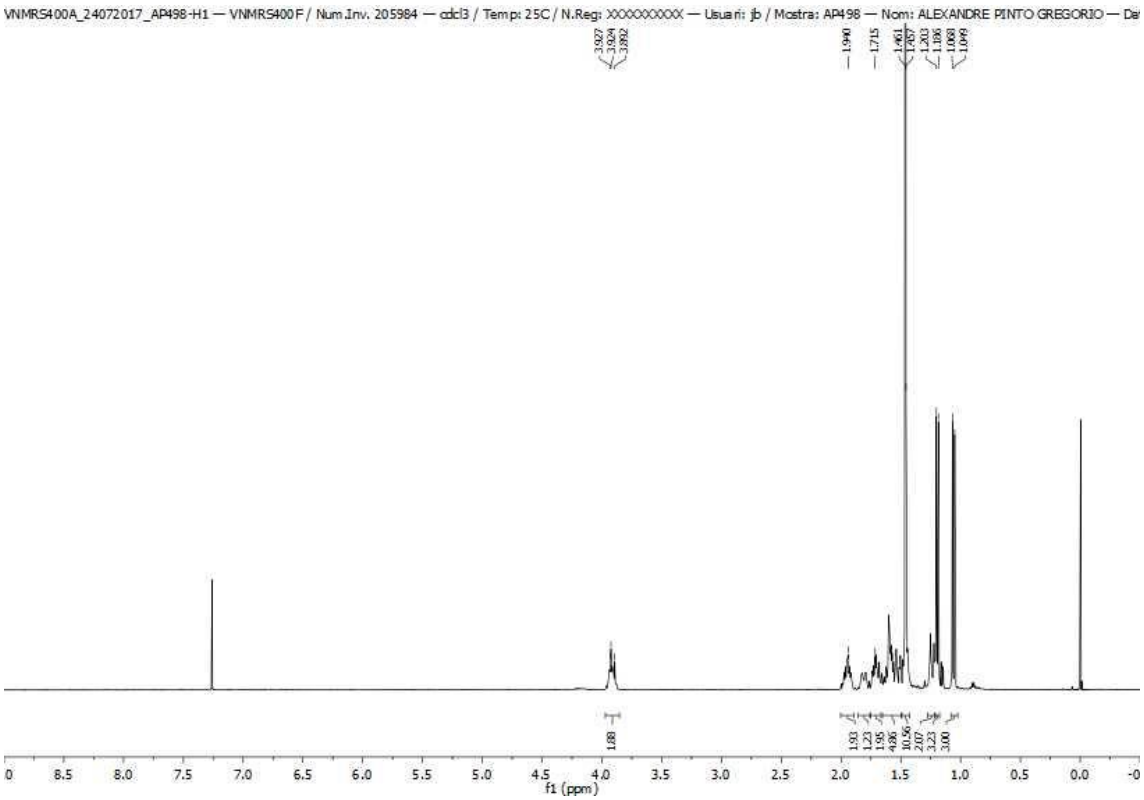
First step: MeLi (1.56 mL, of a 1.6 M solution in Et_2O, 2.50 mmol) was added to a suspension of CuI (238 mg, 1.25 mmol) in THF (6.3 mL) at –20 ºC, and the mixture was stirred at this temperature for 30 min. After cooling to –78 ºC, the vinyl triflate **19** (100 mg, 0.25 mmol) in THF (1 mL) was added dropwise. Stirring was continued overnight, allowing the mixture to slowly reach room temperature. Hexane was added, and the resulting suspension was filtered over Celite®, which was then washed with EtOAc. The filtrates were concentrated, and the resulting residue was dissolved in Et_2O. The solution was filtered through 0.45 μm HPLC filters and concentrated to afford enecarbamate **20**, which was used without further purification in the next step.

Second step: $NaBH_3CN$ (94 mg, 1.50 mmol) was added to a stirred solution of the above residue in dry CH_2Cl_2 (113 mL) and the stirring was continued for 15 minutes. Then, the mixture was cooled to –42 ºC, TFA (110 μL) was slowly added and the stirring was continued for 3 h. A solution of saturated aqueous $NaHCO_3$/THF (1:1) (60 mL) was added and the biphasic mixture was stirred for 10 minutes. The mixture was extracted with EtOAc and the combined organic extracts were washed with brine, dried and concentrated. Flash chromatography (95:5 hexane–EtOAc) afforded compound **116** (50 mg, 75%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) *δ:* 1.05 (d, *J* = 7.6 Hz, 3H, CH_3), 1.19 (d, *J* = 6.8 Hz, 3H, CH_3), 1.21-1.25 (m, 2H), 1.44-1.48 (m, 2H), 1.45 [br s, 9H, C(C*H*$_3$)$_3$], 1.45-1.51 (m, 1H), 1.49-1.64 (m, 4H), 1.67-1.74 (m, 2H, H-4a), 1.76-1.86 (m, 1H), 1.91-2.00 (m, 1H, H-5), 3.88-3.96 (m, 2H, H-2, H-8a).

^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ:* 19.1 (CH_3), 19.8 (CH_2), 20.0 (CH_2), 21.6 (CH_3), 26.0 (CH_2), 26.5 (CH_2), 28.5 [C(*C*H_3)], 29.8 (CH_2), 32.2 (C-4a), 36.3 (C-5), 46.7 (C-2), 50.0 (C-8a), 78.7 [*C*(CH_3)], 155.2 (NCO).

HRMS calcd for [$C_{16}H_{29}NO_2$ + H^+]: 268.2271, found 268.2272.
$[\alpha]^{23}_D$ = − 11.7 (c 0.42, MeOH).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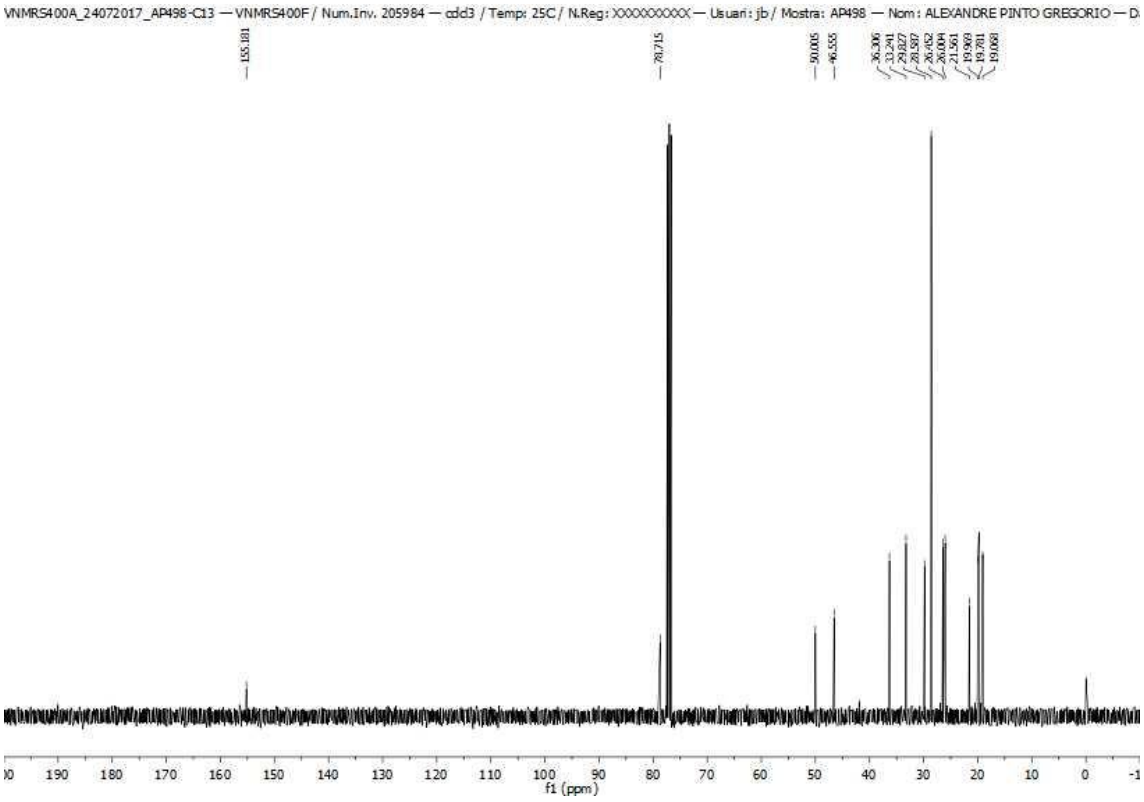
3.927
3.924
3.892
1.990
1.715
1.461
1.457
1.203
1.196
1.068
1.099
1.88
1.93
1.23
1.95
4.86
10.56
2.07
3.23
3.00
f1 (ppm)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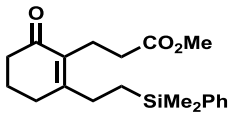
155.181
78.715
50.005
46.555
36.306
33.241
29.827
28.587
26.462
26.084
21.455
19.969
19.781
19.068
f1 (ppm)



Methyl 2-[2-(dimethylphenylsilyl)ethyl]-6-oxocyclohexenepropanoate (120)

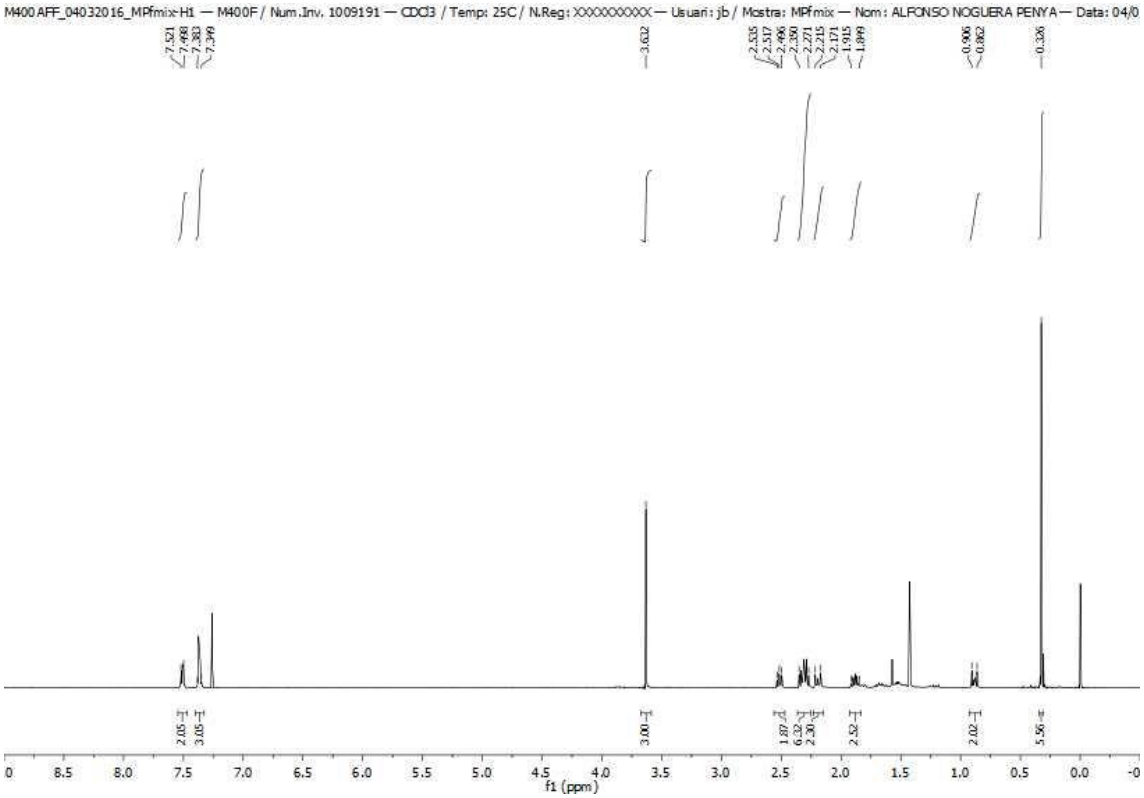
Dimethylphenylvinylsilane (3.20 mL, 17.23 mmol) was slowly added to a solution of 9-BBN (51.7 mL of a 0.5 M solution in THF, 25.8 mmol) at 0 ^{0}C, and the mixture was stirred at 60 ^{0}C for 14 h. Then, dry DMF (53 mL), K_2CO_3 (3.65 g, 19.1 mmol), $PdCl_2$(dppf)·CH_2Cl_2 (1.17 g, 1.44 mmol) and compound **1** (2.5 g, 9.57 mmol) were added sequentially at room temperature, and the mixture was stirred overnight at 60 ^{0}C. Water (53 mL) was added, and the resulting mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried and concentrated. Flash chromatography (8:2 hexane–AcOEt) afforded silyl derivative **120** as a yellow oil (3.1 g, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 0.33 [s, 6H, $Si(CH_3)_2$], 0.86-0.91 (m, 2H, $SiCH_2$), 1.86-1.92 (m, 2H), 2.17-2.22 (m, 2H, C*H*$_2$$CH_2Si$), 2.27-2.35 (m, 6H), 2.52 (t, *J* = 7.8 Hz, 2H), 3.63 (s, 3H, OCH_3), 7.35-7.38 (m, 3H, H-Ar), 7.50-7.52 (m, 2H, H-Ar).

^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ:* –3.4 [$Si(CH_3)_2$], 14.6 ($SiCH_2$), 20.7 (CH_2), 22.5 (CH_2), 28.9 (*C*H_2CH_2Si), 30.2 (CH_2), 33.5 (CH_2), 37.9 (CH_2), 51.4 (CO_2CH_3), 127.9 (CH-Ar), 129.1 (CH-Ar), 132.4 (Cq-Ar), 133.5 (CH-Ar), 138.2 (C*q*), 162.8 (C*q*), 173.5 (*C*OO), 198.9 (CO).

IR (NaCl): 1740, 1656 cm^{-1}.

HRMS calcd for [$C_{20}H_{28}O_3Si$ + H^+]: 345.1880, found 345.1885.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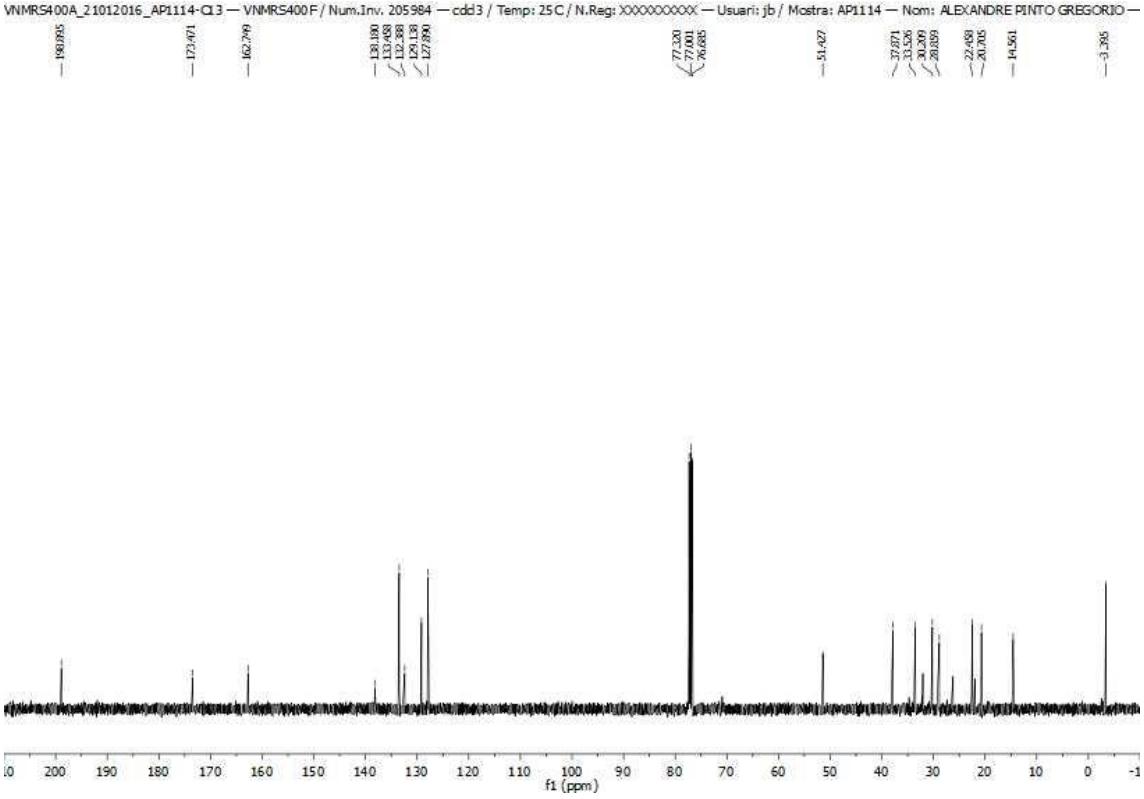
7.488
7.383
7.349
3.632
2.535
2.517
2.496
2.390
2.271
2.215
2.171
1.915
1.899
0.906
0.862
0.326
2.05
3.05
3.00
1.87
6.32
2.30
2.52
2.02
5.56
f1 (ppm)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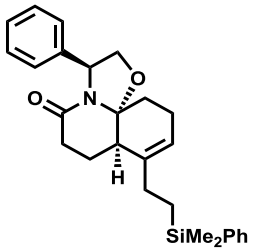
190.935
173.971
162.749
138.180
133.458
132.388
129.138
127.890
77.320
77.001
76.685
51.427
37.871
33.526
30.209
28.859
22.458
20.705
14.561
-3.395
f1 (ppm)

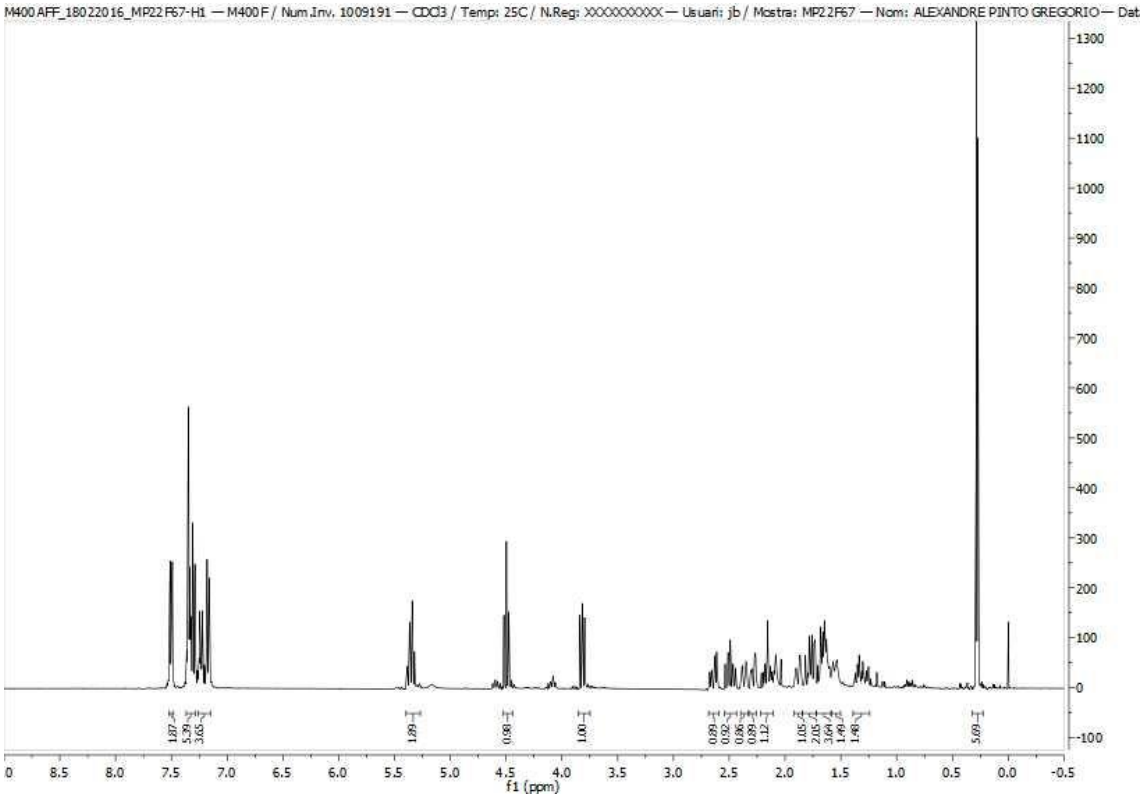


(3*S*,7a*R*,11a*R*)-8-[2-(Dimethylphenylsilyl)ethyl]-5-oxo-3-phenyl-2,3,5,6,7,7a,10,11-octahydrooxazolo[2,3-*j*]quinolone (121)

Method A: (*S*)-Phenylglycinol (113 mg, 0.83 mmol) was added to a solution of keto ester **120** (184 mg, 0.55 mmol) and AcOH (50 μL, 0.83 mmol) in benzene (7 mL). The mixture was heated at reflux temperature with azeotropic elimination of water by a Dean-Stark system. Additional 1.5 equiv of (*S*)-phenylglycinol and AcOH were added every 24 h to the reaction mixture, until all starting material was consumed. After 72 h, the mixture was cooled and concentrated, and the resulting oil was taken up with EtOAc. The organic solution was washed with saturated aqueous $NaHCO_3$ and brine, dried and concentrated. Flash chromatography (6:4 hexane–EtOAc) afforded lactam **121** as a colorless oil (90 mg, 38%).
Method B: A sealed tube was charged with (*S*)-Phenylglycinol (123 mg, 0.89 mmol) keto ester **120** (205 mg, 0.60 mmol), PivOH (92 mg, 0.89 mmol), and toluene (1.2 mL). The tube was sealed, and the mixture heated to reflux for 24h. After cooling to room temperature, the mixture was concentrated, and the resulting oil was taken up with EtOAc. The organic solution was washed with saturated aqueous $NaHCO_3$ and brine, dried and concentrated. Flash chromatography (6:4 hexane–EtOAc) afforded lactam **121** as a colorless oil (97 mg, 37%).

^{1}H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) *δ*: 0.28 [s, 6H, $Si(CH_3)_2$], 1.23-1.38 (m, 1H, $SiCH_2CH_2$), 1.54-1.57 (m, 1H, $SiCH_2CH_2$), 1.60-1.70 (m, 3H, H-10, H-7, $SiCH_2CH_2$), 1.73-1.81 (m, 2H, H-10, $SiCH_2CH_2$), 1.87-1-93 (m, 1H, C-11), 2.11-2.21 (m, 1H, H-7), 2.26-2.31 (m, 1H, H-7a), 2.35-2.39 (m, 1H, H-11), 2.49 (ddd, *J* = 18.8, 8.0 Hz,1H, H-6), 2.64 (dd, *J* = 18.0, 6.8 Hz, 1H, H-6), 3.82 (dd, *J* = 9.6, 8.0 Hz, 1H, H-2), 4.50 (t, *J* = 8.8 Hz, 1H, H-2), 5.32-5.39 (m, 2H, H-3, H-9), 7.16-7.25 (m, 3H, H-Ar), 7.29-7.36 (m, 5H, H-Ar), 7.49-7.52 (m, 2H, H-Ar).

^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ:* −3.3 [$Si(CH_3)_2$], 17.6 (CH_2), 22.2 (CH_2), 23.0 (C-10), 24.8 (C-7), 30.5 (C-11), 30.9 (C-6), 51.1 (C-7a), 58.7 (C-3), 69.6 (C-2), 95.3 (C-11a), 121.3 (C-9), 125.3 (C-H_{Ar}), 127.1 (C-H_{Ar}), 127.6 (C-H_{Ar}), 128.5 (C-H_{Ar}), 128.6 (C-H_{Ar}), 128.9 (C-H_{Ar}), 133.6 (C-H_{Ar}), 135.0 (Cq), 138.6 (C-8), 140.1 (Cq), 169.2 (C-5).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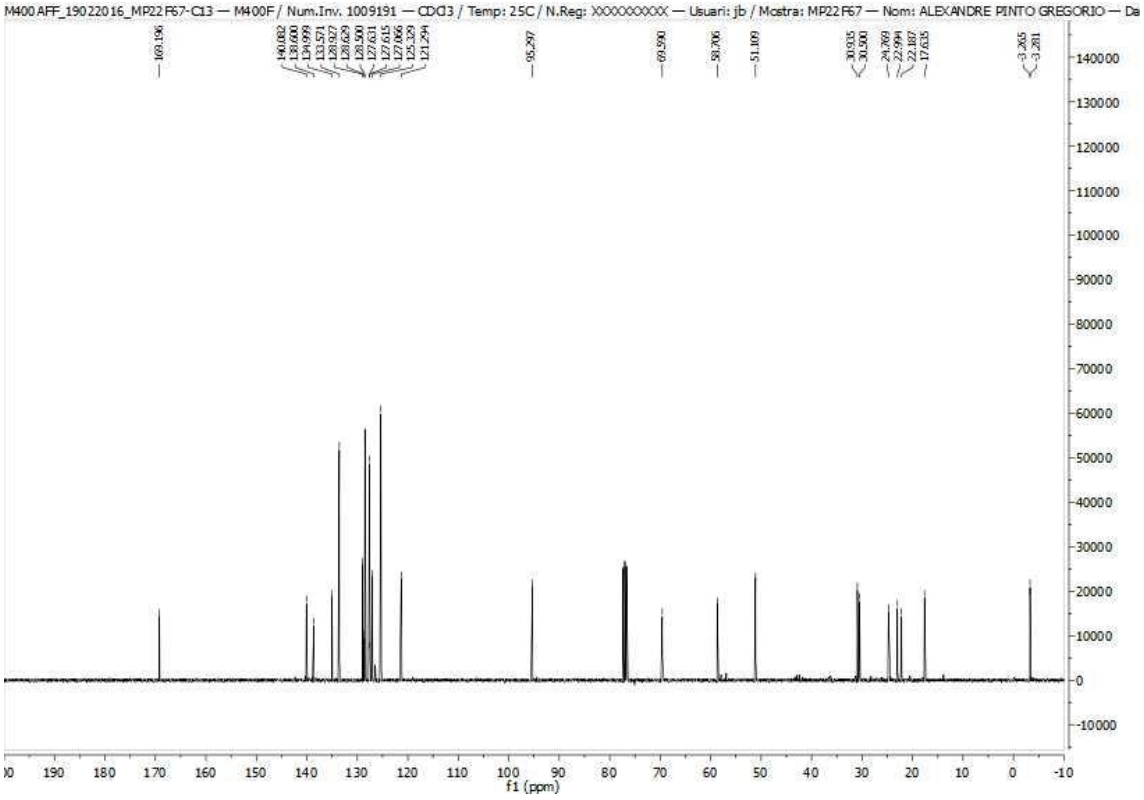
1.87
5.39
3.65
1.89
0.98
1.00
0.89
0.92
0.86
0.89
1.12
1.05
2.05
3.64
1.48
1.40
5.69
f1 (ppm)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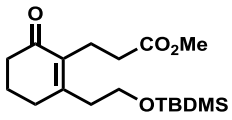
169.196
140.082
138.600
134.999
133.571
128.927
128.629
128.500
127.631
127.615
127.066
125.329
121.294
95.597
69.590
58.706
51.109
30.935
30.500
29.769
22.194
22.107
17.635
-3.265
-3.281
f1 (ppm)



Methyl 2-[2(*tert*-butyldimethylsilyloxy)ethyl]-6-oxocyclohexenepropanoate (125)

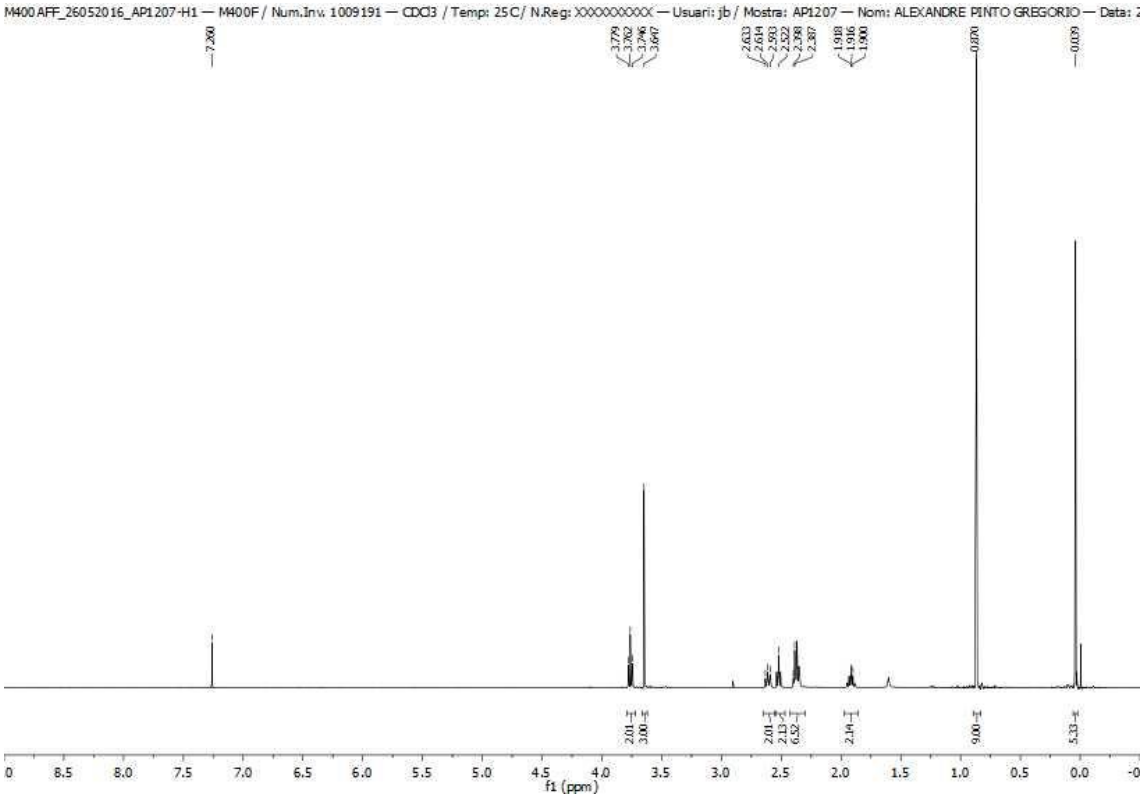
First step: Tetrafluoroboric acid diethyl ether complex (37. 6 mL, 19.2 mmol) was slowly added at 0 °C to a solution of keto ester **120** (3.3 g, 9.58 mmol) in dry CH_2Cl_2 (48 mL), and the mixture was stirred at room temperature for 16 h. Saturated aqueous $NaHCO_3$ was added, the mixture was extracted with EtOAc, and the organic layer was dried and concentrated.
Second step: Anhydrous KF (2.22 g, 38.3 mmol) and *m*-CPBA (5.61 g, 32. 6 mmol) were added to a solution of the above residue in dry DMF (75 mL), and the pale-yellow suspension was stirred for 16 h. The mixture was diluted with EtOAc, and saturated aqueous $NaHCO_3$ was added. After extraction with EtOAc, the organic layer was washed with brine, dried and concentrated.
Third step: TBDMSCl (1.11 g, 7.34 mmol) was added to a solution of the above crude alcohol and imidazole (1.50 g, 22.1 mmol) in dry DMF (18 mL), and the mixture was stirred overnight. The solvent was evaporated and the residue was taken up in CH_2Cl_2. The organic solution was sequentially washed with saturated aqueous $NaHCO_3$ and brine, dried and concentrated. Flash chromatography (6:4 hexane–EtOAc) afforded keto-ester **125** as a yellow oil (1.86 g, 57% overall yield).

^{1}H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ: 0.04 [s, 6H, $Si(CH_3)_2$], 0.87 [s, 9H, $C(CH_3)_3$], 1.89-1.95 (m, 2H), 2.35-2.40 (m, 6H), 2.52 (t, J = 6.4 Hz, 2H, OCH_2CH_2), 2.61 (t, J = 8.0 Hz, 2H), 3.65 (s, 3H, OCH_3), 3.76 (t, J = 6.4 Hz, 2H, OCH_2).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: –5.5 [$Si(CH_3)_2$], 18.2 [$C(CH_3)_3$], 20.9 (CH_2), 22.3 (CH_2), 25.8 [$C(CH_3)_3$], 31.3 (CH_2), 33.5 (CH_2), 37.9 (CH_2), 38.1 (CH_2CH_2CO), 51.4 (OCH_3), 61.2 (CH_2CH_2CO), 135.1 (C*q*), 157.5 (C*q*), 173.7 (COO), 198.7 (CO).

IR (NaCl): 1789, 1667 cm^{-1}.

HRMS calcd for [$C_{18}H_{32}O_4Si + H^+$]: 341.2143, found 341.21411.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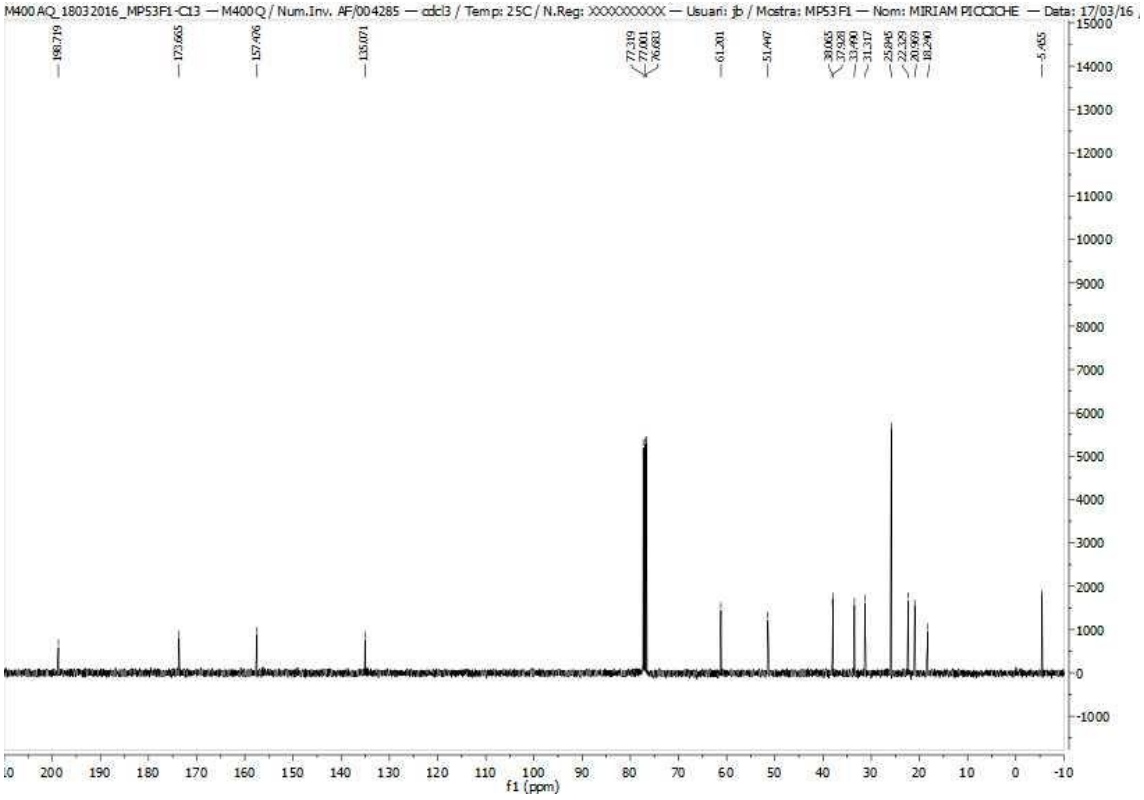
7.260
3.779
3.762
3.746
3.647
2.633
2.614
2.593
2.573
2.388
2.387
1.918
1.916
1.900
0.870
0.039
2.01
3.00
2.01
2.13
6.52
2.14
9.00
5.33
f1 (ppm)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198.719
173.665
157.496
135.071
77.319
77.001
76.683
61.201
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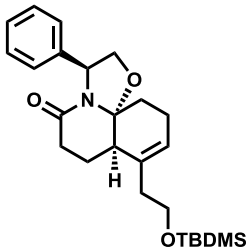
22.329
20.989
10.290
5.455
f1 (ppm)



(3*S*,7a*R*,11a*R*)-8-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-5-oxo-3-phenyl-2,3,5,6,7, 7a,10,11-octahydrooxazolo[2,3-*j*]quinoline (126)

(*S*)-Phenylglycinol (603 mg, 4.40 mmol) was added to a solution of keto ester **125** (1 g, 2.93 mmol) and AcOH (251 µL, 4.40 mmol) in benzene (28 mL). The mixture was heated at reflux temperature with azeotropic elimination of water by a Dean-Stark system. Additional 1.5 equiv of (*S*)-phenylglycinol and AcOH were added every 24 h to the reaction mixture, until all starting material was consumed. After 72 h, the mixture was cooled and concentrated, and the resulting oil was taken up in EtOAc. The organic solution was washed with saturated aqueous $NaHCO_3$ and brine, dried and concentrated. Flash chromatography (6:4 hexane–EtOAc) afforded compound **126** as a colorless oil (589 mg, 47%).

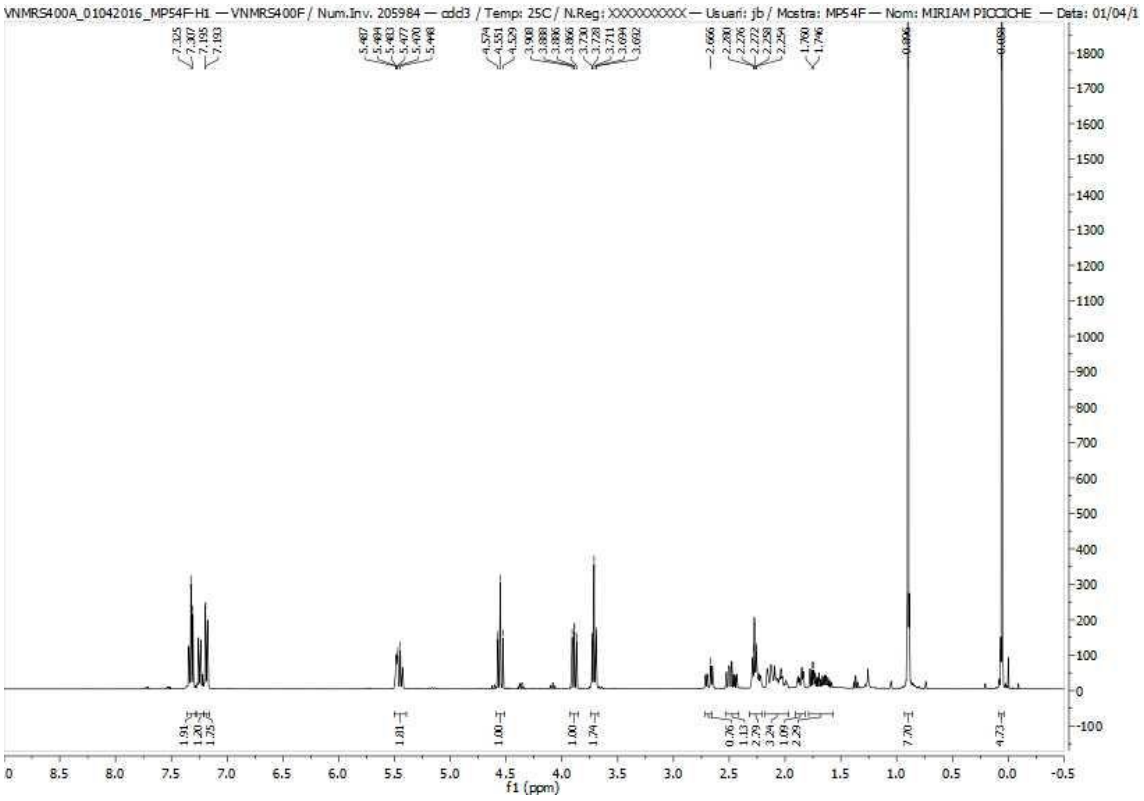
^{1}H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) *δ*: 0.06 [s, 6H, $Si(CH_3)_2$], 0.90 [s, 9H, $C(CH_3)_3$], 1.58-1.78 (m, 2H, H-7, H-11), 1.86 (dd, *J* = 14, 5.8 Hz, 1H, H-11), 1.98-2.16 (m, 3H, H-10, H-7a), 2.21-2.29 (m, 3H, H-7, OCH_2CH_2), 2.48 (ddd, *J* = 18.6, 7.4, 6.0 Hz, 1H, H-6), 2.68 (dd, *J* = 18.6, 6.0 Hz, 1H, H-6), 3.71 (t, *J* = 7.4 Hz, 2H, OCH_2CH_2), 3.89 (dd, *J* = 9.0, 8.0 Hz, 1H, H-2), 4.55 (t, *J* = 9.0 Hz, 1H, H-2), 5.43-5.48 (m, 2H, H-3, H-9), 7.17-7.19 (m, 2H, H-Ar), 7.31-7.34 (m, 3H, H-Ar).

^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ:* –5.3 [$Si(CH_3)_2$], 18.3 [$\underline{C}(CH_3)_3$], 23.0 (C-10), 25.1 (C-7), 25.8 (C-11), 25.9 [$C(CH_3)_3$], 31.4 (C-6), 37.9 ($OCH_2\underline{C}H_2$), 43.8 (C-7a), 58.4 (C-3), 62.7 ($O\underline{C}H_2CH_2$), 69.5 (C-2), 94.3 (C-11a), 122.0 (C-9), 125.2 (C-H_{Ar}), 127.1 (C-H_{Ar}), 128.5 (C-H_{Ar}), 134.7 (C-8), 140.3 (Cq-Ar), 169.6 (C-5).

IR (NaCl): 1659 cm^{-1}.

HRMS calcd for [$C_{25}H_{37}NO_3Si$ + H^+]: 428.2615, found 428.2619

$[\alpha]^{23}_D$ = + 69.5 (c 1.0, $CHCl_3$).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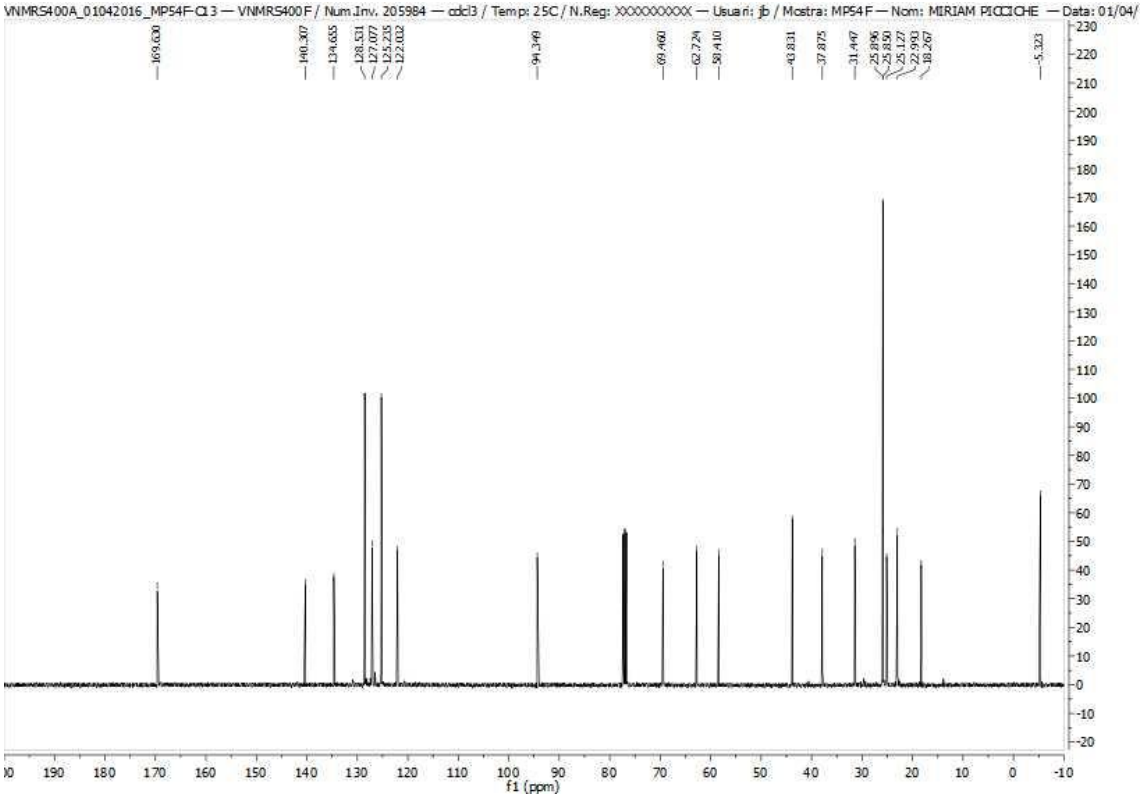
f1 (ppm)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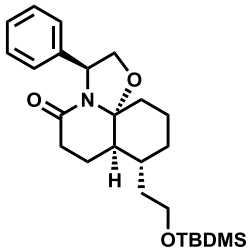


(3*S*,7a*R*,8*R*,11a*R*)-8-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-5-oxo-3-phenyl-2,3,5,6,7,7a,8,9,10,11-decahydrooxazolo[2,3-*j*]quinoline (127)

A solution of the tricyclic lactam **126** (509 mg, 1.2 mmol) in EtOAc (7 mL) containing PtO_2 (102 mg) was stirred under hydrogen at 0 °C overnight. The catalyst was removed by filtration over Celite®, and the filtrate was concentrated to afford compound **127** (507 mg, 99%) as a colorless oil.

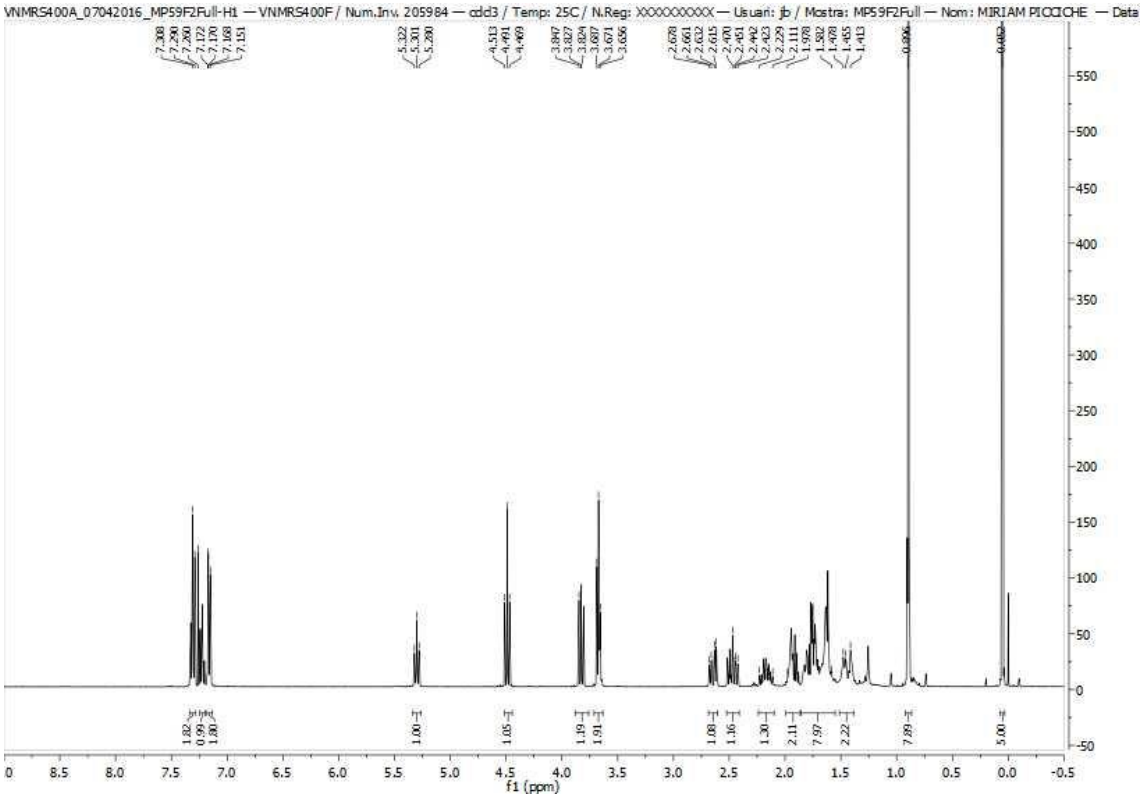
^{1}H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) *δ*: 0.05 [s, 6H, $Si(CH_3)_2$], 0.90 [s, 9H, $C(CH_3)_3$], 1.39-1.43 (m, 1H, H-10), 1.45-1.48 (m, 1H, H-7), 1.56-1.83 (m, 7H, H-7, H-7a, H-9, H-10, H-9, H-11, $OCH_2C\underline{H}_2$), 1.88-1.98 (m, 2H, H-8, $OCH_2C\underline{H}_2$), 2.11-2.23 (m, 1H, H-11), 2.47 (ddd, *J* = 18.4, 10.8, 7.8 Hz, 1H, H-6), 2.65 (dd, *J* = 18.4, 6.8 Hz, 1H, H-6), 3.67 (t, *J* = 6.0 Hz, 2H, $OC\underline{H}_2CH_2$), 3.82 (t, *J* = 8.6 Hz, 1H, H-2), 4.49 (t, *J* = 8.6 Hz, 1H, H-2), 5.30 (t, *J* = 8.4 Hz, 1H, H-3), 7.15-7.17 (m, 2H, H-Ar), 7.20-7.24 (m, 1H, H-Ar), 7.28-7.33 (m, 2H, H-Ar).

^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ:* –5.3 [$Si(CH_3)_2$], 18.1 (C-10), 18.3 [$\underline{C}(CH_3)_3$], 24.5 (C-7), 24.6 (C-11), 25.9 [$C(\underline{C}H_3)_3$], 30.5 (C-9), 31.3 (C-6), 35.5 (C-8), 35.9 ($OCH_2\underline{C}H_2$), 43.1 (C-7a), 58.0 (C-3), 61.5 ($O\underline{C}H_2CH_2$), 69.6 (C-2), 95.4 (C-11a), 125.4 ($C\text{-}H_{Ar}$), 127.0 ($C\text{-}H_{Ar}$), 128.5 ($C\text{-}H_{Ar}$), 140.3 (Cq-Ar), 169.5 (C-5).

IR (NaCl): 1660 cm^{-1}.

HRMS calcd for [$C_{25}H_{39}NO_3Si + H^+$]: 430.2772 found 430.2777

$[\alpha]_D^{23}$ = + 61.2 (c 0.42, $CHCl_3$)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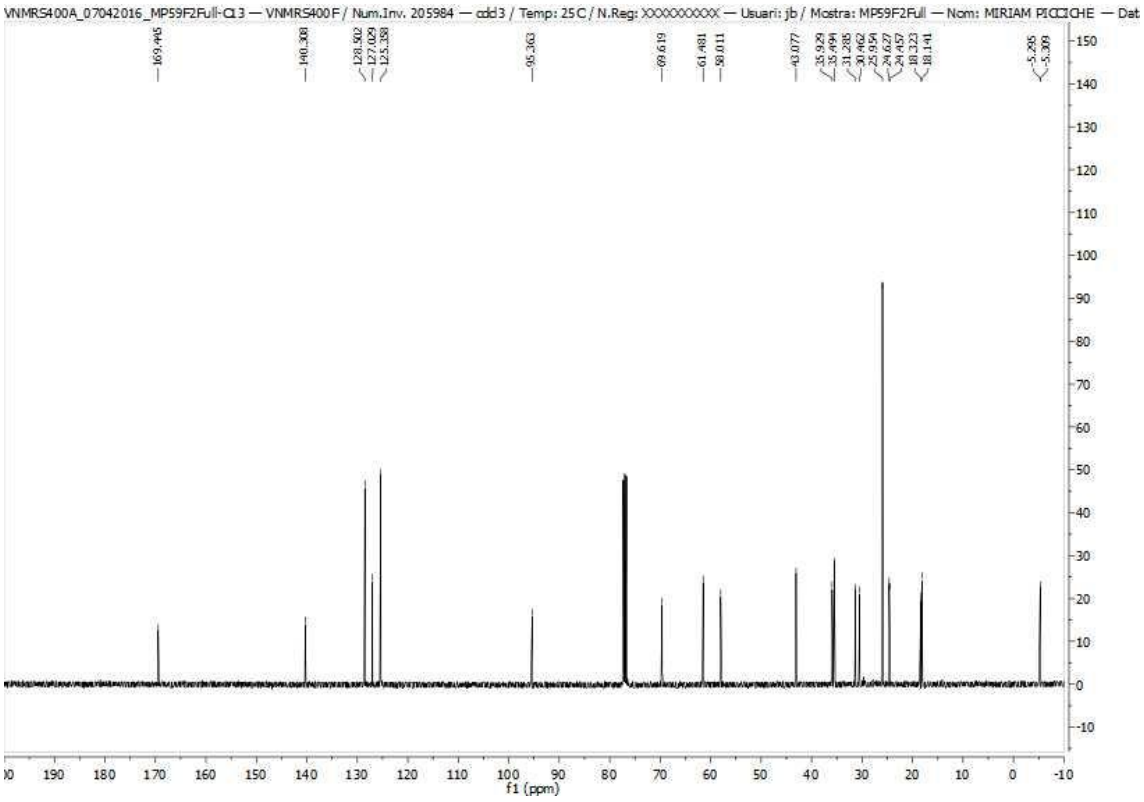
f1 (ppm)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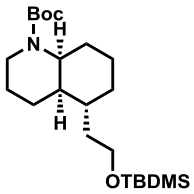
f1 (ppm)



(4a*R*,5*R*,8a*S*)-1-(*tert*-Butoxycarbonyl)-5-[2-(*tert*-butyldimethylsilyloxy)ethyl] decahydroquinoline (128)

First step: $LiAlH_4$ (33.7 mL of a solution 1.0 M in anhydrous THF, 33.7 mmol) was slowly added to a suspension of $AlCl_3$ (1.39 g, 10.4 mmol) in THF (100 mL) at 0 ºC. After 30 minutes, the mixture was cooled at –78 ºC and a solution of lactam **127** (2.23 g, 5.19 mmol) in anhydrous THF (12 mL) was added dropwise. The stirring was continued at –78 ºC for 90 min and at room temperature for 3 h. Water was slowly added, the resulting mixture was filtered over Celite®, and the filtrate was extracted with EtOAc. The organic extracts were dried and concentrated to afford crude *cis*-decahydroquinoline (1.61 g) as a yellow oil.
Second step: A solution of the above crude and Boc_2O (445 mg, 2.0 mmol) in EtOAc (36 mL) containing $Pd(OH)_2$ (284 mg) was stirred under hydrogen at room temperature for 24 h. The catalyst was removed by filtration over Celite®, and the filtrate was concentrated. Flash chromatography (9:1 hexane–Et_2O) afforded *cis*-decahydroquinoline **128** (439 mg, 66% for the two steps) as a colorless oil.

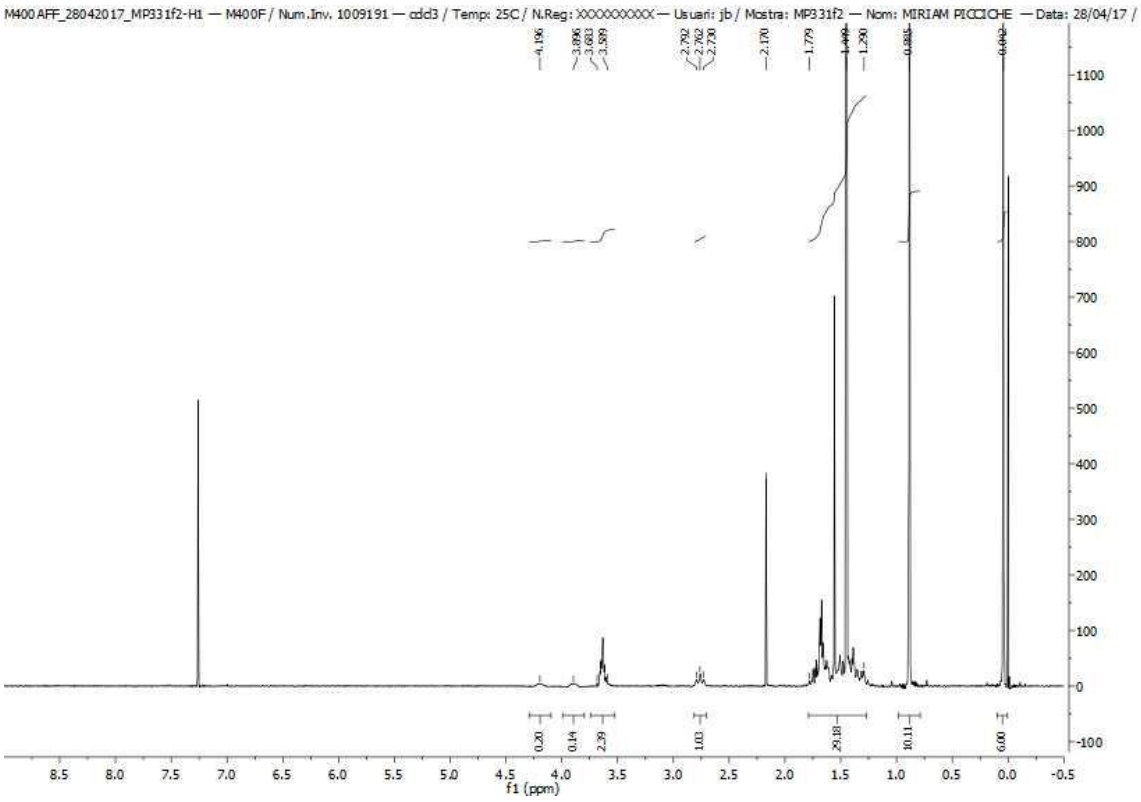
^{1}H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) *δ*: 0.04 [s, 6H, $Si(CH_3)_2$], 0.89 [s, 9H, $SiC(CH_3)_3$], 1.29-1.78 (m, 14H), 1.45 [s, 9H, $C(CH_3)_3$], 2.76 (t, *J* = 12.4 Hz, 1H, H-2), 3.59-3.68 (m, 2H, $OC\underline{H_2}CH_2$), 3.90 (br s, 1H), 4.20 (br s, 1H).

Several of the signals in the 13C NMR spectrum at 25 ºC were broad and ill-defined, even not observed, thus indicating the existence of a slow conformational equilibrium.
^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ:* –5.3 [$Si(CH_3)_2$], 18.3 [$Si\underline{C}(CH_3)_3$], 20.6 (CH_2), 23.8 (CH_2), 24.5 (CH_2), 25.6 (CH_2), 25.8 (CH_2), 25.9 [$SiC(\underline{C}H_3)_3$], 28.5 [$C(\underline{C}H_3)_3$], 35.3 ($OCH_2\underline{C}H_2$), 36.0 (C-5), 39.2 (CH_2), 39.4 (C-4a), 49.4 (C-8a), 61.7 ($O\underline{C}H_2CH_2$), 79.0 [$O\underline{C}(CH_3)_3$], 155.0 (NCO).

IR (NaCl): 1691 cm^{-1}

HRMS calcd for [$C_{22}H_{43}NO_3Si + H^+$]: 398.3085 found 398.3084.

$[\alpha]^{23}_D$ = – 1.96 (c 1.22, $CHCl_3$).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0.692
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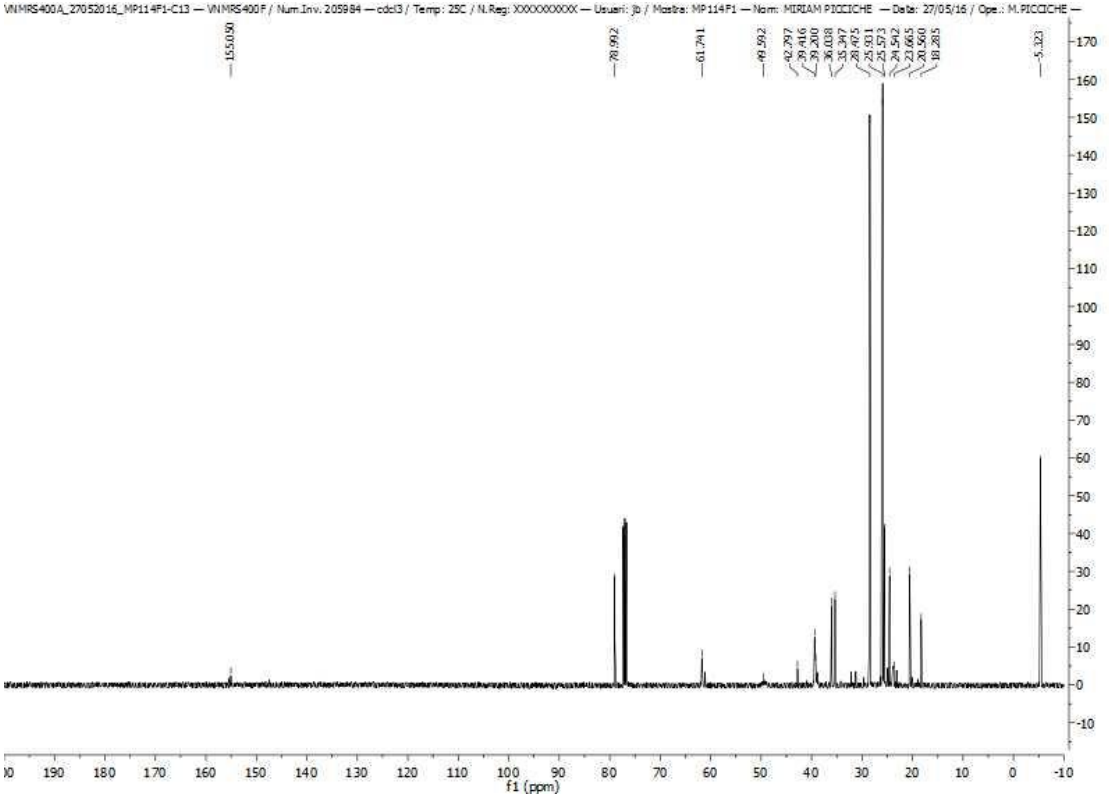
1.03
29.18
10.11
6.00
f1 (ppm)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39.416
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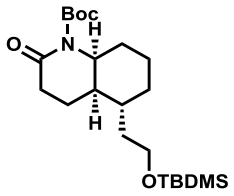
20.560
18.285
-5.323
f1 (ppm)



(4a*R*,5*R*,8a*S*)-1-(*tert*-Butoxycarbonyl)-5-[2-(*tert*-butyldimethylsilyloxy)ethyl]-2-oxodecahydroquinoline (129)

10% aqueous solution of $NaIO_4$ (12.6 mL) and $RuO_2 \cdot nH_2O$ (10 mg, 0.076 mmol) were added to a stirring solution of **128** (1 g, 2.53 mmol) in EtOAc (5 mL). After 2 h, EtOAc (5 mL) was added, the organic layer was separated, and the aqueous phase was extracted with EtOAc. *iPr*OH (2 mL) was added to the combined organic extracts, the resulting suspension was filtered over Celite®, and the filtrate was dried and concentrated. Flash chromatography (95:5 hexane–EtOAc) afforded **129** (760 mg, 73%) as a colorless oil.

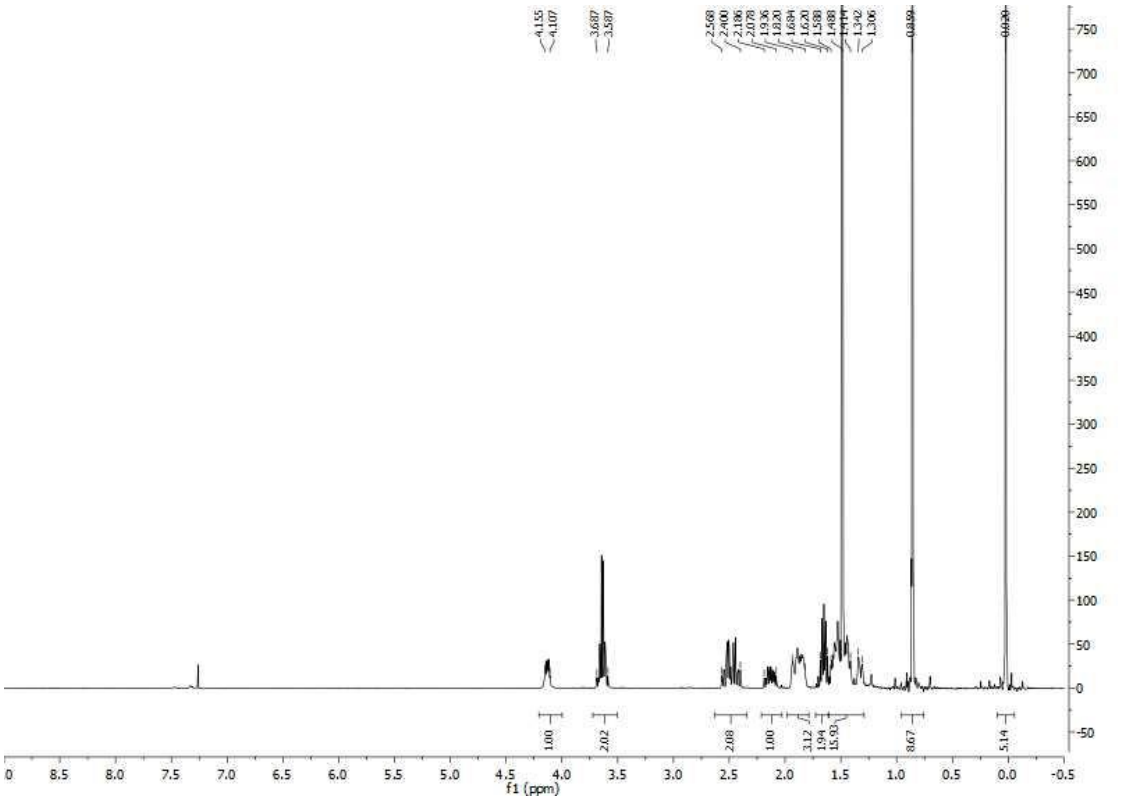
^{1}H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) *δ*: 0.02 [s, 6H, $Si(CH_3)_2$], 0.86 [s, 9H, $SiC(CH_3)_3$], 1.31-1.34 (m, 1H, H-8), 1.41-1.59 [m, 5H, H-4, H-6, H-8, H-7], 1.49 [s, 9H, $OC(CH_3)_3$], 1.62-1.69 (m, 2H, OCH_2CH_2), 1.82-1.94 (m, 3H, H-4a, H-5, H-6), 2.08-2.19 (m, 1H, H-4), 2.40-2.57 (m, 2H, H-3), 3.59-3.69 (m, 2H, OCH_2CH_2), 4.11-4.16 (m, 1H, H-8a).

^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ:* –5.4 [$Si(CH_3)_2$], 18.2 [$SiC(CH_3)_3$], 20.2 (C-7), 22.9 (C-4), 24.4 (C-8), 25.8 [$SiC(CH_3)_3$], 27.9 [$OC(CH_3)_3$], 28.3 (C-6), 34.0 (C-3), 35.2 (C-5), 35.3 (OCH_2CH_2), 37.6 (C-4a), 54.6 (C-8a), 61.4 (OCH_2), 82.6 [$OC(CH_3)_3$], 153.1 (NCO), 171.3 (CO).

IR (NaCl): 1768, 1711 cm^{-1}.

HRMS calcd for [$C_{22}H_{41}NO_4Si + Na^+$]: 434.2697, found 434.2699.

$[\alpha]^{23}_D$ = +15.9 (c 0.53, $CHCl_3$).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1.488
1.342
1.306
0.899
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2.02
2.08
1.00
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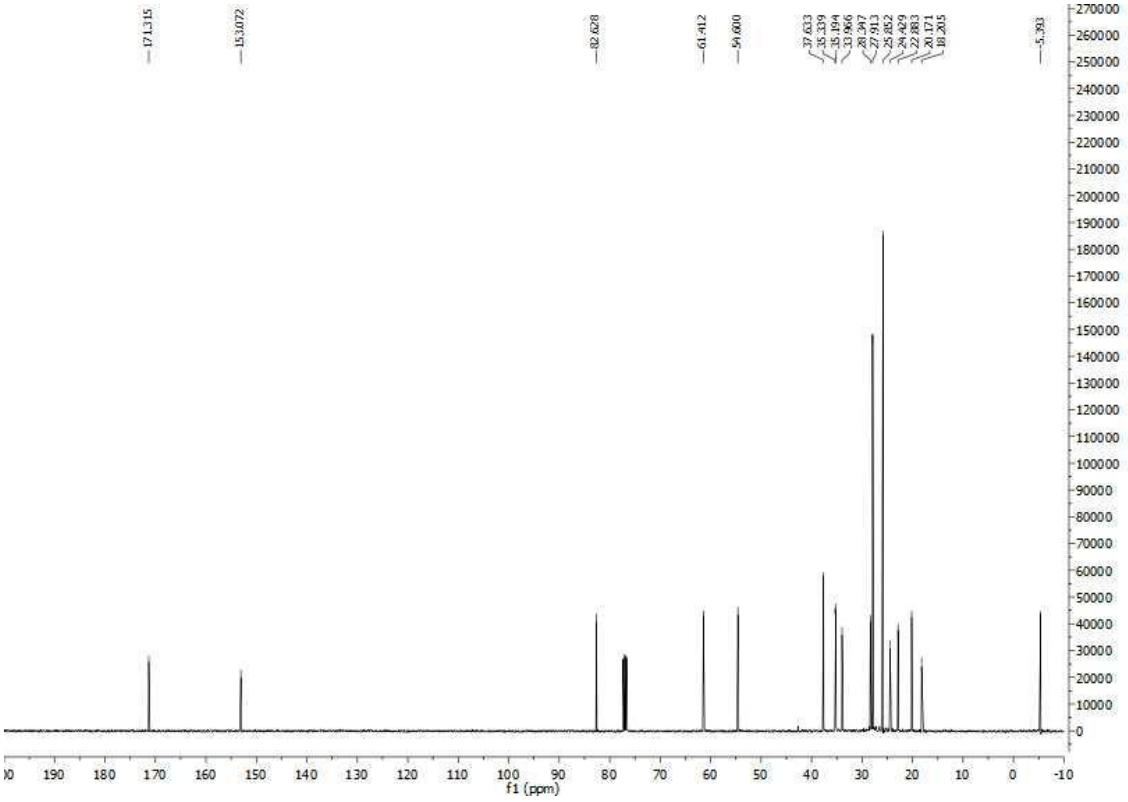
15.93
8.67
5.14
f1 (ppm)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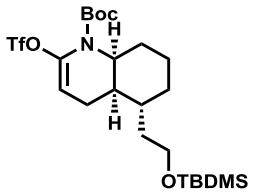
20.171
18.205
-5.393
f1 (ppm)



(4a*R*,5*R*,8a*S*)-1-(*tert*-Butoxycarbonyl)-2-(trifluoromethylsulfonyloxy)-5-[2-(*tert*-butyldimethylsilyloxy)ethyl]-1,4,4a,5,6,7,8,8a-octahydroquinoline (130)

LiHMDS (670 μL of a 1 M solution in anhydrous THF, 0.66 mmol) was added to a solution of lactam **129** (182 mg, 0.44 mmol) in THF (4.4 mL) at –78 ºC, and the mixture was stirred at this temperature for 2 h. Then, a solution of Comins' reagent (347 mg, 0.88 mmol) in THF (4.4 mL) was added, and the mixture was allowed to reach room temperature. After 1.5 h of stirring, 10% aqueous NaOH (7 mL) was added, and the resulting mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried, and concentrated. Flash chromatography (SiO_2 pre-treated with Et_3N; 95:5 hexane–EtOAc) afforded compound **130** (238 mg, 99%) as a yellowish oil.

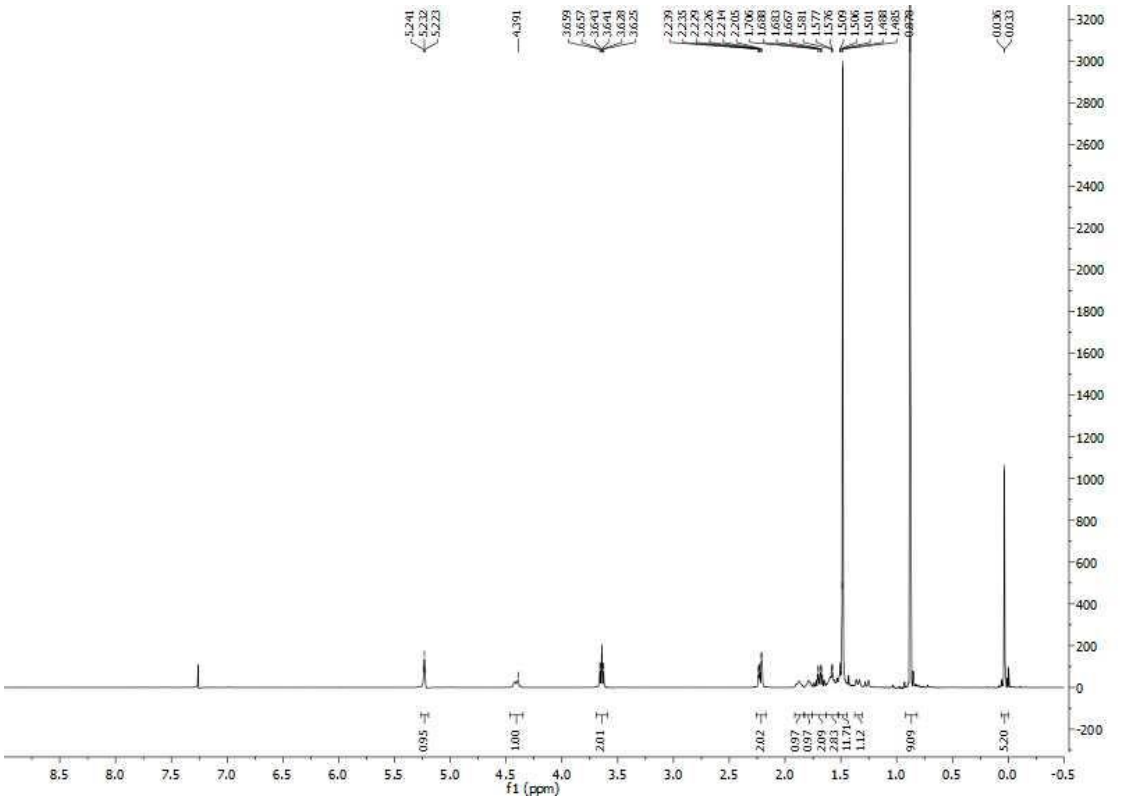
^{1}H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) *δ*: 0.03 [s, 6H, $Si(CH_3)_2$], 0.88 [s, 9H, $SiC(CH_3)_3$], 1.25-1.36 (m, 1H, H-6), 1.38-1.62 (m, 5H), 1.50 [s, 9H, $C(CH_3)_3$], 1.63-1.75 (m, 2H, $OCH_2C\underline{H_2}$), 1.78-1.81 (m, 1H), 1.84-1.90 (m, 1H, H-4a) 2.20-2.24 (m, 2H, H-4), 3.64 (ddd, *J* = 12.4, 5.6 Hz, 2H, $OC\underline{H_2}CH_2$), 4.38-4.43 (m, 1H, H-8a), 5.23 (t, *J* = 3.8 Hz, 1H, H-3).

^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ:* –5.3 [$Si(CH_3)_2$], 18.3 [$Si\underline{C}(CH_3)_3$], 20.6 (C-7), 23.5 (C-8), 24.3 (C-6), 25.1 (C-4), 25.9 [$SiC(\underline{C}H_3)_3$], 28.0 [$C(\underline{C}H_3)_3$], 33.9 (C-5), 35.1 ($OCH_2\underline{C}H_2$), 35.7 (C-4a), 52.6 (C-8a), 61.4 ($O\underline{C}H_2CH_2$), 82.7 [$\underline{C}(CH_3)_3$], 105.8 (C-3), 118.4 (q, *J* = 320 Hz, CF_3), 138.5 (C-2), 152.6 (NCO).

IR (NaCl): 1735, 1648 cm^{-1}.

HRMS calcd for [$C_{23}H_{40}F_3NO_6SSi + NH_4^+$]: 561.2636, found 561.2626.

$[\alpha]^{23}_D$ = +39.7 (c 0.63, $CHCl_3$).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1.683
1.667
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1.577
1.576
1.569
1.506
1.501
1.498
1.485
0.036
0.033
0.95
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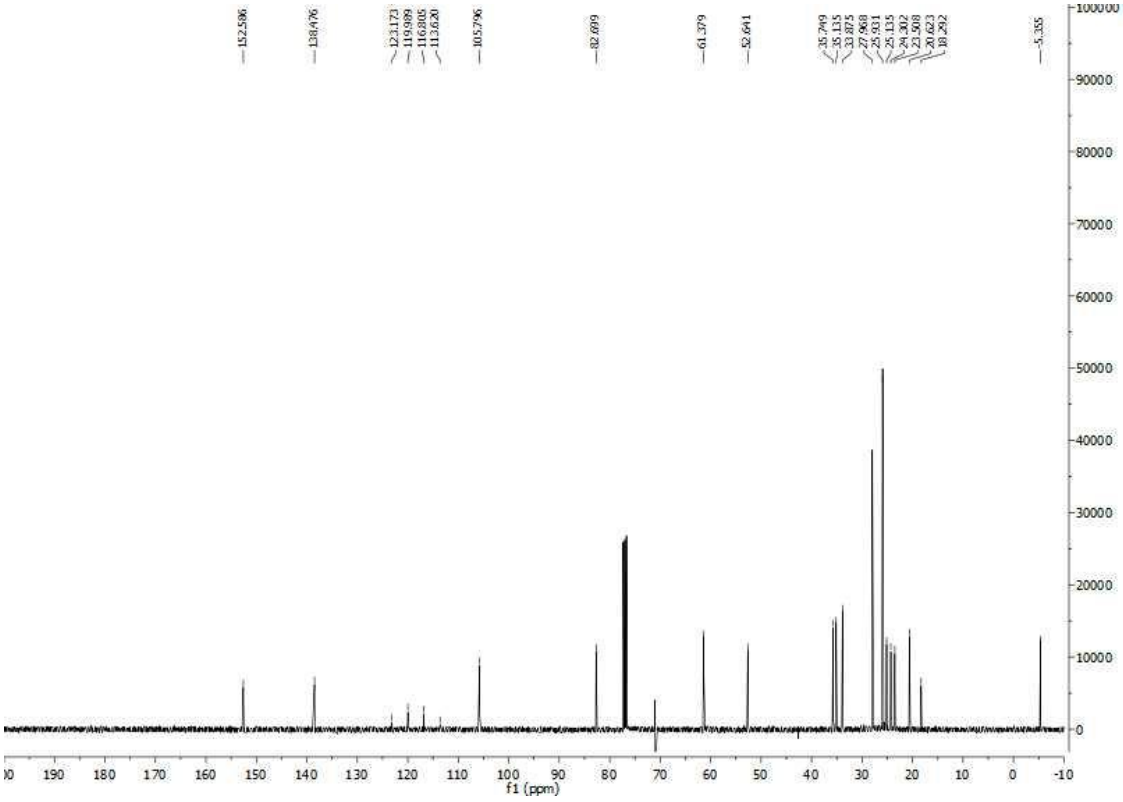
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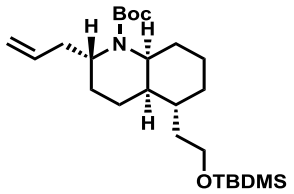
f1 (ppm)



(2*R*,4a*R*,5*R*,8a*S*)-1-(*tert*-Butoxycarbonyl)-5-[2-(*tert*-butyldimethylsilyloxy) ethyl]-2-(2-propenyl)decahydroquinoline (132)

First step: A solution of vinyl triflate **130** (137 mg, 0.19 mmol) in anhydrous THF (2.8 mL) was added to a mixture of LiCl (75 mg, 1.76 mmol), previously dried *in vacuum* at 90 ºC, and $Pd(PPh_3)_4$ (6 mg, 0.005 mmol). Then, allyltributyltin (100 µL, 0.303 mmol) was slowly added and the mixture was heated to reflux temperature for 24 h. After cooling to room temperature, Et_2O and 10% aqueous NH_4OH were added sequentially. The mixture was extracted with EtOAc, and the combined organic extracts were washed with 1 M aqueous KF, dried, and concentrated.

Second step: $NaBH_3CN$ (95 mg, 1.51 mmol) was added to a stirred solution of the above crude enecarbamate in anhydrous CH_2Cl_2 (126 mL), and the stirring was continued for 15 minutes. Then, the mixture was cooled to –42 ºC, TFA (126 µL) was slowly added, and the stirring was continued for 3 h. A solution of saturated aqueous $NaHCO_3$/THF (1:1) (100 mL) was added, and the biphasic mixture was stirred for 10 minutes. The mixture was extracted with EtOAc, and the combined organic extracts were washed with brine, dried and concentrated. Flash chromatography (95:5 hexane–EtOAc) afforded compound **132** (90 mg, 82% for the two steps) as a colorless oil.

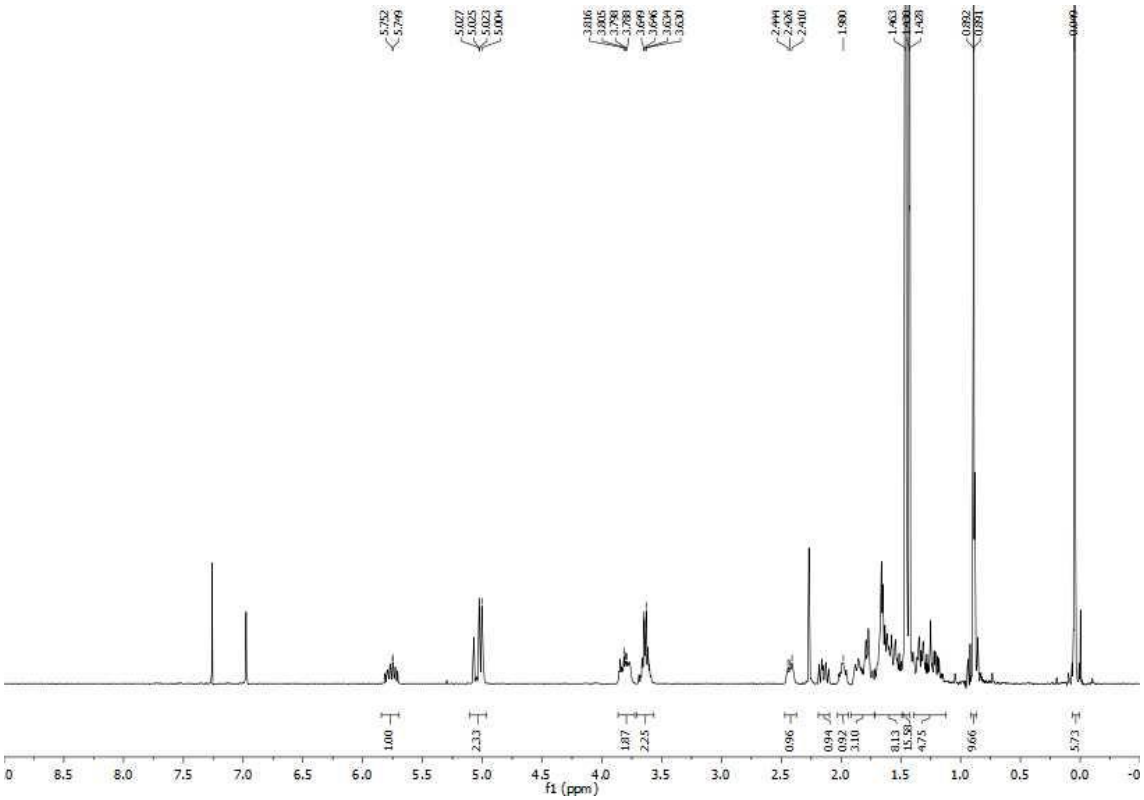
^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) *δ*: 0.05 [s, 6H, $Si(CH_3)_2$], 0.89 [s, 9H, $SiC(CH_3)_3$], 1.15-1.40 (m, 3H), 1.43 (br s, 9H), 1.50-1.72 (m, 7H), 1.74-1.89 (m, 3H), 1.96-2.02 (m, 1H, H-4a), 2.10-2.19 (m, 1H, $\underline{H_2}CHC=CH_2$), 2.40-2.45 (m, 1H, $H_2CHC=CH_2$), 3.59-3.69 (m, 2H, OCH_2CH_2), 3.76-3.86 (m, 2H, H-2, H-8a), 4.99-5.07 (m, 2H, $HC=CH_2$), 5.71-5.81 (m, 1H, $HC=CH_2$).

^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ:* –5.3 [$Si(CH_3)_2$], 18.3 [$Si\underline{C}(CH_3)_3$], 19.5 (C-4), 20.2 (C-7), 22.1 (C-3), 24.2 (C-6), 26.0 [$SiC(\underline{C}H_3)_3$], 28.6 [$OC(\underline{C}H_3)_3$], 29.8 (C-8), 35.0 (C-5), 35.1 (C-4a), 35.4 ($OCH_2\underline{C}H_2$), 40.0 ($H_2\underline{C}HC=CH_2$), 50.4 (C-8a), 50.7 (C-2), 61.8 ($O\underline{C}H_2CH_2$), 78.9 [$\underline{C}(CH_3)_3$], 116.4 ($HC=\underline{C}H_2$), 136.3 ($H\underline{C}=CH_2$), 155.0 (NCO).

IR (NaCl): 2365, 1683 cm^{-1}.

HRMS calcd for [$C_{25}H_{47}NO_3Si + H^+$]: 438.3398, found 439.3390.

$[\alpha]^{23}_D$ = +3.95 (c 1.0, $CHCl_3$).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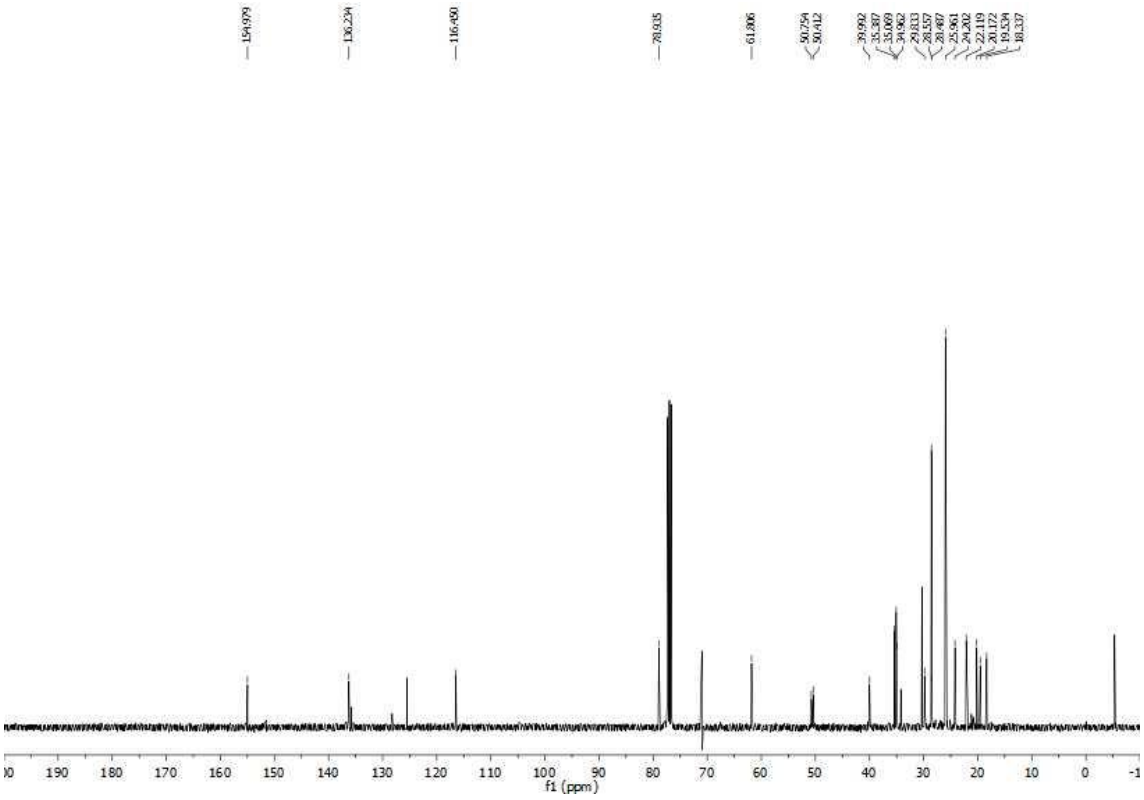
0.000
1.00
2.33
1.87
2.25
0.96
0.94
0.92
3.10
8.13
15.58
4.75
9.66
5.73
f1 (ppm)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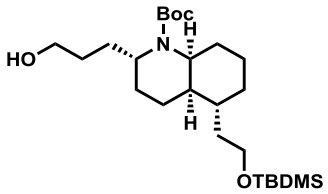
20.172
19.534
18.337
f1 (ppm)



(2*R*,4a*R*,5*R*,8a*S*)-1-(*tert*-Butoxycarbonyl)- 5-[2-(*tert*-butyldimethylsilyloxy)ethyl]-2-(3-hydroxypropyl)-decahydroquinoline (133)

9-BBN (820 μL of a 0.5 M solution in THF, 0.46 mmol) was added dropwise to a solution of compound **132** (100 mg, 0.23 mmol) in dry THF (4 mL) at 0 ºC. The mixture was stirred for 1h 15 min at room temperature. After cooling to 0 ºC, 3 M aqueous NaOH (2.5 mL) and 30% H_2O_2 (1.2 mL) were added, and stirring was continued for 1h at room temperature. The mixture was extracted with CH_2Cl_2, and the combined organic extracts were dried and concentrated. Flash chromatography (8:2 hexane–EtOAc) afforded compound **133** (71 mg, 68%) as a colorless oil.

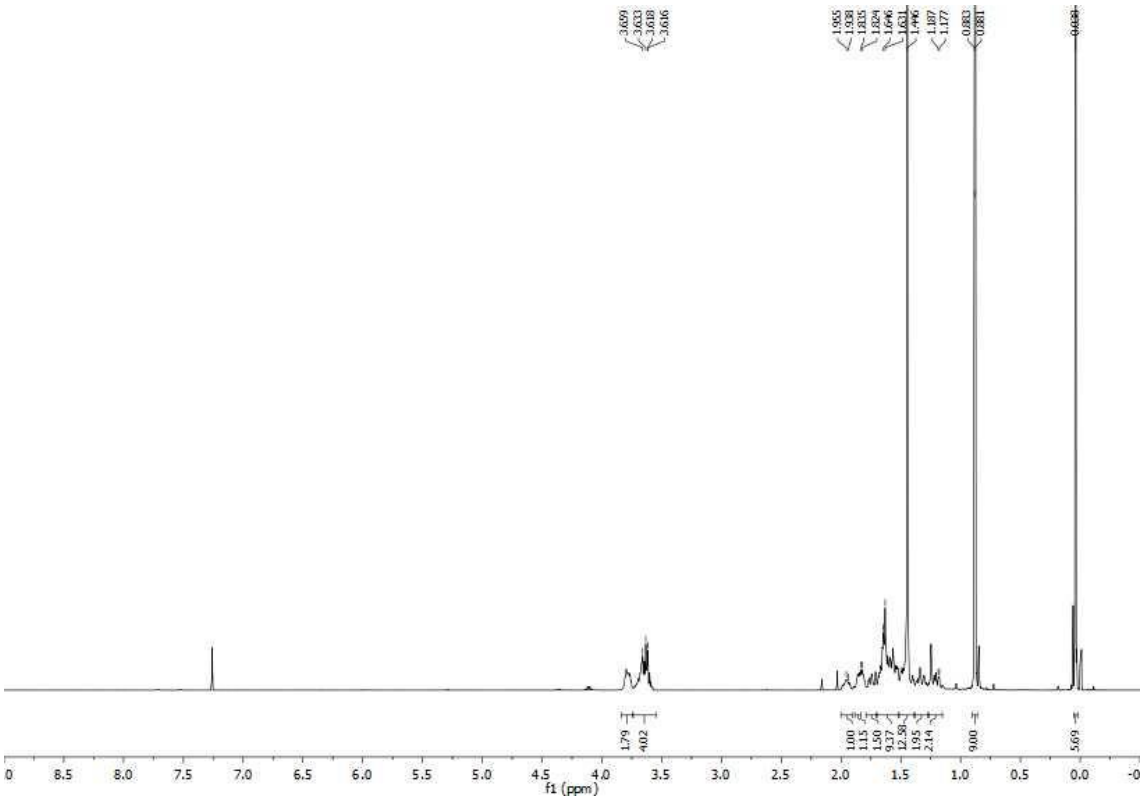
^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) *δ*: 0.02 [s, 6H, $Si(CH_3)_2$], 0.88 [s, 9H, $SiC(CH_3)_3$], 1.11-1.23 (m, 2H), 1.25-1.37 (m, 2H), 1.39-1.46 (m, 2H), 1.40 [s, 9H, $C(CH_3)_3$], 1.49-1.65 (m, 9H), 1.67-1.73 (m, 1H), 1.77-1.85 (m, 2H), 1.89-1.95 (m, 1H), 3.58-3.73 (m, 4H, HOC*H*$_2$, SiOCH_2), 3.76-3.80 (m, 2H, H-2, H-8a).

^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ:* –5.3 [$Si(CH_3)_2$], 18.3 [Si*C*$(CH_3)_3$], 19.5 (C-4), 20.2 (C-7), 22.6 (C-3), 24.1 (C-6), 25.9 [SiC(*C*$H_3)_3$], 28.5 [OC(*C*$H_3)_3$], 29.6 (C-8), 29.8 (CH_2), 31.4 (CH_2), 35.0 (C-5), 35.1 (C-4a), 35.4 (CH_2), 50.5 (C-2, C-8a), 61.9 (CH_2), 62.2 (CH_2), 79.1 [O*C*$(CH_3)_3$], 155.3 (CO).

IR (NaCl): 3447, 1689 cm^{-1}.

HRMS calcd for [$C_{25}H_{49}NO_4Si$ + H^+]: 456.3504, found 456.3500.

$[\alpha]^{23}_D$ = – 3.12 (c 3.56, $CHCl_3$).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1.187
1.177
0.883
0.881
0.838
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4.02
1.00
1.15
1.50
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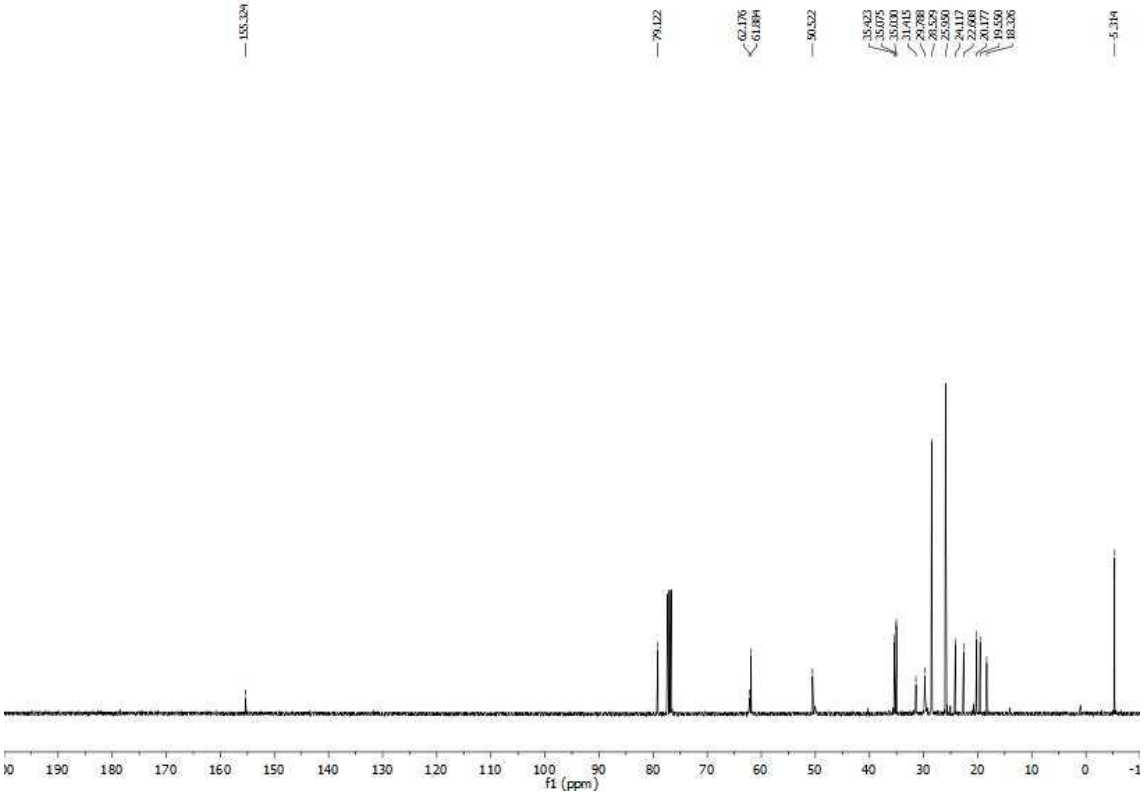
1.95
2.14
9.00
5.69
f1 (ppm)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35.030
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20.177
19.550
18.326
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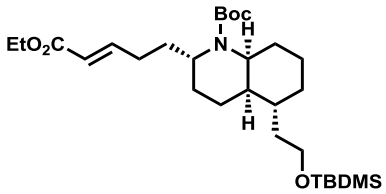
f1 (ppm)



(2*S*,4a*R*,5*R*,8a*S*)-1-*tert*-Butoxycarbonyl-5-[2-(*tert*-butyldimethylsilyloxy)ethyl]-2-[4-(methoxycarbonyl)-3-(*E*)-butenyl]decahydroquinoline (134)

First step: Dess-Martin periodinane (319 mg, 0.75 mmol) was added to a stirring solution of compound **133** (245 mg, 0.54 mmol) in anhydrous CH_2Cl_2 (4.5 mL) at room temperature. After 1.5 h, Et_2O (8 mL), saturated aqueous $Na_2S_2O_3$ (2.2 mL) and saturated aqueous $NaHCO_3$ (2.2 mL) were added sequentially, and the mixture was stirred for 45 minutes. The phases were separated and the aqueous solution was extracted with CH_2Cl_2. The organic extracts were dried and concentrated.

Second step: Methyl (triphenylphosphoranylidene)acetate (215 mg, 0.64 mmol) was added to a stirred solution of the above residue in dry THF (1 mL), and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure. Flash chromatography (95:5 hexane–EtOAc) afforded **134** (208 mg, 76 % for the two steps) as a green oil.

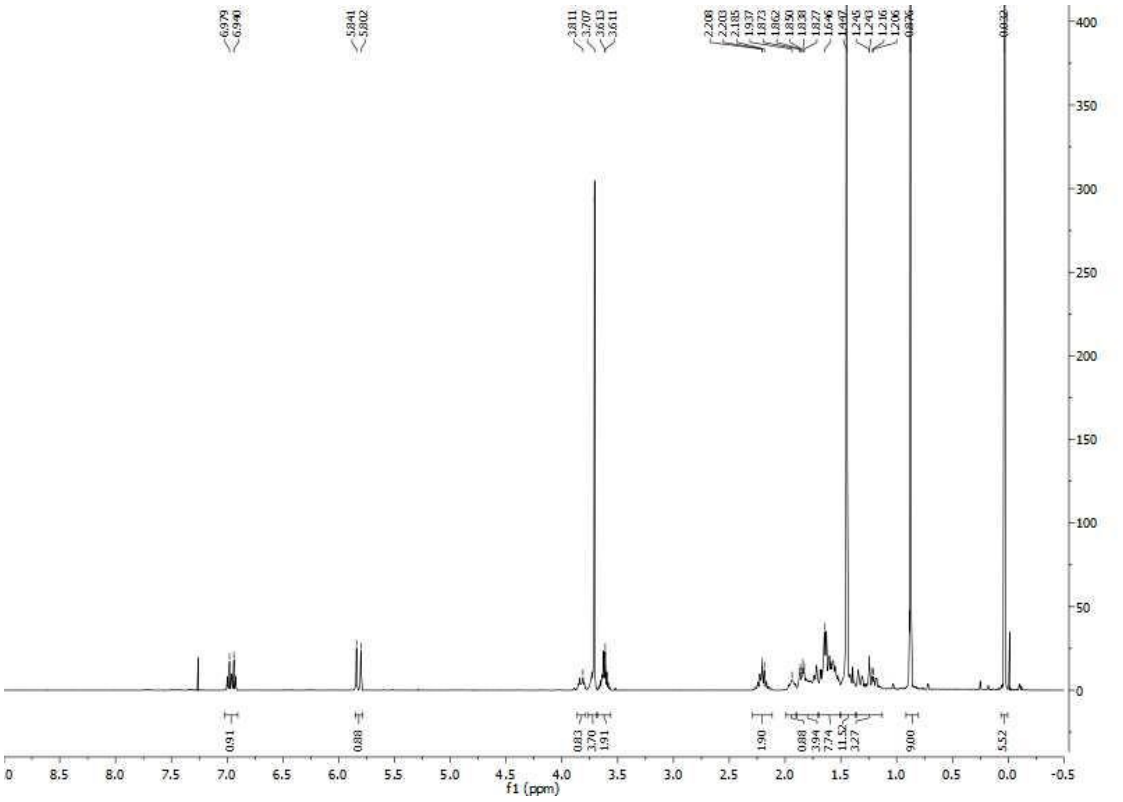
^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ: 0.03 [s, 6H, $Si(CH_3)_2$], 0.88 [s, 9H, $SiC(CH_3)_3$], 1.14-1.87 (m, 15H), 1.45 [s, 9H, $OC(CH_3)_3$], 1.91-1.97 (m, 1H), 2.13-2.28 (m, 2H, OCCH=CH-C*H*$_2$), 3.57-3.67 (m, 2H, OCH_2), 3.69-3.75 (m, 1H, H-2), 3.71 (s, 3H, OCH_3), 3.80-3.85 (m, 1H, H-8a), 5.82 (dt, J = 15.6, 1.4 Hz, 1H, COC*H*=CH), 6.96 (dt, J = 15.6, 7.0 Hz, 1H,COCH=C*H*).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ: –5.3 [$Si(CH_3)_2$], 18.3 [Si*C*$(CH_3)_3$], 19.8 (CH_2), 20.2 (CH_2), 22.9 (CH_2), 24.1 (CH_2), 25.9 [SiC(*C*$H_3)_3$], 28.5 [C(*C*$H_3)_3$], 29.6 (CH_2), 30.0 (CH=CHCH$_2$ *C*H_2), 33.7 (CH=CH-*C*H_2), 35.0 (CH), 35.1 (CH), 35.4 (OCH_2*C*H_2), 50.6 (2 CH), 51.3 (OCH_3), 61.7 (O*C*H_2CH_2), 79.1 [O*C*$(CH_3)_3$], 121.0 (COC*H*=CH), 149.0 (COCH=C*H*), 155.0 (NCO), 167.0 (CO).

IR (NaCl): 1726, 1686 cm^{-1}.

HRMS calcd for [$C_{28}H_{51}NO_5Si$ + H^+]: 510.3609, found 510.3606.

$[\alpha]^{23}_D$ = +0.75 (c 1.19, $CHCl_3$).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1.850
1.838
1.827
1.696
1.546
1.240
1.216
1.206
0.826
0.032
0.91
0.88
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0.88
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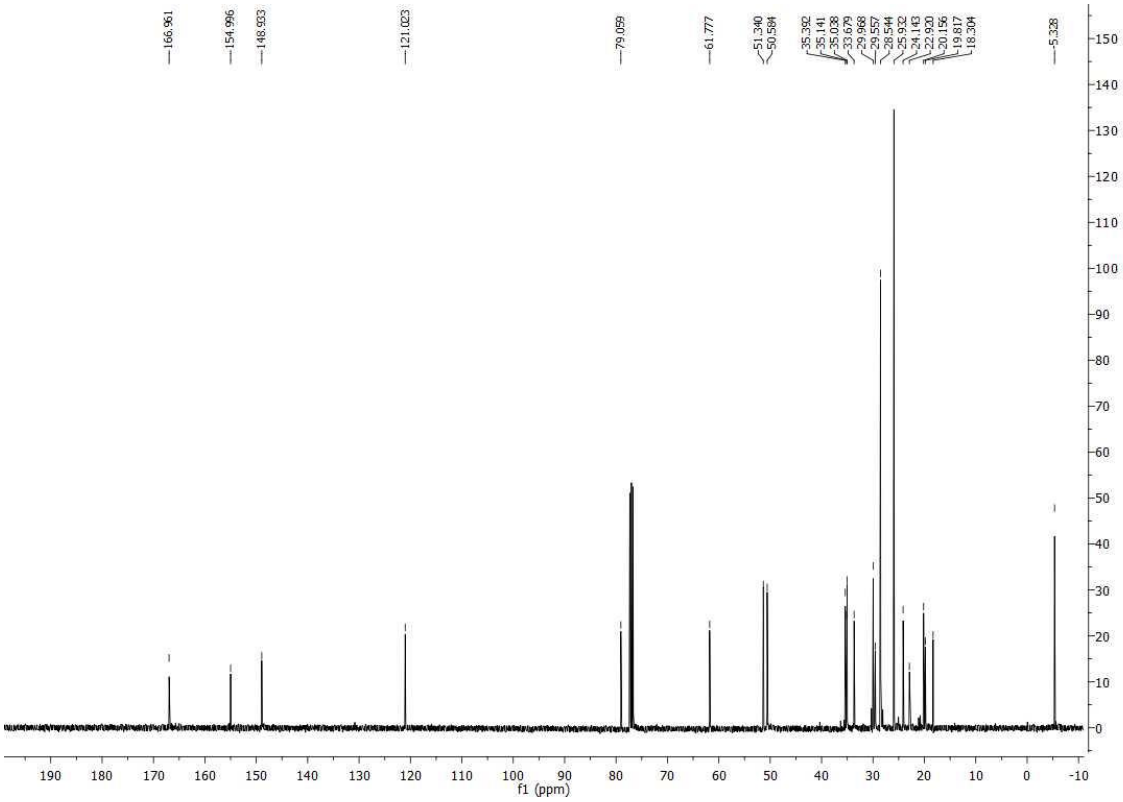
5.52
f1 (ppm)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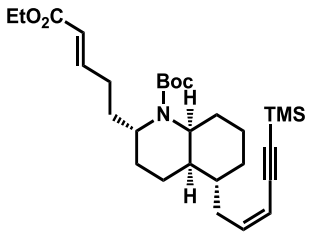
20.156
19.817
18.304
5.328
f1 (ppm)



(2*S*,4a*R*,5*R*,8a*S*)-1-*tert*-Butoxycarbonyl-5-[(*Z*)-5-(trimethylsilyl)pent-2-en-4-ynyl]-2-[(*E*)-4-(methoxycarbonyl)-3-butenyl]decahydroquinoline (138)

First step: Water (32 μL, 1.79 mmol) and $Bi(OTf)_3$ (16 mg, 0.025 mmol) were successively added to a stirring solution of **134** (182 mg, 0.358 mmol) in MeCN (2.3 mL) at room temperature. After 5 h, the mixture was concentrated in vacuo.

Second step: BAIB (184 mg, 0.573 mmol) and TEMPO (4 mg, 0.0251 mmol) were successively added to a solution of the above residue in anhydrous CH_2Cl_2 (1.4 mL) at room temperature. After stirring for 4 h, saturated $Na_2S_2O_3$ solution (560 μL) was added, and the resulting mixture was extracted with CH_2Cl_2. The organic extracts were dried and concentrated. The resulting crude aldehyde was used without further purification in the next step.

Third step: *t*-BuLi (3.15 mL of a 1.7 M solution in pentane, 5.37 mmol) was added dropwise to a stirred solution of a freshly distilled 3-(*t*-butyldimethylsilyl)-1-(trimethylsilyl)propyne (1.2 g, 5.37 mmol) in anydrous THF (9 mL) at −78 ºC. After stirring 1 h at −78 ºC, a solution of titanium (IV) isopropoxide (1.6 mL, 5.37 mmol) in dry THF (4.5 mL) was added dropwise and the resulting solution was stirred for 15 minutes. A portion of this solution (14.5 mL) was withdraw *via* syringe and discarded. A solution of the above crude aldehyde in anhydrous THF (8.95 mL) was added dropwise to the remainder allene solution and the resulting mixture was stirred at −78 ºC for 30 min and at room temperature for 1 h. The mixture was poured into 0.1 N aqueous HCl (44 mL) and extracted with EtOAc. The organic extracts were dried and concentrated. Flash chromatography (95:5 hexane–EtOAc) afforded **138** (63 mg, 36 % overall yield) as a yellow oil.

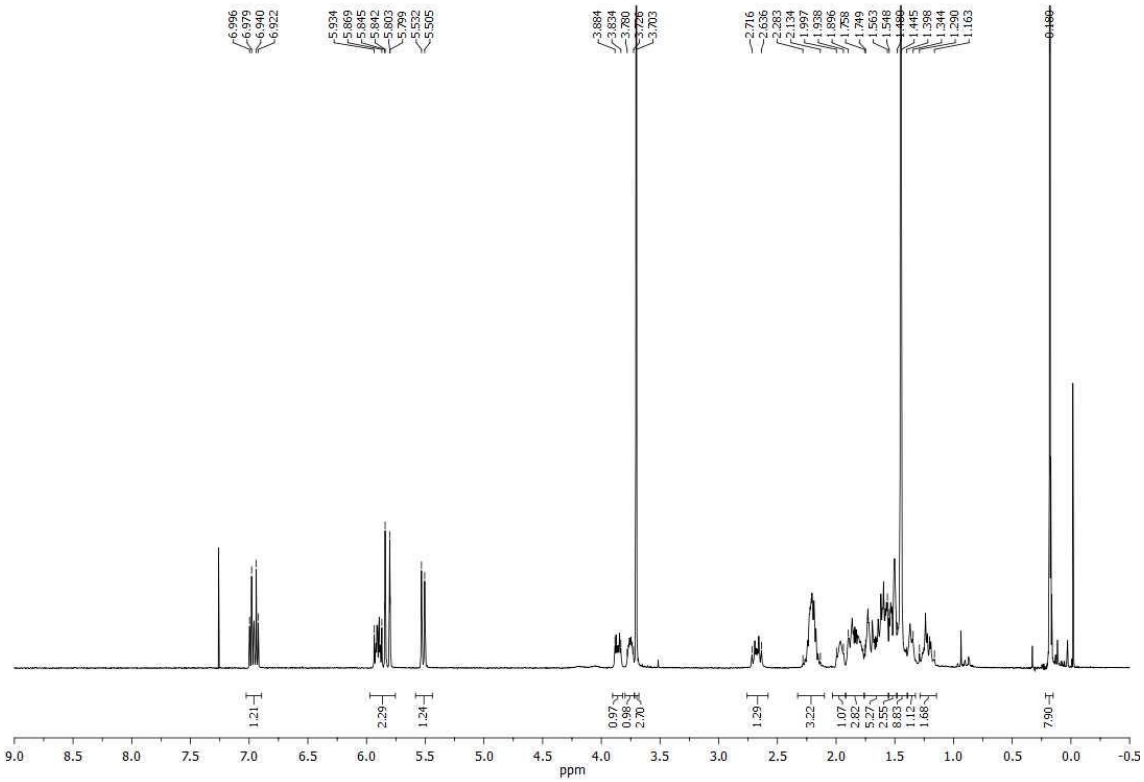
^{1}H-NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ: 0.18 [s, 9H, $Si(CH_3)_3$], 1.16-1.29 (m, 2H), 1.34-1.40 (m, 1H), 1.44 [s, 9H, $C(CH_3)_3$], 1.55-1.48 (m, 3H), 1.56-1.16 (m, 4H), 1.77-1.90 (m, 3H), , 1.94-1.99 (m, 1H, H-4a), 2.13-2.28 [m, 3H, OCCH=CH-C$\underline{H}_2$, $\underline{H}_2$CHC=CH-CC-$Si(CH_3)_3$], 2.64-2.72 [m, 1H, H_2CHC=CH-CC-$Si(CH_3)_3$], 3.70 (s, 3H, OCH_3), 3.73-3.78 (m, 1H), 3.83-3.88 (m, 1H), 5.52 [d, J = 10.8 Hz, 1H, HC=C$\underline{H}$-CC-$Si(CH_3)_3$], 5.82 (dt, J = 15.6, 1.4 Hz, 1H, COC$\underline{H}$=CH), 5.87-5.93 [m, 1H, $\underline{H}$C=CH-CC-$Si(CH_3)_3$], 6.96 (dt, J = 15.6, 7.0 Hz, 1H, COC$\underline{H}$=C).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ: –0.04 [$Si(CH_3)_3$], 20.0 (CH_2), 20.1 (CH_2), 22.9 (CH_2), 23.1 (CH_2), 28.5 [$C(\underline{C}H_3)_3$], 29.5 (CH_2), 30.0 ($CH{=}CH\underline{C}H_2$), 33.5 ($CH{=}CH\text{-}CH_2\underline{C}H_2$), 33.7 [$H_2\underline{C}HC{=}CH\text{-}CC\text{-}Si(CH_3)_3$], 36.1 (CH), 39.0 ($CH_2$), 50.5 (CH), 50.7 (CH), 51.3 (OCH_3), 79.1 [$\underline{C}(CH_3)_3$], 99.0 [$HC{=}CH\text{-}\underline{C}C\text{-}Si(CH_3)_3$], 102.0 [$HC{=}CH\text{-}C\mathit{C}\text{-}Si(CH_3)_3$], 110.2 [$HC{=}\mathit{C}H\text{-}CC\text{-}Si(CH_3)_3$)], 121.0 ($COC\mathit{H}{=}CH$), 144.3 [$H\underline{C}{=}CH\text{-}CC\text{-}Si(CH_3)_3$], 149.0 ($COCH{=}\underline{C}H$), 155.0 (NCO), 167.0 (CO).

IR (NaCl): 1723, 1688 cm^{-1}.

HRMS calcd for [$C_{28}H_{45}NO4_5Si + H^+$]: 488.3191, found 488.3193.

$[\alpha]^{23}_D$ = +20.4 (c 1.38, $CHCl_3$).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3.834
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3.703
2.716
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2.283
2.134
1.997
1.938
1.896
1.758
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1.548
1.445
1.398
1.344
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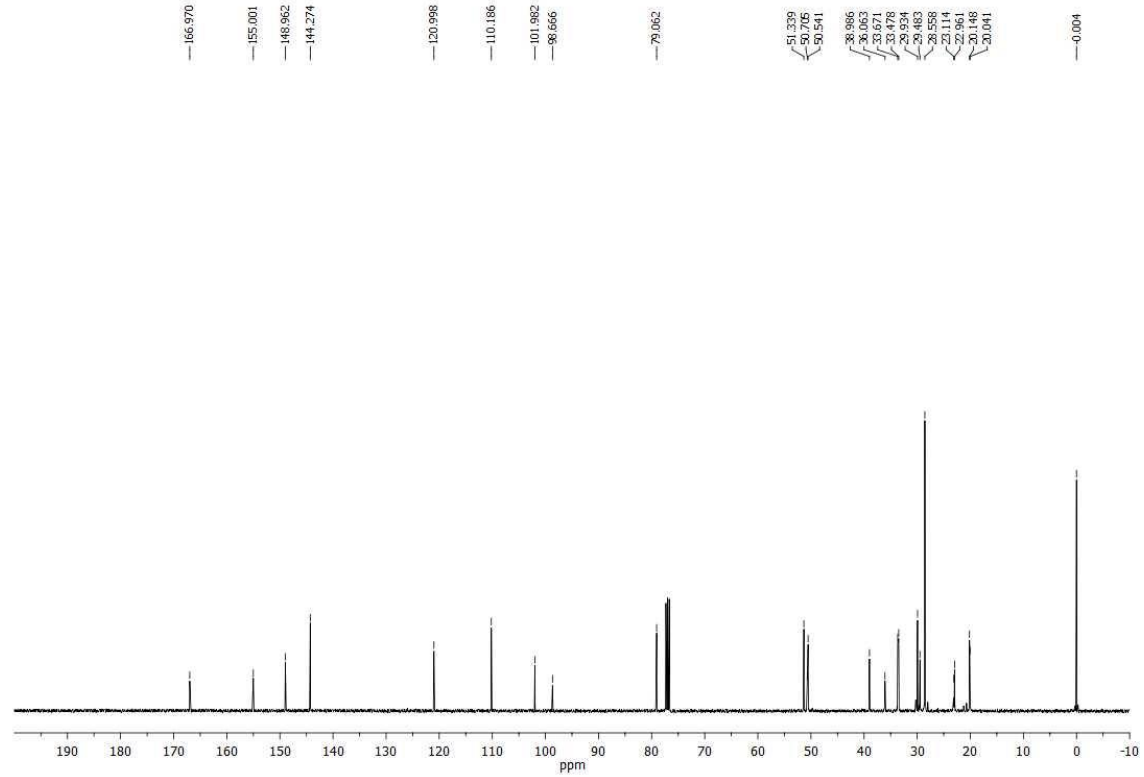
7.90
ppm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38.986
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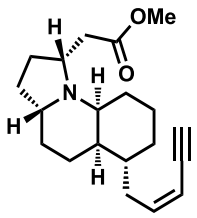
20.148
20.041
-0.004
ppm



(1*R*,3a*R*,5a*R*,6*R*,9a*S*)-1-[(Methoxycarbonyl)methyl]-6-[(*Z*)-pent-2-en-4-ynyl] dodecahydropyrrolo[1,2-*a*]quinoline (139)

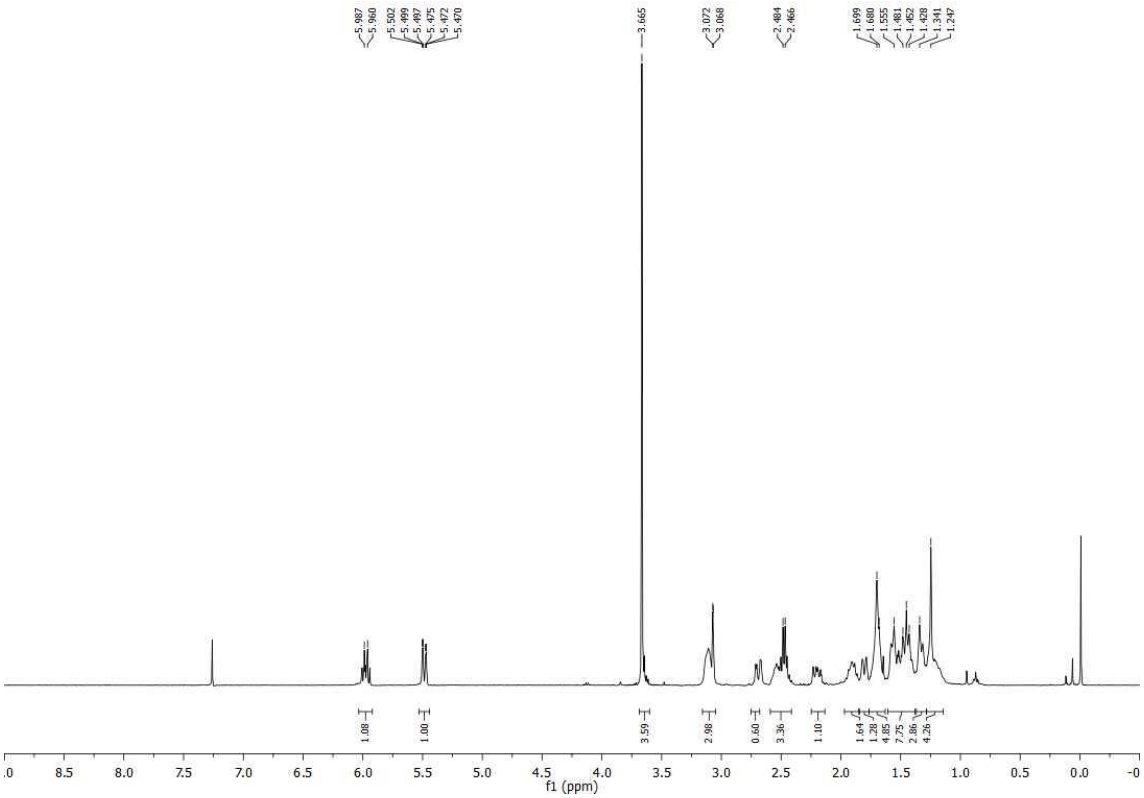
First step: TFA (99 μL, 1.3 mmol) was added to a stirred solution of **138** (63 mg, 0.13 mmol) in CH_2Cl_2 (1.3 mL). After 1 h, the solvent was evaporated and the obtained residue was used without further purification.

Second step: NaOMe (70 mg, 1.3 mmol) was added to a solution of the above crude in anhydrous MeOH (13 mL). After refluxing overnight, the solvent was evaporated under reduced pressure. Flash chromatography (from 75:25 to 1:1 hexane–EtOAc) afforded **139** (22 mg, 54 % for the two steps) as a pale oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.14-1.25 (m, 3H), 1.32-1.34 (m, 2H), 1.40-1.58 (m, 5H), 1.65-1.76 (m, 4H), 1.79-1.82 (m, 1H), 1.86-1.96 (m, 1H), 2.17-2.23 (m, 1H), 2.43-2.58 (m, 3H), 2.69 (dd, J = 14.8, 4.0 Hz, 1H), 3.07-3.12 (m, 3H), 3.67 (s, 3H, OCH_3), 5,49 (d, J = 10.8 Hz, 1H, HC=C*H*-CC), 5.97 (dt, J = 10.8, 7.2, 6.0 Hz, 1H, *H*C=CH-CC).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 16.2 (CH_2), 20.2 (CH_2), 25.0 (CH_2), 26.3 (CH_2), 29.4 (CH_2), 29.7 (CH_2), 32.3 (CH_2), 33.6 (CH_2), 38.7 (CH_2), 39.4 (CH), 40.5 (CH), 50.7 (CH_3), 51.4 (CH), 54.2 (CH), 55.6 (CH), 80.7 (Cq), 81.2 (CH), 108.9 (CH), 145.4 (CH), 173.1 (CO).

$[\alpha]^{23}_D$ = + 54.0 (c 0.15, $CHCl_3$).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1.555
1.481
1.462
1.428
1.341
1.247
1.08
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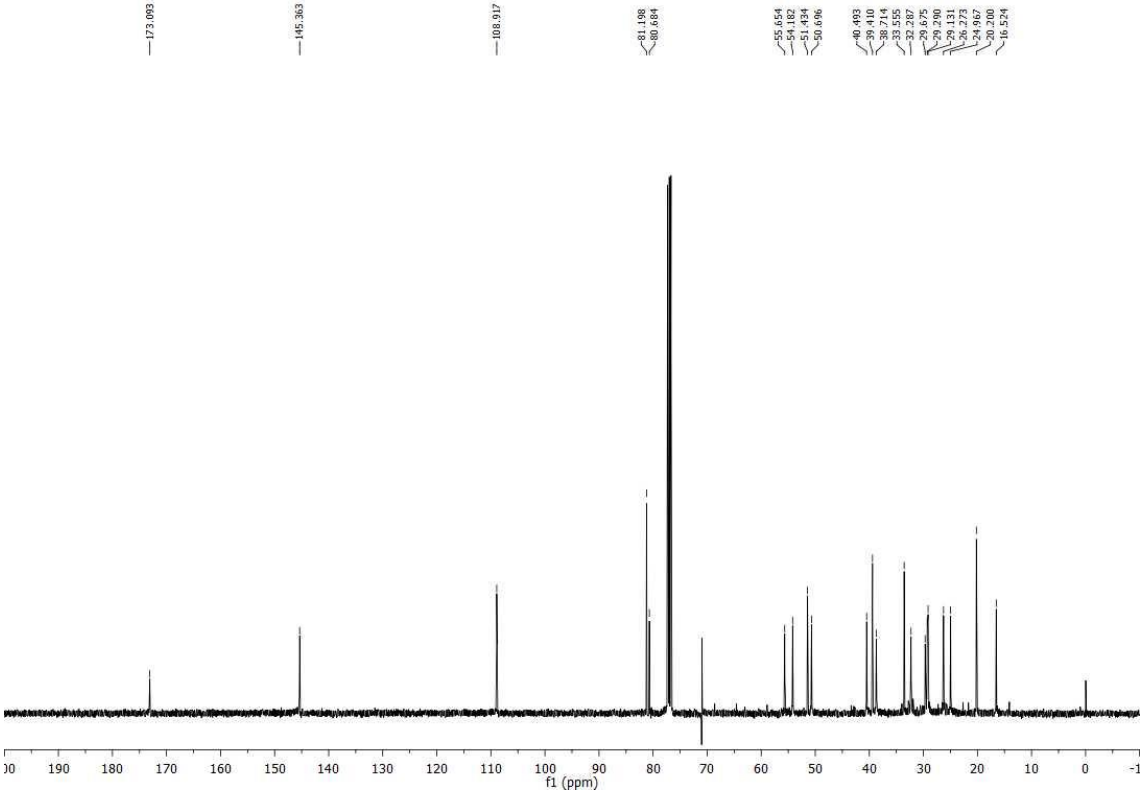
f1 (ppm)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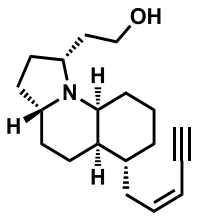
16.524
f1 (ppm)



(+)-Gephyrotoxin 287C

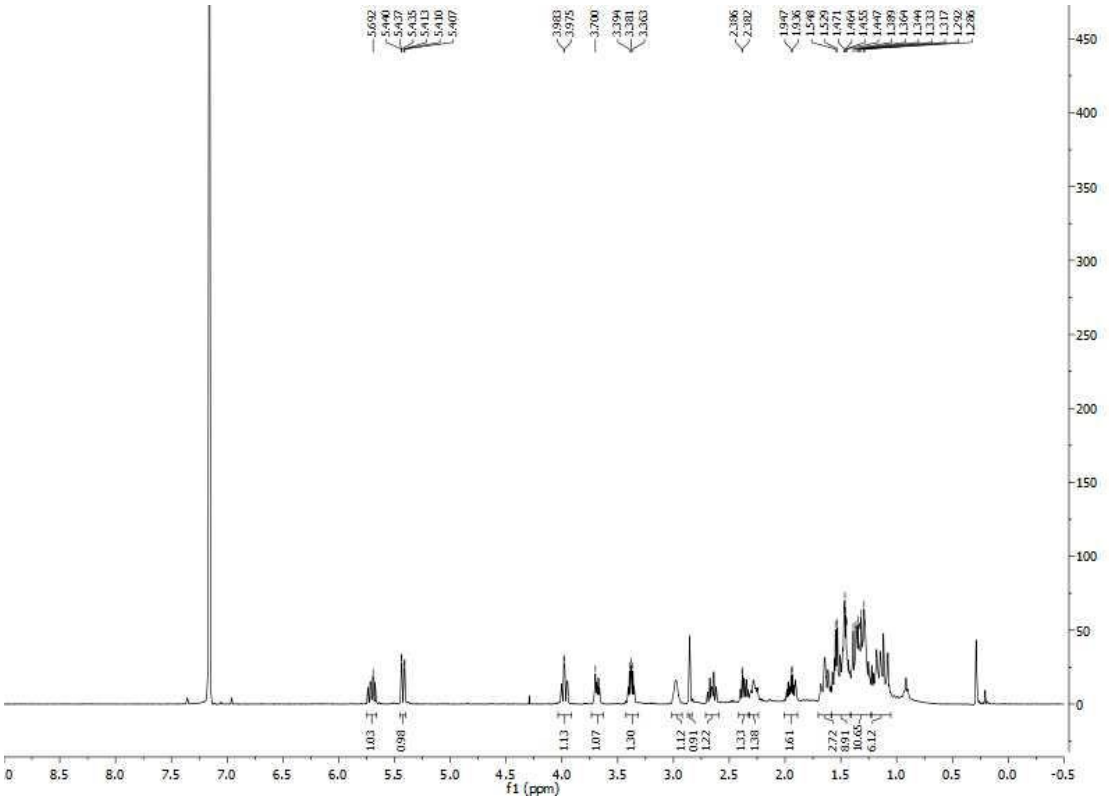
DIBAL-H (207 µL of a 1.02 M solution in hexane, 0.207 mmol) was added to a stirring solution of **139** (22 mg, 0.07 mmol) in Et_2O (3.5 mL) at −78 ºC. After 1 h, MeOH (3.5 mL) was added to the solution at −78 ºC. Sodium borohydride (27 mg, 0.7 mmol) was added at room temperature. After 1 h, 2 M aqueous La Rochelle's salt solution (10 mL) was added, and the resulting mixture was stirred vigorously for 1 h. The phases were separated, and the aqueous layer was further extracted with AcOEt. The combined organic extracts were dried and concentrated. Flash chromatography (KP-NH,[130] from 9:1 to 8:2 hexane–AcOEt) afforded **(+)-gephyrotoxin 287C** (19.8 mg, 99%).

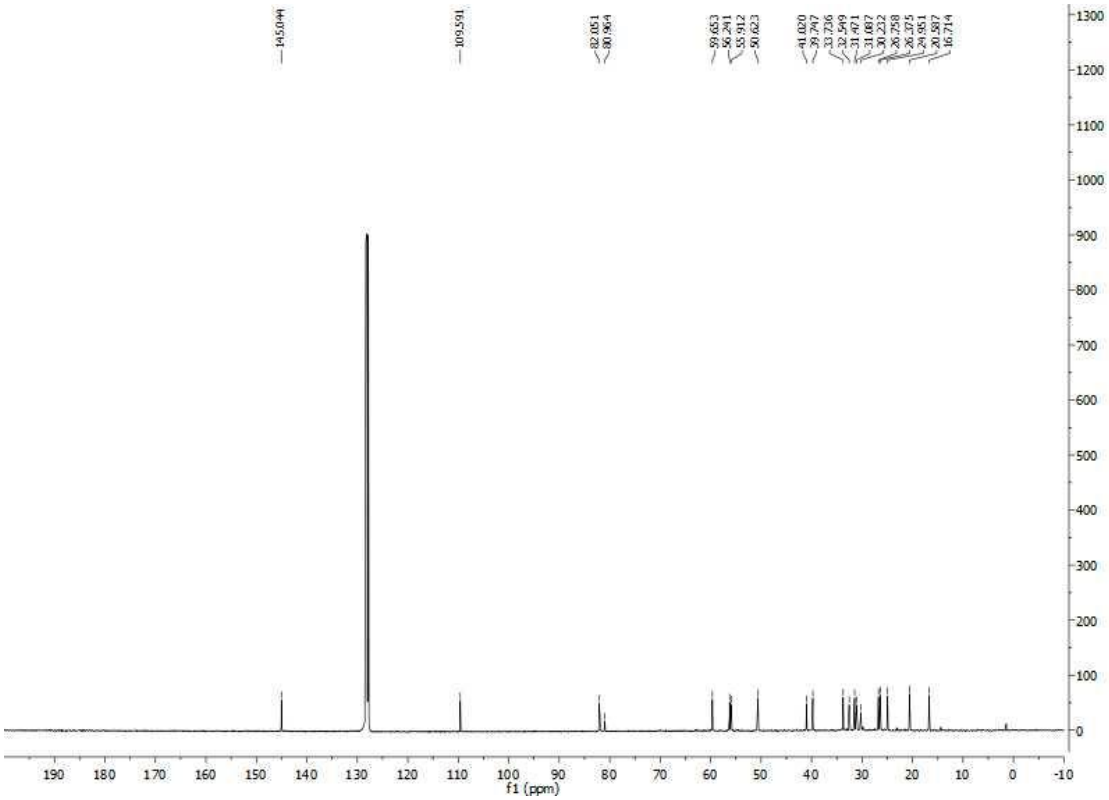
^{1}H NMR (400 MHz, C_6D_6) *δ*: 1.07-1.22 (m, 5H), 1.24-1.40 (m, 7H), 1.58-1.42 (m, 5H), 1.60-1.68 (m, 2H), 1.93 (ddd, *J* = 20.0, 10.2, 4.2 Hz, 1H), 2.23-2.39 (m, 1H), 2.65 (dt, *J* = 14.0, 8.8 Hz, 1H), 2.85 (d, *J* = 2.0 Hz, 1H), 2.94-3.0 (m, 1H), 3.34-3.40 (m, 1H), 3.67 (dt, *J* = 10.8, 3.6 Hz, 1H), 3.97 (td, *J* = 10.8, 3.6 Hz, 1H), 5.41 (ddd, *J* = 10.8, 2.4, 1.2 Hz, 1H, HC=C*H*-CC), 5.66-5.73 (m, 1H, *H*C=CH-CC).

^{13}C-NMR (100.6 MHz, C_6D_3) *δ:*17.3 (CH_2), 21.2 (CH_2), 25.5 (CH_2), 26.9 (CH_2), 27.3 (CH_2), 30.8 (CH_2) 32.0 (CH_2), 33.1 (CH_2), 34.3 (CH_2), 40.3 (CH), 41.6 (CH), 51.2 (CH), 56.5 (CH), 56.8 (CH), 60.2 (CH_2), 81.5 (CH), 82.6 (Cq), 110.2 (CH), 145.6 (CH).

$[\alpha]^{23}_D$ = + 49.0 (c 0.21, EtOH)

[130] SNAP KP-NH cartridges for Biotage Isolera One system, contains amine functionalized silica.


5.692
5.440
5.437
5.435
5.413
5.410
5.407
3.983
3.975
3.700
3.399
3.381
3.363
2.386
2.382
1.947
1.936
1.548
1.529
1.471
1.464
1.455
1.447
1.389
1.364
1.344
1.333
1.317
1.292
1.286
1.03
0.98
1.13
1.07
1.30
1.12
0.91
1.22
1.33
1.38
1.61
2.72
8.91
10.65
6.12
f1 (ppm)


145.044
109.591
82.051
80.964
59.653
56.241
55.912
50.623
41.020
39.947
33.736
32.369
31.471
31.087
30.232
26.758
26.375
24.951
20.587
16.714
f1 (ppm)

Annex – Crystallographic data for compound **91**

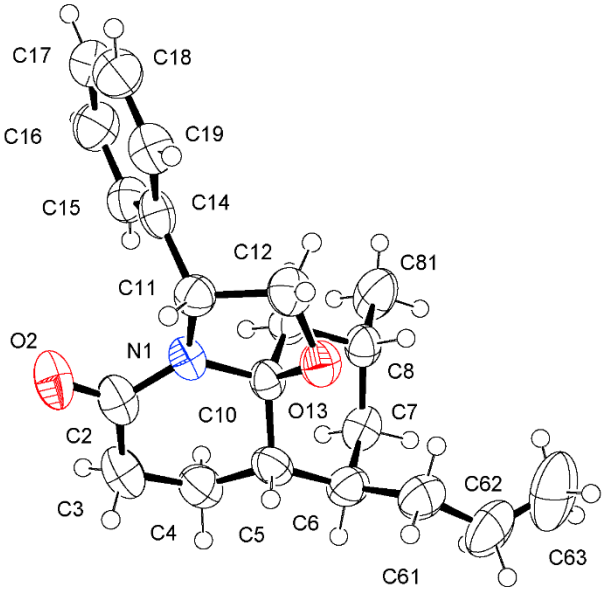

C17
C18
C16
C19
C15
C14
C12
C81
C11
O2
N1
C8
C10
O13
C7
C2
C62
C3
C4
C5
C6
C63
C61

Table 1. Crystal data and structure refinement for **3** (Jb 122c)

Identification code	Jb122c	
Empirical formula	C21 H27 N O2	
Formula weight	325.43	
Temperature	294(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 8.2884(19) Å	α= 90°.
	b = 9.710(4) Å	β= 90°.
	c = 22.524(4) Å	γ = 90°.
Volume	1812.7(9) $Å^3$	
Z	4	
Density (calculated)	1.192 Mg/m^3	
Absorption coefficient	0.076 mm^{-1}	
F(000)	704	
Crystal size	0.420 x 0.330 x 0.300 mm^3	
Theta range for data collection	1.808 to 24.991°.	
Index ranges	-9<=h<=9, -11<=k<=0, 0<=l<=26	
Reflections collected	3449	
Independent reflections	3179 [R(int) = 0.0374]	
Completeness to theta = 24.991°	100.0 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3179 / 0 / 218	
Goodness-of-fit on F^2	1.029	
Final R indices [I>2sigma(I)]	R1 = 0.0535, wR2 = 0.1089	
R indices (all data)	R1 = 0.1131, wR2 = 0.1285	

Largest diff. peak and hole	0.131 and -0.174 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)

for jb122c. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(2)	-2082(4)	5096(4)	4933(1)	72(1)
O(13)	2179(3)	3957(3)	5973(1)	51(1)
N(1)	-279(4)	4636(3)	5653(1)	45(1)
C(2)	-1110(6)	5512(5)	5300(2)	55(1)
C(3)	-750(6)	7014(5)	5365(2)	71(2)
C(4)	357(6)	7437(5)	5871(2)	65(1)
C(5)	1724(5)	6400(4)	5960(2)	51(1)
C(6)	2918(5)	6888(4)	6438(2)	56(1)
C(7)	2197(5)	6730(5)	7060(2)	56(1)
C(8)	1599(5)	5294(5)	7184(2)	51(1)
C(9)	357(5)	4878(4)	6717(2)	45(1)
C(10)	1009(4)	5000(4)	6084(2)	43(1)
C(11)	-256(5)	3163(4)	5531(2)	50(1)
C(12)	1320(5)	2708(5)	5841(2)	56(1)
C(14)	-1729(5)	2375(4)	5733(2)	47(1)
C(15)	-2928(5)	2965(5)	6070(2)	57(1)
C(16)	-4259(6)	2211(5)	6252(2)	64(1)
C(17)	-4393(6)	853(5)	6095(2)	66(1)
C(18)	-3215(6)	257(5)	5755(2)	67(1)
C(19)	-1905(6)	1004(5)	5577(2)	57(1)
C(61)	4581(5)	6208(5)	6391(2)	68(1)

C(62)	5788(6)	6856(6)	6798(3)	88(2)
C(63)	6450(7)	6302(8)	7249(3)	118(3)
C(81)	873(6)	5187(6)	7807(2)	80(2)

Table 3. Bond lengths [Å] and angles [°] for jb122c.

O(2)-C(2)	1.223(5)
O(13)-C(10)	1.424(4)
O(13)-C(12)	1.438(5)
N(1)-C(2)	1.352(5)
N(1)-C(11)	1.457(5)
N(1)-C(10)	1.485(5)
C(2)-C(3)	1.496(6)
C(3)-C(4)	1.518(6)
C(4)-C(5)	1.529(6)
C(5)-C(10)	1.510(5)
C(5)-C(6)	1.537(6)
C(6)-C(7)	1.531(6)
C(6)-C(61)	1.532(6)
C(7)-C(8)	1.505(6)
C(8)-C(9)	1.526(5)
C(8)-C(81)	1.530(6)
C(9)-C(10)	1.529(5)
C(11)-C(14)	1.511(6)
C(11)-C(12)	1.546(5)
C(14)-C(15)	1.376(6)
C(14)-C(19)	1.384(5)
C(15)-C(16)	1.386(6)
C(16)-C(17)	1.369(6)
C(17)-C(18)	1.369(6)
C(18)-C(19)	1.368(6)

C(61)-C(62)	1.495(7)
C(62)-C(63)	1.275(8)

C(10)-O(13)-C(12)	107.4(3)
C(2)-N(1)-C(11)	120.8(4)
C(2)-N(1)-C(10)	126.9(4)
C(11)-N(1)-C(10)	110.4(3)
O(2)-C(2)-N(1)	121.7(4)
O(2)-C(2)-C(3)	121.3(4)
N(1)-C(2)-C(3)	117.0(4)
C(2)-C(3)-C(4)	117.2(4)
C(3)-C(4)-C(5)	111.6(4)
C(10)-C(5)-C(4)	109.0(3)
C(10)-C(5)-C(6)	113.6(3)
C(4)-C(5)-C(6)	111.5(3)
C(7)-C(6)-C(61)	111.7(4)
C(7)-C(6)-C(5)	111.0(3)
C(61)-C(6)-C(5)	113.5(4)
C(8)-C(7)-C(6)	113.0(3)
C(7)-C(8)-C(9)	109.9(3)
C(7)-C(8)-C(81)	111.2(4)
C(9)-C(8)-C(81)	110.4(3)
C(8)-C(9)-C(10)	112.5(3)
O(13)-C(10)-N(1)	101.8(3)
O(13)-C(10)-C(5)	109.9(3)
N(1)-C(10)-C(5)	112.0(3)
O(13)-C(10)-C(9)	110.5(3)

N(1)-C(10)-C(9)	109.7(3)
C(5)-C(10)-C(9)	112.4(3)
N(1)-C(11)-C(14)	115.5(3)
N(1)-C(11)-C(12)	101.9(3)
C(14)-C(11)-C(12)	113.7(3)
O(13)-C(12)-C(11)	105.7(3)
C(15)-C(14)-C(19)	117.7(4)
C(15)-C(14)-C(11)	122.6(4)
C(19)-C(14)-C(11)	119.7(4)
C(14)-C(15)-C(16)	121.2(4)
C(17)-C(16)-C(15)	119.8(5)
C(18)-C(17)-C(16)	119.6(5)
C(19)-C(18)-C(17)	120.4(4)
C(18)-C(19)-C(14)	121.3(4)
C(62)-C(61)-C(6)	112.3(4)
C(63)-C(62)-C(61)	126.8(6)

Table 4. Anisotropic displacement parameters ($Å^2$x 10^3)for jb122c. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(2)	77(2)	86(2)	55(2)	-1(2)	-25(2)	16(2)
O(13)	45(2)	53(2)	56(2)	-2(2)	4(2)	11(2)
N(1)	47(2)	49(2)	40(2)	2(2)	-3(2)	10(2)
C(2)	53(3)	66(3)	45(3)	2(2)	4(2)	21(3)
C(3)	79(3)	65(4)	68(3)	11(3)	-9(3)	22(3)
C(4)	72(3)	57(3)	66(3)	10(2)	-6(3)	5(3)
C(5)	53(3)	55(3)	46(3)	11(2)	5(2)	3(2)
C(6)	49(3)	53(3)	65(3)	3(2)	5(2)	-2(2)
C(7)	46(2)	64(3)	59(3)	-9(2)	-1(2)	0(2)
C(8)	43(2)	68(3)	42(2)	3(2)	0(2)	2(2)
C(9)	41(2)	52(3)	40(2)	5(2)	4(2)	4(2)
C(10)	39(2)	48(3)	41(2)	4(2)	3(2)	8(2)
C(11)	57(3)	54(3)	37(2)	-5(2)	3(2)	9(2)
C(12)	54(3)	54(3)	58(3)	-4(2)	-1(2)	10(2)
C(14)	52(3)	55(3)	35(2)	-5(2)	-7(2)	13(2)
C(15)	54(3)	56(3)	61(3)	-7(2)	-6(3)	2(3)
C(16)	55(3)	70(3)	68(3)	-4(3)	4(2)	4(3)
C(17)	59(3)	66(4)	72(4)	9(3)	-13(3)	-7(3)
C(18)	81(4)	54(3)	65(3)	-7(3)	-11(3)	0(3)
C(19)	65(3)	57(3)	48(3)	-9(2)	-2(2)	10(3)
C(61)	51(3)	82(3)	70(3)	4(3)	10(3)	-3(3)
C(62)	49(3)	94(4)	121(5)	-5(4)	0(4)	-3(3)

C(63)	64(4)	184(8)	106(5)	-23(5)	-2(4)	26(5)
C(81)	68(3)	128(5)	44(3)	2(3)	-4(2)	-20(3)

Table 5. Hydrogen bonds for jb122c [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(12)-H(12B)...O(2)#1	0.97	2.57	3.494(6)	158.5

Symmetry transformations used to generate equivalent atoms:

#1 x+1/2,-y+1/2,-z+1