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Departament de Química

Flexible Approach to *Stemona* Alkaloids: Total Syntheses of (–)-Stemospironine and Three New Diastereoisomeric Analogs

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Vist i plau

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Bellaterra, març 2013

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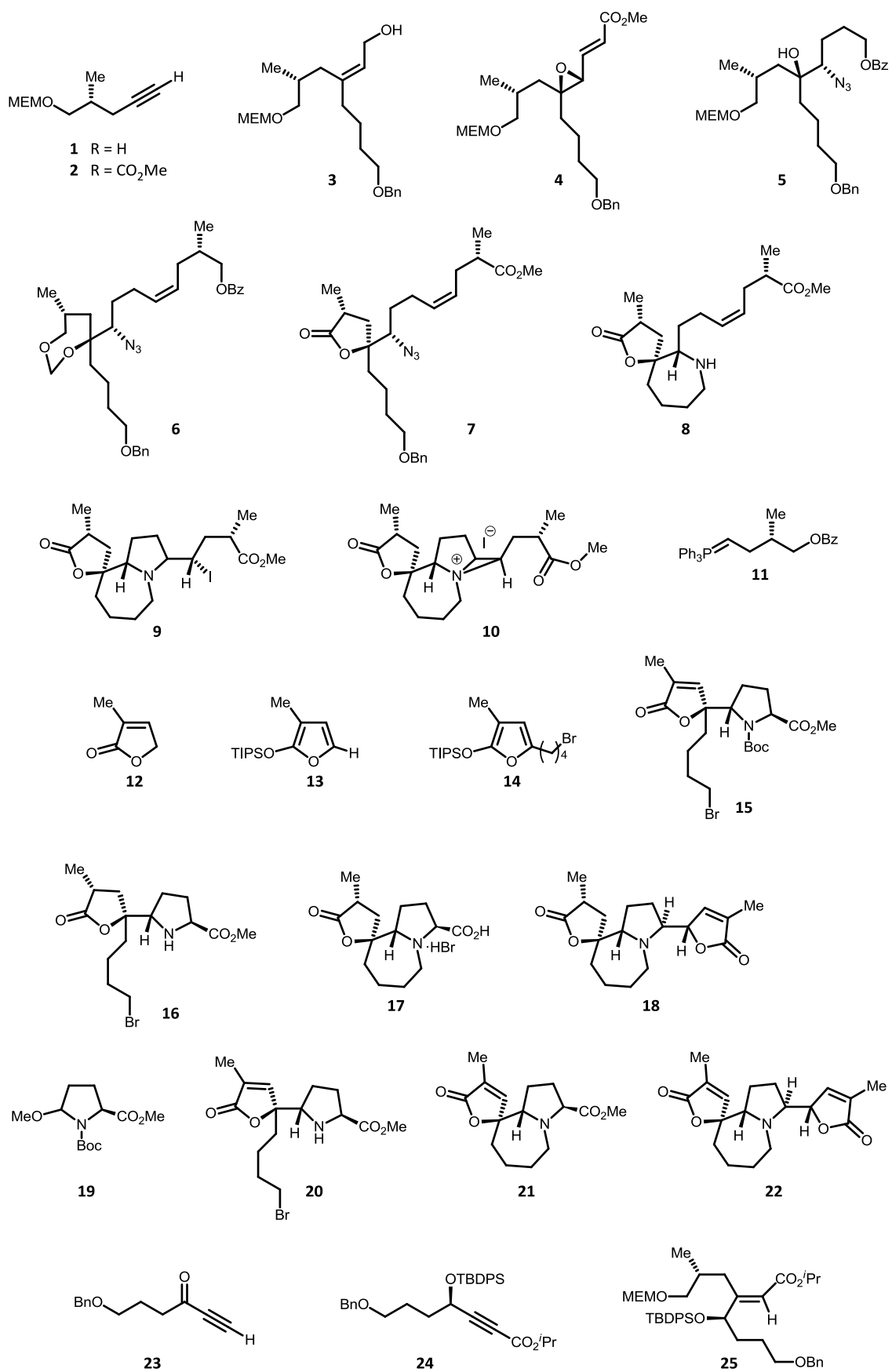
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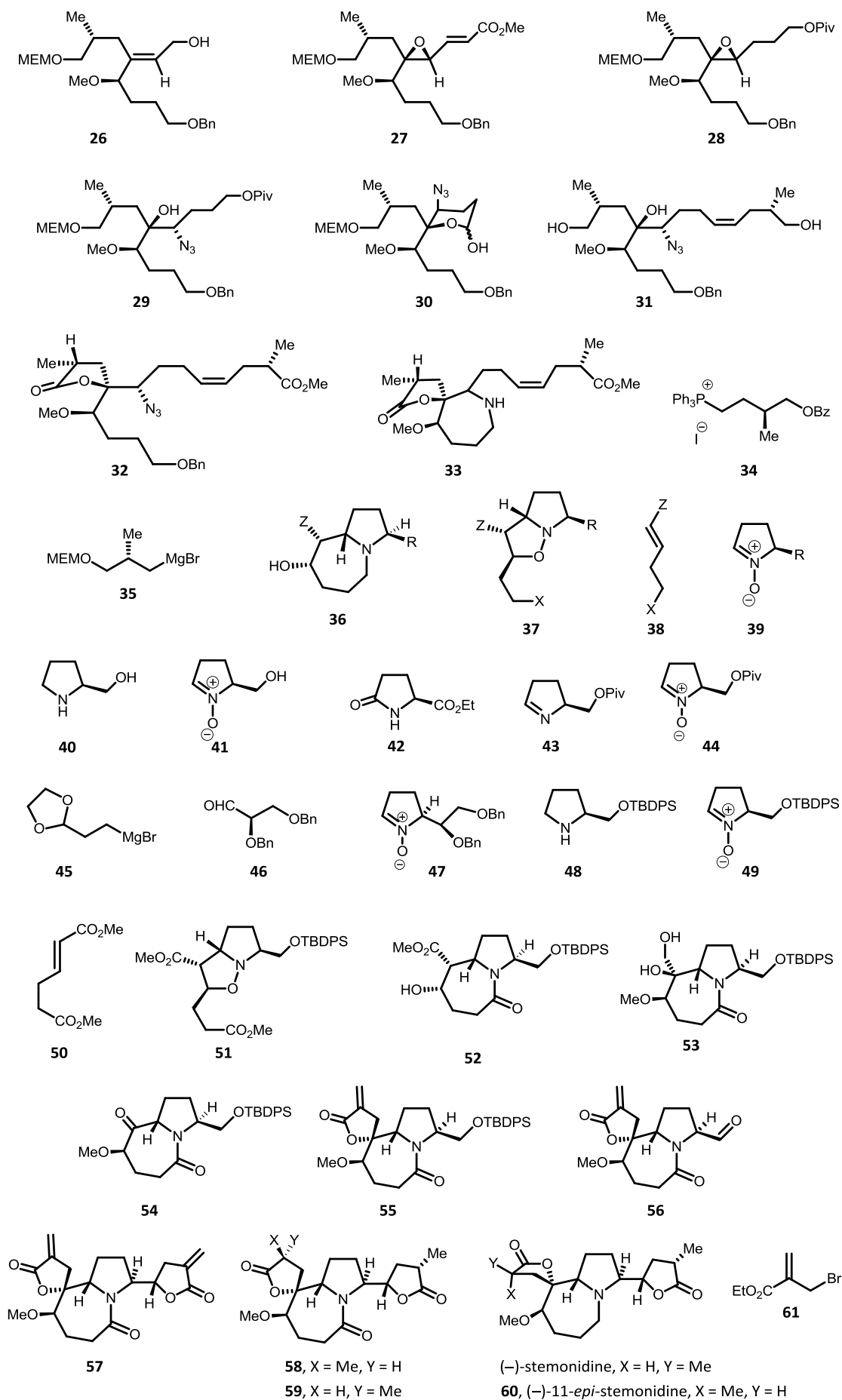
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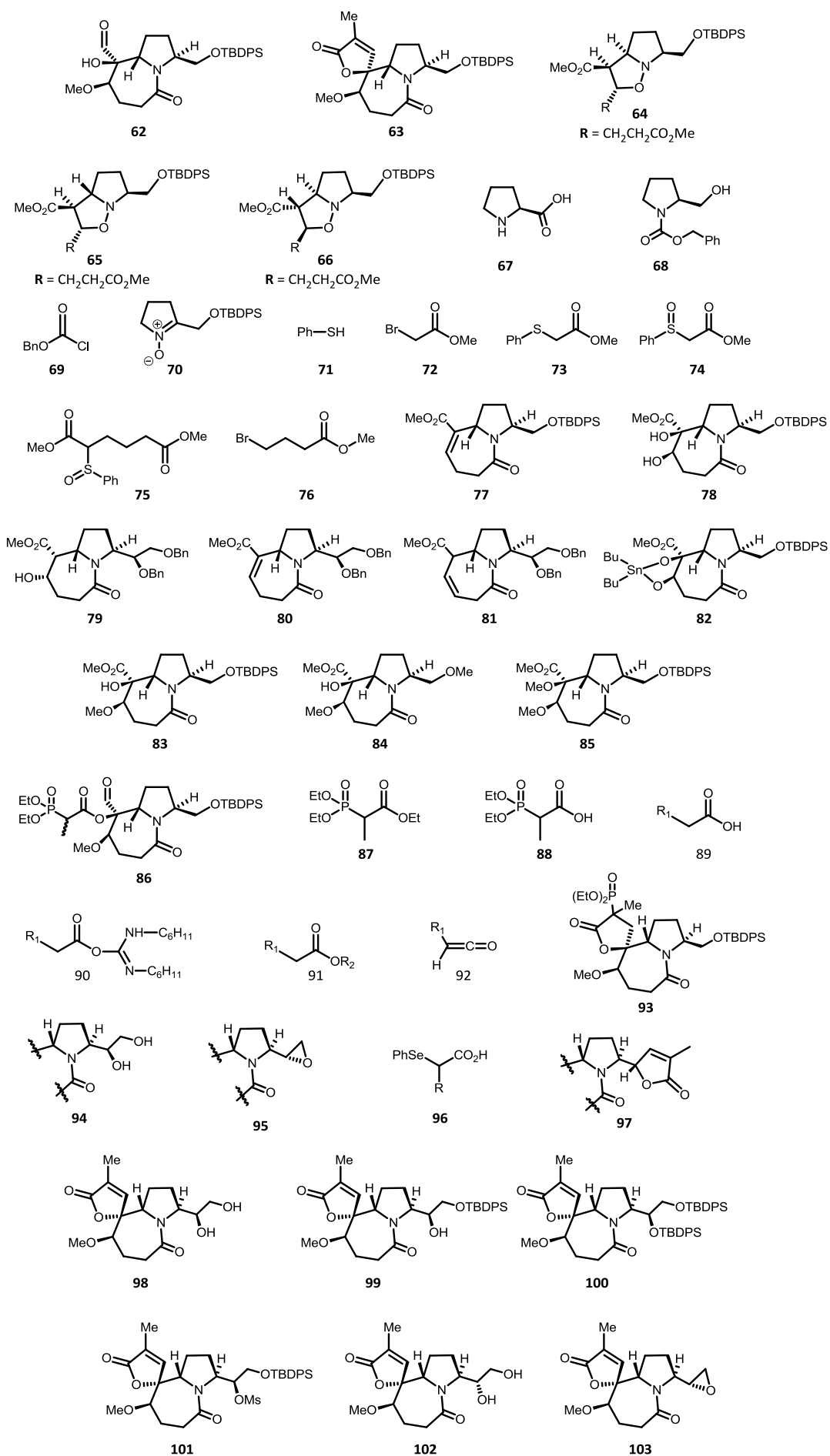
Reagent and Solvent Acronyms

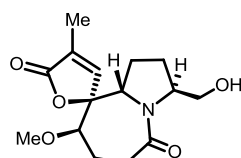
DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DIPT	diisopropyl tartarate
DMAP	4-dimethylaminopyridine
DMD	dimethyldioxirane
DME	dimethoxyethane
DMF	dimethylformamide
DMPI	Dess-Martin periodinane
DMPU	<i>N,N'</i> -dimethylpropylene urea
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
EDTA	ethylenediaminetetraacetic acid
HMPA	hexamethylphosphoramide
Im	imidazole
LiHMDS	lithium bis(trimethylsilyl)amide
MEM	methoxyethoxymethyl
Ms	mesylate
NCS	<i>N</i> -chlorosuccinimide
TBA	tetrabutylammonium
TBDPS	^t butyldiphenylsilyl
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TFA	trifluoroacetic acid
TFMD	(trifluoromethyl)methyldioxirane
THF	tetrahydrofuran
TIPS-OTf	triisopropylsilyl trifluoromethanesulfonate
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMS	trimethylsilyl

Formula Index

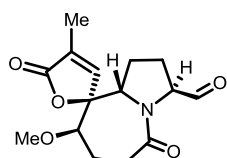




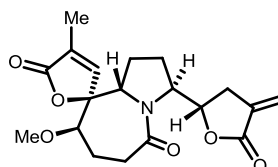




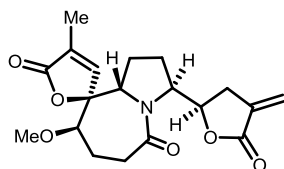
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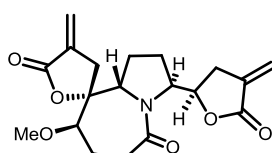
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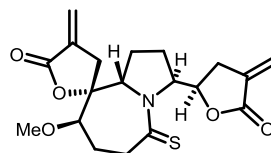
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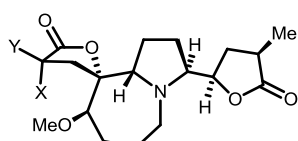
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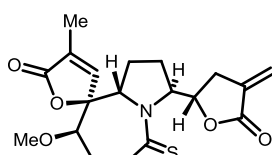


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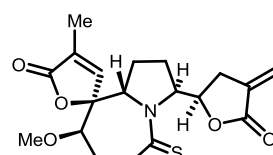


110, X = H, Y = Me

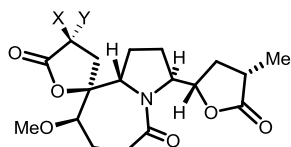
111, X = Me, Y = H



112

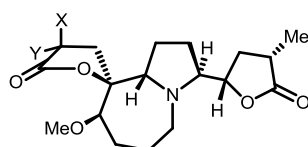


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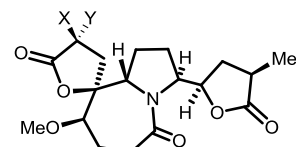
114, X = H, Y = Me

115, X = Me, Y = H



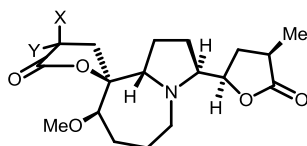
(-)-stemospirinine, X = H, Y = Me

116, X = Me, Y = H



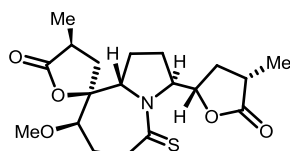
117, X = H, Y = Me

118, X = Me, Y = H

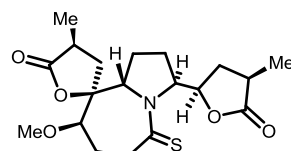


119, X = H, Y = Me

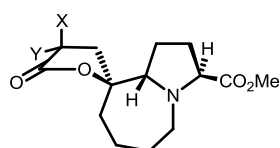
120, X = Me, Y = H



121

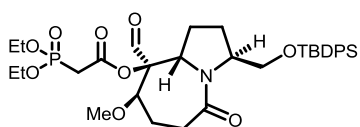


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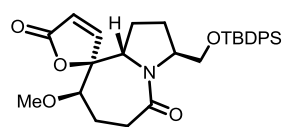


123, X=H, Y=Me

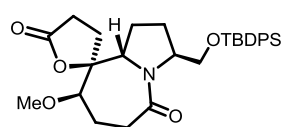
124, X=Me, Y=H



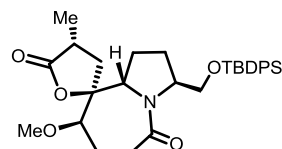
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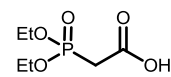
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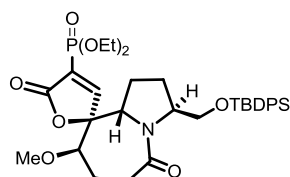
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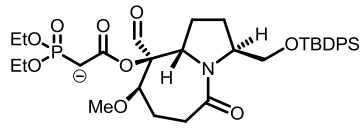
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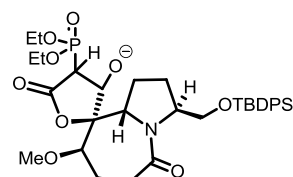
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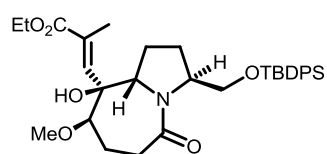
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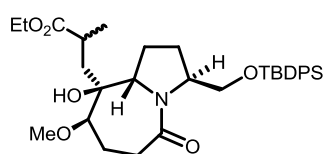
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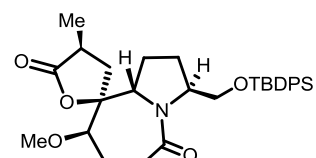
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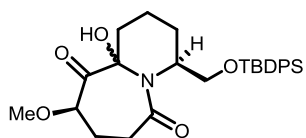
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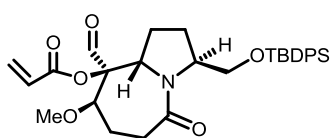
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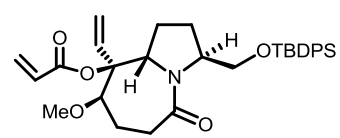
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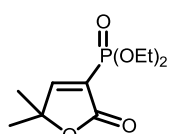
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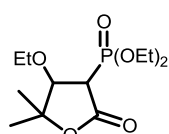
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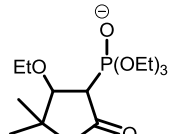
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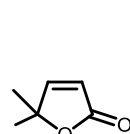
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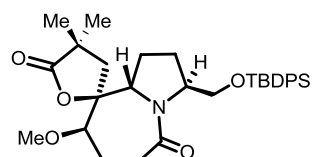
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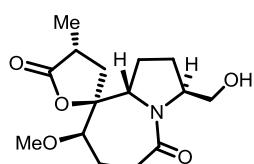
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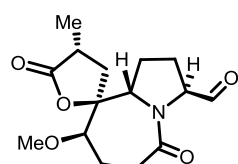
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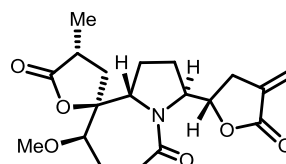
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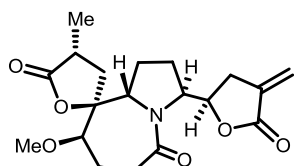
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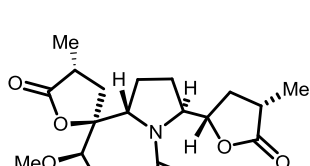
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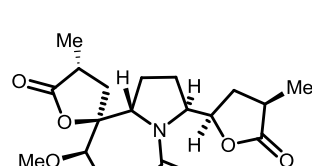
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1. Introduction and Objectives

1.1. INTRODUCTION

1.1.1. *Stemona alkaloids. Natural sources and properties*

Throughout history, folk medicine from all civilizations has found in Nature all kind of plants that provided remedies against a great variety of diseases. The deep knowledge of plant curative properties acquired by this medicine has motivated the scientific community towards the isolation and characterization of their bioactive components in order to develop new drugs.

The extracts of several plants of the *Stemonaceae* family have long been used in China, Japan, and other Asian countries for the treatment of respiratory disorders, such as bronchitis and tuberculosis, as antihelmintics and also as domestic insecticides.¹ The *Stemonaceae* family consists of three genera, being *Stemona* the most representative of them (Figure 1). Three of its species, *S. Tuberosa*, *S. Japonica* and *S. Sessilifolia*, are officially listed in the 2000 Edition of Chinese Pharmacopoeia as medicinal herbs. Significant constituents of these species are a series of structurally related secondary metabolites, named *Stemona* alkaloids, that may be responsible for their medicinal and antiparasitic properties, although studies on the specific biological activities of individual members of this alkaloid family are quite limited.²

Kingdom: *Plantae*

Division: *Magnoliophyta*

Class: *Liliopsida*

Order: *Dioscoreales*

Family: *Stemonaceae*

Genera: *Stemona*: contains 34 species located in Asia and Australia

Croomia: contains 3 species located in North America and Japan

Stichoneuron: contains 2 species located in the west of Asia

Figure 1. Taxonomy tree of the *Stemonaceae* family.

¹ (a) Pilli, R. A.; de Oliveira, M. C. F. *Nat. Prod. Rep.* **2000**, *17*, 117-127; (b) Pilli, R. A.; Rosso, G. B.; de Oliveira, M. C. F.; in: *The Alkaloids* (Ed.: G.A. Cordell), Elsevier, New York, **2005**, *62*, 77-173; (c) Greger, H.; *Planta Med.* **2006**, *72*, 99-113; (d) Pilli, R. A.; Rosso, G. B.; de Oliveira, M. C. F.; *Nat. Prod. Rep.* **2010**, *27*, 1908-1937.

² Figueredo, M.; Alibés, R. *Eur. J. Org. Chem.* **2009**, 2421-2435.

The marketing of mixtures of dry roots from the species *S. japonica*, *S. tuberosa* and *S. sessilifolia*, commonly known as Bai Bu, and their use as infusion is an extended practice in the oriental medicine.³ Moreover, there is a huge amount of patents for the use of the extracts of these plants in a wide range of fields, such as biodegradable insecticides to control plagues,⁴ detergent formulation,⁵ shampoo,⁶ insect repellent,⁷ drugs for the treatment against asthma⁸ and tuberculosis,⁹ among others.

Tuberostemonine was the first *Stemona* alkaloid to have its biological activity tested (Figure 2),¹ showing activity against the helminth *Angiostrongylos cantonensis* (responsible for meningitis), *Dipylidium caninum* (canine intestinal parasite) and *Fasciola hepatica* (parasite that infects herbivorous vertebrate animals). Its activity on the neuromuscular transmission in crayfish (model to study the interaction of drugs in the mammalian central nervous system) revealed that tuberostemonine depressed glutamate-induced responses at similar levels of those of established glutamate inhibitors.¹⁰ The insecticide activity of stemonine, stemospiroline and stemofoline was also tested, revealing positive results against the silk worm larvae.¹¹

Didehydrostemofoline, which has an unsaturated *n*-butenyl side chain, showed high insecticidal activity against the larvae of *Spodoptera littoralis*,¹² whereas stemofoline, characterized by a saturated *n*-butyl side chain, revealed less insecticidal properties. Furthermore, didehydrostemofoline exhibits nanomolar activity against different carcinoma cell lines and possesses potent in vivo anti-oxytocin activity (decreases uterine contractions).¹³

³ There are several webpages where the use and marketing of products containing extracts of these plants are described.

⁴ Shenging, F.Z. CN 102643134 A 20120822; Liren, Z.; Yuebin, Z. CN 1054349 A 19910111; (c) Maoxuan, L.; Guangyu, Y. CN 1308871 A 20010822; (d) Changan, W.; Zhaoming, W. CN 1120890 A 19960424.

⁵ Ahaoli, C. CN 1129733 A 19960828.

⁶ (a) Xianliang, H. CN 1247893 A 20000322; (b) Minqui, D.; Jihua, X.; Chengjing, W. CN 1301533 A 20010704.

⁷ (a) Shenging, Z. CN 102640765 A 20120822; (b) Shuili, X. CN 1186604 A 19980708.

⁸ (a) Shenging, F. Z. CN 102614434 A 20120801; (b) Quingyun, M.; Yingchun, C. CN 102552773 A 20120711; (c) Hongbo, Z.; Xiaming, Z. CN 102526662 A 20120704.

⁹ (a) Junrui, M. CN 1265315 A 20000906; (b) Lisheng, S. CN 102579928 A 20120718; (c) Yanke, L. CN 102166304 B 20120425.

¹⁰ Shinozaki, H.; Ishida, M. *Brain Res.* **1985**, *334*, 33-40.

¹¹ Sakata, K.; Aoki, K.; Chang, C.-F.; Sakurai, A.; Tamura, S.; Murakoshi, S. *Agric. Biol. Chem.* **1978**, *42*, 457-463.

¹² Brem, B.; Seger, C.; Pacher, T.; Hofer, O.; Vajrodaya, S.; Greger, H. *J. Agric. Food Chem.* **2002**, *50*, 6383-6388.

¹³ (a) Sekine, T.; Ikegami, F.; Fukasawa, N.; Kashiwagi, Y.; Aizawa, T.; Fujii, Y.; Ruangrunsi, N.; Murakoshi, I. *J. Chem. Soc. Perkin Trans. 1*, **1995**, 391-393; (b) Tip-Pyang, S.; Tangpraputgul, P.; Wiboonpun, N.; Veerachato, G.; Phuwapraisirisan, P.; Sup-Udompol, B. *ACGC Chem. Res. Commun.* **2000**, *12*, 31-35.

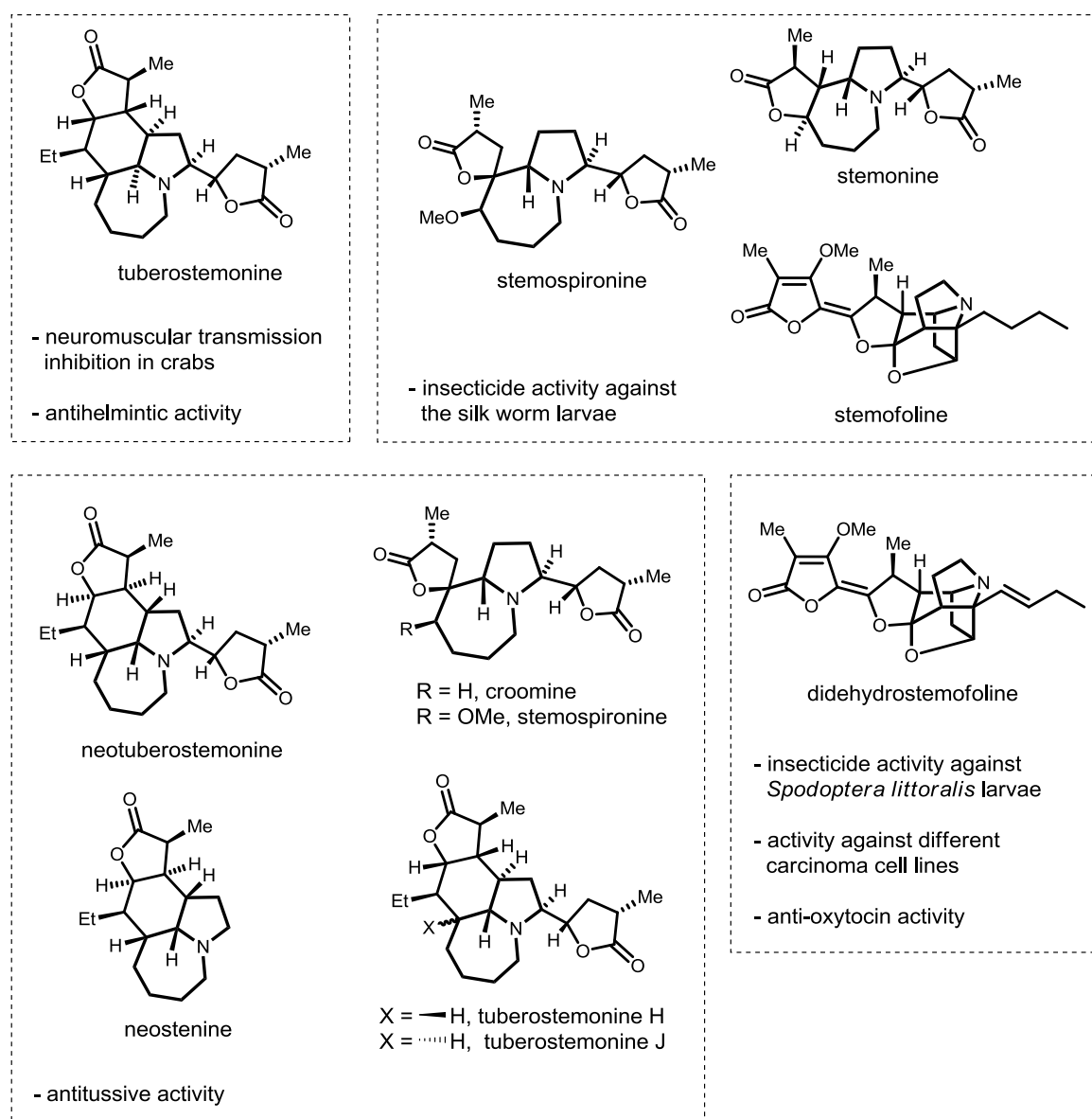


Figure 2. Biological activity of some *Stemona* alkaloids.

On the other hand, croomine, stemospironine, neostenine, tuberostemonine J, tuberostemonine H and neotuberostemonine were examined for antitussive activity in guinea pig after cough induction. It was demonstrated that all these compounds showed significant antitussive activities, although they do not act on the same sites of cough reflex. Further studies on structure-activity relationship with seven related compounds revealed that the saturated tricyclic pyrrolbenzazepine nucleus of tuberostemonine (stenine group) is the prerequisite for antitussive activity.¹⁴

¹⁴ (a) Chung, H.-S.; Hon, P.-M.; Lin, G.; But, P. P.-H.; Dong, H. *Planta Med.* **2003**, *69*, 914; (b) Xu, Y. T.; Shaw, P. C.; Jiang, R. W.; Hon, P. M.; Chan, Y. M.; But, P. P. *J. Ethnopharmacol.* **2010**, *128*, 679-684; (c) Yang, X. Z.; Zhu, J. Y.; Tang, C. P.; Ke, C. Q.; Lin, G.; Cheng, T. Y.; Rudd, J. A.; Ye, Y. *Planta Med.* **2009**, *75*, 174-177; (d) Wang, W.; Wang, X.; Sun, H.; Dong,

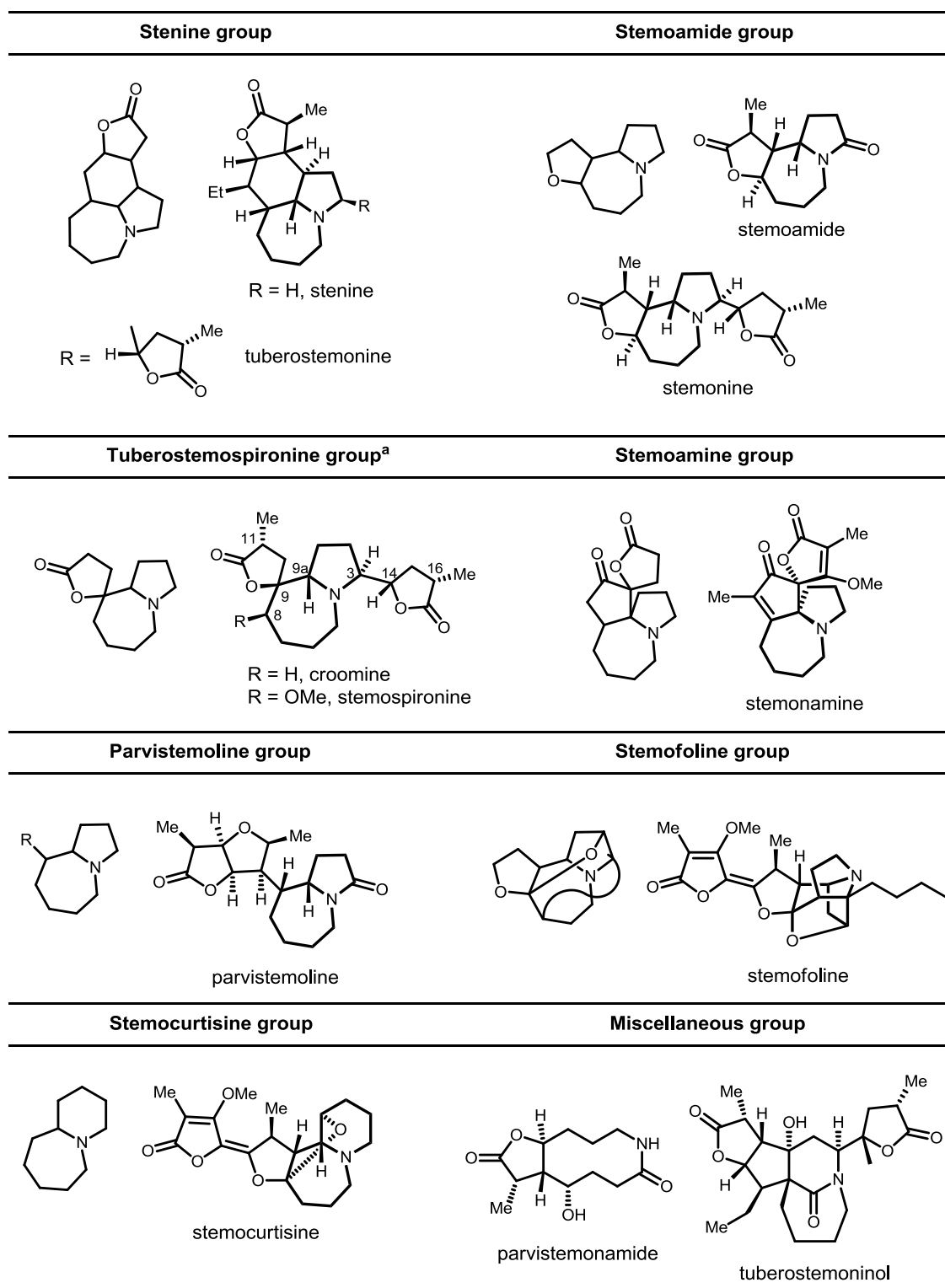
In preliminary anti-tumor tests, crude extracts of plants of the genera *Stemona* were investigated for their effect on medullary thyroid carcinoma cells and *S. tuberosa* extracts showed an enhancement of apoptosis.¹⁵

1.1.2. Structural classification

All the *Stemona* alkaloids are polycyclic and most of them possess a central pyrrolo[1,2-*a*]azepine system as a characteristic structural feature, although a few contain a pyrido[1,2-*a*]azepine core instead. The majority also incorporate at least one α -methyl- γ -butyrolactone substructure, which can be linked to the azabicyclic core in a spiro or fused manner or as a substituent. Considering their structural diversity, Pilli and co-workers classified the *Stemona* alkaloids into eight groups (Figure 3).^{1a,b,d} The stenine, stemoamide, tuberostemospirone, stemonamine, parvistemoline and stemofoline groups present the characteristic pyrrolo[1,2-*a*]azepine core, whereas the stemocurtisine group displays the less usual pyrido[1,2-*a*]azepine nucleus, and a further, miscellaneous group includes those alkaloids which do not display the structural motifs mentioned before, or are the sole representative of a new group.

W.; Zhang, A. *Fitoterapia*, **2012**, *83*, 1699-1705; (e) Lin, L.-G.; Leung, H. P.-H.; Zhu, J.-Y.; Tang, C.-P.; Ke, C.-Q.; Rudd, J. A.; Ye, Y. *Tetrahedron*, **2008**, *64*, 10155-10161; (f) But, P. P.-H.; Shaw, P.-C.; Jiang, R.-W.; Xu, Y.-T. *Adv. Bot. Res.* **2012**, *62*, 1-33.

¹⁵ Rinner, B.; Siegl, V.; Pürstner, P.; Efferth, T.; Brem, B.; Greger, H.; Pfragner, R. *Anticancer Res.* **2004**, *24*, 495-500.



a) For better comprehension, the nomenclature used in the Introduction and Results and Discussion sections is intended to keep fixed numbers in equivalent carbon atoms of related compounds.

Figure 3. Representative members and characteristic structural features of the *Stemona* alkaloid groups according to Pilli's classification.^{1a,b,d}

Recently, Greger has suggested a new classification based on biosynthetic connections. It consists of three skeletal types, differing in the carbon chains attached to C₉ of the pyrroloazepine core (Figure 4).^{1c} In the stichoneurine- and protostemonine-types these chains usually contain eight carbon atoms forming a terminal lactone ring, but differ among each other in the branching pattern. In the croomine-type, by contrast, the chain consists only of four carbon atoms forming a lactone ring directly attached to C₉ in a spiro system.

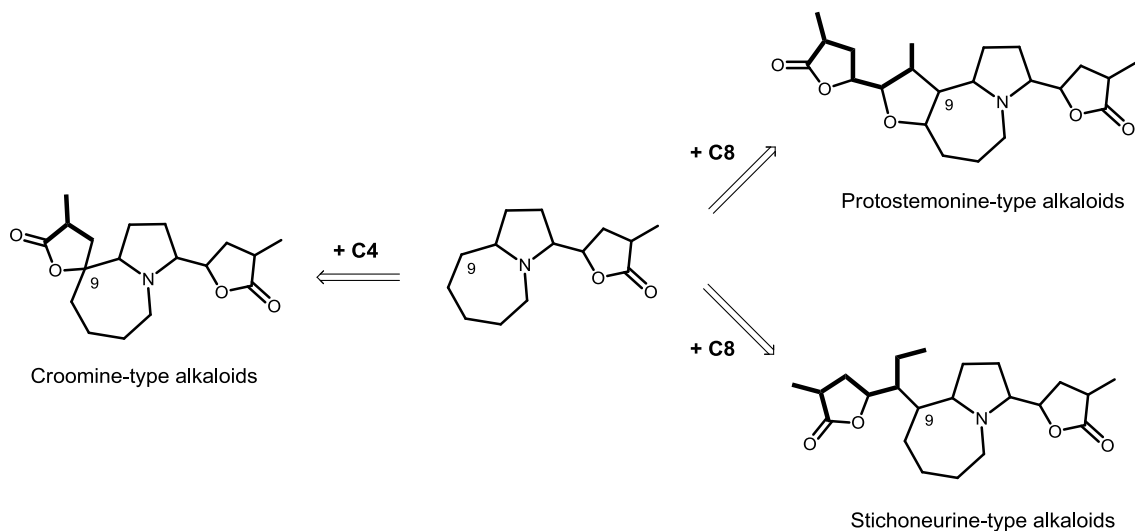


Figure 4. Greger's classification of the *Stemona* alkaloids.^{1c}

To date, around one hundred *Stemona* alkaloids are known, but, in the literature, there is a continuous flow of new reports describing the isolation of previously unknown members of the family. The structural elucidation of 30 of them has been established by X-ray diffraction analysis, whereas the rest has been determined by NMR studies, mass spectrometry, IR spectroscopy and/or by chemical correlation.^{1,2}

1.1.3. Synthetic precedents

The challenging molecular architectures of the *Stemona* alkaloids have motivated the development of new strategies for the construction of their azabicyclic core.¹⁶ However, only a

¹⁶ (a) Xiang, L.; Kozikowski, A. P. *Synlett* **1990**, 279-281; (b) Wipf, P.; Kim, Y. *Tetrahedron Lett.* **1992**, *33*, 5477-5480; (c) Beddoes, R. L.; Davies, M. P. H.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1992**, 538-540; (d) Martin, S. F.; Corbett, J. W. *Synthesis* **1992**, *01/02*, 55-57; (e) Morimoto, Y.; Nishida, K.; Hayashi, Y.; Shirahama, H. *Tetrahedron Lett.* **1993**, *34*, 5773-5776; (f) Morimoto, Y.; Iwahashi, M. *Synlett* **1995**, 1221-1222; (g) Wipf, P.; Goldstein, D. M. *Tetrahedron Lett.* **1996**, *37*, 739-742; (h) Martin, S. F.; Bur, S. K. *Tetrahedron Lett.* **1997**, *38*, 7641-7644; (i) Rigby, J. H.; Laurent, S.; Cavezza, A.; Heeg, M. J. *J. Org. Chem.* **1998**, *63*, 5587-5591; (j) Wipf, P.; Li, W. *J. Org. Chem.* **1999**, *64*, 4576-4577; (k) Pearson, W. H.; Hutta, D. A.; Fang, W.-K. *J. Org. Chem.* **2000**, *65*, 8326-8332; (l) Jung, S. H.; Lee, J. E.; Joo, H. J.; Kim, S.

few total syntheses have been published and they are still limited to a quite small number of targets. So far, 40 total syntheses have been completed,¹⁷⁻³⁸ 22 of which furnished the targeted alkaloid with high enantiomeric excess (Figure 5).

H.; Koh, H. Y. *Bull. Korean Chem. Soc.* **2000**, *21*, 159-160; (m) Pearson, W. H.; Walavalkar, R. *Tetrahedron* **2001**, *57*, 5081-5089; (n) Hinmnan, M. M.; Heathcock, C. H. *J. Org. Chem.* **2001**, *66*, 7751-7756; (o) Velázquez, F.; Olivo, H. F. *Org. Lett.* **2002**, *4*, 3175-3178; (p) Booker-Milburn, K. I.; Hirst, P.; Charamant, J. P. H.; Taylor, L. H. *J. Angew. Chem. Int. Ed.* **2003**, *42*, 1642-1644; (q) Lindsay, K. B.; Pyne, S. G. *Synlett* **2004**, 779-782; (r) Cid, P.; Closa, M.; de March, P.; Figueredo, M.; Font, J.; Sanfeliu, E.; Soria, A. *Eur. J. Org. Chem.* **2004**, 4215-4233; (s) Roberts, E.; Samçon, J. P.; Sweeney, J. B. *Org. Lett.* **2005**, *7*, 2075-2078; (t) Alibés, R.; Blanco, P.; Casas, E.; Closa, M.; de March, P.; Figueredo, M.; Font, J.; Sanfeliu, E.; Álvarez-Larena, A. *J. Org. Chem.* **2005**, *70*, 3157-3167; (u) Gu, P.; Zhao Y.-M.; Tu, Y. Q.; Ma, Y.; Zhang, F. *Org. Lett.* **2006**, *8*, 5271-5273; (v) Antoline, J. E.; Hsung, R. P.; Huang, J.; Song, Z.; Li, G. *Org. Lett.* **2007**, *9*, 1275-1278; (w) Zhu, L.; Lauchli, R.; Loo, M.; Shea, K. J. *Org. Lett.* **2007**, *9*, 2269-2271; (x) Frankowski, K. J.; Neuenswander, B.; Aubé, J. *J. Comb. Chem.* **2008**, *10*, 721-725; (y) Yaji, K.; Shindo, M. *Tetrahedron Lett.* **2010**, *51*, 5469-5472; (z) Burrell, A.; Watson, L.; Martin, N. G.; Oram, N.; Coldham, I. *Org. Biomol. Chem.* **2010**, *8*, 4530-4532; (aa) Dietz, J.; Martin, S. F. *Tetrahedron Lett.* **2011**, *52*, 2048-2050; (ab) Bates, R. W.; Sridhar, S. *J. Org. Chem.* **2011**, *76*, 5026-5035.

¹⁷⁻³⁸ **Total syntheses:**

¹⁷ **(+)-Croomine:** (a) Williams, D. R.; Brown, D. L.; Benbow, J. W. *J. Am. Chem. Soc.* **1989**, *111*, 1923-1925; (b) Martin, S. F.; Barr, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 3299-3300; (c) Martin, S. F.; Barr, K. J.; Smith, D. W.; Bur, S. K. *J. Am. Chem. Soc.* **1999**, *121*, 6990-6997.

¹⁸ **(±)-Stenine:** (a) Chen, C. Y.; Hart, D. J. *J. Org. Chem.* **1990**, *55*, 6236-6240; (b) Chen, C. Y.; Hart, D. J. *J. Org. Chem.* **1993**, *58*, 3840-3849; (c) Ginn, J. D.; Padwa, A. *Org. Lett.* **2002**, *4*, 1515-1517; (d) Golden, J. E.; Aubé, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 4316-4318; (e) Zeng, Y.; Aubé, J. *J. Am. Chem. Soc.* **2005**, *127*, 15712-15713; (f) Frankowski, K. J.; Golden, J. E.; Zeng, Y.; Lei, Y.; Aubé, J. *J. Am. Chem. Soc.* **2008**, *130*, 6018-6024.

¹⁹ **(-)-Stenine:** (a) Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106-11112; (b) Morimoto, Y.; Iwahashi, M.; Nishida, K.; Hayashi, Y.; Shirahama, H. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 904-906; (c) Morimoto, Y.; Iwahashi, M.; Kinoshita, T.; Nishida, K. *Chem. Eur. J.* **2001**, *7*, 4107-4116; (d) Chen, J.; Chen, J.; Xie, Y.; Zhang, H. *Angew. Chem. Int. Ed.* **2012**, *51*, 1024-1027; (e) Fujioka, H.; Nakahara, K.; Kotoku, N.; Ohba, Y.; Nagatomi, Y.; Wang, T.-L.; Sawama, Y.; Murai, K.; Hirano, K.; Oki, T.; Wakamatsu, S.; Kita, Y. *Chem. Eur. J.* **2012**, *18*, 13861-13870.

²⁰ **(±)-Stemoamide:** (a) Kohno, Y.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2063-2070; (b) Jacobi, P. A.; Lee, K. J. *J. Am. Chem. Soc.* **1997**, *119*, 3409-3410; (c) Jacobi, P. A.; Lee, K. J. *J. Am. Chem. Soc.* **2000**, *122*, 4295-4303; (d) Bogliotti, N.; Dalko, P. I.; Cossy, J. *J. Org. Chem.* **2006**, *71*, 9528-9531; (e) Bates, R. W.; Sridhar, S. *Synlett.* **2009**, *12*, 1979-1981; (f) Wang, Y.; Zhu, L.; Zhang, Y.; Hong, R. *Angew. Chem. Int. Ed.* **2011**, *50*, 2787-2790.

²¹ **(-)-Stemoamide:** (a) Williams, D. R.; Reddy, J. P.; Amato, G. S. *Tetrahedron Lett.* **1994**, *35*, 6417-6420; (b) Kinoshita, A.; Mori, M. *J. Org. Chem.* **1996**, *61*, 8356-8357; (c) Kinoshita, A.; Mori, M. *Heterocycles* **1997**, *46*, 287-299; (d) see ref. 20c; (e) Gurjar, M. K.; Reddy, D. S. *Tetrahedron Lett.* **2002**, *43*, 295-298; (f) Sibi, M. P.; Subramanian, T. *Synlett* **2004**, 1211-1214; (g) Olivo, H. F.; Tovar-Miranda, R.; Barragán, E. *J. Org. Chem.* **2006**, *71*, 3287-3290; (h) Torssell, S.; Wanngren, E.; Somfai, P.; *J. Org. Chem.* **2007**, *72*, 4246-4249; (i) Honda, T.; Matsukawa, T.; Takahashi, K. *Org. Biomol. Chem.* **2011**, *9*, 673-675.

²² **(+)-Stemoamide:** Bogliotti, N.; Dalko, P. I.; Cossy, J. *Synlett.* **2006**, 2664-2666.

²³ **(-)-9,10-epi-Stemoamide:** Khim, S.-K.; Schultz, A. G. *J. Org. Chem.* **2004**, *69*, 7734-7736.

²⁴ **(±)-9,10-epi-Stemoamide:** see ref. 20d.

²⁵ **(±)-Isostemofoline:** Kende, A. S.; Smalley, Jr T. L.; Huang, H. *J. Am. Chem. Soc.* **1999**, *121*, 7431-7432.

²⁶ **(±)-Stemonamide and (±)-isostemonamide:** (a) Kende, A. S.; Hernando, J. I. M.; Milbank, J. B. *J. Org. Lett.* **2001**, *3*, 2505-2508; (b) Kende, A. S.; Hernando, J. I. M.; Milbank, J. B. *J. Tetrahedron* **2002**, *58*, 61-74; (c) Taniguchi, T.; Tanabe, O.; Muraoka, O.; Ishibashi, H. *Org. Lett.* **2008**, *10*, 197-199; (d) Taniguchi, T.; Ishibashi, H. *Tetrahedron* **2008**, *64*, 8773-8779; (e) Chen, Z.-H.; Zhang, Y.; Chen, Z.; Tu, Y.; Zhang, F. *Chem. Comm.* **2011**, *47*, 1836-1838; (f) Chen, Z.; Chen, Z.; Zhang, Y.-Q.; Tu, Y.-Q.; Zhang, F.-M. *J. Org. Chem.* **2011**, *76*, 10173-10186.

²⁷ **(-)-Stemospirone:** (a) Williams, D. R.; Fromhold, M. G.; Earley, J. D. *Org. Lett.* **2001**, *3*, 2721-2724; (b) Bardají, N.; Sánchez-Izquierdo, F.; Alibés, R.; Font, J.; Busqué, F.; Figueredo, M. *Org. Lett.* **2012**, *14*, 4854-4857.

²⁸ **(-)-Tuberostemonine:** (a) Wipf, P.; Rector, S. R.; Takahashi, H. *J. Am. Chem. Soc.* **2002**, *124*, 14848-14849; (b) Wipf, P.; Spencer, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 225-235.

²⁹ **(-)-Stemonine:** Williams, D. R.; Shamim, K.; Reddy, J. P.; Amato, G. S.; Shaw, S. M. *Org. Lett.* **2003**, *5*, 3361-3364.

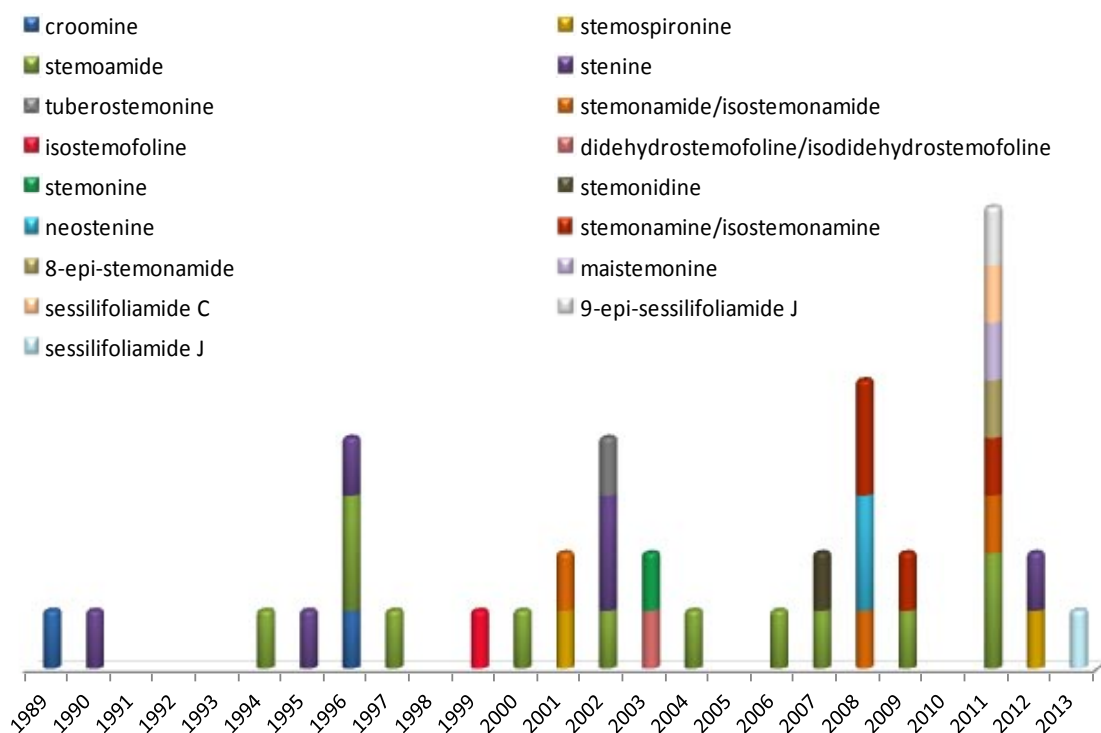


Figure 5. Chronology of the reported total synthesis of *Stemona* alkaloids.

In most of the published syntheses of these secondary metabolites the central azabicyclodecane core is formed by *exo-tet* or *exo-trig* cyclization of a substituted pyrrolidine or azepine, although several authors make use of ring-closing metathesis chemistry or intramolecular cycloaddition processes (Figure 6a). This last methodology is also used to provide the fused lactone ring that is present on several alkaloids of the family.

A detailed study of the reported works reveals a certain parallelism between the approaches developed by different groups. The early syntheses launched different types of strategies, which were later on refined to improve efficiency and/or selectivity, but still relied on

³⁰ (\pm)-**Didehidrostemofoline (asparagamine A) and (\pm)-isodidehidrostemofoline:** Brüggemann, M.; McDonald, A. I.; Overman, L. E.; Rosen, M. D.; Schwink, L.; Scott, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 15284-15285.

³¹ ($-$)-**Didehidrotuberostemonine:** see ref. 28b.

³² (\pm)-**Neostenine:** (a) Lainchbury, M. D.; Medley, M. I.; Taylor, P. M.; Hirst, P.; Dohle, W.; Booker-Milburn, K. I. *J. Org. Chem.* **2008**, *73*, 6497-6505; (b) see ref. 18f.

³³ (\pm)-**Stemonamine and (\pm)-isostemonamine:** (a) see ref. 26d; (b) Zhao, Y.-M.; Gu, P.; Tu, Y.-Q.; Fan, C.-A.; Zhang, Q. *Org. Lett.* **2008**, *10*, 1763-1766; (c) Zhao, Y.-M.; Gu, P.; Zhang, H.-J.; Zhang, Q.-W.; Fan, C.-A.; Tu, Y.-Q.; Zhang, F.-M. *J. Org. Chem.* **2009**, *74*, 3211-3213; (d) Chen, Z.-H.; Tu, Y.-Q.; Zhang, S.-Y.; Zhang, F.-M. *Org. Lett.* **2011**, *13*, 724-727.

³⁴ ($-$)-**Sessilifoliamide J:** (a) Liu, X.-K.; Ye, J.-L.; Ruan, Y.-P.; Li, Y.-X.; Huang, P.-Q. *J. Org. Chem.* **2013**, *78*, 35-41, (b) Tuo, S.; Liu, X.; Huang, P. *Chin. J. Chem.* **2013**, *31*, 55-62.

³⁵ ($-$)-**9-epi-sessilifoliamide J:** Tuo, S.-C.; Ye, J.-L.; Wang, A.-E; Huang, S.-Y.; Huang, P.-Q. *Org. Lett.* **2011**, *13*, 5270-5273.

³⁶ ($-$)-**Sessilifoliamide C and ($-$)-8-epi-stemoamide:** Hoye, A. T.; Wipf, P. *Org. Lett.* **2011**, *13*, 2634-2637.

³⁷ (\pm)-**Maistemonine:** see ref. 26e-f.

³⁸ **Stemonidine** (putative structure): Sánchez-Izquierdo, F.; Blanco, P.; Busqué, F.; Alibés, R.; de March, P.; Figueredo, M.; Font, J.; Parella, T. *Org. Lett.* **2007**, *9*, 1769-1772.

the same retrosynthetic principles. Generally, the lactone rings are formed via intramolecular acyl transfer reactions, iodolactonization processes or vinylogous Mannich reactions with a silyloxyfuran (Figure 6b).

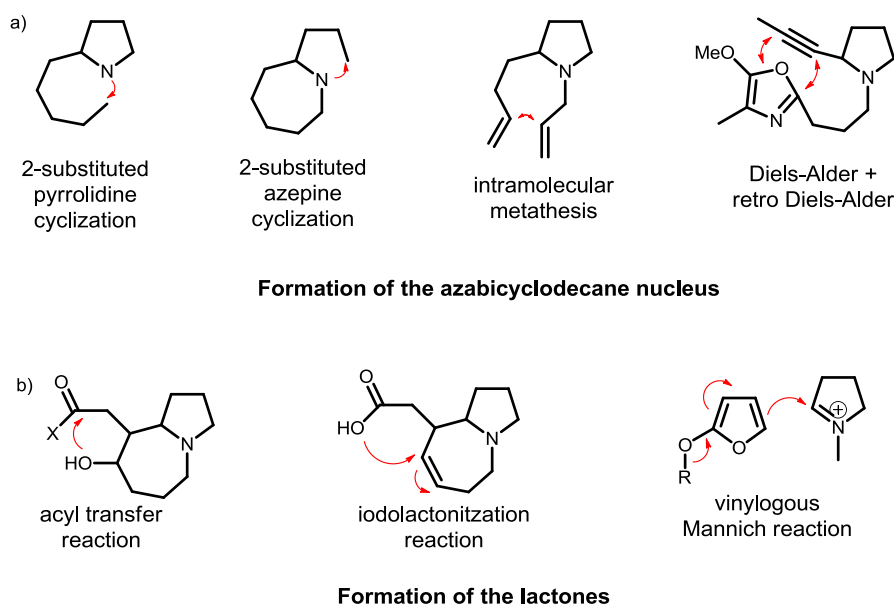


Figure 6. Procedures described for the preparation of the azabicyclic core (a) and lactones (b) of *Stemona* alkaloids.

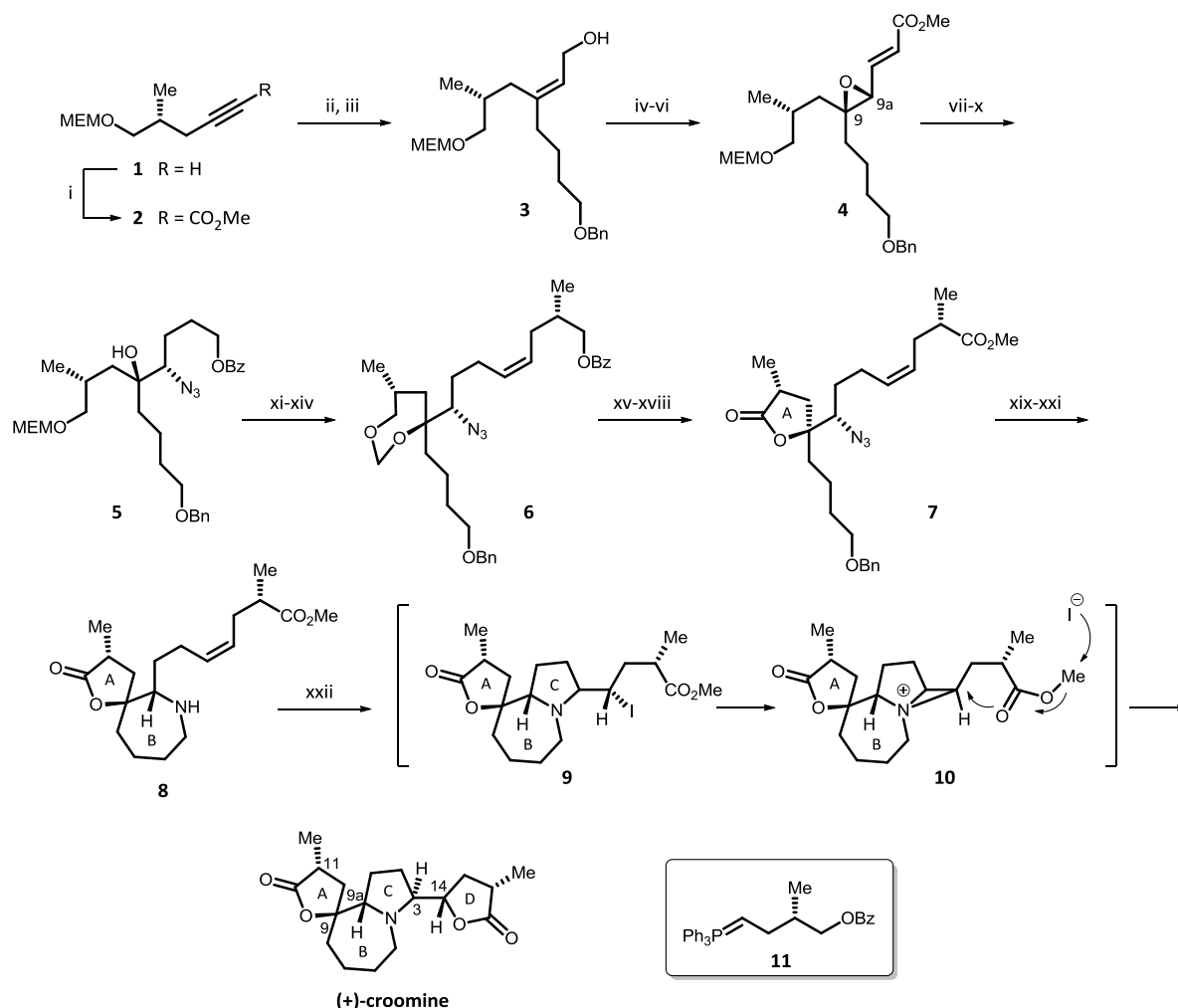
Due to the high structural complexity of these alkaloids, most of the syntheses published to date are intricate and consist of a high number of steps.

The present thesis is focused on the tuberostemospironine group and, for this reason, all the total syntheses published until now for the alkaloids of this group are summarized below.

In 1989, Williams and co-workers published the first total synthesis of a *Stemona* alkaloid.^{17a} In their innovative work, these authors succeeded in completing the preparation of (+)-croomine through an impressive 24-step linear sequence in 0.5% overall yield (Scheme 1). Their strategy involves the preliminary construction of a branched carbon chain, followed by consecutive ring closures to generate each heterocycle. Thus, the synthesis started with the transformation of (+)-methyl 3-hydroxy-2-methylpropionate, through a four-step sequence and 72% overall yield, in alkyne **1** which, in turn, was converted to the (Z)-trisubstituted allylic alcohol **3**. The relative configurations of C₉ and C_{9a} in the alkaloid were established by means of a highly diastereoselective Sharpless epoxidation of **3**, providing an epoxyalcohol that, after a two-carbon chain homologation of the corresponding aldehyde, led to epoxide **4**. The west-side lactone A in **7** was constructed after a regioselective opening of **4** with lithium azide (**4** to **5**), chain homologation (**5** to **6**), deprotection of the 1,4-diol, oxidation and lactonization (**6** to **7**). The central perhydroazepine ring B was formed through a Staudinger-aza-Wittig reaction and the

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rings C and D were accomplished in a single step by an iodine-induced double cyclization reaction of amine **8**.³⁹ This process required the initial formation of the iodoamination product **9**, and then nucleophilic anchimeric assistance by the vicinal tertiary amine led to the aziridinium intermediate **10**, which was captured by the neighboring methyl ester affording (+)-croomine with net retention of configuration at C₁₄.

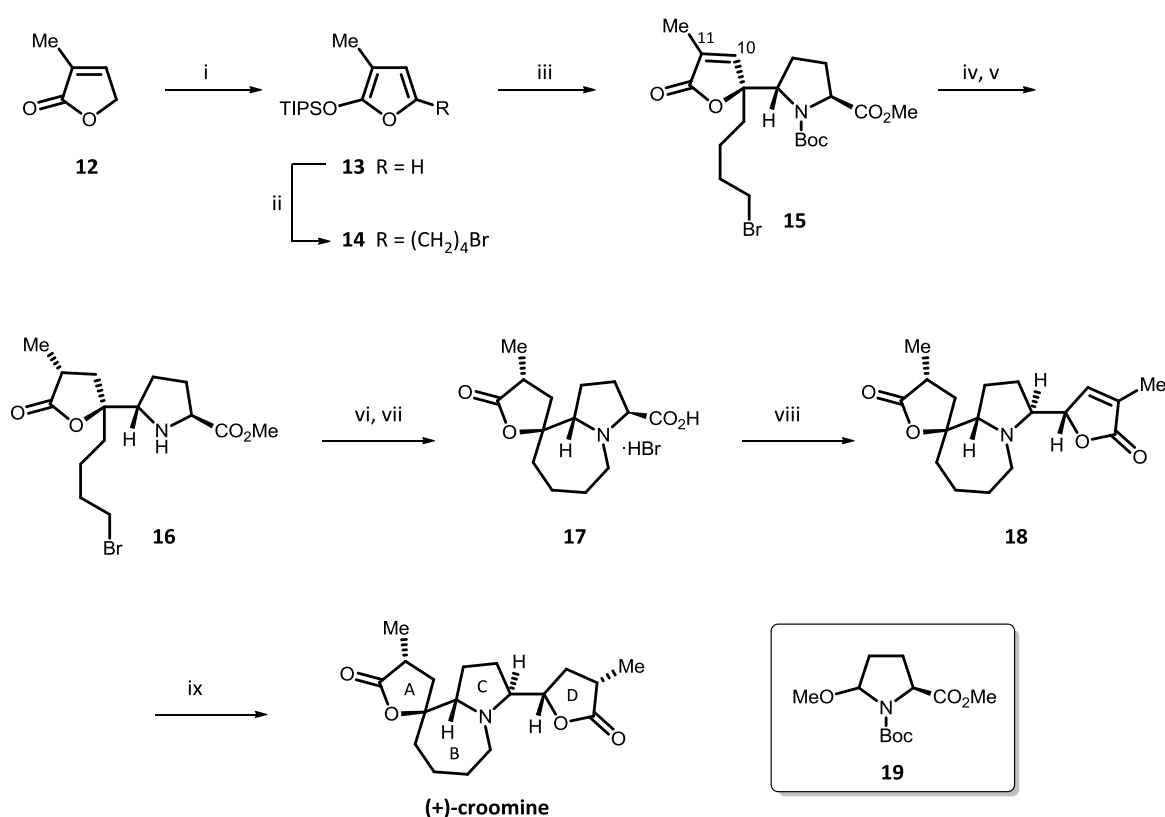


Reagents and conditions: (i) *n*-BuLi, THF, -78 to 0 °C; then, ClCO₂Me, -78 °C (63%); (ii) BnO(CH₂)₃MgBr, DMS, CuBr, TMEDA, Et₂O, -78 °C (95%); (iii) DIBAL-H, CH₂Cl₂, -78 °C (98%); (iv) Ti(OiPr)₄ (cat.), D-DIPT (cat.), ^tBuOOH, MS 4Å, CH₂Cl₂, -50 °C (83%); (v) (COCl)₂, DMSO, CH₂Cl₂, Et₃N, -78 to 0 °C; (vi) Ph₃P=CHCO₂Me, 0 °C to r.t. (89%, 2 steps); (vii) LiBH₄, Et₂O, MeOH, 0 °C (81%); (viii) 5% Rh/Al₂O₃, H₂, THF (62%); (ix) BzCl, Et₃N, CH₂Cl₂, 0 °C to r.t. (97%); (x) LiN₃, DMPU, 110 °C (94%); (xi) BF₃·Et₂O, CH₂Cl₂, 0 °C (81%); (xii) LiOH, THF, aq. MeOH (97%); (xiii) (COCl)₂, DMSO, CH₂Cl₂, Et₃N, -78 to 0 °C (91%); (xiv) **11**, ^tBuOK, THF, -10 °C (70-81%); (xv) aq. HBF₄, MeOH (72%), (xvi) LiOH, THF, MeOH, H₂O, 22 °C (86%); (xvii) Jones' reagent, THF, 0 °C; (xviii) CH₂N₂, Et₂O (78%, 2 steps); (xix) BCl₃, CH₂Cl₂, -78 to 0 °C; then, MeOH, -78 °C (77%); (xx) (COCl)₂, DMSO, CH₂Cl₂, Et₃N, -78 to 0 °C (92%); (xxi) Ph₃P, THF, 22 °C; then, NaBH₄, MeOH (90%); (xxii) I₂, CH₂Cl₂, Et₂O, 22 °C (25%).

Scheme 1. Williams' strategy for the synthesis of (+)-croomine.^{17a}

³⁹ Williams, D. R.; Osterhout, M. H.; McGill, J. M. *Tetrahedron Lett.* **1989**, *30*, 1331-1334.

Some years later, Martin and co-workers published a new asymmetric synthesis of (+)-croomine, which required only 9 steps and was accomplished in 5% total yield (Scheme 2).^{17b} In this case, as in most approaches to these alkaloids, the starting material already contained the pyrrolidine unit (ring C). The authors used methyl L-pyrroglutamate as the source of chirality of the synthetic process and the key transformation of this approach was the vinylogous Mannich reaction between a silyloxyfuran and a cyclic acyliminium ion generated in situ from a derivative of methyl L-pyrroglutamate, to deliver the pyrrolidinyl-lactone system. This transformation, which is also applied to prepare the east-side lactone, produced a very elegant and short synthesis, although its moderate yield and poor stereoselectivity diminished the efficiency of the strategy.



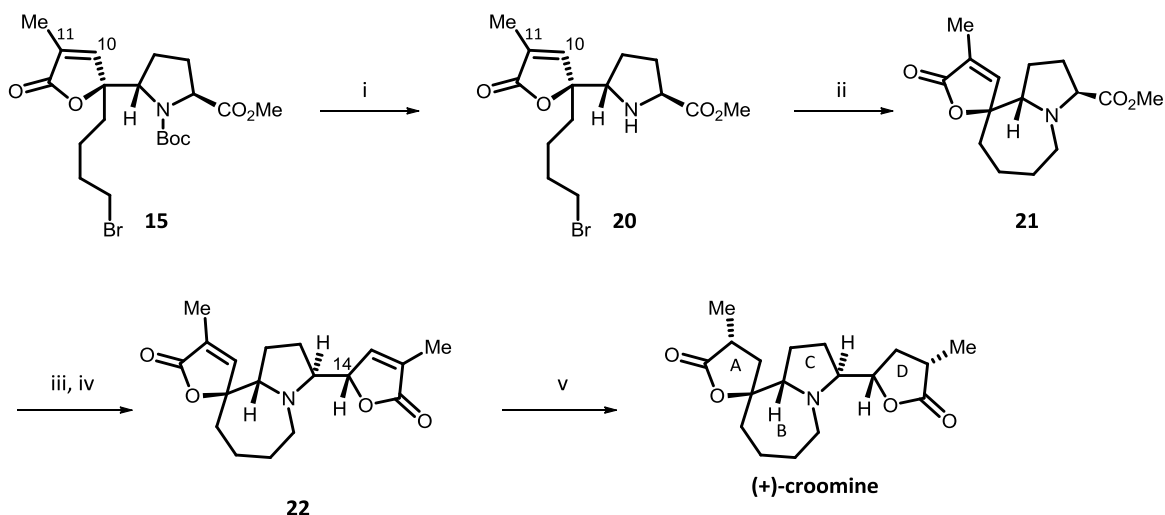
Reagents and conditions: (i) TIPS-OTf, Et₃N, CH₂Cl₂, 0 °C to r.t. (99%); (ii) *s*-BuLi, TMEDA, THF, 0 °C; then, BrCH₂(CH₂)₂CH₂Br (83%); (iii) **19**, 5% TIPS-OTf, CH₂Cl₂, 0 °C (32%); (iv) TFA, CH₂Cl₂, r.t.; (v) 3% Rh/C, H₂, EtOAc, EtOH (>96%, 2 steps); (vi) *N*-methylmorpholine, DMF, reflux; (vii) 3M aq. HBr, 60 °C (74%, 2 steps); (viii) POCl₃, DMF, r.t.; then **13** (32%); (ix) Pd/C, H₂, 10% HCl/EtOAc (85%).

Scheme 2. Martin's strategy for the synthesis of (+)-croomine.^{17b}

In 1999 Martin's group disclosed an improved synthesis of the same alkaloid through an analogous route but postponing the hydrogenation of the C₁₀-C₁₁ double bond (Scheme 3).^{17c} The rest of the sequence proceeded according to the same strategy. Thus, the new shorter route

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consisted on deprotecting the former intermediate amine **15** to obtain pyrrolidine **20**. Intramolecular alkylation of **20** provided pyrroloazepine **21** which, after deprotection of the ester and decarboxylation through the corresponding acid chloride, afforded the iminium intermediate that reacted with the silyloxyfuran **13** to furnish the azatetracyclic compound **22** and its epimer at C₁₄ as a 2:1 mixture of diastereoisomers. Catalytic hydrogenation of **22** delivered (+)-croomine as the only isolable product in 3% overall yield.



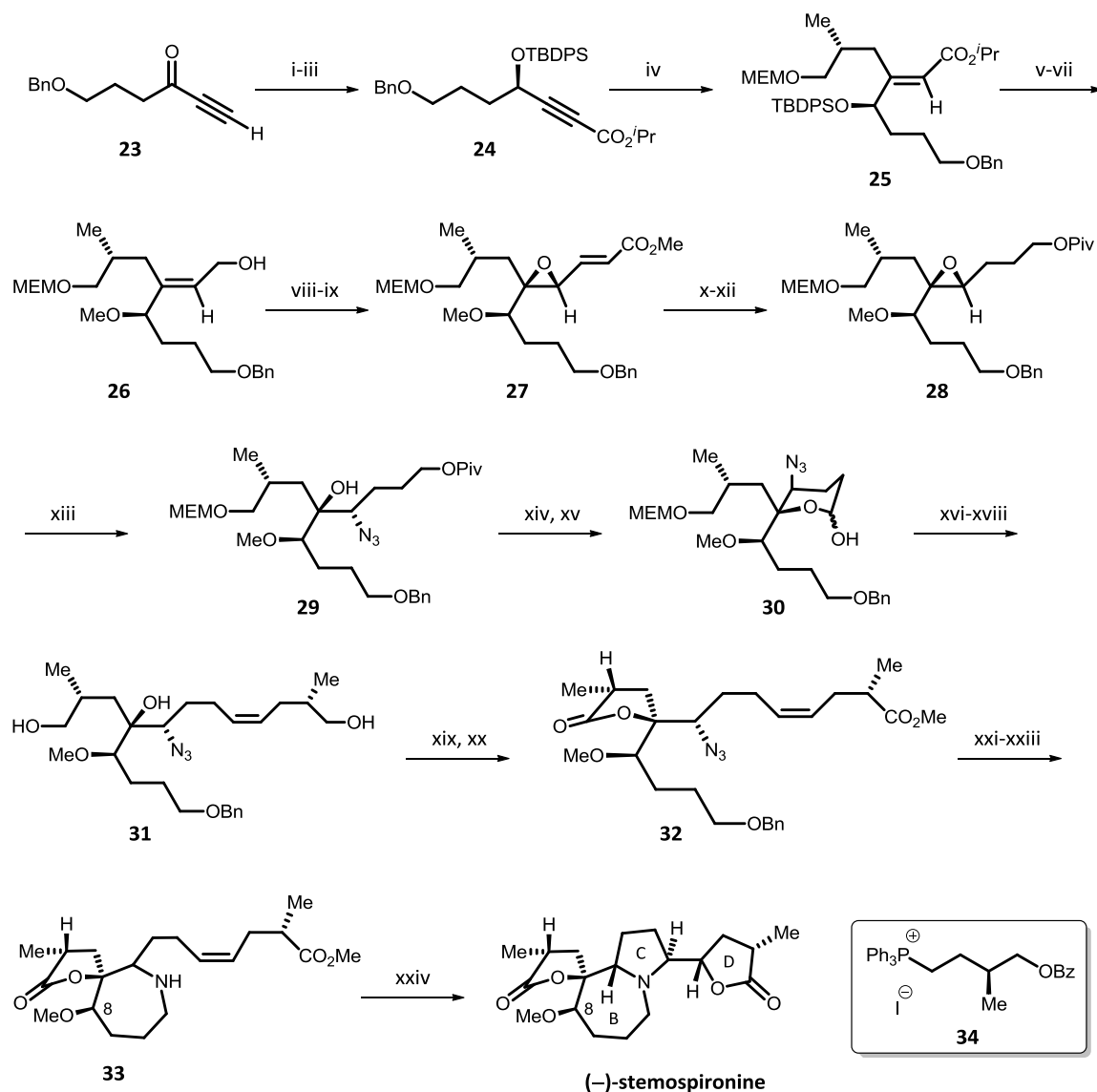
Reagents and conditions: (i) TFA, CH₂Cl₂, r.t. (quant.); (ii) *N*-methylmorpholine, DMF, 160 °C (51%); (iii) 3M aq. HBr, 60 °C; (iv) POCl₃, DMF, r.t.; then **13** (26%); (v) Pd/C, H₂, EtOH, HCl (81%).

Scheme 3. Martin's improved strategy for the synthesis of (+)-croomine.^{17c}

The first, and to date unique reported, synthesis of (–)-stemospirone was accomplished by Williams and co-workers in 2001 (Scheme 4).^{27a} Stemospirone differs from croomine only in the presence of a methoxy group at C₈, which adds an extra stereogenic center. The authors used the same strategy developed by them for the total synthesis of croomine, namely the stereoselective construction of a fully functionalized acyclic carbon chain followed by sequential ring closure reactions.

Beginning with the readily available ketone **23**, chirality at C₈ was introduced via Midland reduction of the conjugated ynone with (*R*)-alpine borane, leading to the *R* alcohol precursor of **24**. After one-carbon homologation, the acetylenic ester underwent a conjugate addition of a cuprate to afford exclusively the *E*- α,β -unsaturated ester **25**. Then, removal of the protecting group of the chiral alcohol, followed by methylation and subsequent reduction of the propargylic ester yielded the trisubstituted allylic alcohol **26**, which provided a 4:1 mixture of oxirane isomers using a modified Sharpless asymmetric epoxidation. The major oxirane was oxidized with Dess-

Martin periodinane, and in situ chain elongation through a Wittig reaction yielded the *E* unsaturated methyl ester **27**. Hydrogenation, reduction of the ester to the corresponding primary alcohol and protection as pivaloyl ester furnished compound **28**, which was submitted to epoxide opening with lithium azide to obtain the hydroxyazide **29**.



Reagents and conditions: (i) (*R*)-Alpine Borane, THF, -10 °C to r.t. (95%, 88, ee); (ii) TBDPSCI, imidazole, CH₂Cl₂, r.t. (80%); (iii) *n*-BuLi, ClCO₂^tPr, THF, -78 °C (92%); (iv) (*S*)-MEMOCH₂(CH₃)CH₂MgBr, **35**, CuBr·DMS, THF, -78 °C to r.t. (70%); (v) TBAF, THF, r.t. (90%); (vi) NaH, MeI, DMF (85%); (vii) DIBAL-H, CH₂Cl₂, -78 °C (92%); (viii) Ti(O^{*i*}Pr)₄, CaH₂, SiO₂, (-)-DIPT, ^tBuOOH, CH₂Cl₂, -20 °C (85-90%, 4:1 mixture of isomers); (ix) Dess-Martin periodinane, pyridine, CH₂Cl₂, -78 °C; then, PPh₃CHCO₂CH₃ (60%, 2 steps); (x) 5% Rh/Al₂O₃, H₂, THF (85%); (xi) LiBH₄, CH₃OH, Et₂O (90%); (xii) PivCl, pyridine, DMAP (91%); (xiii) LiN₃, NH₄Cl, DMPU, 130 °C (83%); (xiv) LiOH, THF, MeOH, H₂O (94%); (xv) Swern oxidation (97%); (xvi) ^tBuOK, **34**, THF, -10 °C (77%); (xvii) HCl, THF, r.t. (85%); (xviii) LiOH, THF, H₂O, MeOH (88%); (xix) Jones' reagent, THF, -10 °C; (xx) CH₂N₂, Et₂O, 0 °C (80%, 2 steps); (xxi) BCl₃, CH₂Cl₂, -78 °C to r.t. (60%); (xxii) Dess-Martin periodinane, CH₂Cl₂ (80%); (xxiii) PPh₃, THF; then, NaBH₄, MeOH, r.t. (60%); (xxiv) I₂, CH₂Cl₂, Et₂O, r.t. (30%).

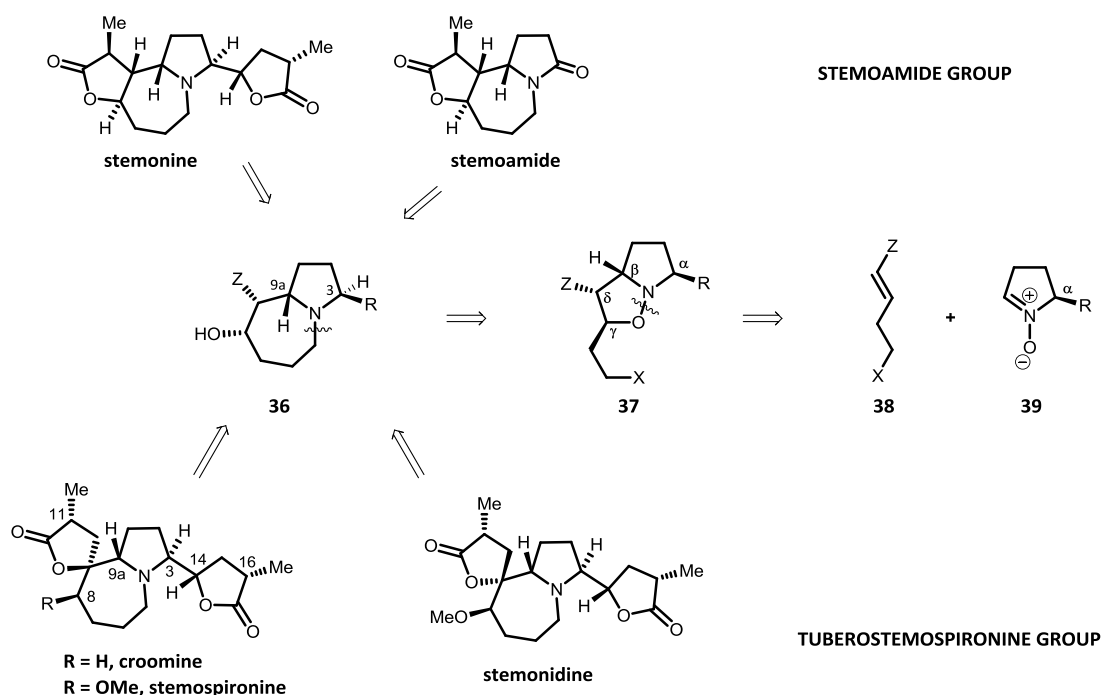
Scheme 4. Williams' strategy for the synthesis of (-)-stemospironine.^{27a}

Saponification of the ester followed by a Swern oxidation led to a 3:1 mixture of diastereomeric lactols **30**. Then, treatment of this mixture with the triphenylphosphorane derived from **34** provided exclusively the *Z* alkene, and subsequent removal of the MEM and benzoyl protecting groups yielded triol **31**, which was submitted to consecutive Jones' oxidation and treatment with diazomethane, affording the spiranic lactone **32**. Cleavage of the benzyl ether was followed by Dess-Martin oxidation to give the crucial azido-aldehyde for the Staudinger-aza-Wittig process. Once the azepine **33** was formed, (–)-stemospirone was produced by the iodine-induced double cyclization reaction of **33**, in 24 steps from **23** and 0.3% overall yield.

In 2007, our research group described the total synthesis of stemonidine, which will be commented later on.³⁸

1.1.4. Retrosynthetic analysis and previous work of the group

Some years ago, our research group started a project towards the development of a new methodology for the synthesis of *Stemona* alkaloids.



Scheme 5. Retrosynthetic analysis for the synthesis of *Stemona* alkaloids.

In most of the previously published syntheses of these natural products, the characteristic azabicyclic core was generated from an advanced intermediate, generally

presenting multiple stereocenters and specifically assembled for the particular target. Our strategy consisted on generating the 1-azabicyclo[5.3.0]decane skeleton at an early stage of the sequence and later on incorporating the α -methyl- γ -butyrolactone units and other specific fragments. Such an approach would benefit from flexibility because the same intermediate could be common to various alkaloids, providing molecular diversity (Scheme 5).^{16r,t}

Thus, alkaloids from stemoamide and tuberostemospironine groups could be prepared from amine **36**. This amine could in turn be prepared from isoxazolidine **37** by reductive cleavage of the N-O bond and subsequent 7-*exo-trig* cyclization. Ultimately, compound **37** would arise from the 1,3-cycloaddition reaction of the cyclic nitron **39** to olefin **38**.

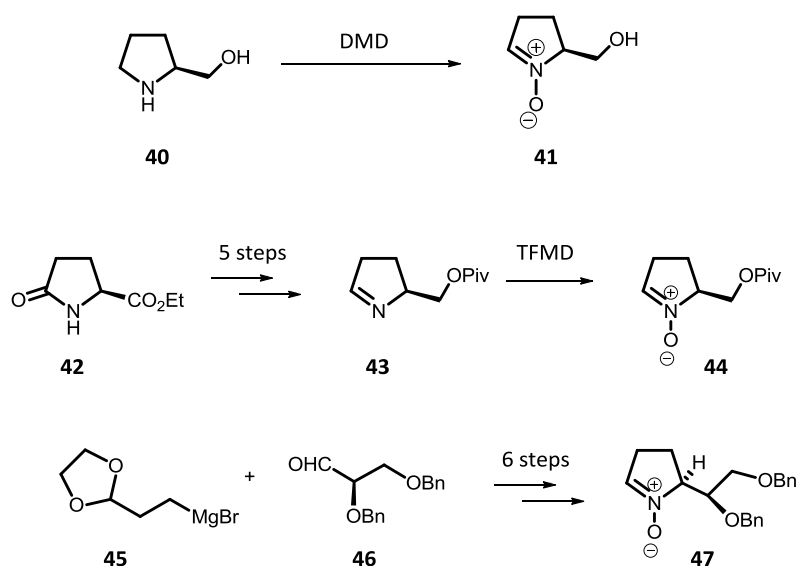
A main advantage of this methodology is the high antifacial selectivity accomplished in the 1,3-dipolar cycloaddition between nitrones such as **39** and electron-deficient olefins of type **38**, delivering isoxazolidine adducts like **37** with relative *trans* configuration of the centers α and β , as required for the targeted alkaloids. The stereogenic center of the nitron (α), which corresponds to C₃ on the alkaloids, would remain unchanged throughout the synthesis. In the 1,3-dipolar cycloaddition reaction three new stereocenters (β , γ and δ) would be formed. From these, β (C_{9a} on the alkaloid) would also remain unchanged throughout the synthesis, whereas γ and δ , which correspond to C₈ and C₉ on the *Stemona* alkaloids, respectively, would be modified depending on the targeted alkaloid.

The efficient preparation of the starting nitron in enantiopure form was a crucial step in this approach, because this nitron is the only source of chirality of our diastereoselective synthetic design. Thus, our research group developed the syntheses of several nitrones synthetically equivalent to **39** (Scheme 6). Nitron **41** was prepared in a single step by oxidation of L-prolinol, **40**, using dimethyldioxirane (DMD) as the oxidant, in 32% yield.⁴⁰ Nitron **44** was prepared from L-pyroglutamate, **42**, through the formation of imine **43**, which was oxidized with (trifluoromethyl)methyldioxirane (TFMD).⁴¹ On the other hand, nitron **47** was obtained from D-glyceraldehyde, **46**, in 6 steps and 33% overall yield.^{16t,42}

⁴⁰ Closa, M.; de March, P.; Figueredo, M.; Font, J. *Tetrahedron Asymmetry* **1997**, *8*, 1031-1037.

⁴¹ Busqué, F.; de March, P.; Figueredo, M.; Font, J.; Gallagher, T.; Milán, S. *Tetrahedron: Asymmetry* **2002**, *13*, 437-445.

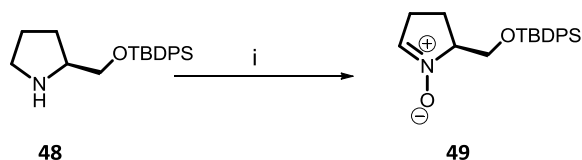
⁴² Alibés, R.; Blanco, P.; de March, P.; Figueredo, M.; Font, J.; Álvarez-Larena, A.; Piniella, J.F. *Tetrahedron Lett.* **2003**, *44*, 523-525.



Scheme 6. Synthesis of enantiopure nitrones.^{16t,40,41,42}

Unfortunately, the two first methodologies proved to be difficult to scale up, essentially because of the problematic preparation of the aforementioned dioxiranes in multigram quantities. On the other hand, nitronium ion **47** a priori presented the advantage of containing an additional stereocenter and the suitable functionalization for the construction of the east-side lactone present in some of the targeted alkaloids, although it required a longer sequence to be obtained. Furthermore, for reasons that would be discussed later, a first generation synthetic approach starting from nitronium ion **47** met with overwhelming difficulties in the installation of the east-side lactone from advanced intermediates. Therefore, additional options for the preparation of a suitable nitronium ion of type **39** were needed.

Some years later, our group developed a straightforward and simple procedure to oxidize secondary amines to nitrones using oxone (KHSO_5) as the sole oxidant.⁴³ This methodology was applied to oxidize the TBDPS derivative of prolinol **48** to the pyrroline *N*-oxide **49**, and it was chosen as the most practical way for preparing the required asymmetric nitronium ion (Scheme 7). Nitronium ion **49** was hence visualized as a suitable precursor for the synthesis of *Stemona* alkaloids.

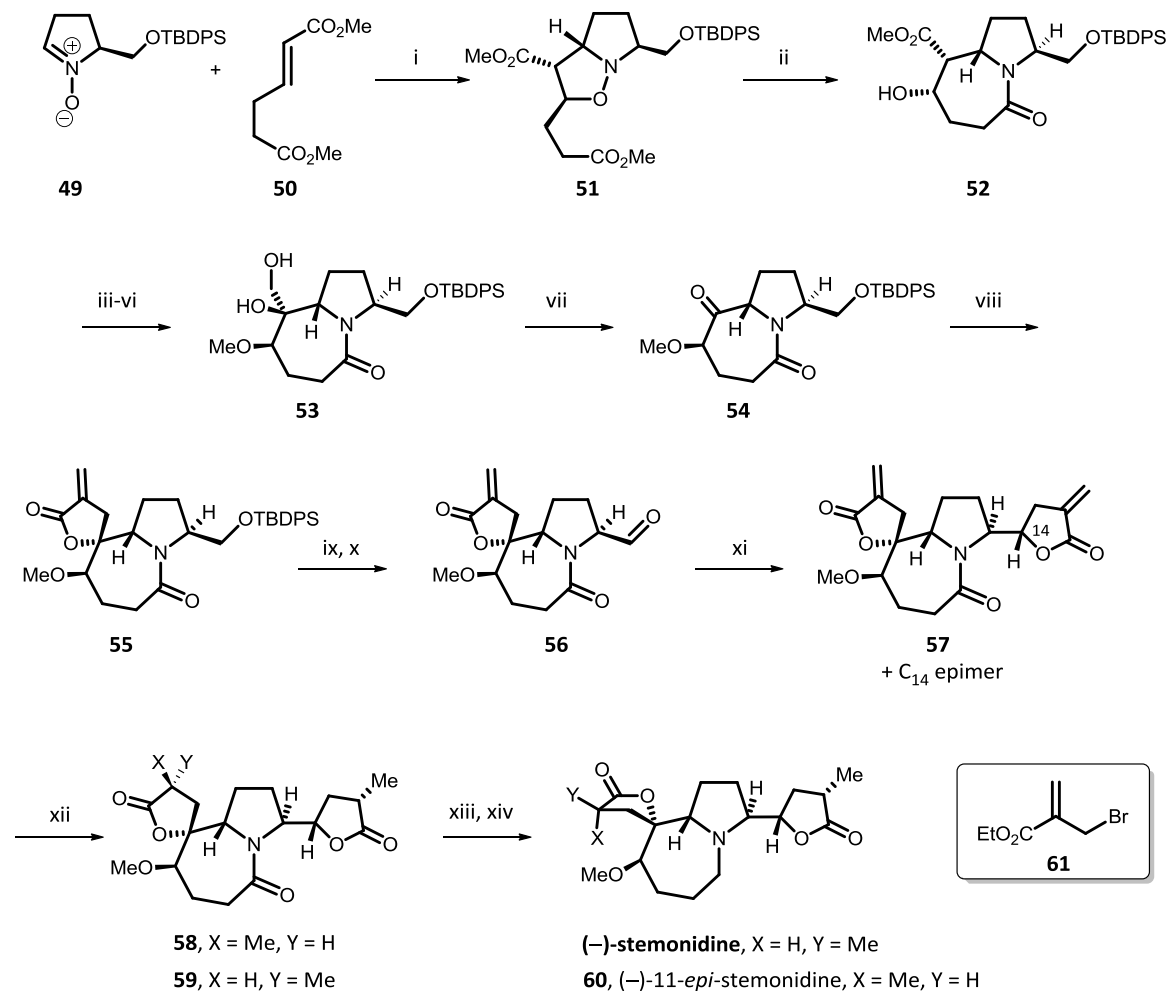


Reagents and conditions: (i) oxone, 0.01 M Na_2EDTA , NaHCO_3 , $\text{MeCN}:\text{THF}$ (4:1), 0°C , 2 h (90%).

Scheme 7. Synthesis of enantiopure nitronium ion **49** using oxone as oxidant.

⁴³ Gella, C.; Ferrer, E.; Alibés, R.; Busqué, F.; de March, P.; Figueredo, M.; Font, J. J. *Org. Chem.* **2009**, *74*, 6365-6367.

Our flexible approach towards these *Stemona* alkaloids has recently culminated with the synthesis of stemonidine,³⁸ a member of the tuberostemospironine group isolated from the roots of *Stemona tuberosa* whose structure was erroneously misassigned as depicted in Scheme 8.⁴⁴



Reagents and conditions: (i) toluene, reflux (78%); (ii) Zn, AcOH; then, aq. NH₃; then, toluene, reflux (84%); (iii) PPh₃, DIAD, PhCO₂H, THF (88%); (iv) OsO₄, NMO, Acetone:H₂O, 60 °C (92%); (v) NaH, THF, 0 °C; then, Me₂SO₄, 0 °C to r.t. (84%); (vi) LiBH₄, THF (97%); (vii) Pb(OAc)₄, THF (92%); (viii) **61**, Zn, THF, reflux (86%); (ix) Et₃N·3HF, THF, reflux (87%); (x) Dess-Martin periodinane, CH₂Cl₂ (92%); (xi) **61**, Zn, THF, reflux (37%); (xii) H₂ (6 bar), Pd/C, EtOH:HCl (2M) (9:1) (68%); (xiii) Lawesson's reagent, THF, reflux; (xiv) Raney-Ni, EtOH, reflux (45%, 2 steps).

Scheme 8. Total synthesis of stemonidine.³⁸

In 2001, Williams and co-workers completed the first synthesis of (-)-stemospironine,^{27a} whose structure had been unequivocally established by X-ray analysis,¹¹ and found that its

⁴⁴ (a) Xu, R.; Lu, Y.; Chu, J.; Iwashita, T.; Naoki, H.; Naya, Y.; Nakanishi, K. *Tetrahedron* **1982**, *38*, 2667-2670; (b) He, X.; Lin, W.; Xu, R. *Huaxue Xuebao* **1990**, *48*, 694-699.

spectral and physical data matched those reported for the natural stemonidine. They also found that the ^{13}C -NMR spectra of synthetic stemospironine and natural stemonidine were virtually identical, but the authors did not exclude the possibility of the two compounds being spirocyclic diastereoisomers.

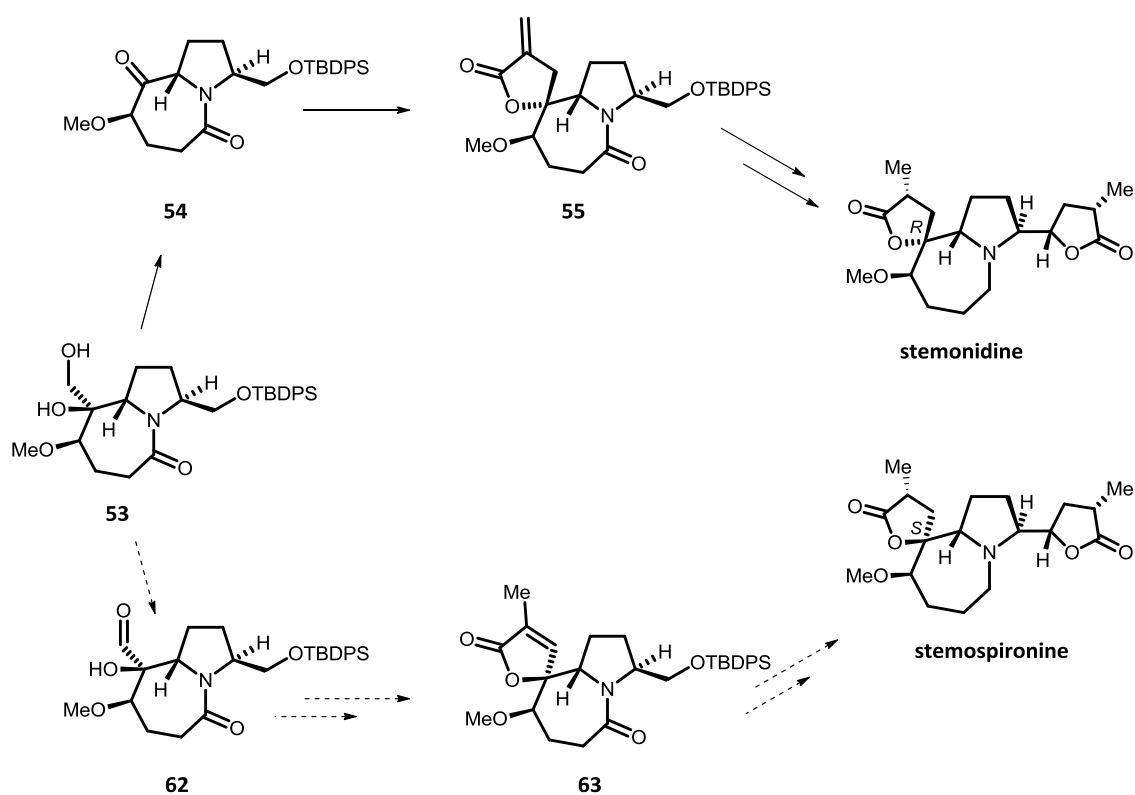
In order to shed some light on the controversy of its uncertain structural assignment, our research group first tackled the synthesis of stemonidine (Scheme 8).

The synthetic sequence to stemonidine started with the 1,3-dipolar cycloaddition reaction of the enantiopure nitron **49** to the α,β -unsaturated ester **50**, which furnished isoxazolidine **51**. After reductive cleavage of the N-O bond and subsequent cyclization, azepinone **52** was formed. In a few steps, the azepinone **52** was transformed into the diol **53**, whose oxidative cleavage with lead tetraacetate afforded ketone **54**. Treatment of **54** with acrylate **61** and zinc rendered the spiro lactone **55** with complete facial selectivity. After removal of the protecting silyl group, Dess-Martin oxidation furnished aldehyde **56**. A Reformatsky-type reaction of **56** with **61** and zinc produced a roughly 1:1 mixture of bis lactone **57** and its C_{14} epimer. Then, hydrogenation of **57** under 6 bar pressure in the presence of Pd/C furnished a mixture of azepinones **58** and **59** epimeric at C_{11} , which were converted into the corresponding thiolactams, and, finally, treatment with Raney-Ni delivered the corresponding azepines, stemonidine and 11-*epi*-stemonidine, **60**.

The spectroscopic data for synthetic stemonidine did not match those of the alkaloid isolated from natural sources and it was thus shown that the putative isolated stemonidine was in fact stemospironine.

1.2. OBJECTIVES

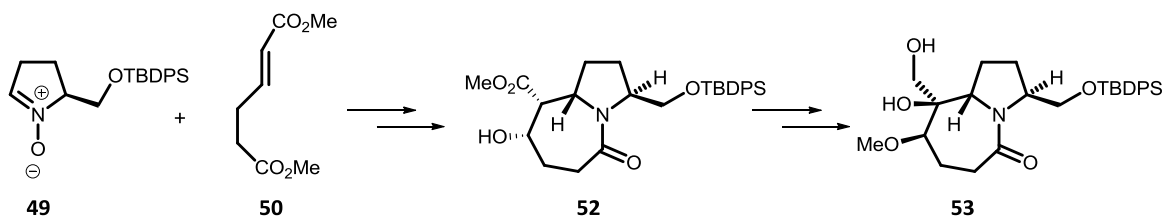
As mentioned above, one of the advantages of our approach is the possibility of synthesizing different *Stemona* alkaloids from common intermediates. Diol **53** (Scheme 9) was visualized as one of this key intermediates because it should allow the construction of the spiranic lactone present in the tuberostemospirone group alkaloids with either *R* or *S* absolute configuration of the spiranic stereocenter, leading the synthesis to stemonidine or stemospirone, respectively.



Scheme 9. Synthetic strategy for the putative structure of stemonidine and stemospirone.

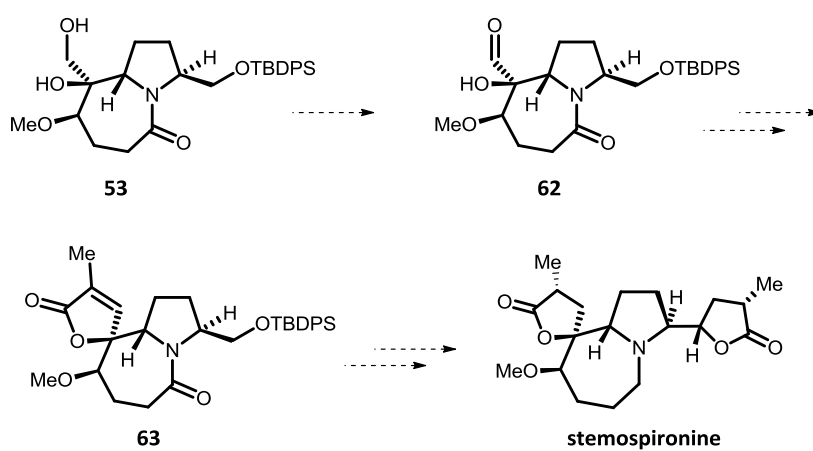
Considering the aforementioned precedents, the objectives of the present work were:

- **Objective 1.** To prepare the key intermediate **53** by reproducing the methodology previously developed by our research group, which culminated with the synthesis of the putative structure of stemonidine,³⁸ trying to improve the yields and scaling up the individual synthetic steps (Scheme 10).



Scheme 10. Synthesis of the key intermediate 53.

- **Objective 2:** To synthesize (-)-stemospirone and some of its stereoisomers (Scheme 11).



Scheme 11. Proposed synthetic strategy for (-)-stemospirone.

2. Results and Discussion

2.1. 1,3-Dipolar Cycloaddition Reaction

2.1.1. General concepts

As it was mentioned in the Introduction, our synthetic approach to *Stemona* alkaloids starts with a 1,3-dipolar cycloaddition reaction of a 5-substituted 1-pyrroline *N*-oxide to an electrondeficient olefin (Scheme 5), affording a cycloadduct with two of the stereogenic centers of the targeted alkaloid. Therefore, some basic concepts of this type of reaction will be first introduced and then we will focus on the synthesis and results.

It is generally accepted that the 1,3-dipolar cycloaddition reactions follow an asynchronous concerted mechanism.⁴⁵ Consequently, the dipole-dipolarophile approach takes place in two parallel planes in such a way that a $\pi 4s + \pi 2s$ orbital interaction occurs according to Woodward and Hoffmann's symmetry rules. The process can be studied by Fukui's Frontier Molecular Orbital (FMO) theory, with which both the regio- and stereoselectivity can be predicted.⁴⁶ Depending on the dominant HOMO-LUMO interaction, there are 3 different types of 1,3-dipolar cycloadditions (Figure 7).⁴⁷

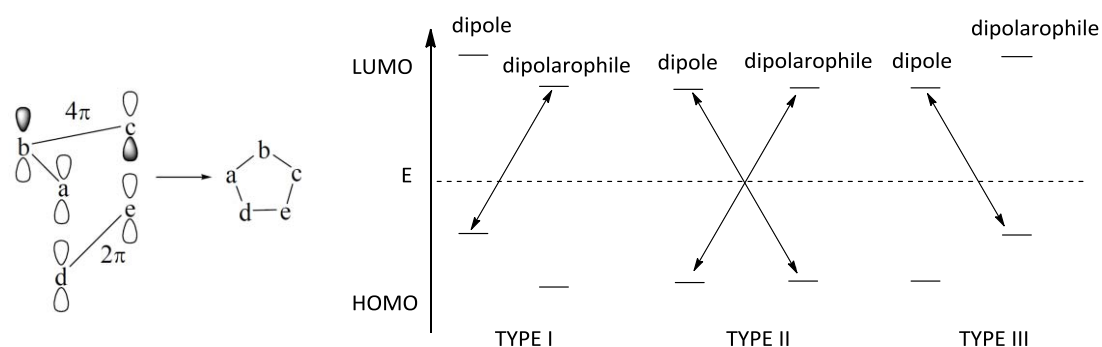


Figure 7. Dipole-dipolarophile interaction and classification of 1,3-dipolar cycloadditions based on the FMO theory.

As nitrones are type II dipoles, the main interaction will depend on the nature of the dipolarophile. Thus, if the dipolarophile contains an electronwithdrawing group, the dominant

⁴⁵ Houk, K. N.; Firestone, R. A.; Münchhausen, L. L.; Mueller, P. H.; Arison, B. H.; García, L. A. *J. Am. Chem. Soc.* **1985**, *107*, 7227-7228.

⁴⁶ (a) Tufariello, J. J. *1,3-Dipolar Cycloaddition Chemistry*, Padwa, A. Ed., John Wiley and Sons, New York, **1984**, Vol. 2, Chapter 9; (b) Torsell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*, H. Feuer Ed., V. C. H. Publishers, Inc., New York, **1988**; (c) Little, R. C. *Comprehensive Organic Chemistry*, Trost, B. M. and Fleming, I. Ed., Pergamon Press **1991**, Vol. 5, Chapter 3.

⁴⁷ Sustmann, R. *Pure Appl. Chem.* **1974**, *40*, 569-593.

interaction will be $\text{HOMO}_{\text{dipole}}-\text{LUMO}_{\text{dipolarophile}}$, whereas if it contains an electron donating group, the main interaction will be $\text{HOMO}_{\text{dipolarophile}}-\text{LUMO}_{\text{dipole}}$.

The FMO theory explains the **regioselectivity** of 1,3-dipolar cycloadditions by considering the different size of the atomic coefficients in the FMO involved on the main interaction. The reaction between a nitron and an electron donating substituted dipolarophile will afford a 5-substituted isoxazolidine, while the reaction with an electron withdrawing substituted dipolarophile will furnish a 4-substituted adduct (Figure 8). However, in some cases steric factors may predominate over electronic ones, and there is experimental evidence for the strong tendency of the oxygen atom to bond the more substituted carbon of the dipolarophile.

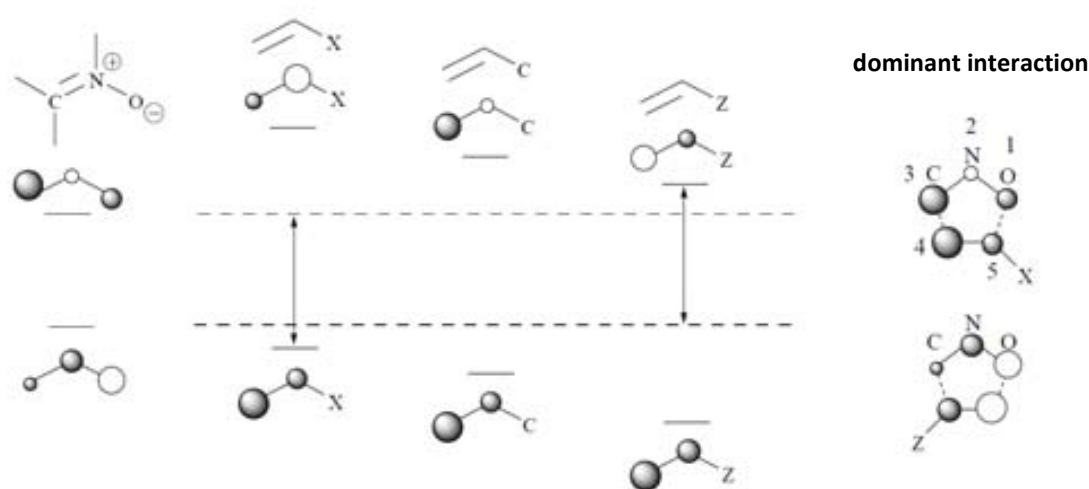


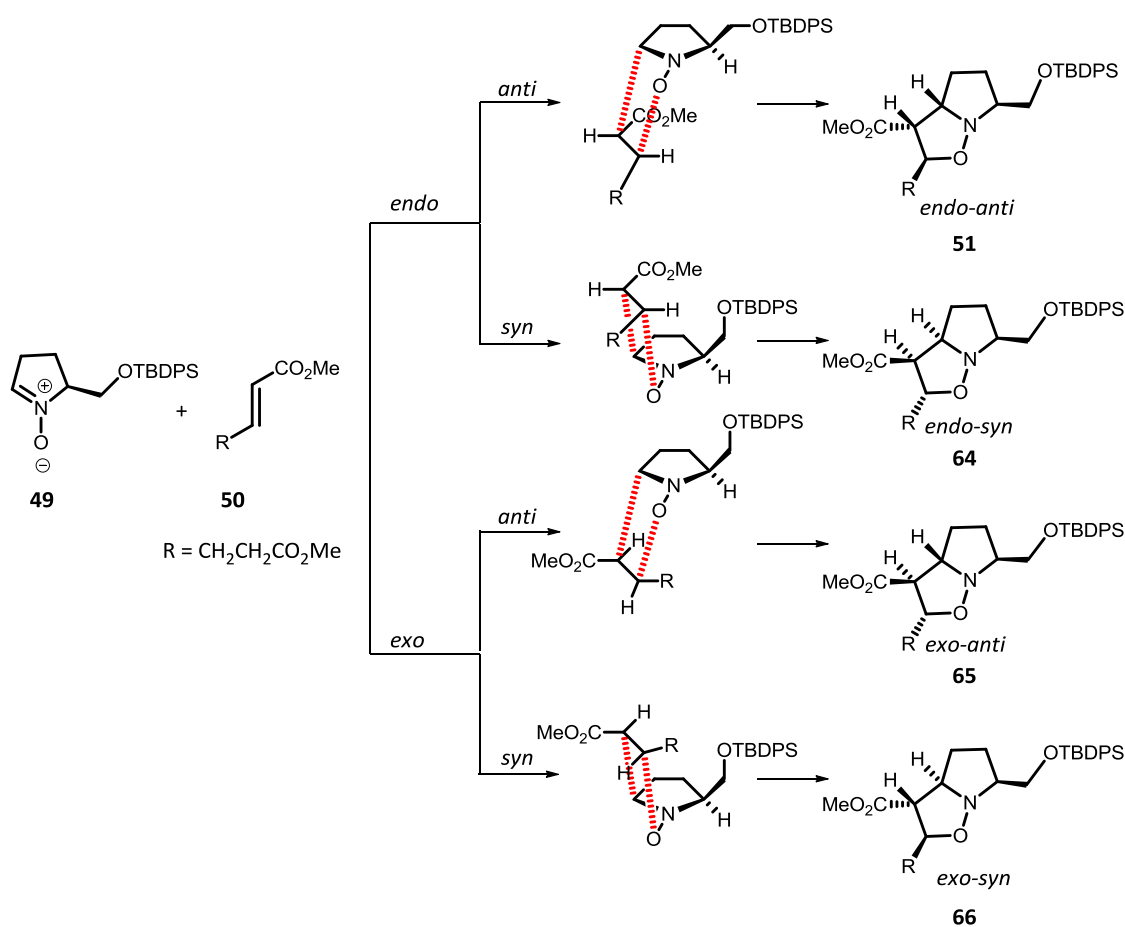
Figure 8. FMO interactions of a nitron with different dipolarophiles.

Another factor to consider in a 1,3-dipolar cycloaddition process is the *endo/exo* **stereoselectivity**. The dipole-dipolarophile approach can take place in two kinds of transition states (TS), considering the orientation of the substituents of the dipolarophile. When the dipolarophile bears an electron withdrawing substituent (as the methyl ester group in **50**, Scheme 12), in the *endo* TS, this substituent is placed towards the dipole, while in the *exo* TS it is placed outwards the dipole, each approach affording diastereoisomeric cycloadducts. In the case of conjugated olefins, electronic factors favour the TS with the electron withdrawing group *endo* oriented, but steric hindrance is also at play. As a general rule, it can be stated that if the 1,2-disubstituted alkene has a *Z* configuration, steric interactions will destabilize the *endo* TS hence playing against electronic interactions. On the other hand, if the olefin has *E* configuration, both steric and electronic factors can point to the same or opposite directions.

In addition to the *endo/exo* selectivity, when the dipole is a chiral substituted nitron as **49**, we also have to consider if the dipolarophile approaches it by the substituent's face (*syn*

approach) or by the opposite face (*anti* approach), being the last one generally preferred. The stereoselectivity of 1,3-dipolar cycloadditions of nitrones has been extensively studied by some groups,⁴⁸ including ours.^{40,41,42,49} In these previous studies, our group used, among others, 5-substituted *N*-oxides as **49** and different olefins to perform the cycloaddition and, in all cases, the reaction took place with complete antifacial diastereoselectivity through *endo* or *exo* approaches in the TS, depending on the *trans* or *cis* configuration of the dipolarophile, respectively.^{40,41,42}

Taking all the possibilities into account, for the cycloaddition between **49** and **50** four possible diastereoisomeric cycloadducts, **51**, **64**, **65** and **66**, can a priori be formed depending on the *endo/exo* orientation of the dipolarophile and its *syn*- or antifacial approach to the nitron.



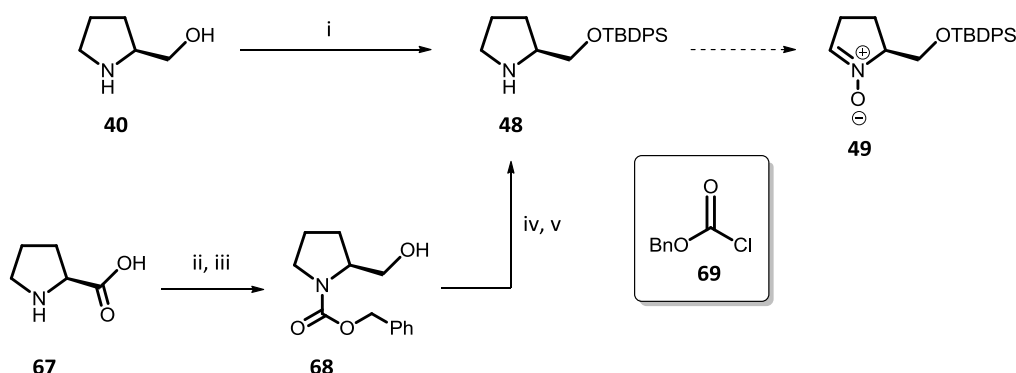
Scheme 12. Transition states and possible adducts of 1,3-dipolar cycloadditions of nitron **49** and disubstituted alkene **50**.

⁴⁸ (a) Plate, R.; Hermkens, P. H. H.; Simits, J. M. M.; Ottenheijm, H. C. J. *J. Org. Chem.* **1986**, *51*, 309-314; (b) Burdisso, M.; Gandolfi, R.; Grünanger, P. *Tetrahedron* **1989**, *45*, 5579-5594; (c) Ali, Sk. A.; Khan, J. H.; Wazeer, M. I. M.; Perzanowski, H. P. *Tetrahedron* **1989**, *45*, 5979-5986.

⁴⁹ (a) Cid, P.; de March, P.; Figueredo, M.; Font, J.; Milán, S.; Soria, A.; Virgili, A. *Tetrahedron* **1993**, *49*, 3857-3870; (b) Alonso-Perarnau, D.; de March, P.; Figueredo, M.; Font, J.; Soria, A. *Tetrahedron* **1993**, *49*, 4267-4274; (c) Busqué, F.; de March, P.; Figueredo, M.; Font, J.; Montsalvatje, M.; Álvarez-Larena, A.; Piniella, J. F. *J. Org. Chem.* **1996**, *61*, 8578-8585, (d) de March, P.; Figueredo, M.; Font, J.; *Heterocycles* **1999**, *50*, 1213-1226.

2.1.2. Preparation of nitron **49** and olefin **50**

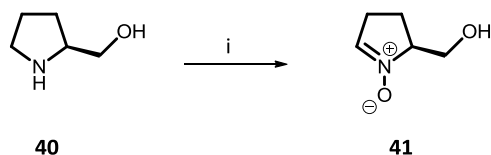
Nitron **49** can be prepared in multigram quantities by oxidation of the corresponding amine **48** (Scheme 13).^{38,43} In order to prepare the amine **48**, we can either use L-prolinol, **40**, as starting material, or L-proline, **67**. The route starting from L-proline is economically advantageous, despite it involves four synthetic steps, because the overall yield is very good (70%) and commercial L-prolinol is much more expensive than L-proline.



Reagents and conditions: (i) TBDPSCl, Imidazole, DMAP, CH₂Cl₂, 0 °C to r.t., 16 h (95%); (ii) **69**, NaOH 2 M, 0 °C, 2 h (97%); (iii) BH₃·THF, THF, 0 °C to r.t., 16 h (93%); (iv) TBDPSCl, Imidazole, THF, r.t., 16 h (87%); (v) HCO₂NH₄, Pd/C, THF:MeOH (2:1), 80 °C, 30 min (89%).

Scheme 13. Synthesis of amine **48**.

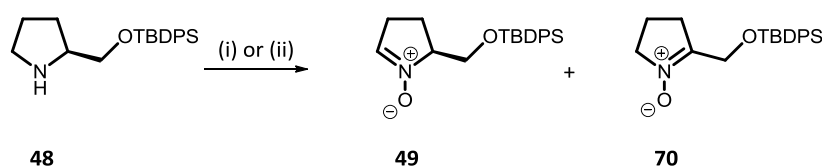
As we mentioned before, nitron **41** was previously prepared in one step by treatment of L-prolinol, **40**, with dimethyldioxirane in acetone at low temperature (Scheme 14).⁴⁰ Although this straightforward methodology competed favourably with other preparations of related nitrones, difficulties associated with the purification of the nitron and the scaling-up of the process led us to abandon its use.



Reagents and conditions: (i) DMD, acetone, -78 °C, 30 min; then, toluene, reflux, 6 h (32%).

Scheme 14. Synthesis of nitron **41** from L-prolinol **40**.

To avoid these drawbacks, we decided to use oxone for the direct oxidation of an L-prolinol derivative.⁴³ After a detailed study, the best result was obtained when the oxidation was carried out starting from the TBDPS derivative of L-prolinol **48** (Scheme 15), with oxone in a mixture of MeCN:THF in the presence of NaHCO₃ and EDTA. In that way, a 1.30:1 mixture of nitrones **49** and **70** could be prepared in multigram quantities and 90% combined yield. The optically pure nitronone **49** was isolated from this mixture and used by our research group for the synthesis of the putative structure of stemonidine.³⁸ In the present work, MeOH was used as solvent instead of the mixture of MeCN:THF while the other conditions remained unchanged, furnishing a 1.34:1 mixture of nitrones **49** and **70** in 87% overall yield. After flash column chromatographic separation, nitronone **49** was obtained in 48% yield. It is important to mention that it was possible to scale up the reaction to obtain 10 g of nitronone **49** in a reproducible manner, without detriment of yield or optical purity.



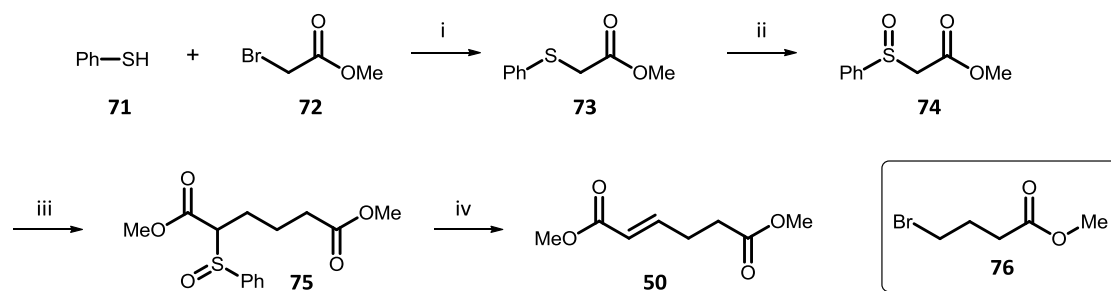
Reagents and conditions: (i) oxone, Na₂EDTA 0.01 M, NaHCO₃, MeCN:THF (4:1), 0 °C, 2 h (90%); (ii) oxone, Na₂EDTA 0.01 M, NaHCO₃, MeOH, 0 °C, 2 h (87%).

Scheme 15. Synthesis of nitronone **49** from the L-prolinol derivative **48**.

With the enantiopure nitronone **49** in hands, olefin **50** was synthesized also in multigram scale (Scheme 16). This olefin would be used later on as dipolarophile in the 1,3-dipolar cycloaddition to **49**.

To prepare alkene **50** we could start from the commercially available sulfoxide **74**, but in this thesis we prepared it through the sequence outlined below (Scheme 16). Reaction of thiophenol, **71**, with methyl bromoacetate, **72**, and subsequent oxidation with NaIO₄ yielded sulfoxide **74**.⁵⁰ The sulfoxide was treated with sodium hydride to afford the corresponding anion, which was subsequently alkylated with methyl 4-bromobutanoate, **76**, rendering sulfoxide **75**. Without further purification, pyrolysis of **75** in DME at the reflux temperature yielded olefin **50** in 45% overall yield from **71**.

⁵⁰ Raghavan, S.; Reddy, S. R.; Tony, K.A.; Kumar, C. N.; Varma, A. K.; Nangia, A. *J. Org. Chem.* **2002**, *67*, 5838-5841.

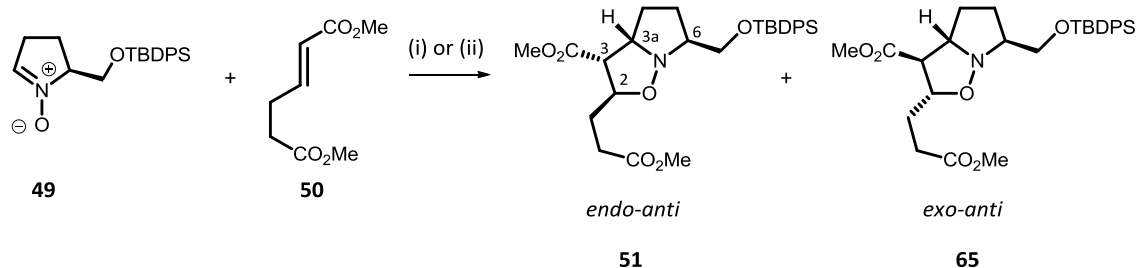


Reagents and conditions: (i) Et_3N , toluene, r.t., 16 h (98%); (ii) NaIO_4 , H_2O , MeOH , r.t., 16 h (93%); (iii) NaH , HMPA , DME , r.t., 30 min; then, **76**, 16 h; (iv) DME , reflux, 16 h (49%, 2 steps).

Scheme 16. Synthesis of dimethyl hexenedioate **50**, from thiophenol **71**, and methyl bromoacetate **72**.

2.1.3. 1,3-Cycloaddition reaction of nitron 49 to olefin 50

In previous work of our group, the 1,3-cycloaddition reaction between nitron **49** and diester **50** was performed in toluene at the reflux temperature for 10 h to obtain a mixture of the expected *endo-anti* isoxazolidine **51** (78% yield), along with a minor quantity of its *exo-anti* diastereoisomer **65** (5% yield) (Scheme 17).³⁸



Reagents and conditions: (i) toluene, reflux, 10 h (78%); **51:65** 15:1; (ii) toluene, 90 °C, 1.5 h (79%); only **51**.

Scheme 17. 1,3-dipolar cycloaddition reaction of nitron **49** to olefin **50**.

In this thesis, the cycloaddition reaction between **49** and **50** lacked reproducibility when performing it in toluene at the reflux temperature during 10 h, rendering sometimes low yields of cycloadducts and/or decomposition products. However, we found out that, when the reaction was carried out in toluene at 90 °C during 1.5 h, **51** was isolated as the only product in 79% yield. Running the reaction for this shorter period of time, equilibration between the kinetical *endo* cycloadduct and the starting material is avoided, preventing the formation of the most stable *exo* cycloadduct and other products resulting from the nitron decomposition.

The isoxazolidine **51** resulting of the cycloaddition contained four stereogenic centers, three of which (C_2 , C_3 and C_{3a}) were generated in the reaction. The relative *trans* geometry between H_2 and H_3 is a consequence of the *E* configuration of the starting olefin **50**. The *trans* configuration between H_{3a} and H_6 is the result of the preferred antifacial approach between the reagents in the TS, which has been extensively demonstrated in precedent works.^{40,41,42}

To determine the complete stereochemistry of the cycloaddition, the relative geometry between protons H_3 and H_{3a} should be also established. The relationship between H_3 and H_{3a} indicates if the cycloadduct comes from an *exo* (*trans* relationship) or *endo* TS (*cis* relationship). Previous studies performed in our group with similar cycloadducts indicated that values of $J_{3,3a} \approx 8$ Hz were characteristic of the *cis* relative geometry of *endo* cycloadducts, while the corresponding *exo* showed a $J_{3,3a} \approx 5-6$ Hz. The $^1\text{H-NMR}$ spectrum of isoxazolidine **51** presents a $J_{3,3a} = 9.3$ Hz and hence it was identified as an *endo* adduct.

In previous works, the enantiomeric purity of **51** was determined.³⁸ It was considered important to determine it at this point, because any epimerization that may take place later on in the synthetic sequence would provide diastereoisomers and therefore it could be readily detected by NMR techniques.

To this end, the synthesis was repeated starting from D-prolinol until achieving the corresponding isoxazolidine *ent-51*. This compound and the cycloadduct obtained from L-prolinol, **51**, were compared using a chiral HPLC analysis (Figure 9). It was found that the racemate could be separated by CHPLC using a Daicel Chiralpak AD-H 4.6 x 250 mm column ($^i\text{PrOH}$:hexanes, 1:99; 0.8 mL \cdot min $^{-1}$). Figure 9 displays three chromatograms. Chromatogram A resulted of an injection of an approximately 6:1 mixture of both enantiomers, **51** and *ent-51*, respectively. Once the best separation conditions were established, each isomer was injected separately. Chromatogram B was obtained from the injection of **51**, which derives from L-prolinol, and chromatogram C from the injection of *ent-51*, that derives from D-prolinol. Thus, the enantiomeric purity was secured and it was proved that undoubtedly there was no racemization of the nitron before the cycloaddition took place.

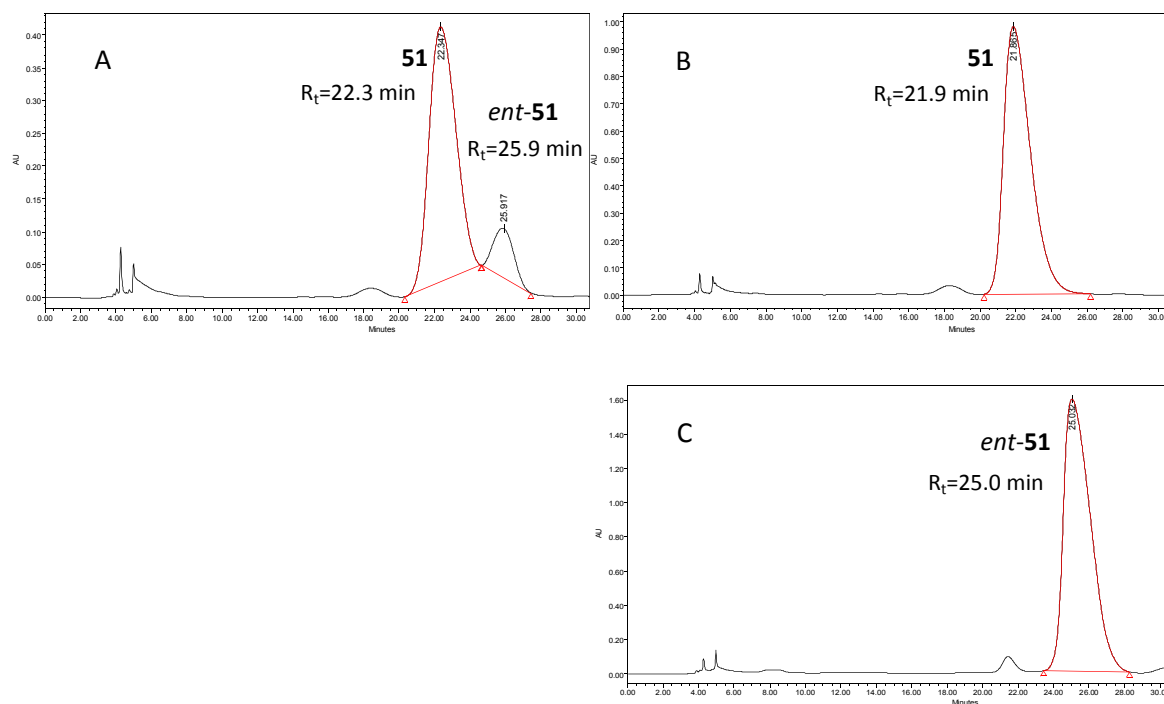
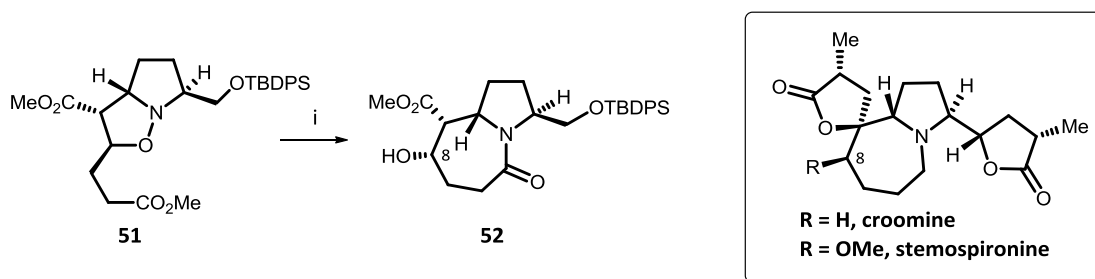


Figure 9. CHPLC chromatograms obtained from the injection of (±)-**51** (A), **51** (B) and *ent*-**51** (C).

2.2. Construction of the pyrrolo[1,2-*a*]azepinone core. Synthesis of intermediate **52**

Once the isoxazolidine **51** had been prepared, the next step was the formation of the characteristic azabicyclic nucleus. Reductive cleavage of the N-O bond of **51** was performed by treatment with activated Zn⁵¹ in glacial acetic acid. Basification of the quaternary ammonium salt with aqueous NH₃ and subsequent heating furnished lactam **52** in 91% yield (Scheme 18).



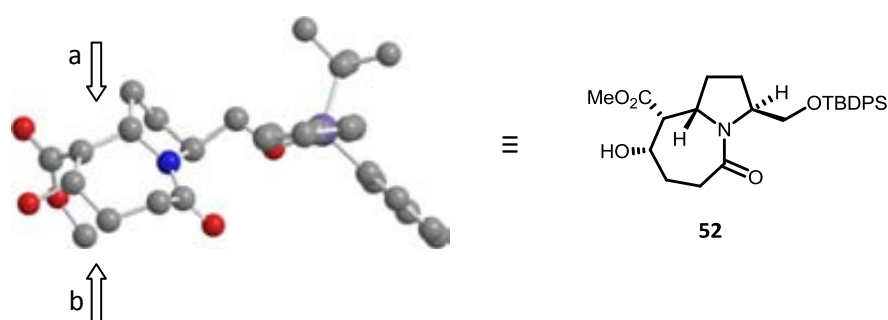
Reagents and conditions: (i) Zn, AcOH; then, aq. NH₃, CHCl₃; then, toluene, reflux, 16 h (91%).

Scheme 18. Synthesis of lactam **52**.

⁵¹ Newman, M. S.; Evans, F. J. *J. Am. Chem. Soc.* **1955**, *77*, 946-497.

In both the tuberostemospironine and stemoamide groups, all the alkaloids bearing an oxygen atom at C₈, such as stemospironine, present the same configuration at this center, which is the opposite to that in lactam **52**. On the other hand, manipulation of the hydroxyl group at C₈ for further synthetic elaboration usually led to elimination products.^{16r,t}

Moreover, a simple conformational analysis of the azabicyclic skeleton of these compounds showed that the concave face was more sterically hindered and, consequently, less accessible (Figure 10). Taking all this information into account, it seemed a good strategy dehydrating lactam **52** firstly and then performing a diastereoselective dihydroxylation of the α,β -unsaturated ester (Scheme 19).

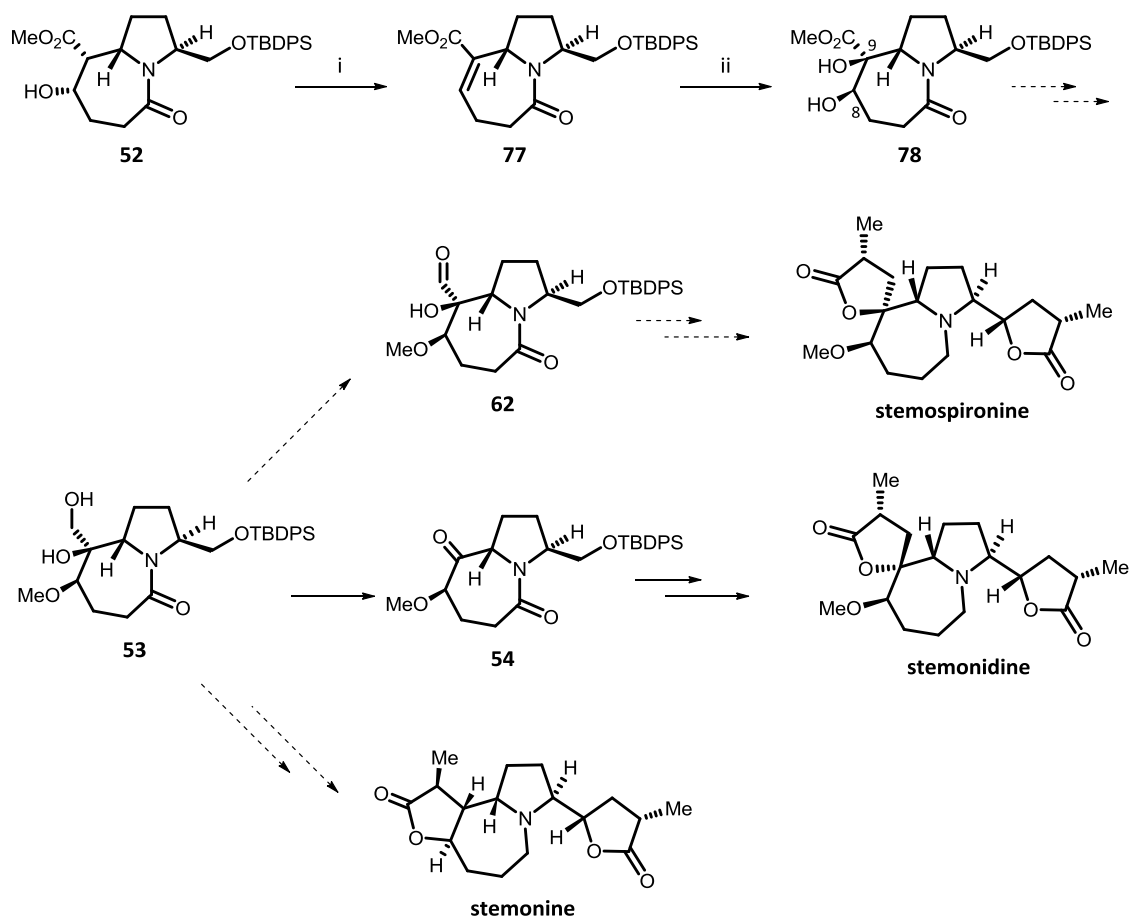


a) convex face, less steric hindrance; b) concave face, less accessible.

Figure 10. Molecular model of lactam **52** (ChemBio3D Ultra 12.0).

2.3. Preparation of the key intermediate **53**

Accordingly, the next step in the sequence was the preparation of the olefin **77** and its subsequent dihydroxylation to yield diol **78** (Scheme 19). This diol **78** should be a suitable precursor of various alkaloids, such as stemospironine (tuberostemospironine group) and stemonine (stemoamide group), because it presents the correct configuration at C₈ and could undergo convenient transformations to form the spiro- or fused lactones with the appropriate configuration at C₉.



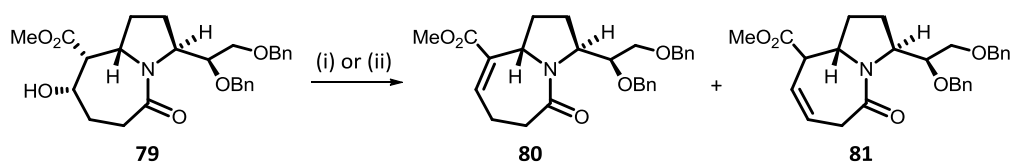
Reagents and conditions: (i) PPh₃, DIAD, PhCO₂H, THF, r.t., 1.5 h (85%); (ii) OsO₄, NMO, acetone:H₂O (9:1), 60 °C, 1.5 h (96%).

Scheme 19. Synthesis of diol **78** and synthetic plan for stemospironine, stemonidine and stemonine.

The dehydration of lactam **52** was accomplished under Mitsunobu's conditions⁵² in THF and in the presence of benzoic acid, furnishing olefin **77** in 85% yield.

In preceding investigations with the related compound **79** (Scheme 20),³⁸ it was observed that the presence of benzoic acid avoids the formation of a byproduct (**81**) resulting of double bond isomerization. The lack of planarity in the preferential conformation of **80** did not allow conjugation, giving more stability to the migration product **81**. The formation of **81** could be easily avoided controlling the pH of the media by adding benzoic acid.

⁵² Mitsunobu, O. *Synthesis*, **1981**, 1-28.

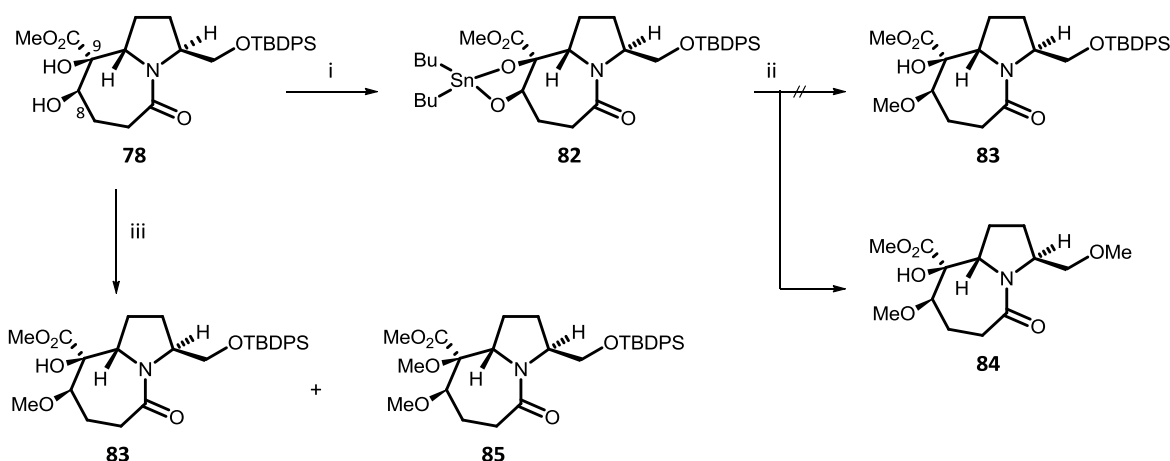


Reagents and conditions: (i) PPh_3 , DIAD, THF, r.t., 1 h (78%); **80:81** 1.9:1; (ii) PPh_3 , DIAD, PhCO_2H , THF, r.t., 1 h (84%); only **80**.

Scheme 20. Dehydration of compound **79**.

The dihydroxylation of the α,β -unsaturated ester **77** was performed by treatment with OsO_4 and NMO, furnishing diol **78** as the only product in 96% yield, with complete facial diastereoselectivity, as it was expected from previous results. We assumed that the reaction took place over the convex face of the molecule. This hypothesis was later corroborated by chemical correlation with the natural product stemospirinine and by means of an X-ray diffraction analysis of an advanced intermediate.

The following step was the regioselective methylation of the secondary alcohol (Scheme 21). Initially, the alkylation was performed through a two-step protocol via the formation of a tin acetal intermediate, which is a common methodology for the selective protection of 1,2-diols.⁵³ Thus, diol **78** was treated with dibutyltin oxide in MeOH at the reflux temperature and, when tin acetal formation was assumed, TBABr and Me_2SO_4 were added to the reaction mixture.



Reagents and conditions: (i) Bu_2SnO , MeOH, reflux, 1.5 h; (ii) TBABr, Me_2SO_4 , toluene, 80 °C; (iii) NaH, THF, 0 °C, 0.5 h; then, Me_2SO_4 , 0 °C to r.t., 16 h (84% yield over unrecovered **78**).

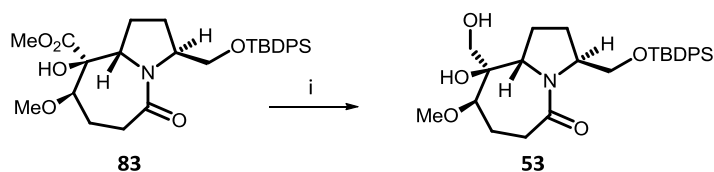
Scheme 21. Methylation of the secondary alcohol in **78**.

⁵³ (a) Wagner, D.; Verheyden, J. P. H.; Moffat, J. G. *J. Org. Chem.* **1974**, *39*, 24-29; (b) Busqué, F.; Hopkins, S. A.; Konopelski, J. P. *J. Org. Chem.* **2002**, *67*, 6097-6103.

Unfortunately, the $^1\text{H-NMR}$ analysis of the crude material allowed the identification of the dimethyl derivative **84** as the main product, instead of the desired monoether **83**. Therefore, not only the expected alkylation of the secondary alcohol was taking place, but also the deprotection and subsequent methylation of the primary one.

A reference experiment carried out without the addition of the ammonium salt rendered a crude material consisting of starting diol **78** and the expected monomethylated product **83**, but none of the dimethyl derivative. This fact proved that the ammonium salt was responsible for the deprotection of the primary alcohol in the reaction medium. Therefore, we moved to a different synthetic methodology. Thus, diol **78** was treated with an excess of NaH in THF at 0 °C and, when dianion formation was assumed, Me_2SO_4 was added. The reaction mixture was warmed up slowly to room temperature and stirred overnight to furnish the monomethyl derivative **83** in 84% yield considering unrecovered **78**, together with a minor amount (2%) of the dimethyl derivative **85**.

Subsequent reduction of the ester functionality with LiBH_4 in THF provided diol **53** in 76% yield (Scheme 22).



Reagents and conditions: (i) LiBH_4 , THF, r.t., 16 h (76%).

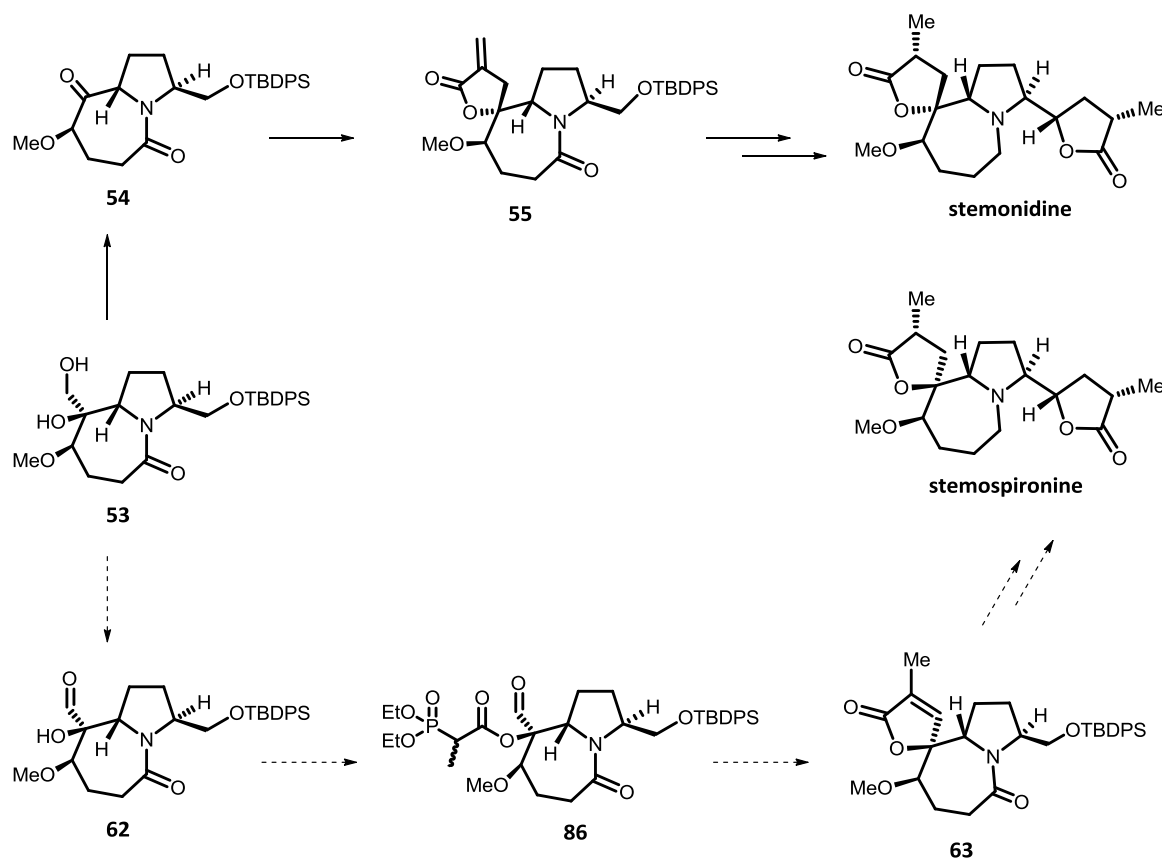
Scheme 22. Preparation of diol **53**.

2.4. Construction of the spiranic lactone. Synthesis of compound **63**

Next, we turned our attention to the construction of the west-side lactone. Diol **53** was visualized as the key intermediate for the collective syntheses⁵⁴ of several *Stemona* alkaloids. In particular, it should give access to a spiranic lactam with either *R* or *S* configuration of the spirocenter, depending on the subsequent transformations applied (Scheme 23). Thus, when the goal was the synthesis of stemonidine,³⁸ diol **53** was transformed by oxidative cleavage to ketone **54** in order to construct the spiro lactone with the required *R* configuration through reaction with

⁵⁴ Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. *Nature* **2011**, *475*, 183-188.

ethyl bromomethylacrylate, **61**, and Zn,⁵⁵ that takes place on the most accessible convex face of ketone **54**. However, for the synthesis of (-)-stemospirone, we planned oxidizing the primary alcohol to aldehyde **62** and then assaying a Wittig type cyclization that should deliver the lactone with the required *S* configuration.



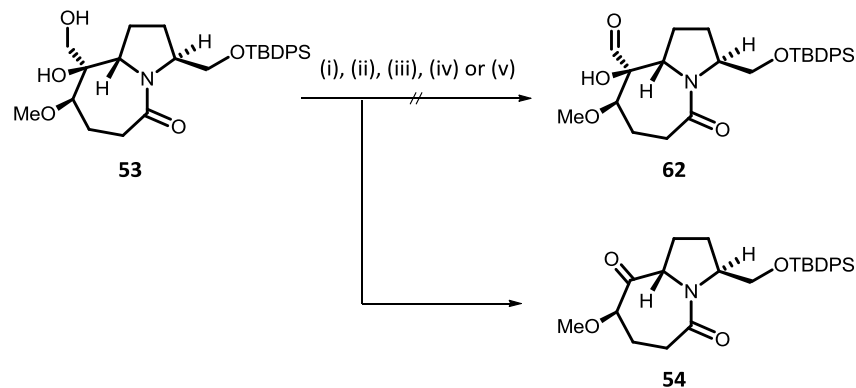
Scheme 23. Synthetic plan for stemonidine and stemospirone.

The oxidation of the primary alcohol in **53** was first attempted by treatment with Dess-Martin periodinane. In the event, the hydroxyaldehyde **62** was obtained in very low yields, along with some starting material and also ketone **54** (Scheme 24). Then, we explored the possibility of forming aldehyde **62** under Swern oxidation conditions, at both -60 °C and -78 °C;⁵⁶ however, in both cases ketone **54** was the only identified product and ¹H-NMR of the crude material showed no signals of the expected aldehyde. Parikh-Doering oxidation was also assayed, which consists on employing a sulfur-trioxide-pyridine complex instead of oxalyl chloride used in the standard

⁵⁵ Rauter, A. P.; Figueiredo, J.; Ismael, M.; Canda, T.; Font, J.; Figueiredo, M. *Tetrahedron: Asymmetry* **2001**, *12*, 1131-1146.

⁵⁶ Corey, E. J.; Li, W.; Reichard, G. A. *J. Am. Chem. Soc.* **1998**, *120*, 2330-2336.

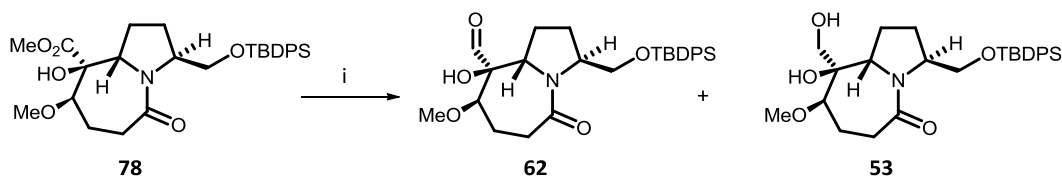
Swern oxidation. We tried two different bases when performing this variation of the Swern oxidation, namely Et_3N ⁵⁷ and $i\text{Pr}_2\text{NEt}$,⁵⁸ but in both cases we only isolated ketone **54**, along with decomposition products.



Reagents and conditions: (i) Dess-Martin periodinane, CH_2Cl_2 , r.t., 1.5 h; (ii) DMSO, Et_3N , $(\text{COCl})_2$, CH_2Cl_2 , $-60\text{ }^\circ\text{C}$, 2 h; (iii) DMSO, Et_3N , $(\text{COCl})_2$, CH_2Cl_2 , $-78\text{ }^\circ\text{C}$, 2 h; (iv) DMSO, Et_3N , $\text{SO}_3\cdot\text{pyridine}$, CH_2Cl_2 , $0\text{ }^\circ\text{C}$, 2 h; (v) DMSO, $i\text{Pr}_2\text{NEt}$, $\text{SO}_3\cdot\text{pyridine}$, CH_2Cl_2 , $0\text{ }^\circ\text{C}$, 2 h.

Scheme 24. Attempted formation of hydroxyaldehyde **62**.

We also explored the possibility of preparing aldehyde **62** directly from hydroxyester **78** by reduction with DIBAL-H at $-78\text{ }^\circ\text{C}$ in dichloromethane (Scheme 25). Unfortunately, this reaction was not reproducible, affording most of the times the over-reduced diol **53** as the major product.



Reagents and conditions: (i) DIBAL-H, CH_2Cl_2 , $-78\text{ }^\circ\text{C}$.

Scheme 25. Attempted reduction of ester **78** to hydroxyaldehyde **62**.

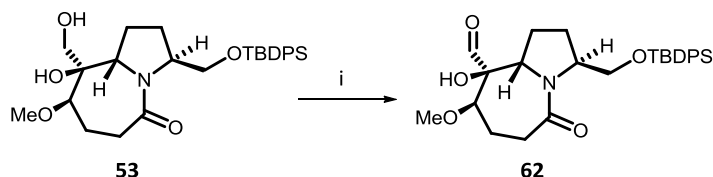
After these failed trials, we succeeded in preparing aldehyde **62** through a mild methodology of oxidation based on the use of TEMPO.⁵⁹ Thus, the oxidation of alcohol **53** was

⁵⁷ Patel, P.; Lee, G.-J.; Kim, S.; Grant, G. E.; Powell, W. S.; Rokach, J. *J. Org. Chem.* **2008**, *73*, 7213-7218.

⁵⁸ Veitch, G. E.; Beckmann, E.; Burke, B. J.; Boyer, A.; Maslen, S. L.; Ley, S. V. *Angew. Chem. Int. Ed.* **2007**, *46*, 7629-2632.

⁵⁹ Einhorn, J.; Einhorn, C.; Ratajczak, F.; Pierre, J.-L. *J. Org. Chem.* **1996**, *61*, 7452-7454.

performed with *N*-chlorosuccinimide (NCS) as stoichiometric oxidant, in the presence of TEMPO and tetrabutylammonium chloride in basic medium and a biphasic system (CH₂Cl₂-water), yielding aldehyde **62** in 91% yield (Scheme 26). Under these conditions, primary alcohols are reported to be oxidized to aldehydes without any noticeable over-oxidation to carboxylic acids, even with an excess of NCS. Using this methodology, the formation of ketone **54** by oxidative cleavage was never observed.



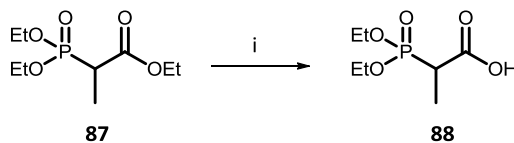
Reagents and conditions: (i) TEMPO, NCS, TBACl, CH₂Cl₂:H₂O (1:1), K₂CO₃, NaHCO₃, r.t., 2 h (91%).

Scheme 26. Synthesis of hydroxyaldehyde **62**.

The ¹H-NMR spectrum of **62** shows a characteristic signal of aldehyde at 9.80 ppm. This signal is consistent with that observed in the ¹³C-NMR spectrum at 202.2 ppm.

The esterification reaction of **62** with 2-diethoxyphosphorylpropionic acid, **88**, should afford aldehyde **86** presumably as a mixture of diastereoisomers, and basic treatment of the intermediate phosphonate should render lactone **63** (Scheme 23).

First of all, acid **88** was prepared by hydrolysis of the corresponding ethyl ester **87**,⁶⁰ commercially available from Aldrich (Scheme 27). Thus, ester **87** was dissolved in 10 M aqueous NaOH and it was stirred for one hour. Then, the corresponding carboxylate anion was protonated with concentrated HCl, rendering acid **88** in quantitative yield.



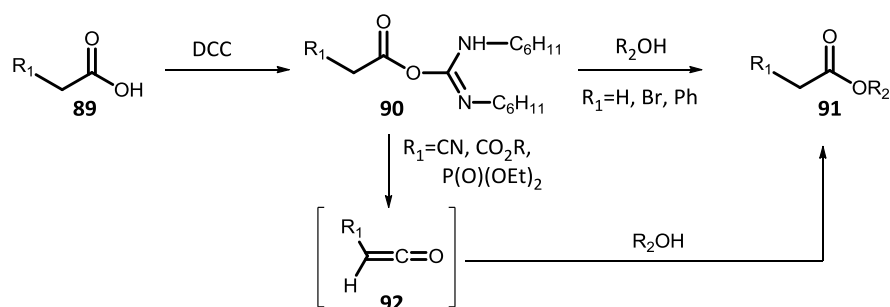
Reagents and conditions: (i) NaOH 10 M, 0 °C, 1 h; then, r.t., 2.5 h; then, concd. HCl (until pH= 1), 0 °C (quant.).

Scheme 27. Hydrolysis of the ester **87**.⁶⁰

⁶⁰ Luke, G. P.; Seekamp, C. K.; Wang, Z.-Q.; Chenard, B. L. *J. Org. Chem.* **2008**, *73*, 6397-6400.

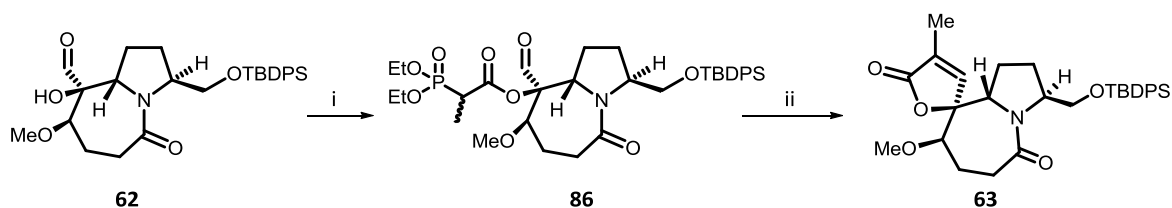
2. RESULTS AND DISCUSSION

To carry out the esterification reaction of the tertiary alcohol (**62** to **86**), we decided to apply a methodology described by Melman and Nahmany for the acylation of sterically hindered alcohols (Scheme 28).⁶¹ According to the authors, this methodology, based on the use of DCC, is specific for carboxylic acids possessing strongly electron withdrawing groups such as CN, CO₂R or P(O)(OEt)₂ at the α -position and occurs through the corresponding ketene intermediate **92**. Even highly hindered and chemically sensitive alcohols are acylated under these neutral conditions at room temperature.



Scheme 28. Mechanistical proposal for the esterification of sterically hindered alcohols.⁶¹

Thus, freshly prepared acid **88** was added to a solution of aldehyde **62**, and then DCC was slowly added (Scheme 29). After 4 hours, a mixture of diastereoisomeric aldehydes **86** was obtained. Although the presence of two diastereoisomers complicated the ¹H-NMR spectrum of the crude reaction material, two aldehyde signals at δ 9.56 and 9.54 ppm could be clearly observed. This mixture was filtered through silica gel and then treated with ^tBuOK to promote the cyclization.

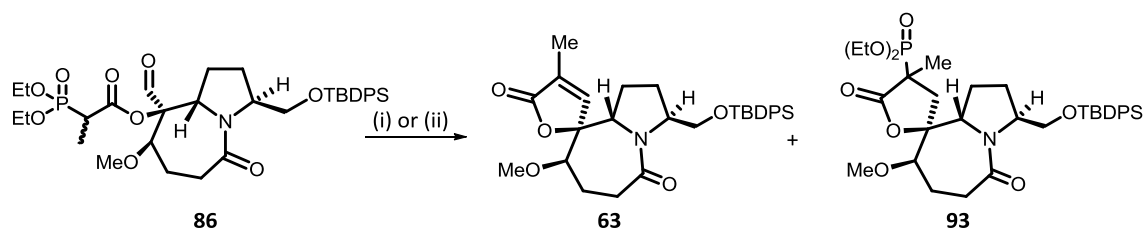


Reagents and conditions: (i) **88**, 1 M in CH₂Cl₂, DCC 1 M, CH₂Cl₂, 4 h; (ii) ^tBuOK, THF, reflux, 2.5 h (71%, 2 steps).

Scheme 29. Construction of lactone **63**.

⁶¹ (a) Nahmany, M.; Melman, A. *Org. Lett.* **2001**, *3*, 3733-3735; (b) Shelkov, R.; Nahmany, M.; Melman, A. *J. Org. Chem.* **2002**, *67*, 8975-8982; (c) Shelkov, R.; Nahmany, M.; Melman, A. *Org. Biomol. Chem.* **2004**, *2*, 397-401.

It was observed that when this Wittig-like reaction is performed at room temperature, after 2 h, the aldehyde is totally consumed. However, the $^1\text{H-NMR}$ spectrum of the crude material shows two compounds. The minor component is the expected lactone **63**, identified by a characteristic signal of the conjugated double bond at 6.93 ppm, whereas the major component was identified as **93**, an addition product of the ylide to the aldehyde that did not evolve to eliminate the phosphate (Scheme 30).



Reagents and conditions: (i) $t\text{BuOK}$, THF, r.t., 2 h; **63**:**93** 1:6.4; (ii) $t\text{BuOK}$, THF, reflux, 16 h; only **63**.

Scheme 30. Optimization of the preparation of olefin **63**.

Fortunately, compound **93** could be transformed into lactone **63** by heating it in THF at the reflux temperature in the presence of $t\text{BuOK}$. Thus, lactone **63** could be directly obtained from the mixture of aldehydes **86** by treatment with $t\text{BuOK}$ in THF at the reflux temperature during 2.5 h. This period of time was enough to render **63** as the sole product in 71% yield from aldehyde **62**. In the $^1\text{H-NMR}$ spectrum of **63**, we could observe the characteristic signal of the olefinic proton at 6.93 ppm as a quartet, and also the vinylic methyl group as a doublet at 1.97 ppm.

At this stage, we had already constructed three of the four rings present in the targeted alkaloid (–)-stemospirone. Now, our efforts were focused on the preparation of the east-side α -methyl- γ -butyrolactone.

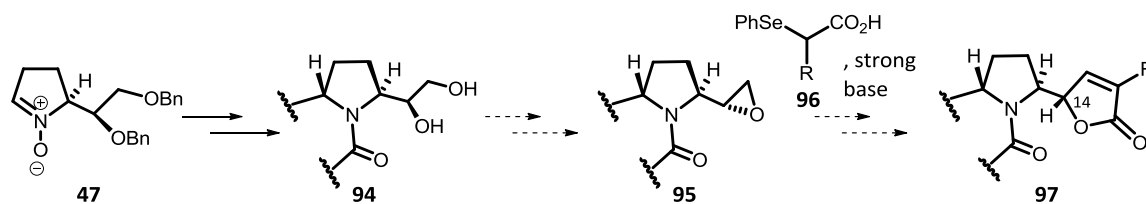
2.5. Construction of the "eastern" lactone. Synthesis of bislactone **106**

2.5.1. Synthetic precedents

In earlier investigations of our research group,⁶² the eastern lactone, which is a common structural feature of several *Stemona* alkaloids, was attempted to be installed through a

⁶² Blanco Merinero, P. *Ph.D. Thesis*, Universitat Autònoma de Barcelona, **2004**.

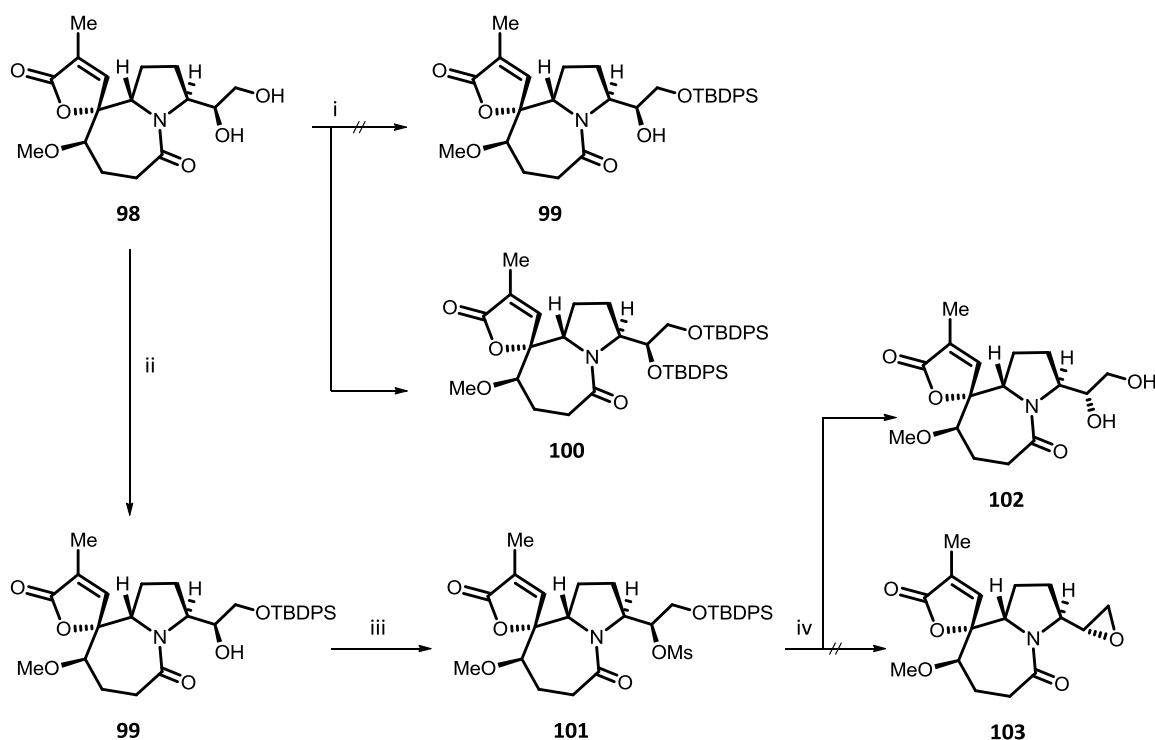
methodology formerly developed in our laboratories and based on a condensation reaction between an epoxide and an α -phenylselenoacetic acid (Scheme 31).⁶³ A main advantage of this method is that the stereochemical information in the precursor epoxide is retained in the lactone product. For this reason our first generation approach to stemonidine started from nitrone **47**, derived from D-glyceraldehyde, which contains an additional stereocenter in respect to nitrone **49**. This additional stereocenter corresponds to C₁₄ in the targeted alkaloid.



Scheme 31. Methodology assayed in a previous thesis to prepare γ -lactones from epoxides.⁶³

Hence, en route to stemonidine, the conversion of diol **98** into epoxide **103** was necessary (Scheme 32). A priori, the dehydration of similar glycols with inversion of configuration is an ordinary transformation requiring only the temporary protection of the primary alcohol before the activation of the secondary one. However, although many efforts were devoted to this endeavour, the transformation of diol **98** into the desired epoxide **103** proved fruitless. The attempted regioselective silylation of the primary alcohol was not achieved and the disilyl derivative **100** was obtained instead, along with unreacted starting material. This fact was attributed to the existence of an arrangement of intramolecular hydrogen bonding that made the secondary alcohol more reactive than the primary one. After extensive experimentation, the monoprotected alcohol **99** could finally be obtained through formation of an intermediate tin acetal, followed by regioselective opening and then silylation, although the overall yield was quite low (42%). In any case, the mesylation of the secondary alcohol in **99**, subsequent deprotection of the silyl protected hydroxyl group, and basic treatment, instead of the expected epoxide **103**, furnished diol **102**, epimer of **98**, presumably formed by rapid hydrolysis of the epoxide.

⁶³ (a) Figueredo, M.; Font, J.; Virgili, A. *Tetrahedron* **1987**, *43*, 1881-1886; (b) Busqué, F.; de March, P.; Figueredo, M.; Font, J.; Sanfeliu, E. *Tetrahedron Lett.* **2002**, *43*, 5583-5585; (c) Blanco, P.; Busqué, F.; de March, P.; Figueredo, M.; Font, L.; Sanfeliu, E. *Eur. J. Org. Chem.* **2004**, 48-53.

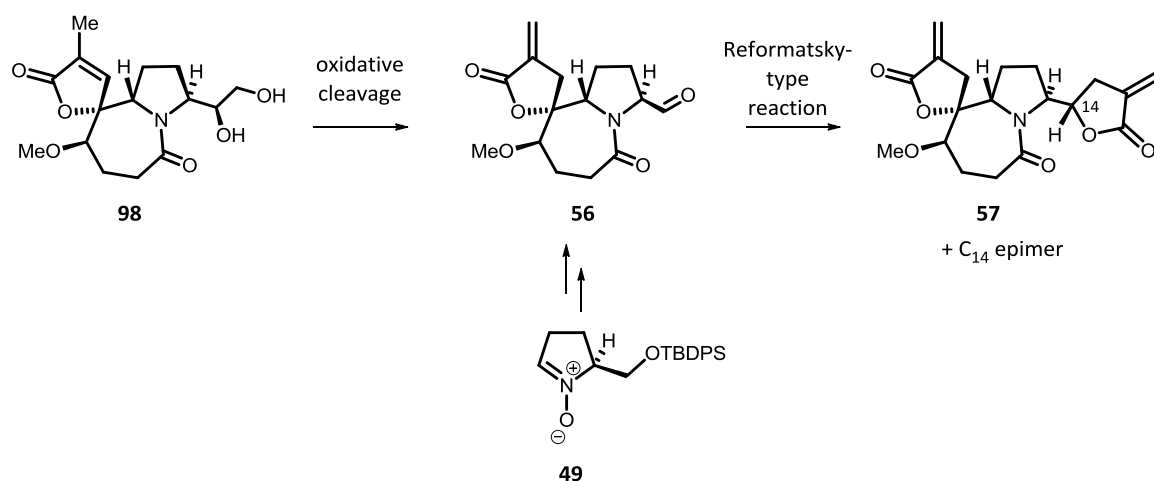


Reagents and conditions: (i) TBDPSOTf, Et₃N, CH₂Cl₂, r.t.; (ii) Bu₂SnO, MeOH, reflux, 2 h; then, TBABr, TBDPSIm, toluene, reflux, 16 h (42%); (iii) MsCl, pyr, CH₂Cl₂, r.t. (71%); (iv) TBAF, THF, r.t., 1 h; then, NaOH, MeOH/THF (88%).

Scheme 32. Attempted formation of epoxide **103**.

Other alternatives for the formation of the epoxide were also investigated, such as transforming the lactam to thiolactam, with the aim of affecting the hydrogen bonding array, and then applying the same previous set of reactions, or performing a Mitsunobu inversion of configuration of the secondary alcohol in **98**, taking advantage of its higher reactivity. Unfortunately, none of these tactical modifications ended up with the expected epoxide **103**.

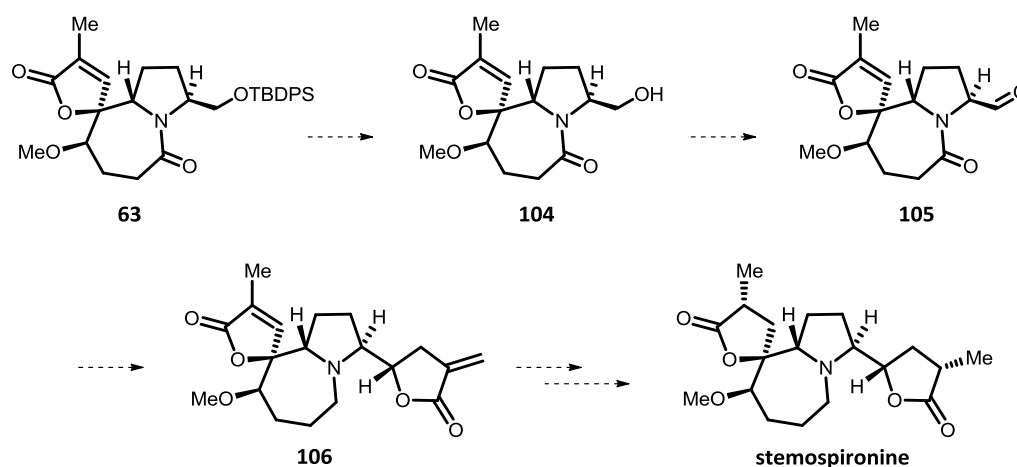
Once all the possibilities related to the epoxide formation were excluded, the oxidative cleavage of the glycol in **98** and then a Reformatsky-type reaction over the corresponding aldehyde **56** was considered the best option to construct the eastern lactone (Scheme 33). Obviously, the stereochemical information provided by the starting nitron **47** that was initially expected to be transferred into the east-side lactone through the corresponding epoxide is lost in that cleavage, but the preparation of diastereoisomers of the naturally occurring alkaloids is also interesting, both in terms of bioactivity tests and structural elucidation. Considering that the preparation of aldehyde **56**, or an analog of it, could be achieved starting from the simpler nitron **49**, and that the preparation of this nitron from L-proline is more straightforward than that of nitron **47** from D-glyceraldehyde, it was decided to continue the synthetic studies towards stemonidine and stemospironine from the former.



Scheme 33. Synthetic alternative for the construction of the east-side lactone **57** followed in the synthesis of the putative structure of stemonidine³⁸ and in the present thesis.

2.5.2. New strategy for the construction of the eastern lactone

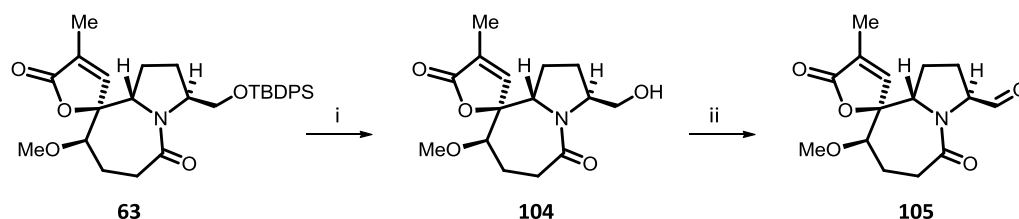
The remaining transformations to conclude the synthesis of (–)-stemospirone from lactone **63** are shown in Scheme 34. After removal of the silyl group, primary alcohol **104** would be oxidized to aldehyde **105**. Further treatment of **105** with Zn and ethyl bromomethylacrylate,⁵⁵ **61**, should provide bislactone **106** which, theoretically, after double bond and lactam reduction would render the targeted alkaloid.



Scheme 34. Planned synthesis of (–)-stemospirone.

The removal of the silyl group was accomplished by treatment of the intermediate **63** with Et₃N·3HF in THF at the reflux temperature, affording alcohol **104** in 92% yield (Scheme 35).

The deprotection of the primary alcohol was clearly evidenced in the $^1\text{H-NMR}$ spectrum of **104** by the absence of the TBDPS typical signals at the aromatic region and the singlet at around 1 ppm of the *tert*-butyl group.

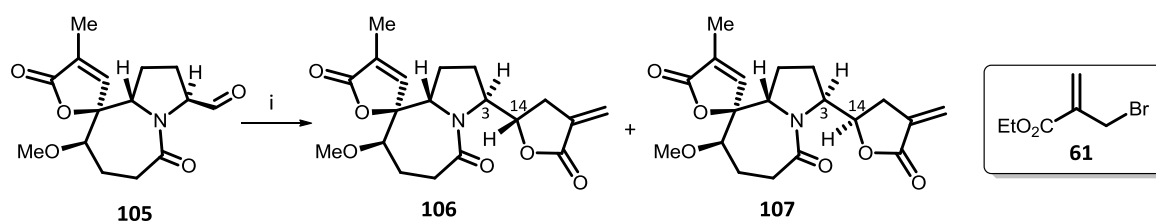


Reagents and conditions: (i) $\text{Et}_3\text{N}\cdot 3\text{HF}$, THF, reflux, 4 h (92%); (ii) Dess-Martin periodinane, CH_2Cl_2 , r.t., 2.3 h (82%).

Scheme 35. Syntheses of alcohol **104** and aldehyde **105**.

Further oxidation of alcohol **104** with Dess-Martin periodinane in CH_2Cl_2 furnished aldehyde **105** as a white solid in 82% yield, which should be the precursor of bislactone **106**. Its $^1\text{H-NMR}$ spectrum presented a doublet at 9.45 ppm, characteristic of the aldehyde functionality. This signal was consistent with that observed in the $^{13}\text{C-NMR}$ spectrum, where a signal corresponding to the new carbonyl group could be observed at 197.3 ppm.

Next, the aldehyde **105** was treated with ethyl bromomethylacrylate, **61**, and freshly activated Zn^{51} under Reformatsky conditions (Scheme 36).⁵⁵ After 1 h in THF at the reflux temperature, a roughly 1:1 mixture of bislactones **106** and **107** was obtained, which were separated by flash column chromatography.



Reagents and conditions: (i) **61**, Zn, THF, reflux, 1 h (74%) **106:107** 1:1.

Scheme 36. Reformatsky-type reaction for the preparation of bislactones **106** and **107**.

The relative *erythro*/*threo* configuration of **106** and **107** was tentatively assigned by NMR in comparison with related compounds in the literature^{17b,c,38,63b,c} and unambiguously established in a more advanced intermediate by means of an X-ray diffraction analysis and by chemical

correlation with the natural product stemospironine, as will be explained later on. The most significant NMR data of the couple of epimers **106** and **107** are summarized in Table 1.

Table 1. Some significant NMR chemical shift of bislactones **106** and **107**.

	δ H ₃ ^a	δ C ₃ ^b	δ H ₁₄ ^a	δ C ₁₄ ^b
106, threo	4.37	60.3	5.06	77.2
107, erythro	4.16	62.2	5.21	75.7

NMR experiments performed in CDCl₃, δ values in ppm. a) 400 MHz. b) 100 MHz.

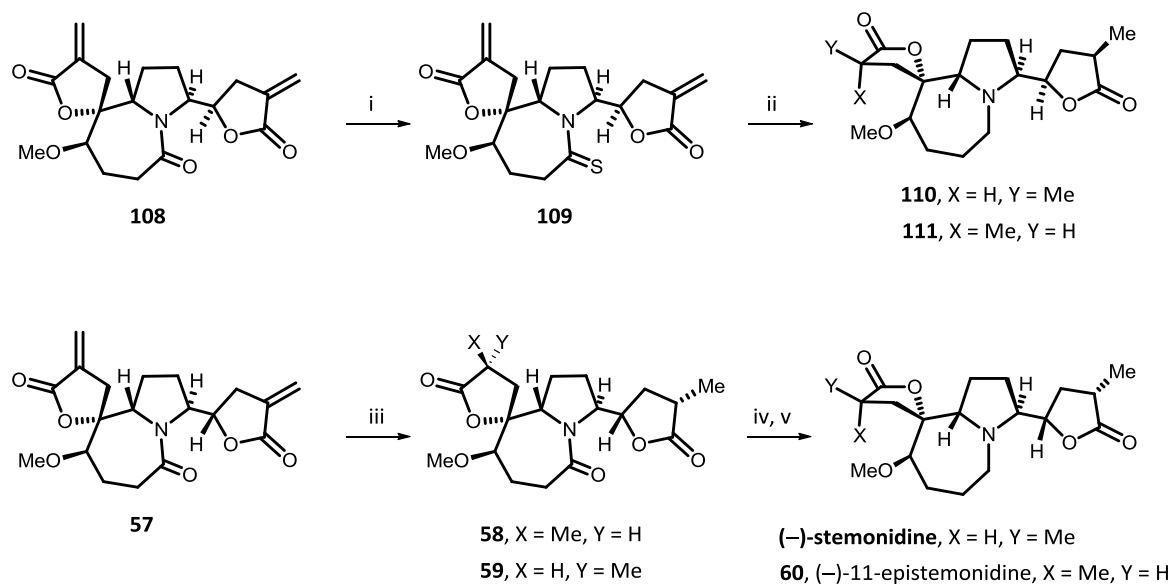
It can be observed that proton H₃ in the *erythro* isomer **107** (4.16 ppm) is upfield shifted in relation to the *threo* isomer **106** (4.37 ppm) and the same trend is observed for carbon C₁₄ (75.7 and 77.2 ppm, respectively), while the opposite occurs for H₁₄ (5.21 and 5.06 ppm, respectively) and C₃ (62.2 and 60.3 ppm, respectively). Moreover, two new olefinic signals appeared in the ¹H-NMR spectrum of each compound between 5.4 and 6.5 ppm, characteristic of the exocyclic double bond.

2.6. Syntheses of two new diastereoisomeric analogs of stemospironine

To complete the synthesis of (–)-stemospironine from the *threo* bislactone **106**, the reduction of the carbon-carbon double bond and lactam functionalities had to be accomplished.

In related compounds containing both a thiolactam and an α,β -unsaturated lactone, it was observed that overexposure to Raney-Ni resulted in desulfuration of the thiolactam and concomitant olefin reduction in one single step.^{38,64} In previous studies of our group towards the synthesis of stemonidine, this methodology was tested starting from the analogous *erythro* isomer **108** (Scheme 37). Thus, treatment of **108** with Lawesson's reagent furnished the expected unsaturated thiolactam **109**, which by reaction with Raney-Ni in EtOH delivered a mixture of amines **110** and **111**. Conversely, when the same procedure was applied to the *threo* bislactone **57**, the corresponding thiolactam underwent rapid decomposition. Accordingly, to complete the syntheses of stemonidine and its epimer at C₁₁, **60**, it became necessary to firstly hydrogenate the carbon-carbon double bonds in **57**, and then proceed to the formation of the derived thiolactams and their subsequent reduction by treatment with Raney-Ni.

⁶⁴ González, D. *Ph.D. Thesis*, Universitat Autònoma de Barcelona, **2009**.



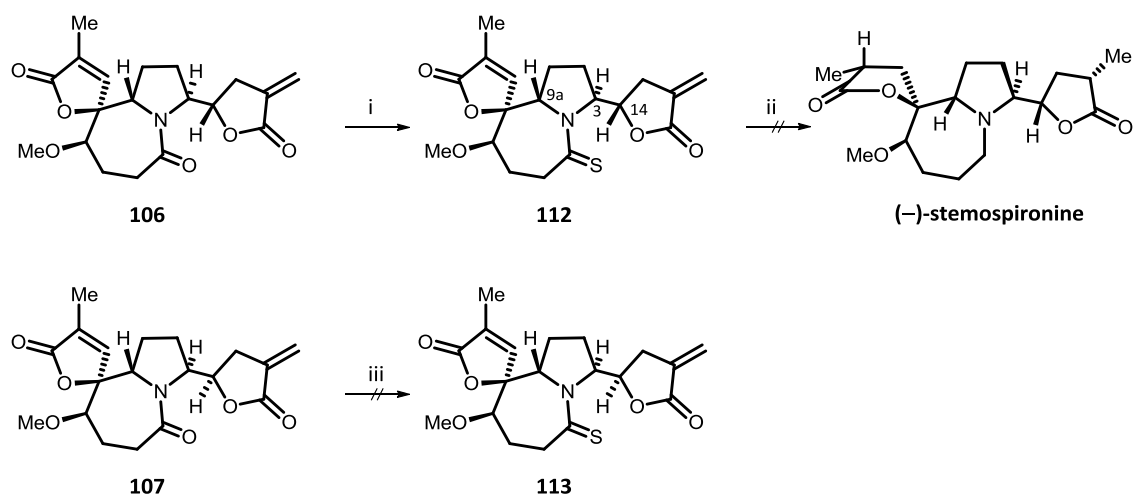
Reagents and conditions: (i) Lawesson's reagent, THF, reflux, 4.5 h; (ii) Raney-Ni, EtOH, reflux, 2 h (54%, 2 steps); (iii) H₂ (6 bar), Pd/C, EtOH:HCl (9:1), 23 h (68%); (iv) Lawesson's reagent, THF, reflux, 4h; (v) Raney-Ni, EtOH, reflux, 2 h (45%, 2 steps).

Scheme 37. Last steps in the syntheses of stemonidine and its analogs.³⁸

In the present work we decided also to explore the possibility of reducing the carbon-carbon double bonds and the thiolactam functionality in one single step (Scheme 38). Hence, lactams **106** and **107** were treated, separately, with Lawesson's reagent. In this case, in contrast to the behaviour of **108** and **57**, the *threo* thiolactam **112** was isolated, although in moderate yield (52%), whereas its *erythro* isomer **113** could not be obtained, rendering only decomposition products.

On the ¹H-NMR spectrum of **112**, the most significant change with respect to that of its precursor lactam was the downfield shifting experienced by H₁₄ from 5.06 ppm in **106** to 5.46 ppm **112**. The same happened with H_{9a}, that moved from 4.86 to 5.20 ppm, and with H₃, which moved from 4.37 to 5.09 ppm.

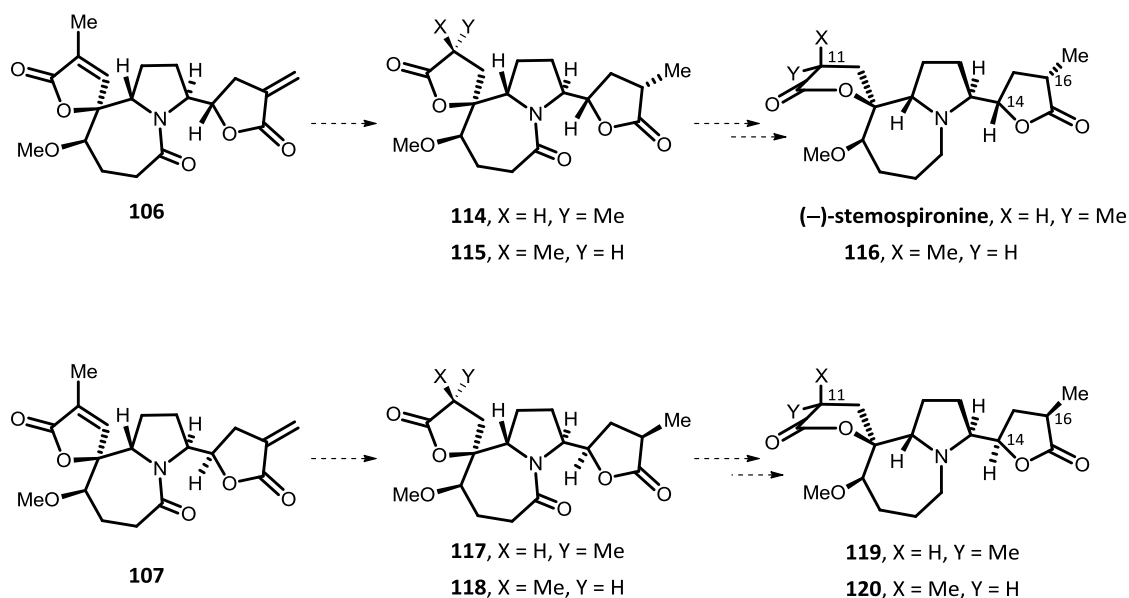
The hydrogenation of thiolactam **112** was attempted by treatment with Raney-Ni, but unfortunately it ended up with decomposition products.



Reagents and conditions: (i) Lawesson's reagent, THF, reflux, 45 min (52%); (ii) Raney-Ni, EtOH, reflux, (iii) Lawesson's reagent, THF, reflux.

Scheme 38. Attempts of reducing carbon-carbon double bonds and thiolactam functionality in one step.

Considering these results, we decided, for both isomers **106** and **107**, to perform the hydrogenation of the endo- and exocyclic olefins in the first place and then carry out the deoxygenation of the lactam. The devised plan is shown in Scheme 39.

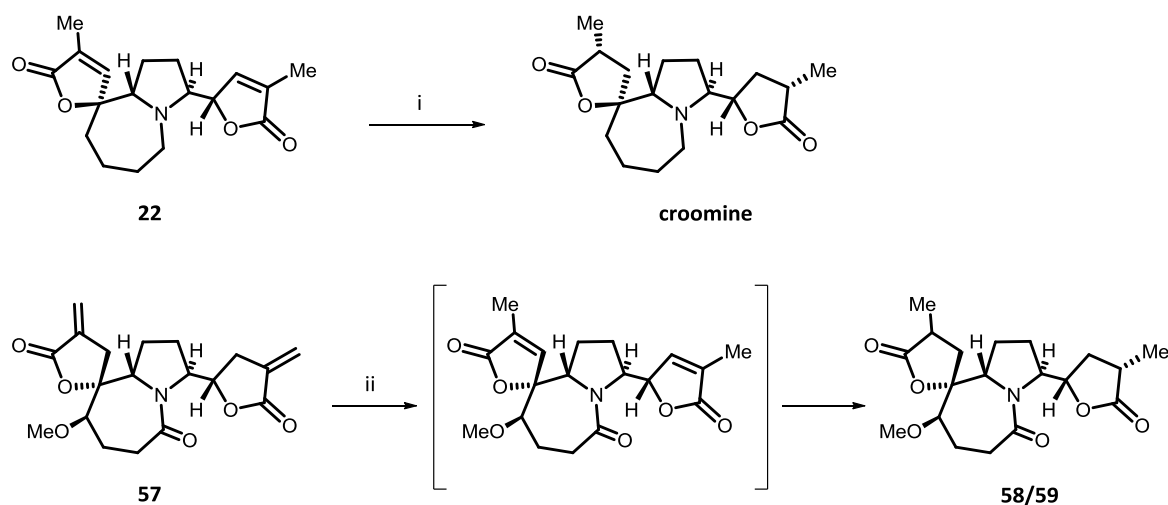


Scheme 39. Planned final steps for the syntheses of (-)-stemospirone and its analogs.

2.6.1. *Hydrogenation of the carbon-carbon double bonds of bislactones 106 and 107*

Thus, we proceeded to assay the simultaneous hydrogenation of both the endo- and exocyclic olefins. In this reaction, two new stereogenic centers are created at the α -carbonyl positions. The reduction was performed for both epimeric bislactones **106** and **107**, separately. Hence, in each hydrogenation process up to four stereoisomers could be obtained.

However, on the basis of bibliographic precedents (Scheme 40),^{17b,c,38} we expected that the hydrogenation of the eastern lactone would occur in a stereoselective manner through the less hindered face, leading to a *cis* relationship of the substituents of the ring. This trend was observed in precedent examples, even for substrates where the conjugated double bond was exocyclic. We assumed that in the acidic media in which the hydrogenation was performed, the migration of the exocyclic double bond to the endocyclic position would be faster than the reduction. On the contrary, for the spiranic lactone we assumed that the reduction could be unselective, rendering both C₁₁ epimers.



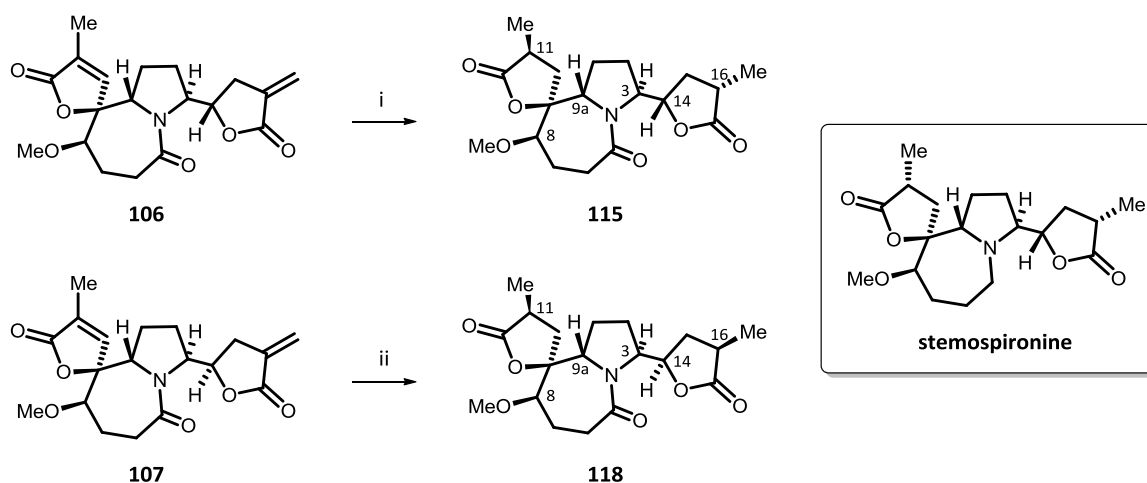
Reagents and conditions: (i) H₂, Pd/C, EtOH, HCl (81%); (ii) H₂, Pd/C, EtOH, HCl (68%).

Scheme 40. Catalytic hydrogenation of α,β -unsaturated furanones structurally related to our compounds.^{17c,38}

With these predictions in mind, from the hydrogenation of each substrate **106** and **107**, we were expecting the two isomers depicted on Scheme 39. Thus, **106** and **107** were submitted to hydrogenation at atmospheric pressure in the presence of Pd/C under standard conditions

2. RESULTS AND DISCUSSION

(Scheme 41).^{17b,c,38} To our surprise, these reactions delivered only one product from each bislactone in good yields.



Reagents and conditions: (i) H₂ (1 atm), Pd/C, EtOH:HCl 10% (1:1), 24 h (81%); (ii) H₂ (1 atm), Pd/C, EtOH:HCl 10% (1:1), 24 h (84%).

Scheme 41. Catalytic hydrogenation of bislactones **106** and **107**.

The hydrogenated *threo* derivative **115** presents on its ¹H-NMR spectrum (Figure 11) a double triplet at 5.21 ppm, a doublet of doublets at 4.75 ppm and a double triplet at 4.56, corresponding to H₁₄, H_{9a} and H₃, respectively. The most significant change with respect to the precursor **106** is the absence of the olefinic signals and the presence of two doublets at 1.29 and 1.25 ppm of the methyl groups instead. The ¹H-NMR spectrum of bislactone **118** (Figure 13) displays a doublet of doublets at 5.07 ppm, a doublet at 4.80 ppm and a doublet at 4.29, corresponding to H₁₄, H_{9a} and H₃, respectively, and the characteristic doublets of the methyl groups at 1.29 and 1.25 ppm.

The *cis* relationship between proton H₁₄ and H₁₆ in **115** and **118** was determined by n.O.e. experiments. Figure 11 shows the n.O.e. experiment for **115** when proton H₁₄ was irradiated, where we can see a remarkable effect at H₁₆, proving that H₁₄ and H₁₆ are *cis* to each other. Moreover, Figure 12 shows that the irradiation of H₈ in **115** resulted in a considerable n.O.e. on proton H₁₁. Hence, this experiment allowed to establish the proximity between H₈ and H₁₁, demonstrating that the configuration of the stereocenter at C₁₁ is the opposite for stemospirone, as depicted in Scheme 41 for **115**.

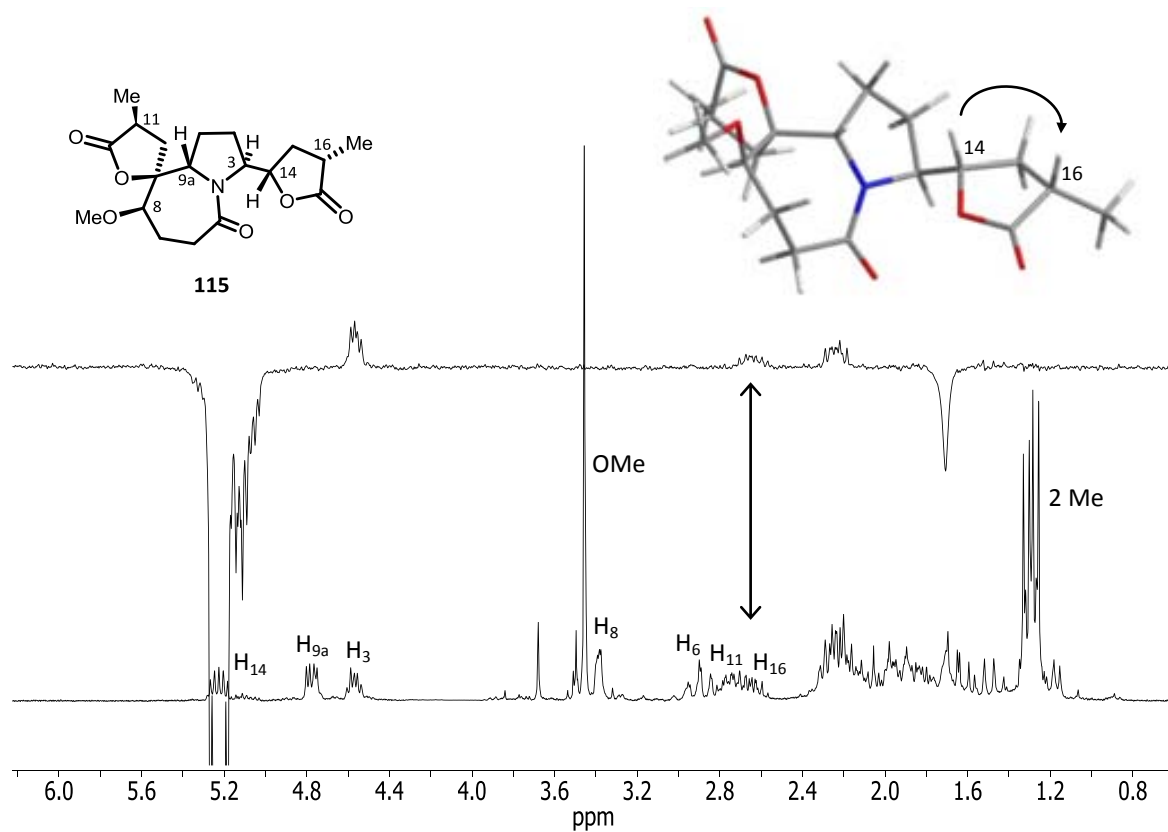


Figure 11. n.O.e. experiment (250 MHz, CDCl₃) on irradiating H₁₄ in **115**.

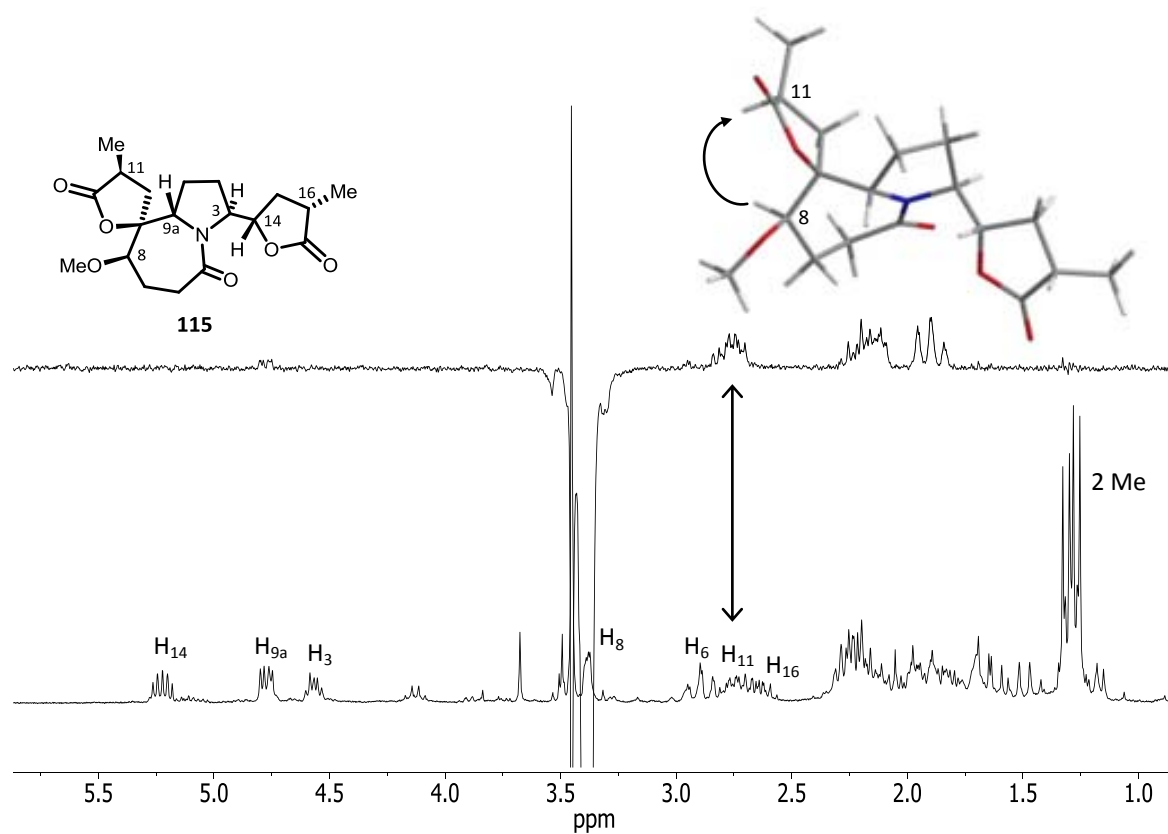


Figure 12. n.O.e. experiment (250 MHz, CDCl₃) on irradiating H₈ in **115**.

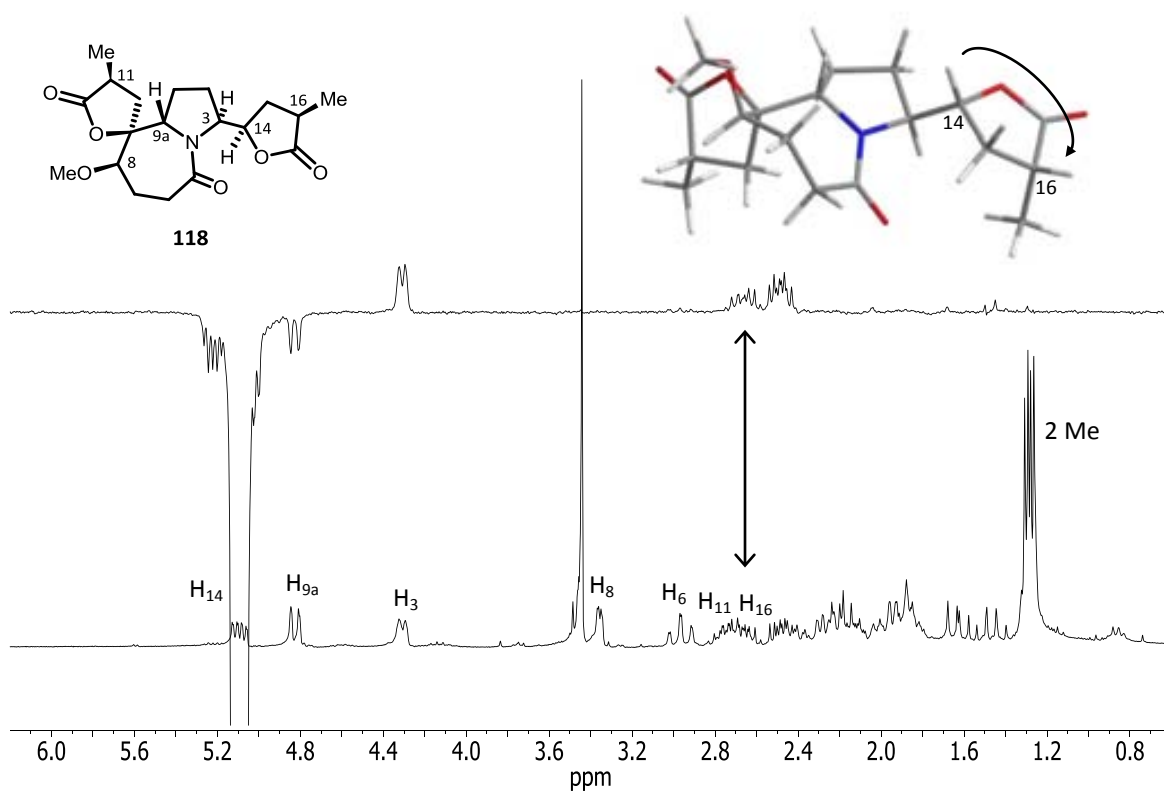


Figure 13. n.O.e. experiment (250 MHz, CDCl₃) on irradiating H₁₄ in **118**.

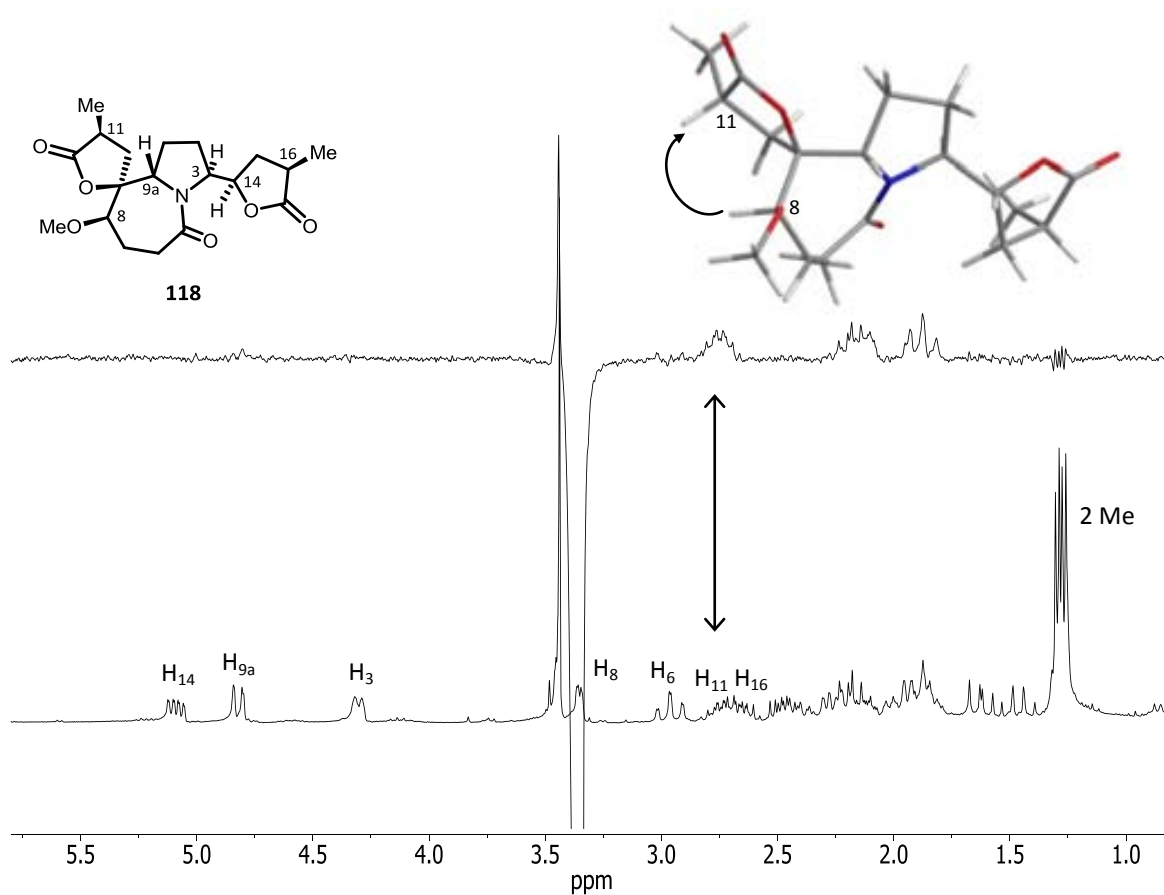
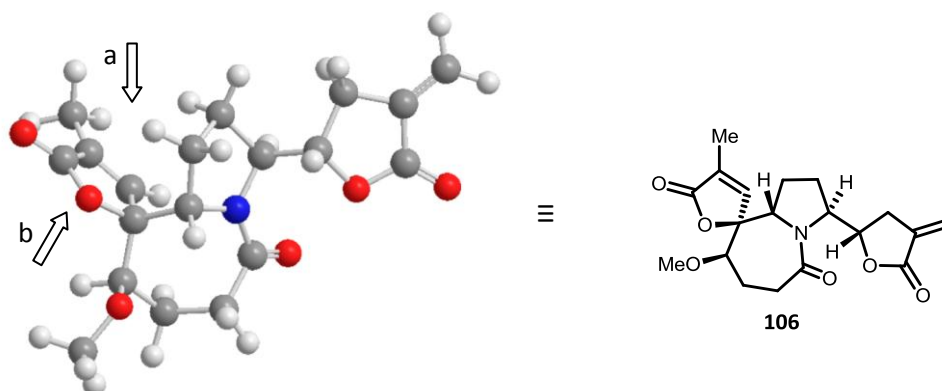


Figure 14. n.O.e. experiment (250 MHz, CDCl₃) on irradiating H₈ in **118**.

Parallel n.O.e. experiments were carried out for compound **118** too. When proton H₁₄ was irradiated, a n.O.e. could be observed on proton H₁₆ (Figure 13), proving again that H₁₄ and the methyl group at C₁₆ are *trans* to each other. Furthermore, irradiation of proton H₈ showed a n.O.e. on H₁₁, as we can observe in Figure 14, indicating that the configuration at C₁₁ in **118** is also contrary to that of the natural alkaloid.

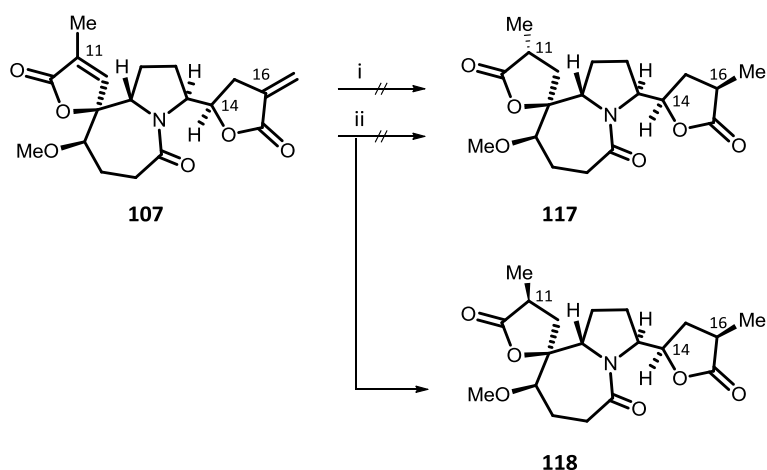
For both bislactones **115** and **118**, the configuration at C₁₆ was consistent with the expected approach of the hydrogen by the less hindered face of the east-side lactone. On the other hand, a rational explanation of the configuration at C₁₁ may be found by observation of simple tridimensional molecular models of bislactone **106** (Figure 15) or **107**. It can be observed that the pyrrolidine ring obstructs one of the faces of the spiranic lactone forcing the hydrogen attack by the other side.



a) more hindered face; b) more accessible face.

Figure 15. Molecular model of bislactone **106** (ChemBio3D Ultra 12.0).

In view of these results, we decided to assay alternative methodologies to reduce the C-C double bonds in **106** and **107** in order to get the opposite *R* configuration at C₁₁. The new protocols were tested with the *erythro* isomer **107**, which cannot generate the natural stemosponine. The reduction through hydride conjugate addition to the α,β -unsaturated lactones was explored with two different sets of reagents and conditions (Scheme 42).



Reagents and conditions: (i) Ph_2SiH_2 , $\text{Pd}(\text{PPh}_3)_4$, ZnCl_2 , CHCl_3 , r.t.; (ii) NiCl_2 , NaBH_4 , MeOH , H_2O , r.t.

Scheme 42. Attempts of preparing lactam **117** from **107**.

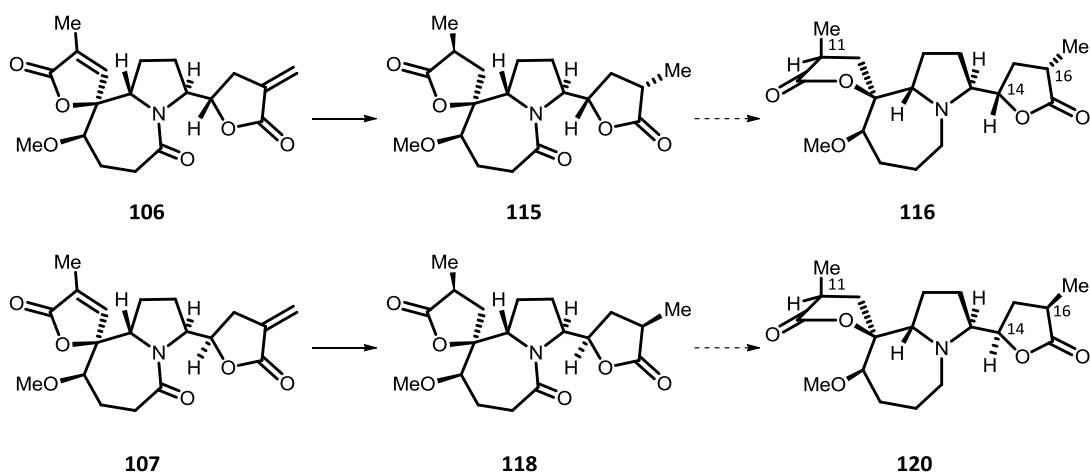
Firstly, bislactone **107** was treated with a three-component reducing mixture, which comprised $\text{Pd}(\text{PPh}_3)_4$ as catalyst, diphenylsilane as hydride donor and zinc chloride.⁶⁵ From this experiment, we were not able to isolate or identify any reaction products. Then, we decided to test the methodology described by Khurana and Sharma.⁶⁶ Thus, compound **107** was treated with NaBH_4 and NiCl_2 , to generate nickel boride in situ as the reducing species. In this trial, the reaction rendered again **118** as the only product and the C_{11} epimer of **118** was not detected.

2.6.2. Reduction of the lactam functionality in **115** and **118**

In view of the previous results, we decided to continue with the deoxygenation of the lactam present in bislactones **115** and **118**, as depicted in Scheme 43. These reactions would provide two new diastereoisomeric analogs of the natural alkaloid stemospironine and, besides, experience in this last reductive transformation would be acquired. On the other hand, considering the high and continuously increasing number of *Stemona* alkaloids isolated from natural sources and the subtle structural differences between some of them, we considered of special interest to achieve the corresponding amines **116** and **120**, although up to the moment none of them have been isolated as natural alkaloids.

⁶⁵ Keinan, E.; Greenspoon, N. *J. Am. Chem. Soc.* **1986**, *108*, 7314-7325.

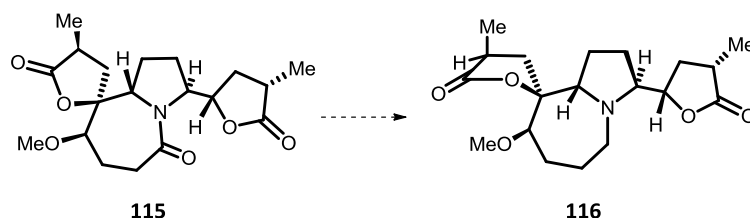
⁶⁶ Khurana, J.M.; Sharma, P. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 549-552.



Scheme 43. Synthetic plan for the construction of amines **116** and **120**.

We first studied the direct reduction of the lactam functionality to amine for both compounds **115** and **118**. The use of borane to selectively reduce a lactam without affecting the ester moiety has been documented in the literature,^{67,68} and it is also known that AlH_3 is able to reduce lactams much faster than esters.^{68,69} Hence, we submitted bislactones **115** and **118** to treatment with these reagents under different conditions, as it is shown in Table 2.

Table 2. Attempted direct reduction of lactam **115** to amine **116**.



Entry ^a	Reductive agent	Temp.	time	115:116 ^c
1	$\text{BH}_3 \cdot \text{THF}$	0 °C	3.5 h	1: -
2	$\text{BH}_3 \cdot \text{THF}$	r.t.	48 h	2.6:1
3	$\text{BH}_3 \cdot \text{THF}$	reflux	0.8 h	-
4	AlH_3 ^b	0 °C	10 min	1: -

a) All reactions were performed in dry THF. b) AlH_3 was freshly prepared from LiAlH_4 and AlCl_3 .⁷⁰ c) The crude reaction material was not purified. The ratio was determined by $^1\text{H-NMR}$.

⁶⁷ (a) Kling, A.; Backfish, G.; Delzer, J.; Geneste, H.; Graef, C. Hornberger, W.; Lange, U. E. W.; Lauterbach, A.; Seitz, W.; Subkowski, T. *Bioorg. Med. Chem.* **2003**, *11*, 1319-1341; ; (b) Garrido, N. M.; Sánchez, M. R.; Díez, D.; Sanz, F.; Urones, J. G. *Tetrahedron: Assymetry* **2011**, 872-880; (c) Dupont, C.; Guénard, D.; Tchertanov, L.; Thoret, S.; Guéritte, F. *Bioorg. Med. Chem.* **1999**, *7*, 2961-2969.

⁶⁸ González-Gálvez, D.; García-García, E.; Alibés, R.; Bayón, P.; de March, P.; Figueredo, M.; Font, J. *J. Org. Chem.* **2009**, *74*, 6199-6211.

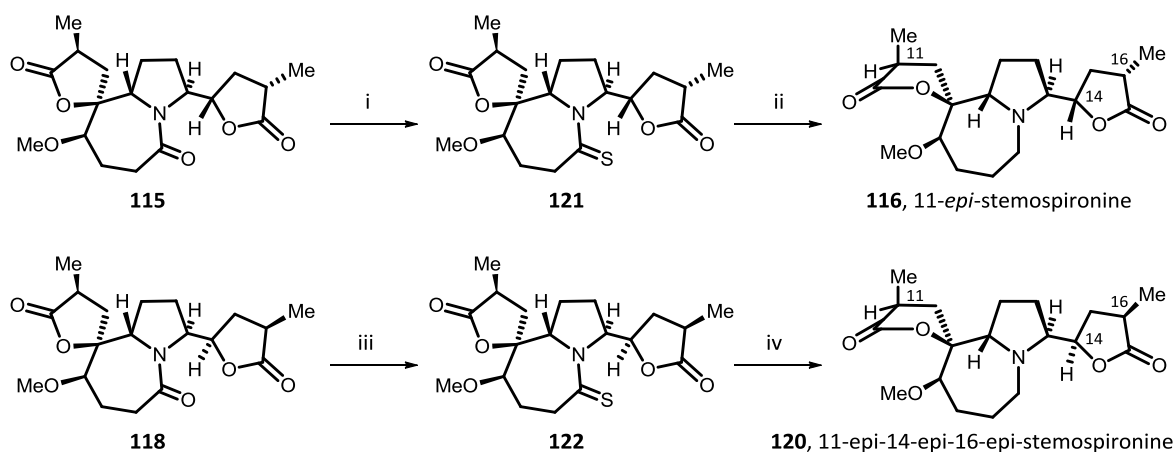
⁶⁹ Brown, H. C.; Yoon, N. M. *J. Am. Soc. Chem.* **1966**, *88*, 1464-1472.

⁷⁰ Giraud, L.; Huber, V.; Jenny, T. *Tetrahedron* **1998**, *54*, 11899-11906.

When the *threo* isomer **115** was treated with the complex $\text{BH}_3\cdot\text{THF}$ at $0\text{ }^\circ\text{C}$ (entry 1), there was no reaction, but we could observe the signals of the amine **116** in the $^1\text{H-NMR}$ spectrum of the crude material when the reduction was performed at room temperature (entry 2). Nevertheless, after 48 h most of the starting material remained unchanged. Unfortunately, when the reaction was run in THF at the reflux temperature (entry 3) we ended up with decomposition products. When AlH_3 was used as reducing agent at $0\text{ }^\circ\text{C}$ for 10 min (entry 4), we could only observe the presence of the starting lactam **115**.

For the *erythro* isomer **118**, we were not able to identify the expected amine **120** in any of the reactions assayed in the conditions that were used for the attempted reduction of **115**.

After these failed tests, we decided to reduce the lactam functionality in two steps, through the intermediate thiolactam, as shown in Scheme 44.



Reagents and conditions: (i) Lawesson's reagent, THF, reflux, 45 min; (ii) Raney-Ni, EtOH, reflux, 1 h (51% yield, 2 steps); (iii) Lawesson's reagent, THF, reflux, 45 min (72% yield); (iv) Raney-Ni, EtOH, reflux, 1 h (71% yield).

Scheme 44. Syntheses of amines **116** and **120**.

This protocol was first tested starting from the *erythro* isomer **118**. Accordingly, bislactone **118** was treated with Lawesson's reagent in THF at the reflux temperature to afford the corresponding thiolactam **122** in 72% yield. It is important to mention that the use of neutral Al_2O_3 for the flash chromatographic purification substantially reduced the impurities associated to the use of the Lawesson's reagent. On the $^1\text{H-NMR}$ spectrum of **122** (Figure 16), the most significant change with respect to that of the precursor was the downfield shifting experienced by H_{14} from 5.07 ppm in **118** to 5.52 ppm in **122**. H_{9a} was also shifted from 4.80 ppm to 5.11 ppm, and H_3 from 4.29 ppm to 4.96 ppm.

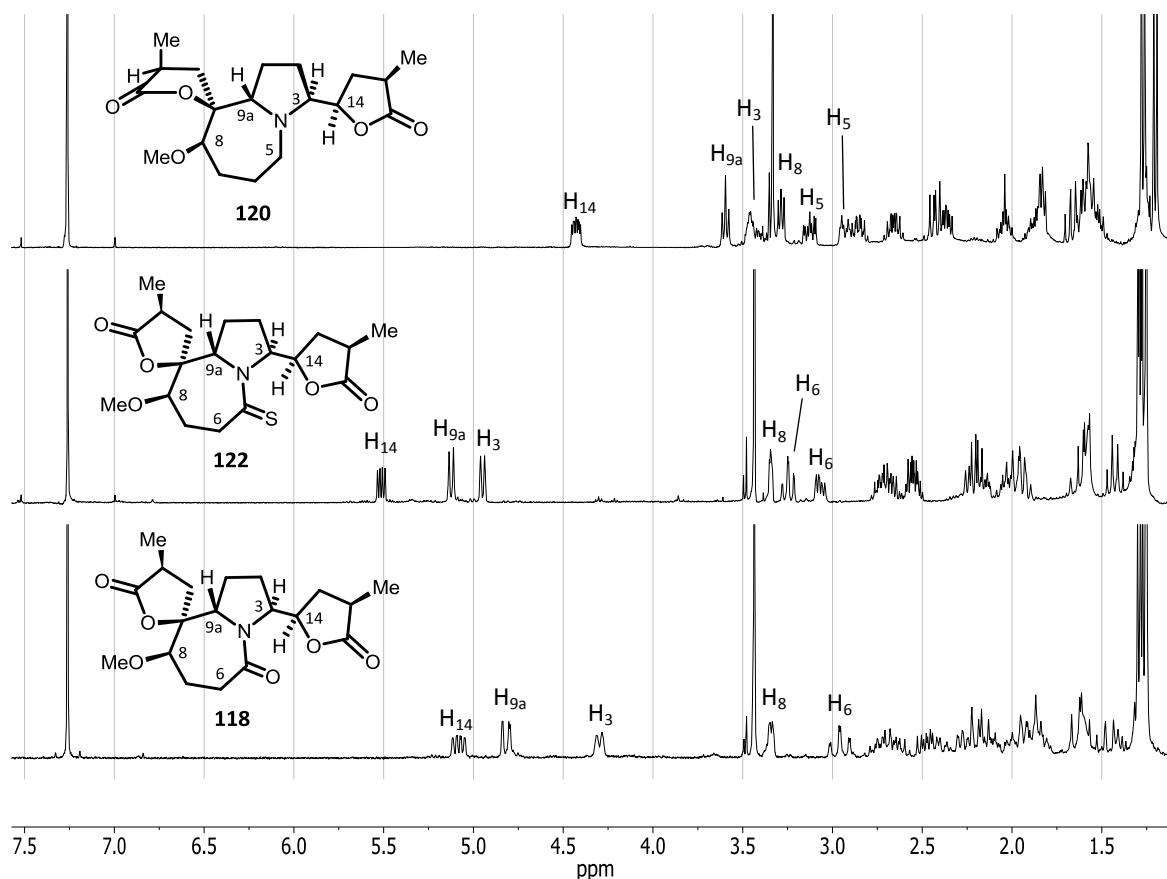


Figure 16. Comparison of the ^1H -NMR spectra (400 MHz, CDCl_3) of lactam **118**, thiolactam **122** and 11-*epi*-14-*epi*-16-*epi*-stemospiroline, **120**.

Fortunately, we could analyse the structure of this thiolactam by X-ray crystallography, which confirmed the structural assignment of this compound and, consequently, of all the other intermediates involved in the synthesis (Figure 17).

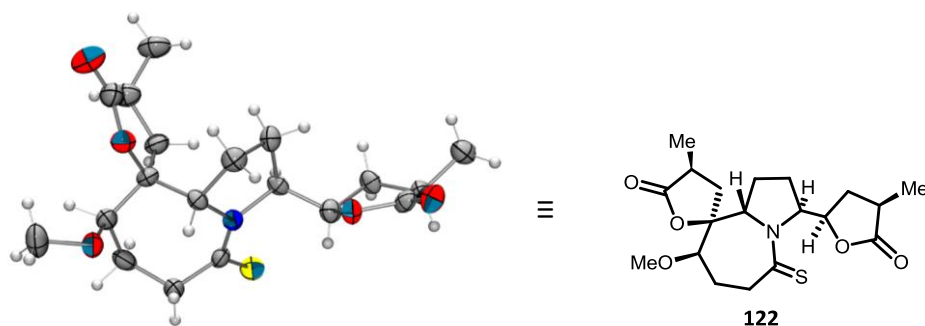


Figure 17. Crystal structure of thiolactam **122**.

2. RESULTS AND DISCUSSION

Further treatment of **122** with Raney-Ni in EtOH at the reflux temperature afforded exclusively amine **120**, namely 11-*epi*-14-*epi*-16-*epi*-stemospironine, in 71% yield, with an optical rotation $[\alpha]_D^{20} = -30.3$ (c 0.45, CHCl_3). Thus, we achieved this analog in 15 steps starting from nitron **49** and 3.3% overall yield.

We can clearly see on its $^1\text{H-NMR}$ spectrum (Figure 16) that the chemical shift of protons H_{14} , H_{9a} and H_3 experienced a considerable shielding due to the reduction of the thiolactam functionality.

On the other hand, bislactone **115** was also treated with Lawesson's reagent in THF at the reflux temperature to yield the thiolactam **121** (Scheme 44). In this case, the intermediate thiolactam was not purified, the crude material was simply filtered through Al_2O_3 and directly submitted to reduction with Raney-Ni. Thus, we obtained 11-*epi*-stemospironine, **116**, in 51% yield for the two steps, with an optical rotation $[\alpha]_D^{20} = -20.3$ (c 0.41, CHCl_3). Hence, this analog was prepared in 15 steps starting from nitron **49** and 3.0% overall yield.

The most significant difference between the $^1\text{H-NMR}$ spectra of **116** (Figure 18) and **120** is the chemical shift of proton H_{14} (4.24 ppm and 4.42 ppm for **116** and **120**, respectively). Hence, with this synthetic route we achieved two new diastereoisomeric analogs of the natural alkaloid (–)-stemospironine.

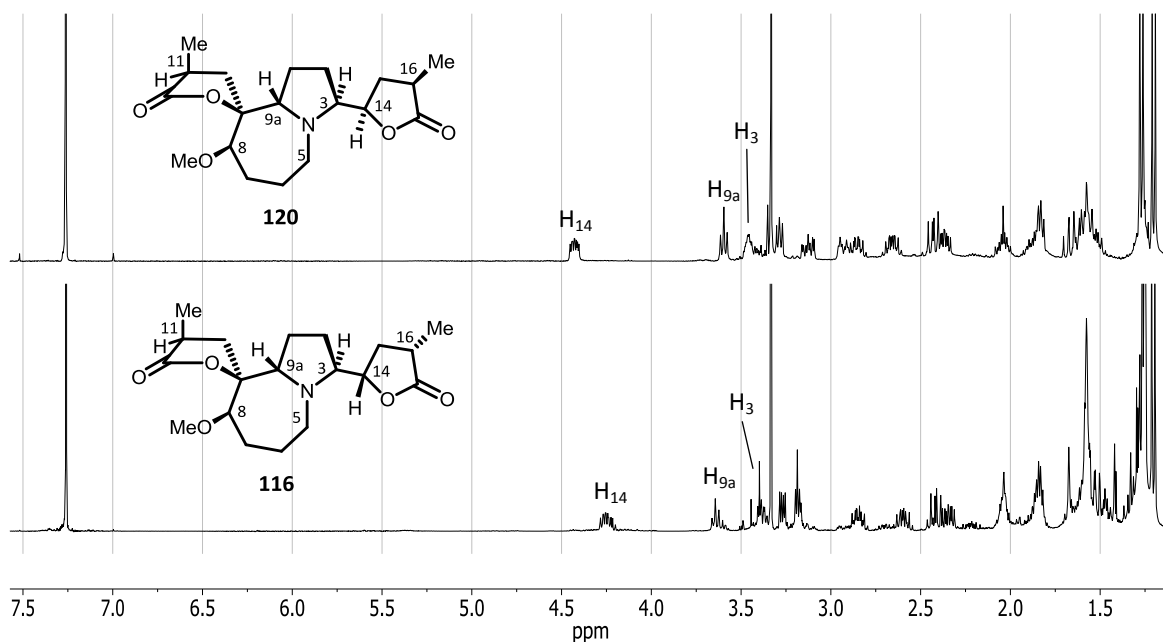
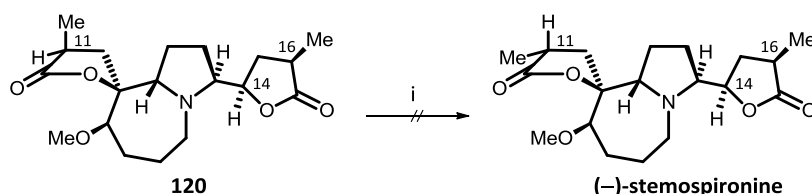


Figure 18. Comparison of the $^1\text{H-NMR}$ spectra (400 MHz, CDCl_3) of 11-*epi*-stemospironine, **116** and 11-*epi*-14-*epi*-16-*epi*-stemospironine, **120**.

2.6.3. *Attempt to epimerize 11-epi-stemospironine, 120*

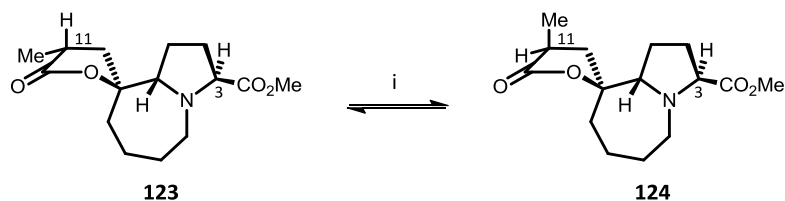
Considering that **120** is an epimer of (–)-stemospironine at an α -carbonyl position (C_{11}), we thought it could be worthy to try if base-promoted epimerization of **120** furnished the natural product (Scheme 45).



Reagents and conditions: (i) MeONa, MeOH, r.t.

Scheme 45. Attempted epimerization of **120**.

Epimerization of C_{11} was attempted by using MeONa in MeOH, but the starting material was recovered as a sole product. This fact was consistent with the results obtained by Martin and co-workers with a structurally related compound, which was an intermediate in their synthesis of (+)-croomine.^{17c} In their work, they made a separate study to epimerize **124** to **123** (Scheme 46). In this study, a (2:1) mixture of **123** and **124** was treated with methanolic MeONa and they obtained a (1:2) mixture of diastereoisomers in which **124** was the major product. No epimerization of C_3 was observed and, hence, they concluded that the unnatural configuration at C_{11} in these tricyclic compounds was the thermodynamically preferred.



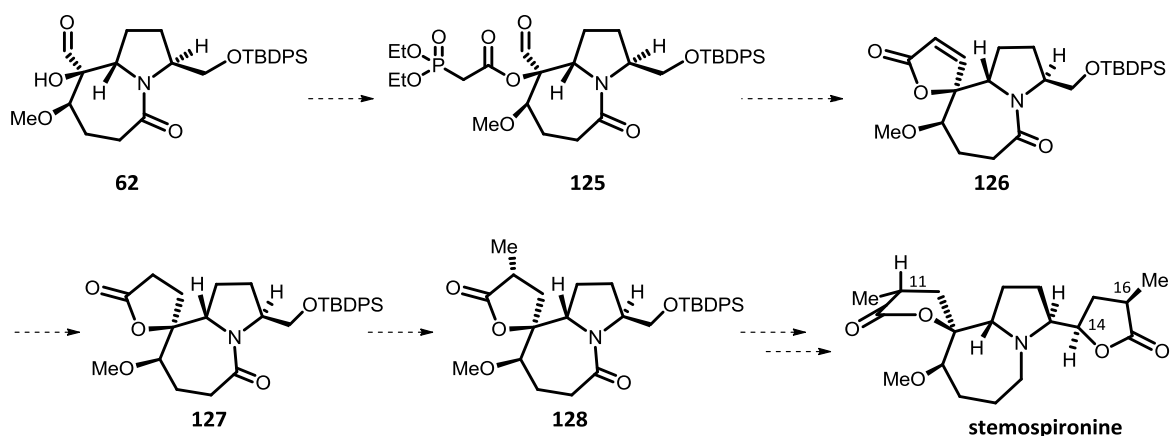
Reagents and conditions: (i) MeONa, MeOH, r.t.

Scheme 46. Epimerization study carried out by Martin and co-workers.^{17c}

2.7. New approach to the synthesis of (-)-stemospironine

In view of the high diastereoselectivity accomplished in the reduction of the C₁₀-C₁₁ double bond in intermediates **106** and **107** by the less hindered face, we reasoned that the methylation of an enolate formed by deprotonation of C₁₁ of an intermediate lacking the methyl group should occur with the same facial selectivity, leading to the correct stemospironine-like configuration.

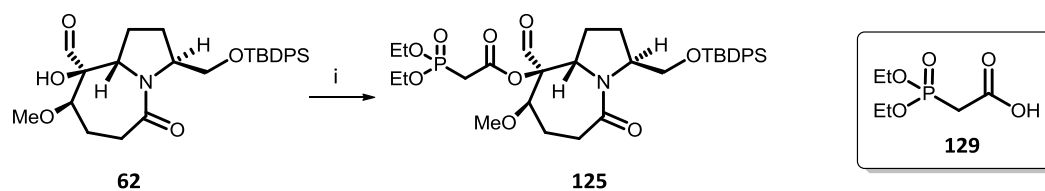
To test this hypothesis, we decided to undertake the sequence depicted in Scheme 47. The spirocyclization of hydroxyaldehyde **62** by treatment with diethoxyphosphorylacetic acid should render **126**. After hydrogenation of the double bond and then methylation we should presumably obtain the west-side lactone with the correct configuration at C₁₁. The following transformations to achieve the alkaloid would be the same as in the previous syntheses of the two diastereoisomeric analogs **116** and **120**.



Scheme 47. Proposed new route for the synthesis of (-)-stemospironine.

2.7.1. Construction of the spiranic lactone. Synthesis of **126**

The synthesis of the ester **125** was performed in the same way as that of ester **86**.⁶¹ Thus, a solution of the commercially available acid **129** was added to a solution of aldehyde **62**, and then DCC was slowly added (Scheme 48). After 1.5 h, ester **125** was obtained in 79% yield. On its ¹H-NMR spectrum one can clearly see the characteristic aldehyde signal at 9.56 ppm and the α -phosphoryl protons at 3.10 ppm, which appear as a doublet of doublets with a coupling constant of 22 Hz with the phosphorus atom and a geminal coupling of 14 Hz (Figure 19).



Reagents and conditions: (i) **129**, 1 M in CH_2Cl_2 , DCC 1 M, CH_2Cl_2 , r.t., 1.5 h (79%).

Scheme 48. Construction of phosphoryl acetate **125**.

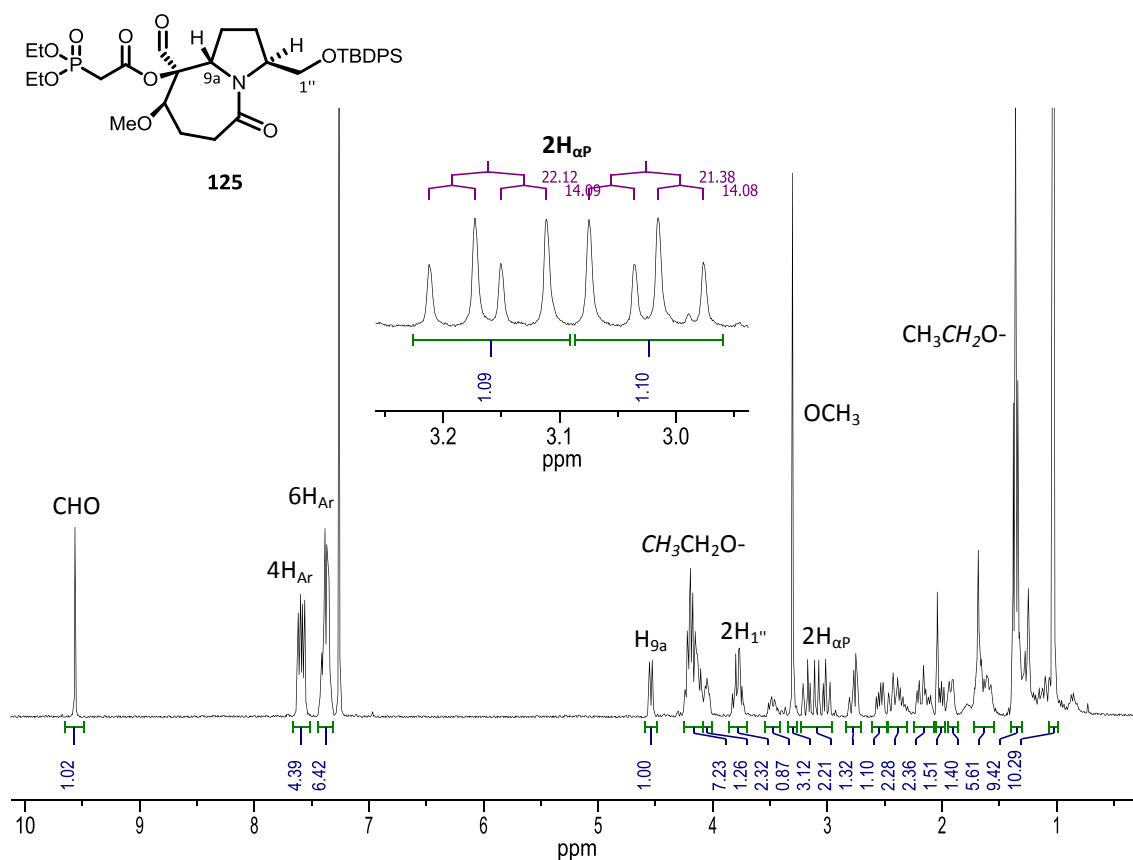
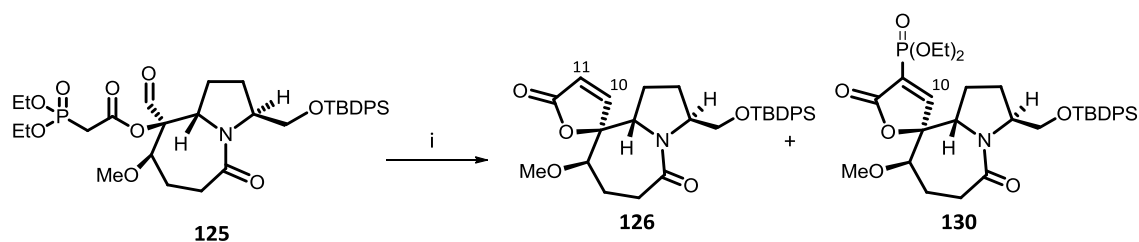


Figure 19. ^1H -NMR spectrum (250 MHz, CDCl_3) of compound **125**.

Then, compound **125** was treated with $t\text{BuOK}$ (Scheme 49). This reaction delivered the expected lactone **126**, along with another product that, after a thorough analysis of its spectroscopic data, was identified as the phosphonate **130**, which was obtained via a competitive Knoevenagel reaction.



Reagents and conditions: (i) t BuOK, THF, r.t., 15 min (29% for **126**, 41% for **130**).

Scheme 49. Construction of the west-side lactone.

The $^1\text{H-NMR}$ spectrum of **126** shows a doublet at 6.27 ppm corresponding to proton H_{11} , while the other olefinic proton H_{10} is hidden under the aromatic signals of the TBDPS group, at 7.38 ppm. For compound **130**, the most characteristic signal is the doublet at 7.92 ppm for proton H_{10} , which has a coupling constant of 9.8 Hz with the phosphorus atom.

This competitive Knoevenagel reaction has been described in the literature in a similar process and the authors affirm that the choice of the base for the intramolecular Horner-Wadsworth-Emmons (HWE) reaction proved to be critical.⁷¹ Thus, we decided to test different reaction conditions in order to avoid this competitive pattern (Table 3).

Table 3. Base-promoted cyclization of **125**.

Entry	Base	Solvent	Temp.	time	126:130 ^a
1	t BuOK	THF	-20 °C	30 min	1:1
2	t BuOK	THF	r.t.	15 min	1:1.4
3	t BuOK	THF	reflux	15 min	-
4	t BuOK	toluene	reflux	15 min	-
5 ^{71,72}	K_2CO_3 , 18-crown-6	THF	r.t.	30 min	1:23
6 ⁷³	NaH	THF	r.t.	15 min	1:5
7 ⁷¹	LiOH	THF	-20 °C	15 min	1:2
8 ^{72b,74}	NEt_3 , LiBr	THF	r.t.	1 h	1:2.5

a) The crude reaction material was not purified. The conversion is, in all cases, 100%. The ratio and conversion were determined by $^1\text{H-NMR}$.

⁷¹ Yan, B.; Spilling, C. D. *J. Org. Chem.* **2008**, *73*, 5385-5396.

⁷² (a) Carson, C. A.; Kerr, M. A. *Angew. Chem. Int. Ed.* **2006**, *45*, 6560-6563; (b) Krawczyk, E.; Koprowski, M.; Luczak, J. *Tetrahedron: Asymmetry* **2007**, *18*, 1780-1787.

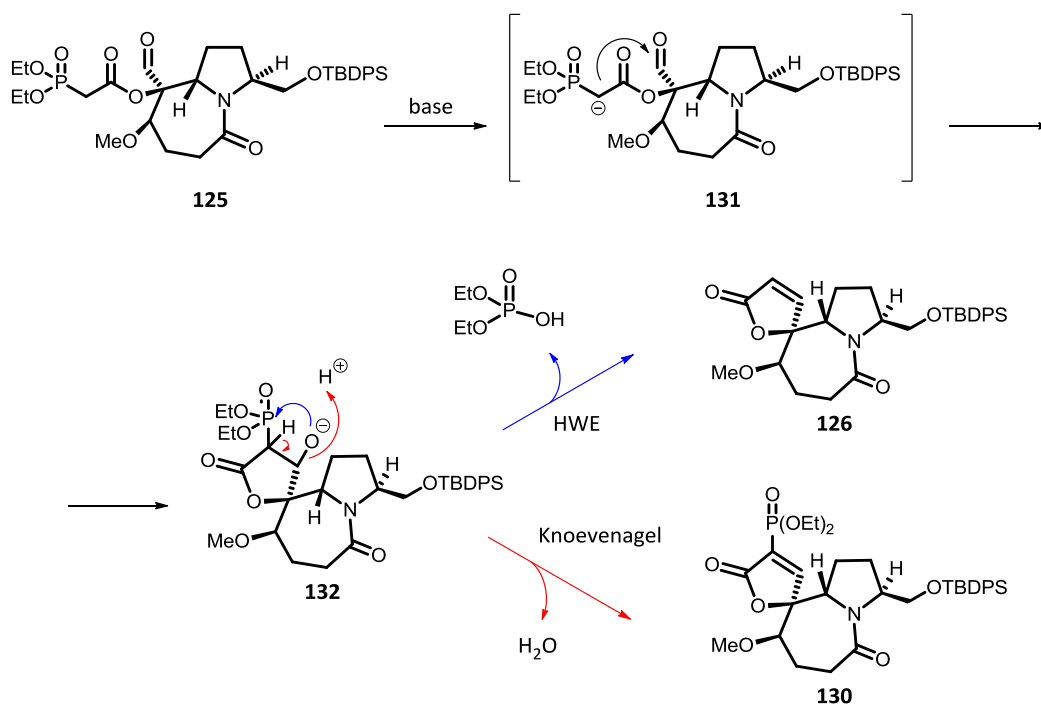
⁷³ Medeiros, M. R.; Wood, J. L. *Tetrahedron* **2010**, *66*, 4701-4709.

⁷⁴ Leduc, A. B.; Kerr, M.A. *Angew. Chem. Int. Ed.* **2008**, *47*, 7945-7948.

It is noteworthy that we performed preliminary qualitative experiments and after we found the best conditions, the reaction products were isolated and the respective yields determined.

The initial experiments (entries 1-4) were performed with $t\text{BuOK}$, according to the conditions previously and successfully applied to the HWE cyclization of the methyl analog **86**. Although the conditions of entry 1 afforded a more favourable 1:1 mixture of **126** and **130**, those of entry 2 rendered more reproducible results and were considered the best conditions within this series of trials with $t\text{BuOK}$. According to the literature,⁷¹ the desired HWE reaction appeared to be favoured by the use of K_2CO_3 in the presence of 18-crown-6. However, in our case the opposite trend was observed (entry 5). This combination of reagents furnished a 23:1 mixture, where **130** was the major component. Other bases such as NaH (entry 6), LiOH (entry 7) and NEt_3 (entry 8) were also tested, but in all cases the competitive Knoevenagel reaction was the preferred pathway. It is noteworthy that the ratio **126**:**130** was determined by the relative area of the signal corresponding to proton H_{11} for lactone **126** and proton H_{10} for phosphonate **130** in the $^1\text{H-NMR}$ spectrum of the crude reaction material. Considering all the tested reactions, entry 2 was the most reproducible and cleaner, and hence these conditions were considered those of choice (Scheme 49), affording **126** and **130** in 29% and 41% yield, respectively.

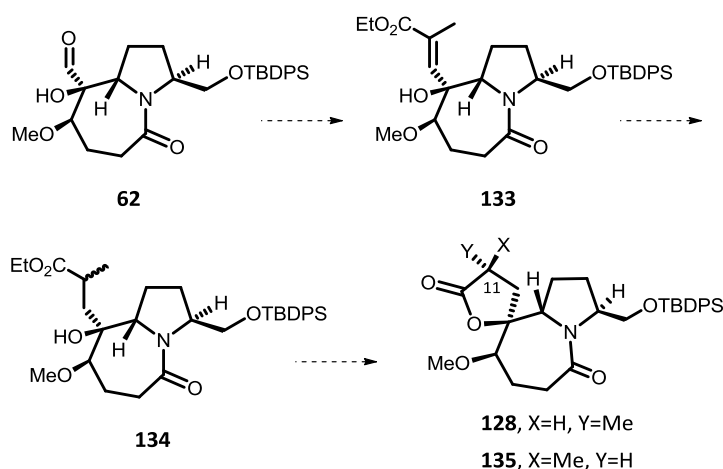
The mechanism of the two competitive reactions is shown in Scheme 50.



Scheme 50. Mechanism of the HWE and the competitive Knoevenagel reaction.⁷¹

Since this side reaction could not be inhibited, we tried to develop other synthetic transformations in order to obtain lactone **126** as the major product. Two alternative methodologies were considered. The first one was based on an intermolecular HWE reaction, and the second in an intramolecular ring closing metathesis as the key steps.

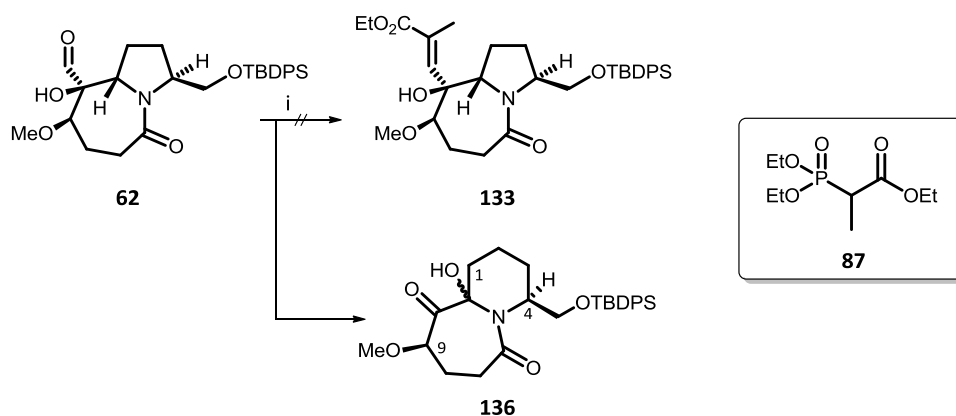
The plan for preparing the spiranic lactone through an intermolecular HWE reaction is shown in Scheme 51. After the HWE, the subsequent hydrogenation may generate two epimeric esters which, upon acyl transfer would render the corresponding epimeric lactones **128** and/or **135**, with **128** having the appropriate configuration at C₁₁ for stemospirone.



Scheme 51. Proposed transformations for the construction of the spiranic lactone.

According to the plan, aldehyde **62** was submitted to the intermolecular HWE olefination by reaction with ethyl 2-(diethoxyphosphoryl)propanoate, **87**, using ^tBuOK as base (Scheme 52). In some reported examples, a similar intermolecular reaction was performed over substrates containing a free hydroxyl group,⁷⁵ that is why the reaction was attempted directly on the hydroxyaldehyde **62** without any protection of the alcohol.

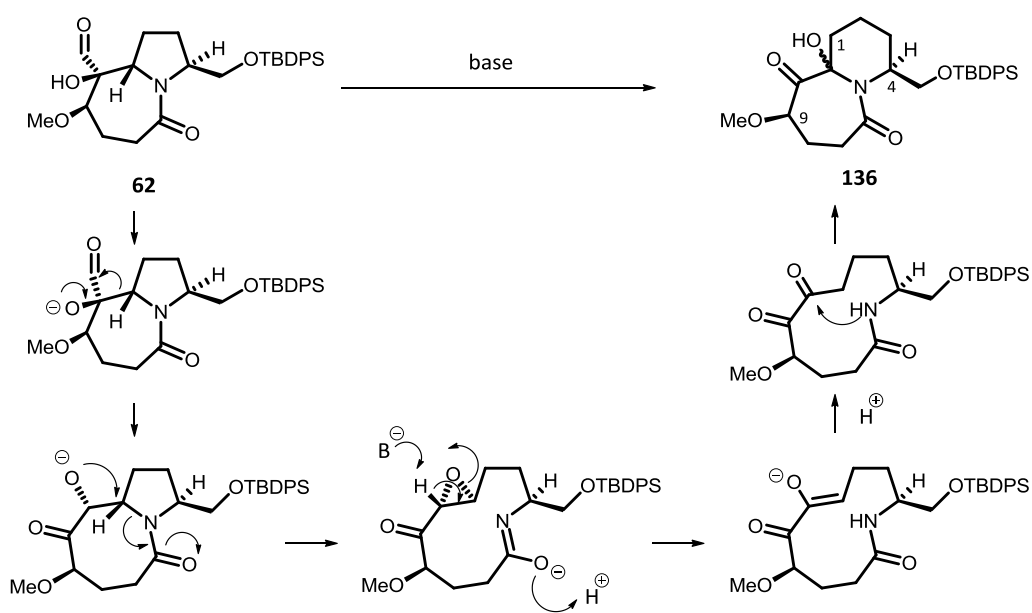
⁷⁵ (a) Meyers, Spohn, R. F.; Linderman, R. J. *J. Org. Chem.* **1985**, *50*, 3633-3635, (b) Hicks, D. R.; Fraser-Reid, B. *Chem. Comm.* **1976**, 869-870; (c) Olejniczak, K.; Frank, R. W. *J. Org. Chem.* **1982**, *47*, 380-381; (d) Bonadies, F.; Cardilli, A.; Lattanzi, A.; Pesci, S.; Scettri, A. *Tetrahedron Lett.* **1995**, *36*, 2839-2840.



Reagents and conditions: (i) t BuOK, **87**, r.t., 5 min; then, **62**, THF, -78 °C to r.t. (30%).

Scheme 52. Attempted preparation of **133**.

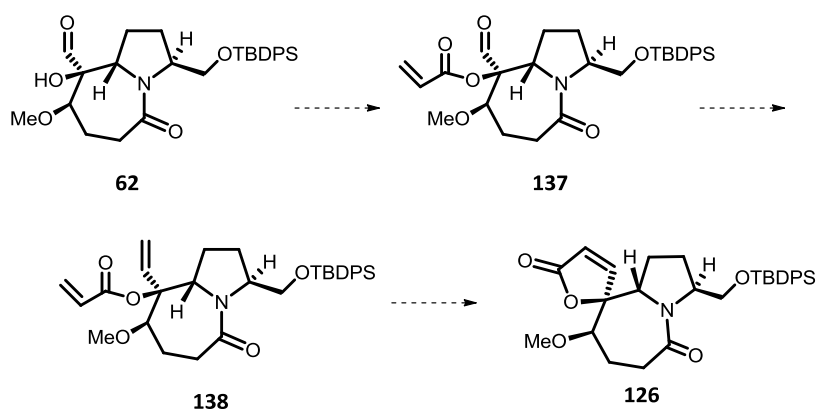
In the event, a mixture of phosphonate **87** and t BuOK was stirred at room temperature for 5 min, and then hydroxyaldehyde **62** was added. Under these conditions, instead of the expected olefin **133**, we isolated **136** as the only product in 30% yield. On its 1 H-NMR spectrum it could be observed that the signal corresponding to proton H_4 is upfield shifted due to the change of the ring size, and the 13 C-NMR displays a signal at 214.2 ppm corresponding to a new carbonyl group. This reaction had been already observed in our research group for a similar compound under basic treatment.⁶² According to our mechanistic proposal (Scheme 53), the phosphonate does not play any role in the formation of **136**, the reaction takes place due to the presence of the base and hence the formation of an α -oxoalkoxide initiates the process.



Scheme 53. Proposed mechanism for the formation of **136**.

Accordingly, we decided to protect the tertiary alcohol before performing the HWE reaction, as in other intermolecular HWE olefinations described in the literature.⁷⁶ Although some other more robust protecting groups were attempted, due to the steric hindrance, we were only successful in making the TMS ether.⁷⁷ Unfortunately, this silyl ether was too labile to withstand the subsequent HWE reaction with ^tBuOK in the media.

After these frustrated trials, we decided to assay the pathway based on intramolecular metathesis and depicted on Scheme 54. The devised plan starts with the formation of acrylate **137**, followed by a Wittig olefination to diene **138**, which should render spirolactone **126** after the ring closing metathesis.



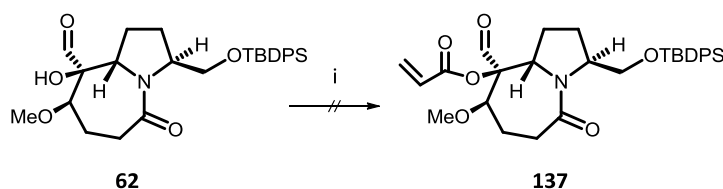
Scheme 54. Synthetic plan for the construction of lactone **126**.

Since the use of a strong base was precluded to avoid the formation of the pyridoazepinone **136**, we used Et₃N (Scheme 55),⁷⁸ but, unfortunately, the reaction did not take place, rendering decomposition products.

⁷⁶ (a) Kitazume, T.; Kobayashi, T.; Yamamoto, T.; Yamazaki, T. *J. Org. Chem.* **1987**, *52*, 3218-3223; (b) Ishihara, K.; Kawaguchi, T.; Matsuya, Y.; Sakurai, H.; Saiki, I.; Nemoto, H. *Eur. J. Org. Chem.* **2004**, 3973-3978; (c) Ensich, C.; Hesse, M. *Helv. Chim. Acta* **2003**, *86*, 233-246; (d) Suenaga, K.; Mutou, T.; Shibata, T.; Itoh, T.; Fujita, T.; Takada, N.; Hayamizu, K.; Takagi, M.; Irifune, T.; Kigoshi, H.; Yamada, K. *Tetrahedron* **2004**, *60*, 8509-8527.

⁷⁷ Crisóstomo, F. R.; Lledó, A.; Shenoy, S. R.; Iwasawa, T.; Rebek, J. *J. Am. Chem. Soc.* **2009**, *131*, 7402-7410.

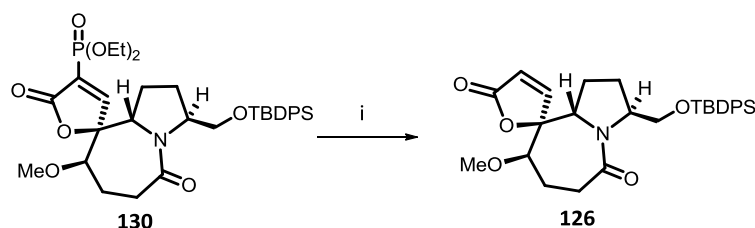
⁷⁸ D'Annibale, A.; Ciaralli, L. *J. Org. Chem.* **2007**, *72*, 6067-6074.



Reagents and conditions: (i) acryloyl chloride, Et₃N, CH₂Cl₂, 0 °C.

Scheme 55. Attempt of preparation of **137**.

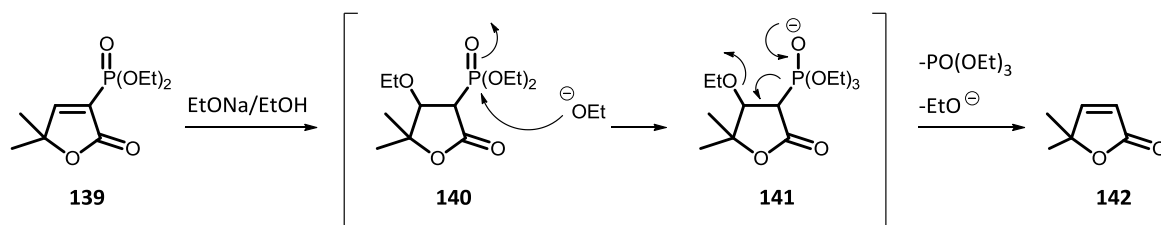
In parallel studies, we investigated the transformation of the Knoevenagel product **130** to the required lactone **126**, and we found that, fortunately, compound **130** could be converted to **126** by treatment of the former with MeONa in MeOH to afford the latter in 93% yield (Scheme 56).⁷⁹



Reagents and conditions: (i) MeONa, MeOH, r.t., 16 h (93%).

Scheme 56. Transformation of **130** to **126**.

The formation of **126** can be rationalised by the mechanism shown in Scheme 57 for the simplified compound **139**, described by Janecki and Blaszczyk.⁷⁹ Firstly, a base-promoted conjugate addition of the ethanol to butenolide **139** furnishes compound **140**, which suffers nucleophilic attack of the ethoxide ion on the phosphorous atom to produce the anion **141**. Subsequent elimination of triethylphosphate and ethoxide ion from **141** renders butenolide **142**.



Scheme 57. Mechanism for the transformation of **139** to butenolide **142**.⁷⁹

⁷⁹ Janecki, T.; Blaszczyk, E. *Synthesis* **2001**, 3, 403-408.

In view that compound **130** could be reprocessed to **126** by treatment with MeONa in MeOH, we attempted the formation of lactone **126** from ester **125** using two equivalents of MeONa, one for the HWE reaction and one for the conversion of **130** to **126** (Scheme 58). However, we were not able to identify or isolate any product from this reaction.



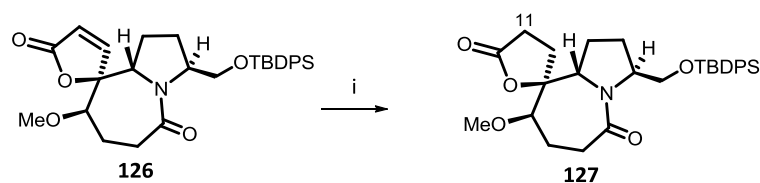
Reagents and conditions: (i) MeONa, MeOH, r.t.

Scheme 58. Attempted HWE reaction with MeONa.

Considering these results, we decided to prepare the west-side lactone **126** through the esterification reaction of aldehyde **62** (Scheme 48), subsequent HWE reaction rendering both lactone **126** and phosphonate **130** (Scheme 49), and then reprocessing of the latter under methanolysis conditions (Scheme 56). In this way, the unsaturated lactone **126** could be obtained in a reasonable 53% yield from hydroxyaldehyde **62**.

2.7.2. Hydrogenation of the double bond and methylation. Synthesis of **128**

Following our synthetic plan (Scheme 47), the next transformation was the reduction of the carbon-carbon double bond of the spiranic lactone. For this purpose, compound **126** was submitted to hydrogenation at atmospheric pressure in the presence of Pd/C in ethanolic media (Scheme 59). After 4h, the saturated lactone **127** was obtained in 93% yield. On its ¹H-NMR spectrum we could clearly observe the disappearance of the olefinic proton and the new signal at 2.60 ppm for the α -carbonyl protons H₁₁.



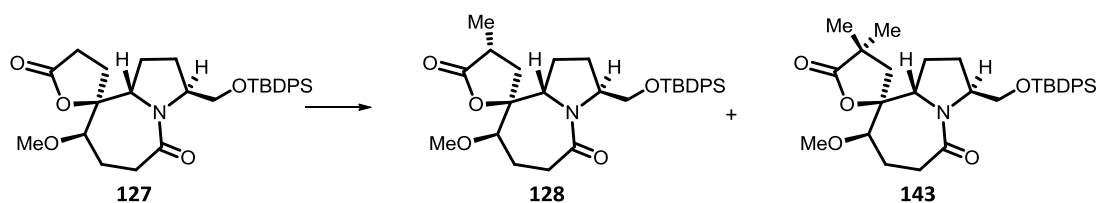
Reagents and conditions: (i) H₂ (1 atm), Pd/C, EtOH, 4 h (93%).

Scheme 59. Hydrogenation of compound **126**.

The following step was the methylation of the α -carbonyl position. If we were right with our previous predictions, the reaction would occur stereoselectively to afford exclusively the methylated lactone with the same configuration at C₁₁ as in stemosporine.

The α -methylation of similar lactones has been widely reported in literature in relation with the synthesis of *Stemona* alkaloids.^{16n,18d,e,f,21f,g,h,i,32a,36} In most examples of these works, LiHMDS is used as the base and MeI as the alkylating agent. Accordingly, we assayed the same combination of reagents for the methylation of lactone **127** under various reaction conditions (Table 4).

Table 4. Methylation of **127**.



Entry ^a	LiHMDS		MeI		127:128:143 ^b
	Equiv.	time	Equiv.	time	
1	2	45 min	10	45 min	- :1:1.9
2	1.4	45 min	4	2 h	1:2.1:1.25
3	1.1	45 min	5	1 h	1:1.6: -
4	1.1	45 min	15	45 min	1:5: -

a) All reactions were performed in dry THF at -78 °C. b) The crude reaction material was not purified. The ratio was determined by ¹H-NMR.

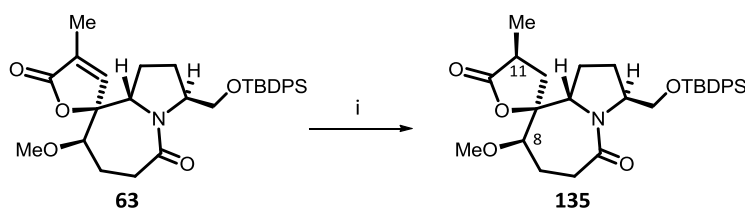
As it can be observed in Table 4, when a large excess of base and MeI were used (entry 1), all the starting material was consumed, but the dimethylated lactone **143** was mainly obtained, along with a minor quantity of the monomethylated one **128**. Unfortunately, these two compounds could not be separated even after repetitive flash column chromatography. Decreasing the excess of base and MeI (entry 2) led to recovering of some starting material but the dimethylation was not inhibited. Thus, in the next experiments we used only 1.1 equivalents of LiHMDS and, once the formation of the enolate was assumed, it was trapped with a fast addition of a large excess of MeI, in order to avoid the equilibrium between the enolates of compounds **127** and **128** (entries 3 and 4). The best results were obtained when 15 equivalents of alkylating agent were used, affording a 5:1 mixture of the desired methylated compound **128**

and unreacted starting material **127**, which could be easily separated by flash column chromatography. The overall yield was 83% over unrecovered **127**.

The $^1\text{H-NMR}$ spectra of compounds **127**, **128** and **143** were performed in deuterated benzene because it was easier to identify each product, since in CDCl_3 some signals were overlapped preventing the determination of the product ratio.

The most significant difference on their $^1\text{H-NMR}$ spectra (Figure 20) is the chemical shift of proton H_8 , whose signal is downfield shifted on going from **127** (2.71 ppm) to **128** (2.75 ppm) to **143** (3.03 ppm).

To confirm that compound **128** had the same configuration at C_{11} as in stemospironine, we decided to perform the hydrogenation of the TBDPS derivative **63** (Scheme 60), intermediate in the syntheses of the diastereoisomeric analogs 11-*epi*-stemospironine, **116**, and 11-*epi*-14-*epi*-16-*epi*-stemospironine, **120**, and then compare their $^1\text{H-NMR}$ spectra.



Reagents and conditions: (i) H_2 (1 atm), Pd/C, EtOH:HCl (1:1), 24 h (90%).

Scheme 60. Hydrogenation of compound **63**.

According to our predictions, hydrogenation of **63** should also be stereoselective, as hydrogen would approach by the less hindered face of the spiranic lactone and should furnish, therefore, the C_{11} epimer of **128**. Hence, the hydrogenation was carried out in acidic ethanol and Pd/C as catalyst and delivered **135** as a sole product in 90% yield. A remarkable n.o.e. between H_8 and H_{11} evidenced the *S* configuration of the α -carbonyl stereocenter at C_{11} . A comparison of the $^1\text{H-NMR}$ spectra of **135** and **128** confirmed that the later presents *R* configuration at C_{11} and hence the methylation of **127** takes place with the predicted stereoselectivity.

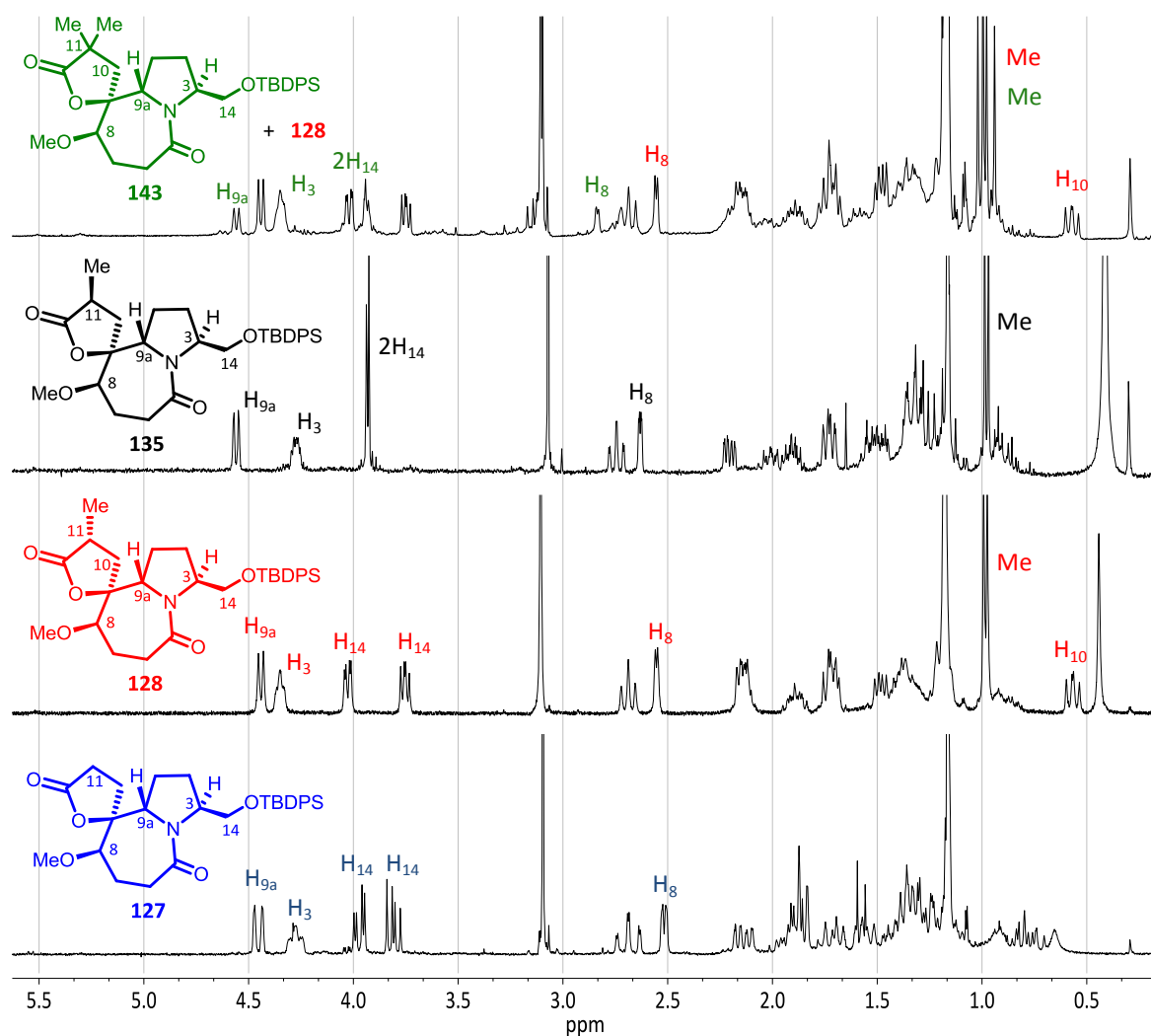
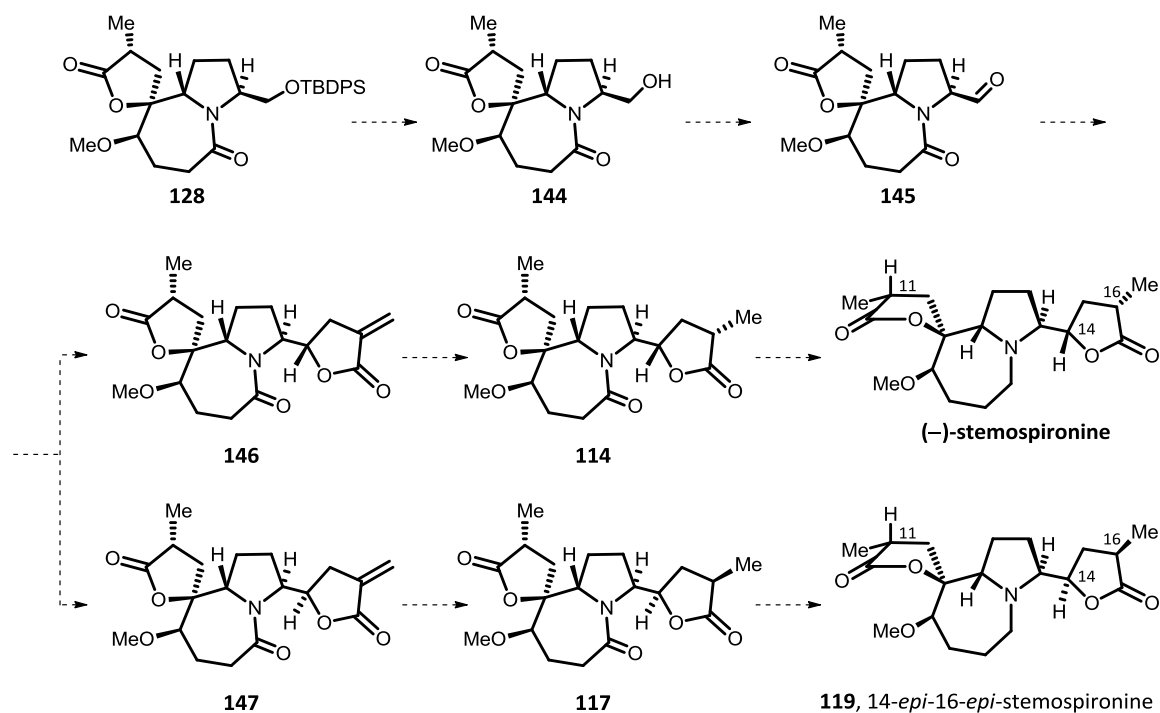


Figure 20. Comparison of the $^1\text{H-NMR}$ spectra (250 MHz, C_6D_6) of lactones **127**, **128**, **143** and an unseparable mixture of **128** and **143**.

2.7.3. Construction of the east-side lactone. Syntheses of **146** and **147**

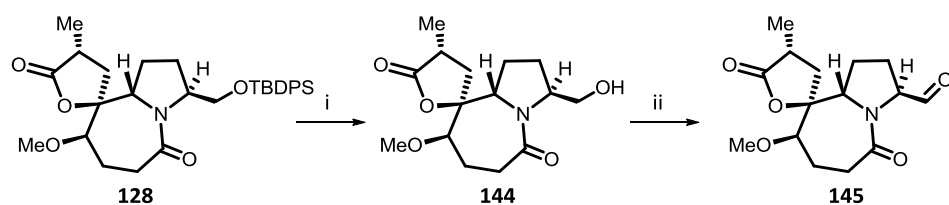
Once the key methylation step was successfully solved, the eastern lactone should be constructed. The planned transformations are depicted in Scheme 61.



Scheme 61. Devised plan for the syntheses of stemospirone and 14-*epi*-16-*epi*-stemospirone, **119**.

The syntheses of (-)-stemospirone and 14-*epi*-16-*epi*-stemospirone, **119**, were completed using the previously established protocols during the syntheses of the other analogs of the natural alkaloid, **116** and **120**.

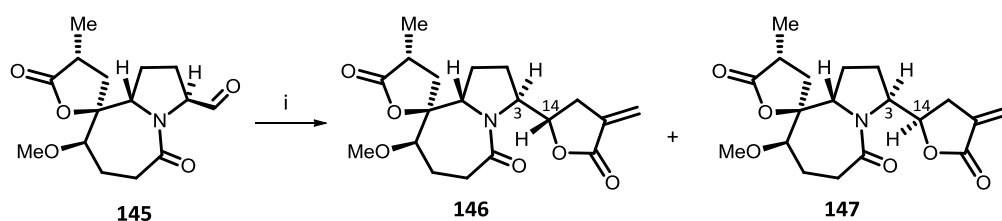
Thus, silyl group removal in lactone **128** was accomplished by treatment with $\text{Et}_3\text{N}\cdot 3\text{HF}$ in THF in 85% yield, and subsequent oxidation with Dess-Martin periodinane delivered aldehyde **145** in 83% yield (Scheme 62). The formation of **145** was evidenced by the appearance of the characteristic doublet at 9.45 ppm in its ^1H -NMR spectrum and a signal at 197.2 ppm in its ^{13}C -NMR spectrum, both corresponding to the new aldehyde moiety.



Reagents and conditions: (i) $\text{Et}_3\text{N}\cdot 3\text{HF}$, THF, reflux, 4 h (85%); (ii) Dess-Martin periodinane, CH_2Cl_2 , 2 h (83%).

Scheme 62. Preparation of alcohol **144** and further oxidation to aldehyde **145**.

As expected, the reaction of aldehyde **145** with ethyl bromomethylacrylate, **61**, and activated zinc^{51,55} furnished a mixture of the *threo*, **146**, and *erythro*, **147**, epimers in a roughly 1:1 ratio and excellent overall yield of 91% (Scheme 63). The two isomers were separable by flash column chromatography, and their stereochemical assignment was confirmed by their further conversion to the targeted alkaloids.



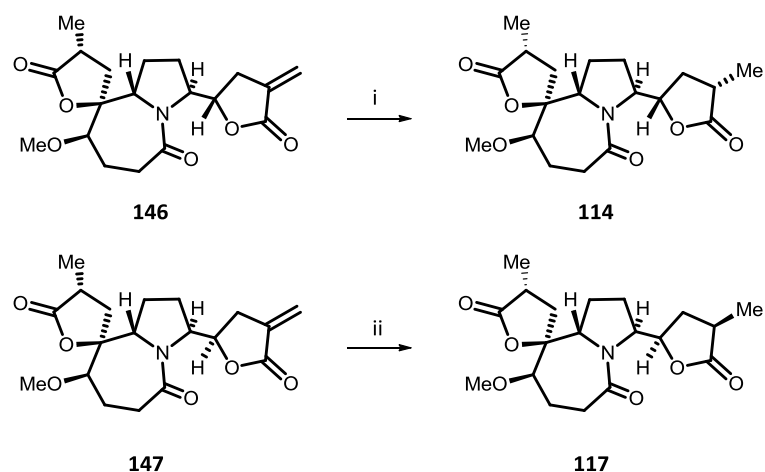
Reagents and conditions: (i) **61**, Zn, THF, reflux, 1 h (91%) **146:147** 1:1.

Scheme 63. Reformatsky-type reaction performed for the preparation of bislactones **146** and **147**.

The formation of **146** and **147** was clearly evidenced by the appearance of the two olefinic signals on their ¹H-NMR spectra around 6.2 ppm and 5.6 ppm. Proton H₃ in bislactone **146** experienced a deshielding compared to that of the *erythro* isomer, while the opposite occurred with proton H₁₄.

2.7.4. Hydrogenation of the eastern lactone. Syntheses of **114** and **117**

Next, the bislactones **146** and **147** were separately submitted to hydrogenation, at atmospheric pressure in the presence of Pd/C in ethanol (Scheme 64). Again, hydrogenation of the eastern lactone occurred in a stereoselective manner through the less hindered face, leading to a *cis* relationship of the substituents of the ring. Thus, a single saturated isomer was obtained from each bislactone in very good yields.



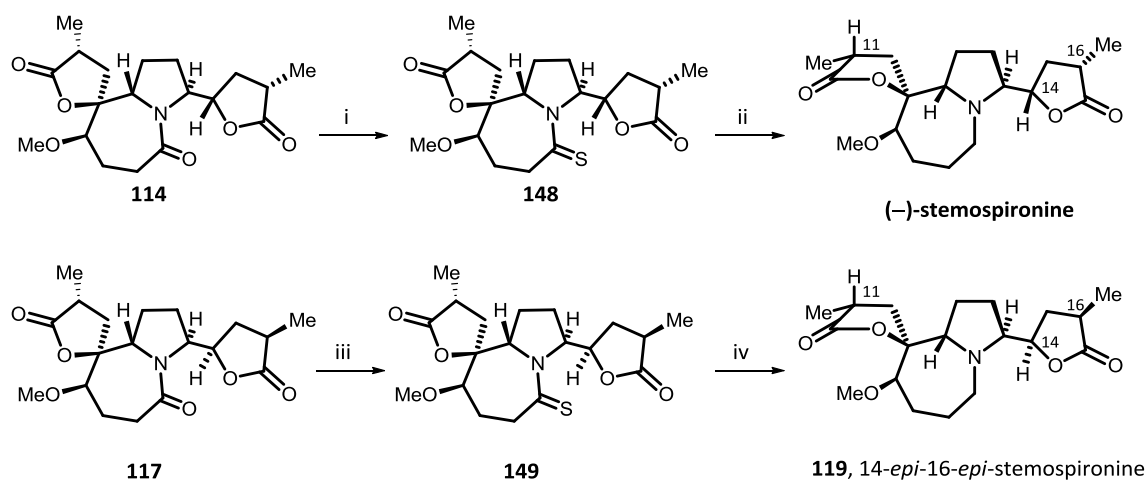
Reagents and conditions: (i) H₂ (1 atm), Pd/C, EtOH, 4 h (quant.); (ii) H₂ (1 atm), Pd/C, EtOH, 4 h (94%).

Scheme 64. Catalytic hydrogenation of bislactones **146** and **147**.

The ¹H-NMR spectra of both compounds **114** and **117** do not present any olefinic signals and, compared to their precursors, one can observe the appearance of a new doublet around 1.2 ppm corresponding to the new methyl group.

2.7.5. Reduction of the lactam functionality. Syntheses of (–)-stemospirone and 14-*epi*-16-*epi*-stemospirone, **119**

To complete the synthesis, lactams **114** and **117** were deoxygenated via the corresponding thiolactams **148** and **149**, respectively (Scheme 65).



Reagents and conditions: (i) Lawesson's reagent, THF, reflux, 45 min; (ii) Raney-Ni, EtOH, reflux, 1 h (54% yield, 2 steps); (iii) Lawesson's reagent, THF, reflux, 45 min; (iv) Raney-Ni, EtOH, reflux, 1 h (52% yield, 2 steps).

Scheme 65. Syntheses of stemospirone and 14-*epi*-16-*epi*-stemospirone, **119**.

Hence, bislactone **114** was treated with Lawesson's reagent in refluxing THF to render thiolactam **148**. As previously observed for thiolactam **122**, protons H₁₄, H_{9a} and H₃ experienced a considerable deshielding of approximately 0.5 ppm compared to those of **114** (Figure 21). Further treatment with Raney-Ni in ethanol at the reflux temperature afforded stemospironine in 54% yield for the two steps. Therefore, we synthesized the alkaloid in 17 steps, starting from nitrone **49**, in 2.1% overall yield. The analytical data of our synthetic stemospironine including optical rotation, $[\alpha]_D^{20} = -8.6$ (*c* 0.23, CHCl₃), are in total agreement with those described for the natural alkaloid, $[\alpha]_D^{27} = -8.2$ (*c* 0.92, CHCl₃).¹¹

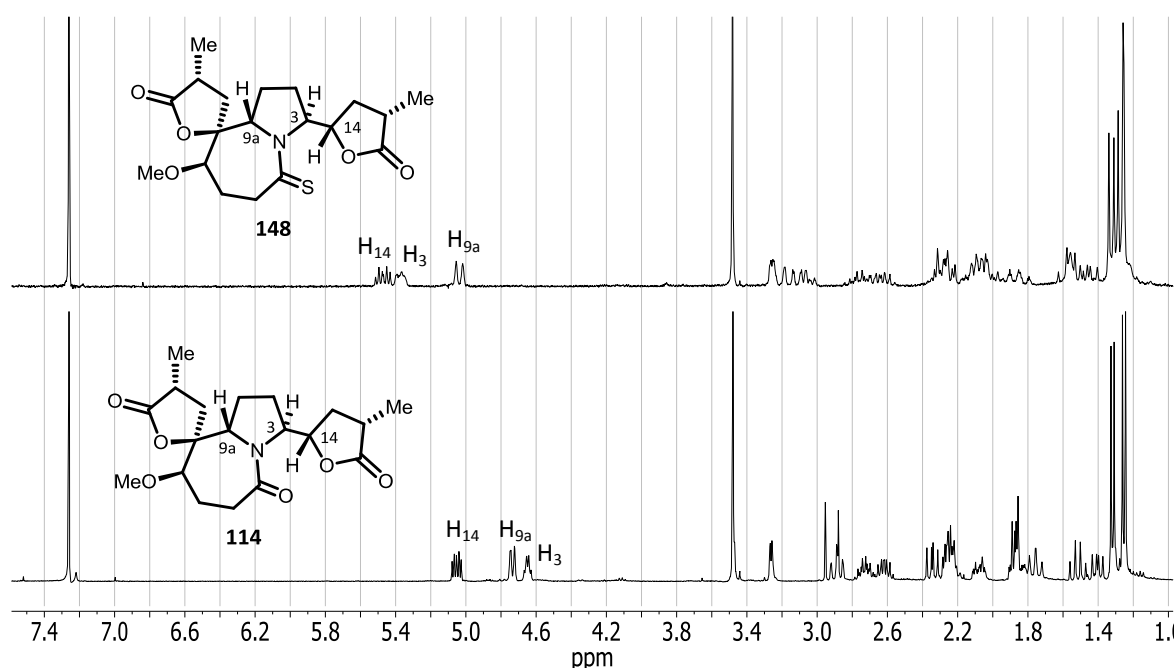


Figure 21. Comparison of the ¹H-NMR spectra (400 MHz, CDCl₃) of bislactone **114** and thiolactam **148**.

We wanted to compare the ¹H-NMR data of stemospironine with that of the isolated natural alkaloid. However, in the literature¹¹ only a few characteristic signals were described. Accordingly, this comparison was made with the ¹H-NMR data provided by Williams and co-workers.^{27a} Figure 22 shows the perfect matching between the ¹H-NMR spectrum of the stemospironine synthesized by Williams (a), and the one synthesized in this thesis (b).^{27b} Likewise, the comparison in Table 5 for the ¹³C-NMR data published for the natural alkaloid¹¹ and the corresponding ¹³C-NMR data that we have obtained for the synthetic stemospironine exhibits a perfect correlation.

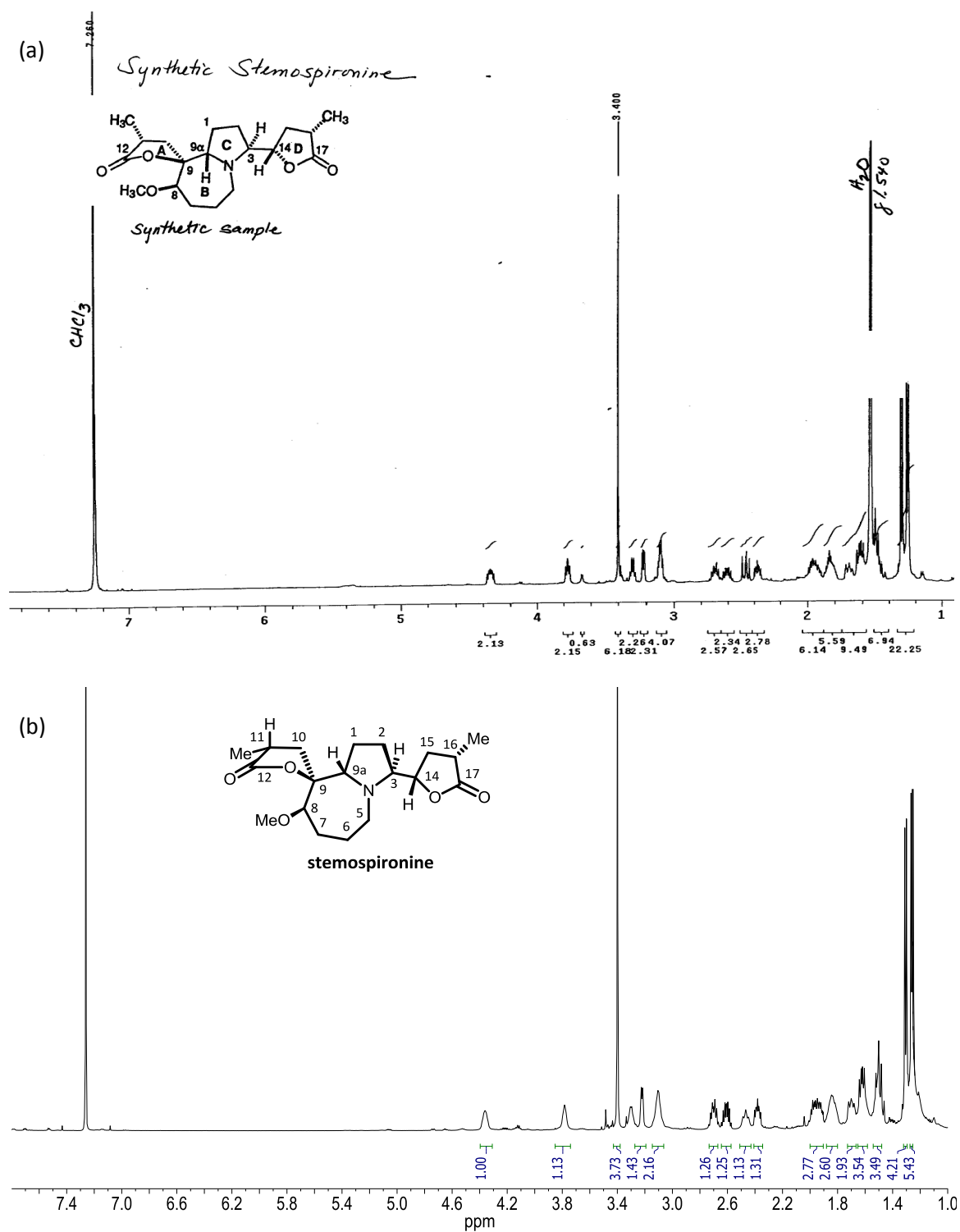


Figure 22. $^1\text{H-NMR}$ spectrum of synthetic stemospironine: (a) prepared by Williams and co-workers (500 MHz, CDCl_3);^{27a} (b) prepared in this thesis (600 MHz, CDCl_3).^{27b}

Table 5. Comparison of ^{13}C -NMR data of isolated stemospironine¹¹ and the one prepared in this thesis.^{27b}

C_n	stemospironine ¹¹	synthetic stemospironine ^{27b}
$\text{C}_{12} + \text{C}_{17}$	179.5 (2)	179.5 (2)
C_9	90.5	90.6
C_8	85.2	85.4
C_{14}	80.0	80.1
C_{9a}	67.7	67.9
C_3	63.1	63.2
OCH_3	58.0	58.2
C_5	48.9	49.0
$\text{C}_{11}/\text{C}_{16}/\text{C}_{10}/\text{C}_{15}$	35.7	35.8
	35.0	35.3
	35.0	35.1
	34.6	34.7
$\text{C}_1/\text{C}_2/\text{C}_6/\text{C}_7$	27.0	27.2
	26.5	26.7
	25.7	25.8
	22.4	22.4
CH_3	17.5	17.7
CH_3	14.8	15.0

¹³C-NMR experiments performed in CDCl_3 , a) 100 MHz, b) 150 MHz. δ values in ppm.

On the other hand, bislactone **117** was also treated with Lawesson's reagent in THF at the reflux temperature to yield thiolactam **149**, which was subsequently submitted to reduction with Raney-Ni (Scheme 68). Thus, we obtained 14-*epi*-16-*epi*-stemospironine, **119**, in 52% yield for the two steps. Hence, **119** was prepared in 17 steps starting from nitron **49** in a 2.0% overall yield. On its ^1H -NMR (Figure 23) we can observe that protons H_{14} , H_{9a} and H_3 suffered a significant shielding compared to the precursor lactam. Proton H_{14} moved from 5.02 in **117** to 4.52 ppm in **119**, proton H_{9a} from 4.80 to 3.77 ppm, and proton H_3 from 4.35 to 3.38 ppm. This is in agreement with the conversion of the lactam to amine.

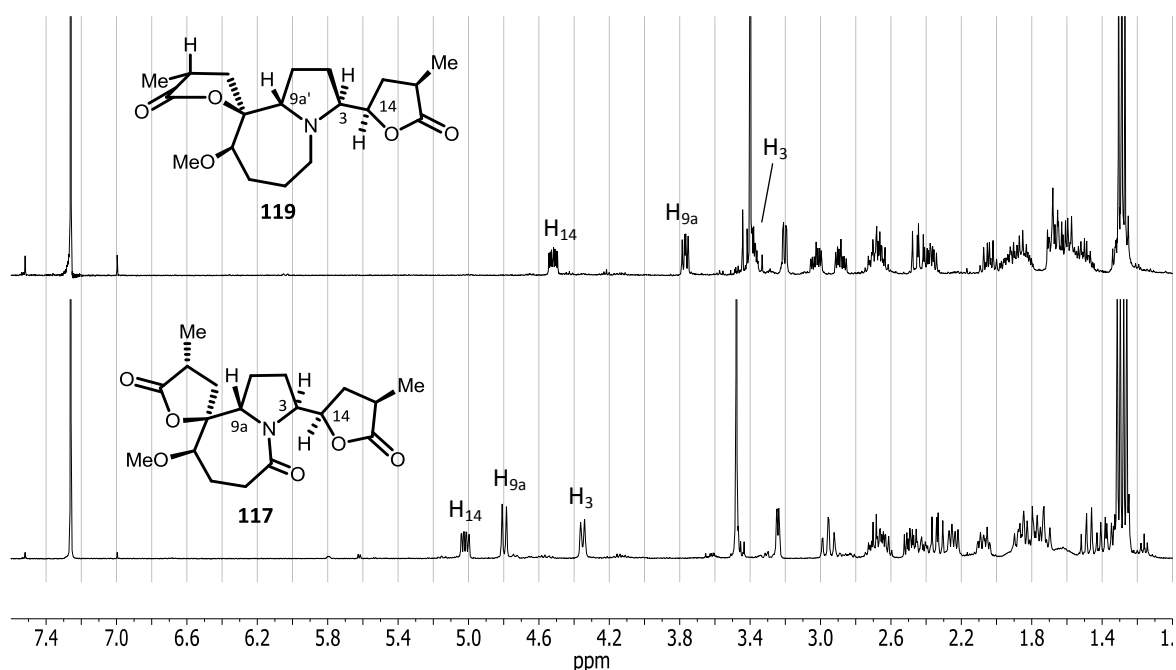
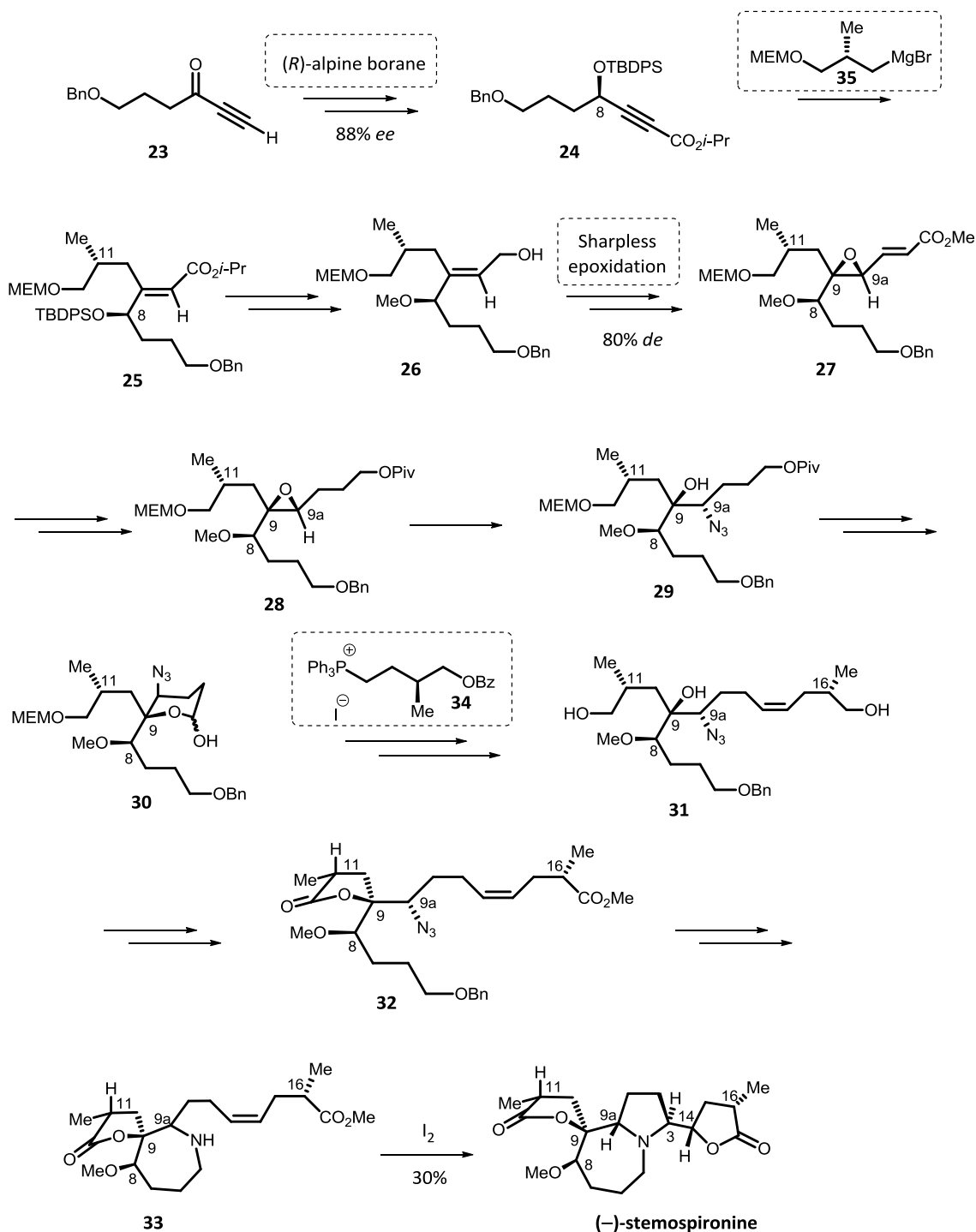


Figure 23. Comparison of the ^1H -NMR spectra (400 MHz, CDCl_3) of lactam **117** and 14-*epi*-16-*epi*-stemospironine, **119**.

Thus, by means of this tactical modification consisting on introducing the methyl group of the west-side lactone in a later step of the sequence, we were able to synthesize stemospironine and its analog 14-*epi*-16-*epi*-stemospironine, **119**, completing a series of four different stereoisomers. Stemospironine was synthesized in 17 steps starting from nitron **49** and 2.1% overall yield, which is a considerable improvement if we compare it with the previous synthesis performed by Williams and co-workers in 2001,^{27a} that featured 27 steps starting from ketone **23** and 0.3% overall yield (Scheme 66).

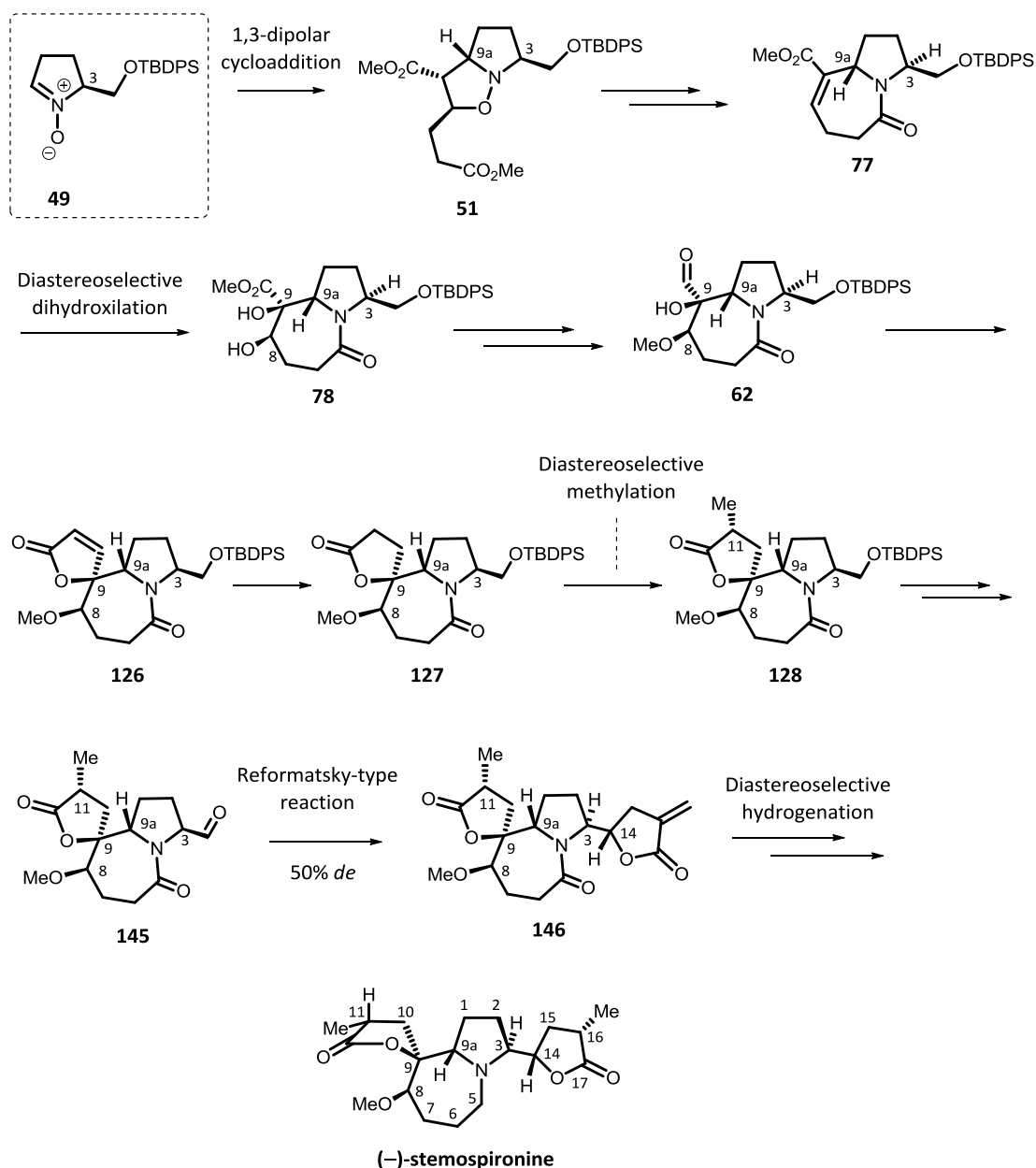
If we make a more detailed analysis of William's synthesis of stemospironine, we can observe that they used four chiral pool materials to induce the stereochemistry. Chirality at C_8 was introduced via Midland reduction of the conjugated ynone **23** with (*R*)-alpine borane, leading to **24** in 88% *ee*. The configurations of the stereogenic centers at C_{11} and C_{16} were controlled by the use of **35** and **34**, whose syntheses from commercial materials required several steps, to elaborate the corresponding fragments of the "west"- and "east"-side lactones, respectively. The relative configurations at C_9 and C_{9a} were established by means of a highly diastereoselective Sharpless epoxidation (80% *de*) of the allylic alcohol **26**. Configuration at C_3 and C_{14} was induced through an impressive iodine-induced double cyclization reaction, but even though it was

reproducible, it had low yield (30%). As it was commented in the Introduction section, in this synthesis the azabicyclic core was prepared from an advanced intermediate (in fact, in the last step) containing all the stereocenters and specifically assembled for the target alkaloid stemospirine.



Scheme 66. Williams' strategy for the synthesis of (-)-stemospirine.^{27a}

Conversely, in our syntheses of stemospironine and analogs (Scheme 67),^{27b} the azabicyclic core was generated at an early stage of the sequence, and the butyrolactone motifs and other specific fragments were incorporated later. In this way, we developed a very flexible approach, with some intermediates being common precursors for various alkaloids of the family. The starting material was a chiral pool compound derived from L-proline, establishing the configuration at C₃ that remained unchanged throughout the entire synthetic route. The stereochemistry in the other centers was induced by the substrate involved in each individual step. Thus, the configuration of the stereocenter at C_{9a} was mainly secured via a highly regio- and stereoselective 1,3-dipolar cycloaddition between nitron **49** and alkene **50** to afford **51** as a sole product; and the sense of chirality in C₈ and C₉ was induced via a totally diastereoselective dihydroxylation of olefin **77**. On the other hand, the relative configuration at C₁₁ was introduced via a diastereoselective methylation of lactone **127**, and the chirality in C₁₆ was induced via a selective hydrogenation of the advanced intermediate **146**. However, the configuration of C₁₄ could not be selectively generated because the Reformatsky-type reaction of aldehyde **145** with bromoacrylate **61** is not stereoselective.



Scheme 67. Our strategy for the synthesis of (-)-stemospirine.^{27b}

Taking everything into account, we have accomplished the syntheses of stemospirine and three additional diastereoisomers 11-*epi*-stemospirine, **116**, 11-*epi*-14-*epi*-16-*epi*-stemospirine, **120**, and 14-*epi*-16-*epi*-stemospirine, **119**, through a flexible strategy that allows the preparation of different *Stemona* alkaloids. The configuration of the stereogenic center at C₁₁ has been totally controlled by a fine-tuning of the synthetic pathway.

Table 6 shows the ¹³C-NMR data of stemospirine and its three analogs **116**, **119**, and **120**. The most significant differences between them are that the carbon atoms C₈ and C₅ are downfield shifted in stemospirine and **119** compared to **120** and **116**.

2. RESULTS AND DISCUSSION

Table 6. Comparison of the ^{13}C -NMR data of stemospiroline, 11-*epi*-stemospiroline, **116**, 11-*epi*-14-*epi*-16-*epi*-stemospiroline, **120**, and 14-*epi*-16-*epi*-stemospiroline, **119**.^{27b}

C_n	Stemospiroline ^a	14- <i>epi</i> -16- <i>epi</i> -stemospiroline, 120 ^b	11- <i>epi</i> -14- <i>epi</i> -16- <i>epi</i> -stemospiroline, 121 ^b	11- <i>epi</i> -stemospiroline, 117 ^b
C_{12}/C_{17}	179.5 (2)	179.5	180.2	180.2
C_{12}/C_{17}		179.3	179.3	179.6
C_9	90.6	90.4	91.3	91.6
C_8	85.4	85.5	82.9	82.8
C_{14}	80.1	78.6	79.2	81.4
C_{9a}	67.9	66.1	67.4	66.7
C_3	63.2	63.6	63.5	64.8
OCH_3	58.2	58.2	57.9	57.9
C_5	49.0	49.1	45.9	45.9
$C_{11}/C_{16}/C_{10}/C_{15}$	35.8	35.8	38.0	37.5
	35.3	35.7	35.7	35.1
	35.1	35.1	35.0	35.0
	34.7	33.9	33.5	34.6
$C_1/C_2/C_6/C_7$	27.2	27.1	27.4	27.5
	26.7	26.2	26.4	26.4
	25.8	25.9	25.6	26.3
	22.4	22.9	22.4	21.2
CH_3	17.7	17.5	16.0	16.0
CH_3	15.0	15.3	15.3	15.0

¹³C-NMR experiments performed in CDCl_3 , a) 150 MHz, b) 100 MHz. δ values in ppm.

This NMR data collection can provide some useful information for further structural elucidations and studies for possible biological activities.

3. Summary and Conclusions

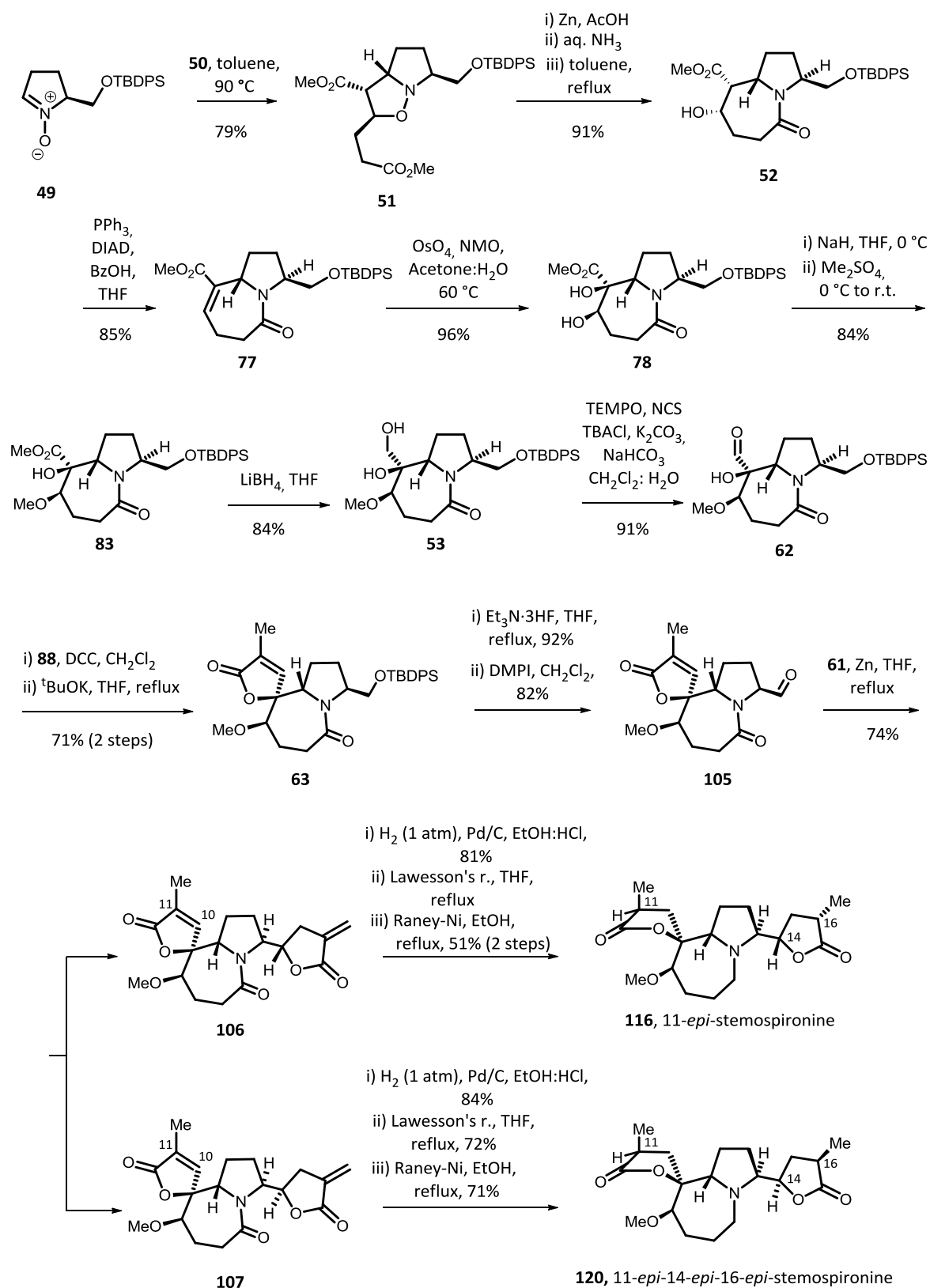
3. Summary and Conclusions

The work developed in the present thesis is part of a research project that pursues the preparation of a group of compounds known as *Stemona* alkaloids. In the strategy designed, the azabicyclic core is generated at an early stage of the sequence, with the aim of developing a flexible approach, where some intermediates could be common precursors to various alkaloids.

This approach previously succeeded in culminating the synthesis of stemonidine,³⁸ and has now been applied to the preparation of stemospironine and three new analogs 11-*epi*-stemospironine, **116**, 14-*epi*-16-*epi*-stemospironine, **119**, and 11-*epi*-14-*epi*-16-*epi*-stemospironine, **120**. Such achievements evidence that our synthetic design is a reliable methodology for the syntheses of these alkaloids.

The first step in the syntheses of stemospironine and its analogs was the 1,3-dipolar cycloaddition between nitron **49** and diester **50** (Scheme 68), followed by reductive cleavage of the N-O bond in **51** and then 7-*exo-trig* cyclization, furnishing azepinone **52**. Then, dehydration and subsequent diastereoselective dihydroxylation rendered diol **78**, which was regioselectively methylated delivering methyl ether **83**. Reduction of **83** with LiBH₄ furnished diol **53**, the branching point where the synthetic pathways to stemonidine and stemospironine diverge, depending on the further transformations. Next, alcohol **53** was oxidized with *N*-chlorosuccinimide in the presence of TEMPO, providing aldehyde **62** in 91% yield. Spirolactonization was accomplished by esterification of the tertiary alcohol by reaction with 2-(diethoxyphosphoryl)propanoic acid, **88**, and dicyclohexylcarbodiimide, followed by basic treatment of the intermediate phosphonate, in 71% yield. Then, the silyl protection was removed and the primary alcohol was oxidized to the corresponding aldehyde **105**, which treated with ethyl bromomethylacrylate, **61**, and zinc furnished a 1:1 mixture of bislactones **106** and **107**. Hydrogenation of the C-C double bonds in **106** and **107**, and subsequent deoxygenation of the lactam functionality in each saturated bislactone by treatment with Lawesson's reagent and then Raney-Ni, provided 11-*epi*-stemospironine, **116**, and 11-*epi*-14-*epi*-16-*epi*-stemospironine, **120**, respectively. Hence, we obtained the stemospironine analogs **116** and **120** in 15 steps starting from nitron **49**, and 3.0% and 3.3% overall yield, respectively.

3. SUMMARY AND CONCLUSIONS



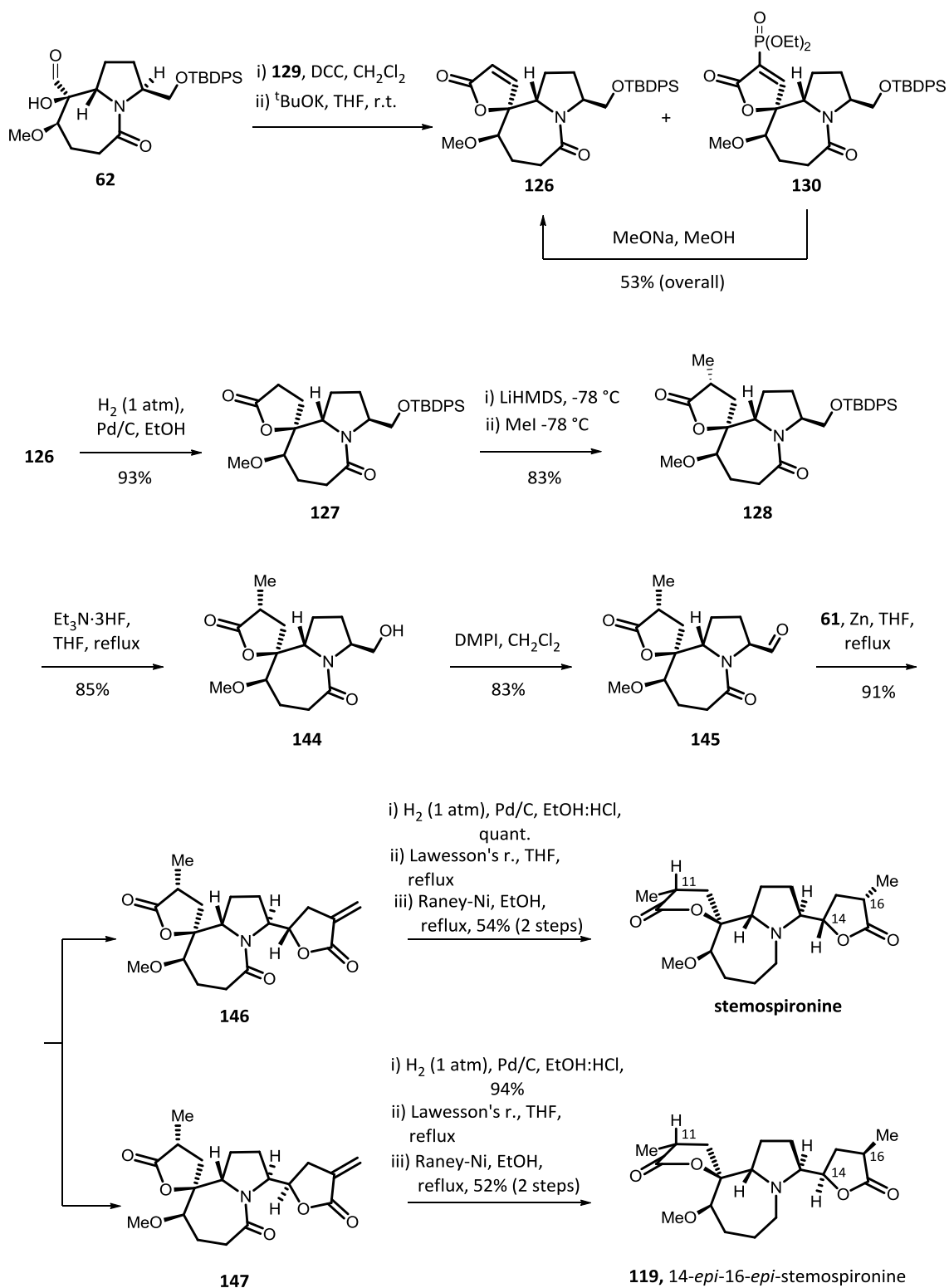
Scheme 68. Synthesis of 11-*epi*-stemospirone, **116**, and 11-*epi*-14-*epi*-16-*epi*-stemospirone, **120**.

In view of the high diastereoselectivity accomplished in the reduction of the C₁₀-C₁₁ double bond in intermediates **106** and **107** by the less hindered face, we reasoned that the methylation of an enolate formed by deprotonation of C₁₁ should occur with the same facial selectivity, leading to the correct stemospironine-like configuration.

Thus, spiro-lactonization of aldehyde **62** with diethoxyphosphorylacetic acid, **129**, and subsequent basic treatment was studied (Scheme 69). This reaction furnished a mixture of the expected lactone **126** and the undesired Knoevenagel product **130**. Although many conditions such as changing the base, temperature and solvent were attempted, this competitive pattern could not be completely inhibited. Fortunately, compound **130** could be reprocessed to **126** by treatment with MeONa in MeOH, rendering **126** in 53% overall yield from aldehyde **62**. Catalytic hydrogenation furnished lactone **127**, which was α -methylated with the predicted stereochemistry delivering **128** in 83% yield (over unrecovered **127**). Installation of the east-side lactone was made as before. Hence, the silyl protection was removed to give alcohol **144**, which was oxidized with Dess-Martin periodinane to furnish aldehyde **145** in 83% yield. As expected, reaction of **145** with ethyl bromomethylacrylate, **61**, and zinc yielded a 1:1 mixture of bislactones threo, **146**, and erythro, **147** in 91% combined yield. These bislactones were separately submitted to catalytic hydrogenation and deoxygenation of the lactam functionality via the corresponding thiolactams, rendering stemospironine and 14-*epi*-16-*epi*-stemospironine, **119**, respectively. Hence, stemospironine and its diastereomeric analog **119** were obtained in 17 steps, starting from nitrone **49**, in 2.1% overall yield for each one. The analytical data of our synthetic stemospironine including optical rotation, $[\alpha]_D^{20} = -8.6$ (*c* 0.23, CHCl₃), are in total agreement with those described for the natural alkaloid, $[\alpha]_D^{27} = -8.2$ (*c* 0.92, CHCl₃),¹¹ and a comparison of the ¹H- and ¹³C-NMR data published in literature with the one we have obtained exhibits also a perfect correlation.

Most of this work has been published in *Organic Letters*. The corresponding paper^{27b} is enclosed below.

3. SUMMARY AND CONCLUSIONS



Scheme 69. Synthesis of stemosporinine and 14-*epi*-16-*epi*-stemosporinine, **119**.

Flexible Approach to *Stemona* Alkaloids: Total Syntheses of (–)-Stemospirone and Three New Diastereoisomeric Analogs

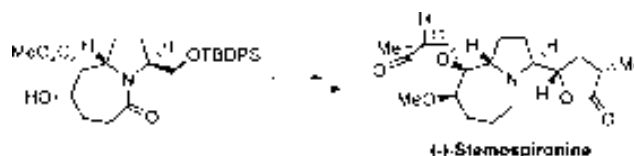
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ABSTRACT



Total syntheses of (–)-stemospirone and three new diastereoisomeric analogs have been completed through a flexible strategy devised for *Stemona* alkaloids. The azabicyclic **7** is the pivotal intermediate, from which the sequence splits according to each particular target. The most remarkable differential feature for stemospirone is the installation of the spiranic γ -lactone through an intramolecular Horner–Wadsworth–Emmons olefination. The configuration of the stereogenic center at C-11 was controlled by fine-tuning of the synthetic sequence.

The extracts of several plants of the *Stemonaceae* family have long been used in East Asian countries for the treatment of respiratory disorders, as antihelmintics, and also as domestic insecticides. Significant constituents of these extracts are a series of structurally related alkaloids that may be responsible for their medicinal and antiparasitic properties, although studies on the specific activity of individual members of this alkaloid family are scarce.¹

All the *Stemona* alkaloids are polycyclic and most of them enclose a pyrrolo[1,2-*a*]azepine core and one or more α -methyl- γ -butyrolactone units as the most characteristic structural features (Figure 1). Their intricate architectures have motivated the development of imaginative strategies for the construction of their skeletons.² Nevertheless, among the roughly 140 natural *Stemona* alkaloids currently known,^{1a} the reported total syntheses target fewer than 20 members of the family, and in most of them, the azabicyclic skeleton is generated from a quite advanced intermediate, usually with several stereogenic centers, and, therefore, specifically assembled for one particular target.

Considering the high and continuously increasing number of *Stemona* alkaloids isolated from natural sources, and the subtle structural differences between some of them, we thought that a flexible synthetic design with some common intermediates was very desirable. Therefore, we devised a strategy in which the azabicyclic core was generated at an early stage of the sequence and the γ -butyrolactone moieties and other specific fragments were incorporated later (Scheme 1).³ We planned the formation of the azabicyclic core via 1,3-dipolar cycloaddition of a pyrroline *N*-oxide to a suitable olefin, followed by reductive cleavage of the N–O bond and then 7-*exo-trig* cyclization. Previous studies regarding the cycloadditions of nitrones such as **4**, to electron-deficient olefins of type **3**, had indicated the relative trans configuration of the stereogenic centers at C-3 and C-9a would be attained as required for the target alkaloids.^{3b,4}

With respect to their connectivity pattern^{1b} and biogenetic relations,^{1c} the *Stemona* alkaloids have been classified into several groups. The tuberostemospirone group is characterized by the presence of a spiro- γ -butyrolactone

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(2) For a recent review on synthetic strategies to *Stemona* alkaloids, see: Alibés, R.; Figueredo, M. *Eur. J. Org. Chem.* **2009**, 2421.

(3) (a) Cid, P.; Closa, M.; de March, P.; Figueredo, M.; Font, J.; Sanfeliu, E.; Soria, A. *Eur. J. Org. Chem.* **2004**, 4215. (b) Alibés, R.; Blanco, P.; Casas, E.; Closa, M.; de March, P.; Figueredo, M.; Font, J.; Sanfeliu, E.; Alvarez-Larena, A. *J. Org. Chem.* **2005**, *70*, 3157.

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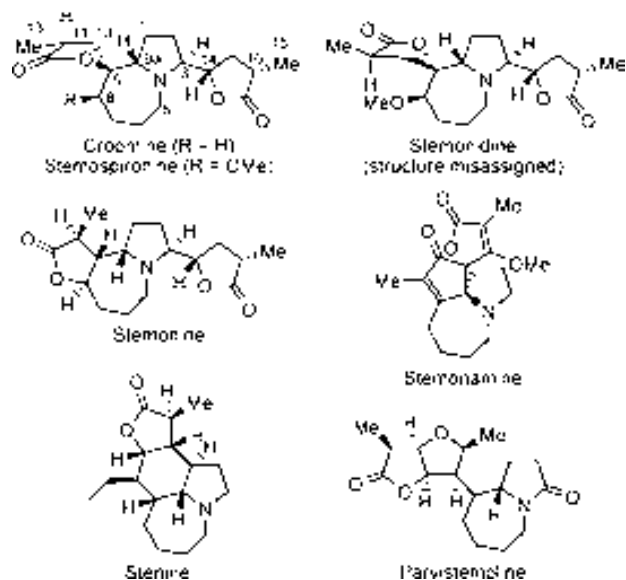
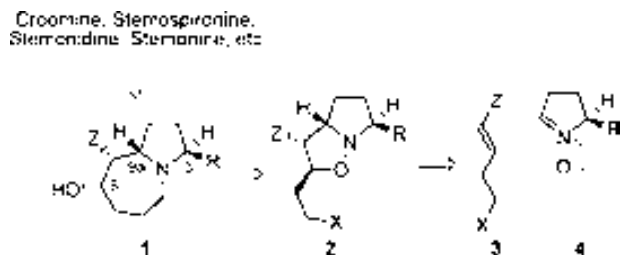


Figure 1. Some representative examples of *Stemona* alkaloids.

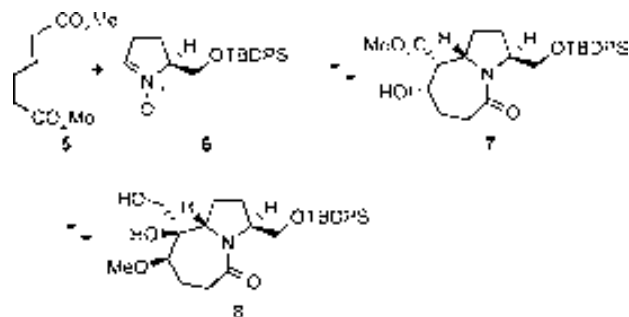
Scheme 1. Retrosynthetic analysis for some *Stemona* alkaloids



attached to C-9 and includes 12 members. Within this group, only four successful total syntheses have been described to date. The first one (which was also the first described synthesis of any *Stemona* alkaloid) was that of (+)-croomine reported by Williams and co-workers in 1989,⁵ through an impressive 24-step linear sequence, involving the preliminary construction of a branched carbon chain, followed by consecutive ring closures to generate each heterocycle. Some years later, the same group completed, by an analogous pathway, the synthesis of (–)-stemospironine.⁶ A second synthesis of (+)-croomine, starting from L-pyroglutamic acid, was described by Martin and Barr.⁷ We recently described the synthesis of the proposed stemonidine⁸ and, in so-doing, demonstrated that the hypothetical stemonidine was in fact stemospironine, as had been previously suggested.⁶ Starting from

diol **8**, an intermediate en route to stemonidine, we have now completed the synthesis of stemospironine and three additional analogs, thus demonstrating the flexibility of our synthetic design.

Scheme 2. Preparation of Diol **8**



Stemospironine possesses a methoxy group at C-8 with the same stereochemical orientation as that of the putative stemonidine, but requires the formation of the spiranic lactone with the opposite configuration. We envisaged the installation of this lactone through an intramolecular Horner–Wadsworth–Emmons olefination of a derivative of the common intermediate **8**, which was prepared from the α,β -unsaturated diester **5** and the enantiomerically pure nitronone **6**,⁹ derived from L-(+)-prolinol, as previously reported (Scheme 2).⁸ It is remarkable that, after the initial formation of the azabicyclic **7**, the inversion of configuration at C₈ and the diastereofacial oxidation at C₉ was efficiently accomplished in a cooperative manner through dehydration and subsequent dihydroxylation. The “eastern” lactone, appended to the pyrrolidine ring, features identically in both alkaloids.

Progression of our synthesis of stemospironine was attempted as shown in Scheme 3. The oxidation of alcohol **8** with *N*-chlorosuccinimide in the presence of TEMPO and tetrabutylammonium chloride in basic medium and a biphasic system¹⁰ provided aldehyde **9** in 91% yield. Spiro-lactonization was accomplished by esterification of the tertiary alcohol by reaction with 2-(diethoxyphosphoryl)propanoic acid and cyclohexylcarbodiimide,¹¹ followed by a basic treatment of the intermediate phosphonate, in 71% yield. Next, the silyl protection was removed and the primary alcohol was oxidized to the corresponding aldehyde **12**, which treated with ethyl bromomethylacrylate and zinc¹² furnished a roughly 1:1 mixture of bislactones **13** and **14** in 74% overall yield. The relative erythro/threo configuration of **13** and **14** was tentatively assigned by NMR in comparison with literature data^{7,13} and unambiguously established in a more advanced intermediate (*vide infra*).

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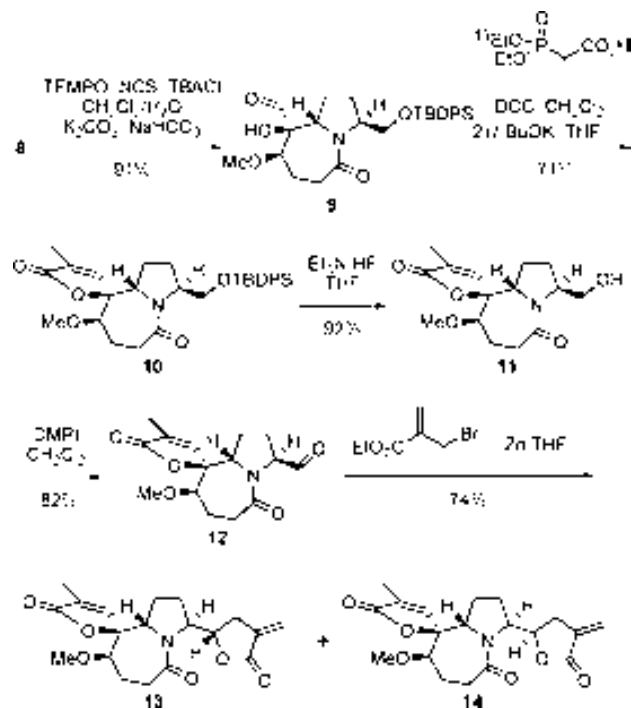
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Scheme 3. Preparation of Bislactones 13 and 14



From the threo isomer **13**, the remaining transformations to conclude the synthesis of stemospiroline were, theoretically, the hydrogenation of the endo- and exocyclic C–C double bonds and the deoxygenation of the lactam. These transformations were undertaken from both epimeric bislactones, **13** and **14**, separately (Scheme 4).

Despite the fact that the hydrogenation reaction generates two new stereogenic centers at C₁₁ and C₁₆, lactams **15** and **18** were exclusively isolated from **13** and **14**, respectively, in good yields. The configuration at C₁₆ was consistent with the approach of the hydrogen by the less hindered face of the “eastern” lactone, as expected,⁸ while a rational explanation of the configuration at C₁₁, which is the opposite in stemospiroline, may be found by observation of a simple tridimensional molecular model of compound **13** (Figure 2) that shows how the pyrrolidine ring obstructs one of the faces of the “western” lactone. Although other reduction protocols were tried, the C₁₁ epimers of **15** or **18** were never detected. The deoxygenation of lactams **15** and **18**, accomplished by treatment with Lawesson’s reagent and then Ra–Ni, gave 11-*epi*-stemospiroline, **17**, and 11-*epi*-14-*epi*-16-*epi*-stemospiroline, **20**, respectively. The structural assignment of all the intermediates was confirmed by X-ray analysis of thiolactam **19** (Figure 3).

In view of the high diastereoselectivity accomplished in the reduction of the C₁₀–C₁₁ double bond, we reasoned that the methylation of an enolate formed by deprotonation of C₁₁ should occur with the same facial selectivity, leading to the correct stemospiroline-like configuration.

Scheme 4. Synthesis of 11-*epi*-Stemospiroline, **17, and 11-*epi*-14-*epi*-16-*epi*-Stemospiroline, **20****

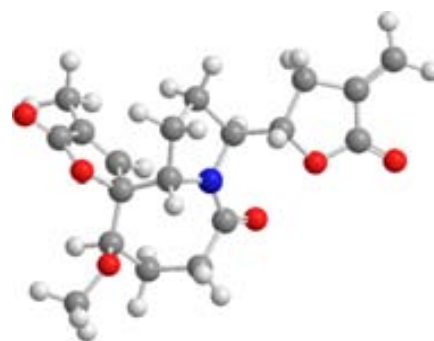
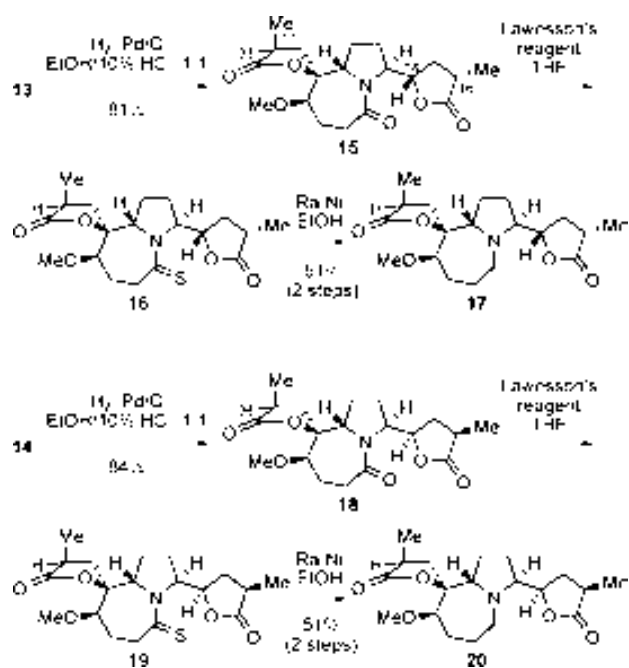


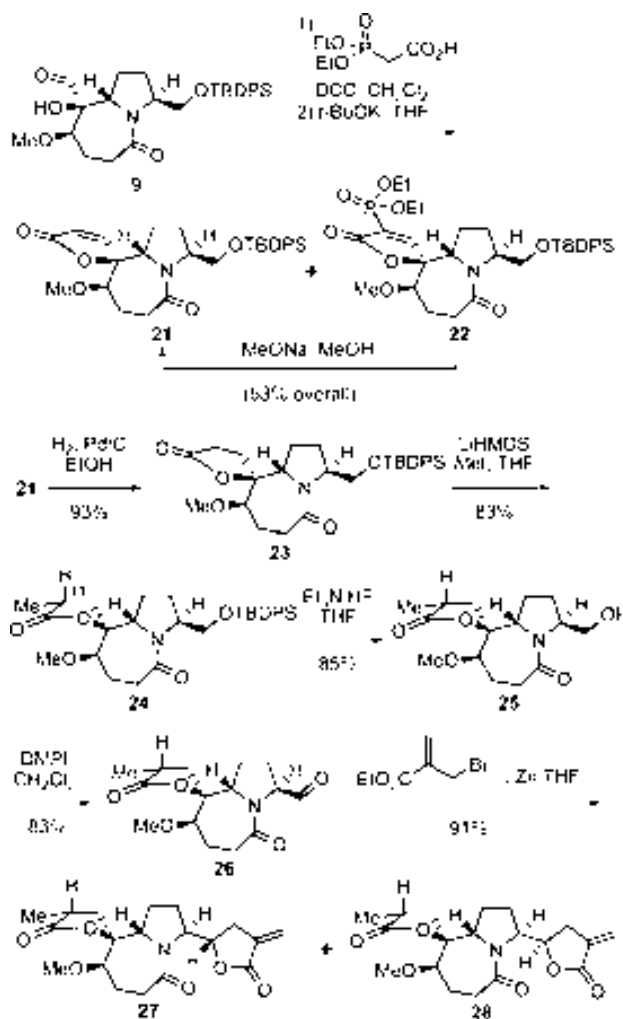
Figure 2. Molecular model of bislactone **13** (ChemBio3D Ultra 12.0).



Figure 3. Crystal structure of thiolactam **19**.

(13) Blanco, P.; Busqué, F.; de March, P.; Figueredo, M.; Font, J.; Sanfeliu, E. *Eur. J. Org. Chem.* **2004**, 48.

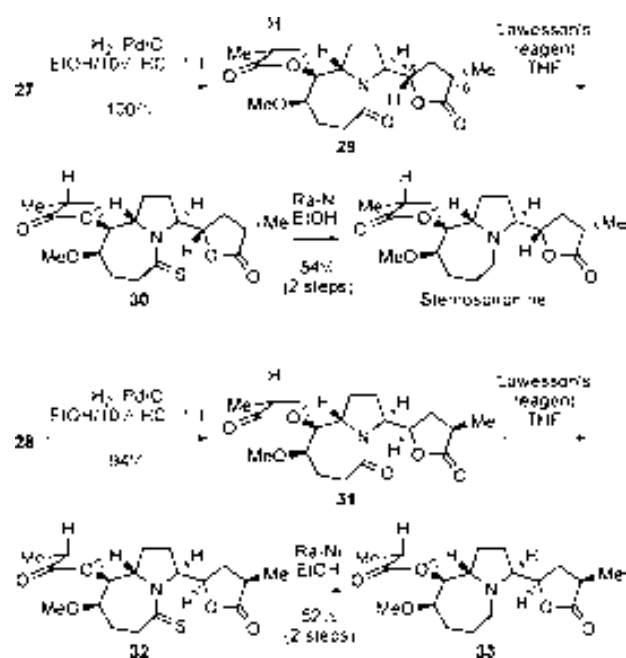
Scheme 5. Preparation of Bislactones **27** and **28**



To test this hypothesis, we decided to investigate the spiro-lactonization of aldehyde **9** with diethoxyphosphorylacetic acid (Scheme 5). This reaction delivered the expected lactone **21**, along with the undesired Knoevenagel product **22**, and despite many attempts including changing the base, solvent, and other experimental conditions, this competitive pattern could not be completely inhibited. Fortunately, compound **22** could be recycled to **21** by treatment of the former with MeONa in MeOH to afford the latter in a reasonable 53% yield. Catalytic hydrogenation furnished the saturated lactone **23**, which was α -methylated without problems and with the previously predicted stereoselectivity to furnish **24** in good yield. Installation of the second lactone was made, as before, by desilylation of **24**, followed by oxidation to the aldehyde **25** and then reaction with ethyl bromomethylacrylate and zinc. As expected, this last reaction furnished a mixture of the threo, **27**, and erythro, **28**, epimers in a roughly 1:1 ratio and excellent overall yield. The stereochemical assignment of these bislactones was confirmed by their conversion to the target alkaloids (Scheme 6).

The syntheses of stemospirine and 14-*epi*-16-*epi*-stemospirine, **33**, were completed using the previously

Scheme 6. Synthesis of Stemospirine and 14-*epi*-16-*epi*-Stemospirine, **33**



established protocols, namely, catalytic hydrogenation of the precursor bislactones **27** and **28**, followed by deoxygenation via the corresponding thiolactams **30** and **32**, respectively. The analytical data of our synthetic stemospirine including optical rotation, $[\alpha]_D^{20} -8.6$ (c 0.23, CHCl₃), are in total agreement with those described for the natural alkaloid, $[\alpha]_D^{27} -8.2$ (c 0.92, CHCl₃).¹⁴

In summary, we have accomplished the syntheses of stemospirine and the three additional diastereoisomers 11-*epi*-stemospirine, **17**, 11-*epi*-14-*epi*-16-*epi*-stemospirine, **20**, and 14-*epi*-16-*epi*-stemospirine, **33**, through a flexible strategy, which allows the preparation of different *Stemona* alkaloids by splitting the sequence in the appropriate late-stage step. The configuration of the stereogenic center at C₁₁ has been totally controlled by a fine-tuning of the synthetic pathway.

Acknowledgment. We acknowledge financial support from DGI (Project CTQ2010-15380) and grants from MECO (F.S.) and MCI (N.B.). We are grateful to Dr. Inhar Imaz, Catalan Institute of Nanotechnology, for performing the X-ray analysis of **19** and to Dr. Tamsyn Montagnon, University of Crete, for her critical reading of the manuscript.

Supporting Information Available. Experimental details, spectral data and copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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The authors declare no competing financial interest.

4. Experimental Part

4.1. GENERAL PROCEDURES

All commercially available reagents were used as received. The solvents were dried by distillation over the appropriate drying agents: CH_2Cl_2 (CaH_2), THF (Na^0), toluene (Na^0 , without benzophenone). When needed, reactions were performed avoiding moisture by standard procedures and under nitrogen atmosphere.

4.1.1. Spectroscopy

Nuclear magnetic resonance spectra (NMR) have been registered at the *Servei de Ressonància Magnètica Nuclear* in the *Universitat Autònoma de Barcelona*. ^1H -NMR spectra were recorded on Bruker DPX250 (250 MHz), Bruker DPX360 (360 MHz) and Bruker ARX400 (400 MHz) spectrometers. Proton chemical shifts are reported in ppm (δ) (CDCl_3 , δ 7.26 ppm and C_6D_6 , 7.16 ppm). ^{13}C -NMR spectra were recorded with complete proton decoupling on Bruker DPX250 (63 MHz), Bruker DPX360 (90 MHz) and Bruker ARX400 (100 MHz) spectrometers. Carbon chemical shifts are reported in ppm (CDCl_3 , δ 77.16 ppm and C_6D_6 , 128.06 ppm). NMR signals were assigned with the help of COSY, selective NOE, NOESY, HSQC and HMBC experiments. All spectra have been registered at 298 K.

The abbreviation used to describe signal multiplicities are: s (singlet), d (doublet), brd (broad doublet), t (triplet), q (quadruplet), dd (double doublet), ddd (double double doublet), dt (double triplet), ddt (double double triplet), td (triple doublet), tt (triple triplet), m (multiplet) and J to indicate the coupling constants.

Infrared spectra were recorded on a Sapphire-ATR Spectrophotometer. Peaks are reported in cm^{-1} .

4.1.2. Mass spectrometry

High resolution mass spectra (HRMS) were recorded at the *Servei d'Anàlisi Química* in the *Universitat Autònoma de Barcelona* in a Bruker micrOTOFQ spectrometer using ESIMS (QTOF).

4.1.3. Chromatography

All reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F254 pre-coated aluminum plates (0.25 mm thickness). Developing has been made using an UV lamp at 254 nm and/or using a KMnO_4/KOH aqueous solution.

4. EXPERIMENTAL PART

Flash column chromatography was performed using silica gel (230-400 mesh), Florisil® (100-200 mesh) or alumina Brockman I (when so indicated).

4.1.4. Optical rotatory power

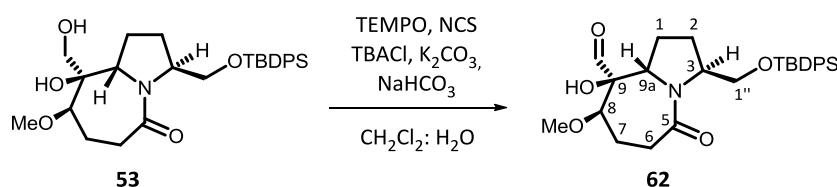
Specific optical rotations were measured on Propol Automatisches Dr. Kermchen polarimeter at 20 ± 2 °C and through a 0.05 dm optical path length or by a J-715 (Jasco) polarimeter with temperature regulator, using a 0.1 dm long tray.

4.1.5. Melting point

Melting points were determined on a REICHERT Koffler hot stage melting point apparatus, and are uncorrected.

4.2. EXPERIMENTAL DESCRIPTION

(3*S*,8*R*,9*S*,9*aS*)-3-*tert*-Butyldiphenylsilyloxymethyl-9-hydroxy-8-methoxy-5-oxooctahydro-1*H*-pyrrolo[1,2-*a*]azepine-9-carbaldehyde, **62****



To a stirred solution of alcohol **53**³⁸ (450 mg, 0.90 mmol) in CH₂Cl₂ (9.4 mL), water (9.4 mL), NaHCO₃ (454 mg, 5.40 mmol), K₂CO₃ (99 mg, 0.71 mmol), TBACl (46 mg, 0.17 mmol) and NCS (233 mg, 1.74 mmol) were added at room temperature. Then, TEMPO (36 mg, 0.23 mmol) was added portion-wise over 15 min. After 2 h, TLC analysis (EtOAc) of the reaction mixture revealed the absence of starting alcohol. The two phases were separated and the aqueous one was extracted with CH₂Cl₂ (3x8 mL). The combined organic extracts were dried over anhydrous MgSO₄ and concentrated under reduced pressure. The resulting oil was purified by flash column chromatography on silica gel (EtOAc:hexanes 9:1) to afford aldehyde **62** (408 mg, 0.82 mmol, 91% yield).

Physical and spectroscopic data of 62:

$[\alpha]_D^{20} = -80.0$ (c 0.90, CH₂Cl₂).

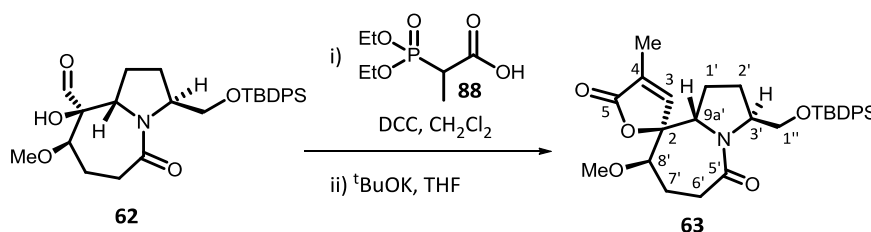
IR (ATR): 3338, 3070, 2954, 2929, 2856, 1731, 1626, 1447, 1426, 1391, 1376, 1360, 1190, 1174, 1094, 1044, 1012 cm⁻¹.

¹H-NMR (360 MHz, CDCl₃): δ 9.80 (s, 1H:CHO), 7.61 (m, 4H_{Ar}), 7.38 (m, 6H_{Ar}), 4.27 (m, 1H:H_{9a}), 4.12 (m, 1H:H₃), 3.79 (m, 2H:2H_{1''}), 3.57 (s, 1H:OH), 3.41 (s, 3H:OCH₃), 3.38 (dd, *J* = 1.5, 2.4 Hz, 1H:H₈), 2.79 (ddd, *J* = 14.6, 11.0, 4.1 Hz, 1H:H₆), 2.27 (m, 3H:H₁,H₂,H₆), 2.08 (m, 2H:2H₇), 1.98 (m, 1H:H₁), 1.56 (m, 1H:H₂), 1.04 (s, 9H:C(CH₃)₃).

¹³C-NMR (90 MHz, CDCl₃): δ 202.2 (CHO), 172.4 (C₅), 135.6 (C_{Ph}), 135.5 (C_{Ph}), 133.5 (C_{Ph}), 133.4 (C_{Ph}), 129.7 (C_{Ph}), 129.6 (C_{Ph}), 127.7 (C_{Ph}), 127.6 (C_{Ph}), 79.6 (C₈), 79.5 (C₉), 63.1 (C_{1''}), 60.3 (C_{9a}), 59.9 (C₃), 57.4 (OCH₃), 30.4 (C₆), 26.9 (C(CH₃)₃), 25.7 (C₁/C₂), 25.5 (C₁/C₂), 22.0 (C₇), 19.2 (C(CH₃)₃).

HRMS (ESI+): calcd for C₂₈H₃₈NO₅Si: 496.2514 [M+H⁺]; found 496.2510.

(2*S*,3'*S*,8'*R*,9a'*S*)-3'-*tert*-butyldiphenylsilyloxymethyl-8'-methoxy-4-methyl-1',2',3',7',8', 9a'-hexahydro-5*H*-spiro{furan-2,9'-pyrrolo[1,2-*a*]azepine}-5,5'(6'*H*)-dione, 63



A recently prepared solution of 2-diethoxyphosphorylpropionic acid, **88**,⁶⁰ in dry CH₂Cl₂ (1M, 0.92 mL, 0.92 mmol) was added to a stirred solution of aldehyde **62** (378 mg, 0.76 mmol) in dry CH₂Cl₂ (2.8 mL) under N₂ atmosphere at room temperature. Then, a solution of DCC (1M in CH₂Cl₂, 1.3 mL, 1.3 mmol) was slowly added. After 4 h, TLC analysis (EtOAc) showed no starting material. The mixture was filtered through a sintered glass and the organic solvent was evaporated under vacuum. The remaining residue was filtered through silica gel (EtOAc) and the solvent was evaporated *in vacuo* to afford a colorless oil, which was dissolved in THF (5 ml). Then, ^tBuOK (173 mg, 1.54 mmol) was added and the reaction mixture was heated at the reflux temperature for 2.5 h. The organic solvent was evaporated under reduced pressure and the

4. EXPERIMENTAL PART

resulting oil was purified on silica gel (EtOAc:hexanes 1:1) to furnish **63** (288 mg, 0.54 mmol, 71% yield for the two steps) as a yellowish oil.

Physical and spectroscopic data of **63**:

$[\alpha]_D^{20} = -114.9$ (*c* 1.01, CHCl₃).

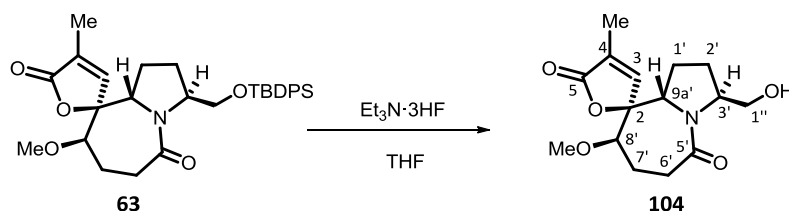
IR (ATR): 3070, 2929, 2855, 1760, 1640, 1447, 1444, 1411, 1376, 1360, 1194, 1163, 1105, 1042 cm⁻¹.

¹H-NMR (400 MHz, CDCl₃): δ 7.62 (m, 4H_{Ar}), 7.40 (m, 6H_{Ar}), 6.93 (q, *J* = 1.5 Hz, 1H:H₃), 4.74 (d, *J* = 8.7 Hz, 1H:H_{9a'}), 4.19 (m, 1H:H_{3'}), 3.83 (dd, *J* = 9.9, 3.1 Hz, 1H:H_{1''}), 3.71 (dd, *J* = 9.9 Hz, 6.1 Hz, 1H:H_{1''}), 3.50 (s, 3H: OCH₃), 3.15 (dd, *J* = 4.7, 1.5 Hz, 1H:H_{8'}), 2.79 (t, *J* = 13.5 Hz, 1H:H_{6'}), 2.26 (m, 1H:H_{6'}), 2.15 (m, 2H:H_{1',H7'}), 1.97 (d, *J* = 1.5 Hz, 3H:CH₃), 1.93 (m, 1H:H_{2'}), 1.81 (t, *J* = 13.5 Hz, 1H:H_{7'}), 1.67 (m, 1H:H_{1'}), 1.50 (m, 1H:H_{2'}), 1.06 (s, 9H:C(CH₃)₃).

¹³C-NMR (100 MHz, CDCl₃): δ 173.4 (C_{5'}), 172.7 (C₅), 146.9 (C₃), 135.7 (C_{Ph}), 135.6 (C_{Ph}), 133.6 (C_{Ph}), 133.5 (C₄), 133.4 (C_{Ph}), 129.9 (C_{Ph}), 127.84 (C_{Ph}), 127.83 (C_{Ph}), 89.2 (C₂), 83.1 (C_{8'}), 63.1 (C_{1''}), 60.1 (C_{3'}), 59.2 (OCH₃), 57.2 (C_{9a'}), 30.5 (C_{6'}), 27.1 (C(CH₃)₃), 26.8 (C_{2'}), 26.4 (C_{1'}), 25.1 (C_{7'}), 19.4 (C(CH₃)₃), 11.2 (CH₃).

HRMS (ESI+): calcd for C₃₁H₃₉NO₅Si: 556.2490 [M+Na⁺]; found 556.2480.

(2*S*,3'*S*,8'*R*,9a'*S*)-3'-Hydroxymethyl-8'-methoxy-4-methyl-1',2',3',7',8',9a'-hexahydro-5*H*-spiro{furan-2,9'-pyrrolo[1,2-*a*]azepine}-5,5'(6'*H*)-dione, **104**



To a stirred solution of **63** (581 mg, 1.09 mmol) in dry THF (19 mL), Et₃N·3HF (3.5 mL, 21.47 mmol) was added. The reaction mixture was heated at the reflux temperature for 4 h, when TLC analysis showed no starting material. The excess of Et₃N·3HF was quenched with NaHCO₃ saturated solution. Then, EtOAc was added and the aqueous phase was extracted with

CH₂Cl₂ (2x18 mL). The combined organic extracts were dried over anhydrous MgSO₄ and concentrated *in vacuo*. The resulting oil was filtered through silica gel (EtOAc) to furnish alcohol **104** (296 mg, 1.00 mmol, 92% yield) as a white solid.

Physical and spectroscopic data of **104**:

$[\alpha]_D^{20} = -70.6$ (*c* 0.96, CHCl₃).

m.p. = 178-181 °C.

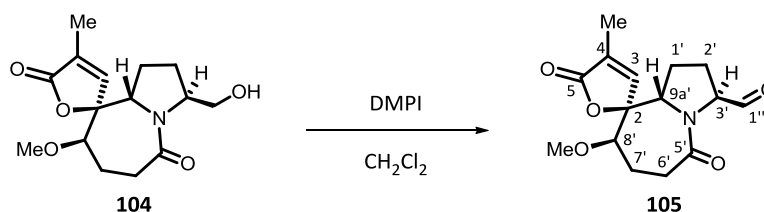
IR (ATR): 3302, 2953, 2835, 1754, 1613, 1439, 1370, 1351, 1198, 1184, 1160, 1095, 1059 cm⁻¹.

¹H-NMR (400 MHz, CDCl₃): δ 6.90 (q, *J* = 1.5 Hz, 1H:H₃), 4.85 (dd, *J* = 8.5, 3.1 Hz, 1H:H_{9a'}), 4.40 (dd, *J* = 8.0, 3.5 Hz, 1H:OH), 4.00 (m, 1H:H_{3'}), 3.64 (m, 2H:2H_{1''}), 3.49 (s, 3H:OCH₃), 3.16 (dd, *J* = 1.7, 4.7 Hz, 1H:H_{8'}), 3.01 (td, *J* = 13.7, 1.7 Hz, 1H:H_{6'}), 2.36 (dd, *J* = 13.9, 1.3 Hz, 1H:H_{6'}), 2.15 (m, 1H:H_{7'}), 2.05 (m, 1H:H_{1'}), 1.97 (d, *J* = 1.6 Hz, 3H:CH₃), 1.81 (tt, *J* = 15.9, 1.6 Hz, 1H:H_{7'}), 1.62 (m, 3H:H_{1'},2H_{2'}).

¹³C-NMR (100 MHz, CDCl₃): δ 175.4 (C_{5'}), 172.4 (C₅), 146.1 (C₃), 134.2 (C₄), 89.1 (C₂), 82.7 (C_{8'}), 65.8 (C_{1''}), 63.0 (C_{3'}), 59.2 (OCH₃), 57.6 (C_{9a'}), 30.5 (C_{6'}), 27.8 (C_{2'/C7'}), 26.3 (C_{1'}), 24.9 (C_{2'/C7'}), 11.2 (CH₃).

HRMS (ESI+): calcd for C₁₅H₂₁NO₅: 318.1312 [M+Na⁺]; found 318.1313.

(2S,3'S,8'R,9a'S)-8'-Methoxy-4-methyl-5,5'-dioxo-1',2',3',5',6',7',8',9a'-octahydro-5H-spiro{furan-2,9'-pyrrolo[1,2-*a*]azepine}-3'-carbaldehyde, **105**



A commercially available solution of Dess-Martin periodinane in CH₂Cl₂ (15% wt, 2.4 mL, 1.16 mmol) was added *via* syringe to a solution of alcohol **104** (290 mg, 0.99 mmol) in dry CH₂Cl₂ (8.3 mL). After 2.3 h of stirring at room temperature, TLC analysis indicated the complete consumption of the starting material. The solution was washed with NaHCO₃ saturated solution

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containing a sevenfold excess of $\text{Na}_2\text{S}_2\text{O}_3$, the aqueous phase was extracted with CH_2Cl_2 (2x7 mL), and the combined organic extracts were dried over anhydrous MgSO_4 and concentrated *in vacuo*. Flash column chromatography on silica gel (EtOAc) provided aldehyde **105** (238 mg, 0.81 mmol, 82% yield) as a white solid.

Physical and spectroscopic data of **105**:

$[\alpha]_{\text{D}}^{20} = -101.7$ (*c* 0.8, CHCl_3).

m.p. = 182-184 °C.

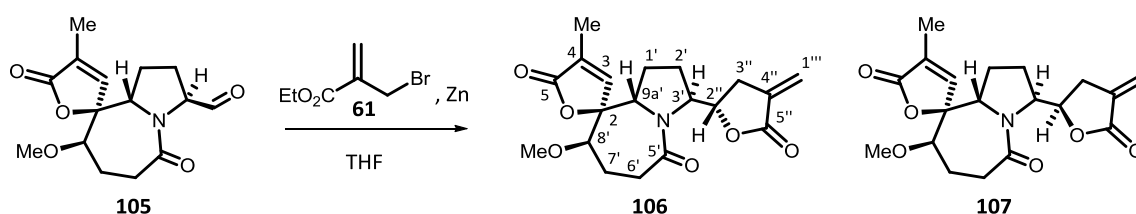
IR (ATR): 2982, 2944, 2856, 1743, 1720, 1633, 1416, 1372, 1353, 1195, 1163, 1096, 1064, 1023, 1000 cm^{-1} .

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 9.45 (d, $J = 2.1$ Hz, 1H:CHO), 6.93 (m, 1H: H_3), 4.92 (dd, $J = 8.6, 3.3$ Hz, 1H: $\text{H}_{9a'}$), 4.34 (m, 1H: $\text{H}_{3'}$), 3.50 (s, 3H: OCH_3), 3.20 (dd, $J = 5.0, 1.5$ Hz, 1H: $\text{H}_{8'}$), 3.11 (td, $J = 13.4, 1.7$ Hz, 1H: $\text{H}_{6'}$), 2.37 (dd, $J = 6.7, 14.2$ Hz, 1H: $\text{H}_{6'}$), 2.17 (m, 1H: $\text{H}_{7'}$), 2.03 (m, 1H: $\text{H}_{1'}$), 1.98 (d, $J = 1.6$ Hz, 3H: CH_3), 1.85 (m, 2H: H_2, H_7), 1.67 (m, 2H: $\text{H}_2, \text{H}_{1'}$).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 197.3 ($\text{C}_{1''}$), 173.7 ($\text{C}_{5'}$), 172.2 (C_5), 145.6 (C_3), 134.6 (C_4), 89.0 (C_2), 82.4 ($\text{C}_{8'}$), 66.2 ($\text{C}_{3'}$), 59.2 (OCH_3), 56.6 ($\text{C}_{9a'}$), 29.4 ($\text{C}_{6'}$), 26.1 (C_2/C_7), 25.4 (C_2/C_7), 24.9 ($\text{C}_{1'}$), 11.2 (CH_3).

HRMS (ESI+): calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_5$: 316.1155 [$\text{M}+\text{Na}^+$]; found 316.1161.

(2*S*,3'*S*,8'*R*,9*a*'*S*,2''*S*)-, **106**, and (2*S*,3'*S*,8'*R*,9*a*'*S*,2''*R*)-8'-Methoxy-4-methyl-3'-(4-methylene-5-oxotetrahydrofuran-2-yl)-1',2',3',7',8',9*a*'-hexahydro-5*H*-spiro{furan-2,9'-pyrrolo[1,2-*a*]azepine}-5,5'(6'*H*)-dione, **107**



To a stirred solution of aldehyde **105** (220 mg, 0.75 mmol) in dry THF (3.8 mL) under N_2 atmosphere, activated Zn^{51} (152 mg, 2.34 mmol) was added. The solution was heated up and,

when reflux started, a solution of ethyl 2-(bromomethyl)acrylate, **61** (153 μL , 1.1 mmol), in dry THF (3.5 mL) was added. After 1 h, TLC analysis of the reaction mixture (EtOAc:MeOH 9:1) revealed the absence of the starting aldehyde. The reaction mixture was filtered through Celite® and the organic solvent was evaporated under vacuum to afford a mixture of diastereoisomers (201 mg, 0.55 mmol, 74% yield). The remaining colorless oil was purified by flash column chromatography on Florisil® (EtOAc) to provide the following fractions: i) *threo*-bislactone **106** (97.6 mg, 0.27 mmol, 36% yield); ii) *erythro*-bislactone **107** (103 mg, 0.28 mmol, 38% yield).

Physical and spectroscopic data of **106** (*threo*):

$[\alpha]_{\text{D}}^{20} = -85.4$ (c 0.10, CHCl_3).

m.p. = 70-72 °C.

IR (ATR): 2929, 1753, 1643, 1443, 1403, 1274, 1252, 1143, 1097, 1055, 1031, 1000 cm^{-1} .

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 6.85 (q, $J = 1.5$ Hz, 1H:H₃), 6.18 (t, $J = 2.6$ Hz, 1H:H_{1'''}), 5.59 (t, $J = 2.6$ Hz, 1H:H_{1''''}), 5.06 (td, $J = 6.7, 3.9$ Hz, 1H:H_{2''}), 4.86 (dd, $J = 8.5, 3.0$ Hz, 1H:H_{9a'}), 4.37 (dt, $J = 7.6, 3.8$ Hz, 1H:H_{3'}), 3.48 (s, 3H:OCH₃), 3.15 (dd, $J = 4, 3, 1.7$ Hz, 1H:H_{8'}), 2.95 (td, $J = 13.5, 1.9$ Hz, 1H:H_{6'}), 2.85 (dt, $J = 6.8, 2.7$ Hz, 2H:2H_{3''}), 2.30 (m, 1H:H_{6'}), 2.15 (m, 2H:H_{7', H_{1'}}), 1.94 (d, $J = 1.5$ Hz, 3H:CH₃), 1.78 (tt, $J = 14.4, 1.7$ Hz, 1H:H_{7'}), 1.64 (m, 3H:2H_{2', H_{1'}}).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 174.5 (C_{5'}), 172.3 (C₅), 170.0 (C_{5''}), 145.8 (C₃), 134.4 (C₄), 134.2 (C_{4''}), 122.0 (C_{1'''}), 89.4 (C₂), 83.0 (C_{8'}), 77.2 (C_{2''}), 60.3 (C_{3'}), 59.2 (OCH₃), 57.7 (C_{9a'}), 30.5 (C_{3''}), 29.9 (C_{6'}), 26.5 (C₇), 26.1 (C_{1'}), 25.4 (C_{2'}), 11.2 (CH₃).

HRMS (ESI+): calcd for C₁₉H₂₃NO₆: 384.1418 [M+Na⁺]; found 384.1414.

Physical and spectroscopic data of **107** (*erythro*):

$[\alpha]_{\text{D}}^{20} = -105.2$ (c 0.17, CHCl_3).

m.p. = 72-75 °C.

IR (ATR): 2928, 1755, 1638, 1444, 1409, 1278, 1254, 1166, 1097, 1057, 1024 cm^{-1} .

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 6.90 (q, $J = 1.5$ Hz, 1H:H₃), 6.26 (t, $J = 2.9$ Hz, 1H:H_{1'''}), 5.66 (t, $J = 2.6$ Hz, 1H:H_{1''''}), 5.21 (ddd, $J = 8.2, 6.3, 1.7$ Hz, 1H:H_{2''}), 4.96 (d, $J = 8.8$ Hz, 1H:H_{9a'}), 4.16 (d, $J = 8.5$ Hz, 1H:H_{3'}), 3.50 (s, 3H:OCH₃), 3.15 (d, $J = 4.8$ Hz, 1H:H_{8'}), 3.08 (m, 2H:H_{6', H_{3''}}), 2.51 (ddt, $J = 17.8, 6.1,$

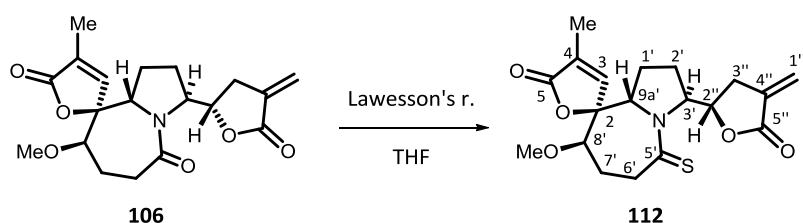
4. EXPERIMENTAL PART

2.9 Hz, 1H:H_{3''}), 2.35 (m, 1H:H_{6'}), 2.19 (m, 2H:H_{1'},H_{7'}), 1.95 (d, *J* = 1.5 Hz, 3H:CH₃), 1.83 (t, *J* = 15.2 Hz, 1H:H_{7'}), 1.65 (m, 2H:H_{1'}, H_{2'}), 1.48 (m, 1H:H_{2'}).

¹³C-NMR (100 MHz, CDCl₃): δ 174.4 (C_{5'}), 172.4 (C₅), 170.0 (C_{5''}), 146.2 (C₃), 134.0 (C₄), 133.6 (C_{4''}), 123.2 (C_{1'''}), 89.0 (C₂), 82.9 (C_{8'}), 75.7 (C_{2''}), 62.2 (C_{3'}), 59.3 (OCH₃), 57.4 (C_{9a'}), 30.5 (C_{3''}), 30.46 (C_{6'}), 26.5 (C_{7'}), 25.6 (C_{1'}), 23.5 (C_{2'}), 11.2 (CH₃).

HRMS (ESI+): calcd for C₁₉H₂₃NO₆: 384.1418 [M+Na⁺]; found 384.1427.

(2*S*,3'*S*,8'*R*,9a'*S*,2''*S*)-8'-Methoxy-4-methyl-3'-(4-methylene-5-oxotetrahydrofuran-2-yl)-5'-thioxo-1',2',3',5',6',7',8',9a'-octahydro-5*H*-spiro{furan-2,9'-pyrrolo[1,2-*a*] azepine}-5-one, **112**



Lawesson's reagent (10.1 mg, 25 μmol) was added to a solution of **106** (16 mg, 44 μmol) in dry THF (2 mL) and the mixture was heated at the reflux temperature for 45 min. The solvent was removed under vacuum and the residue was filtered through Al₂O₃ Brockman I using EtOAc as eluent. Evaporation of the solvent under reduced pressure afforded **112** as a white solid (8.6 mg, 22.8 μmol, 52% yield).

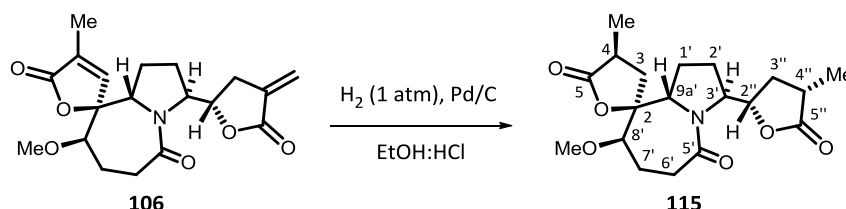
Spectroscopic data of **112**:

¹H-NMR (400 MHz, CDCl₃): δ 6.83 (m, 1H:H₃), 6.23 (t, *J* = 2.9 Hz, 1H:H_{1'''}), 5.64 (t, *J* = 2.5 Hz, 1H:H_{1'''}), 5.47 (m, 1H:H_{2''}), 5.21 (d, *J* = 8.9 Hz, 1H:H_{9a'}), 5.09 (m, 1H:H_{3'}), 3.50 (s, 3H:OCH₃), 3.31 (t, *J* = 12.9 Hz, 1H:H_{6'}), 3.13 (m, 2H:H_{6'},H_{8'}), 2.91 (ddt, *J* = 17.4, 8.2, 2.5 Hz, 1H:H_{3''}), 2.76 (ddt, *J* = 17.4, 5.9, 2.7 Hz, 1H:H_{3''}), 2.20 (m, 2H:H_{1'},H_{7'}), 1.99 (m, 1H:H_{1'}), 1.97 (s, 3H:CH₃), 1.89 (m, 1H:H_{7'}), 1.79 (m, 1H:H_{2'}), 1.71 (m, 1H:H_{2'}).

¹³C-NMR (100 MHz, CDCl₃): δ 207.8 (C_{5'}), 172.2/169.6 (C_{5''}/C₅), 146.1 (C₃), 134.3/133.9 (C₄/C_{4''}), 122.6 (C_{1'''}), 88.4 (C₂), 83.3 (C_{8'}), 74.4 (C_{2''}), 65.2 (C_{3'}), 62.3 (C_{9a'}), 59.3 (OCH₃), 41.0 (C_{6'}), 30.1 (C_{1'/C_{2'/C_{7'}}), 28.6 (C_{3''}), 26.3/25.9 (C_{1'/C_{2'/C_{7'}}), 11.2 (CH₃).}}

HRMS (ESI⁺): calcd for C₁₉H₂₃NO₅S: 400.1189 [M+Na⁺]; found 400.1195.

(2*S*,3'*S*,4*S*,8'*R*,9*a*'*S*,2''*S*,4''*S*)-8'-Methoxy-4-methyl-3'-(4-methyl-5-oxotetrahydrofuran-2-yl)hexahydro-3*H*-spiro[furan-2,9'-pyrrolo[1,2-*a*]azepine]-5,5'(4*H*,6'*H*)-dione, **115**



To a solution of bislactone **106** (29.1 mg, 80 μmol) in a 1:1 mixture of EtOH and 10% HCl (3.2 ml), 10% Pd/C (54 mg, 50.8 μmol) was added. The reaction mixture was stirred at atmospheric pressure of H₂ for 24 h. Then, it was filtered through Celite[®] and the filtrate was washed with saturated solution of NaHCO₃. The aqueous layer was extracted with CH₂Cl₂ (3x2 mL). The combined organic extracts were dried over anhydrous MgSO₄ and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (EtOAc) furnished bislactone **115** (23.8 mg, 40 μmol , 81% yield) as a white solid.

Physical and spectroscopic data of **115**:

$[\alpha]_{\text{D}}^{20} = -100.4$ (*c* 0.68, CHCl₃).

m.p. = 155-157 °C.

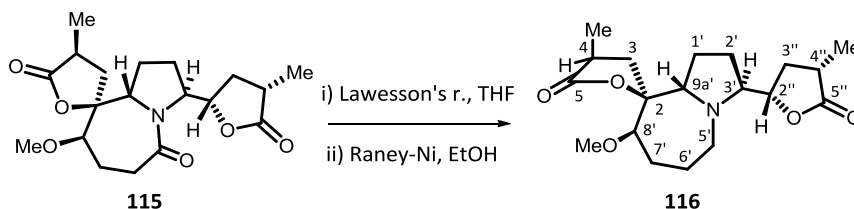
IR (ATR): 3513, 2954, 2935, 1766, 1641, 1447, 1411, 1378, 1296, 1191, 1169, 1101, 1013 cm⁻¹.

¹H-NMR (400 MHz, CDCl₃): δ 5.21 (dt, *J* = 8.2, 6.3 Hz, 1H:H_{2''}), 4.75 (dd, *J* = 8.8, 3.2 Hz, 1H:H_{9a'}), 4.56 (dt, *J* = 7.4, 3.6 Hz, 1H:H_{3'}), 3.43 (s, 3H:OCH₃), 3.38 (m, 1H:H_{8'}), 2.88 (t, *J* = 13.2, 1H:H_{6'}), 2.72 (m, 1H:H₄), 2.63 (m, 1H:H_{4''}), 2.20 (m, 5H:H_{6'},H₃,H_{3'},H_{1'},H_{7'}), 1.95 (m, 3H:H_{2'},H_{1'},H_{7'}), 1.80 (m, 1H:H_{2'}), 1.62 (dd, *J* = 8.7, 7.1 Hz, 1H:H₃), 1.48 (dd, *J* = 12.1, 7.6 Hz, 1H:H_{3''}), 1.29 (d, *J* = 7 Hz, 3H:CH₃), 1.25 (d, *J* = 7.4 Hz, 3H:CH₃).

¹³C-NMR (100 MHz, CDCl₃): δ 178.8 (C_{5''}), 177.8 (C₅), 173.7 (C_{5'}), 86.4 (C₂), 80.9 (C_{8'}), 76.1 (C_{2''}), 60.2 (C_{3'}), 59.0 (OCH₃), 57.8 (C_{9a'}), 35.7 (C_{4''}), 34.5 (C₄), 33.3 (C₃), 31.8 (C_{3''}), 30.8 (C_{6'}), 26.2 (C₇), 24.5 (C_{1'/C_{2'}}), 24.4 (C_{1'/C_{2'}}), 15.8 (CH₃), 15.0 (CH₃).

HRMS (ESI+): calcd for C₁₉H₂₇NO₆: 388.1731 [M+Na⁺]; found 388.1736.

(2S,3'S,4S,8'R,9a'S,2''S,4''S)-8'-Methoxy-4-methyl-3'-(4-methyl-5-oxotetrahydrofuran-2-yl)octahydro-3H-spiro{furan-2,9'-pyrrolo[1,2-*a*]azepin}-5(4H)-one, **116**



Lawesson's reagent (9.4 mg, 23 μ mol) was added to a solution of **115** (18 mg, 44 μ mol) in dry THF (2 mL) and the mixture was heated at the reflux temperature for 45 min. The solvent was removed under vacuum and the residue was filtered through Al₂O₃ Brockman I using EtOAc as eluent. Evaporation of the solvent under reduced pressure afforded a colorless oil, which was dissolved in EtOH (1 mL). Next, Raney-Ni (170 mg) was added to the solution and the reaction mixture was heated at the reflux temperature for 1 h. Then, it was filtered through Celite[®] and the solvent was evaporated *in vacuo*. Purification of the residue by flash chromatography on silica gel (EtOAc) furnished the amine **116** (9.3 mg, 26.4 μ mol, 51% yield) as an oil.

Physical and spectroscopic data of **116**:

$[\alpha]_D^{20} = -20.3$ (*c* 0.41, CHCl₃).

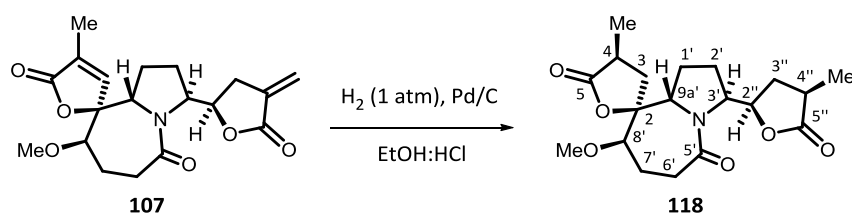
IR (ATR): 3510, 2934, 2876, 2360, 1761, 1455, 1376, 1295, 1195, 1168, 1099, 1017 cm⁻¹.

¹H-NMR (400 MHz, CDCl₃): δ 4.24 (m, 1H:H_{2''}), 3.63 (t, *J* = 8.0 Hz, 1H:H_{9a'}), 3.41 (m, 1H:H_{3'}), 3.35 (s, 3H:OCH₃), 3.26 (dd, *J* = 8.1, 4.2 Hz, 1H:H_{8'}), 3.18 (m, 2H:H_{5'}), 2.85 (m, 1H:H₄), 2.59 (m, 1H:H_{4''}), 2.37 (m, 2H:H₃,H_{3''}), 2.03 (m, 1H:H_{1'}), 1.84 (m, 3H:H_{2'},2H_{7'}), 1.55 (m, 6H:H_{1'},H_{2'},H_{3''},H₃,2H_{6'}), 1.26 (d, *J* = 4.2 Hz, 3H:CH₃), 1.20 (d, *J* = 4.0 Hz, 3H:CH₃).

¹³C-NMR (100 MHz, CDCl₃): δ 180.2 (C_{5''}/C₅), 179.6 (C_{5''}/C₅), 91.6 (C₂), 82.8 (C_{8'}), 81.4 (C_{2''}), 66.7 (C_{9a'}), 64.8 (C_{3'}), 57.9 (OCH₃), 45.9 (C_{5'}), 37.5 (C₃), 35.1/35.0/34.6 (C_{4''}/C₄/C_{3''}), 27.5 (C_{2'}), 26.4 (C_{1'/C7'}), 26.3 (C_{1'/C7'}), 21.2 (C_{6'}), 16.0 (CH₃), 15.0 (CH₃).

HRMS (ESI+): calcd for C₁₉H₂₉NO₅: 352.2118 [M+H⁺]; found 352.2119.

(2*S*,3'*S*,4*S*,8'*R*,9*a*'*S*,2''*R*,4''*R*)-8'-Methoxy-4-methyl-3'-(4-methyl-5-oxotetrahydrofuran-2-yl)hexahydro-3*H*-spiro{furan-2,9'-pyrrolo[1,2-*a*]azepine}-5,5'(4*H*,6'*H*)-dione, **118**



To a solution of bislactone **107** (45.9 mg, 127 μmol) in a 1:1 mixture of EtOH and 10% HCl (3.2 ml), 10% Pd/C (72 mg, 67.7 μmol) was added. The reaction mixture was stirred at atmospheric pressure of H_2 for 24 h. Then, it was filtered through Celite® and the filtrate was washed with saturated solution of NaHCO_3 . The aqueous layer was extracted with CH_2Cl_2 (3x2 mL). The combined organic extracts were dried over anhydrous MgSO_4 and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (EtOAc) furnished bislactone **118** (39.0 mg, 94 μmol , 84% yield).

Physical and spectroscopic data of **118**:

$[\alpha]_{\text{D}}^{20} = -122.1$ (*c* 0.34, CHCl_3).

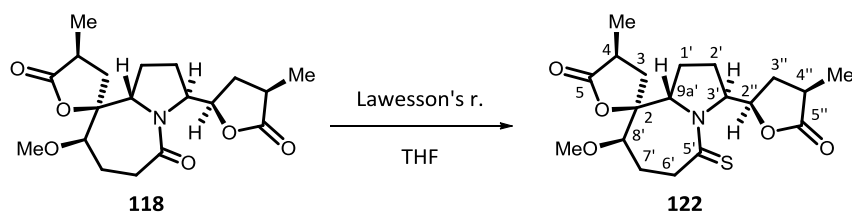
IR (ATR): 2930, 2360, 1764, 1637, 1444, 1411, 1294, 1169, 1097, 1012 cm^{-1} .

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 5.07 (dd, $J = 11.1, 5.7$ Hz, 1H: $\text{H}_{2''}$), 4.80 (d, $J = 9.5$ Hz, 1H: $\text{H}_{9a'}$), 4.29 (d, $J = 8.2$ Hz, 1H: $\text{H}_{3'}$), 3.42 (s, 3H: OCH_3), 3.33 (d, $J = 2.6$ Hz, 1H: $\text{H}_{8'}$), 2.94 (t, $J = 13.3$, 1H: $\text{H}_{6'}$), 2.72 (m, 1H: H_4), 2.63 (m, 1H: $\text{H}_{4''}$), 2.46 (m, 1H: $\text{H}_{3''}$), 2.39 (m, 1H: $\text{H}_{1'}$), 2.25 (m, 1H: $\text{H}_{6'}$), 2.15 (m, 2H: H_3, H_7), 1.90 (m, 4H: $2\text{H}_2, \text{H}_{1'}, \text{H}_7$), 1.61 (dd, $J = 13.9, 11.2$ Hz, 1H: H_3), 1.45 (q, $J = 12.1$ Hz, 1H: $\text{H}_{3''}$), 1.29 (d, $J = 4.5$ Hz, 3H: CH_3), 1.25 (d, $J = 4.4$ Hz, 3H: CH_3).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 179.0 ($\text{C}_{5''}$), 177.9 (C_5), 173.8 ($\text{C}_{5'}$), 86.1 (C_2), 81.0 ($\text{C}_{8'}$), 76.7 ($\text{C}_{2''}$), 61.7 ($\text{C}_{3'}$), 59.0 (OCH_3), 57.1 ($\text{C}_{9a'}$), 35.6/34.6/33.3/31.8 ($\text{C}_{4''}/\text{C}_4/\text{C}_3/\text{C}_{3''}$), 30.9 ($\text{C}_{6'}$), 26.1/24.5/23.4 ($\text{C}_{1'}/\text{C}_{2'}/\text{C}_7$), 15.9 (CH_3), 15.1 (CH_3).

HRMS (ESI+): calcd for $\text{C}_{19}\text{H}_{27}\text{NO}_6$: 388.1731 [$\text{M}+\text{Na}^+$]; found 388.1724.

(2*S*,3'*S*,4*S*,8'*R*,9*a*'*S*,2''*R*,4''*R*)-8'-Methoxy-4-methyl-3'-(4-methyl-5-oxotetrahydrofuran-2-yl)-5'-thioxooctahydro-3*H*-spiro[furan-2,9'-pyrrolo[1,2-*a*]azepin]-5(4*H*)-one, **122**



Lawesson's reagent (9.2 mg, 23 μmol) was added to a solution of **118** (16 mg, 44 μmol) in dry THF (2 mL) and the mixture was heated at the reflux temperature for 45 min. The solvent was removed under vacuum and the residue was filtered through Al_2O_3 Brockman I using EtOAc as eluent. Evaporation of the solvent under reduced pressure afforded **122** as a white solid (12.0 mg, 31.5 μmol , 72% yield).

Physical and spectroscopic data of **122**:

$[\alpha]_D^{20} = -38.3$ (c 0.65, CHCl_3).

m.p. = 180-182 $^\circ\text{C}$ (hexane).

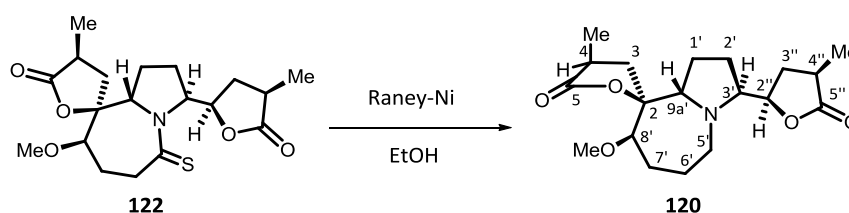
IR (ATR): 2929, 2362, 1770, 1440, 1377, 1294, 1171, 1090 cm^{-1} .

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 5.52 (dd, $J = 11.1, 5.7$ Hz, 1H: $\text{H}_{2''}$), 5.11 (d, $J = 9.5$ Hz, 1H: $\text{H}_{9a'}$), 4.96 (d, $J = 8.2$ Hz, 1H: $\text{H}_{3'}$), 3.42 (s, 3H: OCH_3), 3.34 (m, 1H: $\text{H}_{8'}$), 3.25 (td, $J = 13.3, 1.8$ Hz, 1H: $\text{H}_{6'}$), 3.07 (dd, $J = 13.3, 6.8$ Hz, 1H: $\text{H}_{6'}$), 2.72 (m, 2H: $\text{H}_{4''}, \text{H}_4$), 2.55 (m, 2H: $\text{H}_{3''}, \text{H}_1$), 2.29 (m, 3H: $\text{H}_3, \text{H}_7, \text{H}_1$), 1.95 (m, 3H: $2\text{H}_2, \text{H}_7$), 1.61 (m, 1H: H_3), 1.42 (q, $J = 12.1$ Hz, 1H: $\text{H}_{3''}$), 1.29 (d, $J = 3.1$ Hz, 3H: CH_3), 1.25 (d, $J = 3.0$ Hz, 3H: CH_3).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 204.8 ($\text{C}_{5'}$), 178.9 ($\text{C}_{5''}$), 177.7 (C_5), 85.1 (C_2), 80.9 ($\text{C}_{8'}$), 76.0 ($\text{C}_{2''}$), 67.0 ($\text{C}_{3'}$), 61.6 ($\text{C}_{9a'}$), 59.0 (OCH_3), 41.1 ($\text{C}_{6'}$), 35.5/34.6/34.5/34.2 ($\text{C}_{4''}/\text{C}_4/\text{C}_3/\text{C}_{3''}$), 26.5/26.4 (C_1/C_2), 23.8 (C_7), 15.9 (CH_3), 15.2 (CH_3).

HRMS (ESI+): calcd for $\text{C}_{19}\text{H}_{27}\text{NO}_5\text{S}$: 404.1502 [$\text{M}+\text{Na}^+$]; found 404.1497.

(2*S*,3'*S*,4*S*,8'*R*,9*a*'*S*,2''*R*,4''*R*)-8'-Methoxy-4-methyl-3'-(4-methyl-5-oxotetrahydrofuran-2-yl)octahydro-3*H*-spiro{furan-2,9'-pyrrolo[1,2-*a*]azepin}-5(4*H*)-one, **120**



To a solution of **122** (8 mg, 21 μmol) in EtOH (1 mL), Raney-Ni (170 mg) was added and the reaction mixture was heated at the reflux temperature for 1.3 h. Then, it was filtered through Celite[®] and the solvent was evaporated *in vacuo*. Purification of the residue by flash chromatography on silica gel furnished amine **120** (5.2 mg, 14.8 μmol , 71% yield) as an oil.

Physical and spectroscopic data of **120**:

$[\alpha]_{\text{D}}^{20} = -30.3$ (*c* 0.45, CHCl_3).

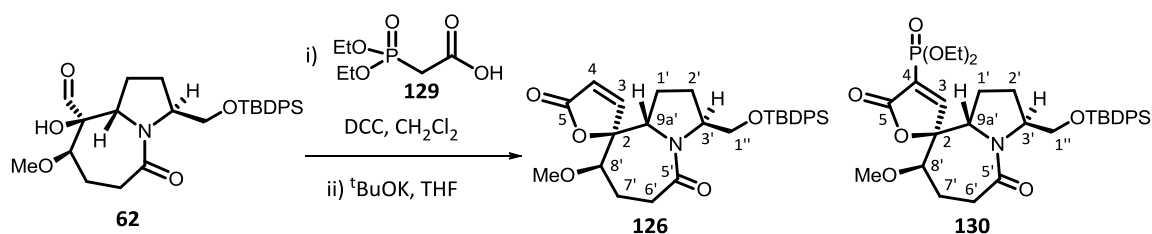
IR (ATR): 2935, 2360, 2341, 1764, 1456, 1376, 1196, 1169, 1100, 1018 cm^{-1} .

¹H-NMR (400 MHz, CDCl_3): δ 4.42 (ddd, *J* = 10.6, 5.7, 3.2 Hz, 1H:H_{2''}), 3.60 (t, *J* = 8.0 Hz, 1H:H_{9a'}), 3.46 (m, 1H:H_{3'}), 3.35 (s, 3H:OCH₃), 3.28 (dd, *J* = 8.1, 4.2 Hz, 1H:H_{8'}), 3.12 (ddd, *J* = 10.6, 5.7, 3.2 Hz, 1H:H_{5'}), 2.95 (m, 1H:H_{5'}), 2.85 (m, 1H:H₄), 2.66 (m, 1H:H_{4''}), 2.43 (dd, *J* = 12.7 9.3 Hz, 1H:H₃), 2.36 (m, 1H:H_{3''}), 2.03 (m, 1H:H_{1'}), 1.84 (m, 3H:H_{2'},2H_{7'}), 1.60 (m, 6H:H_{1'},H_{2'},H_{3''},H₃,2H_{6'}), 1.26 (d, *J* = 4.2 Hz, 3H:CH₃), 1.20 (d, *J* = 4.0 Hz, 3H:CH₃).

¹³C-NMR (100 MHz, CDCl_3): δ 180.2/179.3 (C_{5''}/C₅), 91.3 (C₂), 82.9 (C_{8'}), 79.2 (C_{2''}), 67.4 (C_{9a'}), 63.5 (C_{3'}), 57.9 (OCH₃), 45.9 (C_{5'}), 38.0 (C₃), 35.7/35.0/33.5 (C_{4''}/C₄/C_{3''}), 27.4/26.4/25.6 (C_{2'}/C_{1'}/C_{7'}), 22.4 (C₆), 16.0 (CH₃), 15.3 (CH₃).

HRMS (ESI+): calcd for C₁₉H₂₉NO₅: 352.2118 [M+H⁺]; found 352.2119.

(2*S*,3'*S*,8'*R*,9a'*S*)-3'-*tert*-Butyldiphenylsilyloxymethyl-8'-methoxy-1',2',3',7',8',9a'-hexa-hydro-5*H*-spiro{furan-2,9'-pyrrolo[1,2-*a*]azepine}-5,5'(6'*H*)-dione, **126**, and Diethyl (2*S*,3'*S*, 8'*R*,9a'*S*)-3'-*tert*-butyldiphenylsilyloxymethyl-8'-methoxy-5,5'-dioxo-1',2',3',5',6',7',8',9a'-octahydro-5*H*-spiro{furan-2,9'-pyrrolo[1,2-*a*]azepin}-4-yl}phosphonate, **130**



A solution of diethylphosphonoacetic acid, **129**, in dry CH_2Cl_2 (1M, 1.20 mL, 1.20 mmol) was added to a stirred solution of lactam **62** (507.4 mg, 1.02 mmol) in dry CH_2Cl_2 (3.8 mL) under N_2 atmosphere at room temperature. Then, a solution of DCC (1M, 1.2 mL, 1.2 mmol) was slowly added. After 1.5 h, TLC analysis (EtOAc) showed no starting material. The mixture was filtered through a sintered glass and the organic solvent was evaporated under vacuum. The remaining residue was filtered through silica gel (EtOAc) and the solvent was evaporated *in vacuo* to afford a colorless oil, which was dissolved in THF (14 ml). Then, $t\text{BuOK}$ (90 mg, 0.80 mmol) was added and the reaction mixture was stirred at room temperature for 20 min. The organic solvent was evaporated under reduced pressure and the resulting oil was purified on silica gel (EtOAc:hexanes 1:1) to furnish **126** (154.8 mg, 0.24 mmol, 23% yield) and **130** (168.7 mg, 0.33 mmol, 32% yield) as yellowish oils.

Physical and spectroscopic data of **126**:

$[\alpha]_{\text{D}}^{20} = -71.0$ (c 0.99, CHCl_3).

IR (ATR): 2928, 2854, 1756, 1643, 1444, 1415, 1178, 1080 cm^{-1} .

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.60 (m, 4 H_{Ar}), 7.38 (m, 7 H :6 H_{Ar} , H_3), 6.27 (d, $J = 5.8$ Hz, 1 H : H_4), 4.77 (d, $J = 8.9$ Hz, 1 H : $\text{H}_{9a'}$), 4.18 (m, 1 H : H_3'), 3.82 (dd, $J = 10.0, 3.1$ Hz, 1 H : $\text{H}_{1''}$), 3.75 (dd, $J = 10.0, 5.9$ Hz, 1 H : $\text{H}_{1''}$), 3.51 (s, 3 H : OCH_3), 3.19 (d, $J = 3.7$ Hz, 1 H : H_8'), 2.96 (t, $J = 13.1$ Hz, 1 H : H_6'), 2.20 (m, 3 H : $\text{H}_{1'}$, H_6' , H_7'), 1.94 (dd, $J = 13.0, 7.9$ Hz, 1 H : H_2'), 1.81 (t, $J = 14.3$ Hz, 1 H : H_7'), 1.72 (dd, $J = 14.0, 7.5$ Hz, 1 H : H_1'), 1.53 (m, 1 H : H_2'), 1.04 (s, 9 H : $\text{C}(\text{CH}_3)_3$).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 173.3 (C_5), 171.4 (C_5'), 154.7 (C_3), 135.72 (C_{Ph}), 135.69 (C_{Ph}), 133.6 (C_{Ph}), 133.5 (C_{Ph}), 129.9 (C_{Ph}), 127.9 (C_{Ph}), 124.7 (C_4), 91.8 (C_2), 83.0 (C_8'), 63.1 ($\text{C}_{1''}$), 60.1 (C_3'), 59.3 (OCH_3), 57.2 ($\text{C}_{9a'}$), 30.4 (C_6'), 27.1 ($\text{C}(\text{CH}_3)_3$), 26.8/26.5/25.2 ($\text{C}_{1'}/\text{C}_2'/\text{C}_7'$), 19.4 ($\text{C}(\text{CH}_3)_3$).

HRMS (ESI+): calcd for $\text{C}_{30}\text{H}_{37}\text{NO}_5\text{Si}$: 542.2323 [$\text{M}+\text{Na}^+$]; found 542.2329.

Physical and spectroscopic data of **130**:

$[\alpha]_{\text{D}}^{20} = -59.6$ (c 0.90, CHCl_3).

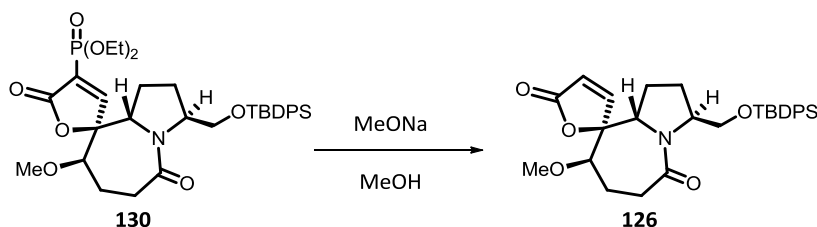
IR (ATR): 2929, 2850, 1767, 1646, 1444, 1408, 1256, 1163, 1104, 1019 cm^{-1} .

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.92 (d, $J = 9.8$ Hz, 1H: H_3), 7.62 (m, 4 H_{Ar}), 7.40 (m, 6 H_{Ar}), 4.78 (d, $J = 9.0$ Hz, 1H: $\text{H}_{9a'}$), 4.28 (m, 4H: $2\text{OCH}_2\text{CH}_3$), 4.21 (m, 1H: H_3'), 3.79 (m, 2H: $2\text{H}_{1''}$), 3.51 (s, 3H: OCH_3), 3.25 (m, 1H: H_8), 2.94 (td, $J = 13.7, 1.5$ Hz, 1H: H_6'), 2.28 (m, 2H: $\text{H}_{1'}$, H_6'), 2.17 (m, 1H: H_7'), 1.97 (dd, $J = 13.2, 7.6$ Hz, 1H: H_2'), 1.84 (m, 1H: H_7), 1.70 (m, 1H: $\text{H}_{1'}$), 1.50 (m, 1H: H_2'), 1.40 (t, $J = 7.1$ Hz, 6H: $2\text{OCH}_2\text{CH}_3$), 1.06 (s, 9H: $\text{C}(\text{CH}_3)_3$).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 173.1 (C_5'), 168.1+167.9 (C_5), 164.6+164.5 (C_3), 135.7 (C_{Ph}), 135.6 (C_{Ph}), 133.4 (C_{Ph}), 129.90 ($\text{C}_{\text{Ph}}/\text{C}_4$), 127.8 ($\text{C}_{\text{Ph}}/\text{C}_4$), 91.4 (C_2), 82.3 (C_8'), 63.8 (OCH_2CH_3), 63.1 ($\text{C}_{1''}$), 60.1 (C_3'), 59.3 (OCH_3), 57.5 ($\text{C}_{9a'}$), 30.2 (C_6'), 27.0 ($\text{C}(\text{CH}_3)_3$), 26.8/26.4/25.3 ($\text{C}_{1'}/\text{C}_2'/\text{C}_7'$), 19.3 ($\text{C}(\text{CH}_3)_3$), 16.5 (OCH_2CH_3).

HRMS (ESI+): calcd for $\text{C}_{34}\text{H}_{46}\text{NO}_8\text{PSi}$: 678.2623 [$\text{M}+\text{Na}^+$]; found 678.2612.

*Conversion of phosphonate **130** into **126***

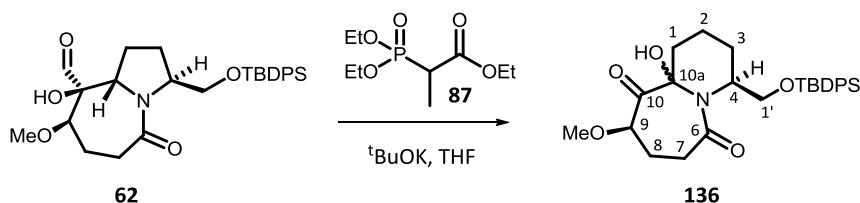


To a stirred solution of **130** (134.4 mg, 205 μmol) in MeOH (4 mL), NaOMe (22.2 mg, 410 μmol) was added at room temperature. After 16 h, TLC analysis (EtOAc) of the reaction mixture revealed the absence starting material. Then, the solvent was evaporated under vacuum, CH_2Cl_2 (3 mL) was added and the organic phase was washed with water (3x3 mL). The combined organic

4. EXPERIMENTAL PART

extracts were dried over anhydrous MgSO_4 and concentrated under reduced pressure to afford **126** (98.6 mg, 189.7 μmol , 93% yield).

(4*S*,9*R*)-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-10*a*-hydroxy-9-methoxyhexahydropyrido[1,2-*a*]zepine-6,10(2*H*,7*H*)-dione, **136**



To a solution of ethyl ester **87** (14 mg, 58.8 μmol) in dry THF (0.5 mL) under N_2 atmosphere, $^t\text{BuOK}$ (7 mg, 62.3 μmol) was added at -78°C . After stirring 5 min, a solution of hydroxyaldehyde **62** (22 mg, 44.4 μmol) in dry THF (0.2 mL) was slowly added. Then, the reaction mixture was slowly warmed up to room temperature and stirred overnight. The solution was washed with NH_4Cl saturated solution, the two phases were separated and the aqueous one was extracted with CH_2Cl_2 . The combined organic extracts were dried over anhydrous MgSO_4 and concentrated *in vacuo*. Flash column chromatography on silica gel (EtOAc) provided **136** (6.6 mg, 13.3 μmol , 30% yield).

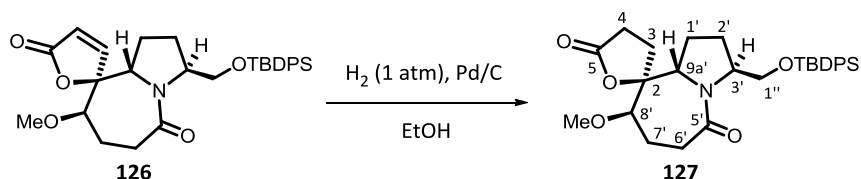
Spectroscopic data of **136**:

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.63 (m, 4H_{Ar}), 7.38 (m, 6H_{Ar}), 4.15 (dd, $J = 9.9, 7.5$ Hz, $1\text{H}:\text{H}_{1'}$), 4.05 (s, $1\text{H}:\text{OH}$), 4.03 (dd, $J = 9.9, 5.7$ Hz, $1\text{H}:\text{H}_{1'}$), 3.41 (m, $1\text{H}:\text{H}_9$), 3.22 (s, $3\text{H}:\text{OCH}_3$), 3.06 (ddd, $J = 12.9, 11.9, 3.3$ Hz, $1\text{H}:\text{H}_7$), 2.74 (dddd, $J = 11.1, 7.4, 5.7, 1.5$ Hz, $1\text{H}:\text{H}_4$), 2.52 (m, $2\text{H}:\text{H}_7, \text{H}_{1'}$), 2.32 (m, $1\text{H}:\text{H}_1$), 2.05 (m, $4\text{H}:\text{H}_3, \text{H}_2, 2\text{H}_8$), 1.79 (m, $1\text{H}:\text{H}_{10}$), 1.51 (m, $1\text{H}:\text{H}_9$), 1.02 (s, $9\text{H}:\text{C}(\text{CH}_3)_3$).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 214.2 (C_{10}), 169.9 (C_6), 135.8 (C_{Ph}), 135.7 (C_{Ph}), 133.8 (C_{Ph}), 129.7 (C_{Ph}), 127.8 (C_{Ph}), 89.5 ($\text{C}_{10\text{a}}$), 80.6 (C_9), 64.8 ($\text{C}_{1'}$), 63.4 (C_4), 56.4 (OCH_3), 41.7 (C_7), 27.5/27.36/27.35/19.3 ($\text{C}_1/\text{C}_2/\text{C}_3/\text{C}_8$), 27.0 ($\text{C}(\text{CH}_3)_3$), 19.0 ($\text{C}(\text{CH}_3)_3$).

HRMS (ESI+): calcd for $\text{C}_{34}\text{H}_{46}\text{NO}_8\text{PSi}$: 518.2333 [$\text{M}+\text{Na}^+$]; found 518.2339.

(2*S*,3'*S*,8'*R*,9*a*'*S*)-3'-*tert*-Butyldiphenylsilyloxymethyl-8'-methoxy-hexahydro-3*H*-spiro{furan-2,9'-pyrrolo[1,2-*a*]azepine}-5,5'(4*H*,6'*H*)-dione, **127**



To a solution of compound **126** (62.4 mg, 120 μmol) in EtOH (5 mL), 10% Pd/C (56 mg, 52.6 μmol) was added. The reaction mixture was stirred in atmospheric pressure of H_2 for 4 h. Then, it was filtered through Celite[®] and the solvent was evaporated under reduced pressure to provide **127** (58 mg, 111 μmol , 93% yield).

Physical and spectroscopic data of **127**:

$[\alpha]_{\text{D}}^{20} = -54.2$ (c 0.60, CHCl_3).

IR (ATR): 2930, 2845, 1765, 1645, 1460, 1443, 1178, 1080, 1019 cm^{-1} .

¹H-NMR (400 MHz, CDCl_3): δ 7.61 (m, 4H:4H_{Ar}), 7.38 (m, 6H:6H_{Ar}), 4.63 (d, $J = 9.4$ Hz, 1H:H_{9a'}), 4.33 (m, 1H:H_{3'}), 3.81 (m, 2H:2H_{1''}), 3.46 (s, 3H:OCH₃), 3.30 (d, $J = 3.7$ Hz, 1H:H_{8'}), 2.82 (td, $J = 13.5, 1.5$ Hz, 1H:H_{6'}), 2.60 (m, 2H:2H₄), 2.32 (m, 1H:H_{1'}), 2.12 (m, 4H:H_{2',H6',H7',H3}), 1.81 (m, 4H:H_{1',H2',H7',H3}), 1.06 (s, 9H:C(CH₃)₃).

¹³C-NMR (100 MHz, CDCl_3): δ 175.8 (C₅), 173.3 (C_{5'}), 135.72 (C_{Ph}), 135.70 (C_{Ph}), 133.67 (C_{Ph}), 133.61 (C_{Ph}), 129.9 (C_{Ph}), 127.86 (C_{Ph}), 127.85 (C_{Ph}), 88.5 (C₂), 83.2 (C_{8'}), 63.2 (C_{1''}), 61.0 (C_{3'}), 58.8 (OCH₃), 57.4 (C_{9a'}), 30.5 (C_{6'}), 28.7 (C₄), 27.1 (C(CH₃)₃), 26.8/26.0/25.5/23.8 (C₃/C_{1'}/C_{2'}/C₇), 19.4 (C(CH₃)₃).

HRMS (ESI⁺): calcd for C₃₀H₃₉NO₅Si: 544.2490 [M+Na⁺]; found 544.2500.

(2*S*,4*R*,3'*S*,8'*R*,9*a*'*S*)-3'-*tert*-Butyldiphenylsilyloxymethyl-8'-methoxy-4-methylhexahydro-3*H*-spiro{furan-2,9'-pyrrolo[1,2-*a*]azepine}-5,5'(4*H*,6'*H*)-dione, **128**



To a stirred solution of **127** (23 mg, 44 μ mol) in dry THF (0.9 mL) under N₂ atmosphere at -78 °C, a THF solution of LiHMDS (1M, 48 μ L, 48 μ mol) was added. After 45 min, MeI (41 μ L, 658 μ mol) was added fast. After 45 min, NH₄Cl (1 mL) was added and the reaction was allowed to warm up to room temperature. The two phases were separated and the aqueous one was extracted with CH₂Cl₂ (3x8 mL). The combined organic extracts were dried over anhydrous MgSO₄ and concentrated under reduced pressure. The resulting oil was purified by flash column chromatography on silica gel (EtOAc:hexanes 1:1) to afford **128** (19.5 mg, 36 μ mol, 83% yield over recovered **127**).

Physical and spectroscopic data of **128**:

$[\alpha]_D^{20} = -36.5$ (*c* 2.6, CHCl₃).

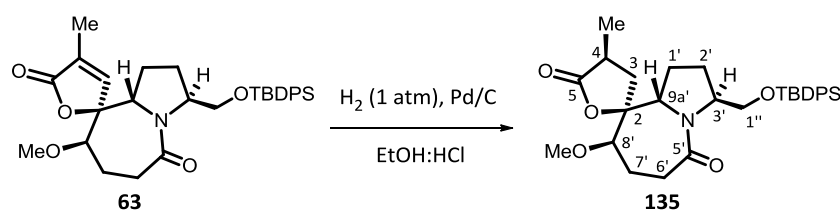
IR (ATR): 2930, 2856, 1771, 1643, 1442, 1410, 1229, 1170, 1105 cm⁻¹.

¹H-NMR (400 MHz, C₆D₆): δ 7.75 (m, 4H:4H_{Ar}), 7.24 (m, 6H:6H_{Ar}), 4.43 (d, *J* = 9.5 Hz, 1H:H_{9a'}), 4.34 (m, 1H:H_{3'}), 4.00 (dd, *J* = 9.7, 2.9 Hz, 1H:H_{1''}), 3.74 (dd, *J* = 9.7, 6.7 Hz, 1H:H_{1''}), 3.10 (s, 3H:OCH₃), 2.68 (t, *J* = 13.1 Hz, 1H:H_{6'}), 2.57 (d, *J* = 4.2 Hz, 1H:H_{8'}), 2.14 (m, 2H:H_{6'},H₄), 1.89 (m, 1H:H_{1'}), 1.71 (m, 2H:H₃,H_{1'}), 1.40 (m, 3H:2H₂,H_{7'}), 1.17 (m, 1H:H_{7'}), 1.16 (s, 9H:C(CH₃)₃), 0.98 (d, *J* = 7.1 Hz, 3H:CH₃), 0.58 (dd, *J* = 13.7, 10.7 Hz, 1H:H₃).

¹³C-NMR (100 MHz, C₆D₆): δ 178.2 (C₅), 172.8 (C_{5'}), 136.60 (C_{Ph}), 136.58 (C_{Ph}), 134.6 (C_{Ph}), 134.5 (C_{Ph}), 130.7 (C_{Ph}), 86.1/85.5 (C₂/C_{8'}), 63.9 (C_{1''}), 61.6 (C_{3'}), 59.3 (OCH₃), 57.5 (C_{9a'}), 35.4 (C₄), 35.0 (C₃), 31.1 (C_{6'}), 27.7 (C(CH₃)₃), 27.3 (C_{2'}), 26.3 (C_{1'}), 24.2 (C_{7'}), 20.1 (C(CH₃)₃), 17.6 (CH₃).

HRMS (ESI⁺): calcd for C₃₁H₄₁NO₅Si: 558.2646 [M+Na⁺]; found 558.2645.

(2*S*,4*S*,3'*S*,8'*R*,9*a*'*S*)-3'-*tert*-Butyldiphenylsilyloxymethyl-8'-methoxy-4-methylhexahydro-3*H*-spiro{furan-2,9'-pyrrolo[1,2-*a*]azepine}-5,5'(4*H*,6'*H*)-dione, 135



To a solution of lactone **63** (12.2 mg, 23 μmol) in a 1:1 mixture of EtOH and 10% HCl (1.4 ml), 10% Pd/C (11 mg, 10.2 μmol) was added. The reaction mixture was stirred at atmospheric pressure of H_2 for 24 h. Then, it was filtered through Celite[®] and the filtrate was washed with saturated solution of NaHCO_3 . The aqueous layer was extracted with CH_2Cl_2 (3x2 mL). The combined organic extracts were dried over anhydrous MgSO_4 and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (EtOAc) furnished saturated lactone **135** (11 mg, 20.5 μmol , 90% yield).

Physical and spectroscopic data of **135**:

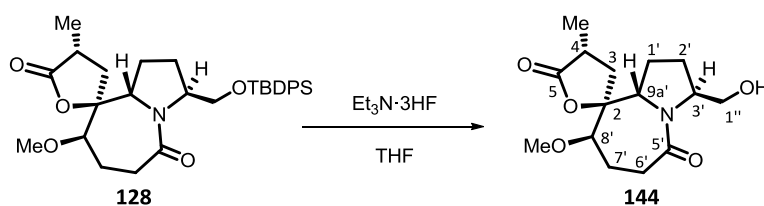
$[\alpha]_{\text{D}}^{20} = -71.0$ (c 0.1, CHCl_3).

IR (ATR): 2929, 2360, 2341, 1773, 1645, 1446, 1412, 1191, 1109, 1010 cm^{-1} .

¹H-NMR (400 MHz, C_6D_6): δ 7.76 (m, 4H:4H_{Ar}), 7.24 (m, 6H:6H_{Ar}), 4.56 (dd, $J = 9.8, 2.0$ Hz, 1H:H_{9a'}), 4.27 (m, 1H:H_{3'}), 3.93 (m, 2H:2H_{1''}), 3.07 (s, 3H:OCH₃), 2.74 (td, $J = 13.5, 2.2$ Hz, 1H:H_{6'}), 2.63 (dd, $J = 4.7, 1.9$ Hz, 1H:H_{6''}), 2.20 (ddd, $J = 13.6, 6.7, 1.8$ Hz, 1H:H_{6'}), 2.00 (m, 1H:H_{1'}), 1.90 (1H:H₄), 1.72 (m, 2H:2H₂), 1.50 (2H:H₁,H₇), 1.33 (m, 3H:2H₃,H₇), 1.16 (s, 9H:C(CH₃)₃), 0.98 (d, $J = 7.1$ Hz, 3H:CH₃).

¹³C-NMR (100 MHz, C_6D_6): δ 177.1 (C₅), 172.2 (C_{5'}), 136.1 (C_{Ph}), 134.0 (C_{Ph}), 133.9 (C_{Ph}), 130.1 (C_{Ph}), 85.9 (C₂), 81.2 (C_{8'}), 63.5 (C_{1''}), 61.0 (C_{3'}), 58.9 (OCH₃), 57.2 (C_{9a'}), 34.2 (C₄), 33.3 (C₃), 31.0 (C_{6'}), 27.2 (C(CH₃)₃), 27.0 (C_{2'}), 25.6/24.9 (C_{1'/}C_{7'}), 19.5 (C(CH₃)₃), 15.8 (CH₃).

HRMS (ESI⁺): calcd for C₃₁H₄₁NO₅Si: 558.2646 [M+Na⁺]; found 558.2640.

(2*S*,4*R*,3'*S*,8'*R*,9*a*'*S*)-3'-Hydroxymethyl-8'-methoxy-4-methylhexahydro-3*H*-spiro{furan-2,9'-pyrrolo[1,2-*a*]azepine}-5,5'(4*H*,6'*H*)-dione, 144

Et₃N·3HF (0.2 mL, 1.3 mmol) was added to a stirred solution of **128** (35 mg, 65 μmol) in THF (1.4 mL). The reaction mixture was heated at the reflux temperature for 4 h, when TLC analysis showed no starting material. The excess of Et₃N·3HF was quenched with NaHCO₃ saturated solution. Then, EtOAc was added and the aqueous phase was extracted with CH₂Cl₂ (2x2 mL). The combined organic extracts were dried over anhydrous MgSO₄ and concentrated *in vacuo*. The resulting oil was filtered through silica gel (EtOAc) to furnish alcohol **144** (16.5 mg, 55.5 μmol, 85% yield).

Physical and spectroscopic data of **144**:

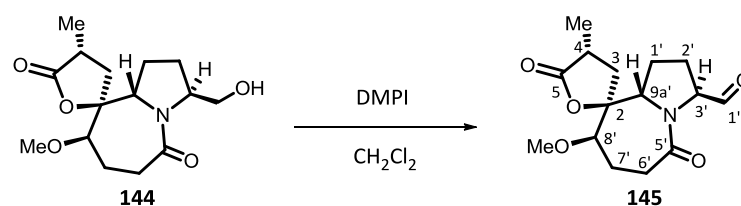
[α]_D²⁰ = -44.8 (c 1.53, CHCl₃).

IR (ATR): 3392, 2936, 1768, 1622, 1447, 1421, 1226, 1171, 1102 cm⁻¹.

¹H-NMR (400 MHz, CDCl₃): δ 4.73 (dd, *J* = 8.7, 4.2 Hz, 1H:H_{9a'}), 4.47 (s, 1H:OH), 4.18 (m, 1H:H_{3'}), 3.69 (m, 2H:2H_{1''}), 3.48 (s, 3H:OCH₃), 3.26 (d, *J* = 3.6 Hz, 1H:H_{8'}), 2.94 (td, *J* = 13.7, 1.7 Hz, 1H:H_{6'}), 2.75 (m, 1H:H₄), 2.40 (m, 1H:H₃), 2.27 (m, 1H:H_{6'}), 2.19 (m, 1H:H_{1'}), 2.08 (m, 1H:H_{7'}), 1.90 (m, 1H:H_{2'}), 1.71 (m, 3H:H_{1'},H_{2'},H_{7'}), 1.41 (dd, *J* = 14.1, 9.4 Hz, 1H:H₃), 1.32 (d, *J* = 7.2 Hz, 3H:CH₃).

¹³C-NMR (100 MHz, CDCl₃): δ 178.5 (C₅), 175.4 (C_{5'}), 86.3 (C₂), 84.3 (C_{8'}), 66.1 (C_{1''}), 64.6 (C_{3'}), 58.8 (OCH₃), 58.0 (C_{9a'}), 35.4 (C₄), 34.3 (C₃), 30.5 (C_{6'}), 27.8 (C_{2'}), 26.1 (C_{1'}), 23.3 (C_{7'}), 17.7 (CH₃).

HRMS (ESI⁺): calcd for C₁₅H₂₃NO₅: 320.1468 [M+Na⁺]; found 320.1472.

(2*S*,4*R*,3'*S*,8'*R*,9*a*'*S*)-8'-Methoxy-4-methyl-5,5'-dioxodecahydro-3*H*-spiro{furan-2,9'-pyrrolo[1,2-*a*]azepine}-3'-carbaldehyde, **145**

A commercially available solution of Dess-Martin periodinane in CH_2Cl_2 (15% wt, 285 μL , 137.3 μmol) was added *via* syringe to a solution of alcohol **144** (32 mg, 107.6 μmol) in dry CH_2Cl_2 (0.9 mL). After 2 h of stirring at room temperature, TLC analysis indicated the complete consumption of the starting material. The solution was washed with NaHCO_3 saturated solution containing a sevenfold excess of $\text{Na}_2\text{S}_2\text{O}_3$, the aqueous phase was extracted with CH_2Cl_2 (2x2 mL) and the combined organic extracts were dried over anhydrous MgSO_4 and concentrated under vacuum. Flash column chromatography of the residue on silica gel (EtOAc) provided aldehyde **145** (26.4 mg, 89.4 μmol , 83% yield).

Physical and spectroscopic data of **145**:

$[\alpha]_{\text{D}}^{20} = -126.5$ (*c* 0.54, CHCl_3).

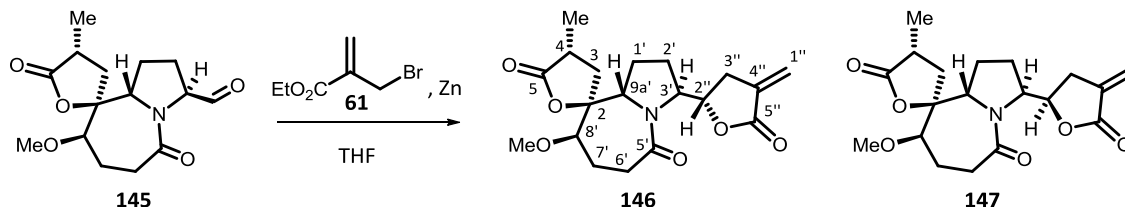
IR (ATR): 2936, 1752, 1714, 1622, 1422, 1236, 1197, 1100, 1011 cm^{-1} .

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 9.45 (d, $J = 2.1$ Hz, 1H: $\text{H}_{1''}$), 4.81 (dd, $J = 8.9, 4.4$ Hz, 1H: $\text{H}_{9a'}$), 4.51 (t, $J = 6.7$ Hz, 1H: $\text{H}_{3'}$), 3.49 (s, 3H: OCH_3), 3.29 (d, $J = 4.8$ Hz, 1H: $\text{H}_{8'}$), 3.00 (t, $J = 13.8$ Hz, 1H: $\text{H}_{6'}$), 2.74 (m, 1H: H_4), 2.41 (dd, $J = 14.2, 10.8$ Hz, 1H: H_3), 2.31 (dd, $J = 14.5, 6.9$ Hz, 1H: $\text{H}_{6'}$), 2.19 (m, 1H: $\text{H}_{1'}$), 2.10 (m, 1H: H_7), 1.94 (m, 2H: $\text{H}_{2'}$), 1.79 (m, 2H: $\text{H}_{1'}$, H_7), 1.44 (dd, $J = 14.2, 9.4$ Hz, 1H: H_3), 1.33 (d, $J = 7.2$ Hz, 3H: CH_3).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 197.2 ($\text{C}_{1''}$), 178.3 (C_5), 173.8 ($\text{C}_{5'}$), 86.2 (C_2), 84.1 (C_8), 67.2 (C_3), 58.8 (OCH_3), 57.1 ($\text{C}_{9a'}$), 35.4 (C_4), 34.2 (C_3), 29.2 ($\text{C}_{6'}$), 26.8 ($\text{C}_{1'}$), 24.8 (C_2), 23.1 (C_7), 17.7 (CH_3).

HRMS (ESI+): calcd for $\text{C}_{15}\text{H}_{21}\text{NO}_5$: 318.1317 [$\text{M}+\text{Na}^+$]; found 318.1312.

(2*S*,4*R*,3'*S*,8'*R*,9*a*'*S*,2''*S*)-, **146**, and (2*S*,4*R*,3'*S*,8'*R*,9*a*'*S*,2''*R*)-8'-Methoxy-4-methyl-3'-(4-methylene-5-oxotetrahydrofuran-2-yl)hexahydro-3*H*-spiro{furan-2,9'-pyrrolo[1,2-*a*]azep-ine}-5,5'(4*H*,6'*H*)-dione, **147**



To a stirred solution of aldehyde **145** (18.1 mg, 61.3 μmol) in dry THF (0.6 mL) under N_2 atmosphere, activated Zn^{51} (14.1 mg, 0.22 mmol) was added. The solution was heated up and, when reflux started, a solution of ethyl 2-(bromomethyl)acrylate, **61** (9.3 μL , 67.3 μmol), in dry THF (0.38 mL) was added. After 1 h, TLC analysis of the reaction mixture (EtOAc) revealed the absence of the starting aldehyde. The reaction mixture was filtered through Celite[®] and the organic solvent was evaporated under vacuum to afford a mixture of diastereoisomers **146** and **147** (20.3 mg, 55.9 μmol , 91% yield), as a colorless oil. This residue was purified by flash column chromatography on Florisil[®] (EtOAc) to provide the following fractions: i) *threo*-bislactone **146** (7.9 mg, 21.7 μmol , 36% yield); ii) a mixture of bislactones **146** and **147** (4 mg, 11.0 μmol , 18% yield); iii) *erythro*-bislactone **147** (8.3 mg, 22.8 μmol , 37% yield).

Physical and spectroscopic data of **146** (*threo*):

$[\alpha]_{\text{D}}^{20} = -33.2$ (c 0.79, CHCl_3).

IR (ATR): 2934, 1761, 1641, 1445, 1408, 1232, 1164, 1103, 1014 cm^{-1} .

¹H-NMR (400 MHz, CDCl_3): δ 6.21 (m, 1H:H_{1''}), 5.64 (m, 1H:H_{1'''}), 5.17 (m, 1H:H_{2''}), 4.77 (dd, $J = 9.1, 2.8$ Hz, 1H:H_{9a'}), 4.61 (m, 1H:H_{3'}), 3.48 (s, 3H:OCH₃), 3.26 (d, $J = 4.0$ Hz, 1H:H_{8'}), 2.89 (m, 3H:2H_{3''},H_{6'}), 2.76 (m, 1H:H₄), 2.31 (m, 3H:H_{1'},H_{6'},H₃), 2.08 (m, 1H:H_{7'}), 1.82 (m, 4H:2H_{2'},H_{1'},H_{7'}), 1.42 (dd, $J = 14.2, 9.6$ Hz, 1H:H₃), 1.32 (d, $J = 7.2$ Hz, 3H:CH₃).

¹³C-NMR (100 MHz, CDCl_3): δ 178.4 (C₅), 175.5 (C_{5'}), 170.0 (C_{5''}), 134.0 (C_{1'''}), 122.5 (C_{4''}), 86.1 (C₂), 84.3 (C_{8'}), 76.5 (C_{2''}), 61.9 (C_{3'}), 58.8 (OCH₃), 58.2 (C_{9a'}), 35.4 (C₄), 34.3 (C₃), 30.3 (C_{6'}), 29.7 (C_{3''}), 26.3 (C_{1'}), 25.6 (C_{2'}), 23.2 (C_{7'}), 17.6 (CH₃).

HRMS (ESI⁺): calcd for C₁₉H₂₅NO₆: 386.1574 [M+Na⁺]; found 386.1573.

Physical and spectroscopic data of **147** (erythro):

$[\alpha]_D^{20} = -78.0$ (c 0.83, CHCl₃).

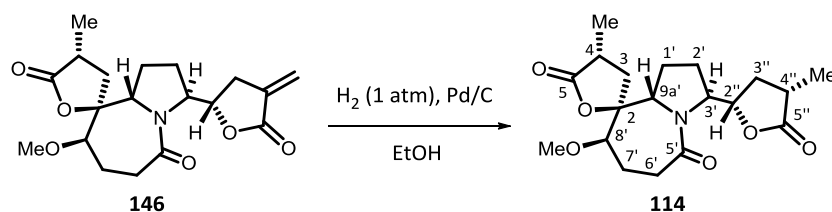
IR (ATR): 2935, 1763, 1638, 1444, 1412, 1257, 1166, 1105 cm⁻¹.

¹H-NMR (400 MHz, CDCl₃): δ 6.27 (t, *J* = 2.7 Hz, 1H:H_{1'''}), 5.68 (t, *J* = 2.7 Hz, 1H:H_{1'''}), 5.26 (dd, *J* = 8.2, 6.5 Hz, 1H:H_{2''}), 4.85 (d, *J* = 9.9 Hz, 1H:H_{9a'}), 4.38 (m, 1H:H_{3'}), 3.48 (s, 3H:OCH₃), 3.25 (d, *J* = 4.4 Hz, 1H:H_{8'}), 3.11 (ddt, *J* = 17.7, 8.4, 2.6 Hz, 1H:H_{3''}), 3.00 (t, *J* = 12.9 Hz, 1H:H_{6'}), 2.67 (m, 1H:H₄), 2.54 (ddt, *J* = 17.7, 6.2, 3.0 Hz, 1H:H_{3''}), 2.33 (m, 3H:H_{1'},H_{6'},H₃), 2.08 (m, 1H:H₇), 1.79 (m, 4H:H_{1'},2H_{2'},H₇), 1.40 (dd, *J* = 14.0, 10.4 Hz, 1H:H₃), 1.30 (d, *J* = 7.1 Hz, 3H:CH₃).

¹³C-NMR (63 MHz, CDCl₃): δ 178.4 (C₅), 174.6 (C_{5'}), 170.0 (C_{5''}), 133.6 (C_{4''}), 123.3 (C_{1'''}), 85.7 (C₂), 84.5 (C_{8'}), 75.5 (C_{2''}), 63.2 (C_{3'}), 58.9 (OCH₃), 57.4 (C_{9a'}), 35.2/34.7 (C₄/C₃), 30.5/30.4 (C_{3''}/C_{6'}), 26.4/23.5 (C₁/C₂), 23.4 (C₇), 17.3 (CH₃).

HRMS (ESI+): calcd for C₁₉H₂₅NO₆: 386.1574 [M+Na⁺]; found 386.1569.

(2*S*,4*R*,3'*S*,8'*R*,9*a*'*S*,2''*S*,4''*S*)-8'-Methoxy-4-methyl-3'-(4-methyl-5-oxotetrahydrofuran-2-yl)hexahydro-3*H*-spiro{furan-2,9'-pyrrolo[1,2-*a*]azepine}-5,5'(4*H*,6'*H*)-dione, **114**



To a solution of bislactone **146** (8.0 mg, 21.7 μmol) in a EtOH (1 ml), 10% Pd/C (9.2 mg, 8.6 μmol) was added. The reaction mixture was stirred at atmospheric pressure of H₂ for 4 h. Then, it was filtered through Celite® and concentrated under reduced pressure to furnish bislactone **114** (8.0 mg, 21.6 μmol, quantitative yield).

Physical and spectroscopic data of **114**:

$[\alpha]_D^{20} = -31.6$ (c 0.82, CHCl₃).

IR (ATR): 2937, 1769, 1645, 1448, 1412, 1380, 1169, 1103, 1012 cm⁻¹.

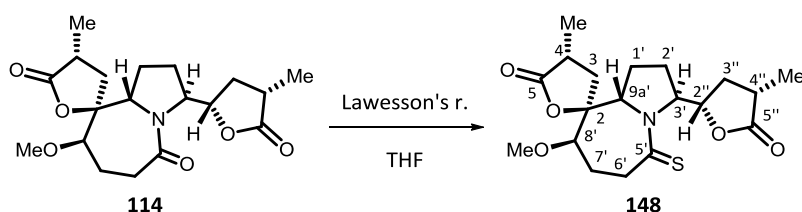
4. EXPERIMENTAL PART

¹H-NMR (400 MHz, CDCl₃): δ 5.05 (ddd, *J* = 11.0, 5.3, 4.6 Hz, 1H:H_{2''}), 4.74 (m, 1H:H_{9a'}), 4.65 (m, 1H:H_{3'}), 3.48 (s, 3H:OCH₃), 3.26 (d, *J* = 3.7 Hz, 1H:H_{8'}), 2.88 (m, 1H:H_{6'}), 2.73 (m, 1H:H₄), 2.61 (m, 1H:H_{4''}), 2.34 (dd, *J* = 14.1, 10.7 Hz, 1H:H₃), 2.25 (m, 3H:H_{1'},H_{6'},H_{3''}), 2.08 (m, 1H:H_{7'}), 1.86 (m, 3H:2H_{2'},H_{1'}), 1.74 (m, 1H:H_{7''}), 1.52 (q, *J* = 12.0 Hz, 1H:H_{3''}), 1.40 (dd, *J* = 14.1, 9.9 Hz, 1H:H₃), 1.32 (d, *J* = 7.2 Hz, 3H:CH₃), 1.25 (d, *J* = 7.0 Hz, 3H:CH₃).

¹³C-NMR (100 MHz, CDCl₃): δ 178.8 (C₅), 178.4 (C_{5''}), 174.0 (C_{5'}), 86.2 (C₂), 84.5 (C_{8'}), 76.8 (C_{2''}), 60.1 (C_{3'}), 58.8 (OCH₃), 57.7 (C_{9a'}), 35.9 (C_{4''}), 35.3 (C₄), 34.3 (C₃), 32.6 (C_{3''}), 30.5 (C_{6'}), 26.6 (C_{1'}), 25.0 (C_{2'}), 23.4 (C_{7'}), 17.5 (CH₃), 15.0 (CH₃).

HRMS (ESI⁺): calcd for C₁₉H₂₇NO₆: 388.1731 [M+Na⁺]; found 388.1734.

(2*S*,4*R*,3'*S*,8'*R*,9*a*'*S*,2''*S*,4''*S*)-8'-Methoxy-4-methyl-3'-(4-methyl-5-oxotetrahydrofuran-2-yl)-5'-thioxooctahydro-3*H*-spiro[furan-2,9'-pyrrolo[1,2-*a*]azepin]-5(4*H*)-one, **148**



Lawesson's reagent (5.7 mg, 14.1 μmol) was added to a solution of **114** (8.2 mg, 22.4 μmol) in dry THF (1 mL) and the mixture was heated at the reflux temperature for 45 min. The solvent was removed under vacuum and the residue was filtered through Al₂O₃ Brockman I using EtOAc as eluent. Evaporation of the solvent under reduced pressure afforded a residue, which was identified as the thiolactam **148**.

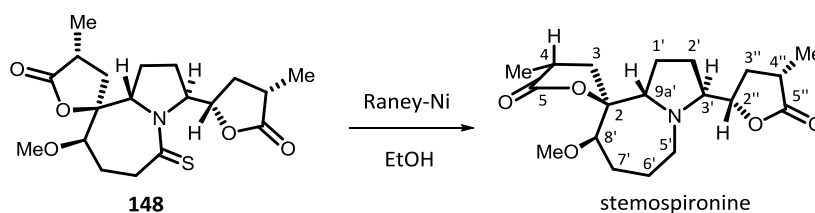
Spectroscopic data of **148:**

IR (ATR): 2926, 1769, 1428, 1376, 1333, 1260, 1222, 1193, 1166, 1088, 1059, 1023 cm⁻¹.

¹H-NMR (400 MHz, CDCl₃): δ 5.47 (dt, *J* = 11.3, 4.9 Hz, 1H:H_{2''}), 5.37 (m, 1H:H_{3'}), 5.04 (d, *J* = 9.3 Hz, 1H:H_{9a'}), 3.48 (s, 3H:OCH₃), 3.26 (d, *J* = 2.6 Hz, 1H:H_{8'}), 3.18 (td, *J* = 12.7, 1.5 Hz, 1H:H_{6'}), 3.06 (m, 1H:H_{6'}), 2.75 (m, 1H:H₄), 2.63 (m, 1H:H_{4''}), 2.27 (m, 3H:H_{2'},H₃,H_{3''}), 2.07 (m, 4H:2H_{1'},H_{2'},H_{7'}), 1.85 (m, 1H:H_{7''}), 1.57 (m, 1H:H_{3''}), 1.45 (dd, *J* = 14.3, 10.1 Hz, 1H:H₃), 1.32 (d, *J* = 7.2 Hz, 3H:CH₃), 1.27 (d, *J* = 7.0 Hz, 3H:CH₃).

$^{13}\text{C-NMR}$ (63 MHz, CDCl_3): δ 207.0 (C_5), 178.3/178.2 ($\text{C}_5/\text{C}_{5''}$), 85.3/84.6 (C_2/C_8), 74.3 ($\text{C}_{2''}$), 65.0 ($\text{C}_{3'}$), 62.3 ($\text{C}_{9a'}$), 58.9 (OCH_3), 40.9, 36.1, 35.1, 33.0, 29.9, 27.1, 25.5, 25.1, 17.4 (CH_3), 15.0 (CH_3).

(2*S*,4*R*,3'*S*,8'*R*,9*a*'*S*,2''*S*,4''*S*)-8'-Methoxy-4-methyl-3'-(4-methyl-5-oxotetrahydrofuran-2-yl)octahydro-3*H*-spiro{furan-2,9'-pyrrolo[1,2-*a*]azepine}-5(4*H*)-one, stemospirone



Thiolactam **148** was dissolved in EtOH (1 mL), Raney-Ni (aprox. 50 mg) was added and the reaction mixture was heated at the reflux temperature for 1 h. Then, it was filtered through Celite® and the solvent was evaporated *in vacuo* to provide stemospirone (4.1 mg, 11.8 μmol , 54% yield from **114**, two steps).

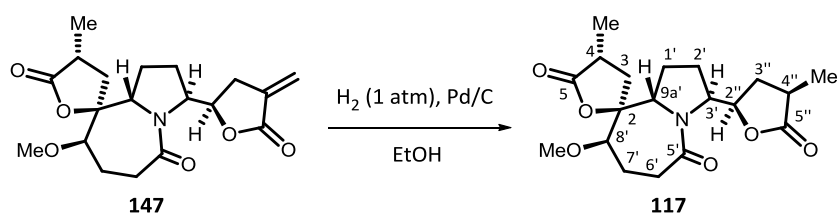
Physical and spectroscopic data of stemospirone:

$[\alpha]_{\text{D}}^{20} = -8.6$ (c 0.46, CHCl_3). (lit.¹¹ $[\alpha]_{\text{D}}^{27} = -8.2$ (c 0.92, CHCl_3)).

$^1\text{H-NMR}$ (600 MHz, CDCl_3): δ 4.36 (m, 1H: $\text{H}_{2''}$), 3.78 (m, 1H: $\text{H}_{9a'}$), 3.40 (s, 3H: OCH_3), 3.30 (m, 1H: $\text{H}_{3'}$), 3.22 (d, $J = 5.6$ Hz, 1H: $\text{H}_{8'}$), 3.11 (m, 2H: $\text{H}_{5'}$), 2.70 (m, 1H)/2.61 (m, 1H)/2.47 (m, 1H)/2.38 (m, 1H) ($\text{H}_4/\text{H}_{4''}/\text{H}_3/\text{H}_{3''}$), 1.95 (m, 2H)/1.83 (m, 2H)/1.62 (m, 6H) ($\text{H}_{1'}/\text{H}_{2'}/\text{H}_{6'}/\text{H}_{7'}/\text{H}_3/\text{H}_{3''}$), 1.31 (d, $J = 7.3$ Hz, 3H: CH_3), 1.26 (d, $J = 7.1$ Hz, 3H: CH_3).

$^{13}\text{C-NMR}$ (150 MHz, CDCl_3) δ : 179.5 ($\text{C}_5 + \text{C}_{5''}$), 90.6 (C_2), 85.4 ($\text{C}_{8'}$), 80.1 ($\text{C}_{2''}$), 67.9 ($\text{C}_{9a'}$), 63.2 ($\text{C}_{3'}$), 58.2 (OCH_3), 49.0 ($\text{C}_{5'}$), 35.8/35.3/35.1/34.7 ($\text{C}_4/\text{C}_{4''}/\text{C}_3/\text{C}_{3''}$), 27.2/26.7/25.8/22.4 ($\text{C}_{1'}/\text{C}_{2'}/\text{C}_{6'}/\text{C}_{7'}$), 17.7 (CH_3), 15.0 (CH_3).

(2*S*,4*R*,3'*S*,8'*R*,9*a*'*S*,2''*R*,4''*R*)-8'-Methoxy-4-methyl-3'-(4-methyl-5-oxotetrahydrofuran-2-yl)hexahydro-3*H*-spiro{furan-2,9'-pyrrolo[1,2-*a*]azepine}-5,5'(4*H*,6'*H*)-dione, **117**



To a solution of bislactone **147** (8.3 mg, 22.8 μmol) in EtOH (1 mL), 10% Pd/C (10.9 mg, 10.2 μmol) was added. The reaction mixture was stirred at atmospheric pressure of H_2 for 4 h. Then, it was filtered through Celite[®] and concentrated under reduced pressure to furnish bislactone **117** (7.8 mg, 21.3 μmol , 94% yield).

Physical and spectroscopic data of **117**:

$[\alpha]_{\text{D}}^{20} = -41.4$ (c 0.73, CHCl_3).

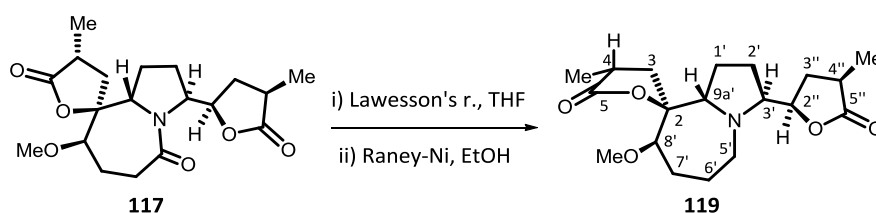
IR (ATR): 2935, 1768, 1639, 1444, 1412, 1232, 1173, 1103, 1021 cm^{-1} .

¹H-NMR (400 MHz, CDCl_3): δ 5.02 (ddd, $J = 11.0, 5.6, 1.6$ Hz, 1H:H_{2''}), 4.80 (d, $J = 9.7$ Hz, 1H:H_{9a'}), 4.35 (brd, $J = 9.1$ Hz, 1H:H_{3'}), 3.48 (s, 3H:OCH₃), 3.24 (d, $J = 4.1$ Hz, 1H:H_{8'}), 2.95 (td, $J = 13.7, 1.6$ Hz, 1H:H_{6'}), 2.67 (m, 2H:H₄,H_{4''}), 2.47 (m, 2H:H_{3''},H_{1'}), 2.34 (dd, $J = 14.0, 10.5$ Hz, 1H:H₃), 2.24 (dd, $J = 13.7, 6.0$ Hz, 1H:H_{6'}), 2.07 (m, 1H:H_{7'}), 1.80 (m, 4H:H_{1'},2H_{2'},H_{7'}), 1.47 (q, $J = 12.0$ Hz, 1H:H_{3''}), 1.38 (dd, $J = 13.9, 10.4$ Hz, 1H:H₃), 1.31 (d, $J = 7.2$ Hz, 3H:CH₃), 1.27 (d, $J = 7.0$ Hz, 3H:CH₃).

¹³C-NMR (63 MHz, CDCl_3): δ 179.0 (C₅), 178.4 (C_{5''}), 174.0 (C_{5'}), 85.9 (C₂), 84.6 (C_{8'}), 77.2 (C_{2''}), 61.8 (C_{3'}), 58.8 (OCH₃), 57.1 (C_{9a'}), 35.7/35.2/34.7/34.4 (C₃/C_{3''}/C₄/C_{4''}), 30.5 (C_{6'}), 26.5/23.8/23.5 (C_{1'}/C₂/C_{7'}), 17.3 (CH₃), 15.1 (CH₃).

HRMS (ESI+): calcd for C₁₉H₂₇NO₆: 388.1731 [M+Na⁺]; found 388.1727.

(2*S*,4*R*,3'*S*,8'*R*,9*a*'*S*,2''*R*,4''*R*)-8'-Methoxy-4-methyl-3'-(4-methyl-5-oxotetrahydrofuran-2-yl)octahydro-3*H*-spiro{furan-2,9'-pyrrolo[1,2-*a*]azepine}-5(4*H*)-one, **119**



Lawesson's reagent (6.3 mg, 15.6 μmol) was added to a solution of **117** (7.8 mg, 21.3 μmol) in dry THF (1 mL) and the mixture was heated at the reflux temperature for 45 min. The solvent was removed under vacuum and the residue was filtered through Al_2O_3 Brockman I, using EtOAc as eluent. After evaporation of the solvent under reduced pressure, the resulting solid was dissolved in EtOH (1 mL). Next, Raney-Ni (50 mg) was added to the solution and the reaction mixture was heated at the reflux temperature for 1 h. Then, it was filtered through Celite® and the solvent was evaporated *in vacuo* to furnish amine **119** (2.8 mg, 8.1 μmol , 52% yield).

Physical and spectroscopic data of **119**:

$[\alpha]_{\text{D}}^{20} = -28.2$ (*c* 0.28, CHCl_3).

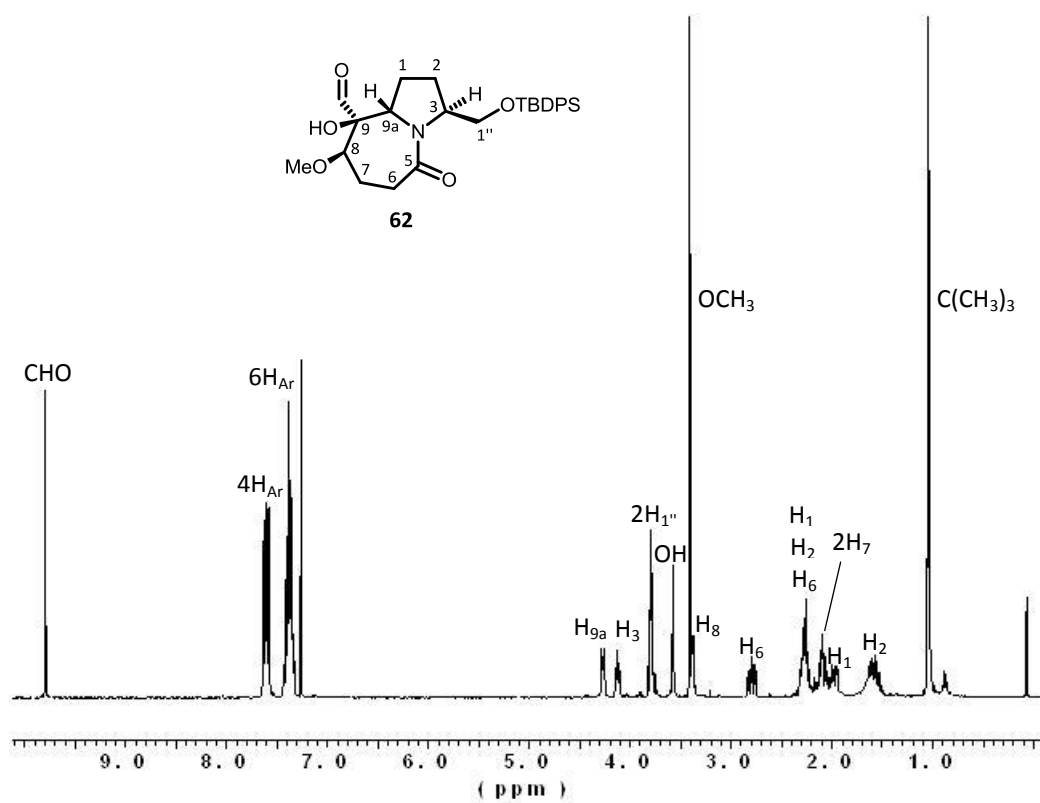
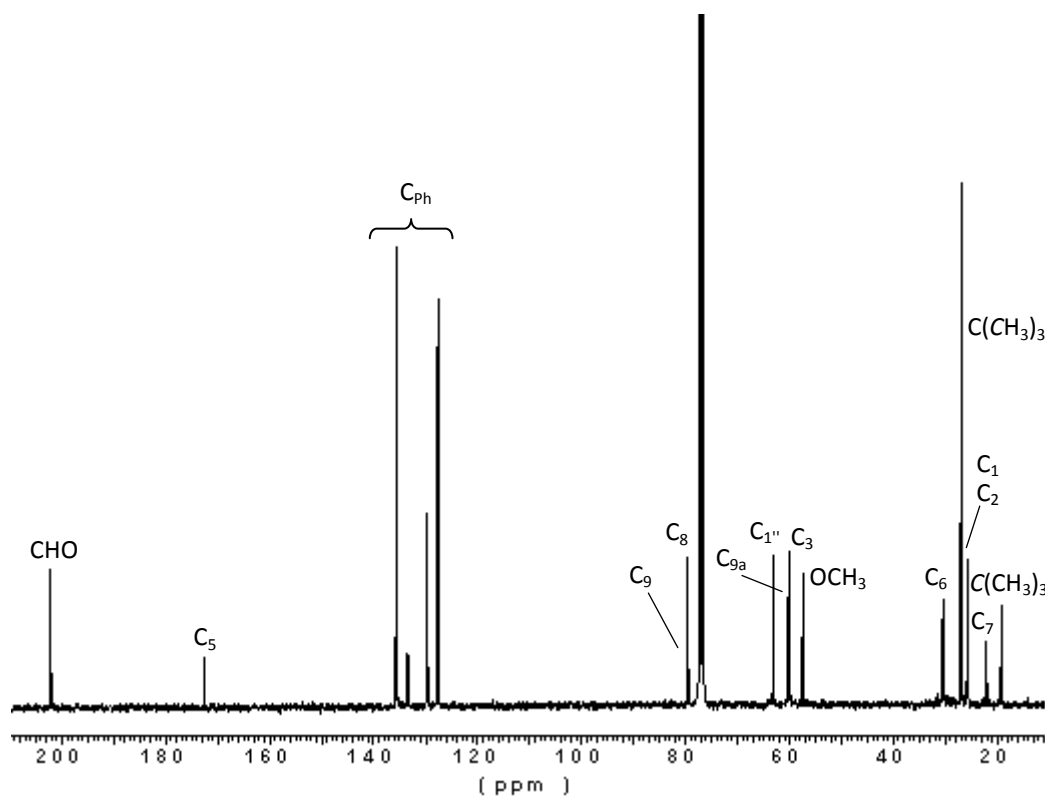
IR (ATR): 2935, 2877, 1764, 1456, 1376, 1335, 1264, 1198, 1173, 1106, 1014 cm^{-1} .

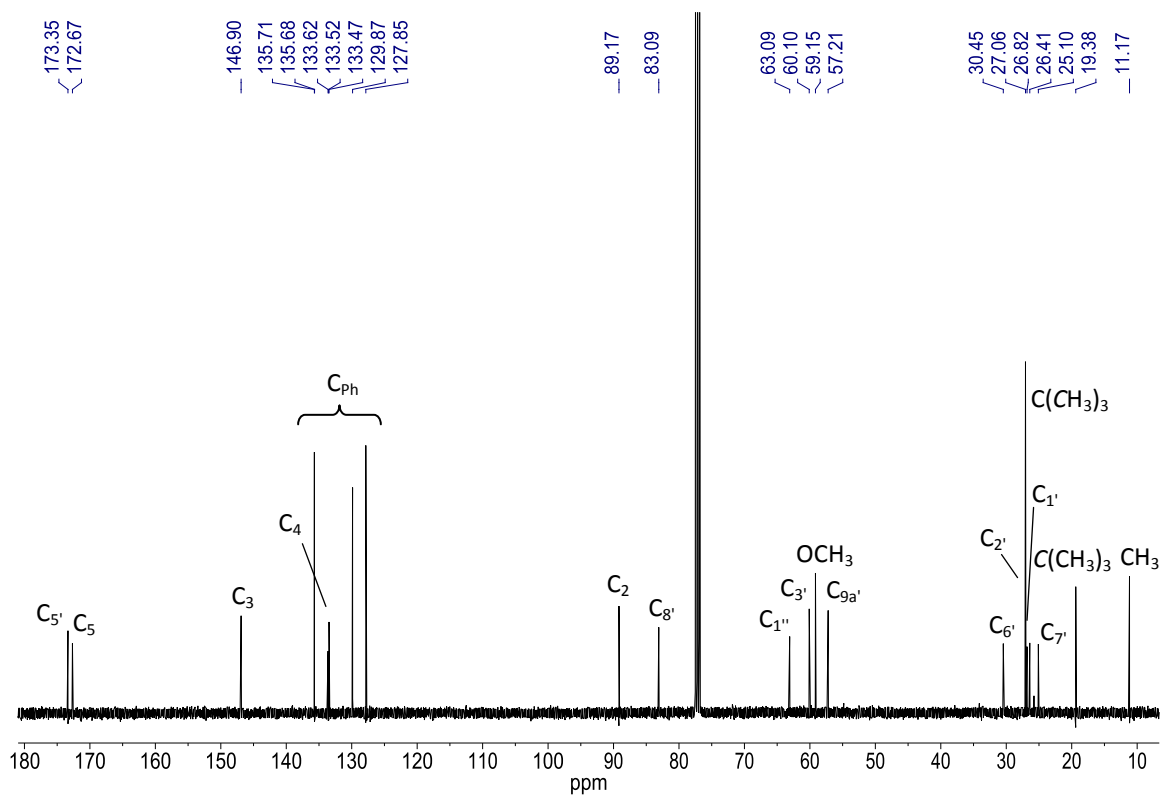
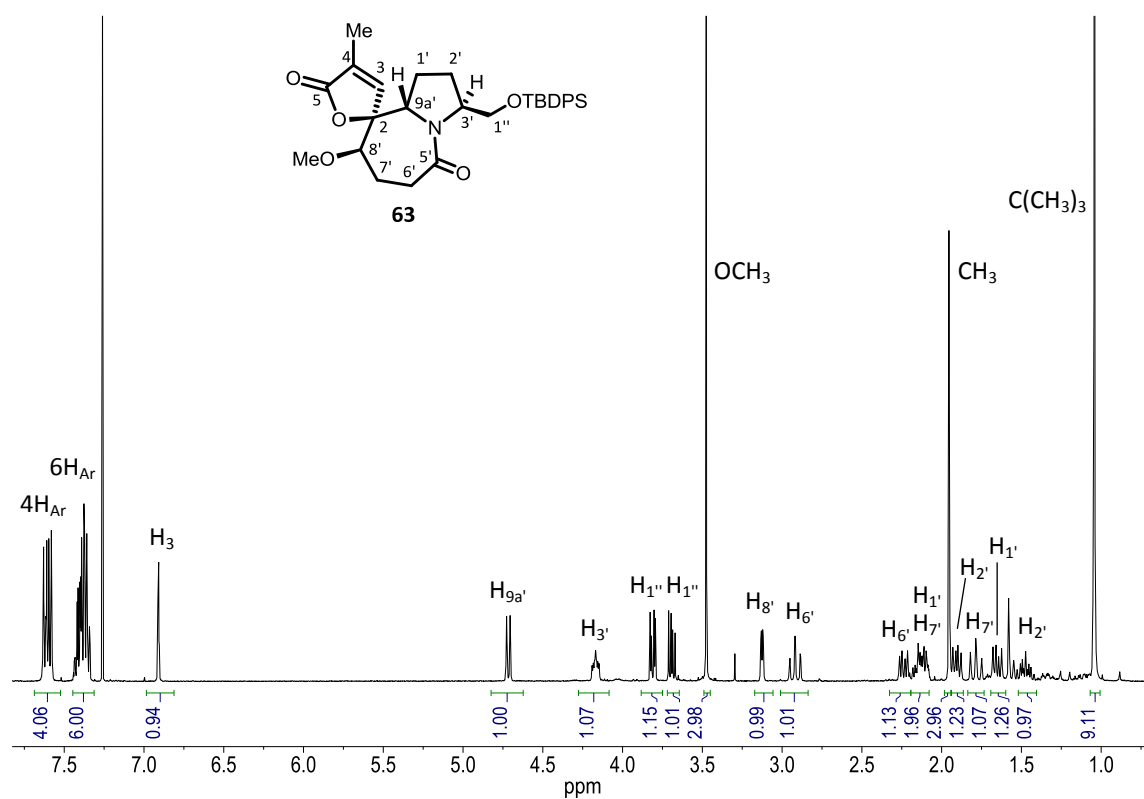
$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 4.52 (ddd, $J = 10.5, 5.8, 3.1$ Hz, 1H: $\text{H}_{2''}$), 3.77 (dd, $J = 8.1, 5.4$ Hz, 1H: $\text{H}_{9a'}$), 3.40 (s, 3H: OCH_3), 3.38 (m, 1H: $\text{H}_{3'}$), 3.20 (dd, $J = 7.1, 2.1$ Hz, 1H: $\text{H}_{8'}$), 3.03 (ddd, $J = 12.0, 8.0, 3.7$ Hz, 1H: $\text{H}_{5'}$), 2.88 (ddd, $J = 12.0, 7.5, 4.3$ Hz, 1H: $\text{H}_{5'}$), 2.68 (m, 2H: $\text{H}_4, \text{H}_{4''}$), 2.45 (dd, $J = 13.6, 10.9$ Hz, 1H: H_3), 2.37 (ddd, $J = 12.5, 8.8, 5.8$ Hz, 1H: $\text{H}_{3''}$), 2.05 (ddd, $J = 16.2, 13.0, 8.2$ Hz, 1H: $\text{H}_{1'}$), 1.88 (m, 3H: $\text{H}_2, \text{H}_{6'}, \text{H}_7$), 1.60 (m, 6H: $\text{H}_{1'}, \text{H}_2, \text{H}_{6'}, \text{H}_7, \text{H}_3, \text{H}_{3''}$), 1.29 (t, $J = 7.2$ Hz, 6H: 2CH_3).

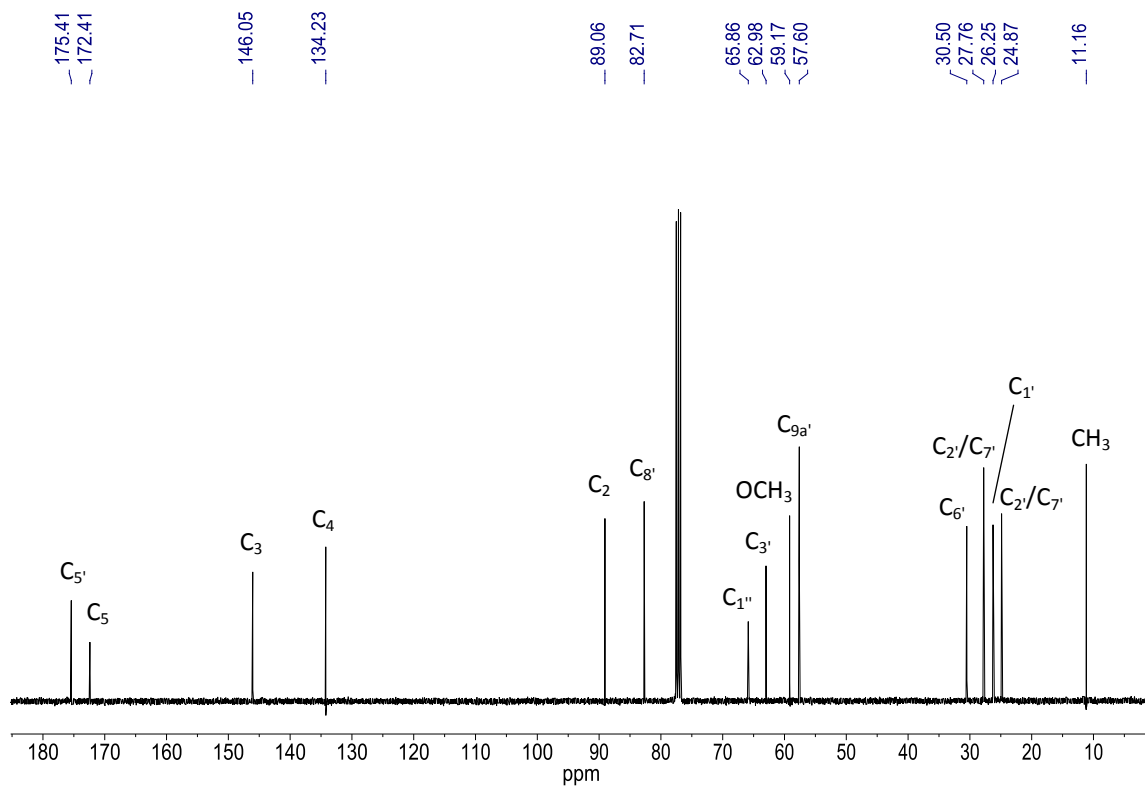
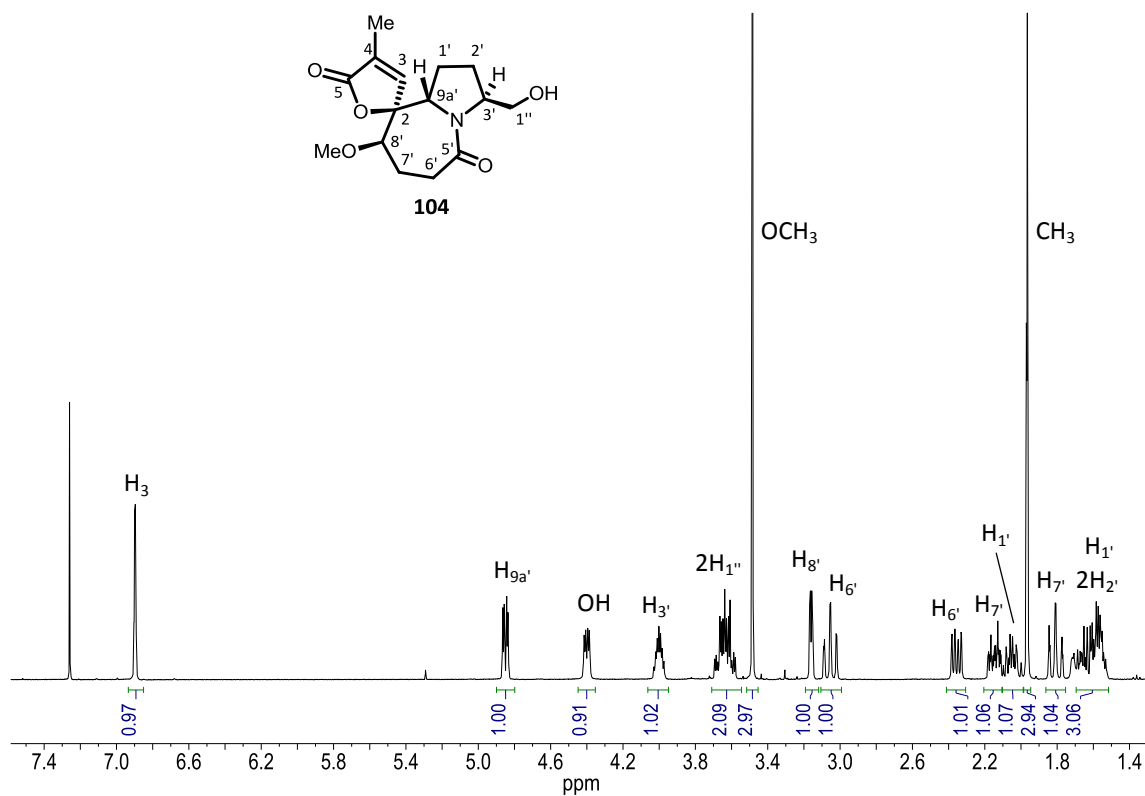
$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 179.5/179.3 ($\text{C}_5/\text{C}_{5''}$), 90.4 (C_2), 85.5 ($\text{C}_{8'}$), 78.6 ($\text{C}_{2''}$), 66.1 ($\text{C}_{9a'}$), 63.6 ($\text{C}_{3'}$), 58.2 (OCH_3), 49.1 ($\text{C}_{5'}$), 35.8/35.7/35.1/33.9 ($\text{C}_4/\text{C}_{4''}/\text{C}_3/\text{C}_{3''}$), 27.1/26.2/25.9/22.9 ($\text{C}_6'/\text{C}_{1'}/\text{C}_2'/\text{C}_7'$), 17.5 (CH_3), 15.3 (CH_3).

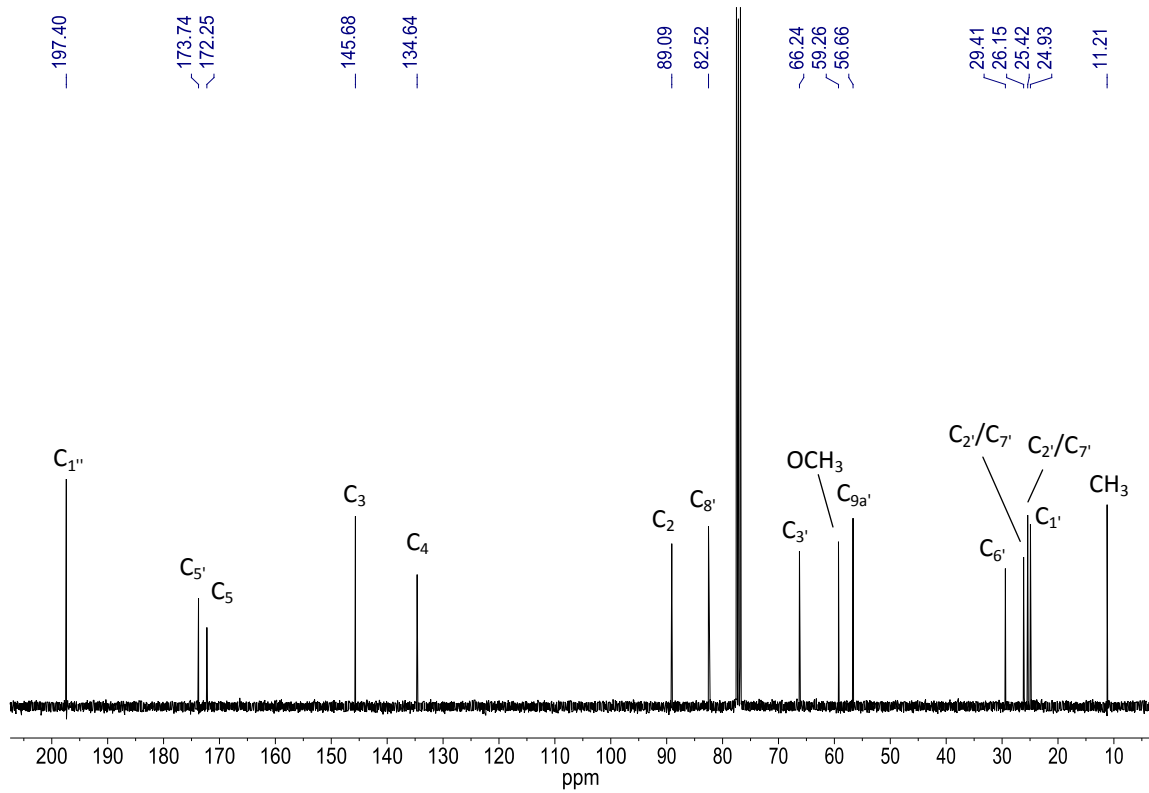
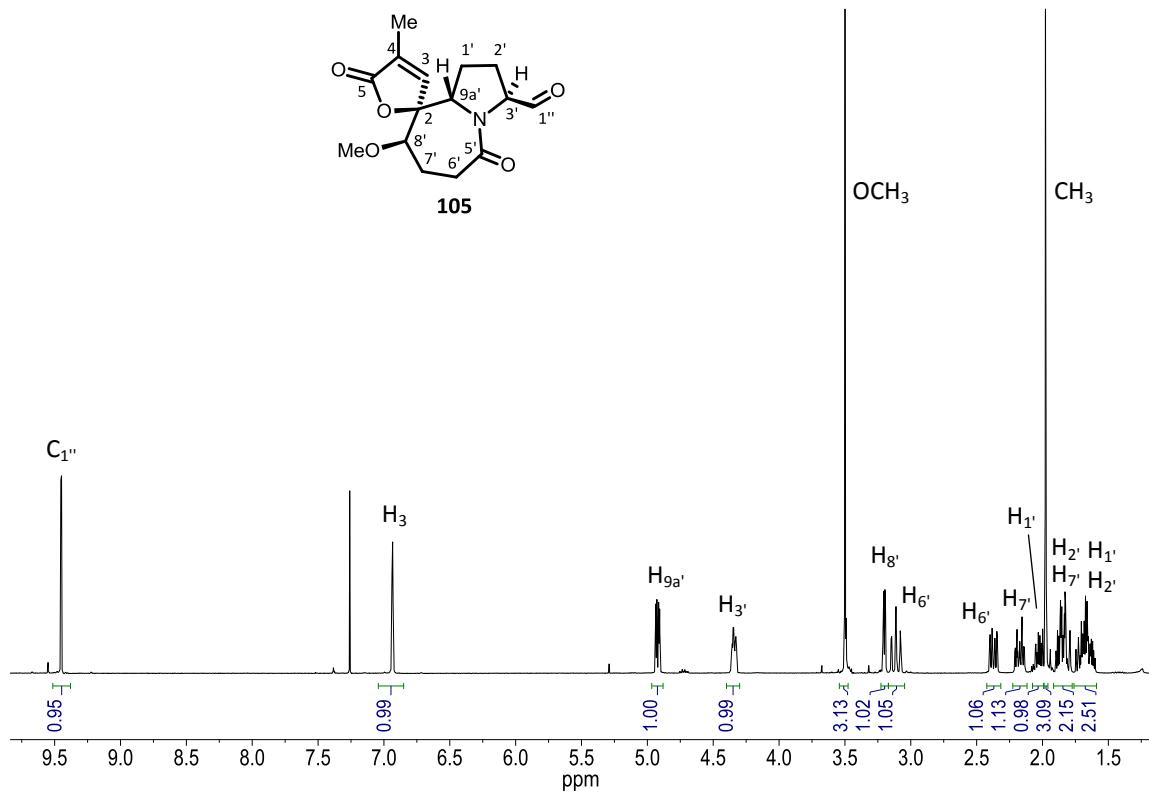
HRMS (ESI+): calcd for $\text{C}_{19}\text{H}_{29}\text{NO}_5$: 352.2118 [$\text{M}+\text{H}^+$]; found 352.2120.

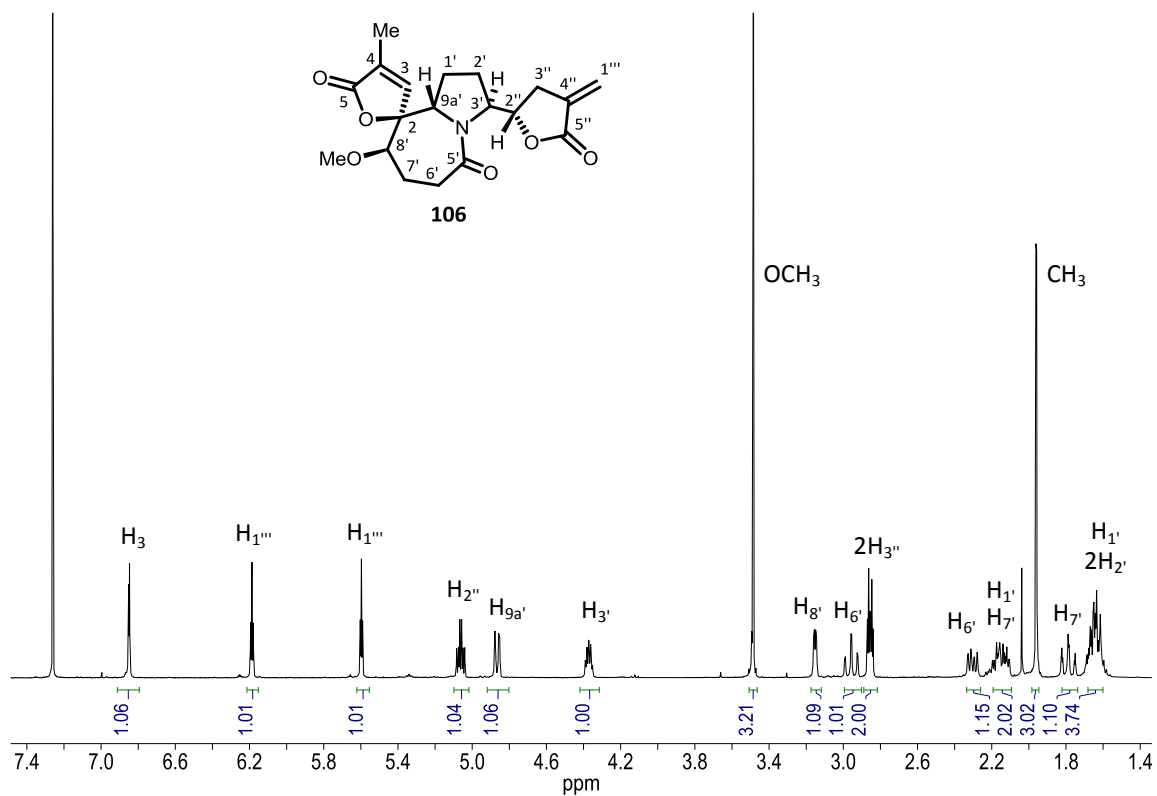
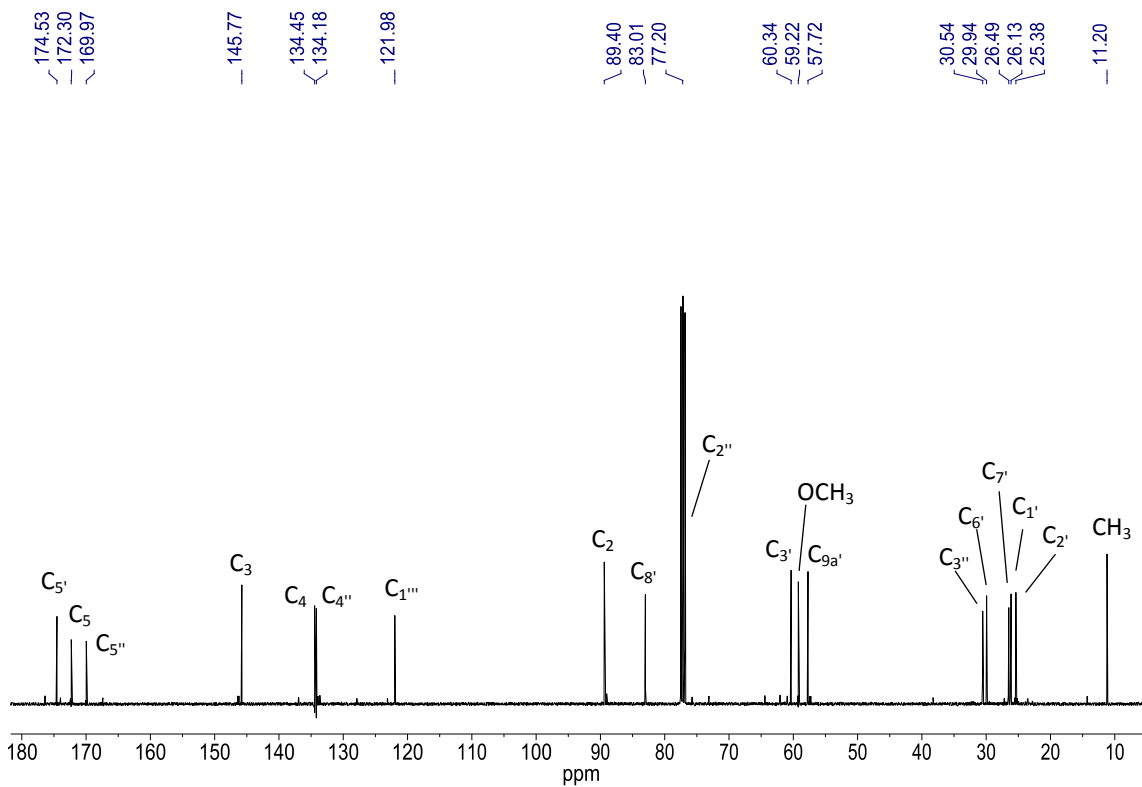
5. Annex Spectra

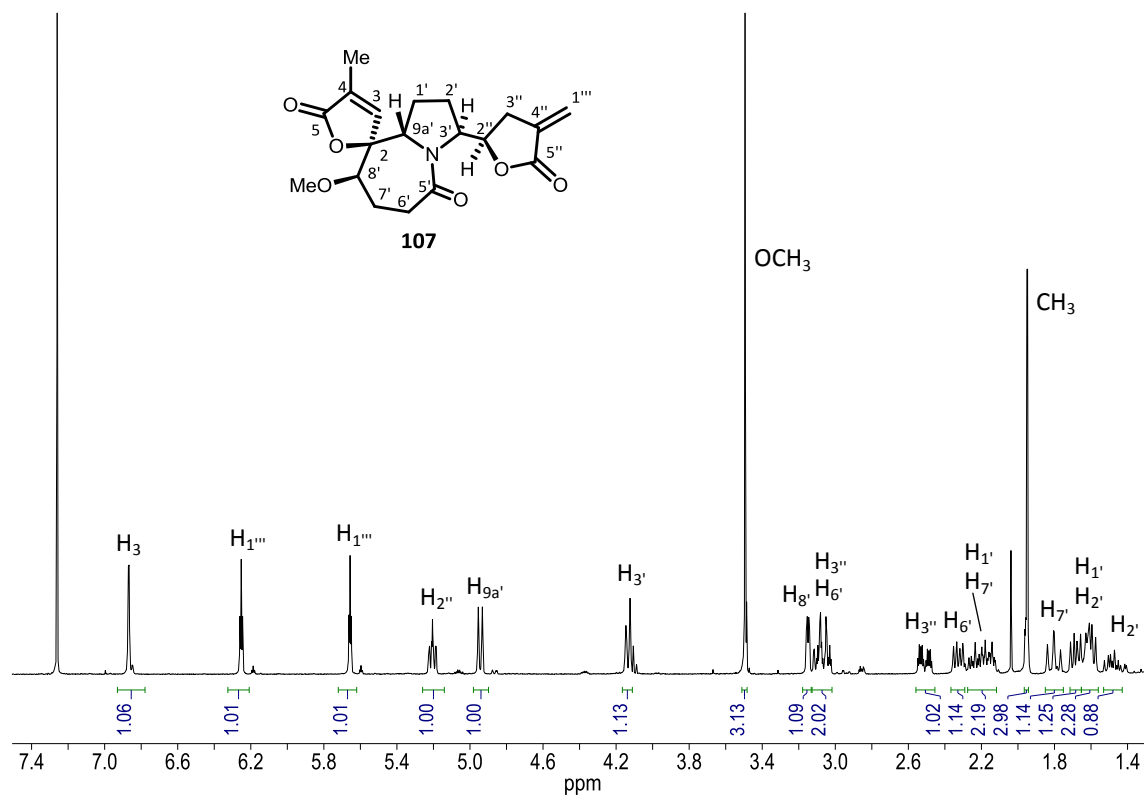
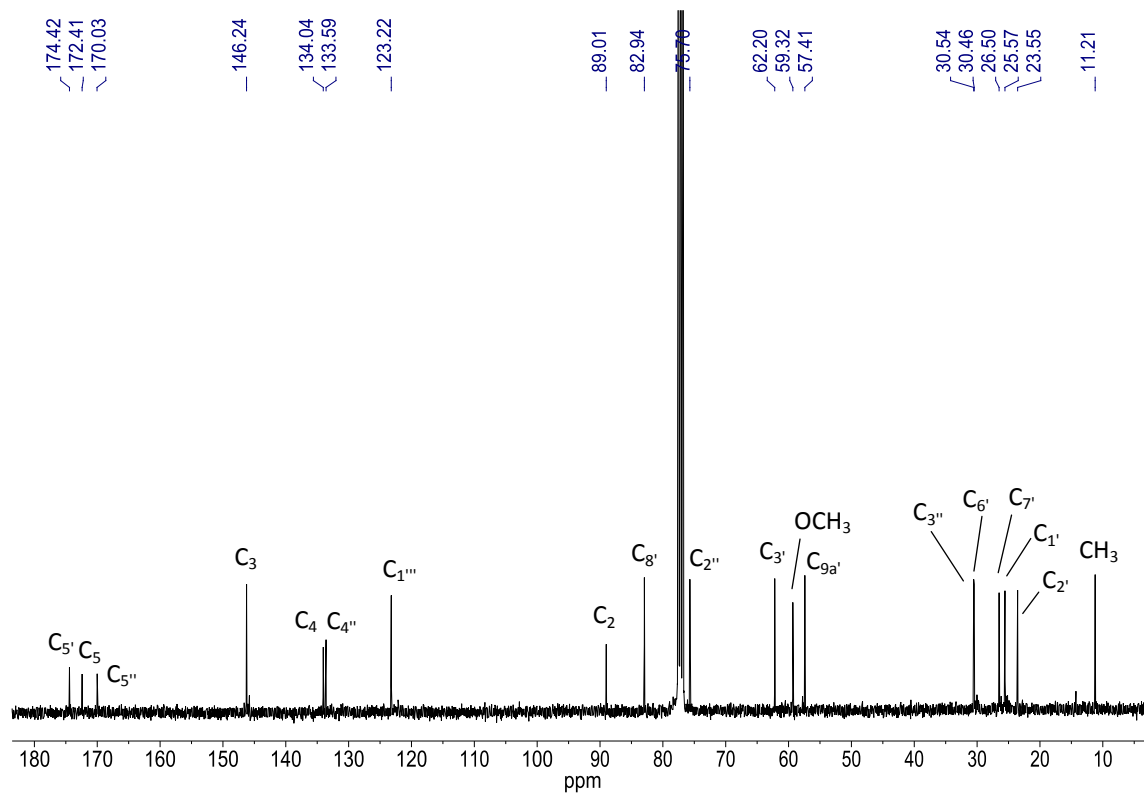
 $^1\text{H-NMR}$ (250 MHz, CDCl_3) $^{13}\text{C-NMR}$ (63 MHz, CDCl_3)

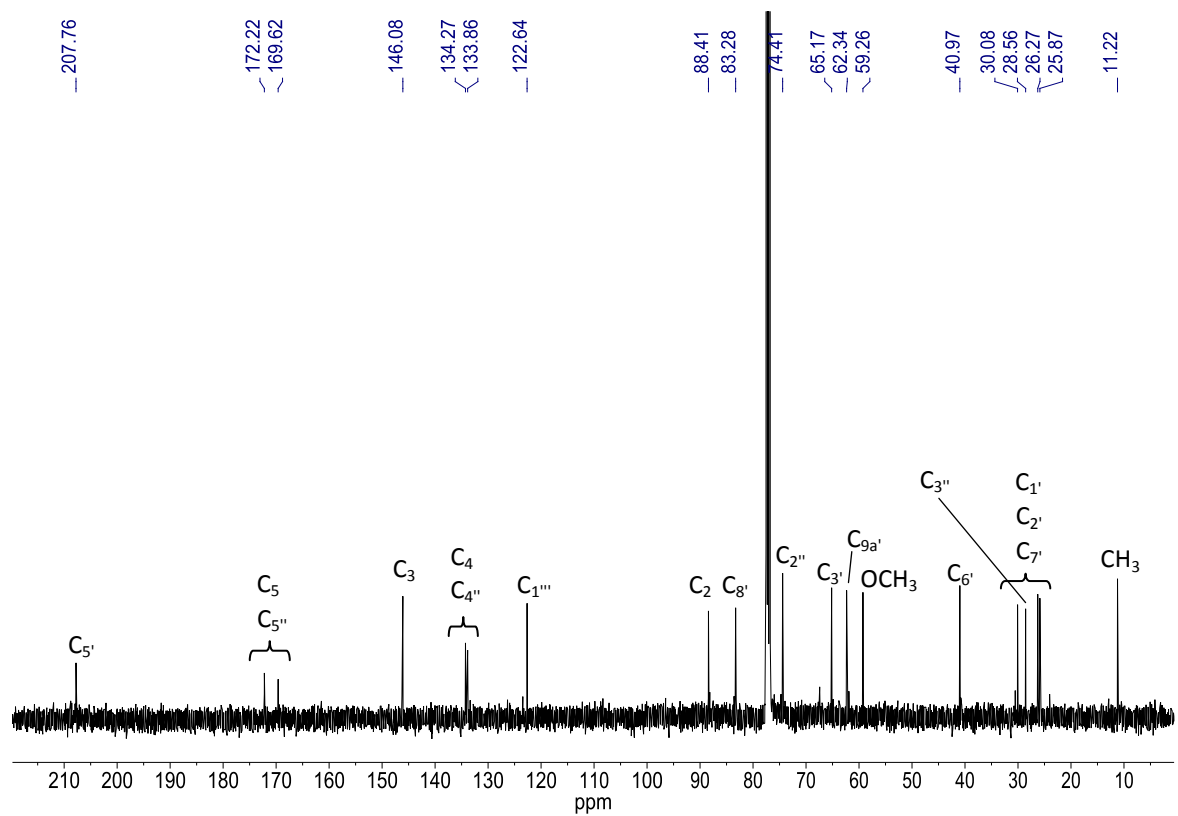
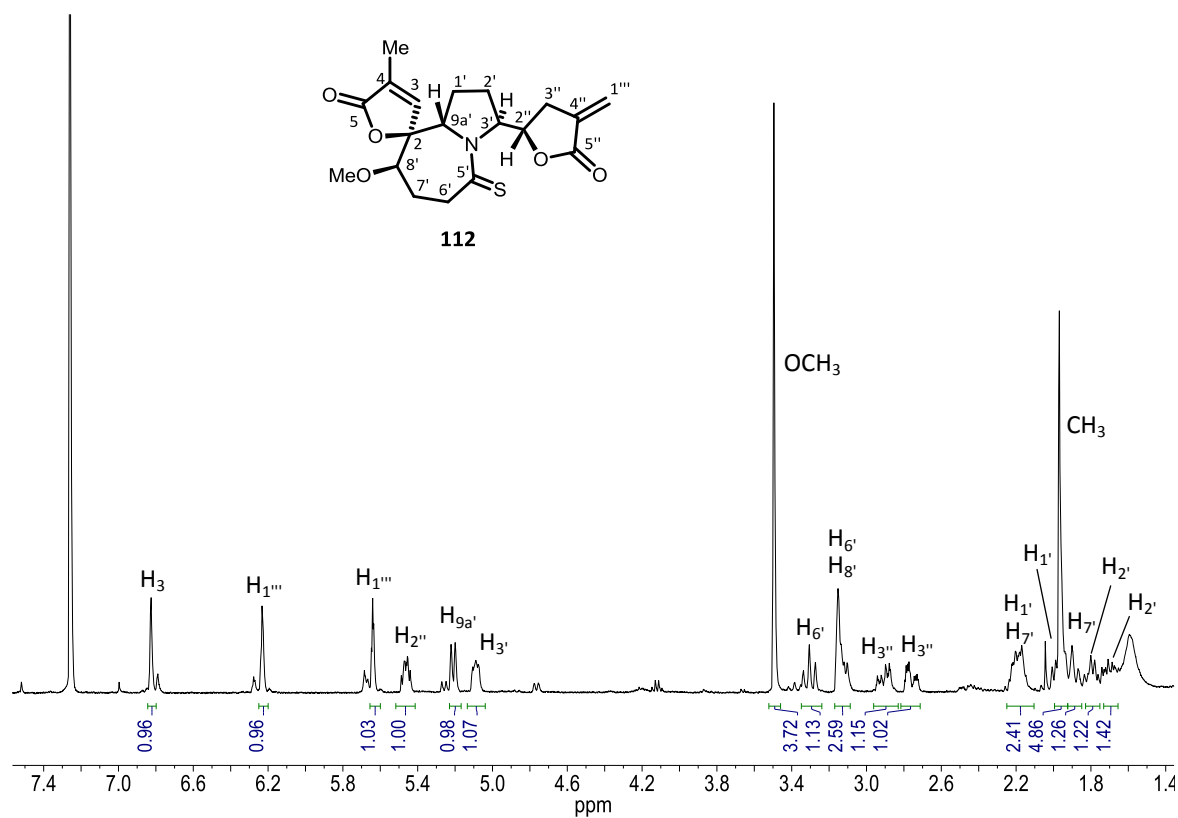


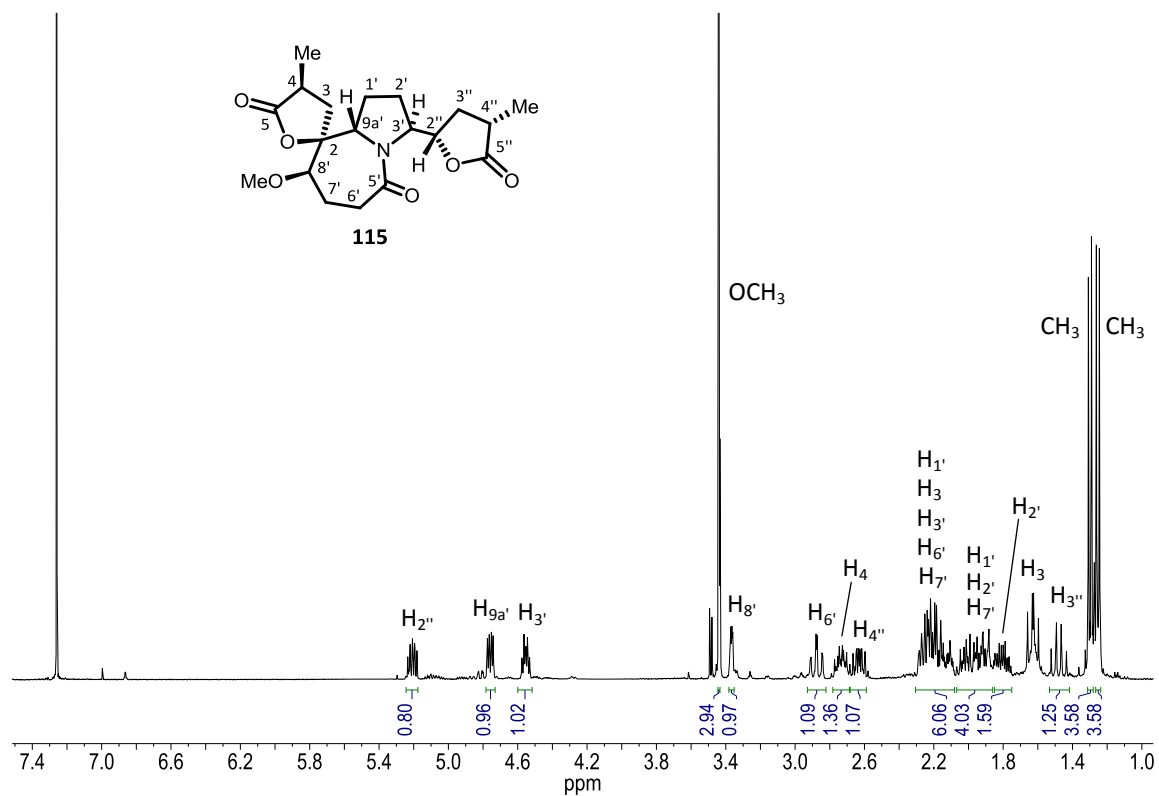
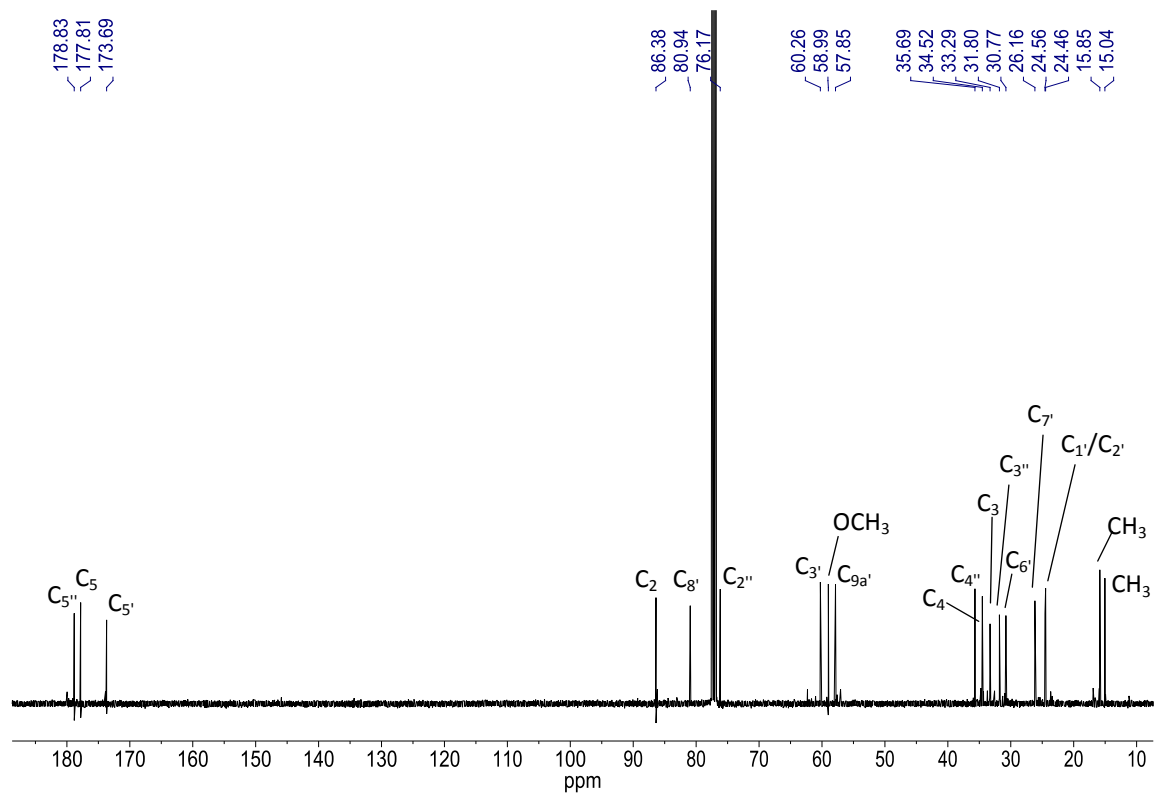


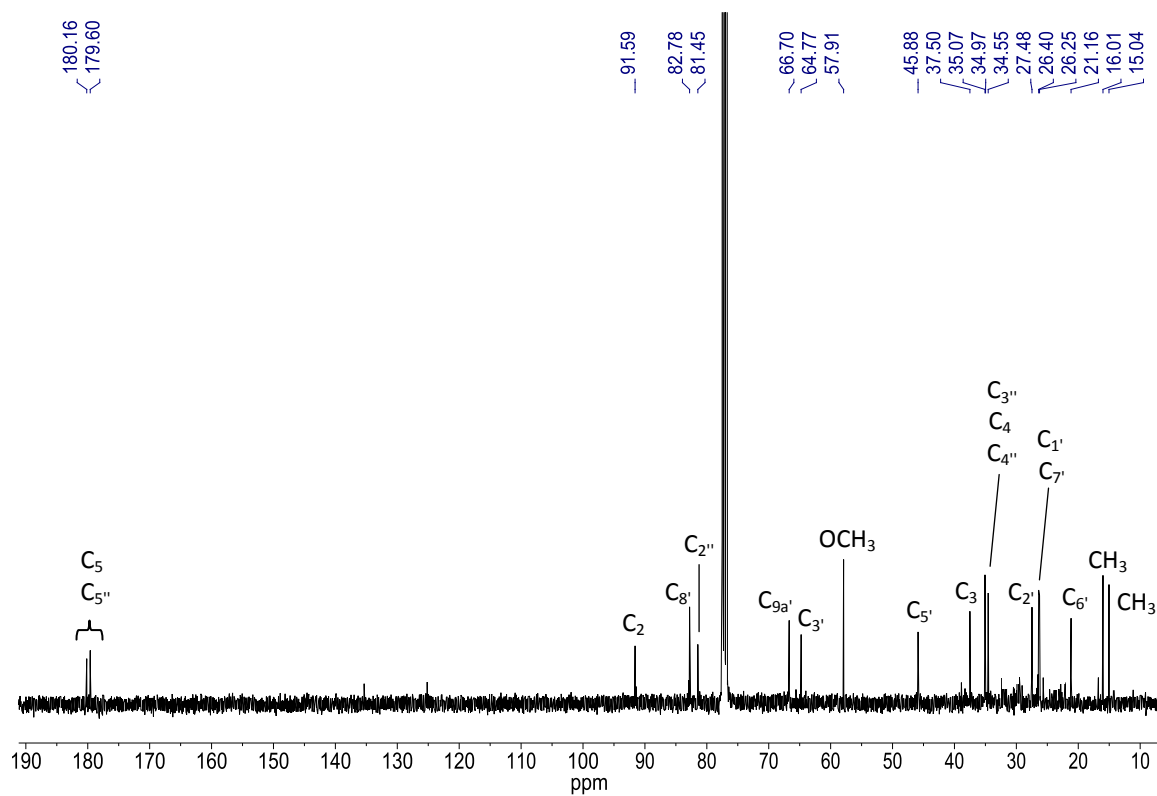
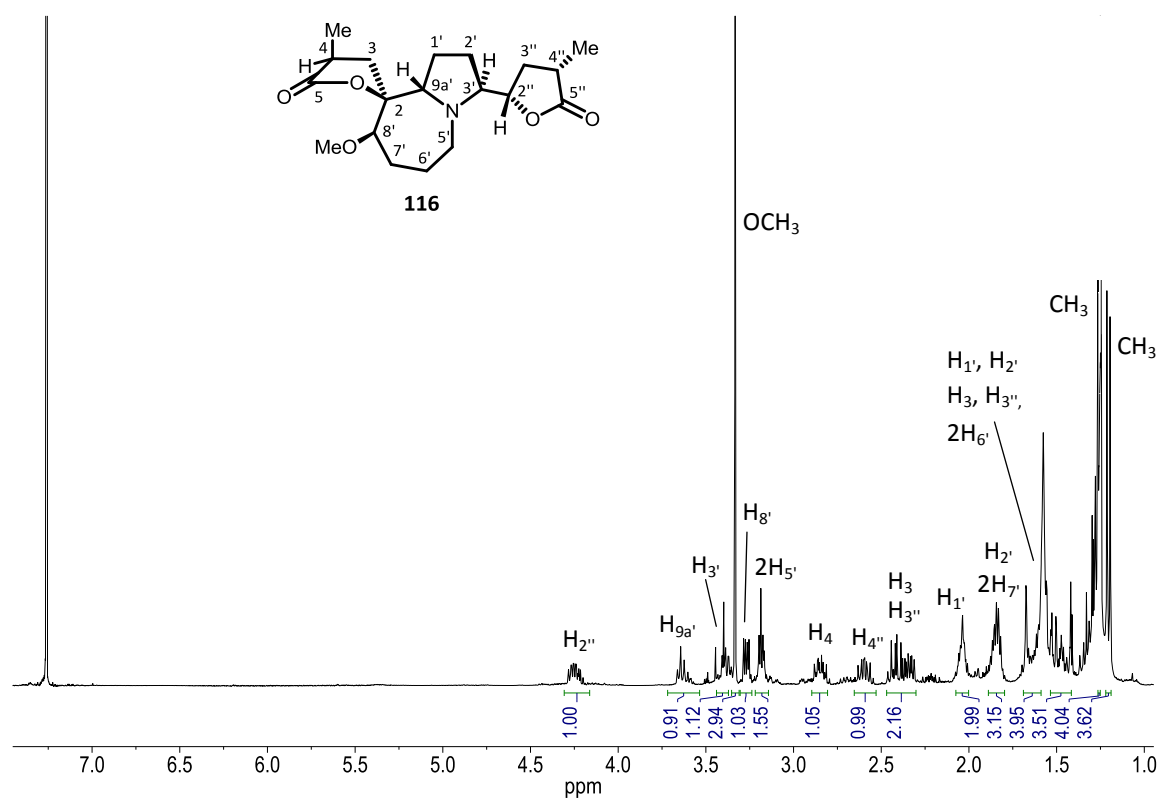


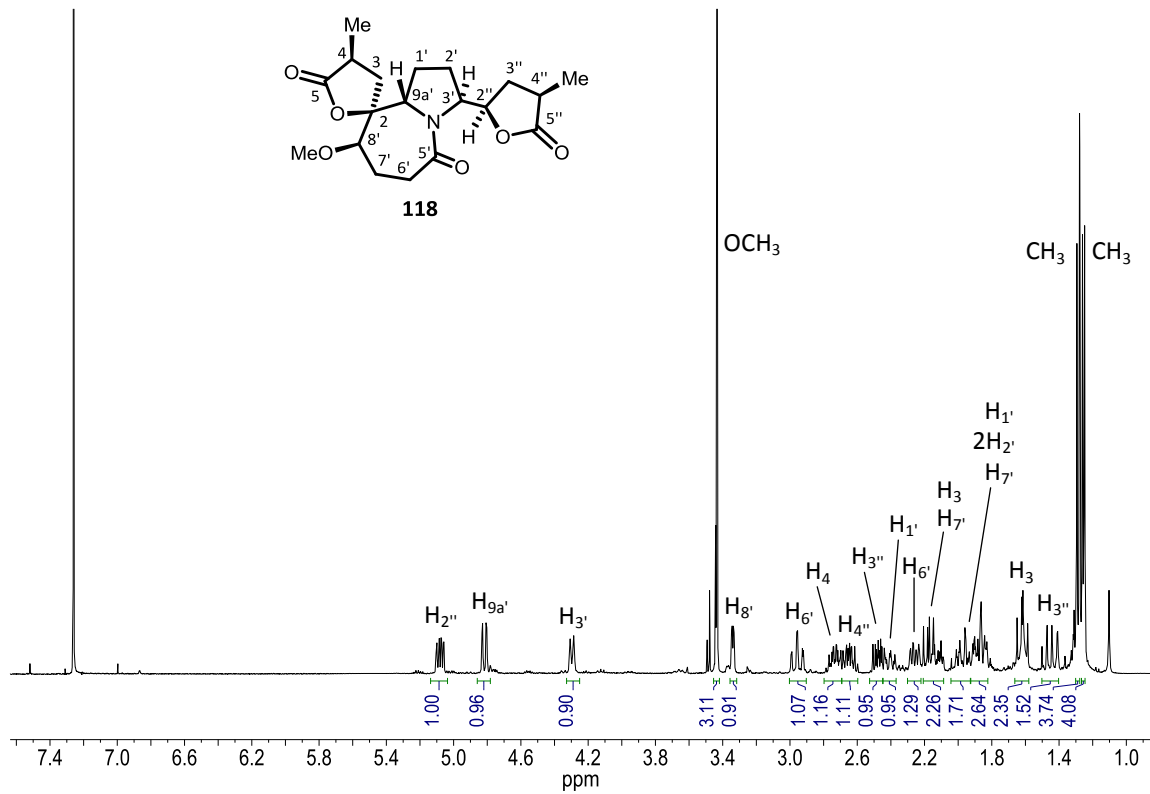
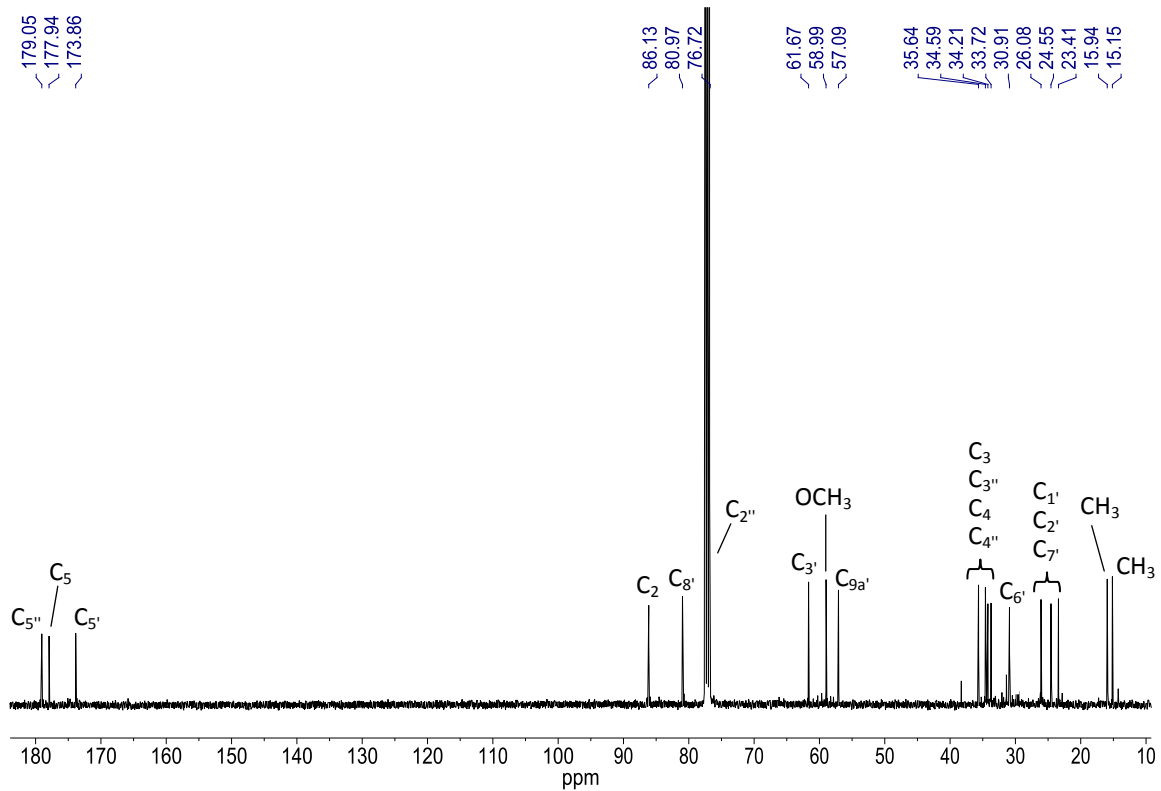
¹H-NMR (400 MHz, CDCl₃)¹³C-NMR (100 MHz, CDCl₃)

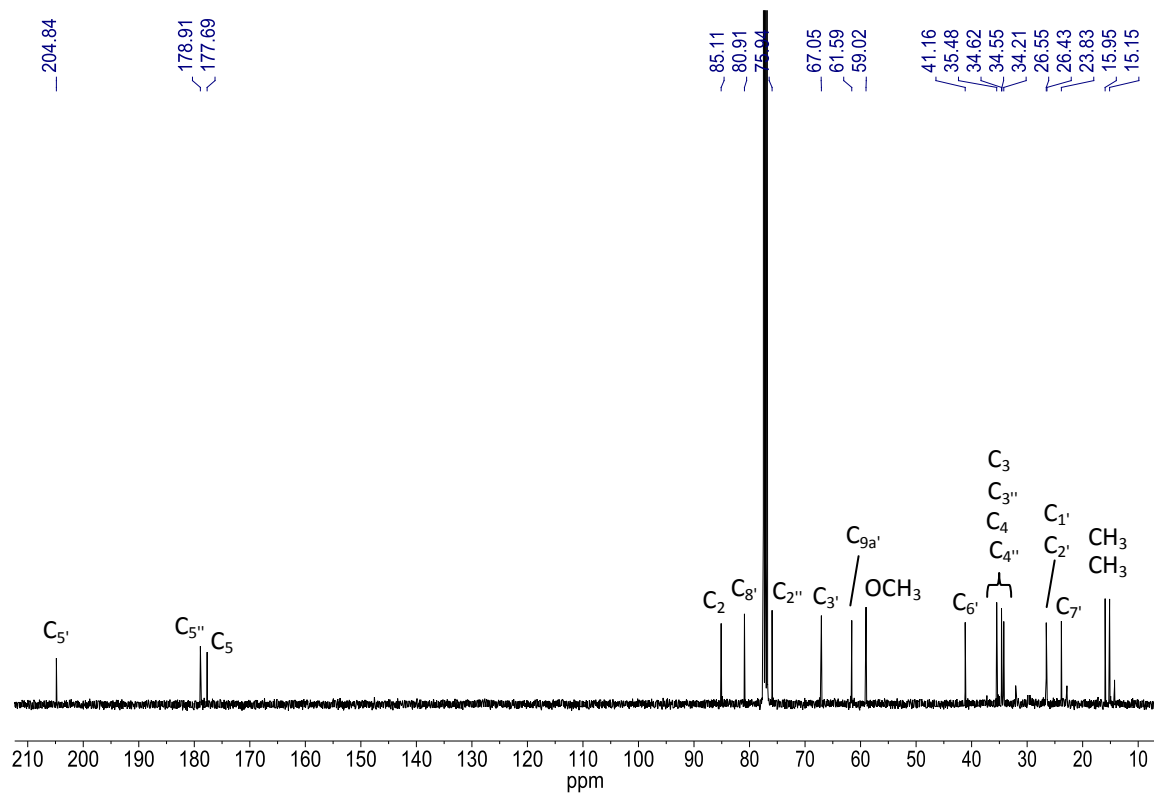
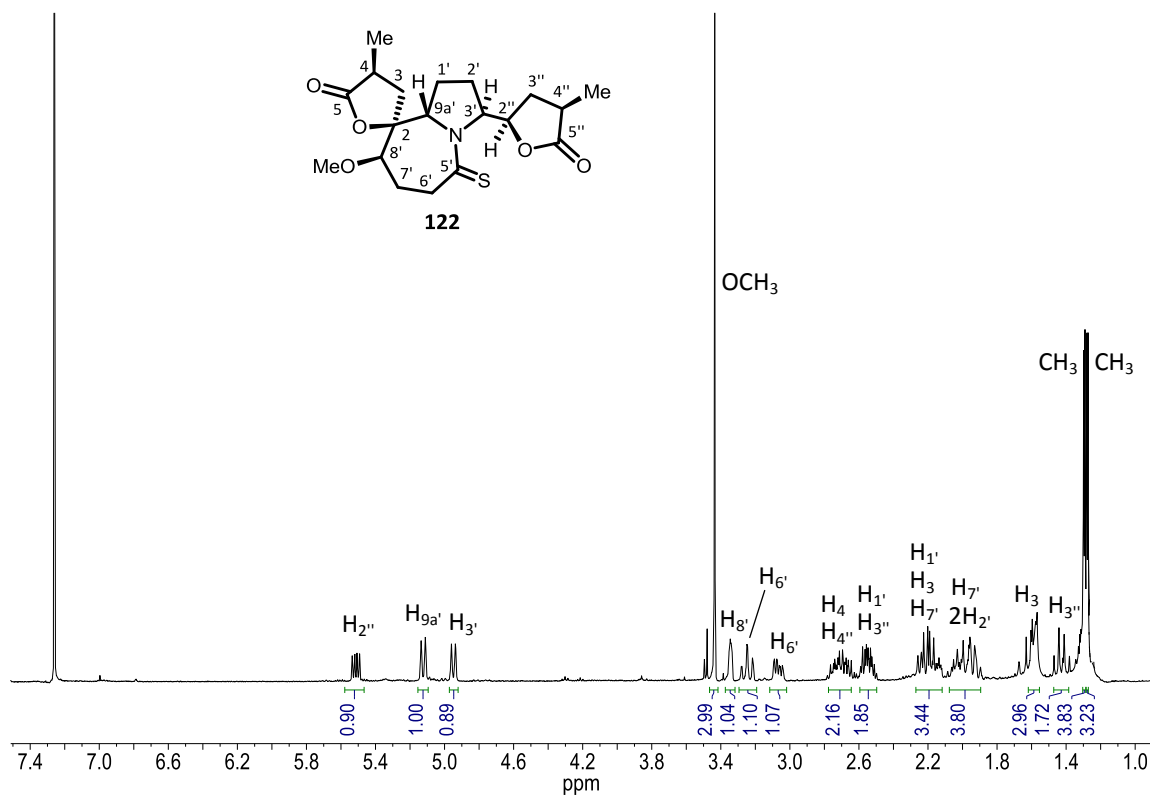
**¹H-NMR (400 MHz, CDCl₃)****¹³C-NMR (100 MHz, CDCl₃)**

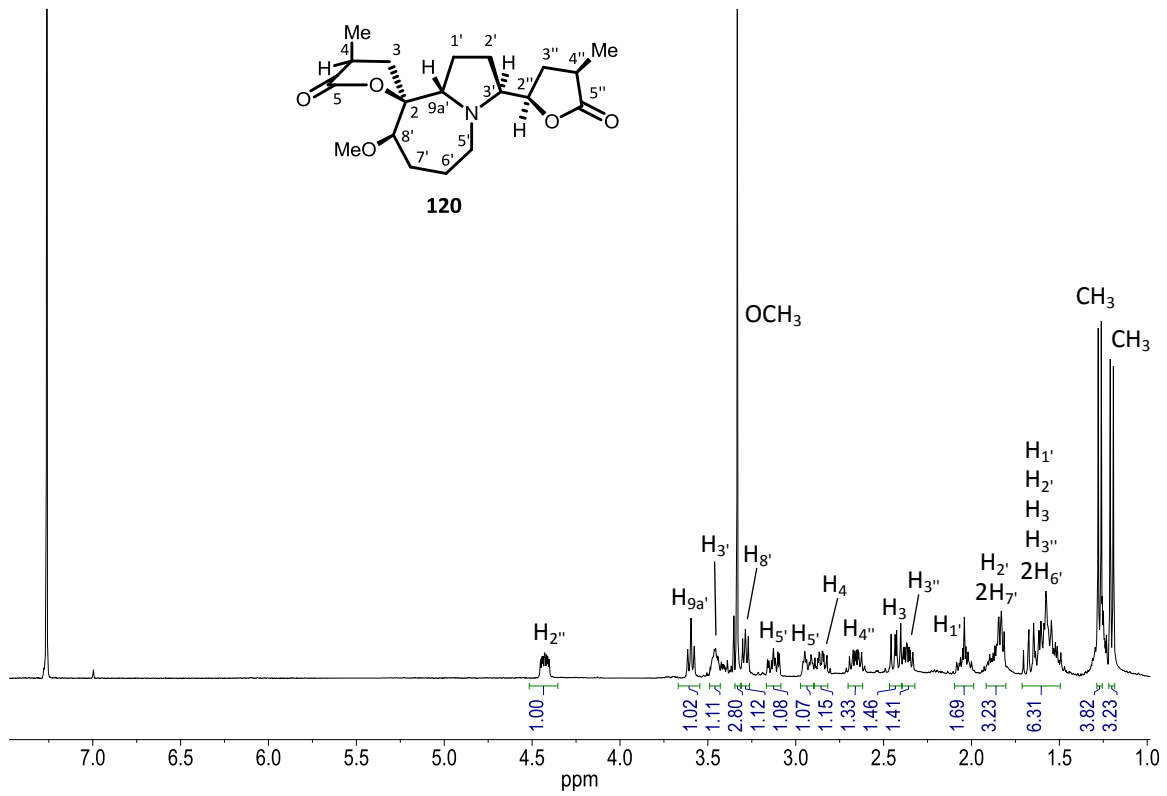


¹H-NMR (400 MHz, CDCl₃)¹³C-NMR (100 MHz, CDCl₃)

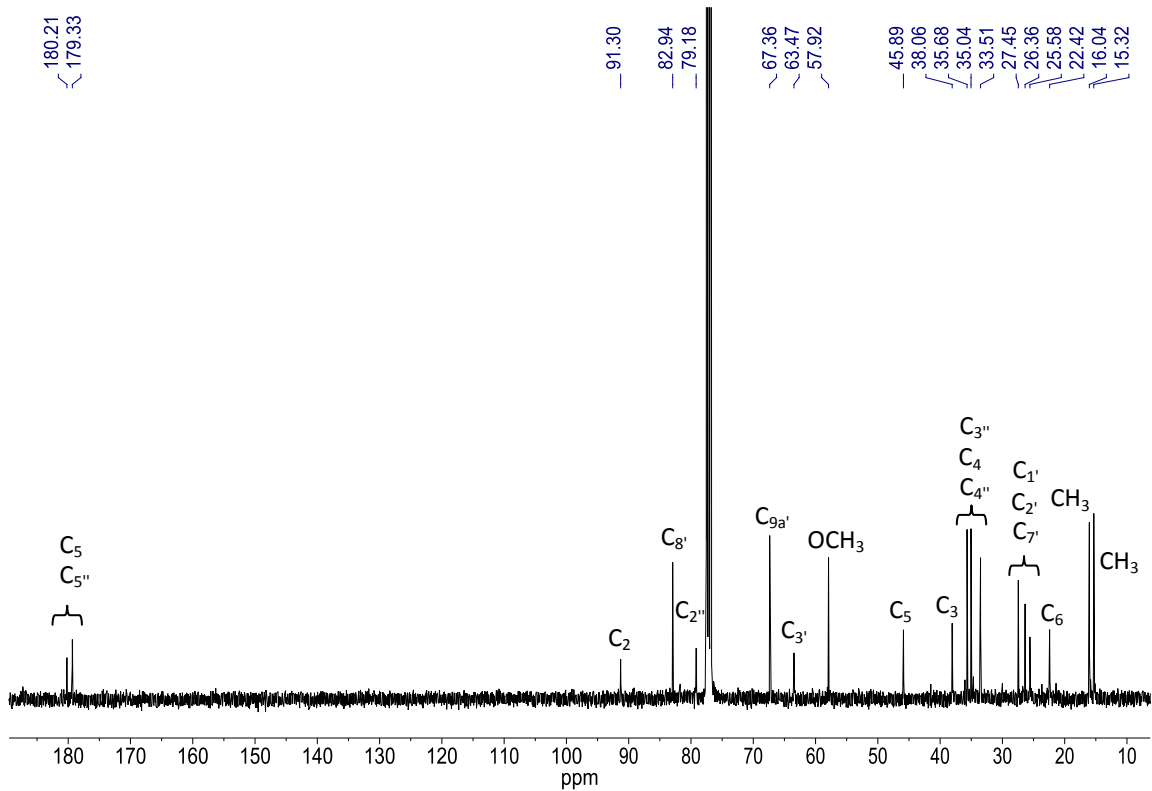
 **$^{13}\text{C-NMR}$ (100 MHz, CDCl_3)**

¹H-NMR (400 MHz, CDCl₃)¹³C-NMR (100 MHz, CDCl₃)

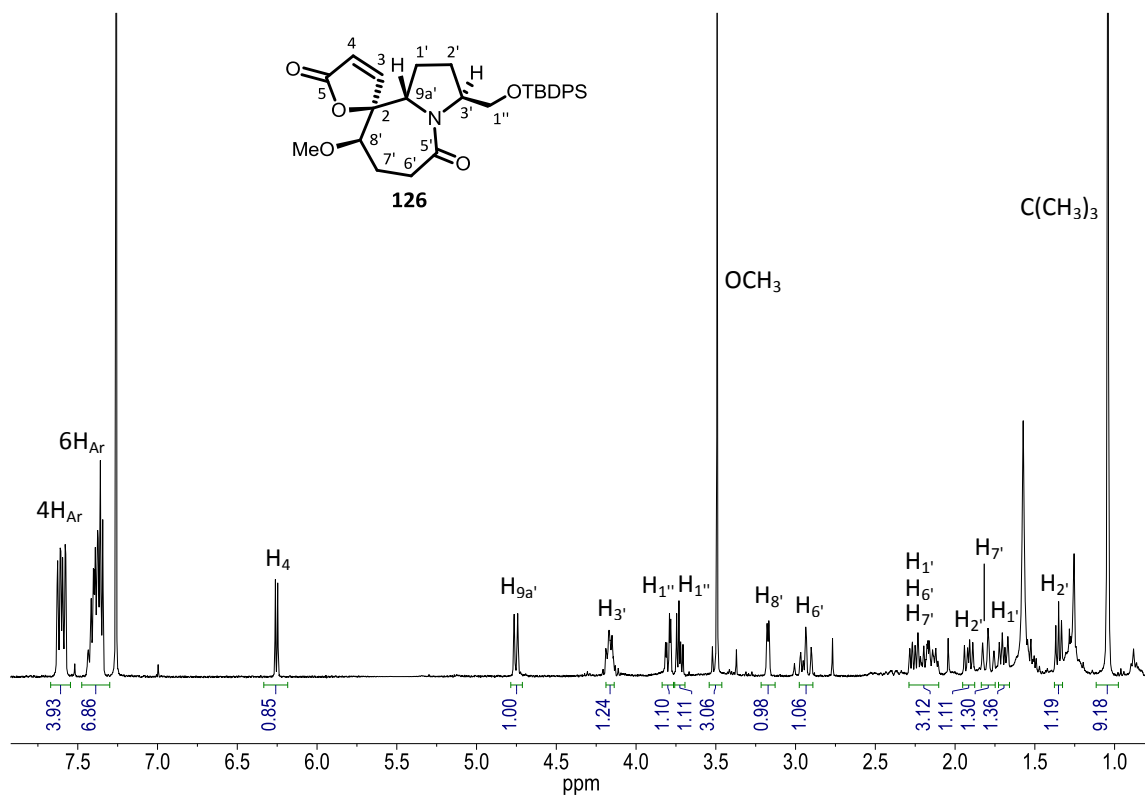
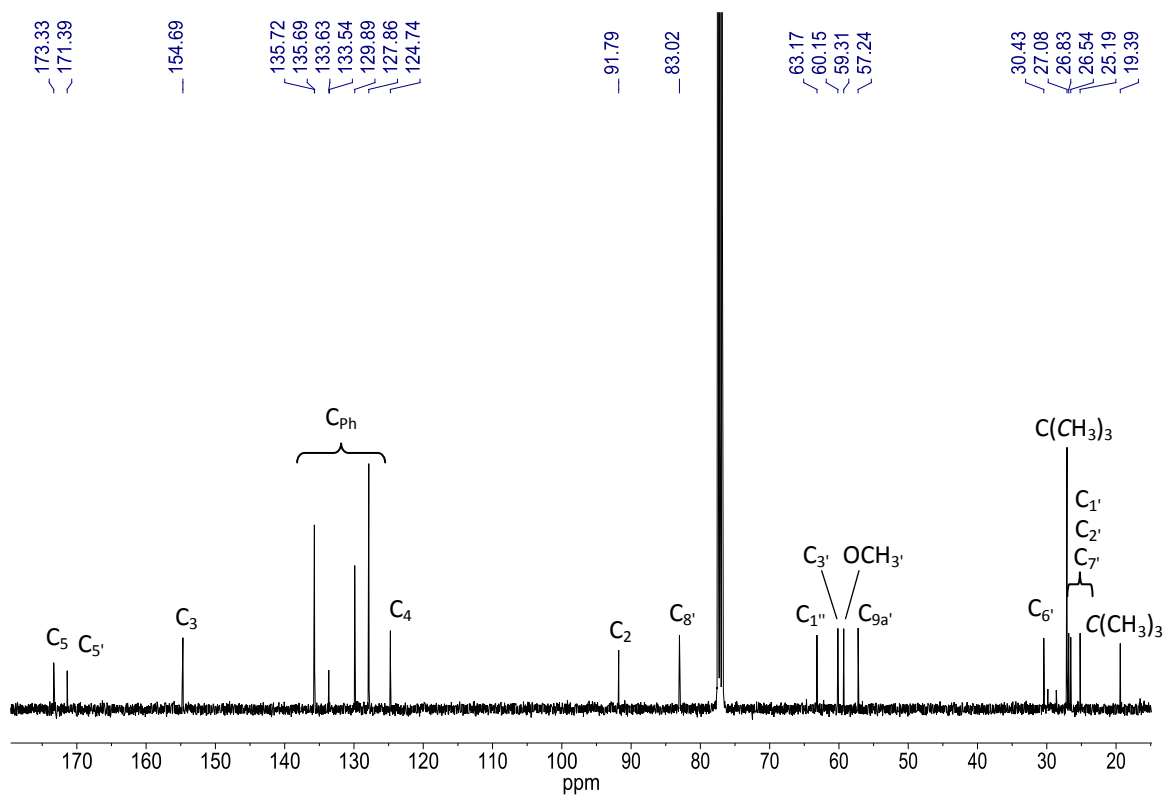


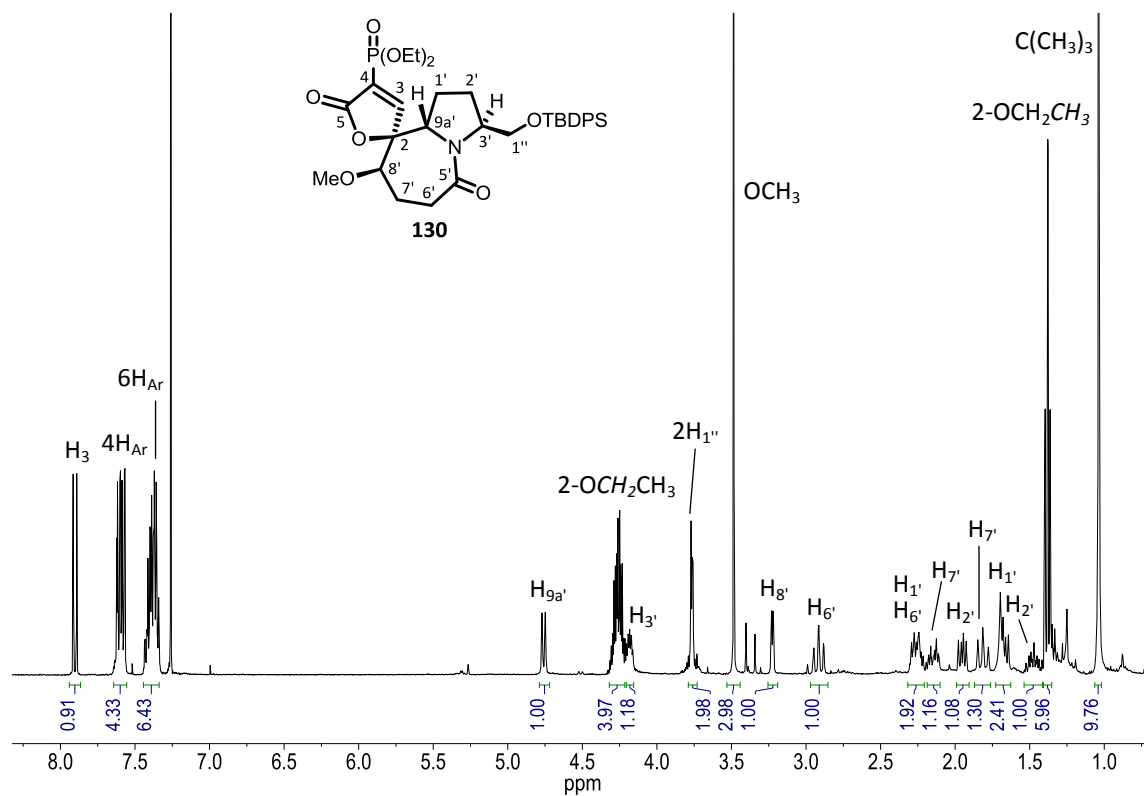


¹H-NMR (400 MHz, CDCl₃)



¹³C-NMR (100 MHz, CDCl₃)

 $^1\text{H-NMR}$ (400 MHz, CDCl_3) $^{13}\text{C-NMR}$ (100 MHz, CDCl_3)

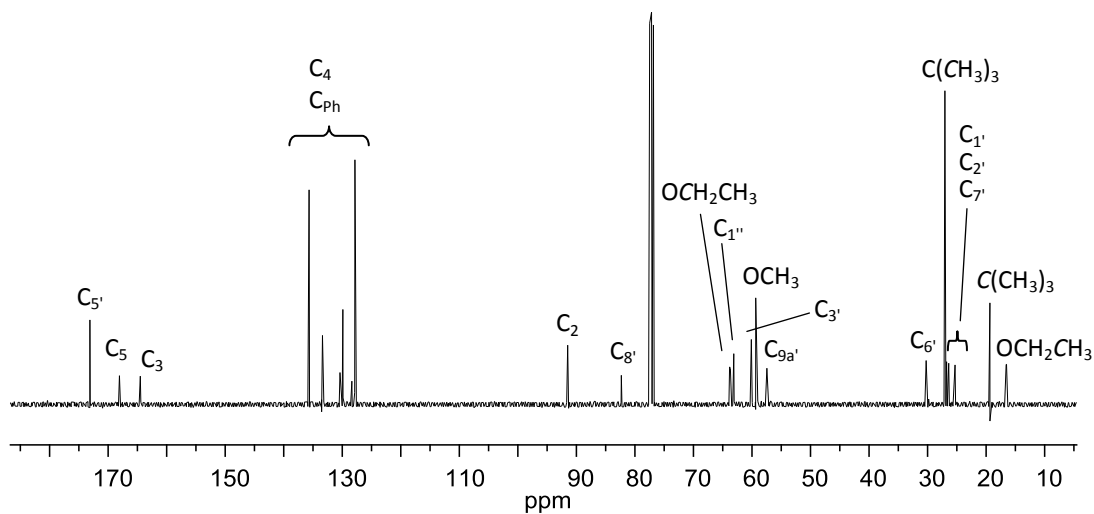


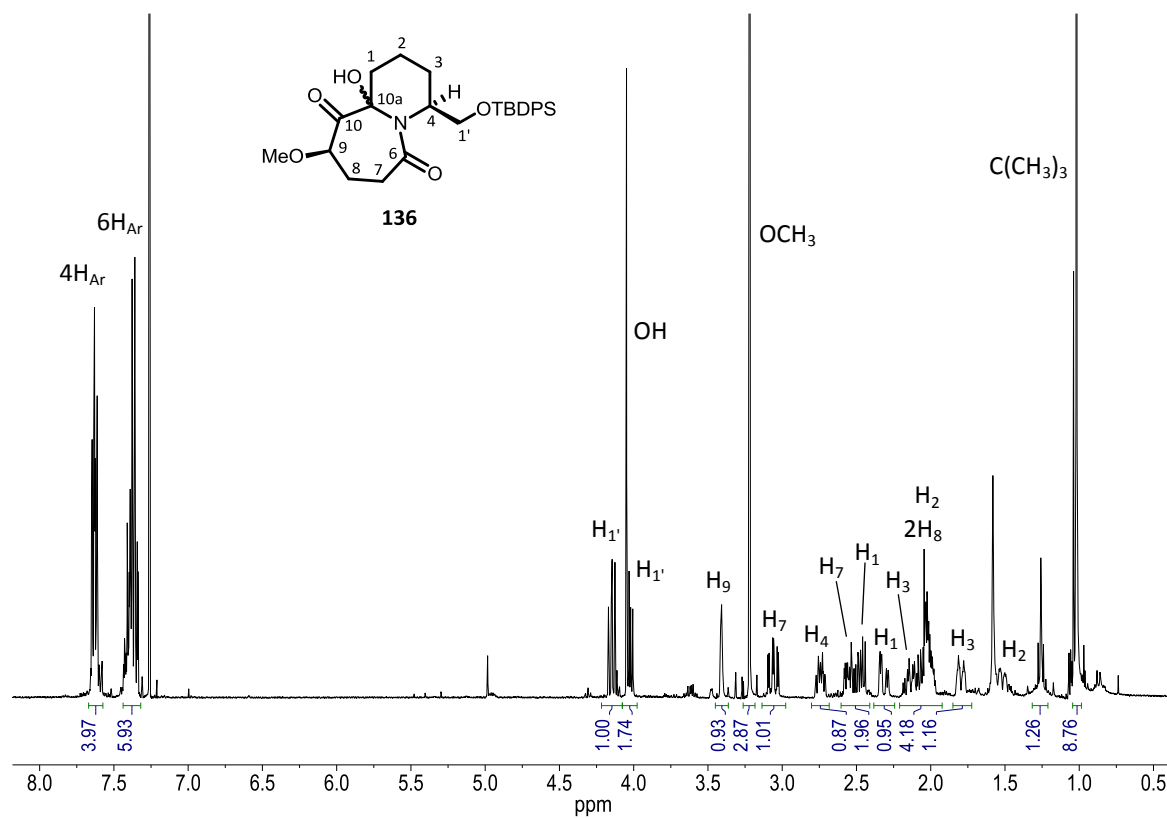
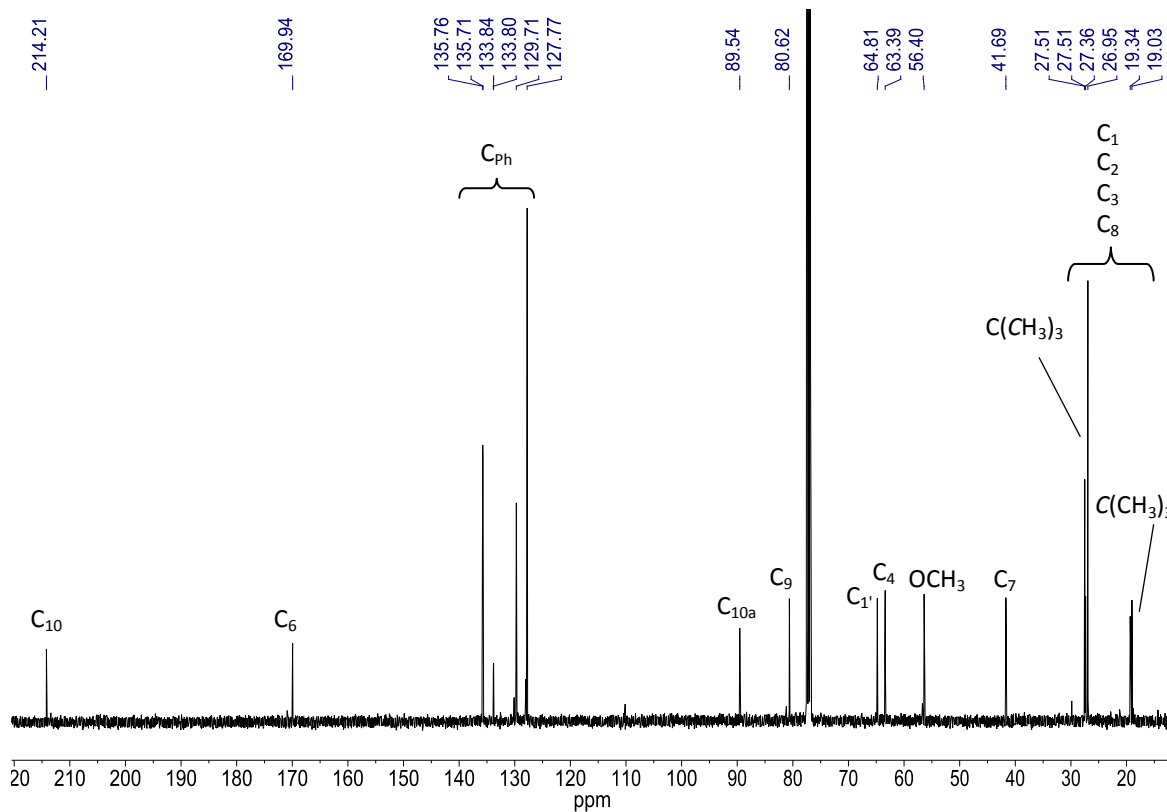
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168.07
167.87
164.59
164.50

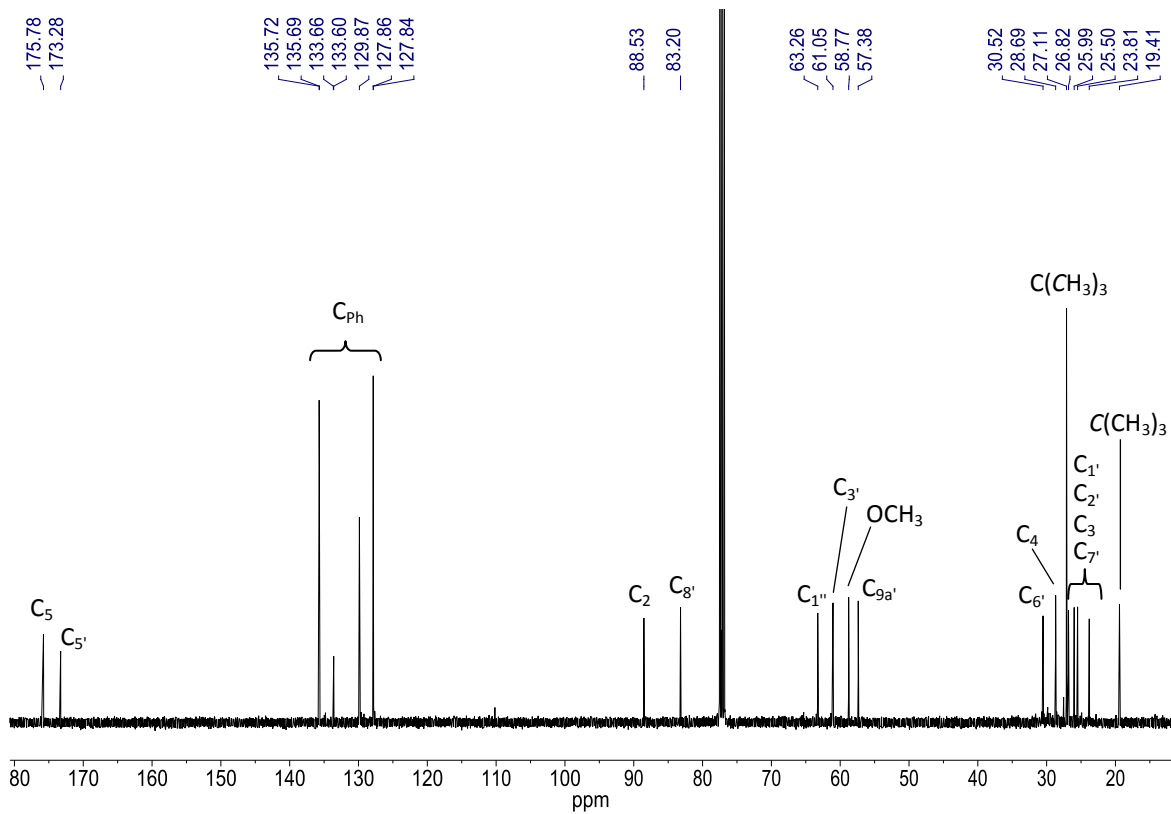
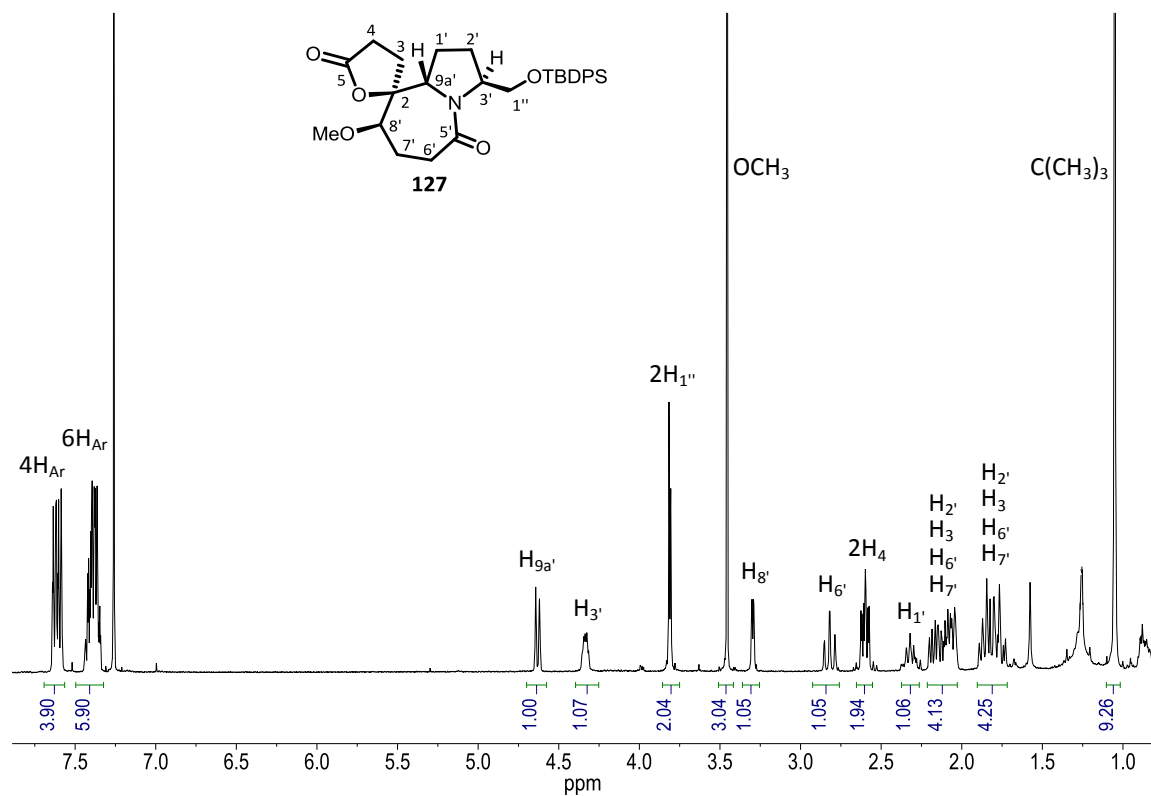
135.67
135.64
133.38
129.90
129.88
127.85
127.84

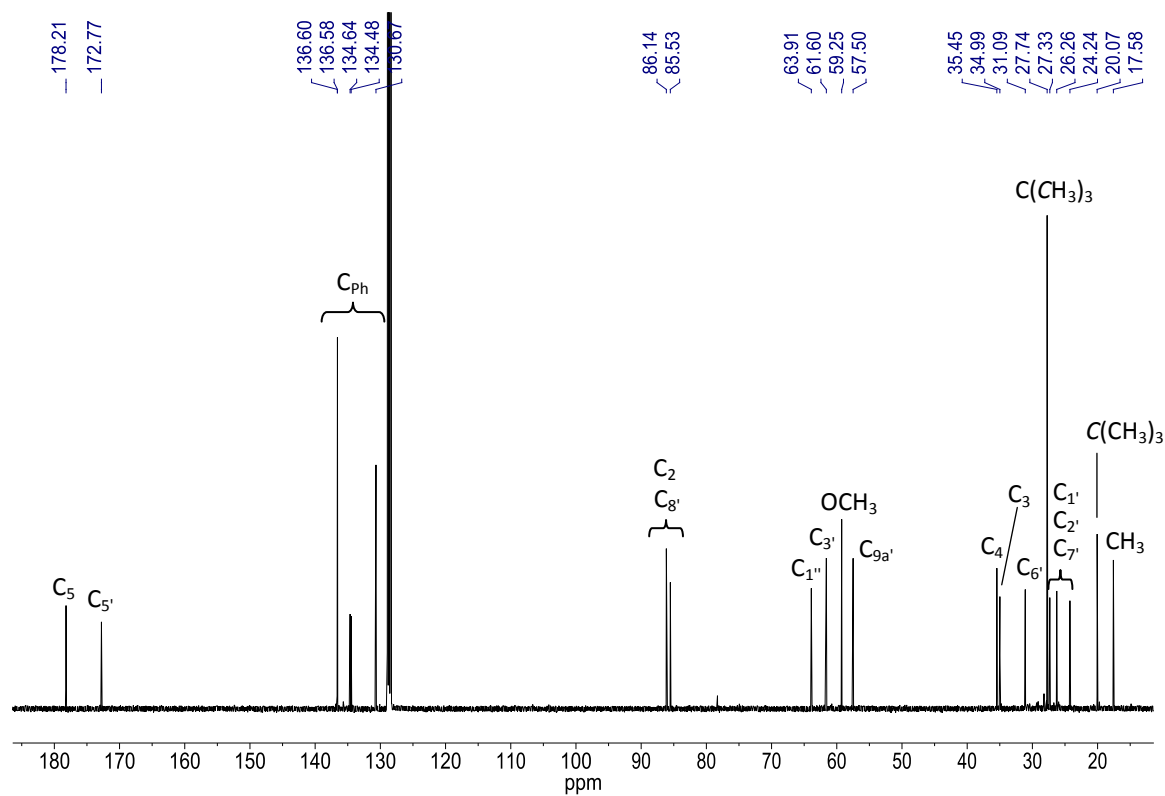
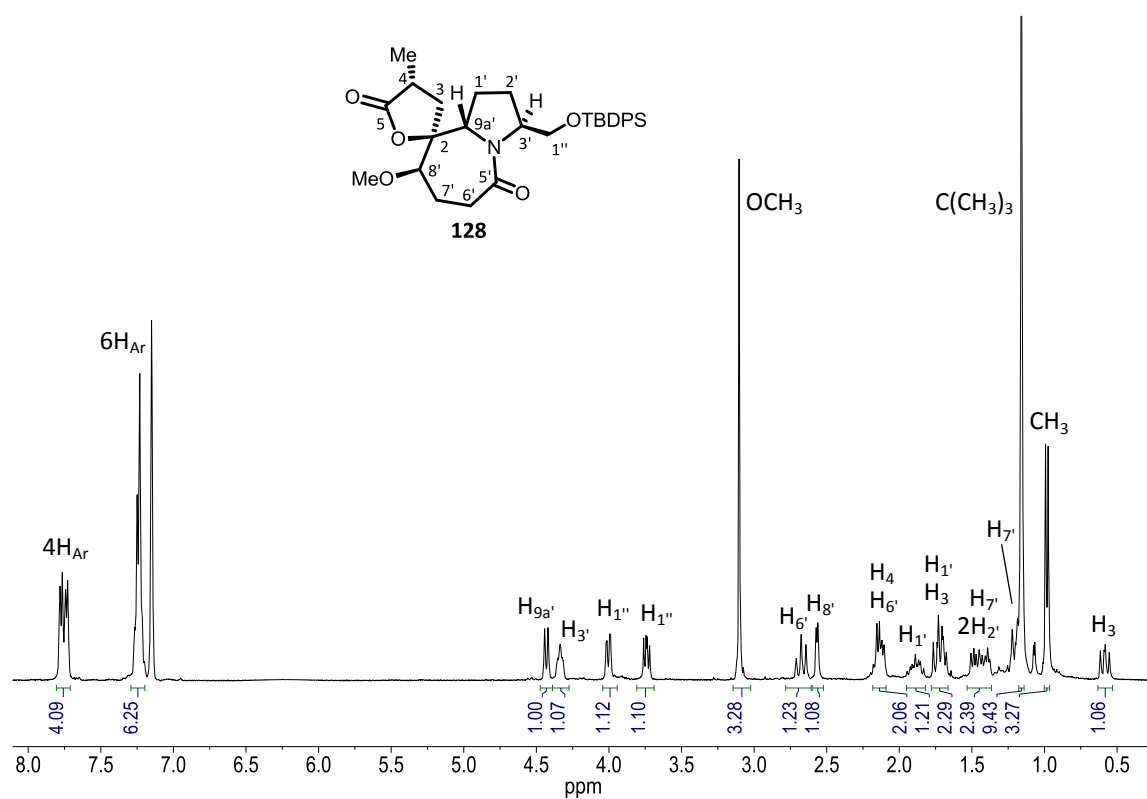
91.49
91.34
82.32
82.31
63.83
63.77
63.69
63.63
63.11
60.11
59.36
57.46
57.45

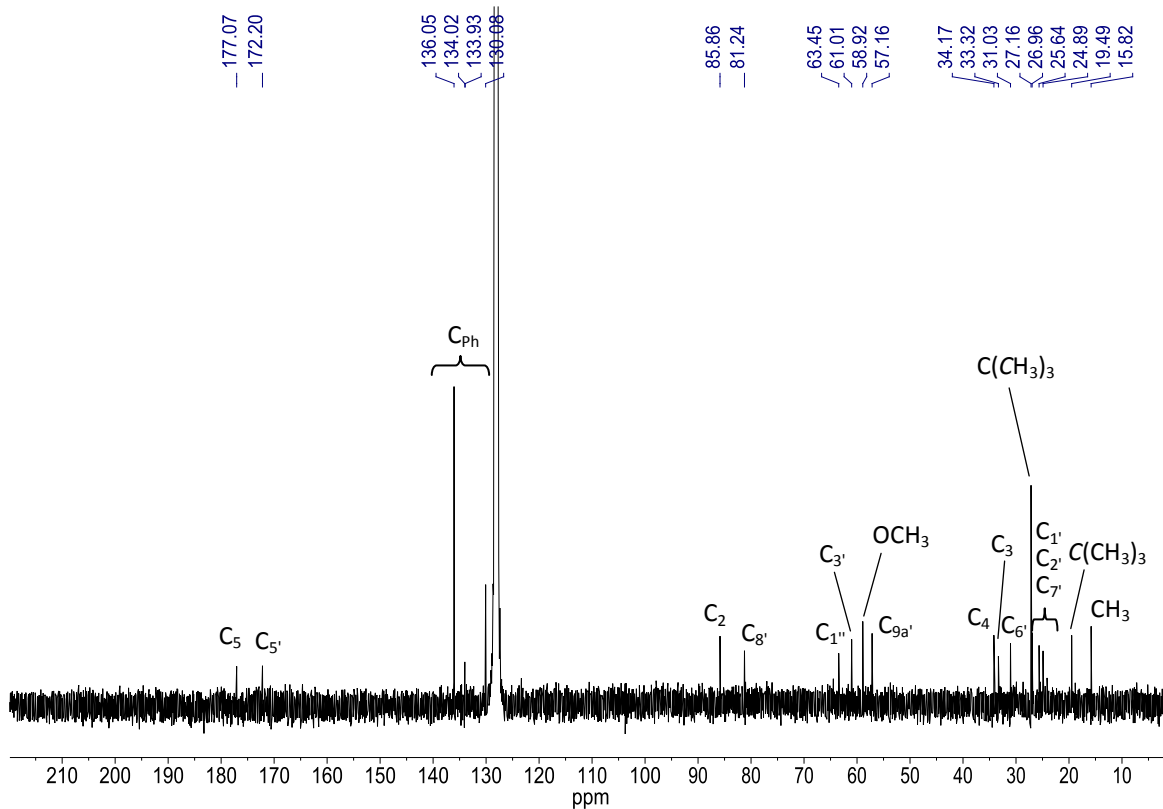
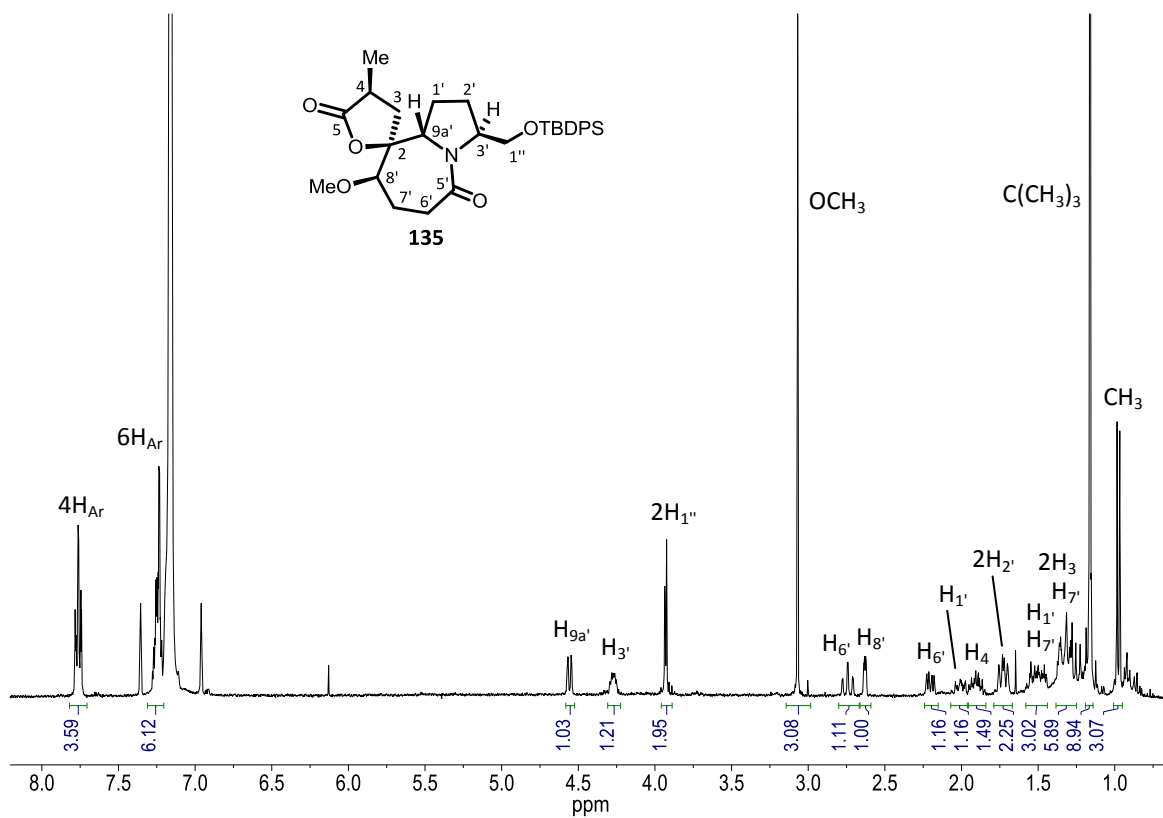
30.25
27.04
26.75
26.39
25.31
19.35
16.58
16.55
16.52
16.49

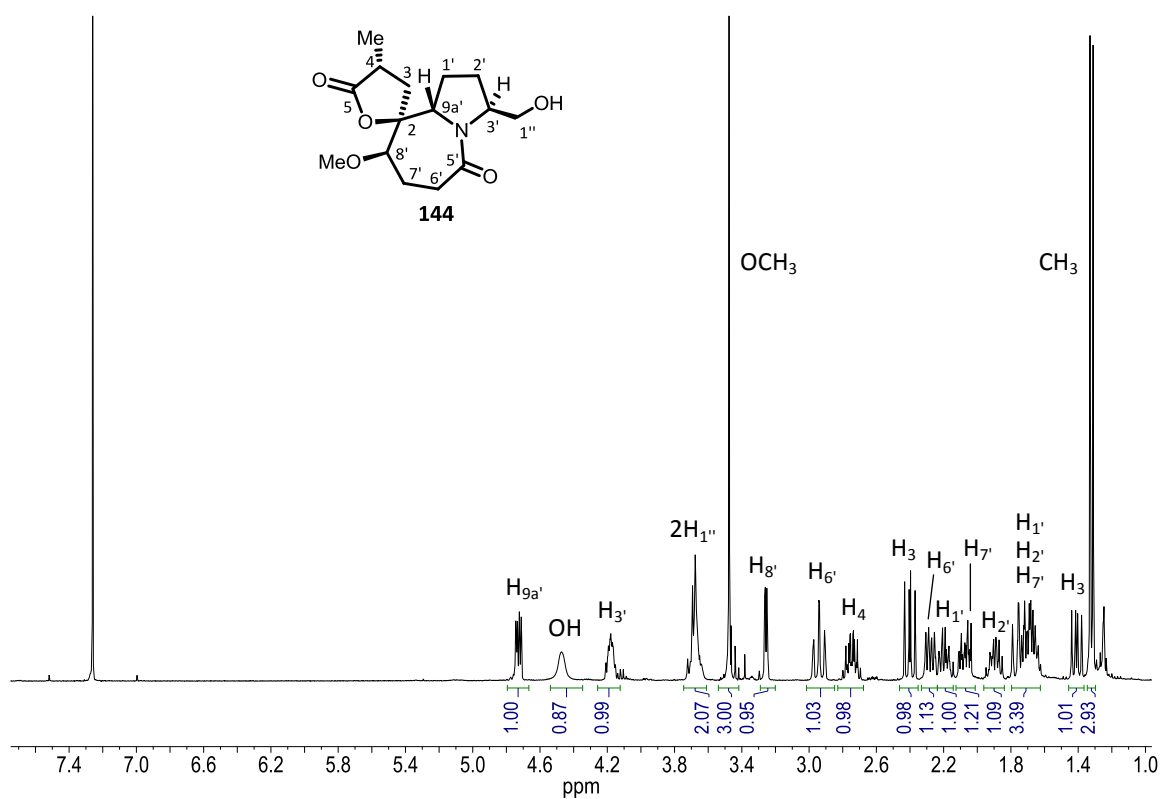
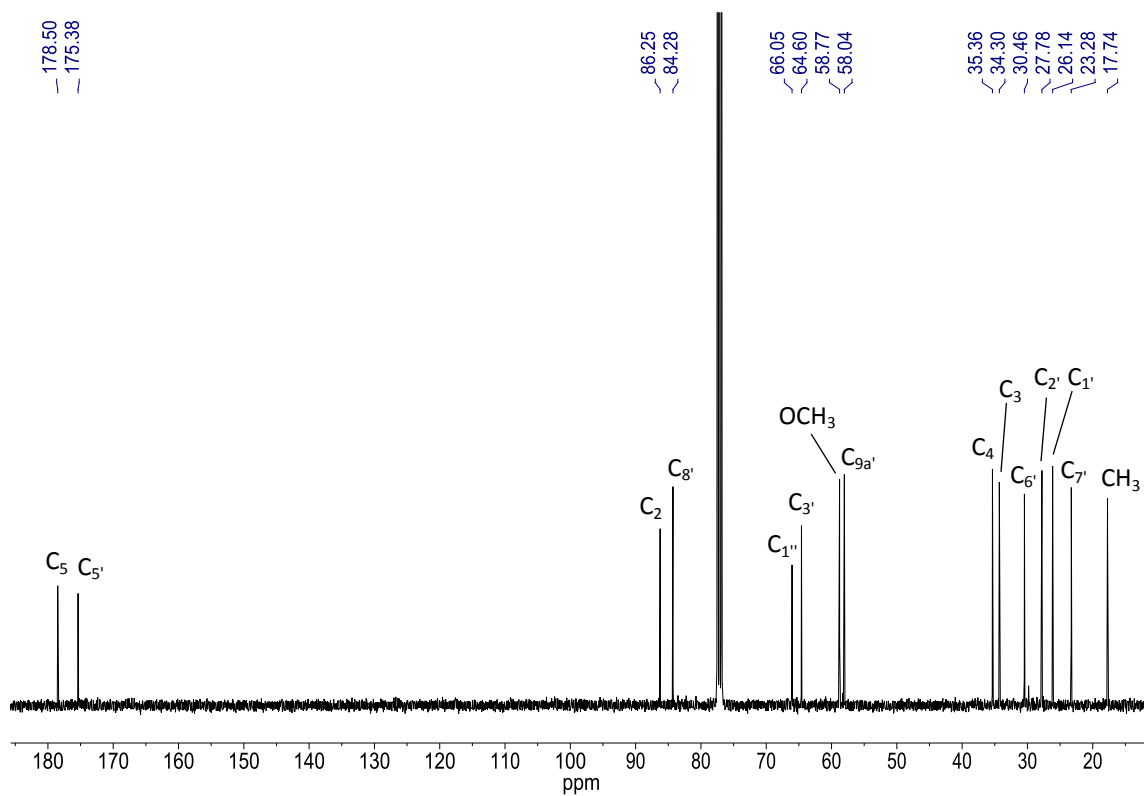


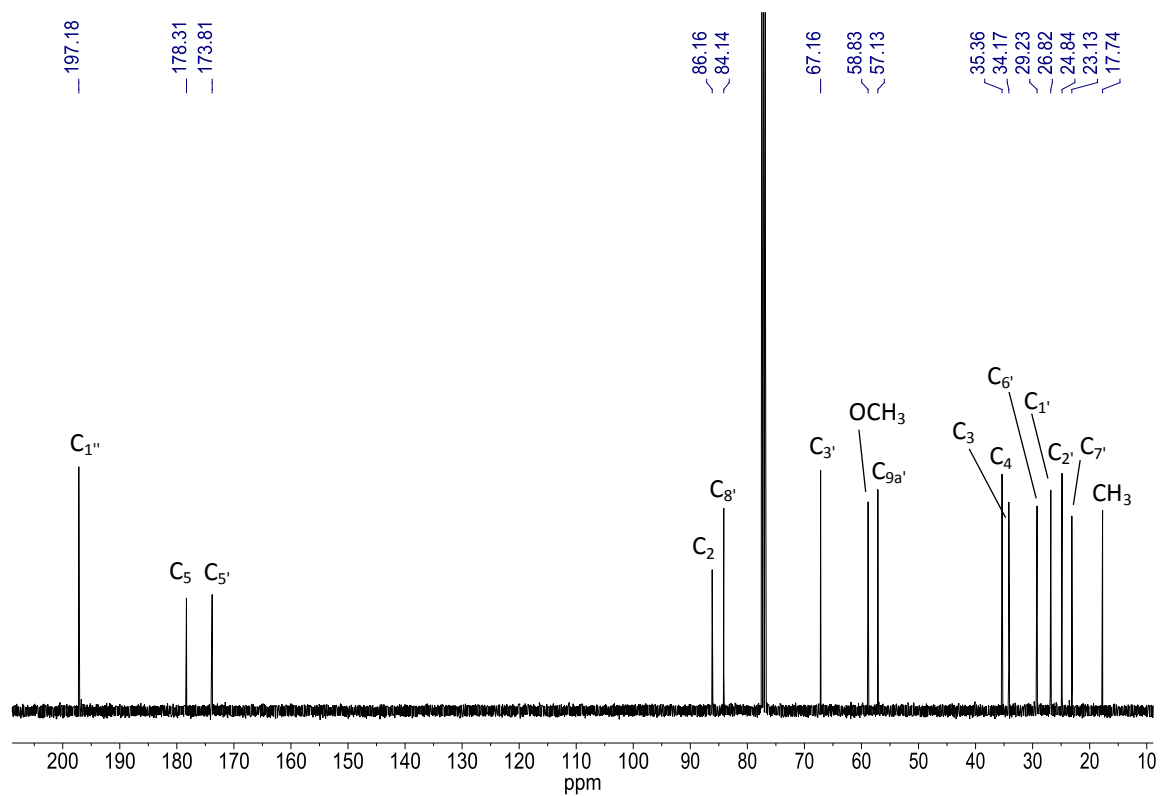
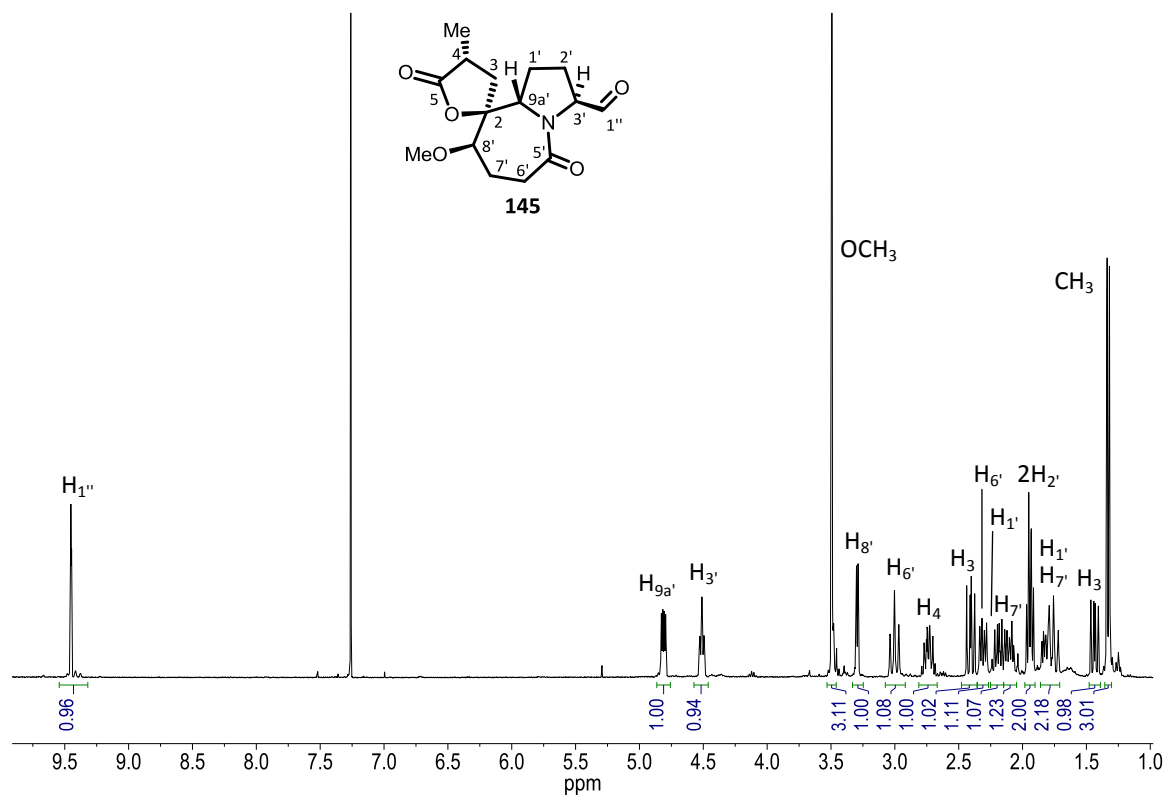
¹H-NMR (400 MHz, CDCl₃)¹³C-NMR (100 MHz, CDCl₃)

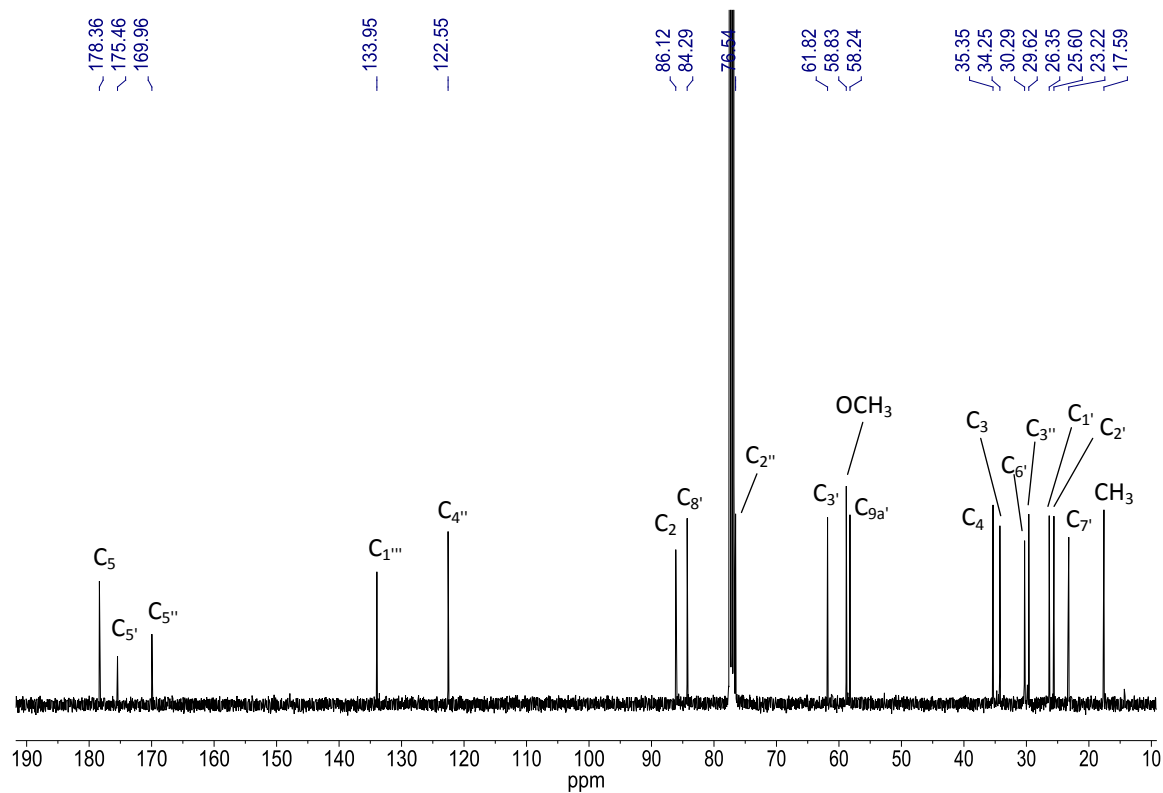
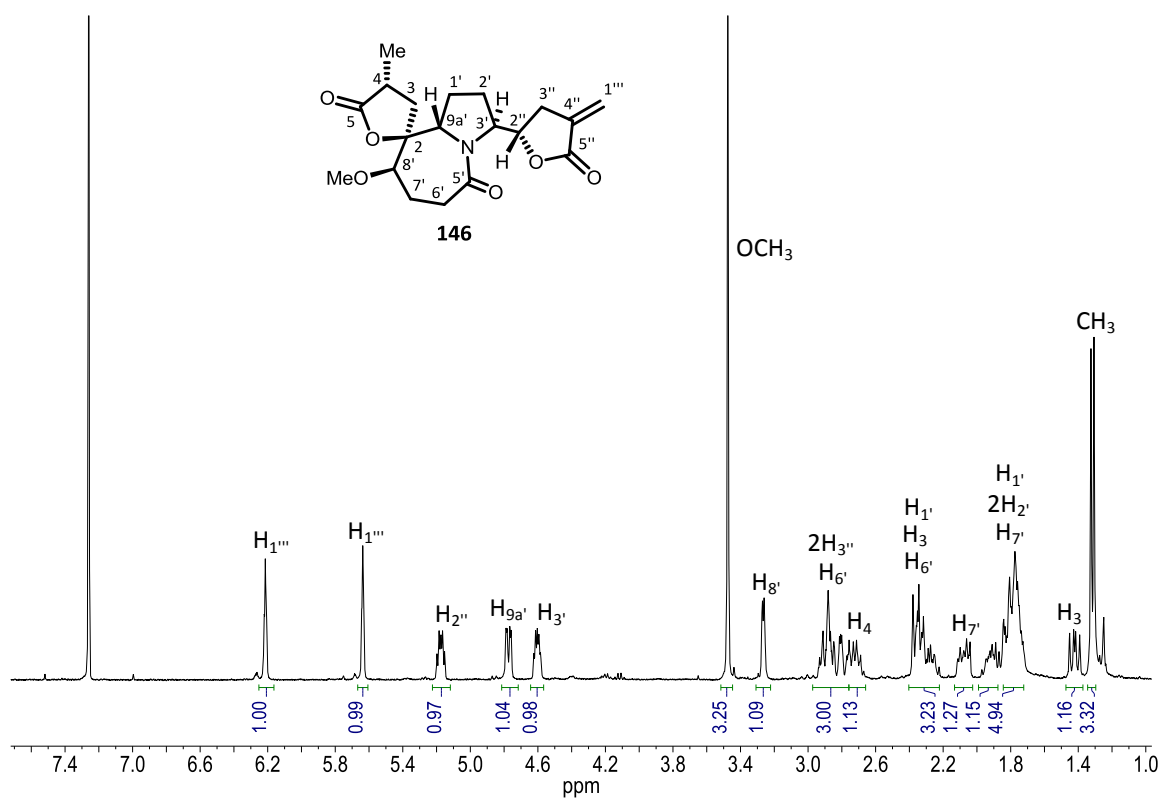


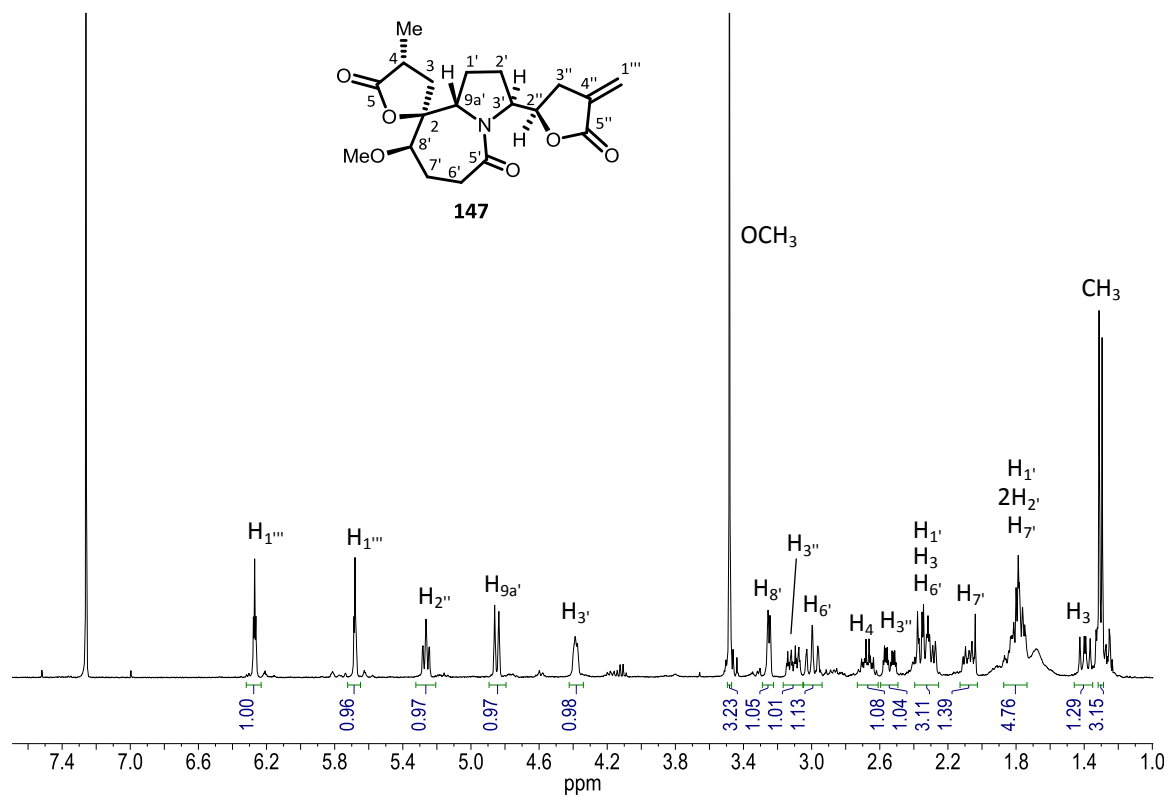
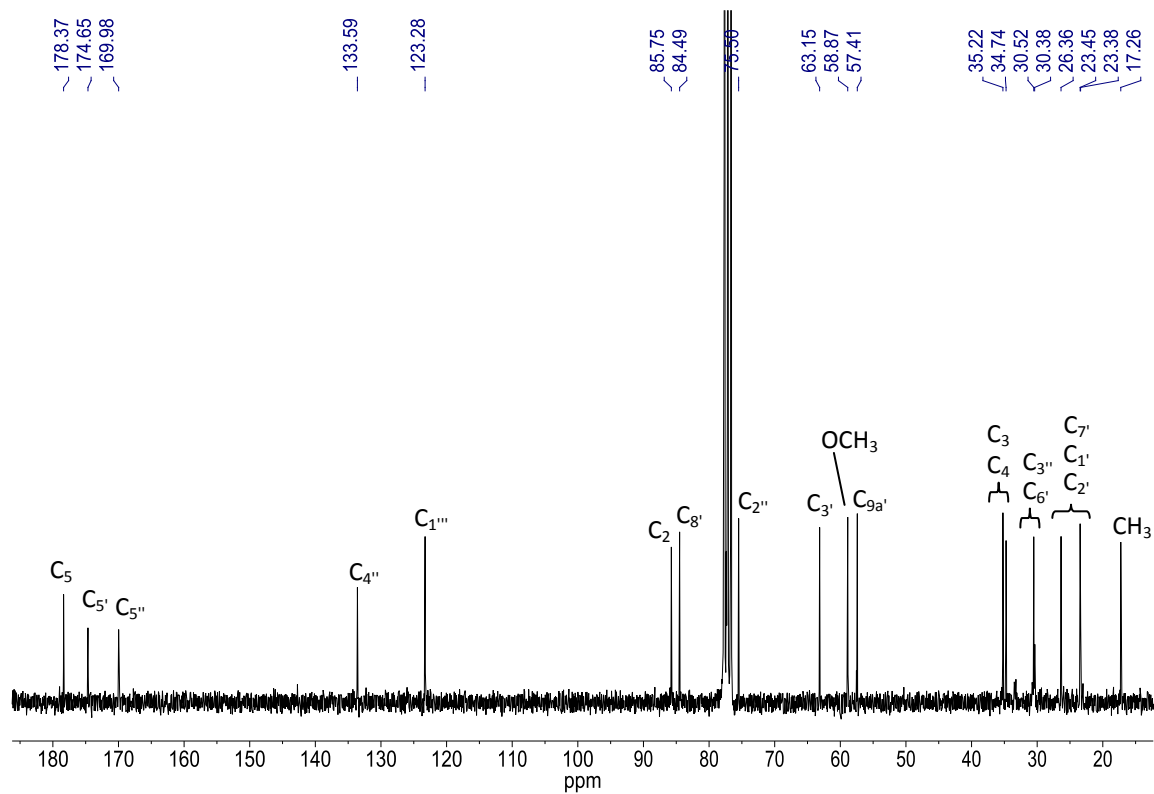


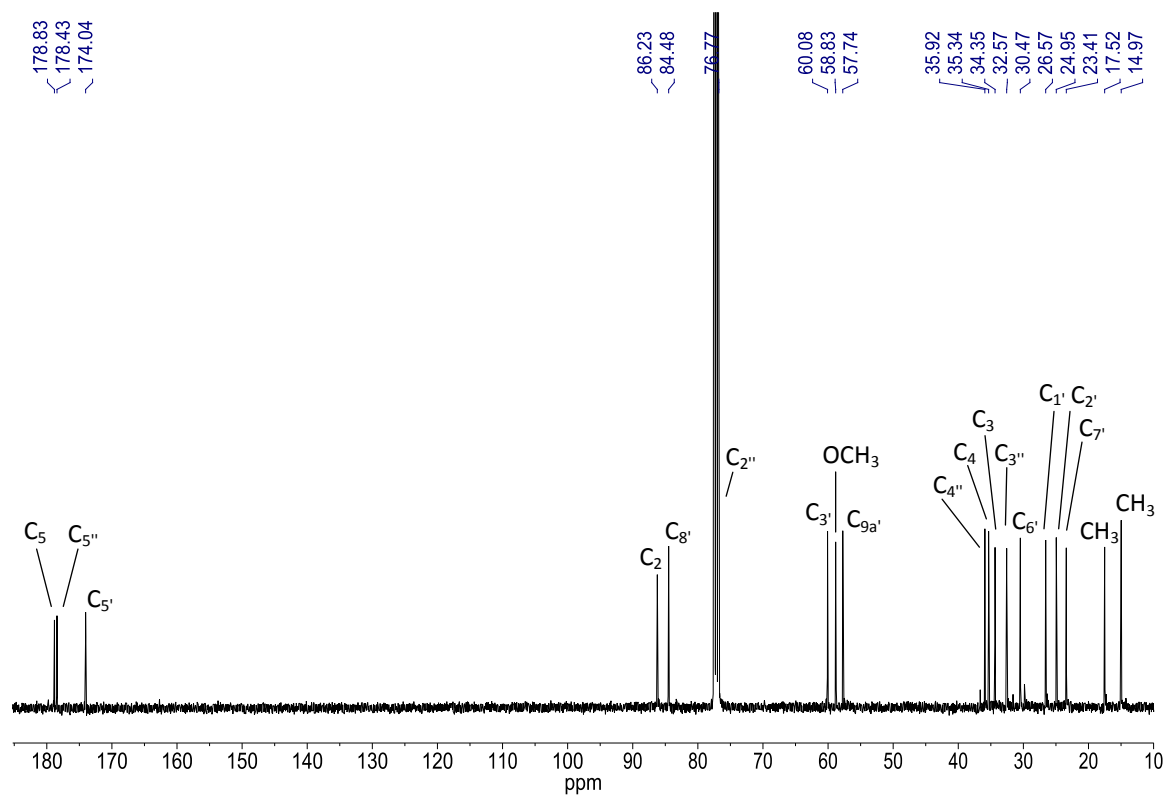
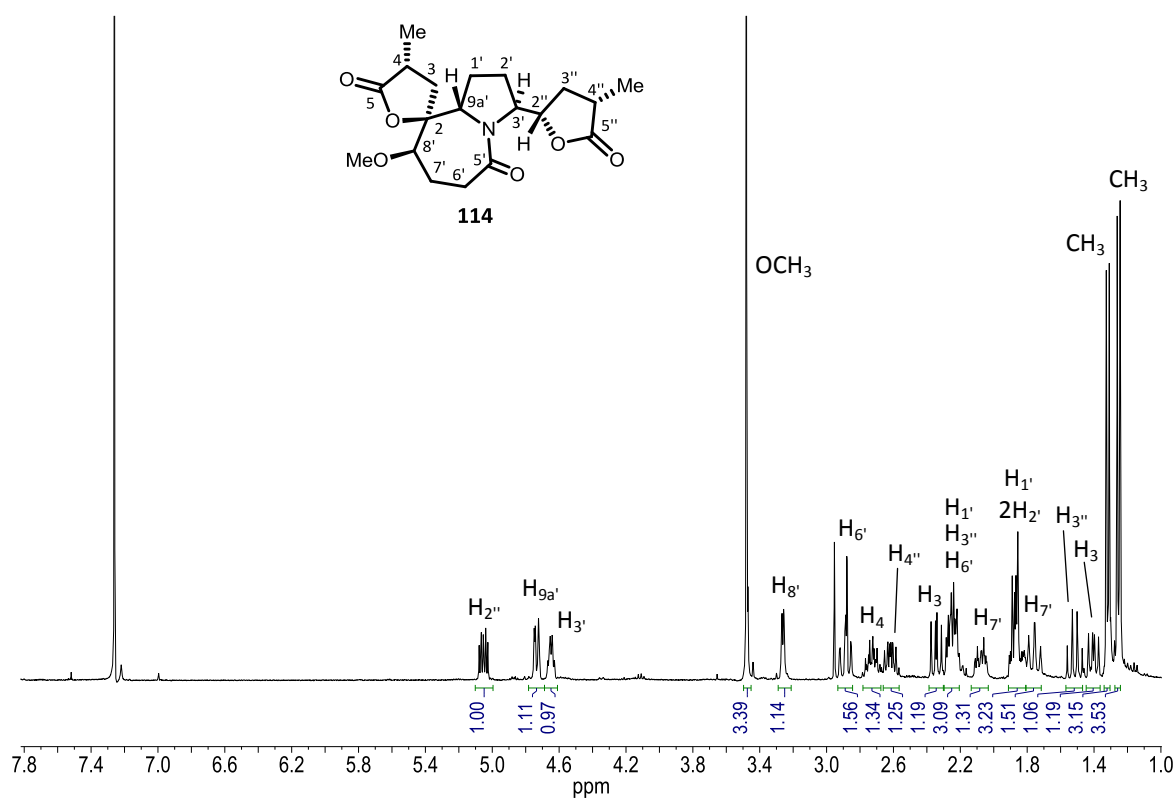


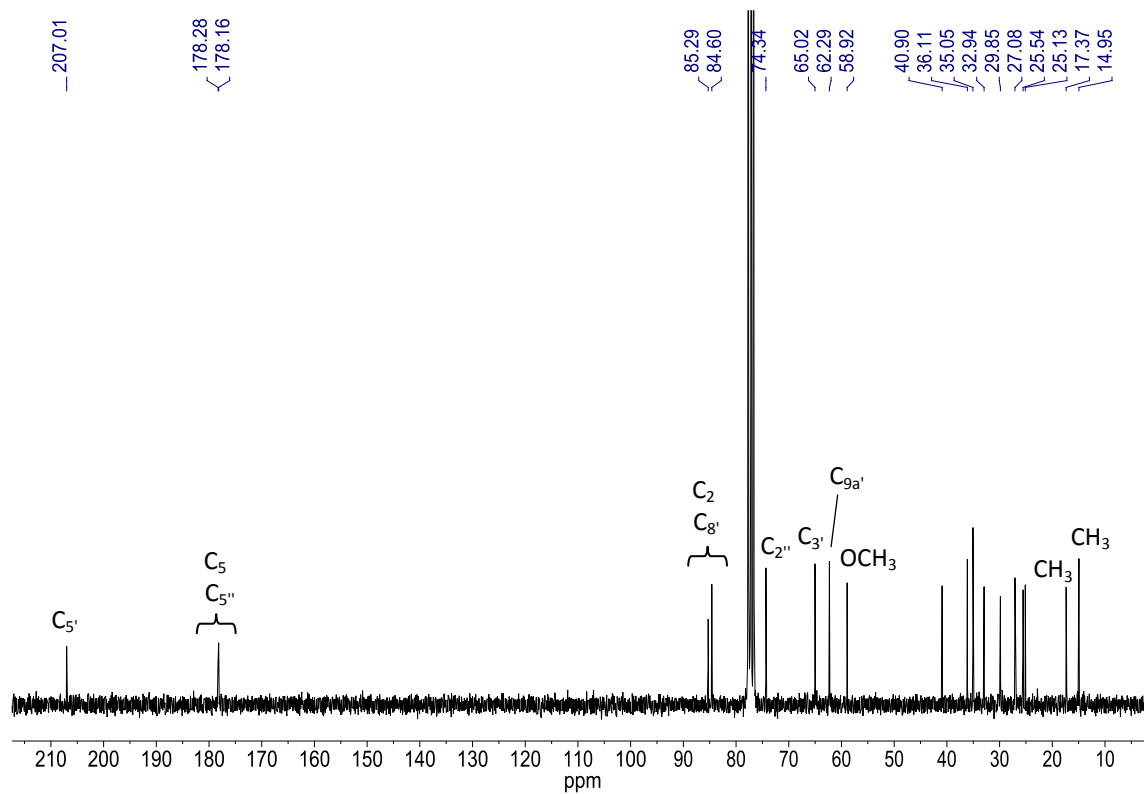
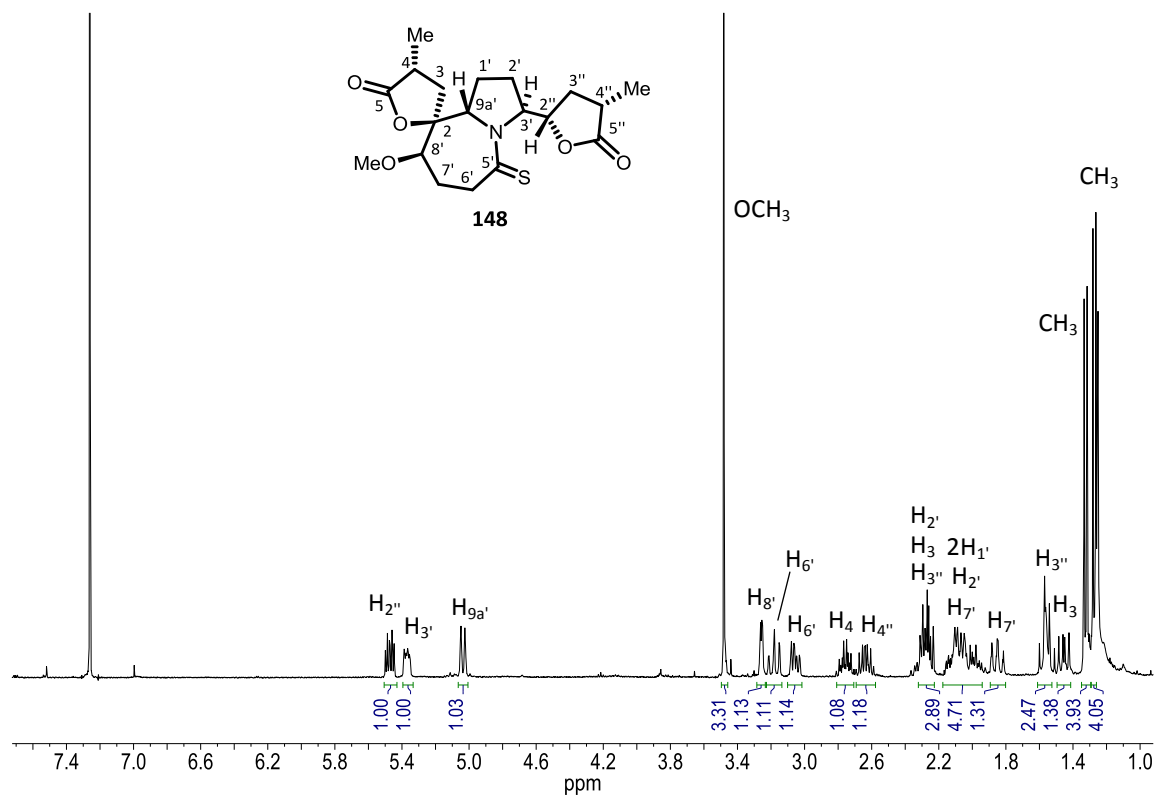
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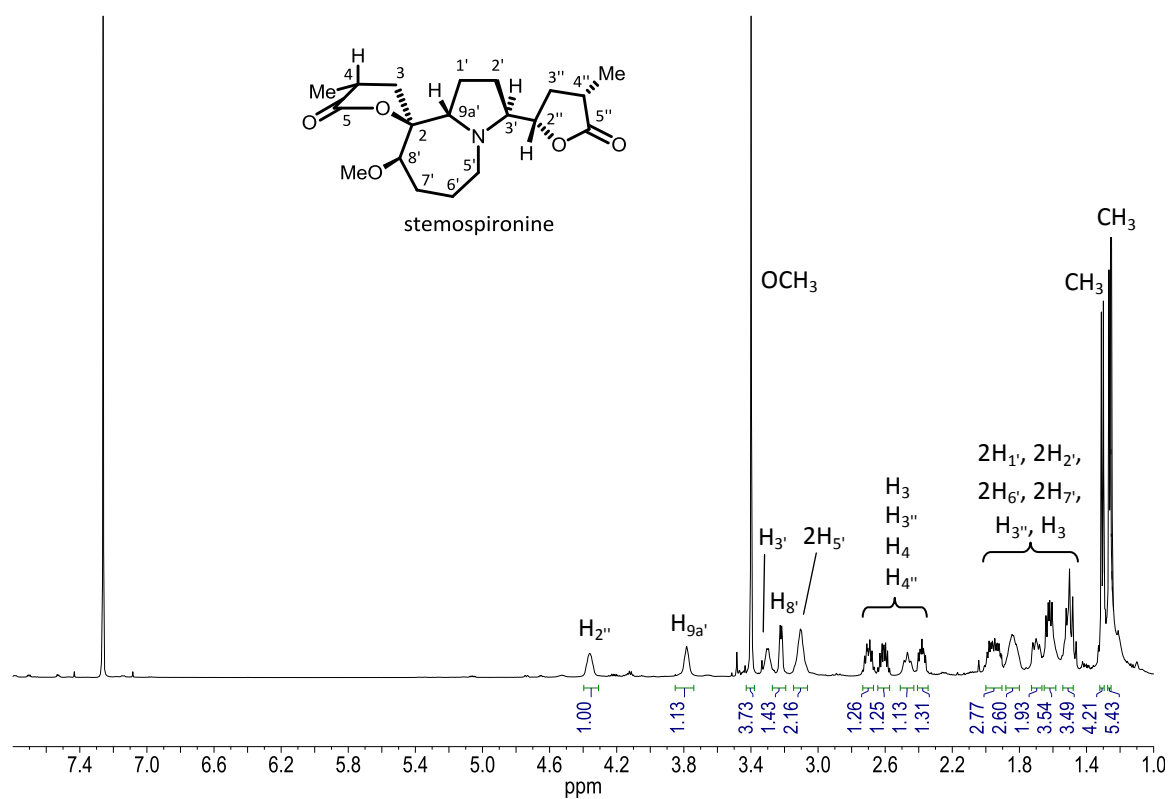
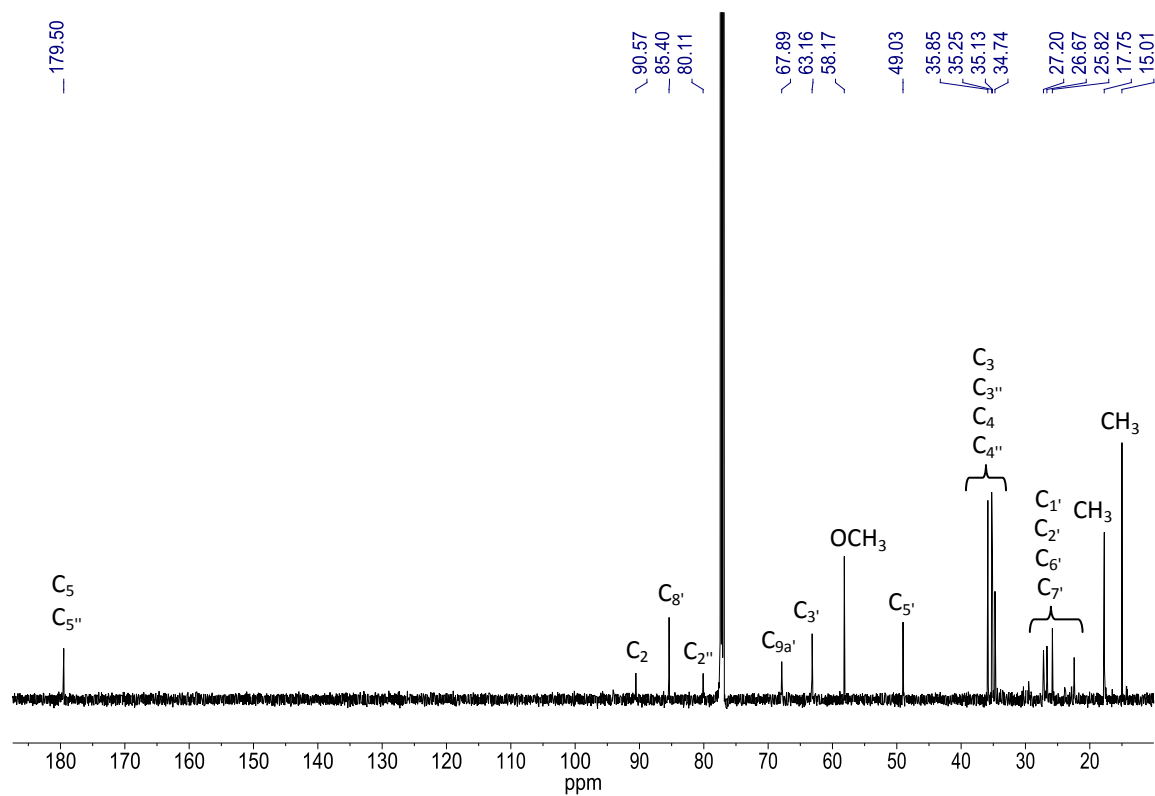


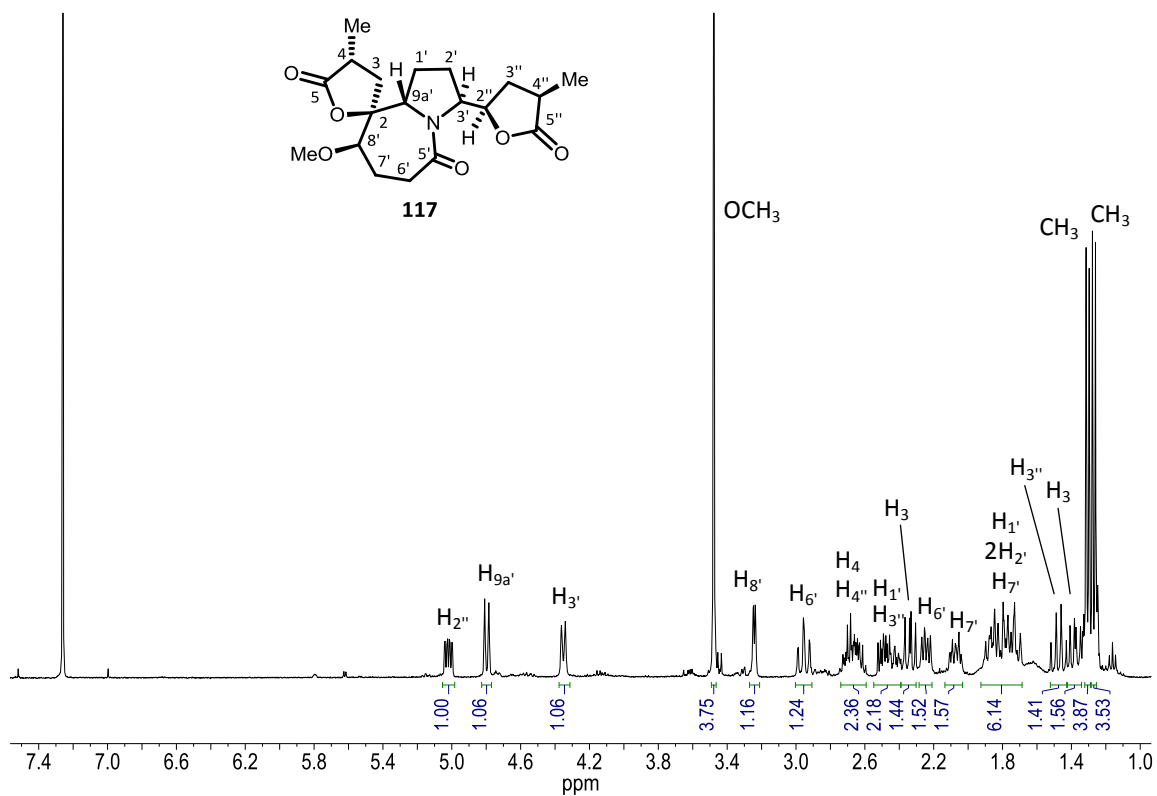
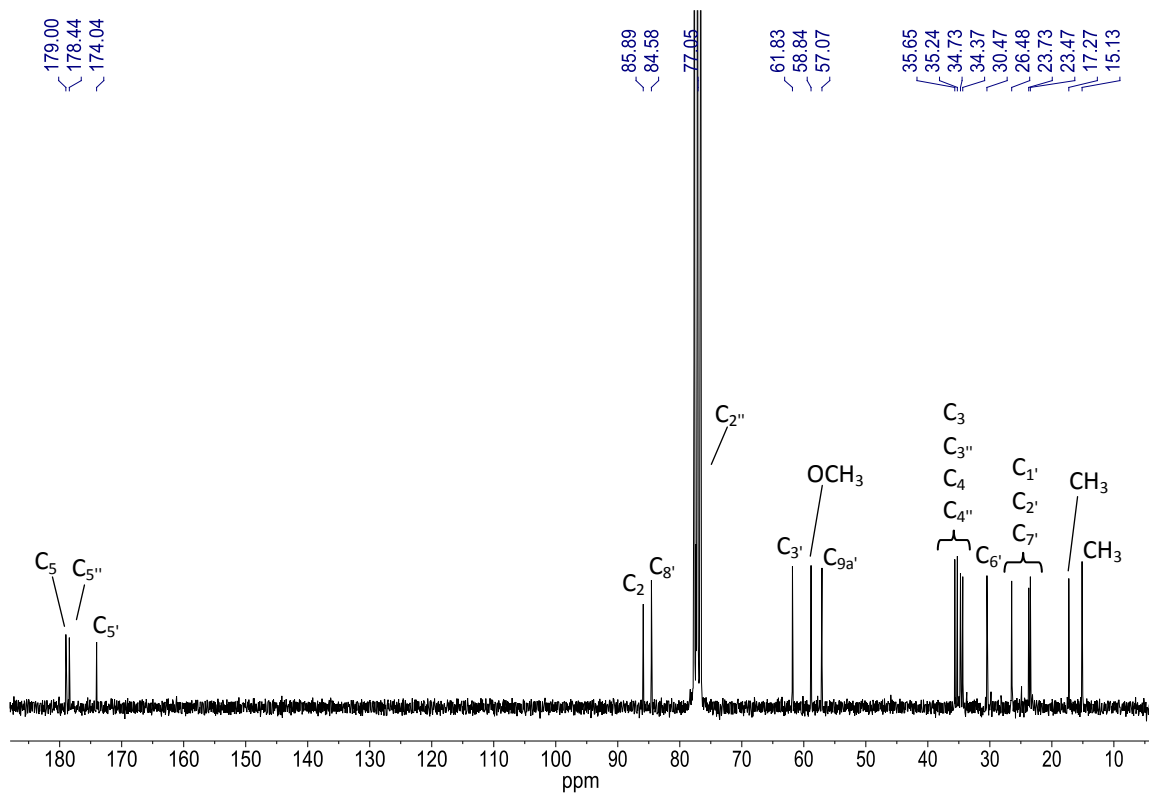


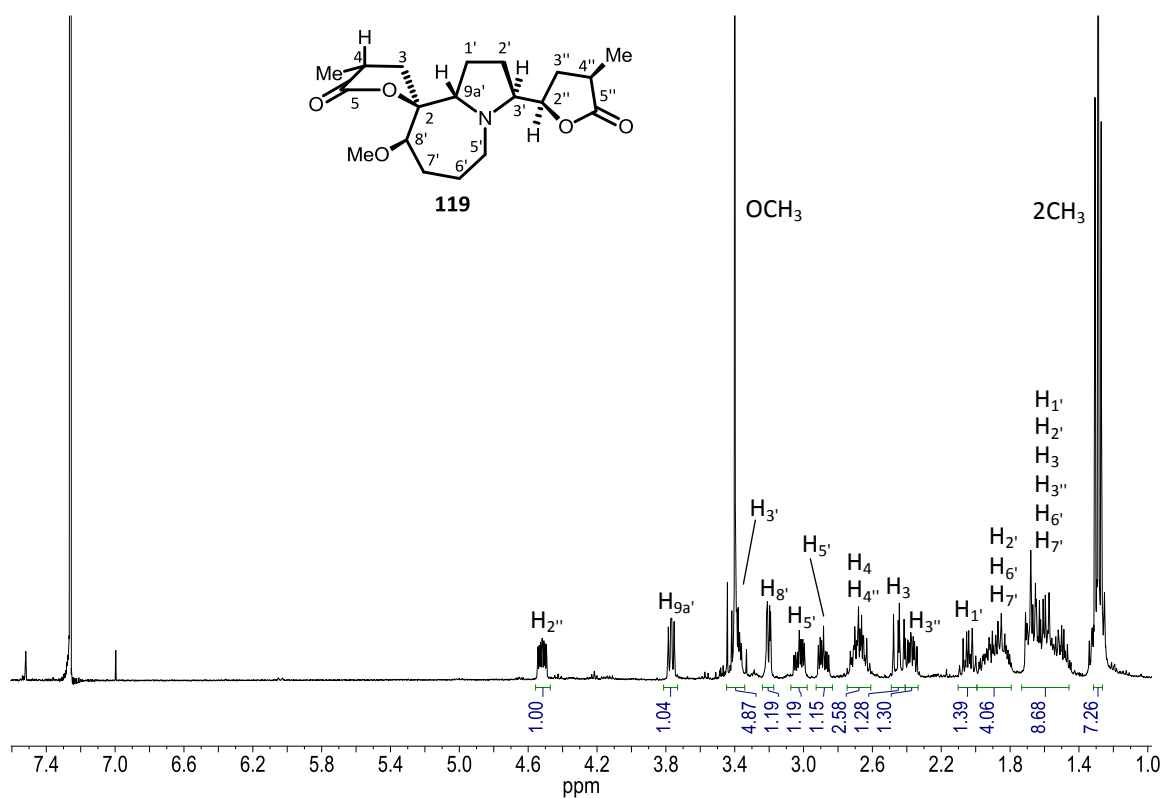
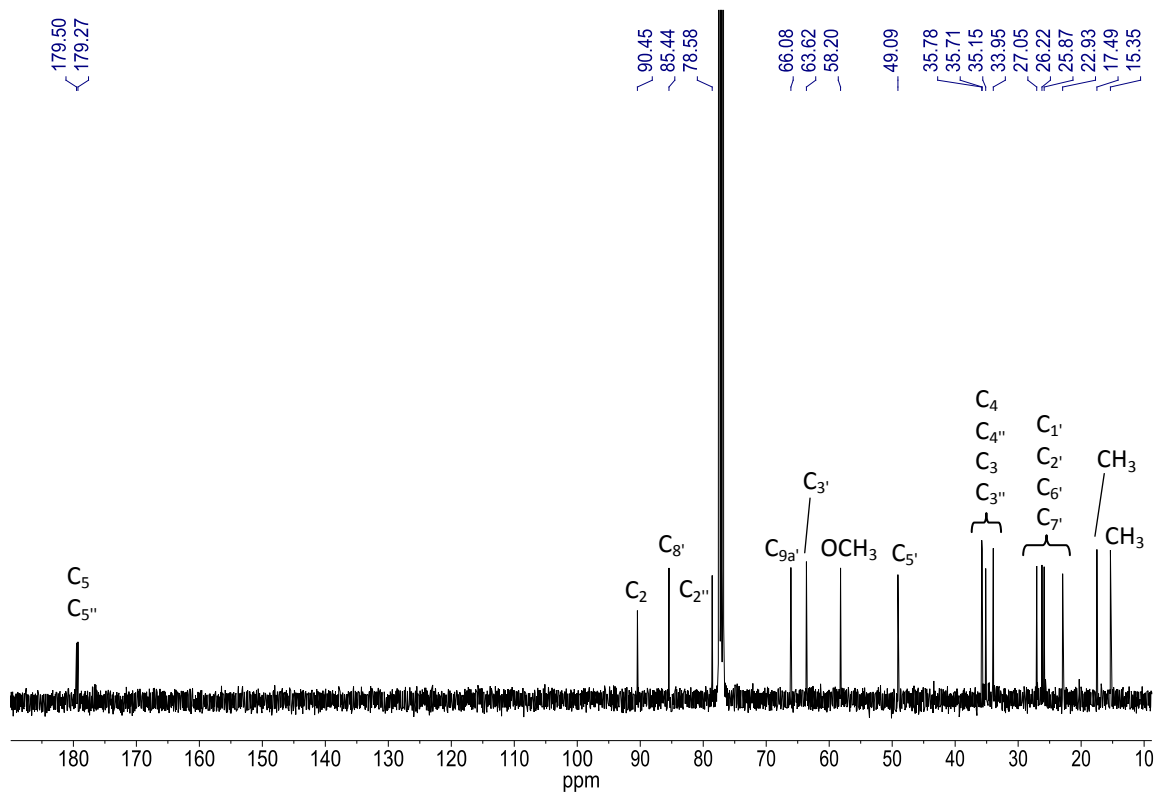
¹H-NMR (400 MHz, CDCl₃)¹³C-NMR (63 MHz, CDCl₃)





¹H-NMR (600 MHz, CDCl₃)¹³C-NMR (150 MHz, CDCl₃)

¹H-NMR (400 MHz, CDCl₃)¹³C-NMR (63 MHz, CDCl₃)

¹H-NMR (400 MHz, CDCl₃)¹³C-NMR (100 MHz, CDCl₃)

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