Universitat Autònoma de Barcelona
Facultat de Ciències
Departament de Química

Stereodivergent Synthesis of Polyoxygenated Cyclohexanes

Tesi Doctoral

Gladis Toribio Villarroya

Dirigida per:

Dr. Josep Font Cierco

Dra. Marta Figueredo Galimany

Memòria presentada per aspirar al grau
de Doctor en Química per Gladis Toribio Villarroya

Gladis Toribio Villarroya

Vist-i-plau

Dra. Marta Figueredo Galimany

Dr. Josep Font Cierco

Bellaterra, Juny 2011

Omplint aquestes pàgines m'envaeixen una gran quantitat de records, centenars de moments viscuts fora, però sobretot dins del laboratori. No puc evitar somriure i alhora sentir enyorança, tot plegat ha estat una època tan bonica i enriquidora, i tot això es deu a tota la gent que he tingut el plaer de conèixer i m'ha acompanyat en aquest camí. I per això voldria dedicar-vos aquestes paraules.

En primer lloc, voldria agrair al Dr. Josep Font i la Dra. Marta Figueredo, directors d'aquest treball, l'amabilitat, la dedicació i la disponibilitat oferta en tot moment. Gràcies pels múltiples consells, xerrades i explicacions de les que tant he après i m'han permès iniciar-me dins el món de la investigació.

Destacar especialment el Dr. Pau Bayón, al qual he d'agrair el seu entusiasme per la química i la il·lusió transmesa al llarg d'aquests anys, per ser un director més. I, sobretot pel suport rebut en tot moment, tant a nivell professional com personal.

Vull fer extensiu l'agraïment al Dr. Ramón Alibés pel seu tracte humà i el bon humor que el caracteritza, així com al Dr. Pere de March i al Dr. Fèlix Busqué.

No voldria deixar d'agrair al Dr. Josep López-Santín i la Dra. Gloria Caminal, del "Grup d'Enginyeria de Bioprocessos i Biocatàlisi Aplicada" l'amabilitat i disponibilitat en respondre'm els dubtes en l'àmbit dels processos enzimàtics. I al Dr. Jordi Hernando per les converses pels passadissos plenes de disbauxa.

M'agradaria destacar l'ajuda de tots els membres que integren el Servei de Ressonància Magnètica Nuclear i el Servei d'Anàlisi Química, els quals faciliten realment la nostra feina.

Molt especialment voldria agrair-vos-ho a tots vosaltres amb qui comparteixo el dia a dia al laboratori/s. Als que hi eren quan vaig arribar i em van fer sentir una més. A la Montserrat, per la teva bogeria i per introduir-me al "lleidetà", al Fran, que tot i fer de "poli" és un bon mestre, al David, per la teva gran disposició a resoldre'm dubtes i per tots els moments viscuts a la vitrina. Als 457, a la Sònia, sempre tant atenta i a la Gisela pel teu gran somriure encomanadís. I no puc deixar-me a l'Àlex, tot i que vam coincidir poc temps he trobat en tu un bon amic.

Al Javi (present només aixecar el cap) i l'Èric, perquè és amb vosaltres amb qui he compartit plenament l'estada al laboratori, caminant plegats. Els inicis plens de cursos, els assajos de la tesina, els nervis i festetes als congressos... gràcies per totes les estones viscudes.

Als ja no tan nous, al Guillaume, per les seves creps boníssimes, a la Rosa, per regalar-me tetines en secret, i al meu company de gabosines Miguel, ànims i moltíssima sort. A la Marta, per ser-hi sempre, per permetre el meu desordre a la vitrina en l'última etapa, ets un sol! Amorín!!! Ai, Laura, perquè realment omples el laboratori de rialles i positivisme, em transmets una gran confiança! A la Cristina Benaiges i l'Enrico per les estonetes al boulder que tant m'ajuden a desconnectar. No em vull deixar l'Alfons, perquè en poc temps ens vas deixar petjada i la Cristina Oliveres, pels acudits?! No, millor per la teva simpatia i bogeria, i a l'Arnau per la teva enorme motivació i les sorprenents "sortides" que tant ens fan riure... Als les noves generacions que tot i que no he tingut el plaer de conèixer massa m'han mostrat el seu somriure, al Marc, la Mireia i la Bea. Molta sort.

A la "meva Núria i al meu Toni", permeteu-me l'expressió. Moltes gràcies a tots dos, hem compartit moments molt bons, i d'altres no tant, sempre sou al meu costat. Sempre al peu del canó! A la Núria, agrair els soparets (que ara enyoro), les xerrades sense fi, les visites a "Lleide" i les "nits plenes d'estrelles", el "fer anar", el panís, per saltar per les roques amb "io"... per la bonica amistat sorgida entre nosaltres! Al Toni, perquè saps arrencar-me un somriure en qualsevol moment, per entendre'm "un pilot", per fer-me sentir especial, per la nostra complicitat... penso que no cal dir massa més! Saps que un trosset d'aquesta tesi et pertany!

Als companys de promoció amb qui he compartit uns anys extraordinaris. A l'Ariadna per acompanyar-me ens els inicis i seguir estant a prop. A la Marta i l'Anna, ja són molts anys al vostre costat, "ai! cuques" simplement perquè sou increïbles! I no em puc deixar al Marc, l'última incorporació que ens ajuda a posar una mica de seny a tot plegat. Per les birretes a la "tete"... que sempre m'animen, les escapadetes a la muntanya... que m'omplen d'aire fresc, les nits de festeta... rialles i bogeria... és un privilegi haver-vos conegut! Perquè continuem trobant moments per desconnectar i intentar arreglar una micona el món!

I, sobretot, als amics i amigues de fora el món de la química. Susana, carinyu, perquè ens coneixem de ben petitones i no m'imagino la meva vida sense tu. A vegades ben a prop, a vegades molt lluny, però sempre, sempre al meu costat! No calen les paraules, tan sols una mirada. I a l'Enrique, tot i que no fa massa que estàs amb nosaltres ens has ben conquistat! Alba, Pep, ai... que difícil... com us puc agrair tot el que heu fet i feu per mi? Sempre és un plaer estar amb vosaltres i sentir-me tant estimada. Pels milers de partits del Barça que compartim, sempre nerviosos i amb molta il·lusió, pels soparets i les birretes parlant de tot i de res, per fer de casa vostra casa meva. Sou uns tresors!

El més sincer agraïment a la meva família, a tots els d'Andújar que tot i ser lluny sempre se'n recorden de mi. I als de Mollet, moltes, moltíssimes gràcies per tot! Especialment a l'Oriol i a la Isa, al Marc i a la Luci, a l'Isaac, m'imagino que ja ho sabeu, sou imprescindibles per mi. I, sobretot a la nena més bonica del món, la Júlia! Gràcies petitona per dibuixar-me sempre un somriure als llavis. No em voldria deixar als meus "iaia i iaio", i a la meva tieta Dolors, sóc tan afortunada de tenir-te a prop, penso que no cal que et digui massa res, simplement gràcies, milers de gràcies. Als meus pares, pel seu suport incondicional i la confiança que sempre han dipositat en mi, per estimar-me. Especialment a la meva mare, per donar-m'ho tot, per mimar-me infinitament. "Mai deixis que una llàgrima no et deixi veure el sol". Sempre em tindràs al teu costat.

A TOTS VOSALTRES, MOLTÍSSIMES GRÀCIES!

“Llença´t, cada instant és únic
no es repetirà,
sento que el cor ja no para de bategar
i diu que em llenci,
que no pensi en tot el que vindrà,
que un llapis mai no dibuixa sense una mà.”

Llença't, Lax'n'busto

A la meva família
Als meus amics

Part of the results of this thesis are described in the the following scientific publications:

- "An Efficient Protocol for the Enantioselective Preparation of a Key Polyfunctionalized Cyclohexane. New Access to (R)- and (S)-4-Hydroxy-2-cyclohexenone and (R)- and (S)-trans-Cyclohex-2-ene-1,4-diol. Bayón, P.; Marjanet, G.; Toribio, G.; Alibés R.; de March, P.; Figueredo, M.; Font, J. *J. Org. Chem.* **2008**, *73*, 3486-3491."

- "Divergent Approach to Gabosines and Anhydrogabosines: Enantioselective Synthesis of (+)-Epiepofromin, (+)-Epoformin, (+)-Gabosine A, and Gabosines B and F. Toribio, G.; Marjanet, G.; Alibés, R.; de March, P.; Font, J.; Bayon, P.; Figueredo, M. *Eur. J. Org. Chem.* **2011**, 1534-1543."

For better comprehension, the nomenclature used in the present work is intended to keep fixed numbers in equivalent carbon atoms of related compounds.

INDEX

INDEX

Acronyms

AIBN	azabis(isobutyronitrile)
ACN	acetonitrile
CALB	C*andida Antarctica* Lipase B
m-CPBA	*m*-chloroperbenzoic acid
CSA	camphorsulfonic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DMF	dimethylformamide
DHP	dihydropyran
DIBAL-H	diisobutylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
IBDA	iodobenzene diacetate
LDA	lithium diisopropylamide
Me-CBS	methyl oxazaborolidine (Corey-Bakshi-Shibata)
MOM	methoxymethyl
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMP	*N*-methylpyrrolidinone
PIFA	phenyliodonium *bis*-(trifluoroacetate)
PPTS	pyridinium *p*-toluenesufonate
PTSA	*p*-toluenesulfonic acid
TBS	^{t}butyldimethylsilyl
TBDPS	^{t}butyldiphenylsilyl
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMS	tetramethylsilane
TPAP	tetra-*n*-propylammonium perruthenate
Ts	tosyl

I. Introduction and objectives

Cyclohexane ring in nature

1. BIOLOGICALLY ACTIVE CYCLOHEXANES

Nature synthesizes a vast number of products that contain a densely functionalized cyclohexane core. Frequently, several stereocentres are found in these structures, resulting in a rich array of stereochemical diversity. The importance of these compounds lies in the fact that they show a wide variety of interesting biological activities.

Conduritols, conduramines and inositols are well-known representative members of cyclohexane natural products (Figure 1). Conduritols, a group of 5-cyclohexen-1,2,3,4-tetrols, were first isolated in 1908 from the dry bark of *Marsdenia condurango*.[1] This family of compounds comprises 10 stereomeric forms (two *meso* forms and four enantiomeric pairs) named A to F. Inositols and conduramines, closely related to conduritols, are valuable synthetic intermediates as precursors to amino-inositols. D-Glycosidase inhibitory activity has been reported for all of them.[2] Shikimic acid and quinic acid are present in the vegetal kingdom, especially in higher plants. They constitute some of the key intermediates of the shikimate

[1] Kubler, K. *Arch. Pharm.* (Weinheim) **1909**, *246*, 620-660.

[2] (a) Legler, G.; Bause, E. *Carbohydr. Res.* **1973**, *28*, 45-52. (b) Legler, G.; Lotz, W. *Z. Physiol. Chem.* **1973**, *354*, 243-254. (c) Umezawa, S. *Adv. Carbohydr. Chem. Biochem.* **1974**, *30*, 111-182. (d) Atsumi, S.; Umezawa, K.; Iinuma, H.; Naganawa, H.; Nakamura, H.; Iitaka, Y.; Takeuchi, T. *J. Antibiot.* **1990**, *43*, 49-53. (e) Mahapatra, T.; Nanda, S. *Tetrahedron: Asymmetry* **2010**, *21*, 2199-2205.

pathway,[3] which gives rise to a large number of aromatic compounds such as the aminoacids phenylalanine and tyrosine.

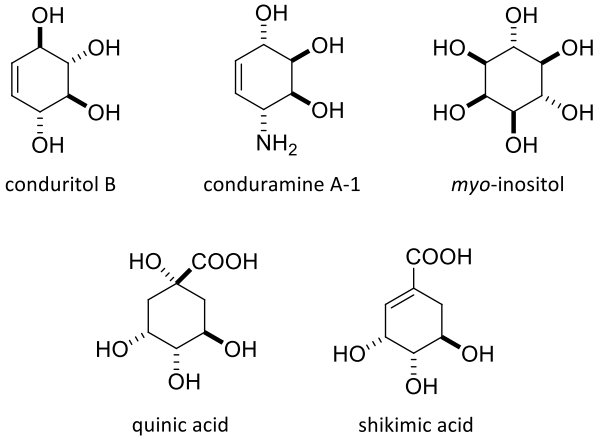


Figure 1. Examples of natural cyclohexanes.

The gabosine family (Figure 2) comprises a group of secondary metabolites isolated from various *Streptomyces* strains with a closely related carba-sugar structure.[4-8] All gabosines present a polyoxygenated methyl cyclohexane system as the common constitutional feature. Their structural diversity is originated by differences in the substituent positions, unsaturation degree, and/or relative and absolute configuration of their stereogenic centres. A plethora of biological activities have been reported for them, such as plant growth regulating effects,[9] DNA-binding properties,[8] anti-bacterial behaviour,[4] glycosidase and glyoxalase I inhibitory activity[10] (and, consequently, potential anticancer properties). [10]

[3] Mann. J. *Secondary Metabolism*, Oxford University Press, Oxford **1987**.

[4] First isolation of gabosine C, named KD16-U1: Tatsuta, K.; Tsuchiya, T.; Mikami, N.; Umezawa, S.; Umezawa, H.; Naganawa, H. *J. Antibiot.* **1974**, *27*, 579-586.

[5] Takeuchi, T.; Chimura, H.; Hamada, M.; Umezawa, H.; Yoshioka, O. *J. Antibiot.* **1975**, *28*, 737-742.

[6] Isolation and structural assignment of gabosines A-K: Bach, G.; Breiding,-Mack, S.; Grabley, S.; Hamman, P.; Hütter, K.; Thiericke, R.; Uhr, H.; Wink, J.; Zeeck, A. *Liebigs Ann. Chem.* **1993**, 241-250.

[7] Synthetic studies indicate that the structure of gabosine K needs to be revised: Metha, G.; Lakshminath, S. *Tetrahedron Lett.* **2000**, *41*, 3509-3512.

[8] Isolation and structural assignment of gabosines L, N and O: Tang, Y.-Q.; Maul, C.; Höfs, R.; Sattler, I.; Grabley, S.; Feng, X.-Z.; Zeeck, A.; Thiericke, R. *Eur. J. Org. Chem*. **2000**, 149-153.

[9] Banwell, M. G.; Bray, A.; M. Wong, D. *New J. Chem.* **2001**, *25*, 1351-1354 (Gabosine A).

[10] Chimura, H.; Nakamura, J.; Takita, T.; Takeuchi, T.; Umezawa, H.; Kato, K.; Saito, S.; Tomisawa, T.; Iitaka, Y. *J. Antibiot.* **1975**, *28*, 743-748.

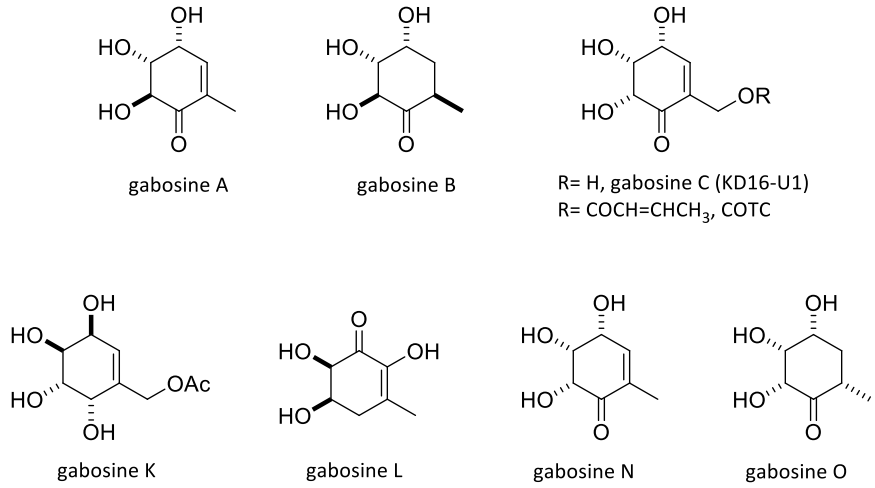


Figure 2. Examples of gabosine family of secondary metabolites

Recently, two new families of gabosine-related compounds have been identified (Figure 3). Thus, a family of antitumor metabolites named pericosines A-E were isolated from a strain of *Periconia byssoides*.[11] Among them, pericosines A-C exhibited significant growth inhibition against tumor cell lines, with pericosine A showing a significant *in vivo* activity.

In 2009, it was described the isolation of seven new polyoxigenated methyl cyclohexanes closely related to carbasugars, ampelomins A-G, from *Ampelomyces fungus.*[12] These compounds show antibacterial and/or α-glycosidase inhibitory activity.

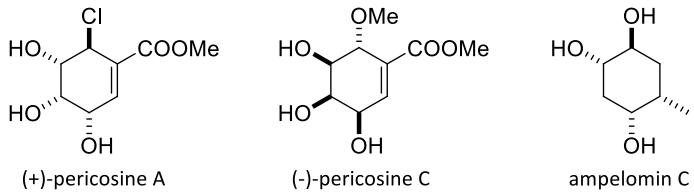


Figure 3. Examples of the pericosine and ampelomin families.

There is also a growing class of epoxyquinol-based natural products which exhibit remarkable biological activities, mainly as antibiotics and antitumor agents. Some examples of compounds related to this group are phyllostine, epoxydon, epoformin and theobroxide (Figure 4). Most of them present anhydrogabosine structure and they all show interesting biological activities, such as phytotoxicity, enzymatic inhibition, antibiotic and antibacterial properties.

[11] (a) Donhoe, T. J.; Blades, K.; Helliwell, M.; Waring, M. J. *Tetrahedron Lett.* **1998**, *39*, 8755-8758. (b) Yamada, T.; Iritani, M.; Ohishi, H.; Tanaka, K.; Minoura, K.; Doi, M.; Numata, A. *Org. Biomol. Chem.* **2007**, *5*, 3979-3986.

[12] Zhang, H.; Xue, J.; Wu, P.; Xu, L.; Xie, H.; Wei, X. *J. Nat. Prod.* **2009**, *72*, 265-269.

Phyllostine[13] and epoxydon[14] are phytotoxic metabolites isolated from the culture broth of *Phyllosticta sp*., known as the pathogenic red clover fungus. Epoformin is an antibiotic and cytotoxic substance isolated from the culture broth of *Penicillium claviforme*[15] and theobroxide is a potato micro-tuber growth inducing substance isolated from the fungus *Lasiodiplodia theobromae*.[16]

Harveynone and tricholomenyn are two related compounds that contain an acetylenic chain. (-)-Harveynone was originally isolated from the *Curvularia Harvey*[17a] plant and it shows anticancerous properties, whereas its enantiomer, (+)-harveynone, has been isolated from *Pestalotiopsis* theae,[17b] a causal fungi for the tea gray blight disease, and it is a phytotoxin. Tricholomenyn A was isolated from the fruiting bodies of *Tricholoma acerbum*[18] and it shows antimitotic activity.

Other representative examples of epoxycyclohexenones are bromoxone, the antibiotic LL-C10037α, manumycin A and the palmarumycin and preussomerin families. Bromoxone and its acetate, were isolated from marine *Ptychodera* acorn worm in the sea depths of the Maui island.[19] The antibiotic LL-C10037α was isolated from *Streptomyces* strains.[20]

The isolation of manumycin A was described in 1963,[21] but its structure was not established until 1973.[21b] More recently, its stereochemical assignment has been confirmed by the first total synthesis.[21c] This metabolite possesses a *syn*-hydroxy epoxide arrangement in the cyclohexenone core and two unsaturated side chains at C_2 and C_4. Its potent inhibitory activity of

[13] (a) Sakamura, S.; Ito, J.; Sakai, R. *Agric. Biol. Chem.* **1970**, *34*, 153-155; (b) ibid. **1971**, *35*, 105-110.

[14] (a) Closse, A.; Mauli, R.; Sigg, H. P. *Helv Chim. Acta* **1965**, *49*, 204-213. (b) Sakamura, S.; Niki, H.; Obata, Y.; Sakai, R.; Matsumoto, T. *Agric. Biol. Chem.* **1969**, *33*, 698-703.

[15] (a) Yamamoto, I.; Mizuta, E.; Henmi, T.; Yamano, T.; Yamatodani, S. *Takeda Kenkyusho Ho* **1973**, *32*, 532-538. *Chem. Abstr.* **1974**, *80*, 106812. (b) Venkatasubbaiah, P.; Tisserat, N. A.; Chilton, W. S. *Mycopathologia* **1994**, *128*, 155-159.

[16] (a) Nakamori, K.; Matsuura, H.; Yoshihara, T.; Ichihara, A.; Koda, Y. *Phytochemistry* **1994**, *35*, 835-839. (b) Yoshihara T.; Ohmori, F.; Nakamori, K.; Amanuma, M.; Tsutsumi, T.; Ichihara, A.; Matsuura, H. *J. Plant Growth Reg.* **2000**, *19*, 457-461.

[17] (a) Kawazu, K.: Kobayashi, A.; Oe, K. JP 1991, 0341075 (*Chem. Abstr.* **1991**, *115*, 181517k). (b) Nagata, T.; Ando, Y.; Hirrota, A. *Biosci. Biotechnol. Biochem.* **1992**, *56*, 810-811.

[18] Garlaschelli, L.; Magistrali, E.; Vidari, G.; Zuffardi, O. *Tetrahedron Lett.* **1995**, *36*, 5633-5636.

[19] Higa, T.; Okuda, R. K.; Severns, R. M.; Scheuer, P. J.; He, C. H.; Changfu, X.; Clardy, J. *Tetrahedron* **1987**, *43*, 1063-1070.

[20] Lee, M.; Fantini, A. A.; Morton G. O.; James, J. C.; Borders, D. B.; Testa, R. T. *J. Antibiot.* **1984**, *37*,1149-1152.

[21] (a) Buzzetti, F.; Gaümann, E.; Hütler, R.; Séller-Schierlein, W.; Neipp, L.; Prelog, V.; Zähner, H. *Pharm. Acta Helv.* **1963**, *38*, 871. (b) Scröder, K.; Zeeck, A. *Tetrahedron Lett.* **1973**, 4495-4498. (c) , L.; Macdonald, G.; Ragot, J. P.; Lewis, N.; Taylor, R. J. K. *J. Org. Chem*. **1998**, *63*, 3526-3527.

ras farnesyl-protein transferase (FPTase) is due to the epoxycyclohexenone unit and the east chain. This activity may led to a possible application in chemotherapy.

In 1990 a group of antifungal metabolites, preussomerins, were isolated from cultures of *Preussia isomera*. They are also inhibitors of FPTase.[22] The spiroketal family named palmarumycins, which have herbicidal activity, were isolated in 1994 from several strains of *Coniothyrium* fungi species.[23]

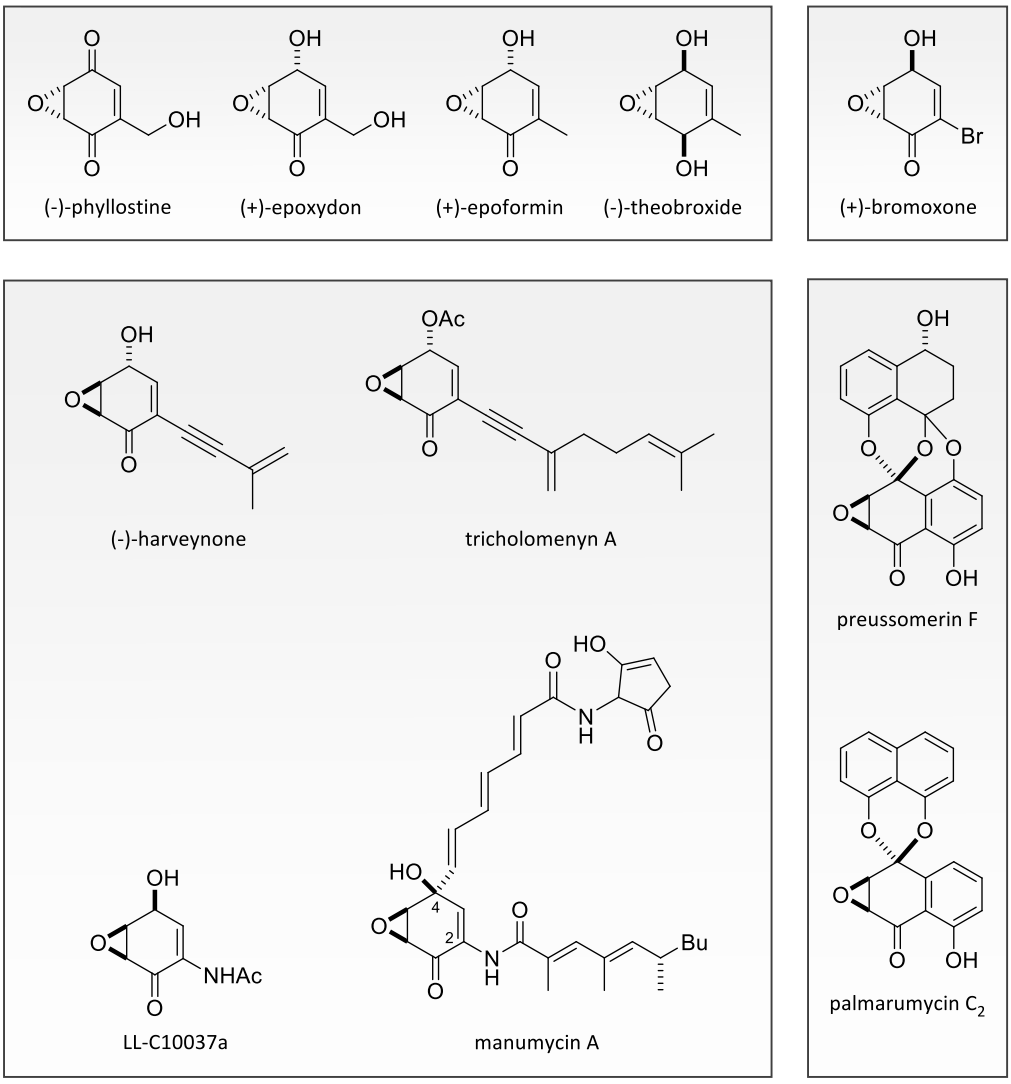
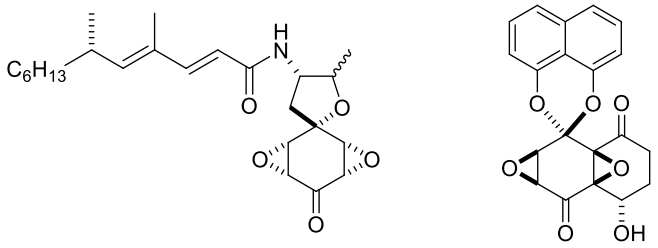


Figure 4. Examples of natural epoxyciclohexenones.

[22] (a) Weber, H. A.; Bänziger, N. C.; Gloer, J. B.; *J. Am. Chem. Soc.* **1990**, *112*, 6718-6719. (b) Weber, H.A.; Gloer, J. B. *J. Org. Chem.* **1991**, *56*, 4355-4360.

[23] (a) Krohn, K.; Michel, A.; Florke, U.; Aust, H. J.; Dräger, S.; Schulz, B. *Liebigs Ann. Chem.* **1994**, 1099. (b) Singh, S. B.; Zink, D. L.; Liesch, J. M.; Ball, R. G.; Goetz, M. A.; Bolessa, E. A.; Giacobbe, R. A.; Silverman, K. C.; Bills, G. F.; Pelaez, F.; Cascales, C.; Gibbs, J. B.; Lingham, R. B. *J. Org. Chem.* **1994**, *59*, 6296-6302. (c) Krohn, K.; Beckmann, K.; Flörke, U.; Aust, H.-J.; Dräger, S.; Schulz, B.; Busemann, S.; Bringmann, G. *Tetrahedron* **1997**, *53*, 3101-3110.

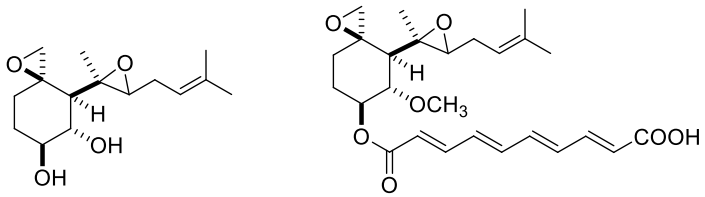
Examples of diepoxycyclohexenone natural compounds include aranorosin and diepoxin α (Figure 5). Aranorosin has been isolated from the *Pseudoarachniotus roseus* fungal strain[24] and shows antitumor properties whereas diepoxin α[25] has the same carbonate skeleton as palmarumycins and displays similar biological activities.



aranorosin diepoxin

Figure 5. Examples of diepoxycyclohexenone compounds.

Other examples of densely functionalized bioactive cyclohexanes are the immunosuppressant FR65814[26] and fumagillin,[27] both compounds feature a spiroepoxide system (Figure 6). The first one is a sesquiterpene isolated from the culture of *Penicillium* that shows potent immunosuppressive activity. The second one is a derivative displaying a potent anticancer activity.



FR65814 fumagillin

Figure 6. Examples of bioactive and densely functionalized cyclohexanes.

[24] (a) Fehlhaber, H. W.; Koegler, H.; Mukhopadhyay, T.; Vijayakumar, E. K. S.; Ganguli, G. N. *J. Am. Chem. Soc.* **1988**, *110*, 8242-8244. (b) Roy, T.; Mukhopadhyay, T.; Reddy, G. C. S.; Desikan, K. R.; Rupo, R. H.; Ganguli, B. N. *J. Antibiot.* **1988**, *41*, 1780-1784. (c) Fehlaber, H. W.; Kogler, H.; Mukhopadhyay, T.; Vijayakumar, E. K. S.; Roy, K.; Rupp, R. H.; Ganguli, B. N. *J. Antibiot.* **1988**, *41*, 1785-1794.

[25] Ragot, J. P.; Alcaraz, M.-L.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 4921-4924.

[26] Amano, S.; Ogawa, N.; Ohtsuka, M.; Ogawa, S.; Chida, N. *Chem, Commun.* **1998**, 1263-1264.

[27] Taber, D. F.; Christos, T. E.; Rheingold, A. L.; Guzei, I. A. *J. Am. Chem. Soc.* **1999**, *121*, 5589-5590.

2. CYCLOHEXANE BUILDING BLOCKS IN STEREOSELECTIVE SYNTHESIS

As it has been shown, a great number of compounds isolated from natural sources present a cyclohexane core as the main structural feature, decorated with diverse oxygen-based substituents. These compounds have deserved special attention of synthetic chemists because of their diverse biological activities and the challenge that represents binding oxygen atoms to the carbocycle in a regio- and stereoselective manner. Even though considerable efforts have been devoted to this endeavour, much work is still needed in this area. In particular, there is a need for chiral raw materials, which have to be available in sufficient quantities and enantiomerically pure form and should be versatile enough to handle the structural diversity occurring among the pursued polyoxygenated cyclohexanes.

An attractive method to prepare such interesting synthons is the use of chiral α,β-cyclohexenones as starting material taking advantage of their various reactive sites. *p*-Benzoquinone is *a priori* an appropriate precursor for the synthesis of these compounds due to its easy accessibility and high functionality. However, its functionalization requires the development of selective transformations because of the equivalence of the two carbonyl groups and the carbon-carbon double bonds. Since quinones are very reactive substrates, the protection of either one or both carbonyl groups and/or double C-C bonds can be very useful for synthetic purposes.

In recent years, a series of chiral derivatives of *p*-benzoquinone have been prepared in our laboratories, with one or both pairs of the originally identical functional groups differentiated (Figure 7).

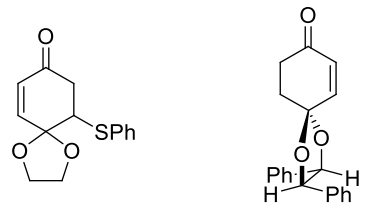


Figure 7. Synthetic equivalents of *p*-benzoquinone.

Ketal **1** was prepared using ethylene glycol to protect one of the carbonyl groups and masking one of the C-C double bonds through a conjugate addition of thiophenol,[28] whereas ketal **2** could be obtained after carbonyl protection with a chiral C_2-symmetric diol.[29] In principle, the introduction of this chiral moiety may allow control of the reactivity and stereoselectivity not only in the acetal function itself, but also in the prochiral vicinal groups. On the contrary, as ketone **1** was prepared in racemic form, it required some kind of enantioselective transformation.

Ketals of quinones have shown a wide range of possibilities in our research. For instance, monoketal **2**, apart from being applied in several stereocontroled processes,[30] has also been used as starting material for the preparation of a wide range of enantiopure chiral synthons with cyclohexane core.[31] This strategy has successfully led to the synthesis of some natural products, including (+)-rengyolone,[32a,b] (+)- and (-)-menisdaurilide,[32a,b] allosecurinine[32c] and different cyclohexenyl nucleosides.[32d] Likewise, monoketal **1** has been used as a synthetic precursor to other natural products, such as gabosines N and O.[33]

The masked *p*-benzoquinone **1** was origillay synthesized in our laboratories by a three steps sequence (Scheme 1) involving transketalization of 3,3,6,6-tetramethoxy-1,4-cyclohexadiene, **3**, with ethylene glycol, followed by ketal monohydrolysis and then conjugated addition of thiophenol. The main drawback of this synthesis came from the tedious chromatographic separation involved in the isolation protocol of **1**. This compound was prepared by the conjugate addition of thiophenol to ketal **5** under thermodynamic control conditions, being, therefore, obtained along with the diaddition products *cis*- and *trans*-**6** (Figure 8) and some unreacted **4**. Recently, the 3,3,6,6-tetramethoxy-1,4-cyclohexadiene, **3**, which was used as the starting material, ceased to be commercial. All these facts made it necessary to consider an

[28] a) de March, P.; Escoda, M.; Figueredo, M.; Font, J. *Tetrahedron Lett.* **1995**, *36*, 8665-8668. (b) de March, P.; Escoda, M.; Figueredo, M.; Font, J.; Medrano, J. *An. Quim. Int. Ed.* **1997**, *93*, 81-87.

[29] de March, P.; Escoda, M.; Figueredo, M.; Font, J.; Álvarez-Larena, A.; Piniella, J. F. *J. Org. Chem.* **1995**, *60*, 3895-3897.

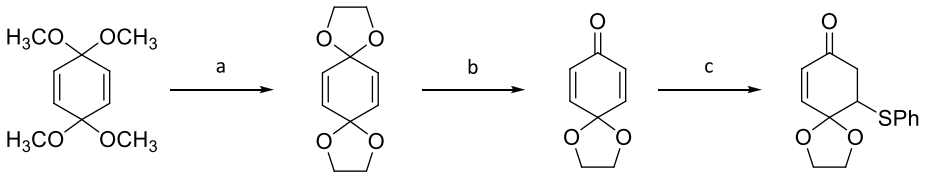
[30] (a) de March, P.; Escoda, M.; Figueredo, M.; Font, J.; Álvarez-Larena, A.; Piniella, J. F. *J. Org. Chem.* **1997**, *62*, 7781-7787. (b) de March, P.; Figueredo, M.; Font, J.; Rodríguez, S. *Tetrahedron* **2000**, *56*, 3603-3609.

[31] Busqué, F.; de March, P.; Escoda, M.; Figueredo, M.; Font, J.; Rodríguez, S. *Tetrahedron: Asymmetry* **2001**, *12*, 3077-3080.

[32] (a) Cantó, M.; de March, P.; Figueredo, M.; Font, J.; Rodríguez, S.; Álvarez-Larena, A.; Piniella, J. F. *Tetrahedron: Asymmetry* **2002**, *13*, 455-459. (b) Busqué, F.; Cantó, M.; de March, P.; Figueredo, M.; Font, J.; Rodríguez, S. *Tetrahedron: Asymmetry* **2003**, *14*, 2021-2032. (c) Bardagí, G. G.; Cantó, M.; Alibés, R.; Bayón, P.; Busqué, F.; de March, P.; Figueredo, M.; Font, J. *J. Org. Chem*. **2008**, *73*, 7657-7662. (d) Ferrer, E.; Alibés, R.; Busqué, F.; Figueredo, M.; Font, J.; de March, P. *J. Org. Chem*. **2009**, *74*, 2425-2432.

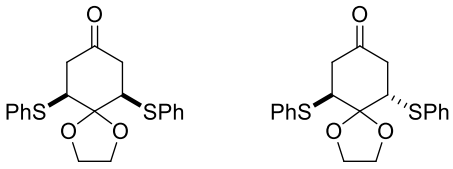
[33] Alibés, R.; Bayón, P.; de March, P.; Figueredo, M.; Font, J.; Marjanet, G. *Organic Lett.* **2006**, *8*, 1617-1620.

alternative route to prepare monoketal **1** through a practical methodology, easy to scale up, for accessing it in substantial amounts.



Reagents: (a) ethylene glycol, AcOH, 92%; (b) AcOH 2%, acetone, 83%; (c) PhSH, $LiOH \cdot H_2O$, $CHCl_3$ reflux.

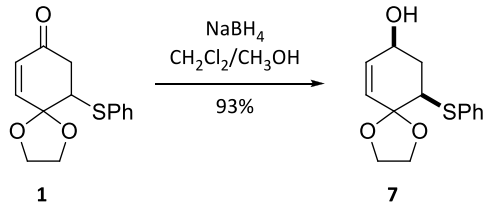
Scheme 1. Synthesis of monoketal **1**.



cis-**6** *trans*-**6**

Figure 8. Compounds *cis*- and *trans*-**6**.

Initially, the resolution of (±)-**1** was carried out by chiral HPLC on cellulose triacetate. The major weakness of this procedure was that the individual enantiomers were only available on a limited scale of 200 mg.[28] Later on, on the basis of a closely related literature precedent,[34] Dr. Georgina Marjanet investigated the enzyme-catalyzed enantioselective acetylation of the alcohol (±)-**7** obtained from the $NaBH_4$ reduction of ketone (±)-**1** (Scheme 2). Previous to the present work, this enzymatic methodology had been carried out starting from 1 g of the alcohol with successful results, but, for synthetic purposes, it would be interesting scaling it up to 5-10 g.



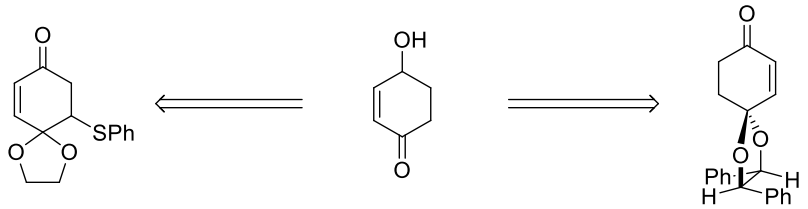
Scheme 2. Synthesis of alcohol **7**.

Also in previous investigations of our group, two stereoselective synthesis of (*R*)- and (*S*)-4-hydroxy-2-cyclohexenone, **8**, were developed starting from *p*-benzoquinone acetals **1** and **2** (Scheme 3).[35] The main drawback of these syntheses was again the limited amount of starting materials available in enantiopure form. Ketone **8** has been widely used as a building block in the

[34] (a) Morgan, B. S.; Hoenner, D.; Evans, P.; Roberts, S. M.; *Tetrahedron: Asymmetry* **2004**, *15*, 2807-2809. (b) Raminielli, C.; Comasseto, J. V.; Andrade, L. H.; Porto, A. L. M. *Tetrahedron: Asymmetry* **2004**, *15*, 3117-3122. (c) Haeffner, F.; Norin, T.; Hult, K. *Biophys. J.* **1998**, *74*, 1251-1262.

[35] de March, P.; Escoda, M.; Figueredo, M.; Font, J.; García, E.; Rodríguez, S. *Tetrahedron: Asymmetry* **2000**, *11*, 4473-4483.

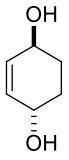
synthesis of several bioactive compounds such as the anticholesterol agents compactin and ML-263A,[36] and the immunosuppressant FK-506.[37] A practical procedure to access ketal **1** in significant amounts should allow us to synthesize any enantiomer of 4-hydroxy-2-cyclohexenone in multigram scale, increasing its usefulness as synthetic precursor of more complex molecules.



1 **8** **2**

Scheme 3. Starting materials in the synthesis of **8**.

Starting also from **1**, another previous achievement of our research group was the first stereoselective synthesis of the cyclohexenediol *trans*-**9**,[38] which is closely related to ketone **8** (Figure 9). A monoprotected derivative of *trans*-**9** has been used as intermediate for the synthesis of petasins[39] and cyclohexane prostanoids.[40] Moreover, it could also be employed as a precursor in the synthesis of chiral polycarbonates, which are useful to prepare new biodegradable medical materials.[41]



trans-**9**

Figure 9. Cyclohexenediol **9**.

[36] Danishefsky, S. J.; Simoneau, B. *J. Am. Chem. Soc.* **1989**, *111*, 2599-2604.

[37] Jones, A. B.; Yamaguchi, M.; Patten, A.; Danishefsky, S. J.; Ragan, J. A.; Smith, D. B.; Schreiber, S. L. *J. Org. Chem.* **1989**, *54*, 17-19.

[38] Alibés, R.; de March, P.; Figueredo, M.; Font, J.; Marjanet, G. *Tetrahedron: Asymmetry* **2004**, *15*, 1151-1155.

[39] Witschel, M. C.; Bestmann, H. J. *Synthesis* **1997**, 107-112.

[40] López-Pelegrín, J. A.; Janda, K. D. *Chem. Eur. J.* **2000**, *6*, 1917-1922.

[41] (a) Pulapura, S.; Kohn, J. *Journal of Biomaterials Applications* **1992**, *6*, 216-250. (b) Tangpasuthadol, V.; Shefer, A.; Hooper, K. A.; Kohn, J. *Biomaterials* **1996**, *17*, 463-468. (c) Tangpasuthadol, V.; Pendharkar, S. M.; Kohn, J. *Biomaterials* **2000**, *21*, 2371-2378.

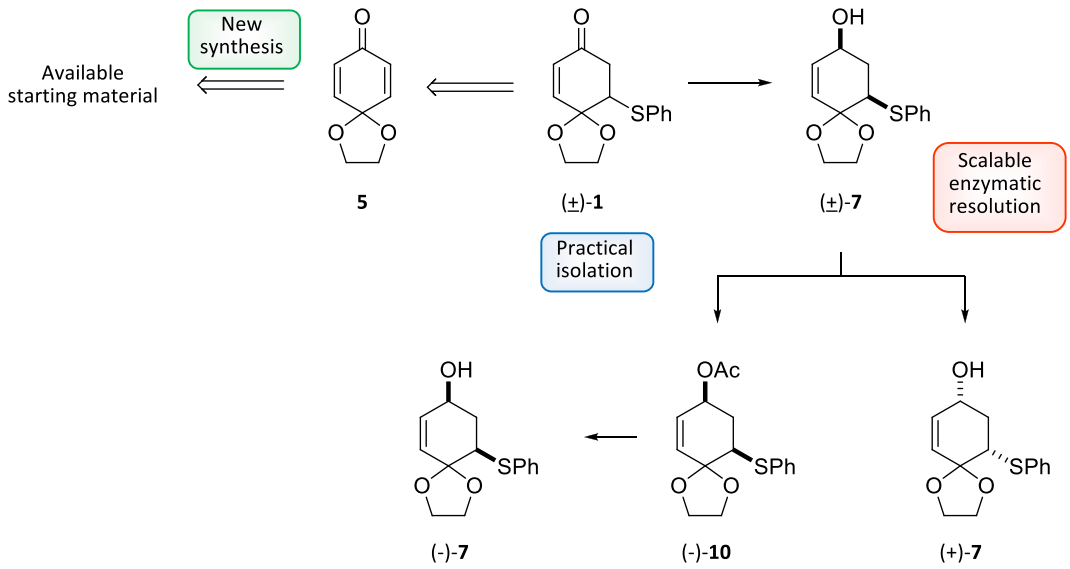
3. OBJECTIVES

The synthesis of bioactive natural products is still a challenge for organic chemists. As we have seen, there are many bioactive compounds with cyclohexane core. The potential biological properties of these cyclohexane compounds together with our background in the field, prompted us to design new synthetic strategies towards these promising targets. Hence, in the present thesis the potential of monoketal **1** as a chiral precursor of different natural compounds is further explored. This cyclohexane-cored monoketal has been successfully used as a building block for the synthesis of different targets of increasing structural complexity.

- **OBJECTIVE 1: Synthesis of both antipodes of the alcohol 7**

  To further extend the use of (*R*)-, and (*S*)-**7** as precursors to more sophisticated molecules we judged convenient to search for a practical synthesis, which should allow the access to any enantiomer of **7** in multigram scale (Scheme 4). Therefore, we will need to:

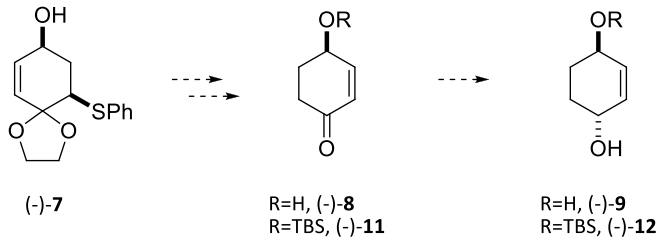
  - Change the starting material 3,3,6,6-tetramethoxy-1,4-cyclohexadiene which is no longer commercially available.
  - Assay new methods that avoid the laborious chromatographic separation involved in the isolation protocol of **1**, which is prepared by the conjugate addition of thiophenol to ketal **5**.
  - Carry out a study of the enzymatic resolution of (±)-**7** in order to scale up the preparation of any enantiomer.



Scheme 4. Synthetic pathway to (+)- and (-)-**7.**

- **OBJECTIVE 2: Synthesis of (*R*)- and (*S*)-4-hydroxy-2-cyclohexenone and (1*R*,4*R*)- and (1*S*,4*S*)-*trans*-cyclohex-2-ene-1,4-diol**

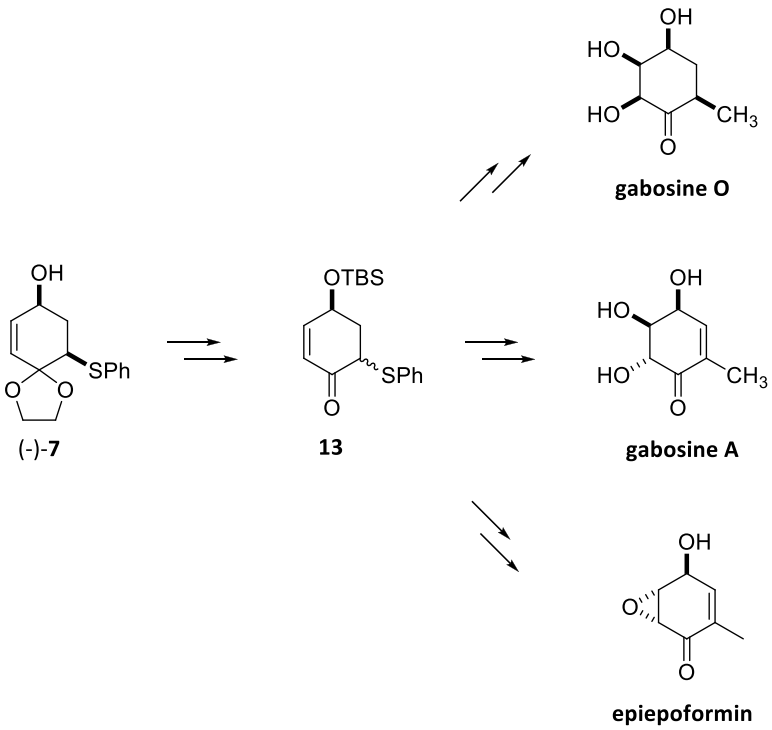
  When a practical synthesis of **7** has been achieved, we are going to focus on the multigram synthesis of (*R*)-, and (*S*)-4-hydroxy-2-cyclohexenone, **8**, and the enantiopure *trans*-cyclohex-2-ene-1,4-diol, **9**, as well as their useful monoprotected derivatives **11** and **12** (Scheme 5).



Scheme 5. Synthesis of the enone **8**, the diol **9** and their *O*-protected derivatives **11** and **12**.

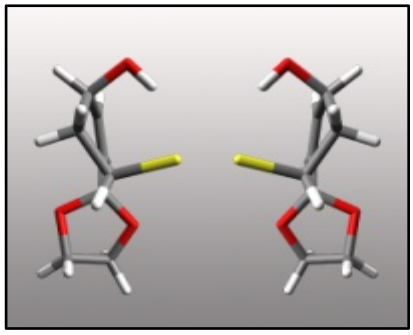
- **OBJECTIVE 3: Synthesis of gabosines and anhydrogabosines**

  Finally, our efforts will be centered on the synthesis of the largest possible number of gabosines and related compounds from the common intermediate **7** by a stereodivergent strategy (Scheme 6).



Scheme 6. Stereodivergent strategy for the synthesis of gabosines and anhydrogabosines.

II. Enantioselective synthesis of a key polyfunctionalized cyclohexane



(+)- and (-)-**7**

1. ENANTIOSELECTIVE SYNTHESIS OF THE KEY POLYFUNCTIONALIZED CYCLOHEXANE **7**

1.1. SYNTHESIS AND ISOLATION OF THE RACEMIC KETONE (±)-**1**

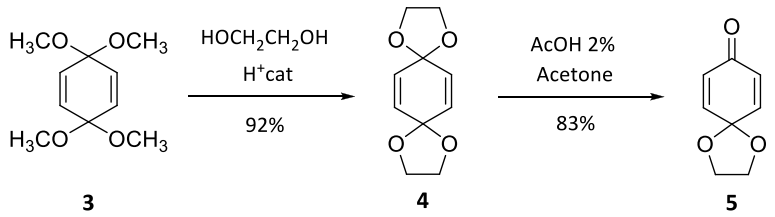
As mentioned above, our previously developed synthetic sequence for the preparation of ketone **1** has important drawbacks that should be overcomed.

1.1.1. Synthesis of ketal **5**

Following the route previously developed in our laboratories,[28] the first step for the synthesis of **1** was the preparation of the *p*-benzoquinone monoketal **5**. This two-step sequence started from 3,3,6,6-tetramethoxy-1,4-cyclohexadiene, **3**, and had been carried out with an overall yield up to 76% (Scheme 7). Bisketal **4** was prepared by transketalitzation with ethylene glycol and acetic acid as catalyst,[42] and then subjected to monohydrolysis following the methodology reported by Heller and coworkers[43] which uses 2% acetic acid aqueous solution and acetone at 50 °C.

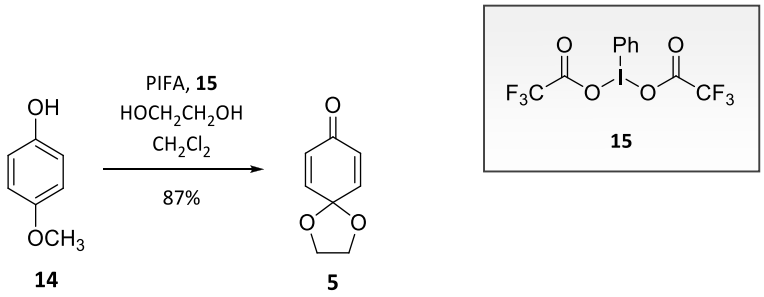
[42] Capparelli, M. P.; Swenton, J. S. *J. Org. Chem.* **1987**, *52*, 5360-5364.

[43] Heller, J.E.; Dreiding, A. S.; O'Connor, B. R.; Simmons, H. E.; Buchanan, G. L.; Raphael, R. A.; Taylor, R. *Helv. Chim Acta* **1973**, *56*, 272-280.



Scheme 7. Synthesis of the monoketal **5**.

The fact that compound **3** ceased to be commercial led us to seek a new synthesis for monoketal **5**. Wong and coworkers published in 2001 a general procedure for the synthesis of monoketals of *p*-benzoquinone, which could be applied to the synthesis of monoketal **5**, among others.[44] Their procedure involved the treatment of the commercially available *p*-methoxyphenol, **14**, with phenyliodonium bis-(trifluoroacetate) (PIFA, **15**)[45] and ethylene glycol in anhydrous dichloromethane (Scheme 8).



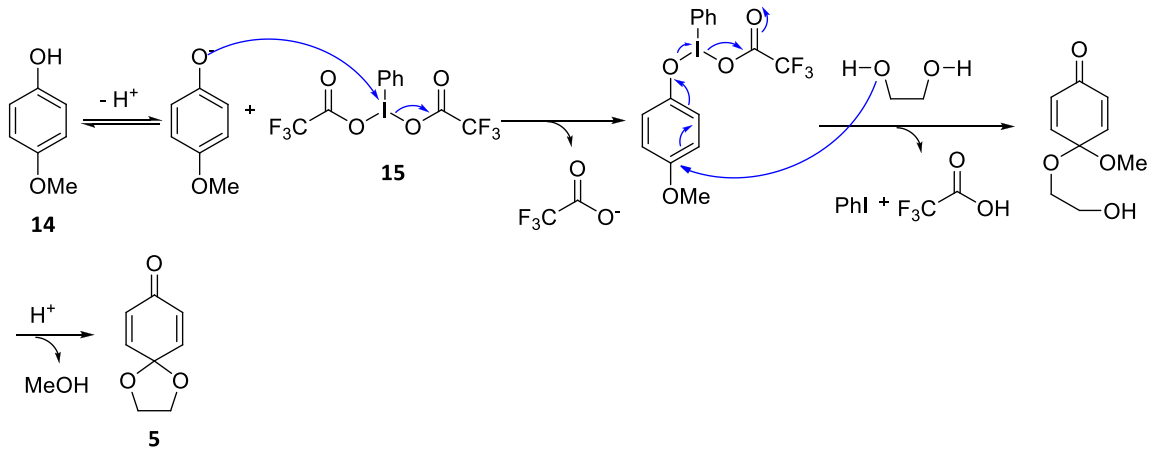
Scheme 8. Alternative synthesis of the monoketal **5**.

According to the authors, the role of PIFA in the reaction mechanism is still not clearly known. Nevertheless, they suggested a mechanistic proposal involving a phenolic oxidation followed by the attack of one of the hydroxyl groups of the diol (ethylene glycol in this case) to the phenolic intermediate and, finally, intramolecular transketalization to obtain monoketal **5**. The last step could be catalyzed by the trifluoracetic acid generated in situ from PIFA. More recently, in 2005, two possible mechanisms for PIFA-mediated (or other related hypervalent iodine reagents) oxidation processes were suggested by Westwell and coworkers. According to them, the reaction could follow a nucleophilic attack or a redox pathway.[46] Taking these ideas into consideration, two mechanisms can be proposed for the formation of **5** (Schemes 9 and 10).

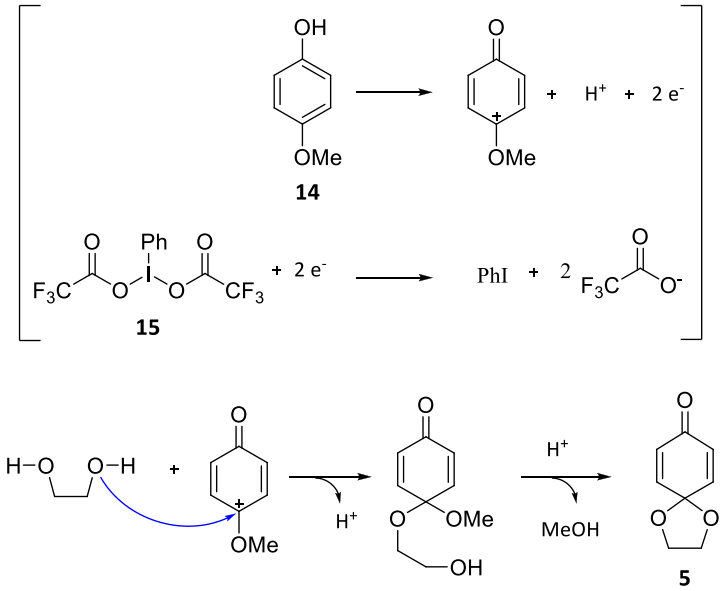
[44] Trân-Huu-Dâu, M. E.; Wartchow, R.; Winterfeldt, E. Wong, Y. S. *Chem. Eur. J.* **2001**, *7*, 2349-2369.

[45] Polhnert, G. *J. Prakt. Chem.* **2000**, *342*, 731-734.

[46] Lion, C.J.; Vasselin, D. A.; Schwalbe, C. H.; Matthews, C. S.; Stevens, M. F .G.; Westwell, A. D. *Org. Biomol. Chem.* **2005**, *3*, 3996-4001.



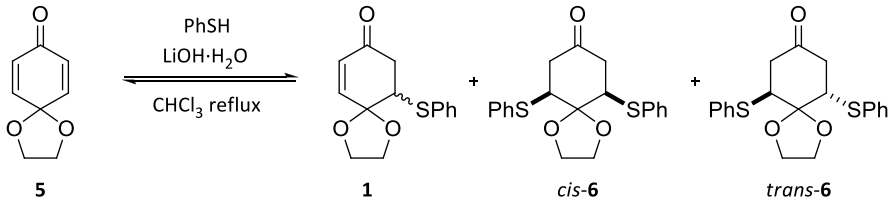
Scheme 9. Suggested mechanism via nucleophilic attack.[46]



Scheme 10. Suggested mechanism via redox reaction.[46]

In the present work, monoketal **5** was initially prepared in a 0.5 g scale under the same conditions described in the literature with comparable yields. To scale up the reaction, a slight modification of the reported method was assayed. Thus, the same yield (87%) is obtained using a 0.3 M solution of PIFA (instead of 0.1 M), saving a considerable volume of anhydrous dichloromethane, in a 4 g scale. In this way, the preparation of **5** has been reduced from two synthetic steps to a single one, increasing the yield from 76% up to 87% and decreasing the reaction time from 2 days to 45 min. Considering the interest in obtaining ketone **1** in large quantities, the most significant improvement is that the reaction can be performed in multigram scale and the product can be purified by a simple filtration through a small path of silica gel.

1.1.2. Synthesis of ketone **1**



5 **1** *cis*-**6** *trans*-**6**

Scheme 11. Conjugated addition of tiophenol to **5**.

In our previously established procedure,[28] compound **1** was prepared by reaction between thiophenol and ketal **5** (1:1.8 ratio, thiophenol:**5**) in the presence of lithium hydroxide. The reaction was carried out in chloroform at the reflux temperature (Scheme 11) and **1** was isolated from the crude product mixture by column chromatography. The main drawbacks of this procedure were the rather difficult separation of the products and the use of large quantities of solvent. Moreover, this chromatographic purification hampered the scaling up of the process. In this thesis, it was decided to explore the possibility of separating the monoaddition product **1** by fractional crystallization. Thus, the relative solubility of each of the four compounds (**1**, **5**, *cis*-**6** and *trans*-**6**) present in the crude reaction product in a series of solvents was qualitatively examined (Table 1).

Table 1. Qualitative solubility of compounds **1**, **5**, *cis*-**6**, and *trans*-**6** in different solvents at room and boiling temperatures.[a]

	1		**5**		*cis*-**6**		*trans*-**6**	
Solvent	rt	bt	rt	bt	rt	bt	rt	bt
pentane	i	i	i	i	i	i	i	i
hexane	i	s	i	i[b]	i	i	i	i
cyclohexane	i	i[b]	i	i[b]	i	i	i	i[b]
$^{i}Pr_2O$	s	s	s	s	s	s	s	s
^{t}BuOMe	s	s	s	s	i	i	i	i
toluene	s	s	s	s	s	s	s	s
CH_2Cl_2	s	s	s	s	s	s	s	s
acetonitrile	s	s	s	s	s	s	s	s
^{i}PrOH	i	s	s	s	i	i	i	i
EtOH	i	i[b]	s	s	i	δ	i	δ
H_2O	δ	s	δ	s	i	δ	i	δ
^{i}PrOH/H_2O	δ	s	s	s	i	i	δ	s
EtOH/H_2O	δ	s	s	s	i	i	δ	s
acetonitrile/H_2O	δ	s	s	s	i	i	i	i

[a] If 25 mg of the pure compound are completely dissolved in 0.25 mL of the solvent at room temperature (rt) or boiling temperature (bt) the experiment is labelled as s (soluble); if dilution up to 0.75 mL leads to total dissolution, the experiment is labelled as δ (partially soluble); if some solid still remains, the experiment is labelled as i (insoluble).[47]

[b] Insoluble oily material is observed.

[47] Baumann, J. B. *J. Chem. Educ.* **1979**, *56*, 64.

It was observed that the four compounds show low solubility in apolar solvents and were quite soluble in polar aprotic solvents. Fortunately, a distinct behaviour was found in polar protic solvents, where the diaddition compounds *cis*- and *trans*-**6** are poorly soluble compared to **1** and **5**, but the most remarkable observation was that the unreacted ketal **5** was noticeably more soluble than the monoaddition product **1** in 2-propanol at room temperature. Thus, crystallization of the crude reaction product from 2-propanol yielded a solid material containing mainly the monoaddition product, along with small amounts of monoketal **5**. Considering the information showed in Table 1, one should expect the presence of diaddition compounds after the crystallization because of their insolubility in 2-propanol. Nevertheless, these products were not observed. The most consistent explanation is that there is so little amount of *cis*-, and *trans*-**6** respect to the monoketals **5** and **1** that the volume of solvent added is large enough to dissolve these products.

One or two recrystallizations from the same solvent, allowed the isolation of pure **1** in 60-70% overall yield from thiophenol (Figure 10). Following this protocol, quantities over 4 g of (±)-**1** have been obtained in a single operation. Since the conjugate addition of thiophenol to ketal **5** is a reversible process, the crystallization residue can be easily recycled.

In conclusion, a new protocol for the synthesis and isolation of ketone (±)-**1** which can be performed in multigram scale has been developed.

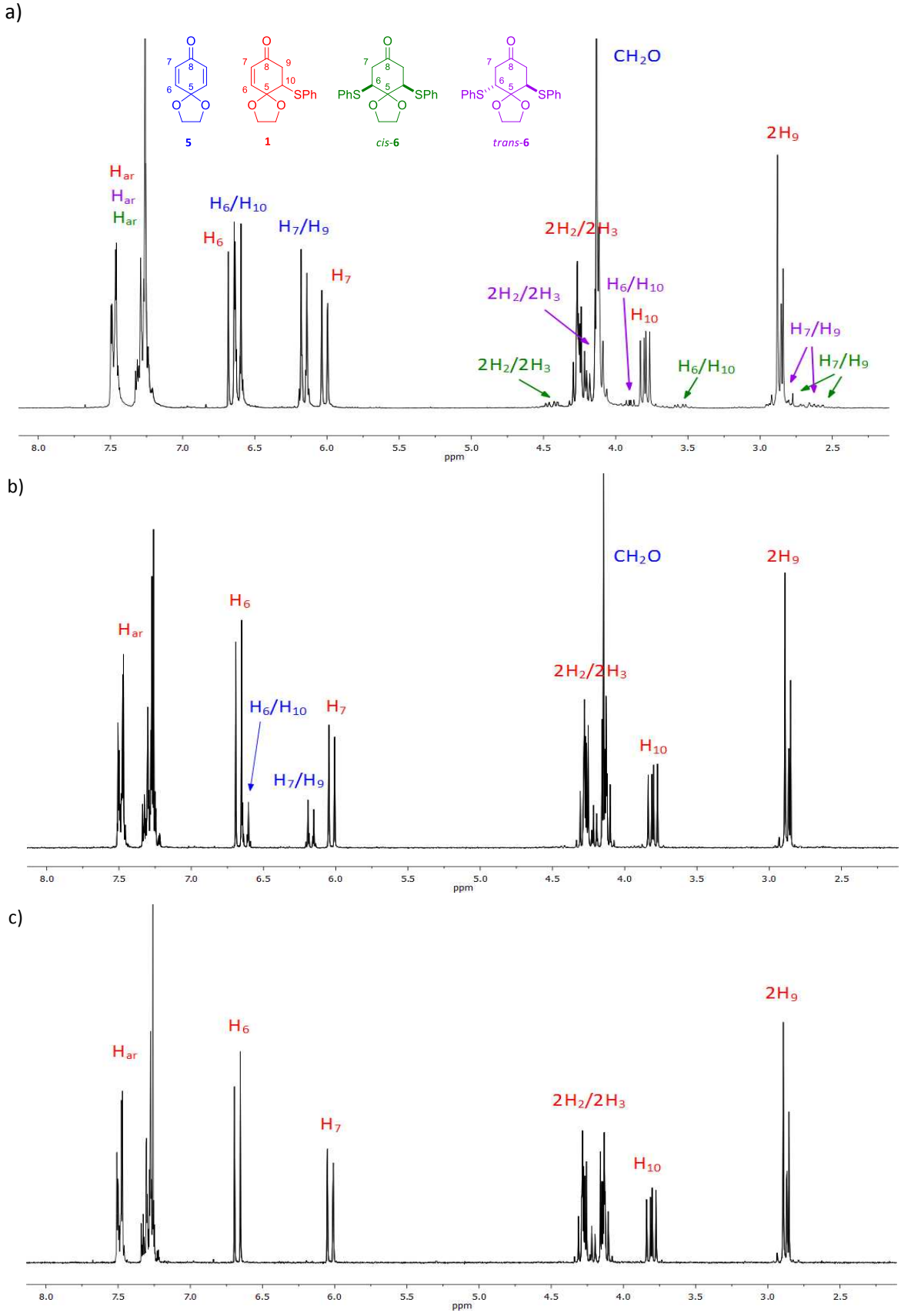


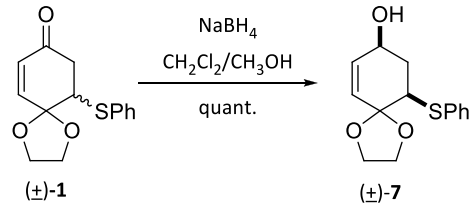
Figure 10. ^{1}H-NMR spectra (250 MHz, $CHCl_3$): a) crude material of the reaction between thiophenol and ketal **5**, b) solid material obtained from the first crystallization, c) solid material obtained from the third crystallization.

1.2. RESOLUTION OF (±)-**7**

As previously mentioned, the enantiomers of ketone (±)-**1** could only be resolved on a 200 mg scale by liquid chromatography on cellulose triacetate. In her doctoral thesis Dr. Georgina Marjanet attempted to achieve this resolution by means of an enantioselective reduction with borane in the presence of different chiral oxazaborolidines.[48] Unfortunately, her results were not satisfactory.[49] Later on, working on the basis of a closely related literature precedent, she investigated the enzyme-catalyzed enantioselective acetylation of the allylic cyclohexenol (±)-**7**, provided from the reduction of (±)-**1**, with much better results. We therefore focused our attention in this transformation.

1.2.1. Synthesis of the racemic alcohol (±)-**7**

Treatment of ketone (±)-**1** with $NaBH_4$ furnished exclusively the *cis* alcohol (±)-**7** in quantitative yield. This total diastereoselectivity indicates that the hydride approach takes place exclusively by the opposite face to the bulky phenylsulfenyl group (Scheme 12).



(±)-**1** (±)-**7**

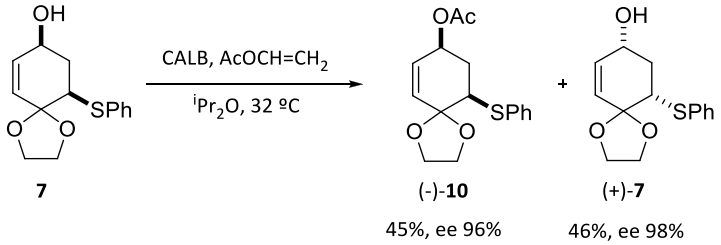
Scheme 12. Synthesis of (±)-**7** from (±)-**1**.

[48] (a) Corey, E. J.; Kigoshi, H. *Tetrahedron Lett.* **1991**, *32*, 5025-5028. (b) Mori, K.; Amaike, M.; Itou, M. *Tetrahedron* **1993**, *49*, 1871-1878.

[49] Marjanet. G. *Tesi doctoral, UAB*, **2006**.

1.2.2. Enzymatic acetylation. Synthesis of the acetate (-)-**10** and the alcohol (+)-**7**

Once the alcohol (±)-**7** was synthesized in substantial amounts, the next step was the differentiation of both antipodes by the enzymatic transformation (Scheme 13).



7 (-)-**10** (+)-**7**

45%, ee 96% 46%, ee 98%

Scheme 13. Enzymatic acetylation of (±)-**7**.

Previous work carried out in our research group allowed a noteworthy improvement of the conditions described in the literature for analogous reactions.[34a,b] In particular, shorter reaction times were required because of the higher efficiency of the enzyme. Different weight of alcohol:enzyme ratios were screened, leading to the conclusion that, using a 1:0.25 ratio rather than 1:2, comparable results to those previously described could be obtained. At the same time, optimal concentrations were found to be 18 mM of (±)-**7** and 1 mg/ml of *Candida Antarctica Lipase B* (CALB).[49]

The acetylation is best stopped when the ee of both compounds is the highest possible. While CHPLC is a really effective technique for determining ee's, it proved to be not fast enough to determine the exact moment for stopping the reaction. GC analysis of various samples, along wiht ^{1}H-NMR determination of compound ratio, showed that the ideal moment to stop the reaction was when the two peaks corresponding to alcohol **7** and acetate **10** (7.9 min and 9.1 min respectively by GC) display a relative area of 1:1.1 (program 1 GC, see Experimental Section).

The initial experiments were performed with quantities around 1 g of the racemic substrate **7** with excellent results. Then, the challenge proposed in this thesis was to scale up the enzymatic acetylation with comparable yields and ee's.

It is worth mentioning that, maintaining the original conditions, an increase in the scale of work would require an important increase of the amount of solvent, hence difficulting the temperature control, a crucial factor in this type of transformations. For that reason, we contacted Dr. Josep Lopez-Santín and Dr. Gloria Caminal, two experts in enzyme-catalyzed reactions from the *Grup d'Enginyeria de Bioprocessos i Biocatàlisi Aplicada, Departament d'Enginyeria Química, UAB.*

First of all we decided to study the effect of initial substrate concentration versus reaction rate. Various experiments were performed starting from 9, 36, and 72 mM solutions of (±)-**7** and keeping the same (±)-**7**/vinyl acetate/enzyme ratio. It was observed that the reaction rate increased with the substrate concentration without any enzyme inhibition being detected.

At this point, the reaction evolution was studied in-depth with an initial substrate concentration of 72 mM (Table 2).

Table 2. Ee evolution in the CALB-catalyzed enantioselective acetylation of (±)-7.[a]

Entry	Time (min)	(+)-7/(-)-10[b]	ee of (+)-7[c] (%) (calcd ee, %)[d]	ee of (-)-10[c] (%)
1	30	1:0.38	24 (43)	100
2	40	1:0.57	40 (56)	100
3	50	1:0.76	56 (75)	97
4	60	1:0.96	73 (98)	95
5	90	1:1.15	95	92
6	105	1:1.21	93	89

[a] $[(\pm)\text{-}\mathbf{7}]_0$= 72 mM; weight proportion (±)-**7**/CALB= 1:0.25.

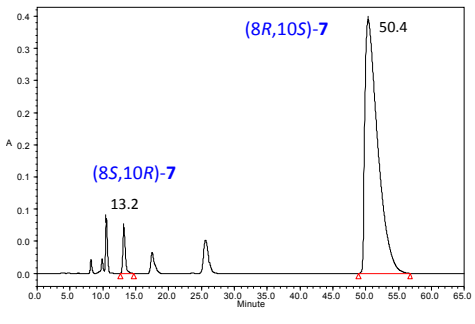
[b] Ratio determined by ^{1}H-NMR.

[c] Ee's were determined by CHPLC (CHIRACEL OD, 0.7 ml/min, hexane/^{i}PrOH 4:1).

[d] Calculated ee value considering the conversion and assuming that the only process occurring was the acetylation of (-)-**7**.

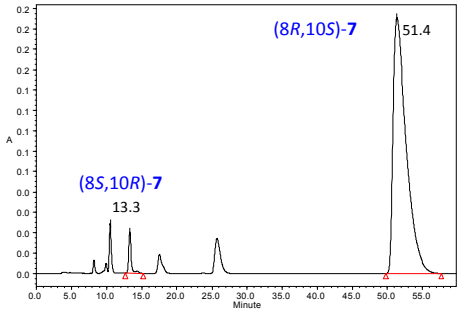
At this higher initial concentration of (±)-**7**, the ee of the residual alcohol (+)-**7** increased more slowly than expected (entries 1–4), indicating that, simultaneously to the enantioselective acetylation, at least another competitive process was occurring that diminished the ee of the residual alcohol. Epimerization of the remaining alcohol (+)-**7** in the reaction medium was discarded because, after submitting a sample of enantiomerically pure (+)-**7** to the same reaction conditions for 90 min, the alcohol was recovered without any loss of diastereomeric purity (Figure 11).

a) Alcohol (+)-**7**



Peak	R_t (min)	% Area
(8*S*,10*R*)-**7**	13.2	3.3
(8*R*,10*S*)-**7**	50.4	96.7

b) Alcohol (+)-**7**+CALB+^{i}PrOH, 90 min 32°C

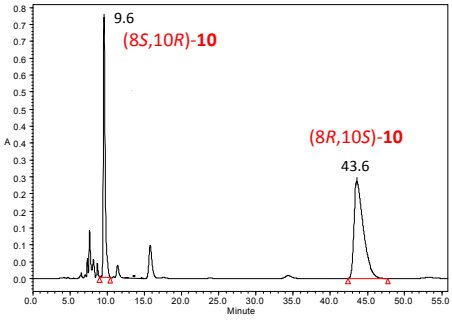


Peak	R_t (min)	% Area
(8*S*,10*R*)-**7**	13.2	3.3
(8*R*,10*S*)-**7**	51.4	96.7

Figure 11. CHPLC of (+)-**7** before and after being submitted to the enzymatic reaction conditions.

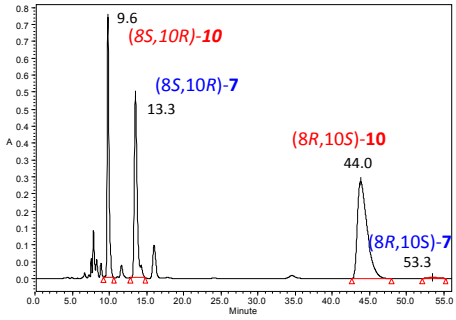
An analogous reference experiment was performed with a sample of racemic acetate (±)-**10**, and, after 90 min, CHPLC analysis of the recovered material showed three peaks, corresponding to the acetate (-)-**10** (27%), the alcohol (-)-**7** (24%), and the acetate (+)-**10** (48%) (Figure 12). Consequently, the lower than expected ee of the residual alcohol was attributed to partial hydrolysis of the formed acetate.

a) Acetate (±)-**10**



Peak	R_t (min)	% Area
(8*S*,10*R*)-**10**	9.6	48.6
(8*R*,10*S*)-**10**	43.6	51.4

b) Acetate (±)-**10**+CALB+^{i}PrOH, 90 min 32°C



Peak	R_t (min)	% Area
(8*S*,10*R*)-**7**	13.3	26.8
(8*R*,10*S*)-**7**	53.3	0.5
(8*S*,10*R*)-**10**	9.6	24.5
(8*R*,10*S*)-**10**	44.0	48.2

Figure 12 CHPLC of (-)-**10** before and after being submitted to the enzymatic reaction conditions.

In an attempt to minimize this undesired hydrolysis reaction, the concentration of enzyme was further reduced to a weight proportion (±)-**7**/CALB = 1:0.06. Reference experiments, analogous to the previously described, showed that, at this lower enzyme concentration, the hydrolysis of the acetate (-)-**10** is considerably slower (21% instead of 52%). Under these new conditions, it took 3 h 20 min to complete the enantioselective acetylation, with ee values of 93% for both compounds, (+)-**7** and (-)-**10**. Taking all this data into account, it seems that the main drawback in terms of competitive reactions catalyzed by the enzyme is the hydrolysis of acetate (-)-**10**, since acetylation of alcohol (+)-**7** by enzyme was never detected. Therefore, from this study it can be concluded that the enzyme CALB accelerates the acetylation of (-)-**7** prior to (+)-**7**, as well as the hydrolysis of (-)-**10** prior to (+)-**10**. In view of the precedent study, the last conditions (72mM of (±)-**7** and 1 mg/ml of CALB) were established as the best to scale up the reaction.

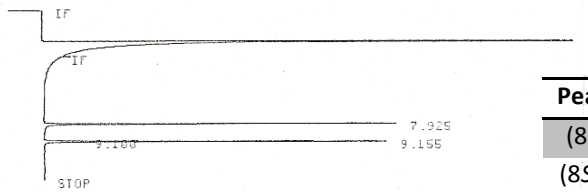
1.2.2.1. Enzymatic acetylation at multigram scale

The procedure was then scaled up to 5 g of starting substrate, taking aliquots every 20 min and analyzing them by GC. The reaction finished after 3.5 h, and the residual alcohol (+)-**7** (81% ee) and the acetate (-)-**10** (95% ee) were isolated in 46% and 45% yield, respectively (Table 3, Figures 13 and 14).

Table 3. 7:**10** Ratio by GC in the enzymatic acetylation of 5 g of (±)-**7** (72 mM) and 1 mg/ml of CALB.

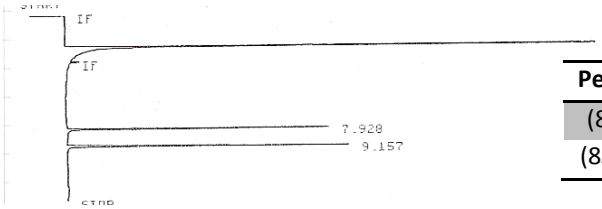
	Time										
	20 min	40 min	1 h	1 h 20 min	1 h 40 min	2 h	2 h 20 min	2 h 40 min	3 h	3 h 20 min	3 h 36 min
7:**10** (GC)	1:0.10	1:0.19	1:027	1:0.41	1:0.49	1:0.70	1:0.76	1:0.78	1:0.89	1:0.9	1:1.06

3 h 20 min



Peak	R_t (min)	% Area
(8*R*,10*S*)-**7**	7.9	50.08
(8*S*,10*R*)-**10**	9.2	49.2

3 h 36 min



Peak	R_t (min)	% Area
(8*R*,10*S*)-**7**	7.9	48.5
(8*S*,10*R*)-**10**	9.2	51.5

Figure 13. Gas chromatogram after 3 h 20 min and 3 h 36 min of reaction (program 1 GC).

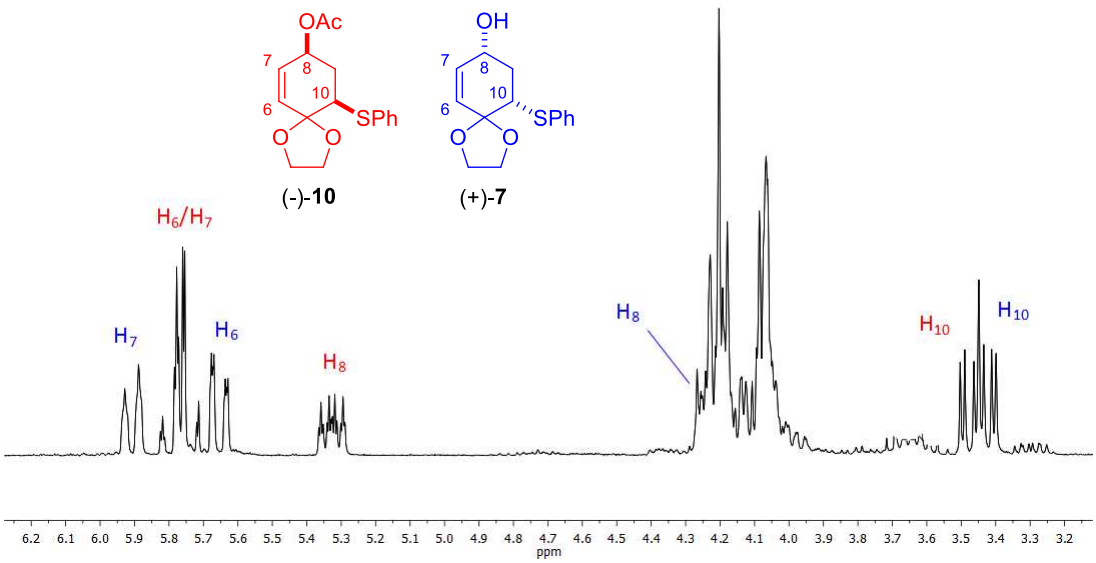


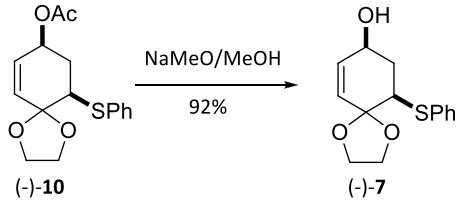
Figure 14. ^{1}H-NMR spectrum (250 MHz, $CHCl_3$) of the enzymatic acetylation crude material.

The ^{1}H-NMR spectrum in Figure 14 shows that H_8 of (-)-**10**, which is affected by acetate protection, resonates at lower fields (5.33 ppm) than H_8 of alcohol (+)-**7** (4.22 ppm) and appears as a ddt with coupling constants of 10.0, 5.9, 1.7 and 1.7 Hz with H_{9ax}, H_{9eq}, H_7 and H_6, respectively.

Using the last conditions, the enzymatic acetylation allowed us to prepare alcohol (+)-**7** in 46% yield and 98% ee, and acetate (-)-**10** in 45% yield and 96% ee, from 10 g of (±)-**7**. Compounds (+)-**7** and (-)-**10** are easily separable by a fast column chromatography on silica gel.

1.2.3. Methanolysis of the acetate (-)-**10**. Synthesis of the alcohol (-)-**7**

If we are interested in the free alcohol (-)-**7** rather than in its acetate-protected counterpart, it can be easily prepared by treatment of (-)-**10** with NaMeO in MeOH (Scheme 14). The white solid, delivered in 92% yield, was identified as (8*S*,10*R*)-10-phenylthio-1,4-dioxaspiro[4.5]dec-6-ene-8-ol, (-)-**7**.

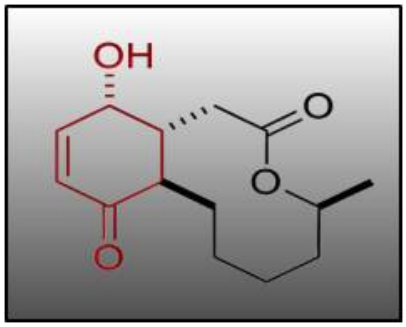


(-)-**10** (-)-**7**

Scheme 14. Synthesis of the alcohol (-)-**7**.

To conclude, a new methodology for the preparation of both enantiomers of **7** in a 10 g scale has been established. The synthetic sequence involves 4-5 steps with yields ranging between 23-26% and ee's around 97% for each enantiomer. These results encouraged us to use these chiral alcohols as starting materials for the synthesis of diverse natural products and interesting chemical intermediates.

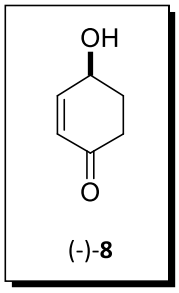
III. Synthesis of 4-hydroxy-2-cyclohexenone and *trans*-cyclohex-2-en-1,4-diol



Bacterial DNA primase inhibitor
(+)-Sch 642305

1. SYNTHESIS OF (*R*)- AND (*S*)-4-HYDROXY-2-CYCLOHEXENONE, (*R*)- AND (*S*)-**8**, AND (1*R*,4*R*)- AND (1*S*,4*S*)-*trans*-CYCLOHEX-2-EN-1,4-DIOL, (1*R*,4*R*)- AND (1*S*,4*S*)-**9**

1.1. INTRODUCTION



(-)-**8**

4-Hydroxy-2-cyclohexenone, **8**, has been widely used as a building block for the synthesis of several bioactive compounds such as the anticholesterol agents compactin and ML-236A,[35] and the immunosuppressant FK-506.[36] Moreover, non-bioactive natural compounds have also been obtained using ketone **8** as precursor.[50] In these syntheses, the relative configuration of the stereogenic centers of the target molecules is induced by the stereogenic center at C_4 of the hydroxyenone **8**.

[50] (a) Iwasawa, N.; Funahashi, M.; Narasaka, K. *Chem. Lett.* **1994**, 1697-1700. (b) Pour, M.; Negishi, E. *Tetrahedron Lett.* **1996**, *37*, 4679-4682.

The graphic in Figure 15 summarizes all the syntheses of either 4-hydroxy-2-cyclohexenone or its *O*-protected derivatives published until the present date.

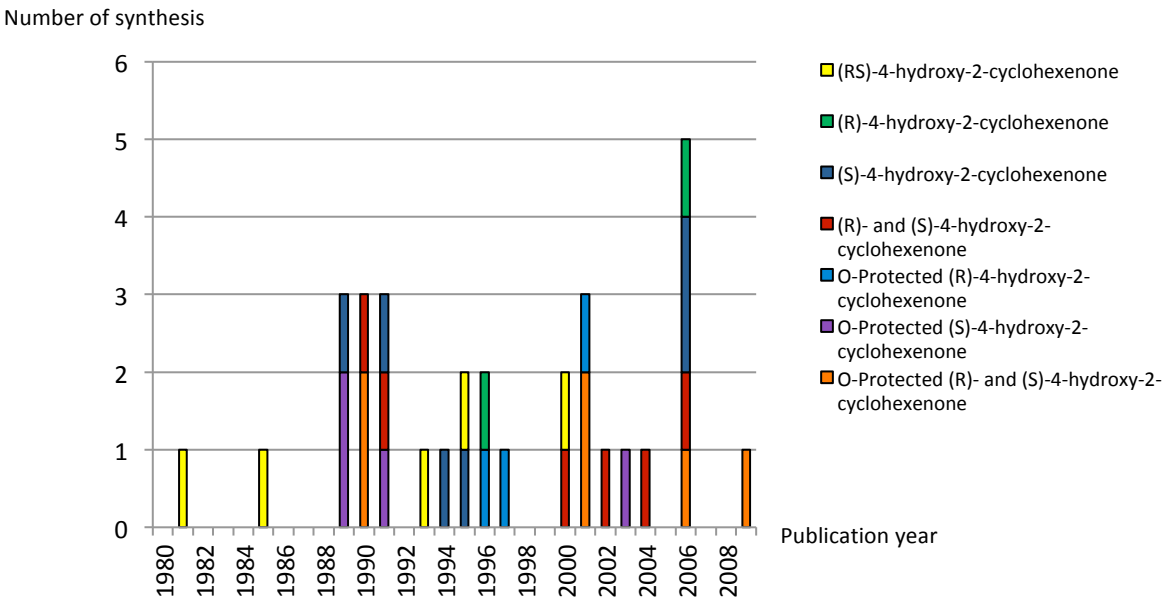


Figure 15. Published syntheses of 4-hydroxy-2-cyclohexenone and its *O*-protected derivative.

Several preparations of racemic **8** have been published, usually embodied into wider reactivity studies.[51,52,53] Until 2000, some reported syntheses of (*S*)-**8** (or *O*-protected derivatives of it) made use of enzymatic[54-55] or other catalytic[56] transformations in the key step, or came from Diels Alder adducts.[53] Additionally, Witschel and coworkers have prepared the *R* antipode of **8** protected as a silyl ether by an enzymatic process.[39] Alternatively, strategies based on the use of chiral auxiliaries have been employed for the preparation of both enantiomers of **8**,[57-58] (along with some *O*-protected derivatives) and two complementary approaches starting from (-)-quinic acid, leading to (*S*)-[59] and (*R*)-**8**,[60] and *O*-protected derivatives of them have also been developed.

[51] (a) Suzuki, M.; Oda, Y.; Noyori, R. *Tetrahedron Lett.* **1981**, *22*, 4413-4416. (b) Balci, M.; Akbulut, N. *Tetrahedron* **1985**, *41*, 1315-1322.

[52] Bäckvall, J.-E.; Andreasson, U. *Tetrahedron Lett.* **1993**, *34*, 5459-5462.

[53] Marchand, A. P.; Xing, D.; Wang, Y.; Bott, S. G. *Tetrahedron: Asymmetry* **1995**, *6*, 2709-2714.

[54] Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656-2665.

[55] Essig, S.; Scheffold, R. *Chimia* **1991**, *45*, 30-32.

[56] Chang, S.; Heid, R. M.; Jacobsen, E. N. *Tetrahedron Lett.* **1994**, *35*, 669-672.

[57] Carreño, M. C.; García-Ruano, J. L.; Garrido, M.; Ruiz, M. P.; Solladié, G. *Tetrahedron Lett.* **1990**, *31*, 6653-6656.

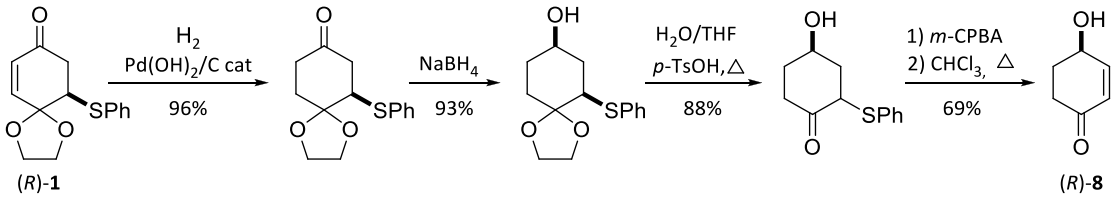
[58] (a) Brünjes, R.; Tilstam, U.; Winterfeldt, E. *Chem. Ber.* **1991**, *124*, 1677-1678. (b) Matcheva, K.; Beckmann, M.; Schomburg, D.; Winterfeldt, E. *Synthesis* **1989**, 814-817.

[59] (a) Trost, B. M.; Romero, A. G. *J. Org. Chem.* **1986**, *51*, 2332-2342. (b) Audia, J. E.; Boisvert L.; Patten, A. D.; Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 3738-3740.

[60] Gebauer, O.; Brückner, R. *Liebigs Ann.* **1996**, 1559-1563.

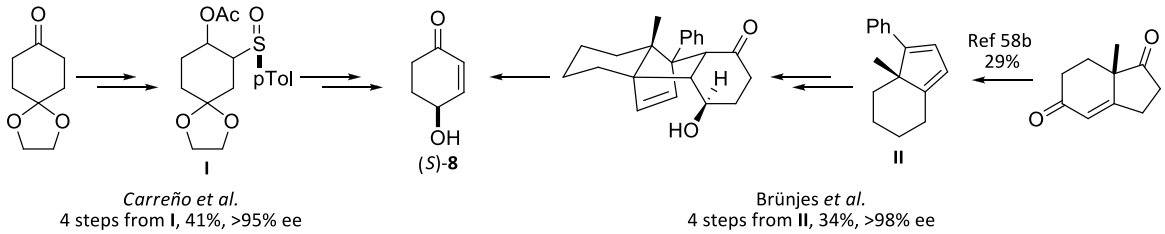
Furthermore, Noyori and coworkers have reported access to both antipodes by desymmetrization of the racemic *cis*-cyclohex-2-en-1,4-diol.[61] Many of these syntheses involve multistep sequences with low overall yields or poor enantioselectivities. Moreover, there are some practical problems associated to the isolation of ketone **8**, because it is a volatile compound, highly soluble in water. As Brückner pointed out, this can be the cause for the wide dispersion of published specific rotations of (*R*)- and (*S*)-**8**.[60]

Taking advantage of the chiral *p*-benzoquinone derivatives widely used in our laboratories, a competitive synthesis giving access to both enantiomers of **8** was developed in only 4 steps from **1**[35] in 37% yield and 98% ee (GC) (Scheme 15).



Scheme 15. Synthesis of (*R*)-**8**, which has also been applied to (*S*)-**8**.[35]

These results were similar in efficiency and enantioselectivity to the best precedents described in the literature (Scheme 16).[57,58a]



Scheme 16. Synthesis of (*S*)-**8**, also applied to (*R*)-**8**, by Carreño *et al*.[57] and Brünjes *et al*.[58a]

The main drawback of our synthetic approach was the scale of work due to the limitations related to the early preparation of chiral enone **1** used as starting material, which has been discussed in the previous chapter.

[61] Hashiguchi, S.; Fuji, A.; Haack, K. J.; Matsumura, K.; Ikariya, T.; Noyori, R. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 288-290.

Current literature reveals that ketone **8** is still important as a precursor of biologically active compounds. Since 2000, it has been used to prepare different targets such as the structurally related metabolites (+)-epiepoformin, (+)-epiepoxydon, and (+)-bromoxone;[62] the analgesic alkaloids (+)- and (-)-epibatidine;[63] the antifungal and antibiotic (+)-apiosporamide;[64] the fungal metabolite diversonol;[65] the bacterial DNA primase inhibitor Sch 642305;[66] the antibacterial Dictyosphaeric acid A;[67] the anticancer agents otteliones A and B[68] and the antifeedant sesquiterpene (1*S*,3*R*,6*R*)-1-hydroxy-7(14),10-bisaboladien-4-one.[69]

Focusing on the publications in which the synthesis of ketone **8** is the main objective, new works have appeared since 2000. In some of them only one of the enantiomers was prepared. Referring to the synthesis of the *S* enantiomer, Linker and coworkers prepared it in a three step sequence and 16% total yield, with an auxiliary controlled singlet-oxygen ene reaction being the key step.[70] Toste and coworkers described the first enantioselective Kornblum-DeLaMare rearrangement based on the desymmetrization of *meso*-endoperoxides with cinchona alkaloids as chiral catalysts, furnishing ketone (*S*)-**8** in one step and 89% yield but only with 50% ee.[71] Finally, the silyl ether derivative of (*S*)-**8** was synthesized as an intermediate in 8 steps and 40% yield by Kitahara *et al.*[62]

The *R* enantiomer of **8** was prepared by Fuchs and coworkers from a (+)-limonene oxide in 8 steps (48% yield and 97.8% ee), as an intermediate in the synthesis of (±)-mesmembranol,[72]

[62] Tachihara, T.; Kitahara, T. *Tetrahedron* **2003**, *59*, 1773-1780.

[63] Barros, M. T.; Maycock, C. D.; Ventura, M. R. *J. Chem. Soc., Perkin Trans 1* **2001**, 166-173.

[64] Williams, D. R.; Kammler, D. C.; Donnell, A. F.; Goundry, W. R. F. *Angew. Chem. Int. Ed.* **2005**, *44*, 6715-6718.

[65] Nising, C. F.; Ohnemüller, U. K.; Bräse, S. *Angew. Chem. Int. Ed.* **2006**, *43*, 307-309.

[66] (a) Wilson, E. M.; Trauner, D. *Org. Lett.* **2007**, *9*, 1327-1329. (b) García-Fortanet, J.; Carda, M.; Marco, J. A. *Tetrahedron* **2007**, *63*, 12131-12137.

[67] (a)Barfoot, C. W.; Burns, A. R.; Edwards, M. G.; Kenworthy, M. N.; Ahmer, M.; Shanahan, S. E.; Taylor, R. J. K. *Org. Lett.* **2008**, *10*, 353-356. (b) Burns, A. R.; McAllister, G. D.; Shanahan, S. E.; Taylor, R. J. K. *Angew. Chem. Int. Ed.* **2010**, *49*, 5574-5577.

[68] Chen, C-H.; Chen, Y-K.; Sha, C-K. *Org. Lett.* **2010**, *12*, 1377-1379.

[69] Matsui, M.; Tashiro, T.; Sasaki, M.; Takikawa, H. *Biosci. Biotechnol. Biochem.* **2010**, *74*, 683-684.

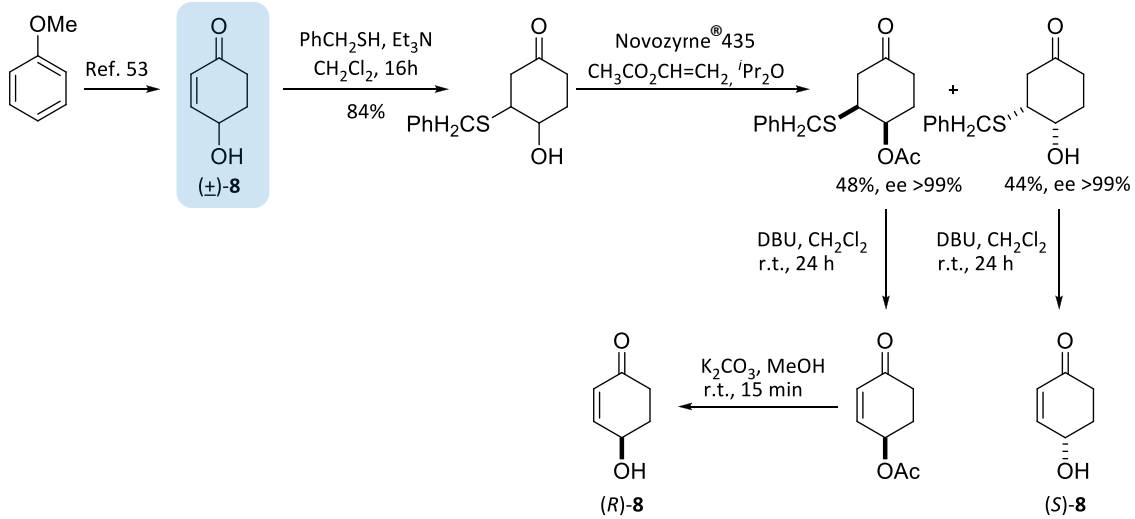
[70] Fudickar, W.; Vorndran, K.; Linker, T. *Tetrahedron* **2006**, *62*, 10639-10646.

[71] Staben, S. T.; Linghu, X.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 12658-12659.

[72] Evarts, J.; Fuchs, P. *Tetrahedron Lett.* **2001**, *42*, 3673-3675.

and by Roberts and coworkers in 4 steps from the ethylenic monoketal of 1,4-cyclohexadione and using L-proline as the chiral auxiliary, in 28% yield and 94% ee.[73]

Regarding the preparation of both enantiomers of **8**, seven new syntheses have appeared since our publication in 2000. Four of them are based on the resolution of the racemate (±)-**8**. In the first one, Kibayashi and coworkers prepared the *O*-benzyl derivatives of **8** using a tandem asymmetric deprotonation-palladium(II)-induced dehydrosilylation with a chiral amide as catalyst,[74] in 81-85% yield and 80-81% ee. On the second one, Roberts and coworkers resolved the racemate, which was prepared following Marchand protocol,[53] by an enzymatic transformation. Ketone (*R*)- and (*S*)-**8** were obtained in 4-5 steps and >99% ee,[34a] although the authors did not provide the total yield, giving only the information that appears in Scheme 17. The third publication comes from the same authors, who also synthesized both antipodes of TBS-protected **8** in 4-5 steps, 15% yield and >99 ee%.[73] The most recent synthesis of this category has been published by Evans and coworkers.[75] They employed a thiol addition to ketone **8** to improve an enzymatic kinetic resolution, obtaining *S* and *R* silyl protected 4-hydroxy-2-cyclohexenone in 3-4 steps, 98% ee and 21% and 16% yield, respectively.



Scheme 17. Synthesis of (*R*)- and (*S*)-**8** by Roberts *et al*.[34a]

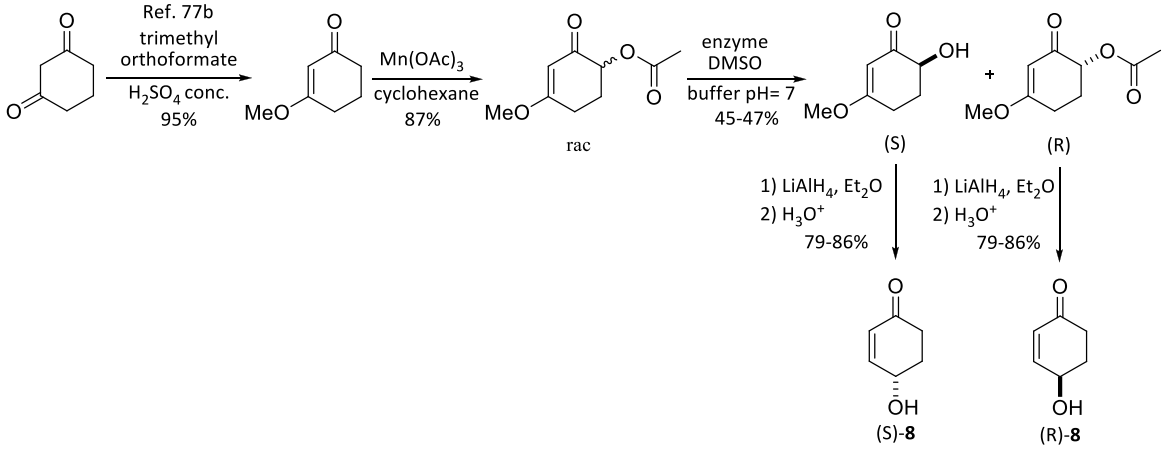
The other three enantioselective syntheses do not have racemic (±)-**8** as intermediate. In 2001, Zhang *et al.* reported a new procedure that involved 11 steps from D-mannitol but neither

[73] Bickley, J. F.; Evans, P.; Meek, A.; Morgan, B. S.; Roberts, S. M. *Tetrahedron: Asymmetry*. **2006**, *17*, 355-362.

[74] Suzuki, H.; Yamazaki, N., Kibayashi, C. *J. Org. Chem.* **2001**, *66*, 1494-1496.

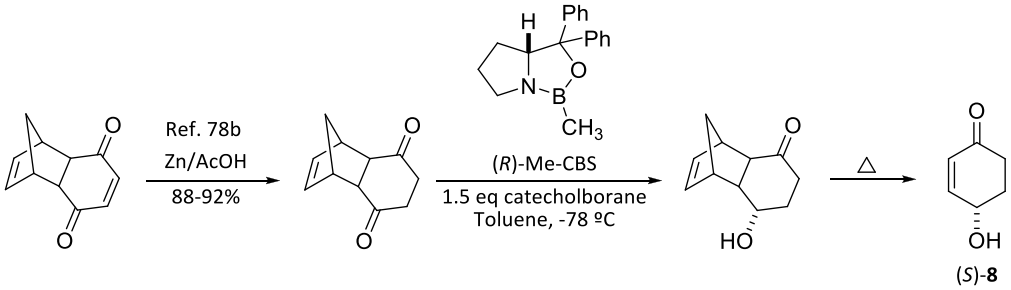
[75] O'Byrne, A.; Murray, C.; Keegan, D.; Palacio, C.; Evans, P.; Morgan, B. S. *Org. Biomol. Chem.* **2010**, *8*, 539-545.

yield nor ee were described.[76] Probably, the most interesting syntheses which have been published so far are those from Demir and coworkers[77] and Bräse and coworkers.[78] Demir proposes a four step synthesis from commercially available cyclohexane-1,3-dione, where the key steps are a $Mn(OAc)_3$ mediated acetoxylation followed by an enzymatic hydrolysis of the α-acetoxy group to resolve the racemate. Each enantiomer was obtained in yields between 29-33% and 96-98% ee (Scheme 18).



Scheme 18. Synthesis of (*R*)- and (*S*)-**8** by Demir *et al*.[77a]

Besides, Bräse *et al.* developed a practical access to both enantiomers of **8** making use of an unprecedented CBS-catalyzed (Corey-Bakshi-Shibata) reductive desymmetrization of a *meso*-diketone. The starting material was the Diels-Alder adduct from *p*-benzoquinone and cyclopentadiene. Target (*R*)- and (*S*)-**8** were obtained in 53-56% yield and 78% ee, and 61-63% yield and 96% ee, respectively (Scheme 19).



Scheme 19. Synthesis of the (*S*)-**8** by Bräse *et al*.[78a]

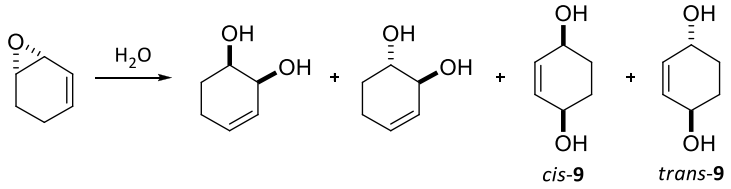
[76] Yu, S.; Zhang, R.; Wang, Z. *J. Chem., Perkin Trans 1* **2001**, 2958-2961.

[77] (a) Demir, A. S.; Sesenoglu, O. *Organic Lett.* **2002**, *4*, 2021-2023. (b) Quesada, M. L.; Schessinger, R. H.; Parsons, W. H. *J. Org. Chem.* **1978**, *43*, 3968-3970.

[78] (a) Nising, C. F.; Ohnemüller, U. K.; Bräse, S. *Synthesis* **2006**, *16*, 2643-2645. (b) Oda, M.; Kawase, T.; Okada, T.; Enomoto, T. *Org. Synth.* **1996**, *73*, 253-261.

Cyclohexendiols are also very important intermediates in the synthesis of organic compounds as well as in polymer chemistry. Hence, there is a special interest in the development of easy and high-yielding synthetic routes towards these targets. However, there are scarce precedents in which they are reached in an enantiopure form.

A mechanistic study of epoxide opening made by Whalen and coworkers[79] is one of the first works where cyclohexendiols appear. In this study, different epoxides were hydrolyzed in aqueous medium varying pH. Starting from 3,4-epoxycyclohexene, diols *cis*- and *trans*-***9*** were obtained as major products (Scheme 20).



Scheme 20. Synthesis of cyclohexendiols by Whalen *et al*.[79]

In 1984 Bäckvall *et al.* reported the stereoselective synthesis of both diastereomers, *cis*- and (±)-*trans*-**9**, through a palladium-catalyzed 1,4-diacetoxylation of 1,3-cyclohexadiene.[80] In addition, two other syntheses of diol **9** were subsequently published. One of them from 3,4-epoxycyclohexene by nucleophilic opening with silicon reagents[81a] and the other by a ring closing metathesis (RCM) reaction of a double allylic diol.[81b]

Nowadays, the racemate of *trans*-**9** is commercially available, but only one procedure has been reported to prepare non-racemic *trans*-**9**. This procedure, which is based on a chloroperoxidase-catalyzed oxidation of cyclohexa-1,3-diene using *tert*-butylhydroperoxide as the terminal oxidant, leads to (+)-*trans*-**9** in 34% yield and 70% ee.[82] Comparison with the major oxidation product, along with mechanistic considerations, led the authors to assign the (1*R*,4*R*) configuration to the dextrorotatory enantiomer of *trans*-**9**. Additionally, a lipase-based protocol developed for the desymmetrisation of the diacetate of *cis*-**9** gave access to an alternative chiral equivalent of *trans*-**9**, which has been used as an intermediate for the synthesis of petasins[39] and cyclohexane prostanoids.[40]

---

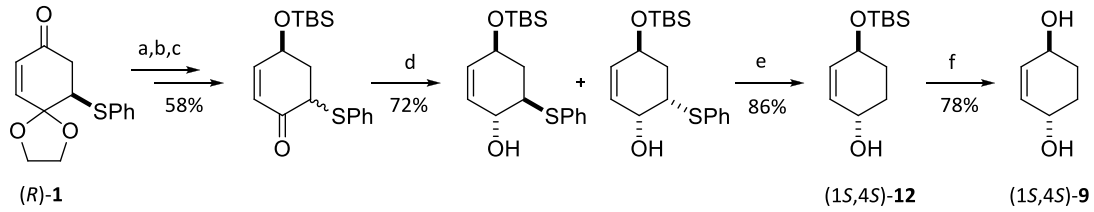
[79] Ross, A. M.; Pohl, T. M.; Piazza, K.; Thomas, M.; Fox, B. M.; Whalen, D. L. *J. Am. Chem. Soc.* **1982**, *104*, 1658-1665.

[80] Bäckvall, J.-E.; Byström, S. E.; Nordberg, R. E. *J. Org. Chem*. **1984**, *49*, 4619-4631.

[81] (a) Tamao, K.; Kawachi, A.; Tanaka, Y.; Ohtani, H.; Ito, Y. *Tetrahedron* **1996**, *52*, 5765-5772. (b) Davoille, R. J.; Rutherford, D. T.; Christie, S. D. R. *Tetrahedron Lett.* **2000**, *41*, 1255-1259.

[82] Sanfilippo, C.; Patti, A.; Nicolosi, G. *Tetrahedron: Asymmetry* **2000**, *11*, 3269-3272.

This scarce precedents encouraged our research group to develop a new approach to either enantiomer of *trans*-cyclohex-2-en-1,4-diol, as well as their monoprotected derivatives (Scheme 21). The overall sequence involves 5 synthetic steps from ketone (*R*)-**1** giving silyl ether (1*S*,4*S*)-**12** in 38% yield. An additional hydrolysis step leads to diol (1*S*,4*S*)-**9** in 78% yield (30% overall yield from (*R*)-**1**).[38]



Reagents and conditions: (a) $NaBH_4$, CH_2Cl_2 /CH_3OH, 0ºC, 1.5 h; (b) TBS-imidazole, CH_2Cl_2, rt, 5 d; (c) Montmorillonite K-10, CH_2Cl_2, rt, 18 h; (d) DIBAL-H, THF, -78 ºC, 2.5 h; (e) Bu_3SnH, AIBN, toluene, Δ, 5 h; (f) Bu_4NF, THF, rt, 20 h.

Scheme 21. Synthesis of (1*S*,4*S*)-cyclohex-2-en-1,4-diol, (-)-**9**, also applied to (+)-**9** from (*S*)-**1**.[38]

In connection with our previous work and to further extend the use of (*R*)- and (*S*)-**8**, and (1*S*,4*S*)- and (1*R*,4*R*)-**9**, as precursors to more sophisticated molecules, we judged convenient to search for a new synthetic approach which should be easy to scale and should avoid tedious chromatographic separations which are a severe limitation for multigram availability. Moreover, we also planned to direct the synthesis to a suitable protected derivative of **8**, in order to circumvent some practical problems associated to its isolation, related to its volatility and high solubility in water. A protected derivative of the diol **9** was also envisaged as an ideal intermediate, formally resulting from the differentiation of the two initially equivalent alcohols.

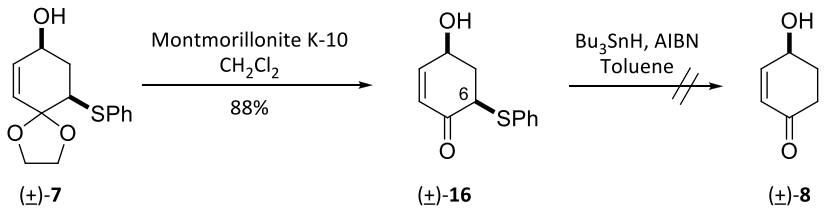
1.2. SYNTHESIS OF 4-HYDROXY-2-CYCLOHEXENONE, **8**, AND ITS DERIVATIVE **11**

1.2.1. Synthesis of 4-hydroxy-2-cyclohexenone, **8**

It is important to mention that the best conditions for the synthesis of the enone **8** and its derivative **11** were first established using the corresponding racemates. Later on, we headed for the enantioselective syntheses.

Focusing our attention on ketone **8**, the two transformations required for the conversion of alcohol **7** into **8** were ketal hydrolysis and hydrodesulfuration. Thus, the first approach considered is depicted in Scheme 22.

i) Approach 1:



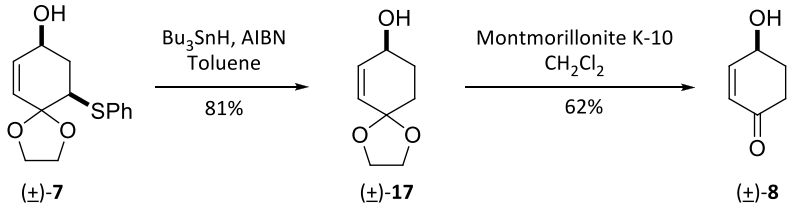
(±)-**7** (±)-**16** (±)-**8**

Scheme 22. First attempt to synthesize **8** from **7**.

The hydrolysis of the ketal **7** was easily accomplished following a method widely used in our laboratories for similar substrates, which was developed by Taylor and coworkers, based on the use of montmorillonite K-10 in anhydrous dichloromethane at room temperature.[21c,83] Deprotection of the carbonyl group furnished *cis*-6-phenylthio-4-hydroxy-2-cyclohexenone, **16**, in 88% yield. Its ^{1}H-NMR spectrum shows H_6 as a dd (δ 3.89, $J_{6,5ax}$= 11.5 Hz, $J_{6,5eq}$= 4.7 Hz) in accordance with the pseudoaxial orientation of this proton. For the *trans* isomer, we would expect the H_6 signal as a false triplet, since in the *trans* isomer of closely related compounds the phenylsulfur group occupies a pseudoaxial position, causing H_6 to be pseudoequatorial and, hence, the coupling constants with the two H_5 protons should be similar.

Unfortunately, the foreseen reduction of the carbon-sulfur bond on substrate (±)-**16** was unsuccessful, only unidentified degradation products were recovered, together with some unreacted starting material. Thus, we decided to invert the order of the synthetic steps (Scheme 23).

ii) Approach 2:



(±)-**7** (±)-**17** (±)-**8**

Scheme 23. Alternative approach to obtain **8** from **7**.

In former experiments in our laboratories, the desulfurated ketal **17** had only been detected as a minor product of reaction mixtures from the reduction of **7** with Bu_3SnH/AIBN in

[83] (a) Gautier, E. C. L.; Lewis, N.; McKillop, A.; Taylor, R. J. K. *Tetrahedron Lett.* **1994**, *35*, 8759-8760.; (b) Gautier, E. C. L.; Graham, A. E.; McKillop, A.; Standen, S. P.; Taylor, R. J. K. *Tetrahedron Lett.* **1997**, *38*, 1881-1884.

toluene. After several experiments we thought that the problem could rely on a too fast radical collapse, so we decided to add the reagents in a continuous manner, especially the radical initiator AIBN (Table 4).

Table 4. Reduction of C-S bond of (±)-**7** to obtain (±)-**17**, using 1:10 (±)-**7**:Bu_3SnH ratio, in refluxing toluene.

Entry	(±)-7	Conditions	(±)-11 % yield
1	50-100 mg	4h, Bu_3SnH, AIBN continuously added	68-78% (81-83%)[a]
2	1 g	4h, Bu_3SnH, AIBN continuously added	47% (75%)[a]
3	0.5-1.25 g	4h, Bu_3SnH each 30 min, AIBN continuously added	81-83% (85-89%)[a]

[a] with respect to starting material consumed

In initial experiments carried out on milligram scale, Bu_3SnH was added at once whereas AIBN was added dropwise during 4 h (entry 1) obtaining alcohol (±)-**17** in good yields. Contrarily, applying the same conditions at gram scale significantly lower yields were found (47%, entry 2), because part of the starting material was recovered unaltered. With these experiments, we could prove that the reaction stopped at a determined conversion. Thus, we decided to perform a steadily addition of Bu_3SnH. In this way, AIBN was slowly and continuously added to the reaction medium and Bu_3SnH was added in portions along 30 min to a total amount of 10 eq. Using this new conditions, an oily product was obtained in 81-83% yield, which could be identified as 1,4-dioxaspiro[4.5]dec-6-en-8-ol, (±)-**17**.

Hydrolysis of the desulfurated ketal (±)-**17** by treatment with montmorillonite K-10 in dichloromethane furnished the target enone **8** in 62% yield (Figure 16). It is worth mentioning that this yield may not be representative due to the volatility of 4-hydroxy-2-cyclohexenone.

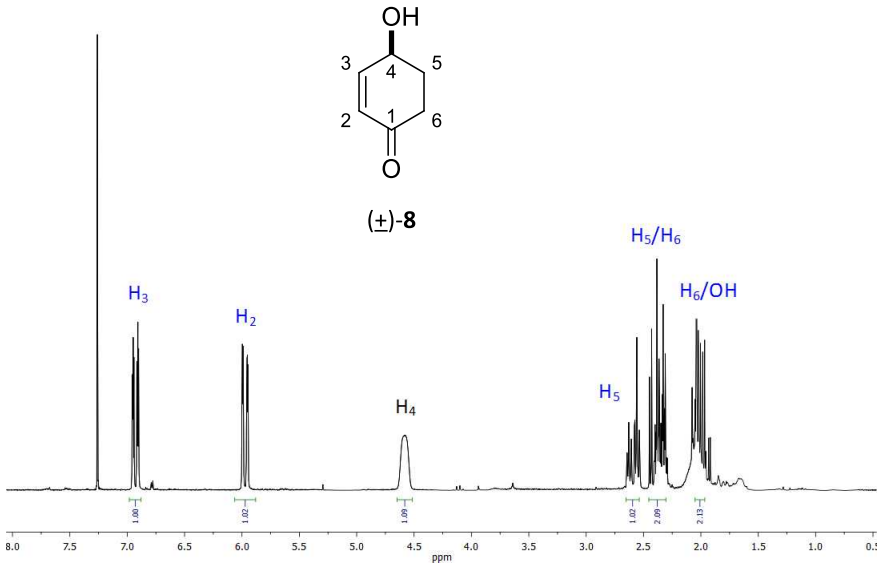
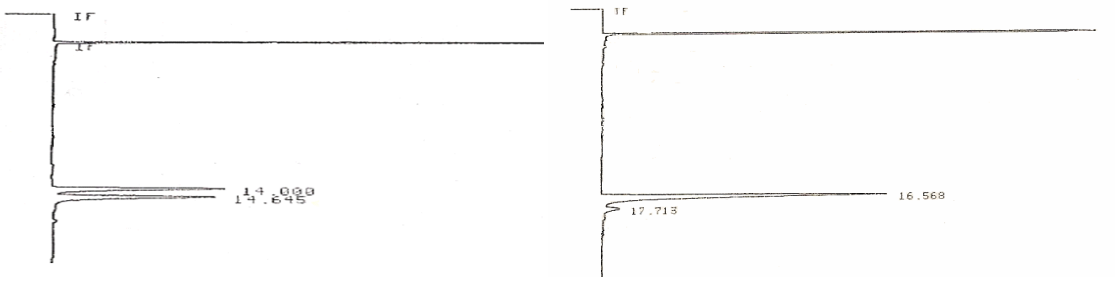


Figure 16. ^{1}H-NMR spectrum (250 MHz, $CDCl_3$) of 4-hydroxy-2-cyclohexenone, **8**.

At this point, we repeated the synthesis with enantiomerically pure compounds aiming towards the preparation of both antipodes of 4-hydroxy-2-cyclohexenone. Thus, starting from (8*S*,10*R*)-**7** (prepared by the enzymatic kinetic resolution), we expected to obtain ketone (*S*)-**8**. To verify that C_4 maintained its configuration at the end of the synthesis, the ee was determined using a chiral GC column (program 2, see Experimental Section) (Figure 17). From the relative area of the peaks, it can be inferred that the ee was 88% (93.9% vs 6.91% area).

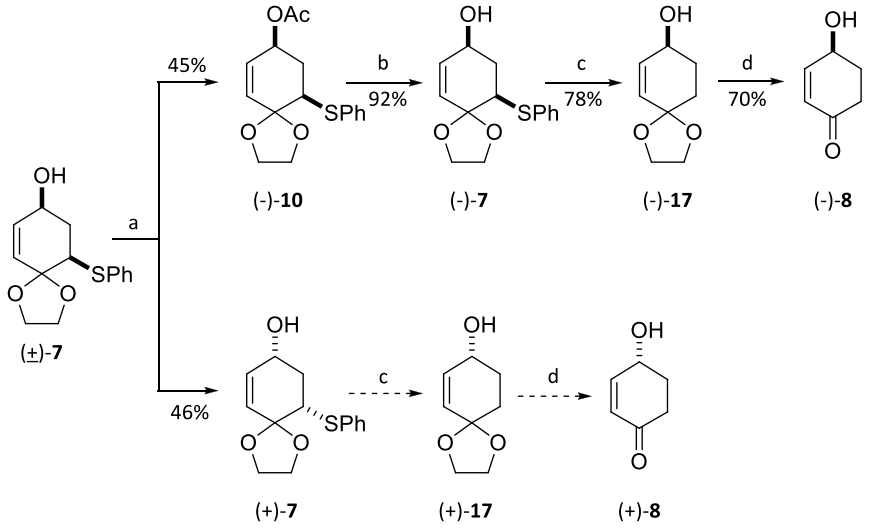


i) GC chromatogram of (±)-**8**. ii) GC chromatogram of (S)-**8**.

Figure 17. GC chromatograms of (*RS*) and (*S*)-**8**.

In conclusion, the synthesis of (*S*)-**8** has been accomplished in 2 steps from (-)-**7** and 55% overall yield (Scheme 24). [84] Complementary, the enantiomer (*R*)-**8** would be available in 2 steps from (+)-**7**.

[84] Bayón, P.; ;Marjanet, G.; Toribio, G.; Alibés, R.; de March, P.; Figueredo, M.; Font, J. *J. Org. Chem.* **2008**, *73*, 3486-3491.

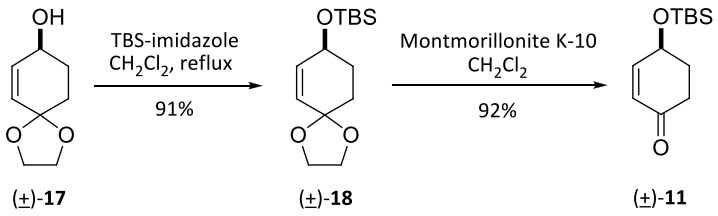


Reagents and conditions: (a) Novozyme®435, $CH_3CO_2CH=CH_2$, diisopropyl ether; (b) NaOMe, MeOH; (c) Bu_3SnH, AIBN, toluene; (d) Montmorillonite K-10, CH_2Cl_2.

Scheme 24. Synthesis of (*S*)-**8** from (±)-**7**, which could be extended to (*R*)-**8**.[84]

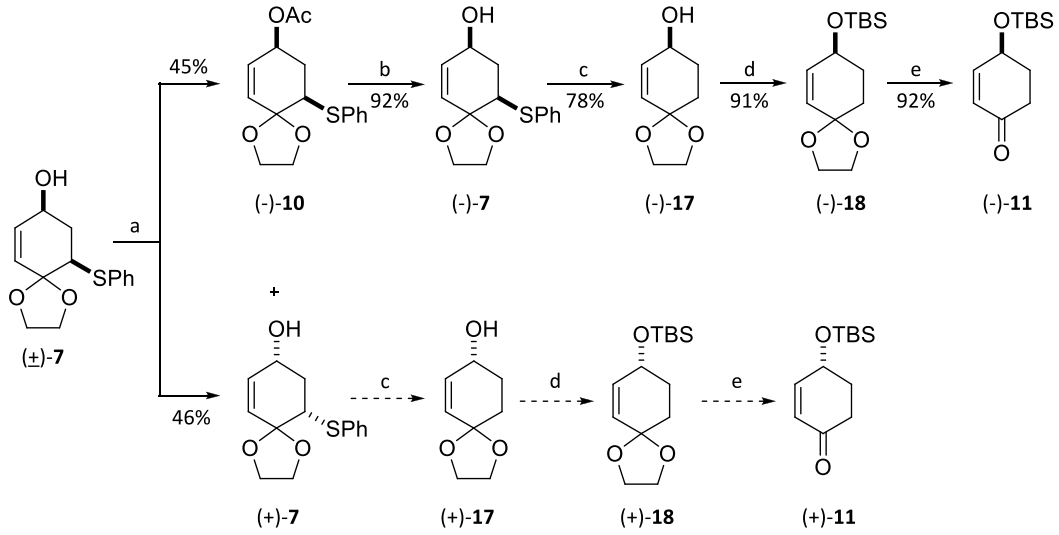
1.2.2. Synthesis of the silyl ether derivative of 4-hydroxy-2-cyclohexenone, **11**

The protection of alcohol **17** was initially carried out by treatment with TBS-imidazole in anhydrous dichloromethane at room temperature (Scheme 25). This methodology gives good yields (around 80%) although it takes long reaction times (5 d). When the temperature was increased to reflux, the starting material was consumed in 20 h (Table 5), and 8-*tert*-butyldimethylsililoxy-1,4-dioxaspiro[4.5]dec-6-ene, (±)-**18**, was isolated as an oil in 91% yield. Applying the methodology of Kitahara and coworkers on the substrate **18**,[62] ketal hydrolysis was achieved by treatment with pyridinium *p*-toluensulfonate in an acetone aqueous solution at reflux temperature. Unfortunately we obtained a mixture of ketones (±)-**11** and (±)-**8**, indicating partial cleavage of the silyl ether. Then, deprotection was tried using montmorillonite K-10 in dichloromethane, which furnished exclusively 4-*tert*-butyldimethylsililoxy-2-cyclohexenone, (±)-**11**, in 92% yield (55% yield from **7**).



Scheme 25. Protection-deprotection series to synthesize (±)-**11**.

Conclusively, the synthesis of the silyl ether of (*S*)-4-hydroxy-2-cyclohexenone, (*S*)-**11**, was accomplished in 3 steps from (-)-**7** and 65% overall yield (Scheme 26). The specific rotation of the synthetic material was $[\alpha]_D^{20}$= -100 (*c* 0.16, CH_2Cl_2) (lit.[73] $[\alpha]_D^{20}$= -109.6 (*c* 1.46, CH_2Cl_2)) Complementary, the enantiomer (*R*)-**11** would be available in 3 steps from (+)-**7**.[84]

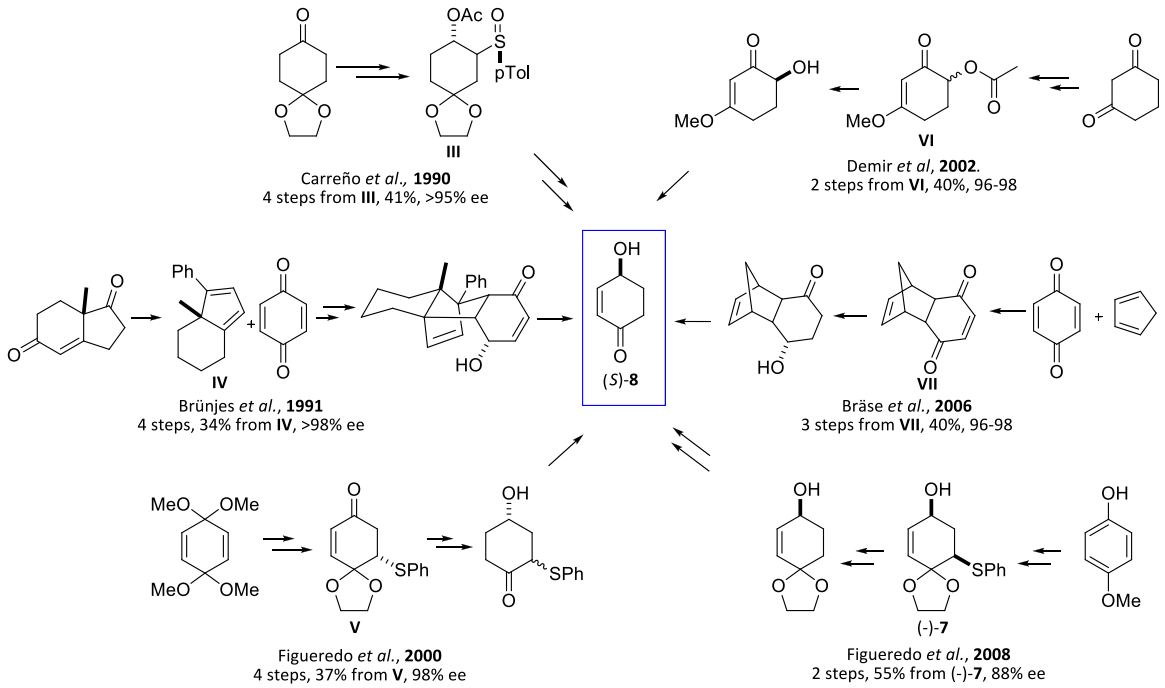


Reagents and conditions: (a) Novozyme®435, $CH_3CO_2CH=CH_2$, diisopropyl ether; (b) NaOMe, MeOH; (c) Bu_3SnH, AIBN, toluene; (d) TBS-imidazole, CH_2Cl_2; (e) Montmorillonite K-10, CH_2Cl_2.

Scheme 26. Synthesis of (*S*)-**11** from (±)-**7**, which could be extended to (*R*)-**8**.[84]

Comparing our results with the previous syntheses of both antipodes reported in literature hitherto (Scheme 27), it can be noticed that in terms of yield and scale of work, our new protocol has important advantages over our previous one.[35] Considering the best published approaches from Carreño[57], Brünjes[58a] and Demir,[77a] their yields are slightly lower. The best yield corresponds to the Bräse synthesis,[78a] but it is needless to say that both antipodes can not be prepared with the same CBS-catalyst. It is important to note that only in Demir and Bräse syntheses the authors claim that their sequences may be performed in multigram scale, but all the reactions are described with significantly lower amounts than in our approximation.

Equally important are the ee values accomplished. The previously mentioned synthesis achieved ee's between 78-98%. Taking into account that, for our starting material (-)-**7** we measured 93% ee (CHPLC), and for our final ketone (*S*)-**8** 88% ee (GC), we can presumably conclude that there is no lost of enantiomeric purity during the process. Therefore, we could obtain higher ee values by recrystallizating the starting alcohol (-)-**7**, a procedure already established by Dr. Georgina Marjanet in her thesis (CH_2Cl_2/pentane, >99% in the second crystallization).[49]

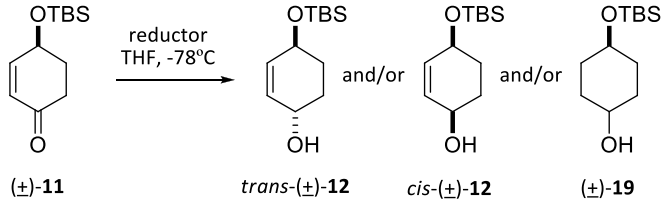


Scheme 27. Synthesis of (*S*)-**8**, which could be extended to (*R*)-**8**.

As a whole, we have achieved one of the objectives of the present thesis, which was establishing a new procedure to prepare (*R*)- and (*S*)-4-hydroxy-2cyclohexenone and a protected derivative of it. This methodology has allowed the practical preparation of compounds which are widely used in the literature as precursors for the synthesis of complex molecules with biological activity.

1.3. SYNTHESIS OF *trans*-CYCLOHEX-2-ENE-1,4-DIOL, **9**, AND ITS MONOPROTECTED DERIVATIVE **12**.

Only the reduction of the carbonyl group from monoprotected ketone (±)-**11** is required for the synthesis of *O*-protected alcohols **12** (Scheme 28). This transformation was attempted using two different reducing agents to modulate the facial diastereoselectivity (Table 6).



Scheme 28. Reduction of enone **11**.

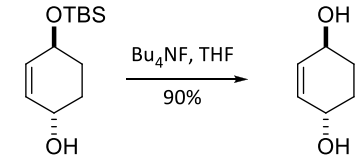
Table 6. Reduction of ketone **11**.

Reductor	Conditions	11:reductor	Products
L-selectride	THF, -78ºC, 2.5 h	1:4	**11**+**19**
DIBAL-H	THF, -78ºC, 1.5 h	1:4	*trans*-**12** (72%) + *cis*-**12** (26%) + **19** (2%)
DIBAL-H	THF, -78ºC, 3 h	1:2	**11**+**12**

Reduction with L-selectride not only reduced the ketone but also the conjugated C-C double bond, whereas DIBAL-H led to a 2.8:1 mixture of *trans*:*cis* alcohols **12**, respectively, in excellent overall yield. By decreasing the amount of DIBAL-H in the reaction medium, part of the starting material was recovered unaltered. Alcohols *trans*- and *cis*-**12** were easily separable by flash chromatography.

Compound *trans*-(±)-**12** had been previously prepared in our laboratories,[38] and the *cis* isomer was also a known compound.[39] The spectral data of the synthesized alcohols matched that reported in literature.

The only step remaining to prepare *trans* diol **9** was the hydrolysis of the silyl ether of *trans*-**12**. This desilylation was accomplished using TBAF in THF at room temperature, delivering *trans*-cyclohex-2-ene-1,4-diol, **9**, in 90% yield (Scheme 29, Figure 18).



trans-(±)-**12** *trans*-(±)-**9**

Scheme 29. Deprotection of silyl ether to furnish *trans*-(±)-**9**.

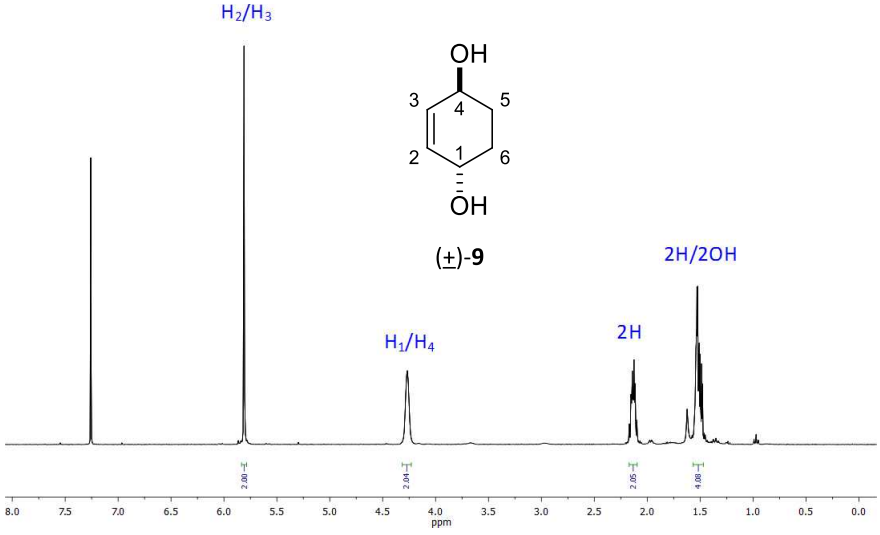
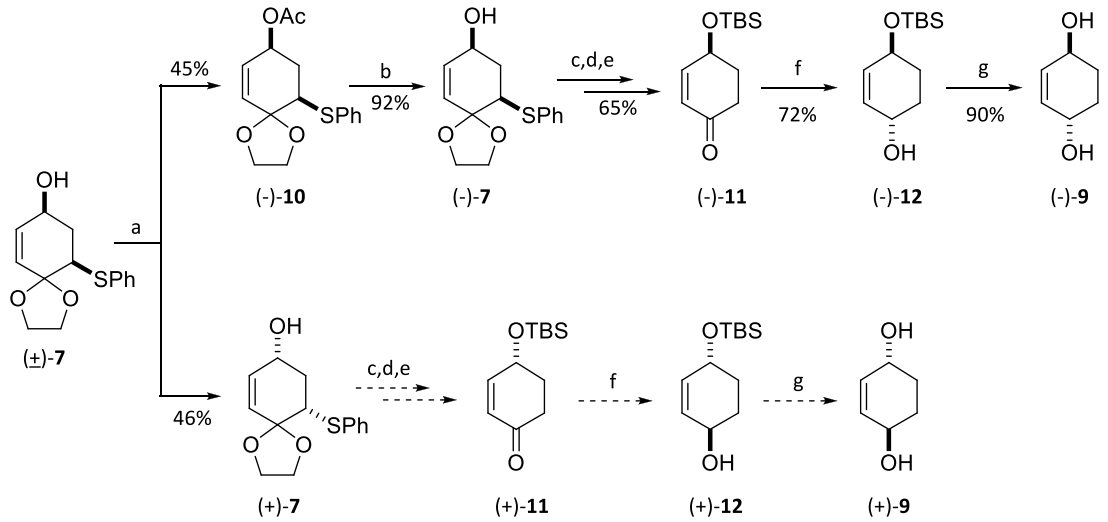


Figure 18. ^{1}H-NMR spectrum (360 MHz, $CDCl_3$) of *trans*-cyclohex-2-ene-1,4 diol, **9**.

Referring to the enantiopure pathway, starting from (*S*)-**11** furnishes (1*S*,4*S*)-**12** and (1*S*,4*S*)-***9***. The specific rotation of the monoprotected alcohol (1*S*,4*S*)-**12** is -96 (*c* 0.96, $CHCl_3$) (lit.[38]

$[\alpha]_D^{20}$= -95 (*c* 0.95, $CHCl_3$)) and that of the diol (1*S*,4*S*)-**9** is -112 (*c* 0.25, $CHCl_3$) (lit. for the enantiomer[82] $[\alpha]_D^{20}$= +114.7 (*c* 0.15, $CHCl_3$)). CHPLC analysis of both compounds (1*S*,4*S*)-**12** and (1*S*,4*S*)-**9** have also been registered mesuring 94% ee and 95% ee, respectively.

In summary, the synthesis of (1*S*,4*S*)-**12** (ee 94%; CHPLC hexanes/2 propanol, 99:1) and (1*S*,4*S*)-**9** (ee 92%; CHPLC hexanes/2 propanol, 98:2) were accomplished in 4-5 steps from (-)-**7** in 47% and 42% yield, respectively (Scheme 30).[84] Complementary, the (1*R*,4*R*)-**12** and (1*R*,4*R*)-**9** would be available in 4-5 steps from (+)-**7**.

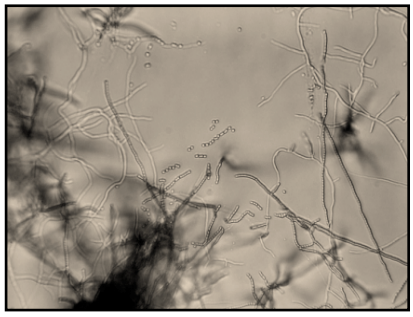


Reagents and conditions: (a) Novozyme®435, $CH_3CO_2CH{=}CH_2$, diisopropyl ether; (b) NaOMe, MeOH; (c) Bu_3SnH, AIBN, toluene; (d) TBS-imidazole, CH_2Cl_2; (e) Montmorillonite K-10, CH_2Cl_2; (f) DIBAL-H, THF, -78 ºC; (g) Bu_4NF, THF.

Scheme 30. Synthesis of (1*S*,4*S*)-**12** and (1*S*,4*S*)-**9** from (±)-**7**, which could be extended to (1*R*,4*R*)-**12** and (1*R*,4*R*)-**9**.[84]

Among the previous synthesis of the *trans* diol **9** only two were enantioselective, the one of Sanfilippo and coworkers[82] and our previous work published in 2004.[38] Sanfilippo *et al.* obtained a mixture of (1*R*,2*R*)-cyclohex-3-ene-1,2-diol and (1*R*,4*R*)-cyclohex-2-ene-1,4-diol, (+)-**9**, in 50% and 34% yield, respectively, and 70% ee for both alcohols. In our previous synthesis, we accesed both antipodes of *trans*-cyclohex-2-ene-1,4-diol with a divergent synthesis in 5-6 steps and 30% yield. Herein, we have developed a new approach at multigram scale, which is suitable to prepare both antipodes of the diol **9** in 5 steps starting from the appropiate enantiomer of **7**. For instance, starting from (-)-**7**, diol (1*S*,4*S*)-**9** was accomplished in 5 steps and 42% overall yield, and its derivative (1S,4S)-**12** in 4 steps in 47% yield. With this efficient approach we have been able to improve the previously published works.

IV. Synthesis of gabosines and anhydrogabosines



Streptomyces strains

1. SYNTHESIS OF GABOSINES AND ANHYDROGABOSINES

1.1. INTRODUCTION

1.1.1. Origin

The gabosine family comprises a group of secondary metabolites isolated from various *Streptomyces* strains with closely related carba-sugar structure. In 1993, Thiericke, Zeeck and coworkers isolated eleven compounds that were named gabosines A-K (Figure 19) and classified them in four different structural types, I to IV.[6,7] In 2000, the same authors disclosed the isolation of three additional members of the family, gabosines L, N and O.[8] All the gabosines present a polyhydroxylated methyl cyclohexane system as the common constitutional feature. Their structural diversity is originated by differences in the substituent positions, unsaturation degree, and/or relative and absolute configuration of their stereogenic centres. In gabosines A, B, C, D, E, F, N, and O the carbon substitution is located at the α-carbonyl position, whereas in gabosines G, H, I, J and L it is located at the β-carbonyl position.

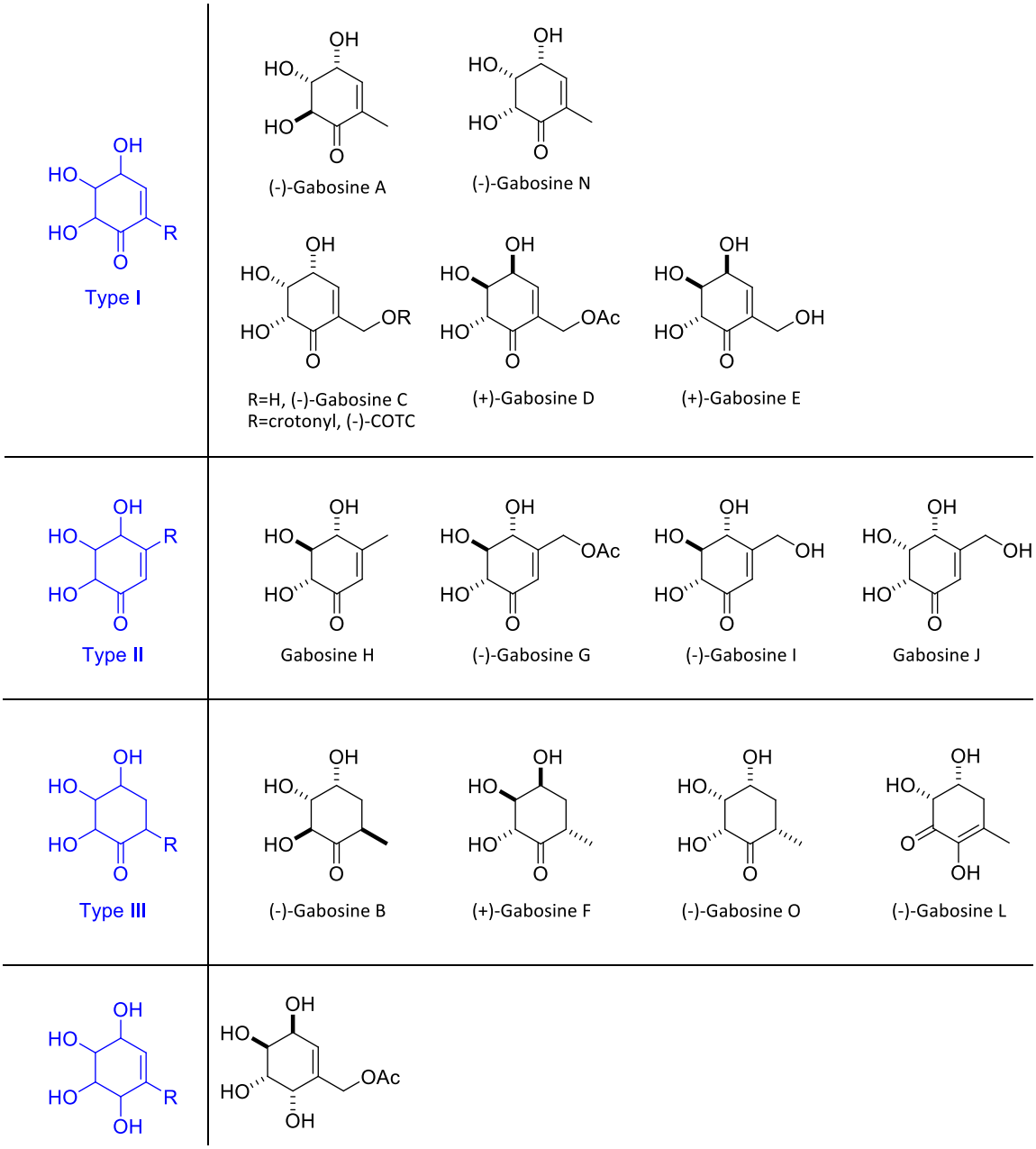


Figure 19. The gabosine family of secondary metabolites.

Before they were named gabosines, some of these compounds were already known. Thus, gabosine B had been formerly isolated from *Actinomycetes* strains.[85] Gabosine C is identical to the previously known antibiotic KD16-U1,[4] and its crotonyl ester, named COTC, is a recognized antitumor agent.[5,10,86]

The absolute configurations of natural gabosines A, F, and L were determined by the Helmchen method,[6] as was that of gabosine N, which was then confirmed by X-ray analysis.[8] The absolute configuration of gabosine B, which is the enantiomer of gabosine F, was established by degradation to (+)-(*R*)-methylsuccinic acid[85] and later confirmed by chemical correlation to gabosine A.[6] The absolute stereochemistry of gabosine C was also determined by correlation to gabosine A, while that of its crotonyl ester, COTC, had been previously established by X-ray analysis of the addition product of *p*-bromothiophenol.[5,10] The absolute configurations of gabosines D and E were deduced by their correlation to gabosine F[6] and that of gabosines I,[87] O[33] and G[88] were established by total synthesis.

The relative stereochemistry of natural gabosines H and J was deduced from their NMR data and their absolute configurations remain unknown. Synthetic studies indicated that the structure assigned to gabosine K needed to be revised[7,89] and, recently, its absolute configuration was established by total synthesis.[90] Table 7 summarizes the origin and optical rotation values of gabosines.

[85] Müller, A.; Keller-Scierlein, W.; Bielecki, J.; Rak, G.; Stuempfel, J.; Zëhner, J. *Helv. Chim. Acta* **1986**, *69*, 1829-1832.

[86] (a) Huntley, C.F. M.; Hamilton, D. S.; Creighton, D. J.; Ganem, B. *Org. Lett.* **2000**, *2*, 3143-3144. (b) Sugimoto, Y.; Suzuki, H.; Yamaki, H.; Nishimura, T.; Tanaka, N. *J. Antibiot.* **1982**, *35*, 1222-1230. (c) Kamiya, D.; Uchihata, Y.; Ichikawa, E.; Kato, K.; Umezawa, K. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1111-1114.

[87] Lubineau, A.; Billault, I. *J. Org. Chem.* **1998**, *63*, 5668-5671.

[88] Shing, T. K. M.; Cheng, H. M. *J. Org. Chem.* **2007**, *72*, 6610-6613.

[89] Mehta, G.; Laskshminath, S. *Tetrahedron Lett.* **2000**, *41*, 3505-3508.

[90] Shing, T. K. M.; Cheng, H. M. *Synlett* **2010**, *1*, 142-144.

Table 7. Occurrence of gabosines.

Compound	$[\alpha]_D^{20}$	Configuration	Source	Year
Gabosine A	-132 (*c* 1, MeOH)[6] -131 (*c* 0.27, MeOH)[9] -125 (*c* 0.8, CD_3OD)[91a]	Absolute	*Streptomyces* strains[6,8]	1993
Gabosine B	-91 (*c* 1.5, MeOH) [6] -106 (*c* 0.45, MeOH)[85]	Absolute	*Actinomycetes* strains[85] *Streptomyces* strains[6] *Actinocycetes* strains[8]	1986 1993 2000
Gabosine C ((-)-KD16-U1)	-168 (*c* 1, H_2O)[4] -166 (*c* 0.2, H_2O)[6] -170 (*c* 1, H_2O)[10] -166 (*c* 0.13, H_2O)[91b] -166 (*c* 0.13, H_2O)[91c]	Absolute	*Streptomyces filipinensis*[4] *Streptomyces* strains[6]	1974 1993
Gabosine D	+86 (*c* 1, MeOH)[6] +71 (*c* 0.54, MeOH)[91j]	Absolute	*Streptomyces* strains[6]	1993
Gabosine E	+148 (*c* 0.95, MeOH)[6] +152 (*c* 1, H_2O)[6] +136 (*c* 0.46, MeOH)[91j]	Absolute	*Streptomyces* strains[6]	1993
Gabosine F	+94 (*c* 1, MeOH)[6] +88 (*c* 0.69, MeOH)[91k]	Absolute	*Streptomyces* strains[6,8]	1993
Gabosine G	+42 (*c* 1.34, MeOH)[88]	Absolute	*Streptomyces* strains[6]	1993
Gabosine H	-68 (*c* 0.58, MeOH)[6]	Relative	*Streptomyces* strains[6]	1993
Gabosine I (Valienone)	-61 (*c* 1, MeOH)[6] -40 (*c* 1.0, MeOH)[87] -59 (*c* 0.79, MeOH)[88]	Absolute	*Streptomyces* strains[6] *Streptomyces lincolnensis* DSM 40 355[91i]	1993 2009
Gabosine J		Relative	*Streptomyces* strains[6]	1993
Gabosine K	-48 (*c* 0.52, MeOH)[90]	Absolute	*Streptomyces* strains[6]	1993
Gabosine L	-13 (*c* 0.10, MeOH)[8]	Absolute	*Streptomyces* strains[8]	2000
Gabosine N	-152 (*c* 0.89, H_2O)[8] -150 (*c* 0.30, CD_3OD)[91a] -142 (*c* 0.16, MeOH)[33]	Absolute	*Streptomyces* strains[8]	2000
Gabosine O	-21 (*c* 0.1, MeOH)[8] -11 (*c* 0.15, MeOH)[91d] -11 (*c* 0.38, MeOH)[33]	Absolute	*Streptomyces* strains[8]	2000
COTC	-109 (*c* 1.5, MeOH)[5,10] -108 (*c* 0.23, MeOH)[91e] -106 (*c* 0.6, MeOH)[91f,g] -111 (MeOH)[91h]	Absolute	*Streptomyces griseosporeus*[5,10,86a] *Streptomyces* strains[86b] *Streptomyces griseosporeus*[86a]	1975 1982 2000

[91] (a) Monrad, R. N.; Fanefjord, M.; Hansen, F. G.; Jensen, N. M. E.; Madsen, R. *Eur. J. Org. Chem.* **2009**, 396-402. (b) Mirza, S.; Molleyres, L.-P.; Vasella, A. *Helv. Chim. Acta* **1985**, *68*, 988-996. (c) Ramana, G. V.; Rao, B. V. *Tetrahedron Lett.* **2005**, *46*, 3049-3051. (d) Carreño, M. C.; Merino, E.; Ribagorda, M.; Somoza, A.; Urbano, A. *Chem. Eur. J.* **2007**, *13*, 1064-1077. (e) Takayama, H.; Hayashi, K.; Koizumi, T. *Tetrahedron Lett*. **1986**, *27*, 5509-5512. (f) Shing, T. K. M.; Tang, Y. *J. Chem. Soc. Chem. Comm.* **1990**, 312. (g) Shing, T. K. M.; Tang, Y. *Tetrahedron* **1990**, *46*, 6575-6584. (h) Mehta, G.; Pujar, S. R.; Ramesh, S. S.; Islam, K. *Tetrahedron Lett.* **2005**, *46*, 3373-3376. (i) Sedmera, P.; Halada, P.; Pospĭsil, S. Magn. Reson. Chem. **2009**, *47*, 519-522. (j) Shing, T. K. M.; Cheng, H. M. *Org. Biomol. Chem.* **2009**, *7*, 5098-5102. (k) Sing, T. K. M.; So, K. H.; Kwok, W. S. *Org. Lett.* **2009**, *11*, 5070-5073.

Some other compounds, whose isolation from natural sources is described in the literature, are epoxyquinols and -quinones. They present a structural pattern closely related to the gabosine family, specifically they display anhydrogabosine structure (Figure 20).[92] Most of these compounds are phytotoxins.

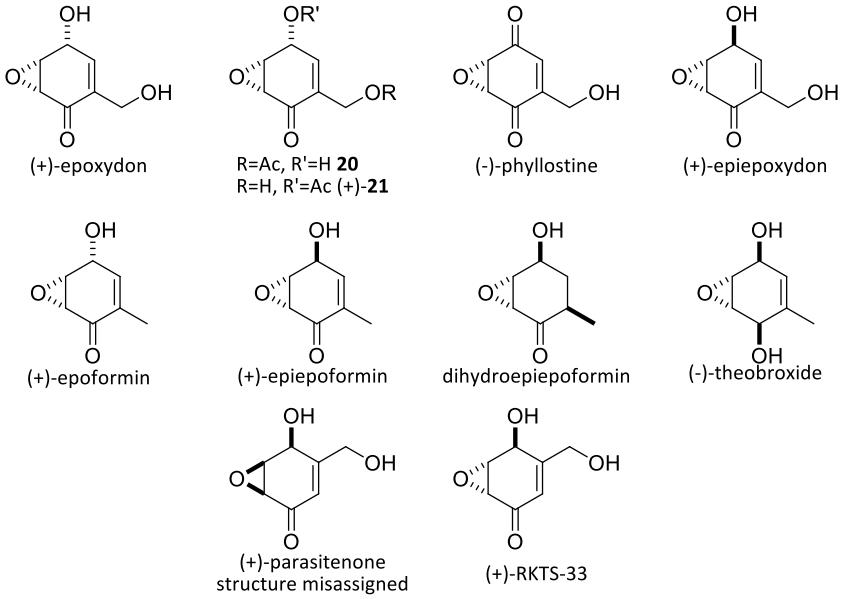


Figure 19. Epoxiquinone natural products with anhydrogabosine structure.

Among them, the first structural assignment corresponded to (+)-epoxydon (also named phyllosinol), which presents an oxymethyl substituent at the α-carbonyl position, as in gabosines C, D, and E. The C_4 epimer of (+)-epoxydon, (+)-epiepoxydon (also named isoepoxydon) is another secondary metabolite. Other phytotoxins closely related to (+)-epoxydon and (+)-epiepoxydon are (-)-phyllostine and the epoxydon monoacetates **20** and (+)-**21**.

There are also several anhydrogabosines exhibiting a methyl group at the α-carbonyl position as in gabosines A and N. (+)-Epoformin (also named desoxyepoxydon) was first isolated from *Penicillium claviforme*.[15a] (+)-Epiepoformin was isolated from *Lagerstroemia indic*a L.,[93] and dihydroepiepoformin was extracted from *Penicillium patulum*.[94] Three additional related natural products are (+)-parasitenone, which presents a hydroxymethyl substituent at the β-carbonyl position as in gabosines I and J, its C_4 epimer (+)-RKTS-33, and (-)-theobroxide.

Table 8 summarizes the origin and optical rotation values of epoxiquinol and -quinones with anhydrogabosine structure.

[92] (a) Marco-Contelles, J.; Molina, M. T.; Anjum, S. *Chem. Rev.* **2004**, *104*, 2857-2899. (b) Miyashita, K.; Imanishi, T. *Chem. Rev.* **2005**, *105*, 4515-4536. (c) Shoji, M.; Hayashi, Y. *Eur. J. Org. Chem.* **2007**, 3783-3800.

[93] Nagasawa, H.; Suzuki, A.; Tamura, S. *Agr. Biol. Chem.* **1978**, *42*, 1303-1304.

[94] Kuo, M.-S.; Yurek, D. A.; Mizsak, S. A.; Marshall, V. P.; Liggett, W. F.; Cialdella, J. I.; Laborde, A. L.; Shelly, J. A.; Truesdell, S. E. *J. Antibiot.* **1995**, *48*, 888-890.

Table 8. Occurrence of epoxiquinones with anhydrogabosine structure (absolute configuration).

Compound	$[\alpha]_D^{20}$	Source	Year
Epoxydon (Phyllosinol)	+102 (*c* 1, EtOH)[14b]	*Phoma* sp.[14a]	1965
	+92 (*c* 0.123, EtOH)[95a]	*Phyllostica* sp.[14b]	1969
	+72 (*c* 0.3, MeOH)[95j]	*Diospyrous kaki* L.[95b]	1979
	+98 (*c* 0.1, EtOH)[91h]	*Mycosphaerella ligulicola*[95a]	1981
		Phoma sp.[95e]	1992
		Phoma sorghina[95f]	1994
		Ophiosphaerella herpotricha[15b]	1994
		Phoma glomerata JCM9972[95b]	1999
		Aspergillus[95b]	2005
		Nigrospora sp. PSU-F5[95k]	2008
20		*Mycosphaerella ligulicola*[95a]	1981
21	+66 (*c* 0.5, MeOH)[95b]	*Aspergillius*[95b]	2005
Epiepoxydon (Isoepoxydon)	+194 (*c* 1.57, EtOH)[93]	*Lagerstroemia indica* L. fungus[93]	1978
	+206 (*c* 0.17, MeOH)[95l]	*Penicillium urticae*[95l]	1979
	+192 (*c* 7.5, MeOH)[95m]	*Penicillium urticae* NRRL 2159A[95g]	1979
	+261 (*c* 1.00, MeOH)[17b]	*Poronia punctata* NRRL 6457[95m]	1988
	+114 (*c* 0.92, MeOH)[95c]	*Pestalotiopsis longireta* and *P. theae*[17b]	1992
	+256 (*c* 0.8, EtOH)[95n]	Unspecified fungi[95o]	1993
	+256 (*c* 0.95, EtOH)[62]	*Penicillium* sp. from *Enteromorpha intestinalis*[95c]	1999
	+250 (*c* 1.4, EtOH)[91h]	*Aspiospora montagnei*[95p]	2004
Phyllostine	-105.6 (*c* 1, EtOH)[13]	*Phyllostica* sp.[13]	1971
	-105.6 (*c* 1, EtOH)[95n]	*Penicillium urticae* NRRL 2159A[95g]	1979
	-120 (*c* 0.28, EtOH)[95q]	*Phoma sorghina*[95f]	1994
	-108 (*c* 1.61, EtOH)[91h]	*Ophiosphaerella herpotricha*[15b]	1994
Epoformin (Desoxyepoxydon)	+114 (EtOH)[15a]	Unidentified fungus from *Lagerstroemia indica L.*[93]	1978
	+109 (*c* 0.21, EtOH)[95r]	*Phoma* sp.[95e]	1992
		Phoma sorghina[95f]	1994
		Ophiosphaerella herpotricha[15b]	1994
		Penicillium vulpinum[95h]	1998
Epiepoformin (Desoxyepiepoxydon)	+221 (*c* 0.83, EtOH)[93]	Unidentified fungus from *Lagerstroemia indica L.*[93]	1978
	+316 (*c* 0.37, EtOH)[95n]		
	+310 (*c* 0.46, EtOH)[95q]		
	+314 (*c* 0.49,EtOH)[95s]		
	+320 (*c* 0.06, EtOH)[62]		
	+303 (*c* 1.1, EtOH)[91d]		
Dihydroepiepoformin	+22 (*c* 0.1, acetone)[91d]	*Penicillium patulum*[94]	1995
Parasitenone	+72 (*c* 0.3, MeOH)[95d]	*Penicillium parasiticus*[95d]	2002
Theobroxide	-6.12 (*c* 0.20, EtOH)[16a]	*Lasidiplodia theobromae* IFO31059[16a,103b]	1994
	-6.25 (*c* 0.40, EtOH)[119a]		
	-6.18 (*c* 0.35, EtOH)[126b]		
	-8.0 (*c* 0.10, EtOH)[91d]		
RKTS-33	-276 (*c* 0.26, EtOH)[91h]	Synthetic[104a]	2003
Isoepiepoformin	+310 (*c* 0.46, EtOH)[125b]	*Myrothecium roridum* CL-514[95i]	

[95] (a) Assante, G.; Camarda, L.; Merlini, L.; Nasini, G. *Phytochemistry* **1981**, *20*, 1955-1957. (b) Arie, T.; Kobayashi, Y.; Kono, Y.; Gen, O.; Yamaguchi, I. *Pestic. Sci.* **1999**, *55*, 602-604. (c) Iwamoto, C.; Minoura, K.; Oka, T.; Ohta, T.; Hagishita, S.; Numata, A. *Tetrahedron* **1999**, *55*, 14353-14368. (d) Son, B. W.; Choi, J. S.; Kim, J. C.; Nam, K. W.; Kim, D.-S.; Chung, H. Y.; Kang, J. S.; Choi, H. D. *J. Nat. Prod.* **2002**, *65*, 794-795. (e) Venkatasubbaiah, P.; Chilton, W. S. *J. Nat. Prod.* **1992**, *55*, 639-643. (f) Venkatasubbaiah, P.; Van Dyke, C. G.; Chilton, W. S. *Mycologia* **1992**, *84*, 715-723. (g) Sekiguchi, J.; Gaucher, G. M.; Can, J. *Microbiol*. **1979**, *25*, 881-887. (h) Makino, M.; Endoh, T.; Ogawa, Y.; Watanabe, K.; Fujimoto, Y. *Heterocycles* **1998**, *48*, 1931-34.

1.1.2. Biological activity

Gabosines A-K exhibit no significant activity in the fundamental antibacterial, antifungal, antiviral, herbicidal, and insecticidal assays, but they show a weak antiprotozoal activity. Gabosine E showed a weak inhibitory effect on the cholesterol biosynthesis in cell lines test with HEP-G2 live cells.[6] Gabosines A, B, F, N and O present DNA-binding properties.[8,96] As already mentioned, gabosine C is the known antibiotic KD16-U1[4] and its crotonyl ester, COTC, is an antitumor agent.[5] It has been long assumed that the activity of COTC was the result of glioxalase I inhibition[86] and its effects in macromolecular synthesis, mitosis and membrane functions have been attributed to the interaction with the sulhydryl group of various enzymes. A more recent hypothesis proposes that COTC is an enzyme-activated product in which the crotonate ester serves as a leaving group, in a process triggered by glutathionyl transferase, which produces a transient, highly electrophilic glutathionated 2-exomethylenecyclohexanone that can covalently modify proteins and nucleic acids.[97]

Among the epoxide derivatives, epoxydon has been the most extensively investigated. It showed antibiotic,[95j,k,98] antitumor,[14b] radical scavenging[95j] and anti-auxin activities. Some of these activities were also described for the epoxydon monoacetate (+)-**21**.[95j] Epiepoxydon showed antibiotic and antifungal activity,[95l,m] β-1,3-glucan inhibition,[95o] and it is strongly cytotoxic.[95p] Moreover, epoxydon, epiepoxydon and epiepoformin inhibited the germination of lettuce seeds[13,93] and the first also reduced growth in rice seedings.[98]

[95 (cont.)] (i) Jarvis, B. B.; Yatawara, S. S.; *J. Org. Chem.* **1986**, *51*, 2906-2910. (j) Li, Y.; Xi, X.; Son, B. W. *Nat. Prod. Sci.* **2005**, *11*, 136-138. (k) Trisuwan, K.; Rukachaisirikul, V.; Sukpondma, Y.; Preedanon, S.; Phongpaichit, S.; Rungjindamai, V.; Sakayaroj, J. *J. Nat. Prod.* **2008**, *71*, 1323-1326. (l) Sekiguchi, J.; Gaucher, G. M. *Biochem. J.* **1979**, *182*, 445-453. (m) Gloer, J. B.; Truckenbrod, S. M. *Appl. Environ. Microb.* **1988**, *54*, 861-884. (n) Kamikubo, T.; Ogasawara, K. *Tetrahedron Lett.* **1995**, *36*, 1685-1688. (o) Fukushima, Y.; Sakagami, Y.; Marumo, S. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1219-1222. (p) Klemke, C.; Kehraus, S.; Wright, A. D.; König, G. M. *J. Nat. Prod.* **2004**, *67*, 1058-1063. (q) Shimizu, H.; Okamura, H.; Yamashita, N.; Iwagawa, T.; Nakatani, M. *Tetrahedron Lett.* **2001**, *42*, 8649-8651. (r) Barros, M. T.; Maycock, C. D.; Ventura, M. R. *Tetrahedron* **1999**, *55*, 3233-3244. (s) Barros, M. T.; Maycock, C. D.; Ventura, M. R. *Chem. Eur. J.* **2000**, *6*, 3991-3996. (t) Li, P.; Takei, R.; Takahashi, K.; Nabeta, K. *Phytochemistry* **2007**, *68*, 819-823. (u) Kakeya, H.; Miyake, Y.; Shoji, M.; Kishida, S.; Hayashi, Y.; Kataoka, T.; Osada, H. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3743-3746. (v) White, L. V.; Dietinger, C. E.; Pinkerton, D. M.; Willis, A. C.; Banwell, M. G. *Eur. J. Org. Chem.* **2010**, 4365-4367.

[96] Maier, A.; Maul, C.; Zerlin, M.; Grabley, S.; Thiericke, R. *J. Antibiot.* **1999**, *52*, 952-959.

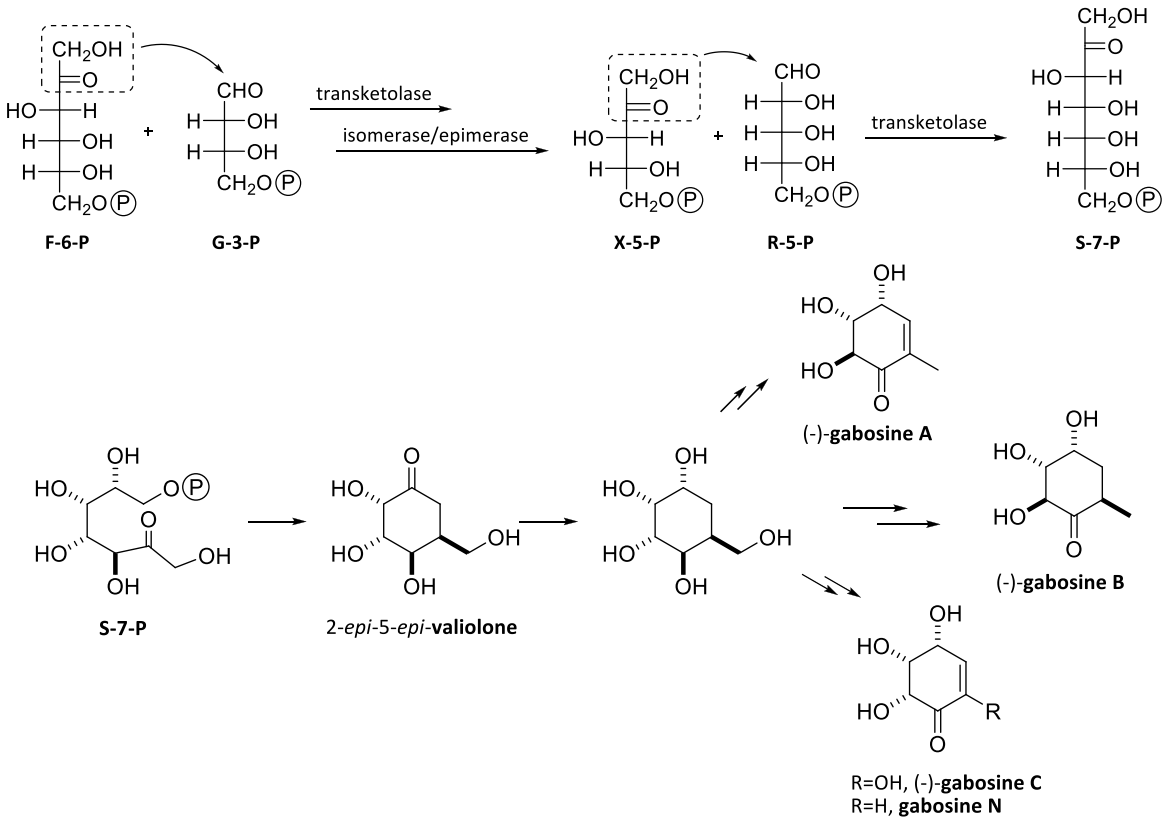
[97] Hamilton, D. S.; Ding, Z.; Ganem, B.; Creighton, D. J. *Org. Lett.* **2002**, *4*, 1209-1212.

[98] Sakai, R.; Sato, R.; Niki, H.; Sakamura, S. *Plant. Cell. Physiol.* **1970**, *11*, 907-920.

Phyllostine is a tumor inhibitor, dihydroepiepoformin is an antagonist for the interleukin-1 receptor[94] and theobroxide is a potato microtuber inducing substance.[95t,99] The synthetic compound (+)-RKTS-33 has inhibitory activity towars death receptor-mediated apoptosis.[95u,100]

1.1.3. Biogenetic studies

Biosynthetic studies on gabosines A, B, C, with ^{13}C-labeded precursors indicated that their origin is different to the shikimate pathway (Scheme 31) despite their structural similarities.[101] The observed labelling pattern indicates that the biosynthesis of gabosines follows a pentose phosphate pathway in which seudoheptulose 7-phosphate (**S-7-P**) is a key intermediate. **S-7-P** is originated from glyceraldehyde 3-phosphate (**G-3-P**) by transfer of a C2 fragment from fructose 6-phosphate (**F-6-P**) by a transketolase. The resulting xylulose 5-phosphate (**X-5-P**) can be converted into ribose 5-phosphate (**R-5-P**) by isomerization. In the next step, a second fragment transfer from **X-5-P** to **R-5-P** occurs to form **S-7-P**. It is assumed that **S-7-P** cyclises by an aldol reaction between C_2 and C_7.



Scheme 31. Biosynthetic pathway of gabosines.

[99] Nakamori, K.; Matsuura, H.; Yoshihara, T.; Ichihara, A.; Koda, Y. *Phytochemistry* **1994**, *35*, 835-839.

[100] Mitsui, T.; Miyake, Y.; Kakeya, H.; Hayashi, Y.; Osada, H.; Kataoka, T. *Biosci. Biotechnol. Biochem.* **2005**, *69*, 1923-1928.

[101] Höfs, R.; Schoppe, S.; Thiericke, R.; Zeeck, A. *Eur. J. Org. Chem.* **2000**, 1883-1887.

1.1.4. Synthetic approaches

An analysis of the published work devoted to the synthesis of compounds with gabosine and anhydrogabosine structure discloses common trends between the approaches developed in different laboratories. Moreover, quite often the synthetic pathway splits into two or more parallel or alternative routes leading to different targets. It is also noticeable that some early syntheses have been later modified in order to improve them in terms of chemical yield and selectivity or to develop an enantioselective version.

In the following description these syntheses have been organized focusing on the strategy used, rather than considering the specific target or the chronological order. In general, only one representative example of each kind will be illustrated by a scheme.

i) Gabosines

Gabosine's peculiar structure and their promising biological activity have motivated synthetic studies directed towards these targets. Figure 20 summarizes all the published synthesis of gabosines until the present date, many of which have appeared in recent years.

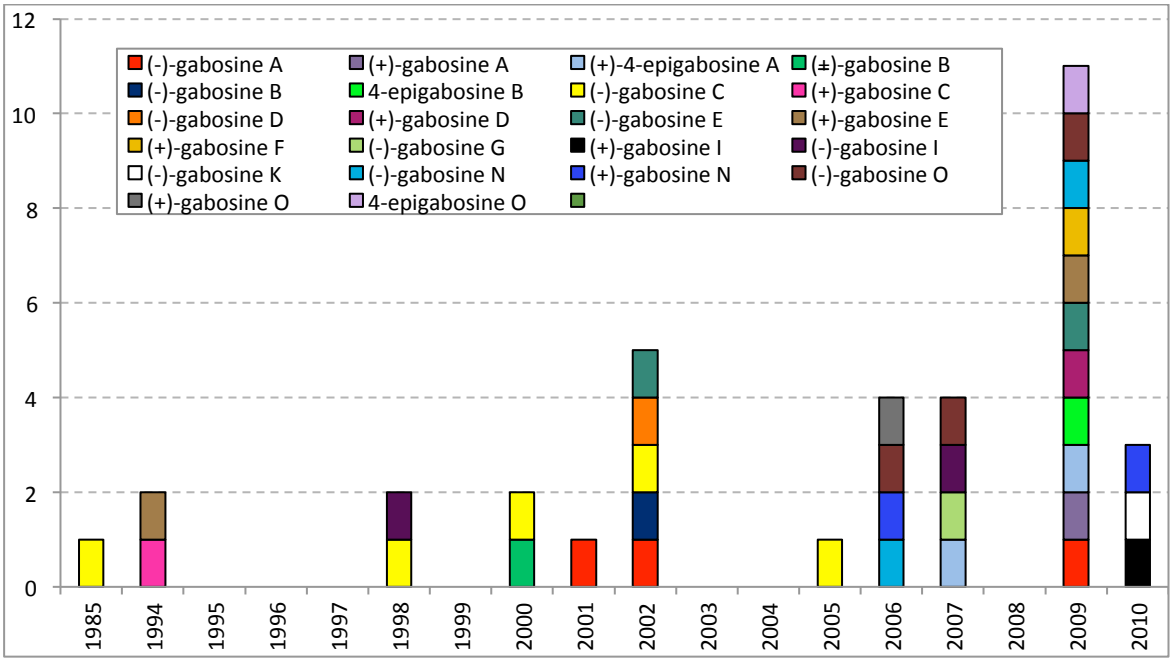


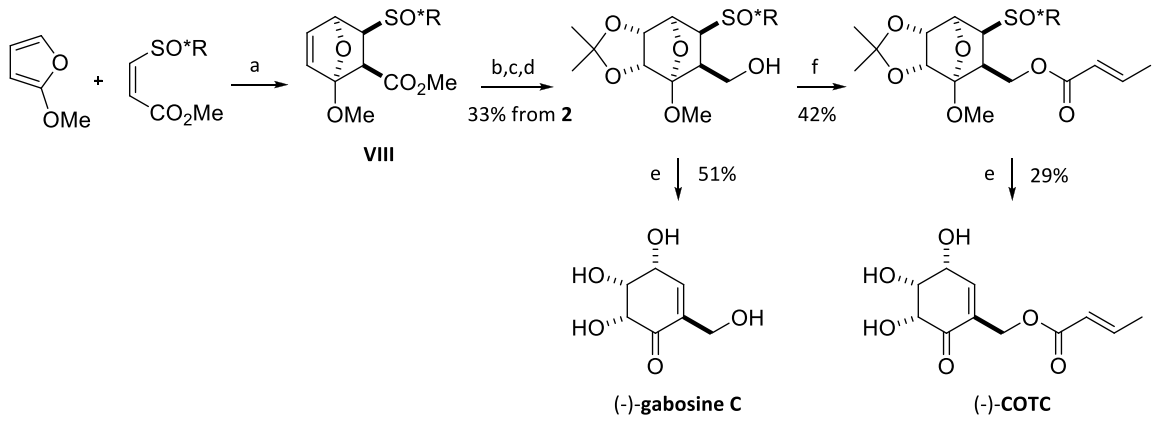
Figure 20. Synthesis of gabosines.

- *Diels-Alder strategies*

Several successful approaches to gabosines rely on Diels-Alder methodologies. In some cases, a Diels-Alder adduct derived from *p*-benzoquinone is conveniently elaborated and then a retro Diels-Alder process allows recovering of the cyclohexene moiety. In other cases, both the diene and dienophile are incorporated in the final compound. Using this strategy, Koizumi and coworkers reported in 1986 the first enantioselective synthesis of (-)-COTC in 8 steps and 30% overall yield, starting from 2-methoxyfuran as diene and a chiral arylsulfinylacrylate as dienophile.[102]

In 2000, Mehta and Lakshminath described the first racemic synthesis of gabosine B in 9 steps and 15% overall yield, from a Diels-Alder adduct of vinyl acetate and a polysubstituted cyclpentadiene. These authors also prepared a compound with the structure previously assigned to gabosine K, but its physical data did not match those of the natural product.[7,89]

As part of their investigations devoted to the study of the high-pressure mediated asymmetric Diels-Alder reaction of chiral sulfinylacrylate derivatives, Takashi and coworkers obtained the *endo* Diels-Alder adduct **VIII**, whose stereochemistry was confirmed by the synthesis of (-)-gabosine C and (-)-COTC, in 17% and 4% overall yield, respectively (Scheme 32).[103]



Reagents and conditions: (a) CH_2Cl_2, 1.2 GPa; (b) OsO_4, Me_3NO, acetone; (c) 2,2-dimethoxypropane, PTSA, acetone; (d) $LiAlH_4$, THF; (e) TFA, H_2O; (f) crotonic anhydride, pyridine, DMAP, benzene.

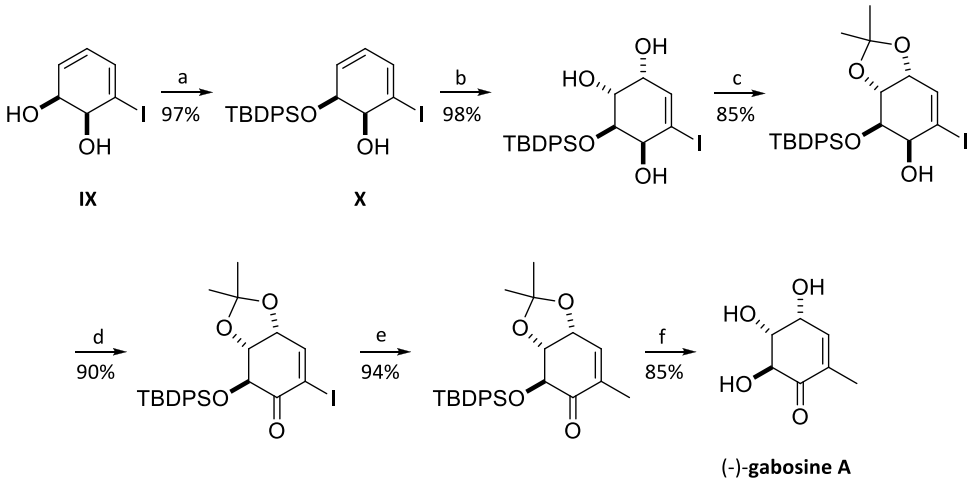
Scheme 32. Syntheses of (-)-gabosine C and (-)-COTC by Takashi *et al*.[103]

[102] Takayama, H.; Hayashi, K.; Koizumi, T. *Tetrahedron Lett.* **1986**, *27*, 5509-5512.

[103] Takashi, T.; Yamakoshi, Y.; Okayama, K.; Yamada, J.; Ge, W.-Y.; Koizumi, T. *Heterocycles* **2002**, *56*, 209-220.

- *From benzene derivatives*

In two approximations, the precursor of the cyclohexene core of the target compound is a benzene derivative, which is subjected to an oxidative desymmetrization. The first synthesis of (-)-gabosine A belongs to this category. It was reported in 2001 by Banwell and coworkers through a very short and efficient sequence starting from the *cis*-1,2-dihydrocatechol **IX**, a material readily prepared in enantiopure form by toluene dioxygenase mediated dihydroxylation of iodobenzene. The crucial step was a selective dihydroxylation of the more nucleophilic double bond of alcohol **X**. (-)-Gabosine A was prepared in 6 steps and 58% overall yield (Scheme 33).[9]



IX **X** (-)-**gabosine A**

Reagents and conditions: (a) TBDPS, imidazole, CH_2Cl_2; (b) OsO_4, NMO, acetone, H_2O; (c) 2,2-dimethoxypropane, PTSA, TEA; (d) $(COCl)_2$, DMSO, TEA; (e) MeMgCl, $FeCl_3$, NMP, THF; (f) i) HCl aq, MeOH, ii) $((Me)_2N)_3S^+FSiMe_3^-$, THF.

Scheme 33. Synthesis of (-)-gabosine A by Banwell *et al*.[9]

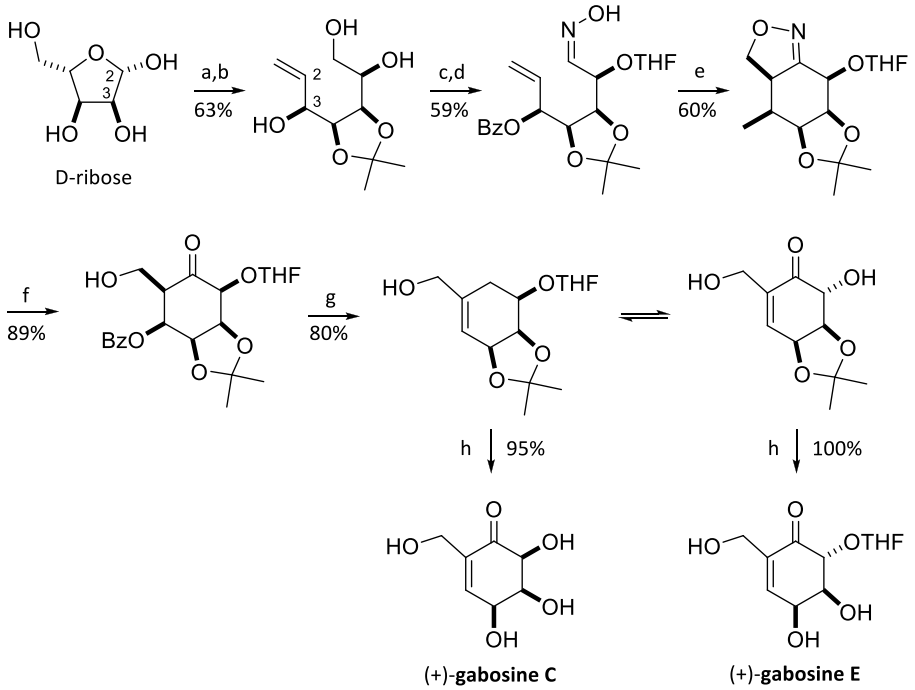
Recently, Whitehead *et al.* described the synthesis of (-)-6-*epi*-COTC in 8 steps and 3.4% overall yield,[104a] starting from diol **IX**. As part of these studies, other COTC-analogues were also prepared and their activity as anti-tumor agents investigated.[104b,c]

- *From carbohydrates*

Most successful syntheses of gabosines have been accomplished starting from carbohydrates. Pioneer among them were the synthesis of (-)-gabosine C and (-)-COTC developed by Vasella and coworkers starting from methyl α–D-mannopyranoside.[91b]

[104] (a) Arthurs, C. L.; Raftery, J.; Whitby, H. L.; Whitehead, R. C.; Wind, N. S.; Stratford, I. J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5974-5977. (b) Arthurs, C. L.; Wind, N. S.; Whitehead, R. C.; Stratford, I. J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 553-557. (c) Arthurs, C. L.; Lingley, K. F.; Piacenti, M.; Stratford, I. J.; Tatic, T.; Whitehead, R. C.; Wind, N. S. *Tetrahedron Lett.* **2008**, *49*, 2410-2413.

In 1994, Lygo and coworkers described the synthesis of unnatural (+)-gabosine C, along with that of its epimer at C_2, (+)-gabosine E, starting from D-ribose (Scheme 34).[105] The carba-sugar skeleton was formed via an intramolecular nitrile oxide cycloadditon (INOC).



Reagents and conditions: (a) 2,2-dimethoxypropane, acetone, CSA; (b) CH_2=CHMgBr, THF; (c) i) TBSCl, pyridine, DMAP, ii) BzCl, pyridine, iii) 2,3-DHF, PPTS, CH_2Cl_2; (d) i) Bu_4NF, THF, ii) $(COCl)_2$, DMSO, TEA, THF, iii) $HCl{\cdot}H_2NOH$, pyridine, MeOH; (e) NaClO, TEA, CH_2Cl_2; (f) H_2, Ni-Raney, EtOH, AcOH; (g) DABCO,THF, CH_2Cl_2.

Scheme 34. Synthesis of (+)-gabosine C and (+)-gabosine E by Lygo *et al*.[105]

Four years later, Lubineau and Billault reported a concise synthesis of (-)-gabosine I (9 steps and 15% overall yield) starting from a D-glucose derivative using an intramolecular Nozaki-Hiyama-Kishi cyclization as a key step.[87] The absolute configuration of natural gabosine I had not been previously reported. The negative value of specific rotation of the synthesized material indicated that the natural compound had *gluco* configuration.

A contemporary publication of Tatsuta and coworkers disclosed new syntheses of (-)-gabosine C and (-)-COTC starting from a D-ribose derivative,[106] in 22% and 16% overall yield, respectively.

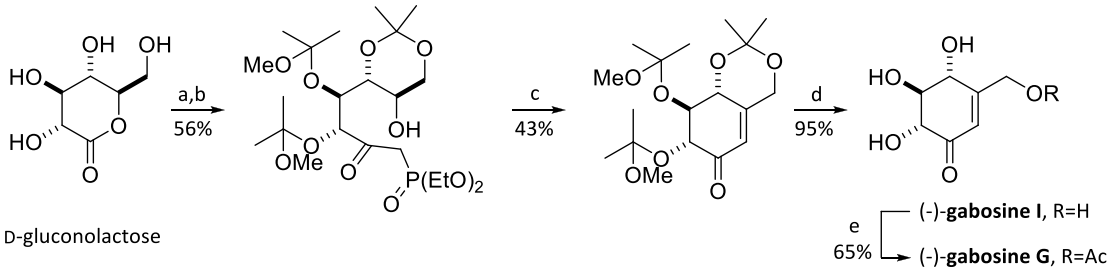
[105] Lygo, B.; Swiatyj, M.; Trabsa, H.; Voyle, M. *Tetrahedron Lett*. **1994**, *35*, 4197-4200.

[106] Tatsuta, K.; Yasuda, S.; Araki, N.; Takahashi, M.; Kamiya, Y. *Tetrahedron Lett.* **1998**, *39*, 401-402.

Rao and coworkers prepared three gabosines starting also from a derivative of D-ribose and using a Nozaki-Hiyama-Kishi reaction followed by ring closing metathesis (RCM) as the key steps. In an earlier publication, they obtained (-)-gabosine C in 6% overall yield,[91c] and, recently, they have published the synthesis of (+)-gabosine N and (+)-gabosine O in 30% and 32% overall yield, respectively. [107]

In 2006, Corsaro and coworkers described a procedure for the conversion of a D-galactose derivative into gabosine type compounds. Their approach comprised a stereoselective Simmons-Smith cyclopropanation and a mercury-mediated cyclopropane ring opening as crucial steps.[108]

Starting from 2007, Shing and coworkers have published several papers related to the synthesis of some gabosine family members. In the first one, they reported a new synthesis of (-)-gabosine I starting from a D-glucose derivative as in the previous approach of Lubineau and Billault.[87] (-)-Gabosine I was synthesized in 4 steps and 23% overall yield using a Horner-Wadsworth-Emmons olefination as the key step (Scheme 35). Subsequent regioselective acetylation afforded the first synthesis of (-)-gabosine G.[88]



Reagents and conditions: (a) 2-methoxypropene, (±)-CSA, DMF; (b) $MePO(OEt)_2$, LDA, THF; (c) TPAP, NMO, 3Å MS, MeCN, K_2CO_3; (d) TFA, H_2O, CH_2Cl_2; (e) AcCl, collidine.

Scheme 35. Synthesis of (-)-gabosines I and G by Shing *et al*.[88]

In 2009, they disclosed the first synthesis of (+)-gabosine F by an INOC reaction as a crucial step, in 12 steps and 24% overall yield from L-arabinose. Similarly, (-)-gabosine O and its epimer at C_4 were accomplished from D-mannose in 9 and 11 steps with 41% and 38% overall yield, respectively. [91k]

[107] Rao, J. P.; Rao, B. V. *Tetrahedron: Asymmetry* **2010**, *21*, 930-935.

[108] Corsaro, A.; Pistarà, V.; Catelani, G.; D'Andrea, F.; Adamo, R.; Chiacchio, M. A. *Tetrahedron Lett.* **2006**, *47*, 6591-6594.

In two recent publications, the same authors use D-glucose as starting material. They synthesized natural gabosines D and E and unnatural gabosine A, which share the same trihydroxycyclohexenone skeleton, in 16%, 17% and 14% overall yield, respectively.[91j] They also reported an interesting work about gabosine K,[90] which structure, as mentioned before, needed to be revised.[7] Thus, they prepared (-)-7-*O*-acetylstreptol, **35**, and (-)-7-*O*-acetyl-1-epistreptol, **39,** and compared their spectral data with those of natural gabosine K (Figure 21). They found that **39** was in accord with the literature values,[6] and therefore, the absolute configuration of (-)-gabosine K was established as 1*R*,2*S*,*3S*,4*R*. However, the specific rotation of natural gabosine K has not been reported. As a consequence, the absolute configuration of the natural product remains unknown.

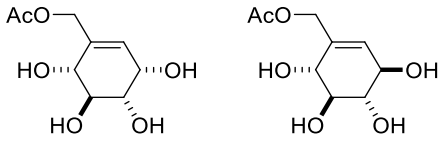


Figure 21. (-)-7-O-acetylstreptol, **35**, and (-)-7-O-acetyl-1-epi-streptol, **39**.

In 2009, Madsen and coworkers disclosed a 8-step synthesis of (-)-gabosine N and a 9-step synthesis of (-)-gabosine A, in 21% and 18% overall yield, respectively. In both cases, D-ribose served as the starting material and the cyclohexene skeleton was created by a zinc-mediated tandem reaction followed by ring closing methathesis.[91a]

Also in 2009, Grée and coworkers reported the synthesis of 4-*epi*-gabosine A and 4-*epi*-gabosine B, in 15% and 24% overall yield respectively, starting from D-glucose by a tandem isomerisation-intramolecular aldol reaction as the key step.[109]

Finally, Gallos *et al.* prepared the unnatural (-)-gabosine E[110] using the previously reported INOC reaction,[91k] and starting from methyl α-D-mannopyranoside.

- *From (-)-Quinic acid*

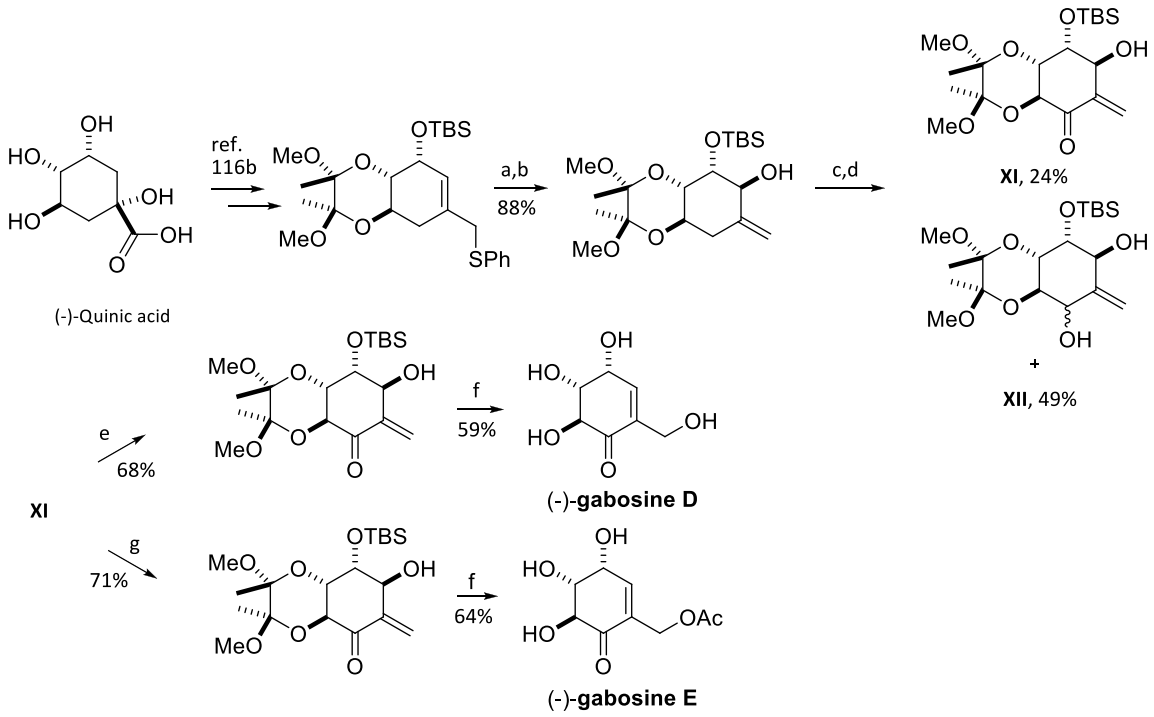
Complementary to carbohydrates, another chiral pool material employed in several successful syntheses of gabosines has been (-)-quinic acid. The pioneer work among this group was the synthesis of (-)-COTC in 13 steps and 13% overall yield reported by Shing and Tang in 1990.[91f,g]

[109] Mac, D. H.; Samineni, R.; Petrignet, J.; Srihari, P.; Chandrasekhar, S.; Yadav, J. S.; Grée, R. *Chem. Commun.* **2009**, 4717-4719.

[110] Stathakis, C. I.; Athanatou, M. N.; Gallos, J. K. *Tetrahedron Lett.* **2009**, *50*, 6916-6918.

In 2000, Ganem and coworkers disclosed new syntheses of (-)-gabosine C and (-)-COTC starting also from a derivative of (-)-quinic acid, by a regioselective epoxide opening under oxidative conditions.[111]

In 2002, Shinada, Ohfune and coworkers published the synthesis of (-)-gabosines A, B, D and E starting from an allyl sulphide derived from (-)-quinic acid (Scheme 36).[112] The key step of their approach was the conversion of the allylic sulphide moiety into the required cyclohexenone. (-)-gabosines D and E, which are the enantiomers of the naturally occurring metabolite, were prepared in 23% and 20% overall yield, respectively. From a common synthetic intermediate, they also prepared natural (-)-gabosine A and B in 13% and 7.6% overall yield, respectively.

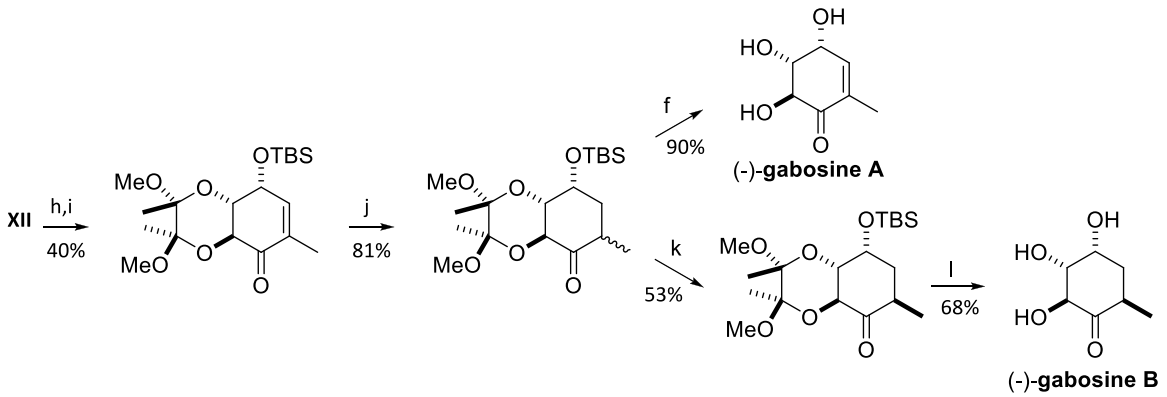


Reagents and conditions: (a) m-CPBA, CH_2Cl_2; (b) $(EtO)_3P$, EtOH; (c) MOMCl, DIPEA, CH_2Cl_2; (d) SeO_2, pyridine-N-oxide, dioxane; (e) NaOH, THF; (f) TFA, H_2O, CH_2Cl_2; (g) AcONa, AcOH.

Scheme 36. Synthesis of (-)-gabosines D, E, A and B by Shinada *et al*.[112]

[111] Huntley, C. F. M.; Wood, H. B.; Ganem, B. *Tetrahedron Lett.* **2000**, *41*, 2031-2034.

[112] (a) Shinada, T.; Fuji, T.; Ohtani, Y.; Yoshida, Y.; Ohfune, Y. *Synlett* **2002**, 1341-1343, (b) Shinada, T.; Yoshida, Y.; Ohfune, Y. *Tetrahedron Lett.* **1998**, *39*, 6027-6028.

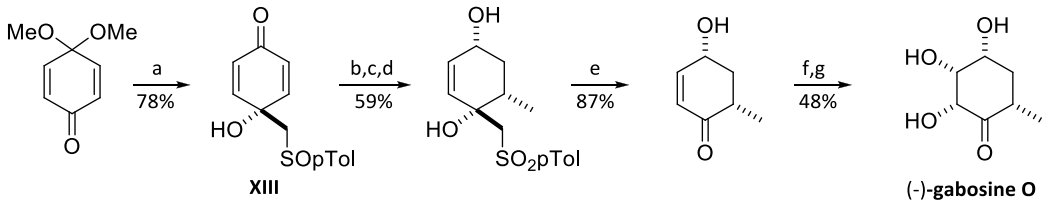


Reagents and conditions: (h) H_2, Pd/C, CH_3OH; (i) DMP, CH_2Cl_2; (j) NaOH, H_2O, THF; (k) i) H_2, Pd/C, CH_3OH, ii) DBU, benzene; (l) TFA, H_2O.

Scheme 36 (continued). Synthesis of (-)-gabosines D, E, A and B by Shinada *et al*.[112]

- *From monoketals of cyclohexan-1,4-diones*

Recently, Carreño and coworkers developed a strategy that involves the use of chiral (*p*-tolylsulphinyl)methyl-*p*-quinols as starting materials for the synthesis of gabosines and other polyoxygenated methylcyclohexanes. Using this methodology they achieved the synthesis of (-)-gabosine O in 6 steps from **XIII** and 26% overall yield (Scheme 37).[91d]



Reagents and conditions: (a) i) (*SS*)-p-TolSOMe, LDA, THF, ii) $(COOH)_2$, H_2O; (b) $AlMe_3$, CH_2Cl_2; (c) *m*-CPBA, CH_2Cl_2; (d) DIBALH, THF; (e) i) TBSOTF, 2,6-lutidine, CH_2Cl_2, ii) Cs_2CO_3, MeCN; (f) Bu_4NF, THF; (g) OsO_4, TMEDA, CH_2Cl_2.

Scheme 37. Synthesis of (-)-gabosine O by Carreño *et al*.[91d]

ii) Anhydrogabosines

Anhydrogabosines, embodying a compact epoxyquinone motif as the core structure, have also motivated a wide diversity of syntheses, either to be used as precursors of natural products or for their range of biological activities and high versatility. Figure 21 summarizes all the published syntheses of anhydrogabosines until the present date.

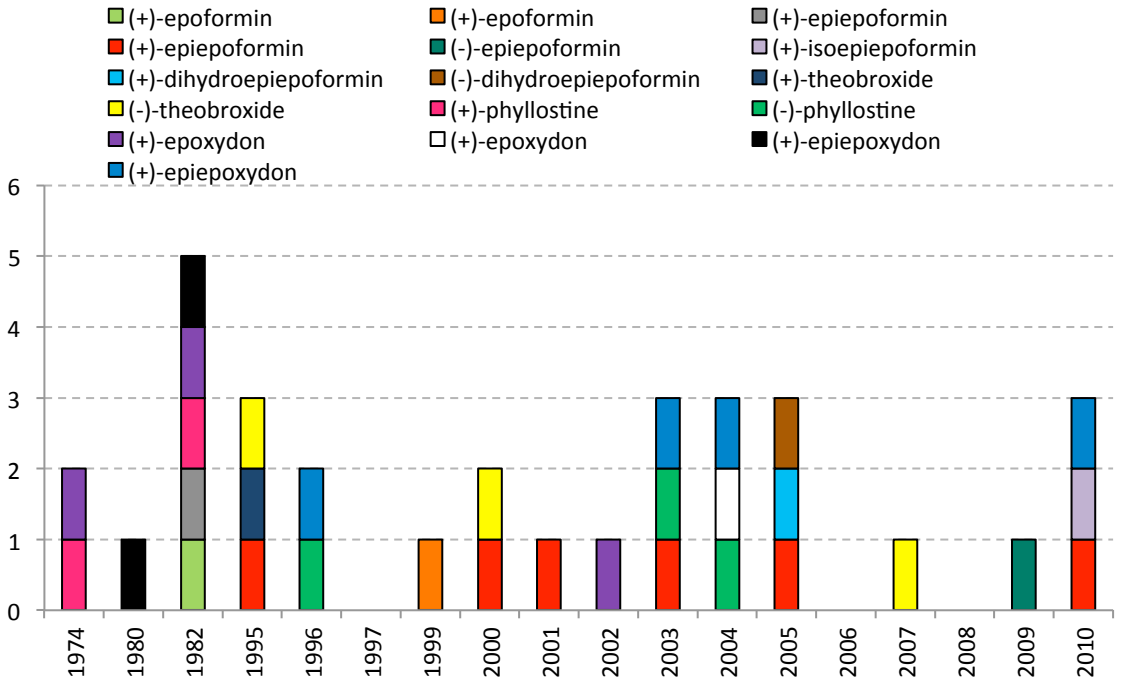
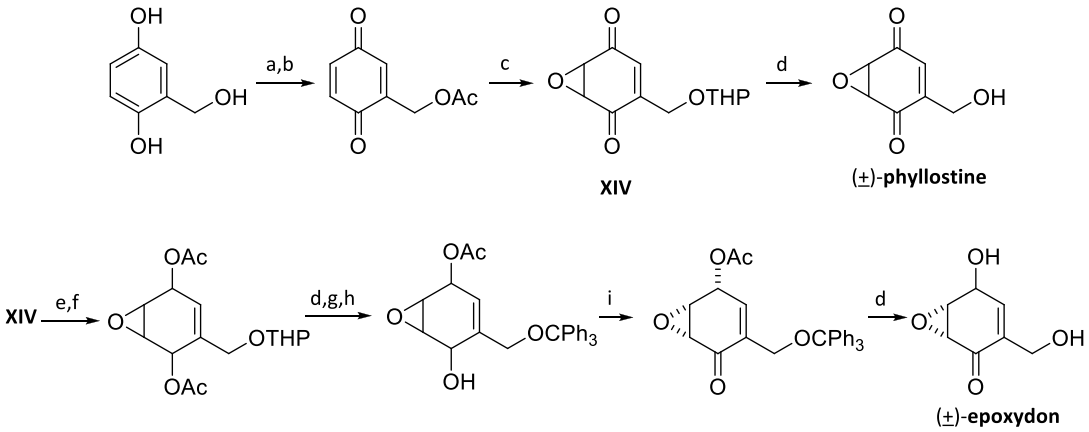


Figure 21. Synthesis of anhydrogabosines.

As in the case of gabosines, the following comments of the published syntheses have been organized according to the strategy used and each strategy will be illustrated with only one scheme.

- *A biomimetic approach to (±)-phyllostine and (±)-epoxydon*

Pioneer syntheses of (±)-phyllostine and (±)-epoxydon were reported in the seventies of past century, by Ichihara and coworkers using gentisyl alcohol as the starting material (Scheme 38).[113]



Reagents and conditions: (a) $PbAcO_4$; (b) DHP, PTSA; (c) $NaBO_3$, AcOH, EtOH/H_2O (ph=8); (d) PTSA; (e) $NaBH_4$; (f) Ac_2O, pyridine; (g) $KHCO_3$; (h) TrCl, pyridine; (i) MnO_2.

Scheme 38. Synthesis of (±)-phyllostine and (±)-epoxydon by Ichihara *et al.*[113]

- *Diels-Alder strategies*

Ichihara and coworkers were also the first to report a strategy based on a Diels-Alder/retro Diels-Alder process, that allowed the preparafion of (±)-phyllostine, (±)-epoxydon, (±)-epiepoxydon, (±)-epoformin and (±)-epiepoformin.[114]

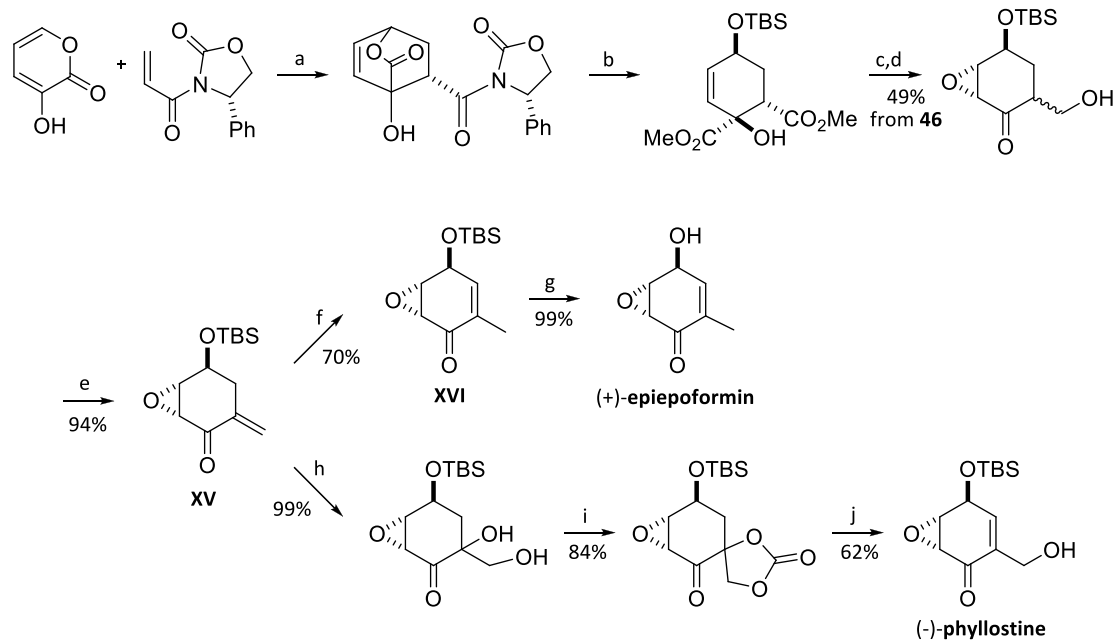
Some years later, Ogasawara and coworkers developed an enantioselective version of Ichihara strategy, accomplishing the synthesis of natural (-)-theobroxide and (+)-epiepoformin, as well as non-natural (+)-theobroxide.[95n] The enantioselectivity found on this synthesis is due to a lipase mediated desymmetritzation of a *meso* intermediate. In a subsequent publication, [115] the resolution of the antipodes was performed by a Rh^{I}-(S)-BINAP-catalyzed asymmetrisation, furnishing natural (+)-epiepoxydon and (-)-phyllostine and verifying unambiguously their absolute configurations.

[113] (a) Ichihara, A.; Oda, K.; Sakamura, S. *Agr. Biol. Chem.* **1971**, *35*, 445-446. (b)Ichihara, A.; Oda, K.; Sakamura, S. *Tetrahedron Lett.* **1972**, *13*, 5105-5108. (c) Ichihara, A.; Oda, K.; Sakamura, S. *Agr. Biol. Chem.* **1974**, *38*, 163-169.

[114] (a) Ichihara, A.; Kimura, R.; Oda, K.; Sakamura, S. *Tetrahedron Lett.* **1976**, 17, 4741-4744. (b) Ichihara, A.; Kimura, R.; Oda, K.; Moriyasu, K.; Sakamura, S. *Agr. Biol. Chem.* **1982**, *46*, 1879-1883.

[115] Kamikubo, T.; Hiroya, K.; Ogasawara, K. *Tetrahedron Lett.* **1996**, *37*, 499-502.

Enone **XVI**, which is the ultimate precursor of (+)-epiepoformin in Ogasawara's synthesis,[95n] was later prepared by Okamura and coworkers through a different pathway involving an asymmetric base-catalyzed Diels-Alder reaction (Scheme 39). (+)-Epiepoformin was obtained in 9 steps and 32% yield.[95q] The main drawback of this synthesis is the isomerisation of the *exo*-olefin **XV**, that could only be accomplished by treatment with Pd/C pre-activated under hydrogen atmosphere. Under these conditions the reaction proceeded slowly to give cyclohexenone **XVI**, but an important yield dispersion (31-71%) was observed. Complementary, in a subsequent publication the same authors prepared (-)-phyllostine in 11 steps and 24% overall yield from the common intermediate **XV**. [116]



Reagents and conditions: (a) cinchonidine, ^{i}PrOH, H_2O; (b) i) MeONa, MeOH, ii) TBSCl, imidazole; (c) i) $LiAlH_4$, THF, ii) $NaIO_4$, THF, H_2O; (d) 30% H_2O_2, Triton B, THF; (e) TsCl, TEA, DMAP; (f) Pd/C; (g) HF, MeCN; (i) $COIm_2$, DMAP, CH_2Cl_2; (j) i) CSA, MeOH, ii) CrO_3, H_2SO_4, acetone.

Scheme 39. Synthesis of (+)-epiepoformin and (-)-phyllostine by Okamura *et al*.[95q,116]

In 2002, Taylor's group described a new synthesis of racemic epiepoxydon in 6.7% overall yield from *p*-benzoquinone. The most significant feature was the use of a Baylis-Hillman reaction to introduce the hydroxymethyl substituent.[117]

[116] Okamura, H.; Shimizu, H.; Yamashita, N.; Iwagawa, T.; Nakatani, M. *Tetrahedron* **2003**, *59*, 10159-10164.

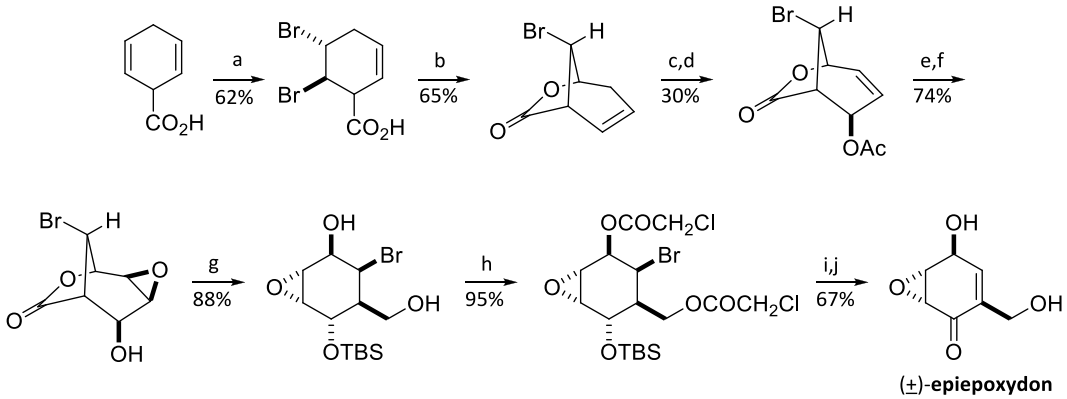
[117] Genski, T.; Taylor, R. J. K. *Tetrahedron Lett.* **2002**, *43*, 3573-3576.

Mehta and coworkers, making use of a lipase-catalyzed acetylation of a Diels-Alder adduct which was previously used by Taylor, accomplished the synthesis of natural (+)-epiepoxydon (17% overall yield), (+)-epoxydon (11% overall yield), and (-)-phyllostine (14% overall yield), all of them in 8 steps.[118]

Recently, Hwang, Ryu and co-workers have described the synthesis of (+)-epiepoxydon and (+)-epiepoformin through a catalytic asymmetric Diels-Alder reaction, in 9 steps, 46% and 48% yield, respectively.[119]

- *From benzene derivatives*

The first synthesis of (±)-epiepoxydon belongs to this category. It was reported in 1980 by Ganem and Chou as part of a study dedicated to the biosynthesis of patulin.[120] (±)-Epiepoxydon was prepared in 6 steps and 52% overall yield (Scheme 40).



Reagents and conditions: (a) Br_2, CH_2Cl_2; (b) $NaHCO_3$ aq; (c) NBS, CCl_4; (d) AcONa, HMPA; (e) 10% H_2SO_4, THF; (f) TFA, CH_2ClCH_2Cl; (g) i) TMSCl, TEA, ii) $LiBH_4$, THF; (h) $(ClCH_2CO)_2O$, pyridine, CH_2Cl_2; (i) CrO_3; (j) $NaHCO_3$, CH_3OH.

Scheme 40. Synthesis of (±)-epiepoxydon by Ganem *et al*.[120]

[118] Mehta, G.; Islam, K. *Tetrahedron Lett.* **2004**, *45*, 7683-7687.

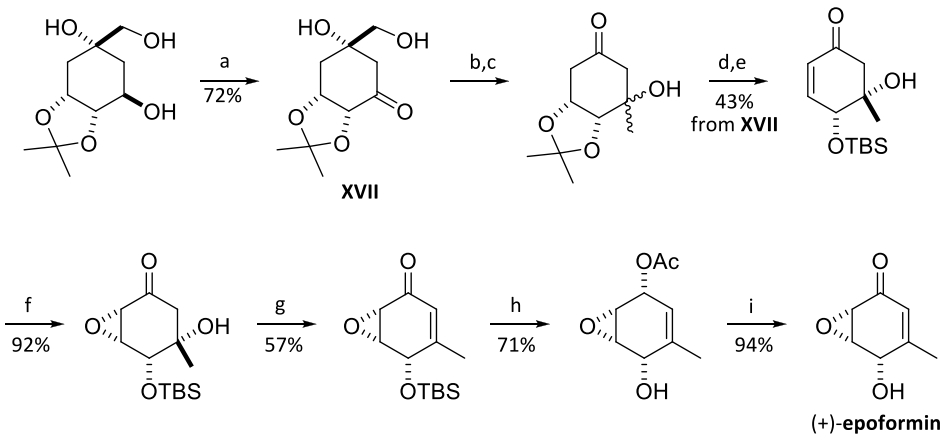
[119] (a) Jin, M. Y.; Hwang, G-S.; Chae, H. I.; Jung, S. H.; Ryu, D. H. *Bull. Korean Chem. Soc.* **2010**, *31*, 727-730. (b) Lee, M. Y.; Kim, K. H.; Jiang, S.; Jung, Y. H.:Sim, J. Y.; Hwang, G-S.; Ryu, D. H. *Tetrahedron Lett.* **2008**, *49*, 1965-1967.

[120] (a) Chou, D. T.-W.; Ganem, B. *J. Am. Chem. Soc.* **1980**, *102*, 7987-7988.

In 2009, Banwell and coworkers disclosed the synthesis of non-natural epiepoformin and other epoxyquinol derivates. (-)-Epiepoformin was prepared in 8 steps and 4.2% overall yield starting from a dihydrocatecol **IX** (Scheme 33) by a Stille cross coupling as the key step.[121] Lately, using an analogous procedure, they prepared (+)-isoepiepoformin in 9 steps and 3.2% overall yield, confirming the structure assigned to this natural product.[95v]

- *From (-)-quinic acid*

During 1999-2000, the group of Maycock and Barros described the syntheses of (+)-epoformin, (+)-epiepoformin and (-)-theobroxide employing (-)-quinic acid as starting material. Firstly, they reported the synthesis of (+)-epoformin, in 14 steps and 12% overall yield (Scheme 41).[95r] One year later, using a Stille coupling reaction as the key step, they also prepared (+)-epiepoformin and (-)-theobroxide in 10 and 11 steps, and 19% and 15% overall yield, respectively.[95s]



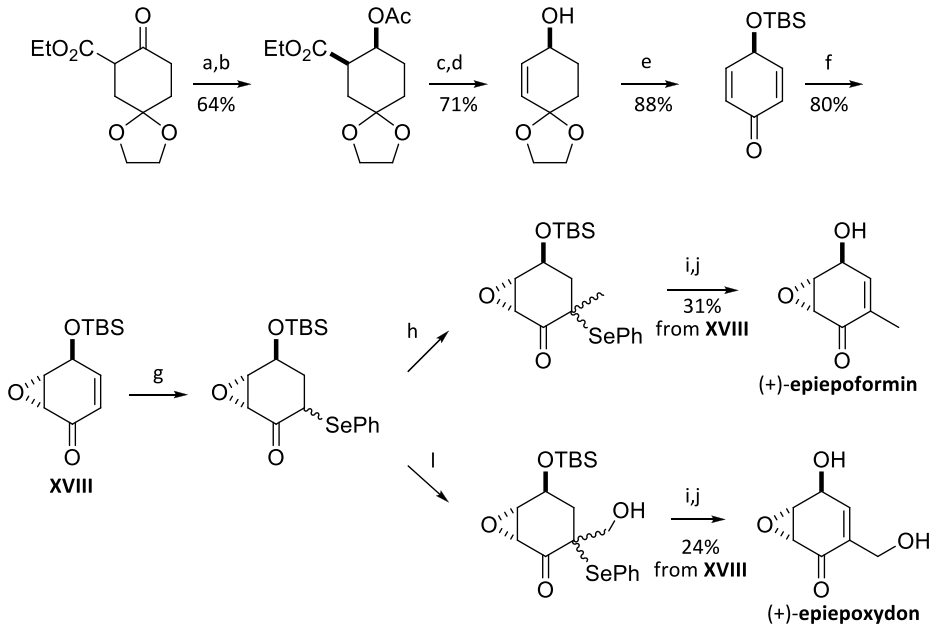
Reagents and conditions: (a) i) BzCl,pyridine, ii) DMP, pyridine, CH_2Cl_2; (b) CH_3CeCl_2, THF; (c) $NaIO_4$, H_2O; (d) NaOH, THF; (e) TBSCl, imidazole, DMF; (f) H_2O_2, Triton B, THF; (g) Tf_2O, DIPEA, DMAP, CH_2Cl_2; (h) i) L-selectride, THF, ii) Ac_2O, DIPEA, DMAP, iii) Bu_4NF, THF; (i) i) DMP, pyridine, CH_2Cl_2, ii) KOH, THF.

Scheme 41. Synthesis of (+)-epoformin by Barros *et al*.[95r]

[121] (a) Pinkerton, D. M.; Banwell, M. G.; Willis, A. C. *Org. Lett.* **2009**, *11*, 4290-4293. (b)

- *From monoketals of cyclohexan-1,4-diones*

In 2003, Tachihara and Kitahara reported the synthesis of a cyclohexanic monoketal derivative which could be interesting as a new chiral building block, and they transformed it into (+)-epiepoformin and (+)-epiepoxydon (Scheme 42). Both syntheses were accomplished in 12 steps and 13% and 10% overall yield, respectively.[62]



Reagents and conditions: (a) Dry baker's yeast; (b) i) LiOH, CH_3OH, H_2O, ii) Ac_2O, pyridine; (c) IBDA, I_2, CCl_4, hv (d) i) DBU, toluene, ii) K_2CO_3, CH_3OH; (e) i) TBSCl, imidazole, DMF, ii) PPTS, acetone, H_2O; (f) H_2O_2, Triton B, THF; (g) i) LiHMDS, TMSCl, ii) PhSeCl, CH_2Cl_2; (h) NaH, CH_3I, THF; (i) 35% H_2O_2, $NaHCO_3$; (l) DBU, HCHO, THF.

Scheme 42. Synthesis of (+)-epiepoformin and (+)-epiepoxydon by Tachihara *et al.*[62]

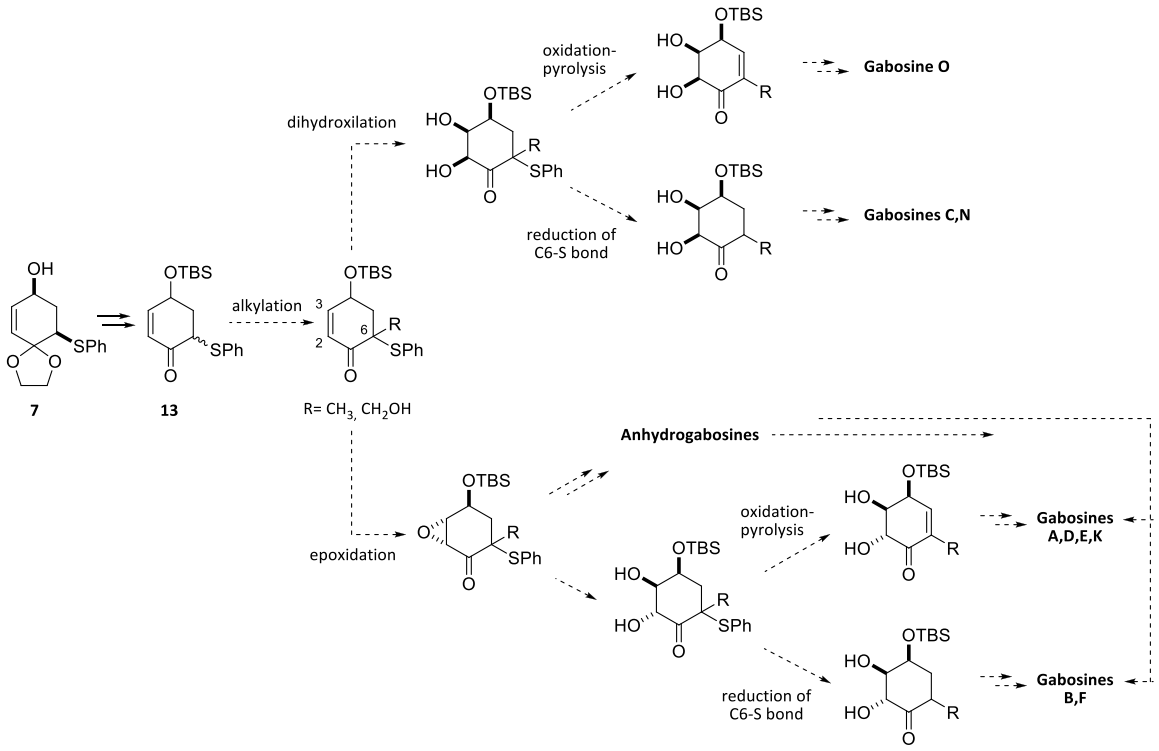
In 2005, Carreño and coworkers using their sulfoxide-mediated methodology,[91d] described the first total synthesis of (+)-dihydroepiepoformin, in 7 steps and 32% overall yield; and the natural (-)-dihydroepiepoformin.[122] Moreover, they reported a new enantioselective approach to (+)-epiepoformin, in 7 steps and 12% overall yield, which was quantitatively converted to (-)-theobroxide by reduction.

In conclusion, several syntheses of gabosines and anhydrogabosines have already been accomplished hitherto. However, there was no suitable synthetic approach to prepare a large number of these compounds from common synthetic intermediates and in any antipodal form. These precedents encouraged us to develop a stereodivergent design for the enantioselective synthesis of this family of compounds.

[122] Carreño, M. C.; Merino, E.; Ribagorda, M.; Somoza, A.; Urbano, A. *Org. Lett.* **2005**, *7*, 1419-1422.

1.2. SYNTHETIC STRATEGY

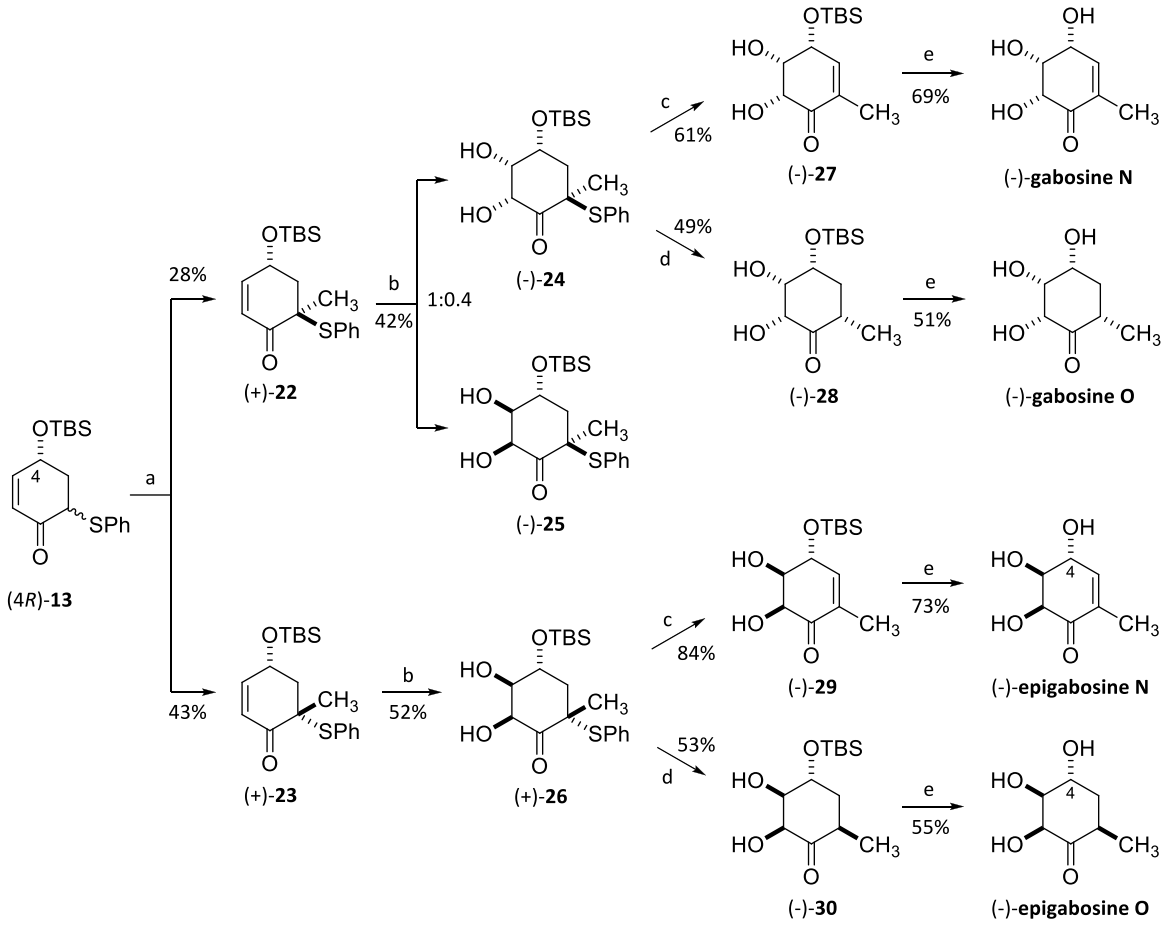
Enone **13**, which could be easily obtained from the previously synthesized alcohol **7**, was our material of choice to undertake a systematic synthesis of gabosines and anhydrogabosines through the strategy depicted in Scheme 43. Our synthetic design involves the following transformations: i) alkylation of the doubly activated C_6 position of **13** to introduce the methyl or hydroxymethyl group; ii) dihydroxylation of the double bond to provide the *cis* α,β-carbonyl glycol unit or epoxidation that can eventually give access to the *trans* glycol; and iii) reduction of the C_6-S bond or oxidation to the sulfoxide followed by pyrolysis to generate the conjugated C-C double bond, depending on the target compound.



Scheme 43. Stereodivergent strategy for the synthesis of gabosines and anhydrogabosines.

In contrast to other previous enantioselective syntheses which started from chiral pool materials, this stereodivergent approach should give access to a large number of gabosine and anhydrogabosine type compounds within both enantiomeric series.

As the first application of our synthetic strategy, Dr. Georgina Marjanet completed the synthesis of (+)- and (-)-gabosine N, (+)- and (-)-gabosine O, as well as their C_4 epimers, (+)- and (-)-epigabosine N and (+)- and (-)-epigabosine O, with satisfactory results (Scheme 44).[33]



Reagents and conditions: (a) NaH, MeI, THF; (b) OsO_4, NMO, acetone, H_2O (8:1); (c) i) *m*-CPBA, $CHCl_3$, ii) $CHCl_3$, Δ; (d) Bu_3Sn, AIBN, toluene; (e)Bu_4NF, THF.

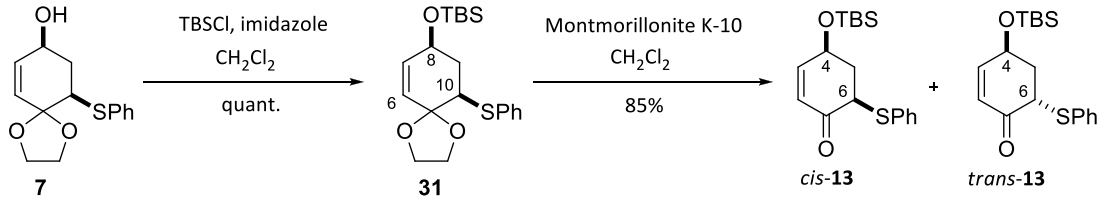
Scheme 44. Synthesis of (-)-gabosine O, (-)-gabosine N and their epimers at C_4 by Figueredo *et al*.[33]

Starting from (4*R*)-**13**, the syntheses of (-)-gabosines N and O and their C_4 epimers were accomplished in only 4 steps and moderate yields. Emphasis should be put on the fact that the previously unknown absolute configuration of natural gabosine O was established as 2*R*,3*R*,4*R*,6*S*. Starting from (4*S*)-**13** and applying the same sequence of reactions, Dr. Georgina Marjanet accomplished the syntheses of the corresponding enantiomeric gabosines and 4-epigabosines.

In the present thesis we decided to explore the methylation-epoxidation pathway. The best conditions for most reactions were established using racemic compounds and then applied to enantiopure substrates.

1.3. SYNTHESIS OF KETONE **13**

The key intermediate **13** had been previously prepared by Dr. Georgina Marjanet in a protection-deprotection sequence from alcohol **7** (Scheme 45). The silylation of the alcohol was accomplished in 83% yield by treatment with TBS-imidazole at room temperature (entry 1, Table 9). With the aim to further improve this protection, some experiments were performed increasing the temperature as well as changing the silylating agent. As we can see in Table 8, increasing the temperature to reflux allowed us to obtain silyl ether **31** in shorter time and better yields. Analogue results were obtained using the TBS-Cl with imidazole.



Scheme 45. Synthesis of *cis*-**13** from **7**.

Table 9. Protection of hydroxyl group of **7**.

Silylating agent	Conditions	Products (yield)
TBS-imidazole	CH_2Cl_2, 25°C, 5 d	**31** (83%)
TBS-imidazole	CH_2Cl_2, reflux, 24 h	**31** (quant.)
TBS-Cl	Imidazole, CH_2Cl_2, reflux, 24 h	**31** (quant.)

In the ^{1}H-NMR spectrum of **31**, it can be observed that both protons H_8 (4.26 ppm) and H_{10} (3.42 ppm) present different coupling constants values with each proton H_9: $^{cis}J_{8,9}$= 5.7 Hz, $^{trans}J_{8,9}$= 9.8 Hz, $^{cis}J_{10,9}$= 3.1 Hz and $^{trans}J_{10,9}$= 14.0 Hz. These values denote a basically pseudoaxial position for H_8 and H_{10}. Consequently, the phenylsulphur and *tert*-butyldimethylsilyl groups present pseudoequatorial orientation.

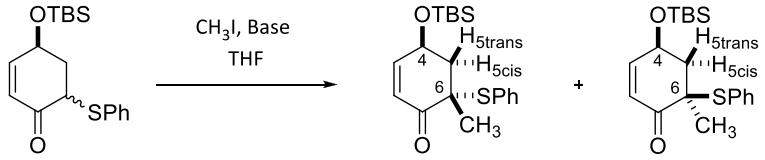
Hydrolysis of the dioxolane ring was carried out using a mild methodology compatible with a wide range of labile groups.[21c] Silyl ether **31** was treated with montmorillonite K-10 in CH_2Cl_2 at 25°C furnishing *cis*-4-*tert*-butyldimethylsilyiloxy-2-cyclohexenone, *cis*-**13**, in 85% yield. The *cis* relative configuration was confirmed by NOE experiments irradiating at H_4 and H_6 frequencies.[49]

The isomer *cis*-**13** initially formed slowly became contaminated with its *trans* diastereomer, due to the configurational instability of the α-carbonyl stereogenic centre. In the ^{1}H-NMR spectrum of *cis*-**13**, the proton at the epimerisable centre (H_6) displayed a signal at 3.78 ppm with $2H_9$ coupling constants of 13.1 and 4.6 Hz, in agreement with a pseudoaxial orientation. For *trans*-**13**, the signal at 3.97 ppm corresponding to H_6 showed two similar vicinal coupling constants with the two H_9 of around 4.4 Hz and a long distance coupling of 1.0 Hz with H_2 (W), in agreement with its pseudoequatorial location.

1.4. METHYLATION AND EPOXIDATION STUDIES

According to the synthetic plan, the following stages required the introduction of α-methyl substituent and an epoxidation to accomplish the appropiate oxidation degree.

1.4.1. Methylation



13 **22** 43% **23** 48%

Scheme 46. α-Methylation of cyclohexenone **13.**

Methylation of ketone **13** (Scheme 46) was accomplished by reaction of its enolate with methyl iodide in THF. This transformation was attempted using three different bases as a means of modulating the diastereofacial selectivity of the reaction. Considering that the counterion may play a pivotal role in the diastereoselectivity of the reaction, the three tested bases were: K^{t}BuO, NaH and ^{t}BuLi (Table 10).

Table 10. Methylation of ketone **13**.

Base	Equivalents	Yield	Products
K^{t}BuO	1.1	98%	**22:23** (1:2.3)
NaH	1.5	93%	**22:23** (1:1.1)
^{t}BuLi	1.3	76%	**22:23** (1:1.6)

Methylation using K^{t}BuO furnished a *ca.* 1:2.3 mixture of the two epimers **22** and **23** in high yield. Similar amounts (1:1.1, **22**:**23**) of the two methylated isomers were obtained using NaH. Contrary to what it was expected, ^{t}BuLi afforded a mixture of **22** and **23** in *ca.* 1:1.6; again favouring epimer **23**. Therefore, it can be deduced that there is no correlation between the counterion size and the ratio of products formed.

The two diastereomers were separated by column chromatography and identified by their spectroscopic data an elemental analysis.[123] Although both **22** and **23** showed new and similar methyl signals at 1.33 and 1.40 ppm respectively in the ^{1}H-NMR spectra, the corresponding signals of the two protons H_5 can be clearly differentiated. In the spectrum of **22**, H_{5cis} (δ 2.41) appears as a ddd with coupling constants of 13.7, 5.3 and 2.1 Hz, whereas H_{trans} (δ 2.19) appears as dd, showing values of 13.7 and 10.0 Hz. In the case of **23**, both H_5 appear at δ 2.23 as a multiplet. The relative configuration of the methylated compounds had been previously determined by NOE experiments.[49]

Within the enantioselective pathway, methylation of (4*S*)-**13** using sodium hydride as the base furnished a 1:1.1 mixture of the two epimers (4*S*,6*S*)-**22** ($[\alpha]_D^{20}$ = -127 (*c* 1.0, $CHCl_3$), lit.[33] $[\alpha]_D^{20}$ = -127 (*c* 1.0, $CHCl_3$)) and (4*S*,6*R*)-**23** ($[\alpha]_D^{20}$ = -20 (*c* 0.3, $CHCl_3$)), lit.[33] $[\alpha]_D^{20}$ = -20 (*c* 0.3, $CHCl_3$)). Analogously, starting from (4*R*)-**13** the enantiomers (4*R*,6*R*)-**22** ($[\alpha]_D^{20}$ = +127 (*c* 1.03, $CHCl_3$), lit.[33] $[\alpha]_D^{20}$ = +127 (*c* 1.0, $CHCl_3$)) and (4*R*,6*S*)-**23** ($[\alpha]_D^{20}$ = +19 (*c* 0.84, $CHCl_3$), lit.[33] $[\alpha]_D^{20}$ = +19 (*c* 0.8, $CHCl_3$)) were isolated.

1.4.2. Epoxidation

Next, the epoxidation reaction of the double bond of the methyl derivatives **22** and **23** was assayed. The targets were anhydrogabosines, as well as gabosines with a *trans* α,β-carbonyl-glycol unit which could be obtained after the subsequent hydrolysis (see Scheme 43).

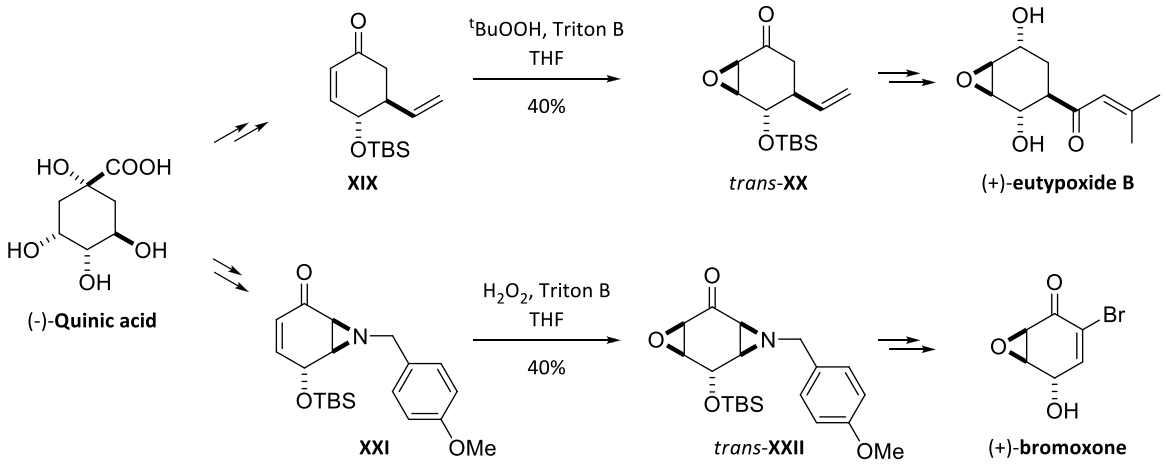
The epoxidation of enones **22** and **23** was assayed by reaction with either hydrogen peroxide (method A) or potassium *tert*-butylhydroperoxide (method B) and Triton B in THF. Both methodologies had been previously applied by Barros, Maycock and coworkers in the total synthesis of the natural products (+)-eutypoxide[124a] and (+)-bromoxone,[124b] where the epoxidation occurred with moderate yield (Scheme 47). In this precedent work, treatment of **XIX** with hydrogen peroxide provided a mixture of the *cis* and *trans* epoxides, whereas the exposure of the same substrate to ^{t}BuOOH afforded exclusively *trans*-**XX**.[125] The authors explain that the selective formation of *trans*-**XX** is in accordance with a steric congestion between the adjacent TBS ether group of **XIX** and the bulkier epoxidizing agent. Hence, the use of ^{t}BuOOH can induce better diastereofacial selectivity than H_2O_2 in epoxidation reactions.

[123] Here and aforhead H_{5cis} and H_{5trans} are referred to the relative geometry respect the H_4.

[124] (a) Barros, M. T.; Maycock, C. D.; Ventura, M. R. *J. Org. Chem.* **1997**, *62*, 3984-3988. (b) Barros, M. T.; Matias, P. M.; Maycock, C.; Ventura, R. *Org. Lett.* **2003**, *5*, 4321-4323.

[125] For Barros and Maycock epoxides *cis* and *trans* is referred to the relative geometry respect the OTBS group.

However, in their subsequent publication in which the synthesis of (+)-bromoxone was described, the epoxidation step using H_2O_2 gave exclusively epoxide *trans*-**XXII**. In this case, they conclude that the aziridine group directs the steroselectivity of the process.

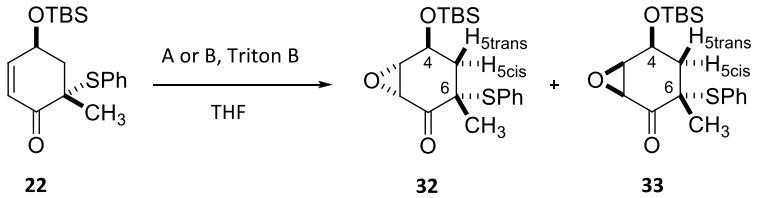


Scheme 47. Synthesis of (+)-eutypoxide and (+)-bromoxone by Barros *et al.*[124]

Considering these precedents, both oxidizing agents were assayed on enones **22** and **23**.

1.4.2.1. Synthesis of epoxides **32** and **33**

In the quest for optimal epoxidation conditions, ketone **22** was exposed to different amounts of both epoxidizing agents, H_2O_2 (method A) and ^{t}BuOOH (method B) (Scheme 48, Table 11).



Scheme 48. Epoxidation of **22**.

Table 11. Epoxidation of enone **22.**

Method	Epoxidazing agent	Equivalents	Yield	Products
A	**H_2O_2**	7.6	71%	**32:33** (1:5)
A	**H_2O_2**	6.5	80%	**32:33** (1:5)
A	**H_2O_2**	3.5	42%	**22:32:33** (4.7:1:5)
B	**^{t}BuOOH**	5	94%	**32**
B	**^{t}BuOOH**	3.5	96%	**32**

Using the first reagent (method A), the epoxidation of enone **22** delivered a mixture of the oxiranes **32** and **33** in a 1:5 ratio and 80% overall yield. Similar results were obtained when the amount of H_2O_2 was decreased from 7.6 to 6.5 equivalents, whereas part of starting material was recovered unaltered when 3.5 equivalents were used. This stereoselectivity was in good agreement with previous dihydroxylation reactions carried out in our research group (Scheme 44).[49] In these reactions the oxidant OsO_4/NMO approached the enone mainly to the opposite face where the bulky phenylsulphenyl group was allocated.

When epoxidation was performed employing the more sterically demanding oxidant (method B), only epoxide **32** was obtained in 96% yield, in which the epoxide moiety and the phenylsulphenyl group shared the same face. As we can see in Table 11, equivalent results were obtained reducing the equivalents of ^tBuOOH from 5 to 3.5. This exclusive formation of **32** involves a complete reversion of the facial selectivity. This switch evidences that the stereoselectivity of the former processes (epoxidation with H_2O_2/Triton B and dihydroxylation with OsO_4/NMO) was not merely governed by steric factors.

An analysis of our results along with those of Barros' group shows that the stereoselectivity in such kind of processes is deeply dependent of the particular substitution pattern of each substrate as well as the nature of the oxidant. Both factors are essential to determine the diastereoafacial differentiation. In any case, the inversion of facial selectivity by changing the oxidazing agent from H_2O_2 to ^tBuOOH was very interesting from a synthetic point of view. In particular, it was very convenient for our stereodivergent synthetic design.

The configuration assignment of diastereomer **32** was performed by ^1H-NMR including NOESY experiments (Figure 22). In the ^1H-NMR spectrum a new signal assigned to the oxiranic protons (H_2 and H_3) appeared as a narrow multiplet at δ 3.55. H_4 displayed a signal at δ 4.53 as a false quadruplet with three vicinal coupling constants (H_3 and $2H_5$) around 2.8 Hz, denoting that H_4 presents a pseudoequatorial orientation. One of the H_5 protons (δ 2.30) had NOE with the methyl group and thus, it should be assigned as H_{5trans}. Consequently, the H_5 signal at δ 2.01, which had important NOE with H_4, should be assigned to H_{5cis}. The ^1H-NMR spectrum shows a coupling constant of 1.0 Hz between H_{5trans} and H_3, denoting their *cis* relative position. These facts are in accordance with a *trans* relative configuration between the bulky OTBS group and the epoxide moiety of **32**.

Proton	δ and coupling constants
H_{5trans}	2.01 (ddd, $J_{5trans,5cis}$= 14.6 Hz, $J_{5trans,4}$= 4.0 Hz, $J_{5trans,3}$= 1.0 Hz)
H_4	4.53 (q, $J_{4,3}$≈$J_{4,5cis}$≈$J_{4,5trans}$≈ 2.8Hz)

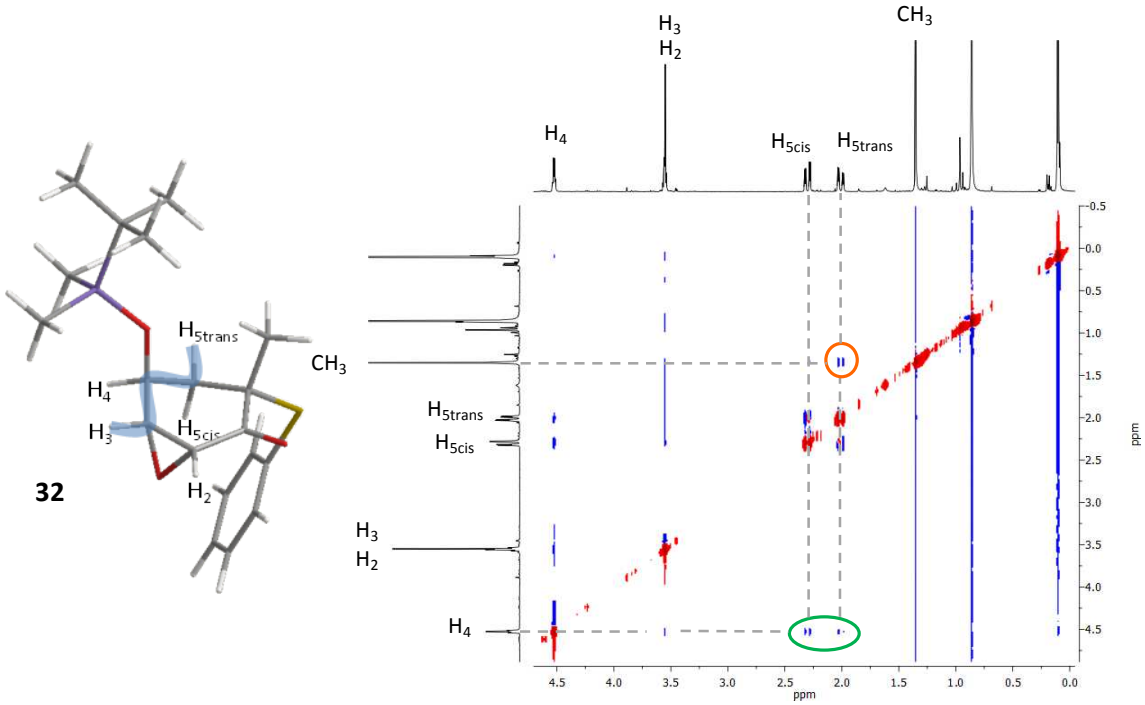
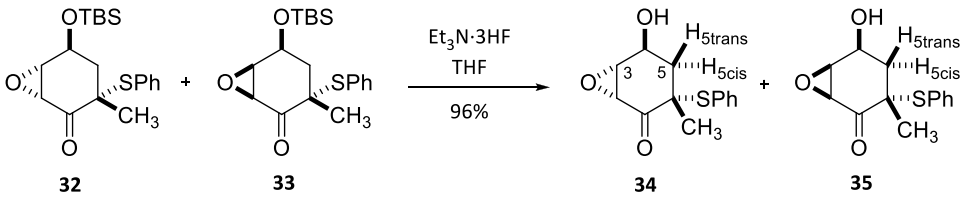


Figure 22. NOESY spectrum (400 MHz, $CDCl_3$) of **32**.

Within the enantioselective pathway, epoxidation of (4*S*,6*S*)-**22** using H_2O_2 furnished an inseparable 5:1 mixture of (2*R*,3*S*,4*S*,6*S*)-**32** and (2*S*,3*R*,4*S*,6*S*)-**33** in 78% total yield. The parallel reaction with ^{t}BuOOH afforded exclusively (2*R*,3*S*,4*S*,6*S*)-**32** ($[\alpha]_D^{20}$= +6.7 (*c* 0.79, $CHCl_3$)) in 96% yield. Analogous reaction with enantiomer (4*R*,6*R*)-**22** was carried out with H_2O_2 providing a 5:1 mixture of (*2S*,*3R*,*4R*,*6R*)-**32** and (2*R*,3*S*,*4R*,*6R*)-**33** in 80% yield.

For synthetic purposes, we judged convenient to isolate epoxide **33**, which is the major product of the oxidation of **22** with hydrogen peroxide and, relative to C_4, it presents a configuration of the oxirane stereocentres opposite to that of **32**; which is really interesting to achieve some particular natural products. As **32** and **33** exhibited identical polarities, their separation by column chromatography using a wide variety of eluents was unsuccessful. This fact made us to attempt the separation after silyl ether cleavage (Scheme 49).



Scheme 49. Synthesis of the desilylated epoxides **34** and **35**.

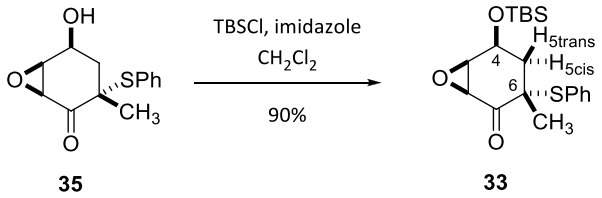
To this end, the mixture of epoxides **32** and **33** was treated with $Et_3N{\cdot}3HF$ in THF at room temperature, producing a 1:5 mixture of alcohols **34** and **35**. These alcohols exhibited slightly different polarities, so after several column chromatography operations pure **35** could be isolated (62% yield), but the spectroscopic date of **34** were recorded from an enriched fraction.

In the ^{1}H-NMR spectrum of the major isomer **35**, the signal corresponding to H_{5cis} (2.20 ppm) appears as a ddd with coupling constants of 13.7, 5.8 and 1.1 Hz, the last one with proton H_3 (3.73 ppm) evidencing the *cis* relative disposition between these two protons. H_4 displayed a signal at 4.59 ppm with a coupling constant of 10.3 Hz with H_{5trans} (2.08 ppm), in agreement with a pseudoaxial orientation of both protons. These aspects are in accordance with a *cis* relative configuration among H_4, H_{5cis} and H_3, so, a pseudoequatorial orientation of the hydroxyl group, and confirm the *cis* relative configuration between the hydroxyl group and the epoxide moiety.

The ^{1}H-NMR sprectrum of **34** shows clear similarities with that of the corresponding silyl ether **32**, the main difference is that in the free alcohol **34** the oxiranic protons H_2 (3.57 ppm) and H_3 (3.67 ppm) can be differentiated. As previously mentioned for **34**, H_{5trans} (2.09 ppm) presents a small coupling constant (1.2 Hz) with H_3 denoting the *cis* relative configuration between them. The pseudoequatorial position of H_4 is evidenced by an identical coupling constant of 3.2 Hz with H_3 and the two protons H_5. This data are in agreement with the *trans* relative configuration between the epoxide moiety and the hydroxyl group.

Within the optically active series hydrolysis of silyl ethers (2*R*,3*S*,4*S*,6*S*)-**32** and (2*S*,3*R*,4*S*,6*S*)-**33** afforded alcohols (2*R*,3*R*,4*S*,6*S*)-**34** and (2*S*,3*S*,4*S*,6*S*)-**35** ($[\alpha]_D^{20}$= -32 (*c* 1.25, $CHCl_3$)) in 87% yield. The analogous reaction starting from the enantiomeric mixture (2*S*,3*R*,4*R*,6*R*)-**32** and (2*R*,3*S*,4*R*,6*R*)-**33** gave (2*S*,3*S*,4*R*,6*R*)-**34** and (2*R*,3*R*,4*R*,6*R*)-**35** ($[\alpha]_D^{20}$= +30 (*c* 0.75, $CHCl_3$)) in 85% yield.

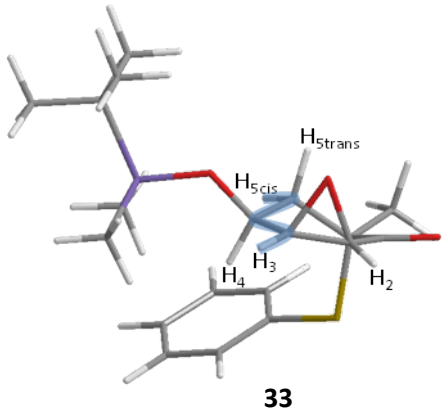
Finally, alcohol **35** was reverted to the corresponding silylether **33** (Scheme 50).[126] This reaction was carried out using *tert*-butyldimethylsilyl chloride and imidazole in CH_2Cl_2 at the reflux temperature, providing **33** as a white solid in 90% yield.



35 **33**

Scheme 50. Synthesis of the epoxide **33**.

The configuration of **33** (Figure 23) was confirmed by ^{1}H-NMR. H_4 displayed a ddd signal at 4.60 ppm with a characteristic coupling constant of 10.8 Hz with H_{5trans} (2.20 ppm), evidencing the pseudoaxial orientation of both protons. In turn, H_{5cis} (1.99 ppm) showed a coupling constant of 1.1 Hz with H_3 (3.57 ppm), denoting their *cis* relative configuration. By this way, we could confirm the *cis* configuration between the epoxide moiety and the OTBS group.



33

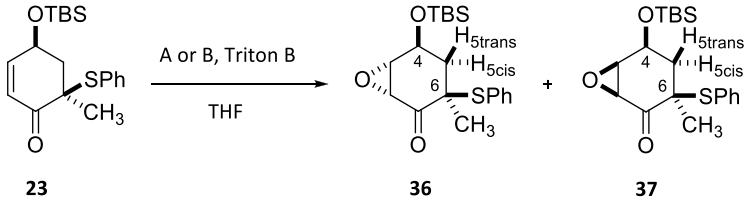
Figure 23. Epoxide **33**.

Within the enantioselective pathway silylation of (2*S*,3*S*,4*S*,6*S*)-**35** afforded (2*S*,3*R*,4*S*,6*S*)-**33** ($[\alpha]_D^{20}$= +53 (*c* 0.73, $CHCl_3$)), whereas starting from (2*R*,3*R*,4*R*,6*R*)-**35** the silyl ether (2*R*,3*S*,4*R*,6*R*)-**33** ($[\alpha]_D^{20}$= -54 (*c* 0.62, $CHCl_3$)) was prepared.

[126] The protection of the hydroxyl group proved necessary for the next synthetic steps.

1.4.2.2. Synthesis of epoxides **36** and **37**

Once the best reaction conditions were established for the metlyl derivative **22**, the same procedures were subsequently applied to its epimer at C_6, the enone **23** (Scheme 51).



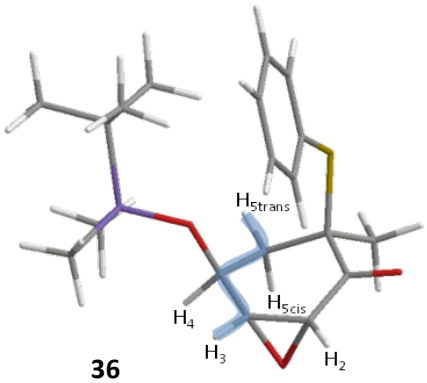
23 **36** **37**

Scheme 51. Synthesis of epoxides **36** and **37**.

Epoxidation of enone **23** using H_2O_2 (method A) furnished a 5:1 mixture of oxiranes **36** and **37** in 91% yield, whereas employing ^{t}BuOOH (method B) epoxide **36** was exclusively formed in 98% yield. In contrast with the former epoxidation of the epimer **22**, in this case both H_2O_2 and ^{t}BuOOH delivered epoxide **36** as the major product. Since substrate **23** present both the OTBS and SPh groups on the same side of the ring, electronic and steric effects caused by them apparently point to the same direction. It seems that, whatever is the influence of the OTBS and the PhS groups, this is a case of "matching effects" whereas the previous oxidation of the epimeric substrate **22** must be a mismatching combination.

In the ^{1}H-NMR spectrum of **36** the signals of the oxiranic protons appear very close, with H_2 (3.52 ppm) showing a dd and H_3 (3.49 ppm) a ddd. The signals of both H_5 protons display coupling with H_4, the signal at 2.25 ppm presents a $J_{5,4}$= 4.1 Hz and the other one at 2.09 ppm has a $J_{5,4}$= 2.0 Hz (Figure 21). This fact is in agreement with a pseudoequatorial location of H_4. Specifically, the H_5 which displays a signal at 2.09 ppm has also a coupling contant of 1.2 Hz with H_3, denoting the *cis* relative configuration between them and thus, it should be assigned as H_{5trans}. Consequently, the signal at 2.25 ppm should be assigned at H_{5cis}. The described situation is only possible if the epoxide is in a *trans* relative configuration with the TBS group.

Proton	δ and coupling constants
H_{5cis}	2.25 (dd, $J_{5cis,5trans}$= 15.3 Hz, $J_{5cis,4}$= 4.1 Hz)
H_{5trans}	2.09 (ddd, $J_{5trans,5cis}$= 15.3 Hz, $J_{5trans,4}$= 2.0 Hz, $J_{5trans,3}$= 1.2 Hz)



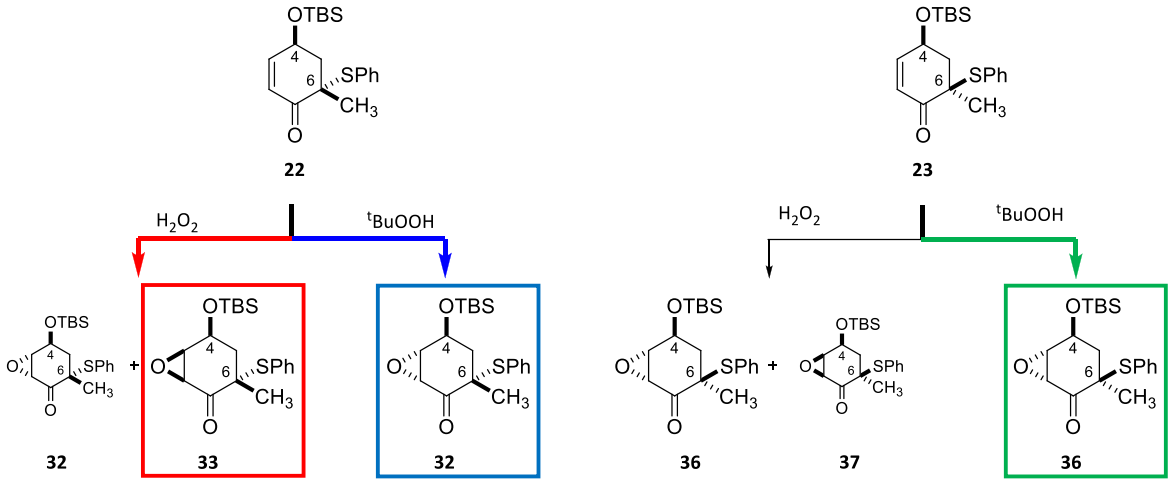
36

Figure 24. Epoxide **36**.

The spectroscopic data of **37** were extracted from an enriched fraction obtained after repeated column chromatographic operations. In its ^{1}H-NMR spectrum, the signals of the oxiranic protons emerge at 3.53 ppm (H_3) and 3.46 ppm (H_2). The proton H_{5cis} (1.83 ppm) displays a coupling constant of 1.4 Hz with H_3, showing the *cis* relative configuration between them. The axial position of H_4 (4.22 ppm) is confirmed by a coupling constant of 11.3 Hz with H_{5trans} (2.36 ppm). This fact is in accordance with the *cis* relative configuration between H_3, H_4 and H_{5cis} as in epoxide **33,** previously analyzed.

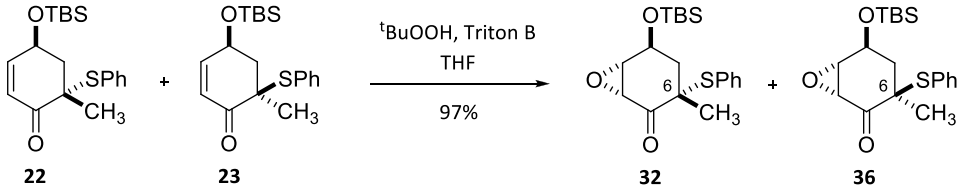
Within the optically active series, the epoxidation of (4*S*,6*R*)-**23** with ^{t}BuOOH furnished (2*R*,3*S*,4*S*,6*R*)-**36** ($[\alpha]_D^{20}$= +55 (*c* 0.84, $CHCl_3$)) in 98% yield.

To sum up, the combination of both epoxidation methodologies allowed access to three epoxide intermediates: **33**, **36** and **37** (Scheme 52). These three epoxides will be later used as the substrates on the oxidation/pyrolysis, and C_6-S bond reduction pathways, aiming towards the synthesis of gabosines and anhydrogabosines.



Scheme 52. Epoxidation of **22** and **23**.

It is important to highlight that using method B (^{t}BuOOH) epoxides **32** and **36** were exclusively obtained from **22** and **23**, respectively. These two epoxides differ only in the configuration of the stereogenic centre C_6, which is not important along the oxidation/pyrolysis pathway since the stereochemical information at this centre will be lost later on (see Scheme 43). For this reason, the chromatographic separation of enones **22** and **23** can be eluded simplifying the overall process. Thus, the epoxidation of a mixture of **22** and **23** according to method B (Scheme 53) provided a clean material, which after purification by flash chromatography furnished a mixture of epoxides **32** and **36** as a white solid in 97% yield.



Scheme 53. Epoxidation of the mixture of enones **22** and **23**.

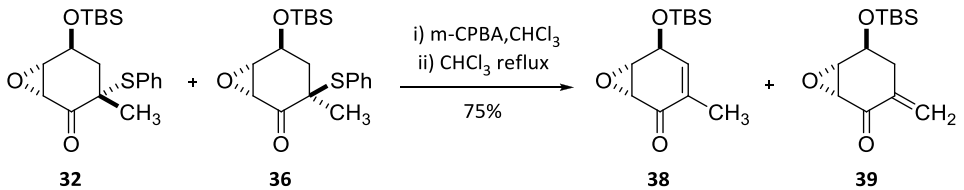
Within the enantioselective pathway, a mixture of (4*S*,6*S*)-**22** and (4*S*,6*R*)-**23** provided epoxides (2*R*,3*S*,4*S*,6*S*)-**32** and (2*R*,3*S*,4*S*,6*R*)-**36** in quantitative yield. Analogous results were achieved starting from (4*R*,*6R*)-**22** and (4*R*,6*S*)-**23** to obtain (2*S*,3*R*,4*R*,6*R*)-**32** and (2*S*,3*R*,4*R*,6*S*)-**36**.

1.5. GENERATION OF THE C_5-C_6 DOUBLE BOND: TOTAL SYNTHESIS OF EPIEPOFORMIN AND EPOFORMIN

Since there is a wide group of gabosines and anhydrogabosines exhibiting an α,β-cyclohexenone structure, Dr. Georgina Marjanet studied the generation of the C_5-C_6 double bond on different dihydroxylated substrates. This work allowed access to both antipodes of gabosine N.[33] In the present work, this methodology has been extended and applied to the intermediate epoxides newly synthesized.

- Synthesis of epiepoformin

Both epimeric epoxides **32** and **36** are suitable precursors of epiepoformin. Thus, an oxidation/pyrolysis protocol should provide access to the same olefin. Nevertheless, first trials were carried out with **32** and **36** separately, treating each one with *m*-CPBA in chloroform at 0 ºC and then heating at the reflux temperature. Under these conditions, an inseparable mixture of the endo- and exocyclic olefins **38**[91d,119a] and **39**[95q,116] was obtained in the same 5.5:1 ratio for both substrates and good overall yield. As it was expected, the same methodology applied to a mixture of **32** and **36** delivered a 5.5:1 mixture of **38** and **39** in 75% yield (Scheme 54).



Scheme 54. Oxidation/pyrolysis of a mixture of epoxides **32** and **36**.

Figure 25 shows the ^{1}H-NMR spectrum of the mixture of olefins **38** and **39**. It is noticeable that there are three signals of olefinic protons. The upfield signal at 6.28 ppm belongs to proton H_5 of the endocyclic olefin **38** whereas the minor signals at 6.22 ppm and 5.28 ppm belong to protons H_7 of the exocyclic olefin **39**. Other characteristic signals are the methylenic protons H_5 (δ 2.82 and 2.43) of **39** as well as the downfield singlet (δ 1.82) corresponding to the methyl group of **38**.

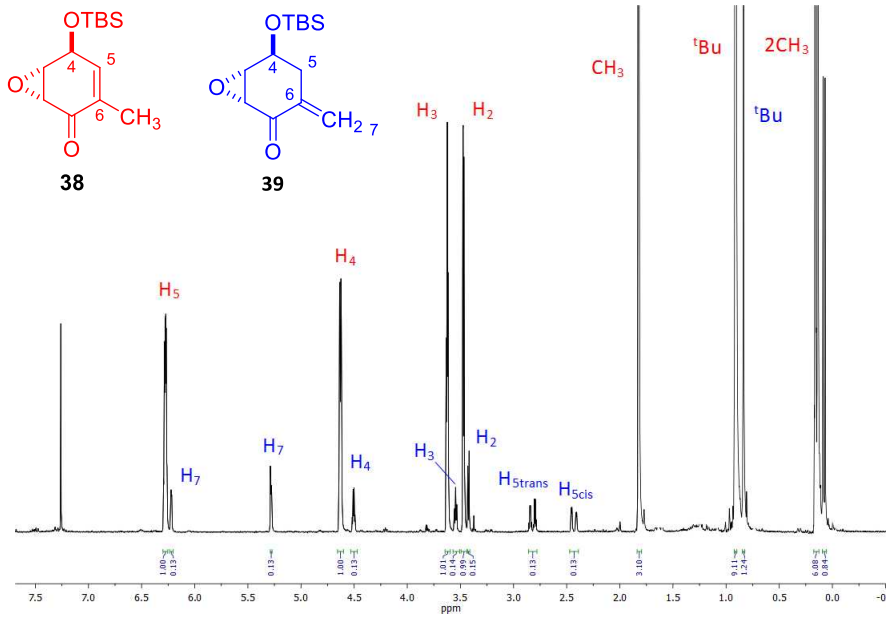
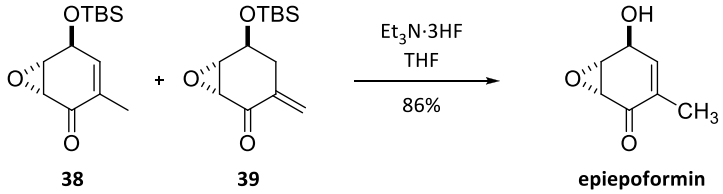


Figure 25. ^{1}H-NMR spectrum (360 MHz, $CDCl_3$) of the mixture of olefins **38** and **39**.

Within the enantioselective pathway, the oxidation/pyrolysis of the mixture (2*R*,3*S*,4*S*,6*S*)-**32** and (2*R*,3*S*,4*S*,6*R*)-**36** delivered a 5.5:1 mixture of the olefins (2*R*,3*S*,4*S*)-**38** and (2*R*,3*S*,4*S*)-**39** in 88% yield.

As it was previously discussed, the isomerization of the exocyclic olefin **39** was not a trivial step. According to Okamura and co-workers,[95q,116] this reaction can be accomplished by treatment with Pd/C preactivated under hydrogen atmosphere. However, small changes in the reaction conditions led to an important yield dispersion (31-71%), due to the high sensitivity of the reaction. Thus, we decided to try the isomerisation using trifluoroacetic acid in a catalytic amount in $CHCl_3$, which afforded satisfactory results in dihydroxylated compounds.[49] Unfortunately, neither at room temperature nor at reflux, the isomerisation of epoxide **39** occured. At this point, several assays were performed changing the reaction conditions trying to minimize the exocyclic olefin formation, such as decreasing the temperature or adding *m*-CPBA dropwise. Nevertheless, the same ratio of olefins was obtained in all trials. Fortunately, this transformation later revealed unnecessary, because treatment of the mixture of epoxides **38** and

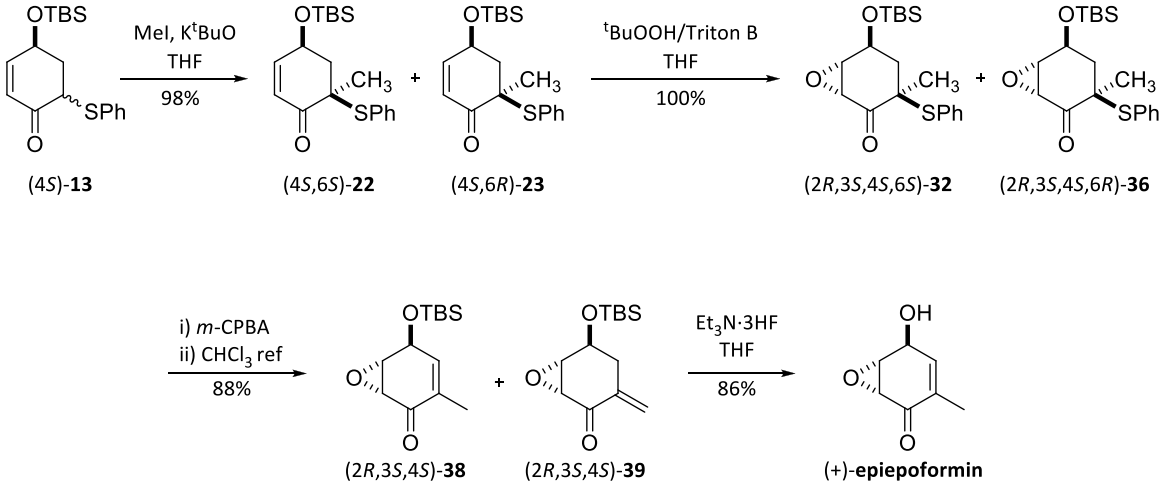
39 with the complex $Et_3N{\cdot}3HF$ furnished epiepoformin as the sole product in 86% isolated yield (Scheme 55).



Scheme 55. Synthesis of epiepoformin.

Within the optically active series, deprotection of the mixture (2*R*,3*S*,4*S*)-**38** and (2*R*,3*S*,4*S*)-**39** delivered natural (+)-epiepoformin ($[\alpha]_D^{20}$ = +315 (*c* 1.1, EtOH))[127] in 86% yield.[128]

It was important to remark that, in view of these results, a straightforward and highly efficient synthesis of epiepoformin was completed in four steps from **13**: i) methylation to **22**+**23**; ii) epoxidation to **32**+**36**; iii) oxidation/pyrolysis to **38**+**39**; and iv) deprotection, without performing any chromatographic separation, in 74% total yield (Scheme 56).



Scheme 56. Synthesis of (+)-epiepoformin from **13**.[128]

The ^{1}H-NMR, ^{13}C-NMR and COSY spectra of epiepoformin were registered. The COSY spectrum allowed us to assign the ^{1}H-NMR signals as depicted in Figure 26.

[127] The values of specific rotation described in the literature for epiepoformin oscillate between $[\alpha]_D$= +221 (*c* 0.83, EtOH)[93] and $[\alpha]_D$= +320 (*c* 0.06, EtOH)[63].

[128] Toribio, G.; Marjanet, G.; Alibés, R.; de March, P.; Font, J.; Bayon, P.; Figueredo, M. *Eur. J. Org. Chem.* **2011**, 1534-1543.

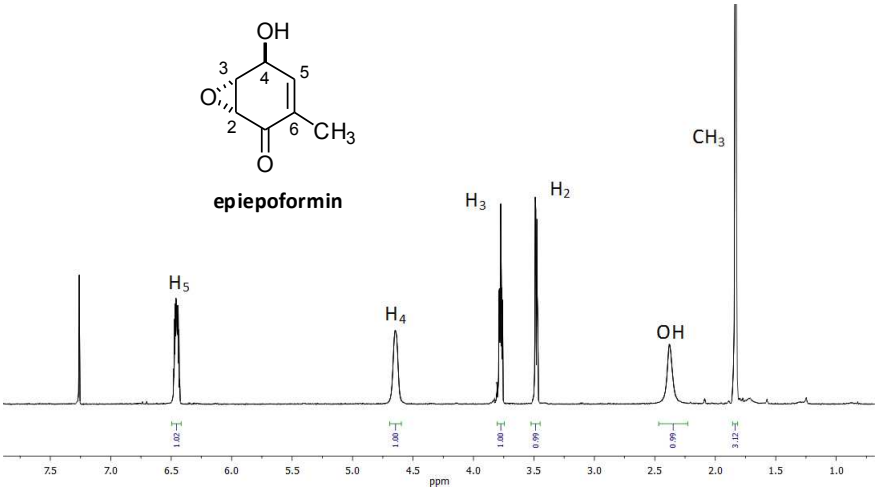


Figure 26. ^{1}H-NMR spectrum (250 MHz, $CDCl_3$) of epiepoformin.

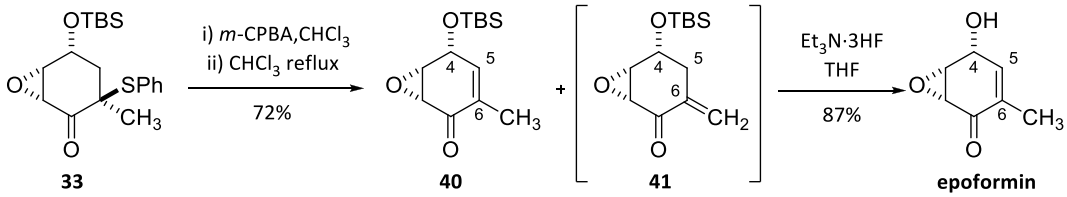
	Epiepoformin
H_5	**6.45 ppm** (ddq, $J_{5,4}$=5.5 Hz, $J_{5,3}$=2.6 Hz, $J_{5,CH3}$=1.3 Hz)
H_4	**4.65 ppm** (bs)
H_3	**3.77 ppm** (ddd, $J_{3,2}$=3.7 Hz, $J_{3,5}$=2.6 Hz, $J_{3,4}$=1.3 Hz)
H_2	**3.48 ppm** (dd, $J_{2,3}$=3.7 Hz, $J_{2,4}$=1.1 Hz)
OH	**2.38 ppm** (bs)
CH_3	**1.83 ppm** (dd, $J_{CH3,5}$=1.3 Hz, $J_{CH3,4}$=1.2 Hz)

When this sequence of reactions was applied to (4*S*)-**13**, we finished up with the dextrorotatory enantiomer of epiepoformin. As the conversion of (+)-epiepoformin into (-)-theobroxide and (+)-4-epigabosine A has been described,[91d] this strategy establishes a new formal synthesis of both compounds. Analogously, starting from (4*R*)-**13**, (-)-epiepoformin, (+)-theobroxide and (-)-4-epigabosine could be obtained.

As we mentioned in the Introduction section, various articles have been published describing the synthesis of (+)-epiepoformin, and one refered to its antipode (-)-epiepoformin. The overall yields of these syntheses fluctuate from 12 to 51% (7-9 steps). It is important to notice that our approach has fewer steps, slightly higher yields (6 steps and 63% overall yield from **7**, 4 steps and 74% overall yield from **13**) and, more importantly, it allows access to both enantiomers.

- Synthesis of epoformin

According to the relative *cis* configuration between the epoxide moiety and the OTBS group in **33**, this compound was a suitable intermediate for the synthesis of epoformin. Therefore, the same synthetic sequence that had successfully led us to epiepoformin was applied to epoxyketone **33** (Scheme 57).



Scheme 57. Synthesis of epoformin.

The oxidation to the sulfoxide and subsequent pyrolysis delivered the expected mixture of *endo* and *exo*cyclic olefins **40** and **41** in a non reproducible ratio, due to the fact that the less stable isomer **41** isomerized to **40** during the chromatographic purification on silica gel. The following deprotection of the hydroxyl group in **40** furnished the target compound, epoformin (Figure 27).

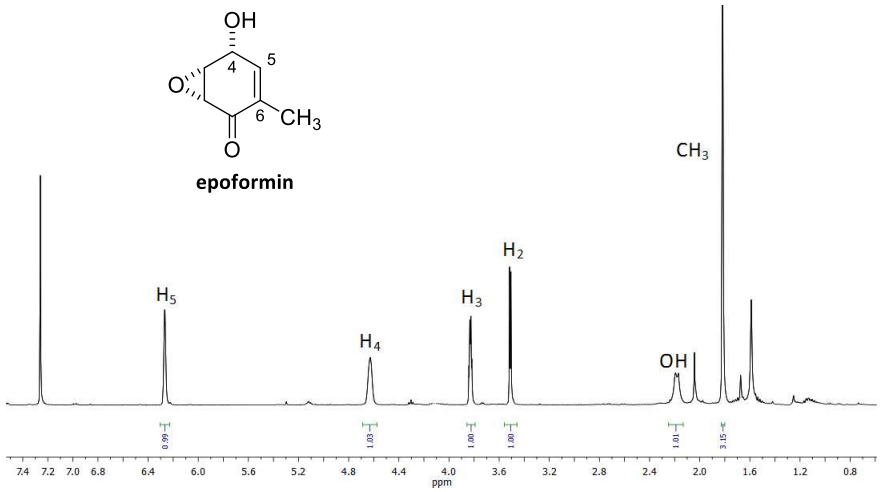


Figure 27. ^{1}H-NMR spectrum (400 MHz, $CDCl_3$) of epoformin.

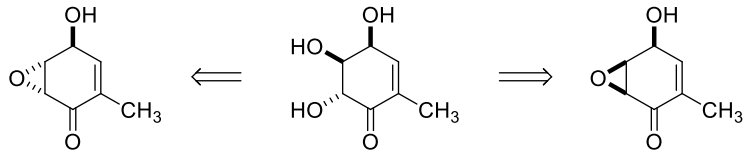
Epoformin	
H_5	**6.27** ppm (s)
H_4	**4.63 ppm** (bs)
H_3	**3.83 ppm** (m)
H_2	**3.51 ppm** (d, $J_{2,3}$=4.0 Hz)
OH	**2.19 ppm** (d, $J_{OH,4}$=9.9 Hz)
CH_3	**1.82 ppm** (s)

The parallel enantioselective pathway starting from (2*R*,3*S*,4*R*,6*R*)-**33** furnished natural epoformin in 63% overall yield.[128] The specific rotation value of the synthetic material, $[\alpha]_D^{20}$ = +109 (*c* 0.20, EtOH), was in agreement with the previous published data.[15a,95r]

This new route to (+)-epoformin presents equivalent yields to that of Barros,[95r] but our procedure has lower number of steps and provides accessibility to both antipodes.

1.5.1. Cleavage of the epoxide: Total synthesis of gabosine A

Formally, a regioselective hydrolysis of the epoxide in (+)-epiepoformin or (-)-epoformin could deliver (+)-gabosine A (Scheme 58), whereas the corresponding antipodes, equally available through our approach, would deliver the naturally occurring enantiomer. However, it was described that the hydrolysis of the epoxide in epiepoformin was a troublesome transformation that could only be achieved by treatment with aqueous NaOAc in 45% yield[91d] and, furthermore, this reaction delivered 4-epigabosine A, an epimer of the natural product.



Scheme 58. Possible precursors of (+)-gabosine A by a regioselective hydrolysis.

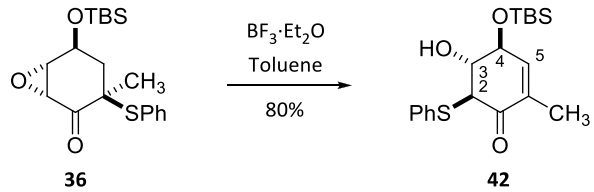
In view of this precedent, for the synthesis of gabosine A, we decided to assay the hydrolysis of the epoxide in a former intermediate lacking the conjugated C-C double bond, where a higher flexibility could benefit the desired transformation. Accordingly, ketone **36** was treated with various hydrolytic reagents. Our first attempt consisted in applying the methodology of Carreño and coworkers[91d] mentioned above. Thus **36** was treated with NaOAc in water at the reflux temperature for 3 days, but only unaltered starting material was recovered.

The next attempt to open the epoxide was an acid hydrolysis rather than a basic one. In 2006, Barret and coworkers published the hydrolysis of a quinone epoxide derivative, using TFA (16 eq) in CH_2Cl_2, with excellent yields.[129] Unfortunately, treatment of epoxide **36** in these acidic conditions only led to deprotection of the silyl ether group.

[129] Henderson, D. A.; Collier, P. N.; Pav, G.; Rzepa, P.; White, A. J. P.; Burrows, J. N.; Barrett, G. M. *J. Org. Chem.* **2006**, *71*, 2434-2444.

In the literature there are some papers dealing with epoxide opening in which scandium or other lanthanide triflates have been used successfully.[130] With this in mind, we conducted a preliminary trial using $Sc(OTf)_3$ (0.18 eq) in AcOH at room temperature.[130a,e] Unfortunately, only unaltered starting material was recovered. Increasing the temperature to reflux led only to decomposition products.

Another interesting methodology widely used in the literature is the hydrolysis with the Lewis acid $BF_3{\cdot}Et_2O$.[131] When epoxyenone **36** was treated with $BF_3{\cdot}Et_2O$ in toluene, a single product, identified as **42**, was formed in 80% yield (Scheme 59).



Scheme 59. Opening of epoxide **36**.

The regio- and stereochemical characterization of **42** was undertaken in an attempt to find and explanation to its formation.

While HRMS confirmed its molecular formula ($C_{19}H_{28}O_3SSi$), a variety of NMR experiments were also registered (Figure 28). The COSY spectrum was again very useful to assign the proton signals, while NOE experiments allowed the determination of its configuration. According to the COSY spectrum, the signals at δ 3.67 and 3.59 belonged to H_3 and H_2, respectively. Besides, the signal at 2.94 ppm disappeared when adding D_2O to the solution and should therefore be attributed to the OH group.

[130] (a) Shan, M.; Xing, Y.; O'Doherty, A. G. *J. Org. Chem.* **2009**, *74*, 5961-5966. (b) Ogawa, C.; Wang, N.; Kobayashi, S. *Chem. Lett.* **2007**, *36*, 34-35. (c) Tschöp, A.; Marx, A.; Sreekanth, A. R.; Schneider, C. *Eur. J. Org. Chem.* **2007**, 2318-2327. (d) Percy, J.; Roig, R.; Singh, K. *Eur. J. Org. Chem.* **2009**, 1058-1071. (e) Emmanuel, L.; Shaikh, T. M. A.; Sudalai, A. *Org. Lett.* **2005**, *30*, 5071-5074.

[131] (a)Yoshitake, M.; Kobayashi, H.; Yamamoto, M.; Kohmoto, S.; Yamada, K. *Chem. Lett.* **1991**, 1865-1868. (b) Honzumi, M.; Hiroya, K.; Taniguchi, T.; Ogasawara, K. *Chem. Commun.* **1999**, 1985-1986. (c) Yoshida, N.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 1461-1463. (d) Honzumi, M.; Taniguchi, T.; Ogasawara, K. *Org. Lett.* **2001**, *3*, 1355-1358.

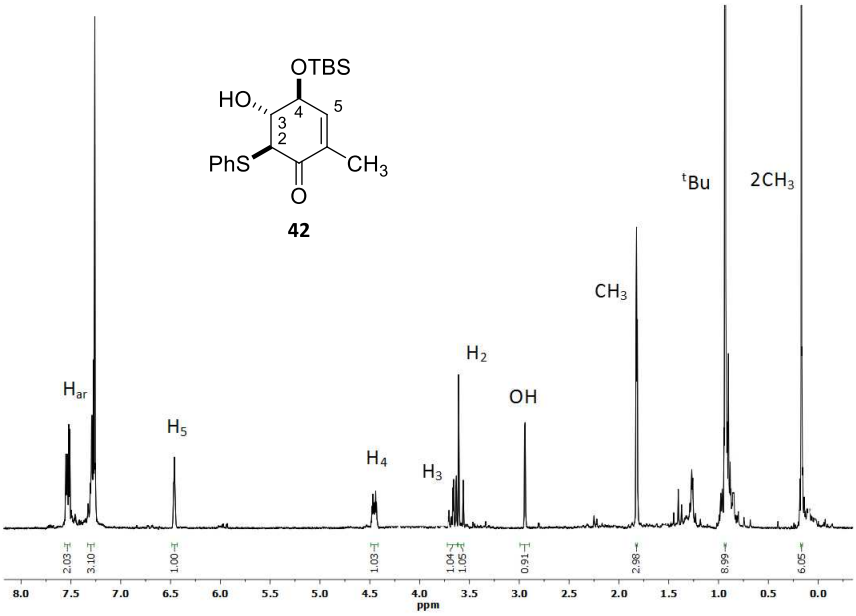


Figure 28. ^{1}H-NMR spectrum (250 MHz, $CDCl_3$) of **42.**

The NOESY spectrum was registered but the information gathered from it was not conclusive. Hence, we moved on to selective monodimensional experiments (Figure 29). Irradiation at the H_2 frequency (red spectrum) caused NOE on H_4, meaning that H_2 and H_4 were in *cis* relative configuration. A small NOE with the aromatic protons was also observed, confirming the geminal location of H_2 and the PhS group. Irradiation at the H_4 frequency caused NOE on H_2 and H_5, confirming that H_4 and H_2 were in *cis* relationship. Upon saturation of H_3 (blue one) no NOE was observed neither with H_2 nor H_4. This fact made us think that H_3 was *trans* to H_2 and H_4, but the absence of effect cannot assure this supposition.

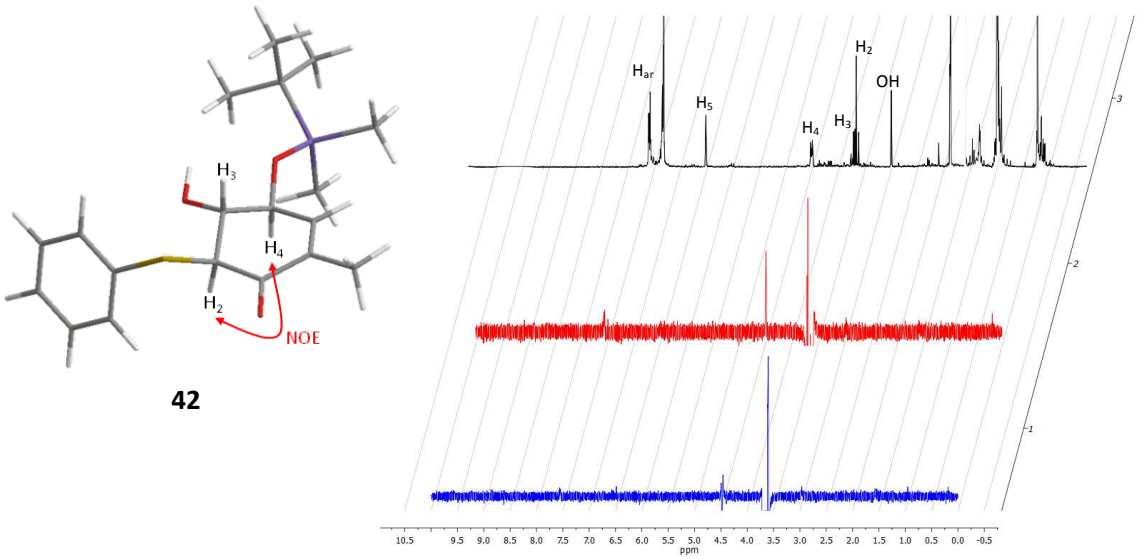


Figure 29. ^{1}H-NMR spectrum (400 MHz, $CDCl_3$) of compound **42** (black), NOE spectrum irradiated at 3.59 ppm (red) and NOE spectrum irradiated at 3.67 ppm (blue).

An expansion of ^{1}H-NMR spectrum of **42** (Figure 30) shows that H_2 and H_3, which displayed signals at 3.59 and 3.67 ppm respectively, present a coupling constant of 11,5 Hz between them, denoting a *trans* relative configuration. Consequently, we can conclude that the relative configuration of **42** is (2*S*,3*R*,4*S*).

Proton	δ and coupling constants
H_3	3.67 (ddd, $J_{3,2}$= 11.5 Hz, $J_{3,4}$= 7.0 Hz, $J_{3,OH}$= 1.6 Hz)
H_2	3.59 (d, $J_{2,3}$= 11.5 Hz)

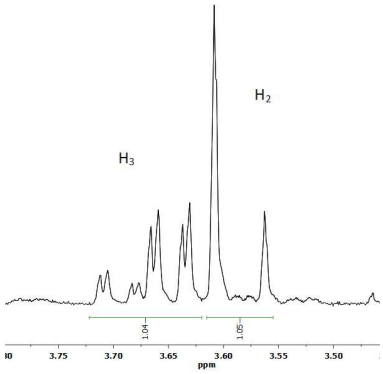
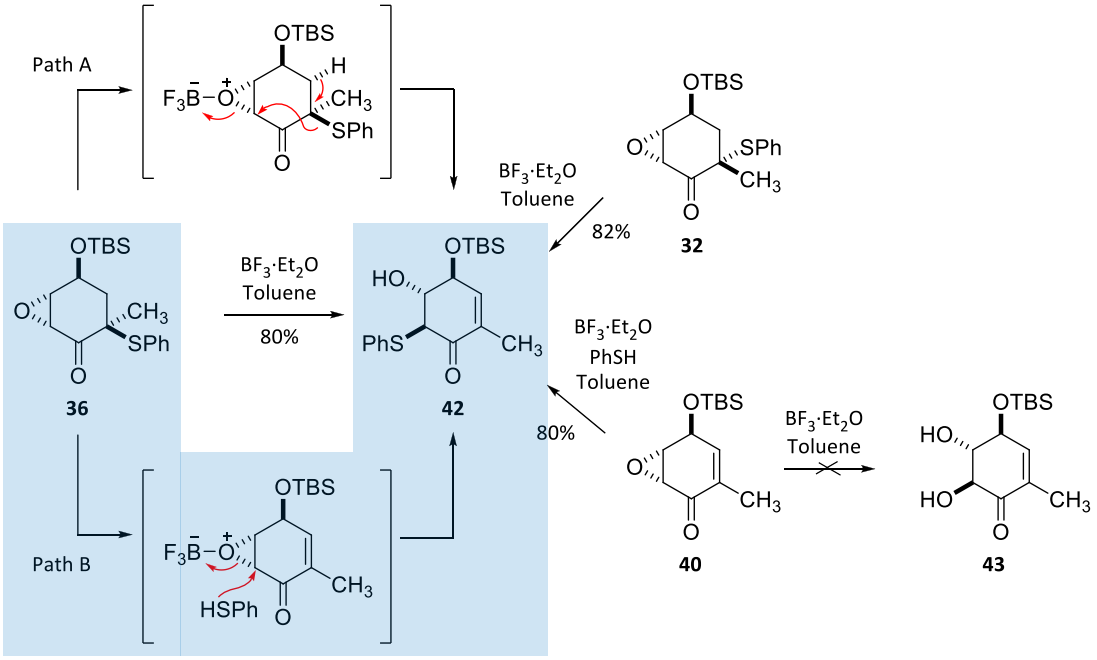


Figure 30. Expansion of ^{1}H-NMR spectrum (250 MHz, $CDCl_3$) of **42**.

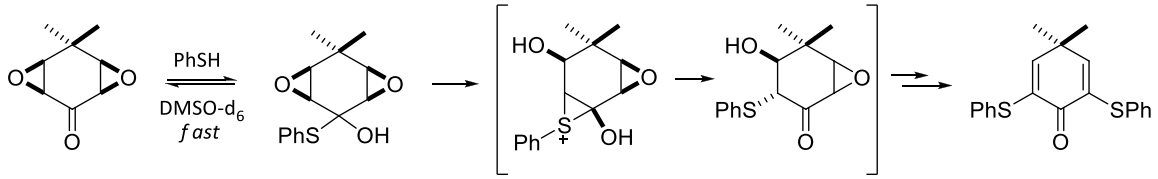
Considering the relative configuration of the stereocentres in **42**, we speculated that its formation may have occurred via an intramolecular process with migration of the sulphide group to open the oxirane electronically activated by the Lewis acid (Scheme 60, path A). To test this hypothesis, the diastereomeric ketone **32** was submitted to identical reaction conditions and it was found that compound **42** was also formed in similar yield. This result suggested that the elimination of thiophenol was probably previous to the epoxide opening (path B). In agreement with this assumption was the fact that enone **40**, when treated with $BF_3{\cdot}Et_2O$ in toluene in the presence of 1 eq of thiophenol, readily delivered alcohol **42** as the sole product.

Enone **40** was then submitted to identical reaction conditions except for the absence of thiophenol to attempt the formation of the corresponding trans diol **43**, but it was recovered unaltered.



Scheme 60. Attempted hydrolysis of oxirane **36** and formation of **42.**

The addition of thiophenol to related epoxyquinones under neutral conditions was described to occur with identical regioselectivity, although in much lower rate, by Wipf and coworkers.[132] Their studies on aranosin and manumycin model systems have revealed general reactivity patterns for the addition of thiophenol and other sulphur nucleophiles to epoxyquinone natural products. Their mechanistic hypothesis for this process was supported by spectroscopic and kinetic studies. According to this work, thiophenol would initially attack the carbonyl group, following with an irreversible 1,2-rearrangement, which would result in epoxide opening (Scheme 61).

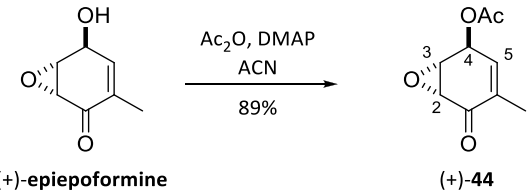


Scheme 61. Postulated mechanism for epoxide opening.[132]

Within the enantioselective pathway, epoxide (2*R*,3*S*,4*S*,6*S*)-**32** delivered (2*S*,3*R*,4*S*)-**42** ($[\alpha]_D^{20}$= +8.5 (*c* 0.47, $CHCl_3$)) in 82% yield.

[132] Wipf, P.; Jeger, P.; Kim, Y. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 351-356.

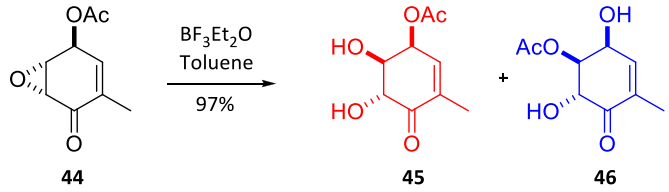
Recently, Metha and coworkers described the cleavage of a 2,3-epoxycyclohexanone to the *trans* diol through a $BF_3{\cdot}Et_2O$ mediated and acetate-assisted process, which took place in 67% yield.[91h] Considering this precedent, the acetyl derivative of (+)-epiepoformin, (+)-**44**, was synthesized by treatment with acetic anhydride and DMAP in acetonitrile, in 93% yield (Scheme 62).



(+)-**epiepoformine** (+)-**44**

Scheme 62. Synthesis of the acetate (+)-**44**.

The ^{1}H-NMR spectrum of (+)-**44** shows a singlet signal of the acetate group at 2.12 ppm, with H_4 appearing at higher fields (5.72 ppm) compared to the precursor alcohol, due to the electron withdrawing effect of the acetate group. Acetate (+)-**44** was treated with $BF_3{\cdot}Et_2O$ in toluene at 0 °C for 2 h (Scheme 63). This reaction furnished a mixture of acetates in a ratio aprox. 3:1, temptatively identified as **45** and **46** by ^{1}H-NMR (Figure 31).



44 **45** **46**

Scheme 63. Acetate-assisted regioselective cleavage of epoxide **44**.

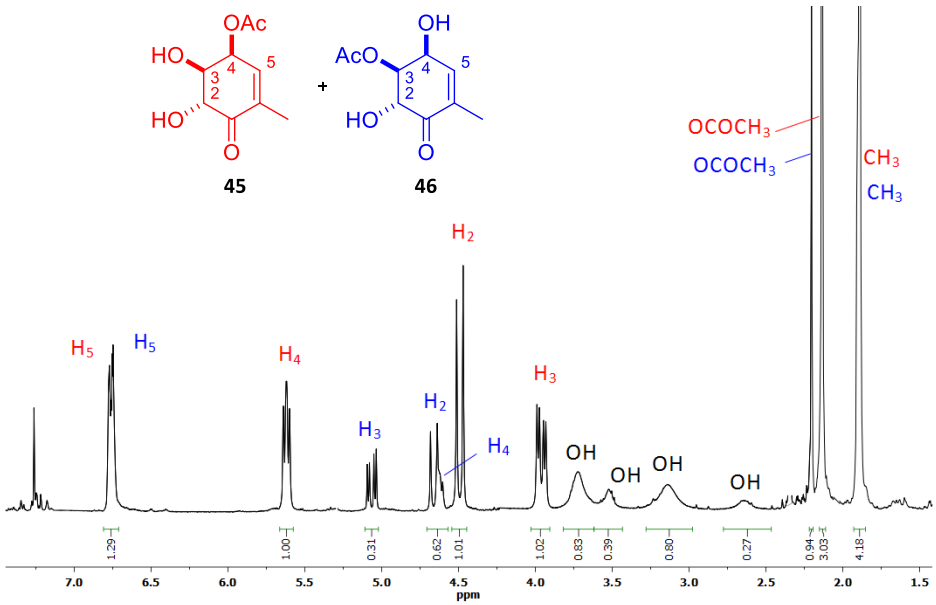
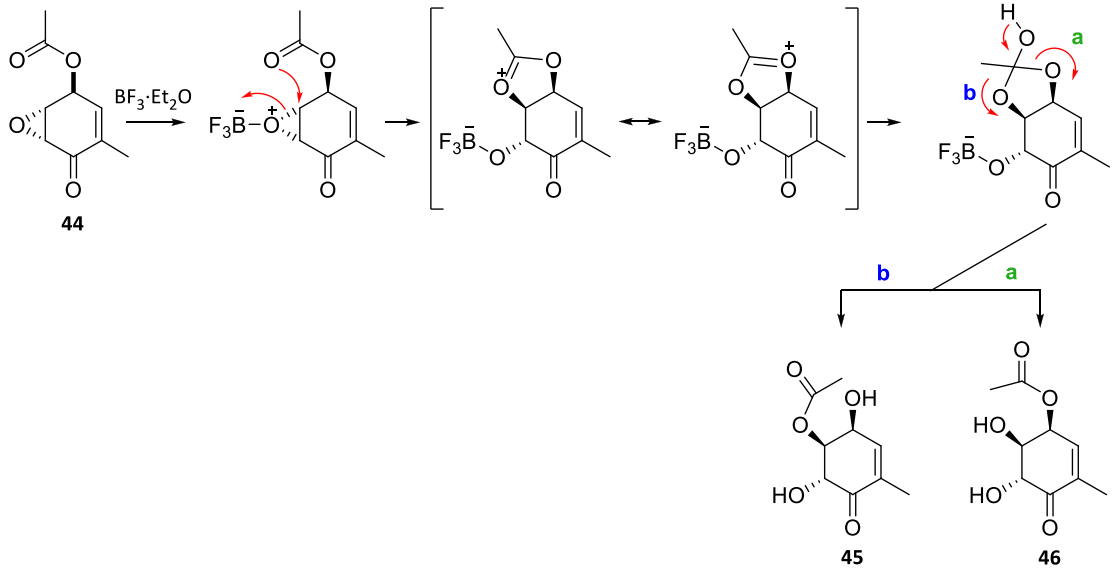


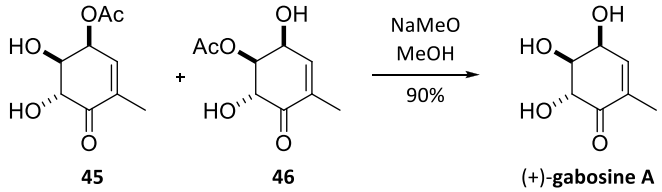
Figure 31. ^{1}H-NMR spectrum (250 MHz, $CDCl_3$) of the mixture of acetates **45** and **46**.

The ^{1}H-NMR spectrum of the mixture shows two singlet signals (δ 2.20 and 2.13) evidencing the formation of two new acetates during the reaction. The H_5 protons of both compounds appear collapsed at δ ~ 6.85, suggesting similarities in this part of the molecule. As we can see, there are two sets of signals, the red ones assigned to **45** (major) and the blue ones to **46** (minor). The signal at δ 5.62 should belong to proton H_4 attached to a carbon atom bearing an electronwithdrawing group in **45**. The roof effect between the signals at δ 4.49 and 3.96 is in agreement with the assignation of H_2 and H_3 of **45**, respectively. In addition, the signals displayed at 5.06 and 4.66 ppm ought to belong to H_3 (attached to the carbon bearing the acetate group) and H_2 of **46**, respectively. Finally, H_4 of acetate **46** appear collapsed with H_2. In view of the formation of this mixture of acetates and according to the precedents, the following mechanism is suggested (Scheme 64).



Scheme 64. Suggested mechanism for epoxide ring opening.

In order to continue with the synthesis, the inseparable mixture of acetates **45** and **46** was submitted to methanolysis in basic medium, affording (+)-gabosine A in 90% yield as a white crystalline solid (Scheme 65, Figure 32).[128] The specific rotation of the synthetic material was $[\alpha]_D^{20}$ = +128 (*c* 0.30, MeOH) (lit.[6] $[\alpha]_D^{20}$ = -132 (*c* 1, MeOH)) for the natural antipode. Analogously, if the starting material was (-)-epiepoformin, (-)-gabosine A could be synthesized.



Scheme 65. Synthesis of gabosine A.

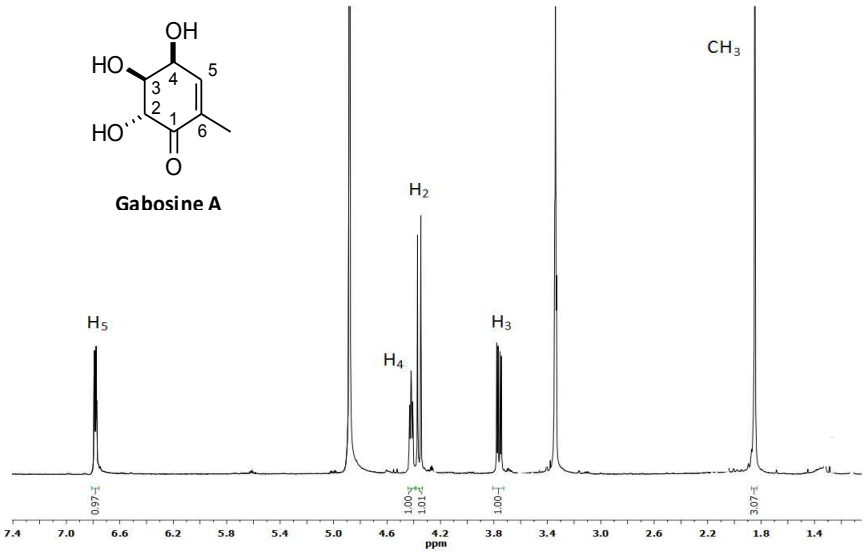
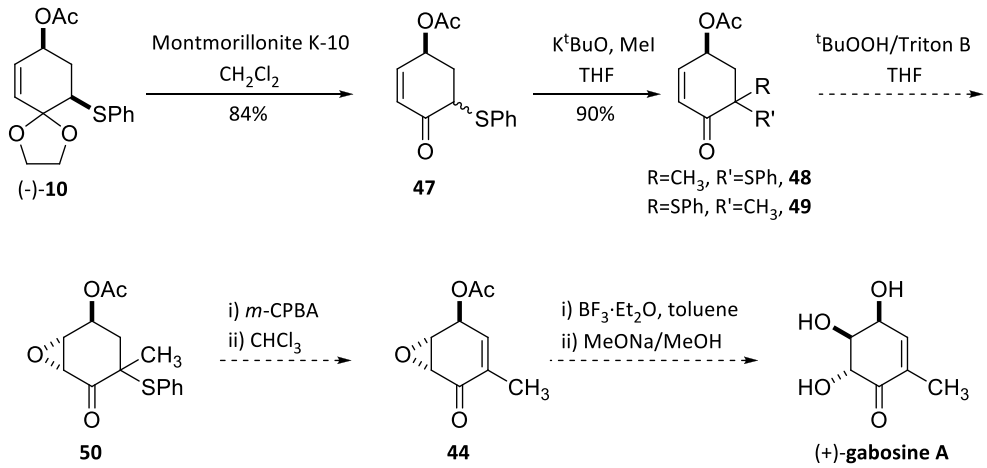


Figure 32. ^{1}H-NMR spectrum (400 MHz, MeOD) of (+)-gabosine A.

(+)-**Gabosine A**	
H_5	**6.78 ppm** (dq, $J_{5,4}$=5.6 Hz, $J_{5,CH3}$=1.4 Hz)
H_4	**4.42 ppm** (m)
H_2	**4.36 ppm** (d, $J_{2,3}$=10.0 Hz)
H_3	**3.76 ppm** (dd, $J_{3,2}$=10.0 Hz, $J_{3,4}$=3.9 Hz)
CH_3	**1.85 ppm** (dd, $J_{CH3,5}$=1.4Hz, $J_{CH3,4}$=1.2 Hz)

As the presence of the vicinal acetate proved crucial for the cleavage of the epoxide, we decided to intend a more straightforward synthesis of gabosine A starting from the acetate (-)-**10**, produced in the enzymatic resolution of (±)-**7**. The synthetic plan, shown in Scheme 66, would involve seven chemical transformations in only five experimental operations: i) hydrolysis of the ketal; ii) methylation; iii) stereoselective epoxidation; iv) oxidation/pyrolysis; and v) epoxide cleavage/methanolysis. Along this sequence, the separation of isomers in each individual step would be unnecessary.



Scheme 66. Attempted synthesis of (+)-gabosine A from acetate (-)-**10**.

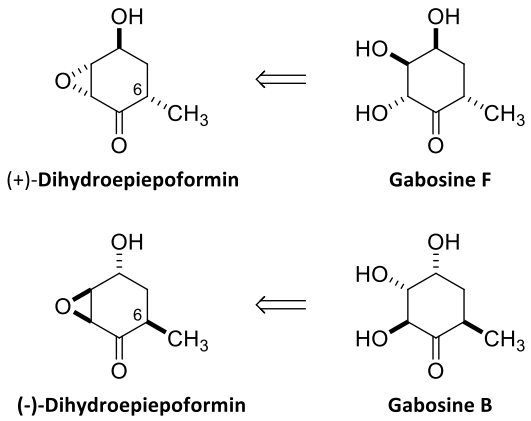
In practice, the two initial transformations took place as expected, but, unfortunately, the epoxidation of the acetate **48** and/or **49** was less stereoselective than the corresponding reaction with the silyl ether analogues **22** and **23**. Moreover, partial hydrolysis of the epoxyacetates took place spontaneously, furnishing a complex mixture of products that could not be converted into the target compound in a reproducible manner. Consequently, in this case, the most straightforward approach from (-)-**10** to (+)-gabosine A proved ineffective.

To sum up, starting from chiral pool materials, two syntheses of (-)-gabosine A,[91a,112] the natural enantiomer, and one of its levorotatory antipode[91j] had been published with overall yields below 15%. A third synthesis of (-)-gabosine A was completed by Banwell and coworkers from the enzymatic dihydroxilation product of iodobenzene in 58% yield.[9] Our synthetic approach (49% yield from **7**, 57% yield from **13**)[128] is comparable to Banwell's procedure with the added advantage that it allows access to both antipodes.

1.6. REDUCTION OF THE C_6-S DOUBLE BOND: TOTAL SYNTHESIS OF DIHYDROEPIEPOFORMINS

Since some gabosines and anhydrogabosines exhibit cyclohexanone structure, Dr. Georgina Marjanet performed during her PhD, the reduction of the C_6-S bond on different dihydroxylated substrates. This strategy allowed her to synthesize both antipodes of gabosine O.[33] This methodology has been applied in the present work on the intermediate epoxide newly synthesized.

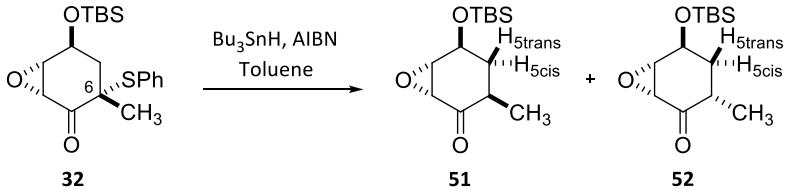
Formally, the synthesis of gabosines B and F could be accomplished from dihydroepiepoformin by stereoselective hydrolysis of the epoxide function (Scheme 67). Assuming the same mechanistic behaviour as in the case of gabosine A, the hydroxyl group activated as acetate and the epoxide should be in *trans* relative configuration for this hydrolysis to take place. The appropriate precursors of dihydroepiepoformin are epoxides **32** and **36**, in which the C-S bond will have to be reduced.



Scheme 67. Possible precursors of (+)-gabosine A by a regeoselective hydrolysis.

- Synthesis of dihydroepiepoformins

Our first trial was attempted by treatment of **32** with Bu_3SnH in the presence of AIBN in toluene under the conditions previously used in our research group for similar transformations (Table 12, entry 1), delivering an inseparable 6.6:1 mixture of epoxides **51** and **52** in 60% yield (Scheme 68). This fact indicates that during the reaction epimerization occurred at C_6.



Scheme 68. Reduction of C-S bond in epoxide **32.**

The main drawbacks of this procedure are the lack of reproducibility and some isolation problems due to the large excess of Bu_3SnH used. Trying to improve these results, and according to a Danheiser and co-workers publication,[133] a new protocol was assayed (entry 2). This new conditions allowed lower reducer loadings by continuously adding a solution of the reducing agent to the reaction mixture. Thus, a solution of Bu_3SnH and AIBN in toluene was prepared and added continuously. With this procedure, the same 6.6:1 ratio of a mixture of epoxides was obtained, but the yield increased up to 80% in a reproducible manner.

Table 12. Reduction of C_6-S bond in the epoxide **32**.

Entry	Equivalents Bu_3SnH:AIBN	Conditions	Yield	Products
1	2.17:0.01	1h, AIBN and Bu_3SnH added once	60%	**51:52** (6.6:1)
2	1.19:0.10	Solution of Bu_3SnH+AIBN continuously added (1.1 ml/h)	80-85%	**51:52** (6.6:1)

[133] Lawlor, M. D.; Lee, T. W.; Danheiser, R. L. *J. Org. Chem.* **2000**, *65*, 4375-4384.

Figure 33 shows the ^{1}H-NMR spectrum of the mixture of epoxides **51** and **52**. Analyzing the signals of the major product (red labels), it displays an upfield signal at 4.35 ppm (H_4) with coupling constants with the two protons H_5 of 7.8 Hz (with the signal at 1.57 ppm) and 5.5 Hz (with the signal at 2.18 ppm), and of 1.2 Hz with H_3. This fact is in agreement with a pseudoaxial orientation of H_4 and indicates that H_5 at 1.57 should be assigned as H_{5trans} and the other one (2.18 ppm) as H_{5cis}. H_6 (δ 2.66) shows a value of coupling constant of 11.0 Hz with H_{5trans}, denoting their *trans* diaxial orientation. These facts evidence a *cis* relationship among H_4, H_{5cis} and H_6. Therefore, the OTBS and methyl groups should also be in *cis* relative configuration and pseudoequatorial position. Consequently, the major product could be temptatively assigned as epoxide **51**.

Then, signals with blue labels can be attributed to **52**. H_4 shows a signal as a quadruplet at δ 4.46 with three similar vicinal coupling constants (J≈ 2.9 Hz) with H_3 and both protons H_5, denoting a pseudoequatorial orientation of H_4 and thus, a pseudoaxial one of the OTBS group. The H_6 signal appears at 2.46 ppm as dqn, presenting coupling constants of 11.6 Hz with one H_5 proton, which could be assigned at H_{5cis}, and of 7.1 Hz with the other H5 (assigned as H_{5trans}) and the methyl group. These facts are in accordance with a *trans* diaxial relationship between H_6 and H_{5cis} and, therefore, the methyl group occups the pseudoequatorial orientation, in *trans* relationship respect to the OTBS group.

Epoxide 51	
Proton	**δ and coupling constants**
H_4	4.35 ppm (ddd , $J_{4,5ax}$= 7.8 Hz, $J_{4,5eq}$= 5.5 Hz, $J_{4,3}$= 1.2 Hz)
H_6	2.66 ppm (dqd, $J_{6,5ax}$= 11.0 Hz, $J_{6,CH3}$= 6.8 Hz, $J_{6,5eq}$= 1.2 Hz)

Epoxide 52	
Proton	**δ and coupling constants**
H_4	4.46 ppm (q, $J_{4,3}$≈$J_{4,5}$≈$J_{4,5'}$≈ 2.9 Hz)
H_6	2.46 ppm (dqn, $J_{6,5'}$= 11.6 Hz, $J_{6,5}$=$J_{6,CH3}$= 7.1 Hz)

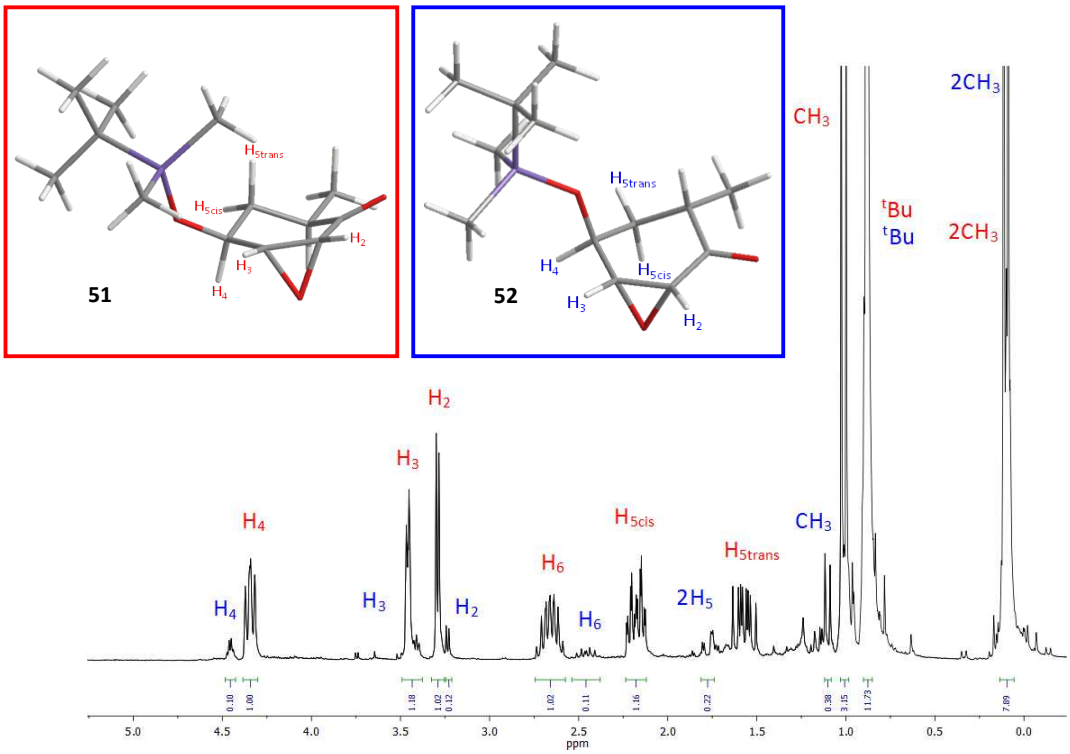
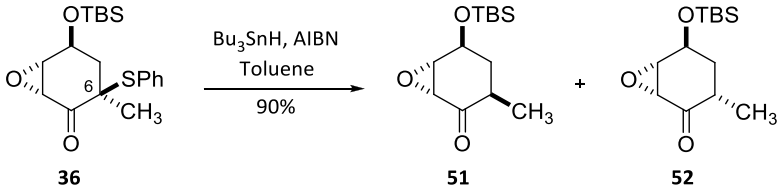


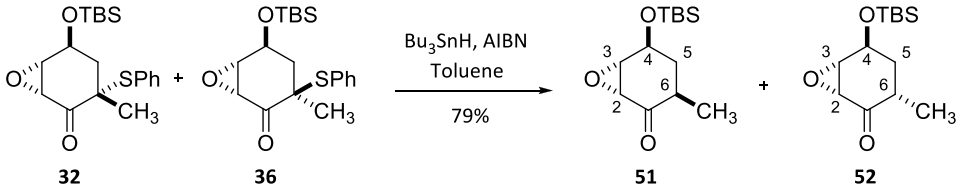
Figure 33. ^{1}H-NMR spectrum (250 MHz, $CDCl_3$) of the mixture of epoxides **51** and **52.**

Then, we applied the same reduction methodology to the epimeric epoxide **36** (Scheme 69) that afforded a mixture of cyclohexanones **51** and **52** in identical 6.6:1 ratio and similar yield than **32**.



Scheme 69. Reduction of C-S bond in epoxide **36.**

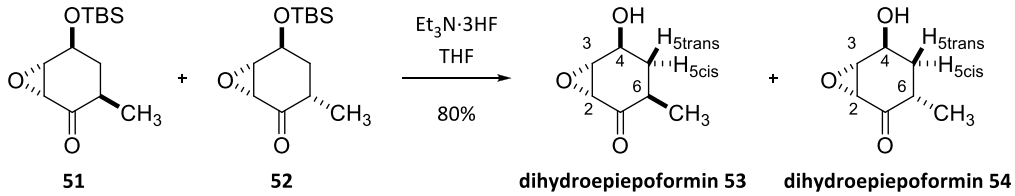
The constant ratio **51**:**52** is consistent with the relative stability of both isomers since they can equilibrate under the reaction conditions. It is important to remark that, analogously to what happened in the oxidation/pyrolysis pathway, the chromatographic separation of the precursor thioeters **32** and **36** revealed unnecessary because both diastereomers furnished the mixture of cyclohexanones **51** and **52** in the same ratio. Therefore, a mixture of **32** and **36** was treated with Bu_3SnH and AIBN in toluene at the reflux temperature delivering the expected results (Scheme 70).



Scheme 70. Reduction of C_6-S bond in a mixture of epoxides **32** and **36.**

Within the enantioselective pathway, a 6.6:1 mixture of epoxides (2*R*,3*S*,4*S*,6*S*)-**32** and (2*R*,3*S*,4*S*,6*R*)-**36** provided a 6.6:1 mixture of cyclohexanones (2*R*,3*S*,4*S*,6*R*)-**51** and (2*R*,3*S*,4*S*,6*S*)-**52** in 79% yield. Analogously, starting from (2*S*,3*R*,4*R*,6*R*)-**32** and (2*S*,3*R*,4*R*,6*S*)-**36** the isomers (2*S*,3*R*,4*R*,6*S*)-**51** and (2*S*,3*R*,4*R*,6*R*)-**52** were isolated in 81% yield.

Desilylation of the mixture **51** and **52** was carried out using $Et_3N{\cdot}3HF$ in THF at room temperature to deliver alcohols **53** and **54** (Scheme 71). It was observed that the alcohols were obtained in a variable ratio in different operations and that this ratio did not correlate with the composition of the starting mixtures, denoting that epimerization at C_6 occured during the reaction.



Scheme 71. Deprotection of a mixture of epoxides **52** and **53.**

The newly formed alcohols exhibit slightly different polarity, so, after several column chromatography operations, a sample of each one, dihydroepiepoformin **53** (Figure 34) and dihydroepiepoformin **54** (Figure 35) could be isolated and their spectroscopic data determined.

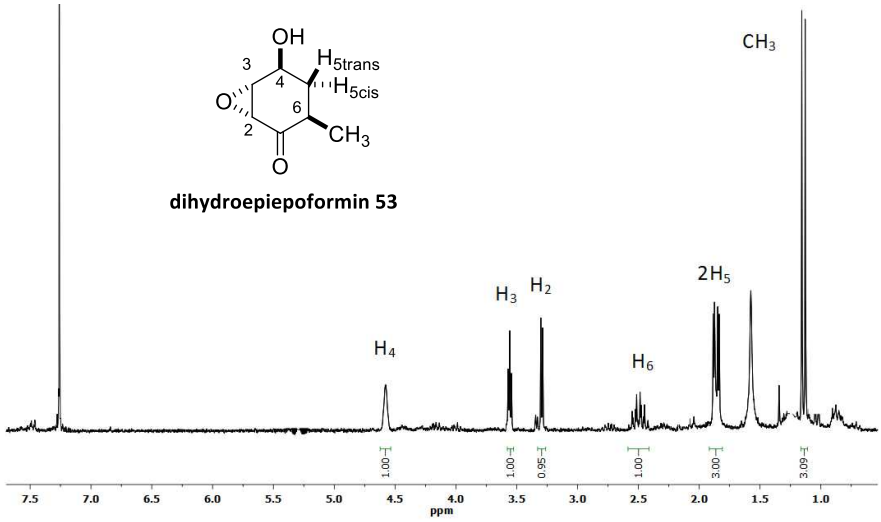


Figure 34. ^{1}H-NMR spectrum (250 MHz, $CDCl_3$) of dihydroepiepoformin **53**.

Dihydroepiepoformin 53	
H_4	**4.45 ppm** (bs)
H_3	**3.56 ppm** (t, $J_{3,2}$=$J_{3,4}$=3.5 Hz)
H_2	**3.29 ppm** (d, $J_{2,3}$=3.5 Hz)
H_6	**2.48 ppm** (tq, $J_{6,5}$=$J_{6,5'}$=9.3 Hz, $J_{6,CH3}$=7.2 Hz
$2H_5$,OH	**1.86 ppm** (m)
CH_3	**1.14 ppm** (d, $J_{CH3,6}$=7.2 Hz)

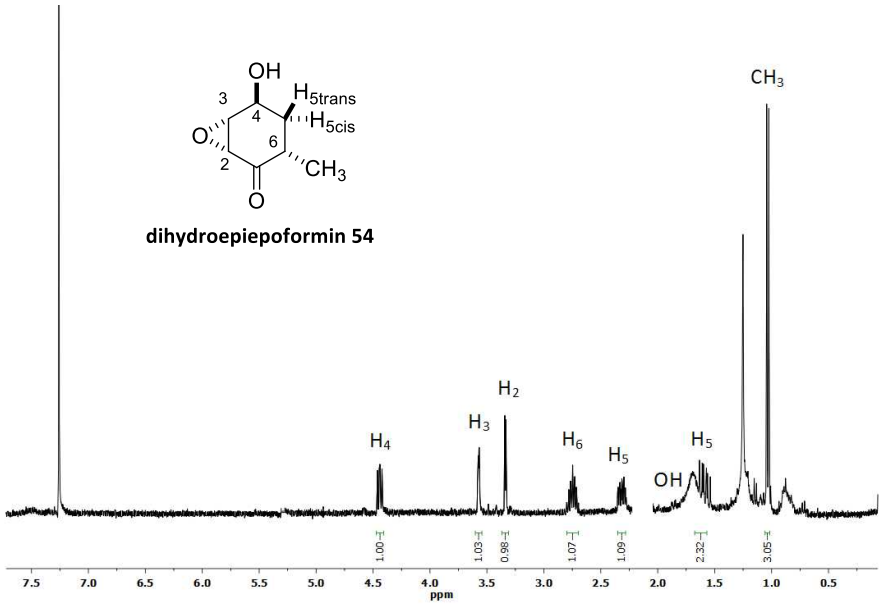


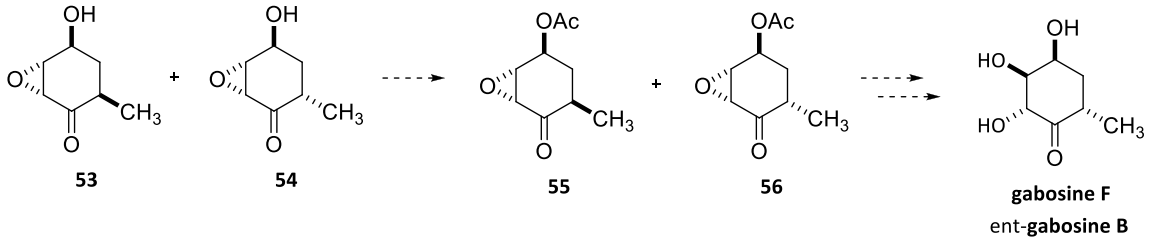
Figure 35. ^{1}H-NMR spectrum (360 MHz, $CDCl_3$) of dihydroepiepoformin **54**.

Dihydroepiepoformin 54	
H_4	**4.44 ppm** (bdd, $J_{4,5cis}$= 8.6 Hz, $J_{4,5trans}$= 5.9 Hz)
H_3	**3.57 ppm** (m)
H_2	**3.34 ppm** (d, $J_{2,3}$= 3.8 Hz)
H_6	**2.75 ppm** (dqd, $J_{6\text{-}5trans}$= 12.1 Hz, $J_{6,CH3}$= 6.7 Hz, $J_{6,5trans}$= 5.4 Hz)
H_{5trans}	**2.32 ppm** (m)
OH	**1.70 ppm** (bs)
H_{5cis}	**1.59 ppm** (ddd, $J_{5cis,5trans}$= 13.5 Hz, $J_{5cis,6}$= 12.1 Hz, $J_{5cis,4}$= 8.6 Hz)
CH_3	**1.03 ppm** (d, $J_{CH3,6}$= 6.7 Hz)

Within the enantioselective pathway, a mixture of epoxides (2*R*,3*S*,4*S*,6*R*)-**51** and (2*R*,3*S*,4*S*,6*S*)-**52** furnished a mixture of alcohols (2*R*,3*R*,4*S*,6*R*)-**53** and (2*R*,3*R*,4*S*,6*S*)-**54** in 79% yield. The same reaction starting from (2*S*,3*R*,4*R*,6*S*)-**51** and (2*S*,3*R*,4*R*,6*R*)-**52** afforded a mixture of alcohols (2*S*,3*S*,4*R*,6*S*)-**53** and (2*S*,3*S*,4*R*,6*R*)-**54** in 80% yield.

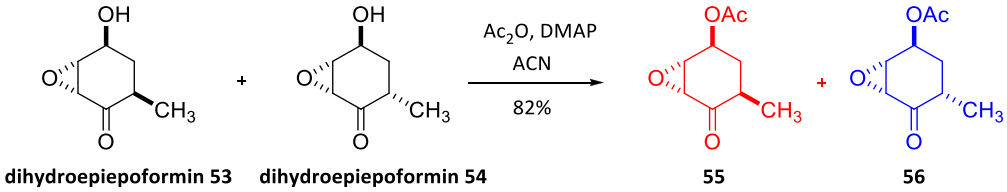
1.6.1. Cleavage of the epoxide: Total synthesis of gabosines B and F

To proceed with the synthesis of gabosines B/F, the mixture of alcohols required to be acetylated in order to cleave the epoxide (Scheme 72). This transformation would be accomplished utilizing the same protocol as for gabosine A.



Scheme 72. Approach to gabosines F and B.

A mixture of dihydroepiepoformins **53** and **54** were treated with acetic anhydride and DMAP in acetonitrile, delivering the predictable mixture of acetates **55** and **56** in 82% yield (Scheme 73).



Scheme 73. Synthesis of the acetates **55** and **56**.

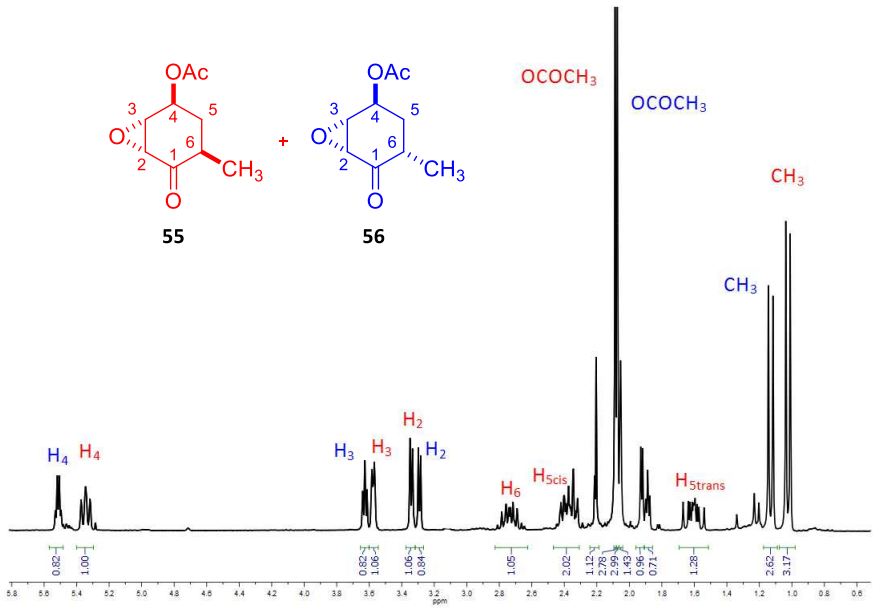


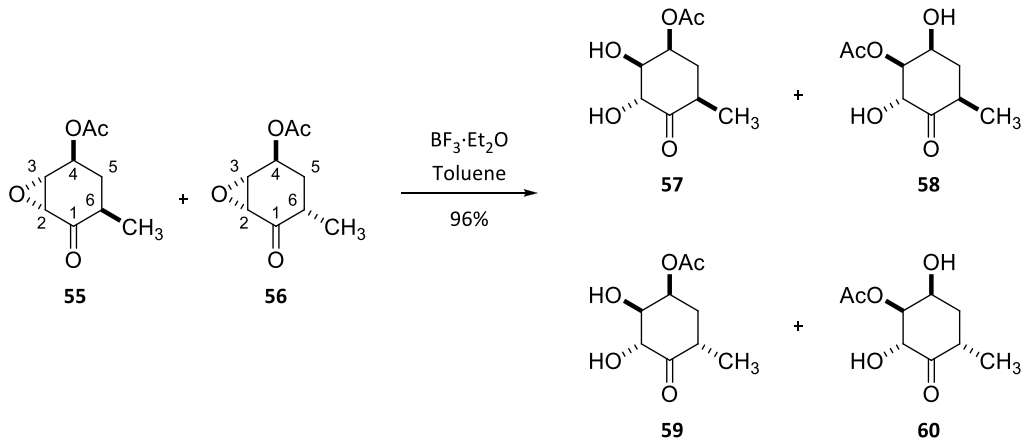
Figure 36. ^{1}H-NMR spectrum (250 MHz, $CDCl_3$) of the mixture of the acetates **56** and **57**.

As we can see in Figure 36, there are two characteristic singlet signals (2.08 and 2.09 ppm) evidencing that activation of the alcohol as acetate was successfully accomplished. It Is important to mention that the first acetylation reaction was carried out with a pure sample of dihydroepiepoformin **53**, thus allowing the assignment of the signals labelled in red on Figure 36 to **55**. Consequently, the blue labels correspond to the signals assigned to **56**.

Significantly, the ratio of alcohols used as the starting material remained unaltered in the mixture of acetates obtained, confirming that no epimerization occurred in the course of the reaction.

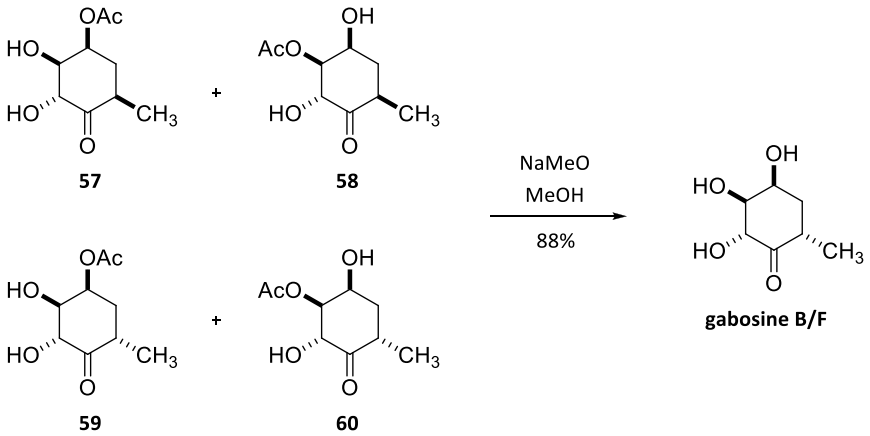
Within the optically active series, a mixture of alcohols (2*R*,3*R*,4*S*,6*R*)-**53** and (2*R*,3*R*,4*S*,6*S*)-**54** delivered acetates (2*R*,3*R*,4*S*,6*R*)-**55** and (2*R*,3*R*,4*S*,6*S*)-**56** in 80% yield. Analogously, enantiomeric acetates (2*S*,3*S*,4*R*,6*S*)-**55** and (2*S*,3*S*,4*R*,6*R*)-**56** were obtained in 84% yield starting from (2*S*,3*S*,4*R*,6*S*)-**53** and (2*S*,3*S*,4*R*,6*R*)-**54**.

The acetates were subjected to epoxide cleavage using $BF_3{\cdot}Et_2O$ in toluene. As we could envisage, a mixture of four acetates (**57**-**60**) were obtained in 96% yield (Scheme 74).



Scheme 74. Epoxide opening of a mixture of the acetates **55** and **56**.

To complete the synthesis, the mixture of acetates **57**-**60**, were submitted to methanolysis in basic medium without previous purification. This hydrolysis afforded exclusively gabosine B/F in 88% total yield, so concomitant epimerization at C_6 occurs during the methanolysis reaction (Scheme 75, Figure 37).



Scheme 75. Synthesis of Gabosine B/F.

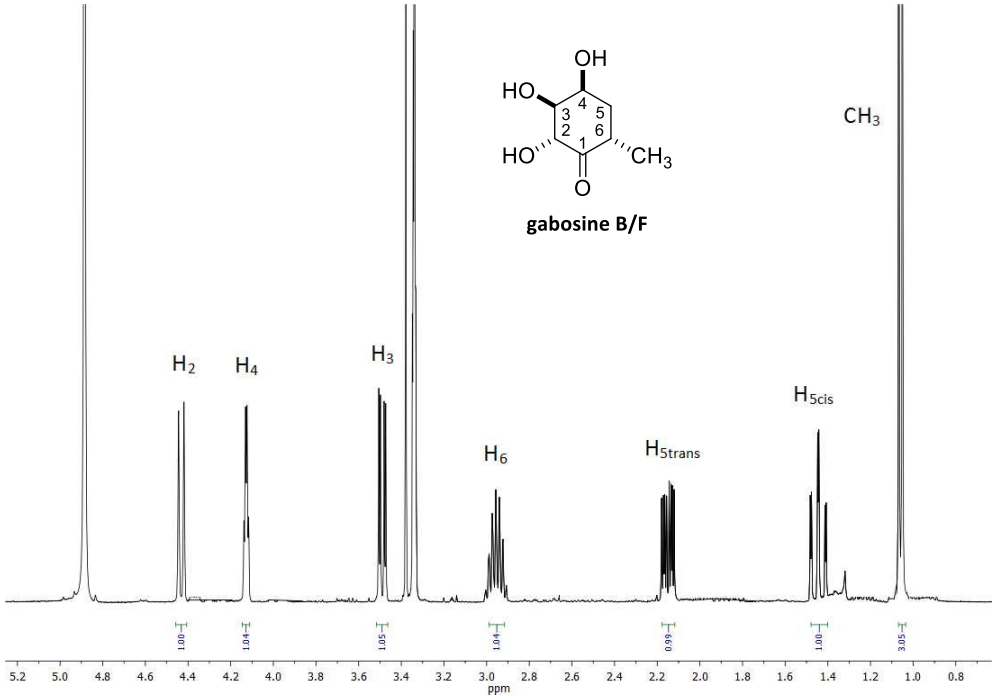


Figure 37. ^{1}H-NMR spectrum (400 MHz, MeOD) of gabosine B/F.

	Gabosine B/F
H_2	**4.43 ppm** (d, $J_{2,3}$=10.0 Hz)
H_4	**4.13 ppm** (bq, $J_{4,3}\approx J_{4,5trans}\approx J_{4,5acis}$≈3.0 Hz)
H_3	**3.49 ppm** (dd, $J_{3,2}$=10.0 Hz, $J_{3,4}$=3.0 Hz)
H_6	**2.96 ppm** (dqd, $J_{6,5cis}$=13.0 Hz, $J_{6,CH3}$=6.6 Hz, $J_{6,5trans}$=5.9 Hz)
H_{5trans}	**2.15 ppm** (ddd, $J_{5trans,5cis}$=14.0 Hz, $J_{5trans,6}$=5.9 Hz, $J_{5trans,4}$=3.2 Hz)
H_{5cis}	**1.45 ppm** (td, $J_{5cis,5trans}\approx J_{5cis,6}$≈14.0 Hz, $J_{5cis,4}$=2.6 Hz)
CH_3	**1.06 ppm** (d, $J_{CH3,6}$=6.6 Hz)

Within the enantioselective pathway, a mixture of (2*R*,3*R*,4*S*,6*R*)-**55** and (2*R*,3*R*,4*S*,6*S*)-**56** delivered gabosine F as a white crystalline solid.[128] The specific rotation of the synthetic material was $[\alpha]_D^{20}$= +88 (*c* 0.15, MeOD) (lit.[6] $[\alpha]_D^{20}$= +94 (*c* 1.0, MeOH)).

In addition, starting from the enantiomeric mixture (2*S*,3*S*,4*R*,6*S*)-**55** and (2*S*,3*S*,4*R*,6*R*)-**56**, gabosine B was also obtained as a white crystalline solid.[128] The specific rotation was $[\alpha]_D^{20}$= -89 (*c* 0.30, MeOD) (lit.[6] $[\alpha]_D^{20}$= -91 (*c* 1.5, MeOH)).

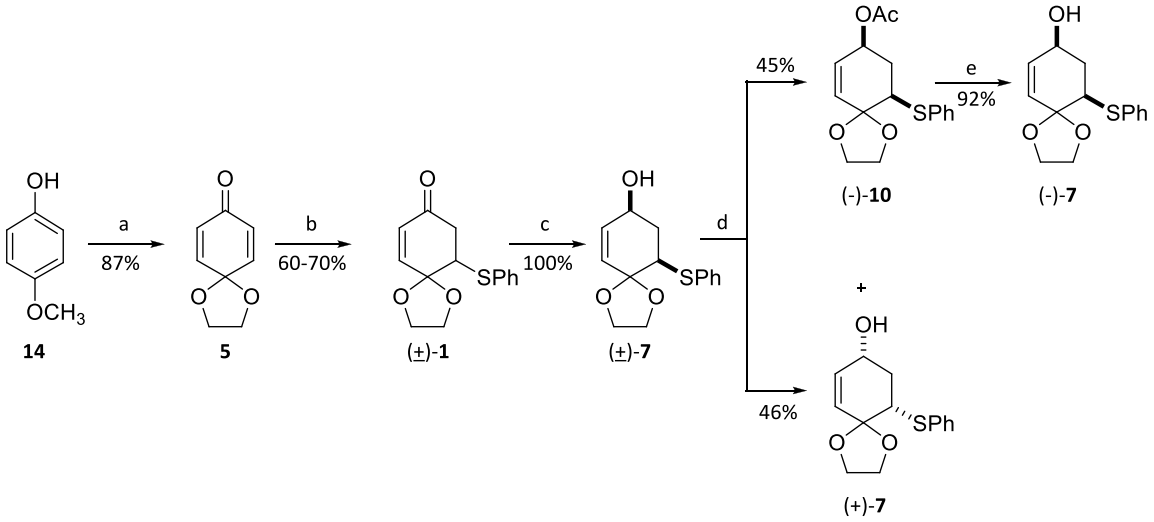
It is important to remind that starting from (-)-**22**, (-)-**23** or any mixture of both epimers, the sequence ended up with the dextrorotatory product, gabosine F. Analogously, the levorotatory antipode, gabosine B, was prepared from (+)-**22**, and/or (+)-**23**.

H<As mentioned in the Introduction, Shinada and Ohfune described an enantioselective synthesis of (-)-gabosine B in 9 steps and 7.6% yield starting from (-)-quinic acid.[112] Recently, an enantioselective synthesis of the dextrorotatory antipode, the natural gabosine F, has been accomplished in 12 steps and 24% yield from L-arabinose.[91k] Our approach has the advantage of allowing the synthesis of both antipodes with similar number of steps and somewhat higher yields, 7 steps and 48% yield from **13**, or 9 steps and 38-40% yield respect to **7**.

V. Summary

1. SUMMARY

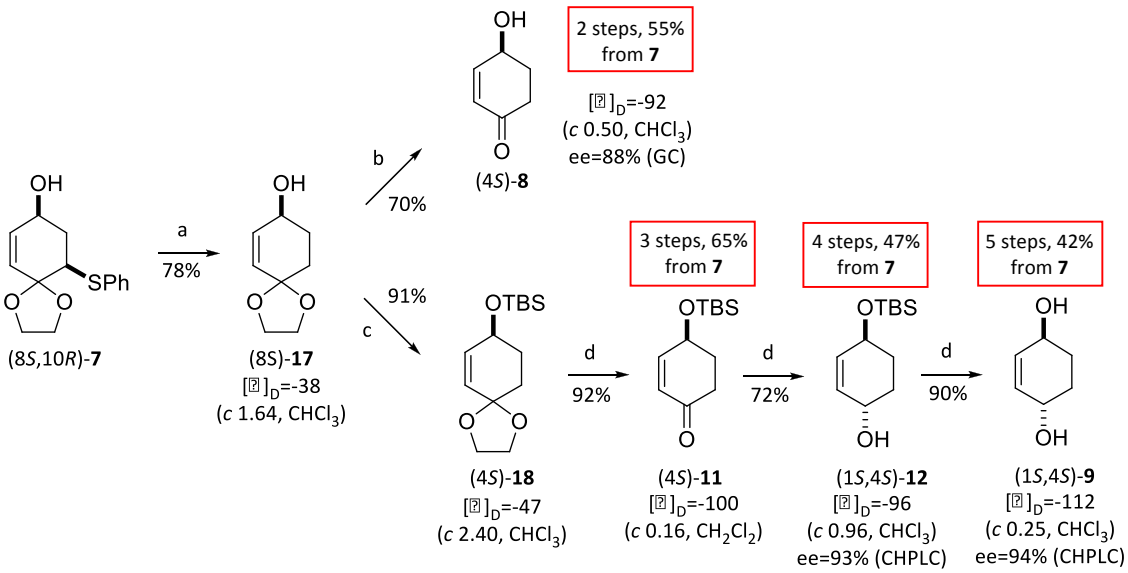
In this thesis a methodology for the preparation of both enantiomers of **7** in a 10 g scale as been established by taking advantage of an enzymatic acetylation to resolve the racemate (Scheme 76). These chiral alcohols have been used as starting materials for the synthesis of diverse natural products with potential biological properties, as well as interesting chemical intermediates.



Reagents and conditions: (a) PIFA, $HOCH_2CH_2OH$, CH_2Cl_2; (b) PhSH, $LiOH{\cdot}H_2O$, $CHCl_3$ reflux; (c) $NaBH_4$, CH_2Cl_2/CH_3OH; (d) Novozyme®435, $CH_3CO_2CH{=}CH_2$, diisopropyl ether; (e) NaOMe, CH_3OH.

Scheme 76. Synthesis of (+)- and (-)-**7**.

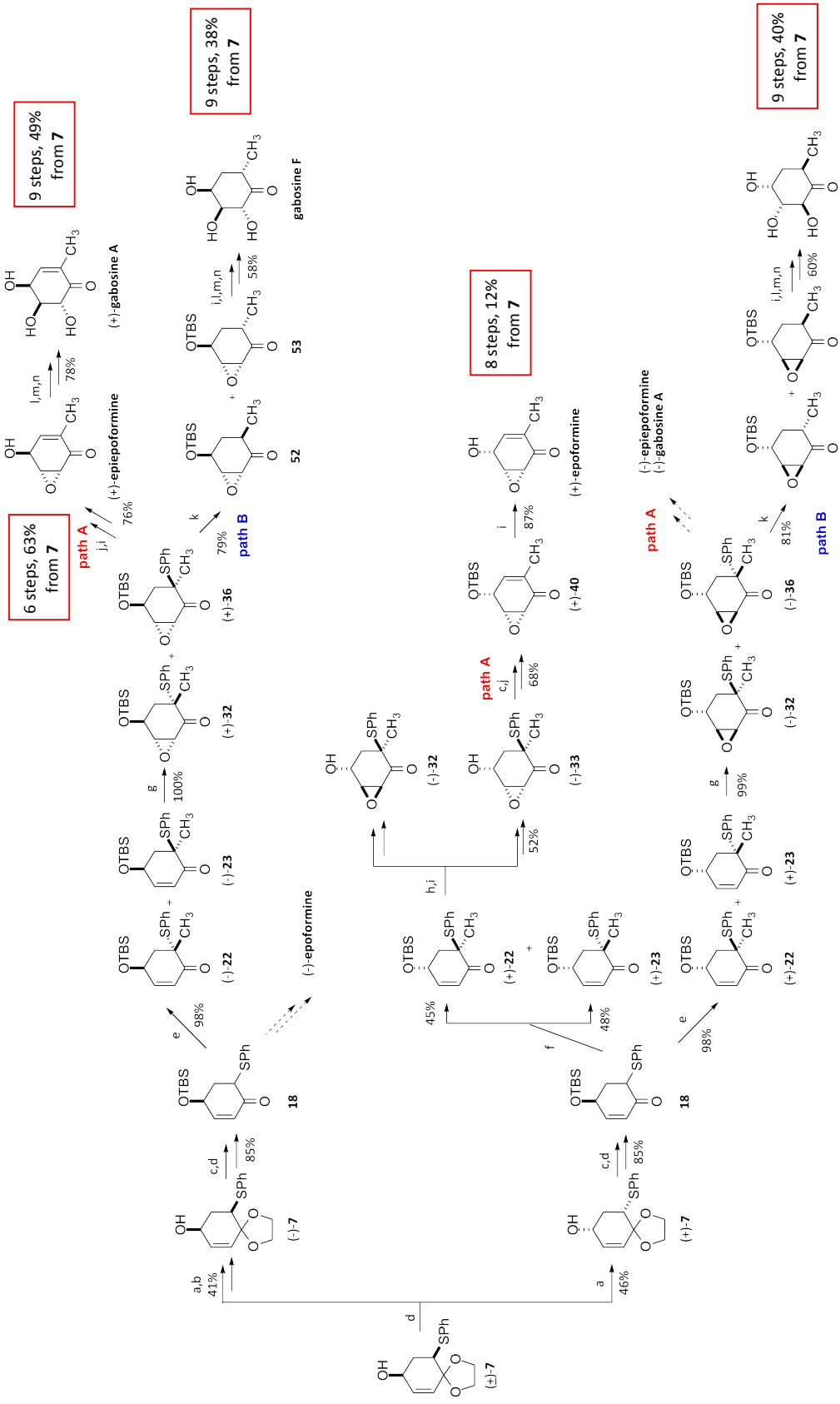
First, we dealt with the synthesis of both enantiomers of the 4-hydroxy-2-cyclohexenone, (+)- and (-)-**8**, and their silyl ethers (+)- and (-)-**11**. Application of the synthetic sequence depicted in Scheme 77 starting from (8*S*,10*R*)-**7** delivered the levorotatory enantiomer (4*S*)-**8** in 2 steps and 48% yield, and, the levoratory derivative (4*S*)-**11** in 3 steps and 57% yield. The practical syntheses developed in our laboratories deliver these compounds in high enantiomeric excesses and good yields. Moreover, the multigram scale preparation favours their use as precursors for the synthesis of more complex molecules with potential biological activity. Starting from ketone (4*S*)-**11**, the syntheses of both antipodes of *trans*-cyclohex-2-ene-1,4-diol, (+)- and (-)-**9**, and its silyl ether (+)- and (-)-**12**, which are very important intermediates in the synthesis of organic compounds as well as in polymer chemistry. Their syntheses have been successfully carried out in 65% and 72% yield, respectively, improving the previously published works.



Reagents and conditions: (a) Bu_3SnH, AIBN, toluene; (b) montmorillonite K-10, CH_2Cl_2; (c) TBS-im., CH_2Cl_2.

Scheme 77. Synthesis of (4*S*)-**8**, (4*S*)-**11** (1*S*,4*S*)-**12** and (1*S*,4*S*)-**9**.

On the other hand, both enantiomers of **7** were our material of choice to undertake a systematic synthesis of gabosines and anhydrogabosines through a sterodivergent strategy involving an oxidation/pyrolysis or a reduction of the C-S bond. The oxidation/pyrolysis pathway (path A) allowed the synthesis of (+)- and (-)-epiepoformin, (+)- and (-)-epoformin and (+) and (-)-gabosine A (Scheme 78). Finally, reduction of C-S bond (path B) delivered gabosines B and F.



Reagents and conditions: (a) Novozyme 435®, $CH_3CO_2CH{=}CH_2$, diisopropyl ether; (b) NaOMe, CH_3OH; (c) TBSCl, imidazole, CH_2Cl_2; (c) Montmorillonite K-10, CH_2Cl_2; (e) CH_3I, NaH, THF; (f) CH_3I, K^tBuO, THF; (g) ^tBuOOH, Triton B, THF; (h) H_2O_2, Triton B, THF; (i) $Et_3N{\cdot}3HF$, THF (j) i) *m*-CPBA, $CHCl_3$, ii) $CHCl_3$ reflux; (k) Bu_3SnH, AIBN, toluene; (l) Ac_2O, DMAP, ACN; (m) $BF_3{\cdot}Et_2O$, toluene; (n) MeONa, CH_3OH.

Scheme 78. Synthesis of (+)- and (-)-epiepoformin, (+)- and (-)-epoformin, (+)- and (-)-gabosine A, gabosine F and gabosine B.

VI. Experimental section

Chemical laboratory.

1. GENERAL PROCEDURES

All commercially available reagents including Lipase acrylic resin from *Candida Antarctica* (or Novozyme® 435 Lipase B) were used as received. Solvents were purified by distillation over the appropriate drying agents when required: CH_2Cl_2 (CaH_2), THF (Na), toluene (Na, without benzophenone).

1.1. SPECTROSCOPY

Nuclear magnetic resonance (NMR) spectra have been registered at the *Servei de Ressonància Magnètica Nuclear* in the *Universitat Autònoma de Barcelona*. ^{1}H-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 MeOH-d4, 3.34 ppm). ^{13}C-NMR spectra were recorded on Bruker DPX250 (62.5 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 MeOH-d4, 49.86 ppm). NMR signals were assigned with the help of COSY, NOE, NOESY, HMQCed and HMBC experiments. All spectra have been registered at 298 K.

The abbreviation used to describe signals multiplicities are: s (singlet), bs (broad singlet), d (doublet), bd (broad doublet), t (triplet), bd (broad triplet), q (quadruplet), bq (broad quadruplet), dd (double doublet), bdd (broad double doublet), ddd (double double doublet), dt (double triplet), bdt (broad double triplet), dqn (double quintuplet), dtt (double 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}.

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).

1.3. ELEMENTAL ANALYSIS

Elemental analyses have been done at the *Servei d'Anàlisi Química* in the *Universitat Autònoma de Barcelona* with an EA1108 analyzer (Carlo Erba), CHNS type.

1.4. CHROMATOGRAPHY

Thin-layer chromatographies have been done over 0.25 mm thick plates Alugram Sil G/UV_{254}. Developing has been realized using an UV lamp at 254 nm and/or using a $KMnO_4$/KOH aqueous solution. TLC Rf values are reported.

Flash chromatography was performed using 230-400 mesh or 40 μm (when so indicated) silica gel.

Gas chromatography (GC) analyses were performed using a Hewlett Packard 6890 GC coupled to a Hewlett Packard 3390A integrator using a capillary column coated with a cross linked dimethyl silicon phase (12 m x 0.2 mm x 0.22 μm). For chiral-GC analyses a FS-Lipodex B/20 m x 0.25 mm was used. The programs used were:

- Program 1: $T_{injector}$: 240 ºC, $T_{detector}$: 300 ºC, T_1: 200 ºC, t_1: 1 min, rate: 6 ºC/min, T_2: 260 ºC
- Program 2: $T_{injector}$: 240 ºC, $T_{detector}$: 300 ºC, T_1: 140 ºC, t_1: 20 min, rate: 2 ºC/min, T_2: 145 ºC

Chiral HPLC analyses were performed using a Watters 2690 instrument coupled to a UV Watters 2487 detector and with a Daicel Chiracel OD 4.6 x 250 mm column (detector at 210 nm) (pressure between 270-295 psi and flow of 0.7 ml/min).

1.5. OPTICAL ROTATION

Specific optical rotations were measured on a Propol Automatisches Dr. Kermchen polarimeter at 20±2 ºC 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.

1.6. MELTING POINT

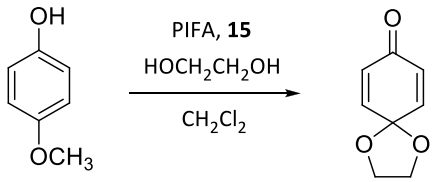
Melting points were determined on a REICHERT Koffler hot stage melting point apparatus and are uncorrected.

For better comprehension, the nomenclature used in the tittles, schemes and spectral assignments is intended to keep fixed numbers in equivalent carbon atoms of related compounds. The IUPAC names of the new compounds are given with their physical and spectroscopic properties.

2. AN EFFICIENT PROTOCOL FOR THE ENANTIOSELECTIVE PREPARATION OF A KEY POLYFUNCTIONALIZED CYCLOHEXANE: (±)-*cis*-10-PHENYLTHIO-1,4-DIOXASPIRO[4.5]DEC-6-EN-8-OL, **7**

2.1. PREPARATION OF RACEMIC **1**

2.1.1. 1,4-Dioxaspiro[4.5]deca-6,9-dien-8-one, **5**



14 **5**

Ethylene glycol (2.8 mL, 50.21 mmol) was added to a solution of 4-methoxyphenol, **14**, (4.08 g, 32.87 mmol) in anhydrous CH_2Cl_2 (33 mL) placed in a 100 mL Schlenk flask under nitrogen. The resulting solution was added dropwise to a solution of PIFA (18.38 g, 42.74 mmol) in anhydrous CH_2Cl_2 (140 mL) placed in a 500 mL three necked flask under nitrogen at 0 ºC. The reaction mixture was warmed up to room temperature and so left for 45 min. Then, it was neutralized by addition of saturated aq. Na_2CO_3, the organic layer was separated and the aqueous one was extracted with CH_2Cl_2 (2 x 60 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to furnish an oily residue (4.37 g). Purification of this material by a quick filtration through a short pad of silica gel (hexanes/EtOAc, from 9:1 to 3:1) gave **5**[44] (4.35 g, 28.60 mmol, 87% yield) as a yellow solid.

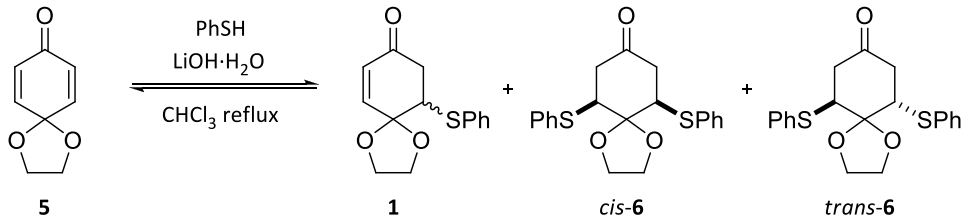
Physical and spectroscopic data of **5**:

R_f= 0.47 (hexanes/EtOAc, 1:2).

m.p.= 49-50 ºC (Et_2O/cyclohexane).

^{1}H-NMR (250 MHz, $CDCl_3$): δ 6.62 (d, $J_{7,6}$= 10.2 Hz, 1H: H_6), 6.17 (d, $J_{6,7}$= 10.2 Hz, 1H: H_7), 4.15 (s, 2H: OCH_2).

2.1.2. (±)-10-Phenylthio-1,4-dioxaspiro[4.5]dec-6-en-8-one, (±)-**1**



5 **1** *cis*-**6** *trans*-**6**

Thiophenol (2.6 mL, 25.25 mmol) and $LiOH·H_2O$ (433 mg, 10.32 mmol) were added to a solution of monoketal **5** (6.99 g, 45.94 mmol) in $CHCl_3$ (60 mL) and the mixture was stirred at the reflux temperature for 4.5 h. Then, it was neutralized with 2% AcOH, the organic layer was separated, washed with H_2O and dried over anhydrous $MgSO_4$. Removal of the solvent furnished a brownish residue (9.80 g). This residue was filtered through a short pad of silica gel with hexanes:Et_2O, 1:1. Evaporation of the solvent under vacuum gave an oily material (9.19 g), which was crystallized from 2-propanol obtaining (±)-**1** as the major product (81% respect to PhSH), as well as some starting monoketal and a little amount of diaddition products **6**. Two consecutive recrystallizations from the same solvent delivered pure (±)-**1**[30] (4.09 g, 15.59 mmol, 62%).

Physical and spectroscopic data of (±)-**1**:

R_f= 0.32 (toluene/Et_2O, 9:1).

m.p. 48-51 ºC (2-propanol).

^{1}H-NMR (250 MHz, $CDCl_3$): δ 7.52-7.46 (m, 2H: H_{ar}), 7.34-7.24 (m, 3H: H_{ar}), 6.67 (d, $J_{6,7}$= 10.1 Hz, 1H: H_6), 6.03 (d, $J_{7,6}$= 10.1 Hz, 1H: H_7), 4.27 (m, 2H: OCH_2CH_2O), 4.14 (m, 2H: OCH_2CH_2O), 3.81 (dd, $J_{10,9}$= 9.6 Hz, $J_{10,9}$= 6.5 Hz, 1H: H_{10}), 2.88 (d, $J_{9,10}$= 6.5 Hz, 1H: H_9), 2.87 (d, $J_{9,10}$=9.6 Hz, 1H: H_9).

Physical and spectroscopic data of *cis*-(±)-**6**:[30]

R_f= 0.54 (toluene/Et_2O, 9:1).

m.p.= 121-124 ºC (CH_2Cl_2/pentane).

^{1}H-NMR (250 MHz, $CDCl_3$): δ 7.52-7.46 (m, 2H: H_{ar}), 7.32-7.26 (m, 3H: H_{ar}), 4.45 (m, 2H: OCH_2), 3.56 (dd, $J_{6,7ax}$= 13.9 Hz, $J_{6,7eq}$= 5.2 Hz, 1H: H_6), 2.88 (dd, $J_{7ax,7eq}$= 14.6 Hz, $J_{7ax,6}$=13.9 Hz, 1H: H_{7ax}), 2.68 (dd, $J_{7eq,7ax}$=14.6 Hz, $J_{7eq,6}$= 5.2 Hz, 1H: H_{7eq}).

Physical and spectroscopic data of *trans*-(±)-**6**:[30]

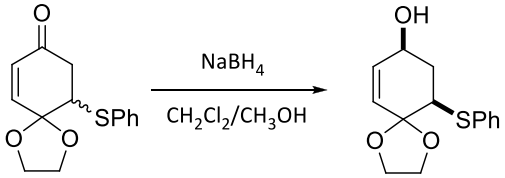
R_f= 0.45 (toluene/Et_2O, 9:1).

m.p. = 68-69 ºC (CH_2Cl_2/pentane).

^{1}H-NMR (250 MHz, $CDCl_3$): δ 7.53-7.48 (m, 2H: H_{ar}), 7.38-7.26 (m, 3H: H_{ar}), 4.23 (s, 2H: OCH_2), 3.91 (dd, $J_{6,7}$=8.0 Hz, $J_{6,7}$= 5.2 Hz, 1H: H_6), 2.93 (ddd, $J_{7,7}$= 15.2 Hz, $J_{7,6}$= 5.2 Hz, $J_{7,9}$= 1.6 Hz, 1H: H_7), 2.63 (ddd, $J_{7,7}$= 15.2 Hz, $J_{7,6}$= 8.0 Hz, $J_{7,9}$= 1.6 Hz, 1H: H_7).

2.2. RESOLUTION OF THE RACEMIC **1**

2.2.1. (±)-*cis*-10-Phenylthio-1,4-dioxaspiro[4.5]dec-6-en-8-ol, (±)-**7**[38]



1 **7**

To a solution of enone (±)-**1** (1.50 g, 5.72 mmol) in a mixture of CH_3OH (15 mL) and CH_2Cl_2 (15 mL) at 0 ºC, $NaBH_4$ (64 mg, 1.69 mmol) was added portionwise. The reaction mixture was stirred at 0 ºC for 1 h and then at room temperature until TLC control showed complete conversion. The solvent was removed under reduced pressure, water (50 mL) was added, and then it was acidified with 4% HCl. The aqueous solution was extracted with CH_2Cl_2 (3 x 30 mL), the combined organic extracts were dried over $MgSO_4$, and the solvent was evaporated under vacuum to yield a white solid residue (2.20 g). This solid was purified by flash chromatography (CH_2Cl_2/Et_2O, 9:1) to yield (±)-**7** (1.41 g, 5.33 mmol, 93%) as a white solid.

Physical and spectroscopic data of (±)-**7**:

R_f= 0.30 (CH_2Cl_2/Et_2O, 9:1).

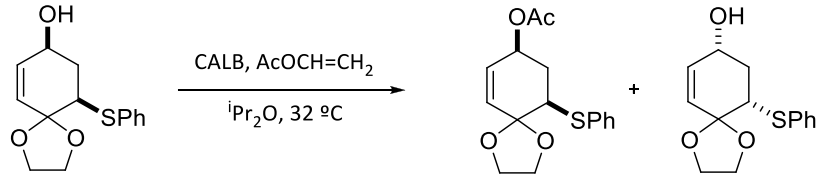
m.p. = 62-64 ºC (CH_2Cl_2/pentane).

^{1}H-NMR (360 MHz, $CDCl_3$): δ 7.51-7.47 (m, 2H: H_{ar}), 7.32-7.19 (m, 3H: H_{ar}), 5.91 (ddd, $J_{7,6}$= 10.1 Hz, $J_{7,8}$= 2.2 Hz, $J_{7,9eq}$= 1.6 Hz, 1H: H_7), 5.66 (dd, $J_{6,7}$= 10.1 Hz, $J_{6,8}$= 1.9 Hz, 1H: H_6), 4.22 (m, 3H: OCH_2CH_2O, H_8), 4.06 (m, 2H: OCH_2CH_2O), 3.45 (dd, $J_{10,9ax}$= 12.8 Hz, $J_{10,9eq}$= 3.2 Hz, 1H: H_{10}), 2.46 (dddd, $J_{9eq,9ax}$= 12.8 Hz, $J_{9eq,8}$= 5.6 Hz, $J_{9eq,10}$= 3.2 Hz, $J_{9eq,7}$= 1.6 Hz, 1H: H_{9eq}), 2.01 (dt, $J_{9ax,9eq}$=$J_{9ax,10}$=12.8 Hz, $J_{9ax,8}$=9.3 Hz, 1H: H_{9ax}).

This reaction was scaled using up to 4.25 g of (±)-**1**, providing (±)-**7** in quantitative yields. For synthetic purposes the crude reaction mixture was used in the next step without any purification.

2.2.2. Kinetic resolution of (±)-**7**

2.2.2.1. (8*R*,10*S*)-10-Phenylthio-1,4-dioxaspiro[4.5]dec-6-en-8-ol, (+)-**7** and (8*S*,10*R*)-10-phenylthio-1,4-dioxaspiro[4.5]dec-6-en-8-yl acetate, (-)-**10**



7 (-)-**10** 45%, 96% ee (+)-**7** 46%, 91% ee

Alcohol (±)-**7** (9.35 g, 35.37 mmol) was placed in a 1 L reactor provided with mechanical stirrer,dissolved in $^{i}Pr_2O$ (515 mL), and the solution was warmed to 32 ºC. Then, lipase acrylic resin from C. *Antarctica* (536 mg) and vinyl acetate (19.6 mL, 212.64 mmol) were added. The reaction evolution was monitored by TLC (CH_2Cl_2/Et_2O, 9:1) and GC analyses (program 1 GC, see Experimental Section). Once the alcohol/acetate (R_t= 7.9 min)/(R_t= 9.1 min) ratio reached 1:1.1, the enzyme was recovered by simple filtration and the solvent was evaporated under vacuum. Purification of the residue by flash chromatography (CH_2Cl_2 to CH_2Cl_2/Et_2O, 9:1) furnished (-)-**10**[33] (4.87 g, 15.89 mmol, 45% yield, 96% ee) (CHPLC, hexanes/2-propanol 80:20) and (+)-**7**[33] (4.30 g, 16.27 mmol, 46% yield, 98% ee) (CHPLC, hexanes/2-propanol 80:20).

(+)-**7**: **m.p.** = 77-78 ºC (CH_2Cl_2/pentane). **$[\alpha]_D^{20}$**= +14 (*c* 0.86, $CHCl_3$) (lit.[38] for the enantiomer $[\alpha]_D^{20}$= -15 (*c* 0.95, $CHCl_3$)).

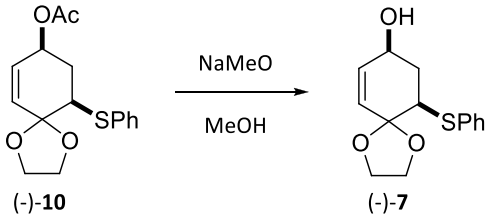
Physical and spectroscopic data of (-)-**10**:

R_f= 0.72 (CH_2Cl_2/Et_2O, 9:1).

^{1}H-NMR (360 MHz, $CDCl_3$): δ 7.50-7.45 (m, 2H: H_{ar}), 7.31-7.20 (m, 3H: H_{ar}), 5.80 (dt, $J_{7,6}$= 10.2 Hz, $J_{7,8}\approx J_{7,9eq}\approx$ 1.7 Hz, 1H: H_7), 5.74 (dd, $J_{6,7}$= 10.2 Hz, $J_{6,8}$= 1.7 Hz, 1H: H_6), 5.33 (ddt, $J_{8,9ax}$= 10.0 Hz, $J_{8,9eq}$= 5.9 Hz, $J_{8,7}\approx J_{8,6}\approx$ 1.7 Hz, 1H: H_8), 4.14 (m, 4H: OCH_2CH_2O), 3.47 (dd, $J_{10,9ax}$= 13.8 Hz, $J_{10,9eq}$= 3.3 Hz, 1H: H_{10}), 2.48 (dddd, $J_{9eq,9ax}$= 12.6 Hz, $J_{9eq,8}$= 5.9 Hz, $J_{9eq,10}$= 3.2 Hz, $J_{9eq,7}$= 1.7 Hz, 1H: H_{9eq}), 2.12 (ddd, $J_{9ax,10}$= 13.8 Hz, $J_{9ax,9eq}$= 12.6 Hz, $J_{9ax,8}$= 10.0 Hz, 1H: H_{9ax}), 2.03 (s, 3H: $OCOCH_3$).

$[\alpha]_D^{20}$= -7.7 (*c* 1.0, $CHCl_3$) (lit.[33] $[\alpha]_D^{20}$= -7.7 (*c* 1.0, $CHCl_3$)).

2.2.2.2. (8*S*,10*R*)-10-Phenylthio-1,4-dioxaspiro[4.5]dec-6-en-8-ol, (-)-**7**



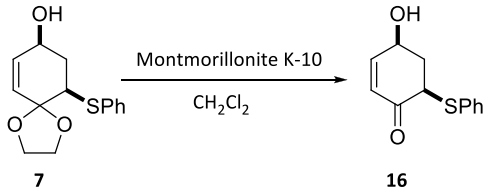
(-)-**10** (-)-**7**

To a solution of acetate (-)-**10** (980 mg, 3.20 mmol) in MeOH (11 mL), NaMeO (173 mg, 3.21 mmol) was added and the mixture was stirred at room temperature for 0.5 h. Then, the solvent was removed under reduced pressure and the residue was diluted with water and slightly acidified with 2% HCl. The aqueous solution was extracted with CH_2Cl_2 (3 x 35 mL), the combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was evaporated under vacuum. Purification of the residue by flash chromatography (CH_2Cl_2/Et_2O, 9:1) furnished alcohol (-)-**7**[33] (770 mg, 2.91 mmol, 92% yield, 96% ee) as a white solid.

(-)-**7**: **m.p.**= 79-80 ºC (CH_2Cl_2/pentane). **$[\alpha]_D^{20}$**= -15 (*c* 0.95, $CHCl_3$) (lit.[38] $[\alpha]_D^{20}$= -15 (*c* 0.95, $CHCl_3$)).

3. SYNTHESIS OF (*R*)- AND (*S*)-4-HYDROXY-2-CYCLOHEXENONE, **8**, AND (*R*)- AND (*S*)-*trans*-CYCLOHEX-2-ENE-1,4-DIOL, **9**

3.1. (±)-*cis*-6-Phenylthio-4-hydroxy-2-cyclohexenone, (±)-**16**



7 **16**

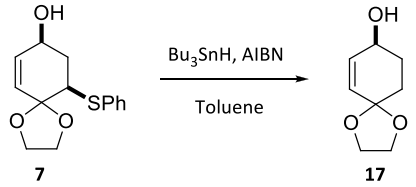
Montmorillonite K-10 (590 mg) was added to a solution of acetal (±)-**7** (100 mg, 0.38 mmol) in CH_2Cl_2 (4.4 mL) and the mixture was stirred at room temperature for 2 h. Then, it was filtered and the solvent removed under vacuum to furnish (±)-**16**[35] (73 mg, 0.33 mmol, 88%) as an oil.

Physical and spectroscopic data of (±)-**16**:

R_f= 0.66 (CH_2Cl_2/Et_2O, 3:1).

^{1}H-RMN (250 MHz, $CDCl_3$): δ 7.51-7.45 (m, 2H: H_{ar}), 7.34-7.29 (m, 3H: H_{ar}), 6.92 (ddd, $J_{3,2}$= 10.2 Hz, $J_{3,4}$= 2.6 Hz, $J_{3,5eq}$= 1.6 Hz, 1H: H_3), 6.06 (dd, $J_{2,3}$= 10.2 Hz, $J_{2,4}$= 2.0 Hz, 1H: H_2), 4.56 (m, 1H: H_4), 3.89 (dd, $J_{6,5ax}$= 11.5 Hz, $J_{6,5eq}$= 4.7 Hz, 1H: H_6), 2.59 (dtd, $J_{5eq,5ax}$= 13.0 Hz, $J_{5eq,6}$≈$J_{5eq,4}$≈ 4.7 Hz, $J_{5eq,3}$= 1.6 Hz, 1H: H_{5eq}), 2.13 (d, $J_{OH,4}$= 7.4 Hz, 1H: OH), 2.13 (ddd, $J_{5ax,5eq}$= 13.0 Hz, $J_{5ax,6}$= 11.5 Hz, J_{5ax-4}= 8.1 Hz, 1H: H_{5ax}).

3.2. (**±**)-1,4-Dioxaspiro[4.5]dec-6-en-8-ol, (±)-**17**



7 **17**

To a boiling solution of alcohol (±)-**7** (1.25 g, 4.73 mmol) in anhydrous toluene (48 mL) under nitrogen atmosphere, Bu_3SnH (2.5 mL, 9.29 mmol, dropwise addition) and a small quantity of AIBN were initially added. Then, a solution of AIBN (2.44 g, 14.86 mmol) in toluene (96 mL) was added continuously during 4 h, and additional portions of Bu_3SnH (1.25 mL, 4.65 mmol) were added every 30 min. After that time, the solvent was evaporated under vacuum and the residue was purified by flash chromatography (CH_2Cl_2 to CH_2Cl_2/Et_2O, 10:3), providing unreacted (±)-**7** (120 mg, 0.45 mmol) and alcohol (±)-**17**[62] (595 mg, 3.81 mmol, 81%, 89% from unrecovered (±)-**7**) as an oil.

Physical and spectroscopic data of (±)-**17**:

R_f= 0.14 (CH_2Cl_2/Et_2O, 10:3).

^{1}H-RMN (360 MHz, $CDCl_3$): δ 5.91 (ddd, $J_{7,6}$= 10.1 Hz, J'= 2.6 Hz, J''= 0.9 Hz, 1H: H_7), 5.57 (dt, $J_{6,7}$= 10.1 Hz, J'≈J''≈ 1.5 Hz, 1H: H_6), 4.16 (bs, 1H: H_8), 3.92 (m, 4H: OCH_2CH_2O), 2.39 (bs, 1H: OH), 2.05 (m, 1H: H_9), 1.89 (m, 1H: H_9)2.05 (m, 2H: H_9), 1.72 (m, 2H: H_{10}).

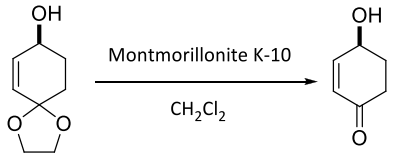
^{13}C-RMN (91 MHz, $CDCl_3$): δ 135.3 (C_7), 129.0 (C_6), 105.2 (C_5), 65.9 (C_8), 64.8 (C_2/C_3), 64.6 (C_2/C_3), 31.1 (C_{10}), 30.7 (C_9).

COSY and **HMQCed** spectra have been registered.

3.2.1. The same reaction starting from (8*S*,10*R*)-**7** (45 mg, 0.17 mmol) in anhydrous toluene (1.5 mL), Bu_3SnH (450 μl, 1.67 mmol) and solution of AIBN (87 mg, 0.53 mmol) in toluene (3.5 mL) , furnished (*S*)-**17** (20 mg, 0.13 mmol, 78%, 90% from unrecovered (8*S*,10*R*)-**7**).

(-)-**17**: $[\alpha]_D^{20}$= -38 (*c* 1.64, $CHCl_3$) (lit.[62] $[\alpha]_D^{20}$= -40.5 (*c* 1.24, $CHCl_3$)).

3.3. (±)-4-Hydroxy-2-cyclohexenone, (±)-**8**



17 **8**

Montmorillonite K-10 (383 mg) was added to a solution of acetal (±)-**17** (45 mg, 0.29 mmol) in CH_2Cl_2 (3.4 mL) and the mixture was stirred at room temperature for 2 h. Then, it was filtered and the solvent removed under vacuum to furnish an oily residue, which was purified by flash chromatography in Baker silica gel (hexanes/EtOAc, from 7:4 to 1:1) to provide (±)-**8**[35] (20 mg, 0.18 mmol, 62%) as an oil.

Physical and spectroscopic data of (±)-**8**:

$\mathbf{R_f}$= 0.40 (EtOAc).

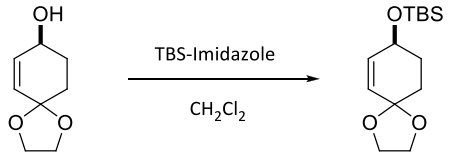
^{1}H-RMN (250 MHz, $CDCl_3$): δ 6.93 (ddd, $J_{3,2}$= 10.2 Hz, J'= 2.4 Hz, J''= 1.6 Hz, 1H: H_3), 5.97 (dt, $J_{2,3}$= 10.2 Hz, J'= 2.0 Hz, J''= 1.0 Hz, 1H: H_2), 4.58 (bs, 1H: H_4), 2.59 (dt, J= 17.0 Hz, J'≈J''≈ 4.3 Hz , 1H: H_6), 2.36 (m, 2H: H_6, H_5), 1.95 (m, 1H: H_5).

^{13}C-RMN (90 MHz, $CDCl_3$): δ 199.4 (C_1), 153.6 (C_3), 129.0 (C_2), 66.2 (C_4), 35.4 (C_5/C_6), 32.4 (C_5/C_6).

3.3.1. The same reaction starting from (*S*)-**17** (18 mg, 0.11 mmol) in CH_2Cl_2 (13 mL) and 0.15 mg of montmorillonite K-10 furnished (*S*)-**8** (9 mg, 0.08 mmol, 70%).

(*S*)-**8**: ee 88% (GC, chiral column, program 2). $[\alpha]_D^{20}$= -92 (*c* 0.50, $CHCl_3$) (lit.[35] $[\alpha]_D^{20}$= -92.3 (*c* 1.3, $CHCl_3$)).[60]

3.4. (±)-8-*tert*-Butyldimethylsilyloxy-1,4-dioxaspiro[4.5]dec-6-ene, (±)-**18**



17 **18**

To a solution of alcohol (±)-**17** (763 mg, 4.88 mmol) in anhydrous CH_2Cl_2 (34 mL) at 0 ºC under N_2 atmosphere, TBDMS-imidazole (1.3 mL, 6.69 mmol) was added dropwise and the reaction mixture was heated at reflux temperature for 20 h. After that time, water (3 mL) was added, and the resulting suspension was acidified with 2 M HCl. The organic layer was separated, the aqueous one extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic extracts were dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography (CH_2Cl_2/Et_2O, 9:1) to provide silyl ether (±)-**18**[62] (1.20 g, 4.44 mmol, 91%) as a colourless oil.

Physical and spectroscopic data of (±)-**18**:

R_f= 0.66 (CH_2Cl_2/Et_2O, 9:1).

^{1}H-RMN (250 MHz, $CDCl_3$): δ 5.84 (ddd, $J_{7,6}$= 10.1 Hz, J'= 2.6 Hz, J''= 0.9 Hz, 1H: H_7), 5.55 (dt, $J_{6,7}$= 10.1 Hz, J'≈J''≈ 1.5 Hz, 1H: H_6), 4.21 (m, 1H: H_8), 3.94 (m, 4H: OCH_2CH_2O), 1.96 (m, 2H: H_9, H_{10}), 1.75 (m, 2H: H_9, H_{10}), 0.88 (s, 9H: ^{t}Bu), 0.07 (s, 3H: $SiCH_3$), 0.06 (s, 3H: $SiCH_3$).

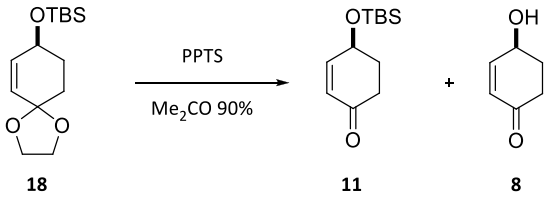
^{13}C-RMN (91 MHz, $CDCl_3$): δ 136.4 (C_7), 127.9 (C_6), 105.4 (C_5), 66.8 (C_8), 64.8 (C_2/C_3), 64.7 (C_2/C_3), 31.4 (C_9/C_{10}), 31.2 (C_9/C_{10}), 26.0 ($C(\underline{C}H_3)_3$), 18.3 ($\underline{C}(CH_3)_3$), -4.4 ($SiCH_3$), -4.5 ($SiCH_3$).

COSY and **HSQCed** spectra have been registered.

3.4.1. The same reaction starting from (*S*)-**17** (77 mg, 0.49 mmol) in CH_2Cl_2 (3.9 mL) and TBDMS-imidazole (55 µL, 0.28 mmol) furnished (*S*)-**18** (108 mg, 0.40 mmol, 81%).

(*S*)-**18**: **$[\alpha]_D^{20}$**= -47 (*c* 2.40, $CHCl_3$) (lit.[62] $[\alpha]_D^{20}$ = -54.9 (*c* 0.70, $CHCl_3$)).

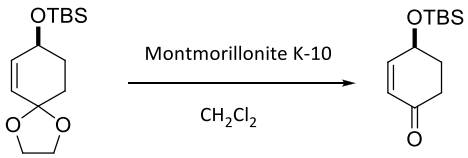
3.5. (±)-4-*tert*-Butyldimethylsilyloxy-2-cyclohexenone, (±)-**11**



18 **11** **8**

To a boiling solution of acetal (±)-**18** (27 mg, 0.10 mmol) in 90% Me_2CO (0.45 mL), pyridinium *p*-toluenesulfonate (1.5 mg, 0.006 mmol) was added, and the mixture was stirred at room temperature for 1 h. After that time, the solvent was evaporated under vacuum to give an oily residue. ^{1}H-NMR spectra showed the presence of (±)-**11** and part of the silyl deprotected product (±)-**8**.

3.6. (±)-4-*tert*-Butyldimethylsilyloxy-2-cyclohexenone, (±)-**11**



18 **11**

Montmorillonite K-10 (5.81 g) was added to a solution of acetal (±)-**18** (1.18 g, 4.36 mmol) in CH_2Cl_2 (50 mL), and the mixture was stirred at room temperature for 1 h. Then, it was filtered and the solvent removed under vacuum to furnish an oily residue, which was purified by flash chromatography in Baker silica gel (CH_2Cl_2/Et_2O, 10:3) to provide (±)-**11**[73] (905 mg, 4.00 mmol, 92%) as an oil.

Physical and spectroscopic data of (±)-**11**:

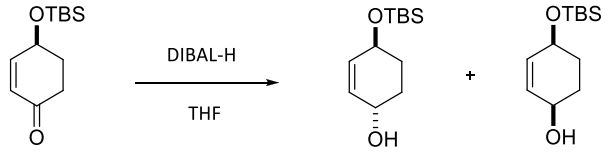
R_f= 0.66 (CH_2Cl_2/Et_2O, 10:3).

^{1}H-RMN (360 MHz, $CDCl_3$): δ 6.83 (ddd, $J_{3,2}$= 10.2 Hz, $J_{3,4}$= 2.4 Hz, $J_{3,5eq}$= 1.7 Hz, 1H: H_3), 5.92 (ddd, $J_{2,3}$= 10.2 Hz, $J_{2,4}$= 2.0 Hz, $J_{2,6eq}$= 1.1 Hz, 1H: H_2), 4.53 (ddt, $J_{4,5ax}$= 9.1 Hz, $J_{4,5eq}$= 4.7 Hz, $J_{4,2}$≈$J_{4,3}$≈ 2.1 Hz, 1H: H_4), 2.57 (dtd, $J_{6eq,6ax}$= 16.8 Hz, $J_{6eq,5ax}$≈$J_{6eq,5eq}$≈ 4.7 Hz, $J_{6eq,2}$= 1.1 Hz, 1H: H_{6eq}), 2.34 (ddd, $J_{6ax\text{-}6eq}$= 16.8 Hz, $J_{6ax,5ax}$= 12.8 Hz, $J_{6ax,5eq}$= 4.7 Hz, 1H: H_{6ax}), 2.21 (dqd, $J_{5eq,5ax}$= 12.8 Hz, $J_{5eq,4}$≈ $J_{5eq,6eq}$≈ $J_{5eq,6ax}$≈ 4.7 Hz, $J_{5eq,3}$= 1.7 Hz, 1H: H_{5eq}), 2.00 (tdd, $J_{5ax,5eq}$=$J_{5ax,6ax}$= 12.8 Hz, $J_{5ax,4}$= 9.1 Hz, $J_{5ax,6eq}$= 4.7 Hz, 1H: H_{5ax}), 0.92 (s, 9H: ^{t}Bu), 0.13 (s, 3H: $SiCH_3$), 0.12 (s, 3H: $SiCH_3$).

3.6.1. The same reaction starting from (*S*)-**18** (82 mg, 0.30 mmol) in CH_2Cl_2 (3.5 mL) and 403 mg of montmorillonite K-10, furnished (*S*)-**11** (60 mg, 0.26 mmol, 87%).

(*S*)-**11**: **$[\alpha]_D^{20}$**= -100 (*c* 0.16, CH_2Cl_2). (lit.[73] $[\alpha]_D^{20}$= -109.6 (*c* 1.46, CH_2Cl_2)).

3.7. (±)-*trans*-4-*tert*-Butyldimethylsilyloxy-2-cyclohexenol, (±)- *trans*- **12**



11 *trans*-**12** *cis*-**12**

To a solution of (±)-**11** (505 mg, 2.23 mmol) in anhydrous THF (30 mL) at -78 ºC, DIBAL-H (1 M in THF, 9 mL, 9.00 mmol) was added dropwise. The mixture was stirred for 50 min, then quenched with MeOH (30 mL), and allowed to warm to room temperature. After 1 h of additional stirring, the mixture was filtered through a Celite pad and the solvent was evaporated. The residue obtained was purified by flash chromatography (hexanes/EtOAc, from 20:1 to 12:1) to provide (±)-*trans*-**12**[38] (365 mg, 1.60 mmol, 72%) and (±)-*cis*-**12**[38] (135 mg, 0.59 mmol, 26%) as an oil.

Physical and spectroscopic data of (±)-*trans*-**12**:

R_f= 0.38 (hexanes/EtOAc, 7:3).

^{1}H-RMN (360 MHz, $CDCl_3$): δ 5.71 (m, 2H: H_2, H_3), 4.26 (m, 2H: H_1, H_4), 2.16-1.94 (m, 2H: $2H_5$/$2H_6$), 1.60-1.40 (m, 3H: $2H_5$/$2H_6$/OH), 0.89 (s, 9H: ^{t}Bu), 0.08 (s, 3H: $SiCH_3$), 0.07 (s, 3H: $SiCH_3$).

Physical and spectroscopic data of (±)-*cis*-**12**:

R_f= 0.44 (hexanes/EtOAc, 7:3).

^{1}H-RMN (360 MHz, $CDCl_3$): δ 5.78 (m, 2H: H_2, H_3), 4.14 (m, 1H: H_4), 4.09 (m, 1H: H_1), 1.85-1.60 (m, 2H: $2H_5$/$2H_6$), 1.46 (bs, 1H: OH), 1.35-1.20 (m, 2H: $2H_5$/$2H_6$), 0.89 (s, 9H: ^{t}Bu), 0.08 (s, 3H: $SiCH_3$), 0.07 (s, 3H: $SiCH_3$).

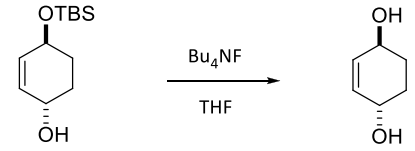
3.7.1. The same reaction starting from (*S*)-**11** (105 mg, 0.46 mmol) in THF (6.2 mL) and DIBAL-H (1M in THF, 1.9 mL, 1.9 mmol) furnished (1*S*,4*S*)-**12** (72 mg, 0.31 mmol, 68 %) and (1*R*,4*S*)-**12** (24 mg, 0.10 mmol, 23%).

(1*S*,4*S*)-**12**: **$[\alpha]_D^{20}$**= -96 (*c* 0.96, $CHCl_3$) (lit.[38] $[\alpha]_D^{20}$ = -95 (*c* 0.95, $CHCl_3$)). ee 94% (CHPLC, hexanes/2-propanol, 99:1).

(1*R*,4*S*)-**12**: **$[\alpha]_D^{20}$**= -30 (*c* 0.40, EtOH). (lit.[1] $[\alpha]_D^{20}$ = -95 (*c* 0.95, $CHCl_3$)).

[1] Gatti, R. G. P.; Larsson, A. L. E.; Bäckvall, J.-E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 577-584.

3.8. (±)-*trans*-Cyclohex-2-ene-1,4-diol, (±)-*trans*-**9**



trans-**12** *trans*-**9**

To a solution of silyl ether (±)-*trans*-**12** (334 mg, 1.46 mmol) in THF (2.9 mL) at room temperature, Bu_4NF (1 M in THF, 2.9 mL, 2.90 mmol) was added and the mixture was stirred for 14 h. Then, the solvent was evaporated under reduced pressure and the residue was purified by flash chromatography ($CHCl_3$/MeOH, 30:1) to provide (±)-*trans*-**9**[38] (151 mg, 1.32 mmol, 90%) as a white solid.

Physical and spectroscopic data of (±)-*trans*-**9**:

R_f= 0.30 (EtOAc).

^{1}H-RMN (360 MHz,CDCl3): δ 5.81 (s, 1H: H_2, H_3), 4.27 (bt, 1H: H_1, H_4), 2.14 (m, 1H: H_5/H_6), 1.50 (m, 1H: H_5/H_6).

^{13}C-RMN (90 MHz, $CDCl_3$): δ 132.8 (C_2/C_3), 66.4 (C_1/C_4), 30.5 (C_5/C_6).

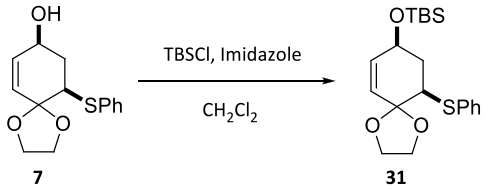
3.8.1. The same reaction starting from (1*S*,4*S*)-**12** (70 mg, 0.31 mmol) in THF (0.6 mL) and TBAF (1M in THF, 0.6 mL, 0.60 mmol) furnished (1*S*,4*S*)-**9** (30 mg, 0.26 mmol, 87%)

(1*S*,4*S*)-**9**: **$[\alpha]_D^{20}$**= -112 (*c* 0.25, $CHCl_3$). (lit.[38] $[\alpha]_D^{20}$= -112 (*c* 0.25, $CHCl_3$)). ee 93% (CHPLC, hexanes/2-propanol, 98:2).

4. SYNTHESIS OF GABOSINES AND ANHYDROGABOSINES

4.1. SYNTHESIS OF KETONE **13**

4.1.1. *cis*-8-*tert*-Butyldimethylsilyloxy-10-phenylthio-1,4-dioxaspiro[4.5]dec-6-ene, (±)-**31**



7 **31**

To a solution of alcohol (±)-**7** (2.30 g, 8.70 mmol) in anhydrous CH_2Cl_2 (70 mL) at 0 ºC under nitrogen atmosphere, TBDMS-imidazole (2.7 mL, 13.91 mmol) was added dropwise, and the reaction mixture was heated at reflux temperature for 24 h. After that time, water (6 mL) was added and the resulting suspension was acidified with 2M HCl. The organic layer was separated, the aqueous one extracted with CH_2Cl_2 (3 x 30 mL), and the combined organic extracts were dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexanes/EtOAc, 5:1) to provide silylether (±)-**31**[38] (3.29 g, 8.69 mmol, quant. yield) as a white solid.

Physical and spectroscopic data of (±)-**31**:

R_f= 0.54 (hexanes/EtOAc, 5:1).

m.p.= 35-37 ºC ($CHCl_3$).

^{1}H-RMN (360 MHz, $CDCl_3$): δ 7.51-7.46 (m, 2H: $2H_{ar}$), 7.32-7.18 (m, 3H: $3H_{ar}$), 5.79 (dt, $J_{7,6}$= 10.1 Hz, $J_{7,8}$≈$J_{7,9}$≈ 1.9 Hz, 1H: H_7), 5.60 (dd, $J_{6,7}$= 10.1 Hz, $J_{6,8}$= 1.9 Hz, 1H: H_6), 4.26 (ddt, $J_{8,9ax}$= 9.8 Hz, $J_{8,9eq}$= 5.7 Hz, $J_{8,7}$≈$J_{8,6}$≈ 1.9 Hz 1H: H_8), 4.12 (m, 4H: OCH_2CH_2O), 3.42 (dd, $J_{10,9ax}$= 14.0 Hz, $J_{10,9eq}$= 3.1, 1H: H_{10}), 2.31 (dddd, $J_{9eq,9ax}$= 12.7 Hz, $J_{9eq,8}$= 5.7 Hz, $J_{9eq,10}$= 3.1 Hz, $J_{9eq,7}$= 1.8 Hz, 1H: H_{9eq}), 2.07 (ddd, $J_{9ax,10}$= 14.0 Hz, $J_{9ax,9eq}$= 12.7 Hz, $J_{9ax,8}$= 9.8 Hz, 1H: H_{9ax}), 0.86 (s, 9H: ^{t}Bu), 0.04 (s, 3H: $SiCH_3$), 0.03 (s, 3H: $SiCH_3$).

To scale up, TBDMSCl and Imidazole were used instead of TBDMS-imidazole.

To a solution of alcohol (±)-**7** (5.8 g, 21.94 mmol) in anhydrous CH_2Cl_2 (175 mL) under N_2 atmosphere, imidazole (2.24 g, 32.90 mmol) was added. The reaction mixture was cooled at 0 ºC and TBDMSCl (4.3 g, 28.53 mmol) was added dropwise. Then, the mixture was heated at reflux temperature for 24 h. After that time, water (15 mL) was added and the resulting suspension was acidified with 2M HCl. The organic layer was separated, the aqueous one extracted with CH_2Cl_2 (3 x 75 mL), and the combined organic extracts were dried over anhydrous $MgSO_4$. The solvent was

evaporated under reduced pressure and the residue was purified by flash chromatography (hexanes/EtOAc, 5:1) to provide silylether (±)-**31** (7.6 g, 20.07 mmol, 92% yield) as a white solid.

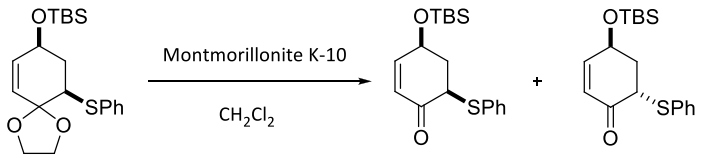
4.1.1.1. The same reaction starting from (8*S*,10*R*)-**7** (5.86 g, 22.17 mmol) in anhydrous CH_2Cl_2 (177 ml), TBSCl (4.35 g, 28.86 mmol) and imidazole (2.26 g, 33.20 mmol) furnished (8*S*,10*R*)-**31** (8.37 g, 22.11 mmol, quant. yield).

(8*S*,10*R*)-**31**: **m.p. =** 49-51 ºC ($CHCl_3$). **$[\alpha]_D^{20}$**= -56 (*c* 0.85, $CHCl_3$) (lit.[38] $[\alpha]_D^{20}$**=** -56 (*c* 0.85, $CHCl_3$)). ee 100% (CHPLC, hexanes/2-propanol, 90:10).

4.1.1.2. The same reaction starting from (8*R*,10*S*)-**7** (4.04 g, 15.28 mmol) in anhydrous CH_2Cl_2 (122 ml), TBSCl (3.0 g, 19.90 mmol) and imidazole (1.56 g, 22.91 mmol) furnished (8*R*,10*S*)-**31** (5.78 g, 15.27 mmol, quant. yield)

(8*R*,10*S*)-**31**: **m.p.=** 50-52 ºC ($CHCl_3$). **$[\alpha]_D^{20}$**= +55 (*c* 0.90, $CHCl_3$). ee 99.9% (CHPLC, hexanes/2-propanol, 90:10).

4.1.2. (±)-*cis*-4-*tert*-Butyldimethylsilyloxy-6-phenylthio-2-cyclohexenone, *cis*-(±)-**13**[33]



31 *cis*-**13** *trans*-**13**

Montmorillonite K-10 (22.3 g) was added to a solution of acetal (±)-**31** (6.4 g, 16.90 mmol) in CH_2Cl_2 (195 mL) and the mixture was stirred at room temperature for 2.5 h. Then, it was filtered and the solvent removed under reduced pressure to furnish an oily residue, which was purified by flash chromatography (hexanes/Et_2O, 10:1) to provide *cis*-(±)-**13** (5.0 g, 14.94 mmol, 88%) as an oil.

This product slowly epimerized to the *trans* isomer (±)-**13** due to H_6's acidity. Analytical samples of the *trans* isomer could be obtained and some spectroscopic data were registered.

Physical and spectroscopic data of (±)-*cis*-**13**:

R_f= 0.13 (hexanes/EtOAc, 10:1).

^{1}H-RMN (360 MHz, $CDCl_3$): δ 7.43-7.38 (m, 2H: $2H_{ar}$), 7.27-7.19 (m, 3H: $3H_{ar}$), 6.75 (dt, $J_{3,2}$= 10.2 Hz, $J_{3,4}\approx J_{3,5eq}\approx$ 2.0 Hz, 1H: H_3), 5.97 (dd, $J_{2,3}$= 10.2 Hz, $J_{2,4}$= 2.0 Hz, 1H: H_2), 4.51 (ddt, $J_{4,5ax}$= 9.5 Hz, $J_{4,5eq}$= 4.6 Hz, $J_{4,3}\approx J_{4,2}\approx$ 2.0 Hz, 1H: H_4), 3.78 (dd, $J_{6,5ax}$= 13.1 Hz, $J_{6,5eq}$= 4.6 Hz, 1H: H_6), 2.41 (dtd, $J_{5eq,5ax}$= 13.1 Hz, $J_{5eq,4}\approx J_{5eq,6}\approx$ 4.6 Hz, $J_{5eq,3}$= 2.0 Hz, 1H: H_{5eq}), 2.03 (td, $J_{5ax,5eq}\approx J_{5ax,6}$= 13.1 Hz, $J_{5ax,4}$=9.5 Hz, 1H: H_{5ax}), 0.84 (s, 9H: ^{t}Bu), 0.02 (s, 3H: $SiCH_3$), 0.00 (s, 3H: $SiCH_3$).

Physical and spectroscopic data of (±)-*trans*-**13**:

R_f= 0.18 (hexanes/EtOAc, 10:1).

^{1}H-RMN (250 MHz, $CDCl_3$): δ 7.50-7.43 (m, 2H: $2H_{ar}$), 7.34-7.28 (m, 3H: $3H_{ar}$), 6.78 (ddd, $J_{3,2}$= 10.3 Hz, $J_{3,4}$= 2.3 Hz, $J_{3,5}$=1.2 Hz, 1H: H_3), 5.93 (ddd, $J_{2,3}$= 10.3 Hz, $J_{2,4}$= 1.8 Hz, $J_{2,6}$= 1.0 Hz 1H: H_2), 4.75 (dddd, $J_{4,5}$= 10.0 Hz, $J_{4,5}$= 3.2 Hz, $J_{4,3}$= 2.3 Hz, $J_{4,2}$= 1.8 Hz, 1H: H_4), 3.97 (td, $J_{6,5}\approx J_{6,5'}\approx$ 4.4 Hz, $J_{6,2}$= 1.0 Hz, 1H: H_6), 2.35 (m, 2H: $2H_5$), 0.88 (s, 9H: ^{t}Bu), 0.12 (s, 3H: $SiCH_3$), 0.09 (s, 3H: $SiCH_3$).

4.1.2.1. The same reaction starting from (8*S*,10*R*)-**31** (8.37 g, 22.11 mmol) in CH_2Cl_2 (255 mL) and montmorillonite K-10 (29.2 g) furnished (8*S*,10*R*)-**13**. This product slowly epimerized to (8*S*,10*S*)-**13** (6.0 g, 17.93 mmol, 81%).

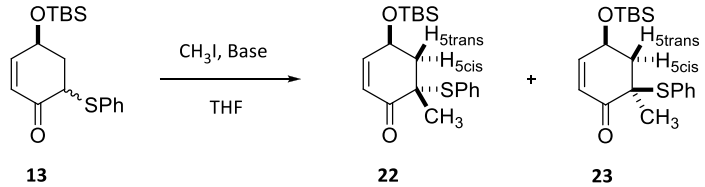
4.1.2.2. The same reaction starting from (8*R*,10*S*)-**31** (5.4 g, 14.26 mmol) in CH_2Cl_2 (164 mL) and montmorillonite K-10 (18.8 g) furnished (8*R*,10*S*)-**13**. This product slowly epimerized to (8*R*,10*R*)-**13**.

Pure diastereomers could not be isolated, therefore the specific rotations were not determined.

4.2. METHYLATION AND EPOXIDATION STUDIES

4.2.1. Methylation reactions

4.2.1.1. (4*RS*,6*RS*)-, (±)-**22**, and (4*RS*,6*SR*)-4-*tert*-Butyldimethylsilyloxy-6-methyl-6-phenylthio-2-cyclohexenone, (±)-**23**



13 **22** **23**

i) using K^{t}BuO as base

A solution of ketone (±)-**13** (232 mg, 0.69 mmol) in anhydrous THF (3 mL) was added to a stirred solution of K^{t}BuO (90 mg, 0.80 mmol) in anhydrous THF (2 mL) at -78 ºC, under nitrogen atmosphere. After stirring the mixture at -78 ºC for 15 min, MeI (436 μL, 7.00 mmol) was added

and the solution was allowed to warm to room temperature. After 2 h, the reaction mixture was acidified by addition of NH_4Cl saturated aqueous solution and then extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and the solvent was evaporated under vacuum. The residue (260 mg) was purified by flash chromatography (hexanes/Et_2O, 10:1), affording (±)-**22**[33] (72 mg, 0.21 mmol, 30%) and (±)-**23**[33] (162 mg, 0.46 mmol, 67%).

Physical and spectroscopic data of (±)-**22**:

R_f= 0.50 (hexanes/EtOAc, 10:1).

R_t (GC) = 9.565 min, program 1.

m.p.= 69-71 ºC (hexanes/EtOAc).

^{1}H-RMN (360 MHz, $CDCl_3$): δ 7.42-7.34 (m, 5H: H_{ar}), 6.75 (dt, $J_{3,2}$= 10.3 Hz, $J_{3,4}$=$J_{3,5cis}$= 2.1 Hz, 1H: H_3), 5.94 (dd, $J_{2,3}$= 10.3 Hz, $J_{2,4}$= 2.1 Hz, 1H: H_2), 4.91 (ddt, $J_{4\text{-}5trans}$= 10.0 Hz, $J_{4,5cis}$= 5.3 Hz, $J_{4,3}$=$J_{4,2}$= 2.1 Hz, 1H: H_4), 2.41 (ddd, $J_{5cis\text{-}5trans}$= 13.7 Hz, $J_{5cis,4}$= 5.3 Hz, $J_{5cis,3}$= 2.1 Hz, 1H: H_{5cis}), 2.19 (dd, $J_{5trans,5cis}$= 13.7 Hz, $J_{5trans,4}$= 10.0 Hz, 1H: H_{5trans}), 1.33 (s, 3H: CH_3), 0.93 (s, 9H: ^{t}Bu), 0.16 (s, 3H: $SiCH_3$), 0.15 (s, 3H: $SiCH_3$).

Physical and spectroscopic data of (±)-**23**:

R_f= 0.42 (hexanes/EtOAc, 10:1)**.**

R_t (GC) = 9.583 min, program 1.

m.p.= 52-53 ºC (hexanes/EtOAc).

^{1}H-RMN (360 MHz, $CDCl_3$): δ 7.50-7.45 (m, 2H: H_{ar}), 7.37-7.27 (m, 3H: H_{ar}), 6.70 (dd, $J_{3,2}$= 10.2 Hz, J= 2.5 Hz, 1H: H_3), 5.95 (dd, $J_{2,3}$= 10.2 Hz, J= 1.8 Hz, 1H: H_2), 4.53 (m, 1H: H_4), 2.23 (m, 2H: H_5), 1.40 (s, 3H: CH_3), 0.90 (s, 9H: ^{t}Bu), 0.10 (s, 3H: $SiCH_3$), 0.09 (s, 3H: $SiCH_3$).

ii) using ^{t}BuLi as base

A solution of ketone (±)-**13** (30 mg, 0.090 mmol) in anhydrous THF (0.4 mL) was added to a stirred solution of ^{t}BuLi (1.7 M in pentane, 58 μL, 0.099 mmol) in anhydrous THF (0.3 mL) at -78 ºC, under nitrogen atmosphere. After stirring the mixture at -78 ºC for 15 min, MeI (56 μL, 0.90 mmol) was added and the solution was allowed to warm to room temperature. After 2 h, the reaction mixture was acidified by addition of NH_4Cl saturated aqueous solution and then extracted with EtOAc (3 x 0.30 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and the solvent was evaporated. The residue (32.2 mg) was purified by flash chromatography (hexanes/Et_2O, 10:1), affording (±)-**22** (9 mg, 0.026 mmol, 29%) and (±)-**23** (14.7 mg, 0.042 mmol, 47%).

iii) using NaH as base

A solution of ketone (±)-**13** (2.20 g, 6.57 mmol) in anhydrous THF (31 mL) was added to a stirred solution of NaH 60% (394 mg, 9.85 mmol) in anhydrous THF (8.4 mL) at -78 ºC, under nitrogen atmosphere. After stirring the mixture at -78 ºC for 15 min, MeI (4.1 mL, 65.85 mmol) was added and the solution was allowed to warm to room temperature. After 1 h 15 min, the reaction mixture was acidified by addition of NH_4Cl saturated aqueous solution and then extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and the solvent was evaporated under vacuum. The residue (2.57 g) was purified by flash chromatography (hexanes/Et_2O, 10:1), affording (±)-**22** (982 mg, 2.82 mmol, 43%) and (±)-**23** (1.11 g, 3.18 mmol, 48%).

4.2.1.1.1. The same reaction starting from (4*S*,6*RS*)-**13** (6.03 g, 18.02 mmol) in anhydrous THF (85 mL), NaH (1.08 g, 27 mmol) in anhydrous THF (23 mL) and MeI (11.2 mL, 180.00 mmol), furnished (4*S*,6*S*)-**22** (2.76 g, 7.92 mmol, 44%) and (4*S*,6*R*)-**23** (3.08 g, 8.84 mmol, 49%).

(4*S*,6*S*)-**22**: white solid; **m.p.=** 92-94 ºC (hexanes); $\mathbf{[\alpha]_D^{20}}$= -127 (*c* 1.0, $CHCl_3$). (lit.[33] $[\alpha]_D^{20}$= -127 (*c* 1.0, $CHCl_3$)).

(4*S*,6*R*)-**23**: oil; $\mathbf{[\alpha]_D^{20}}$= -20 (*c* 0.3, $CHCl_3$) (lit.[33] $[\alpha]_D^{20}$= -20 (*c* 0.3, $CHCl_3$)).

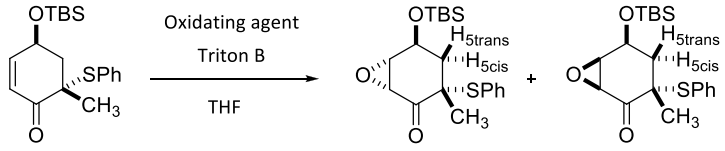
4.2.1.1.2. The same reaction starting from (4*R*,6*RS*)-**13** (4.22 g, 12.61 mmol) afforded (4*R*,6*R*)-**22** (1.98 g, 5.68 mmol, 45%) and (4*R*,6*R*)-**23** (2.11 g, 6.05 mmol, 48%).

(4*R*,6*R*)-22: white solid; **m.p**.= 94-96 ºC (hexanes); $\mathbf{[\alpha]_D^{20}}$= +127 (*c* 1.03, $CHCl_3$) (lit.[33] $[\alpha]_D^{20}$= +127 (*c* 1.0, $CHCl_3$)).

(4*R*,6*S*)-23: oil; $\mathbf{[\alpha]_D^{20}}$= +19 (*c* 0.84, $CHCl_3$) (lit.[33] $[\alpha]_D^{20}$= +19 (*c* 0.8, $CHCl_3$)).

4.2.2. Epoxidation reactions

4.2.2.1. (2*RS*,3*SR*,4*SR*,6*SR*)-, (±)-**32**, and (2*RS*,3*SR*,4*RS*,6*RS*)-4-*tert*-Butyldimethylsilyloxy-2,3-epoxy-6-methyl-6-phenylthiocyclohexanone, (±)-**33**



22 **32** **33**

Method A) To an ice-cooled solution of (±)-**22** (500 mg, 1.43 mmol) in THF (8.3 mL) H_2O_2 (30% in water, 950 μL, 9.29 mmol) and Triton B (40% in water, 65.2 μl, 0.14 mmol) were added. After stirring at 0 °C for 15 min, the reaction mixture was warmed to room temperature and the progress of the reaction was monitored by GC (program 1). After disappearance of the starting olefin, the reaction mixture was diluted with EtOAc (10 mL) and washed with a saturated solution of NH_4Cl. The organic layer was separated, the aqueous one extracted with EtOAc (3 x 10 mL), and the combined organic extracts were dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexanes/EtOAc, from 20:1 to 5:1) to furnish a white solid identified as an inseparable 1:5 mixture of epoxides (±)-**32** and (±)-**33** (397 mg, 1.09 mmol, 76%).

(±)-**32**: **IUPAC name:** (1*RS*,3*SR*,5*SR*,6*SR*)-5-*tert*-Butyldimethylsilyloxy-3-methyl-3-phenylthio-7-oxabicyclo[4.1.0]heptan-2-one. **R_t (GC)** = 11.545 min, program 1.

(±)-**33**: **IUPAC name:** (1*RS*,3*RS*,5*RS*,6*SR*)-5-*tert*-Butyldimethylsilyloxy-3-methyl-3-phenylthio-7-oxabicyclo[4.1.0]heptan-2-one. **R_t (GC)** = 10.755 min, program 1.

i) The same reaction starting from (4*S*,6*S*)-**22** (1.0 g, 2.87 mmol) in THF (17 mL), H_2O_2 (30% in water, 1.9 mL, 18.65 mmol) and Triton B (40% in water, 0.13 mL, 0.28 mmol) furnished a 1:5 inseparable mixture of (2*R*,3*S*,4*S*,6*S*)-**32** and (2*S*,3*R*,4*S*,6*S*)-**33** (820 mg, 2.25 mmol, 78%).

ii) The same reaction starting from (4*R*,6*R*)-**22** (122 mg, 0.35 mmol) in THF (2 mL), H_2O_2 (30% in water, 240 μL, 2.3 mmol) and Triton B (40% in water, 16 μL, 0.035 mmol), furnished a 1:5 inseparable mixture of (2*S*,3*R*,4*R*,6*R*)-**32** and (2*R*,3*S*,4*R*,6*R*)-**33** (102 mg, 0.28 mmol, 80%).

Method B) The same procedure using a solution of (±)-**22** (780 mg, 2.24 mmol) in THF (13 mL), ^{t}BuOOH (70% in water, 1.08 mL, 7.86 mmol) and Triton B (40% in water, 102 μl, 0.22 mmol) afforded a solid residue, which was purified by flash chromatography (hexanes/EtOAc, 5:1) to provide exclusively epoxide (±)-**23** (765 mg, 2.10 mmol, 94%) as a white solid.

Physical and spectroscopic data of (±)-**32**:

R_f= 0.48 (hexanes/EtOAc, 5:1)**.**

m.p.= 71-74 ºC (hexanes/EtOAc).

^{1}H-RMN (360 MHz, $CDCl_3$): δ 7.45-7.38 (m, 3H: H_{ar}), 7.36-7.31 (m, 2H: H_{ar}), 4.53 (q, $J_{4,3}\approx J_{4,5cis}\approx J_{4,5trans}\approx$ 2.8Hz, 1H: H_4), 3.57-3.53 (m, 2H: H_3+H_2), 2.30 (dd, $J_{5cis,5trans}$= 14.6 Hz, $J_{5cis,4}$= 2.8 Hz, 1H: H_{5cis}), 2.01 (ddd, $J_{5trans,5cis}$= 14.6 Hz, $J_{5trans,4}$= 4.0 Hz, $J_{5trans,3}$= 1.0 Hz, 1H: H_{5trans}), 1.35 (s, 3H: CH_3), 0.86 (s, 9H: ^{t}Bu), 0.11 (s, 3H: $SiCH_3$), 0.10 (s, 3H: $SiCH_3$).

^{13}C-NMR (90 MHz, $CDCl_3$): δ 201.3 (C_1), 137.7 (C_{Ar}), 130.4 (C_{Ar}), 129.8 (C_{Ar}), 128.8 (C_{Ar}), 67.1 (C_4), 59.3 (C_3), 55.2 (C_2), 50.5 (C_6), 40.1 (C_5), 27.3 (CH_3), 25.8 ($C(\underline{C}H_3)_3$), 18.1 ($\underline{C}(CH_3)_3$), -4.7 ($2SiCH_3$).

NOESY and **HSQCed** spectra have been registered.

IR (ATR): 2927, 2855, 1704, 1132, 1105 cm^{-1}.

HRMS (CI+): Calcd. for [$C_{19}H_{28}O_3SSi$+Na]: 387.1421

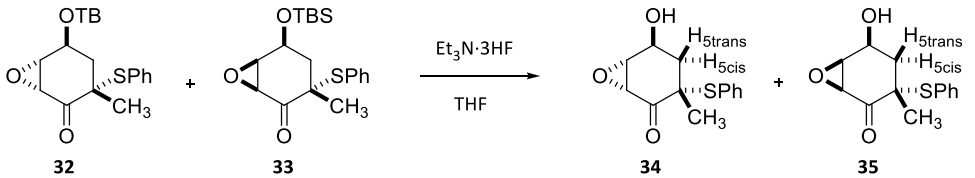
Found ($M+Na^+$): 387.1431

i) The same reaction starting from (4*S*,6*S*)-**22** (200 mg, 0.57 mmol) in THF (3.3 mL), ^{t}BuOOH (70% in water, 276 μL, 2.01 mmol) and Triton B (40% in water, 26 μL, 0.06 mmol) furnished (2*R*,3*S*,4*S*,6*S*)-**32** (200 mg, 0.55 mmol, 96%).

(2*R*,3*S*,4*S*,6*S*)-**32: m.p.=** 126-128 ºC (hexanes/EtOAc); **$[\alpha]_D^{20}$**= +6.7 (*c* 0.79, $CHCl_3$).

(2*S*,3*R*,4*S*,6*S*)-**33** was *isolated and characterized after flash chromatography separation of the unprotected analogues* **34** *and* **35** *and subsequent TBS protection (see below)*.

4.2.2.2. (2*RS*,3*RS*,4*SR*,6*SR*)-, (±)-**34**, and (2*RS*,3*RS*,4*RS*,6*RS*)-2,3-epoxy-4-hydroxy-6-methyl-6-phenylthiocyclohexanone, (±)-**35**



A solution of a 1:5 mixture of epoxides (±)-**32** and (±)-**33** (390 mg, 1.07 mmol) in THF (9 mL), at room temperature, was treated with $Et_3N{\cdot}3HF$ (665 μL, 4.08 mmol). The reaction mixture was stirred overnight at the same temperature. Then, CH_2Cl_2 (6 mL) and saturated solution of $NaHCO_3$ (6 mL) were added. The organic layer was separated and the aqueous one

extracted with CH_2Cl_2 (3 x 3 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under vacuum to give a 1:5 mixture of alcohols (±)-**34** and (±)-**35** (169 mg, 0.67 mmol, 96%) as an oily residue. After several flash chromatography purifications (hexanes to hexanes/EtOAc, 5:1), pure (±)-**35** (110 mg, 0.44 mmol, 62%) was obtained as a white solid and an analytical sample of (±)-**34** was also isolated.

Physical and spectroscopic data of (±)-**34**:

IUPAC name: (1*RS*,3*SR*,5*SR*,6*RS*)-5-Hydroxy-3-methyl-3-phenylthio-7-oxabicyclo[4.1.0]heptan-2-one.

R_f= 0.38 (hexanes/EtOAc, 1:1)**.**

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.44-7.38 (m, 3H: H_{ar}), 7.36-7.30 (m, 2H: H_{ar}), 4.62 (q, $J_{4,3}$=$J_{4,5cis}$=$J_{4,5trans}$= 3.2 Hz, 1H: H_4), 3.67 (ddd, $J_{3,2}$= 4.2 Hz, $J_{3,4}$= 3.2 Hz, $J_{3,5trans}$= 1.2 Hz, 1H: H_3), 3.57 (d, $J_{2,3}$= 4.2 Hz, 1H: H_2), 2.33 (dd, $J_{5cis,5trans}$= 15.0 Hz, $J_{5cis,4}$= 3.2 Hz, 1H: H_{5cis}), 2.09 (ddd, $J_{5trans,5cis}$= 15.0 Hz, $J_{5trans,4}$= 3.2 Hz, $J_{5trans,3}$= 1.2 Hz, 1H: H_{5trans}), 1.36 (s, 3H:CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 201.1 (C_1), 137.7 (C_{ar}), 130.3 (C_{ar}), 129.9 (C_{ar}), 128.9 (C_{ar}), 66.6 (C_4), 58.8 (C_3), 55.2 (C_2), 50.3 (C_6), 40.1 (C_5), 27.4 (CH_3).

HSQCed spectra has been registered.

Physical and spectroscopic data of (±)-**35**:

IUPAC name: (1*RS*,3*RS*,5*RS*,6*RS*)-5-Hydroxy-3-methyl-3-phenylthio-7-oxabicyclo[4.1.0]heptan-2-one.

R_f= 0.44 (hexanes/EtOAc, 1:1)**.**

m.p. = 123-126 ºC (hexanes/EtOAc).

^{1}H-RMN (250 MHz, $CDCl_3$): δ 7.47–7.28 (m, 5H: H_{ar}), 4.59 (dd, $J_{4,5trans}$= 10.3 Hz, $J_{4,5cis}$= 5.8 Hz, 1H: H_4), 3.73 (dt, $J_{3,2}$= 3.8 Hz, $J_{3,4}$=$J_{3,5cis}$= 1.1 Hz, 1H: H_3), 3.51 (d, $J_{2,3}$= 3.8 Hz, 1H: H_2), 2.20 (ddd, $J_{5cis,5trans}$= 13.7 Hz, $J_{5cis,4}$= 5.8 Hz, $J_{5cis,3}$= 1.1 Hz, 1H: H_{5cis}), 2.08 (dd, $J_{5trans,5cis}$= 13.7 Hz, $J_{5trans,4}$= 10.3 Hz, 1H: H_{5trans}), 1.95 (bs, 1H: OH), 1.25 (s, 3H: CH_3).

^{13}C-RMN (90 MHz, $CDCl_3$): 194.1 (C_1), 138.0 (C_{ar}), 130.3 (C_{ar}), 129.1 (C_{ar}), 128.6 (C_{ar}), 64.6 (C_4), 57.5 (C_3), 54.7 (C_6), 54.3 (C_2), 37.2 (C_5), 22.8 (CH_3).

NOESY and **HSQCed** spectra have been registered.

IR (ATR): 3483, 1702, 1025 cm^{-1}.

HRMS (ESI-): Calcd. for [$C_{13}H_{14}O_3S$+Na]: 273.0556

Found ($M+Na^+$): 273.0561

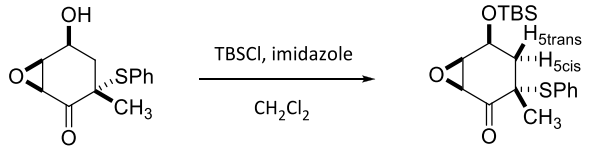
4.2.2.2.1. The same reaction starting from a 1:5 mixture of epoxides (2*R*,3*S*,4*S*,6*S*)-**32** and (2*S*,3*R*,4*S*,6*S*)-**33** (800 mg, 2.19 mmol) in THF (22.4 mL) and $Et_3N{\cdot}3HF$ (2.1 mL, 12.88 mmol) furnished a 1:5 mixture of (2*R*,3*R*,4*S*,6*S*)-**34** and (2*S*,3*S*,4*S*,6*S*)-**35** (476 mg, 1.90 mmol, 87%). After several flash chromatography purifications a sample of (2*S*,3*S*,4*S*,6*S*)-**35** (350 mg, 1.40 mmol, 64%) was isolated as a white solid.

(2*S*,3*S*,4*S*,6*S*)-**35**: **m.p.**= 125-127 ºC (hexanes/EtOAc); $[\alpha]_D^{20}$= -32 (*c* 1.25, $CHCl_3$).

4.2.2.2.2. The same reaction starting from a 1:5 mixture of epoxides (2*S*,3*R*,4*R*,6*R*)-**32** and (2*R*,3*S*,4*R*,6*R*)-**33** (130 mg, 0.36 mmol) in THF (4.6 mL) and $Et_3N{\cdot}3HF$ (0.34 mL, 2.08 mmol) furnished a 1:5 mixture of (2*S*,3*S*,4*R*,6*R*)-**34** and (2*R*,3*R*,4*R*,6*R*)-**35** (76 mg, 0.30 mmol, 85%). After several flash chromatography purifications a sample of (2*R*,3*R*,4*R*,6*R*)-**35** (58 mg, 0.23 mmol, 65%) was isolated as a white solid.

(2*R*,3*R*,4*R*,6*R*)-**35**: **m.p.**= 123-125 ºC (hexanes/EtOAc); $[\alpha]_D^{20}$= +30 (*c* 0.75, $CHCl_3$).

4.2.2.3. (2*RS*,3*SR*,4*RS*,6*RS*)-4-*tert*-Butyldimethylsilyloxy-2,3-epoxy-6-methyl-6-phenylthiocyclohexanone, (±)-**33**



35 **33**

To a solution of epoxide (±)-**35** (88 mg, 0.35 mmol) in anhydrous CH_2Cl_2 (1.5 mL) under nitrogen atmosphere, imidazole (36 mg, 0.52 mmol) was added. The reaction mixture was cooled to 0 ºC and TBSCl (69 mg, 0.46 mmol) was added dropwise. Then, the mixture was stirred at the reflux temperature for 16 h. Water (0.3 mL) was added and the resulting suspension was acidified with 2M HCl. The organic layer was separated, the aqueous one extracted with CH_2Cl_2 (3 x 1 mL), and the combined organic extracts were dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexanes/EtOAc, 5:1) to provide ketone (±)-**33** (115 mg, 0.31 mmol, 90%) as a white solid.

Physical and spectroscopic data of (±)-**33**:

R_f= 0.42 (hexanes/EtOAc, 5:1)**.**

m.p.= 96-98 ºC (hexanes/EtOAc).

^{1}H-RMN (250 MHz, $CDCl_3$): δ 7.49–7.29 (m, 5H: H_{ar}), 4.60 (ddd, $J_{4,5trans}$= 10.8 Hz, $J_{4,5cis}$= 5.5 Hz, $J_{4,3}$= 1.1 Hz, 1H: H_4), 3.57 (dt, $J_{3,2}$= 3.7 Hz, $J_{3,4}$=$J_{3,5cis}$= 1.1 Hz, 1H: H_3), 3.43 (d, $J_{2,3}$= 3.7 Hz, 1H: H_2), 2.20 (dd, $J_{5trans,5cis}$= 13.9 Hz, $J_{5trans,4}$= 10.8 Hz, 1H: H_{5trans}), 1.99 (ddd, $J_{5cis,5trans}$= 13.9 Hz, $J_{5cis,4}$=5.5, $J_{5cis,3}$= 1.1 Hz, 1H: H_{5cis}), 1.24 (s, 3H: CH_3), 0.95 (s, 9H: ^{t}Bu), 0.18 (s, 3H: $SiCH_3$), 0.17 (s, 3H: $SiCH_3$).

^{13}C-RMN (90 MHz, $CDCl_3$): δ 194.6 (C_1), 137.7 (C_{Ar}), 130.2 (C_{Ar}), 129.0 (C_{Ar}), 128.8 (C_{Ar}), 65.0 (C_4), 57.9 (C_3), 54.8 (C_6), 53.8 (C_2), 37.3 (C_5), 25.9 ($\underline{C}(CH_3)_3$), 23.0 (CH_3), 18.3 ($C(\underline{C}H_3)_3$), -4.5 ($2SiCH_3$).

NOESY and **HSQCed** spectra have been registered.

IR (ATR): 2955, 2928, 2855, 1702, 1467, 1435, 1253 cm^{-1}.

EM m/z (ESI+): 387.1 ($[M+Na]^+$, 100).

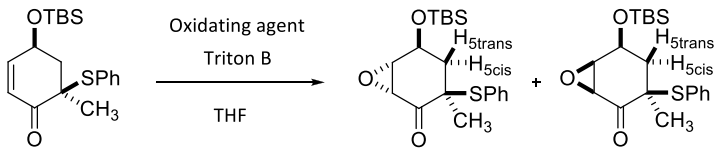
Elemental analysis calcd (%) for **(±)-10**:

$C_{19}H_{28}O_3SSi$**:**	C: 62.59, H: 7.74, S: 8.80
Found:	C: 62.54, H: 7.70, S: 8.50.

4.2.2.3.1. The same reaction starting from (2*S*,3*S*,4*S*,6*S*)-**35** (215 mg, 0.86 mmol) in CH_2Cl_2 (3.7 mL), imidazole (88 mg, 1.29 mmol) and TBDMSCl (168 mg, 1.12 mmol) furnished (2*S*,3*R*,4*S*,6*S*)-**33** (284 mg, 0.94 mmol, 94%).
(2*S*,3*R*,4*S*,6*S*)-**33**: **m.p.**= 109-111 ºC (hexanes/EtOAc); **$[\alpha]_D^{20}$**= +53 (*c* 0.73, $CHCl_3$).

4.2.2.3.2. The same reaction starting from (2*R*,3*R*,4*R*,6*R*)-**35** (35 mg, 0.14 mmol) in CH_2Cl_2 (0.8 mL), imidazole (14 mg, 0.20 mmol) and TBDMSCl (28 mg, 0.18 mmol) furnished (2*R*,3*S*,4*R*,6*R*)-**33** (47 mg, 0.13 mmol, 94%).
(2*R*,3*S*,4*R*,6*R*)-**33**: **m.p.**= 112-114 ºC (hexanes/EtOAc); **$[\alpha]_D^{20}$**= -54 (*c* 0.62, $CHCl_3$).

4.2.2.4. (2*RS*,3*SR*,4*SR*,6*RS*)-, (±)-**36**, and (2*RS*,3*SR*,4*RS*,6*SR*)-4-*tert*-Butyldimethylsilyloxy-2,3-epoxy-6-methyl-6-phenylthiocyclohexanone, (±)-**37**



23 **36** **37**

Method A) To an ice-cooled solution of (±)-**23** (250 mg, 0.72 mmol) in THF (4.1 mL), H_2O_2 (30% in water, 478 μL, 4.68 mmol) and Triton B (40% in water, 33 μL, 0.07 mmol) were added. After stirring at 0 ºC for 15 min, the reaction mixture was allowed to warm to room temperature. The reaction evolution was monitored by GC (program 1). The crude was diluted with EtOAc (5 mL) and washed with a saturated solution of NH_4Cl. The organic layer was separated, the aqueous one extracted with EtOAc (3 x 5 mL), and the combined organic extracts were dried over anhydrous $MgSO_4$. Then, the solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexanes/EtOAc, 5:1) to furnish a white solid identified as an inseparable 5:1 mixture of epoxides (±)-**36** and (±)-**37** (239 mg, 0.65 mmol, 91%).

Physical data of (±)-**36**:

IUPAC name: (1*RS*,3*RS*,5*SR*,6*SR*)-5-*tert*-Butyldimethylsilyloxy-3-methyl-3-phenylthio-7-oxabicyclo[4.1.0]heptan-2-one.

R_t (GC) = 10.878 min, program 1.

In an attempt to isolate **(±)-37** an enriched fraction was obtained.

Physical and spectroscopic data of (±)-**37**:

IUPAC name: (1*RS*,3*SR*,5*RS*,6*SR*)-5-*tert*-Butyldimethylsilyloxy-3-methyl-3-phenylthio-7-oxabicyclo[4.1.0]heptan-2-one.

R_t (GC) = 11.185 min, program 1.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.34 (m, 5H: H_{ar}), 4.22 (dd, $J_{4,5trans}$= 11.3 Hz, $J_{4,5cis}$= 4.8 Hz, 1H: H_4), 3.53 (dd, $J_{3,2}$= 4.3 Hz, $J_{3,5cis}$= 1.4 Hz, 1H: H_3), 3.46 (d, $J_{2,3}$= 4.3 Hz, 1H: H_2), 2.36 (dd, $J_{5trans,5cis}$= 13.1 Hz, $J_{5trans,4}$= 11.3 Hz, 1H: H_{5trans}), 1.83 (ddd, $J_{5cis,5trans}$= 13.1 Hz, $J_{5cis,4}$= 4.8 Hz, $J_{5cis,3}$= 1.4 Hz, 1H: H_{5cis}), 1.27 (s, 3H: CH_3), 0.91 (s, 9H: ^{t}Bu), 0.11 (s, 3H: $SiCH_3$), 0.10 (s, 3H: $SiCH_3$).

^{13}C-RMN (100 MHz, $CDCl_3$): δ 202.2 (C_1), 137.8 (C_{Ar}), 137.7 (C_{Ar}), 130.3 (C_{Ar}), 129.8 (C_{Ar}), 66.1 (C_4), 60.2 (C_3), 56.0 (C_2), 50.7 (C_6), 38.7 (C_5), 25.8 (^{t}Bu), 25.1 (CH_3), 18.2 (^{t}Bu), -4.5 ($SiCH_3$), -4.6 ($SiCH_3$).

Method B) The same procedure using a solution of (±)-**23** (512 mg, 1.47 mmol) in THF (9.0 mL), ^{t}BuOOH (70% in water, 706 μL, 5.14 mmol) and Triton B (40% in water, 67 μL, 0.15 mmol) afforded a solid residue, which was purified by flash chromatography (hexanes/EtOAc, 5:1) to provide exclusively epoxide (±)-**36** (525 mg, 1.44 mmol, 98%) as a white solid.

Physical and spectroscopic data of (±)-**36**:

R_f= 0.44 (hexanes/EtOAc, 5:1)**.**

m.p.= 100-102 ºC (hexanes/EtOAc).

^{1}H-RMN (360 MHz, $CDCl_3$): δ 7.43 – 7.28 (m, 5H: H_{ar}), 4.45 (m, 1H: H_4), 3.52 (dd, $J_{2,3}$= 3.4 Hz, J= 0.9 Hz, 1H: H_2), 3.49 (ddd, $J_{3,2}$= 3.4 Hz, $J_{3,4}$= 2.2 Hz, $J_{3,5trans}$= 1.2 Hz, 1H: H_3), 2.25 (dd, $J_{5cis,5trans}$= 15.3 Hz, $J_{5cis,4}$= 4.1 Hz, 1H: H_{5cis}), 2.09 (ddd, $J_{5trans,5cis}$= 15.3 Hz, $J_{5trans,4}$= 2.0 Hz, $J_{5trans,3}$= 1.2 Hz, 1H: H_{5trans}), 1.27 (s, 3H: CH_3), 0.98 (s, 9H: ^{t}Bu), 0.18 (s, 6H: 2 $SiCH_3$).

^{13}C-RMN (90 MHz, $CDCl_3$): δ 194.0 (C_1), 137.9 (C_{ar}), 130.9 (C_{ar}), 129.7 (C_{ar}), 128.7 (C_{ar}), 64.3 (C_4), 56.7 (C_3), 52.9 (C_2), 52.1 (C_6), 38.7 (C_5), 26.0 ($C(\underline{C}H_3)_3$), 22.9 (CH_3), 18.3 ($\underline{C}(CH_3)_3$), -4.6 (2 $SiCH_3$).

IR (ATR): 2957, 2926, 2855, 1703, 1248, 1107 cm^{-1}.

EM m/z (ESI+) of the 5:1 mixture (±)-**36**:(±)**-37**: 387 ($M+Na^+$, 100).

Elemental analysis calcd. (%) for a mixture (±)-**36**:(±)**-37**:

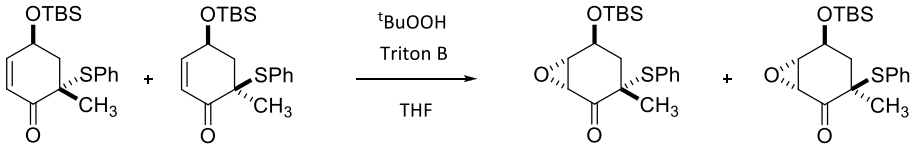
Calcd.$C_{19}H_{28}O_3SSi$**:** C: 62.59, H: 7.74, S: 8.80

Found: C: 62.36, H: 7.90, S: 8.62;

i) The same reaction starting from (4*S*,6*R*)-**23** (1.00 g, 2.87 mmol) in THF, ^{t}BuOOH (70% in water, 1.4 mL, 10.04 mmol) and Triton B (40% in water, 130 μL, 0.29 mmol), furnished (2*R*,3*S*,4*S*,6*R*)-**36** (1.02 g, 2.80 mmol, 98%).

(2*R*,3*S*,4*S*,6*R*)-**36**: **m.p.=** 126-128 ºC (hexanes/EtOAc). **$[\alpha]_D^{20}$**= +5.5 (*c* 0.84, $CHCl_3$).

4.2.2.5. (2*RS*,3*SR*,4*SR*,6*SR*)-, (±)-**32**, and (2*RS*,3*SR*,4*SR*,6*RS*)-4-*tert*-butyldimethylsilyloxy-2,3-epoxy-6-methyl-6-phenylthiocyclohexanone, (±)-**36**



To an ice-cooled solution mixture of (±)-**22** and (±)-**23** (230 mg, 0.66 mmol) in THF (3.8 mL) ^{t}BuOOH (70% in water, 0.32 mL, 2.33 mmol) and Triton B (40% in water, 30 μl, 0.066 mmol) were added. After 15 min of stirring at 0 °C, the reaction mixture was allowed to warm to room temperature. The reaction evolution was monitored by GC (program 1). Then, the solution was diluted with EtOAc (2 mL) and washed with a saturated solution of NH_4Cl. The organic layer was separated, the aqueous one extracted with EtOAc (3 x 2 mL), and the combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. Purification the residue by flash chromatography (hexanes/EtOAc, 5:1) furnished a white solid identified as a mixture of epoxides (±)-**32** and (±)-**36** (233 mg, 0.64 mmol, 97%).

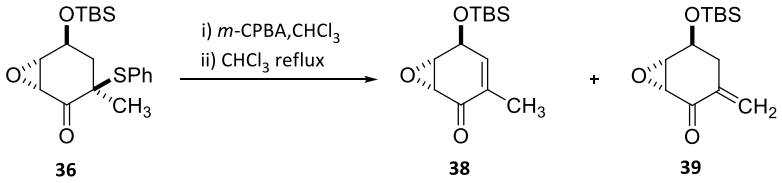
4.2.2.5.1. The same reaction starting from (4*S*,6*S*)-**22** and (4*S*,6*R*)-**23** (600 mg, 1.72 mmol) in THF (10 ml), ^{t}BuOOH (70% in water, 0.83 mL, 6.02 mmol) and Triton B (40% in water, 78.2 μL, 0.17 mmol) furnished a mixture of epoxides (2*R*,3*S*,4*S*,6*S*)-**32** and (2*R*,3*S*,4*S*,6*R*)-**36** (627 mg, 1.72 mmol, 100%).

4.2.2.5.2. The same reaction starting from (4*R*,6*R*)-**22** and (4*R*,6*S*)-**23** (1.24 g, 3.56 mmol) in THF (20 ml), ^{t}BuOOH (70% in water, 1.7 ml, 12.38 mmol) and Triton B (40% in water, 157 μL, 0.34 mmol) furnished a mixture of epoxides (2*S*,3*R*,4*R*,6*R*)-**32** and (2*S*,3*R*,4*R*,6*S*)-**36** (1.28 g, 3.51 mmol, 99%).

4.3. GENERATION OF THE C_5-C_6 DOUBLE BOND

4.3.1. Total synthesis of epoformin and epiepoformin

4.3.1.1. (2*RS*,3*SR*,4*SR*)-4-*tert*-Butyldimethylsilyloxy-2,3-epoxy-6-methyl-5-cyclohexenone, (±)-**38**, and (2*RS*,3*SR*,4*SR*)-4-*tert*-Butyldimethylsilyloxy-2,3-epoxy-6-methylenecyclohexanone, (±)-**39**



36 **38** **39**

To an ice-cooled solution of (±)-**36** (400 mg, 1.09 mmol) in $CHCl_3$ (13 mL), a solution of *m*-CPBA (previously extracted from water with $CHCl_3$) (224 mg, 1.09 mmol) in $CHCl_3$ (3 mL) was continuously added during 1 h at the same temperature. The reaction mixture was monitored by GC analysis (program 1) until completion. The solution was washed with a saturated solution of $NaHCO_3$, the organic layer was separated and dried over anhydrous $MgSO_4$. The solution was concentrated to around 15 mL and heated at the reflux temperature for 1 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (hexanes/EtOAc, from 15:1 to 5:1) to afford a 5.5:1 mixture of inseparable epoxides (±)-**38**[91d,119a] and (±)-**39**[95q,116] (215 mg, 0.84 mmol, 69%).[91d,120b]

Physical and spectroscopic data of (±)-**38** and (±)-**39**:

IUPAC name 38: (1*RS*,5*SR*,6*SR*)-5-*tert*-Butyldimethylsilyloxy-3-methyl-7-oxabicyclo[4.1.0]hept-3-en-2-one.

IUPAC name 39: (1*RS*,5*SR*,6*SR*)-5-*tert*-Butyldimethylsilyloxy-3-methylene-7-oxabicyclo[4.1.0]heptan-2-one.

R_f (**38** and **39**)= 0.52 (hexanes/EtOAc, 5:1).

(±)-**38: R_t** (GC): 3.620 min, program 1.

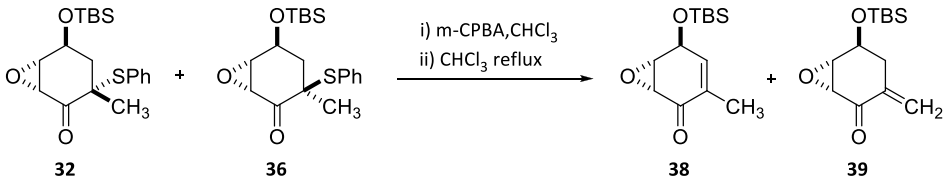
(±)-**39: R_t** (GC): 5.194 min, program 1.

^{1}H-NMR (360 MHz, $CDCl_3$) of **38**: δ 6.28 (ddq, $J_{5,4}$= 4.8 Hz, $J_{5,3}$= 2.6 Hz, $J_{5,CH3}$= 1.3 Hz, 1H: H_5), 4.63 (dst, $J_{4,5}$= 4.8 Hz, $J_{4,3}\approx J_{4,2}\approx J_{4,CH3}\approx$1.3 Hz, 1H: H_4), 3.62 (ddd, $J_{3,2}$= 3.7 Hz, $J_{3,5}$= 2.6 Hz, $J_{3,4}$= 1.3 Hz, 1H: H_3), 3.47 (dd, $J_{2,3}$= 3.7 Hz, $J_{2,4}$= 1.2 Hz, 1H: H_2), 1.82 (t, $J_{CH3,5}\approx J_{CH3,4}\approx$ 1.3 Hz, 1H: CH_3), 0.91 (s, 9H: ^{t}Bu), 0.36 (s, 3H: $SiCH_3$), 0.34 (s, 3H: $SiCH_3$).

^{1}H-NMR (360 MHz, $CDCl_3$) of **39**: δ 6.22 (m, 1H: H_7), 5.28 (m, 1H:H_7), 4.51 (q, $J_{4,5trans}$=$J_{4,5cis}$= 2.9 Hz, 1H: H_4), 3.55 (m, 1H: H_3), 3.42 (d, $J_{2,3}$= 4.3 Hz, 1H: H_2), 2.82 (dq, $J_{5trans,5cis}$= 16.0 Hz, $J_{5trans,4}$= $J_{5trans,3}$=$J_{5trans,7}$= 2.9 Hz, 1H: H_{5trans}), 2.43 (dd, $J_{5cis,5trans}$= 16.0 Hz, $J_{5cis,4}$= 2.9 Hz, 1H: H_{5cis}), 0.84 (s, 9H: ^{t}Bu), 0.09 (s, 3H: $SiCH_3$), 0.07 (s, 3H: $SiCH_3$).

4.3.1.1.1. The same reaction starting from (2*R*,3*S*,4*S*,6*R*)-**36** (614 mg, 1.68 mmol) in $CHCl_3$ (20 mL) and a solution of dried *m*-CPBA (344 mg, 1.68 mmol) in $CHCl_3$ (4.6 mL) furnished a 5.5:1 mixture of (2*R*,3*S*,4*S*)-**38** and (2*R*,3*S*,4*S*)-**39** (373 mg, 1.47 mmol, 87%).

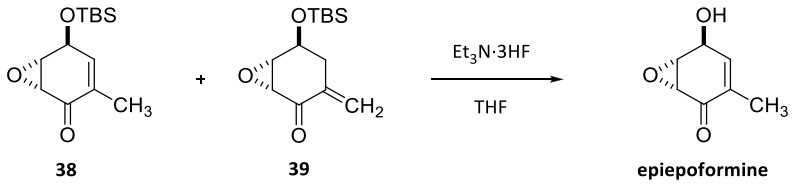
4.3.1.2. (2*RS*,3*SR*,4*SR*)- 4-*tert*-Butyldimethylsilyloxy-2,3-epoxy-6-methyl-5-cyclohexenone, (±)-**38**, and (2*RS*,3*SR*,4*SR*)-4-*tert*-Butyldimethylsilyloxy-2,3-epoxy-6-methylcyclohexanone, (±)-**39**



To an ice-cooled solution of a 1:7.6 mixture of (±)-**32** and (±)-**36** (396 mg, 1.09 mmol) in $CHCl_3$ (13 mL), a solution of *m*-CPBA (previously extracted from water with $CHCl_3$) (221 mg, 1.09 mmol) in $CHCl_3$ (3 mL) was continuously added during 1 h at the same temperature. The reaction mixture was monitored by GC (program 1). Then, the solution was washed with a saturated solution of $NaHCO_3$, the organic layer was separated and dried over anhydrous $MgSO_4$. The solution was concentrated to around 15 mL and heated at the reflux temperature for 1 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (hexanes/EtOAc, from 15:1 to 5:1) affording a 5.5:1 mixture of inseparable epoxides (±)-**38**[91d,119a] and (±)-**39**[95q,116] (207 mg, 0.81 mmol, 75%).

4.3.1.2.1. The same reaction starting from a mixture of epoxides (2*R*,3*S*,4*S*,6*S*)-**32** and (2*R*,3*S*,4*S*,6*R*)-**36** (610 mg, 1.68 mmol) in $CHCl_3$ (20 mL) and a solution of dried *m*-CPBA (344 mg, 1.68 mmol) in $CHCl_3$ (4.6 mL) furnished a 5.5:1 mixture of (2*R*,3*S*,4*S*)-**38** and (2*R*,3*S*,4*S*)-**39** (376 mg, 1.48 mmol, 88%).

4.3.1.3. (2*RS*,3*RS*,4*SR*)-2,3-Epoxy-4-hydroxy-6-methyl-5-cyclohexenone, (±)-**epiepoformin**



A solution of epoxides (±)-**38** and (±)-**39** (280 mg, 1.10 mmol) in THF (14.5 mL), at room temperature was treated with $Et_3N{\cdot}3HF$ (1.0 mL, 6.13 mmol). The reaction mixture was stirred for 12 h at the same temperature. Then, CH_2Cl_2 (16 mL) and a saturated aqueous solution of $NaHCO_3$ (16 mL) were added. The organic layer was separated and the aqueous one extracted with CH_2Cl_2 (3 x 8 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under vacuum. The oily residue was purified by flash chromatography (hexanes/EtOAc, 5:1) to give (±)-**epiepoformin** (132 mg, 0.94 mmol, 86%) as a white solid.[91d,119a]

Physical and spectroscopic data (±)-**epiepoformin**:

IUPAC name: (1*RS*,5*SR*,6*RS*)-5-Hydroxy-3-methyl-3-phenylthio-7-oxabicyclo[4.1.0]hept-3-en-2-one.

***R*$_f$=** 0.56 (EtOAc).

m.p.= 59-61 ºC (hexanes/EtOAc).

^{1}H-NMR (250 MHz, $CDCl_3$): δ 6.45 (ddq, $J_{5,4}$= 5.5 Hz, $J_{5,3}$= 2.6 Hz, $J_{5,CH3}$= 1.3 Hz, 1H: H_5), 4.65 (bs, 1H: H_4), 3.77 (ddd, $J_{3,2}$= 3.7 Hz, $J_{3,5}$= 2.6 Hz, $J_{3,4}$= 1.3 Hz, 1H: H_3), 3.48 (dd, $J_{2,3}$= 3.7 Hz, $J_{2,4}$= 1.1 Hz, 1H: H_2), 2.38 (bs, 1H: OH), 1.83 (dd, $J_{CH3,5}$= 1.3 Hz, $J_{CH3,4}$= 1.2 Hz, 3H: CH_3).

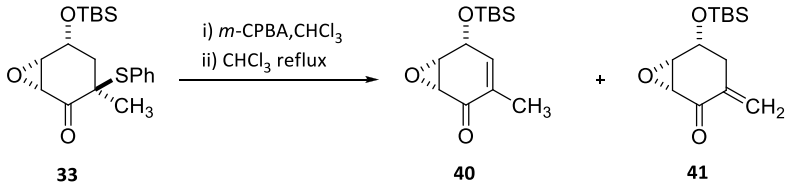
^{13}C-NMR (100 MHz): δ 194.3 (C_1), 138.9 (C_5), 134.8 (C_6), 63.5 (C_4), 57.8 (C_3), 53.5 (C_2), 16.1 (CH_3).

COSY spectra has been registered.

4.3.1.3.1. The same reaction starting from (2*R*,3*S*,4*S*)-**15** and (2*R*,3*S*,4*S*)-**16** (376 mg, 1.48 mmol) in THF (20 mL) and $Et_3N{\cdot}3HF$ (1.4 mL, 8.54 mmol), furnished (2*R*,3*R*,4*S*)-**epiepoformin** (178 mg, 1.27 mmol, 86%).

(2*R*,3*R*,4*S*)-**epiepoformin**: **m.p.**= 88-90 ºC (hexanes/EtOAc); **$[\alpha]_D^{20}$**= +315 (*c* 1.10, EtOH).[132]

4.3.1.4. (2RS,3SR,4RS)-4-*tert*-Butyldimethylsilyloxy-2,3-epoxy-6-methyl-5-cyclohexenone, (±)-**40**, and (2*RS*,3*SR*,4*RS*)-4-*tert*-Butyldimethylsilyloxy-2,3-epoxy-6-methylenecyclohexanone, (±)-**41**



33 **40** **41**

To an ice-cooled solution of (±)-**33** (119 mg, 0.33 mmol) in $CHCl_3$ (4 mL), a solution of *m*-CPBA (previously extracted from water with $CHCl_3$) (67 mg, 0.33 mmol) in $CHCl_3$ (0.8 mL) was continuously added during 1 h at the same temperature. The reaction mixture was monitored by GC (program 1). Then, the solution was washed with a saturated solution of $NaHCO_3$, the organic layer was separated and dried over anhydrous $MgSO_4$. The solution was concentrated to around 4.5 mL and stirred at the reflux temperature for 1 h. The solvent was removed under reduced pressure and the oily residue was identified as a 1:1 mixture of epoxides (±)-**40** and (±)-**41**, which after purification by flash chromatography (hexanes/EtOAc, from 15:1 to 5:1) afforded the single isomer (±)-**40** (57 mg, 0.22 mmol, 69%).

Physical and spectroscopic data of (±)-**40**:

IUPAC name: (1*RS*,5*RS*,6*SR*)-5-*tert*-Butyldimethylsilyloxy-3-methyl-7-oxabicyclo[4.1.0]hept-3-en-2-one.

R_t= 5.145 min, program 1.

^{1}H-RMN (250 MHz, $CDCl_3$)**:** δ 6.17- 6.10 (m, 1H: H_5), 4.74 (m, 1H: H_4), 3.67 (dt, $J_{3,2}$= 4.0 Hz, $J_{3,4}$=$J_{3,5}$= 2.7 Hz, 1H: H_3), 3.43 (d, $J_{2,3}$= 4.0 Hz, 1H: H_2), 1.80 (m, 3H: CH_3), 0.96 (s, 9H: ^{t}Bu), 0.18 (s, 6H: 2SiCH_3).

^{13}C-RMN (100 MHz, $CDCl_3$): δ 194.4 (C_1), 141.5 (C_5), 131.8 (C_6), 66.3 (C_4), 54.6 (C_3), 53.2 (C_2), 25.9 ($\underline{C}(CH_3)_3$), 15.9 (CH_3), 14.2 ($C(\underline{C}H_3)_3$), -4.4 ($SiCH_3$), -4.5 ($SiCH_3$).

HSQCed spectra has been registered.

HRMS (ESI+): Calcd. for [$C_{13}H_{22}O_3Si$+Na]: 277.1230

Found (M+Na^+): 277.1232

Physical data of (±)-**41**:

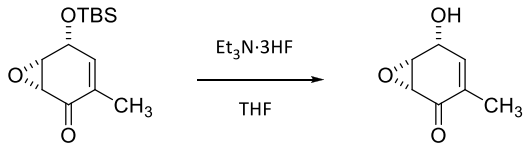
IUPAC name: (1*RS*,5*RS*,6*SR*)-5-*tert*-Butyldimethylsilyloxy-3-methylene-7-oxabicyclo[4.1.0]heptan-2-one.

R_t= 3.678 min , program 1.

4.3.1.4.1. The same reaction starting from (2*R*,3*S*,4*R*,6*R*)-**33** (116 mg, 0.32 mmol) in $CHCl_3$ (4.0 mL) and a solution of dried *m*-CPBA (65 mg, 0.32 mmol) in $CHCl_3$ (1.0 mL) furnished exclusively (2*R*,3*S*,4*R*)-**40** (58 mg, 0.23 mmol, 72%).

(2*R*,3*S*,4*R*)-**40**: **$[\alpha]_D^{20}$**= +86 (*c* 0.85, $CHCl_3$).

4.3.1.5. (2*RS*,3*RS*,4*RS*)-2,3-Epoxy-4-hydroxy-6-methyl-5-cyclohexenone, (±)-**epoformin**



40 **epoformin**

A solution of epoxide **40** (45 mg, 0.18 mmol) in THF (2.5 mL) at room temperature was treated with $Et_3N{\cdot}3HF$ (167 μL, 1.03 mmol). The reaction mixture was stirred at the same temperature for 48 h. Then, CH_2Cl_2 (2.5 mL) and a saturated aqueous solution of $NaHCO_3$ (2.5 mL) were added. The organic layer was separated and the aqueous one was extracted with CH_2Cl_2 (3 x 2 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under vacuum. The oily residue was purified by flash chromatography (hexanes/EtOAc, 5:1) to give **epoformin** (21 mg, 0.15 mmol, 85%).[95r]

Physical and spectroscopic data of (±)-**Epoformin**:

IUPAC name: (1*RS*,5*RS*,6*RS*)-5-Hydroxy-3-methyl-7-oxabicyclo[4.1.0]hept-3-en-2-one.

R_f= 0.40 (hexanes/EtOAc, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.27 (s, 1H: H_5), 4.63 (bs, 1H: H_4), 3.83 (m, 1H: H_3), 3.51 (d, $J_{2,3}$= 4.0 Hz, 1H: H_2), 2.19 (d, $J_{OH,4}$= 9.9 Hz, 1H: OH), 1.82 (s, 3H: CH_3).

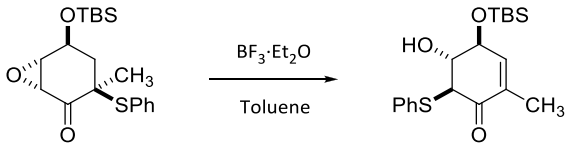
^{13}C NMR (100 MHz, $CDCl_3$): δ 193.9 (C_1), 140.3 (C_5), 132.6 (C_6), 65.2 (C_4), 54.6 (C_3), 53.9 (C_2), 15.9 (CH_3).

4.3.1.5.1. The same reaction starting from (2*R*,3*S*,4*R*)-**40** (34 mg, 0.13 mmol) in THF (2.0 mL) and $Et_3N{\cdot}3HF$ (128 μL, 0.78 mmol), furnished (2*R*,3*R*,4*R*)-**epoformin** (16.3 mg, 0.12 mmol, 87%) as a colourless oil.

(2*R*,3*R*,4*R*)-**epoformin**: **$[\alpha]_D^{20}$**= +109 (*c* 0.20, EtOH) (lit.[126a] $[\alpha]_D^{20}$= +108.6 (*c* 0.21, EtOH)).

4.3.2. Cleavage of the epoxide: Total synthesis of Gabosine A

4.3.2.1. (2*RS*,3*SR*,4*RS*)-4-*tert*-Butyldimethylsilyloxy-3-hydroxy-6-methyl-2-phenylthiocyclohex-5-enone, (±)-**42**



36 **42**

To an ice-cooled solution of epoxide (±)-**36 (**50 mg, 0.14 mmol) in toluene (1.5 ml), $BF_3{\cdot}Et_2O$ (17 µl, 0.14 mmol) was added. The reaction mixture was stirred at 0 ºC for 1.5 h. Then, it was neutralized with $NaHCO_3$ and then extracted with EtOAc (3 x 1 ml). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was evaporated under vacuum. The residue was purified by flash chromatography (hexanes/EtOAc, 5:1), affording (±)-**42** (40 mg, 0.11 mmol, 80%) as an oil.

Physical and spectroscopic data (±)-**42**:

IUPAC name: (4*RS*,5*SR*,6*RS*)-4-*tert*-Butyldimethylsilyloxy-5-hydroxy-2-methyl-6-phenylthiocyclohex-2-enone.

R_f= 0.44 (hexanes/EtOAc, 5:1).

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.56-7.49 (m, 2H: H_{ar}), 7.31–7.25 (m, 3H: H_{ar}), 6.46 (m, 1H: H_5), 4.45 (dqn $J_{4,3}$= 7.0 Hz, $J_{4,5}$=$J_{4,CH3}$= 2.1 Hz, 1H: H_4), 3.67 (ddd, $J_{3,2}$= 11.5 Hz, $J_{3,4}$= 7.0 Hz, $J_{3,OH}$= 1.6 Hz, 1H: H_3), 3.59 (d, $J_{2,3}$= 11.5 Hz, 1H: H_2), 2.94 (d, $J_{OH,3}$= 1.6 Hz, 1H: OH), 1.82 (m, 3H: CH_3), 0.93 (m, 9H: ^{t}Bu), 0.17 (s, 6H: 2SiCH$_3$).

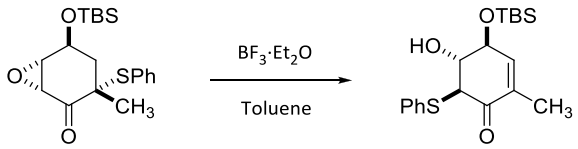
^{13}C-RMN (100 MHz, $CDCl_3$): δ 193.1 (C_1), 146.4 (C_5), 135.3 ($C_{Ar/6}$), 133.7 (C_{Ar}), 132.6 ($C_{Ar/6}$), 129.2 (C_{Ar}), 128.2 (C_{Ar}), 74.6 (C_3), 73.4 (C_4), 62.2 (C_2), 25.9 (^{t}Bu), 18.4 (^{t}Bu), 16.1 (CH_3), -4.7 (2 SiCH$_3$).

IR (ATR): 3505, 2928, 2855, 1738, 1683, 1221 cm^{-1}.

HRMS (CI+): Calcd. for [$C_{19}H_{28}O_3SSi$+Na]: 387.1421

Found (M+Na$^+$): 387.1417

i)

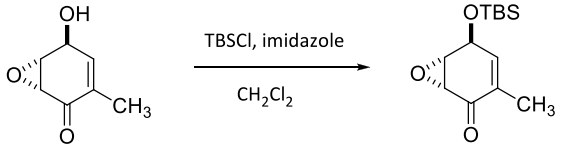


32 **42**

Enone (±)-**42** (38 mg, 0.10 mmol, 79%) was also obtained in the same conditions starting from epoxide (±)-**32**. Enone (2*S*,3*R*,4*S*)-**42** (40 mg, 0.11 mmol, 82%) was prepared starting from (2*R*,3*S*,4*S*,6*S*)-**32** (49 mg, 0.13 mmol).

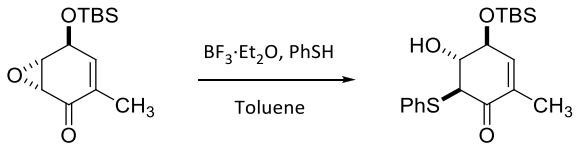
(2*S*,3*R*,4*S*)-**42**: oil; $[\alpha]_D^{20}$= +8.5 (*c* 0.47, $CHCl_3$).

ii) (2*RS*,3*SR*,4*SR*)-4-*tert*-Butyldimethylsilyloxy-2,3-epoxy-6-methyl-5-cyclohexenone, (±)-3**8**



epiepoformine **38**

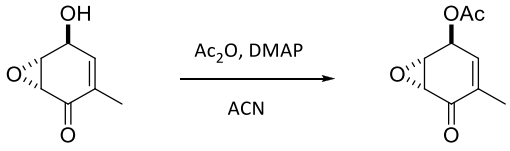
To a solution of (±)-**epiepoformin** (34 mg, 0.24 mmol) in anhydrous CH_2Cl_2 (1 mL) under nitrogen atmosphere, imidazole (25 mg, 0.37 mmol) was added. The reaction mixture was cooled to 0 ºC and TBSCl was added dropwise (47 mg, 0.31 mmol). Then, it was stirred at room temperature for 16 h. Then, water (0.3 mL) was added and the resulting suspension was acidified with 2M HCl. The organic layer was separated, the aqueous one extracted with CH_2Cl_2 (3 x 1 mL), and the combined organic extracts were dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexanes/EtOAc, 5:1) to provide ketone (±)-**38** (52 mg, 0.20 mmol, 84%) as a colourless oil.



38 **42**

Enone (±)-**42** was also prepared treating a solution of (±)-**38** (23 mg, 0.09 mmol) in toluene (1.0 mL) with $BF_3{\cdot}Et_2O$ (11 μL, 0.09 mmol) and thiophenol (9.4 μL, 0.09 mmol) at 0 ºC for 2 h. Purification by flash chromatography (hexanes/EtOAc, 5:1) afforded (±)-**42** (26 mg, 0.07 mmol, 80%).

4.3.2.2. (2*R*,3*S*,4*S*)-4-Acetoxy-2,3-epoxy-6-methyl-5-cyclohexenone, (+)-**44**



(+)-**epiepoformine** (+)-**44**

To a solution of (2*R*,3*R*,4*S*)-epiepoformin (131 mg, 0.93 mmol) in anhydrous acetonitrile (4.5 mL) at 0 ºC under nitrogen atmosphere, DMAP (126 mg, 1.03 mmol) and acetic anhydride (350 µl, 3.74 mmol) were added. The reaction was warmed to room temperature and stirred for 5 min, then, the reaction mixture was poured into ice-cooled water and extracted with CH_2Cl_2 (3 x 1.5 mL). The combined organic layers were washed with cold water and a saturated aqueous solution of $NaHCO_3$. The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure to furnish an oily residue. Purification of this material by flash chromatography (EtOAc) yielded (2*R*,3*R*,4*S*)-**44** as an oil (151 mg, 0.83 mmol, 89%).

Physical and spectroscopic data of (2*R*,3*R*,4*S*)-**44**:

IUPAC name: (1*R*,2*S*,6*R*)-4-Methyl-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-2-yl acetate.

R_f= 0.68 (EtOAc).

$[\alpha]_D^{20}$= +94 (*c* 0.17, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.36 (dqn, $J_{5,4}$= 6.3 Hz, $J_{5,3}$=$J_{5,CH3}$= 1.4 Hz, 1H: H_5), 5.72 (ddd, $J_{4,5}$= 6.3 Hz, $J_{4,3}$= 2.5 Hz, $J_{4,2}$= 1.1 Hz, 1H: H_4), 3.72 (ddd, $J_{3,2}$= 3.5Hz, $J_{3,4}$= 2.5 Hz, $J_{3,5}$= 1.4 Hz, 1H: H_3), 3.52 (dd, $J_{2,3}$= 3.5 Hz, $J_{2,4}$= 1.1 Hz, 1H: H_2), 2.12 (s, 3H: AcO), 1.86 (d, $J_{CH3,5}$= 1.4 Hz, 3H: CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 193.7 (C_1), 170.0 ($O\underline{C}OCH_3$), 136.7 (C_6), 134.4 (C_5), 64.7 (C_4), 55.2 (C_3), 53.1 (C_2), 20.9 ($OCO\underline{C}H_3$), 16.1 (CH_3).

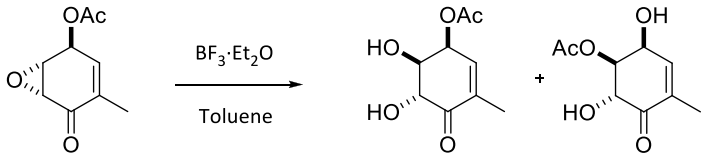
HSQCed spectra has been registered.

IR (ATR): 2928, 1737, 1684, 1369, 1219 cm^{-1}.

HRMS (ESI+): Calcd. for [$C_9H_{10}O_4$+Na]: 205.0471

Found ($M+Na^+$): 205.0472

4.3.2.3. (2*R*,3*R*,4*S*)-4-Acetoxy-2,3-dihydroxy-6-methyl-5-cyclohexenone, **45**, and (2*R*,3*S*,4*S*)-3-acetyloxy-2,4-dihydroxy-6-methyl-5-cyclohexenone, **46**



44 **45** **46**

To an ice-cooled solution of acetate (+)-**44** (17 mg, 0.09 mmol) in toluene (1 mL), $BF_3{\cdot}Et_2O$ (12 µl, 0.09 mmol) was added. The reaction mixture was stirred at 0 ºC for 2 h. Then, it was neutralized with $NaHCO_3$ and then extracted with EtOAc (3 x 0.5 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was evaporated under vacuum. The residue was purified by flash chromatography (EtOAc), affording a 3.1:1 mixture of acetates **45** and **46** (18 mg, 0.09 mmol, 97%) as an oil.

Physical and spectroscopic data of **45** and **46**:

IUPAC name 45: (1*S*,5*R*,6*R*)-5,6-Dihydroxy-3-methyl-4-oxocyclohex-2-enyl acetate.

IUPAC name 46: (1*S*,2*S*,6*R*)-2,6-Dihydroxy-4-methyl-5-oxocyclohex-3-enyl acetate.

R_f (**45** and **46**)= 0.34 (EtOAc).

^{1}H-RMN (250 MHz, $CDCl_3$) of **45**: δ 6.75 (m, 1H: H_5), 5.62 (dd, $J_{4,5}$= 5.4 Hz, $J_{4,3}$= 4.2 Hz, 1H: H_4), 4.49 (d, $J_{2,3}$= 10.6 Hz, 1H: H_2), 3.96 (dd, $J_{3,2}$= 10.6 Hz, $J_{3,4}$= 4.2 Hz, 1H: H_3), 2.13 (s, 3H: $OCOCH_3$), 1.89 (m, 3H: CH_3).

^{13}C-RMN (100 MHz, $CDCl_3$) of **45**: δ 198.1 (C_1), 170.7 ($O\underline{C}OCH_3$), 138.7 (C_6), 137.7 (C_5), 74.0 (C_2), 71.6 (C_3), 67.0 (C_4), 20.9 ($OCO\underline{C}H_3$), 15.5 (CH_3).

^{1}H-RMN (250 MHz, $CDCl_3$) of **46**: δ 6.75 (m, 1H: H_5), 5.06 (dd, $J_{3,2}$= 10.9 Hz, $J_{3,4}$= 3.8 Hz, 1H: H_3), 4.66 (d, $J_{2,3}$= 10.9 Hz, 1H: H_2), 4.64 (m, 1H: H_4), 2.20 (s, 3H: $OCOCH_3$), 1.90 (m, 3H: CH_3).

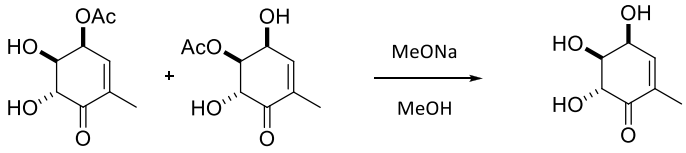
^{13}C-RMN (100 MHz, $CDCl_3$) of **46**: δ 197.9 (C_1), 170.3 ($O\underline{C}OCH_3$), 140.5 (C_5), 137.0 (C_6), 74.4 (C_3), 71.4 (C_2), 64.7 (C_4), 21.0 ($OCO\underline{C}H_3$), 15.6 (CH_3).

HSQCed spectra has been registered.

HRMS (ESI+): Calcd. for [$C_9H_{12}O_5$+Na]: 223.0577

Found (M+Na^+): 223.0581

4.3.2.4. (2*R*,3*S*,4*S*)-2,3,4-Trihydroxy-6-methyl-5-cyclohexenone, (+)-**gabosine A**



45 **46** (+)-**gabosine A**

To a solution of a mixture of acetates **45** and **46** (18 mg, 0.09 mmol) in MeOH (0.2 mL), NaMeO (4.8 mg, 0.09 mmol) was added and the mixture was stirred at room temperature for 1 h. Then, the solvent was removed under reduced pressure and the residue was diluted with water and made slightly acidic with 2% HCl. The aqueous solution was extracted with CH_2Cl_2 (3 x 0.1 ml), the combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was evaporated under vacuum. Purification of the residue by flash chromatography (EtOAc) furnished (+)-**gabosine A** (12.6 mg, 0.08 mmol, 90%) as a white crystalline solid.[91j]

Physical and spectroscopic data of (+)-**gabosine A**:

IUPAC name: (4*S*,5*S*,6*R*)-4,5,6-trihydroxy-2-methylcyclohex-2-enone.

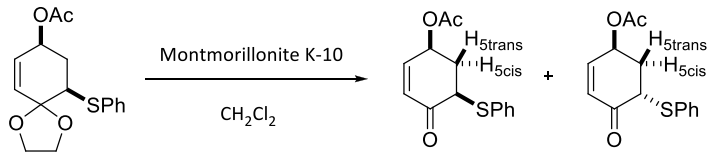
***R*$_f$=** 0.20 (EtOAc).

[α]$_D^{20}$= +128 (*c* 0.30, MeOH) (lit.[91j] [α]$_D^{20}$= +146 (*c* 0.64, MeOH)).

^{1}H NMR (400 MHz, MeOD): δ 6.78 (dq, $J_{5,4}$= 5.6 Hz, $J_{5,CH3}$= 1.4 Hz, 1H: H_5), 4.42 (m, 1H: H_4), 4.36 (d, $J_{2,3}$= 10.0 Hz, 1H: H_2), 3.76 (dd, $J_{3,2}$= 10.0 Hz, $J_{3,4}$= 3.9 Hz, 1H: H_3), 1.85 (dd, $J_{CH3,5}$= 1.4 Hz, $J_{CH3,4}$= 1.2 MHz, 3H: CH_3).

^{13}C-RMN (100 MHz, Me_3OD): δ 201.3 (C_1), 143.9 (C_5), 137.7 (C_6), 75.9 (C_2), 74.8 (C_3), 68.3 (C_4), 16.4 (CH_3)**.**

4.3.2.5. (±)-4-acetoxy-6-phenylthio-2-cyclohexenone, **47**



10 *cis*-**47** *trans*-**47**

Montmorillonite K-10 (1.8 g) was added to a solution of acetal (±)-**10** (380 mg, 1.45 mmol) in CH_2Cl_2 (16 mL) and the mixture was stirred at room temperature for 2.5 h. Then, it was filtered and the solvent removed under reduced pressure to furnish an oily residue, which was purified by flash chromatography (hexanes/Et_2O, 10:1) to provide *cis*-(±)-**47** (274 mg, 1.04 mmol, 84%) as an oil. This product slowly epimerized to the *trans* isomer (±)-**47** due to H_5's acidity.

Physical and spectroscopic data of (±)-*cis*-**47**:

IUPAC name: (1*RS*,5*SR*)-4-Oxo-5-phenylthiocyclohex-2-enyl acetate.

R_f= 0.32 (hexanes/EtOAc, 5:2).

^{1}H-RMN (400 MHz, $CDCl_3$): δ 7.50-7.45 (m, 2H: H_{ar}), 7.34-7.28 (m, 3H: H_{ar}), 6.79 (ddd, $J_{3,2}$= 10.3 Hz, $J_{3,4}$= 2.4 Hz, $J_{3,5cis}$= 1.8 Hz, 1H: H_3), 6.15 (dd, $J_{2,3}$= 10.3 Hz, $J_{2,4}$= 2.2 Hz, 1H: H_2), 5.61 (ddt, $J_{4,5trans}$= 9.4 Hz, $J_{4,5cis}$= 5.1 Hz, $J_{4,3}$≈$J_{4,2}$≈ 2.3 Hz, 1H: H_4), 3.93 (dd, $J_{6,5trans}$= 12.3 Hz, $J_{6,5cis}$= 4.8 Hz, 1H: H_6), 2.62 (dtd, $J_{5cis,5trans}$= 12.8 Hz, $J_{5cis,6}$≈$J_{5cis,4}$≈ 5.0 Hz, $J_{5cis,3}$= 1.8 Hz, 1H: H_{5cis}), 2.19 (td, $J_{5trans,5cis}$≈$J_{5trans,6}$≈ 12.5 Hz, $J_{5trans,4}$= 9.4 Hz, 1H:H_{5trans}).

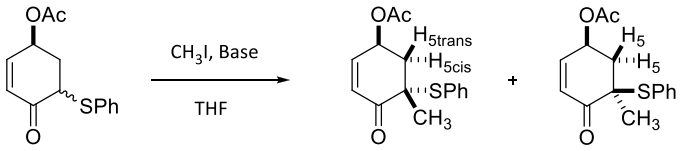
Physical and spectroscopic data of (±)-*trans*-**47**:

IUPAC name: (1*RS*,5*RS*)-4-Oxo-5-phenylthiocyclohex-2-enyl acetate.

R_f= 0.38 (hexanes/EtOAc, 5:2).

^{1}H-RMN (400 MHz, $CDCl_3$) of *trans*-**47** in a mixture: δ 7.48-7.38 (m, 2H: H_{ar}), 7.33-7.23 (m, 3H: H_{ar}), 6.78 (m, 1H: H_3), 6.03 (ddd, $J_{2,3}$= 10.3 Hz, J= 1.9 Hz, J'= 1.0 Hz, 1H: H_2), 5.76 (m, 1H: H_4), 2.50 (dtd, $J_{5cis,5trans}$= 13.6 Hz, J= 5.0 Hz, J'= 1.6 Hz, 1H: H_{5cis}), 2.39 (ddd, $J_{5trans,5cis}$= 13.6 Hz, J= 8.6 Hz, J'= 4.5 Hz, 1H: H_{5trans}).

4.3.2.6. (4*S*,6*S*)-, **48**, and (4*S*,6*R*)-4-acetoxy-6-methyl-6-phenylthio-2-cyclohexenoneylthiocyclohex-2-enyl acetate, **49**



47 **48** **49**

A solution of ketone (4*S*)-**47** (250 mg, 0.95 mmol) in anhydrous THF (4.5 mL) was added to a stirred solution of K^{t}BuO (160 mg, 1.42 mmol) in anhydrous THF (1.2 mL) at -78 ºC, under nitrogen atmosphere. After stirring the mixture at -78 ºC for 15 min, MeI (593 µL, 9.52 mmol) was added and the solution was allowed to warm to room temperature. After 1 h 45 min, the reaction mixture was acidified by addition of a saturated aqueous solution of NH_4Cl and then extracted with EtOAc (3 x 3 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and the solvent was evaporated under vacuum. The residue was purified by flash chromatography (hexanes/EtOAc, 5:2), affording a 2.5:1 mixture of (4*S*,6*S*)-**48** and (4*S*,6*R*)-**49** (237 g, 0.86 mmol, 90%). Repeated flash chromatography allowed the isolation of a pure sample of (4*S*,6*S*)-**48**. The same reaction using NaH instead of K^{t}BuO gave an identical ratio of isomers and the same yield.

Physical and spectroscopic data of **48**:

IUPAC name: (1*S*,5*S*)-5-Methyl-4-oxo-5-phenylthiocyclohex-2-enyl acetate.

R_f= 0.44 (hexanes/EtOAc, 5:2).

^{1}H-RMN (400 MHz, $CDCl_3$): δ 7.46-7.36 (m, 3H: H_{ar}), 7.35-7.29 (m, 2H: H_{ar}), 6.74 (dt, $J_{3,2}$= 10.3 Hz, $J_{3,4}$=$J_{3,5cis}$= 2.3 Hz, 1H: H_3), 6.05 (dd, $J_{2,3}$= 10.3 Hz, $J_{2,4}$=2.3 Hz, 1H: H_2), 5.99 (ddt, $J_{4,5trans}$= 10.3 Hz, $J_{4,5cis}$= 5.4 Hz, $J_{4,3}$=$J_{4,2}$= 2.3 Hz, 1H: H_4), 2.55 (ddd, $J_{5cis,5trans}$= 13.5 Hz, $J_{5cis,4}$= 5.4 Hz, $J_{5cis,3}$= 2.3 Hz, 1H: H_{5cis}), 2.19 (dd, $J_{5trans,5cis}$= 13.5 Hz, $J_{5trans,4}$= 10.3 Hz, 1H: H_{5trans}), 2.12 (s, 3H: $COCH_3$), 1.34 (s, 3H: CH_3).

^{13}C-NMR (400 MHz, $CDCl_3$): δ 193.9 (C_1), 170.2 ($\underline{C}OCH_3$), 146.4 (C_3), 137.6 (C_{ar}), 129.9 (C_{ar}), 129.0 (C_{ar}), 128.5 (C_2), 67.4 (C_4), 54.1 (C_6), 41.9 (C_5), 24.1 (CH_3), 21.1 ($CO\underline{C}H_3$).

HSQCed spectrum have been registered.

Physical and spectroscopic data of **49**:

IUPAC name: (1*S*,5*R*)-5-Methyl-4-oxo-5-phenylthiocyclohex-2-enyl acetate.

R_f= 0.38 (hexanes/EtOAc, 5:2).

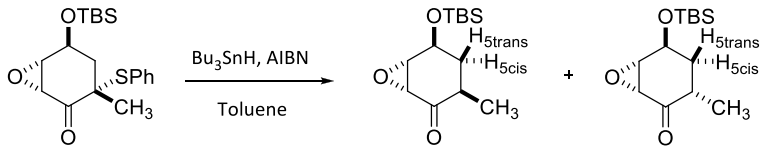
^{1}H-RMN (360 MHz, $CDCl_3$) of **49** in a mixture: δ 7.49-7.29 (m, 5H: H_{ar}),6.72 (ddt, $J_{3,2}$=10.2 Hz, $J_{3,4}$= 3.3 Hz, $J_{3,5}$≈$J_{3,5}$≈0.8 Hz, 1H:H_3), 6.12 (dd, $J_{3,2}$= 10.2 Hz, $J_{2,4}$= 1.6 Hz, 1H: H_2), 5.54 (dddd, $J_{4,2}$= 1.6 Hz, $J_{4,3}$= 3.3 Hz, $J_{4,5}$= 5.6 Hz, $J_{4,5}$=6.4 Hz, 1H: H_4), 2.41 (ddd, $J_{5,5}$= 14.2 Hz, $J_{5,4}$= 5.6 Hz, $J_{5,3}$= 0.9 Hz, 1H: H_5), 2.35 (ddd, $J_{5,5}$= 14.2 Hz, $J_{5,4}$= 6.4 Hz, $J_{5,3}$=0.7 Hz, 1H: H_5), 2.12 (s, 3H: $COCH_3$), 1.39 (s, 3H: CH_3).

^{13}C-RMN (360 MHz, $CDCl_3$) of **49** in a mixture: δ 195.8 (C_1), 170.4 ($\underline{C}OCH_3$), 143.94 (C_3), 137.3 (C_{ar}), 129.7 (C_{ar}/C_2), 129.6 (C_{ar}/C_2), 128.9 (C_{ar}), 65.9 (C_4), 53.9 (C_6), 40.9 (C_5), 23.5 (CH_3), 21.3 ($CO\underline{C}H_3$).

4.4. REDUCTION OF THE C6-BOND

4.4.1. Total synthesis of dihydroepiepoformin

4.4.1.1. (2*RS*,3*SR*,4*SR*,6*RS*)-, (±)-**51**, and (2*RS*,3*SR*,4*SR*,6*SR*)-4-*tert*-Butyldimethylsilyloxy-2,3-epoxy-6-methylcyclohexanone, (±)-**52**



32 **51** **52**

To a boiling solution of (±)-**32** (363 mg, 0.99 mmol) in anhydrous toluene (9.0 mL), a solution of AIBN (17.3 mg, 0.10 mmol) and Bu_3SnH (315 μL, 1.19 mmol) in anhydrous toluene (5.1 mL) was continuously added over 73 min. After 1 min, the reaction was cooled and the solvent was evaporated under vacuum to give an oily residue, which was purified by flash chromatography (hexanes to hexanes/EtOAc, 5:1) to provide an inseparable 6.6:1 mixture of epoxides (±)-**51**[91d] and (±)-**52** (204 mg, 0.79 mmol, 80%) as an oil.

Physical and spectroscopic data of (±)-**51** and (±)-**52:**

IUPAC name 51: (1*RS*,3*RS*,5*SR*,6*SR*)-5-*tert*-Butyldimethylsilyloxy-3-methyl-oxabicyclo[4.1.0]heptan-2-one.

IUPAC name 52: (1*RS*,3*SR*,5*SR*,6*SR*)-5-*tert*-Butyldimethylsilyloxy-3-methyl-oxabicyclo[4.1.0]heptan-2-one.

R_f (**51** and **52**)= 0.50 (hexanes/EtOAc, 5:1).

^{1}H-RMN (250 MHz, $CDCl_3$) of **51**: δ 4.35 (ddd, $J_{4,5trans}$= 7.8 Hz, $J_{4,5cis}$= 5.5 Hz, $J_{4,3}$= 1.2 Hz, 1H: H_4), 3.46 (dt, $J_{3,2}$= 3.8 Hz, $J_{3,4}$=$J_{3,5cis}$= 1.2 Hz, 1H: H_3), 3.29 (d, $J_{2,3}$= 3.8 Hz, 1H: H_2), 2.66 (dqd, $J_{6,5trans}$= 11.0 Hz, $J_{6,CH3}$= 6.8 Hz, $J_{6,5cis}$= 1.2 Hz, 1H: H_6), 2.18 (ddt, $J_{5cis,5trans}$= 13.5 Hz, $J_{5cis,4}$= 5.5 Hz, $J_{5cis,6}$=$J_{5cis,3}$= 1.2 Hz, 1H: H_{5cis}), 1.57 (ddd, $J_{5trans,5cis}$= 13.5 Hz, $J_{5trans,6}$= 11.0 Hz, $J_{5trans,4}$= 7.8 Hz, 1H: H_{5trans}), 1.01 (d, $J_{CH3,6}$= 6.8 Hz, 3H: CH_3), 0.89 (s, 9H: ^{t}Bu), 0.11 (s, 3H: $SiCH_3$), 0.09 (s, 3H: $SiCH_3$).

^{13}C-RMN (100 MHz, $CDCl_3$) of **51**: δ 208.4 (C_1), 65.9 (C_4), 63.4 (C_3), 55.5 (C_2), 41.1 (C_5), 34.7 (C_6), 18.1 (CH_3), 15.2 ($C(\underline{C}H_3)_3$), 14.2 ($\underline{C}(CH_3)_3$), 4.7 (CH_3), -4.7($SiCH_3$), -4.8($SiCH_3$).

^{1}H-RMN (250 MHz, $CDCl_3$) of **52**: δ 4.46 (q, $J_{4,3}$≈$J_{4,5trans}$≈$J_{4,5cis}$≈ 2.9 Hz, 1H: H_4), 3.41 (m, 1H: H_3), 3.24 (d, $J_{2,3}$= 3.8 Hz, 1H: H_2), 2.46 (dqn, $J_{6,5cis}$= 11.6 Hz, $J_{6,5trans}$=$J_{6,CH3}$= 7.1 Hz, 1H: H_6), 1.77 (m, 2H: H_{5trans}, H_{5cis}), 1.10 (d, $J_{CH3,6}$= 7.1 Hz, 1H: CH_3), 0.89 (s, 9H: ^{t}Bu), 0.10 (s, 3H: $SiCH_3$), 0.08 (s, 3H: $SiCH_3$).

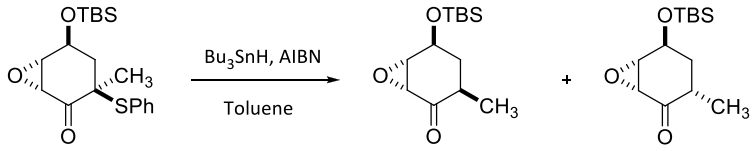
^{13}C-RMN (100 MHz, $CDCl_3$) of **52**: δ 206.4 (C_1), 65.5 (C_4), 56.7 (C_3), 54.4 (C_2), 36.4 (C_5), 32.3 (C_6), 18.2 (CH_3), 15.5 ($C(\underline{C}H_3)_3$), 14.3 ($\underline{C}(CH_3)_3$), -4.6 ($SiCH_3$), -4.7($SiCH_3$).

HSQCed spectra has been registered.

HRMS (ESI+): Calcd. for $[C_{13}H_{24}O_3Si+Na]$: 279.1387

Found ($M+Na^+$): 279.1387.

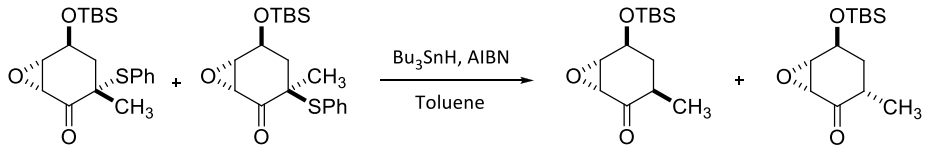
i)



36 **51** **52**

A (±)-**51** and (±)-**52** mixture (33 mg, 0.13 mmol, 90%) with the same ratio was also obtained starting from (±)-**36** (52 mg, 0.14 mmol).

ii)

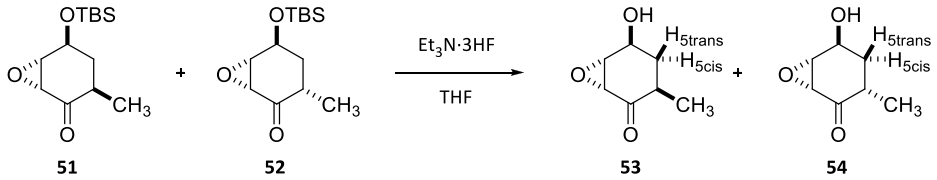


32 **36** **51** **52**

A (2*R*,3*S*,4*S*,6*R*)-**51** and (2*R*,3*S*,4*S*,6*S*)-**52** mixture (278 mg, 1.08 mmol, 79%) with the same ratio was also obtained starting from a mixture of (2*R*,3*S*,4*S*,6*S*)-**32** and (2*R*,3*S*,4*S*,6*R*)-**36** (500 mg, 1.37 mmol).

The same reaction starting from a mixture of (2*S*,3*R*,4*R*,6*R*)-**32** and (2*S*,3*R*,4*R*,6*S*)-**36** (800 mg, 2.19 mmol) in anhydrous toluene (20 ml), a solution of Bu_3SnH (695 µl, 2.62 mmol) and AIBN (38 mg, 0.23 mmol) in anhydrous toluene (11.2 ml) furnished a mixture of (2*S*,3*R*,4*R*,6*S*)-**51** and (2*S*,3*R*,4*R*,6*R*)-**52** (456 mg, 1.78 mmol, 81%).

4.4.1.2. (2*RS*,3*RS*,4*SR*,6*RS*)-, (±)-**53**, and (2*RS*,3*RS*,4*SR*,6*SR*)-2,3-epoxy-4-hydroxy-6-methylcyclohexanone, (±)-**54**



A solution of a 6.6:1 mixture of epoxides (±)-**51** and (±)-**52** (336 mg, 1.31 mmol) in THF (17.4 mL) at room temperature was treated with $Et_3N{\cdot}3HF$ (1.24 mL, 7.61 mmol). The reaction mixture was stirred for 20 h at the same temperature. Then, CH_2Cl_2 (23 mL) and a saturated solution of $NaHCO_3$ (23 mL) were added. The organic layer was separated and the aqueous one extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under vacuum to give a 1:1 mixture of alcohols (±)-**53** and (±)-**54** (149 mg, 1.05 mmol, 80%) as an oily residue. After repeated flash chromatographies (hexanes/EtOAc, from 10:1 to 1:1) analytical samples of (±)-**53**[91d] and (±)-**54** were isolated.

Physical and spectroscopic data of (±)-**53:**

IUPAC name: (1*RS*,3*RS*,5*SR*,6*RS*)-5-Hydroxy-3-methyl-7-oxabicyclo[4.1.0]heptan-2-one.

***R*$_f$=** 0.20 (EtOAc).

^{1}H-NMR (250 MHz, $CDCl_3$): δ 4.58 (bs, 1H: H_4), 3.56 (t, $J_{3,4}$=$J_{3,2}$= 3.5 Hz, 1H: H_3), 3.29 (d, $J_{2,3}$= 3.5 Hz, 1H: H_2), 2.48 (tq, $J_{6,5trans}$=$J_{6,5cis}$= 9.3 Hz, $J_{6,CH3}$= 7.2 Hz, 1H: H_6), 1.86 (m, 3H: H_{5trans},H_{5cis}, OH), 1.14 (d, $J_{CH3,6}$= 7.2 Hz, 3H: CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 205.8 (C_1), 64.9 (C_4), 56.2 (C_3), 54.4 (C_2), 36.3 (C_6), 32.3 (C_5), 15.5 (CH_3).

IR (ATR): 3401, 2932, 1704, 1058 cm^{-1}.

HRMS (ESI+): Calcd. for [$C_7H_{10}O_3$+Na]: 165.0528

Found (M+Na^+): 165.0527

Physical and spectroscopic data of (±)-**54:**

IUPAC name: (1*RS*,3*SR*,5*SR*,6*RS*)-5-Hydroxy-3-methyl-7-oxabicyclo[4.1.0]heptan-2-one.

***R*$_f$= 0.18** (EtOAc).

^{1}H-NMR (360 MHz, $CDCl_3$): δ 4.44 (bdd, $J_{4,5cis}$= 8.6 Hz, $J_{4,5trans}$= 5.9 Hz, 1H: H_4), 3.57 (m, 1H: H_3), 3.34 (d, $J_{2,3}$= 3.8 Hz, 1H:H_2), 2.75 (dqd, $J_{6,5cis}$= 12.1 Hz, $J_{6,CH3}$= 6.7 Hz, $J_{6,5trans}$= 5.4 Hz, 1H: H_6), 2.32 (m, 1H: H_{5trans}), 1.70 (bs, 1H: OH), 1.59 (ddd, $J_{5cis,5trans}$= 13.5 Hz, $J_{5cis,6}$= 12.1 Hz, $J_{5cis,4}$= 8.6 Hz, 1H: H_{5cis}), 1.03 (d, $J_{CH3,6}$= 6.7 Hz, 3H: CH_3).

^{13}C-NMR (90 MHz, $CDCl_3$): δ 208.3 (C_1), 65.3 (C_4), 63.3 (C_3), 55.5 (C_2), 34.4 (C_6), 31.2 (C_5), 14.8 (CH_3).

IR (ATR): 3430, 2926, 1714, 1082 cm^{-1}.

HRMS (ESI+): Calcd. for [$C_7H_{10}O_3$+Na]: 165.0528

Found ($M+Na^+$): 165.0525

4.4.1.2.1. The same reaction starting from a 6.6:1 mixture of epoxides (2*R*,3*S*,4*S*,6*R*)-**51** and (2*R*,3*S*,4*S*,6*S*)-**52** (114 mg, 0.44 mmol) in THF (6 mL) treated with $Et_3N{\cdot}3HF$ (420 μL, 2.58 mmol) furnished a 1:1 mixture of alcohols (2*R*,3*R*,4*S*,6*R*)-**53** and (2*R*,3*R*,4*S*,6*S*)-**54** as an oil (50 mg, 0.35 mmol, 79%).

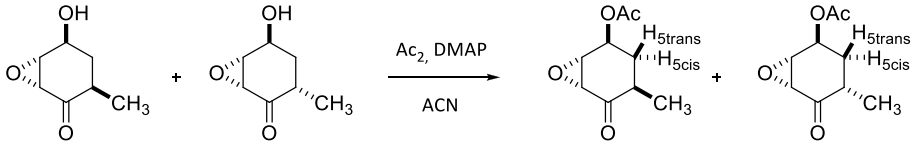
4.4.1.2.2. The same reaction starting from a 6.6:1 mixture of epoxides (2*S*,3*R*,4*R*,6*S*)-**51** and (2*S*,3*R*,4*R*,6*R*)-**52** (180 mg, 0.70 mmol) in THF (9.5 mL) treated with $Et_3N{\cdot}3HF$ (663 μL, 4.10 mmol) furnished a mixture of alcohols (2*S*,3*S*,4*R*,6*S*)-**53** and (2*S*,3*S*,4*R*,6*R*)-**54** (80 mg, 0.56 mmol, 80%) as an oil. After repeated flash chromatography (hexanes/EtOAc, from 10:1 to 1:1) analytical samples of (2*S*,3*S*,4*R*,6*S*)-**53** and (2*S*,3*S*,4*R*,5*6*)-**54** were isolated.

(2*S*,3*S*,4*R*,6*S*)-**53**: **$[\alpha]_D^{20}$**= -28 (*c* 0.14, $CHCl_3$) (lit.[91d] $[\alpha]_D^{20}$= -27 (*c* 1.2, $CHCl_3$)).

(2S,3S,4R,6R)-**54**: **$[\alpha]_D^{20}$**= -36 (*c* 0.11, $CHCl_3$).

4.4.2. Cleavage of the epoxide: Total synthesis of gabosine B and F

4.4.2.1. (2*RS*,3*RS*,4*SR*,6*RS*)-, (±)-**55**, (2*RS*,3*RS*,4*SR*,6SR)-4-Acetoxy-2,3-epoxy-6-methylcyclohexanone, (±)-**56**



53 **54** **55** **56**

To a solution a 1:1 mixture of alcohols (±)-**53** and (±)-**54** (64 mg, 0.45 mmol) in anhydrous acetonitrile (4.2 ml) at 0 ºC under nitrogen atmosphere, DMAP (61 mg, 0.50 mmol) and acetic anhydride (171 µl, 1.81 mmol) were added. The reaction mixture was warmed to room temperature and stirred for 5 min. Then, it was poured into ice water and extracted with CH_2Cl_2 (3 x 1.5 mL). The combined organic extracts were washed with cold water, saturated aqueous solution of $NaHCO_3$ and dried over $MgSO_4$. Removal of the solvent under reduced pressure furnished an oily residue, which was purified by flash chromatography (EtOAc) to yield a 1:1 mixture of (**±**)-**55** and (**±**)-**56** (68 mg, 0.37 mmol, 82%) as an oil.

Physical and spectroscopic data of (±)-**55** and (**±**)-**56:**

IUPAC name 55: (1*RS*,2*SR*,4*RS*,6*RS*)-4-Methyl-5-oxo-7-oxabicyclo[4.1.0]heptan-2-yl acetate.

IUPAC name 56: (1*RS*,2*SR*,4*SR*,6*RS*)-4-Methyl-5-oxo-7-oxabicyclo[4.1.0]heptan-2-yl acetate.

R_f(56 and **57**)= 0.60 (hexanes/EtOAc, 1:1).

^{1}H-RMN (250 MHz, $CDCl_3$) of **55:** δ = 5.35 (bt, $J_{4,5trans}$≈$J_{4,5trans}$≈ 7.8 Hz, 1H: H_4), 3.58 (bdt, $J_{3,2}$= 3.8 Hz, $J_{3,4}$≈$J_{3,5cis}$≈ 1.3 Hz, 1H: H_3), 3.79 (d, $J_{2,3}$= 3.8 Hz, 1H: H_2), 2.74 (dqn, $J_{6,5trans}$= 10.6 Hz, $J_{6,5cis}$≈$J_{6,CH3}$≈ 6.8 Hz, 1H: H_6), 2.37 (m, 1H: H_{5cis}), 2.08 (s, 3H: $OCOCH_3$), 1.60 (ddd, $J_{5trans,5cis}$= 13.8 Hz, $J_{5trans,6}$= 10.6 Hz, $J_{5trans,4}$= 7.8 Hz, 1H: H_{5trans}), 1.02 (d, $J_{CH3,6}$=6.8 Hz, 3H: CH_3).

^{13}C NMR (63 MHz, CDCl3) of **55**: δ 205.3 (C_1), 170.3 ($O\underline{C}OCH_3$), 67.4 (C_4), 54.4 (C_3), 53.9 (C_2), 36.9 (C_6), 29.1 (C_5), 21.0 ($OCO\underline{C}H_3$), 15.8 (CH_3).

^{1}H-RMN (250 MHz, $CDCl_3$) of **56:** δ 5.51 (q, $J_{4,3}$≈$J_{4,5trans}$≈$J_{4,5cis}$≈ 3.5 Hz, 1H: H_4), 3.63 (bt, $J_{3,4}$≈$J_{3,2}$≈ 3.5 Hz, 1H: H_3), 3.29 (d, $J_{2,3}$= 3.5 Hz, 1H: H_2), 2.09 (s, 3H: $OCOCH_3$), 1.13 (d, $J_{CH3,6}$= 7.0 Hz, 3H: CH_3).

^{13}C NMR (63 MHz, CDCl3) of **56**: δ 207.5 (C_1), 170.1 ($O\underline{C}OCH_3$), 66.9 (C_4), 60.1 (C_3), 55.1 (C_2), 36.7 (C_5/C_6), 34.6 (C_5/C_6), 21.0 ($OCO\underline{C}H_3$), 15.1 (CH_3).

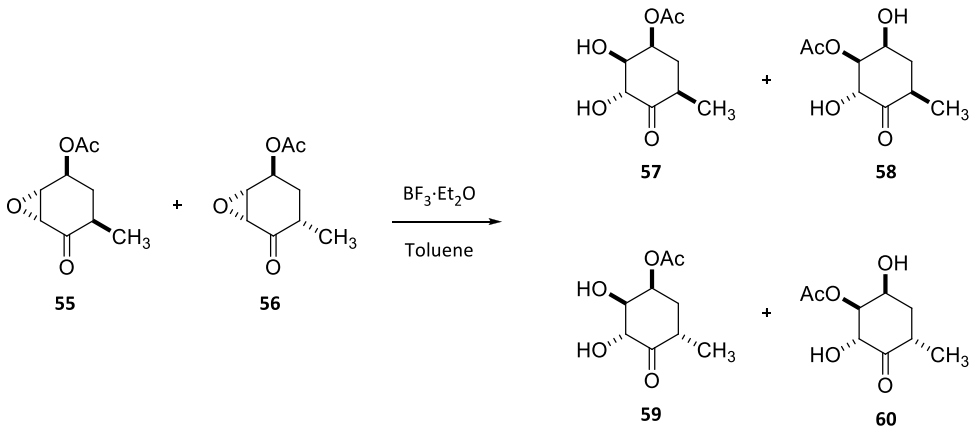
HRMS (ESI+): Calcd. for [$C_9H_{12}O_4$+Na]: 207.0633

Found (M+Na^+): 207.0629

4.4.2.1.1. The same reaction starting from a 1:1 mixture of alcohols (2*R*,3*R*,4*S*,6*R*)-**53** and (2*R*,3*R*,4*S*,6*S*)-**54** (46 mg, 0.32 mmol) in anhydrous acetonitrile (1.6 mL), DMAP (44 mg, 0.36 mmol) and Ac_2O (122 μL, 1.29 mmol), furnished a 1:1 mixture of acetates (2*R*,3*R*,4*S*,6*R*)-**55** (and (2*R*,3*R*,4*S*,6*S*)-**56** (48 mg, 0.25 mmol, 80%).

4.4.2.1.2. The same reaction starting from a 1:1 mixture of alcohols (2*S*,3*S*,4*R*,6*S*)-**53** and (2*S*,3*S*,4*R*,6*R*)-**54** (36 mg, 0.26 mmol) in anhydrous acetonitrile (1.3 mL), DMAP (34 mg, 0.28 mmol) and Ac_2O (97 μL, 1.03 mmol), furnished a 1:1 mixture of acetates (2*S*,3*S*,4*R*,6*S*)-**55** and (2*S*,3*S*,4*R*,6*R*)-**56** (40 mg, 0.22 mmol, 84%).

4.4.2.2. (2*R*,3*R*,4*S*,6*R*)-, (±)-**57**, (2*R*,3*R*,4*S*,6*S*)-4-Acetoxy-2,3-dihydroxy-6-methylcyclohexanone, (±)-**59**, (2*R*,3*S*,4*S*,6*R*)-, (±)-**58**, and (2*R*,3*S*,4*S*,6*S*)-3-acetoxy-2,4-dihydroxy-6-methylcyclohexanone, (±)-**60**



To an ice-cooled solution of acetates (±)-**55** and (±)-**56 (**76.2 mg, 0.41 mmol) in toluene (4.5 mL) $BF_3{\cdot}Et_2O$ (52 μL, 0.41 mmol) was added and the mixture was stirred at 0 ºC for 2 h. Then, the reaction was neutralized with $NaHCO_3$ and the aqueous phase was extracted with EtOAc (3 x 2 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was evaporated under vacuum. The residue was purified by flash chromatography (EtOAc) to afford a mixture of the expected diols (±)-**57,** (±)-**58,** (±)-**59** and (±)-**60** (79.2 mg, 0.39 mmol, 96%) as a yellow oil.

IUPAC name 57: (1*S*,2*R*,3*R*,5*R*)-2,3-Dihydroxy-5-methyl-4-oxocyclohexyl acetate.

IUPAC name 58: (1*S*,2*R*,4*R*,6*S*)-2,6-Dihydroxy-4-methyl-3-oxocyclohexyl acetate.

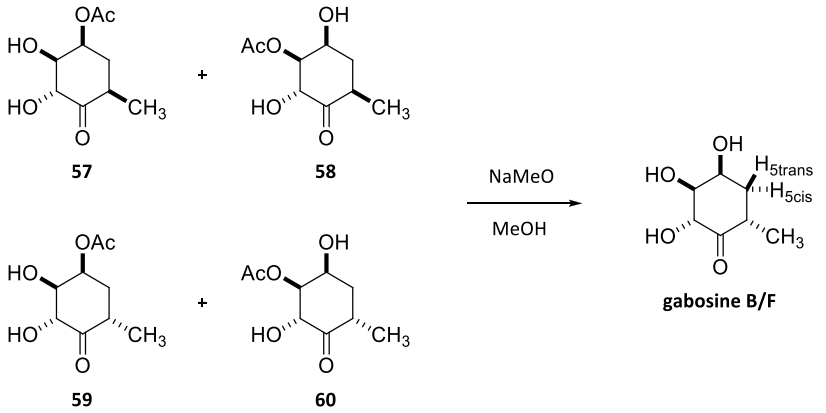
IUPAC name 59: (1*S*,2*R*,3*R*,5*S*)-2,3-Dihydroxy-5-methyl-4-oxocyclohexyl acetate.

IUPAC name 60: (1*S*,2*R*,4*S*,6*S*)-2,6-Dihydroxy-4-methyl-3-oxocyclohexyl acetate.

4.4.2.2.1. The same reaction starting from (2*R*,3*R*,4*S*,6*R*)-**55** and (2*R*,3*R*,4*S*,6*S*)-**56** (30 mg, 0.16 mmol) in toluene (2.0 mL) and $BF_3{\cdot}Et_2O$ (21 μL, 0.16 mmol) furnished (2*R*,3*R*,4*S*,6*R*)-**57**, (2*R*,3*S*,4*S*,6*R*)-**58**, (2*R*,3*R*,4*S*,6*S*)-**59** and (2*R*,3*S*,4*S*,6*S*)-**60** (29 mg, 0.14 mmol, 86%).

4.4.2.2.2. The same reaction starting from (2*S*,3*S*,4*R*,6*S*)-**55** and (2*S*,3*S*,4*R*,6*R*)-**56** (22 mg, 0.12 mmol) in toluene (1.3 mL) and $BF_3{\cdot}Et_2O$ (15 μL, 0.12 mmol) furnished (2*S*,3*S*,4*R*,6*S*)-**57**, (2*S*,3*R*,4*R*,6*S*)-**58**, (2*S*,3*S*,4*R*,6*R*)-**59** and (2*S*,3*R*,4*R*,6*R*)-**60** (22 mg, 0.11 mmol, 89%).

4.4.2.3. (2*RS*,3*SR*,4*SR*,6*SR*)-2,3,4-trihydroxy-6-methylcyclohexanone, **gabosine B/F**



To a solution of a mixture of acetates (±)-**57-60** (48 mg, 0.24 mmol) in MeOH (0.53 mL) was added NaMeO (12.8 mg, 0.24 mmol) and the mixture was stirred at room temperature for 1 h. Then, the solvent was removed under reduced pressure, and the residue was diluted in water and neutralized with TFA (to ca. pH 7). Purification of the residue by flash chromatography ($CHCl_3$/MeOH, 20:1) furnished gabosine B/F (35 mg, 0.22 mmol, 92%) as a white crystalline material.

Physical and spectroscopic data of **gabosine B/F:**

***R*$_f$=** 0.24 ($CHCl_3$/MeOH, 9:1).

^{1}H-NMR (400 MHz, MeOD): δ 4.43 (d, $J_{2,3}$= 10.0 Hz, 1H: H_2), 4.13 (bq, $J_{4,3}\approx J_{4,5trans}\approx J_{4,5cis}\approx$ 3.0 Hz, 1H: H_4), 3.49 (dd, $J_{3,2}$= 10.0 Hz, $J_{3,4}$= 3.0 Hz, 1H: H_3), 2.96 (dqd, $J_{6,5cis}$= 13.0 Hz $J_{6,CH3}$= 6.6 Hz, $J_{6,5trans}$= 5.9 Hz, 1H: H_6), 2.15 (ddd, $J_{5trans,5cis}$= 14.0 Hz, $J_{5trans,6}$= 5.9 Hz, $J_{5trans,4}$= 3.2 Hz, 1H: H_{5trans}), 1.45 (td, $J_{5cis,5trans}=J_{5cis,6}\approx$ 14.0 Hz, $J_{5cis,4}$= 2.6 Hz, 1H: H_{5cis}), 1.06 (d, $J_{CH3,6}$= 6.6 Hz, 3H: CH_3).

^{13}C NMR (101 MHz, MeOD): δ 212.3 (C_1), 80.0 (C_3), 79.0 (C_2), 70.6 (C_4), 39.0 (C_5), 38.7 (C_6), 14.6 (CH_3).

HSQCed spectra has been registered.

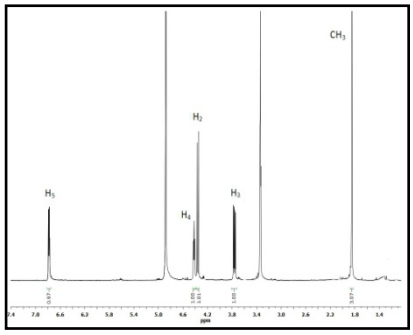
4.4.2.3.1. The same reaction starting from the mixture of acetates (2*R*,3*R*,4*S*,6*R*)-**57,** (2*R*,3*S*,4*S*,6*R*)-**58,** (2*R*,3*R*,4*S*,6*S*)-**59** and (2*R*,3*S*,4*S*,6*S*)-**60** (20 mg, 0.10 mmol) in MeOH (220 μL) and NaMeO (5 mg, 0.10 mmol) furnished (2R,3S,4S,6S)-2,3,4-trihydroxy-6-methylenecyclohexanone, **gabosine F** (15 mg, 010 mmol, 92%).[91k]

Gabosine F: **$[\alpha]_D^{20}$**= +89.3 (*c* 0.32, MeOH). (lit.[91k] $[\alpha]_D^{20}$= +94 (*c* 1.0, MeOH)).

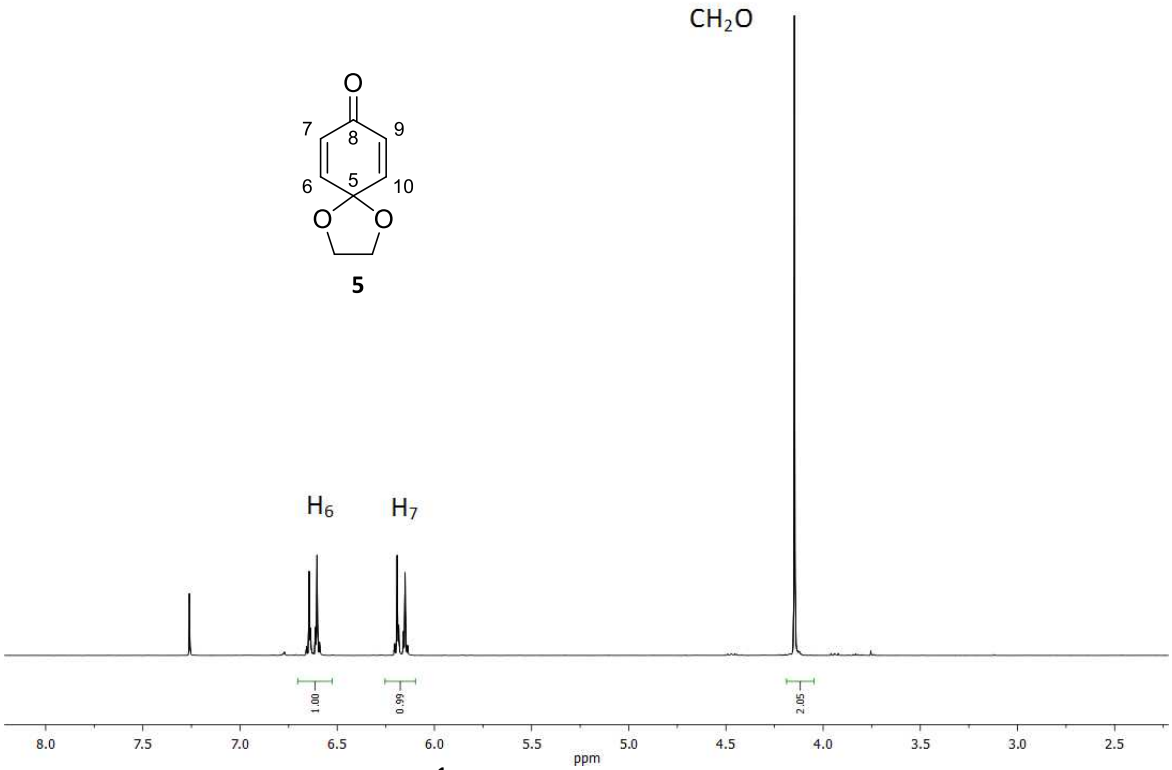
4.4.2.3.2. The same reaction starting from (2*S*,3*S*,4*R*,6*S*)-**57d**, (2*S*,3*R*,4*R*,6*S*)-**58**, (2*S*,3*S*,4*R*,6*R*)-**59** and (2*S*,3*R*,4*R*,6*R*)-**60** (14 mg, 0.07 mmol) in MeOH (150 μL) and NaMeO (4 mg, 0.07 mmol), furnished (2*S*,3*R*,4*R*,6*R*)-2,3,4-trihydroxy-6-methylenecyclohexanone, **Gabosine B** (10 mg, 0.06 mmol, 90%).[112]

Gabosine B: $[\alpha]_D^{20}$= -88.4 (*c* 0.51, MeOH). (lit.[6] $[\alpha]_D^{20}$=-91.1 (*c* 1.5, MeOH)).

VII. NMR Spectra

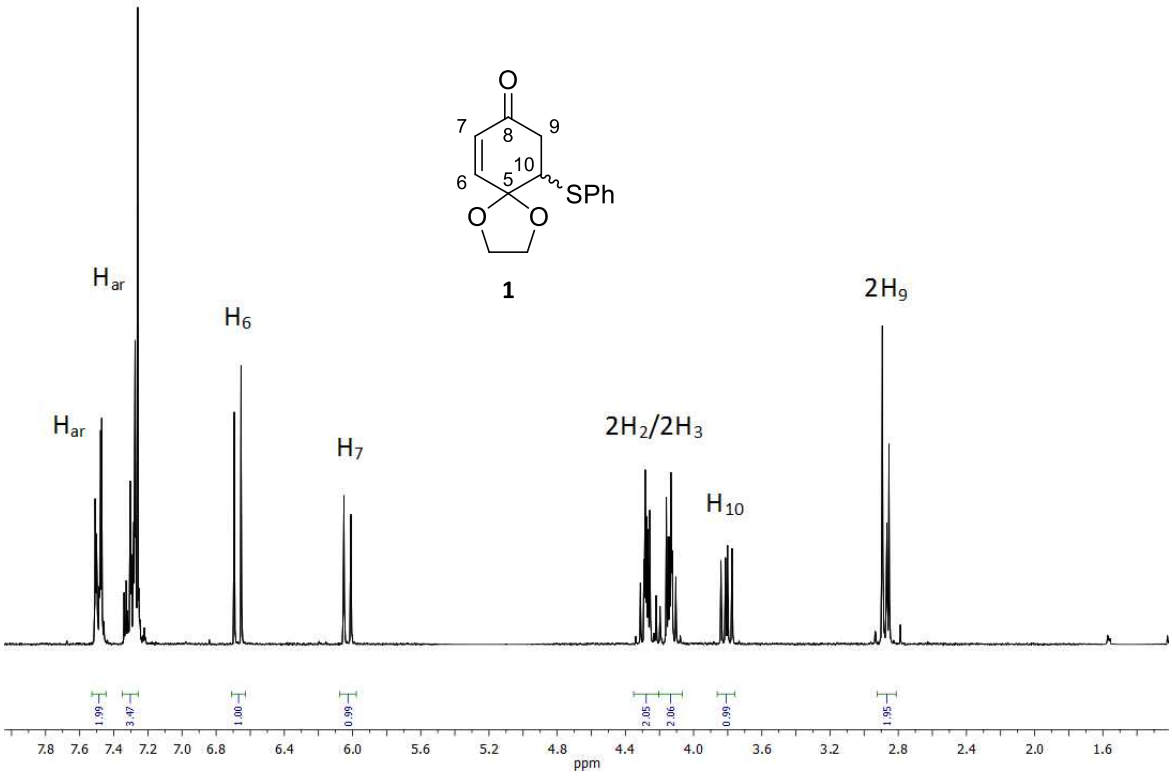


^{1}H-NMR spectrum

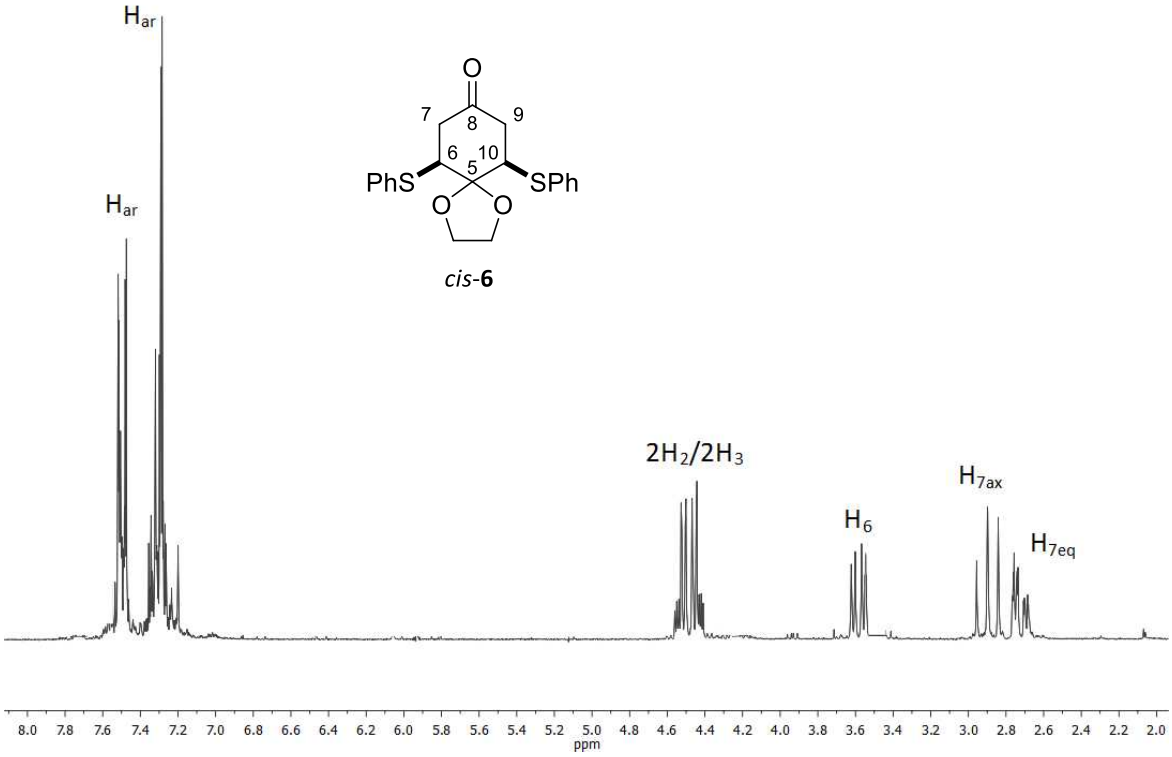


5

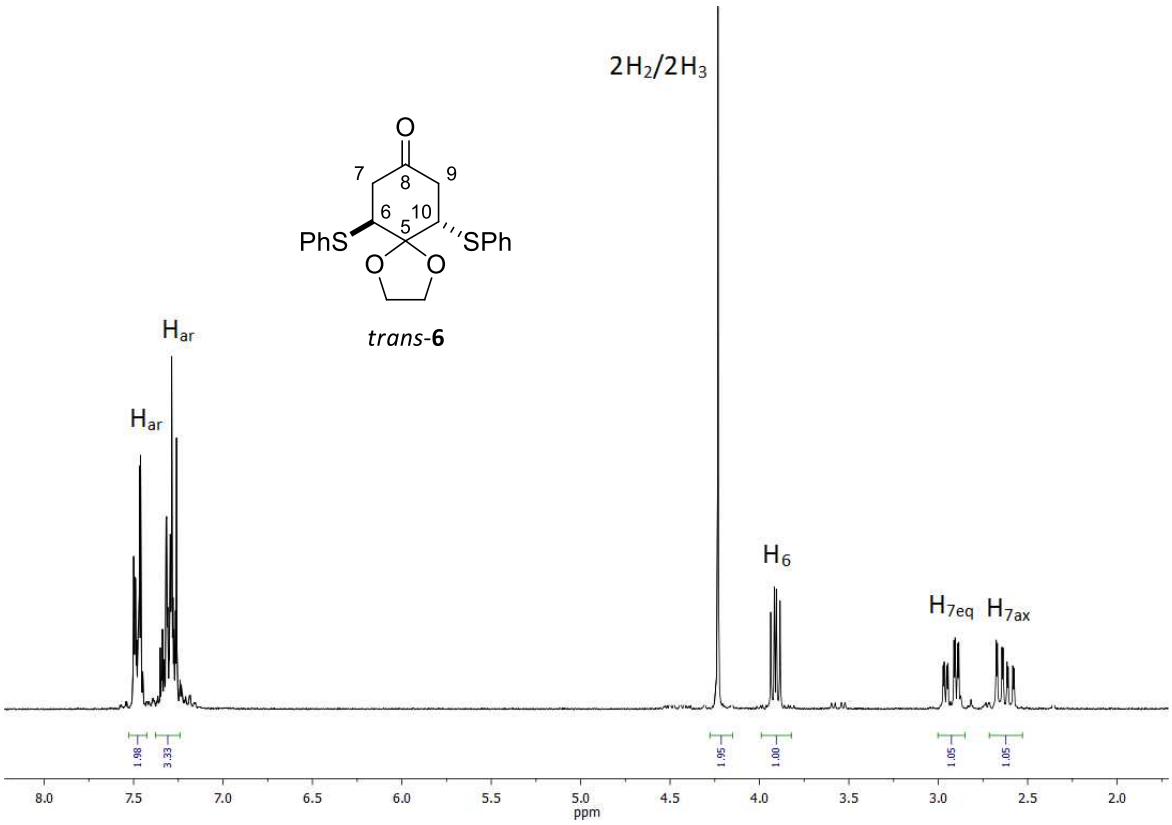
^{1}H-NMR (250 Mz, $CDCl_3$)



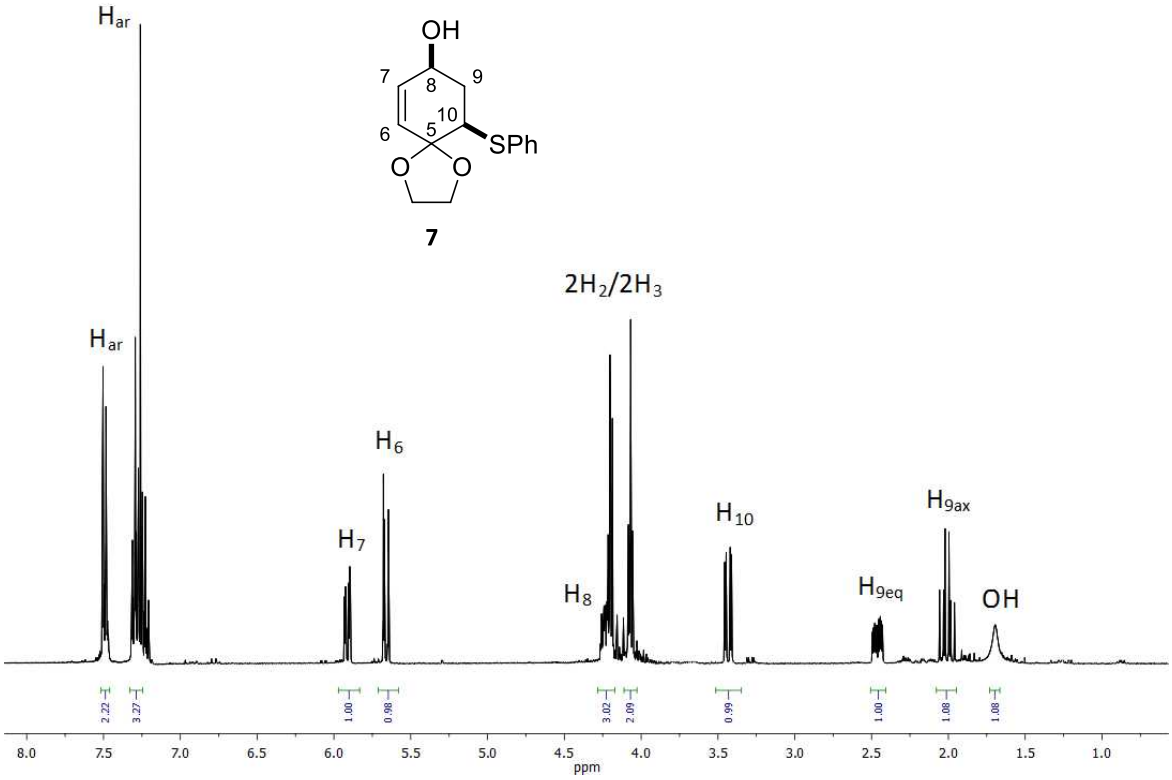
^{1}H-NMR (250 MHz, $CDCl_3$)



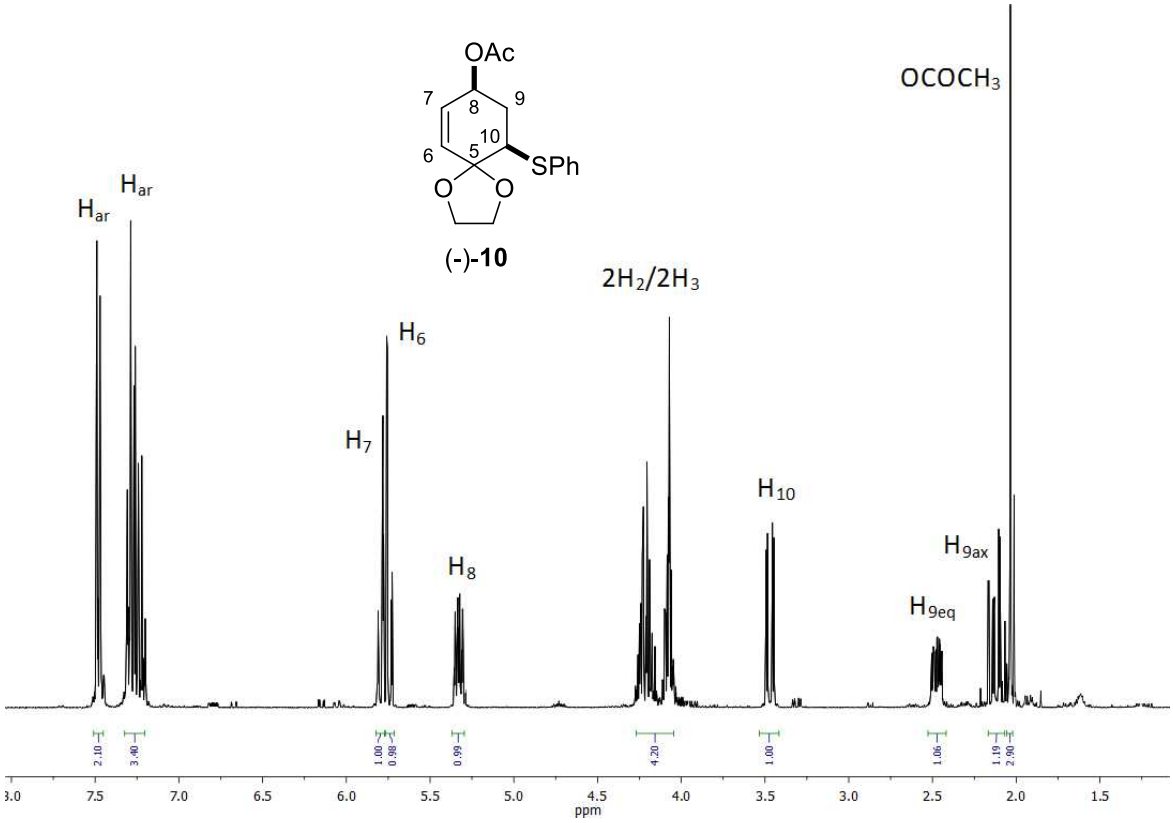
^{1}H-NMR (250 MHz, $CDCl_3$)



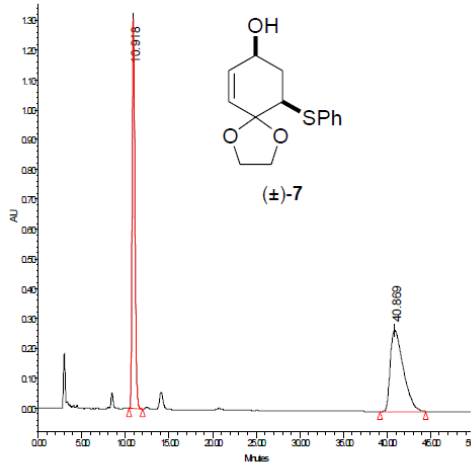
^{1}H-NMR (250 MHz, $CDCl_3$)



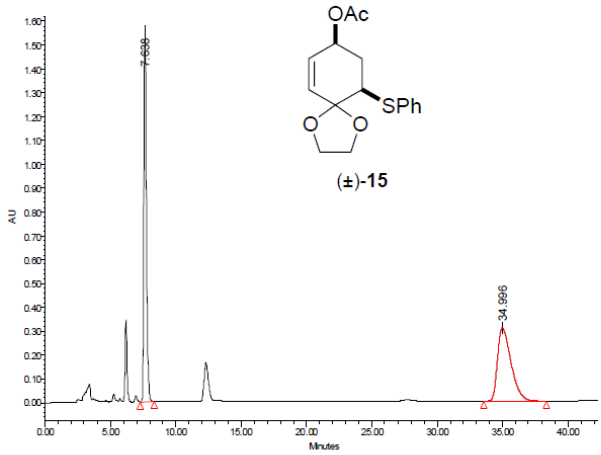
^{1}H-NMR (360 MHz, $CDCl_3$)



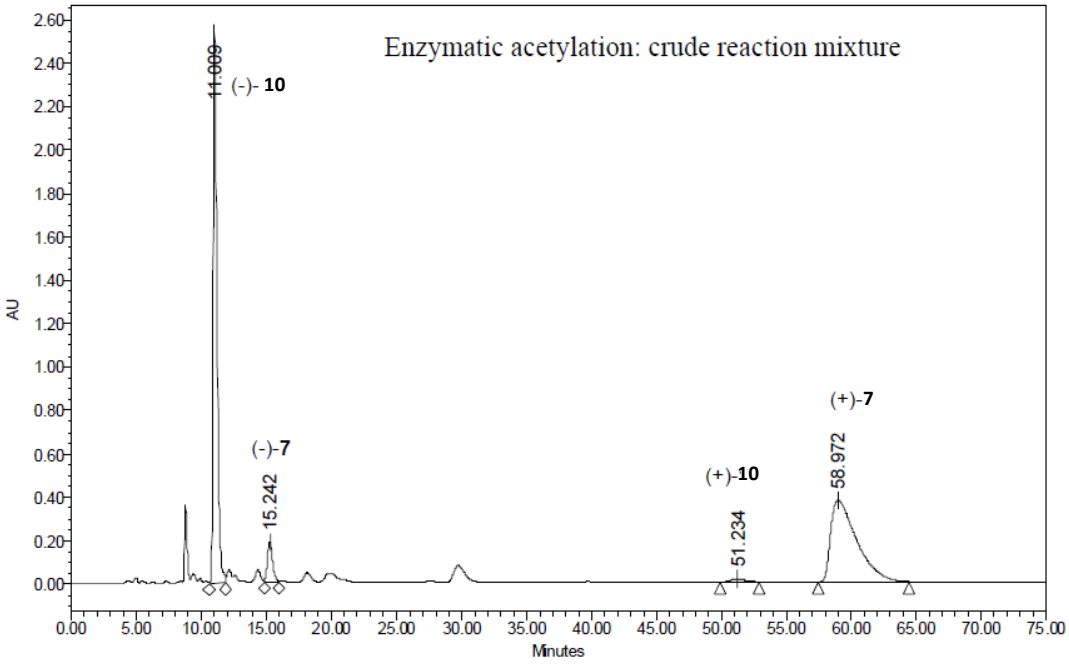
^{1}H-NMR (360 MHz, $CDCl_3$)



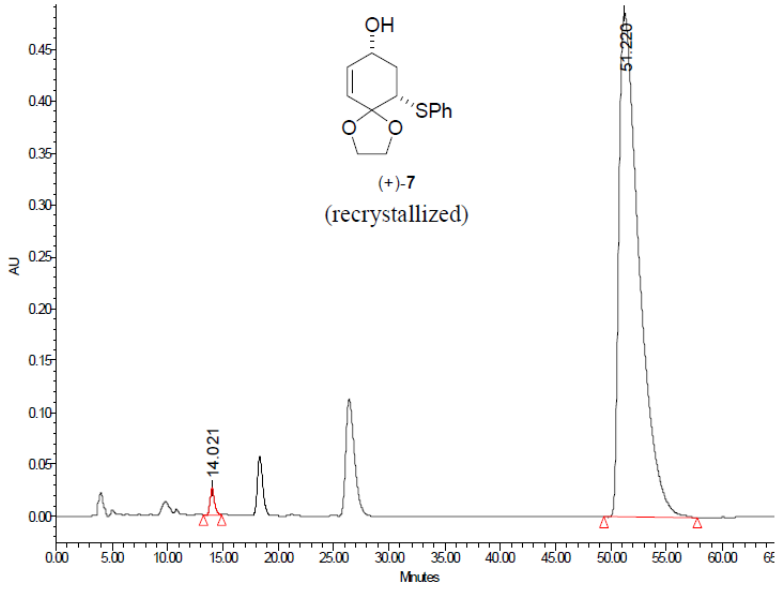
Retention time	% Area
10.918 min	49.91
40.869 min	50.09



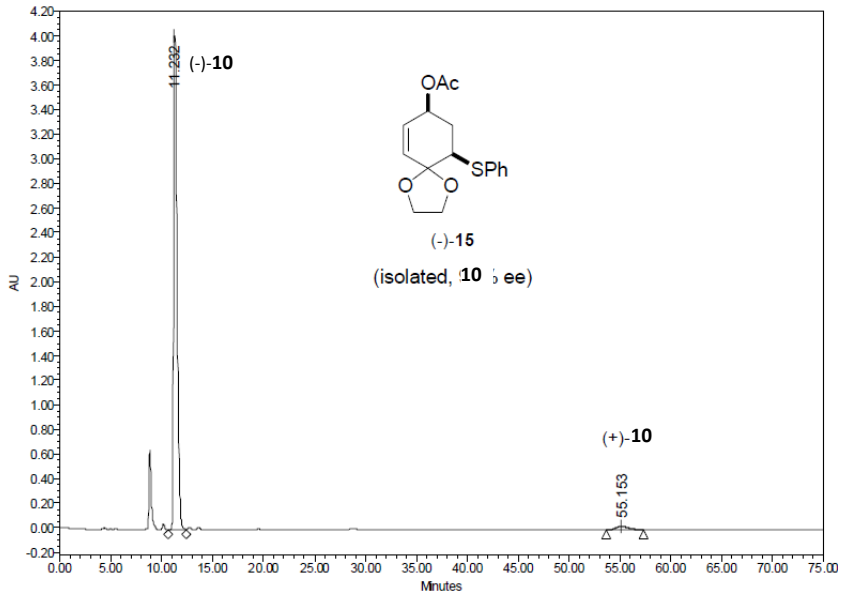
Retention time	% Area
7.636 min	50.01
34.996 min	49.99



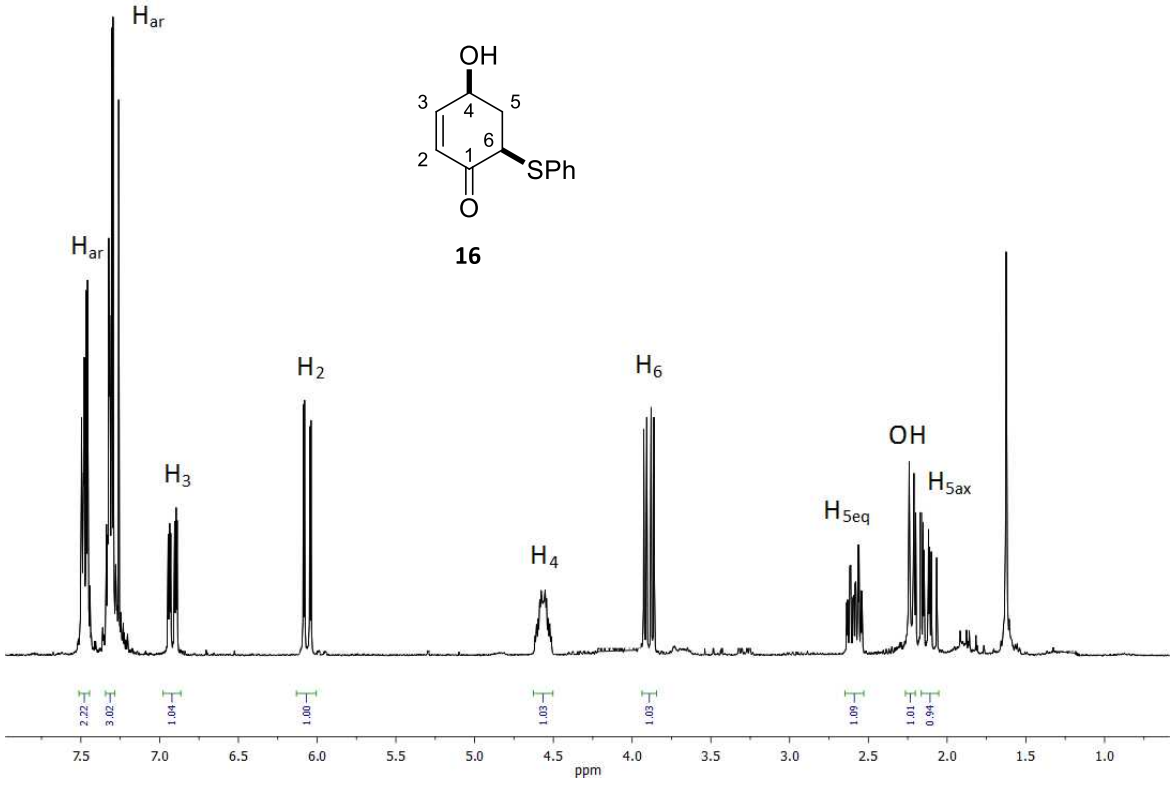
Retention time (min)	% Area
11.009	45.89
15.242	4.86
51.234	1.06
58.972	48.20



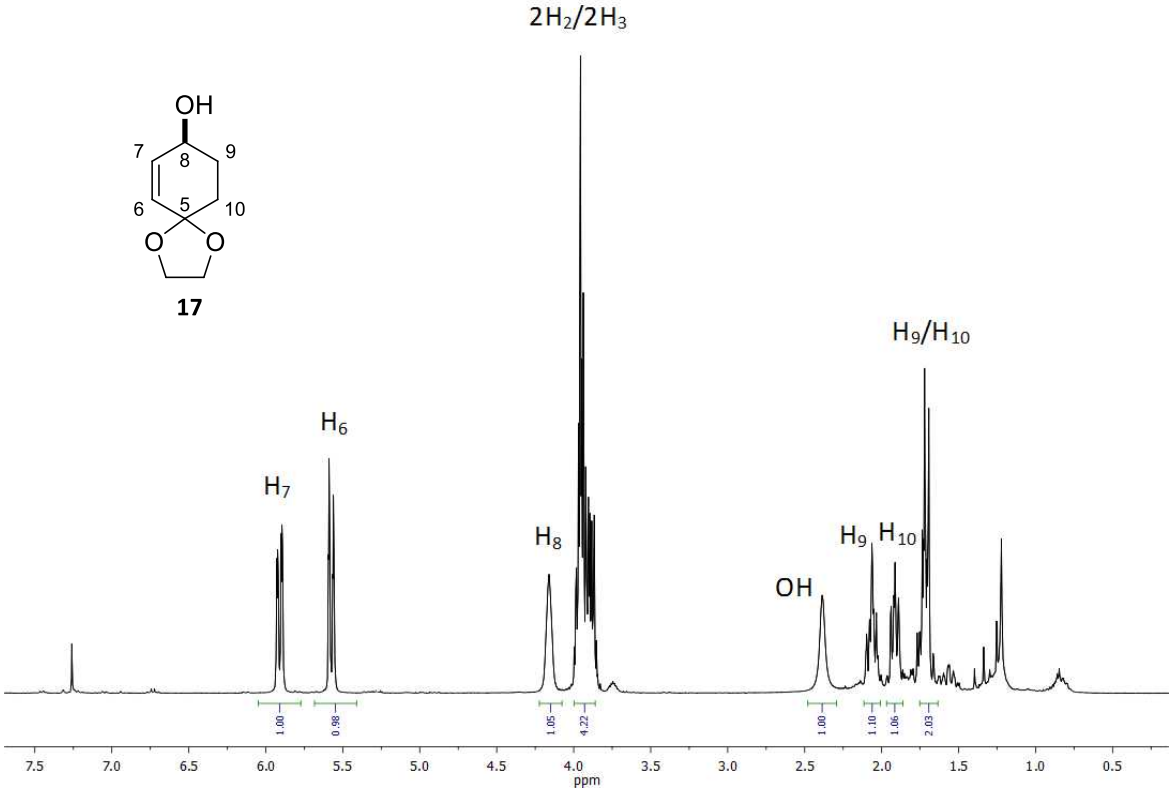
Retention time (min)	% Area
14.021	1.13
51.220	98.87



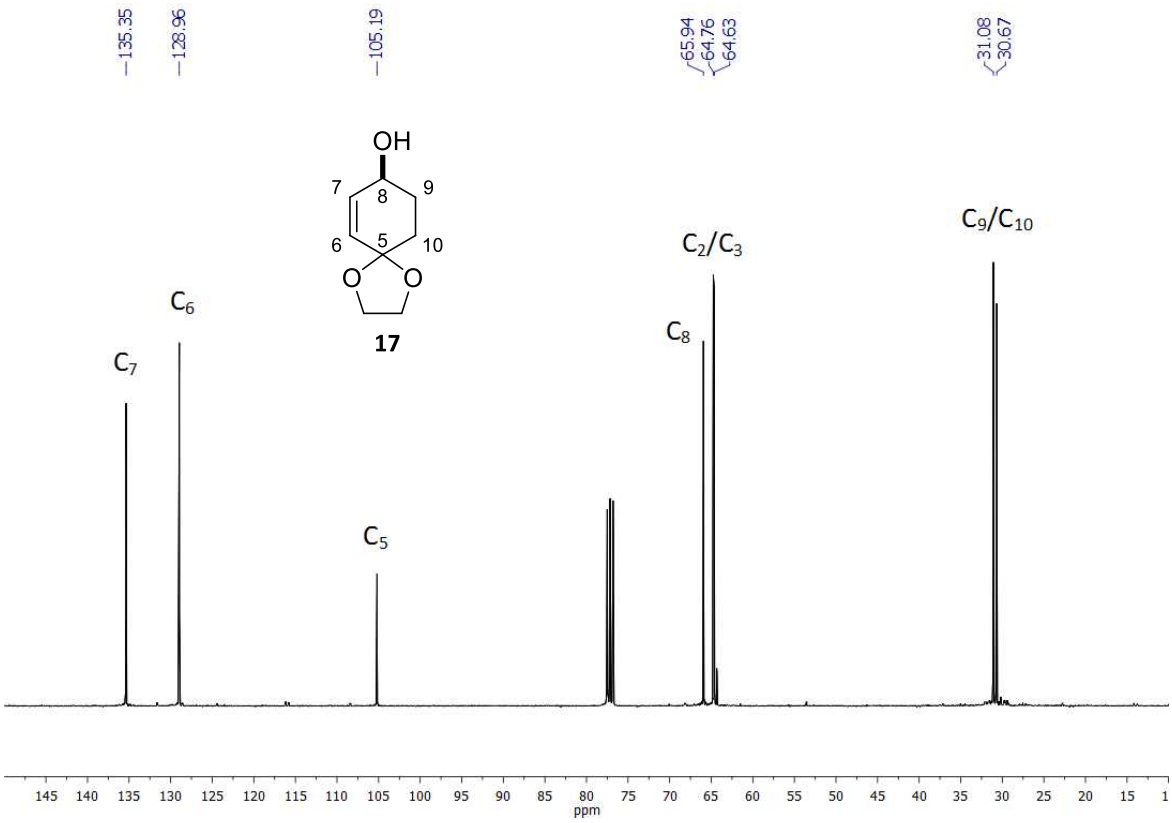
Retention time (min)	% Area
11.232	97.42
51.220	2.58



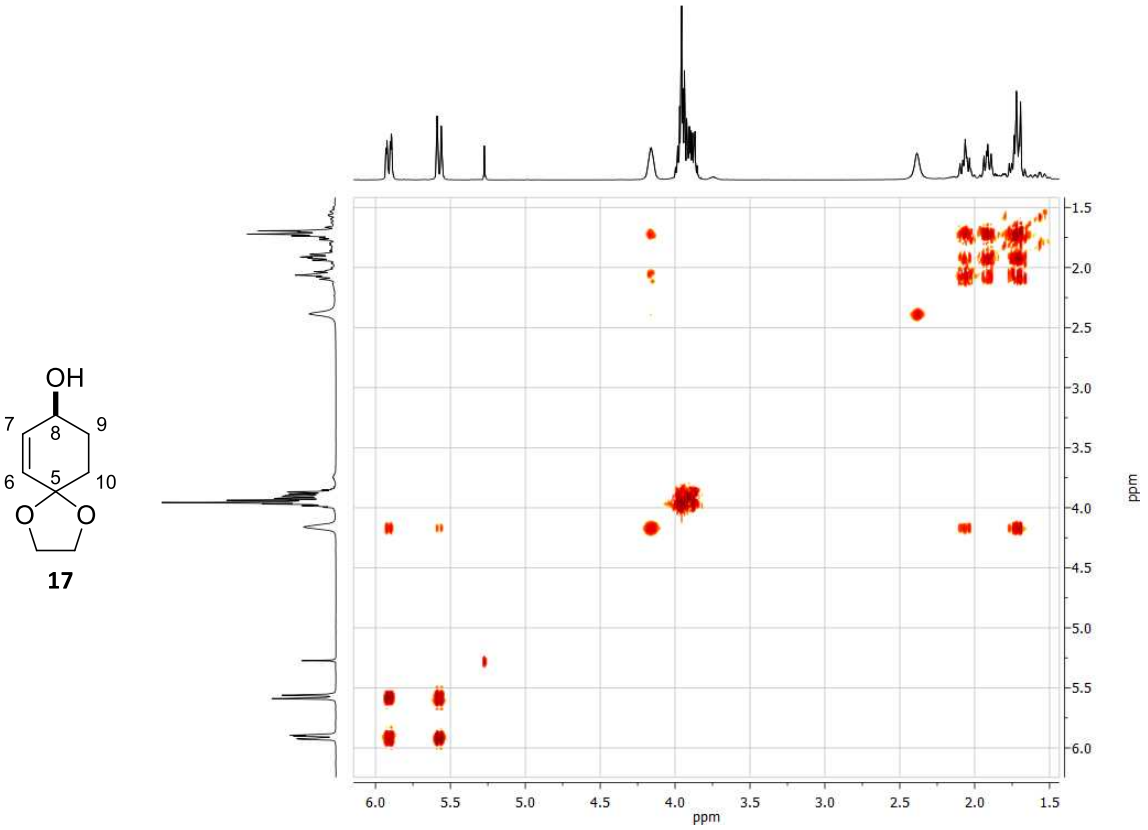
^{1}H-NMR (250 MHz, $CDCl_3$)



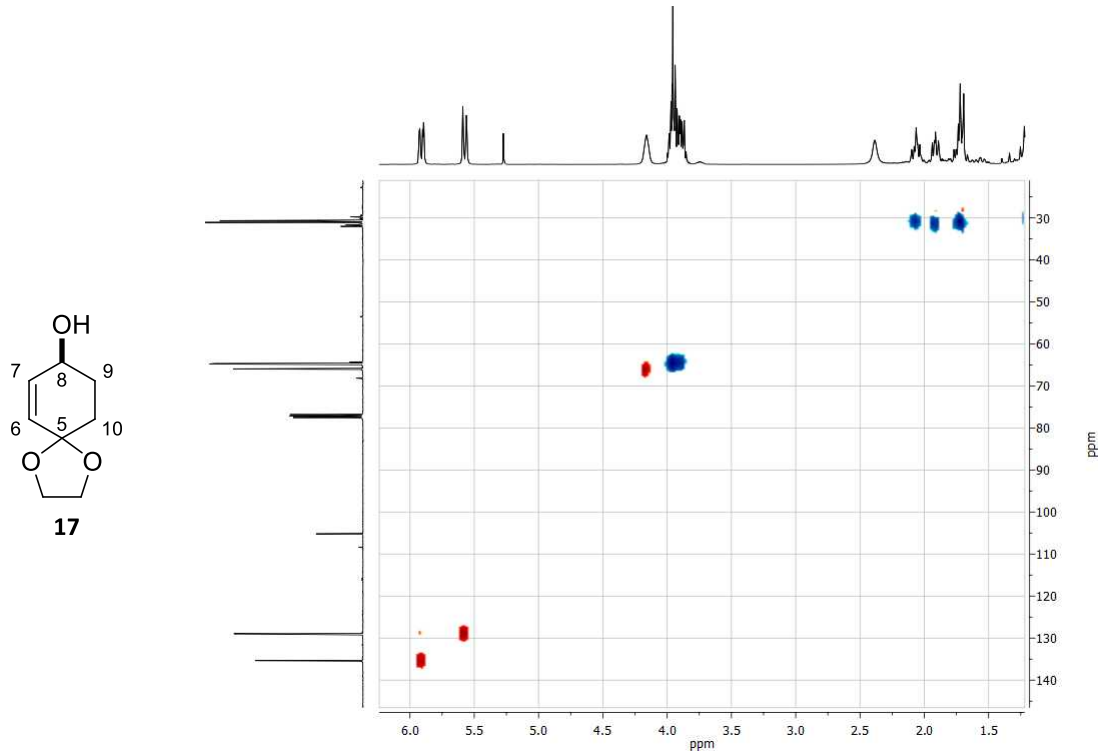
^{1}H-NMR (360 MHz, $CDCl_3$)



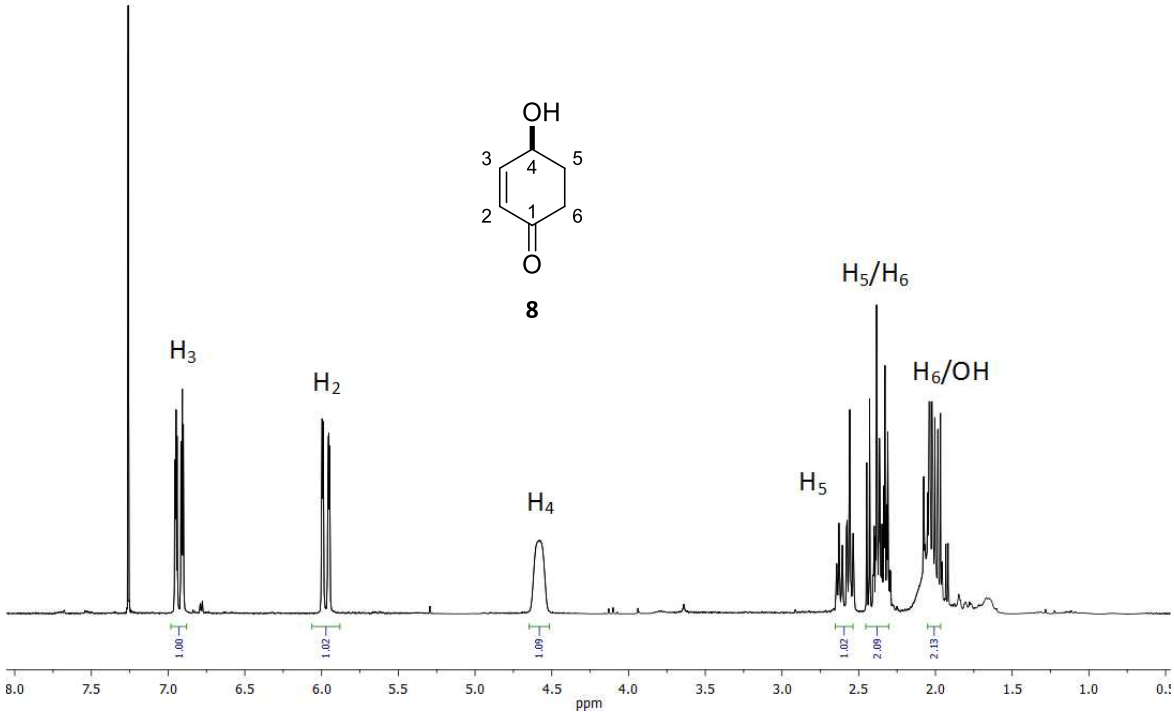
^{3}C-NMR (91 MHz, $CDCl_3$)



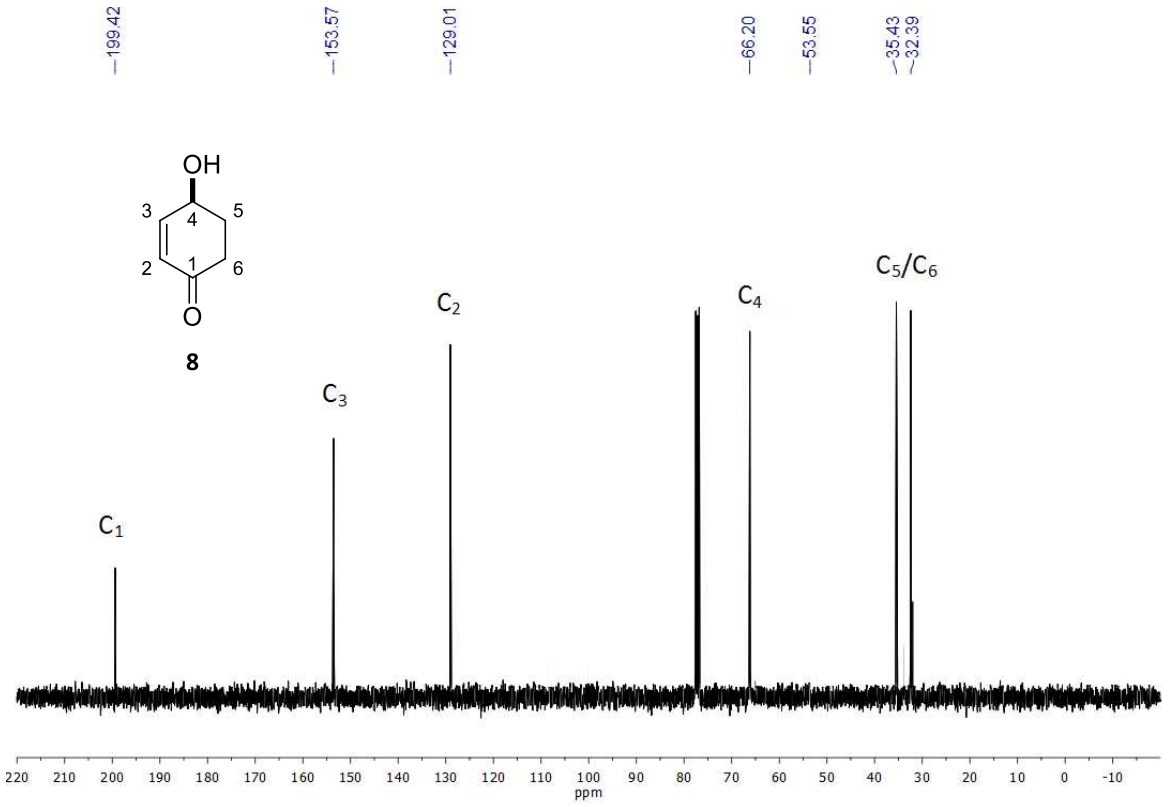
COSY (360 MHz, $CDCl_3$)



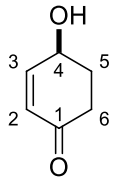
HSQCed ($CDCl_3$, ^{1}H-NMR: 360 MHz. ^{13}C-NMR: 91 MHz. CH, CH_3: red, CH_2: blue)



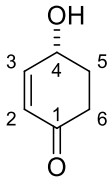
^{1}H-NMR (250 MHz, $CDCl_3$)



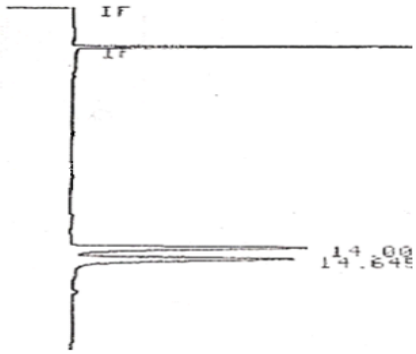
^{13}C-NMR (90 MHz, $CDCl_3$)



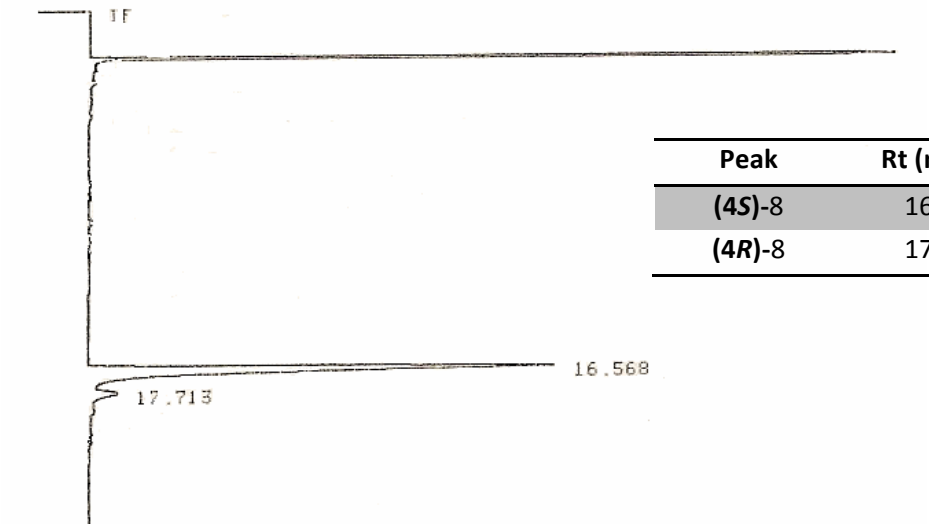
(4*S*)-**8**



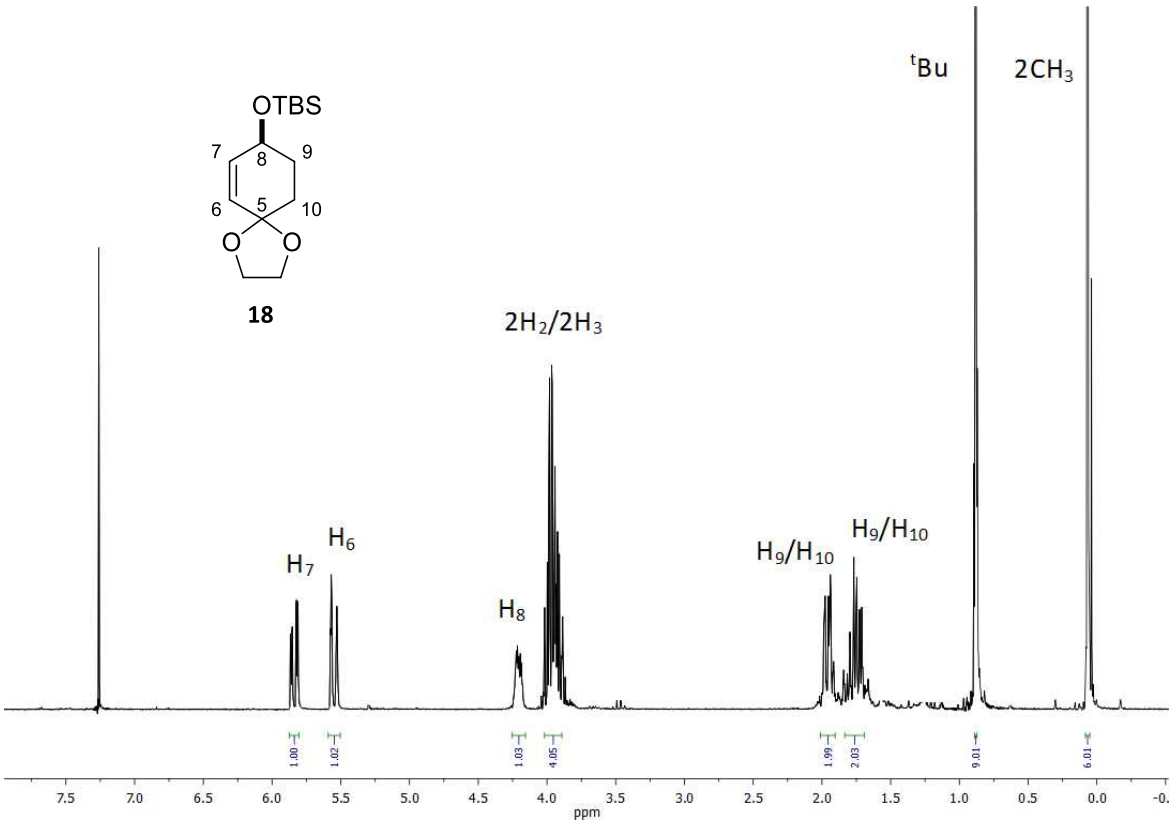
(4*R*)-**8**



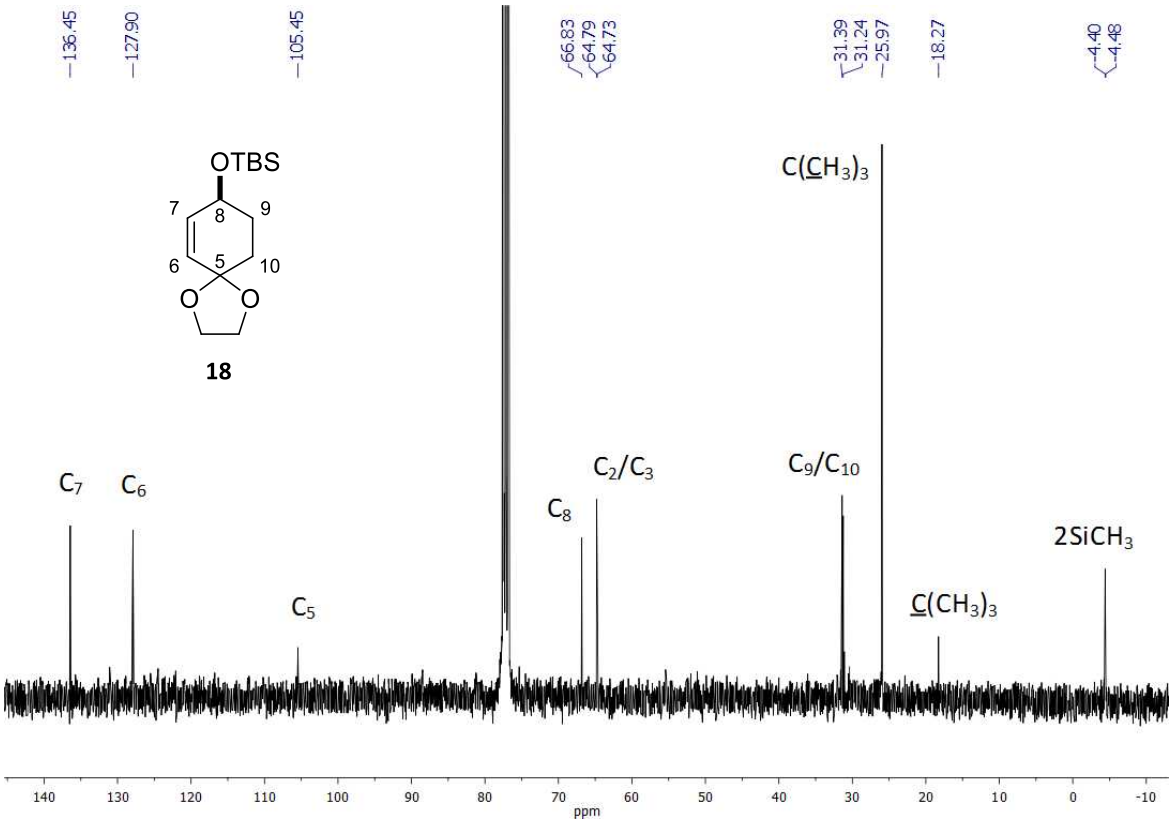
Peak	Rt (min)	%Area
(4*S*)-8	14.0	49.5
(4*R*)-8	14.6	50.5



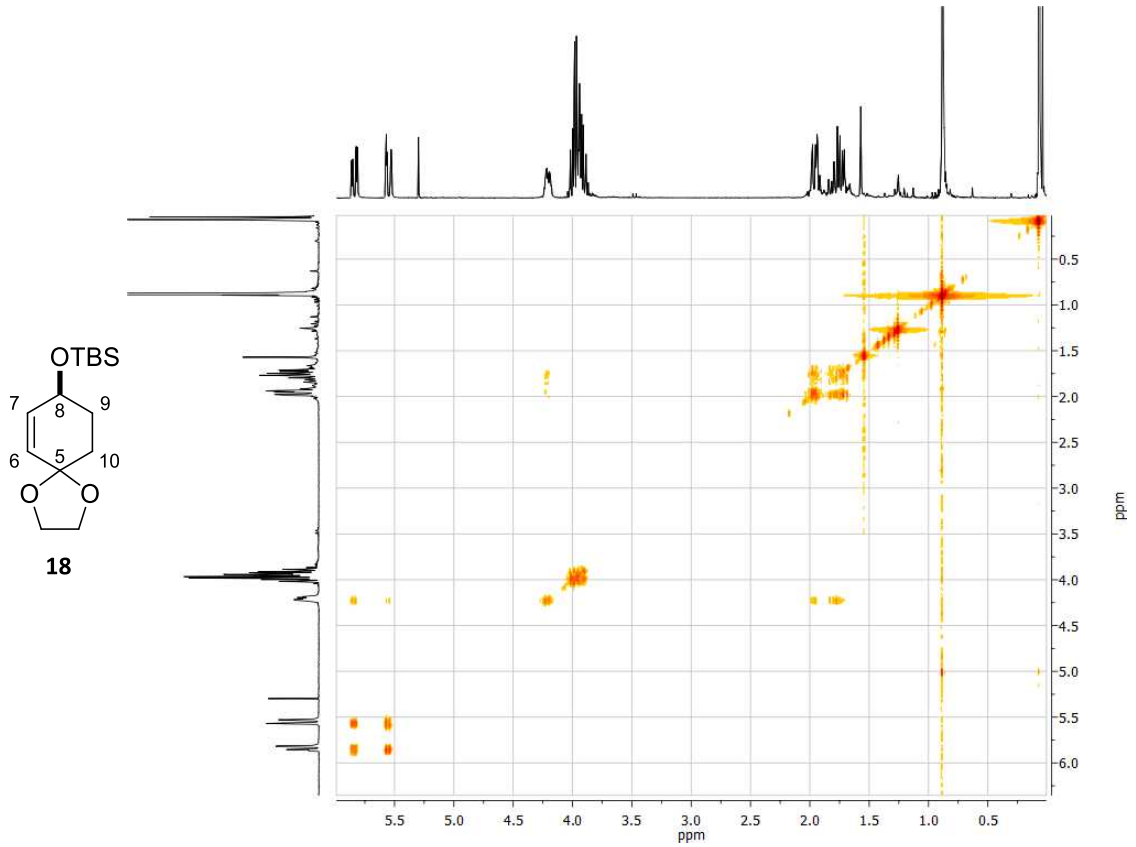
Peak	Rt (min)	%Area
(4*S*)-8	16.6	93.9
(4*R*)-8	17.7	6.1



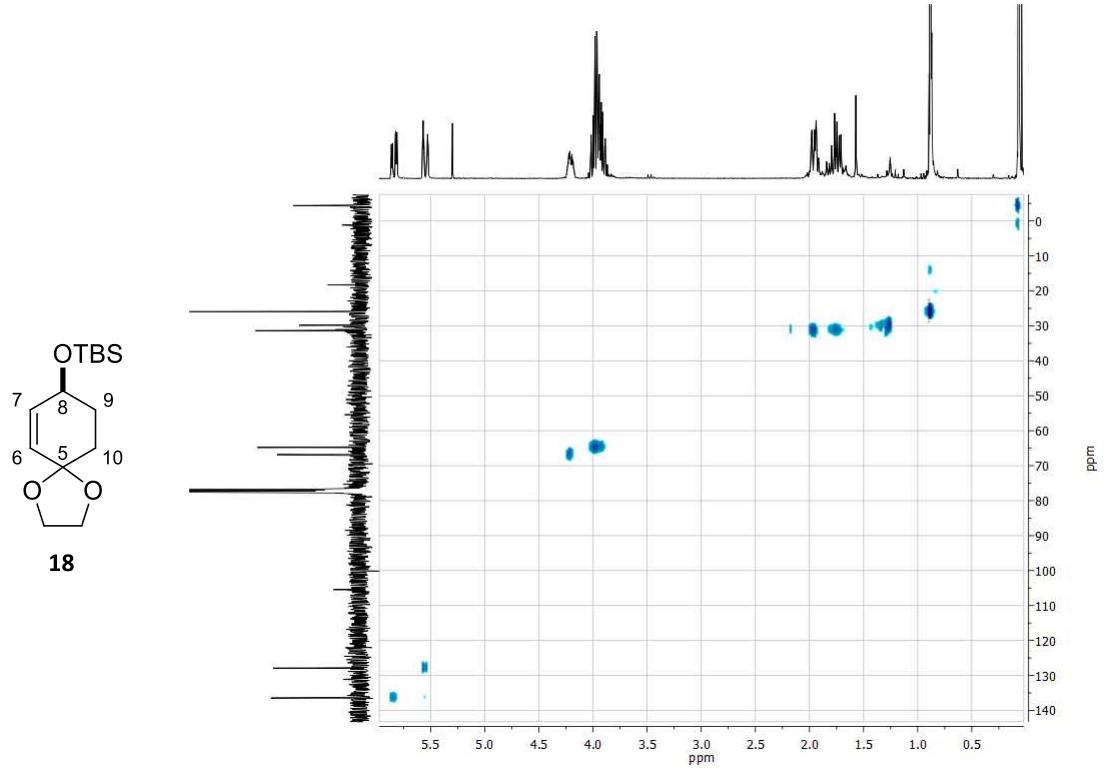
^{1}H-NMR (250 MHz, $CDCl_3$)



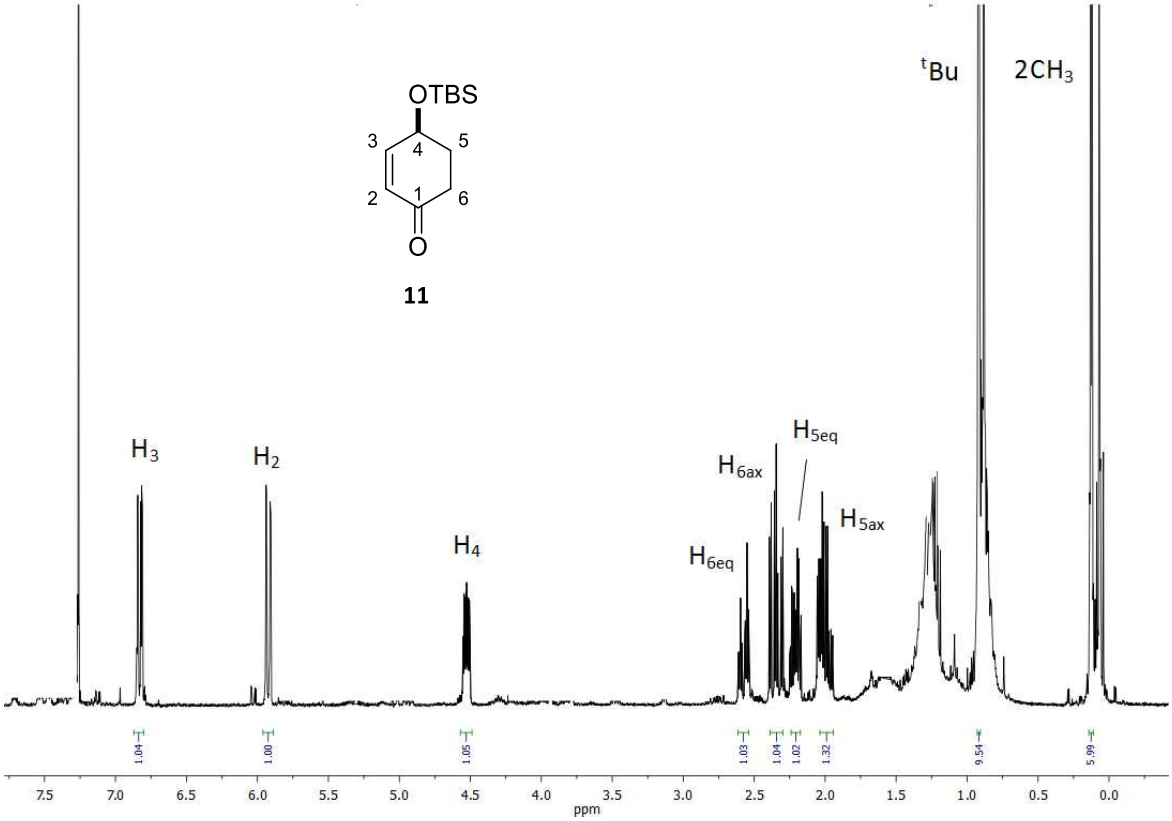
^{13}C-NMR (90 MHz, $CDCl_3$)



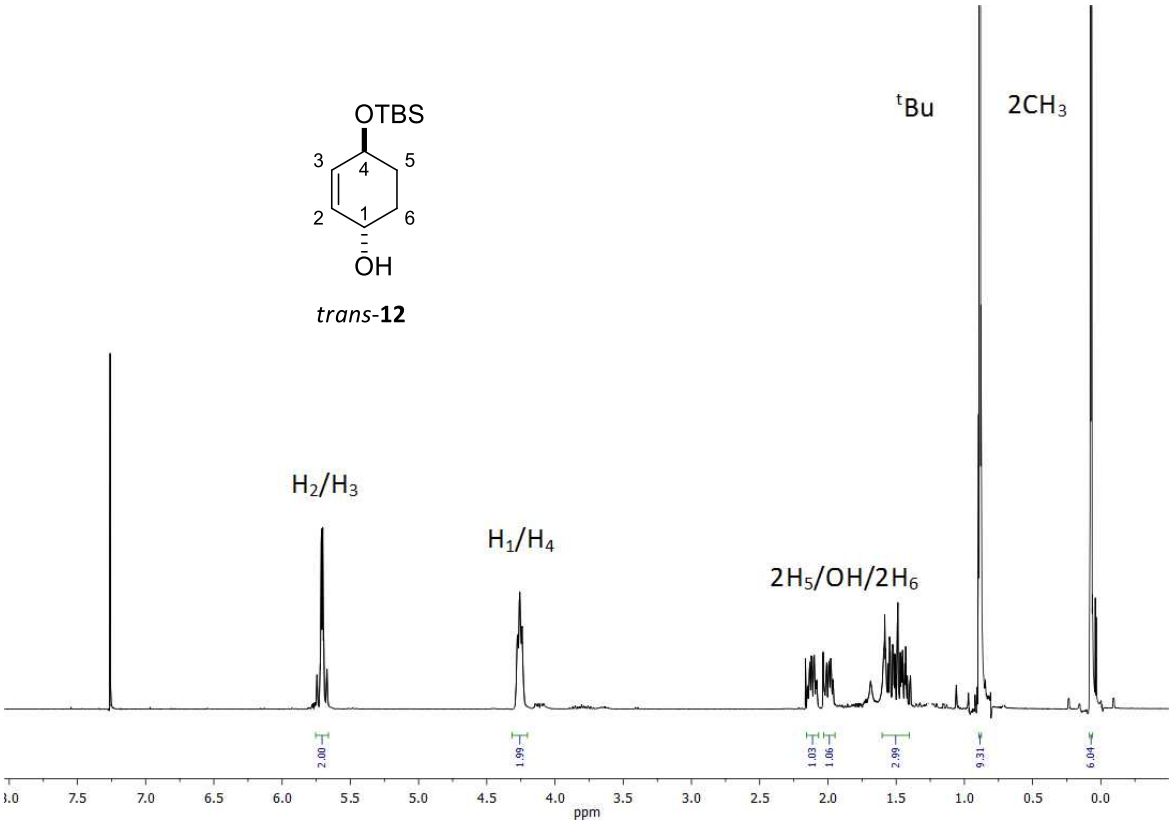
COSY (360 MHz, $CDCl_3$)



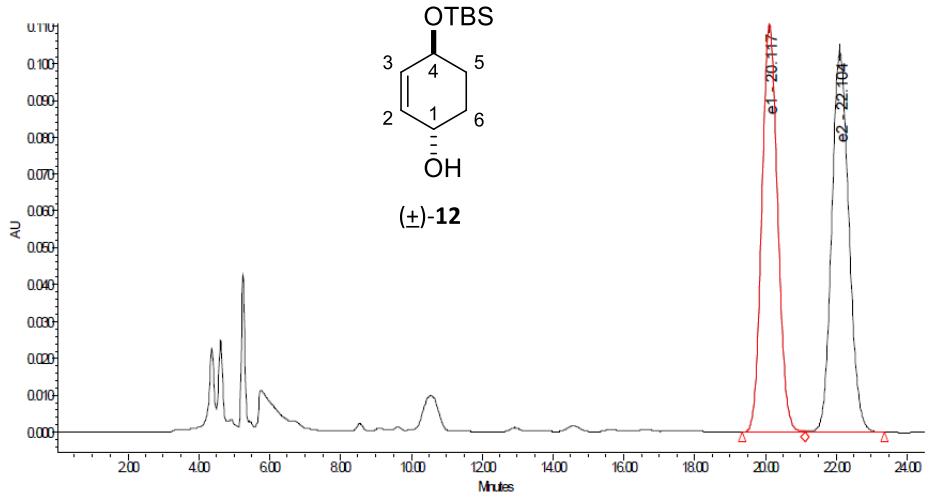
HSQC ($CDCl_3$, ^{1}H-NMR: 360 MHz. ^{13}C-NMR: 91 MHz)



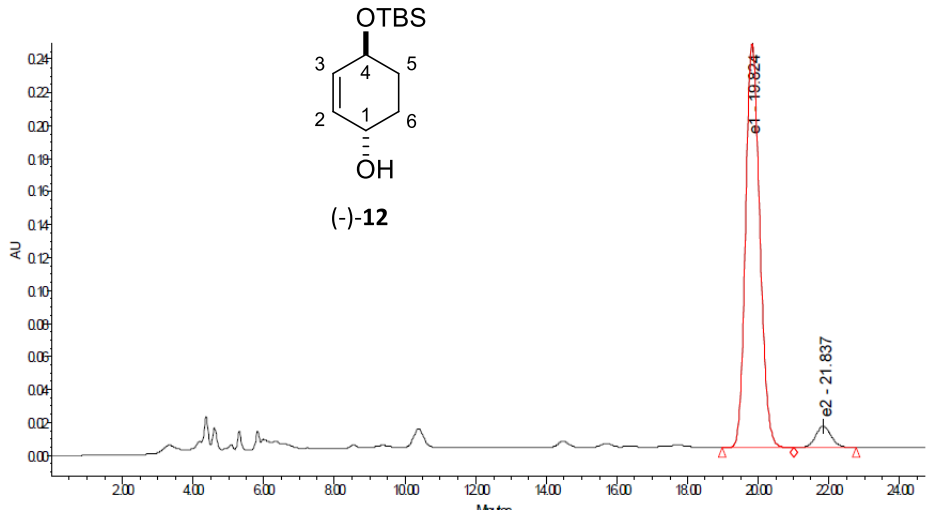
^{1}H-NMR (360 MHz, $CDCl_3$)



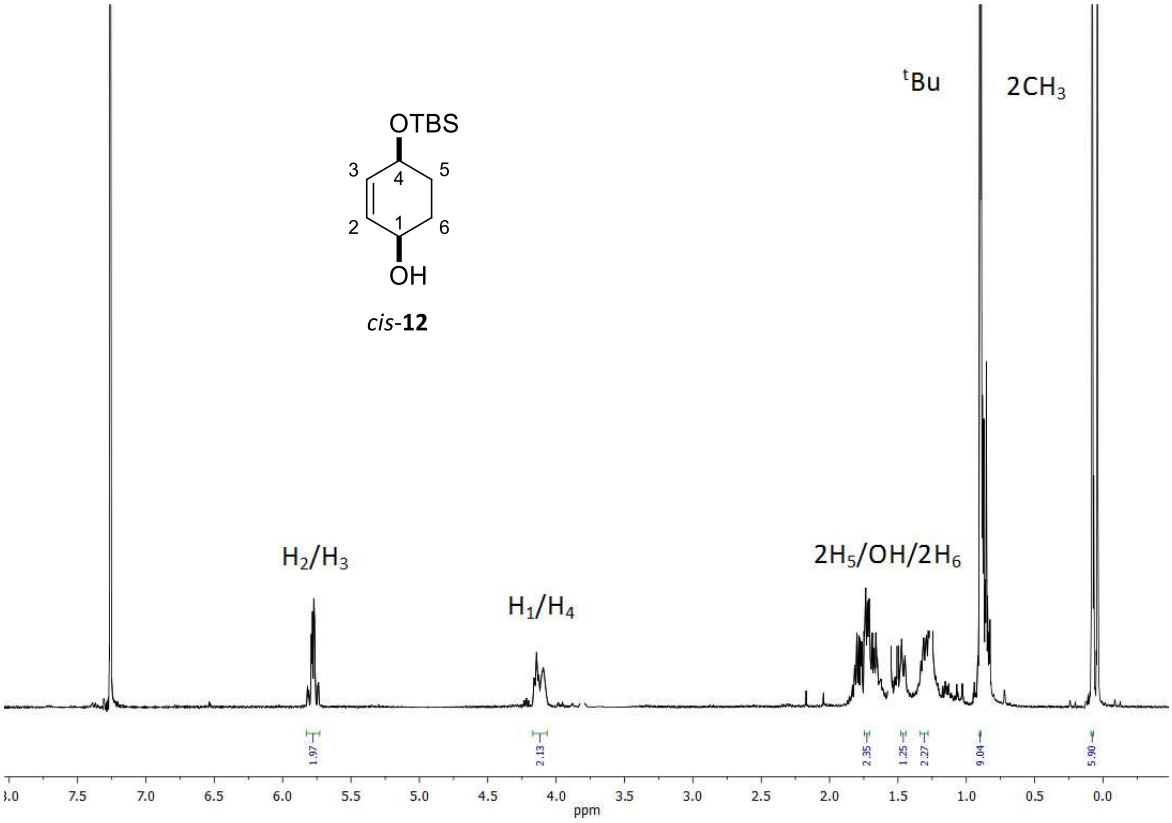
^{1}H-NMR (360 MHz, $CDCl_3$)



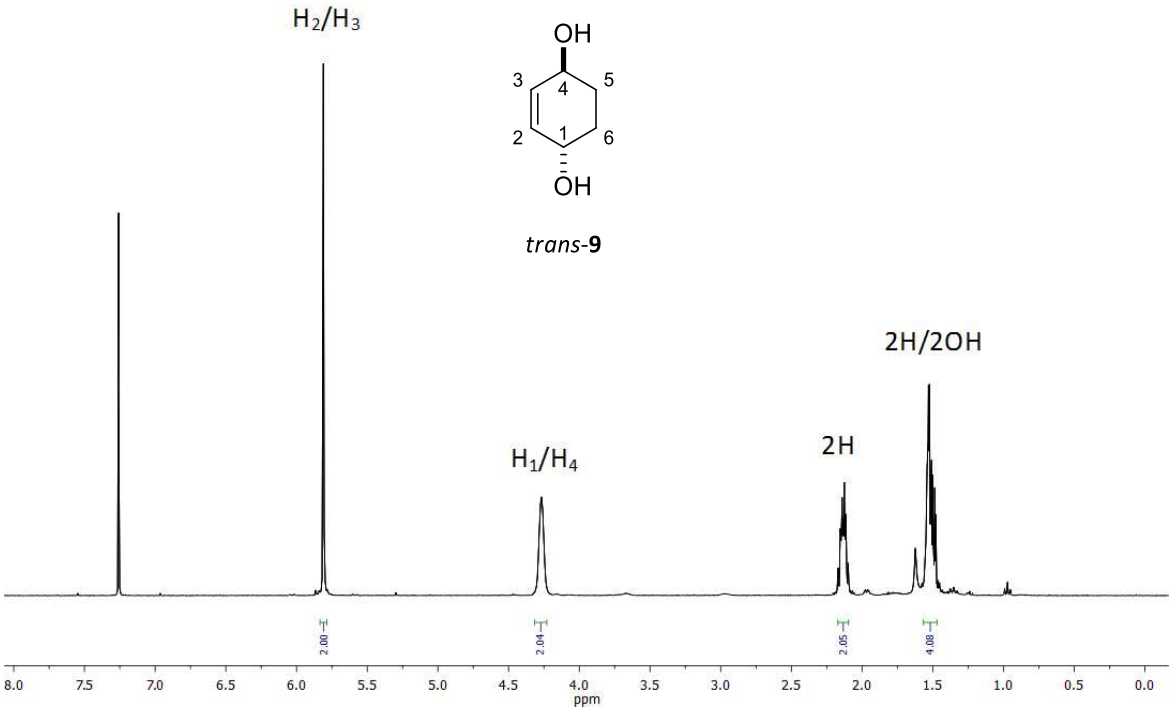
Retention time (min)	% Area
20.117	49.68
22.104	50.32



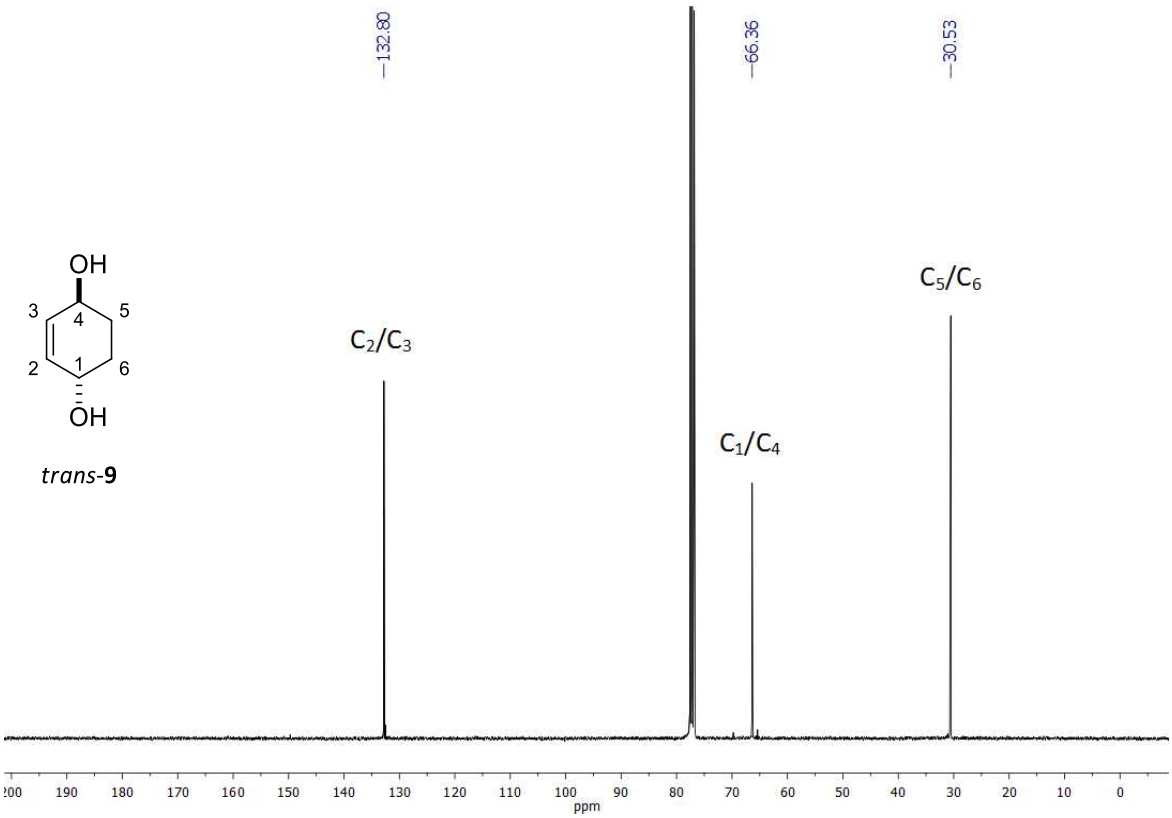
Retention time (min)	% Area
19.824	94.49
21.83	5.51



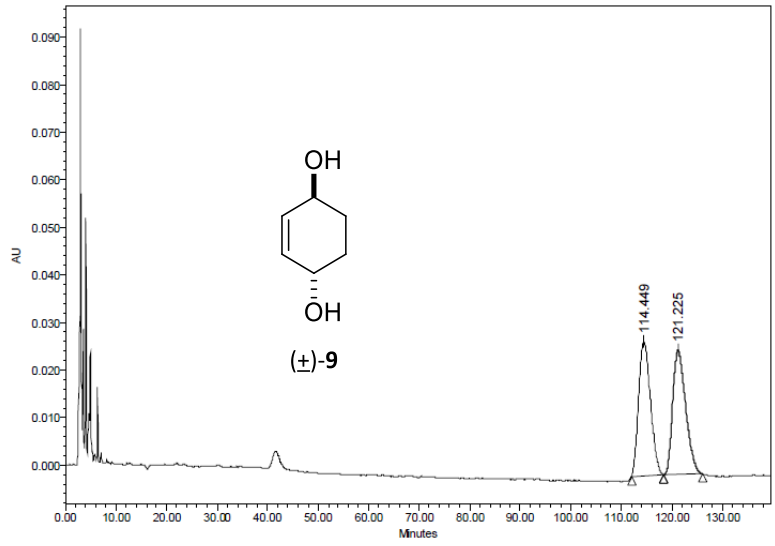
^{1}H-NMR (360 MHz, $CDCl_3$)



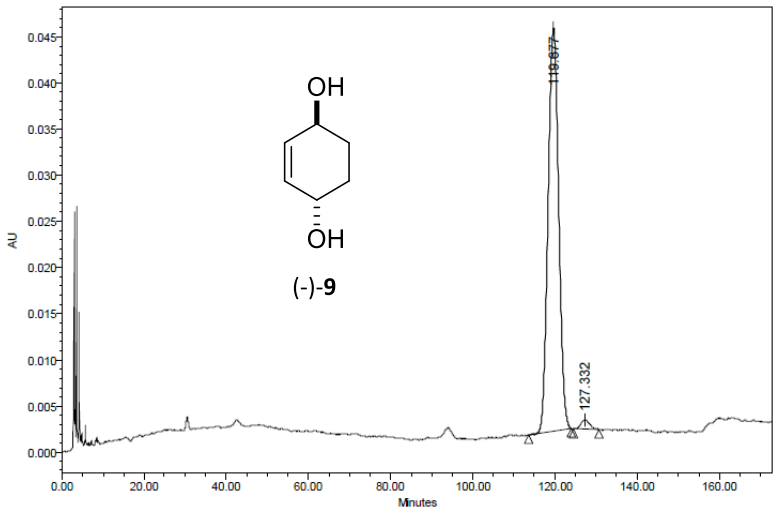
^{1}H-NMR (360 MHz, $CDCl_3$)



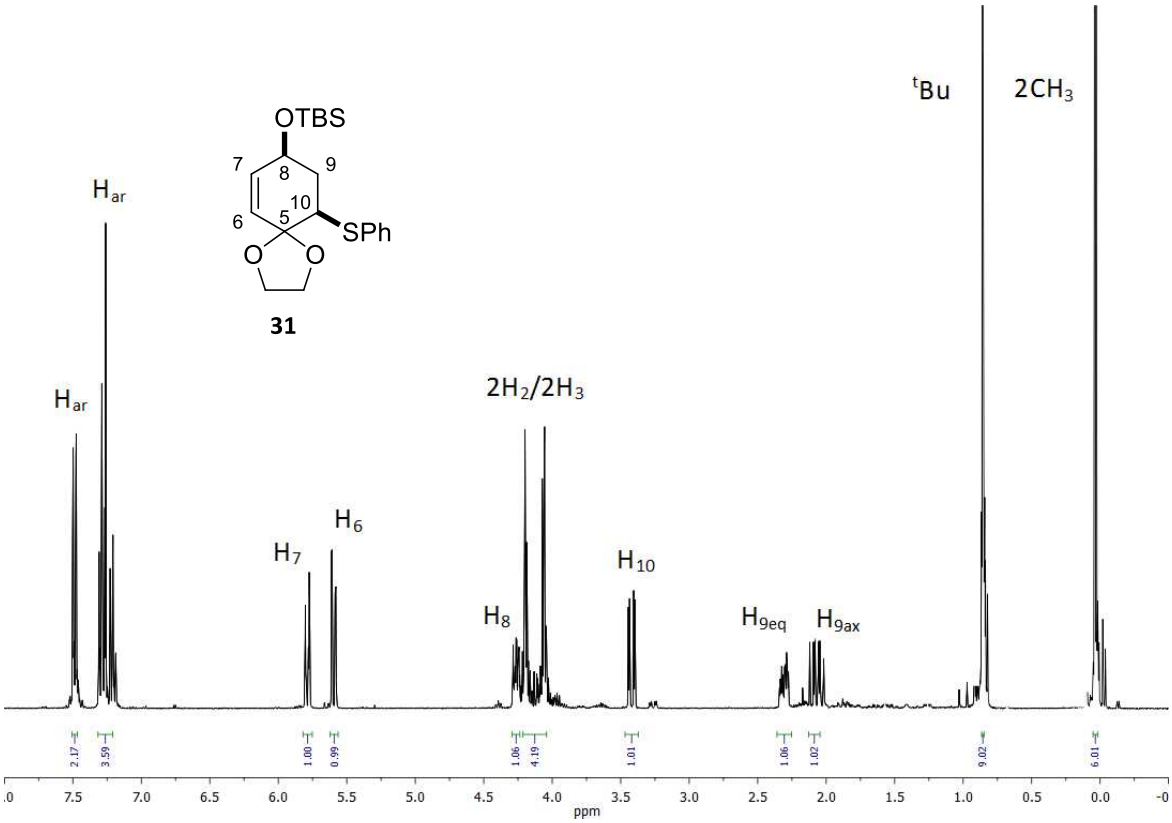
^{13}C-NMR (90 MHz, $CDCl_3$)



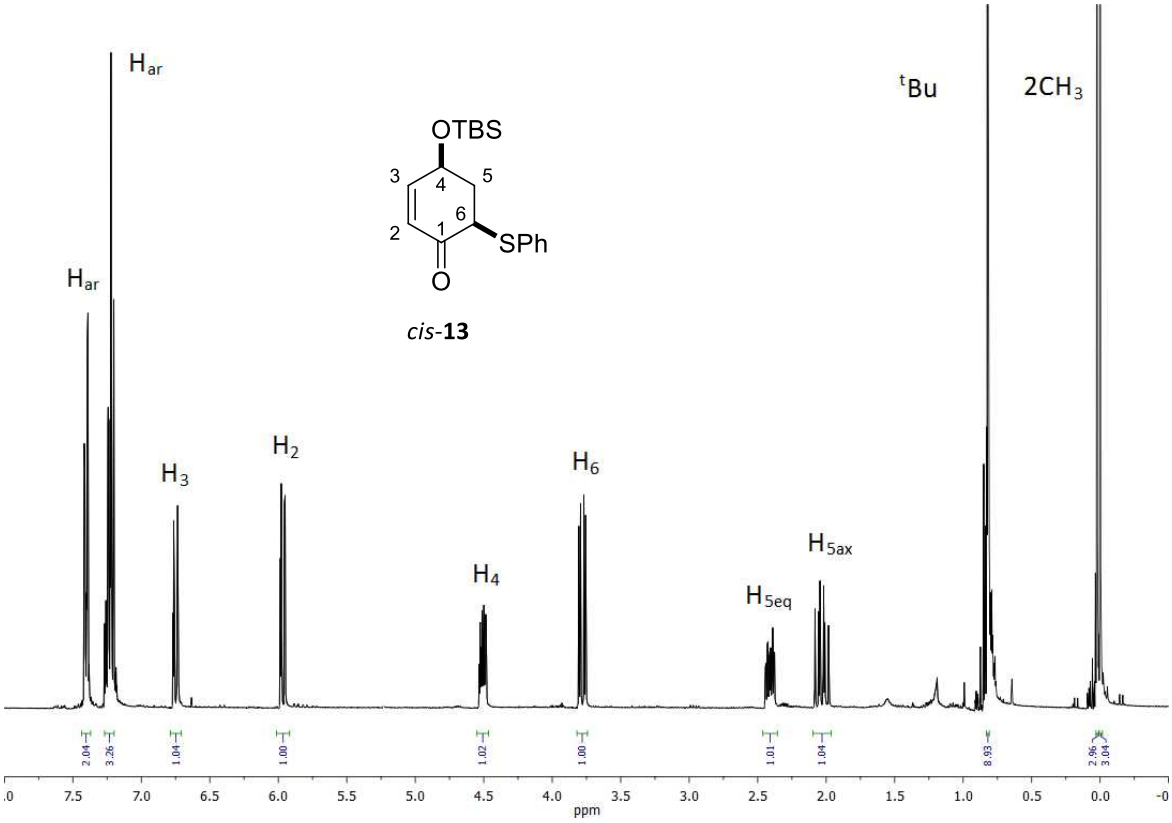
Retention time (min)	% Area
114.449	49.69
121.225	50.31



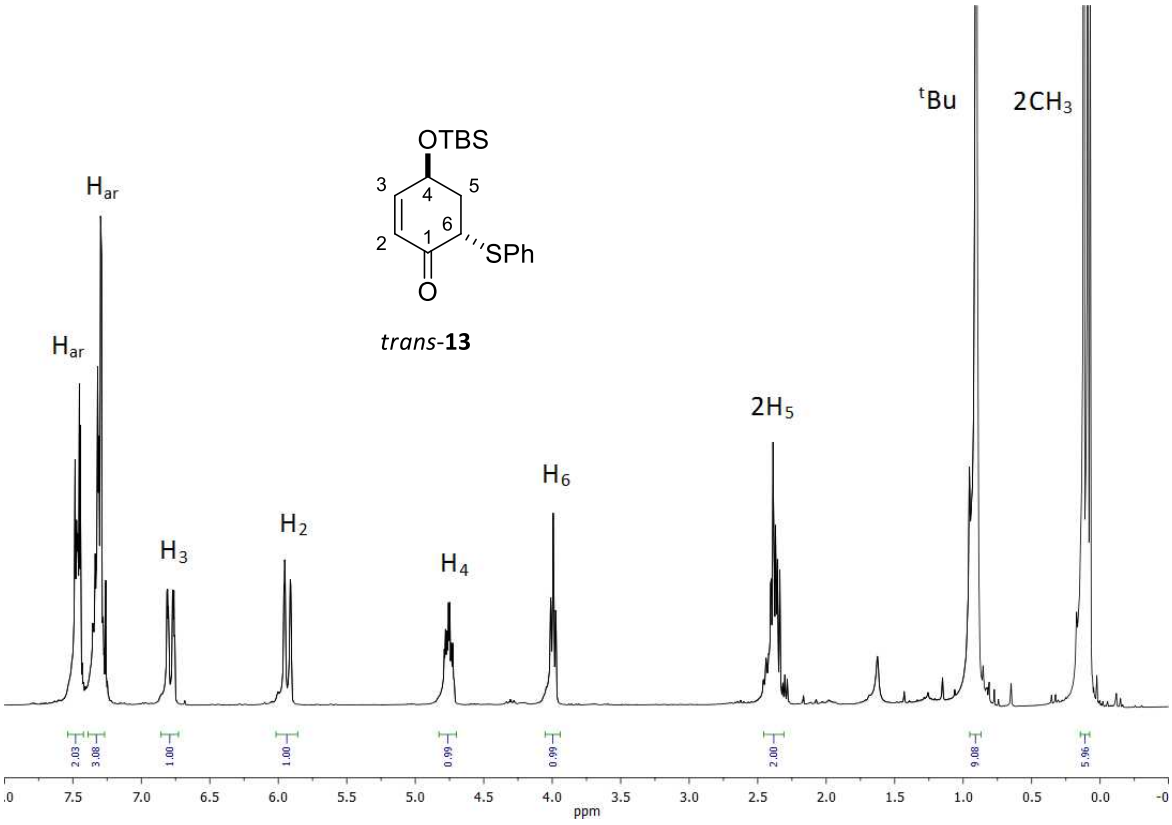
Retention time (min)	% Area
119.677	98.03
127.332	1.97



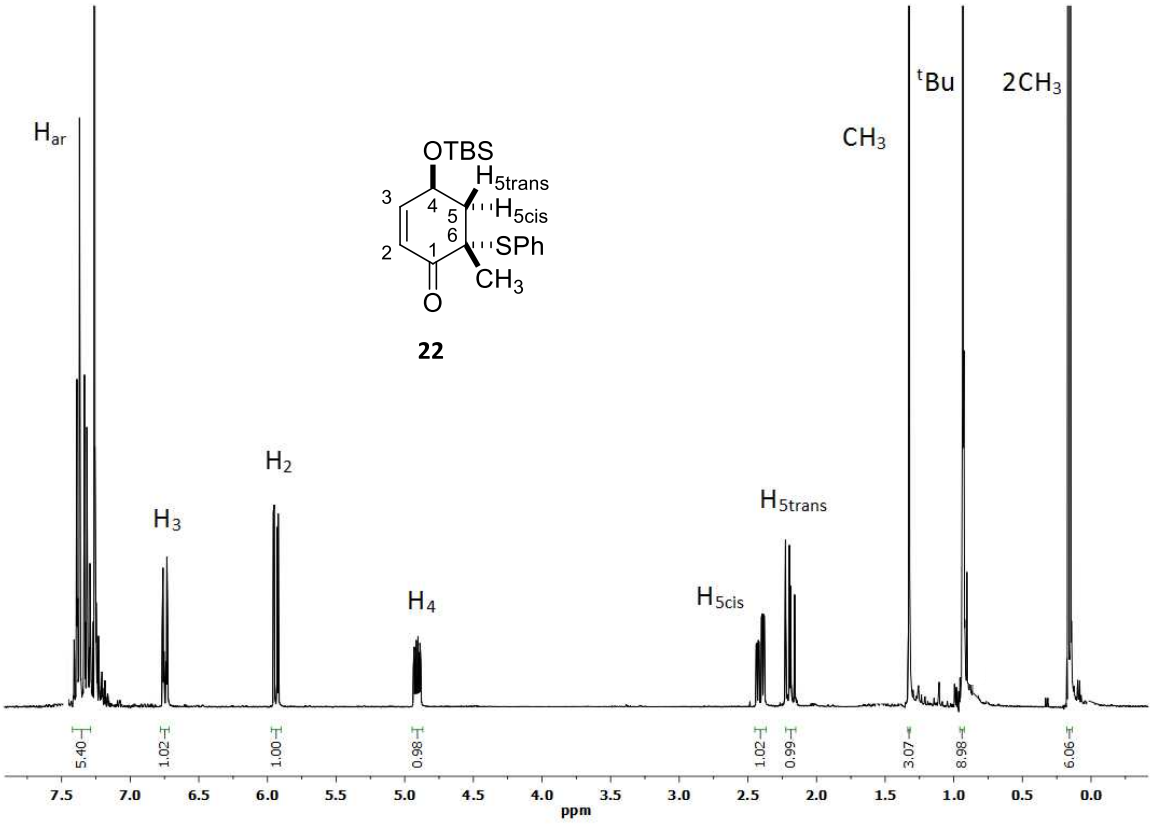
^{1}H-NMR (360 MHz, $CDCl_3$)



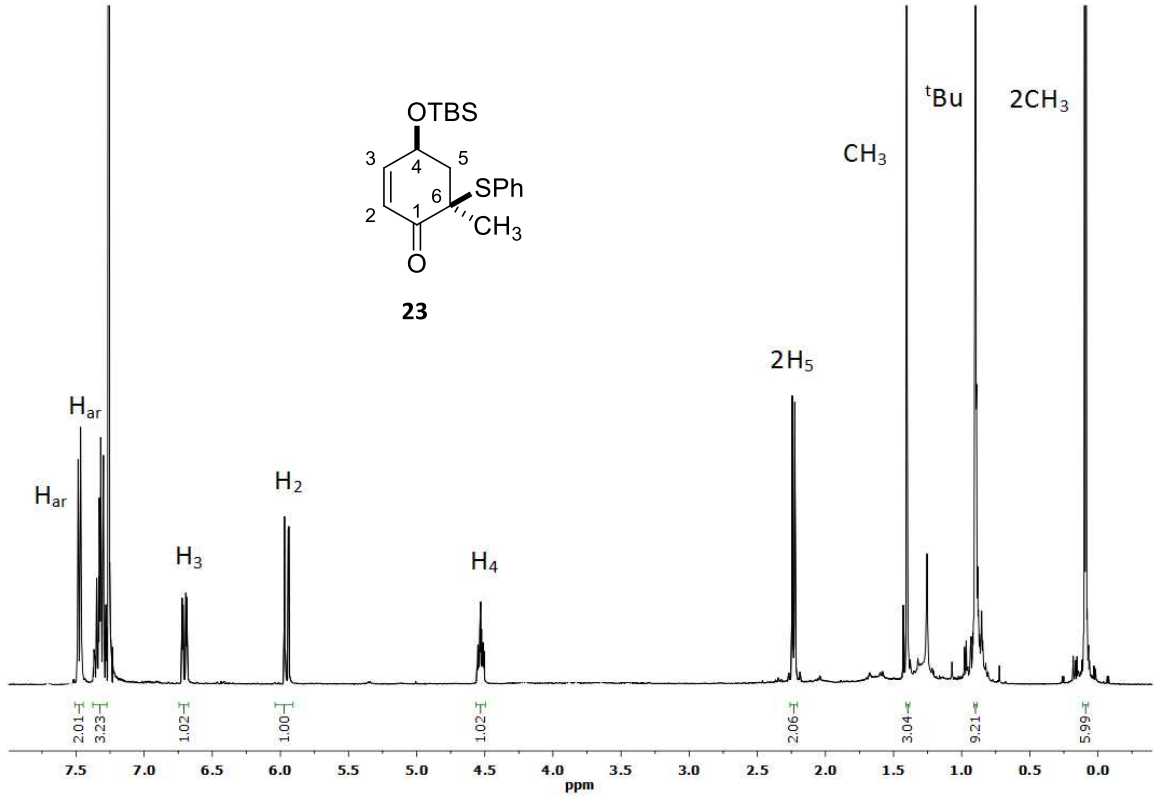
^{1}H-NMR (360 MHz, $CDCl_3$)



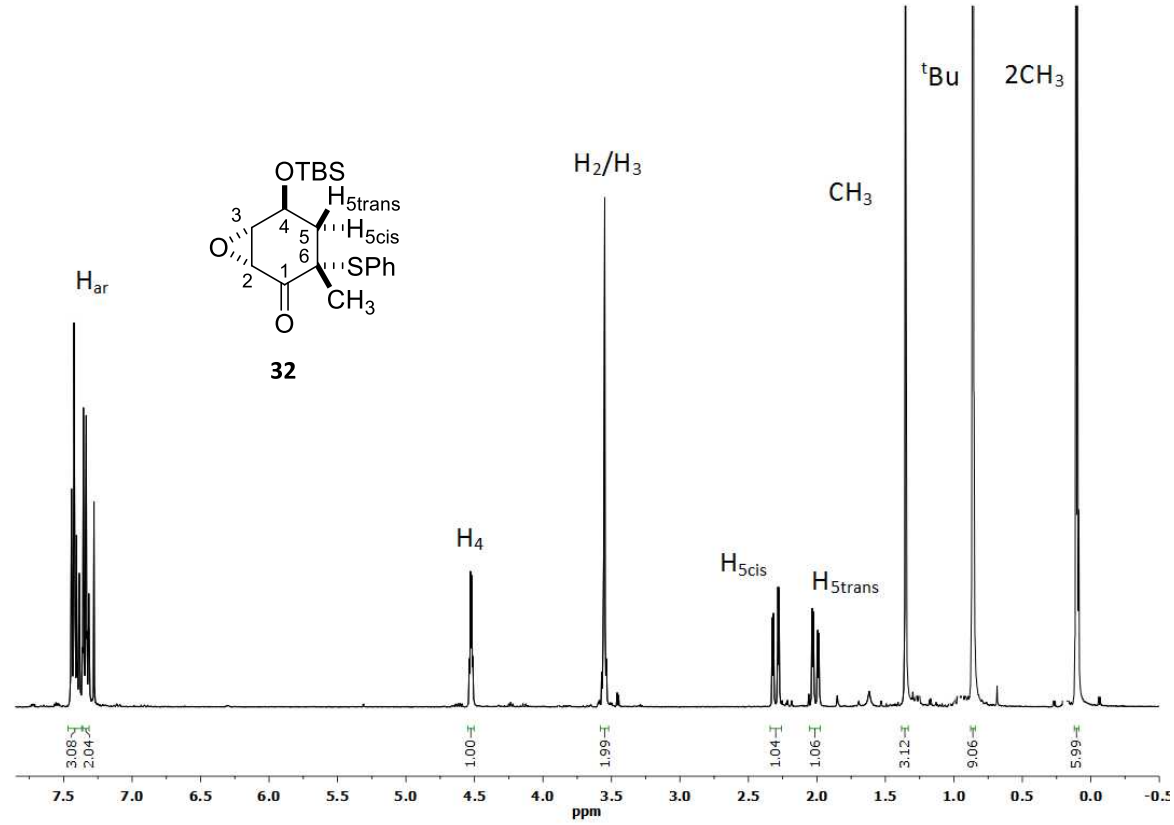
^{1}H-NMR (250 MHz, $CDCl_3$)



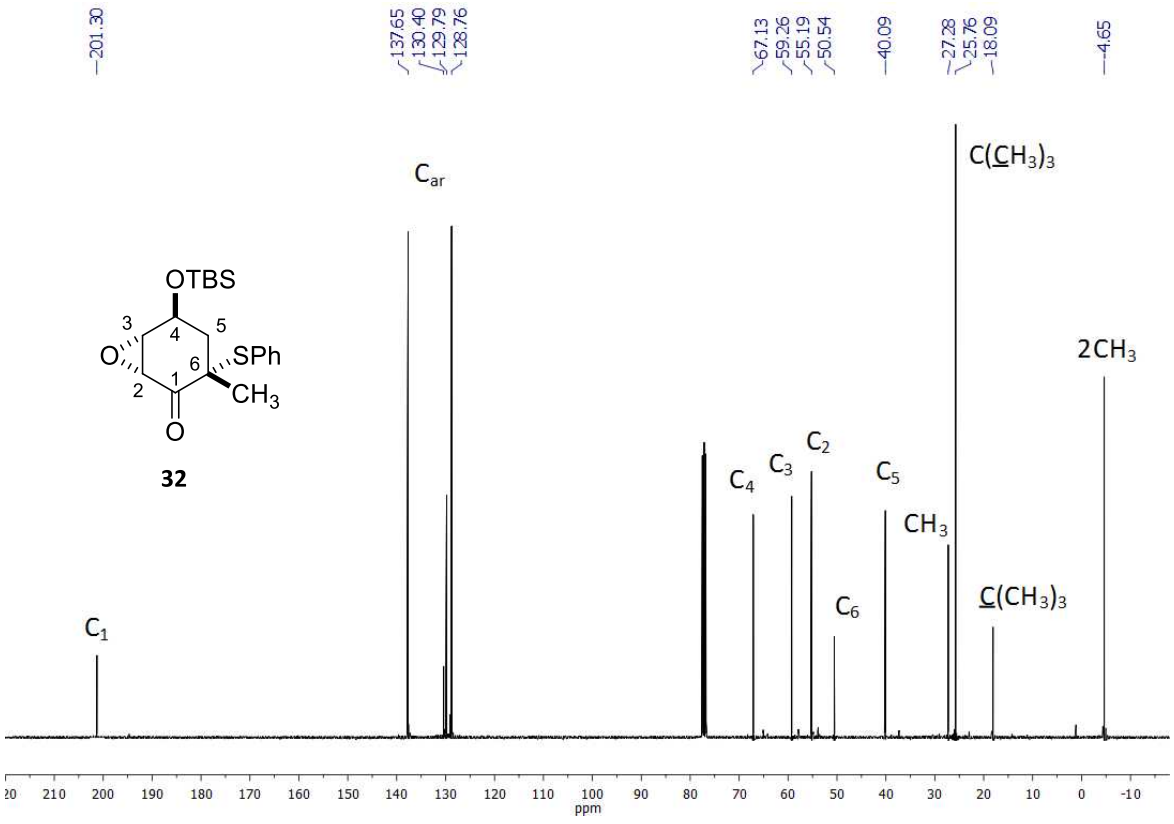
^{1}H-NMR (360 MHz, $CDCl_3$)



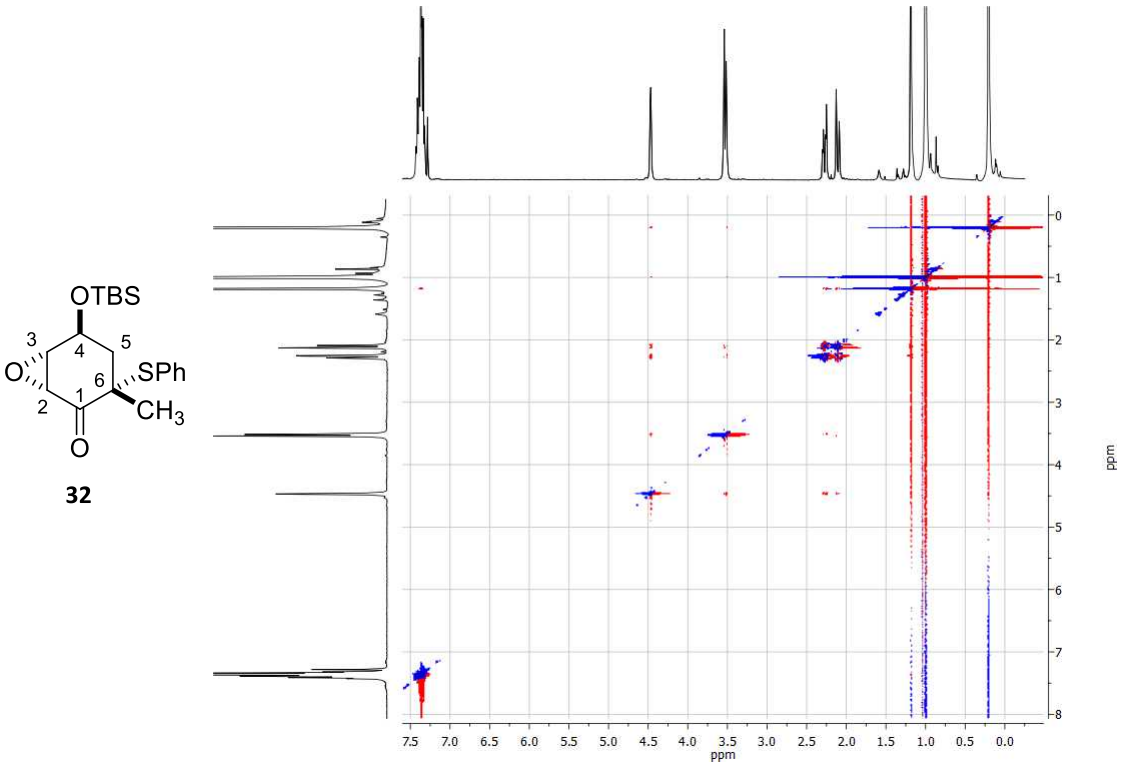
^{1}H-NMR (360 MHz, $CDCl_3$)



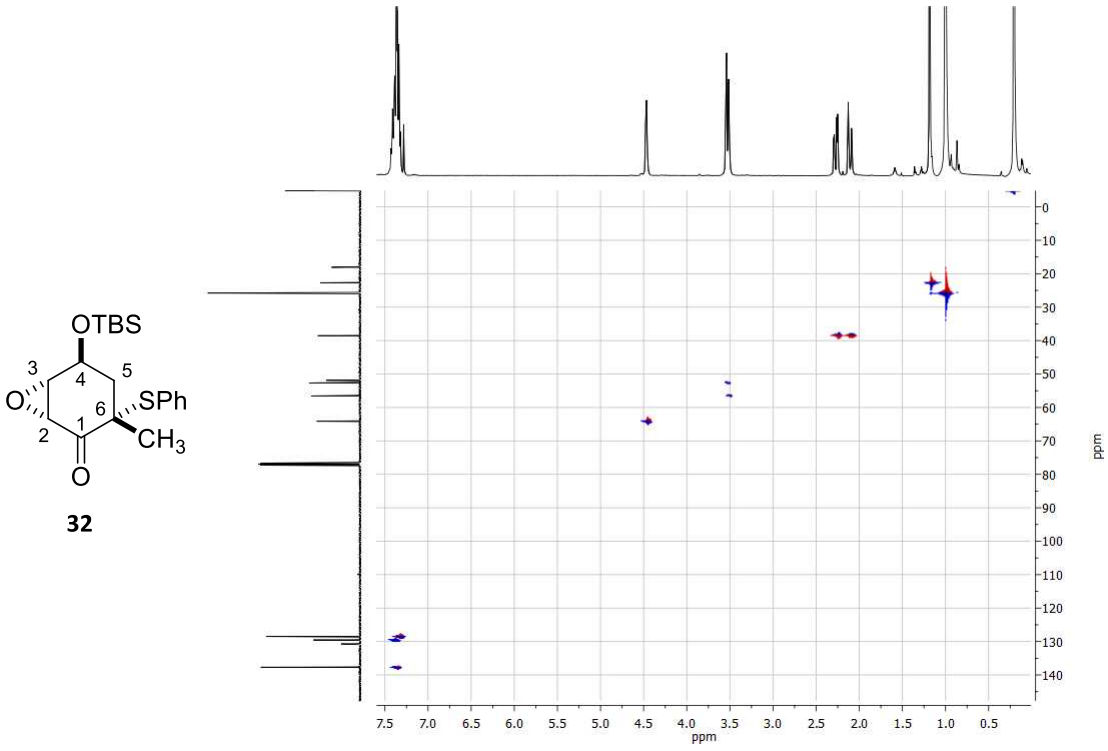
^{1}H-NMR (360 MHz, $CDCl_3$)



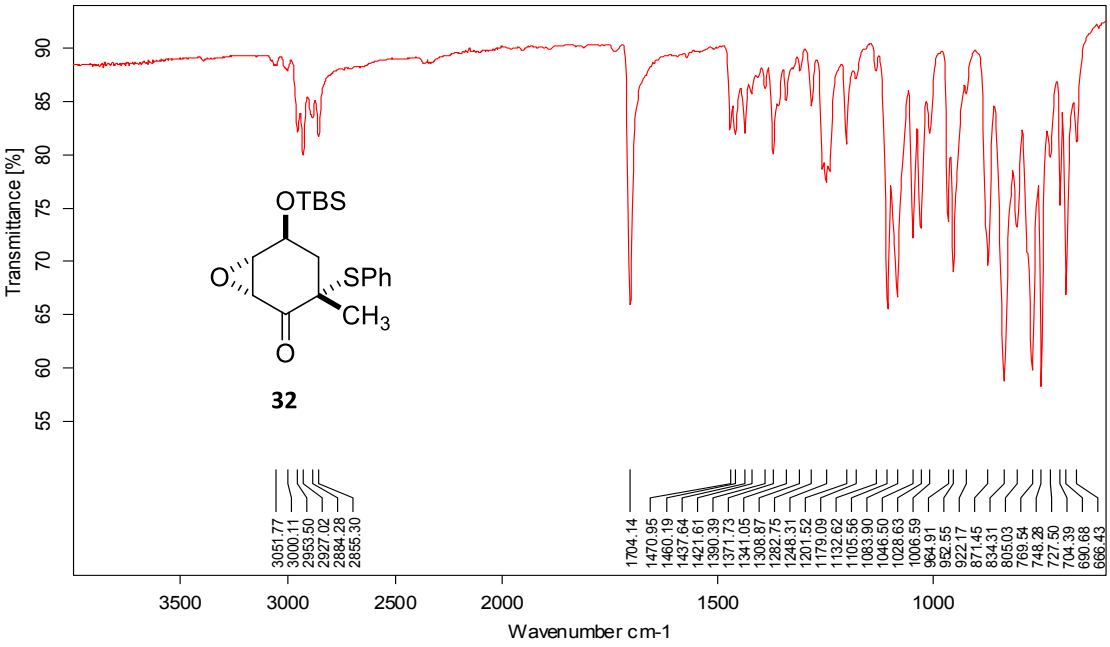
^{13}C-NMR (90 MHz, $CDCl_3$)



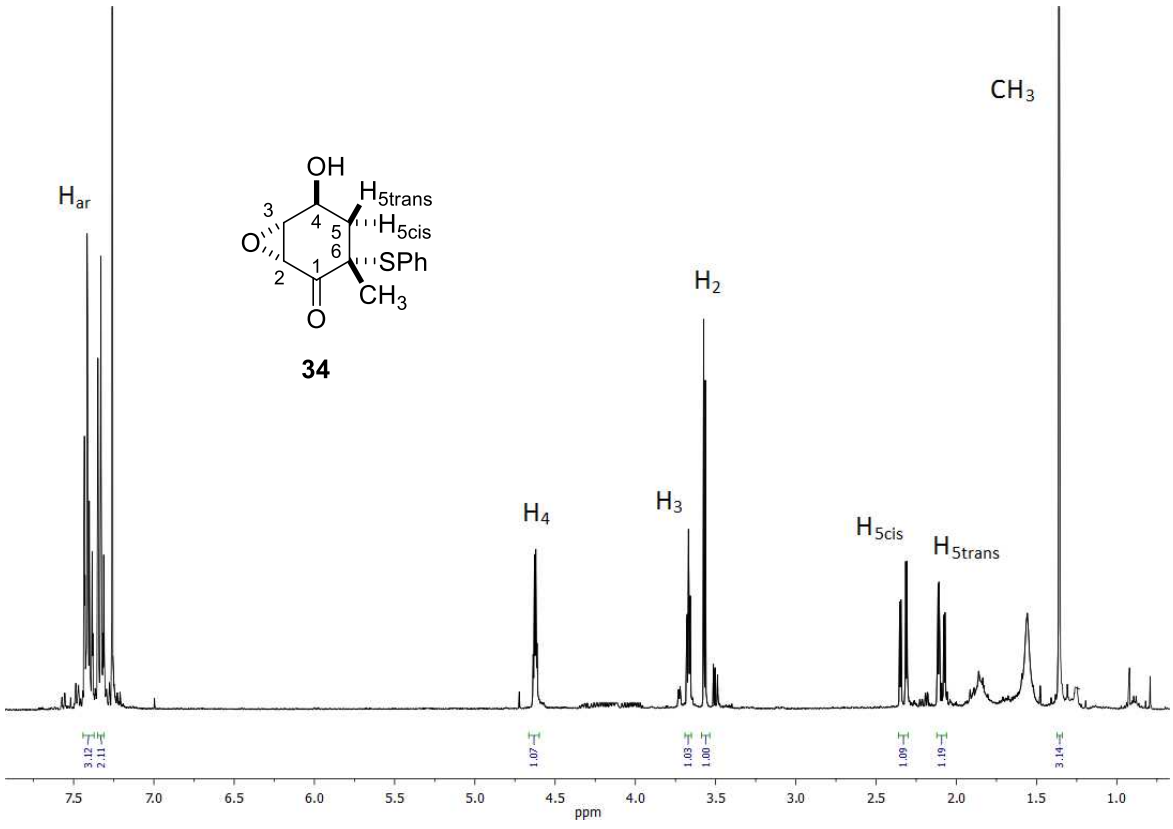
NOESY (400 MHz, $CDCl_3$)



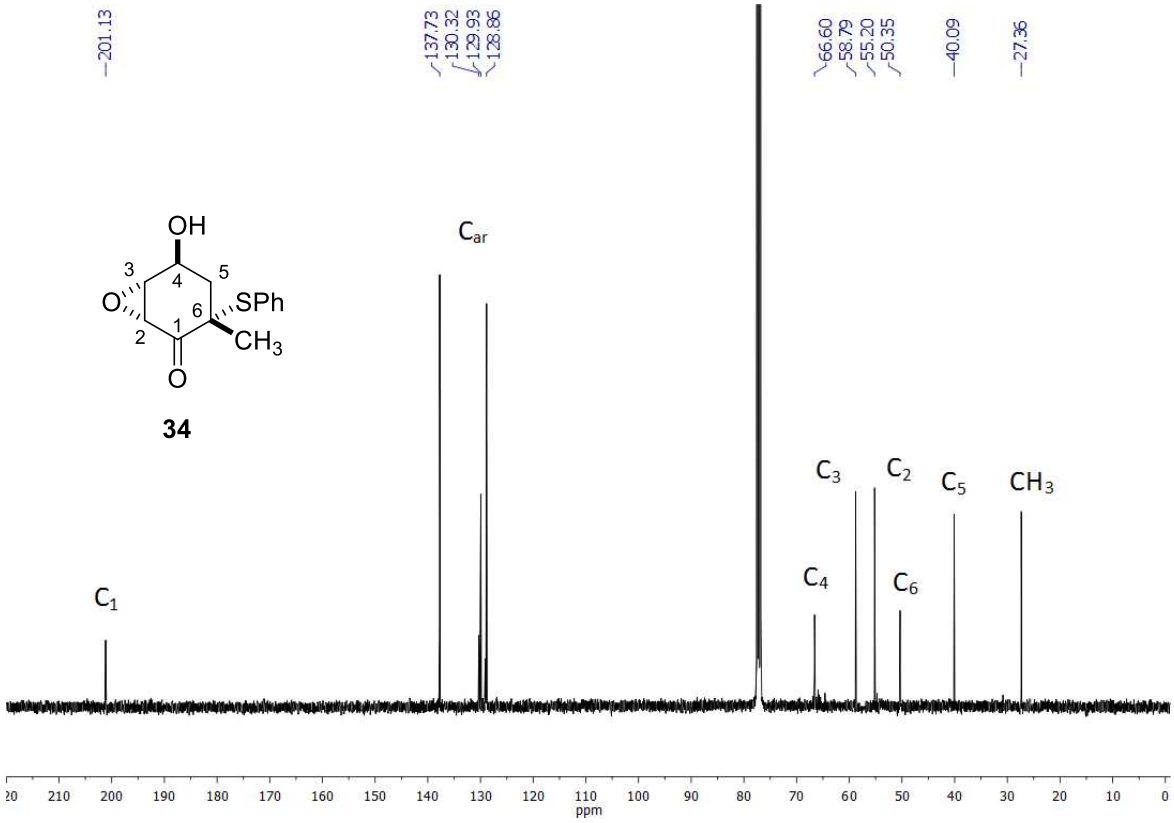
HSQCed ($CDCl_3$, ^{1}H-NMR: 400 MHz. ^{13}C-NMR: 100 MHz. CH, CH_3: blue, CH_2: red)



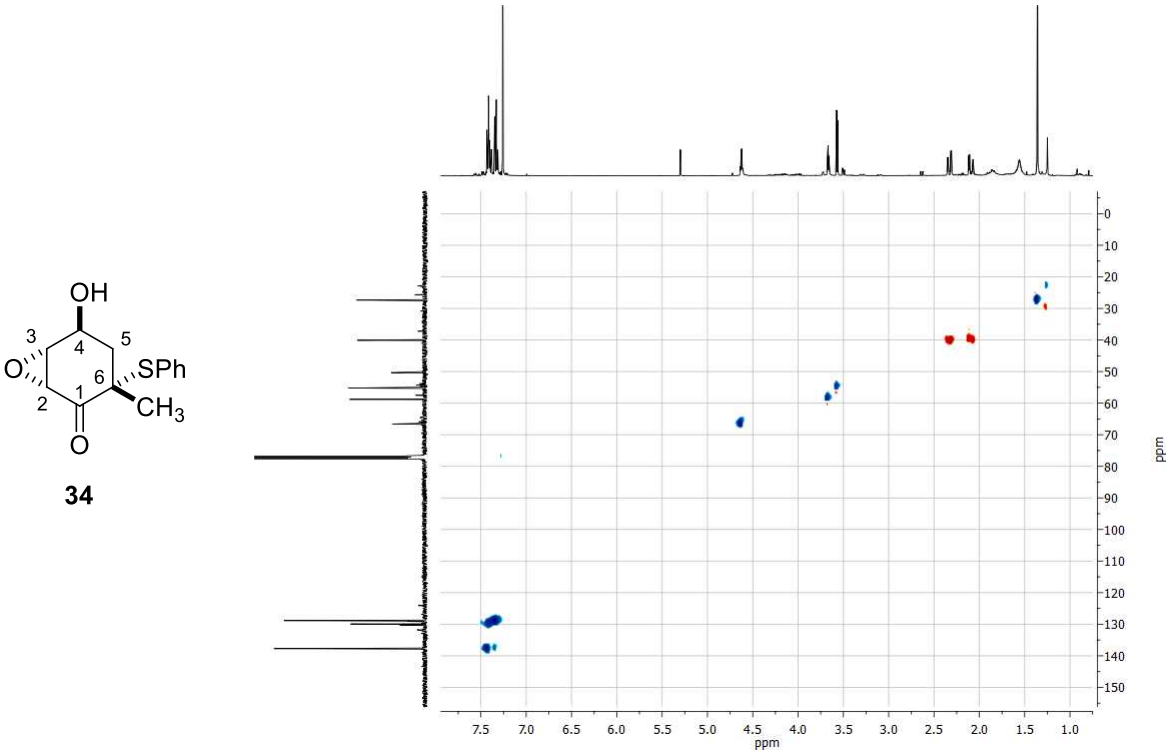
IR



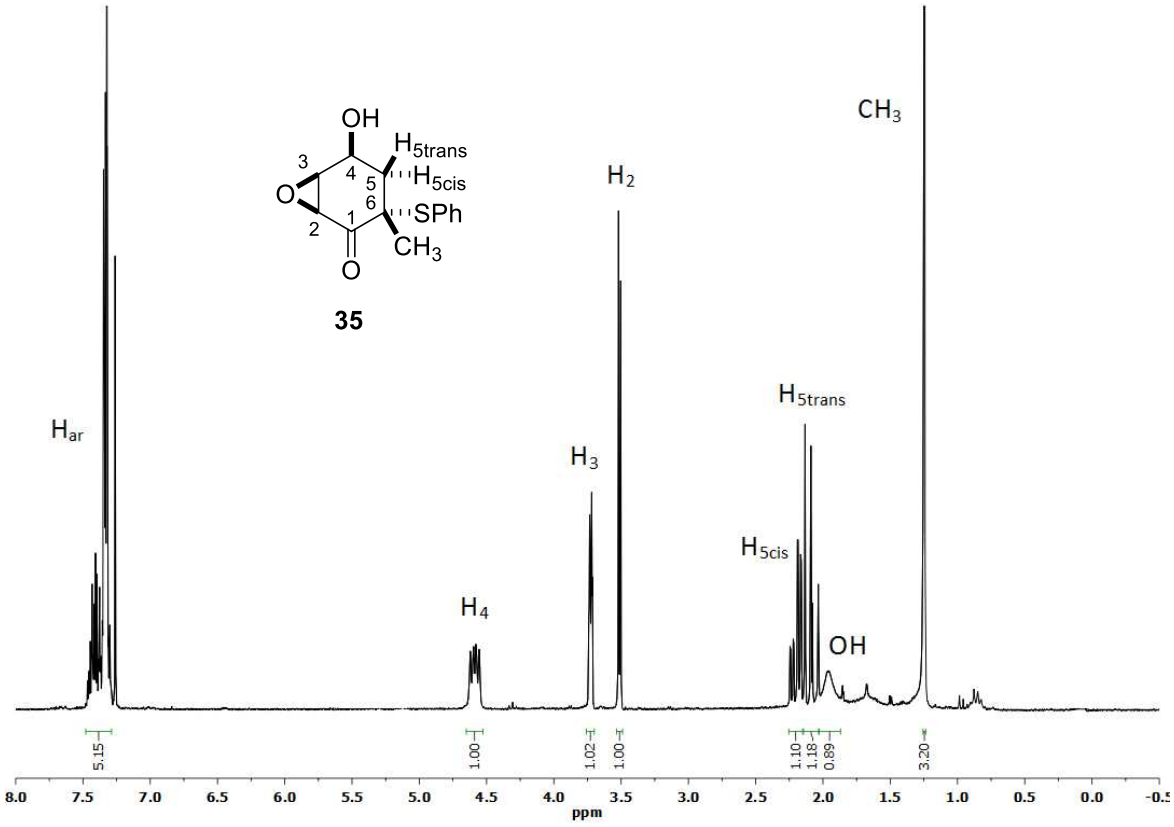
^{1}H-NMR (400 MHz, $CDCl_3$)



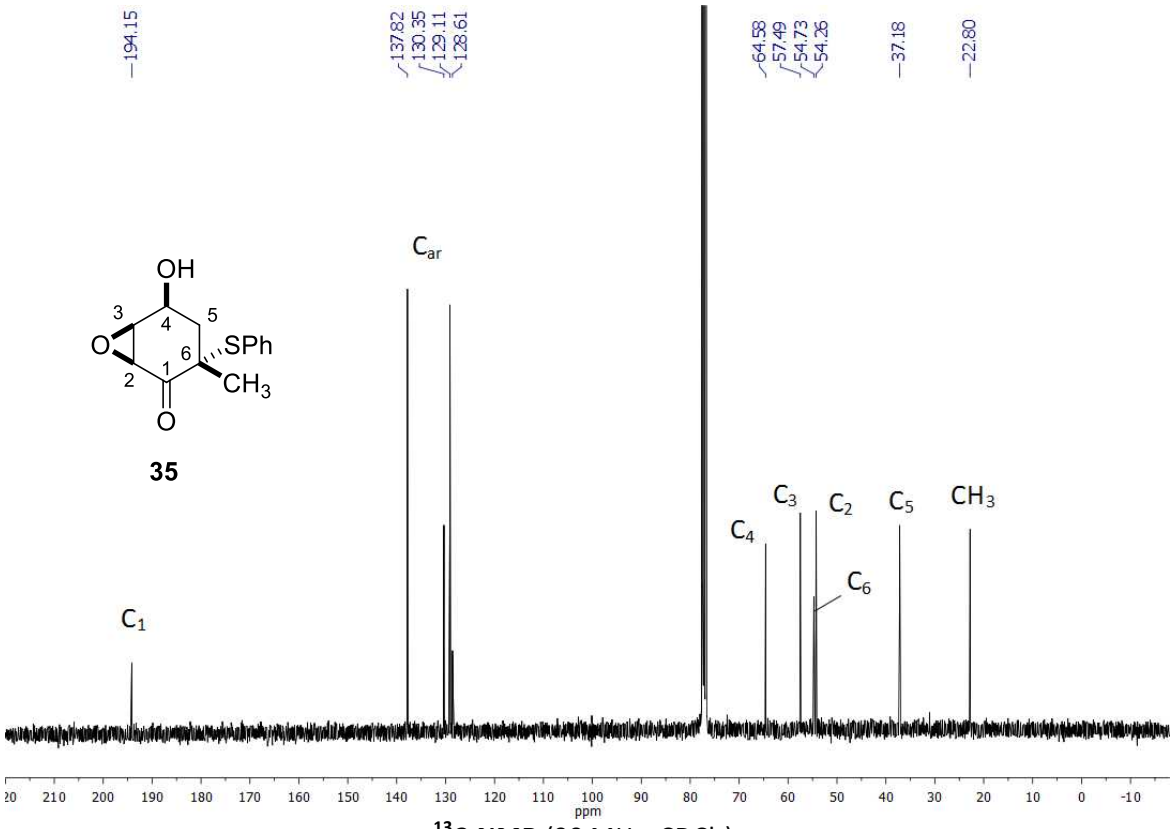
^{13}C-NMR (100 MHz, $CDCl_3$)



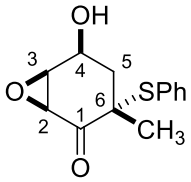
HSQCed ($CDCl_3$, ^{1}H-NMR: 400 MHz. ^{13}C-NMR: 100 MHz. CH, CH_3: blue, CH_2: red)



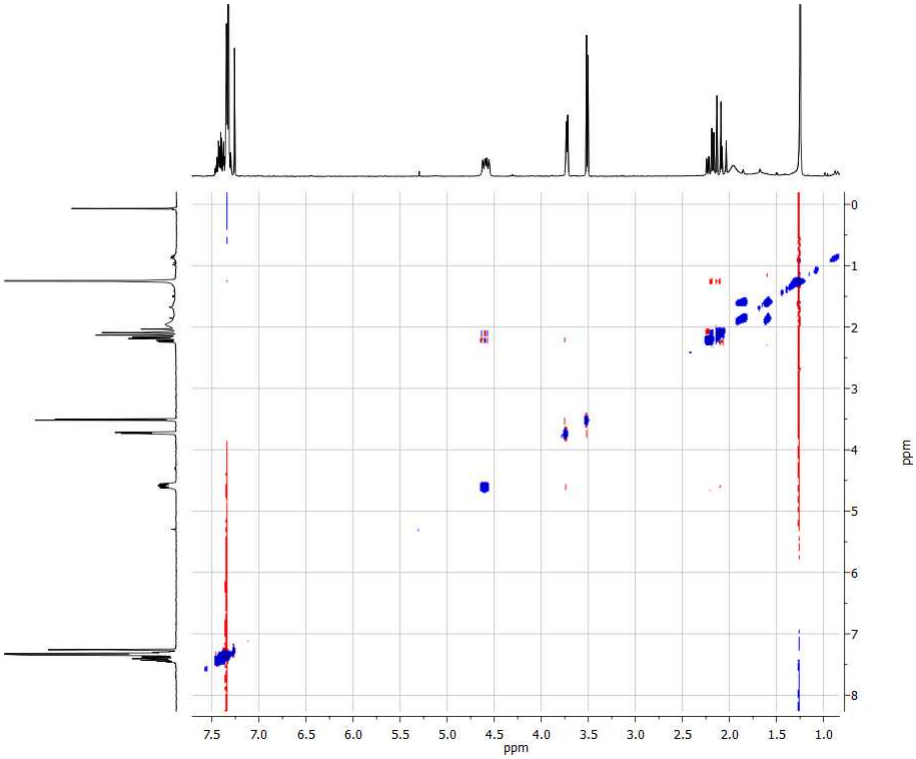
^{1}H-NMR (250 MHz, $CDCl_3$)



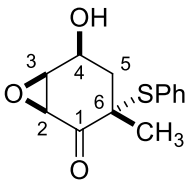
^{13}C-NMR (90 MHz, $CDCl_3$)



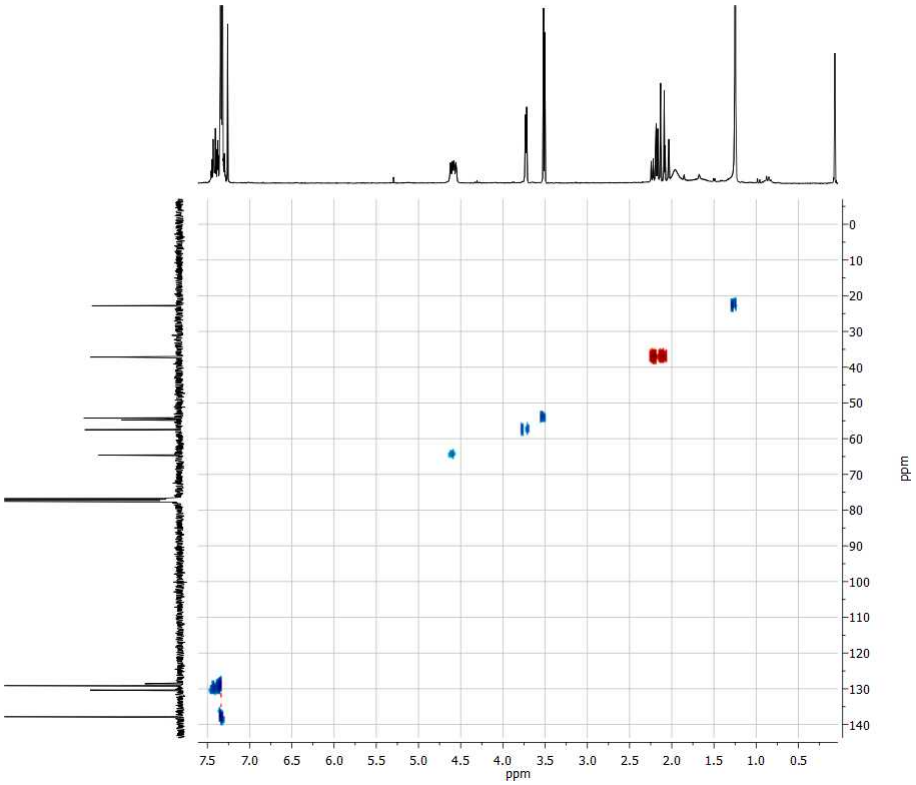
35



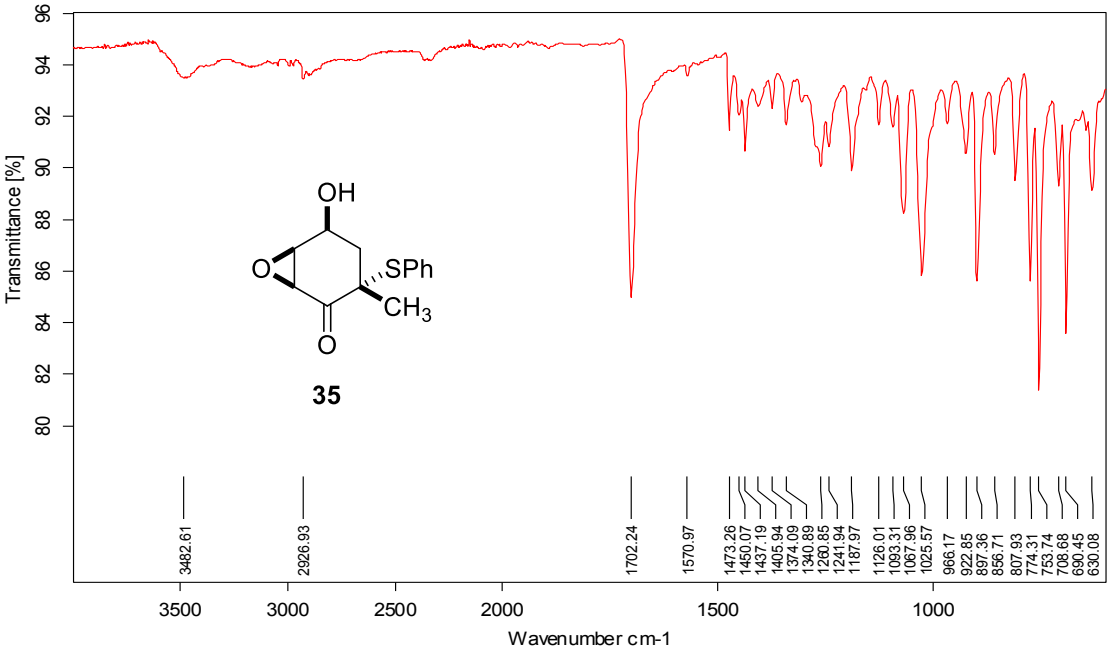
NOESY (360 MHz, $CDCl_3$)



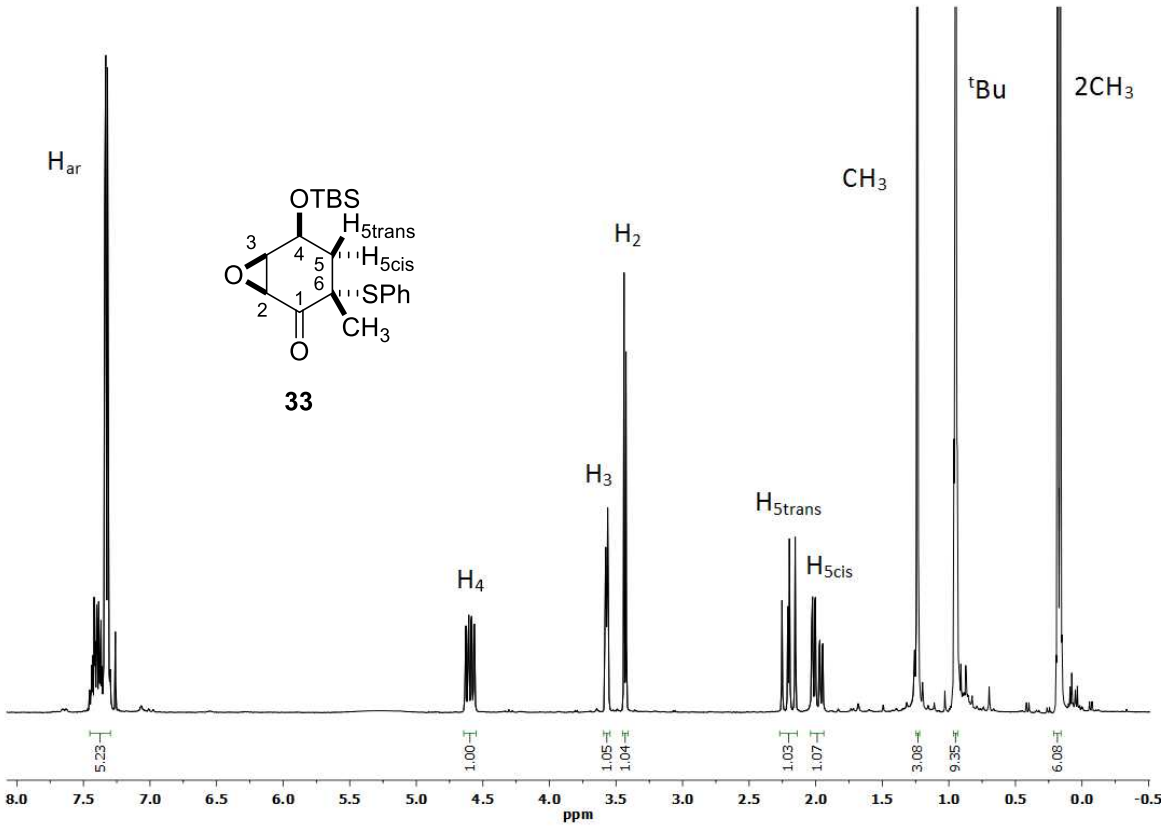
35



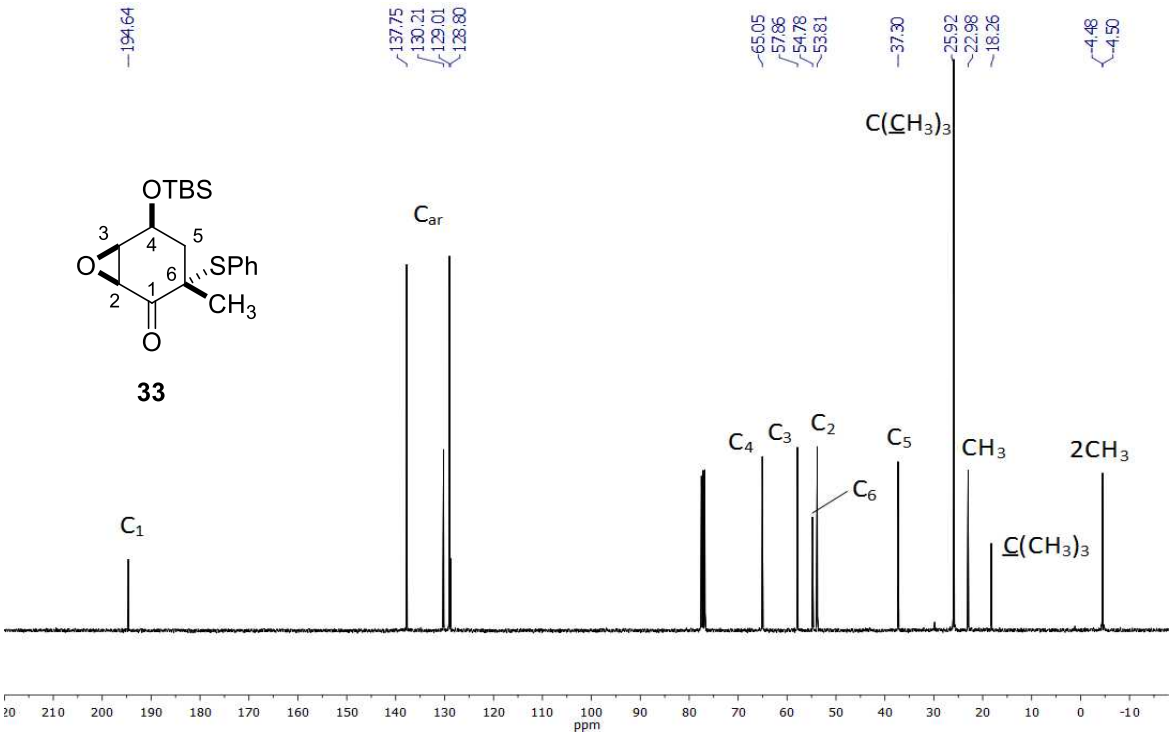
HSQCed ($CDCl_3$, ^{1}H-NMR: 360 MHz. ^{13}C-NMR: 91 MHz. CH, CH_3: blue, CH_2: red)



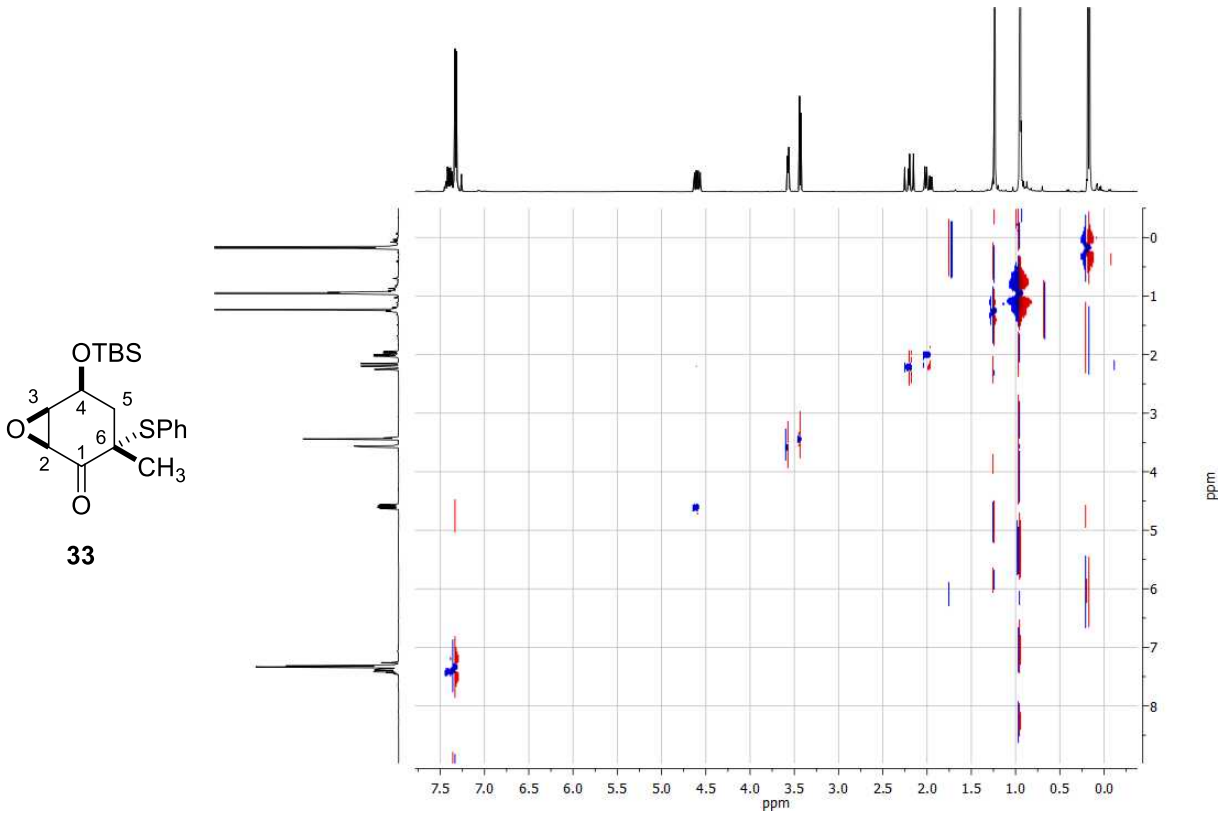
IR



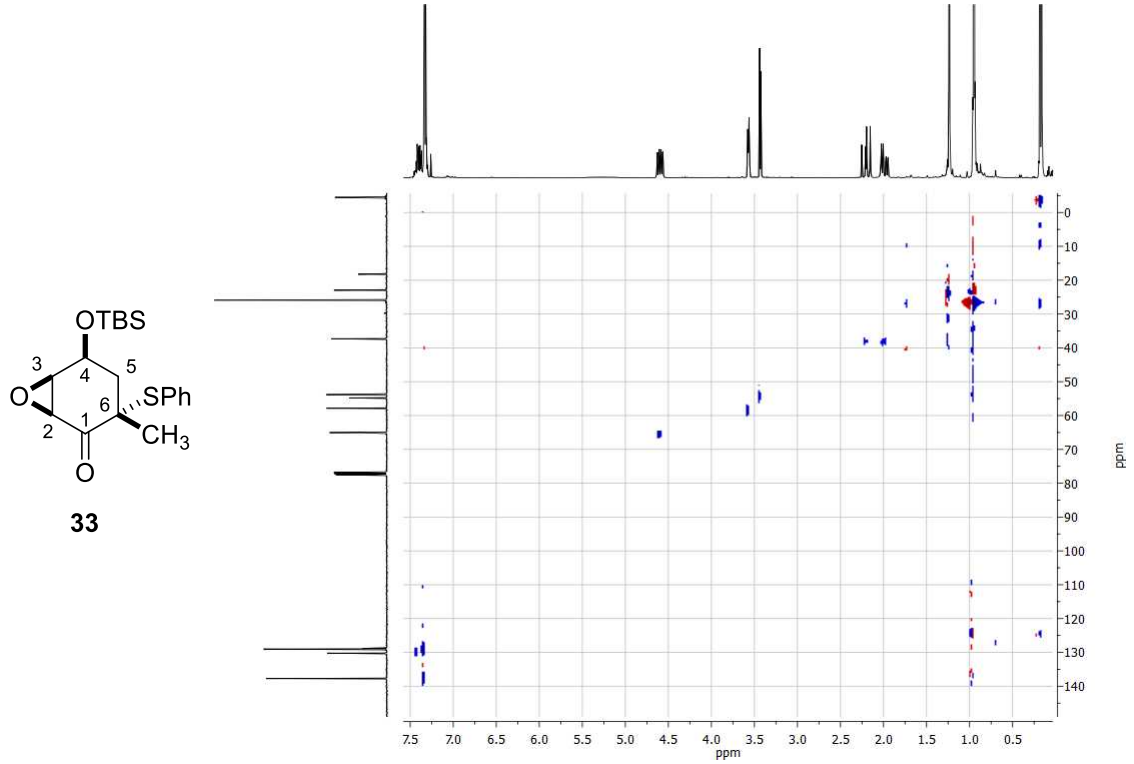
^{1}H-NMR (250 MHz, $CDCl_3$)



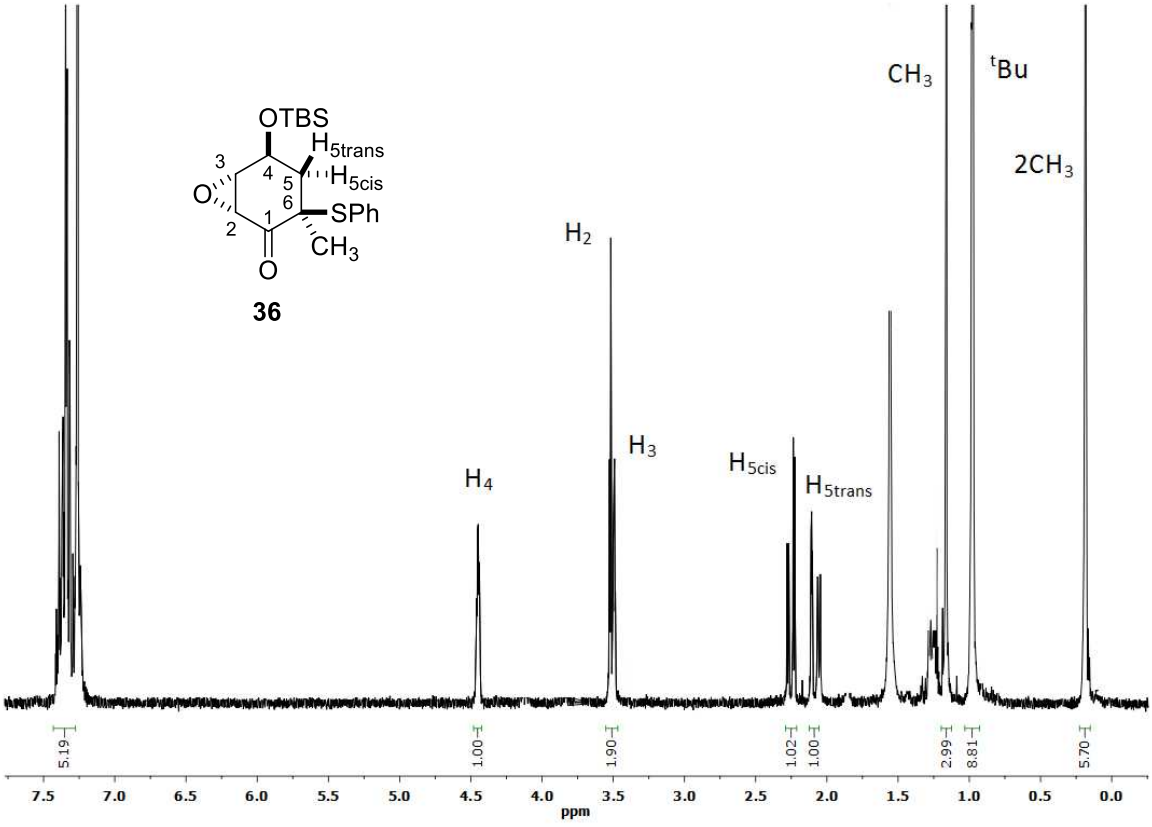
^{13}C-NMR (90 MHz, $CDCl_3$)



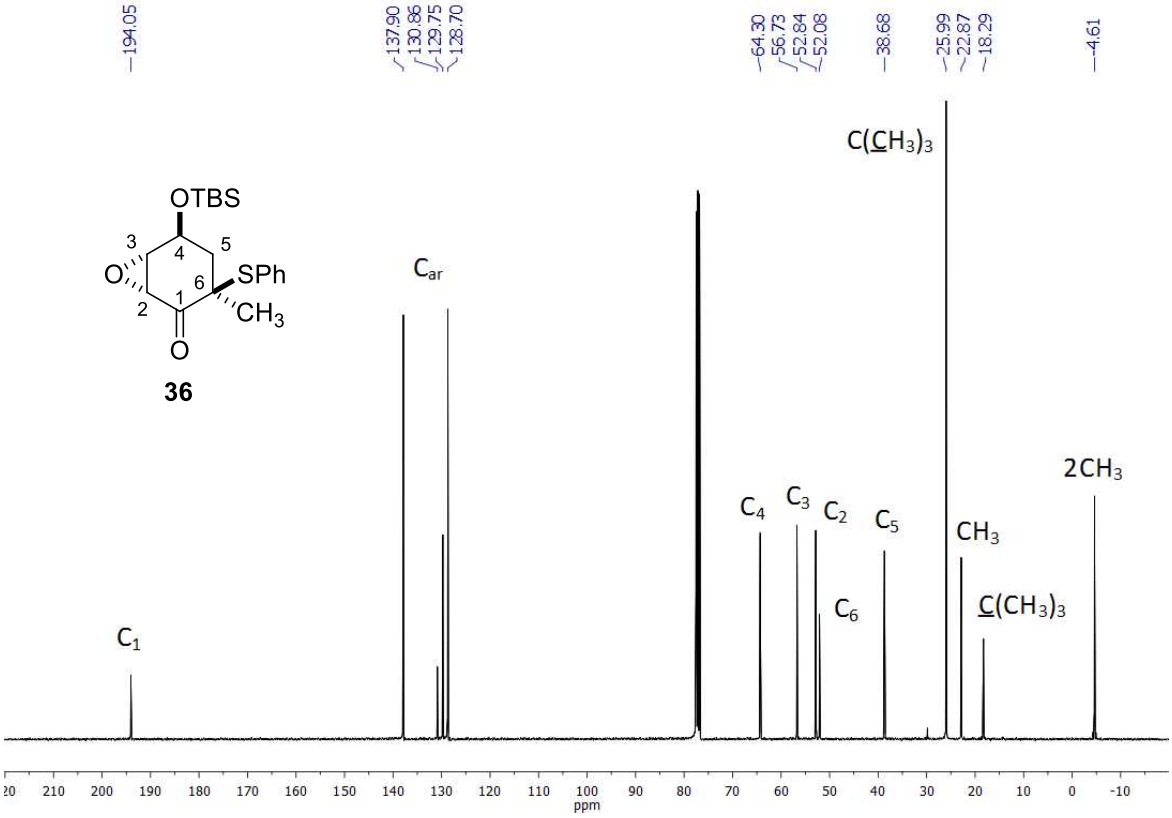
NOESY (360 MHz, $CDCl_3$)



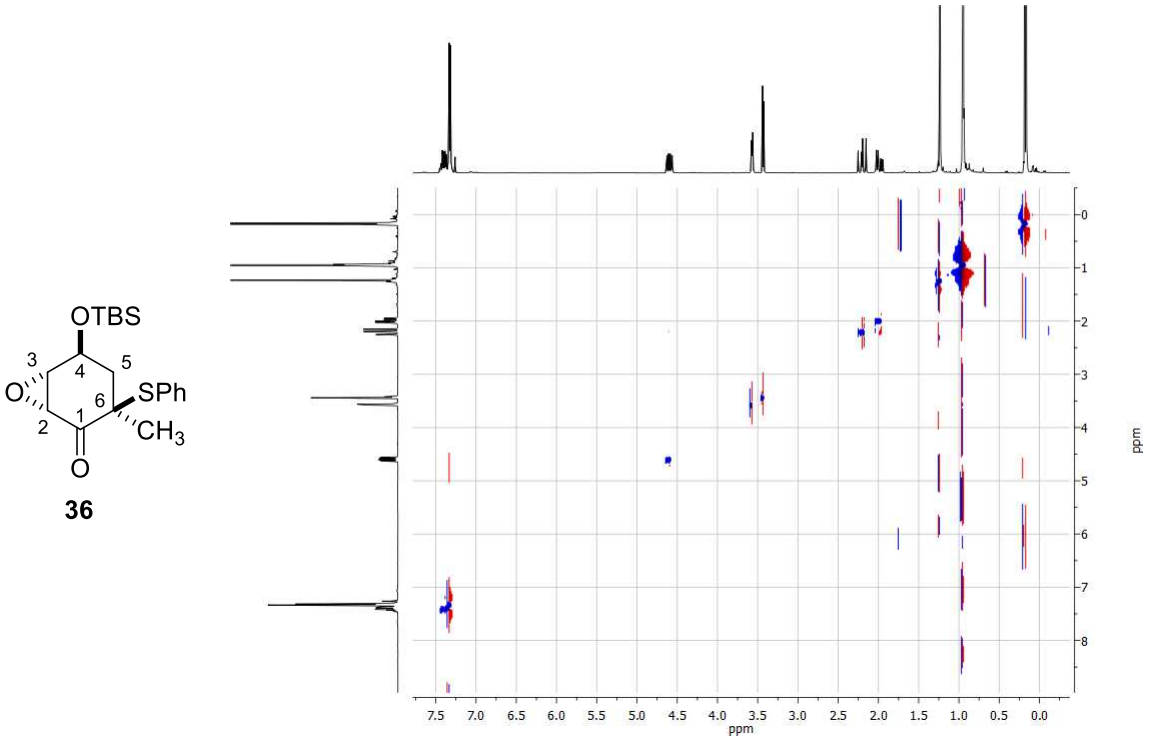
HSQC (360 MHz, $CDCL_3$)



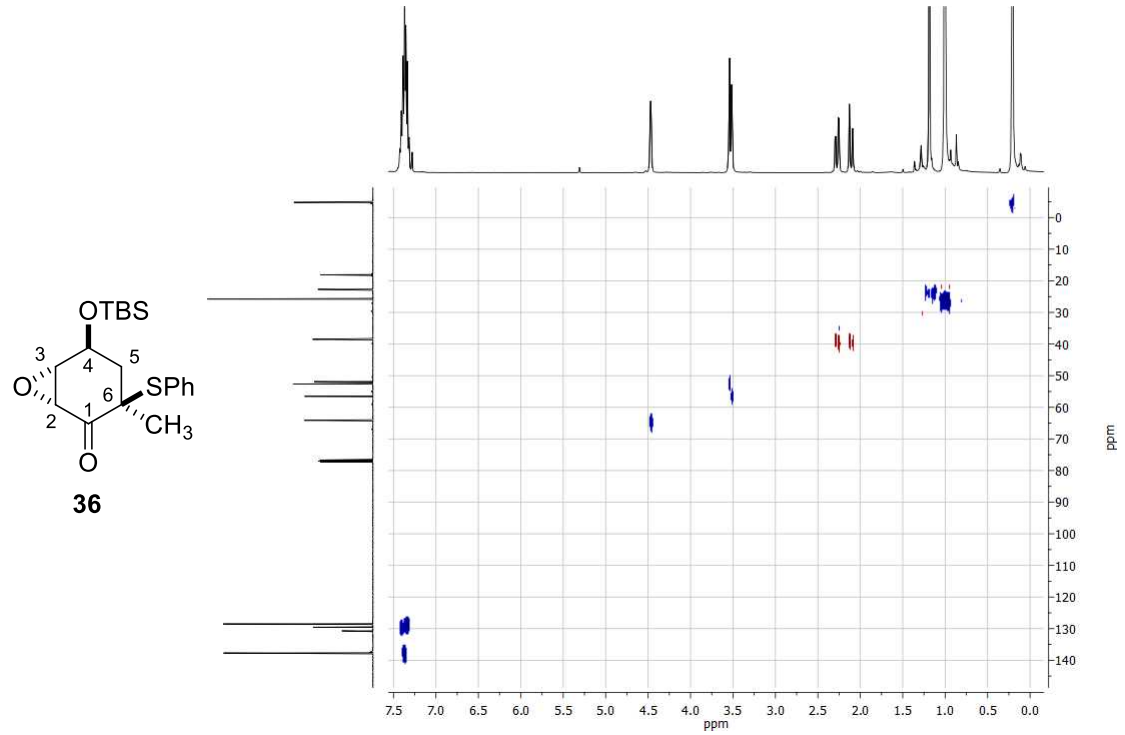
^{1}H-NMR (360 MHz, $CDCl_3$)



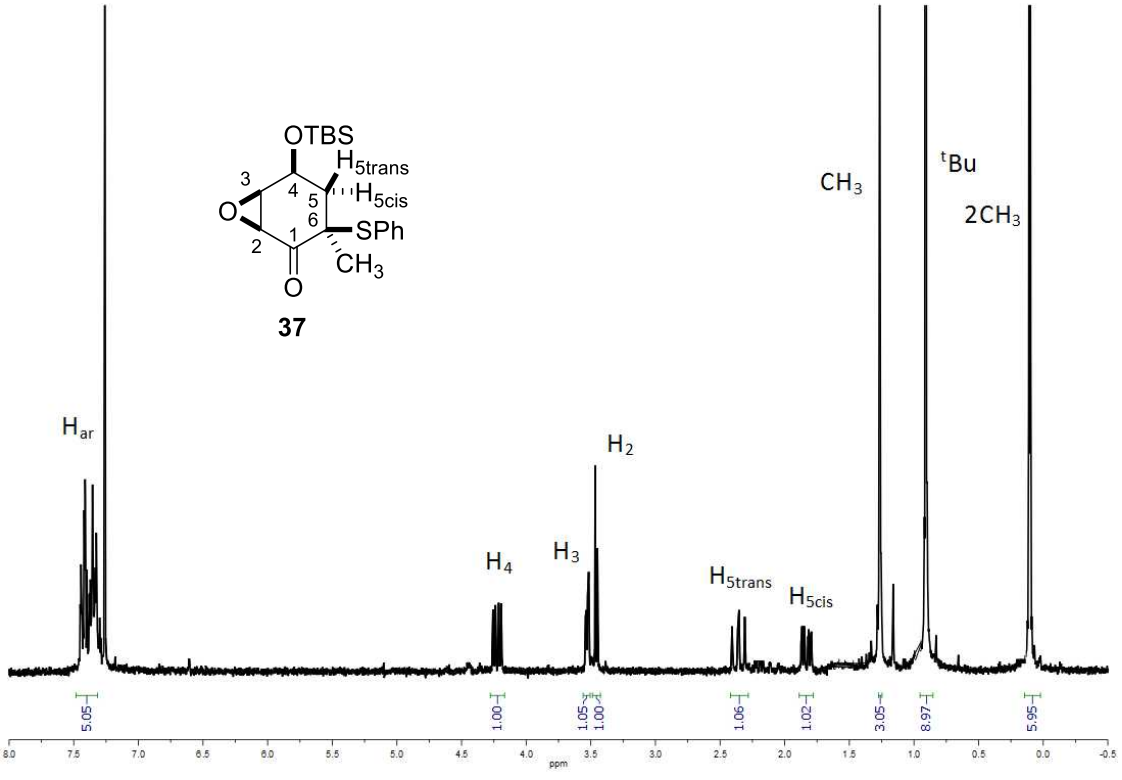
^{13}C-NMR (90 MHz, $CDCl_3$)



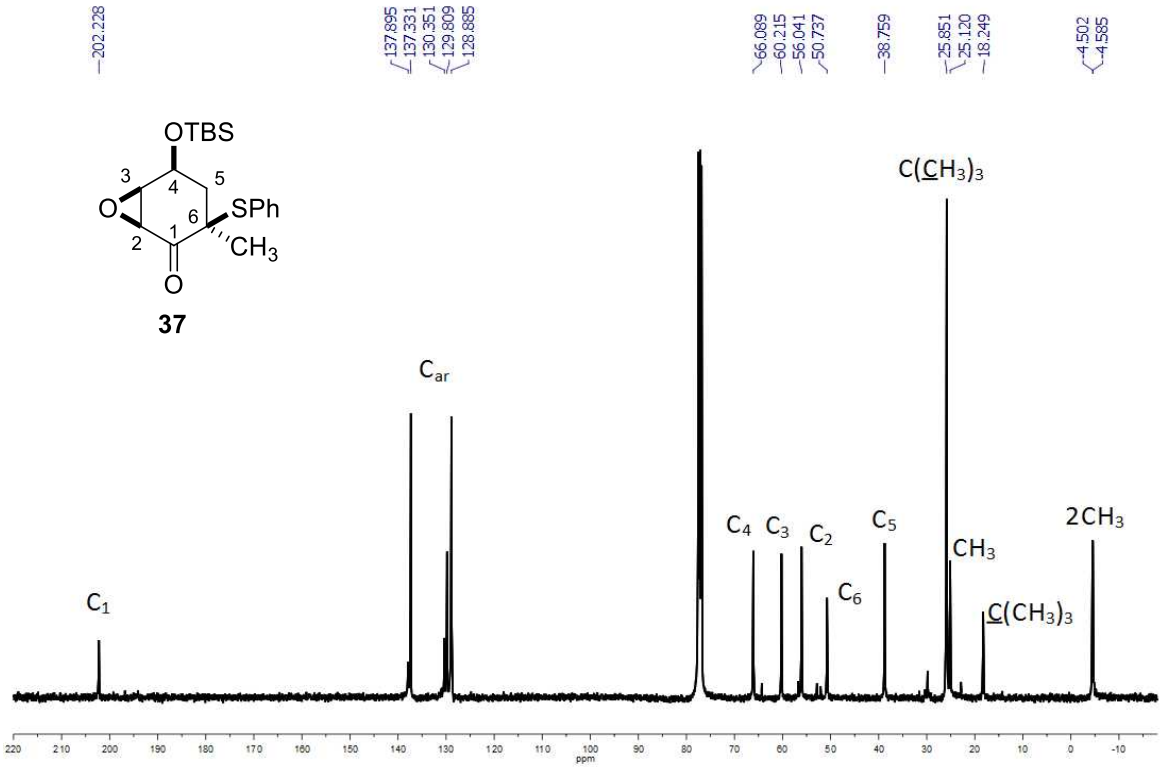
NOESY (400 MHz, $CDCl_3$)



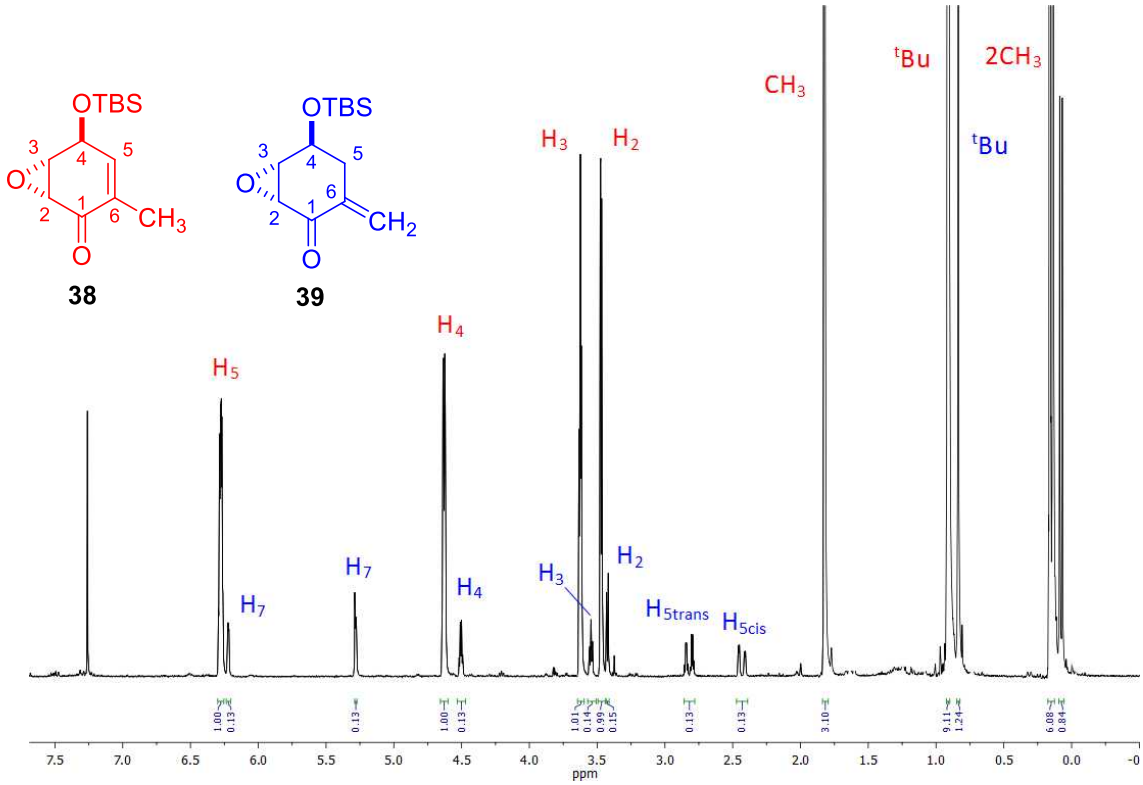
HSQCed ($CDCl_3$, ^{1}H-NMR: 400 MHz. ^{13}C-NMR: 100 MHz. CH, CH_3: blue, CH_2: red)



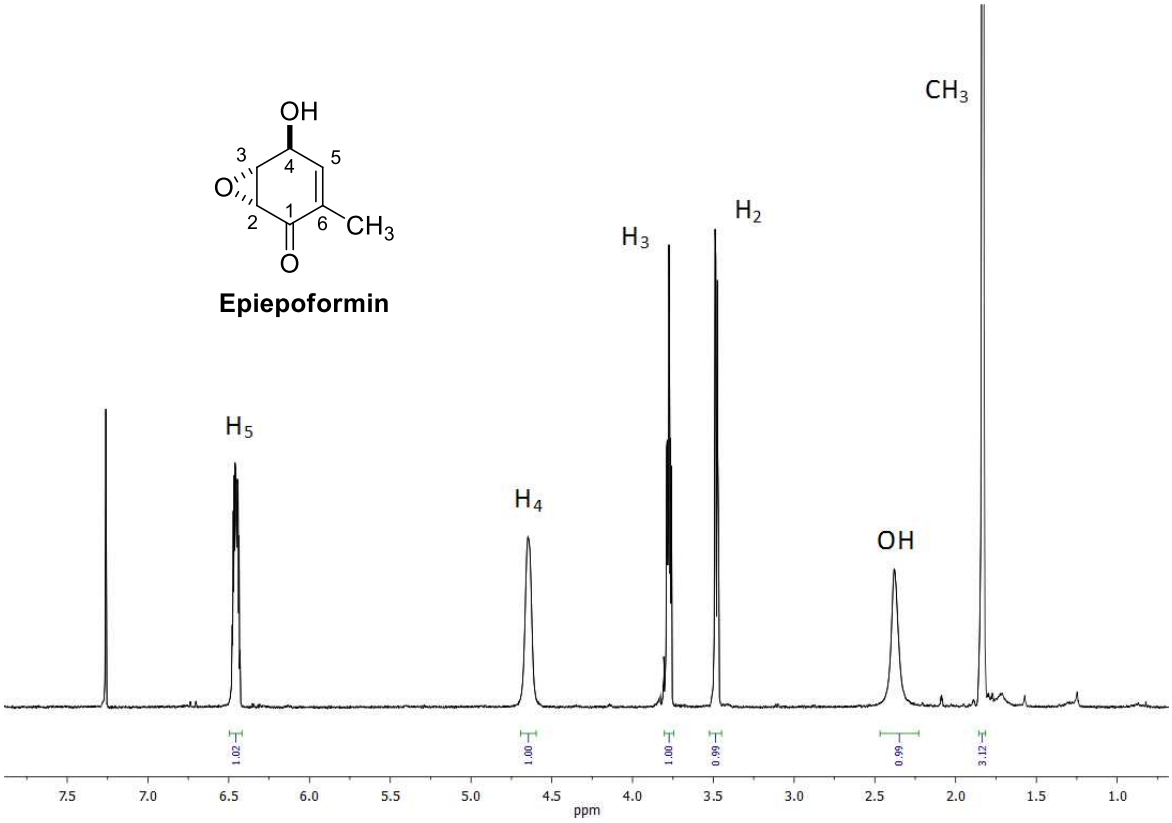
^{1}H-NMR (400 MHz, $CDCl_3$)



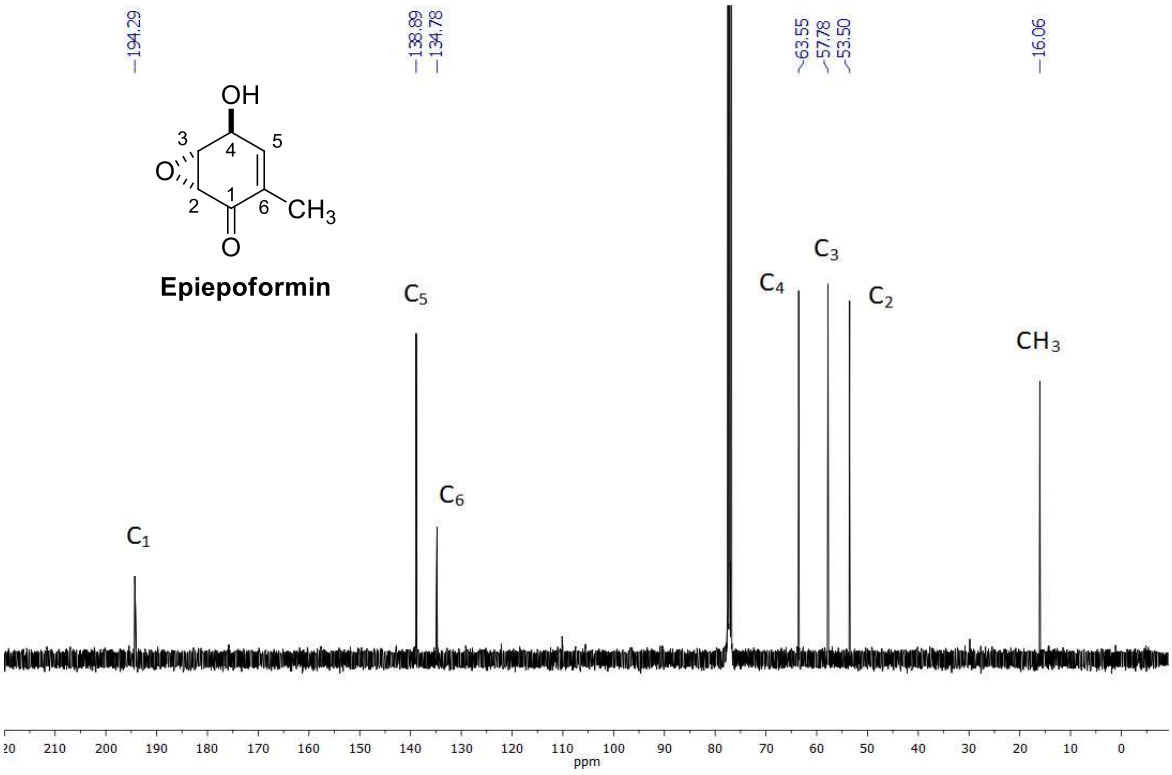
^{13}C-NMR (100 MHz, $CDCl_3$)



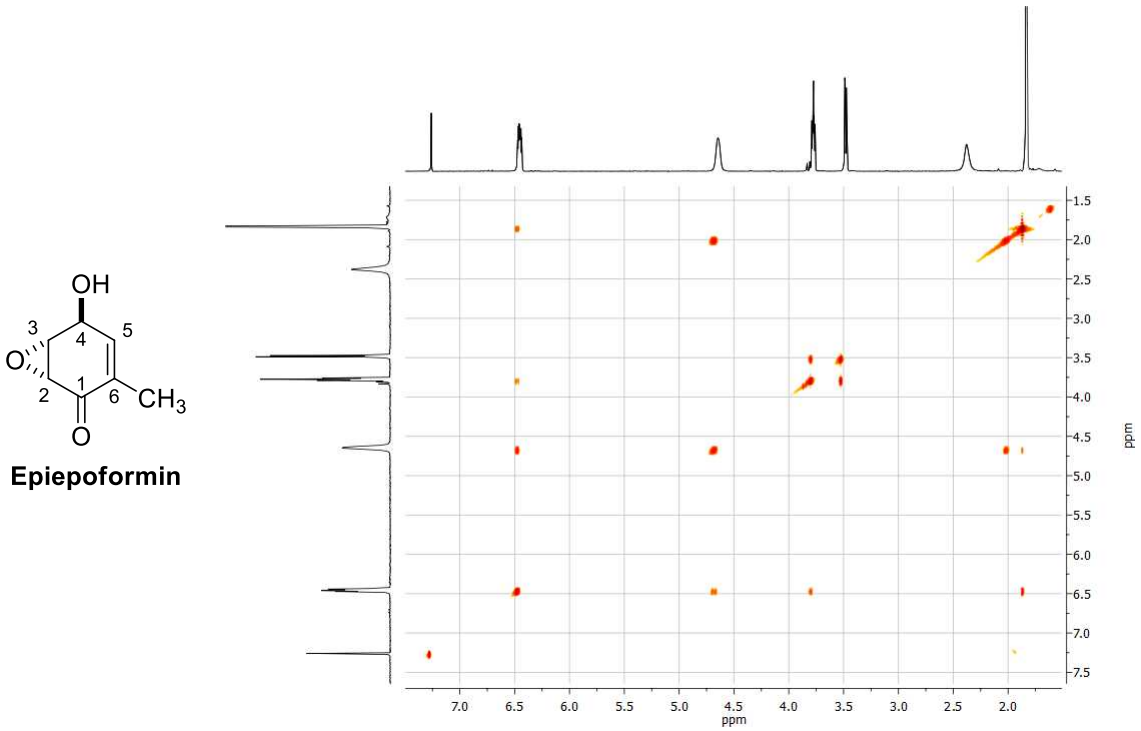
^{1}H-NMR (360 MHz, $CDCl_3$)



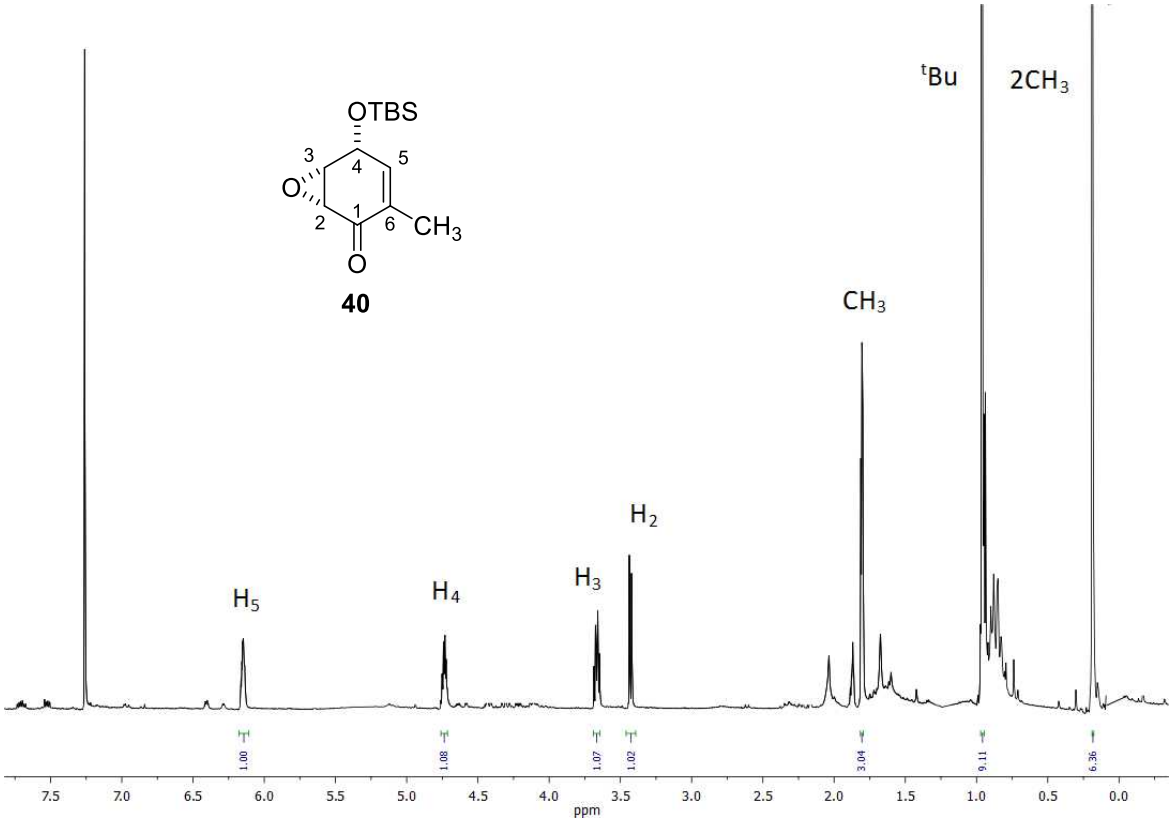
^{1}H-NMR (250 MHz, $CDCl_3$)



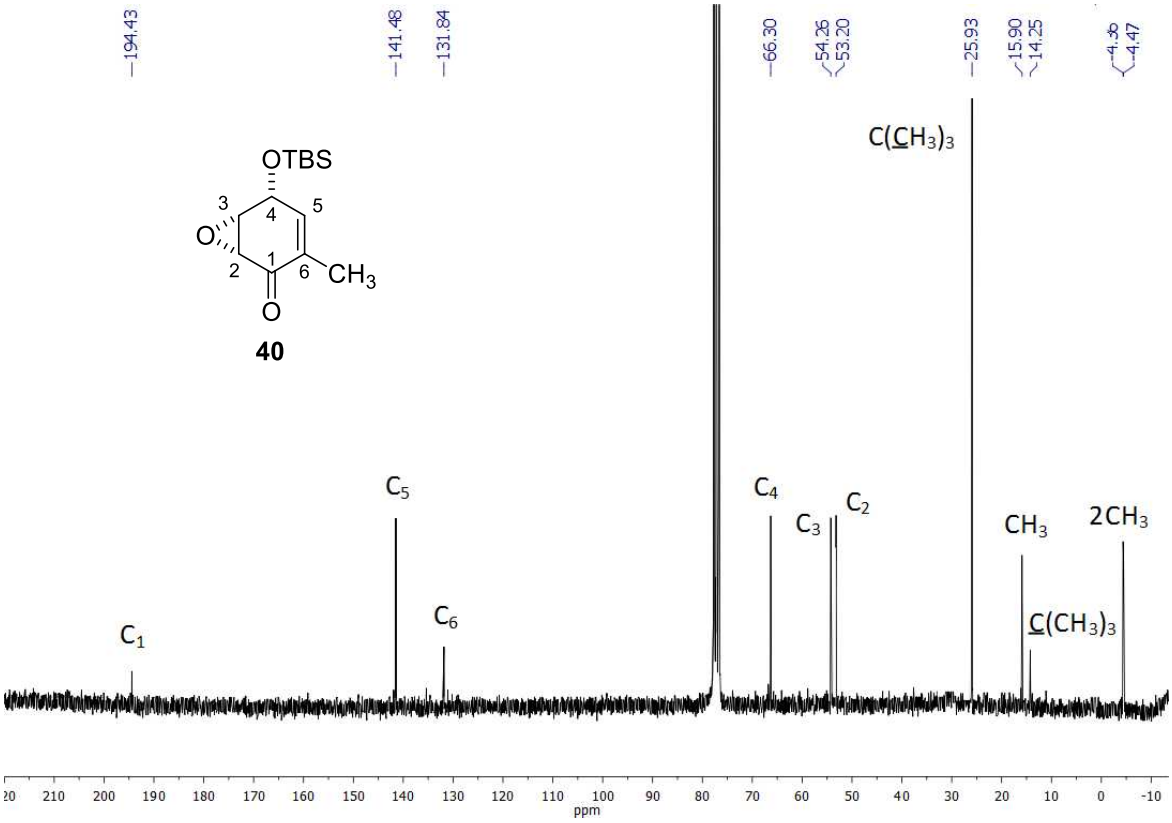
^{13}C-NMR (100 MHz, $CDCl_3$)



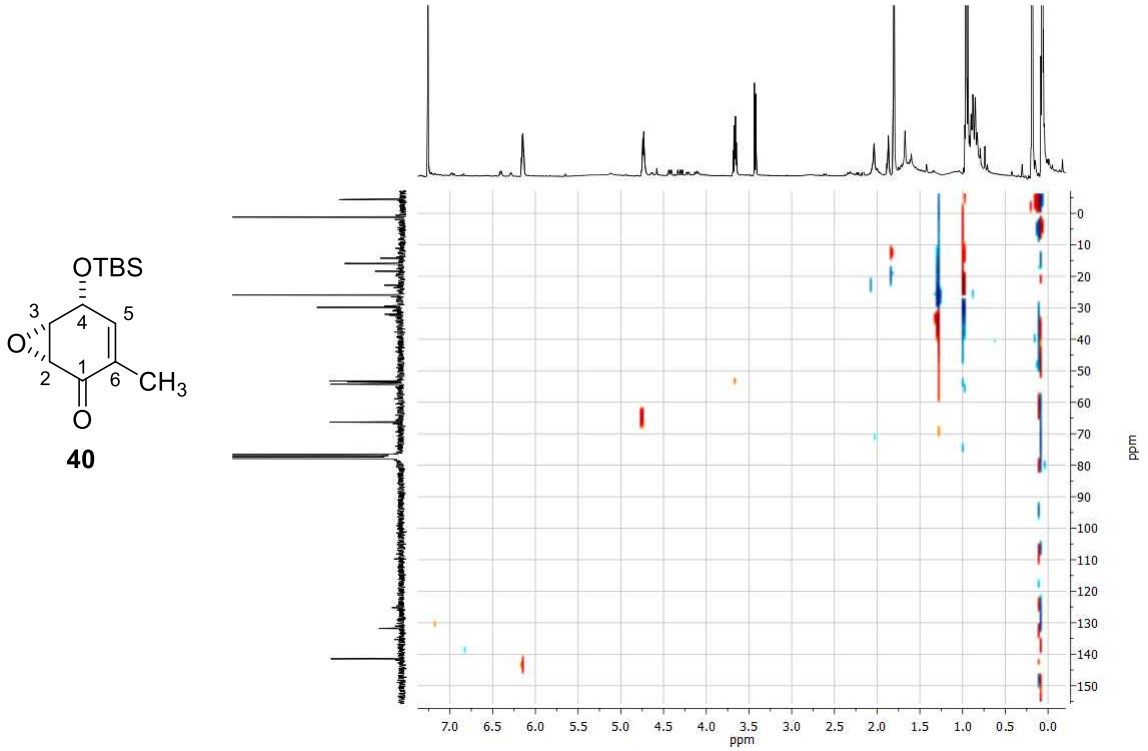
COSY (400 MHz, $CDCl_3$)



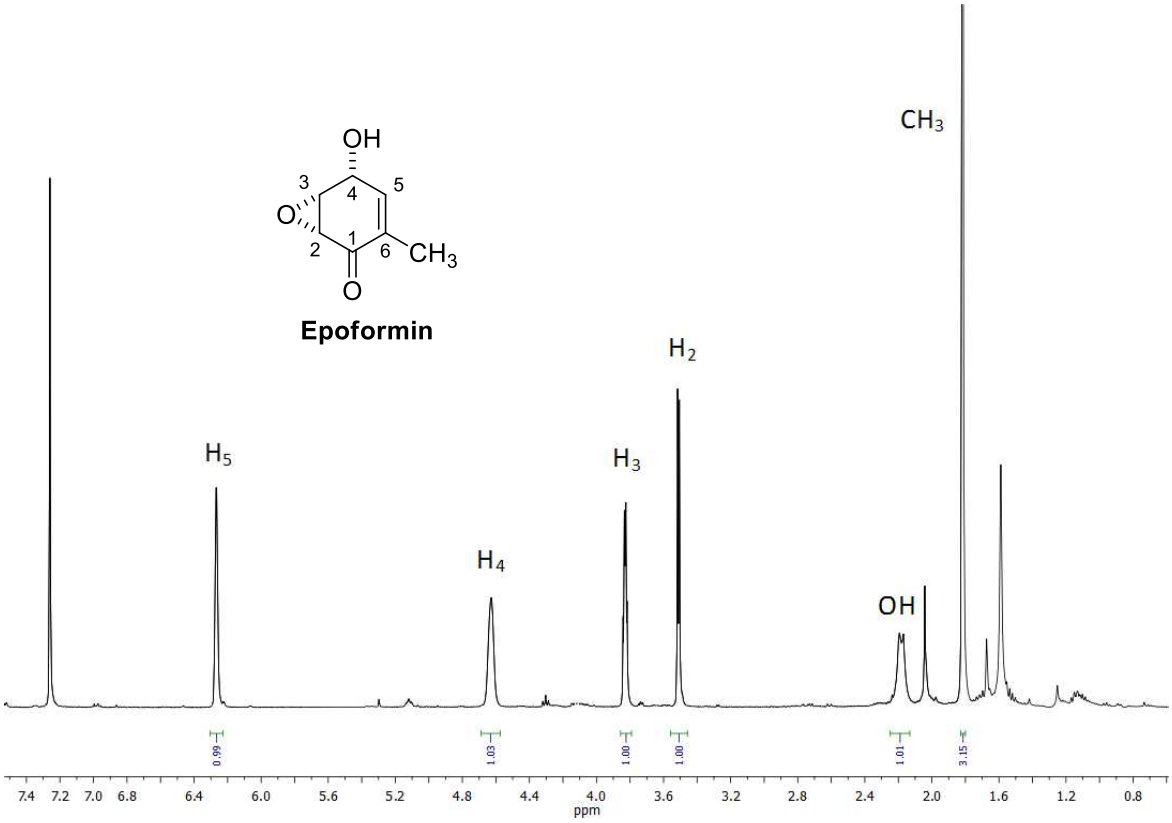
^{1}H-NMR (250 MHz, $CDCl_3$)



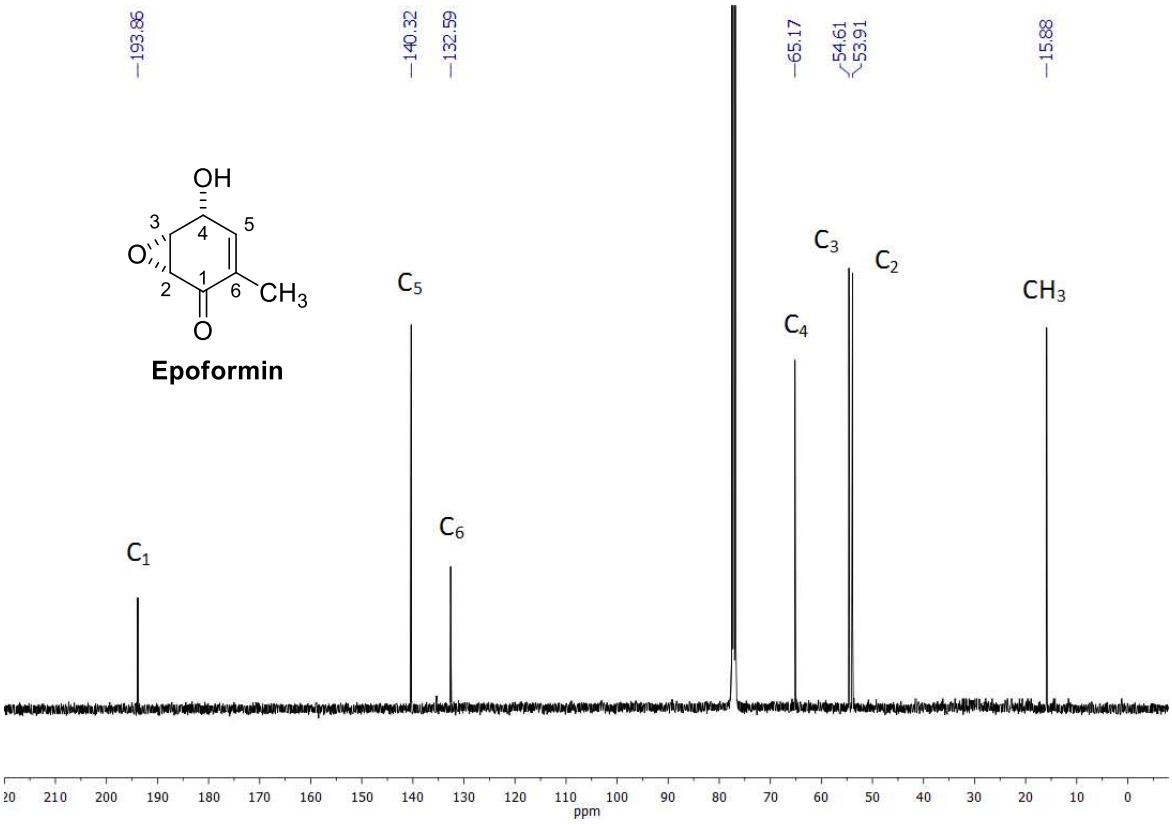
^{13}C-NMR (100 MHz, $CDCl_3$)



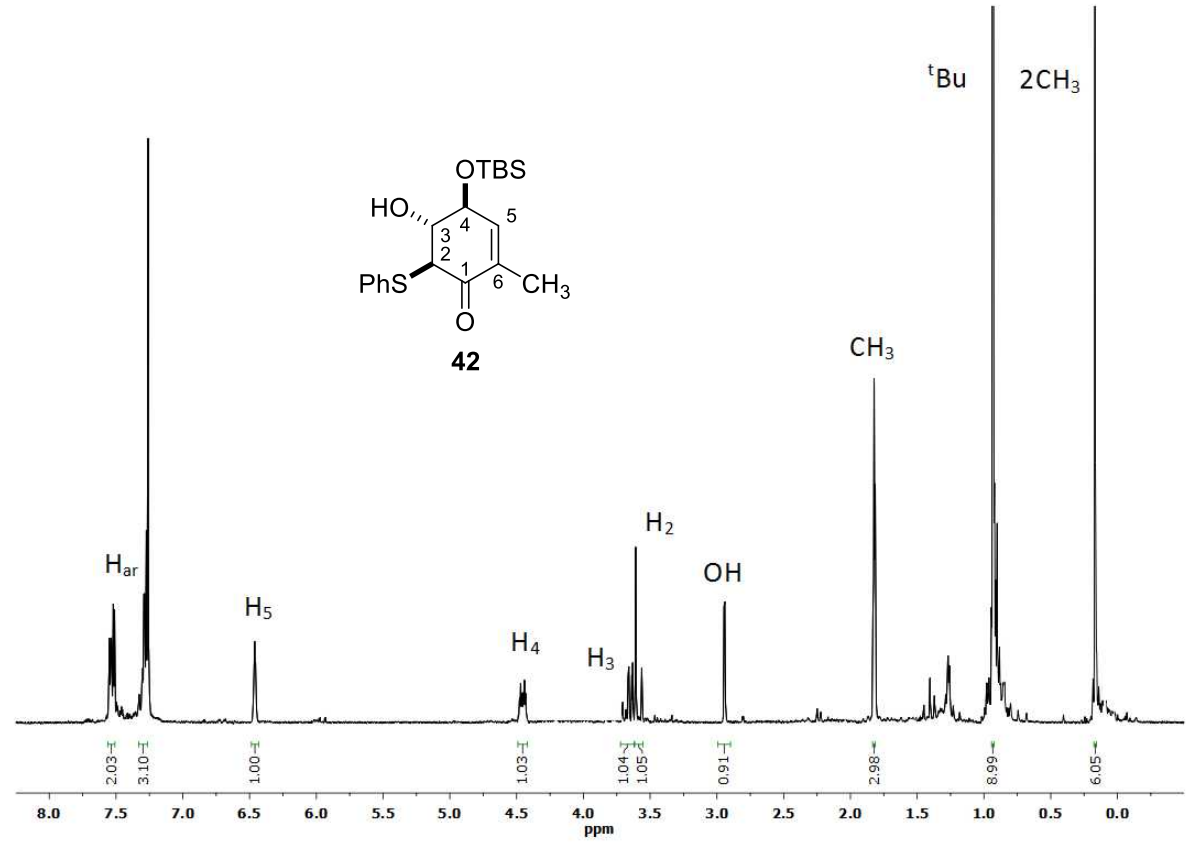
HSQCed ($CDCl_3$, ^{1}H-NMR: 360 MHz. ^{13}C-NMR: 90 MHz. CH, CH_3: red, CH_2: blue)



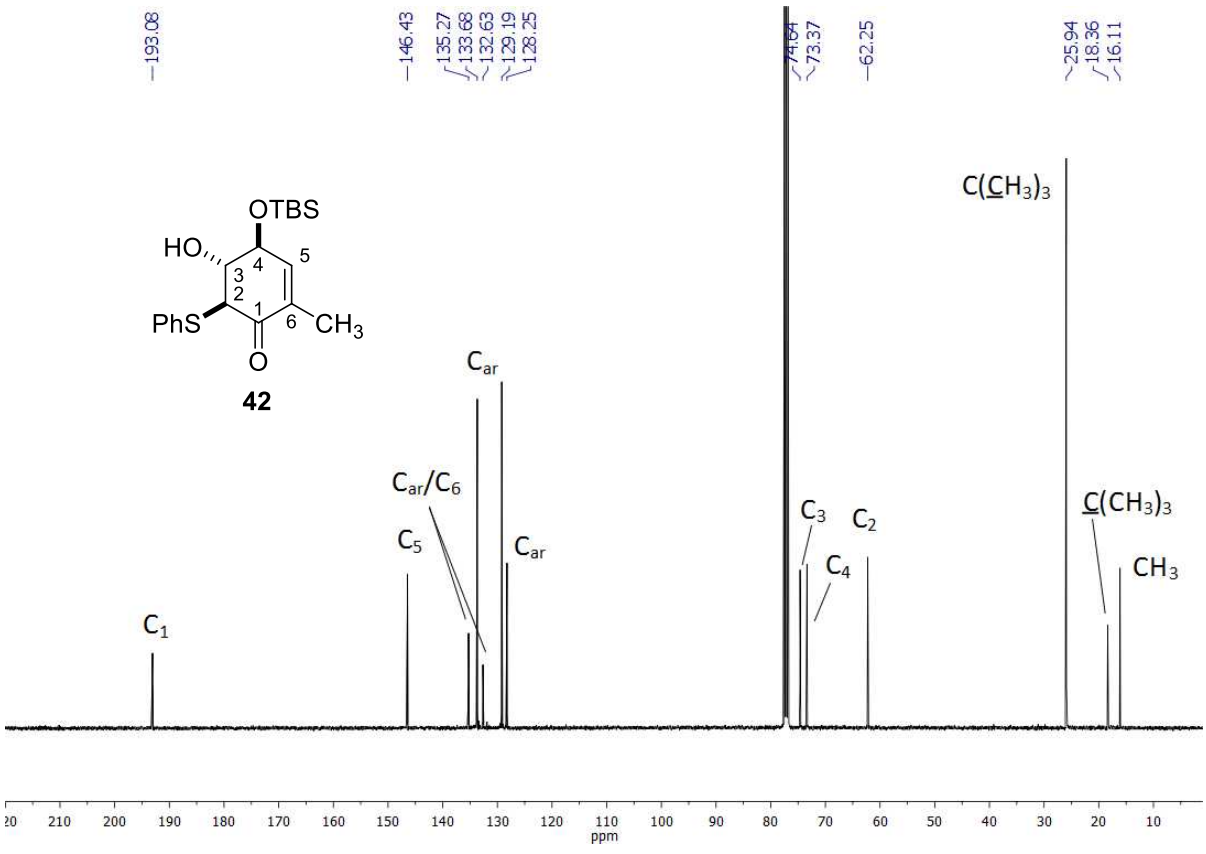
^{1}H-NMR (400 MHz, $CDCl_3$)



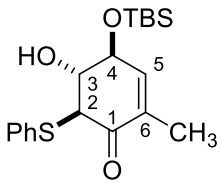
^{13}C-NMR (100 MHz, $CDCl_3$)



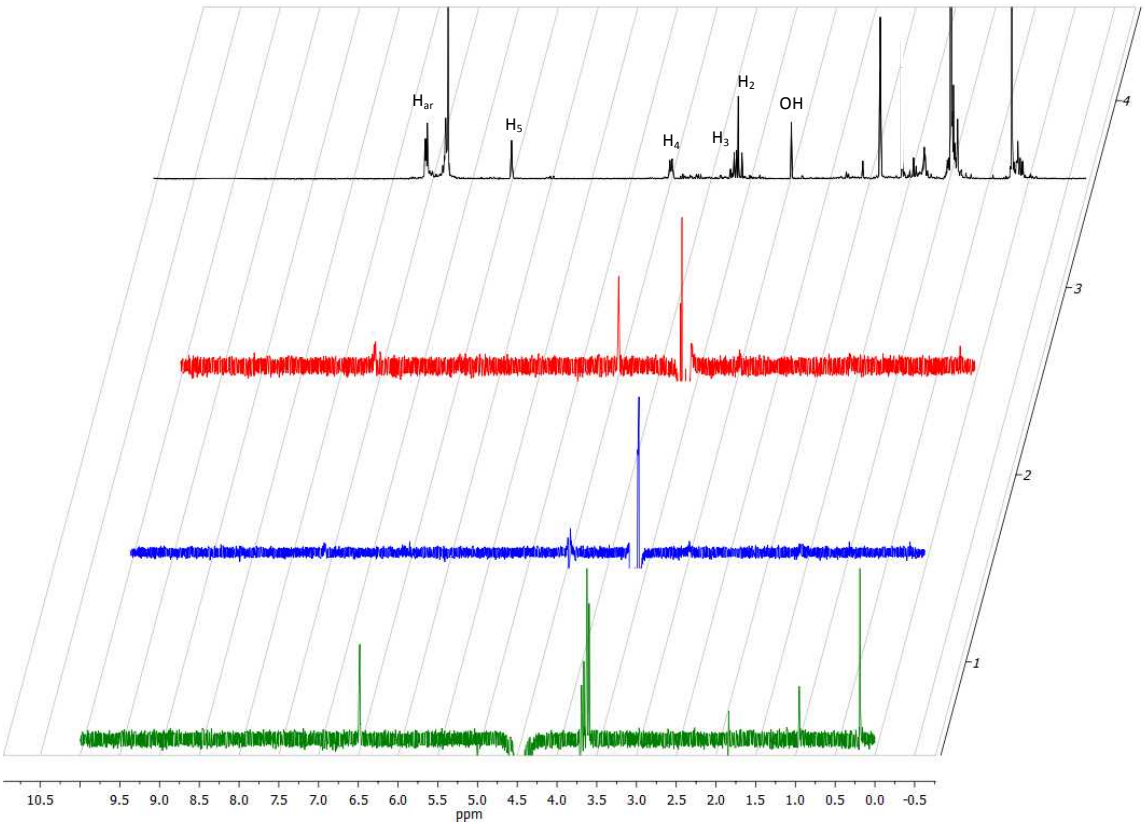
^{1}H-NMR (250 MHz, $CDCl_3$)



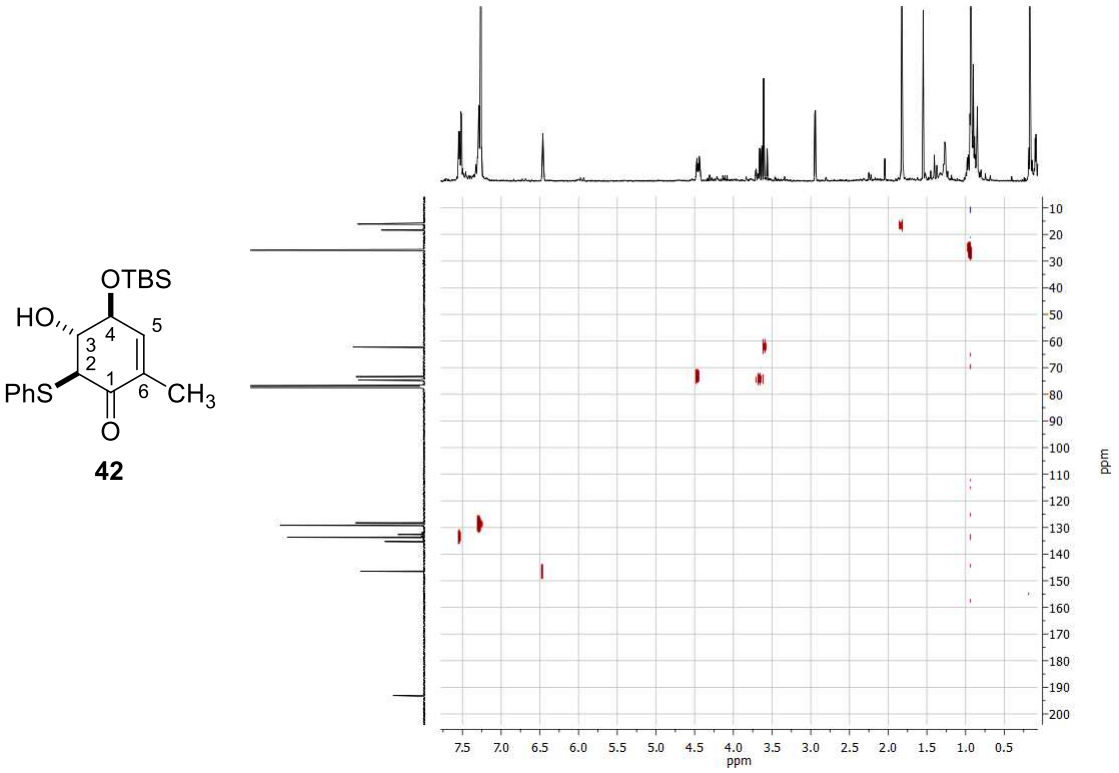
^{13}C-NMR (100 MHz, $CDCl_3$)



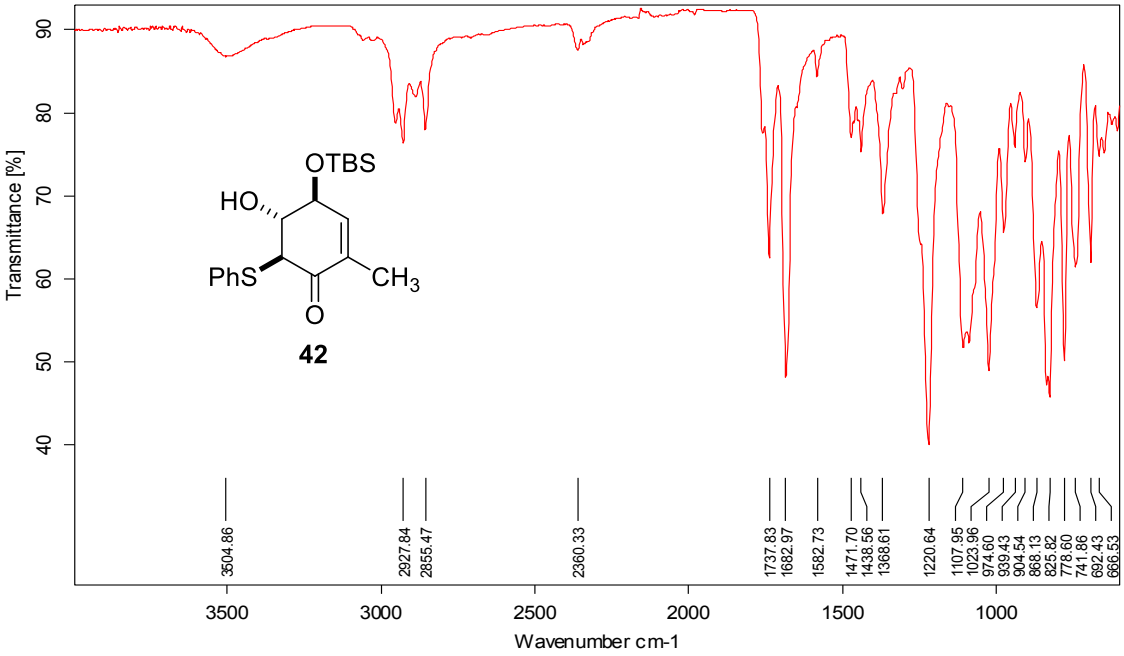
42



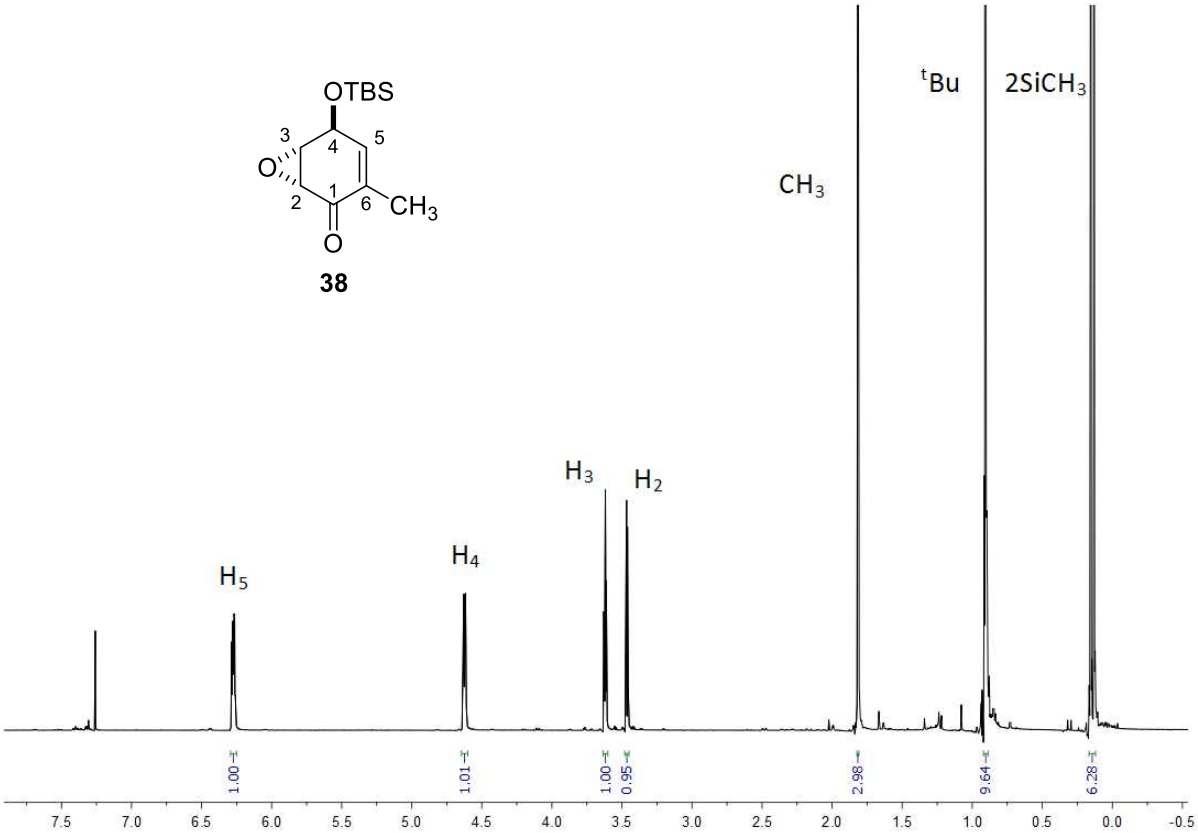
^{1}H-NMR (400 MHz, $CDCl_3$) spectrum of compound **42** (black), n.O.e. spectrum irradiated at 3.59 ppm (red) and n.O.E. spectrum irradiated at 3.67 ppm (blue), n.O.e. spectrum irradiated at 4.45 ppm (green).



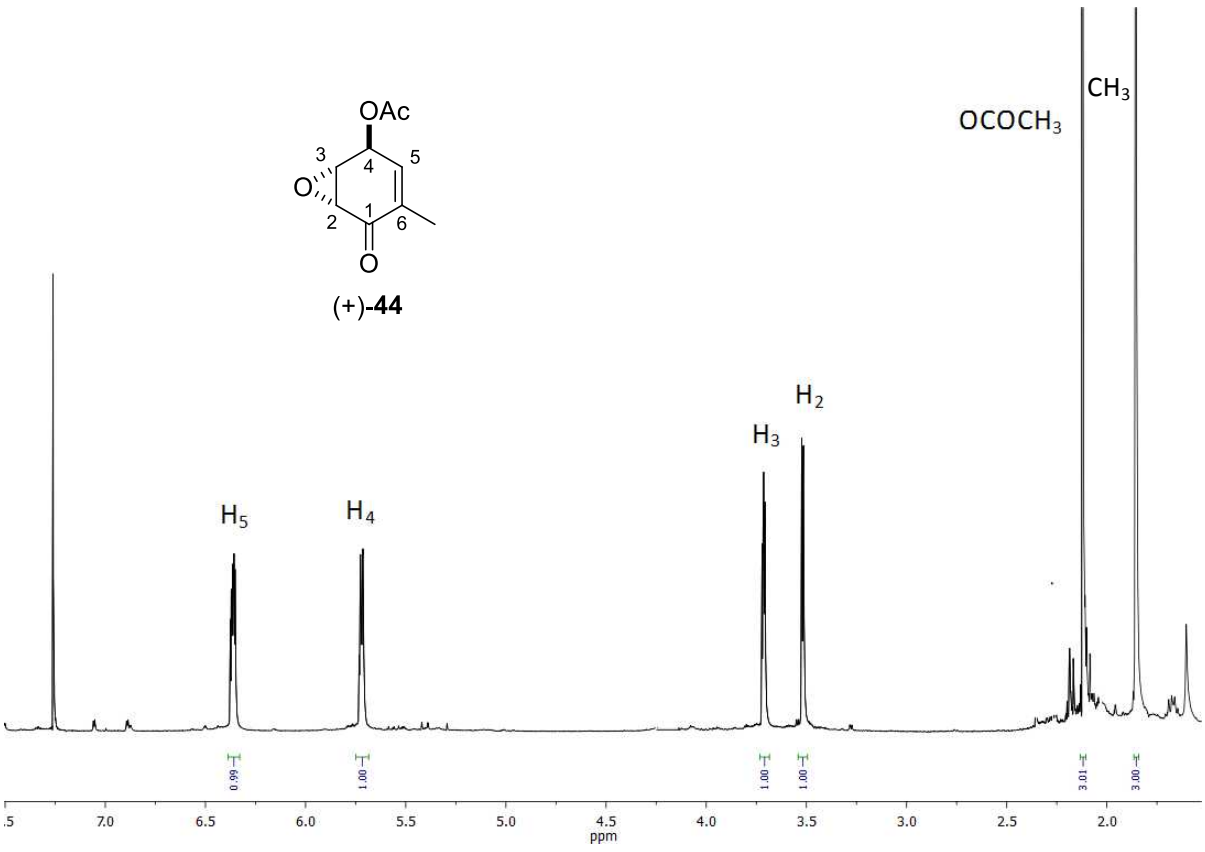
HSQCed ($CDCl_3$, ^{1}H-NMR: 400 MHz. ^{13}C-NMR: 100 MHz. CH, CH_3: red, CH_2: blue)



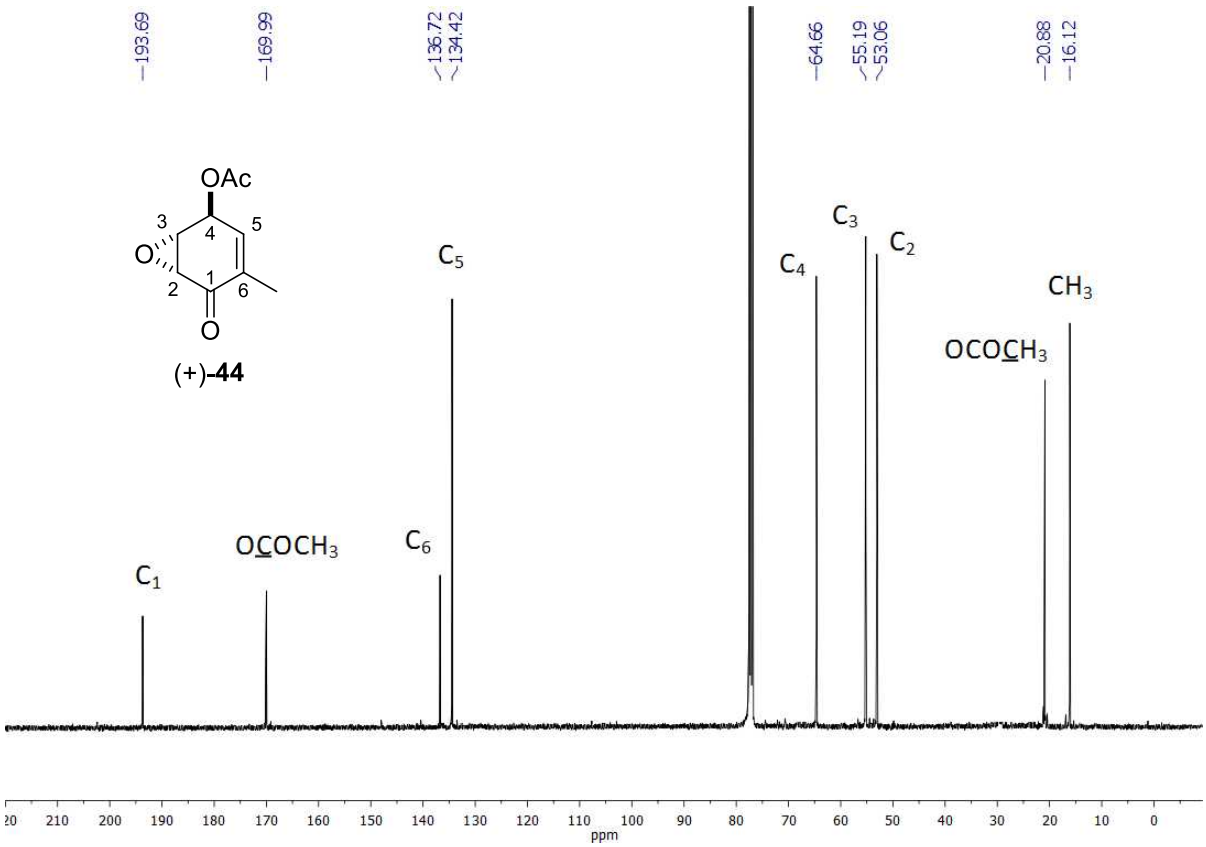
IR



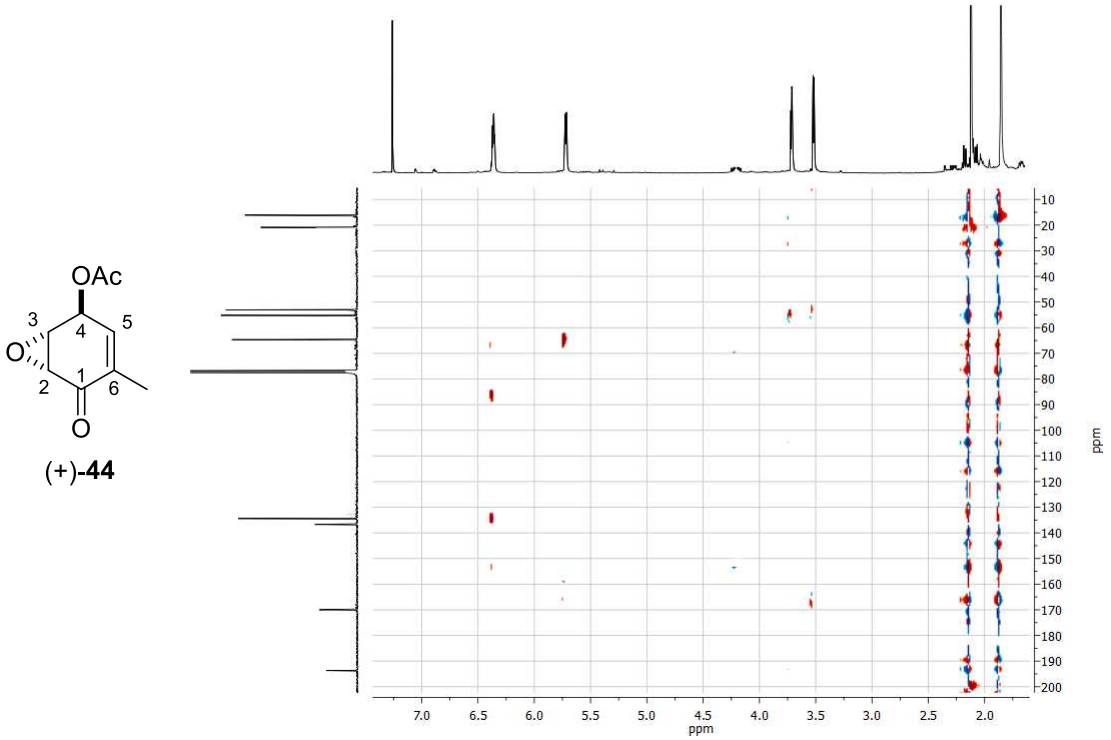
^{1}H-NMR (360 MHz, $CDCl_3$)



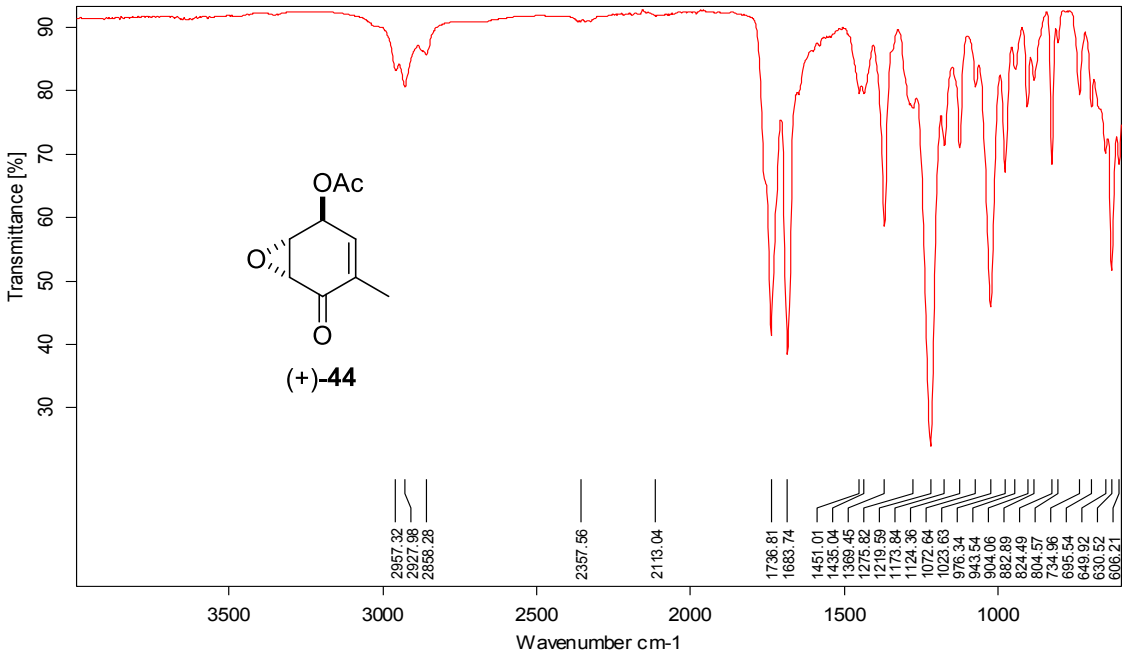
^{1}H-NMR (400 MHz, $CDCl_3$)



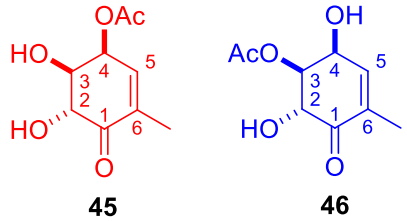
^{13}C-NMR (100 MHz, $CDCl_3$)



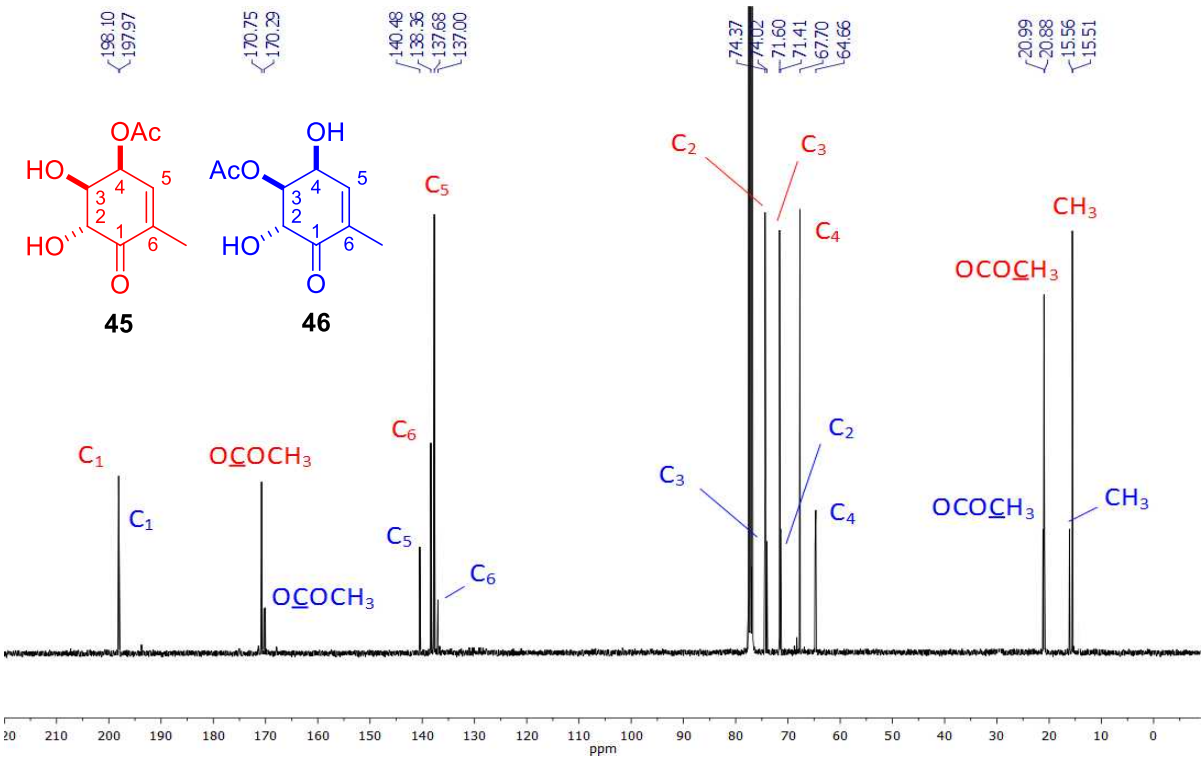
HSQCed ($CDCl_3$, ^{1}H-NMR: 400 MHz. ^{13}C-NMR: 100 MHz. CH, CH_3: red, CH_2: blue)



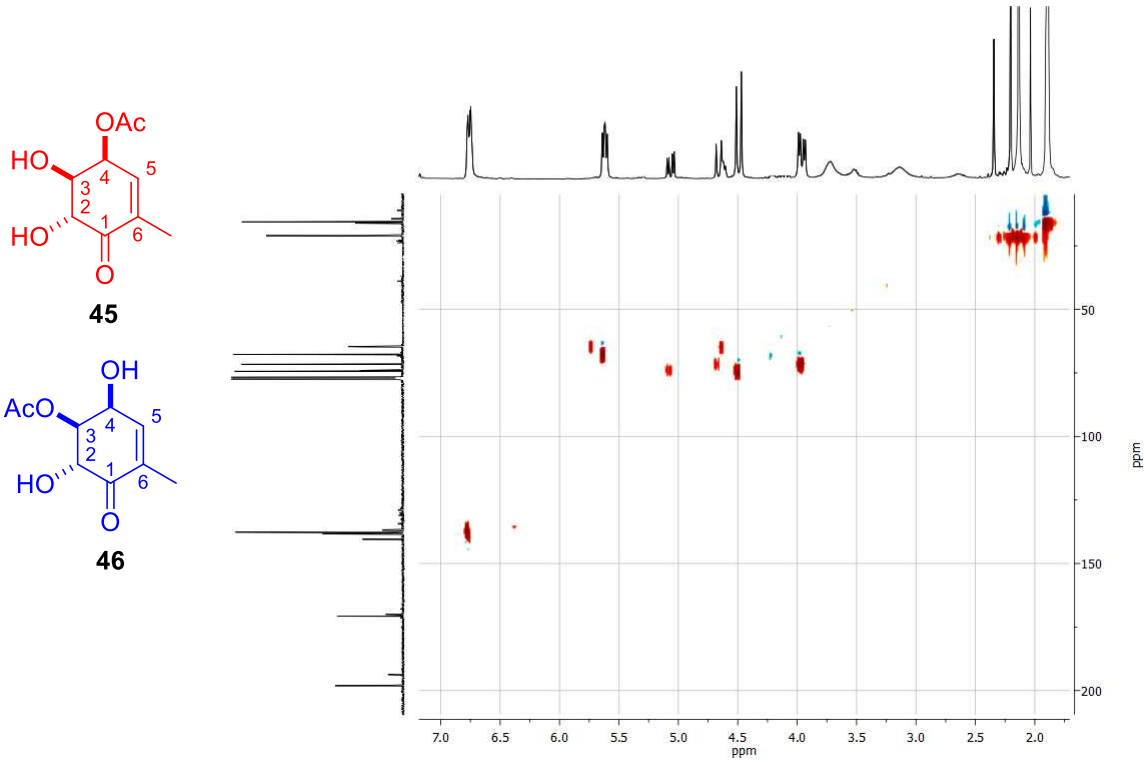
IR



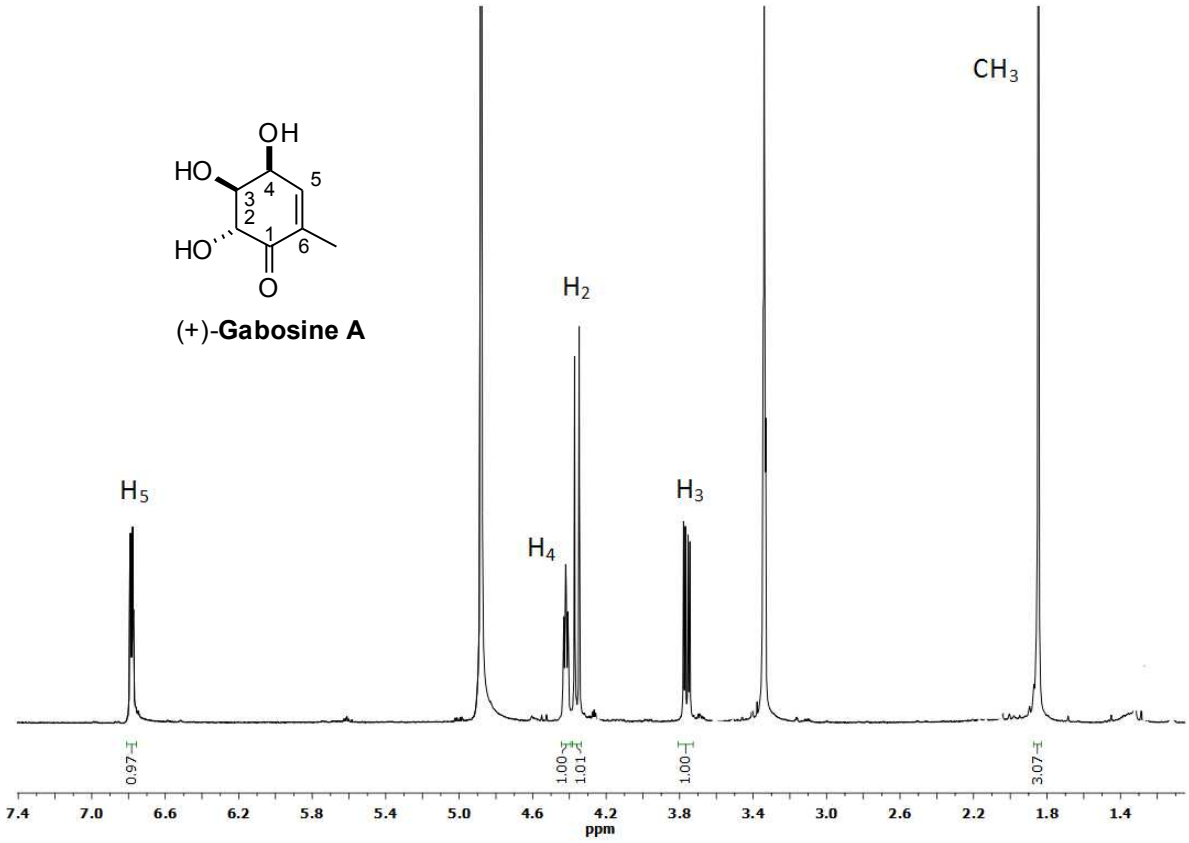
^{1}H-NMR (250 MHz, $CDCl_3$)



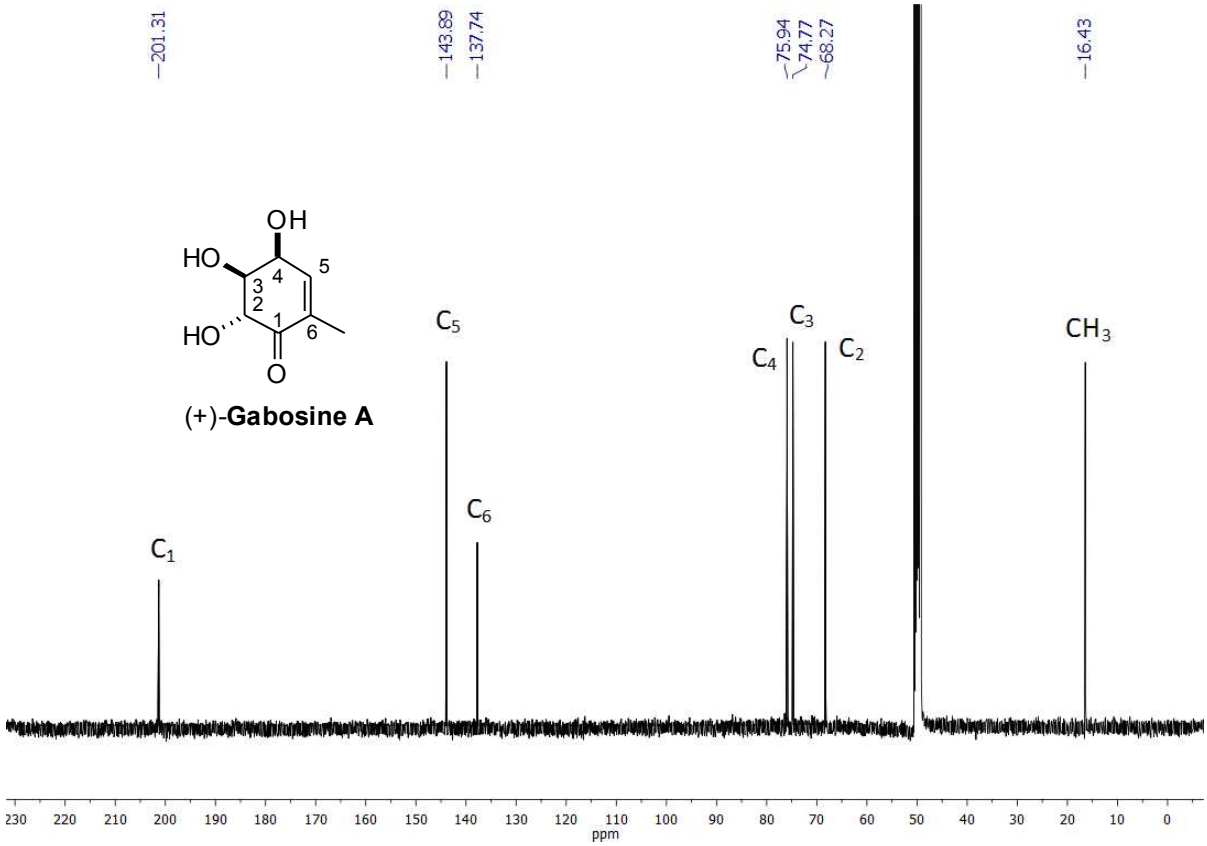
^{13}C-NMR (100 MHz, $CDCl_3$)



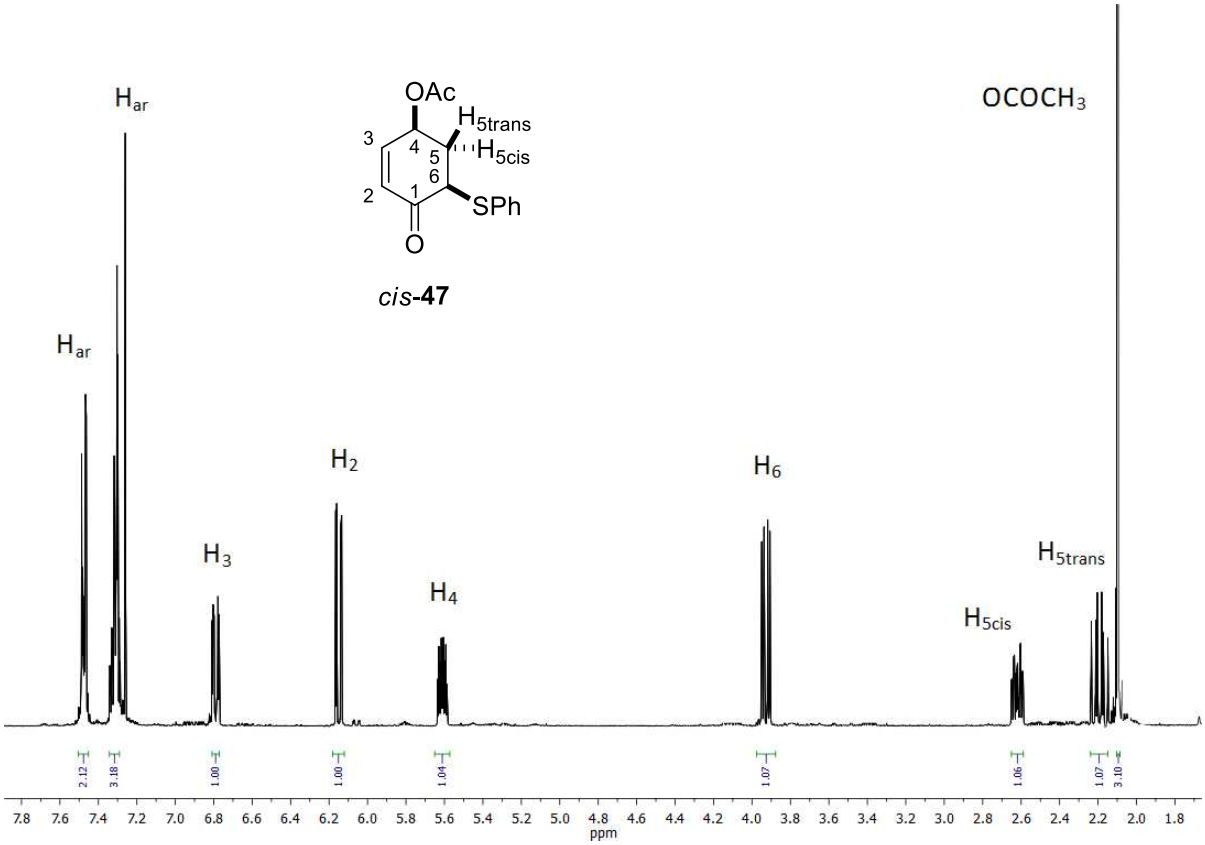
HSQCed ($CDCl_3$, ^{1}H-NMR: 400 MHz. ^{13}C-NMR: 100 MHz. CH, CH_3: red, CH_2: blue)



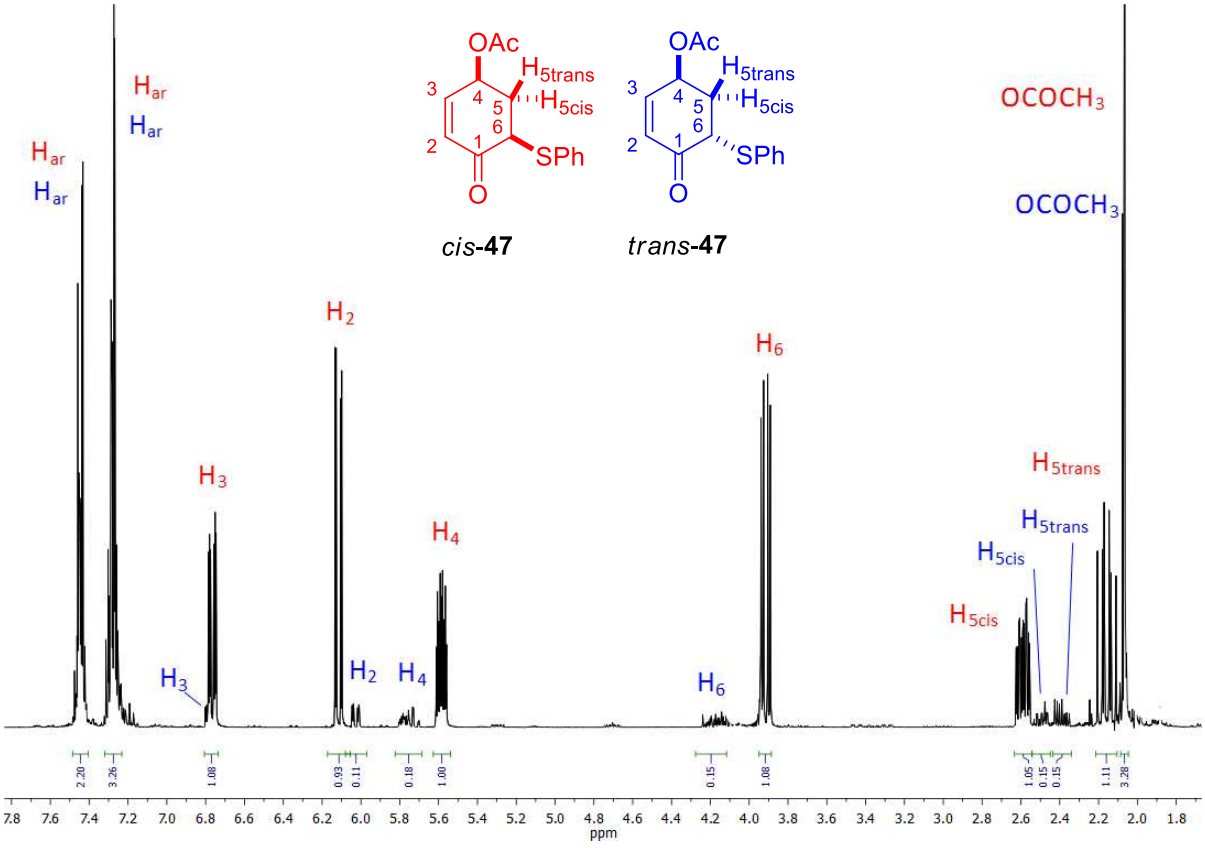
^{1}H-NMR (400 MHz, $CDCl_3$)



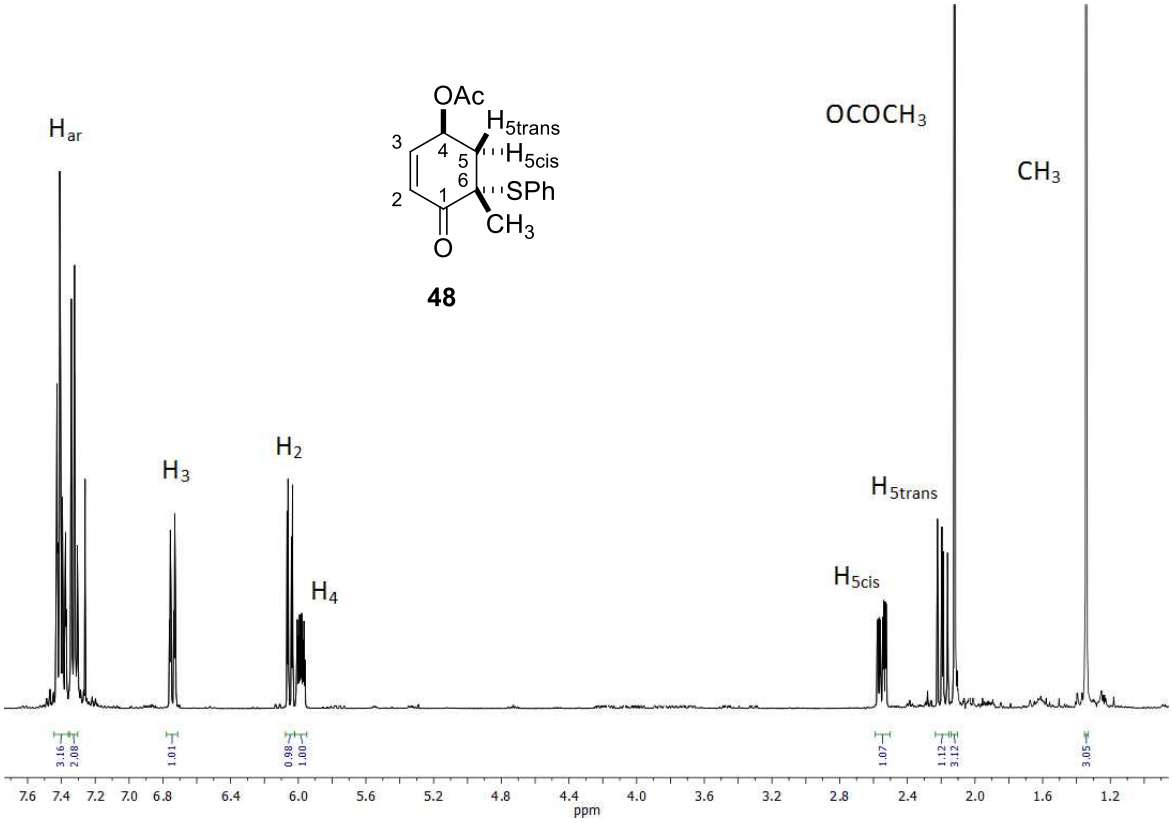
^{13}C-NMR (100 MHz, $CDCl_3$)



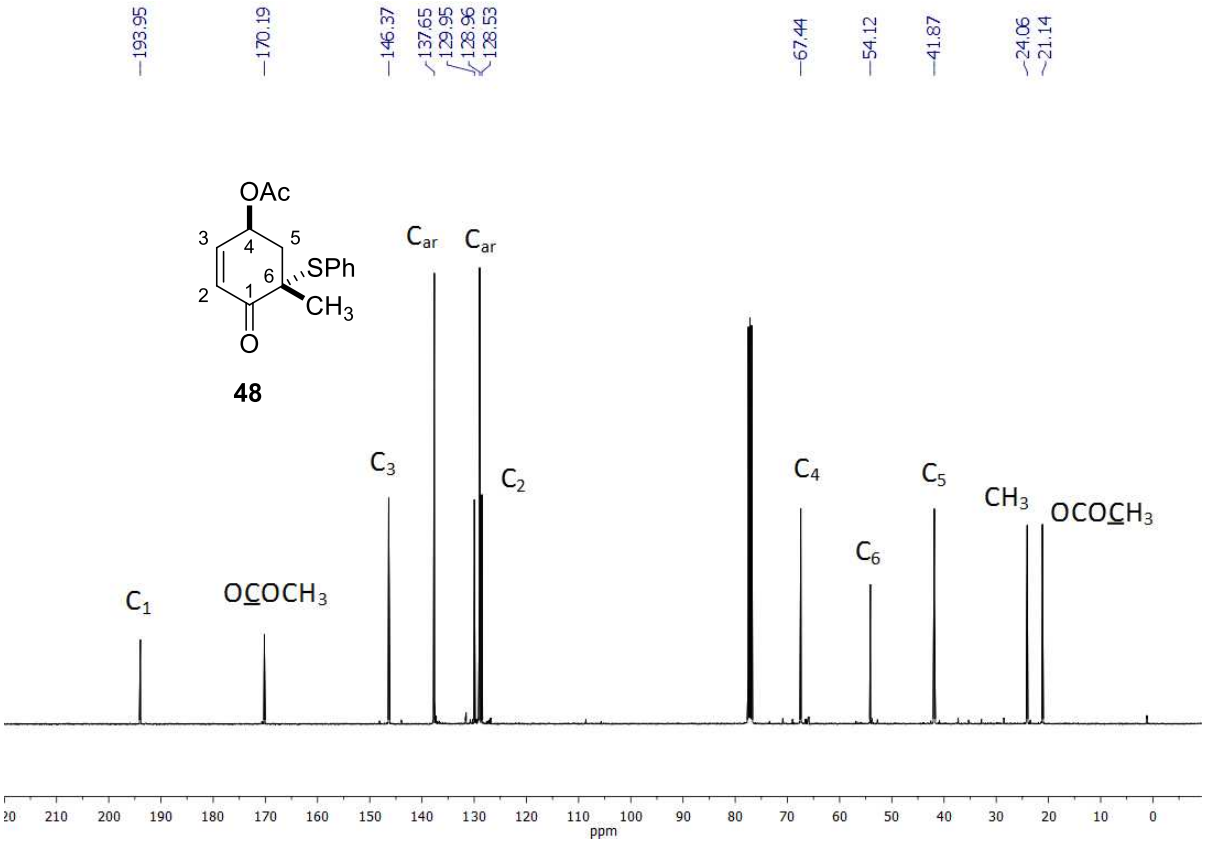
^{1}H-NMR (400 MHz, $CDCl_3$)



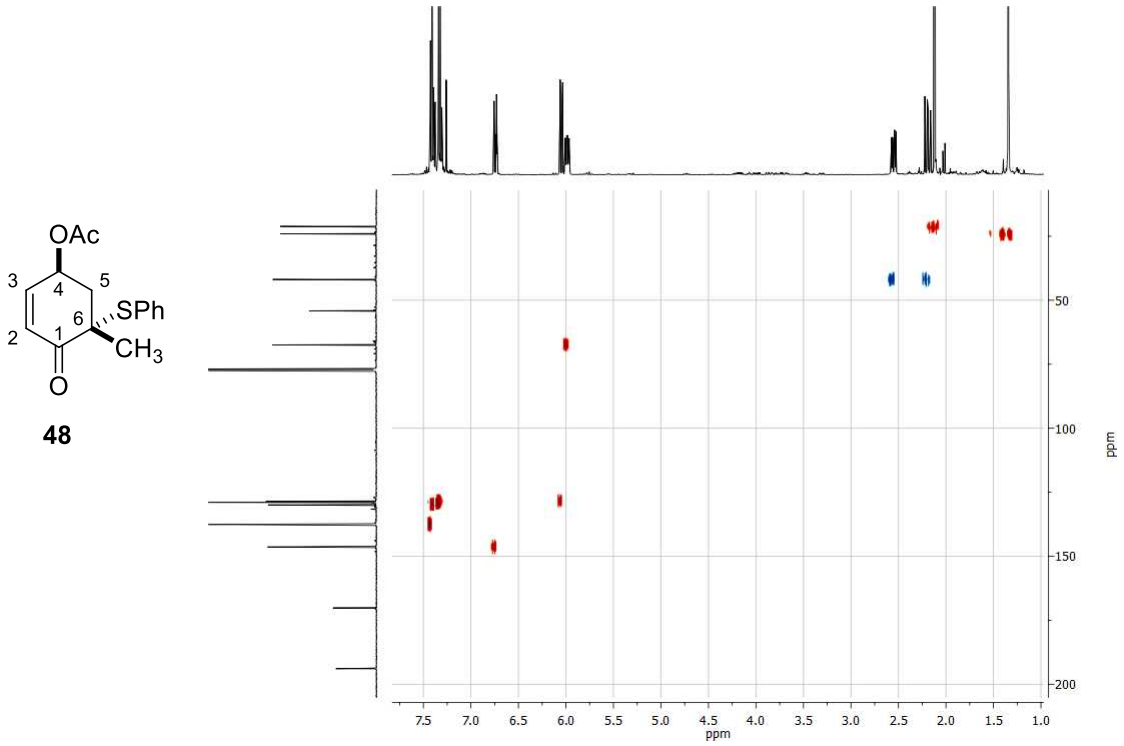
^{1}H-NMR (400 MHz, $CDCl_3$)



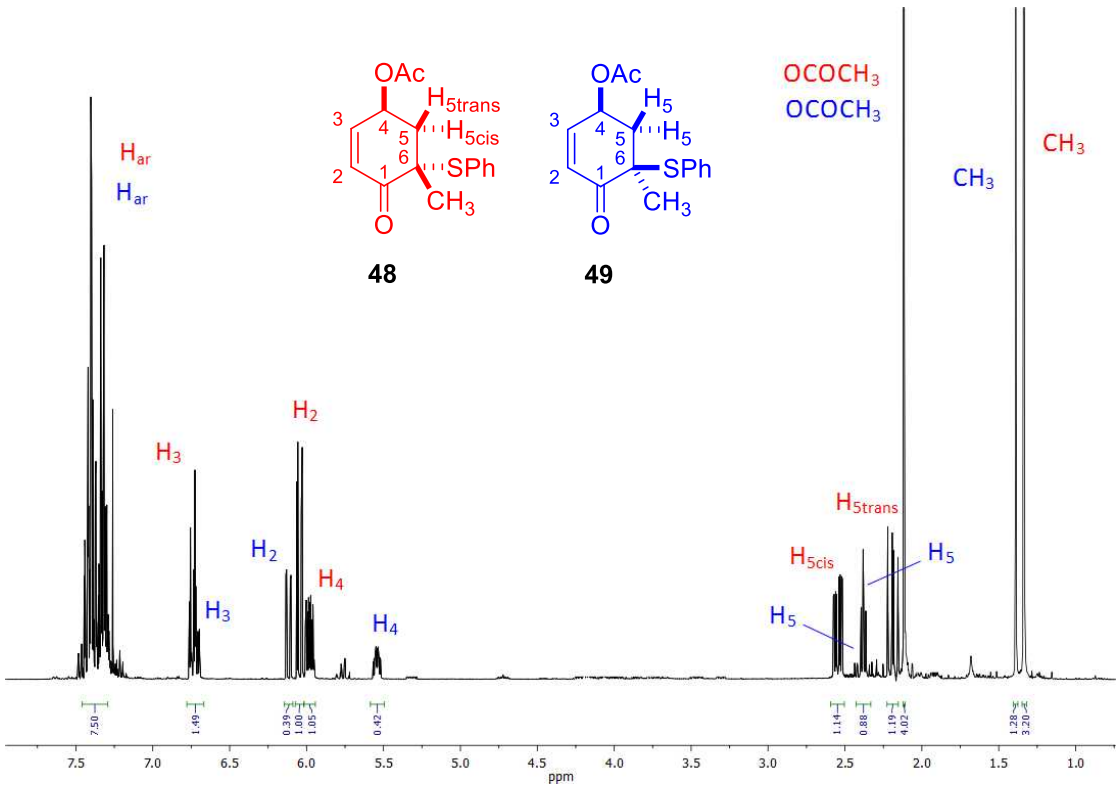
^{1}H-NMR (400 MHz, $CDCl_3$)



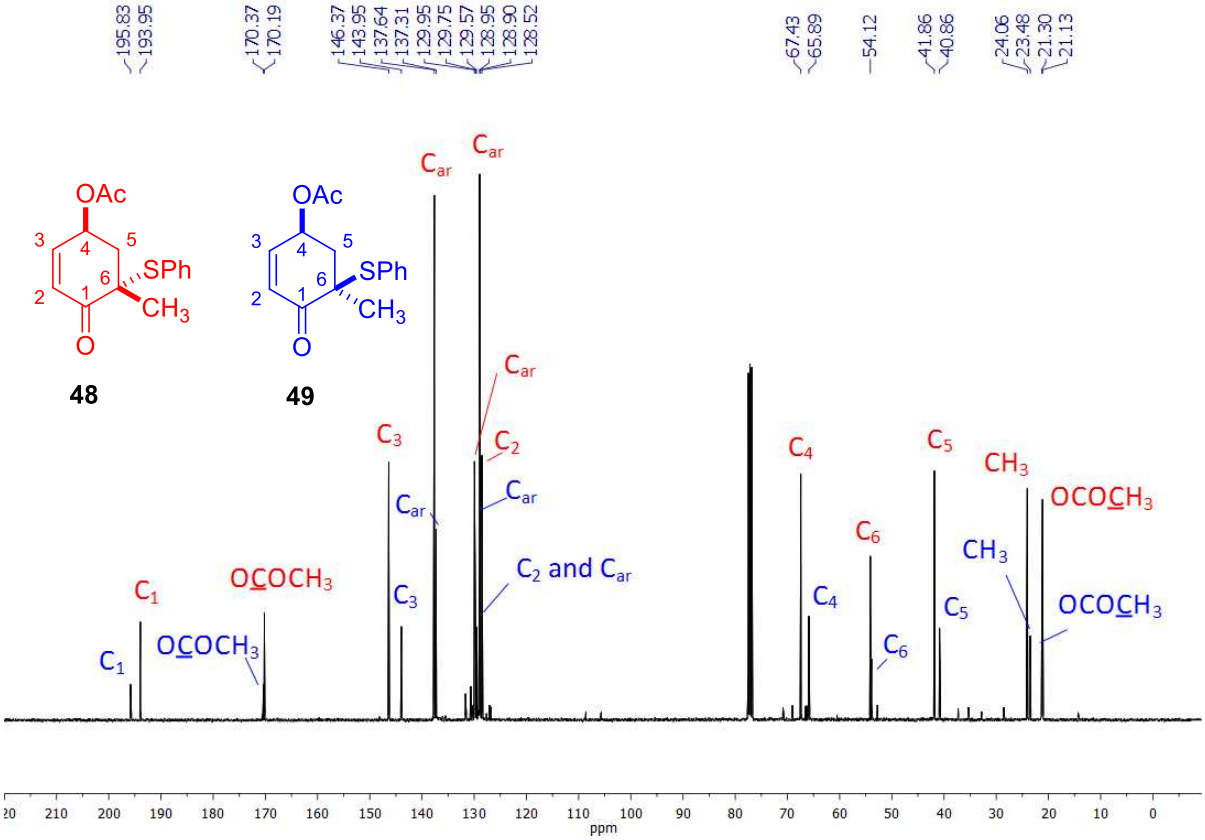
^{13}C-NMR (100 MHz, $CDCl_3$)



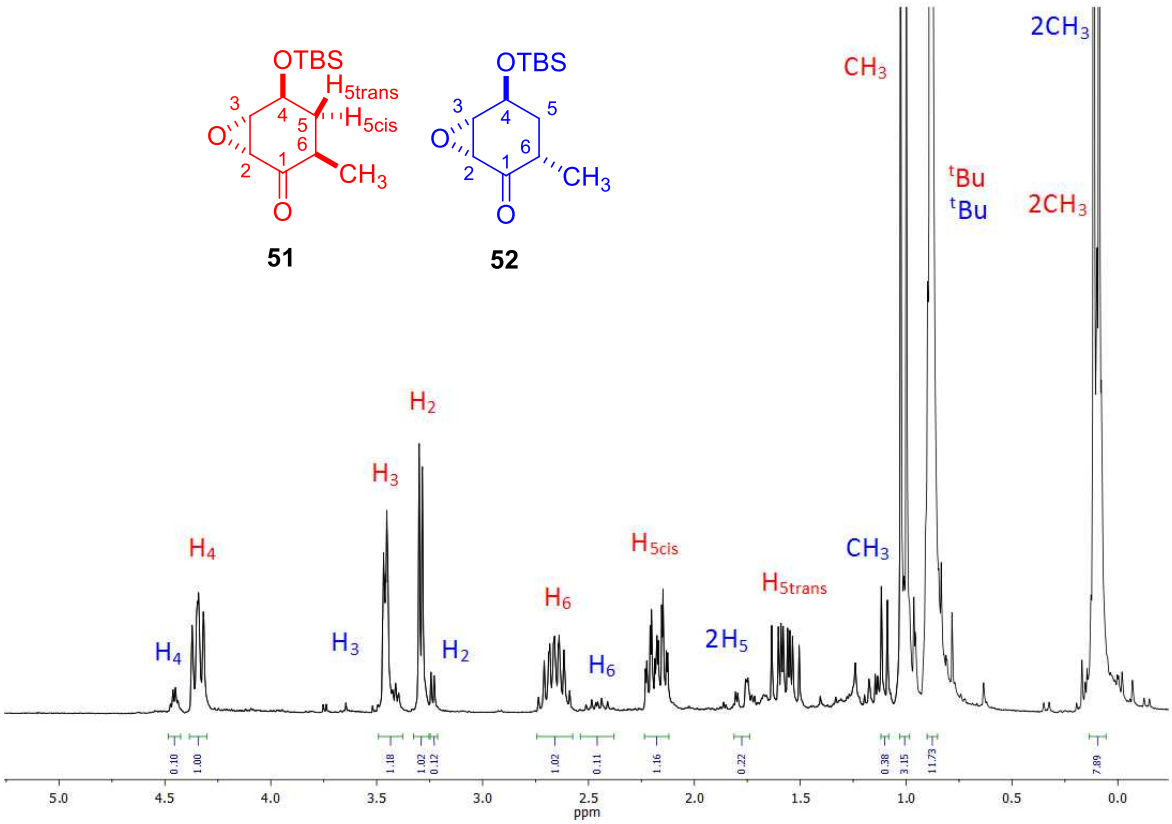
HSQCed ($CDCl_3$, ^{1}H-NMR: 400 MHz. ^{13}C-NMR: 100 MHz. CH, CH_3: red, CH_2: blue)



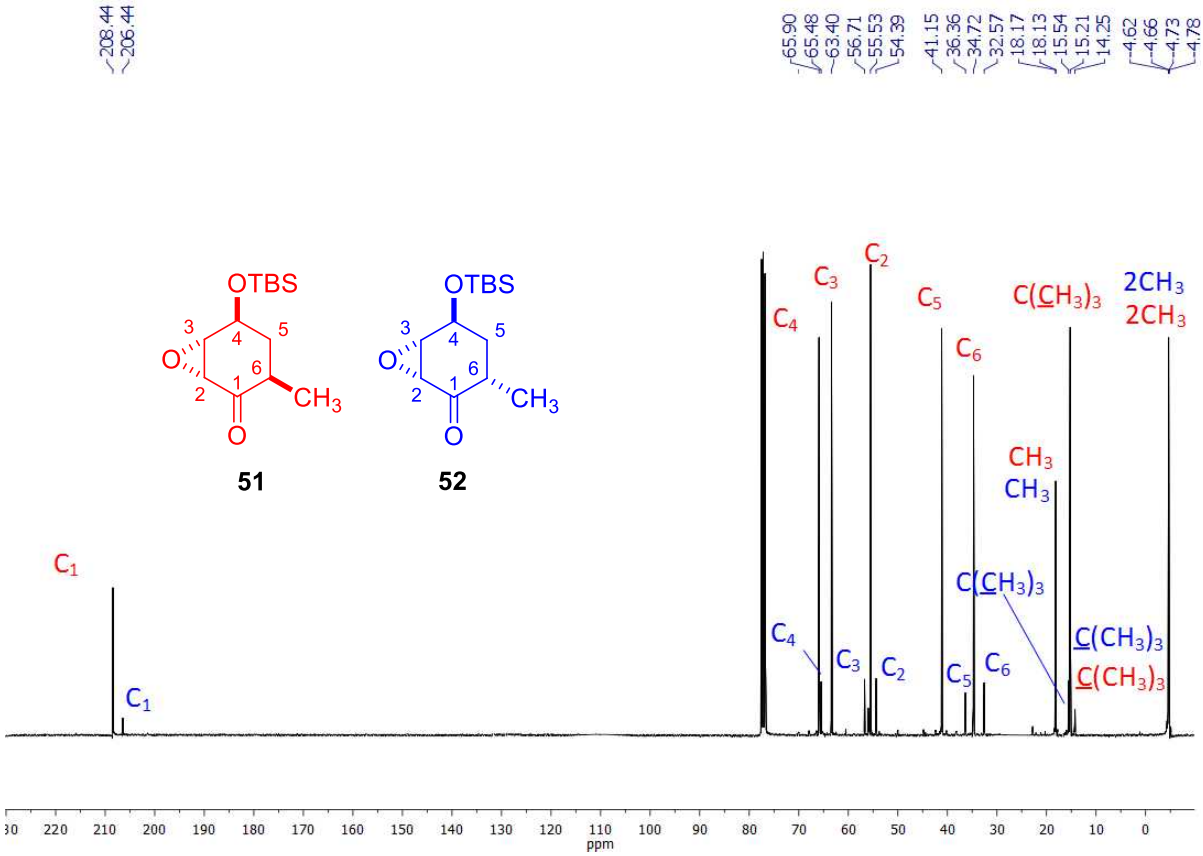
^{1}H-NMR (360 MHz, $CDCl_3$)



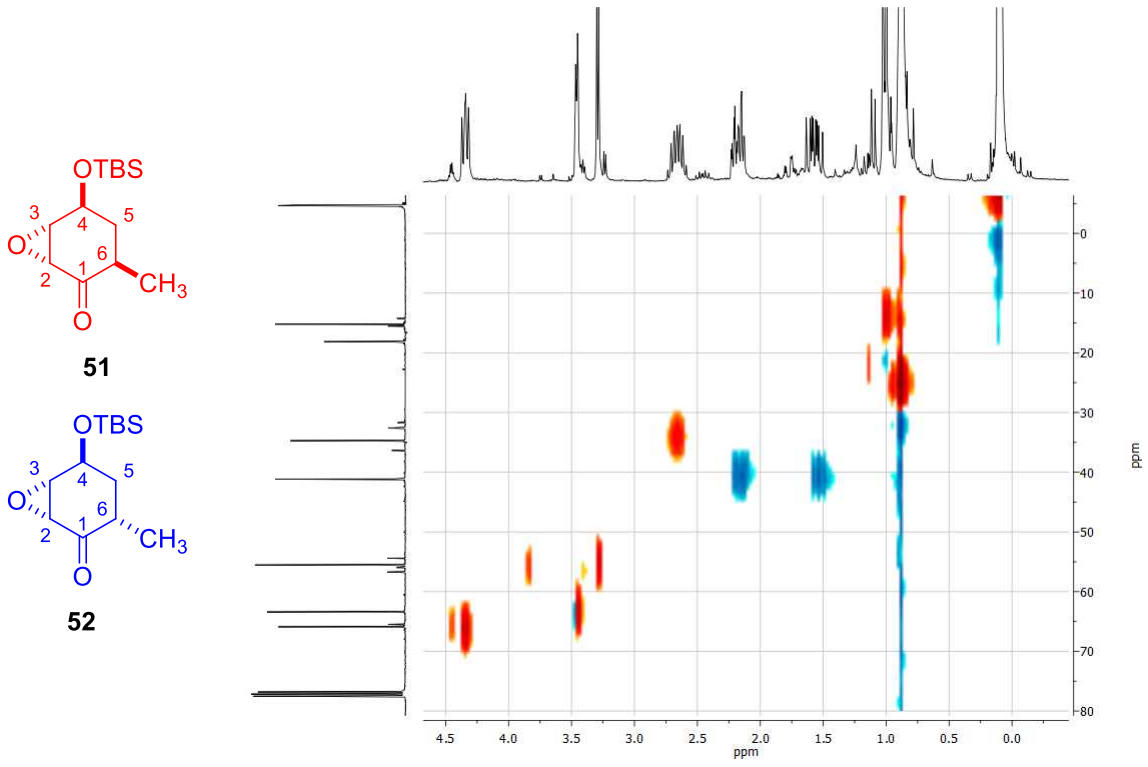
^{13}C-NMR (90 MHz, $CDCl_3$)



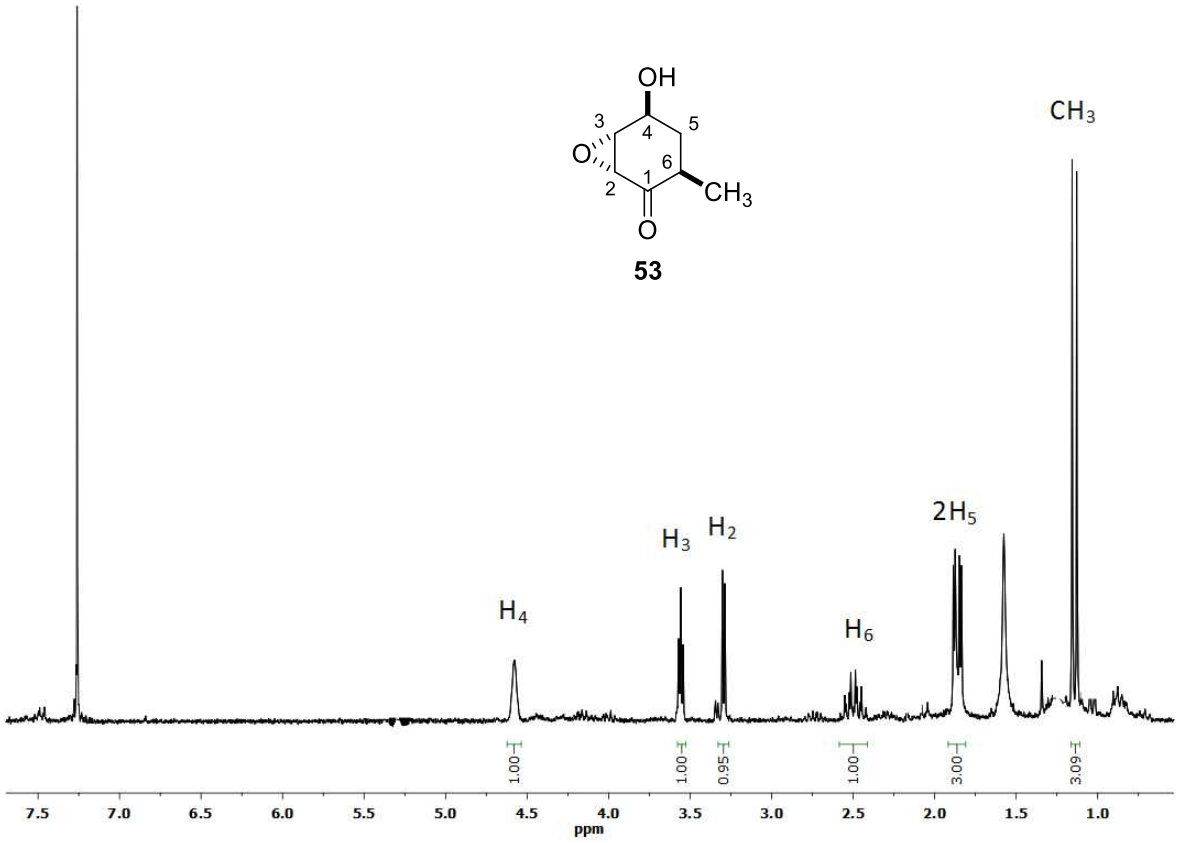
^{1}H-NMR (250 MHz, $CDCl_3$)



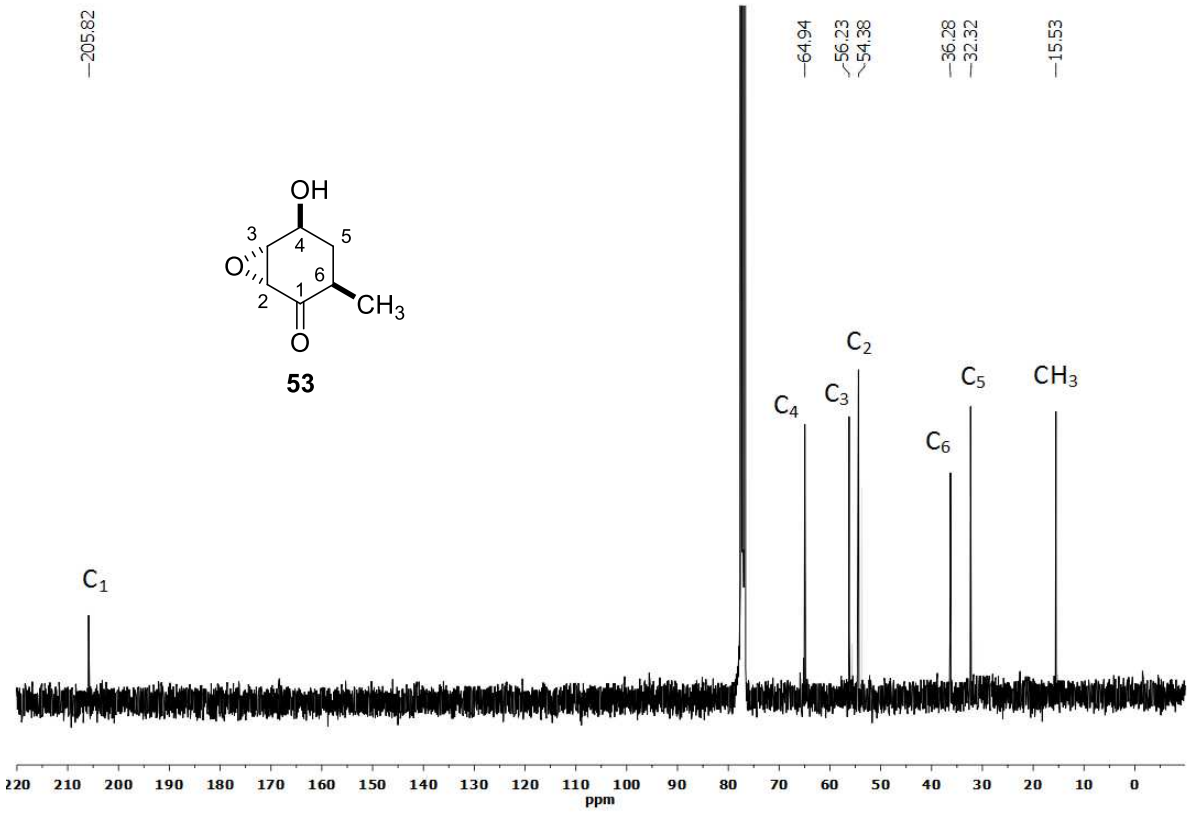
^{13}C-NMR (100 MHz, $CDCl_3$)



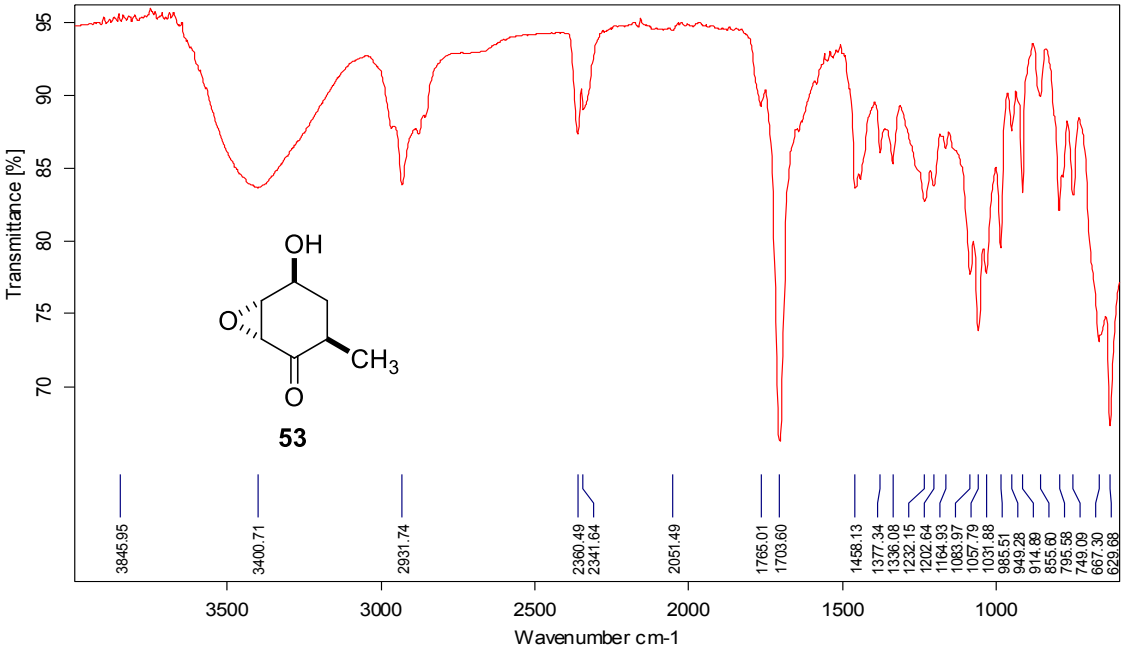
HSQCed ($CDCl_3$, ^{1}H-NMR: 400 MHz. ^{13}C-NMR: 100 MHz. CH, CH_3: red, CH_2: blue)



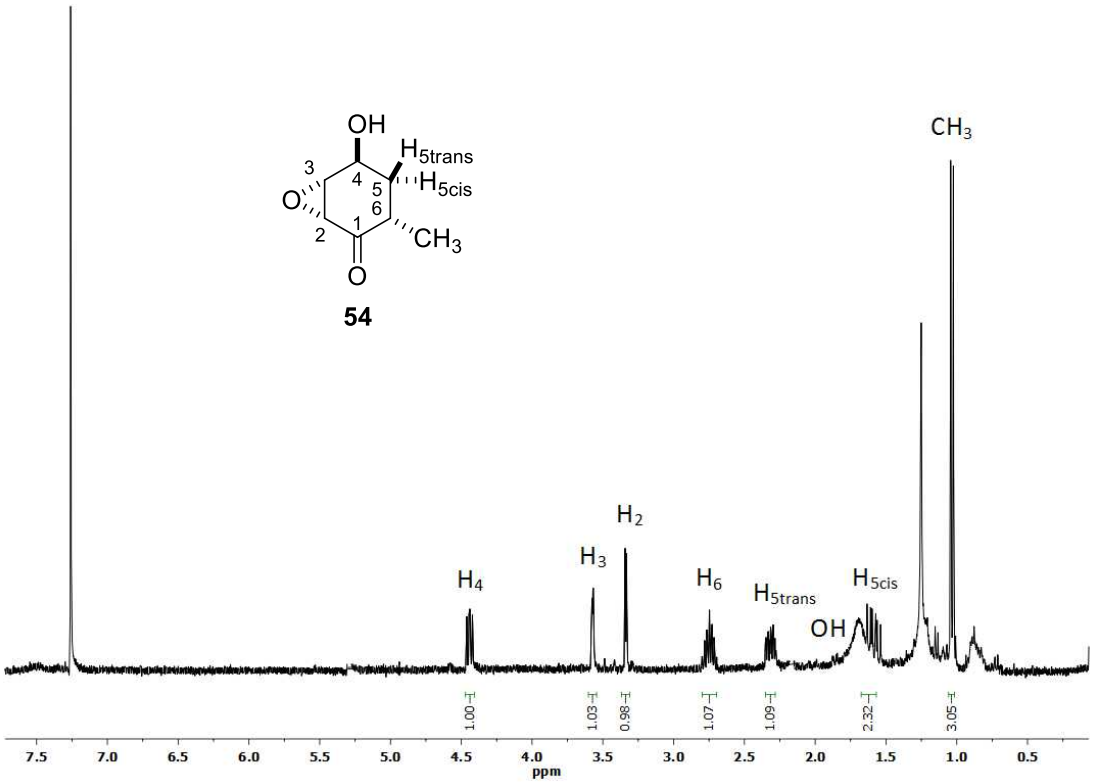
^{1}H-NMR (250 MHz, $CDCl_3$)



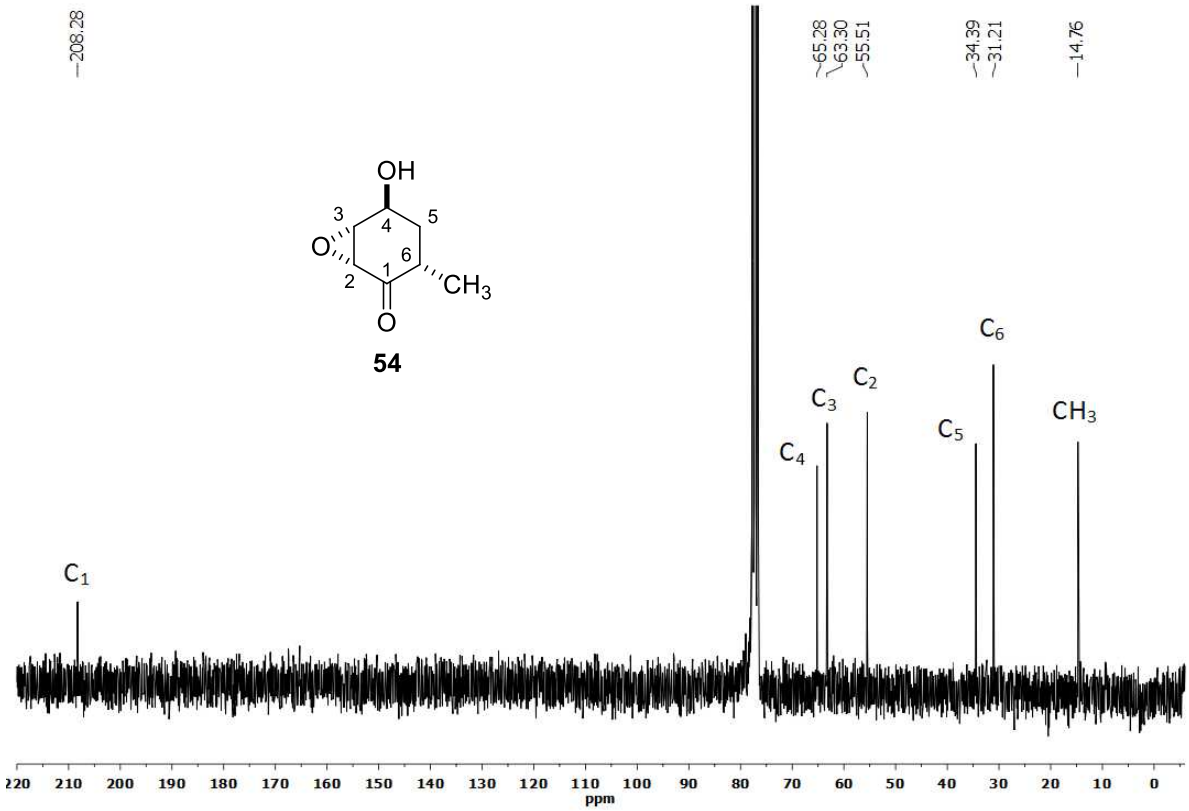
^{13}C-NMR (90 MHz, $CDCl_3$)



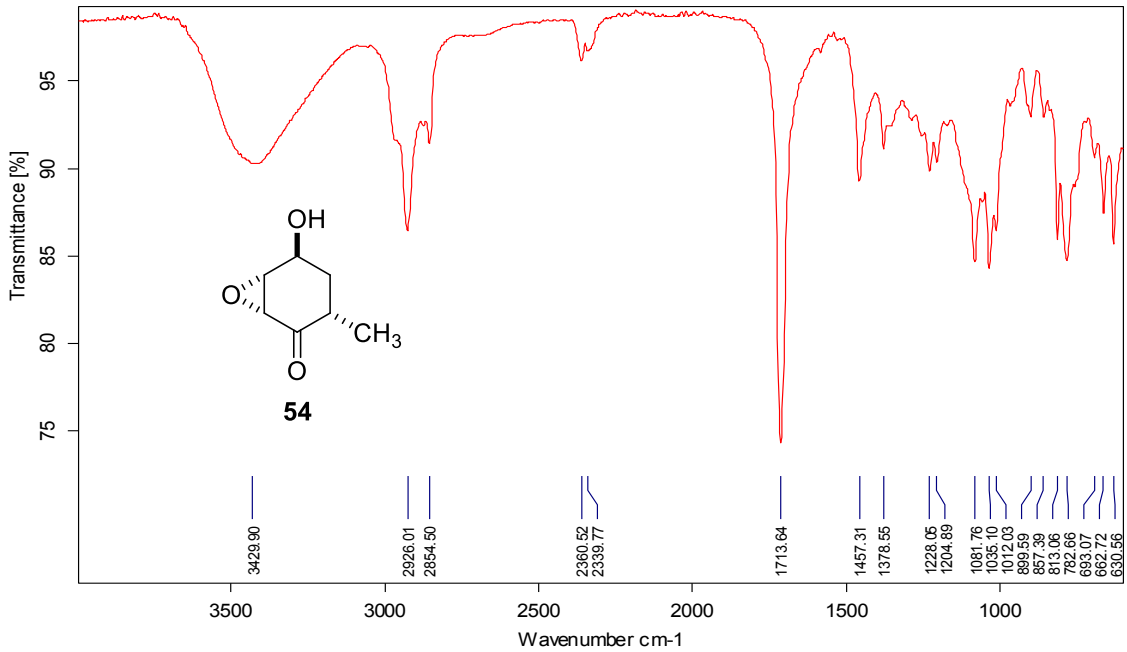
IR



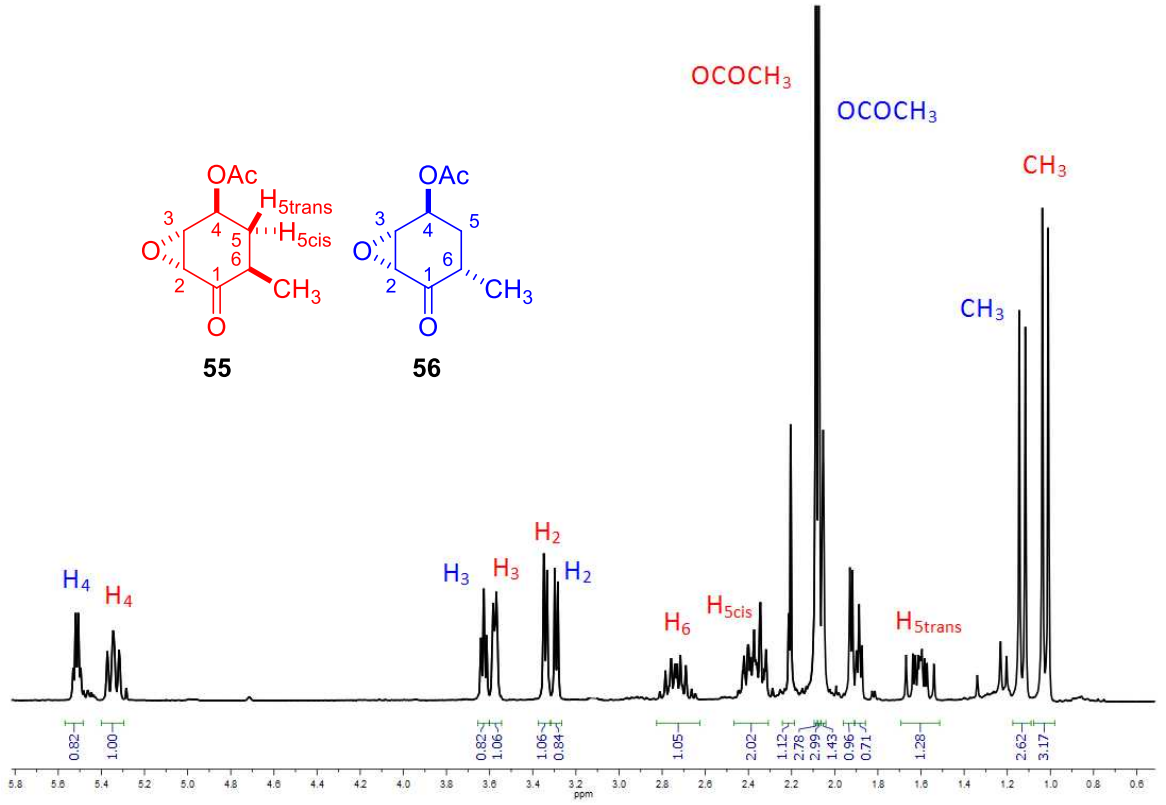
^{1}H-NMR (360 MHz, $CDCl_3$)



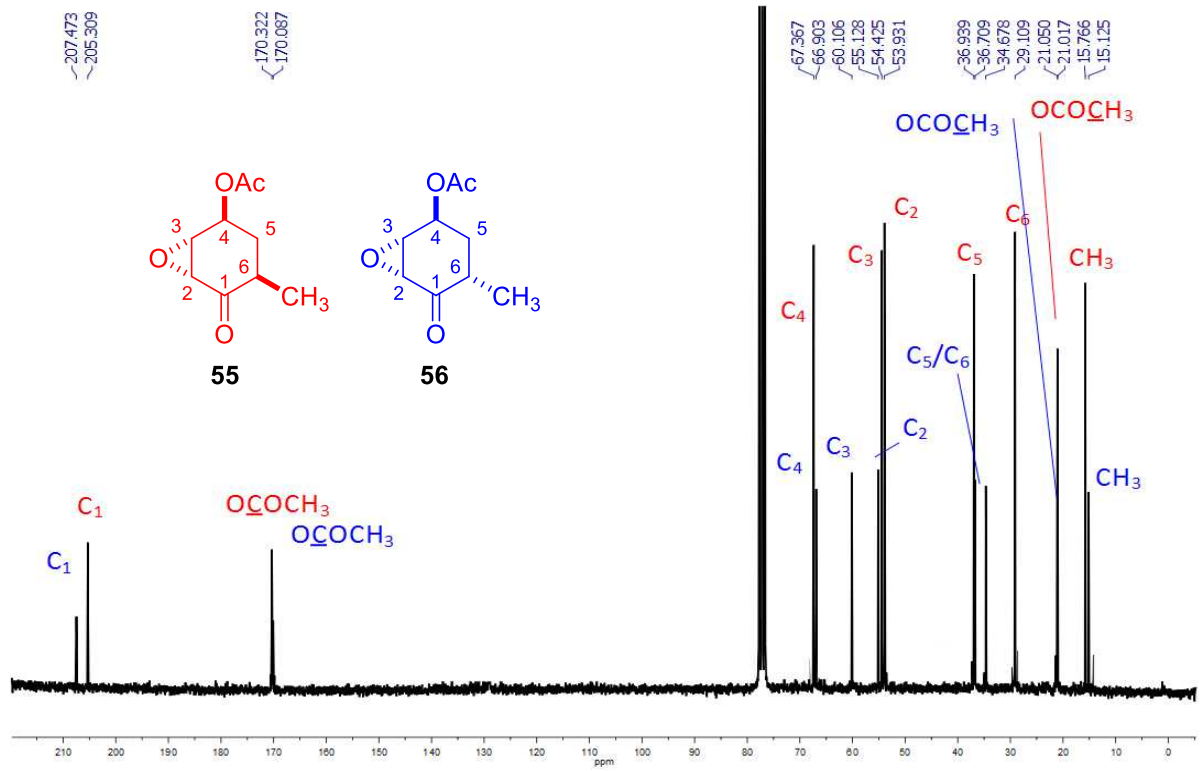
^{13}C-NMR (90 MHz, $CDCl_3$)



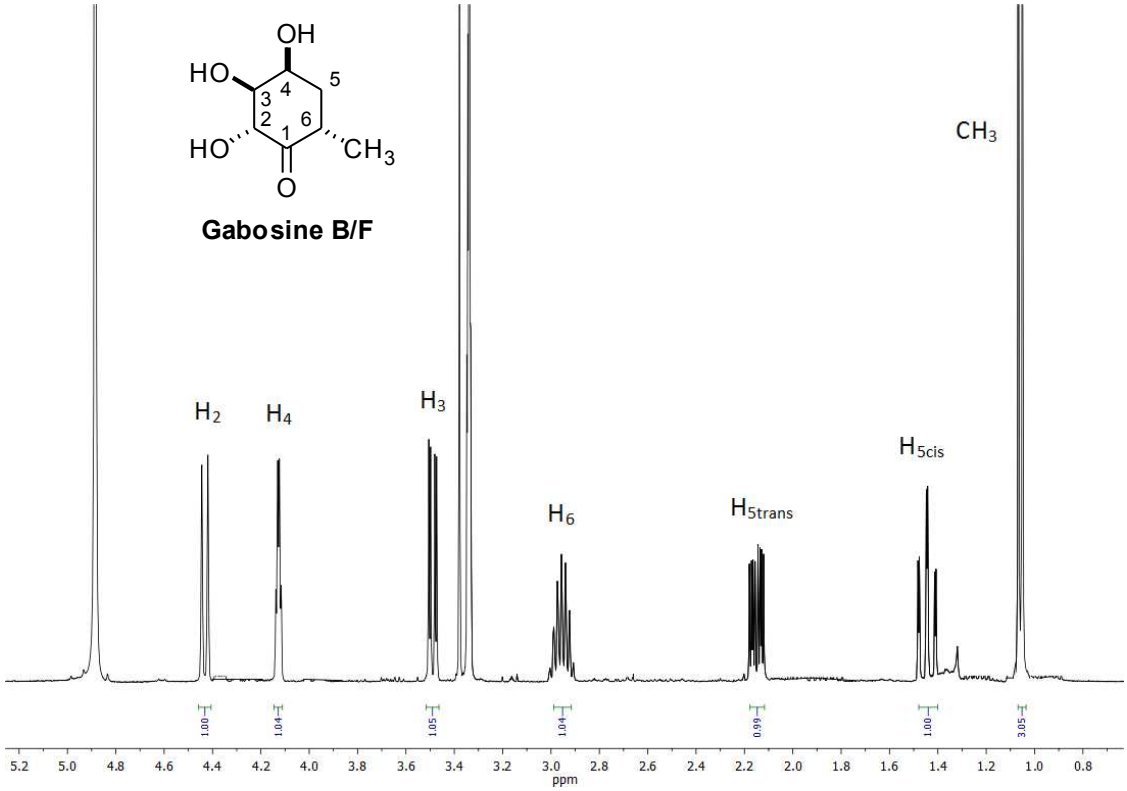
IR



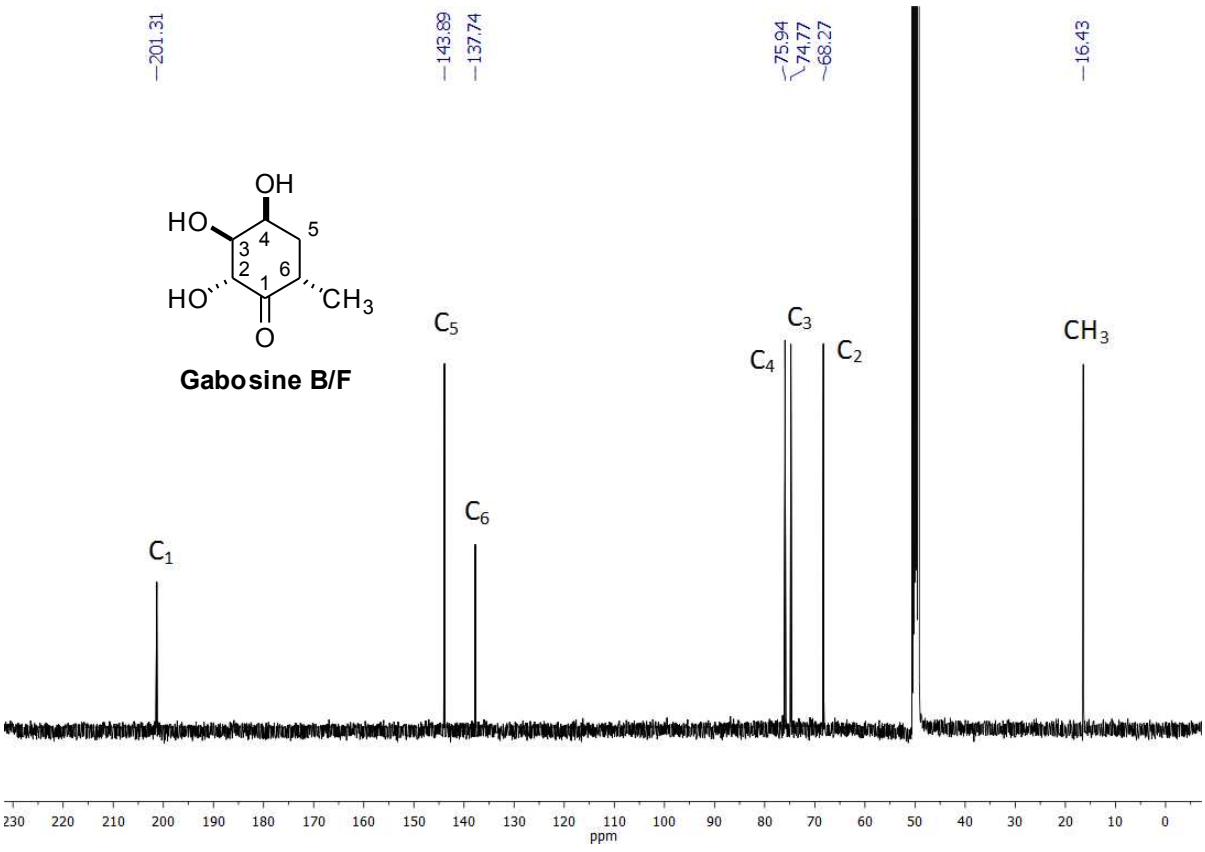
^{1}H-NMR (250 MHz, $CDCl_3$)



^{13}C-NMR (63 MHz, $CDCl_3$)



^{1}H-NMR (400 MHz, MeOD)



^{13}C-NMR (150 MHz, MeOD)

VIII. Index of references

1. Kubler, K. *Arch. Pharm.* (Weinheim) **1909**, *246*, 620-660.

2. (a) Legler, G.; Bause, E. *Carbohydr. Res.* **1973**, *28*, 45-52. (b) Legler, G.; Lotz, W. *Z. Physiol. Chem.* **1973**, *354*, 243-254. (c) Umezawa, S. *Adv. Carbohydr. Chem. Biochem.* **1974**, *30*, 111-182. (d) Atsumi, S.; Umezawa, K.; Iinuma, H.; Naganawa, H.; Nakamura, H.; Iitaka, Y.; Takeuchi, T. *J. Antibiot.* **1990**, *43*, 49-53 (e) Mahapatra, T.; Nanda, S. *Tetrahedron: Asymmetry* **2010**, *21*, 2199-2205.

3. Mann. J. *Secondary Metabolism*, Oxford University Press, Oxford **1987**.

4. First isolation of gabosine C, named KD16-U1: Tatsuta, K.; Tsuchiya, T.; Mikami, N.; Umezawa, S.; Umezawa, H.; Naganawa, H. *J. Antibiot.* **1974**, *27*, 579-586.

5. Takeuchi, T.; Chimura, H.; Hamada, M.; Umezawa, H.; Yoshioka, O. *J.Antibiot.* **1975**, *28*, 737-742.

6. Isolation and structural assignment of gabosines A-K: Bach, G.; Breiding,-Mack, S.; Grabley, S.; Hamman, P.; Hütter, K.; Thiericke, R.; Uhr, H.; Wink, J.; Zeeck, A. *Liebigs Ann. Chem.* **1993**, 241-250.

7. Synthetic studies indicate that the structure of gabosine K needs to be revised: Metha, G.; Lakshminath, S. *Tetrahedron Lett.* **2000**, *41*, 3509-3512.

8. Isolation and structural assignment of gabosines L, N and O: Tang, Y.-Q.; Maul, C.; Hoefs, R.; Sattler, I.; Grabley, S.; Feng, X.-Z.; Zeeck, A.; Thiericke, R. *Eur. J. Org. Chem*. **2000**, 149-153.

9. Banwell, M. G.; Bray, A. M. Wong, D. *J. New J. Chem.* **2001**, *25*, 1351-1354 (Gabosine A).

10. Chimura, H.; Nakamura, J.; Takita, T.; Takeuchi, T.; Umezawa, H.; Kato, K.; Saito, S.; Tomisawa, T.; Iitaka, Y. *J. Antibiot.* **1975**, *28*, 743-748.

11. (a) Donhoe, T. J.; Blades, K.; Helliwell, M.; Waring, M. J. *Tetrahedron Lett.* **1998**, *39*, 8755-8758. (b) Yamada, T.; Iritani, M.; Ohishi, H.; Tanaka, K.; Minoura, K.; Doi, M.; Numata, A. *Org. Biomol. Chem.* **2007**, *5*, 3979-3986.

12. Zhang, H.; Xue, J.; Wu, P.; Xu, L.; Xie, H.; Wei, X. *J. Nat. Prod.* **2009**, *72*, 265-269.

13. Sakamura, S.; Ito, J.; Sakai, R. *Agric. Biol. Chem.* **1970**, *34*, 153-155; ibid. **1971**, *35*, 105-110.

14. (a) Closse, A.; Mauli, R.; Sigg, H. P. *Helv Chim. Acta* **1965**, *49*, 204-213. (b) Sakamura, S.; Niki, H.; Obata, Y.; Sakai, R.; Matsumoto, T. *Agric. Biol. Chem.* **1969**, *33*, 698-703.

15. (a) Yamamoto, I.; Mizuta, E.; Henmi, T.; Yamano, T.; Yamatodani, S. *Takeda Kenkyusho Ho* **1973**, *32*, 532-538. *Chem. Abstr.* **1974**, *80*, 106812. (b) Venkatasubbaiah, P.; Tisserat, N. A.; Chilton, W. S. *Mycopathologia* **1994**, *128*, 155-159.

16. (a) Nakamori, K.; Matsuura, H.; Yoshihara, T.; Ichihara, A.; Koda, Y. *Phytochemistry* **1994**, *35*, 835-839. (b) Yoshihara T.; Ohmori, F.; Nakamori, K.; Amanuma, M.; Tsutsumi, T.; Ichihara, A.; Matsuura, H. *J. Plant Growth Reg.* **2000**, *19*, 457-461.

17. (a) Kawazu, K.: Kobayashi, A.; Oe, K. **Jpn. Kokai Tokkyo Koho 03 41,075, 1991**; *Chem. Abstr.* **1991**, *115*, 181517k. (b) Nagata, T.; Ando, Y.; Hirrota, A. *Biosci. Biotechnol. Biochem.* **1992**, *56*, 810-811.

18. Garlaschelli, L.; Magistrali, E.; Vidari, G.; Zuffardi, O. *Tetrahedron Lett.* **1995**, *36*, 5633-5636.

19. Higa, T.; Okuda, R. K.; Severns, R. M.; Scheuer, P. J.; He, C. H.; Changfu, X.; Clardy, J. *Tetrahedron* **1987**, *43*, 1063-1070.

20. Lee, M.; Fantini, A. A.; Morton G. O.; James, J. C.; Borders, D. B.; Testa, R. T. *J. Antibiot.* **1984**, *37*,1149-1152.

21. (a) Buzzetti, F.; Gaümann, E.; Hütler, R.; Séller-Schierlein, W.; Neipp, L.; Prelog, V.; Zähner, H. *Pharm. Acta Helv.* **1963**, *38*, 871. (b) Scröder, K.; Zeeck, A. *Tetrahedron Lett.* **1973**, 4495-4498. (c) Alcaraz, L.; Macdonald, G.; Ragot, J. P.; Lewis, N.; Taylor, R. J. K. *J. Org. Chem*. **1998**, *63*, 3526-3527.

22. (a) Weber, H. A.; Bänziger, N. C.; Gloer, J. B.; *J. Am. Chem. Soc.* **1990**, *112*, 6718-6719. (b) Weber, H.A.; Gloer, J.B. *J. Org. Chem.* **1991**, *56*, 4355-4360.

23. (a) Krohn, K.; Michel, A.; Florke, U.; Aust, H.J.; Dräger, S.; Schulz, B. *Liebigs Ann. Chem.* **1994**, 1099. (b) Singh, S. B.; Zink, D. L.; Liesch, J. M.; Ball, R. G.; Goetz, M. A.; Bolessa, E. A.; Giacobbe, R. A.; Silverman, K. C.; Bills, G. F.; Pelaez, F.; Cascales, C.; Gibbs, J. B.; Lingham, R. B. *J. Org. Chem.* **1994**, *59*, 6296-6302. (c) Krohn, K.; Beckmann, K.; Flörke, U.; Aust, H.-J.; Dräger, S.; Schulz, B.; Busemann, S.; Bringmann, G. *Tetrahedron* **1997**, *53*, 3101-3110.

24. (a) Fehlhaber, H. W.; Koegler, H.; Mukhopadhyay, T.; Vijayakumar, E. K. S.; Ganguli, G. N. *J. Am. Chem. Soc.* **1988**, *110*, 8242-8244. (b) Roy, T.; Mukhopadhyay, T.; Reddy, G. C. S.; Desikan, K. R.; Rupo, R. H.; Ganguli, B. N. *J. Antibiot.* **1988**, *41*, 1780-1784. (c) Fehlaber, H. W.; Kogler, H.; Mukhopadhyay, T.; Vijayakumar, E. K. S.; Roy, K.; Rupp, R. H.; Ganguli, B. N. *J. Antibiot.* **1988**, *41*, 1785-1794.

25. Ragot, J.P.; Alcaraz, M.-L.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 4921-4924.

26. Amano, S.; Ogawa, N.; Ohtsuka, M.; Ogawa, S.; Chida, N. *Chem, Commun.* **1998**, 1263-1264.

27. Taber, D. F.; Christos, T. E.; Rheingold, A. L.; Guzei, I. A. *J. Am. Chem. Soc.* **1999**, *121*, 5589-5590.

28. a) de March, P.; Escoda, M.; Figueredo, M.; Font, J. *Tetrahedron Lett.* **1995**, *36*, 8665-8668. (b) de March, P.; Escoda, M.; Figueredo, M.; Font, J.; Medrano, J. *An. Quim. Int. Ed.* **1997**, *93*, 81-87.

29. de March, P.; Escoda, M.; Figueredo, M.; Font, J.; Álvarez-Larena, A.; Piniella, J. F. *J. Org. Chem.* **1995**, *60*, 3895-3897.

30. (a) de March, P.; Escoda, M.; Figueredo, M.; Font, J.; Álvarez-Larena, A.; Piniella, J. F. *J. Org. Chem.* **1997**, *62*, 7781-7787. (b) de March, P.; Figueredo, M.; Font, J.; Rodríguez, S. *Tetrahedron* **2000**, *56*, 3603-3609.

31. Busqué, F.; de March, P.; Escoda, M.; Figueredo, M.; Font, J.; Rodríguez, S. *Tetrahedron: Asymetry* **2001**, *12*, 3077-3080.

32. (a) Cantó, M.; de March, P.; Figueredo, M.; Font, J.; Rodríguez, S.; Álvarez-Larena, A.; Piniella, J. F. *Tetrahedron: Asymmetry* **2002**, *13*, 455-459. (b) Busqué, F.; Cantó, M.; de March, P.; Figueredo, M.; Font, J.; Rodríguez, S. *Tetrahedron: Assymetry* **2003**, *14*, 2021-2032. (c) Bardagí, G. G.; Cantó, M.; Alibés, R.; Bayón, P.; Busqué, F.; de March, P.; Figueredo, M.; Font, J. *J. Org. Chem*. **2008**, *73*, 7657-7662. (d) Ferrer, E.; Alibés, R.; Busqué, F.; Figueredo, M.; Font, J.; de March, P. *J. Org. Chem*. **2009**, *74*, 2425-2432.

33. Alibés, R.; Bayón, P.; de March, P.; Figueredo, M.; Font, J.; Marjanet, G. *Organic Lett.* **2006**, *8*, 1617-1620.

34. (a) Morgan, B. S.; Hoenner, D.; Evans, P.; Roberts, S. M.; *Tetrahedron: Assymetry* **2004**, *15*, 2807-2809. (b) Raminielli, C.; Comasseto, J. V.; Andrade, L. H.; Porto, A. L. M. *Tetrahedron: Assyemtry* **2004**, *15*, 3117-3122. (c) Haeffner, F.; Norin, T.; Hult, K. *Biophys. J.* **1998**, *74*, 1251-1262.

35. de March, P.; Escoda, M.; Figueredo, M.; Font, J.; García, E.; Rodríguez, S. *Tetrahedron: Assymetry* **2000**, *11*, 4473-4483.

36. Danishefsky, S. J.; Simoneau, B. *J. Am. Chem. Soc.* **1989**, *111*, 2599-2604.

37. Jones, A. B.; Yamaguchi, M.; Patten, A.; Danishefsky, S. J.; Ragan, J. A.; Smith, D. B.; Schreiber, S. L. *J. Org. Chem.* **1989**, *54*, 17-19.

38. Alibés, R.; de March, P.; Figueredo, M.; Font, J.; Marjanet, G. Tetrahedron: Asymmetry **2004**, 15, 1151

39. Witschel, M. C.; Bestmann, H. J. *Synthesis* **1997**, 107-112.

40. López-Pelegrín, J. A.; Janda, K. D. *Chem. Eur. J.* **2000**, *6*, 1917-1922.

41. (a) Pulapura, S.; Kohn, J. *Journal of Biomaterials Applications* **1992**, *6*, 216-250. (b) Tangpasuthadol, V.; Shefer, A.; Hooper, K. A.; Kohn, J. *Biomaterials* **1996**, *17*, 463-468. (c) Tangpasuthadol, V.; Pendharkar, S. M.; Kohn, J. *Biomaterials* **2000**, *21*, 2371-2378.

42. Capparelli, M. P.; Swenton, J. S. *J. Org. Chem.* **1987**, *52*, 5360-5364.

43. Heller, J.E.; Dreiding, A. S.; O'Connor, B. R.; Simmons, H. E.; Buchanan, G. L.; Raphael, R. A.; Taylor, R. *Helv. Chim Acta* **1973**, *56*, 272-280.

44. Trân-Huu-Dâu, M. E.; Wartchow, R.; Winterfeldt, E. Wong, Y. S. *Chem. Eur. J*. **2001**, *7*, 2349-2369.

45. Polhnert, G. *J. Prakt. Chem.* **2000**, *342*, 731-734.

46. Lion, C.J.; Vasselin, D. A.; Schwalbe, C. H.; Matthews, C. S.; Stevens, M. F .G.; Westwell, A. D. *Org. Biomol. Chem.* **2005**, *3*, 3996-4001.

47. Baumann, J. B. *J. Chem. Educ.* **1979**, *56*, 64.

48. (a) Corey, E. J.; Kigoshi, H. *Tetrahedron Lett.* **1991**, *32*, 5025-5028. (b) Mori, K.; Amaike, M.; Itou, M. *Tetrahedron* **1993**, *49*, 1871-1878.

49. Marjanet, G. *Tesis doctoral, UAB*, **2006**.

50. (a) Iwasawa, N.; Funahashi, M.; Narasaka, K. *Chem. Lett.* **1994**, 1697-1700. (b) Pour, M.; Negishi, E. *Tetrahedron Lett. 1996, 37, 4679-4682.*

51. (a) Suzuki, M.; Oda, Y.; Noyori, R. *Tetrahedron Lett.* **1981**, *22*, 4413-4416. (b) Balci, M.; Akbulut, N. *Tetrahedron* **1985**, *41*, 1315-1322.

52. Bäckvall, J.-E.; Andreasson, U. *Tetrahedron Lett.* **1993**, *34*, 5459-5462.

53. Marchand, A. P.; Xing, D.; Wang, Y.; Bott, S. G. *Tetrahedron: Asymmetry* **1995**, *6*, 2709-2714.

54. Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656-2665.

55. Essig, S.; Scheffold, R. *Chimia* **1991**, *45*, 30-32.

56. Chang, S.; Heid, R. M.; Jacobsen, E. N. *Tetrahedron Lett.* **1994**, *35*, 669-672.

57. Carreño, M. C.; García-Ruano, J. L.; Garrido, M.; Ruiz, M. P.; Solladié, G. *Tetrahedron Lett.* **1990**, *31*, 6653-6656.

58. Brünjes, R.; Tilstam, U.; Winterfeldt, E. *Chem. Ber.* **1991**, *124*, 1677-1678.

59. (a) Trost, B. M.; Romero, A. G. *J. Org. Chem.* **1986**, *51*, 2332-2342. (b) Audia, J. E.; Boisvert L.; Patten, A. D.; Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 3738-3740.

60. Gebauer, O.; Brückner, R. *Liebigs Ann.* **1996**, 1559-1563.

61. Hashiguchi, S.; Fuji, A.; Haack, K. J.; Matsumura, K.; Ikariya, T.; Noyori, R. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 288-290.

62. Tachihara, T.; Kitahara, T. *Tetrahedron* **2003**, *59*, 1773-1780.

63. Barros, M. T.; Maycock, C. D.; Ventura, M. R. *J. Chem. Soc., Perkin Trans 1* **2001**, 166-173.

64. Williams, D. R.; Kammler, D. C.; Donnell, A. F.; Goundry, W. R. F. *Angew. Chem. Int. Ed.* **2005**, *44*, 6715-6718.

65. Nising, C. F.; Ohnemüller, U. K.; Bräse, S. *Angew. Chem. Int. Ed.* **2006**, *43*, 307-309.

66. (a) Wilson, E. M.; Trauner, D. *Org. Lett.* **2007**, *9*, 1327-1329. (b) García-Fortanet, J.; Carda, M.; Marco, J. A. *Tetrahedron* **2007**, *63*, 12131-12137.

67. (a) Barfoot, C. W.; Burns, A. R.; Edwards, M. G.; Kenworthy, M. N.; Ahmer, M.; Shanahan, S. E.; Taylor, R. J. K. *Org. Lett.* **2008**, *10*, 353-356. (b) Burns, A. R.; McAllister, G. D.; Shanahan, S. E.; Taylor, R. J. K. *Angew. Chem. Int. Ed*. **2010**, *49*, 5574-5577.

68. Chen, C-H.; Chen, Y-K.; Sha, C-K. *Org. Lett.* **2010**, *12*, 1377-1379.

69. Matsui, M.; Tashiro, T.; Sasaki, M.; Takikawa, H. *Biosci. Biotechnol. Biochem.* **2010**, *74*, 683-684.

70. Fudickar, W.; Vorndran, K.; Linker, T. *Tetrahedron* **2006**, *62*, 10639-10646.

71. Staben, S. T.; Linghu, X.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 12658-12659.

72. Evarts, J.; Fuchs, P. *Tetrahedron Lett.* **2001**, *42*, 3673-3675.

73. Bickley, J. F.; Evans, P.; Meek, A.; Morgan, B. S.; Roberts, S. M. *Tetrahedron: Asymetry*. **2006**, *17*, 355-362.

74. Suzuki, H.; Yamazaki, N., Kibayashi, C. *J. Org. Chem.* **2001**, *66*, 1494-1496.

75. O'Byrne, A.; Murray, C.; Keegan, D.; Palacio, C.; Evans, P.; Morgan, B. S. *Org. Biomol. Chem.* **2010**, *8*, 539-545.

76. Yu, S.; Zhang, R.; Wang, Z. *J. Chem., Perkin Trans 1* **2001**, 2958-2961.

77. (a) Demir, A. S.; Sesenoglu, O. *Organic Lett.* **2002**, *4*, 2021-2023. (b) Quesada, M. L.; Schessinger, R. H.; Parsons, W. H. *J. Org. Chem.* **1978**, *43*, 3968-3970.

78. (a) Nising, C. F.; Ohnemüller, U .K.; Bräse, S. *Synthesis* **2006**, *16*, 2643-2645. (b) Oda, M.; Kawase, T.; Okada, T.; Enomoto, T. *Org. Synth.* **1996**, *73*, 253-261.

79. Ross, A. M.; Pohl, T. M.; Piazza, K.; Thomas, M.; Fox, B.M.; Whalen, D. L. *J. Am. Chem. Soc.* **1982**, *104*, 1658-1665.

80. Bäckvall, J.-E.; Byström, S. E.; Nordberg, R.E. *J. Org. Chem*. **1984**, *49*, 4619-4631.

81. (a) Tamao, K.; Kawachi, A.; Tanaka, Y.; Ohtani, H.; Ito, Y. *Tetrahedron* **1996**, *52*, 5765-5772. (b) Davoille, R. J.; Rutherford, D. T.; Christie, S. D. R. *Tetrahedron Lett.* **2000**, *41*, 1255-1259.

82. Sanfilippo, C.; Patti, A.; Nicolosi, G. *Tetrahedron: Asymmetry* **2000**, *11*, 3269-3272.

83. (a) Gautier, E. C. L.; Lewis, N.; McKillop, A.; Taylor, R. J. K. *Tetrahedron Lett.* **1994**, *35*, 8759-8760.; (b) Gautier, E. C. L.; Graham, A. E.; McKillop, A.; Standen, S. P.; Taylor, R. J. K. *Tetrahedron Lett.* **1997**, *38*, 1881-1884.

84. Bayón, P.; Marjanet, G.; Toribio, G.; Alibés R.; de March, P.; Figueredo, M.; Font, J. *J. Org. Chem.* **2008**, *73*, 3486-3491.

85. Müller, A.; Keller-Scierlein, W.; Bielecki, J.; Rak, G.; Stuempfel, J.; Zëhner, J. *Helv. Chim. Acta* **1986**, *69*, 1829-1832.

86. (a) Huntley, C.F. M.; Hamilton, D. S.; Creighton, D. J.; Ganem, B. *Org. Lett.* **2000**, *2*, 3143-3144. (b) Sugimoto, Y.; Suzuki, H.; Yamaki, H.; Nishimura, T.; Tanaka, N. *J. Antibiot.* **1982**, *35*, 1222-1230. (c) Kamiya, D.; Uchihata, Y.; Ichikawa, E.; Kato, K.; Umezawa, K. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1111-1114.

87. Lubineau, A.; Billault, I. *J. Org. Chem.* **1998**, *63*, 5668-5671.

88. Shing, T. K. M.; Cheng, H. M. *J. Org. Chem.* **2007**, *72*, 6610-6613.

89. Mehta, G.; Laskshminath, S. *Tetrahedron Lett.* **2000**, *41*, 3505-3508.

90. Shing, T. K. M.; Cheng, H. M. *Synlett* **2010**, *1*, 142-144.

91. (a) Monrad, R. N.; Fanefjord, M.; Hansen, F. G.; Jensen, N. M. E.; Madsen, R. *Eur. J. Org. Chem.* **2009**, 396-402. (b) Mirza, S.; Molleyres, L.-P.; Vasella, A. *Helv. Chim. Acta* **1985**, *68*, 988-996. (c) Ramana, G. V.; Rao, B. V. *Tetrahedron Lett.* **2005**, *46*, 3049-3051. (d) Carreño, M. C.; Merino, E.; Ribagorda, M.; Somoza, A.; Urbano, A. *Chem. Eur. J.* **2007**, *13*, 1064-1077. (e) Takayama, H.; Hayashi, K.; Koizumi, T. *Tetrahedron Lett*. **1986**, *27*, 5509-5512. (f) Shing, T. K. M.; Tang, Y. *J. Chem. Soc. Chem. Commun.* **1990**, 312. (g) Shing, T. K. M.; Tang, Y. *Tetrahedron* **1990**, *46*, 6575-6584. (h)

Mehta, G.; Pujar, S. R.; Ramesh, S. S.; Islam, K. *Tetrahedron Lett.* **2005**, *46*, 3373-3376. (i) Sedmera, P.; Halada, P.; Pospĭsil, S. Magn. Reson. Chem. **2009**, *47*, 519-522. (j) Shing, T. K. M.; Cheng, H. M. *Org. Biomol. Chem.* **2009**, *7*, 5098-5102. (k) Sing, T. K. M.; So, K. H.; Kwok, W. S. *Org. Lett.* **2009**, *11*, 5070-5073.

92. (a) Marco-Contelles, J.; Molina, M. T.; Anjum, S. *Chem. Rev.* **2004**, *104*, 2857-2899. (b) Miyashita, K.; Imanishi, T. *Chem. Rev.* **2005**, *105*, 4515-4536. (c) Shoji, M.; Hayashi, Y. *Eur. J. Org. Chem.* **2007**,3783-3800.

93. Nagasawa, H.; Suzuki, A.; Tamura, S. *Agr. Biol. Chem.* **1978**, *42*, 1303-1304.

94. Kuo, M.-S.; Yurek, D. A.; Mizsak, S. A.; Marshall, V. P.; Liggett, W. F.; Cialdella, J. I.; Laborde, A. L.; Shelly, J. A.; Truesdell, S. E. *J. Antibiot.* **1995**, *48*, 888-890.

95. (a) Assante, G.; Camarda, L.; Merlini, L.; Nasini, G. *Phytochemistry* **1981**, *20*, 1955-1957. (b) Arie, T.; Kobayashi, Y.; Kono, Y.; Gen, O.; Yamaguchi, I. *Pestic. Sci.* **1999**, *55*, 602-604. (c) Iwamoto, C.; Minoura, K.; Oka, T.; Ohta, T.; Hagishita, S.; Numata, A. *Tetrahedron* **1999**, *55*, 14353-14368. (d) Son, B. W.; Choi, J. S.; Kim, J. C.; Nam, K. W.; Kim, D.-S.; Chung, H. Y.; Kang, J. S.; Choi, H. D. *J. Nat. Prod.* **2002**, *65*, 794-795. (e) Venkatasubbaiah, P.; Chilton, W. S. *J. Nat. Prod.* **1992**, *55*, 639-643. (f) Venkatasubbaiah, P.; Van Dyke, C. G.; Chilton, W. S. *Mycologia* **1992**, *84*, 715-723. (g) Sekiguchi, J.; Gaucher, G. M.; Can, J. *Microbiol*. **1979**, *25*, 881-887. (h) Makino, M.; Endoh, T.; Ogawa, Y.; Watanabe, K.; Fujimoto, Y. *Heterocycles* **1998**, *48*, 1931-34. (i) Jarvis, B. B.; Yatawara, S. S.; *J. Org. Chem.* **1986**, *51*, 2906-2910. (j) Li, Y.; Xi, X.; Son, B. W. *Nat. Prod. Sci.* **2005**, *11*, 136-138. (k) Trisuwan, K.; Rukachaisirikul, V.; Sukpondma, Y.; Preedanon, S.; Phongpaichit, S.; Rungjindamai, V.; Sakayaroj, J. *J. Nat. Prod.* **2008**, *71*, 1323-1326. (l) Sekiguchi, J.; Gaucher, G. M. *Biochem. J.* **1979**, *182*, 445-453. (m) Gloer, J. B.; Truckenbrod, S. M. *Appl. Environ. Microb.* **1988**, *54*, 861-884. (n) Kamikubo, T.; Ogasawara, K. *Tetrahedron Lett.* **1995**, *36*, 1685-1688. (o) Fukushima, Y.; Sakagami, Y.; Marumo, S. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1219-1222. (p) Klemke, C.; Kehraus, S.; Wright, A. D.; König, G. M. *J. Nat. Prod.* **2004**, *67*, 1058-1063. (q) Shimizu, H.; Okamura, H.; Yamashita, N.; Iwagawa, T.; Nakatani, M. *Tetrahedron Lett.* **2001**, *42*, 8649-8651. (r) Barros, M. T.; Maycock, C. D.; Ventura, M. R. *Tetrahedron* **1999**, *55*, 3233-3244. (s) Barros, M. T.; Maycock, C. D.; Ventura, M. R. *Chem. Eur. J.* **2000**, *6*, 3991-3996. (t) Li, P.; Takei, R.; Takahashi, K.; Nabeta, K. *Phytochemistry* **2007**, *68*, 819-823. (u) Kakeya, H.; Miyake, Y.; Shoji, M.; Kishida, S.; Hayashi, Y.; Kataoka, T.; Osada, H. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3743-3746. (v) White, L. V.; Dietinger, C. E.; Pinkerton, D. M.; Willis, A. C.; Banwell, M. G. *Eur. J. Org. Chem.* **2010**, 4365-4367.

96. Maier, A.; Maul, C.; Zerlin, M.; Grabley, S.; Thiericke, R. *J. Antibiot.* **1999**, *52*, 952-959.

97. Hamilton, D. S.; Ding, Z.; Ganem, B.; Creighton, D. J. *Org. Lett.* **2002**, *4*, 1209-1212.

98. Sakai, R.; Sato, R.; Niki, H.; Sakamura, S. *Plant. Cell. Physiol.* **1970**, *11*, 907-920.

99. Nakamori, K.; Matsuura, H.; Yoshihara, T.; Ichihara, A.; Koda, Y. *Phytochemistry* **1994**, *35*, 835-839.

100. Mitsui, T.; Miyake, Y.; Kakeya, H.; Hayashi, Y.; Osada, H.; Kataoka, T. *Biosci. Biotechnol. Biochem.* **2005**, *69*, 1923-1928.

101. Höfs, R.; Schoppe, S.; Thiericke, R.; Zeeck, A. *Eur. J. Org. Chem.* **2000**, 1883-1887.

102. Takayama, H.; Hayashi, K.; Koizumi, T. *Tetrahedron Lett.* **1986**, *27*, 5509-5512.

103. Takashi, T.; Yamakoshi, Y.; Okayama, K.; Yamada, J.; Ge, W.-Y.; Koizumi, T. *Heterocycles* **2002**, *56*, 209-220.

104. (a) Arthurs, C. L.; Raftery, J.; Whitby, H. L.; Whitehead, R. C.; Wind, N. S.; Stratford, I. J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5974-5977. (b) Arthurs, C. L.; Wind, N. S.; Whitehead, R. C.; Stratford, I. J. *Bioorg. Med. Chem. Lett.* **2007**,

17, 553-557. (c) Arthurs, C. L.; Lingley, K. F.; Piacenti, M.; Stratford, I. J.; Tatic, T.; Whitehead, R. C.; Wind, N. S. *Tetrahedron Lett.* **2008**, *49*, 2410-2413.

105. Lygo, B.; Swiatyj, M.; Trabsa, H.; Voyle, M. *Tetrahedron Lett*. **1994**, *35*, 4197-4200.

106. Tatsuta, K.; Yasuda, S.; Araki, N.; Takahashi, M.; Kamiya, Y. *Tetrahedron Lett.* **1998**, *39*, 401-402.

107. Rao, J. P.; Rao, B. V. *Tetrahedron: Asymmetry* **2010**, *21*, 930-935.

108. Corsaro, A.; Pistarà, V.; Catelani, G.; D'Andrea, F.; Adamo, R.; Chiacchio, M. A. *Tetrahedron Lett.* **2006**, *47*, 6591-6594.

109. Mac, D. H.; Samineni, R.; Petrignet, J.; Srihari, P.; Chandrasekhar, S.; Yadav, J. S.; Grée, R. *Chem. Commun.* **2009**, 4717-4719.

110. Stathakis, C. I.; Athanatou, M. N.; Gallos, J. K. *Tetrahedron Lett.* **2009**, *50*, 6916-6918.

111. Huntley, C. F. M.; Wood, H. B.; Ganem, B. *Tetrahedron Lett.* **2000**, *41*, 2031-2034.

112. (a) Shinada, T.; Fuji, T.; Ohtani, Y.; Yoshida, Y.; Ohfune, Y. *Synlett* **2002**, 1341-1343, (b) Shinada, T.; Yoshida, Y.; Ohfune, Y. *Tetrahedron Lett.* **1998**, *39*, 6027-6028.

113. (a) Ichihara, A.; Oda, K.; Sakamura, S. *Agr. Biol. Chem.* **1971**, *35*, 445-446. (b)Ichihara, A.; Oda, K.; Sakamura, S. *Tetrahedron Lett.* **1972**, *13*, 5105-5108. (c) Ichihara, A.; Oda, K.; Sakamura, S. *Agr. Biol. Chem.* **1974**, *38*, 163-169.

114. (a) Ichihara, A.; Kimura, R.; Oda, K.; Sakamura, S. *Tetrahedron Lett.* **1976**, 17, 4741-4744. (b) Ichihara, A.; Kimura, R.; Oda, K.; Moriyasu, K.; Sakamura, S. *Agr. Biol. Chem.* **1982**, *46*, 1879-1883.

115. Kamikubo, T.; Hiroya, K.; Ogasawara, K. *Tetrahedron Lett.* **1996**, *37*, 499-502.

116. Okamura, H.; Shimizu, H.; Yamashita, N.; Iwagawa, T.; Nakatani, M. *Tetrahedron* **2003**, *59*, 10159-10164.

117. Genski, T.; Taylor, R. J. K. *Tetrahedron Lett.* **2002**, *43*, 3573-3576.

118. Mehta, G.; Islam, K. *Tetrahedron Lett.* **2004**, *45*, 7683-7687.

119. (a) Jin, M. Y.; Hwang, G-S.; Chae, H. I.; Jung, S. H.; Ryu, D. H. *Bull. Korean Chem. Soc.* **2010**, *31*, 727-730. (b) Lee, M. Y.; Kim, K. H.; Jiang, S.; Jung, Y. H.:Sim, J. Y.; Hwang, G-S.; Ryu, D. H. *Tetrahedron Lett.* **2008**, *49*, 1965-1967.

120. (a) Chou, D. T.-W.; Ganem, B. *J. Am. Chem. Soc.* **1980**, *102*, 7987-7988.

121. (a) Pinkerton, D. M.; Banwell, M. G.; Willis, A. C. *Org. Lett.* **2009**, *11*, 4290-4293. (b)

122. Carreño, M. C.; Merino, E.; Ribagorda, M.; Somoza, A.; Urbano, A. *Org. Lett.* **2005**, **7**, 1419-1422.

123. Here and aforhead H_{5cis} and H_{5trans} are referred to the relative geometry respect the H_4.

124. (a) Barros, M. T.; Maycock, C. D.; Ventura, M. R. *J. Org. Chem.* **1997**, *62*, 3984-3988. (b) Barros, M. T.; Matias, P. M.; Maycock, C.; Ventura, R. *Org. Lett.* **2003**, *5*, 4321-4323.

125. For Barros and Maycock epoxides *cis* and *trans* is referred to the relative geometry respect the OTBS group.

126. The protection of the hydroxyl group proved necessary for the next synthetic steps.

127. The values of specific rotation described in the literature for epiepoformin oscillate between $[\alpha]_D$= +221 (*c* 0.83, EtOH)[93] and $[\alpha]_D$= +320 (*c* 0.06, EtOH)[63].

128. Toribio, G.; Marjanet, G.; Alibés, R.; de March, P.; Font, J.; Bayon, P.; Figueredo, M. *Eur. J. Org. Chem.* **2011**, 1534-1543.

129. Henderson, D. A.; Collier, P. N.; Pav, G.; Rzepa, P.; White, A. J. P.; Burrows, J. N.; Barrett, G. M. *J. Org. Chem.* **2006**, *71*, 2434-2444.

130. (a) Shan, M.; Xing, Y.; O'Doherty, A. G. *J. Org. Chem.* **2009**, *74*, 5961-5966. (b) Ogawa, C.; Wang, N.; Kobayashi, S. *Chem. Lett.* **2007**, *36*, 34-35. (c) Tschöp, A.; Marx, A.; Sreekanth, A. R.; Schneider, C. *Eur. J. Org. Chem.* **2007**, 2318-2327. (d) Percy, J.; Roig, R.; Singh, K. *Eur. J. Org. Chem.* **2009**, 1058-1071. (e) Emmanuel, L.; Shaikh, T. M. A.; Sudalai, A. *Org. Lett.* **2005**, *30*, 5071-5074.

131. (a)Yoshitake, M.; Kobayashi, H.; Yamamoto, M.; Kohmoto, S.; Yamada, K. *Chem. Lett.* **1991**, 1865-1868. (b) Honzumi, M.; Hiroya, K.; Taniguchi, T.; Ogasawara, K. *Chem. Commun.* **1999**, 1985-1986. (c) Yoshida, N.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 1461-1463. (d) Honzumi, M.; Taniguchi, T.; Ogasawara, K. *Org. Lett.* **2001**, *3*, 1355-1358.

132. Wipf, P.; Jeger, P.; Kim, Y. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 351-356.

133. Lawlor, M. D.; Lee, T. W.; Danheiser, R. L. *J. Org. Chem.* **2000**, *65*, 4375-4384.