UNIVERSITY
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GLASGOW

Studies Towards the Total Synthesis of Labiatin A

By

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Declaration

I hereby declare that the substance of this thesis has not been submitted, nor is concurrently submitted, in candidature for any other degree.

I also declare that the work presented in this thesis is the result of my own investigations and where the work of the other investigators has been used, this has been fully acknowledged in the text.

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(D. Vignard)

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(Professor J. S. Clark)

Acknowledgements

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Many thanks to the past and present members of the Clark group for creating a high quality and stimulating environment in which to carry out my research. I would like to specially thank Carine, Delphine, Jérôme and Guang-Xing for bringing the good spirit from Nottingham to Glasgow and Jean-Pierre, Damian, Stewart, Joanne, Alexandra and Thomas for their help and support during the first two years in Nottingham.

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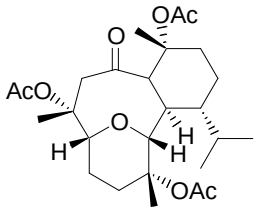
Contents……..Page

Abstract

This thesis is concerned with studies towards the total synthesis of labiatin A using metal carbenoid methodology. The work described herein shows the most recent contribution to this field from our research group.



labiatin A

Chapter I provides an introduction to metal carbenoids and their uses in organic synthesis. In particular, the synthesis of diazo carbonyl compounds, their decomposition by metal catalysts leading to the formation of metal carbenoids and the reactions involving metal carbenoids is described. A retrosynthesis of labiatin A involving the use of two metal-carbenoid transformations – intramolecular C-H insertion reaction and oxonium ylide formation followed by [2,3]-sigmatropic rearrangement – is presented.

In Chapter II, the successful applications of these two reactions to the enantioselective synthesis of the tricyclic core of labiatin A is described. This is followed by the description of the different attempts to complete the synthesis of labiatin A. Finally, the exploration of a modified approach to the total synthesis of labiatin A is described.

Chapter III provides the analytical support to this thesis.

Abbreviations

p-ABSA	–	*p*-Acetamidobenzenesulfonyl azide
Ac	–	Acetyl
acac	–	Acetylacetonate
acam	–	Acetamide
AIBN	–	2,2'-Azobis(2-methyl propionitrile)
Ar	–	Aromatic
Bn	–	Benzyl
brsm	–	Based on recovered starting material
Bz	–	Benzoyl
Bu	–	Butyl
m-CPBA	–	*m*-chloroperbenzoic acid
CSA	–	(+/-)-camphorsulfonic acid
dba	–	Dibenzylidene acetone
DBU	–	1,8-Diazobicyclo[5.4.0]undec-7-ene
DDQ	–	2,3-Dichloro-4,5-dicyanobenzoquinone
DIBAL-H	–	Diisobutylaluminium hydride
DFT	–	Density Functional Theory
DMA	–	*N*,*N*-dimethylaniline
DMAP	–	*N*,*N*-dimethyl-4-aminopyridine
DMF	–	Dimethylformamide
DMPU	–	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone
DMS	–	Dimethylsulfide
DMSO	–	Dimethylsulfoxide
DOSP	–	(*N*-dodecylbenzenesulfonyl)prolinate
dppf	–	1,1'-Bis(diphenylphosphino)ferrocene
d.r.	–	Diastereomeric ratio
E	–	Electron withdrawing group
ED	–	Effective Dose
ee	–	Enantiomeric excess

e.r.	–	Enantiomeric ratio
eq	–	Equivalent(s)
Et	–	Ethyl
hfacac	–	Hexafluoroacetylacetonate
HMDS	–	Hexamethyldisilazide
IBX	–	2-Iodoxybenzoic acid
L	–	Ligand
LDA	–	Lithium diisopropylamide
Liq.	–	Liquid
M	–	Metal
MAD	–	Methylaluminium bis(2,6-di-tert-butyl-4-methylphenoxide)
Me	–	Methyl
Men	–	*d*-Menthyloxy
MEOX	–	Oxazolidine-4-carboxylic acid methyl ester
MEPY	–	Pyrrolidine-4-carboxylic acid methyl ester
mol. sieves	–	Molecular sieves
MOM	–	Methoxymethyl
MPM	–	*p*-Methoxy benzyl
Ms	–	Methanesulfonyl
NBS	–	*N*-Bromosuccinimide
NMP	–	*N*-Methylpyrrolidinone
OTf	–	Trifluoromethane sulfonate
Pfb	–	Perfluorbutyrate
PG	–	Protecting group
Ph	–	Phenyl
PMB	–	*p*-Methoxybenzyl
PMP	–	*p*-Methoxyphenyl
Pr	–	Propyl
PPTS	–	Pyridinium *p*-toluensulfonate
PTPA	–	*N*-phtaloyl-phenylalaninate

PTTL	–	*N*-phtaloyl-*tert*-leucinate
Pv	–	Pivaloyl
rt	–	Room temperature
SM	–	Starting material
T	–	Temperature
TBAF	–	Tetra-*n*-butylammonium fluoride
TBATB	–	Tetrabutylammonium tribromide
TBDMS or TBS	–	*t*-Butyldimethylsilyl
TBDPS	–	*t*-Butyldiphenylsilyl
TES	–	Triethylsilyl
tfacac	–	Trifluoroacetylacetonate
tfacam	–	Trifluoroacetamide
THF	–	Tetrahydrofuran
TIPS	–	Triisopropylsilyl
TMEDA	–	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMS	–	Trimethylsilyl
TPA	–	Triphenylacetate
Trisyl	–	2,4,6-triisopropylbenzenesulfonyl
Ts	–	*p*-Toluene sulfonate (Tosyl)
Z	–	Benzyloxy carbonyl

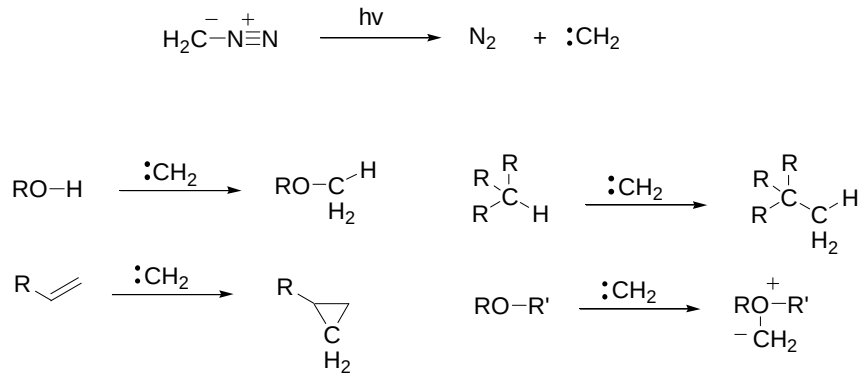
Chapter I

Introduction

Chapter I – Introduction

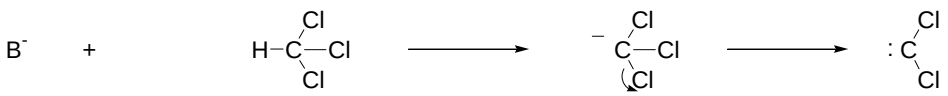
1.1 Carbenes and carbenoids

Carbenes are neutral species containing a carbon atom with only six valence electrons: two in each bond and two nonbonding electrons. They are highly reactive species due to their extreme electrophilicity. To gain two electrons, carbenes typically undergo insertion reactions, either into O–H, C=C or C–H bonds. They can also react with a heteroatom to form an ylide. Methylene (**:**CH_2) is the most simple carbene and is formed by irradiation of diazomethane with light (**Scheme 1**).



Scheme 1

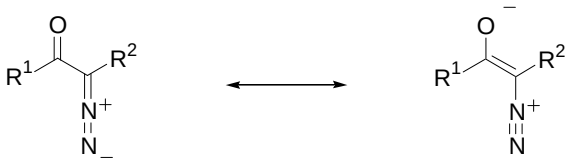
Carbenes can be formed by two main processes: α-elimination reactions or thermal decomposition of diazo compounds. The α-elimination follows the mechanism shown in **Scheme 2**. A strong base removes an acidic proton adjacent to an electron-withdrawing group to give a carbanion. Subsequent loss of a leaving group from the carbanion forms a carbene.



Scheme 2

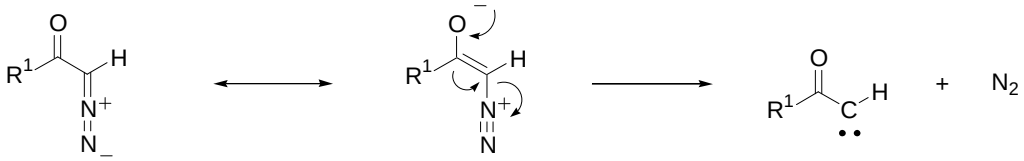
Even though the formation of a carbene by an α-elimination reaction is of great importance in organic chemistry – Simmons-Smith cyclopropanation and the Reimer-Tieman reaction are important examples – the most common method to form carbenes

is the decomposition of diazo compounds. The formation of a carbene from diazomethane is described above, but this reaction is rarely used because of the explosive nature of diazoalkanes. However, diazocarbonyl compounds are much more stable because the electron-withdrawing carbonyl group stabilizes the diazo dipole (**Equation 1**). They can therefore be generated and handled in a relatively safe manner.



Equation 1

Despite this relative stability diazocarbonyl compounds can be fairly easily decomposed by light or heat to give carbenes as shown in **Scheme 3**. The very favourable formation of gaseous nitrogen compensates for the formation of the unstable carbene.



Scheme 3

The chemistry based on thermal or photochemical decomposition of diazo compounds has been of relatively little use due to the extreme reactivity of free carbenes which often leads to non-selective reactions. However, the utility of diazocarbonyl compounds as carbene precursors became more attractive once the decomposition of diazo compounds by transition metal had been discovered. Indeed, this led to the formation of metal-complexed carbenes known as metal carbenoids. Carbenoids are less reactive species than carbenes but they will undergo the same types of reaction with more selectivity.

The first part of this introduction will deal with the chemistry of diazo compounds: their formation, their decomposition by metal catalysts and their subsequent reactions, focusing on C–H insertion reactions and oxonium ylide formation and rearrangement.

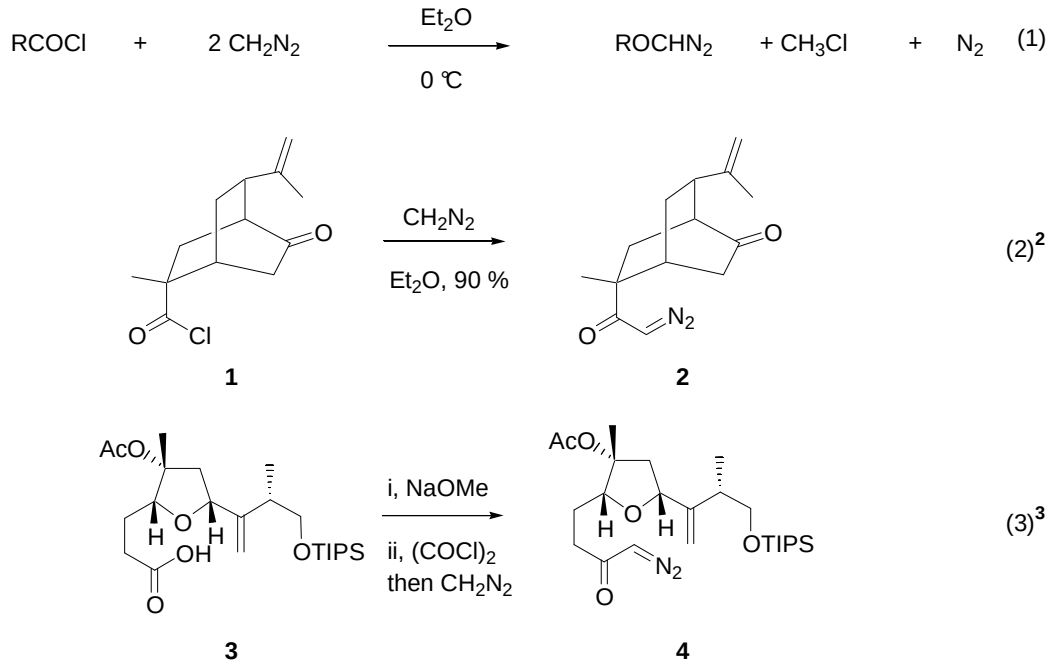
1.2 Synthesis of diazo compounds

Curtius was the first chemist to report the synthesis of ethyl diazoacetate from glycine in 1883 but the routine formation of simple α-diazocarbonyl compounds dates from the work of Arndt and Eistert in the late 1920's.[1] They discovered that these compounds are readily available by reaction of an acid chloride with an excess of diazomethane (**Scheme 4**, equation (1)). Almost 90 years later, this method is still the most widely used for the preparation of diazoketones. As shown in **Scheme 4** (equations (2) and (3)), formation of diazoketones **2** and **4**, key intermediates in the total synthesis of (±)-9-isocyanoneopupukeanane by Srikrishna[2] and the synthesis of the tricyclic core of neoliacinic acid by Clark,[3] were accomplished using this technique.

[1] Doyle, M. P.; McKervey, M. A.; Ye T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides.*, Wiley, New York, **1998** and references cited herein.

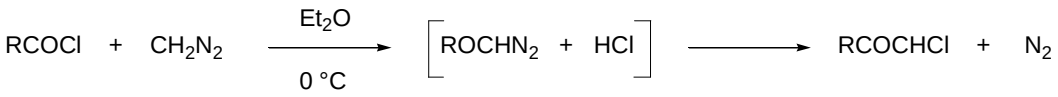
[2] Srikrishna, A.; Satyanarayana, G. *Tetrahedron* **2005**, *61*, 8855-8859.

[3] Clark, J. S.; Dossetter, A. G.; Blake, A. J.; Li, W. S.; Whittingham, W. G. *Chem. Commun.* **1999**, 749-750.



Scheme 4

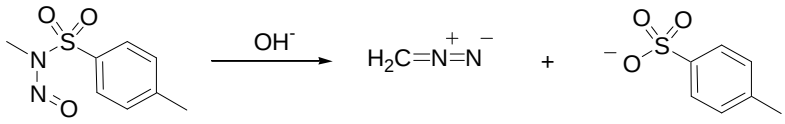
An excess of diazomethane (at least two equivalents) is required for this reaction to give a diazocarbonyl coumpound. One equivalent of diazomethane is required to quench the hydrogen chloride liberated in the reaction and prevent it reacting with the diazoketone to give a chloromethyl ketone (**Scheme 5**). Typically, between 5 and 10 equivalents of diazomethane are used.



Scheme 5

It is important to note that the use of explosive and very toxic diazomethane implies working using appropriate safety measures. Diazomethane is a toxic gas which is usually used as a cold (0 °C or below) dilute solution in ether. It is known to easily explode in contact with rough surfaces and therefore must be handled using only special clear joint apparatus. The most common way to prepare diazomethane involves reacting a solution of Diazald® (**5**) in ether with a warm (70 °C) aqueous solution of

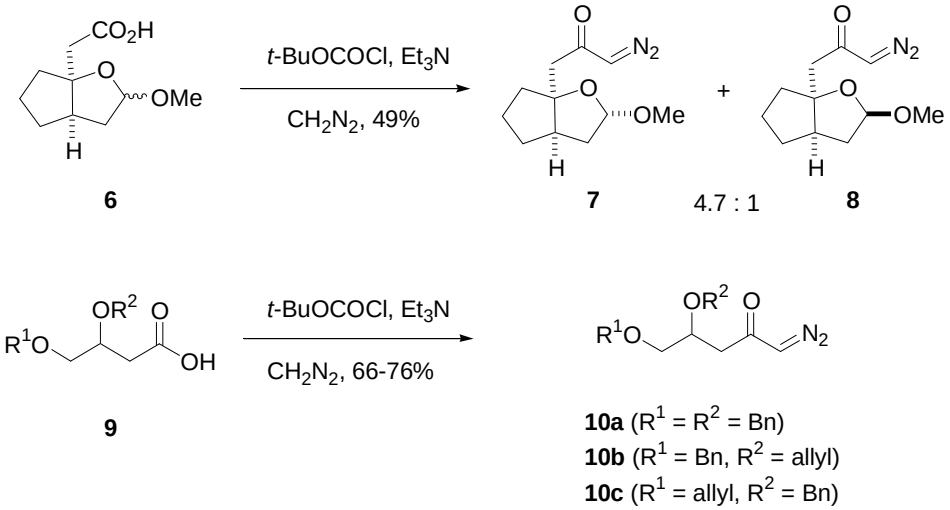
sodium hydroxide. Condensation of the vapours produced in the reaction mixture affords an ethereal solution of diazomethane (**Equation 2**).



Diazald (**5**)

Equation 2

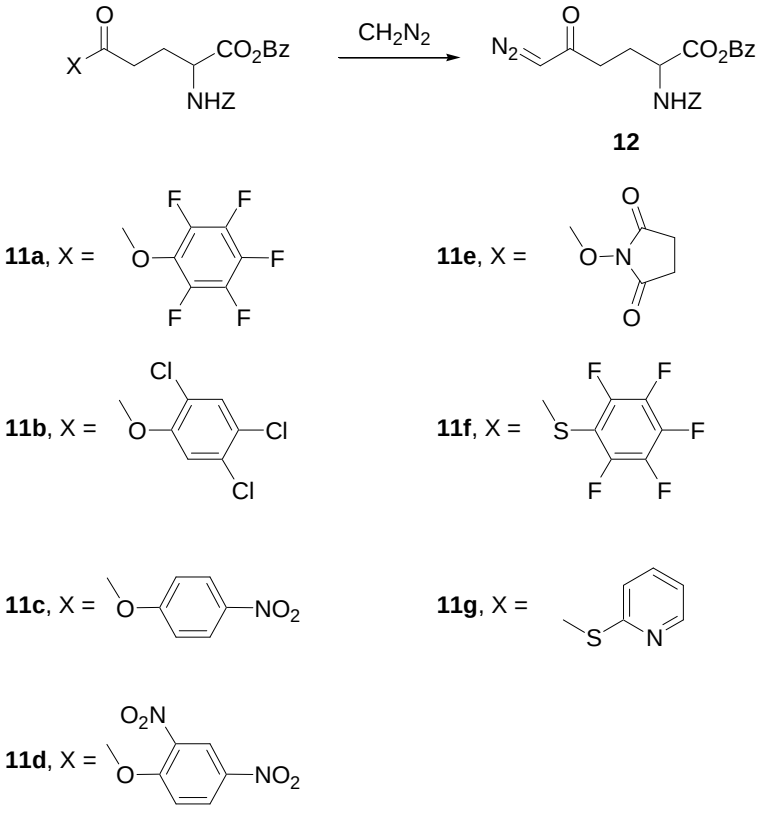
The acylation of diazomethane can also be performed using acid anhydrides. This method is usually chosen for acid sensitive substrates or when the formation of the corresponding acid chloride is problematic. The anhydride is often a carboxylic-carbonic anhydride and can be easily formed by reaction of a carboxylic acid with a chloroformate (e.g. methyl, ethyl or isobutyl chloroformate). Subsequent treatment of the anhydride with ethereal diazomethane affords the corresponding diazoketone in usually good yields as shown in **Scheme 6**.[4a,b] The reactivity of the carbonyl group flanked by two oxygen atoms is reduced and so that diazomethane attacks only the original carboxy component of these particular mixed anhydrides.



Scheme 6

[4] (a) Murphy, G. K.; Marmsäter, F. P; West, F. G. *Can. J. Chem.* **2006**, *84*, 1470-1486 (b) Marmsäter, F. P.; Vanecko, J. A.; West, F. G. *Org. Lett.* **2004**, *10*, 1657-1660.

Pettit and Nelson have studied alternative ways of activating a carboxylic acid to bring about the acylation of diazomethane, but they discovered that only esters **11d** and **11f** reacted (at least partially) with diazomethane (**Equation 3**).[5]

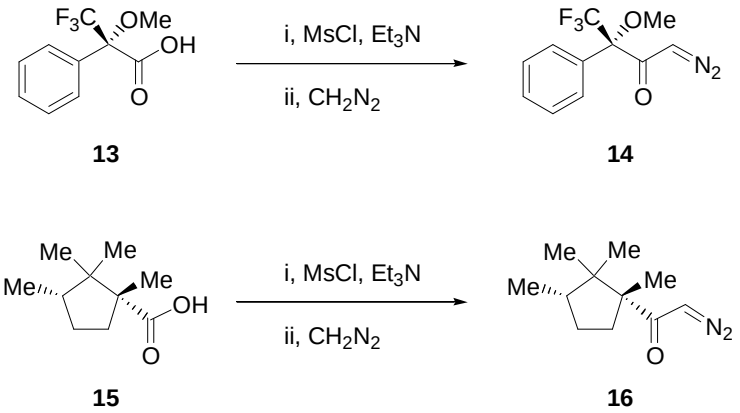


Equation 3

Nicolaou *et al* managed to synthesise elaborated diazoketones by conversion of a carboxylic acid into an acyl mesylate prior to addition of diazomethane and reported that this method is particularly efficient in the case of hindered diazoketones (**Scheme 7**).[6] Nevertheless, the reaction of diazomethane with acid chlorides and mixed anhydrides still remains the most commonly used method for the synthesis of simple diazoketones.

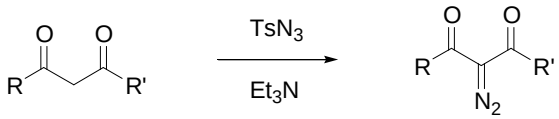
[5] Pettit, G. R.; Nelson, P. S. *Can. J. Chem.* **1986**, *64*, 2097-3102.

[6] Nicolaou, K. C.; Baran, P. S.; Zhong, Y. L.; Choi, H. S.; Fong, K. C.; He, Y.; Yoon, W. H. *Org. Lett.* **1999**, 1, 883-886.



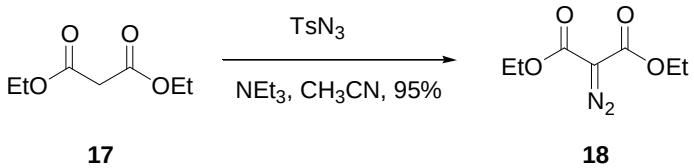
Scheme 7

The major limitation of the formation of α-diazo carbonyl compounds by acylation of diazomethane is that its use is restricted to acyclic carboxylic acid derivatives. The synthesis of cyclic diazoketones nearly always involves a diazo transfer reaction. The concept of diazo transfer was introduced by Dimroth in 1910 and was later studied in depth by Regitz *et al*.[7] It consists of the transfer of a diazo group from a sulfonyl azide to a carbon adjacent to a carbonyl group (**Equation 4**).



Equation 4

It requires the presence of a base to deprotonate the carbon α to the carbonyl group prior to diazo transfer. When this position is quite acidic, only a weak base such as triethylamine is required and the reaction usually proceeds smoothly. This is notably the case with α,β-dicarbonyl compounds (**Equation 5**).[8]

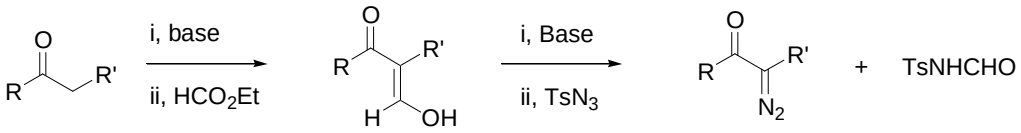


Equation 5

[7] Regitz, M. *Synthesis* **1972**, 351-373.

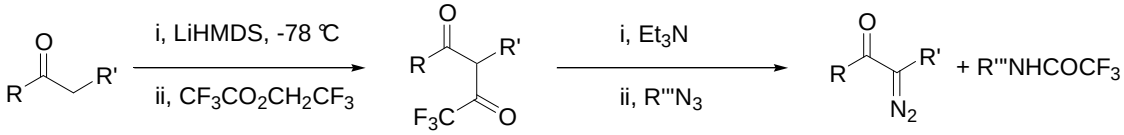
[8] Regitz, M.; Liedhegener, A. *Chem. Ber.* **1966**, *99*, 3128-3147.

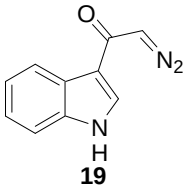
The simple diazo transfer procedure fails in the case of non-activated carbonyl compounds and extensive efforts have been made to develop an efficient diazo transfer reaction for those compounds over many years. In 1967, Regitz was the first to describe the deformylating diazo transfer procedure as a method for the synthesis of diazocarbonyl compounds.[9] A strongly activating formyl group is introduced using a Claisen condensation of a ketone with ethyl formate which then allows the diazo transfer to occur (**Scheme 8**).



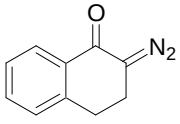
Scheme 8

Although deformylating diazo transfer is a useful procedure, it is frequently low yielding and a related procedure developed by Doyle and improved by Danheiser is generally preferred.[10] In the Doyle and Danheiser procedure, the formyl activating group is replaced by a trifluoroacetyl group which is easier to introduce and usually leads to higher yield for the diazo transfer step (**Scheme 9**).





19 0% *via* formylation, 86% *via* trifluoroacetylation



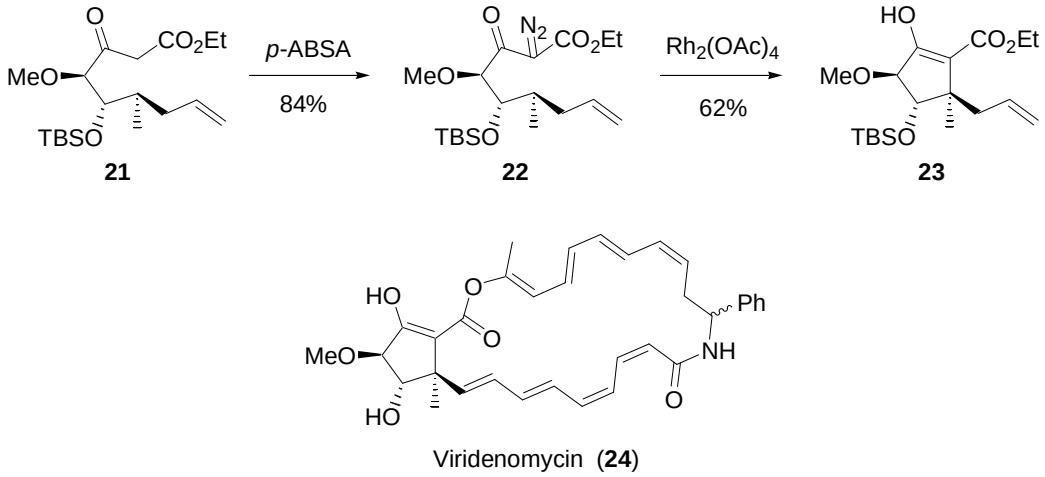
20 56% *via* formylation, 81% *via* trifluoroacetylation

Scheme 9

[9] Regitz, M. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 733-749.

[10] (a) Doyle, M. P.; Dorow, R. L.; Terpstra, J. W.; Rodenhouse, R. A. *J. Org. Chem.* **1985**, *50*, 1663-1666 (b) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959-1964.

It is also worth noting that *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) is often preferred to the potentially explosive and toxic reagent tosyl azide. It indeed allows safer working conditions and usually leads to better yields. This reagent has been employed by Pattenden *et al* for the formation of the key α-diazo β-keto ester **22** during the synthesis of the cyclopentane unit **23** of viridenomycin (**24**) (**Scheme 10**).[11]



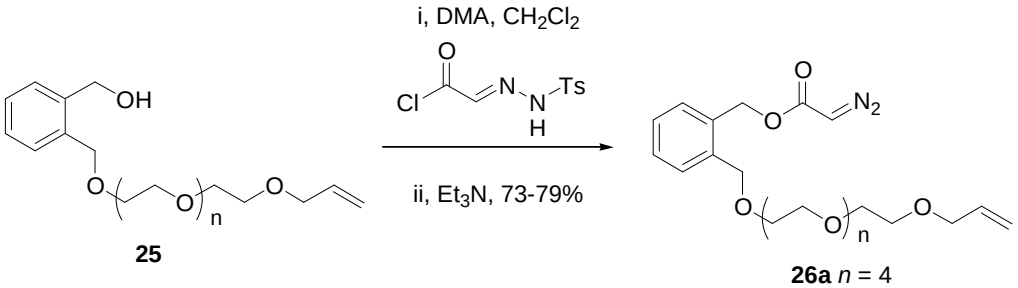
Scheme 10

Finally, the formation of diazo compounds can be achieved using the Corey-Myers diazoacetate transfer protocol.[12] It has the advantage of being a single-step process that is performed in an organic solvent. In this case, aqueous conditions are avoided allowing easy purification of water soluble or water sensitive products. The Corey-Myers protocol has been used recently by Doyle and co-workers for the synthesis of the hygroscopic diazoacetates **26** (**Equation 6**).[13]

[11] Pattenden, G.; Blake, A. J.; Constandinos, L. *Tetrahedron Lett.* **2005**, *46*, 1913-1915.

[12] Corey, E. J.; Myers, A. G. *Tetrahedron Lett.* **1984**, *25*, 3359.

[13] Weathers, Jr., T. M.; Wang, Y.; Doyle, M. P. *J. Org. Chem.* **2006**, *71*, 8183-8189.



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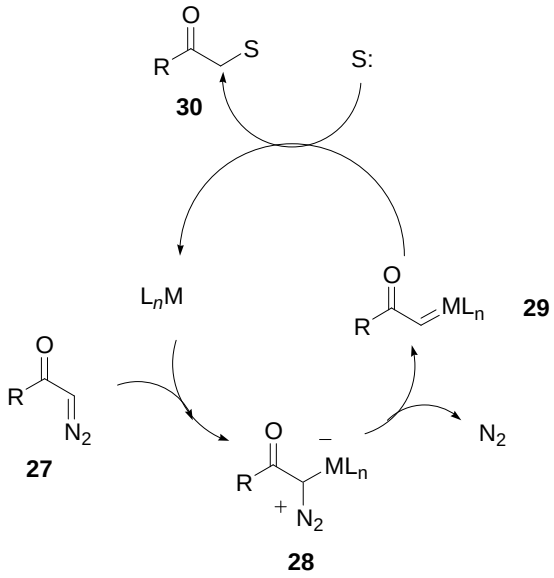
26a *n* = 4
26b *n* = 3
26c *n* = 5

Equation 6

1.3 Metal catalysed decomposition of diazo compounds

The thermal decomposition of diazo compounds produces carbenes by elimination of nitrogen. At the beginning of the 20th century, it was found that this reaction could be performed at lower temperatures by treatment of the substrate with copper bronze or copper(II) sulphate.[1] Since then a multitude of metal catalysts have been used to study the mechanism of the formation of metal stabilised carbenes and their subsequent reactions.

The generally accepted catalytic cycle for this decomposition is shown in **Scheme 11**. Electrophilic attack of the metal complex onto the carbon bearing the dinitrogen group produces the metal-bound diazonium intermediate **28** which readily loses nitrogen to afford the metal carbenoid **29**. Nucleophilic attack by the electron-rich substrate S: onto the electrophilic carbenoid regenerates the metal complex and completes the catalytic cycle.

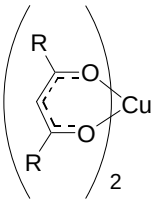


Scheme 11

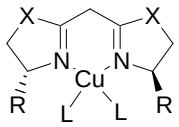
The electrophilicity of the transition metal catalyst and the stability of the diazocompound are the two main factors influencing the rate of diazo decomposition. Diazo compounds in which there are two carbonyl groups flanking a diazomethylene carbon are more stable towards these catalysts than those possessing only one carbonyl group. Diazoesters are generally more stable than diazoketones and diazoamides are more stable than diazoesters. Diazo compounds are decomposed by transition metal complexes that are Lewis acids. They are usually “late“ transition metals in the third and fourth periods, typically copper, rhodium, ruthenium, cobalt, palladium and iron complexes.

Copper catalysts (**Figure 1**) are of major importance firstly because they were historically the first to be used (copper bronze and copper sulphate), secondly because nowadays copper(II) acetylacetonate **31** and its fluorinated derivative **32** are the catalysts of choice for diazo decomposition, and thirdly because chiral copper complexes (for example structures **33** and **34**) have been developed for asymmetric diazo decomposition. It is important to note that despite the fact copper(II) catalysts are used, the active species is thought to be copper(I) complex. Therefore one of the

bidentate ligands (e.g., acetylacetonate) is dissociated from the metal centre upon reduction of copper(II) to copper(I) by the diazocompound.



$Cu(acac)_2$ (**31**, R = CH_3)
$Cu(hfacac)_2$ (**32**, R = CF_3)



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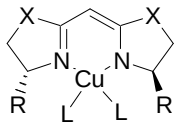

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X = C, O

Figure 1

Another extremely important class of catalysts are the dirhodium(II) metal complexes (**Figure 2**). The ligands play a key role in the reactivity of metal carbenoids and the possible carboxylate and carboxamides ligand for attachment to dirhodium complexes are of such a variety that it is often possible to obtain a higher degree of regio- and chemoselectivity for reactions involving rhodium-stabilised carbenoids than with other catalysts.

Dirhodium(II) tetraacetate **35** was first introduced in the 1970's by Teyssie and co-workers and since that time it has been the single most widely used catalyst for metal carbenoid generation.[14] Dirhodium(II) carboxamidates [dirhodium(II) tetraacetamide {$Rh_2(acam)_4$} **36** and derivatives] are also very important catalysts due to their propensity to increase reaction selectivity. It is also relatively easy to prepare chiral derivatives such as catalysts **38** to **42**.

[14] Paulissenen, R.; Reimlinger, H.; Hayez, E.; Hubert, A. J.; Teyssie, P. *Tetrahedron Lett.* **1973**, 2233-2236.

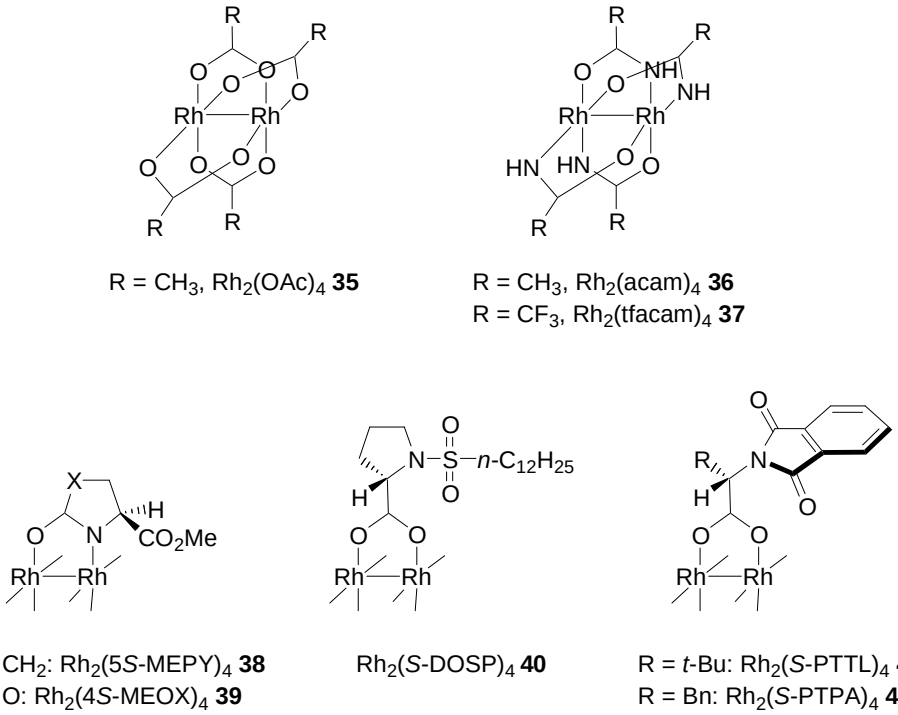


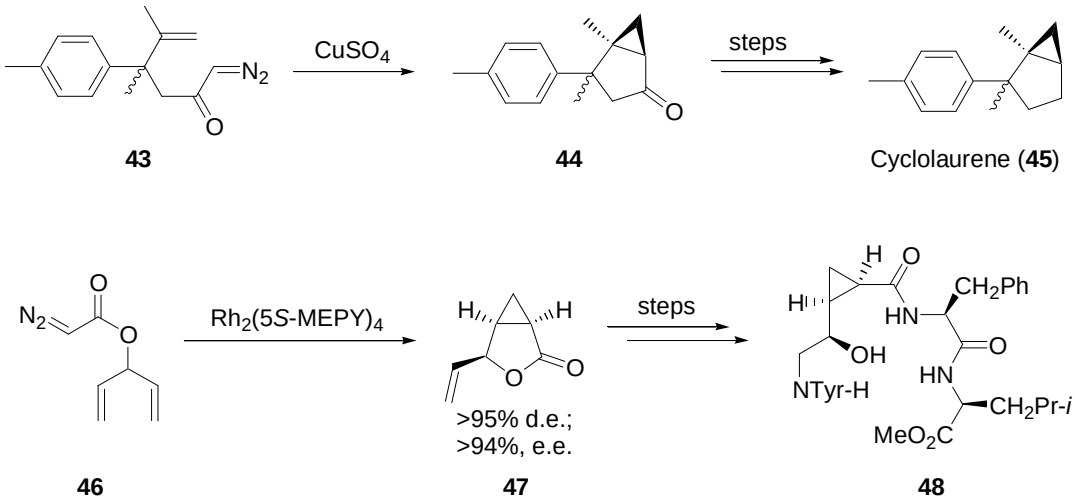
Figure 2

1.4 Reactions of metal carbenoids

1.4.1 Cyclopropanation reactions of carbenoids

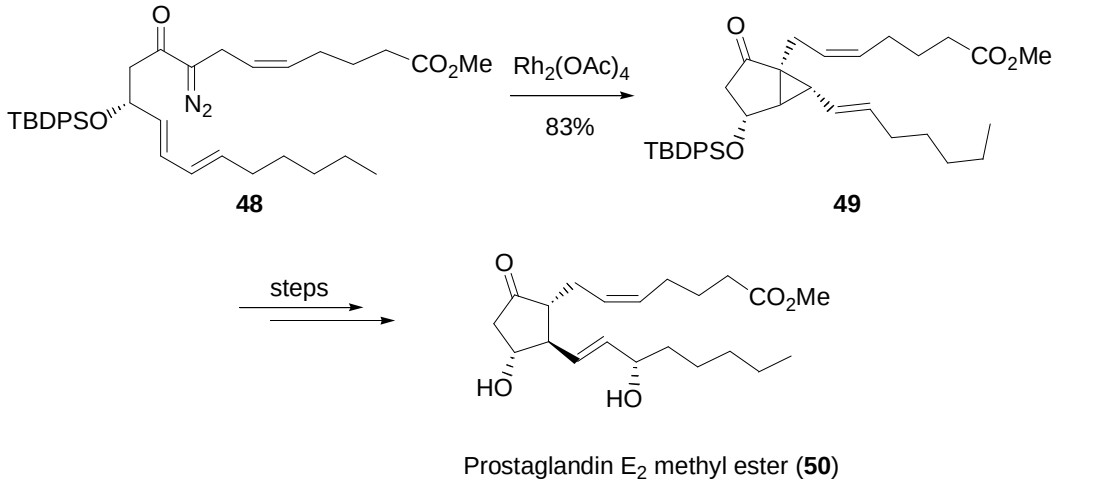
Metal-stabilised carbenes are highly electrophilic species and therefore react with electron-rich substrates and undergo insertion reactions. Insertion into the electron-rich π-system of an alkene leads to cyclopropane formation. This reaction has been widely used in natural product synthesis and some notable examples are presented in **Scheme 12**. For instance (±)-cyclolaurene (**45**) and the cyclopropane **47** have been synthesised using an intramolecular cyclopropanation reaction as the key step.[15]

[15] (a) Srikrishna, A.; Krishnan, K. *Tetrahedron* **1992**, *48*, 3429-3436 (b) Martin, S. F.; Dwyer, M. P.; Hartmann, B.; Knight, K. S. *J. Org. Chem.* **2000**, *65*, 1305-1318.



Scheme 12

Cyclopropane formation from a diazoketone has also been used for the synthesis of valuable intermediates which can be further elaborated to highly functionalised skeletons. Indeed, cyclopropanes can undergo various reactions due to their inherent strain. For example, prostaglandin E_2 methyl ester (**50**) has been synthesised by Taber and co-workers via a cyclopropanation reaction followed by ring opening to install the required side chain (**Scheme 13**).[16]

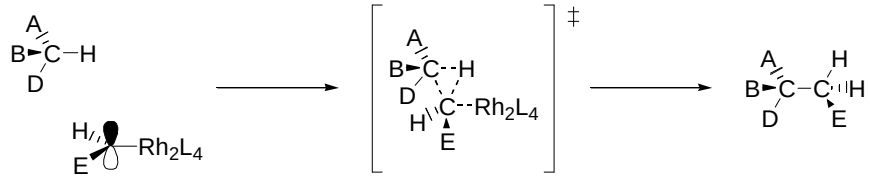


Scheme 13

[16] Taber, D. F.; Hoerner, R. S. *J. Org. Chem.* **1992**, *57*, 441-447.

1.4.2 C–H Insertion reactions of metal carbenoids

In the 1940's, Meerwein, Rathjen and Werner discovered that metal carbenoids can also insert into C–H bonds opening a new area of carbon-carbon bond formation.[17] The generally accepted mechanism proposed by Doyle for this reaction involves an electrophilic metal carbene intermediate.[18] Overlap of the p-orbital with the σ-orbital of the reactive carbon-hydrogen bond is believed to occur and formation of the new C–C bond results once the metal dissociates from the 3-centre transition state (**Scheme 14**).



Scheme 14

Further studies based on Density Functional Theory (DFT) performed by Nakamura showed that the mechanism is probably more complex than Doyle's model and that it notably involves both rhodium atoms from the dirhodium catalyst (**Scheme 15**).[19] According to Nakamura, the process starts with the complexation of the diazo compound with the dirhodium catalyst. Back donation of a rhodium d orbital to the C–N σ*-orbital leads to the extrusion of nitrogen to form a metal-stabilised carbenoid species. The key step then involves hydride transfer from a C–H bond followed by C–C bond formation and regeneration of the Rh–Rh bond. Although only one rhodium atom functions as a carbene-binding site, the other rhodium atom assists the overall process which explains the efficiency of dirhodium(II) carboxylates for C–H insertion reactions.

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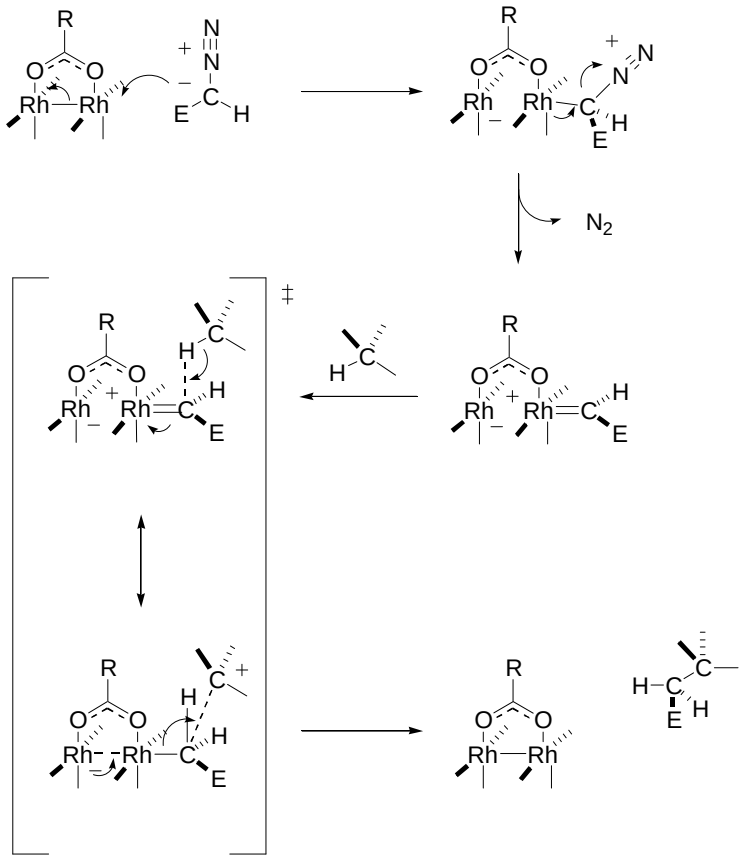
[17] Meerwein, H.; Rathjen, H.; Werner, H. *Ber. Dtsch. Chem. Ges.* **1942**, *75*, 1610.

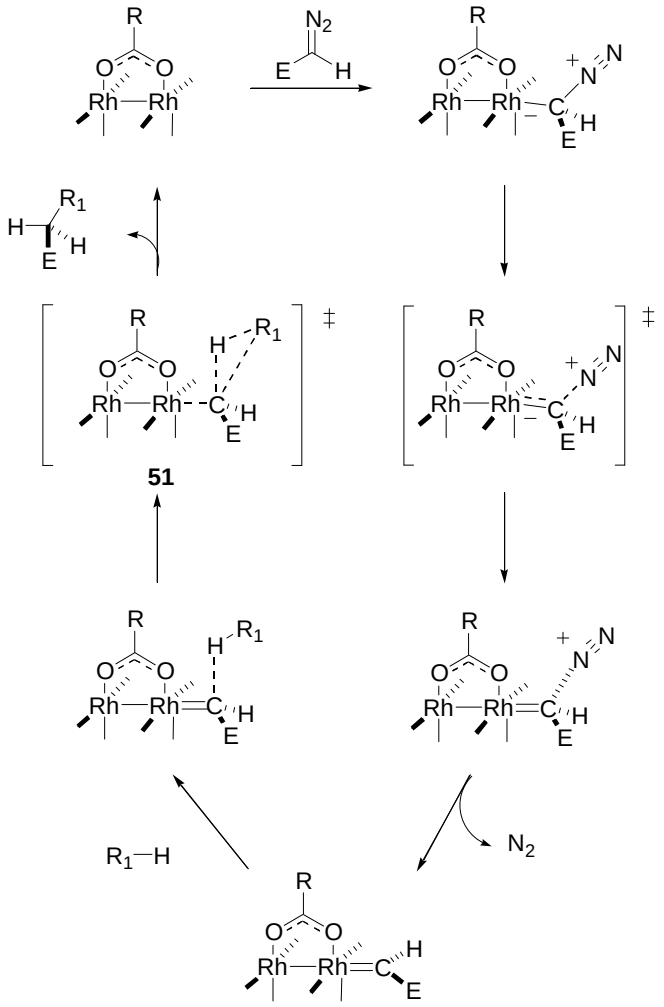
[18] Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958-964.

[19] (a) Nakamura, E.; Yoshikai, N.; Yamanaka, M. *J. Am. Chem. Soc.* **2002**, *124*, 7181-7192 (b) Yoshikai, N.; Nakamura, E. *Adv. Synth. Catal.* **2003**, *345*, 1159-1171.



Scheme 15 *Mechanism of the C–H insertion reaction of rhodium(II) carboxylate stabilised carbenes into an alkane according to Nakamura and co-workers.*

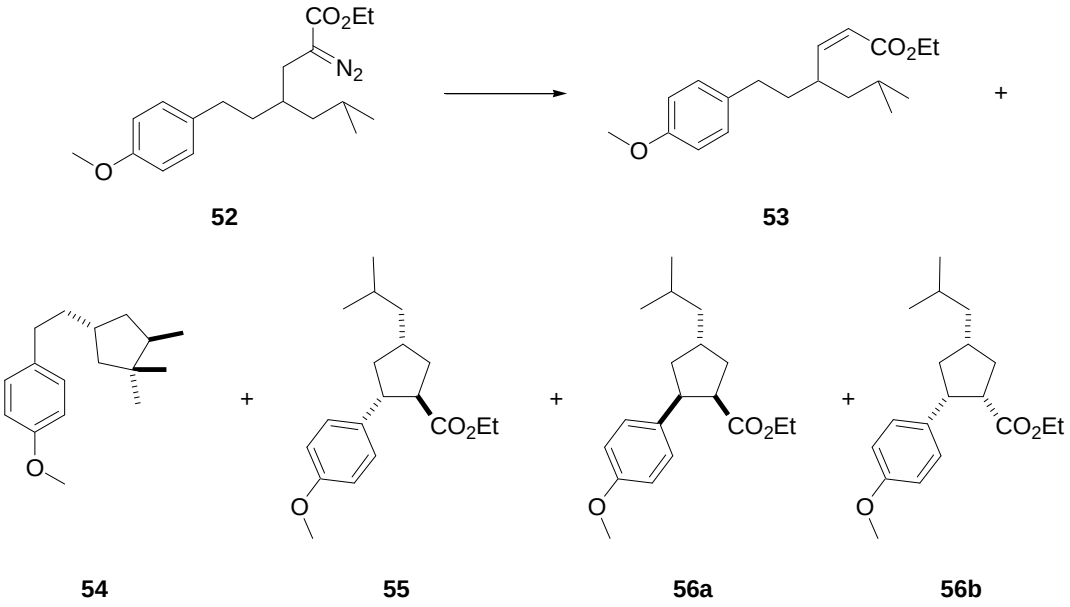
A slightly different model has been used by Nakamura in an effort to explain the diastereoselectivities obtained when forming 5-membered rings by carbenoid C–H insertion (**Scheme 16**).[19b] He claimed that the diastereoselectivity depends on the configuration of the three-centre transition state **51**.



Scheme 16 *Origin of the diastereoselectivity of the C-H insertion reactions according to Nakamura.*

However, in 2004 Taber thoroughly studied the relative reactivity of a range of rhodium catalysts on cyclopentane formation by C–H insertion and concluded that there was no obvious rational for the observed selectivities.[20] He particularly focused on the ratio of C–H insertion to β-hydride elimination [(**54** + **55** + **56**)/ **53**], the chemoselectivity [**54**/ (**55** +**56**)] and the diastereoselectivity (**55**/**56**) of the insertion reaction and did not find any correlation between the characteristics of the catalysts employed and the ratio of products obtained (**Equation 7**). These results clearly show that the mechanism for the C–H insertion reaction of metal carbenoids is still not well defined.

[20] Taber, D. F.; Joshi, P. V. *J. Org. Chem.* **2004**, *69*, 4276-4278.

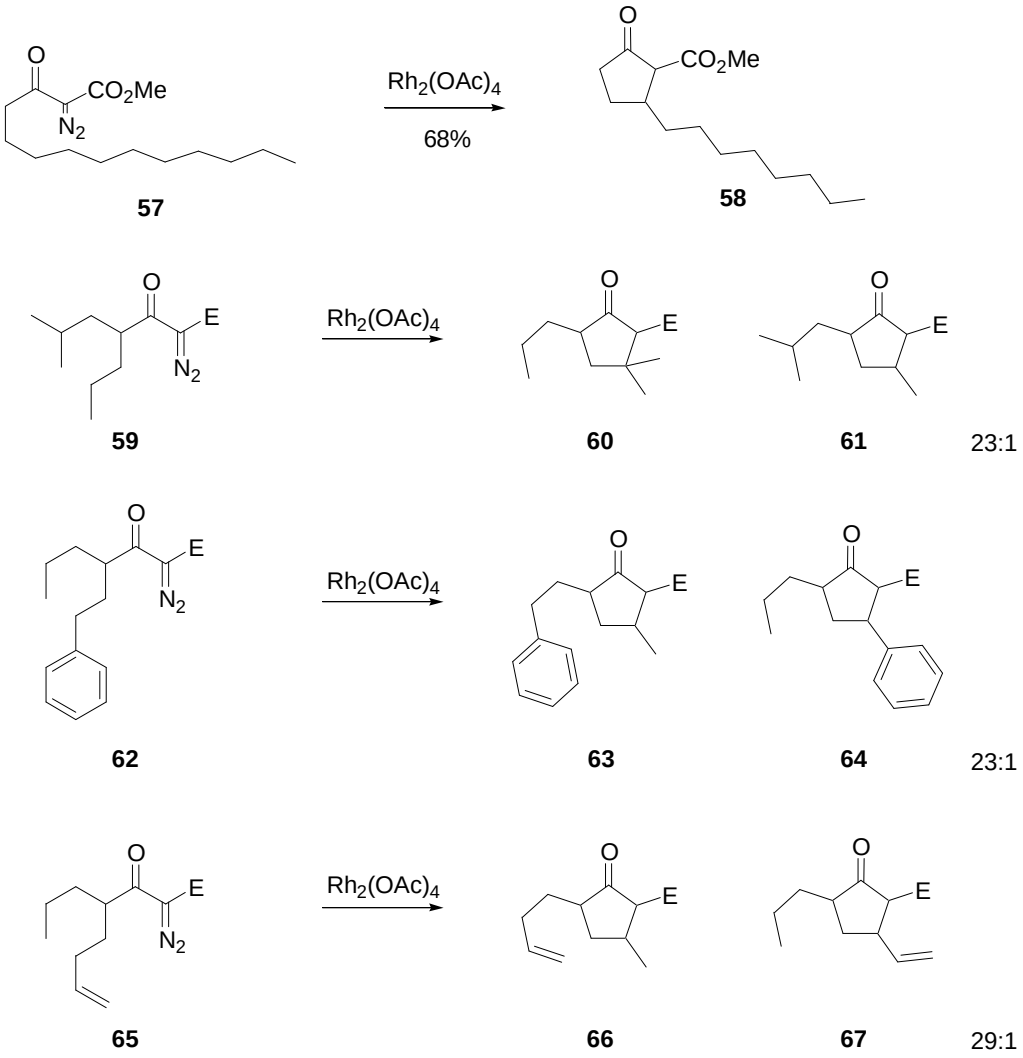


Equation 7

It is worth noting that a metal carbene complex can potentially insert into any C–H bond. This characteristic raises both regio- and chemoselectivity issues. Taber and co-workers reported that the formation of a five-membered ring is the favoured outcome of the C–H insertion reaction of a α-diazo β-keto ester into a freely rotating aliphatic side chain.[21] He also showed that the more substituted the γ-carbon is, the faster the insertion reaction. Finally he showed that both allylic and benzylic positions are disfavoured sites for C–H insertion compared to aliphatic positions (**Scheme 17**). [22]

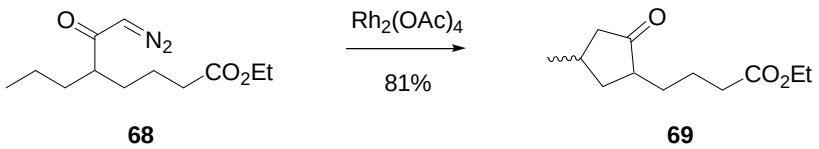
[21] Taber, D. F.; Petty, E. H. *J. Org. Chem.* **1982**, *47*, 4808-4809.

[22] (a) Taber, D. F.; Raman, K. *J. Am. Chem. Soc.* **1983**, *105*, 5935-5937 (b) Taber, D. F.; Ruckle, R. E., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7686-7693.



Scheme 17

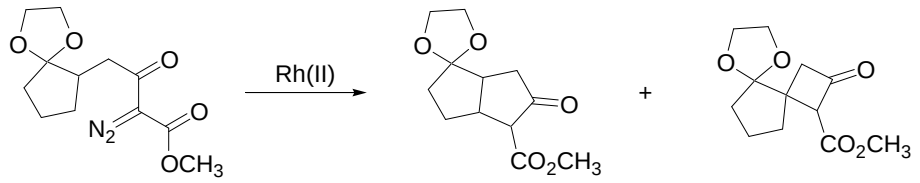
Stork and Nakatani investigated the influence of electronic effects on the regioselectivity of the C–H insertion reactions of metal carbenoids. They demonstrated that electron-withdrawing groups such as carboxyl groups can deactivate a β- or γ-methylene group to carbenoid C–H insertion (**Equation 8**).[23]



Equation 8

[23] Stork, G.; Nakatani, K. *Tetrahedron Lett.* **1988**, *29*, 2283-2286.

Rhodium(II) carboxylates are the catalysts of choice for carbenoid generation when performing C–H insertion reactions. Variation of the ligands, and in particular their steric bulk, greatly influences the selectivity. For instance, Ikegami showed that the bulky rhodium(II) triphenylacetate favours insertion into a methylene C–H bond rather a methine C–H bond in the case of substrates where an α-diazo β-keto ester is tethered to a carbocycle (**Equation 9**).[24]



69 **70** **71**

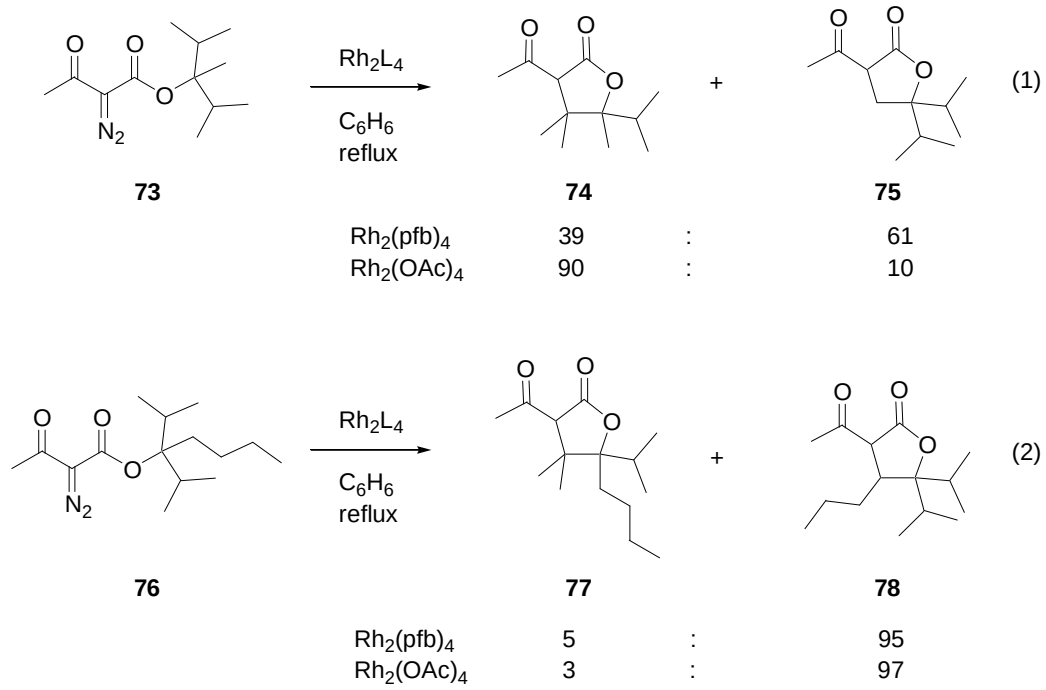
37 ; 63 with $Rh_2(OAc)_4$
96 : 4 with $Rh_2(TPA)_4$

Equation 9

Finally, it is important to bear in mind that conformational preferences can be more influential than electronic effects on the regioselectivity of C–H insertion reactions. Indeed, Doyle and co-workers confirmed Taber's observations in terms of regioselectivity,[18] namely that the preference tertiary > secondary > primary C–H bond insertion is expected for systems in which each of the possible sites for insertion can present a C–H bond to the carbene centre with equal probability for insertion. This effect can be amplified by decreasing the electrophilicity of the metal carbenoid by changing the catalyst ligands (**Scheme 18**, equation (1)). Doyle and co-workers also showed that when the possible sites for insertion do not present their C–H bonds to the carbene centre with equal probability, conformational preferences govern the process and electronic effects can not be used to predict the outcome of the reaction on their own (**Scheme 18**, equation 2). This finding can probably be explained by the fact that the C–H insertion reaction is governed by the overlapping of the p-orbital of the metal

[24] Hashimoto, S.; Watanabe, N.; Ikegami, S. *Tetrahedron Lett.* **1992**, *33*, 2709-2712.

carbenoid with the σ-orbital of the reactive C–H bond. Therefore, a conformationaly constrained system where these two orbitals are close to each other will be favoured.

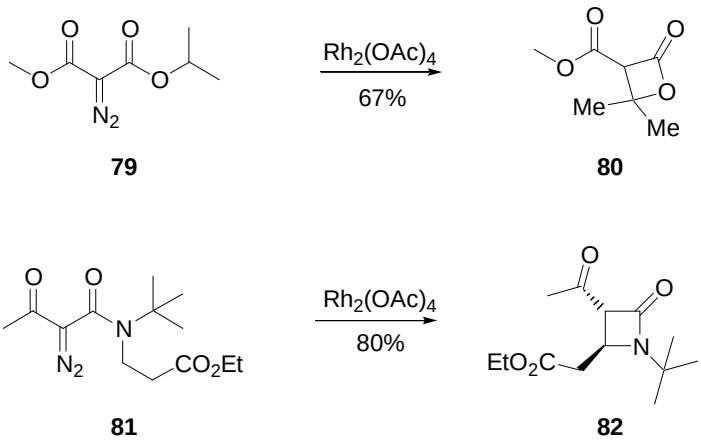


Scheme 18

Despite being limited to intramolecular processes, metal carbenoid C–H insertion reactions can be used to form of three- to six-membered carbocycles and heterocycles. In general five-membered ring formation is the favoured process, but four-membered heterocycles such as β-lactones and β-lactams are also synthesised efficiently by catalytic decomposition of diazo compounds. Lee and co-workers have described the synthesis of β-lactones from alkyl methyl diazomalonates[25] and Doyle has shown that rhodium(II) carboxylates are ideal catalysts for the formation of β-lactams from α-diazo amides giving the desired lactams in high yields and with good selectivity (**Scheme 19**).[26]

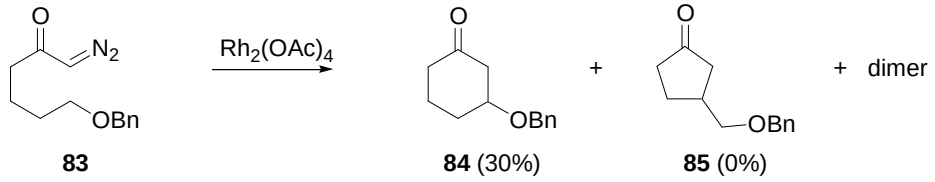
[25] Lee, E.; Jung, K. W.; Kim, Y. S. *Tetrahedron Lett.* **1990**, *31*, 1023-1026.

[26] Doyle, M. P.; Pieters, R. J.; Taunton, J.; Pho, H. Q.; Padwa, A.; Hertzog, D. L.; Precedo, L. *J. Org. Chem.* **1991**, *56*, 820-829.



Scheme 19

Six-membered ring formation can compete with five-membered ring formation when a δ-C–H bond is activated by an adjacent heteroatom. Adams showed that the presence of a heteroatom makes the adjacent C–H bond(s) more likely to undergo the insertion with a metal carbenoid.[27] For instance the cyclohexanone **84** is the main product obtained from the reaction of diazoketone **83** promoted by $Rh_2(OAc)_4$ (**Equation 10**).

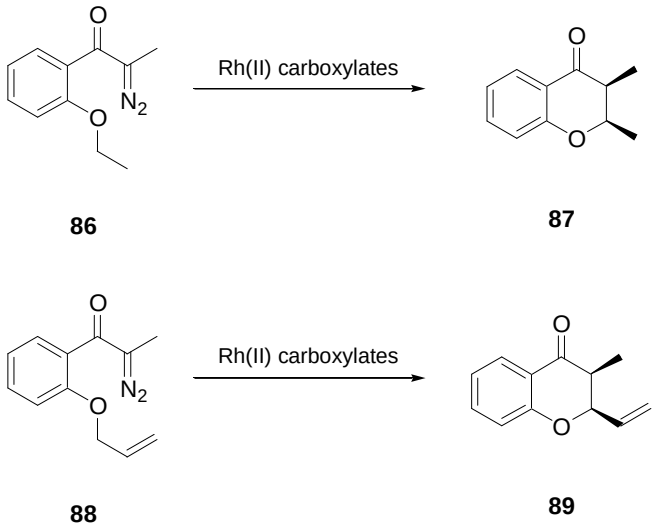


Equation 10

The formation of six-membered heterocycles by C–H insertion is usually disfavoured because the presence of a heteroatom at the γ-position of the diazoketone can result in the formation of an ylide intermediate which can then undergo a variety of subsequent reactions, as described in part **1.4.3**. Nevertheless, McKervey *et al* have demonstrated that rhodium(II) carboxylate catalysed decomposition of diazoketones **86** and **88** furnishes the chromanones **87** and **89** (**Scheme 20**).[28]

[27] (a) Adams, J.; Poupart, M. E.; Grenier, L.; Schaller, C.; Ouimet, N.; Frenette, R. *Tetrahedron Lett.* **1989**, *30*, 1749-1752 (b) Adams, J.; Poupart, M. E.; Grenier, L. *Tetrahedron Lett.* **1989**, *30*, 1753-1756.

[28] McKervey, M. A.; Ye, T. J. *J. Chem. Soc., Chem. Commun.* **1992**, 823-824.



86 **87**

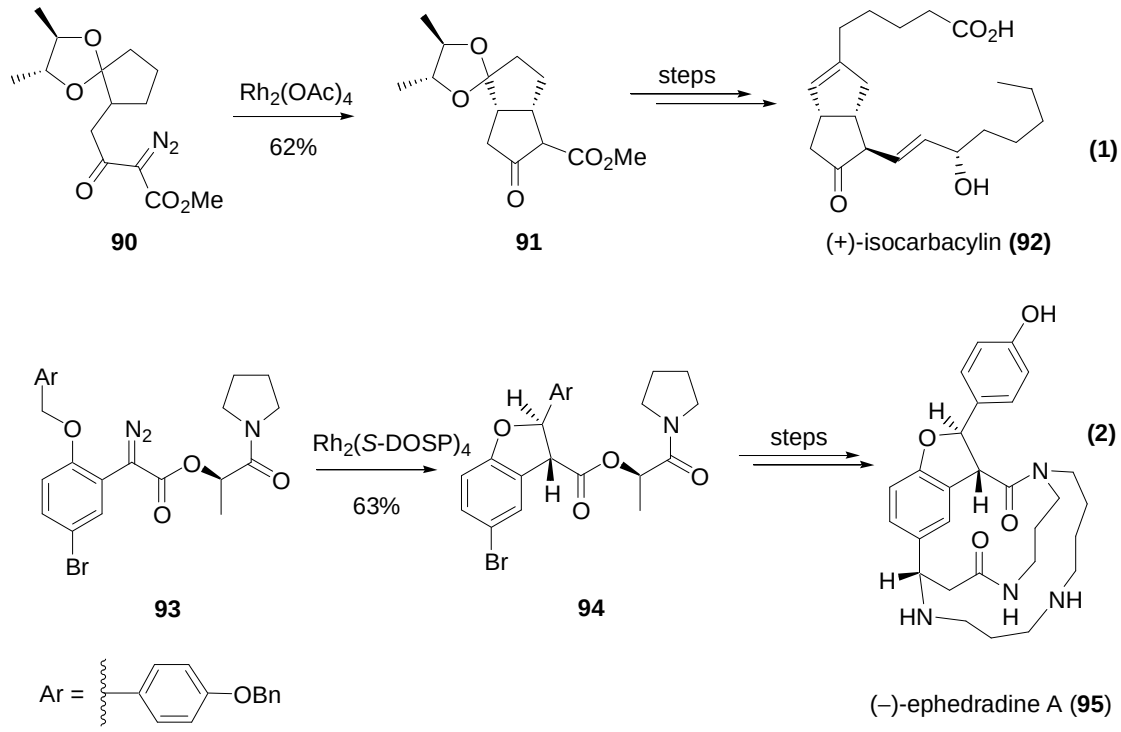
88 **89**

Scheme 20

The construction of 5-membered rings is by far the most successful application of C–H insertion reactions. The reaction has largely been employed in the total syntheses of natural products due to the very frequent presence of cyclopentane structural units in these compounds. For instance, the key step in the total synthesis of (+)-isocarbacylin (**92**) by Ikegami and co-workers is a rhodium catalysed C–H insertion reaction (example 1, **Scheme 21**).[29] More recently, Fukuyama's group achieved the first enantioselective total synthesis of (-)-ephedradine A (Orantine) (**95**) using intramolecular carbenoid C–H insertion to construct the optically active dihydrobenzufuran core (example 2, **Scheme 21**).[30]

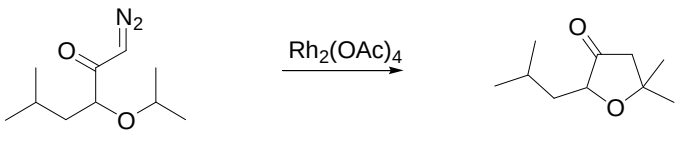
[29] Hashimoto, S.; Shinoda, T.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1988**, 1137-1139.

[30] Kurosawa, W.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 8112-8113.



Scheme 21

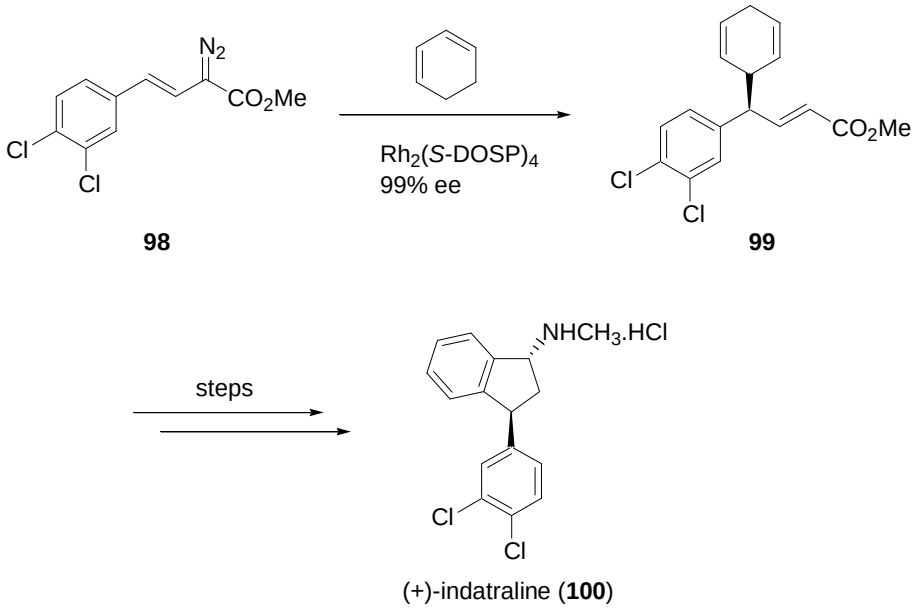
Methods for the formation of 5-membered heterocycles are of great importance and are particularly useful for the preparation of reduced furans. Adams and co-workers showed that furanones can be obtained in very good yield and selectivity using carbenoid C–H insertion reactions (**Equation 11**).[28] This demonstrated once more that the presence of a heteroatom increases the reactivity of adjacent C–H bonds towards insertion of a metal carbenoid.



Equation 11

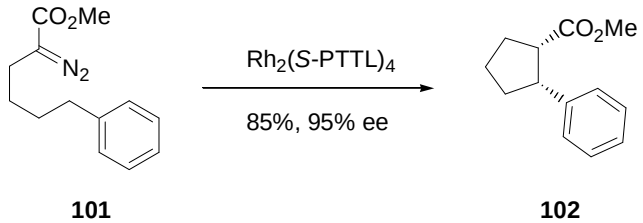
In the recent years, important progress has been made in the field of enantioselective rhodium-catalysed C–H insertion reactions and there are now many instances in which these reactions have been used in total synthesis. For example, Davies and co-workers

used dirhodium tetrakis-[(*S*)-N-dodecylbenzenesulfonyl]prolinate [Rh_2(*S*-DOSP)$_4$] as a catalyst in the asymmetric total synthesis of (+)-indatraline (**100**) (**Scheme 22**).[31]



Scheme 22

Hashimoto's group recently reported the highly enantio- and diastereoselective construction of 1,2-disubstituted cyclopentane compounds by dirhodium(II) tetrakis[*N*-phtaloyl-(*S*)-*tert*-leucinate]-catalysed C–H insertion reactions of α-diazo esters (**Equation 12**).[32]



Equation 12

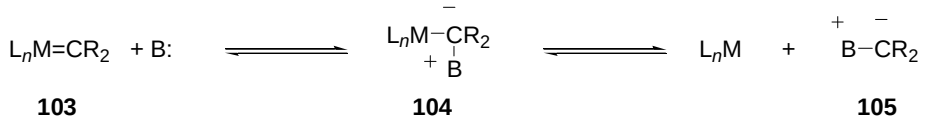
1.4.3 Oxonium ylide formation and subsequent reactions

Metal-stabilised carbenoid species are Lewis acids that can therefore undergo addition of a Lewis base (B:) at the carbene carbon. This leads to the formation of a metal

[31] Davies, H. M. L.; Gregg, T. M. *Tetrahedron Lett.* **2002**, *43*, 4951-4953.

[32] Minami, K.; Saito, H.; Tsutsui, H.; Nambu, H.; Anada, M.; Hashimoto, S. *Adv. Synth. Catal.* **2005**, *347*, 1483-1487.

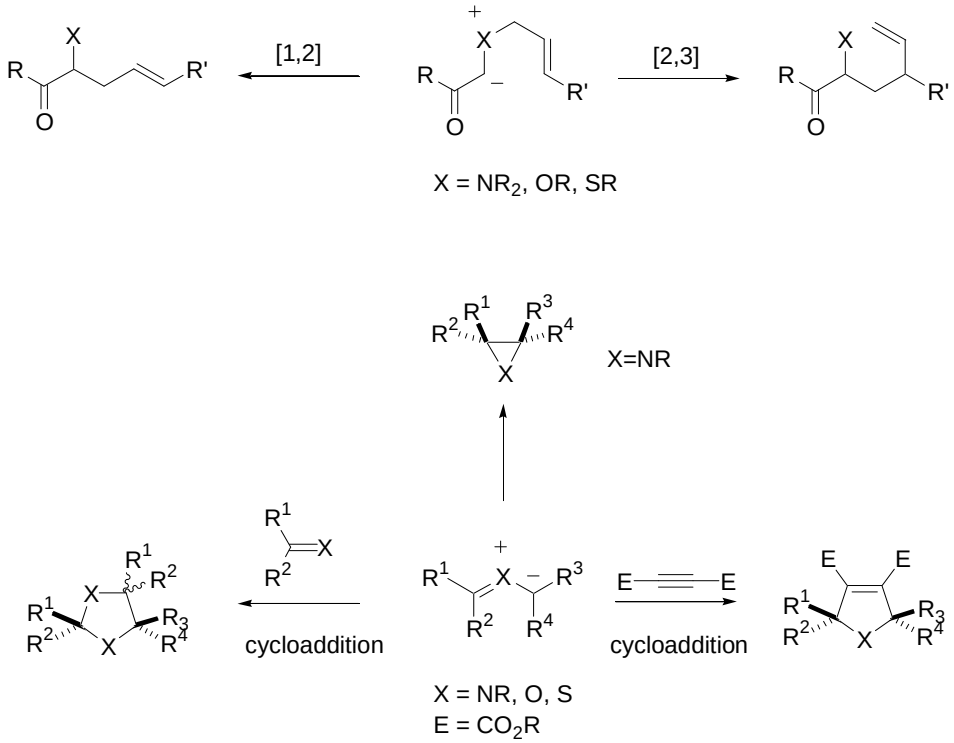
stabilised ylide **104** which can dissociate to form a "free" ylide **105** (**Scheme 23**). In principle, all these processes are reversible and the formation of a free ylide will depend on the strength of the metal-carbene bond. Lewis bases associated with the formation of ylides are usually heteroatoms and a sulfur, nitrogen or oxygen atom is most commonly involved.



103 **104** **105**

Scheme 23

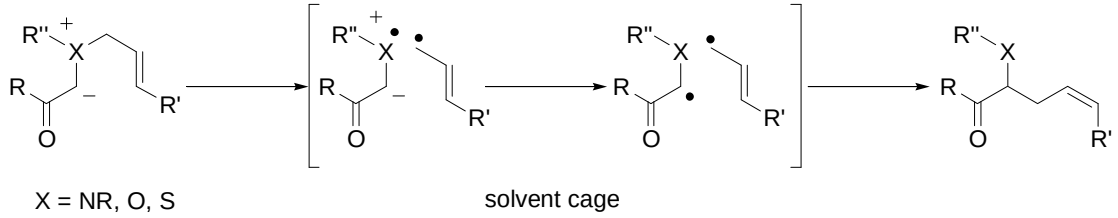
Ylides generated by the catalytic decomposition of diazo compounds can undergo four different types of reactions: the [2,3]-sigmatropic rearrangement of allyl-substituted ylides, the [1,2] rearrangement (Stevens rearrangement), β-hydride elimination and dipolar cycloaddition when the Lewis base is an imine, carbonyl or thiocarbonyl group (**Scheme 24**). These four types of transformation can compete with each other and the outcome of the reaction of ylides is governed by the nature of the substrate, the experimental conditions and the catalyst involved.



Scheme 24

Stevens rearrangement ([1,2]-shift)

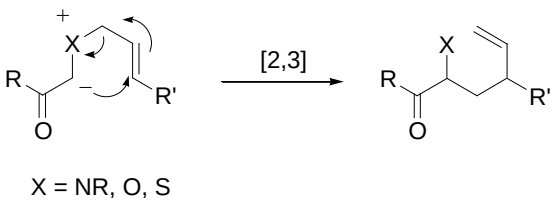
The 1,2-shift of an ylide is formally a symmetry-forbidden process according to the Woodward-Hoffmann rules. Nevertheless, this transformation is frequently observed when ylide intermediates are involved. Mechanistic investigations suggest that the ylide intermediate undergoes homolytic cleavage to produce a radical pair which then undergoes rapid recombination within the solvent cage in which the radicals were trapped during their formation (**Scheme 25**).[33]



Scheme 25

[2,3]-Sigmatropic rearrangement

This rearrangement is one of the most widely used transformations of catalytically generated ylides. It is a very versatile method for C–C bond formation and allows the rapid construction of structurally complex intermediates from simple starting materials (**Equation 13**). This rearrangement reaction can only occur in the case of allylic ylides but the presence of an alkene also means that competitive processes such as cyclopropanation can intervene. Substrates which can undergo [2,3]-sigmatropic rearrangement can also undergo a [1,2]-shift but the latter reaction is usually disfavoured.

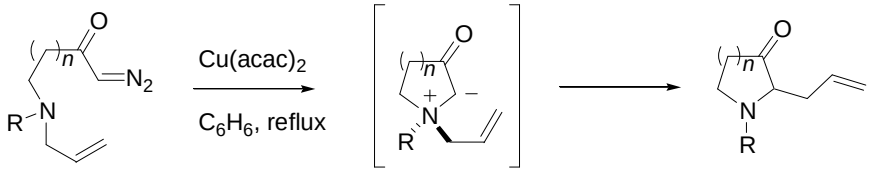


Equation 13

[33] (a) Iwamura, H.; Imahashi, Y. *Tetrahedron Lett.* **1975**, 1401-1404 (b) Maeda, Y.; Sato, Y. *J. Chem. Soc. Perkin Trans. 1* **1997**, 1491-1493.

Reactions of metal-stabilised sulfur and nitrogen ylides

The chemistry of nitrogen and sulfur ylides generated from carbenes and carbenoids is too vast an area of organic chemistry to be described fully in this thesis. To summarise, both types of ylide have been used most frequently as intermediates for [2,3]-sigmatropic rearrangement reactions. Our group has shown that cyclic amines of various sizes can be generated from ammonium ylides (**Scheme 26** and **Table 1**).[34]



106 **107**

Scheme 26

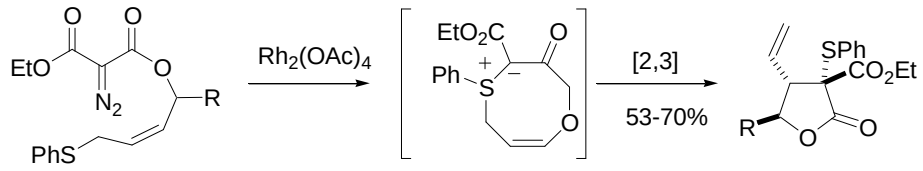
Substrate	*n*	R	Isolated yield of **107** (%)
106a	1	CH_2CHCH_2	76
106b	1	Me	72
106c	2	CH_2CHCH_2	79
106d	3	Me	84
106e	4	CH_2CHCH_2	39

Table 1

A typical example of sulfonium ylide generation and subsequent rearrangement is shown in **Scheme 27**. In this example, the diazo ester **108** was treated with rhodium(II) acetate dimer affording the ylide intermediate **109**. [2,3]-Sigmatropic rearrangement of this ylide afforded the trisubstituted furanone **110** in yields ranging from 53 to 70% depending on the nature of the substituent R (methyl, *n*-propyl, isopropyl, benzyl and *n*-pentyl).[35]

[34] Clark, J. S.; Hodgson, P. B. *J. Chem. Soc., Chem. Commun.* **1994**, 2701-2702.

[35] Kido, F.; Sinha, S. C.; Abiko, M.; Yoshikoshi, A *Tetrahedron Lett.* **1989**, *30*, 1575-1578.



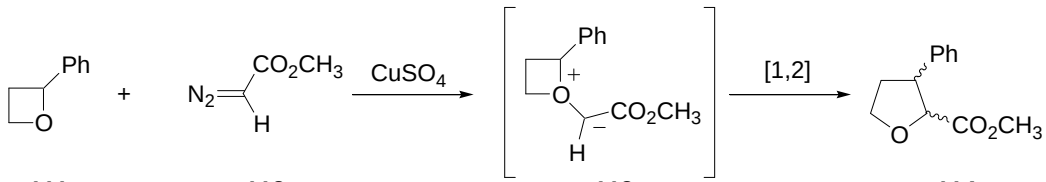
108 **109** **110**

Scheme 27

Oxonium ylides

Even though oxygen-based ylides are nowadays widely used, the development of this chemistry is a relatively recent innovation compared to the chemistry of sulfonium and ammonium ylides. The relatively recent introduction of rhodium(II) acetate as a catalyst is responsible for this late development. This catalyst allows metal carbenoid generation to be performed at room temperature, a temperature at which oxonium ylides are stable enough to undergo further controlled reactions. Oxonium ylides are indeed less stable than the corresponding ammonium or sulfonium ylides. The relative instability of oxonium ylides was believed to influence the competition with other processes.

Historically one of the first examples of the use of oxonium ylides was described by Nozaki in 1966. It involved the copper(II)-catalysed reaction of phenyl oxetane **111** with the diazo ester **112** to give the oxonium ylide **113**. A [1,2]-Stevens rearrangement subsequently afforded the tetrahydrofuran **114** in 87% yield (**Scheme 28**).[36]

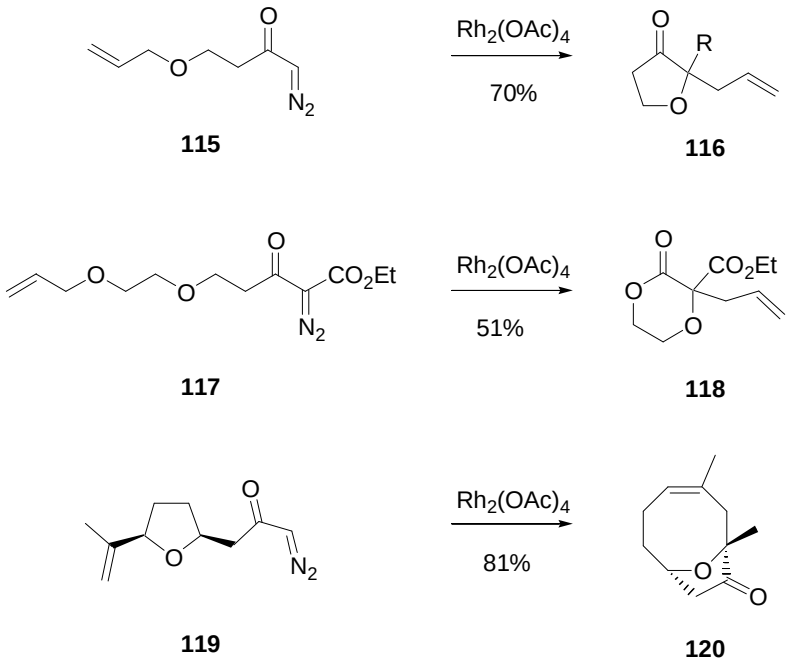


111 **112** **113** **114**

Scheme 28

[36] (a) Nozaki, H.; Takaya, H.; Noyori, R. *Tetrahedron* **1966**, *22*, 3393-3401 (b) Nozaki, H.; Takaya, H.; Moriuti, S.; Noyori, R. *Tetrahedron* **1968**, *24*, 3655-3669.

In spite of the example above, intermolecular reactions involving oxonium ylides are very scarce compared to the much more frequently encountered intramolecular process. As for sulfonium and ammonium ylides, the main interest in oxonium ylides as reactive intermediates relies on their ability to undergo [2,3]-sigmatropic rearrangement. The first examples of [2,3] rearrangement reactions of cyclic oxonium ylides were described by Pirrung and Werner in 1986.[37] In these examples, rhodium(II) acetate catalysed decomposition of several diazoketones afforded cyclic ethers with various ring sizes (**Scheme 29**).



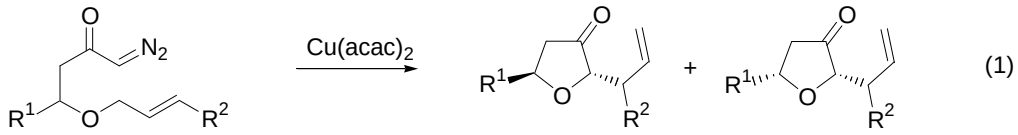
Scheme 29

The Clark group was the first to introduce copper(II) acetylacetonate as a catalyst for the efficient formation of furanones **122** and **124** in high yield and excellent diastereoselectivities (**Scheme 30**).[38] Copper(II) acetylacetonate was found to be an excellent catalyst in cases where competing C–H insertion is problematic. Copper

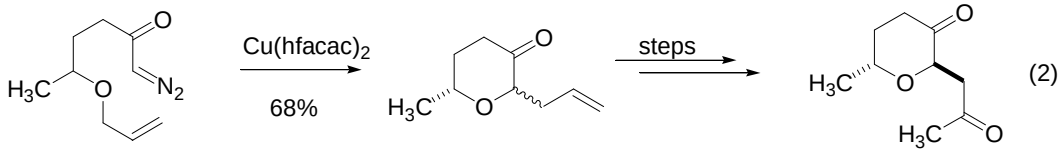
[37] Pirrung, M. C.; Werner, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 6060-6062.

[38] Clark, J. S. *Tetrahedron Lett.* **1992**, *33*, 6193-6196.

catalysts have been used again by our group in the key step leading to the total synthesis of (+)-decarestrictine L (**127**).[39]



121 $R^1 = (CH_3)_2CH$, $R^2 = H$ **122a**,82% **122b**, 2.5%
123 $R^1 = CH_3(CH_2)_2$, $R^2 = H$ **124a**, 82% **124b**, 2.5%



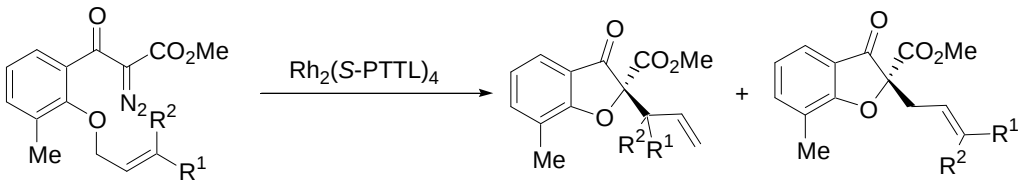
125 **126** (±)-decarestrictine L (**127**)

Scheme 30

Although [2,3]-sigmatropic rearrangement is the major reaction of cyclic allylic oxonium ylides, it is important to note that [1,2]-Stevens rearrangement often competes with [2,3]-rearrangement. For instance, Hashimoto and co-workers have studied the enantioselective generation and rearrangement of allylic oxonium ylides from the α-diazo β-ketoesters **128**.[40] Using dirhodium(II) tetrakis[*N*-phtaloyl-(*S*)-*tert*-leucinate] as a catalyst they obtained mixtures of benzofuranones **129** and **130**, and the ratio of products arising from [2,3]-rearrangement and [1,2]-shift was found to be dependent on the substitution pattern of the substrate (**Equation 14**).

[39] (a) Clark, J. S.; Whitlock, G. A. *Tetrahedron Lett.* **1994**, *35*, 6381-6382 (b) Clark, J. S.; Fessard, T. C.; Whitlock, G. A. *Tetrahedron* **2006**, 62, 73-78.

[40] Kitagaki, S.; Yanamoto, Y.; Tsutsui, H.; Anada, M.; Nakajima, M.; Hashimoto, S. *Tetrahedron Lett.* **2001**, *42*, 6361-6364.

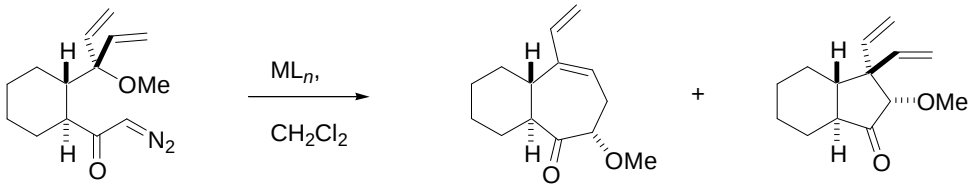


128 **129** [2,3] **130** [1,2]

R^1 = Me and R^2 = H	92	:	8
R^1 = H and R^2 = Me	82	:	18
R^1 = Me and R^2 = Me	71	:	29

Equation 14

Clark and co-workers obtained mixtures of [2,3] and [1,2]-rearrangement products when attempting to construct fused medium-ring carbocycles by catalytic generation and rearrangement of oxonium ylides (**Equation 15**).[41] For example, treatment of the diazoketone **131** with $Rh_2(OAc)_4$ afforded the desired [2,3]-sigmatropic rearrangement product **132** in 70% yield alongside 5% of the [1,2]-shift product **133**.



131 **132** [2,3] **133** [1,2]

ML_n = $Rh_2(OAc)_4$	70%	5%
$Cu(hfacac)_2$	49%	9%

Equation 15

The [2,3]-sigmatropic rearrangement reaction of an oxonium ylides obviously requires the presence of an alkene. Consequently, there is the possibility of competing cyclopropanation during ylide formation. For example, decomposition of the diazo ester **135** with $Rh_2(OAc)_4$ in the presence of the allylic acetal **134** led to the formation of the desired enol ether **136** as well as the formation of cyclopropane **137** (**Equation 16**).[42]

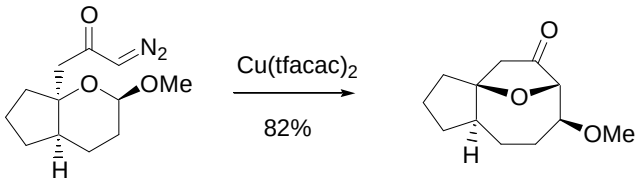
[41] Clark, J. S.; Walls, S. B.; Wilson, C.; East, S. P.; Drysdale, M. *J. Eur. J. Org. Chem.* **2006**, 323-327.

[42] Doyle, M. P.; Griffin, J. H.; Chinn, M. S.; Van Leusen, D. *J. Org. Chem.* **1984**, *49*, 1917-1925.

134 **135** **136** 77% **137** 23%

Equation 16

The [1,2]-Stevens rearrangement reaction cannot be considered only as side reaction to the [2,3]-rearrangement. It is also a reaction of potential synthetic utility as shown recently by West and co-workers who used cyclic acetals precursors to construct fused bicyclic compounds containing a medium ring via a copper(II)-catalysed ylide formation and [1,2]-shift sequence (**Equation 17**).[4a]

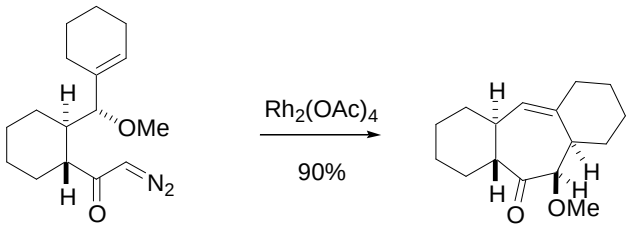


138 **139**

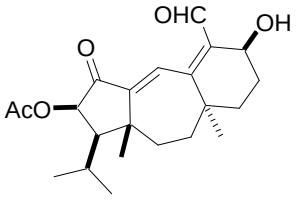
Equation 17

Our group has demonstrated that metal carbenoids derived from diazo compounds can be used for the formation of a great variety of cyclic structures. For instance, fused carbocycles can be prepared in good yield following the synthetic pathway described in **Equation 18**.[43] Upon treatment with rhodium(II) acetate dimer, diazoketone **140** was converted into the fused tricyclic ketone **141** in 90% yield and with excellent selectivity. This methodology has direct application towards the total synthesis of fused polycarbocyclic natural products such as Guanacastepene A (**142**).

[43] Clark, J. S.; Guérot, C.; Wilson, C.; Blake, A. *J. Chem. Commun.* **2007**, 4134-4136.



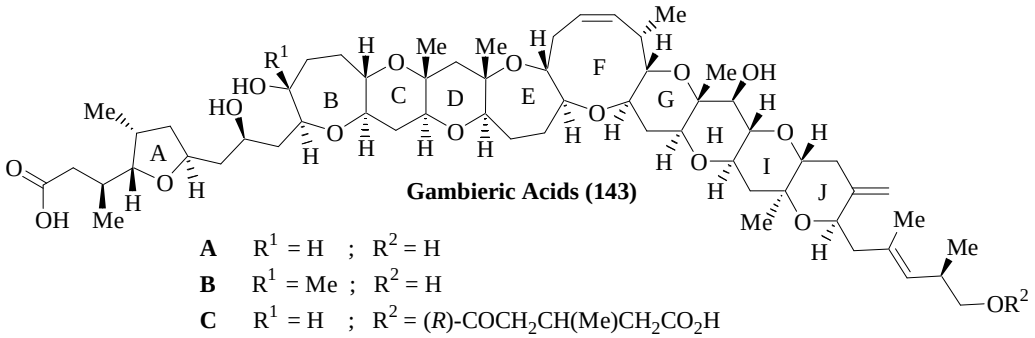
140 **141**

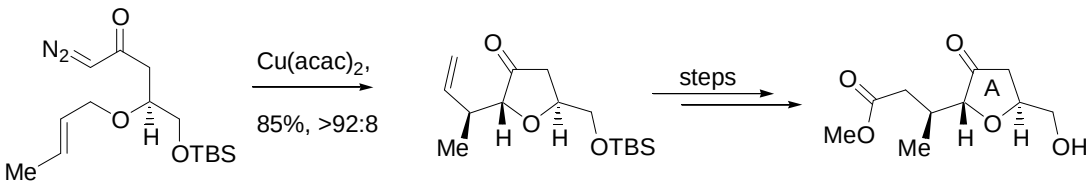


guanacastepene (**142**)

Equation 18

Tandem oxonium ylide formation and [2,3]-sigmatropic rearrangement is also the key step in the synthesis of the A-ring fragment of gambieric acid A (**143A**) (**Scheme 31**).[44] Treatment of diazoketone **144** with $Cu(acac)_2$ afforded furanone **145** in 85% yield as a 92:8 mixture of diastereoisomers.





144 **145** **146**

Scheme 31

[44] Clark, J. S.; Fessard, T. C.; Wilson, C. *Org. Lett.* **2004**, *11*, 1773-1776.

Last but not least, the Clark group has shown that the [2,3]-sigmatropic rearrangement is a powerful tool for the rapid construction of fused cyclic ethers. This particular transformation has fantastic direct applications in natural product synthesis notably towards the syntheses of neoliacinic acid and the eunicellin class of compounds. This will be described in detail hereafter.

1.5 Labiatin A and related natural products

Labiatin A (**147**) was isolated in 1996 from *Eunicellia labiata*, a relatively deep water gorgonian coral collected near Dakar in Senegal, along with the labiatins B (**148**) and C (**149**) and labiatamides A and B (**Figure 3**).[45]

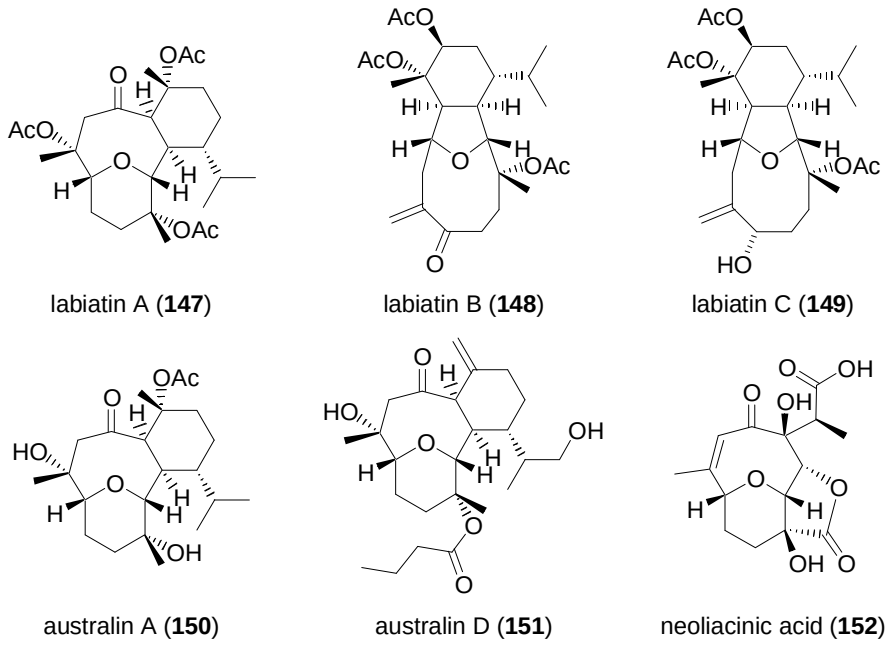


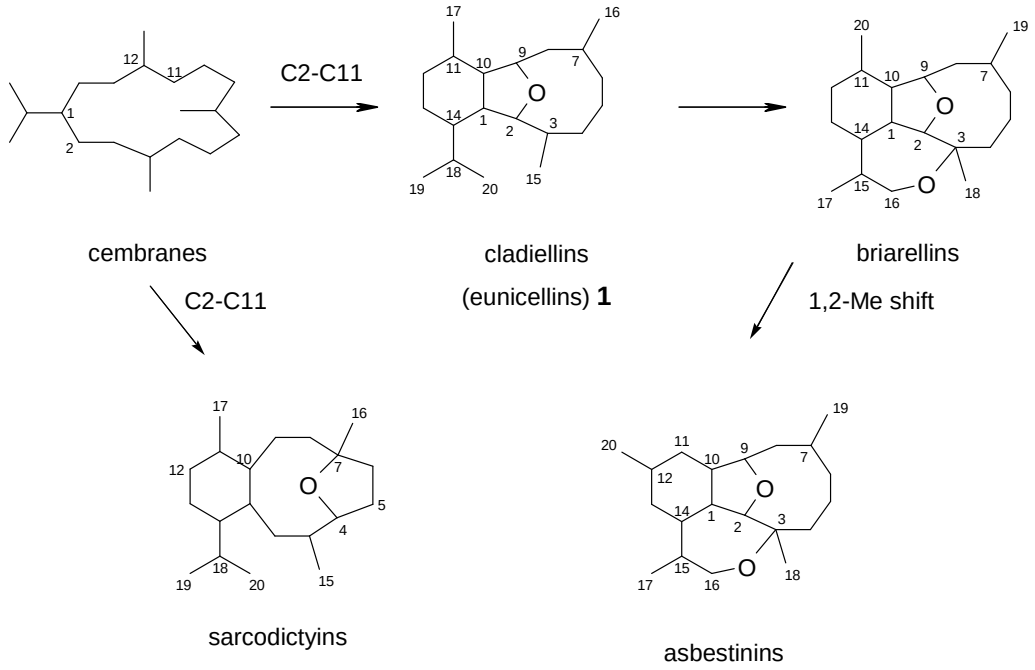
Figure 3 *The labiatin family of marine natural products, australins A and D, and neoliacinic acid.*

These four molecules belong to the cladiellin (eunicellin) family of natural products which is characterised by the general tricyclic diterpenoid carbon skeleton shown in **Scheme 32**.[46] The eunicellin class includes more than 60 members and is one of the

[45] Roussis, V.; Fenical, W.; Vagias, C.; Kornprobst, J. M.; Miralles, J. *Tetrahedron* **1996**, *52*, 2735-2742.

[46] Bernardelli, P.; Paquette, L. A. *Heterocycles* **1998**, *49*, 531-556.

four known classes of oxygenated 2,11-cyclized cembranoids, the others being the briarellins, asbestinins and sarcodictyins. In each of these classes, several members exhibit significant biological activity: the cladiellins exhibit molluscicidal and repellent activity, insect growth inhibitory activity, anti-inflammatory and anti-tumor properties whilst several of the sarcodictyins exhibit very high cytotoxicity.[47]



Scheme 32 *Presumed biosynthesis of the four known classes of 2,11-cyclised cembranoids.*

Labiatin A (**147**) has a rather unusual structure compared to the other eunicellan diterpenoids, possessesing an ether-linkage between C2 and C6 rather than the C2-C9 ether-linkage found in labiatin B (**148**) and C (**149**) and characteristic of this entire class of natural products. Only recently have two other eunicellins possessing structures similar to labiatin A been isolated: australins A (**150**) and D (**151**).[47]

The core structure of labiatin A (**147**) is similar to neoliacinic acid (**152**) a natural product first isolated along with a related compound – neoliacine – from the leaves of

[47] Ahmed, A. F.; Wu, M. H.; Wang, G. H.; Wu, Y. C.; Sheu, J. H. *J. Nat. Prod*. **2005**, *68*, 1051-1055.

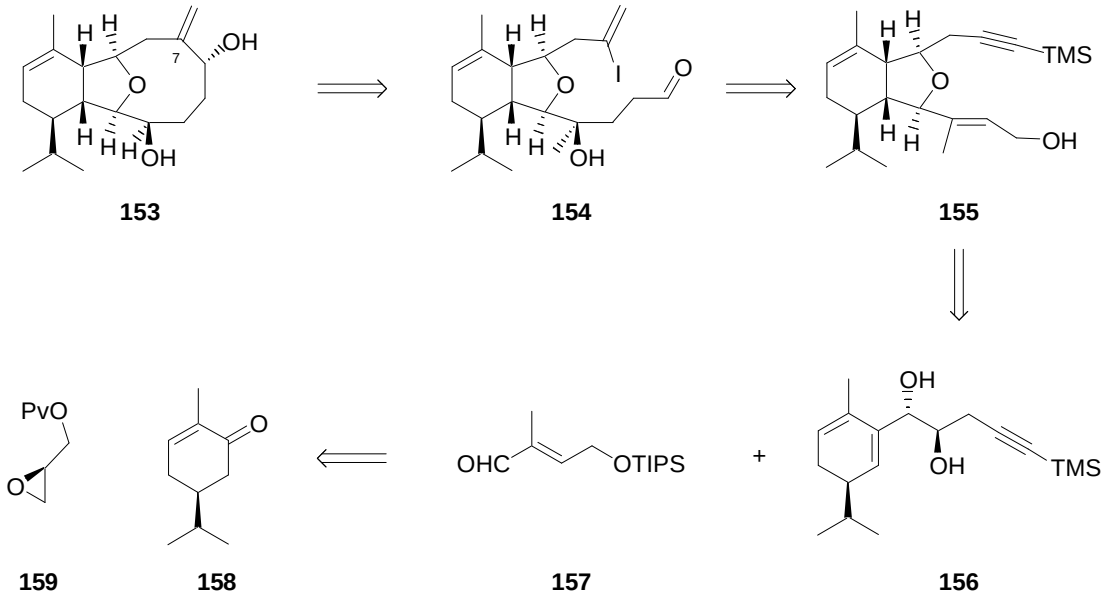
the plant *Neolitsea acciculata Koidz* by Nakayama and co-workers in 1983.[48] The moderate cytotoxicity of neoliacine against HeLa cell culture and the various biological activities exhibited by several eunicellan diterpenoids [e.g., labiatin B (**148**) shows cytotoxic activity against human colon cancer cells with ED_{50} = 0.85 µg/mL] suggest that labiatin A (**147**) might also exhibit interesting biological properties. The remarkable tricyclic core of labiatin A (**147**) and the numerous contiguous stereocentres that it possesses combined with this potential bioactivity make it a particularly interesting target for synthetic chemists.

1.5.1 Chemistry of labiatin A and related compounds

The eunicellin family of natural products has attracted much attention in the scientific community. The first synthesis of a eunicellin diterpene {(–)-7-deacetoxyalcyonin acetate (**153**)} was achieved by Overman and MacMillan in 1995 (**Scheme 33**).[49] The first disconnection reveals the intermediate **154** which contains an aldehyde and a vinyl iodide; a $NiCl_2.CrCl_2$ catalysed intramolecular coupling between those two functional groups would allow the final cyclisation to occur. A key retrosynthetic Prins-pinacol condensation affords the alcohol **156** and the aldehyde **157**. These intermediates could be prepared from (*S*)-carvone (**158**) and the epoxide **159** respectively.

[48] (a) Nozaki, H.; Hiroi, M.; Takaoka, D.; Nakayama, M. *J. Chem. Soc., Chem. Commun.* **1983**, 1107-1108 (b) Takaoka, D.; Nozaki, H.; Nakayama, M. *J. Chem. Soc. Chem. Commun.* **1987**, 1861-1862.

[49] MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391-10392.

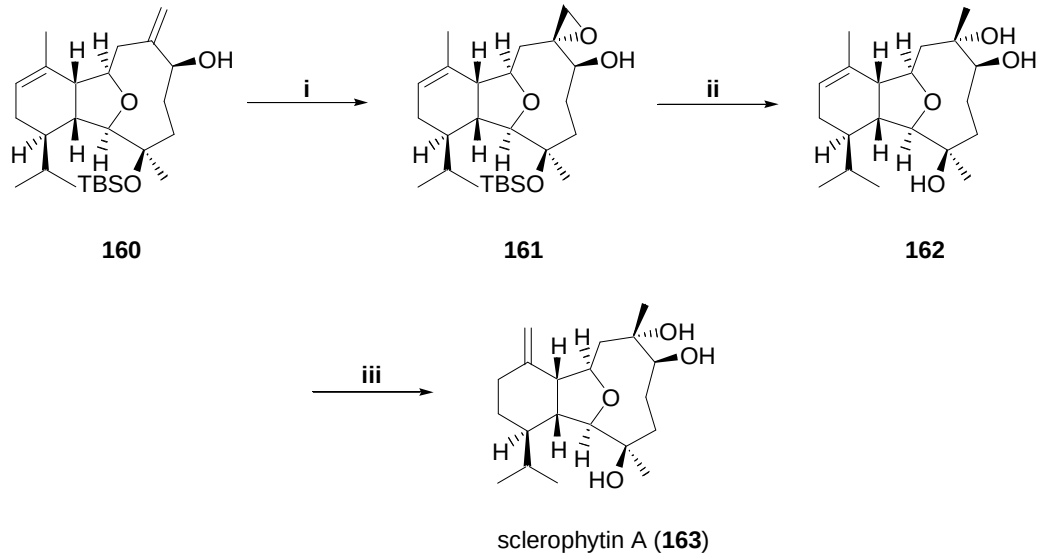


153 **154** **155**

159 **158** **157** **156**

Scheme 33 *Overman's synthetic approach to (–)-7-deacetoxyalcyonin acetate (**153**)*

Following the synthesis of (–)-7-deacetoxyalcyonin acetate (**153**), Overman and co-workers managed to complete a synthesis of sclerophytin A (**163**) by isomerisation of cladiell-11-ene-3,6,7-triol **162**, the latter being readily obtained from allylic alcohol **160** which was an intermediate in the synthesis of **153** (**Scheme 34**).[50]



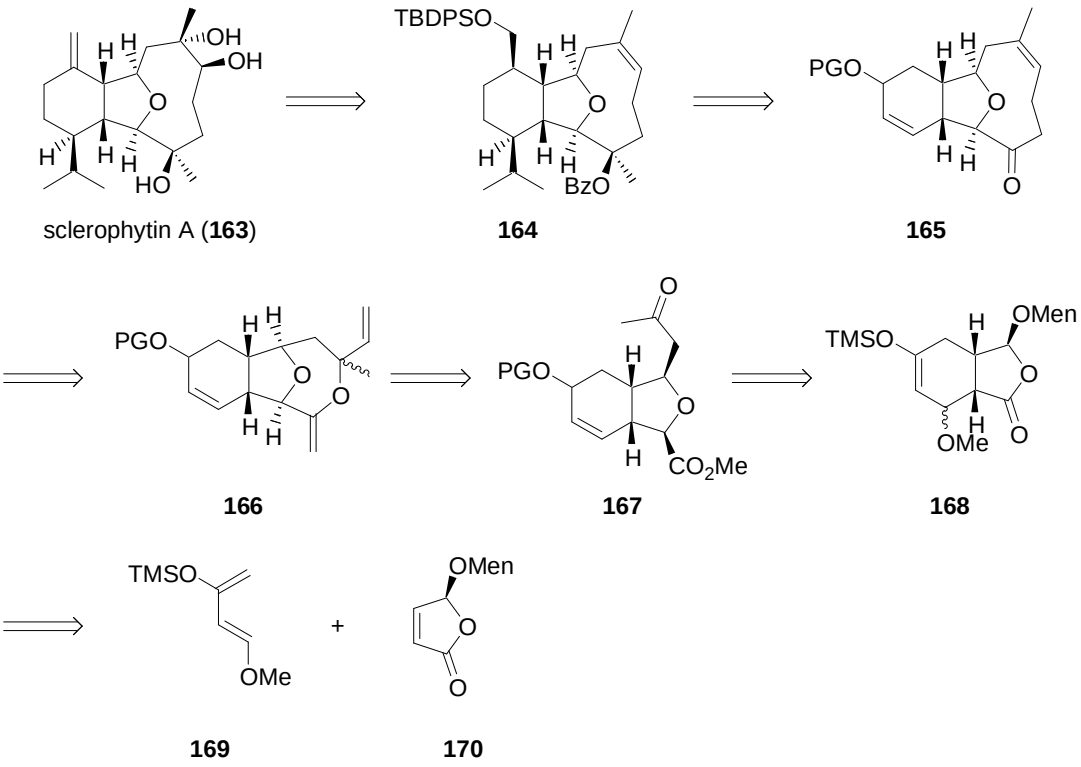
160 **161** **162**

sclerophytin A (**163**)

Scheme 34 *reagents and conditions* **i**, $VO(acac)_2$, *t*-BuO_2H, benzene, 99%; **ii**, (a) DIBAL-H, benzene, 78% (b) TBAF, THF, reflux, 96%; **iii**, hν, *p*-xylene, AcOH, *i*-PrOH, 28%.

[50] MacMillan, D. W. C.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2001**, *123*, 9033-9044.

Just before Overman's publication of a synthesis of sclerophytin A (**163**), Paquette disclosed a total synthesis of this natural product which also revealed its authentic structure.[51] The retrosynthesis described in **Scheme 35** starts with several FGIs which successively lead to the intermediates **164** and **165**. Intermediate **165** was expected to be accessible by Claisen rearrangement of the enol ether **166**. Chemoselective vinyl anion addition to the ketone **167** with accompanying ring closure would deliver a tricyclic lactone, Tebbe olefination of which would afford the enol ether **166**. Further simplifications then revealed intermediate **168**. A retro-Diels-Alder reaction finally afforded Danishefsky's diene **169** and lactone **170**.



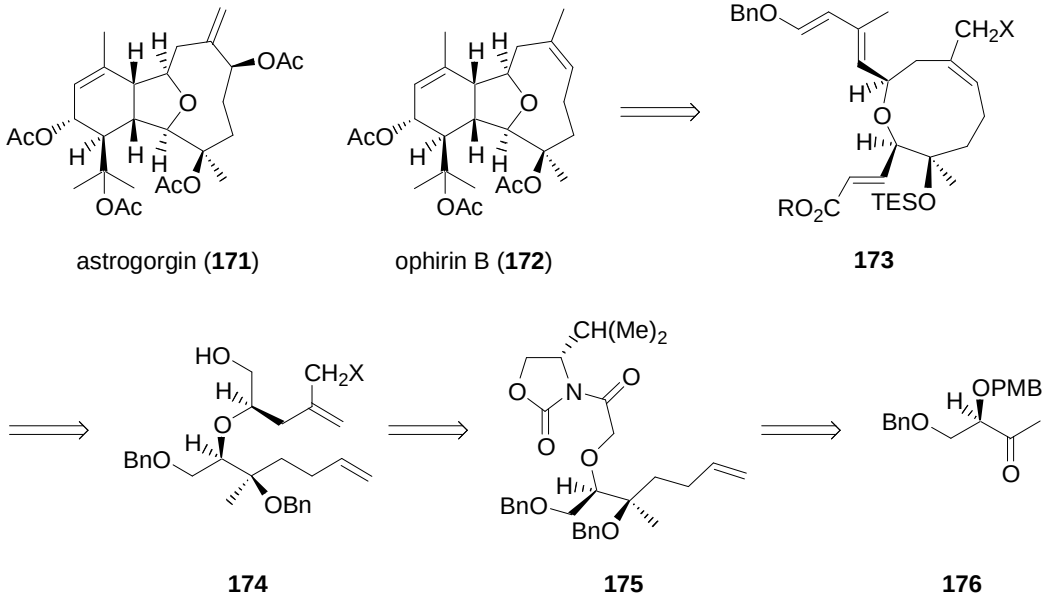
Scheme 35

Crimmins has also been prolific in the area completing the synthesis of ophirin B (**172**) in 2004 and related astrogorgin (**171**) in 2006.[52] Both natural products have been

[51] Bernardelli, P.; Moradei, O. M.; Friedrich, D.; Yang, J.; Gallou, F.; Dyck, B. P.; Doskotch, R. W.; Lange, T.; Paquette, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 9021-9032.

[52] (a) Crimmins, M. T.; Brown, B. H *J. Am. Chem. Soc*. **2004**, *126*, 10264-10266 (b) Crimmins, M. T.; Brown, B. H.; Plake, H. R. *J. Am. Chem. Soc*. **2006**, *128*, 1371-1378.

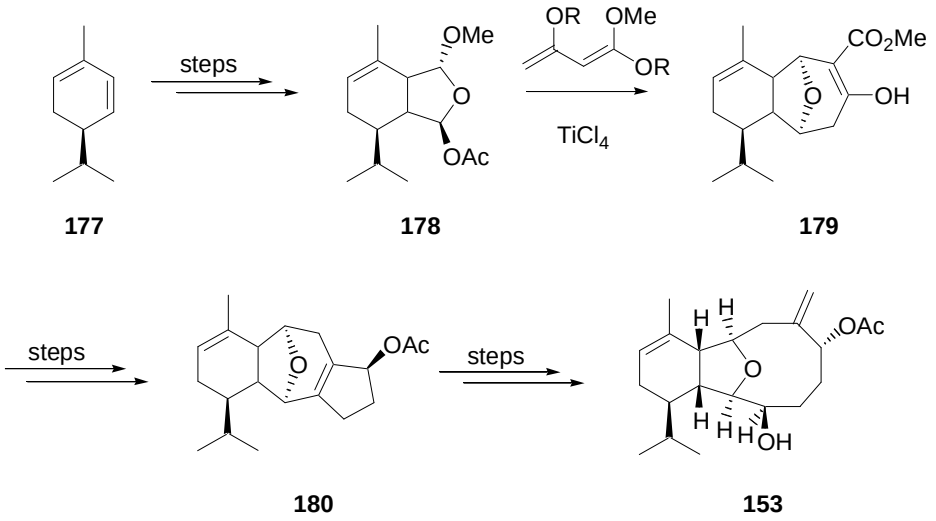
synthesised following the retrosynthesis shown in **Scheme 36**. Synthesis of the tricyclic core would be constructed via a strategic intramolecular Diels-Alder cycloaddition of the tetraene **173**. The nine membered ring of **173** could arise from the ring-closing metathesis of diene **174** which could come from the intermediate **175**. Ultimately **175** could be produced in a couple of steps from the ketone **176**.



Scheme 36

A second synthesis of deacetoxyalcyonin acetate (**153**) was published in 2004 by Molander.[53] As shown in **Scheme 37**, the synthesis starts from commercially available α-phellandrene **177** which was converted into the key mixed acetal **178** in 2 steps. A Lewis acid mediated [4+3] cycloaddition reaction with 1-methoxy-1,3-bis(triethylsilanyloxy)buta-1,3-diene afforded the desired annulation product **179** with complete regio- and stereoselectivity. The hydroxyl group and the methyl ester intermediate **179** were then used to build the cyclopentene **180** and subsequent ozonolysis and final functionalisations afforded the natural product **153**.

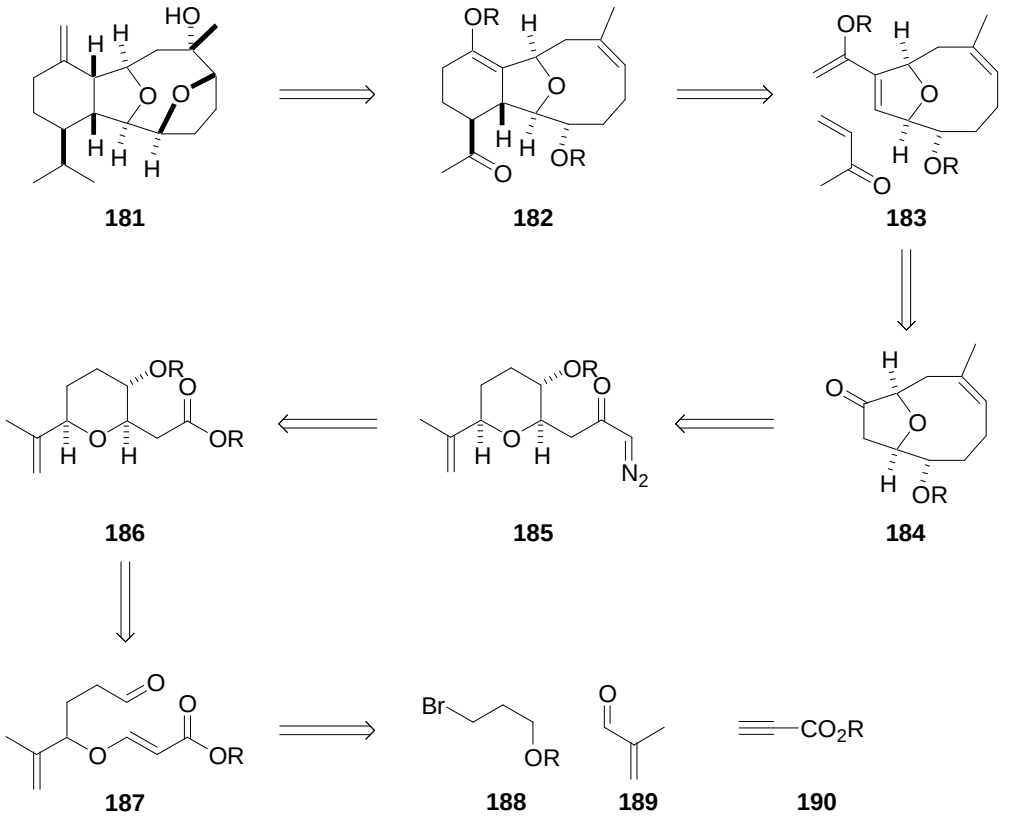
[53] Molander, G. A.; St. Jean, Jr.; D. J.; Haas, J. *J. Am. Chem. Soc*. **2004**, *126*, 1642-1643.



Scheme 37

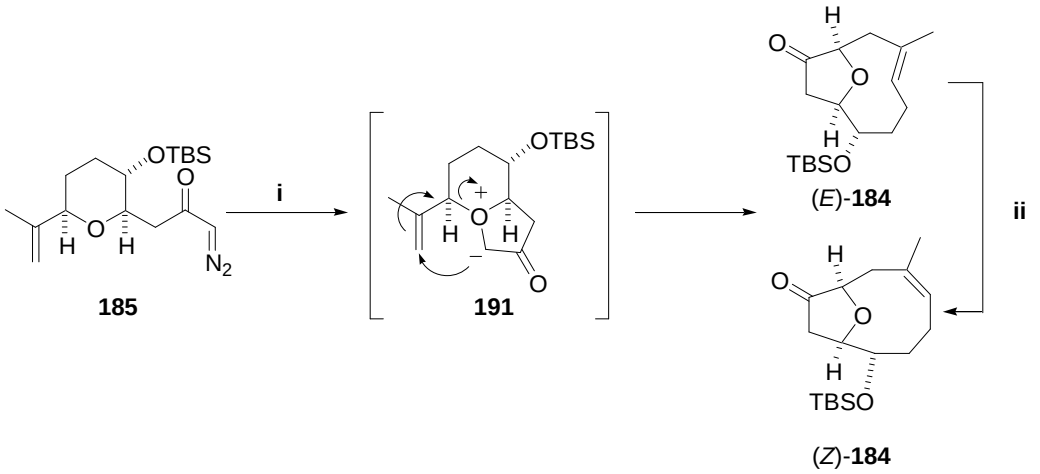
The most recent publication of a total synthesis of a member of the eunicellin family comes from the Clark group with the total synthesis of (±)-vigulariol **181**.[54] The retrosynthetic approach to this compound starts with epoxide opening and further functional group interconversion to produce the ketone **182**. A Diels-Alder disconnection then reveals diene **183** and methyl vinyl ketone. Conversion of the diene unit into a carbonyl group leads to the ketone **184**. This ketone is the product of the key tandem oxonium ylide formation and [2,3]-sigmatropic rearrangement sequence starting from the diazoketone **185**. Finally C–C bond disconnection of the tetrahydropyran **186** produces the ketone **187**, precursor for a samarium diiodide induced cyclisation reaction (**Scheme 38**).

[54] Clark, J. S.; Hayes, S. T.; Wilson, C., Gobbi, L. *Angew. Chem. Int. Ed.* **2007**, *46*, 437-440.



Scheme 38

The key metal carbenoid reaction proved to be extremely efficient (**Scheme 39**). Indeed, treatment of diazoketone **185** with $Cu(hfacac)_2$ in CH_2Cl_2 at reflux afforded the desired bicyclic ketone **184** in 96% yield as a 5:1 mixture of *Z*/*E* geometrical isomers. It is worth noting that the undesired *E*-isomer was smoothly converted to the *Z*-isomer upon treatment with AIBN and a sub-stoichiometric amount of ethanethiol in benzene at reflux. The use of our metal carbenoid chemistry provides an extremely quick and efficient entry to the bicyclic core of vigulariol. Construction of the cyclohexyl ring using a Diels-Alder reaction and then final functionalisation resulted in the shortest synthesis for a cladiellin compound to date.

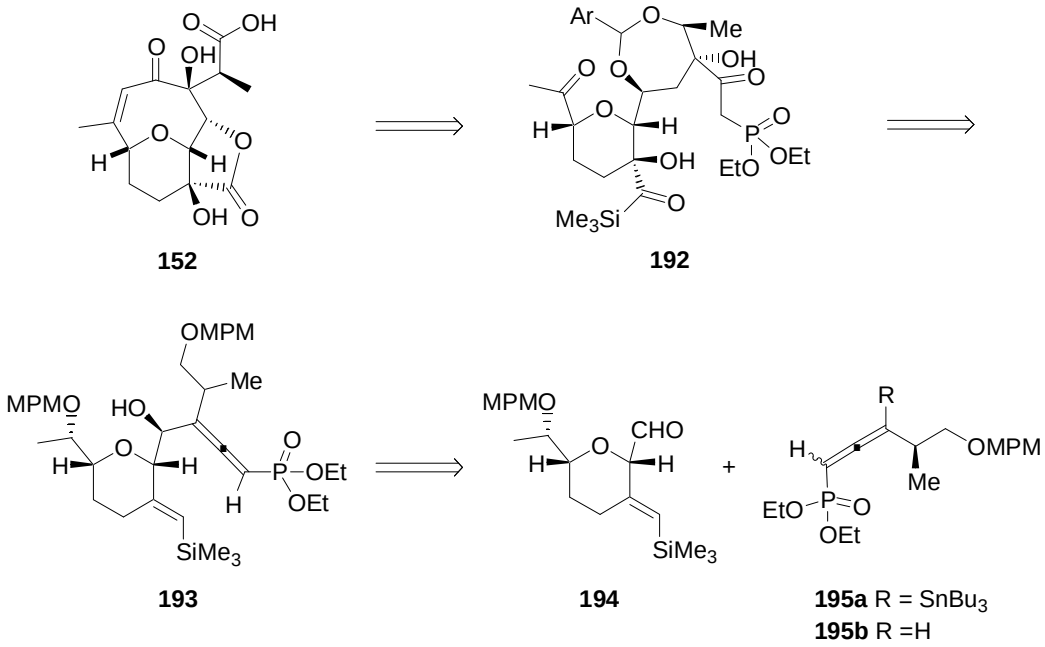


Scheme 39 *Reagents and conditions:* **i**, $Cu(hfacac)_2$ (5 mol%), CH_2Cl_2, reflux (96%, 5:1 *Z*/*E*); **ii**, AIBN, EtSH, PhH, reflux (56%).

In spite of the considerable efforts devoted to the total synthesis of the cladiellin natural products, there are no reports of attempts to synthesise labiatin A (**147**) other than that published by our group.[55] There have been few attempts to synthesise natural products that possess the same core structure as labiatin A (**147**) and these dealt with the synthesis of neoliacinic acid (**152**). The first attempt was reported in a PhD thesis from the University of Wisconsin-Madison USA in 1994[56] and the retrosynthetic analysis employed by the author is shown in **Scheme 40**. The first disconnection of the oxabicyclo[5.3.1]undecenone system led to an intramolecular Horner-Wadsworth-Emmons precursor **192** which was expected to arise from oxidative manipulation of the allenylphosphonate **193**. In turn, this phosphonate was to be prepared by condensation of the aldehyde **194** and the α,γ-dianion derived from the allene **195a** or **195b**. It was believed that this would allow the application of a dioxanone-to-dihydropyran lactonic enolate Claisen rearrangement in an attempt to make the aldehyde **194**. The most advanced intermediate synthesised was the allene **195b**. Three attempts including Ireland-Claisen rearrangement and radical cyclisation failed to give tetrahydropyran **194**.

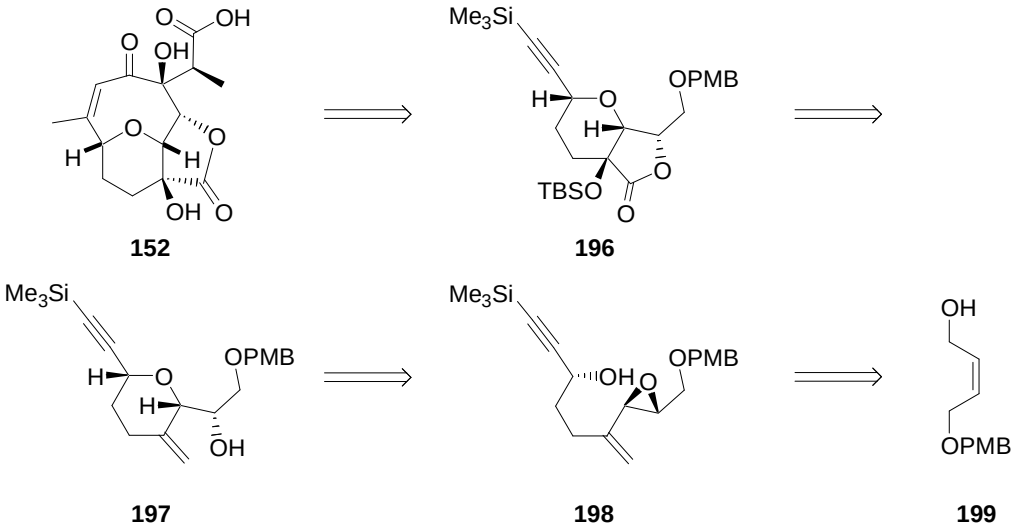
[55] Clark, J. S.; Baxter, C. A.; Castro, J. B. *Synthesis* **2005**, *19*, 3398-3404.

[56] Kort, M. E., PhD Thesis, University of Wisconsin-Madison, **1994**.



Scheme 40 *Kort's retrosynthetic analysis for neoliacinic acid*.

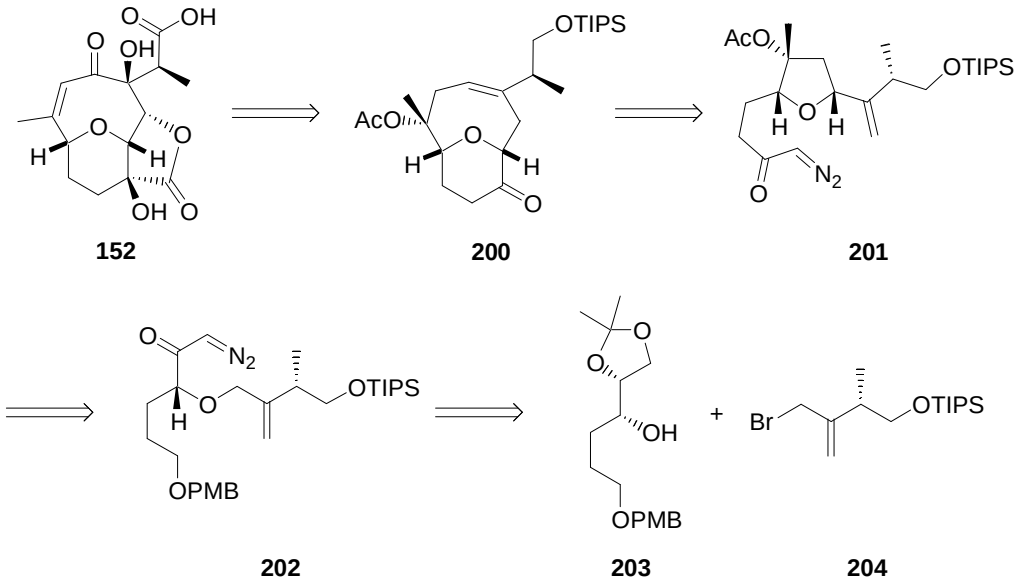
In 1999, Paquette and Paget reported another attempted synthesis of neoliacinic acid using the retrosynthetic analysis shown in **Scheme 41**. The strategy centred around the construction of the lactone **196** by chemoselective oxygenation of the homoallylic alcohol **197**. It was anticipated that the tetrahydropyran **197** would be prepared by cyclisation of the allylic epoxide **198**. To date, only the five-step synthesis of the intermediate epoxide **198** from the allylic alcohol **199** has been described.[57]



Scheme 41 *Paquette's retrosynthetic analysis for neoliacinic acid*.

[57] Paget, S. D.; Paquette, L. A. *J. Indian Chem. Soc.* **1999**, 76, 515.

The work in the Clark group has been the most successful to date and concentrates on the use of two metal carbenoid reactions to prepare the bicyclic core of neoliacinic acid (**152**).[58] As shown in **Scheme 42**, it was expected that neoliacinic acid (**152**) could be constructed from intermediate **200** which possesses the bicyclic core of the natural product. The latter was to be introduced by an oxonium ylide formation and [2,3]-sigmatropic rearrangement starting from the diazoketone **201**. Further disconnection of the tetrahydrofuran reveals a second diazoketone **202** which could be subjected to a metal carbenoid C–H insertion reaction. This diazoketone was to be synthesised from the alcohol **203** and the allylic bromide **204**.



152 **200** **201**

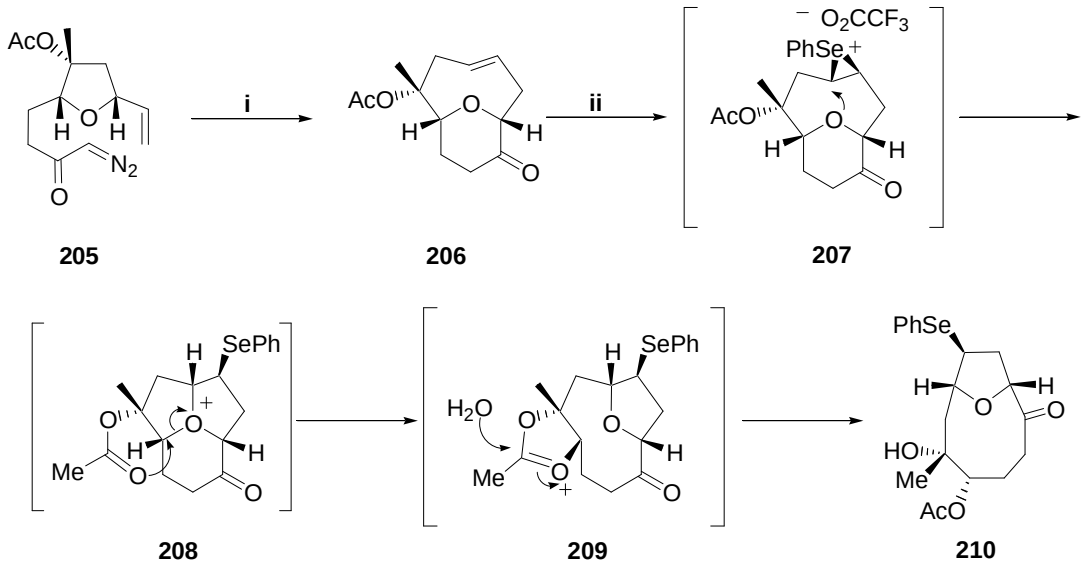
202 **203** **204**

Scheme 42 *Clark's retrosynthetic analysis for neoliacinic acid.*

The bicyclic ketone **200** was synthesised on a multi-gram scale but unfortunately further work on functionalising this system to afford neoliacinic acid (**152**) was unsuccessful. Although the lactone ring was efficiently introduced attempts to introduce the α,β-unsaturated ketone functionality failed.

[58] Clark, J. S.; Baxter, C. A.; Dosseter, A. G.; Poigny, S.; Castro, J. L.; Whittingham, W. G. *J. Org. Chem.* **2008**, *73*, 1040-1055.

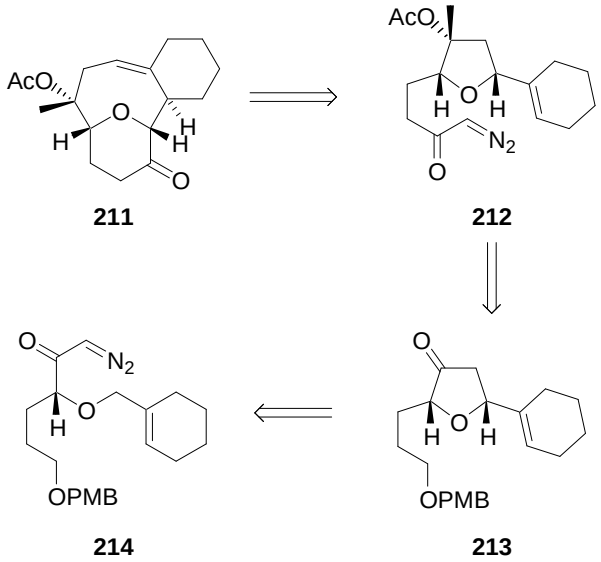
This methodology has also been applied for the synthesis of the lytophinins (**Scheme 43**).[59] An episelenonium ion mediated rearrangement of the [2,3]-sigmatropic rearrangement product **207** led to the formation of the core structure found in the lytophinins **210** and can allow access to the whole range of eunicellins.



Scheme 43 *Construction of the core of the lytophinins by a episelenonium ion mediated rearrangement reaction:* **i**, $Cu(hfacac)_2$, CH_2Cl_2, reflux, 50%; **ii**, $PhSeO_2CCF_3$, CH_2Cl_2, 0 °C, 31%.

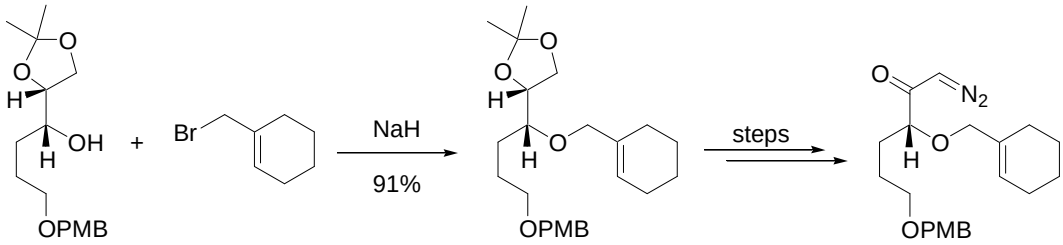
Recently, the Clark group published the synthesis of a model of the core structure of labiatin A (**147**).[55] The strategy for the synthesis of the tricyclic core of labiatin A (**147**) is similar to the one used for neoliacinic acid (**152**) and relies on carbenoid C–H insertion and subsequent tandem oxonium ylide formation-[2,3]-sigmatropic rearrangement as the two key steps (**Scheme 44**).

[59] Clark, J. S.; Wong, Y. S. *Chem. Commun.*, **2000**, 1079-1080.



Scheme 44 *Retrosynthetic approach towards a model of the tricyclic core of labiatin A.*

The synthesis starts from the known alcohol **203** which was converted into the ether **216** by standard Williamson coupling with 1-(bromomethyl)cyclohexene (**215**) (prepared from a commercially available ester in two steps).[60] The acetonide was then converted into the corresponding diazoketone **214** in 5 steps (**Scheme 45**).



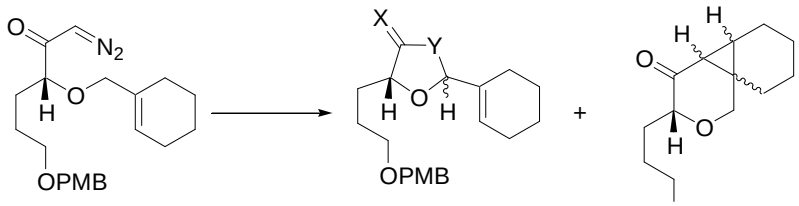
Scheme 45

The influence of several rhodium catalysts and reaction conditions on the carbenoid C–H insertion reaction was then studied (**Table 2**). Mixtures of three different products were obtained in different ratios depending on those conditions: the desired furanone **213** (obtained as an inseparable mixture of *cis* and *trans* diastereoisomers), the acetal

[60] Lythgoe, B.; Trippett, S.; Watkins, J. C. *J. Chem. Soc.* **1956**, 4060.

217, arising from anomalous C–H insertion,[61] and the intramolecular cyclopropanation product **218**. When the reaction was performed using rhodium(II) trifluroacetamide (entries 1–4) the desired furanone **213** was generally the major product except when CH_2Cl_2 was used as a solvent. The use of CH_2Cl_2 as the reaction solvent tends to result in as an increase in the amount of cyclopropanation product **218** obtained. It is interesting to observe that lowering the temperature from reflux to room temperature results in an increase in the *cis-trans* ratio of **213**. The desired *cis* furanone was obtained in up to 6:1 ratio (entry 2). The use of the traditional rhodium(II) acetate dimer resulted in a decrease in the yield of the C–H insertion product **213**. In the studies concerning neoliacinic acid (**152**), the bulky catalyst rhodium(II) triphenylacetate had given good results for this particular transformation,[58] but this was not the case when dealing with diazoketone **214** (entry 7).

[61] (a) Mander, L. N.; Owen, D. J. *Tetrahedron Lett.* **1996**, *37*, 723-726 (b) Clark, J. S.; Dossetter, A. G.; Russel, C. A.; Whittingham, W. G. *J. Org. Chem.* **1997**, *62*, 4910-4911 (c) Clark, J. S.; Wong, Y.-S.; Townsend, R. J. *Tetrahedron Lett.* **2001**, *42*, 6187-6190 (d) Clark, J. S.; Dossetter, A. G.; Wong, Y.-S.; Townsend, R. J. Whittingam, W. G.; Russel, C. A. *J. Org. Chem.* **2004**, *69*, 3886-3898.



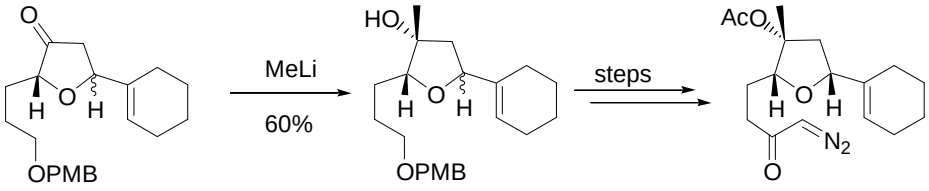
214 **213** X = O, Y = CH_2; **217** X = CH_2, Y =O **218**

Entry	Ligand	Solvent	Temp	Yield **213** (%) (*cis*:*trans*)[a]	Yields **217**, **218** (%)
1	$HNCOCF_3$	THF	reflux	60 (2:1)	**217** (13), **218** (16)
2	$HNCOCF_3$	THF	rt	59 (6:1)	**218** (13)
3	$HNCOCF_3$	CH_2Cl_2	reflux	21 (2:1)	**218** (35)
4	$HNCOCF_3$	CH_2Cl_2	rt	33 (3:1)	**218** (27)
5	O_2CCH_3	THF	reflux	26 (7:1)	**217** (2), **218** (36)
6	O_2CCH_3	THF	rt	16 (4:1)	**218** (21)
7	O_2CCPH_3	CH_2Cl_2	rt	32 (2:3)	**217** (7), **218** (16)

[a] Diastereoisomeric ratio determined by ^{1}H NMR analysis

Table 2

A couple of steps were then required to access the key cyclisation precursor **212** (**Scheme 45**). Notably, addition of methyllithium to ketone **213** afforded the alcohol **219** stereochemistry of which has been determined by a observing nOe effects in the ^{1}H NMR spectrum. This confirmed that the *cis* furanone **213** was the major product from the C–H insertion reaction. Six additional steps led to diazoketone **212**.

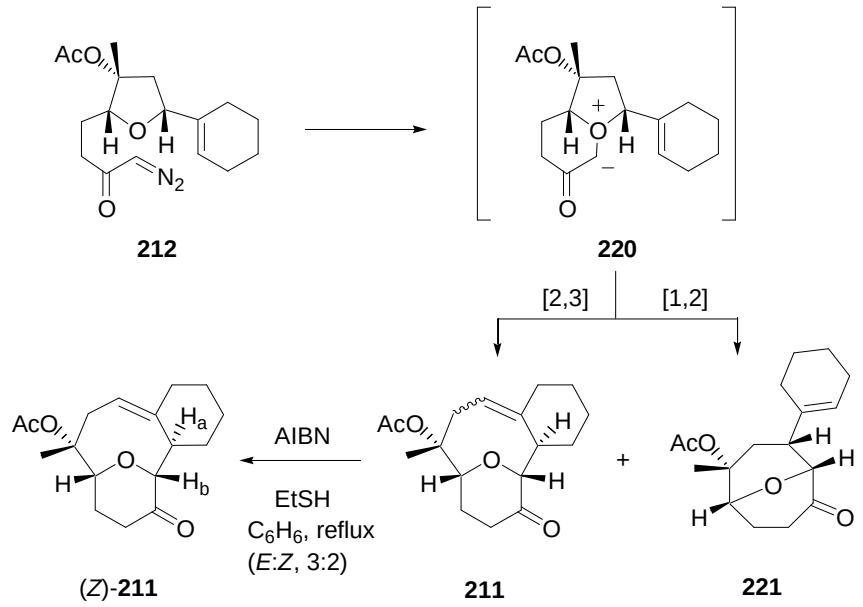


213 **219** **212**

Scheme 45

Based on the results obtained from the key cyclisation reaction used to prepare the core of neoliacinic, several conditions were investigated for the key oxonium ylide

formation and [2,3]-sigmatropic rearrangement reaction starting from the diazoketone **212** (**Table 3**). Copper(II) hexafluoroacetylacetonate [Cu(hfacac)$_2$] was the catalyst of choice for this reaction (entry 1). A mixture of [2,3]- and [1,2]-sigmatropic rearrangement products was obtained in a very good 86% yield. The two compounds were separated after isomerisation of the 3:2 *E*:*Z* mixture of geometrical isomers **211** to give the thermodynamically favoured alkene *Z*-**211** in 64% yield. Better selectivity in favour of the desired [2,3] product has been obtained when the reaction was performed in benzene but the yield was much lower than in the case where dichloromethane was used as the solvent (entry 2). The use of either Cu(acac)$_2$ or Rh$_2$(OAc)$_4$ resulted in relatively poor yields and did not significantly improve the **211**:**221** ratio (entries 3 and 4).



Entry	ML$_n$	Solvent	Yield **211** + **221** (%), Ratio[a] **211**:**221**	Ratio **211** (*E*:*Z*)
1	Cu(hfacac)$_2$	CH_2Cl_2	83, 2:1	3:2
2	Cu(hfacac)$_2$	C_6H_6	52, 6:1	4:1
3	Cu(acac)$_2$	CH_2Cl_2	35, 2:1	1:1
4	Rh$_2$(OAc)$_4$	CH_2Cl_2[b]	22, 3:1	1:6

[a] Product and diastereoisomeric ratio determined by NMR. [b] Reaction performed at rt

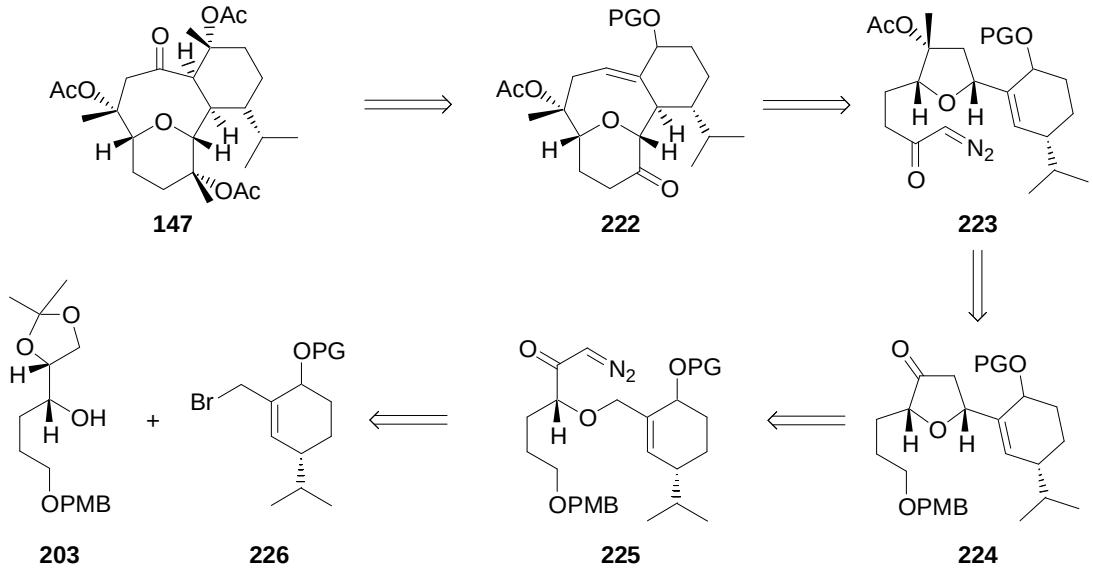
Table 3

The last important result that arose from the synthesis of this model was obtained by NMR studies. The signal for the proton H_b is a doublet with a coupling constant of 12.6 Hz corresponding to the coupling with proton H_a. The value for this coupling constant is indicative of a large dihedral angle and that protons H_b and H_a are in a *trans* relationship which is the stereochemistry required for labiatin A (**147**).

The model studies clearly showed that our methodology based on two successive carbenoid reactions is a viable approach to the total synthesis of labiatin A (**147**).

1.5.2 Retrosynthetic analysis for labiatin A

Following the positive results obtained with using the model compound **211**, the objective was the total synthesis of labiatin A. The retrosynthetic approach envisaged for the total synthesis of labiatin A (**147**) is presented in **Scheme 46**. Functional group interconversions produce the tricyclic system **222** which could arise from [2,3]-sigmatropic rearrangement of the oxonium ylide generated by treatment of the diazoketone **223** with a suitable catalyst. Further simplification reveals the dihydro-3(2*H*)-furanone **224**. A retrosynthetic carbenoid C–H insertion reaction produces the diazoketone **225** which could be prepared from the known alcohol **203**[60a] and bromide **226**.



Scheme 46 *Retrosynthetic analysis of labiatin A.*

Conclusion

The chemistry of metal carbenoids produced by the catalytic decomposition of diazo compounds has gained considerable attention for the past three decades. Thanks to the discovery of new catalysts, reactions that were once considered to be non-selective have become extremely useful processes allowing the formation of very elaborated substrates with high diastereo-, regio- and enantioselectivities. The synthetic utility of metal carbenoid reactions is evident from their involvement in a large number of natural product syntheses. The next part of this thesis will describe the very challenging and successful application of the chemistry of metal carbenoids towards the total synthesis of labiatin A.

Chapter II

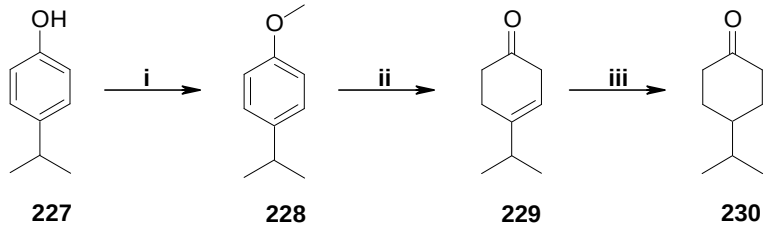
Results and Discussion

Chapter II – Results and Discussion

Our retrosynthetic analysis for labiatin A (**147**) ultimately led to the cyclohexenyl unit **226**. The first part of the project would therefore involve the synthesis of this intermediate for coupling to the alcohol **203**. Before embarking on an enantioselective synthesis, preparation of the cyclohexene unit in racemic form was investigated.

2.1 Synthesis of the cyclohexene fragment

The starting material required for our synthesis is 4-isopropylcyclohexanone **230**, which is commercially available but can also be obtained in four steps from much cheaper and commercially available compound 4-isopropylphenol (**Scheme 47**).[62] An alkaline solution of 4-isopropylphenol **227** was methylated with dimethylsulfate and a Birch reduction followed by ether hydrolysis gave the unsaturated ketone **229** in 80% yield over 2 steps. Hydrogenation of the double bond afforded 4-isopropylcyclohexanone **230** in 83% yield.



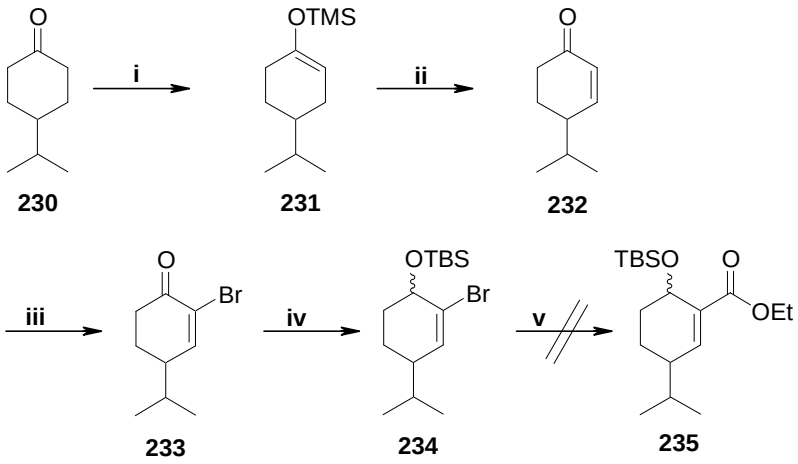
Scheme 47 *Reagents and conditions*: **i**, dimethylsulfate (7.0 eq.), 15% aq. KOH solution, rt, 2.5 h [95%]; **ii**, (a) liq. ammonia, lithium (8.3 eq.), EtOH, –78 °C, (b) 0.6 N oxalic acid, acetone, MeOH, H_2O, rt, 3 h [80%, 2 steps]; **iii**, H_2, Pd/C, MeOH, rt, 18 h [83%].

4-Isopropylcyclohexanone **230** was first treated with LDA to give the corresponding enolate which was quenched with TMSCl. A Saegusa reaction afforded the *α,β*-unsaturated ketone **232** in very good 85% yield over 2 steps.[63] In contrast to what was

[62] Nelson, N .A.; Mortimer, G. A. *J. Org. Chem* **1957**, *22*, 1146-1153.

[63] (a) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011-1013 (b) Larock, R. C.; Hightower, T. R. *Tetrahedron Lett.* **1995**, *36*, 2423-2426.

described in the literature, bromination on the double bond using triethylamine and bromine was unsuccessful.[64] It only led to the aromatisation of the ketone **232** and therefore to 4-isopropylphenol. Fortunately, bromoketone **233** was obtained in 82% yield by refluxing ketone **232** in CH_2Cl_2 in the presence of tetrabutylammonium tribromide (TBATB) and potassium carbonate for two days.[65] The TBS protected alcohol **234** was then obtained in 88% yield by the Luche reduction of the ketone **233** followed by treatment with TBDMS triflate. Unfortunately, and contrary to results obtained by Smith III and co-workers,[65] halogen-metal exchange by treatment of bromoketone **234** with *n*-BuLi followed by electrophilic capture of the resulting anion by ethylchloroformate did not afford the desired ester **235**. Instead, a mixture of several unidentified products was obtained and, due to their relatively similar polarity, it was not possible to isolate them individually (**Scheme 48**).

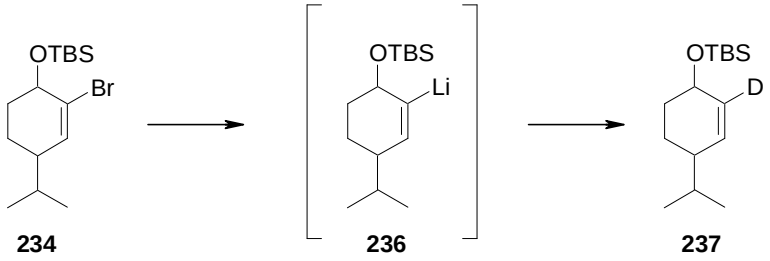


Scheme 48 *Reagents and conditions:* **i**, *n*-BuLi (2.2 eq.), *i*-Pr_2NH (1.5 eq.), TMSCl (5.0 eq.), THF, –78 °C, 3 h; **ii**, $Pd(OAc)_2$ (0.1 eq.), O_2 atmosphere, DMSO, rt, 15 h [85%, 2 steps]; **iii**, TBATB (2.0 eq.), K_2CO_3 (3.0 eq.), CH_2Cl_2, 0 °C (45 min) then reflux 2 days [82%]; **iv**, (a) $CeCl_3$ (1.3 eq.), $NaBH_4$ (1.1 eq.), MeOH, –20 °C, 15 min; (b) TBDMSOTf (2.0 eq.), 2,6-lutidine (3.0 eq.), CH_2Cl_2, –78 °C to rt, 14 h [88%, 2 steps]; **v**, *n*-BuLi (1.5 eq.), $ClCO_2Et$ (3.0 eq.), THF, –78 °C to rt, 1.5 h [0%].

[64] Smith, A. B., III.; Branca, S. J.; Pilla, N. N.; Guaciaro, M. A. *J. Org. Chem.* **1982**, *47*, 1855-1869.

[65] Gopal, B.; Bujar Barua, P. M.; Chaudhuri, M. K.; Kalita, D.; Khan, T.A. *Chem. Lett.* **2001**, *4*, 290-291.

Adding DMPU to the reaction mixture or using methyl cyanoformate (Mander's reagent)[66] as an electrophile did not improve the results. In an attempt to understand why this reaction failed, a deuterium oxide quench of the lithium anion of bromoketone **234** was performed (**Scheme 49**). This reaction led to the formation of the alkene **237** which demonstrates, that the anion **236** is clearly formed, and that the electrophile is attacked (otherwise a protonated product rather than the deuterated product **237** would be obtained when the reaction mixture is quenched with water), but something else happens as well. Attempts to reduce the potentially formed ester with $LiAlH_4$ led to desilylated products. These observations suggest that a subsequent reaction with the silyl protecting group occurs and this could explain why in the literature a ketal protected ketone is used.



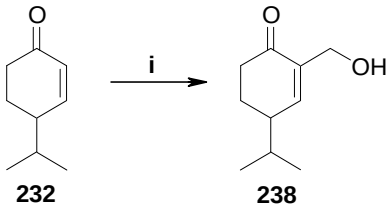
Scheme 49 *Reagents and conditions:* **i**, *n*-BuLi (1.5 eq.), THF, –78 °C to rt, 1.5 h; **ii**, D_2O (excess), –78 °C, 30 min.

As a consequence of the failure of the route shown in **Scheme 48**, an alternative route involving the use of a Baylis-Hillman reaction between the *α,β*-unsaturated ketone **6** and formaldehyde was explored (**Equation 19**). Due to the poor reactivity of cycloalkenones in the Baylis-Hillman reaction, many different catalysts have been described in the literature[67] (e.g. DMAP, *n*-tributylphosphine, DBU, *N,N,N',N'*-

[66] Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425-5428.

[67] (a) Gatri, R.; El Gaïed, M. M. *Tetrahedron Lett.* **2002**, *43*, 7835-7836; (b) Aggarwal, V. K.; Mereu, A. *Chem. Commun.* **1999**, 2311-2312; (c) Kabat, M. M.; Kiegel, J.; Cohen, N.; Toth, K.; Wovkulich, P. M.; Uskokovic, M. R. *J. Org. Chem.* **1996**, *61*, 118-124; (d) Taylor, R. J. K.; Thorsten, G. *Tetrahedron Lett.* **2002**, *43*, 3573-3576; (e) Lee, K. Y.; GowriSankar, S.; Kim, J. N. *Tetrahedron Lett.* **2004**, *45*, 5485-5488.

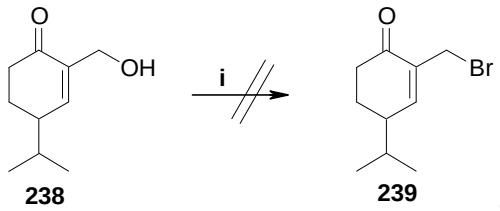
tetramethyl-1,3-propanediamine) with DMAP and *n*-Bu_3P being the most widely used. Treatment of ketone **232** with aqueous formaldehyde and a catalytic amount of DMAP was very sluggish and afforded the allylic alcohol **238** in a modest yield of 51% after two weeks. A similar yield was obtained using *n*-Bu_3P after only 15 h. Scale up of this reaction proved difficult and it has been found that addition of triethylamine to the reaction mixture greatly increased the amount of recovered unreacted starting material.



232 **238**

Equation 19 *Reagents and conditions:* **i**, *n*-Bu_3P (0.8 eq.), CH_2O (37% solution in water, 2.0 eq.), NEt_3 (1.0 eq.), THF, rt, 3 h, [50%, 70% brsm].

The alcohol **238** was converted into the corresponding mesylate which upon treatment with LiBr did not afford the expected bromoketone **239** (**Equation 20**) Attempts to obtain bromide **239** in a one step procedure using phosphorus tribromide or triphenylphosphine/carbon tetrabromide resulted in the formation of an unidentified product

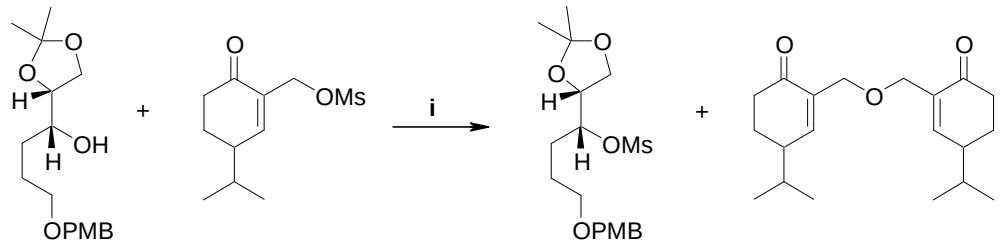


238 **239**

Equation 20 *Reagents and conditions*: **i**, (a) Et_3N (2.0 eq.), MsCl (1.5 eq.), CH_2Cl_2, –78 °C, 1.5 h, [100% crude yield] (b) LiBr (1.5 eq.), THF, rt, 2 h; or PBr_3 (0.5 eq.), hexane : THF (2:1), –20 °C, 30 min; or CBr_4 (3.0 equiv), PPh_3 (3.0 equiv.), CH_3CN, 0 °C, 30 min, [0%].

Attempts to couple the alcohol **203** with the mesylate derived from alcohol **238** led to a very surprising result. Heating a solution of the alkoxide of alcohol **203** with the

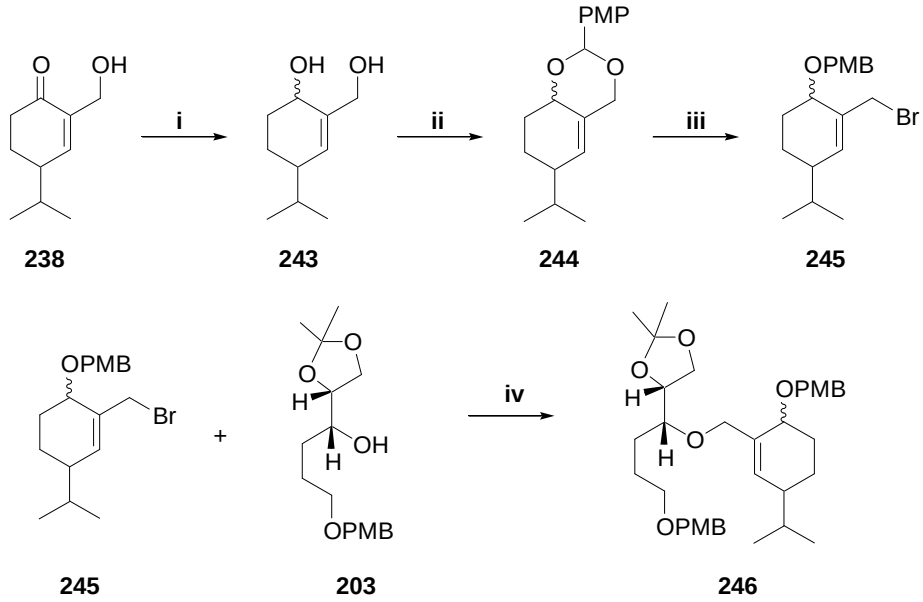
mesylate **240** at reflux in THF resulted in the formation of the mesylate **241** and a product which was tentatively assigned by NMR as being the ether **242** resulting from dimerization of the initial mesylate **240** (**Equation 21**).



203 **240** **241** **242**

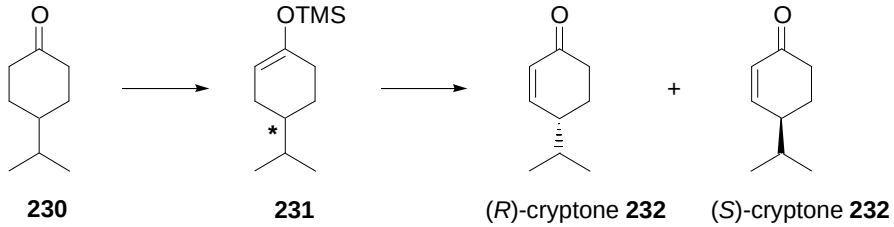
Equation 21 *Reagents and conditions:* **i**, NaH (1.1 eq.), THF, rt, 1 h, then *n*-Bu_4NI (0.03 eq.), **240** (1.2 eq.), THF, rt, 1 h [**241** (75%), **242** (80%)].

The presence of the *α,β*-unsaturated ketone was possibly the source of the problems and so it was reduced to the corresponding allylic alcohol using Luche conditions just after the Baylis-Hillman reaction to afford the diol **243** in 97% yield as a 7:1 diastereomeric mixture (**Scheme 50**). The two diastereoisomers were inseparable by chromatography and so the mixture was used in the next step which consisted of a PMP acetal protection (80% yield). Reductive opening of the acetal **244** with DIBAL-H afforded selectively the desired alcohol (primary alcohol free and secondary protected with a PMB group) in 93% yield. Bromination using triphenylphosphine and carbon tetrabromide afforded bromide **245** in a very satisfying 90% yield. Finally, heating a solution of the alkoxide derived from alcohol **203** with the bromide **245** at reflux in THF for 2 h afforded the desired ether **246** in 79% yield.



Scheme 50 *Reagents and conditions:* **i**, $CeCl_3 \cdot 7H_2O$ (1.5 eq.), $NaBH_4$ (1.1 eq.), MeOH, –20 °C, 30 min, [97%]; **ii**, *p*-$MeOC_6H_4CH(OMe)_2$ (1.3 eq.), CSA (0.2 eq.), 4 Å mol. sieves, CH_2Cl_2, rt, 2 days [80%]; **iii**, (a) DIBAL-H (3.1 eq.), CH_2Cl_2, –78 °C, 2 h [93%] (b) CBr_4 (3.0 eq.), PPh_3 (3.0 eq.), CH_3CN, 0 °C, 20 min [90%]; **iv**, NaH, rt to reflux, 1 h, then bromide **245**, rt to reflux, 15 h [79%].

Having discovered an efficient way to synthesize ether **246** (31 % yield over 8 steps) it was decided to directly apply this route to the synthesis of the bromide coupling partner **245** as a non-racemic form, replacing LDA by a chiral lithium amide base in the first step to desymmetrize 4-isopropylcyclohexanone (**Scheme 51**).

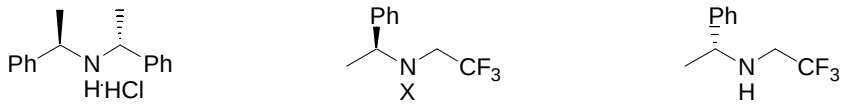


Scheme 51

The desymmetrization of *para*-substituted cyclohexanones has been widely studied by the Simpkins and Koga groups.[68] They have developed a series of structurally diversified chiral amines which enabled them to synthesize highly enantioenriched

[68] (a) Cox, P. J.; Simpkins, N. S. *Tetrahedron Asym.*, **1991**, *2*, 1-26, (b) Aoki, K.; Koga, K. *Tetrahedron Lett.*, **1997**, *38*, 2505-2506 and references cited herein.

cyclohexanones. Three of their chiral bases were tested on our ketone, namely [*R*-(*R**, *R**)]-(+)-bis(α-methylbenzyl)amine hydrochloride **(*R*,*R*)-247**, (–)-(*S*)-(1-phenylethyl)(2,2,2-trifluoroethyl)-amine **(*R*)-248** and (+)-(*R*)-(1-phenylethyl)(2,2,2-trifluoroethyl)amine **(*S*)-248** (**Figure 4**).



247 **(*S*)-248a** X =H, **(*S*)-248b** X = H·HCl **(*R*)-248**

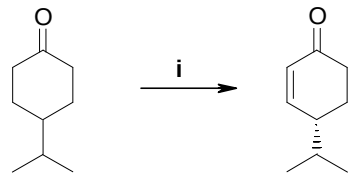
Figure 4 *Amines for chiral lithium amide base generation.*

The different conditions that were tested are summarized in **Table 4**. The influences of the chiral amine, the temperature and the concentration of the different reagents involved were studied. The enantiomeric excesses of the *α,β*-unsaturated ketone **232** were measured by chiral HPLC (Chiracel AD column with hexane/*iso*propanol 98:2 as an eluent). The best enantiomeric excess (89%) was obtained using amine **(*R*)-248a** (*entry 4*). It was also found that the enantiomeric ratios were only slightly affected by the concentration of the reagents (*entries 6 and 7*) so it was decided to work with concentrations as high as possible to allow the reaction to be scaled-up. *Entry 5* shows that it is essential to perform the reaction at low temperature in order to obtain high enantiomeric excesses.

Entry	amine	Concentration (mol.L^{-1}) Amine/ substrate	Temperature	ee% (e.r. ((*R*)-**232**:(*S*)-**232**)
1	**(*R*,*R*)-247**	0.09 / 0.36	–100 °C	86% (93:7)
2	**(*S*)-248a**	0.09 / 0.36	–100 °C	86% (7:93)
3	**(*S*)-248b**	0.09 / 0.36	–100 °C	81% (9.5:90.5)
4	**(*R*)-248**	0.09 / 0.36	–100 °C	89% (94.5:5.5)
5	**(*R*)-248**	0.09 / 0.36	–78 °C	76% (88:12)
6	**(*R*)-248**	0.37 / 0.72	–100 °C	83% (91.5:8.5)
7	**(*R*)-248**	0.41 / 0.82	–100 °C	80% (90:10)

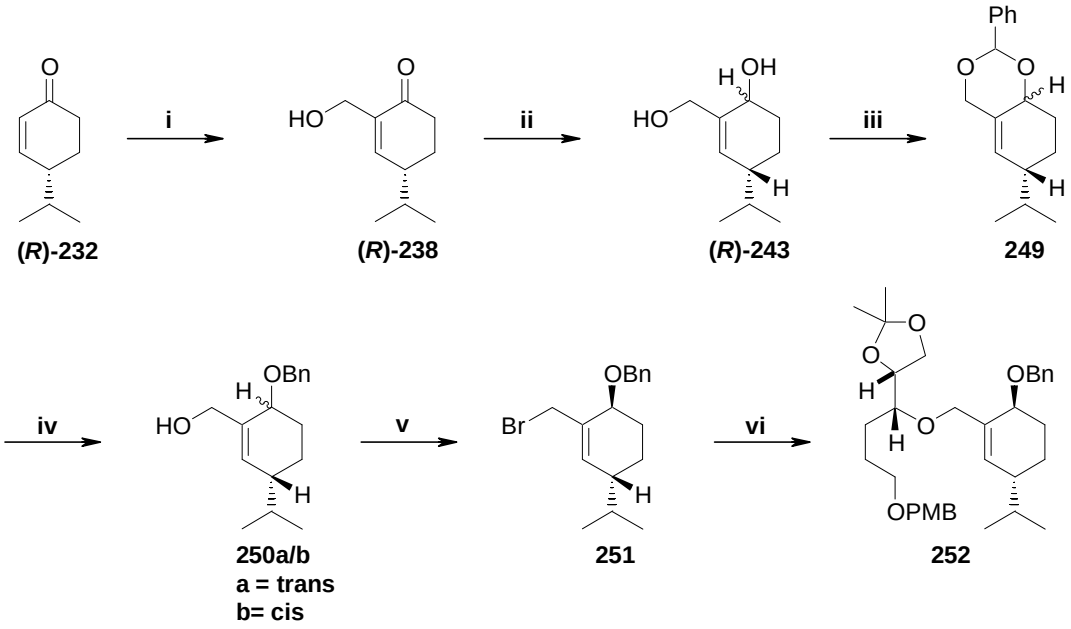
Table 4 *4-Isopropylcyclohexanone desymetrisation.*

Ultimately, this reaction was scaled up to 11.5 g (82 mmol) of 4-isopropylcyclohexanone **230** leading to (*R*)-cryptone **232** in 87% yield over two steps and 83% ee. It is also worth noticing that the chiral amine **248** could be recovered in 80% yield from the reaction mixture and used again without any erosion of enantiomeric excess (**Equation 22**).



Equation 22 *Reagents and conditions:* **i**, (a) *n*-BuLi (1.3 eq.), (+)-(*R*)-(1-phenylethyl)-2,2,2-trifluoroethylamine **248** (1.2 eq.), TMSCl (3.5 eq.), THF, –100 °C, 1.5 h (b) $Pd(OAc)_2$ (0.1 eq.), O_2, DMSO, rt, 15 h [87% yield, 83% ee].

At this juncture it was decided to follow the same procedure as for the synthesis of bromide **245** in racemic form except that the PMB protecting group was replaced by a benzyl ether (**Scheme 52**). As previously, the synthesis starts with a Baylis-Hillman reaction to give the alcohol **(*R*)-238** in 52% yield (70% yield based on recovered starting material). The ketone was then reduced under Luche conditions to give the diol **(*R*)-243** in 98% yield and as an inseparable 10:1 mixture of diastereoisomers, the diasteroselectivity was improved by lowering the temperature to –78°C. This diol was then protected as a benzylidene acetal **249** in 98% yield. Regioselective reduction of the acetal with DIBAL-H afforded two diastereomeric alcohols **250a** and **250b** which were separable by silica gel chromatography at this stage. Only the major diastereoisomer was brough through the next step although its relative configuration was not determined at the time. The configuration of the carbon atom bearing the benzyl ether was determined by X-ray crystallography later in the synthesis (*see page **78***). The major alcohol **250a** (having the benzylether and the isopropyl group in the trans configuration) was converted to the corresponding mesylate and subsequent displacement with lithium bromide afforded bromide **251** in 94% over two steps. The one-step bromination procedure using triphenylphosphine and carbon tetrabromide used previously proved to be unreliable on large scale. Finally, bromide **251** was coupled with alcohol **203** (enantio-pure synthesis of which from D-Mannitol was elaborated in our laboratory when working on the synthesis of neoliacinic acid **152**)[3] in 87% yield to give the ether **252** as the sole isolated diastereoisomer after purification by chromatography. The enantiopure ether **252** was therefore synthesized in 9 steps and an excellent 39% yield.

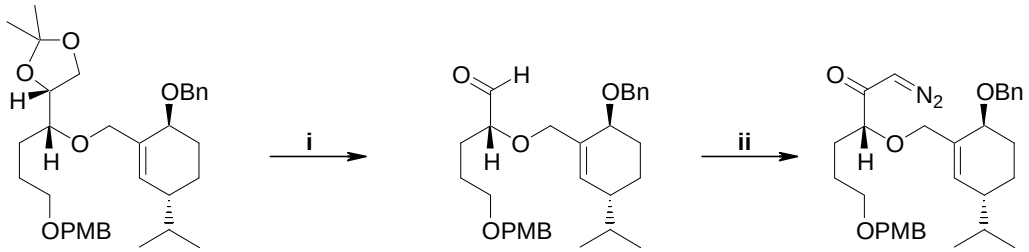


Scheme 52 *Reagents and conditions:* **i**, *n*-Bu_3P (0.8 eq.), CH_2O (37% solution in water, 2.0 eq.), NEt_3 (1.0 eq.), THF, rt, 3 h, [52%, 70% brsm]; **ii**, $CeCl_3$ (2.0 eq.), $NaBH_4$ (1.1 eq.), MeOH, –78 °C, 20 min, 98%, 10:1 d.r.; **iii**, benzaldehydedimethylacetal (1.4 eq.), camphor sulfonic acid (0.2 eq.), 4 Å mol. sieves, CH_2Cl_2, rt, 15 h [98%]; **iv**, DIBAL-H (4.0 eq.), CH_2Cl_2, –78 °C to rt, 15 h [82%]; **v,** on major alcohol only: (a) MsCl (1.5 eq.), Et_3N (2.0 eq.), CH_2Cl_2, –78 °C to 0 °C, 1.5 h, (b) LiBr (1.5 eq.), THF, rt, 2.5 h [94%, 2 steps]; **vi**, NaH (2.0 eq.), reflux, 1 h, then **203** (1.1 eq.), 18-crown-6 (0.5 eq.), *n*-Bu_4NI (0.03 eq.), THF, rt, 15 h [87%].

2.2 Synthesis of the tricyclic core of labiatin A

Acetal **252** was cleaved under acidic conditions to give the corresponding diol which underwent an oxidative cleavage using sodium metaperiodate to afford the aldehyde **253** in 92% yield over two steps. Oxidation using Pinnick conditions[69] gave the corresponding carboxylic acid which was converted into a mixed anhydride by treatment with isobutylchoroformate. Addition of the crude mixed anhydride to a freshly distilled solution of diazomethane afforded the diazoketone **254** in 86% yield over 2 steps (**Scheme 53**).

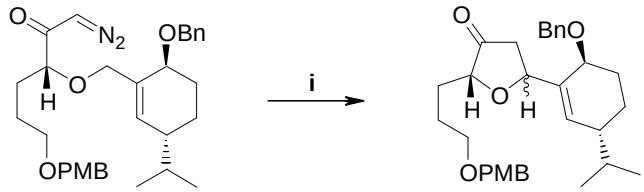
[69] Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091-2096.



252 **253** **254**

Scheme 53 *Reagents and conditions:* **i**, (a) PPTS (0.2 eq.), ethylene glycol, CH_2Cl_2, THF, reflux, 15 h, (b) $NaIO_4$ (4.0 eq.), THF, H_2O, 45 min [92%]; **ii**, (a) $NaClO_2$ (7.5 eq.), NaH_2PO_4 (6.5 eq.), 2-methyl-2-butene (8.0 eq.), *t*-butanol, H_2O, rt, 30 min [100%]; (b) i, NEt_3 (1.1 eq.), *i*-butylchloroformate (1.1 eq.), Et_2O, rt, 2 h, ii, CH_2N_2 (10 eq.), Et_2O, 0 °C, 1 h [86%].

At this stage, the first key carbenoid reaction was explored. Treatment of the diazoketone **254** with rhodium (II) trifluoroacetamide dimer gave the C–H insertion product **255** in 66% yield and a 7:1 *cis*:*trans* ratio along with 11% of a side product (**Equation 23**). Although NMR studies were carried out, the structure of this side-product could not be determined. Encouragingly, this crucial reaction resulted in the formation of the desired dihydrofuranone not only in a yield similar to that obtained during the model studies but also with a much higher *cis*:*trans* ratio.

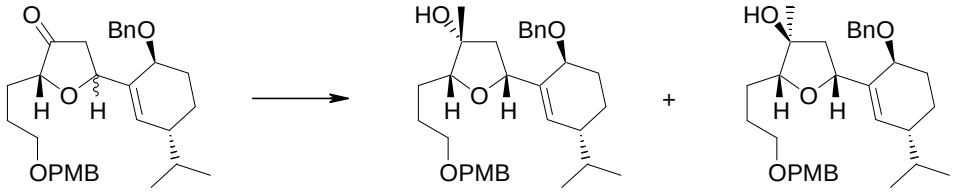


254 **255**

Equation 23 *Reagents and conditions:* $Rh_2(tfacam)_4$ (0.04 eq.), THF, rt, 2 h, [66%].

Nucleophilic addition of a methyl group to the ketone **255** proved to be challenging (**Table 5**). Using trimethylaluminium, the ketone was converted into a 7:3 mixture of two products in 62% yield. NMR studies showed that the major product was the desired tertiary alcohol **256** (**Figure 5**). Based on the results obtained with the model compound, the minor product was assumed to be the opposite diastereoisomer **257** but no further analyses to confirm this hypothesis were carried out, as this compound was of no use for our synthesis. Using methyllithium, the reaction did not go to completion

even using three equivalents of the alkyl metal reagent but the diastereoselectivity was better (8:1 d.r). Moreover, it was possible to recover unreacted starting material, and so methyllithium seems to be the reagent of choice for this nucleophilic addition reaction.



255 **256** **257**

Methylating agent	d.r. (**256**:**257**)	Conversion (isolated yield for **256**)
$AlMe_3$ (2 M in toluene)	7:3	100% (62%)
MeLi (1.6 M in Et_2O)	8:1	80% (61%)

Table 5

Studies on the tetrahydrofuran **256** (**Figure 5**) confirmed that the C–H insertion reaction gave essentially the *cis* furanone: there is an nOe of 1.8% between the protons H_a and H_b and 2.7% between the proton H_a and the methyl group. This is in agreement with the ketone being attacked from the top face (face presenting the two protons H_a and H_b), and so the stereochemistry is that required for labiatin A (**147**).

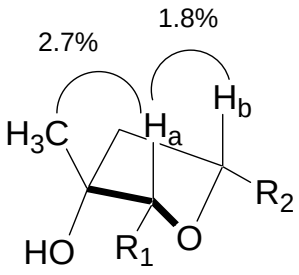
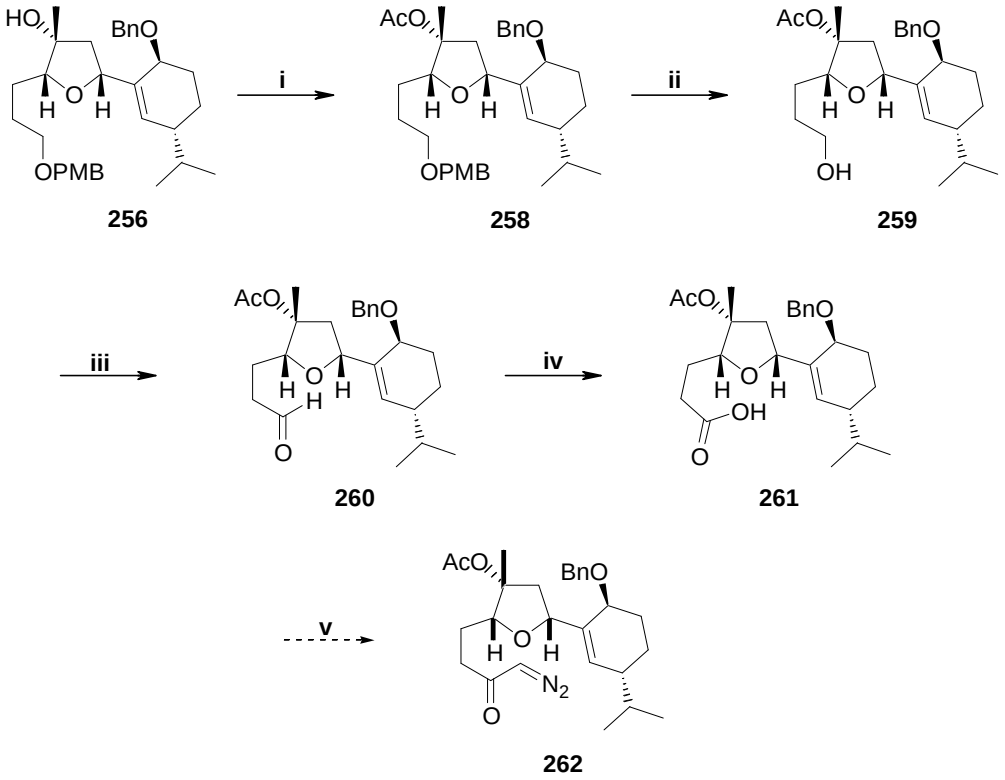


Figure 5 *nOe studies on the furan system **256**.*

Following the success of the C-H insertion reaction, attention was directed towards the second key step of the synthesis, namely the treatment of the diazoketone **262** with a metal catalyst leading to a tandem oxonium ylide formation/[2,3] sigmatropic rearrangement. Our efforts towards the synthesis of diazoketone **262** are described in

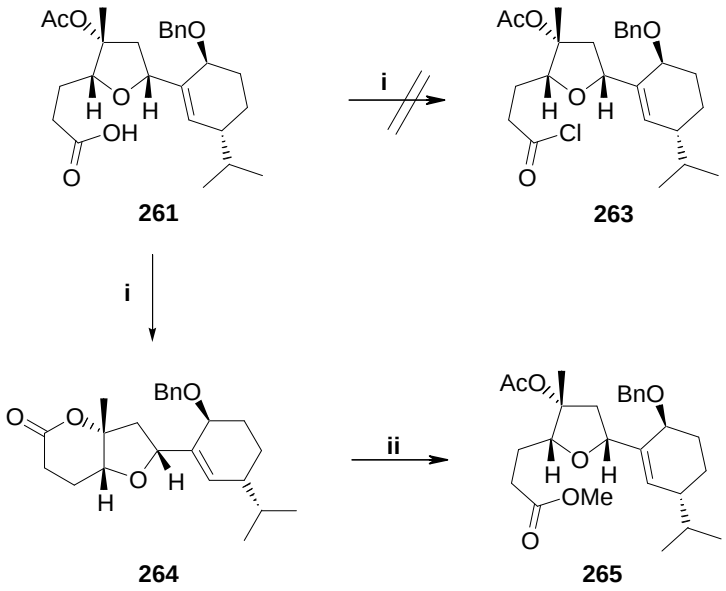
Scheme 54. Firstly, alcohol **256** was protected with an acetate group in 79% yield using freshly distilled acetic anhydride and DMAP. The PMB group was then removed with DDQ leading to the formation of the alcohol **259** in 71% yield. This alcohol was oxidised into the corresponding aldehyde **260** using Dess-Martin periodinane in 89% yield. The aldehyde was then quantitatively oxidised to the carboxylic acid **261** under Pinnick conditions.



Scheme 54 *Reagents and conditions:* **i**, Ac_2O (2.0 eq.), DMAP (3.0 eq.), CH_2Cl_2, rt, 15 h [79%]; **ii**, DDQ (1.5 eq.), CH_2Cl_2/H_2O 20:1, rt, 1 h [71%]; **iii**, Dess-Martin periodinane (2.0 eq.), CH_2Cl_2, 0 °C to rt, 15 h [89%]; **iv**, $NaClO_2$ (7.5 eq.), NaH_2PO_4 (6.5 eq.), 2-methyl-2-butene (8.0 eq.), *t*-butanol, H_2O, rt, 30 min [100%].

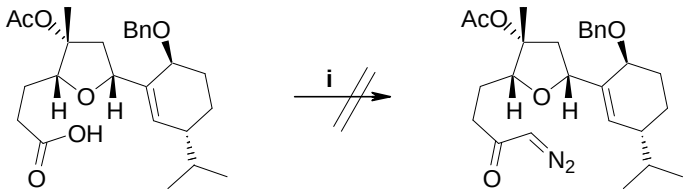
Unfortunately, formation of diazoketone **262** proved troublesome (**Scheme 55**). Reactions on the model system suggested that this diazoketone could be formed by the reaction of diazomethane with the acid chloride derived from carboxylic acid **261**. Carboxylic acid **261** was first treated with sodium methoxide in methanol to form the corresponding sodium salt. Subsequent treatment with oxalyl chloride was expected to give the acid chloride **263** which would then react with diazomethane to give the

diazoketone **262**. Unfortunately the product we obtained at this stage was the lactone **264**. The use of sodium methoxide was responsible for the cleavage of the acetate protecting group giving the free alcohol which then cyclised to give lactone **264**. This lactone was successfully opened upon treatment with triethylamine in methanol.



Scheme 55 *Reagents and conditions:* **i**, sodium methoxide (1.05 eq.), oxalyl chloride (5 eq.); **ii**, (a) NEt_3 (1.5 eq.), MeOH, reflux, 2 days, (b) Ac_2O (2.0 eq.), DMAP (3.0 eq.), CH_2Cl_2, rt, 16 h.

Alternative methods for the formation of the acid chloride **263** were then investigated (**Table 6**). The carboxylic acid **261** was treated with oxalyl chloride and a catalytic amount of DMF and the reaction was stirred overnight at rt under an atmosphere of argon. It was then added to a solution of diazomethane in diethyl ether; unfortunately this only resulted in the degradation of the starting material (*entry 1*). Attempt to synthesise the diazoketone **262** via the formation of an acyl mesylate[6] also led to the decomposition of the starting material (*entry 2*). Finally, the last attempt to form the diazoketone **262** consisted of the formation of a mixed anhydride using the same conditions as that had been used to prepare the first diazoketone **254** earlier in the synthesis: namely treatment with isobutylchloroformate. The mixed anhydride was formed in quantitative yield but unfortunately it did not react with diazomethane (*entry 3*).

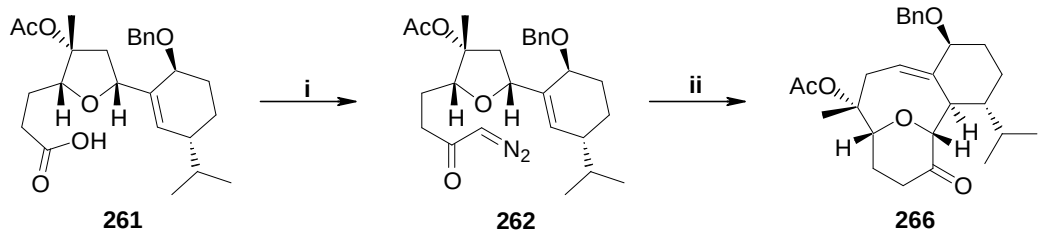


261 **262**

Entry	Conditions	Result
1	1) $(COCl)_2$ (1.2 eq.), cat. DMF, CH_2Cl_2, rt, 16 h 2) CH_2N_2 (c.a 10 eq.), Et_2O, 0 °C, 2 h	Decomposition
2	1) Et_3N (10.0 eq.), MsCl (5.0 eq.), CH_3CN, 10 min 2) CH_2N_2 (c.a 10 eq.), Et_2O, 0 °C, 2 h	Decomposition
3	1) ClCOOisobutyl (1.1 eq.), Et_3N (1.1 eq), rt, 1.5 h 2) CH_2N_2 (c.a 10 eq.), Et_2O, 0 °C, 2 h	Mixed anhydride

Table 6

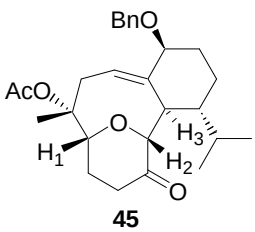
These very disapointing results prompted us to reconsider the initial attempt to synthesize diazoketone **262** when 1.05 equivalents of sodium methoxide were used to produce the sodium salt of the acid. As described before the addition of sodium methoxide led to the cleavage of the acetate group and was followed by lactonisation. Consequently, it was thought that by using only 0.95 equivalents the methanolysis of the acetate could be avoided. To our delight, treatment of acid **261** with a sub-stoichiometric amount of sodium methoxide followed by reaction with oxalyl chloride afforded the corresponding acid chloride **263**. Pleasingly, addition of this acid chloride to a solution of freshly distilled diazomethane in ether finally afforded the diazoketone **262** in 79% yield along with 10% of methyl ester **265**. Addition of diazoketone **262** to a solution of $Cu(hfacac)_2$ (the catalyst of choice according to the model studies[12]) in CH_2Cl_2 at reflux afforded the core structure **266** in 76% yield and as a single geometrical isomer (**Scheme 56**).



261 262 266

Scheme 56 *Reagents and conditions:* **i**, (a) sodium methoxide (0.95 eq.), MeOH, rt, 15 min, (b) oxalyl chloride (5.0 eq.), benzene, rt, 1.5 h, (c) CH_2N_2 (10.0 eq., solution in Et_2O), CH_2Cl_2, 0 °C [79%]; **ii**, $Cu(hfacac)_2$ (5 mol%), CH_2Cl_2, reflux, 1 h [76%].

The successful application of the Clark group methodology to such an elaborate diazoketone proves once more the efficacy and versatility of this reaction. Indeed, the yield for this transformation is even higher than that obtained using the model system. In addition, it is also worth noting that a substantial amount of [1,2]-sigmatropic rearrangement product was obtained from the reaction of the model system but reaction of our key diazoketone **262** gave only the [2,3]-sigmatropic rearrangement product **266**, the desired tricyclic core. Last but not least, we were extremely pleased to see that the relative stereochemistry of **266** (**Figure 6**) is that required for labiatin A. ^{1}H NMR studies show that the signal for proton 2 is a doublet and couples to proton 3 with a coupling constant of 12.6 Hz, the magnitude of this *J* value is indicative of a large dihedral angle and that the relationship between protons 2 and 3 is *anti*. Moreover in contrast to what was obtained using the model compound, only one geometrical isomer was isolated. The geometry of the double bond was determined later in the synthesis thanks to the X-ray crystal structure of a more advanced intermediate (*see page **78***).

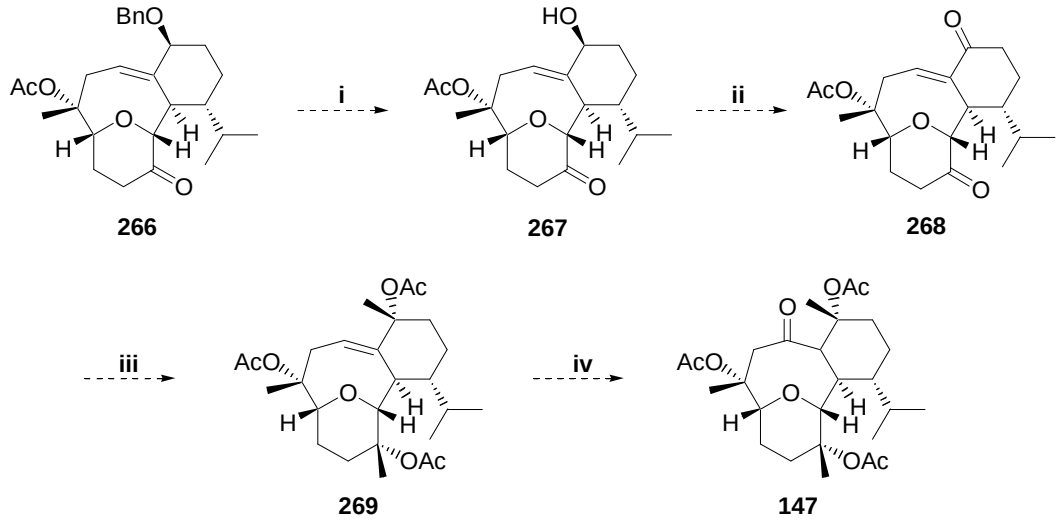


45

Figure 6 *Tricyclic core structure of labiatin A*

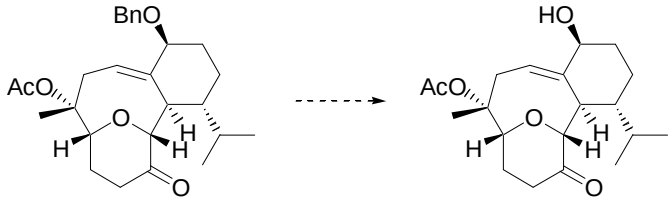
2.3 Studies towards the completion of the synthesis

A possible route for the completion of the synthesis of labiatin A (**147**) is shown in **Scheme 57**. Debenzylation followed by oxidation should afford the *α,β*-unsaturated ketone **268** and a double methyl addition/acetylation sequence is envisaged to give the intermediate **269**. Finally, hydroboration of the double bond and further oxidation should lead to the formation of labiatin A (**147**).



Scheme 57 *Reagents and conditions:* **i**, Birch reduction; **ii**, allylic oxidation; **iii**, (a) methyl addition, (b) acetate protection; **iv**, (a) hydroboration, (b) oxidation.

We firstly turned our attention to the debenzylation reaction. The presence of the double bond in the 8-membered ring prevented us from performing the classic hydrogenolysis of the benzyl group. Despite various attempts, it was not possible to obtain the desired allylic alcohol (**Table 7**). The use of liquid metals (*entries 1, 2 and 3*) led to the decomposition of the starting material, and Lewis acid mediated debenzylation (*entries 4 to 7*) led a mixture of two inseparable and unidentified products in which the benzyl protecting had been removed. Finally, hydrogenolysis (*entries 8 and 9*) also led to a similar mixture of products.



266 **267**

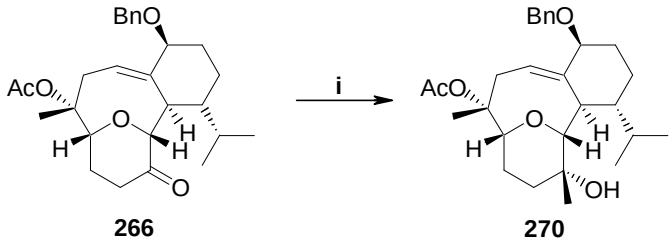
Entry	Conditions	Result
1	Na (3.5 eq.), liq. NH_3, –78 °C, 30 min	Decomposition
2	Li (3.5 eq.), liq. NH_3, –78 °C, 1.5 h	Decomposition
3	1M lithium naphtalenide solution (3.0 eq.), –78 °C to rt, 15 h	Decomposition
4	BCl_3·DMS (2 M in CH_2Cl_2, 3.0 eq.), CH_2Cl_2, –78 °C, 1.5 h	Debenzylation
5	DDQ (10 eq.), CH_2Cl_2, rt, 17 h	Debenzylation
6	$AlCl_3$ (3.1 eq), dimethylaniline (4.2 eq.), CH_2Cl_2, 20 h	No reaction
7	$AlCl_3$ (2.0 eq.), CH_2Cl_2/*m*-xylene 2:1, –15 °C, 30 min	Debenzylation
8	Ammonium formate (4.8 eq.), Pd (10% on carbon) (4.8 eq.), MeOH, rt, 20 h	No reaction
9	H_2, Pd (10% on carbon) (0.3 eq.), EtOAc, 3 days	Debenzylation

Table 7 Debenzylation on the core structure.

These results show that the removal of the benzyl protecting group at this stage of the synthesis was extremely complicated and the results obtained with Lewis acids and by hydrogenolysis led us to conclude that even if the benzyl group could be removed, the resulting allylic alcohol is probably unstable and may rearrange to give unidentified debenzylated compounds.

The fact that the debenzylation reaction was troublesome at this stage led us to perform methyl addition to the ketone **266** prior to deprotection. Several organometallic

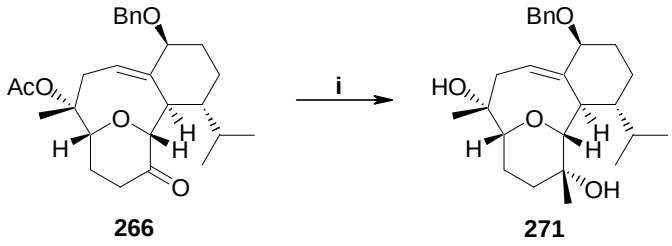
reagents were tested (**Table 8**), but methyl lithium proved to be the only one having sufficient reactivity. Nevertheless, the reaction was very sluggish and had to be performed at least twice in order to achieve complete conversion. The reaction conditions used also led to the removal of the acetate group (**Equation 24**).



266 **270**

Entry	Conditions **I**	Result
1	MeMgCl (3 M in THF), 5 eq, –78 °C to rt, 2 h	Decomposition
2	MeMgBr (1.4 M in Tol/THF 3:1), 5 eq, –78 °C to rt, 15 h	no conversion
3	MeMgI (c. a. 1 M in Et_2O), 5 eq, –78 °C to rt, 16 h	No conversion
4	$AlMe_3$ (2 M in hexanes), 5 eq, –78 °C to rt, 16 h	No conversion
5	$ZrMe_4$ (c.a. 13 M in THF), 1 eq, –78 °C, 1 h	44% conversion
6	MeLi (1.6 M in Et_2O), 1 eq, –78 °C, 1 h	58% conversion
7	MeLi (1.6 M in Et_2O), 5 eq, –78 °C to rt, 16 h, two runs	100% conversion

Table 8 *Methyl addition to the ketone* **266**.



266 **271**

Equation 24 *Reagents and conditions:* **i**, MeLi (1.6 M in Et_2O, 5 eq.), toluene, –78 °C to rt, 2 runs, [82%].

The methyl addition on ketone **266** was stereoselective and the stereochemistry was established by the X-ray crystallographic analysis of diol **271** which showed that the compound possesses the relative configuration required for labiatin A (**Figure 7**). This

X-ray structure confirmed the correct installation of six stereocentres present in labiatin A, five of them being contiguous. It also showed that the endocyclic alkene in the 8-membered ring possesses the E geometry.

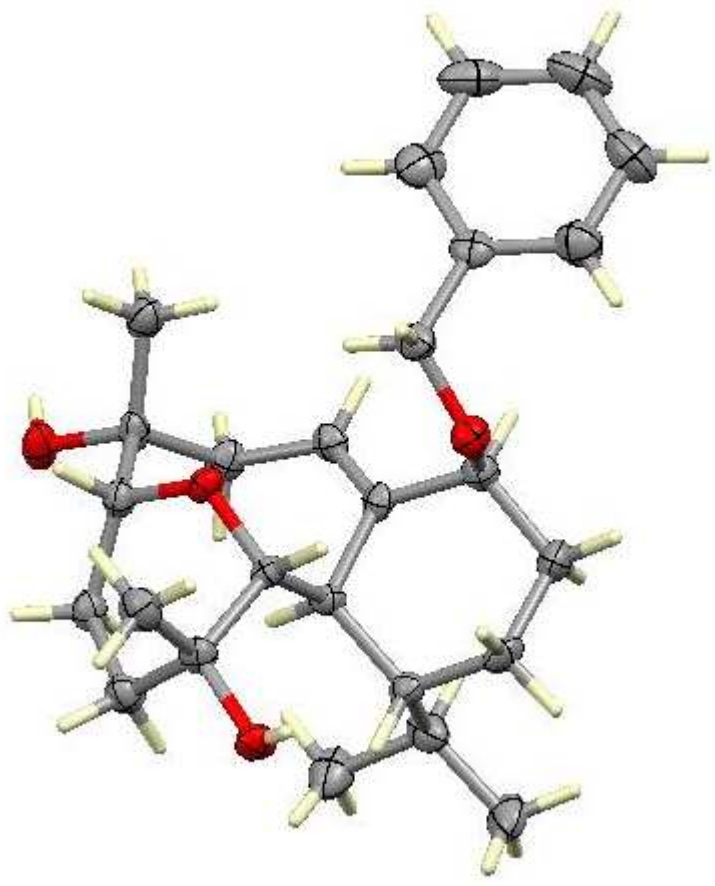
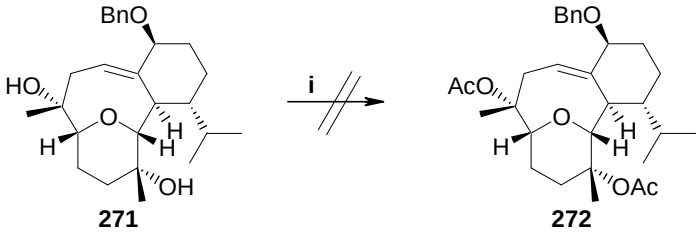


Figure 7 *X-ray structure of diol* **271**.

In labiatin A, the two hydroxyl groups in diol **271** are acetylated. We firstly performed the bis-acetylation (**Equation 25**) using acetic anhydride and DMAP in CH_2Cl_2. In this case only one acetate was installed after 24 h; leaving the reaction for a further 24 hours led to the total decomposition of the starting material and the product. Addition of TMSOTf to the reaction mixture is known to accelerate the acetylation of alcohols and to give particularly good results with tertiary alcohols.[70] In our case the use of

[70] Procopiou, P. A.; Baugh, S. P. D.; Flack, S. S.; Inglis, G. G. *J. Org. Chem* **1998**, *63*, 2342-2347.

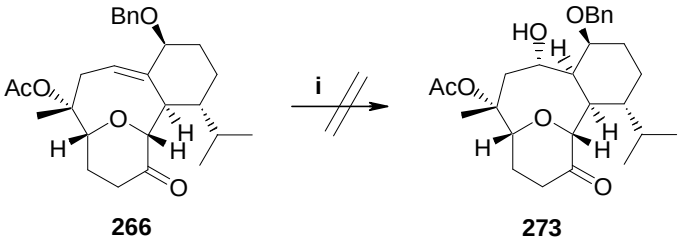
TMSOTf only led to the decomposition of the starting material and notably the cleavage of the benzyl protecting group.



271 272

Equation 25 *Reagents and conditions:* **i**, Ac_2O (3.0 eq), TMSOTf (1 M in CH_2Cl_2, 0.04 eq), CH_2Cl_2, 0 °C to rt, 2.5 h, [0%].

In parallel to work concerning the methyl addition to ketone **268** followed by acetylation, we focused on another interesting feature in labiatin A, namely the presence of the ketone in the 8-membered ring. As described earlier (**Scheme 57**), the intention was to introduce this ketone by hydroboration of the double bond and oxidation of the resulting alcohol. With the tricyclic core **268** now available, we attempted to hydroborate the trisubstituted alkene (**Equation 26**). Addition of thexyl borane followed by sodium perborate at pH 7 resulted in the recovery of starting material. The use of a more reactive borane instead of the bulky reagent thexyl borane led to consumption of the starting material but did not deliver the expected alcohol **273** and instead gave a complex mixture of unidentifiable polar by-products.

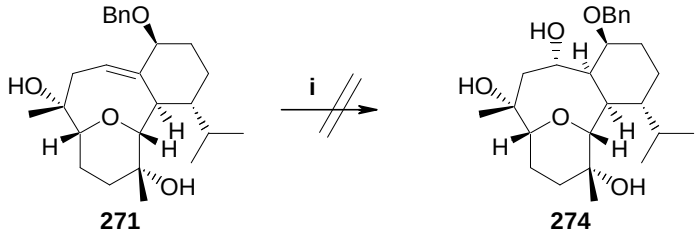


266 273

Equation 26 *Reagents and conditions:* **i**, BH_3 (1 M in THF, 2.0 eq), THF, 0 °C, 50 min then pH 7 buffer, $NaBO_3 \cdot 4H_2O$ (2.0 eq), rt, 2 h, [0%].

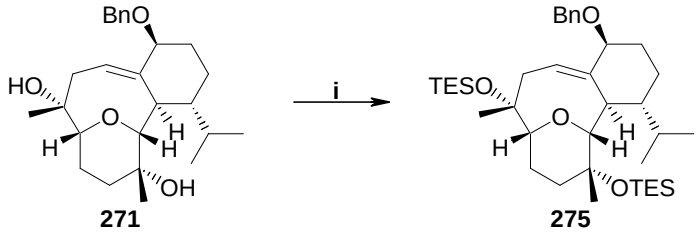
It was thought that the presence of the ketone and/or the acetate group might be responsible for this failure and therefore the hydroboration reaction was attempted on

the diol **271** (**Equation 27**). Unfortunately, in this case the starting material was consumed but none of the required alcohol **274** was obtained.



Equation 27 *Reagents and conditions:* **i**, BH_3 (1 M in THF, 3.2 eq), THF, 0 °C to rt, 1.5 h then pH 7 buffer, $NaBO_3{\cdot}4H_2O$ (3.2 eq), rt, 2 h [0%].

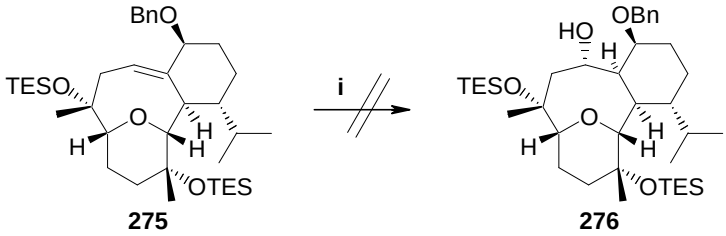
As a consequence of the results above, the decision was taken to bis protect the diol **271** with TES groups. The use of TESCl and imidazole in DMF led once more to the decomposition of the starting material. However the two TES groups could be successfully introduced in 48% yield using TESOTf and 2,6-lutidine in CH_2Cl_2 (**Equation 28**).



Equation 28 *Reagents and conditions:* **i**, TESOTf (10.0 eq), 2,6-lutidine (15.0 eq), CH_2Cl_2, –78 °C, 4 h [48%].

The X-ray crystal structure of diol **271** suggests that the double bond is hindered by the presence of the benzyl group. Attack of the double bond by borane could probably only occur from the bottom face which is encouraging because this is the outcome required to give the required product. However because of the steric hindrance, we thought that the eventual organoborane intermediate could only be oxidised only by a small and highly reactive oxidising agent. Therefore we performed the hydroboration on alkene **275** using borane and hydrogen peroxide instead of sodium perborate (**Equation 29**).

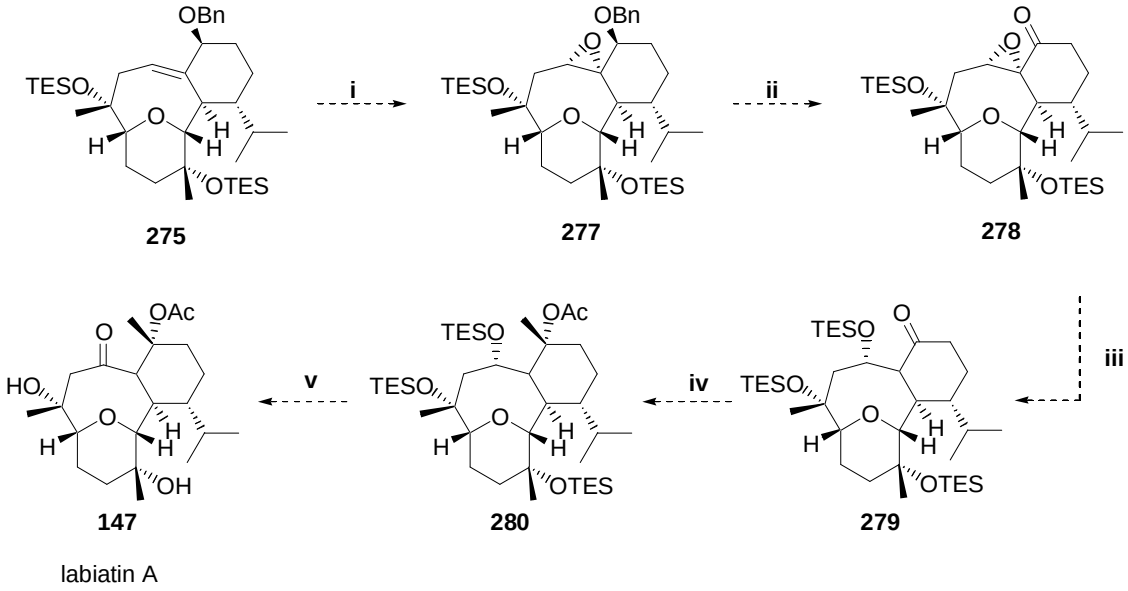
Unfortunately, this reaction led once again to the formation of polar by-products and none of the required alcohol **276**.



Equation 29 *Reagents and conditions:* **i**, BH_3 (1 M in THF, 6.0 eq), THF, 0 °C to rt, 1.5 h then pH 7 buffer, H_2O_2 (37% in water, 2.0 eq), 0 °C, 20 min, [0%].

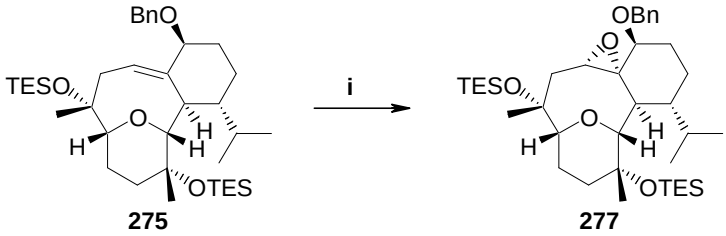
After the failure of various attempts to hydroborate the double bond in the 8-membered, a modified route was designed (**Scheme 58**). In this route the alkene **275** would be epoxidised using *m*-CPBA. Removal of the benzyl protecting group by hydrogenation should afford an alcohol that would be oxidised to the corresponding ketone **278**. Reductive opening of the epoxide using diphenyldiselenide and sodium borohydride should afford an alcohol on the 8-membered ring.[71] It would subsequently be TES protected to give the intermediate **279**. Methyl addition to the ketone **279** followed by acetylation should afford intermediate **280**. Finally, removal of the TES groups followed by oxidation of the secondary hydroxyl group and acetylations of the two tertiary alcohols would lead to the formation of labiatin A (**147**).

[71] Miyashita, M.; Suzuki, T.; Hoshino, M.; Yoshikoshi, A. *Tetrahedron* **1997**, *53*, 12469-12486.



Scheme 58 *Reagents and conditions:* **i**, *m*CPBA; **ii**, (a) H_2, Pd/C, H-cube for pressure, (b) oxidation; **iii**, (a) PhSeSePh, $NaBH_4$, (b) TESOTf, 2,6-lutidine; **iv**, (a) methyl addition, (b) Ac_2O, DMAP; **v**, (a) TBAF, (b) oxidation, (c) Ac_2O, DMAP.

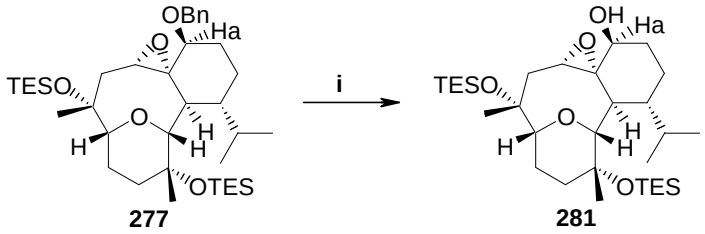
The alkene **275** was first epoxidised using freshly purified *m*-CPBA (**Equation 30**). The reaction proceeded smoothly but three equivalents of *m*-CPBA were required for complete consumption of the alkene **275**. The stereochemistry of the epoxide **277** has not been confirmed but it is thought to be *trans* to the OBn group not only because the double bond upper face is hindered but also because a similar epoxidation performed by our group on the bicyclic core of neoliacinic acid occurred from the bottom face.[59]



Equation 30 *Reagents and conditions:* **i**, *m*-CPBA (3.0 eq.), CH_2Cl_2, rt, 2 h, [100% crude].

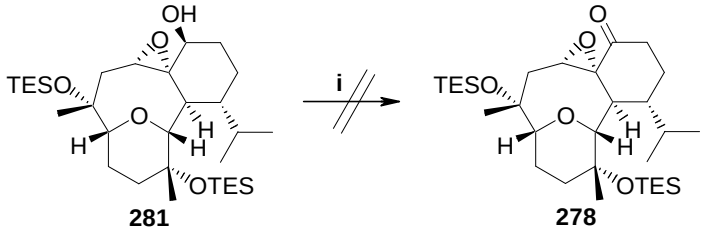
The crude epoxide was then hydrogenated in the presence of palladium on carbon in an effort to remove the benzyl protecting group (**Equation 31**). Following the work of Crimmins on the total synthesis of ophirin B,[53] the hydrogenation was performed at rt

in EtOAc but after 24 h a 72% conversion was obtained. Encouragingly ^{1}H NMR analysis of the unpurified product shows that one compound is formed and the only difference between the ^{1}H NMR of the starting material and of this new product is the proton Ha. After heating the mixture at 40 °C, the benzyl group was nearly completely cleaved as judged by ^{1}H NMR analysis but unfortunately other products were also produced. Hydrogenolysis reactions performed in MeOH or THF were actually even more sluggish (virtually no debenzylation was observed after 24 h).



Equation 31 *Reagents and conditions:* **i**, Pd (10% on C, 0.2 eq), EtOAc [72% conversion].

The crude mixture resulting from the hydrogenolysis reaction was treated with Dess-Martin periodinane in an attempt to obtain the ketone **278**, but unfortunately unidentifiable products were obtained (**Equation 32**).

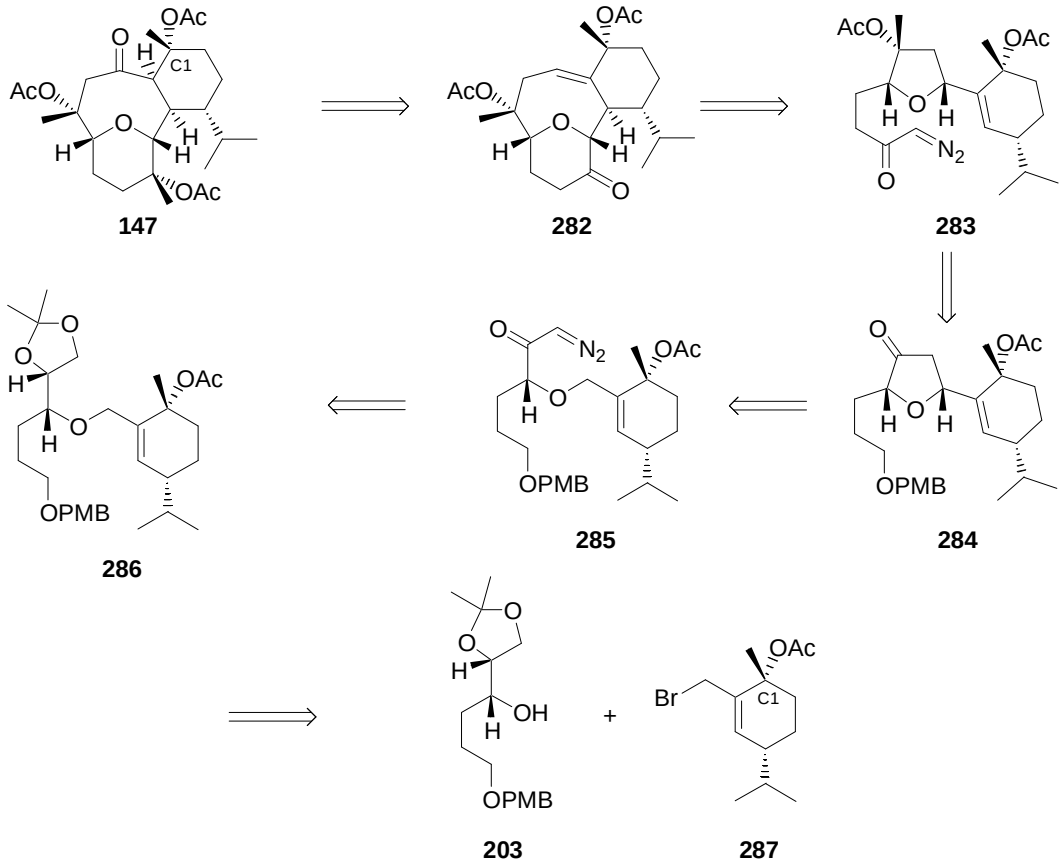


Equation 32 *Reagents and conditions:* **i**, Dess-Martin periodinane (2.0 eq.), CH_2Cl_2, 0 °C to rt, 3 h [0%].

2.4 Modified approach towards labiatin A

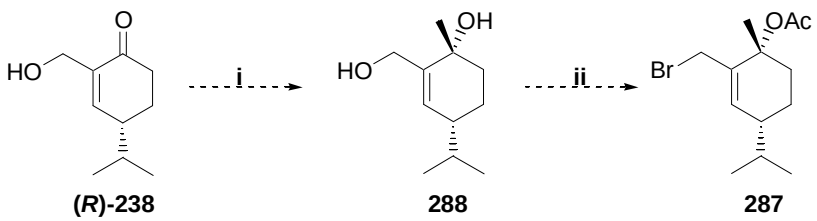
After our unsuccessful attempts to remove the benzyl protecting group from the rearrangement product **266**, we envisaged modifying the synthesis to install the stereocentre C1 earlier in the synthesis. Not only would this prevent the problematic

debenzylation but also it would dramatically decrease the number of steps required to complete the synthesis after our key rearrangement reaction (**Scheme 59**).



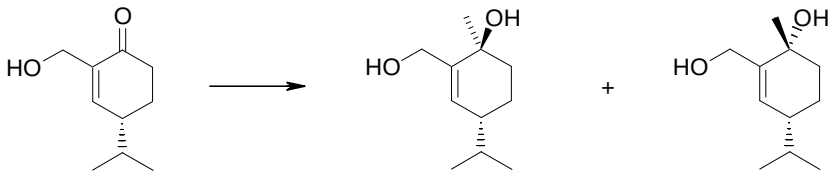
Scheme 59 *New retrosyntetic approach.*

The key compound in this modified approach is the bromide **287**, the synthesis of which could be achieved following the route shown **Scheme 60**. Addition of an alkylmetal reagent to the hydroxyl ketone **(*R*)-238** (resulting from a Baylis-Hillman reaction on the α/β-unsaturated ketone **(*R*)-232** as shown above) would give us the diol **288**. Bromination of the primary alcohol and acetylation of the tertiary alcohol would then lead to formation of bromide **287**.



Scheme 60 *Proposed synthetic pathway to bromide **287**.*

Ketone **(*R*)-238** was treated with several alkylating agents (**Table 7**). The use of methyllithium or trimethylaluminium led to the formation of alcohol **289** as the major product. Unfortunately, the stereochemistry is opposite to that desired for labiatin A (**147**). The desired product is the minor product, alcohol **288**, the structure of which has been confirmed by X-ray crystallography (**Figure 8**). To invert the stereoselectivity, the ketone **(*R*)-238** was first treated with MAD reagent[72] but no change in the diastereoisomeric ratio was observed.



(*R*)-238 **289** **288**

Entry	Conditions	d.r. **289**/**288**
1	MeLi (1.6 M in Et_2O, 5 eq.), toluene, –78 °C, 2 h	2.0 : 1
2	$AlMe_3$ (2 M in heptane, 10 eq.), toluene –78 °C to rt, 18 h	5.7 : 1
3	MAD reagent (3 eq.), MeLi (1.6 M in Et_2O, 8 eq.), toluene, –78 °C to rt, 20 h.	2.0 : 1

Table 7 *Methyl addition to the ketone* **(*R*)-238**.

[72] Maruoka, K.; Itoh, Y.; Sakurai, M.; Nonoshita, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 3588-2597.

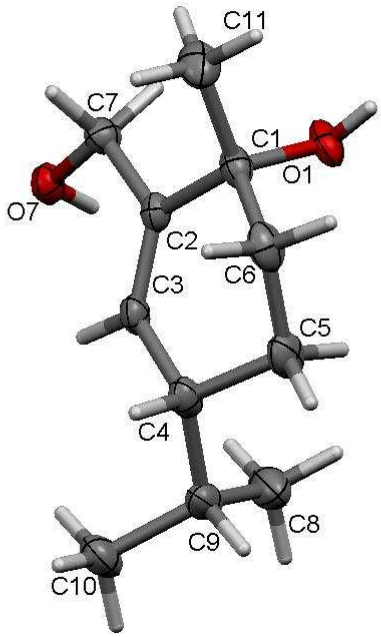
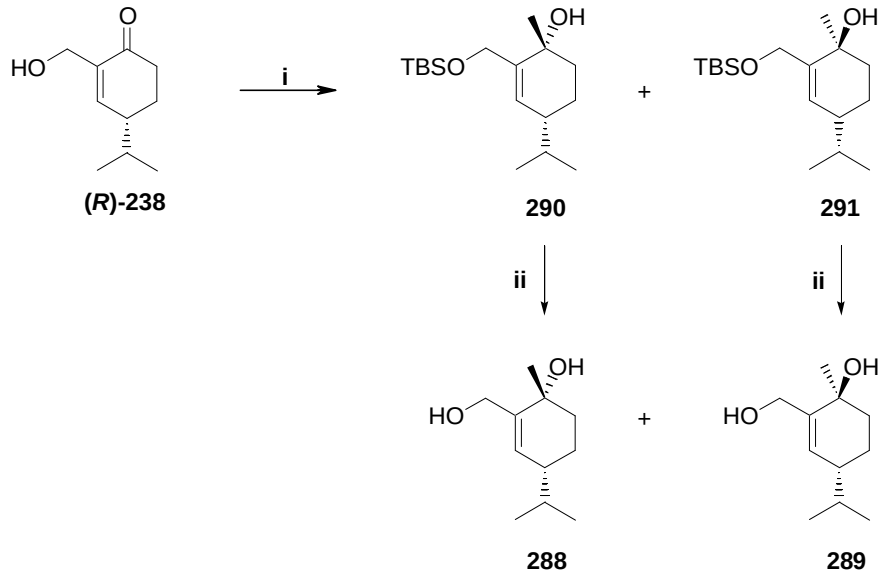


Figure 8 *X-ray structure of minor alcohol* **288**.

In an effort to reverse the selectivity, the alcohol was converted into a bulky TBS ether. The resulting compound displayed increased selectivity during addition of the methyl group but unfortunately the major product was still the undesired alcohol as confirmed by removal of the TBS group using TBAF to give known alcohols **289** and **288** (**Scheme 61**). In a final attempt to invert the selectivity, introduction of a MOM protecting group was attempted. The idea was to utilise chelation control to achieve selectivity, but attempts to install the MOM group using sodium hydride and MOMCl were not successful and led to decomposition of the starting material.

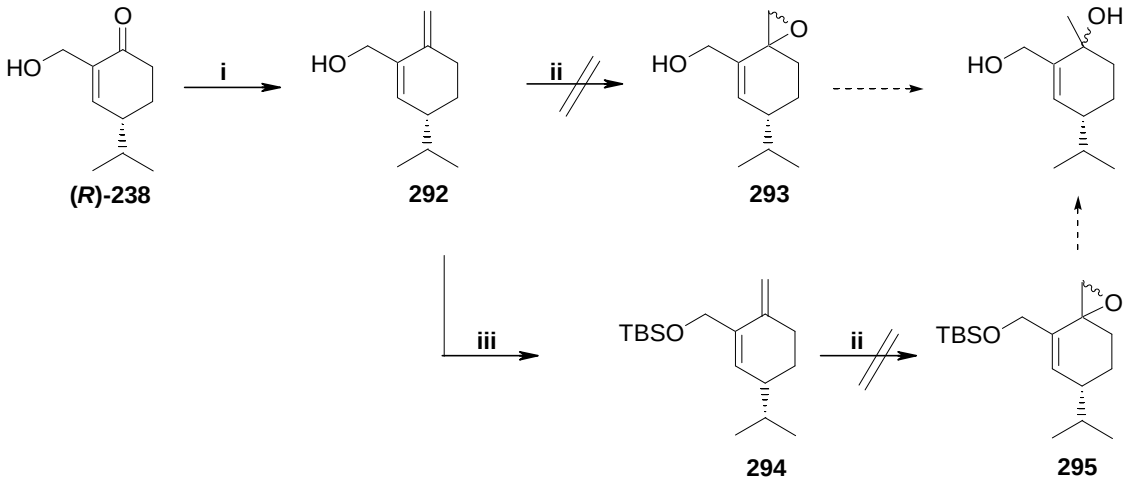


Conditions **(i, (b))**	d.r. **291**/**290**
MeLi (1.6 M in Et_2O, 5 eq.), toluene, –78 °C, 2 h	2:1
$AlMe_3$ (2 M in heptane, 10 eq.), toluene –78 °C to rt, 18 h	9:1

Scheme 61 *Reagents and conditions:* **i**, (a) TBSCl (1.6 eq.), imidazole (2.5 eq.), DMF, RT, 3 h; (b) see above; **ii**, TBAF (1 M in THF, 5 eq.), THF, rt, 1 h.

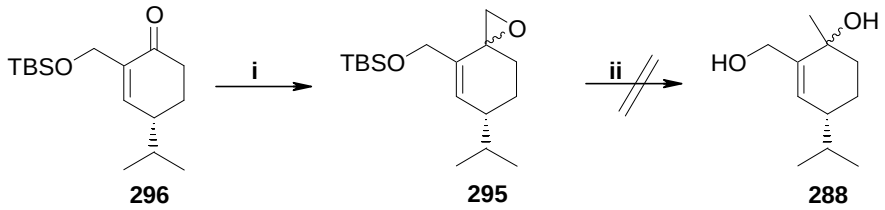
It was also thought that alcohol **288** could be obtained by opening of the epoxide **293** (**Scheme 62**). A Wittig olefination of ketone **(*R*)-238** led to the formation of diene **292** in 66% yield. Unfortunately epoxidation of either alkene **292** or the TBS protected alcohol **294** with *m*-CPBA led to the formation of a complicated mixture even though we expected to accomplish selective epoxidation of the exocyclic alkene.[73]

[73] Urones, J. G.; Marcos, I. S.; Pérez, B. G.; Lithgow, A. M.; Diez, D.; Gómez, P. M.; Basabe, P.; Garrido, N. M. *Tetrahedron* **1995**, *51*, 1845-1860.



Scheme 62 *Reagents and conditions* **i**, Ph_3PCH_3Br (9.0 eq.), KO^{t}Bu (9.0 eq.), toluene, reflux, 1.5 h, [66%]; **ii,** *m*-CPBA (1.1 eq.), CH_2Cl_2, rt, 0 °C, [0%]; **iii**, TBSCl (1.6 eq.), imidazole (2.5 eq.), DMF, RT, 2 h [84%].

The epoxide **295** was ultimately obtained via a Corey-Chaykovsky reaction.[74] Treatment of ketone **296** with the sulfur ylide generated by deprotonation of trimethylsulfonium iodide led to the formation of epoxide **295** as a 6:1 mixture of diastereoisomers. Unfortunately, treatment of this epoxide with $LiAlH_4$ did not deliver the desired tertiary alcohols but instead resulted in decomposition of the starting material (**Scheme 63**).

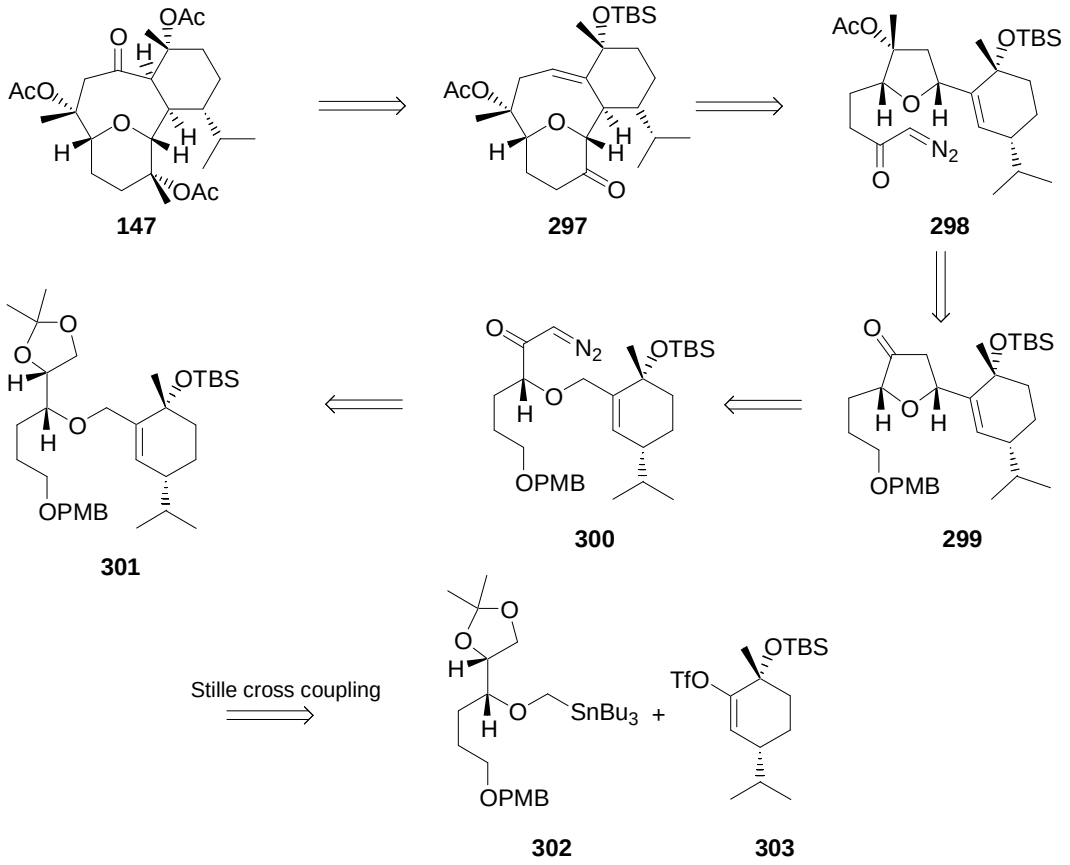


Scheme 63 *Reagents and conditions* **i**, (a) KHMDS (1.3 eq.), $Me_3S^+I^-$ (1.5 eq.), THF, 0 °C, 30 min, (b) ketone **72** (1.0 eq.), THF, 0 °C, 30 min [100%]; **ii**, $LiAlH_4$ (2.0 eq.), 0 °C to rt, 2 h, [0 %].

At this stage it was decided to design another new route (**Scheme 64**). The strategic concept of introducing the C1 stereocentre early in the synthesis was retained and the

[74] (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 867-868; (b) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353-1364.

main new feature in the retrosynthetic approach was to be a Stille coupling reaction between the stannane **302** and the triflate **303**.

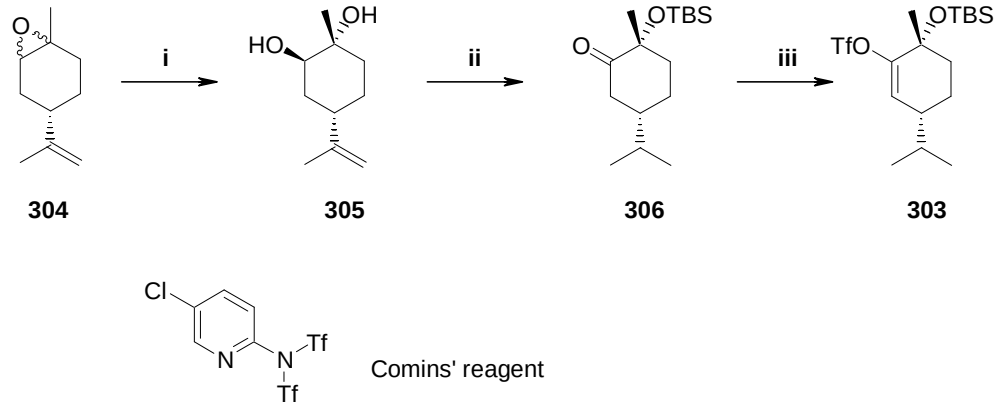


Scheme 64 *Retrosynthetic approach involving a Stille cross coupling reaction.*

The enantiopure triflate **303** was synthesised in 5 steps and 23% yield from commercially available (*S*)-(–)-limonene oxide (1:1 mixture of diastereoisomers) as described in **Scheme 65**. (*S*)-(–)-limonene oxide **304** was first heated at reflux in water with a catalytic amount of pyrazole to give *trans*-limonene oxide **304a** and the diol **305** as a 1:1 mixture in 96% yield.[75] The double bond was then hydrogenated using 20 mol% of Wilkinson's catalyst in 88% yield and the resulting diol was then oxidised to the corresponding ketone using IBX in 89% yield. After protection of the tertiary

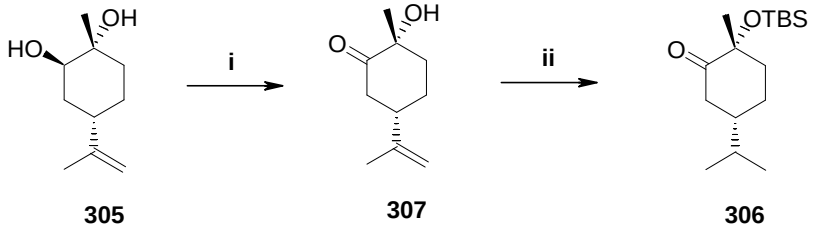
[75] Steiner, D.; Ivison, L.; Goralski, C. T.; Appell, R. B.; Gojkovic, J. R.; Singaram, B.; *Tetrahedron: Asymmetry* **2002**, 13, 2359-2363.

alcohol with a TBS group in 72% yield, the ketone **306** was treated with KHMDS and Comins' reagent to afford the enol triflate **303** in 90% yield.[76]



Scheme 65 *Reagents and conditions:* **i**, pyrazole (0.17 eq.), H_2O, reflux, 5 h [48%]; **ii**, (a) $(PPh_3)_3RhCl$ (20 mol%), H_2, toluene, rt, 6 h [88%], (b) IBX (4.0 eq.), EtOAc, reflux, 6 h [89%], (c) TBSOTf (3.0 eq.), 2,6-lutidine (4.5 eq.), CH_2Cl_2, –78 °C, 2.5 h [72%]; **iii**, KHMDS (2.5 eq.), Comins' reagent (2.0 eq.), –20 °C, 30 min [90%].

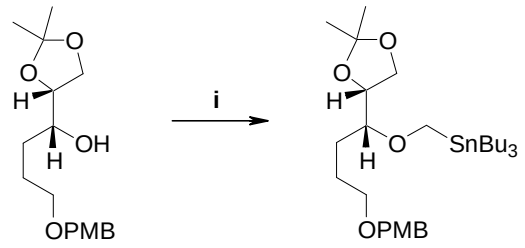
A drawback of this synthesis is the use of a large amount of Wilkinson's catalyst for the hydrogenation which can make it expensive to perform on large scale. But we were happy to find out that oxidation of the secondary alcohol **305** prior to the hydrogenation reaction allowed us to reduce the double bond using only 0.05 mol% catalyst (**Scheme 66**).



Scheme 66 *Reagents and conditions:* **i**,, IBX (4.0 eq.), EtOAc, reflux, 6 h, [89%]; **ii**, (a) $(PPh_3)_3RhCl$ (0.05 mol%), H_2, toluene, rt, 6 h [95%], (b) TBSOTf (3.0 eq.), 2,6-lutidine (4.5 eq.), CH_2Cl_2, –78 °C, 2.5 h, [96%].

[76] Comins, D. L.; Dehgani, A. *Tetrahedron Lett.* **1992**, *33*, 6299-6302.

Having designed an efficient synthesis of the enol triflate **303**, we focused on the synthesis of the stannane **302**. Treatment of alcohol **203** with potassium hydride followed by addition of ICH_2SnBu_3[77] afforded stannane **302** in a relatively good 73% yield (**Equation 33**).



203 **302**

Equation 33 *Reagents and conditions:* **i**, KH (2.0 eq.), THF, 0 °C to rt, 3 h, then ICH_2SnBu_3 (2.0 eq.), THF, 0 °C to rt, 15 h [73%].

The Stille coupling reaction between an alkoxymethylstannane and a triflate is a reaction rarely described in the literature but we were pretty confident that conditions developed by Blaszczack *et al.* could be applied to our substrate.[78] Unfortunately, as shown in **Table 8** (*entry 2*), those conditions were unsuccessful with our substrate. The coupling also failed using a variety of catalysts, solvents and additives, as summarized in **Table 8**. The classic method, in which palladium tetrakistriphenylphosphine and lithium chloride are used, led to the recovery of starting materials (*entry 1*) whereas the use of $(MeCN)_2PdCl_2$ and $Pd_2dba_3.CHCl_3$ led to the decomposition of one or both starting materials (*entries 2 to 4*).

[77] For a preparation see: Ahman, J.; Somfai, P. *Synthetic Commun.* **1994**, 24, 1117-1120.

[78] Blaszczak, L. C.; Brown, R. F.; Cook, G. K.; Hornback, W. J.; Hoying, R. C.; Indelicato, J. M.; Jordan, C. L.; Katner, A. S.; Kinnick, M. D.; McDonald, III, J.H.; Morin, J. M., Munroe, J. E., Pasini, C. E. *J. Med. Chem.* **1990**, *33*, 1656-1662.

Entry	Stannane	Triflate	Catalyst	Additives	Result
1[79]	1.5 eq.	1-cyclohexen-1-yl-trifluoromethanesulfonate (1.0 eq)	$Pd(PPh_3)_4$ (0.15 eq)	LiCl (6.0 eq.)	Recovered starting materials
2[18]	1.0 eq.	**303** (2.2 eq.)	$(MeCN)_2PdCl_2$ (0.1 eq.)	LiCl (2.0 eq.)	Decomposition of the stannane
3[18]	1.1 eq.	**303** (1.0 eq)	$(MeCN)_2PdCl_2$ (0.1 eq.)	LiCl (2.0 eq.)	Decomposition of the triflate
4[80]	2.0 eq.	**303** (1.0 eq.)	$Pd_2dba_3.CHCl_3$ (0.1 eq)	LiCl (6.0 eq.) Tri-2-furylphosphine (0.8 eq.)	Decomposition of both starting materials

Table 8 *Stille cross-coupling reactions of the stannane* **302**.

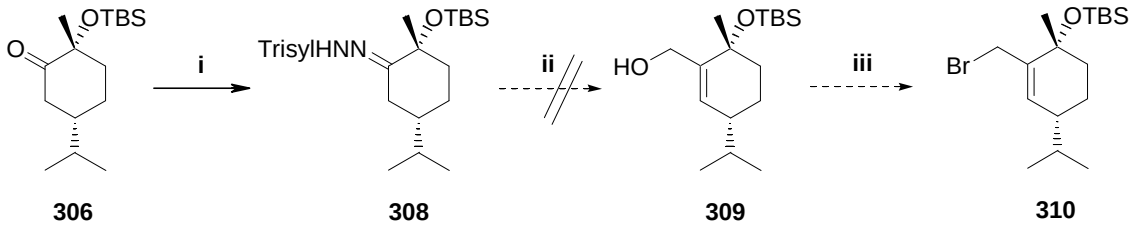
The fact that the enol triflate **303** could not be coupled to the stannane **302** meant that other avenues had to be explored. The bromide **310** was an attractive coupling partner. It was thought that that the alcohol precursor **309** could be prepared by using a Shapiro reaction.[81] Treatment of the hydrazone **308** with butyllithium followed by electrophilic trapping of the anion by DMF should afford an aldehyde and a subsequent Luche reduction would lead to the formation of alcohol **309** (**Scheme 67**). This alcohol could then be converted into the corresponding bromide **310** using carbon tetrabromide and triphenylphosphine. Ketone **306** was converted into the hydrazone **308** in 79% yield using commercially available 2,4,6-triisopropylbenzenesulfonyl hydrazide. Unfortunately, treatment of this hydrazone with 4.0 equivalents of *n*-BuLi, followed by the addition of DMF did not afford the expected aldehyde and most of the hydrazone

[79] Scott, W. J.; Crisp, G. T.; Stille, J. *J. Am. Chem. Soc.* **1984**, *106*, 7500-7506.

[80] Nicolaou, K. C.; Pihko, P. M.; Bernal, F.; Frederick, M. O.; Quian W.; Uesaka, N.; Diedrichs, N.; Hinrichs, J.; Koftis, T.; Loizidou, E.; Petrovic, G.; Rodriguez, M.; Sarlah, D.; Zou, N. *J. Am. Chem. Soc.* **2006**, *126*, 2244-2257.

[81] Roy, O.; Pattenden G.; Pryde, D. C.; Wilson, C. *Tetrahedron* **2003**, *59*, 5115-5121.

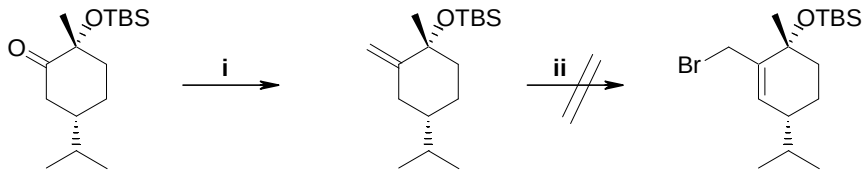
was recovered instead. *t*-BuLi and MeLi were also used as bases but in both cases the hydrazone remained intact. Addition of TMEDA to the reaction to enhance the formation of the anionic intermediate, as recommended by Chamberlin *et al.*,[82] did not give a better result.



306 **308** **309** **310**

Scheme 67 *Reagents and conditions:* **i**, 2,4,6-triisopropylbenzenesulfonylhydrazide (1.0 eq.), CH_2Cl_2, rt, 1 h [79%]; **ii**, (a) *n*-BuLi (4.0 eq.), THF, –78 °C to rt, 30 min then DMF (8.0 eq.), –78 °C to rt, 2 h (b) $NaBH_4$ (1.1 eq.), $CeCl_3.7H_2O$ (2.0 eq.), MeOH, –20 °C; **iii**, CBr_4, PPh_3, CH_3CN, 0 °C.

An alternative method to prepare bromide **310** is shown in **Scheme 68**. The ketone **306** was successfully converted into the alkene **311** in 92% yield *via* a Wittig methylenation reaction. However, allylic bromination using *N*-bromosuccinimide under various reaction conditions did not deliver the desired allylic bromide **310** (**Table 9**).



306 **311** **310**

Scheme 68 *Reagents and conditions:* **i**, (a) KO*t*Bu (6.0 eq.), Ph_3PCH_3Br (6.0 eq.), toluene, reflux, 1 h (b) ketone **306**, refllux, 30 min [81%]; **ii**, see **Table 9**.

[82] Chamberlin, A. R.; Stemke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147-154.

Entry	NBS (eq.)	Solvent	T	Time	Result
1[83]	2.0	DMSO/H_2O 70:1	rt	15 min	Recovered SM
2	2.0	DMSO/H_2O 70:1	rt	20 h	Mixture of SM + one product
3	2.0	DMSO/H_2O 70:1	rt	40 h	Unidentified products
4[84,a]	0.4	CCl_4	rt to reflux	3.5 h	-
5	1.5	DME/H_2O 2:1	0 °C	2 h	Recovered SM
6	3.0	DME/H_2O 2:1	0 °C to rt	24 h	-
7	3.0	DME/H_2O 2:1	0 °C	6 h	-

[a] a catalytic amount of benzoyl peroxide was added.

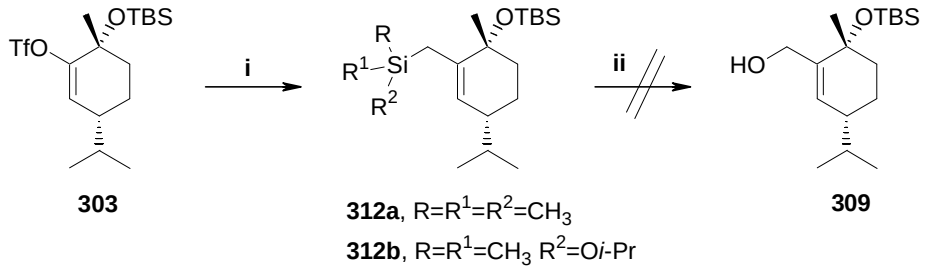
Table 9 *Allylic bromination.*

The failure to effect direct bromination of the alkene **311** meant that our attention turned back to the synthesis of the alcohol **309**. One possibility would be to prepare a silane **312** from the corresponding triflate **303** and then perform a Fleming-Tamao oxidation.[85] Treatment of triflate **303** with trimethylsilylmethyl magnesium chloride afforded the silane **312a** in 73%, but it transpired that this was not a suitable substrate for Fleming-Tamao oxidation. Attempted preparation of a silane bearing an isopropyloxy substituent **312b** was not successful. This compound turned out to be unstable to silica gel and treatment of the crude reaction mixture with KF, $KHCO_3$ and hydrogen peroxide did not lead to the formation of alcohol **309** (**Scheme 69**).

[83] Paquette, L. A.; Underiner T. L.; Galluci, J. C. *J. Org. Chem.* **1992**, *57*, 86-96.

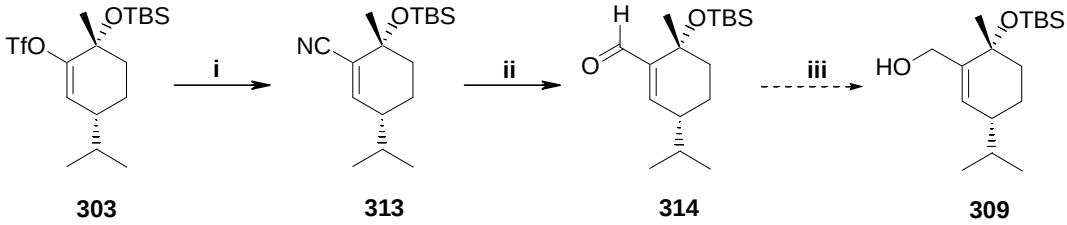
[84] Baguley, P. A.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 1*, **1998**, 2073-2082.

[85] (a) Tamao, K.; Ishida, N. *Tetrahedron Lett.* **1984**, *25*, 4245-4248 (b) Kobayashi, Y.; Takeuchi, A.; Wang, Y-G. *Org. Lett.* **2006**, *8*, 2699-2702.



Scheme 69 *Reagents and conditions:* **i**, $Pd(PPh_3)_4$ (0.3 eq.), $RR^1R^2SiMgCl$ (5.0 eq.), Et_2O, rt, 30 min, $R=R^1=R^2=CH_3$ [73%] and $R=R^1=CH_3$ and $R^2=O$*i*-Pr [0%]; **ii**, $KHCO_3$ (6.0 eq.), KF (6.0 eq.), H_2O_2 (27.5% 15.0 eq.), THF/MeOH 1:1, 50 °C, 3 h.

The triflate intermediate **303** is very versatile and a large number of conditions could lead us to the formation of the alcohol **309**. For instance this triflate was converted into the corresponding nitrile **313** using zinc (II) cyanide and $Pd(PPh_3)_4$ and the nitrile group was then treated with DIBAL-H to afford the aldehyde **314** in a very low 12% conversion from the triflate.[86] This result was not satisfactory because the yield is low and very toxic zinc cyanide is required, so this route was abandoned (**Scheme 70**).



Scheme 70 *Reagents and conditions:* **i**, $Zn(CN)_2$ (0.6 eq.), $Pd(PPh_3)_4$ (0.03 eq.), DMF, 60 °C, 18 h; **ii**, DIBAL-H (1 M in cyclohexane, 1.2 eq.), toluene, 0 °C, 2 h [12% conversion], **iii**, Luche reduction.

We also attempted to convert the triflate **303** into the methyl susbstituted alkene **315**.[87] The alkene **315** would be an ideal substrate for allylic oxidation with selenium dioxide[88] or direct allylic bromination. However, to our great disappointment, treatment of triflate **303** with methyl magnesium iodide in the presence of $Fe(acac)_3$ did not afford the desired intermediate **315** (**Scheme 71**).

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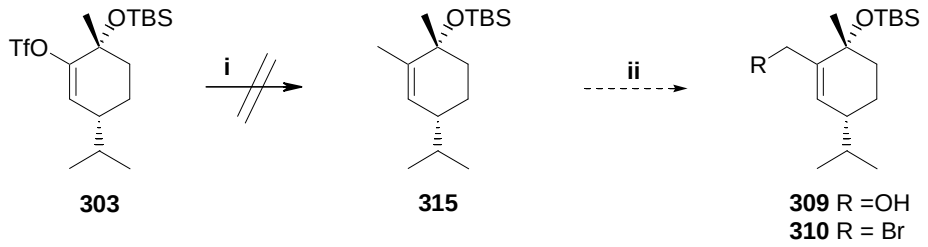
[86] Peese, K. M.; Gin, D. Y. *J. Am. Chem. Soc.* **2006**, *128*, 8734-8735.

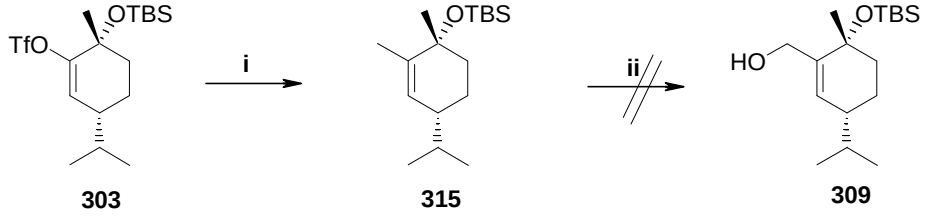
[87] Maulide, N.; Vanherck, J-C.; Markó, I. E. *Eur. J. Org. Chem.* **2004**, 3962-3967.

[88] Garlaschelli, L.; Vidari, G. *Tetrahedron* **1989**, *45*, 7371-7378.



Scheme 71 *Reagents and conditions:* **i**, MeMgI (2.2 M in Et_2O, 2.8 eq.), $Fe(acac)_3$ (0.02 eq.), THF, NMP (2:1), –15 °C, 30 min.; **ii**, R = OH: SeO_2 (6 eq.), dioxane, reflux; R = Br: NBS.

The methyl group could be introduced using a Negishi type coupling reaction with dimethylzinc catalysed by $Pd(dppf)Cl_2$.[89] Complete consumption of starting material was observed after heating the reaction mixture at reflux in THF for 16 h but a poor yield (25%) of the product was obtained possibly due to decomposition of the product on silica gel during the purification process. Allylic oxidation of the alkene **315** using selenium dioxide was then performed, but this only led to decomposition of the starting material (**Scheme 72**).[90]



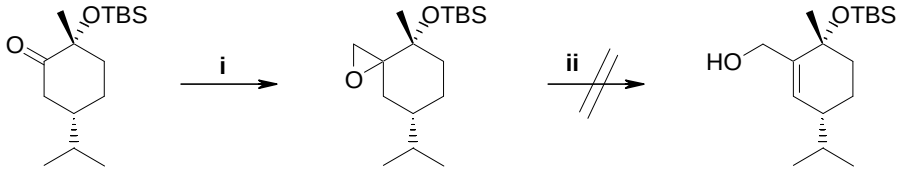
Scheme 72 *Reagents and conditions:* **i**, Me_2Zn (2 M in toluene, 2.0 eq.), $Pd(dppf)Cl_2.CH_2Cl_2$, THF, 60 °C, 16 h [25%]; **ii**, t-butylhydroperoxide (5.0 eq.), SeO_2 (2.0 eq.), salicylic acid (0.02 eq.), CH_2Cl_2, reflux, 2 h, [0%].

An alternative sequence for the preparation of the alcohol **309**, involving epoxide ring opening, was explored. The ketone **306** was easily converted into the epoxide **316** using sulfur ylide chemistry (**Scheme 73**). Various conditions have been used to open epoxides of this type. However, to our great surprise, numerous procedures described

[89] Nicolaou, K. C.; Nold, L. A.; Milburn, R. R.; Schindler, C. S.; Cole, K. P.; Yamaguchi, J. *J. Am. Chem. Soc*. **2007**, *129*, 1760-1768.

[90] Winkler, J. D.; Rouse, M. B.; Greaney, M. F.; Harrison, S. J.; Jeon. Y. T. *J. Am. Chem. Soc* **2002**, *124*, 9726-9728.

in the literature did not furnish the alcohol **309** from the epoxide **316** and the epoxide either remained intact or decomposed (**Table 10**).



306 **316** **309**

Scheme 73 *Reagents and conditions:* **i**, (a) Me_3SI (1.5 eq.), KHMDS (0.5 M in toluene, 1.3 eq.), THF, 0 °C, 30 min (b) ketone **306**, 0 °C, 30 min; **ii**, see **Table 10**.

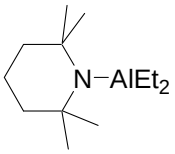
Entry	Conditions **ii**	Result
1	CSA (5.0 eq.), MeCN, rt, 16 h	Decomposition
2	Al(*i*-PrO)$_3$ (2.9 eq), toluene, reflux, 22 h	Recovery of SM
3	Al(*i*-PrO)$_3$ (10.0 eq), toluene, reflux, 22 h	Decomposition
4	Et_2NLi (2.5 eq.), Et_2O, reflux, 5 h	Recovery of SM
5	 (4.0 eq.), benzene, 0 °C to rt, 5 h	Decomposition
6[91]	TMSOTf (1.0 eq), 2,6-lutidine (1.0 eq), -78 °C, 3h, benzene then DBU (1.0 eq), rt, 14 h	Decomposition

Table 10 *Epoxide opening.*

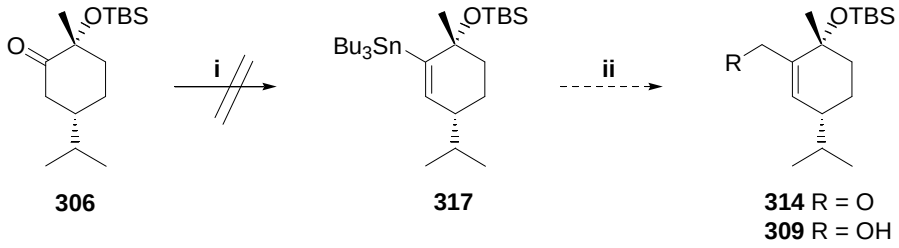
The final route to be explored involved the conversion of the ketone **306** into the corresponding vinylic stannane **317** followed by treatment with *n*-BuLi and electrophilic capture of the vinyl lithium species with DMF or formaldehyde (**Scheme 74**). This sequence was expected to lead to the formation of aldehyde **314** or alcohol **309** respectively. A one-pot procedure developed by Chong *et al*[92] in which addition of

[91] Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1979**, *101*, 2738-2739.

[92] Darwish, A.; Chong, J. M. *J. Org. Chem.* **2007**, *72*, 1507-1509.

Bu_3SnLi to the ketone is followed by dehydration with MsCl and triethylamine, led to decomposition of the starting material.

We also explored a two-step procedure in which the triflate **303** was utilised in a Stille cross coupling reaction using Pd_2dba_3 as a catalyst.[82] However, only the triflate **303** was recovered from this reaction.

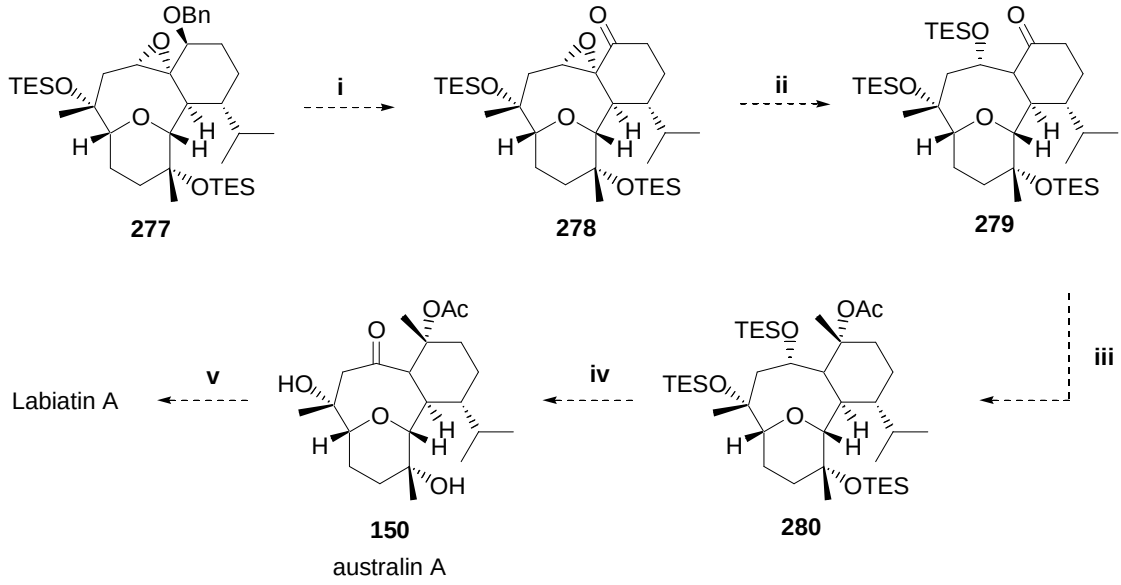


Scheme 74 *Reagents and conditions:* **i**, (a) LDA (1.10 eq.), Bu_3SnH (1.02 eq.), 0 °C, 10 min, (b) ketone (1.0 eq.), 10 min, (c) Et_3N (4.0 eq.), MsCl (4.0 eq.), 0 °C to rt, 30 min **or** (a) KHMDS (2.5 eq.), Commins' reagent (2.0 eq.), –20 °C, 30 min, 90%, (b) tri-2-furylphosphine (0.5 eq.), LiCl (3.0 eq.), Sn_2Bu_6 (2.0 eq.), Pd_2dba_3 (0.1 eq.), THF, rt, 22 h; **ii**, *n*-BuLi then HCOH or DMF.

2.5 Conclusion and future work

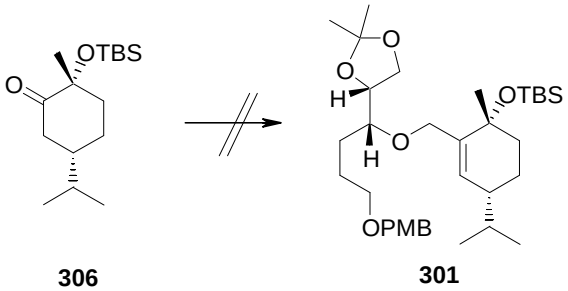
The tricyclic core of labiatin A (**147**) has been synthesised in 27 steps (23 steps as the longest linear sequence) using two metal carbenoid reactions: a rhodium catalysed C-H insertion reaction and a copper catalysed tandem oxonium ylid formation and [2,3]-sigmatropic rearrangement. The outstanding yields and selectivities obtained for these two reactions emphasise the efficacy of this methodology and its versatility regarding very elaborate and sensitive substrates. Completion of the synthesis has proved troublesome. Nevertheless, an X-ray structure of a very advanced intermediate has been obtained, demonstrating that the stereocentres have been correctly installed. The few remaining steps could be realized as described in **Scheme 75**. Removal of the benzyl protecting group by hydrogenation under pressure (H-cube) should afford a free alcohol that would be oxidised to the corresponding ketone **278**. Opening of the epoxide using diphenyldiselenide and sodium borohydride and subsequent TES protection would afford silyl ether **279**. Methyl addition to the ketone **279** followed by

acetylation should afford intermediate **280**. Removal of the TES groups followed by oxidation of the secondary hydroxyl group would lead to the formation of australin A (**150**) and finally double acetylation would give labiatin A (**147**). If the debenzylation step proves troublesome, a change of protecting groups will be necessary. A PMB protecting group could be installed instead of the benzyl group and this could be removed using DDQ.



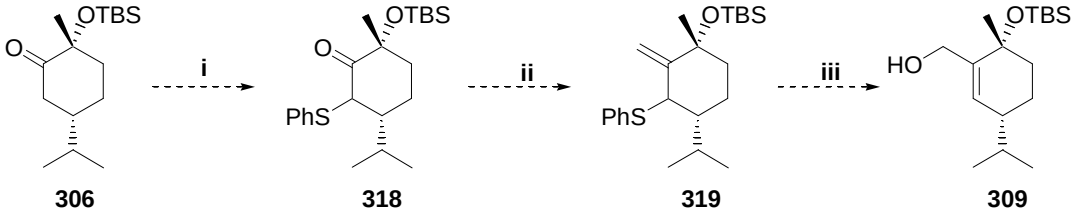
Scheme 75 *Reagents and conditions:* **i**, (a) H_2, Pd/C, H-cube, pressure, (b) oxidation; **ii**, (a) PhSeSePh, $NaBH_4$, (b) TESOTf, 2,6-lutidine; **iii**, (a) methyl addition, (b) Ac_2O, DMAP; **iv**, (a) TBAF, (b) oxidation; **v**, Ac_2O, DMAP.

Substantial work has also been completed on an alternative synthetic route to labiatin A (**147**). Unfortunately, despite the efficient synthesis of the ketone **306** from the chiral pool, it was not possible to couple this building block with alcohol **203** and progress any further (**Equation 34**).



Equation 34

Various unsuccessful attempts to synthesise the alcohol **309** from ketone **306** have been described, but the versatility of this ketone means that alternative methods deserve to be explored. As shown in **Scheme 76**, methylenation of the ketone **318** followed by oxidation of the sulfide **319** should lead to an allylic sulfoxide which would undergo a Mislow-Evans rearrangement to give alcohol **309**.[93]



306 **318** **319** **309**

Scheme 76 *Reagents and conditions:* **i**, KHMDS, PhSCl; **ii**, Wittig; **iii**, H_2O_2, R_3P.

[93] (a) Bickart, P.; Carson, F. W.; Jacobus, J.; Miller, E. G., Mislow K. *J. Am. Chem. Soc* **1968**, 90, 4869-4876 (b) Tang, R.; Mislow, K. *J. Am. Chem. Soc.* **1970**, *92*, 2100-2104 (c) Evans, D. A.; Andrews, G. C.; Sims, C. L. *J. Am. Chem. Soc.* **1971**, *93*, 4956-4957.

Chapter III

Experimental

Chapter III – Experimental

3.1 General information

^{1}H NMR spectra were recorded on a Bruker DRX 500 or a Brucker AV 400 FT or a JEOL EX270 spectrometer at room temperature. Spectra were run in deuterochloroform, using residual chloroform as the internal standard (δ = 7.26 ppm) or in deuterated benzene, using residual benzene as the internal standard (δ 7.16 ppm). *J* values are given in Hertz. Signals in NMR spectra are described as singlets (s), doublets (d), triplets (t), quartets (q), multiplets (m), broad (b), pseudo (ps) or combination of these, which refers to the spin-spin coupling pattern observed. Data are reported as follows; chemical shifts in ppm, multiplicity, integration, coupling constant and assignment. ^{13}C NMR spectra were recorded on Bruker DRX 500 or a Bruker AV 400 FT or a JEOL EX270 spectrometer at room temperature. Spectra were run in deuterochloroform, using residual chloroform as the internal standard (δ 77.0 ppm) or in deuterated benzene, using residual benzene as the internal standard (δ 128.1 ppm). Data are reported as follows; chemical shifts in ppm and assignment. Assignments were based on DEPT 135 and DEPT 90 pulse experiments and HMQC and HMBC experiments.

IR spectra were recorded in the range 4000–600 cm^{-1} on a Perkin-Elmer 1600 series FT-IR spectrometer with internal calibration using solution cells and a JASCO FT/IR 4100 using NaCl plates. High resolution mass spectra were recorded under EI, FAB, CI and ES conditions by the analytical services of the University of Nottingham or the analytical services of the University of Glasgow. Optical rotations were determined using a Jasco DIP-370 digital polarimeter or an Autopol®V Automatic polarimeter (Rudolph Research Analytical). $[\alpha]_D$ values are measured at the concentration and temperature shown. Elemental analyses were

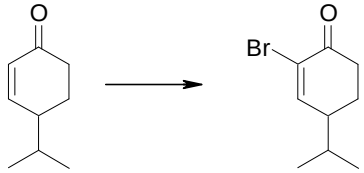
carried out on an Exeter Analytical Elemental Analyser EA 440. Melting points were recorded with an Electrothermal IA 9100 apparatus.

Reactions were monitored by TLC performed on Merck Kieselgel 60 F_{254} plates and visualization was peformed using a combination of UV light, ethanolic anisaldehyde, ethanolic phosphomolybdic acid or potassium permanganate with heat. Flash chromatography was performed using Fluorochem LC60A, 35–70 micron silica gel.

Reagents were used as supplied unless otherwise stated. Dry solvent reactions were performed in flame-dried glassware under argon. Petroleum Ether 40-60 °C is described as Petroleum Ether in the text. THF was distilled from potassium-benzophenone, dichloromethane was distilled from calcium hydride and EtOH was distilled from sodium. Dry toluene and dry Et_2O were dried by filtration through towers of activated alumin, through a 7 micron filter and through a non-metering hand operated valve to Luer-lock connector. Dry benzene, methanol, DMF and DMSO were purchased and used as supplied. Triethylamine and 2,6-lutidine were distilled from calcium hydride and were stored under argon over KOH, TMSCl was distilled from calcium hydride.

3.2 Procedures and analytical data

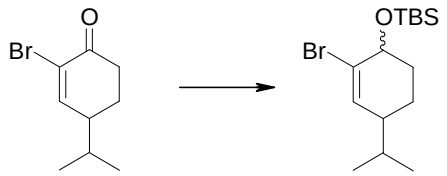
2-Bromo-4-isopropyl-cyclohex-2-enone (233)



232 **233**

TBATB (3.77 g, 7.82 mmol) and K_2CO_3 (1.62 g, 11.7 mmol) were added to a solution of ketone **232** (540 mg, 3.91 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C under argon. The mixture was stirred at 0 °C for 30 min, then at rt for 20 min and finally at reflux temperature for 2.5 days. The mixture was filtered and the filtrate was washed with water (1 × 15 mL) and brine (1 × 15 mL), dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum ether/EtOAc 19:1) gave bromide **233** (698 mg, 82%) as a yellow oil. R_f = 0.45 (petroleum ether/EtOAc, 9:1). ν_{max} ($CHCl_3$) 2959, 2931, 2872, 1697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, 1H, *J* = 2.6, 1.4 Hz, O=C-C-C**H**), 2.76 (dt, 1H, *J* = 16.6, 4.1 Hz, 1 × O=C-C**H**$_2$), 2.51–2.39 (m, 2H, H_3C-CH-C**H** and 1 × O=C-C**H**$_2$), 2.04 (m, 1H, 1 × O=C-CH_2-C**H**$_2$), 1.89–1.78 (m, 2H, H_3C-C**H** and 1 × O=C-CH_2-C**H**$_2$), 0.99 (d, 3H, *J* = 6.3 Hz, **H**$_3$C-CH), 0.98 (d, 3H, *J* = 6.3 Hz, **H**$_3$C-CH) ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.5 (**C**=O), 154.8 (O=C-C-**C**H), 123.8 (O=C-**C**-CH), 45.6 (H_3C-CH-**C**H), 37.4 (O=C-**C**H_2), 31.5 (H_3C-**C**H), 25.1 (O=C-CH_2-C**H**$_2$), 19.5 (H_3**C**-CH), 19.4 (H_3**C**-CH). HRMS (CI) mass calc. for $C_9H_{13}BrO$ 217.0228 $(M+H)^+$, found 217.0221.

2-Bromo-1-(*tert*-Butyldimethylsilyloxy)-4-isopropylcyclohex-2-ene (234)

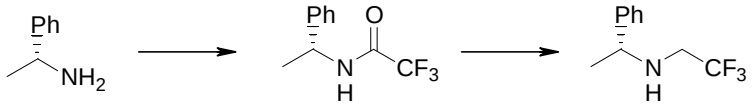


233 **234**

$CeCl_3 \cdot 7H_2O$ (1.55 g, 4.16 mmol) was added to a solution of bromoketone **233** (695 mg, 3.20 mmol) in MeOH (10 mL). The mixture was stirred at rt for 15 min, then cooled (–20 °C) and sodium borohydride (133 mg, 3.52 mmol) was added portionwise. The reaction mixture was stirred at –20 °C for 10 min and then quenched with saturated aqueous NH_4Cl (10 mL). EtOAc (20 mL) was added, the layers were separated and the organic layer was washed with water (1 × 10 mL) and

brine (1 × 10 mL), dried ($MgSO_4$), filtered and evaporated under vacuum to give a crude alcohol (670 mg) as a colourless oil. 2,6-Lutidine (1.1 mL, 9.17 mmol) and TBSOTf (1.4 mL, 6.12 mmol) were successively added to a solution of the alcohol (670 mg, 3.06 mmol) in dry CH_2Cl_2 (7 mL) at –78 °C under argon. The mixture was stirred for 15 h being allowed to slowly warm to rt over this period. It was quenched with water (10 mL), saturated aqueous $CuSO_4$ solution (10 mL) was added and the layers were separated. The organic layer was washed with saturated aqueous $CuSO_4$ solution (2 × 10 mL) and water (1 × 10 mL), dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum ether) gave bromide **234** (894 mg, 88%) as a colourless oil and as of separable mixture of diastereoisomers (6:1). R_f (major) = 0.31 (petroleum ether) R_f (minor) = 0.50 (petroleum ether). ν_{max} ($CHCl_3$, major) 2956, 2929, 2857, 1103 cm^{-1}. ^1H NMR (major) (400 MHz, $CDCl_3$) δ 6.09 (ddd, 1H, *J* = 2.5, 1.2, 1.2 Hz, TBSOCH-C=C**H**), 4.21 (dddd, 1H, *J* = 8.4, 5.5, 2.7, 1.0 Hz, TBSOC**H**), 2.14–2.00 (m, 2H, 1 × TBSOCH-C**H**$_2$ and H_3C-CH-C**H**), 1.79–1.55 (m, 3H, H_3C-C**H**, 1 × TBSOCH-C**H**$_2$ and 1 × TBSOCH-CH_2-C**H**$_2$), 1.43–1.33 (m, 1H, 1 × TBSOCH-CH_2-C**H**$_2$), 0.92 (s, 9H, Si-C-{C**H**$_3$}$_3$), 0.89 (d, 3H, *J* = 6.9 Hz, **H**$_3$C-CH), 0.87 (d, 3H, *J* = 6.9 Hz, **H**$_3$C-CH), 0.17 (s, 3H, Si-C**H**$_3$), 0.11 (s, 3H, Si-C**H**$_3$) ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.4 (TBSOCH-C=**C**H), 127.5 (TBSOCH-**C**=CH), 70.9 (TBSO**C**H), 44.7 (HC-**C**H-CH_2), 33.6 (TBSOCH-**C**H$_2$), 31.7 (H_3C-**C**H), 25.9 (Si-C-{**C**H$_3$}$_3$), 22.9 (TBSOCH-CH_2-**C**H$_2$), 19.6 (H_3**C**-CH), 19.5 (H_3**C**-CH), 18.2 (Si-**C**-{CH_3}$_3$), –4.5 (Si-**C**H$_3$), –4.6 (Si-**C**H$_3$).

((*R*)-1-Phenylethyl)-2,2,2-trifluoroethylamine {(*R*)-248}



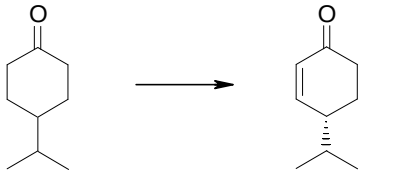
320 **321** **(*R*)-248**

(*R*)-(+)-1-Phenylethylamine **320** (5.74 g, 47.4 mmol) was added dropwise to a suspension of NaH (2.08 g of a 60% suspension in oil, 52.0 mmol) in dry Et_2O (86 mL) at 0 °C under argon. The resulting mixture was stirred at 0 °C for 20 min and then at rt for 2 h. After cooling (0 °C), ethyltrifluoroacetate (6.4 mL, 57 mmol) was added dropwise and the mixture was stirred at 0 °C for 1 h and then at rt for 18 h. It was carefully quenched with 1 M aqueous HCl solution (69 mL), the layers were separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The organic extracts were combined, washed with brine (1 × 100 mL), dried ($MgSO_4$), filtered and evaporated under vacuum to give crude amide **321** as a white powder.

BH_3·THF (186 mL of a 1 M solution in THF, 186 mmol) was transferred by canula to a solution of crude amide **321** (10.3 g, 47.4 mmol) in dry THF (200 mL) and the resulting mixture was stirred at reflux temperature for 2 days. The reaction was very carefully quenched with MeOH (100 mL) and water (50 mL) at 0 °C. Concentrated HCl (40 mL) was then added, followed by water (150 mL) and the mixture was extracted with Et_2O (2 × 150 mL). The organic extracts were discarded. The aqueous phase was made strongly basic (pH 14) by addition of NaOH (powder) and was extracted with Et_2O (3 × 200 mL). The organic extracts were combined, washed with brine (1 × 200 mL), dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum ether/EtOAc 3:2) gave amine **(*R*)-248** (8.33 g, 86%) as a slightly yellow oil. R_f = 0.70 (petroleum ether/EtOAc, 3:2). $[\alpha]_D$ +50.7 (*c* = 1.00, $CHCl_3$, 22 °C) (Litt. $[\alpha]_D^{20}$ +115.3 (*c* = 1.24, CH_2Cl_2), ν_{max} ($CHCl_3$) 2959, 2931, 2872, 1697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 5H, C-**H** *Ar*), 3.92 (q, 1H, *J* = 6.5 Hz, H_3C-C**H**), 3.07 (d, 1H, *J* = 9.5 Hz, 1 × C**H**$_2CF_3$), 3.02 (d, 1H, *J* = 9.5 Hz, 1 × C**H**$_2CF_3$), 1.62 (bs, 1H, N**H**), 3.12 (d, 3H, *J* = 6.5 Hz, **H**$_3$C-CH) ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1 (**C** *Ar*), 128.6 (**C**H *Ar*), 127.0 (ddd, *J* = 225 Hz, **C**F_3), 127.3 (**C**H *Ar*), 126.6 (**C**H *Ar*), 57.3 (H_3C-**C**H), 48.3 (ddd, *J* = 31 Hz,

CH_2CF_3), 24.5 (**C**H_3). HRMS (CI+) mass calc. for $C_{10}H_{12}F_3N$ 204.1000 $(M+H)^+$, found 204.0999.

(*R*)-(–)-4-Isopropylcyclohex-2-enone [(*R*)-(–)-Cryptone] (232)



230 **(*R*)-(-)-232**

n-BuLi (39 mL of a 2.5 M solution in hexanes, 98.2 mmol) was added dropwise to a solution of ((*R*)-1-Phenylethyl)-2,2,2-trifluoroethylamine **(*R*)-248** (18.3 g, 82.2 mmol) in dry THF (220 mL) at –78 °C under argon. The mixture was stirred at –78 °C for 20 min, freshly distilled TMSCl (36 mL, 286 mmol) was added and the resulting mixture was cooled down to –100 °C. A cold (–78 °C) solution of 4-isopropylcyclohexanone (11.45 g, 81.66 mmol) in dry THF (80 mL) was added using a canula over 1 h. After the addition was complete, the mixture was stirred for an additional 15 min at –100 °C and quenched with triethylamine (85 mL). Saturated aqueous $NaHCO_3$ solution (85 mL) was then added and the mixture was allowed to warm to rt. After addition of water (500 mL), the mixture was extracted with petroleum ether (2 × 200 mL). The organic extracts were combined, partially evaporated under vacuum (~50 mL remaining), washed with saturated aqueous citric acid solution (6 × 70 mL), brine (1 × 50 mL), saturated aqueous $NaHCO_3$ (1 × 50 mL), dried ($MgSO_4$), filtered and evaporated under vacuum to give the crude TMS-enol ether **231** (19.9 g) as a yellow oil.* $Pd(OAc)_2$ (1.83 g, 8.15 mmol) was added to a solution of **231** in dry DMSO (280 mL), and the resulting mixture was stirred at rt under O_2 for 18 h. The reaction was quenched by the additon of saturated aqueous NH_4Cl (100 mL) at 0 °C and the mixture was extracted with Et_2O (3 × 150 mL). The organic extracts were combined, washed with brine (1 × 100 mL), dried

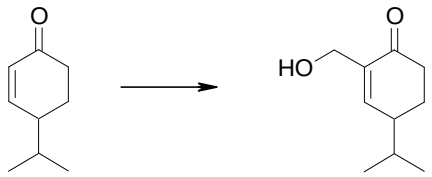
($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum ether/EtOAc, 9:1) gave (*R*)-(–)-cryptone **232** (9.85 g, 87%) as a colourless oil. R_f = 0.40 (petroleum ether/EtOAc, 4:1). 83% ee HPLC Chiralcel AD 1.00 mL/min 99.5:0.5 Hexane:2-propanol. 15.8 min minor enantiomer, 20.0 min major enantiomer. $[\alpha]_D$ –97.9 (*c* = 1.00, $CHCl_3$, 30 °C). (Litt. (*R*)-(–)-Cryptone was first reported to show $[\alpha]_D^{20}$ –119.3 (*c* = 2.0, EtOH),[94] whereas **(*R*)-232** obtained from optical purification *via* (–)-cryptol showed $[\alpha]_D^{20}$ –91.7 (*c* = 2.2, EtOH).[95] ν_{max} ($CHCl_3$) 2960, 2873, 1673, 1388 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.89 (ddd, 1H, *J* = 10.3, 2.0, 2.0 Hz, O=C-CH=C**H**), 6.00 (ddd, 1H, *J* = 10.3, 2.7, 0.8 Hz, O=C-C**H**=CH), 2.50 (dt, 1H, *J* = 16.6, 4.2 Hz, 1 × O=C-C$\mathbf{H}_2$), 2.39–2.25 (m, 2H, 1 × O=C-C$\mathbf{H}_2$ and 1 × O=C-CH_2-C$\mathbf{H}_2$), 2.00 (dddd, 1H, *J* = 9.2, 6.1, 4.7, 1.6 Hz, H_3C-CH-C**H**), 1.87–1.69 (m, 2H, 1 × O=C-CH_2-C$\mathbf{H}_2$ and H_3C-C**H**), 0.97 (d, 3H, *J* = 6.1 Hz, $\mathbf{H}_3$C-CH), 0.95 (d, 3H, *J* = 6.1 Hz, $\mathbf{H}_3$C-CH) ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1 (**C**=O), 154.3 (O=C-CH-**C**H), 129.7 (O=C-**C**H-CH), 42.5 (H_3C-CH-**C**H), 37.4 (O=C-**C**H_2), 31.5 (H_3C-**C**H), 25.2 (O=C-CH_2-**C**H_2), 19.6 (H_3**C**-CH), 19.5 (H_3**C**-CH). HRMS (ESI) mass calc. for $C_9H_{14}O$ 139.1123 $(M+H)^+$, found 139.1014.

*NB: the chiral amine could be recovered using the following procedure: The aqueous layers were combined and made strongly basic by addition of sodium hydroxide. It was extracted with Et_2O (3 × 150 mL), dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum/EtOAc 7:3) gave chiral amine **(*R*)-248** (15.6 g, 85% recovery).

[94] Galloway, A. S.; Dewar, J.; Read, J. *J. Chem. Soc.* **1936**, 1595.

[95] Tanis, S. P.; Herrinton, P. M. *J. Org. Chem.* **1985**, *50*, 632.

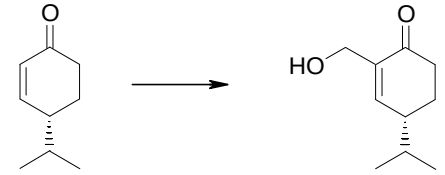
2-Hydroxymethyl-4-isopropylcyclohex-2-enone (238)



232 **238**

n-Tributylphosphine (0.72 mL, 2.9 mmol) and aqueous formaldehyde (0.67 mL of a 37% solution in water, 9.0 mmol) were successively added to a solution of ketone **232** (0.50 g, 3.6 mmol) in THF (10 mL) at rt under argon and the reaction mixture was stirred at rt for 5 h. The solvent was removed under vacuum (but not until complete dryness) to give an oily residue. Silica gel chromatography (petroleum ether/EtOAc, 3:2) gave alcohol **238** (0.32 g, 50 %, 70% brsm) as a colourless oil. R_f = 0.47 (petroleum ether/EtOAc, 2:3). ^{1}H NMR (400 MHz, $CDCl_3$) 6.83 (bs, 1H), 4.28 (ddd, 1H, *J* = 13.2, 1.3, 1.3 Hz), 4.23 (ddd, 1H, *J* = 13.2, 1.3, 1.3 Hz), 2.65 (bs, 1H,), 2.53 (dt, 1H, *J* = 16.7, 4.1 Hz), 2.42–2.26 (m, 2H), 1.98 (dddd, 1H, *J* = 9.3, 5.6, 4.9, 1.6 Hz), 1.88–1.66 (m, 2H), 0.97 (d, 3H, *J* = 7.1 Hz), 0.96 (d, 3H, *J* = 7.1 Hz) ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.0 (C), 150.7 (CH), 138.0 (C), 62.2 (CH_2), 42.5 (CH), 37.8 (CH_2), 31.7 (CH), 25.3 (CH_2), 19.7 (H_3C), 19.5 (H_3C).

(4*R*)-2-Hydroxymethyl-4-isopropylcyclohex-2-enone (238)

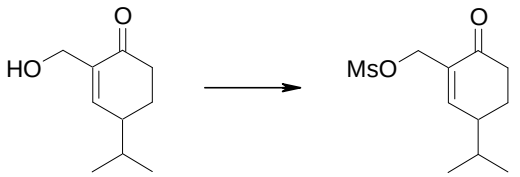


(*R*)-(-)-232 **(*R*)-238**

n-Tributylphosphine (2.9 mL, 12 mmol), aqueous formaldehyde (2.7 mL of a 37% solution in water, 36 mmol) and freshly distilled triethylamine (2.0 mL, 15 mmol) were successively added to a solution of (*R*)-(–)-cryptone **232** (2.0 g, 15 mmol) in dry THF (40 mL) at rt under argon and the reaction mixture was stirred at rt for 21

h. Water (20 mL) was added and the mixture was extracted with CH_2Cl_2 (4 × 50 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum ether/EtOAc, 3:2) gave alcohol **(*R*)-238** (1.27 g, 52 %, 70% brsm) as a colourless oil. R_f = 0.47 (petroleum ether/EtOAc, 2:3). $[\alpha]_D$ –55.9 (*c* = 1.00, $CHCl_3$, 29 °C). ν_{max} ($CHCl_3$) 3604, 2960, 2873, 1667, 1380 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) 6.83 (bs, 1H, O=C-C=C**H**), 4.28 (ddd, 1H, *J* = 13.2, 1.3, 1.3 Hz, 1 × C**H**$_2$OH), 4.23 (ddd, 1H, *J* = 13.2, 1.3, 1.3 Hz, 1 × C**H**$_2$OH), 2.64 (bs, 1H, CH_2O**H**), 2.52 (dt, 1H, *J* = 16.7, 4.1 Hz, 1 × O=C-C**H**$_2$), 2.40–2.27 (m, 2H, 1 × O=C-C**H**$_2$ and 1 × O=C-CH_2-C**H**$_2$), 1.98 (dddd, 1H, *J* = 9.3, 5.6, 4.9, 1.6 Hz, H_3C-CH-C**H**), 1.86–1.66 (m, 2H, 1 × O=C-CH_2-C**H**$_2$ and H_3C-C**H**), 0.98 (d, 3H, *J* = 7.1 Hz, **H**$_3$C-CH), 0.96 (d, 3H, *J* = 7.1 Hz, **H**$_3$C-CH) ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.0 (**C**=O), 150.6 (O=C-C=**C**H), 137.9 (O=C-**C**=CH), 62.1 (**C**H_2OH), 42.4 (H_3C-CH-**C**H), 37.6 (O=C-**C**H_2), 31.5 (H_3C-**C**H), 25.2 (O=C-CH_2-**C**H_2), 19.6 (H_3**C**-CH), 19.4 (H_3**C**-CH). HRMS (ESI) mass calc. for $C_{10}H_{16}O_2Na$ 191.1048 $(M+Na)^+$, found 191.0867.

Methanesulfonic acid 3-isopropyl-6-oxo-cyclohex-1-enylmethyl ester (240)

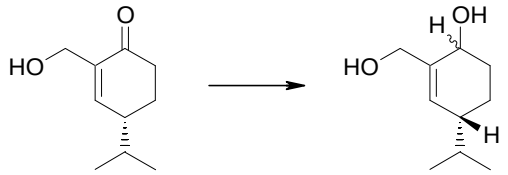


238 **240**

Methanesulfonyl chloride (0.20 mL, 2.5 mmol) was added dropwise to a solution of alcohol **250** (0.44 g, 1.68 mmol) and triethylamine (0.47 mL, 3.4 mmol) in dry CH_2Cl_2 (10 mL) at –78 °C under argon and the reaction mixture was stirred at 0 °C for 1.5 h. The reaction was quenched by the additon of saturated aqueous $NaHCO_3$ solution (5 mL) and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and evaporated under vacuum to

give the crude mesylate **323** (415 mg, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (s, 1H), 4.85 (d, 1H, *J* = 11.6 Hz), 4.80 (d, 1H, *J* = 11.6 Hz), 3.07 (s, 3H), 2.59 (dt, 1H, *J* = 16.8, 4.2 Hz), 2.44–2.32 (m, 2H), 2.08–1.98 (m, 1H), 1.92–1.72 (m, 2H), 1.45–1.34 (m, 1H), 1.00 (d, 3H, *J* = 6.7 Hz), 0.97 (d, 3H, *J* = 6.7 Hz).

(1*R*,4*R*)- and (1*S*,4*R*)-2-Hydroxymethyl-4-isopropylcyclohex-2-enol (243)

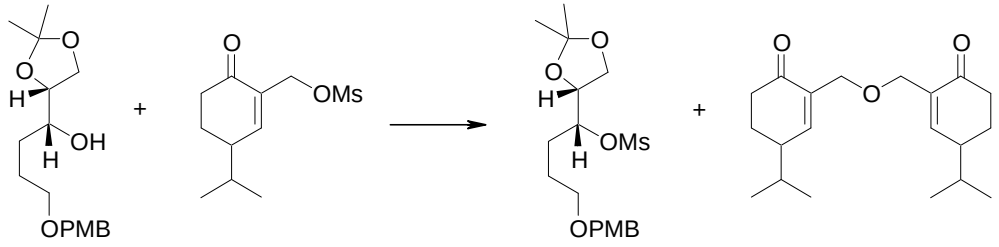


(*R*)-238 **243**

Cerium trichloride heptahydrate (22.8 g, 61.2 mmol) was added to a solution of ketone **(*R*)-238** (5.15 g, 30.6 mmol) in methanol (150 mL) and the mixture was stirred at rt for 15 min until $CeCl_3$ completely dissolved. The solution was cooled to –78 °C and solid sodium borohydride (1.27 g, 33.7 mmol) was added portionwise. After stirring at –78 °C for 20 min, the mixture was carefully quenched with saturated aqueous NH_4Cl (58 mL) at 0 °C. Water (300 mL) was added and the mixture was extracted with EtOAc (5 × 100 mL). The organic extracts were combined, washed with brine (100 mL), dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum ether/EtOAc, 2:3) gave diol **243** (5.10 g, 98%) as a colourless oil and a 10:1 mixture of diastereoisomers. R_f = 0.23 (petroleum ether/EtOAc, 2:3). $[\alpha]_D$ –50.8 (*c* = 1.00, $CHCl_3$, 26 °C). ν_{max} ($CHCl_3$) 3605, 2958, 2871, 1386 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (s, 1H, HOCH-C=C**H** minor), 5.65 (s, 1H, HOCH-C=C**H** major), 4.53 (d, 1H, *J* = 11.2 Hz, C**H**OH minor), 4.35 (t, 1H, *J* = 7.9 Hz, C**H**OH major), 4.24–4.13 (m, 4H, C**H**$_2$OH major and C**H**$_2$OH minor), 2.76 (bs, 4H, CH_2O**H** major, CH_2O**H** minor, CHO**H** major, CHO**H** minor), 2.07 (dddd, 1H, *J* = 12.3, 8.6, 5.8, 2.8 Hz, 1 × HOCH-C**H**$_2$ major), 2.03–1.94 (m, 1H, H_3C-CH-C**H** major), 1.92–1.83 (m, 2H, 1 × HOCH-C**H**$_2$

minor, H_3C-CH-C**H** minor) 1.77–1.67 (m, 1H, 1 × HOCH-CH_2-C$\mathbf{H}_2$ major), 1.67–1.39 (m, 6H, 1 × HOCH-C$\mathbf{H}_2$ major, H_3C-C**H** major, 1 × HOCH-C$\mathbf{H}_2$ minor, H_3C-C**H** minor), 1.36–1.24 (m, 1H, 1 × HOCH-CH_2-C$\mathbf{H}_2$ major), 0.94–0.89 (m, 6H, $\mathbf{H}_3$C-CH-C$\mathbf{H}_3$ minor), 0.88 (d, 3H, *J* = 6.8 Hz, $\mathbf{H}_3$C-CH major), 0.84 (d, 3H, *J* = 6.8 Hz, $\mathbf{H}_3$C-CH major) ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.8 (HOCH-**C**=CH major), 137.8 (HOCH-**C**=CH minor), 132.3 (HOCH-C=**C**H minor), 131.3 (HOCH-C=**C**H major), 69.0 (HO**C**H major and HO**C**H minor), 66.3 (**C**H_2OH major), 66.5 (**C**H_2OH minor), 42.2 (H_3C-CH-**C**H minor), 41.8 (H_3C-CH-**C**H major), 32.2 (HOCH-**C**H_2 major), 31.9 (H_3C-**C**H major), 31.8 (HOCH-**C**H_2 minor), 30.9 (H_3C-**C**H minor), 23.2 (HOCH-CH_2-**C**H_2 major), 23.0 (HOCH-CH_2-**C**H_2 minor), 19.8 (H_3**C**-CH minor), 19.7 (H_3**C**-CH major), 19.4 (H_3**C**-CH major), 19.3 (H_3**C**-CH minor). HRMS (ESI) mass calc. for $C_{10}H_{18}O_2$ 193.1204 $(M+Na)^+$, found 193.1156.

Methanesulfonic acid 1-(2,2-dimethyl-[1,3]dioxolan-4-yl)-4-(4-methoxy-benzyloxy)-butyl ester (241) and dimer (242)

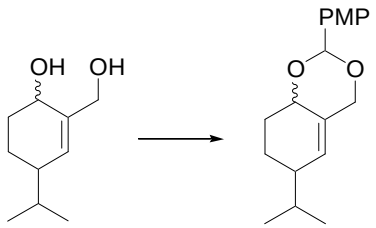


203 **240** **241** **242**

A solution of alcohol **203** (435 mg, 1.40 mmol) in dry THF (4.5 mL) was added to a suspension of sodium hydride (62.0 mg of a 60% suspension in oil, 1.54 mmol) in dry THF (0.2 mL) at rt under Argon. The resulting mixture was stirred at rt for 1.5 h and then a solution of mesylate **240** (415 mg, 1.68 mmol) in THF (0.5 mL) was added dropwise at rt. The reaction mixture was then stirred at reflux temperature for

2.5 h. It was quenched with saturated aqueous NH_4Cl (5 mL) at 0 °C, CH_2Cl_2 (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum ether/EtOAc 4:1) gave mesylate **241** (415 mg, 75%) and dimer **242** (214 mg, 80%). ^{1}H NMR **241** (270 MHz, $CDCl_3$) δ 7.23 (d, 2H, *J* = 9.3 Hz), 6.82 (d, 2H, *J* = 9.5 Hz), 4.40–4.28 (m, 1H), 4.09 (s, 2H), 3.85 (dd, 1H, *J* = 15.1, 7.5 Hz), 3.68 (dd, 1H, *J* = 9.5, 7.5 Hz), 3.41 (s, 3H), 3.32 (dd, 1H, *J* = 9.5, 7.5 Hz), 3.13–2.98 (m, 2H), 2.63 (s, 3H), 1.29–0.96 (m, 4H), 0.78 (s, 3H), 0.69 (s, 3H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3 (C), 130.5 (C), 129.4 (CH), 113.9 (CH), 110.2 (C), 84.0 (CH), 77.7 (CH), 69.0 (CH_2), 65.9 (CH_2), 55.4 (CH_3), 39.0 (CH_3), 28.2 (CH_2), 26.4 (CH_3), 25.5 (CH_3), 25.3 (CH_2). ^{1}H NMR **242** (270 MHz, $CDCl_3$) δ 6.97 (s, 2H), 3.90–3.75 (m, 4H), 2.01 (dt, 2H, *J* = 18.5, 4.7 Hz), 1.88–1.69 (m, 4H), 1.47–1.31 (m, 2H), 1.29–0.99 (m, 4H), 0.24 (d, 6H, *J* = 4.8 Hz), 0.22 (d, 6H, *J* = 4.8 Hz) ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.5 (2 × C), 152.9 (2 × CH), 135.6 (2 × C), 42.7 (2 × CH), 40.9 (2 × CH_2), 37.3 (2 × CH_2), 31.5 (2 × CH), 24.9 (2 x CH_2), 19.5 (2 × CH_3), 19.3 (2 × CH_3).

6-Isopropyl-2-(4-methoxy-phenyl)-6,7,8,8a-tetrahydro-4H-benzo[1,3]dioxine (244)

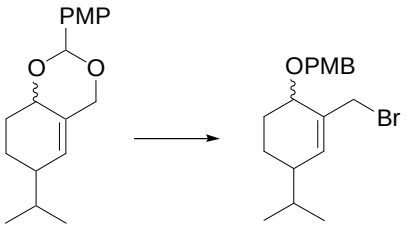


243 **244**

p-Methoxybenzaldehyde dimethylacetal (0.849 mL,4.98 mmol) followed by camphorsulfonic acid (165 mg, 0.710 mmol) and 4 Å molecular sieves were added to a solution of diol **243** (606 mg, 3.56 mmol) in dry CH_2Cl_2 (25 mL). The reaction

mixture was stirred at rt for 2 days and then filtered through celite. Triethylamine (3.60 mL) was added to the filtrate and the mixture was then washed with water (1 × 20.0 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 15.0 mL). The organic layers were combined, dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum ether/EtOAc, 9:1) gave acetal **244** (826 mg, 80 %) as a colourless oil. R_f = 0.54 (petroleum ether/EtOAc, 9:1). ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.45 (d, 2H, J = 9.6 Hz), 6.84 (d, 2H, J = 9.8 Hz), 5.61 (s, 1H), 5.43 (s, 1H), 4.24–4.01 (m, 2H), 3.41 (s, 3H), 1.68–1.50 (m, 2H), 1.27–0.84 (m, 4H), 0.68-0.48 (m, 1H), 0.18 (d, 3H, *J* = 7.9 Hz), 0.15 (d, 3H, *J* = 7.9 Hz) ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0 (C), 132.1 (C), 131.0 (C), 127.6 (CH), 113.6 (CH), 101.3 (CH), 75.1 (CH), 71.6 (CH_2), 55.3 (CH_3), 42.1 (CH), 32.0 (CH), 29.1 (CH_2), 27.5 (CH_2), 19.5 (CH_3), 19.1 (CH_3)

1-(2-Bromomethyl-4-isopropyl-cyclohex-2-enyloxymethyl)-4-methoxy-benzene (245)

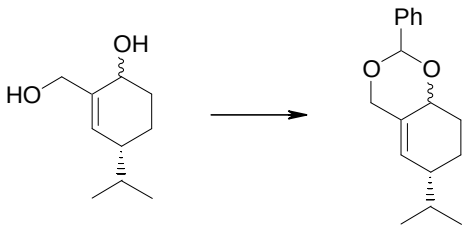


244 **245**

Diisobutylaluminium hydride (7.10 mL of a 1.5 M solution in toluene, 4.70 mmol) was added dropwise to a solution of acetal 244 (1.00 g, 3.50 mmol) in dry CH_2Cl_2 (20 mL) at –78 °C under argon. The reaction mixture was stirred at –78 °C for 2 h. Then it was quenched by addition of methanol (5 mL). The mixture was partitioned between aqueous potassium sodium tartrate solution (50 mL) and CH_2Cl_2 (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel

chromatography (petroleum ether/EtOAc, 9:1) gave the desired alcohol (964 mg, 96 %) as a thick yellow oil. Triphenylphosphine (2.59 g, 9.87 mmol) was added portionwise at 0 °C to a solution of the primary alcohol and carbon tetrabromide (3.27 g, 9.87 mmol) in acetonitrile (15 mL). The resulting mixture was stirred at 0 °C for 20 min. The white precipitate was filtered off, water was added to the filtrate and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, washed with water (1 × 15 mL), dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum ether/EtOAc, 9:1) gave bromide **245** (1.05 g, 90 %) as a yellow oil. R_f = 0.45 (petroleum ether/EtOAc, 9:1). ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.33 (d, 2H, *J* = 8.7 Hz), 6.89 (d, 2H, *J* = 8.7 Hz), 5.88 (s, 1H), 4.63 (d, 1H, *J* = 10.8 Hz), 4.50 (d, 1H, *J* = 10.8 Hz), 4.45 (dd, 1H, *J* = 9.2, 2.3 Hz), 4.24 (t, 1H, *J* = 7.6 Hz), 3.86 (d, 1H, *J* = 9.2 Hz), 3.81 (s, 3H), 2.25–2.16 (m, 1H), 2.02–1.95 (m, 1H), 1.80–1.70 (m, 1H), 1.68–1.52 (m, 2H), 1.38–1.25 (m, 1H), 0.90 (d, 3H, *J* = 6.8 Hz), 0.87 (d, 3H, *J* = 6.8 Hz) ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2 (C), 136.9 (C), 134.7 (CH), 130.7 (C), 129.5 (CH), 113.8 (CH), 72.9 (CH), 71.2 (CH_2), 55.2 (CH_3), 42.0 (CH), 35.8 (CH_2), 31.8 (CH), 28.0 (CH_2), 22.8 (CH_2), 19.7 (CH_3), 19.3 (CH_3).

6-Isopropyl-2-phenyl-6,7,8,8*a*-tetrahydro-4*H*-benzo[1,3]dioxine (249)



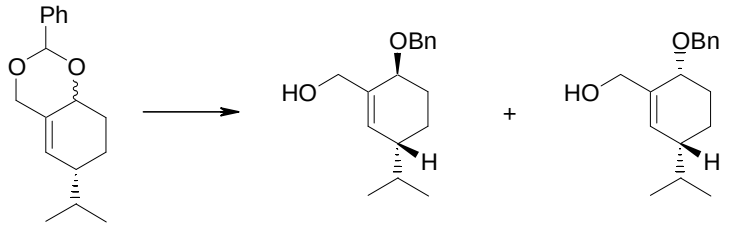
243 **249**

Benzaldehyde dimethylacetal (12.5 mL, 83.1 mmol) followed by camphorsulfonic acid (2.70 g, 11.9 mmol) and 4 Å molecular sieves were added to a solution of diol **243** (10.1 g, 59.3 mmol) in dry CH_2Cl_2 (400 mL). The reaction mixture was stirred

at rt for 40 h and then filtered through celite. Triethylamine (70 mL) was added to the filtrate and the mixture was then washed with water (1 × 70 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (1 × 100 mL). The organic layers were combined, dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum ether/EtOAc, 19:1) gave acetal **249** (14.8 g, 98 %) as a colourless oil. R_f = 0.63 (petroleum ether/EtOAc, 9:1). $[\alpha]_D$ –33 (*c* = 0.75, $CHCl_3$, 25 °C). ν_{max} ($CHCl_3$) 2958, 2253, 1382 cm^{-1}. ^1H NMR (400 MHz, C_6D_6) δ 7.75–7.68 (m, 4H, 2 × C**H** *Ar* minor, 2 × C**H** *Ar* major), 7.24–7.09 (m, 6H, 3 × C**H** *Ar* major, 3 × C**H** *Ar* minor), 5.60 (s, 1H, Ph-C**H** minor), 5.59 (s, 1H, Ph-C**H** major), 5.39 (s, 1H, OCH-C=C**H** minor), 5.23 (s, 1H, OCH-C=C**H** major), 4.29–4.16 (m, 5H, C**H**$_2$OCH major, C**H**$_2$OCH minor, OC**H**-C=CH major), 4.09–4.02 (m, 1H, OC**H**-C=CH minor), 2.13–2.03 (m, 2H, 1 × OCH-C**H**$_2$ major, 1 × OCH-C**H**$_2$ minor), 1.92–1.81 (m, 2H, H_3C-CH-C**H** major, H_3C-CH-C**H** minor), 1.79–1.66 (m, 2H, 1 × OCH-C**H**$_2$ major, 1 × OCH-C**H**$_2$ minor), 1.57–1.48 (m, 2H, 1 × OCH-CH_2-C**H**$_2$ minor, H_3C-C**H** minor), 1.48–1.39 (m, 1H, 1 × OCH-CH_2-C**H**$_2$ major), 1.34 (sext, 1H, *J* = 6.9 Hz, H_3C-C**H** major), 1.06–0.93 (m, 1H, 1 × OCH-CH_2-C**H**$_2$ major), 0.93–0.87 (m, 1H, 1 × OCH-CH_2-C**H**$_2$ minor), 0.84 (d, 3H, *J* = 6.5 Hz, **H**$_3$C-CH minor), 0.80 (d, 3H, *J* = 6.5 Hz, **H**$_3$C-CH minor), 0.75 (d, 3H, *J* = 6.9 Hz, **H**$_3$C-CH), 0.72 (d, 3H, *J* = 6.9 Hz, **H**$_3$C-CH) ^{13}C NMR (101 MHz, C_6D_6) δ 139.7 (**C** major), 139.6 (**C** minor), 133.2 (**C** major), 133.1 (**C** minor), 128.8 (**C**H *Ar* major), 128.7 (**C**H *Ar* minor), 128.3 (**C**H *Ar* major), 128.2 (**C**H *Ar* minor), 126.8 (**C**H *Ar* major), 126.8 (**C**H *Ar* minor), 126.6 (OCH-C=**C**H major and OCH-C=**C**H minor), 101.7 (Ph-**C**H minor), 101.3 (Ph-**C**H major), 75.0 (O**C**H-C=CH major), 74.1 (O**C**H-C=CH minor), 71.5 (**C**H$_2$OCH minor), 71.0 (**C**H$_2$OCH major), 42.3 (H_3C-CH-**C**H major), 41.2 (H_3C-CH-**C**H minor), 32.2 (H_3C-**C**H major), 32.1 (H_3C-**C**H minor), 29.5 (OCH-**C**H$_2$ major), 27.2 (OCH-**C**H$_2$ minor), 23.4 (OCH-CH_2-**C**H$_2$

major), 22.7 (OCH-CH_2-**C**H_2 minor), 20.8 (H_3**C**-CH minor), 20.7 (H_3**C**-CH minor), 19.5 (H_3**C**-CH major), 19.2 (H_3**C**-CH major). HRMS (ESI) mass calc. for $C_{17}H_{22}O_2$ 281.512 $(M+Na)^+$, found 281.1505.

((3*R*,6*S*)-6-Benzyloxy-3-isopropyl-cyclohex-1-enyl)-methanol (250)



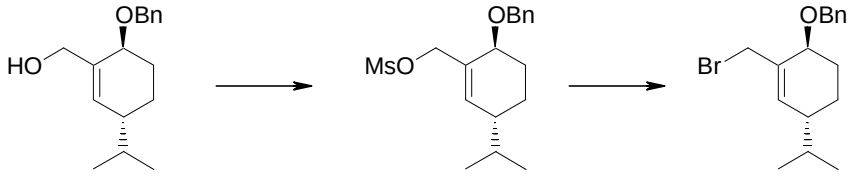
249 **250a** **250b**

DIBAL-H (229 mL of 1M solution in CH_2Cl_2, 229 mmol) was added dropwise to a solution of acetal **249** (14.8 g, 57.3 mmol) in dry CH_2Cl_2 (300 mL) at –78 °C under argon. The reaction mixture was stirred for 15 h being allowed to warm to rt over this period and then very carefully quenched with MeOH (40 mL) at 0 °C. Saturated aqueous potassium sodium tartrate solution (200 mL) was added and the mixture was vigorously stirred for 1 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum ether/EtOAc 85:15) gave alcohol **250a** (10.5 g, 70%) and diastereoisomer **250b** (1.65 g, 12%) as a separable mixture of colourless oils. R_f (major) = 0.34 (petroleum ether/EtOAc, 4:1). $[\alpha]_D$ +7.5 (*c* = 1.0, $CHCl_3$, 22 °C). ν_{max} ($CHCl_3$) 3525, 2958, 2869, 1710, 1364 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, 4H, *J* = 4.0 Hz, C**H** *Ph*), 7.32–7.27 (m, 1H, C**H** *Ph*), 5.73 (s, 1H, BnOCH-C=C**H**), 4.72 (d, 1H, *J* = 11.6 Hz, 1 × OC$\mathbf{H}_2$Ph), 4.50 (d, 1H, *J* = 11.6 Hz, 1 × OC$\mathbf{H}_2$Ph), 4.18 (d, 1H, *J* = 12.0 Hz, 1 × C$\mathbf{H}_2$OH), 4.20–4.13(m, 1H, BnOC**H**), 4.05 (d, 1H, *J* = 12.0 Hz, 1 × C$\mathbf{H}_2$OH), 2.53 (bs, 1H, CH_2O**H**), 2.23 (dddd, 1H, *J* = 12.5, 8.3, 5.6 Hz, 2.9 Hz, 1 × BnOCH-C$\mathbf{H}_2$), 2.04 (bs, 1H, H_3C-CH-C**H**), 1.82–1.74 (m, 1H, 1 ×

BnOCH-CH_2-C**H**$_2$), 1.65–1.54 (m, 2H, 1 × BnOCH-C**H**$_2$ and H_3C-C**H**), 1.36–1.25 (m, 1H, 1 × BnOCH-CH_2-C**H**$_2$), 0.89 (d, 3H, *J* = 6.8 Hz, **H**$_3$C-CH), 0.86 (d, 3H, *J* = 6.8 Hz, **H**$_3$C-CH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.3 (**C**), 138.0 (**C**), 132.0 (BnOCH-C=**C**H), 128.5 (**C**H *Ph*), 127.8 (**C**H *Ph*), 127.7 (**C**H *Ph*), 76.5 (BnO**C**H), 70.6 (O**C**H_2Ph), 66.2 (**C**H_2OH), 41.7 (H_3C-CH-**C**H), 31.9 (H_3C-**C**H), 28.1 (BnOCH-**C**H_2), 23.2 (BnOCH-CH_2-**C**H_2), 19.6 (H_3**C**-CH), 19.3 (H_3**C**-CH). HRMS (ESI) mass calc. for $C_{17}H_{24}O_2$ 283.1669 $(M+Na)^+$, found 283.1653.

Minor diastereoisomer **250b** has not been fully characterised but crude ^{1}H NMR showed the CH alkene peak for **250b** at 5.80 ppm.

((1*S*,4*R*)-2-Bromomethyl-4-isopropyl-cyclohex-2-enyloxymethyl)-benzene (251)

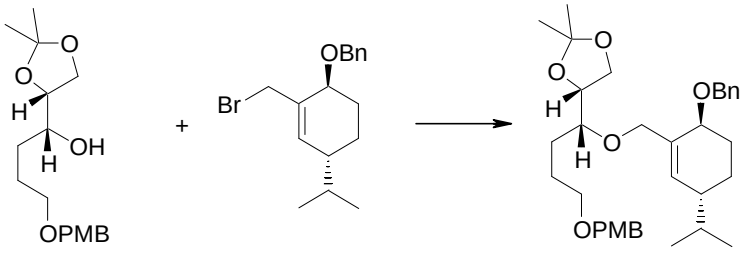


250a **323** **251**

Methanesulfonyl chloride (2.3 mL, 29 mmol) was added dropwise to a solution of alcohol **250** (5.10 g, 19.5 mmol) and triethylamine (5.4 mL, 39 mmol) in dry CH_2Cl_2 (120 mL) at –78 °C under argon and the reaction mixture was stirred at 0 °C for 1.5 h. The reaction was quenched by the additon of saturated aqueous $NaHCO_3$ solution (50 mL) and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and evaporated under vacuum to give the crude mesylate **323**. Mesylate **323** was dissolved in dry THF (120 mL) and LiBr (2.50 g, 29.3 mmol) was added at rt under argon. The mixture was stirred at rt for 2.5 h and the reaction was then quenched by the addition saturated aqueous $NaHCO_3$ solution (40 mL). The mixture was extracted with Et_2O (3 × 100 mL) and the organic extracts were combined, dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum ether/EtOAc, 9:1)

gave bromide **251** (5.97 g, 94%) as a colourless oil. R_f = 0.59 (petroleum ether/EtOAc, 4:1). $[\alpha]_D$ –17.6 (*c* = 1.00, $CHCl_3$, 22 °C). ν_{max} ($CHCl_3$) 2958, 2869, 1071 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.45–7.24 (m, 5H, **C**H *Ph*), 5.90 (s, 1H, BnOCH-C=C**H**), 4.70 (d, 1H, *J* = 11.2 Hz, 1 × OC**H**$_2$Ph), 4.58 (d, 1H, *J* = 11.2 Hz, 1 × OC**H**$_2$Ph), 4.47 (d, 1H, *J* = 9.3 Hz, 1 × C**H**$_2$Br), 4.30–4.24 (m, 1H, BnOC**H**), 3.88 (d, 1H, *J* = 9.3 Hz, 1 × C**H**$_2$Br), 2.23 (dddd, 1H, *J* = 12.0, 5.4, 2.8, 2.8 Hz, 1 × BnOCH-C**H**$_2$), 2.01 (dddd, 1H, *J* = 10.8, 8.0, 5.8, 2.8 Hz, H_3C-CH-C**H**), 1.82–1.72 (m, 1H, 1 × BnOCH-CH_2-C**H**$_2$), 1.67–1.53 (m, 2H, H_3C-C**H** and 1 × BnOCH-C**H**$_2$), 1.39–1.30 (m, 1H, 1 × BnOCH-CH_2-C**H**$_2$), 0.91 (d, 3H, *J* = 6.8 Hz, **H**$_3$C-CH), 0.88 (d, 3H, *J* = 6.8 Hz, **H**$_3$C-CH) ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.6 (**C**), 136.9 (**C**), 134.8 (BnOCH-C=**C**H), 128.3 (**C**H *Ph*), 127.9 (**C**H *Ph*), 127.6 (**C**H *Ph*), 73.2 (BnO**C**H), 71.5 (C**H**$_2$OPh), 42.0 (HC-**C**H-CH_2), 35.7 (**C**H_2Br), 31.8 (H_3C-**C**H), 28.0 (BnOCH-**C**H_2), 22.8 (BnOCH-CH_2-**C**H_2), 19.7 (H_3**C**-CH), 19.3 (H_3**C**-CH). HRMS (ESI) mass calc. for $C_{17}H_{23}BrO$ 345.0824 $(M+Na)^+$, found 345.0835.

(*R*)-4-((*R*)-1-(((3*R*,6*S*)-6-(benzyloxy)-3-isopropylcyclohex-1-enyl)methoxy)-4-(4-methoxybenzyloxy)butyl)-2,2-dimethyl-1,3-dioxolane (252)



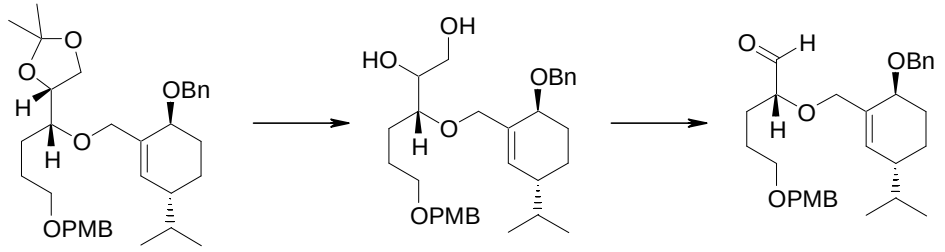
203 **251** **252**

A solution of alcohol **203**[3] (3.90 g, 12.6 mmol) in dry THF (38 mL) was added dropwise to a suspension of sodium hydride (1.00 g of a 60% suspension in oil, 25.1 mmol) in dry THF (75 mL) at rt under argon. The resulting mixture was stirred at reflux for 1 h. The mixture was cooled to rt and a solution of bromide **251** (4.50 g, 14.0 mmol) in dry THF (38 mL) was added dropwise, followed by 18-crown-6 (1.65

g, 6.24 mmol) and *n*-Bu_4NI (139 mg, 0.376 mmol). After stirring the mixture at rt for 15 h, it was quenched with saturated aqueous NH_4Cl (35 mL) at 0 °C and it was extracted with EtOAc (3 × 100 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum ether/EtOAc, 9:1 to 7:3) gave ether **252** (6.08 g, 87%) as a yellow oil. R_f = 0.38 (petroleum ether/EtOAc, 4:1). $[\alpha]_D$ +8.30 (*c* = 1.00, $CHCl_3$, 22 °C). ν_{max} ($CHCl_3$) 2956, 2868, 1070 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.39–7.29 (m, 4H, C**H** *Ph*), 7.29–7.26 (m, 1H, C**H** *Ph*), 7.25 (d, 2H, *J* = 8.5 Hz, C**H** *Ar*), 6.88 (d, 2H, *J* = 8.5 Hz, C**H** *Ar*), 5.79 (s, 1H, BnOCH-C=C**H**), 4.65 (d, 1H, *J* = 11.6 Hz, 1 × OC$\mathbf{H}_2$Ph), 4.53 (d, 1H, *J* = 11.6 Hz, 1 × OC$\mathbf{H}_2$Ph), 4.45–4.40 (m, 3H, OC$\mathbf{H}_2$PMP and 1 × C$\mathbf{H}_2$OPMB), 4.18 (dd, 1H, *J* = 13.6, 6.6 Hz, CH_2OCHC**H**O), 4.08 (t, 1H, *J* = 6.4 Hz, BnOC**H**), 4.00 (d, 1H, *J* = 11.8 Hz, 1 × C$\mathbf{H}_2$OPMB), 3.94 (dd, 1H, *J* = 8.0, 6.6 Hz, 1 × $(H_3C)_2$COC$\mathbf{H}_2$), 3.80 (s, 3H, OC$\mathbf{H}_3$), 3.67 (dd, 1H, *J* = 7.8, 7.8 Hz 1 × $(H_3C)_2$COC$\mathbf{H}_2$), 3.46–3.41 (m, 2H, BnOCH-C-C$\mathbf{H}_2$), 3.40–3.34 (m, 1H, BnOCH-C-CH_2O-C**H**), 2.13–2.04 (m, 1H, 1 × BnOCH-C$\mathbf{H}_2$), 2.00–1.92 (m, 1H, H_3C-CH-C**H**), 1.82–1.70 (m, 1H, 1 × BnOCH-CH_2-C$\mathbf{H}_2$), 1.67–1.43 (m, 6 H, 1 × BnOCH-C$\mathbf{H}_2$, H_3C-C**H**-CH_3 and 2 × C$\mathbf{H}_2$), 1.41 (s, 3H, **H**$_3$C-C-CH_3), 1.34 (s, 3H, **H**$_3$C-C-CH_3), 1.33–1.29 (m, 1H, 1 × BnOCH-CH_2-C$\mathbf{H}_2$), 0.92 (d, 3H, *J* = 6.7 Hz, **H**$_3$C-CH), 0.89 (d, 3H, *J* = 6.7 Hz, **H**$_3$C-CH) ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1 (BnOCH-**C**=CH), 139.0 (**C** *Ph*), 136.3 (**C** *Ar*), 132.3 (BnOCH-C=**C**H), 130.6 (**C** *Ar*), 129.1 (**C**H *Ar*), 128.2 (**C**H *Ph*), 127.6 (**C**H *Ph*), 127.3 (**C**H *Ph*), 113.7 (**C**H *Ar*), 109.1 (H_3C-**C**-CH_3), 78.6 (BnOCH-C-CH_2O-**C**H), 78.0 (CH_2OCH**C**HO), 73.7 (BnO**C**H), 72.4 (O**C**H_2PMP), 71.6 (**C**H_2OPMB), 70.8 (O**C**H_2Ph), 69.7 (BnOCH-C-**C**H_2), 65.8 ({H_3C}$_2$CO**C**H_2), 55.2 (O**C**H_3), 41.6 (H_3C-CH-**C**H), 31.9 (H_3C-**C**H), 27.7 (BnOCH-**C**H_2), 27.3 (**C**H_2), 26.5 (H_3**C**-C-CH_3), 25.9 (**C**H_2), 25.4 (H_3**C**-C-CH_3),

22.8 (BnOCH-CH_2-**C**H_2), 20.0 (H_3**C**-CH), 19.7 (H_3**C**-CH). HRMS (ESI) mass calc. for $C_{34}H_{48}O_6$ 575.3343 $(M+Na)^+$, found 575.3321.

(*R*)-2-(((3*R*,6*S*)-6-(benzyloxy)-3-isopropylcyclohex-1-enyl)methoxy)-5-(4-methoxybenzyloxy)pentanal (253)

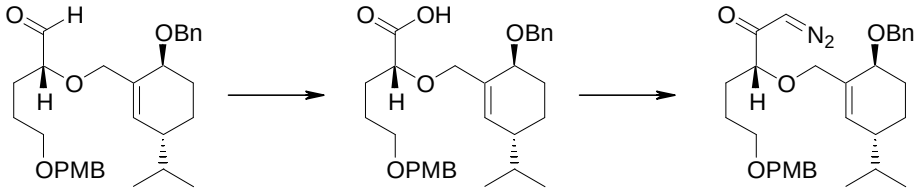


252 **324** **253**

PPTS (945 mg, 3.76 mmol) was added to a solution of ether **252** (10.4 g, 18.8 mmol) in ethylene glycol (220 mL), THF (110 mL) and CH_2Cl_2 (110 mL) and was heated at reflux for 15 h. The reaction mixture was cooled down to rt and then CH_2Cl_2 (170 mL) and water (170 mL) were added followed by neutralisation with concentrated ammonia (9 pasteur pipette drops). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The organic layers were combined, washed with water (1 × 100 mL), dried ($MgSO_4$), filtered and evaporated under vacuum to give the diol **324** as a yellow crude oil. The crude diol was dissolved in THF/water (330 mL of a 2:1 mixture) and sodium metaperiodate (16.1 g, 75.9 mmol) was added portionwise at rt. The mixture was stirred at rt for 1 h and then water (350 mL) and brine (100 mL) added. The resulting mixture was extracted with Et_2O (3 × 200 mL) and the organic extracts were combined, dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum ether/EtOAc, 7:3) gave aldehyde **253** (8.26 g, 92%). R_f = 0.7 (petroleum ether/EtOAc, 1:1). $[\alpha]_D$ +18.3 (*c* = 1.00, $CHCl_3$, 25 °C). ν_{max} ($CHCl_3$) 2955, 2863, 1731, 1095 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.60 (d, 1H, *J* = 2.2 Hz, **H**-C=O), 7.36–7.26 (m, 5H, C**H** *Ph*), 7.24 (d, 2H, *J* = 8.7 Hz, C**H** *Ar*), 6.87 (d, 2H, *J* = 8.7

Hz, C**H** *Ar*), 5.74 (s, 1H, BnOCH-C=C**H**), 4.65 (d, 1H, *J* = 11.6 Hz, 1 × OC**H**$_2$Ph), 4.50 (d, 1H, *J* = 11.6 Hz, 1 × OC**H**$_2$Ph), 4.44 (d, 1H, *J* = 12.0 Hz, 1 × C**H**$_2$OPMP), 4.41 (s, 2H, OC**H**$_2$PMB), 4.07–4.01 (m, 1H, BnOC**H**), 3.81 (d, 1H, *J* = 12.0 Hz, 1 × C**H**$_2$OPMP), 3.80 (s, 3H, OC**H**$_3$), 3.70–3.65 (m, 1H, O=C-C**H**), 3.45–3.39 (m, 2H, BnOCH-C-C**H**$_2$), 2.14–2.06 (m, 1H, 1 × BnOCH-C**H**$_2$), 2.01–1.93 (m, 1H, H$_3$C-CH-C**H**), 1.81–1.54 (m, 7H, H$_3$C-C**H**, 1 × BnOCH-C**H**$_2$, 1 × BnOCH-CH$_2$-C**H**$_2$, O=C-CH-C**H**$_2$ and C**H**$_2$-CH$_2$OPMB), 1.37–1.24 (m, 1H, 1 × BnOCH-CH$_2$-C**H**$_2$), 0.91 (d, 3H, *J* = 6.8 Hz, **H**$_3$C-CH), 0.88 (d, 3H, *J* = 6.8 Hz, **H**$_3$C-CH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.3 (H**C**=O), 159.1 (BnOCH-**C**=CH), 138.7 (**C** *Ph*), 135.2 (**C** *Ar*), 133.6 (BnOCH-C=**C**H), 130.5 (**C** *Ar*), 129.2 (**C**H *Ar*), 128.3 (**C**H *Ph*), 127.8 (**C**H *Ph*), 127.5 (**C**H *Ph*), 113.7 (**C**H *Ar*), 82.2 (O=C-**C**H), 73.4 (BnO**C**H), 72.5 (O**C**H$_2$PMP), 71.5 (**C**H$_2$OPMB), 71.0 (O**C**H$_2$Ph), 69.4 (BnOCH-C-**C**H$_2$), 55.2 (O**C**H$_3$), 41.6 (H$_3$C-CH-**C**H), 31.8 (H$_3$C-**C**H), 27.7 (BnOCH-**C**H$_2$), 26.9 (**C**H$_2$), 25.2 (**C**H$_2$), 22.8 (BnOCH-CH$_2$-**C**H$_2$), 19.9 (H$_3$**C**-CH), 19.6 (H$_3$**C**-CH). HRMS (ESI) mass calc. for $C_{30}H_{40}O_5$ 503.2768 $(M+Na)^+$, found 503.2747.

(*R*)-3-(((3*R*,6*S*)-6-(benzyloxy)-3-isopropylcyclohex-1-enyl)methoxy)-1-diazo-6-(4-methoxybenzyloxy)hexan-2-one (254)



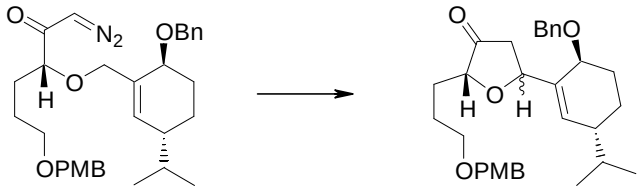
253 **325** **254**

A solution of sodium chlorite (11.7 g, 129 mmol) and sodium dihydrogenophosphate dihydrate (17.4 g, 112 mmol) in water (47 mL) was added dropwise at rt to a solution of aldehyde **253** (8.26 g, 17.2 mmol) in *t*-BuOH (94 mL) and 2-methyl-2-butene (14.6 mL, 137 mmol). The mixture was stirred at rt for 40 min and then extracted with Et_2O (3 × 100 mL). The organic extracts were

combined, washed with brine (1 × 100 mL), dried ($MgSO_4$), filtered and evaporated under vacuum to give the corresponding carboxylic acid **325** (9.05 g) as a colourless thick oil. The crude acid **325** was dissolved in dry Et_2O (164 mL), stirred at rt under argon and triethylamine (2.6 mL, 18.9 mmol) and *iso*-butylchloroformate (2.4 mL, 19 mmol) were added sequentially. The mixture was stirred at rt under argon for 2 h and then filtered and added dropwise to a solution of freshly distilled diazomethane in Et_2O (~172 mmol in 260 mL of Et_2O) at 0 °C. The resulting mixture was stirred at 0 °C for 1.5 h and then the excess diazomethane was consumed using glacial acetic acid (12 mL). The mixture was stirred for 15 min and then neutralized by the addition of saturated aqueous $NaHCO_3$ (80 mL). The mixture was then washed with saturated aqueous $NaHCO_3$ (3 × 150 mL), brine (1 × 150 mL), dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum ether/EtOAc, 7:3) gave diazoketone **254** (7.66 g, 86%) as a yellow oil. R_f = 0.35 (petroleum ether/EtOAc, 7:3). $[\alpha]_D$ +30.5 (*c* = 1.00, $CHCl_3$, 25 °C). ν_{max} ($CHCl_3$) 2954, 2934, 2864, 2105, 1349, 1097 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5H, C**H** *Ph*), 7.24 (d, 2H, *J* = 8.7 Hz, C**H** *Ar*), 6.86 (d, 2H, *J* = 8.7 Hz, C**H** *Ar*), 5.80–5.63 (m, 2H, BnOCH-C=C**H** and C**H**N_2), 4.67 (d, 1H, *J* = 11.6 Hz, 1 × OC**H**$_2$Ph), 4.47 (d, 1H, *J* = 11.6 Hz, 1 × OC**H**$_2$Ph), 4.40 (s, 2H, OC**H**$_2$PMP), 4.38 (d, 1H, *J* = 11.0 Hz, 1 × C**H**$_2$OPMB), 4.06 (t, 1H, *J* = 6.8 Hz, BnOC**H**), 3.80 (s, 3H, OC**H**$_3$), 3.76–3.67 (m, 1H, O=C-C**H**), 3.70 (d, 1H, *J* = 11.0 Hz, 1 ×C**H**$_2$OPMB), 3.42 (t, 2H, *J* = 6.0 Hz, BnOCH-C-C**H**$_2$), 2.20–2.10 (m, 1H, 1 × BnOCH-C**H**$_2$), 2.03–1.95 (m, 1H, H_3C-CH-C**H**), 1.80–1.56 (m, 7H, H_3C-C**H**, 1 × BnOCH-C**H**$_2$, 1 × BnOCH-CH_2-C**H**$_2$, O=C-CH-C**H**$_2$ and C**H**$_2$-CH_2OPMB), 1.29 (m, 1H, 1 × BnOCH-CH_2-C**H**$_2$), 0.91 (d, 3H, *J* = 6.8 Hz, **H**$_3$C-CH), 0.88 (d, 3H, *J* = 6.8 Hz, **H**$_3$C-CH) ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.9 (**C**=O), 159.1 (BnOCH-**C**=CH), 138.7 (**C** *Ph*), 135.3 (**C** *Ar*), 133.5 (BnOCH-C=**C**H), 130.6 (**C** *Ar*), 129.1 (**C**H *Ar*),

128.3 (**C**H *Ph*), 127.6 (**C**H *Ph*), 127.5 (**C**H *Ph*), 113.7 (**C**H *Ar*), 82.7 (O=C-**C**H), 73.6 (BnOC**H**), 72.5 (O**C**H_2PMP), 71.7 (**C**H_2OPMB), 70.5 (O**C**H_2Ph), 69.6 (BnOCH-C-**C**H_2), 55.2 (O**C**H_3), 52.5 (**C**HN_2), 41.6 (H_3C-CH-**C**H), 31.8 (H_3C-**C**H) 30.1 (**C**H_2), 27.7 (BnOCH-**C**H_2), 25.5 (**C**H_2), 22.8 (BnOCH-CH_2-**C**H_2), 19.8 (H**C**$_3$-CH), 19.5 (H_3**C**-CH). HRMS (FAB+) mass calc. for $C_{31}H_{40}N_2O_5$ 521.3015 $(M+H)^+$, found 521.3013.

(2*R*)-5-((3*R*,6*S*)-6-(benzyloxy)-3-isopropylcyclohex-1-enyl)-2-(3-(4-methoxybenzyloxy)propyl)dihydrofuran-3(2H)-one (255)



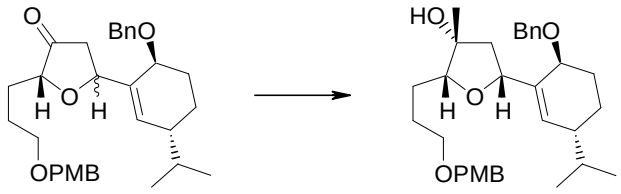
254 **255**

A solution of diazoketone **254** (4.68 g, 8.99 mmol) in dry THF (470 mL) was added dropwise over 2 h to a solution of Rh_2(tfacam)$_4$ (272 mg, 0.499 mmol) in dry THF (78 mL) at rt under argon. The solvent was removed under vacuum and the purple residue was purified by silica gel chromatography (petroleum ether/EtOAc, 9:1 to 4:1) to give furanone **255** (2.93 g, 66%) as a diastereoisomeric mixture (7:1 *cis*:*trans*). R_f = 0.40 (petroleum ether/EtOAc, 8:2). ν_{max} ($CHCl_3$) 2954, 2935, 2866, 2105, 1754, 1095 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.27 (m, 5H, C**H** *Ph*), 7.25 (d, 2H, *J* = 8.7 Hz, C**H** *Ar*), 6.87 (d, 2H, *J* = 8.7 Hz, C**H** *Ar*), 5.98 (s, 1H, BnOCH-C=C**H**), 4.72 (dd, 1H, *J* = 10.6, 6.0 Hz, BnOCH-C-C**H**O), 4.64 (d, 2H, *J* = 11.5 Hz, 1 × OC**H**$_2$Ph), 4.42 (s, 2H, OC**H**$_2$PMP), 4.38 (d, 2H, *J* = 11.5 Hz, 1 × OC**H**$_2$Ph), 4.07 (t, 1H, *J* = 4.3 Hz, BnOC**H**), 3.83–3.81 (m, 1H, O=C-C**H**O), 3.80 (s, 3H, OC**H**$_3$), 3.47 (dt, 2H, *J* = 6.2, 1.3 Hz, C**H**$_2$OPMB), 2.50 (dd, 1H, *J* = 18.0, 6.0 Hz, 1 × O=C-C**H**$_2$), 2.39 (dd, 1H, *J* = 18.0, 10.6 Hz, 1 × O=C-C**H**$_2$), 2.09–1.99 (m, 2H, BnOCH-C**H**$_2$), 1.92–1.60 (m, 7H, O=C-CH-C**H**$_2$, C**H**$_2$-CH_2OPMB, 1 ×

BnOCH-CH_2-C**H**$_2$, H_3C-C**H**, H_3C-CH-C**H**), 1.41–1.32 (m, 1H, 1 × BnOCH-CH_2-C**H**$_2$), 0.92 (d, 3H, *J* = 6.8 Hz, **H**$_3$C-CH), 0.89 (d, 3H, *J* = 6.8 Hz, **H**$_3$C-CH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.4 (O=**C**), 159.0 (BnOCH-**C**-CH), 138.3 (**C**), 137.0 (**C**), 130.6 (**C**), 130.3 (BnOCH-C=**C**H), 129.1 (**C**H *Ar*), 128.4 (**C**H *Ph*), 127.8 (**C**H *Ph*), 127.6 (**C**H *Ph*), 113.7 (**C**H *Ar*), 81.0 (O=C-**C**H-O), 76.1 (BnOCH-C-C**H**O), 73.1 (BnO**C**H), 72.5 (O**C**H_2Ph), 72.4 (O**C**H_2PMP), 70.2 (**C**H_2OPMB), 55.2 (O**C**H_3), 43.3 (O=C-**C**H_2), 41.0 (H_3C-CH-**C**H), 31.9 (H_3C-**C**H), 27.6 (BnOCH-**C**H_2), 26.8 (**C**H_2), 25.5 (**C**H_2), 22.0 (BnOCH-CH_2-**C**H_2), 20.0 (H_3**C**-CH), 19.7 (H_3**C**-CH). HRMS (ESI) mass calc. for $C_{31}H_{40}O_5$ 515.2768 $(M+Na)^+$, found 515.2770.

Due to the impossibility of getting a clean sample of the minor diasteromer, this compound is not fully caracterised in this thesis. Nevertheless, ^{1}H NMR of the crude mixture showed that this product is caracterised by a CH alkene peak at 5.90 ppm.

(2*R*,3*R*,5*R*)-5-((3*R*,6*S*)-6-(benzyloxy)-3-isopropylcyclohex-1-enyl)-2-(3-(4-methoxybenzyloxy)propyl)-3-methyltetrahydrofuran-3-ol (256)

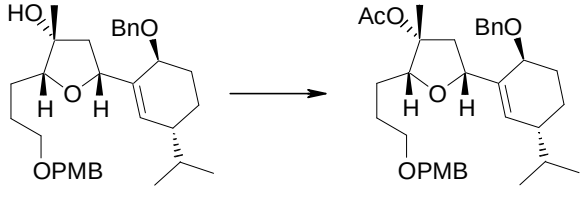


255 **256**

Methyllithium (20 mL of a 1.6 M solution in Et_2O, 32 mmol) was added dropwise to a solution of ketone **255** (3.10 g, 6.29 mmol) in dry toluene (150 mL) at –78 °C under argon. The reaction mixture was stirred for 18 h being allowed to warm to rt during this period. The reaction was quenched by the addition of saturated aqueous NH_4Cl (30 mL) at 0 °C and the mixture was extracted with Et_2O (3 × 100 mL). The organic extracts were combined, washed with brine (1 × 50 mL), dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum

ether/EtOAc, 4:1) gave alcohol **256** (3.47 g, 54%). R_f = 0.28 (petroleum ether/EtOAc, 7:3). $[\alpha]_D$ +125 (*c* = 0.550, $CHCl_3$, 18 °C). ν_{max} ($CHCl_3$) 3534, 2938, 2867, 1713, 1095 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.30 (m, 4H, C**H** *Ph*), 7.29–7.24 (m, 3H, C**H** *Ph* and 2 × C**H** *Ar*), 6.87 (d, 2H, *J* = 8.7 Hz, C**H** *Ar*), 5.89 (d, 1H, *J* = 1.2 Hz, BnOCH-C=C**H**), 4.62 (d, 1H, *J* = 12.0 Hz, 1 × OC**H**$_2$Ph), 4.66–4.59 (m, 1H, BnOCH-C-C**H**O), 4.47–4.40 (m, 3H, OC**H**$_2$PMP, 1 × OC**H**$_2$Ph), 4.15–4.09 (m, 1H, BnOC**H**), 3.80 (s, 3H, OC**H**$_3$), 3.57–3.42 (m, 3H, C**H**$_2$OPMB and H_3C-C{OH}-C**H**), 2.42 (bs, 1H, O**H**), 2.16–2.06 (m, 2H, 1 × H_3C-C(OH)-C**H**$_2$ and 1 × BnOCH-C**H**$_2$), 2.04–1.95 (m, 1H, H_3C-CH-C**H**), 1.93–1.85 (m, 1H, 1 × H_3C-C(OH)-C**H**$_2$), 1.82–1.51 (m, 7H, 1 × BnOCH-C**H**$_2$, 1 × BnOCH-CH_2-C**H**$_2$, H_3C-C-CH-C**H**$_2$, C**H**$_2$-CH_2OPMB, H_3C-C**H**), 1.32–1.22 (m, 1H, 1 × BnOCH-CH_2-C**H**$_2$), 1.20 (s, 3H, H_3**C**-COH), 0.88 (d, 3H, *J* = 6.8 Hz, **H**$_3$C-CH), 0.85 (d, 3H, *J* = 6.8 Hz, **H**$_3$C-CH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1 (BnOCH-**C**=CH), 141.0 (**C**), 138.4 (**C**), 130.8 (**C**), 129.2 (**C**H *Ar*), 128.3 (BnOCH-C=**C**H), 127.7 (**C**H *Ph*), 127.6 (**C**H *Ph*), 127.5 (**C**H *Ph*), 113.7 (**C**H *Ar*), 86.4 (H_3C-C(OH)-**C**H), 78.2 (HO**C**-CH_3), 76.0 (BnOCH-C-**C**HO), 74.2 (BnO**C**H), 72.5 (O**C**H$_2$PMP), 70.1 (**C**H$_2$OPMB), 69.9 (OC**H**$_2$Ph), 55.3 (OC**H**$_3$), 46.8 (H_3CC(OH)**C**H$_2$), 41.3 (H_3C-CH-**C**H), 32.0 (H_3C-**C**H), 27.5 (BnOCH-**C**H$_2$), 27.1 (**C**H$_2$), 25.2 (**C**H$_2$), 22.6 (BnOCH-CH_2-**C**H$_2$), 22.3 (H_3**C**COH), 22.6 (H_3**C**-CH), 22.3 (H_3**C**-CH). HRMS (ESI) mass calc. for $C_{32}H_{44}O_5$ 531.3081 $(M+Na)^+$, found 531.3086.

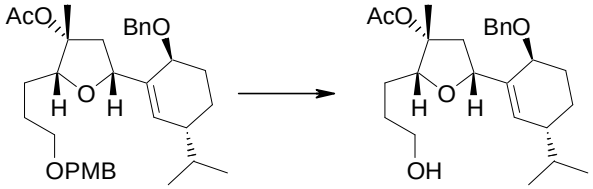
(2*R*,3*R*,5*R*)-5-((3*R*,6*S*)-6-(benzyloxy)-3-isopropylcyclohex-1-enyl)-2-(3-(4-methoxybenzyloxy)propyl)-3-methyltetrahydrofuran-3-yl acetate (258)



256 **258**

DMAP (841 mg, 6.89 mmol) was added to a solution of alcohol **256** (1.17 g, 2.30 mmol) and freshly distilled acetic anhydride (434 μL, 4.59 mmol) in dry CH_2Cl_2 (20 mL). The resulting mixture was stirred at rt under argon for 18 h. Water (100 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 50 mL) and the organic extracts were combined, dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum ether/EtOAc, 7:3) gave furan **258** (1.00 g, 79%). R_f = 0.43 (petroleum ether/EtOAc, 7:3). $[\alpha]_D$ +4.9 (*c* = 1.0, $CHCl_3$, 20 °C). ν_{max} ($CHCl_3$) 3534, 2938, 2867, 1713, 1095 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.30 (m, 5H, C**H** *Bn*), 7.27 (d, 2H, *J* = 8.6 Hz, C**H** *PMB*), 6.88 (d, 2H, *J* = 8.6 Hz, C**H** *PMB*), 5.90 (s, 1H, BnOCH-C=C**H**), 4.62 (d, 1H, *J* = 11.7 Hz, 1 × OC**H**$_2$Ph), 4.50 (t, 1H, *J* = 6.1 Hz, BnOCH-C-C**H**O), 4.45 (s, 2H, OC**H**$_2$PMP), 4.39 (d, 1H, *J* = 11.7 Hz, 1 × OC**H**$_2$Ph), 3.94 (bs, 1H, BnOC**H**), 3.80 (s, 3H, OC**H**$_3$), 3.56–3.46 (m, 3H, C**H**$_2$OPMB and H_3C-C-C**H**), 2.32–2.17 (m, 2H, H_3C-C-C**H**$_2$), 2.09–2.01 (m, 1H, 1 × BnOCH-C**H**$_2$), 2.01–1.95 (m, 1H, H_3C-CH-C**H**), 1.92 (s, 3H, **H**$_3$C-CO-O), 1.91–1.87 (m, 1H, 1 × BnOCH-C**H**$_2$), 1.79–1.49 (m, 6H, H_3C-C**H**, 1 × BnOCH-CH_2-C**H**$_2$, H_3C-C-CH-C**H**$_2$ and C**H**$_2$-CH_2OPMB), 1.47 (s, 3H, **H**$_3$C-COAc), 1.24 (m, 1H, 1 × BnOCH-CH_2-C**H**$_2$), 0.90 (d, 3H, *J* = 6.8 Hz, **H**$_3$C-CH), 0.85 (d, 3H, *J* = 6.8 Hz, **H**$_3$C-CH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4 (**C**=O), 159.1 (BnOCH-**C**=CH), 138.9 (**C**), 138.7 (**C**), 130.7 (**C**), 129.2 (**C**H *Ar*), 128.3 (BnOCH-C=**C**H), 127.6 (**C**H *Ph*), 127.4 (**C**H *Ph*), 127.0 (**C**H *Ph*), 113.7 (**C**H *Ar*), 86.9 (H_3C-C-**C**H), 86.3 (H_3C-**C**OAc), 76.0 (BnOCH-C-**C**HO), 74.0 (BnO**C**H), 72.4 (O**C**H$_2$PMP), 70.1 (**C**H$_2$OPMB), 70.0 (O**C**H$_2$Ph), 55.2 (O**C**H$_3$), 44.2 (H_3C-C-**C**H$_2$), 41.0 (H_3C-CH-**C**H), 32.1 (H_3C-**C**H), 27.4 (BnOCH-**C**H$_2$), 26.9 (**C**H$_2$), 26.1 (**C**H$_2$), 22.4 (BnOCH-CH_2-**C**H$_2$), 22.1 (H_3**C**-COAc), 22.0 (H_3**C**-COO), 19.9 (H_3**C**-CH), 19.6 (H_3**C**-CH). HRMS (ESI) mass calc. for $C_{34}H_{46}O_6$ 573.3187 $(M+Na)^+$, found 573.3191.

(2*R*,3*R*,5*R*)-5-((3*R*,6*S*)-6-(benzyloxy)-3-isopropylcyclohex-1-enyl)-2-(3-hydroxypropyl)-3-methyltetrahydrofuran-3-yl acetate (259)

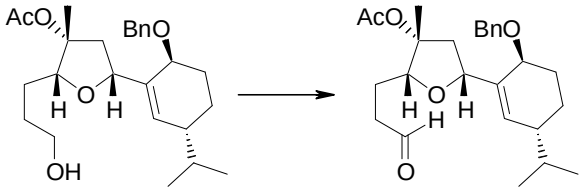


258 **259**

DDQ (616 mg, 2.71 mmol) was added in one portion to a solution of furan **258** (996 mg, 1.81 mmol) in CH_2Cl_2/H_2O (38.8 mL of a 20:1 mixture) at 0 °C and the mixture was stirred at rt for 1.5 h. The solution was diluted with CH_2Cl_2 (35 mL) and washed with saturated aqueous Na_2CO_3 (2 × 35 mL) and brine (1 × 35 mL). The aqueous layers were combined and extracted with further CH_2Cl_2 (1 × 50 mL). The organic layers were combined, dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum ether/EtOAc 7:3) gave alcohol **259** (550 mg, 71%) as a colourless oil. R_f = 0.11 (petroleum ether/EtOAc, 7:3). $[\alpha]_D$ +11 (*c* = 0.55, $CHCl_3$, 20 °C). ν_{max} ($CHCl_3$) 3421, 2939, 2869, 1726.1, 1623, 1369, 1097 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.25 (m, 5H, C**H** *Ph*), 5.87 (d, 1H, *J* = 1.3 Hz, BnOCH-C=C**H**), 4.62 (d, 1H, *J* = 11.7 Hz, 1 × OC**H**$_2$Ph), 4.54 (t, 1H, *J* = 7.8 Hz, BnOCH-C-C**H**O), 4.38 (d, 1H, *J* = 11.7 Hz, 1 × OC**H**$_2$Ph), 3.96–3.90 (m, 1H, BnOC**H**), 3.73–3.67 (m, 2H, C**H**$_2$OH), 3.53–3.49 (m, 1H, H_3C-C-C**H**), 2.53 (bs, 1H, CH_2O**H**), 2.28 (d, 2H, *J* = 7.7 Hz, H_3C-C-C**H**$_2$), 2.11–2.02 (m, 1H, 1 × BnOCH-C**H**$_2$), 2.01–1.95 (m, 1H, H_3C-CH-C**H**), 1.92 (s, 3H, H_3**C**-CO-O), 1.82–1.70 (m, 5H, 1 × BnOCH-CH_2-C**H**$_2$, C**H**$_2$-CH_2OH, H_3C-C-CH-C**H**$_2$), 1.67–1.60 (m, 1H, 1 × BnOCH-C**H**$_2$), 1.59–1.52 (m, 1H, H_3C-C**H**), 1.50 (s, 3H, H_3**C**-COAc), 1.30–1.20 (m, 1H, 1 × BnOCH-CH_2-C**H**$_2$), 0.90 (d, 3H, *J* = 6.8 Hz, H_3**C**-CH), 0.85 (d, 3H, *J* = 6.8 Hz, H_3**C**-CH) ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4 (**C**=O), 138.8 (**C**), 138.3 (**C**), 128.3 (BnOCH-C=**C**H), 127.6 (**C**H *Ph*), 127.4 (**C**H *Ph*), 127.2 (**C**H *Ph*), 87.3 (H_3C-C-**C**H), 86.3 (H_3C-**C**OAc), 76.3 (BnOCH-C-**C**HO), 74.0 (BnO**C**H), 70.2

(OC**H**$_2$Ph), 62.3 (**C**H$_2$OH), 43.9 (H$_3$C-C-**C**H$_2$), 41.0 (H$_3$C-CH-**C**H), 32.1 (H$_3$C-**C**H), 30.4 (**C**H$_2$), 27.4 (BnOCH-**C**H$_2$), 26.3 (**C**H$_2$), 22.4 (BnOCH-CH$_2$-**C**H$_2$), 22.0 (H$_3$**C**-CO-O), 21.8 (H$_3$**C**-COAc), 20.0 (H$_3$**C**-CH), 19.6 (H$_3$**C**-CH). HRMS (ESI) mass calc. for $C_{26}H_{38}O_5$ 453.2611 $(M+Na)^+$, found 453.2609.

(2*R*,3*R*,5*R*)-5-((3*R*,6*S*)-6-(benzyloxy)-3-isopropylcyclohex-1-enyl)-3-methyl-2-(3-oxopropyl)tetrahydrofuran-3-yl acetate (260)

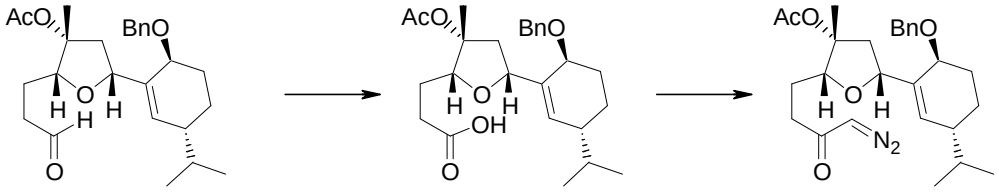


259 **260**

Dess-Martin periodinane (1.40 g, 3.38 mmol) was added in two portions at 30 min intervals to a solution of alcohol **259** (717 mg, 1.69 mmol) in dry CH_2Cl_2 (23 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min and then at rt for 1 h. The reaction was quenched with saturated aqueous thiosulfate solution (40 mL) and stirred for 15 min. The mixture was extracted with CH_2Cl_2 (3 × 50 mL) and the organic extracts were combined, washed with saturated aqueous Na_2CO_3 (1 × 50 mL) and brine (1 × 50 mL), dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum ether/EtOAc, 7:3) gave aldehyde **260** (645 mg, 89 %). R_f = 0.43 (petroleum ether/EtOAc, 7:3). $[\alpha]_D$ +18 (*c* = 0.33, $CHCl_3$, 24 °C). ν_{max} ($CHCl_3$) 2955, 2936, 2869, 1731, 1246, 1096 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.83 (t, 1H, *J* = 1.3 Hz, O=C-**H**), 7.36–7.26 (m, 5H, C**H** *Ph*), 5.85 (d, 1H, *J* = 1.3 Hz, BnOCH-C=C**H**), 4.62 (d, 1H, *J* = 11.7 Hz, 1 × OC**H**$_2$Ph), 4.49 (t, 1H, *J* = 8.5 Hz, BnOCH-C-C**H**O), 4.38 (d, 1H, *J* = 11.7 Hz, 1 × OC**H**$_2$Ph), 3.92 (s, 1H, BnOC**H**), 3.52 (t, 1H, *J* = 6.9 Hz, H$_3$C-C-C**H**), 2.80–2.56 (m, 2H, C**H**$_2$C=O), 2.30 (dd, 1H, *J* = 13.8, 7.2 Hz, 1 × H$_3$C-C-C**H**$_2$), 2.20 (dd, 1H, *J* = 13.8, 7.2 Hz, 1 × H$_3$C-C-C**H**$_2$),

2.11–2.02 (m, 1H, 1 × BnOCH-C**H**$_2$), 2.00–1.70 (m, 8H, **H**$_3$C-CO-O, H$_3$C-CH-C**H**, H$_3$C-C**H**, 1 × BnOCH-CH$_2$-C**H**$_2$, C**H**$_2$-CH$_2$-CO), 1.67–1.59 (m, 1H, 1 × BnOCH-C**H**$_2$), 1.59–1.52 (m, 1H, H$_3$C-C**H**), 1.51 (s, 3H, **H**$_3$C-COAc), 1.31–1.20 (m, 1H, 1 ×x BnOCH-CH$_2$-C**H**$_2$), 0.89 (d, 3H, *J* = 6.8 Hz, **H**$_3$C-CH), 0.85 (d, 3H, *J* = 6.8 Hz, **H**$_3$C-CH) ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.3 (O=**C**-H), 170.3 (H$_3$C-**C**O-O), 138.8 (**C**), 138.5 (**C**), 128.3 (BnOCH-C=**C**H), 127.6 (**C**H *Ph*), 127.4 (**C**H *Ph*), 127.1 (**C**H *Ph*), 86.2 (H$_3$C-**C**OAc), 85.9 (H$_3$C-C-**C**H), 76.2 (BnOCH-C-**C**HO), 74.0 (BnO**C**H), 70.2 (O**C**H$_2$Ph), 44.1 (**C**H$_2$C=O), 41.2 (H$_3$C-C-**C**H$_2$), 41.0 (H$_3$C-CH-**C**H), 32.1 (H$_3$C-**C**H), 27.4 (BnOCH-**C**H$_2$), 22.4 (**C**H$_2$), 22.0 (BnOCH-CH$_2$-**C**H$_2$), 22.0 (H$_3$**C**-CO-O), 22.0 (H$_3$**C**-COAc), 19.9 (H$_3$**C**-CH), 19.6 (H$_3$**C**-CH). HRMS (CI+) mass calc. for $C_{26}H_{36}O_5$ 429.2641 $(M+H)^+$, found 429.2640.

(2*R*,3*R*,5*R*)-5-((3*R*,6*S*)-6-(benzyloxy)-3-isopropylcyclohex-1-enyl)-2-(4-diazo-3-oxobutyl)-3-methyltetrahydrofuran-3-yl acetate (262)



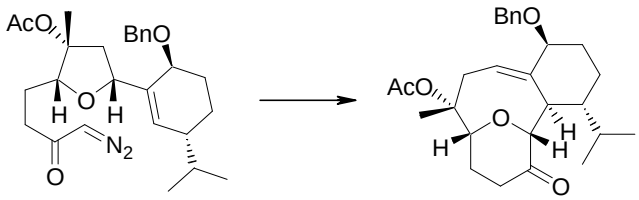
260 **261** **262**

A solution of sodium chlorite (794 mg, 8.78 mmol) and sodium dihydrogenophosphate dihydrate (1.18 g, 7.61 mmol) in water (7 mL) was added dropwise at rt to a solution of aldehyde **260** (500 mg, 1.17 mmol) in *t*-BuOH (14 mL) and 2-methyl-2-butene (995 µL, 9.36 mmol). The mixture was stirred at rt for 30 min, then Et_2O (50 mL) was added, the layers were separated and the organic layer was washed with water (1 × 50 mL) and brine (1 × 50 mL), dried ($MgSO_4$), filtered and evaporated under vacuum to give carboxylic acid **261** (522 mg) as thick yellow oil. The crude acid **261** was dissolved in dry MeOH (10 mL) under argon

and sodium methoxide (60 mg, 1.1 mmol) was added in one portion. The resulting mixture was stirred at rt for 15 min, concentrated under vacuum and dried under high vacuum for 1 h. The white foam was dissolved in dry benzene (10 mL) and oxalyl chloride (497 μL, 5.87 mmol) was added dropwise at rt. The mixture was stirred at rt for 2 h, concentrated under vacuum and dissolved in dry CH_2Cl_2 (60 mL). The dichloromethane solution of the acid chloride was then added dropwise at 0 °C to a solution of freshly distilled diazomethane (~11.7 mmol in 46 mL of Et_2O) and the resulting mixture was stirred at 0 °C for 1 h. The excess diazomethane was quenched with acetic acid (1.5 mL) and the mixture was diluted with Et_2O (50 mL), washed with saturated aqueous $NaHCO_3$ (3 × 50 mL), brine (1 × 50 mL), dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum ether/EtOAc, 7:3) gave diazoketone **262** (435 mg, 79%) as a yellow oil. R_f = 0.25 (petroleum ether/EtOAc, 7:3). $[\alpha]_D$ +15 (*c* = 0.33, $CHCl_3$, 22 °C). ν_{max} ($CHCl_3$) 2938, 2870, 2108, 1728, 1386, 1066 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.26 (m, 5H, C**H** *Ph*), 5.87 (s, 1H, BnOCH-C=C**H**), 5.28 (bs, 1H, C**H**N_2), 4.62 (d, 1H, *J* = 11.7 Hz, 1 × OC**H**$_2$Ph), 4.50 (t, 1H, *J* = 7.5 Hz, BnOCH-C-C**H**O), 4.38 (d, 1H, *J* = 11.7 Hz, 1 × OC**H**$_2$Ph), 3.91 (s, 1H, BnOC**H**), 3.49 (dd, 1H, *J* = 9.6, 3.2 Hz, H_3C-C-C**H**), 2.61–2.46 (m, 2H, C**H**$_2$COCHN_2), 2.32–2.17 (m, 2H, H_3C-C-C**H**$_2$), 2.10–2.02 (m, 1H, H_3C-CH-C**H**), 2.01–1.94 (m, 2H, 1 × C**H**$_2$-CH_2COCHN_2 and 1 × BnOCH-C**H**$_2$), 1.93 (s, 3H, **H**$_3$C-CO-O), 1.82–1.73 (m, 1H, 1 × C**H**$_2$-CH_2COCHN_2), 1.70–1.48 (m, 3H, H_3C-C**H**, 1 × BnOCH-C**H**$_2$ and 1 × BnOCH-CH_2-C**H**$_2$), 1.50 (s, 3H, **H**$_3$C-C), 1.31–1.20 (m, 1H, 1 × BnOCH-CH_2-C**H**$_2$), 0.89 (d, 3H, *J* = 6.8 Hz, **H**$_3$C-CH), 0.85 (d, 3H, *J* = 6.8 Hz, **H**$_3$C-CH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.8 (**C**OCHN_2), 170.4 (H_3C-**C**O), 138.8 (**C**), 138.7 (**C**), 128.3 (BnOCH-C=**C**H), 127.6 (**C**H *Ph*), 127.5 (**C**H *Ph*), 127.00 (**C**H *Ph*), 86.2 (H_3C-**C**OAc), 86.0 (H_3C-C-**C**H), 76.1 (BnOCH-C-**C**HO), 74.0 (BnO**C**H), 70.2 (O**C**H_2Ph), 54.5

(CO**C**HN$_2$) 44.1 (**C**H$_2$COCHN$_2$), 41.0 (H$_3$C-CH-**C**H and H$_3$C-C-**C**H$_2$), 32.1 (H$_3$C-**C**H), 27.4 (BnOCH-**C**H$_2$), 22.4 (**C**H$_2$-CH$_2$COCHN$_2$), 22.0 (H$_3$**C**-CO-O), 21.9 (H$_3$**C**-COAc and BnO-CH$_2$-**C**H$_2$), 20.0 (H$_3$**C**-CH), 19.6 (H$_3$**C**-CH). HRMS (FAB+) mass calc. for $C_{27}H_{36}N_2O_5$ 469.2702 $(M+H)^+$, found 469.2707.

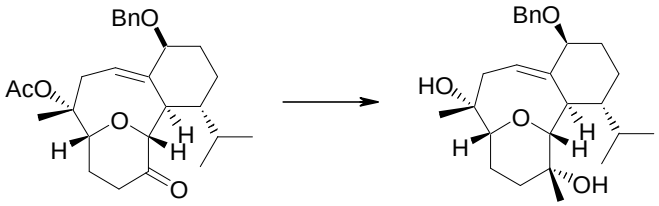
6-Benzyloxy-3-isopropyl-10-methyl-14-oxo-15-oxatricyclo[9.3.1.0^{2,7}]pentadec-7-en-10-yl acetate (266)



A solution of diazoketone **262** (162 mg, 0.346 mmol) in dry CH_2Cl_2 (24 mL) was added dropwise over 20 min to a solution of Cu(hfacac)$_2$ (9 mg, 0.02 mmol) in dry CH_2Cl_2 (5.5 mL) at reflux under argon. The mixture was stirred at reflux for 30 min, the solvent was removed under vacuum and the residue was purified by silica gel chromatography (petroleum ether/EtOAc. 4:1) to give the [2,3]-rearrangement product **266** (116 mg, 76%) as white foam. R_f = 0.50 (petroleum ether/EtOAc, 7:3). $[\alpha]_D$ +66 (*c* = 0.80, $CHCl_3$, 20 °C). ν_{max} ($CHCl_3$) 2955, 2871, 1724, 1241, 1084 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.21 (m, 5H, C**H** *Ph*), 5.77 (t, 1H, *J* = 8.2 Hz, BnOCH-C=C**H**), 4.68 (d, 1H, *J* = 11.5 Hz, 1 × OC**H**$_2$Ph), 4.42 (dd, 1H, *J* = 11.2 Hz, 7.3 Hz, **H**C-CH$_2$-CH$_2$-C=O), 4.28 (d, 1H, *J* = 11.5 Hz, 1 × OC**H**$_2$Ph), 4.17 (d, 1H, *J* = 12.6 Hz, O=C-C**H**O), 3.79 (t, 1H, *J* = 2.6 Hz, BnOC**H**), 2.78 (d, 1H, *J* = 12.1 Hz, O=C-CH-C**H**), 2.81–2.71 (m, 1H, 1 × C**H**$_2$-CH=C), 2.68–2.40 (m, 3H, 1 × C**H**$_2$-CH=C, C**H**$_2$-C=O), 2.29–2.16 (m, 2H, **H**$_2$C-CH$_2$-C=O), 2.05–1.95 (m, 4H, H$_3$**C**-CO-O, 1 × BnOCH-CH$_2$-C**H**$_2$), 1.89 (s, 3H, **H**$_3$C-CH), 1.81–1.38 (m, 5H, BnOCH-C**H**$_2$, 1 × BnOCH-CH$_2$-C**H**$_2$, H$_3$C-C**H**, HC-C**H**-CH$_2$), 0.86 (d, 3H, *J* = 6.0 Hz, **H**$_3$C-

CH), 0.85 (d, 3H, *J* = 6.4 Hz, **H**$_3$C-CH) ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.5 (H_2C-**C**=O), 169.9 (H_3C-**C**=O), 139.0 (**C**), 136.6 (**C**), 129.4 (BnOCH-C=**C**H), 128.3 (C**H** *Ph*), 127.7 (C**H** *Ph*), 127.3 (C**H** *Ph*), 87.1 (H_3C-**C**OAc), 82.1 (O=C-C**H**O), 78.3 (BnO**C**H), 77.5 (**H**C-CH_2-CH_2-C=O), 69.0 (O**C**H_2Ph), 42.3 (O=C-CH-**C**H), 37.9 (HC-**C**H-CH_2), 34.1 (**C**H_2C=O), 31.2 (**C**H_2-CH=C), 28.2 (H_3C-**C**H), 26.8 (BnOCH-**C**H_2), 23.1 (H_3**C**-CO-O), 22.4 (H_3**C**-C), 21.1 (H_3**C**-CH), 20.3 (H_3**C**-CH), 19.8 (H_2**C**-CH_2-C=O), 17.6 (BnOCH-CH_2-**C**H_2). HRMS (ESI) mass calc. for $C_{27}H_{36}O_5$ 463.2455 $(M+Na)^+$, found 463.2440.

6-Benzyloxy-3-isopropyl-10,14-dimethyl-15-oxatricyclo[9.3.1.0^{2,7}]pentadec-7-ene-10,14-diol (271)



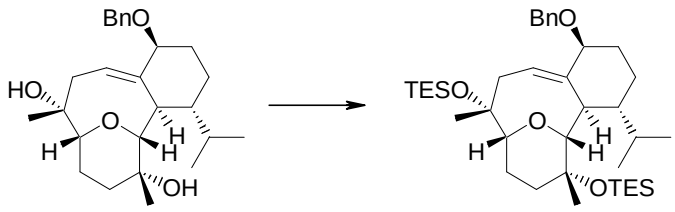
266 **271**

MeLi (920 μL of 1.6 M solution in Et_2O, 1.47 mmol) was added dropwise to a solution of ketone **266** (81 mg, 0.18 mmol) in dry toluene (10 mL) at –78 °C under argon and the resulting mixture was stirred for 6.5 h being allowed to warm to rt over this period. The reaction was quenched by the addition of water (15 mL) and the mixture was diluted with Et_2O (10 mL) and brine (10 mL) and then extracted with Et_2O (3 × 20 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and evaporated under vacuum. The crude mixture was dissolved in dry toluene (10 mL) and treated with MeLi (920 μL of 1.6 M solution in Et_2O, 1.47 mmol) at –78 °C under argon. The reaction mixture was stirred for 6 h and then quenched with water (15 mL). The mixture was diluted with Et_2O (10 mL) and brine (10 mL) and then extracted with Et_2O (3 × 20 mL). The organic extracts were

combined, dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum ether/EtOAc, 7:3 to 1:1) gave the diol **271** (62 mg, 82%) as a white solid. R_f = 0.14 (petroleum ether/EtOAc, 7:3). $[\alpha]_D$ –1.4 (*c* = 0.45, $CHCl_3$, 20 °C). ν_{max} ($CHCl_3$) 3419, 2957, 2869, 1065 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 4H, C**H** *Ph*), 7.39–7.23 (m, 1H, C**H** *Ph*), 5.65 (t, 1H, *J* = 8.0 Hz, BnOCH-C=C**H**), 4.77 (d, 1H, *J* = 12.0 Hz, 1 × OC**H**$_2$Ph), 4.35 (d, 1H, *J* = 12.0 Hz, 1 × OC**H**$_2$Ph), 3.96 (d, 1H, *J* = 12.0 Hz, HC=C-CH-C**H**), 3.73 (dd, 1H, *J* = 2.7, 2.7 Hz, BnOC**H**), 3.63 (dd, 1H, *J* = 11.2, 7.4 Hz, H_3C-C-CH_2-CH_2-C**H**), 2.91 (d, 1H, *J* = 11.9 Hz, HC=C-C**H**-CH), 2.73 (dd, 1H, *J* = 13.0, 8.7 Hz, 1 × **H**$_2$C-CH=C), 2.00–1.86 (m, 5H, 1 × **H**$_2$C-CH=C, 1 × BnOCH-CH_2-C**H**$_2$, H_3C-C-CH_2-C**H**$_2$, H_3C-CH-C**H**), 1.76–1.59 (m, 5H, BnOCH-C**H**$_2$, H_3C-C-C**H**$_2$-CH_2, O**H**), 1.58–1.47 (m, 5H, 1 × BnOCH-CH_2-C**H**$_2$, C**H**$_3$-COH, O**H**), 1.46–1.40 (m, 4H, C**H**$_3$-COH, H_3C-C**H**), 1.01 (d, 3H, *J* = 6.5 Hz, **H**$_3$C-CH), 0.86 (d, 3H, *J* = 6.5 Hz, **H**$_3$C-CH) ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.7 (**C** *Ph*), 138.6 (HC=**C**), 129.2 (BnOCH-C=**C**H), 128.3 (**C**H *Ph*), 127.7 (**C**H *Ph*), 127.1 (**C**H *Ph*), 82.1 (HC=C-CH-**C**H), 81.7 (H_3C-C-CH_2-CH_2-**C**H), 79.0 (BnO**C**H), 76.7 (H_3C-**C**OH), 72.3 (H_3C-**C**OH), 68.8 (O**C**H_2Ph), 43.5 (HC=C-C**H**-CH), 39.5 (H_3C-CH-**C**H), 36.2 (C**H**$_2$), 35.6 (H_2**C**-CH=C), 30.3 (**C**H_3-COH), 29.0 (H_3C-**C**H-CH), 28.5 (**C**H_3-COH), 26.7 (**C**H_2), 21.9 (H_3**C**-CH), 20.6 (H_3**C**-CH), 18.3 (**C**H_2), 17.7 (**C**H_2). HRMS (ESI) mass calc. for $C_{26}H_{38}O_4$ 437.2662 $(M+Na)^+$, found 437.2658. Crystal data for **271**: Crystallisation performed in a mixture of hexane, Et_2O and CH_2Cl_2; $C_{26}H_{38}O_4$. ¼ (C_7H_8), M_r = 437.62, crystal dimensions 0.40 × 0.30 × 0.15 mm^3, tetragonal, space group *P* 4_3 2_1 2, *a* = 13.7906(10), *b* = 13.7906(10), *c* = 26.375(4) Å, *α* = 90, *β* = 90, *γ* = 90°, *V* = 5016.1(9) $Å^3$, *Z* = 8, ρ_{calcd} = 1.16 $Mg.m^{-3}$, μ($Mo_{K\alpha}$) 0.072 mm^{-1}, *T* = 100(2) K, 24,286 reflections collected of which 3593 independent, 2θmax = 56.6°. Structure

solved by direct methods (SIR92) and refined by full-matrix least squares against F^2 (CRYSTALS), R_1 = 0.0529, wR_2 = 0.1552, 379 parameters, 144 restraints.

6-Benzyloxy-3-isopropyl-10,14-dimethyl-10,14-bis(triethylsilanyloxy)-15-oxatricyclo[9.3.1.0^{2,7}]pentadec-7-ene (275)

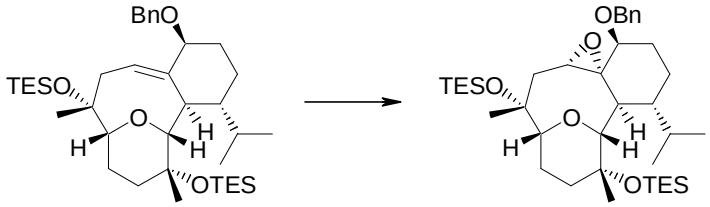


271 **275**

TESOTf (172 μL, 0.76 mmol) was added dropwise to a solution of diol **271** (63 mg, 0.15 mmol) and 2,6-lutidine (133 μL, 1.11 mmol) in dry CH_2Cl_2 (3.5 mL) at –78 °C under argon. The mixture was stirred at –78 °C for 1 h. TLC indicates some starting material remaining, therefore 2,6-lutidine (133 μL, 1.11 mmol) and TESOTf (172 μL, 0.760 mmol) were successively added and the mixture was stirred at –78 °C for an additional 3 h period. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (3 mL) and allowed to warm to rt. Water (10 mL) and Et_2O (10 mL) were added and the mixture was extracted with saturated aqueous $CuSO_4$ solution (2 × 20 mL). The aqueous layers were combined and extracted with Et_2O (3 × 20 mL). The organic layers were combined, washed with water (1 × 20 mL) and brine (1 × 20 mL), dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum ether/EtOAc, 99:1 to 9:1) gave doubly protected compound **275** (54 mg, 48%). R_f = 0.68 (petroleum ether/EtOAc, 9:1). $[\alpha]_D$ –0.7 (*c* = 0.3, $CHCl_3$, 19 °C). ν_{max} ($CHCl_3$) 2955, 2875, 1005 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.21 (m, 4H, C**H** *Ph*), 7.25 (m, 1H, C**H** *Ph*), 5.57 (t, 1H, *J* = 8.1 Hz, **H**C=C), 4.74 (d, 1H, *J* = 11.7 Hz, 1 × OC**H**$_2$Ph), 4.29 (d, 1H, *J* = 11.7 Hz, 1 × OC**H**$_2$Ph), 3.80 (d, 1H, *J* = 11.4 Hz, HC=C-CH-C**H**), 3.71 (t, 1H, *J* = 2.8 Hz,

BnOC**H**), 3.59 (dd, 1H, *J* = 10.6, 8.1 Hz, H_3C-C-CH_2-CH_2-C**H**), 2.87 (d, 1H, *J* = 11.4 Hz, HC=C-C**H**-CH), 2.71 (dd, 1H, *J* = 13.4, 8.1 Hz, 1 × **H**$_2$C-CH=C), 2.34 (ddd, 1H, *J* = 8.6, 3.5, 3.5 Hz, H_3C-CH-C**H**), 2.20–2.08 (m, 1H, 1 × H_3C-C-CH_2-C**H**$_2$), 2.02–1.84 (m, 4H, 1 × H_3C-C-CH_2-C**H**$_2$, 1 × **H**$_2$C-CH=C, 1 × BnOCH-CH_2-C**H**$_2$, 1 × H_3C-C-C**H**$_2$-CH_2), 1.81–1.60 (m, 3H, 1 × H_3C-C-C**H**$_2$-CH_2, BnOCH-C**H**$_2$), 1.52–1.45 (m, 4H, C**H**$_3$-COTES, 1 × BnOCH-CH_2-C**H**$_2$), 1.44–1.39 (m, 4H, C**H**$_3$-COTES, H_3C-C**H**), 1.02 (d, 3H, *J* = 6.5 Hz, **H**$_3$C-CH), 0.98-0.90 (m, 18 H, 2 × Si{CH_2C**H**$_3$}$_3$), 0.84 (d, 3H, *J* = 6.7 Hz, **H**$_3$C-CH), 0.65–0.53 (m, 12H, 2 × Si{C**H**$_2$$CH_3$}$_3$) ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.7 (**C**), 138.7 (**C**), 129.4 (H**C**=C), 128.2 (**C**H *Ph*), 128.0 (**C**H *Ph*), 127.0 (**C**H *Ph*), 79.7 (HC=C-CH-**C**H), 79.3 (BnO**C**H), 78.9 (H_3C-C-CH_2-CH_2-C**H**), 78.0 (H_3C-**C**OTES), 74.9 (H_3C-**C**OTES), 68.6 (OC**H**$_2$Ph), 43.1 (HC=C-**C**H-CH), 38.8 (H_3C-CH-C**H**), 36.0 (**H**$_2$C-CH=C), 33.0 (H_3C-C-**C**H_2-CH_2), 31.8 (H_3**C**-COTES), 28.1 (H_3C-**C**H), 27.8 (H_3**C**-COTES), 27.0 (BnOCH-**C**H_2), 22.2 (H_3**C**-CH), 20.6 (H_3**C**-CH), 19.4 (H_3C-C-CH_2-**C**H_2), 17.9 (BnOCH-CH_2-**C**H_2), 7.1 (2 × Si{CH_2**C**H_3}$_3$), 6.9 (Si{C**H**$_2$$CH_3$}$_3$), 6.8 (Si{C**H**$_2$$CH_3$}$_3$). HRMS (CI+) mass calc. for $C_{38}H_{66}O_4Si_2$ 643.4578 $(M+H)^+$, found 643.4577.

Epoxide (277)

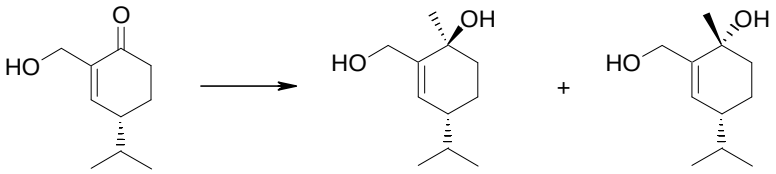


275 **277**

m-CPBA (6 mg, 0.04 mmol) was added to a solution of alkene **275** (15 mg, 0.023 mmol) in dry CH_2Cl_2 (1.8 mL) at rt under argon. The mixture was stirred for 45 min and then *m*-CPBA (6 mg, 0.04 mmol) was added again and the mixture stirred for an

additional 1 h at rt. The reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$ solution (2 mL) and extracted with Et_2O (2 × 10 mL). The organic extracts were combined, washed with saturated aqueous $NaHCO_3$ (2 × 10 mL) and brine (1 × 10 mL), dried ($MgSO_4$), filtered and evaporated under vacuum to give crude epoxide **277** (15 mg, 100% crude). The epoxide was used in the next step without any further purification. R_f = 0.50 (petroleum ether/EtOAc, 19:1). ν_{max} ($CHCl_3$) 3442, 2956, 2875, 1007 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.23 (m, 5H, C**H** *Bn*), 4.82 (d, 1H, *J* = 11.6 Hz, 1 × OC**H**$_2$Ph), 4.46 (d, 1H, *J* = 11.6 Hz, 1 × OC**H**$_2$Ph), 4.28 (d, 1H, *J* = 11.9 Hz, H_3C-C-C**H**-CH), 3.60 (dd, 1H, *J* = 10.2, 7.1 Hz, H_3C-C-C**H**-CH_2), 2.85–2.79 (m, 2H, BnOC**H**, C**H**O-C-), 2.30 (d, 1H, *J* = 10.5 Hz, H_3C-CH-C**H**), 2.09–1.30 (m, 19 H, H_3C-CH-C**H**, H_3C-C-CH-C**H**, **H**$_2$C-CHO-C-, H_3C-C-CH-C**H**$_2$, H_3C-C-CH-CH_2-C**H**$_2$, 2 × **H**$_3$C-COTES, BnOCH-C**H**$_2$, BnOCH-CH_2-C**H**$_2$, H_3C-C**H**), 1.04–0.78 (m, 24 H, **H**$_3$C-C**H**-C**H**, 2 × Si{CH_2C**H**$_3$}$_3$), 0.67–0.51 (m, 12 H, 2 × Si{C**H**$_2$$CH_3$}$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.1 (**C**), 128.2 (CH *Ph*), 127.6 (CH *Ph*), 127.3 (CH *Ph*), 81.1 (BnOC**H**), 77.4 (H_3C-C-C**H**-CH_2), 77.2 (H_3C-C-C**H**-CH), 75.6 (H_3C-**C**OTES), 74.9 (H_3C-**C**OTES), 70.8 (**C**H_2OPh), 61.4 (H_2C-CHO-**C**-), 59.6 (H_2C-**C**HO-C-), 42.1 (H_3C-C-CH-**C**H), 40.2 (H_3C-CH-**C**H), 37.8 (**C**H_2), 33.1 (**C**H_3), 32.5 (**C**H_2), 30.3 (**C**H_2), 29.7 (**C**H_3), 29.4 (**C**H_2), 27.3 (**C**H_2), 26.2 (H_3C-**C**H), 23.8 (**C**H_3), 21.9 (**C**H_2), 21.2 (**C**H_2), 18.6 (**C**H_3), 17.2 (**C**H_3), 7.1 (**C**H_2), 7.1 (**C**H_2), 6.8 (**C**H_3), 6.8 (**C**H_3). HRMS (CI+) mass calc. for $C_{38}H_{66}O_5Si_2$ 659.4534 $(M+H)^+$, found 659.4527.

(1*S*,4*R*)-2-Hydroxymethyl-4-isopropyl-1-methyl-cyclohex-2-enol (289) and (1*R*,4*R*)-2-Hydroxymethyl-4-isopropyl-1-methyl-cyclohex-2-enol (288)

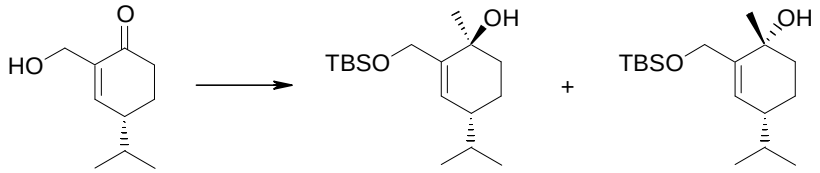


(*R*)-238 **289** **288**

Trimethylaluminium (3 mL of a 2 M solution in hexanes, 6 mmol) was added dropwise to a solution of ketone **(*R*)-238** (200 mg, 1.17 mmol) in dry toluene (20 mL) at –78 °C under argon. The mixture was stirred for 18 h being allowed to slowly warm to rt over this period. The reaction was quenched by careful addition of a saturated aqueous NH_4Cl (5 mL) at 0 °C. The layers were separated and the aqueous layer was extracted with Et_2O (2 × 20 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum ether/EtOAc, 1:1) gave major diol **289** (140 mg, 65%) and minor diol **288** (27 mg, 13%). R_f (**289**) = 0.19 (petroleum ether/EtOAc, 1:1) ^{1}H NMR (**289**, 400 MHz, $CDCl_3$) δ 5.59 (s, 1H), 4.45 (d, 1H, *J* = 12.1 Hz), 4.00 (d, 1H, *J* = 12.1 Hz), 2.98 (bs, 2H), 2.08–2.01 (m, 1H), 1.88–1.80 (m, 1H), 1.79–1.68 (m, 2H), 1.63–1.53 (m, 1H), 1.41–1.34 (m, 4H), 0.88 (d, 3H, *J* = 6.7 Hz), 0.85 (d, 3H, *J* = 6.7 Hz) ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.9 (quat.), 130.9 (**C**H), 72.6 (quat.), 65.2 (**C**H_2), 42.1 (**C**H), 39.5 (**C**H_2), 31.8 (**C**H), 27.6 (**C**H_3), 23.2 (**C**H_2), 19.6 (**C**H_3), 19.2 (**C**H_3). R_f (**288**) = 0.23 (petroleum ether/EtOAc, 1:1). ^{1}H NMR (**288**, 400 MHz, $CDCl_3$) δ 5.67 (s, 1H), 4.49 (s, 1H), 4.00 (t, 1H, *J* = 12.1 Hz), 2.98 (bs, 2H), 2.00–1.97 (m, 1H), 1.88–1.80 (m, 1H), 1.79–1.68 (m, 2H), 1.63–1.53 (m, 1H), 1.41–1.34 (m, 4H), 0.93 (d, 3H, *J* = 6.9 Hz), 0.91 (d, 3H, *J* = 6.9 Hz). Crystal data for **288**: $C_{11}H_{20}O_2$, M_r = 184.27, crystal dimensions 1.00 × 0.30 × 0.07 mm^3, monoclinic, space group $P2_1$, *a* = 8.682(2), *b* = 6.764(2), *c* = 9.255(2) Å, *α* = 90(/), *β* = 98.746(4), *γ* = 90(/)°, *V* = 537.2(4) Å^3, *Z* = 2, ρ_{calcd} = 1.139 Mg.m^{-3}, μ($Mo_{K\alpha}$) 0.076

mm^{-1}, T = 150(2) K, 3342 reflections collected of which 1325 independent, 2θmax = 55°. Structure solved by direct methods (SHELXS-97) and refined by full-matrix least square against F^2 (SHELXTL), R_1 = 0.0356, wR_2 = 0.0915, 120 parameters.

(1*S*,4*R*)-2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-4-isopropyl-1-methyl-cyclohex-2-enol (291) and (1*R*,4*R*)-2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-4-isopropyl-1-methyl-cyclohex-2-enol (290)



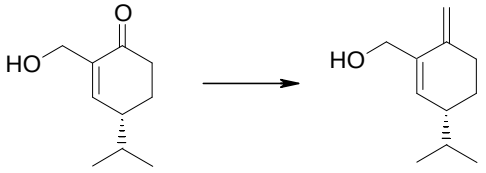
(*R*)-238 **291** **290**

TBSCl (177 mg, 1.17 mmol) and imidazole (125 mg, 1.84 mmol) were added to a solution of alcohol **(*R*)-238** (125 mg, 0.744 mmol) in dry DMF (6 mL) at rt under argon. The mixture was stirred at rt for 1.5 h, then diluted with Et_2O (6 mL) and washed with water (5 × 12 mL). The aqueous layers were combined and extracted with Et_2O (1 × 6 mL). The organic layers were combined, dried ($MgSO_4$), filtered and evaporated under vacuum to give a crude silyl protected alcohol (223 mg,). MeLi (1.4 mL of a 1.6 M solution in Et_2O) was added dropwise to a solution of crude TBS alcohol (140 mg, c.a. 0.46 mmol) in dry toluene (8.5 mL) at –78 °C under argon. The resulting mixture was stirred at –78 °C for 1 h. It was quenched with water (10 mL) at 0 °C. Et_2O (10 mL) was added, the layers were separated and the aqueous layer was extracted with Et_2O (2 × 10 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum ether/EtOAc 19:1) gave major alcohol **291** (65 mg, 47%) and minor alcohol **290** (31 mg, 23%) as colourless oils. R_f (**291**) = 0.31 (petroleum ether/EtOAc, 9:1) ν_{max} ($CHCl_3$) 3480, 2956, 2931, 2857, 836 cm^{-1}. ^1H

NMR (**291**, 400 MHz, $CDCl_3$) δ 5.53 (d, 1H, *J* = 1.5 Hz, C=C**H**), 4.50 (ddd, 1H, *J* = 12.0, 2.0, 2.0 Hz, 1 × C**H**$_2$OTBS), 4.10 (d, 1H, *J* = 12.0 Hz, 1 × C**H**$_2$OTBS), 3.66 (bs, 1H, O**H**), 2.03–1.95 (m, 1H, H_3C-CH-C**H**), 1.83–1.66 (m, 3H, H_3C-C-C**H**$_2$ and 1 × H_3C-C-CH_2-C**H**$_2$), 1.55 (sept, 1H, *J* = 6.5 Hz, H_3C-C**H**), 1.37–1.31 (m, 4H, **H**$_3$C-C-OH and 1 × H_3C-C-CH_2-C**H**$_2$), 0.90 (s, 9H, Si-C-{C**H**$_3$}$_3$), 0.87 (d, 3H, *J* = 6.5 Hz, **H**$_3$C-CH), 0.84 (d, 3H, *J* = 6.5 Hz, **H**$_3$C-CH), 0.09 (s, 3H, Si-C**H**$_3$), 0.09 (s, 3H, Si-C**H**$_3$) ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.0 (**C**=CH), 129.0 (C=**C**H), 71.3 (H_3C-**C**-OH), 65.9 (**C**H_2OTBS), 42.0 (H_3C-CH-**C**H), 38.6 (H_3C-C-**C**H_2), 31.8 (H_3C-**C**H), 27.8 (H_3**C**-COH), 25.8 (Si-C-(**C**H_3)$_3$), 22.9 (H_3C-C-CH_2-**C**H_2), 19.8 (H_3**C**-CH), 19.4 (H_3**C**-CH), 18.1 (Si-**C**-$(CH_3)_3$), –5.4 (Si-**C**H_3), –5.6 (Si-**C**H_3) .

R_f (**290**) = 0.44 (petroleum ether/EtOAc, 9:1) ν_{max} ($CHCl_3$) 3500, 2956, 2930, 2857, 836 cm^{-1}. ^{1}H NMR (**290**, 400 MHz, $CDCl_3$) δ 5.57 (s, 1H, C=C**H**), 4.51 (ddd, 1H, *J* = 11.5, 2.9 Hz, 1.3 Hz, 1 × C**H**$_2$OTBS), 4.02 (ddd, 1H, *J* = 11.5, 1.1, 1.1 Hz, 1 × C**H**$_2$OTBS), 3.27 (s, 1H, O**H**), 1.87–1.79 (m, 2H, H_3C-CH-C**H** and 1 × H_3C-C-C**H**$_2$), 1.64 (sept, 1H, *J* = 6.9 Hz, H_3C-C**H**), 1.54–1.42 (m, 3H, 1 × H_3C-C-C**H**$_2$ and H_3C-C-CH_2-C**H**$_2$), 1.34 (s, 3H, **H**$_3$C-C-OH), 0.99–0.83 (m, 15H, 2 × **H**$_3$C-CH and Si-C-{C**H**$_3$}$_3$), 0.10 (s, 3H, Si-C**H**$_3$), 0.09 (s, 3H, Si-C**H**$_3$) ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.3 (**C**=CH), 130.6 (C=**C**H), 69.1 (H_3C-**C**-OH), 66.5 (**C**H_2OTBS), 42.5 (H_3C-CH-**C**H), 38.1 (H_3C-C-**C**H_2), 31.9 (H_3C-**C**H), 28.0 (H_3**C**-COH), 25.8 (Si-C-{**C**H_3}$_3$), 21.4 (H_3C-C-CH_2-**C**H_2), 19.7 (H_3**C**-CH), 19.3 (H_3**C**-CH), 18.1 (Si-**C**-{CH_3}$_3$), –5.4 (Si-**C**H_3), –5.5 (Si-**C**H_3).

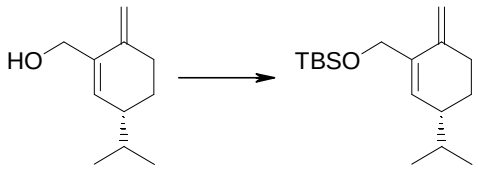
((*R*)-3-Isopropyl-6-methylene-cyclohex-1-enyl)-methanol (292)



(*R*)-238 **(*R*)-292**

Methyltriphenylphosphonium bromide (1.08 g, 3.01 mmol) was added to a suspension of KO*t*Bu (338 mg, 3.01 mmol) in dry toluene (11 mL) at rt under argon. The yellow solution was stirred at reflux for 1 h. A solution of ketone **(*R*)-238** (57 mg, 0.33 mmol) in dry toluene (11 mL) was then added and the mixture was stirred at reflux for 1.5 h. The reaction mixture was cooled to rt and water (20 mL) was added. The mixture was then extracted with Et_2O (3 × 15 mL) and the organic layers were combined, dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum ether/EtOAc, 9:1) gave diene **(*R*)-292** (38 mg, 72%) as a colourless oil. R_f = 0.61 (petroleum ether/EtOAc, 3:2). $[\alpha]_D$ +1.3 (*c* = 0.30, $CHCl_3$, 20 °C). ν_{max} ($CHCl_3$) 3346, 2956, 2932, 2870 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.87 (s, 1H, C=C**H**), 4.97 (s, 1H, 1 × $\mathbf{H}_2C$=C), 4.83 (s, 1H, 1 × $\mathbf{H}_2C$=C), 4.27 (ddd, 1H, *J* = 12.5, 1.3, 1.3 Hz, 1 × C$\mathbf{H}_2$OH), 4.19 (ddd, 1H, *J* = 12.5, 1.1, 1.1 Hz, 1 × C$\mathbf{H}_2$OH), 2.46 (dt, 1H, *J* = 14.5, 4.9 Hz, 1 × H_2C=C-C$\mathbf{H}_2$), 2.34–2.25 (m, 1H, 1 × H_2C=C-C$\mathbf{H}_2$), 2.10 (bs, 1H, H_3C-CH-C**H**), 1.81–1.72 (m, 1H, 1 × H_2C=C-CH_2-C$\mathbf{H}_2$), 1.71–1.59 (m, 2H, H_3C-C**H** and CH_2O**H**), 1.37 (dddd, 1H, *J* = 13.0, 13.0, 10.3, 3.8 Hz, 1 × H_2C=C-CH_2-C$\mathbf{H}_2$), 0.92 (d, 3H, *J* = 6.8 Hz, $\mathbf{H}_3C$-CH), 0.89 (d, 3H, *J* = 6.8 Hz) ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.2 (**C**), 136.2 (**C**), 133.3 (C=**C**H), 107.4 (H_2**C**=C), 64.2 (**C**H_2OH), 42.7 (H_3C-CH-**C**H), 32.0 (H_2C=C-**C**H_2), 32.0 (H_3C-**C**H), 25.8 (H_2C=C-CH_2-**C**H_2), 19.7 (H_3**C**-CH), 19.4 (H_3**C**-CH). HRMS (EI+) mass calc. for $C_{11}H_{18}O$ 165.1358 $(M+H)^+$, found 165.1357.

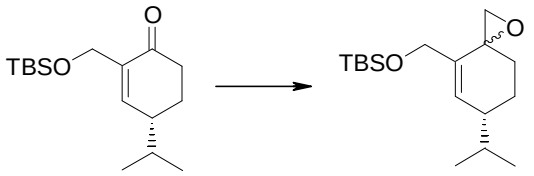
***tert*-Butyl-((*R*)-3-isopropyl-6-methylene-cyclohex-1-enylmethoxy)-dimethyl-silane (294)**



(*R*)-292 **(*R*)-294**

TBSCl (39 mg, 0.26 mmol) and imidazole (27 mg, 0.40 mmol) were added to a solution of alcohol **(*R*)-292** (25 mg, 0.16 mmol) in dry DMF (1 mL) at rt under argon. The mixture was stirred at rt for 2 h, then diluted with Et_2O (5 mL) and washed with water (5 × 10 mL). The aqueous layers were combined and extracted with Et_2O (1 × 5 mL). The organic layers were combined, dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum ether) gave diene **(*R*)-294** (38 mg, 84%) as a colourless oil. R_f = 0.79 (9:1 petroleum ether/EtOAc). $[\alpha]_D$ –29 (*c* = 0.50, $CHCl_3$, 20 °C). ν_{max} ($CHCl_3$) 2930, 2857, 1080 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.93 (s, 1H, C=C**H**), 4.79 (bs, 1H, 1 × $\mathbf{H}_2C$=C), 4.72 (bs, 1H, 1 × $\mathbf{H}_2C$=C), 4.35 (ddd, 1H, *J* = 13.5, 2.0, 2.0 Hz, 1 × C$\mathbf{H}_2$OTBS), 4.30 (ddd, 1H, *J* = 13.5, 2.5, 1.7 Hz, 1 × C$\mathbf{H}_2$OTBS), 2.42 (dt, 1H, *J* = 14.5, 4.1 Hz, 1 × H_2C=C-C$\mathbf{H}_2$), 2.34–2.24 (m, 1H, 1 × H_2C=C-C$\mathbf{H}_2$), 2.13–2.05 (m, 1H, H_3C-CH-C**H**), 1.80–1.71 (m, 1H, 1 × H_2C=C-CH_2-C$\mathbf{H}_2$), 1.70–1.60 (m, 1H, H_3C-C**H**), 1.42–1.30 (m, 1H, 1 × H_2C=C-CH_2-C$\mathbf{H}_2$), 0.95–0.87 (m, 15H, Si(C{C$\mathbf{H}_3$}$_3$) and 2 × $\mathbf{H}_3C$-CH), 0.08 (s, 6H, Si{C$\mathbf{H}_3$}$_2$) ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.4 (**C**), 135.3 (**C**), 130.4 (C=**C**H), 106.1 (H_2**C**=C), 63.1 (**C**H_2OTBS), 42.6 (H_3C-CH-**C**H), 32.3 (H_2C=C-**C**H_2), 32.2 (H_3C-**C**H), 26.2 (H_2C=C-CH_2-**C**H_2), 26.0 (Si(C{**C**H_3}$_3$), 19.7 (H_3**C**-CH), 19.6 (H_3**C**-CH), 18.4 (Si**C**{CH_3}$_3$), –5.3 (Si{**C**H_3}$_2$). HRMS (CI+) mass calc. for $C_{17}H_{32}OSi$ 281.2301 $(M+H)^+$, found 281.2293.

***tert*-Butyl-((*R*)-6-isopropyl-1-oxa-spiro[2.5]oct-4-en-4-ylmethoxy)-dimethyl-silane (295)**

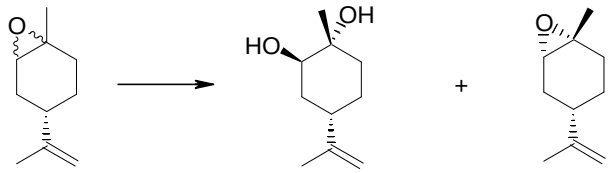


(*R*)-294 **295**

KHMDS (0.70 mL of a 0.5 M solution in toluene, 0.35 mmol) was added dropwise to a solution of trimethylsulfonium iodide (83 mg, 0.41 mmol) in dry THF (1 mL) at 0 °C under Ar. After 30 min, a solution of crude ketone **(*R*)-294** (76 mg, 0.27 mmol) in dry THF (0.5 mL) was added dropwise and the mixture was stirred at 0 °C for 30 min. The reaction was quenched by the addition of water (5 mL) and allowed to warm to rt. The mixture was extracted with Et_2O (2 × 10 mL) and the organic extracts were then combined, dried ($MgSO_4$), filtered and evaporated under vacuum to give crude epoxide **295** (80 mg, 100%) as a yellow oil (6:1 mixture of diastereoisomers). It was used without any further purification. R_f = 0.51 (petroleum ether/EtOAc, 9:1). ν_{max} ($CHCl_3$) 2956, 2858, 1078 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.07 (dt, 1H, *J* = 2.6, 1.3 Hz, C=C**H** minor), 6.00 (dt, 1H, *J* = 3.0, 1.5 Hz, C=C**H** major), 4.00–3.90 (m, 2H, C**H**$_2$OTBS major), 3.90–3.85 (m, 2H, C**H**$_2$OTBS minor), 3.18 (d, 1H, *J* = 4.6 Hz, 1 × C**H**$_2$OC minor), 3.02 (dd, 1H, *J* = 5.1, 1.5 Hz, 1 × C**H**$_2$OC major), 2.71 (d, 1H, *J* = 4.6 Hz, 1 × C**H**$_2$OC, minor), 2.67 (d, 1H, *J* = 5.1 Hz, 1 × C**H**$_2$OC major), 2.15–1.49 (m, 12H, H_3C-CH-C**H** minor, H_3C-C**H** minor, C**H**$_2$-CH_2 minor, CH_2-C**H**$_2$ minor, H_3C-CH-C**H** major, H_3C-C**H** major, C**H**$_2$-CH_2 major, CH_2-C**H**$_2$ major), 0.95–0.86 (m, 30 H, **H**$_3$C-CH-C**H**$_3$ minor, SiC{C**H**$_3$}$_3$ minor, **H**$_3$C-CH-C**H**$_3$ major, SiC{C**H**$_3$}$_3$ major), 0.06–0.02 (m, 12H, Si{C**H**$_3$}$_2$ minor, Si{C**H**$_3$}$_2$ major) ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.1 (C=**C**H minor), 135.5 (**C**=CH major), 134.3 (**C**=CH minor), 133.0 (C=**C**H major), 61.7 (C**H**$_2$OTBS

minor), 61.1 (C**H**$_2$OTBS major), 57.8 (CH_2O**C** major), 55.4 (CH_2O**C** minor), 54.3 (**C**H_2OC major), 52.8 (**C**H_2OC minor), 42.2 (H_3C-CH-**C**H minor), 42.1 (H_3C-CH-**C**H major), 32.3 (**C**H_2 minor), 32.0 (H_3C-**C**H major), 31.9 (**C**H_2 major), 30.3 (H_3C-**C**H minor), 25.9 (SiC{**C**H_3}$_3$ major), 25.8 (SiC{**C**H_3}$_3$ minor), 24.9 (**C**H_2 major), 23.4 (**C**H_2 minor), 19.8 (H_3**C**-CH major), 19.7 (H_3**C**-CH minor), 19.6 (H_3**C**-CH major), 19.5 (H_3**C**-CH minor), 18.3 (Si**C**{CH_3}$_3$ minor), 18.3 (Si**C**{CH_3}$_3$ major), –5.1 (Si{**C**H_3}$_2$ minor), –5.3 (Si{**C**H_3}$_2$ major), –5.4 (Si{**C**H_3}$_2$ major), –5.4 (Si{**C**H_3}$_2$ minor). HRMS (CI+) mass calc. for $C_{17}H_{32}O_2Si$ 297.2250 $(M+H)^+$, found 297.2249.

(1*R*,2*R*,4*S*)-4-Isopropenyl-1-methyl-cyclohexane-1,2-diol (305)

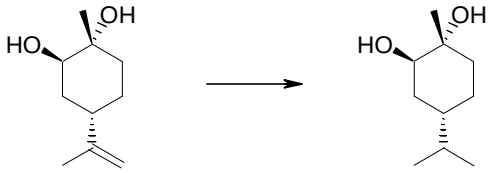


304 **305** **326**

A mixture of (*S*)-(–)-limonene oxide **304** (7.8 g, 51 mmol), pyrazole (590 mg, 8.67 mmol) and deionised water (27.7 mL) was heated at reflux temperature for 5 h. After cooling to rt, the mixture was extracted with EtOAc (4 × 40 mL). The organic layers were combined, dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum ether/EtOAc, 4:1 to 3:2) gave diol **305** (4.18 g, 48%) along with epoxide **326** (3.70 g, 48%). R_f (**305**) = 0.24 (petroleum ether/EtOAc, 3:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74 (s, 2H), 3.65 (dd, 1H, *J* = 3.3, 3.3 Hz), 2.32–2.22 (m, 1H), 1.94 (ddd, 1H, *J* = 14.6, 11.8, 2.8 Hz), 1.82–1.64 (m, 5H), 1.61–1.50 (m, 3H), 1.27 (s, 3H). Spectroscopic data for diol **305** were in accordance with the literature.[77]

^{1}H NMR for **326** (400 MHz, $CDCl_3$) δ 4.71 (s, 2H), 3.70 (dd, 1H, J = 11.8, 4.4 Hz), 2.09–1.99 (m, 1H), 1.98–1.89 (m, 1H), 1.85 (td, 1H, J = 12.8, 3.0 Hz), 1.75–1.64 (m, 4H), 1.60–1.50 (m, 1H), 1.42–1.22 (m, 5H).

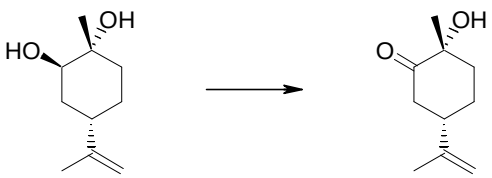
(1*R*,2*R*,4*S*)-4-Isopropyl-1-methyl-cyclohexane-1,2-diol (327)



305 **327**

Wilkinson's catalyst (870 mg, 0.940 mmol) was added to a solution of alkene **305** (787 mg, 4.62 mmol) in dry toluene (15 mL) at rt under Ar and the resulting mixture was hydrogenated at rt under atmospheric pressure of hydrogen for 6 h. The solvent was removed under vacuum and the brown residue was purified by silica gel chromatography (petroleum ether/EtOAc, 1:1) to give diol **327** (701 mg, 88%) as a thick, colourless oil. R_f = 0.19 (petroleum ether/EtOAc, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60 (t, 1H, *J* = 3.5 Hz, C**H**OH), 1.76–1.27 (m, 10H, CHOH-C**H**$_2$, H_3C-C**H**, H_3C-CH-C**H**, H_3C-C-C**H**$_2$, H_3C-C-CH$_2$-C**H**$_2$, CHO**H**, CO**H**), 1.25 (s, 3H, **H**$_3$C-C-OH), 0.89 (d, 3H, *J* = 5.8 Hz, **H**$_3$C-CH), 0.87 (d, 3H, *J* = 5.8 Hz, **H**$_3$C-CH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 74.0 (**C**HOH), 71.8 (H_3C-**C**OH), 36.8 (**C**H), 33.7 (**C**H$_2$), 32.6 (**C**H$_2$), 31.4 (**C**H), 26.1 (H_3**C**-COH), 24.3 (**C**H$_2$), 20.1 (H_3**C**-CH), 20.0 (H_3**C**-CH). HRMS (CI+) mass calc. for $C_{10}H_{20}O_2$ 169.1229 $(M+H)^+$, found 169.1225.

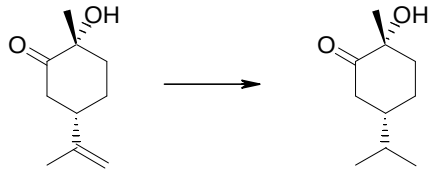
(2*R*,5*S*)-2-Hydroxy-5-isopropenyl-2-methyl-cyclohexanone (307)



305 **307**

IBX (7.85 g, 28.2 mmol) was added to a solution of diol **305** (1.60 g, 9.40 mmol) in EtOAc (56 mL) and the resulting mixture was stirred at reflux temperature for 3.5 h. The mixture was filtered and the filtrate was evaporated under vacuum. Silica gel chromatography (petroleum ether/EtOAc, 1:1) gave ketone **307** (1.43 g, 89%) as a yellow oil. R_f = 0.45 (1:1 petroleum ether/EtOAc). $[\alpha]_D$ +50 (*c* = 0.33, $CHCl_3$, 23 °C). ν_{max} ($CHCl_3$) 3436, 2935, 1714, 1644 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.84 (s, 1H, 1 × C**H**$_2$-C-CH_3), 4.69 (s, 1H, 1 × C**H**$_2$-C-CH_3), 3.36 (bs, 1H, CO**H**), 2.78 (ddd, 1H, *J* = 6.8, 5.2, 1.8 Hz, 1 × C**H**$_2$), 2.63 (dd, 1H, *J* = 9.0, 4.5 Hz, H_3C-C-C**H**), 2.57 (dd, 1H, *J* = 13.7, 5.8 Hz, 1 × C**H**$_2$), 2.00–1.89 (m, 1H, 1 × C**H**$_2$), 1.89–1.74 (m, 3H, C**H**$_2$ and 1 × C**H**$_2$), 1.71 (s, 3H, **H**$_3$C-C-CH), 1.35 (s, 3H, **H**$_3$C-COH) ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.6 (**C**=O), 145.9 (CH_2-**C**-CH_3), 112.1 (**C**H_2-C-CH_3), 75.7 (H_3C-**C**OH), 43.9 (H_3C-C-**C**H), 41.4 (**C**H_2), 37.0 (**C**H_2), 25.2 (H_3**C**-COH), 25.1 (**C**H_2), 21.6 (H_3**C**-C-CH). HRMS (CI+) mass calc. for $C_{10}H_{16}O_2$ 169.1229 $(M+H)^+$, found 169.1228.

(2*R*,5*S*)-2-Hydroxy-5-isopropyl-2-methyl-cyclohexanone (328)

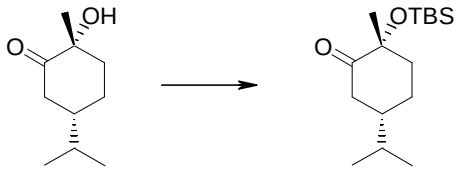


307 **328**

Wilkinson's catalyst (393 mg, 0.425 mmol) was added to a solution of alkene **307** (1.43 g, 8.50 mmol) in dry toluene (27 mL) and the resulting mixture was stirred under H_2 for 24 h. The solvent was removed under vacuum and the brown residue was purified by silica gel chromatography (petroleum ether/EtOAc, 3:2) to give ketone **328** (1.37 g, 8.0 mmol, 95%) as a colourless oil. R_f = 0.51 (petroleum ether/EtOAc, 3:2). $[\alpha]_D$ +36 (*c* = 0.33, $CHCl_3$, 23 °C). ν_{max} ($CHCl_3$) 3436, 2959, 1714 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.17 (s, 1H, H_3C-CO**H**), 2.63 (dd, 1H, *J*

= 13.3, 6.2 Hz, 1 × O=C-C**H**$_2$), 2.49 (ddd, 1H, *J* = 13.3, 5.0, 1.2 Hz, 1 × O=C-C**H**$_2$), 1.93–1.70 (m, 4H, H_3C-COH-C**H**$_2$ and H_3C-COH-CH_2-C**H**$_2$), 1.69–1.64 (m, 1H, H_3C-CH-C**H**), 1.47 (sept, 1H, *J* = 6.7 Hz, H_3C-C**H**), 1.36 (s, 3H, **H**$_3$C-COH), 0.91 (d, 3H, *J* = 6.7 Hz, **H**$_3$C-CH), 0.89 (d, 3H, *J* = 6.7 Hz, **H**$_3$C-CH) ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.8 (C=O), 75.7 (H_3C-**C**OH), 45.3 (H_3C-CH-**C**H), 40.9 (O=C-**C**H_2), 38.4 (**C**H_2), 29.4 (H_3C-**C**H), 25.0 (H_3**C**-COH), 24.8 (**C**H_2), 20.3 (H_3**C**-CH), 20.2 (H_3**C**-CH). HRMS (CI+) mass calc. for $C_{10}H_{18}O_2$ 171.1385 $(M+H)^+$, found 171.1381.

(2*R*,5*S*)-2-(*tert*-Butyldimethylsilanyloxy)-5-isopropyl-2-methylcyclohexanone (306)

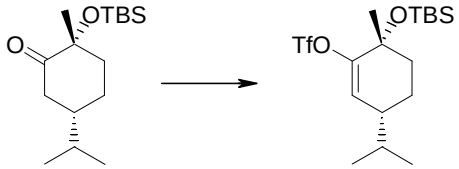


328 **306**

2,6-Lutidine (2.5 mL, 22 mmol) and TBSOTf (2.8 mL, 12 mmol) were successively added to a solution of ketone **328** (822 mg, 4.83 mmol) in dry CH_2Cl_2 (20 mL) at –78 °C under Ar. The resulting mixture was stirred at –78 °C for 6 h. The reaction was quenched by the additon of water (20 mL) and then left to warm to rt. Saturated aqueous $CuSO_4$ solution (30 mL) was added and the layers were separated. The organic layer was washed with further saturated aqueous $CuSO_4$ solution (3 × 30 mL) and water (1 × 30 mL), then dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum ether, 100%) gave ketone **306** (1.32 g, 96%) as a colourless oil. R_f = 0.76 (petroleum ether/EtOAc, 7:3). $[\alpha]_D$ –63 (*c* = 0.33, $CHCl_3$, 22 °C). ν_{max} ($CHCl_3$) 2957, 2857, 1723 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.71 (dd, 1H, *J* = 12.4, 12.4 Hz, 1 × O=C-C**H**$_2$), 2.17 (ddd, 1H, *J* = 12.4, 2.1, 1.3 Hz, 1 × O=C-C**H**$_2$), 2.01 (dt, 1H, *J* = 13.9, 3.3 Hz, 1 × C**H**$_2$), 1.75 (ddd, 1H,

J = 16.3, 13.0, 3.4 Hz, 1 × C**H**$_2$), 1.60–1.44 (m, 3H, 1 × C**H**$_2$, O=C-CH$_2$-C**H**, H$_3$C-C**H**-CH$_3$), 1.43–1.33 (m, 1H, 1 × C**H**$_2$), 1.27 (s, 3H, **H**$_3$C-C-OTBS), 0.89 (s, 9H, Si-C-{C**H**$_3$}$_3$), 0.87 (d, 6H, *J* = 2.0 Hz, **H**$_3$C-CH-C**H**$_3$), 0.09 (s, 3H, Si-C**H**$_3$), 0.00 (s, 3H, Si-C**H**$_3$) ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.6 (O=**C**), 77.4 (H$_3$C-**C**-OTBS), 46.8 (O=C-CH$_2$-**C**H), 41.7 (**C**H$_2$), 41.1 (O=C-**C**H$_2$), 32.8 (H$_3$C-**C**H), 25.9 (H$_3$**C**-C-OTBS), 23.9 (**C**H$_2$), 23.6 (Si-C{**C**H$_3$}$_3$), 19.6 (H$_3$**C**-CH), 19.3 (H$_3$**C**-CH), 18.2 (Si-**C**{CH$_3$}$_3$), –2.0 (Si-**C**H$_3$), –3.2 (Si-**C**H$_3$). HRMS (CI+) mass calc. for $C_{16}H_{32}O_2Si$ 285.2250 $(M+H)^+$, found 285.2251.

(3*R*,6*R*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-3-isopropyl-6-methyl-cyclohex-1-en-ol trifluoromethanesulfonate (303)

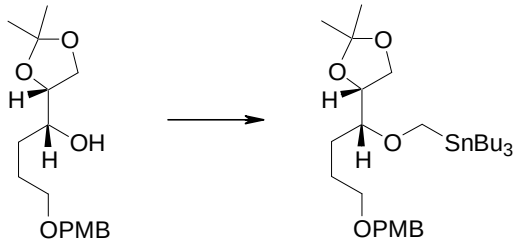


306 **303**

KHMDS (3.0 mL of a 0.5 M solution in toluene, 1.5 mmol) was added dropwise to a solution of ketone **306** (170 mg, 0.598 mmol) and Commins' reagent (469 mg, 1.19 mmol) at –20 °C and the resulting mixture was stirred at that temperature for 30 min. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution (15 mL) and the mixture was allowed to warm to rt. Water (15 ml) was added and the mixture was extracted with Et_2O (3 × 25 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and evaporated under vacuum. The residue was taken up in petroleum ether and filtrated. The filtrate was evaporated under vacuum to give triflate **303** (208 mg, 90%) as a yellow oil which was used without any further purification. R_f = 0.67 (petroleum ether/EtOAc, 19:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.06 (d, 1H, J = 1.4 Hz), 2.73 (t, 1 H, J = 12.4 Hz), 2.22–2.15 (m,

1H), 2.10–1.99 (m, 2H), 1.92–1.85 (m, 1H), 1.81–1.71 (m, 1H), 1.27 (s, 3H), 0.91–0.88 (m, 15H), 0.11 (s, 3H), 0.00 (s, 3H).

Tributyl-[(*R*)-1-((*R*)-2,2-dimethyl-[1,3]dioxolan-4-yl)-4-(4-methoxy-benzyloxy)-butoxymethyl]-stannane (302)

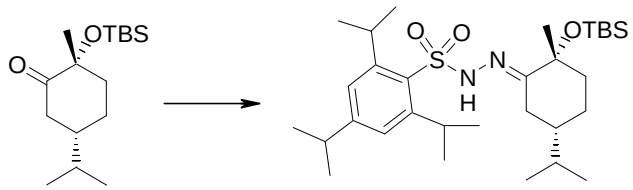


203 **302**

A solution of alcohol **203** (95 mg, 0.31 mmol) in dry THF (0.4 mL) was added dropwise at 0 °C to a suspension of petroleum ether washed KH (86 mg of 30% suspension in oil, 0.64 mmol) in dry THF (4 mL). The mixture was stirred for 3.5 h being allowed to warm to rt over this period. A solution of ICH_2SnBu_3 (197 mg, 0.46 mmol) in dry THF (0.2 mL) was then added dropwise at 0 °C. The mixture was stirred for an additional 18 h being allowed to warm to rt over this period. It was quenched with saturated aqueous NH_4Cl solution (5 mL) at 0 °C and extracted with Et_2O (2 × 20 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum ether/EtOAc, 4:1) gave the stannane **302** (138 mg, 73%) as a colourless oil. R_f = 0.69 (petroleum ether/EtOAc, 3:2). ν_{max} ($CHCl_3$) 2955, 2926, 1870 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, 2H, *J* = 8.8 Hz, C**H** *Ar*), 6.87 (d, 2H, *J* = 8.8 Hz, C**H** *Ar*), 4.43 (s, 2H, OC**H**$_2$PMP), 4.20 (dd, 1H, *J* = 6.7, 6.7 Hz, OC**H**CH_2O), 3.90 (dd, 1H, *J* = 6.7, 6.7 Hz, 1 × OCHC**H**$_2$O), 3.87 (d, 1H, *J* = 9.8 Hz, 1 × OC**H**$_2SnBu_3$), 3.80 (s, 3H, OC**H**$_3$), 3.75 (d, 1H, *J* = 9.8 Hz, 1 × OC**H**$_2SnBu_3$), 3.69 (dd, 1H, *J* = 7.9, 7.9 Hz, 1 × OCHC**H**$_2$O), 3.45 (dt, 2H, *J* = 2.3, 6.8 Hz, C**H**$_2$OPMB), 3.13 (td, 1H, *J* = 8.8, 4.0

Hz, OC**H**CH_2CH_2), 1.82–1.71 (m, 1H, 1 × OCHC**H**$_2CH_2$), 1.70–1.59 (m, 2H, C**H**$_2$-CH_2OPMB), 1.50 (q, 6H, *J* = 7.5 Hz, Sn{CH_2-CH_2-C**H**$_2$-CH_3}$_3$), 1.43–1.38 (m, 4H, **H**$_3$C-C and 1 × OCHC**H**$_2CH_2$), 1.34 (s, 3H, **H**$_3$C-C), 1.29 (sext, 6H, *J* = 7.5 Hz, Sn{CH_2-C**H**$_2$-CH_2-CH_3}$_3$), 0.92–0.82 (m, 15H, Sn{C**H**$_2$-CH_2-CH_2-C**H**$_3$}$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1 (**C**OCH_3 *Ar*), 130.7 (OCH_2**C** *Ar*), 129.2 (**C**H *Ar*), 113.7 (**C**H *Ar*), 109.0 (**C**$(CH_3)_2$), 84.1 (O**C**HCH_2CH_2), 77.1 (O**C**HCH_2O), 72.5 (O**C**H_2PMP), 70.1 (**C**H_2OPMB), 65.6 (OCHC**H**$_2$O), 61.8 (OC**H**$_2$SnBu_3), 55.3 (O**C**H_3), 29.2 (C**H**$_2$-CH_2OPMB), 27.4 (Sn{CH_2-C**H**$_2$-CH_2-CH_3}$_3$), 26.5 (H_3**C**-C), 26.3 (OCHC**H**$_2CH_2$), 26.0 (Sn{CH_2-CH_2-C**H**$_2$-CH_3}$_3$), 25.4 (H_3**C**-C), 13.8 and 9.0 (Sn{C**H**$_2$-CH_2-CH_2-C**H**$_3$}$_3$).

Trisylhydrazone (308)

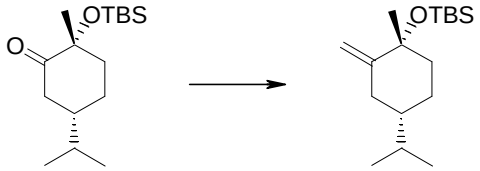


306 **308**

2,4,6-Triisopropylbenzenesulfonylhydrazide (157 mg, 0.527 mmol) was added to a solution of ketone **306** (150 mg, 0.527 mmol) in dry CH_2Cl_2 (1.5 mL) at rt and the resulting mixture was stirred at rt under Ar for 1.5 h. The solvent was removed under vacuum and the residue was purified by silica gel chromatography (petroleum ether/EtOAc, 19:1) to give hydrazone **308** (234 mg, 79%) as a white solid. R_f = 0.45 (petroleum ether/EtOAc, 9:1). mp 118–120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (bs, 1H, N**H**), 7.37 (s, 1H, C**H** *Ar*), 7.26 (s, 1H, C**H** *Ar*), 4.29 (sept., 2H, *J* = 6.7 Hz, 2 × C-C**H**-{CH_3}$_2$), 3.00 (sept., 1H, *J* = 6.9 Hz, C-C**H**-{CH_3}$_2$), 2.45–2.38 (m, 1H, 1 × N=C-C**H**$_2$), 2.03 (dd, 1H, *J* = 13.2, 13.2 Hz, 1 × C**H**$_2$), 1.96 (ddd, 1H, *J* = 13.5, 3.2, 3.2 Hz, 1 × C**H**$_2$), 1.78–1.49 (m, 5H, 1 × C**H**$_2$, H_3C-C**H**, CH_2-C**H**, C**H**$_2$), 1.42–

1.31 (m, 27H, **H**$_3$C-C, 3 × C-CH-{C**H**$_3$}$_2$, Si-C{C**H**$_3$}$_2$), 1.03–0.97 (m, 9H, Si-C{C**H**$_3$}$_3$, H$_2$C-CH-CH-{C**H**$_3$}$_2$), 0.90–0.86 (m, 6H, Si{C**H**$_3$}$_2$) ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.7 (**C**), 153.2 (**C**), 151.0 (**C**), 131.2 (**C**), 123.6 (**C**H *Ar*), 74.9 (**C**), 44.0 (**C**H), 42.0 (**C**H$_2$), 34.2 (**C**H), 32.7 (**C**H), 29.9 (**C**H), 25.9 (**C**H$_3$), 25.8 (2 × **C**H$_2$), 24.9 (**C**H$_3$), 23.6 (**C**H$_3$), 19.6 (**C**H$_3$), 19.4 (**C**H$_3$), 18.2 (quat.), –2.2 (**C**H$_3$), –3.4 (**C**H$_3$). HRMS (CI+) mass calc. for $C_{31}H_{56}N_2O_3SSi$ 565.3859 $(M+H)^+$, found 565.3868.

***tert*-Butyl-((1*R*,4*S*)-4-isopropyl-1-methyl-2-methylene-cyclohexyloxy)-dimethyl-silane (311)**

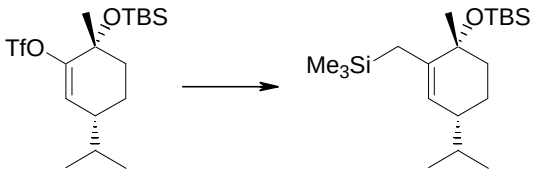


306 **311**

To a suspension of KO*t*Bu (241 mg, 2.15 mmol) in dry toluene (12 mL) was added Ph_3PCH_3Br (768 mg, 2.15 mmol) and the resulting mixture was stirred at reflux for 1 h. Then a solution of ketone **306** (102 mg, 0.36 mmol) in dry toluene (12 mL) was added and the mixture was stirred at reflux for 30 min. It was cooled down to rt, Et_2O (20 mL) and water (20 mL) were added. The layers were separated and the aqueous layer was extracted with Et_2O (2 × 10 mL). The organic layers were combined, dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum ether, 100%) gave alkene **311** (89 mg, 92%) as a colourless oil. R_f = 0.76 (petroleum ether/EtOAc, 19:1). ν_{max} ($CHCl_3$) 2956, 2929, 2857 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.75 (s, 1H, 1 × **H**$_2$C=C-CH$_2$), 4.68 (s, 1H, 1 × **H**$_2$C=C-CH$_2$), 2.23 (dd, 1H, *J* = 12.4, 12.4 Hz, 1 × H$_2$C=C-C**H**$_2$), 2.07 (ddd, 1H, *J* = 1.9, 3.7, 12.4 Hz, 1 × H$_2$C=C-C**H**$_2$), 1.81 (ddd, 1H, *J* = 13.1, 3.4, 3.4 Hz, 1 × TBSOC-C**H**$_2$-CH$_2$), 1.60–1.42 (m, 3H, 1 × TBSOC-CH$_2$-C**H**$_2$, H$_3$C-C**H** and 1 ×

TBSOC-CH_2-C**H**$_2$), 1.38 (s, 3H, **H**$_3$C-C-OTBS), 1.26 (ddd, 1H, *J* = 13.1, 3.4, 3.4 Hz, 1 × TBSOC-C**H**$_2$-CH_2), 1.17–1.08 (m, 1H, H_2C=C-CH_2-C**H**), 0.93–0.85 (m, 15H, **H**$_3$C-CH-C**H**$_3$ and Si-C-{C**H**$_3$}$_3$), 0.07 (s, 3H, Si-C**H**$_3$), 0.02 (s, 3H, Si-C**H**$_3$) ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.2 (H_2C=**C**), 106.0 (H_2**C**=C), 73.4 (H_3C-**C**-OTBS), 46.1 (H_2C=C-CH_2-**C**H), 42.8 (TBSOC-**C**H_2-CH_2), 36.1 (H_2C=C-**C**H_2), 32.6 (H_3C-**C**H), 27.3 (H_3**C**-C-OTBS), 26.0 (Si-C-{**C**H_3}$_3$), 24.9 (TBSOC-CH_2-**C**H_2), 19.9 (H_3**C**-CH), 19.8 (H_3**C**-CH), 18.4 (Si-**C**-{CH_3}$_3$), –1.9 (Si-**C**H_3), –3.0 (Si-**C**H_3). HRMS (CI+) mass calc. for $C_{17}H_{34}OSi$ 283.2457 $(M+H)^+$, found 283.2442.

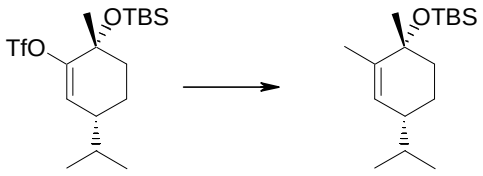
(3*R*,6*R*)-6-(tert-Butyl-dimethyl-silanyloxy)-3-isopropyl-6-methyl-1-trimethylsilanylmethyl-cyclohexene (312a)



303 **312a**

$Pd(PPh3)_4$ (103 mg, 0.09 mmol) and $TMSCH_2MgCl$ (1.48 mL of a 1M solution in Et_2O, 1.48 mmol) was added to a solution of crude triflate **303** (114 mg, 0.300 mmol) in dry Et_2O (5 mL) at rt under Argon. The resulting mixture was stirred at rt for 30 min. It was then quenched with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted with Et_2O. The organic layers were combined, dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum ether, 100%) gave **312a** (72 mg, 73%) as a colourless oil. R_f = 0.65 (petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20 (s, 1H), 1.89–1.76 (m, 2H), 1.68–1.38 (m, 6H), 1.31–1.18 (m, 6H), 0.99–0.80 (m, 12H), 0.13–0.11 (m, 15H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.9 (C), 126.2 (CH), 73.7 (C), 42.8 (CH), 39.4 (CH_2), 32.8 (CH), 29.2 (CH_3), 26.3 (CH_3), 22.2 (CH_3), 20.4 (CH_3), 20.1 (CH_3), 19.3 (CH_2), 18.7 (C), 0.0 (3 × CH_3), -1.6 (CH_3), -1.8 (CH_3).

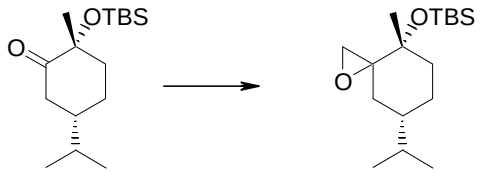
tert-Butyl-((1_R_,4_R_)-4-isopropyl-1,2-dimethyl-cyclohex-2-enyloxy)-dimethyl-silane (315)



303 **315**

[1,1'-*bis*(Diphenylphosphino)ferrocene]dichloropalladium(II) complex with CH_2Cl_2 (1:1) ($Pd(dppf)Cl_2 \cdot CH_2Cl_2$) (14 mg, 17 μmol) and dimethylzinc (338 μL of a 2 M solution in toluene, 0.676 mmol) were added sequentially to a solution of crude triflate **303** (130 mg, 0.34 mmol) in dry THF (1.9 mL) at rt under Ar. The mixture was degassed twice and heated at 60 °C for 16 h (during this process the yellow solution turned black). The reaction was quenched by the addition of saturated aqueous NH_4Cl (5 mL) at 0 °C and the mixture was extracted with Et_2O (3 × 10 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum ether) gave alkene **315** (24 mg, 25%) as a colourless oil. R_f = 0.75 (petroleum ether/EtOAc, 19:1). ν_{max} ($CHCl_3$) 2957, 834 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.25 (dq, 1H, *J* = 2.5, 1.5 Hz, H_3C-C=C**H**), 1.80 (m, 2H, HC-C**H**-CH_2, 1 × H_3C-C-C**H**$_2$), 1.70 (dd, 3H, *J* = 2.5 Hz, 1.5 Hz, **H**$_3$C-C=CH), 1.63-1.42 (m, 4H, 1 × H_3C-C-C**H**$_2$, HC-CH-C**H**$_2$, H_3C-C**H**), 1.26 (s, 3H, **H**$_3$C-COTBS), 0.89 (d, 3H, *J* = 6.8 Hz, **H**$_3$C-CH), 0.88–0.84 (m, 12H, **H**$_3$C-C, SiC{C**H**$_3$}$_3$), 0.07 (s, 6H, Si(C**H**$_3$)$_2$) ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.9 (H_3C-**C**=CH), 127.1 (H_3C-C=**C**H), 72.4 (H_3C-**C**OTBS), 42.5 (HC-**C**H-CH_2), 39.1 (H_3C-C-**C**H$_2$), 32.1 (H_3C-**C**H), 28.5 (H_3**C**-COTBS), 25.8 (SiC{**C**H$_3$}$_3$), 21.6 (HC-CH-**C**H$_2$), 19.8 (H_3**C**-CH), 19.4 (H_3**C**-CH), 18.3 (H_3**C**-C=CH), 18.3 (Si**C**{CH_3}$_3$), –2.1 (SiC**H**$_3$), –2.4 (SiC**H**$_3$). HRMS (CI+) mass calc. for $C_{17}H_{34}OSi$ 283.2457 $(M+H)^+$, found 283.2460.

***tert*-Butyl-((4*R*,7*S*)-7-isopropyl-4-methyl-1-oxa-spiro[2.5]oct-4-yloxy)-dimethyl-silane (316)**



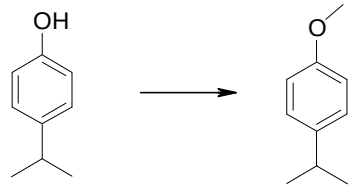
306 **316**

KHMDS (3.2 mL of 0.5 M solution in toluene, 1.6 mmol) was added dropwise to a solution of trimethylsulfonium iodide (382 mg, 1.87 mmol) in dry THF (3.7 mL) at 0 °C under Ar. After 30 min, a solution of ketone **306** (355 mg, 1.25 mmol) in dry THF (1.5 mL) was added dropwise and the resulting mixture was stirred at 0 °C for 30 min. It was quenched with water (10 mL) and allowed to warm to rt. The mixture was extracted with Et_2O (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under vacuum to give epoxide **316** (378 mg) as a yellow oil which was used without any further purification. R_f = 0.52 (petroleum ether/EtOAc, 19:1). ν_{max} ($CHCl_3$) 2955, 2857, 1474 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.90 (d, 1H, *J* = 4.5 Hz, 1 × C-C**H**$_2$O), 2.47 (d, 1H, *J* = 4.5 Hz, C-C**H**$_2$O), 2.12 (dd, 1H, *J* = 11.9, 11.9 Hz, 1 × C**H**$_2$), 1.70–1.66 (m, 1H, C**H**), 1.57–1.41 (m, 5H, C**H**$_2$, C**H** and C**H**$_2$), 1.04 (s, 3H, **H**$_3$C-C-OTBS), 0.99 (d, 1H, *J* = 13.4 Hz, 1 × C**H**$_2$), 0.90 (s, 9H, Si-C-(C**H**$_3$)$_3$), 0.87 (s, 3H, **H**$_3$C-CH), 0.86 (s, 3H, **H**$_3$C-CH), 0.09 (s, 3H, Si-C**H**$_3$), 0.06 (s, 3H, Si-C**H**$_3$) ^{13}C NMR (101 MHz, $CDCl_3$) δ 73.7 (**C**-CH_2O), 61.5 (H_3C-**C**-OTBS), 51.0 (C-**C**H_2O), 40.9 (**C**H), 39.2 (**C**H_2), 33.3 (**C**H_2), 32.4 (**C**H), 25.9 (Si-C-(**C**H_3)$_3$), 24.2 (**C**H_2), 22.9 (H_3**C**-C-OTBS), 19.7 (**H**$_3$C-CH), 19.5 (**H**$_3$C-CH), 18.3 (Si-**C**-{CH_3}$_3$), –1.9 (Si-**CH**$_3$), –2.0 (Si-C**H**$_3$). HRMS (CI+) mass calc. for $C_{17}H_{34}O_2Si$ 299.2406 $(M+H)^+$, found 299.2403.

Apendix 1

Synthesis of 4-isopropylcyclohexanone

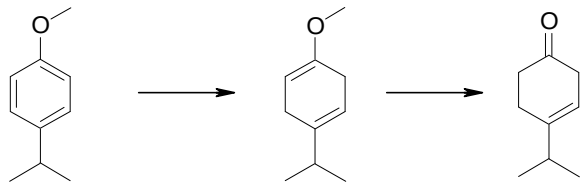
1-Isopropyl-4-methoxybenzene (228)



227 **228**

Dimethylsulfate (122 mL, 1.29 mol) was added dropwise over 30 min to a cooled (0°C) solution of 4-isopropylphenol **227** (25.0 g, 184 mmol) in a 15% aqueous KOH solution (500 mL). The reaction mixture was stirred at rt for 2.5 h. Then it was extracted with CH_2Cl_2 (3 × 200 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum ether/ EtOAc, 19:1) gave ether **228** (26.1 g, 95%) as a yellow oil. R_f = 0.3 petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, 2H, *J* = 9.6 Hz, C**H** *Ar*), 6.80 (d, 2H, *J* = 9.6 Hz, C**H** *Ar*), 3.41 (s, 3H, OC**H**$_3$), 2.39 (sept., 1H, *J* = 7.8 Hz, H_3C-C**H**), 0.57 (d, 6H, *J* = 7.8 Hz, **H**$_3$C-CH-C**H**$_3$) ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.6 (**C**OCH_3), 141.0 (**C**-CH-CH_3), 127.2 (**C**H *Ar*), 113.7 (**C**H *Ar*), 55.2 (O**C**H_3), 33.2 (H_3C-**C**H), 24.2 (H_3**C**-CH-**C**H_3). NMR data are in accordance with the literature.[53]

4-Isopropylcyclohex-3-enone (229)

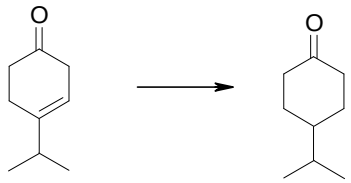


228 **329** **229**

Ether **228** (19.0 g, 127 mmol) was dissolved in dry Et_2O (125 mL) and the resulting mixture was cooled down to –78 °C. Liquid ammonia (c.a 1 L) was added followed

by pieces of lithium (4.60 g, 663 mmol) bit by bit over 10 min. After 10 min, dry EtOH (65 mL) was added dropwise over 10 min. When the blue colour has been discharged, lithium (2.80 g, 403 mmol) was added bit by bit over 5 min and the mixture was stirred for 5 min after the addition was finished. Dry EtOH (35 mL) was added dropwise over 8 min and the mixture was allowed to warm to rt to evaporate the ammonia. The residue was dissolved in Et_2O (500 mL), water (500 mL) was added, the layers were separated and the aqueous phase was extracted with Et_2O (3 × 200 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and evaporated under vacuum. The crude oil **329** was dissolved in methanol (193 mL), acetone (340 mL) and water (147 mL). Oxalic acid dihydrate (1.6 g, 13 mmol) was added and the mixture was stirred at rt for 3 h. The mixture was partially evaporated under vacuum and the residue was diluted with water (600 mL) and extracted with CH_2Cl_2 (3 × 300 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and evaporated under vacuum. Silica gel chromatography (petroleum ether/EtOAc, 9:1) gave ketone **229** (14.1 g, 80%) as a colourless oil. R_f = 0.43 (petroleum ether/EtOAc, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24 (ddd, 1H, *J* = 3.6 Hz, 3.6 Hz, 1.3 Hz, C=C**H**), 2.36 (t, 2H, *J* = 1.3 Hz, O=C-C**H**$_2$), 1.98–1.81 (m, 4H, O=C-C**H**$_2$-CH and O=C-C**H**$_2$-CH$_2$), 1.76 (sept., 1H, *J* = 7.8 Hz, **H**$_3$C-CH), 0.34 (d, 6H, *J* = 7.8 Hz, **H**$_3$C-CH-C**H**$_3$) ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.5 (**C**=O), 144.6 (**C**=CH), 115.4 (C=**C**H), 39.6 (**C**H$_2$), 38.8 (**C**H$_2$), 34.7 (**C**H), 26.2 (**C**H$_2$), 21.1 (2 × **C**H$_3$). NMR data are in accordance with the literature.[53]

4-Isopropylcyclohexanone (230)



229 **230**

A solution of ketone **229** (11.4 g, 82.5 mmol) in EtOAc (110 mL) was hydrogenated over palladium (10% on activated carbon, 435 mg, 0.41 mmol) for 18 h. The catalyst was filtered off trough celite and the filtrate was evaporated under vacuum. Silica gel chromatography (petroleum ether/EtOAc, 9:1) gave ketone **230** (9.6 g, 83%) as a colourless oil. R_f = 0.3 (petroleum ether/EtOAc, 19:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89–1.70 (m, 4H, **H**$_2$C-CO-C**H**$_2$), 1.49–1.35 (m, 2H, C**H**$_2$), 1.03–0.74 (m, 4H, C**H**$_2$, H_3C-C**H**, H_3C-CH-C**H**), 0.21 (d, 6H, *J* = 7.3 Hz, **H**$_3$C-CH-C**H**$_3$). NMR data are in accordance with the literature.[53]

Crystallographic data

Crystal data for **288** :

Table 1. Crystal data and structure refinement for HMIPMC at 150(2)K.

Empirical formula	C11 H20 O2
Formula weight	184.27
Crystal description	colourless lath
Crystal size	1.00 x 0.30 x 0.07 mm
Crystal system	Monoclinic
Space group	P 21
Unit cell dimensions	a = 8.682(2) Å alpha = 90 deg. b = 6.764(2) Å beta = 98.746(4) deg. c = 9.255(2) Å gamma = 90 deg.
Volume	537.2(4) Å^3

Reflections for cell refinement 2315

Range in theta 2.2 to 27.5 deg.

Z 2

Density (calculated) 1.139 Mg/m^3

Absorption coefficient 0.076 mm^{-1}

F(000) 204

Diffractometer type Bruker SMART APEX CCD area detector

Wavelength 0.71073 Å

Scan type omega

Reflections collected 3342

Theta range for data collection 2.23 to 27.52 deg.

Index ranges -8<=h<=8, -11<=k<=11, -5<=l<=12

Independent reflections 1325 [R(int) = 0.017]

Observed reflections 1298 [I>2sigma(I)]

Absorption correction Semi-empirical from equivalents (Tmin = 0.777, Tmax = 1.000)

Decay correction none

Structure solution by	direct methods
Hydrogen atom location	OH from delta-F; others placed geometrically
Hydrogen atom treatment	rigid rotor; riding model
Data / restraints / parameters	1325/1/120 (least-squares on F^2)
Final R indices [I>2sigma(I)]	R1 = 0.0351, wR2 = 0.0911
Final R indices (all data)	R1 = 0.0356, wR2 = 0.0915
Goodness-of-fit on F^2	1.06
Absolute structure parameter	Not reliably determined
Final maximum delta/sigma	0.001
Weighting scheme calc w=1/[\s^2^(Fo^2^)+(0.066P)^2^+0.039P] where P=(Fo^2^+2Fc^2^)/3	
Largest diff. peak and hole	0.27 and -0.15 e. $Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for HMIPMC. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O1	-119(1)	10568(2)	6357(1)	30(1)
C1	83(2)	9560(2)	7748(1)	25(1)
C2	200(2)	7378(2)	7377(1)	21(1)

C3	1551(2)	6405(2)	7575(2)	23(1)
C4	3113(2)	7282(2)	8178(2)	26(1)
C5	3025(2)	9533(2)	8104(2)	31(1)
C6	1582(2)	10266(2)	8691(2)	31(1)
O7	-1088(1)	4505(2)	6077(1)	25(1)
C7	-1303(2)	6371(2)	6719(2)	25(1)
C8	4200(2)	6708(3)	5795(2)	42(1)
C9	4456(2)	6444(2)	7449(2)	30(1)
C10	4769(2)	4268(3)	7824(2)	37(1)
C11	-1324(2)	10025(3)	8506(2)	35(1)

Table 3. Bond lengths [A], angles and torsions [deg] for HMIPMC.

O1-C1	1.4435(17)
O1-H1O	0.8400
C1-C2	1.522(2)
C1-C6	1.529(2)
C1-C11	1.531(2)
C2-C3	1.333(2)
C2-C7	1.515(2)
C3-C4	1.5074(19)
C3-H3A	0.9500
C4-C5	1.525(2)
C4-C9	1.542(2)
C4-H4A	1.0000
C5-C6	1.523(2)
C5-H5A	0.9900
C5-H5B	0.9900
C6-H6A	0.9900

C6-H6B	0.9900
O7-C7	1.4191(19)
O7-H7O	0.8400
C7-H7B	0.9900
C7-H7C	0.9900
C8-C9	1.523(3)
C8-H8A	0.9800
C8-H8B	0.9800
C8-H8C	0.9800
C9-C10	1.527(2)
C9-H9A	1.0000
C10-H10A	0.9800
C10-H10B	0.9800
C10-H10C	0.9800
C11-H11A	0.9800
C11-H11B	0.9800
C11-H11C	0.9800

C1-O1-H1O	109.5
O1-C1-C2	105.09(11)
O1-C1-C6	109.79(13)
C2-C1-C6	110.56(12)
O1-C1-C11	108.36(12)
C2-C1-C11	112.80(13)
C6-C1-C11	110.07(13)
C3-C2-C7	121.26(14)
C3-C2-C1	122.37(14)
C7-C2-C1	116.34(13)
C2-C3-C4	125.43(14)
C2-C3-H3A	117.3
C4-C3-H3A	117.3
C3-C4-C5	109.90(13)
C3-C4-C9	113.02(13)
C5-C4-C9	112.53(14)

C3-C4-H4A	107.0
C5-C4-H4A	107.0
C9-C4-H4A	107.0
C6-C5-C4	110.32(14)
C6-C5-H5A	109.6
C4-C5-H5A	109.6
C6-C5-H5B	109.6
C4-C5-H5B	109.6
H5A-C5-H5B	108.1
C5-C6-C1	111.73(12)
C5-C6-H6A	109.3
C1-C6-H6A	109.3
C5-C6-H6B	109.3
C1-C6-H6B	109.3
H6A-C6-H6B	107.9
C7-O7-H7O	109.5
O7-C7-C2	114.10(12)
O7-C7-H7B	108.7
C2-C7-H7B	108.7
O7-C7-H7C	108.7
C2-C7-H7C	108.7
H7B-C7-H7C	107.6
C9-C8-H8A	109.5
C9-C8-H8B	109.5
H8A-C8-H8B	109.5
C9-C8-H8C	109.5
H8A-C8-H8C	109.5
H8B-C8-H8C	109.5
C8-C9-C10	109.56(15)
C8-C9-C4	113.07(13)
C10-C9-C4	112.04(14)
C8-C9-H9A	107.3
C10-C9-H9A	107.3
C4-C9-H9A	107.3

C9-C10-H10A	109.5
C9-C10-H10B	109.5
H10A-C10-H10B	109.5
C9-C10-H10C	109.5
H10A-C10-H10C	109.5
H10B-C10-H10C	109.5
C1-C11-H11A	109.5
C1-C11-H11B	109.5
H11A-C11-H11B	109.5
C1-C11-H11C	109.5
H11A-C11-H11C	109.5
H11B-C11-H11C	109.5

O1-C1-C2-C3	104.28(16)
C6-C1-C2-C3	-14.12(18)
C11-C1-C2-C3	-137.85(15)
O1-C1-C2-C7	-73.79(15)
C6-C1-C2-C7	167.80(12)
C11-C1-C2-C7	44.07(17)
C7-C2-C3-C4	178.16(13)
C1-C2-C3-C4	0.2(2)
C2-C3-C4-C5	-16.9(2)
C2-C3-C4-C9	-143.54(15)
C3-C4-C5-C6	47.02(17)
C9-C4-C5-C6	173.94(11)
C4-C5-C6-C1	-63.94(17)
O1-C1-C6-C5	-70.32(17)
C2-C1-C6-C5	45.18(17)
C11-C1-C6-C5	170.47(13)
C3-C2-C7-O7	-12.36(19)
C1-C2-C7-O7	165.74(11)
C3-C4-C9-C8	56.67(19)
C5-C4-C9-C8	- 68.55(18)
C3-C4-C9-C10	-67.74(17)

C5-C4-C9-C10	167.04(13)

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for HMIPMC.
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O1	46(1)	17(1)	28(1)	4(1)	9(1)	8(1)
C1	35(1)	17(1)	24(1)	1(1)	8(1)	3(1)
C2	27(1)	16(1)	21(1)	0(1)	5(1)	-2(1)
C3	27(1)	15(1)	26(1)	2(1)	2(1)	-3(1)
C4	27(1)	19(1)	30(1)	1(1)	-2(1)	-4(1)
C5	34(1)	18(1)	40(1)	-2(1)	-1(1)	-7(1)
C6	45(1)	17(1)	32(1)	-4(1)	2(1)	-3(1)
O7	29(1)	18(1)	29(1)	-1(1)	4(1)	-3(1)
C7	24(1)	20(1)	32(1)	-1(1)	4(1)	1(1)
C8	40(1)	40(1)	48(1)	14(1)	16(1)	11(1)
C9	22(1)	22(1)	44(1)	3(1)	-1(1)	-2(1)
C10	36(1)	25(1)	48(1)	5(1)	-2(1)	5(1)
C11	46(1)	26(1)	38(1)	-3(1)	19(1)	5(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for HMIPMC.

	x	y	z	U(eq)

H1O	-348	11757	6477	45
H3A	1527	5046	7314	27
H4A	3333	6915	9236	31
H5A	3969	10106	8689	38
H5B	2988	9970	7079	38
H6A	1592	11729	8717	38
H6B	1605	9782	9703	38
H7O	-750	4672	5282	38
H7B	-1961	6191	7494	30
H7C	-1872	7248	5964	30
H8A	3998	8105	5556	63
H8B	3304	5913	5361	63
H8C	5132	6277	5404	63
H9A	5419	7197	7847	36
H10A	4943	4102	8888	55
H10B	5695	3830	7425	55
H10C	3869	3474	7398	55
H11A	-2279	9575	7891	53
H11B	-1383	11454	8663	53
H11C	-1211	9342	9451	53

Crystal data for **271**:

Table 1. Crystal data and structure refinement for HMIPMC at 150(2)K.

Empirical formula	C26 H38 O4 . ¼ C7 H8
Formula weight	437.62
Crystal size	0.40 × 0.30 × 0.15 mm^3

Crystal system	tetragonal
Space group	$P\,4_3\,2_1\,2$
Unit cell dimensions	a = 13.7906(10) Å alpha = 90 deg. b = 13.7906(10) Å beta = 90 deg. c = 26.375(4) Å gamma = 90 deg.
Volume	V = 5016.1(9) Å^3
Z	8
Density (calculated)	1.16 Mg/m^3
Absorption coefficient	0.072 mm^{-1}
Reflections collected	24286
Structure solution by	direct methods

Hydrogen atom location The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically.

Hydrogen atom treatment The H atoms were refined with soft restraints on the bond lengths and angles to regularise their geometry

Final R indices (all data)	R1 = 0.0529, wR2 = 0.1552

Absolute structure parameter assigned from a known chiral centre in the starting material

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C1	0.2683	0.8600	0.5618	0.0152
C2	0.2735	0.7666	0.5948	0.0149
C3	0.3055	0.7773	0.6502	0.0180
C4	0.4013	0.8319	0.6522	0.0218
C5	0.4700	0.8093	0.6074	0.0189
C6	0.4401	0.7257	0.5717	0.0183
O7	0.3391	0.7004	0.5711	0.0169
C8	0.4752	0.7392	0.5166	0.0184
C9	0.4296	0.8265	0.4880	0.0203
C10	0.3238	0.8157	0.4755	0.0185
C11	0.2510	0.8303	0.5072	0.0161
C12	0.1471	0.8104	0.4912	0.0192
C13	0.0778	0.8890	0.5089	0.0226
C14	0.0921	0.9096	0.5659	0.0207
C15	0.1955	0.9400	0.5785	0.0169
C16	0.2254	1.0392	0.5554	0.0239
C17	0.3265	1.0724	0.5714	0.0324
C18	0.1538	1.1187	0.5700	0.0315
O19	0.1097	0.7222	0.5135	0.0199
C20	0.1547	0.6350	0.4959	0.0221
C21	0.1309	0.6099	0.4418	0.0204
C22	0.1968	0.5617	0.4113	0.0305
C23	0.1739	0.5352	0.3620	0.0353
C24	0.0832	0.5592	0.3420	0.0370
C25	0.0185	0.6072	0.3716	0.0349
C26	0.0408	0.6324	0.4215	0.0298
O27	0.5778	0.7573	0.5224	0.0229

C28	0.4584	0.6464	0.4862	0.0235
O29	0.2367	0.8324	0.6794	0.0204
C30	0.3141	0.6765	0.6740	0.0263

Table 3. Bond lengths [Å].

C1-C2	1.555
C1-C11	1.517
C1-C15	1.555
C1-H11	1.001
C2-C3	1.533
C2-O7	1.429
C2-H21	1.002
C3-C4	1.522
C3-O29	1.439
C3-C30	1.530
C4-C5	1.544
C4-H41	0.980
C4-H42	0.953
C5-C6	1.546
C5-H51	0.933
C5-H52	0.955
C6-O7	1.435
C6-C8	1.543
C6-H61	0.982
C8-C9	1.553
C8-O27	1.445
C8-C28	1.528
C9-C10	1.503
C9-H91	0.974
C9-H92	0.976
C10-C11	1.322

C10-H101	0.931
C11-C12	1.519
C12-C13	1.519
C12-O19	1.446
C12-H121	0.981
C13-C14	1.542
C13-H131	0.990
C13-H132	0.982
C14-C15	1.523
C14-H141	0.987
C14-H142	0.997
C15-C16	1.554
C15-H151	0.995
C16-C17	1.527
C16-C18	1.525
C16-H161	0.985
C17-H171	0.948
C17-H172	0.968
C17-H173	0.958
C18-H181	0.957
C18-H182	0.954
C18-H183	0.972
O19-C20	1.430
C20-C21	1.505
C20-H201	0.968
C20-H202	0.974
C21-C22	1.383
C21-C26	1.389
C22-C23	1.388
C22-H221	0.938
C23-C24	1.397
C23-H231	0.951
C24-C25	1.357
C24-H241	0.925

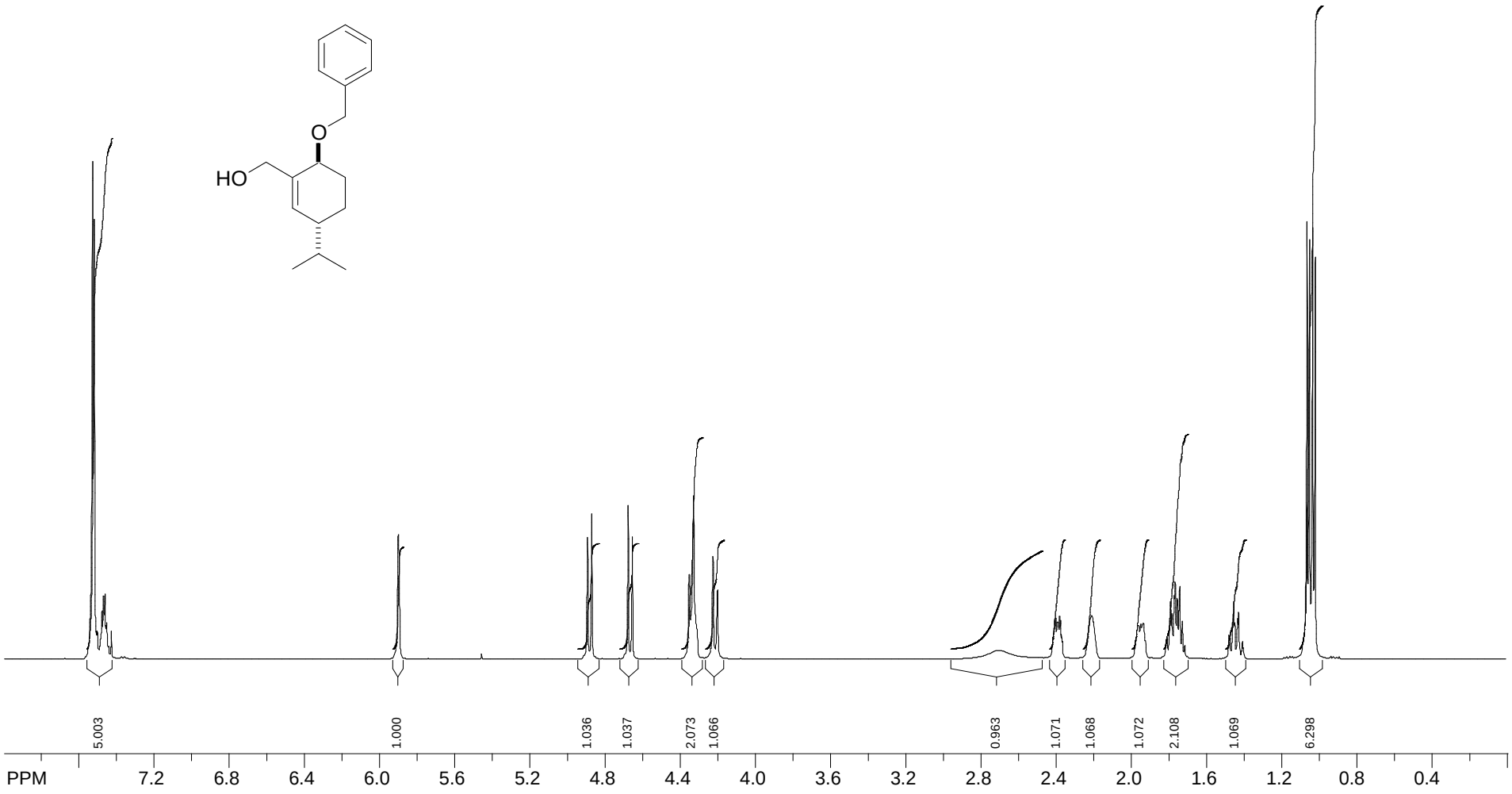
C25-C26	1.396
C25-H251	0.924
C26-H261	0.943
O27-H27	0.902
C28-H281	0.965
C28-H282	0.983
C28-H283	0.971
O29-H1	0.803
C30-H301	0.963
C30-H302	0.960
C30-H303	0.976

Table 4. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3).

	x	y	z	U(eq)
H11	0.3351	0.8879	0.5644	0.0152
H21	0.2081	0.7352	0.5926	0.0154
H41	0.4344	0.8177	0.6842	0.0236
H42	0.3870	0.8995	0.6516	0.0236
H51	0.5307	0.7949	0.6211	0.0195
H52	0.4771	0.8675	0.5882	0.0195
H61	0.4742	0.6683	0.5846	0.0177
H91	0.4395	0.8855	0.5077	0.0214
H92	0.4646	0.8316	0.4560	0.0214
H101	0.3090	0.7946	0.4429	0.0208
H121	0.1437	0.8047	0.4542	0.0199
H131	0.0891	0.9478	0.4882	0.0237
H132	0.0118	0.8658	0.5020	0.0237
H141	0.0448	0.9603	0.5751	0.0202
H142	0.0781	0.8481	0.5844	0.0202
H151	0.1998	0.9487	0.6159	0.0168

H161	0.2228	1.0338	0.5182	0.0253
H171	0.3377	1.1370	0.5605	0.0377
H172	0.3336	1.0680	0.6078	0.0377
H173	0.3738	1.0310	0.5559	0.0377
H181	0.1752	1.1816	0.5595	0.0374
H182	0.1440	1.1178	0.6058	0.0374
H183	0.0913	1.1058	0.5544	0.0374
H201	0.2245	0.6401	0.4987	0.0252
H202	0.1335	0.5813	0.5172	0.0252
H221	0.2594	0.5484	0.4234	0.0328
H231	0.2197	0.4985	0.3431	0.0371
H241	0.0695	0.5412	0.3090	0.0442
H251	-0.0410	0.6246	0.3583	0.0393
H261	-0.0049	0.6657	0.4416	0.0347
H281	0.4926	0.6498	0.4543	0.0243
H282	0.4851	0.5896	0.5038	0.0243
H283	0.3902	0.6353	0.4791	0.0243
H301	0.3300	0.6831	0.7094	0.0294
H302	0.2523	0.6446	0.6721	0.0294
H303	0.3643	0.6388	0.6569	0.0294
H1	0.1890	0.8022	0.6868	0.0500
H27	0.6084	0.7557	0.4922	0.0500

Selected spectra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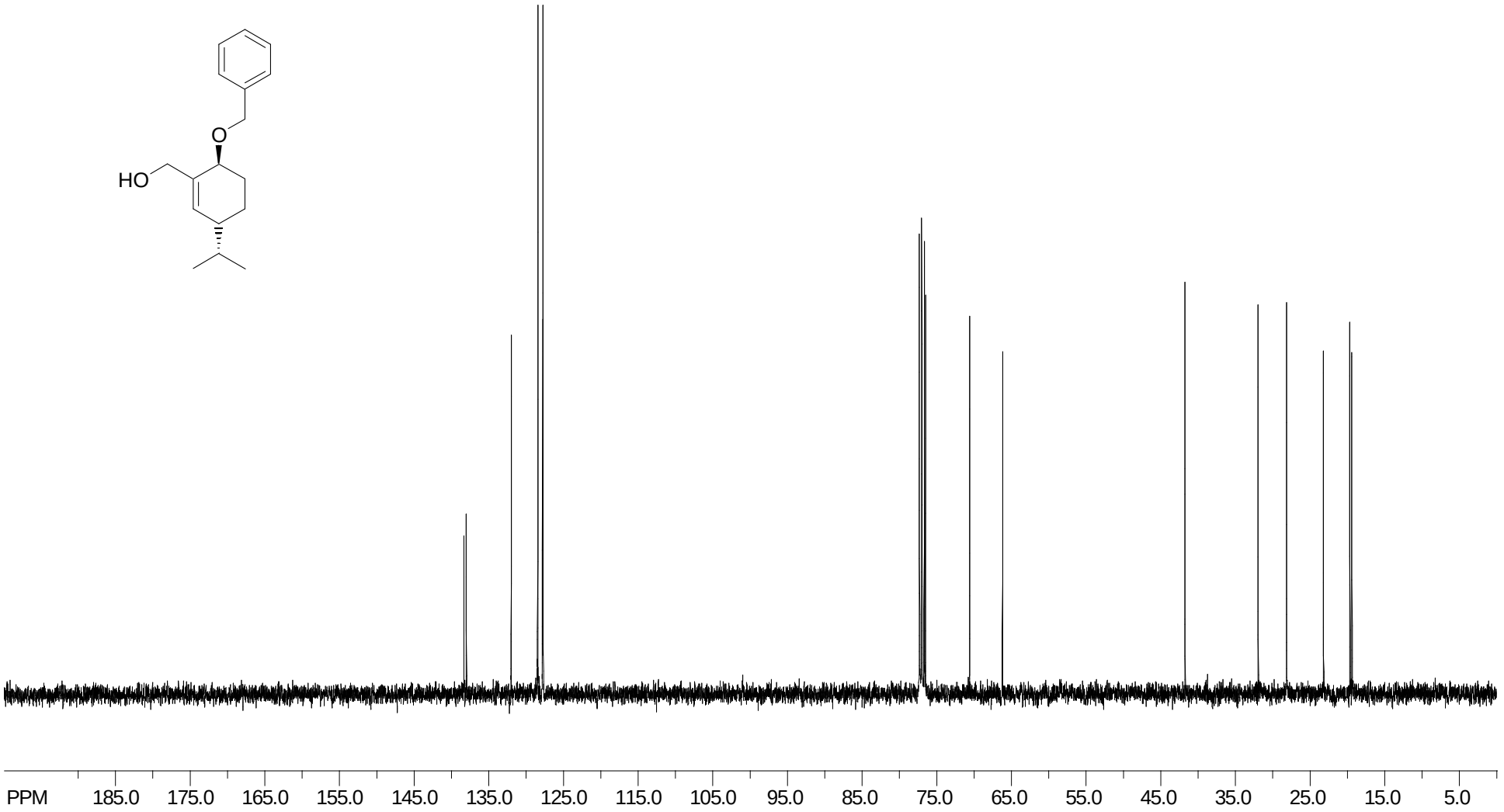
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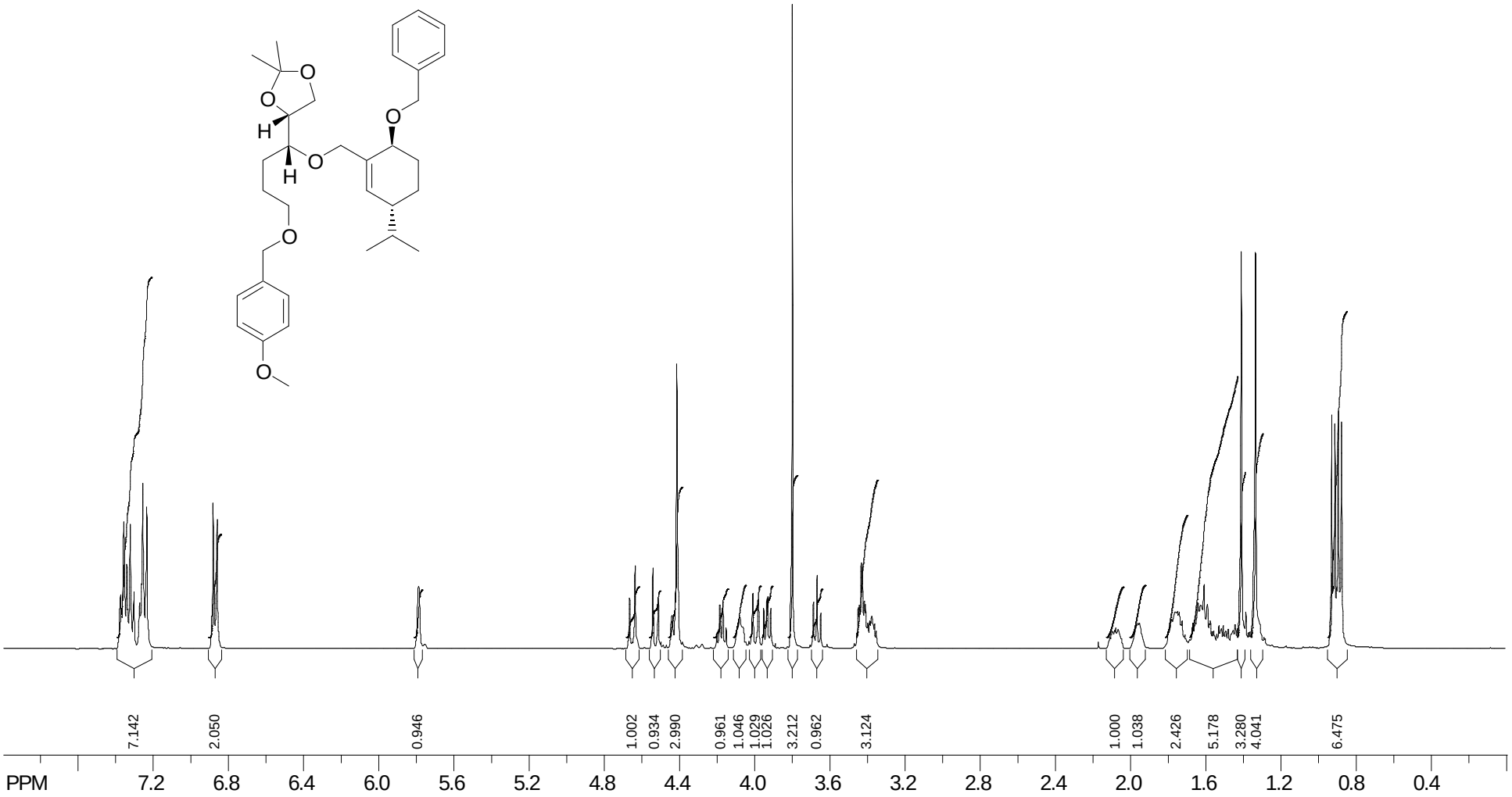
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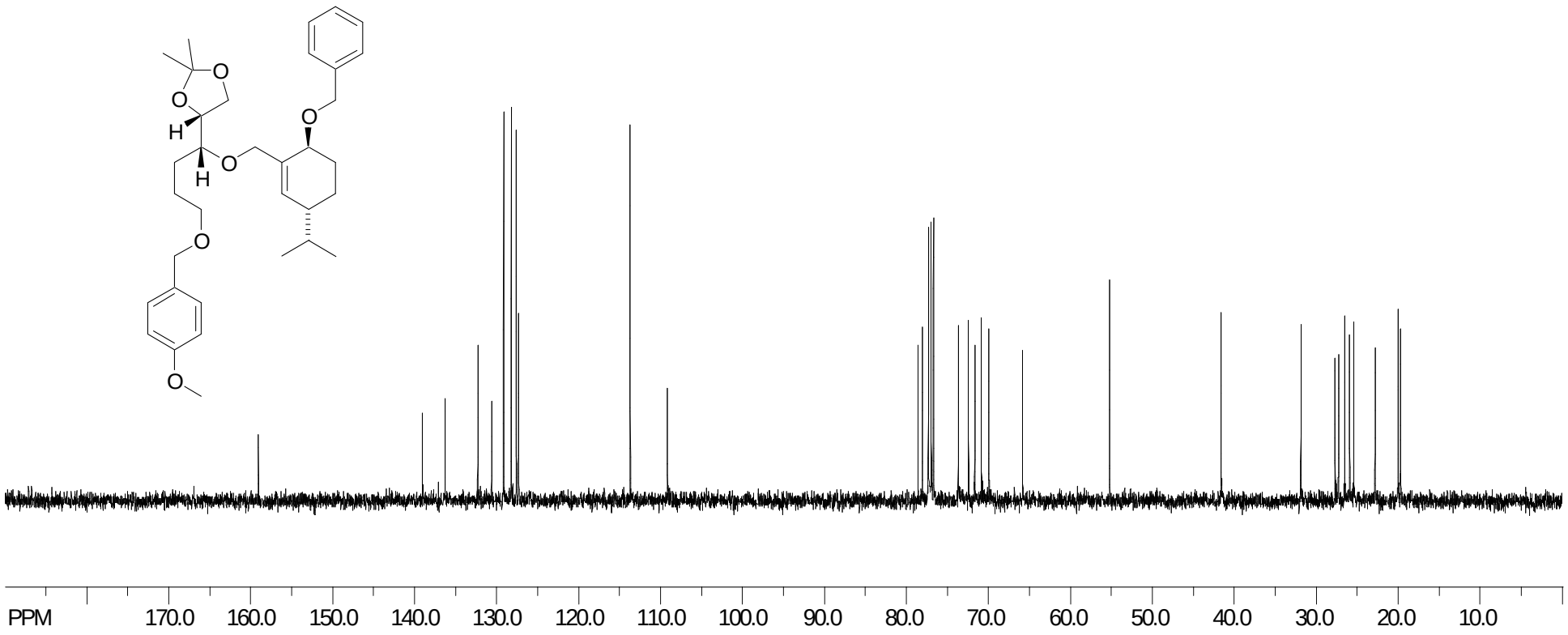
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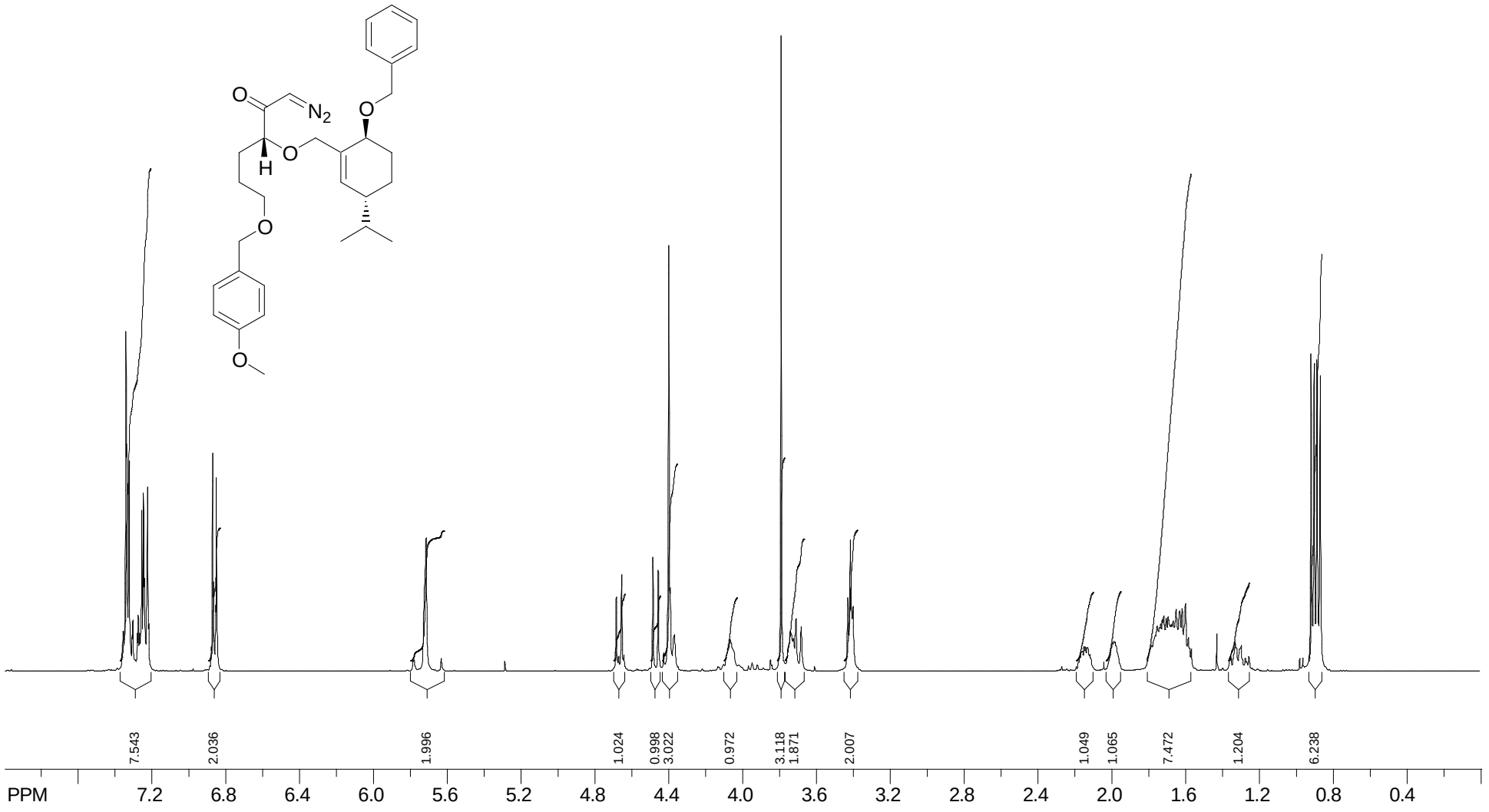
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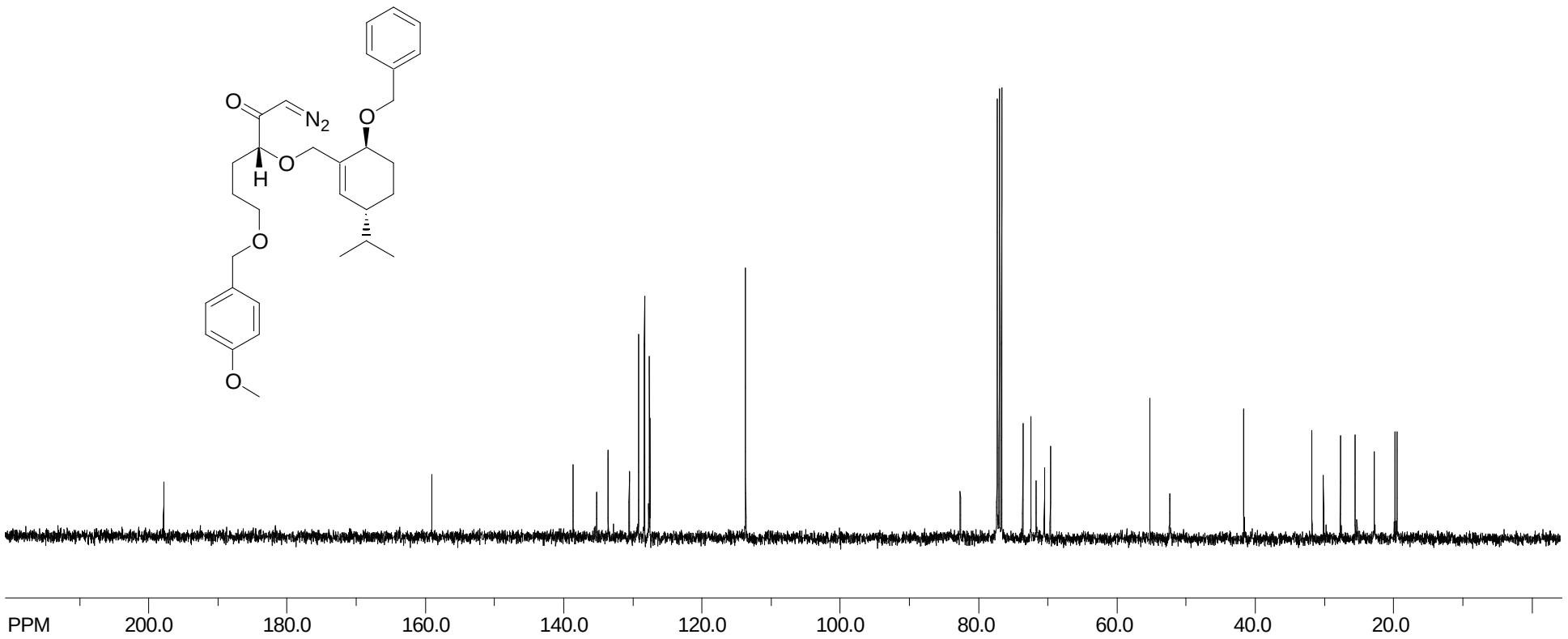
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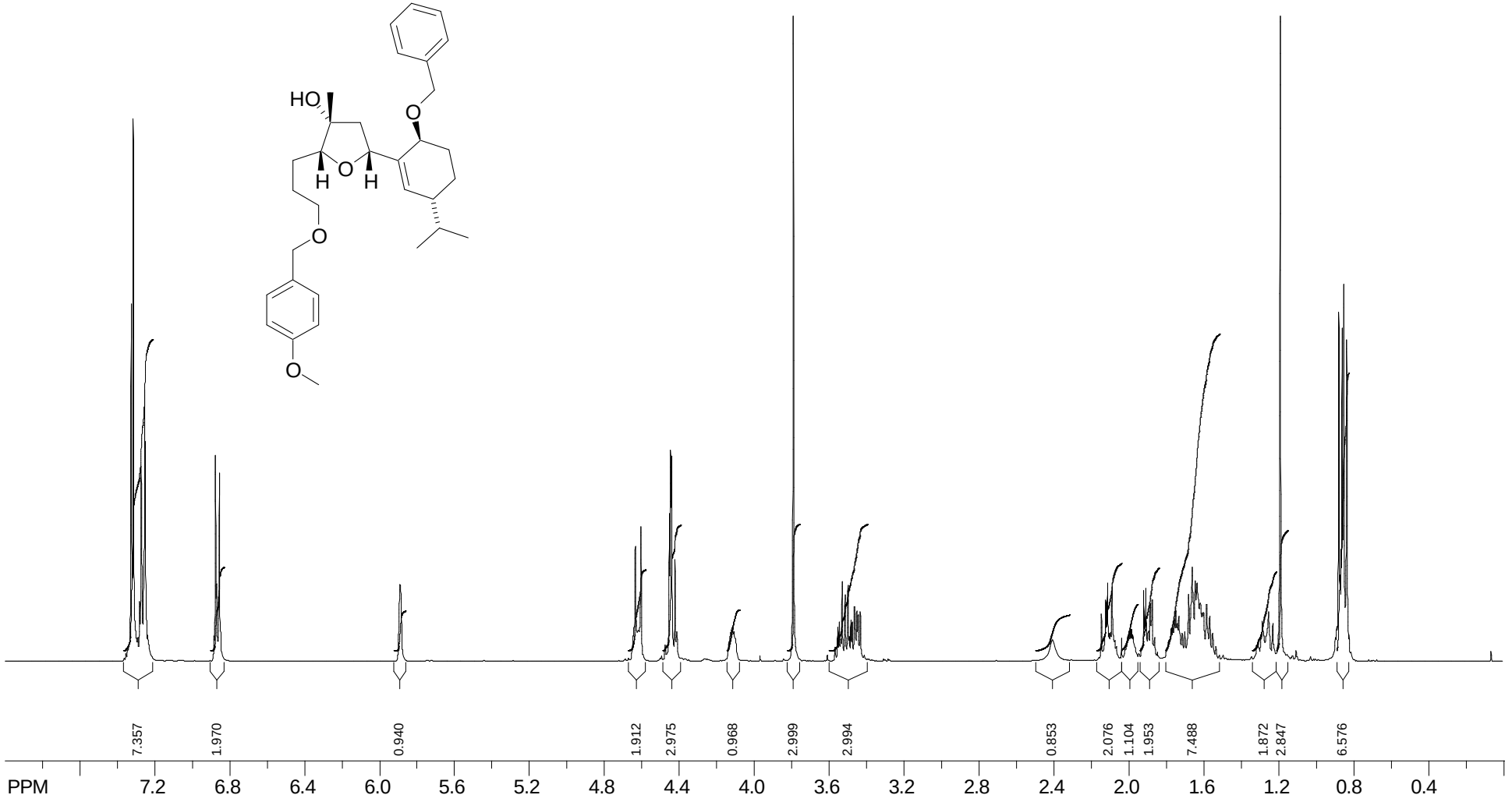
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5.2
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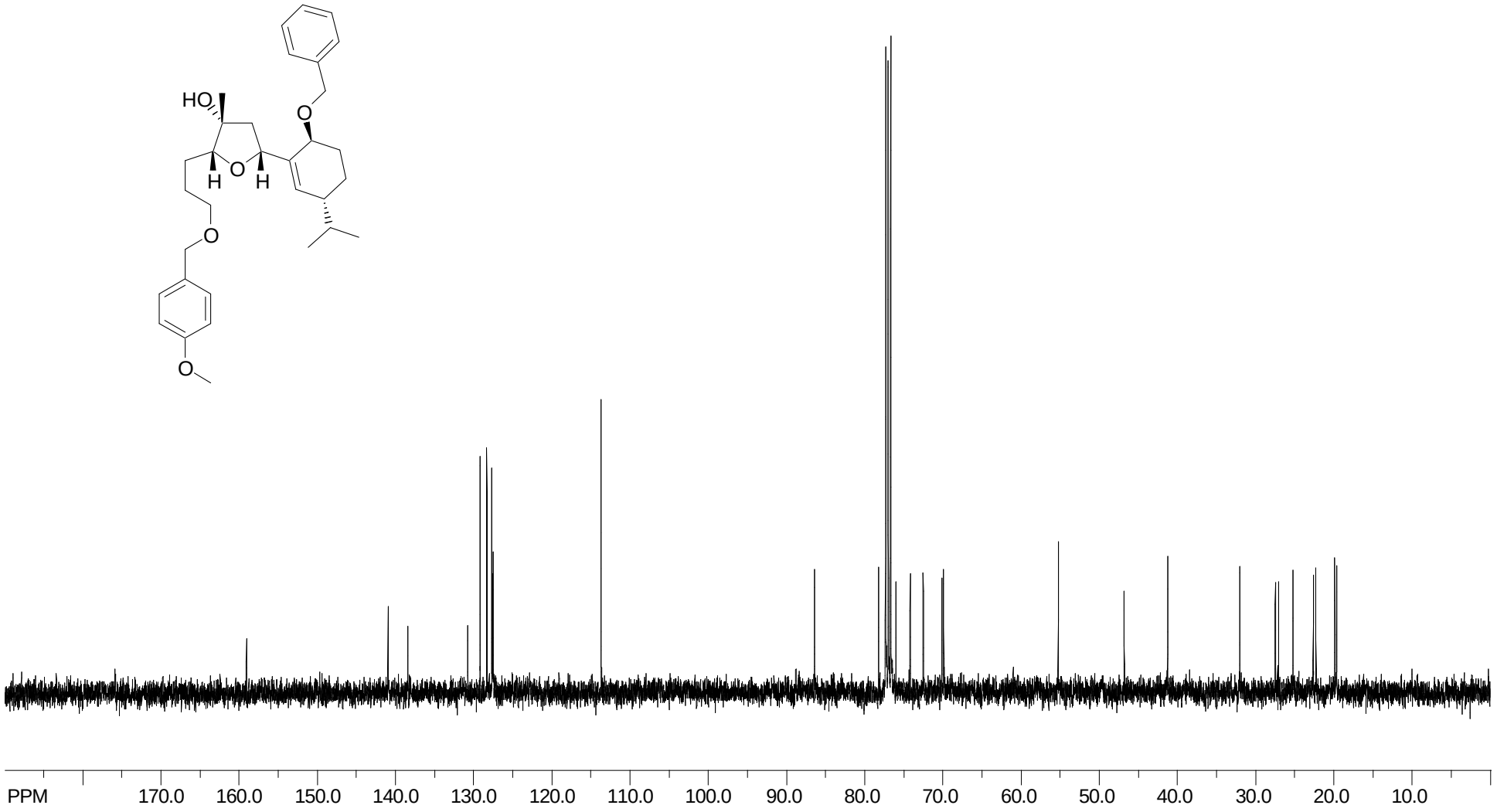
HO
O
H
O
H
O
O
PPM
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150.0
140.0
130.0
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90.0
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70.0
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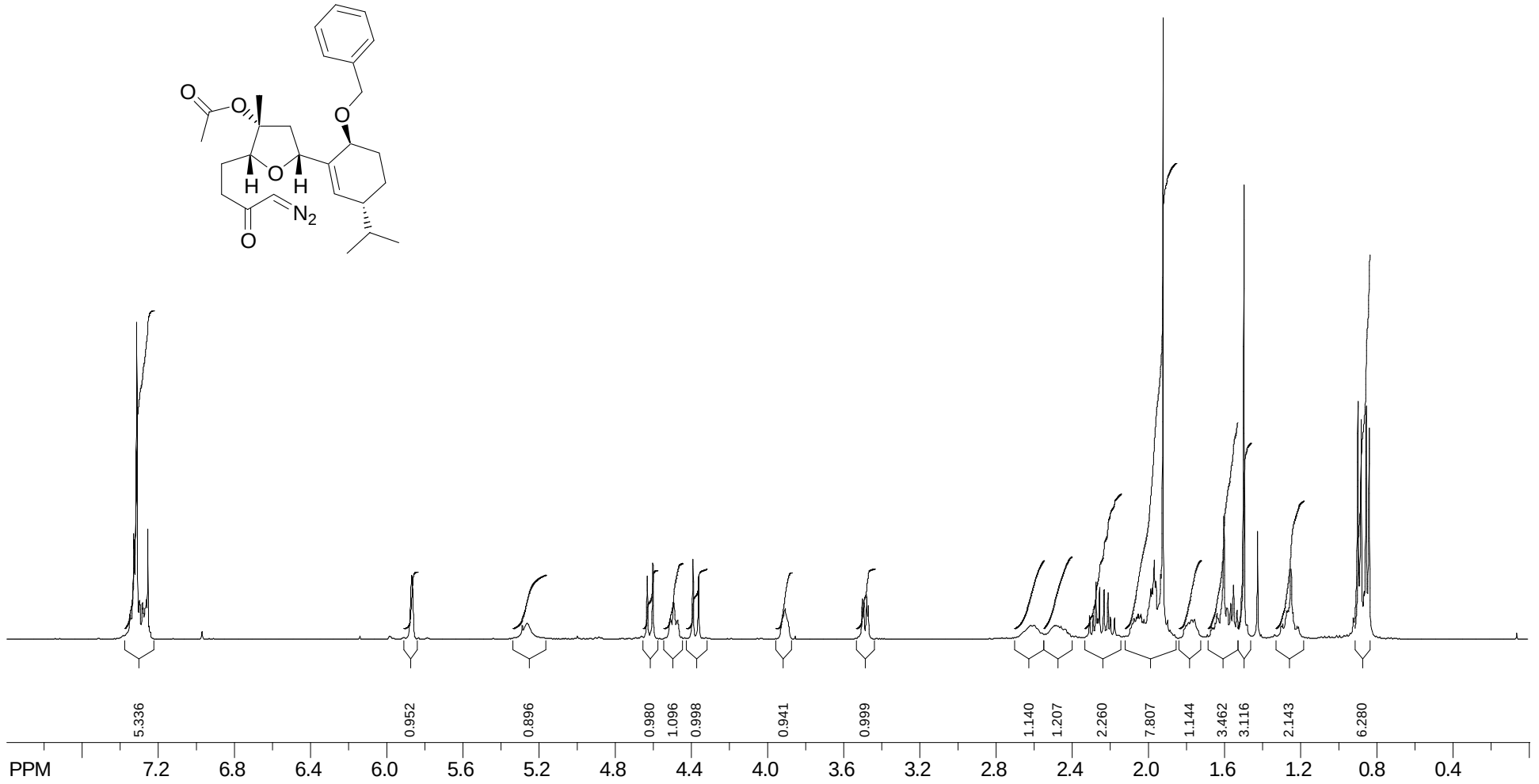
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O
H
N2
O
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0.980
1.096
0.998
0.941
0.999
1.140
1.207
2.260
7.807
1.144
3.462
3.116
2.143
6.280
PPM
7.2
6.8
6.4
6.0
5.6
5.2
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2.0
1.6
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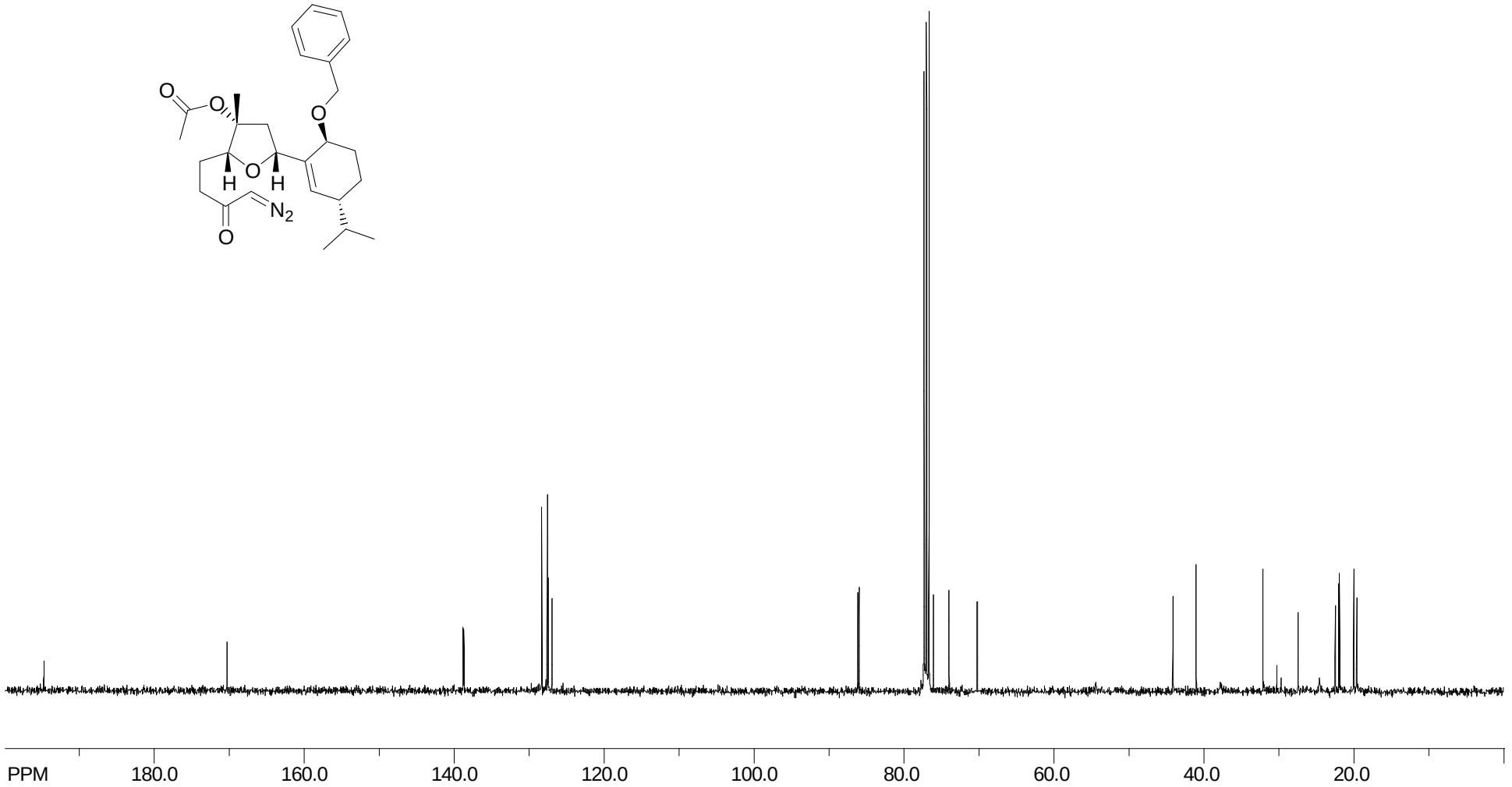
O
O
O
H
O
H
N2
O
PPM
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100.0
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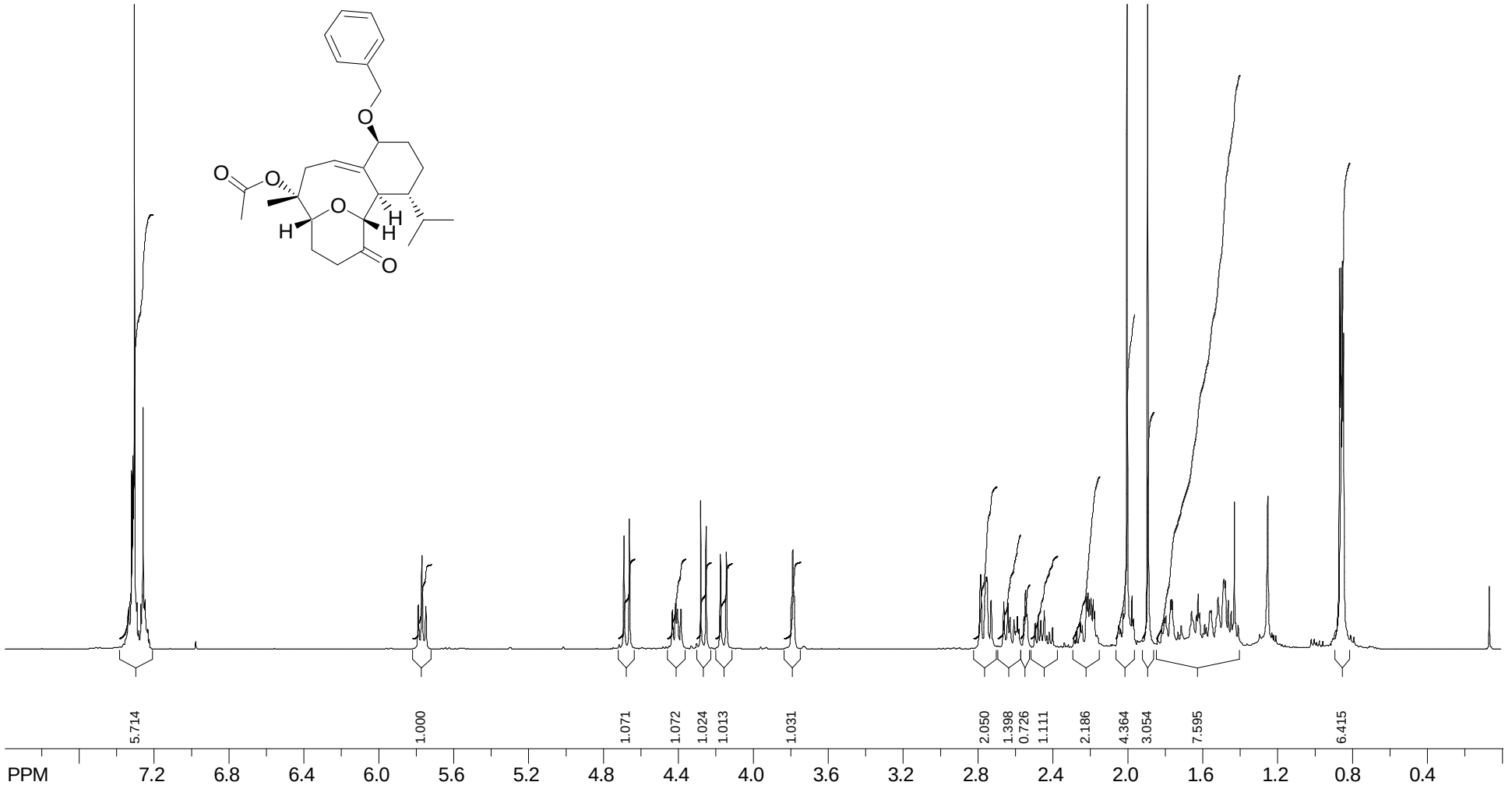
60.0
40.0
20.0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H
O
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2.050
1.398
0.726
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2.186
4.364
3.054
7.595
6.415
PPM
7.2
6.8
6.4
6.0
5.6
5.2
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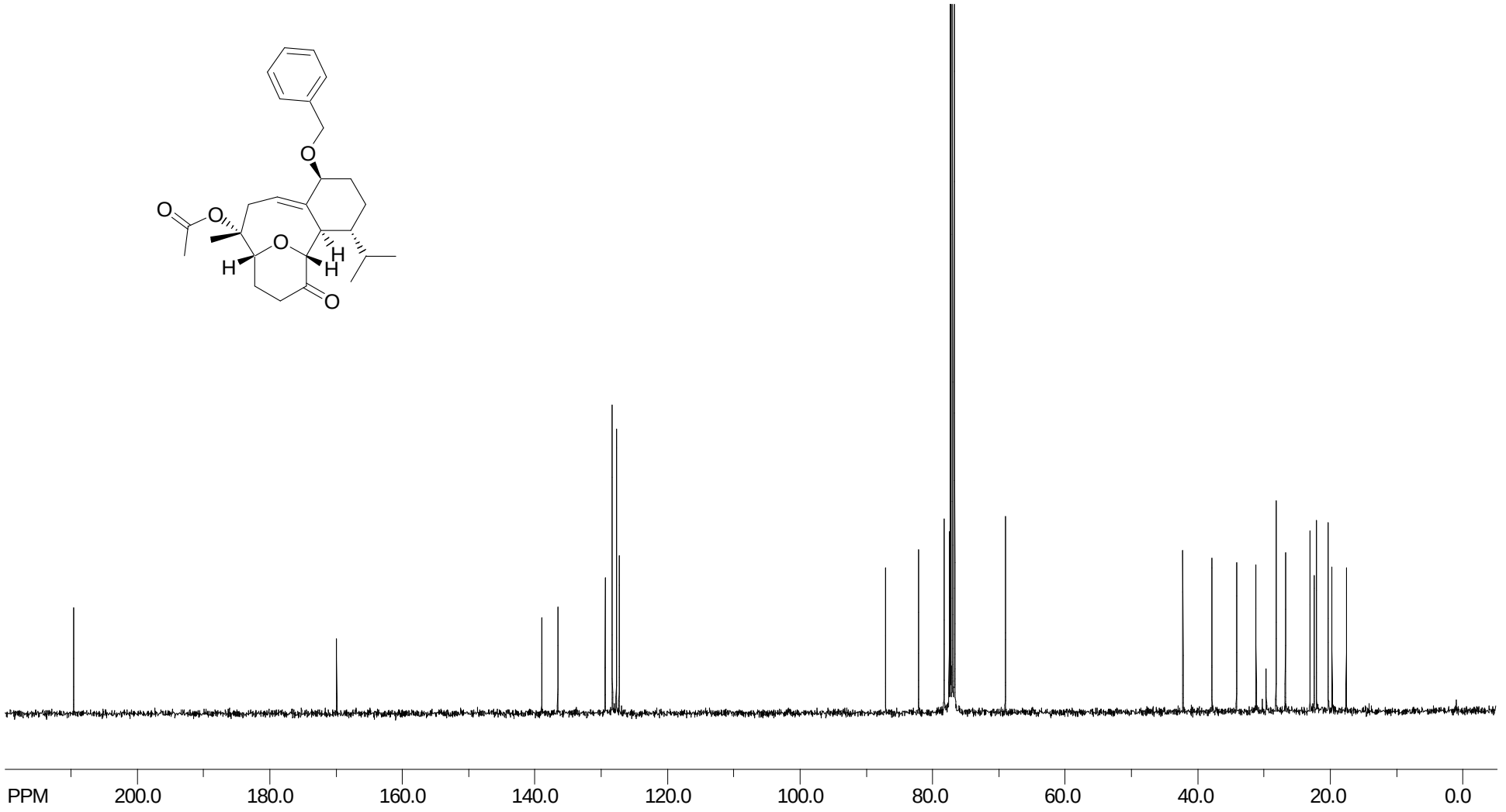
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O
O
O
H
H
H
O
PPM
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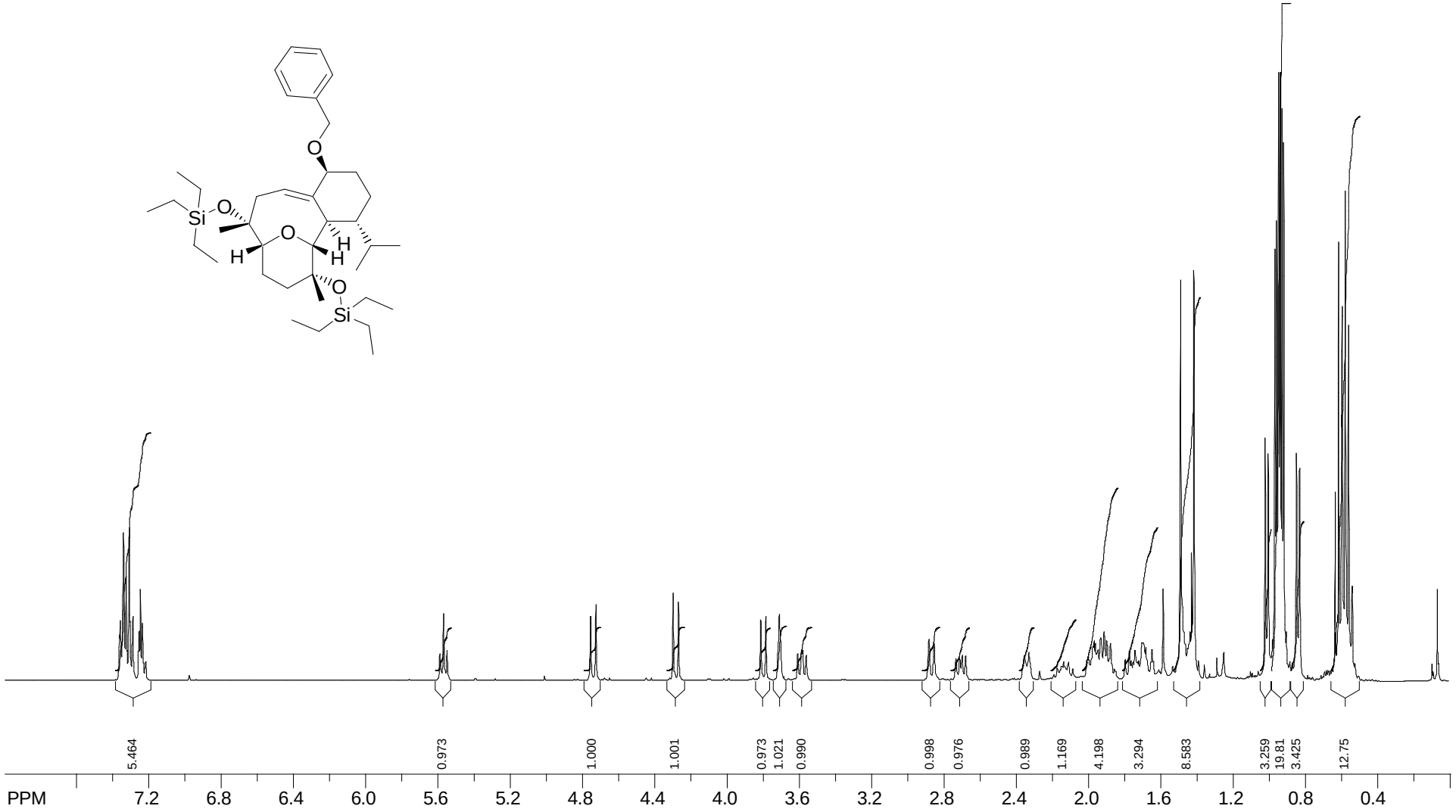
20.0
0.0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H
H
H
O
Si
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0.990
0.998
0.976
0.989
1.169
4.198
3.294
8.583
3.259
19.81
3.425
12.75
PPM
7.2
6.8
6.4
6.0
5.6
5.2
4.8
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3.2
2.8
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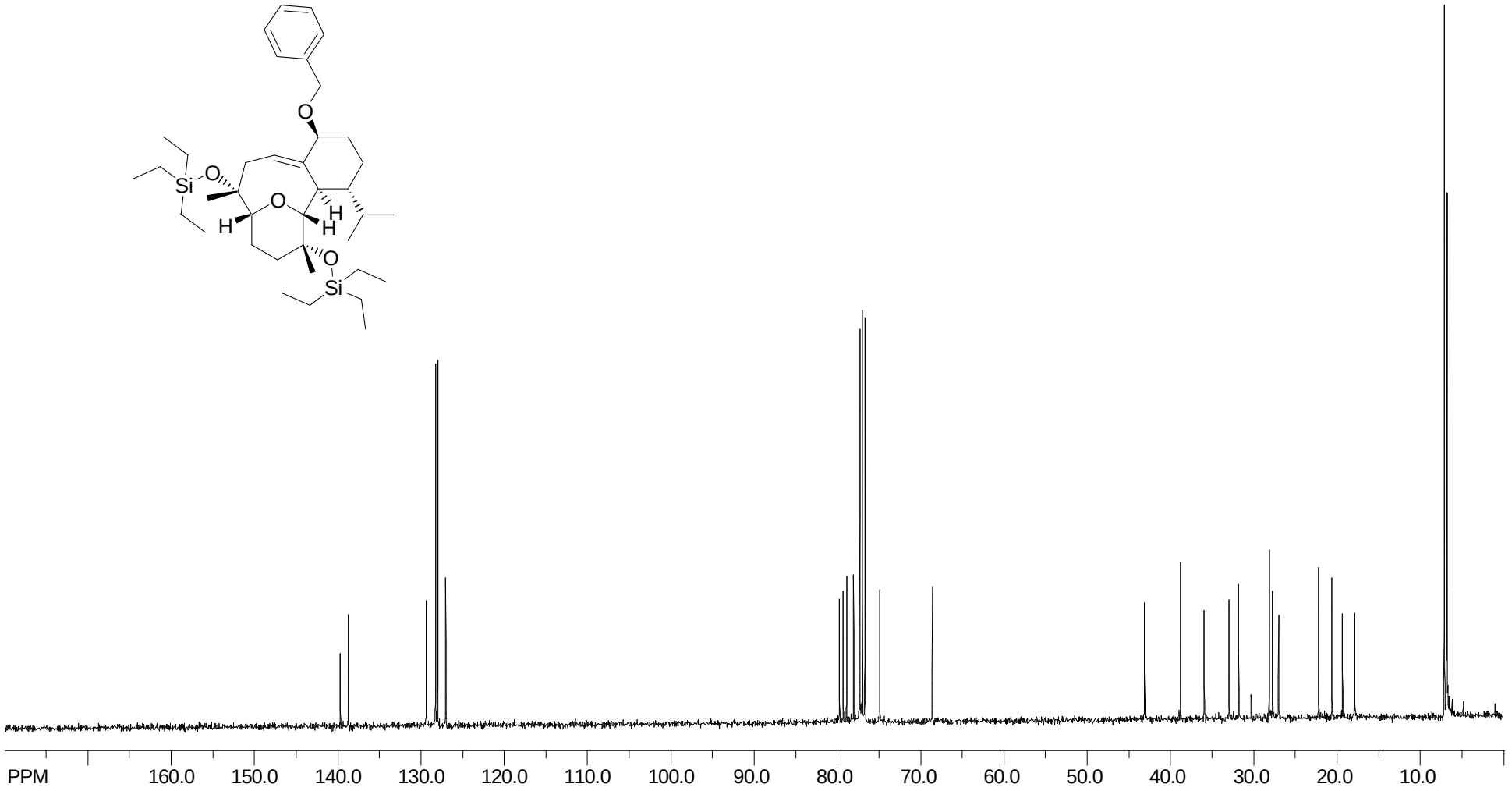
2.0
1.6
1.2
0.8
0.4


O
Si
O
O
H
H
H
O
Si
PPM
160.0
150.0
140.0
130.0
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100.0
90.0
80.0
70.0
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50.0
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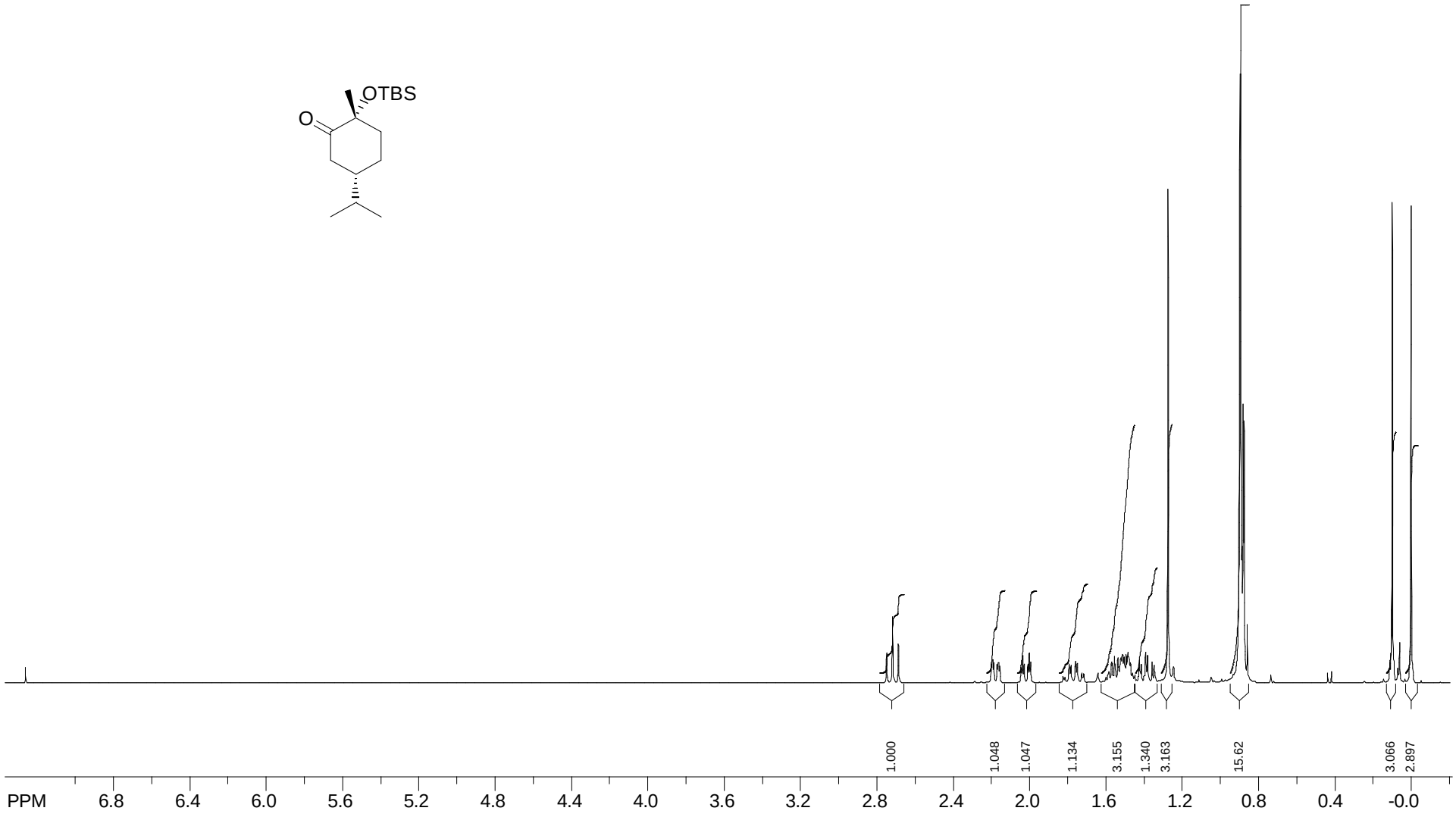
10.0


OTBS
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3.163
15.62
3.066
2.897
PPM
6.8
6.4
6.0
5.6
5.2
4.8
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2.4
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1.6
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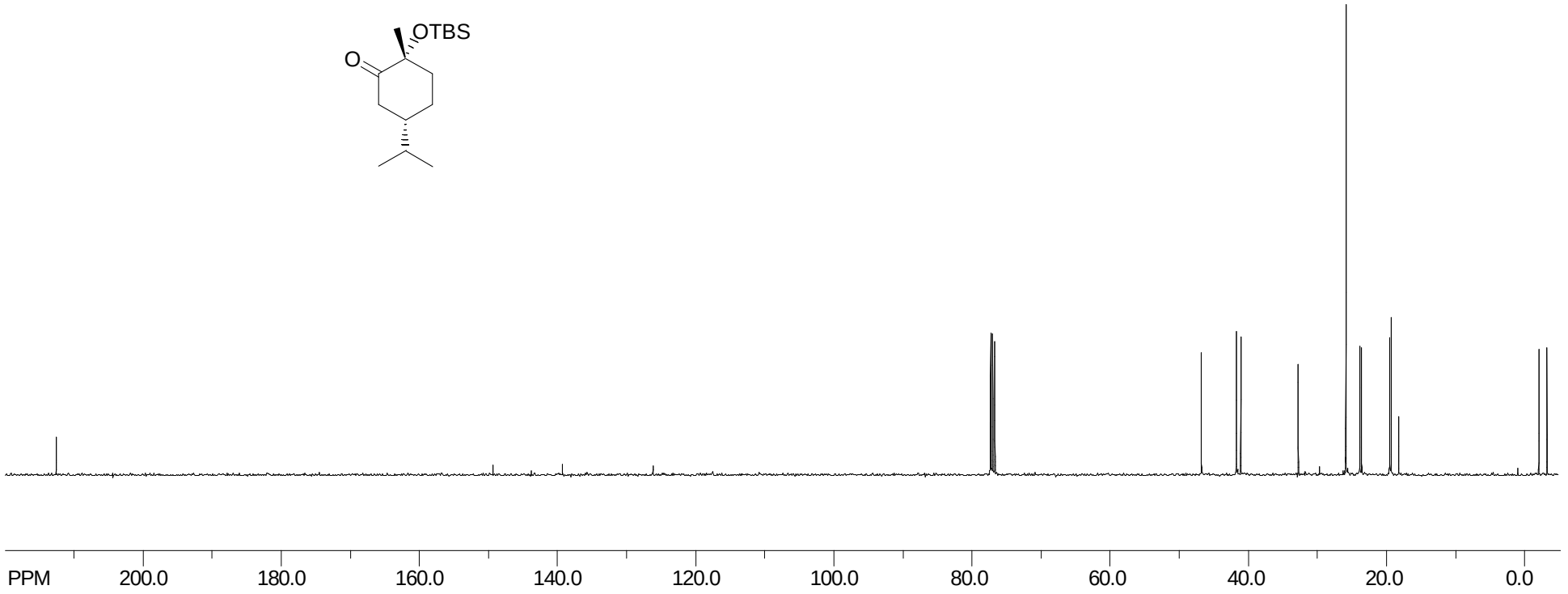
0.8
0.4
-0.0


OTBS
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PPM
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180.0
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0