Studies Towards the Total Synthesis of Neoliacinic Acid

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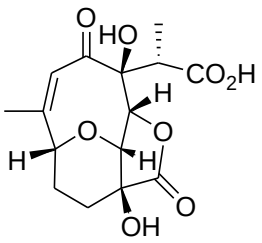
Gone but never forgotten

Monique Nuter and Jean Chabert.

Abstract

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



Neoliacinic acid

Chapter 1 provides an introduction to metal carbenoids, their preparation and uses in organic synthesis. Cyclopropanation reaction, C-H insertion and oxonium ylide formation and their subsequent rearrangements are discussed in detail.

The target molecule is described followed by previous synthetic attempts toward neoliacinic acid. The Clark group strategy toward neoliacinic acid is explained with a retrosynthetic analysis using two metal-carbenoid transformations: intramolecular C-H insertion and oxonium ylide formation followed by [2,3]-sigmatropic rearrangement.

Chapter 2 describes efforts towards the total synthesis of the target molecule from commercially chiral pool materials. A synthetic route is described in which construction of the two precursors required for metal carbenoid formation is followed by the application of the two key reactions to build the oxabicyclic core of the natural product. Efforts to generate an advanced intermediate containing the third ring (the lactone) including all six stereocentres present in the natural product are detailed. Finally, various options for completion of the synthesis as future work are discussed.

Contents

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Finally, thank you to all my friends and colleagues from the lab, especially Anna, Derek, Emelie, Guang and Ralph, I have really enjoyed to work with them and they made this thesis unforgettable and pleasant. To all, thank you.

Declaration

I hereby declare that the substance of this thesis has not been submitted, nor is being 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 when the work of other investigators has been used, this has been fully acknowledged in the text.

Frédérick Nuter

Professor J. S. Clark

Abbrevation

p-ABSA	*p*-acetamidobenzenesulfonyl azide
Ac	acetyl
acac	acetylacetonate
acam	acetamide
Ac_2O	acetic anhydride
AIBN	2,2-azobis(2-methylpropionitrile)
B-Br-9-BBN	9-bromo-9-boracyclo-[3.3.1]nonane)
Bn	benzyl
BNP	binaphthyl phosphate
°C	degrees Celsius
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DDQ	2,3-dichloro-4,5-dicyanobenzoquinone
de	diastereomeric excess
DIBAL–H	diisobutyl aluminium hydride
DMAP	*N*,*N*-dimethyl-4-aminopyridine
2,2-DMB	2,2-dimethylbutane
DME	dimethyl ether
DMDO	dimethyldioxirane
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
DOSP	*p*-dodecylphenylsulfonyl
dr	diastereomeric ratio
ee	enantiomericexcess
Et	ethyl
Et_3N	triethylamine

EtOAc	ethyl acetate
Et_2O	diethyl ether
g	gramme(s)
h	hour(s)
Hal	halide
hfacac	hexafluoroacetylacetonate
Hz	hertz
IC_{50}	half maximal inhibitory concentration
Imid	imidazole
^{i}Pr	isopropyl
NaHMDS	sodium bis(trimethylsilyl)amide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
MACIM	methyl l-acetylimidazolidin-2-one-4(*S*)-carboxylate
*m*CPBA	*meta*-chloroperbenzoic acid
M	mole(s) per litre of solvent
Me	methyl
MEOX	methyl 2-oxooxazolidine-carboxylate
MEPY	methyl 2-oxopyrrolidine-5(*S*))-carboxamide
mg	milligramme(s)
min	minute(s)
μL	microlitre(s)
mL	millitre(s)
mmol	millimole(s)
ML_n	Transition metal with ligand
MPPIM	methyl 3-phenylpropanoyl-2-oxoimidazolidine-carboxylate
MS	molecular sieves
Ms	methanesulfonyl
MTM	methylthiomethyl ether
OAc	acetate
Oct	octanoate dimer
OP	protected hydroxyl group
PDC	pyridinium dichromate

Pet. Ether	petroleum ether
pfb	perfluorobutyrate
Ph	phenyl
PHT	pyrrolidonehydrotribromide
PHOX	4-phenyloxazolidin-2-one
PMB	*para*-methoxybenzyl
PPTS	pyridinium-*para*-toluenesulfonate
PTPA	*N*-phthaloyl-(*S*)-phenylalaninate
PTSA	pyridinium-*para*-toluenesulfonic acid
PTTL	*N*-phthaloyl-(*S*)-*t*-leucinate
Py	pyridine
Quant	quantitative yield
R	general substituent
rt	room temperature
S	substrate
TBAI	tetrabutylammonium iodide
^{t}Bu	*tert*-butyl
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TBSP	*tert*-(butylphenyl)sulfonyl-(2*S*)-pyrrolidinecarboxylate
Temp	temperature
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
tfa	trifluoroacetate
tfacac	trifluoroacetylacetonate
tfacam	trifluoroacetamide
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
TPA	triphenylacetate
TPAP	tetrapropylammonium perruthenate
Ts	*para*-toluensulfonyl

UHP	urea-hydrogen peroxide complex

Chapter I Introduction

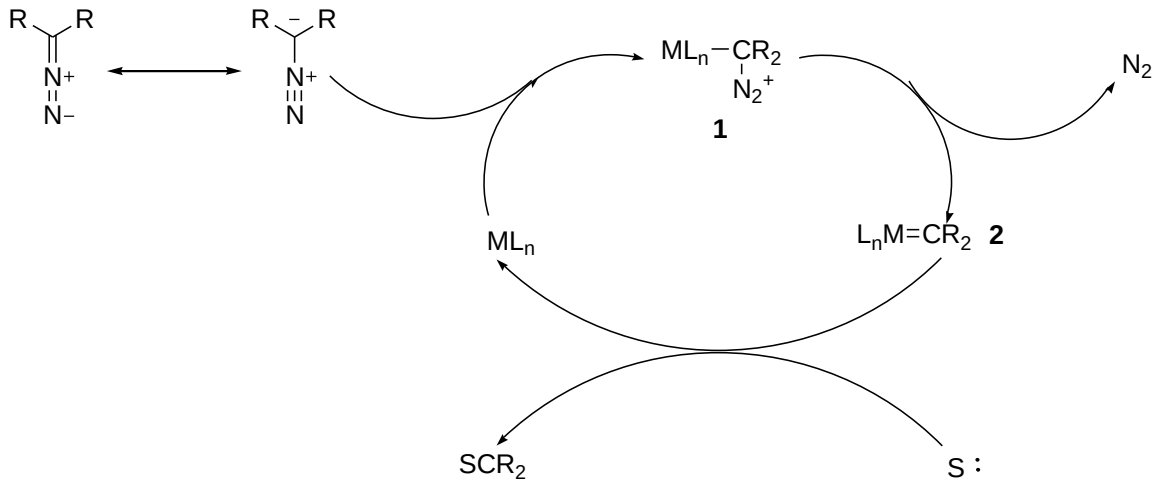
1 Introduction to metal carbenoid reactions

Due to their instability and high reactivity, free carbenes have not extensively been used in organic synthesis. However, the development of transition metal chemistry gives access to the more stable metal-carbene complex which has been found to be useful as synthetic intermediate. Metal carbene generation is usually obtained by transition metal catalysed decomposition of a diazo compound and the resulting complex is normally described as a metal carbenoid. The reactivity of the carbene is tempered by the transition metal and this complex metal-carbene can undergo subsequent reactions with a greater degree of control over stereoselectivity, chemoselectivity and reactivity.[1]

1.1 Metal carbenoid reactions

Reactions involving a metal carbenoid have become increasingly useful in carbon-carbon bond formation. Lewis acidic transition metals are especially efficient at catalysing the decomposition of the diazo compound. Their catalytic activity depends on coordinative unsaturation at the metal centre, and the generally accepted mechanism for catalytic decomposition of a diazo compound is shown in Scheme 1. The formation of the metal-stabilised carbene or metal carbenoid **2** is achieved by electrophilic addition of the metal complex involving the loss of dinitrogen. Transfer of the electrophilic carbene to an electron-rich substrate S regenerates the catalyst and completes the cycle with the formation of the new carbon-carbon bond.

[1] Doyle, M. P. *Chem, Rev.* **1986**, *86*, 919; Merlic, C. A.; Zechman, A. L. *Synthesis*, **2003**, 1137.



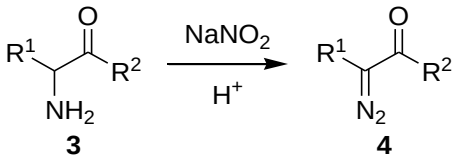
Scheme 1. Mechanism for the catalytic decomposition of a diazo compound.

1.2 Preparation of diazo carbonyl compounds

There is a variety of methods for the preparation of diazo compounds and the choice of the method depends upon the nature of the functional groups present in the diazo compound. The most commonly used and widely applicable methods for the synthesis of diazo compounds fall into three general categories:

1.2.1 Reaction between two nitrogen-containing compounds

Diazotisation of an α-amino carbonyl compound to form a diazo carbonyl compound is possible (Scheme 2). This reaction was the first used to synthesise ethyl diazo acetate from glycine ethyl ester hydrochloride.[2]

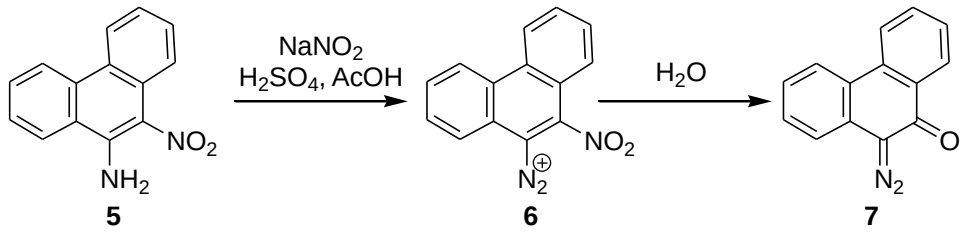


Scheme 2. Diazotisation of an α-amino carbonyl compound. R^1or R^2 = Electron withdrawing group.

The diazotisation of certain aromatic amines with nitrous acid under acid conditions furnishes the corresponding α-diazo compound, for example the conversion of

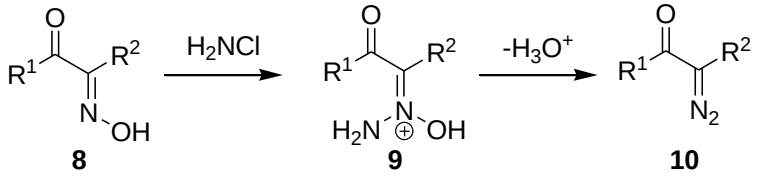
[2] Curtius, T. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2230.

9-amino-10-nitrophenanthrene **5** to form 9-diazo-10-phenanthrenone **7** (Scheme 3).[3]



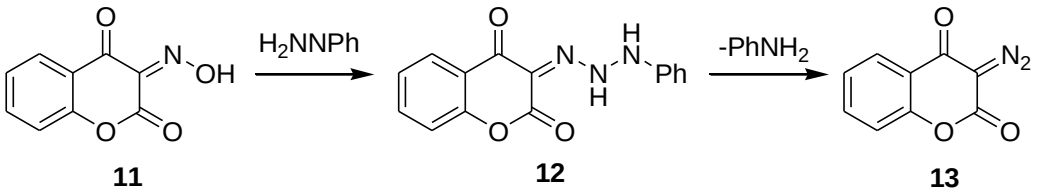
Scheme 3. Diazotation of aromatic amines.

Conversion of an α-keto oxime into a α-diazo ketone can be performed with the Forster reaction. To this end, an α-keto oxime **8** is treated with chloroamine to give the intermediate **9** which suffers dehydration to give the diazo ketone **10** (Scheme 4).[4]



Scheme 4. The Forster reaction. R^1or R^2 = H, aryl group.

An alternative to this transformation is the condensation of an oxime directly with phenylhydrazine. For example, this reaction has been used to prepare 3-diazo-2,4-chromanedione **13** from the oxime **11** (Scheme 5).[5]

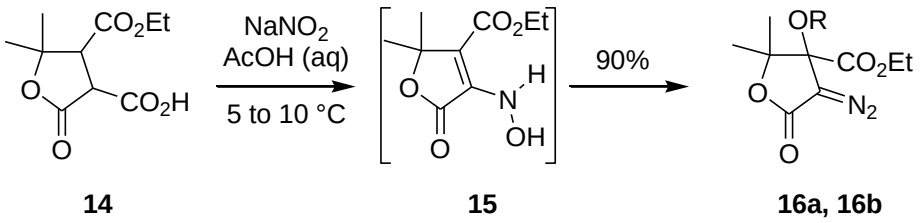


Scheme 5. The Forster reaction with phenylhydrazine

Direct nitrosation of carbonyl compounds is also a good method for preparation of an α-diazo carbonyl compound. For example the nitrosation of the lactone **14** leads to the

[3] Barton, J. W.; Grinham, A. R.; Whitaker, K. E. *J. Chem. Soc*. **1971**, *8*, 1384.
[4] Forster, M. O. J. *Chem. Soc., Transaction*, **1915**, *107*, 260.
[5] Casini, G.; Gualtieri, F.; Stein, M. L. *Gazz. Chem. Ital*. **1965**, *95*, 983.

formation of the diazo lactones **16a** and **16b** (Scheme 6). [6]

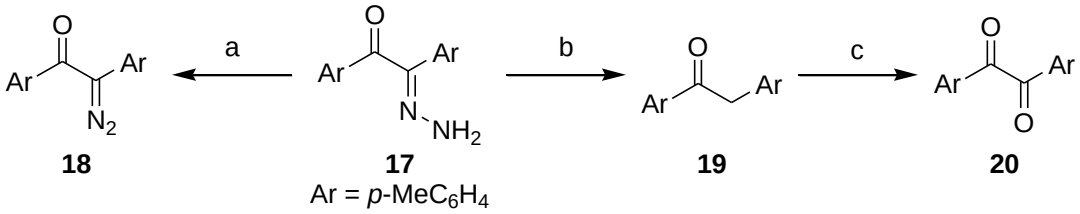


14 **15** **16a, 16b**

Scheme 6. Nitrosation of the lactone **14**. **16a** R = H, **16b** R = OAc.

1.2.2 Conversion of a group containing two nitrogen atoms into a diazo group

Dehydrogenation of hydrazones is an option to prepare *α*-diazo carbonyl compounds. This alternative is especially useful when the hydrazone precursor can be prepared directly from the corresponding carbonyl compound. Mercury(II),[7] silver(II)[8] and manganese(IV)[9] oxide are the oxidising agents most commonly used. The reaction can be performed in a variety of solvents, using sodium sulfate to trap the water liberated during the reaction. Addition of a trace of potassium hydroxide promotes the deprotonation step and accelerates the reaction.[7b] The quality of the reagent has shown significant influence on the success of the dehydrogenation reaction. For example, treatment of the hydrazone **17** with activated mercury(II) oxide results in the formation of the α-diazo ketone **18**, whereas in case of treatment with a reagent of lower activity, a Wolff-Kishner reduction followed by subsequent oxidation lead to the *α*-diketone **20** (Scheme 7).[10]



18 **17** **19** **20**

Ar = *p*-MeC_6H_4

Scheme 7. Conditions: (a) Hg(II)O, THF, Na_2SO_4, KOH, –20 °C. (b) Deactivated HgO. (c) Oxidation.

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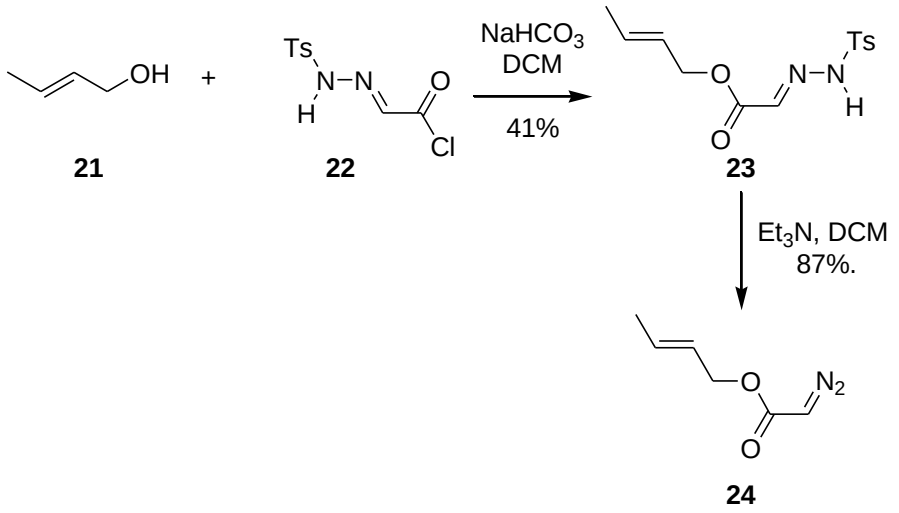
[6] Torii, S.; Endo, S.; Oka, H.; Kariya, Y. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2707.
[7] (a) Newman, M. S.; Arkell, A. *J. Org. Chem.* **1959**, *24*, 385. (b) Miller, J. B.; *J. Org. Chem.* **1959**, *24*, 560.
[8] Heyns, V. K.; Heins, A. *Liebigs Ann. Chem.* **1957**, *604*, 133.
[9] (a) Morrison, H.; Danishefsky, S., Yates, P. *J. Org. Chem.* **1961**, *26*, 2617.
[10] Droescher, H.; Jenny, E. F. *Helv. Chem. Acta.* **1968**, *51*, 643.

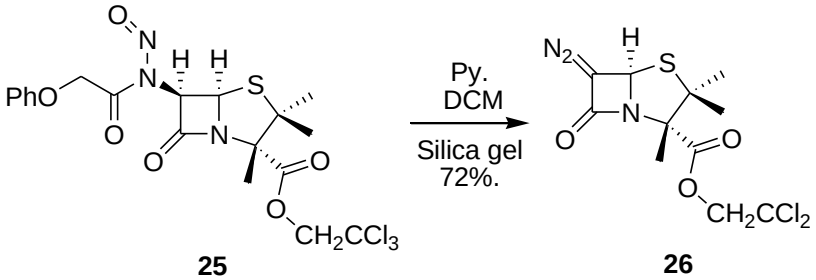
The Bamford-Stevens reaction provides a versatile method for converting a carbonyl compound into a diazo compound.[11] During the reaction, tosyl hydrazone is cleaved to give a diazo compound and a sulfinate. The reaction is usually achieved by heating the substrate in a presence of a base and the harsh conditions often lead to low yields of sensitive diazo compounds. The Bamford-Stevens reaction has been used for the preparation of α-diazoacetates of unsaturated alcohols. For example, acylation of (*E*)-but-2-en-1-ol **21** with tosyl hydrazonoacetyl chloride **22** gives the ester **23,** which upon treatment with triethylamine in dichloromethane affords the α-diazoacetate **24** (Scheme 8).[12]



21 **22** **23** **24**

Scheme 8. The Bamford-Stevens reaction.

There are some examples of the preparation of α-diazo carbonyl compounds from the cleavage of *N*-alkyl-*N*-nitrosocarboxamides. Scheme 9, using pyridine as the base for the cleavage reaction, the sensitive α-diazo penicillin **26** has been prepared from the N-nitrosoamide **25**[13] which was prepared from penicillin derivative according the method of Hauser and Sigg. [14]



25 **26**

Scheme 9. Cleavage of *N*-nitrosamide.

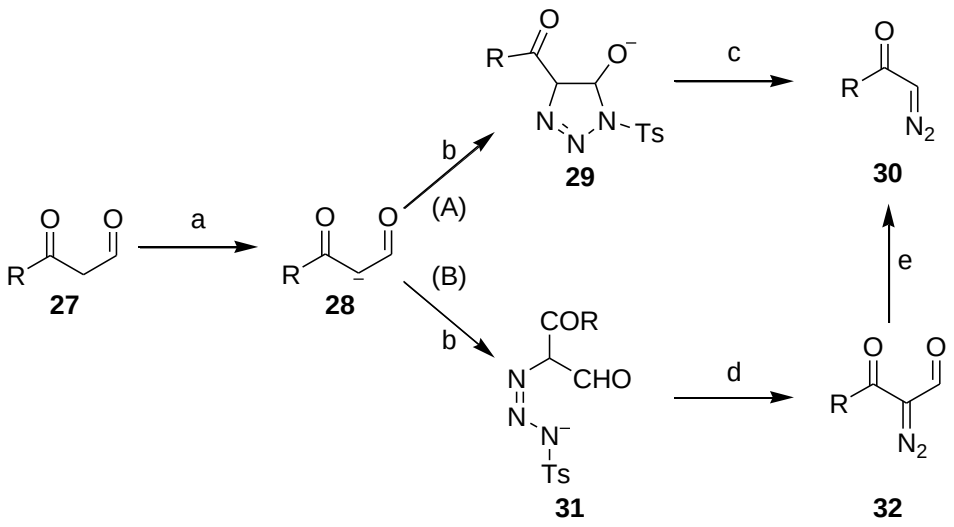
[11] Bamford, W. R.; Stevens, T. S. *J. Chem. Soc.* **1952**, 4735.
[12] House, H. O.; Blankley, C. J. *J. Org. Chem.* **1968**, *33*, 53.
[13] Sheehan, J. C.; Lo, Y. S.; Löliger, J.; Podewell, C. C. *J. Org. Chem.* **1974**, *39*, 1444.
[14] Hauser, D.; Sigg, H. P. *Helv. Chim. Acta.* **1967**, *50*, 1327.

1.2.3 Diazo group transfer to a carbonyl compound

Diazo group transfer reactions are transformations in which an intact diazo unit is transferred from a donor to an acceptor molecule. In this case, the explosion, toxicity and carcinogenic risks, associated with the use of diazo alkane reagents, are avoided. Because of its mildness, simplicity and reliability, the reaction became the method of choice for the preparation α-diazo-β-dicarbonyl compounds and the best substrates for diazo group transfer are those possessing active methylene groups. Formation of an intermediate triazine occurred during the diazo transfer, resulting from attack of the azide to an anion of the active methylene compound. Then, spontaneous decomposition of this intermediate, accompanied by a proton shift, leads to the diazo compound. A large variety of azides, including tosyl azide,[15] methanesulfonyl azide,[16] and *para*-carboxybenzenesulfonyl azide,[17] have been used as the transfer reagent in this reaction.

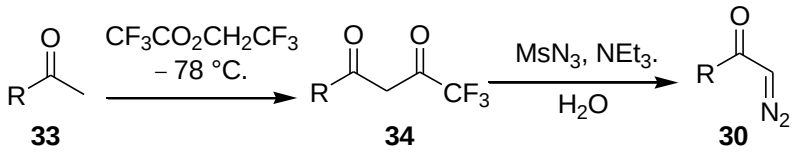
However, a limitation of diazo transfer reactions of this type is the requirement for two electron-withdrawing substituents to activate the methylene group. This problem can be avoided with the introduction of a formyl group by Claisen condensation which activates temporarily the methylene group. The deformylation reaction can proceed during the diazo transfer via two possible pathways: (a) a triazoline intermediate **29** is formed followed by a spontaneous decomposition to give the sulfonylformamide and the α-diazo ketone product **30** or (b) An intermediate triazine **31** is formed, and loss of the formyl group occurs by alcoholysis. (Scheme 10). [18]

[15] (a) Koskinen, A. M. P.; Munoz, L. *J. Chem. Soc., Chem. Commun.* **1990**, 652. (b) Regitz, M. *Angew. Chem. Int. Ed.* **1967**, *6*, 733.
[16] Taber, D. F.; Ruckle, R. E.; Hennessy, M. J. *J. Org. Chem.* **1986**, *51*, 4077.
[17] Hendrickson, J. B.; Wolf, W. A. *J. Org. Chem.* **1968**, *33*, 3610.
[18] Regitz, M.; Menz, F. *Chem. Ber.* **1968**, *101*, 2622.



Scheme 10. Diazo transfer. Conditions: (a) base, $-H^+$. (b) TsN_3, ROH. (c) $-Ts(CHO)N^-$. (d) $-TsNH^-$. (e) ROH, $-HCO_2R$.

The diazo transfer reaction can be improved dramatically by a trifluoroacetylation of a ketone followed by treatment with methanesulfonyl azide in the presence of triethylamine (Scheme 11).[19] This procedure is generally superior to that involving ketone formylation and deformylative diazo transfer.



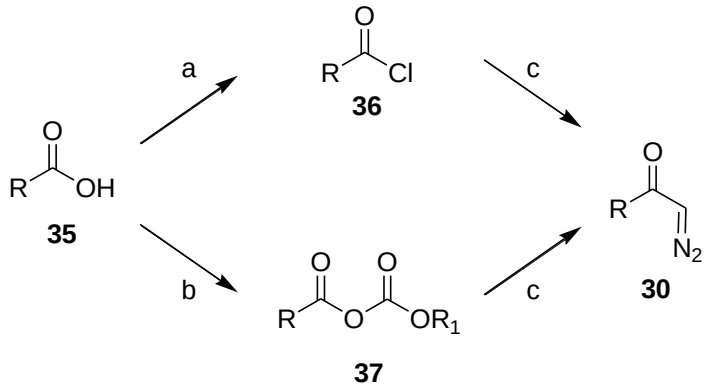
Scheme 11. Trifluoroacetylation of a ketone

Acylation of diazomethane remains the single most important route for the synthesis of terminal diazoketones. The procedure usually involves addition of an acyl chloride to an ethereal solution of diazomethane at or below 0 °C. Treatment of the carboxylic acid **35** with oxalyl chloride, triethylamine, and a catalytic amount of DMF furnishes the acyl chloride **36**. The resulting solution is filtered and treated with an excess of diazomethane[20] to furnish **30** (Scheme 12). Undesirable hydrochloric acid is generally produced during the reaction and this side product may lead to product degradation. To circumvent this problem, an excess of diazomethane is usually used to quench the acid

[19] Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959.
[20] Pettit, G. R; Nelson, P. S. *J. Org. Chem.* **1986**, *51*, 1282.

produced.

Anhydrides are also suitable acylating substrates for diazomethane (Scheme 12).[21] In this case, reaction of the carboxylic acid **35** and a chloroformate delivers the mixed anhydride **37**, which is followed by treatment with ethereal solution of diazomethane.[22] Methyl chloroformate, ethyl chloroformate and isobutyl chloroformate are commonly used to generate the mixed anhydride **37**. The reactivity of the carbonyl group bordered by two oxygen groups is decreased; consequently the diazomethane attack is directed towards the carbonyl group originating from the carboxylic acid. To minimise side reactions, low temperatures are usually employed. This method appears to be the one of choice for the generation of diazoketones when acid chloride formation is inappropriate because of the reactivity of other functional groups in the molecule. Generally, high yields can be obtained by using either acyl chloride route or anhydride route (Scheme 12).



Scheme 12. Acylation of diazomethane. Conditions: (a) $(COCl_2)_2$, DCM, DMF (cat). (b) R_2OCOCl, NEt_3, Et_2O. (c) CH_2N_2, Et_2O, –78 °C.

The most common and convenient method of generating diazomethane is by base-catalysed decomposition of *N*-methyl-*N*-nitroso amines. There are three *Organic Synthesis* procedures from three different precursors.[23] Currently, the majority of users employ one of two commercialy available precursors: (i) *N*-methyl-*N*-nitroso-*N*-nitroguanidine (NNMG) **38**, or (ii) *p*-tolylsulfonylmethylnitrosamide (DIAZALD) **39**.[24,25] (Figure 1).

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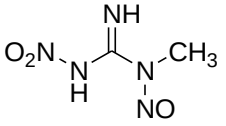
[21] (a) Bradley, W.; Robinson, R. *J. Am. Chem. Soc.* **1930**, *52*, 1558.(b) Weygand, F.; Bestmann, H. J. *Angew. Chem.* **1960**, *72*, 535.

[22] (a) Tarbell, D. S.; Price, J. A. *J. Org. Chem.* **1957**, *22*, 245.(b) Harbeson, S. L.; Rich, D. H. *J. Med. Chem.* **1989**, *32*, 1378.

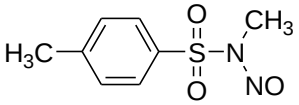
[23] (a) Arndt, F. Amstutz, E. D.; Myers, R. R. *Org. Synth.* **1935**, *15*, 48. (b) De Boer, T. J.; Backer, H. J. *Org. Synth.* **1956**, *36*, 16. (c) Moore, J. A.; Reed, D. E. *Org. Synth.* **1961**, *41*, 16.

[24] McKay, A. F. *J. Am. Chem. Soc.* **1948**, *70*, 1974.

[25] DeBoer, T. J.; Backer, H. J. *Org. Synth.* **1954**, *34*, 96.



38 MNNG



39 DIAZALD

Figure 1. Commercially available diazomethane precursors.

1.3 Diazocarbonyl compounds as carbene precursors

The electrophilicity of the metallocarbenoid intermediates affects the chemo-, regio-, and stereoselectivity on the C–H insertion reaction. This electrophilic character results not only from the effect of the associated ligated metal complex but also from the interactions with the substituents on the carbenoid carbon.[26] Consequently, the stability and the reactivity of the metallocarbenoid complex depend also on the nature of the carbonyl group and additional substituents at the carbene carbon.[27] Metallocarbenoids can be subdivided into three categories: (a) carbenoids containing one electron-withdrawing group (acceptor substituent), (b) those possessing two electron-withdrawing groups (two acceptors substituents) and (c) those having an electron-donating and an electron-withdrawing group (donor/acceptor substituents). An electron-withdrawing group will tend to make the carbenoid more electrophilic and reactive whereas a donor group makes the carbenoid more stable and chemoselective.

Acceptor substituted carbenoids are derived from diazo compounds possessing a single electron withdrawing substituent (Figure 2).[28] Nitrogen extrusion from these diazo compounds to generate highly reactive metallocarbenoid species can be achieved using a variety of metal catalysts. The most widely employed acceptor-substituted α-diazocarbonyl compounds in metallocarbenoid chemistry are alkyl diazoacetates **40**. The carbenoids derived from diazoketones **41** are usually more reactive than those generated from diazoacetates **40**, whereas the carbenoids from diazoacetamides **42** are the least reactive in the series.

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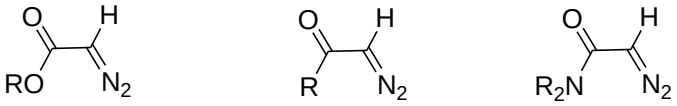
[26] (a) Doyle, M. P.; Shanklin, M. S.; Pho, H. G.; Mahapatro, S. N. *J. Org. Chem.* **1988**, *53*, 1017. (b) Ceccherilli, P.; Curini, M.; Marcotullio, M. C.; Rosati, O. *Tetrahedron* **1992**, *48*, 9767. (c) Doyle, M. P.; Dyatkin, A. B. *J. Org. Chem.* **1995**, *60*, 3035. (d) Pirrung, M. C.; Liu, H.; Morehead, A. T. *J. Am. Chem. Soc.* **2002**, *124*, 1014.

[27] (a) Wee, A. G. H; Yu, Q. *J. Org. Chem.* **1997**, *62*, 3324. (b) Wang, J.; Liang, F.; Chen, B. *J. Org. Chem.* **1998**, *63*, 8589.

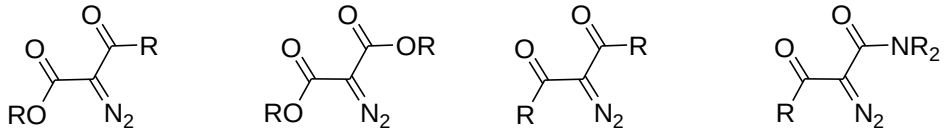
[28] Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091.



40 diazoacetate **41** diazoketone **42** diazoacetamide

Figure 2. Common precursors to acceptor-substituted carbenoid.

The acceptor/acceptor-substituted carbenoids are obtained from diazo compounds bearing two electron withdrawing groups such as carbenoids derived from diazoacetacetates **43**, diazomalonates **44**, diazo-1,3-diketones **45** and diazoacetoacetamides **46** (Figure 3).[25] The presence of the second electron withdrawing group stabilises the diazo compound, consequently very reactive metal complexes are required to decompose the diazo function. After the formation of the metal carbenoid, its electrophilic character is increased dramatically and the complex becomes very reactive for C–H bond insertion. Acceptor/acceptor-substituent carbenoids would be expected to be more reactive and less selective than the donor/acceptor-substituted carbenoids.[29]



43 diazoacetoacetate **44** diazomalonate **45** diazoketone **46** diazoacetoacetamide

Figure 3. Common precursors to acceptor/acceptor-substituted carbenoid.

The third group, encompassing donor/acceptor-substituted carbenoids, is a relatively late arrival to the field of metallocarbenoid chemistry. In this category, a donor substituent, such as aryl **47** or vinyl **48**, stabilises the carbenoid through resonance (Figure 4). There were very few reports concerning this class of carbenoid prior to 1985, and the first example of C–H insertion with this type of carbenoid was reported in 1997.[30] In the past few years, this class of carbenoids has been developed and because of their stability, they have proved to be able of undergoing highly chemoselective intermolecular C–H insertions.[31] However, the aryl and vinyl substituents stabilise the diazo precursor, and so very active catalysts are required to generate the corresponding metal carbenoids.

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[29] Davies, H. M. L.; Panaro, S. A. *Tetrahedron* **2000**, *56*, 4871.
[30] Davies, H. M.; Hansen, T. *J. Am. Chem. Soc.* **1997**, *119*, 9075.
[31] (a) Davies, H. M. L; Antoulinakis, E. G. *J. Organomet. Chem.* **2001**, *617*, 47. (b) Davies, H. M. *J. Mol. Catal.* **2002**, *189*, 125.

47 aryldiazoacetate **48** vinyldiazoacetate

Figure 4. Common precursors to donor/acceptor-substituted carbenoids.

1.4 Catalysts for diazo decomposition

Although the use of metal catalysts for the decomposition of diazo compounds has been known for more than 100 years,[32] the use of diazo compounds as precursors for metal carbenoid transformations has received much more attention in recent years due to the development of new transition metal catalysts. The use of a transition metal catalyst has proven to be capable of reducing the problems of selectivity and reactivity associated with the use of free carbenes. The catalytic activity of the transition metal complexes depends on coordinative unsaturation at the metal centre which allows them to react as electrophiles with diazo compounds. To create such metal carbenoids, a complex possessing sufficient electron-withdrawing ligands around an electron deficient metal is required. The choice of the metal-ligand combination is crucial for the outcomes of the reaction and increasing the electron withdrawal by the ligands on the metal generates a more reactive carbenoid that displays lower selectivity.

There is now general agreement that transition metal catalysts react with the diazo compound to generate an electrophilic metal carbene, as originally suggested by Yates.[33] A wide range of transition metal complexes have been used for the decomposition of α-diazo carbonyl compounds. Copper and rhodium complexes are particularly effective catalysts for reactions with diazo compounds and an increasing number of chemical syntheses are based on these catalytic complexes.

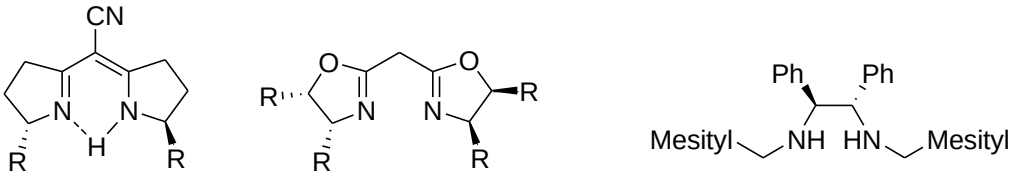
1.4.1 Copper catalysts for diazo decomposition

Insoluble copper bronze and copper(II) salts are the oldest of the copper catalysts employed for diazo decomposition. In the 1960s, Nozaki introduced soluble copper

[32] Silberrad, O.; Roy, C. S. *J. Chem. Soc.* **1906**, *89*, 179.
[33] Yates, P. *J. Am. Chem. Soc*. **1952**, *74*, 5376.

chelates such as bis(acetylacetate)copper(II)[34] and Moser reported the use of soluble (trialkyl) and (triarylphosphite)copper(I).[35] In 1972, Salomon and Kochi described the copper triflate complex as very good catalyst for the cyclopropanation of olefins with diazo compounds and during the reaction, the diazo compounds reduced copper(II) to copper(I). There is a general agreement that the active form of copper is in the +1 oxidation state. Firstly, addition of a small amount of the diazo compound to a solution of copper(II) catalyst results in a colour change corresponding to the reduction to copper(I), then the diazo compound and the catalyst form the metal carbenoid complex.[36] Initially, two bidendate ligands are bound to the copper(II), but upon reduction to copper(I) one of those bidendate ligands is presumed to dissociate from the metal, whereas the second ligand remains bound to the active copper(I) during diazo decomposition.[37] Today, the catalysts of choice are copper(II) acetylacetonate [$Cu(acac)_2$], copper(II) trifluoroacetylacetonate [$Cu(tfacac)_2$], and copper(II) hexafluoroacetylacetonate [$Cu(hfacac)_2$].

Copper catalysts with chiral ligands were developed to effect asymmetric induction in metal carbene transformations. Chiral ligands that are effective for enantioselective carbene formations include Pfaltz's chiral semicorrins **49**,[38] C_2-symmetric *bis*-oxazolines **50**,[39] and Kanemasa's C_2-symmetric diamine **51** (Figure 5).[40]



49 **50** **51**

R = CMe_2OH, $CH_2OSiMe_2(^tBu)$, COOMe

R = Ph

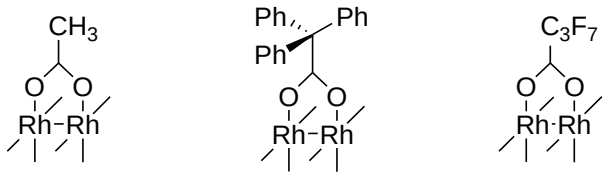
Figure 5. Chiral copper complexes.

1.4.2 Rhodium catalyst for diazo decomposition

Dirhodium(II) complexes are among the most effective and versatile catalysts for diazo decomposition. There is a variety of possible bridging carboxylate and carboxamide

[34] Nozaki, H.; Moriuti, S.; Yamabe, M.; Noyori, R. *Tetrahedron Lett.* **1966**, *1*, 59.
[35] Moser, W. R. *J. Am. Chem. Soc.* **1969**, *91*, 1135.
[36] Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Helv. Chim. Acta* **1988**, *71*, 1553.
[37] Evans, D. A.; Woerpel, K. A.; Hinman, M., M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726.
[38] Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Angew. Chem.* **1988**, *98*, 1028.
[39] Lowenthal, R. E.; Masamune, S. *Tetrahedron Lett.* **1991**, *32*, 7373.
[40] Kanemasa, S.; Hamura, S.; Harada, E.; Yamamoto, H. *Tetrahedron Lett.* **1994**, *35*, 7985.

ligands providing a degree of control and selectivity which is not possible with copper catalysts. rhodium(II) acetate dimer $[Rh_2(OAc)_4]$ **52** was prepared and characterised in the 1960s and shortly after it was introduced as a catalyst for diazo decomposition.[41] Then, replacement of the acetate ligands with other carboxylate functions was investigated. For example, rhodium(II) triphenylacetate dimer $[Rh_2(TPA)_4]$ **53** has been introduced as a highly efficient catalyst for the C–H insertion of α-diazo-β-keto esters.[42] (Figure 6). The substituent on the ligand changes the physical and chemical properties of the complex. rhodium(II) perfluorobutyrate dimer $[Rh_2\{pfb\}_4]$ **54** is an example of a catalyst in which an electron-withdrawing ligand alters the reactivity of the rhodium metal centre making this complex a very reactive catalyst but in some cases non-selective where competing metal carbenoid transformations are possible.[43]



52 **53** **54**

Figure 6. Rhodium complexes used to mediate carbenoid reactions.

The utility of dirhodium(II) carboxamidates as catalysts was made possible by the development of convenient procedures for their synthesis. Ligand replacement of acetate by the carboxamide is accomplished by heating $Rh_2(OAc)_4$ under reflux in chlorobenzene using a soxhlet extractor containing sodium carbonate to trap the generated acetic acid. Using the procedure, it became possible to change the acetate ligand by acetamide ligand and electron-rich catalysts were accessible. rhodium(II) acetamide dimer $Rh_2(acam)_4$ **55** tends to be less reactive than both $Rh_2(pfb)_4$ **54** and $Rh_2(OAc)_4$ **52**, but is more selective (Figure 7).[44]

[41] Paulissen, R.; Reimlinger, H.; Hayez, E.; Hubert, A. J.; Teyssié, P. *Tetrahedron Lett.* **1973**, *24*, 2233.
[42] Hashimoto, S.; Watanabe, N.; Ikegami, S. *Tetrahedron Lett*, **1992**, *33*, 2709.
[43] 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.
[44] Doyle, M. P.; Bagheri, V.; Wandless, T. J.; Harn, N. K.; Brinker, D. A.; Eagle, C. T.; Loh, K.-L. *J. Am. Chem. Soc*. **1990**, *112*, 1906.

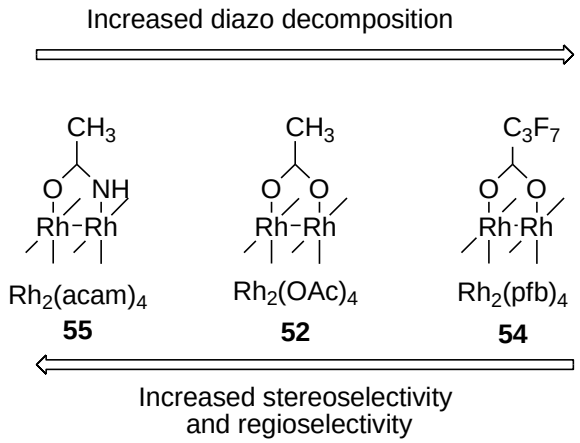
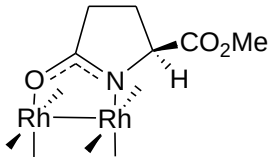


Figure 7. Examples of rhodium(II) catalysts used for diazo decomposition.

Doyle has synthesised some of the most successful chiral rhodium(II) carboxamidate ligands for carbenoid generation. The complex rhodium(II) tetrakis(methyl-2-oxopyrrolidine-5(*S*))-carboxamide (**56**) is the simplest and it has been applied to the synthesis of enantiomerically enriched lactones and lactams by carbenoid C–H insertion reaction (Figure 8). [45]



56 $Rh_2(5S\text{-MEPY})_4$

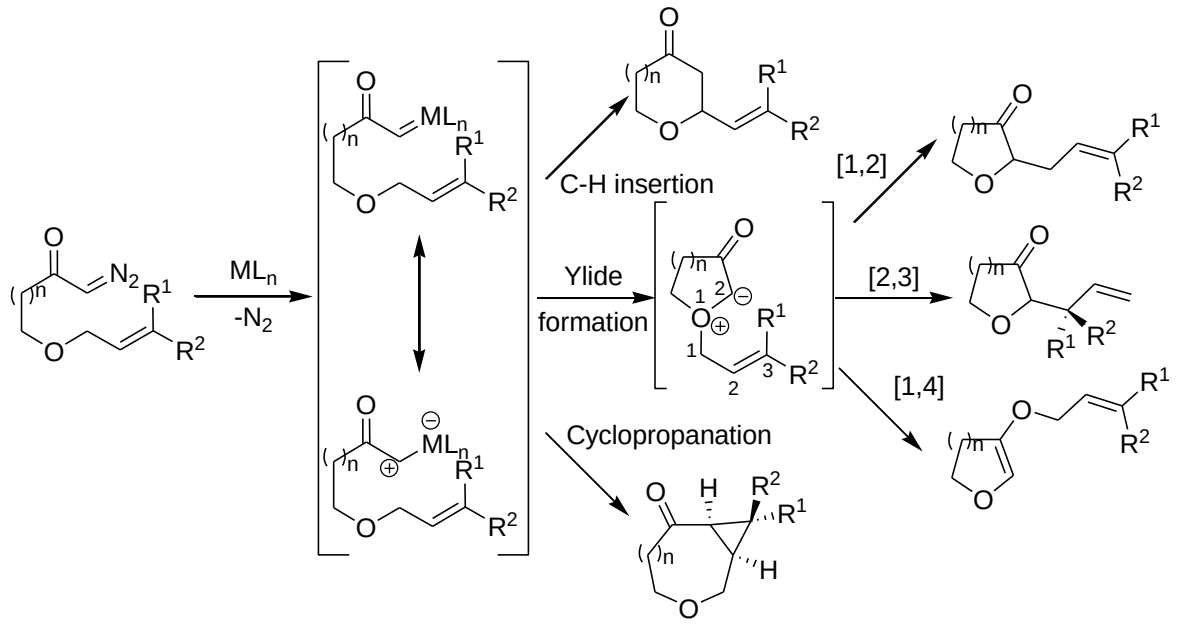
Figure 8. Doyle's rhodium(II) tetrakis(methyl 2-oxopyrrolidine-5(*S*))-carboxamide catalyst.

1.5 Transformation of metal carbenoids

The metal-catalysed reactions of *α*-diazo compounds are not limited to cyclopropanation, even though this transformation has been the subject of many studies. Metallocarbenoid reactions such as X–H insertion (X = C, O, N) or ylide generation followed by rearrangement have also proved their utility in synthetic chemistry and have been used to prepare complex synthetic targets. Cyclopropanation will be discussed briefly whereas C–H insertion, oxonium ylide formation and their subsequent rearrangement will

[45] Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911.

be considered more fully (Scheme 13).



Scheme 13. Representative reactions of metal carbenoids.

1.5.1 Cyclopropanation reactions of alkenes

Three-membered rings are very important buildings blocks in organic synthesis because of their presence in many biologically active natural compounds. Consequently, the development of efficient stereoselective methods for the preparation of cyclopropanes has received considerable attention, especially methodologies involving the use of diazo compounds. Since the first report in 1966 that reported enantiocontrol during cyclopropanation using a chiral catalyst,[34] both stereocontrolled (diastereoselective and enantioselective) intermolecular and intramolecular cyclopropanation reactions have been studied extensively using chiral catalysts based on copper, rhodium, and more recently ruthenium.[46] For example, the enantioselective intramolecular cyclopropanation of the allylic diazoacetate **57** has been developed to synthesise the bicyclic lactone **58** with very high enantioselectivity using the chiral rhodium complex Rh_2(5*S*-MEPY)$_4$ (**56**) (Scheme 14).[47]

This reaction has recently been used in a synthesis of the optically active cyclopropane subunit of the antifungial antibiotic (+)-ambruticin S (**59**).[48]

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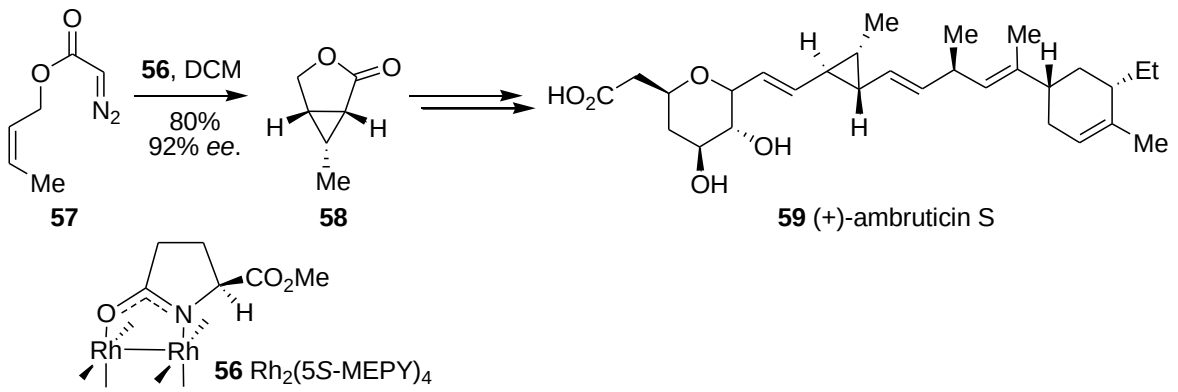
[46] (a) Zhang, Z.; Wang, J. *Tetrahedron* **2008**, *64*, 6577. (b) Wee, A. G. H. *Curr. Org. Synth.* **2006**, *3*, 499.

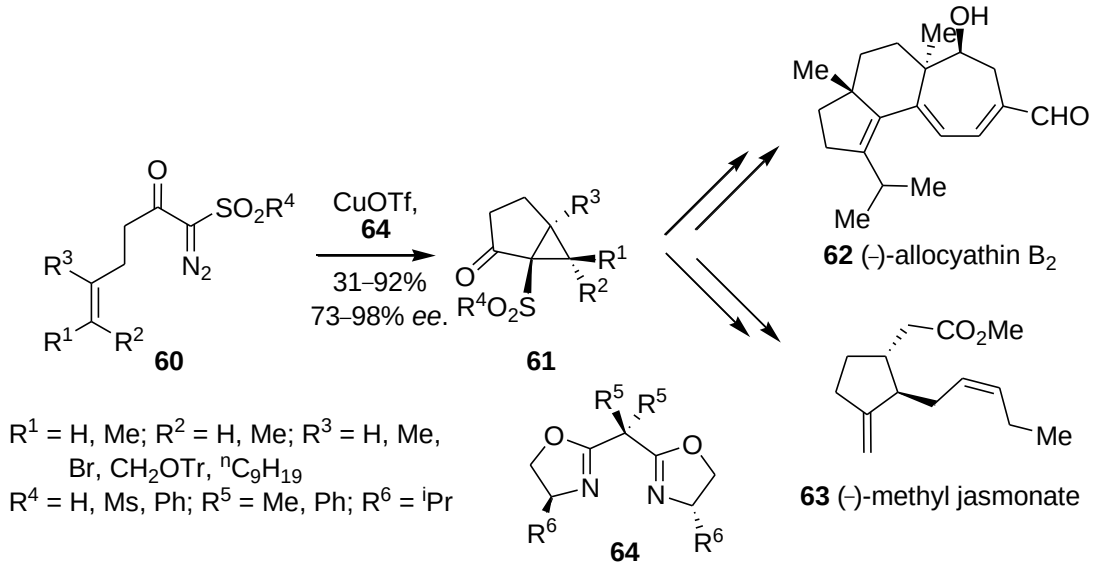
[47] Doyle, M. P.; Austin, R. E.; Bailey, A. S.; Dwyer, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Kwan, M. M. Y.; Liras, S.; Oalmann, C. J.; Pieters, R. J.; Protopopova, M. N.; Raab, C. E.; Roos, G. H. P.; Zhou, Q.-L.; Martin, S. F. *J. Am. Chem. Soc.* **1995**, *117*, 5763.

[48] Kirkland, T. A.; Colucci, J.; Geraci, L. S.; Marx, M. A.; Schneider, M.; Kaelin, D. E.; Martin, F. *J. Am Chem. Soc.* **2001**, *123*, 12432.



Scheme 14. Synthesis of the antifungial antibiotic (+)-ambruticin S **59**.

Recently, Nakada described highly enantioselective copper-catalysed intramolecular cyclopropanation reactions of the *α*-diazo-*β*-keto sulfone **60** (Scheme 15).[49] Nakada's methodology proved to be very efficient in the total synthesis of several biologically active natural compounds such as (–)-allocyathin **62** and (–)-methyl jasmonate **63**.[50]



Scheme 15. Total synthesis of (-)-allocyarthin B_2 **62** and (–)-methyl jasmonate **63**.

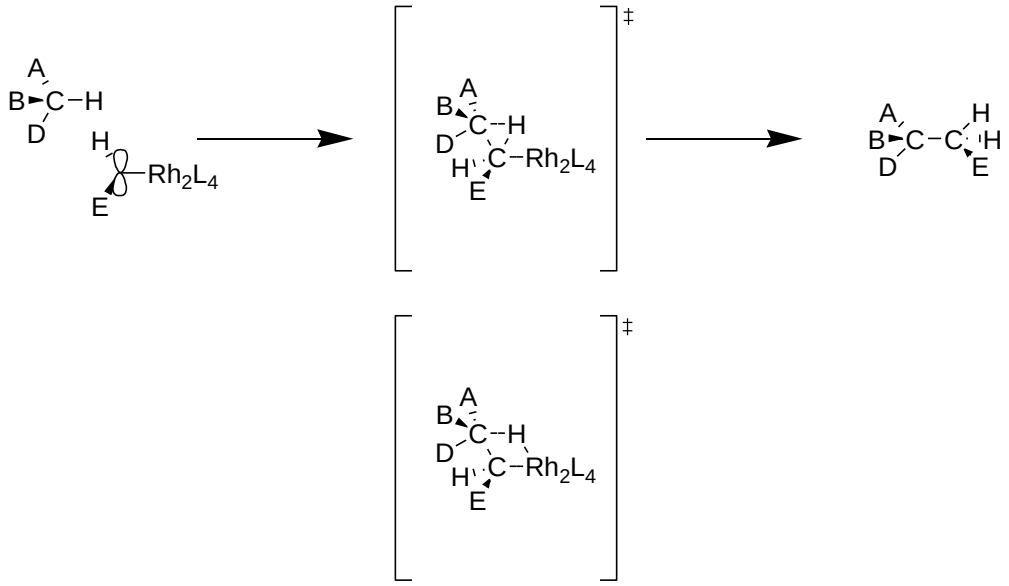
[49] (a) Honma, M.; Sawada, T.; Fujisawa, Y.; Utsugi, M.; Watanabe, H.; Umino, A.; Matsumura, T.; Hagihara, T.; Hagihara, T.; Takano, M.; Nakada, M. *J. Am. Chem. Soc*. **2003**, *125*, 2860. (b) Honma, M.; Nakada, M. *Tetrahedron Lett.* **2003**, *44*, 9007.

[50] (a) Takeda, H.; Watanabe, W.; Nakada, M, *Tetrahedron* **2006**, *62*, 8054. (b) Takano, M.; Umino, A.; Nakada, M. *Org. Lett.* **2004**, *6*, 4897.

1.5.2 C–H insertion

Insertion reactions are common with metal carbenoids and they have proven their utilities for insertion into carbon-hydrogen and heteroatom-hydrogen bonds. Insertion has been shown to be possible into C–H, O–H, S–H, N–H and Si–H bonds although the most synthetically useful reaction is C–H insertion. The reaction is used to create a new carbon–carbon bond and only activation of the diazo group is required, the other C–H site being unactivated.

Great efforts have been made to understand the precise mechanism of the transition metal catalysed C–H insertion reaction of carbenes generated from diazo compounds. The results of these investigations indicate the mechanism depicted in Scheme 16 in which there is formation of a three centre complex.[51] Also, Taber has suggested a transition state model in which transfer of hydrogen to rhodium occurs to give the four centre complex (Scheme 16).[52] Overlap of the metal *p*-orbitals with the σ-orbital of the reacting C–H bond initiates a process in which C–C and C–H bond formation with the carbene carbon proceeds with dissociation of the ligated metal.



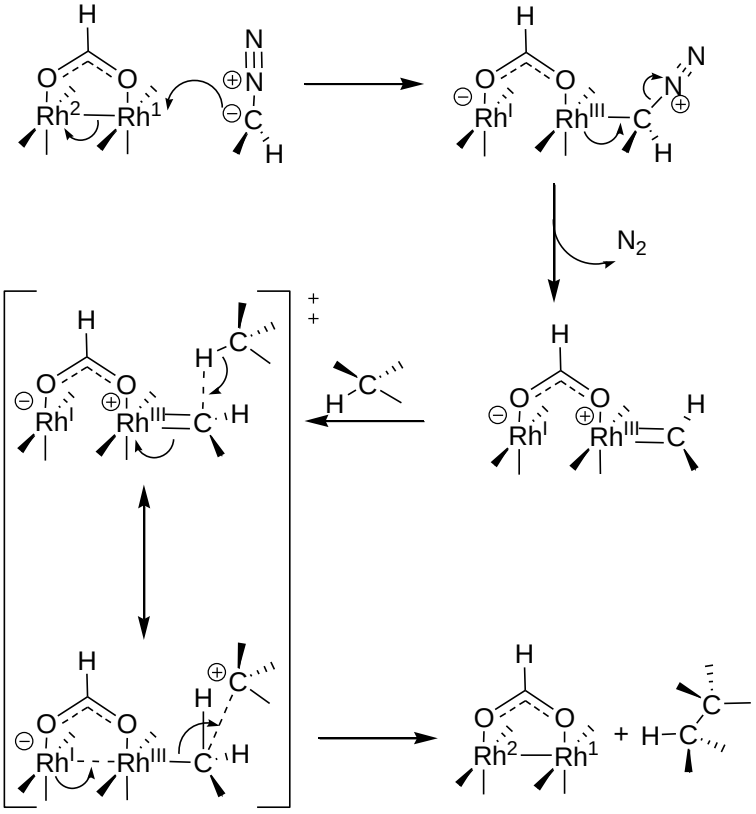
Scheme 16. Mechanism of C–H insertion catalysed by dirhodium.

[51] (a) Doyle, M. P. *Comprehensive Organometallic Chemistry II*, **1995**, *12*, chapter 5.2. (b) Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, W. P.; Pearson, M. M. *J. Am. Chem. Soc*. **1993**, *115*, 958.

[52] Taber, D. F.; You, K. K.; Rheingold, A. L. *J. Am. Chem. Soc*. **1996**, *118*, 547.

While mechanisms for carbenoid C–H insertion reactions have been suggested based on the results of synthetic applications and by the resulting structural relationships, little has been done to investigate the actual mechanism of C–H bond activation/C–H bond formation. Computational studies were employed to investigate the energetic and electronic nature of the reaction and elucidate the 3D structures of the intermediates and the transition states in the catalytic cycle.[53] One of the main components of the study involved the reactions of methyl diazoacetates with various simple alkanes, in the presence of dirhodium tetracarboxylate (Scheme 17). These studies suggested that the process commences with an interaction between the diazo compound and rhodium to give a rhodium diazocomplex from which loss of the dinitrogen gives a rhodium-methylene carbene complex. Then the reaction continues with an electrophilic attack of the carbene 2-*p*-orbital onto the C–H σ-bonding orbital of an alkane. The reaction proceeds through a relatively late transition state, involving the Rh–C bond cleavage. There is a general agreement to say that the dirhodium complex is the best catalyst for C–H bond activation because the second rhodium atom (Rh^2) acts as a bifunctional electron pool. Thus, when Rh^2 is detached from the Rh^1–C bond, the electrophilicity and the reactivity of the carbene centre is increased whereas when is attached, the cleavage of the Rh^1–C is facilitated. The carboxylate ligands serve as anchors to the Rh^2 atom and also as electron-withdrawing groups that enhance the electrophilicity of the carbene centre.

[53] Nakamura, E.; Yoshikai, N.; Yamanaka, M. *J. Am. Chem. Soc.* **2002**, *124*, 7181.



Scheme 17. Theoretical analysis of a rhodium carbenoid C–H insertion reaction.

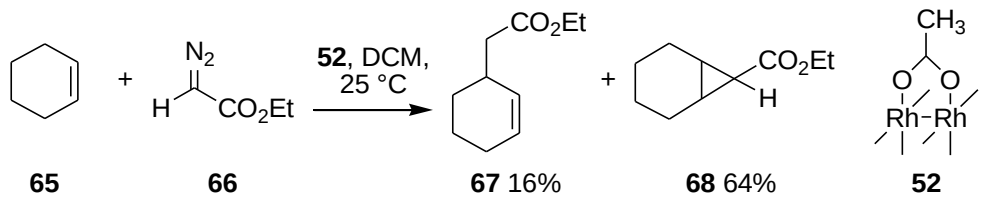
1.5.2.1 Catalytic intermolecular C-H insertion reaction

For a long time, intermolecular C–H reactions have received little attention because of the very poor chemoselectivity displayed by the reaction. However, since the development of donor/acceptor substituted carbenoids, intermolecular carbenoid C–H insertion reactions have undergone explosive growth.

1.5.2.1.1 Acceptor substituted carbenoids

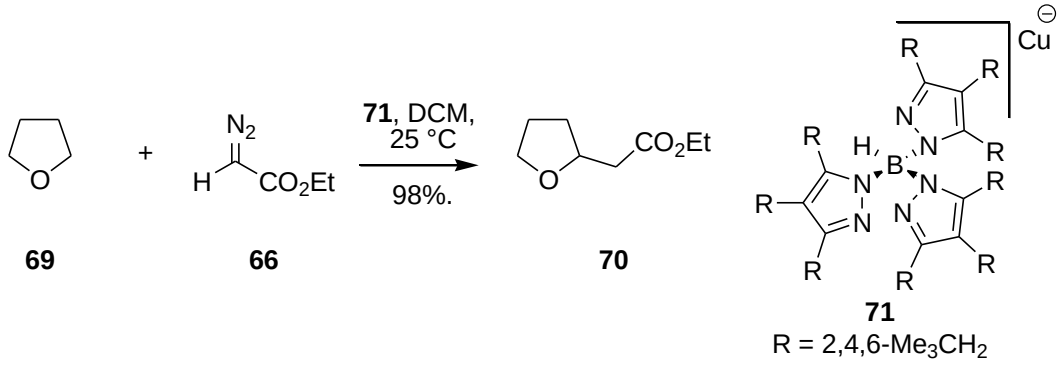
The reactions of these carbenoids were not considered to have synthetic utility because of their poor regioselectivity. The regiochemical problem was illustrated with the reaction of ethyl diazoacetate **66** with cyclohexene **65**. When $Rh_2(OAc)_4$ (**52**) is used as the catalyst, the reaction displayed a preference for the cyclopropanation product **68** over the C–H insertion product **67** (Scheme 18).[54,55]

[54] Davies, H. M. L.; Hansen, T. *J. Am. Chem. Soc.* **1997**, *119*, 9075.
[55] Müller, P.; Tohill, S. *Tetrahedron* **2000**, *56*, 1725.



Scheme 18. Cyclopropanation versus C–H insertion with acceptor substituted carbenoids.

Tetrahydrofuran has been described to undergo selective C–H insertion and the bulky copper catalyst **71** was reported as an excellent catalyst for this transformation (Scheme 19). Reaction between ethyl diazoacetate **66** and tetrahydrofuran **69** with **71**, furnished the C–H insertion product in an excellent 98% yield. The main advantage of using this copper catalyst appears to be its bulky nature which disfavours carbenoid dimerisation.[56]



Scheme. 19.C–H insertion of tetrahydrofuran **70**.

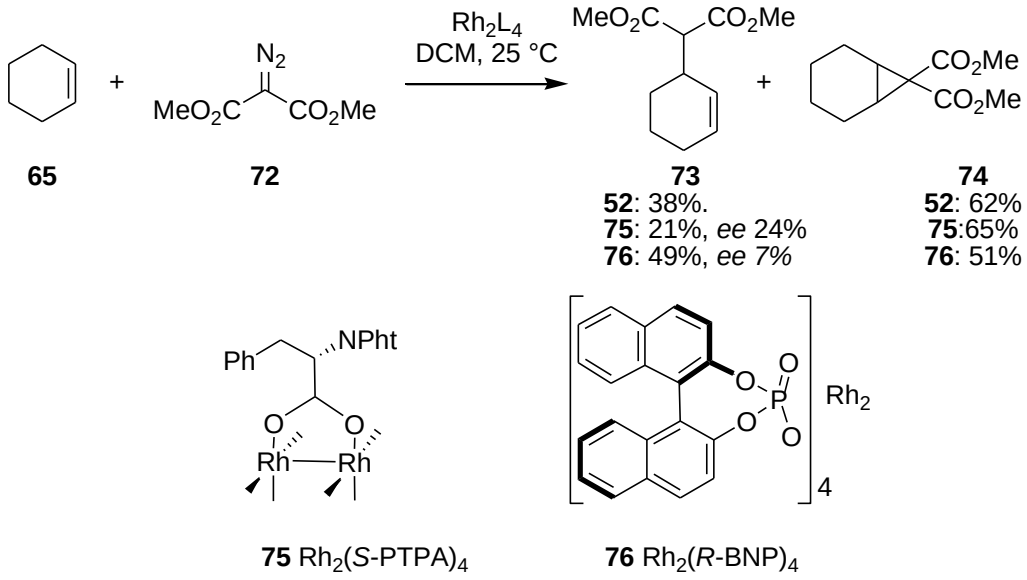
In summary, asymmetric C–H insertions using an acceptor substituted carbenoid have seen very limited advances. A suitable catalyst system needs to be developed so that the reactivity of these acceptor substituted carbenoids is sufficiently tamed to allow controlled transformations to take place.

1.5.2.1.2 Acceptor/acceptor substituted carbenoids

With these carbenoids, cyclopropanation is a major competing reaction, but the catalyst can have an effect on the chemoselectivity in favour of the C–H insertion. For example, treatment of diazomalonate **72** with Hashimoto's phenylalanine-derived catalyst

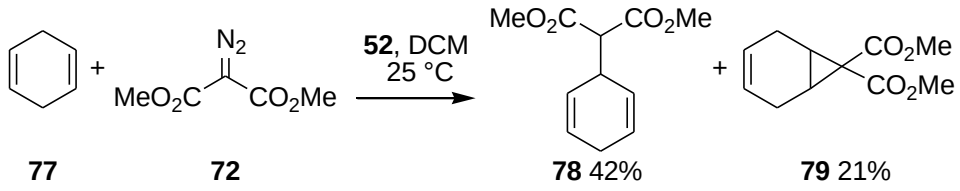
[56] Mar Diaz-Requejo, M.; Belderrain, T. R.; Carmen Nicosio, M.; Trofimenko, S.; Pérez, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 896.

Rh_2(*S*-PTPA)$_4$ (**75**) in the presence of cyclohexene **65** resulted in a 3:1 mixture of cyclopropane **74** and the C–H insertion product **73** with an overall yield of 86%. However, when Pirrung's binaphthyl phosphate catalyst, Rh_2(*R*-BNP)$_4$ (**76**), a 1:1 mixture of the C–H insertion and cyclopropanation products was isolated. The enantioinduction for the C–H insertion reaction was poor with both chiral catalysts (Scheme 20).[55]



Scheme 20. Cyclopropanation versus C–H insertion of cyclohexene.

When the insertion site is highly activated, greater preference for C–H insertion over cyclopropanation was observed with an acceptor/acceptor substituted carbenoids (Scheme 21). For example, with the doubly allylic methylene position of the 1,4-diene **77**, formation of the C–H insertion product **78** was favoured over the cyclopropanation by a ratio of 2:1.[55]

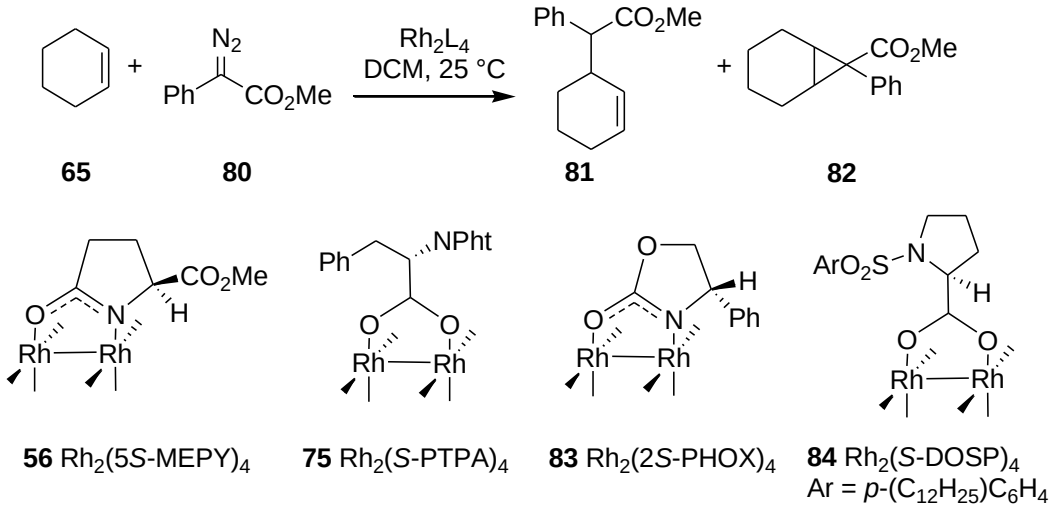


Scheme 21. Cyclopropanation versus C–H insertion of 1,4-diene **77**.

1.5.2.1.3 Donor/acceptor substituted carbenoids

Donor/acceptor-substituted carbenoids are the best reagents for intermolecular C–H insertion chemistry, displaying remarkable chemoselectivity and regioselectivity. The two most widely studied classes of donor/acceptor substituted carbenoids are those derived from aryldiazoacetate and vinyldiazoacetate.

In 2000, Müller and Tohill reported a study on the factors influencing the chemoselectivity between C–H insertion and cyclopropanation. The reactions exhibited a preference for C–H insertion over cyclopropanation with the carbenoid derived from methylphenyldiazoacetate **80**.[55] In their studies, reaction of **80** with a variety of chiral catalysts in the presence of cyclohexene **65** resulted in the formation of both C–H insertion product **81** and cyclopropane **82**. (Scheme 22, Table 1) The carbenoid generated with the pyrrolidone catalyst Rh_2(5*S*-MEPY)$_4$ (**56**) displayed excellent chemoselectivity for formation of the ester **81**, although enantiocontrol was moderate. However, the catalysts Rh_2(2*S*-PHOX)$_4$ (**83**) and Rh_2(*S*-PTPA)$_4$ (**75**) showed lower chemoselectivity but delivered moderate enantioselectivity. The Rh_2(*S*-DOSP)$_4$ (**84**) was the best catalyst for this reaction and very high enantioselectivity were observed for the C–H insertion product **81** but the yield was poor when DCM was used as the solvent. The C–H insertion product was obtained in better yield (58%) and with excellent enantioselectivity when 2,2-dimethylbutane was used as the solvent.[57]



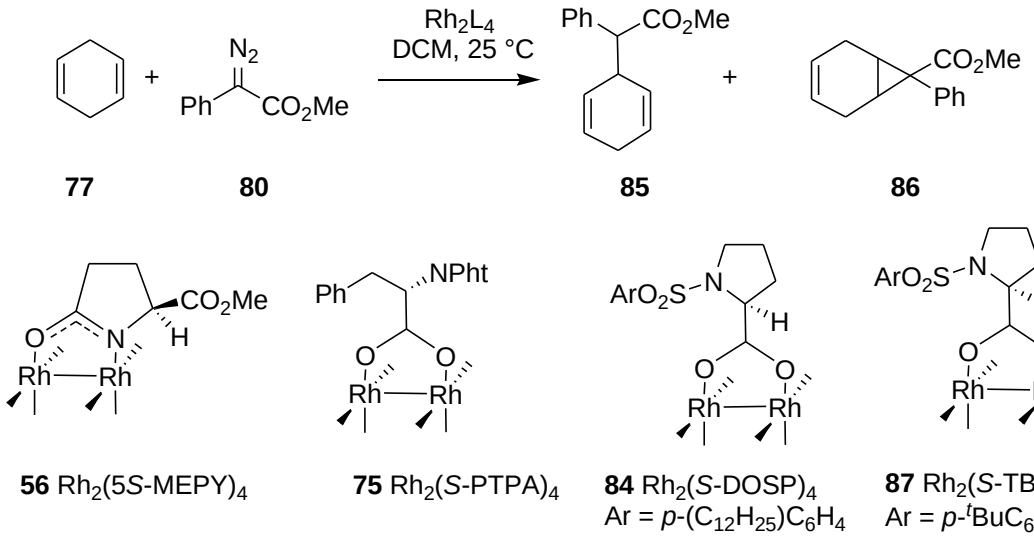
Scheme 22. C–H insertion of cyclohexene.

[57] Davies, H. M. L.; Ren, P.; Jin, Q. *Org. Lett.* **2001**, *3*, 3587.

Entry	Catalyst	Yield 81 + 82 %	Ratio 81:82	*de* 81 %	*ee* 81 %
1	$Rh_2(OAc)_4$ (**52**)	50	75:25	24	
2	Rh_2(2*S*-PHOX)$_4$ (**83**)	52	66:34	14	4
3	Rh_2(5*S*-MEPY)$_4$ (**56**)	50	93:7	26	45 (*S*)
4	Rh_2(*S*-PTPA)$_4$ (**75**)	45	50:50	6	53 (*S*)
5	Rh_2(*S*-DOSP)$_4$ (**84**)	33	80:20	4	75 (*R*)
6	Rh_2(*S*-DOSP)$_4$ (**84**)	73	79:21	0	93 (*R*)

Table 1. C–H insertion of cyclohexene.

When two alkenes exist in a 1,4-relationship, the presence of the proximal alkene is known to activate the allylic position towards C–H insertion (Scheme 23). For example, excellent selectivity for the C–H insertion reaction was observed during the reaction of **80** with 1,4-cyclohexadiene **77**. A screen of different chiral rhodium catalysts (Table 2) has been undertaken and in each case, the formation of the cyclopropane **86** was not observed in the crude reaction mixture. This result contrasts to that obtained using a corresponding acceptor/acceptor-substituted carbenoid, where the cyclopropanation product was a significant component of the reaction mixture.[55]

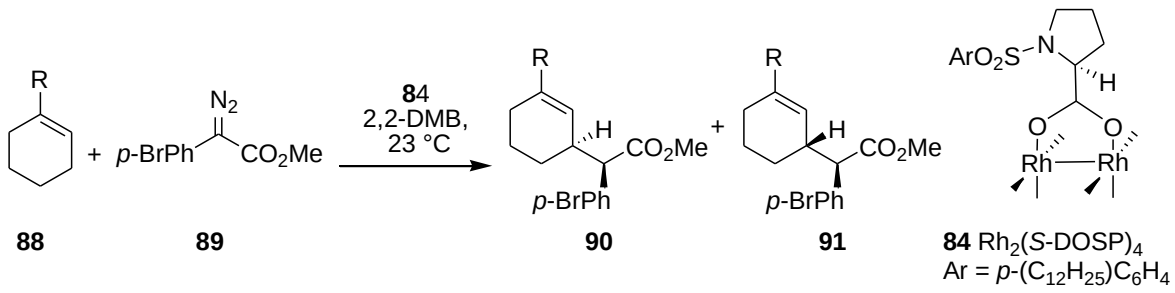


Scheme 23. C–H insertion of 1,4-cyclohexadiene

Entry	Catalyst	Yield 85 %	Ration 85:86	*ee* 85 %
1	Rh_2(*S*-DOSP)$_4$ (**84**)	98	>98:2	65 (*R*)
2	Rh_2(*S*-TBSP)$_4$ (**87**)	98	>98:2	74 (*R*)
3	Rh_2(5*S*-MEPY)$_4$ (**56**)	98	>98:2	4
4	Rh_2(*S*-PTPA)$_4$ (**75**)	98	>98:2	40 (*S*)

Table 2. C–H insertion of 1,4-cyclohexadiene.

Highly regioselective reactions of donor/acceptor substituted carbenoid have been observed when cyclic alkenes such as 1-substituted cyclohexenes are employed as substrates. In the example shown in Scheme 24, two or three allylic sites in each substrate **88** are present, but Davies and co-workers observed the formation of only one single C–H insertion regioisomer (**90** + **91**).[57] Table 3 demonstrates that methylene sites are favoured for intermolecular C–H insertion, presumably because methylene C–H bonds are weaker than methyl C–H bonds and more accessible to the bulky rhodium-carbenoid complex than methine C–H bonds. Consequently, the C–H insertion occurred only at the least crowded allylic methylene site. In each example, excellent enantioselectivity was obtained but the diastereoselectivity was moderate.

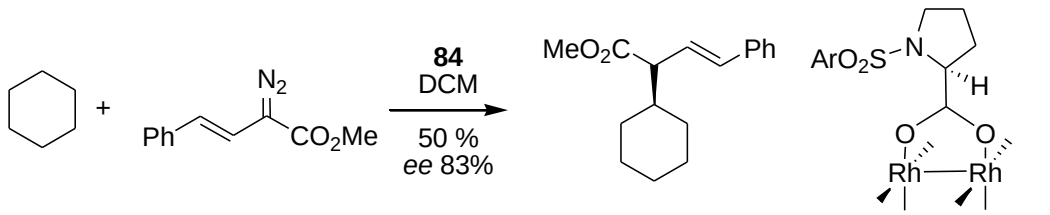


Scheme 24. C–H insertion of 1-substituted cyclohexene

Entry	R	Yield %	Ratio 90:91	*ee* 90 (%)	*ee* 91 (%)
1	Me	53	17:83	94	98
2	Et	46	25:75	90	94
3	^{i}Pr	65	36:64	90	93
4	^{t}Bu	46	62:38	91	81
5	Ph	65	23:77	90	95
6	Cl	58	65:35	96	91

Table 3. C–H insertion of 1-substituted cyclohexene.

Studies into vinyldiazocarbenoid structures have revealed that *cis*-vinyldiazoacetates are poor substrates for performing intermolecular C–H insertion, but *trans*-vinyldiazoacetates are much better substrates. The first example of a C–H insertion reaction using vinydiazoacetate involved intermolecular insertion into cyclohexane **92** by the carbenoid derived from the vinyldiazoacetate **93** (Scheme 25).[58]



92 **93** **94** **84** Rh_2(*S*-DOSP)$_4$ Ar = *p*-($C_{12}H_{25}$)C_6H_4

Scheme 25. C–H insertion using vinyldiazocarbenoid reagent.

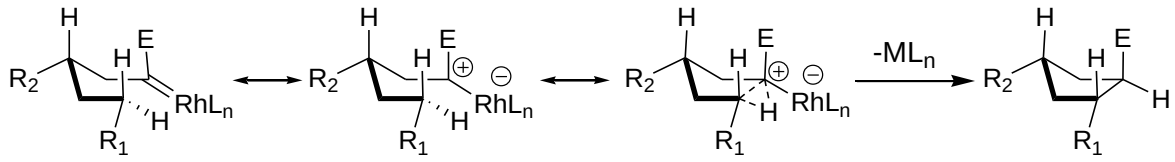
1.5.2.2 Catalytic intramolecular C–H insertion reaction

Catalytic intramolecular C–H insertion reaction offers a general approach for the synthesis of a variety of carbocyclic and heterocyclic structures in a regioselective and stereoselective manner. Great efforts have been made on this process, especially since the introduction of rhodium carboxylate dimers as catalysts. The chemoselective and the regioselective outcome of the reaction have shown to be dependent on the nature of the catalyst. However, the regioselectivity, which leads to the control of ring size, also depends

[58] Davies, H. M. L.; Jin, Q.; Ren, P.; Kovalevsky, A. Y. *J. Org. Chem.* **2002**, *67*, 4165.

upon the type of diazo function, the degree of substitution of the carbon where insertion takes place, steric and electronic factors. In general, the regiochemical preference of the reaction shows a strong tendency for five-membered ring formation.

According to the mechanism proposed by Taber,[52] it is assumed that the rhodium centre and the reacting C–H bond must overlap to allow C–C bond formation. The new bond created the transfer of hydrogen and the exit of the metal occur in a concerted manner (Scheme 26). Thus, the transition state of the reaction would involve a six-membered ring. Energies for the various conformations of the metal carbenoid were calculated in order to have smallest interaction between the C–Rh bond and the C–H bond.[48] Results showed that conformation **95** was the lowest in energy. In this configuration, R^1 and R^2 groups were placed in pseudo-equatorial positions leading to a *cis* relationship in the product. The rhodium complex is also in a pseudo-equatorial position and is aligned to the target C–H bond, which can process through a three-centre two-electron bond **97** to give the insertion product. In this case, the E group was placed in axial position giving a *trans* relationship with R^1 and R^2 in the product. The main consideration when predicting the stereochemical outcome of these reactions is to place the rhodium in a pseudo-equatorial position.



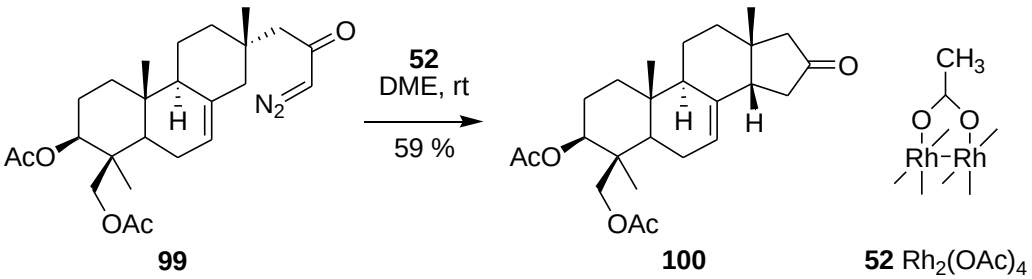
95 **96** **97** **98**

Scheme 26. Lowest energy conformation for C–H insertion.

1.5.2.2.1 Acceptor substituted carbenoid

One of the first results that illustrated the utility of this simple method for cyclopentanone synthesis was described by Wenkert in 1982.[59] In this example, treatment of the diazo ketone **99** with rhodium(II) acetate dimer (**52**) delivered the C–H insertion product **100** in good yield (Scheme 27). In this example, there were three different sites of intramolecular C–H insertion but the reaction displayed a preference for the allylic γ-position to furnish the five-membered ring.

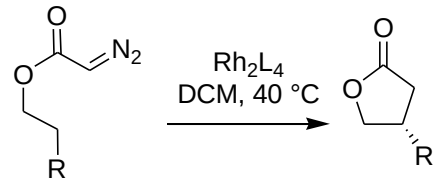
[59] Wenkert, E.; Davis, L. L.; Mylari, B. L.; Solomon, M. F.; Da Silva, R. R.; Shulman, S.; Warnet, R. J. *J. Org. Chem.* **1982**, *47*, 3242.



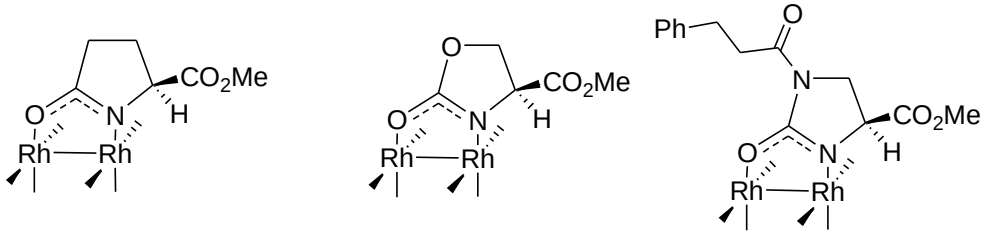
99 **100** **52** $Rh_2(OAc)_4$

Scheme 27. Cyclopentanone synthesis by intramolecular C–H insertion.

Doyle's rhodium(II) chiral carboxamidate complexes have been presented as very good catalysts in asymmetric intramolecular C–H insertion of diazoacetates.[40,60] For example, the decomposition of the 2-substituted diazo acetate **101** conducted with chiral Rh(II) carboxamidate dimer favoured the formation of the γ-butyrolactone **102** (Scheme 28, Table 4).[61]



101 **102**



56 $Rh_2(5S\text{-MEPY})_4$ **103** $Rh_2(4S\text{-MEOX})_4$ **104** $Rh_2(4S\text{-MPPIM})_4$

Scheme 28. Asymmetric synthesis of 4-substituted γ-butyrolactone.

[60] Timmons, D. J.; Doyle, M. P. *Organomet. Chem.* **2001**, *617*, 98.

[61] (a) Bode, J. W.; Doyle, M. P.; Protopopova, M. N.; Zhou, Q.-L. *J. Org. Chem.* **1996**, *61*, 9146. (b) Doyle, M. P.; Hu, W.; Valenzuela, M. V. *J. Org. Chem.* **2002**, *67*, 2954. (c) Doyle, M. P.; Protopopova, M. N.; Zhou, Q.-L.; Bode, J. W. *J. Org. Chem.* **1995**, *60*, 6654.

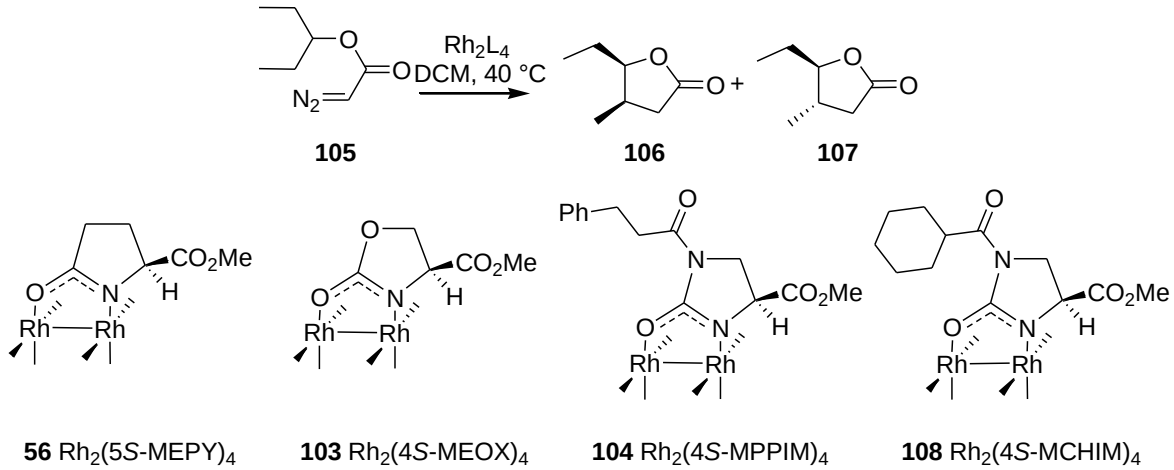
Entry	R	Catalyst	Yield 102 (%)	*ee* 102 (%)
1	$CH_2C_6H_5$	Rh_2(5*R*-MEPY)$_4$ (**56**)	23	72 (*R*)
2	$CH_2C_6H_5$	Rh_2(4*S*-MEOX)$_4$ (**103**)	42	51 (*S*)
3	$CH_2C_6H_5$	Rh_2(4*S*-MPPIM)$_4$ (**104**)	50	87 (*S*)
4	$CH_2C_6H_5$	Rh_2(4*R*-MPPIM)$_4$ (**104**)	56	91 (*R*)
5	CH_2Ar	Rh_2(4*R*-MPPIM)$_4$(**104**)	59	97 (*R*)
6	OCH_3	Rh_2(4*S*-MPPIM)$_4$(**104**)	>98	95 (*S*)

Table 4. Asymmetric synthesis of 4-substituted γ-butyrolactone.

The first generation catalyst, Rh_2(5*R*-MEPY)$_4$ (**56**) and Rh_2(4*S*-MEOX)$_4$ (**103**), gave moderate asymmetric induction (Table 4, entry 1, 2), whereas better enantioselectivity was observed using the second generation catalyst Rh_2(4*S*-MPPIM)$_4$ (**104**). (Table 4, entries 3–6).[62] The success of this catalyst is likely due to the greater steric influence of the *N*-3-phenylpropanoyl attachment, which provides greater control over carbenoid orientation than in the case of the first generation catalyst.[63]

Intramolecular C–H insertion of secondary alkyl diazoacetates gave access to the construction of chiral 4,5-disubstituted γ-butyrolactone. For example, using diazo esters possessing simple alkyl groups such as 3-pentyl diazoacetate **105**, the choice of the catalyst has shown significant influence on the outcomes of the reaction. Treatment with Doyle's imidazolidinone catalyst Rh_2(4*S*-MCHIM)$_4$ (**108**) and Rh_2(4*S*-MPPIM)$_4$ (**104**) gave selectively the *cis* isomer **106** in 81–87% yield with >94% *de* and 99% *ee* (Scheme 29, Table 5). [64]

[62] Doyle, M. P.; Hu, W. *Chirality* **2002**, *14*, 169.
[63] Doyle, M. P.; Kalinin, A. V.; Ene, D. G. *J. Am. Chem. Soc.* **1996**, *118*, 8837.
[64] Doyle, M. P.; Zhou, Q.-L.; Dyatkin, A. B.; Ruppar, D. A.; *Tetrahedron Lett*. **1995**, *36*, 7579.



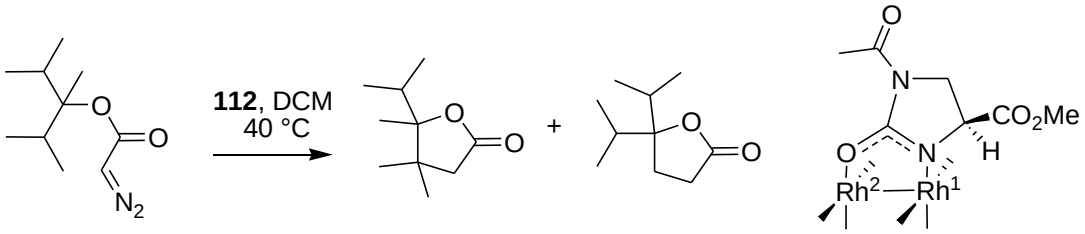
Scheme 29. Asymmetric synthesis of 4,5-disubstituted γ-butyrolactones **106** and **107**.

Entry	Catalyst	Yield 106 + 107 %	Ratio 106:107	*ee* 106 (%)	*ee* 107 (%)
1	Rh_2(4S-MCHIM)$_4$ (**108**)	87	98:2	99	
2	Rh_2(4S-MPPIM)$_4$ (**104**)	81	97:3	99	
3	Rh_2(5S-MEPY)$_4$ (**56**)	70	78:22	98	71
4	Rh_2(4S-MEOX)$_4$ (**103**)	75	69:31	98	92

Table 5. Asymmetric synthesis of 4,5-disubstituted γ-butyrolactones **106** and **107**.

Diazocompounds containing a methine site are also good substrates for intramolecular the C–H insertion reaction. Shown in Scheme 30, the reaction between the tertiary alkyl diazoacetates **109** and Rh_2(4*S*-MACIM)$_4$ (**112**) presented a good level of asymmetric induction[65] but the enantioselectivity is not as high as that obtained when performing insertion into a methylene C–H bond.[64] However, the reactions was not highly regioselective and competition between methine and methyl C–H insertion was observed, leading to the formation of a mixture of the butyrolactones **110** and **111**.[65]

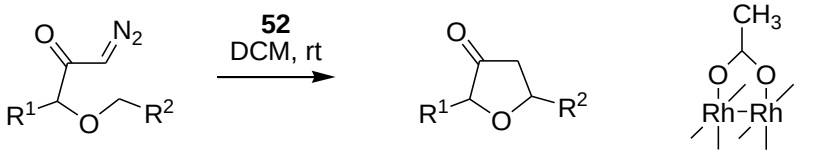
[65] Doyle, M. P.; Zhou, Q.-L.; Raab, C. E.; Roos,G. H. P. *Tetrahedron Lett.* **1995**, *36*, 4745.



109 **110** 61%, *ee* 85% **111** 13% **112** Rh_2(4*S*-MACIM)$_4$

Scheme 30. C–H insertion at the methine site.

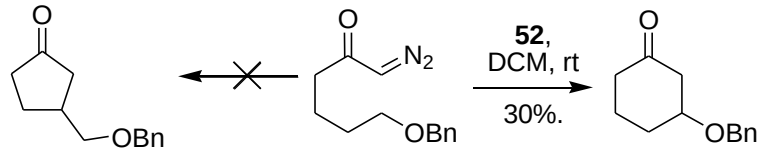
Decompositions of diazoacetates or diazoketones using rhodium(II) acetate dimer (**52**) as catalyst often generate products arising from intermolecular process such as carbene dimerisation. However, Adams described intermolecular C–H insertion on substrates possessing an ethereal oxygen atom which activates the adjacent carbon.[66] Applying these results on an intramolecular system, he was able to increase the probability of the five-membered ring formation (Scheme 31). A range of 2,5-substituted furanones **114** was synthesised from acyclic ethers **113** using rhodium(II) acetate dimer (**52**).[67]



113 **114** 34– 84%. **52** $Rh_2(OAc)_4$

Scheme 31. R^1 = alkyl, aromatic, CF_3, alkoxy. R^2 = alkyl aromatic, alkoxy.

Moreover, the directing effect of an oxygen atom has been demonstrated with the decomposition of the *α*-diazo ketone **115**. In this case, the reaction exhibited a preference in the formation of the six-membered cyclic ketone **116** rather than the five-membered cyclic ketone **117** (Scheme 32). Thus, this method gave access to the larger cyclic ketone via intramolecular C–H insertion as a result of activation of the δ-position by the ether.

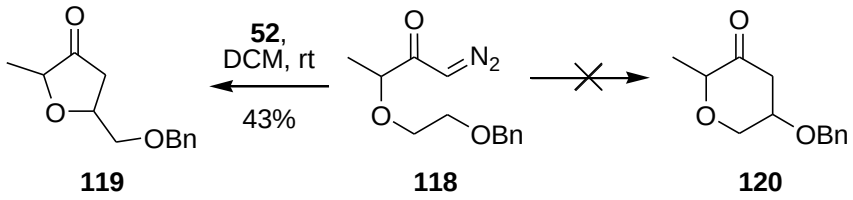


117 **115** **116**

Scheme 32. Directing effect of an ethereal oxygen atom.

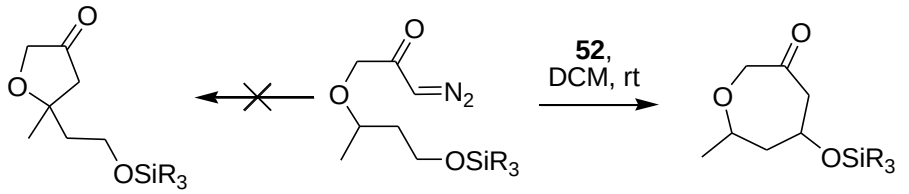
[66] Wang, P.; Adams, J. *J. Am. Chem. Soc.* **1994**, *116*, 3296.
[67] Adams, J.; Poupart, M.-A.; Grenier, L. *Tetrahedron Lett.* **1989**, *30*, 1753.

However, by incorporation of a second ether oxygen atom into the substrate, the selectivity of the above reaction was reversed and the formation of the five-membered ring was preferred. For example, treatment of the α-diazo ketone **118** under standard conditions gave the dihydrofuranone **119** instead of the dihydropyranone **120** (Scheme 33).



Scheme 33. Directing effect of two ethereal oxygen atoms.

Lee and co-workers described the formation of larger ring sizes product by intramolecular C–H insertion using the directing effect of an oxygen substituent.[68] In the example in Scheme 34, a directing effect of the silyl protecting group during the intramolecular C–H insertion was observed, and the seven-membered cyclic ether **122** was generated rather than cyclopentanone **123**. This surprising result was confirmed when Lee replaced the silyl protecting group by a benzyl group. In this case, the regioselectivity was reversed and the corresponding cyclopentanone **123** was isolated. Consequently, it was though that the silyl group increased the directing influence of the oxygen atom of the side chain by providing additional electron donation through the β-effect.

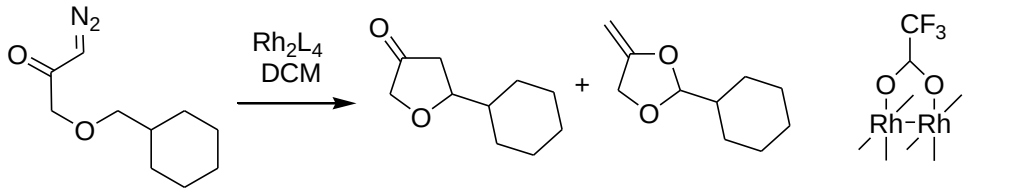


Scheme 34. Effect of silicon protecting group altering the position of C–H insertion.

Clark *et al.* isolated anomalous C–H insertion products during the preparation of 3(2*H*)-dihydrofuranones by intramolecular C–H insertion using the directing effect of an

[68] Lee, E.; Choi, I.; Song, S. Y. *J. Chem. Soc. Chem. Commun.* **1995**, *3*, 321.

ether.[69] The treatment of the diazoketone **124** with a variety of rhodium catalysts resulted in the formation of the unusual enol ether acetal **126** and the conventional C–H insertion product **125** (Scheme 35). The amount of each product was strongly influenced by the metal complex used for carbenoid generation. When $Rh_2(OAc)_4$ (**52**) was used, the formation of the conventional C–H insertion product was preferred, whereas treatment with the electron-deficient catalyst $Rh_2(tfa)_4$ (**127**) furnished the anomalous C–H insertion product **126** in higher yield.

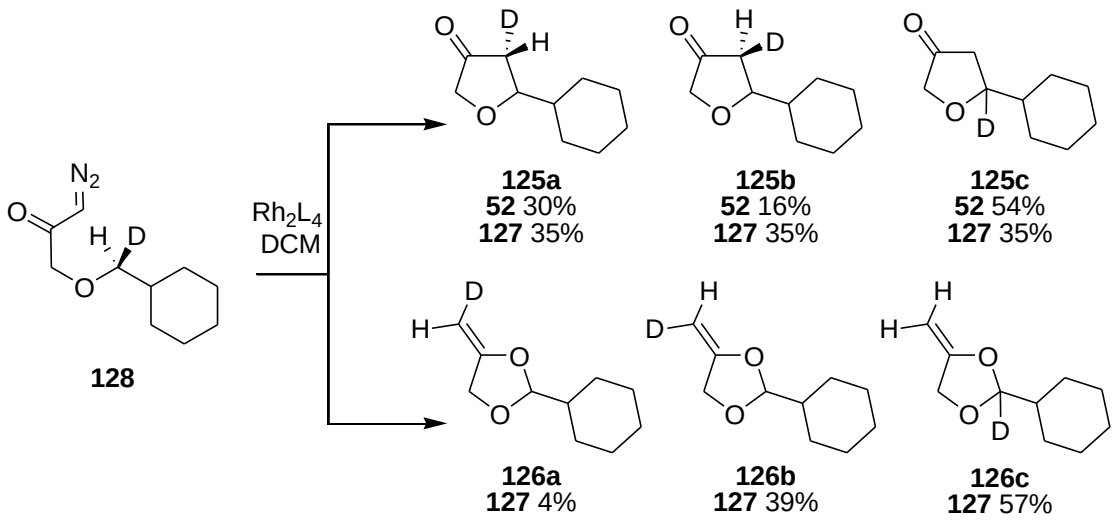


124 | **125** **52** 55% **127** 35% | **126** **52** 8% **127** 40% | **127** $Rh_2(tfa)_4$

Scheme 35. Isolation of an anomalous C–H insertion product

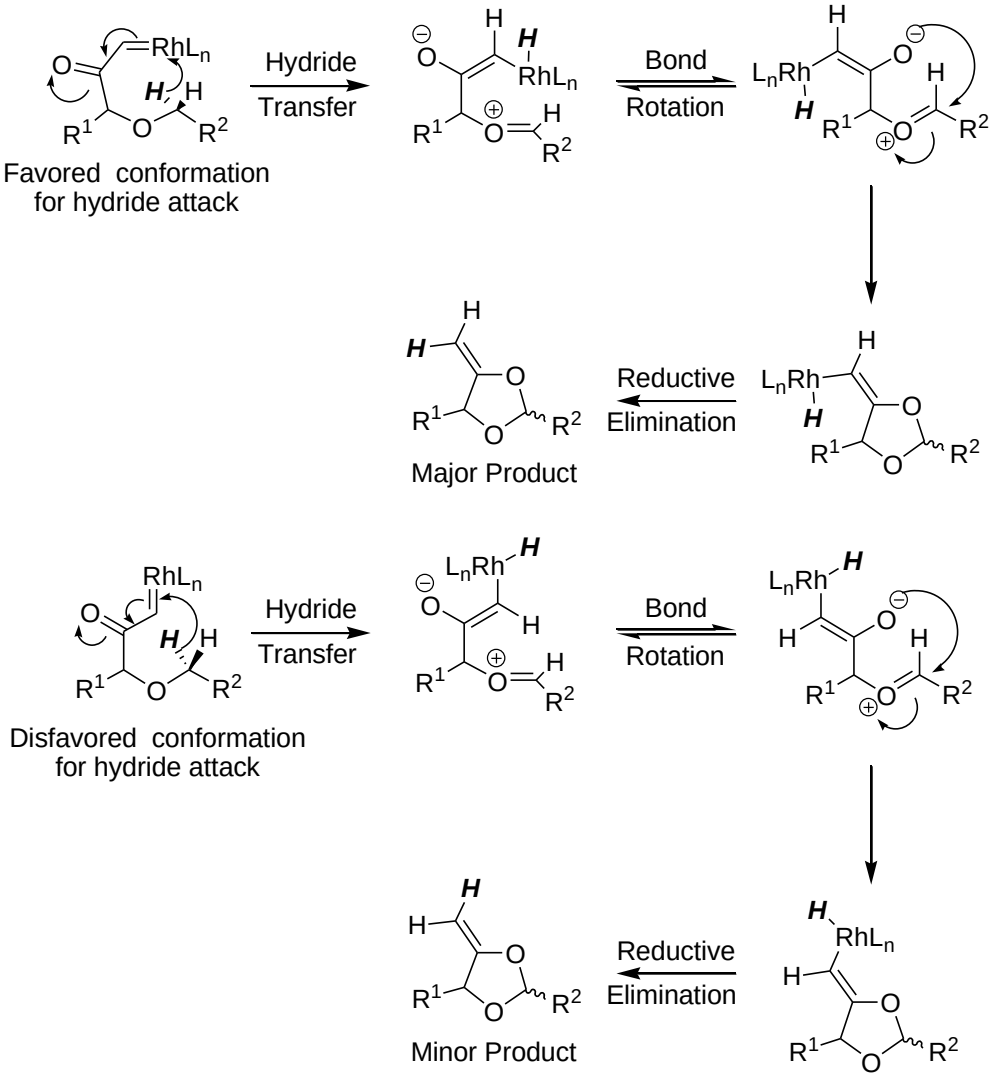
In subsequent studies, cyclisation reactions of the deuterated *α*-diazo ketone **124** (derived from deuterated cyclohexane methanol) were studied and deuterium isotope effects in both conventional and anomalous C–H insertion reactions were calculated.[69c] Treatment of the *α*-diazo ketone **128** with $Rh_2(OAc)_4$ (**52**) in dichloromethane at room temperature and subsequent ^{1}H NMR analysis of the conventional C-H insertion products indicated a 65:35 ratio of the diastereoisomers **125a** and **125b** and a kinetic isotope effect (**125c**/[**125a** + **125b**]) 1.2. Unfortunately, it was not possible to isolate sufficient quantities of the products **126a**, **126b**, and **126c** arising from the anomalous C–H insertion reaction. However, both sets of products were isolable from the $Rh_2(tfa)_4$ (**127**)-catalyzed reaction. In this case, the diastereoisomers **125a** and **125b** were obtained in a 66:34 ratio and the kinetic isotope effect (**125c**/[**125a** + **125b**]) was 1.0. In contrast, isomeric anomalous products **126a** and **126b** were obtained as a 9:91 mixture and the kinetic isotope effect (**126c**/ [**126a** + **126b**]) was 1.3.

[69] (a) Clark, J. S.; Dossetter, A. G.; Russell, C. A.; Whittingham, W. G. *J. Org. Chem.* **1997**, *62*, 4910. (b) Clark, J. S.; Wong, Y.-S.; Townsend, R. J. *Tetrahedron Lett.* **2001**, *42*, 6187. (c) Clark, J. S.; Dossetter, A. G.; Wong, Y.-S.; Townsend, R. J.; Whittingham, W. G.; Russell, C. A. *J. Org. Chem.* **2004**, *69*, 3886.



Scheme 36. Cyclization reactions of the deuterated α-diazo ketone **128**.

The most plausible explanation of the data obtained from the reactions of deuterium-labeled precursors is that the conventional C–H insertion product **125** was produced by the mechanism described by Taber,[52] whereas the anomalous C–H insertion product **126** was formed by a mechanism displayed in Scheme 37. In this mechanism, oxygen-assisted hydride migration to the rhodium centre of the carbenoid results in enolate formation. Bond rotation then allows C–O bond formation by trapping of the oxenium ion with the enolate oxygen. Subsequent reductive elimination then delivers the acetal product and allows catalyst regeneration. The stereochemical outcome of the reaction is determined by attack of the hydride on the metal centre of the carbenoid in the most favourable conformation (Scheme 37).



Scheme 37. Plausible mechanism for acetal formation.

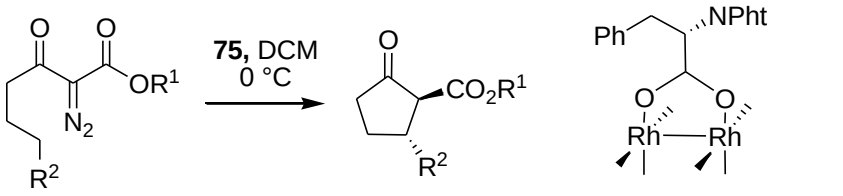
1.5.2.2.2 Acceptor/Acceptor substituted carbenoid

Diazo compounds containing two acceptor groups are less reactive towards metal-catalysed diazo decomposition than unsubstituted α-diazocarbonyl compounds. Consequently, most rhodium(II) carboxamidate complexes are unreactive on this system at ambient temperature.[70] However, rhodium carboxylates are much more kinetically active and are capable of decomposing diazo compounds containing two acceptor substituents.[71]

The catalyst Rh_2(*S*-PTPA)$_4$ (**75**) has been described as a very good catalyst for intramolecular C–H activation of acceptor/acceptor substituted carbenoid.[72] This catalyst

[70] Doyle, M. P.; Davies, S. B.; Hu, W. *Org. Lett.* **2000**, *2*, 1145.
[71] Davies, H. M. L. *Eur. J. Org. Chem.* **1999**, 2459.
[72] (a) Hashimoto, S.-I.; Watanabe, N.; Ikegami, S. *Synlett*, **1994**, 353. (b) Hashimoto, S.-I.; Watanabe, N.; Sato, T.; Shiro, M; Ikegami, S. *Tetrahedron Lett.* **1993**, *34*, 5109.

proved to be efficient in the conversion of the *α*-diazo-*β*-ketoester **129** into the cyclopentanone **130** (Scheme 38). In this case, the size of the ester group and the nature of the substituent R^2 at the site of insertion had significant influence on the enantioselectivity of the reaction.[73] For example, when substrates containing very large ester groups were employed and when the reactions occurred at benzylic positions, very good levels of asymmetric induction were observed. (Scheme 38, Table 6). However, very low asymmetric induction was obtained with Rh_2(*S*-DOSP)$_4$ (**84**) and Rh_2(5*S*-MEPY)$_4$ (**56**).[73]



129 **130** **75** Rh_2(*S*-PTPA)$_4$

Scheme 38. Rh_2(*S*-PTPA)$_4$ (**75**) catalysed cyclisation of *α*-diazo-*β*-ketoester.

Entry	R^1	R^2	Yield 130 (%)	*ee* %
1	CH_3	CH_3	76	24
2	CH_3	C_5H_{11}	43	29
3	CH_3	C_6H_5	96	46
4	CH^iPr_2	C_6H_5	86	76
5	CH^iPr_2	*p*-$MeOC_6H_5$	86	57
6	CH^iPr_2	*p*-$CF_3SO_3C_6H_4$	84	80

Table 6. Rh_2(*S*-PTPA)$_4$ (**75**) catalysed cyclisation of α-diazo-β-ketoester.

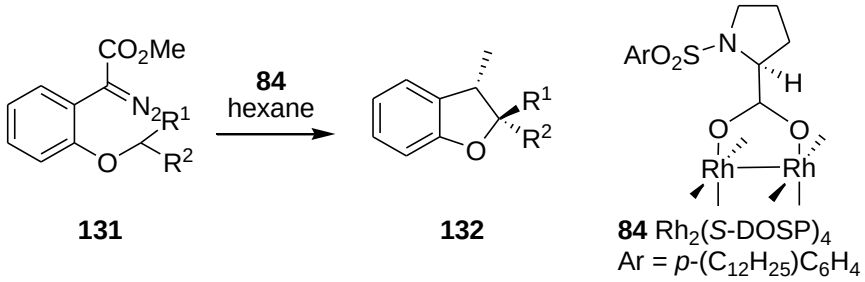
1.5.2.2.3 Donor/Acceptor substituted carbenoid

Highly regioselective and stereoselective C–H insertion reactions are possible with donor/acceptor-substituted carbenoids.[71,74] However, because of their stability provided by the *α*-substituents at the carbenoid carbon, the carbene precursor is not so sensitive to the choice of the metal catalyst, and a range of chiral rhodium(II) carboxylates

[73] Taber, D. F.; Malcolm, S. C. *J. Org. Chem.* **2001**, *66*, 944.
[74] (a) Davies, H. M. L. *Curr. Org. Chem.* **1998**, *2*, 463. (b) Davies, H. M. L.; Antoulinakis, E. G. *J. Organomet. Chem.* **2001**, *617-618*, 47. (c) Davies, H. M. L. *J. Mol. Catal. A.* **2002**, *189*, 125.

and rhodium(II) carboxamidates have been used with reasonable success in intramolecular cyclisation reactions.[75] Metallocarbenoids generated from rhodium(II) carboxylates tend to give the best levels of selectivity.

The control and selectivity exhibited by this class of carbenoids in intramolecular reactions has been described by Davies in the construction of chiral dihydrobenzofurans **132**.[76] C–H insertion at the methyl ether position of **131** was achieved in excellent yield when Rh_2(*S*-DOSP)$_4$ (**84**) was used as the catalyst (Scheme 39, Table 7 Compound **132a**), but the poor level of enantioselectivity led Davies to investigate alternative reaction conditions. After a small screen, he found that Rh_2(*S*-DOSP)$_4$ (**84**) is the best catalyst for C–H insertion at the tertiary site, giving the dihydrobenzofuran **132b** and **132c** in excellent yield and *ee* (Table 7, products **132b** and **132c**). However, reaction involving the corresponding cyclohexyl derivative **131** gave the desired spirocycle **132d** [R^1,R^2 = -$(CH_2)_5$-] in only 12% yield with carbene dimerisation being the predominant product.



131 **132** **84** Rh_2(*S*-DOSP)$_4$
Ar = *p*-$(C_{12}H_{25})C_6H_4$

Scheme 39. Intramolecular C–H insertion of aryldiazoacetate into methyl and methane C–H bond.

Product	R^1	R^2	Temp °C	Yield %	*ee* %
132a	H	H	23	98	<5
132b	CH_3	CH_3	–50	98	94
132c	*cyclo*-C_4H_8	*cyclo*-C_4H_8	–50	93	90
132d	*cyclo*-C_5H_{10}	*cyclo*-C_5H_{10}	–50	12	80

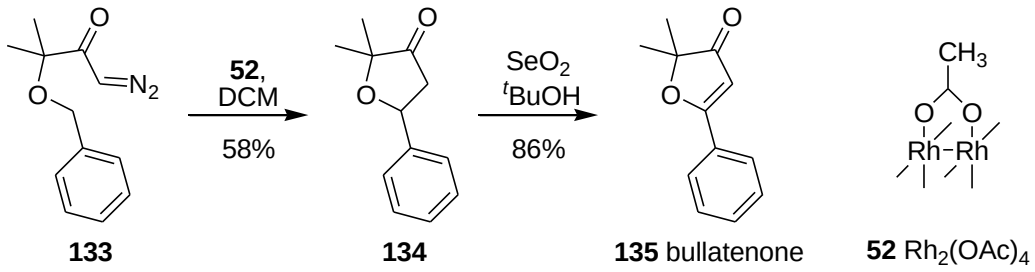
Table 7. Intramolecular C–H insertion of aryldiazoacetate into methyl and methane C–H bond.

[75] (a) Doyle, M. P.; May, E. J. *Synlett.* **2001**, 967. (b) Saito, H.; Oishi, H.; Kitagaki, S.; Nakamura, S.; Anada, M.; Hashimoto, S. *Org. Lett.* **2002**, *4*, 3887.
[76] Davies, H. M. L.; Grazini, M. V. A.; Aouad, E. *Org. Lett.* **2001**, *3*, 1475.

1.5.2.3 Intramolecular C–H insertion reactions in synthesis of natural compound.

As has been demonstrated throughout the previous sections of this chapter, transition metal carbenoids, particularly those of dirhodium carboxylates, are capable of undergoing selective C–H insertion reactions with a wide range of substrates. Consequently, these transformations have been applied as key C–C bond-forming steps in several total syntheses of important natural and bioactive products.

The tendency of five-membered heterocycle formation has been demonstrated with the total synthesis of the natural product bullatenone[77] (**135**). Intramolecular C–H insertions reaction to the adjacent carbon of the ether oxygen is especially preferred, as illustrated by the cyclisation of **133** to **134**. Oxidation of furanone **134** with SeO_2 according to the procedure of Smith and Jerris provided bullatenone (**135**) (Scheme 40).[78]

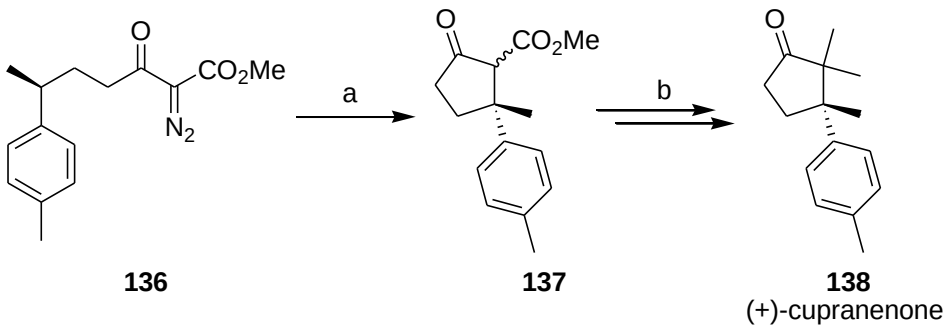


133 **134** **135** bullatenone **52** $Rh_2(OAc)_4$

Scheme 40. Total synthesis of bullatenone **135**.

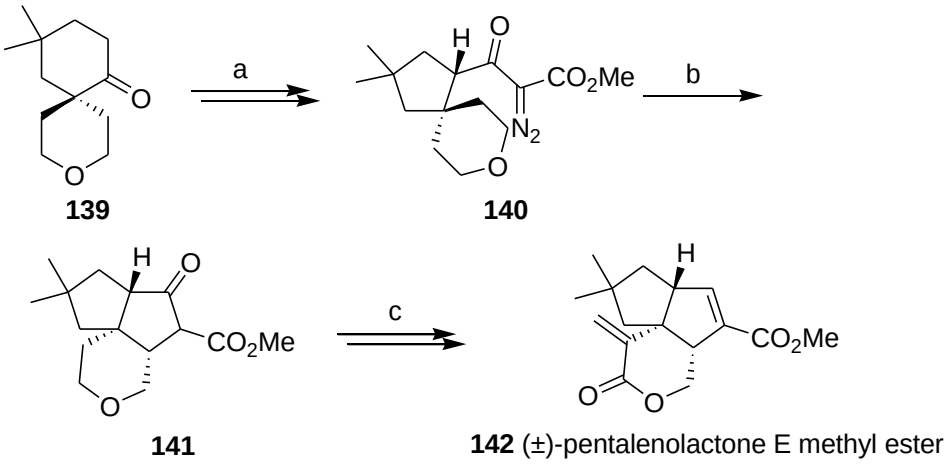
Retention of configuration of a stereogenic centre during an intramolecular C–H insertion has been demonstrated in the total synthesis of the natural product (+)-*α*-cupranenone (**138**).[79] In the synthesis, the treatment of *α*-diazo-*β*-keto ester **136** with $Rh_2(OAc)_4$ (**52**) resulted in the C–H insertion with retention of configuration to give the cyclopentanone **137**. Subsequent functionalisation of the cyclopentanone **137** led to the natural product (Scheme 41)**.**

[77] Adams, J; Poupart, M. A.; Grenier, L.; Schaller, C.; Ouimet, N.; Frenette, R. *Tetrahedron Lett*. **1989**, *30*, 1749.
[78] Smith, A. B.; Jerris, P. J. *Synth. Commun*. **1978**, *8*, 421.
[79] Taber, D. F.; Petty, E. H.; Raman, K. *J. Am. Chem. Soc*. **1985**, *107*, 196.



Scheme 41. Total synthesis of the natural product (+)-cupranenone (**138**). Conditions: (a) $Rh_2(OAc)_4$ **52**, 67%. (b) 4 steps, 36%.

In the same year, Taber and Schuchardt completed the total synthesis of (±)-pentalenolactone E methyl ester (**142**). The key step of the synthesis was a stereoselective intramolecular C–H insertion into a methylene group to build the tricyclic core **141** found in the natural product (Scheme 42).[80] Six steps from the commercially available starting material **139** were required to construct the α-diazo β-keto ester **140** and the treatment with rhodium(II) acetate dimer (**52**) gave the tricyclic core **141**. The completion of the synthesis of the natural product **142** was accomplished from **141** in 3 steps.



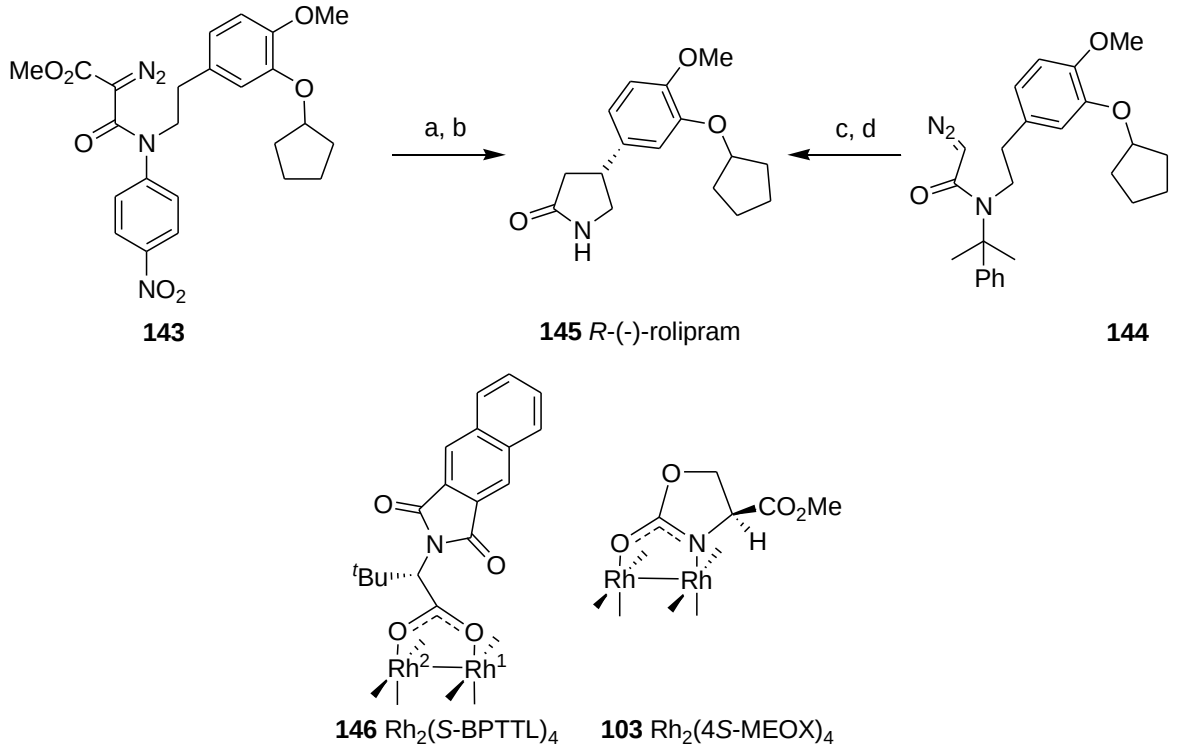
Scheme 42. Total synthesis of the natural product (±)-pentalenolactone E. Conditions: (a) 5 steps, 29%. (b) $Rh_2(OAc)_4$ (**52**), 91%. (c) 3 steps, 4%.

Enantioselective intramolecular carbenoid C–H insertion reactions have been employed in two very similar total syntheses of the PDE 4 inhibitor *R*-(−)-rolipram (**145**)

[80] Taber, D. F.; Schuchardt, J. L. *J. Am. Chem. Soc.* **1985**, *107*, 5289.

(Scheme 43).[81] In 1999, Hashimoto and co-workers found that the treatment between the acceptor/acceptor diazo compound **143** and Rh_2(*S*-BPTTL)$_4$ (**146**) provided the best conditions for this transformation and furnished the cyclised product **145** in 74% yield and 88% *ee*.[81a]

Hu and co-workers utilised a very similar cyclisation precursor **144** in 2005.[81b] The main differences were the absence of the second acceptor group on the diazo function. They also chose to screen a range of catalyst and Rh_2(4*S*-MEOX)$_4$ **103** provided the best enantioselectivity, though still only at the level of 46% *ee*. After two recrystallisations of the final product, the enantiomeric purity was increased to 88% *ee*, but Hashimoto's protocol is clearly superior but longer.



143 **145** *R*-(-)-rolipram **144**

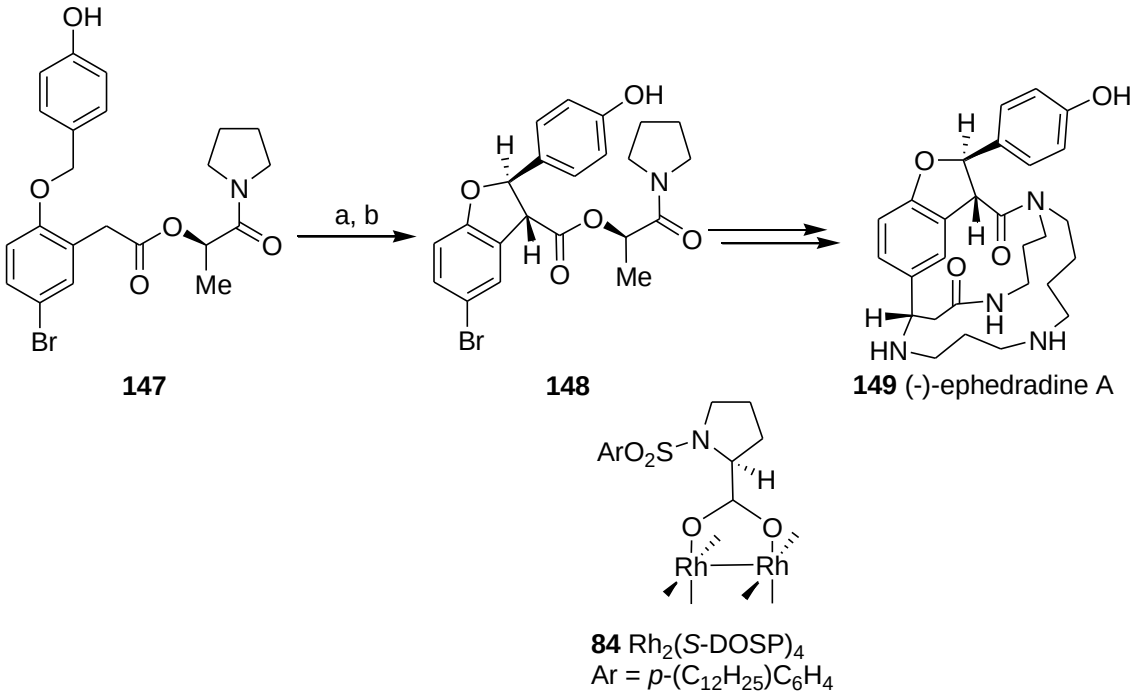
146 Rh_2(*S*-BPTTL)$_4$ **103** Rh_2(4*S*-MEOX)$_4$

Scheme 43. Total synthesis of the natural product *R*-(-)-rolipram **145**. Conditions: (a) 2% Rh_2(*S*-BPTTL)$_4$ (**146**), DCM, rt, 74%, 88% *ee*. (b) 4 steps, 50%. (c) Rh_2(4*S*-MEOX)$_4$ (**103**), DCM, reflux, 64%, 46% *ee*. (d) TFA, 65% (46% when recryst. to 88% *ee*).

In certain cases, a chiral catalyst alone is not sufficient to furnish the necessary asymmetric induction and combination with a chiral auxiliary is required. For example, Fukuyama and co-workers used a stereoselective C–H insertion as the key reaction of their

[81] (a) Anada, M.; Mita, O.; Watanabe, H.; Kitagaki, S.; Hashimoto, S. *Synlett* **1999**, 1775. (b) Liu, W.-J.; Chen, Z.-L.; Chen, Z.-Y.; Hu, W.-H. *Tetrahedron; Asymm.* **2005**, *16*, 1693.

total synthesis of the natural product (−)-ephedradine A (**149**) (Scheme 44).[82] Substrate **147** was treated with diazo transfer reagent *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) and DBU to afford the required diazo ester. Then treatment of the substrate with Rh_2(*S*-DOSP)$_4$, (**84**) furnished a 13:1 mixture of diastereomers of the C–H insertion product **148** in 63% yield. Removal of the chiral auxiliary was easily accomplished, and recrystallisation of the resulting acid provided enantiomerically pure product in 90% yield, which was ultimately taken to the natural product **149**.



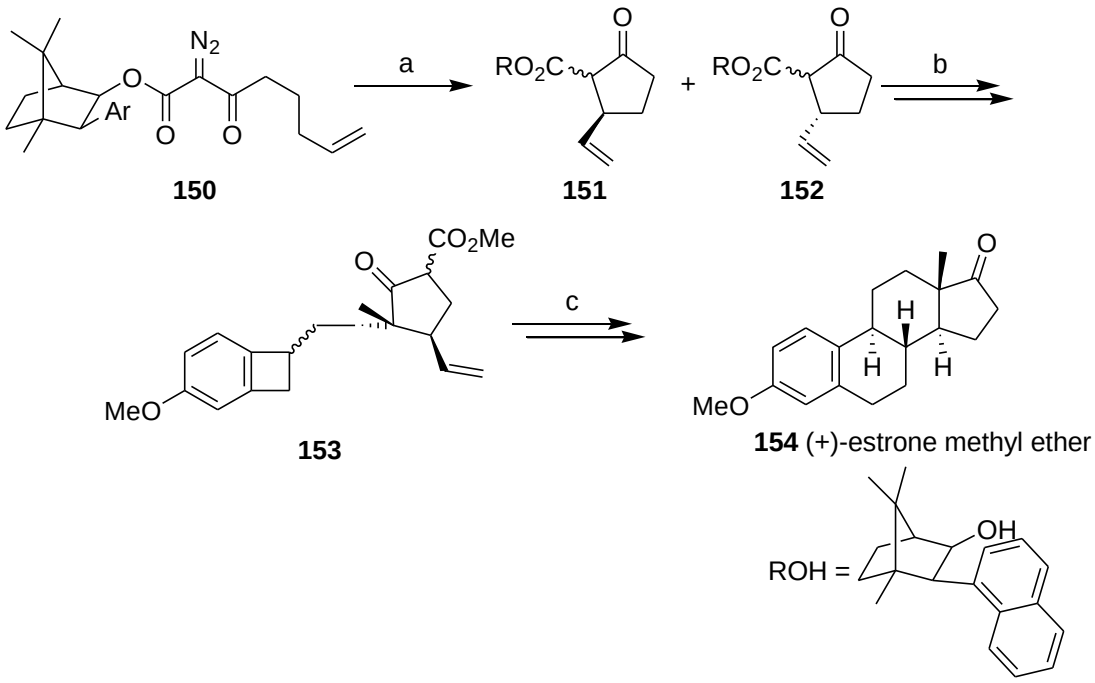
147 **148** **149** (-)-ephedradine A

84 Rh_2(*S*-DOSP)$_4$
Ar = *p*-($C_{12}H_{25}$)C_6H_4

Scheme 44. Total synthesis of the natural product (-)-ephedradine (**149**). Conditions: (a) *p*-ABSA, DBU, MeCN. (b) Rh_2(*S*-DOSP)$_4$ (**84**), DCM, 13:1 *dr* 63% (2 steps).

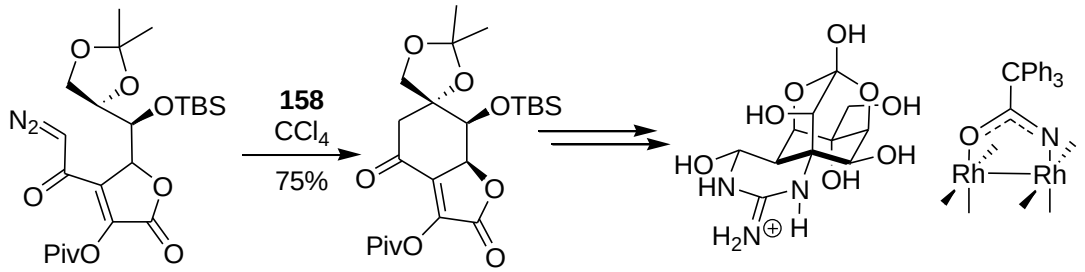
Enantioselective construction of a polycyclic target using a chiral auxiliary has been described in the synthesis of (+)-estrone methyl ether (**154**).[83] In order to construct the first cyclic stereogenic centre, Taber and co-workers synthesised the α-diazo β-keto ester **150** which directed Rh-mediated intramolecular C–H insertion selectively toward one of two diastereotopic C–H bonds in the methylene group. The new tertiary centre created, thus directed the subsequent formation of the adjacent quaternary centre by an alkylation reaction. The chirality of the product cyclopentanone **153** directed the intramolecular cycloaddition reaction, to give the steroid (+)-estrone methyl ether (**154**) (Scheme 45).

[82] (a) Kurosawa, W.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 8112. (b) Kurosawa, W.; Kobayashi, H.; Kan, T.; Fukuyama, T. *Tetrahedron* **2004**, *60*, 9615.
[83] Taber, D. F.; Raman, K.; Gaul, M. D. *J. Org. Chem*. **1987**, *52*, 28.



Scheme 45. Total synthesis of the natural product (+)-estrone methyl ether. Conditions: (a) $Rh_2(OAc)_4$ (**52**), 62%, **151** 92%, **152**, 8%. (b) 3 steps, 38% (c) 2 steps, 41%.

The most complex natural product synthesis in which a carbenoid C–H insertion reaction has been employed as a key step is the recent total synthesis of (−)-tetrodotoxin (**157**), reported by Hinman and Du Bois in 2003 (Scheme 46).[84] In this synthesis, C–H insertion occurred at the carbon adjacent to the acetal oxygen atom of the substrate **155**, and rhodium(II) triphenylacetamide dimer (**158**) was the catalyst of choice for the diastereospecific transformation.



Scheme 46. Total synthesis of the natural product (-)-tetrodotoxin

[84] Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510.

1.5.2.4 Conclusion

Metal mediated carbenoid C–H insertion is a highly effective method of introducing new C–C bonds into organic substrates in both regioselective and stereoselective manner through judicious choice of catalyst. Although early reactions were carried out with ethyl diazoacetate as the carbenoid source, donor/acceptor carbenes are quickly becoming key precursors in this field due to their excellent selectivity in many instances. Moreover, rhodium carboxylates and carboxamidates remain the catalysts of choice for most transformations, particularly those requiring asymmetric induction. Although, intramolecular carbenoid C–H insertion is also in constant progress and great efforts are focused to apply this reaction to complex substrates.

The outcomes of the reaction can be predicted according the structure of the substrate. C–H insertion generally occurs at methine > methylene > methyl group due to electronic and steric effect. An electron-donating substituent such as an ether function or a siloxy group is able to direct C–H insertion reaction towards the adjacent site. Moreover, catalyst development gave access to high levels of regioselectivity and enantioselectivity.

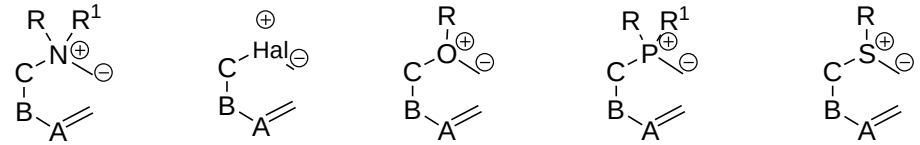
As a consequence of the synthetic utility of the reaction, it has already been utilised as a key step in many partial and complete total syntheses of natural products and pharmaceuticals. Efforts are now focused on the development of new and more selective chiral catalysts, as well as on the development of donor and acceptor groups on the carbenoids.

1.5.3 Oxonium ylide formation and their subsequent rearrangement

Reaction between an electron-deficient carbenoid with a non-bonding electron pair from a Lewis base generates a metal complex-associated ylide or a free ylide. The ylide or ylide-like intermediate generated is usually highly reactive and can be used for the formation of highly functionalised compounds from relatively simple components. Heteroatom substituted cations, exhibiting excess valency (-onium state), are normally more stable than those possessing reduced valency (the -enium state), consequently ylides are usually derived from onium species. Nitrogen, halogen, oxygen, phosphorus, and sulfur are the most commonly used Lewis base heteroatoms used to generate ylides (Figure 9).[85]

[85] Sweeney, J. B. *Chem. Soc. Rev.* **2009**, *38*, 1027.

Thus, ammonium, halonium, oxonium, phosphonium and sulfonium ylides are the most widely used ylide intermediates and over the past three decades, their development and exploitation in organic synthesis have received considerable attention.



159 Ammonium **160** Halonium **161** Oxonium **162** Phosphonium **163** Sulfonium

Figure 9. Onium ylide species.

Until relatively recently, because of their instability and high reactivity, very little attention has been paid on the chemistry of oxonium ylides compared to their ammonium and sulfonium counterparts.[86] Unlike the ammonium and sulfonium ylide, oxonium ylides have not yet been isolated. However proof of their existence relies upon the isolation of similar products resulting from rearrangement of the corresponding sulfur, nitrogen, and phosphorus ylides.

Common reactions of ylides include:

[2,3]-Sigmatropic rearrangement of allylic, propargylic and allenic ylides.

[1,2]-Shift (Stevens rearrangement).

[1,4]-Shift reaction.

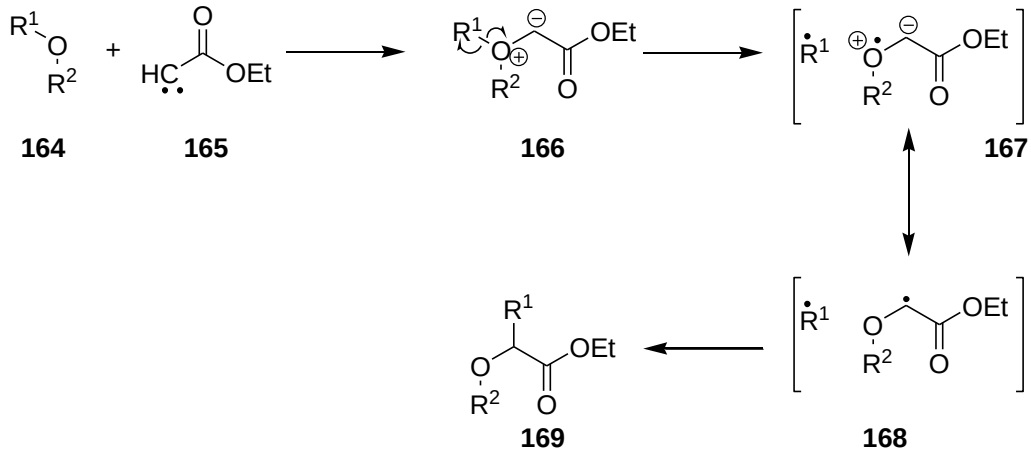
Since the area of nitrogen, halogen, oxygen, phosphorus and sulfur ylide chemistry is too vast to cover in this review, only the generation of oxonium ylides from catalytically generated metal carbenoids and their subsequent rearrangement reactions will be discussed in the chapter.

1.5.3.1 [1,2]-Shift (Stevens rearrangement)

A [1,2]-Stevens rearrangement arises by the insertion of an electrophilic carbene into an ether oxygen lone pair followed by migration of one of the alkyl groups.[81,87] According to the Woodward-Hoffmann rules,[88] a concerted [1,2]-shift is a symmetry-forbidden process, even though isolations of products resulting from a [1,2]-shift are obtained in many cases. For this reason, a homolysis recombination mechanism has been

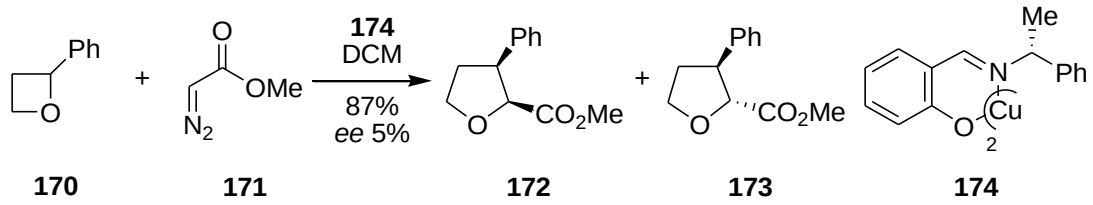
[86] (a) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091. (b) Adams, J.; Spero, D. M. *Tetrahedron*, **1991**, *47*, 1765.
[87] Iwamura, H.; Imahashi, Y. *Tetrahedron Lett.* **1975**, *17*, 1401.
[88] Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *78*, 2511.

proposed to explain the product formation (Scheme 47).



Scheme 47. Homolysis recombination mechanism for [1,2]-shift.

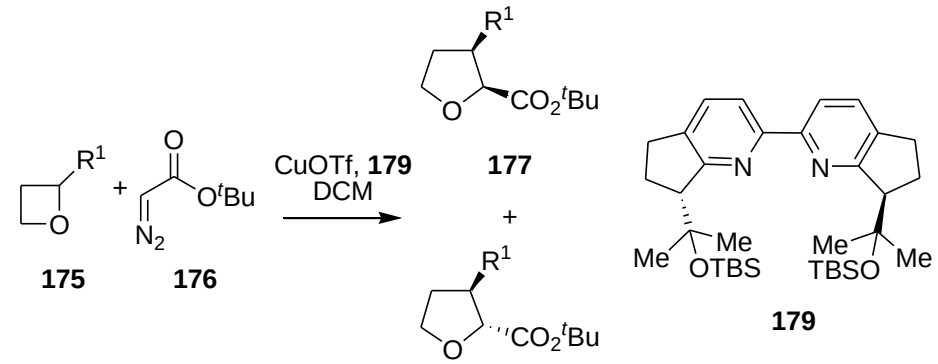
One of the earliest report describing the formation and rearrangement of a catalytically generated oxonium ylide was reported by Nozaki.[89] Treatment of methyl diazoacetate (**171**) and phenyloxetane (**170**) with the copper catalyst **174** resulted in [1,2]-benzylic rearrangement to furnish a *cis-trans* mixture of ethyl 3-phenyltetrahydrofuran-2-carboxylates (**172** and **173**) (Scheme 48). Although the products were obtained in reasonable yield, the level of asymmetric induction was very low in both cases.



Scheme 48. Intermolecular [1,2]-Shift (Stevens rearrangement)

This example showed that an enantioselective reaction is possible by using a racemic starting material and a chiral metal catalyst. Katsuki described the treatment of a racemic 2-substituted oxetane **175** with the diazo ester **176** in the presence of the chiral copper complex **179** (Scheme 49). Isolation of a 1:1 mixture of the diastereoisomer tetrahydrofurans **177** and **178** was observed in modest overall yield but with reasonable enantiomeric excess.[90]

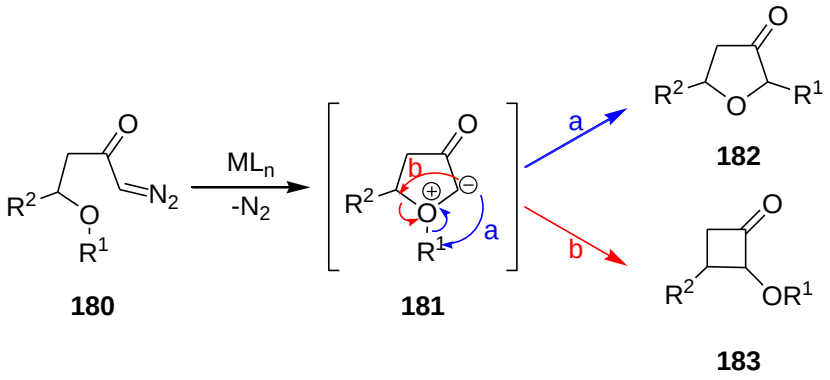
[89] Nozaki, H.; Takaya, H.; Moriuti, S.; Noyori, R. *Tetrahedron*, **1968**, *24*, 3655.
[90] (a) Ito, K.; Katsuki, T. *Chem. Lett.* **1994**, 1857. (b) Ito, K.; Yoshitake, M.; Katsuki, T. *Chem. Lett.* **1995**, 1027. (c) Ito, K.; Yoshitake, M.; Katsuki, T. *Heterocycles* **1996**, *42*, 305.



177 R^1 = Ph; 21%; *ee* 75%
R^1 = *p*-CH_3CPh; 15%; *ee* 76%
178 R^1 = Ph; 15%; *ee* 81%
R^1 = *p*-CH_3CPh; 15%, *ee* 71%

Scheme 49. Enantioselective oxonium ylide generation and [1,2]-shift reaction.

Since this report, great efforts have been made of the oxonium ylide generation followed by [1,2]-Stevens rearrangement and this transformation has been found to have a synthetic utility in the formation of new C–C bonds. Johnson reported two possible outcomes for the decomposition of the diazo ketone **180** and the [1,2]-shift reaction (Scheme 50).[91] One outcome resulted in formation of the expected tetrahydrofuran **182** (path a) from the formal Stevens rearrangement and the second resulted in formation of the carbocycle **183** by ring contraction (path b).

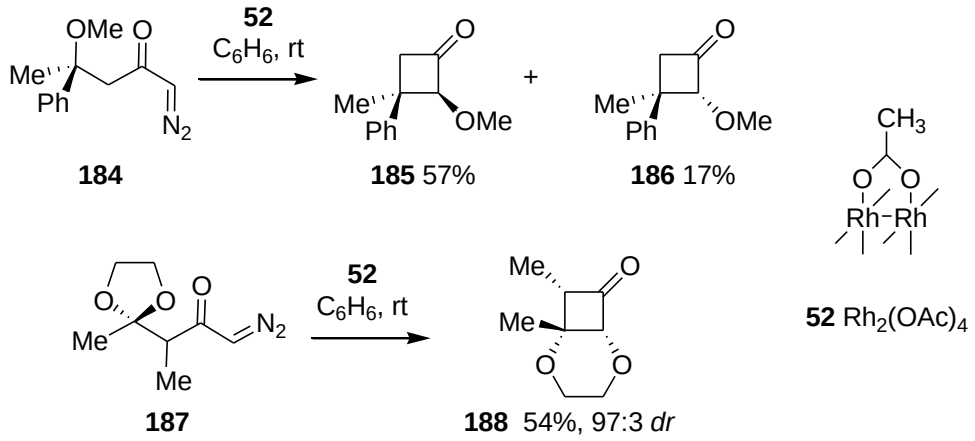


Scheme 50. Two possible pathways; (path a) Formal [1,2]-shift reaction; (path b) Ring contraction.

Examples of ring contraction processes are displayed in Scheme 51. Treatment of diazoketone **184** with $Rh_2(OAc)_4$ (**52**) led to a mixture of cyclobutanones **185** and **186**.[91] In

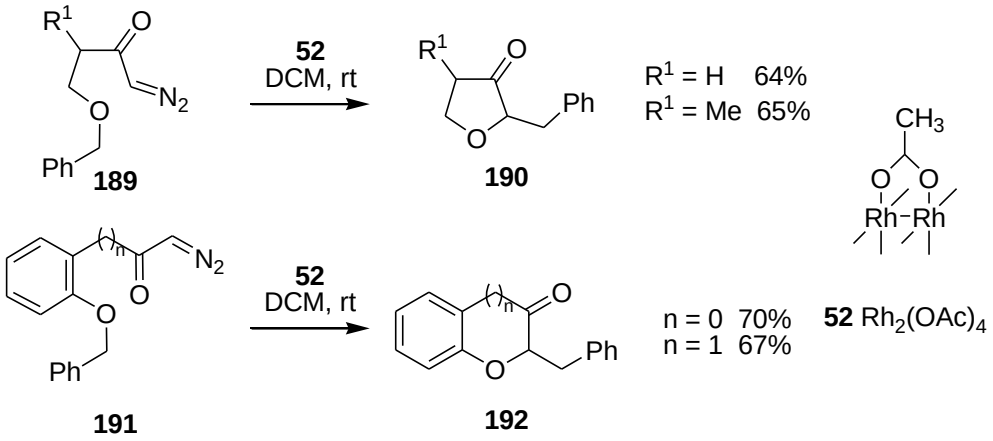
[91] Roskamp, E. J.; Johnson, C. R. *J. Am. Chem. Soc.* **1986**, *108*, 6062.

this reaction, the rearrangement process positioned the ether oxygen substituent outside the ring. Consequently, the ring contraction occurred and cyclobutanone formation was observed instead of the cyclic ether formation. Decomposition of the diazoketone **187** furnished the ring contraction product **188** with high diastereoselectivity following the same process.[91] The key to the cyclobutanone formation or the ring contraction appears to be the electron deficiency at the carbon adjacent to the oxygen, vinyl, or aryl substituent.



Scheme 51. Ring contraction process versus Stevens rearrangement.

The transformation of simple acyclic diazoketones into cyclic ethers by oxonium ylides and [1,2]-shift reaction has been investigated by West and co-workers.[92] For example, treatment of the benzylic ethers diazoketones **189** and **191** with $Rh_2(OAc)_4$ (**52**) resulted in the migration of the aromatic substituent to produce, respectively, the furanone **190** and the pyranone **192** in excellent yield (Scheme 52).

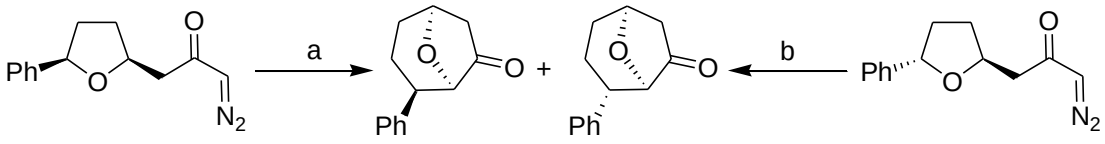


Scheme 52. Conversion of simple acyclic diazoketones into cyclic ethers by oxonium

[92] Eberlein, T. H.; West, F. G.; Tester, R.W. *J. Org. Chem.* **1992**, *57*, 3479.

ylides and [1,2]-shift reaction

West has also exploited this methodology to construct oxygen-bridged ring systems via bicyclic oxonium ylides.[93] Decomposition of the diazoketones **193** and **194** delivered a diastereoisomeric mixture of the cyclopentanones **195** and **196** (Scheme 53). Complete selectivity for migration of the benzylic group was observed and the relative stereochemistry of the diazoketone had a significant influence on the stereochemical outcome of the reaction. The major diastereoisomer in each case arose from migration with retention of configuration; the *cis*-tetrahydrofuran **193** gave a higher degree of retention.

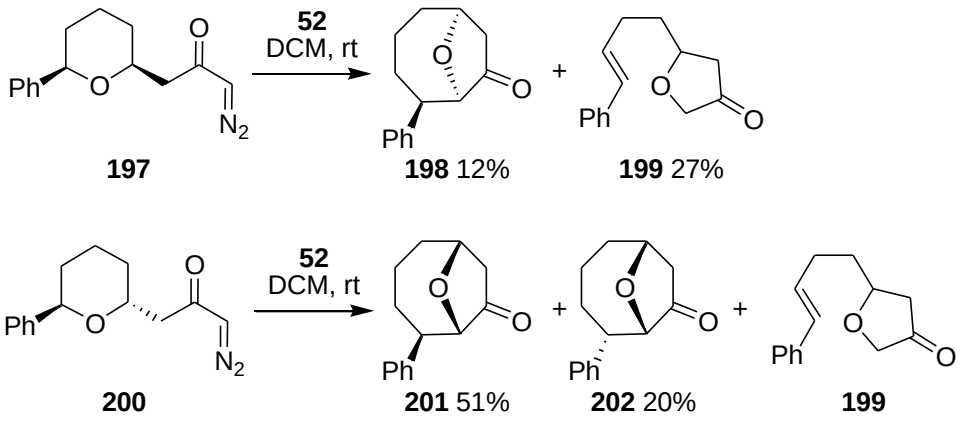


193 **195** **196** **194**

Scheme 53. Conditions: (a) $Rh_2(OAc)_4$ (**52**), DCM, rt, 60%; *dr* **195**:**196** 19:1. (b) $Rh_2(OAc)_4$ (**52**), DCM, rt, 90%, *dr* **195**:**196** 1:2.

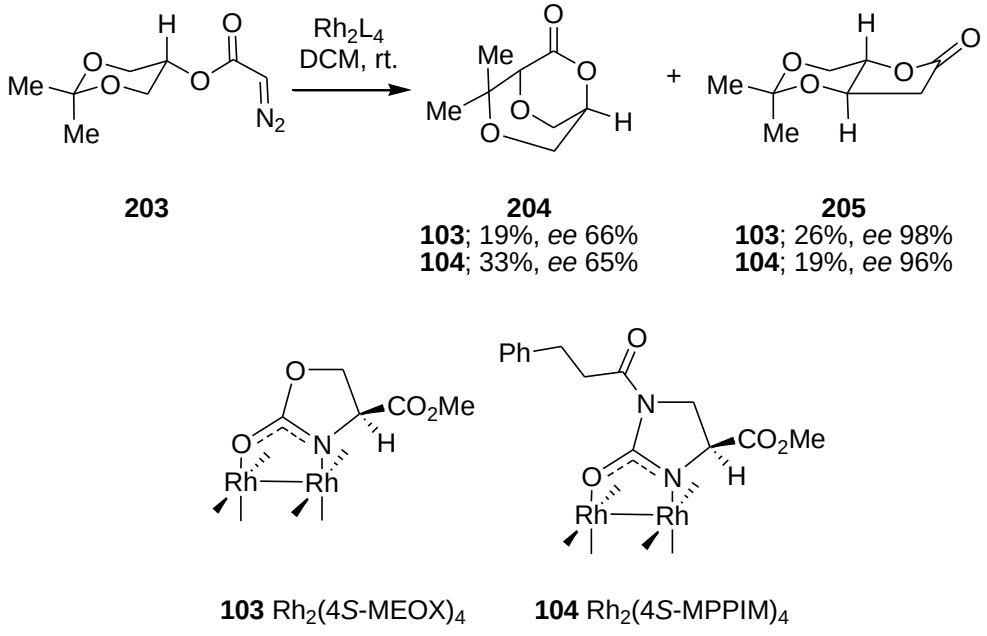
The homologous tetrahydropyran series gave rather disappointing results.[93] Oxonium ylide generation from the *cis*-tetrahydropyran **197** followed by its [1,2]-shift reaction afforded cyclooctanone **198** as a single diastereoisomer in very low yields. During the reaction, the formation of tetrahydrofuranone **199** was also observed and this side-product was presumed to result from the *β*-elimination of the intermediate oxonium ylide. The *trans*-isomer **200** underwent also the same process to give the cyclooctanone **201** and **202** from migration of the benzyl group in good yield. The major diastereoisomer **201** arose again from migration with retention of configuration (Scheme 54). However, formation of the tetrahydrofuranone **199** was again obtained as a minor product.

[93] West, F. G.; Eberlein, T. H.; Tester, R. W. *J. Chem. Soc.; Perkin Trans.1* **1993**, 2857.



Scheme 54. Synthesis of oxygen-bridged ring systems via bicyclic oxonium ylides.

Asymmetric tandem intramolecular ylide formation and Stevens rearrangement using an achiral substrate and a chiral catalyst has been demonstrated firstly by Doyle and co-workers.[94] In his studies, he described the treatment of the diazoketone **203** with chiral rhodium carboxamidate **103** or **104** to furnish the bridged bicyclic lactone **204**. However, the substrate also underwent a C–H insertion to give the side-product **205** in moderate yields. The Stevens rearrangement product was obtained with moderate enantioselectivity whereas the C–H insertion product was isolated with an impressive enantiomeric excess. It is thought that the predominance of C–H insertion was due to the metal carbenoid reacting preferentially in an equatorial position (Scheme 55).

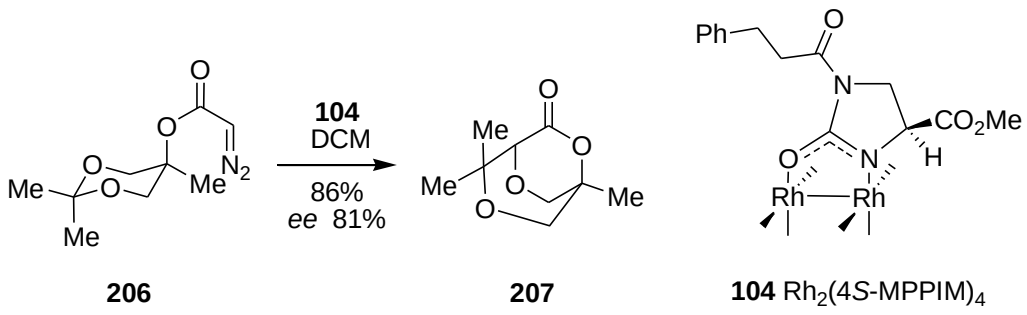


Scheme 55. Asymmetric oxonium ylide formation/[1,2]-shift and C–H insertion generated

[94] Tester, R. W.; West, F. G. *Tetrahedron Lett.* **1998**, *39*, 4631.

by chiral catalyst

To control the chemoselectivity in favour of the ylide generation/[1,2]-shift tandem reaction, the diazoketone **206** was constructed in order to position the diazo ester functionality in axial position in the chair conformation.[94] Exposure of **206** to the chiral catalyst Rh_2(4*S*-MPPIM)$_4$ (**104**) afforded the bridged bicyclic lactone **207** in good yield and with high *ee* (Scheme 56).



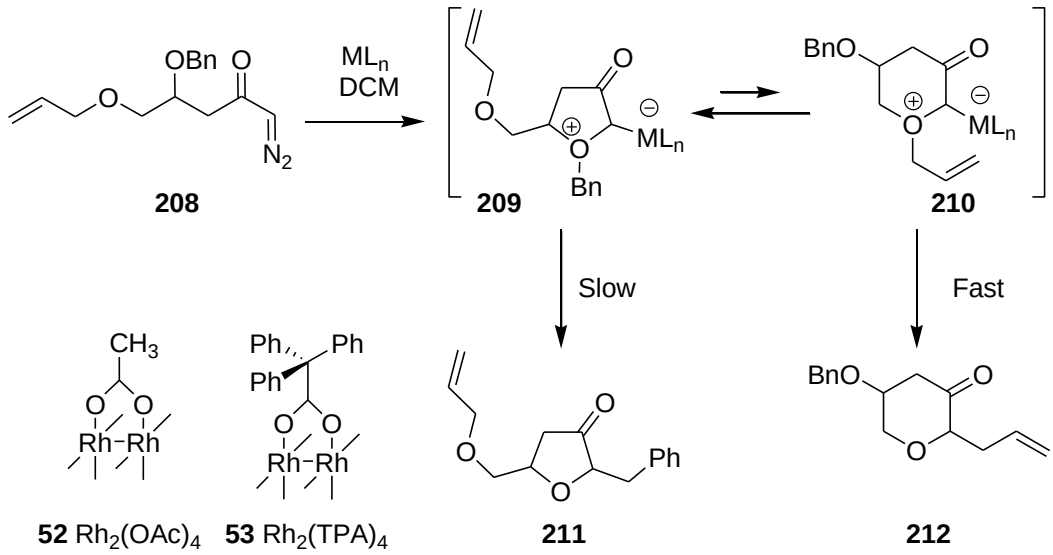
206 **207** **104** Rh_2(4S-MPPIM)$_4$

Scheme 56. Asymmetric oxonium ylide formation/[1,2]-shift by chiral catalyst

West and co-workers investigated reactions of diazoketones in which competition between the formations of two different oxonium ylides from the same metallocarbene was possible.[95] The metallocarbene could undergo intramolecular transformation to give the five- or the six-membered ring products (Scheme 57). The investigations showed that the five-membered cyclic ylide formation is favoured. In the example shown in the Scheme 57, migration of the allyl group, the preferred migrating group, can occur via the six-membered cyclic ylide **210**, or benzyl migration can occur through the intermediacy of the kinetically favored five-membered cyclic ylide **209**. When the diazoketone **208** was treated with Cu(tfacac)$_2$, selective allyl migration can override the kinetic preference for formation of a five-membered ring and the pyranone **212** is the major product (Table 8). This can be explained by slow rearrangement of the initially formed five-membered *O*-benzyl oxonium ylide, which can permit equilibration with the six-membered *O*-allyl isomer and its relatively fast rearrangement. West and co-workers also reported that the catalyst can have a significant influence on the reaction selectivity. When $Rh_2(OAc)_4$ (**52**) and $Rh_2(TPA)_4$ (**53**) were employed, the reaction exhibited a preference for the formation of the five-membered ylide and subsequent Stevens rearrangement furnished the product **211**

[95] Marmsäter F. P.; Vanecko, J. A.; West, F. G. *Org. Lett.* **2004**, *6*, 1657.

predominantly. Only $Cu(hfacac)_2$ was relatively unselective, giving similar amounts of **211** and **212**.



Scheme 57. Catalyst and ring size effects on preselectivity of oxonium ylide rearrangement

ML_n	211 yield %	212 yield %
$Cu(tfacac)_2$	16	67
$Cu(hfacac)_2$	38	29
$Rh_2(OAc)_4$	50	27
$Rh_2(TPA)_4$	54	22

Table 8. Catalyst and ring size effects on preselectivity of oxonium ylide rearrangement.

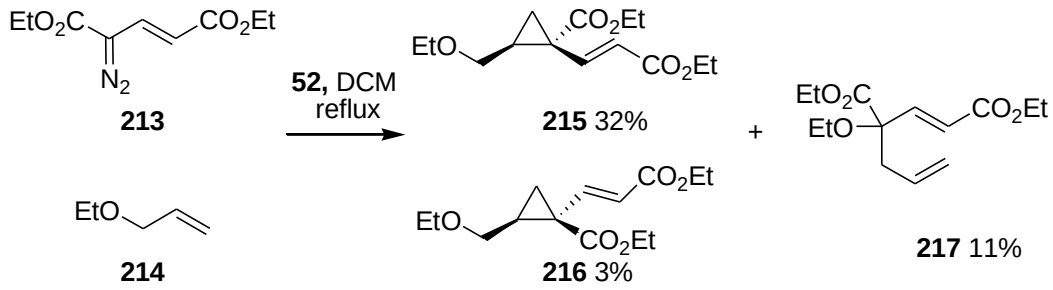
The catalyst-dependent selectivity strongly suggests the involvement of a metal-associated ylide in the product-forming steps of the reaction. The catalyst may alter the properties of ylide and affect the equilibrium between different species.

1.5.3.2 [2,3]-Sigmatropic rearrangement of allylic oxonium ylides.

When an allylic ether is present during the ylide formation, the generated oxonium ylide may undergo [2,3]-sigmatropic rearrangement. Davies and co-workers were the first to isolate a product generated from [2,3]-sigmatropic rearrangement of an oxonium ylide.[96] During their studies to investigate stereoselective cyclopropanations

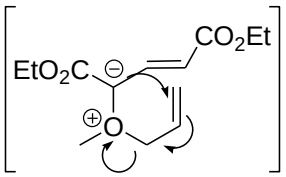
[96] Davies, H. M. L.; Clark, T. J.; Church, L. A. *Tetrahedron Lett*. **1989**, *30*, 5057.

using vinylcarbenoids, an unusual product along with the expected cyclopropane products was isolated. They reported that the reaction of vinyl diazoketone **213** with ethyl allyl ether **214** in the presence of $Rh_2(OAc)_4$ (**52**) afforded a mixture of the desired cyclopropanes **215** and **216** as well as the diene **217** (Scheme 58).



Scheme 58. Davies investigation to stereoselective cyclopropanations using vinylcarbenoids

This process affording **217** involves the decomposition of the diazoketone **213** to generate the rhodium carbenoid followed by attack of the ethereal oxygen leading to the oxonium ylide intermediate **218** (Figure 10). A [2,3]-sigmatropic rearrangement may undergo to give the new product **217**. The overall process involves formation of carbon–oxygen bond and rearrangement to form the carbon–carbon bond.



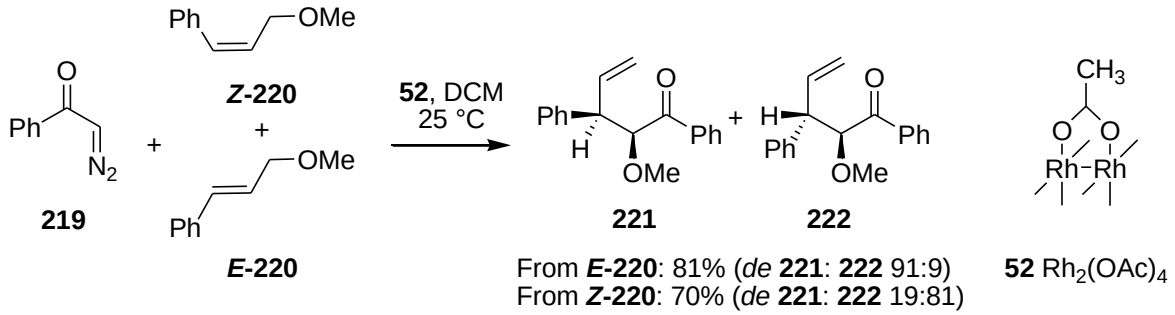
218

Figure 10. The oxonium ylide intermediate **218**

Since this report, the intermolecular ylide formation and [2,3]-sigmatropic rearrangement reaction has received considerable attention. The diastereoselectivity of intermolecular ylide formation and rearrangement of allyl methyl ether with phenyl diazoacetates has been described,[97] and Doyle discovered that decomposition of the diazo compound **219** using $Rh_2(OAc)_4$ (**52**) gave two diastereomers depending on the geometry of the alkene (Scheme 59). Reaction of the *trans*-cinnamyl ether **220** at room temperature

[97] Doyle, M. P.; Bagheri, V.; Harn, N. K. *Tetrahedron Lett.* **1988**, *29*, 5119.

gave predominately the *erythro*-isomer **221** and the *threo*-isomer **222** was obtained preferentially from the reaction with the *cis*-cinnamyl ether.



Scheme 59. Diastereoselectivity of intermolecular oxonium ylide formation and subsequent [2,3]-sigmatropic rearrangement.

The results obtained by Doyle and co-workers can be rationalised by steric and/or electronic influences in the competing transition states (Figure 11). The transition states **224** and **226** are of higher energy than **223** and **225** because of eclipsing interactions between the *O*-methyl and COR groups. Consequently, the observed diastereoselectivity is dependent on the relative energies of the transition states **223** and **225**. In the case where R^2 = Ph, the *erythro* product is formed from the transition state **225** and when R^1 = Ph, transition state **223** is lower in energy and so the *threo* product predominates.

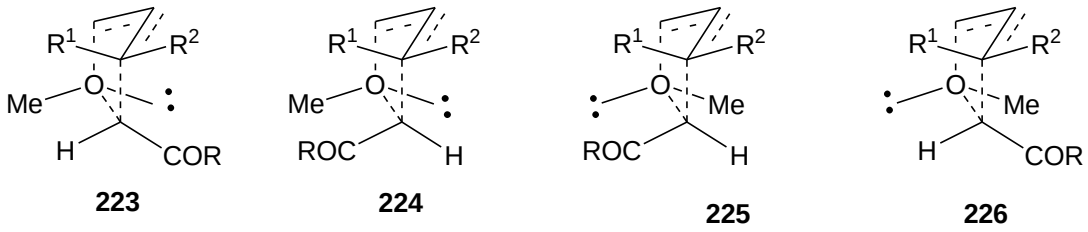
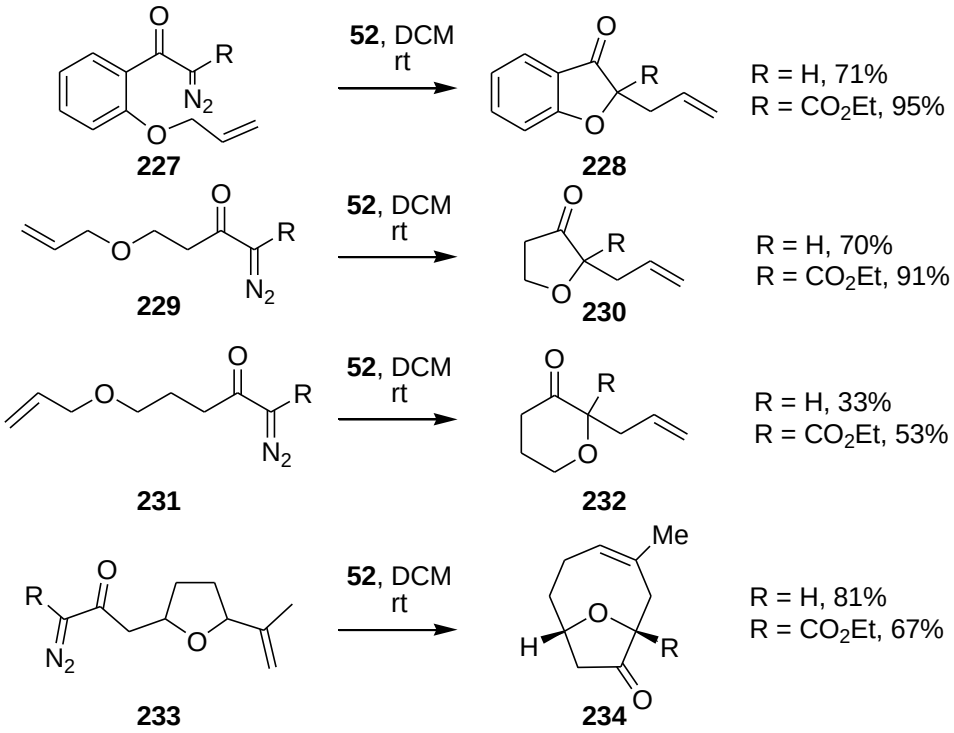


Figure 11. Steric and/or electronic influences on transition state structures for [2,3] rearrangement.

The application of the intermolecular oxonium ylide formation and subsequent [2,3]-sigmatropic rearrangement reaction has been limited in organic synthesis, however the intramolecular processes has been extensively studied. A cyclic oxonium ylide is generated by intramolecular reaction of a metal carbene and suitably positioned ethereal oxygen. The first application of the methodology has been described by Pirrung and co-

workers.[98] They reported their preliminary results on the intramolecular generation of allylic oxonium ylides and their subsequent [2,3]-sigmatropic rearrangement to give five-, six-, and eight-membered cyclic ethers. The two first examples shown in Scheme 60 established the utility of the process with the construction of furanones **228** and **230** in good to excellent yields. Extension of the chain length to afford the six-membered cyclic ether **232** resulted in a low yield because of the competing C–H insertion pathway. The three-carbon ring expansion to form bridged bicyclic ether **234** is noteworthy because it illustrated the synthetic potential of this reaction as a general approach to the synthesis of medium-ring oxygen heterocycles.

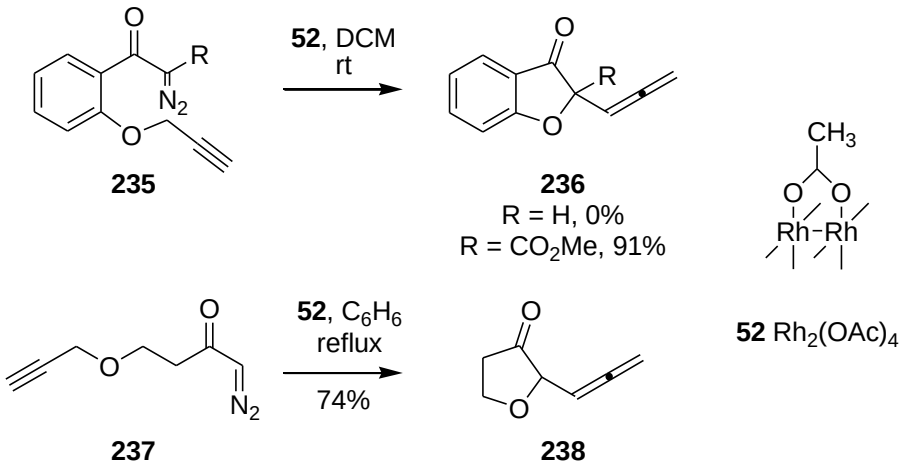


Scheme 60. intramolecular oxonium ylide formation and subsequent [2,3]-sigmatropic rearrangement.

The [2,3]-sigmatropic rearrangement reaction of oxonium ylides is not limited to those generated from reaction of allylic ethers with metal carbenoid. Propargylic ethers are also good substrates and [2,3]-sigmatropic rearrangement results in the production of an allene (Scheme 61). For example, reaction between the α-diazoketone **235** (R = CO_2Me) and **237** with $Rh_2(OAc)_4$ (**52**) furnished the allenes **236** and **238**. Pirrung also showed that the substrate structure have significant influence on the success of the reaction and the

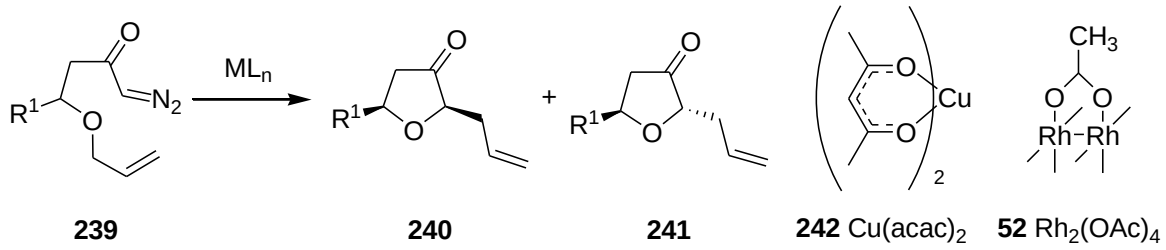
[98] Pirrung, M.C.; Werner, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 6060.

corresponding *α*-diazoketone **235** (R = H) failed to undergo the same reaction.[98]



Scheme 61. [2,3]-sigmatropic rearrangement from propargylic ether.

The diastereoselectivity of ylide formation and rearrangement to form cyclic ether was examined by Johnson and Roskamp.[91] Using simple compounds such as the diazo ketone **239** (Scheme 62, Table 9), they showed that the decomposition of the substrate **239,** when R^1 = Me, using $Rh_2(OAc)_4$ (**52**) gave preferentially the *trans*-furanone **241**. However, using a similar substrate (R^1 = ^{i}Pr), Clark reported poorer levels of diastereocontrol when rhodium(II) acetate dimer (**52**) was used as catalyst.[99] Although, he described a dramatic increase in the level of selectivity when the reaction was accomplished using copper(II) acetylacetonate $Cu(acac)_2$ (**242**) as the catalyst. Almost complete selectivity for the *trans*-furanone **241** was observed in this case.



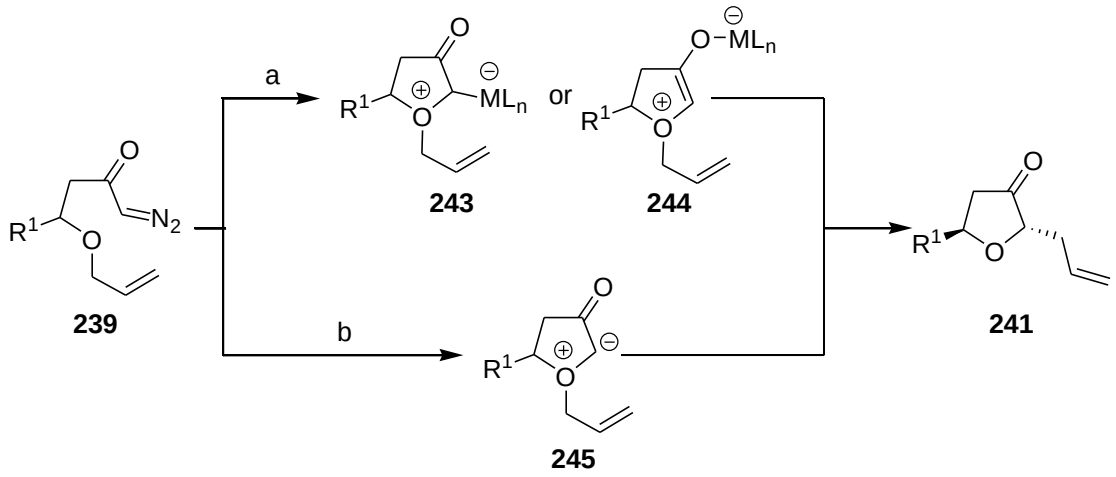
Scheme 62. Diastereoselectivity of ylide formation and sigmatropic rearrangement.

[99] Clark, J. S. *Tetrahedron Lett.* **1992**, *33*, 6193.

R^1	ML_n	Solvent	temp	yield %	*de* 240:241
Me	$Rh_2(OAc)_4$ (**52**)	DCM	rt	65	3:97
^{i}Pr	$Rh_2(OAc)_4$ (**52**)	DCM	rt	51	35:65
^{i}Pr	$Cu(acac)_2$ (**242**)	C_6H_6	reflux	85	3:97
^{i}Pr	$Cu(acac)_2$ (**242**)	THF	reflux	83	3:97

Table 9. Diastereoselectivity of ylide formation and sigmatropic rearrangement.

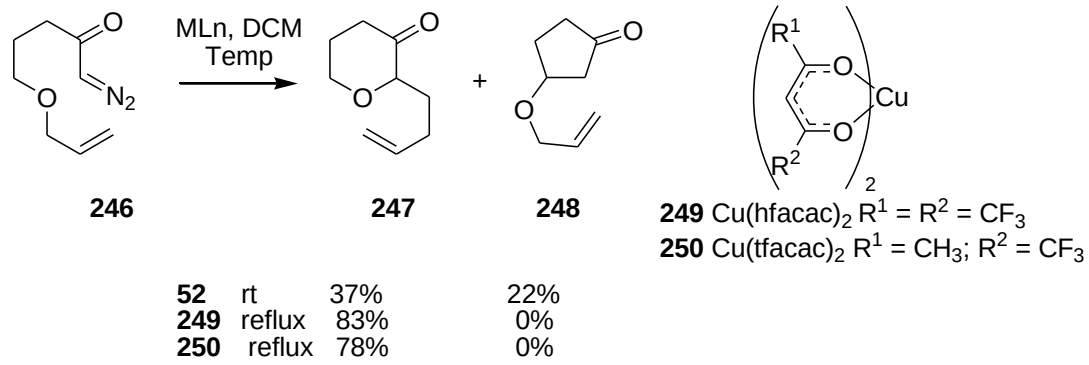
These results suggest that the rearrangement occurs *via* a metal-bound ylide-enolate species **243** or **244** (path a, Scheme 63). In this case, the metal centre is bound to the intermediate and controls the rearrangement process. Without the control of the metal, the formation of the intermediate **245** must occur by selective insertion of one of the diastereotopic oxygen lone pairs. Then, efficient transfer of stereochemical information from oxygen to carbon gives the rearrangement product **241** (path b, Scheme 63). The rate of inversion of analogous oxonium centres is known to be low.[100] Thus, to have retention of configuration, the rearrangement of **245** to **241** has to be much faster than the rate of inversion at the oxonium centre. Given the low barrier to inversion at the oxonium centre, it seems unlikely that the configuration at the oxonium centre of the free ylide **245** would be preserved prior to rearrangement.



Scheme 63. Oxonium ylide intermediate

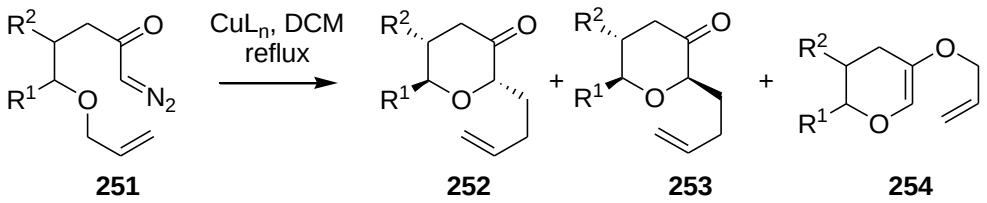
[100] Lambert, J. B.; Johnson, D. H. *J. Am; Chem. Soc*. **1968**, *90*, 1349.

Reaction conditions giving exclusively chemoselective oxonium ylide formation and rearrangement over competing C–H insertion have been described by Clark and co-workers.[101] For the reaction of the α-diazo ketone **246**, it was found that Cu(tfacac)$_2$ (**250**) and Cu(hfacac)$_2$ (**249**) gave exclusively the ylide rearrangement product **247** (Scheme 64).



Scheme 64. Exclusive oxonium ylide formation over competing C–H insertion.

To explain the role of the catalyst in influencing the outcome of the reaction and to understand the mechanism, Clark explored the generation and rearrangement of related oxonium ylides or their metal-bound equivalent.[102] The main objective of this research was to develop a mechanistic model. To this end, a range of products resulting from the reactions of a variety of α-diazo ketones **251** were analysed and the outcomes of the reaction were shown to be dependent on the catalyst electrophilicity. Table 10, only the catalysts that have given the highest yield and selectivity are shown for each substrate (Scheme 65). All the results showed that the thermodynamically less favourable *trans*-isomer **252** was isolated preferentially. However, when the alkyl group was not immediately adjacent to the site of the ylide formation, a mixture of the diastereomeric ketones **252** and **253** was obtained with a modest preference for the thermodynamically less favourable *trans*-isomer. The allylic ether **254** was not obtained from this reaction.



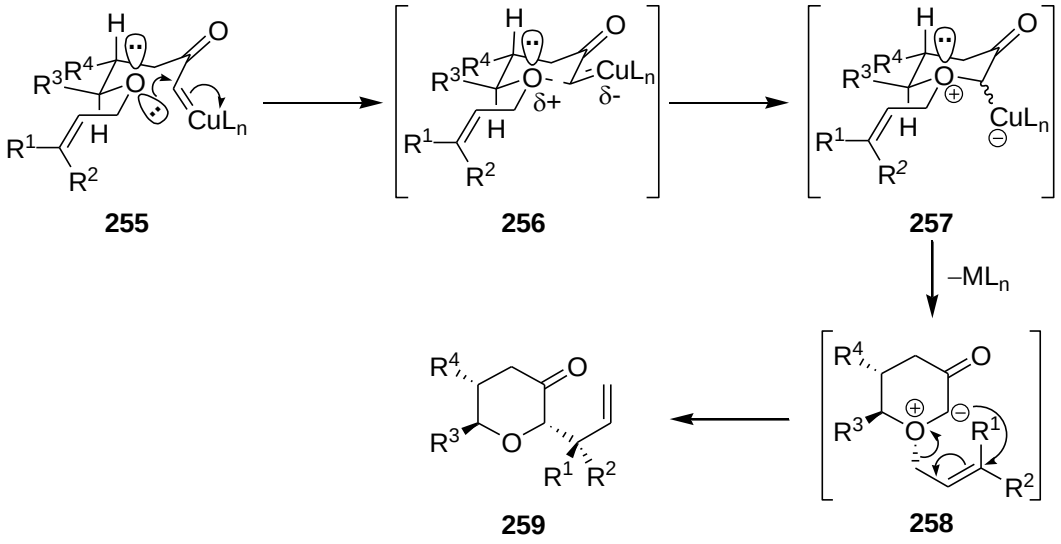
Scheme 65. Role of the catalyst

[101] Clark, J. S.; Krowiak, S. A; Street, L. J. *Tetrahedron Lett.* **1993**, *34*, 4385.
[102] Clark, J. S.; Whitlock, G.; Jiang, S.; Onyia, N. *Chem. Commun.* **2003**, 2578.

R^1	R^2	ML_n	Yield % 252 + 253	252 : 253	yield % 254
Me	H	$Cu(tfacac)_2$ (**250**)	65	91:9	5
^{i}Pr	H	$Cu(tfacac)_2$ (**250**)	64	94:6	9
H	^{i}Pr	$Cu(acac)_2$ (**242**)	80	81:19	0
H	Ph	$Cu(acac)_2$ (**242**)	61	86:14	0

Table 10. Role of the catalyst.

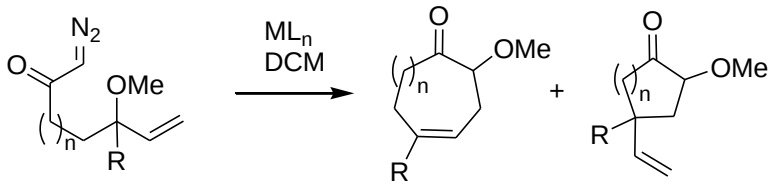
The stereochemical outcome can be rationalised as shown in Scheme 66.[97] The lone pairs of the ether oxygen are diastereotopic, and attack of the indicated lone pair on the carbenoid **255** is favoured because the allyl group and the substituent R^3 and R^4 are placed in equatorial positions. After the loss of the copper species from the metal bound ylide **257**, the resulting ylide **258** rearranges via a twist boat conformation. The activation energy for rearrangement must be lower than the barrier for inversion at the oxonium centre so that the configuration at the transient stereogenic centre is preserved prior to rearrangement.



Scheme 66. Stereochemical outcome of oxonium ylide and [2,3]-sigmatropic rearrangement.

Clark thought that it was possible to use ylide generation and rearrangement methodology to prepare carbocycles. The access of this product was possible using a substrate in which the unsaturated group was incorporated as a branching group from the

main chain joining the ether group to the diazo carbonyl functionality. During the rearrangement process, the ring size would be increased by one and the ether substituent would be positioned outside the ring.[103] In this paper, Clark and co-workers explored the construction of cycloheptenones and cyclooctenones by ylide formation and rearrangement process (Scheme 67, Table 11). The results showed that treatment of the diazoketone **260** with a range of catalysts afforded in each case mainly the medium-ring ketone **261** resulting from the ring-expanding [2,3]-sigmatropic rearrangement. However in some cases, a ring-contracting [1,2]-shift reaction was also observed to give the cyclic ketone **262** as a minor product $Rh_2(OAc)_4$ (**52**) was the best catalyst over the usual copper catalysts. When R = H, modest yields were obtained due to the relatively low rate of [2,3]-rearrangement. This result can be rationalised by the equatorial position of the vinyl group in the lowest energy conformation of the generated ylide. When R is an additional vinyl substituent, products resulting from the rhodium- and copper-catalysed cyclisation reactions were in better yield.



260 **261** **262**

Scheme 67. Construction of cycloheptenones and cyclooctenones by an analogous ylide formation and rearrangement process.

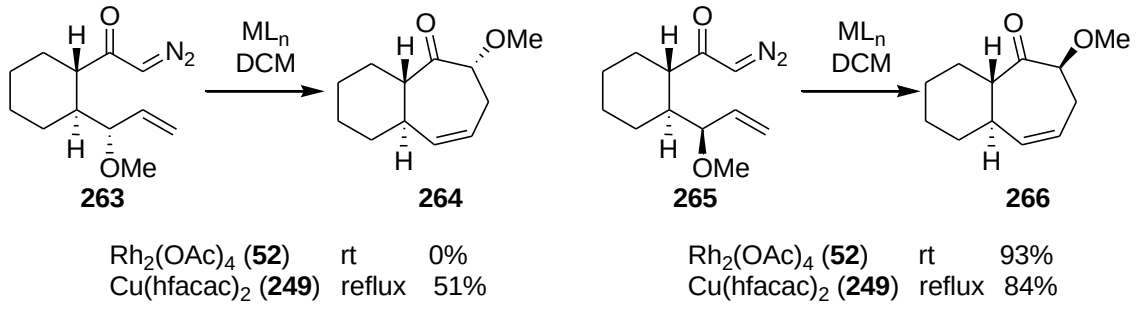
n	R	ML_n	Temp.	Yield %
1	H	$Rh_2(OAc)_4$ (**52**)	rt	39 **261**
1	H	$Cu(hfacac)_2$ (**249**)	reflux	11 **261**
1	$CHCH_2$	$Rh_2(OAc)_4$ (**52**)	rt	63 **261**, 11 **262**
1	$CHCH_2$	$Cu(hfacac)_2$ (**249**)	reflux	46 **261**
2	$CHCH_2$	$Rh_2(OAc)_4$ (**52**)	rt	26 **261**, 9 **262**

Table 11. Construction of cycloheptenones and cyclooctenones by an analogous ylide formation and rearrangement process.

[103] Clark, J. S.; Bate, A. L.; Grinter, T. *Chem. Commun.* **2001**, 459.

This result obtained from the metal mediated reactions of acyclic diazo ketone precursors encouraged Clark and co-workers to investigate this methodology for the synthesis of fused polycyclic compounds.[104] During these studies, they investigated the reaction on diazo ketones containing a cyclohexane because of the well known conformational behaviour of six membered rings. Initially, substrates containing *geminal* divinyl substitution were studied and the reaction gave very good results with substrates containing a *trans*-substituted cyclohexane.[104] However, the metal-catalysed reactions of substrates containing a *cis*-substituted cyclohexane produced lower yields.

Then, in order to discover whether substrates containing a single vinyl group would undergo the required rearrangement reaction, the reaction was explored with diastereomeric monovinyl systems. The *trans*-substituted cyclohexyl systems **263** and **265** differed only in the relative configuration at the vinyl-bearing stereogenic centre. Interestingly, both substrates underwent the required ylide formation and rearrangement reaction, but the choice of the catalyst had significant influence on the outcomes of the reaction (Scheme 68). For example, the sigmatropic rearrangement product **264** was obtained exclusively with $Cu(hfacac)_2$ (**249**) in a modest 51% yield and no reaction was observed with $Rh_2(OAc)_4$ (**52**). In contrast, the rhodium- and copper-catalysed reactions of the substrate **265** both furnished the desired ketone **266** in excellent yield.

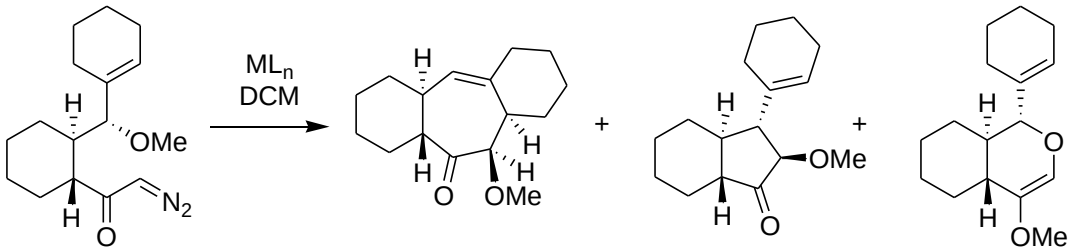


Scheme 68. Catalytic carbenoid generation, ylide formation and rearrangement using the mono-vinyl diazo ketones **263** and ***2*65**.

The strategy was envisaged to be a novel way to synthesise fused polycarbocyclic systems.[105] Diazocarbonyl precursors containing two carbocycles – one attached to the diazocarbonyl functionality and the other containing an alkene – once exposed to the reaction conditions, would lead to the union of these two single rings with the creation of a

[104] Clark, J. S.; Walls, S. B.; Wilson, C.; East, S. P.; Drysdale, M. J. *Eur. J. Org. Chem.* **2006**, 323.
[105] Clark,J. S.; Guérot, C.; Wilson, C.; Blake, A. *J. Chem. Commun.* **2007**, 4134.

third between them. Treatment of the substrate **267** with the a copper catalyst afforded modest yields of three ylide-derived products: the [2,3]-rearrangement product **268**, the ring-contracted [1,2]-shift product **269** and the [1,4]-migration product **270**. In contrast, reaction between the substrate **267** and rhodium(II) acetate (**52**) as the catalyst gave exclusively the tricyclic [2,3]-rearrangement product **268** with excellent yield (Scheme 69).

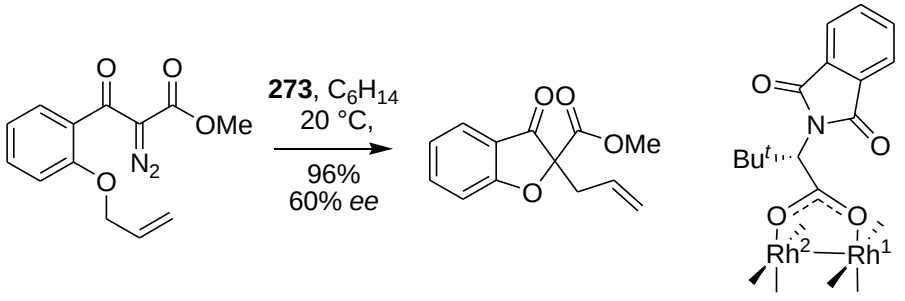


267 **268** **269** **270**

$Cu(hfacac)_2$ (**249**)	reflux	10%	34%	28%
$Rh_2(OAc)_4$ (**52**)	rt	90%	0%	0%

Scheme 69. Synthesis of polycarbocyclic systems.

In 1997, McKervey discovered that it was possible to perform asymmetric tandem intramolecular ylide formation and rearrangement using an achiral substrate and a chiral catalyst.[106] For example, treatment of the diazo ketone **271** with a chiral rhodium(II) complex **273** prepared from ^{t}butyl glycine, afforded the benzofuranone **272** in excellent yield and with reasonable enantiomeric purity (Scheme 70).



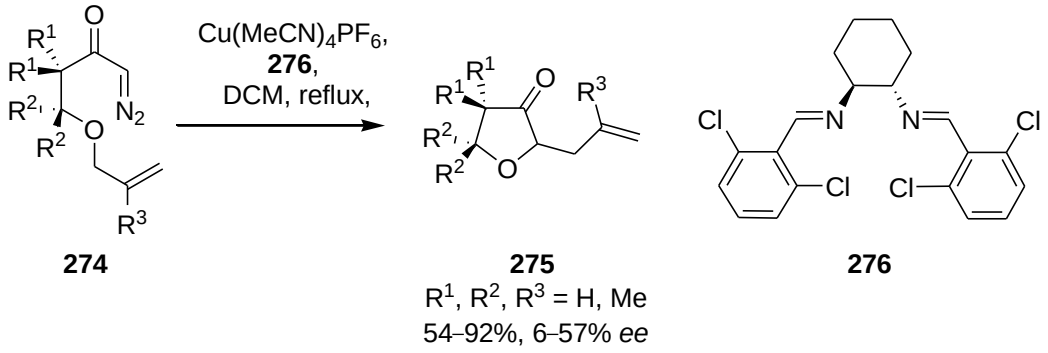
271 **272** **273**

Scheme 70. [2,3]-Sigmatropic rearrangement with chiral catalyst.

Shortly after the first report, Clark described the preparation of enantiopure cyclic ethers by intramolecular asymmetric tandem oxonium ylide formation and [2,3]-rearrangement (Scheme 71).[107] Treatment of the achiral α-diazoketone **274** with the chiral

[106] Pierson, N.; Fernández-García, C.; McKervey, M. A *Tetrahedron Lett.* **1997**, *38*, 4705.
[107] Clark, J. S.; Fretwell, M.; Whitlock, G. A.; Burns, C. J.; Fox, D. N. A. *Tetrahedron Lett.* **1998**, *39*, 97.

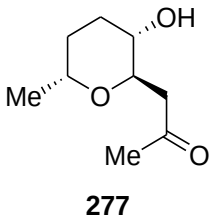
copper complex furnished the cyclic ether **275** with up to 57% *ee*. This was the first use of a chiral copper catalyst in the [2,3]-rearrangement process. The level of asymmetric induction was found to be variable and highly dependent on substitution pattern of the substrate.



Scheme 71. [2,3]-sigmatropic rearrangement with copper chiral catalyst

1.5.3.3 [2,3]-Sigmatropic rearrangement in organic synthesis.

Clark and Whitlock exploited the oxonium ylide rearrangement reaction to accomplish a short synthesis of (±)-decarestrictine L **277** (Figure 12), a minor metabolite isolated from the culture of *Penicillum simplicissimum* shown to inhibit the biosynthesis of cholesterol.[108]

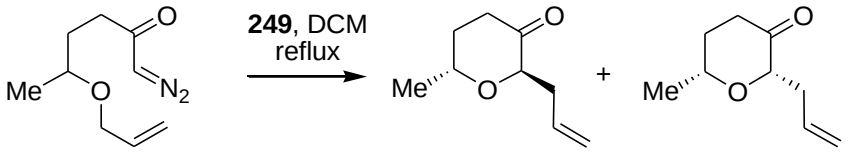


277

Figure 12. (±)-Decarestrictine L **277**

Decomposition of the diazoketone **278** using Cu(hfacac)$_2$ (**249**) as catalyst in DCM at reflux was achieved in good yield and high *trans* selectivity (Scheme 72). The total synthesis of the natural product was completed in ten steps in an overall yield of 5%.

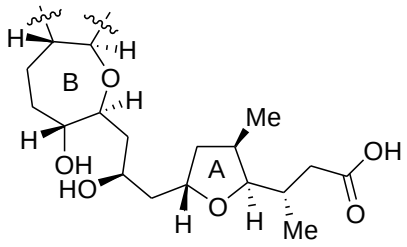
[108] Clark, J. S.; Whitlock; G. A. *Tetrahedron Lett.* **1994**, *35*, 6381.



278 **279** 52% **280** 15%

Scheme 72. Key step of the total synthesis of the natural product (±)-decarestrictine L **277**

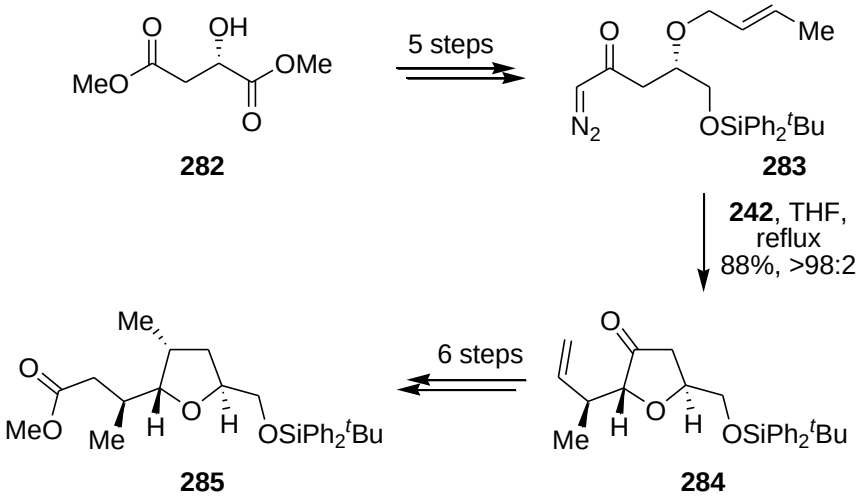
The studies on the preparation of *trans*-tetrahydrofurans gave access to the concise and stereoselective synthesis of the A-ring fragment of the marine polyether natural product gambieric acid A (Figure 13).[109]



281

Figure 13. The A and B rings of gambieric acid showing the tetrahydrofuran A-ring.

The synthesis of the the diazo ketone **283** was accomplished from the commercially available L-dimethyl malate **282** in five steps. Then, treatment of **283** with $Cu(acac)_2$ (**242**) resulted in the formation of the *trans*-tetrahydrofuran **284** in excellent yield and high diastereoselectivity. Further transformations completed the synthesis of the A-ring of the natural product (Scheme 73).[109]



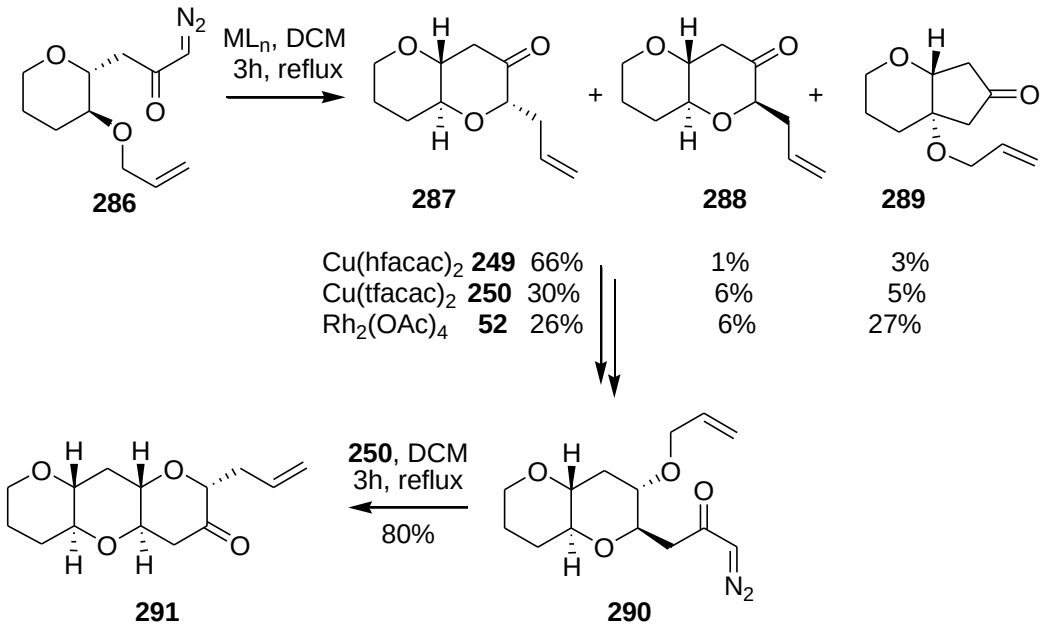
282 **283** **285** **284**

Scheme 73. Stereoselective synthesis of the A-ring fragment of gambieric acid A.

[109] Clark, J. S.; Fessard, T. C.; Wilson, C. *Org. Lett.* **2004**, *6*, 1773.

West and co-worker have developed an efficient approach to polycyclic ethers based on the [2,3]-sigmatropic rearrangement of cyclic oxonium ylides (Scheme 74). [110] The strategy gives access to polycyclic ether structures found in marine toxins, such as the brevetoxins and ciguatoxins. In West's approach, the diazoketone **286** was treated with $Cu(tfacac)_2$ (**250**) to give [2,3]-sigmatropic rearrangement product **287** and **288** with high diastereoselectivity and good yield, along with a small amount of the C–H insertion product **289**.

This study proved once again that copper catalysts favored ylide formation, while rhodium catalysts promote carbenoid C–H insertion. Fortunately, after the conversion of **287** into the desired isomer **288**, the synthesis continued with the formation of the diazoketone **290**, which was then subjected to $Cu(tfacac)_2$-catalysed ylide formation and subsequent rearrangement. Tris(tetrahydropyran) **291** was isolated in an excellent yield as the only detectable isomer.[111]

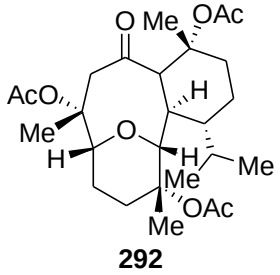


Scheme 74. Iterative approach to polycyclic ether based on stereoselective oxonium ylide [2,3]-shift.

The Clark group has explored the use of sequential one-pot catalytic carbenoid generation, intramolecular oxonium ylide formation, and ylide rearrangement to construct cyclic ethers in a diastereoselective manner. This powerful methodology has been used as

[110] Marmsäter, F. P.; West, F. G. *J. Am. Chem. Soc.* **2001**, *123*, 5144.
[111] Marmsäter, F. P.; Vanecko, J. A.; West, F. G. *Tetrahedron* **2002**, *58*, 2027.

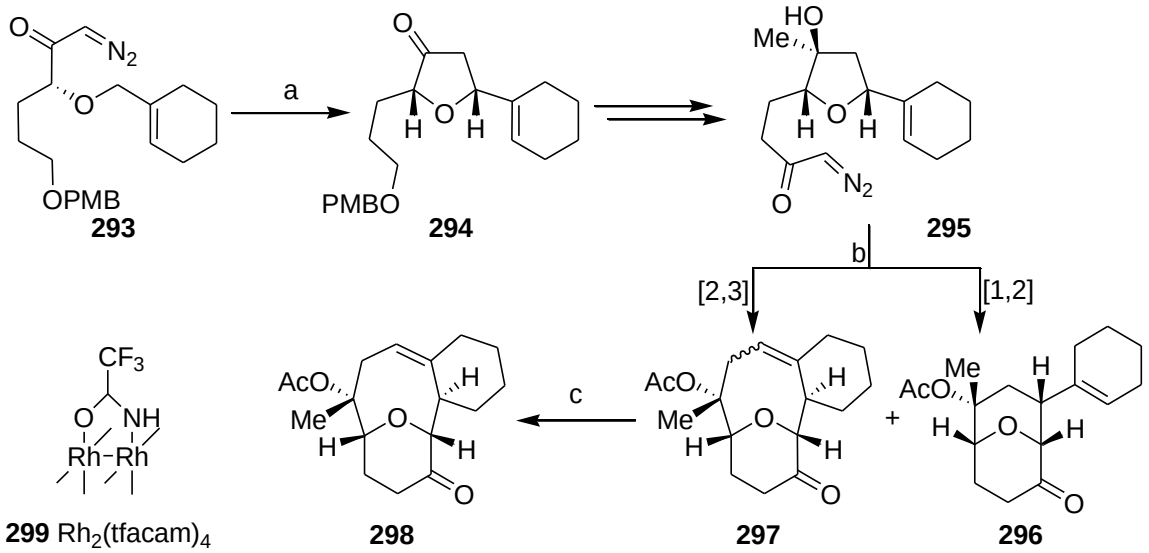
the key ring-forming step to construct the bridged bicyclic ether. Great efforts have been made on the synthesis of the core structure of labiatin A **292** (Figure 14)[112] and the tricyclic core of labiatin A has been synthesised, using two metal carbenoid reactions: C–H insertion followed by tandem oxonium ylide formation and sigmatropic rearrangement.



292

Figure 14. Labiatin A **292**.

For the preparation of a model of the labiatin A core system, the first key step involved reaction of the diazo ketone **293** with $Rh_2(tfacam)_4$ (**299**) in THF at rt. This reaction resulted in rhodium carbenoid formation and subsequent intramolecular C–H insertion to give the required dihydro-3(*2H*)-furanone **294** as a mixture of diastereomers (6:1 *cis:trans*) in 60% yield. The conversion of furanone **294** into the key cyclisation precursor **295** was accomplished in 7 steps (Scheme 75).

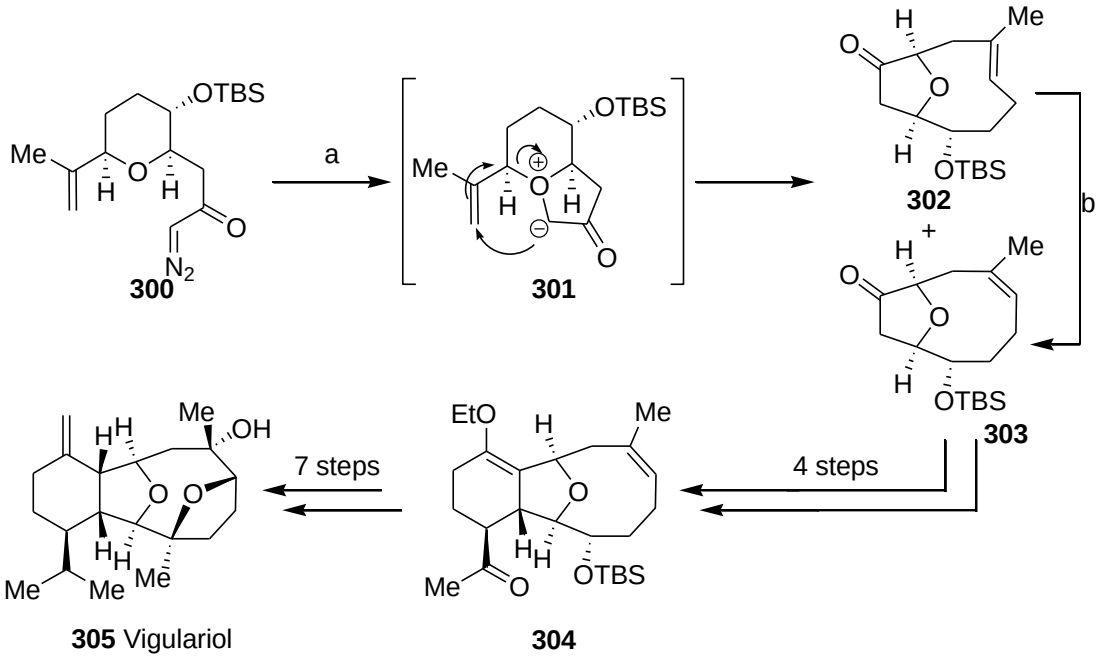


Scheme 75. Preparation of a model of the labiatin A core system. Conditions: (a) $Rh_2(tfacam)_4$ (**299**), THF, reflux, 60%. (b) $Cu(hfacac)_2$, (**250**) DCM, reflux, 61% **297**, 22% **296**. (c) AIBN, C_6H_6, reflux, 64%.

[112] Clark, J. S.; Baxter, C. A.; Castro, J. L. *Synthesis*, **2005**, 3398.

Treatment of the *α*-diazoketone **295** with Cu(hfacac)$_2$ (**250**) as the catalyst afforded the ether bridged isomers **297** (61% yield; 3:2 *E:Z*) resulting from the required [2,3]-sigmatropic rearrangement and **296** (22% yield) resulting from Stevens rearrangement. The mixture of alkenes **297** was then subjected to isomerization to give the more thermodynamically stable favoured *Z*-product in 64% yield. Studies towards the total synthesis of labiatin A are ongoing in the Clark group using this strategy.

Recently, a concise and highly efficient total synthesis of the marine diterpene natural product (±)-vigulariol **305** has been completed in the Clark group using intramolecular oxonium ylide generation and subsequent [2,3]-sigmatropic rearrangement (Scheme 76).[113] The key metal-mediated reaction proved once again to be extremely efficient. Treatment of the diazoketone **300** with Cu(hfacac)$_2$ (**249**) afforded the bridged bicyclic ethers **302** and **303** in 96% yield (5:1 *Z:E*). The undesired *E*-isomer was smoothly converted to the *Z*-isomer upon treatment with AIBN and ethanethiol. Intermolecular Diels-Alder cycloaddition to construct the cyclohexyl ring and complete the tricyclic core was followed by further transformations and the synthesis of (±)-vigulariol **305** was completed in 20 steps with an overall yield of 4.0%.



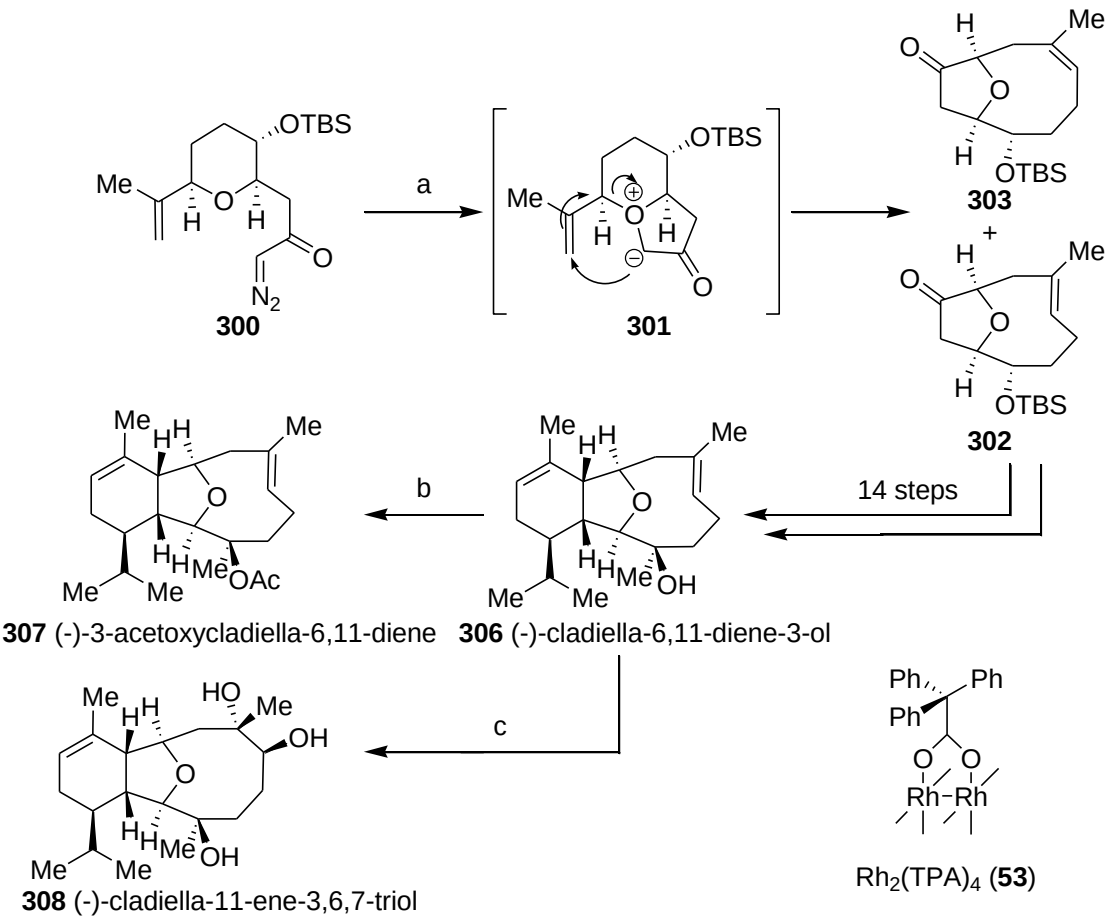
Scheme 76. Total synthesis of (±)-vigulariol **305.** Conditions: (a) Cu(hfacac)$_2$ (**249**) (5 mol%), DCM, reflux, 96% (5:1 *Z*:*E*). (b) AIBN, EtSH, PhH, reflux, 56%.

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

The most recent success of the methodology has been in the asymmetric total synthesis of cladiellins possessing 6*E* configuration. The vast majority of the cladiellins possess 6*E* configuration or contain an *anti*-1,2-diol at the C-6 and C-7 positions resulting from dihydroxylation of a 6*E* alkene. In this synthesis, the main challenge was to bias the rearrangement reaction in favor of the less-stable *E* isomer in order to have access to the entire family.[114]

In an effort to bias the reaction toward formation of the *E* configured rearrangement product, studies were extended to the use of rhodium catalysts. Although copper(II) catalysed reaction gave higher yield than those obtained using rhodium(II) complexes, the use of rhodium catalyst provides additional opportunities to tune the reaction towards the *E*-isomer by varying the properties of the ligand. Reactions catalyzed by $Rh_2(tfacam)_4$ (**299**) or $Rh_2(pfb)_4$ (**55**) increased the proportion of the *E* isomer, and the highest *E/Z* ratio was obtained using $Rh_2(TPA)_4$ (**53**) in 1,2-dichloroethane at reflux in 56% yield (6.3:1 *E:Z*). The ketones *E*-**302** and *Z*-**303** were separated and the *E*-isomer converted into the tricyclic ring system with the same methodology used in the vigulariol synthesis. Further transformations completed the total synthesis of three *E*-cladiellin natural products **306**–**308** (Scheme 77).

[114] Clark, J. S.; Berger, R.; Hayes, S. T.; Thomas, L. H.; Morrison, A. J.; Gobbi, L. *Angew. Chem. Int. Ed.* **2010**, *49*, 9867.

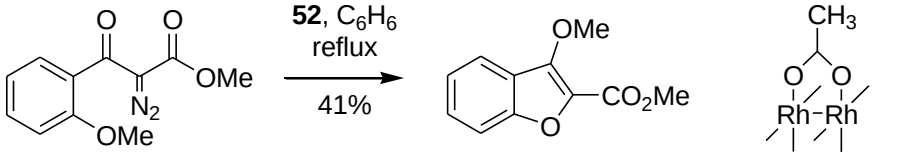


Scheme 77. Total synthesis of three *E*-cladiellins. Conditions : (a) $Rh_2(TPA)_4$ (**53**), DCE, reflux, 56% (6.3:1 *E*:*Z*). (b) Ac_2O, DMAP, Et_3N, rt, 25%. (c) OsO_4, NMO, THF/H_2O (1:1), 0 °C to rt, 66%.

1.5.3.4 The [1,4]-shift reaction.

When oxonium ylide formation occurs, products derived from a formal [1,4]-rearrangement are occasionally observed but are relatively rare compared to the products formed from the [2,3]- and [1,2]-rearrangements. Pirrung and co-workers were the first to observe the [1,4]-shift reaction during studies for the total synthesis of the natural compound griseofulvin.[115] Treatment of the diazo ketone **309** with $Rh_2(OAc)_4$ (**52**) furnished the [1,4]-shift product **310** in 41% yield (Scheme 78).

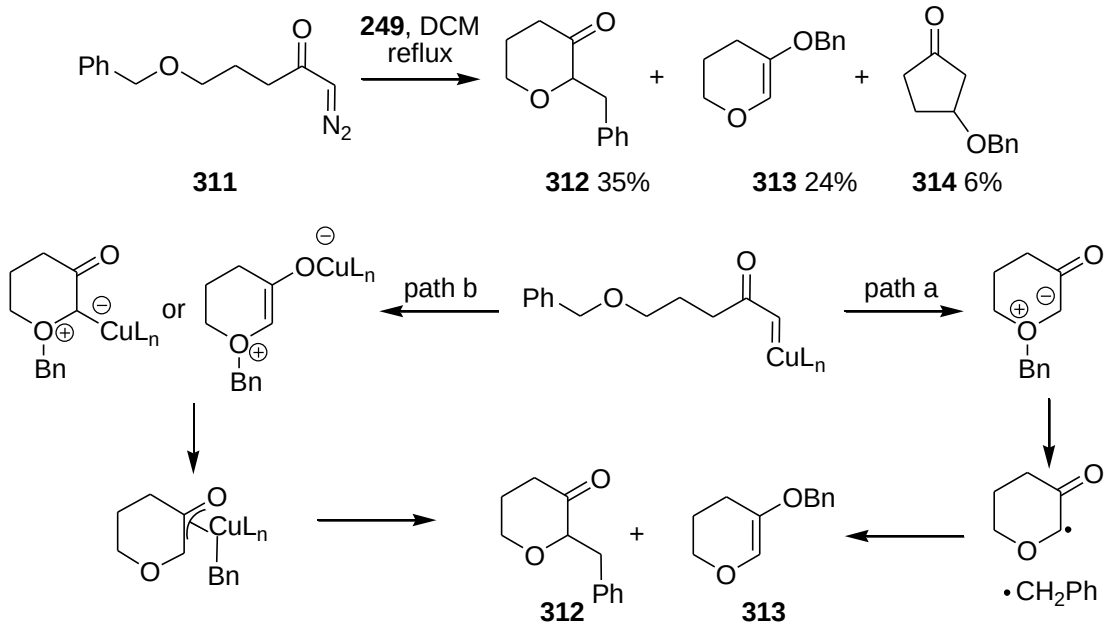
[115] Pirrung, M. C.; Brown, W. L.; Rege, S.; Laughton, P. *J. Am. Chem. Soc.* **1991**, *113*, 8561.



309 **310** **52** $Rh_2(OAc)_4$

Scheme 78. The [1,4]-shift reaction.

West[116] and Clark[101] described the isolation of [1,4]-migration products in low yield when oxonium ylides were generated from copper carbenoids. Treatment of the diazoketone **311** with Cu(hfacac)$_2$ (**249**) underwent both [1,2]- and [1,4]-migration to give products **312** and **313**. A small amount of the C–H insertion product **314** was also isolated from the reaction. West proposed a mechanism for the formation of the [1,2]- and [1,4]-migrated products. He suggested that the [1,4]-migration product **313** and the [1,2]-shift product **312** are derived from the same oxonium ylide and radical pair, but with different recombination sites (path a, scheme 79). However, because the radical homodimer was not isolated, an alternative metal-assisted mechanism (path b, scheme 79) was also suggested.



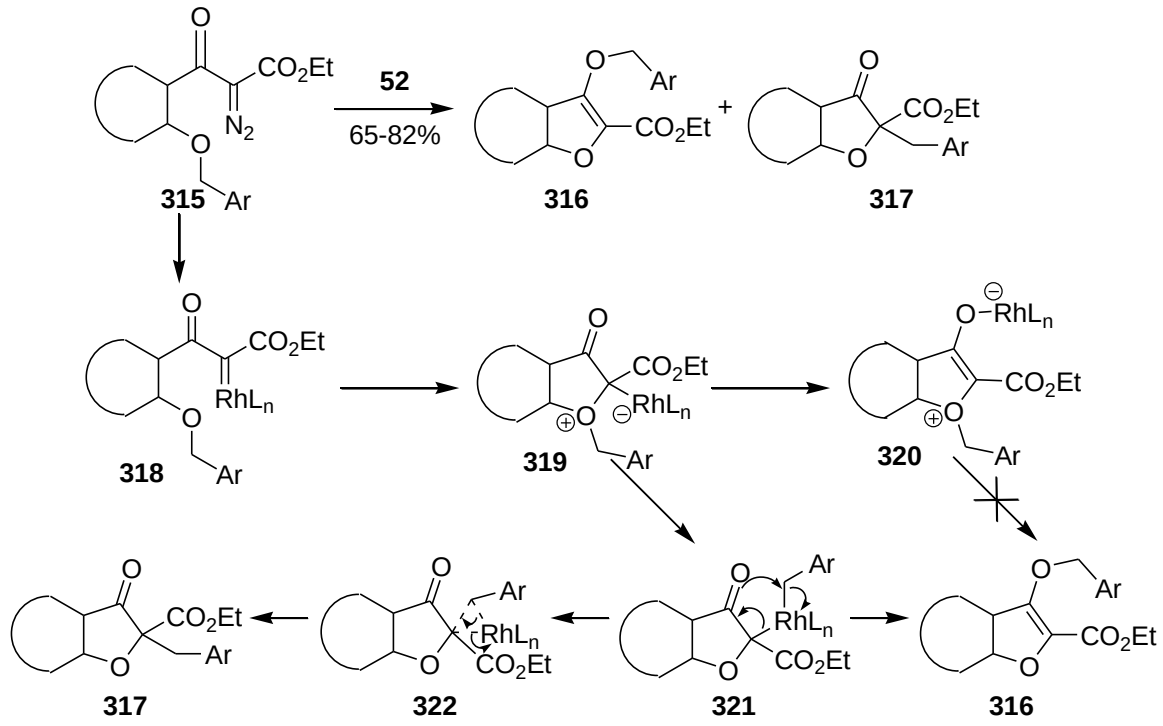
311 **312** 35% **313** 24% **314** 6%

Scheme 79. Copper-catalysed [1,4]-migration mechanism.

[1,4]-Migration has been observed as a dominant reaction in the rhodium(II) catalysed decomposition of α-diazo-β-keto esters in certain cases. Dhavale and co-workers

[116] West, F. G.; Naidu, B. N.; Tester, R. W. *J. Org. Chem.* **1994**, *59*, 6892.

proposed an independent mechanism for the rhodium carbenoid-mediated [1,4]-rearrangement reaction.[117] Because of the distance between the migration origin and terminus, they suggested that the oxonium ylide **320** cannot be an intermediate in the [1,4]-rearrangement reaction and that a migration of CH_2Ar from the oxygen to the Rh centre furnished what they considered as the real intermediate **321** of the reaction. Then depending on the electronic nature of the migrating group, subsequent [1,2]- or [1,4]-migration furnished both products **316** or **317** respectively (Scheme 80).



Scheme 80. Rhodium-catalysed [1,4]-migration mechanism.

2 Introduction to neoliacinic acid and neoliacine

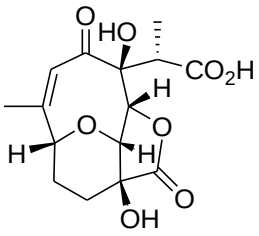
2.1 Neoliacinic acid

Sesquiterpene lactones neoliacinic acid **323** and the related compound neoliacine **324** were first isolated from the leaves of the plant *neolitsea aciculata Koidz* by a group of Japanese scientists (Figure 15).[118] The biological activity of neoliacinic acid was not determinated but Takaoka suggested that it might possess anti-tumor activity because

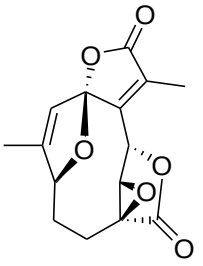
[117] (a) Karche, N. P.; Jachak, S. M.; Dhavale, D. D. *J. Org. Chem.* **2001**, *66*, 6323. (b) Desai, V. N.; Saha, N. N.; Dhavale, D. D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 147.

[118] Nozaki, H.; Hiroi, M.; Takaoka, D.; Nakayama, M. *J. Chem. Soc., Chem. Commun.* **1983**, 1107.

neoliacine exhibited moderate cytoxicity against Hela cell culture *in vitro*. This undetermined biological activity makes neoliacinic acid an interesting target molecule from a biological perspective.



323 Neoliacinic acid



324 Neoliacine

Figure 15.

Neoliacinic acid **323** is a highly oxygenated sesquiterpene lactone consisting of a tricyclic core with six stereocentres, five of which are contiguous. The skeleton of the natural product contains an oxacyclooctenone and a tetrahydropyran ring, sharing bridging oxygen. The core also possesses a bridging γ-lactone, an α,β-unsaturated ketone, two tertiary hydroxyl groups and a side chain terminated by a carboxylic acid functionality. The unique and complex structure including the [5.3.1]-oxabicyclic core and the dense functionalities make it a very attractive, and challenging synthetic target for total synthesis.

The unusual oxabicyclic core of neoliacinic acid can also be found in other plant-derived sesquiterpene lactones. Figure 16 shows compounds which were all isolated from the leaves of trees across the globe and all containing a similar core structure to neoliacinic acid. They contain either the same [5.3.1]-oxabicyclic structure or a [6.2.1]-ring system. Targitinin A **325** was isolated from an Indian collection of *Tithonia diversifolia*.[119] The core of the natural product possesses a 12-oxabicyclic-[6.2.1]-dodecane core, a *trans*-fused lactone and seven stereogenic centres. Another sesquiterpene lactone which contains the same bicyclic ether core and *trans*-fused lactone is tarnargyrolide **326**. This compound was isolated from the leaves of *Tanacetum argyrophyllum* var. *argyrophyllum*, a plant growing in Turkey.[120] The structure of achillifolin **327** is a very similar to tarnargyrolide **326** but they differ with the location of lactone ring to the nine-membered ring.[121] It was isolated from the aerial part of Turkish *A millefonium* (subsp. *Millefolium*). The most structurally interesting of these analogous compounds, mainly due to the same core dimensions as

[119] Baruah, N. C.; Sharma, R. P.; Madhusudanan, K. P.; Thyagarajan, G. *J. Org. Chem.* **1979**, *44*, 1831.
[120] Bohlmann, F.; Grenz, M.; Jakupovic, J.; King, R. M.; Robinson, H. *Phytochem.* **1983**, *22*, 1213.
[121] Ulubelen, A.; Öksüz, S.; Schuster, A. *Phytochem*. **1990**, *29*, 3948.

neoliacinic acid, are the epoxide **328**, isolated from a sample of the plant *Milleria Quiqueflora*, collected in Costa Rica,[122] and badgerin **329**, isolated from the Montana sagebrush *Artemisia arbuscula*,[123] and the lactone **330** isolated from *Tanacetum argyrophyllum*.[124] They have the same [5.3.1] oxabicyclic core as neoliacinic acid and possess significant anti-bacterial activity.

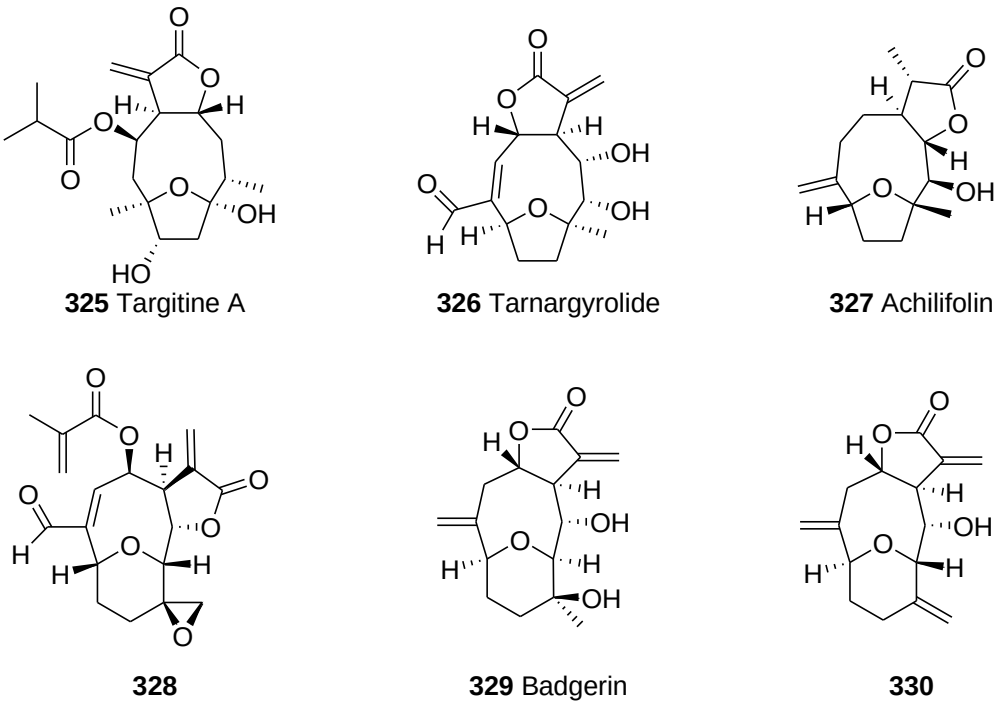
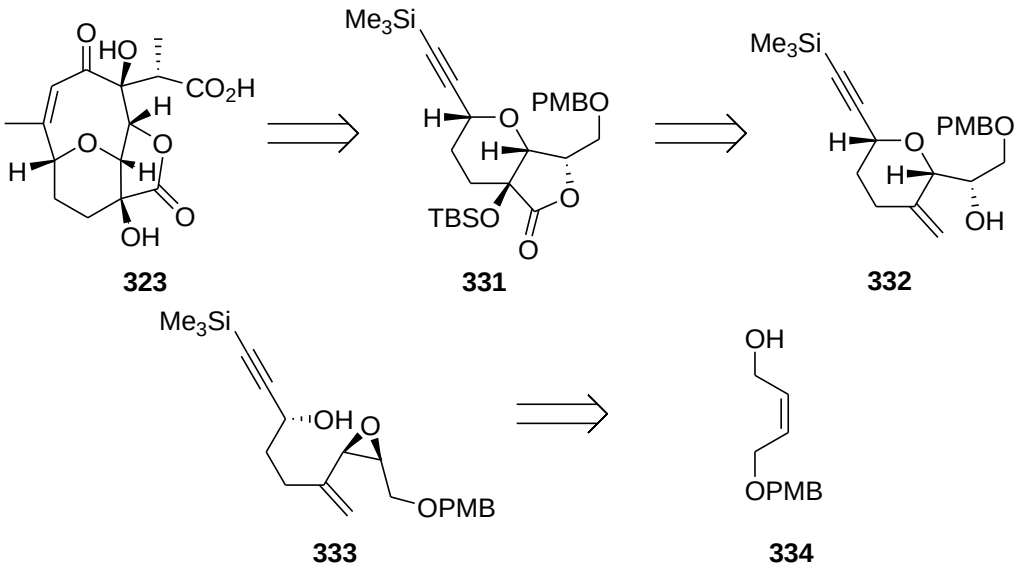


Figure 16. Plant-derived sesquiterpene natural products related to neoliacinic acid.

2.2 Previous synthetic attempts toward neoliacinic acid

An unsuccessful attempt to synthesise neoliacinic acid has been published by Paquette and Paget in 1999.[125] Their strategy is described in the retrosynthetic analysis shown in Scheme 81 and based on the construction of the lactone **331** from the alcohol **332**. Unfortunately, only the synthesis of intermediate **332** was achieved. Starting from the allylic alcohol **334**, the construction of the epoxide **333** was accomplished in five steps, which upon treatment with CSA gave the required cyclisation product **332**.

[122] Jakupovic, J.; Castro, V.; Bohlmann, F. *Phytochem.* **1987**, *26*, 451.
[123] Shafizadeh, F.; Bhadane, N. R. *J. Org. Chem.* **1972**, *37*, 274.
[124] Gören, N.; Jakupovic, J.; Topal, S. *Phytochem.* **1990**, *29*, 1467.
[125] Paget, S. D.; Paquette, L.A. *J. Indian Chem. Soc*. **1999**, *76*, 515.



Scheme 81. The strategy of Paquette and Paget.

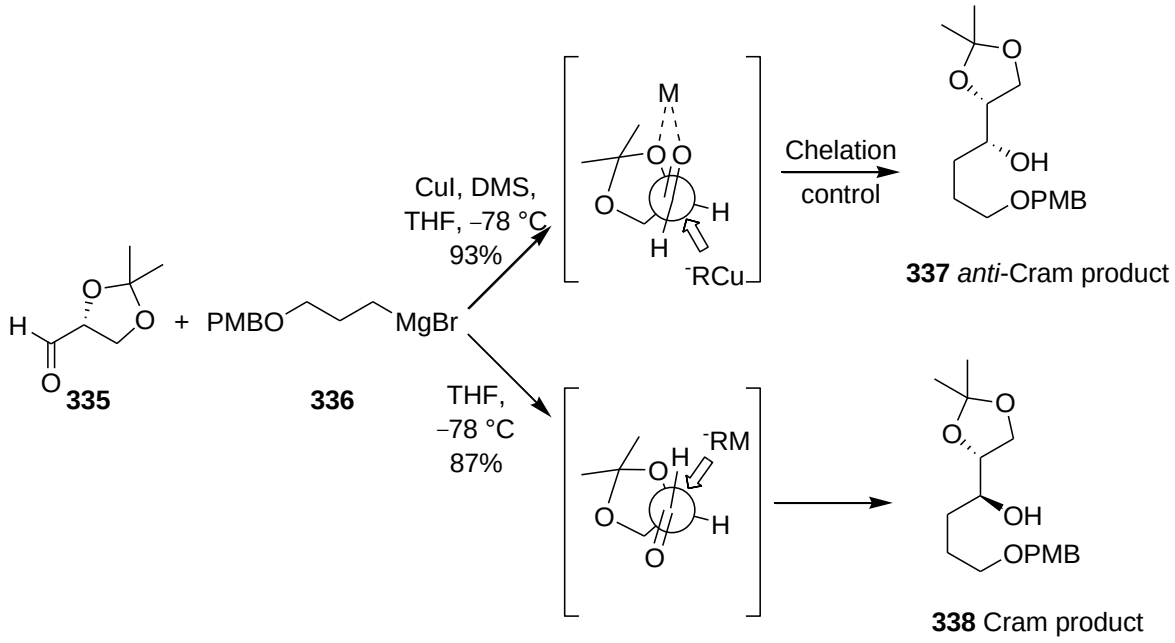
2.3 The Clark group strategy for the synthesis of neoliacinic acid.

As has been shown throughout the previous sections of this chapter, the Clark group has explored the use of sequential one-pot catalytic carbenoid generation, intramolecular oxonium ylide formation, and ylide rearrangement in the synthesis of natural products. Previous PhD students have used this key reaction sequence to construct the bridged ether cores of marine diterpene natural products of the cladiellen/eunicellin family and this work has culminated in the total synthesis of (+)-vigulariol **311**[108] and other members of cladiellin family.[109] Consequently, we wished to employ this powerful methodology to construct bridged bicyclic ether core of neoliacinic acid. The PhD theses of Dossetter and Baxter contained the results of preliminary work toward the synthesis of neoliacinic acid, showing the viability of the metal carbenoid transformations.[126,127]

The preliminary work commenced with the addition of the organo metallic **336** to the (*R*)-glyceraldehyde acetonide **335**. Depending on the organometallic reagent used, the reaction can furnish two diastereomers with or without chelation control. In general, the reaction proceeded without chelation and most metal reagents give the Cram product **338** with a *trans* configuration, but mono-organocopper reagents have shown to be capable in

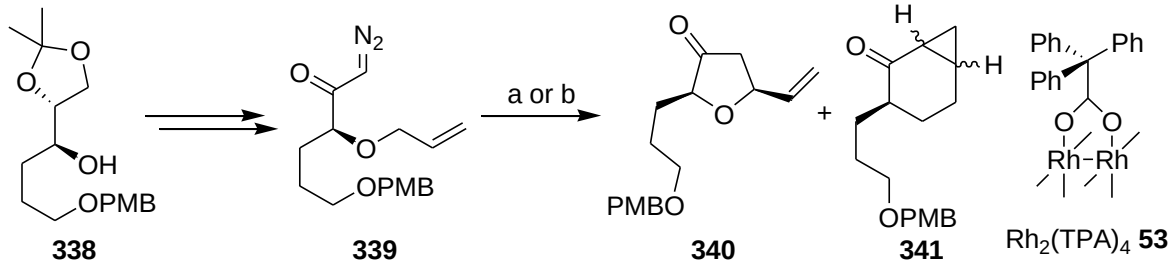
[126] Clark, J. S.; Dossetter, A.G.; Whittingham, W. G. *Tetrahedron Lett.* **1996**, *31*, 5605.
[127] Clark, J. S.; Baxter, C. A.; Dossetter, A. G.; Poigny, S.; Castro, J. L.; Whittingham, W. G. *J. Org. Chem.* **2008**, *73*, 1040.

giving the *anti*-cram product **337** through chelation control.[128] To establish the stereochemistry required for neoliacinic acid, formation of the anti-Cram (or *syn*) product is necessary. However, for the purposes of the model system, the Cram product was sufficient (Scheme 82).



Scheme 82. Cram versus anti-Cram selectivity

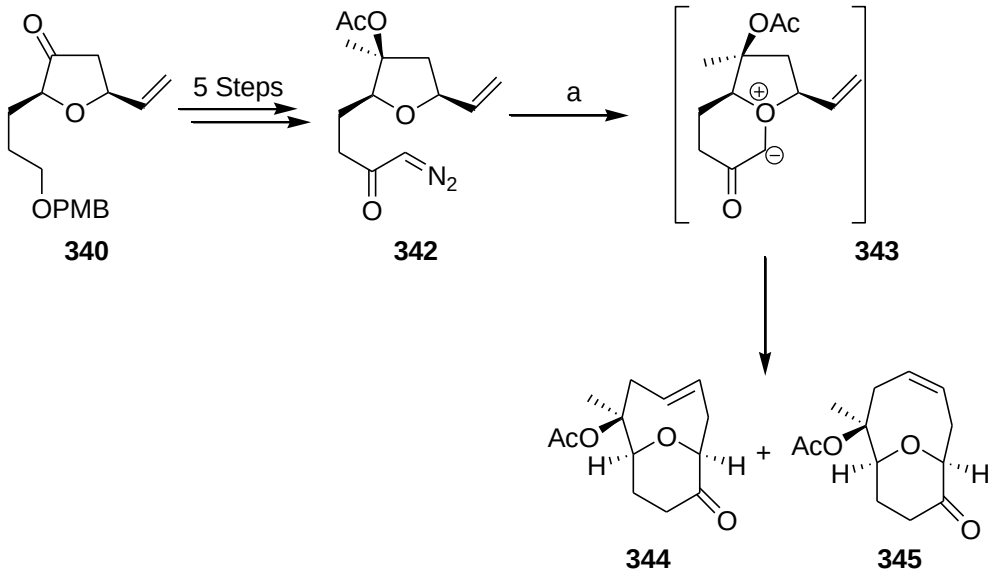
The secondary alcohol **338** was converted into the diazoketone **339** in 4 steps. Treatment of this diazoketone with $Rh_2(OAc)_4$ (**52**) provide the desired C–H insertion product **340** in 43% yield, but also afforded 39% of a diastereomeric mixture of the unwanted cyclopropanation products **341.** Several other rhodium complexes were screened, with $Rh_2(TPA)_4$ providing the best result: 65% of the desired product and only 25% of the mixture of cyclopropanes (Scheme 83).[126]



Scheme 83. Conditions: (a) $Rh_2(OAc)_4$, DCM, reflux, 43% **340**, 39% **341**. (b) $Rh_2(TPA)_4$, DCM, reflux, 65% **340**, 25% **341**.

[128] Sato, F.; Kobayashi, Y.; Takahashi, O.; Chiba, T.; Takeda, Y.; Kusakabe, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1636.

The tetrahydrofuran **340** was transformed into the diazoketone **342**, which was then treated with $Rh_2(OAc)_4$ (**52**). Attack of the carbenoid by the oxygen ether formed the oxonium ylide **343**, affording the six-membered ring of the on the natural product. The ylide underwent [2,3]-sigmatropic rearrangement with expansion of the THF ring forming the desired bicycle [5.3.1]-undecane core structure **345**. Curiously, if copper catalysts were used for this reaction, the isomeric product **344**, with an *E*-alkene in the ring was obtained (Scheme 84).

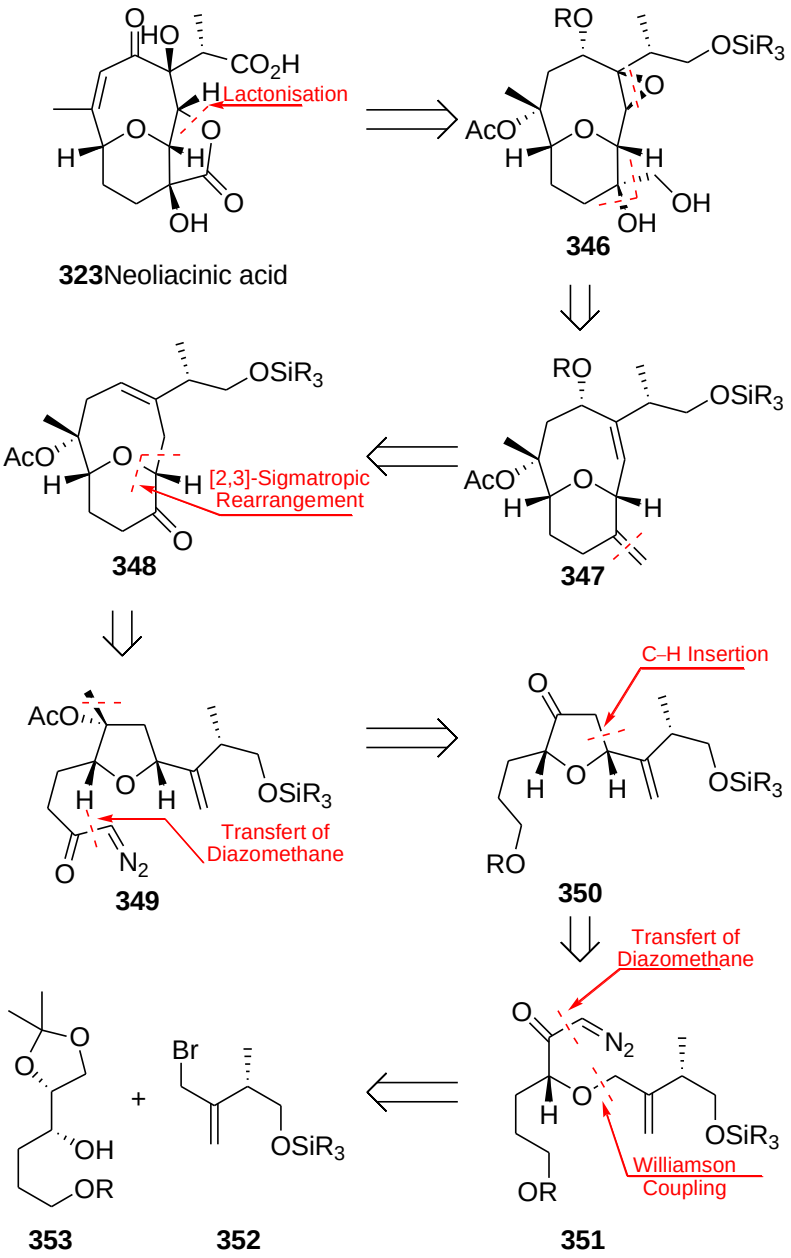


Scheme 84. Conditions: (a) $Rh_2(OAc)_4$ (**52**), DCM, reflux, 17% **345**. (b) $Cu((hfacac)_2$ (**249**), DCM, reflux, 51% **344**, 5% **345**.

Having shown the method of ring construction was viable, the more highly functionalised core of neoliacinic acid, including the side chain at C-7, was the next target. The retrosynthetic analysis of neoliacinic acid **323** including two metal carbenoid reactions is described in Scheme 85. The synthesis of the natural product would be constructed from the ether-bridged bicyclic **346**. The tricyclic core of the natural product would completed by an intramolecular nucleophilic epoxide opening. In principle, carboxylic acid or ester would be used to effect the cyclisation reaction. Then introduction of the *α*-*β*-unstaurated ketone would be accomplished.

The intermediate **346** possesses the six stereogenic centres found in neoliacinic acid and the functionalities would be introduced from the bicyclic ether **347** by diastereoselective epoxidation of the trisubstituted alkene and dihydroxylation of the *exo*-methylene group. Because of the steric hindrance of the compound **347**, we expected that the dihydroxylation

and the epoxidation would lead to the required stereochemical outcome. The diene **347** would arise from the ketone **348** with different functional group manipulations such as olefination of the ketone, epoxidation of the alkene followed by an isomerisation into allylic alcohol. The ether-bridged bicyclic **348** would be the key intermediate in our synthesis because it would result from the oxonium ylide formation and [2,3] sigmatropic rearrangement of the diazoketone **349**. The substrate of the metal-catalysed reaction would be derived from the dihydro-3(2*H*)-furanone **350** which would arise from carbenoid C–H insertion reaction of the diazoketone **351**. The allylic ether **351** would be constructed from the allylic bromide **352** and the alcohol **353** by a standard coupling reaction.



Scheme 85: Retrosynthetic analysis of neoliacinic acid.

Chapter II Results and Discussion

1 Attempt towards the total synthesis of neoliacinic acid

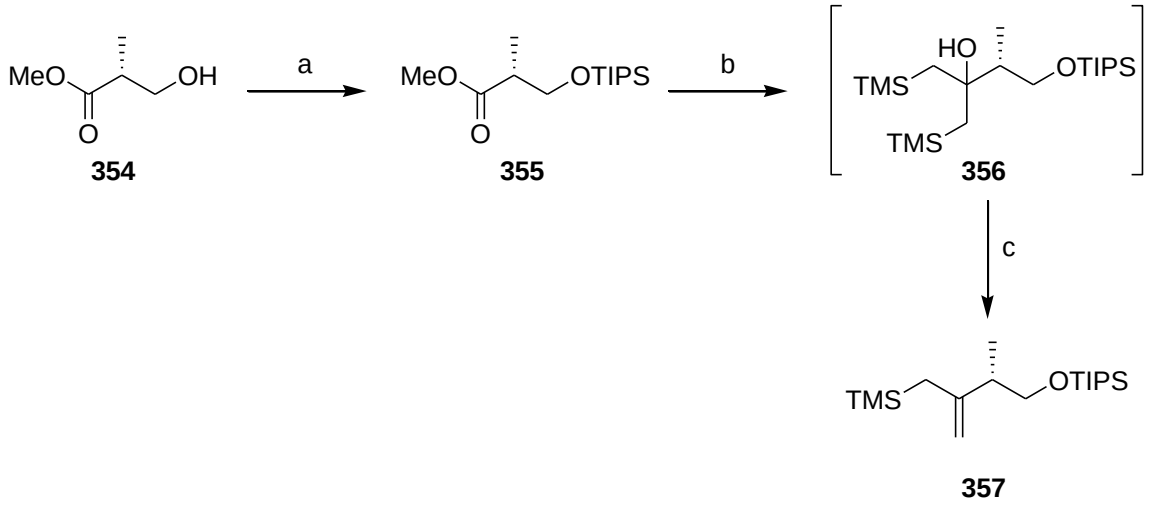
With the significant advances made towards the total synthesis of neoliacinic acid and in particular the construction of the ether bridged bicyclic structure, the first objective of the project was the synthesis of sufficient gram quantities of the key intermediate **347** shown in the retrosynthetic analysis (Scheme 85). This was done in order to discover a successful strategy to form the third lactone ring with all the functionality required to complete the synthesis of the natural product. It was thought that improvements could be made to the synthesis of the bicyclic core.

2 Synthesis of the bicyclic core of neoliacinic acid

The chiral allylic silane **357** was synthesised from the commercially available methyl (*R*)-(–)-3-hydroxy-2-methylpropionate **354** in two steps. (Scheme86) The tri-*iso*propylsilyl group was chosen to protect the primary alcohol of **354** and was introduced using standard conditions to give the silyl ether **355** in quantitative yield. This silyl protecting group was chosen because of its relative stability to both acidic and basic conditions. The ester was then treated with trimethylsilylmethylmagnesium chloride in the presence of anhydrous cerium(III) chloride.[129] Conversion of the Grignard reagent into its organocerium analogue greatly increased the nucleophilicity and reduced the basicity of the reagent. Treatment of the ester with five equivalents of the organocerium reagent resulted in double addition of the alkyl chain to give a clean conversion of the ester into the tertiary alcohol **356** at low temperature. The low basicity of the reagent reduced the probability of racemisation of the stereogenic centre adjacent to the site of nucleophilic addition. When treated with a 1M HCl solution during the work-up or on stirring with silica gel, the intermediate tertiary alcohol **356** underwent a Peterson elimination to yield the allylic silane **357** in an optimum yield of 85% from the ester **355**. The cerium(III)-

[129] (a) Narayanan, B. A.; Bunnelle, W. H. *Tetrahedron Lett.* **1987**, *28*, 6261. (b) Narayanan, B. A.; Bunelle, W. H. *Org. Synth.*, **1989**, *68*, 89. (c) Lee, T. L.; Channon, J. A.; Cregg, C.; Porter, J. R.; Roden, F. S.; Yeoh, H. T.-L. *Tetrahedron*, **1989**, *18*, 5877. (d) Liu, H.-J.; Shia, K.-S.; Shang, X.; Zhu, B.-Y. *Tetrahedron*, **1999**, *55*, 3803.

mediated Grignard reaction proved to be laborious to perform and was frequently capricious in terms of yield. The success of the organometallic addition to the ester was found to depend strongly on the activity of the $CeCl_3$ and on the scrupulous but careful drying of the cerium(III) chloride heptahydrate prior to reaction with the Grignard reagent.[130] It appeared that when the cerium(III) chloride was not sufficiently dried or over-heated, the reaction failed to progress and the starting material **355** was recovered without loss of material and stereochemical integrity.[131] When heating the cerium(III) chloride heptahydrate *in vacuo*, the hydrate water began to hydrolyse the metal chloride to form $CeCl_3.(H_2O)_n$[132] and the liquid collected in the liquid nitrogen trap during the drying was found to be hydrochloric acid. Consequently when drying the precursor $CeCl_3.7H_2O$, the majority of the water has to be removed by increasing the temperature slowly in order to keep the $CeCl_3$ activated. The residual hydrate water could be then removed by increasing the temperature without significant deactivation of the $CeCl_3$. However, the reaction proved to be difficult to reproduce and it was thought that most of the time during the drying procedure, deactivated $CeCl_3.(H_2O)_n$ was formed resulting in a failure to form the Ce/THF complex occurred.

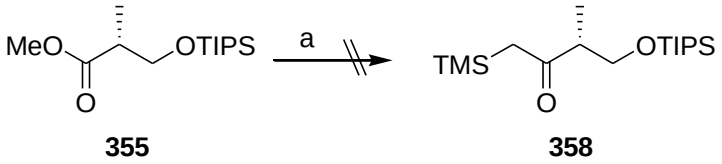


Scheme 86. Conditions: (a) TIPSCl, imid., DMF, 48 h, rt, 98%. (b) $CeCl_3$ (5 eq), $TMSCH_2MgCl$, THF, 12 h, –78 °C to rt. (c) HCl (1 M), 85%, (2 steps).

To circumvent problems associated with reproducibility of the synthetic route shown in Scheme 86, and in order to scale up the synthesis of the allylic silane **357** to

[130] Dimitrov, V.; Kostova, K.; Genov, M. *Tetrahedron Lett.* **1996**, *37*, 6787.
[131] Paquette, L. A.; Huber, S. K.; Thompson, R. C. *J. Org. Chem.* **1993**, *58*, 6874.
[132] Evans, W. J.; Feldman, J. D.; Ziller, J. W. J. *Am. Chem. Soc.* **1996**, *118*, 4581.

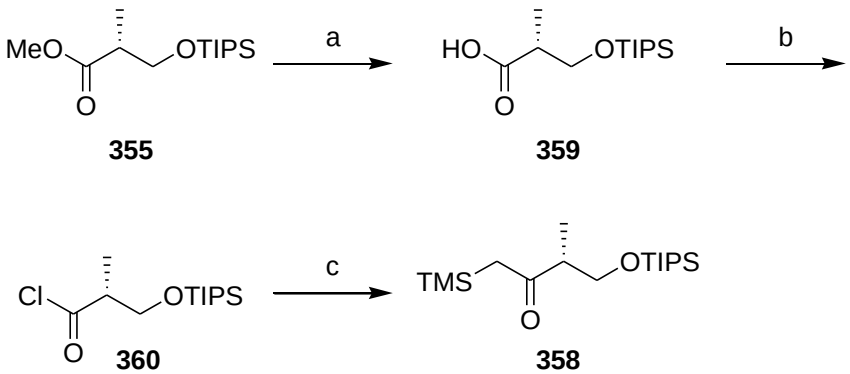
produce gram quantities required for this challenging synthesis, it was decided to change the synthetic route, and to develop an alternative which, although longer, would be more efficient. The first attempt was to react the same Grignard reagent with the protected Roche ester but without the use of $CeCl_3$. The reaction would undergo one nucleophilic addition to the carbonyl group to furnish **358**. Olefination of the ketone function would then produce the desired allylic silane. Unfortunately, there was no reaction when **355** was treated with trimethylsilylmethylmagnesium chloride in excess (5 eq.) and all the starting material was recovered (Scheme 87).



355 **358**

Scheme 87. Conditions: (a) $TMSCH_2MgCl$ (5 eq.), THF, 12 h, –78 °C to rt

Having found that the ester function failed to react with the Grignard reagent, it was decided to add this organometallic reagent to the acid chloride **360** which is a more electrophilic and reactive substrate than **355**. To this end, **355** was converted into the corresponding carboxylic acid **359** and the crude acid was treated with oxalyl chloride in presence of DMF as the catalyst to give the acid chloride **360**. DMF reacted with oxalyl chloride in the first step to give the iminium intermediate which then reacted with the carboxylic acid to deliver the acid chloride and regenerate DMF. Then, the crude acid chloride **360** was treated with trimethylsilylmethylmagnesium chloride in excess (2 eq.) and underwent the desired nucleophilic attack to furnish the ketone **358** in 25% yield over 3 steps (Scheme 88).



Scheme 88. Conditions: (a) TMSOK, Et_2O, rt, 24 h. (b) $(COCl)_2$, DMF, DCM, rt, 3 h. (c) $TMSCH_2MgCl$, THF, 12 h, –78 °C to rt, 25% (over 3 steps).

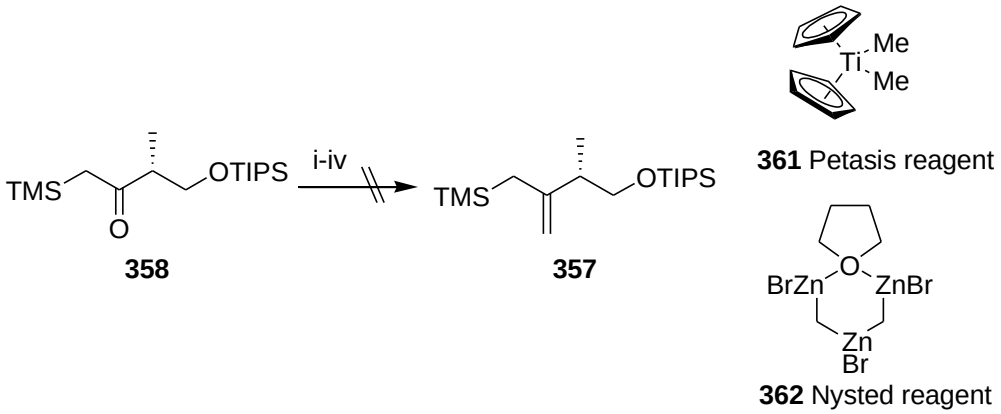
Having prepared the ketone **358**, progression towards the allylic silane **357** was the next synthetic step. Unfortunately, olefination to give the desired product proved to be difficult and so various conditions were investigated (Scheme 89). Firstly Wittig reaction, which is generally considered as the most effective method for the synthesis of alkenes, was attempted, but treatment of **358** with methylenetriphenylphosphorane led to the decomposition of the starting material. The Petasis reagent **361**, which is capable of transfering a methylene group efficiently to various carbonyl groups, was also used in an attempt to methylenate the ketone.[133] This reagent is not commercially available but it can be prepared by reacting titanocene dichloride with methyl magnesium iodide.[134] However, the Petasis reagent **361** is unstable when stored as a solid and can decompose with heat and gas evolution. In order to store the reagent, it should be kept diluted in dry THF which has a stabilising effect on the labile reagent.

Following Verhoesen's protocol,[134] the Petasis reagent was synthesised and kept as a 1 M solution in dry THF. Because of the instability of the reagent in solid phase, it was difficult to estimate the yield of the reaction but NMR spectroscopic analysis confirmed the complete conversion of the titanocene dichloride into the dimethyltitanocene. The Petasis olefination was attempted using freshly prepared reagent but, unfortunately, using 3 equivalents of the reagent under reflux, no reaction was observed and all of the starting material was recovered (Scheme 89). With this disappointing result in mind, it was decided to investigate other olefination conditions. As previously described, the use of the Peterson olefination would have been a possible option for the synthesis of the allylic silane **357** from the ketone **358**. Addition of α-trimethylsilylmethyl organometallic compound could be used to convert carbonyl compounds to their corresponding olefin. However, using the trimethylsilylmethylmagnesium chloride as the α-silyl carbanion, nucleophilic addition to the carbonyl was not observed and only starting material was isolated from the reaction. The final attempt at olefination of the ketone **358** was performed with Nysted reagent **362** [135] and $TiCl_4$ as the Lewis acid (Scheme 89). Unfortunately, this methodology proved to be inappropriate and the reaction led to the decomposition of the starting material.

No further conditions of olefination were investigated and the lack of reactivity of the carbonyl function led us to explore another synthetic pathway to access the required

[133] Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.
[134] Payack, J. F.; Hughes, D. L.; Cai, D.; Cottrell, I. F.; Verhoeven, T. R. *Organic Synthesis*, **2002**, *79*, 19.
[135] Matsubara, S.; Sugihara, M.; Utimoto, K. *Synlett.* **1998**, 313.

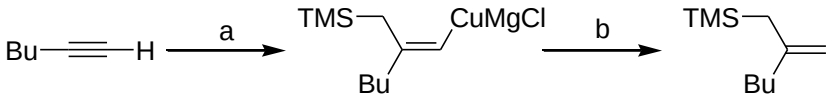
allylic silane **357**.



358 **357** **361** Petasis reagent **362** Nysted reagent

Scheme 89. Conditions: (i) PPh_3CH_2, ^tBuOK, THF, 0 °C. (ii) Petasis reagent **361**, THF, reflux, 24 h. (iii) $TMSCH_2MgCl$, THF, 12 h, –78 °C to rt. (iv) Nysted reagent **362**, $TiCl_4$, DCM, THF, 0 °C, 3 h.

The next approach was to effect a carbocupration reaction of an alkyne. Some examples of this reaction are described in the literature[136] and show that treatment of a terminal alkyne with a trimethylsilylmethyl copper reagent generated *in situ* leads to the formation of an allylic silane. Foulon and co-workers studied this methodology and showed that treatment of the 1-hexyne **363** with the desired organocopper reagent furnished the allylic silane **365** (Scheme 90). The results quoted in Table 12 showed that the best results were obtained when the reaction was conducted in the presence of lithium iodide as an additive, in order to increase the rate of reaction. Lithium bromide destabilises the intermediate vinyl copper species **364** and alkene **365** was obtained in poor yield, while addition of DMS slowed the rate of the addition and furnished **365** in 17% yield.



363 **364** **365**

Scheme 90. Conditions: (a) $TMSCH_2MgCl$, CuBr, Additive, Temp., Et_2O. (b) H_2O.

[136] (a) Foulon, J. P.; Bourgain-Commerçon, M.; Normant, J. F. *Tetrahedron*, **1986**, *42*, 1389. (b) Denmark, S. E.; Guagnano, V.; Dixon, J. A.; Stolle, A. *J. Org. Chem.* **1997**, *62*, 4610.

Entry	Additive	Temp (°C)	Time (h)	Yield (%)
1	None	–13	72	40
2	LiBr	–10	19	17
3	Me_2S	20	48	17
4	LiI	10	18	78
5	$P(OEt)_3$	35	62	78

Table 12. Addition of trimethylsilylmethylcopper reagent to 1-hexyne **363**.

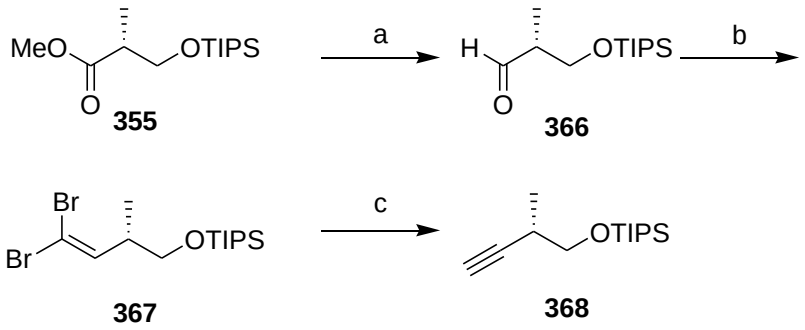
We thought that this strategy might be applicable to the formation of **357** and a synthetic route was designed to synthesise the substrate necessary for this reaction and ultimately the allylic silane **357** (Scheme 91). The methyl ester function of **355** was reduced carefully using DIBAL-H at low temperature, furnishing the aldehyde **366** in good yield. Moreover, using 1.5 equivalent of diisobutylaluminium hydride as the source of hydride, over-reduction to the primary alcohol was not observed. At this stage of the synthesis, it was important to verify whether isomerisation of the stereogenic centre had occurred during the formation of **366**. Fortunately, the $[\alpha]_D$ value was very similar to that described in the literature[137]. This result means that the generated aldehyde **366** was isolated as single enantiomer and not as a racemic mixture.

Having synthesised the aldehyde **366**, we were in a position prepare the precursor of the key reaction. Two different routes were apparent for the transformation of the aldehyde **366** into the terminal alkyne **368**. Firstly, a two-step sequence using the Corey-Fuchs methodology was possible to form the alkyne **368**. This methodology has been described in the literature and proved to be a very useful reaction in the synthesis of natural products.[138] The second approach was to treat the aldehyde with dimethyl 1-diazo-2-oxopropylphosphonate.[139] This reagent allows one-pot conversion under very mild

[137] Komatsu, K.; Tanino, K.; Miyashita, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 4341.
[138] (a) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769. (b) Bonazzi, S.; Güttinger, S.; Zemp, I.; Kutay, U.; Gademann, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 8707. (c) Organ, M. G.; Wang, J. J. *Org. Chem.* **2003**, *68*, 5568. (d) Ugele, M.; Sasse, F.; Knapp, S.; Fedorov, O.; Zubriene, A.; Matulis, D.; Maier, M. E. *Chem. Bio. Chem.* **2009**, *10*, 2203.
[139] Mueller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett*, **1996**, 521.

conditions and delivers alkynes in excellent yield when used in the synthesis of natural products.[140] However, this reagent is not commercially available but can be obtained from dimethyl 2-oxopropylphosphonate in a single step by diazo transfer with TsN_3 following a literature procedure.[141] In order to verify the feasibility of the key steps, the Corey-Fuchs reaction was used due to the commercial availability of the reagents. It was anticipated, in the case of success for the key step, that the one-pot procedure would be also attempted to check its viability and yield.

The aldehyde **366** was submitted to the first step of the Corey-Fuchs sequence and the dibromide **367** was obtained in good yield (79%) after isolation. Treatment of the dibromide **367** with *n*-BuLi at low temperature then furnished the terminal alkyne **368** in modest yield (50%).

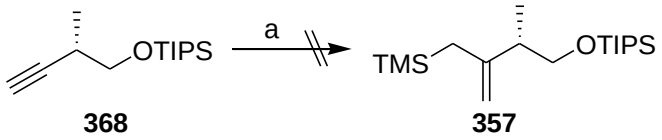


Scheme 91. Conditions: (a) DIBAL-H, DCM, –100 °C, 1 h, 64%. (b) CBr_4, PPh_3, DCM, 0 °C, 2h, 79%. (c) *n*-BuLi, THF, –78 °C to rt, 2 h, 50%.

The alkyne **368** was the key intermediate in our revised strategy for the synthesis of the allylic silane **357** and we hoped that treatment of this compound with the organocopper reagent generated *in situ* from the trimethylsilylmethylmagnesium chloride and copper(I) bromide would give the desired alkene (Scheme 92). Firstly the reaction was attempted at 0 °C without any additive but formation of the required cuprate reagent was not observed. At lower temperature, the formation of the organocopper reagent was observed, but reaction with the alkyne **368** did not occur and all of the starting material was recovered. With the lack of reactivity of the cuprate, we decided to change the conditions and attempt the reaction in the presence of an additive. Reaction of the alkyne with the cuprate was performed first in the presence of lithium bromide, at different low

[140] (a) White, J. D.; Kuntiyong, P.; Lee, T. H. *Org. Lett*, **2006**, *26*, 6039. (b) Trost. B. M.; Papillon, J. P. N. *J. Am. Chem. Soc*. **2004**, *126*, 13618.
[141] Gallent, P.; D'haenens, L.; Vandewalle, M. *Synth. Commun.*, **1984**, *14*, 155.

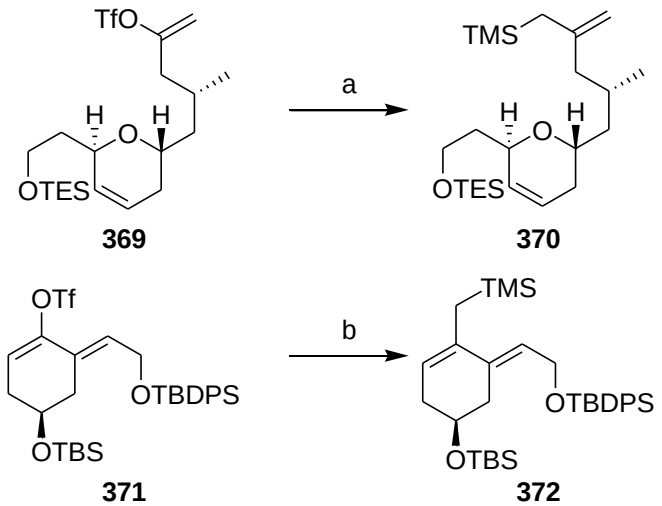
temperatures (–78 °C and –90 °C). In these cases, production of the desired compound was not detected and all the starting material was recovered. These disappointing results even in the presence of an additive, led us to think that the cuprate strategy was not the best approach and that other attempts with different additives would likely fail, therefore no further reactions were attempted.



368 **357**

Scheme 92. Conditions: (a) $TMSCH_2MgCl$, CuBr, THF, additive, Temp.

The poor results obtained from the carbocupration reactions led to a change in our strategy to find another way of producing gram quantities of the desired allylic silane. In the literature, it has been reported that an alkenyl silane can be formed upon C-C coupling between a triflate, derived from a ketone, with excess of the Grignard reagent generated from the trimethylsilylmethyl chloride in presence of LiCl and a catalytic amount of $Pd(PPh_3)_4$ (Scheme 93). This reaction has proved to be very efficient and has delivered very good results in terms of yield and reproducibility.[142]



369 **370**

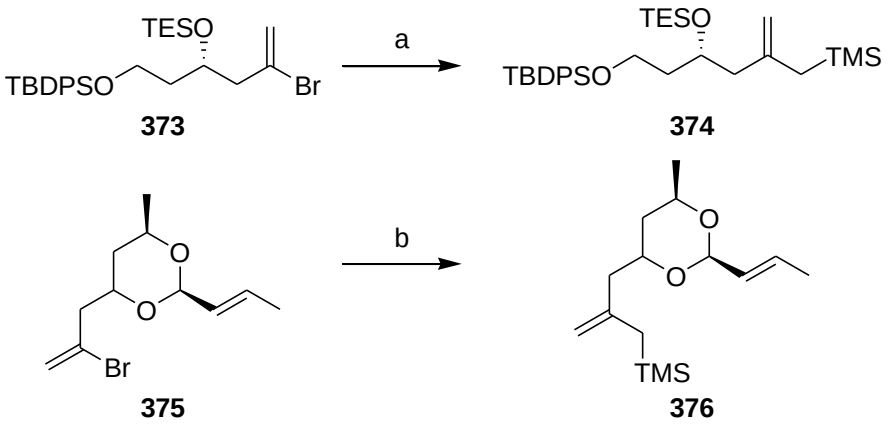
371 **372**

Scheme 93. Conditions: (a) LiCl (0.2 eq), $Pd(PPh_3)_4$ (0.07 eq.), $TMSCH_2MgCl$ (2 eq.), Et_2O, rt, 97%. (b) LiCl (5 eq.), $Pd(PPh_3)_4$ (0.1 eq.), $TMSCH_2MgCl$ (5 eq.), THF, reflux,

[142] (a) Giuffredi, G.; Bobbio, C.; Gouverneur V. *J. Org. Chem.* **2006**, *71*, 5361. (b) Ahmed, A.; Hoegenauer, E. K.; Enev, V. S.; Hanbauer, M.; Kaehlig, H.; Öhler, E.; Mulzer, J. *J. Org. Chem.* **2003**, *68*, 3026. (c) Kamikawa, T.; Hayashi, T. *J. Org. Chem.* **1998**, *63*, 8922.

98%.

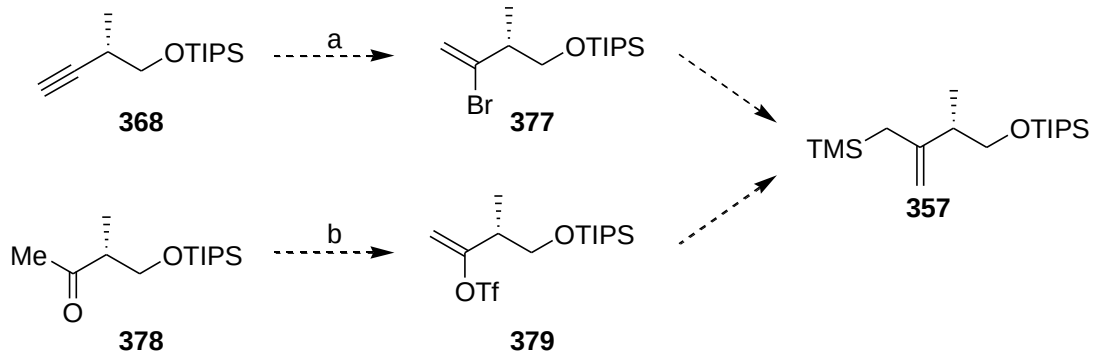
An alternative to this method would be to perform the same the cross-coupling reaction but instead of reacting with a vinyl triflate, the organometallic reagent would react with a vinyl bromide in presence of a nickel or palladium catalyst leading to the same transformation. Examples of this alternative procedure have been described in the literature and also delivered very good results in terms of both yield and reproducibility (Scheme 94).[142a,143]



Scheme 94. Conditions: (a) $TMSCH_2MgCl$ (1.5 eq.), $NiCl_2(dppp)$ (0.1 mol%), THF, reflux. 86%. (b) $Pd(PPh_3)_4$ (0.1 mol%), $TMSCH_2MgCl$ (3 eq.), THF, reflux, 92%.

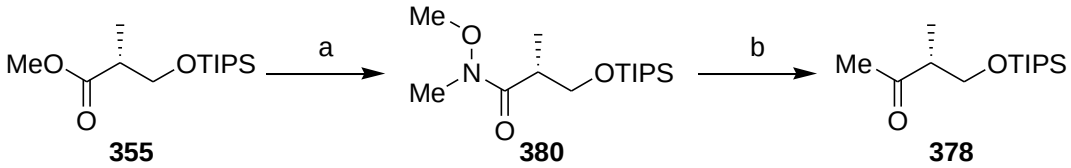
However, the synthetic pathway that would be used to construct the vinyl substituted precursors required for the cross-coupling reactions would be different (Scheme 95). Vinyl triflate **379** construction would be accomplished by treatment of the corresponding methyl ketone **378** with a base under kinetic conditions to form an enolate which would be trapped with a triflate reagent. In contrast, vinyl bromide **377** formation would be performed by bromoboration of the alkyne **368** with 9-bromo-9-boracyclo-[3.3.1]nonane (B-Br-9-BBN) (Scheme 95). This reaction have been used for the synthesis of natural products and has delivered impressive results.[142a,142b] However, this approach requires the use of B-Br-9-BBN, which is both pyrophoric and toxic. Moreover, the synthesis of the alkyne **368** was already explored and the Corey-Fuchs reaction had been shown to deliver a modest yield.

[143] (a) Aubele, D. L.; Lee, C. A.; Floreancig, P. E. *Org. Lett.* **2003**, *5*, 4521.



Scheme 95. Potential synthetic pathway (a) Bromoboration using B-Br-9-BBN. (b) Triflate formation (c) Cross-coupling reaction.

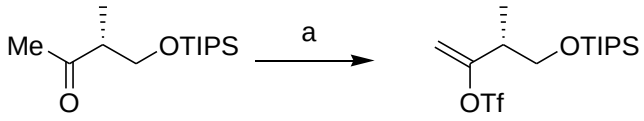
We thought that the palladium strategy would be applicable to the synthesis of the required alkenylsilane **357**. For safety reasons on larger scale and in order to explore new chemistry, the triflate route was investigated first (Scheme 96). Due to the poor reactivity of the starting Roche ester **355** with organometallic reagent such as trimethylsilylmethylmagnesium chloride, it was decided to convert **355** into the corresponding Weinreb amide **380**. The transformation was accomplished using standard conditions and furnished the desired compound **380** in quantitative yield. The Weinreb amide **380** was then submitted to a freshly prepared 1M solution of methylmagnesium iodide and the methyl ketone **378** was isolated in excellent yield (91%).



Scheme 96. Conditions: (a) Me(OMe)NH.HCl, ^{i}PrMgBr, THF, 2 h, –20 °C, quant. (b) MeMgI, THF, 2 h, 0 °C, 91%.

The construction of the vinyl triflate proved to be difficult and so various reaction conditions were investigated (Scheme 97). Firstly, potassium hexamethyldisilazide (KHMDS) was used under kinetic conditions for the deprotonation in the presence of $PhNTf_2$ as the triflate agent. Unfortunately, using these conditions, the desired vinyl triflate **379** was isolated after purification in 10% yield (Table 13, entry 1). Using the same base

but in the presence of the Comins reagent,[144] which is also used to trap an enolate as an enol triflate, the yield of the reaction increased to 40% (Table 13, entry 2). It was thought that the strong base deprotonated the ketone but that the enolate was strongly coordinated to the potassium counterion. If this was the case, the reaction needed a coordinative agent to increase the availability of the enolate. The reaction was attempted under the same conditions but in the presence of DMPU, and the vinyl triflate **379** was isolated after purification in a improved yield of 67% (Table 13, entry 3). This result encouraged us to pursue our investigations and other deprotonation conditions were tested. The use of sodium hexamethyldisilazide (NaHMDS) resulted in a further improvement and the enol triflate **379** was obtained in good yield (82%) (Table 13, entry 4). The Comins reagent is commercially available but it is very expensive and in order to decrease the cost of the reaction for larger scale, it would be necessary to synthesise our own Comins reagent **382**. Following the experimental procedure describe by Comins,[145] the synthesis of the triflate agent was attempted. The procedure afforded the required reagent in 62% yield (Scheme 98) but purification by sublimation was found to be very difficult. Consequently, due to the difficulties in obtaining a sufficient amount of a clean reagent, the production of **379** seemed not to be feasible. Consequently, we turned our attention to the original triflate agent tested for the last attempt of our screen. The reaction was performed under the same conditions as entry 4, but in the presence of $PhNTf_2$. Fortunately, the reaction delivered very good results and furnished the vinyl triflate in excellent yield (91%, Table 13, entry 5).



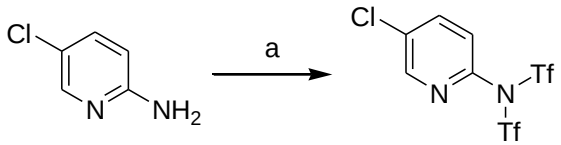
378 **379**

Scheme 97. (a) Bases, Triflate agent, Chelation agent, THF, –78 °C.

[144] Comins, D. L.; Dehghani, A.; *Tetrahedron Lett.* **1992**, *33*, 6299.
[145] Comins, D. L.; Dehghani, A.; Foti, C. J.; Joseph, S. P. *Organic Syntheses*, **1997**, *74*, 77.

Entry	Base	Triflate agent	Chelation Ligand	Yield (%)
1	KHMDS	$PhNTf_2$	-	10
2	KHMDS	Comins reagent	-	40
3	KHMDS	Comins reagent	DMPU	67
4	NaHMDS	Comins reagent	DMPU	82
5	NaHMDS	$PhNTf_2$	DMPU	91

Table 13.

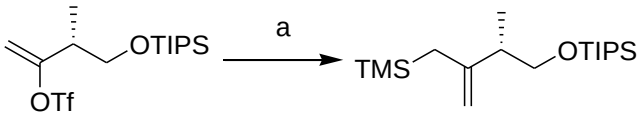


381 **382**

Scheme 98. Experimental procedure to the formation of the Comins reagent: Conditions: (a) $(CF_3SO_2)_2O$, Pyr. DCM, –78 °C to rt, 19 h, 62%.

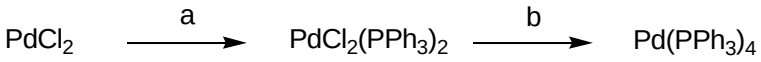
Having successfully prepared the enol triflate precursor **379**, the key cross-coupling reaction to construct the desired allylic silane **357** was investigated. Following the protocols reported in the literature,[142] enol triflate **379** was subjected to the key reaction. Firstly, treatment of **379** with freshly prepared trimethylsilylmagnesium chloride (5 eq.) in a presence of the palladium(0) catalyst (10 mol%) and LiCl (5 eq.) gave the desired allylic silane **357** in good yield (87%) (Scheme 99). This very good result proved that the described synthetic route to construct **357** was a complete success and synthesis of the allylic silane in gram quantities was now feasible. However, tetrakistriphenylphosphine palladium is an expensive catalyst and in order to decrease the cost of the reaction on large scale, other conditions were explored. We decided first to decrease the loading of the catalyst (5 mol%) and the reaction produced the desired product **357** in comparative yield. It was evident that the preparation of the catalyst in our laboratory would decrease the cost of the key step. Following the experimental procedure described by Coulson and co-

workers,[146] the tetrakistriphenylphosphine palladium was prepared in quantitative yield from the commercially available palladium dichloride (Scheme 100). With a freshly prepared catalyst, allylic silane **357** was isolated in an excellent 91% yield. Having demonstrated the viability of the new synthetic route, we performed the construction of the allylic silane **357** on larger scale, but the reaction proceeded in lower yield (76%). To conclude, a new synthetic route for construction of the allylic silane **357** has been developed, the synthesis displayed excellent yields for each step with an overall yield of 62%. Moreover, the optimised synthetic route showed excellent reproducibility and was performed in 30 gram batches (76 mmol).



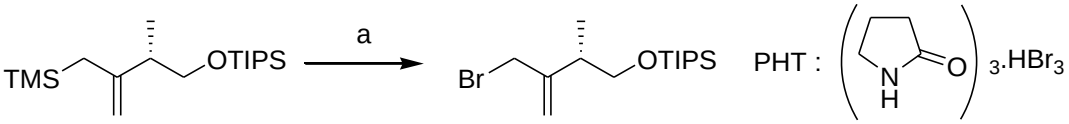
379 **357**

Scheme 99. Conditions: $TMSCH_2MgCl$ (5 eq), LiCl (5 eq), $Pd(PPh_3)_4$ (5 mol%), THF, 3 h, 0 °C, 76%.



Scheme 100. Conditions (a) PPh_3, DMF, refux, (b) NH_2-NH_2·H_2O 95%.

The allylic silane **357** was then converted into the allylic bromide **383** by bromination with pyrrolidone hydrotribromide **384** (PHT) (Scheme 101).[147] At –10 °C, this reagent reacted selectively on the methylene function of **357**. Pyridine was added to prevent the over-bromination by proto-desilylation of the allylic silane **357** with the HBr present in the reaction mixture. In this manner, the allylic bromide **383** was obtained in excellent yield (95%).

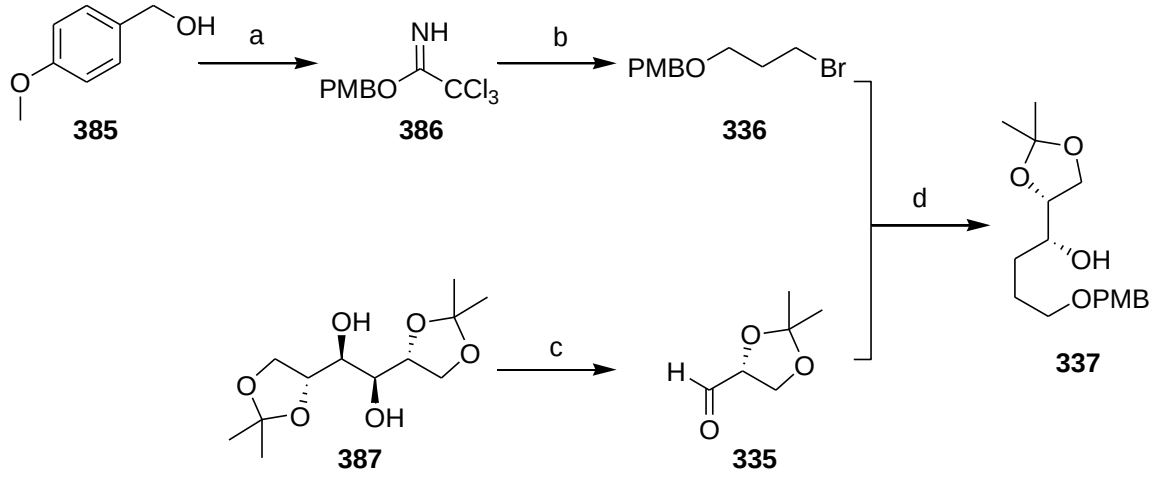


357 **383** **384**

Scheme 101. Conditions: (a) PHT (**384**), pyridine, THF, 1.5 h, –10 °C, 95%.

[146] Coulson, D. R.; Satek, L. C.; Grim, S. O. *Inorg. Synth.* **1990**, 107.
[147] Awang, D. V. C.; Wolfe, S. *Can. J. Chem.* **1969**, *47*, 706.

The alcohol required for coupling with the bromide was prepared using the route shown in the Scheme 102. Sodium periodate cleavage of the di-*O*-isopropylidene-d-mannitol **387** furnished the aldehyde **335** in good yield.[148] Formation of the PMB ether **336** was performed in 71% yield via the trichloroacetimidate **386** which was prepared by treatment of *p*-methoxybenzyl alcohol (PMB-OH) **385** with trichloroacetonitrile. Bromide **336** was then converted into an organocopper reagent, generated *in situ* from the Grignard reagent and copper(I) iodide. Treatment of the freshly distilled 2,3-(*R*)-*O*-isopropylglyceraldehyde **335** with the cuprate reagent gave the secondary alcohol **337** as an inseparable 10:1 mixture of diastereoisomers, the major product being the *syn* isomer (anti-Cram product). The *syn* product is obtained by chelation with mono-organocopper reagents and most other organometallic reagents (e.g. Li, Mg, Zn reagents) give the *anti* (Cram) product without chelation control.[149] However the reaction proved to be capricious in terms of yield and the success of the addition of the organocopper reagent to the aldehyde depended strongly on the quality of the copper(I) iodide reagent.



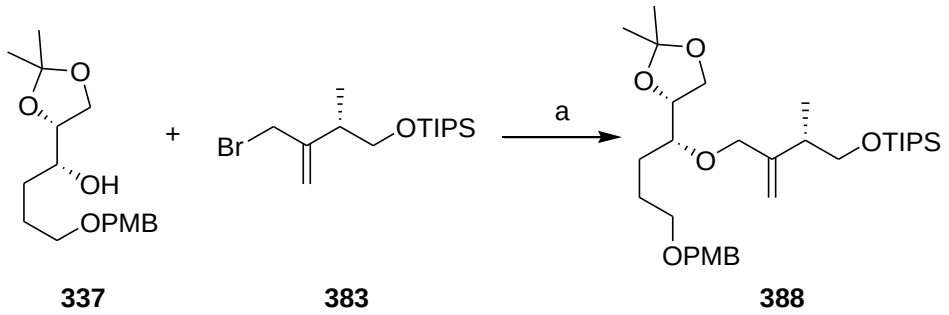
Scheme 102. Conditions: (a) Cl_3CCN, *n*-Bu_4NHSO_4, KOH (50 % aq.), DCM, 0 °C to rt. (b) 3-bromopropanol, PPTS, DCM, rt, 71% (2 steps). (c) (i) $NaIO_4$, DCM, H_2O, rt. (ii) $MgSO_4$, 64%. (d) Mg, CuI, DMS, THF, –78 °C to rt, 76%.

At this stage, we were in the position to attempt the etherification between the bromide **383** and the secondary alcohol **337** (Scheme 103). Ether formation was first

[148] (a) Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447. (b) Jackson, D. Y. *Synth. Commun.* **1988**, *18*, 337.

[149] (a) Mulzer, J.; Angermann, A. *Tetrahedron Lett.* **1983**, *24*, 2843. (b) Sato, F.; Kobayashi, Y.; Takahashi, O.; Chiba, T.; Takeda, M.; Kusakabe, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1636.

achieved using the standard Williamson conditions with an excess of the bromide. Unfortunately, the optimised conditions of Baxter[127] were not reproducible and the protocol furnished the desired allylic ether **388** in poor yield. This procedure was very interesting because it had the advantage of recovery the excess of allylic bromide during the purification process. By changing the experimental procedure to generate the allylic iodide from **383** *in situ* using TBAI (0.4 eq), and adding 18-crown-6 (0.4 eq) to coordinate the sodium cation, ether coupling was accomplished in quantitative yield. However in this case, the allylic halide was not recovered from this reaction when the allylic bromide was used in excess. Moreover, it is worth noting that the success of the coupling was not affected by the scale of the reaction and very good yields were obtained when the reaction was performed on both small (5 mmol of the alcohol **337**) and larger (85 mmol) scale.

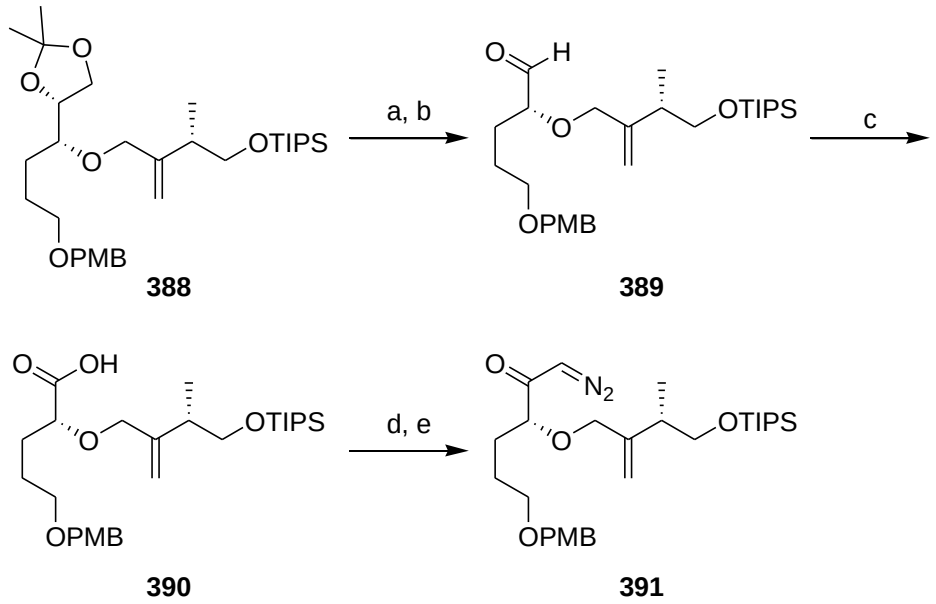


337 **383** **388**

Scheme 103. Condition: (a) NaH, TBAI, 18-crown-6, THF, 12 h, reflux, 95%.

The successful formation of the allylic ether **388** allowed us to proceed with the synthesis of the key precursor **391** necessary to undertake metal-catalysed carbenoid generation and intramolecular C-H insertion (Scheme 104). Construction of this key intermediate was achieved in five steps starting with removal of the acetonide using mild conditions, pyridinium *p*-toluenesulfonate proving to be the ideal acid. Ethylene glycol was used as a substitute for water to promote removal of the *iso*-propylidene group by the formation of 2,2-dimethyl-1,3-dioxane. THF and DCM were used as co-solvent to provide a homogeneous solution, which under reflux with the other reagents cleanly removed the protecting group without isomerisation of the double bond or removal of the tri-*iso*-propylsilyl group. Cleavage of the resulting diol with sodium periodate gave the aldehyde **389** in 95% yield over two steps after isolation. The next step was the oxidation of **389** to the corresponding carboxylic acid. Instead of using the toxic PDC oxidation, described by

Dossetter,[150] chlorite oxidation was preferred because of the milder conditions of the work-up. Using this oxidation protocol, complete conversion into the carboxylic acid **390** was obtained.[151] The crude acid was then treated with isobutylchloroformate in the presence of triethylamine to form the mixed anhydride. The formation of the diazo ketone **391** was accomplished by treatment of the mixed anhydride with an ethereal solution of diazomethane to furnish the diazo ketone **391** in 91% yield over 3 steps.

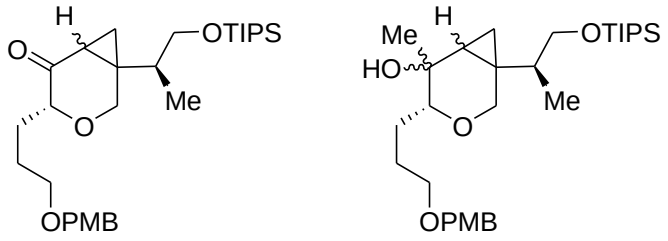


388 **389** **390** **391**

Scheme 104. Conditions: (a) PPTS, ethylene glycol, THF, DCM, reflux, 12 h. (b) $NaIO_4$, THF, H_2O, rt, 95% (2 steps). (c) $NaClO_2$, $NaH_2PO_4 \cdot H_2O$, 2-methyl-2-butene, ^{t}butanol, H_2O, rt. (d) *i*-BuO_2CCl, Et_3N, Et_2O, rt, 3 h. (e) CH_2N_2, Et_2O, 12 h, 0 °C, 91% (3 steps)

The key C–H insertion reaction to give the 3(2*H*)-furanone **394** was investigated throughly by Dossetter and Baxter.[127] During these studies, intramolecular cyclopropanation was observed as a side reaction. During Dossetter's work, the cyclopropane **392** was isolated as a mixture of assignable diastereomers upon purification of the C–H insertion product. However, upon subsequent addition of methylmagnesium chloride, the product **393** was isolated as a complex mixture of diastereomers that proved difficult to characterise fully (Figure 17).

[150] Dossetter , A. G. PhD Thesis. University of Nottingham, **1997**.
[151] Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, 37, 2091.



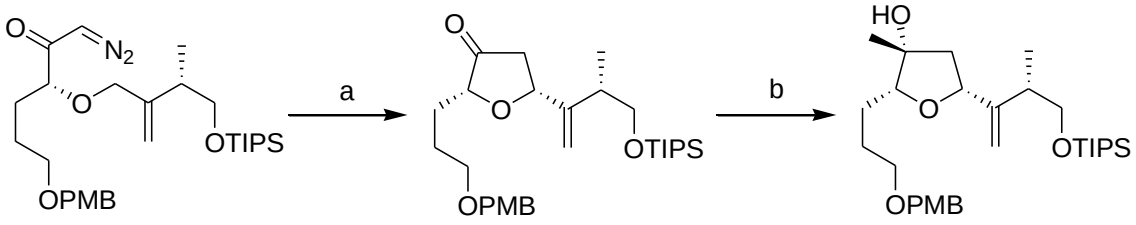
392 **393**

Figure 17. Side product resulting from the cyclopropanation

These studies showed also that the resulting dihydrofuranone **394** obtained from the intramolecular C–H insertion reaction was not stable and isolation of the material without loss was not possible.[150] Previous co-workers had shown that the highest yields of the tertiary alcohol **395** were obtained when intramolecular C-H insertion and nucleophilic addition of the methyl fragment were performed without isolation of the intermediate ketone **394**. Separation of the alcohol from minor products arising from the C-H insertion and the intramolecular cyclopropanation was more straightforward at this stage than at the ketone stage, and the alcohol **395** was more stable to purification. Consequently the two-step sequence was used in which introduction of the methyl group afforded the tertiary alcohol **395** which was isolated and characterised (Scheme 105).

In his original studies, Dossetter[126] found that the use of rhodium(II) trifluoroacetamide dimer (**299**), in DCM under reflux followed by a treatment of the resulting ketone **394** with $AlMe_3$ were the conditions of choice for the formation of **395** (Table 14, entry 1). Unfortunately, using these optimised conditions, C–H insertion occurred (50% yield) but methyl addition was not observed (Table 14, entry 2). Baxter investigated this sequence,[127] and although rhodium(II) trifluoroacetamide (**299**) remained the catalyst of choice for the C–H insertion, it was found that alternative sources of methyl nucleophile increased the product yield, particularly methylmagnesium chloride (Table 14, entry 3). Using these conditions, the tertiary alcohol **395** was isolated in modest yield (Table 14, entry 4). However, changing the methyl source to freshly prepared methylmagnesium iodide in diethyl ether delivered the desired compound **395** in comparable yield (Table 14, entry 5). Grignard addition was highly diastereoselective, but it was difficult to gauge the exact level of diastereoselectivity resulting from the addition of the methyl group to the C–H insertion major product because of the presence of several minor products, including small amounts of those arising from the Grignard addition to the minor *trans*-substituted furanone. Complete separation of the minor products was not

possible. It is important to note that using the conditions given in entry 5 of Table 14, the $[\alpha]_D$, ^1H, ^{13}C NMR spectra were identical to those reported by Baxter.[127] This indicated that the required diastereomer had been formed.



391 **394** **395**

Scheme 105. Conditions: (a) $Rh_2(tfacam)_4$, THF, reflux, 1h. (b) Me^-, solvent, Temp.

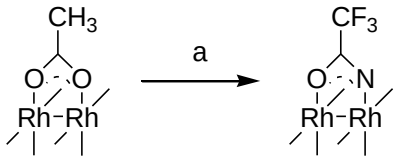
Entry	Nucleophile	Solvent	Temp	Yield (%) (over 2 steps)
1[a]	$AlMe_3$	DCM	rt	60
2	$AlMe_3$	DCM	rt	50 (**394**)
3[b]	MeMgCl	THF	rt	56
4	MeMgCl	THF	rt	30
5	MeMgI	Et_2O	rt	50

Table 14. Study of the methyl addition reaction [a] Optmised conditions from Dossetter, [b] Optmised conditions from Baxter.

Rhodium(II) trifluoroacetamide is not commercially available and synthesis in our laboratory was investigated. The synthesis of $Rh_2(tfacam)_4$ has already been described by Dennis and co-workers in 1983.[152] Following the experimental procedure, the ligand 2,2,2-trifluoroacetamide was also used as the solvent of the reaction and rhodium(II) trifluoroacetamide was synthesised in a 60% yield from commercially available rhodium(II) acetate (Scheme 106). However, purification of the complex proved to be difficult and a sublimation followed by column chromatography on alumina gel was required. To optimise the reaction conditions, a small screen of alternative procedures was conducted. Firstly the reaction was performed in a soxhlet extractor with chlorobenzene as the solvent under reflux over 48 hours but the starting material showed some

[152] Dennis, A. M.; Korp, J. D.; Bernal, I.; Howard, R. A.; Bear, J. L. *Inorg. Chem.* **1983**, *22*, 1522.

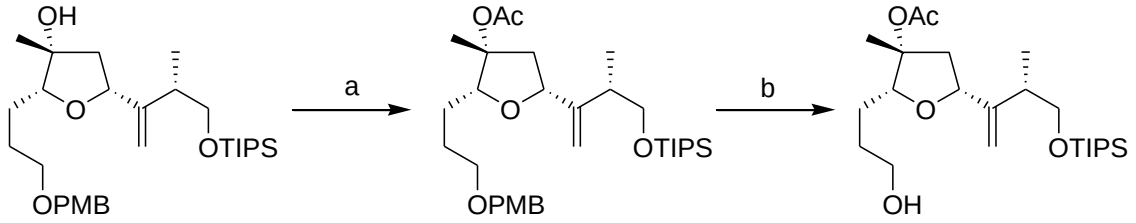
decomposition and the reaction led to the desired rhodium(II) trifluoroacetamide in very poor yield (15%). Reaction in a sealed tube was also attempted and using 2,2,2-trifluoroacetamide as the ligand and the solvent, the reaction led only to the decomposition of the rhodium acetate.



52 **299**

Scheme 106. Conditions: (a) $C_2H_2F_3NO$, 150 °C, 8 h, 60%.

The successful synthesis of the tertiary alcohol **395** meant that preparation of the second diazoketone precursor required for the key step was now the main objective. The synthetic pathway started with an acetate protection of the free tertiary hydroxyl group using acetic anhydride to give the ester **396** in good yield. Subsequent removal of the PMB protecting group with DDQ[153] under aqueous conditions furnished the primary alcohol **397** in quantitative yield (Scheme 107).



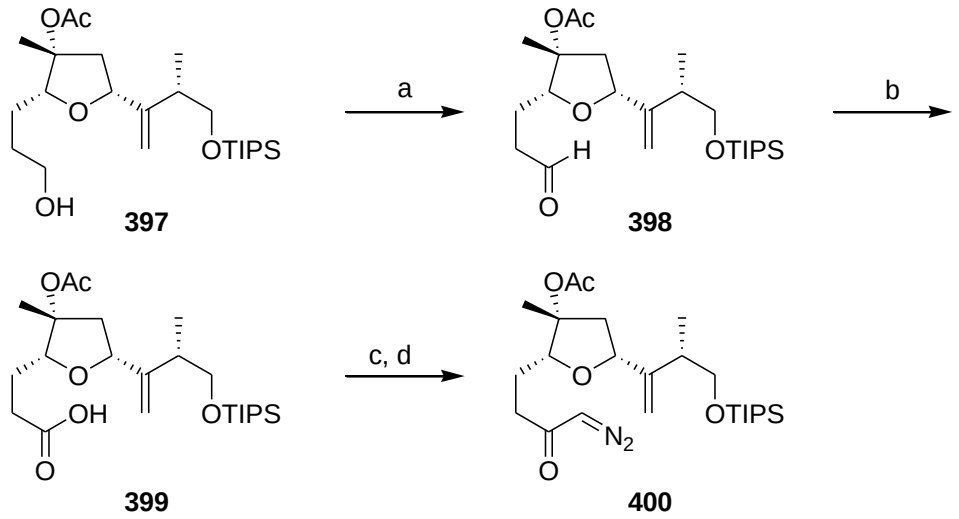
395 **396** **397**

Scheme 107. Conditions: (a) Ac_2O, DMAP, Et_3N, Et_2O, 20 h, rt, 80%. (b) DDQ, DCM, H_2O, 3 h, rt, 93%.

With the primary alcohol **397** in hand, oxidation to the corresponding carboxylic acid was performed. The most direct route would be to use a PDC oxidation reaction but previous co-workers proved that these conditions were not satisfactory in term of yield.[154] Consequently, a two-step oxidation procedure was used (Scheme 108). Firstly, a Dess-

[153] Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, 23, 885.
[154] Baxter, C. A. PhD Thesis. University of Nottingham, **2004**.

Martin periodinane oxidation[155] was performed to give the corresponding aldehyde **398** in good yield (80%) after purification. The aldehyde **398** was then converted into the carboxylic acid **399** using the Pinnick procedure.[151] Completion of the synthesis was performed by treatment of the crude acid **399** with sodium methoxide to give the corresponding sodium salt which then reacted with oxalyl chloride to furnish an intermediate acid chloride. This was then added to an ethereal solution of diazomethane to yield the diazoketone **400** in 79% yield from the aldehyde **398**.

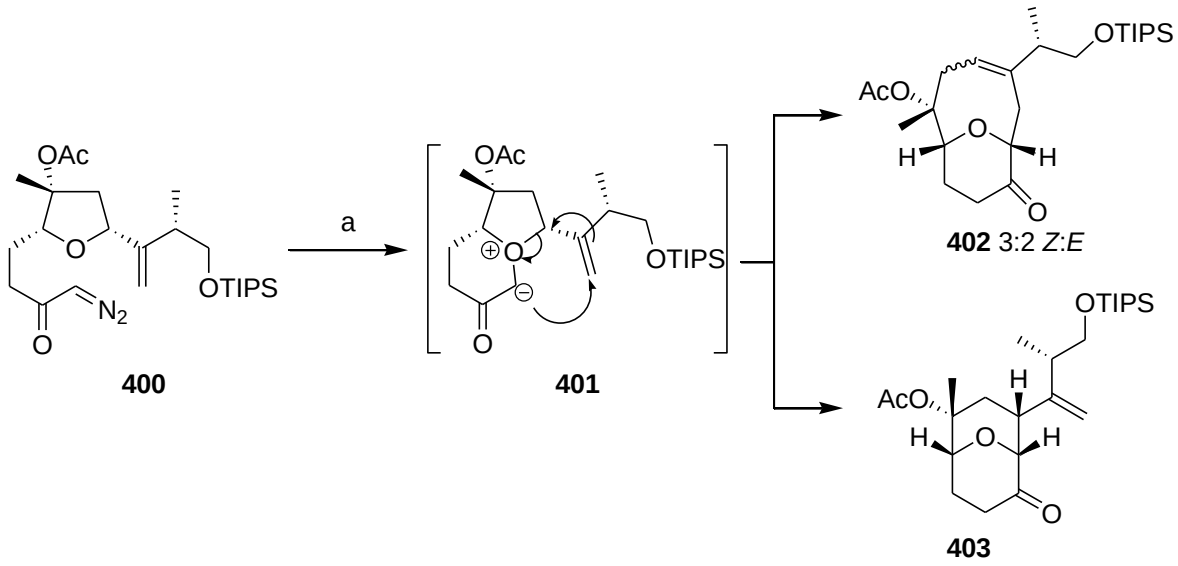


Scheme 108. Conditions: (a) DMP, DCM, 2 h, 0 °C to rt, 80%. (b) $NaClO_2$, $NaH_2PO_4 \cdot H_2O$, 2-methyl-2-butene, ^{t}butanol, H_2O, rt. (c) NaOMe, MeOH, 10 min, rt, then $(COCl)_2$, C_6H_6, 3 h, rt. (d) CH_2N_2, Et_2O, 12 h, 0 °C, 79% (4 steps).

Having prepared the diazoketone **400**, the key reaction in our synthesis, which would deliver the bicyclic system containing the ether bridge of the natural compound, was investigated. Using the optimised conditions developed by Dossetter[150] and Baxter,[127] treatment of the diazoketone with copper(II) hexafluoroacetylacetonate (**249**) as the catalyst resulted in apparent intramolecular oxonium ylide **401** formation and [2,3]-sigmatropic ylide rearrangement sequence to give the required [5.3.1] oxabicyclic compound **402** in 61% yield as an inseparable mixture of isomers (3:2 *Z:E* ratio of isomers) with *cis* relative configuration at the ring junction (Scheme 109). A side product was isolated resulting from the intramolecular oxonium ylide generation and apparent [1,2]-shift rearrangement; the undesired 9-oxabicyclo[3.3.1]nonane product **403** was obtained in 18% yield. Alternative reactions were not investigated because ylide-derived

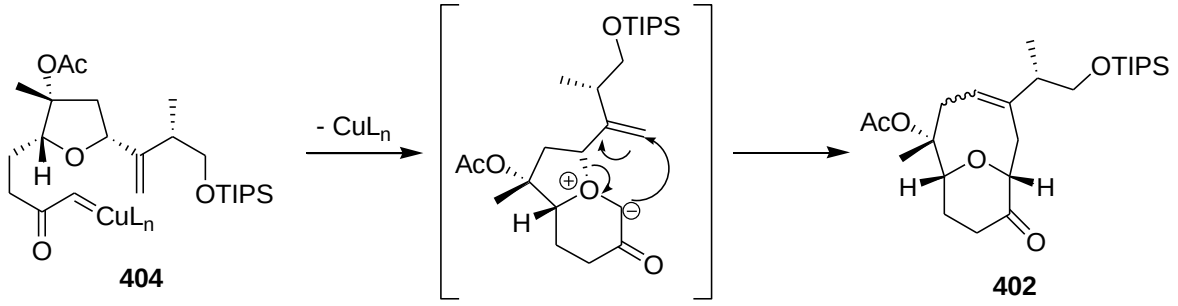
[155] Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

products were obtained in an overall yield of 79%, with an isolated yield of 61% for the desired compound, which was considerable acceptable.



Scheme 109. Conditions: (a) $Cu(hfacac)_2$, DCM, reflux, 1 h, 61% **402**, 18% **403**.

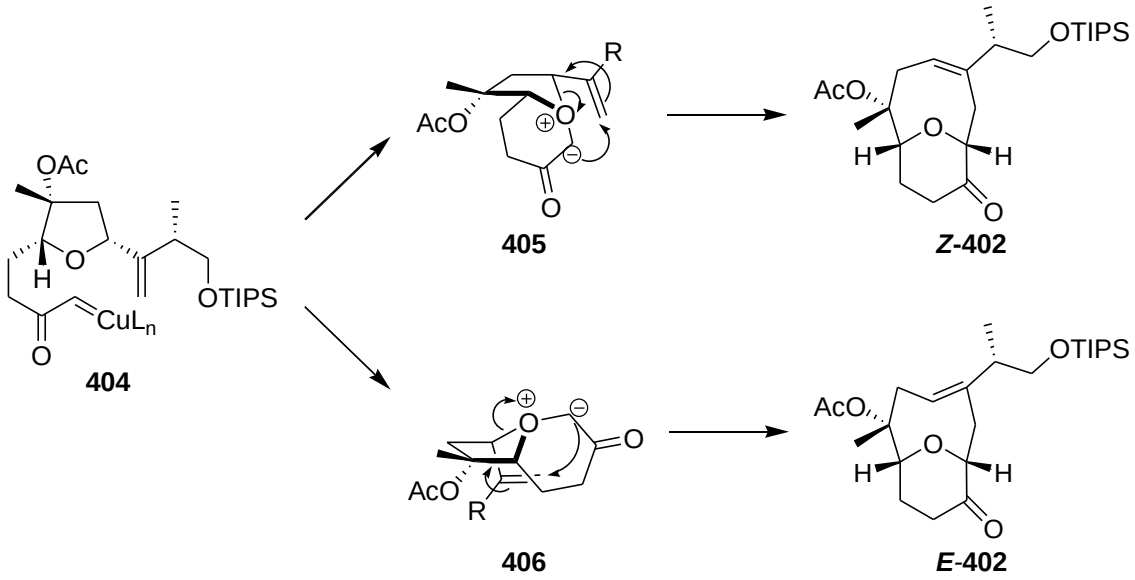
The *cis* stereochemical outcome is explained in Scheme 110. Because of the fixed configuration of stereocentre on the tetrahydrofuran, and in order to reach the vinylic chain, the newly created bond resulting from the sigmatropic rearrangement must be in an equatorial position. In this case, the substituents forming the eight-membered ring system are both in equatorial positions on the lower face leading to a *cis* configuration in the product.



Scheme 110. Stereochemical outcome of oxonium ylide and [2,3]-sigmatropic rearrangement.

In Scheme 110, selectivity for the *Z* and *E* isomers was not considered. It is known that *Z*-isomers are energetically more favorable for rings of eight members than *E*-isomers, which led us to believe that the *Z*-isomer *Z*-**402** was the more thermodynamically

stable.[156] The isomer *E*-**402** must be produced by kinetic control during the rearrangement process. In Scheme 111, there are the two possible conformations for the intermediate ylide which would give rise to the *Z* and *E* isomers. The oxonium ylide **405** should give the *Z*-bicyclic ketone *Z*-**402** whereas [2,3]-sigmatropic rearrangement of the oxonium ylide **406** would form the *E*-bicyclic ketone *E*-**402**. Moreover, results obtained by a previous co-worker,[150] have shown also that catalyst, solvent and temperature have a significant influence of the formation of the bicyclic ketone which means that the rearrangement cannot be explained by a "free" oxonium ylide representation. This finding tends to support the intermediary of a metal-bound ylide intermediate.



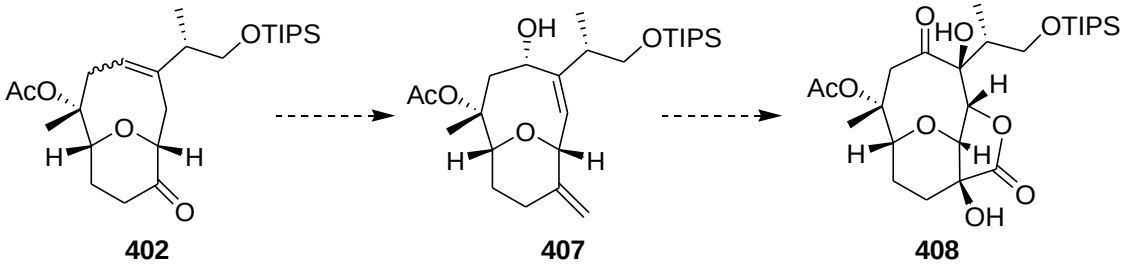
Scheme 111. Two possible conformations for the intermediate ylide.

In conclusion, the [5.3.1]-oxabicyclic core of the neoliacinic acid was constructed by tandem oxonium ylide formation and [2,3]-sigmatropic rearrangement. A diastereoselective C-H insertion reaction was used to construct the tetrahydrofuran ring of the key *α*-diazo ketone **400**. Thus, two different metal carbenoid transformations were used for ring construction during the synthesis.

The success of the key steps in our synthesis allowed us to investigate the synthesis of the allylic alcohol **407**. This compound would contain two different alkenes which would allow the introduction of the functionality required to construct the lactone

[156] Marshall, J. A. *Acc. Chem. Res.* **1980**, *13*, 213.

and the two tertiary alcohols found in **408**. It was anticipated that at this stage, the two alkenes would possess sufficient variation in reactivity to allow them to be differentiated.



402 **407** **408**

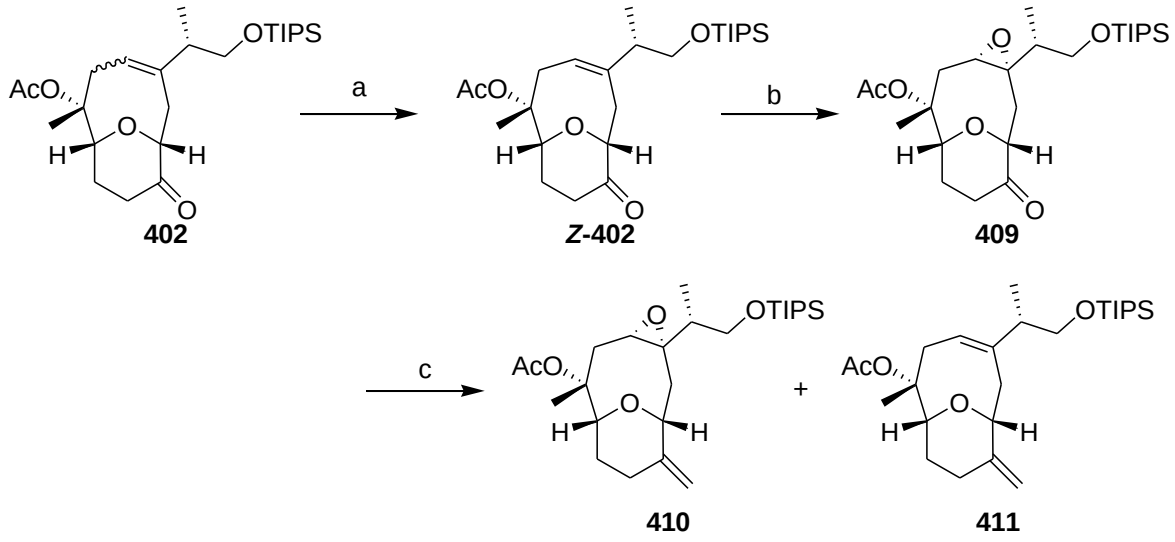
Scheme 112. Progression towards introduction of the lactone.

The synthetic pathway began with isomerisation of the double bond using AIBN and ethanethiol to provide the more stable alkene ***Z*-402** thereby completing the synthesis of the bicyclic core of the natural product (Scheme 113). At this point in the synthesis, there were two synthetic alternatives: epoxidation of the endocyclic double bond or olefination of the exocyclic ketone. If olefination was undertaken first, there would be potential competition between the two alkenes in the later steps. In order to avoid this problem, diastereoselective epoxidation of the double bond group was investigated. This reaction afforded the epoxy ketone **409** in 91% as 10:1 mixture of diastereomers. A crystal structure was obtained and the X-ray analysis confirmed the relative stereochemistry of the epoxide as well as the [5.3.1]-oxabicyclic core (Figure 18). Methylenation of the ketone could be undertaken before or after conversion of the epoxide into the required allylic alcohol **407**. In principle, a Lewis acidic reagent is required for the desired epoxide rearrangement reaction. However, the ketone present on the starting material could function as a substrate for the Lewis acid reagent in a competing Meerwein-Ponndorf-Verley[157] reaction which would reduce the ketone into the alcohol. In order to avoid this potential side reaction, we opted to continue our synthesis by performing methylenation of the carbonyl group prior to formation of the allylic alcohol.

Olefination of the exocyclic ketone **409** proved to be problematic and several experimental procedures were investigated. Firstly, a standard Wittig methylenation reaction was attempted but without success and all of the starting material was recovered. Petasis olefination, as used by previous co-workers, could have been a good alternative to

[157] Moulton, W. N.; Atta, R. E. V.; Ruch, R. R. *J. Org. Chem.* **1961**, *26*, 290.

methylenate the ketone.[133,134,154] However using the optimised conditions of Baxter[127] and freshly prepared Petasis reagent **361**, the reaction did not give reproducible results and starting material was recovered. As previously, Peterson olefination was an option, but nucleophilic addition of trimethylsilymethylmagnesium chloride to the carbonyl group failed and only starting material was recovered from the reaction. Finally, methylenation was attempted with the Nysted reagent **362** using $TiCl_4$ as the Lewis acid.[135] The procedure was undertaken and delivered the alkene **410** in modest yield (63%). Unfortunately, the Nysted methodology was inconsistent and complete conversion of the substrate **409** into the alkene **410** was difficult to accomplish. Moreover, during purification, a side product was isolated, resulting from the deoxygenation of the epoxide to give the diene **411** was isolated in 12% yield.



Scheme 113. Conditions (a) AIBN, ethanethiol, C_6H_6, reflux, 1 h, quant. (b) *m*-CPBA, DCM, reflux, 1 h, 91%. (c) Nysted reagent, $TiCl_4$, DCM, THF, 0 °C, 3 h, 63% **410**, 12% **411**.

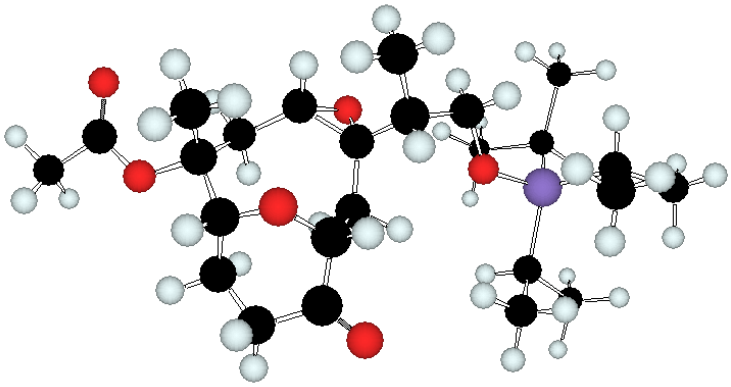
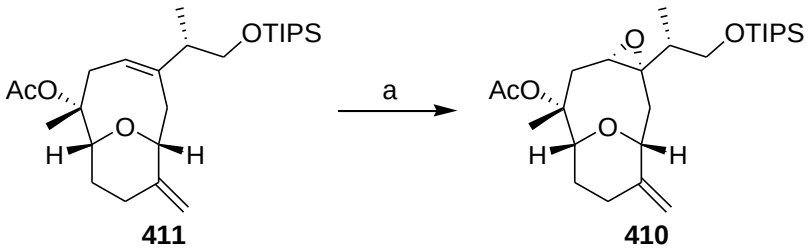


Figure 18. The X-ray crystallography of the epoxide **409**.

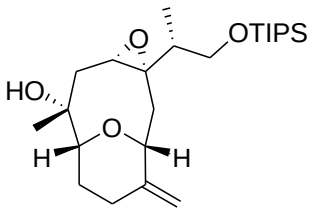
Fortunately, it appeared that this side product **411** could be recovered and converted into the required product **410.** Thus treatment of **411** with *m*-CPBA resulted in a regio- and diastereoselective epoxidation of the substituted endocyclic double bond to give the desired epoxide **410** in 66% yield with the same level of diastereoselectvity observed when preparing the ketone **409** from the alkene ***Z*-402** (Scheme 114).



Scheme 114. Conditions: (a) *m*-CPBA, DCM, 0 °C to rt, 12 h, 66%.

This result means that the two alkenes present in the diene **411** are sufficiently different in term of their reactivity to allow the selective epoxidation of the trisubstituted alkene. Potential competition between the two double bonds for the desired transformation was not observed. Consequently, an alternative strategy would have been possible. Instead of starting the sequence with the diastereoselective epoxidation on ***Z*-402**, it would have been interesting in terms of yield and especially reproducibility to attempt methylenation of the ketone to furnish the diene **411**, prior to diastereoselective epoxidation to form the epoxide **410**.

The next objective was regioselective ring-opening of the epoxide to deliver **407**, a transformation that had been investigated previously by Baxter.[154] A limited screen of various Lewis acids and conditions was performed to optimise epoxide ring-opening. Treatment of the epoxide **410** with $TiCl_4$ and $Ti(O^iPr)_4$ gave disappointing results and only starting material was recovered from these reactions. Reaction with KO^tBu was also attempted but instead of giving the desired product, it resulted in the removal the acetate protecting group to give the alcohol **412** (Figure 19). The use of PPTS in different solvents, under reflux was also explored, but unfortunately no reaction was observed under these conditions. Using $Al(O^iPr)_3$[158] the reaction underwent the desired transformation, but with concomitant removal of the acetate group to give the diol **413** (Scheme 115).



412

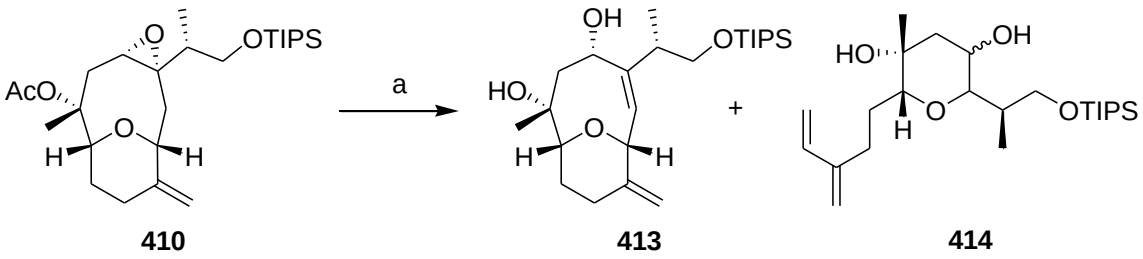
Figure 19.

Based on the results of previous studies performed in our laboratory, it was deemed necessary to explore other conditions. According to the literature information, epoxides have been shown to undergo ring opening using PTSA to deliver the corresponding allylic alcohols.[159] Disappointingly, treatment of **410** with this reagent failed to give the required product and led to decomposition of the starting material. Stratakis and co-workers reported that TiO_2-supported gold nanoparticles could be used for the isomerisation of epoxides to give allylic alcohols.[160] They suggested that this mild heterogeneous catalyst reacts as an acid-base reagent in which the gold particle could act as Lewis acid to activate the epoxide while the surrounding oxygen atoms from the TiO_4 act as basic sites to catalyse isomerisation of the epoxide. Based on the procedure described by Stratakis and co-workers, epoxide rearrangement to generate the allylic alcohol was attempted. However formation of the required allylic alcohol **407** was not observed and the starting material was recovered.

No further conditions were investigated and the original method using the

[158] Matsui, J.; Yokota, T.; Bando, M.; Takeuchi, T.; Mori, K. *Eur. J. Org. Chem.* **1999**, 2201.
[159] Sharma, V.; Kelly, G. T.; Watanabe, C. M. H. *Org. Lett.* **2008**, *10*, 4815.
[160] Raptis, C.; Garcia, H.; Stratakis, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 3133.

$Al(O^iPr)_3$ was employed for this transformation. Disappointingly, as discovered by previous co-workers,[127,154] the procedure gave inconsistent results and afforded the allylic alcohol **413** in modest yield with concomitant loss of the acetate protecting group under the Lewis acidic conditions. During the experiment, a pyran by-product **414** was isolated in 22% yield (Scheme 115).

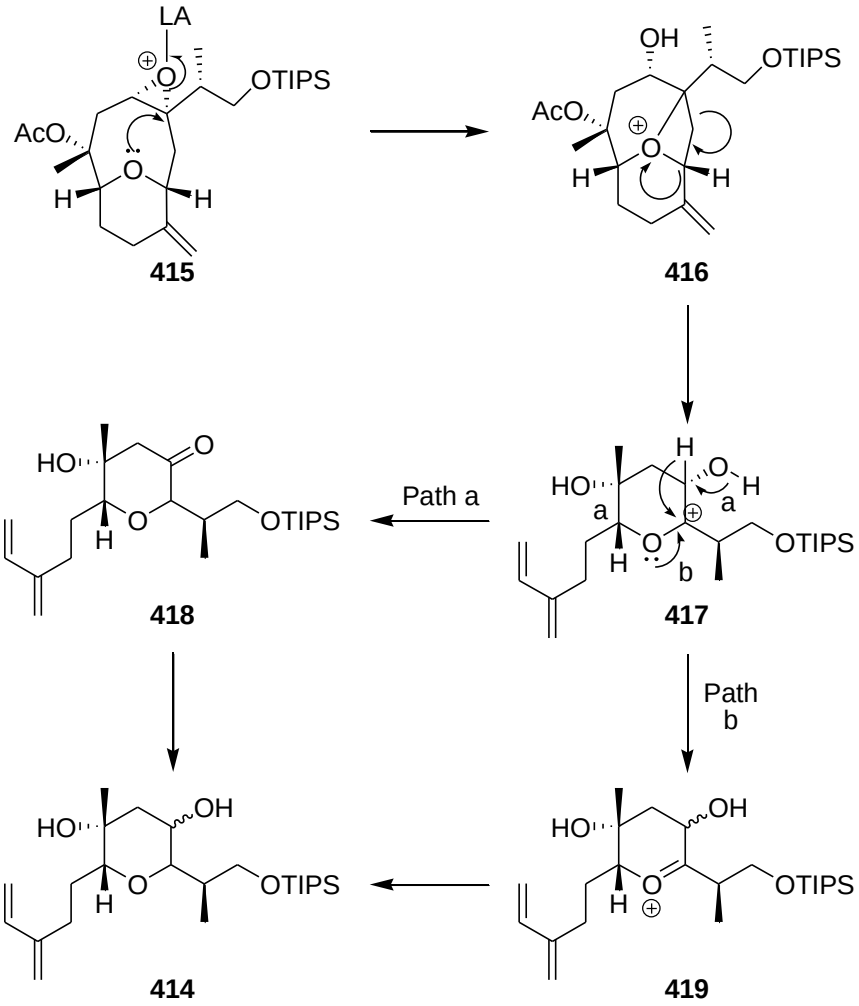


410 **413** **414**

Scheme 115. Conditions: (a) $Al(O^iPr)_3$, toluene, reflux, 12 h, **413** 49%, **414** 22%.

The pyran by-product is thought to originate from a Lewis acid assisted opening of the epoxide and subsequent rearrangement (Scheme 116). In 2000, Clark and Wong showed that an ether bridge can participate in a transannular reaction with a selenonium ion generated in a similar system.[161] It is thought that formation of **414** occurred by a similar mechanism, with Lewis acid chelation to the epoxide **415**. Nucleophilic attack by the non-bonding lone pair of the ether bridge to the epoxide would furnish the oxonium ion **416** and subsequent rearrangement would give the diene **417**. However, it is unclear if the synthetic pathway would proceed through the oxocarbenium ion **419** (path b) or via the ketone **418** generated by a 1,2 hydride shift (path a). It is believed that the next step from **418** would be a Meerwein-Ponndorf-Verley reduction to give the tertiary alcohol **414** as a mixture of diastereomers.

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

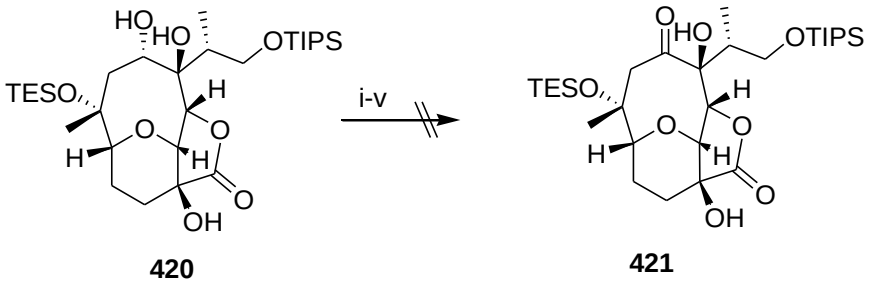


Scheme 116. Possible mechanism for formation of by-product **414**.

3 Progress towards the lactone ring of neoliacinic acid.

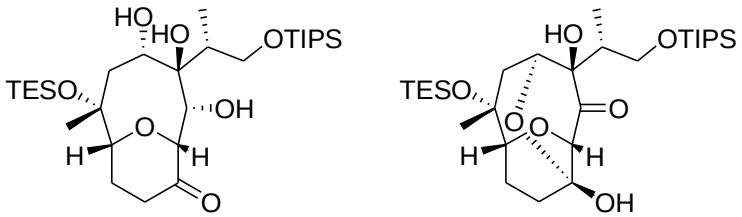
Having synthesised the allylic alcohol **413** in sufficient quantities, progression towards the completion of third ring was the next synthetic challenge. Based on the results from a previous co-worker,[154] several routes were apparent. Previously, the lactone found in the natural product was successfully synthesised to give the tricyclic system **420**, but to complete the synthesis, oxidation of the secondary alcohol into the ketone **421** was required. Using the conditions shown in the Scheme 117, it proved impossible to perform the desired transformation.[154] Under Swern and modified Swern conditions only starting material was recovered. Dess-Martin periodinane and PCC oxidation reaction produced complex mixtures of products and gave what was assigned as **422** (Figure 20). There was

no oxidation of the secondary alcohol and spectroscopic data showed the disappearance of the lactone. TPAP[162] oxidation gave a different material which was not the required ketone **421** but the lactol **423**



420 **421**

Scheme 117. Attempted oxidation of alcohol **420** by Baxter. (i) PCC, NaOAc, DCM, 3 Å MS, rt. (ii) SO_3.Py, NEt_3, DMSO. (iii) DMP, DCM, 0 °C. (iv) $(COCl)_2$, DMSO, NEt_3, DCM, –78 °C to rt. (v) TPAP (cat), NMO, DCM, 4 Å MS.

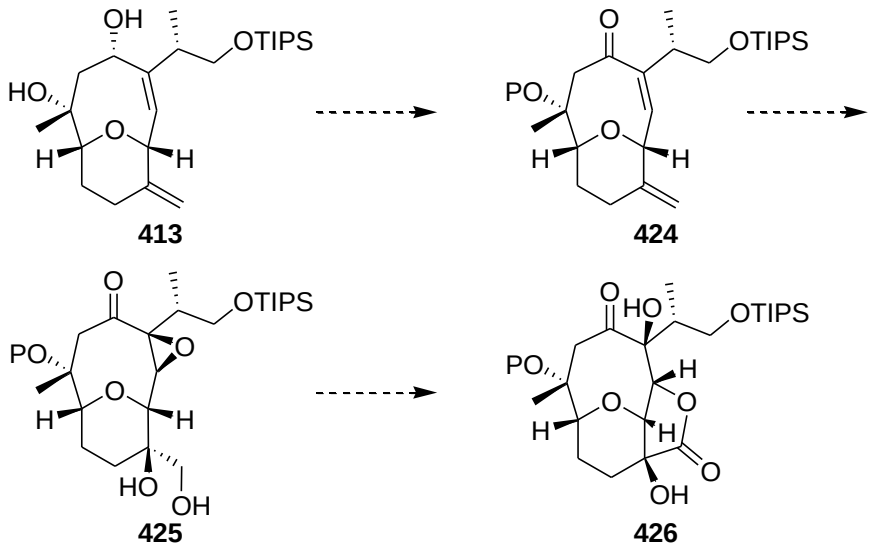


422 **423**

Figure 20. Side products isolated from the oxidation of alcohol **420**.

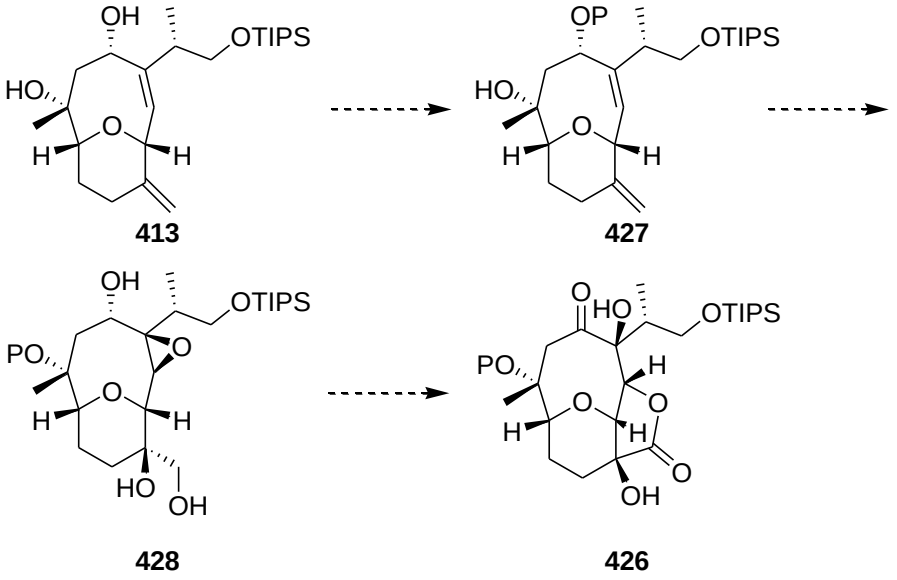
With this information from previous experiments, it appeared that it would be necessary to perform oxidation of the secondary alcohol prior to formation of the lactone. To achieve this goal, two synthetic pathways were conceivable. Following *route a* (Scheme 118), firstly the free secondary hydroxyl group would be oxidised to give the ketone then protection of the tertiary alcohol could be performed to give **424**. The choice of the protecting group would be crucial to the success of this strategy because it would allow the generation of a good leaving group necessary to form the enone system of the natural product and also allow differentiation between the various hydroxyl groups. After introduction of the functional groups required to construct the lactone, full oxidation of **425** to give a carboxylic acid and acid treatment would furnish the tricyclic core **426** of the target.

[162] Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.



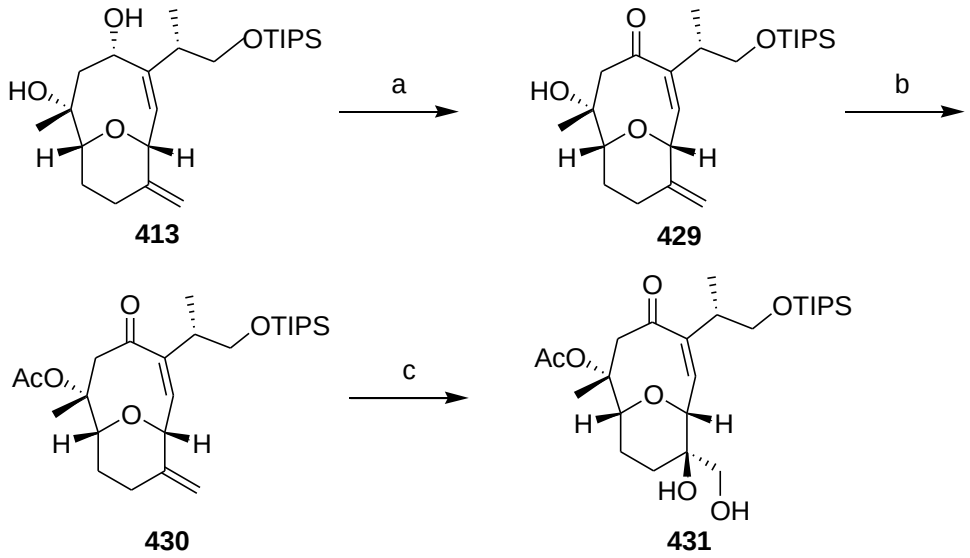
Scheme 118. Route a: Potential synthetic pathway to install the lactone.

Following *route b* (Scheme 119), we expect that the free hydroxyl groups of the diol **413** would possess sufficient differences in reactivity to allow completion of the synthesis. Firstly, a bulky protecting group would be introduced on the secondary alcohol, then a good leaving group would be formed at the tertiary alcohol site. The first protection would direct the diastereoselective epoxidation of the endocyclic double bond and selective deprotection would furnish **428**. Full oxidation of the free hydroxyl groups would furnish the corresponding carboxylic acid and ketone which would be treated under acid conditions to give the core of neoliacinic acid.



Scheme 119. Route b: Potential synthetic pathway to install lactone.

Route a was explored first and commenced by oxidation of the allylic alcohol **413** using the Dess-Martin periodinane protocol to furnish the ketone **429** in 70% yield. The acetate protecting group was then introduced on the tertiary alcohol site furnishing the intermediate **430** in good yield. The choice of the acetate group was in correlation with our strategy because formation of the enone functionality of the natural product could be achieved by base induced elimination[163] of this group or treatment with IBX.[164] As was anticipated in the strategy shown in *route a*, dihydroxylation using a catalytic amount of osmium tetroxide was undertaken and the regioselectivity of the reaction favored oxidation of the exocyclic alkene. The diol **431** was synthesised in 70% yield as single diastereomer with no dihydroxylation of the trisubstituted alkene observed (Scheme 120). The relative configuration of **431** was assigned on the basis of NOE studies (Figure 21) and no additional studies were performed to confirm the stereochemistry.



Scheme 120. Conditions: (a) DMP, DCM, 2 h, rt, 75%. (b) Ac_2O, DMAP, Et_3N, Et_2O, rt, 20 h, 72%. (c) OsO_4, NMO, acetone, H_2O, 24 h, rt, 70%.

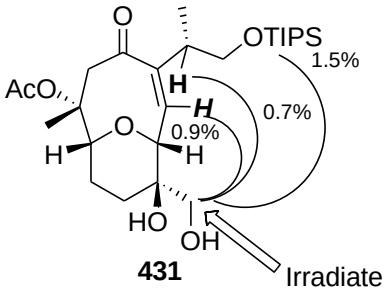
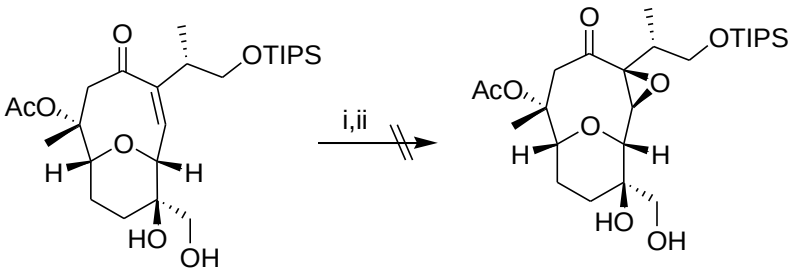


Figure 21. NOE studies of **431**.

[163] (a) Arai, H.; Ohno, A.; Tani,Y.-I.; Imachi, S.; Mukaiyama, T. *Chem. Lett.* **2002**, 92. (b) Serra, S.; Fuganti, C. *Tetrahedron Asymmetry* **2006**, *17*, 1573.
[164] Aslaoui, J.; Li, H.; Morin,C. *Tetrahedron Lett.* **2005**, *46*, 1713.

Following our strategy, diastereoselective epoxidation of the enone was investigated. It was anticipated that *m*-CPBA would not be the reagent of choice for epoxidation of electron-poor trisubstituted alkene, so the use of a sub-stoichiometric amounts of aqueous hydrogen peroxide under basic conditions was explored in initial studies. These conditions are well known to result in epoxidation of an *α,β*-unsaturated ketones.[165] Unfortunately, following the standard reaction conditions (Scheme 121), epoxidation was not observed and all the starting material **431** was recovered. This disappointing result was not expected and due to the lack of reactivity of hydrogen peroxide, another protocol was explored in which dimethyldioxirane (DMDO) was employed as the oxidant.[166] The use of DMDO as an epoxidation reagent has been described extensively in the literature[166] and there are many examples where treatment of electron-poor alkenes has resulted in the formation of epoxides in excellent yield. Unfortunately, using freshly prepared DMDO and following procedures described in the literature,[166] the desired epoxidation reaction did not take place and decomposition of the starting material was observed instead (Scheme 121).



431 **432**

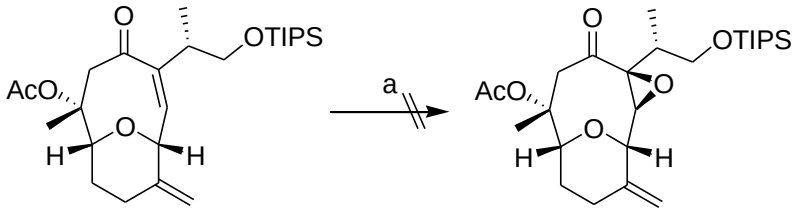
Scheme 121. Conditions: (i) H_2O_2 (30% aq.), $NaHCO_3$, EtOH, H_2O, 12 h, rt. (ii) DMDO, DCM, 24 h, 0 °C.

The reason for the poor reactivity of **431** when attempting to prepare the epoxide is unclear but one possible explanation could be that an extremely hindered environment created by the diol which obstructs approach of the reagents. One last attempt to effect *route a*, was made by performing epoxidation prior to dihydroxylation of the *exo*-methylene group. Many examples in the literature have described the epoxidation of an

[165] (a) Jung, M. E.; Piizzi, G. *Org. Lett.* **2003**, *5*, 137. (b) Hrycko, S.; Morand, P. *J. Org. Chem.* **1988**, *53*, 1515. (c) Adam, W.; Halasz, J.; Jambor, Z.; Lévai, A.; Nemes, C.; Patonay, T.; Toth, G. *J. Chem. Soc., Perkin Trans. 1* **1996**, 395.

[166] (a) Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377. (b) Adam, W.; Hadjiarapoglou, L.; Nestler, B. *Tetrahedron Lett.* **1990**, *31*, 331. (c) Nemes, C.; Lévai, A.; Patonay, T. *J. Org. Chem.* **1994**, *59*, 900.

α,β-unsaturated ketones with urea-hydroperoxide complex (UHP) and excellent results in terms of yield have been reported.[167] However, when this reaction was performed under anhydrous conditions, the desired epoxide **433** was not obtained and the reaction led to decomposition of the starting material (Scheme 122).



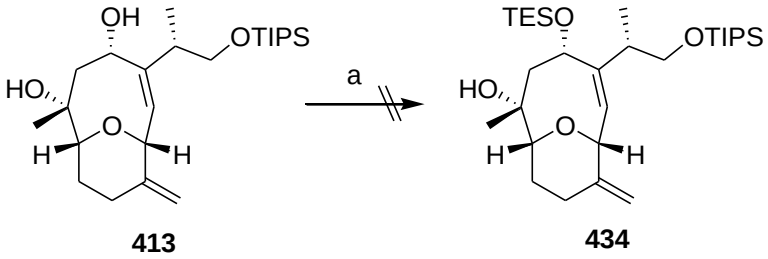
430 **433**

Scheme 122. Conditions: (a) UHP, DBU, THF, rt, 12 h.

As a consequence of the difficulties encountered when trying to convert trisubstituted alkenes into the corresponding epoxide, it was decided to abandon *route a* and to turn our attention to the implementation of *route b*.

In the case of *route b*, the choice of protecting group for the secondary alcohol was likely to be crucial because steric hindrance might direct the diastereoselective epoxidation of the trisubstituted alkene group. Based on the previous work of Baxter,[127] the triethylsilyl ether group was deemed to be best choice because it would be sufficiently hindered to guide the formation of the epoxide to the top face of the molecule. Consequently selective protection of the secondary hydroxyl group to give the triethylsilyl ether **434** was investigated. The first attempt at selective protection of the secondary hydroxyl group was performed using standard conditions (Scheme 123). Unfortunately, reaction of the diol **413** with triethylsilyl chloride as the reagent under basic reaction conditions furnished only the starting material.

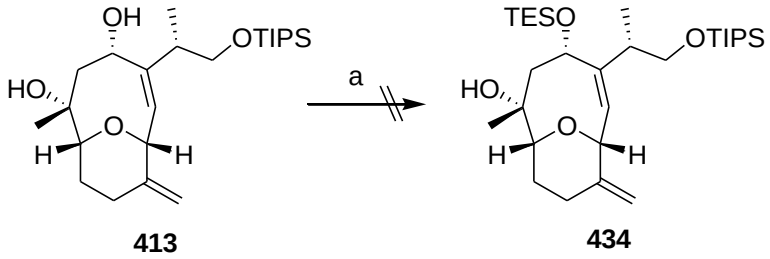
[167] (a) Tietze, L. F.; Güntner, C.; Gericke, K. M.; Schuberth, I.; Bunkoczi, G. *Eur. J. Org. Chem.* **2005**, 2459. (b) Colonna, S.; Manfredi, A.; Annunziata, R.; Gaggero, N. *J. Org. Chem.* **1990**, *55*, 5862. (c) Allen, J. V.; Bergeron, S.; Griffiths, M.; Mukherjee, S.; Robert, S. M.; Williamson, N. M.; Wu, L. E. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3171.



413 **434**

Scheme 123. Conditions: (a) TESCl, imid., DMF, rt, 20 h.

Due to the lack of reactivity of triethylsilyl chloride, triethylsilyl trifluoromethanesulfonate was used instead. This reagent is known to protect both secondary and tertiary alcohols but we expected that by using one equivalent of the reagent at low temperature, the difference in reactivity of the two free alcohols would result in a selective protection of the secondary hydroxyl. The reaction was performed using the conditions quoted in Scheme 124, but unfortunately careful monitoring of the reaction by TLC showed the formation of three new products. The result suggested that there was little selectivity for protection of the hydroxyl groups and that the alcohols possessed similar reactivity with triethylsilyltrifluoromethane sulfonate. We assumed that the products formed during the reaction were those arising from the mono-protection of tertiary alcohol, the mono-protection of the secondary alcohol and, silylation of both hydroxyl groups.

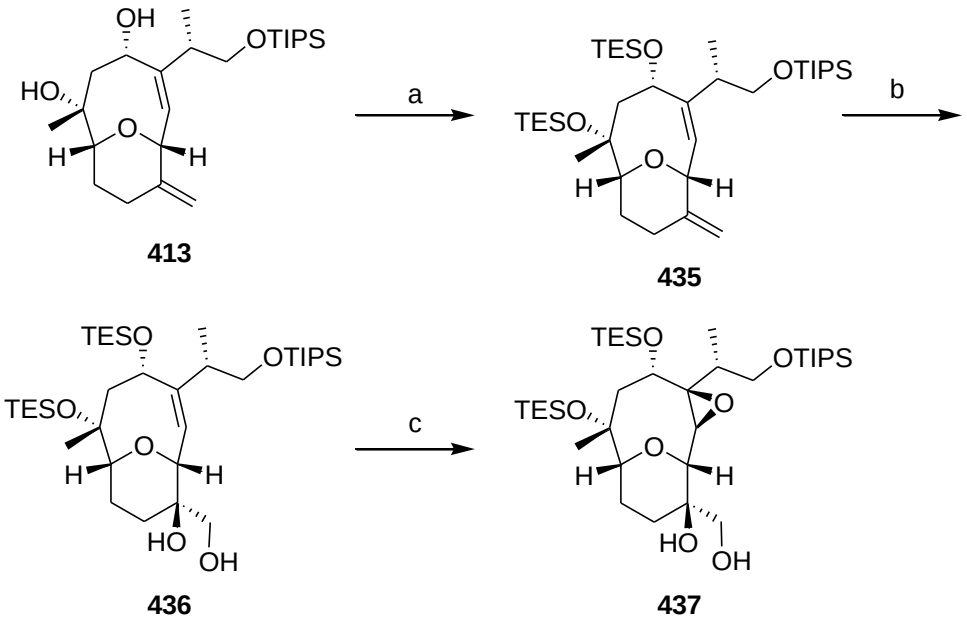


413 **434**

Scheme 124. Conditions: (a) TESOTf (1 eq.), 2,6-lutidine, DCM, 2 h, –78 °C.

This result above suggested that there was no other choice but to protect both hydroxyl groups. The conditions used were similar to those employed previously but in order to obtain complete conversion of the starting material, the reaction was performed with a large excess of triethylsilyl trifluoromethanesulfonate. The reaction furnished the desired fully protected silyl ether diene **435** in 85% yield (Scheme 125). Following our synthetic strategy, the next transformation was dihydroxylation of the exocyclic double bond. As observed previously in *route a*, treatment of diene **435** with a catalytic amount of osmium tetroxide resulted in the dihydroxylation of the exocyclic alkene furnishing diol

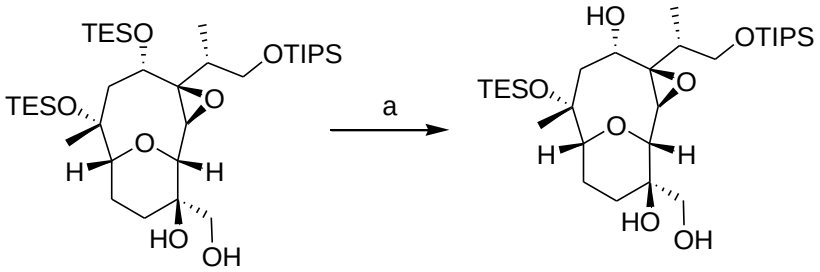
436 in good yield (74% yield) as single diastereomer. Once again, the difference in reactivity of the two alkenes allowed a completely regioselective reaction and dihydroxylation of the trisubstituted alkene did not occur. Subsequently, diastereoselective epoxidation was investigated and treatment of the alkene **436** with *m*-CPBA furnished the epoxide **437** in 89% yield as single diastereomer. The structural assignment was supported by ^{1}H and ^{13}C NMR spectroscopy. It was anticipated that the lower face of **436** would possess significant steric hindrance due to the silyl ether, suggesting that the shape of the molecule would allow approach of the epoxidation reagent to the alkene from the top face only.



Scheme 125. Conditions: (a) TESOTf (5 eq.), 2,6-lutidine, DCM, 2 h, –78 °C, 85%. (b) OsO_4, NMO, acetone, H_2O, 24 h, rt, 74%. (c) *m*-CPBA, DCM, 0 °C to rt, 4 h, 89%.

Successful formation of the epoxide allowed us to investigate the construction of the lactone. In order to follow the strategy outlined in *route b*, selective removal of the triethylsilyl group on the secondary hydroxyl group was required. The main challenge of this transformation was to use a procedure in which the other silyl ether function would not be affected. In 2009, Lee and co-worker published the total syntheses of several natural products and during this synthetic route, selective deprotection of a secondary triethylsilyl ether was performed in the presence of a primary TIPS protecting group using HF.Pyr at 0

°C.[168] We thought that this reaction was applicable to our substrate and fortunately treatment of the epoxide **437** with HF.Pyr resulted in a selective deprotection to give the desired alcohol **438** in 70% yield (Scheme 126). However, the reaction was particularly capricious and needed to be monitored carefully by TLC. It appeared that after the formation of the triol, removal of the TIPS group occurred to give the tetraol which was difficult to isolate. In order to avoid over-deprotection, the reaction was quenched as soon as the tetraol appeared on TLC; isolation of desired triol and recovery of the starting material **437** was thereby achieved.



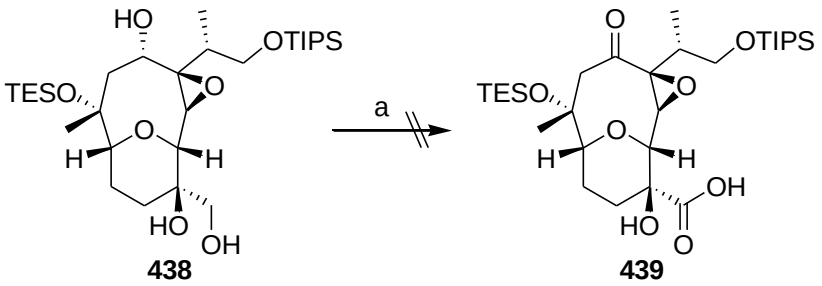
437 **438**

Scheme 126. Conditions: (a) HF.Pyr, Pyridine, THF, 2 h, 0 °C, 70%.

Following the synthesis of the triol **438**, it was necessary to oxidise the free hydroxyl groups to generate the required functionality prior to cyclisation to form the lactone. In principle, a carboxylic acid or ester would be used to effect the cyclisation reaction.[169] The double oxidation sequence proved to be problematic to implement and various oxidation procedures were investigated.

The first attempt involved a one-step oxidation to the corresponding keto acid **439**. Pyridinium dichromate (PDC) is often used for the oxidation of primary and secondary alcohols to aldehydes and ketones respectively, and the reaction of saturated primary alcohols in DMF can result in further oxidation to the corresponding carboxylic acids after aldehyde formation.[170] Using the Corey and Schmidt protocol[170] neither the primary nor the secondary alcohol was oxidised under standard reaction conditions and all of the starting material was recovered (Scheme 127).

[168] Li, J.; Park, S.; Miller, R. L.; Lee, D. *Org. Lett.* **2009**, *11*, 571.
[169] (a) Paquette, L. A.; Sturino, C. F.; Wang, X.; Prodger, J. C.; Koh, D. *J. Am. Chem. Soc.* **1996**, *118*, 5620. (b) Paquette, L. A.; Koh, D.; Wang, X.; Prodger, J. C. *Tetrahedron Lett.* **1995**, *36*, 673.
[170] Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *5*, 399.



438 **439**

Scheme 127. Conditions: (a) PDC (6 eq.), DMF, rt.

Following this disappointing result, a two-step oxidation procedure was investigated. The first sequence to be investigated involved the use of the Parikh-Doering protocol[171] to oxidise the primary and secondary hydroxyl groups to the corresponding aldehyde and ketone followed by Pinnick oxidation[151] of the aldehyde to furnish the carboxylic acid **439** (Table 15). Unfortunately, this sequence failed at the first step leading to the decomposition of the starting material. TEMPO oxidation[172] was then used to accomplish the first step, but the use of sodium hypochlorite as the regenerating oxidant in a biphasic solvent system furnished only the starting material **438**. Interestingly using the same oxidant in homogeneous and anhydrous conditions, with $PhI(OAc)_2$ as the regenerating oxidant followed by chlorite oxidation led to the formation of **440** and **441** (Figure 22) in 90% overall yield. There was no oxidation of the secondary alcohol and competing oxidative cleavage of the diol gave the ketone **440**. Moreover, we assumed that the isomerisation of the epoxide to furnish the allylic alcohol **441** is due to the presence of acetic acid in the reaction released by oxidant.

First oxidation reagent	Second oxidation reagent	Lactone cyclisation reagent	Yield (%)
SO_3.Py, NEt_3, DMSO	$NaClO_2$	-	Decomposed
TEMPO, $^tBu_4NBr$, DCM, NaOCl, $NaHCO_3$, NaCl.	-	-	**438**
TEMPO, $PhI(OAc)_2$, DCM	$NaClO_2$	CSA	50% **440**, 40% **441**

Table 15. Conditions used for the oxidation of the triol **438**.

[171] Magnus, P.; Mendoza, J. S.; Stamford, A.; Ladlow, M.; Willis, P. *J. Am. Chem. Soc.* **1992**, *114*, 10232.
[172] (a) Siedlecka, R.; Skarzewski, J.; Mochowski, J. *Tetrahedron Lett*. **1990**, *31*, 2177. (b) De Nooy, A. E. J.; Besemer, A. C.; Van Bekkum, H. *Synthesis* **1996**, 1153.

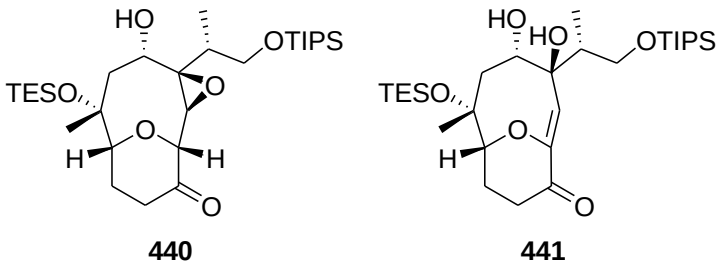
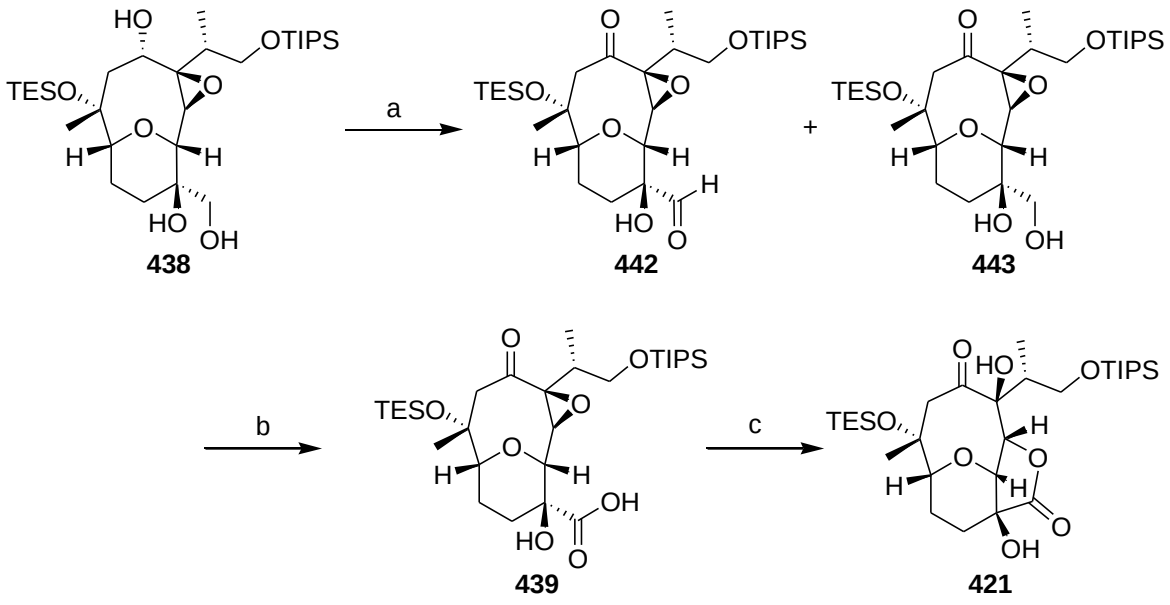


Figure 22. Side products formed during the TEMPO oxidation on **438.**

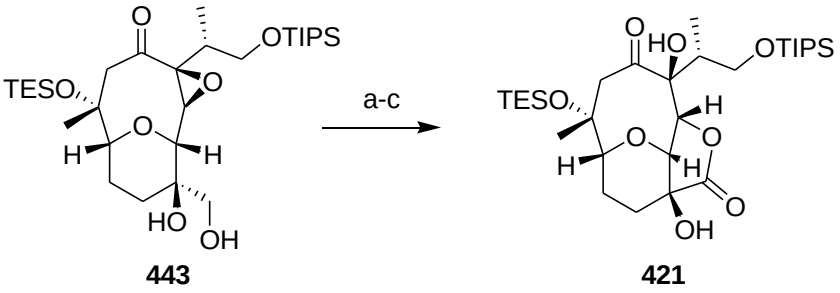
The reagent used to obtain the correct oxidation state at both sites was Dess-Martin periodinane, which gave the corresponding keto-aldehyde **442**. Chlorite oxidation of **442** gave the carboxylic acid **439**. Treatment of **439** with CSA resulted in the cyclisation onto the epoxide to give the lactone **421** in 29% yield over 3 steps (Scheme 128). During the purification process, a side product **443** was isolated in 39% yield. It appeared that **443** resulted from mono-oxidation of the secondary alcohol to give the ketone as the first step in the sequence. This result suggests that the primary hydroxyl group on triol **438** is very difficult to oxidise, probably due to the extremely hindered environment of the diol and likely strong H-bonding with the tertiary alcohol which made reaction of the Dess-Martin reagent with the secondary hydroxyl group more facile.



Scheme 128. Conditions: (a) DMP, DCM, 5 h, rt. (b) $NaClO_2$, $NaH_2PO_4.H_2O$, 2-methyl-2-butene, ^{t}butanol, H_2O, rt. (c) CSA, DCM, rt, 45 min, 29% **421** (3 steps), 39% **443**.

Fortunately, it was possible to undertake the same sequence of oxidation steps with **443**, as previously shown. Reaction with DMP furnished the corresponding aldehyde

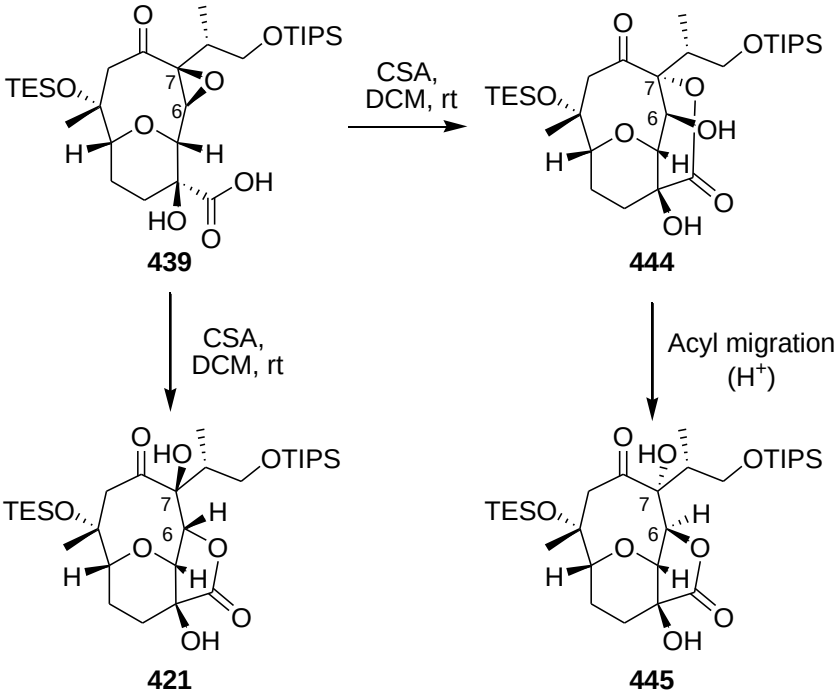
followed by Pinnick oxidation[151] to deliver the carboxylic acid **439**. Subsequent treatment with CSA resulted in cyclisation to deliver the tricyclic core **421** of the natural product (Scheme 129).



443 **421**

Scheme 129. Conditions (a) DMP, DCM, 5 h, rt. (b) $NaClO_2$, $NaH_2PO_4.H_2O$, 2-methyl-2-butene, ^{t}butanol, H_2O, rt. (c) CSA, DCM, rt, 45 min, 30% **421** (3 steps).

The major problem with assigning the structure of the lactone **421** was centred upon the mode of cyclisation. In principle, both the 5-*exo* and the 6-*endo* modes of cyclisation were possible. The IR spectrum of the cyclisation product showed a peak at 1791 cm^{-1} which is indicative of a five-membered lactone, but it is conceivable that two different products may be isolated. Compound **421** having the relative stereochemistry found in the natural product at carbons 6 and 7 would arise from direct 5-*exo* cyclisation of the acid onto the epoxide (Scheme 130). Compound **445** would arise from the 6-*endo* cyclisation to form **444** followed by acyl group migration to the secondary hydroxyl group to form the lactone **445** which would have incorrect stereochemistry at the carbons 6 and 7.



Scheme 130. Possible acid-catalysed direct 5-*exo* cyclisation and 6-*endo* cyclisation with acyl group migration.

The key spectroscopic data indicating formation of the lactone **421** is the magnitude of the coupling constant between proton **a** and **b** and how they relate to the natural product (Figure 23). The previous co-worker[154] who synthesised lactone **420** had encountered a similar problem and in order to validate the relative stereochemistry of **420**, he had synthesised the lactone **447** which should have a similar coupling constant to the tricyclic core resulting from 6-*endo* cyclisation. With this coupling constant information, we were in the position to compare and to validate the relative stereochemistry of our lactone intermediate **421** with the lactone **447** and the natural product methyl ester **446.** The ^{1}H NMR data shows a coupling constant of 4.7 Hz for **421** which correlates well with the corresponding *J* value in the methyl ester **446** of the natural product (5.3 Hz). In contrast, the lactone **447** has a considerably larger constant coupling between $H_{\mathbf{a}}$ and $H_{\mathbf{b}}$ than in lactone **421** and **446**. Based on this, the lactone generated as shown in Scheme 128 and 129 has been confidently assigned as compound **421**. Therefore, all three rings of the natural product have been synthesised with the correct stereochemistry.

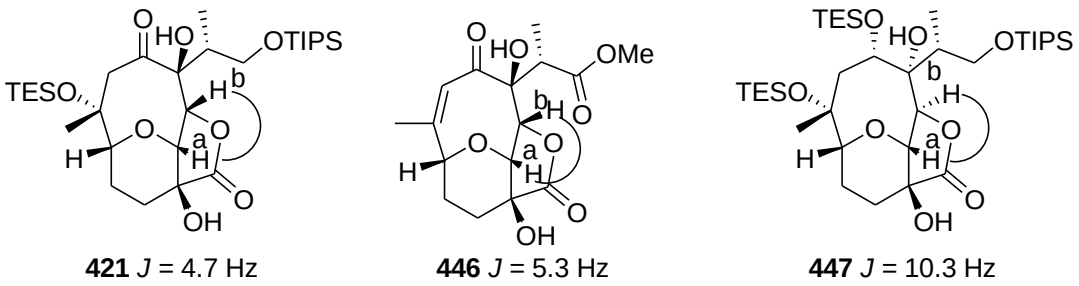
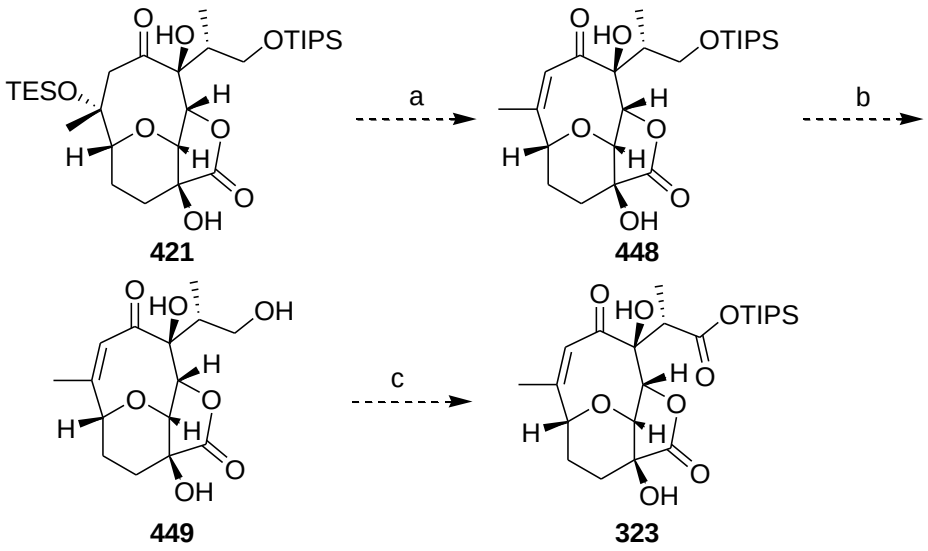


Figure 23. Comparaison of coupling constant of key protons.

4 Attempts to complete the synthesis of neoliacinic acid.

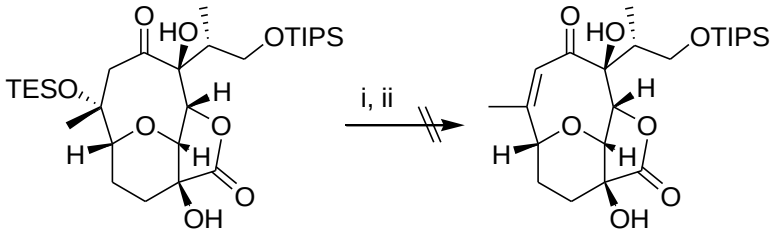
Following successful synthesis of the tricyclic lactone **421,** attention turned to the completion of the synthesis and in particular the introduction of the *α*,*β*-unsaturated ketone (Scheme 131). The steps towards neoliacinic acid involve the elimination of the silyl ether to give the enone product **448**. Deprotection of the primary alcohol followed by oxidation to the carboxylic acid which would then give the natural product neoliacinic acid **323**.



Scheme 131. Conditions: (a) Elimination. (b) Deprotection. (c) Oxidation.

β-Elimination of a silyl ether to furnish *α*-*β*-unsaturated ketones has been described in the literature. There have been many reports showing that *β*-silyloxy ketones

can be converted into the corresponding enone by the use of DBU.[173] With these encouraging examples as a precedent, we decided to follow this strategy and the formation of the enone system was attempted by treatment of **421** using experimental procedures described in the literature. Unfortunately the elimination reaction did not give reproducible results on our substrate and the reaction led only to the decomposition of the starting material. As a consequence of the lack of reactivity under basic conditions, acid conditions[174] were also investigated. However, treatment of **421** with *p*-TsOH led to decomposition and starting material was not recovered (Scheme 132).



421 **448**

Scheme 132. Condition (i) DBU DCM, rt, 5 h. (ii) *p*-TsOH, toluene, rt, 2 h.

As a consequence of these disappointing results, it was decided to change our strategy. In 1970, Burgess *et al.*, discovered that treatment of secondary and tertiary alcohols with the salt of (methoxycarbonylsulfamoyl)triethylammonium hydroxide caused their smooth dehydration to give the corresponding olefins.[175] Reports in the literature show that the Burgess reagent is a powerful dehydrating agent in various situations[176] and has also proved to be efficient for the synthesis of α,β-unsaturated ketones.[177] Inspired by these examples, a new strategy was conceived in which the Burgess reagent would be used to perform a selective dehydration of the tertiary alcohol **450** to form the desired enone **448**. To attempt this, the required alcohol needed to be prepared by selective deprotection (Scheme 133). After selective deprotection, it was anticipated that because of the likely

[173] (a) Hodgson, D. M.; Galano, J.-M.; Christlieb, M. *Chem. Commun.* **2002**, 2436. (b) Usuda, H.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 3621. (c) Hareau, G. P.-J.; Koiwa, M.; Hikichi, S.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 3640. (d) Hagiwara, H.; Sakai, H.; Uchiyama, T.; Ito, Y.; Morita, N.; Hoshi, T.; Suzuki, T.; Ando, M. *J. Chem. Soc., Perkin Trans. 1*, **2002**, 583. (e) Ito, H.; Takeguchi, S.; Kawagishi, T.; Iguchi, K. *Org. Lett.* **2006**, *8*, 4883.

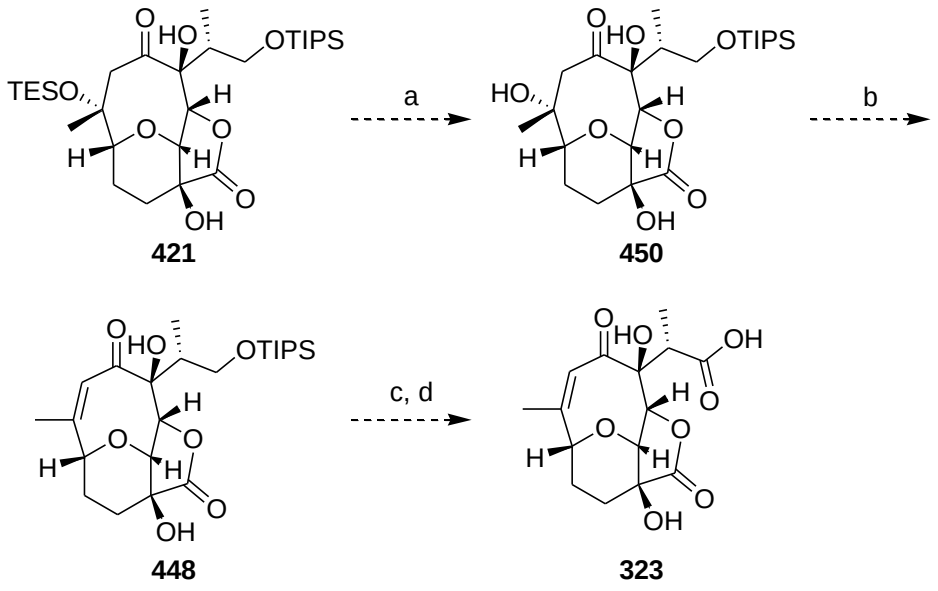
[174] Liao, C.-C.; Zhu, J.-L. *J. Org. Chem.* **2009**, *74*, 7873.

[175] (a) Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Org. Chem*. **1973**, *38*, 26. (b) Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Am. Chem. Soc*. **1970**, *92*, 5224.

[176] Carrets, S.; Blanc, A.; Coquerel, Y.; Berthod, M.; Greene, A. E.; Deprés, J. –P. *Angew. Chem. Int. Ed.* **2005**, *44.* 5130.

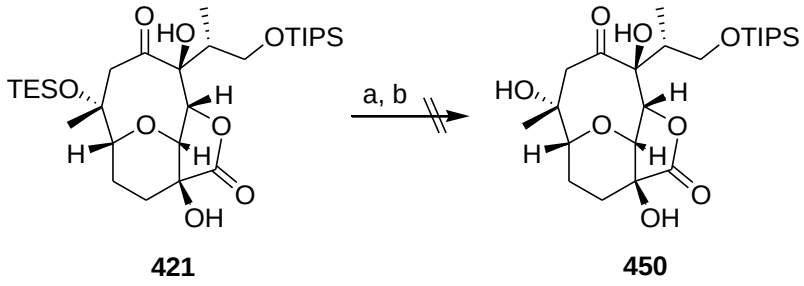
[177] Shiina, I.; Iwadare, H.; Saitoh, M.; Ohkawa, N.; Nishimura, T.; Mukaiyama, T. *Chemistry Letters* **1995**, 781.

strong H-bonding between the alcohols at the α-position of the carbonyl functions, the more reactive and the more accessible hydroxyl group of **450** to the reagent would be the alcohol at the β-position of the ketone. Then, as previously, full deprotection and oxidation would give the target molecule **323** (Scheme 133).



Scheme 133. Conditions: (a) Selective deprotection. (b) Burgess reagent. (c) Deprotection. (d) Oxidation.

Due to the previously observed reactivity of the TIPS protecting group, it was expected that the first free alcohol formed would be the primary alcohol and then removal of TES group would follow. Therefore a two step sequence was investigated in which firstly full desilylation would furnish the tretraol and then without purification, reprotection of the primary alcohol would give the desired triol **450**. Unfortunately, following the conditions shown in Scheme 134, none of the desired compound was isolated and reactions led to the decomposition of the lactone during deprotection.



Scheme 134. Conditions: (a) HF.Pyr, Pyridine, THF, 2 h, rt, (b) TIPSCl, imid., DMF, 12 h, rt.

As a consequence to the difficulties encountered when trying to convert the tertiary silyl ether **421** into the corresponding *α,β*-unsaturated ketones **448**, we ran out of material. Unfortunately, the lack of product occurred during the end of third year of work and there was not enough time remaining to synthesise gram quantities of the desired lactone **421** necessary to find the best conditions for the next transformation. Consequently, it was decided to stop our studies in the laboratory and the lactone **421** was the last compound synthesised during this three years of work.

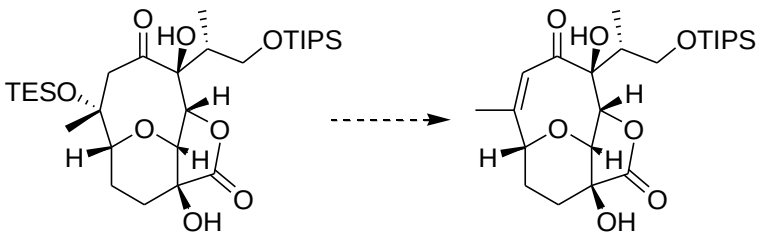
5 Conclusion.

A new efficient synthesis has been developed to construct the allylic silane **357**. The synthesis is two steps longer than the route involving organocerium reaction, but is both more efficient and reproducible with excellent yields for each step.

Two metal carbenoid reactions have been utilised to construct the oxabicyclic core of the target molecule in a novel and efficient manner. The strategy utilised tandem oxonium ylide formation and [2,3]-sigmatropic rearrangement for ring formation with concomitant ring expansion to give the required [5.3.1]-oxabicyclic core. In addition, a stereoselective C–H insertion reaction was used to generate the required tetrahydrofuran ring in the precursor. Finally, formation of the three rings with incorporation of all six stereocentres present in the natural product gave the tricyclic core of the natural product in a total of 24 steps from methyl (*R*)-(-)-3-hydroxy-2-methylpropionate **354**. However, attempts to install the *α,β*-unsaturated ketone in the bridged tricyclic system failed because of an inability to remove the triethylsilyl protecting group.

6 Future Work.

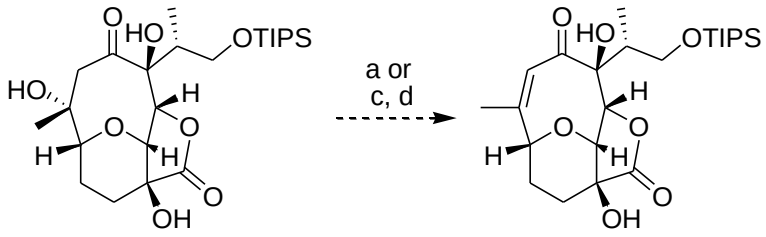
Future work would concentrate on incorporating the *α,β*-unsaturated ketone into the main tricyclic system of neoliacinic acid. The incorporation of the enone in the presence of the lactone ring by elimination of the triethylsilyl ether group has proven to be difficult. The first attempts would involve a screening of various basic and acid reagents using a range of protocols in order to identify the best elimination conditions of the silyl ether to give *α,β*-unsaturated ketone **448**(Scheme 135).



421 **448**

Scheme 135.

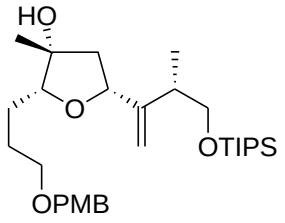
An alternative solution would be to obtain the hydroxyl ketone **450** possessing a free hydroxyl group at the *β*-position of the ketone. It is anticipated that the alcohol would be more accessible and hence more reactive than the two other hydroxyl groups that lie at the *α*-position of the carbonyls groups. With this compound, two different alternative routes to obtain the enone are apparent: (i) Direct dehydration using the Burgess reagent or (ii) introduction of a good leaving group (e.g. a triflate or mesylate) followed by treatment under basic conditions (Scheme 136).



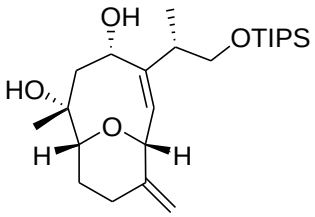
450 **448**

Scheme 136. Conditions: (a) Burgess reagent. (b) Formation of the leaving group. (c) Elimination in basic condition.

The synthesis of the lactone **450** could be achieved by selective deprotection of the tertiary hydroxyl group. The two free hydroxyl groups of the allylic alcohol **413** (Figure 24) showed comparable reactivity, and selective protection is not possible. The appropriate substrate for the selective protection would be the tetrahydrofuran **395** (Figure 24) where only one free hydroxyl group is available.



395



413

Figure 24.

However, the choice of protecting group will be crucial to enable differentiation with it and the primary TIPS group during the deprotection. Consequently, a silyl protecting group is not appropriate. A protecting group labile to acid conditions is also not appropriate and a bulky protecting group would also be unsuitable due to the hindered environment of the **395**. Therefore the group of choice would be a protecting group that is not hindered, is resistant to Lewis acid conditions and can be removed under mild basic conditions without affecting the TIPS group.

In the literature, methylthiomethyl ether (MTM) is quite stable to acid conditions and can be removed under mild basic conditions using sodium carbonate in aqueous solution and so would be a candidate protecting group in our synthesis.

Allyl esters provide well-established and highly reliable protecting groups for alcohols and acids.[178] Among others, allyoxycarbonyl-protected alcohols are frequently used and would also afford the required differentiation to obtain **450**. Their deprotection is achievable in the presence of catalytic amounts of tetrakistriphenylphosphine palladium or related soluble Pd complex in aprotic solvent.[179]

The route outlined in Scheme 137 shows two possible synthetic options where an allyl carbonate or an MTM ether could be introduced into the alcohol **395** to form **452**.[179,180] Following the same strategy described previously, the relative stereochemistry of the allylic alcohol **453** and **454** would need to be confirmed. Inversion of configuration of the hydroxyl group may be required using the Mitsunobu protocol to obtain only **453**. Then

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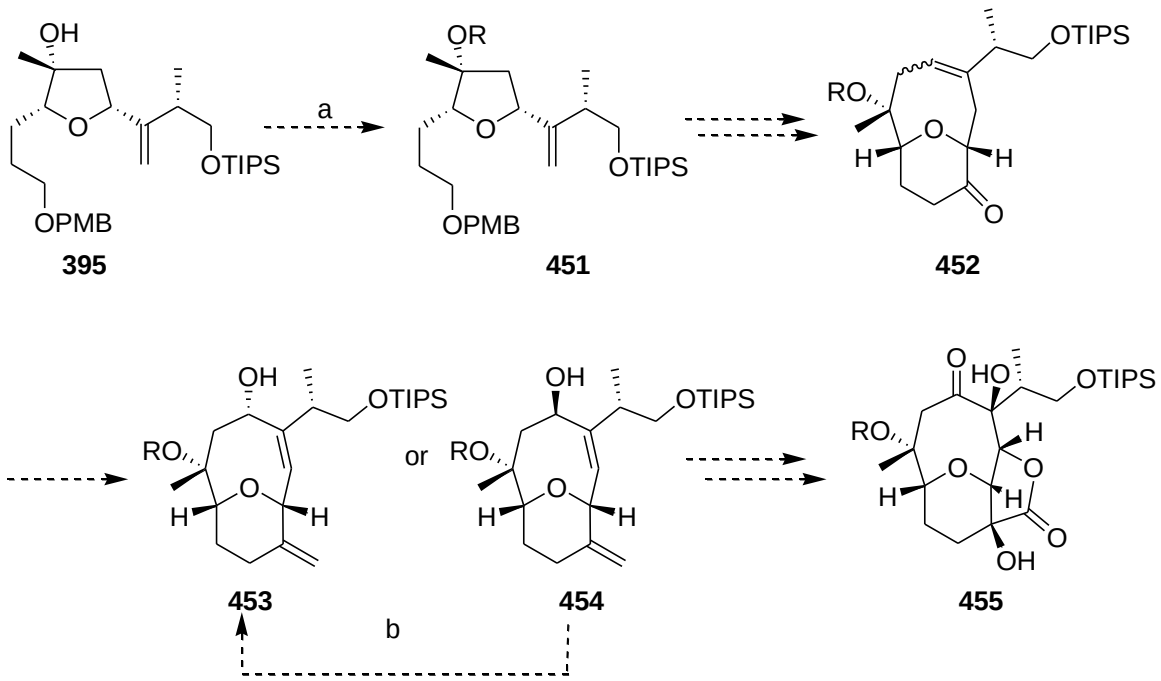
[178] Guibé, F. *Tetrahedron* **1998**, *54*, 2967.

[179] (a) Michelet, V.; Adiey, K.; Tanier, S.; Dujardin, G.; Genêt, J. P. *Eur. J. Org*. **2003**, 2947. (b) Takano, D.; Nagamitsu, T.; Ui, H.; Shiomi, K.; Yamaguchi, Y.; Masuma, R.; Kuwajima, I.; Omura, S. *Org. Lett.* **2001**, *3*, 2289. (c) Kang, Y.; Lou, C.; Ahmed, K. B. R.; Huang P.; Jin, Z. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 5166. (d) Boullanger, P.; Chatelard, P.; Descotes, G.; Kloosterman, M.; Van Boom, J. H. J. *J. Carbohydr. Chem.* **1986**, *5*, 541. (e) Shiozaki, M.; Iwano, Y.; Doi, H.; Tanaka, D.; Shimozato, T.; Kurakata, S. –I. *Carbohydr. Res.* **2006**, *341*, 811. (f) Minami, I.; Tsuji, J. *Tetrahedron* **1987**, *43*, 3903. (g) Genêt, J. P.; Blart, E.; Savignac, M.; Lemeune, S.; Lemaire-Audoire, S.; Paris, J. M. ; Bernard J. –M. *Tetrahedron*, **1994**, *50*, 497.

[180] (a) Corey, E. J.; Bock, M. G. *Tetrahedron Lett.* **1975**, 3269. (b) Yamada, K.; Kato, K.; Nagase, H.; Hirata, Y. *Tetrahedron Lett.* **1976**, *1*, 65. (c) Pojer, P. M.; Angyal, S. J. *Aust. J. Chem.* **1978**, *31*, 1031.

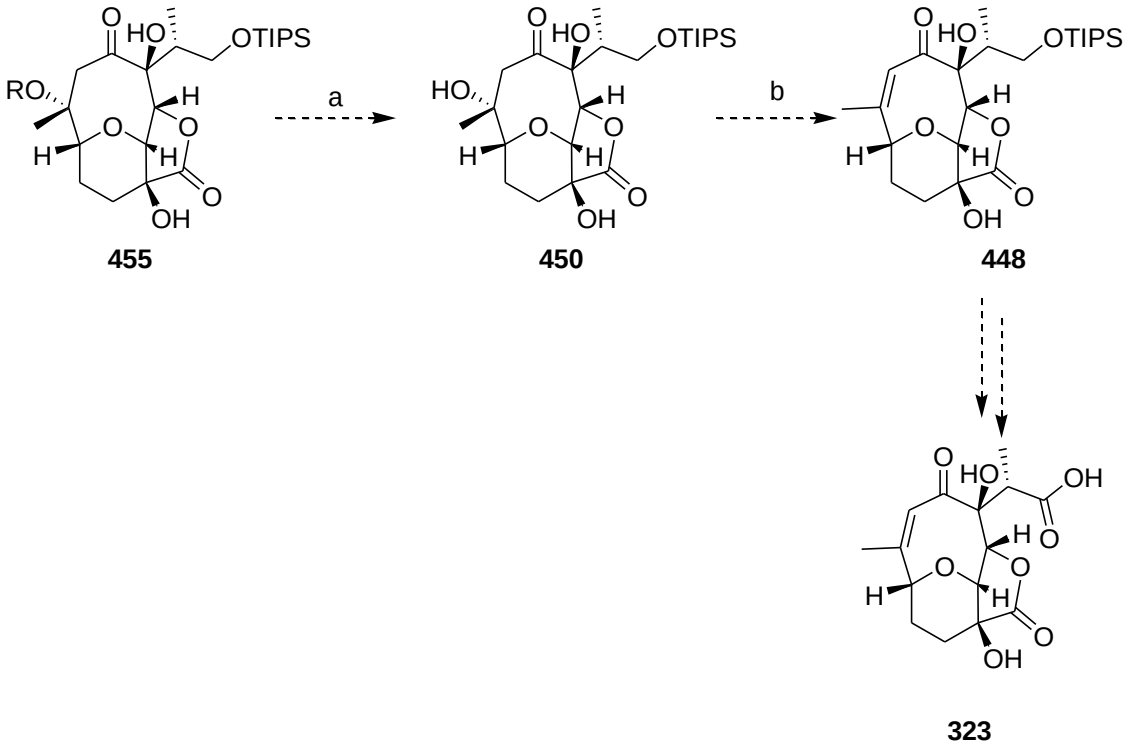
using the same optimised synthetic route as described previously, it would be possible to construct the lactone **455**.



Scheme 137. Conditions (a) R = MTM; NaH, DME, CH_3SCH_2Cl, NaI, 0 °C. R = $CO_2CH_2CH{=}CH_2$; $ClCO_2CH_2CH{=}CH_2$, base, THF, –78 °C to rt. (b) Mitsonobu inversion.

Then following the revised strategy, the next step would be the selective deprotection of the tertiary hydroxyl group. If the protecting group R is an MTM ether function, treatment of **455** with the sodium carbonate[181] would result in the selective deprotection of the tertiary hydroxyl without affecting the primary TIPS group to furnish the triol **450**. If R is an allyloxycarbonyl group, selective deprotection would be undertaken under mild conditions using $Pd(PPh_3)_4$, HCO_2H, Et_3N to give the triol **450**.[179] Subsequent reaction with the Burgess reagent or formation of a good leaving group, followed by treatment with base could furnish **448**. Full deprotection and oxidation would give neoliacinic acid **323** (Scheme 138).

[181] (a) Kozaki, S.; Sakanaka, O.; Yasuda, T.; Shimizu, T.; Ogawa, S.; Suami, T. *J. Org.* Chem. **1988**, *53*, 281.



Scheme 138. Conditions: (a) R = MTM, MeI, Acetone, H_2O, $NaHCO_3$. R = $CO_2CH_2CH{=}CH_2$, HCO_2H, Et_3N, catalytic $Pd(PPh_3)_4$,THF. (b) Burgess reagent.

Chapter III Experimental Part

Apparatus

NMR spectra were recorded on a Bruker 400 MHz Spectrospin spectrometer (^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz) and on a Bruker 500 MHz Spectrospin spectrometer (^{1}H NMR at 500 MHz and ^{13}C NMR at 125 MHz). The chemical shifts are reported in ppm. ^{1}H NMR spectra were recorded with $CDCl_3$ as solvent using (δ = 7.26) as internal standard, and for the ^{13}C NMR spectra, the chemical shifts are reported relative to the central resonance of $CDCl_3$ (δ = 77.16).

Nomenclature

Compounds were named according to the IUPAC rules, whereas numbering of the carbons has been done independently to these rules to help at their identification.

Chromatography

Column chromatography was performed under pressure using silica gel as solid support and analytical solvents as eluent. The reactions were monitored by thin-layer chromatography (TLC) on Fisher and Merck silica gel 60 covered alumina plates. The TLC plates were developed under UV-light and/or with phosphomolybdic acid hydrate solution (formed by dissolving 5 g phosphomolybdic acid hydrate ($H_3Mo_{12}O_{40}P \times H_2O$) in EtOH (96%) (100 mL) or using a $KMnO_4$-solution (3 g $KMnO_4$, 20 g K_2CO_3, 5 mL 5% NaOH (aq) and 300 mL H_2O) or an ammonium molybdate solution (ammonium molybdate (5 g), ceric sulfate (0.2 g), 5% aq H_2SO_4 (100 mL)) or in an anisaldehyde solution (anisaldehyde (15 g), EtOH (250 mL), concentrated H_2SO_4 (2.5 mL)).

Solvents and Reagents

Liquid reagents were distilled prior to use if needed. All reagents were purchased from commercial suppliers and used without further purification except where it is stated.

General Reaction Conditions

Reactions involving air-sensitive reagents and dry solvents were performed in glassware dried in an oven (120 °C) or flame dried prior to use. These reactions were carried out with the exclusion of air using a nitrogen or an argon atmosphere.

Petasis reagent.[133]

Methyl magnesium iodide (1.0 M solution in Et_2O, 20 mL, 20 mmol) was added dropwise over 10 min to a solution of Cp_2TiCl_2 (2.0 g, 8.0 mmol) in dry Et_2O (20 mL) under Ar. The rate of the addition was adjusted to maintain an internal temperature of 0 to 5 °C. The reaction was allowed to stir at 0 °C for 3 h, until the insoluble purple Cp_2TiCl_2 was no longer seen in suspension. The mixture was carefully quenched by the addition of cold water (10 mL). The solution was extracted with Et_2O (3 × 20 mL). The ether extracts were combined and washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give the Petasis reagent as orange crystals. To conserve the reagent, it was diluted in dry THF (8 mL) to give a 1.0 M solution. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (10 H, s, CH-Ar), -0.14 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.5 (CH-Ar), 45.9 (CH_3).

Tetrakis(triphenylphosphine)palladium (0).[146]

Triphenylphosphine (14.0 g, 56.3 mmol) was added to a solution of palladium dichloride (2.00 g, 11.2 mmol) in dry DMF (180 mL) under Ar. The yellow mixture was heated under reflux until complete disolution occurred. Hydrazine hydrate (1.83 mL, 44.8 mmol) was added rapidly and the dark solution was crystallised at 0 °C to give yellow crystals. The mixture was filtered under Ar, and the solid was washed successively with MeOH (2 × 50 mL) and ether (2 × 50 mL). The solid was dried under high vacuum for 12 h to give tetrakis(triphenylphosphine)palladium (0) as a yellow crystalline product (12.28 g, 95%).

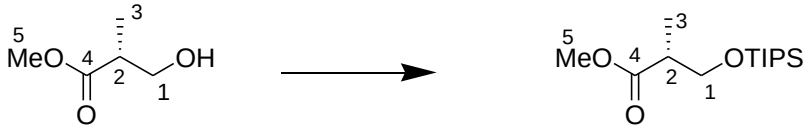
Rhodium dimer trifluoroacetamide.[182]

A 0.50 g (1.16 mmol) of $Rh_2(O_2CH_3)_4$ was mixed with 15.0 g (11.3 mmol) of 2,2,2-trifluoroacetamide in a 100-mL round bottom flask. The flask was fitted with a condenser and placed in an oil bath at 100 °C. The mixture was magnetically stirred at this temperature for 6 h. The originally deep blue solution slowly turned reddish purple during the reaction. After the reaction was complete, the excess of 2,2,2-trifluoroacetamide was removed by sublimation (80 °C under high vacuum) and column chromatography (MeOH) on alumina gel gave the rhodium dimer trifluoroacetamide (0.45 mg, 60%) as a purple solid.

Comins Reagent.[144,145]

To a mixture of *N*-(5-chloro-2-pyridyl)triflimide (14.7 g, 114 mmol) and pyridine (18.5, 229.0 mmol) in dry DCM (150 mL) under Ar at –78 °C was added triflic anhydride (38.6 mL, 229 mmol). The mixture was allowed to stir for 19 h warming to rt during this time. The reaction was quenched with cold water (60 mL) and the aqueous layer was extracted with DCM (4 × 60 mL). The organic extracts were combined and washed with 10% sodium hydroxide (60 mL), water (60 mL) and brine (60 mL), then dried ($MgSO_4$) and concentrated in *vacuo* to give the crude reagent. Sublimation under high vacuum (100 °C) gave the clean Comins reagent (28.00 g, 62%) as a colour less solid.

Methyl (*R*)-(-)-3-triisopropysilyloxy-2-methylpropionate 355.[127]



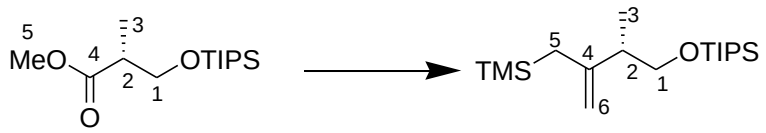
354 **355**

Triisopropylsilylchloride (41.2 g, 214.0 mmol) was added over 10 min to a solution of methyl (*R*)-(-)-3-hydroxy-2-methylpropionate **354** (25.28 g, 214.0 mmol) and imidazole (30.0 g, 440 mmol) in dry DMF (75 mL) at rt under Ar. The mixture was stirred at rt for 5

[182] Dennis, A. M.; Korp, J. D.; Bernal, I.; Howard, R. A.; Bear, J. L. *Inorg. Chem.* **1983**, *22*, 1522.

days then poured into a two-phase mixture of water (70 mL) and ether (200 mL). The organic layer was separated and the aqueous layer extracted with ether (2 × 200 mL). The ether extracts were combined and washed with water (2 × 150 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated in *vacuo* to give a colourless oil. Vacuum distillation (80 °C at 0.5 mmHg, [Lit. [159] 86 °C at 0.5 mmHg]) gave the silyl ether **355** (55.7 g, 95%) as a colourless oil. R_f = 0.56 (95:5 pet. ether–EtOAc); $[\alpha]_D^{20}$ –20.5 (*c* = 1.55, $CHCl_3$) [Lit[159] $[\alpha]_D^{24}$ –19.7 (*c* = 1.17, $CHCl_3$)]; ν_{max} 2943, 2893, 2866, 1743, 1462, 1197, 1105 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.86 (1H, dd, *J* = 9.5, 6.7 Hz, CH_2-C1), 3.76 (1H, dd, *J* = 9.5, 6.0 Hz, CH_2-C1), 3.67 (3H, s, CH_3-C5), 2.66 (1H, qdd, *J* = 7.0, 6.7, 6.0 Hz, CH-C2), 1.15 (3H, d, *J* = 7.0 Hz, CH_3-C3), 0.99–1.10 (21H, m, ^{i}Pr-TIPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7 (C-C4), 64.8 (CH_2-C1), 50.7 (CH_3-C5), 41.9 (CH-C2), 17.0 (CH_3-TIPS), 13.0 (CH_3-C3), 12.2 (CH-TIPS); HRMS (FAB) for $C_{14}H_{30}O_3Si$ [M^+] Calcd 274.1964, found 274.1967.

(-)-(*S*)-2-Methyl-3-(trimethylsilylmethyl)-1-triisopropylsilyloxybut-3-ene 357.[127]



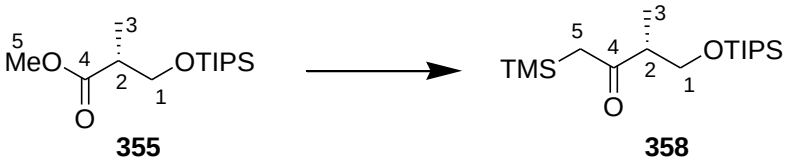
355 **357**

Cerium(III) chloride heptahydrate (60.0 g, 160 mmol) was added to a 1 L 3-necked round bottom flask and dried under vacuum at 130 °C overnight. The flask was allowed to cool and purged with Ar for 2 min and equiped for mechanical stirring. Dry THF (320 mL) was then added slowly and the mixture was sonicated for 2 h followed by one hour of stirring at rt under Ar to gave the Ce/THF complex (as a white precipitate).

A solution of chloromethyl(trimethylsilane) (22.16 mL, 160.0 mmol) in dry THF (150 mL) was added dropwise to a stirred suspension of Mg (3.86 g, 160 mmol) and iodine (1 crystal) in dry THF (10 mL) under Ar. The formation of the Grignard reagent was accomplished by heating the mixture under reflux, then slow addition of the halide over 30 min to maintain the reflux. The Grignard reagent was stirred at rt for 2 h, then added over 5 min to the Ce/THF mixture at –78 °C under Ar. The grey solution was stirred for 90 min, then the ester **355** (8.40 g, 32.0 mmol) in dry THF (40 mL) was added over 2 min at –78

°C. The reaction was allowed to stir at –78 °C for 2 h, then removed from the cold bath and allowed to warm to rt overnight. The reaction was quenched by a dropwise addition of aqueous hydrochloric acid solution (160 mL of 1.0 M solution) at 0 °C, and then stirred for 20 min. The mixture was extracted with ether (2 × 150 mL), the ether extracts were combined and washed with water (150 mL) and brine (150 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Column chromatography (Pet. ether) gave the allylic silane **357** (9.03 g, 86%) as a colourless oil. R_f = 0.67 (Pet. ether); $[\alpha]_D^{20}$ – 21.8 (*c* = 1.01, $CHCl_3$) [Lit.[127] $[\alpha]_D^{25}$ –22.0 (*c* = 0.50, $CHCl_3$)]; ν_{max} 2944, 1866, 1464, 1247, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.59 (2H, d, *J* = 9.7 Hz, CH_2-C6), 3.73 (1H, dd, *J* = 9.4, 4.9 Hz, CH_2-C1), 3.43 (1H, dd *J* = 9.4, 7.0 Hz, CH_2-C1), 2.09 (1H, qdd, *J* = 7.0, 7.0, 4.9 Hz, CH-C2), 1.56 (2H, d, *J* = 13.5 Hz, CH_2-C5), 1.06–1.03 (24H, m, CH_3-C3, ^{i}Pr-TIPS), 0.01 (9H, s, CH_3-TMS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2 (C-C4), 107.4 (CH_2-C6), 69.4 (CH_2-C1), 43.8 (CH-C2), 28.3 (CH_2-C5), 19.3 (CH_3-TIPS), 17.4 (CH_3-C3), 13.3 (CH-TIPS), 1.3 (CH_3-TMS); HRMS (CI, isobutane) for $C_{18}H_{41}OSi_2$ $[M+H]^+$, Calcd 329.2696, found 329.2698.

(*R*)-3-Methyl-4-(triisopropylsilyloxy)-1-(trimethylsilyl)butan-2-one 358.

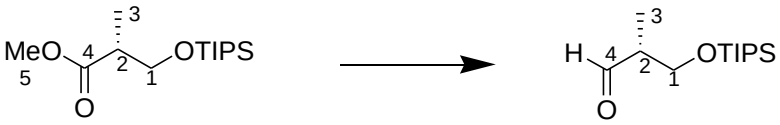


TMSOK (0.51 g, 4.00 mmol) was added to a solution of the ester **355** (1.00 g, 3.64 mmol) in dry Et_2O (16 mL) and the mixture was stirred for 24 h. A solution of HCl (1M, 10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 10 mL). Combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give a colorless oil The crude acid was diluted in dry DCM and DMF (3 drops) followed by oxalyl chloride (1.58 mL, 18.2 mmol) were added dropwise under Ar. The mixture was stirred for 3 h, concentrated *in vacuo*, and the residue was dissolved in dry THF (30 mL).

A solution of chloromethyl(trimethylsilane) (1.00 mL, 7.28 mmol) in dry THF (7.00 mL) was added dropwise to a stirred suspension of Mg (0.17 g, 7.28 mmol) and iodine in dry ether (0.50 mL) under Ar. Heating the mixture under reflux, then slow addition of the halide to maintain the reflux accomplished formation of the Grignard reagent. The Grignard reagent was stirred at rt for 2 h under Ar. The Grignard reagent was

added dropwise at –78 °C under Ar, and the reaction stirred over night under Ar, warming to rt during this time. The reaction was cooled to 0 °C and quenched with a saturated aqueous solution of ammonium chloride (10 mL). The aqueous layer was separated and extracted with ether (3 × 10 mL). The ether extracts were washed with water (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to deliver a yellow oil. Flash chromatography on silica gel (Pet. ether) gave the ketone **358** (0.30 g, 25%) as a colourless oil. R_f = 0.65 (95:5 pet. ether–EtOAc) ν_{max} 2943, 2866, 1735, 1242, 1176, 1099 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.90 (1H, dd, *J* = 9.2, 6.4 Hz, CH_2-C1), 3.76 (2H, d, *J* = 7.6 Hz, CH_2-C5), 3.71 (1H, dd, *J* = 9.4, 6.4 Hz, CH_2-C1), 2.68 (1H, m, CH-C2), 1.16 (3H, d, *J* = 6.8 Hz, CH_3-C3), 1.04 (21H, m, ^{i}Pr-TIPS), 0.06 (9H, c, CH_3-TMS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6 (C-C4), 64.7 (CH_2-C1), 56.7 (CH_2-C5), 41.9 (CH-C_2), 16.9 (CH_3-TIPS), 12.7 (CH_3-C3), 10.9 (CH-TIPS), -4,0 (CH_3-TMS).

(*R*)-2-methyl-3-(triisopropylsilyloxy)propanal 366.[183]



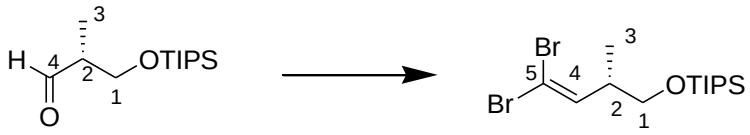
355 **366**

To a solution of the ester **355** (500 mg, 1.82 mmol) in dry DCM (10 mL) at –100 °C was added dropwise DIBAL (2.7 mL, 1.0 M solution in hexane, 2.7 mmol) under Ar. After 1 h at –100 °C, the reaction was quenched with MeOH (5 mL) and a saturated solution of potassium sodium tartrate (5 mL), and the mixture was then diluted with DCM (10 mL). The layers were separated and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic extracts were washed with water (10 mL), and brine (10 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Flash chromatopraphy on silica gel (Pet. ether–EtOAc 19:1 to 3:1) gave the aldehyde **366** (0.288 mg, 64%) as a colourless oil. R_f = 0.40 (Pet. ether–EtOAc 9:1); $[\alpha]_D^{18}$ –33.5 (*c* = 1.35, $CHCl_3$) [Lit.[178] $[\alpha]_D^{25}$ – 35.6 (*c* = 0.45, $CHCl_3$)]; ν_{max} 2957, 2943, 2892, 1738, 1726, 1463, 1100, 881 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.17 (1H, d, *J* = 1.6 Hz, CH-C4), 3.91 (1H, dd, *J* = 10.0, 4.8 Hz, CH_2-C1), 3.8 (1H, dd, *J* = 10.0, 6.4 Hz, CH_2-C1), 2.46 (1H, qdd, *J* = 7.2, 6.4, 4.8 Hz, CH-C2), 1.05 (3H, d, *J* = 7.2 Hz, CH_3-C3), 0.98–0.97 (21H, m, ^{i}Pr-TIPS); ^{13}C

[183] Bonazzi, S.; Güttinger, S.; Zemp, I.; Kutay, U.; Gadermann, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 8707.

NMR (100 MHz, $CDCl_3$) δ 203.8 (C-C4), 62.9 (CH_2-C1), 48.0 (CH-C2), 17.1 (CH_3-TIPS), 17.0 (CH_3-C3), 10.6 (CH-TIPS); HRMS (CI, isobutane) for $C_{13}H_{29}O_2Si$ $[M+H]^+$, Calcd 245.1937, found 245.1934.

(*S*)-(4,4-dibromo-2-methylbut-3-enyloxy)triisopropylsilane 367.[184]

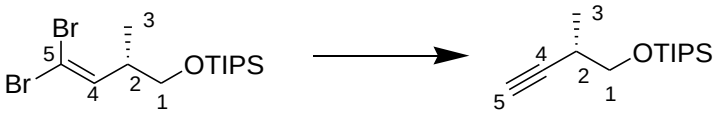


366 **367**

The Corey-Fuchs reagent was prepared by the addition of a solution of CBr_4 (700 mg, 2.11 mmol) in dry DCM (4 mL) at 0 °C under Ar and Ph_3P (1.1 g, 4.2 mmol) followed by stirring for 20 min. A solution of the aldehyde **366** (246 mg, 0.960 mmol) in dry DCM (4 mL) was added to the mixture and stirred at rt for 2 h. The reaction was quenched with a saturated solution of ammonium chloride (5 mL) and water (5 mL) then diluted with DCM (5 mL). The layers were separated and the aqueous layer was extracted with DCM (3 × 5 mL). The combined organic extracts were washed with water (5 mL), brine (5 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to a brown solid. Flash chromatography on silica gel (Pet. ether) gave the dibromo olefin **367** (273 mg, 79%) as a colourless oil. R_f = 0.40 (Pet. ether–EtOAc 19:1); $[\alpha]_D^{23}$ +15.7 (*c* = 1.29, $CHCl_3$) [Lit.[184] $[\alpha]_D^{26}$ +17.2 (*c* = 1.0, $CHCl_3$)]; ν_{max} 2941, 2891, 2864, 1462, 1105, 1068, 881, 781, 659 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.32 (1H, d, *J* = 9.2 Hz, CH-C4), 3.60 (2H, dd, *J* = 6.0, 3.6 Hz, CH_2-C1),2.65 (1H, m, CH-C2), 1.06–1.02 (24H, m, ^{i}Pr-TIPS, CH_3-C3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5 (CH-C4), 88.3 (C-C5), 66.3 (CH_2-C1), 41.2 (CH-C2), 17.9 (CH_3-TIPS), 15.5 (CH_3-C3), 12.5 (CH-TIPS); HRMS (EI) for $C_{11}H_{21}OSi^{79}Br_2$ $[M–C_3H_7]^+$, Calcd 354.9728, found 354.9731.

[184] Komatsu, K.; Tanino, K.; Miyashita,M. *Angew. Chem. Int. Ed.* **2004**, *43*, 4341.

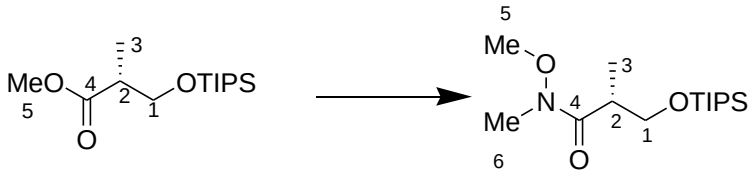
(*S*)-triisopropyl(2-methylbut-3-ynyloxy)silane 368.



367 **368**

To a solution of the dibromo olefin **367** (274 mg, 0.75 mmol) in dry THF (3 mL) at –78 °C under Ar was added *n*-BuLi (800 µL of a 2.0 M solution in hexane, 1.97 mmol). The solution was allowed to warm to rt over 2 h. The reaction was cooled to –78 °C and quenched with a saturated solution of ammonium chloride (1 mL). The aqueous layer was extracted with ether (3 × 3 mL). The combined organic extracts were washed with water (5 mL), brine (5 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Flash chromatography on silica gel (Pet. ether) gave the alkyne **368** (76 mg, 50%) as a colourless oil. R_f = 0.40 (Pet. ether–EtOAc 9:1); $[\alpha]_D^{24}$ –2.3 (*c* = 0.85, $CHCl_3$); ν_{max} 3313, 2943, 2866, 2362, 2007, 1464, 1099, 881 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.72 (1H, dd, *J* = 9.4, 5.6 Hz, CH_2-C1), 3.48 (1H, dd, *J* = 9.4, 8.0 Hz, CH_2-C1), 2.58–2.49 (1H, m, CH-C2), 1.96 (1H, d, *J* = 2.4 Hz, CH-C5), 1.10 (1H, d, *J* = 7.2 Hz, CH_3-C3), 1.03–0.99 (21H, m, ^{i}Pr-TIPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 85.8 (C-C4), 67.8 (CH-C5), 66.2 (CH_2-C1), 28.0 (CH-C2), 16.9 (CH_3-TIPS), 16.2 (CH_3-C3), 11.6 (CH-TIPS); HRMS (CI, isobutane) for $C_{14}H_{29}OSi$ $[M+H]^+$, Calcd 241.1988, found 241.1990.

(*R*)-N-methoxy-N,2-dimethyl-3-(triisopropylsilyloxy)propanamide 380.[185]



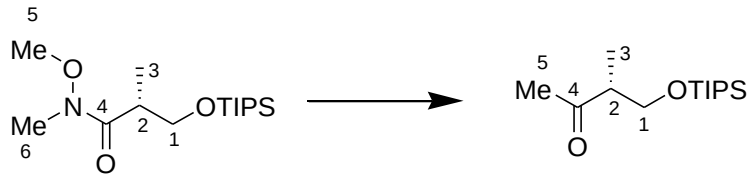
355 **380**

To a mixture of ester **355** (40.00 g, 145.4 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (18.00 g, 195.5 mmol) in dry THF (300 mL) at –20 °C was added dropwise *i*-PrMgBr (365 mL, 1.0 M solution in THF, 365 mmol) under Ar. After 1 h at –20 °C, the

[185] Paterson, I.; Oballa, R. M. *Tetrahedron Lett.* **1997**, *38*, 8241.

reaction was quenched with a saturated aqueous solution of ammonium chloride (300 mL), the layers were separated, and the aqueous phase was extracted with ether (3 × 300 mL). The combined organic extracts were washed with water (300 mL), brine (300 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give a colourless oil. Flash chromatography on silica gel (Pet. ether–Et_2O 19:1) gave the Weinreb amide **380** (42.32 g, 95%) as a colourless oil. R_f = 0.36 (Pet. ether–EtOAc 19:1); $[\alpha]_D^{25}$ –14.4 (*c* = 1.8, $CHCl_3$); ν_{max} 2956, 1662, 1463, 1383, 1102, 996, 881 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 3.95 (1H, dd, *J* = 9.2, 8.0 Hz, CH_2-C1), 3.71 (1H, s, CH_3-C6), 3.63 (1H, dd, *J* = 9.2, 6.0 Hz, CH_2-C1), 3.19 (4H, brs, CH_3-C5, CH-C2), 1.03 (3H, d, *J* = 6.8 Hz, CH_3-C3), 1.10–1.02 (21H, m, [{CH_3}$_2$CH]$_3$-TIPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4 (C-C4), 66.0 (CH_2-C1), 61.4 (CH_3-C5), 38.2 (CH-C2), 32.0 (CH_3-C6), 17.9 (CH_3-TIPS), 15.2 (CH_3-C3), 12.1 (CH-TIPS); HRMS (CI, isobutane) for $C_{15}H_{34}O_3NSi$ $[M+H]^+$, Calcd 304.2308, found 304.2311.

(*R*)-3-methyl-4-(triisopropylsilyloxy)butan-2-one 378.[185]

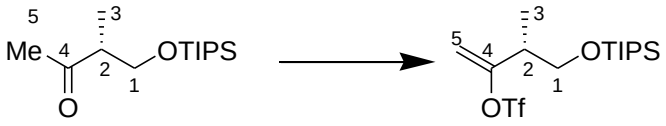


380 **378**

To a solution of the Weinreb amide **380** (42.32 g, 137.8 mmol) in dry THF (780 mL) at 0 °C under Ar was added dropwise methylmagnesium bromide (275 mL, 1.0 M solution in THF, 275 mmol). The reaction was allowed to stir for 2 h warming to rt during this period. The reaction was cooled to 0 °C and quenched with a saturated aqueous solution of ammonium chloride (250 mL) The aqueous layer was removed and extracted with ether (2 × 250 mL) and the combined organic extracts were washed with water (250 mL), and brine (250 mL), then dried ($MgSO_4$), and concentrated *in vacuo* to give a colourless oil. Flash chromatography on silica gel (Pet. ether) gave the methylketone **378** (34.84 g, 97%) as a colourless oil. R_f = 0.56 (Pet. ether–EtOAc 19:1); $[\alpha]_D^{25}$ –30.5 (*c* = 1.19, $CHCl_3$); ν_{max} 2942, 1717, 1463, 1383, 1356, 1096, 881 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 3.85 (1H, dd, *J* = 9.6, 7.2 Hz, CH_2-C1), 3.75 (1H, dd *J* = 9.6, 5.6 Hz, CH_2-C1), 2.78 (1H, m, CH-C2), 2.20 (3H, s, CH_3-C5), 1.06–1.02 (24H, m, CH_3-C3, [^{i}Pr-TIPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.0 (C-C4), 65.9 (CH_2-C1), 49.4 (CH-C2), 29.8 (CH_3-C5),

17.94 (CH_3-TIPS), 13.1 (CH_3-C3), 12.1 (CH-TIPS); HRMS (CI, isobutane) for $C_{14}H_{31}O_2Si$ $[M+H]^+$, Calcd 254.2093, found 254.2092.

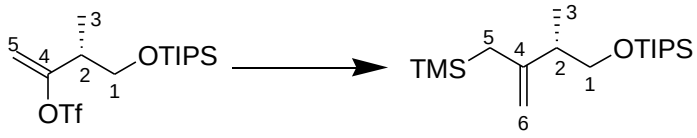
(*R*)-3-methyl-4-(triisopropylsilyloxy)but-1-en-2-yl trifluoromethanesulfonate 379.



378 **379**

The methyl ketone **378** and *N*-phenylbis(trifluoromethanesulfonimide) (21.0 g, 84.4 mmol) were dissolved in THF (900 mL) and the solution was cooled to –78 °C. DMPU (15 mL) was the added followed by NaHMDS (166 mL, 1.0 M solution in THF, 166 mmol) over a period of 5 min. After 1 h, the reaction was quenched by addition of water (500 mL) and warmed to rt. The phases were separated and the aqueous phase was extracted with ether (2 × 500 mL). The combined organic phases were washed with a solution of sodium hydroxide (10 %), water (500 mL), brine (500 mL) then dried ($MgSO_4$) and concentrated *in vacuo* to give a colourless oil. The residue was purified by flash chromatography on silica gel (Pet. ether) to give the triflate **379** (30.11g, 91%) as a yellow oil. R_f = 0.68 (Pet. ether–EtOAc 19:1); $[\alpha]_D^{20}$ +10.8 (*c* = 0.95, $CHCl_3$); ν_{max} 2947, 2870, 1419, 1141, 933 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.17 (1H, d, *J* = 3.6 Hz, CH_2-C5), 5.01 (1H, d, *J* = 3.6 Hz, CH_2-C5), 3.78 (1H, dd, *J* = 10.0, 5.6 Hz, CH_2-C1), 3.71 (1H, dd, *J* = 9.6, 5.6 Hz, CH_2-C1), 2.64 (1H, ddq, *J* = 10.0, 9.6, 6.6 Hz, CH-C2), 1.19 (3H, d, *J* = 6.6 Hz, CH_3-C3), 1.08–1.01 (21H, m, [{CH_3}$_2$CH]$_3$-TIPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4 (C-C4), 104.0 (CH_2-C5), 68.8 (CH_2-C1), 41.4 (CH-C2), 17.9 (CH_3-TIPS), 14.5 (CH_3-C3), 11.8 (CH-TIPS); HRMS (CI, isobutane) for $C_{15}H_{30}O_4F_3SiS$ $[M+H]^+$, Calcd 391.1536, found 391.1583.

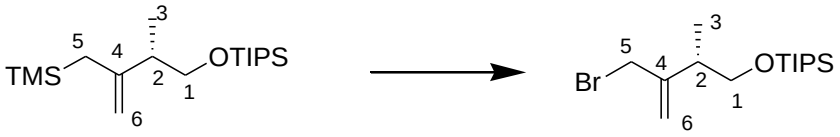
(*S*)-triisopropyl(2-methyl-3-((trimethylsilyl)methyl)but-3-enyloxy)silane 357.



379 **357**

A solution of chloromethyl(trimethylsilane) (53.10 mL, 384.4 mmol) in dry ether (365 mL) was added dropwise to a stirred suspension of Mg (9.22 g, 384.4 mmol) and iodine (1 crystal) in dry ether (20 mL) under Ar. Heating the mixture to reflux, then slow addition of the halide over a period of 30 min to maintain the reflux accomplished formation of the Grignard reagent. The Grignard reagent was stirred at rt for 2 h under Ar. Tetrakis(triphenylphosphine)palladium(0) (4.4 g, 3.8 mmol) was added to a suspension of triflate **379** (30.1 g, 76.8 mmol) and lithium chloride(16.29 g, 384.4 mmol) in dry ether (400 mL) under Ar. After 30 min, the Grignard reagent was added dropwise over 10 min at 0 °C under Ar. After being stirred for a further 2 h, the reaction mixture was quenched with a saturated solution of sodium bicarbonate (500 mL). The phases were separated and the aqueous phase was extracted with ether (3 × 500 mL). The combined organic layers were washed with water (500 mL) and brine (500 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Flash column chromatography on silica gel (Pet. ether) afforded pure allylic silane **357** (19.30 g, 76%).

(-)-(*S*)-3-(bromomethyl)-2-methyl-1-triisopropylsilylloxy-but-3-ene 383.[127]

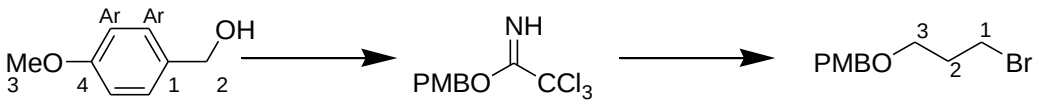


357 **383**

Pyrrolidone hydrotribromide (36.0 g, 74.3 mmol) was added to a stirred solution of the allylic silane **357** (24.40 g, 74.36 mmol) and pyridine (38 mL) in dry THF (2.5 L) at – 10 °C under Ar. The mixture was stirred for 2 h, and allowed to warm to rt during this period. The reaction was quenched with saturated aqueous sodium thiosulfate solution (500 mL). The aqueous layer was removed and extracted with ether (4 × 500 mL). The ether

extracts were combined and washed with water (3 × 500 mL) and brine (2 × 500 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Column chromatography (Pet. ether) gave the bromide **383** (23.09 g, 93%) as a clear oil. R*f* = 0.37 (Pet. ether); $[\alpha]_D^{20}$ –32.2 (*c* = 1.67, $CHCl_3$) [Lit.[127] $[\alpha]_D^{25}$ –31.5 (*c* = 2.67, $CHCl_3$)]; ν_{max} 2943, 2866, 1462, 1207, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.24 (1H, s, CH_2-C6), 5.02 (1H, s, CH_2-C6), 4.09 (1H, d, *J* = 10.0 Hz, CH_2-C5), 4.02 (1H, d, *J* = 10.0 Hz, CH_2-C5), 3.69 (1H, dd, *J* = 9.4, 6.0 Hz, CH_2-C1), 3.63 (1H, dd, *J* = 9.4, 6.4 Hz, CH_2-C1), 2.58 (1H, qdd, *J* = 6.8, 6.4, 6.0 Hz, CH-C2), 1.13 (3H, d, *J* = 6.8 Hz, CH_3-C3), 1.11–1.04, (21H, m, ^{i}Pr-TIPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6 (C-C4), 114.8 (CH_2-C6), 68.3 (CH_2-C5), 41.3 (CH-C2), 37.5 (CH_2-C1), 18.0 (CH_3-TIPS), 16.7 (CH_3-C3), 11.4 (CH-TIPS); HRMS (CI, isobutane) for $C_{15}H_{32}OSiBr$ $[M+H]^+$ Calcd 335.1406, found 335.1396. Anal. Calcd for $C_{15}H_{31}OSi^{79}Br$: C, 53.72%; H, 9.32%. Found C, 54.09%; H, 9.53%.

***p*-Methoxybenzyl-3-bromopropylether 336.**[127]

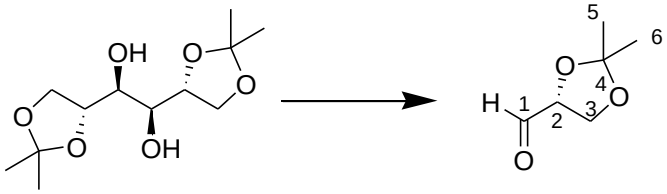


385 **386** **336**

Tetra-*n*-butylammonium hydrogen sulfate (0.23 g, 0.60 mmol) was added to a mixture of 4-*p*-methoxybenzyl alcohol **385** (30.0 g, 217 mmol) in DCM (200 mL) and aqueous potassium hydroxide (50%, 200 mL) and the resulting mixture stirred in an ice/water bath for 10 min. Trichloroacetonitrile (26.0 mL, 260 mmol) was added dropwise over 10 min and the mixture was stirred at 0 °C for 30 min, then at rt for 2 h. The organic layer was separated and the aqueous layer extracted with DCM (2 × 200 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo* to yield 4-*p*-methoxybenzyltrichloroacetimidate **386** as a yellow oil. 3-Bromopropanol (18.8 mL, 217 mmol) was added to a solution of PPTS (2.71 g, 10.8 mmol) and 4-*p*-methoxybenzyltrichloroacetamidate **386** in dry DCM (200 mL) at rt under Ar. The mixture was stirred at rt for 18 h, then diluted with cyclohexane (200 mL) and the precipitate removed by filtration. The filtrate was washed with a saturated aqueous solution of sodium bicarbonate (200 mL), water (2 × 200 mL) and brine (100 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (Pet. Ether, Pet. ether–EtOAc 9:1) gave the bromide **336** (35 g, 71%) as a colourless oil. R_f = 0.34 (Pet. ether–EtOAc 19:1); ν_{max}

2858, 1612, 1512, 1244, 1097, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (2H, d, *J* = 8.6 Hz, CH-CAr), 6.87 (2H, d, *J* = 8.6 Hz, CH-CAr), 4.44 (2H, s, CH_2-C2PMB), 3.79 (3H, s, CH_3-C3PMB), 3.56 (2H, t, *J* = 6.0 Hz, CH_2-C3), 3.51 (2H, t, *J* = 6.8 Hz, CH_2-C1), 2.11 (2H, tt, *J* = 6.8, 6.0 Hz, CH_2-C2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2 (C-C2PMB), 130.4 (C-C1PMB), 129.3 (CH-CAr), 113.8 (CH-CAr) 72.8 (CH_2-C3PMB), 67.4 (CH_2-C3), 55.3 (CH_3-C4PMB), 32.9 (CH_2-C1), 30.7 (CH_2-C2); HRMS (EI) for $C_{11}H_{16}O_2{}^{79}Br$ $[M+H]^+$ Calcd 259.1439, found 259.1476. Anal. Calcd for $C_{11}H_{15}O_2{}^{79}Br$: C, 50.98%; H, 5.83%. Found: C, 51.36%; H, 5.79%.

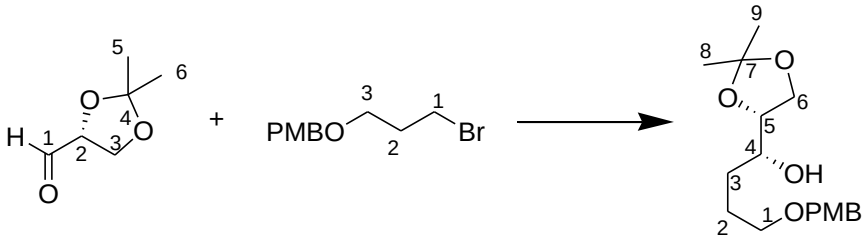
(*R*)-2,3-isopropylidene glyceraldehyde 335.[127]



387 **335**

Sodium periodate (3.25 g, 1.50 mmol) was added to a solution of 1,2:5,6-di-*O*-isopropylidene-D-mannitol **387** (2.0 g, 7.6 mmol) in DCM (15 mL) and water (1mL). The temperature of the reaction during the addition of $NaIO_4$ was kept below 30 °C. After the reaction was stirred at rt for 90 min, $MgSO_4$ (1 g) was added and the mixture stirred at rt for 15 min. The solids were removed by filtration and washed with CH_2Cl_2 (2 × 10 mL). The solvent was removed by careful distillation and the residual aldehyde was purified by distillation (50 °C at 15 mmHg) to give aldehyde **335** (1.27 g, 64%) as a colourless oil. $[\alpha]_D{}^{20}$ +79.3 (*c* = 1.25, $CHCl_3$); ν_{max} 2987, 2936, 2893, 2821, 1735. ^1H NMR (400 MHz, $CDCl_3$) δ 9.72 (1H, d, *J* = 1.8 Hz, CH-C1), 4.39 (ddd, 1H, *J* = 7.4, 4.7, 1.8 Hz, CH-C2), 4.18 (1H, dd, *J* = 8.8, 7.4 Hz, CH_2-C3), 4.10 (1H, dd, *J* = 8.8, 4.7 Hz, CH_2-C3), 1.49 (3H, s, CH_3-C6), 1.42 (3H, s, CH_3-C5). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.7 (CH-C1), 111.2 (C-C4), 79.8 (CH-C2), 65.5 (CH_2-C3), 26.2 (CH_3-C5), 25.0 (CH_3-C6).

(2*R*,3*R*)-3-Hydroxy-1,2-isopropylidene-6-*p*-Methoxybenzyloxy-2-oxy-hexanol 337.[127]

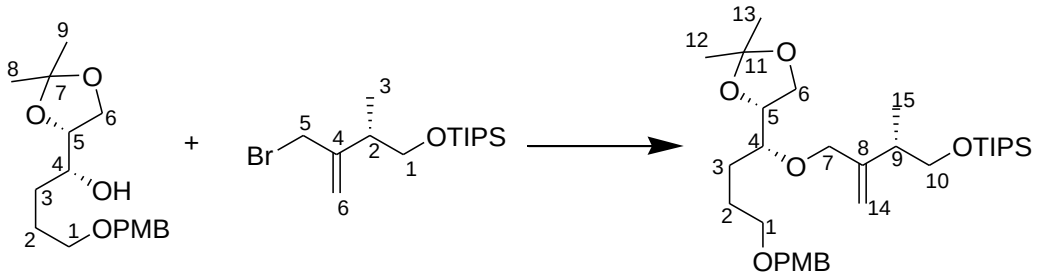


335 **336** **337**

A solution of 4-*p*-methoxybenzyl-3-bromopropyl ether **336** (43.0 g, 166 mmol) in dry THF (150 mL) was added to a solution of magnesium (3.98 g, 166 mmol) and iodine in dry THF (16 mL) under Ar. Formation of the Grignard reagent was accomplished by heating the mixture to reflux, and then slow addition of the halide to maintain reflux. The Grignard reagent was stirred at rt for 2 h then added to a solution of copper (I) iodide (36.0 g, 189 mmol), dry dimethylsulfide (107 mL) and dry THF (500 mL) at –78 °C under Ar. The solution changed from a clear yellow/orange to bright orange colour upon addition of the Grignard reagent. The mixture was allowed to stir at –78 °C for 15 min, then (*R*)-2,3-isopropylidene glyceraldehyde **335** (14.60 g, 111.3 mmol) in dry THF (25 mL) was added over 5 min at –78 °C under Ar. The reaction was allowed to stir for 15 h warming to rt during this period. The reaction was quenched by the addition of crushed ice (2 g), and a mixture (9:1) of saturated aqueous solutions of ammonium chloride and ammonium hydroxide (500 mL). The aqueous layer was removed and extracted with ether (2 × 500 mL). The ether extracts were combined and washed with a mixture (9:1) of saturated aqueous solutions of ammonium chloride and ammonium hydroxide (1.5 L), water (300 mL) and brine (300 mL) then dried ($MgSO_4$) and concentrated in *vacuo* to give a yellow oil. Column chromatography (Pet. ether–EtOAc 4:1to 1:1) gave the alcohol **337** (26.2 g, 76%) as a colourless oil. R_f = 0.07 (Pet. Ether–EtOAc 4:1); $[\alpha]_D^{20}$ +11.5 (*c* = 1.33, $CHCl_3$) [Lit.[127] $[\alpha]_D^{24}$ +15.0 (*c* = 1.0, $CHCl_3$)]; ν_{max} 2935, 2860, 1612, 1512, 1369, 1246, 1064, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (2H, d, *J* = 8.7 Hz, CH-CAr), 6.87 (2H, d, *J* = 8.7 Hz, CH-CAr), 4.43 (2H, s, CH_2-C3PMB), 4.01–3.98 (2H, m, CH-C5, CH_2-C6), 3.79 (3H, s, CH_3-C4PMB), 3.74–3.69 (1H, m, CH_2-C6), 3.50–3.46 (3H, m, CH-C4, CH_2-C1), 2.57 (1H, s, OH), 1.82–1.70 (2H, m, CH_2-C2), 1.57–1.44 (2H, m, CH_2-C3), 1.42 (3H, s, CH_3-C8), 1.36 (3H, s, CH_3-C9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9 (C-C2PMB), 130.1 (C-C1PMB), 129.1 (CH-CAr), 113.5 (CH-CAr), 109.1 (C-C7), 78.8 (CH-C5), 72.7

(CH_2-C3PMB), 72.0 (CH-C4), 68.9 (CH_2-C1), 65.9 (CH_2-C6), 55.0 (CH_3-C4PMB), 30.4 (CH_2-C3), 26.4 (CH_2-C2), 25.1 (CH_3-C8), 24.1 (CH_3-C9); HRMS (CI, isobutane) for $C_{17}H_{27}O_5$ $[M+H]^+$ Calcd 311.3995, found 311.4002.

(2*R*,3*R*,3'*R*)-1,2-isopropylidene-6-*p*-methoxybenzyloxy-3-(-2'-methylene-3'-methyl-4'-triisoproylsilyloxy-butanoxy)-hexanol 388.[127]

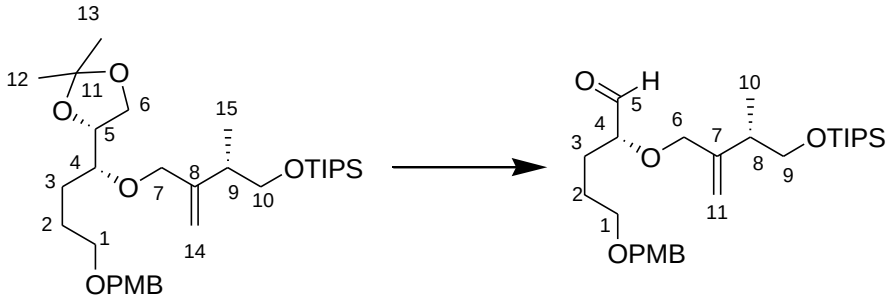


337 **383** **388**

A solution of the alcohol **337** (25.7 g, 83.0 mmol) in dry THF (133 mL) was added to a stirred solution of NaH (10.0 g, 249 mmol) in dry THF (1 L) at rt under Ar. The mixture was heated at reflux for 2 h under Ar, The mixture was cooled to rt then the bromide **383** (36.0 g, 108 mmol) in dry THF (340 mL) was added under Ar followed by tetrabutylammonium iodide (12.0 g, 33.0 mmol) and 18-crown-6 (8.77 g, 33.0 mmol). The mixture was heated at reflux for 14 h then allowed to cool to rt. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution (500 mL), water (500 mL) and extracted with ether (3 × 500 mL). The ether extracts were combined and washed with water (500 mL) and brine (500 mL), and then dried ($MgSO_4$) and concentrated *in vacuo* to give a brown oil. Column chromatography (Pet. ether–EtOAc 19:1 to 5:1) gave the allylic ether **388** (45 g, 96%) as a clear oil. R_f = 0.20 (Pet. ether–EtOAc 9:1); $[\alpha]_D^{20}$ 9.42 (*c* = 1.08, $CHCl_3$) [Lit.[127] $[\alpha]_D^{25}$ +14.0 (*c* = 0.90, $CHCl_3$)]; ν_{max} 2941, 2891, 2864, 1512, 1246, 1084, 1066 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (2H, d, *J* = 8.5 Hz, CH-CAr) 6.87 (2H, d, *J* = 8.5 Hz, CH-CAr) 5.09 (1H, s, CH_2-C14), 4.90 (1H, s CH_2-C14), 4.42 (2H, s, CH_2-C3PMB), 4.20 (1H, d, *J* = 12.8 Hz, CH_2-C7), 4.16 (1H, d, *J* = 6.5 Hz, CH-C5), 4.04 (1H, d, *J* = 12.8 Hz, CH_2-C7), 3.97 (1H, dd, *J* = 8.0, 6.5 Hz, CH_2-C6), 3.79 (3H, s, CH_3-C4PMB), 3.71–3.66 (2H, m, CH_2-C6, CH_2-C10), 3.53 (1H, dd, *J* = 9.5, 7.5 Hz, CH_2-C10), 3.44 (2H, dd, *J* = 6.4, 4.0 Hz, CH_2-C1), 3.36–3.33 (1H, m, CH-C4), 2.40–2.36 (1H, m, CH-C9), 1.85–1.75 (1H, m, CH_2-C2), 1.71–1.63 (1H, m, CH_2-C2), 1.58–1.42 (2H, m,

CH_2-C3), 1.41 (3H, s,CH_3-C12), 1.34 (3H, s, CH_3-C13), 1.10 (3H, d, J = 7.0 Hz, CH_3-C15), 1.07–1.05 (21H, m, ^{i}Pr-TIPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1 (C-C2PMB), 149.0 (C-C8), 130.6 (CH_2-C1PMB), 129.3 (CH-CAr), 113.7 (CH-CAr), 110.7 (CH_2-C14), 109.2 (C-C11), 79.7 (CH-C4), 78.1 (CH-C5), 73.5 (CH_2-C7), 72.5 (CH_2-C3PMB), 69.9 (CH_2-C1), 67.9 (CH_2-C10), 65.8 (CH_2-C6), 55.2 (CH_3-C4PMB), 39.3 (CH-C9), 27.3 (CH_2-C3), 26.6 (CH_3-C12), 26.5 (CH_2-C2), 25.5 (CH_3-C13), 18.0 (CH_3-TIPS), 16.4 (CH_3-C15), 11.9 (CH-TIPS); HRMS (CI, isobutane) for $C_{32}H_{57}O_6Si$ $[M+H]^+$ Calcd 565.3924, found 565.3928. Anal. Calcd for $C_{32}H_{56}O_6Si$: C, 68.04%; H, 9.99%. Found C, 67.96%; H, 9.92%.

(*2R*)-5-[(4-Methoxybenzyll)oxy]-2-{(*3S*)-3-methyl-2-methylene-4-[(triisopropylsilyl)oxy]butoxy}pentanal 389.[127]

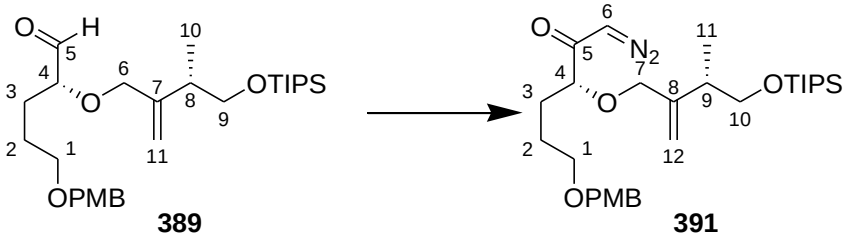


388 **389**

PPTS (4.01 g, 16.0 mmol) was added to a solution of the acetonide **388** (45.0 g, 79.7 mmol) in ethylene glycol (1 L), THF (500 mL), DCM (500 mL) and the mixture was heated to reflux for 20 h under Ar. The reaction was allowed to cool to room temperature and neutralised with concentrated ammonia solution (50 mL). The mixture was diluted with water (500 mL) and extracted with ether (3 × 500 mL). The combined organic extracts were washed with water (500 mL), brine (500 mL), then dried with ($MgSO_4$), and concentrated *in vacuo* to give a yellow oil. The crude product was dissolved in THF (600 mL) and water (250 mL), then $NaIO_4$ (67.67 g, 316.5 mmol) was added at rt. The mixture was stirred for 90 min at rt, then water (1 L) was added. The reaction mixture was extracted with ether (3 × 500 mL), and the combined ether extracts were washed with water (500 mL) and brine (500 mL), then dried ($MgSO_4$), and concentrated *in vacuo* to give a yellow oil. Flash chromatography on silica gel (Pet. ether–EtOAc 10:1) gave the aldehyde **389** (37.3 g, 95%) as a colourless oil. R_f = 0.32 (Pet. ether–EtOAc 10:1); $[\alpha]_D^{20}$

+17.6 (*c* = 1.08, $CHCl_3$) [Lit.[127] $[\alpha]_D^{21}$ +23.0 (*c* = 0.84, $CHCl_3$)]; ν_{max} 2941, 2864, 1734, 1512, 1464, 1246, 1091, 1068 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.63 (1H, d, *J* = 2.1 Hz, CH-C5), 7.25 (2H, d, *J* = 10.0 Hz, CH-CAr), 6.86 (2H, d, *J* = 10.0 Hz, CH-CAr), 5.10 (1H, s, CH_2-C11), 4.96 (1H, s, CH_2-C11), 4.40 (2H, s, CH_2-C3PMB), 4.16 (1H, d, *J* = 12.4 Hz, CH_2-C6), 3.94 (1H, d, *J* = 12.4 Hz, CH_2-C6), 3.79 (3H, s, CH_3-C4PMB), 3.74–3.70 (1H, m, CH-C4), 3.67 (1H, dd, *J* = 9.4, 6.0 Hz, CH_2-C9), 3.55 (1H, dd, *J* = 9.4, 6.8 Hz, CH_2-C9), 3.46–3.43 (2H, m, CH_2-C1), 2.38 (1H, qdd, *J* = 7.0, 6.8, 6.0 Hz, CH-C8), 1.76–1.69 (4H, m, CH_2-C2, CH_2-C3), 1.09 (3H, d, *J* = 7.0 Hz, CH_3-C10), 1.07–1.02 (21H, m, ^{i}Pr-TIPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.8 (CH-C5), 158.1 (C-C2PMB), 146.9 (C-C7), 129.4 (C-C1PMB), 128.2 (CH-CAr), 112.7 (CH-CAr), 111.3 (CH_2-C11), 82.0 (CH-C4), 72.0 (CH_2-C6), 71.4 (CH_2-C3PMB), 68.3 (CH_2-C1), 66.9 (CH_2-C9), 54.2 (CH_3-C4PMB), 38.4 (CH-C8), 25.8 (CH_2-C3), 24.0 (CH_2-C2), 17.0 (CH_3-TIPS), 15.3 (CH_3-C10), 10.9 (CH-TIPS); HRMS (CI, isobutane) for $C_{28}H_{49}O_5Si$ $[M+H]^+$ Calcd 493.3349, found 493.3351. Anal. Calcd for $C_{28}H_{48}O_5Si$: C, 68.25%; H, 9.82%. Found: C, 68.20%; H, 9.98%.

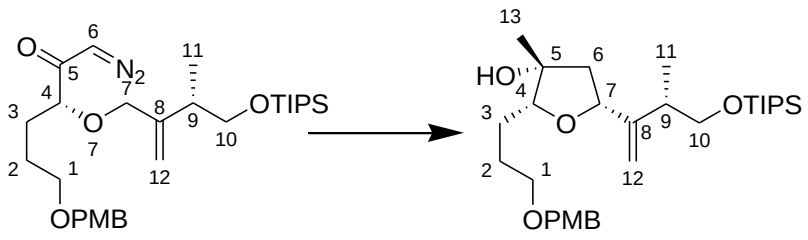
(*3R*)-1-diazo-6-[(4-methoxybenzyl)oxyl]-2-{(*3S*)-3-methyl-2-methylen-4-{triisopropylsilyl)oxy}butoxy}hexan-2-one 391.[127]



A solution of sodium chlorite (80%, 5.39 g, 59.7 mmol) and sodium dihydrogen orthophosphate dihydrate (10.0 g, 64.6 mmol) in water (100 mL) was added dropwise at rt to a solution of the aldehyde **389** (4.9 g, 9.9 mmol) in *t*-butanol (50 mL) and 2-methyl-2-butene (85%, 10.0 mL, 79.6 mmol). The mixture was stirred for 90 min under Ar, and the volatiles were removed *in vacuo.* The resulting solution was extracted with ether (3 × 80 mL) and the extracts were combined and washed with water (80 mL) and brine (80 mL), then dried ($MgSO_4$*)* and concentrated *in vacuo*. The crude acid was dissolved in dry ether (100 mL) under Ar and triethylamine (1.50 mL, 10.8 mmol) and *i*-butylchloroformate (1.48 mL, 10.8 mmol) were added sequentially. The mixture was stirred for 3 h, then

filtered and added to a solution of diazomethane (100 mmol, 300 mL) at 0 °C. The resulting solution was stirred overnight and the excess diazomethane was consumed by the addition of acetic acid (3 mL). After 30 min, the mixture was washed with saturated aqueous solution of sodium bicarbonate (100 mL) and brine (100 mL). The yellow solution was dried ($MgSO_4$), then concentrated *in vacuo* to a give yellow oil. Flash chromatography on silica gel (Pet. ether–EtOAc 10:1to 7:1) gave the diazo ketone **391** (4.8 g, 91%) as yellow oil. R_f = 0.27 (Pet. ether–EtOAc 7:1); $[\alpha]_D^{25}$ +23.1 (*c* = 1.18, $CHCl_3$) [Lit.[127] $[\alpha]_D^{23}$ +28.6 (*c* = 1.30, $CHCl_3$)]; ν_{max} 2941, 2891, 2864, 2102, 1645, 1512, 1346, 1246, 1093, 1068 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 7.24 (2H, d, *J* = 8.7 Hz, CH-CAr), 6.86 (2H,d, *J* = 8.7 Hz, CH-CAr), 5.71 (1H, s, CH-C6), 5.10 (1H, s, CH_2-C12), 4.96 (1H, s, CH_2-C12), 4.41 (2H, s, CH_2-C3PMB), 4.05 (1H, d, *J* = 12.8 Hz, CH_2-C7), 3.90 (1H, d, *J* = 12.8 Hz, CH_2-C7), 3.80 (3H, s, CH_3-C4PMB), 3.81–3.76 (1H, m, CH-C4), 3.66 (1H, dd, *J* = 9.4, 5.9 Hz, CH_2-C10), 3.55 (1H, dd, *J* =9.4, 6.8 Hz, CH_2-C10), 3.43 (2H, t, *J* = 6.1 Hz, CH_2-C1), 2.35 (1H, qdd, *J* = 6.9, 6.8, 5.9 Hz, CH-C9), 1.81–1.67 (4H, m, CH_2-C2, CH_2-C3), 1.09 (3H, d, *J* = 6.9 Hz, CH_3-C11), 1.07–1.02 (21H, m, ^{i}Pr-TIPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0 (C-C5), 159.1 (C-C2PMB), 148.0 (C-C8), 130.6 (C-C1PMB), 129.2 (CH-CAr), 113.7 (CH-CAr), 111.4 (CH_2-C12), 83.5 (CH-C4), 72.9 (CH_2-C7), 72.5 (CH_2-C3PMB), 69.6 (CH_2-C1), 68.0 (CH_2-C10), 55.2 (CH_3-C4PMB), 52.3 (CH-C6), 41.3 (CH-C9), 30.0 (CH_2-C2), 25.3 (CH_2-C3), 18.0 (CH_3-TIPS), 16.4 (CH_3-C11), 11.4 (CH-TIPS); HRMS (FAB) for $C_{29}H_{47}O_5N_2Si$ $[M+H]^+$ calcd 533.34311, found 533.3394. Anal. Calcd for $C_{29}H_{48}O_5N_2Si$: C, 65.38%; H, 9.08%; N, 5.26%. Found: C, 65.47%; H, 9.36%; N, 5.31%.

(1*R*,6*S*)-1,4-Anhydro-3,5,6-trideoxy-1-{3-[(4-methoxybenzyl)oxy]propyl}-6-methyl-2-*C*-methyl-5-methylene-7-*O*-(triisopropylsilyl)-D-*xylo*-heptitol 395.[127]

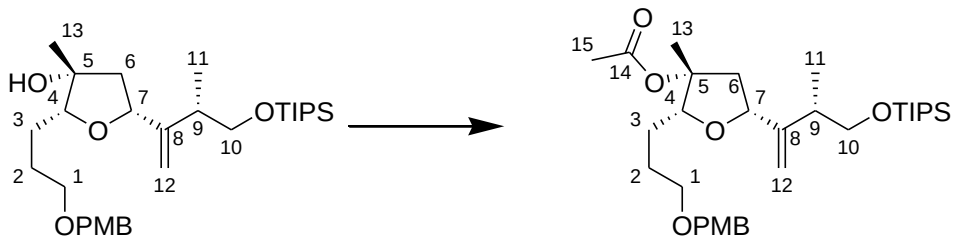


391 **395**

A solution of α-diazoketone **391** (8.57 g, 16.0 mmol) in dry THF (580 mL) was added dropwise to a solution of rhodium (II) trifluoroacetamide (**299**) (38 mg, 0.058 mmol,

0.4 mol%) in dry THF (200 mL) at reflux under Ar. The reaction was stirred at reflux for 10 min, allowed to cool to rt and concentrated *in vacuo*. The crude dihydrofuranone was dissolved in dry THF (100 mL) and stirred under an atmosphere of Ar. Methylmagnesium iodine (50.0 mL, 1.0 M solution in ether, 50.0 mmol) was added dropwise at –78 °C and the reaction stirred over night under Ar, warming to rt during this time. The reaction was cooled to 0 °C and quenched with a saturated aqueous solution of ammonium chloride (100 mL). The aqueous layer was separated and extracted with ether (3 × 100 mL). The ether extracts were washed with water (100 mL) and brine (100 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to deliver a yellow oil. Flash chromatography on silica gel (Pet. ether–EtOAc 19:1 to 3:1) gave the alcohol **395** (4.0 g, 50%) as a colourless oil. R_f = 0.38 (Pet. ether–EtOAc 3:1); $[\alpha]_D^{20}$ –6.06 (*c* = 1.00, $CHCl_3$) [Lit.[127] $[\alpha]_D^{20}$ –6.70 (*c* = 0.80, $CHCl_3$)]; ν_{max} 2941, 2891, 2864, 1612, 1512, 1246, 1091, 1066 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* = 8.5 Hz, CH-CAr), 6.87 (2H, d, *J* = 8.5 Hz, CH-CAr), 5.33 (1H, s, CH_2-C12), 4.89 (1H, s, CH_2-C12), 4.44 (2H, s, CH_2-C3PMB), 4.39 (1H, dd, *J* = 9.5, 5.0 Hz, CH-C7), 3.79 (3H, s, CH_3-C4PMB), 3.66 (1H, dd, *J* = 9.3, 5.5 Hz, CH_2-C10), 3.54 (1H, m, CH_2-C1), 3.50–3.47 (2H, m, CH-C4, CH_2-C1) 3.44 (1H, dd, *J* = 9.3, 7.5 Hz, CH_2-C10), 2.21 (1H, dqd, *J* = 7.5, 7.0, 5.5, CH-C9), 2.21 (1H, dd, *J* = 13.5, 9.5 Hz, CH_2-C6), 1.92 (1H, dd, *J* = 13.5, 5.0 Hz, CH_2-C6), 1.88–1.86 (1H, m, CH_2-C2), 1.85 (1H, s, OH), 1.72–1.66 (3H, m, CH_2-C3, CH_2-C2), 1.24 (3H, s, CH_3-C13), 1.13 (3H, d, *J* = 7.0 Hz, CH_3-C11), 1.04–1.03 (21H, m, ^{i}Pr-TIPS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1 (C-C2PMB), 154.8 (C-C1PMB), 130.7 (C-C8), 129.2 (CH-CAr), 113.7 (CH-CAr), 107.1 (CH_2-C12), 86.7 (CH-C4), 78.4 (C-C5), 77.9 (CH-C7), 72.5 (CH_2-C5PMB), 70.1 (CH_2-C1), 68.8 (CH_2-C10), 55.3 (CH_3-C6PMB), 46.4 (CH_2-C6), 39.1 (CH-C9), 27.0 (CH_2-C3), 25.2 (CH_2-C2), 22.7 (CH_3-C13), 18.0 (CH_3-TIPS), 17.2 (CH_3-C11), 11.9 (CH-TIPS); HRMS (CI, isobutane) for $C_{30}H_{53}O_5Si$ $[M+H]^+$ calcd 521.3662, found 521.3658. Anal. Calcd for $C_{30}H_{52}O_5Si$: C, 69.18%; 9.99%. Found: 68.93%; 10.14%.

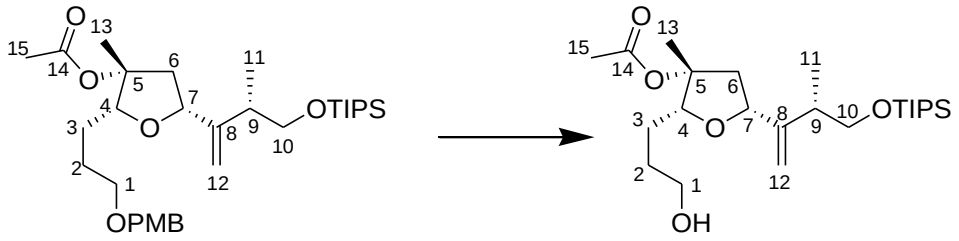
(1*R*,6*S*)-2-*O*-Acetyl-1,4-anhydro-3,5,6-trideoxy-1-{3-[(4-methoxybenzyl)oxy]propyl}-6-methyl-2-*C*-methyl-5-methylene-7-*O*-(triisopropylsilyl)-D-*xylo*-heptitol 396.[127]



395 **396**

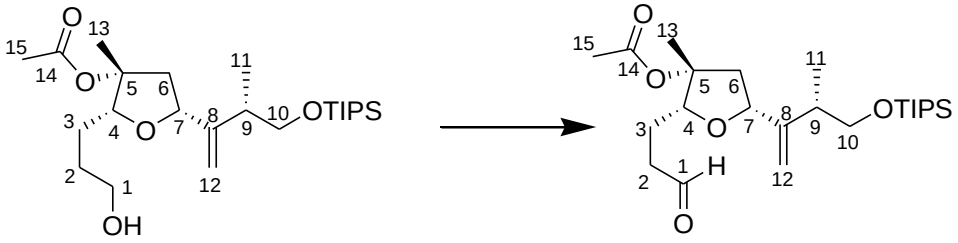
Acetic anhydride (3.00 mL, 37.3 mmol) was added to a solution of **395** (4.0 g, 7.8 mmol), DMAP (2.80 g, 23.5 mmol), and Et_3N (8.73 mL, 62.0 mmol) in dry ether (104 mL) at rt under Ar and the resulting solution stirred for 20 h. Water (300 mL) was added and the mixture was extracted with ether (3 × 100 mL). The ether extracts were washed with water (100 mL), and brine (100 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Flash chromatography on silica gel (Pet. ether–EtOAc 19:1 to 4:1) afforded the acetate **396** (3.52 g, 80%) as a clear oil. R_f = 0.40 (Pet. ether–EtOAc 4:1); $[\alpha]_D^{20}$ –7.58 (*c* = 1.07, $CHCl_3$) [Lit.[127] $[\alpha]_D^{23}$ –6.80 (*c* = 1.7, $CHCl_3$)]; ν_{max} 2941, 2891, 2864, 1735, 1612, 1512, 1246, 1093, 1066, 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* = 9.0 Hz, CH-CAr), 6.86 (2H, d, *J* = 9.0 Hz, CH-CAr), 5.20 (1H, s, CH_2-C12), 4.84 (1H, s, CH_2-C12), 4.45 (1H, d, *J* = 11.4 Hz, CH_2-C3PMB), 4.44 (1H, d, *J* = 11.4 Hz, CH_2-C3PMB), 4.30 (1H, dd, *J* = 7.5, 7.5 Hz, CH-C7), 3.80 (3H, s, CH_3-C4PMB), 3.64 (1H, dd, *J* = 9.5, 5.5 Hz, CH_2-C10), 3.56–3.52 (1H, m, CH_2-C1), 3.51–3.46 (2H, m, CH_2-C1, CH-C4), 3.42 (1H, dd, *J* = 9.5, 8.0 Hz, CH_2-C10), 2.36 (1H, dd, *J* = 14.0, 7.5 Hz, CH_2-C6), 2.33 (1H, dd, *J* = 14.0, 7.5 Hz, CH_2-C6), 2.20 (1H, dqd, *J* = 8.0, 6.5, 5.5 Hz, CH-C9), 1.90 (3H, s, CH_3-C15), 1.90–1.88 (1H, m, CH_2-C2), 1.72–1.55 (3H, m, CH_2-C2, CH_2-C3), 1.51 (3H, s, CH_3-C13), 1.07 (3H, d, *J* = 6.5 Hz, CH_3-C11), 1.07–1.04 (21H, m, ^{i}Pr-TIPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5 (C-C14), 159.1 (C-C2PMB), 151.3 (C-C1PMB), 129.8 (C-C8), 129.3 (CH-CAr), 113.7 (CH-CAr), 110.0 (CH_2-C12), 87.3 (CH-C4), 86.3 (C-C5), 79.1 (CH-C7), 72.4 (CH_2-C3PMB), 70.0 (CH_2-C1), 68.7 (CH_2-C10), 55.2 (CH_3-C4PMB), 43.5 (CH_2-C6), 38.7 (CH-C9), 26.9 (CH_2-C2), 25.7 (CH_2-C3), 21.6 (CH_3-C15), 21.7 (CH_3-C13), 18.3 (CH_3-TIPS), 18.0 (CH_3-C11), 11.9 (CH-TIPS); HRMS (ES) for $C_{32}H_{58}O_6NSi$ $[M+NH_4]^+$ calcd 580.4043, found 580.4044.

1*R*,6*S*)-2-*O*-Acetyl-1,4-anhydro-3,5,6-trideoxy-1-(3-hydroxypropyl)-6-methyl-2-*C*-methyl-5-methylene-7-*O*-(triisopropylysilyl)-*D*-*xylo*-heptitol 397.[127]



DDQ (4.76 g, 21.0 mmol) was added in one portion to a solution of **396** (7.90 g, 14.0 mmol) in DCM (240 mL) and water (25 mL), and the reaction was stirred at rt for 3 h. The mixture was diluted with DCM (100 mL) and washed successively with a saturated aqueous solution of sodium bicarbonate (100 mL), water (100 mL), and brine (100 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to give a red/brown oil. Flash column chromatography on silica gel (Pet. ether–EtOAc 10:1 to 3:1) gave the alcohol **397** (5.56 g, 93%) as a colourless oil. R_f = 0.08 (Pet. ether–EtOAc 4:1); $[\alpha]_D^{25}$ –10.7 (*c* = 1.05, $CHCl_3$) [Lit.[127] $[\alpha]_D^{21}$ –11.0 (*c* = 0.55, $CHCl_3$)]; ν_{max} 2941, 2891, 2866, 1731, 1464, 1367, 1234, 1097, 1064, 1014 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.19 (1H, s, CH_2-C12), 4.87 (1H, s, CH_2-C12), 4.38 (1H, dd, *J* = 7.8, 7.4 Hz, CH-C7), 3.71 (2H, brs, CH_2-C1), 3.64 (1H, dd, *J* = 9.5, 5.7 Hz, CH_2-C10), 3.51 (1H, dd, *J* = 7.5, 4.5 Hz, CH-C4), 3.46 (1H, dd, *J* = 9.5, 8.0 Hz, CH_2-C10), 2.52 (1H, brs, OH), 2.46 (1H, dd, *J* = 14.2, 7.4 Hz, CH_2-C6), 2.35 (1H, dd, *J* =14.2, 7.8, CH_2-C6), 2.18 (1H, dqd, *J* = 8.0, 6.5, 5.7 Hz, CH-C9), 1.95 (3H, s, CH_3-C15), 1.80–1.76 (4H, m, CH_2-C2, CH_2-C3), 1.53 (3H, s, CH_3-C13), 1.08 (3H, d, *J* = 6.5 Hz, CH_3-C11), 1.06–1.02 (21H, m, ^{i}Pr); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5 (C-C14), 152.0 (C-C8), 108.3 (CH_2-C12), 87.8 (CH-C4), 86.0 (C-C5), 79.3 (CH-C7), 68.7 (CH_2-C10), 62.9 (CH_2-C1), 43.3 (CH_2-C6), 38.5 (CH-C9), 30.5 (CH_2-C2), 25.9 (CH_2-C3), 22.1 (CH_3-C15), 21.5 (CH_3-C13), 18.0 (CH_3-TIPS), 17.5 (CH_3-C11), 12.0 (CH-TIPS); HRMS (CI, isobutane) for $C_{24}H_{47}O_5Si$ $[M+H]^+$ calcd 443.3193, found 443.3190. Anal. Calcd for $C_{24}H_{46}O_5Si$: C, 65.11%; H, 10.47%. Found: C, 64.94%; H, 10.42%.

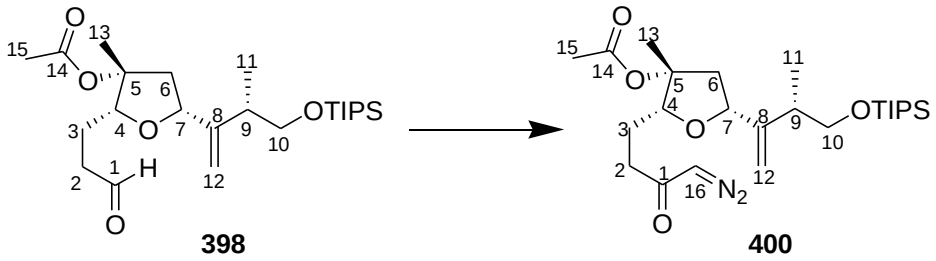
(1*R*,6*S*)-2-*O*-Acetyl-1,4-anhydro-3,5,6-trideoxy-1-(3-oxopropyl)-6-methyl-2-*C*-methyl-5-methylene-7-0-(triisopropylsilyl)-*D*-*xylo*-heptitol 398.[127]



397 **398**

Dess-Martin periodinane (8.00 g, 18.7 mmol) was added in one portion to a solution of the alcohol **397** (5.56 g, 12.5 mmol) in dry DCM (60 mL) at 0 °C under Ar. The mixture was stirred for 2 h at rt, then quenched by the addition of a saturated aqueous solution of sodium thiosulfate (150 mL) and extracted with ether (3 × 200 mL). The ether extracts were combined and washed successively with a saturated aqueous solution of sodium bicarbonate (100 mL), water (100 mL) and brine (100 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to give a cloudy oil. Flash column chromatography on silica gel (Pet. ether–EtOAc 19:1 to 3:1) gave the aldehyde **398** (4.44 g, 80%) as a colourless oil. R_f = 0.60 (Pet. Ether–EtOAc 4:1); $[\alpha]_D^{20}$ –8.06 (*c* = 1.25, $CHCl_3$) [Lit.[127] $[\alpha]_D^{23}$ –3.8 (*c* = 0.90, $CHCl_3$)]; ν_{max} 2958, 2941, 2866, 2719, 1732, 1464, 1367, 1240, 1093, 1066, 1014 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.83 (1H, d, *J* = 1.3 Hz, CH-C1), 5.16 (1H, s, CH_2-C12), 4.86 (1H, s, CH_2-C12), 4.33 (1H, $_{ap}$t, *J* = 7.5 Hz, CH-C7) 3.64 (1H, dd, *J* = 9.3, 5.5 Hz, CH_2-C10), 3.53 (1H, dd, *J* = 9.5, 3.6 Hz, CH-C4), 3.45 (1H, dd, *J* = 9.3, 8.0 Hz, CH_2-C10), 2.78–2.71 (1H, dddd, *J* = 18.0, 8.3, 6.5, 1.3 Hz, CH_2-C2), 2.62 (1H, dddd, *J* = 18.0, 8.3, 6.5, 1.3 Hz, CH_2-C2), 2.38 (2H, dd, *J* = 7.5, 2.5 Hz CH_2-C6), 2.19 (1H, dqd, *J* = 8.0, 7.0, 5.5 Hz, CH-C9), 2.01–1.94 (2H, m, CH_2-C3), 1.96 (3H, s, CH_3-C15), 1.55 (3H, s, CH_3-C13), 1.08 (3H, d, *J* = 7.0 Hz, CH_3-C11), 1.06–1.02 (21H, m, ^{i}PrTIPS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.2 (CH-C1), 170.3 (C-C14), 151.1 (C-C8), 107.3 (CH_2-C12), 85.3 (CH-C4), 84.8 (C-C5), 78.2 (CH-C7), 67.7 (CH_2-C10), 42.4 (CH_2-C6), 40.1 (CH_2-C2), 37.6 (CH-C9), 21.0 (CH_3-C15), 20.6 (CH_2-C3), 20.5 (CH_3-C13), 17.0 (CH_3-TIPS), 16.4 (CH_3-C11), 10.9 (CH-TIPS); HRMS (CI, isobutane) for $C_{24}H_{45}O_5Si$ $[M+H]^+$ calcd 441.3036, found 441.3041.

(1*R*,6*R*)-2-*O*-Acetyl-1,4-anhydro-3,5,6-trideoxy-1-(4-diazo-3-oxobutyl)-6-methyl-2-*C*-methyl-5-methylene-7-*O*-(triisopropylsilyl)-*D*-*xylo*-heptatol 400.[127]

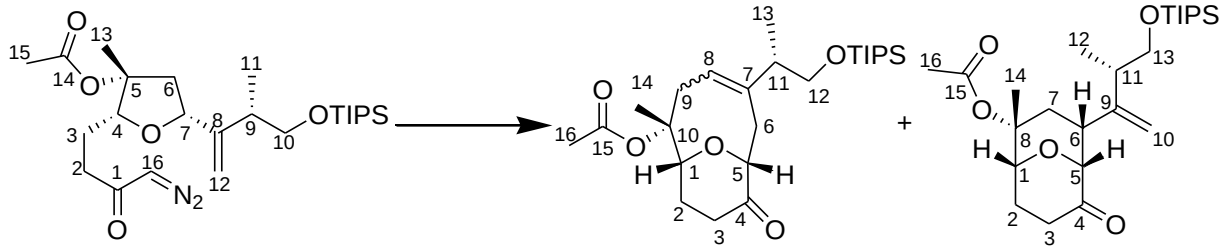


A solution of sodium chlorite (80%, 6.77 g, 60.0 mmol) and sodium dihydrogen orthophosphate (10.1 g, 65.0 mmol) in water (100 mL), was added dropwise to a solution of the aldehyde **398** (4.44 g, 10.6 mmol) in *t*-butanol (51 mL) and 2-methyl-2-butene (8.47 mL, 80.0 mmol). The reaction was stirred at rt for 90 minutes, then the volatile compounds were removed *in vacuo*. The mixture was extracted with ether (3 × 100 mL), the ether extracts were combined and washed with water (100 mL) and brine (100 mL), then dried ($MgSO_4$), and concentrated *in vacuo* to give the carboxylic acid **399** as a pale yellow oil. The crude acid **399** was dissolved in dry MeOH (100 mL) under Ar and sodium methoxide (0.69 g, 11.0 mmol) was added in one portion. The mixture was stirred for 15 min, concentrated *in vacuo*, and dried overnight under high vacuum. The white solid was dissolved in dry benzene (100 mL) and oxalyl chloride (5.52 mL, 50.0 mmol) was added dropwise under Ar. The mixture was stirred for 2 h, concentrated *in vacuo*, and the residue was dissolved in DCM (100 mL). The solution was added dropwise to a solution of diazomethane (100 mmol, 300 mL) at 0 °C. The resulting mixture was stirred for 2 h and the excess of diazomethane was then consumed by the addition of acetic acid (5 mL). After 30 minutes the ethereal solution was washed with a saturated solution of sodium bicarbonate (200 mL). The aqueous layer was separated and extracted with ether (3 × 200 mL). The ether extracts were combined and washed with water (200 mL) and brine (200 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Flash column chromatography (Pet. ether–EtOAc 9:1 to 4:1) gave the *α*-diazo ketone **400** (3.80 g, 79%) as a yellow oil: R_f. = 0.25 (Pet. ether–EtOAc 4:1); $[\alpha]_D^{29}$ –10.7 (*c* = 1.04, $CHCl_3$) [Lit.[127] $[\alpha]_D^{23}$ –0.98 (*c* = 0.62, $CHCl_3$)]; ν_{max} 2958, 2941, 2891, 2866, 2100, 1735, 1645, 1367, 1089, 881 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.28 (1H, brs, CH-C16), 5.16 (1H, s, CH_2-C12), 4.84 (1H, s, CH_2-C12), 4.31 (1H, dd, *J* = 7.5, 7.5 Hz, CH-C7), 3.63 (1H, dd, *J* = 10.0, 6.0 Hz, CH_2-C10), 3.49 (1H, dd, *J* = 9.5, 3.5 Hz, CH-C4), 3.45 (1H, dd, *J* = 10.0, 8.0

Hz, CH_2-C10), 2.59 (1H, brs, CH_2-C2), 2.46 (1H, brs, CH_2-C2), 2.35 (1H, dd, *J* = 14.2, 7.5 Hz, CH_2-C6), 2.34 (1H, dd, *J* = 14.2, 7.5 Hz, CH_2-C6), 2.18 (1H, dqd, *J* = 8.0, 7.0, 6.0 Hz, CH-C9), 2.06–1.97 (2H, m, CH_2-C3), 1.93 (3H, s, CH_3-C15), 1.52 (3H, s, CH_3-C13), 1.09 (3H, d, *J* = 7.0 Hz, CH_3-C11), 1.06–1.02 (21H, m, ^{i}Pr-TIPS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.7 (C-C1), 170.3 (C-C14), 152.9 (C-C8), 108.4 (CH_2-C12), 86.4 (CH-C4), 85.8 (C-C5), 79.2 (CH-C7), 68.7 (CH_2-C10), 54.4 (CH-C16), 43.3 (CH_2-C6), 38.6 (CH-C9), 37.7 (CH_2-C2), 24.3 (CH_2-C3), 22.0 (CH_3-C15), 21.4 (CH_3-C13) 18.0 (CH_3-TIPS), 17.4 (CH_3-C11), 11.9 (CH-TIPS); HRMS (FAB) for $C_{24}H_{45}N_2O_5Si$ $[M+H]^+$ calcd 481.3098, found 481.3132. Anal. Calcd for $C_{25}H_{44}N_2O_5Si$: C, 62.46%; H, 9.23%; N, 5.83%. Found: C, 62.79%; H, 9.37%; N, 5.92%.

1*R*,2*R*,4*Z*,7*R*)-2-Methyl-5-{(1*S*)-1-methyl-2-[(triisopropylsilyl)oxy]ethyl}-8-oxo-11-oxabicyclo[5,3,1]undec-4-en-2-yl acetate 402.[127]

(1*R*,2*R*,4*R*,5*R*)-2-methyl-4-{(2*S*)-2-methyl-1-methylene-3-[(triisopropylsilyl)oxy]propyl}-6-oxo-9-oxabicyclo[3.3.1]non-2-yl acetate 403.[127]



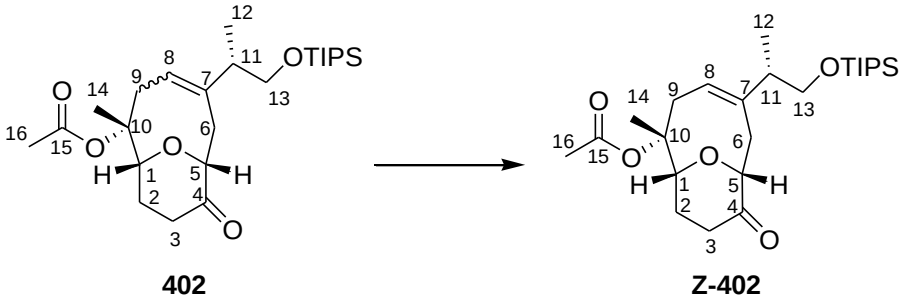
400 **402** **403**

A solution of the α-diazo ketone **400** (3.8 g, 7.9 mmol) in dry DCM (474 mL) was added dropwise to a solution of copper(II) hexafluoroacetylacetonate (90 mg, 0.18 mmol, 2.2 %) in dry DCM (118 mL) at reflux under Ar. The reaction was stirred at reflux for 5 minutes, cooled to rt and concentrated *in vacuo* to a green oil. Flash column chromatography on silica gel (Pet. ether–EtOAc 19:1 to 7:3) gave the [2,3]-rearrangement product **402** (2.25 g, 61%), 2:3 mixture of E : Z isomers) as a white solid and the [1,2]-shift product **403** (0.68 g, 18%) as a colourless oil.

(1*R*,2*R*,4*R*,5*R*)-2-methyl-4-{(2*S*)-2-methyl-1-methylene-3-[(triisopropylsilyl)oxy]propyl}-6-oxo-9-oxabicyclo[3.3.1]non-2-yl acetate 403.[127]

R_f = 0.40 (Pet. ether–EtOAc 4:1); $[\alpha]_D^{21}$ –6.9 (*c* = 0.90, $CHCl_3$) [Lit.[127] $[\alpha]_D^{21}$ –7.1 (*c* = 1.1, $CHCl_3$)]; ν_{max} 2942, 2891, 2865, 1734, 1366, 1240 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.84 (1H, s, CH_2-C10), 4.67 (1H, s, CH_2-C10), 4.49 (1H, d, *J* = 8.5 Hz, CH-C1), 4.18 (1H, d, *J* = 6.0 Hz, CH-C5), 3.90 (1H, dd, *J* = 9.5, 4.5 Hz, CH_2-C13), 3.52 (1H, dd, *J* = 9.5, 8.9 Hz, CH_2-C13), 2.82–2.77 (1H, m, CH-C6), 2.64–2.59 (1H, m, CH_2-C3), 2.33–2.24 (3H, m, CH_2-C3, CH-C11, CH_2–C2), 2.13 (1H, dd, *J* = 13.5, 4.0 Hz, CH_2-C7), 2.20–2.02 (1H, m, CH_2-C2), 2.02 (3H, s, CH_3-C16), 1.85 (1H, t, *J* = 13.5 Hz, CH_2-C7), 1.78 (3H, s, CH_3-C14), 1.14 (3H, d, *J* = 6.8 Hz, CH_3-C12), 1.12–1.02 (21H, m, ^{i}Pr-TIPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.4 (C-C4), 170.2 (C-C15), 150.0 (C-C9), 110.5 (CH_2-C10), 81.3 (C-C8), 79.5 (CH-C5), 71.5 (CH-C1), 67.5 (CH_2-C13), 41.8 (CH-C6), 41.6 (CH-C11), 36.0 (CH_2-C3), 34.6 (CH_2-C7), 23.2 (CH_3-C14), 22.2 (CH_3-C16), 21.7 (CH_2-C2), 18.8 (CH_3-C12), 18.3 (CH_3-TIPS), 12.3 (H-CTIPS); HRMS (FAB) for $C_{25}H_{44}O_5Si$ $[M+H]^+$ calcd 453.3036, found 453.3040.

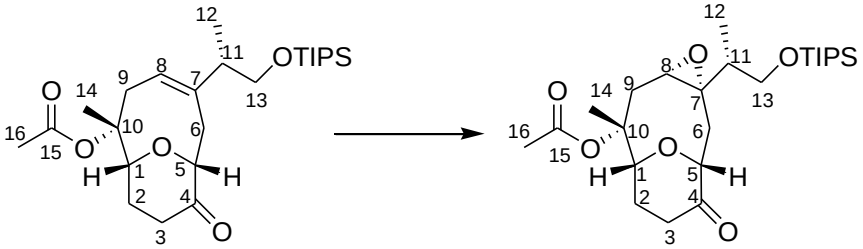
***Z*-(1*R*,2*R*,4*Z*,7*R*)-2-Methyl-5-{(1*S*)-1-methyl-2-[(triisopropylsilyl)oxy]ethyl}-8-oxo-11-oxabicyclo[5,3,1]undec-4-en-2-yl acetate *Z*-402.**[127]



AIBN (0.20 g, 0.46 mmol) was added to a solution of the ketone **402** (2.10 g, 4.64 mmol, 3:1 *Z:E* isomer mixture,) and ethanethiol (8 mL) and dry benzene (100 mL) at reflux under Ar and the resulting solution was stirred 1 hour at reflux. The solution was then cooled and concentrated in *vacuo* to yield a yellow oil. Flash chromatography on silica gel (Pet. ether–EtOAc 19:1 to 9:1) afforded the alkene ***Z*-402** (2.10 g, 100%) as a white solid. M. P. 50-53 °C. R_f = 0.38 (Pet. ether–EtOAc 4:1); $[\alpha]_D^{23}$ +56.5 (*c* = 1.3, $CHCl_3$) [Lit.[127] $[\alpha]_D^{23}$ +57.0 (*c* = 1.3, $CHCl_3$)]; ν_{max} 2956, 2941, 2865, 1729, 1463, 1367,

1091 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.55 (1H, t, *J* = 8.2 Hz, CH-C8), 4.35 (1H, t, *J* = 9.2 Hz, CH-C1), 3.96 (1H, brs, CH-C5), 3.57 (1H, dd, *J* = 9.6, 6.0 Hz, CH_2-C13), 3.41 (1H, dd, *J* = 9.6, 7.2 Hz, CH_2-C13), 2.50–2.36 (4H, m, CH_2-C9, CH_2-C3), 2.30–2.20 (3H, m, CH-C11, CH_2-C6), 2.07 (2H, m, CH_2-C2), 1.98 (3H, s, CH_3-C16), 1.65 (3H, s, CH_3-C14), 1.08–0.96 (24H, m, CH_3-C12, ^{i}Pr-TIPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.0 (C-C4), 170.0 (C-C15), 140.9 (C-C7), 123.4 (CH-C8), 87.3 (C-C10), 79.6 (CH-C5), 77.3 (CH-C1), 67.7 (CH_2-C13), 43.3 (CH-C6), 35.4 (CH-C11), 34.5 (CH_2-C9), 32.2 (CH_2-C3), 22.4 (CH_3-C16), 22.1 (CH_3-C14), 20.1 (CH_2-C2), 18.1 (CH_3-TIPS), 16.3 (CH_3-C12), 12.0 (CH-TIPS); HRMS (CI, isobutane) for $C_{25}H_{45}O_5Si$ $[M+H]^+$ cacld 453.3036, found 453.3039.

1*R*,3*S*,5*S*,7*R*,8*R*)-7-Methyl-3-{(1*R*)-1-methyl-2[(triisopropylsilyl)oxy]ethyl}-11-oxo-4,12-dioxatricyclo[6.3.1.0]dodec-7-yl acetate 409.[127]



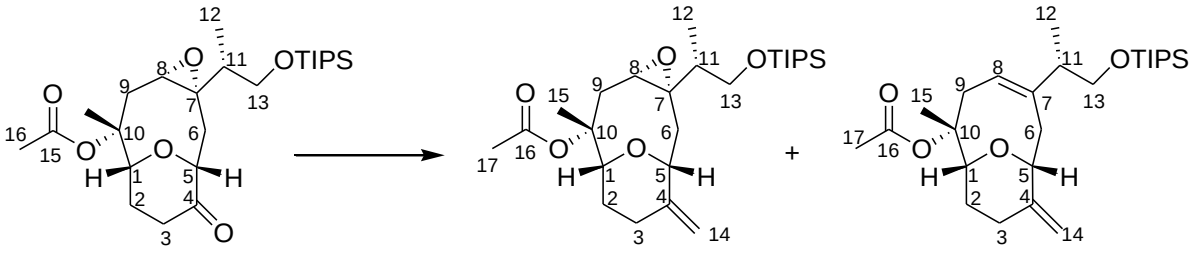
Z-402 **409**

Recrystallised *m*-CPBA (1.5 g, 6.6 mmol) was added to a solution of the alkene ***Z*-402** (1.9 g, 4.4 mmol) in dry DCM (200 mL) under Ar. The reaction mixture was heated at reflux for 1 h then allowed to cool to rt. The reaction was quenched with a saturated aqueous solution of sodium thiosulfate (250 mL) and the mixture was extracted with DCM (2 × 250 mL). The organic extracts were combined and washed sequentially with a saturated aqueous solution of sodium bicarbonate (250 mL) water (250 mL), and brine (250 mL) then dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography on silica gel (Pet. ether–EtOAc 9:1 to 4:1) gave the epoxide **409** (1.77 g, 91%, 10:1 mixture of diastereoisomeres) as a white solid. M. P. 83-85 °C. R_f = 0.37 (Pet. ether–EtOAc 4:1); $[\alpha]_D^{23}$ –6.5 (*c* = 0.4, $CHCl_3$) [Lit.[127] $[\alpha]_D^{21}$ –6.5 (*c* = 0.46, $CHCl_3$)]; ν_{max} 2958, 2943, 2891, 2866, 1733, 1463, 1368, 1240, 1091 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.39 (1H, dd, *J* = 15.5, 6.0 Hz, CH-C1), 4.19 (1H, dd, *J* = 13.6, 4.8 Hz, CH-C5), 3.76 (1H, dd, *J* = 9.8, 6.0 Hz, CH_2-C13), 3.43 (1H, dd, *J* = 9.8, 6.8 Hz, CH_2-C13), 3.04 (1H, dd,

J = 9.8, 5.2 Hz, CH-C8), 2.68 (1H, dd, *J* = 14.2, 5.2 Hz, CH_2-C9), 2.58 (1H, dd, *J* = 14.4, 4.8 Hz, CH_2-C6), 2.49–2.43 (2H, m, CH_2-C3) 2.09–2.07 (1H, m, CH_2-C2), 1.91 (3H, s, CH_3-C16), 1.89–1.82 (1H, m, CH-C11), 1.82–1.77 (1H, m, CH_2-C2), 1.74 (3H, s, CH_3-C14), 1.60 (1H, dd, *J* = 14.2, 9.8 Hz, CH_2-C9), 1.28 (1H, dd, *J* = 14.4, 13.6 Hz, CH_2-C6), 1.05–0.98 (21H, m, ^{i}Pr-TIPS), 0.85 (3H, d, *J* = 6.8 Hz, CH_3-C12); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.9 (C-C4), 169.9 (C-C15), 83.2 (C-C10), 77.5 (CH-C1), 76.7 (CH-C5), 65.9 (CH_2-C13), 62.6 (C-C7), 57.2 (CH-C8), 39.2 (CH-C11), 37.8 (CH_2-C6), 37.0 (CH_2-C3), 35.4 (CH_2-C9), 22.7 (CH_3-C16), 22.3 (CH_3-C14), 20.1 (CH_2-C2), 19.9 (CH_3-TIPS), 13.2 (CH_3-C12), 12.2 (CH-TIPS); HRMS (CI, isobutane) for $C_{25}H_{45}O_6Si$ $[M+H]^+$ calcd 469.2985, found 469.2982. Anal. Calcd for $C_{25}H_{44}O_6Si$: C, 64.06%; H, 9.46%. Found: C, 63.75%; H, 9.53%.

(1*R*,3*S*,5*S*,7*R*,8*R*)-7-Methyl-11-methylene-3-{(1*R*)-1-methyl-2-[(triisopropylsilyl)oxy]ethyl}-4,12-dioxatricyclo[6.3.1.0]dodec-7-yl acetate 410.[127]

(1*R*,2*R*,7*R*,*E*)-2-methyl-8-methylene-5-((S)-1-(triisopropylsilyloxy)propan-2-yl)-11-oxa-bicyclo[5.3.1]undec-4-en-2-yl acetate 411.



409 **410** **411**

Titanium(IV) chloride (4.26 mL of a 1.0 M solution in dry DCM, 4.26 mmol) was added to a solution of Nysted reagent (10.2 mL of a 20% wt suspension in THF, 5.34 mmol) in dry THF (16 mL) at 0 °C under Ar. After stirring the brown mixture for 5 min, a solution of the ketone **409** (1.00 g, 2.32 mmol) in dry THF (40 mL) was added at 0 °C under Ar. The reaction was stirred 2 h and warmed to rt during this period. TLC showed that the reaction was not complted and titanium(IV) chloride (4.26 mL of a 1.0 M solution in dry DCM, 4.26 mmol) and Nysted reagent (10.2 mL of a 20% wt suspension in THF, 5.34 mmol) was added to the mixture at 0 °C under Ar. The reaction was stirred 1 h and warmed to rt during this period. The reaction was quenched by the addition of 0.5 N HCl (50 mL) and extracted with ether (3 × 50 mL). The ether extracts were combined and

washed with water (50 mL) and brine (50 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to give an oil. Flash column chromatography on silica gel (Pet. ether–EtOAc 19:1 to 4:1) afforded the alkene **410** (0.68 g, 63%) as a colourless oil and the diene **411** (0.13, 12%) as a colourless oil.

(1*R*,3*S*,5*S*,7*R*,8*R*)-7-Methyl-11-methylene-3-{(1*R*)-1-methyl-2-[(triisopropylsilyl)oxy]ethyl}-4,12-dioxatricyclo[6.3.1.0]dodec-7-yl acetate 410.[127]

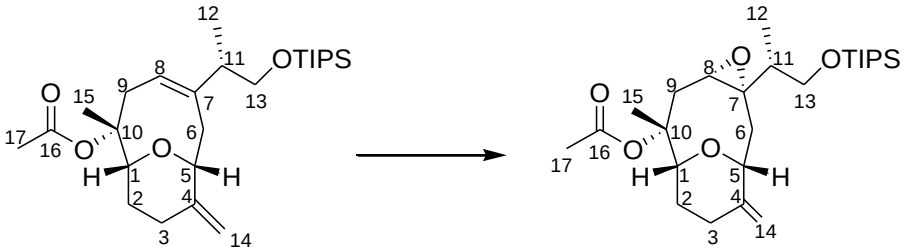
R_f = 0.51 (Pet. ether–EtOAc 4:1); $[\alpha]_D^{21}$ –7.1 (*c* = 1.1, $CHCl_3$) [Lit.[127] $[\alpha]_D^{25}$ –6.6 (*c* = 1.4, $CHCl_3$)]; ν_{max} 2941, 2891, 2866, 1735, 1464, 1435, 1369, 1240, 1043 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.74 (1H, s, CH_2-C14), 4.60 (1H, s, CH_2-C14), 4.49 (1H, dd, *J* = 13.2, 4.8 Hz, CH-C5), 4.14 (1H, dd, *J* = 12.4, 6.0 Hz, CH-C1), 3.81 (1H, dd, *J* = 10.0, 6.0 Hz, CH_2-C13) 3.44 (1H, dd, *J* = 10.0, 7.2 Hz, CH_2-C13), 3.03 (1H, dd, *J* = 9.6, 4.8 Hz, CH-C8), 2.66 (1H, dd, *J* = 13.8, 4.8 Hz, CH_2-C9), 2.74–2.43 (1H, m, CH_2-C3), 2.34 (1H, dd, *J* = 14.8, 4.8 Hz, CH_2-C6), 2.66–2.28 (1H, m, CH_2-C3), 1.99 (1H, dqd, *J* = 7.2, 6.8, 6.0 Hz, CH-C11), 1.89 (3H, s, CH_3-C17), 1.73–1.70 (1H, m, CH_2-C2), 1.89 (3H, s, CH_3-C15), 1.60 (1H, dd, *J* = 13.8, 9.6 Hz, CH_2-C9), 1.53 (1H, dd, *J* = 12.4, 3.2 Hz, CH_2-C2), 1.32 (1H, dd, *J* = 14.8, 13.2 Hz, CH_2-C6), 1.06–0.98 (21H, m, ^{i}Pr-TIPS), 0.86 (3H, d, *J* = 6.8 Hz, CH_3-C12); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9 (C-C16), 146.2 (C-C4), 106.2 (CH_2-C14), 82.2 (C-C10), 76.2 (CH-C1), 71.4 (CH-C5), 64.7 (CH_2-C13), 61.6 (C-C7), 55.8 (CH-C8), 42.1 (CH_2-C6), 37.4 (CH-C11), 32.3 (CH_2-C9), 25.6 (CH_2-C3), 21.4 (CH_3-C17), 21.0 (CH_3-C15),19.6 (CH_2-C2), 17.0 (CH_3-TIPS), 11.9 (CH_3-C12), 10.9 (CH-TIPS); HRMS (CI, isobutane) for $C_{26}H_{47}O_5Si$ $[M+H]^+$ calcd 467.3193, found 467.3196.

(1*R*,2*R*,7*R*,*E*)-2-methyl-8-methylene-5-((*S*)-1-(triisopropylsilyloxy)propan-2-yl)-11-oxa-bicyclo[5.3.1]undec-4-en-2-yl acetate 411.

R_f = 0.45 (Pet. ether–EtOAc 9:1); $[\alpha]_D^{18}$ +13.6 (*c* = 0.14, $CHCl_3$); ν_{max} 2939, 2862, 1735, 1465, 1365, 1244, 1080, 1010 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 5.53 (1H, t, *J* = 8.4 Hz, CH-C8), 4.82 (1H, s, CH_2-C14), 4.68 (1H, s, CH_2-C14), 4.29 (1H, dd, *J* = 12.4, 4.8 Hz, CH-C5), 4.19 (1H, dd, *J* = 10.8, 7.6 Hz, CH-C1), 3.69 (1H, dd, *J* = 9.6, 5.2 Hz, CH_2-C13), 3.48 (1H, dd, *J* = 9.6, 7.6 Hz, CH_2-C13), 2.54–2.44 (3H, m, CH_2-C9, CH_2-C3), 2.36–2.29 (3H, m, CH-C11, CH_2-C6, CH_2-C3), 2.15 (1H, dd, *J* = 14.0, 4.8 Hz, CH_2-C6), 1.95 (3H, s, CH_3-C17), 1.85–1.82 (2H, m, CH_2-C2), 1.67 (3H, s, CH_3-C15), 1.95 (3H, d, *J* = 6.4 Hz,

CH_3-C12), 1.05–1.02 (21H, m, ^{i}Pr-TIPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0 (C-C16), 147.1 (C-C4), 141.1 (C-C7), 121.2 (CH-C8), 105.8 (CH_2-C14), 85.5 (C-C10), 76.8 (CH-C1), 74.4 (CH-C5), 67.3 (CH_2-C13), 42.0 (CH-C11), 41.7 (CH_2-C6), 30.9 (CH_2-C9), 25.2 (CH_2-C3), 21.4 (CH_3-C17), 21.1 (CH_3-C15), 20.0 (CH_2-C2), 16.6 (CH_3-TIPS), 14.2 (CH_3-C12), 10.6 (CH-TIPS); HRMS (CI, isobutane) for $C_{26}H_{47}O_4Si$ $[M+H]^+$ calcd 451.3244, found 451.3249.

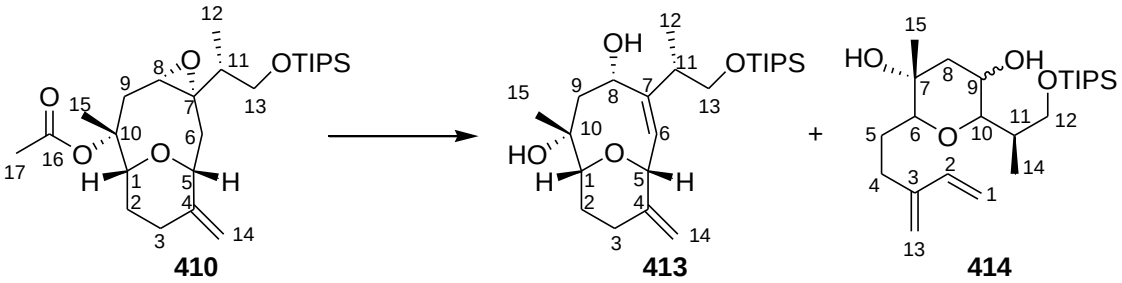
1*R*,3*S*,5*S*,7*R*,8*R*)-7-Methyl-11-methylene-3-{(1*R*)-1-methyl-2-[(triisopropylsilyl)oxy]ethyl}-4,12-dioxatricyclo[6.3.1.0]dodec-7-yl acetate 410.



Recrystallised *m*-CPBA (0.13 g, 0.30 mmol) was added to a solution of the alkene **411** (130 mg, 0.20 mmol) in dry DCM (14 mL) at 0 °C under Ar. The reaction mixture was stirred overnight allowed to warm to rt. The reaction was quenched with a saturated aqueous solution of sodium thiosulfate (10 mL) and the mixture was extracted with DCM (2 × 10 mL). The organic extracts were combined and washed with a saturated aqueous solution of sodium bicarbonate (10 mL), water (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography on silica gel (Pet. ether–EtOAc 9:1) gave the epoxide **410** (92.1 mg, 66%) as a colourless oil.

(1*R*,2*R*,4*S*,5*Z*,7*R*)-2-methyl-8-methylene-5-{(1*S*)-1-methyl-2-[(triisopropylsilyl)oxy]ethyl}-11-oxabicyclo[5.3.1]undec-5-ene—2,4-diol 413.[127]

(1*R*,6*R*)-1,5-anhydro-3,6-dideoxy-6-methyl-2-*C*-methyl-1-(3-methylenepent-4-en-1-yl)-7-*O*-(triisopropylsillyl)-D-*erythro*-heptitol 414.[127]



Aluminium isopropoxide (1.8 g, 8.8 mmol) was added to a solution of the epoxide **410** (410 g, 0.88 mmol) in dry toluene (56 mL) at rt under Ar. The reaction mixture was heated at reflux for 20 h then allowed to cool to rt. The reaction mixture was quenched by the addition of 0.5 N of HCl (50 mL) and the mixture was extracted with ether (3 × 50 mL). The ether extracts were washed with water (50 mL) and brine (50 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography on silica gel (Pet. ether–EtOAc 3:1 to 2:1) gave the diol **413** (186 mg, 49%) and the diene **414** (86 mg, 22%, mixture of diastereoisomers) as colourless oils.

(1*R*,2*R*,4*S*,5*Z*,7*R*)-2-methyl-8-methylene-5-{(1*S*)-1-methyl-2-[(triisopropylsilyl)oxy]ethyl}-11-oxabicyclo[5.3.1]undec-5-ene—2,4-diol 413.[127]

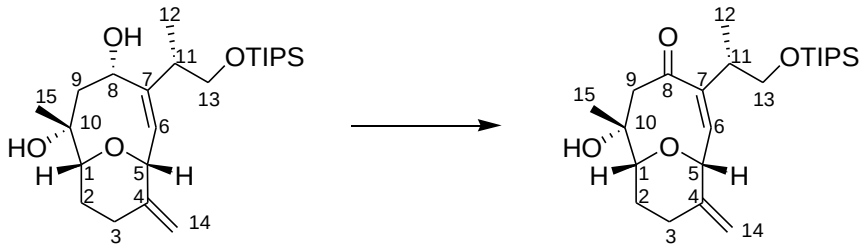
R_f = 0.23 (Pet. ether–EtOAc 3:1); $[\alpha]_D^{25}$ –31.5 (*c* = 1.0, $CHCl_3$) [Lit.[127] $[\alpha]_D^{24}$ –31.0 (*c* = 1.0, $CHCl_3$)]; ν_{max} 3300, 2939, 2862, 1458, 1057, 1003, 879, 794, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.51 (1H, m, CH-C8), 5.21 (1H, s, CH-C6), 4.81 (1H, s, CH-C5), 4.79 (2H, s, CH_2-C14), 4.15 (1H, s, OH), 3.80 (1H, dd, *J* = 8.4, 5.1 Hz, CH_2-C13), 3.71 (1H, dd, *J* =7.2, 6.6 Hz, CH-C1), 3.30 (1H, dd, *J* =10.5, 8.4 Hz, CH_2-C13), 3.17 (1H, dqd, *J* = 10.5, 7.0, 5.1 Hz, CH-C11), 2.75–2.60 (1H, m, CH_2-C3), 2.30–2.22 (1H, m, CH_2-C3), 2.20–2.12 (1H, m, CH_2-C2), 2.08 (1H, dd, *J* = 14.0, 4.0 Hz, CH_2-C9), 2.00–1.92 (1H, m, OH), 1.95 (1H, dd, *J* = 14.0, 9.4 Hz, CH_2-C9), 1.89–1.80 (1H, m, CH_2-C2), 1.35 (3H, s, CH_3-C15), 1.07–1.04 (21H, m, ^{i}Pr-TIPS), 1.01 (3H, d, *J* = 7.0 Hz, CH_3-C12); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1 (C-C7), 149.8 (C-C4), 125.5 (CH-C6), 107.3 (CH_2-C14), 78.9

(CH-C1), 75.1 (CH-C5), 73.6 (CH_2-C13), 65.5 (CH-C8), 47.2 (CH_2-C9), 32.0 (CH-C11), 27.3 (CH_3-C15), 25.1 (CH_2-C3), 21.8 (CH_2-C2), 16.7 (CH_3-TIPS), 16.5 (CH_3-C12), 10.45 (CH-TIPS); HRMS (FAB) for $C_{24}H_{45}O_4Si$ $[M+H]^+$ calcd 425.3087, found 425.3083.

(1*R*,6*R*)-1,5-anhydro-3,6-dideoxy-6-methyl-2-*C*-methyl-1-(3-methylenepent-4-en-1-yl)-7-*O*-(triisopropylsillyl)-D-*erythro*-heptitol 414.[127]

R_f = 0.21 (Pet. ether–EtOAc 3:1); $[\alpha]_D^{24}$ +16.2 (*c* = 1.05, $CHCl_3$) [Lit.[127] $[\alpha]_D^{24}$ +19.0 (*c* = 0.45, $CHCl_3$)]; ν_{max} 3300, 2958, 2941, 2866, 1595, 1462, 881 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.40 (1H, dd, *J* = 17.5, 10.5 Hz, CH-$C2_{min}$), 6.39 (1H, dd, *J* = 18.0, 11.0 Hz, CH-$C2_{maj}$), 5.28 (1H, d, *J* = 18.0 Hz, CH_2-$C1_{maj}$), 5.26 (1H, d, *J* = 17.5 Hz, CH_2-$C1_{min}$), 5.04–5.01 (3H, m, CH_2-C13, CH_2-C1), 4.14 (1H, ddd, *J* = 10.0, 3.0, 1.5 Hz, CH-$C9_{min}$), 4.06 (1H, ddd, *J* = 10.0, 3.5, 2.5 Hz, CH-$C9_{maj}$), 4.01 (1H, dd, *J* = 4.0, 2.5 Hz, CH-C10 + CH_2-$C12_{min}$), 3.85 (1H, dd, *J* = 10.0, 3.5 Hz, CH_2-C12), 3.81 (1H, dd, *J* = 9.5, 3.5 Hz, CH_2-$C12_{min}$), 3.72 (1H, dd, *J* = 10.0, 3.5 Hz, CH_2-$C12_{maj}$), 3.72 (1H, dd, *J* = 10.0, 5.5 Hz, CH_2-$C12_{maj}$) 3.46 (1H, dd, *J* = 9.5, 3.0 Hz, CH-$C6_{min}$), 3.36 (1H, dd, *J* = 9.5, 3.0 Hz, CH-$C6_{maj}$), 2.50 (1H, ddd, *J* = 15.0, 10.5, 5.0 Hz, CH_2-C4), 2.28–2.23 (1H, m, CH_2-$C4_{maj}$ + CH_2-$C8_{min}$), 2.21 (1H, dd, *J* = 13.5, 3.5 Hz, CH-$C8_{maj}$), 2.10–2.07 (1H, m, CH-$C11_{min}$), 2.07 (1H, dd, *J* = 13.5, 9.5 Hz, CH_2-C8), 1.98 (1H, dd, *J* = 13.5, 3.0 Hz, CH_2-$C8_{min}$), 1.84–1.78 (2H, m, CH-$C11_{maj}$, CH_2-C5),1.74–1.67 (1H, m, CH_2-C5), 1.24 (3H, s, CH_3-15), 1.22 (3H, s, CH_3-C15), 1.05 (21H, m, $[\{CH_3\}_2CH]_3$-TIPS), 1.00 (3H, d, *J* = 7.0 Hz, CH_3-C14); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.5 (C-C3), 139.3 (CH-C2), 115.9 (CH_2-C13), 113.5 (CH_2-C1), 85.8 (CH-C6), 78.4 (CH-C9), 77.0 (C-C7), 76.9 (CH-C10), 69.2 (CH_2-C12), 42.0 (CH_2-C8), 37.9 (CH-C11), 28.6 (CH_2-C4), 26.8 (CH_2-C5), 22.4 (CH_3-C15), 18.2 (CH_3-TIPS), 12.4 (CH_3-C14), 12.0 (CH-TIPS); HRMS (CI, isobutane) for $C_{24}H_{47}O_4Si$ $[M+H]^+$ calcd 427.3244, found 427.3245.

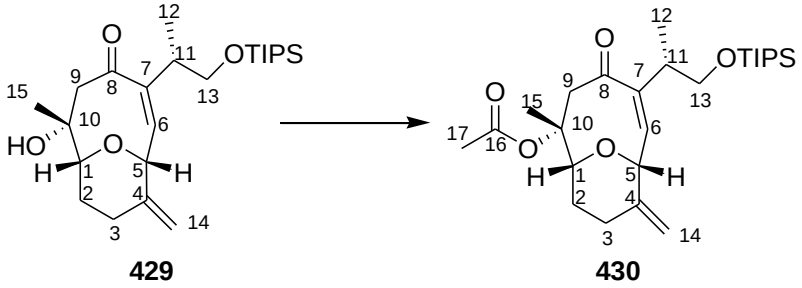
(1*R*,2*R*,5*Z*,7*R*)-2-methyl-8-methylene-5-{(1*S*)-1-methyl-2-[(triisopropylsilyl)oxy]ethyl}-11-oxabicyclo[5.3.1]undec-5-ene-4-one-2-ol 429.



413 **429**

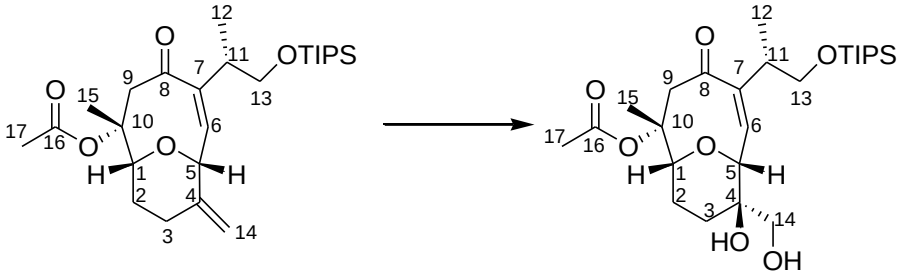
Dess-Martin periodinane (64.0 mg, 0.15 mmol) was added in one portion to a solution of the diol **413** (43.0 mg, 0.10 mmol) in dry DCM (1 mL) at rt under Ar. The mixture was stirred for 2 h at rt, then quenched by the addition of a saturated aqueous solution of sodium thiosulfate (1 mL) and extracted with ether (3 × 1 mL). The organic extracts were combined and washed successively with a saturated solution of sodium bicarbonate (1 mL), water (1 mL) and brine (1 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to give a colourless oil. Flash column chromatography on silica gel (Pet. ether–EtOAc 9:1) gave the ketone **429** (32 mg, 75%) as a colourless oil. R_f = 0.43 (Pet. ether–EtOAc 3:1); $[\alpha]_D^{25}$ –24.5 (c = 1.03, $CHCl_3$); ν_{max} 2941, 2865, 1676, 1462, 1101 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.43 (1H, s, CH-C6), 4.88 (1H, s, CH-C5), 4.86 (2H, s, CH_2-C14), 3.68 (1H, dd, *J* = 6.8, 6.0 Hz, CH-C1), 3.63 (1H, dd, *J* = 12.4, 8.0 Hz, CH_2-C13), 3.58 (1H, dd, *J* = 12.4, 5.6 Hz, CH_2-C13), 2.92 (1H, d, *J* = 13.4 Hz, CH_2-C9), 2.79–2.74 (1H, m, CH_2-C3), 2.58–2.47 (1H, m, CH-C11), 2.53 (1H, d, *J* = 13.4 Hz, CH_2-C9), 2.30–2.22 (1H, m, CH_2-C3), 2.20–2.11 (1H, m, CH_2-C2), 1.96–1.88 (1H, m, CH_2-C2), 1.34 (3H, s, CH_3-C15), 1.10–1.05 (24H, m, ^{i}Pr-TIPS, CH_3-C12); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.0 (C-C8), 144.6 (C-C4), 144.5 (C-C7), 132.5 (CH-C6),125.5 (CH_2-C14), 79.0 (CH-C1), 77.2 (C-C10), 76.0 (CH-C5), 67.0 (CH_2-C13), 54.1 (CH_2-C9), 42.1 (CH-C11), 27.5 (CH_3-C15), 25.8 (CH_2-C3), 22.5 (CH_2-C2), 18.3 (CH_3-TIPS), 16.3 (CH_3-C12), 12.0 (CH-TIPS); HRMS (CI, isobutane) for $C_{24}H_{43}O_4Si$ $[M+H]^+$ calcd 423.2931, found 423.2935.

(1*R*,2*R*,7*R*,*Z*)-2-methyl-8-methylene-4-oxo-5-((*S*)-1-(triisopropylsilyloxy)propan-2-yl)-11-oxa-bicyclo[5.3.1]undec-5-en-2-yl acetate 430.



Acetic anhydride (40 μL, 0.42 mmol) was added to a solution of **429** (30 mg, 7.0 10^{-2} mmol), DMAP (26 mg, 0.23 mmol), and Et_3N (80 μL, 0.60 mmol) in dry ether (1 mL) at rt under Ar and the resulting solution stirred for 20 h. The reaction was quenched with water (30 mL) was added and the mixture was extracted with ether (3 × 3 mL). The ether extracts were combined and washed with water (3 mL) and brine (3 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to give a colourless oil. Flash chromatography on silica gel (Pet. ether –EtOAc 9:1) afforded the acetate **430** (24 mg, 72%) as a clear oil. R_f = 0.57 (Pet. ether–EtOAc 9:1); $[\alpha]_D^{20}$ –34.7 (*c* = 1.05, $CHCl_3$); ν_{max} 2941, 2865, 1743, 1689, 1462, 1366, 1238, 1092 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.33 (1H, s, CH-C5), 5.01 (1H, s, CH_2-C14), 4.91 (1H, s, CH_2-C14), 4.80 (1H, s, CH-C6), 4.10 (1H, dd, *J* = 12.0, 4.0 Hz, CH_2-C1), 3.60 (1H, dd, *J* = 10.4, 8.0 Hz, CH_2-C13), 3.55 (1H, dd, *J* = 10.4, 6.0 Hz, CH_2-C13), 3.32 (1H, d, *J* = 11.0 Hz, CH_2-C9), 2.89 (1H, d, *J* = 11.0 Hz, CH_2-C9), 2.70–2.66 (1H, m, CH_2-C3), 2.47–2.42 (1H, m, CH-C11), 2.38–2.29 (1H, m, CH_2-C2), 2.28–2.16 (1H, ddd, *J* = 16.8, 12.8, 4.4 Hz, CH_2-C3), 1.97 (3H, s, CH_3-C15), 1.82–1.75 (1H, m, CH_2-C2), 1.75 (3H, s, CH_3-C15), 1.06–1.02 (24H, m, ^{i}Pr-TIPS, CH_3-C12); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.6 (C-C8), 168.4 (C-C16), 143.6 (C-C7), 142.5 (C-C4), 130.9 (CH-C6), 109.9 (CH_2-C14), 85.0 (C-C10), 77.1 (CH-C1), 74.7 (CH-C5), 65.5 (CH_2-C13), 47.0 (CH_2-C9), 41.1 (CH-C11), 24.3 (CH_2-C3), 21.1 (CH_3-C17), 21.0 (CH_3-C15), 19.6 (CH_2-C2), 16.9 (CH_3-TIPS), 15.2 (CH_3-C12), 11.2 (CH-TIPS); HRMS (CI, isobutane) for $C_{26}H_{45}O_5Si$ $[M+H]^+$ calcd 465.3036, found 465.3035.

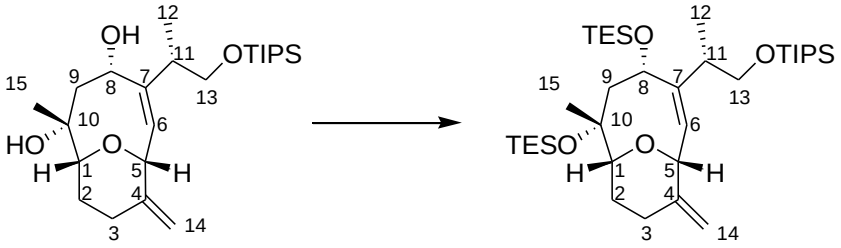
(1*R*,2*R*,7*R*,8*R*,*Z*)-8-hydroxy-8-(hydroxymethyl)-2-methyl-4-oxo-5-((*S*)-1-(triisopropylsilyloxy)propan-2-yl)-11-oxa-bicyclo[5.3.1]undec-5-en-2-yl acetate 431.



430 **431**

A solution of osmium tetroxide (4% in H_2O, 12 µL, 5 mol %) was added to a solution of alkene **430** (18 mg, 0.038 mmol) and NMO (10 mg, 0.085 mmol) in acetone (1mL) and water (250 µL) at rt. The mixture was allowed to stir at rt for 24 h. The reaction was quenched with water (5 mL) and extracted with EtOAc (3 × 5 mL). The organic extracts were combined and washed with water (5 mL) and brine (5 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Flash column chromatography on silica gel (Pet. ether–EtOAc 9:1 to 4:1) gave the diol **431** (12 mg, 70%) as a yellow oil. R_f = 0.47 (Pet. ether–EtOAc 3:1); $[\alpha]_D^{25}$ –34.7 (c = 1.05, $CHCl_3$); ν_{max} 2941, 2865, 1689, 1462, 1366, 1238, 1092 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.52 (1H, s, CH-C6), 4.40 (1H, s, CH-C5), 4.27 (1H, dd, *J* = 11.2, 3.6 Hz, CH-C1), 3.60 (2H, s, CH_2-C14), 3.57 (2H, $_{ap}$d, *J* = 6.8 Hz, CH_2-C13), 3.42 (1H, d, *J* = 11.6 Hz, CH_2-C9), 2.88 (1H, d, *J* = 11.6 Hz, CH_2-C9), 2.70 (1H, brs, OH), 2.47 (1H, m, CH-C11), 2.34-2.17 (1H, m, CH_2-C2), 2.13 (1H, brs, OH), 1.93 (3H, s, CH_3-C17), 1.84–1.77 (1H, m, CH_2-C2), 1.85 (3H, s, CH_3-C15), 1.75–1.59 (2H, m, CH_2-C3), 1.19–1.09 (24H, m, ^{i}Pr-TIPS, CH_3-C12); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.2 (C-C8), 169.4 (C-C16), 147.2 (C-C7), 128.2 (CH-C6), 86.1 (C-C10), 76.2 (CH-C1), 75.6 (CH-C5), 67.4 (CH_2-C14), 66.4 (CH_2-C13), 48.1 (CH_2-C9), 42.7 (CH-C11), 27.3 (CH_2-C3), 22.4 (CH_3-C17), 22.1 (CH_3-C15), 18.4 (CH_2-C2), 17.9 (CH_3-TIPS), 16.0 (CH_3-C12), 11.9 (CH-TIPS).

(1*R*,2*R*,4*S*,5*Z*,7*R*)-2-methyl-8-methylene-5-{(1*S*)-1-methyl-2-[(triisopropylsilyl)oxy]ethyl}-2,4-bis(triethylsilyloxy)-11-oxabicyclo[5.3.1]undec-5 435.[127]

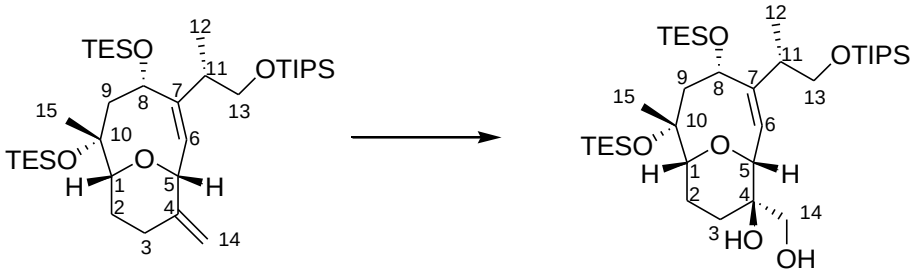


413 **435**

Triethylsilyl trifluoromethanesulfonate (318 µL, 1.42 mmol) was added dropwise over 2 min to a solution of the diol **413** (120 mg, 0.283 mmol) and 2,6-lutidine (496 µL, 4.26 mmol) in dry DCM (7 mL) at –78 °C under Ar. The mixture was stirred at –78 °C for 2 h and the reaction was quenched by the addition of a saturated aqueous solution of sodium carbonate (15 mL) and water (15 mL). The mixture was extracted with ether (3 × 15 mL) and the combined ether extracts were washed with water (15 mL) and brine (15 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to a colourless oil. Flash column chromatography on silica gel (Pet. ether–ether 19:1) gave the diene **435** (160 mg, 85%) as a colourless oil. R_f = 0.72 (Pet. ether–EtOAc 9:1); $[\alpha]_D^{18}$ +29.4 (c = 1.2, $CHCl_3$) [Lit.[127] $[\alpha]_D^{25}$ +26.0 (c = 0.30, $CHCl_3$)]; ν_{max} 2954, 2912, 2875, 2866, 1462, 1240, 1137, 1103, 1084, 1063, 1048, 1008 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.31 (1H, d, *J* = 9.3 Hz, CH-C8), 4.96 (1H, s, CH-C6), 4.69 (2H, s, CH_2-C14), 4.67 (1H, s, CH-C5), 3.65 (1H, dd, *J* = 9.5, 5.0 Hz, CH_2-C13), 3.45 (1H, dd, *J* = 12.7, 4.5 Hz, CH-C1), 3.37 (1H, dd, *J* = 9.5, 7.5 Hz, CH_2-C13), 2.80 (1H, dqd, *J* = 7.5, 7.0, 5.0 Hz, CH-C11), 2.54 (1H, d, *J* = 16.0 Hz, CH_2-C3), 2.27 (1H, dd, *J* = 13.9, 9.3 Hz, CH_2-C9), 2.23–2.17 (1H, m, CH_2-C3), 1.83 (1H, dddd, *J* =13.8, 13.7,12.7, 4.7 Hz, CH_2-C2), 1.76–1.68 (1H, m, CH_2-C2), 1.64 (1H, d, *J* = 13.9 Hz, CH_2-C9), 1.45 (3H, s, CH_3-C15), 1.08 (3H, d, *J* = 7.0 Hz, CH_3-C12), 0.97–0.94 (21H, ^{i}Pr-TIPS), 0.87 (9H, t, *J* = 7.0 Hz, CH_3-TES), 0.85 (9H, t, *J* = 7.0 Hz, CH_3-TES), 0.54 (6H, q, *J* =15.3, 7.0 Hz, CH_2-TES), 0.45 (6H, q, *J* =15.3, 7.0 Hz, CH_2-TES); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.2 (C-C4), 144.7 (C-C7), 126.3 (CH-C6), 107.3 (CH_2-C14), 81.8 (CH-C1), 74.9 (CH-C5), 74.3 (C-C10), 66.9 (CH_2-C13), 65.7 (CH-C8), 49.2 (CH_2-C9), 34.1 (CH-C11), 26.7 (CH_3-C15), 24.7 (CH_2-C3), 19.7 (CH_2-C2), 18.4 (CH_3-C12), 17.0 (CH_3-TIPS), 11.0 (CH-TIPS), 6.0 (CH_3-TES), 5.9 (CH_3-TES), 5.8 (CH_2-TES), 3.9

(CH_2-TES); HRMS (CI, isobutane) for $C_{36}H_{73}O_4Si_3$ $[M+H]^+$ calcd 653.4817, found 653.4827.

(1*R*,2*R*,4*S*,7*R*,8*R*,*Z*)-8-(hydroxymethyl)-2-methyl-2,4-bis(triethylsilyloxy)-5-((*S*)-1-(triisopropylsilyloxy)propan-2-yl)-11-oxa-bicyclo[5.3.1]undec-5-en-8-ol 436.[127]

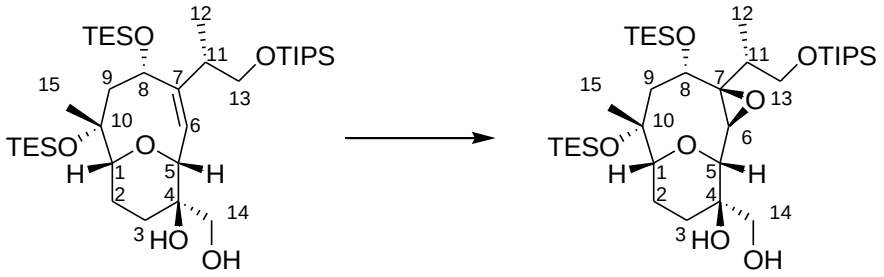


435 **436**

A solution of osmium tetroxide (4% in H_2O, 25 µL, 5 mol %) was added to a solution of alkene **435** (221 mg, 0.338 mmol) and NMO (118 mg, 1.00 10^{-2} mmol) in THF (8 mL) and water (1.3 mL) at rt. The reaction was allowed to stir at rt for 24 h. The reaction was quenched with water (10 mL) and extracted with EtOAc (3 × 10 mL). The organic extracts were combined and washed with water (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to give a colourless oil. Flash column chromatography on silica gel (Pet. ether–EtOAc 4:1) gave the diol **436** (185 mg, 74%) as a colourless oil. R_f = 0.28 (Pet. ether–EtOAc 4:1); $[\alpha]_D^{25}$ +2.3 (c = 1.1, $CHCl_3$) [Lit. [127] $[\alpha]_D^{25}$ +2.3 (c = 1.1, $CHCl_3$)]; ν_{max} 2955, 2915, 2875, 2867, 1460, 1413, 1382, 1370, 1238, 1139, 1089, 1001 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.40 (1H, d, *J* = 8.0 Hz, CH-C8), 5.28 (1H, s, CH-C6), 4.32 (1H, s, CH-C5), 3.74 (1H, dd, *J* = 9.2, 4.8 Hz, CH_2-C13), 3.60 (1H, dd, *J* = 13.6, 5.2 Hz, CH-C1), 3.59 (2H, s, CH_2-C14), 3.41 (1H, dd, *J* = 9.2, 7.6 Hz, CH_2-C13), 3.11 (1H, brs, OH), 2.94 (1H, dqd, *J* = 7.6, 7.2, 4.8 Hz, CH-C11), 2.30 (1H, dd, *J* = 13.6, 10.0 Hz, CH_2-C9), 2.21 (1H, brs, OH), 1.95–1.82 (1H, m, CH_2-C2), 1.79–1.66 (3H, m, CH_2-C2, CH_2-C3, CH_2-C9), 1.54 (3H, s, CH_3-C15), 1.61–1.49 (1H, m, CH_2-C3), 1.65 (3H, d, *J* = 7.2 Hz, CH_3-C12), 1.09–1.04 (21H, m, $[\{CH_3\}_2CH]_3$-TIPS), 0.96 (9H, t, *J* = 7.9 Hz, CH_3-TES), 0.92 (9H, t, *J* = 7.9 Hz, CH_3-TES), 0.61 (6H, q, *J*= 15.4, 7.9 Hz, CH_2-TES), 0.54 (6H, q, *J* = 15.4, 7.9 Hz, CH_2-TES); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8 (C-C7) 120.1 (CH-C6), 80.3 (CH-C1), 75.5 (C-C10), 74.5 (CH-C5), 73.6 (C-C4), 68.1 (CH_2-C13), 66.9 (CH-C8), 66.6 (C-C14), 49.3 (CH_2-C9), 35.5 (CH-C11), 28.3 (CH_2-C3), 27.9 (CH_3-C15), 19.4 (CH_3-C12), 18.9 (CH_2-C2), 18.0 (CH_3-TIPS), 12.0 (CH-TIPS), 7.0

(CH_3-TES), 6.9 (CH_3-TES), 6.8 (CH_2-TES), 4.6 (CH_2-TES); HRMS (FAB) for $C_{36}H_{74}O_6Si_3Na$ $[M+Na]^+$ calcd 709.4691, found 709.4696.

(1*R*,2*R*,4*S*,5*S*,7*R*,8*R*,11*R*)-11-(Hydroxymethyl)-7-methyl-4-{(1R)-1-methyl-2-[(triisopropylsilyl)oxy]ethyl}-5,7-bis[(triethylsilyl)oxy]-3,12dioxatricyclo[6.3.1.0^{2,4}]dodecan-11-ol 437.[127]



m-CPBA (70%, 40.3 mg, 0.28 mmol) was added to a solution of the alkene **436** (0.13 mg, 0.19 mmol) in dry DCM (7 mL) at 0 °C under Ar. The reaction was removed from the ice bath and stirred for 4 h. The reaction was quenched with saturated aqueous sodium thiosulfate solution (10 mL) and extracted with DCM (3 × 10 mL). The organic extracts were combined and washed with a saturated sodium bicarbonate solution (10 mL), water (10 mL) and brine (10 mL), then dried ($MgSO_4$), and concentrated *in vacuo* to give a colourless oil. Flash column chromatography on silica gel (Pet. ether–EtOAc 4:1 to 3:1) gave the epoxide **437** (120.0 mg, 89%) as a colorless oil. R_f = 0.29 (Pet. ether–EtOAc 4:1); $[\alpha]_D^{18}$ +50.9 (c = 1.42, $CHCl_3$) [Lit.[127] $[\alpha]_D^{18}$ +54.2 (c = 0.98, $CHCl_3$)]; ν_{max} 3340, 2956, 2940, 2875, 1462, 1142, 1095 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.22 (1H, $_{ap}$d, *J* = 9.8 Hz, CH-C8), 3.99 (1H, s, CH-C5), 3.81 (1H, dd, *J* = 9.6, 4.5 Hz, CH_2-C13), 3.64 (2H, s, CH_2-C14), 3.59 (1H, dd, *J* = 12.7, 4.1 Hz, CH-C1), 3.30 (1H, dd, *J* = 9.6, 8.0 Hz, CH_2-C13), 2.99 (1H, s, CH-C6), 2.94 (1H, brs, OH), 2.64 (1H, dqd, *J* = 8.0, 7.0, 4.5 Hz, CH-C11), 2.44 (1H, dd, *J* = 14.6, 9.8 Hz, CH_2-C9), 2.10 (1H, brs, OH), 1.94–1.89 (1H, m, CH_2-C2), 1.80–1.72 (2H, m, CH_2-C2, CH_2-C3), 1.66–1.63 (1H, m, CH_2-C3), 1.56 (1H, dd, *J* = 14.6, 9.8 Hz, CH_2-C9), 1.45 (3H, s, CH_3-C15), 1.17 (3H, d, *J* = 7.0 Hz, CH_3-C12), 1.06–1.01 (21H, ^{i}Pr-TIPS), 0.97 (9H, t, *J* = 7.9 Hz, CH_3-TES), 0.93 (9H, t, *J* = 7.9 Hz, CH_3-TES), 0.63 (6H, q, *J* = 15.9, 7.9 Hz, CH_2-TES), 0.56 (6H, q, *J* = 15.9, 7.9 Hz, CH_2-TES); ^{13}C NMR (125 MHz, $CDCl_3$) δ 78.2 (CH-C1), 74.2 (CH-C5), 74.2 (C-C10), 72.6 (C-C4), 71.1 (C-C7),68.0 (C-C7), 65.7 (CH_2-C14), 64.2 (CH_2-C13), 59.6 (CH-C6), 45.0

(CH_2-C9), 32.5 (CH-C11), 26.9 (CH_2-C3), 26.0 (CH_3-C15), 17.8 (CH_2-C2), 17.0 (CH_3-TIPS), 15.6 (CH_3-C12), 10.9 (CH-TIPS), 6.0 (CH_3-TES), 5.8 (CH_3-TES), 5.8 (CH_2-TES), 3.8 (CH_2-TES); HRMS (FAB) for $C_{36}H_{74}O_7Si_3Na$ $[M+Na]^+$ calcd 725.4640, found 709.4642.

(1*R*,2*R*,4*S*,5*S*,7*R*,8*R*,11*R*)-11-(Hydroxymethyl)-7-methyl-4-{(1R)-1-methyl-2-[(triisopropylsilyl)oxy]ethyl}-5-[(triethylsilyl)oxy]-3,12dioxatricyclo[6.3.1.$0^{2,4}$]dodecan-11-ol 438.

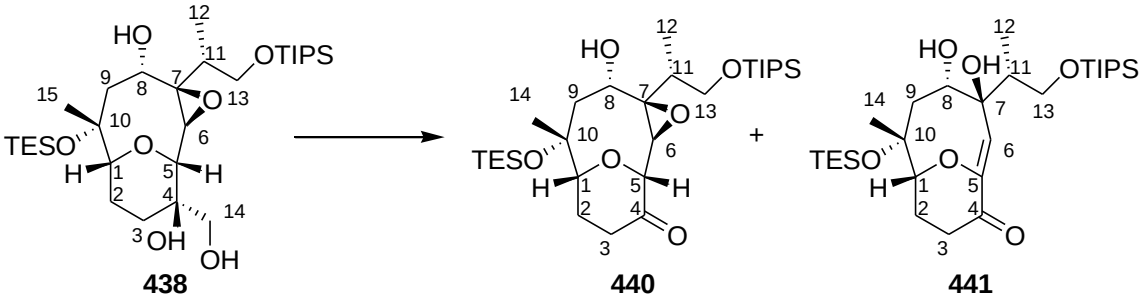
437 **438**

To a solution of **437** (20.0 mg, 0.028 mmol) and pyridine (4 drops) in THF (1.5 mL), was added hydrogen fluoride-pyridine complex (neat, 2 drops) at 0 °C. After stirring at 0 °C for about 2 h, the reaction was quenched with a saturated aqueous sodium bicarbonate solution (1 mL), the aqueous phase was extracted with EtOAc (3 × 1 mL). The organic extracts were washed with water (1 mL) and brine (1 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to yield colourless oil. Flash column chromatography on silica gel (Pet. ether–EtOAc 4:1 to 3:1) gave the triol **438** (10 mg, 71% brsm) as a colourless oil. R_f = 0.29 (Pet. ether–EtOAc 1:1); $[\alpha]_D^{25}$ +20.0 (c = 1.1, $CHCl_3$); ν_{max} 3400, 2955, 2942, 2868, 1462, 1141 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.40 (1H, s, OH), 4.15 (1H, d, *J* = 10.0 Hz, CH-C8), 4.02 (1H, s, CH_2-C5), 3.70 (2H, d, *J* = 4.0 Hz, CH_2-C14), 3.61 (1H, dd, *J* = 11.6, 5.2 Hz, CH-C1), 3.53 (1H, dd, *J* = 9.0, 9.0 Hz, CH_2-C13), 3.45 (1H, dd, *J* = 9.0, 4.4 Hz, CH_2-C13), 3.02 (1H, s, OH), 2.95 (1H, s, CH-C6), 2.75 (1H, m, CH-C11), 2.17 (2H, m, CH_2-C9, OH), 1.95 (1H, m, CH_2-C2), 1.77 (1H, m, CH_2-C3), 1.66–1.62 (3H, m, CH_2-C2, CH_2-C3, CH_2-C9), 1.48 (3H, s, CH_3-C15),1.05–0.92 (21H, m, ^{i}Pr-TIPS), 0.94 (9H, t, *J* = 8.0 Hz, CH_3-TES), 0.91 (3H, d, *J* = 7.2 Hz, CH_3-C12), 0.58 (6H, q, *J* =15.9, 8.0 Hz, CH_2-TES); ^{13}C NMR (100 MHz, $CDCl_3$) δ 79.0 (CH-C1), 75.1 (C-C10), 75.0 (CH-C5), 73.6 (C-C4), 70.2 (CH-C8), 68.3 (C-C7), 66.7 (CH_2-C14), 65.2 (CH_2-C13), 60.6 (CH-C6), 44.9 (CH_2-C9), 32.2 (CH-C11), 27.9 (CH_2-C3), 26.7 (CH_3-C15), 19.0 (CH_2-C2), 17.9

(CH_3-TIPS), 15.8 (CH_3-C12), 11.8 (CH-TIPS), 7.1 (CH_3-TES), 6.83 (CH_2-TES); HRMS (FAB) for $C_{30}H_{59}O_6Si_2$ $[M–OH]^+$ calcd 571.3850, found 571.3849.

(1*R*,2*S*,4*R*,5*S*,7*R*,8*R*)-5-hydroxy-7-methyl-7-[(triethylsilyl)oxy]-4-[(2*R*)-1-{[tris(propan-2-yl)silyl]oxy}propan-2-yl]-3,12-dioxatricyclo[6.3.1.0{2,4}]dodecan-11-one 440.

(1*R*,2*R*,4*S*,5*S*,6*Z*)-4,5-dihydroxy-2-methyl-2-[(triethylsilyl)oxy]-5-[(2R)-1-{[tris(propan-2-yl)silyl]oxy}propan-2-yl]-11-oxabicyclo[5.3.1]undec-6-en-8-one 441.



Iodophenylacetate (40 mg; 0.12 mmol) and TEMPO (1.0 mg, 0.006 mmol) were added to a solution of the triol **438** (12 mg, 0.02 mmol) in dry DCM (1.5 mL) at rt under Ar. The mixture was stirred for 2 h at rt, then quenched by the addition of a saturated aqueous solution of sodium thiosulfate (5 mL). The aqueous phase was separated and extracted with DCM (3 × 5 mL). The organic layers were combined and washed with an aqueous solution of sodium bicarbonate (5 mL), water (5 mL) and brine (5 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to give a colourless oil. Flash column chromatography on silica gel (Pet. ether–EtOAc 2:1) gave the epoxide **440** (5 mg, 50%) as a colourless oil and the diol **441** (4 mg, 40%) as a colourless oil.

(1*R*,2*S*,4*R*,5*S*,7*R*,8*R*)-5-hydroxy-7-methyl-7-[(triethylsilyl)oxy]-4-[(2R)-1-{[tris(propan-2-yl)silyl]oxy}propan-2-yl]-3,12-dioxatricyclo[6.3.1.0{2,4}]dodecan-11-one 440.

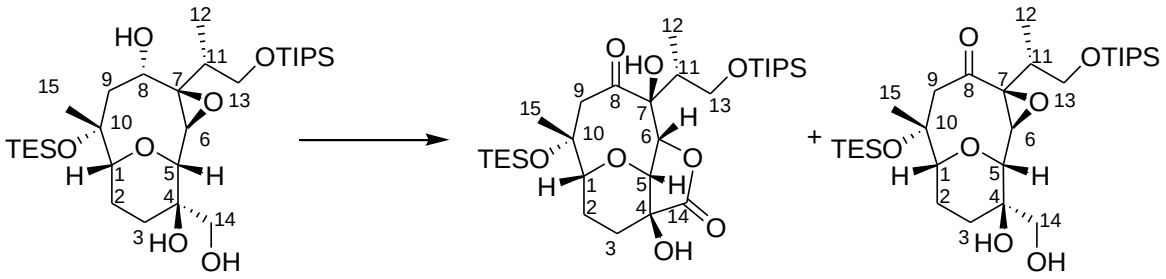
R_f = 0.52 (Pet. ether–EtOAc 9:1); $[\alpha]_D^{16}$ –3.2 (c = 3.0, $CHCl_3$); ν_{max} 3340, 2940, 2870, 1720, 1458, 1249, 1080, 1010 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.41 (1H, s, CH-C5), 4.12 (1H, s, OH), 4.10 (1H, d, *J* = 8.8 Hz, CH-C8), 3.73 (1H, dd, *J* = 12.8, 3.6 Hz, CH-C1), 3.45 (2H, m, CH_2-C13), 2.96 (1H, s, CH-C6), 2.76–2.71 (1H, m, CH-C11), 2.64–2.59

(1H, m, CH_2-C3), 2.43–2.34 (2H, m, CH_2-C3, CH_2-C2), 2.22 (1H, dd, *J* = 14.8, 8.8 Hz, CH_2-C9), 1.70–1.63 (2H, m, CH_2-C9, CH_2-C2), 1.53 (3H, s, CH_3-C14), 1.12–1.04 (21H, m, ^{i}Pr-TIPS), 0.96 (9H, t, *J* = 7.9 Hz, CH_3-TES), 0.89 (3H, d, *J* = 7.2 Hz, CH_3-12), 0.63 (6H, q, *J* = 15.6, 7.9 Hz, CH_2-TES); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.8 (C-C4), 81.8 (CH-C1), 78.6 (CH-C5), 77.2 (C-C10), 74.5 (C-C7), 70.1 (CH-C8), 64.8 (CH_2-C13), 63.4 (CH-C6), 44.5 (CH_2-C9), 35.6 (CH_2-C3), 32.2 (CH-C11), 26.5 (CH_3-C14), 19.8 (CH_2-C2), 17.9 (CH_3-CTIPS), 16.4 (CH_3-C12), 11.8 (CH-TIPS), 7.1 (CH_3-TES), 6.8 (CH_2-TES); HRMS (FAB) for $C_{30}H_{55}O_5Si_2$ $[M–OH]^+$ calcd 539.3588, found 539.3583.

(1*R*,2*R*,4*S*,5*S*,6*Z*)-4,5-dihydroxy-2-methyl-2-[(triethylsilyl)oxy]-5-[(2R)-1-{[tris(propan-2-yl)silyl]oxy}propan-2-yl]-11-oxabicyclo[5.3.1]undec-6-en-8-one 441.

R_f = 0.60 (Pet. ether–EtOAc 9:1); $[\alpha]_D^{15}$ +14.0 (c = 3.0, $CHCl_3$); ν_{max} 3341, 2947, 2870, 1720, 1643, 1458, 1381, 1249, 1057, 1010 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 6.08 (1H, s, CH-C6), 5.19 (1H, s, OH), 4.48–4.46 (1H, m, CH-C8), 4.17 (1H, dd, *J* = 10.0, 7.2 Hz, CH-C1), 4.02 (1H, dd, *J* = 10.6, 10.6 Hz, CH_2-C13), 3.63 (1H, brs, OH), 3.60 (1H, dd, *J* = 10.6, 3.2 Hz, CH_2-C13), 2.58 (1H, ddd, *J* = 15.6, 15.6, 4.4 Hz, CH_2-C3), 2.46–2.40 (2H, m, CH_2-C3, CH-C11), 2.19–2.14 (1H, m, CH_2-C2), 2.18 (1H, dd, *J* = 14.8, 7.6 Hz, CH_2-C9), 1.93–1.84 (1H, m, CH_2-C2), 1.70–1.60 (1H, m, CH_2-C9), 1.62 (3H, s, CH_3-C14), 1.20–1.03 (21H, ^{i}Pr-TIPS), 0.92 (9H, t, *J* = 7.8 Hz, CH_3-TES), 0.82 (3H, d, *J* = 6.8 Hz, CH_3-C12), 0.59 (6H, q, *J* = 15.6, 7.8 Hz, CH_2-TES), ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2 (C-C4), 150.8 (C-C5), 122.1 (CH-C6), 84.4 (CH-C1), 79.3 (C-C7), 77.2 (C-C10), 75.7 (CH-C8), 65.6 (CH_2-C13), 43.2 (CH_2-C9), 39.5 (CH-C11), 34.7 (CH_2-C3), 27.0 (CH_3-C14), 22.3 (CH_2-C2), 17.9 (CH_3-TIPS), 13.0 (CH_3-C12), 11.7 (CH-TIPS), 7.0 (CH_3-TES), 6.8 (CH_2-TES); HRMS (FAB) for $C_{30}H_{55}O_5Si_2$ $[M–OH]^+$ calcd 539.3588, found 539.3583.

(1*S*,4*S*,7*R*,8*R*,12*R*)-4-hydroxy-8-methyl-8-[(triethylsilyl)oxy]-11-[(2*S*)-1-{[tris(propan-2-yl)silyl]oxy}propan-2-yl]-2,13-dioxatricyclo[5.4.2.0{4,12}]tridecane-3,10-dione 421. (1*R*,2*S*,4*S*,7*R*,8*R*,11*R*)-11-hydroxy-11-(hydroxymethyl)-7-methyl-7-[(triethylsilyl)oxy]-4-[(2*R*)-1-{[tris(propan-2-yl)silyl]oxy}propan-2-yl]-3,12-dioxatricyclo[6.3.1.0^{2,4}]dodecan-5-one 443.



Dess-Martin periodinane (186 mg, 0.438 mmol) was added in one portion to a solution of the triol **438** (86.0 mg, 0.146 mmol) in dry DCM (6 mL) at rt under Ar. The mixture was stirred for 5 h at rt, then quenched by the addition of a saturated aqueous solution of sodium thiosulfate (10 mL) and extracted with EtOAc (3 × 10 mL). The organic extracts were combined and washed successively with a saturated aqueous solution of sodium bicarbonate (10 mL), water (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to give a colourless oil. The crude aldehyde **442** was dissolved in *t*-butanol (308 µL) and 2-methyl-2-butene (85%, 55.0 µL, 0.52 mmol). To this mixture was added a solution of sodium chlorite (80%, 35.2 mg, 0.39 mmol) and sodium dihydrogen orthophosphate dihydrate (66.0 mg, 0.42 mmol) in water (260 µL) dropwise at rt. The mixture was stirred 2 h at rt, then the mixture was diluted EtOAc (10 mL). The aqueous phase was separated and extracted with EtOAc (3 × 5 mL). The organic layers were combined and washed with water (5 mL) and brine (5 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to yield a colourless oil. The acid **439** was dissolved in dry DCM (5 mL) and CSA (15 mg, 0.074 mmol) was added at rt under Ar. The reaction was stirred at rt for 45 min then quenched with a saturated aqueous solution of sodium bicarbonate (2 mL). The aqueous layer was separated and extracted with DCM (3 × 5 mL), the organic layers were combined and washed with water (5 mL) and brine (5 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to give colorless oil. Flash column chromatography on silica gel (Pet. ether–EtOAc 2:1) gave the lactone **421** (29 mg, 34%) as a colourless oil and the ketone **443** (32 mg, 39%) as a colourless oil.

(1*S*,4*S*,7*R*,8*R*,12*R*)-4-hydroxy-8-methyl-8-[(triethylsilyl)oxy]-11-[(2S)-1-{[tris(propan-2- yl)silyl]oxy}propan-2-yl]-2,13- dioxatricyclo[5.4.2.0{4,12}]tridecane-3,10-dione 421.

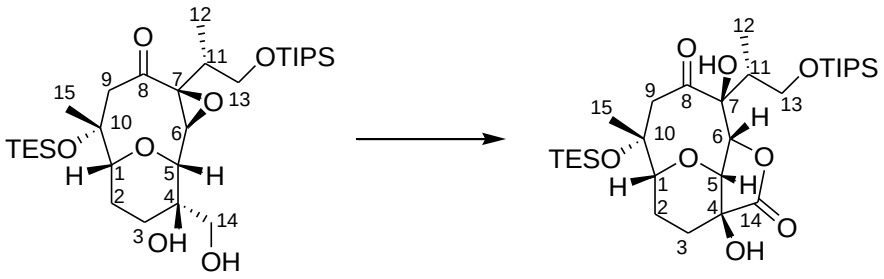
R_f = 0.52 (Pet. ether–EtOAc 4:1); $[\alpha]_D^{18}$ –43.5 (c = 1.65, $CHCl_3$); ν_{max} 3450, 2940, 1791, 1460, 1095, 1014 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.72 (1H, d, *J* = 4.7 Hz, CH-C6), 4.56 (1H, d, *J* = 4.7 Hz, CH-C5), 4.46 (1H, s, OH), 3.77 (1H, dd, *J* = 12.5, 7.0 Hz, CH-C1), 3.50 (1H, dd, *J* = 10.5, 7.0 Hz, CH_2-C13), 3.32 (1H, dd, *J* = 10.5, 5.0 Hz, CH_2-C13), 2.87 (1H, d, *J* = 12.7 Hz, CH_2-C9), 2.53 (1H, s, OH), 2.53–2.16 (2H, m, CH_2-C3, CH-C11), 2.19 (1H, d, *J* = 12.7 Hz, CH_2-C9), 2.01–1.95 (1H, m, CH_2-C2), 1.72 (1H, ddd, *J* = 15.0, 12.0, 9.5 Hz, CH_2-C3), 1.53 (3H, s, CH_3-C15), 1.35–1.22 (1H, m, CH_2-C2), 1.12 (3H, d, *J* = 7.0 Hz, CH_3-C12), 1.04–1.02 (21H, m, ^{i}Pr-TIPS), 0.91 (9H, t, *J* = 8.0 Hz, CH_3-TES), 0.55 (6H, q, *J* = 15.8, 8.0 Hz, CH_2-TES); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.0 (C-C8), 175.9 (C-C14), 84.5 (CH-C6), 80.6 (CH-C1), 80.2 (C-C10), 77.6 (C-C7), 76.1 (CH-C5), 74.9 (C-C4), 62.3 (CH_2-C13), 43.5 (CH_2-C9), 39.1 (CH-C11), 28.0 (CH_3-C15), 26.0 (CH_2-C3), 20.7 (CH_2-C2), 16.9 (CH_3-TIPS), 11.3 (CH_3-C12), 11.1 (CH-TIPS), 5.9 (CH_3-TES), 5.8 (CH_2-TES); HRMS (EI) for $C_{30}H_{52}O_8Si_2$ $[M+H]^+$ calcd 600.3330, found 600.3315.

(1*R*,2*S*,4*S*,7*R*,8*R*,11*R*)-11-hydroxy-11-(hydroxymethyl)-7-methyl-7-[(triethylsilyl)oxy]-4-[(2*R*)-1-{[tris(propan-2-yl)silyl]oxy}propan-2-yl]-3,12-dioxatricyclo[6.3.1.0{2,4}]dodecan-5-one 443.

R_f = 0.25 (Pet. ether–EtOAc 3:1); $[\alpha]_D^{21}$ –80.9 (c = 1.70, $CHCl_3$); ν_{max} 3456, 2944, 2862, 1750, 1475, 1101, 1004 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.07 (1H, s, CH-C5), 3.75 (1H, dd, *J* = 10.4, 7.2 Hz, CH_2-C13), 3.67 (1H, d, *J* = 8.0 Hz, CH-C1), 3.66 (2H, s, CH_2-C14), 3.52 (1H, dd, *J* = 10.4, 7.2 Hz, CH_2-C13), 3.31 (1H, s, CH-C6), 3.21 (1H, d, *J* = 11.0 Hz, CH_2-C9), 2.31 (1H, d, *J* = 11.0 Hz, CH_2-C9), 2.26–2.23 (1H m, CH-C11), 2.11–2.05 (1H, m, CH_2-C2), 2.03–1.91 (1H, m, CH_2-C2), 1.85–1.80 (1H, m, CH_2-C3), 1.75–1.66 (1H, m, CH_2-C3), 2.67 (1H, s, OH), 1.55 (1H, s, OH), 1.46 (3H, s, CH_3-C15), 1.05–1.02 (21H, m, ^{i}Pr-TIPS), 0.97–0.91 (12H, m, CH_3-TES, CH_3-C12), 0.61 (6H, q, *J* = 15.7, 7.8 Hz, CH_2-TES); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.6 (C-C8), 79.5 (C-C10), 78.8 (CH-C1), 74.3 (CH-C5),72.9 (C-C4), 70.6 (C-C7), 66.9 (CH_2-C14), 65.0 (CH_2-C13), 64.9 (CH-C6), 48.7 (CH_2-C9), 38.7 (CH-C11), 27.2 (CH_2-C3), 26.2 (CH_3-C15), 19.3 (CH_2-C2), 18.0

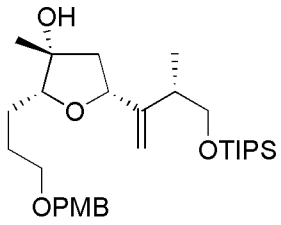
(CH_3-TIPS), 12.1 (CH_3-C12), 12.0 (CH-TIPS), 7.11 (CH_3-TES), 6.7 (CH_2-TES); HRMS (CI) for $C_{30}H_{59}O_7Si_2$ $[M+H]^+$ calcd 587.3799, found 587.3796.

(1*S*,4*S*,7*R*,8*R*,12*R*)-4-hydroxy-8-methyl-8-[(triethylsilyl)oxy]-11-[(2*S*)-1-{[tris(propan-2-yl)silyl]oxy}propan-2-yl]-2,13-dioxatricyclo[5.4.2.0{4,12}]tridecane-3,10-dione 421.



Dess-Martin periodinane (73 mg, 0.17 mmol) was added in one portion to a solution of the diol **443** (34 mg, 0.057 mmol) in dry DCM (3 mL) at rt under Ar. The mixture was stirred for 5 h at rt, then quenched by the addition of a saturated aqueous solution of sodium thiosulfate (5 mL) and extracted with EtOAc (3 × 5 mL). The organic extracts were combined and washed successively with a saturated solution aqueous of sodium bicarbonate (5 mL), water (5 mL) and brine (5 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to give a colourless oil. The crude aldehyde **442** was dissolved in *t*-butanol (120 µL) and 2-methyl-2-butene (85%, 20.0 µL, 0.19 mmol). To this mixture was added a solution of sodium chlorite (80%, 12.0 mg, 0.14 mmol) and sodium dihydrogen orthophosphate dihydrate (24.0 mg, 0.15 mmol) in water (100 µL) was added dropwise at rt. The mixture was stirred 2 h at rt, then diluted EtOAc (5 mL). The aqueous phase was separated and extracted with EtOAc (3 × 5 mL), the organic layer were combined, washed with water (5 mL) and brine (5 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to give a colourless oil. The acid **439** was dissolved in dry DCM (2 mL) and CSA (5 mg, 0.02 mmol) was added at rt under Ar. The reaction was stirred at rt for 45 min then quenched with a saturated aqueous sodium bicarbonate solution (1 mL). The aqueous layer was separated and extracted with DCM (3 × 5 mL), the organic layers were combined and washed with water (5 mL) and brine (5 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to give a colorless oil. Flash column chromatography on silica gel (Pet. ether–EtOAc 2:1) gave the lactone **421** (9 mg, 30%).

Appendices



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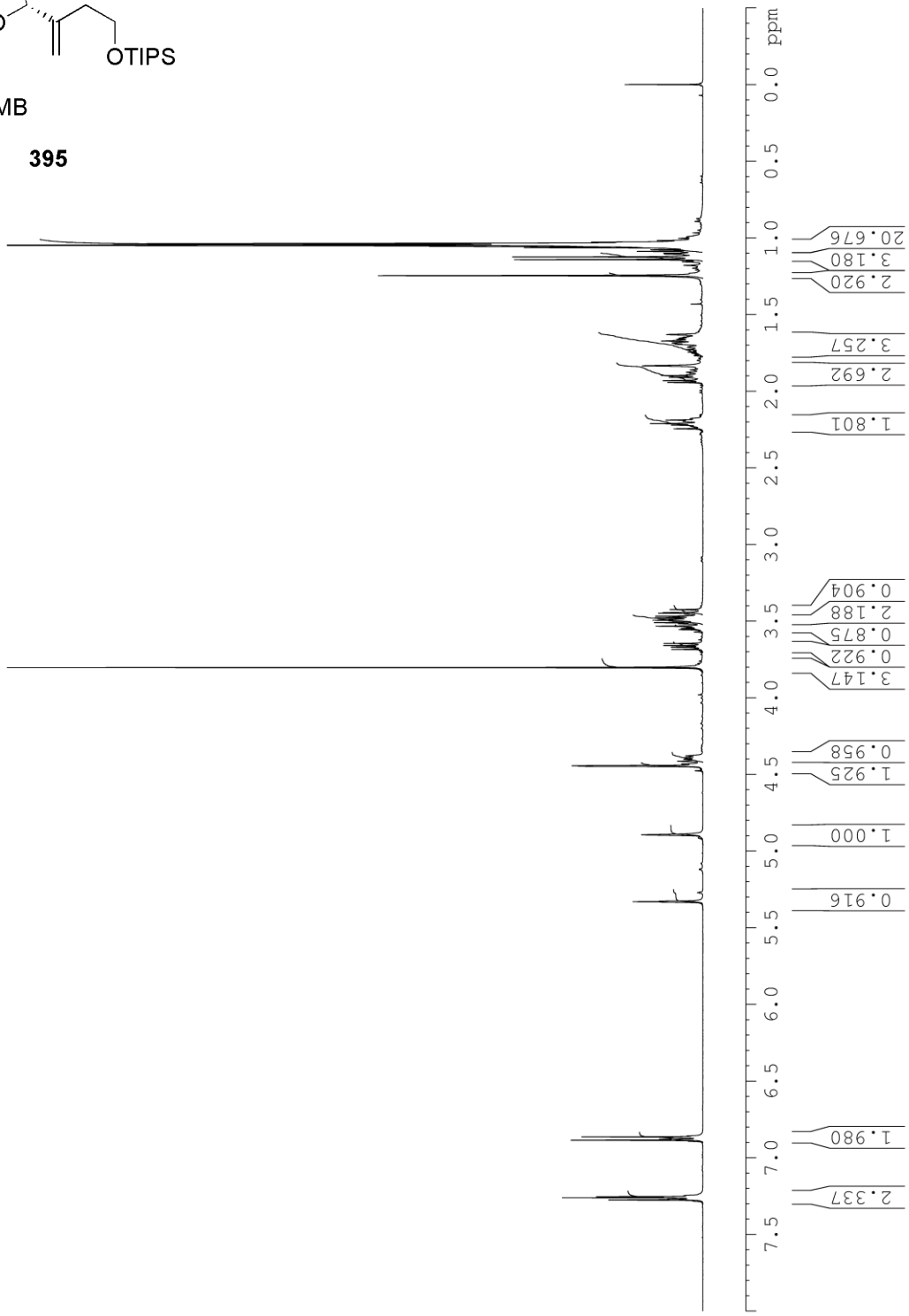

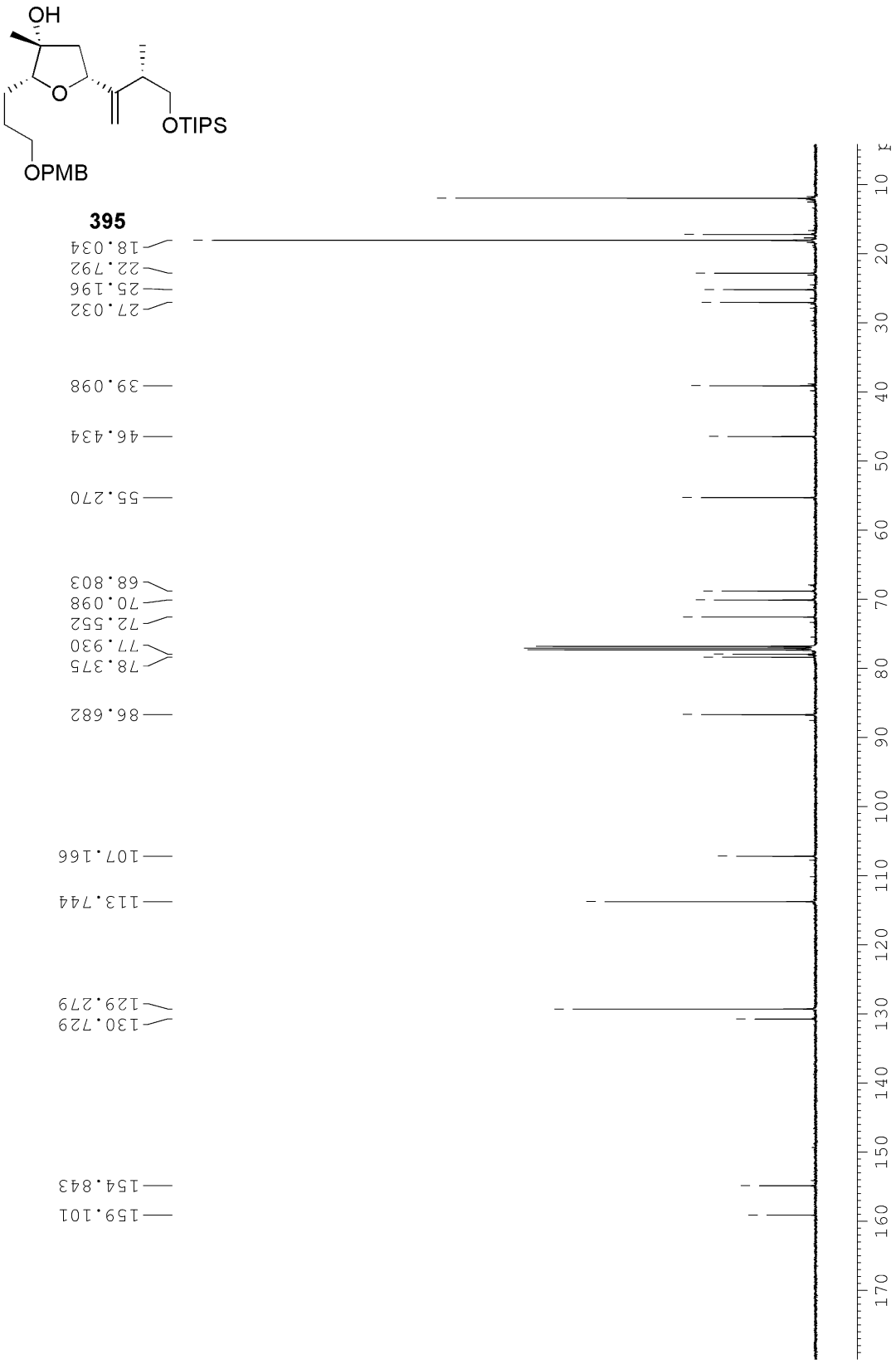
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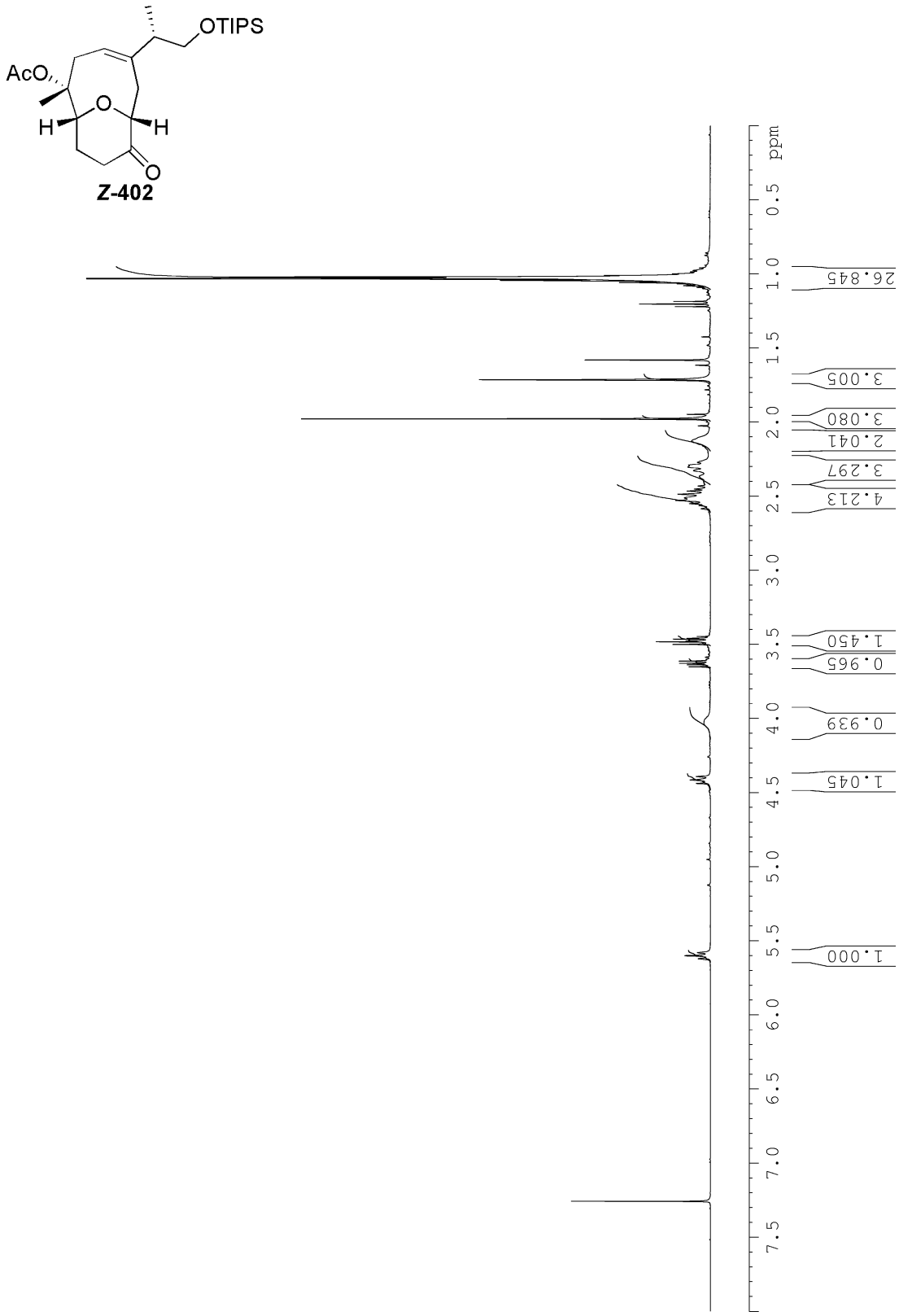
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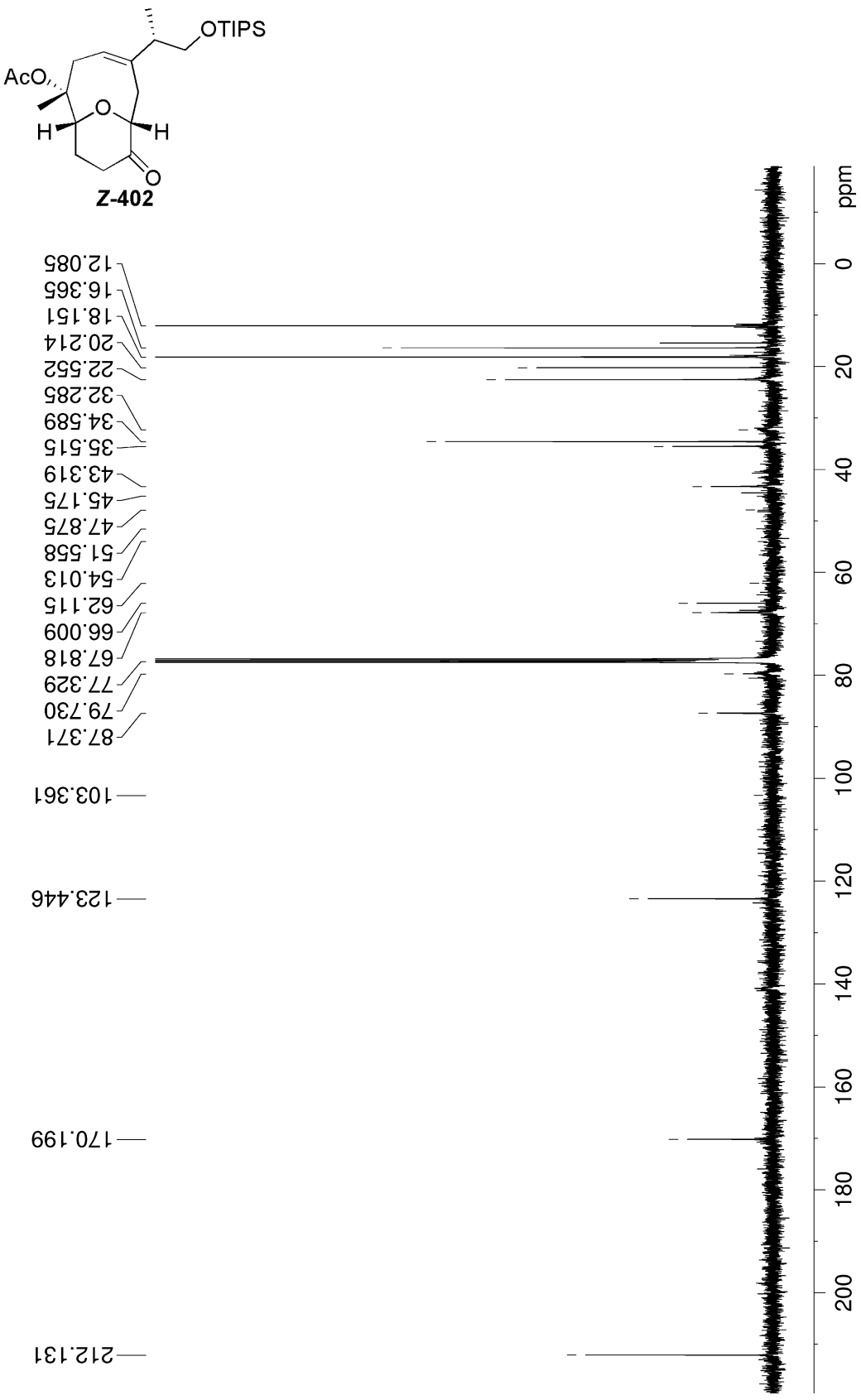
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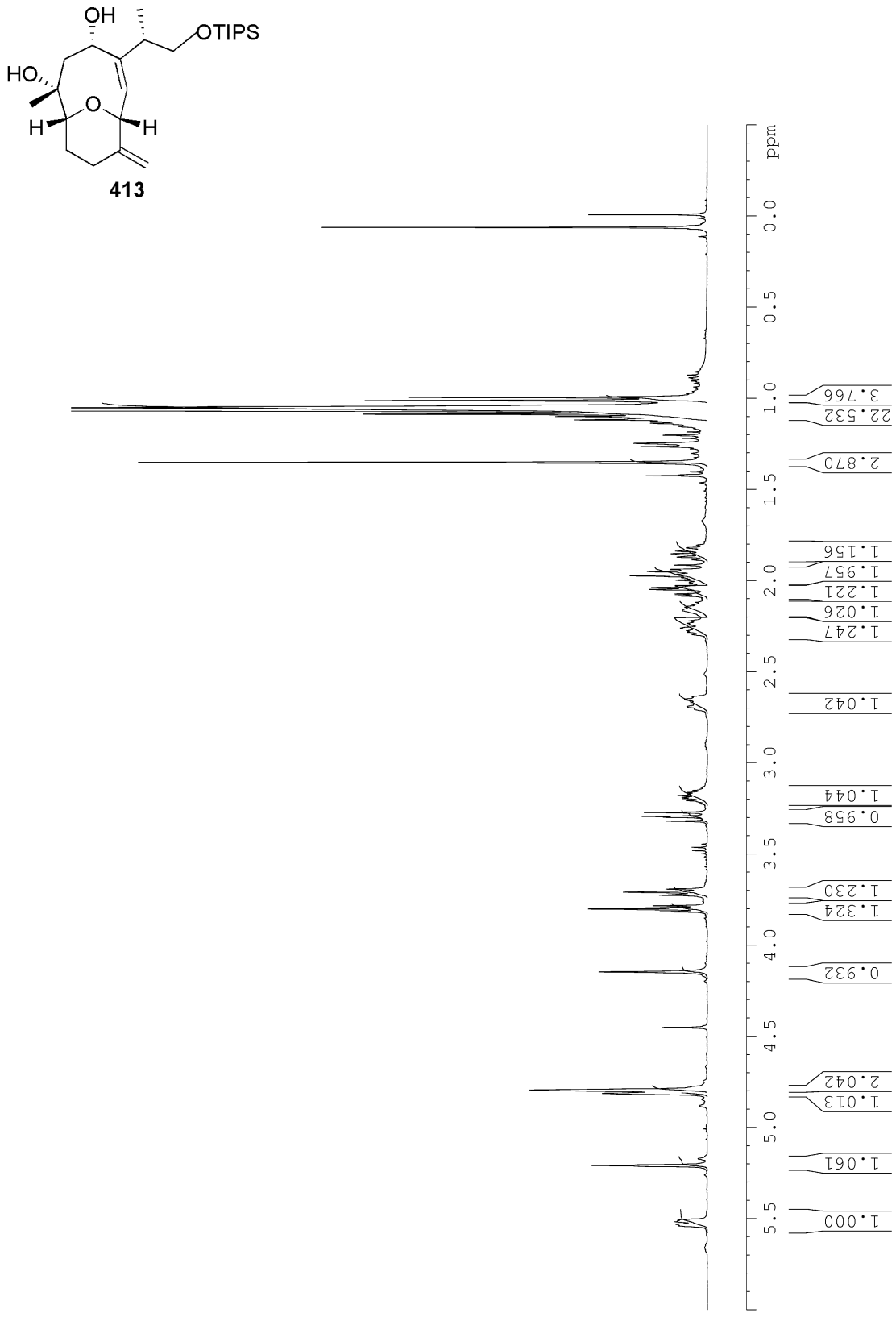
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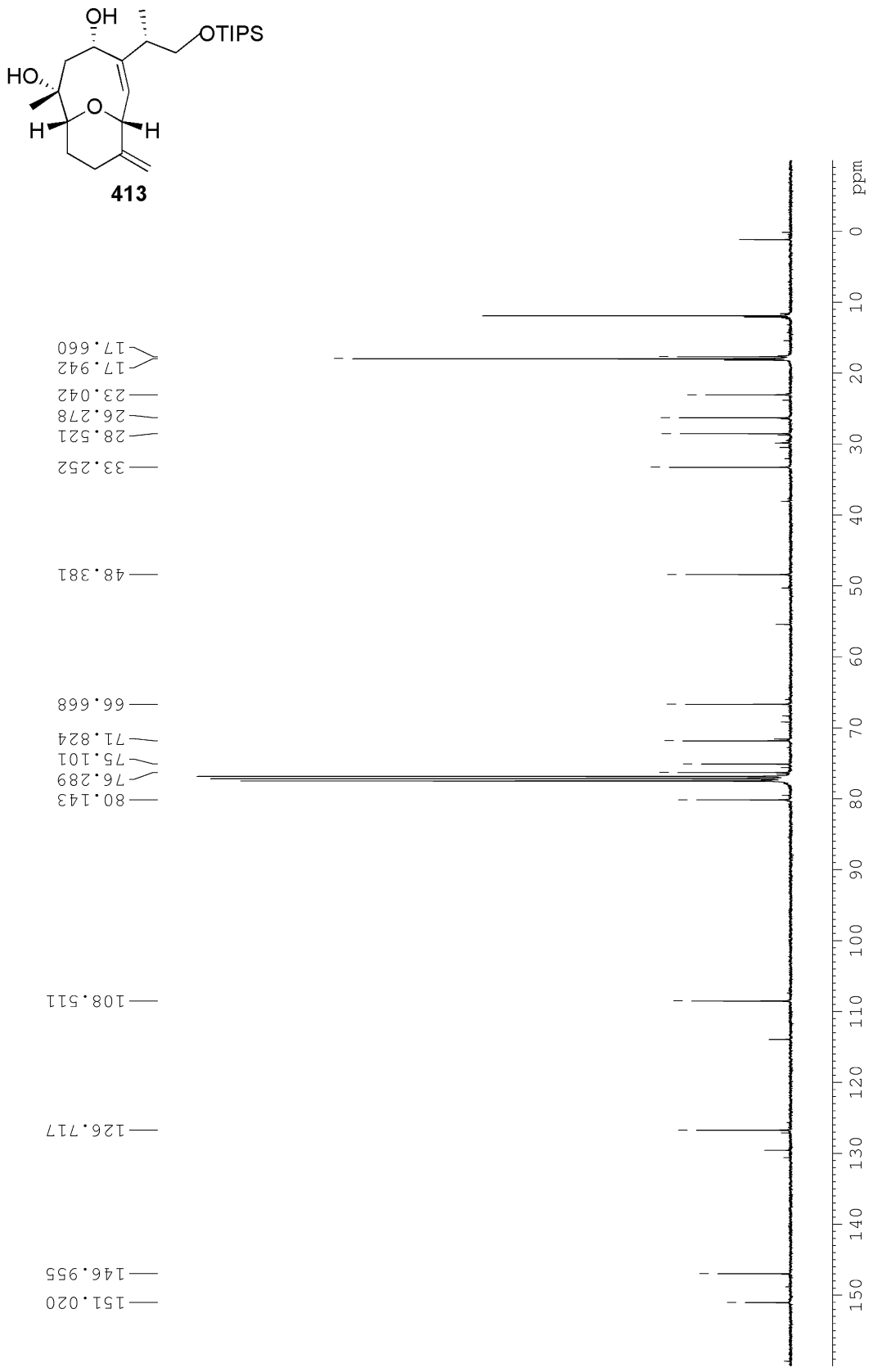
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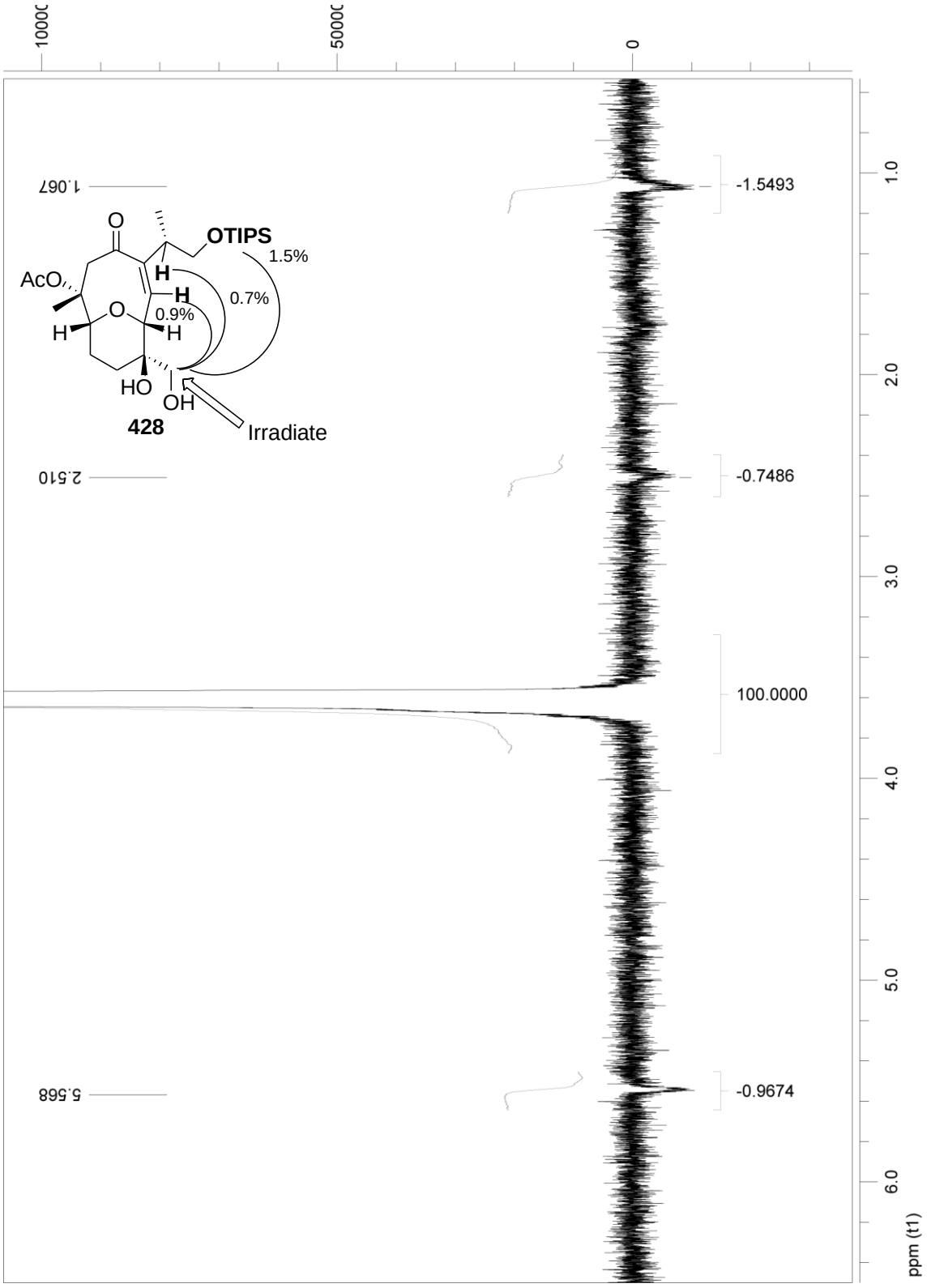
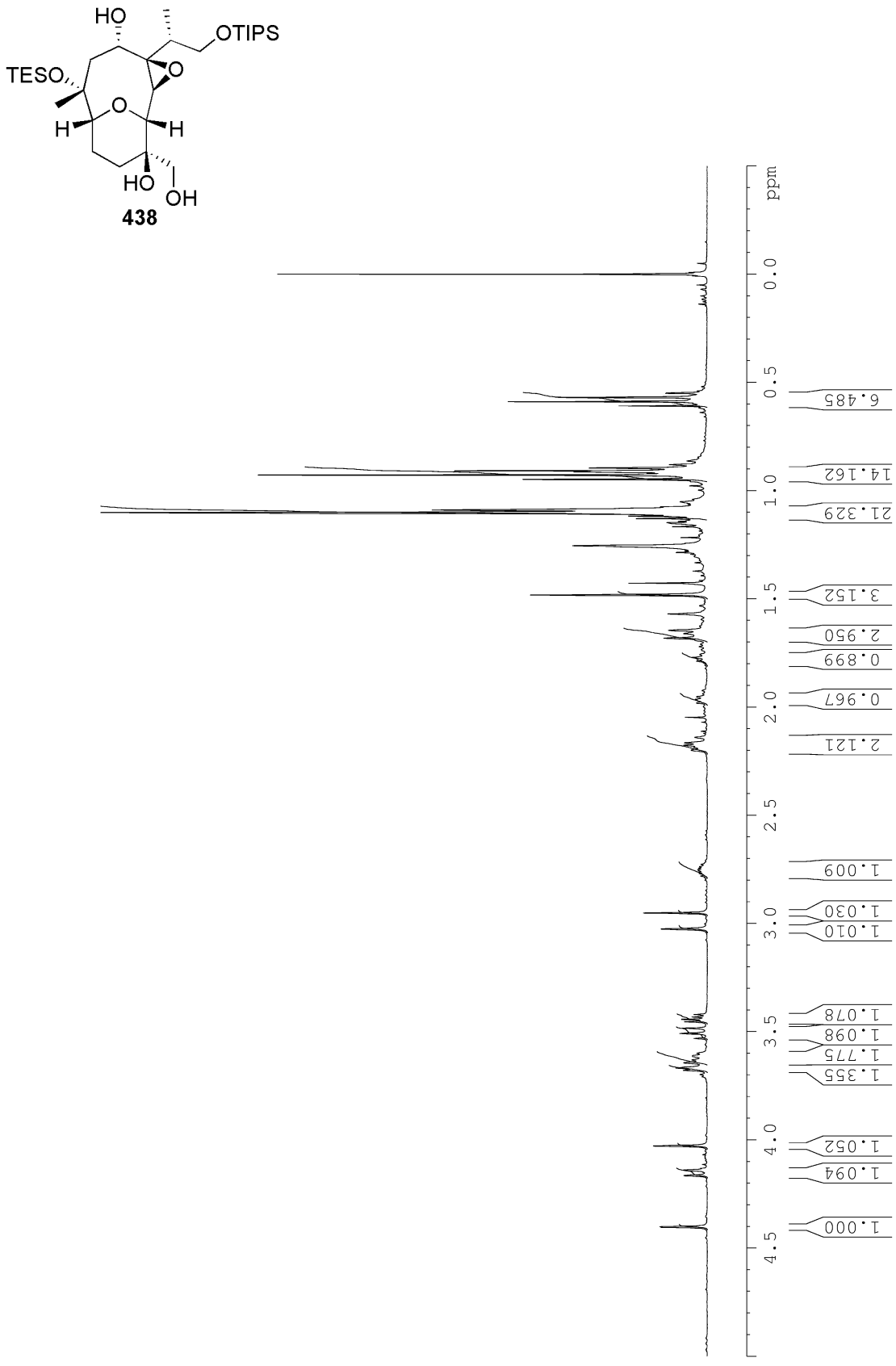
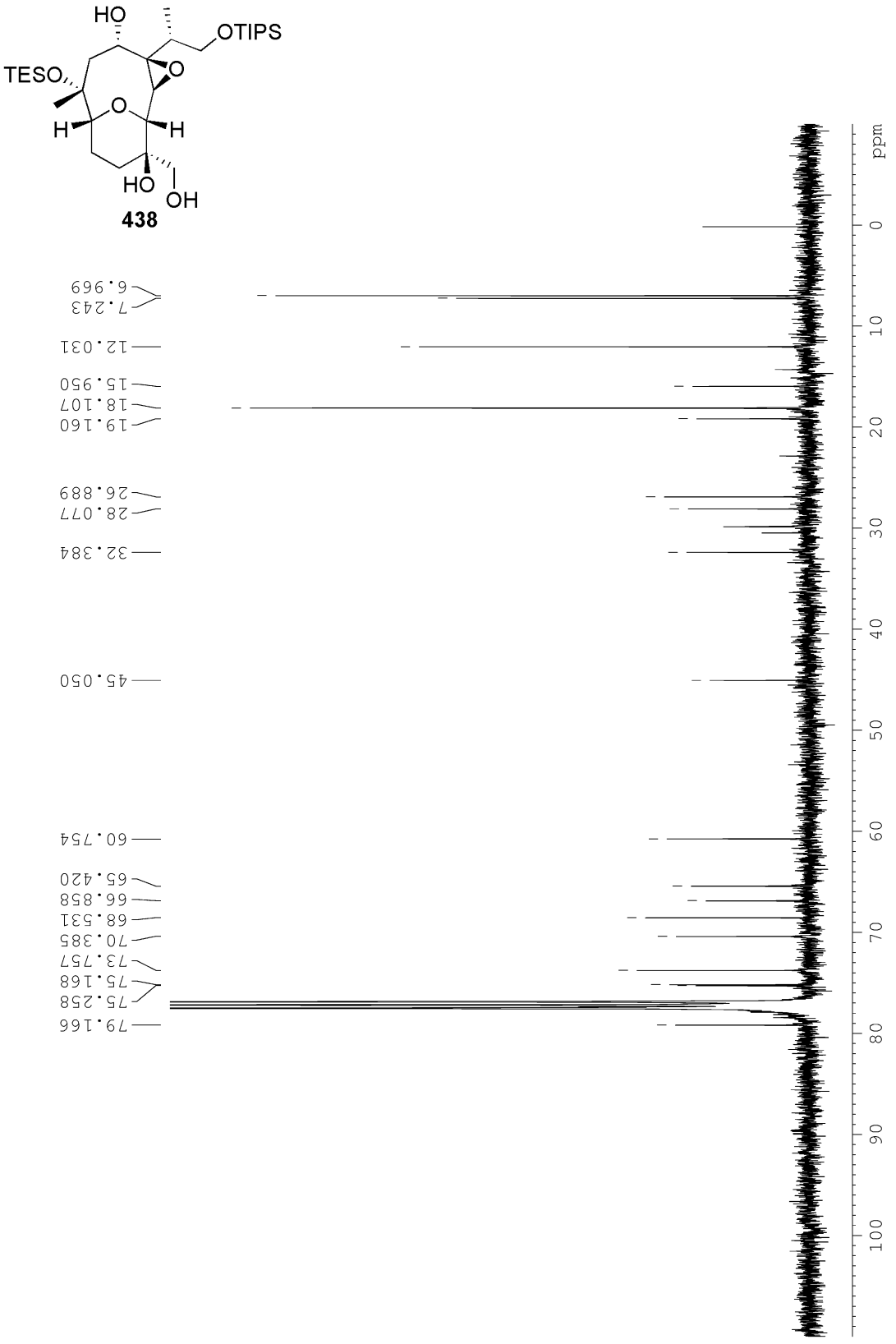
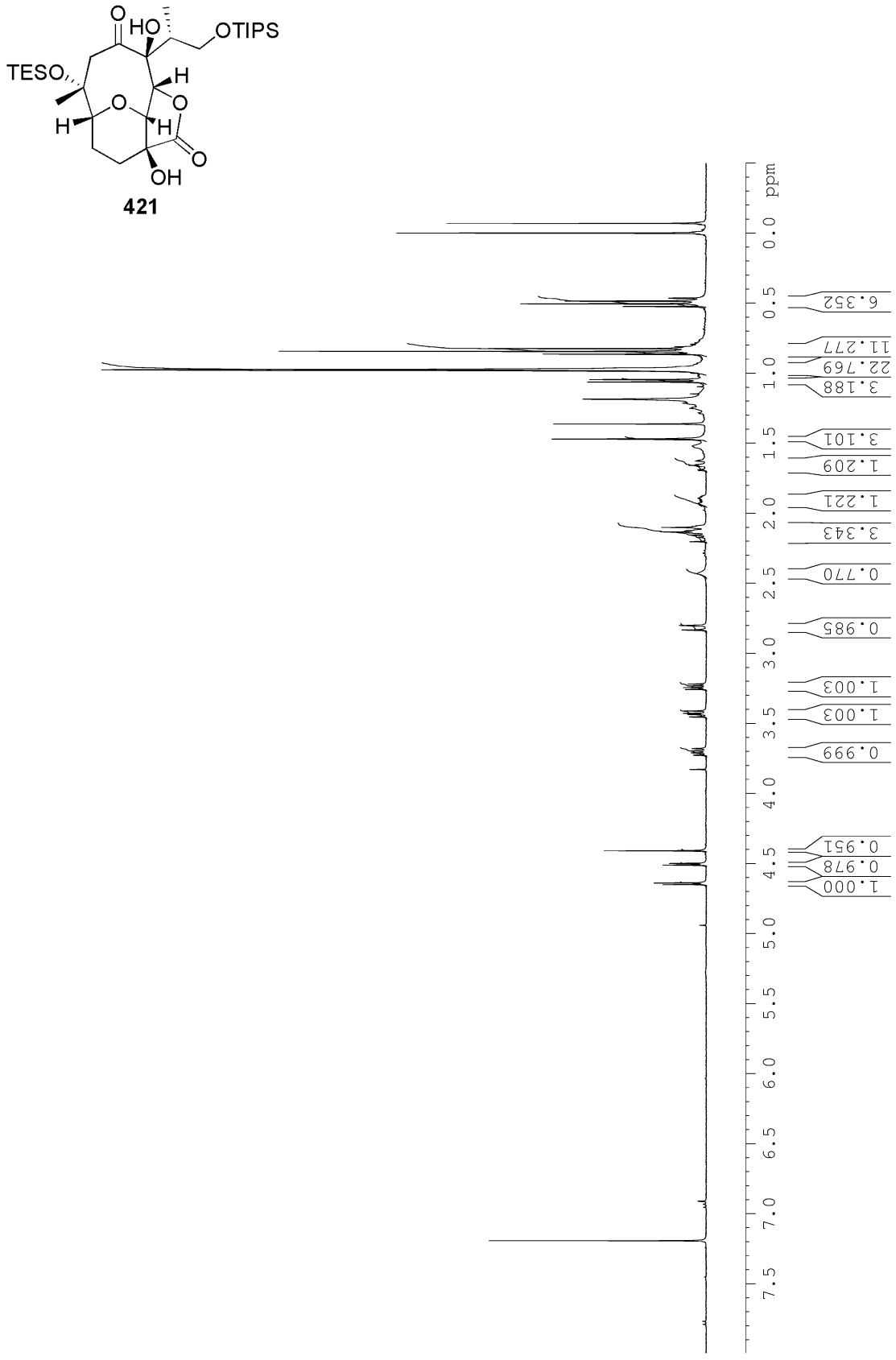

1.067
2.510
5.568
-1.5493
-0.7486
100.0000
-0.9674
OTIPS
AcO
O
H
H
O
H
H
HO
OH
1.5%
0.7%
0.9%
428
Irradiate
1.0
2.0
3.0
4.0
5.0
6.0
ppm (t1)


HO
OTIPS
TESO
O
O
H
H
HO
OH
438
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
6.485
14.162
21.329
3.152
2.950
0.899
0.967
2.121
1.009
1.030
1.010
1.078
1.098
1.775
1.355
1.052
1.094
1.000


HO
OTIPS
TESO
O
O
H
H
HO
OH
438
6.969
7.243
12.031
15.950
18.107
19.160
26.889
28.077
32.384
45.050
60.754
65.420
66.858
68.531
70.385
73.757
75.168
75.258
79.166
ppm
0
10
20
30
40
50
60
70
80
90
100


O
HO
OTIPS
TESO
H
O
O
H
H
O
OH
421
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
6.352
11.277
22.769
3.188
3.101
1.209
1.221
3.343
0.770
0.985
1.003
1.003
0.999
0.951
0.978
1.000