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Towards the Synthesis of the IJK Fragment of the Marine Polyether CTX3C

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Abstract

This thesis details the development of methods for the preparation and the functionalisation of cyclic enones, which may be utilised for the synthesis of marine polycyclic ether natural products. These metabolites are among the most complex and challenging toxins isolated so far.

The first chapter serves as an introduction to such complex natural products and describes their toxicology and biogenetic origins. A literature review of the advances made within the Clark group as well as in other laboratories toward the iterative and biomimetic synthesis of polycyclic ethers is also included with particular emphasis on the ciguatoxins. This is followed by a review of olefin metathesis and the use of ring-closing and ring-rearrangement metathesis reactions for the preparation of cyclic ethers.

Chapter 2 describes efforts towards the synthesis of seven- and eight-membered cyclic enones from commercially available carbohydrate derivatives. Cyclic ethers are prepared by ring closing metathesis of dienone precursors. The functionalisation of seven-membered system involves the utilisation of highly enantioselective reactions, such as copper-catalysed conjugate addition of dialkylzinc reagent and Tsuji-Trost allylation. The cyclisation of the dienone precursor of the eight-membered ring system proved to be problematic. In this case, the importance of the allylic substituent on the RCM reaction was demonstrated. Also, a two-directional approach to the IJK fragment of the marine polycyclic ether CTX3C was proposed. A reliable and relatively inexpensive synthetic pathway has been established to the first key intermediate. This latter was prepared in 1.6% overall yield over fourteen steps. Finally, the different options for the future work are discussed.

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Author's Declaration

I hereby declare that the substance of this thesis has not been submitted, nor is currently submitted, in candidature for any other degree. I further declare that the work presented in this manuscript is the result of my own investigations. Where the work of other investigators has been used, this has been acknowledged in the appropriate manner.

Alexandre Bayle

Prof. J. Stephen Clark

Abbreviations and Symbols

9-BBN	9-Borabicyclo[3.3.1]nonane
Å	Ångstrom
Ac	Acetyl
Ac_2O	Acetic anhydride
ADMET	Acyclic diene metathesis
AIBN	2,2'-Azo *bis*isobutyronitrile
aq	Aqueous
Ar	Aryl
ax	Axial
Bn	Benzyl
brsm	Based on recovered starting material
BTX(s)	Brevetoxin(s)
CAN	Cerium(IV) ammonium nitrate
CM	Cross-metathesis
Cp	Cyclopentadienyl
CSA	Camphorsulphonic acid
CTX(s)	Ciguatoxin(s)
Cy	Cyclohexyl
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DET	Diethyl tartrate
DIBAL	Diisobutylaluminium hydride
DIPA	Diisopropylamine
DIPEA	Diidopropylethyleamine
DMAP	*N,N*-4-Dimethylaminopyridine
DMDO	Dimethyl dioxirane
DME	1,2-Dimethoxyethane
DMF	*N,N*-Dimethylformamide

DMM	Dimethoxymethane
DMP	Dess-Martin periodinane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
DPPA	Diphenylphosphoryl azide
dppf	1,1'-*bis*(diphenylphosphino)ferrocene
DTBMP	2,6-*di*-tert-Butyl-4-methylpyridine
EC50	Half maximal effective concentration
EE	Ethoxyethyl
ELISA	Enzyme-linked immunoabsorbent assay
eq	Equatorial
Et	Ethyl
HFIP	Hexafluoroisopropanol
HMPA	Hexamethylphosphoramide
HRP	Horseradish peroxidase
i-Pr	*iso*-Propyl
L*	Chiral ligand
LD50	Median lethal dose
LDA	Lithium diisopropylamine
LiHMDS	Lithium hexamethyldisilazane
mAbs	Monoclonal antibodies
m-CPBA	*meta* Chloroperbenzic acid
Me	Methyl
MeOH	Methanol
Mes	Mesityl
MOM	Methoxymethyl
MS	Molecular sieves
NaHMDS	Sodium hexamethyldisilazane

NAP	2-Naphthylmethyl
n-Bu	*n*-Butyl
NCH	*N*-Heterocyclic carbene
NCS	*N*-Chlorosuccinimide
NMM	*N*-Methylmorpholine
NMO	*N*-Methylmorpholine oxide
Oct	Octanoate
PFP	Pentafluorophenyl
Ph	Phenyl
PMB (MPM)	*p*-Methoxybenzyl
PMP	4-Methoxyphenyl
ppb	Parts-per-billion
PPTS	Pyridinium *p*-toluenesulfonate
PTSA	*p*-Toluenesulfonic acid
quant.	Quantitative
RCAM	Ring-closing alkyne metathesis
RCEYM	Ring-closing enyne metathesis
RCM	Ring-closing metathesis
ROM	Ring-opening metathesis
ROMP	Ring-opening metathesis polymerisation
RORCM	Ring-opening ring-closing metathesis
RRM	Ring-rearrangement metathesis
rt	Room temperature
SAR	Structure activity relationship
SET	Single electron transfer
S_N	Nucleophilic substitution
TBAF	tetra-*n*-Butylammonium bromide
TBAI	tetra-n-Butylammonium iodide
TBDPS	*t*-Butyldiphenylsilyl

TBHP	*tert*-Butyl hydroperoxide
TBS	*t*-Butyldimethylsilyl
t-Bu	*tert*-Butyl
TES	Triethylsilyl
Tf	Triflic
Tf_2O	Triflic anhydride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
Thx (Thexyl)	1,1,2-Trimethylpropyl
TIPS	Triisopropylsilyl
TMEDA	*N*,*N*,*N*',*N*'-Tetramethylethylenediamine
TMS	Trimethylsilyl
TPAP	tetra-*n*-Propylammonium perruthenate
Ts	4-Toluenesulfonyl
VAZO	1,1'-Azobis(cyclohexanecarbonitrile)
VSSC(s)	Voltage sensitive sodium channel(s)

INTRODUCTION

1 Polyether Marine Toxins

Marine organisms provide an important source of structurally diverse secondary metabolites with unique molecular architecture and significant biological activities.[1] Among these marine natural products, polycyclic ethers have attracted considerable attention of chemists and biologists. Since the isolation and characterisation of brevetoxins (BTXs) A and B (**1**), the first members of the fused polycyclic ether family of natural products, in the early 1980s, a variety of structurally related and more complex laddered polyethers has been isolated from marine dinoflagellates and organisms that feed on these algae. The fused polyether family of marine natural products now includes hemibrevetoxin B,[2] BTXs A and B (**1**),[3,4] ciguatoxins (CTXs),[5] the gamberic acids A-D,[6] gymnocins A and B,[7] the yessotoxins,[8] adriatoxin,[9] the prymnesins,[10] gambierol (**3**),[11] brevenal,[12] and maitotoxin[13] the largest and most toxic non-biopolymeric natural product isolated to date (Figure 1).

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[1] Murata, M.; Yasumoto, T. *Nat. Prod. Rep.* **2000**, *17*, 293.
[2] Prasad, A. V. K.; Shimizu, Y. *J. Am. Chem. Soc.* **1989**, *111*, 6476.
[3] (*a*) Shimizu, Y.; Chou, H. N.; Bando, H.; Van Duyne, G.; Clardy, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 514; (*b*) Pawlak, J.; Tempesta, M. S.; Golik, J.; Zagorski, M. G.; Lee, M. S.; Nakanishi, K.; Iwashita, T.; Gross, M. L.; Tomer, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 1144; (*c*) Zagorski, M. G.; Nakanishi, K.; Qin G. W.; Lee, M. S. *J. Org. Chem.* **1988**, *53*, 4156.
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[7] (*a*) Satake, M.; Shoji, M.; Oshima, Y.; Naoki, H.; Fujita, T.; Yasumoto, T. *Tetrahedron Lett.* **2002**, *43*, 5829; (*b*) Satake, M.; Tanaka, Y.; Ishikura, Y.; Oshima, Y.; Naoki, H.; Yasumoto, Y. *Tetrahedron Lett.* **2005**, *46*, 3537; (*c*) Tanaka, Y.; Itagaki, Y.; Satake, M.; Naoki, H.; Yasumoto, Y.; Nakanishi, K.; Berova, N. *J. Am. Chem. Soc.* **2005**, *127*, 9561.
[8] (*a*) Murata, M.; Kumagai, M.; Lee, J. S.; Yasumoto, T. *Tetrahedron Lett.* **1987**, *28*, 5869; (*b*) Ciminiello, P.; Fattorusso, E.; Forino, M.; Poletti, R.; Viviani, R. *Eur. J. Org. Chem.* **2000**, 291.
[9] Ciminiello, P.; Fattorusso, E.; Forino, M.; Magno, S.; Polettu, R.; Viviani, R. *Tetrahedron Lett.* **1998**, *39*, 8897.
[10] (*a*) Igarashi, I.; Satake, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1996**, *118*, 479; (*b*) Igarashi, I.; Satake, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1999**, *121*, 8499.
[11] (*a*) Satake, M.; Murata, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 361; (*b*) Morohashi, A.; Satake, M.; Yasumoto, T. *Tetrahedron Lett.* **1999**, *40*, 97.

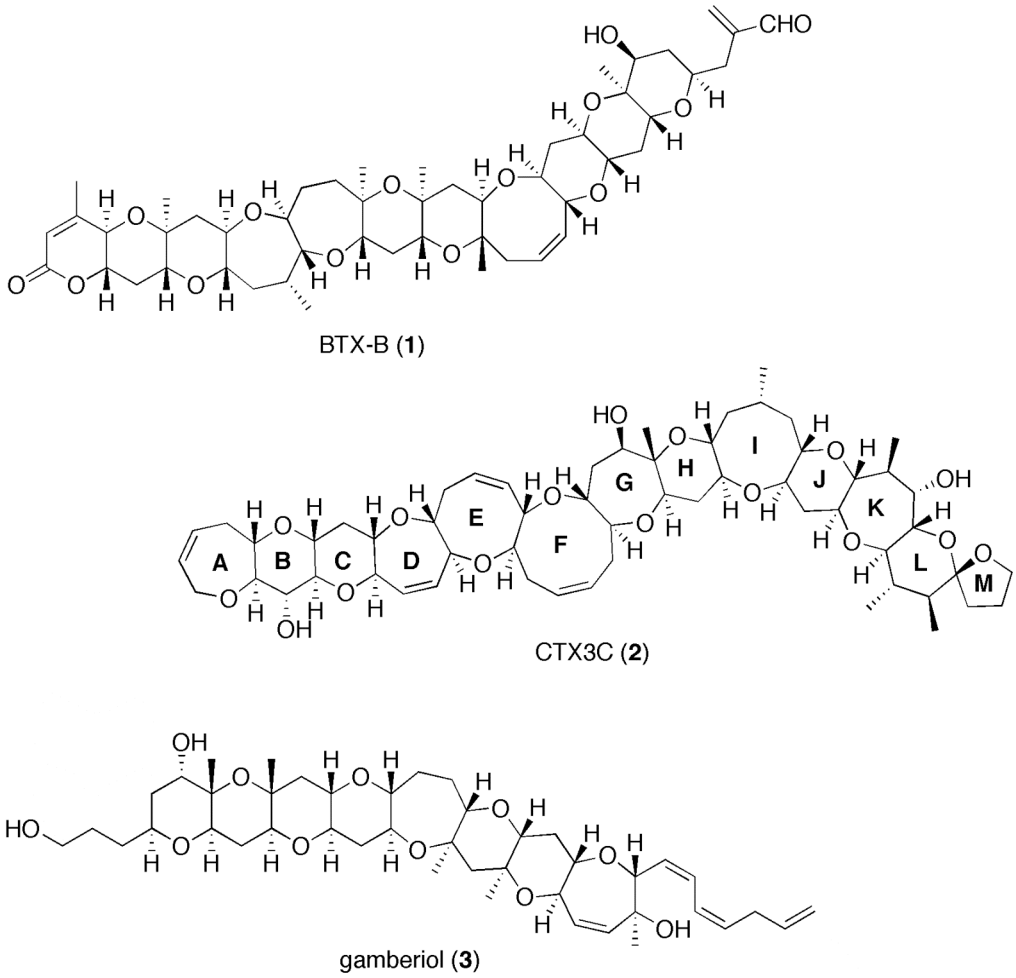

Figure 1: Examples of laddered polyether natural products of marine origin.

The most remarkable feature of polyether marine toxins is their long semi-rigid architecture containing ether rings ranging from five- to nine-membered in size, all fused in a *trans*/*syn*/*trans* fashion. The oxygen atoms of the ether rings are alternatively placed on the northern and southern edges of the molecule. The stereochemistry of the carbon atoms adjacent to the oxygen atoms of the ether units strictly alternates between *R* and *S* configuration giving the general structure as shown in Figure 2.

[12] Bourdelais, A. J.; Jacocks, H. M.; Wright, J. L. C.; Bigwarfe, P. M.: Baden, Jr.; Baden, D. G. *J. Nat. Prod.* **2005**, *68*, 2.
[13] (*a*) Murata, M.; Naohi, H.; Iwashita, T.; Matsunaga, S.; Sasaki, M.; Yokoyama, A.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 2060; (*b*) Nonomura, T.; Sasaki, M.; Matsumori, N.; Murata, M.; Tachibana, K.; Yasumoto, T. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1675.

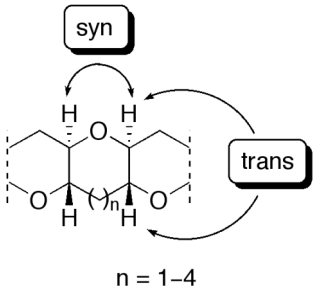

Figure 2: Common structural feature of polycylic ethers.

Unfortunately, the scarcity of natural material has hampered their structural elucidation as well as the understanding of their pharmacological properties and their mechanisms of action. Consequently, the development of general synthetic strategies leading to sufficient amount of the natural compound equivalents appears to be the only solution to these problems.

2 Ciguatera and the Ciguatoxins

2.1 Historical Background

The first descriptions of ciguatera appeared soon after the discovery of the Americas. In 1511, the first account from the Americas, published by Peter Martyr of Anghera, refers to diverse strange maladies caused by eating fish. The fish in turn were believed to have acquired the toxins from the fruits of a tree, which grew on nearby shores. Nearly a century later, in 1606, the Portuguese explorer Pedro Fernandez de Queiros described the first cases of ciguatera in the Pacific regions. Again the assumption was that the fish had acquired toxicity from feeding on poisonous plants. In 1774, William F. Anderson, Captain Cook's surgeon's mate aboard the H.M.S. *Resolution* reported a case of ciguatera poisoning. A few years later in 1787, the term ciguatera appeared for the first time in a book published in Havana. The word itself is derived from *cigua* (the Spanish trivial name of a univalve mollusc, *Turbo pica* reputed to cause indigestion) and referred to a "disease contracted by people who eat fish that is contaminated with disease or jaundice".[14]

[14] (*a)* Scheuer, P. J. *Tetrahedron* **1994**, *50*, 3 and references therein; (*b)* Yasumoto, T. *Chem. Rec.* **2001**, *1*, 228.

Evidence has shown that CTXs, the principal causative agents of ciguatera, are produced by an epiphytic dinoflagellate *Gambierdiscus toxicus* (Figure 3).[15]

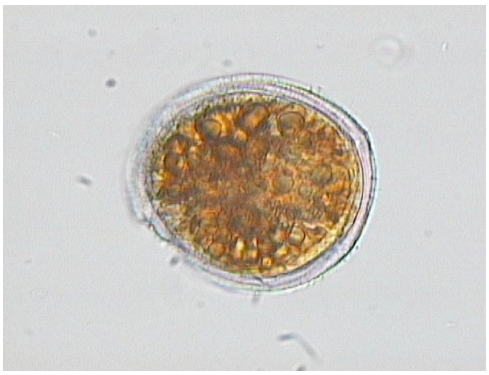

Figure 3: Gambierdiscus Toxicus.[16]

Toxins are accumulated in both herbivorous and carnivorous reef fish and transferred through the aquatic food chain to humans.[17] The disease is characterised by severe neurological, gastrointestinal and cardiovascular disorders. Typically, gastrointestinal symptoms, including vomiting, diarrhoea, nausea and abdominal pain, occur early in the disease and often accompany neurological problems. Neurological disturbances invariably occur and include tingling of the lips, hands and feet, unusual temperature perception disturbances when cold objects give a dry-ice sensation and a severe localised itch of the skin. These symptoms and a profound feeling of fatigue can occur throughout the illness. Muscle, joint and teeth aches occur to varying extents, and mood disorders including depression and anxiety appear less frequently. The most severe cases also involve hypotension with bradycardia, respiratory difficulties and paralysis, but death is uncommon.[18]

Ciguatera symptoms typically can last for from several weeks to several months and in few cases (<5%) may persist for a number of years. The severity, number and duration of ciguatera symptoms reflect a combined influence of dose, toxin profile and individual susceptibility. The relatively low fatality rate

[15] Scheuer, P. J.; Takahashi, W.; Tsutsumi, J.; Yoshida, T. *Science* **1967**, *155*, 1267.
[16] Richlen, M.; copyright WHOI 2007; extracted in march 2011 from http://www.whoi.edu/redtide/page.do?pid=28695&tid=542&cid=83388&c=3&idx=2&slideshow=30812
[17] Yasumoto, T.; Nakajima, I.; Bagnis, R.; Adachi, R. *Bull. Jpn. Soc. Sci. Fish.* **1977**, *43*, 1015.
[18] Lewis, R. J. *Toxicon* **2001**, *39,* 97.

is explained by the fact that fish rarely accumulate sufficient level of CTX to be lethal in a single meal. Nowadays, more than 50,000 people are estimated to suffer annually from ciguatera poisoning, making it one of the largest scale food poisonings of non-bacterial origin. It is obvious that outbreaks of ciguatera cause tremendous damage to public health, but they also affect the fishery resources and the economy of tropical and subtropical regions. Finally, much of the problem is due to the normal appearance, smell and taste of the contaminated fish along with a lack of sensitive and reliable methods to detect ciguateric fish.

2.2 The CTX Family and CTX3C

CTX3C (**2**),[19] CTX1B (**4**),[20] CTX4B (**5**)[21] and 51-hydroxyCTX3C (**6**)[22] are the main representatives of the CTX family. To date, more than twenty congeners have structurally been determined (Figure 4).[23] Interestingly, studies have shown structural distinctions between ciguatoxins from the Caribbean regions (**2**, **4**–**6**)[5c] and those from the Pacific Regions (C-CTX1, (**7**)). Studies also higlighted the higher toxicity of CTX congeners (LD_{50} = 0.25–4 μg/kg by intraperitoneal injection into mice) compared to structurally related red-tide toxins, BTXs (LD_{50} > 100 μg/kg).[14b,18,24]

CTX3C (**2**) was isolated in 1993 by Yasumoto and co-workers from cultured *Gamberdicus toxicus*.[19] CTX3C (**2**) is a 3 nm in length polycyclic ether composed by 13 oxygen atoms and 52 carbon atoms. It possesses 30 stereogenic centres and 13 rings ranging in size from five- to nine-membered; 12 rings are *trans*-fused, one belongs to a spiro ketal function and 4 rings are unsaturated. Efforts to synthesise CTX3C (**2**) culminated in very impressive syntheses reported by Hirama and co-workers. These syntheses being currently used for the development of immunoassays systems.[25]

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[19] Satake, M.; Murata, M.; Yasumoto, T. *Tetrahedron Lett.* **1993**, *34*, 1975.
[20] Murata, M.; Legrand, A. M.; Ishibashi, Y.; Fukui, M.; Yasumoto, T. *J. Am. Chem. Soc*. **1990**, *112*, 4380.
[21] Murata, M.; Legrand, A. M.; Ishibashi, Y.; Yasumoto, T. *J. Am. Chem. Soc*. **1989**, *111*, 8929.
[22] Satake, M.; Fukui M.; Legrand, A. M.; Cruchet, P.; Yasumoto, T. *Tetrahedron Lett.* **1998**, *39*, 1197.
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[25] For recent reviews see: (*a*) Hirama, M. *The Chemical Record* **2005**, *5*, 240; (*b*) Inoue, M.; Hirama, M. *Acc. Chem. Res*. **2004**, *37*, 961; (*c*) Inoue, M.; Miyasaki, K.; Uehara, H.; Maruyama, M.; Hirama, M. *Proc. Natl. Acad. Sci. U.S.A*. **2004**, *101*, 12013.

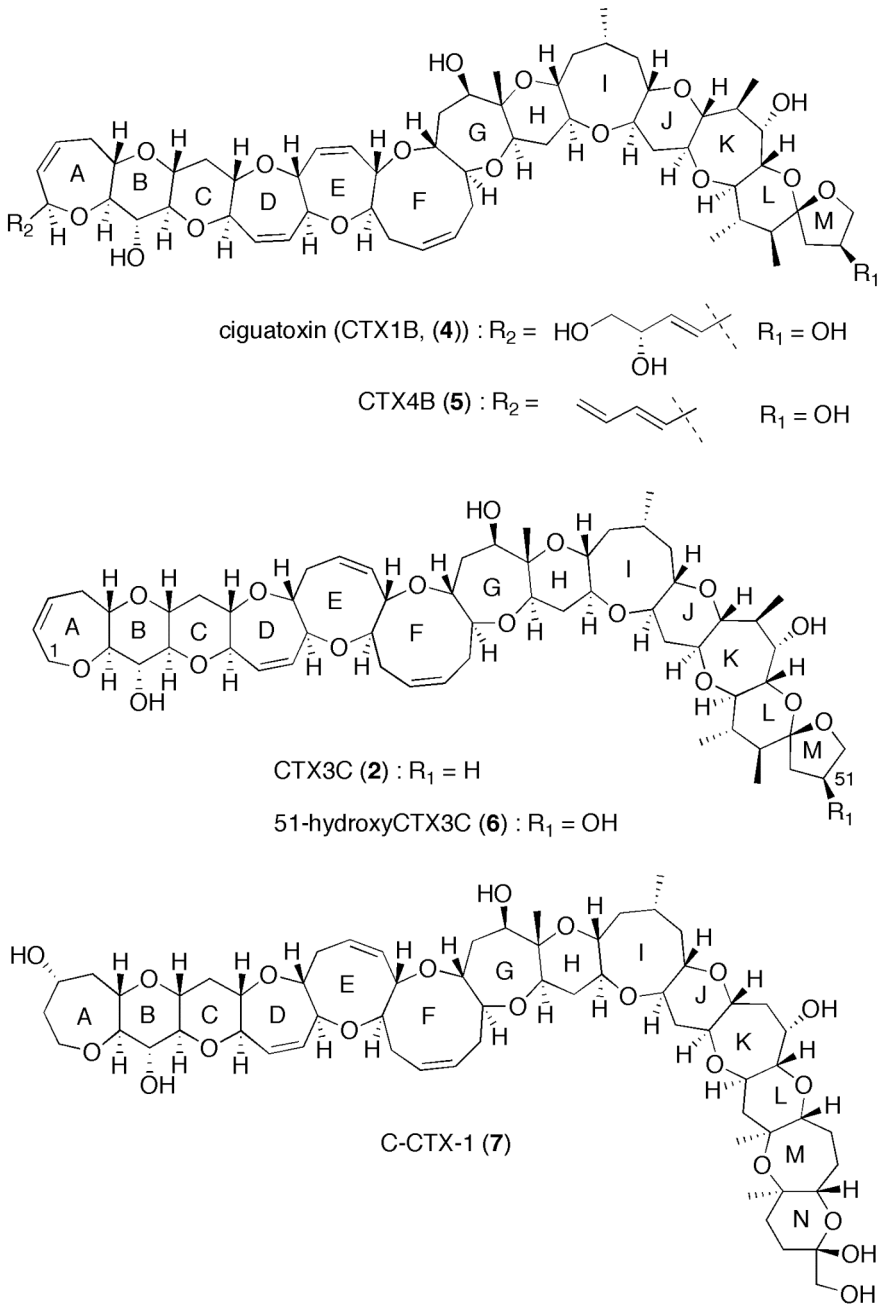

Figure 4: Structures of the main congeners of the CTX family.

2.3 Toxicology and Therapy

It is well established that CTXs can affect the functioning of different cell types (neurons, muscle cells and taste cells) by selectively binding to the voltage sensitive sodium channels (VSSC) at site 5 of excitable membranes, causing them to open, and thereby allowing influx of sodium ions.[26] These effects are extremely specific as demonstrated by the lack of cross reactivity observed with

[26] Yamaoka, K.; Inoue, M.; Miyahara, H.; Miyazaki, K.; Hirama, M. *Br. J. Pharmacol.* **2004**, *142*, 879.

high toxin concentration.[27] Contrary to the case of gambierol (**3**), a polyether also isolated from *Gambierdiscus toxicus*,[11] CTXs do not affect voltage-gated potassium channels.[27] A concerted action of CTX and gambierol (**3**) is likely to lead to strong impairment of the electrical impulses required for cell-cell communication, and this concerted effect can underlie the variety of neurological symptoms described for ciguatera. Finally, pharmacological studies have revealed an apparent relationship between biological activity and two main structural features: (i) the molecular size and (ii) the overall shape.[28]

2.3.1 Structure Activity Relationship (SAR)

In 2006, Isobe and co-workers supplied evidence that the major epitope in CTX associated with the activation of the sodium channels is the west sphere, *ie* the AB fragment.[29] Conversely, the east sphere of CTX, proved unable to activate the sodium channels. A few years later, Hirama's group demonstrated that the F-ring of CTXs plays an important role in the SAR. Using previously reported intermediates, generated in the total synthesis of 51-hydroxyCTX3C (**6**), Hirama and co-workers designed three F-ring modified analogues: the open-chain *O*-linked ether **9**, the eight-membered-ring containing analogue **13** and the ten-membered-ring containing compound **17** (Scheme 1).[30,31]

EC_{50} values, determined using mouse neuroblastoma Neuro-2A cells,[32] indicated that **9**, **13** and **17** were respectively 1/50, 1/52 100 and 1/31 600 less cytotoxic than 51-hydroxyCTX3C (**6**). Clearly, they confirmed the major role played by the nine-membered F-ring in organising the CTX molecule into a shape suitable for potent activity and also demonstrated the profound influence that slight modifications of the central ring have on the overall shape of the molecule.

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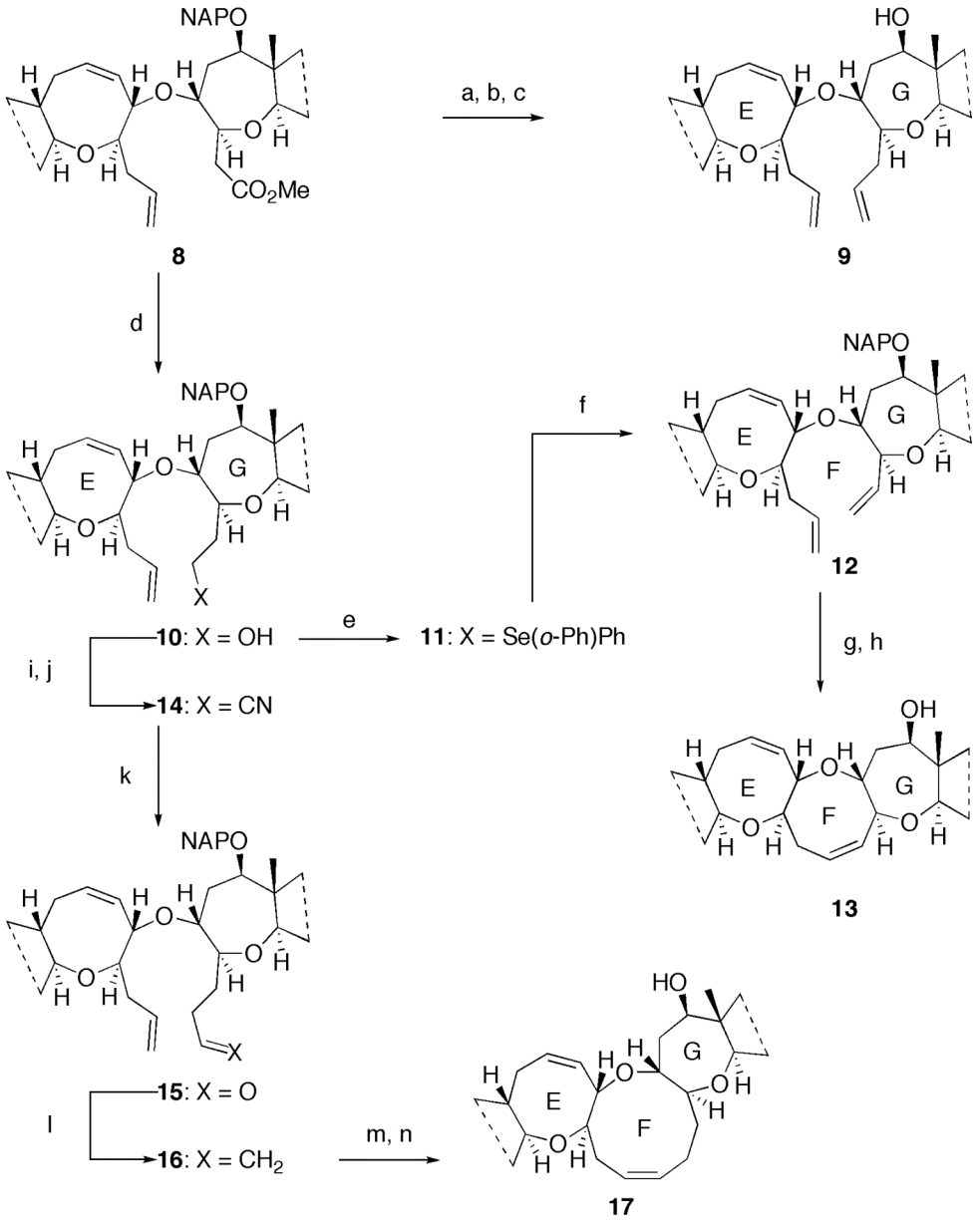
[27] Ghiaroni, V.; Fuwa, H.; Inoue, M.; Sasaki, M.; Miyazaki, K.; Hirama, M.; Yasumoto, T.; Rossini, G. P.; Scalera, G.; Bigiani, A. *Chem. Senses* **2006**, *31*, 673.
[28] Alvarez, E.; Candenas, M. L.; Perez, R.; Ravelo, J. L.; Martin, J. D. *Chem. Rev.* **1995**, 95, 1953.
[29] Hokama, Y.; Chun, K. E.; Campora, C. E.; Higa, N.; Suma, C.; Hamajima, A.; Isobe, M. *J. Clin. Lab. Anal.* **2006**, *20*, 126.
[30] Inoue, M.; Lee, N.; Miyazaki, K.; Usuki, T.; Matsuoka, S.; Hirama, M. *Angew. Chem. Int. Ed.* **2008**, *47,* 8611.
[31] Ishihara, Y.; Lee, N.; Oshiro, N.; Matsuoka, S.; Yamashita, S.; Inoue, M.; Hirama, M. *Chem. Commun.* **2010**, *46,* 2968.
[32] Manger, R. L.; Leja, L. S.; Lee, S. Y.; Hungerford, J. M.; Hokama, Y.; Dickey, R. W.; Granade, H. R.; Lewis, R.; Yasumoto, T.; Wekell, M. M. *J. AOAC Int.* **1995**, *78*, 521.



Scheme 1: *Conditions:* (a) DIBAL, CH_2Cl_2, −90 °C; (b) Ph_3PCH_3Br, *t*BuOK, THF, 0 °C, 98% (2 steps); (c) DDQ, CH_2Cl_2/H_2O, rt, 51%; (d) DIBAL, CH_2Cl_2, −40 to −10 °C, 74%; (e) *o*-NO_2PhSeCN, *n*Bu_3P, THF, rt; (f) H_2O_2, THF, rt to 40 °C, 77% (2 steps); (g) Grubbs first-generation catalyst (30 mol%), CH_2Cl_2, 40 °C, 94%; (h) DDQ, CH_2Cl_2/H_2O, rt, 33%; (i) TsCl, pyridine, rt; (j) NaCN, DMSO, 40 °C, 88% (2 steps); (k) DIBAL, CH_2Cl_2, −78 °C; (l) Ph_3PCH_3Br, *t*BuOK, THF, 0 °C, 90% (2 steps); (m) Grubbs first-generation catalyst (8 mol%), CH_2Cl_2, 40 °C, 100%; (n) DDQ, CH_2Cl_2/H_2O, rt, 42%.

2.3.2 Methods to Detect CTX

In addition to the traditional mouse bioassay of lipid extracts, several methods have recently been developed to detect CTXs, including assays based on cytotoxicity,[32] radioligand binding,[33] high performance liquid chromatography[34] and mass spectrometry.[23] The antibody-based immunoassay

[33] Dechraoui, M. Y.; Naar, J.; Pauillac, S.; Legrand, A. M. *Toxicon* **1999**, *37*, 125.
[34] Yasumoto, T.; Fukui, M.; Sasaki, K.; Sugiyama, K. *J. AOAC Int.* **1995**, *78*, 574.

technique remains the best method for an accurate, sensitive, routine and portable detection. However, the first attempts to develop a practical immuno-chemical test to assess contamination prior to consumption of seafood, has been elusive. The anti-CTX monoclonal antibodies (mAbs), prepared by immunisation of the scarce natural toxins, cross-reacted with another marine toxin, okadaic acid.[35]

2.3.3 Synthetic Haptens for Antibody Development

In 2010, Hirama and co-workers showed that organic synthesis can play a key role in developing a specific detection system for marine toxins.[36] They expected to solve the problem of antibody development using synthetic haptens. To induce mAbs that can strongly bind to CTX, the haptenic group required a surface area larger than 400 Å^2. Taking into account this feature, Hirama's group prepared specific mAbs against the right and the left wings of CTX3C (**2**) by immunisation with protein conjugates of synthetic haptens in place of the natural toxins (Figure 5).[37]

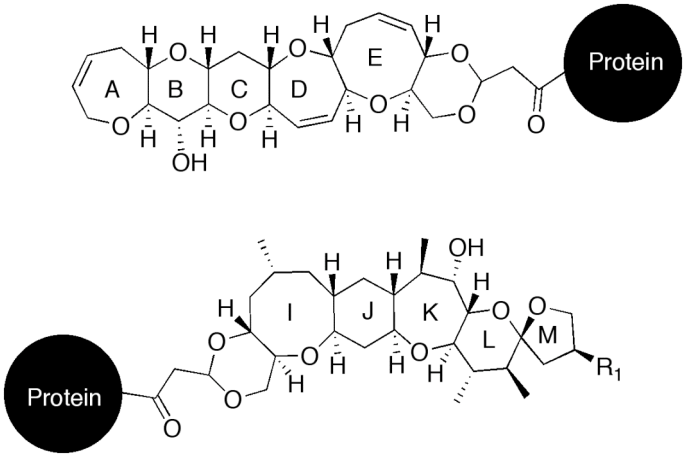


Figure 5: Structures of synthetic haptens used to elicit specific anti-CTX3C antibodies.

They then developed a direct enzyme-linked immunosorbent assay (ELISA) protocol to detect CTX3C (**2**) and 51-hydroxyCTX3C (**6**) at the ppb level with no cross-reactivity against the other marine toxins (Figure 6).

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[35] Hokama, Y. *Food Addit. Contam.* **1993**, *10*, 83.
[36] Tsumuraya, T.; Fujii, I.; Hirama, M. *Toxicon* **2010**, *56*, 797.
[37] Oguri, H.; Hirama, M.; Tsumuraya, T.; Fujii, I.; Maruyama, M.; Uehara, H.; Nagumo, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7608.

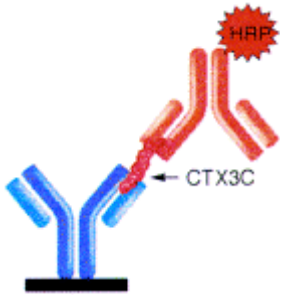


Figure 6: Schematic diagram of the direct sandwich ELISA for CTX3C (red). Specific antibody 10C9 (blue) against the left end of CTX3C is immobilized, and 3D11 (orange) against the right end is conjugated with horseradish peroxidase (HRP).[37]

To further minimise outbreaks of ciguatera seafood poisoning, it is vital to be able to detect other principal CTXs congeners because several are typically present within a single fish. The structural difference between the congeners mainly arises from the substituents on the terminal A and M rings. Thus, syntheses of such ABCDE and IJKLM ring fragments are necessary to prepare mAbs that can differentiate between these terminal structures as well as make this strategy applicable to all CTX congeners.

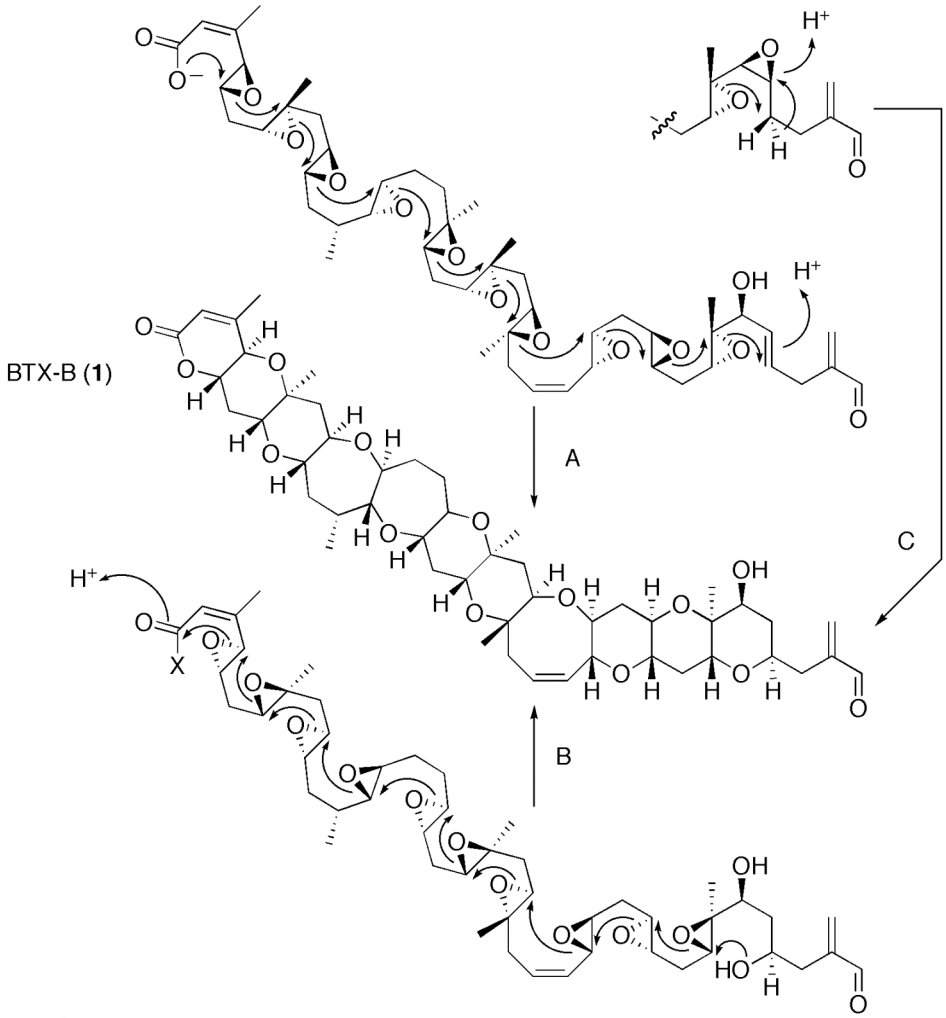
2.3.4 Biosynthesis

Independent biosynthetic studies by Nakanishi[38] and Shimizu[39], using ^{13}C-labelled acetate, described the origin of the carbons in the carbon chain backbone of the BTXs A and B (**1**). The acetate-derived carbons are expected to be neatly arranged in head-to-tail linkage but some of the carboxyl-derived carbons – in some parts several in succession – are missing in the carbon skeleton. Data suggested that BTXs are mixed polyketides whose biosynthesis involves the utilisation of dicarboxylic acids generated by the passage of acetate in the citric acid cycle.[40] In a newly proposed mechanism, the carbon chain is formed exactly as in normal polyketides but the elongation process may occur *via* a modified fatty acid synthesis.[41]

[38] Lee, M. S.; Repta, D. J.; Nakanishi, K.; Zagorski, M. G. *J. Am. Chem. Soc.* **1986**, *108*, 7855.
[39] Chou, H. N.; Shimizu, Y. *J. Am. Chem. Soc.* **1987**, *109*, 2184.
[40] Garson, M. J. *Chem. Rev.* **1993**, *93*, 1699.
[41] Shimizu, Y. *Curr. Opin. Microbiol.* **2003**, *6*, 236.

For many years it has been speculated that the polyether rings of the BTXs, and related natural products, are formed by the opening of epoxide intermediates (Scheme 2).[42,43] Taking BTX-B (**1**) as an example, Nakanishi[44] had initially proposed pathway A, involving successive ring closure reactions of the respective polyepoxide initiated synchronously by the attack of the carboxylate ion on the oxirane carbon at the left terminus of the carbon chain as well as protonation at the olefinic double bond at the right terminus (Scheme 2). Shimizu proposed an alternative pathway B, involving an intramolecular attack of a hydroxyl group on the right-hand terminus, starting a cascade of epoxide opening/ring closure in the opposite direction with protonation to the carbonyl oxygen at the left-hand terminus of the polyepoxide.[45] After isolation of hemibrevetoxin B, Shimizu suggested another pathway, C, in which an initial opening of the *cis*-epoxide at the right-hand terminus followed by hydride transfer and consecutive *trans*-epoxide openings could give rise to a plausible biosynthesis.[40] Unfortunately, attempts to prove the above hypotheses have so far been unsuccessful. The determination of the origin of the ether oxygen atoms in the BTXs would greatly enhance the understanding of the biosynthesis of fused polycyclic ether natural products but ^{18}O labelling studies have not been successfully conducted.

[42] Cane, D. E.; Liang, T.-C.; Hasler, H. *J. Am. Chem. Soc.* **1982**, *104*, 7274.
[43] Fujiwara, K.; Hayashi, N.; Tokiwano, T.; Murai, A. *Heterocycles* **1999**, *50*, 561.
[44] Nakanishi, K. *Toxicon* **1985**, *23*, 473.
[45] Shimizu, Y. *Natural Toxins: Animal, Plant and Microbial*; Harris, J. B. Ed.; Clarendon Press: Oxford, **1986**, 123.



Scheme 2: Nakanishi's and Shimizu's proposed biosyntheses of BTX-B (1).

3 Synthetic Strategies

Since the 1990s the development of new strategies and efficient methodologies for the construction of polycyclic ether ring systems and their application to the total synthesis of marine polycyclic ethers has attracted huge interest. In this field, Nicolaou and co-workers are generally thought of as pioneers and their ambitious research program culminated in the synthesis of many laddered polyether natural products.[46] Several excellent reviews concerning the total synthesis of fused polycyclic ether natural products of marine origin have been published recently.[47] Detailed reviews of all methodologies for the preparation of polycyclic ethers have already been

[46] Nicolaou, K. C.; Frederick, M. O.; Aversa, R. J. *Angew. Chem. Int. Ed.* **2008**, *47*, 7182.
[47] (*a*) Sasaki, M. *Top. Heterocycl. Chem.* **2006**, *5*, 149; (*b)* Nakata, T. *Chem. Rev.* **2005**, *105*, 4314; (*c*) Inoue, M. *Chem. Rev.* **2005**, *105*, 4379.

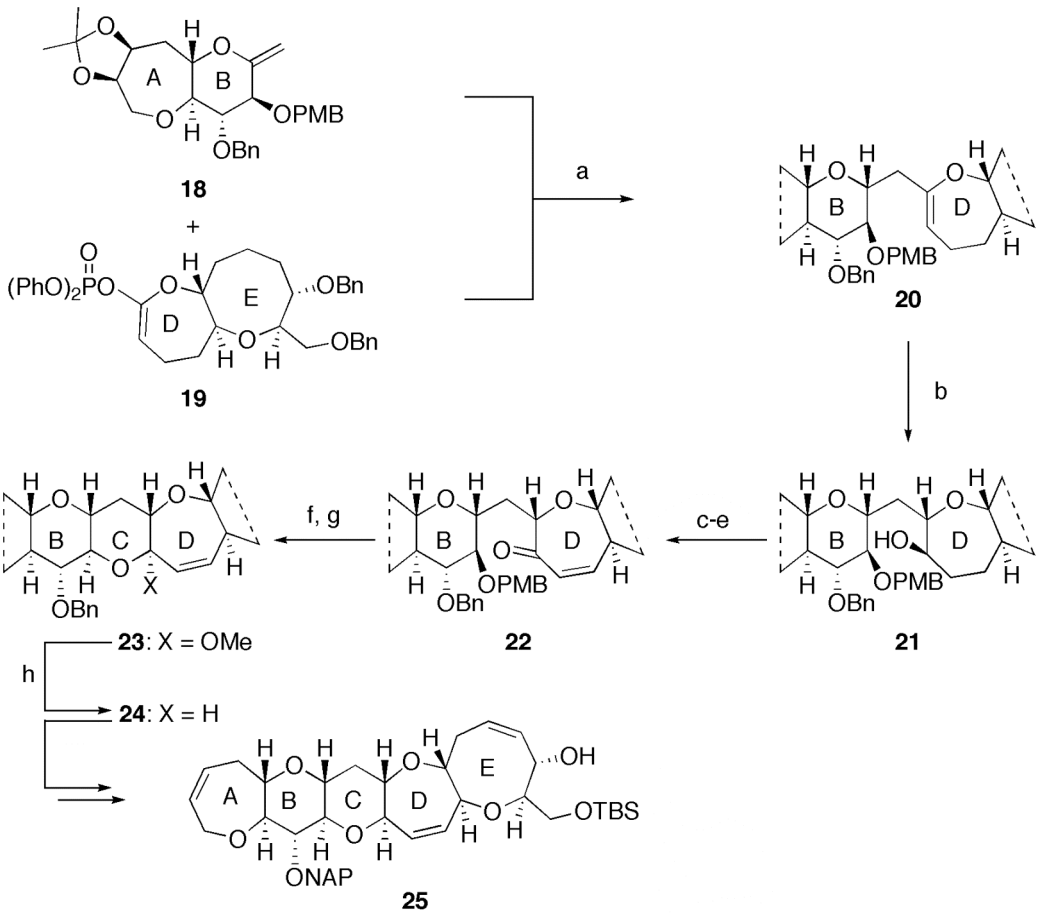
published.[48] All these reports show that the most common method, and by far more effective, is a convergent approach where small cyclic ether units are coupled together. The other alternative is an iterative strategy that has been used extensively for the preparation of small polycyclic units and also for the synthesis of the smallest polycyclic ether, hemibrevetoxin B.[49] The following section gives an overview of recent advances and achievements in the synthesis of CTX3C and congeners.

3.1 Suzuki Coupling/ Reductive Etherification

Sasaki and co-workers developed a convergent, general and highly stereo-controlled strategy based on the β-alkyl Suzuki-Miyaura coupling. They reported the synthesis of both the A-E[50] and the F-M[51] fragments of CTX3C (**2**).

The alkylborane derived from **18** was reacted with phosphonate **19** in situ giving rise to the corresponding cross-coupled product **20** in 73% yield. Stereoselective hydroboration of enol ether **20** occurred *via* an axial hydride attack of thexylborane and afforded alcohol **21** in 78% yield. Enone **22** was obtained in three more steps from **21**. PMB-deprotection followed by cyclisation under acidic conditions afforded the methyl ketal **23**. Finally, the reduction of the latter with Et_3SiH and $BF_3{\cdot}OEt_2$ gave the fused polycyclic ether **24** as a single stereoisomer. Generation of the olefins in the A- and E-rings followed by various functional group manipulations delivered the pentacyclic core **25** (Scheme 3).

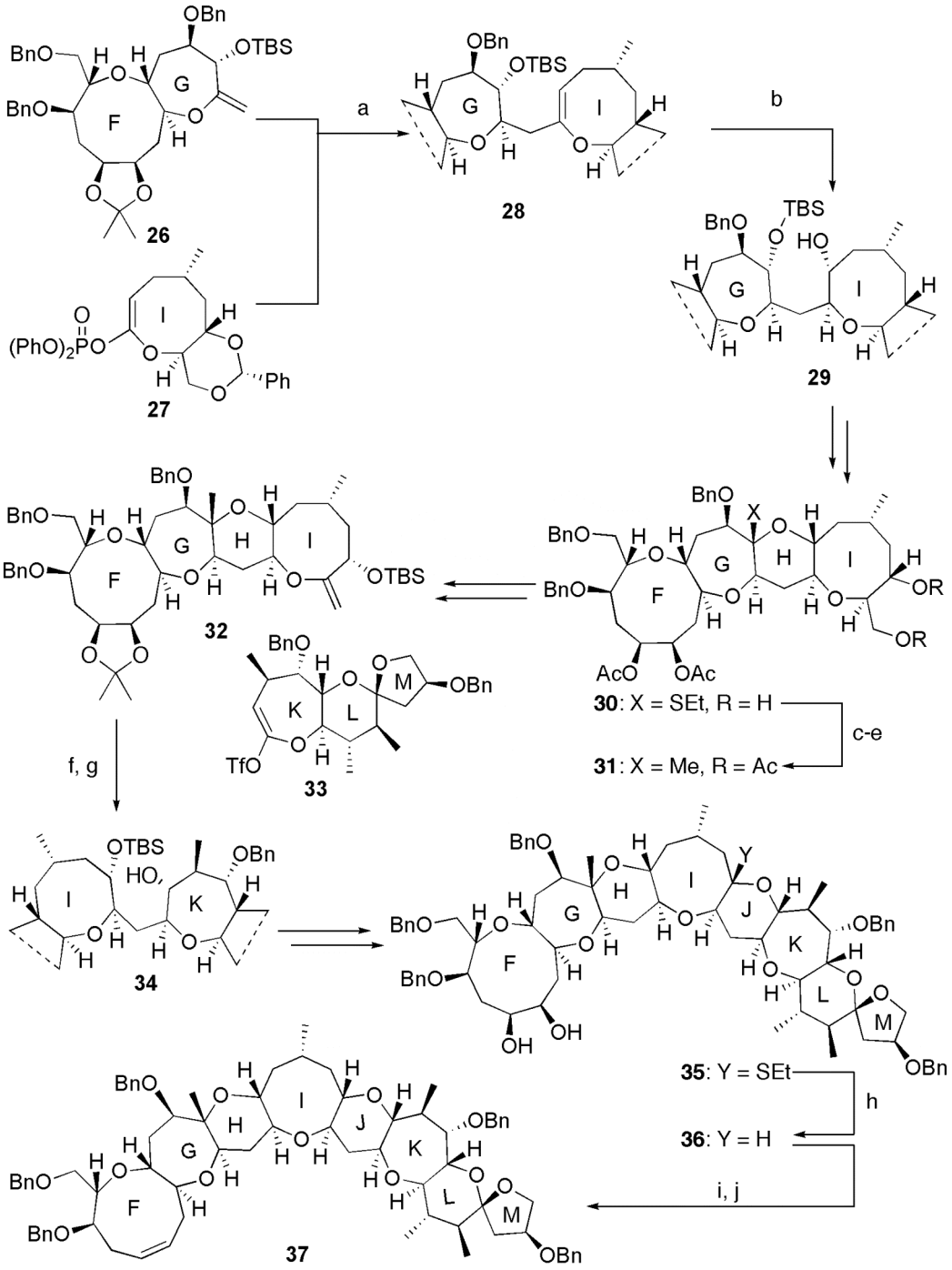
[48] (*a*) Isobe, M.; Hamajima, A. *Nat. Prod. Rep.* **2010**, *27*, 1204; (*b*) Sasaki, M.; Fuwa, H. *Nat. Prod. Rep.* **2008**, *25*, 401; (*c*) Sasaki, M. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 856; (*d*) Kadota, I.; Yamamoto, Y. *Acc. Chem. Res.* **2005**, *38*, 423; (*e*) Sasaki, M.; Fuwa, H. *Synlett* **2004**, *11*, 1851; (*f*) Inoue, M. *Org. Biomol. Chem.* **2004**, *2*, 1811; (*g*) Marmsäter, F. P.; West, F. G. *Chem. Eur. J.* **2002**, *8*, 4347.
[49] (*a*) Evans, A. P.; Delouvrie, B. *Curr. Opin. Drug Discov. Devel.* **2002**, *5*, 986; (*b*) Mori, Y. *Chem. Eur. J.* **1997**, *3*, 849.
[50] (*a*) Fuwa, H.; Fujikawa, S.; Tachibana, K.; Takakura, H.; Sasaki, M. *Tetrahedron Lett.* **2004**, *45*, 4795; (*b*) Sasaki, M.; Ishikawa, M.; Fuwa, H.; Tachibana, K. *Tetrahedron* **2002**, *58*, 1889.
[51] (*a*) Takakura, H.; Sasaki, M.; Honda, S.; Tachibana, K. *Org. Lett.* **2002**, *4*, 2771; (*b*) Takakura, H.; Noguchi, K.; Sasaki, M.; Tachibana, K. *Angew. Chem. Int. Ed.* **2001**, *40*, 1090.



Scheme 3: *Conditions*: (a) 9-BBN, THF, rt; then aq Cs_2CO_3, **19**, $PdCl_2(dppf)\cdot CH_2Cl_2$, DMF, 50 °C, 73%; (b) ThexylBH$_2$, THF, 0 °C; then aq NaOH, 30% H_2O_2, rt, 78%; (c) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt; (d) LiHMDS, THF, −78 °C; then TMSCl, Et_3N, −78 °C; (e) $Pd(OAc)_2$, MeCN, rt, 89% (3 steps); (f) DDQ, pH 7 buffer/CH_2Cl_2, rt, 85%; (g) $HC(OMe)_3$, PPTS, toluene, 50 °C; (h) Et_3SiH, $BF_3\cdot OEt_2$, MeCN/CH_2Cl_2, −15 °C, 73% (2 steps).

Fragments **26** and **27** were coupled using the β-alkyl Suzuki-Miyaura reaction to give the tetracycle **28** in 85% yield. A one-pot epoxidation/reduction sequence resulted in alcohol **29** in 82% yield. Further elaboration afforded the mixed thioketal **30**. Sulfide oxidation followed by *in situ* methylation generated the β-methylated product as the major diastereoisomer. Subsequent deacetylation yielded compound **31**. Functional group modifications afforded the *exo*-enol ether **32** and a second Suzuki cross-coupling was performed between subunit **33** and the borane derived from enol ether **32**. Hydroboration, mixed thioacetal formation and radical-based reduction were performed to give the octacyclic ether **36**. The olefin of the F-ring was regenerated by the ortho ester formation of the vicinal diol followed by thermolysis in acetic anhydride[52] leading to the target fragment **37** (Scheme 4).

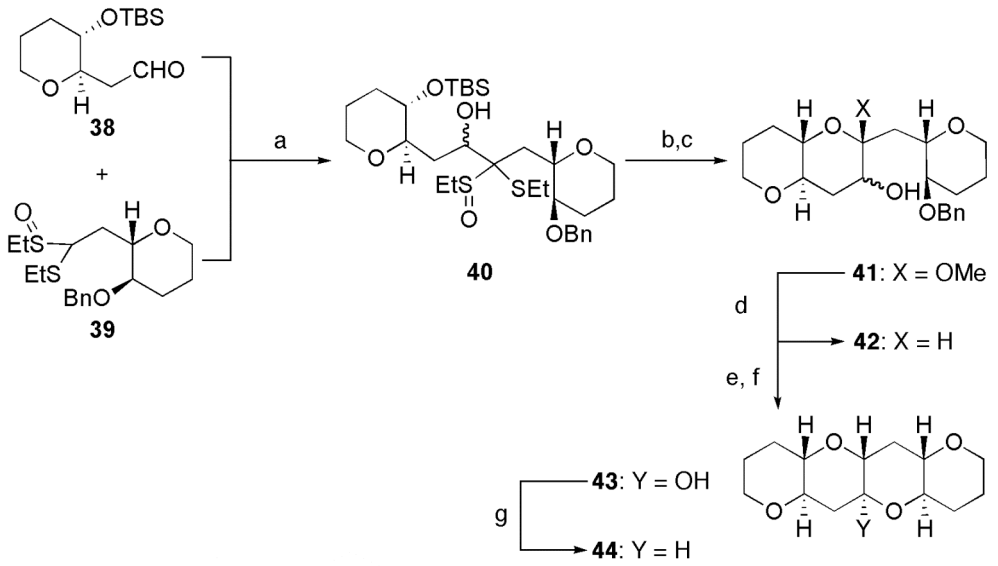
[52] Ando, M.; Ohhara, H.; Takase, K. *Chem. Lett.* **1986**, 879.



Scheme 4: *Conditions:* (a) 9-BBN, THF, rt; then 1 M $NaHCO_3$, **27**, $Pd(PPh_3)_4$, DMF, rt, 85%; (b) DMDO, CH_2Cl_2, –20 °C; then Et_3SiH, BH_3·THF, CH_2Cl_2, –20 °C, 82% (2 steps); (c) Ac_2O, pyridine, rt; (d) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 84% (3 steps); (e) $AlMe_3$, *t*BuOMe, 0 °C; (f) 9-BBN, THF, rt; then 3 M Cs_2CO_3, **33**, $Pd(PPh_3)_4$, DMF, rt, 61%; (g) BH_3·THF, THF, rt; then aq NaOH, 30% H_2O_2, rt, 93%; (h) Ph_3SnH, AIBN, toluene, 110 °C; (i) $HC(OMe)_3$, PPTS, CH_2Cl_2, rt; (j) Ac_2O, 160 °C, 87% (3 steps).

3.2 Dithioacetal *S*-Oxide Coupling/Stepwise Reductive Etherification

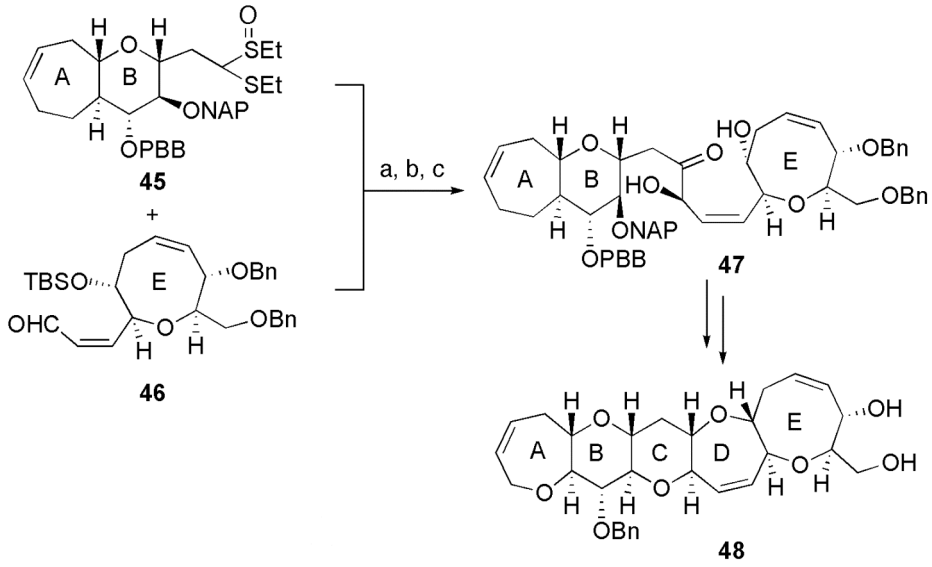
In 1999, Fujiwara and Murai developed a convergent approach to the synthesis of polycyclic ethers based on dithioacetal *S*-oxide aldehyde condensation and subsequent stepwise reductive etherification.[53] Deprotonation of **39** with LDA followed by addition of aldehyde **38** provided the coupled product **40**. Desilylation of **40** and acid treatment in MeOH/$HC(OMe)_3$ led to the formation of **41**, which was reduced with Et_3SiH in the presence of $SnCl_4$ to give **42**. Swern oxidation and hydrogenolysis of the benzyl group followed by a second reductive etherification of **43** gave rise to tetracyclic ether **44** (Scheme 5).



Scheme 5: *Conditions*: (a) LDA, THF, **38**, –78 °C; (b) TBAF, THF, rt, 63% (2 steps); (c) PTSA, $HC(OMe)_3$, MeOH, rt, 89%; (d) Et_3SiH, $SnCl_4$, –78 to 0 °C, 94%; (e) $(COCl)_2$, Et_3N, DMSO, CH_2Cl_2, –78 °C, 90%; f) H_2, 10% Pd/C, MeOH, rt, 81%; (g) Et_3SiH, TMSOTf, CH_2Cl_2, 0 °C, 93%.

The newly developed methodology was then applied to the synthesis of hemibrevetoxin-B[54] as well as the synthesis of the A-E fragment of CTX3C (**2**).[55] Coupling of fragments **45** and **46** was performed in 54% yield. The corresponding adduct was then converted into the α-hydroxyketone **47** in two steps. Finally, the CD-ring system was constructed in a stereoselective manner through stepwise reductive etherification, affording the A-E fragment **48** (Scheme 6).

[53] Fujiwara, K.; Saka, K.; Takaoka, D.; Murai, A. *Synlett* **1999**, 1037.
[54] Fujiwara, K.; Sato, D.; Watanabe, M.; Morishita, H.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2004**, *45*, 5243.
[55] Fujiwara, K; Goto, A.; Sato, D.; Ohaniuchi, Y.; Tanaka, H.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2004**, *45*, 7011.

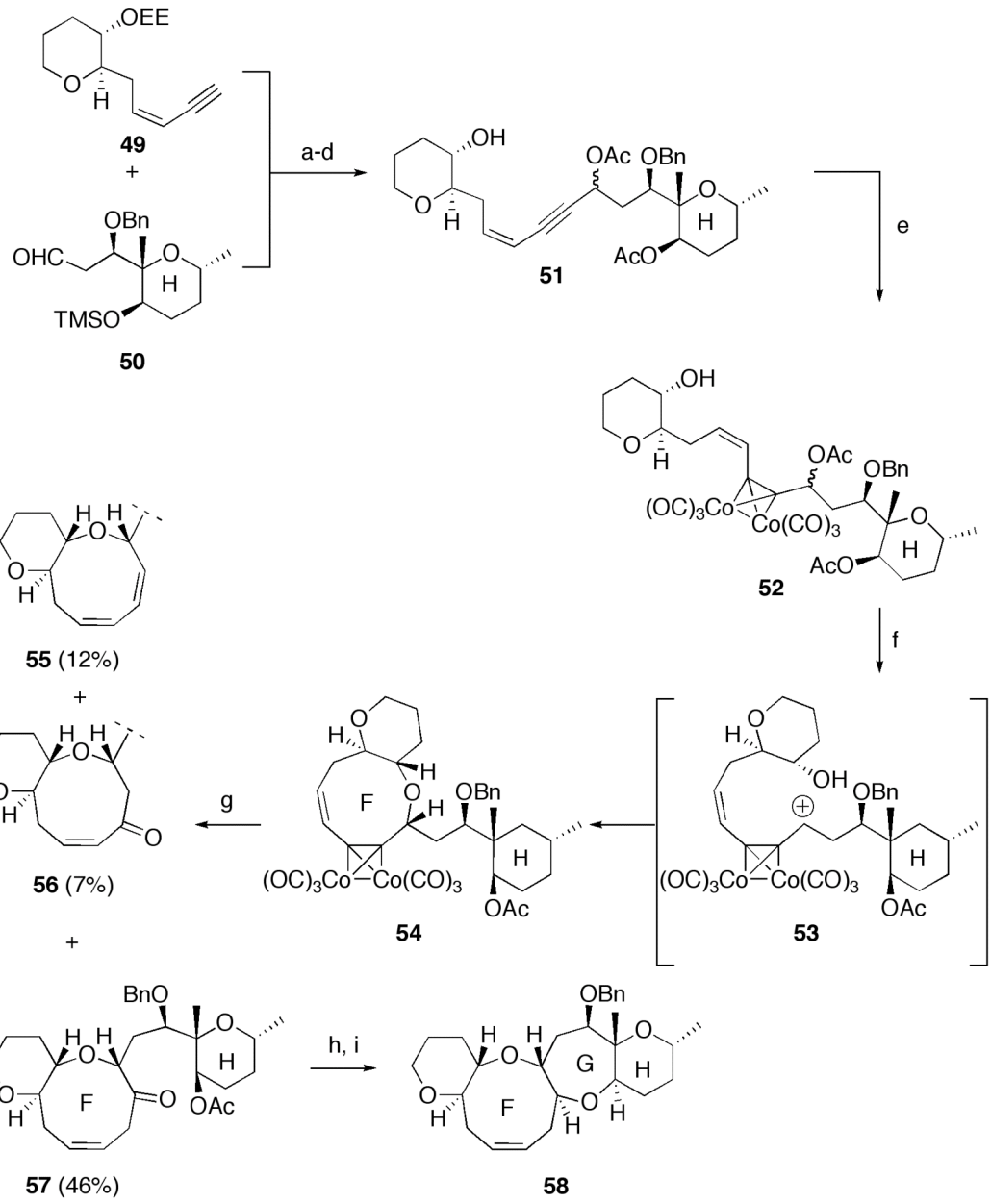


Scheme 6: *Conditions*: (a) NaHMDS, THF, –78 °C, then **46**, 54%; (b) TBAF, THF, rt, 93%; (c) THF/H_2O/TFA (10:10:1), rt, 54%.

3.3 Acetylide-Aldehyde Coupling/Cyclisation of Acetylene Cobalt Complex

In 1994, Isobe and co-workers reported a convergent and innovative approach to medium-sized rings *via* acetylene cobalt complexes.[56] This methodology was used to synthesise the central region of CTX1B (**4**).[57] As depicted in Scheme 7, the reaction of aldehyde **50** with the acetylide derived from enyne **49**, followed by protective group manipulations gave adduct **51**. Conversion into the cobalt complex **52**, followed by acid treatment promoted the F-ring cyclisation in 86% yield to afford **54** as a single stereoisomer, presumably proceeding *via* the cobalt-complex-stabilised propargylic cation **53**.[58] After deacetylation, the treatment with $BF_3{\cdot}OEt_2$ and Et_3SiH accomplished the stereoselective construction of the FH-ring system **58**. This approach can be used in the last stage of the total synthesis of CTXs.

[56] (*a*) Yenjai, C.; Isobe, M. *Tetrahedron* **1998**, *54*, 2509; (*b*) Kira, K.; Isobe, M. *Tetrahedron Lett*. **2000**, *41*, 5951; (*c*) Liu, T. Z.; Isobe, M. *Tetrahedron* **2000**, *56,* 5391.
[57] (*a*) Takai, S.; Sawada, N.; Isobe, M. *J. Org. Chem.* **2003**, *68*, 3225; (*b*) Takai, S.; Isobe, M. *Org. Lett.* **2002**, *4*, 1183.
[58] For review of the use of cobalt-stabilised cations in synthesis see: Teobalt, B. J. *Tetrahedron* **2002**, *58*, 4133.

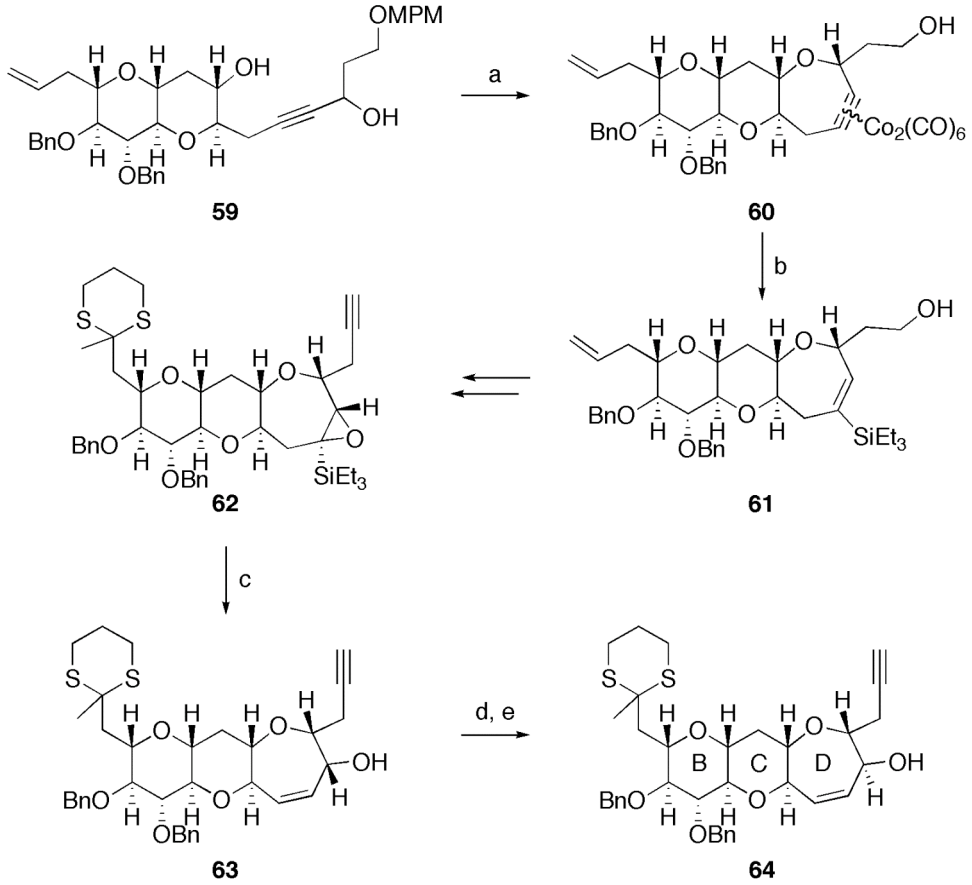


Scheme 7: *Conditions*: (a) *n*-BuLi, THF, –78 °C then **50**, 73%; (b) K_2CO_3, MeOH, rt, 95%; (c) Ac_2O, pyridine, DMAP, CH_2Cl_2, rt, 100%; (d) PPTS, MeOH, rt, 96%; (e) $Co_2(CO)_8$, CH_2Cl_2, 0 °C to rt, 95%; (f) PTSA, CH_2Cl_2, 0 °C to rt, 86%; (g) H_2, 100 kg/cm^2, hexane, 65 °C, 46%; (h) K_2CO_3, MeOH, rt, 97% from **57**; (i) Et_3SiH, $BF_3{\cdot}OEt_2$, MeCN, –15 °C to rt, 72%.

This methology was also used extensively for the formation of the other fragment of CTX1B (**4**)[59] as shown in Scheme 8, where the key steps in the synthesis of the BD-ring system are highlighted. Nicholas reaction between propargylic alcohol **59** and $Co_2(CO)_8$ in the presence of $BF_3{\cdot}OEt_2$ afforded **60** as a single stereoisomer having the *syn* relationship. The hydrosilylation of **60** was conducted with Et_3SiH in dichloroethane at 60 °C (with propargyl alcohol as an additive to suppress isomerisation of the terminal olefin) giving vinyl silane **61** in

[59] (*a*) Baba, T.; Huang, G.; Isobe, M. *Tetrahedron* **2003**, *59*, 6851; (*b*) Kira, K.; Hamajima, A.; Isobe, M. *Tetrahedron* **2002**, *58*, 1875.

89% yield. Several further steps led to the formation of epoxysilane **62** which underwent ring-opening to give the allylic alcohol **63**. Finally, a modified Mitsunobu[60] inversion of alcohol **63** afforded the BCD fragment **64**.



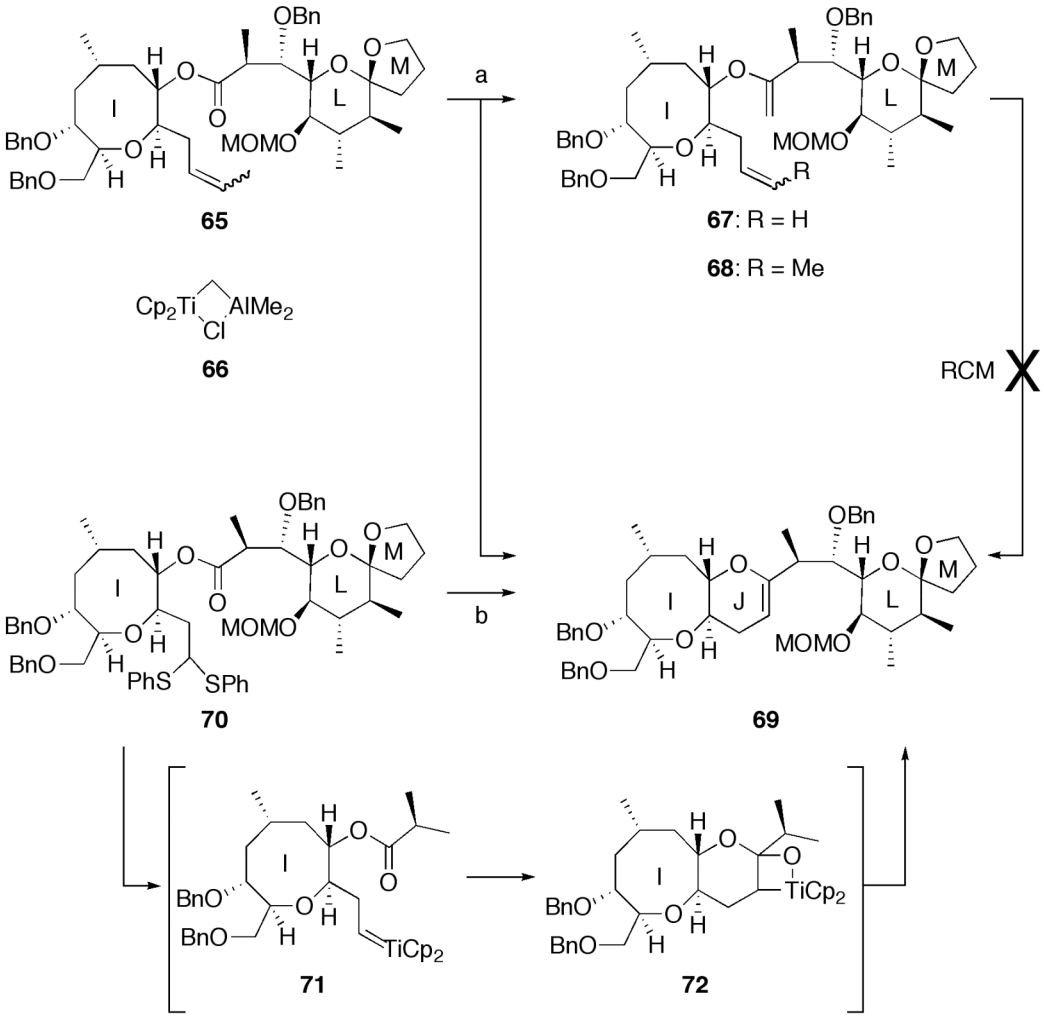
Scheme 8: *Conditions*: (a) $Co_2(CO)_8$, CH_2Cl_2, rt then $BF_3{\cdot}OEt_2$, 0 °C to rt, 78%; (b) Et_3SiH, propargyl alcohol, dichloroethane, 60 °C, 89%; (c) $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, 80%; (d) DEAD, PPh_3, *p*-nitrobenzoic acid, toluene, 0 °C to rt; (e) K_2CO_3, MeOH, rt, 94% (2 steps).

3.4 Esterification/Intramolecular Enol Formation with RCM or Related Reactions

Nicolaou and co-workers first reported the formation of cyclic enol ethers from olefinic esters by means of RCM using the Tebbe reagent **66**.[61] Hirama and co-workers attempted to exploit this methodology in their approach to the synthesis of the I-M fragment of CTX3C (**2**).[62] Unfortunately, the formation of the

[60] Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017.
[61] (*a*) Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565; (*b*) Nicolaou, K. C. Postema, M. H. D.; Yue, E. W.; Nadin, A. *J. Am. Chem. Soc.* **1996**, *118*, 10335. (*c*) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611.
[62] (*a*) Uehara, H,; Oishi, T.; Inoue, M.; Shoji, M.; Nagumo. Y.; Kosaka, M.; Le Brazidec, J. Y.; Hirama, M. *Tetrahedron* **2002**, *58*, 6493; (*b*) Uehara, H,; Oishi, T.; Inoue, M.; Shoji, M.; Nagumo. Y.; Kosaka, M.; Le Brazidec, J. Y.; Hirama, M. *Chem. Commun.* **2001**, 381.

desired cyclic enol ether **69** proceeded with variable yields (0 to 63%) and significant amounts of by-products **67** and **68** were isolated (18 to 70%). Authors postulated that RCM catalysts could not induce the cyclisation due to the steric hindrance around the enol ether. Alternatively, the Takeda carbonyl olefination reaction was used to generate **69** in a reproducible manner. In this case, the strong affinity between titanium and the carbonyl oxygen in **71** could favourably drive the reaction to give the oxatitanacycylobutane **72**, despite the steric hindrance, leading to **69** (Scheme 9).

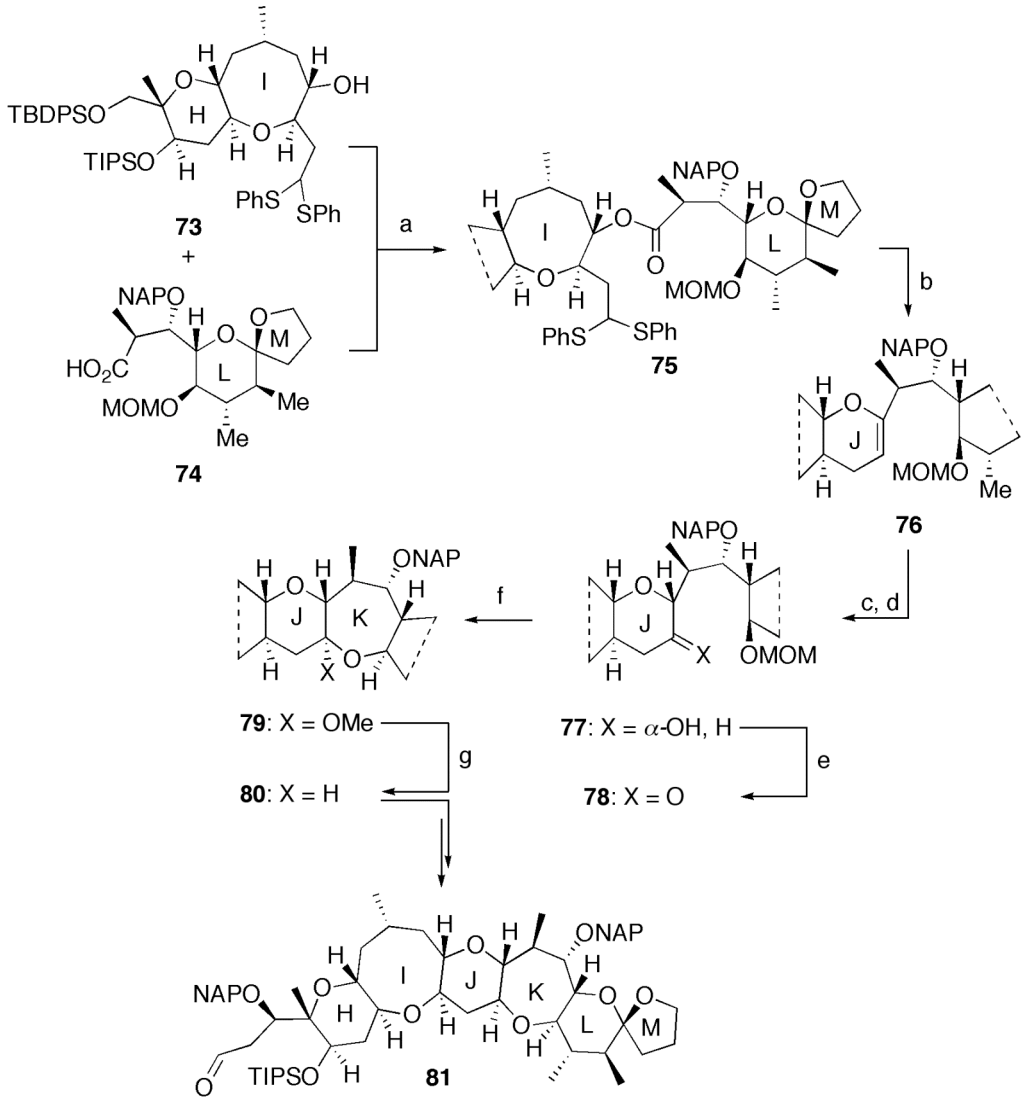


Scheme 9: *Conditions:* (a) **66**, THF, 60 °C, **67** and **68**: 18 to 70%, **69**: 0 to 63%; (b) $Cp_2Ti[P(OEt)_3]_2$ (3 or 4 eq.), THF, rt to reflux, 67%.

Finally, this methodology was incorporated in the synthesis of the right hand fragment of CTX3C (**2**). Ester **75** was formed following the Yamaguchi protocol[63] and the J-ring cyclisation was achieved using the Takeda reagent[64] in

[63] Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn*. **1979**, *52*, 1989.
[64] (*a*) Horikawa, Y.; Watanabe, M.; Fujiwara, T.; Takeda, T. *J. Am. Chem. Soc.* **1997**, *119*, 1127; (*b*) Rahim, M. A.; Fujiwara, T.; Takeda, T. *Tetrahedron* **2000**, *56*, 763; (*c*) Rahim, M. A.; Sasaki, H.; Saito, J.; Fujiwara, T.; Takeda, T. *Chem. Commun.* **2001**, 625.

68% yield.[65] Using DMDO, the resulting enol ether **76** was epoxidised stereoselectively and S_N2-type hydride opening of the intermediate epoxyacetal furnished alcohol **77** in 78% overall yield. The oxidation and subsequent acid treatment afforded the seven-membered methylacetal **79**. Conventional reductive etherification of the latter proceeded with complete stereocontrol to afford **80**. Thus, the synthesis of fragment **80** was completed in seven steps from the advanced-intermediates **73** and **74**. The target molecule **81** was reached by the introduction of the side-chain that would form the G-ring (Scheme 10).



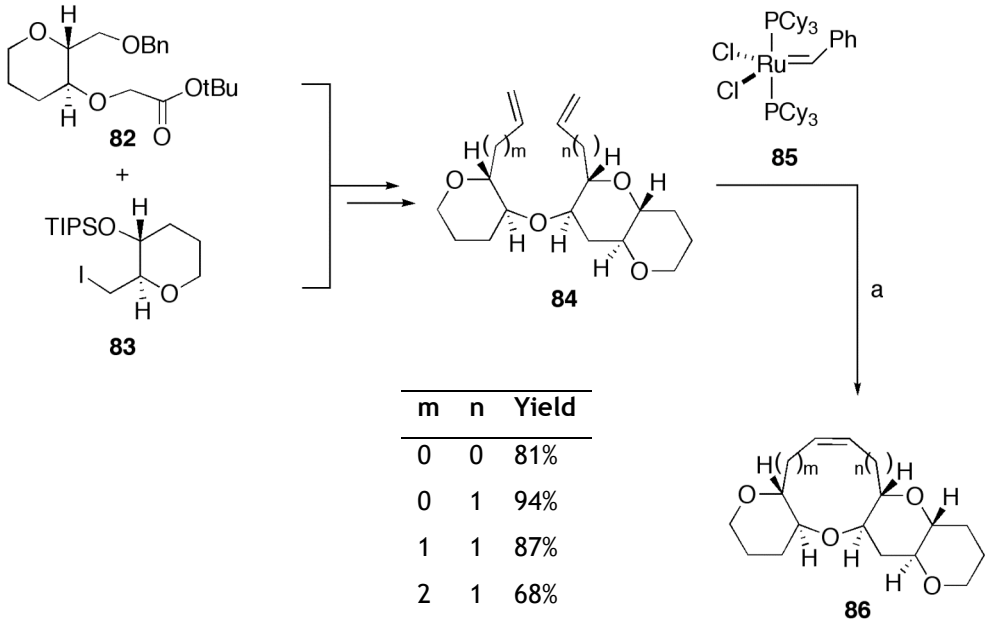
Scheme 10: *Conditions*: (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene; then DMAP, 35 °C, 77%; (b) $Cp_2Ti[P(OEt)_3]_2$ (4 eq.), THF, reflux, 68%; (c) DMDO, CH_2Cl_2, −40 to 0 °C; (d) $LiBHEt_3$, THF, 0 °C to rt, 78% (2 steps); (e) DMP, CH_2Cl_2, rt, 95%; (f) $(MeO)_3CH$, TfOH, hexane, rt, 62%; (g) $BF_3{\cdot}OEt_2$, Et_3SiH, CH_2Cl_2, 4 Å MS, −50 to 20 °C, 78%.

[65] (*a*) Inoue, M.; Yamashita, S.; Tatami, A.; Miyazaki, K.; Hirama, M. *J. Org. Chem*. **2004**, *69*, 2797; (*b*) Tatami, A.; Inoue, M.; Uehara, H.; Hirama, M. *Tetrahedron Lett*. **2003**, *44*, 5229.

Rainier and co-workers also reported that titanium-based reagents were capable of inducing olefinic-ester cyclisation and diene RCM reactions.[66] Rainier's methodology will be discussed in greater details in Ch. 1, § 4.4.2.

3.5 Intermolecular Alkylation/RCM Reaction

In 1998, Hirama synthesised 6/n/6/6-tetracyclic systems (n = 7–10) using alkylation and RCM as the key reactions (Scheme 11).[67] Subunits **82** and **83** were coupled and further functional group manipulations led to diene **84**. Subsequent treatment with the Grubbs catalyst **85**, afforded olefin **86** in good yield. RCM proved to be a good general method for the construction of medium-sized ether rings and has become the most important technology to build seven- to nine-membered ether rings from *O*-linked oxacycles.



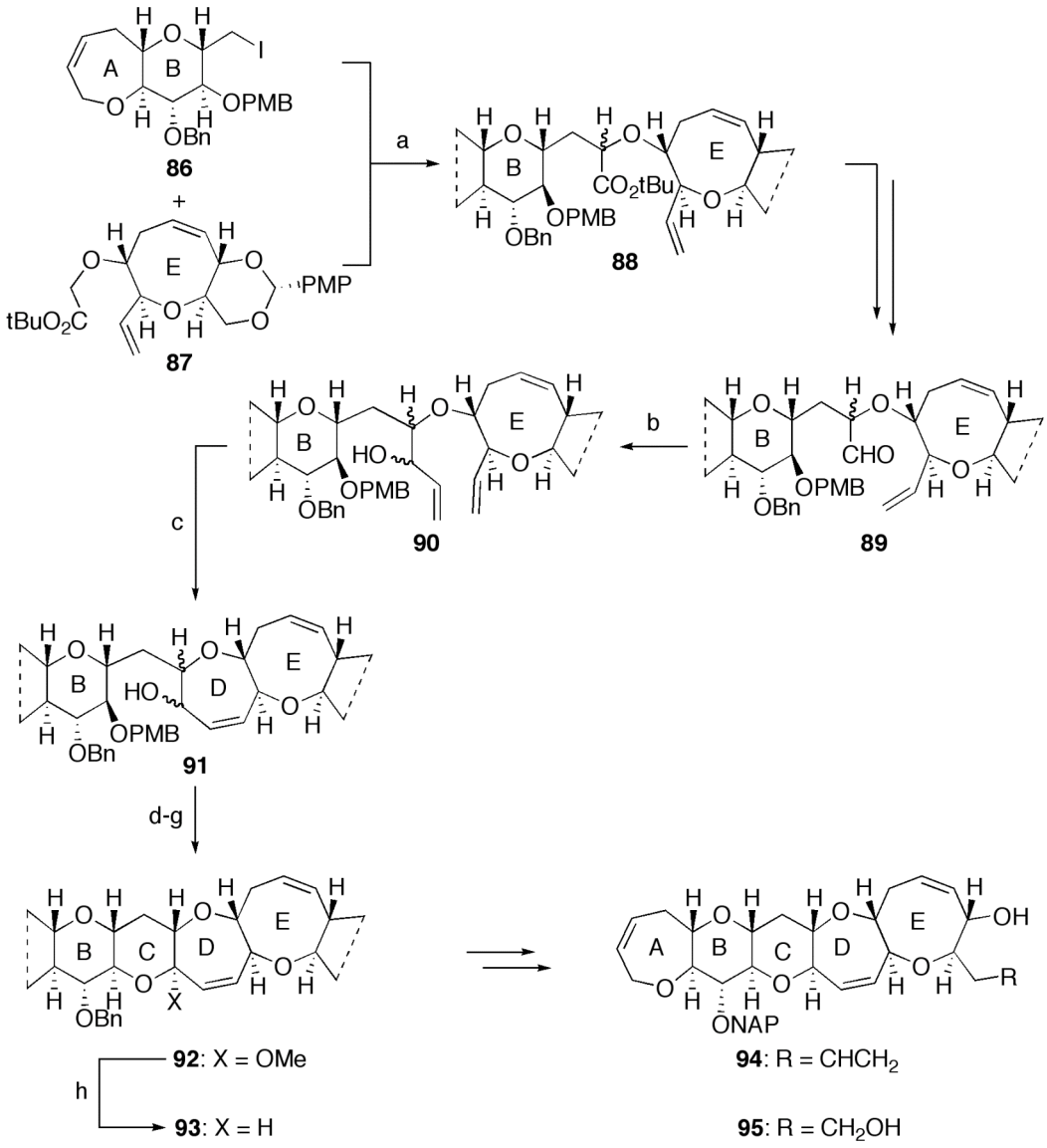
m	n	Yield
0	0	81%
0	1	94%
1	1	87%
2	1	68%

Scheme 11: Conditions: (a) catalyst **85** (12–21 mol%), C_6H_6 or CH_2Cl_2, 35 to 60 °C.

A few years later, Hirama's group exemplified the versatility of this strategy by the synthesis of the left wing fragment of CTX3C.[68] In contrast to the model study, intermolecular alkylation of ester **87** with iodide **86** proceeded in

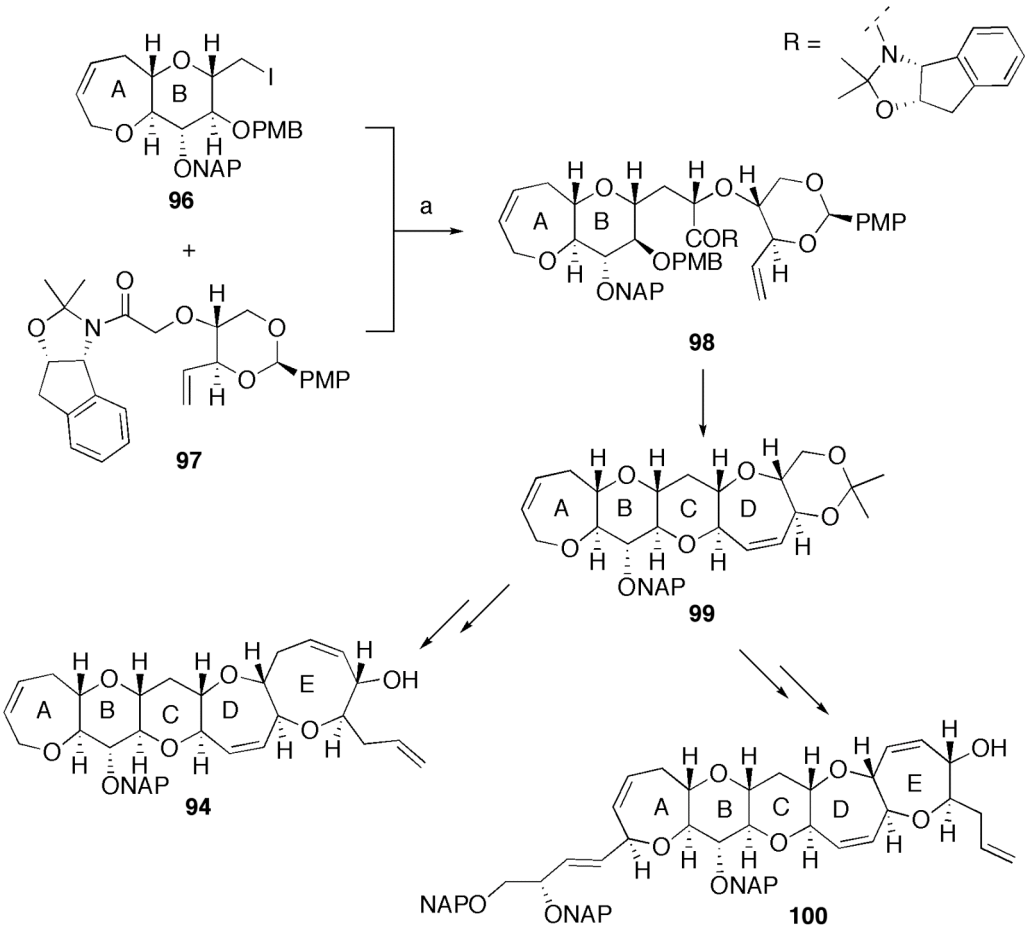
[66] (*a*) Iyer, K.; Rainier, J. D. *J. Am. Chem. Soc.* **2007**, *129*, 12604; (*b*) Roberts, S. W.; Rainier, J. D. *Org. Lett.* **2007**, *9*, 2227; (*b*) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59,* 2668.
[67] Oishi, T.; Nagumo, Y.; Hirama, M. *Chem. Commun*. **1998**, 1041.
[68] Maruyama, Y.; Inoue, M.; Oishi, T.; Oguri, H.; Ogasawara, Y.; Shindo, Y.; Hirama, M. *Tetrahedron* **2002**, *58*, 1835.

favour of the undesired configuration and an epimerisation step was required to obtain sufficient amounts of **88**. Chemical transformations resulted in the formation of the aldehyde **89**, which, upon the addition of vinyl lithium afforded the alcohol **90**. The cyclisation of **90** under RCM conditions followed by an oxidation/ isomerisation procedure led to the formation of the desired secondary alcohol with the correct stereochemistry at the pseudoequatorial position. PMB removal and methyl acetalisation under acidic conditions then gave the A-E fragment **92**. The reductive etherification of **92** followed by subsequent functional group manipulations yielded the left wing fragments **94** and **95** of CTX3C (**2**), (Scheme 12).



Scheme 12: *Conditions*: (a) LDA, THF/HMPA, **80**, –78 °C, 51%; (b) tetravinyltin, MeLi, Et_2O, –78 °C, 94%; (c) catalyst **85** (7 mol%), CH_2Cl_2, 35 °C, 96%; (d) $(COCl)_2$, Et_3N, DMSO, –78 to –35 °C; (e) DBU, toluene, 95 °C, 14 h, 95%; (f) DDQ, CH_2Cl_2, H_2O, rt, 94%; (g) $CH(OMe)_3$, CSA, CH_2Cl_2, rt, 64%; (h) Et_3SiH, $BF_3{\cdot}OEt_2$, MeCN, –78 to –30 °C, 98%.

In a final approach, the stereoselectivity of the alkylation step was controlled. A chiral amino indanol derivative was attached to the substrate and the coupling reaction between **96** and **97** exclusively afforded the desired isomer **98** (Scheme 13). The derivatisation of intermediate **98**, led, in a few steps, to the pentacycle **99** that was used as a common intermediate for the syntheses of **94** and 1**00**, which correspond to the left wings of CTX3C (**2**) CTX1B (**4**), respectively.



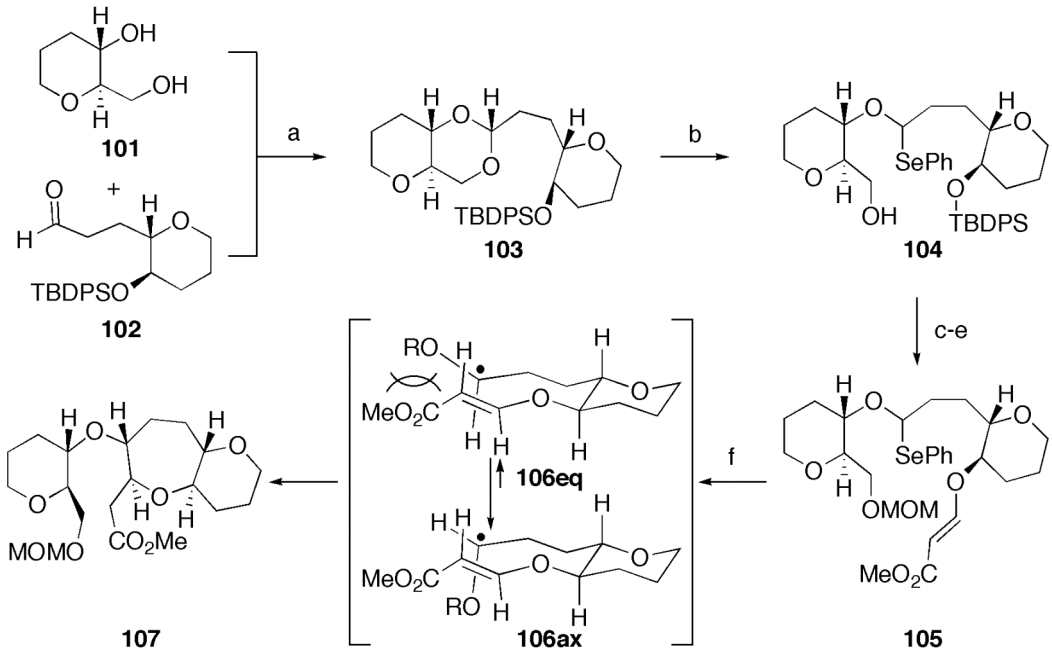
Scheme 13: *Conditions*: (a) *n*-BuLi, DMPU, THF, –78 °C to rt, 96%.

3.6 *O*,*O*-Acetalisation/Intramolecular Radical cyclisation from mixed Acetals

Sasaki and Tachibana were the first to report a convergent synthesis of *O*-linked oxepanes based on an intramolecular radical reaction.[69] Condensation between **101** and **102**, led to the six-membered acetal **103**. Regioselective

[69] (*a*) Sasaki, M.; Noguchi, T.; Tachibana, K. *J. Org. Chem*. **2002**, *67*, 3301; (*b*) Sasaki, M.; Noguchi, T.; Tachibana, K. *Tetrahedron Lett*. **1999**, *40*, 1337; (*c*) Sasaki, M.; Inoue, M.; Noguchi, T.; Takeichi, A.; Tachibana, K. *Tetrahedron Lett*. **1998**, *39*, 2783.

cleavage of the less hindered C–O bond using *i*-$Bu_2AlSePh$ afforded the corresponding *O,Se*-acetal **104**. Three additional synthetic steps afforded the precursor for the radical cyclisation **105**. The treatment of **105** with *n*-Bu_3SnH in presence of Et_3B formed the oxepane **107** diastereoselectively in a mild and effective manner (Scheme 14).[70] Taking into consideration that the stereochemical information of the acetal carbon was lost upon formation of the radical intermediate, the stereoselectivity of this step can be explained easily. In order to avoid the 1,3-diaxial-like interactions, the β-alkoxyacrylate favoured the extended *s-trans*- over the *s-cis*-conformation. Furthermore, steric interactions between the bulky alkoxy group and the *s-trans*-alkoxyacrylate of the pseudoequatorial **106eq** resulted in a preference for the pseudoaxial **106ax**, from which the desired isomer **107** was the only possible product among the four potential isomers.

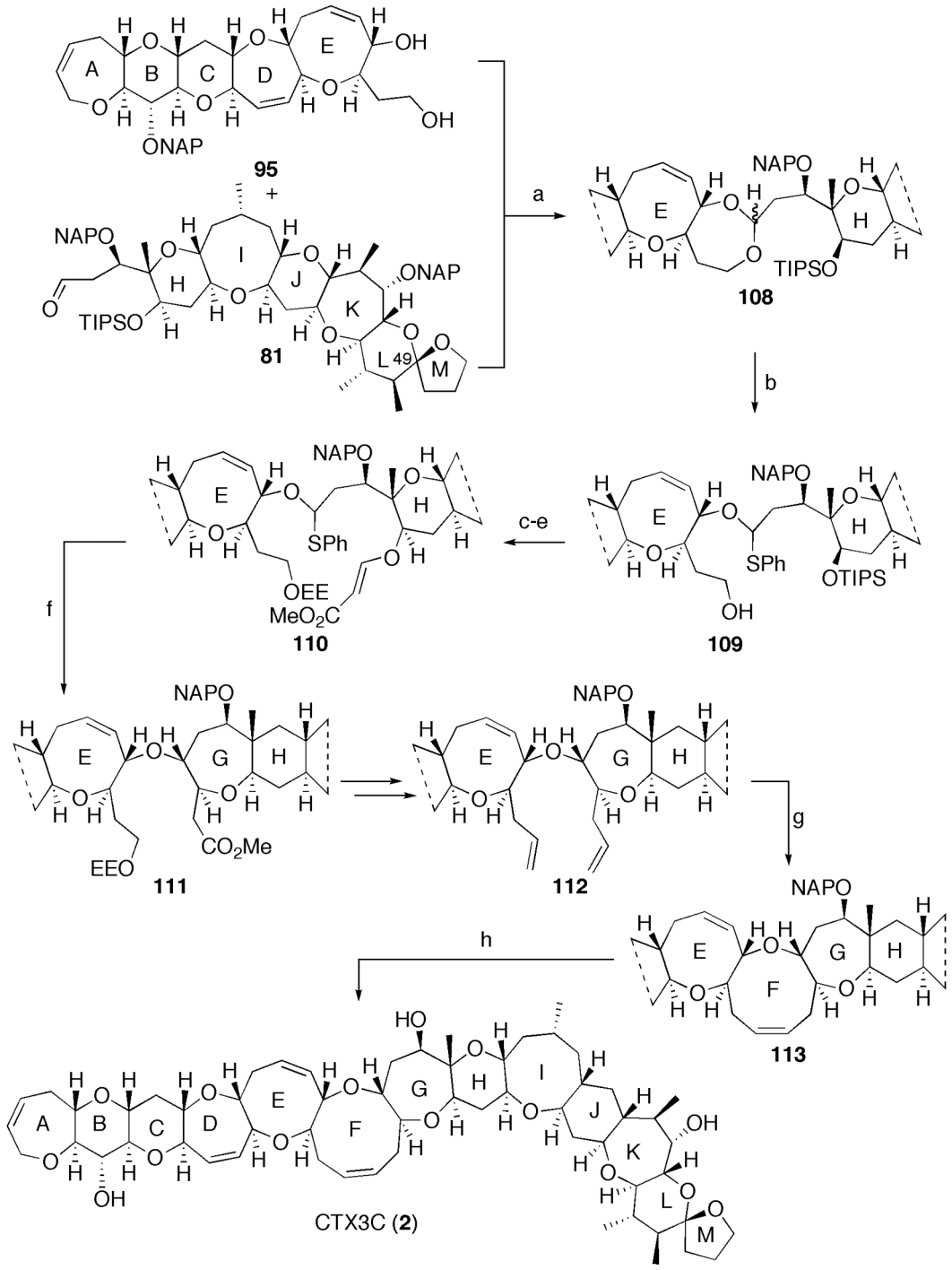


Scheme 14: *Conditions*: (a) CSA, C_6H_6, reflux, quant.; (b) *i*-BuAlSePh, toluene, –20 °C, 94%; (c) MOMCl, DIPEA, CH_2Cl_2, rt; (d) TBAF, THF, rt, 91%; (e) methyl propiolate, *n*-Bu_3P, CH_2Cl_2, rt, 69% (3 steps); (f) *n*-Bu_3SnH, Et_3B, C_6H_6, rt, 75%.

[70] Nozaki, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn*. **1990**, *63*, 2578.

Hirama and co-workers exploited a modified version of this reaction in their total synthesis of CTX3C (**2**).[71] As shown in Scheme 15, acetalisation between **81** and **95** was performed in the presence of $ScOTf_3$ and yielded selectively the seven-membered acetal **108**.[72] The exposure of acetal **108** to TMSOTf and TMSSPh provided the *O,S*-acetal **109** without affecting the C49-spiroacetal. Further functional group elaborations led to the β-alkoxyacrylate **110** that was subjected to the radical cyclisation using *n*-Bu_3SnH and AIBN leading to the oxepane **111**. The intermediate radical added to the α,β-unsaturated ester of **110** in a completely stereo- and chemoselective manner. The final cyclisation precursor **112** was obtained by conventional means and catalyst **85** smoothly promoted the chemoselective RCM reaction. Global NAP-deprotection of **113** afforded the target molecule CTX3C (**2**) in 63% yield.

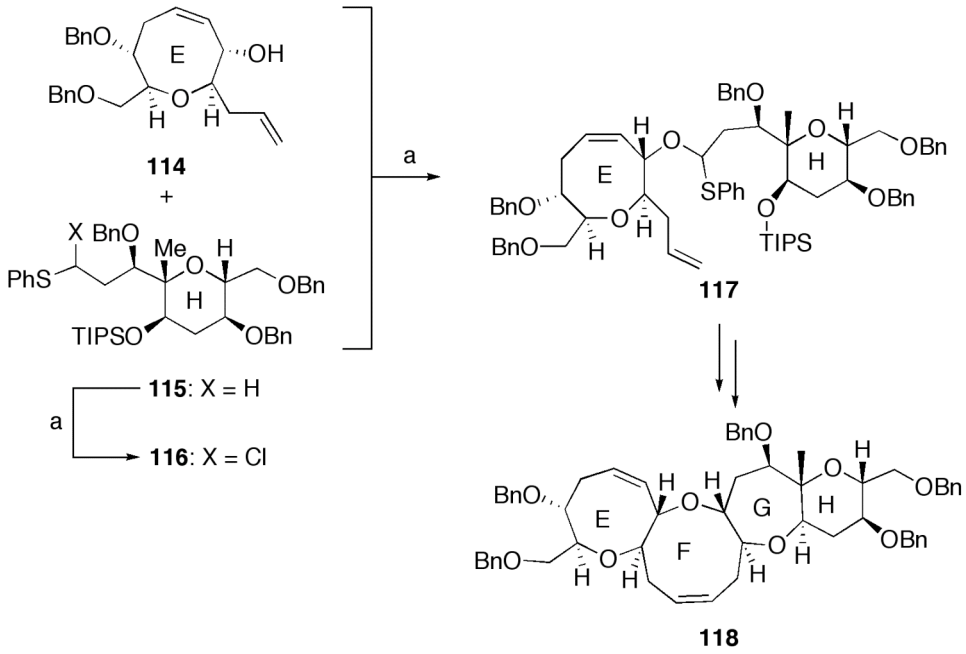
[71] Inoue, M.; Uehara, H.; Maruyama, M.; Hirama, M. *Org. Lett.* **2002**, *4*, 4551.
[72] (*a*) Imai, H.; Uehara, H.; Inoue, M.; Oguri, H.; Oishi, T.; Hirama, M. *Tetrahedron Lett.* **2001**, *42*, 6219; (*b*) Inoue, M.; Sasaki, M.; Tachibana, K. *J. Org. Chem.* **1999**, *64*, 9416; (*c*) Inoue, M.; Sasaki, M.; Tachibana, K. *Angew. Chem. Int. Ed.* **1998**, *37*, 965.



Scheme 15 *Conditions*: (a) $Sc(OTf)_3$, C_6H_6, rt, 69%; (b) TMSSPh, TMSOTf, DTBMP, CH_2Cl_2, rt to 35 °C, 36% (89% brsm); (c) ethyl vinyl ether, PPTS, CH_2Cl_2, rt 73%; (d) TBAF, THF, 40 °C; (e) methyl propiolate, NMM, CH_2Cl_2, rt, 89% (2 steps); (f) *n*-Bu_3SnH, AIBN, toluene, 85 °C; g) catalyst **85** (30 mol%), CH_2Cl_2, 40 °C, 90%; h) DDQ, CH_2Cl_2/H_2O (20:1), rt, 63%.

3.7 Direct *O,S*-Acetal Formation/Intramolecular Radical Cyclisation

Efforts to synthesise CTX congeners with acid-sensitive functionalities, such as CTX1B (**4**) led the Hirama's group to develop an alternative, direct and milder route to the *O,S*-acetals.[73] Treatment of the H-ring sulfide **115** with NCS generated the α-chlorosulfide **116** under neutral conditions. The subsequent activation of **116** with AgOTf in the presence of **114** and DTBMP delivered the mixed-acetal **117** in 70% yield.[74] From model studies, Hirama's laboratory also established that the α-fluorosulfide intermediate can be converted into the mixed-acetal **117** by treatment with $Yb(OTf)_3$.[75] Finally, six steps were required to reach the target model compound **118**, which included radical cyclisation and RCM reaction (Scheme16).

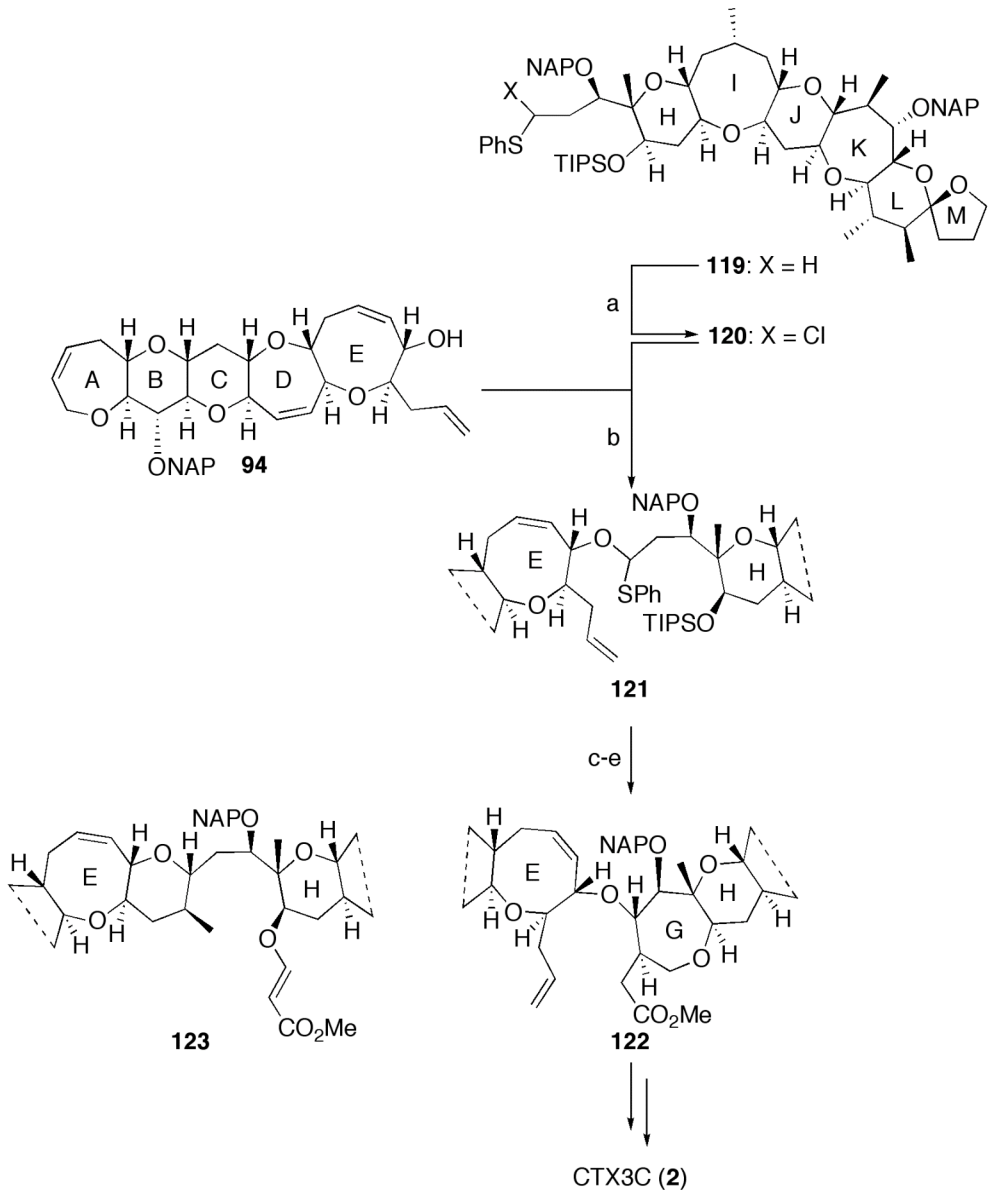


Scheme 16: *Conditions*: (a) NCS, CCl_4, rt; (b) AgOTf, DTBMP, CH_2Cl_2, 4 Å MS, −50 to −30 °C, 70% (2 steps).

The methodology was then applied to their second-generation total synthesis of CTX3C (**2**), (Scheme 17).[25b,c] The α-chlorosulfide **116** and the alcohol **94** were coupled by the action of AgOTf. In this way *O,S*-acetal **118** was formed in high yield, thus accomplishing direct construction of the key

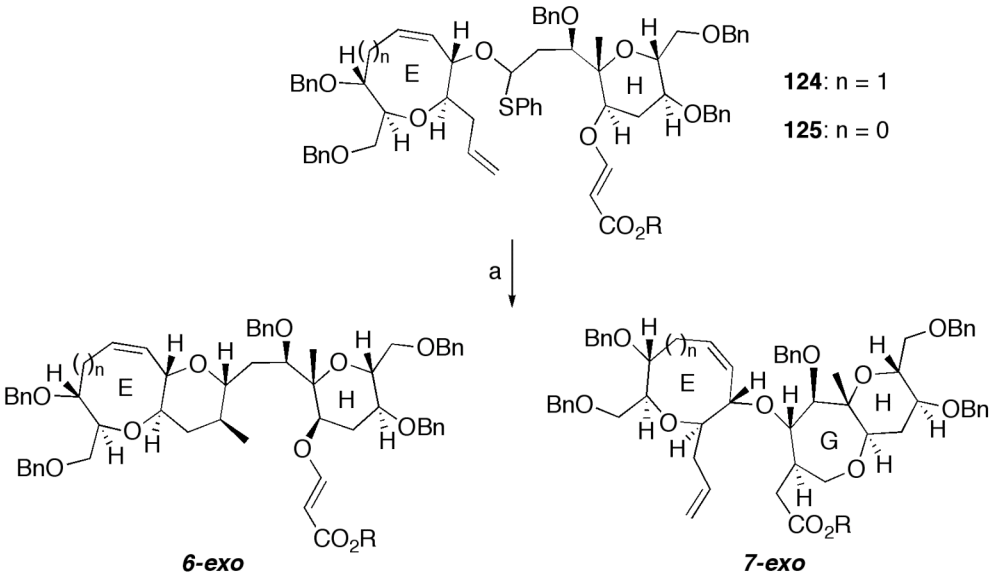
[73] (*a*) Inoue, M.; Wang, J.; Wang, G. X.; Ogasawara, Y.; Hirama, M. *Tetrahedron. Lett.* **2003**, *59*, 5645; (*b*) Inoue, M.; Wang, G. X.; Wang, J.; Hirama, M. *Org. Lett*. **2002**, *4*, 3439.
[74] Mukaiyama, T.; Sugaya, T.; Marui, S.; Nakatsuka, T. *Chem. Lett*. **1982**, 1555.
[75] Inoue, M.; Yamashita, S.; Hirama, M. *Tetrahedron Lett*. **2004**, *45*, 2053.

intermediate. The construction of the F- and G-rings was achieved in a manner similar to the first-generation synthesis. However, in this case, the cyclisation of the G-ring was in competition with the *6-exo* cyclisation of the terminal olefin, the latter giving rise to the by-product **123**. It is noteworthy that the halophilic silver salt used in this coupling is highly chemoselective and is tolerated by various functional groups. In this sequence, two rings were installed in eight synthetic transformations instead of the 12 steps required in the first-generation synthesis.



Scheme 17: *Conditions*: (a) NCS, CCl_4/CH_2Cl_2 (6:1), rt; (b) AgOTf, DTBMP, CCl_4/CH_2Cl_2 (1:5), 4 Å MS, –70 to –30 °C, 70% (2 steps); (c) TBAF, THF, 35 °C, 85%; (d) methyl propiolate, NMM, CH_2Cl_2, rt, 100%; (e) *n*-Bu_3SnH, AIBN, toluene, 85 °C, 54%.

Recently, Hirama and co-workers managed to improve the selectivity of the radical cyclisation step.[76] Remarkably, the replacement of the Me group on the acrylate with pentafluorophenyl (PFP) enables the *7-exo* selectivity to be increased without affecting stereoselectivity. Studies also revealed that the selectivity control of the pentafluorophenyl group depends on the ring size (Scheme 18).



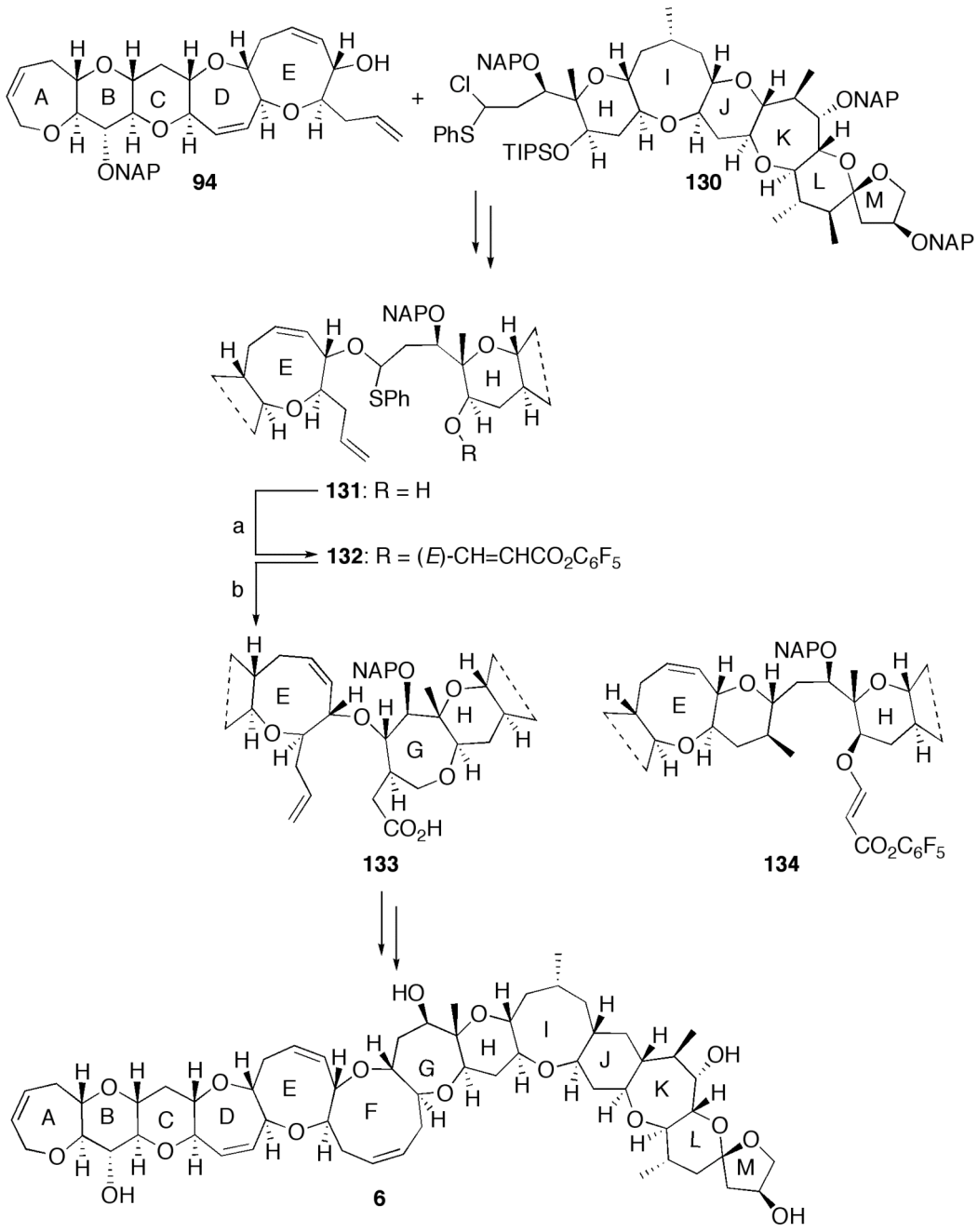
Entry		R	*6-exo:7-exo*	Yield of *7-exo*
1	**124a** (n = 1)	Me	1:2.1	56% (**127a**)
2	**124b** (n = 1)	PFP	1:12.8	77% (**127b** R = H)
3	**125a** (n = 0)	Me	1:1.2	43% (**129a**)
4	**125b** (n = 0)	PFP	1:2.6	51% (**129b**)

Scheme 18: *Conditions*: (a) Bu_3SnH, AIBN, toluene, 85 °C.

Based on these results and their second-generation synthesis of CTX3C (**2**) they embarked on the first total synthesis of 51-hydroxyCTX3C (**6**) (Scheme 19). The construction of the advance intermediate alcohol **131** was achieved by assembling fragments **94** and **130** using conditions previously reported (Scheme 16). The acrylate **132** was prepared using pentafluorophenyl propiolate and PMe_3 in 95% yield. The radical reaction of **132** exhibited significantly higher selectivity for *7-exo* cyclisation (**133**:**134** = 10.6:1) and delivered the carboxylic acid **133** in 74% yield. With the 12 ether rings in place, the final steps were the construction

[76] Inoue, M.; Miyazaki, K.; Ishihara, Y.; Tatami, A.; Ohnuma, Y.; Kawada, Y.; Komano. K.; Yamashita, S.; Lee. N.; Hirama, M. *J. Am. Chem. Soc*. **2006**, *128*, 9352.

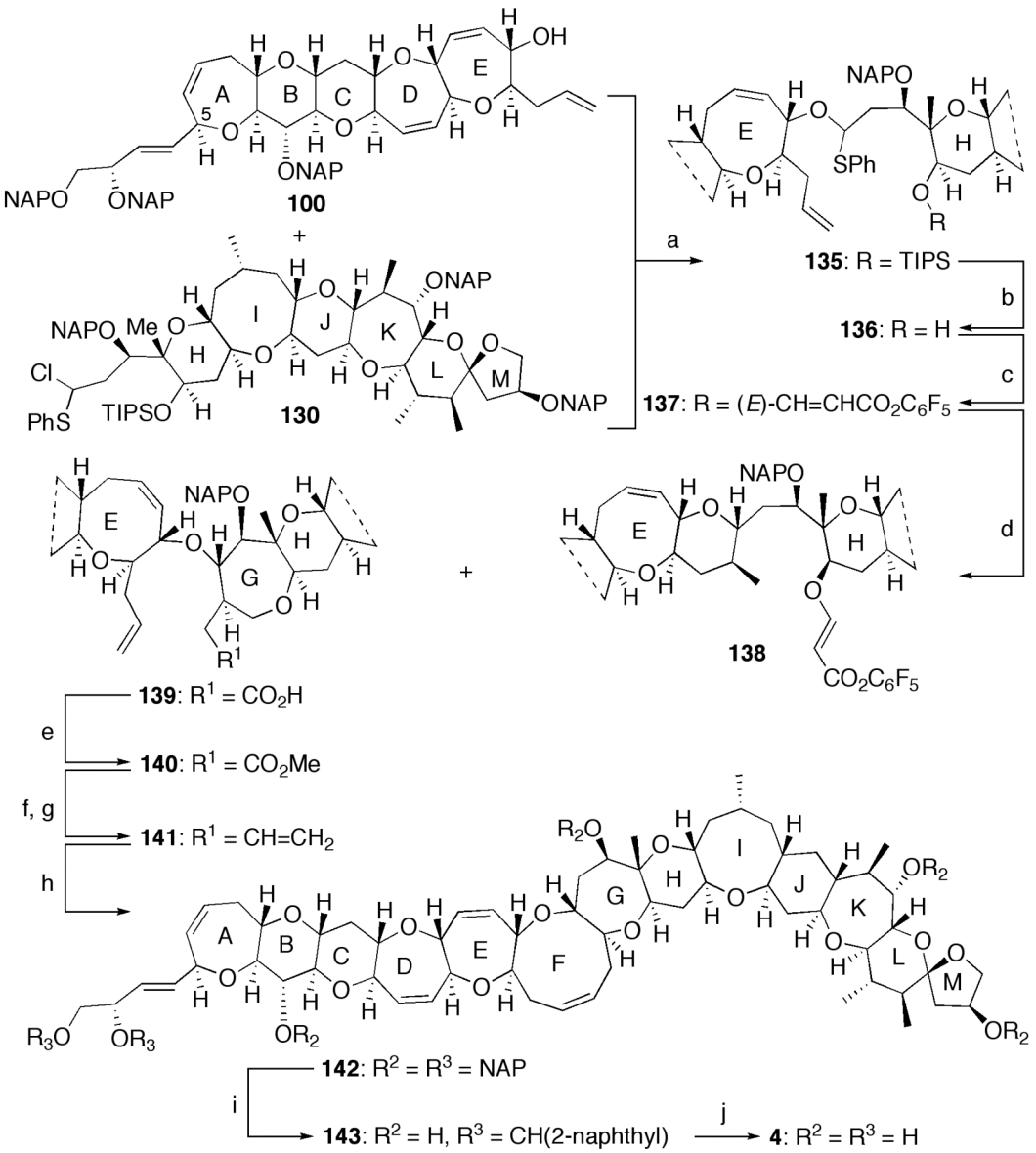
of the F-ring by RCM reaction and the oxidative removal of the NAP groups (Scheme 19).



Scheme 19: *Conditions:* (a) pentafluorophenyl propiolate, PMe_3, CH_2Cl_2, rt, 95%; (b) **130**, *n*-Bu_3SnH, AIBN, toluene, 85 °C, **133**, 74%; **134**, 7%.

Finally, having established the synthetic route to **6** Hirama and co-workers turned to the total synthesis of CTX1B (**4**) (Scheme 20). Here the presence of both the acid/base/oxidant-sensitive bis-allylic C5-ether and the seven-membered E-ring rather than the eight-membered ring of **6** increases the challenge. The coupling of alcohol **100** with α-cholorosulfide **130** afforded the

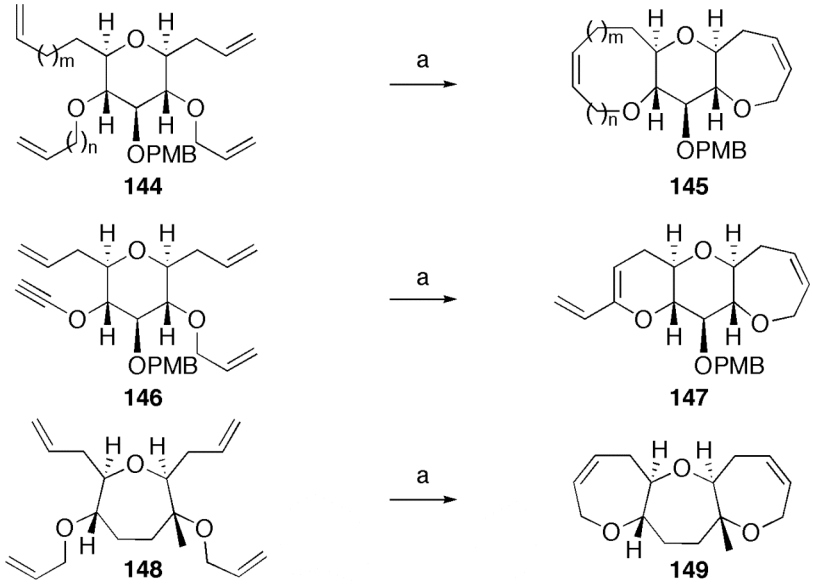
mixed acetal **135** in 63% yield. The TIPS group of **135** was subsequently exchanged for a pentafluorophenyl acrylate to afford **137**. The oxepane **139** was produced with the desired stereochemistry in 59% yield, according to the radical cyclisation protocol, along with the by-product **138** (**139**:**138** = 2.7:1). The decrease in selectivity is mainly explained by the more favourable orientation of the allyl group of the seven-membered E-ring in **137** for the *6-exo* cyclisation. The carboxylic acid **139** was converted into the alkene **141** in three steps. The RCM reaction catalysed by complex **85** afforded the fully protected CTX1B **142** in 78% yield. Finally, the NAP groups were removed in a two-step procedure to give **4** in 30% yield.



Scheme 20: *Conditions*: (a) AgOTf, DTBMP, 4 Å MS, CCl_4/CH_2Cl_2 (5:1), −70 to 0 °C, 63%; (b) TBAF, THF, 35 °C, 92%; (c) pentafluorophenyl propiolate, PMe_3, CH_2Cl_2, rt, 94%; (d) *n*-Bu_3SnH, AIBN, toluene, 85 °C, **139**, 59%; **138**, 22%; (e) $TMSCHN_2$, $MeOH/C_6H_6$, (2:5), 84%; (f) DIBAL, CH_2Cl_2, −90 °C;(g) Ph_3PCH_3Br, *t*-BuOK, THF, 0 °C, 77% (2 steps); (h) catalyst **85** (20 mol%), CH_2Cl_2, 40 °C, 78%, (i) DDQ, CH_2Cl_2/H_2O (1:1), rt; (j) 1 N HCl, MeOH, rt, 30% (2 steps).

3.8 Clark's Two-Directional Synthesis of Fused Polycyclic Ethers

Since the early 1990's, several robust and efficient strategies to construct fused polycyclic ethers using RCM reactions have been devised by Clark and are detailed in a recent review.[77] In 2000, Clark and co-workers disclosed the use of a two-directional double-RCM reaction to synthesise a variety of tricyclic ethers with six- to nine-membered rings. All were prepared in reasonable to excellent yield by two-directional double-RCM of substrates containing combinations of enol, allylic and alkynyl ethers (Scheme 21). The work reported by Rainier's laboratory is closely related to what is described here and will be discussed in greater details in Ch. 1, § 4.4.2.[78]



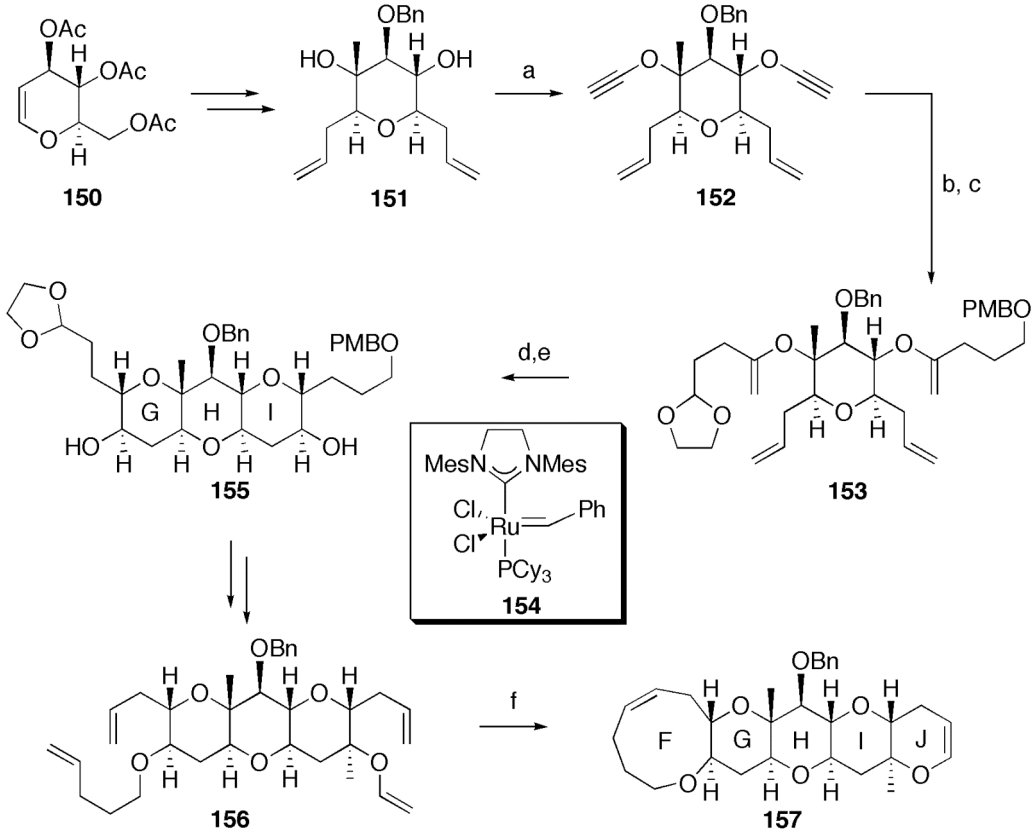
Entry		Catalyst	Yield
1	**144**, (m = 0; n = 1)	20-30 mol%	**145**, 88%
2	**144**, (m = 0; n = 3)	20-30 mol%	**145**, 65%
3	**144**, (m = 0; n = 1)	20-30 mol%	**145**, 77%
4	**144**, (m = 0; n = 0)	20-30 mol%	**145**, 71%
5	**146**	15 mol%	**147**,50%
6	**148**	20 mol%	**149**, 75%

Scheme 21: *Conditions*: (a) catalyst **85**, CH_2Cl_2, reflux.

An iterative double-RCM reaction was successfully applied to the synthesis of the F-J fragment of the gambieric acids[79] and later, to the A-E fragment of CTX3C.[80] The conversion of the commercially available tri-*O*-acetyl-D-glucal **150**

[77] Clark, J. S. *Chem. Commun.* **2006**, 3571.
[78] Zhang, Y.; Rainier, J. D. *Org. Lett.* **2009**, *11*, 237.
[79] Clark, J. S.; Hamelin, O. *Angew. Chem. Int. Ed*. **2000**, *39*, 372.
[80] Clark, J. S.; Conroy, J.; Blake, A. J. *Org. Lett.* **2007**, *9*, 2091.

into diol **151** was performed in 10 steps. The diol **150** was transformed into the bis(alkynyl ether) **152** by using a one-pot alkynylation procedure developed by Greene and co-workers.[81] Sequential carbocupration reactions allowed the preparation of bis(enol ether) **153** in 72% overall yield. It is noteworthy that the first side chain was introduced regioselectively at the less sterically hindered alkynyl ether, allowing the installation of the acetal-containing side chain. Double RCM followed by double hydroboration of the metathesis product afforded the tricyclic diol **155** in 55% yield over two steps. Further manipulations led to the second double-RCM precursor **156** which yielded the pentacyclic core **157** in 60% yield by treatment with the Grubbs second-generation catalyst **154** (Scheme 22).

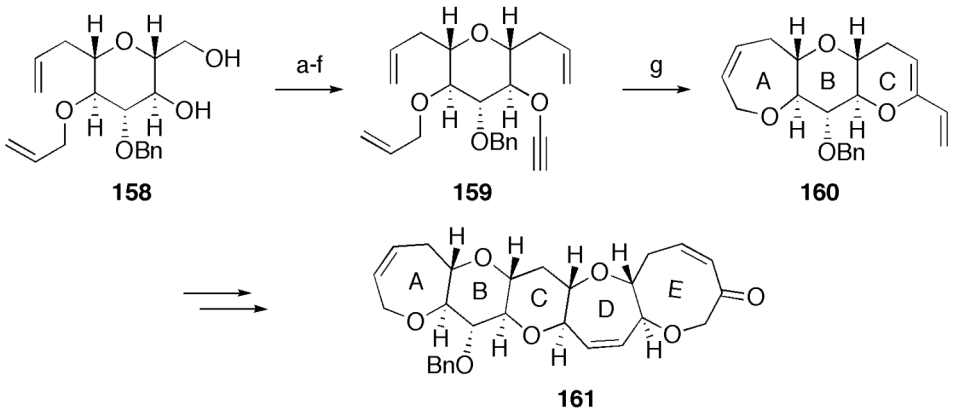


Scheme 22: *Conditions:* (a) KH, Cl_2CCHCl, THF, 0 °C, then *n*-BuLi, Et_2O, −78 to −40 °C, 88%; (b) $PMBO(CH_2)_3MgBr$, CuBr, LiBr, THF, −95 to −78 °C, 85%; (c) $(OCH_2CH_2O)CH(CH_2)_2MgBr$, CuCN, LiCl, THF, −78 °C, 84%; (d) catalyst **154** (10 mol%), toluene, 70 °C, 89%; (e) $ThxBH_2$, THF, 0 °C to rt, then $NaBO_3 \cdot 4H_2O$, pH 7 buffer, 62%; (a) catalyst **154** (10 mol%), toluene, 80 °C, 60%.

In 2007, the ABC fragment of ciguatoxin CTX3C (**2**) was constructed using the same methodology. Starting from diol **158**, the one-pot triflate and triethylsilyl ether formation was followed by triflate displacement with lithium

[81] Moyano, A.; Charbonnier, F.; Greene, A. E. *J. Org. Chem.* **1987**, *52*, 2919.

trimethylsilyl acetylide in the presence of DMPU. Desilylation of both hydroxyl groups, partial hydrogenation of the alkyne and alkynylation of the remaining free hydroxyl group afforded the desired two-directional RCM precursor **159** in good yield. The fused tricyclic ether **160** was obtained in 58% yield by treatment with the ruthenium complex **154** under an ethene atmosphere. Finally, the remaining D- and E-ring were cyclised by sequential RCM reactions to give the A-E fragment **161** (Scheme 23).



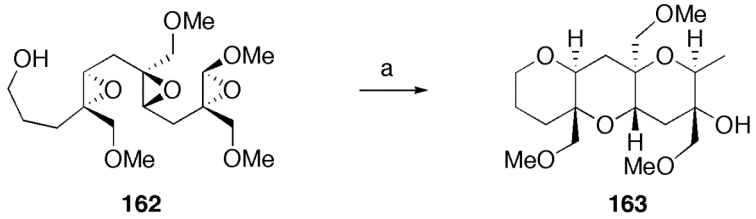
Scheme 23: *Conditions*: (a) Tf_2O, Et_3SiOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; (b) $Me_3SiCCLi$, DMPU, THF, −78 °C to rt; (c) TBAF, THF, rt, 90% (3 steps); (d) H_2, Lindlar's catalyst, quinoline, EtOAc, rt, 95%; (e) KH, Cl_2CCHCl, THF, −78 °C to rt, 95%; (f) *n*-BuLi, Et_2O, −78 to −40 °C, 91%; (g) catalyst **154** (10 mol%), ethene, toluene, 70 °C, 58%.

3.9 Biomimetic Synthesis of *trans,syn,trans*-Fused Polycyclic Ethers

The polyepoxide domino cylclisation hypothesis for the biosynthesis of *trans,syn,trans*-fused polycyclic ethers has been considered since 1980s. At that time, the development of biomimetic strategies was mainly hampered by the lack of methodology for stereoselective epoxidation of acyclic alkyl-substituted alkenes. The development of highly enantioselective methodologies, such as the Sharpless[82] and the Shi[83] epoxidations has enabled the stereoselective synthesis of polyepoxide substrates from acyclic systems.[84]

[82] (*a*) Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2024; (*b*) Katsuki, T; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.
[83](*a*) Shi, Y. *Acc. Chem. Ress.* **2004**, *37*, 488; (*b*) Wang, Z. X.; Tu, Y.; Frohn, M.; Zhang, J. R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224.
[84] Valentine, J. C.; McDonald, F. E. *Synlett* **2006**, 1816.

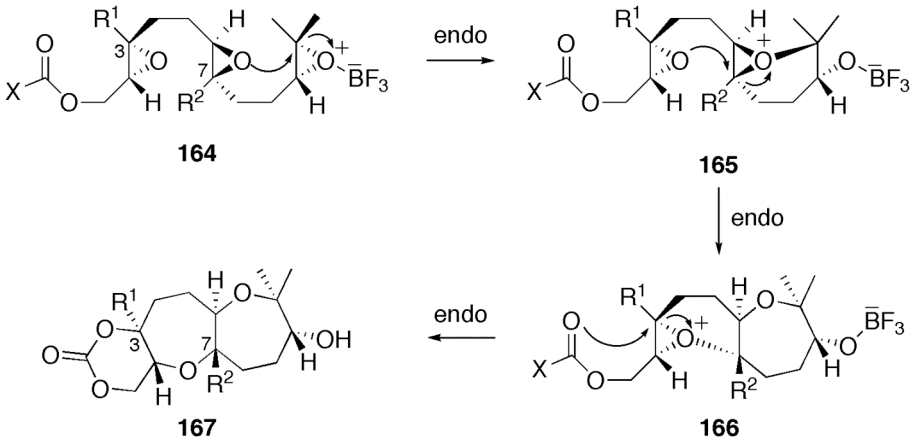
In 2000, Murai's laboratory reported the first tandem *endo*-mode oxacyclisation of the polyepoxide **162** to give the polycyclic ether **163.**[85] The *endo*-regioselective cyclisation was accomplished by chelation of lanthanide Lewis acid with both epoxide and methyl ether oxygens. Nevertheless, the presence of the *C*-methoxy-methyl substituent seems to be a limitation of this methodology (Scheme 24).



162 **163**

Scheme 24: *Conditions:* (a) $La(OTf)_3$, La_2O_3, H_2O, CH_2Cl_2, rt, 9%.

The same year, the McDonald's laboratory proposed a mechanistic hypothesis and proved the critical role played by the carbonyl *O*-nucleophile (Figure 7).[82,86] Lewis acid activation of **164** followed by nucleophilic addition of 6,7-epoxide gave the fused bicyclic epoxonium ion **165**. The subsequent epoxide addition produce the epoxonium **166** from **165** terminating the oxacyclisation cascade, to provide all- *trans*,*syn*,*trans*-polycyclic ether **167**.



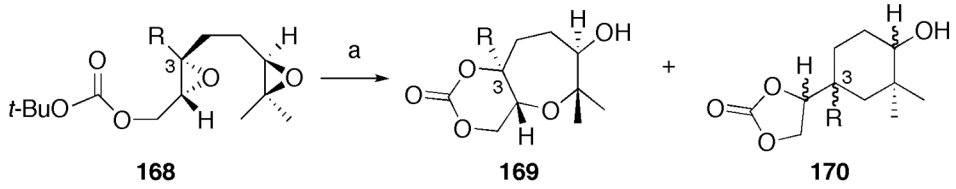
164 **165** **167** **166**

Figure 7: Proposed mechanism of Lewis acid-initiated oxacyclisation.

More recently, McDonald and co-workers demonstrated the remarkable effect of C-3 substituent. Experiments revealed that a C-3 silyl group favoured

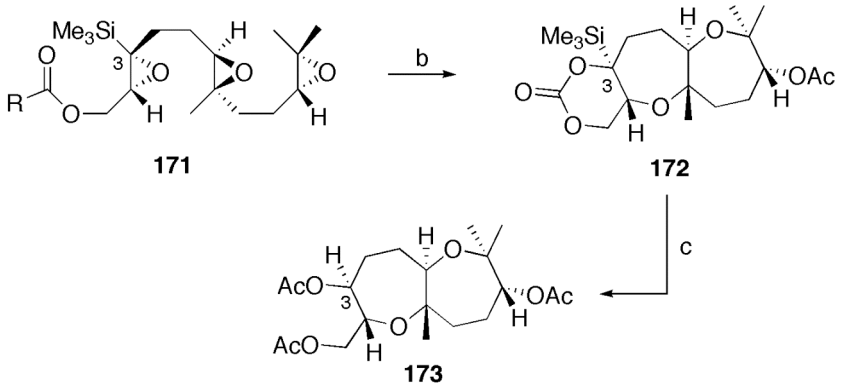
[85] Tokiwano, T.; Fujiwara, K.; Murai, A *Synlett* **2000**, 335.
[86] Mc Donald, F. E.; Wang, X.; Do, B.; Hardcastle, K. I. *Org. Lett.* **2000**, *2*, 2917.

regioselective tandem *endo*-oxacyclisation to afford **169** in good yield. They also proved the viability of disubstituted epoxides in Lewis acid-intiated oxacyclisation of polyepoxides (Scheme 25).[87]

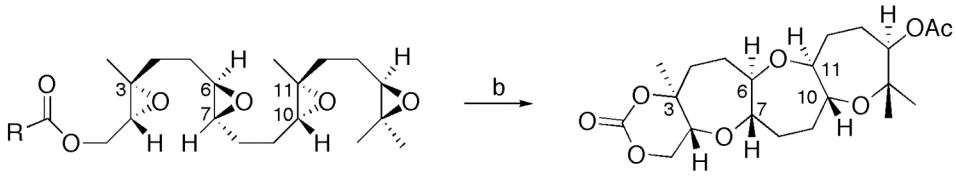


168 **169** **170**

R	Yield of 169	Yield of 170
H	–	15%
Me_3Si	78%	–



171 **172** **173**



174 **175**

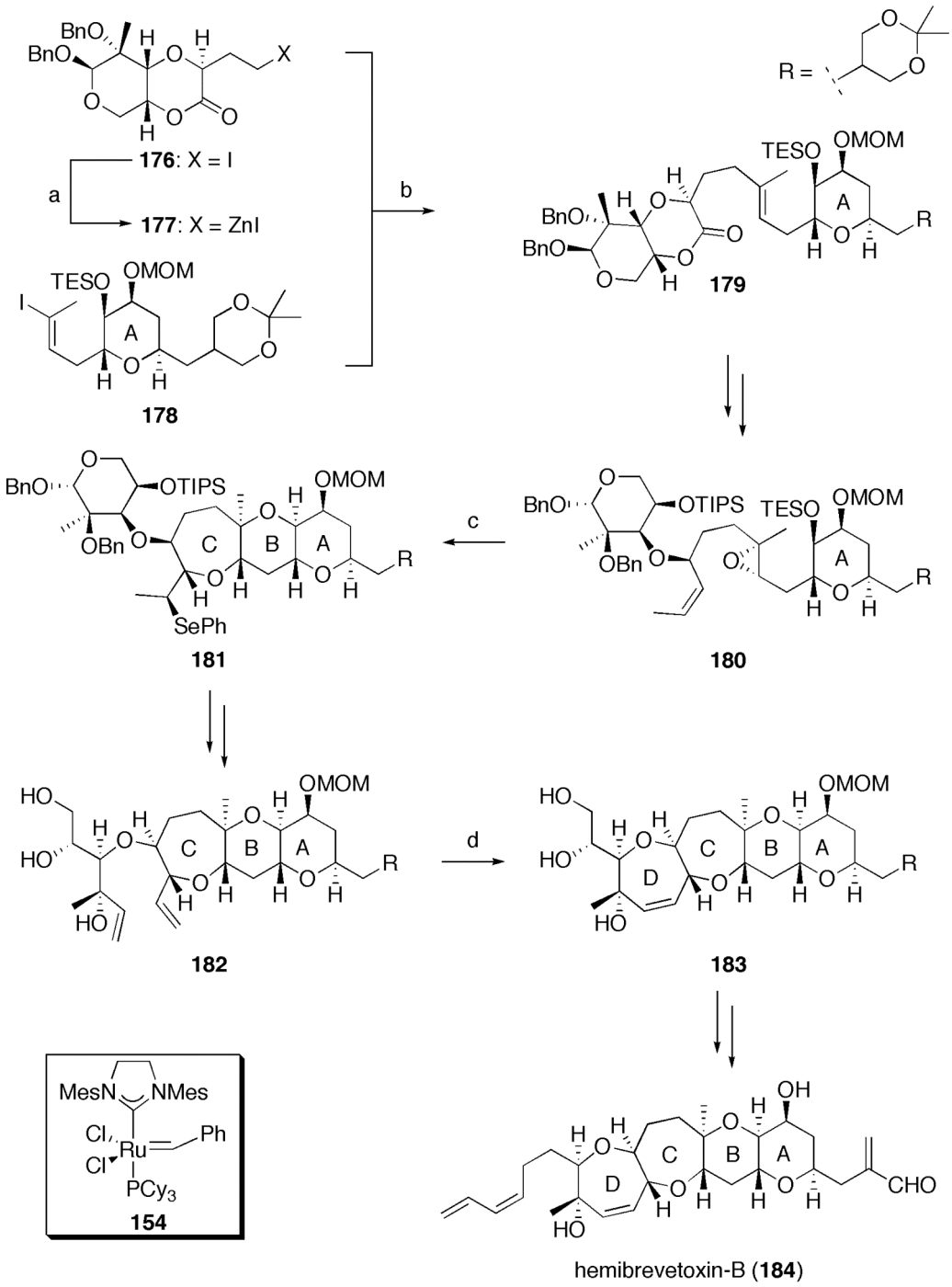
Entry		Yield
1	**171**, R = *t*-BuO	30%, **172**, R = *t*-BuO
2	**171**, R = Me_2N	35%, **172**, R = Me_2N
3	**174**, R = *t*-BuO	20%, **175**
4	**174**, R = Me_2N	25%, **175**

Scheme 25: *Conditions*: (a) $BF_3{\cdot}OEt_2$, CH_2Cl_2, –40 °C; (b) $BF_3{\cdot}OEt_2$, CH_2Cl_2, –40 °C; Ac_2O, pyridine, rt; (c) TBAF, THF, rt; Ac_2O, pyridine, rt, 75%.

In 2003, Holton and coworkers successfully combined the biomimetic approach with a convergent strategy in their total synthesis of hemibrevetoxin-B (**184**).[88] The Pd(0)-catalysed reaction of organozinc iodide **177** with vinyl iodide **178** produce the lactone **179**. Further elaboration led to the epoxide **180**, which

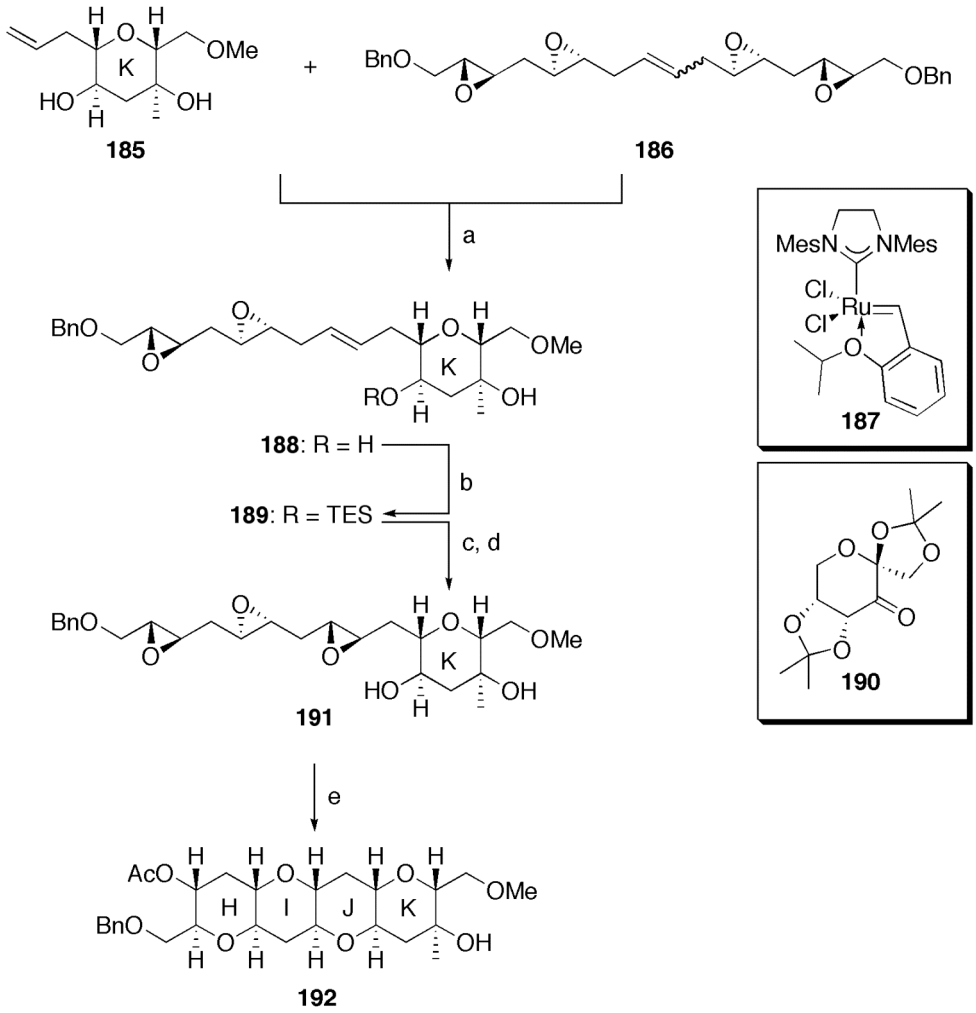
[87] Valentine, J. C.; Mc Donald, F. E.; Neiwert, W. A.; Hardcastle, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 4586.
[88] Zakarian, A.; Batch, A; Holton, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 7822.

upon treatment with *N*-(phenylseleno)phthalimide underwent smooth cyclisation to afford **181** as a single diastereoisomer. Oxidation-elimination of the selenide followed by benzyl ether removal and Peterson elimination gave the diene **182** in high yield. The key RCM reaction and further functional group transformations completed the synthesis of **184** (Scheme 26).



Scheme 26: *Conditions*: (a) Zn, THF, rt; (b) Pd(dppf)Cl_2, THF, rt, 76% (2 steps); (c) *N*-(phenylseleno)phthalimide, HFIP, 0 °C, 83%; (d) catalyst **154** (10 mol%), C_6H_6, 80 °C, 85%.

The convergent assembly of the H-K fragment of Gymnocin A, reported in 2009 by Jamison's laboratory, is another example of a biomimetic synthesis.[89] The functionalised template **185** and epoxide-bearing fragment **186** were coupled by CM reaction using the Hoveyda-Grubbs second-generation catalyst **187**. The separation of the *E* and *Z* isomers and resubjection of the undesired *Z* olefin to the metathesis reaction allowed the moderate *E*/*Z* selectivity (2.6:1 *E*/*Z*) to be circumvented. The mono-protection of diol **188** was followed by epoxidation of alkene **189** in the presence of the Shi catalyst **190**. Subsequent cleavage of the TES ether afforded the polyepoxide **191**. Finally, a water-promoted cascade reaction of **191** folllowed by acetylation afforded the target fragment **192** in 35% overall yield. This corresponds to approximately 70% yield per newly formed ring (Scheme 27).



Scheme 27: *Conditions*: (a) catalyst **187** (15 mol%), CH_2Cl_2, 40 °C, 74%; (b) TESCl, imidazole, DMF, rt, 82%; (c) catalyst **190**, oxone, Bu_4NHSO_4, K_2CO_3, DMM/CH_3CN (2:1), rt, 82%; (d) TBAF, THF, rt, 77%; (e) H_2O, 80 °C, then Ac_2O, Et_3N, 35%.

[89] Van Dyke, A. R.; Jamison, T. F. *Angew. Chem. Int. Ed.* **2009**, *48*, 4430.

3.10 Conclusion

Most of the work directed towards the synthesis of *trans*-fused polycyclic ethers has been concentrated in the last ten years. The synthetic methodologies developed so far have proved to be applicable to complex polycyclic natural products and will further the understanding of their detailed biological mechanisms of action. However, the synthesis of such molecules has not yet become a routine and new preparative methods, to obtain natural products and their analogues, are required. The existing total syntheses typically required more than a hundred steps in total. In addition, the yields and stereoselectivities of these various ring-forming reactions depend on the local structure of the molecules. The development of more practical, concise and general synthetic routes remains a key challenge for the future.

4 Olefin metathesis

4.1 Introduction

Derived from the Greek words *meta* (change) and *thesis* (position), metathesis is the reorganisation of the carbon atoms of two carbon-carbon double bonds, generating two new ones. It can involve unique skeletal rearrangements and allow access to one of the most useful functional groups in organic synthesis (Figure 8).

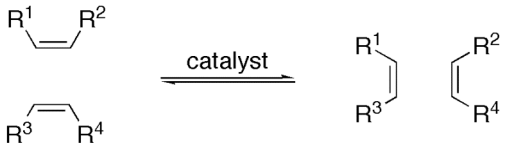


Figure 8: The principle of olefin metathesis.

The importance of olefin metathesis over the last twenty years was recognised in 2005 when Chauvin, Grubbs and Schrock were awarded the Nobel Prize for the development of metathesis reactions.[90] However, the history of alkene metathesis began nearly sixty years ago with the observations of the

[90] "The Nobel Prize in Chemistry 2005." Nobelprizing.org, 19 May 2011, Copyright © The Nobel Foundation. http://nobleprize.org/chemistry/laureates/2005/press.html

polymerisation of ethylene made by Karl Ziegler.[91] At that time, the strongly Lewis-acidic and alkylating character of the catalysts restricted the scope of olefin metathesis reactions to the production of unfunctionalised polymers. The discovery, in the early 1980's, that metal alkylidene complexes could promote olefin metathesis was the first step toward the development of this reaction in organic synthesis. Coupled with the understanding of the mechanism, the development of reasonably stable and functional group tolerant catalysts, or catalyst precursors, led to a dramatic expansion of interest in the application of metathesis reaction during the 1990's.[92]

Olefin metathesis can be extended to different π-systems and has a variety of applications including ring-opening metathesis polymerisation (ROMP), ring-closing metathesis (RCM), acyclic diene metathesis (ADMET), cross-metathesis (CM), ring-closing enyne metathesis (RCEYM) and ring-closing alkyne metathesis (RCAM) (Figure 9).

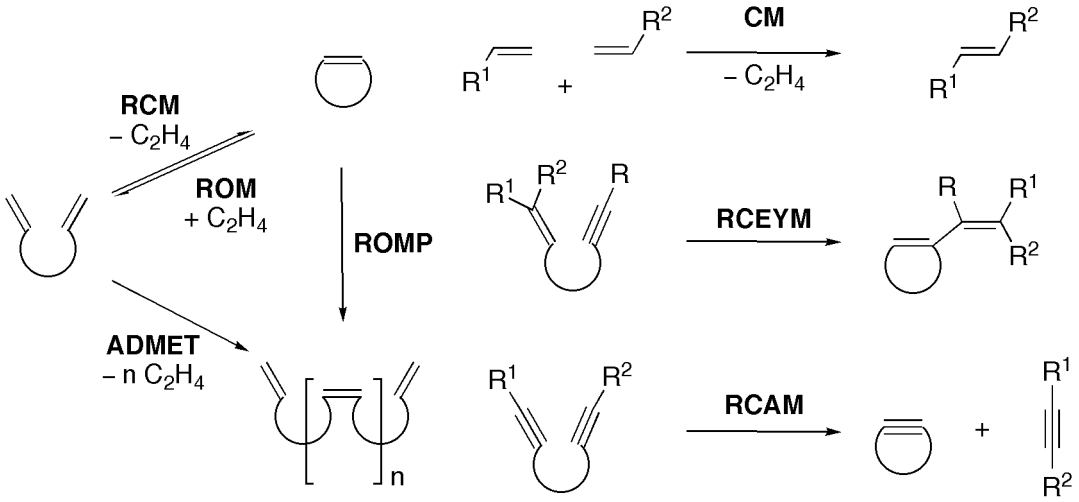


Figure 9: Important types of metathesis reactions.

4.2 Mechanism

Several mechanisms were proposed during the early period of olefin metathesis explorations. Calderon's initially proposed mechanism was that of a

[91] Fink, G.; Mülhaupt, R.; Brintzinger, H. H. *Ziegler Catalysts* **1995**; Eds. Springer: Berlin.
[92] (*a*) Fürstner, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3012; (*b*) Calderon, N. *Acc. Chem. Res*. **1972**, *5*, 127; (*c*) Calderon, N.; Ofstead, E. A.; Ward, J. P.; Judy, W. A.; Scott, K. W.; *J. Am. Chem. Soc.* **1968**, *90*, 4133; (*d*) Calderon, N.; Chen, H. Y.; Scott, K. W. *Tetrahedron Lett.* **1967**, *8, 3327*.

pair-wise exchange of alkylidenes through a "quasi-cyclobutane" mechanism. In this mechanism two olefins coordinated to the metal and exchanged alkylidene groups through a symmetrical intermediate (Figure 10).[93] With a few assumptions, this mechanism could account for most of the fundamental metathesis transformations.

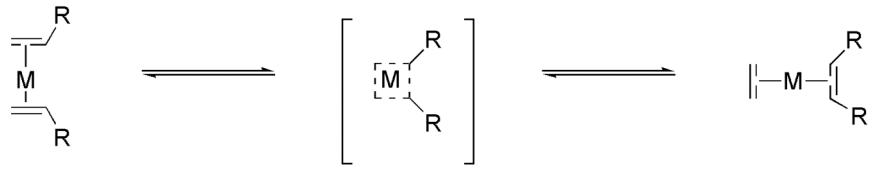


Figure 10: Calderon's mechanism.

A later mechanism proposed by Chauvin was found to be the most consistent with the experimental evidence, and remains the generally accepted mechanism.[94] It consists in a sequence of formal [2+2] cycloadditions/cycloreversions involving alkenes, metal carbenes and a metallocyclobutane intermediate (Figure 11). The first step in the catalytic cycle is a [2+2] cycloaddition reaction between olefin **B** and the transition metal carbene **A** to give metallocyclobutane **C**. The latter collapses to liberate ethene **D** and a new metal carbene **E**, which carries the alkylidene fragment R^1. Similarly, **E** reacts with another alkene **F** to form metallocyclobutane **G**. Further [2+2] cycloreversion liberates the new alkene **H**; the catalyst is reformed and can re-enter the cycle.

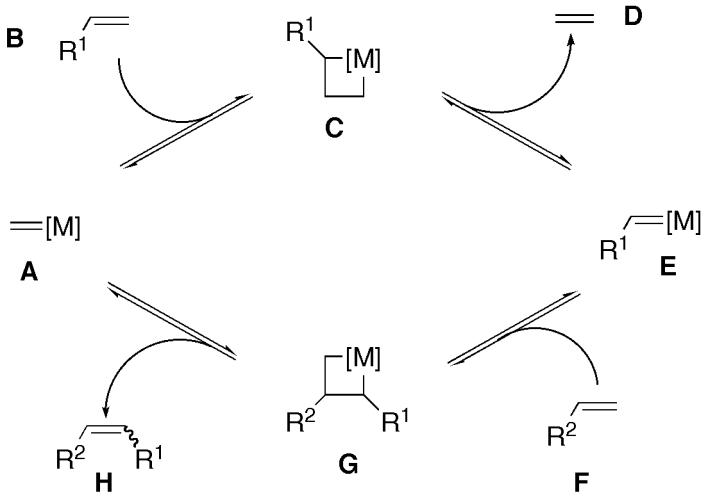


Figure 11: Catalytic cycle of RCM.

[93] Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270.
[94] Hérisson, J.-L.; Chauvin, Y. *Makromol. Chem.* **1971**, *141*, 161.

The individual steps of the catalytic cycle are reversible and therefore it is necessary to shift the equilibrium in favour of the desired product **H**. In the particular case of RCM, the reaction is entropically driven because the reaction divides one substrate molecule into two products.[90a] Moreover, if one of the two products is volatile, the cycloreversion step becomes irreversible. The substitution pattern of the alkene is also an important factor since it determines the kinetics of the reaction. In general, the higher the degree of substitution the less reactive it becomes. In the intermolecular case, the reaction control depends on the substrate design and the reaction conditions.

4.3 Catalysts

Metathesis catalysts developed in the mid 1950's, also called "black box" catalysts, were poorly defined multicomponent homogeneous and heterogeneous catalyst systems.[95] These systems were based upon elements from the early transition metal series, either grafted onto silica or combined with a main group Lewis acid. Classic combinations included WCl_6/Bu_4Sn, $WOCl_4/EtAlCl_2$, MoO_3/SiO_2 and ReO_7/Al_2O_3 amongst many others. Although used in many commercial processes, they were limited in their usage due to their Lewis acidic nature that gives them a low tolerance of many functional groups in organic synthesis. Elucidation of the mechanism of olefin metathesis provided both a rational design and a way to begin to understand catalyst activity. Subsequent efforts to synthesise alkylidene and metallacylobutane complexes led to the discovery of the first single component homogenous catalyst for olefin metathesis during the late 1970's and early 1980's.

4.3.1 Titanocene-Based Catalysts

Tebbe demonstrated that a titanium methylene complex would catalyse the non-productive metathesis exchange of the methylenes between two terminal olefins.[96] The reaction of two equivalents of $AlMe_3$ with Cp_2TiCl_2 produces the complex $Cp_2Ti(\mu\text{-}Cl)(\mu\text{-}CH_2)AlMe_2$, commonly known as Tebbe's

[95] Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.
[96] Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611.

reagent (**66**) (Figure 12). In the presence of a Lewis base, such as pyridine, the reagent is functionally equivalent to "$Cp_2Ti{=}CH_2$" (**193**).[97]

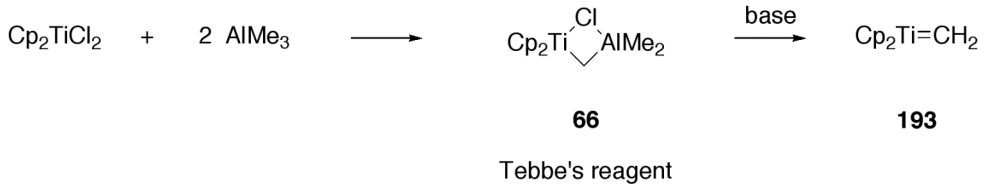
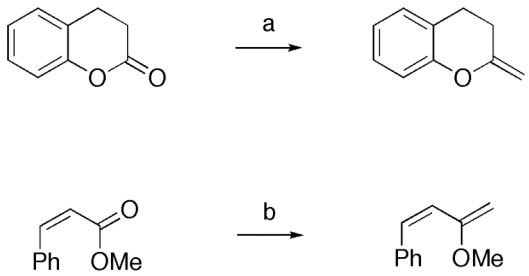


Figure 12: Formation of the Tebbe's catalyst.

Tebbe's reagent did not prove to be a particularly active metathesis reagent but its use highlighted the important link between metathesis and carbonyl olefination. Evans, Grubbs and co-workers demonstrated that these complexes undergo Wittig-like reactions with ketone and aldehydes. In addition, esters can be converted into vinyl ethers, a reaction for which conventional Wittig reagents are not suitable (Scheme 28).[91]



Scheme 28: *Conditions*: (a) Tebbe's reagent, pyridine, toluene/THF (3:1), –40 °C, 85%; (b) Tebbe's reagent, pyridine, toluene/THF (3:1), –40 °C, 79%.

The titanium-based RCM reaction has seen a "renaissance" in recent years and interestingly, a second titanium-based procedure for metathesis has been disclosed. The second generation procedure relies on metal carbene intermediates generated from dithioacetals and low-valent titanium reagents, formed *in situ* from Cp_2TiCl_2, $P(OEt)_3$ and Mg.[98]

[97] Howard, T. R.; Lee, J. B.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 6876.
[98] (*a*) Horikawa, Y.; Wantabe, M.; Fujiwara, T.; Takeda, T. *J. Am. Chem. Soc.* **1997**, *119*, 1127. (*b*) Fujiwara, T.; Takeda, T. *Synlett* **1999**, 354.

4.3.2 Tantalum, Tungsten and Molibdenum-Based Catalysts

The syntheses of tantalum- and tungsten-based metathesis catalysts were the first to be explored.[99] Studies revealed (*i*) high oxidation state alkylidene complexes can be stabilised and isolated and (*ii*) these species can serve in complexes for productive metathesis reactions when substituted with alkoxide ligands, such as complexes **194**, **195** and **196** (Figure 13).

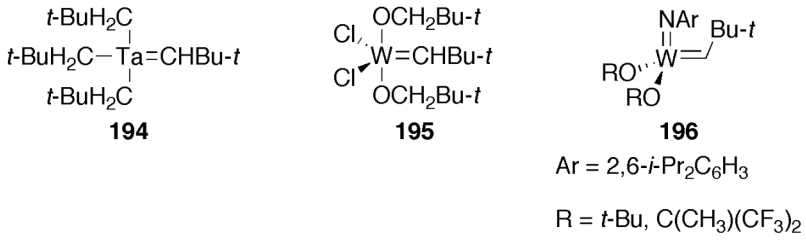


Figure 13: Tantalum and tungsten complexes.

Attention was later focused on molybdenum as the central metal, with the goal of synthesising more functional group-tolerant catalysts. Schrock's molybdenum alkylidenes were the first of the new single-component homogeneous catalysts to become widely used. The best approach to the synthesis of these complexes involves treatment of the bis imido compound **197** with triflic acid in the presence of DME, giving the stable 18-electron imido alkylidene **198**. Subsequent treatment with various lithium alkoxides afforded compounds **199** which are analogous in structure to **196** (Figure 14).

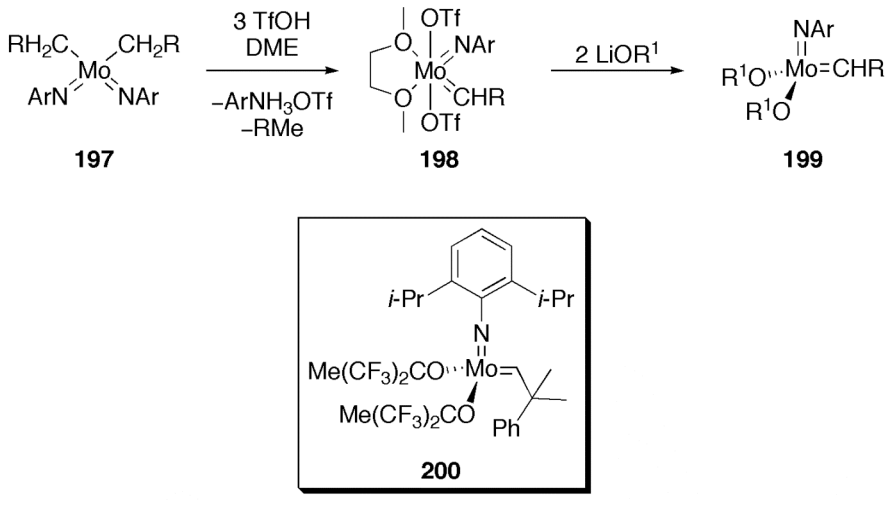


Figure 14: Synthesis of molybdenum-based catalysts.

[99] Deshmukh, P. H.; Blechert, S. *Dalton Trans.* **2007**, 2479.

The molybdenum catalyst **200** allowed metathesis reactions to be performed on substrates bearing functional groups such as phosphines and sulfides for the first time. [100] Moreover, **200** has been shown to react with either electron-poor or electron-rich olefins. Unfortunately, **200** and related catalysts are very sensitive toward oxygen and moisture and must be handled under an inert atomosphere using Schlenk techniques. Aside from these inconveniences, complex **200** is also incompatible with aldehydes and alcohols.[101]

4.3.2 Ruthenium Alkylidene Complexes

The disclosure by Grubbs that ruthenium carbene complexes of the general type **201** are highly active single-component (pre)catalysts, for all types of alkene metathesis reactions, constituted a real breakthrough and has triggered a lot of interest in this transformation (Figure 15).[102] Grubbs and Fu demonstrated that ruthenium-based system **205** promotes many of the same reactions as the Schrock molybdenum-based alkylidene complexes. The ruthenium-based catalysts showed a greater functional group tolerance and could be handled using standard synthetic techniques. As illustrated in Figure 15, the complex **205** can be obtained by phosphine ligand exchange from **204**.[103] The catalytic activity of these complexes increases with the basicity of the phosphines in the order $PPh_3 << P(i\text{-}Pr)_3 < PCy_3$. [104]

[100] (*a*) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875. (*b*) For a review, see: Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4592.
[101] Armstrong, S. K. *J. Chem. Soc. Perkin Trans 1.* **1998**, 371.
[102] Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856.
[103] Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114,* 3974.
[104] Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887.

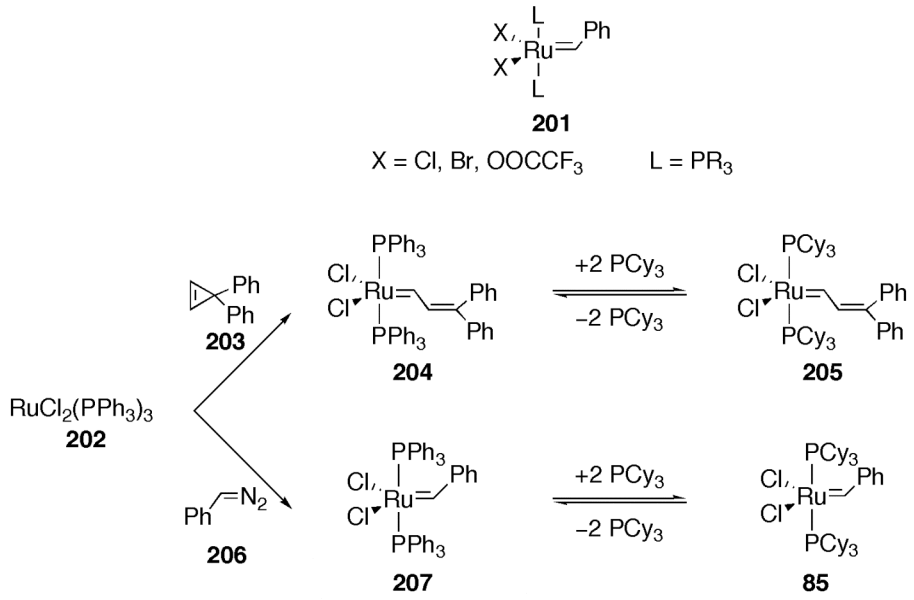


Figure 15: The First stable and active Ruthenium carbene metathesis catalysts.

The rather troublesome preparation of the diphenylvinyl carbene complex **205** has been a drawback to its application in synthesis. This catalyst is prepared by a Ru^{II}-induced rearrangement of diphenylcyclopropene. An alternative preparation involved the reaction of $RuCl_2(PPh_3)_3$ with alkyl and aryl diazo compounds and resulted in good yields of substituted alkylidenes such as **85** also known as the Grubbs first generation catalyst (Figure 15).[105] It has been shown that the dominant pathway for productive metathesis, which accounts for approximately 95% of the catalyst turnover in a typical RCM reaction, involves the dissociation of one of the two PCy_3 ligands from complex **208**. However, it is not clear whether this dissociation occurs before or after the coordination of the alkene substrate (Figure 16).[102]

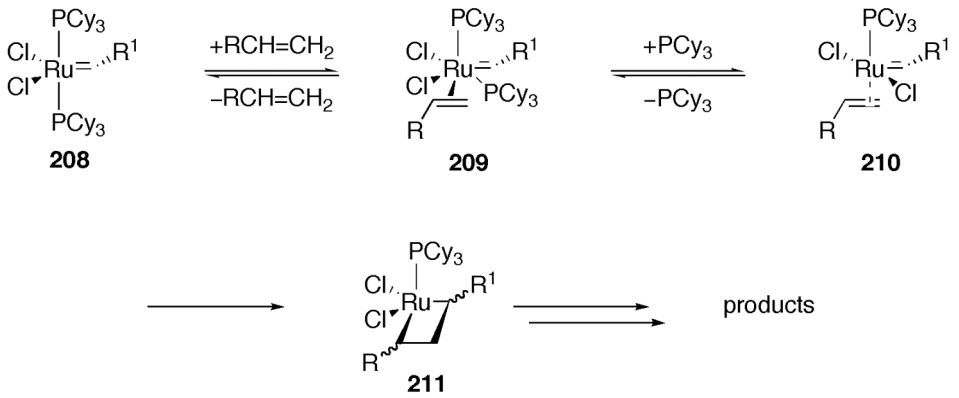


Figure 16: Proposed dissociative mechanism for Grubbs type catalysts.

[105] Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2039.

The steric demand and electron-donating character of the residual phosphine ligand is decisive to stabilise the reactive intermediates formed during this dissociative step. The alternative reaction pathway, in which both phosphines remain attached to the Ru centre is much less efficient. The olefin binding site is presumably *cis* to the carbene and *trans* to one of the chlorines. Subsequent formation of the metallacycle is believed to be the rate determining step in the sequence.[106] Herrmann and co-workers tested ligands that were even more basic and sterically demanding than PCy_3.[107] Complex **213**, in which both PCy_3 units of **85** have been replaced by *N,N'*-disubstituted 2,3-dihydro-1*H*-imidazol-2-ylidene units is more stable than **85**, but does not show an improved reactivity profile (Figure 17).

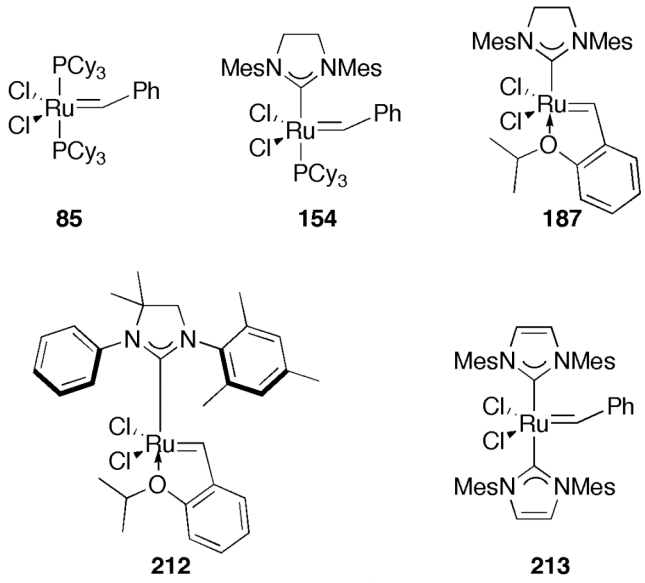


Figure 17: Selected ruthenium catalysts.

The use of a kinetically inert, electron-donating NCH ligand in combination with a coordinatively labile ligand proved to be very effective. Complexes such as the Grubbs second-generation catalyst **154**[108] and the Hoveyda ruthenium catalyst **187**[109] show excellent thermal stability and resistance toward oxygen and moisture and are compatible with most functional groups. The results of solution calorimetry indicate that the NCH ligand has a significantly stronger bonding to ruthenium than PCy_3.[110] Furthermore, X-ray

[106] Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317.
[107] Weskamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A. *Angew. Chem. Int. Ed.* **1998**, *37*, 2490.
[108] Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
[109] Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.
[110] Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674.

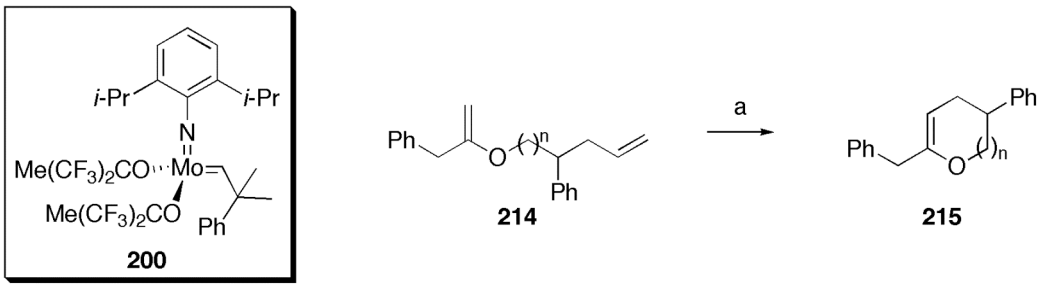
analysis showed that by virtue of the short metal-NCH bond length, the bulky ligand is brought close to the metal centre which is, therefore, effectively shielded against bimolecular decomposition.

4.4 Polyether Synthesis and RCM

The reticence of synthetic chemists to engage in the construction of polycyclic ethers was attributable to their structural complexity and to the scarcity of methods available to stereoselectively synthesise medium-sized cyclic ethers. In thirty years, both RCM and the synthesis of laddered polycyclic ether have attracted the attention of the chemical synthesis community. Nowadays, reports show how vital RCM has been for many successful total syntheses.[48c] The following section details advances in the construction of medium-sized cyclic ethers in recent times, with particular attention given to our group's contribution to this area.

4.4.1 Pioneer Utilisations of RCM

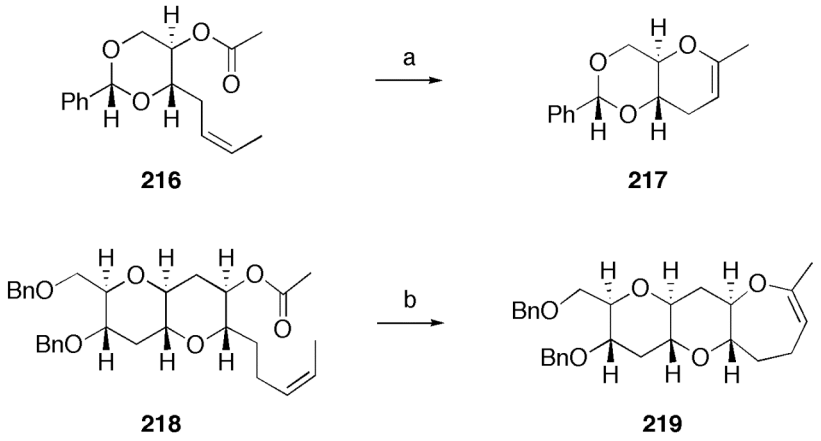
In early work, Grubbs and co-workers demonstrated that it was possible to prepare simple dihydrofurans and dihydropyrans in good yield by RCM of simple acyclic enol ethers (Scheme 29).[111] Although these results were important, relatively simple substrates were used and kinetically favourable rings were synthesised. Further research was necessary to determine whether RCM reactions of enol ethers could be used to prepare the more challenging seven- to nine-membered rings present in polyether natural products.



Scheme 29: *Conditions:* (a) catalyst **200** (5-12 mol%), C_5H_{12}, rt, (n = 0, 81%; n = 1, 84%).

[111] Fujimura, O.; Fu, G. C.; Grubbs, R. H. *J. Org. Chem.* **1994**, *59*, 4029.

In 1996 Nicolaou reported that olefinic esters could be converted directly into six- and seven-membered enol ethers by tandem methylenation and metathesis using an excess of Tebbe's reagent (Scheme 30).[112] Although the yields were modest in nearly all cases and sterically unencumbered acetates were used as cyclisation precursors, this work demonstrated the potential of RCM for the construction of fused polycyclic arrays.



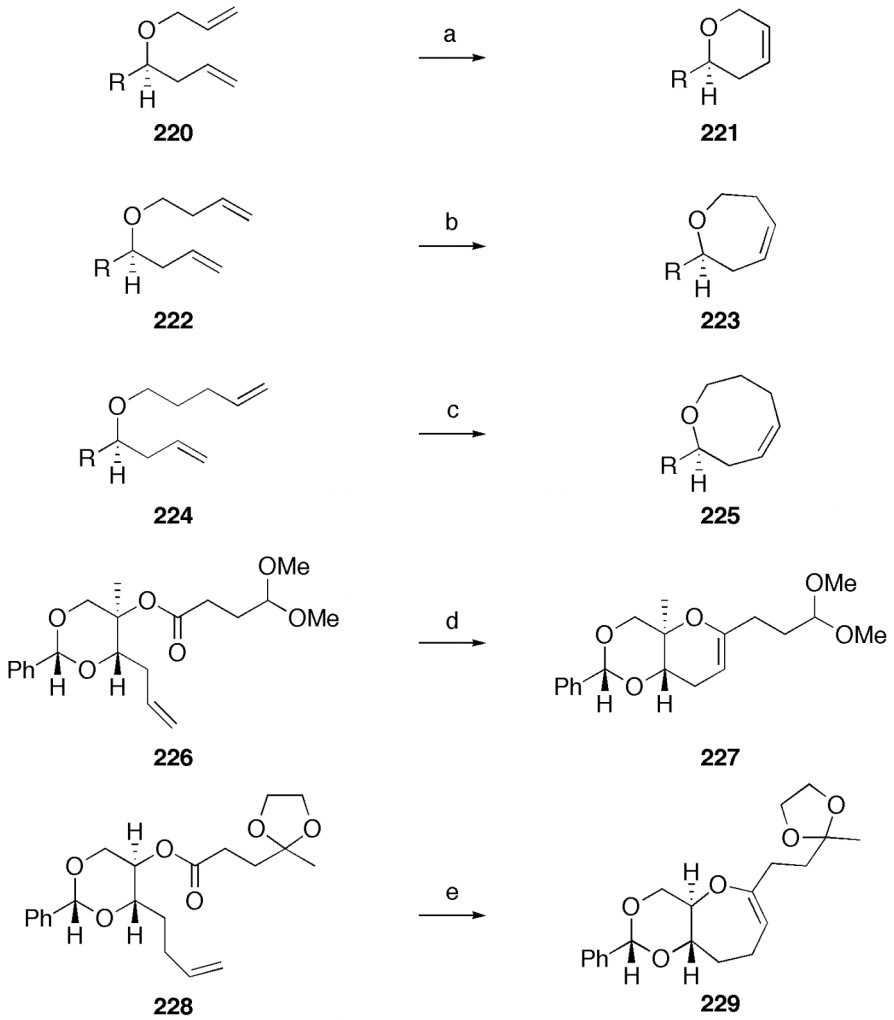
216 **217** **218** **219**

Scheme 30: *Conditions*: (a) Tebbe's reagent (3-6 eq.), THF, rt, 30%; (b) Tebbe's reagent (3-6 eq.), THF, rt, 45%.

4.4.2 Rainier's Contributions

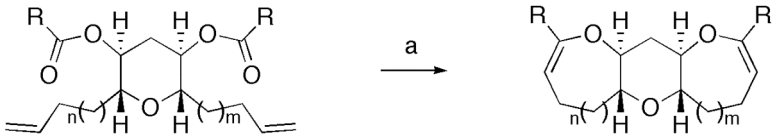
Rainier and co-workers reported the further development of RCM as an approach to the synthesis of polycylic ethers. They demonstrated that titanium ethylidene reagents were capable of inducing olefinic-ester cyclisation and diene RCM reactions. Using the Takai-Utimoto reduced titanium reagent they have shown that the success of the reaction depends upon the nature of the alkylidene reagent used.[66] They also reported the synthesis of dihydropyran **221**, oxepene **223** and oxocene **225** from the reaction of titanium ethylidene reagent with the acyclic allyl ethers **220**, **222** and **224**, respectively (Scheme 31). Furthermore, their methodology was applied successfully to more complex system such as **226** and **228**.[113]

[112] Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565.
[113] Osei Akoto, C.; Rainier, J. D. *Angew. Chem. Int. Ed.* **2008**, *47*, 8055.



Scheme 31: Conditions: (a) $TiCl_4$, Zn, $PbCl_2$, CH_3CHBr_2, TMEDA, THF, rt, 81%; (b) $TiCl_4$, Zn, $PbCl_2$, CH_3CHBr_2, TMEDA, THF, 65 °C, 72%; (c) $TiCl_4$, Zn, $PbCl_2$, CH_3CHBr_2, TMEDA, THF, 65 °C, 60%; (d) $TiCl_4$, Zn, $PbCl_2$, CH_3CHBr_2, TMEDA, THF, CH_2Cl_2, rt, 70%; (e) $TiCl_4$, Zn, $PbCl_2$, CH_3CHBr_2, TMEDA, THF, CH_2Cl_2, 60 °C, 65%.

Finally, the recent application of their strategy to the two-directional olefinic-ester RCM resulted in the construction of various tricyclic skeletons in good yield (Scheme 32).[78] Compared to reagents that carry out related transformations, the titanium reagent is relatively inexpensive. It is generated in situ, avoiding problems linked to air/moisture sensitivity, and is also tolerant of a wide variety of functional groups.



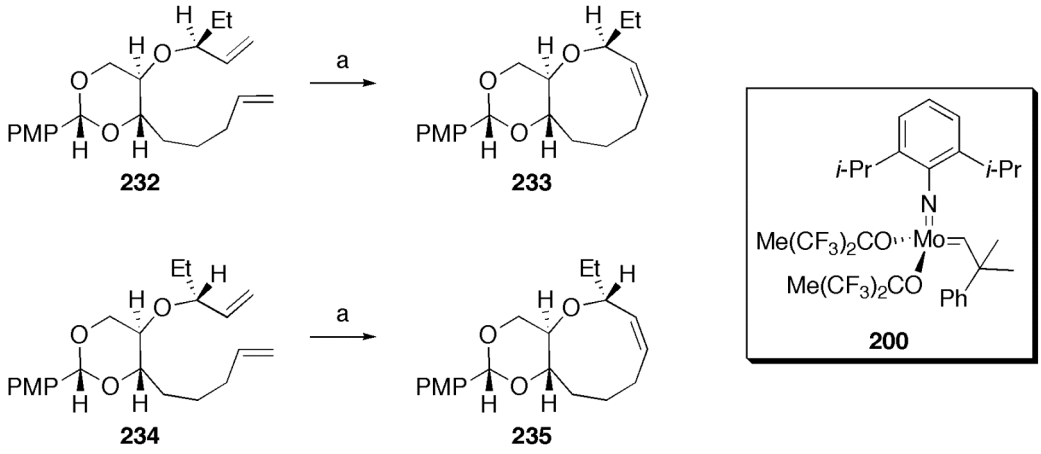
230 **231**

Entry		Yield
1	R = CH_3, m = 1, n = 0	64%
2	R = CH_3, m = 0, n = 0	65%
3	R = CH_3, m = 1, n = 1	65%
4	R = $(CH_3O)_2CHCH_2CH_2$, m = 0, n = 0	64%

Scheme 32: *Conditions*: (a) $TiCl_4$, Zn, $PbCl_2$, $RCHBr_2$, TMEDA, THF, CH_2Cl_2, 65 °C.

4.4.3 Clark's Contributions

The Clark group have also studied enol ether RCM and demonstrated that allyl ethers with pendant olefins undergo RCM to give oxocines and oxonenes.[114] Interestingly, in the formation of oxonenes, the stereochemistry of the ether dictated the efficiency of the reactions. As shown in Scheme 33, diastereoisomers **232** and **234** gave dramatically differents yields of the cyclic ethers **233** and **235**, respectively (Scheme 33). This was one of the first examples that demonstrated the significant influence that substituents and conformational issues have on RCM cyclisations to form medium rings.



232 **233**

234 **235**

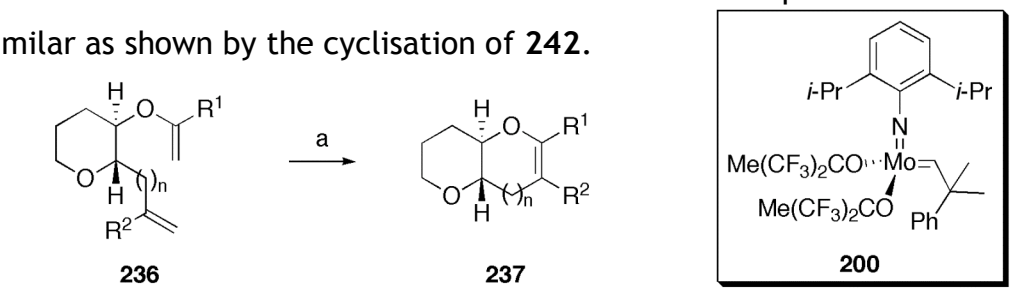
200

Entry	Yield
1	**233**, 86%
2	**235**, 14%

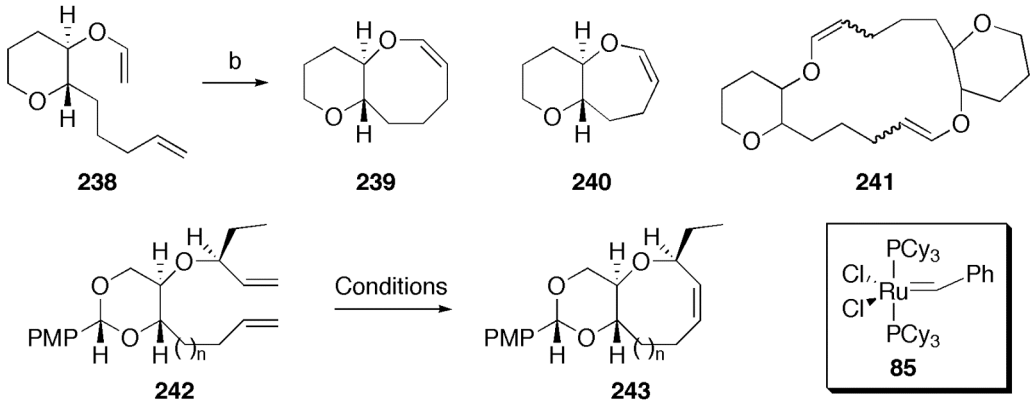
Scheme 33: *Conditions*: (a) catalyst **200** (25 mol%), C_6H_6, 60°C.

[114] Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 127.

The Clark group also proved that Mo(I)-catalyst **200** can be used to synthesise dihydropyrans and oxepines from enol ethers.[115] Cyclisation reactions to form the corresponding oxocines were complicated by competing isomerisation and/or dimerisation reactions as illustrated by the RCM reaction of substrate **238**. In this case, an inseparable mixture of the required cyclic ether **239** and the seven-membered bicyclic enol ether **240** was isolated as well as a significant amount of the cyclo-dimer **241** (Scheme 34). Electron-rich olefins, such as those studied within the Clark's laboratory, continue to be problematic in RCM reactions due to their slow rate of cyclisation, which allows competing reactions to take place. An advantage of these reactions is that they are generally irreversible.[116] The ability of catalysts **85** and **200** to generate oxepines and oxecines from diene RCM reactions was compared and revealed to be similar as shown by the cyclisation of **242**.



Entry		Yield of 237
1	n = 1, R^1 = Et, R^2 = H	72%
2	n = 1, R^1 = H, R^2 = Me	93%
3	n = 2, R^1 = Et, R^2 = H	42%
4	n = 3, R^1 = H, R^2 = Me	94%

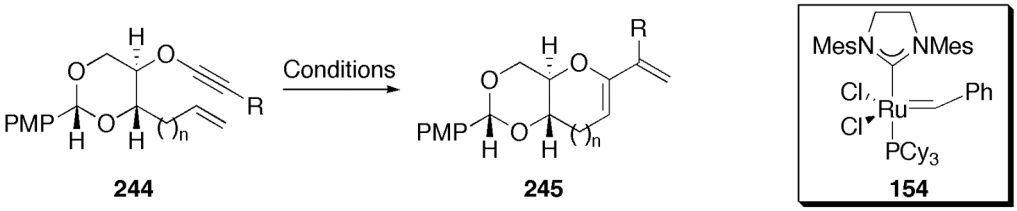


Entry		Conditions	Yield of 243
1	n = 0	c	86%
2	n = 0	d	94%
3	n = 1	b	97%
4	n = 1	d	86%

Scheme 34: *Conditions*: (a) catalyst **200** (9-14 mol%), C_5H_{12}, rt; (b) catalyst **200** (33 mol%), C_6H_6, 60 °C, 40% (**239:240**, 2:1); (c) catalyst **200** (25-30 mol%), C_6H_6, rt; (d) catalyst **85** (10-20 mol%), CH_2Cl_2, rt.

[115] (*a*) Clark, J. S.; Kettle, J. G. *Tetrahedron* **1999**, 55, 8231; (*b*) Clark, J. S.; Hamelin, O.; Hufton, R. *Tetrahedron Lett.* **1998**, *39*, 8321; (*c*) Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 123.
[116] Rainier, J. D. *Metathesis in Natural Product Synthesis*; Wiley-VCH: Weinheim, Germany, **2010**, 89.

Complementary to cyclic enol and cyclic allyl ether formation is the synthesis of cyclic ethers by the RCM of alkynyl ethers. Clark and co-workers explored the RCM reactions of the alkynyl ethers **244** by the catalysts **85** and **154** (Scheme 35).[117] In all but one case, the highest yields were obtained when the more reactive complex **154** was employed. They have demonstrated that alkynyl ethers can be used for ruthenium-catalysed enyne RCM reaction. These studies also highlighted that the formation of seven-membered cyclic ethers is significantly more difficult to achieve than the construction of six-membered cyclic ethers.



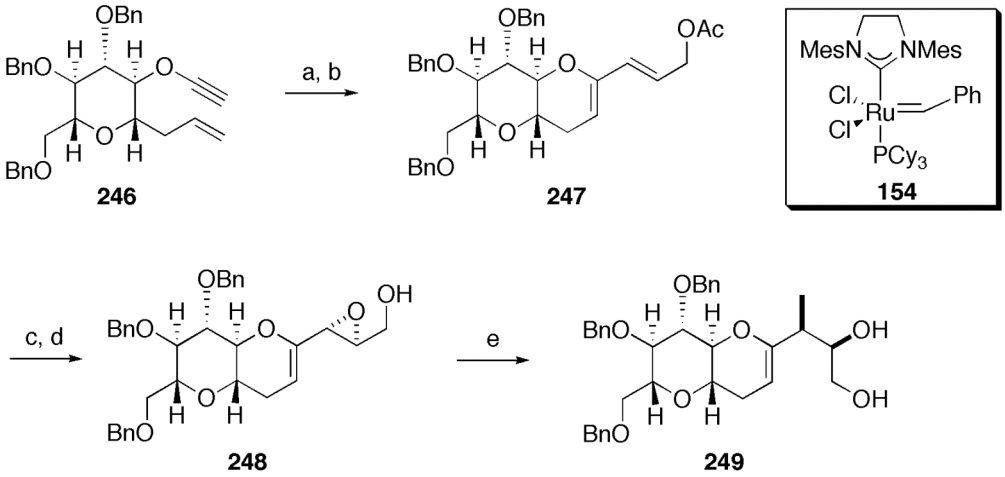
244 **245** **154**

Entry	R	Yield [(a)]	Yield [(b)]
1	H	n = 1, 65%; n = 2, 33%	n = 1, 90%; n = 2, 70%
2	CH_3	n = 1, 77%; n = 2, 27%	n = 1, 98%; n = 2, 72%
3	TMS	n = 1, 20%	n = 1, 88%; n = 2, 0%
4	CH_2OH	n = 1, 84%	n = 1, 8%
5	CH_2OAc	n = 1, 54%	n = 1, 72%
6	$CH_2OTBDPS$	n = 1, 61%	n = 1, 91%

Scheme 35: *Conditions*: (a) catalyst **85** (10 mol%), CH_2Cl_2, reflux; (b) catalyst **154** (10 mol%), CH_2Cl_2, toluene, 80 °C.

Taking into account that RCM is usually carried out under an atmosphere of ethene using moderate dilution and CM is undertaken at higher concentrations with evaporation of volatile ethene, the group developed a set of conditions that allows to perform RCEYM and diene CM in one pot. RCEYM of the alkynyl ether **246** followed by CM of the resulting diene afforded the bicyclic ether **247** in 62% overall yield (Scheme 36).

[117] (*a*) Clark, J. S.; Elustondo, F.; Trevitt, G. P.; Boyall, D.; Robertson, J.; Blake, A. J.; Wilson, C.; Stammen, B. *Tetrahedron* **2002**, *58*, 1973; (*b*) Clark, J. S.; Trevitt, G. P.; Boyall, B.; Stammen, B. *Chem. Commun.* **1998**, 2629.



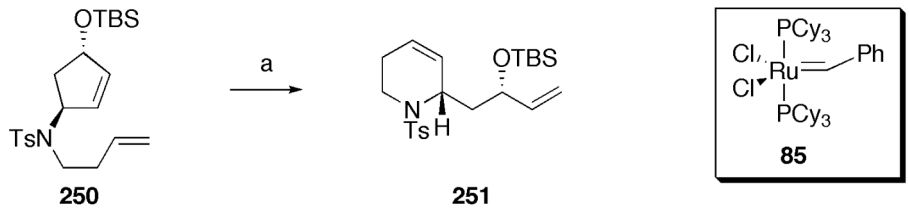
Scheme 36: *Conditions*: (a) catalyst **154** (5 mol%), CH_2CH_2, toluene, 80 °C, 82%; (b) catalyst **154** (5 mol%), (*E*)-2-butene-1,4-diol diacetate, toluene, 80 °C, 75%; (c) K_2CO_3, MeOH, rt, 91%; (d) Ti(*i*-PrO)$_4$, (+)-DET, TBHP, CH_2Cl_2, –20 °C; (e) CH_3Li, CuCN, diethyl ether, –60 to 0 °C, 55% (2 steps).

In addition to allowing rapid chain extension, CM allows selective functionalisation of the side-chain to be performed without affecting the enol ether. Acetate cleavage and Sharpless asymmetric epoxidation of the resulting allylic alcohol led to stereoselective and regioselective side-chain oxidation to deliver the epoxide **248**. A branching methyl substituent was then introduced by regioselective epoxide opening. The resulting diol **249** possessed a variety of functionalities that could be elaborated independently.

4.5 Ring Rearrangement Metathesis

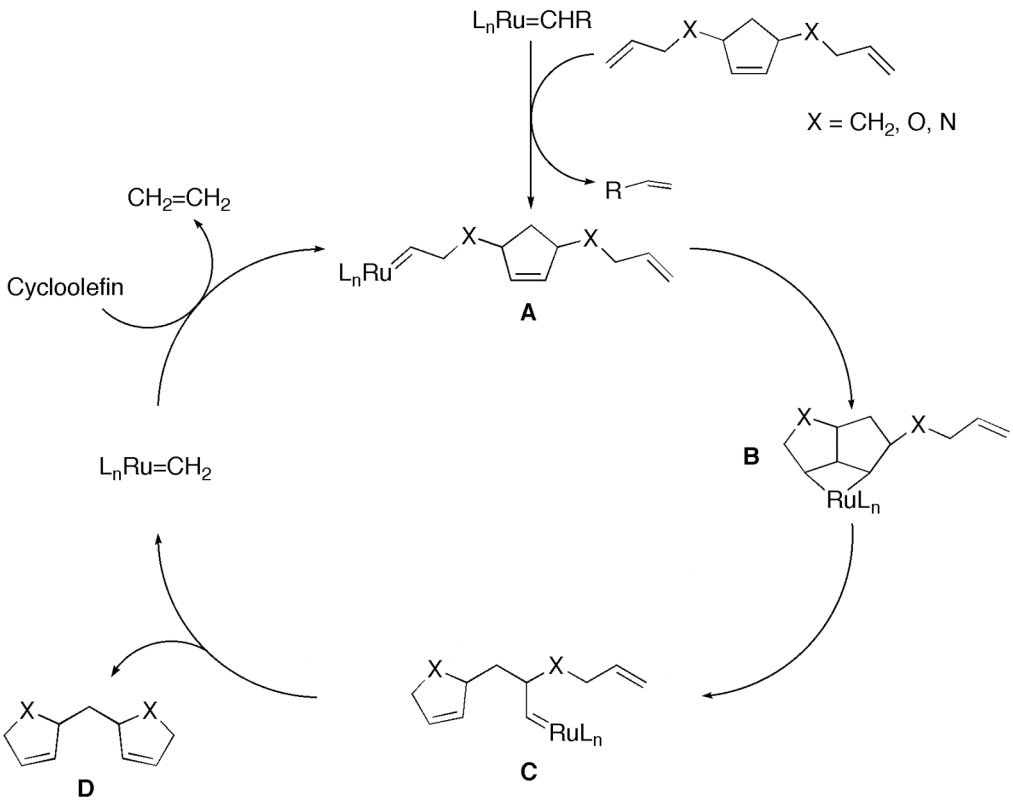
The sequential combination of RCM and ROM is classified as ring-rearrangement metathesis (RRM). Among all the combinations of metathesis reactions, RRM is an extremely powerful tool for the construction of carbocycles and heterocycles. The total synthesis of (–)-halosaline, reported by Blechert and co-workers in 1999, is the first example of the utilisation of the RRM reaction as a key step in total synthesis (Scheme 37).[118] Since then, the RRM reaction has attracted significant interest.[119,120]

[118] Sragies, R.; Blechert, S. *Tetrahedron* **1999**, *55*, 8179.
[119] Porta, M.; Blechert, S. *Metathesis in Natural Product Synthesis*; Wiley-VCH: Weinheim, Germany, **2010**, 325.
[120] (*a*) Donnard, M.; Tshamber, T.; Le Nouën, D.; Desrat, S.; Hinsinger, K.; Eustache, J. *Tetrahedron* **2011**, *67*, 339; (*b*) Clavier, H.; Nolan, S. P. *Chem. Soc. Rev.* **2010**, *39*, 3305; (*c*) Holub, N.; Blechert, S. *Chem.-Asian J.* **2007**, *2*, 1064.



Scheme 37: *Conditions*: (a) catalyst **85** (5 mol%), CH_2Cl_2, rt, 96%.

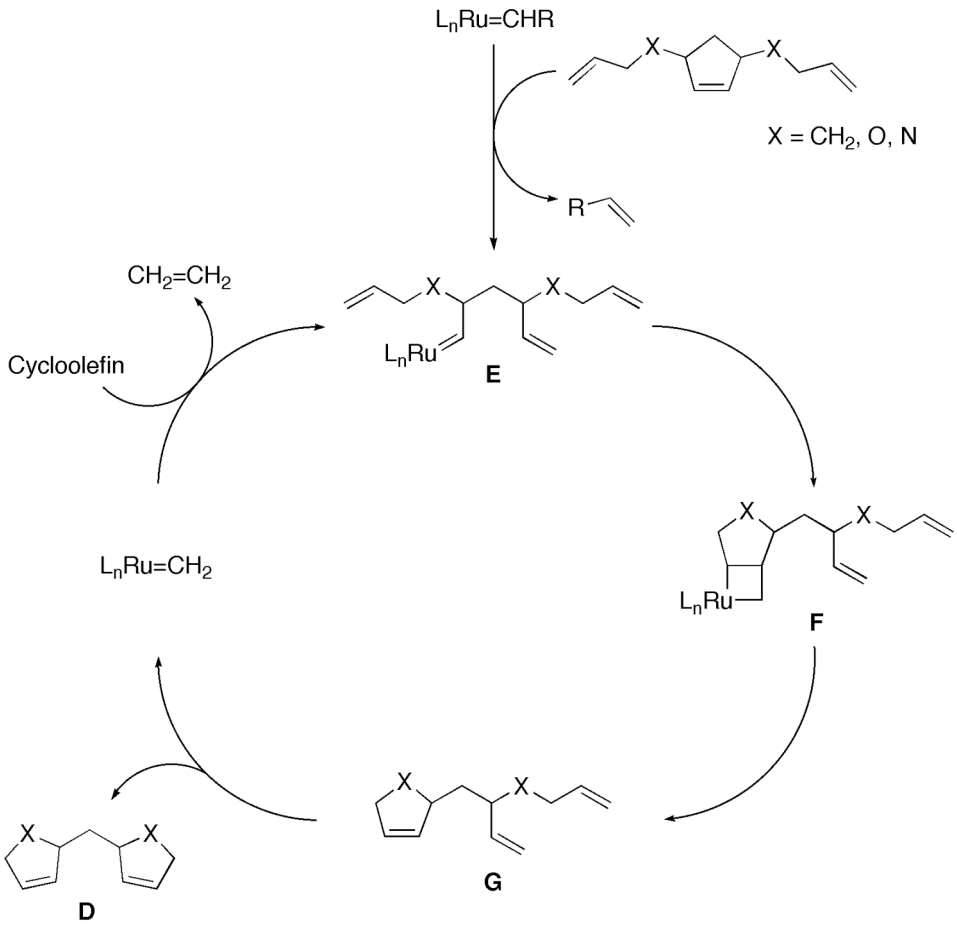
In these domino reactions, a strained carbocyclic alkene is converted into a new alkene by intramolecular ROM-RCM with an exocyclic double bond. The most important feature of RRM is the capacity to transfer stereochemical information from the starting material into the product. Stereocentres from ring system can be transferred to the side chain and *vice versa*, avoiding multistep synthesis of chiral structures. The observed products are consistent with two mechanisms (Scheme 38 and 39).[121] Mechanism 1 involves initial metathesis at the terminal olefin of the allyl group giving the complex **A**. The subsequently formed cyclobutane **B** is cleaved to produce the first ring and metal alkylidene **C**. The final step is the closure of the ring by intramolecular olefin metathesis leading to **D** with concomitant regeneration of the catalyst.



Scheme 38: Mecanism 1: initial metathesis on olefinic side chain.

[121] Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 6634.

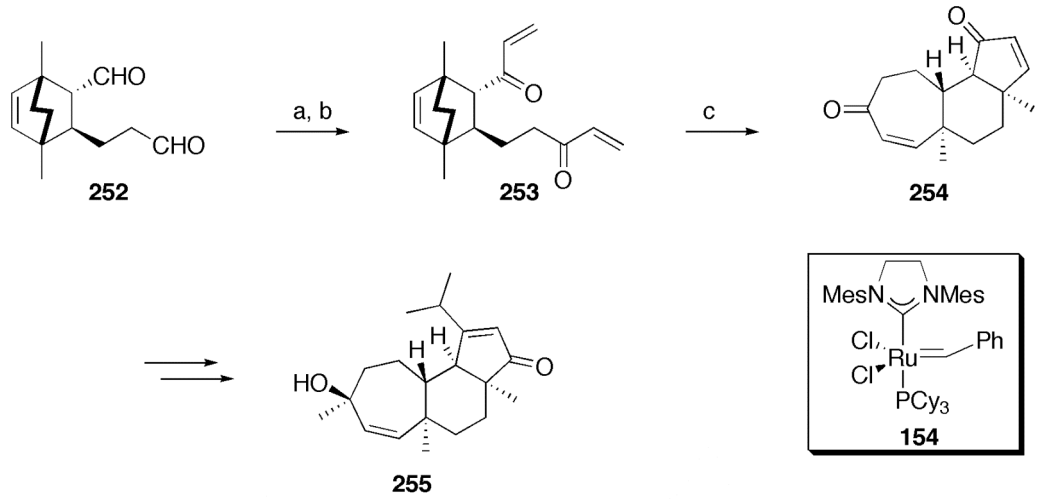
In mechanism 2, the initial metathesis reaction occurs at the disubstituted cyclic olefin to afford **E**. The subsequently formed cyclobutane **F** is cleaved and diene RCM gives **G** followed by **D**. Increasing olefinic substitution decreases the rate of olefin metathesis and so mechanism 1 is expected to predominate over mechanism 2. The observed effects of dilution and substitution are most consistent with mechanism 1. However, mechanism 2 has not been excluded, because ring strain may activate the cyclic olefin and favour it in some cases.[121]



Scheme 39: Mecanism 2: initial metathesis at ring olefin.

RRM domino processes can be applied to mono- and polycyclic structures of different sizes, but bicyclic systems deserve special attention. Owing to their highly strained nature, these substrates are highly reactive and the driving force for the reaction can be attributed to the release of energy. In most cases, the introduction of an external olefin, usually ethylene, is necessary to avoid oligomerisation, which is a common side reaction in RRM.

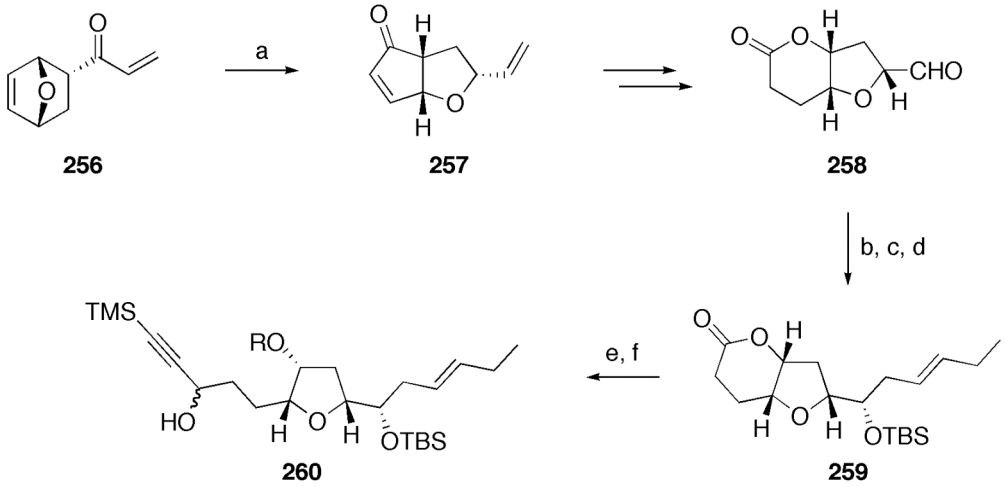
In this field, the work reported by Phillips' laboratory is closely related to what we are aiming to develop in the Clark group. In 2005, they reported a two-directional total synthesis of (+)-cyanthiwigin U (**255**) using RRM for the key stereoselective ring forming reaction.[122] The treatment of the dialdehyde **252** with vinylmagnesium bromide followed by reoxidation with DMP provided the bis-enone **253**. The sequence ROM-RCM afforded the tricyclic diketone **254** in 43% yield from the dialdehyde **252**. Finally, a four-step sequence afforded the target compound **255** in high yield (Scheme 40).



Scheme 40: *Conditions*: (a) vinylmagnesium bromide, $CeCl_3$, THF, –78 °C; (b) DMP, CH_2Cl_2, 0 °C; (c) catalyst **154** (20 mol%), ethylene, toluene, 120 °C, 43% (3 steps).

Shortly after, they applied their methodology to the formation of functionalised tetrahydrofurans.[123] The RRM reaction of the enone **256** gave the tetrahydrofuran **257** in 83% yield. Further functional group modifications delivered the aldehyde **258**. A reduction and protection sequence followed by a CM reaction afforded the lactone **259** in good yield, from which the alkynyl ketone **260** was formed in two steps (Scheme 41).

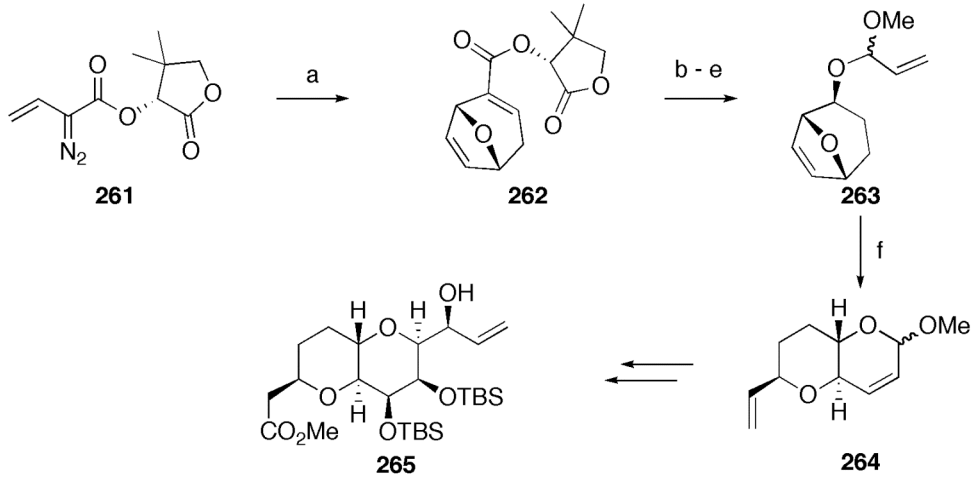
[122] Pfeiffer, M. W. B.; Philips, A. J *J. Am. Chem. Soc.* **2005**, *127*, 5334.
[123] Chandler, C. L.; Philips, A. J. *Org. Lett.* **2005**, *7*, 3493.



256 257 258 260 259

Scheme 41: *Conditions*: (a) catalyst **85** (5 mol%), CH_2Cl_2, ethylene, rt, 83%; (b) allyltrimethylsilane, $BF_3{\cdot}OEt_2$, CH_2Cl_2, –78 °C to rt, 64%; (c) TBSCl, imidazole, DMF, 40 °C, 93%; (d) catalyst **154** (10 mol%), *trans*-3-hexene, CH_2Cl_2, rt, 96%; (e) lithiotrimethylsilylacetylene, THF, –78 °C; (f) Ac_2O, DMAP, pyridine, 0 °C to rt, 85% (2 steps).

Finally their methodology was tested for the synthesis of pyranopyrans (Scheme 42). The rhodium-catalysed addition of diazo ester **261** to furan, gave the oxabicyclo[3.2.1]octene **262** in 59% yield.[124] This bridged bicyclic ether was advanced to **263** by a 4-step sequence. Treatment of ester **263** with catalyst **154** smoothly converted the bridged cyclic structure into the fused pyranopyran **264** in 71% yield. Further tranformations led to **265** that was used as an advanced intermediate in their impressive total synthesis of norhalichondrin B,[125] a marine polyether.



261 262 263 264 265

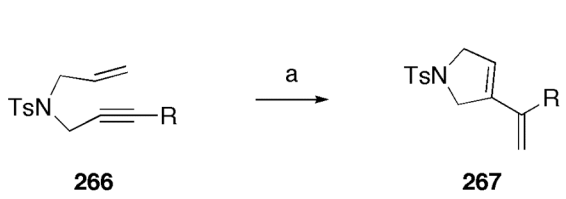
Scheme 42: *Conditions*: (a) $[Rh_2(OOct)_4]$ (1 mol%), furan, hexane, reflux, 59% (dr = 94:6); (b) NaOMe, MeOH then LiOH, $MeOH/H_2O$ (2:1); (c) DPPA, Et_3N, toluene/ CH_3CN (2:1) then H_2O, reflux; (d) L-Selectride, THF, –78 °C to rt, (dr = 10:1); (e) $H_2C{=}CHCH(OMe)_3$, PPTS, toluene, 45 °C, 16% (4 steps); (f) catalyst **154** (3 mol%), ethylene, toluene then ethylvinyl ether, 71%.

[124] (*a*) Jackson, K. L.; Henderson, J. A.; Morris, J. C.; Motoyoshi, H.; Phillips, A. J. *Tetrahedron Lett.* **2008**, *49*, 2939; (*b*) Davies, H. L. M.; Ahmed, G.; Churchill, M. R. *J. Am.Chem. Soc.* **1996**, *118*, 10774.
[125] Jackson, K. L.; Henderson, J. A. Motoyoshi, H.; Philips, A. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 2346.

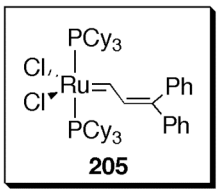
4.6 Ene-Yne Metathesis

Enyne metathesis has become an important addition to the synthetic tool kit.[126] It is defined as the reorganisation of covalent bonds between an alkene and alkyne to afford a 1,3-diene unit. This feature makes it, atom economical. As a widely used new organic reaction, RCEYM has found increased applicability in total synthesis but so far has been less studied than RCM. Both intramolecular and intermolecular variants of the RCEYM have been reported.[127] Metal salts can catalyse enyne metathesis,[128] but only intramolecular enyne metathesis catalysed by ruthenium carbene complexes will be discussed here.

Enyne metathesis with metal carbenes was first reported by Kalz in 1985 in a study involving several tungsten Fischer carbene complexes.[129] In 1994 Kinoshita and Mori reported the first enyne metathesis reaction with a ruthenium carbene complex.[130] They demonstrated that five-, six-, and seven-membered heterocycles could be obtained in good yields by ring-closing enyne metathesis in the presence of catalyst **205** (Scheme 43). The yields were highly dependent upon the nature of the acetylenic substitutent. Terminal alkynes or those bearing a silane or ester group gave low yields but alkyl or alkoxy substituted systems gave much more efficient reactions.



266 **267**



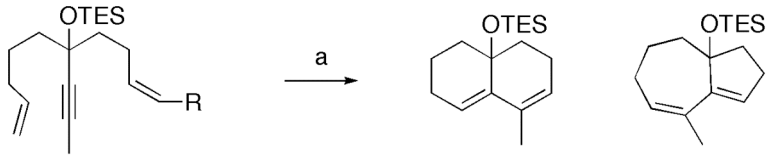
205

R	H	Me	TMS	CO_2Me	OTBS
Yield of 267	36%	91%	7%	18%	83%

Scheme 43: *Conditions*: (a) catalyst **205** (1 mol%), C_6H_6, reflux.

[126] (*a*) Mori, M. *Materials* **2010**, *3*, 2087; (*b*) Chattopadhyay, S. K.; Karmakar, S.; Biswas, T.; Majumdar, K. C.; Rahaman, H.; Roy, B. *Tetrahedron* **2007**, *63*, 3919; (*c*) Mori, M. *Adv. Synth. Catal.* **2007**, *349*, 121; (*d*) Villar, H.; Frings, M.; Bolm, C. *Chem. Soc. Rev.* **2007**, *36*, 55.
[127] Lippstreu, J. J.; Staub, B. F. *J. Am. Chem. Soc*. **2005**, *127*, 7444.
[128] Michelet, V.; Toullec, P. Y.; Genêt, J. P. *Angew. Chem. Int. Ed.* **2008**, *47*, 4268.
[129] Kalz, T. J.; Sivavec, T. M. *J. Am. Chem. Soc*. **1985**, *107*, 737.
[130] Mori, M.; Kinoshita, A. *Synlett* **1994**, 1020.

An interesting result was obtained by Grubbs when studying the cyclisation of dienynes with 3 mol% of catalyst **205**.[131] Unsubstituted dienyne **268a** gave rise to a 1:1 mixture of the two ring isomers **269** and **270** in 86% overall yield while substituted dienyne **268b** gave solely the isomer **270** (Scheme 44).



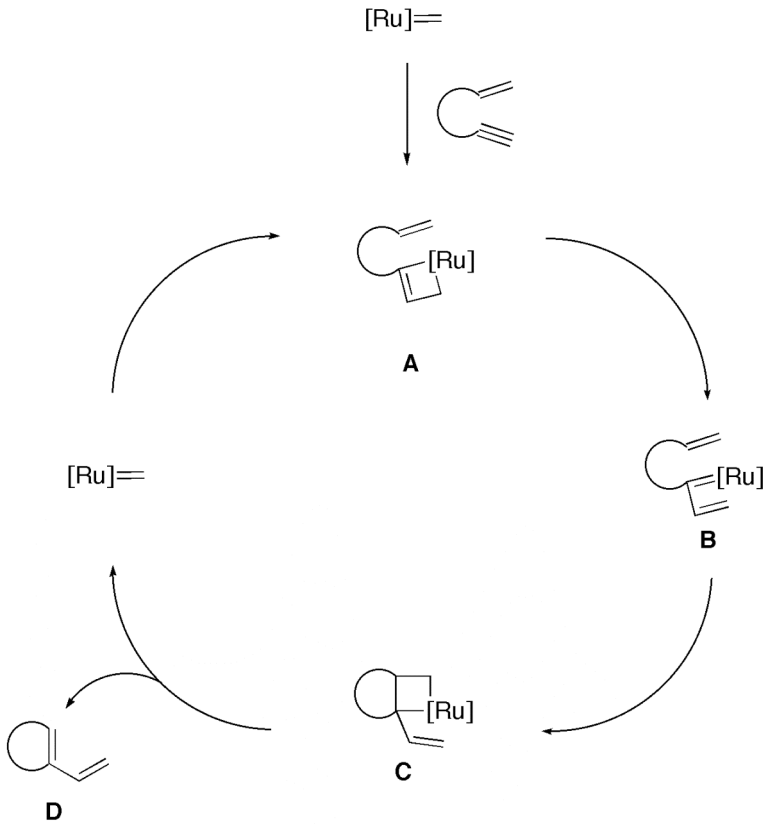
268 **269** **270**

Entry		Yield of 269	Yield of 270
1	**268a**, R = H	43%	43%
2	**268b**, R = Et	0%	83%

Scheme 44: *Conditions*: (a) catalyst **205** (3 mol%), C_6H_6, 65 °C.

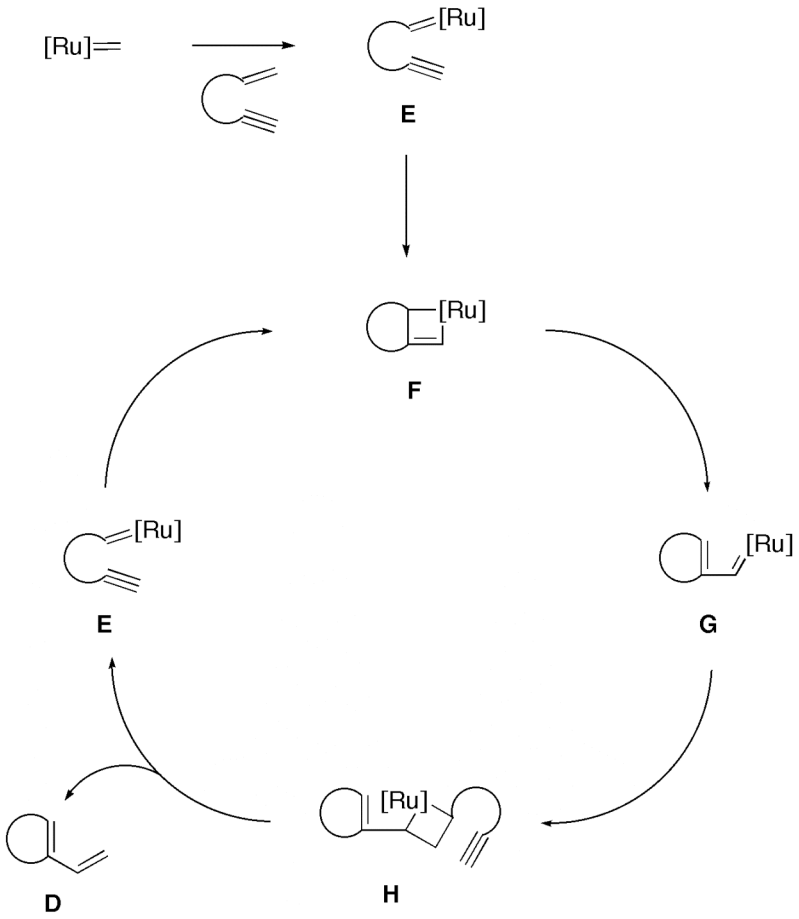
To possible mechanisms were reported when the reaction was carried out with a ruthenium carbene catalyst.[132] Mechanism 1 proceeds *via* a [2+2] cycloaddition of the ruthenium-carbene complex with an alkyne moiety to produce ruthenacyclobutene **A**. Ring opening of **A** affords ruthenium carbene complex **B**, which reacts with the alkene intramolecularly to give an ruthenacyclobutane **C**. The final step is the ring opening of **C** that leads to cyclised product **D**, and the ruthenium-carbene complex is regenerated (Scheme 45).

[131] Grubbs, R. H.; Bowden, N. B.; Zuercher, W. J.; Kim, S. H. *J. Org. Chem*. **1996**, 61, 1073.
[132] Mori, M. *Metathesis in Natural Product Synthesis*; Wiley-VCH: Weinheim, Germany, **2010**, 183.



Scheme 45: Mechanism 1, "yne-then-ene".[132]

Mechanism 2 similarly involves the reaction of the alkene moiety with the ruthenium-carbene complex resulting in the formation of a new ruthenium carbene complex **E**. Complex **E** reacts with the alkyne moiety intramolecularly to produce ruthenacyclobutene **F**. Subsequent ring opening gives ruthenium carbene **G**, which undergoes [2+2] cycloaddition with the alkene moiety of a second ene-yne to produce the ruthenacyclobutane **H**. At this stage, when the reaction is carried out under an ethylene atmosphere, the gas plays the role of the second molecule of ene-yne in the formation of the ruthenacyclobutane **H.** Ring opening of **H** yields diene **D** and the ruthenium-carbene complex is regenerated (Scheme 46). Lippstreu and Staub have demonstrated that the reaction proceeds *via* mechanism 2.[127] Their detailed study showed that ruthenacyclobutene **A** does not exist as a local minimum in the catalytic circle. It is noteworthy that alkyne insertion into a ruthenium carbene bond is the only irreversible step and is slower than the alkene insertion.



Scheme 46: Mechanism 2, "ene-then-yne".[132]

In 1998, Mori and co-workers reported a procedure in which the reaction is carried under an ethylene atmosphere.[133] Even though intramolecular enyne metathesis under Mori's conditions proved successful, there are many cases where the presence of ethylene was found to be problematic.[134,135] So far, the effects of ethylene have not been elucidated clearly. Finally, using ruthenium carbene complexes, various carbo- and heterocycles could be synthesised from the corresponding enynes. Diene-yne metathesis, cross ene-yne metathesis and ring-opening ene-yne metathesis have also been developed.

[133] Mori, M.; Kinoshita, A.; Sakakibara, N. *J. Org. Chem*. **1998**, *63*, 6082.
[134] Lippstreu and Staub also reported that high concentration of ethylene facilitates the competitive displacement of alkyne ligands by ethylene and may thus suppress alkyne insertion into vinylcarbene ruthenium bonds, which may lead to alkyne polymerisation side products (see ref. 127).
[135] Diver, S. T. *J. Mol. Catal. A* **2006**, *254*, 29.

4.7 Conclusion

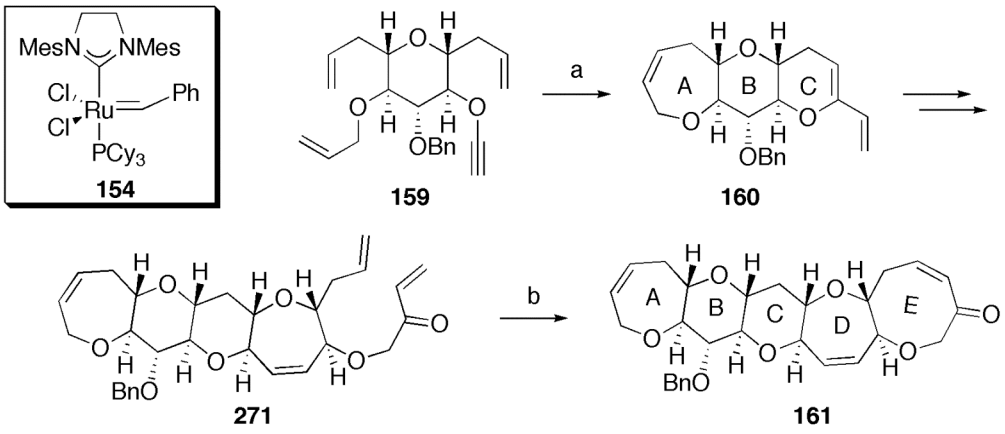
Alkene metathesis is well established as a valuable synthetic tool in organic chemistry, and has proven to be a rapid and effective technique for the construction of carbon-carbon double bonds, especially within complexes structures.[136] The development of well-defined catalysts, which combine high activity, durability, and excellent tolerance towards polar functional groups, was instrumental in revolutionising the field.[137] The popularity of metathesis reactions is also due to the numerous types of transformations that have been developed. The same metal-carbene complex can be used to carry out several reactions depending on the substrates and reaction conditions. RCM is by far the most exploited reaction, but recent developments demonstrate that metathesis of other π-systems will also play a vital role in the advancement of organic synthesis. Finally, the development of asymmetric metathesis reactions[98b,138] as well as more reactive catalytic systems, are still fields of intensive research. Efforts towards "green" metathesis reactins are also being pursued.[139]

[136] (*a*) Hoveyda, A. H.; Malcolmson, S. J.; Meek, S. J.; Zhugralin, A. R. *Angew. Chem. Int. Ed.* **2010**, *49*, 34; (*b*) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4490.
[137] Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746.
[138] (*a*) Sattely, E. S.; Cortez, G. A.; Moebius, D. C.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 8526; (*b*) Gillingham, D. G; Kataoka, O.; Garber, S. B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 12288.
[139] Clavier, H.; Grela, C.; Kirschning, A.; Maudit, M.; Nolan, S.P. *Angew. Chem. Int. Ed.* **2007**, *46*, 6786.

RESULTS and DISCUSSION

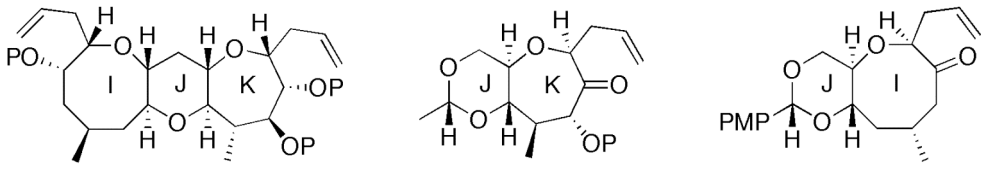
1 Introduction

Previous work within the Clark group has established the synthesis of the A-E ring system of CTX3C (**2**).[78] The key steps of the two directional approach involved simultaneous diene and enyne RCM reactions as well as enone RCM reactions (Scheme 47, see also Ch.1, § 3.8).



Scheme 47: *Conditions:* (a) catalyst **154** (10 mol%), CH_2Cl_2, toluene, 70 °C, 58%; (b) catalyst **154** (10 mol%), CH_2Cl_2, reflux, 50%.

It was suggested that the same approach could be adopted for the synthesis of the H-M fragment of CTX3C (**2**), specially the IJK tricyclic core **272** (Figure 18). The rather modest yield obtained in the formation of the ABC ring system was the main drawback of the method.[78] Performing model studies is a way to explore potential problems of this type. Consequently, the research project began with the synthesis of models of the seven- and eight-membered ring systems representing the K- and I-rings, **273** and **274** respectively (Figure 18). As highlighted in Figure 18, compound **273** represents the enantiomer of the desired K-ring. This target was chosen, since it can be prepared from the inexpensive and commercially available D-glucose. *A* bi-directional and iterative approach emerged from the results of these studies.



272 **273** **274**

Figure 18: The IJK fragment **272** and the target model systems **273** and **274**.

2 Retrosynthetic Analyses for Model Systems

2.1 Synthesis of Cyclic Enones

2.1.1 Cossy's Approach

Cossy and co-workers have reported the efficient cyclisation of 3-oxo oxacycloalkenes **A** to form 3-oxo alkoxy enones **B** *via* RCM (Figure 19).[140]

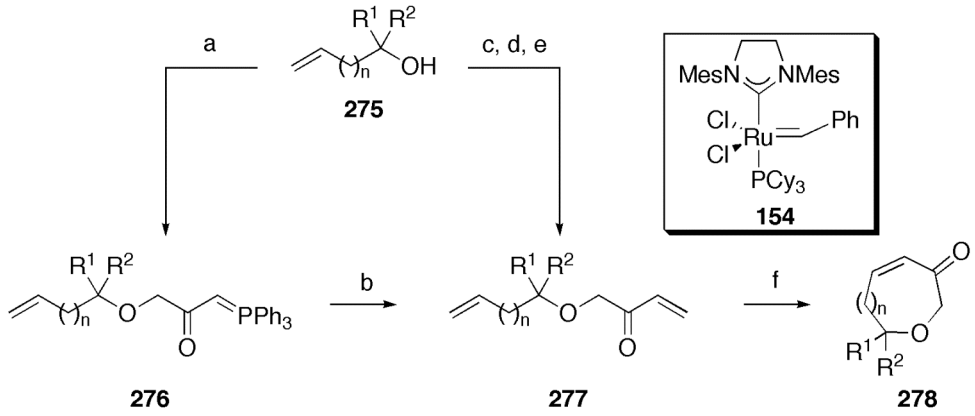
A **B**

Figure 19: Cossy's approach to 3-oxo oxacycloalkenes.[140]

In the case where R^1 = alkyl or aryl and R^2 = H, α-alkoxy enones of type **A** were prepared *via* the stabilised phosphoranes **276**. These were obtained by alkylation of the secondary or tertiary alcohols **275** with triphenylchloroacetonylphosphorane in yields greater than 48%.[141] Reaction of the resulting phosphoranes **276** with formaldehyde afforded the α-alkoxy enones **277** in greater than 50% yield.[142] In cases where R^1 = R^2 = H, an alternative procedure was developed to synthesise compounds **277** using a Stille coupling reaction. The RCM reaction did not proceed when performed with the Grubbs first-generation catalyst **85**. In contrast, six-, seven- and eight membered cyclic enones **278** were prepared in good yield upon treatment of acyclic precursors **277** with the Grubbs second-generation catalyst **154**. It is worth noting that

[140] (*a*) Taillier, C.; Hameury, T.; Bellosta, V.; Cossy, J. *Tetrahedron* **2007**, *63*, 4472; (*b*) Cossy, J.; Taillier, C.; Bellosta, V. *Tetrahedron Lett.* **2002**, *43*, 7263.
[141] Hudson, R. F.; Chopard, P. A. *J. Org. Chem.* **1963**, *28*, 2446.
[142] Hecker, S. J.; Heathcock, C. H. *J. Org. Chem.* **1985**, *50*, 5159.

eight-membered rings, which are usually difficult to synthesise were formed efficiently (Scheme 48).



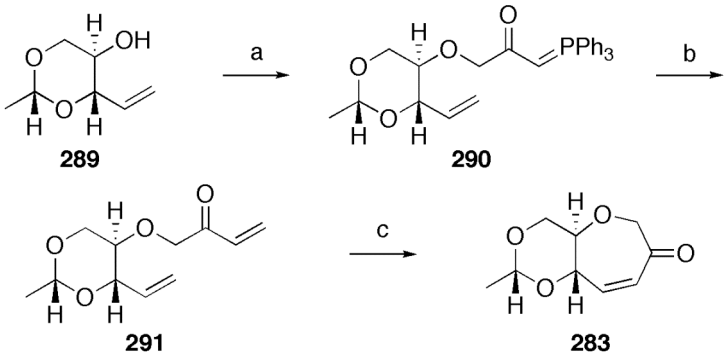
Entry	277	154 (mol%)	Yield of 278
1	n = 0, R^1 = R^2 =H	2.5	69%
2	n = 1, R^1 = R^2 =H	15	58%
3	n = 2, R^1 = R^2 =H	10	66%

Scheme 48: *Conditions*: (a) NaH, triphenylchloroacetonylphosphorane, THF, rt to reflux, 48-94% (n = 0-2); (b) CH_2O, H_2O/Et_2O, rt, 49-73% (n = 0-2); (c) NaH, chloroacetic acid, THF, rt 51-70% (n = 0-2); (d) $(COCl)_2$, DMF, C_6H_6, rt; (e) tri-*n*-butylvinyltin, $Pd(PPh_3)_2BnCl$ (0.4 mol%), HMPA, 65 °C, 37-58% (n = 0-2) (2 steps); (f) catalyst **154**, CH_2Cl_2, reflux.

2.1.2 Clark's Contribution

Based on Cossy's results, Clark and co-workers extended the methodology to synthesise seven-membered cyclic enones using highly functionalised substrates.[143] The alkylation of alcohol **279** with triphenylchloroacetonylphosphorane yielded the phosphorane **280** in 88% yield. Subsequent treatment with formaldehyde afforded RCM reaction precursor **281**, which was treated with the Grubbs second-generation catalyst **154** to deliver the seven-membered ring enone **282** in 84% yield (Scheme 49).

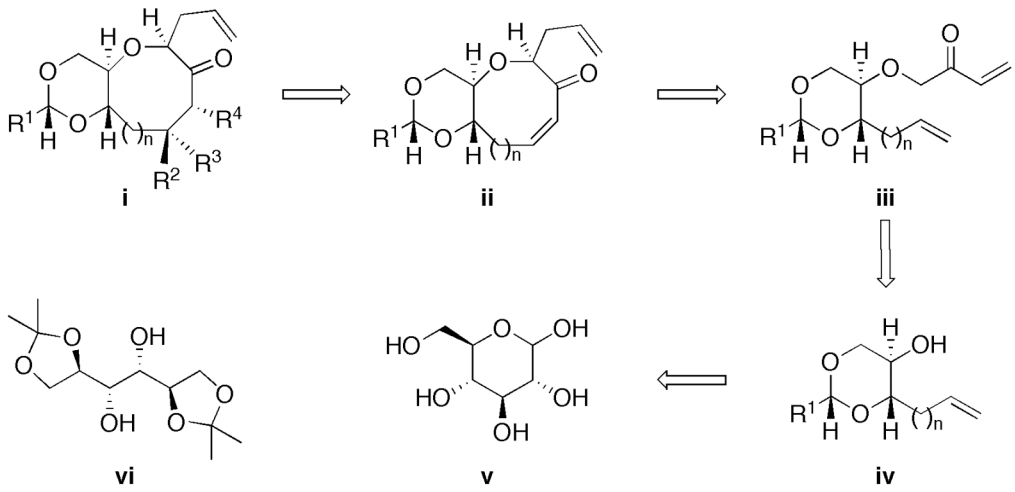
[143] Unpublished results.



Scheme 49: *Conditions*: (a) NaH, triphenylchloroacetonylphosphorane, THF, rt, 88%; (b) CH_2O, H_2O/Et_2O, rt, 86%; (c) catalyst **154**, CH_2Cl_2, reflux, 84%.

2.2 Retrosynthetic analysis

Retrosynthetic analysis based on enone RCM was suggested for the syntheses of the ring systems **273** and **274**. Commencing from ketone **i**, functional group modifications and retro 1,4-conjugate addition lead to the cyclic enone **ii**. Subsequent cleavage of the enone side chain and ROM afford diene **iii**. Removal of the ether linkage provides the secondary alcohol **iv** that can easily be prepared from carbohydrate derivatives **v** and **vi** (Scheme 50).

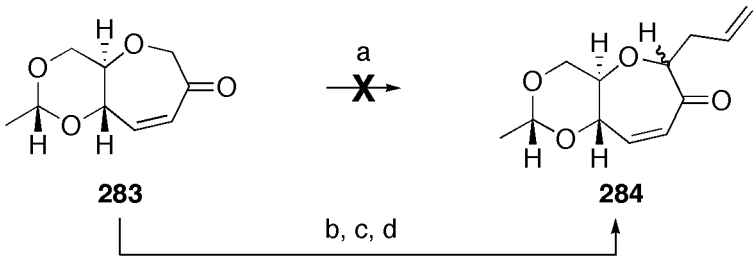


Scheme 50: n = 0 or 1; R^1 = Me or PMP; R^2 = H or Me; R^3 = H or Me; R^4 = H or OH.

3 D-Glucal Derivative Model for K-Ring

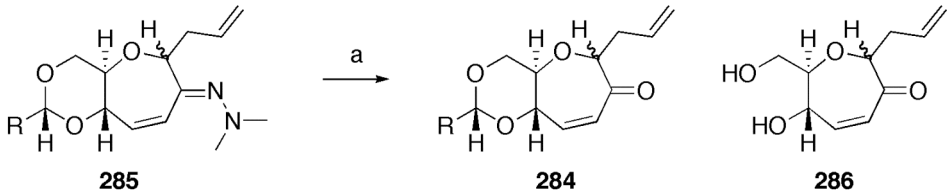
3.1 Synthesis of the Seven-Membered Cyclic Enone 283

Previous studies in the group had allowed a viable route to the cyclic enone **284** to be established.[144] From these studies, it appeared that direct allylation of ketone **283** was not possible and resulted in decomposition (Scheme 47). Instead, a high-yielding three-step procedure was developed. This procedure involved *i)* treatment of enone **283** with *N,N*-dimethylhydrazine *ii)* alkylation of the resulting hydrazone and *iii)* hydrolysis of the hydrazone to regenerate an enone (Scheme 51).



Scheme 51: *Conditions:* (a) base, allyl bromide or allyl iodide, THF, –78 °C to rt; (b) Me_2NNH_2, C_6H_6, reflux;(c) *t*-BuLi, allyl bromide, THF, –78 °C to rt; (d) $CuCl_2$, THF/H_2O (2:1), rt, 50% (3 steps).

It has also been demonstrated that an ethylidene-acetal was a better protecting group than the *p*-methoxybenzylidene analogue. The reduced acid sensitivity allowed the usual acetal cleavage process that occurs during the hydrolysis of hydrazone **285** to be avoided, thereby, preventing the formation of diol **286** (Scheme 52).

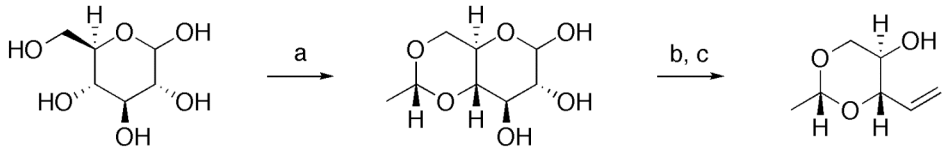


Entry		Mixture	Yield of 284
1	R = PMP	**284 + 285**	27%
2	R = Me	**284**	85%

Scheme 52: *Conditions*: (a) $CuCl_2$, THF/H_2O (2:1), rt.

[144] These results were obtained by Dr McErlean, Dr Grainger and Dr Ehkirch, University of Nottingham.

The requisite ethylidene-acetal **288** was prepared in good yield by treatment of D-(+)-glucose (**287**) with paraldehyde in the presence of a catalytic amount of sulphuric acid.[145] The oxidative cleavage of triol **288**, mediated by sodium periodate, followed by Wittig methylenation of the resultant aldehyde yielded the alkene **289** in 90% yield over the 2 steps (Scheme 53).[146]

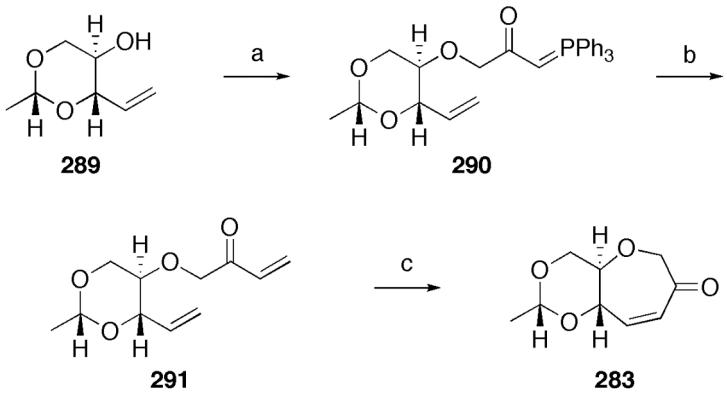


287 **288** **289**

Scheme 53: *Conditions:* (a) paraldehyde, H_2SO_4, rt, 81%; (b) $NaIO_4$, CH_2Cl_2/H_2O (3:1), rt; (c) CH_3PPh_3Br, *t*-BuOK, THF, 0 °C to rt, 90% (2 steps).

The triphenylchloroacetonylphosphorane was prepared by the reaction of 1,3-dichloroacetone with triphenylphosphine in THF, in accordance with literature procedure.[141] The alkylation of alcohol **289** with triphenylchloroacetonylphosphorane afforded the stabilised phosphonium ylide **290**. Subsequent treatment with aqueous formaldehyde under buffered conditions converted **290** into the α-alkoxy enone **291** in 68% overall yield.[142] As previously observed by Grainger,[144] the quality of formaldehyde was very important for the reproducibility of the reaction. The RCM reaction of the enone **291** in the presence of the Grubbs second-generation catalyst **154** provided the oxepenone **283** (Scheme 54)**.** As expected, a colourless solid was isolated and data were in perfect concordance with the one reported by previous members of the group (the X-ray structure is available from Ehkirch thesis).[144] However, the RCM reaction was found somewhat unreliable especially with regard to scaling up and the use of solvent that had not been degassed.

[145] Fringant, C.; Tvaroska, I.; Mazeau, K.; Rinaudo, M.; Desbrieres, J.; *Carbohydr. Res.* **1995**, *278*, 43.
[146] Maruyama, M.; Inoue, M.; Oishi, T.; Oguri, H.; Ogasawara, Y.; Shindo, Y.; Hirama, M. *Tetrahedron* **2002,** *58*, 1835.

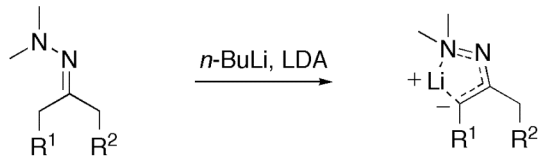


Scheme 54: *Conditions*: (a) NaH, $ClCH_2COCHPPh_3$, TBAI, THF, rt then reflux; (b) CH_2O, pH = 7 buffer solution, Et_2O, rt, 68% (2 steps), (c) catalyst **154** (3 mol%), CH_2Cl_2, 84%.

3.2 Functionalistion of Enone 283

3.2.1 First Approach

Attention was then turned to the formation of the alkylated enone **295**. Corey and Enders have reported examples wherein the carbonyl group is converted to its corresponding *N,N*-dimethylhydrazone prior to deprotonation.[147] In these cases, the anion is stabilised by coordination of the lithium counter-ion to the hydrazone (Scheme 55).

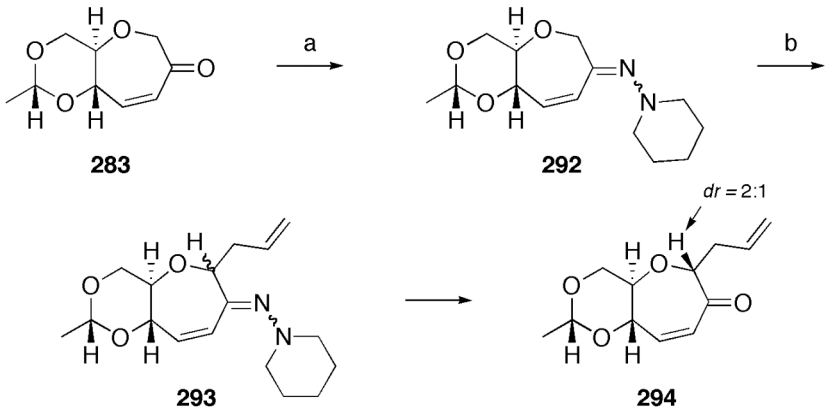


Scheme 55: Stabilisation of the hydrazone anion by coordination of the lithium counter-ion.[148]

This methodology proved successful in the synthesis of the A-E fragment of CTX3C (**2**). Nevertheless, to avoid the drawbacks linked to the toxicity of benzene the procedure was slightly modified. *N,N*-Dimethylhydrazine was replaced by 1-aminopiperidine. The higher molecular weight of this hydrazine avoided loss to the Dean-Stark trap when the reaction was performed in toluene at reflux. A 1:1 mixture of geometric isomers was obtained in 92% yield from the reaction (Scheme 56).

[147] Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, *41*, 3667.

Alkylation was attempted but appeared to be irreproducible. Performing the reaction at −78 °C proved to be successful[148] and the formation of by-products was first attributed to the method by which *t*-BuLi was added. The reaction time was reduced from 60 to 30 min without noticeable changes. Colour changes (turned orange) indicated that the intermediate enolate was formed, so several conditions were tested (Entry 1, Table 1). Complementary results were obtained in increasing the reaction scale (Entries 2-4, Table 1). The rapid decomposition of the intermediate enolate was finally considered and *t*-BuLi was added at −100 °C. From the set of conditions tested, it appeared that the completion of the reaction depends strongly on the speed and temperature at which *t*-BuLi is added. The stirring time before addition of allyl bromide was also important. Scaling-up made the reaction more reproducible as it allowed the utilisation of the syringe pump to control the addition of reagents (Entry 4, Table 1).



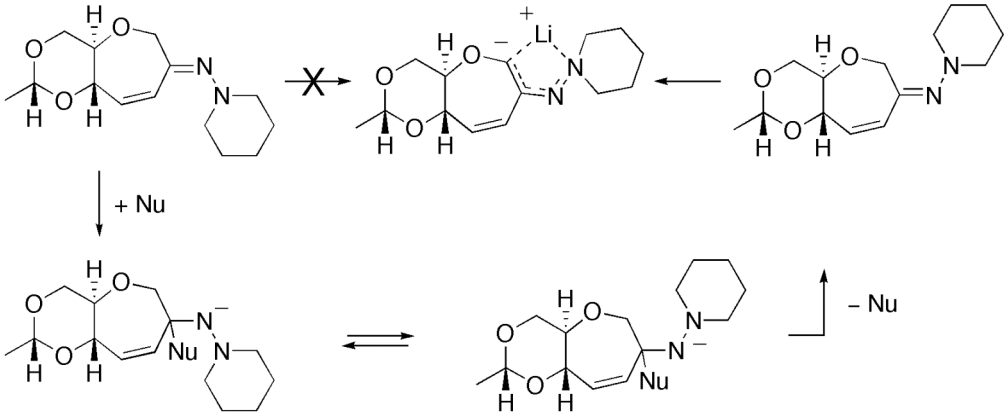
Scheme 56: *Conditions*: (a) 1- aminopiperidine, toluene, reflux, 92%; (b) *t*-BuLi, THF then allyl bromide, −78 °C (overnight).

Entry	292 (mmol)	Equivalents of *t*-BuLi allyl bromide	Addition Conditions of *t*-BuLi	Product	Yield of 294
1	0.22−0.53	1.5 2−4	−78 °C, dropwise add. + 30-60 min at −78 °C	**292** + **293** + decomposition product	26-33%
2	1.05	1.5 3	−78 °C, add. over 5 min + 30 min at −78 °C	**293** + decomposition product	10%
3	1.05-1.12	1.5 3	−78 °C, add. over 15 min + 30 min at −78 °C	**292** + **293**	35-45%
4	2.74	1.5 3	−100 °C, add. over 15 min + 30 min at −78 °C	**293**	63-71%

Table 1: Attempts of allylation.

[148] Post-doctoral report Dr Grainger, University of Nottingham.

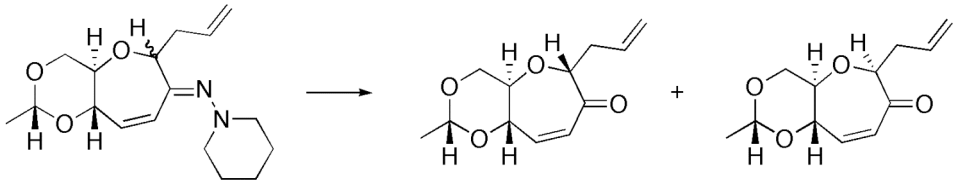
Starting with a 1:1 mixture of geometric isomers of **292** it seems impossible for one of the two isomers to fit with the mechanism of stabilisation proposed by Corey and Enders. As a consequence, the yield of the reaction should be close to 50%. Instead, enone **294** was isolated in 63 to 71% yields. Such a result suggests that something else happened during the reaction, to allow the rotation of the carbon-nitrogen bond as shown in Scheme 57. A reversible nucleophilic addition onto the carbon-nitrogen double bond would allow such a rotation to fit with the mechanism proposed by Corey and Enders and explain why our yield is better than expected. Nevertheless, the nucleophile has not been identified (Scheme 57).



Scheme 57: Proposed mechanism.

Removal of the hydrazone was then investigated using the crude alkylated hydrazone **293**. Using conditions previously developed within the group,[144] only poor to moderate yields were obtained due to problems encountered during the workup (Entry 1, Table 2). The workup conditions were modified to keep pH > 9 and reproducibly good yields were obtained (Entry 2, Table 2). Removal of the hydrazone proceeded smoothly when the substrate was treated with cupric ion, yielding a diastereomeric mixture of enones **294** and **295** in 71% over 2 steps. Enones **294** and **295** had previously been prepared and isolated within the Clark group.[144] The data sets obtained for these compounds were identical to the ones reported. Maintaining the pH >9 during the workup was necessary to obtain reproducible yields. Finally, it was noticed that the storage of the crude ketone

is an important factor that contributes to decomposition whereas the product is stable after purification.[149]



293 **294** **295**

Entry	Conditions	Workup	294:295	Yield
1	$CuCl_2$ (4 eq.), THF/H_2O (2:1), rt	H_2O	2:1	33%
2	$CuCl_2$ (4 eq.), THF/H_2O (1:1), rt	NH_4OH/NH_4Cl	2:1	71%

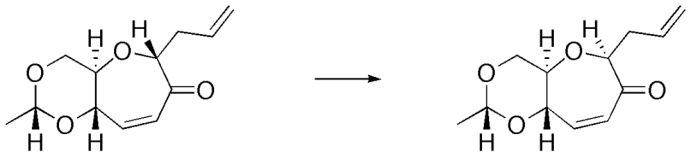
Table 2: Hydrazone removal.

Despite the viability of the synthetic pathway in assembling the carbon skeleton, it led mainly to the undesired diastereomer **294**. Attempts to epimerise the ketone **294** are summarised in Table 3. The structural features of **294** indicated that a strong, non-nucleophilic base would be required to promote the epimerisation and avoid the formation of the Michael adducts. This hypothesis was confirmed when epimerisation was performed in methanol in the presence of K_2CO_3 (Entry 1, Table 3). In this case, the Michael adduct was obtained as the sole product.

A more appropriate base was required and DBU was chosen due to its successful utilisation on similar substrates and its compatibility with the conditions described previously.[144] Unfortunately, all attempts to epimerise **294** using DBU led to the decomposition of the substrate, (Entries 2-7, Table 3). Hünig's base was also tested. Interestingly, although no decomposition was observed, Hünig's base was not efficient enough to afford a significant amount of the desired epimer **295** (Entries 8 and 9, Table 3). Finally using the Proton Sponge®, a 5:1 mixture of epimers was obtained in favour of the desired diastereomer (Entries 10-13, Table 3). Surprisingly, the number of equivalents of Proton Sponge® used only affected the yield of the reaction. The optimal conditions were determined for the reaction and enone **295** was isolated in a

[149] Decomposition was observed after overnight storage in the freezer. It is assumed that the decomposition was linked to the presence of copper salts in the crude oil.

good 75% yield as a 5:1 mixture of isomers favouring **295** (Entry 12, Table 3). The effect of the temperature was also investigated and it appeared that the longer the reaction mixture was heated the poorer was the yield (Entry 13, Table 3).



294 **295**

Entry	Base	Solvent	T (°C)	Time	294:295/Yield
1	K_2CO_3 (1eq.)	MeOH	rt	1 h	1,4-addition
2	DBU (5 eq.)	toluene	rt	24 h	Decomposed
3	DBU (5 eq.)	toluene	110	4 h	Decomposed
4	DBU (5 eq.)	toluene	85	2 h	Decomposed
5	DBU (5 eq.)	THF	70	20 min	Decomposed
6	DBU (1 eq.)	toluene	85	4 h	Decomposed
7	DBU (1 eq.)	toluene	85	4 h	Decomposed
8	DIPEA (10 eq.)	CH_2Cl_2 then toluene	rt to 85	7 d	1:1/–
9	DIPEA	DIPEA	85	overnight	1:1/ 75%
10	Proton Sponge® (5 eq.)	toluene	85	overnight	1:5/66%
11	Proton Sponge® (0.1 eq.)	toluene	85	2 d	1:5/66%
12	Proton Sponge® (1 eq.)	toluene	85 then rt	overnight	1:5/75%
13	Proton Sponge® (1 eq.)	toluene	40 to 85	2 d	1:5/25%

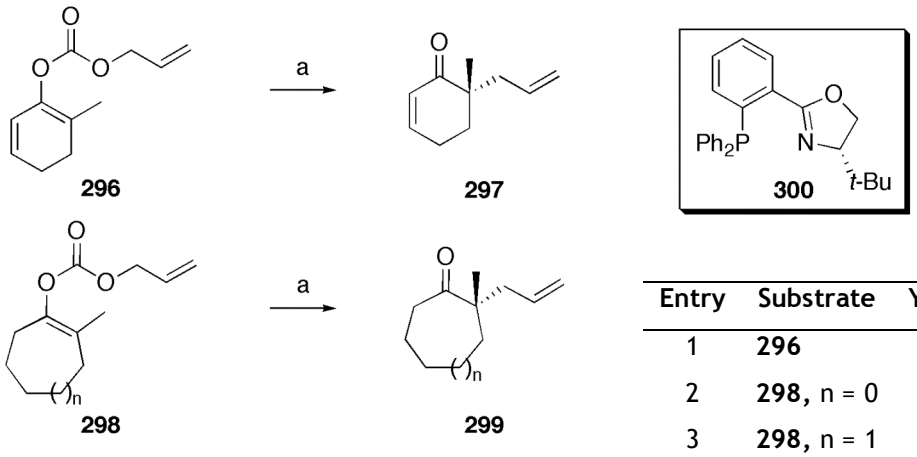
Table 3: Attempts of epimerisation.

Good yields were obtained and the diastereoisomeric ratio between **294** and **295** was sufficiently high for a model study. However, the efficiency of this method, especially with regard to the number of steps and the diastreoselectivity, is not sufficient to be used in the total synthesis of a natural polycyclic ether. Consequently, an alternative route was investigated to achieve

the allylation of **283**.[150] Efforts were focused on the enantioselective variant of the Tsuji-Trost allylation procedure.[151]

3.2.2 Overview of the Tsuji-Trost Allylation

In 2004, the Stoltz' group reported an enantioselective Tsuji allylation from allyl enol carbonate substrates.[151d] A screen of chiral ligands identified that chelating P/N ligands were especially effective in terms of yield and enantioselectivity. Specifically, the *tert*-butyl phosphinooxazoline [(*S*)-*t*-Bu-PHOX (**300**)], originally developed by Pfaltz and co-workers in the 1990s,[152] led to the formation of various enantioenriched cycloalkanones. Selected examples are represented in Scheme 58. Interestingly, the reaction proceeded under mild condition and displayed good tolerance for a variety of substituents and functional groups. It is worth noting that these adapted enantioselective Tsuji allylation conditions were capable of generating a quaternary stereocentre adjacent to another quaternary carbon atom. Another interesting effect is that a range of solvents, including ethereal (THF, 1,4-dioxane, diethyl ether), aromatic (benzene, toluene) and carbonyl containing (ethyl acetate) solvents proved to be nearly equally effective for the reactions of several substrates.



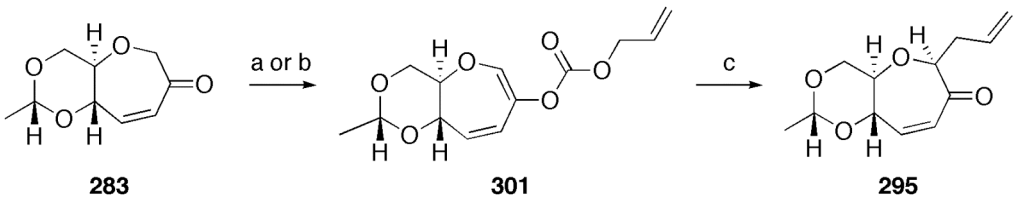
Entry	Substrate	Yield	*ee*
1	**296**	91%	89%
2	**298,** n = 0	85%	87%
3	**298,** n = 1	81%	87%
4	**298,** n = 2	90%	79%

Scheme 58: *Conditions*: (a) $Pd_2(dba)_3$ (2.5 mol%), **300** (6.25 mol%), THF, 25 °C.

[150] This work was realised in conjunction with PhD student B. Sieng, University of Glasgow.
[151] (*a*) Trost, B. M.; Xu, J.; Schmidt, T. *J. Am. Chem. Soc.* **2009**, *131*, 18343; (*b*) Mohr, J. T.; Stoltz, B. M. *Chem. Asian. J.* **2007**, *2*, 1476 ; (*c*) Trost, B. M.; Xu, J.; Reichle, M. *J. Am. Chem. Soc.* **2007**, *129*, 282; (*d*) Behenna, D. C.; Stotz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044; (*e*) Trost, B. M.; Fullerton, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 292; (*f*) Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, *6*, 4348.
[152] (*a*) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336; (*b*) Williams, J. M. J. *Synlett* **1996**, 705.

3.2.3 Application onto Enone 283

Enol carbonate **301** was prepared according to the protocol reported by Trost and co-workers.[151c] TMEDA was used in the original procedure but was found to generate byproducts. Premixing enol carbonate **301** and allylchloroformate before the addition of NaHMDS coupled with the absence of TMEDA yielded the enol carbonate **301** in 93% yield. The compound **301** was then subjected to the enantioselective Tsuji allylation reaction in the presence of $Pd_2(dba)_3$ and (*S*)-*t*-Bu-PHOX (**300**). The reaction afforded the alkylated enone **295** as a sole isomer in 83% yield (Scheme 59).[151d]



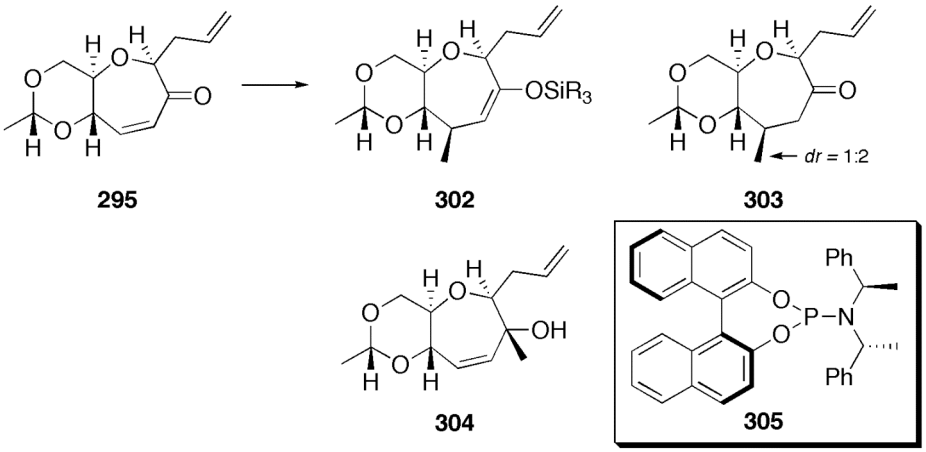
Scheme 59: *Conditions*: (a) NaHMDS, TMEDA, THF, −78 °C then allylchloroformate, −78 °C to rt, 67%; (b) **301**, allylchloroformate, THF, −78 °C then NaHMDS, −78 °C, 93%; (c) $Pd_2(dba)_3$ (2.5 mol%), **300** (6.25 mol%), THF, 25-30 °C, 83%.

At this stage in the synthesis, only a few steps of the proposed synthesis were required to give the desired molecule. Conjugate addition, trapping of enolate and Rubottom oxidation of the resulting silyl enol ether should afford ketone **273**.

3.2.4 Cuprate additon

The 1,4-addition of a methyl group to the enone double bond was explored. Disappointingly, in addition to the lack of diastereoselectivity the trapping of the enolate was unsuccessful. Different silyl groups were tested to circumvent the instability of the generated silyl enol ether, with a preference for the TES group (Entries 1-3, Table 4). Failure of the enolate trapping was attributed to a problem of dilution. So as not to change the concentration of the cuprate, a large excess of TESCl was used, but once again ketone **303** was isolated instead of the silyl enol ether **302** (Entry 4, Table 4). Changing the order of introduction of reagents and using a different source of copper was

unsuccessful (Entries 6-7, Table 4).[153] Finally, the utilisation of a catalytic amount of CuBr·DMS complex in presence of the chiral ligand **305**, afforded a diastereomeric mixture of the 1,2-adduct **304** (Entry 8, Table 4).[154]



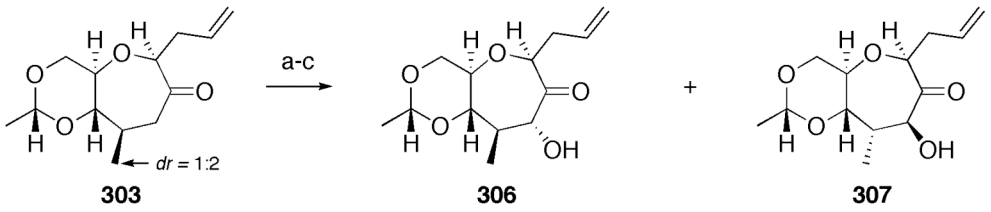
295 **302** **303** **304** **305**

Entry	Conditions	Yield	*dr*
1[a]	CuBr·DMS (4 eq.), MeMgBr (4 eq.), $BF_3{\cdot}OEt_2$ (4 eq.), TMSCl (1.5 eq.), THF	**303**	1:2
2[a]	CuBr·DMS (4 eq.), MeMgBr (4 eq.), $BF_3{\cdot}OEt_2$ (4 eq.), **TIPSCl** (1.5 eq.), THF	**303**	1:2
3[a]	CuBr·DMS (4 eq.), MeMgBr (4 eq.), $BF_3{\cdot}OEt_2$ (4 eq.), **TESCl** (1.5 eq.), THF	**303**	1:2
4[a]	CuBr·DMS (4 eq.), MeMgBr (4 eq.), $BF_3{\cdot}OEt_2$ (4 eq.), TESCl (**4 eq.**), THF	**303**	1:2
5[a]	CuBr·DMS (4 eq.), MeMgBr (4 eq.), **$BF_3{\cdot}OEt_2$ (0 eq.)**, TESCl (**4 eq.**), THF	**303**	1:2
6	**CuI (1.2 eq.), MeLi (2.4 eq.),** TESCl (1.5 eq), THF	**295**	–
7	CuI (1.2 eq.), MeLi (2.4 eq.), TESCl (1.5 eq), **Et_2O**	**295**	–
8[b]	CuBr·DMS **(4 mol%)**, MeMgBr (1.1 eq.), **305 (13.5 mol%), toluene**	**304**	–

Table 4: (a) **303** was isolated in 75% yield; (b) **304** was formed quantitatively.

At this stage of the synthesis the diastereoisomers were not separable and further elaborations were required to determine the stereochemistry of the newly formed stereocentre. As a consequence, the inseparable mixture of diastereomers of ketone **303** was then used to study the Rubottom oxidation reaction. Silyl enol ether was generated quantitatively using LDA in the presence of TESCl.[155] The formation of the silyloxy epoxide using *m*-CPBA, followed by ring opening under acidic conditions afforded the α-hydroxyketones **306** and **307** in moderate overall yield (Scheme 60).[156]

[153] Guinn, D. E.; Martin, S. F. *J. Org. Chem.* **1987**, *52*, 5588.
[154] Lopez, F.; Minnaard, A. J.; Feringa, B. L. *Acc. Chem. Res.* **2007**, *40*, 179.
[155] Pardeshi, S. G.; Ward, D. E. *J. Org. Chem.* **2008**, *73*, 1071.
[156] Thomson, C. F.; Jamison, T. F.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2000**, *122*, 10482.



303 **306** **307**

Scheme 60: *Conditions*: (a) DIPA, *n*-BuLi, TESCl, Et_3N, THF, –78 °C; (b) *m*-CPBA, $NaHCO_3$, toluene, 0 °C; (c) THF/H_2O/AcOH (2:1:0.5), rt, 24% (3steps).

For the first time, it was possible to separate the two diastereoisomers. The structure of **306** was proved thanks to the calculation of the coupling constants. The calculation revealed the *trans* relationship between the methyl group and the hydroxyl ($^3J_{(CH\text{-}C7/CH\text{-}C8)}$ = 11.2 Hz, see experimental p. 123) as well as the *cis* relationship of this methyl with the proton in γ-position relative to the carbonyl ($^3J_{(CH\text{-}C8/CH\text{-}C9)}$ = 9.5 Hz, see experimental p. 123). The NMR spectra also confirmed the presence of the acetal protecting group, the allylic double bond and the carbon-oxygen double bond. The presence of this latter was highlighted by the IR analysis. Similarly to the 1,4-conjugate addition step, a 1:2 mixture of diastereoisomers was obtained in favour of the undesired α-hydroxyketone **307**.

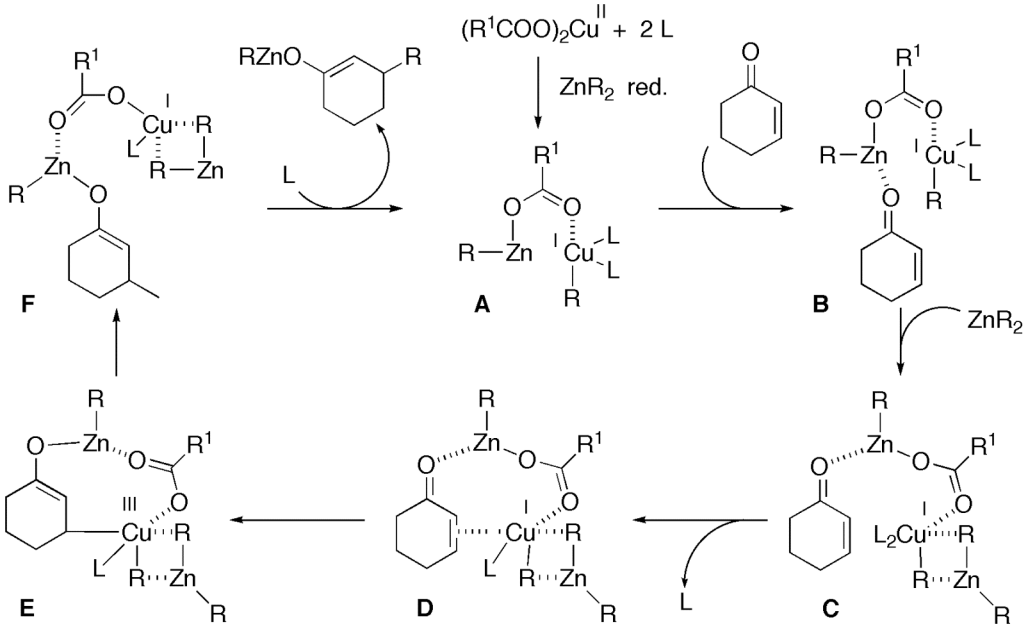
This result highlighted two important things. First, the 1,4-conjugate addition proceeded with the wrong diastereoselectivity (the diastereomeric ratio of the cuprate addition leading to the ketone **303** was deduced from this result). Second, the opening of the silyloxy epoxide was directed by the orientation of the methyl group in β-position relative to the carbonyl. Consequently, the success of this sequence only depends on the diastereoselectivity of the 1,4-conjugate addition. In an attempt to circumvent the lack of diastereselectivity observed with conventional cuprate addition, the use of copper-catalysed asymmetric conjugated addition of dimethylzinc was explored.

3.2.5 Overview of the addition of diorganozinc reagents

Considerable progress has been made during the last decade concerning the design of more effective catalysts and diorganozinc reagents have been added successfully to a variety of substrates.[157] Dimethylzinc has rarely been

[157] (*a*) Wencel-Delord, J.; Alexakis, A.; Crevisy, C.; Maudit, M. *Org. Lett.* **2010**, *12*, 4335; (*b*) Shibata,N.; Okamoto, M.; Yamamoto, Y.; Sakaguchi, S. *J. Org. Chem.* **2010**, *75*, 5707; (*c*) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pamies, O.; Dieguez, M *Chem. Rev.* **2008**, *108*, 2796; (*d*) Brown, M K.; Degrado, S. J.; Hoveyda, H. *Angew. Chem. Int. Ed.* **2005**, *44*, 5306; (*e*) Pena, D.; Lopez, F.; Harutyunyan, S. R.; Minnaard, A. J.;

used, in spite of the fact that it usually provides similar enantioselectivities to diethylzinc. This is because it is much less reactive than diethylzinc and so longer reaction times are required.[157c] The conjugate addition reaction of diorganozinc reagents fits in the generally accepted mechanism of cuprate reactions. The difference lies in the nature of the reactive species, which involve a bimetallic cluster, where copper and zinc are immediately associated. A general scheme can be drawn, although intermediates have not been characterised (Scheme 61).[157c,158]



Scheme 61: Catalytic cycle for the conjugate addition of diorganozinc reagents.[157c]

The copper(II) salt is first reduced to copper(I) by the R_2Zn and reacts with the primary organometallic reagent to form the organocopper reagent **A**. The latter reagent strongly coordinates to the oxygen atom of the enone by the most oxophilic metal (Zn), giving intermediate **B**. However, this type of complex is unable to react and must be transformed into the higher order cuprate **C**. This could also occur before the coordination to the oxygen atom of the enone. The first step toward the conjugate addition is the formation of the π-complex **D**. Following π-complexation, oxidative addition occurs to give the copper(III) intermediate **E**. Reductive elimination then provides the zinc enolate **F** where the zinc is bound to the oxygen atom. The copper species is then released to re-

Feringa, B. L. *Chem. Commun.* **2004**, 1836; (*f*) Knopff, O.; Alexakis, A. *Org. Lett.* **2002**, *4*, 3835; (*g*) March, S.; Alexakis, A. *J. Org. Chem.* **2002**, *67*, 8753; (*h*) Liang, L.; Au-Yeung, T. T. L.; Chan, A. S. C. *Org. Lett.* **2002**, *4*, 3799; (*i*) Leggy, A. A.; Naasz, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2001**, *123*, 5841.

[158] Alexakis, A.; Benhaim, C.; Rosset, M.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262.

enter in the catalytic cycle. The formation of complex **D** determines the absolute configuration of the adduct and the reductive elimination is the rate-determining step. Finally, the nature of the substituents on the phosphorus ligand plays a key role in this step: the higher the number of P–O bonds (versus P–N), the higher the rate of addition.[159]

Recently, phosphoramidite ligands, such as **305** and **308** (Figure 20), have been developed and have been found to afford excellent enantioselectivities in cyclic and linear enones.[154,157e,i]

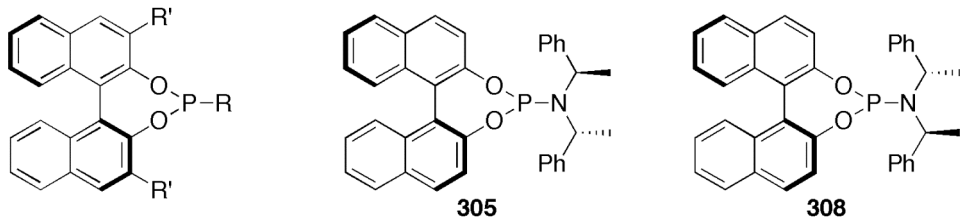


Figure 20: Skeleton of phosphoramidite ligands and selected examples.

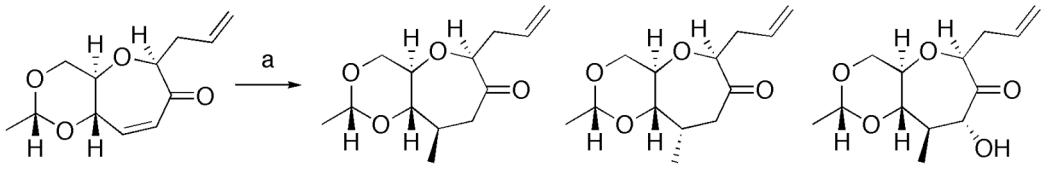
3.2.6 Application to Enone 295

The success of the chiral ligand **305** with related substrates meant that it was a good candidate to test with our substrate. To this end, the general conditions developed by Alexakis and co-workers were exploited (Table 5).[157a,f,g] Starting material was recovered when the reaction was performed at –40 °C and/or at lower concentration than reported by Alexakis (Entries 1-4, Table 5). Performing the reaction at rt for three days afforded a 1:1 mixture of ketone **303** and hydroxyketone **306** (Entries 5, Table 5). As expected from literature precedent,[157f] the utilisation of the chiral ligand **305** afforded a single isomer of the desired adduct. Moreover, the isolation of the hydroxyketone **306** confirmed that the conjugate addition proceeded with the desired selectivity, as only **303** can lead to **306**.

To confirm this result, the reaction was carried out with the chiral ligand **308**. A 10:1 mixture of diastereoimers was obtained (Entry 6, Table 5), and this latter was subjected to the silyl enol ether formation, Rubottom oxidation

[159] Alexakis, A.; Vastra, J.; Mangeney, P. *Tetrahedron Lett.* **1997**, *38*, 7745.

sequence. The resulting mixture was not purified, however, the NMR spectra showed that the compound **307** was the major product obtained. This observation confirmed that the diastereoselectivity of the conjugate addition was reversed affording mainly the adduct **309** (Entry 6, Table 5). It also highlighted the degree of diastereoselectivity induced by the chiral ligand in this reaction. Finally, it has recently been shown that copper salts can catalyse the oxidation of related silyl enol ether in presence of oxygen.[160] Consequently, it was assumed that the oxidation of the intermediate zinc enolate was favoured by the high concentration coupled with the long reaction time and the use of non-degassed toluene.



295 **303** **309** **306**

Entry	Ligand (L*)	T (°C)	[C]	Time	Product(s)
1	**305**	–40	0.1 M	2 h	**295**
2	**308**	–40	0.1 M	2 h	**295**
3	**305**	–40 to rt	0.1 M	overnight	**295**
4	**308**	–40 to rt	0.1 M	overnight	**295**
5	**305**	–40 to rt	0.8 M	3 d	**303:306** = 1:1, 42%:32%
6	**308**	–40 to rt	0.8 M	3 d	**303:309** = 1:10, 75%

Table 5: *Conditions*: (a) Me_2Zn, $CuOTf_2$ (2 mol%), L* (4 mol%), toluene.[157a,f,g]

3.3 Summary

The model study confirmed the viability of the proposed synthetic route and allowed the identification of the key steps of the K-ring synthesis. Seven-membered cyclic enone **283** was synthesised in good yield by RCM reaction of the α-alkoxy enone **291**. A high level of selectivity was obtained from the Tsuji-Trost allylation reaction and the copper-catalysed addition of dimethylzinc proved to be the key step. This reaction delivered good to excellent levels of diastereoselectivity, which is encouraging for its application in the bi-directional

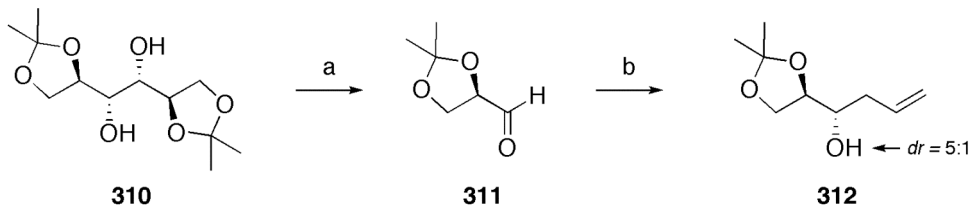
[160] Arai, T.; Takasugi, H.; Sato, T.; Nogushi, H.; Kanoh, H.; Kaneko, K.; Yanagisawa, A. *Chem. Lett.* **2005**, *34*, 1590.

synthesis of the tricyclic core **272**. The unexpected formation of hydroxyketone **306** that occurred during the conjugate addition step is extremely interesting. Quenching the reaction directly with a DMDO solution could be a possible way of reducing the number of steps. Also, the introduction of oxygen gas in the medium would be another solution. Nevertheless, this latter has to be executed carefully due to the presence of highly reactive dimethylzinc.

4 D-Mannitol Derivative Model for I-Ring

4.1 Preparation of Alcohol 315

Following the synthesis of the seven-membered cyclic enone **283**, the enantioselective synthesis of eight-membered congener **319** was explored. Commercially available bisacetonide **310** was subjected to oxidative cleavage using standard sodium periodate conditions[161] to afford two eqivalents of the corresponding aldehyde **311**. Aldehyde **311** was used without further purification in the next step due to its high volatility and its low stability. Previous studies performed in the Clark group have shown that chelation-controlled additions of Grignard reagents to aldehyde **311** proceeded with good diastereocontrol.[162] As a consequence, a solution of **311** in diethyl ether was added to a 1 M solution of allylmagnesium bromide in the presence of $ZnCl_2$. Alcohol **312** was obtainded as a 5:1 mixture of diastereoisomers with the indicated isomer predominating (Scheme 62). The mixture of diastereoisomers was used in the next step as the separation of the epimers was not possible at this stage.

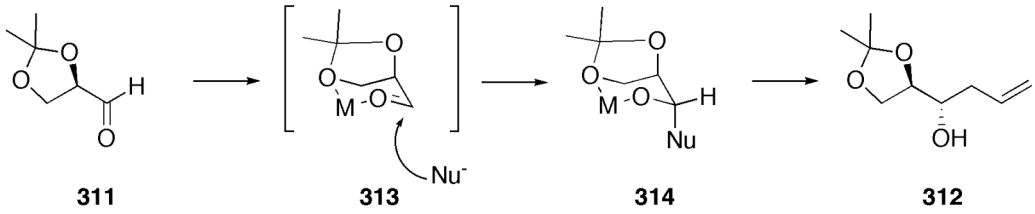


310 **311** **312**

Scheme 62: *Conditions*: (a) $NaIO_4$, CH_2Cl_2/H_2O (22:1), 0 °C to rt; (b) $ZnCl_2$, allylmagnesium bromide, Et_2O, 0 °C to –78 °C then **311**, Et_2O, –78 °C to rt, 73% (2 steps).

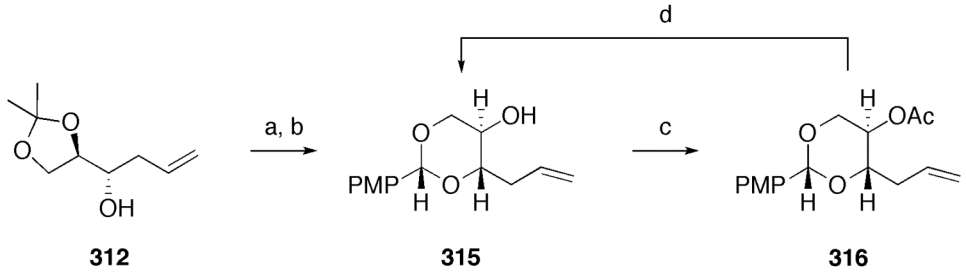
[161] Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447.
[162] Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 127.

The diastereoselectivity of the nucleophilic addition is thought to be linked to the ability of $ZnCl_2$ to chelate glyceraldehydes to form a six-membered chelated system **313** (Scheme 63).[163] The acetonide group protects the upper face forcing the attack to take place from the opposite side.



Scheme 63: Proposed mechanisms.[163]

Acetonide **312** were converted into the corresponding triol by acidic deprotection. Subsequent acid-catalysed reprotection using *p*-methoxybenzaldehyde dimethyl acetal in the presence of CSA and 4 Å molecular sieves afforded acetals **315** as a 5:1 mixture of diastereoisomers. Alcohol **315** was isolated in 50% yield as a sole isomer after crystallisation. The separation of epimers proved easier after conversion into the acetates **316**. Deprotection using K_2CO_3 in methanol proceeded smoothly and gave **315** in quantitative yield (Scheme 64). The NMR data of **312** and **315** were in accordance with the ones reported in the literature and the purity was confirmed by the elemental analysis.[162]



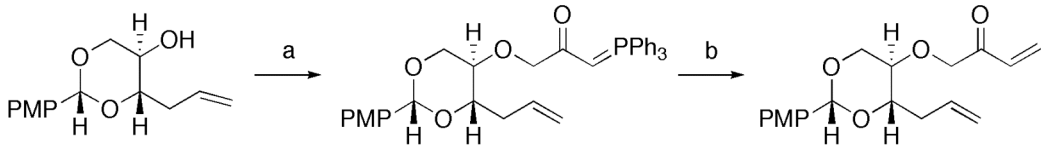
Scheme 64: *Conditions*: (a) TFA, THF/H_2O (9:1), reflux; (b) *p*-methoxybenzaldehyde dimethyl acetal, CSA, CH_2Cl_2, 4 Å MS, rt, 50% (2 steps); (c) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 64%; (d) K_2CO_3, MeOH, rt, quant.

4.2 Synthesis of the Eight-Membered Cyclic Enone 319

With the enantiopure alcohol **315** in hand, the preparation of the RCM precursor **318** was the next objective. Repeating the methodology used

[163] Muzler, J.; Angermann, A. *Tetrahedron Lett.* **1983**, *24*, 2843.

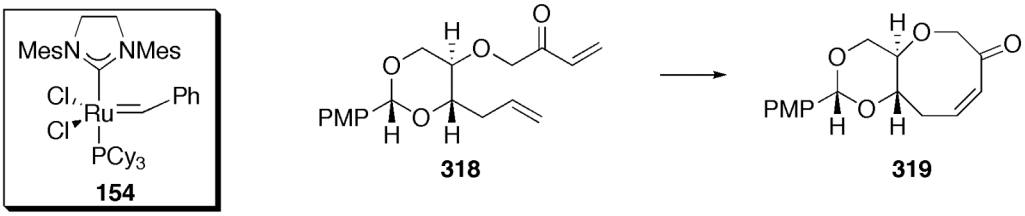
previously, the stabilised phosphonium ylide **317** was formed and treated with aqueous formaldehyde under buffered conditions to afford **318** in 83% yield over two steps (Scheme 65).



315 **317** **318**

Scheme 65: *Conditions*:(a) NaH, $ClCH_2COCHPPh_3$, TBAI, THF, rt then reflux; (b) CH_2O, pH = 7 buffer solution, Et_2O, rt, 83% (2 steps).

The formation of eight-membered heterocycles is widely described in the literature as one of the most difficult challenges in the arena of ring construction.[164] RCM reactions that form medium rings are reported to require high catalyst loading, high dilution, long reaction times, and more importantly, some degree of "gearing" of appropriately placed substituents to deliver acceptable yields of cycloalkene products. These factors combine to severely restrict scaleability.[165] Although, RCM reaction of precursor **318** was carried out immediately after purification, decomposition was a significant problem (Entry 1-3 and 5-8, Table 6).



154 **318** **319**

Entry	Catalyst 154	Solvent	[C]	T (°C)	time	Ti(O*i*-Pr)$_4$	Yield of 319
1	10 mol%	CH_2Cl_2	7.5 mM	reflux	15 h	–	decomposed
2	5 mol%	CH_2Cl_2	5 mM	reflux	15 h	30 mol%	decomposed
3	5 mol%	CH_2Cl_2	5 mM	rt	15 h	30 mol%	decomposed
4	5 mol%	toluene	5 mM	45 °C	3 h	30 mol%	15% (40 brsm)
5	5 mol%	toluene	5 mM	45 °C	24 h	30 mol%	decomposed
6	5 mol%	toluene	5 mM	rt	15 h	30 mol%	decomposed
7	3 mol%	toluene	5 mM	rt	15 h	30 mol%	decomposed
8	5 mol%	toluene	1 mM	rt	15 h	30 mol%	decomposed

Table 6: Attempted RCM reaction.

[164] (*a*) Chattopadhyay, S. K.; Karmakar, S.; Biswas, T.; Majumdar, K. C.; Rahaman, H.; B. Roy *Tetrahedron* **2007**, *63*, 3919; (*b*) Michaut, A.; Rodriguez, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 5740; (*c*) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199.

[165] Mitchell, L.; Parkinson, J. A.; Percy, J. M.; Singh, Kuldip *J. Org. Chem.* **2008**, *73*, 2389 and references therein.

It has been shown that the presence and position of certain functional groups, such as esters, ketones, ethers, in the starting material is crucial to the success of metathesis reactions.[166] The polar group acts as a relay for the evolving carbene species, which positions the reacting sites within the coordination sphere (complex **A** or similar, Figure 21). However, if such a complex becomes too stable, as might be the case with the five- and six-membered chelated structures **B** and **C**, the catalyst can be trapped in the form of an unproductive complex and cyclisation will not occur.

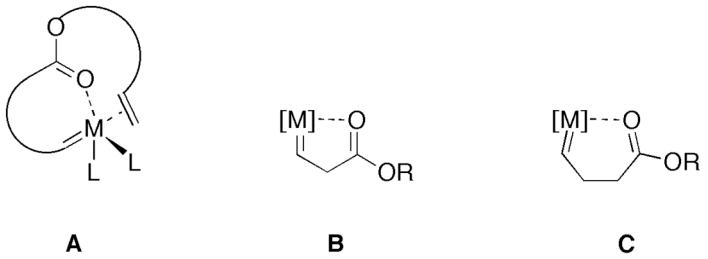


Figure 21: General representation of the chelated structures.[166]

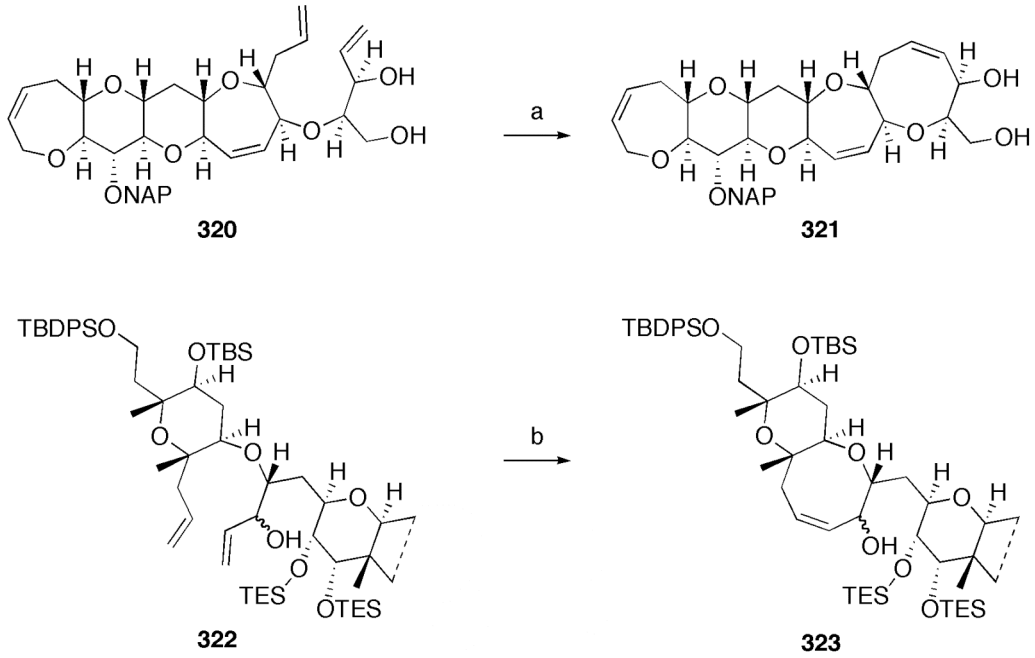
The utilisation of a Lewis acid has been reported to be successful in cases where chelation with polar group is problematic. For example, Ti(O*i*-Pr)$_4$ has been used to prevent the formation of an unproductive complex during the cyclisation process.[167] Unfortunately, no significant changes were observed when the Lewis acid was added to enone **318**. Modifying the reaction time, the temperature of the reaction as well as the concentration and solvent parameters did not make the reaction more successful. In the best case, enone **319** was isolated in only 15% yield (Entry 4, Table 6). The RCM precursor **318** proved to be extremely unstable and it was speculated that structural modifications of this substrate would avoid this problem and improve the rather disappointing yield from the key RCM reaction.

4.3 Tuning of the Synthetic Pathway

Several authors have reported the effects exerted by allylic substituents on RCM reaction yields as well as regiochemical outcome of these reactions.[165] At first, it was believed that the presence of an allylic alcohol adversely affects

[166] (*a*) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792; (*b*) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 8746.
[167] (*a*) Kaliappan, K. P.; Kumar N. *Tetrahedron* **2005,** *61*, 7461; (*b*) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130.

metathesis reactions at the adjacent double bond, presumably by strong coordination with the catalyst thereby arresting the cycle.[168] The literature also refers to the capability of some protecting groups to direct the catalyst selectivity to one olefin moiety.[169] However, recent reports suggested that an allylic hydroxyl group can assist the RCM process.[170] In the most cited article,[170b] Hoye and Zhao concluded that "free allylic hydroxyl groups exerted a large activating effect upon the initial carbene exchange reaction with an adjacent vinyl group...". Moreover, the utilisation of an allylic alcohol as a substrate has proved to be successful in the syntheses of eight- membered ether rings.[171] For example, cyclisation of RCM precursors **320** and **322** in the presence of catalyst **152** afforded **321** and **323** in 92% and 68% yield, respectively (Scheme 66).

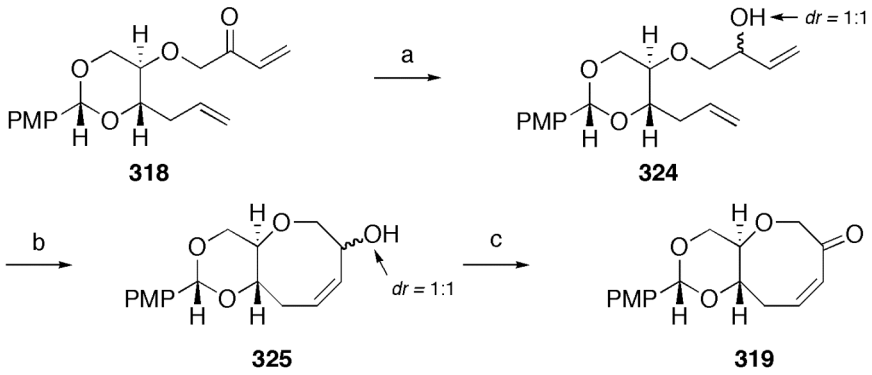


Scheme 66: *Conditions*:(a) catalyst **152** (10 mol%), CH_2Cl_2, rt, 92%; (b) catalyst **152** (8 mol%), toluene, reflux, 68%.

Our synthetic strategy was modified according to these observations. Luche-reduction of enone **318** afforded a 1:1 diastereomeric mixture of allylic alcohols **324** in 90% yield (Scheme 67). Fortunately, dramatic increases of the reaction yield were observed when alcohols **324** underwent RCM reaction in the presence of the Grubbs second-generation catalyst **154** (Entries 1 and 2, Table

[168] Maishal, T. K.; Shinha-Mahapatra, D. K.; paranjape, K.; Sarkar, A. *Tetrahedron Lett.* **2002**, *43*, 2263.
[169] For reports of significant substituent effects on RCM outcomes see ref. 167.
[170] (*a*) Schmidt, B.; Nave, S. *Chem. Commun*. **2006**, 2489; (*b*) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 1123.
[171] (*a*)Kobayashi, S.; Takahashi, Y.; Komano, K.; Alizadeh, B. H.; Kawada, Y.; Oishi, T.; Tanaka, S.; Ogasawara, Y.; Sasaki, S.; Hirama, M. *Tetrahedron* **2004**, 60, 8375; (*b*) Torikai, K.; Watanabe, K.; Minato, H.; Imaizumi, T.; Murata, M.; Oishi, T. *Synlett* **2008**, 2368.

7). Performing the reaction in the presence of the Hoveyda-Grubbs second-generation catalyst **187** afforded even better yields of the alkene **325** (Entries 3 and 4, Table 7). The alcohols **325** were isolated in 73% yield and subsequent oxidation with DMP afforded the eight-membered cyclic enone **319** in 86% yield (Scheme 67). Once again, data were in accordance with the one reported in the literature for the enone **319**.[162]



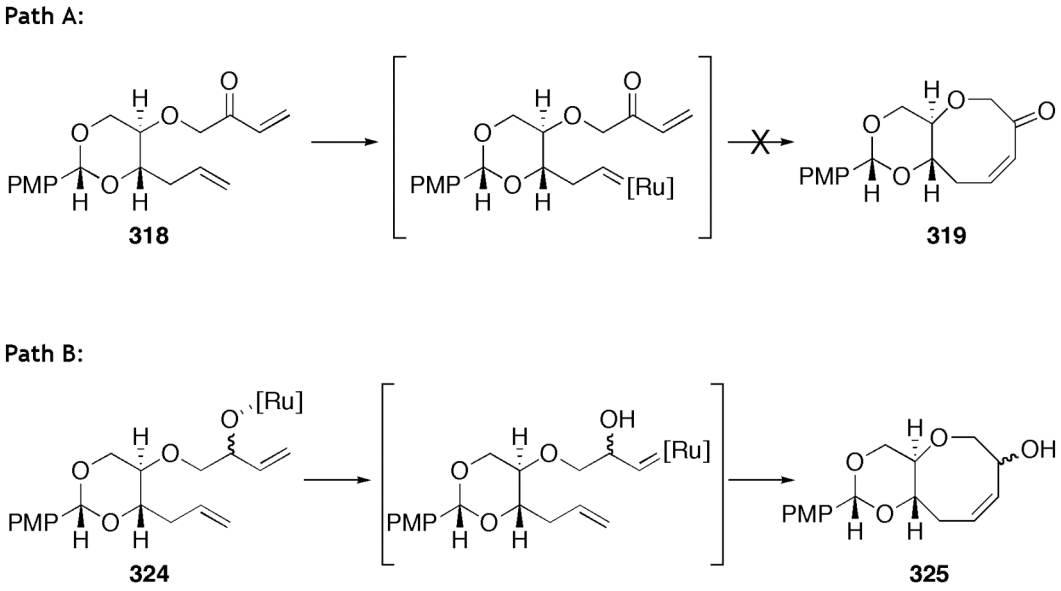
Scheme 67: *Conditions*: (a) $CeCl_3.7H_2O$, $NaBH_4$, MeOH, rt, 90%; (b) catalyst **154** or **187**, CH_2Cl_2, reflux, 56–73%; (c) DMP, CH_2Cl_2, rt, 86%.

Entry	Catalyst	[C]	Yield of 325
1	**154**	5 mM	56%
2	**154**	1 mM	63%
3	**187**	5 mM	63%
4	**187**	1 mM	73%

Table 7: Conditions and results for the RCM reaction.

These contrasting results can be explained as follow. Starting from the dienone **318**, the first [2+2] cycloaddition reaction occurs between the more electron-rich double bond and the catalyst to lead to a new ruthenium carbene. Ideally, the second [2+2] cycloaddition reaction would take place between the newly formed carbene and the enone double bond to afford the metallocyclobutane, which, after [2+2] cycloreversion would deliver the cyclic enone **319** (Path A, Scheme 68). However, the electron deficient character of the enone double bond makes the rate of cyclisation very slow, allowing competing reactions to take place, and the decomposition of the starting material. On the other hand, due to the chelation with the allylic alcohol on diene **324**, the first [2+2] cycloaddition reaction takes place at the electron deficient site. The remaining electron-rich olefin can easily undergo a [2+2] cycloaddition reaction with the newly formed carbene to deliver **325** (Path B,

Scheme 68). In addition, the stability of the RCM precursor was dramatically increased by the reduction of the enone function into the corresponding allylic alcohol.



Scheme 68: Key intermediates for the RCM reaction.

4.4 Summary

This model study led to the eight-membered cyclic enone **319** in a high yielding fashion (17% yield over 8 steps, average of 80% per step). Nevertheless, the problem of stability, and therefore of cyclisation, encountered, will have to be taken into consideration when implementing the bi-directional strategy.

5 Bi-Directional Synthesis

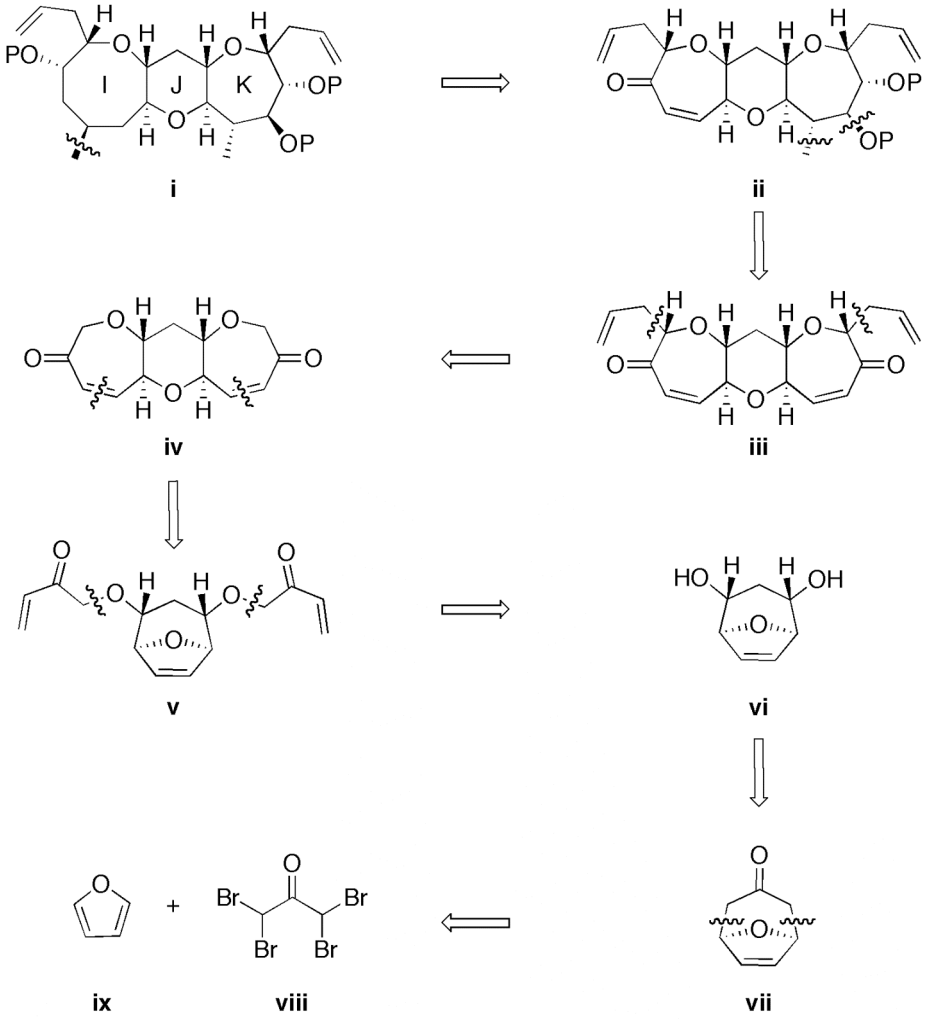
5.1 Retrosynthetic Analysis

Originally, the key step of our analysis was a double RCM reaction of the almost symmetrical tetraene **326**, which was intended to deliver the tricyclic skeleton **327** (Scheme 69).

326 **327**

Scheme 69: Key step of the original approach.

However, the problems encountered during the synthesis of the D-mannitol-derived model system led us to modify our approach to the IJK fragment **i**. As a consequence, our retrosynthetic analysis commences with functional group interconvention on the I-ring. A further 1-C ring contraction of this latter gives ketone **ii**. Ketone **ii** can be seen as the result of the desymmetrisation of tetraene **iii**. Double retro *C*-alkylation affords the meso dienone **iv** from which retro RORCM delivers the bicyclic triene **v**. Cleavage of the ether side chains leads to diol **vi** and further functional group manipulations deliver the ether bridged seven-membered ring **vii**. Finally, retro [4+3] cycloaddition affords tetrabromoacetone **viii** and furan **ix** (Scheme 70).

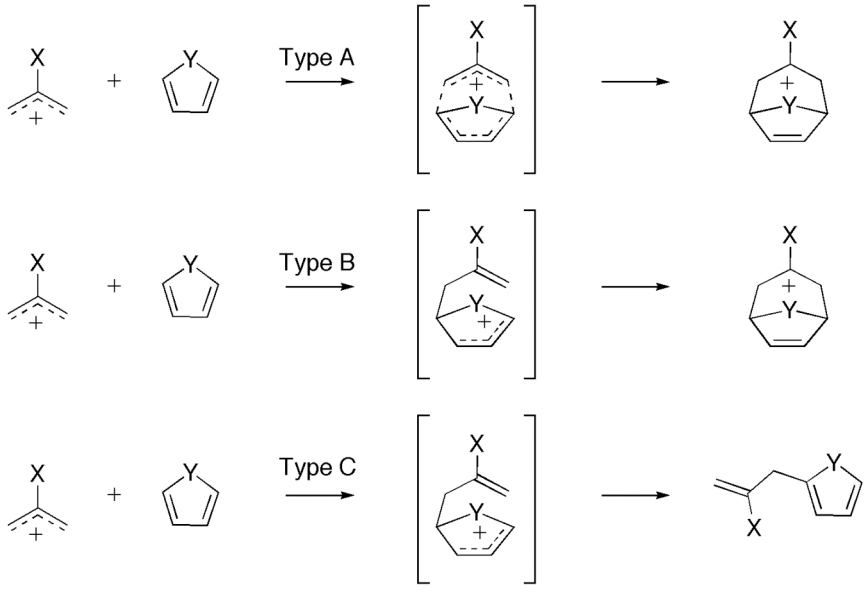


i **ii** **iii** **iv** **v** **vi** **vii** **viii** **ix**

Scheme 70: Retrosynthetic analysis for the two-directional synthesis of the IJK fragment.

5.2 Formation of the Ether-Bridged Seven-Membered Ring 332

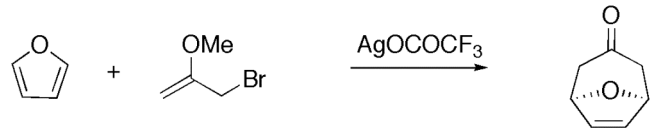
The [4+3] cycloaddition reaction of allylic cations and dienes is a convenient way to prepare complex seven-membered rings from simple starting materials.[172] Several features of this reaction are noteworthy (Scheme 71). Firstly, the product formed from the reaction depends on the nature of the "X and Y" groups. Typically, the "X" group is an oxygen functionality whereas the "Y" group can be an oxygen, nitrogen or sulfur atom. In the early days of [4+3] cycloaddition reactions, Hoffmann defined three categories for the reaction of allylic cations with dienes.[173] Type A processes are concerted reactions that lead to [4+3] cycloadducts. Stepwise processes, to give [4+3] cycloadducts, were also identified (Type B). Theoretical studies suggest that both concerted and stepwise mechanisms are possible.[174] Reactive and strongly electrophilic allylic cations tend to react with nucleophilic dienes *via* stepwise processes, whereas less electrophilic cations and less nucleophilic dienes tend to react *via* concerted mechanisms.[174] Finally, type C products arise *via* a stepwise mechanism in which the final bond-forming step is thwarted in favour of a competing side reaction, leading to products of electrophilic addition or substitution (Scheme 71).



Scheme 71: Mechanisms for the [4+3] cycloaddition.[173]

[172] Harmata, M. *Acc. Chem. Res.* **2001**, *34*, 595.
[173] (*a*) Hoffmann, H. M. R. *Angew. Chem. Int. Ed.* **1984**, *23*, 1; (*b*) Hoffmann, H. M. R. *Angew. Chem. Int. Ed.* **1973**, *12*, 819.
[174] Cramer, C. J.; Barrows, S. E. *J. Phys. Org. Chem.* **2000**, *13*, 176.

Bicyclo[3.2.1]ketones are interesting building blocks as these are potentially versatile platforms for a variety of subsequent transformations and are potential precursors for a broad range of natural products.[175] Originally, oxygen-containing systems were prepared by the reaction of 2-methoxyallyl bromide with silver trifluoroacetate in the presence of furan (Scheme 72).[173]



Scheme 72: Silver salt route to oxabicyle.[173]

Under carefully controlled conditions, the bicyclo[3.2.1]ketones were obtained in greater than 50% yield.[173b] However, important experimental problems had to be circumvented especially the polymerisation of the 2-methoxyallyl bromide. It has been shown that the methoxy grouping alters the reactivity pattern, but the reaction mechanism was not clearly defined.[173b] The nature of the silver anion, which acts as a co-catalyst, appears to be particularly important. Trifluoroacetate represents a good compromise, in that, this anion is not sufficiently nucleophilic to trap substantial amount of the intermediate allyl cation. It was postulated that it might stabilise the intermediate allyl cation (Figure 22).[173b]

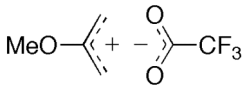
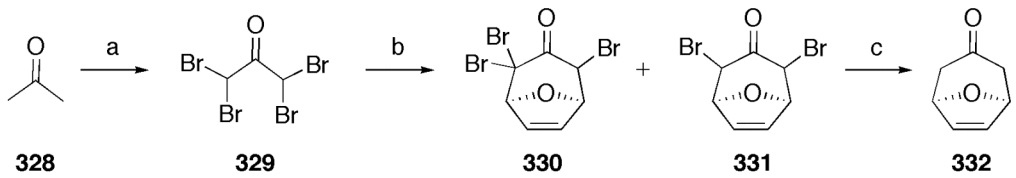


Figure 22: Stabilisation of the allyl cation.[173b]

Further routes to bicyclo[3.2.1]ketones were soon developed.[176] In particular Hoffmann and co-workers developed an inexpensive, easily scalable and reproducible procedure, that has been employed extensively (Scheme 73).[176,177] Utilising the Hoffmann protocol, our synthesis begins with the formation of the 1,1,3,3-tetrabromopropanone (**329**) from acetone (**328**). The [4+3] cycloaddition reaction with furan was initiated by the addition of a

[175] Mihovilovic, M.D.; Grötzl, B.; Kandioller, W.; Snajdrova, R.; Muskotal, A.; Bianchi, D. A.; Stanetty, P. *Adv. Synth. Catal.* **2006**, *348*, 463.
[176] Kim, H.; Hoffmann, H. M. R. *Eur. J. Chem.* **2000**, 2195 and references therein
[177] Hoffmann, H. M. R.; Iqbal, M. N. *Tetrahedron Lett.* **1975**, *16*, 4487.

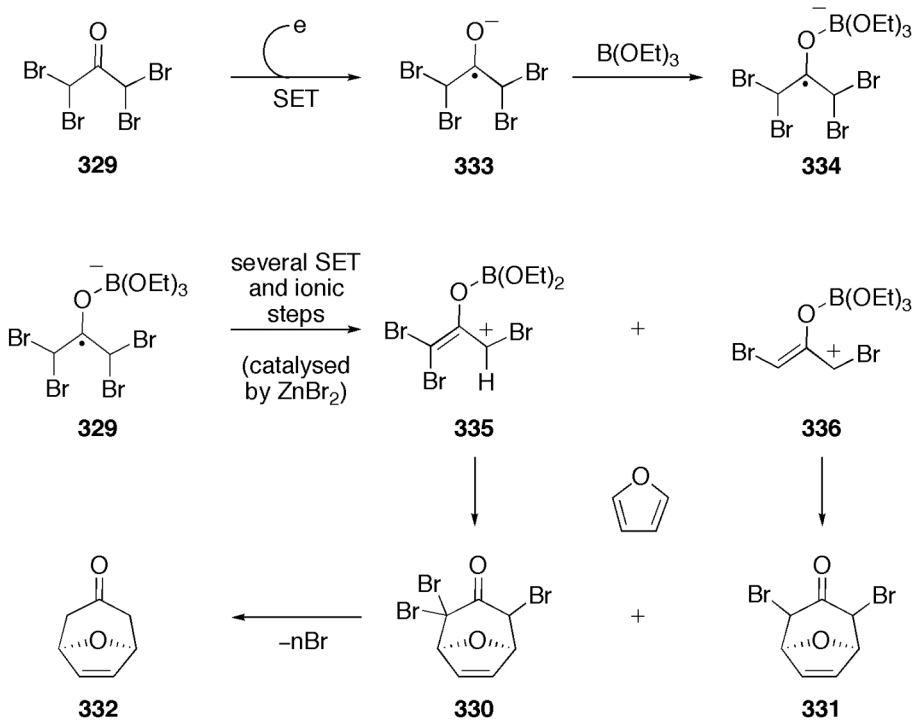
catalytic amount of bromine in the presence of activated zinc and triethylborate to afford a mixture of brominated cycloadducts **330** and **331**. The crude mixture was then subjected to debromination using a suspension of zinc-copper couple and NH_4Cl in methanol. Due to the decomposition of **332** at rt on extended contact with acid, **332** was filtered through a short column of solid K_2CO_3 to remove HBr.[176] The bicyclo[3.2.1]ketone **332** was finally isolated in 47% overall yield, and the data obtained for **332** were in concordance with the ones reported by Hoffmann (Scheme 73).[176]



Scheme 73: *Conditions*: (a) Br_2, HBr (48% aqueous solution), 0 °C to rt, 46%; (b) Furan, activated Zn, $B(OEt)_3$, Br_2, THF, 40 °C; (c) Zn/Cu, NH_4Cl, MeOH, – 78 to 0 °C, 47% (2 steps).

The [4+3] cycloaddition reaction is clearly the limiting step of this sequence. However, the high water solubility of **332** also explained the disappointingly low yield obtained.[178] As mentioned previously, cycloaddition is initiated by the addition of a catalytic amount of bromine and the mechanism can be thought of as single electron transfer (SET) process. The reaction is facilitated by triethyl borate, alternating with Lewis acid mediated ionic steps, to generate the crucial boron oxyallyl cations, such as **335** and **336**, which react with furan to yield the brominated bicyclic ethers **330** and **331** (Scheme 74).[176]

[178] 52-56% yield reported by Hoffmann and co-workers for this sequence.

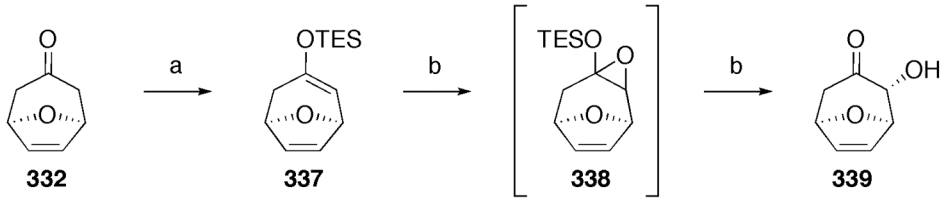


Scheme 74: Mechanism proposed by Hoffmann.[176]

5.3 Functionalisation of *Meso*-Ketones 332

5.3.1 Synthesis of Alcohol 346

With the *meso*-ketone **332** in hand,[179] functionalisation of this scaffold was explored. Once again the procedure reported by Hoffmann was followed. [180] Firstly, the silyl enol ether **337** was prepared by deprotonation with LDA followed by, in situ, quenching with TESCl. Oxidation with *m*-CPBA afforded the corresponding silyloxy epoxide. Treatment with TFA gave the known hydroxyketone **339** in 42% overall yield (Scheme 75).[180]

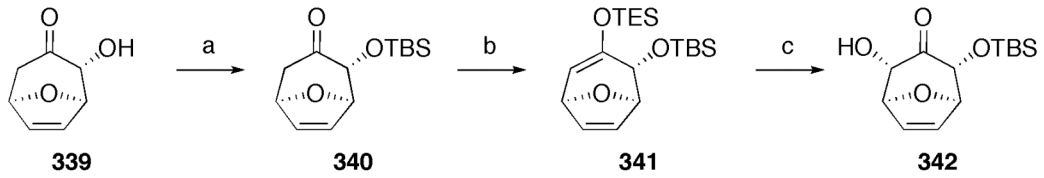


Scheme 75: *Conditions*: (a) DIPA, *n*-BuLi, THF, –78 °C then **332**, TESCl, Et_3N, THF, –78 °C; (b) *m*-CPBA, THF/H_2O (1:1), 0 °C then TFA, 0 °C, 42% (2 steps).

[179] More than 500 mmol were prepared.
[180] Hoffmann, H. M. R.; Dunkel, R.; Mentzel, M.; Reuter, H.; Stark, C. B. W. *Chem. Eur. J.* **2001**, *7*, 4771.

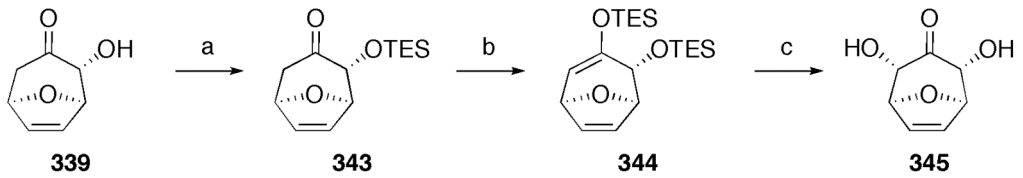
It was found by Hoffmann that a 1:1 mixture of THF/H_2O was essential in order to minimise side reactions. Under optimised conditions, the regeneration of ketone **332** by protonation of enolate intermediate was not observed. An excess of *m*-CPBA may lead to epoxidation of the etheno bridge and may partially explain the low yield of the sequence. Performing the epoxidation reaction with a solution of DMDO should afford better selectivity but this has not been attempted. Finally, a treatment with acid ensured that the Rubottom rearrangement took place and that the hydrolysis of the resulting α-silyloxy ketone delivered **339** (Scheme 75).

The TBS-protection of hydroxyketone **339** gave ketone **340** in 94%. The latter underwent the same sequential silyl enol ether formation, epoxidation and hydrolytic epoxide cleavage as **332** and delivered the α-hydroxyketone **342** in 59% yield overall (Scheme 76).[180]



Scheme 76: *Conditions*: (a) TBSCl, imidazole, CH_2Cl_2, rt, 94%; (b) DIPA, *n*-BuLi, THF, –78 °C then **339**, TESCl, Et_3N, THF, –78 °C; (b) *m*-CPBA, THF/H_2O (1:1), 0 °C then TFA, 0 °C, 59% (2 steps).

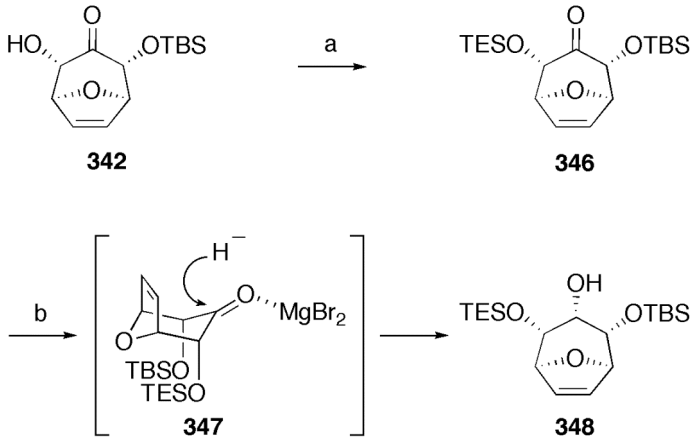
Carrying out the sequence with the TES-protected ketone **343**, in place of the TBS-protected **340**, should have yielded the dihydroxyketone **345** (Scheme 77). However, the water solubility of **345** is so high that it was impossible to extract it from the aqueous layer during workup. The TBS-protecting group was chosen for its relative stability and also for its reasonable bulkiness.[180]



Scheme 77: *Conditions*: (a) TESCl, imidazole, CH_2Cl_2, rt, 27%; (b) DIPA, *n*-BuLi, THF, –78 °C then **339**, TESCl, Et_3N, THF, –78 °C; (b) *m*-CPBA, THF/H_2O (1:1), 0 °C then TFA, 0 °C, not isolated.

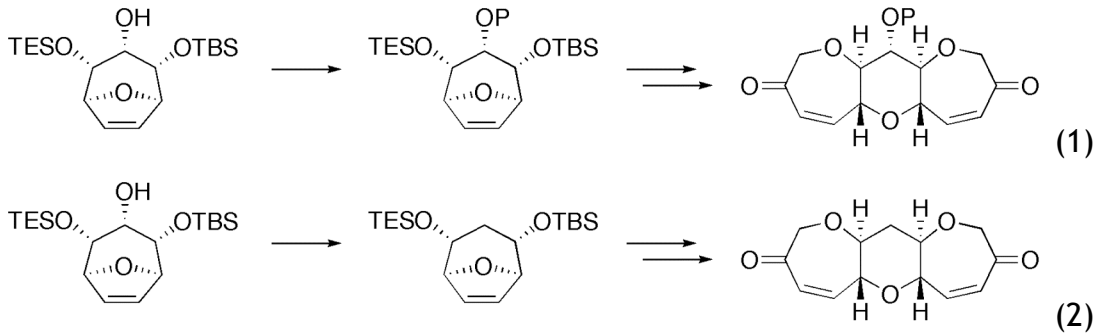
The subsequent protection of the hydroxyl group afforded the silyl ether **346** in good yield. The stereoselective reduction of ketone **346** was performed

with $NaBH_4$ in the presence of $MgBr_2$. Here, the chelation between $MgBr_2$ and the oxygen atoms of **347** is partially inhibited by the sylil groups. As a consequence, $MgBr_2$ play the role of an activating agent of the carbonyl towards the hydride attack. The steric hindrance on the bottom face of **347** orientates the hydride attack from the upper face and alcohol **348** was isolated as the sole isomer, as reported by Hoffmann (Scheme 78).[180,181]



Scheme 78: *Conditions*: (a) TESCl, imidazole, CH_2Cl_2, rt, 80%; (b) $MgBr_2$, $NaBH_4$, MeOH, 0ºC, 96%.

At this stage of the synthesis, two divergent strategies were envisaged. The deoxygenation of bicyclic alcohol **348** could be performed after subsequent transformations or as the next step. While the first possibility would allow us to test the key RORCM reaction more rapidly, the second strategy represents a more direct approach to the synthesis of the target molecule (Scheme 79). Ultimately, both routes were investigated.

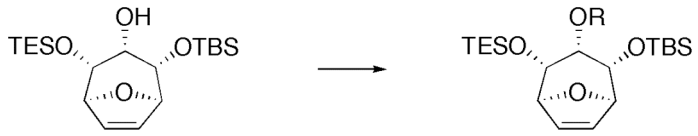


Scheme 79: Divergent strategies envisaged.

[181] Chen, X.; Hortelano, E.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778.

5.3.2 Attempts to Protect Alcohol 346

Protection of alcohols as PMB- or Bn-ethers is commonly used in polycyclic ether synthesis. Unfortunately, none of the numerous attempts to protect the alcohol **348** was successful. Performing the reaction in THF led to the recovery of starting material (Entry 1, Table 8). The reaction was then performed in DMF or a mixture DMF/THF. Screening of hydride sources and a range of reaction temperatures gave only decomposition (Entries 2-7, Table 8). It was hypothesised that the alkoxy intermediate was unstable and the hydroxyl group was too sterically-hindered to be protected. As a consequence this route was abandoned.



348 **349**

Entry	R	Conditions	Base	Yield
1	PMB	a	NaH	**348**
2	PMB	b	NaH	decomposition
3	PMB	c	NaH	decomposition
4	Bn	d	NaH	decomposition
5	Bn	e	NaH	decomposition
6	Bn	f	KH	decomposition
7	Bn	g	KH	decomposition

Table 8: *Conditions*: (a) NaH, PMBCl, TBAI, THF, 0 °C then rt; (b) NaH, PMBCl, TBAI, THF, 0 °C then rt; (c) NaH, PMBCl, TBAI, THF/DMF (3:1), 0 °C then rt; (d) NaH, BnBr, TBAI, THF, 0 °C then reflux; (e) NaH, BnBr, TBAI, THF/DMF (3:1), 0 °C then reflux; (f) KH, BnBr, TBAI, THF/DMF (3:1), 0 °C; (g) KH, BnBr, TBAI, THF/DMF (3:1), −40 to 0 °C.

5.3.3 Deoxygenation Strategy

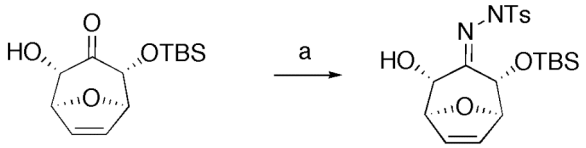
Few methods are available for the direct deoxygenation of ketones. The two principal reactions are the Wolf-Kishner reduction[182] and Barton-McCombie deoxygenation of the corresponding alcohol.[183] It has been shown that sterically hindered carbonyl compounds are slowly deoxygenated under the Wolf-Kishner conditions and the reaction requires high temperature. Conversely, the

[182] (*a*) Kishner, N. J. *Russ. Phys. Chem. Soc.* **1911**, *43*, 582; (*b*) Wolf, L. *Liebigs Ann. Chem.* **1912**, *394*, 23.
[183] Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

tributyltin compounds used in the Barton-McCombie reaction are toxic[184] and frequently cause purification problems.[185] However, a third option for the deoxygenation of ketones *via* their tosylhydrazones by a three step-sequence, represents an interesting alternative.[186]

5.3.3.1 Deoxygenation via the Sinhababu Protocol.[186c]

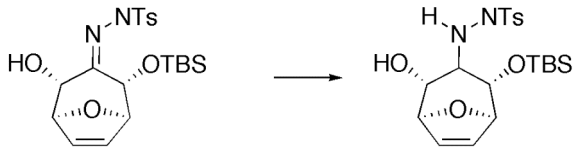
Tosylhydrazone **350** was prepared from hydroxyketone **342** in a quantitative manner (Scheme 80).[186b] Reduction was attempted on the crude hydrazone **350** (Table 9). The pH-dependent reduction of the tosylhydrazone **350** with $NaBH_3CN$ in THF/MeOH led to the recovery of the starting material (Entry 1). The same result was obtained when $NaBH_4$ or $LiBH_4$ was employed as the reductant (Entries 2 and 3).[187] Performing the reaction at reflux led to decomposition of the tosylhydrazone **350** (Entry 4). Finally, attempted reduction with triethylsilane in TFA also gave rise to decomposition (Entry 5).[188] Despite numerous attempts, the tosylhydrazine **351** was never isolated. It was concluded that tosylhydrazone **350** was either too sterically hindered or too stable to be reduced and other approaches were explored.



342 **350**

Scheme 80: *Conditions*: (a) $TsNHNH_2$, MeOH, rt quant.

[184] Boyer, I. J. *Toxicology* **1989**, *55*, 253.
[185] (*a*) Perchyonok, V. T. *Tetrahedron Lett.* **2006**, *47*, 5163; (*b*) Studer, A.; Amrein, S.; Scleth, F.; Schulte, T.; Walton, J. C. *J. Am. Chem. Soc.* **2003**, *125,* 5726; (*c*) Studer, A.; Amrein, S. *Angew. Chem. Int. Ed.* **2000**, *39*, 3080; (*d*) Lopez, R. M.; Hays, D. S.; Fu, G.C. *J. Am. Chem. Soc.* **1997,** *119*, 6949.
[186] (*a*) Ghosh, A. K.; Li, J. *Org. Lett.* **2009**, *11*, 4164; (*b*) Thompson, C. F.; Jamison, T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2000**, *122*, 10482; (*c*) Nair, V.; Sinhababu, A. K. *J. Org. Chem.* **1978**, *43*, 5013.
[187] Hasegawa, K.; Arai, S.; Nishida, A. *Tetrahedron* **2006**, *62*, 1390.
[188] Wu, P. L.; Peng, S. Y.; Magrath, J. *Synthesis* **1996**, 249.



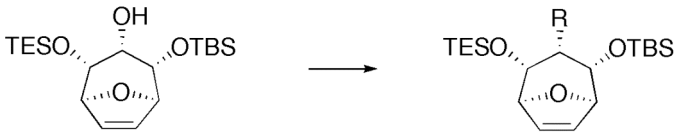
350 **351**

Entry	Conditions	Yield
1	a	**350**
2	b	**350**
3	c	**350**
4	d	decomposition
5	e	decomposition

Table 9: *Conditions*: (A) $NaBH_3CN$, 1.25 N HCl in EtOH, methyl orange, THF/MeOH (1:1), 0 °C, pH >3.8; (b) $NaBH_4$, MeOH, AcOH, rt; (c) $LiBH_4$, THF, 0 °C; (d) $NaBH_4$, MeOH, AcOH, reflux; (e) Et_3SiH, TFA, 0 °C.

5.3.3.2 Leaving Group Displacement

The reductive displacement of the hydroxy group from alcohol **348** after conversion into the corresponding iodide[189] or mesylate[190] was explored. Attempts to form the iodide **352a** resulted in decomposition whereas attempted formation of the mesylate **352b** resulted in the recovery of the starting material (Table 10).



348 **352**

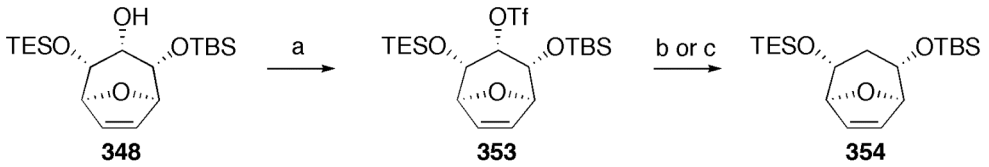
Entry	Conditions	R	Yield
1	a	I	decomposed
2	b	OMs	**348**

Table 10: *Conditions*: (a) PPh_3, imidazole, I_2, toluene, reflux, (b) $MeSO_2Cl$, Et_3N, DMAP, CH_2Cl_2, 0 °C.

Finally, it was possible to form the triflate **353** probably as a result of the higher reactivity of triflic anhydride compared to mesyl chloride. However, the

[189] Filali, H.; Ballereau, S.; Chahdi, F. O.; Baltas, M. *Synthesis* **2009**, 251.
[190] Honzawa, S.; Yamamoto, Y.; Yamashita, A.; Sugiura, T.; Kurihara, M.; Arai, M. A.; Kato, S.; Kittaka, A. *Bioorg. Med. Chem.* **2008**, *16*, 3002.

subsequent hydride displacement reaction proved to be unsuccessful (Table 11).[191]

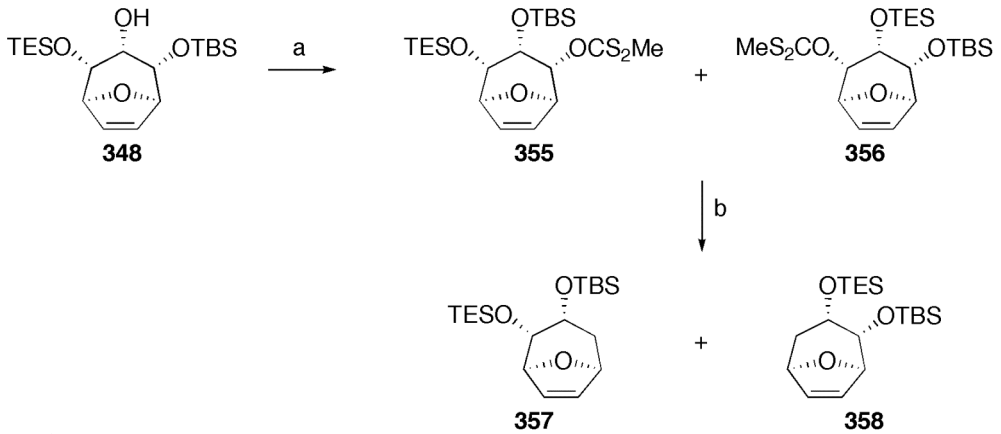


Entry	Conditions	Yield
1	b	**353**
2	c	**353**

Table 11: *Conditions*: (a) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0 °C; (b) $NaBH_4$, MeOH, –78 to 0 °C; (c) *n*-Bu_4NBH_4, CH_2Cl_2, 0 °C.

5.3.3.3 The Barton-McCombie Deoxygenation

Finally, the Barton-McCombie deoxygenation reaction was investigated. Disappointingly, 1,2-migration of both the TES- and TBS-groups occurred during the formation of the dithiocarbonate leading to the formation of xanthates **355** and **356**, respectively. This migration became apparent after the radical-mediated deoxygenation was performed and compounds **357** and **358** were isolated (Scheme 81). These two structures were determined thanks to their two-dimensional NMR analyses (COSY).



Scheme 81: *Conditions*: (a) NaH or KH, CS_2, MeI, THF, 0 °C, quant.; (b) AIBN, Bu_3SnH, C_6H_6, 80-90 °C, 59%.

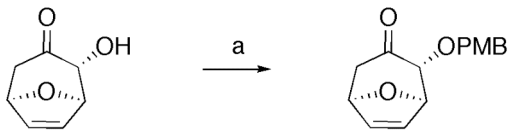
[191] (*a*) Sun, D. Q.; Busson, R.; Herdewij, P *Eur. J. Org. Chem.* **2009**, 5158; (*b*) Böhm, M.; Lorthiois, E. *Helv. Chim. Acta* **2003**, *86*, 3818

In spite of the competing 1,2-migration of the silyl groups, the formation of **357** and **358** was a promising result because it suggested that a change of protecting group should allow the formation of the protected diol **374**.

5.4 Revised Route to the Functionalisation of *Meso*-Diol 374

5.4.1 Synthesis of Alcohol 364

Revising the deoxygenation approach led to changes in the protecting group strategy. The PMB-protecting group offered several advantages including the ability to be installed under either acidic[192] or basic[193] conditions and is generally cleaved using mild conditions that would not interfere with the alkene in the substrate. Due to the base sensitivity of our substrate, the protection of hydroxyketone **339** was performed under acid-catalysis; reaction with 4-methoxybenzyltrichloroacetamidate and a catalytic amount of CSA yielded ketone **359** in 85% yield (Scheme 82).

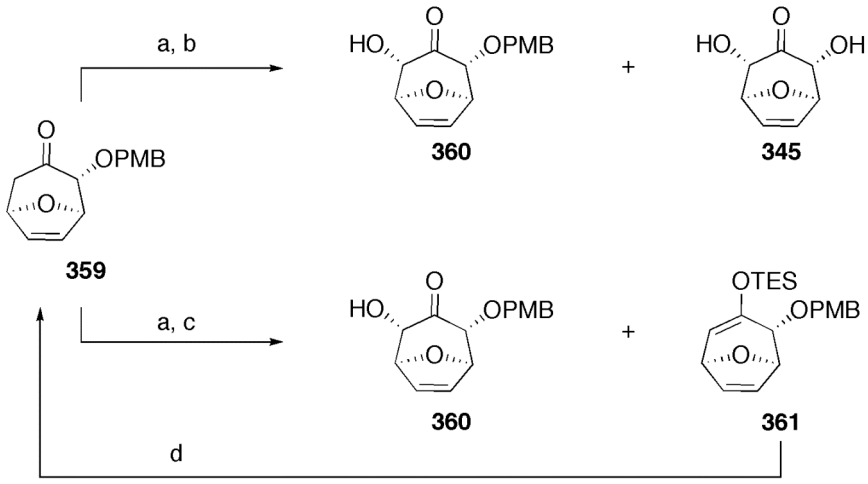


339 **359**

Scheme 82: *Conditions*: (a) 4-methoxybenzyltrichloroacetamidate, CSA, CH_2Cl_2, rt, 85%.

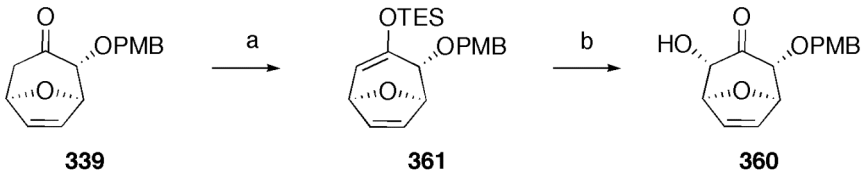
Sequential silyl enol ether formation, epoxidation and hydrolytic epoxide cleavage was repeated on ketone **359**. Using the same conditions as before, the hydroxyketone **360** was obtained in 32% overall yield. The modest yield was attributed to the acidic workup. It has been shown that TFA can deprotect PMB-ethers,[194] which would result in the formation of the water-soluble dihydroxyketone **345**. To circumvent this problem the sequence was performed using $NaHCO_3$ buffered *m*-CPBA and without any acidic treatment. Using these optimised conditions, a mixture of hydroxyketone **360** and silyl enol ether **361** was obtained in 25% yield. TBAF deprotection of **361** afforded the ketone **359** in 71% yield (Scheme 83).

[192] Walkup, R. D.; Kane, R. R.; Boatman, P. D.; Cunningham, R. T. *Tetrahedron Lett.* **1990**, *31*, 7587.
[193] Marco, J. L.; Hueso-Rodriguez, J. A. *Tetrahedron Lett.* **1988**, *29*, 2459.
[194] Yan, L.; Kahne, D. *Synlett* **1995**, 523.



Scheme 83: *Conditions*: (a) DIPA, *n*-BuLi, THF, –78 °C then **359**, TESCl, Et_3N, THF, –78 °C; (b) *m*-CPBA, THF/H_2O (1:1), 0 °C then TFA, 0 °C, 32% (2 steps); (c) *m*-CPBA, $NaHCO_3$, THF/H_2O (1:1), 0 °C, 25% (2 steps); (d) TBAF, THF, rt, 71%.

At this stage, the utilisation of *m*-CPBA appeared as the principal cause of the problems. As a consequence, *m*-CPBA was replaced by DMDO in the epoxidation step and the acidic treatment was performed with AcOH (Scheme 84). As shown in Table 12 better yields were obtained employing these conditions (Entries 1 and 2). Finally, slight modifications of the reaction temperature furnished the hydroxyketone **360** in 52% overall yield, which represented an overall increase in yield of 20% (Entry 3).

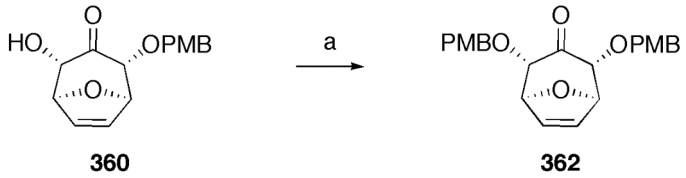


Scheme 84: *Conditions*: (a) DIPA, *n*-BuLi, THF, –78 °C then **359**, TESCl, Et_3N, THF, –78 °C; (b) DMDO, CH_2Cl_2 then THF/H_2O/AcOH (10:5:1), 0 °C.

Entry	Substrate	Temperature	Yield of 358 (2 steps)
1	**361**	0 °C to rt	47%
2	**361**	0 °C	46%
3	**361**	–78 to 0 °C	52%

Table 12: Conditions tested for the epoxidation of the silyl enol ether **361**.

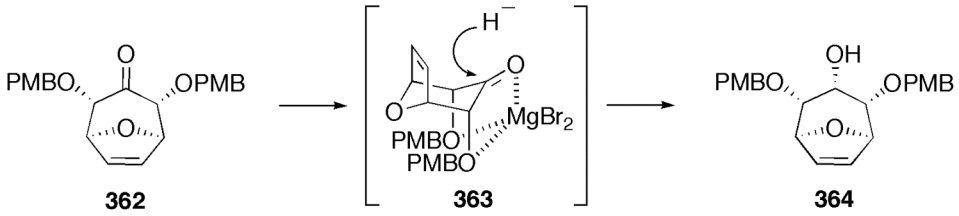
A second PMB protection reaction was performed once again under acid-catalysis, to afford ketone **362** in 76% yield (Scheme 85).



360 **362**

Scheme 85: *Conditions*: (a) 4-methoxybenzyltrichloroacetamidate, CSA, CH_2Cl_2, rt, 76%.

Surprisingly, ketone **362** was rather insoluble in MeOH and a large excess of $NaBH_4$ was required to complete the reduction (Entry 1, Table 13). When ketone **362** was subjected to the reduction in a 5:1 mixture of MeOH/THF the reaction became more viable and a nearly stoichiometric amount of $NaBH_4$ was required. Alcohol **364** was obtained in 90% yield as a 10:1 mixture of diastereoisomers in favour of the isomer shown (Entry 2, Table 13). The *cis* relationship between the three protons of the contiguous stereogenic centres was confirmed by the vicinal coupling constant (reported by Hoffmann: $^3J_{HH}$ = 5 Hz;[180] found: $^3J_{HH}$ = 5.4 Hz). It is likely that, in this case, $MgBr_2$ coordinates with the carbonyl and the two ether oxygens to give rise to the intermediate **363**.



362 **363** **364**

Entry	Substrate	Solvent	$NaBH_4$	Yield of 361
1	**362**	MeOH	2.2-6 eq.	80%
2	**362**	MeOH/THF (5:1)	1.1 eq.	90%

Table 13: *Conditions:* $MgBr_2$, $NaBH_4$, MeOH, 0°C.

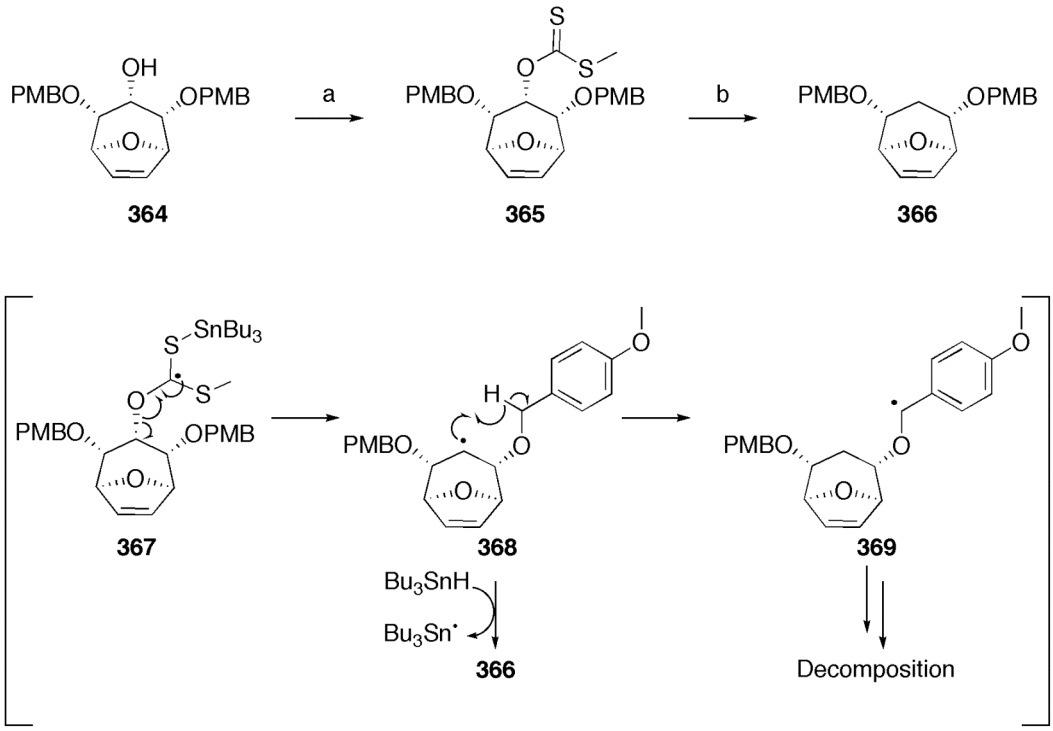
5.4.2 Deoxygenation of alcohol 364

5.4.2.1 Conventional Barton-McCombie Protocol

The synthesis continued with the formation of xanthate **365** that was obtained quantitatively from alcohol **364** (Scheme 86).[195] The presence of a carbone-sulfur double on bond on the molecule was confirmed by the ^{13}CNMR

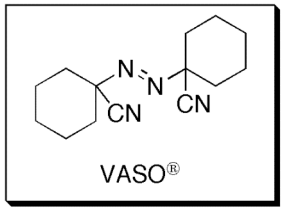
[195] (*a*) Njardarson, J. T.; McDonald, I. M.; Spiegel, D. A.; Inoue, M.; Wood, J. L. *Org. Lett.* **2001**, *3*, 2435; (*b*) De Almeida Barbosa, L.C.; Cutler, D.; Mann, J.; Crabbe, M. J.; Kirby, G. C.; Warhurst, D. C. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1101.

spectrum of the product (signal at 215 ppm). The dithiocarbonate **365** was then deoxygenated by reaction with Bu_3SnH in the presence of either AIBN or VAZO® as the radical initiator (Scheme 86).[196] The reaction was monitored by NMR and the disappearance of the signals corresponding to the dithiocarbonate (a triplet at 6.02 ppm and a singlet at 2.58 ppm) was observed. First, irreproducible yields were obtained with either radical initiator (Entry 1, Table 14). The reaction afforded complex mixtures of the required product **366** and unidentified byproducts. An explanation for this could be the migration of the radical **368** to the stabilised benzylic position **369** *via* an H-abstraction reaction. However, the entire mechanism of decomposition remains unclear. Finally, scaling up the reaction, proved to be beneficial and the protected diol **366** was isolated in 67% overall yield from alcohol **364** (Entry 2, Table 14). The presence of two doublet of triplet on the ^1H NMR spectrum of **366** (2.10 and 1.94 pm, respectively), corresponding to the newly formed CH_2, confirmed the success of the deoxygenation step.



Scheme 86: *Conditions*: (a) KH, CS_2, MeI, THF, 0 °C, quant.; (b) Bu_3SnH, benzene.

[196] Keck, G. Y.; Burnett, D. A. *J. Org. Chem.* **1987**, *52*, 2958.

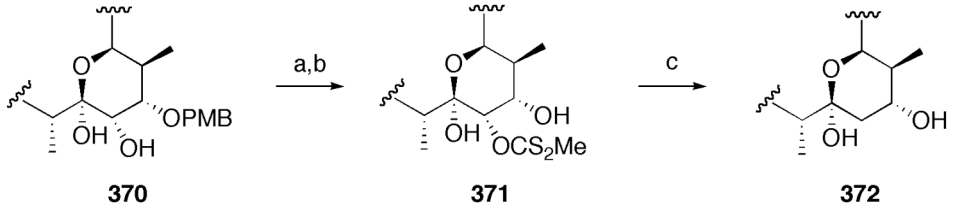


Entry	362 (mmol)	Initiatior	Yield of 366 (2 steps)
1	0.1-1.9	AIBN or VAZO®	36-60%
2	3.1	VAZO®	67%

Table 14: Attempts of deoxygenation.

5.4.2.2 Modified Sequence

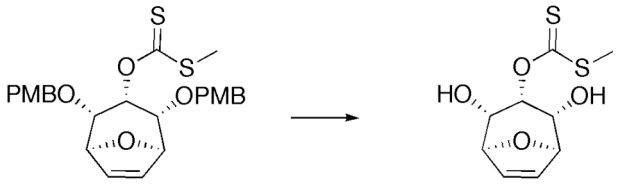
Kiffe and co-workers have reported a synthesis of diol **372** in which the PMB-deprotection was performed prior to radical deoxygenation (Scheme 87).[197]



370 **371** **372**

Scheme 87: *Conditions*: (a) CS_2, KOH, MeI, DMSO, rt, 81%; (b) DDQ, CH_2Cl_2/H_2O, rt, 72%; (c) Bu_3SnH, AIBN, toluene, 100 °C, 99%.

This strategy was applied to **365** in order to avoid the proposed radical migration reaction. Under a variety of reaction conditions a significant decomposition was observed and the diol **373** was never isolated (Table 15). Consequently, this strategy was abandoned.



365 **373**

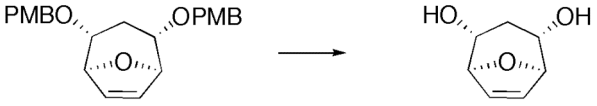
Entry	Conditions	Yield of 373
1	a	decomposition
2	b	decomposition
3	c	decomposition

Table 15: *Conditions*: (a) DDQ, CH_2Cl_2/H_2O (10:1), rt; (b) CAN, CH_3CN/H_2O (10:1), 0 °C; (c) TFA, CH_2Cl_2, rt.

[197] Kiffe, M.; Schummer, D.; Höfle, G. *Liebigs Ann.* **1997**, 245.

5.4.3 Deprotection Leading to Diol 374

Removal of the PMB-groups of *meso*-compound **366** was attempted. Problems with solubility of the diol **374** in water were encountered, especially when DDQ[198] or $CeCl_3 \cdot 7H_2O$[199] were used. Anisaldehyde was characterised by NMR analysis of the crude mixture, proving the deprotection had occured. Unfortunately, only traces of diol **374** were isolated in each case (Entries 1 and 2, Table 16). PMB removal using TFA resulted in the decomposition of the starting material **366** (Entry 3, Table 16).

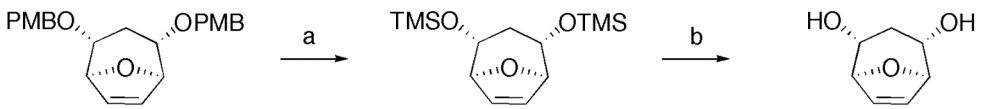


366 **374**

Entry	Conditions	Yield of 374
1	a	traces
2	b	traces
3	c	decomposition

Table 16: *Conditions*: (a) DDQ, CH_2Cl_2/H_2O (10:1), rt; (b) $CeCl_3 \cdot 7H_2O$, NaI, CH_3CN, reflux; (c) TFA, CH_2Cl_2, rt.

In order to reduce the loss of the diol **374** in the aqueous phase, a two-step procedure was envisaged. Conversion of **366** into the silyl-protected alcohol **375** was achieved using TMSOTf in the presence of 2,6-lutidine. Subsequent TBAF deprotection under non-aqueous conditions afforded the desired diol **374** in 78% yield (Scheme 88). The structure of diol **374** was confirmed by the NMR data and its purity highlighted by the elemental analysis.



366 **375** **374**

Scheme 88: *Conditions*: (a) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt; (b) TBAF, THF, rt, 78% (2 steps).

[198] Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885.
[199] Cappa, A.; Marcantoni, E.; Torregiani, E.; Bartoli, G.; Beluuci, M. C.; Bosco, M.; Sambri, L. *J. Org. Chem.* **1999**, *64*, 5696.

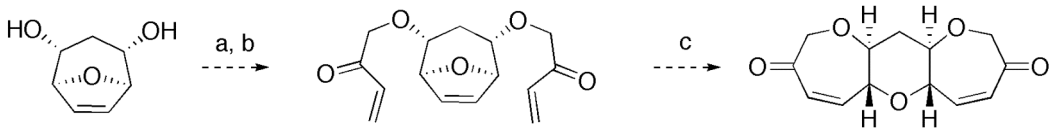
5.5 Summary

A reliable and relatively inexpensive synthetic pathway has been established for the synthesis of diol **374** for which, to the best of our knowledge, there is no literature precedent. Several problems have been identified, including migration and undesired cleavage of the protecting groups, which were circumvented at different stages of the synthesis. Good and reproducible yields were obtained and scale up of individual steps proved possible.

6 Future Work

6.1 Construction of the Tricyclic Core 382

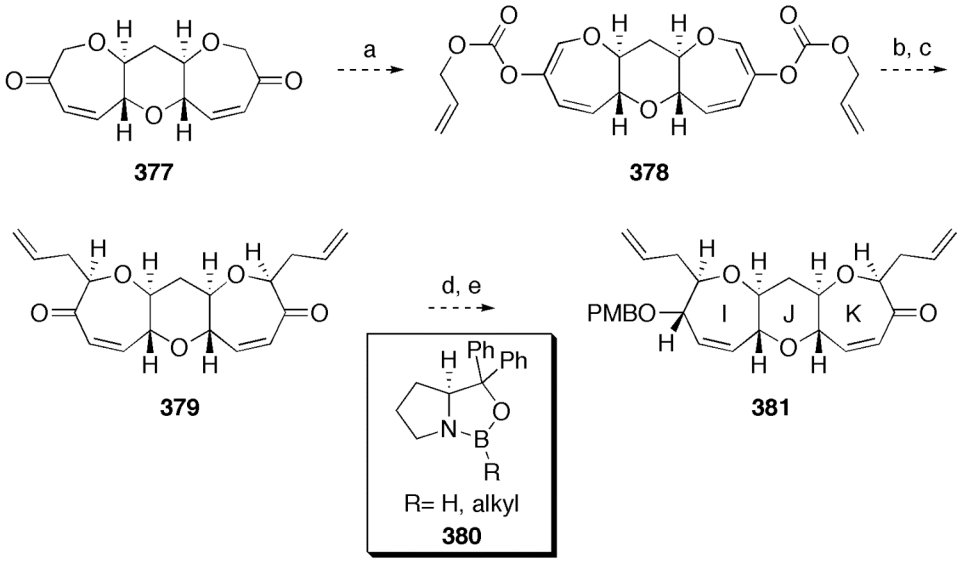
Double deprotonation of diol **374** and treatment of the resulting *bis*-alkoxide with triphenylchloroacetonylphosphorane followed by a double Wittig reaction with formaldehyde should afford triene **376**.[140] The *bis*-enone **376** will be subjected to the RORCM in the presence of the Grubbs second-generation catalyst **152** according to the procedure described by Philips and co-workers.[122] The opening of the bridged alkene and bi-directional ring closure should give the 7,6,7-*meso*-dienone **377** (Scheme 89).



Scheme 89: *Conditions*: (a) NaH, $ClCH_2COCHPPh_3$, TBAI, THF, rt then reflux; (b) CH_2O, pH = 7 buffer solution, Et_2O, rt; 0 °C; (c) catalyst **152** , ethylene, CH_2Cl_2 or toluene, rt or reflux; (d) NaH, NAPBr, DMF; (e) DIBAL, THF, 78 °C; (f) TBSCl, imidazole, DMF, rt.

O-Acylation of the *bis*-enolate of diketone **377** with allylchloroformate should afford the *bis*-carbonate **378**.[151c] Subsequent exposure of *bis*-carbonate **378** to the palladium complex prepared from $Pd_2(dba)_3$ should result in rearrangement of the allylic carbonate groups and deliver the doubly alkylated dienone **379** as a mixture of isomers.[151d] Treatment of this mixture with a suitable base will equilibrate the mixture to give the thermodynamically

favoured *meso* diastereomer **379**. Desymmetrisation of the *meso* tricyclic core **379** will then be investigated. Analogous seven-membered ketones have shown high diastereofacial selectivity during reduction, so only one diastereoisomer is likely to be produced in a mono-reduction reaction due to substrate control of stereochemistry, breaking the symmetry. Using a chiral reducing agent such as the CBS catalyst **380**,[200] it should be possible to select one of the enantiotopic faces. The resulting secondary alcohol will be protected as a PMB ether to form **381** (Scheme 90).

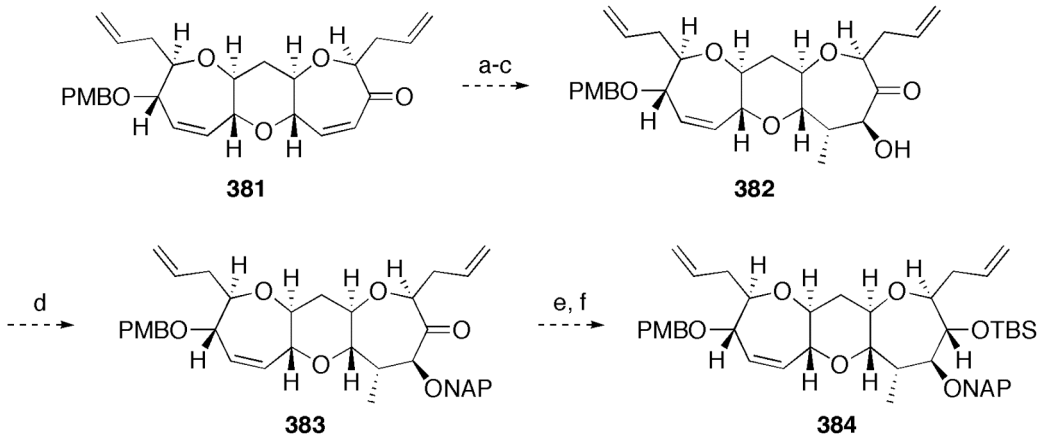


Scheme 90: *Conditions*: (a) **377**, allylchloroformate, THF, −78 °C then NaHMDS, −78 °C; (b) $Pd_2(dba)_3$, PPh_3, THF-toluene, 25-30 °C; (c) DBU, CH_2Cl_2, rt; (d) BH_3, catalyst **380**, THF, −10 °C to rt; (e) NaH, PMBCl, THF, 0 °C to rt.

6.2 Introduction of the K-Ring Substituents

Following our model study, the introduction of the K-ring methyl and hydroxyl substituents will be performed using the copper-catalysed conjugate addition of dimethylzinc[157] and Rubottom oxidation sequence. Subsequent protection of the hydroxyl group as a NAP-ether followed by ketone reduction and TBS protection should yield triene **384** (Scheme 91).[25a]

[200] Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1986.

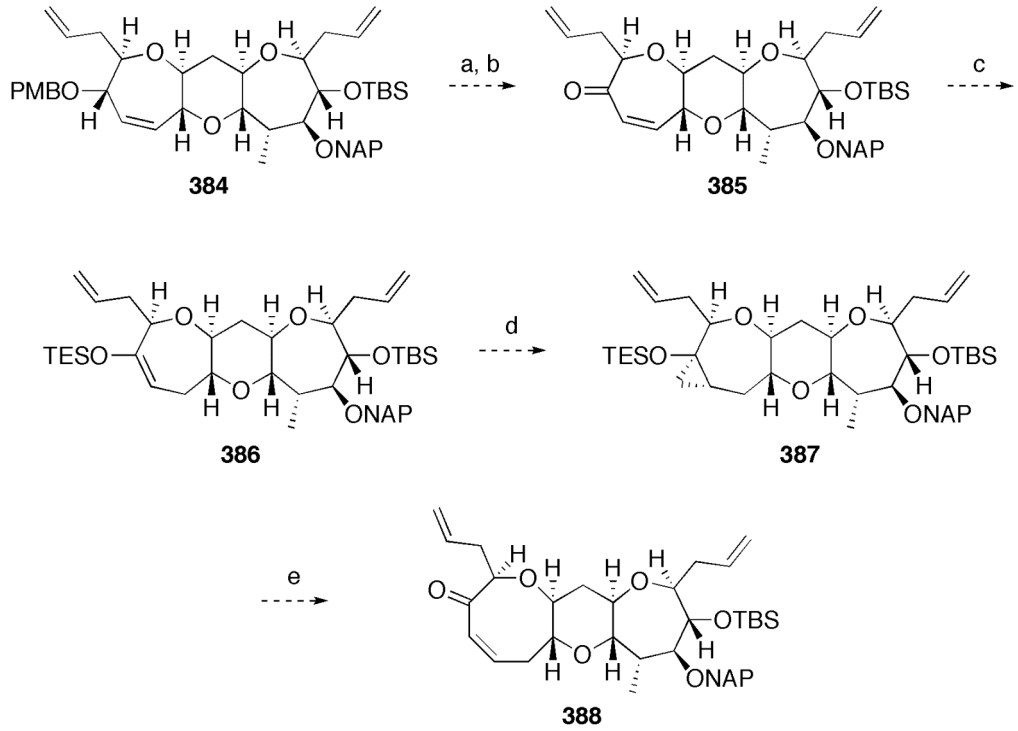


Scheme 91: *Conditions*: (a) Me_2Zn, $CuOTf_2$ (2 mol%), L* (4 mol%), toluene; (b) DIPA, *n*-BuLi, TESCl, Et_3N, THF, –78 °C; (c) *m*-CPBA, $NaHCO_3$, toluene, 0 °C then THF/H_2O/AcOH (2:1:0.5), rt.

6.3 Completion of the IJK Fragment

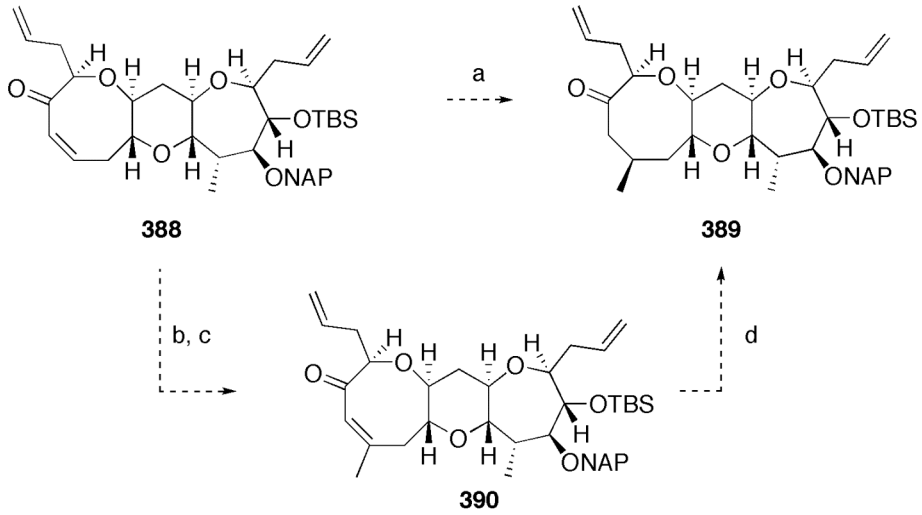
Removal of the PMB group and oxidation of the resulting secondary alcohol should deliver enone **385**. 1,4-Conjugate reduction of enone **385** with enolate trapping should give the silyl enol ether **386**. Utilisation of copper[201] or rhodium[202] hydride reagent can promote such a transformation. However, due to the price difference between the two metals, preference will be given to copper reagents such as the Stryker's catalyst.[201] Regio- and steroselective cyclopropanation of the electron-rich silyl enol ether **386** should deliver the cyclopropane **387**.[157g,203] Treatment with iron (III) chloride in the presence of Et_3N should result in cleavage of the cyclopropane to afford the ring-expanded enone **388** (Scheme 92).[157g,202]

[201] Lipshutz, B. H.; Chrisman, W.; Noson, K.; Papa, P.; Sclafani, J. A.; Vivian, R. W.; Keith, J. M. *Tetrahedron* **2000**, *56*, 2779.
[202] (*a*) Orito, Y.; Hashimoto, S.; Ishizuka, T.; Nakajima, M. *Tetrahedron* **2006**, *62*, 390; (*b*) Anada, M.; Tanaka, M.; Suzuki, K.; Nambu, H.; Hashimoto, S. *Chem. Pharm. Bull.* **2006**, *54*, 1622; (*c*) Zheng, G. Z.; Chan, T. H. *Organometallics* **1995**, *14*, 70.
[203] Ito, Y.; Fujii, S.; Saegusa, T. *J. Org. Chem.* **1976**, *41*, 2073.



Scheme 92: *Conditions*: (a) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt then THF/H_2O/AcOH (10:5:1), rt; (b) DMP, pyridine, CH_2Cl_2, rt; (c) $(PPh_3CuH)_6$, toluene, rt, then TESCl; (d) Et_2Zn, CH_2I_2, CH_2Cl_2, rt; (e) $FeCl_3$, DMF, Et_3N, 0 °C.

Finally, copper-catalysed conjugate addition of dimethylzinc should complete the synthesis of ketone **389**. In the event that the I-ring methyl cannot be introduced to give the desired diastereomer, enone **390** will be generated using the palladium catalysed Saegusa-Ito reaction.[204] Subsequent Stryker-type reduction should then give the desired ketone **389** (Scheme 93).[202]



Scheme 93: *Conditions*: (a) Me_2Zn, $CuOTf_2$ (2 mol%), L* (4 mol%), toluene; (b) $Me_2CuCNLi$, TESCl, Et_2O, −78 °C; (c) $Pd(OAc)_2$, MeCN, rt; (d) $(PPh_3CuH)_6$, toluene, rt.

[204] Ito, Y.; Fujii, S.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

7 Conclusion

In conclusion, a stereoselective pathway has been established on model system to reach the fully functionalised K-ring. The optimisation of the conjugate addition/Rubottom oxidation sequence, should lead to a diminution of the number of steps compare to the model study.

The problems encountered when attempting to form the eight-membered cyclic enone from dienone precursor have been circumvented. It has been shown that by using an allylic alcohol as the RCM precursor, the eight-membered cyclic enone can be synthesised in a high yielding fashion.

Finally, the two-directional synthesis of the IJK fragment was investigated. The major problems linked to the nature of the protecting groups or the hydrophilic character of the synthetic intermediates were encountered and circumvented. So far, fourteen steps have been accomplished and the key diol-intermediate **374** has been isolated in 1.6% overall yield (average of 74% yield per step).

Experimental Section

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 a Bruker 500 MHz Spectrospin spectrometer (^{1}H NMR at 500 MHz and ^{13}C NMR at 125 MHz). Chemical shifts are reported in ppm. ^{1}H NMR spectra were recorded with $CDCl_3$ as solvent using (d = 7.26) as internal standard, and for ^{13}C NMR spectra, the chemical shift are reported relative to the central resonance of $CDCl_3$ (d = 77.16). Signals in NMR spectra are described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), septet (sept), multiplet (m), apparent (app), broad (br) or combination of these, which refers to the spin-spin coupling pattern observed. DEPT 135, and two dimensional (COSY, HSQC) NMR spectroscopy were used where appropriate to assist the assignment of signals in the ^{1}H and ^{13}C NMR spectra. IR spectra were obtained employing a Golden Gate™ attachment that uses a type IIa diamond as a single reflection element so that the IR spectrum of the compound (solid or liquid) could be detected directly (thin layer) without any sample preparation (Shimadzu FTIR-8400). High resolution mass spectra were recorded under EI, FAB, CI and ES conditions by the analytical services at the University of Glasgow. Elemental analysis were carried out on an Exeter Analytical Elemental Analyser EA 440. Melting points were recorded with an Electrothermal IA 9100 apparatus.

Chromatography

Column chromatography was performed under pressure using silica gel (Fluorochem LC60A, 35–70 micron) as solid support and HPLC-graded solvent as eluent. Reactions were monitored by thin layer chromatography (TLC) on Merck silica gel 60 covered alumina plates F_{254}. TLC plates were developed under UV-light and/or with phosphomolybdic acid hydrate solution (formed by dissolving 5 g of phosphomolybdic acid hydrate ($H_3Mo_{12}O_{40}P \times H_2O$) in 100 mL EtOH (96%), a $KMnO_4$-solution (3 g of $KMnO_4$, 20 g K_2CO_3, 5 mL 5% NaOH (aq) and 300 mL H_2O)

or a acidic ethanolic anisaldehyde solution (formed by dissolving 15 g of anisaldehyde in 250 mL ethanol and 2.5 mL conc. sulfuric acid).

Nomenclature

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

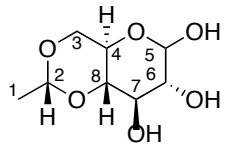
Solvents and Reagents

Liquid reagents were distilled prior to use if needed. All reagents were purchased from commercial suppliers and used without further purification unless otherwise stated.

General Reaction Conditions

Glassware was flame dried prior to use and the reactions were performed using dry solvent and carried out with the exclusion of air using an argon atmosphere.

(2*R*,4a*R*,7*R*,8*R*,8a*S*)-2-Methylhexahydropyrano[3,2-*d*][1,3]dioxine-6,7,8-triol (288).

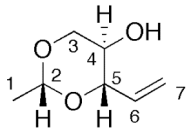


$C_8H_{14}O_6$

To a flask containing D-(+)-glucose (**287**) (50.0 g, 278 mmol) was added a mixture of paraldehyde (37.5 mL, 286 mmol) and conc. H_2SO_4 (0.3 mL). The mixture was stirred until a semi-solid was obtained. After 4 days at rt, ethanol (200 mL) was added and the mixture was neutralised (pH = 7) by addition of ethanolic KOH (1 M, ~12 mL). The white suspension was heated to dissolve the solids with periodic addition of ethanolic KOH (1 M) to maintain a pH of 7. The warm brown solution was decolourised with activated charcoal (3 g), filtered, cooled and allowed to stand for 16 h. The resulting colourless solid was air dried for 15 min, and then dried under high vacuum. The filtrate was reduced to dryness and the resulting solid was re-crystallised from ethanol. The products were combined to give the triol **288** (42.2 g, 81%) as a colourless solid. R_f = 0.35; (ethyl acetate); m.p. 177–180 °C (Lit.[205] m.p. 179–181 °C); $[\alpha]_D^{26}$ +48.2 (*c* = 1.09, in CH_3OH); ν_{max} 3686, 2326, 2144, 1974 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ_H 5.09 (1H, d, *J* = 3.8 Hz, CH-C5), 4.73 (1H, q, *J* = 5.0 Hz, CH-C2), 4.04 (1H, dd, *J* = 10.2, 4.9, CH_2-C3), 3.80 (1H, ddd, *J* = 12.0, 10.0, 4.9, CH-C4), 3.76 (1H, dd, *J* = 9.3, 9.2, CH-C7), 3.51 (1H, dd, *J* = 10.2, 10.0, CH_2-C3), 3.41 (1H, dd, *J* = 9.3, 3.8, CH-C6), 3.21 (1H, dd, *J* = 12.0, 9.2, CH-C8), 1.38 (3H, d, *J* = 5.0, CH_3-C1); ^{13}C NMR (100 MHz, CD_3OD) δ_C 98.9 (CH-C2), 94.7 (CH-C5), 81.9 (CH-C8), 74.6 (CH-C6), 71.8 (CH-C7), 69.5 (CH_2-C3), 63.5 (CH-C4); 19.3 (CH_3-C1); HRMS (CI+, isobutane) for $C_8H_{15}O_6$ ($[M+H]^+$) calcd 207.0869, found 207.0873; Anal. calcd for $C_8H_{15}O_6$: C, 46.60%; H, 6.84%. Found: C, 46.43%; H, 6.84%.

[205] (*a*) Sah, A. K.; Rao, C. P.; Saarenketo, P. K.; Wegelius, E. K.; Rissanen, K.; Kolehmainen, E. *J. Chem. Soc. Dalton Trans.* **2000**, 20, 3681; (*b*) Barker, R.; MacDonald, D. L., *J. Am. Chem. Soc.* **1960,** *82*, 2301.

(2*R*,4*S*,5*R*)-2-Methyl-4-vinyl-1,3-dioxan-5-ol (289).

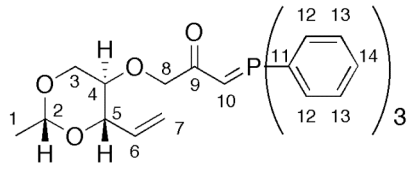


$C_7H_{12}O_3$

To a vigorously stirred solution of the triol **288** (10.6 g, 51.9 mmol) in dichloromethane (180 mL) and water (60 mL) was added solid $NaHCO_3$ (4.74 g, 57.3 mmol). $NaIO_4$ (22.2 g, 104 mmol) was added portionwise and the mixture was stirred for 1.5 h. The mixture was concentrated *in vacuo* and the residue was extracted with warm ethyl acetate (4 × 200 mL). The combined organic layers were concentrated *in vacuo* to give the crude aldehyde as a white foam, which was used without further purification.

To a stirred suspension of dry methyltriphenylphosphonium bromide (27.9 g, 78.1 mmol) in THF (150 mL) at 0 ºC was added *t*-BuOK (8.74 g, 77.9 mmol). After 30 min, a solution of crude aldehyde (7.5 g, 52 mmol) in THF (40 mL) was added. The resulting brown suspension was stirred for 1 h at rt before being quenched with water (150 mL). Phases were separated and the aqueous layer was extracted with diethyl ether (3 × 400 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether–diethyl ether, 3:1) gave alcohol **289** (6.8 g, 90% two steps) as a colourless oil. R_f = 0.30; (petroleum ether–diethyl ether, 1:1); $[\alpha]_D^{27}$ –23.8 (*c* = 1.00, in $CHCl_3$); ν_{max} 3400, 2854, 1405, 1148, 1125, 1080, 1040, 904, 845 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 5.85 (1H, ddd, *J* = 17.3, 10.5, 6.9 Hz, CH-C6), 5.37 (1H, ddd, *J* = 17.3, 1.4, 1.3 Hz, CH_2-C7), 5.28 (1H, ddd, *J* = 10.5, 1.4, 0.9 Hz, CH_2-C7), 4.66 (1H, q, *J* = 5.1 Hz, CH-C2), 4.09 (1H, dd, *J* = 10.1, 4.5 Hz, CH_2-C3), 3.76–3.70 (1H, m, CH-C5), 3.43 (1H, dddd, *J* = 10.2, 8.9, 4.5, 4.2 Hz, CH-C4), 3.36 (1H, dd, *J* = 10.2, 10.1 Hz, CH_2-C3), 1.90 (1H, d, *J* = 4.2 Hz, OH-C4), 1.29 (3H, d, *J* = 5.1 Hz, CH_3-C1); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 135.0 (CH-C6), 119.7 (CH_2-C7), 99.1 (CH-C2), 83.2 (CH-C5), 70.6 (CH_2-C3), 65.3 (CH-C4), 20.8 (CH_3-C1); HRMS (CI+, isobutane) for $C_7H_{13}O_3$ ($[M+H]^+$) calcd 145.0865, found 143.0859.

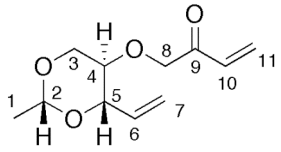
1-((2*R*,4*S*,5*R*)-2-Methyl-4-vinyl-[1,3]dioxan-5-yloxy)-3-triphenyl-phosphonylidene) propan-2-one (290).



$C_{28}H_{29}O_4P$

A solution of alcohol **289** (5.5 g, 38 mmol) in THF (70 mL) was added slowly at 0 ºC to a stirred suspension of NaH (1.97 g of a 60% suspension in mineral oils, 49.3 mmol) in THF (10 mL). The mixture was allowed to warm to rt and triphenylchloroacetonylphophorane (16.1 g, 45.6 mmol) was added followed by TBAI (421 mg, 1.14 mmol). The mixture was heated to reflux for 2 h and allowed to cool and quenched with water (80 mL). The aqueous layer was extracted with diethyl ether (3 × 150 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Filtration through a plug of silica gel (chloroform–methanol, 97:3 to 95:5) afforded the phosphorane **290** that was used in the next step without further purification.

1-((2*R*,4*S*,5*R*)-2-Methyl-4-vinyl-1,3-dioxan-5-yloxy)but-3-en-2-one (291).

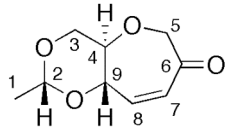


$C_{11}H_{16}O_4$

To a vigorously stirred solution of phosphorane **290** (11.4 g, 24.7 mmol) in diethyl ether (140 mL) at rt was added phosphate buffer (pH 7, 220 mL) and formaldehyde (37% w/w in water, 19.0 mL, 247 mmol). The mixture was stirred at rt for 2 h. The aqueous layer was extracted with diethyl ether (3 × 200 mL) and the combined organic layers were washed with brine (200 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether–diethyl ether, 3:1 to 1:1) resulted in the diene **291** (5.5 g, 68% two steps) as a colourless oil. R_f = 0.36; (petroleum ether–diethyl ether, 1:1); $[\alpha]_D^{25}$ −14.3 (*c* = 1.00, in $CHCl_3$); ν_{max} 2855, 1700, 1615, 1404, 1112, 986, 901, 844 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 6.40 (1H, dd, *J* = 17.6, 10.6 Hz, CH-C10),

6.24 (1H, dd, *J* = 17.6, 1.3 Hz, CH_2-C11), 5.91 (1H, ddd, *J* = 17.2, 10.6, 6.4 Hz, CH-C6), 5.77 (1H, dd, *J* = 10.6, 1.3 Hz, CH_2-C11), 5.39 (1H, dd, *J* = 17.2, 1.3 Hz, CH_2-C7), 5.24 (1H, dd, *J* = 10.6, 1.3 Hz, CH_2-C7), 4.65 (1H, q, *J* = 5.1 Hz, CH-C2), 4.31 (1H, d, *J* = 16.9 Hz, CH_2-C8), 4.23 (1H, d, *J* = 16.9 Hz, CH_2-C8), 4.21 (1H, dd, *J* = 10.9, 5.1 Hz, CH_2-C3), 3.88 (1H, dd, *J* = 9.1, 6.4 Hz, CH-C5), 3.44 (1H, dd, *J* = 10.9, 10.2 Hz, CH_2-C3), 3.17 (1H, ddd, *J* = 10.2, 9.1, 5.1 Hz, CH-C4), 1.28 (3H, d, *J* = 5.1 Hz, CH_3-C1); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 196.5 (C-C9), 135.3 (CH-C10), 132.5 (CH-C6), 129.7 (CH_2-C11), 118.9 (CH_2-C7), 99.0 (CH-C2), 81.1 (CH-C5), 75.0 (CH_2-C8), 74.7 (CH-C4), 69.0 (CH_2-C3), 20.8 (CH_3-C1); HRMS (CI+, isobutane) for $C_{11}H_{17}O_4$ ($[M+H]^+$) calcd 213.1127, found 213.1132.

(*Z*,2*R*,4a*R*,9a*S*)-4,4a-Dihydro-2-methyl-6*H*-[1,3]dioxino[5,4-*b*]oxepin-7(9a*H*)-one (283).

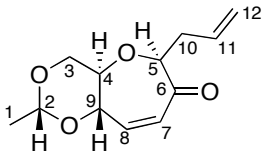


$C_9H_{12}O_4$

To a stirred solution of diene **291** (1.6 g, 7.5 mmol) in dry and degassed dichloromethane (800 mL) was added the Grubbs catalyst second-generation (192 mg, 0.226 mmol). The mixture was heated for 18 h to reflux, cooled and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether–diethyl ether, 3:1) gave the cyclic enone **283** (1.3 g, 84%) as a colourless solid. R_f = 0.48; (petroleum ether–diethyl ether, 1:1); m.p. 87–89 ºC; $[\alpha]_D^{26}$ +113 (*c* = 1.00, in $CHCl_3$); ν_{max} 2867, 1648, 1293, 1157, 1112, 1010, 985, 901, 845 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.46 (1H, dd, *J* = 12.8, 1.9 Hz, CH-C8), 5.99 (1H, dd, *J* = 12.8, 3.6 Hz, CH-C7), 4.69 (1H, q, *J* = 5.0 Hz, CH-C2), 4.39 (1H, d, *J* = 18.1 Hz, CH_2-C5), 4.28 (1H, d, *J* = 18.1 Hz, CH_2-C5), 4.23 (1H, ddd, *J* = 8.6, 3.6, 1.9 Hz, CH-C9), 4.19 (1H, dd, *J* = 10.2, 5.3 Hz, CH_2-C3), 3.51 (1H, ddd, *J* = 10.1, 8.6, 5.3 Hz, CH-C4), 3.44 (1H, dd, *J* = 10.2, 10.1 Hz, CH_2-C3), 1.30 (3H, d, *J* = 5.0 Hz, CH_3-C1); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 201.1 (C-C6), 145.3 (CH-C8), 128.7 (CH-C7), 99.8 (CH-C2), 80.3 (CH-C9), 77.8 (CH_2-C5), 75.1 (CH-C4), 68.7 (CH_2-C3), 20.6 (CH_3-C1); HRMS (CI+, isobutane) for $C_9H_{13}O_4$ ($[M+H]^+$) calcd

185.0814, found 185.0811; Anal. calcd for $C_9H_{12}O_4$: C, 58.69%; H, 6.57%. Found: C, 58.68%; H, 6.59%.

(2*S*,4a*R*,6*S*,9a*S*,*Z*)-6-Allyl-2-methyl-4,4a-dihydro-6*H*-[1,3]dioxino[5,4-*b*]oxepin-7(9a*H*)-one (295)



$C_{12}H_{16}O_4$

Method A:

To a stirred solution of the enone **283** (548 mg, 2.97 mmol) in toluene (20 mL) was added 1-aminopiperidine (1.66 mL, 14.9 mmol). The mixture was heated to 85 ºC overnight using a Dean Stark trap. Solvent was removed and the crude product was filtered over neutral alumina to remove the excess of 1-aminopiperidine. A 2:1 mixture of diastereoisomers of the hydrazone **292** was obtained (727 mg, 92%) and was used in the next step without further purification.

To a solution of the hydrazones **292** (727 g, 2.73 mmol) in dry THF (25 mL) at −100 ºC was added dropwise over 15 min a solution of *t*-BuLi (2.6 mL of a 1.6 M solution in pentane, 4.1 mmol). After stirring at −78 ºC for 30 min, freshly distilled allyl bromide (0.71 mL, 8.2 mmol) was added dropwise over 15 min. The mixture was stirred at −78 ºC overnight. The reaction was placed at 0 ºC and water (25 mL) was added. The aqueous layer was extracted with ethyl acetate (3 × 30 mL) and the combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude allylated hydrazone **293** (837 mg) as an inseparable mixture of diastereoisomers that was used in the next step without further purification.

To a stirred solution of $CuCl_2$ (1.47 g, 10.9 mmol) in water (10 mL) was added at rt a solution of the crude hydrazones **293** (837 mg, 2.72 mmol) in THF (10 mL). The mixture was then allowed to stir for 1h at this temperature. Diethyl ether (15 mL) was added followed by a 1:1 solution of a saturated aqueous solution of NH_4Cl/NH_4OH (10 mL, pH >9). The aqueous layer was extracted with diethyl ether (3 × 30 mL) and the combined organic layers were

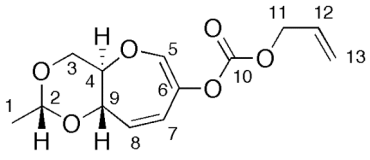
washed with brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether–diethyl ether, 3:1) afforded a 2:1 mixture of diastereoisomers of enone **294** (387 mg, 70% over 3 steps) as a colorless oil.

To a stirred solution of the 2:1 mixture of diastereoisomers of enones **294** (345 mg, 1.54 mmol) in dry toluene (16 mL) was added Proton Sponge® (330 mg, 1.54 mmol). The mixture was heated to 95 ºC for 4 h and then stirred at rt overnight. Solvent was removed and purification by flash column chromatography (petroleum ether–diethyl ether, 9:1) afforded a 5:1 mixture of diastereomers (261 mg; 76%) in favour of enone **295**, which possess the desired configuration.

Method B:

To a stirred solution of $Pd_2(dba)_3$ (94.0 mg, 0.102 mmol) in degassed THF (95 mL) at 25 ºC was added (*S*)-*t*-Bu-PHOX (**300**) (98.4 mg, 0.254 mmol). After 30 min a solution of allyl enol carbonate **301** (1.1 g, 4.1 mmol) in degased THF (30 mL) was added in a dropwise manner. The resulting mixture was allowed to stir for 1 h at 25 °C and concentrated *in vacuo*. The resulting oil was filtered through Celite® and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether–diethyl ether, 9:1) afforded enone **295** (760 mg, 83%) as a colourless oil. R_f = 0.63; (petroleum ether–diethyl ether, 1:1); $[\alpha]_D^{26}$ +31 (*c* = 0.93, in $CHCl_3$); ν_{max} 2864, 1725, 1663, 1407, 1287, 1160, 1113, 1021, 905, 880, 845 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 6.46 (1H, dd, *J* = 12.6, 2.0 Hz, CH-C8), 6.02 (1H, dd, *J* = 12.6, 2.7 Hz, CH-C7), 5.77 (1H, dddd, *J* = 16.7, 10.2, 6.9, 6.9 Hz, CH-C11), 5.11–5.04 (2H, m, CH_2-C12), C12), 4.75 (1H, q, *J* = 5.0 Hz, CH-C2), 4.25 (1H, dd, *J* = 7.2, 4.2 Hz, CH-C5), 4.20–4.14 (2H, m, CH_2-C3, CH-C9), 3.56–3.52 (2H, m, CH_2-C3, CH-C4), 2.61–2.53 (1H, m, CH_2-C10), 2.47–2.38 (1H, m, CH_2-C10), 1.36 (3H, d, *J* = 5.0 Hz, CH_3-C1); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 202.6 (C-C6), 143.4 (CH-C8), 133.1 (CH-C11), 128.6 (CH-C7), 117.9 (CH_2-C12), 99.5 (CH-C2), 87.0 (CH-C5), 79.6 (CH-C9), 73.7 (CH-C4), 68.5 (CH_2-C3), 37.7 (CH_2-C10), 20.3 (CH_3-C1); HRMS (CI+, isobutane) for $C_{12}H_{17}O_4$ ($[M+H]^+$) calcd 225.1127, found 225.1125.

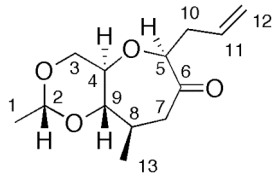
Allyl (2*R*,4a*R*,9a*S*,*Z*)-2-methyl-4a,6,7,9a-tetrahydro-4*H*-[1,3]dioxino[5,4-*b*]oxepin-7-yl carbonate (301)



$C_{13}H_{16}O_6$

To a stirred solution of enone **283** (2.04 g, 11.1 mmol) in THF (110 mL) at −78 °C was added dropwise allylchloroformate (1.41 mL, 13.3 mmol). After 10 min at −78 °C, NaHMDS (2 M in THF, 6.64 mL, 13.3 mmol) was added dropwise over 15 min. The resulting mixture was allowed to stir for 2 h at −78 °C, quenched with an aqueous KH_2PO_4 solution (5%, 100 mL) and allowed to warm. The aqueous layer was extracted with diethyl ether (3 × 200 mL) and the combined organic layers were washed with brine (200 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether−diethyl ether, 3:1) afforded the allyl enol carbonate **301** (2.7 g, 93%) as a colourless solid. R_f = 0.81; (petroleum ether−diethyl ether, 1:1); m.p. 70−71 °C; $[\alpha]_D^{24}$ −7.9 (*c* = 1.10, in $CHCl_3$); ν_{max} 2867, 1743, 1281, 1227, 1127, 1041, 941 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 6.73−6.70 (1H, m, CH-C5), 5.95 (1H, dddd, *J* = 17.0, 10.6, 5.9, 5.9 Hz, CH-C12), 5.84−5.76 (2H, m, CH-C7, CH-C8), 5.39 (1H, ddd, *J* = 17.0, 2.6, 1.3 Hz, CH_2-C13), 5.31 (1H, ddd, *J* = 10.6, 2.6, 1.3 Hz, CH_2-C13), 4.71 (1H, q, *J* = 5.0 Hz, CH-C2), 4.67 (2H, ddd, *J* = 5.9, 1.3, 1.3 Hz, CH_2-C11), 4.36 (1H, dd, *J* = 10.5, 4.9 Hz, CH_2-C3), 4.09−4.07 (1H, m, CH-C9), 3.60 (1H, ddd, *J* = 10.4, 7.0, 4.9 Hz, CH-C4), 3.53 (1H, dd, *J* = 10.5, 10.4 Hz, CH_2-C3), 1.38 (3H, d, *J* = 5.0 Hz, CH_3-C1); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 154.6 (C-C10), 142.3 (CH-C5), 133.5 (CH-C6), 131.2 (CH-C12), 129.6 (CH-C7), 121.5 (CH-C8), 119.7 (CH_2-C13), 99.8 (CH-C2), 77.1 (CH-C9), 70.9 (CH-C4), 69.3 (CH-C11), 68.4 (CH_2-C3), 20.5 (CH_3-C1); HRMS (EI+) for $C_{13}H_{16}O_6$ ($[M]^+$) calcd 268.0947, found 268.0949; Anal. calcd for $C_{13}H_{16}O_6$: C, 58.20%; H, 6.01%. Found: C, 58.36%; H, 6.03%.

(2*S*,4a*R*,6*S*,9*R*,9a*S*)-6-Allyl-2,9-dimethyl-tetrahydro-6*H*-[1,3]dioxino[5,4-*b*]oxepin-7(8*H*)-one (303)



$C_{13}H_{20}O_4$

Method A:

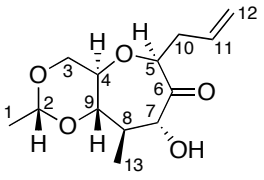
To a stirred suspension of CuBr.DMS complex (956 mg, 4.65 mmol) in THF (20 mL) at −50 ºC was added, dropwise, MeMgBr (680 µL of a 1.4 M solution in toluene, 4.65 mmol). The resulting mixture was stirred at this temperature for 1 h, cooled to −78 ºC and $BF_3.OEt_2$ (580 µL, 4.65 mmol) was added. The resulting mixture was stirred for 1h at −78 ºC and then a solution of enone **295** (261 mg, 1.16 mmol) in THF (13 mL) was added. After 1 h at −78 °C the reaction mixture was allowed to warm to 0 ºC and quenched with a 10% solution of NH_4OH in a saturated aqueous solution of NH_4Cl (16 mL). The aqueous layer was extracted with diethyl eher (3 × 30 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether-diethyl, ether 9:1) afforded an inseparable mixture of diastereoisomers (2:1 favouring the undesired configuration) of ketone **303** (210 mg, 75%).

Method B:

To a stirred suspension of $CuOTf_2$ (3.5 mg, 9.4 µmol) in toluene (0.3 mL) was added at rt the (*R,S,S*)-Feringa phosphoramidate ligand **305** (10.1 mg, 18.8 µmol). The resulting mixture was stirred for 30 min at rt, cooled to −40 ºC and dimethylzinc (353 µL, 0.706 mmol) was added dropwise followed by a solution of enone **295** (105 mg, 470 µmol) in dry toluene (0.3 mL). The resulting mixture was allowed to warm up and was stirred at rt for 48 h. After that time the reaction was quenched with a saturated aqueous solution of NH_4Cl (5 mL). The aqueous layer was extracted with diethyl ether (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether−diethyl

ether, 3:1 to 1:1) afforded a mixture of ketone **303** (48 mg, 42%) as a colourless oil and hydroxyketone **306** (39 mg, 32%) as colourless oil. R_f = 0.69; (petroleum ether–diethyl ether, 6:4); $[\alpha]_D^{19}$ –80 (*c* = 0.97, in $CHCl_3$); ν_{max} 2970, 2862, 1712, 1411, 1296, 1257, 1118, 1041, 910 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *desired diastereoisomer* δ_H 5.77 (1H, dddd, *J* = 16.7, 10.2, 6.9, 6.9 Hz, CH-C11), 5.12–5.04 (2H, m, CH_2-C12), 4.66 (1H, q, *J* = 5.1 Hz, CH-C2), 4.09 (1H, dd, *J* = 11.0, 4.9 Hz, CH_2-C3), 3.87 (1H, dd, *J* = 7.2, 5.5 Hz, CH-C5), 3.44 (1H, dd, *J* = 11.0, 9.6 Hz, CH_2-C3), 3.18–3.09 (2H, m, CH-C4, CH-C9), 2.80 (1H, dd, *J* = 12.0, 11.8 Hz, CH_2-C7), 2.37–2.31 (2H, m, CH_2-C10), 2.20 (1H, dd, *J* = 11.8, 1.9 Hz, CH_2-C7), 1.84–1.72 (1H, m, CH-C8), 1.32 (3H, d, *J* = 5.1 Hz, CH_3-C1), 1.12 (3H, d, *J* = 6.6 Hz, CH_3-C13); ^{13}C NMR (100 MHz, $CDCl_3$) *desired diastereoisomer* δ_C 214.4 (C-C6), 132.8 (CH-C11), 118.2 (CH_2-C12), 99.2 (CH-C2), 86.8 (CH-C5), 85.3 (CH-C9), 75.2 (CH-C4), 68.8 (CH_2-C3), 45.3 (CH_2-C7), 37.3 (CH_2-C10), 35.7 (CH-C8), 20.6 (CH_3-C1), 19.3 (CH_3-C13); HRMS (CI+, isobutane) for $C_{13}H_{21}O_4$ ($[M+H]^+$) calcd 241.1440, found 241.1439.

(2*S*,4a*R*,6*S*,8*R*,9*R*,9a*S*)-6-Allyl-8-hydroxy-2,9-dimethyl-tetrahydro-6*H*-[1,3]dioxino[5,4-*b*]oxepin-7(8*H*)-one (306)



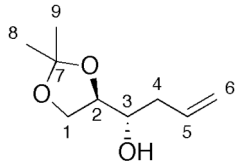
$C_{13}H_{20}O_5$

To DIPA (0.24 mL, 1.7 mmol) in dry THF (3 mL) was added *n*-BuLi (2.5 M in hexane, 520 µL, 1.3 mmol) at 0 °C. The mixture was stirred for 10 min at 0 °C, cooled to –78 °C and TESCl (360 µL, 2.17 mmol) was added followed by a solution of a 1:2 diastereoisomeric mixture of ketones **303** (154 mg, 0.434 mmol) in dry THF (1 mL). The mixture was stirred for 5 min and Et_3N (70 µL, 0.48 mmol) was added. The resulting mixture was stirred for 30 min and quenched with water (6 mL) at 0 °C. The aqueous layer was extracted with dichloromethane (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The resulting silyl enol ether was used without further purification.

To a stirred suspension of *m*-CPBA (0.15 g, 0.65 mmol) in dry toluene (7.5 mL) was added solid $NaHCO_3$ (110 mg, 1.30 mmol). The mixture was stirred for 30 min at rt and water (1.5 mL) was added and the resulting mixture was cooled to 0 ºC. While stirring rapidly, a solution of silyl enol ether (155 mg, 0.434 mmol) in toluene (1.5 mL) was added dropwise. After 30 min at 0 ºC, the reaction was quenched with a saturated aqueous solution of $Na_2S_2O_3$ solution (10 mL) and stirred for 10 min at 0°C. The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the combined organic layer were washed with a saturated aqueous solution of $NaHCO_3$ solution (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting oil was dissolved in a 2:1 mixture of tetrahydrofuran and water (3mL) and AcOH (0.5 mL) was added. The reaction mixture was stirred at rt for 7 h, diluted with ethyl acetate and gently neutralised with a saturated aqueous solution of $NaHCO_3$ solution (15 mL). After the gas evolution ceased, the aqueous layer was extracted with ethyl acetate (3 ×10 mL) and the combined organic layers were washed with brine (10 mL) dried, ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether–diethyl ether, 9:1 to 7:3) afforded a 1:2 diastereomeric mixture (in favour of the undesired configuration) of the hydroxyketones **306** and **307** (26.3 mg, 24% over 3 steps) as a colourless solid. R_f = 0.54; (petroleum ether–diethyl ether, 7:3); $[\alpha]_D^{21}$ –69 (*c* = 1.00, in $CHCl_3$); ν_{max} 3479, 2978, 2862, 1712, 1407, 1257, 1118, 1026, 902 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *desired diastereoisomer* δ_H 5.78 (1H, dddd, *J* = 16.7, 10.2, 6.9, 6.9 Hz, CH-C11), 5.11–5.04 (2H, m, CH_2-C12), 4.66 (1H, q, *J* = 5.1 Hz, CH-C2), 4.27 (1H, dd, *J* = 11.2, 6.4 Hz, CH-C7), 4.15 (1H, dd, *J* = 7.1, 5.3 Hz, CH-C5), 4.11 (1H, dd, *J* = 11.0, 5.4 Hz, CH_2-C3), 3.43 (1H, dd, *J* = 11.0, 10.3 Hz, CH_2-C3), 3.38 (1H, d, *J* = 6.4 Hz, OH-C7), 3.24 (1H, dd, *J* = 9.6, 9.5 Hz, CH-C9), 3.11 (1H, ddd, *J* = 10.3, 9.6, 5.4 Hz, CH-C4), 2.49–2.36 (2H, m, CH_2-C10), 1.69–1.59 (1H, m, CH-C8), 1.33 (3H, d, *J* = 5.1 Hz, CH_3-C1), 1.29 (3H, d, *J* = 6.4 Hz, CH_3-C13); ^{13}C NMR (100 MHz, $CDCl_3$) *desired diastereoisomer* δ_C 215.0 (C-C6), 132.0 (CH-C11), 119.0 (CH_2-C12), 99.5 (CH-C2), 85.7 (CH-C5), 82.9 (CH-C9), 75.4 (CH-C7), 75.3 (CH-C4), 68.5 (CH_2-C3), 43.1 (CH-C8), 38.0 (CH_2-C10), 20.5 (CH_3-C1), 14.5 (CH_3-C13); ^1H NMR (400 MHz, $CDCl_3$) *undesired diastereoisomer* δ_H 5.78 (1H, dddd, *J* = 16.7, 10.2, 6.9, 6.9 Hz, CH-C11), 5.15–5.10 (2H, m, CH_2-C12), 4.66 (1H, q, *J* = 5.0 Hz, CH-C2), 4.11 (1H, dd, *J* = 10.9, 5.1 Hz, CH_2-C3), 4.06 (1 H, br s, CH-C7), 4.01

(1H, dd, *J* = 8.3, 5.7 Hz, CH-C5), 3.49–3.41 (2H, m, CH_2-C3, CH-C9), 3.23 (1H, ddd, *J* = 14.6, 5.1, 4.8 Hz, CH-C4), 2.57 (1H, br s, OH-C7), 2.63–2.50 (2H, m, CH_2-C10), 1.91–1.84 (1H, m, CH-C8), 1.33 (3H, d, *J* = 5.0 Hz, CH_3-C1), 1.26 (3H, d, *J* = 6.7 Hz, CH_3-C13); ^{13}C NMR (100 MHz, $CDCl_3$) un*desired diastereoisomer* δ_C 211.8 (C-C6), 132.7 (CH-C11), 118.4 (CH_2-C12), 99.5 (CH-C2), 87.4 (CH-C5), 83.3 (CH-C9), 81.0 (CH-C7), 75.5 (CH-C4), 68.4 (CH_2-C3), 40.3 (CH-C8), 37.9 (CH_2-C10), 20.5 (CH_3-C1), 15.1 (CH_3-C13); HRMS (CI+, isobutane) for $C_{13}H_{21}O_5$ ($[M+H]^+$) calcd 257.1389, found 257.1392.

(*S*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)but-3-en-1-ol (312)



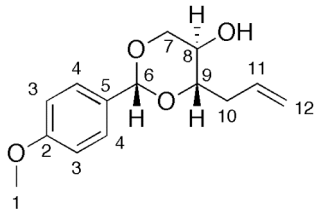
$C_9H_{16}O_3$

To a stirred solution of diol **310** (6.38 g, 24.3 mmol) in dichloromethane (46 mL) and water (2 mL) was added portionwise at 0 °C $NaIO_4$ (10.4 g, 48.7 mmol). The cooling bath was removed and the mixture was allowed to stir at rt for 2 h before $MgSO_4$ was added. Salts were removed by filtration and solvent was carefully removed *in vaccuo* to yield the crude compound. The resulting aldehyde **311** was used without further purification.

To a stirred solution of dry zinc chloride (13.3 g, 97.4 mmol) in diethyl ether (120 mL) was added dropwise at 0 °C allylmagnesium bromide (98 mL of a 1 M solution in diethyl ether, 97 mmol) over 20 min. The resulting mixture was sonicated for 30 min at 0 °C and was stirred for 1h at rt. The mixture was cooled to –78 °C and a solution of the crude aldehyde **311** in diethyl ether (45 mL) was added dropwise over 30 min. The solution was stirred and allowed to warm to rt overnight and quenched with a saturated aqueous solution of NH_4Cl solution (200 mL). The aqueous layer was extracted with diethyl ether (3 × 200 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude alcohol as a 5:1 mixture of diastereoisomers. Flash column chromatography (petroleum ether–diethyl ether, 7:3 to pure diethyl ether) afforded the desired diastereoisomer **312** (6.2 g, 73% over 2 steps) as a

colourless oil. R_f = 0.41; (dichloromethane–methanol, 97:3); $[\alpha]_D^{25}$ +18.1 (*c* = 1.02, in $CHCl_3$); ν_{max} 3462, 2986, 2887, 1726, 1642, 1456, 1249, 1214, 1158, 1063, 1060, 989, 916, 854 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 5.86 (1H, dddd, *J* = 17.2, 10.1, 7.1, 7.1 Hz, CH-C5), 5.18–5.14 (2H, m, CH_2-C6), 4.04–4.00 (2H, m, CH_2-C1), 3.96–3.91 (1H, m, CH-C2), 3.80–3.76 (1H, m, CH-C3), 2.37–2.30 (1H, m, CH_2-C4), 2.24–2.16 (1H, m, CH_2-C4), 1.99 (1H, d, *J* = 3.1 Hz, OH-C3), 1.44 (3H, s, CH_3-C8), 1.37 (3H, s, CH_3-C9); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 134.0 (CH-C5), 118.4 (CH_2-C6), 109.1 (C-C7), 78.1 (CH-C2), 70.4 (CH-C3), 65,2 (CH_2-C1), 37.6 (CH_2-C4), 26.6 (CH_3-C8), 25.3 (CH_3-C9); HRMS (CI+, isobutane) for $C_9H_{17}O_3$ ($[M+H]^+$) calcd 173.1178, found 173.1176.

(2*R*,4*S*,5*R*)-4-Allyl-2-(4-methoxyphenyl)-1,3-dioxan-5-ol (315)



$C_{14}H_{18}O_4$

Method A:

To a stirred solution of alcohol **312** (5.66 g, 32.8 mmol) in THF (120 mL) were added water (14 mL) and TFA (3 mL, 40 mmol) at rt. The solution was heated to reflux overnight and cooled to 0 °C. The mixture was neutralised by addition of solid K_2CO_3 (5.45 g, 39.4 mmol) and filtered. After azeotropic removal of water with toluene (3 × 50 mL), the resulting oil was diluted in ethyl acetate (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the corresponding triol, which was used without further purification.

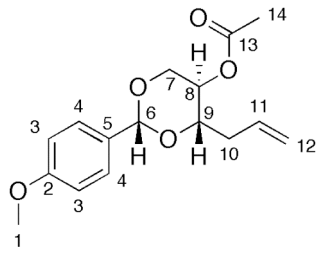
To a suspension of the resulting triol (4.34 g, 32.8 mmol) in dry dichloromethane (100 mL) were added *p*-methoxybenzaldehyde dimethyl acetal (7 mL, 40 mmol) and CSA (1.5 g, 6.6 mmol) in the presence of activated 4 Å molecular sieves. The reaction was stirred 4 days at rt. The resulting mixture was filtered through Celite® and the solvent removed *in vacuo*. The resulting oil was dissolved in diethyl ether (300 mL) and Et_3N (25 mL) and water (200 mL) were added. The aqueous layer was extracted with diethyl ether (3 × 200 mL)

and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petroleum ether–diethyl ether, 1:1). Crystallisation (dichloromethane–petroleum ether) afforded alcohol **315** (4.11 g, 50%) as a colourless solid.

Method B:

To a stirred solution of acetate **316** (504 mg, 1.72 mmol) in dry methanol (17 mL) at rt was added K_2CO_3 (24 mg, 0.17 mmol). The resulting mixture was allowed to stir at rt overnight. The mixture was concentrated *in vacuo* and the resulting oil was diluted with diethyl ether (50 mL) and quenched with a saturated aqueous solution of NH_4Cl solution (50 mL). The aqueous layer was extracted with diethyl ether (3 × 50 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petroleum ether–diethyl ether, 5:2) to afford alcohol **315** (430 mg,) in quantitative yield as a colourless solid. R_f = 0.29; (petroleum ether–diethyl ether, 1:1); m.p. 56–57 °C; $[\alpha]_D^{25}$ −23.2 (*c* = 1.00, in $CHCl_3$); ν_{max} 3418, 2936, 2859, 1612, 1518, 1250, 1076, 1060, 1020, 964, 831 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.40 (2H, d, *J* = 8.7 Hz, CH-C3), 6.88 (2H, d, *J* = 8.7 Hz, CH-C4), 6.00 (1H, dddd, *J* = 17.2, 10.2, 7.0, 7.0 Hz, CH-C11), 5.45 (1H, s, CH-C6), 5.20 (1H, ddd, *J* = 17.2, 2.7, 1.5 Hz, CH_2-C12), 5.12 (1H, ddt, *J* = 10.2, 2.7, 1.0 Hz, CH_2-C12), 4.25 (1H, dd, *J* = 10.5, 5.1 Hz, CH_2-C7), 3.80 (3H, s, CH_3-C1), 3.68 (1H, dddd, *J* = 11.7, 10.1, 5.1, 5.0 Hz, CH-C8), 3.63 (1H, ddt, *J* = 11.7, 6.7, 4.4 Hz, CH-C9), 3.57 (1H, dd, *J* = 10.5, 10.1 Hz, CH_2-C7), 2.66–2.59 (1H, m, CH_2-C10), 2.51–2.44 (1H, m, CH_2-C10), 1.70 (1H, d, *J* = 5.0 Hz, OH-C8); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 160.1 (C-C2), 134.4 (CH-C11), 130.4 (C-C5), 127.5 (2 × CH-C3), 117.7 (CH_2-C12), 113.7 (2 × CH-C4), 101.0 (CH-C6), 81.1 (CH-C9), 71.1 (CH_2-C7), 65.9 (CH-C8), 55.4 (CH_3-C1), 36.9 (CH_2-C10); HRMS (EI+) for $C_{14}H_{18}O_4$ ($[M]^+$) calcd 250.1205, found 250.1204; Anal. calcd for $C_{14}H_{18}O_4$: C, 67.18%; H, 7.25%. Found: C, 67.15%; H, 7.29%.

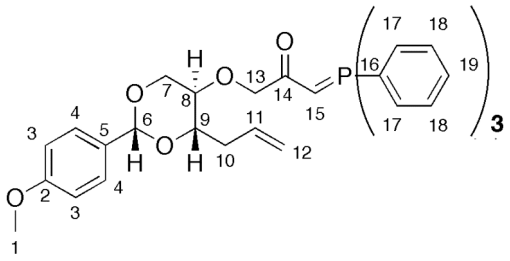
4-Allyl-2-(4-methoxyphenyl)-1,3-dioxan-5-yl acetate (316)



$C_{16}H_{20}O_5$

The mixture (5:1) of diastereoisomeric alcohols **315** (5.37 g, 21.5 mmol) was dissolved in dichloromethane (70 mL). Et_3N (4.5 mL, 32 mmol) and DMAP (100 mg, 1.07 mmol) were added at rt followed by acetic anhydride (3.1 mL, 32 mmol). The reaction was stirred at rt overnight and was quenched with a saturated aqueous solution of $NaHCO_3$ solution (70 mL). The aqueous layer was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (1% Et_3N, petroleum ether–diethyl ether, 95:5 to 90:10). Crystallisation (dichloromethane–petroleum ether) afforded the desired acetate **316** (4.01 g, 64%) as a colourless solid. R_f = 0.63; (petroleum ether–diethyl ether, 1:1); m.p. 50–51 °C; $[\alpha]_D^{25}$ −45.1 (*c* = 0.97, in $CHCl_3$); ν_{max} 2938, 2859, 1740, 1614, 1517, 1369, 1227, 1086, 1032, 825 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.41 (2H, d, *J* = 8.7 Hz, CH-C3), 6.89 (2H, d, *J* = 8.7 Hz, CH-C4), 5.91 (1H, dddd, *J* = 17.1, 10.2, 6.9, 6.9 Hz, CH-C11), 5.46 (1H, s, CH-C6), 5.14–5.08 (2H, m, CH_2-C12), 4.82 (1H, ddd, *J* = 10.1, 9.8, 5.3 Hz, CH-C8), 4.35 (1H, dd, *J* = 10.5, 5.3 Hz, CH_2-C7), 3.84–3.80 (1H, m, CH-C9), 3.81 (3H, s, CH_3-C1), 3.58 (1H, dd, *J* = 10.5, 10.1 Hz, CH_2-C7), 2.49–2.44 (1H, m, CH_2-C10), 2.40–2.34 (1H, m, CH_2-C10), 2.07 (3H, s, CH_3-C14); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 169.9 (C-C13), 160.2 (C-C2), 133.6 (CH-C11), 130.1 (C-C5), 127.6 (2 × CH-C3), 117.6 (CH_2-C12), 113.8 (2 × CH-C4), 101.2 (CH-C6), 78.7 (CH-C9), 68.1 (CH_2-C7), 66.6 (CH-C8), 55.4 (CH_3-C1), 36.6 (CH_2-C10), 21.0 (CH_3-C14); HRMS (EI+) for $C_{16}H_{20}O_5$ ($[M]^+$) calcd 292.1311, found 292.1314; Anal. calcd for $C_{16}H_{20}O_5$: C, 65.74%; H, 6.90%. Found: C, 65.65%; H, 6.86%.

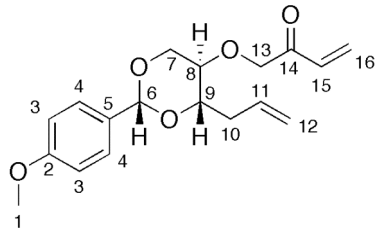
(*E*)-1-((2*R*,4*S*,5*R*)-4-Allyl-2-(4-methoxyphenyl)-1,3-dioxan-5-yloxy)-3-(triphenylphosphinylidene)propan-2-one (317)



$C_{35}H_{35}O_5P$

NaH (121 mg of a 60% suspension in mineral oils, 3.02 mmol) was suspended in THF (2 mL) and cooled to 0 ºC. A solution of alcohol **315** (582 mg, 2.32 mmol) in THF (5 mL) was added dropwise at 0 ºC and the resulting mixture was allowed to warm to rt. Triphenylchloroacetonylphosphorane (984 mg, 2.79 mmol) was added followed by TBAI (27 mg, 70 μmol). The mixture was heated to reflux for 2 h, cooled and quenched with water (7 mL). The aqueous layer was extracted with diethyl ether (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (chloroform–methanol, 97:3 to 95:5) gave the phosphorane **317** as a pale brown foam that was used immediately. R_f = 0.90; (dichloromethane–methanol, 95:5); $[\alpha]_D^{25}$ −18.8 (*c* = 0.97, in $CHCl_3$); ν_{max} 2936, 1531, 1518, 1437, 1399, 1250, 1102, 1060, 1020, 828, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.68–7.63 (6H, m, CH-C17), 7.59–7.54 (3H, m, CH-C19), 7.49–7.44 (6H, m, CH-C18), 7.40 (2H, d, *J* = 8.7 Hz, CH-C3), 6.88 (2H, d, *J* = 8.7 Hz, CH-C4), 5.97 (1H, dddd, *J* = 17.1, 10.2, 6.9, 6.9 Hz, CH-C11), 5.43 (1H, s, CH-C6), 5.12–5.03 (2H, m, CH_2-C12), 4.48 (1H, dd, *J* = 10.5, 4.9 Hz, CH_2-C7), 4.10 (1H, d, J_{H-P} = 25.4 Hz, CH-C15), 4.06 (2H, s, CH_2-C13), 3.79 (3H, s, CH_3-C1), 3.75 (1H, ddd, *J* = 9.1, 8.5, 3.7 Hz, CH-C9), 3.67 (1H, dd, *J* = 10.5, 10.1 Hz, CH_2-C7), 3.50 (1H, ddd, *J* = 10.1, 9.1, 4.9 Hz, CH-C8), 2.78–2.72 (1H, m, CH_2-C10), 2.48–2.41 (1H, m, CH_2-C10); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 189.2 (C-C14), 160.0 (C-C2), 134.6 (CH-C11), 133.2 (6 × CH-C17), 132.3 (3 × CH-C19), 130.7 (C-C5), 129.0 (6 × CH-C18), 127.5 (2 × CH-C3), 126.4 (3 × C-C16), 117.2 (CH_2-C12), 113.7 (2 × CH-C4), 100.9 (CH-C6), 80.4 (CH-C9), 75.0 (CH_2-C13), 73.6 (CH-C8), 69.7 (CH_2-C7), 55.4 (CH_3-C1), 50.6 (CH-C15), 36.6 (CH_2-C10); HRMS (FAB+) for $C_{35}H_{36}O_5P$ ($[M+H]^+$) calcd 567.2300, found 567.2302.

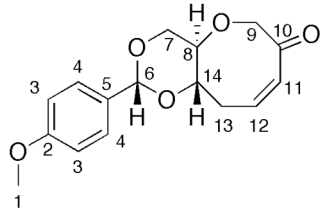
1-((2*R*,4*S*,5*R*)-4-Allyl-2-(4-methoxyphenyl)-1,3-dioxan-5-yloxy)but-3-en-2-one (318)



$C_{18}H_{22}O_5$

To a vigorously stirred solution of phosphorane **317** (1.3 g, 2.3 mmol) in diethyl ether (27 mL) at rt were added phosphate buffer (pH = 7, 22 mL) and formaldehyde (1.89 mL of a 37% w/w solution in water, 23.2 mmol). The resulting mixture was stirred at rt for 2 h. The aqueous layer was extracted with diethyl ether (3 × 30 mL) and the combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether–diethyl ether, 3:1 to 1:1) afforded diene **318** (61 mg, 83% two steps) as a colorless oil. R_f = 0.74; (diethyl ether–methanol, 95:5); $[\alpha]_D^{25}$ −26.9 (*c* = 1.00, in $CHCl_3$); ν_{max} 2856, 1700, 1614, 1517, 1397, 1248, 1111, 1084, 1031, 987, 825 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.40 (2H, d, *J* = 8.7 Hz, CH-C3), 6.88 (2H, d, *J* = 8.7 Hz, CH-C4), 6.50 (1H, dd, *J* = 17.6, 10.7 Hz, CH-C15), 6.35 (1H, dd, *J* = 17.6, 1.1 Hz, CH_2-C16), 5.98 (1H, dddd, *J* = 17.1, 10.2, 7.0, 6.9 Hz, CH-C11), 5.87 (1H, dd, *J* = 10.7, 1.1 Hz, CH_2-C16), 5.44 (1H, s, CH-C6), 5.13 (2H, m, CH_2-C12), 4.41 (1H, dd, *J* = 10.7, 5.0 Hz, CH_2-C7), 4.38 (2H, d, *J* = 1.2 Hz, CH_2-C13), 3.80 (3H, s, CH_3-C1), 3.77 (1H, ddd, *J* = 9.4, 7.1, 3.3, CH-C9), 3.67 (1H, dd, *J* = 10.7, 10.1 Hz, CH_2-C7), 3.39 (1H, ddd, *J* = 10.1, 9.4, 5.0 Hz, CH-C8), 2.73–2.68 (1H, m, CH_2-C10), 2.48–2.42 (1H, m, CH_2-C10); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 196.2 (C-C14), 160.1 (C-C2), 134.3 (CH-C11), 132.3 (CH-C15), 130.4 (C-C5), 129.6 (CH-C16), 127.5 (2 × CH-C3), 117.5 (CH_2-C12), 113.7 (2 × CH-C4), 101.0 (CH-C6), 79.9 (CH-C9), 74.4 (CH_2-C13), 73.9 (CH-C8), 69.1 (CH_2-C7), 55.4 (CH_3-C1), 36.3 (CH_2-C10); HRMS (EI+) for $C_{18}H_{22}O_5$ ($[M]^+$) calcd 318.1467, found 318.1465.

(2*R*,4a*R*,10a*S*,*Z*)-2-(4-Methoxyphenyl)-4,4a,10,10a-tetrahydro-[1,3]dioxino[5,4-*b*]oxocin-7(6*H*)-one (319)

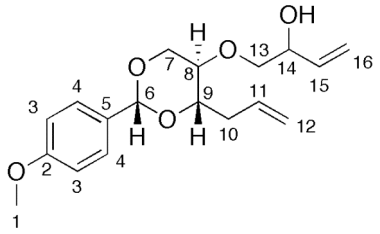


$C_{16}H_{18}O_5$

To a stirred solution of allylic alcohols **325** (1:1 mixture of diastereomers) (59 mg, 0.20 mmol) in dry dichloromethane (4 mL) was added Dess-Martin periodinane (115 mg, 0.263 mmol). The mixture was stirred for 30 min at rt. The reaction was quenched with a saturated aqueous solution of $Na_2S_2O_3$ solution (5 mL) and was allowed to stir for 20 min at rt. The aqueous layer was extracted with diethyl ether (3 × 20 mL) and combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (petroleum ether–diethyl ether, 9:1 to 1:1) afforded the cyclic enone **319** (51 mg, 86%) as a colorless solid.

R_f = 0.40; (petroleum ether–diethyl ether, 1:1); m.p. 166–167 °C; $[\alpha]_D^{18}$ −100 (*c* 0.93, in $CHCl_3$); ν_{max} 2939, 2862, 1674, 1519, 1249, 1180, 1033, 830 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.39 (2H, d, *J* = 8.7 Hz, CH-C3), 6.89 (2H, d, *J* = 8.7 Hz, CH-C4), 6.50 (1H, ddd, *J* = 12.4, 9.3, 7.9 Hz, CH-C12), 5.94–5.87 (1H, m, CH-C11), 5.45 (1H, s, CH-C6), 4.54 (1H, dd, *J* = 17.8, 1.2 Hz, CH_2-C9), 4.28 (1H, dd, *J* = 17.8, 1.2 Hz, CH_2-C9), 4.26 (1H, dd, *J* = 9.9, 4.5 Hz, CH_2-C7), 3.84–3.59 (3H, m, CH_2-C7, CH-C8, CH-C14), 3.80 (3H, s, CH_3-C1), 2.86–2.78 (1H, m, CH_2-C13), 2.65–2.59 (1H, m, CH_2-C10); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 202.0 (C-C10), 159.3 (C-C2), 135.9 (CH-C12), 128.8 (C-C5), 128.6 (CH-C11), 126.5 (2 × CH-C3), 112.9 (2 × CH-C4), 100.6 (CH-C6), 81.5 (CH-C14), 78.7 (CH_2-C9), 76.7 (CH-C8), 68.3 (CH_2-C7), 54.5 (CH_3-C1), 33.6 (CH_2-C13); HRMS (EI+) for $C_{16}H_{18}O_5$ ($[M]^+$) calcd 290.1154, found 290.1158.

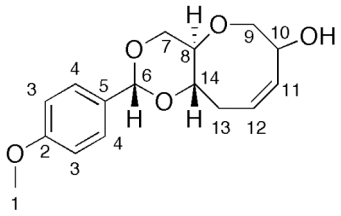
1-((2*R*,4*S*,5*R*)-4-Allyl-2-(4-methoxyphenyl)-1,3-dioxan-5-yloxy)but-3-en-2-ol (324)



$C_{18}H_{24}O_5$

To a stired solution of enone **318** (560 mg, 1.76 mmol) in methanol (20 mL) were added at rt $CeCl_3.7H_2O$ (1.3 g, 3.5 mmol) and $NaBH_4$ (76 mg, 1.9 mmol). The resulting mixture was stirred for 45 min at rt. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl solution (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 25 mL) and combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and the concentrated *in vacuo* to give the crude alcohol **324**. Flash column chromatography (petroleum ether–diethyl ether, 9:1 to 1:1) afforded a 1:1 mixture of diastereoisomers of alcohol **324** (510 mg, 90%) as a colourless oil. R_f = 0.69; (petroleum ether–diethyl ether, 3:7); ν_{max} 3451, 3418, 2859, 1614, 1518, 1247, 1105, 1031, 920, 825 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.40 (4H, d, *J* = 8.7 Hz, 2 × CH-C3), 6.88 (4H, d, *J* = 8.7 Hz, 2 × CH-C4), 5.97 (2H, dddd, *J* = 17.2, 10.2, 6.9, 6.9, Hz, 2 × CH-C11), 5.87–5.80 (2H, m, 2 × CH-C15), 5.42 (2H, s, 2 × CH-C6), 5.38 (2H, ddd, *J* = 17.2, 1.4, 1.4 Hz, 2 × CH_2-C16), 5.23 (2H, ddd, *J* = 10.6, 1.4, 1.3 Hz, 2 × CH_2-C16), 5.18–5.10 (4H, m, 2 × CH_2-C12), 4.41–4.37 (2H, m, 2 × CH_2-C7), 4.32–4.25 (2H, m, 2 × CH_2-C7), 3.80 (3H, s, CH_3-C1), 3.71-3.39 (10H, m, 2 × CH_2-C7, 2 × CH-C9, 2 × CH_2-C13, 2 × CH-C8), 2.66-2.61 (2H, m, 2 × CH_2-C10), 2.48-2.40 (2H, m, 2 × CH_2-C10), 2.29 (1H, d, *J* = 3.6 Hz, OH-C14), 2.23 (1H, d, *J* = 3.7 Hz, OH-C14); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 160.1 (C-C2), 136.3 (CH-C15, major), 136.3 (CH-C15, minor), 134.4 (CH-C11, minor), 134.4 (CH-C11, major), 130.4 (C-C5), 127.5 (CH-C3), 117.4 (CH_2-C12), 117.1 (CH_2-C16, minor), 117.0 (CH_2-C16, major), 113.7 (C-C4), 101.1 (CH-C6), 79.9 (CH-C9), 74.2 (CH_2-C13, minor), 74.1 (CH_2-C13, major), 73.4 (CH-C8, minor), 73.1 (CH-C8, major), 72.0 (CH_2-C14, minor), 71.8 (CH_2-C14, major), 69.3 (CH_2-C7, minor), 69.2 (CH_2-C7, major), 55.4 (CH_3-C1), 36.6 (CH_2-C10, minor), 36.5 (CH_2-C10, major); HRMS (FAB+) for $C_{18}H_{25}O_5$ ($[M+H]^+$) calcd 321.1702, found 321.1703; Anal. calcd for $C_{18}H_{24}O_5$: C, 67.48%; H, 7.55%. Found: C, 67.39%; H, 7.69%.

(2*R*,4a*R*,10a*S*,*Z*)-2-(4-Methoxyphenyl)-4,4a,6,7,10,10a-hexahydro-[1,3]dioxino[5,4-*b*]oxocin-7-ol (325)

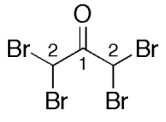


$C_{16}H_{20}O_5$

To stirred solution of alcohols **324** (1:1 mixture of diastereoisomers) (495 mg, 1.54 mmol) in dry and degassed dichloromethane (1.5 L) was added at rt a solution of Hoveyda-Grubbs second generation catalyst (48 mg, 80 μmol). The mixture was heated to reflux overnight and solvent was removed *in vacuo*. Flash column chromatography (dichloromethane–methanol, 97:3 to 95:5) afforded a 1:1 mixture of diastereomers of alcohol **325** (330 mg, 73%) as a colorless solid. R_f = 0.38, (dichloromethane–methanol, 96:4); m.p. 144–146 °C; ν_{max} 3325, 3217, 2931, 2862, 1620, 1518, 1249, 1103, 1033, 979, 826 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *diastereoisomer 1* δ_H 7.40 (2H, d, *J* = 8.7 Hz, CH-C3), 6.88 (2H, d, *J* = 8.7 Hz, CH-C4), 5.95–5.88 (1H, m, CH-C11), 5.62 (1H, ddd, *J* = 10.6, 7.4, 1.3 Hz, CH-C11), 5.41 (1H, s, CH-C6), 4.83–4.75 (1H, m, CH-C10), 4.21–4.16(1H, dd, *J* = 5.1, 5.1 Hz, CH_2-C7), 3.91–3.77 (2H, m, CH_2-C9, CH-C14), 3.79 (3H, s, CH_3-C1), 3.68 (1H, ddd, *J* = 9.7, 9.7, 4.7 Hz, CH-C8), 3.60–3.40 (1H, m, CH_2-C7), 3.29 (1H, dd, *J* = 10.8, 10.8 Hz, CH_2-C9), 2.55–2.39 (2H, m, CH_2-C13), 1.71 (1H, d, *J* = 4.6 Hz, OH-C10); ^{13}C NMR (100 MHz, $CDCl_3$) *diastereoisomer 1* δ_C 160.2 (C-C2), 134.3 (CH-C11), 130.3 (C-C5), 127.6 (2 × CH-C3), 126.4 (CH_2-C12), 113.8 (2 × CH-C4), 101.7 (CH-C6), 82.9 (CH-C14), 73.0 (CH-C8), 71.9 (CH_2-C9), 69.8 (CH_2-C7), 67.5 (CH-C10), 55.5 (CH_3-C1), 33.7 (CH_2-C13); ^1H NMR (400 MHz, $CDCl_3$) *diastereoisomer 2* δ_H 7.40 (2H, d, *J* = 8.7 Hz, CH-C3), 6.88 (2H, d, *J* = 8.7 Hz, CH-C4), 5.85–5.81 (2H, m, CH-C11, CH-C12), 5.38 (1H, s, CH-C6), 4.62–4.55 (1H, m, CH-C10), 4.21–4.16 (1H, dd, *J* = 4.9, 4.8 Hz, CH_2-C7), 3.89 (1H, dd, *J* = 11.6, 3.7 Hz, CH_2-C9), 3.79 (3H, s, CH_3-C1 3.60–3.40 (4H, m, CH_2-C7, CH-C8, CH_2-C9, CH-C14), 3.29 (1H, dd, *J* = 10.8, 10.8 Hz, CH_2-C9), 2.82–2.74 (1H, m, CH_2-C13), 2.55–2.39 (1H, m, CH_2-C13), 1.58 (1H, d, *J* = 4.1 Hz, OH-C10); ^{13}C NMR (100 MHz, $CDCl_3$) *diastereoisomer 2* δ_C 160.2 (C-C2), 137.3 (CH-C11), 130.3 (C-C5), 127.5 (2 × CH-C3), 127.1 (CH_2-C12), 113.8 (2 × CH-C4), 101.2 (CH-C6), 79.9 (CH-C14), 75.6 (CH-C8), 75.4 (CH_2-C9), 69.6 (CH_2-C7), 69.6 (CH-C10), 55.5 (CH_3-C1), 30.7

(CH_2-C13); HRMS (EI+) for $C_{16}H_{20}O_5$ ($[M]^+$) calcd 290.1311, found 250.1316; Anal. calcd for $C_{16}H_{20}O_5$: C, 65.74%; H, 6.90%. Found: C, 65.68%; H, 6.95%.

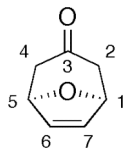
1,1,3,3-Tetrabromopropan-2-one (329)



$C_3H_2OBr_4$

Bromine (65 mL, 1.3 mol) was added dropwise over 3 h to a strirred solution of acetone (25.0 mL, 340 mmol) and HBr (30 mL of a 48% aqueous solution, 265 mmol) at 0 °C. The resulting mixture was allowed to warm to rt and stirred overnight. After cooling to 0 °C, water (200 mL) and dichloromethane (300 mL) were added. Layers were separated and the organic layer was washed with a saturated aqueous solution of $NaHCO_3$ (300 mL) and with a mixture (1:3) of a saturated aqueous solution of $Na_2S_2O_3$ and water (200 mL). The combined aqueous layers were extracted with dichloromethane (2 × 300 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting oil was distilled to afford an orange oil. Crystallisation using petroleum ether and ethyl acetate delivered the tetrabromoacetone **329** (58.6 g, 46%) as a colourless solid. R_f = 0.66; (petroleum ether-diethyl ether, 7:3); m.p. 38–39 °C (Lit.[177] m.p. 38 °C); ν_{max} ($CDCl_3$) 3009, 1753, 1731, 1269, 1141, 1088, 1024 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 6.37 (2H, app. s CH-C2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 183.4 (C-C1), 33.9 (2 × CH-C2); HRMS (CI+, isobutane) for $C_3H_2Br_4O$ ($[M+H]^+$) calcd 374.6877, found 374.6882; Anal. calcd for $C_3H_2Br_4O$: C, 9.64%; H, 0.54%. Found: C, 9.65%; H, 0.49%.

(1*R*,5*S*)-8-Oxabicyclo[3.2.1]oct-6-en-3-one (332)



$C_7H_8O_2$

To a stirred suspension of activated zinc powder (52.8 g, 808 mmol) in THF (135 mL) at rt was added furan (60.0 mL, 810 mmol). A solution of tetrabromoacetone **329** (100.7 g, 269.4 mmol) and triethyl borate (69 mL, 404 mmol) in THF (80 mL) was added dropwise followed by bromine (150 μL). The mixture was gently heated to 35–40 °C until the exothermic reaction started. The oil bath was removed and the reaction was monitored by NMR. Furan (30.0 mL, 404 mmol) and bromine (100 μL) were added and the resulting mixture was stirred overnight at rt. The reaction mixture was cooled to 0 °C, quenched with ice-cold water (300 mL), stirred for 30 min at rt and filtered through a short plug of Celite®. The residue was washed several times with diethyl ether (altogether 1.2 L) and the combined organic layers were washed with water (2 × 300 mL) and brine (2 × 200 mL). The combined aqueous layers were re-extracted with diethyl ether (3 × 200 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* (max 25 °C). The residue was dissolved in dry MeOH (250 mL) to form solution A.

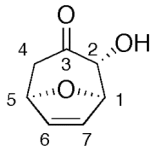
A solution of Zn/Cu couple (70 g, 1.1 mol) and NH_4Cl (43.2 g, 808 mmoL) in dry MeOH (100 mL) was cooled to −78 °C and portion of the solution A (ca.10%) was added dropwise. The resulting mixture was stirred for 15 min at −78 °C and placed into an ice bath. Addition of solution A was completed and the solution was stirred overnight at rt. The mixture was then cooled to 0 °C and filtered through a short plug of Celite®. The residue was washed several times with diethyl ether (altogether 1 L) and the combined organic layers were washed with brine (300 mL). The combined aqueous layers were re-extracted with chloroform (5 × 200 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The resulting oil was filtered through solid K_2CO_3 using chloroform and concentrated to afford a dark-brown oil. Purification by flash column chromatography (petroleum ether-diethyl ether, 9:1 to 3:1) afforded the ketone **332** (15.4 g, 47% 2 steps) as colorless solid. R_f = 0.36; (petroleum ether-

diethyl ether, 1:1); m.p. 38–39 °C (Lit.[1] m.p. 38 °C); ν_{max} 2963, 2859, 1712, 1342, 1080, 1040, 949, 849 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 6.27 (2H, app. s, CH-C6, CH-C7), 5.05 (2H, d, *J* = 5.0 Hz, CH-C1, CH-C5), 2.77 (2H, dd, *J* = 16.5, 5.0, Hz, CH_2-C2, CH_2-C4), 2.34 (2H, dd, *J* = 16.5, 0.6, Hz, CH_2-C2, CH_2-C4); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 205.3 (C-C3), 13.3 (CH-C6, CH-C7), 77.1 (CH-C1, CH-C5), 46.6 (CH_2-C2, CH_2-C4); HRMS (CI+, isobutane) for $C_7H_9O_2$ ($[M+H]^+$) calcd 125.0603, found: 125.0600; Anal. calcd for $C_7H_8O_2$: C, 67.73%; H, 6.50%. Found: C, 67.44%; H, 6.51%.

Preparation of the Zn/Cu couple:

To a vigorously stirred solution of copper(II) acetate monohydrate (31.2 g, 156 mmol) in acetic acid (100 mL) heated to reflux was added zinc dust (50 g, 760 mol), portionwise. After complete addition, the mixture was heated at reflux for 5 min and cooled to rt. The resulting Zn/Cu couple was washed with acetic acid (400 mL), water (400 mL), acetone (400 mL) and diethyl ether (1 L). The Zn/Cu couple was heated to 30 °C under high-vacuum overnight.

(1*R*,2*R*,5*R*)-2-Hydroxy-8-oxabicyclo[3.2.1]oct-6-en-3-one (339)



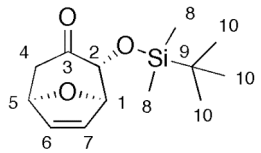
$C_7H_8O_3$

To freshly distilled DIPA (22.5 mL, 161 mmoL) in THF (210 mL) at –78 °C was added dropwise *n*-BuLi (68.9 mL of a 2.5 M solution in hexane, 172 mmol). The mixture was placed at rt and stirred for 30 min before being cooled to –78 °C. A solution of ketone **332** (14.3 g, 115 mmol) and TESCl (32.6 mL, 195 mmol) in THF (220 mL) was added dropwise followed by Et_3N (42 mL, 298 mmol). The reaction was quenched at –78 °C with a saturated aqueous solution of NH_4Cl (300

mL) and the resulting mixture was allowed to warm up. The aqueous layer was extracted with ethyl acetate (3 × 300 mL) and the combined organic layers were washed with brine (250 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting silyl enol ether **337** was used without further purification.

To a solution of the crude silyl enol ether **337** in a 1:1 mixture of THF/H_2O (170 mL) was added at 0 °C *m*-CPBA (25.7 g, 115 mmol). The mixture was allowed to warm to rt overnight. The resulting mixture was cooled at 0 °C and TFA (8.5 mL) was added dropwise, stirred for 1 h and quenched with solid Na_2CO_3 (until 9<pH<10). The aqueous layer was saturated with solid NaCl and the mixture was filtered through cotton to remove the excess salt. The aqueous layer was extracted with ethyl acetate (3 × 200 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether-diethyl ether, 3:1 to 3:2) afforded the hydroxyketone **339** (4.8 g, 42% over 2 steps) as colourless solid. R_f = 0.49; (petroleum ether-ethyl acetate, 4:6); m.p. 47–48 °C (Lit.[181] m.p. 46–48 °C); ν_{max} 3371, 2962, 1720, 1180, 1041, 980, 848 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 6.42 (1H, dd, *J* = 6.0, 1.2 Hz, CH-C6), 6.24 (1, dd, *J* = 6.0, 1.8 Hz, CH-C7), 5.05–4.03 (1H, m, CH-C5), 4.95 (1H, app. s, CH-C1), 3.71 (1H, d, *J* = 8.0 Hz, CH-C2), 3.08 (1H, d, *J* = 8.0 Hz, OH-C2), 3.07 (1H, dd, *J* = 16.5, 4.9 Hz, CH_2-C4), 2.34 (1H, d, *J* = 16.5 Hz, CH_2-C4); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 204.8 (C-C3), 136.7 (CH-C6), 129.5 (C-C7), 82.4 (CH-C1), 77.5 (CH-C5), 75.5 (CH-C2), 44.6 (CH_2-C4); HRMS (EI+) for $C_7H_8O_3$ ($[M]^+$) calcd 140.0473, found 140.0475.

(1*R*,2*R*,5*R*)-2-(*tert*-Butyldimethylsilyloxy)-8-oxabicyclo[3.2.1]oct-6-en-3-one (340)

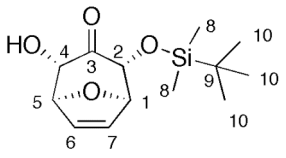


$C_{13}H_{22}O_3Si$

To a stirred solution of hydroxyketone **339** (2.89 g, 20.7 mmol) and imidazole (3.11 g, 45.7 mmol) in dichloromethane (64 mL) was added at 0 °C TBSCl (5.68 g, 36.5 mmol). The resulting mixture was stirred overnight and quenched with a 1:1 mixture of diethyl ether and water (50 mL in total). The

aqueous layer was extracted with diethyl ether (3 × 50 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (1% Et_3N, petroleum ether-diethyl ether, 9:1 to 3:1) afforded the ketone **340** (4.9g, 94%) as a colourless oil. R_f = 0.52; (petroleum ether-diethyl ether, 7:3); ν_{max} 2955, 2854, 1728, 1257, 1095, 1057, 1020, 779 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 6.39 (1H, dd, *J* = 6.0, 1.2 Hz, CH-C6), 6.17 (1, dd, *J* = 6.0, 1.8 Hz, CH-C7), 5.01–4.99 (1H, m, CH-C5), 4.81 (1H, br s, CH-C1), 3.67 (1H, s, CH-C2), 3.06 (1H, dd, *J* = 15.9, 4.8 Hz, CH_2-C4), 2.28 (1H, d, *J* = 15.9 Hz, CH_2-C4), 0.91 (9H, s, 3 × CH_3-C10), 0.14 (3H, s, 3 × CH_3-C8), 0.08 (3H, s, 3 × CH_3-C8); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 204.3 (C-C3), 137.1 (CH-C6), 129.7 (C-C7), 83.2 (CH-C1), 77.4 (CH-C5), 75.8 (CH-C2), 45.2 (CH_2-C4), 25.6 (3 × CH_3-C10), 18.4 (C-C9), –4.7 (CH_3-C8), –4.8 (CH_3-C8); HRMS (FAB+) for $C_{13}H_{22}O_3SiNa$ ($[M+Na]^+$) calcd 277.1236, found: 277.1235.

(1*R*,2*R*,4*S*,5*S*)-2-(*tert*-Butyldimethylsilyloxy)-4-hydroxy-8-oxabicyclo[3.2.1] oct-6-en-3-one (342)



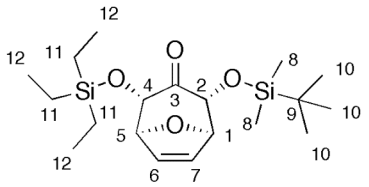
$C_{13}H_{22}O_4Si$

To freshly distilled DIPA (3.69 mL, 26.4 mmoL) in THF (27 mL) at –78 °C was added dropwise *n*-BuLi (11.3 mL of a 2.5 M solution in hexane, 28.3 mmol). The mixture was placed at rt and stirred for 30 min before being cooled to –78 °C. A solution of ketone **340** (4.83 g, 18.8 mmol) and TESCl (5.35 mL, 32.0 mmol) in THF (29 mL) was added dropwise followed by Et_3N (6.83 mL, 49.0 mmol). The reaction was quenched at –78 °C with a saturated aqueous solution of NH_4Cl (60 mL) and the resulting mixture was allowed to warm to rt. The aqueous layer was extracted with ethyl acetate (3 × 60 mL) and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting silyl enol ether **341** was used without further purification.

To a solution of the crude silyl enol ether **341** in a 1:1 mixture of THF/H_2O (56 mL) at 0 °C was added *m*-CPBA (4.22 g, 18.8 mmol). The mixture

was allowed to warm to rt overnight, then cooled to 0 ºC and TFA (1.4 mL) was added dropwise. The mixture was stirred for 1 h and quenched with a saturated aqueous solution of Na_2CO_3 (60 mL, 9<pH<10). The aqueous layer was saturated with solid NaCl and the mixture was filtered through cotton to remove the excess salt. The aqueous layer was extracted with ethyl acetate (3 × 60 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether-ethyl acetate, 8:2) afforded the hydroxyketone **342** (3.0 g, 59% 2 steps) as colourless solid. R_f = 0.20 (petroleum ether–diethyl ether, 3:7); m.p. 48–49 ºC; ν_{max} 3441, 2955, 2862, 1728, 1257, 1066, 1034, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 6.32 (1H, dd, *J* = 6.2, 1.6 Hz, CH-C6), 6.27 (1H, dd, *J* = 6.2, 1.6 Hz, CH-C7), 4.90 (1H, dd, *J* = 1.6, 1.5 Hz, CH-C5), 4.81 (1H, dd, *J* = 1.6, 1.4 Hz, CH-C1), 3.82 (1H, dd, *J* = 1.4, 1.3 Hz, CH-C2), 3.77 (1H, ddd, *J* = 10.5, 1.5, 1.3 Hz, CH-C4), 3.46 (1H, d, *J* = 10.5 Hz, OH-C4), 0.92 (9H, s, 3 × CH_3-C10), 0.14 (3H, s, CH_3-C8), 0.12 (3H, s, CH_3-C8); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 202.5 (C-C3), 132.8 (CH-C6), 132.2 (C-C7), 83.8 (CH-C1), 83.0 (CH-C5), 77.4 (CH-C2), 77.3 (CH-C4), 25.6 (3 × CH_3-C10), 18.2 (C-C9), –4.9 (CH_3-C8), –5.2 (CH_3-C8); HRMS (CI+, isobutane) for $C_{13}H_{23}O_4Si$ ($[M+H]^+$) calcd 271.1366, found 271.1369.

(1*R*,2*R*,4*S*,5*S*)-2-(*tert*-Butyldimethylsilyloxy)-4-(triethylsilyloxy)-8-oxabicyclo [3.2.1]oct-6-en-3-one (346)

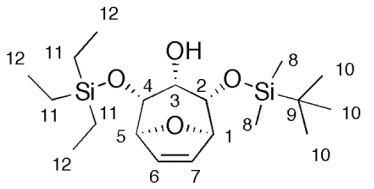


$C_{19}H_{36}O_4Si_2$

To a stirred solution of hydroxyketone **342** (507 mg, 1.87 mmol) and imidazole (191 mg, 2.81 mmol) in dichloromethane (4 mL) was added at 0 ºC TESCl (376 μL, 2.25 mmol). The mixture was stirred overnight and quenched with a mixture (1:1) of diethyl ether and water (50 mL). The aqueous layer was extracted with diethyl ether (3 × 30 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (1% Et_3N, petroleum ether-diethyl ether, 9:1 to 7:3) afforded

the ketone **346** (574 mg, 80% yield) as colourless solid. R_f = 0.76; (petroleum ether-diethyl ether, 7:3); m.p. 34–35 °C; ν_{max} 2954, 2929, 2877, 1729, 1472, 1463, 1252, 1121, 1104, 1066, 1006, 864, 876 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 6.26 (2H, app. s, CH-C6, CH-C7), 4.82–4.81 (2H, m, CH-C1, CH-C5), 3.65 (2H, br d, *J* = 8.1 Hz, CH-C2, CH-C4), 0.96 (9H, t, *J* = 7.9, Hz, 3 × CH_3-C12), 0.91 (9H, s, 3 × CH_3-C10), 0.69–0.63 (6H, m, 3 × CH_2-C11), 0.14 (3H, s, CH_3-C8), 0.10 (3H, s, CH_3-C8); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 204.0 (C-C3), 132.8 (CH-C6), 132.8 (C-C7), 83.6 (CH-C5), 83.5 (CH-C1), 76.1 (CH-C4), 75.9 (CH-C2), 26.0 (3 × CH_3-C10), 18.6 (C-C9), 6.9 (3 × CH_3-C12), 4.7 (3 × CH_2-C11), –4.5 (CH_3-C8), –4.9 (CH_3-C8); HRMS (FAB+) for $C_{19}H_{36}O_4Si_2Na$ ($[M+Na]^+$) calcd 407.2050, found 407.2047; Anal. calcd for $C_{19}H_{36}O_4Si_2$: C, 59.33%; H, 9.43%. Found: C, 59.44%; H, 9.58%.

(1*R*,2*S*,3*S*,4*R*,5*S*)-2-(*tert*-Butyldimethylsilyloxy)-4-(triethylsilyloxy)-8-oxabicyclo[3.2.1]oct-6-en-3-ol (348)



$C_{19}H_{38}O_4Si_2$

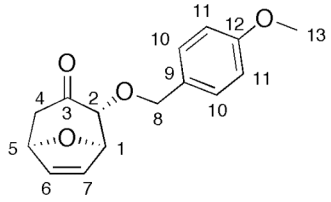
To a stirred solution of ketone **346** (610 g, 1.59 mmol) in methanol (2 mL) at 0 ºC was added a solution of $MgBr_2$ (584 mg, 3.17 mmol) in methanol (7 mL). After 5 min, $NaBH_4$ (69 mg, 1.7 mmol) was added and the mixture was stirred for 1 h at 0 ºC and quenched with a saturated aqueous solution of NH_4Cl (15 mL). The aqueous layer was extracted with ethyl acetate (3 × 30 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (1% Et_3N, petroleum ether-diethyl ether, 9:1 to 7:3) afforded the alcohol **348** (587 mg, 96%) as colourless oil. R_f = 0.65; (petroleum ether-diethyl ether, 7:3); ν_{max} 2954, 2877, 1729, 1472, 1463, 1251, 1131, 1076, 1040, 972, 861 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 6.25 (2H, app. s, CH-C6, CH-C7), 4.67–4.65 (2H, m, CH-C1, CH-C5), 3.84 (1H, ddd, *J* = 12.4, 5.0, 5.0 Hz, CH-C3), 3.71–3.69 (2H, m, CH-C2, CH-C4), 2.70 (1H, d, *J* = 12.4 Hz, OH-C3), 0.99 (9H, t, *J* = 7.9, Hz, 3 × CH_3-C12), 0.94 (9H, s, 3 × CH_3-C10), 0.67–0.63 (6H, m, 3 × CH_2-C11), 0.12 (3H, s, CH_3-C8), 0.10 (3H, s, CH_3-C8);

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 132.7 (CH-C6), 132.7 (C-C7), 82.9 (CH-C5), 82.8 (CH-C1), 68.3 (CH-C4), 68.2 (CH-C2), 64.6 (CH-C3), 26.0 (3 × CH_3-C10), 18.4 (C-C9), 7.0 (3 × CH_3-C12), 5.1 (3 × CH_2-C11), −4.4 (CH_3-C8), −4.6 (CH_3-C8); HRMS (FAB+) for $C_{19}H_{39}O_4Si_2$ ($[M+H]^+$) calcd 387.2387, found 387.2383); Anal. calcd for $C_{19}H_{38}O_4Si_2$: C, 59.02%; H, 9.91%. Found: C, 58.98%; H, 9.98%.

Preparation of the 4-methoxybenzyltrichloroacetamidate:

To a stirred suspension of NaH (190 mg of a 60% suspension in mineral oils, 7.92 mmol) in diethyl ether (40 mL) was added at rt a solution of 4-methoxybenzyl alcohol (5.80 mL, 46.7 mmol) in diethyl ether (60 mL). After 5 min the mixture was cooled to 0 ºC and trichloroacetonitrile (5.00 mL, 49.9 mmol) was added dropwise over 15 min. The resulting mixture was stirred for 30 min at 0 ºC then 45 min at rt, diluted with diethyl ether (100 mL) and quenched with a saturated aqueous solution of $NaHCO_3$ (100mL). The organic layer was washed with brine (100 mL) and concentrated *in vacuo*. The crude 4-methoxybenzyltrichloroacetamidate (13 g) was used without further purification.

(1*R*,2*R*,5*R*)-2-(4-Methoxybenzyloxy)-8-oxabicyclo[3.2.1]oct-6-en-3-one (359)

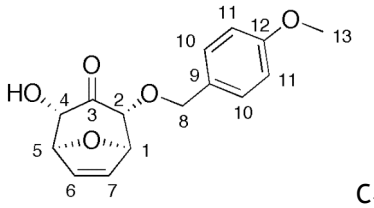


$C_{15}H_{16}O_4$

To a stirred solution of 4-methoxybenzyltrichloroacetamidate (9.56 g, 33.5 mmol) in dichloromethane (15 mL) at 0 ºC, was added CSA (519 mg, 2.23 mmol) and a solution of hydroxyketone **339** (3.13 g, 22.3 mmol) in dichloromethane (30 mL). The resulting mixture was stirred overnight. 4-methoxybenzyltrichloroacetamidate (3.18 g, 11.2 mmol) was added and the reaction mixture was stirred at rt for 12 h, diluted with diethyl ether (200 mL).

The organic layer was washed with an aqueous saturated $NaHCO_3$ solution (100 mL) and brine (100 mL). The combined organic layers were re-extracted with diethyl ether (100 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether-diethyl ether, 9:1 to 8:2) afforded ketone **359** (5 g, 85%) as a colourless solid. R_f = 0.34; (petroleum ether-diethyl ether, 1:1); m.p. 60–61 °C; ν_{max} 2958, 1717, 1611, 1513, 1247, 1174, 1080, 1058, 1030, 819 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.30 (2H, d, *J* = 8.6 Hz, CH-C11), 6.88 (2H, d, *J* = 8.6 Hz, CH-C10), 6.40 (1H, dd, *J* = 6.0, 1.3 Hz, CH-C6), 6.12 (1H, dd, *J* = 6.0, 3.6 Hz, CH-C7), 5.04–5.01 (1H, m, CH-C5), 4.92 (1H, br s, CH-C1), 4.67 (1H, d, *J* = 11.9, CH_2-C8), 4.44 (1H, d, *J* = 11.9, CH_2-C8), 3.81 (3H, s, CH_3-C13), 3.39 (1H, br s, CH-C2), 3.08 (1H, dd, *J* = 16.0, 4.8 Hz, CH_2-C4), 2.32 (1H, d, *J* = 16.0 Hz, CH_2-C4); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 203.6 (C-C3), 159.5 (C-C12), 137.1 (CH-C6), 130.0 (2 × CH-C11), 129.3 (CH-C7), 129.2 (C-C9), 113.8 (2 × CH-C10), 81.2 (CH-C1), 79.7 (CH-C2), 77.4 (CH-C5), 71.8 (CH_2-C8), 55.3 (CH_3-C13), 45.4 (CH_2-C4); HRMS (EI+) for $C_{15}H_{16}O_4$ ($[M]^+$) calcd 260.1049, found 260.1050; Anal. calcd for $C_{15}H_{16}O_4$: C, 69.22%; H, 6.20%. Found: C, 69.19%; H, 6.19%.

(1*S*,2*S*,4*R*,5*R*)-2-Hydroxy-4-(4-methoxybenzyloxy)-8-oxabicyclo[3.2.1]oct-6-en-3-one (360)



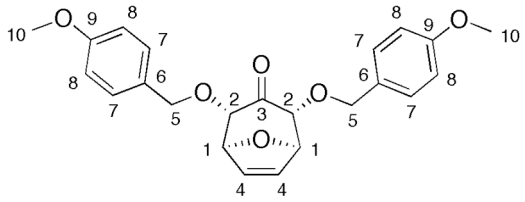
$C_{15}H_{16}O_5$

To freshly distilled diisopropylamine (2.03 mL, 14.5 mmoL) in THF (15 mL) at –78 °C was added dropwise *n*-BuLi (6.07 mL of a 2.5 M solution in hexane, 15.2 mmol). The mixture was placed at rt and stirred for 30 min before being cooled to –78 °C. A solution of ketone **359** (1.9 g, 7.2 mmol) and TESCl (2.06 mL, 12.3 mmol) in THF (11 mL) was added dropwise followed by Et_3N (2.62 mL, 18.8 mmol). The reaction was quenched at –78 °C with a saturated aqueous solution of NH_4Cl (25 mL) and the resulting mixture was allowed to warm to rt. The aqueous layer was extracted with ethyl acetate (3 × 30 mL) and the combined

organic layers were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting silyl enol ether **361** was used without further purification.

To a solution of the crude silyl enol ether **361** in dichloromethane (75 mL) was added at −78 ºC a freshly prepared solution of DMDO (94 mL of a 0.085 M solution in acetone, 8.0 mmol). The mixture was allowed to warm to 0 °C and concentrated *in vacuo*. The resulting oil was dissolved in tetrahydrofuran (25 mL) and water (12.5 mL) and the solution was cooled to 0 ºC. Acetic acid (2.5 mL) was added dropwise and the resulting mixture was stirred at 0 ºC for 1 h. The reaction was neutralised with saturated aqueous solution of $NaHCO_3$ (100 mL). The aqueous layer was extracted with ethyl acetate (3 × 150 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether-diehyl ether, 3:1 to 3:7) afforded the hydroxyketone **360** (1.03 g, 52% 2 steps) as a colourless solid. R_f = 0.34; (petroleum ether-diethyl ether, 3:7); m.p. 104–105 ºC; ν_{max} 3474, 2946, 1725, 1612, 1514, 1248, 1175, 1074, 1033, 815 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.30 (2H, d, *J* = 8.7 Hz, CH-C11), 6.88 (2H, d, *J* = 8.7 Hz, CH-C10), 6.32 (1H, dd, *J* = 6.1, 1.8 Hz, CH-C6), 6.23 (1H, dd, *J* = 6.1, 1.8 Hz, CH-C7), 4.94 (1H, ddd, *J* = 1.8, 1.6, 0.5 Hz, CH-C1), 4.93 (1H, ddd, *J* = 1.8, 1.6, 0.5 Hz, CH-C5), 4.62 (1H, d, *J* = 11.4, CH_2-C8), 4.45 (1H, d, *J* = 11.4, CH_2-C8), 3.81 (3H, s, CH_3-C13), 3.77 (1H, ddd, *J* = 10.9, 1.6, 1.3 Hz, CH-C4), 3.56 (1H, dd, *J* = 1.6, 1.3 Hz, CH-C2), 3.47 (1H, d, *J* = 10.9 Hz, OH-C4); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 202.0 (C-C3), 159.6 (C-C12), 132.8 (CH-C6), 132.2 (CH-C7), 130.2 (2 × CH-C11), 128.7 (C-C9), 113.9 (2 × CH-C10), 82.9 (CH-C5), 81.6 (CH-C1), 81.3 (CH-C2), 77.1 (CH-C4), 72.0 (CH_2-C8), 55.3 (CH_3-C13); HRMS (EI+) for $C_{15}H_{16}O_5$ ($[M]^+$) calcd 276.0998, found 276.0997.

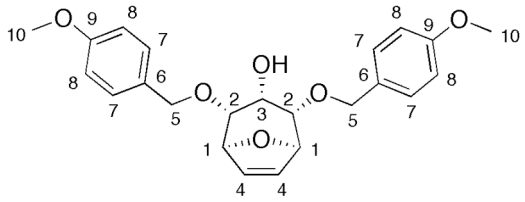
(1*R*,2*R*,4*S*,5*S*)-2,4-bis(4-Methoxybenzyloxy)-8-oxabicyclo[3.2.1]oct-6-en-3-one (362)



$C_{23}H_{24}O_6$

To a stirred solution of 4-methoxybenzyltrichloroacetamidate (1.3 g, 4.7 mmol) in dichloromethane (3 mL) at 0 ºC, was added CSA (72 mg, 0.31 mmol) and a solution of hydroxyketone **360** (861 mg, 3.12 mmol) in dichloromethane (10 mL) and the resulting mixture was then stirred overnight. 4-Methoxybenzyltrichloroacetamidate (890 mg, 3.12 mmol) was added twice and the reaction mixture was stirred for an additional 24 h. the mixture was diluted with diethyl ether (150 mL) and the organic layer was washed with a saturated aqueous solution of $NaHCO_3$ (100 mL) and brine (100 mL). The combined organic layers were re-extracted with diethyl ether (2 × 150 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether-diethyl ether, 3:1 to 1:3) afforded ketone **362** (944 mg, 76%) as a colourless solid. R_f = 0.47; (petroleum ether-diethyl ether, 3:7); m.p. 86–87 ºC; ν_{max} 2955, 1720, 1604, 1512, 1249, 1172, 1087, 1057, 1034, 817 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.31 (4H, d, *J* = 8.7 Hz, CH-C8), 6.87 (4H, d, *J* = 8.7 Hz, CH-C7), 6.20 (2H, app. s, CH-C4), 4.93 (2H, app. s, CH-C1), 4.74 (2H, d, *J* = 11.9 Hz, CH_2-C5), 4.49 (1H, d, *J* = 11.9 Hz, CH_2-C5), 3.80 (6H, s, CH_3-C10), 3.43 (2H, app. s, CH-C2); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 202.4 (C-C3), 159.4 (2 × C-C9), 132.7 (2 × CH-C4), 129.9 (4 × CH-C8), 129.3 (2 × C-C6), 113.8 (4 × CH-C7), 81.3 (2 × CH-C1), 79.7 (2 × CH-C2), 71.6 (2 × CH_2-C5), 55.3 (2 × CH_3-C10); HRMS (EI+) for $C_{23}H_{24}O_6$ ($[M]^+$) calcd 396.1573, found 396.1569; Anal. calcd for $C_{23}H_{24}O_6$: C, 69.68%; H, 6.10%. Found: C, 69.29%; H, 6.10%.

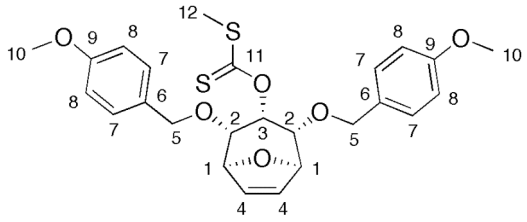
(1*R*,2*S*,3*r*,4*R*,5*S*)-2,4-bis(4-Methoxybenzyloxy)-8-oxabicyclo[3.2.1]oct-6-en-3-ol (364)



$C_{23}H_{26}O_4$

To a stirred solution of ketone **362** (944 mg, 2.38 mmol) in methanol (10 mL) and tetrahydrofuran (4 mL) at 0 ºC was added a solution of $MgBr_2$ (877 mg, 4.76 mmol) in methanol (10 mL). After 10 min, $NaBH_4$ (103 mg, 2.62 mmol) was added and the mixture was stirred for 1 h at 0 ºC and quenched with a saturated aqueous solution of NH_4Cl (40 mL). The aqueous layer was extracted with ethyl acetate (3 × 200 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (dichloromethane-methanol, 100:0 to 99:1) afforded the alcohol **364** (812 mg, 85%, 10:1 mixture of diastereisomers) as colourless oil. R_f = 0.46; (diethyl ether); ν_{max} 3541, 2947, 2839, 1512, 1250, 1172, 1120, 1058, 1034, 818 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *major diastereoisomer* δ_H 7.33 (4H, d, *J* = 8.6 Hz, CH-C8), 6.87 (4H, d, *J* = 8.6 Hz, CH-C7), 6.14 (2H, app. s, CH-C4), 4.75 (2H, br s, CH-C1), 4.74 (2H, d, *J* = 12.3 Hz, CH_2-C5), 4.65 (1H, d, *J* = 12.3 Hz, CH_2-C5), 4.02 (1H, dt, *J* = 11.8, 5.4 Hz, CH-C3), 3.80 (6H, s, CH_3-C10), 3.43 (2H, dd, *J* = 5.4, 1.7 Hz, CH-C2), 3.07 (1H, d, *J* = 11.8 Hz, OH-C3); ^{13}C NMR (100 MHz, $CDCl_3$) *major diastereoisomer* δ_C 159.2 (2 × C-C9), 132.3 (2 × CH-C4), 130.2 (2 × C-C6), 129.7 (4 × CH-C8), 113.8 (4 × CH-C7), 79.9 (2 × CH-C1), 73.0 (2 × CH-C2), 72.3 (2 × CH_2-C5), 64.6 (CH-C3), 55.3 (2 × CH_3-C10); HRMS (EI+) for $C_{23}H_{26}O_6$ ($[M]^+$) calcd 398.1729, found 398.1734; Anal. calcd for $C_{23}H_{26}O_4$: C, 68.10%; H, 5.99%. Found: C, 68.09%; H, 6.16%.

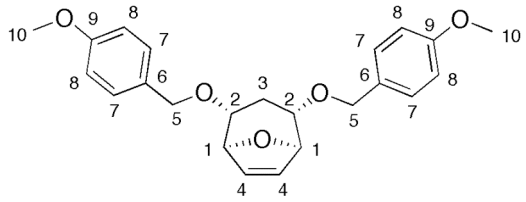
_O_-(1_R_,2_R_,3_s_,4_S_,5_S_)-2,4-bis(4-Methoxybenzyloxy)-8-oxabicyclo[3.2.1]oct-6-en-3-yl _S_-methyl carbonodithioate (365)



$C_{25}H_{28}O_6S_2$

To a stirred suspension of KH (697 mg of a 30% suspension in mineral oils, 5.21 mmol) in tetrahydrofuran (25 mL) at 0 ºC was added dropwise a solution of alcohol **364** (1.4 g, 3.5 mmol) in tetrahydrofuran (25 mL). After 5 min, carbon disulfite (2.09 mL, 34.7 mmol) was added, followed after 10 min by iodomethane (2.16 mL, 34.7 mmol). The resulting mixture was stirred at 0 ºC for 1 h, diluted with ethyl acetate (50 mL) and quenched with a saturated aqueous solution of NH_4Cl (50 mL). The aqueous layer was extracted with ethyl acetate (3 × 50 mL) and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether-diethyl ether, 1:1 to 1:3) afforded the dithiocarbonate **365** (1.52 g, 90 %) as a yellow oil. R_f = 0.38; (petroleum ether-diethyl ether, 3:7); ν_{max} 2955, 2839, 1612, 1512, 1249, 1211, 1072, 817 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.33 (4H, d, *J* = 7.6 Hz, CH-C8), 6.85 (4H, d, *J* = 7.6 Hz, CH-C7), 6.23 (2H, app. s, CH-C4), 6.02 (1H, t, *J* = 5.0 Hz, CH-C3), 4.77 (2H, br s, CH-C1), 4.71 (2H, d, *J* = 12.3 Hz, CH_2-C5), 4.63 (2H, d, *J* = 12.3 Hz, CH_2-C5), 3.80 (6H, s, CH_3-C10), 3.79 (2H, m, CH-C2), 2.58 (3H, s, CH_3-C12); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 215.5 (C-C11), 159.1 (2 × C-C9), 132.8 (2 × CH-C4), 130.4 (2 × C-C6), 129.7 (4 × CH-C8), 113.6 (4 × CH-C7), 81.0 (2 × CH-C1), 77.2 (CH-C3), 72.2 (2 × CH_2-C5), 70.4 (2 × CH-C2), 55.2 (2 × CH_3-C10), 19.1 (CH_3-C12); HRMS (EI+) for $C_{25}H_{28}O_6S_2$ ($[M]^+$) calcd 488.1327, found 488.1322.

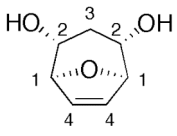
(1*R*,2*S*,4*R*,5*S*)-2,4-bis(4-Methoxybenzyloxy)-8-oxabicyclo[3.2.1]oct-6-ene (366)



$C_{23}H_{26}O_5$

To a stirred solution of dithiocarbonate **365** (1.5 g, 3.1 mmol) in benzene (14 mL) at rt was added VAZO® (62 mg, 0.25 mmol) and Bu_3SnH (1.1 mL, 4.0 mmol). The resulting mixtured was immediately heated to reflux and the reaction monitored by NMR. After 8 h, 90% completion was reached and the reaction mixture was concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether-diethyl ether, 1:1 to 1:3) afforded the protected diol **366** (795 mg, 67 %) as a colourless solid. R_f = 0.25; (petroleum ether-diethyl ether, 3:7); m.p. 109–110 °C; ν_{max} 2930, 2836, 2357, 1612, 1513, 1247, 1174, 1098, 1035 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.31 (4H, d, *J* = 8.6 Hz, CH-C8), 6.86 (4H, d, *J* = 8.6 Hz, CH-C7), 6.21 (2H, app. s, CH-C4), 4.82 (2H, br s, CH-C1), 4.62 (2H, d, *J* = 12.4 Hz, CH_2-C5), 4.59 (2H, d, *J* = 12.4 Hz, CH_2-C5), 3.80 (6H, s, CH_3-C10), 3.26 (2H, ddd, *J* = 5.7, 1.4, 1.3 Hz, CH-C2), 2.10 (1H, dt, *J* = 15.7, 5.7 Hz, CH_2-C3), 1.94 (1H, dt, *J* = 15.7, 1.4 Hz, CH_2-C3); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 159.2 (2 × C-C9), 133.2 (2 × CH-C4), 130.9 (2 × C-C6), 129.7 (4 × CH-C8), 113.8 (4 × CH-C7), 81.2 (2 × CH-C1), 70.0 (2 × CH_2-C5), 69.7 (2 × CH-C2), 55.4 (2 × CH_3-C10), 27.8 (CH_2-C3); HRMS (EI+) for $C_{23}H_{26}O_5$ ($[M]^+$) calcd 382.1780, found 382.1778.

(1*R*,2*S*,4*R*,5*S*)-8-Oxabicyclo[3.2.1]oct-6-ene-2,4-diol (374)



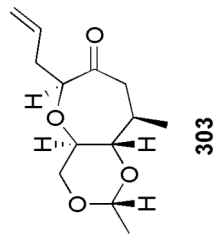
$C_7H_{10}O_3$

To a stirred solution of the protected diol **366** (52.8 mg, 138 µmol) in dichloromethane (1.5 mL) at 0 °C was added 2,6 lutidine (200 µL, 1.67 mmol) and TMSOTf (190 µL, 1.10 mmol). The resulting mixture was stirred 30 min at 0

ºC then at rt overnight. The mixture was cooled to 0 ºC and quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL). The aqueous layer was extracted with diethyl ether (3 ×15 mL) and the combined organic layers were washed with an aqueous saturated $CuSO_4$ solution (2 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting silyl ether **375** was used without further purification.

To a stirred solution of the crude silyl ether **375** in tetrahydrofuran (2.5 mL) at rt was added TBAF (350 µL, 345 µmol). The reaction mixture was stirred for 1 h and concentrated *in vacuo*. Purification by flash column chromatography (ethyl acetate-methanol, 99:1 to 95:5) afforded the diol **374** (15.2 mg, 78%) as a colourless oil. R_f = 0.15; (ethyl acetate-methanol, 95:5); ν_{max} 3356, 2924, 2854, 1458, 1257, 1080 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 6.31 (2H, app. s, CH-C4), 4.70 (2H, app. s, CH-C1), 3.64 (2H, br s, CH-C2), 2.51 (2H, br d, 6.8 Hz, OH-C2), 2.28 (1H, dt, *J* = 15.5, 4.7 Hz, CH_2-C3), 1.77–1.73 (1H, m, CH_2-C3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 133.0 (2 × CH-C4), 83.9 (2 × CH-C1), 65.2 (2 × CH-C2), 33.5 (CH_2-C3); HRMS (CI+, isobutane) for $C_7H_{11}O_3$ ($[M+H]^+$) calcd 143.0708, found 143.0703.

Appendix



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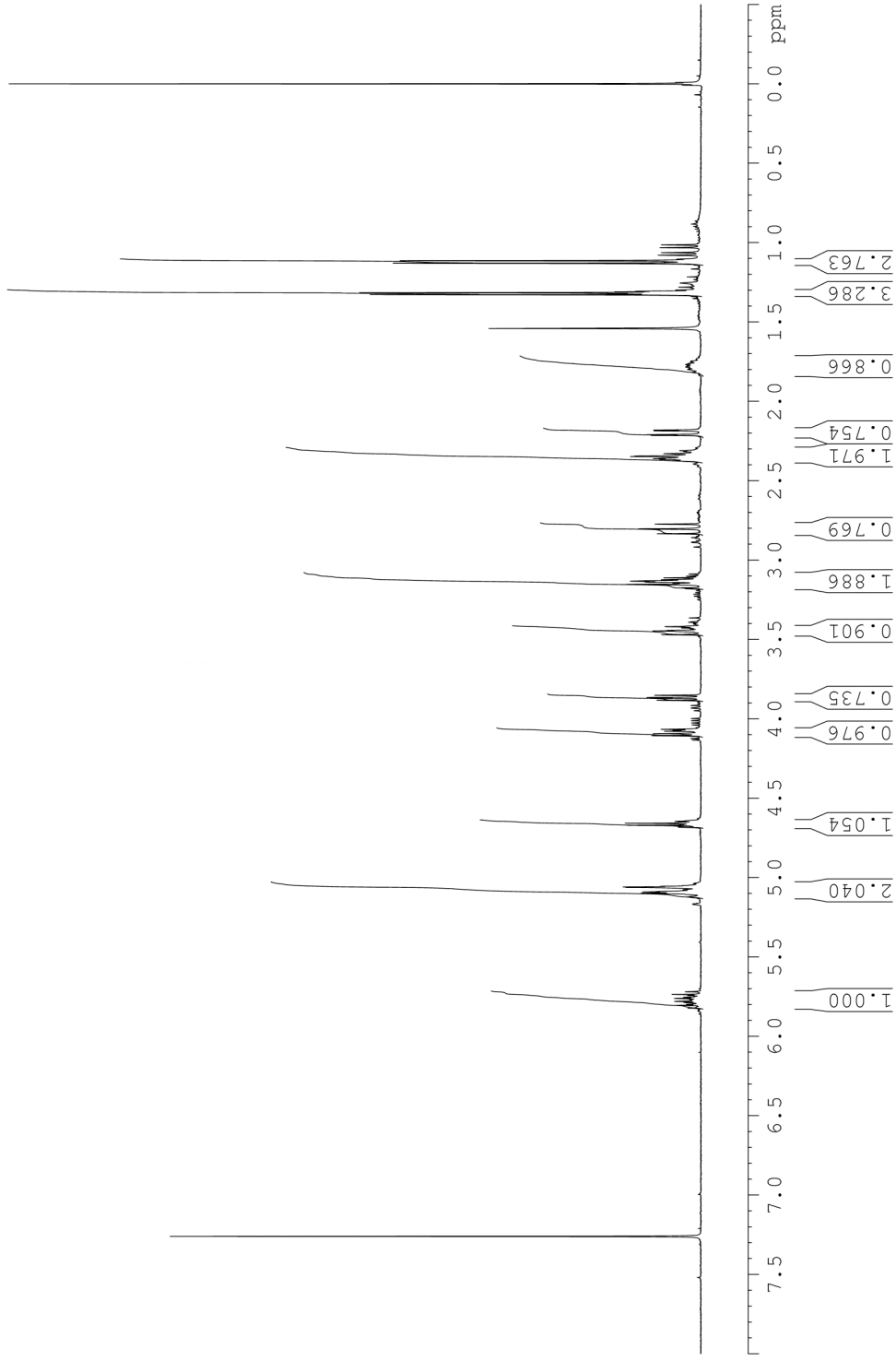
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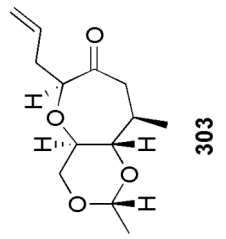

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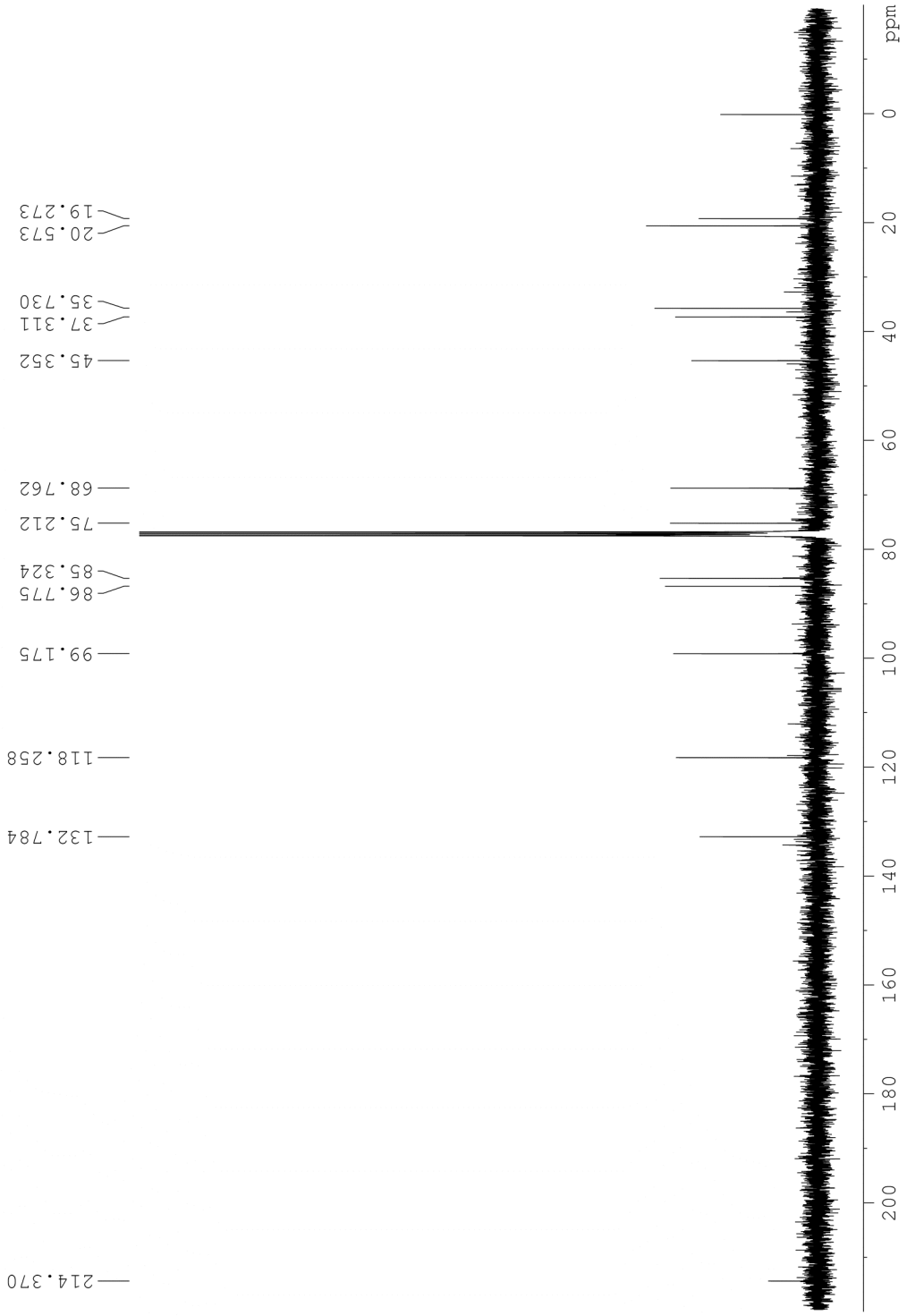
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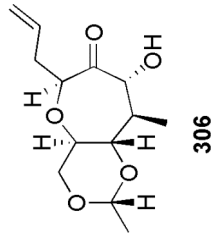

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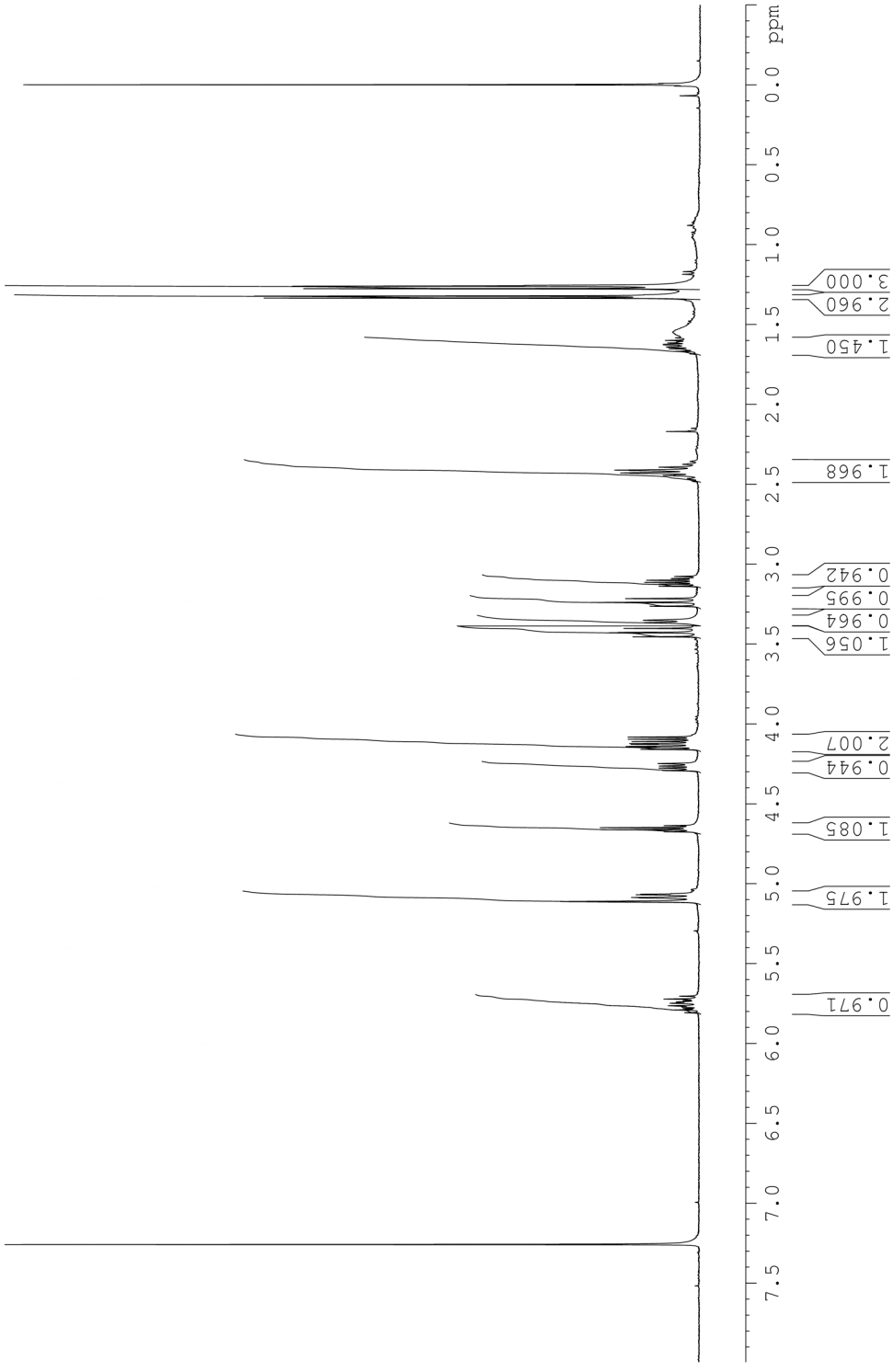
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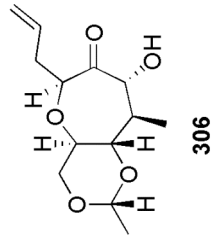

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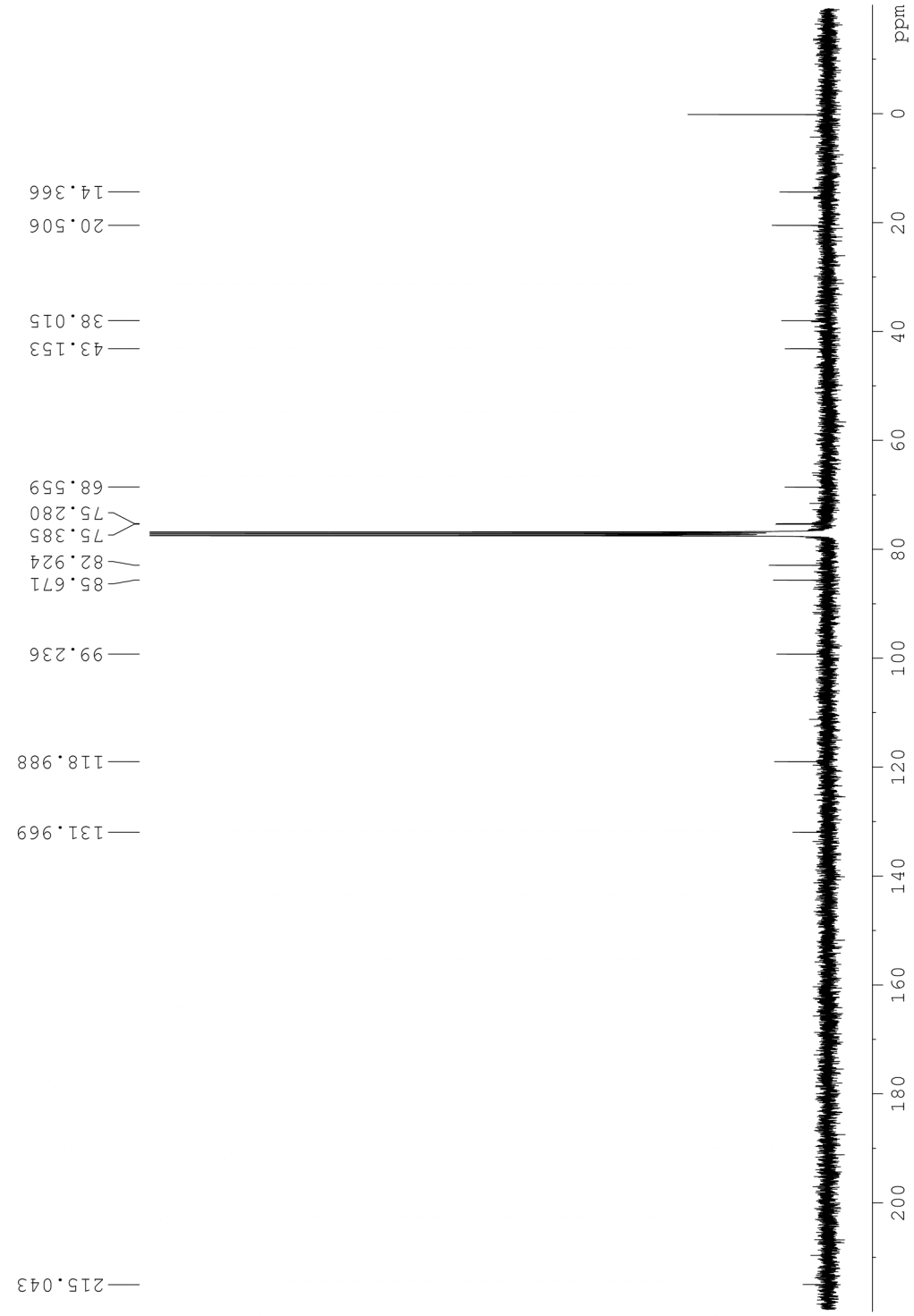
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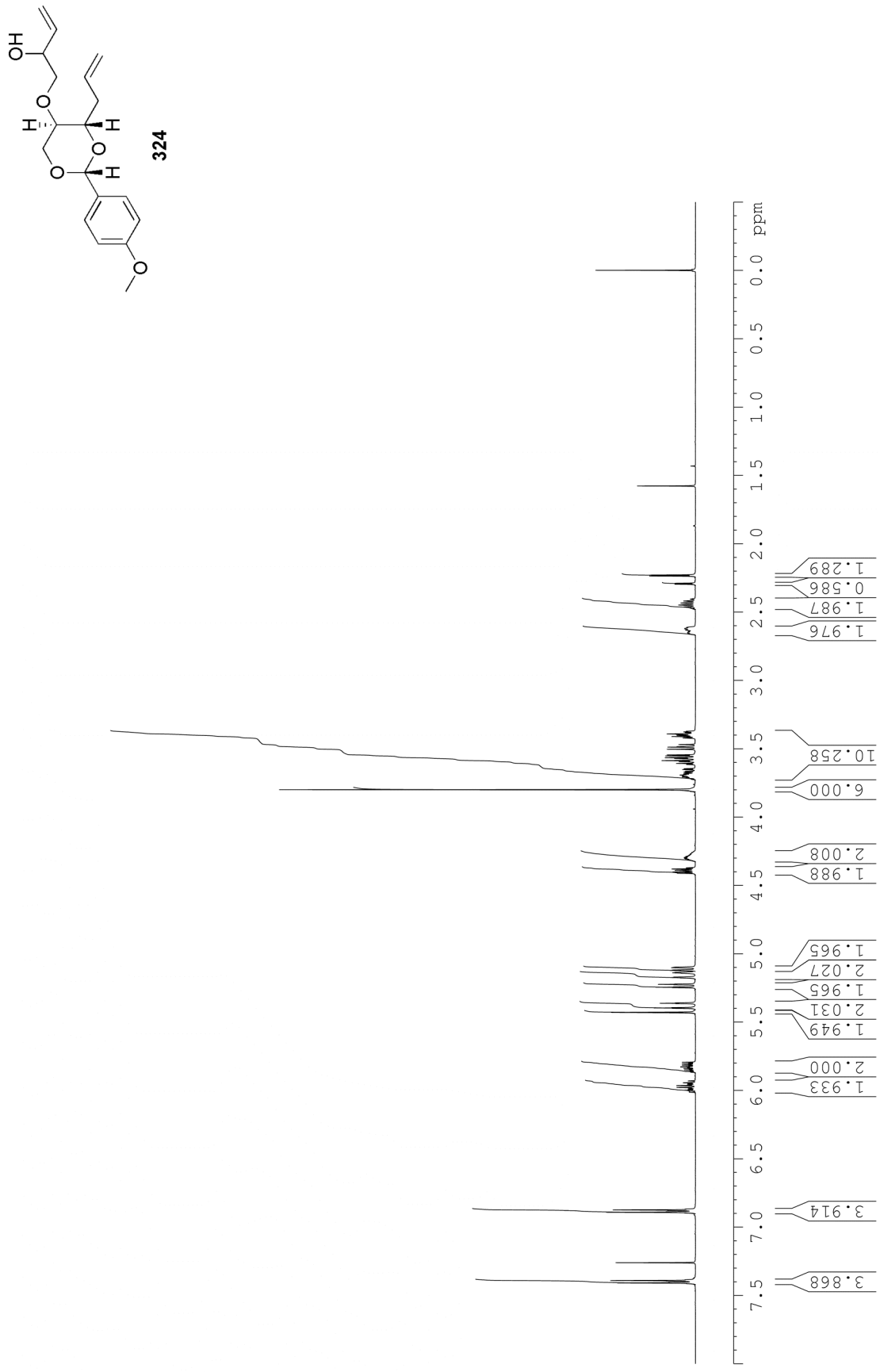
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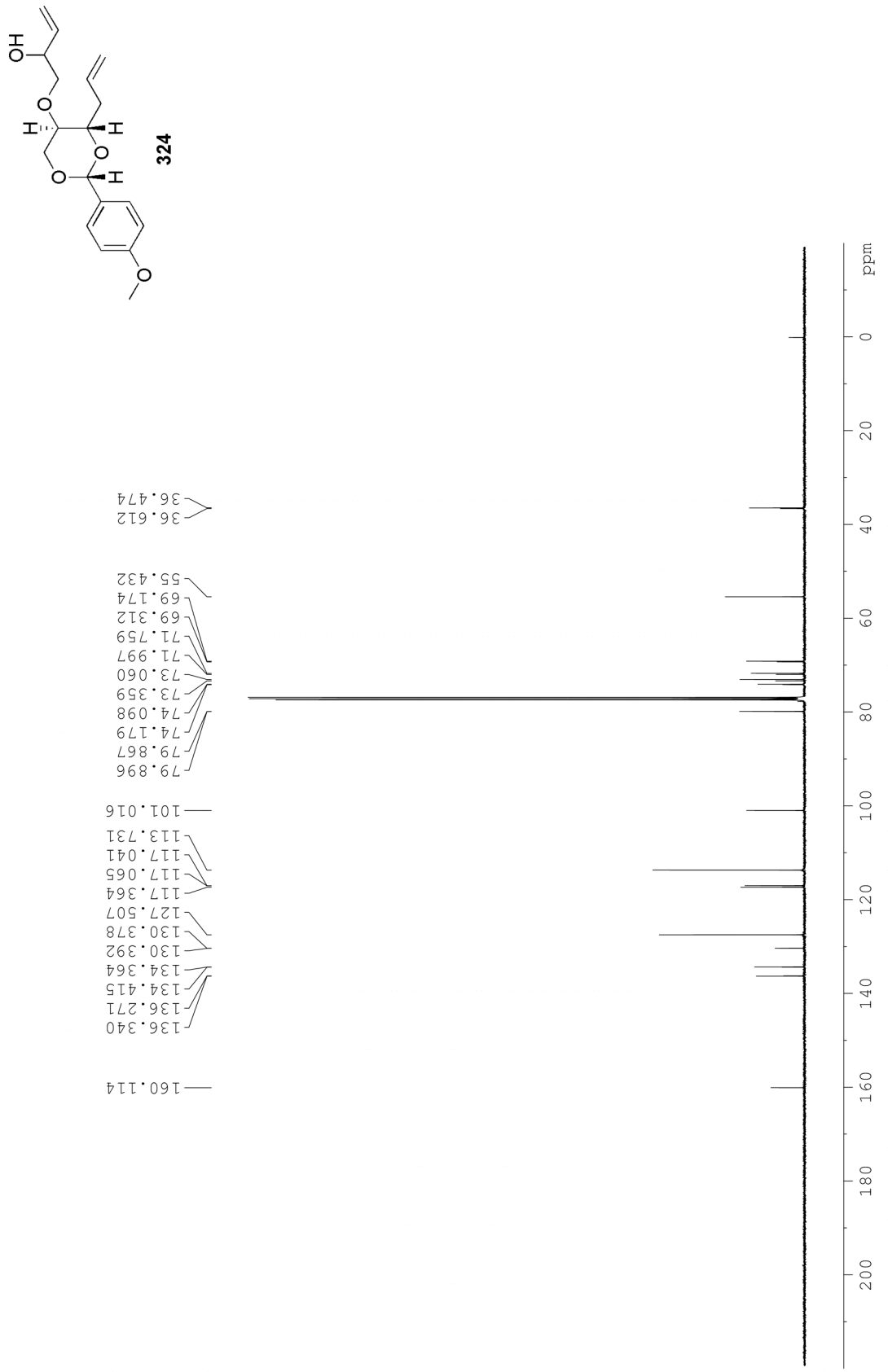
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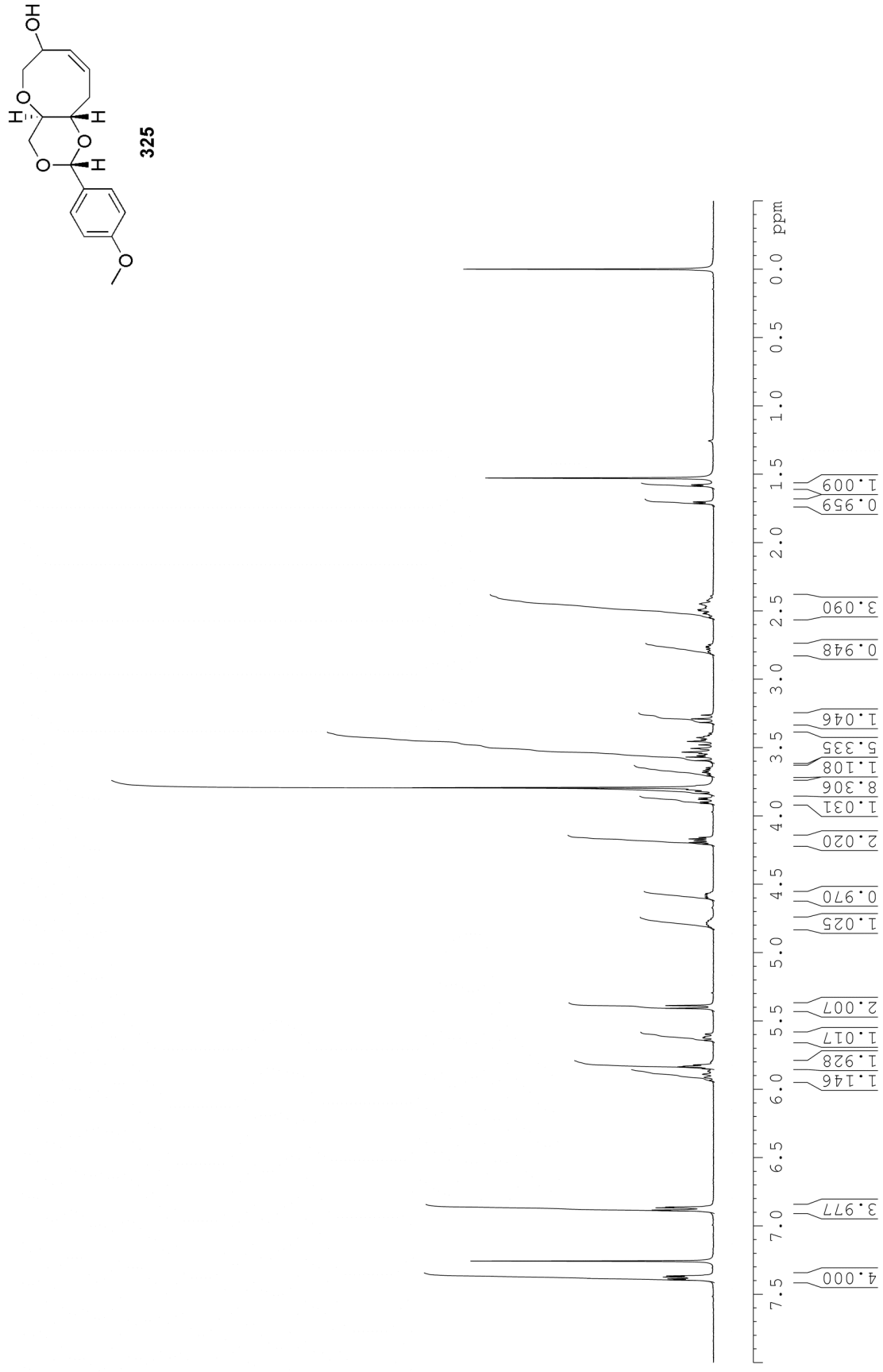
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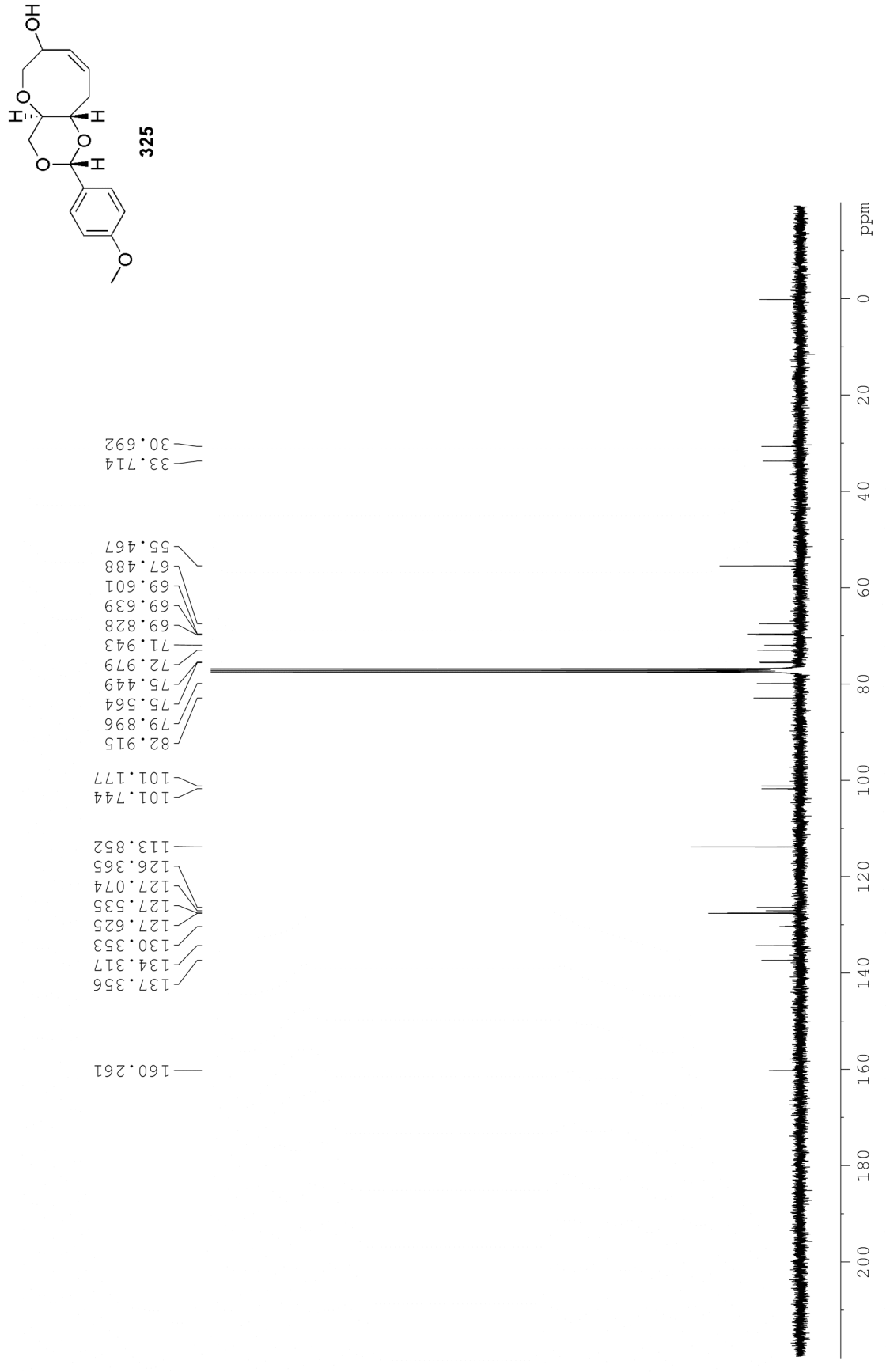
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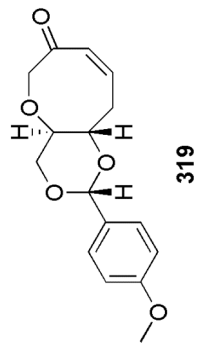

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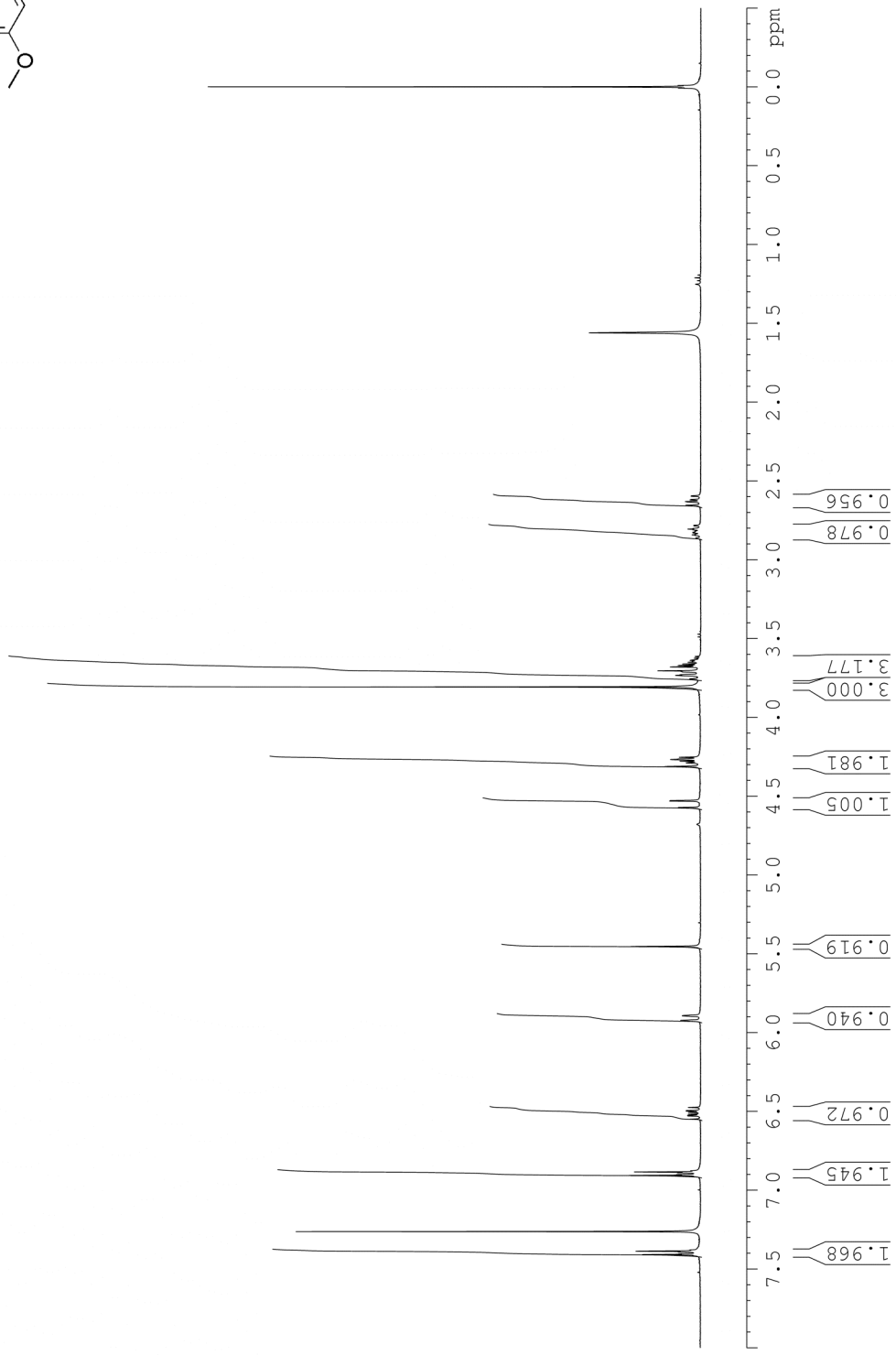
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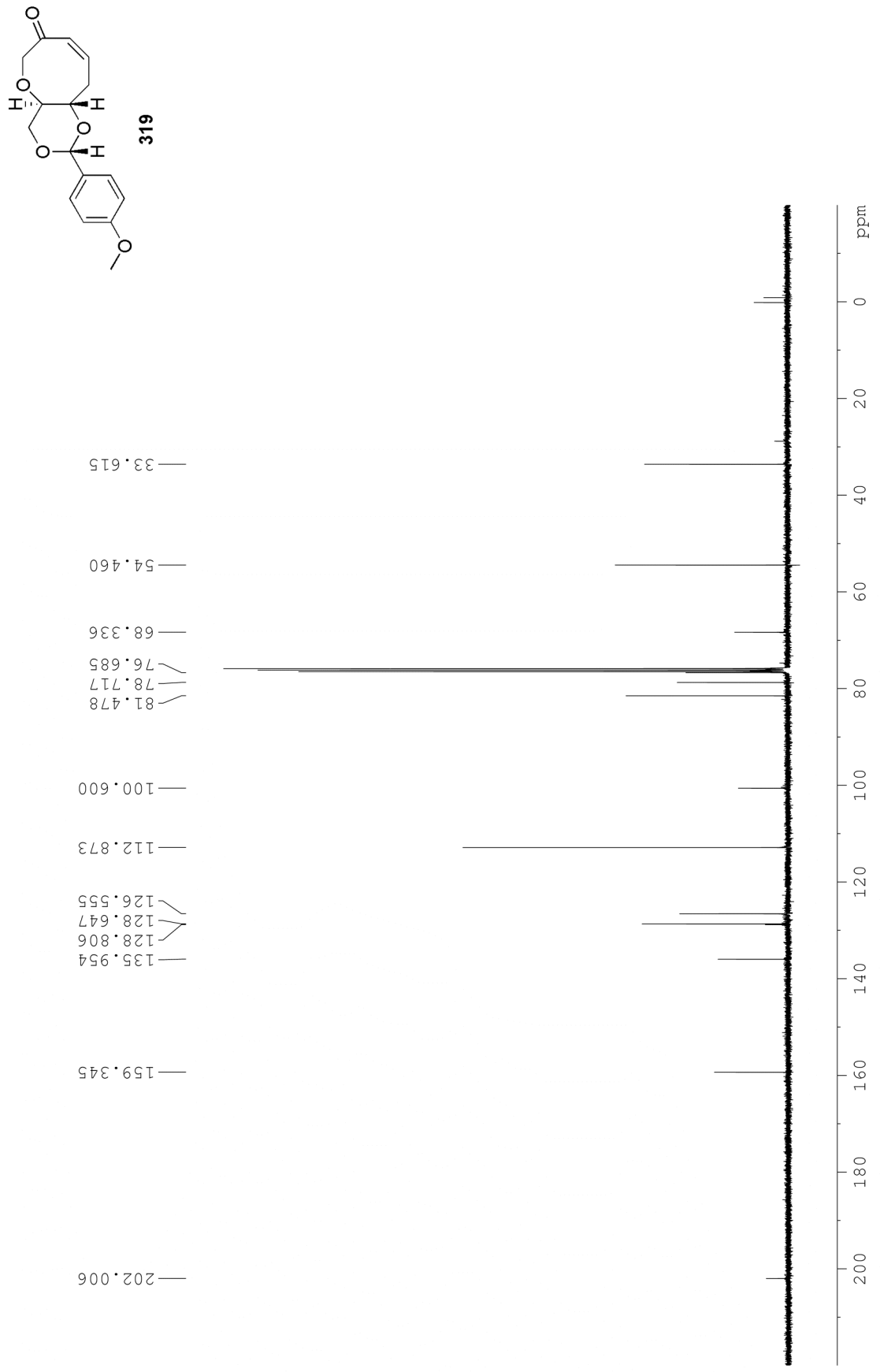
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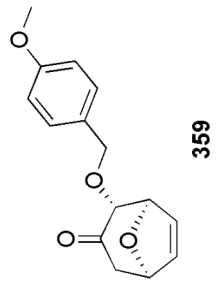

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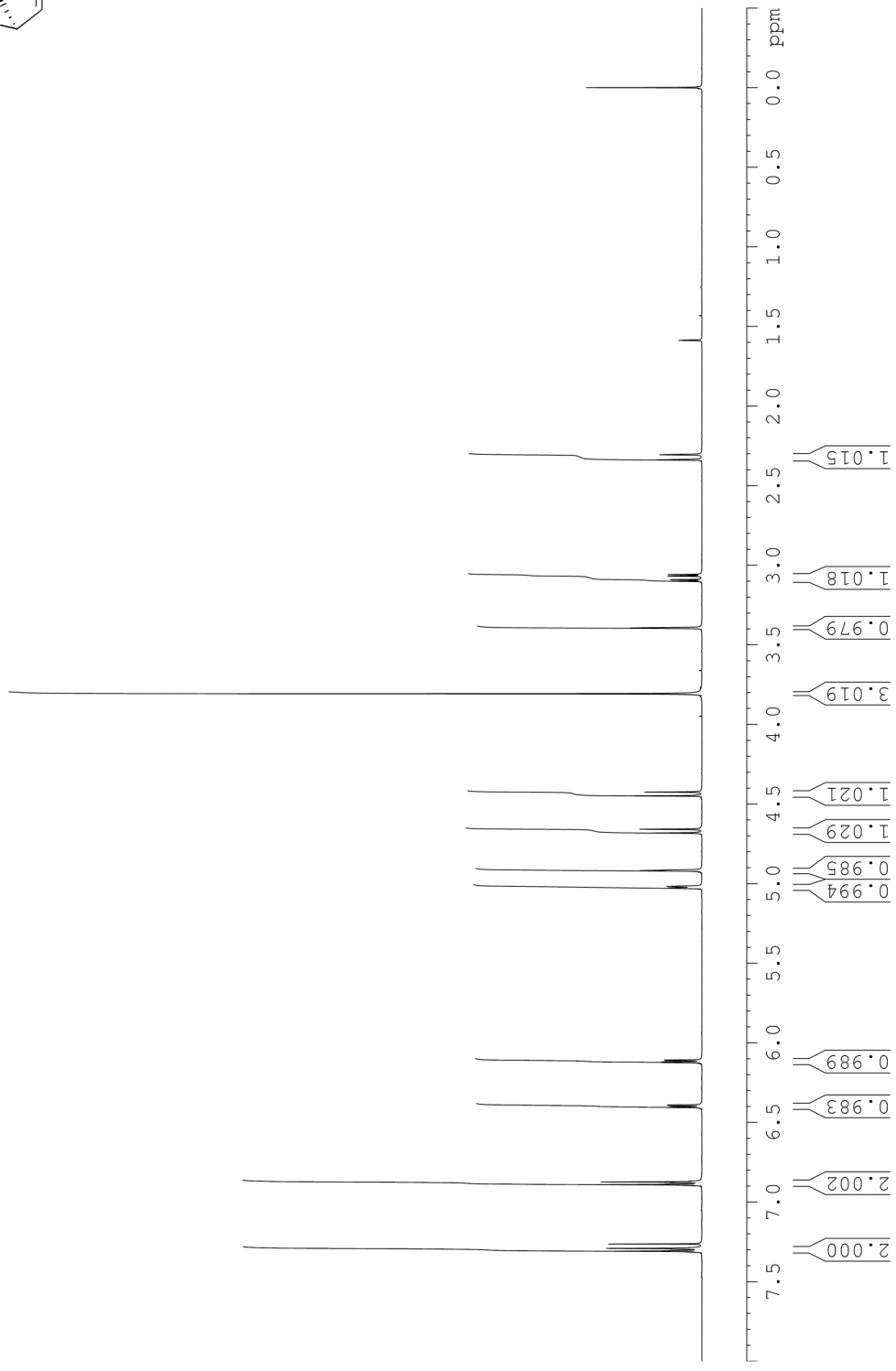
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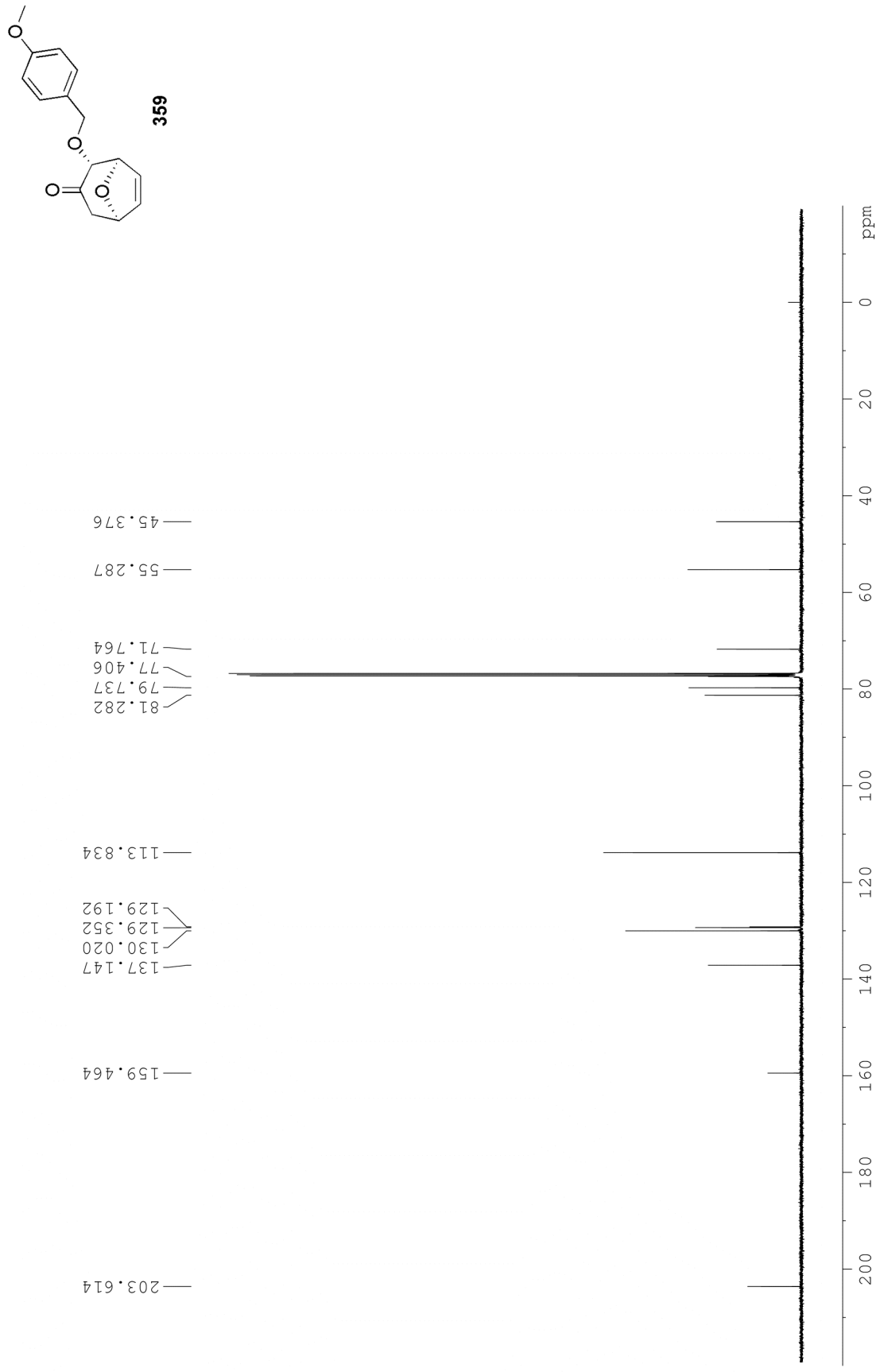
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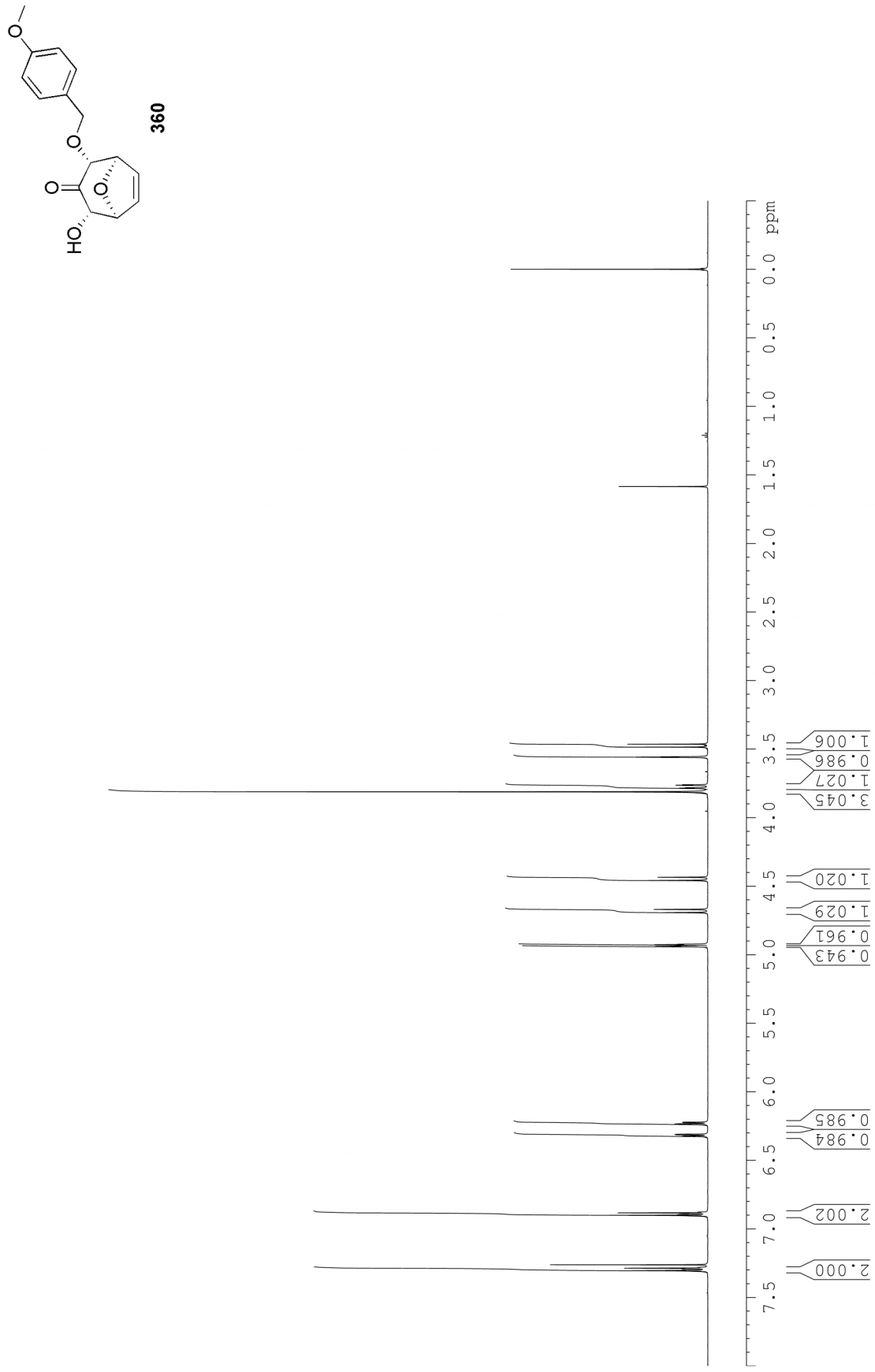
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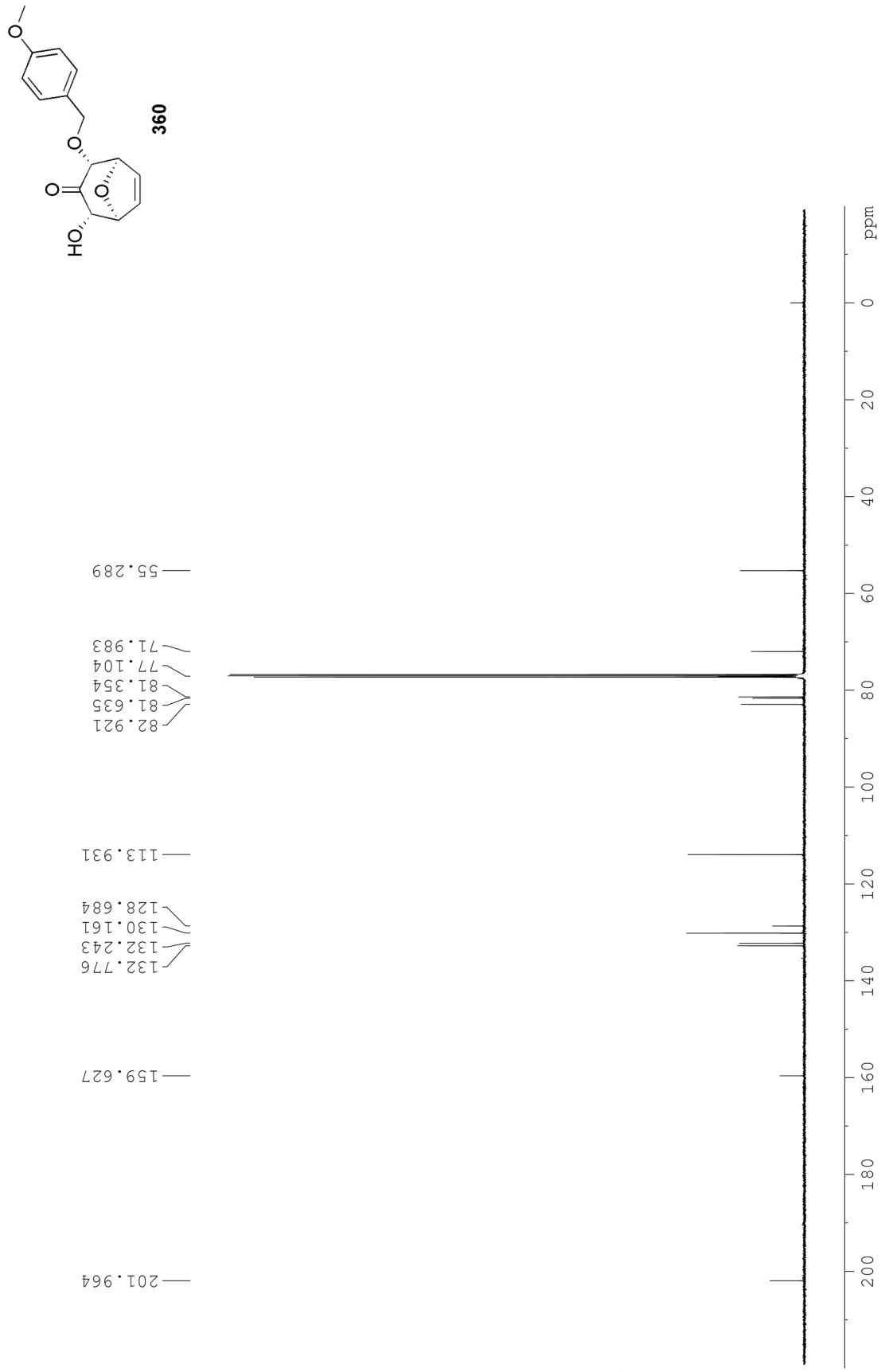
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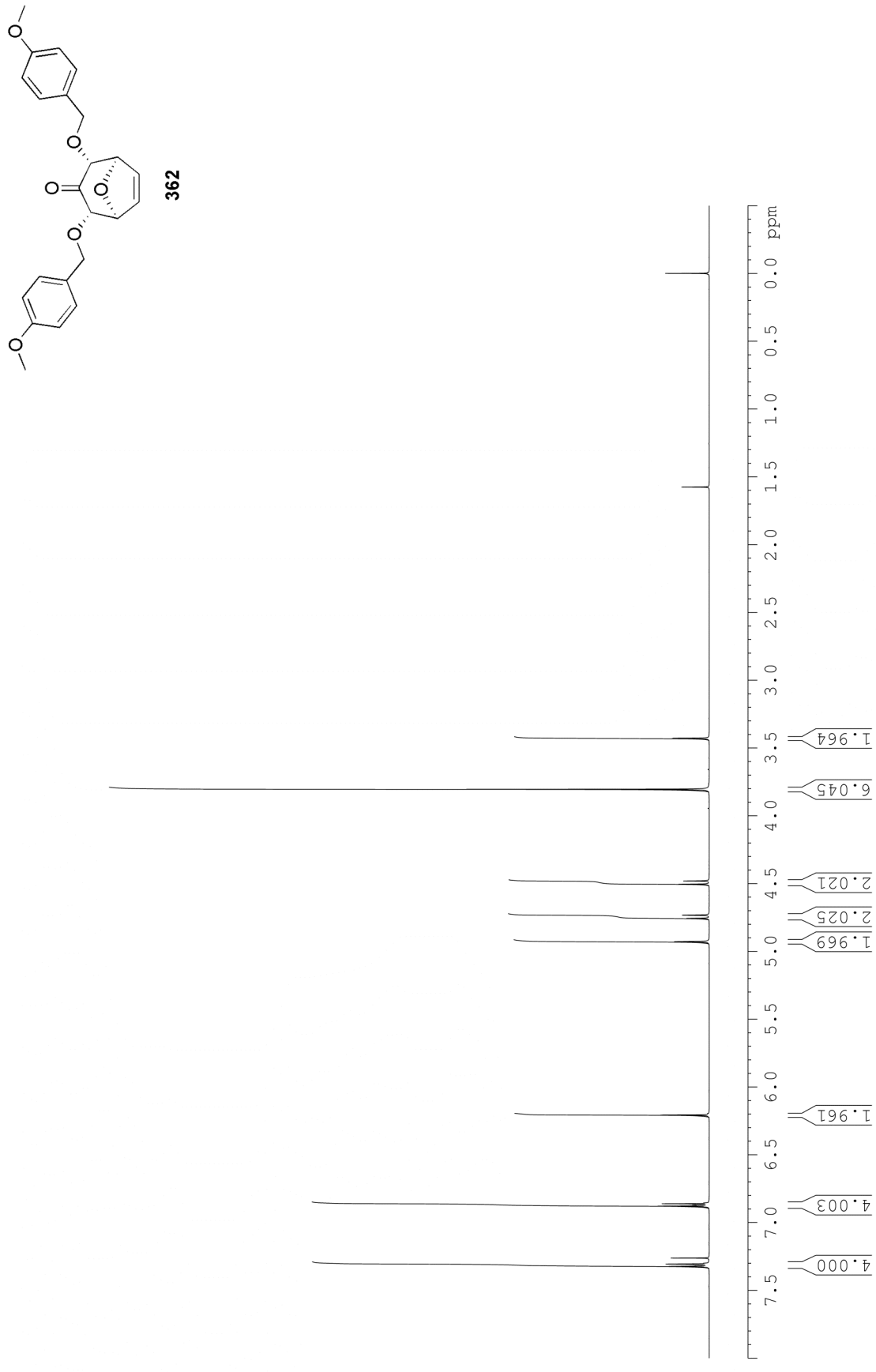
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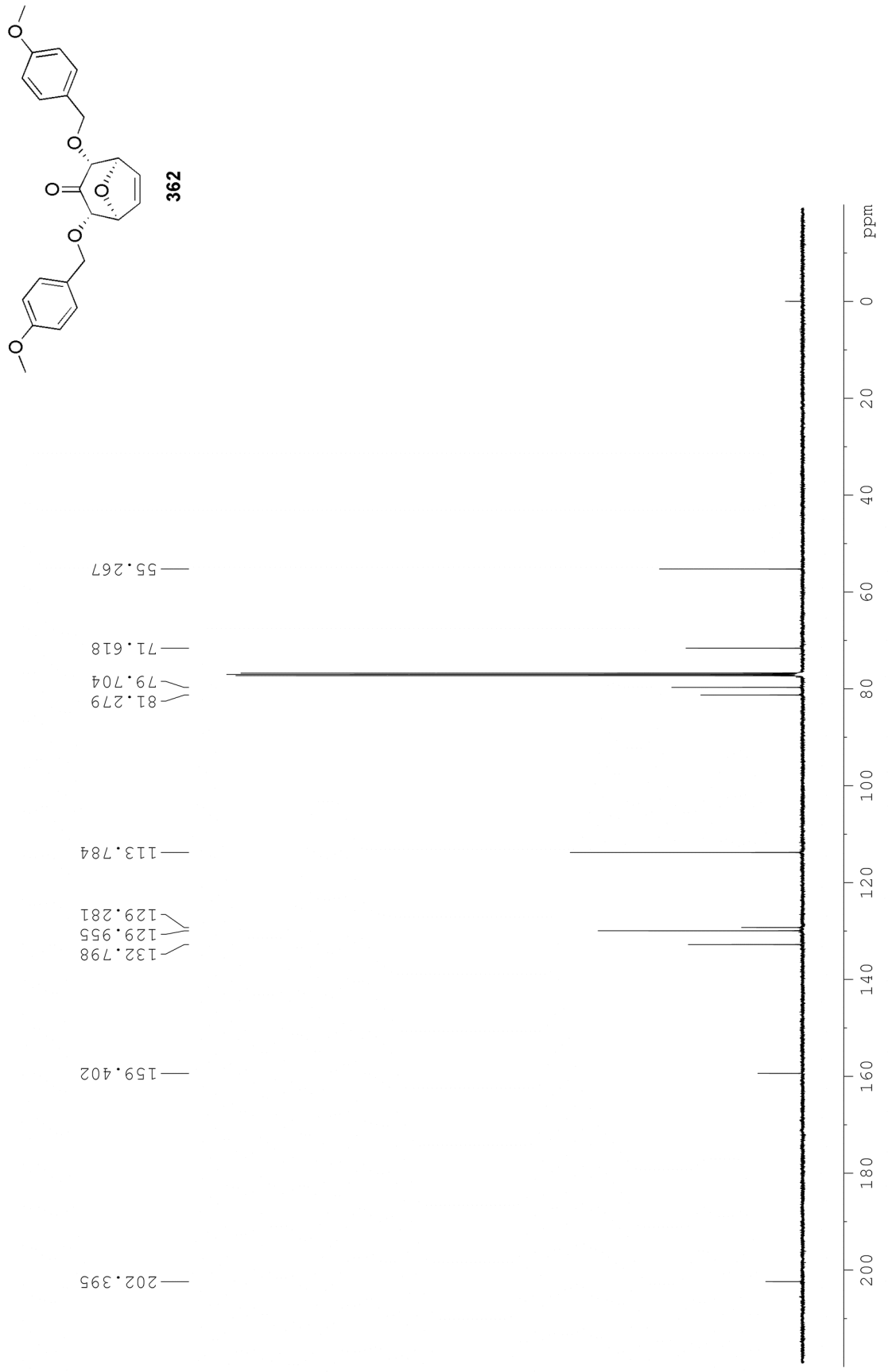
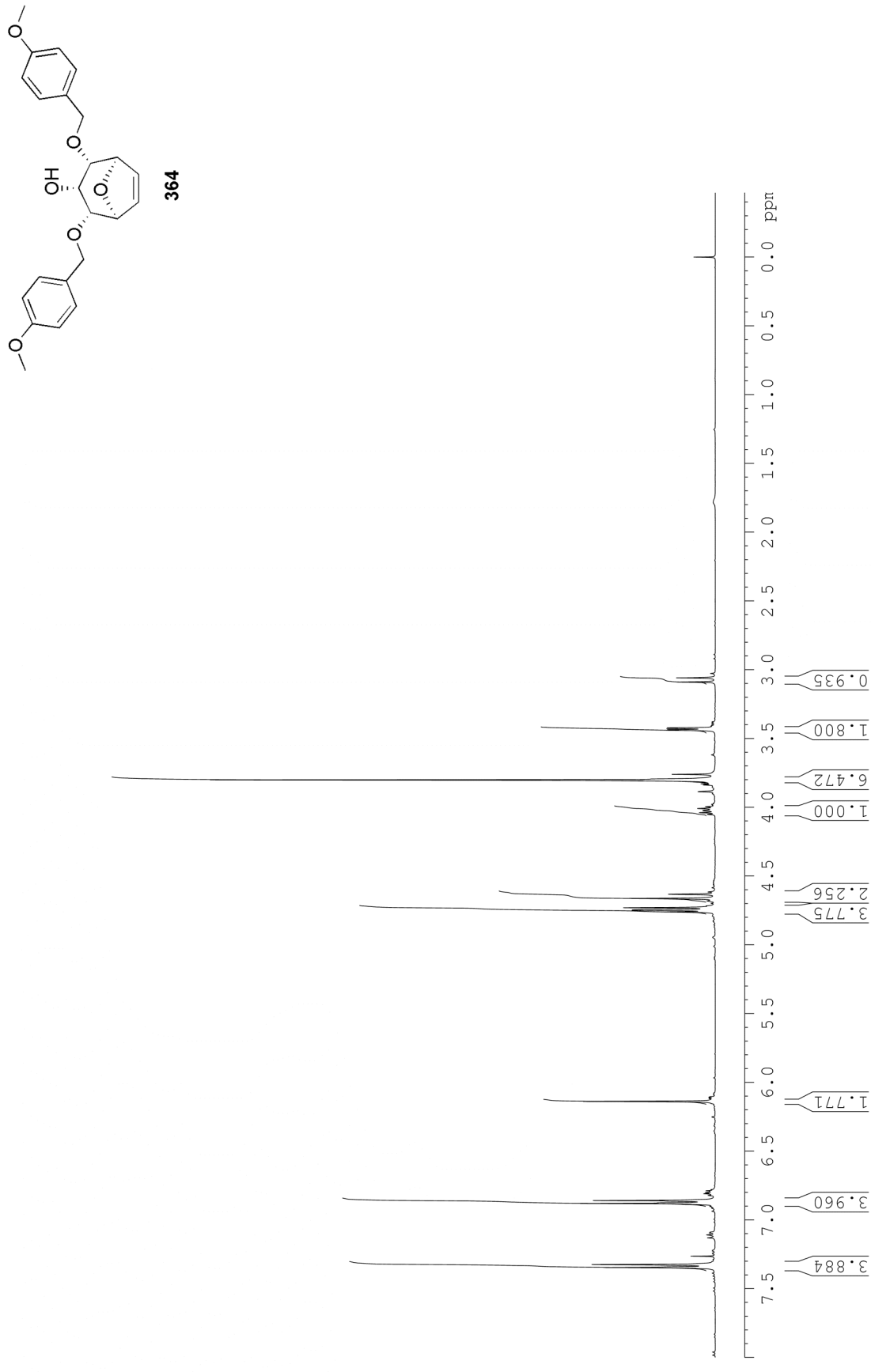
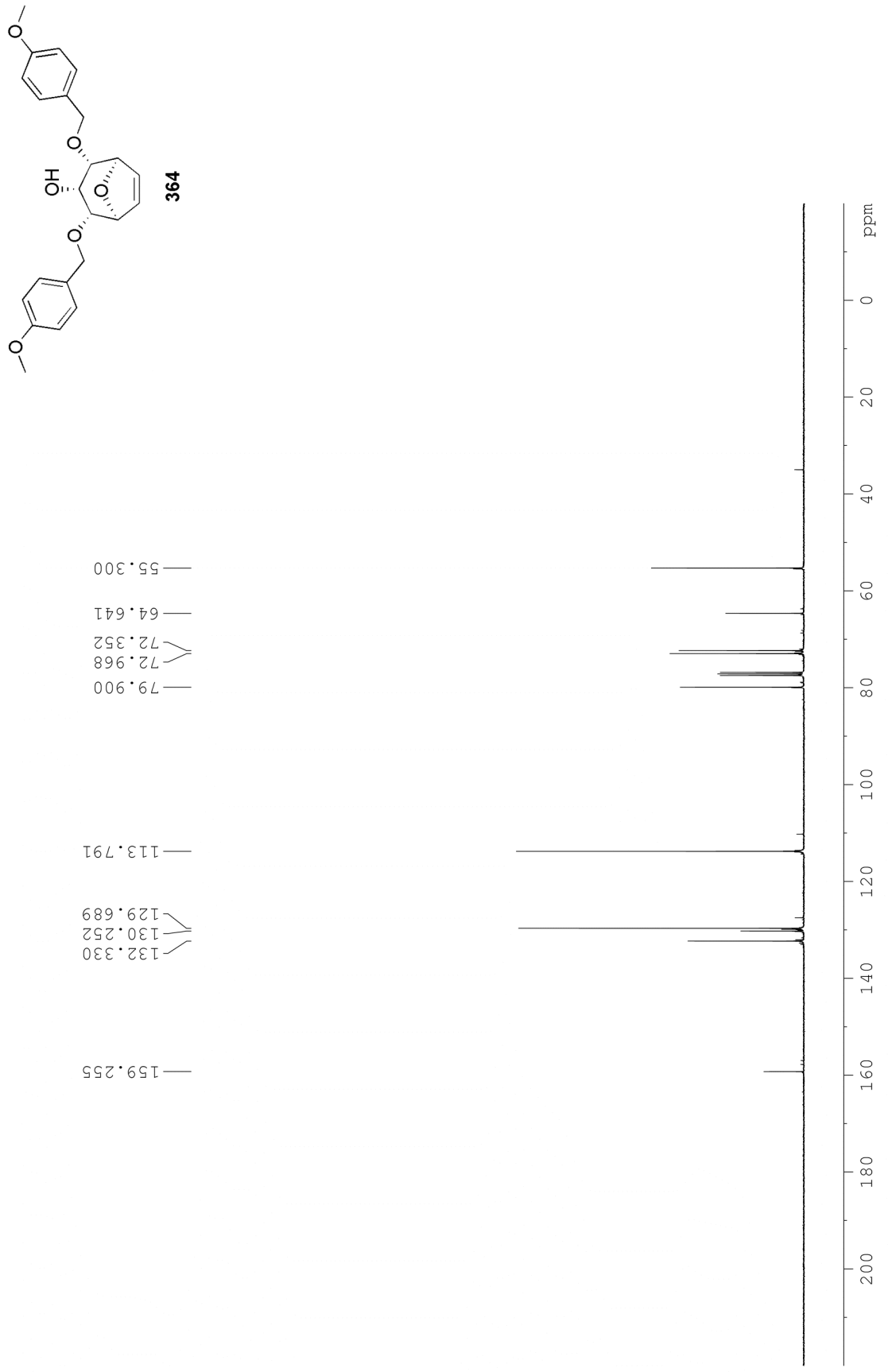
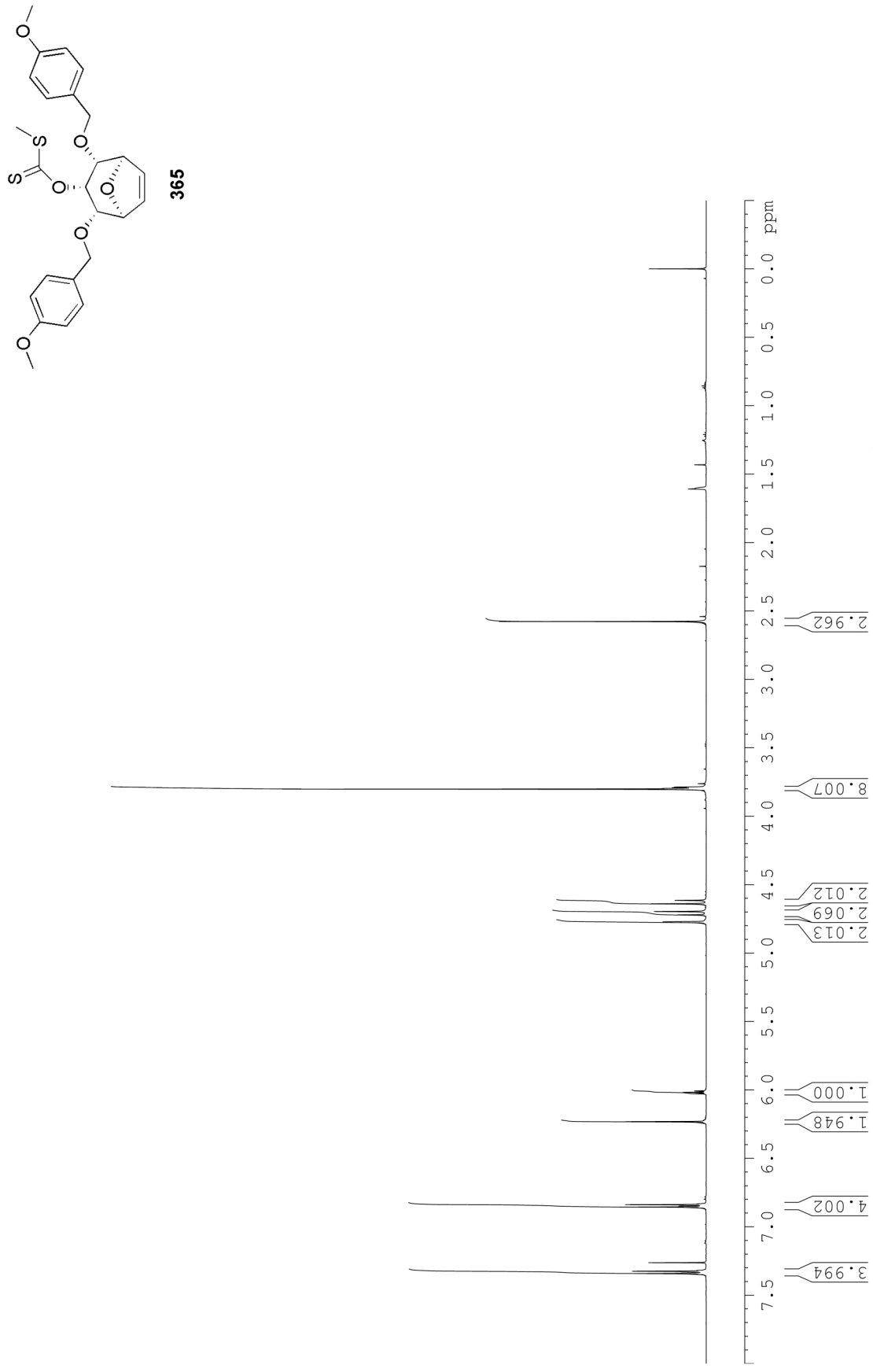
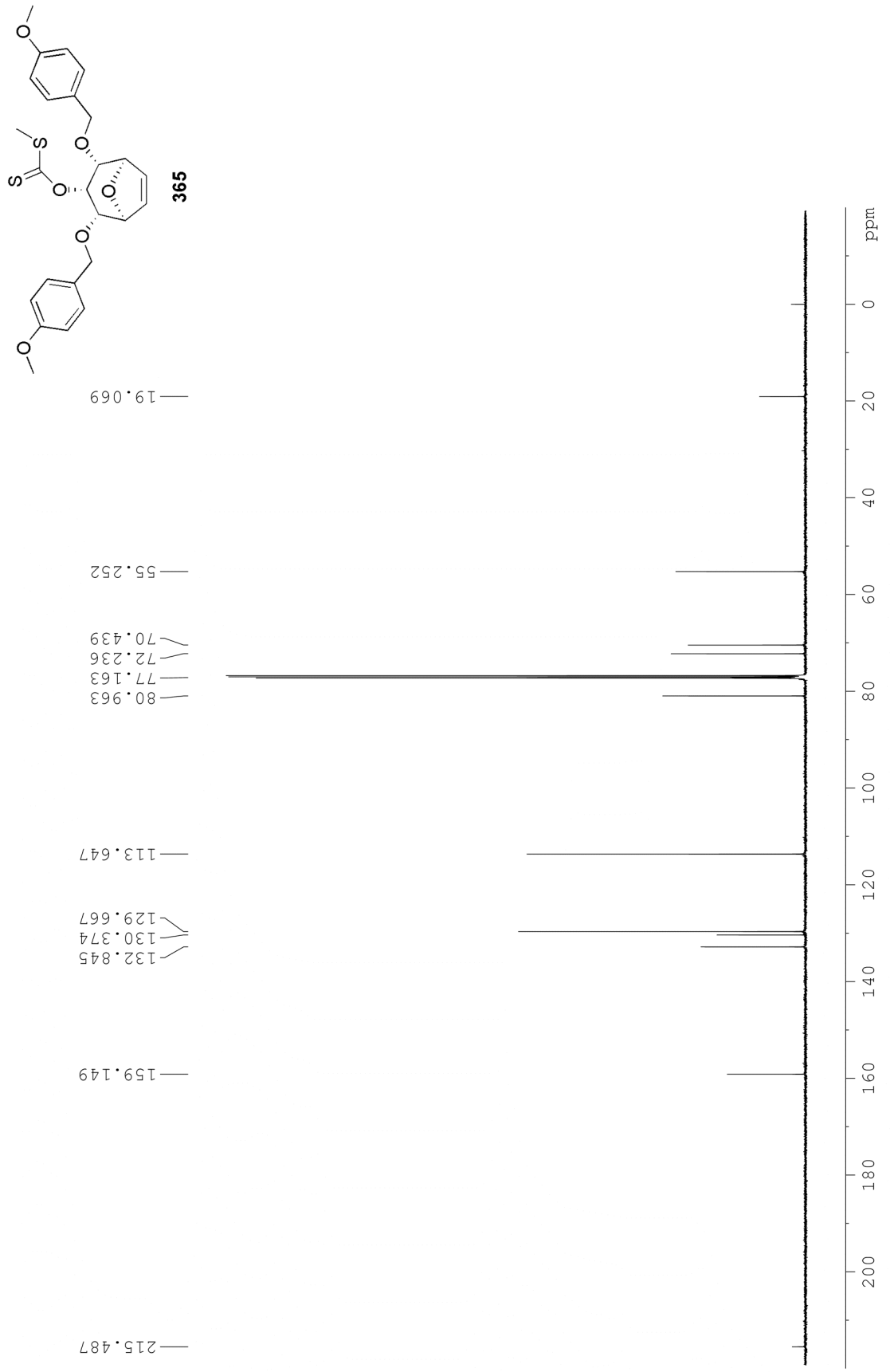

362
55.267
71.618
79.704
81.279
113.784
129.281
129.955
132.798
159.402
202.395
ppm
0
20
40
60
80
100
120
140
160
180
200


364
3.884
3.960
1.771
2.256
3.775
1.000
6.472
1.800
0.935
ppm


364
159.255
132.330
130.252
129.689
113.791
79.900
72.968
72.352
64.641
55.300
ppm
0
20
40
60
80
100
120
140
160
180
200


365
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
3.994
4.002
1.948
1.000
2.013
2.069
2.012
8.007
2.962


365
19.069
55.252
70.439
72.236
77.163
80.963
113.647
129.667
130.374
132.845
159.149
215.487
ppm
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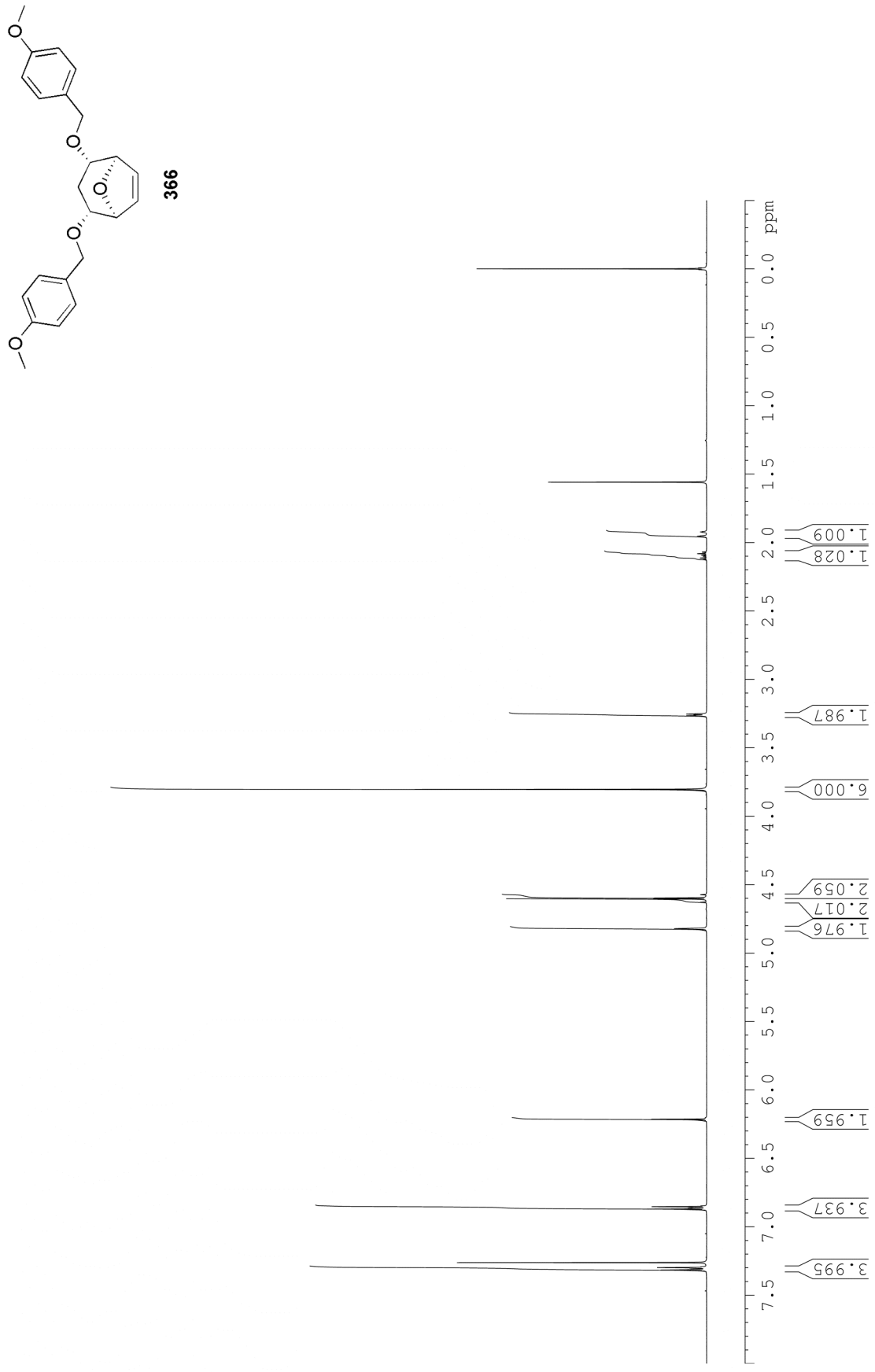
20
40
60
80
100
120
140
160
180
200


366
ppm
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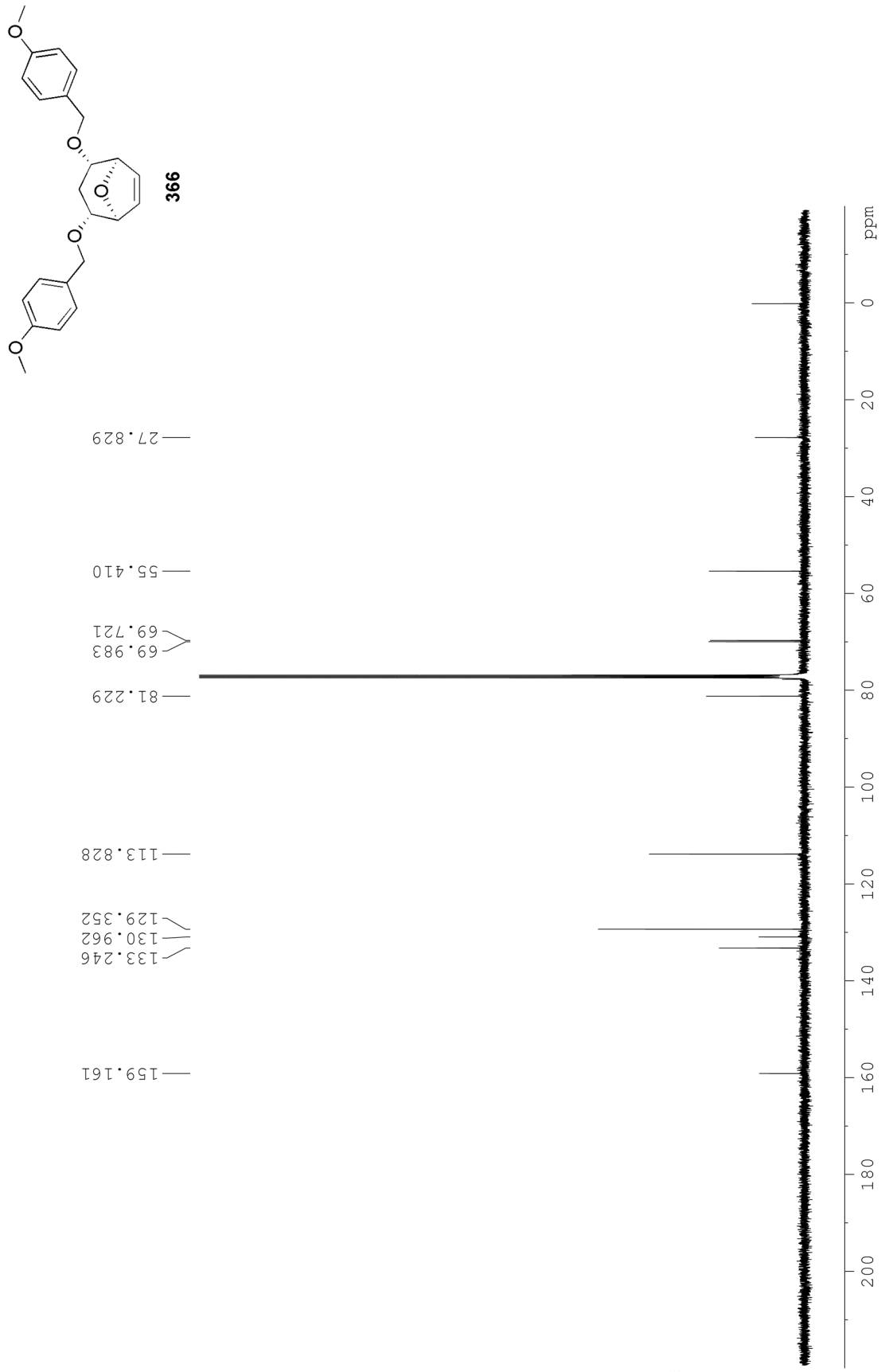
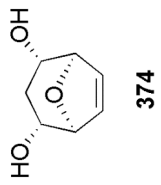
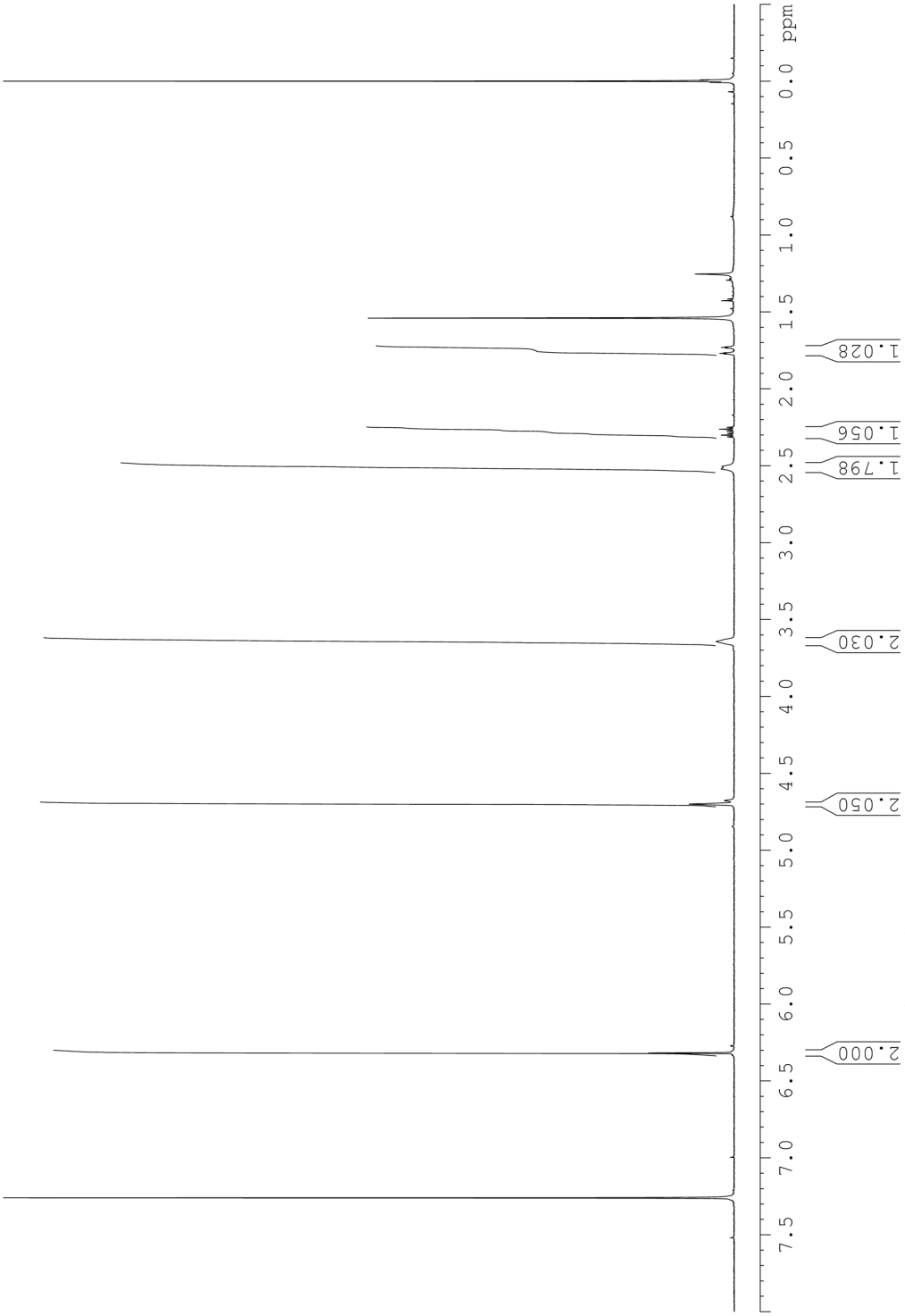
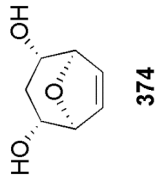
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
1.009
1.028
1.987
6.000
2.059
2.017
1.976
1.959
3.937
3.995


366
27.829
55.410
69.721
69.983
81.229
113.828
129.352
130.962
133.246
159.161
ppm
0
20
40
60
80
100
120
140
160
180
200

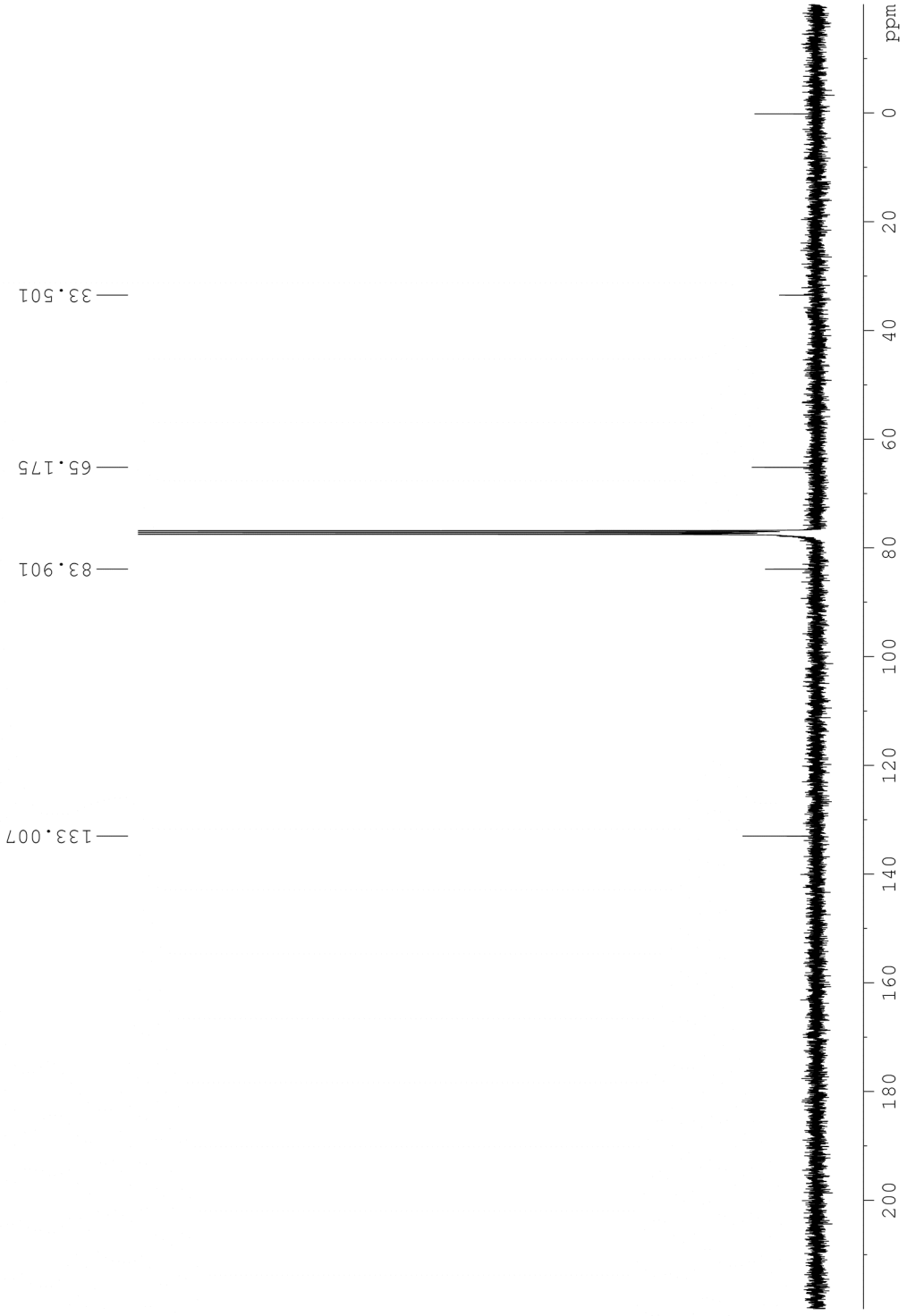

OH
HO
O

374


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
1.028
1.056
1.798
2.030
2.050
2.000


OH
HO
O

374


133.007
83.901
65.175
33.501
ppm
0
20
40
60
80
100
120
140
160
180
200