Studies Towards a Total Synthesis of Manzamine A

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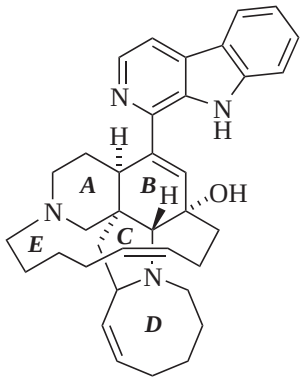
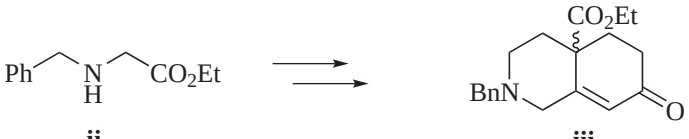
Abstract

Manzamine A has been isolated from various Okinawa Sponges of the genus *Haliclona* and was first characterised by Higa and co-workers in 1986. The unusual and synthetically challenging structure consists of a pentacyclic core containing an array of 5-, 6-, 8-, and 13-membered rings with a pendant β-carboline unit. The complex structure of manzamine A combined with its biological activities has made it a highly attractive synthetic target. The synthetic endeavors in the Clark group to develop a novel approach towards the total synthesis of manzamine A (**i**) with the main focus on the synthesis of the ABC ring fragment as advanced intermediates will be disclosed.



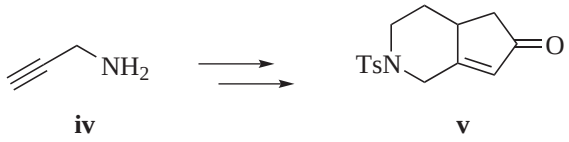
manzamine A (i)

In the first synthetic approach towards the total synthesis of manzamnine A (**i**), bicyclic enone **iii** was constructed from amine **ii** and served as a model system to validate the proposed intermolecular Diels-Alder reaction. Despite several attempts utilising various dienes, the Diels-Alder adduct was not obtained and an alternative bicyclic system was investigated.



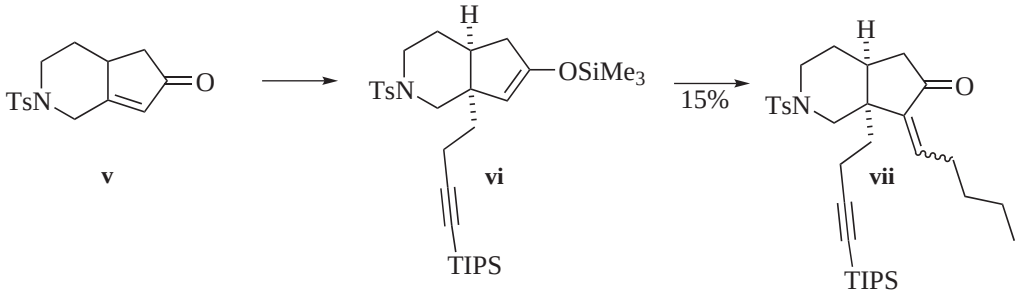
ii **iii**

After accomplishing the synthesis of the simple AB fragment **v** from propargylamine (**iv**), the Diels-Alder reaction was yet again investigated. Due to the failure of the Diels-Alder reaction, this route towards the total synthesis of manzamine A (**i**) was abandoned.



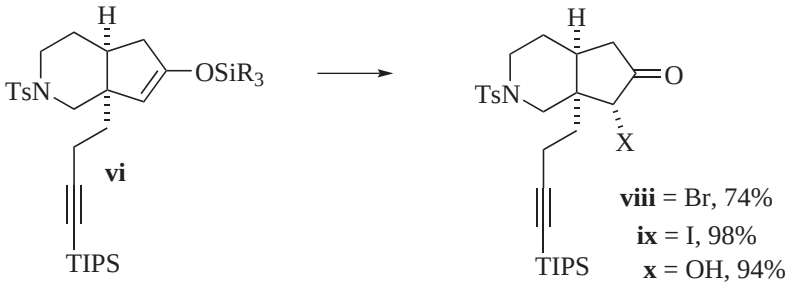
iv **v**

The second approach introduces the conjugate addition reaction towards the total synthesis of manzamine A (**i**). Instead of the Diels-Alder approach, 1,4 addition to enone **v** was explored. Initial attempts to perform the 1,4-addition reaction and subsequent aldol condensation reaction afforded the dehydrated aldol condensation products **vii** *via* silyl enol ether **vi**. Additional investigations to prevent the dehydration reaction taking place proved unsuccessful.



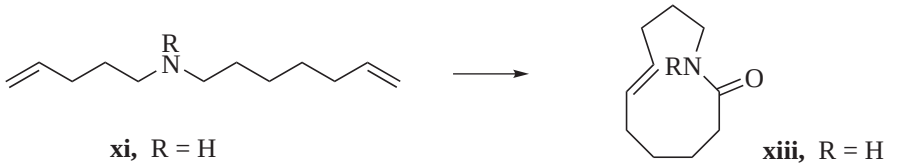
v **vi** **vii**

Thereafter, various methods for the introduction of a substituent in the position α to the ketone were investigated. These included alkylation using chloromethyl phenylsulfide, halogenation using NBS or NCS, Rubottom oxidation using DMDO, direct amination using manganese(V) complexes, azidation using sodium azide and CAN as well as aziridination using PhI=NTs. A number of adducts **viii-x** were succesfully prepared.



vi

Finally, the last part of the thesis describes the efforts towards the synthesis of a model system resembling the CD ring-system. The macrocyles **xiii** and **xiv** were easily synthesised from dienes **xi** and **xii**, although the RCM of diene **xi** gave rise to isolation problems.



xi, R = H
xii, R = Bn

xiii, R = H
xiv, R = Bn

Contents

Acknowledgments

This thesis would not have been completed without the help and assistance from a number of persons whom I am pleased to acknowledge. First and foremost, I would like to thank my supervisor Professor J. Stephen Clark for three years of rewarding collaboration and for his confidence in me and in the project. I am grateful for being given the opportunity to work in his group. Next I offer my gratitude to my industrial supervisor Dr Iain Simpson for his constant support and encouragement over the last three years. Dr Rudi Marquez, my second supervisor, is acknowledged for his support and advice.

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A special thanks to everyone at AztraZeneca, Alderly Park for making me feel very welcome and at "home" in the lab. In particular I would like to express my gratitude to Steve Glossop and Matthew Box for their daily advice and support throughout my three month stay. Not to forget Ryan and the lunch group who made every day a great day.

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I am grateful for financial support from the University of Glasgow, AstraZeneca and WestCHEM.

Last but not least I would like to finish by thanking you, the reader, who, if not interested by profession, will be a close friend and surely should have deserved a special mention.

Author's Declaration

This thesis represents the original work of Anna Mette Hansen unless explicitly stated otherwise in the text. The research upon which this thesis is based was carried out in the Henderson laboratory (C4-08) during the period October 2006−September 2009, under the supervision of Professor J. Stephen Clark. Additional PhD traineeship and research was also carried out at AztraZeneca laboratories, Alderly Park, during the period September 2008−December 2008, under the supervision of Dr Iain Simpson and Professor J. Stephen Clark. No part of this thesis has been previously submitted for a degree at the University of Glasgow or any other University.

Anna Mette Hansen

Glasgow, February 2010

Professor J. S. Clark

Glasgow, February 2010

List of Abbreviations and Symbols

Ac	acetyl
acac	acetylacetonate
Bn	benzyl
Boc	*tert*-butoxycarbonyl
brsm	based on recovered starting material
Bu	butyl
CAN	ceric ammonium nitrate
CBz/Z	carboxybenzyl
CM	cross-metathesis
conc.	concentrated
CSA	camphorsulfonic acid
dba	*E*,*E*-dibenzylideneacetone
DBU	1,8-diazobicyclo-[5,4,0]-undec-7-ene
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
$(DHQD)_2PHAL$	hydroquinidine 1,4-phthalazinediyl diether
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	*N*,*N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(*1H*)-pyrimidinone
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
dppb	diphenylphosphinobutane
Et	ethyl
h	hour(s)
HOBt	1-hydroxybenzotriazole
HRMS	high resolution mass spectrometry
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide

m-CPBA	*m*-chloroperbenzoic acid
Me	methyl
MEM	methoxyethoxymethyl
Ms	methanesulfonyl
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
o/n	overnight
Ph	phenyl
PMB	*p*-methoxybenzyl
PPTS	pyridinium-*p*-toluenesulfonate
P	protecting group
Pr	propyl
quant.	quantitative
RCM	ring-closing metathesis
RT	toom temperature
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
*t*Bu	*tert*-butyl
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TMTU	tetramethyl thiourea
TPAP	tetra-*n*-propylammonium perruthenate
Ts	*para*-toluenesulfonyl
Å	Ångstrom

Introduction

In principle a total synthesis is the complete chemical synthesis of complex organic molecules from smaller fragments, usually without the aid of biological processes. Today, the chemistry of natural products attracts a very vigorous interest and remains one of the most difficult and challenging tasks in organic chemistry. New substances, more or less complicated, more or less useful, are constantly discovered and investigated. Steadily improving synthetic methods make it possible to tackle more and more difficult problems and the ability of Nature to build up complicated substances has, as it seems, no limit.[1] Total synthesis is often justified as the stimulus for the development of new chemical reactions and routes, and highlights the sophistication of modern synthetic organic chemistry. Moreover, it also represents the most humbling, exhilarating and formative enterprise in our science.[2] The development of new powerful synthetic methodologies has enabled organic chemists to build large structures of previously undreamed complexity in a shorter time and in a more efficient manner.[2] The synthesis of a complicated molecule is, however, a very difficult task; every atom must be placed in its proper position and this should be taken in its most literal sense. It is sometimes said that organic synthesis is at the same time an exact science and a fine art.[1] Nowadays, natural product synthesis is associated with a discreet selection of challenging and preferably biologically important target molecules. Being both a precise science and a fine art, total synthesis has been driven by the constant flow of beautiful molecular architectures from Nature and serves as the engine that drives the more general field of organic synthesis forward.[1]

This thesis is divided into six chapters. Chapter 1 provides an introduction to the manzamine alkaloids, the biomimetic synthesis proposed by Baldwin,[3] a presentation of the two more recent total syntheses performed by Winkler[4] and Martin[5] and a brief overview of selected previous synthetic strategies towards the total synthesis of manzamine A. Chapter 2 describes the Diels-Alder route towards manzamine A and Chapter 3 accounts for the 1,4-addition route. Chapter 4 includes efforts to prepare a model of the CD ring system and an overall conclusion of the preceding chapters is provided in Chapter 5. Finally, experimental deatails and data for new compounds are given in Chapter 6.

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1 Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem. Int. Ed.* **2000**, *39*, 44-122.

2 Marko, I. E. *Science* **2001**, *294*, 1842-43.

3 Baldwin, J. E.; Whitehead, R. C. *Tetrahedron Lett.* **1992**, *33*, 2059-2062.

4 Winkler, J. D.; Axten, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 6425-6426.

5 Martin, S.; Humphrey, J.; Ali, A.; Hillier, M. *J. Am. Chem. Soc.* **1999**, *121*, 866-867.

Chapter 1

Manzamine A - a Polycyclic Alkaloid

Manzamine A (**1**) belongs to the manzamine family of alkaloids, a group of natural products extracted from various sponges (Figure 1.1).[6] The unique molecular architecture, consisting of a complex array of rings, combined with their significant biological activities have made manzamine A (**1**) and related alkaloids popular targets for synthetic organic chemists.[1]

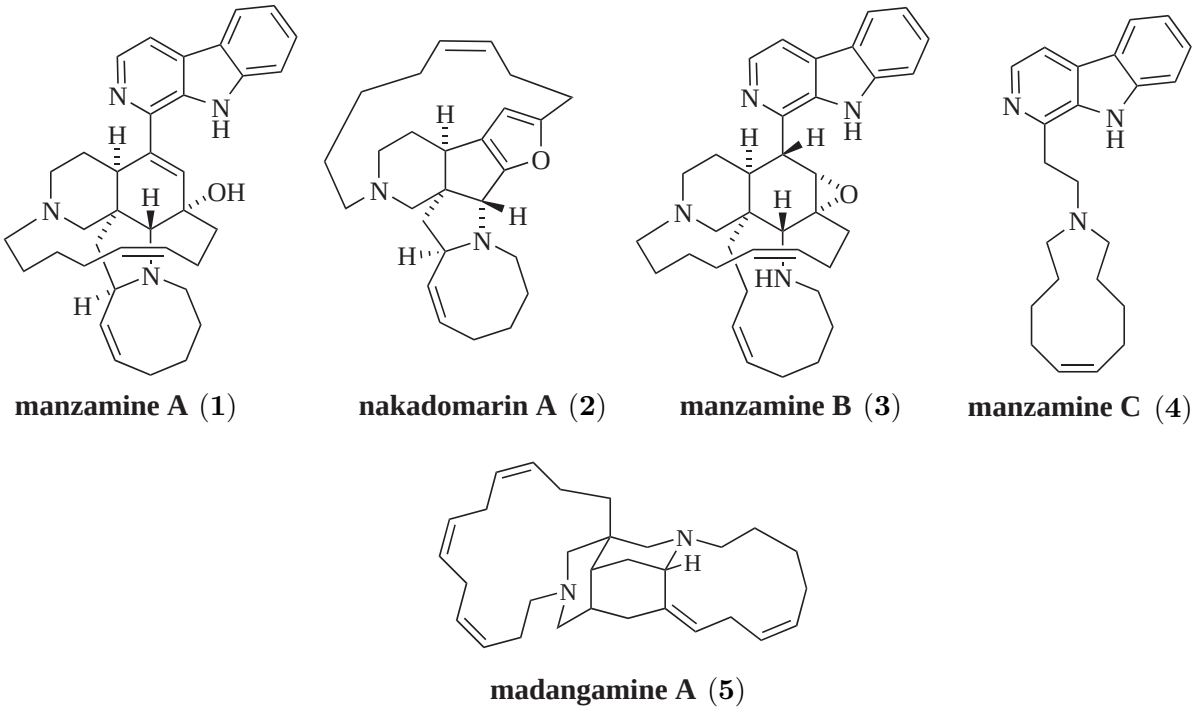

Figure 1.1: Representative members of the manzamine family of alkaloids.

Manzamine A (**1**) was first isolated in 1986 by Higa and co-workers from the marine sponge *Haliclona sp.* found in waters close to Okinawa, Japan.[7] Independent of this discovery, the group of Nakamura described an identical alkaloid extracted from the marine sponge *Pellina sp.*, under the name of kera-

[6] Magnier, E.; Langlois, Y. *Tetrahedron* **1998**, *54*, 6201-6258.

[7] Sakai, R.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *J. Am. Chem. Soc.* **1986**, *108*, 6404-6405.

mamine A (**1**), together with keramamine B (**6**) (Figure 1.2).[8] Following the isolation of keramamine A (**1**) and B (**6**), the group of Higa also isolated two other related alkaloids manzamine B (**3**) and manzamine C (**4**) from the *Haliclona sp.* (Figure 1.2).[6] Manzamine A (**1**) has subsequently been found in other genera of marine sponges, including *Pachypellina*, *Xestospongia*, *Ircinia* and *Amphimedon*. More than 70 other compounds which are structurally related to manzamine A (**1**) have been isolated from sponges and characterised.[9,10] Manzamine A (**1**) is the most complex molecule of the manzamine alkaloid family. It possesses a diazapentacyclic core containing an array of 5-, 6-, 8-, and 13-membered rings with a pendant β-carboline. The core also comprises three alkene bonds, two trialklamines and a tertiary hydroxyl group.[10]

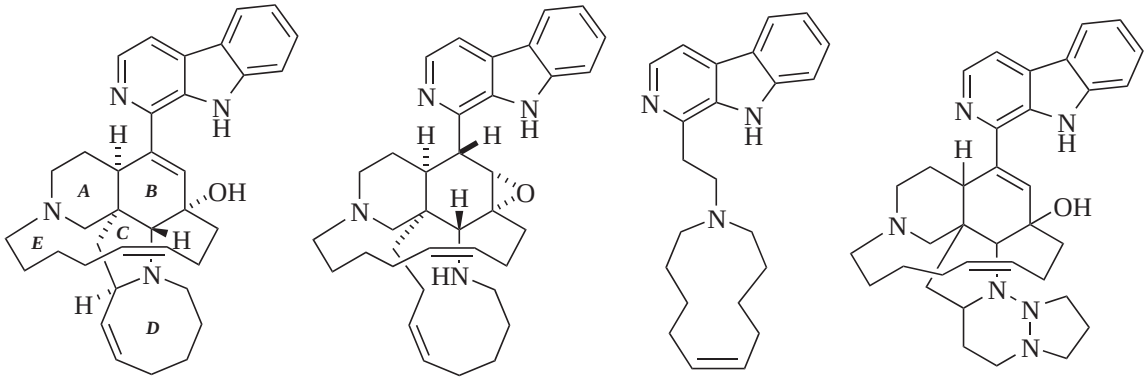

Figure 1.2: Structure of manzamine B (**3**), manzamine C (**4**) and keramamine B (**6**).

1.1 Biological activity

The manzamine alkaloids have shown a diverse range of bioactivities. Reported activities include cytotoxic,[7] insecticidal,[11] antibacterial[8] and antimalarial.[9] To date, manzamine A (**1**) has shown the most potent biological activity among the manzamine family of alkaloids.[12] It was found to have *in vitro* activity against certain tumour cell lines, including P388 mouse leukaemia cells (IC_{50} = 0.07 μg/mL), human colon tumour cells, lung carcinoma cells and breast cancer cells (IC_{50} = 0.5 μg/mL). Moreover, the manzamine alkaloids represent important lead structures for the development of novel anti-infectives.[13,14]

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8 Nakamura, H.; Deng, S.; Kobayashi, J.; Ohizumi, Y.; Tomotake, Y.; Matsuzaki, T.; Hirata, Y. *Tetrahedron Lett.* **1987**, *28*, 621-624.

9 Ang, K. K. H.; Homnes, M. J.; Higa, T.; Hamann, M. T.; Kara, U. A. K. *Antimicrob. Agents Chemother.* **2000**, *44*, 1645-1649.

10 Nishida, A.; Nagata, T.; Nakagawa, M. *Topics in Heterocyclic Chemistry;* Springer Berlin/Heidelberg: 2006.

11 Edrada, R. A.; Proksch, P.; Wray, V.; Witte, L.; Muller, W. E. G.; Soest, R. W. M. V. *J. Nat. Prod.* **1996**, *59*, 1056-1060.

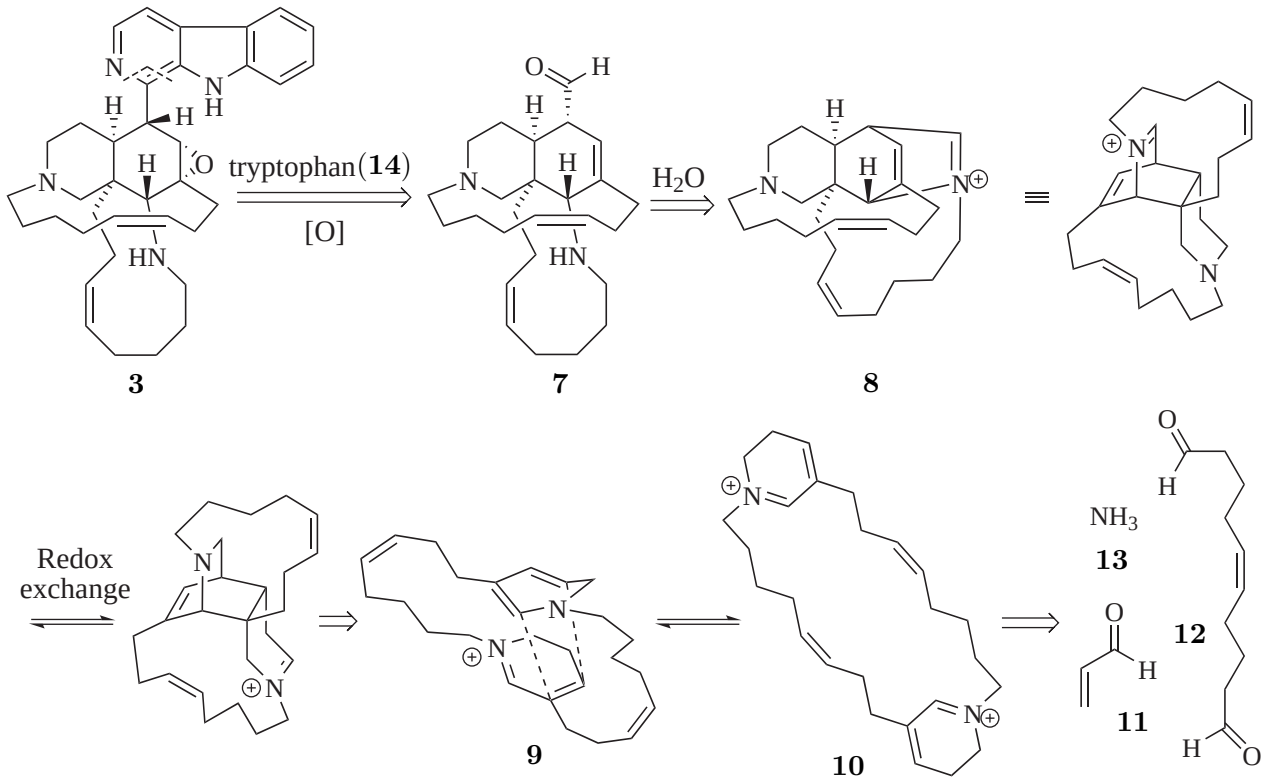
12 Urban, S.; Hickford, J. H.; Blunt, J. W.; Munro, M. H. G. *Curr. Org. Chem.* **2000**, *4*, 765-807.

13 Winkler, J. D.; Londregan, A. T.; Hamann, M. T. *Org. Lett.* **2006**, *8*, 2591-2594.

14 Winkler, J. D.; Londregan, A. T.; Ragains, J. R.; Hamann, M. T. *Org. Lett.* **2006**, *8*, 3407-3409.

1.2 Biosynthesis and biomimetic approach

Despite the isolation of the manzamine alkaloids many years ago, a clear biogenetic route could not be found to reveal how these compounds are created in Nature. As a result, synthetic chemists had few real clues to guide the design of potential biomimimetic syntheses of manzamine A (**1**). However, in 1992 a biosynthetic hypothesis was proposed by Baldwin and Whitehead in which the manzamines are derived *in vivo* from four simple building blocks: tryptophan (**14**), ammonia (**13**), a C10 unit (**12** a symmetrical dialdehyde) and a C3 unit **11** (an acrolein equivalent), as illustrated in Scheme 1.1.[3,15] In this retrosynthesis, manzamine B (**3**) is first converted to aminoaldehyde **7** by removal of the epoxide and the tryptophan unit. This intermediate is simplified to **8** through hydrolysis and a redox exchange event, which is possibly related to keramaphidin B (**18**). Precursor **8** arises from an endo selective Diels-Alder reaction of **9** which is the conjugate base of **10**. **10** can originate from the three building blocks tryptophan (**14**), ammonia (**13**) and a C10 unit **12**.[16] Manzamine B (**3**) can subsequently be converted into manzamine A (**1**) through trans-eliminative opening of the epoxide, followed by allylic hydroxylation of the resulting double bond and ring closure (Scheme 1.1).[3]

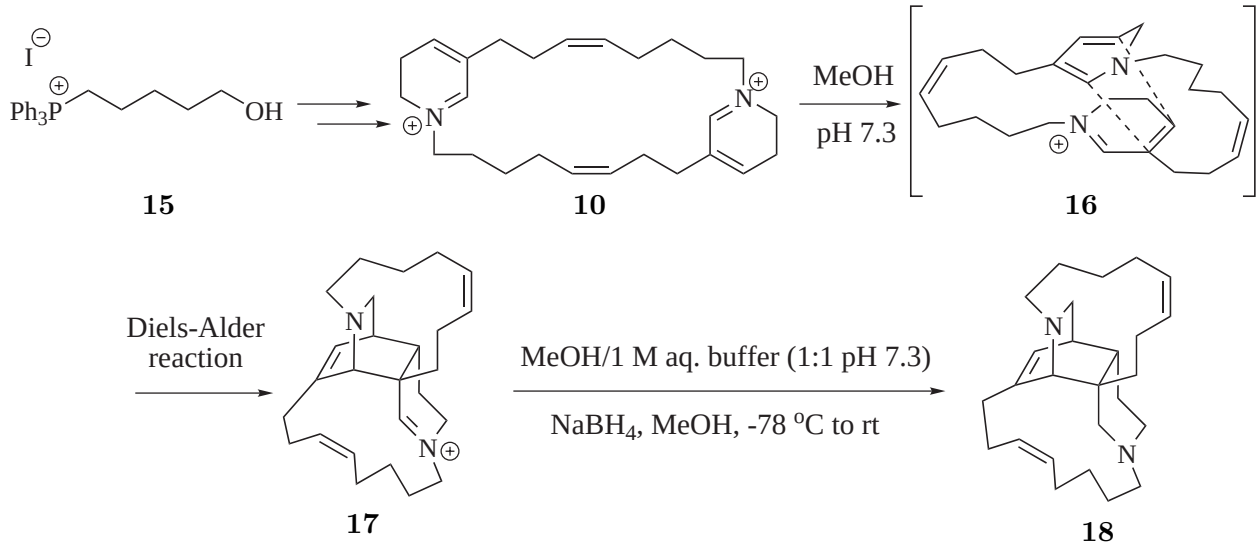


Scheme 1.1: The Baldwin-Whitehead model for the biosynthesis of the manzamine alkaloids.

[15] Snyder, N. *Classics in Total Synthesis II: More Targets, Strategies, Methods.;* WILEY-VCH Verlag GmbH & Co. KG, Weinheim: 2003.

[16] Baldwin, J. E.; Claridge, T. D. W.; Culshaw, A. J.; Heupel, F. A.; Lee, V.; Spring, D. R.; Whitehead, R. C. *Chem. Eur. J.* **1999**, *5*, 3154-3161.

The first experimental proof for this proposed theory was published in 1999, when the Baldwin group completed the total synthesis of keramaphidin B (**18**) as illustrated by Scheme 1.2.[16] The key intermediate **10** was prepared from phosphorane **15** in eight steps. Extensive studies were then carried out to optimise the Diels-Alder reaction by varying the solvents and buffers.[16] Eventually, it was discovered that dissolution of compound **10** in buffered methanol (pH 7.3) for 1 hour followed by reduction afforded a small, but still detectable, amount of keramaphidin B (**18**). Even though this biomimetic synthesis validates the proposed biosynthetic model, the Diels-Alder reaction was unfavourable leading to a very low yield of keramaphidin B (**18**).[15] For this reaction to occur, it is assumed that a "Diels-Alderase" directing enzyme exits in Nature which preorganises the substrate into proper alignment for the pericyclic reaction. Without this, the major product is that arising from competing disproportionation, which results in the reduction of both iminium ions in **10** instead of Diels-Alder cycloaddition.[17]



Scheme 1.2: The Baldwin-Whitehead model for the synthesis of keramaphidin B (**18**).

1.3 Semi-synthesis and the total synthesis of manzamine A

Semi-synthesis of manzamine A (1)

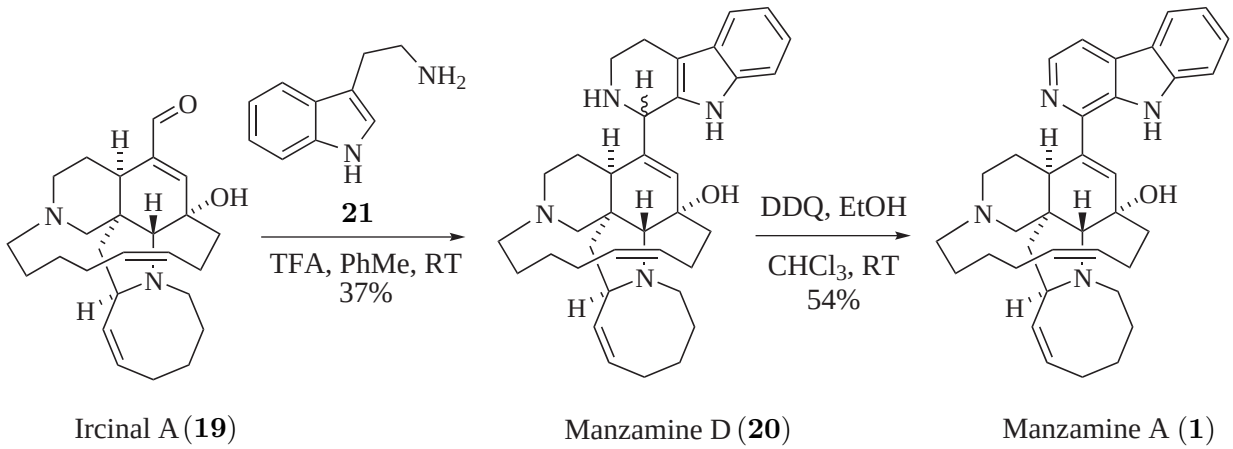
Apart from the biogenesis proposed by Baldwin and Whitehead,[3,18] the only other useful information to guide the development of synthetic routes to manzamine A (**1**) was provided by the Kobayashi group (Scheme 1.3).[15,19] In 1992 the group of Kobayashi isolated the marine alkaloids ircinal A (**19**)

[17] Baldwin, J. E.; Claridge, T. D. W.; Culshaw, A. J.; Heupel, F. A.; Lee, V.; Spring, D. R.; Whitehead, R. C.; Boughtflower, R. J.; Mutton, I. M.; Upton, R. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 2661-2663.

[18] Baldwin, J. E.; Claridge, T. D. W.; Culshaw, A. J.; Heupel, F. A.; Smrckova, S.; Whitehead, R. C. *Tetrahedron Lett.* **1996**, *37*, 6919-6922.

[19] Kondo, K.; Shigemori, H.; Kikuchi, Y.; Ishibashi, M.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.* **1992**, *57*, 2480-2483.

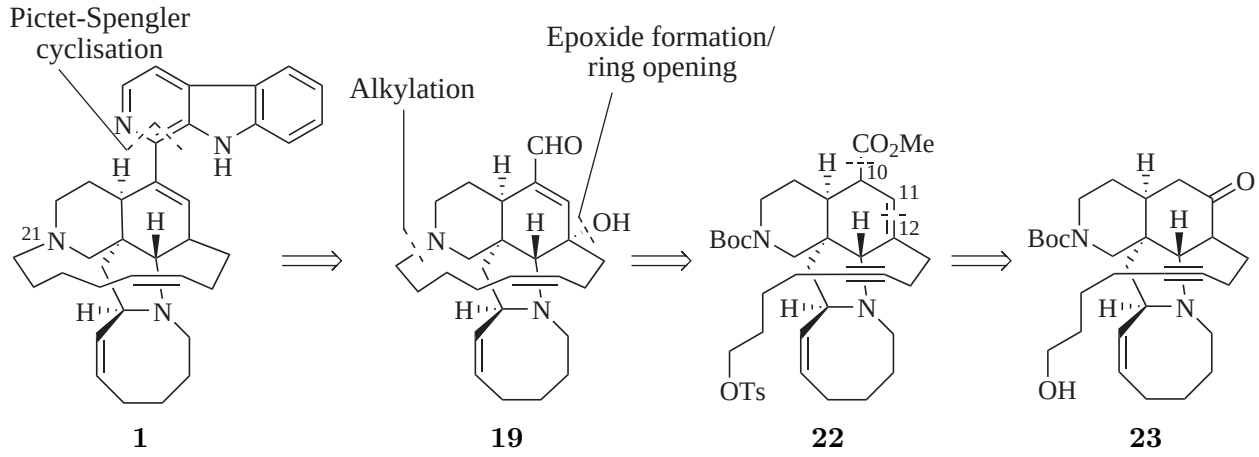
and B from Okinawan marine organisms and both compounds were thought to be plausible biogenetic precursors of the manzamine alkaloids. As a result, Kobayashi and co-workers' converted ircinal A (**19**) into manzamine A (**1**) and completed the first semi-synthesis.[19] The development relied on condensation of ircinal A (**19**) with tryptamine (**21**) followed by acid-mediated Pictet-Spengler cyclisation to deliver manzamine D (**20**). The condensation/cyclisation sequence was followed by DDQ mediated oxidation, that converted manzamine D (**20**) into manzamine A (**1**), and hence the first semi-synthesis of manzamine A (**1**) was accomplished (Scheme 1.3). Although this discovery undoubtedly reduces the complex structure of manzamine A (**1**) to ircinal A (**19**), the latter still constitutes a formidable target which is endowed with all the challenging elements of manzamine A (**1**): five rings of various sizes and a daunting assortment of stereocentres, two of which are quaternary.[15]



Scheme 1.3: Semi-synthesis of manzamnine A (**1**).[19]

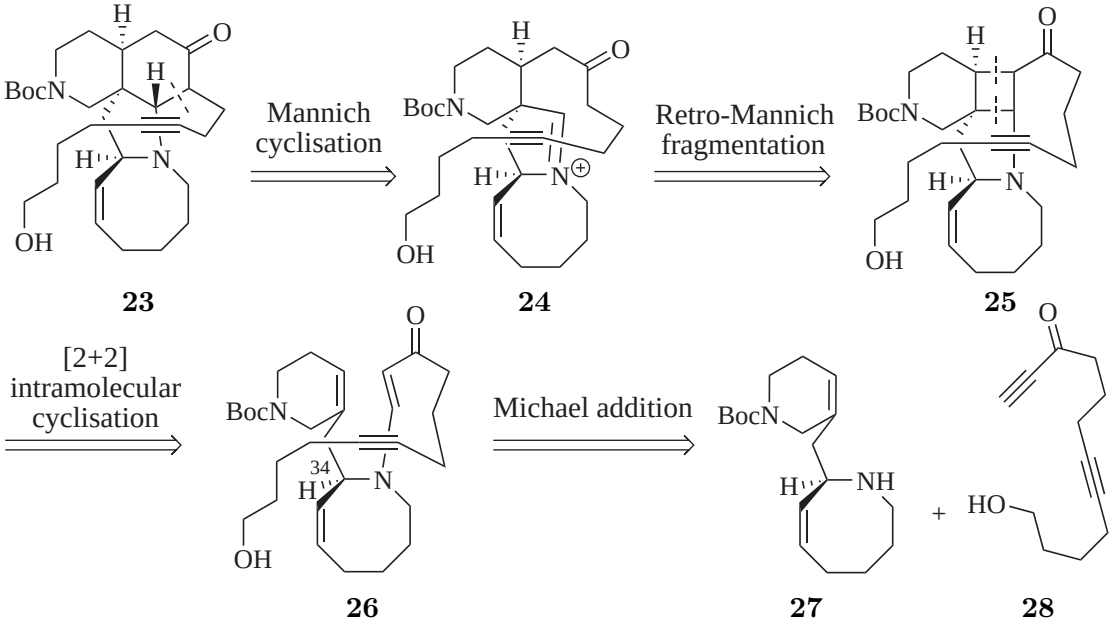
1.4 Winkler's total synthesis of manzamine A

The first total synthesis of manzamine A (**1**) was accomplished by Winkler and co-workers in 1998, using a photochemical cascade reaction as the key step.[4] The retrosynthetic analysis of Winkler and co-workers' synthesis is given in Schemes 1.4 and 1.5. Disconnection of the β-carboline heterocycle from manzamine A (**1**) led to ircinal A (**19**), which was predicted to arise by macrocyclisation of **22** through an alkylation with the amine on the A ring to substitute the tosyl group. The hydroxyl group in ircinal A (**19**) was formed from an epoxidation reaction of the alkene in **22**, followed by base-induced elimination. Retrosynthetic removal of the ester group at the C-10 position and modification of the C10-C11 alkene to a carbonyl led to ketone **23**, which was constructed *via* a photochemical reaction (Scheme 1.4).[15]



Scheme 1.4: Winkler's retrosynthetic analysis of manzamine A **1**.[15]

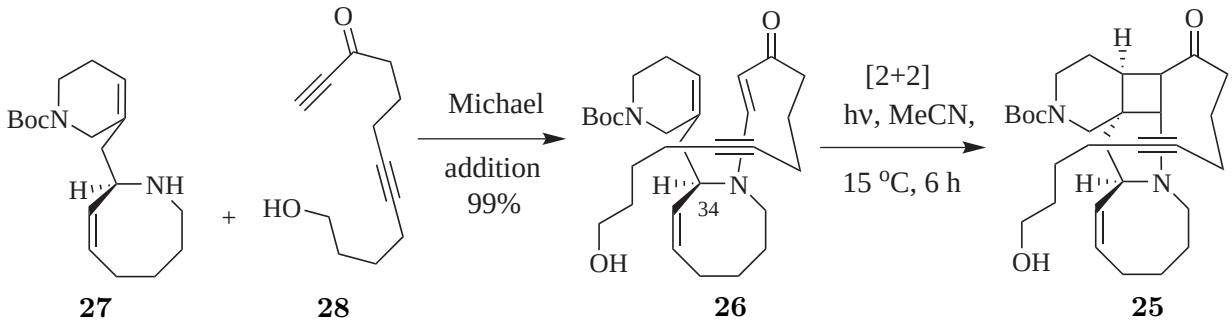
The tetracyclic ring structure **23** can be produced from a Mannich closure of ketoiminium **24**, which was formed by a retro-Mannich fragmentation of **25**, resulting from the photochemically allowed intramolecular cycloaddition of the tertiary enamine **26**. The enamine can be obtained from a Michael-type addition of the amine **27** to the α,β-unsaturated alkyne **28** (Scheme 1.5).[4] Based on the final disconnection, the synthesis of manzamine A (**1**) has been dramatically simplified to the two relatively simple building blocks, **27** and **28**.[15]



Scheme 1.5: Winkler's retrosynthetic analysis of manzamine A **1**.[15]

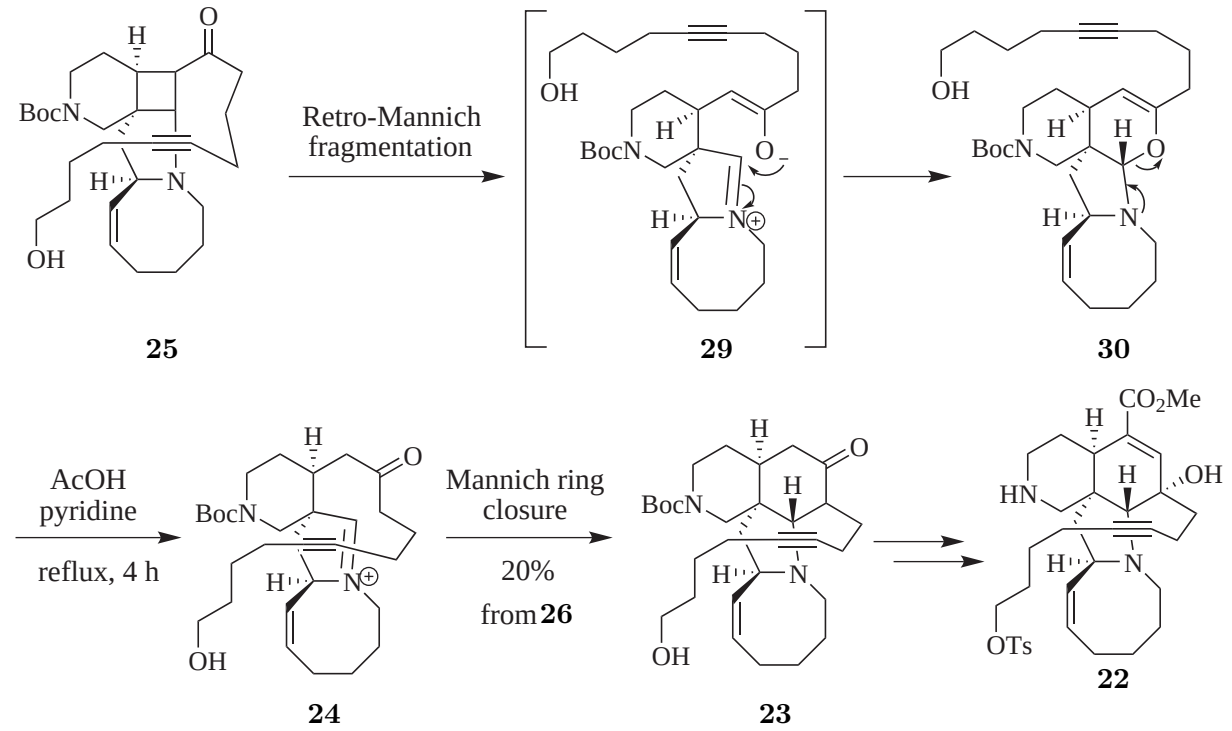
Employing this strategy, formation of the key intermediate, the tertiary vinylogous amide **26**, was performed by Michael addition of the previously prepared amine **27** on to the acetylenic ketone **28**. Exposing a solution of **26** to UV light for six hours resulted in the photochemical cyclisation which led to the tetracyclic ketone **25** (Scheme 1.6).[20]

[20] Winkler, J. D.; Siegel, M. G.; Stelmach, J. E. *Tetrahedron Lett.* **1993**, *34*, 6509-6512.



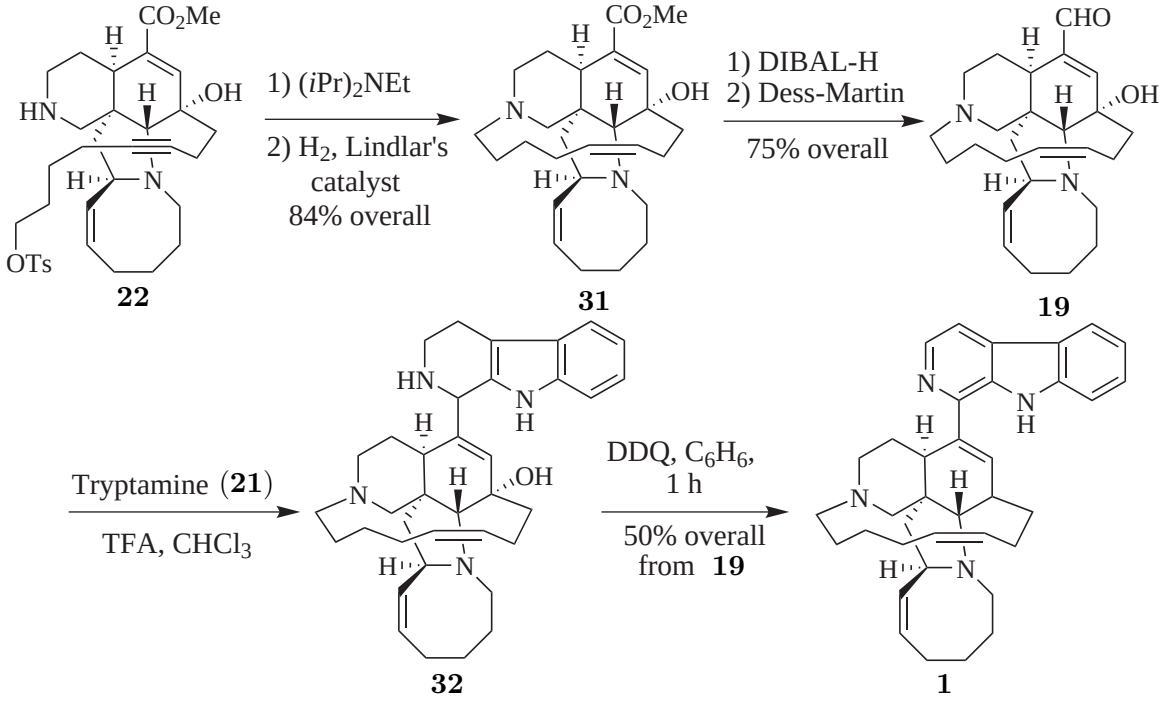
Scheme 1.6: Winkler's synthesis towards manzamine A (**1**).[15]

A subsequent retro-Mannich fragmentation of **25** yielded **30** (Scheme 1.7). Intramolecular nucleophilic attack of the enolate to the iminium ion in intermediate **29** provided amine **30**. The intermediate **30** was treated with acetic acid in pyridine at reflux for 4 hours to afford the iminium compound **24**, which was converted into amine **23** by a Mannich ring closure reaction.[15] It is worth noting that **23** was produced as a single diastereomer, due to the stereocentre at C-34 in **26**, directing the formation of the resultant stereogenic centres during the cascade reaction (Scheme 1.7). Modification of the A and B rings in order to introduce the functionality present in manzamine A (**1**) was achieved in ten steps to afford amino alcohol **22** (Scheme 1.7).[4,15]



Scheme 1.7: Key ring-forming steps in Winkler's synthesis of manzamine A (**1**).[15]

The secondary amine **22** was treated with Hünig's base to generate the desired thirteen-membered ring, which upon Lindlar reduction gave alkene **31** in 84% yield. Reaction of the unsaturated ester **31** with DIBAL-H followed by a Dess-Martin oxidation afforded ircinal A (**19**).[4] Modification of ircinal A (**19**) to yield manzamine A (**1**) was accomplished *via* Pictet-Spengler cyclisation. Reaction of **19** with tryptamine (**21**) in the presence of trifluoroacetic acid afforded manzamine D (**32**), which was converted into manzamine A (**1**) upon oxidation with DDQ (50% yield).[19] Thus, Winkler's group accomplished the total synthesis of manzamine A (**1**) in a total of 17 steps from the readily available precursor **27** (prepared in 14 steps from pyridine-3-methanol) and successfully demonstrated the effectiveness of the photoaddition/fragmentation/Mannich closure reactions (Scheme 1.8).[4]

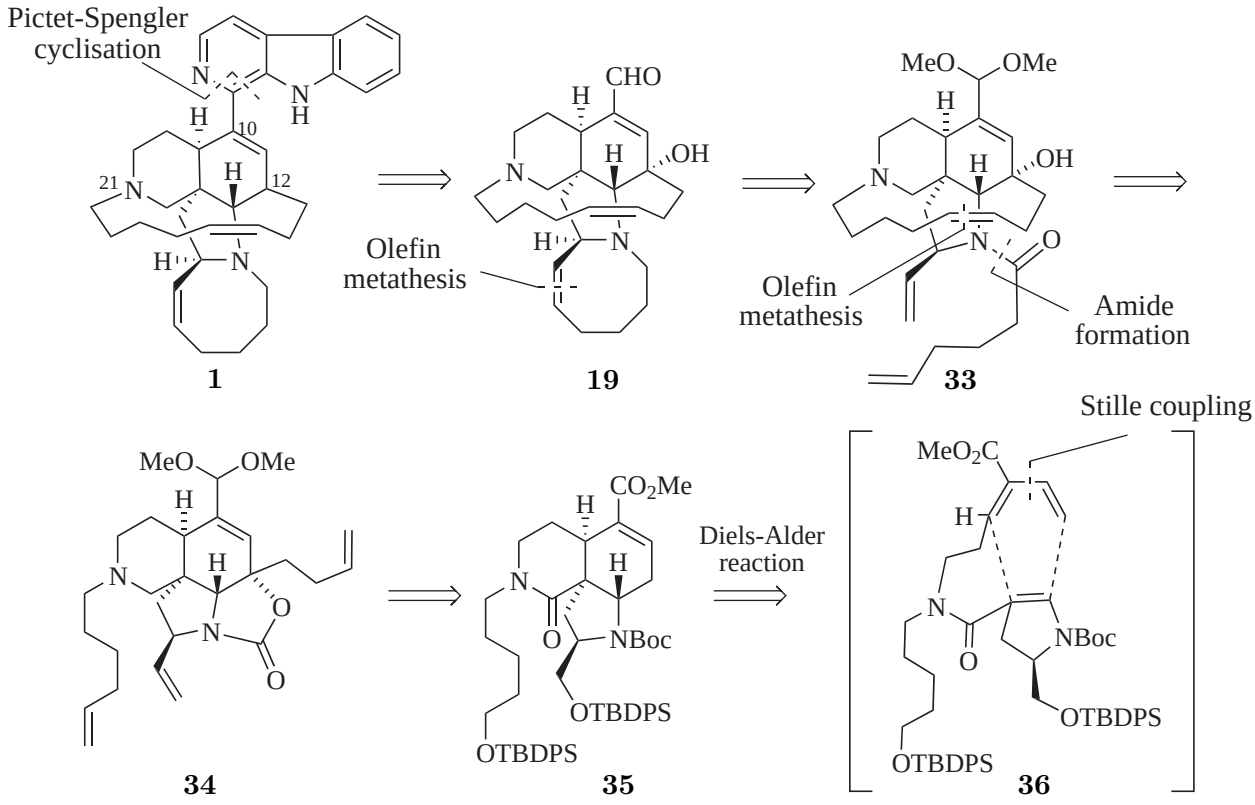


Scheme 1.8: The final steps in Winkler's total synthesis of manzamine A (**1**).[15]

1.5 Martin's total synthesis of manzamine A

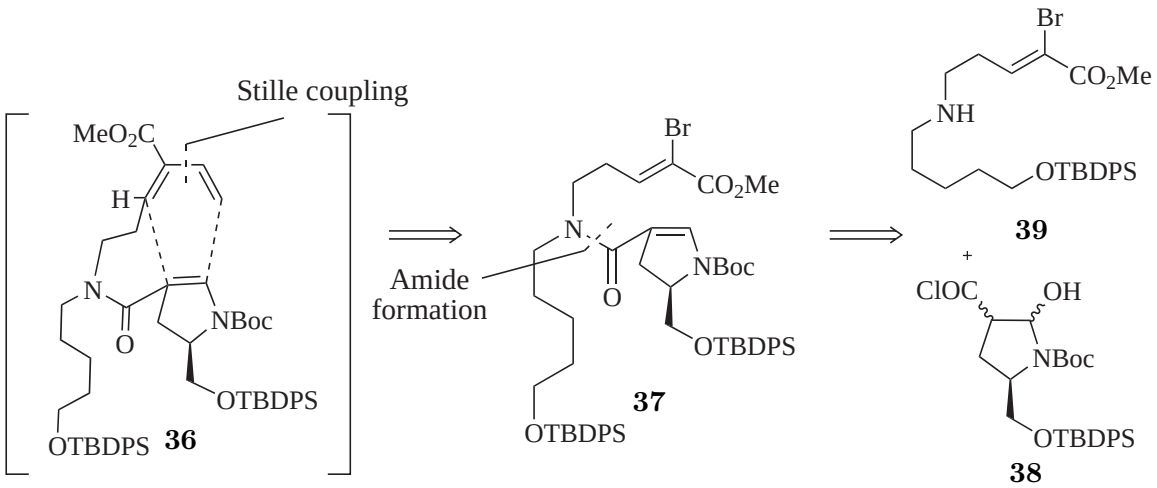
The second approach to the enantioselective total synthesis of manzamine A (**1**) was reported in 1999 by Martin and co-workers.[5] Their approach involved a novel domino Stille/Diels-Alder reaction followed by two sequential ring-closing metathesis reactions (Scheme 1.9).[5] Once again, the first disconnection of the β-carboline heterocycle from manzamine A (**1**) delivered ircinal A (**19**), following the known reaction established by Kobayashi.[19] The key tetracyclic intermediate **33** was formed retrosynthetically by cleavage of the D ring alkene in ircinal A (**19**), which was constructed from a RCM reaction. Following protecting group manipulations of **19**, a second RCM-based disconnection of the E ring in **33** yielded **34**. This was followed by a series of minor modifications of the functional groups and the protecting groups, which delivered **35** from **34**. The stereochemically rich six-membered B

ring could be obtained from the triene **36** through an intramolecular endo [4+2] cycloaddition reacion (Scheme 1.9).



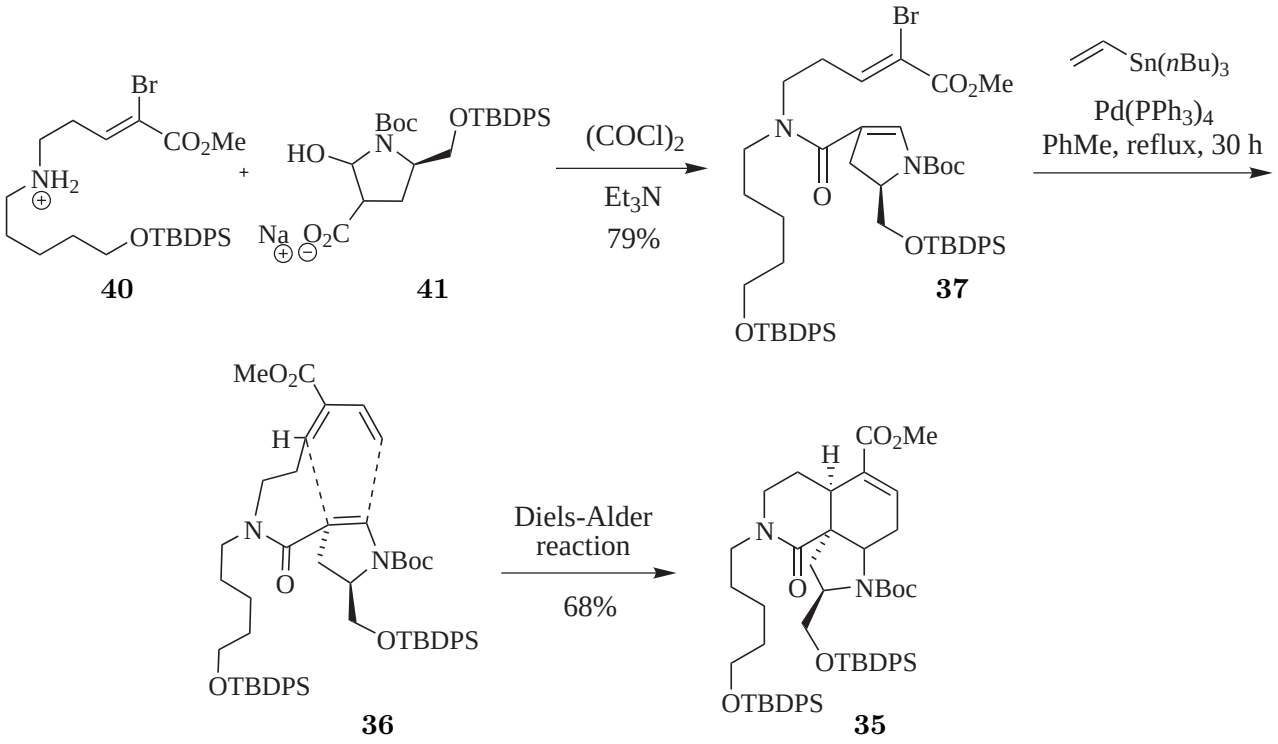
Scheme 1.9: Martin's retrosynthetic analysis of manzamine A (**1**).[15]

The diene in **36** could originate from a Stille reaction of vinylic halide **37** with vinyl tributylstannane, which could incorporated in the same operation as the intramolecular Diels-Alder reaction upon heating. Finally, disconnection of the amide bond in intermediate **37** revealed an unsaturated amino ester **39** and a chiral carboxylic acid derivative **38** (Scheme 1.10).[15]



Scheme 1.10: Martin's retrosynthetic analysis of manzamine A (**1**).[15]

Preliminary studies, were initially carried out by Martin and co-workers, to establish the feasibility of several key steps, including the intramolecular Diels-Alder reaction of a vinylogous imide dienophiles, and ring-closing metathesis.[21,22] Issues such as stereoselectivity were addressed which consequently led to a successful route (Schemes 1.11 to 1.14). The precursor **40** was synthesised in five steps from 5-amino-pentan-1-ol and **41** was prepared in four steps from (*R*)-5-(methoxycarbonyl)-2-pyrrolidinone.[5] Reaction of the carboxylate salt **41** with oxalyl chloride, followed by addition of **40** in the presence of triethylamine gave the amide dienophile **37** in a 79% overall yield. As expected, the stereochemistry in **41** is retained and assisted in the stereocontrolled introduction of the remaining stereogenic centres.[23] The domino Stille/Diels-Alder reaction was then performed - reaction of the bromide **37** with vinyl tributylstannane in the presence of Pd(0) formed the triene **36**, which spontaneously cyclised to afford the tricyclic intermediate **35** in 68% overall yield.[5]



Scheme 1.11: Martin's synthesis towards manzamine A (**1**).[15]

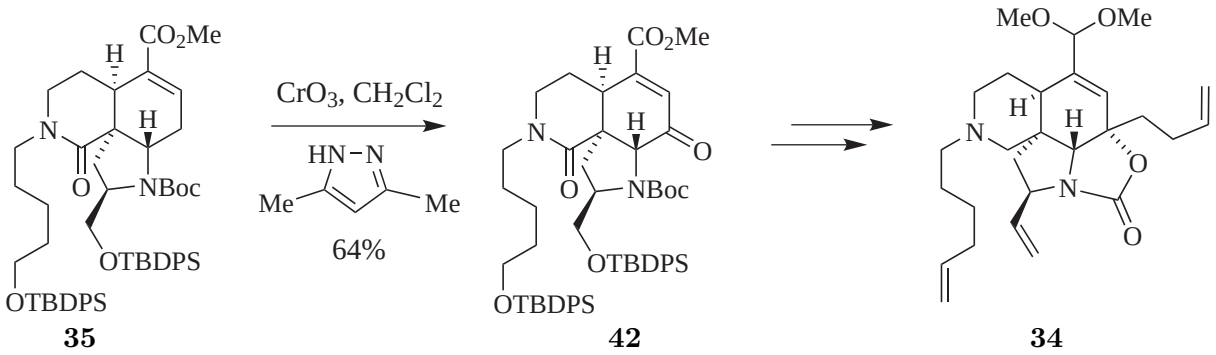
Oxidation of the allylic methylene group in **35** proved difficult but was achieved by application of a modification of Salmond protocol, using an excess of CrO_3 and 3,2-dimethylpyrazole in CH_2Cl_2 at room temperature for two days, to give the enone **42** in 64% yield (Scheme 1.12).[5,24] Subsequently, protecting groups in the tricyclic compound **42** were adjusted and the addition of olefinic side chains provided the RCM substrate **34** in seven steps.[15]

[21] Martin, S. F.; Rein, T.; Liao, Y. *Tetrahedron Lett.* **1991**, *32*, 6481-6484.

[22] Martin, S. F.; Liao, Y.; Wong, Y.; Rein, T. *Tetrahedron Lett.* **1994**, *35*, 691-694.

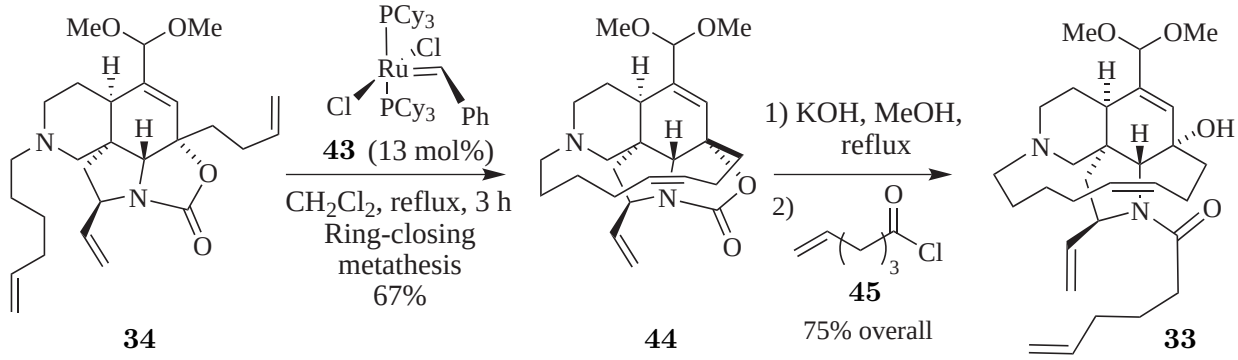
[23] Humphrey, J.; Liao, Y.; Ali, A.; Rein, T.; Wong, Y.-L.; Chen, H.-J.; Courtney, A.; Martin, S. F. *J. Am. Chem. Soc.* **2002**, *124*, 8584-8592.

[24] Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057-2059.



Scheme 1.12: Martin's synthesis of manzamine A (**1**).[15]

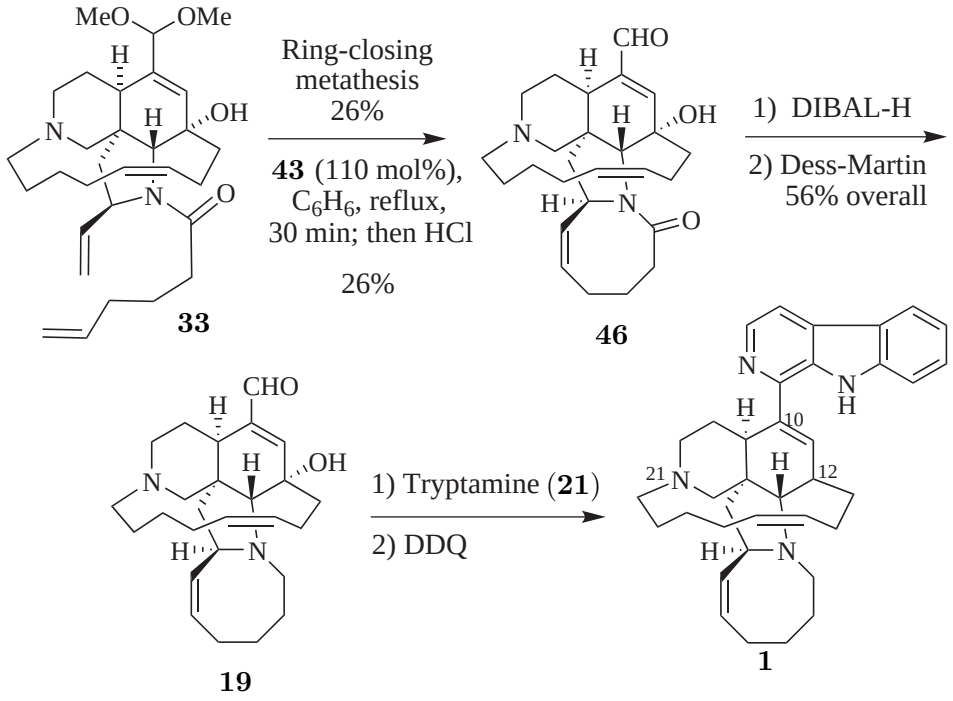
An RCM reaction occurred upon reaction of **34** with the first generation Grubbs ruthenium catalyst **43**, under high dilution conditions (0.005 M), to produce a mixture of Z/E isomers from which the macrocycle **44** was isolated in 67% yield.[5,25] Base-induced removal of the cyclic carbamate and *N*-acylation with 5-hexenoic acid chloride **45** yielded the amide **33** in 75% overall yield (Scheme 1.13).



Scheme 1.13: Martin's synthesis of manzamine A (**1**).[15]

Optimisation of the reaction conditions, for the RCM reaction of alkene **33** with the ruthenium catalyst **43**, followed by acid-catalysed removal of the dimethyl acetal protecting group, afforded aldehyde **46** in 26% yield. This low yield is probably a result of competing metathesis pathways, since the formation of the thirteen-membered D ring is disfavoured. Reduction of the amide and the aldehyde in **46**, followed by re-oxidation of the resultant primary alcohol produced ircinal A (**19**).[15] Finally, as in the synthesis by Winkler's group, ircinal A (**19**) was converted into manzamine A (**1**) through the sequence reported by Kobayashi.[19] In summary, the group of Martin accomplished the second total synthesis of manzamine A (**1**) in a total of 24 synthetic operations from commercially available starting materials, with the longest linear sequence comprising only 21 steps (Scheme 1.14).

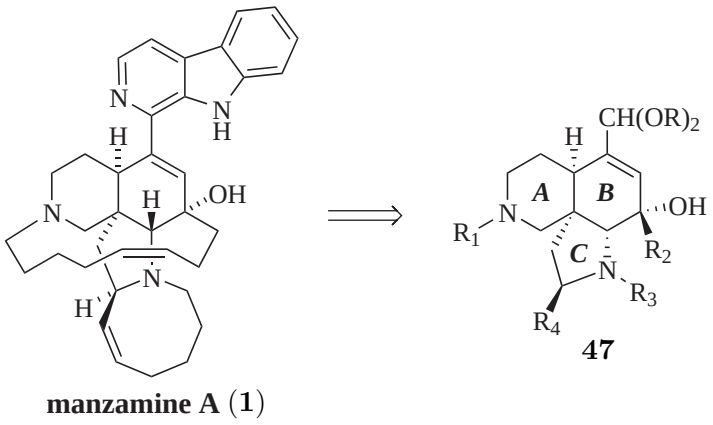
[25] Schwab, P.; Grubbs, R. H.; Ziller, J. *J. Am. Chem. Soc.* **1996**, *118*, 100-110.



Scheme 1.14: Martin's completion of the total synthesis of manzamine A (**1**).[15]

1.6 Synthetic approaches towards manzamine A

The manzamine alkaloids are characterised by a highly substituted central core, in which nitrogen-containing heterocycles are fused to medium or large rings. In addition to the unsaturated medium and large heterocycles, the central core of manzamine A (**1**) was recognised to be a great synthetic challenge.[6,10] Due to their complex structures and cytotoxic activities, the manzamine alkaloids rapidly became the subject of numerous synthetic studies. The common preliminary goal of nearly all these studies towards manzamine A (**1**) is construction of the tricyclic ABC core **47** (Scheme 1.15).[6]



Scheme 1.15: The common preliminary goal - the tricyclic ABC core **47**.

1.6.1 Different strategies examined

The different strategies reported employed to synthesise advanced precursors of manzamine A (**1**) or model systems include[6,10]:

- Inter- and intramolecular Diels-Alder type cycloadditions
- Photochemical and radical cyclisations
- Ionic cyclisation
- Intramolecular Michael and Mannich reactions
- Inter- and intramolecular [3+2] cycloadditions
- Pauson-Khand reactions
- Enyne metathesis reactions
- Biomimetic reactions

The next section is a discussion of selected approaches towards the total synthesis of manzamine A (**1**).

1.6.2 Selected approaches towards the total synthesis of manzamine A

Much work has been published concerning the total synthesis of manzamine A (**1**) and there are more than 180 papers on this subject.[10] A full discussion of all the approaches is beyond the scope of this thesis, and so some selected routes will be presented, with a focus on the key step(s), including a short introduction to the outline of the synthesis. The discussion will be divided into two parts, where part one will cover inter- and intramolecular Diels-Alder cycloaddition reactions, and the second part will be concerned with the Pauson-Khand and [3+2] cycloaddition reaction approaches.

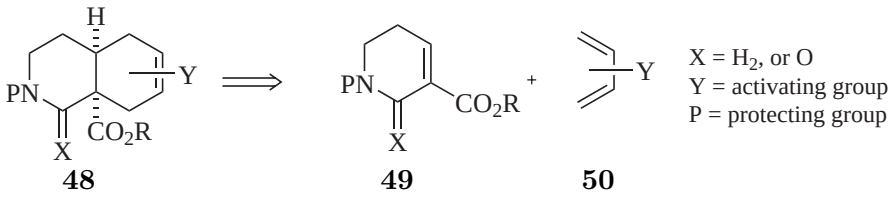
1.6.3 Inter- and intramolecular Diels-Alder cycloaddition approaches

Inter- and intramolecular Diels-Alder cycloaddition reactions, have been used by several groups and have allowed the synthesis of several potential advanced intermediates for the total synthesis of manzamine A (**1**).[6]

The approach of Simpkins and co-workers

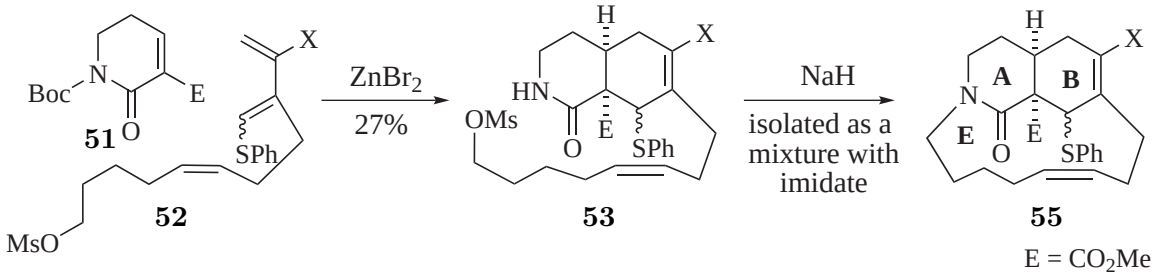
In 1989 Simpkins and co-workers reported their first approach to the synthesis of manzamine A (**1**), which was initially designed to use an intermolecular strategy.[26] Their synthetic plan was to explore the preparation of functionalised *cis*-hydroisoquinolines **48**, employing the general Diels-Alder approach outlined in Scheme 1.16.

[26] Imbroisi, D.; Simpkins, N. S. *Tetrahedron Lett.* **1989**, *30*, 4309-4312.



Scheme 1.16: A synthetic study performed by Simpkins and co-workers to synthesise the AB ring of manzamine A (**1**).[26]

Using this intermolecular Diels-Alder approach they aimed to prepare the ABE ring system **55** as shown in Scheme 1.17. The tricyclic ABE derivative **55** can be obtained from a Diels-Alder reaction of diene **52** with dienophile **51**.[27] Following the synthetic strategy towards the AB ring system of manzamine A (**1**), they designed a concise sequence of reactions to yield the ABE tricyclic derivative **55** that can be obtained in either an inter- or intramolecular fashion (Scheme 1.17).[27] Simpkins and co-workers demonstrated that an intermolecular Diels-Alder reaction can be used to prepare a tricyclic core **55** of manzamine A (**1**) (Scheme 1.17).



Scheme 1.17: Simpkins and co-workers'[27] approach to the ABE fragment (**55**) of manzamine A (**1**).

Synthetic studies of Nakagawa and Hino

The target for the synthetic study of Nakagawa and Hino was the tricyclic core **56** of manzamine A (**1**). The Diels-Alder strategy employed by these co-workers also used a dihydropyridones as a dienophiles, but in their approach the dihydropyridone unit **58** is substituted by an appendage that allows the introduction of the five-membered C ring and subsequently the eight-membered D ring (Scheme 1.18).[28–30] The tricyclic ABC core **56** can be obtained from either an intermolecular Diels-Alder reaction (Path B) of the Danishefsky diene **59** and dienophile **58**, or *via* intramolecular Diels-Alder reaction of the dihydropyridone **57** (Path A).[31] The dieneophiles **57** and **58** can be obtained in

[27] Imbroisi, D.; Simpkins, N. S. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1815-1823.

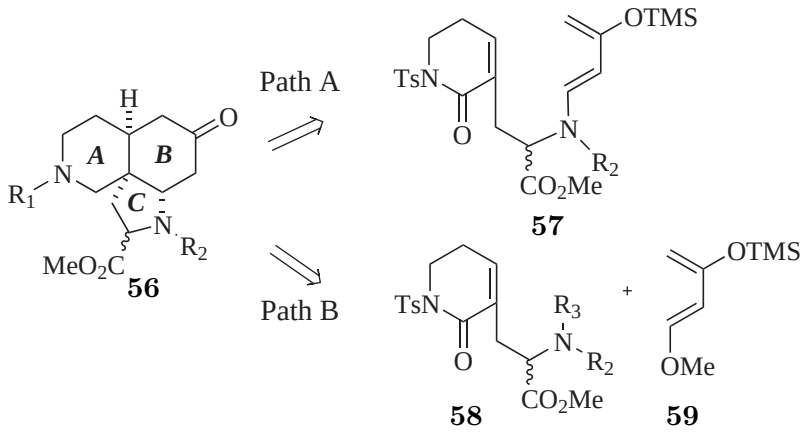
[28] Torisawa, Y.; Nakagawa, M.; Arai, H.; Lai, Z.; Hino, T.; Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1990**, *31*, 3195-3198.

[29] Nakagawa, M. *J. Heterocycl. Chem.* **2000**, *37*, 567-581.

[30] Nakagawa, M.; Torisawa, Y.; Hosaka, T.; Tanabe, K.; Da-te, T.; Okamura, K.; Hino, T. *Tetrahedron Lett.* **1993**, *34*, 4543-4546.

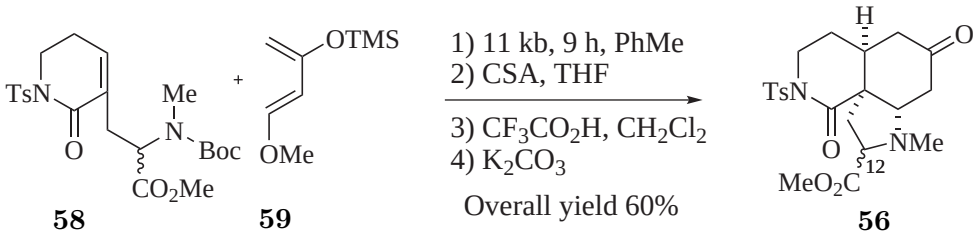
[31] Torisawa, Y.; Nakagawa, M.; Hosaka, T.; Tanabe, K.; Lai, Z.; Ogata, K.; Nakata, T.; Oishi, T.; Hino, T. *J. Org. Chem.* **1992**, *57*, 5741-5747.

four steps starting from 2-piperidinone (Scheme 1.18).[31,32]



Scheme 1.18: Retrosynthetic analysis of the tricyclic ABC core (**56**) of manzamine A (**1**), developed by Nakagawa and co-workers[28].

The *N*-protecting group of the dihydropyridinone played an important role in the achievement of a successful Diels-Alder reaction. In addition, utilization of a high-pressure Diels-Alder reaction of the dihydropyridinone **58** with the Danishefsky diene **59** followed by deprotection and pyrrolidine ring closure, allowed the central skeleton **56** to be synthesised in 60% overall yield as a mixture of epimeric compounds at C12 (Scheme 1.19).[28,31,33]



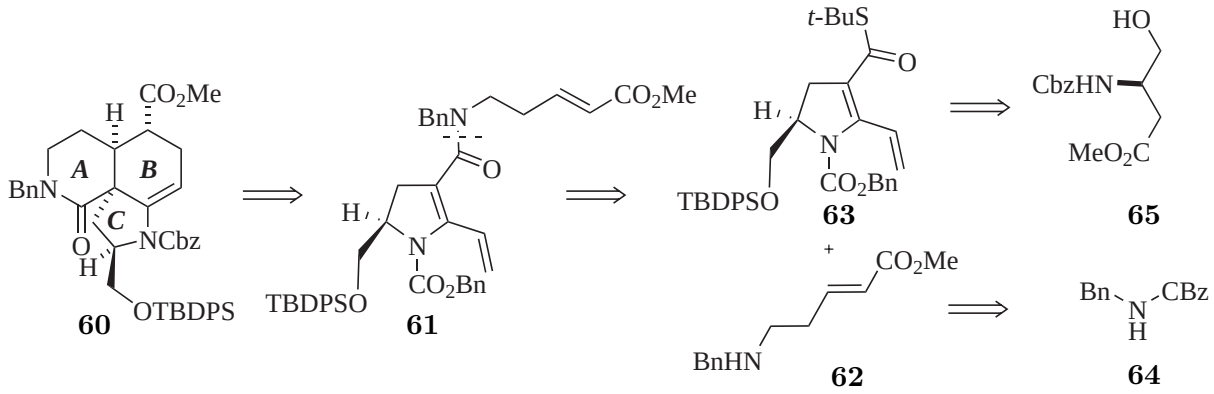
Scheme 1.19: Nakagawa and co-workers' approach to synthesis of the ABC ring **56** of manzamine A (**1**).[29,32]

The work of Pandit and co-workers

The group of Pandit set out to synthesise the tricyclic core **60**, which represents the ABC substructure of manzamine A (**1**), containing four of the five stereogenic centres (Scheme 1.20).[34] The precursor **61** for the tricyclic system was obtained by coupling of the δ-amino ester **62** and thioester **63**. The amino ester **62** was prepared in four steps starting from *N*-(benzyloxycarbonyl)benzylamine (**64**) and the thioester **63** was obtained in ten steps from methyl 3-(benzyloxycarbonyl)amino-4-hydroxybutanoate (**65**). The synthesis by Pandit and co-workers delivered the tricyclic structure ABC **60** containing

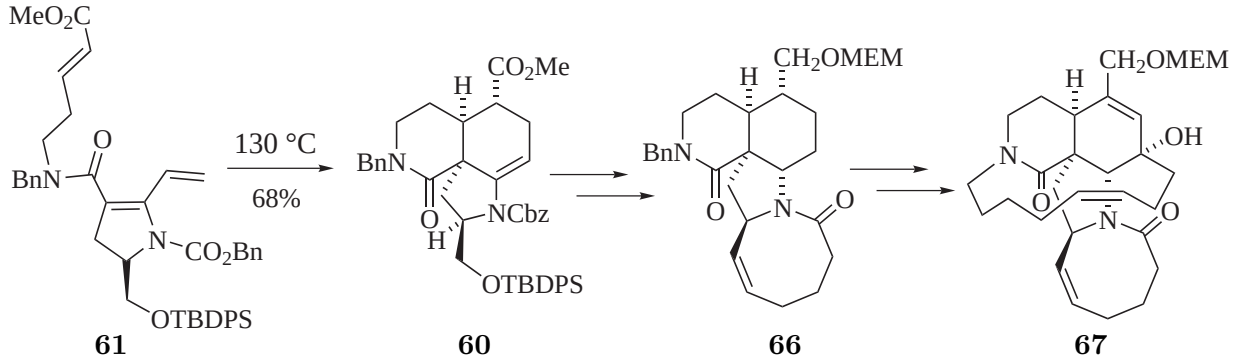
[32] Torisawa, Y.; Nakagawa, M.; Takami, H.; Nagata, T.; Ali, M. A.; Hino, T. *Heterocycles* **1994**, *39*, 277-291.
[33] Nakagawa, M.; Lai, Z.; Torisawa, Y.; Hino, T. *Heterocycles* **1990**, *31*, 999-1002.
[34] Brands, K. M. J.; Meekel, A. A. P.; Pandit, U. K. *Tetrahedron* **1991**, *47*, 2005-2026.

four of the five stereogenic centres and most of the stereochemical information found in manzamine A (**1**).[34]



Scheme 1.20: Retrosynthetic analysis of the strategy employed by Pandit and co-workers.[34]

The requisite dienophile **62** was prepared and was acylated with the thioester **63** to deliver aminoester **61** in 69% yield. With preparation of the trienic derivative **61** achieved, the intramolecular Diels-Alder reaction was performed under relatively mild conditions and resulted in a 68% yield of the tricyclic core **60** (Scheme 1.21). Following this strategy, Pandit and co-workers accomplished the synthesis of the most advanced intermediate **67** resembling the main core of manzamine A (**1**) (Scheme 1.21).[6]



Scheme 1.21: Intramolecular Diels-Alder reaction to obtain the ABC ring system **61** and the following advanced ABCDE pentacyclic intermediate **67**.

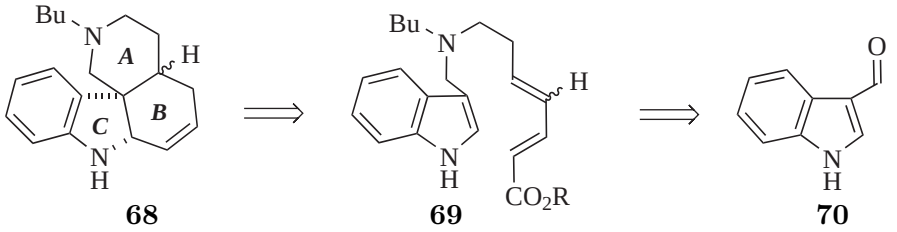
The approach of Marko and co-workers

Marko and co-workers have prepared a model of the ABC ring system found in manzamine A (**1**). The tricyclic ring system **68** can be obtained *via* an intramolecular Diels-Alder cyclisation reaction of diene **69**, which can be obtained in four steps starting from 3-formyl indole (**70**) (Scheme 1.22).[35–37] Initial condensation of aldehyde **70** with *n*-butylamine and subsequent reduction of the formed imine

[35] Marko, I. E.; Southern, J. M.; Adams, H. *Tetrahedron Lett.* **1992**, *33*, 4657-4660.

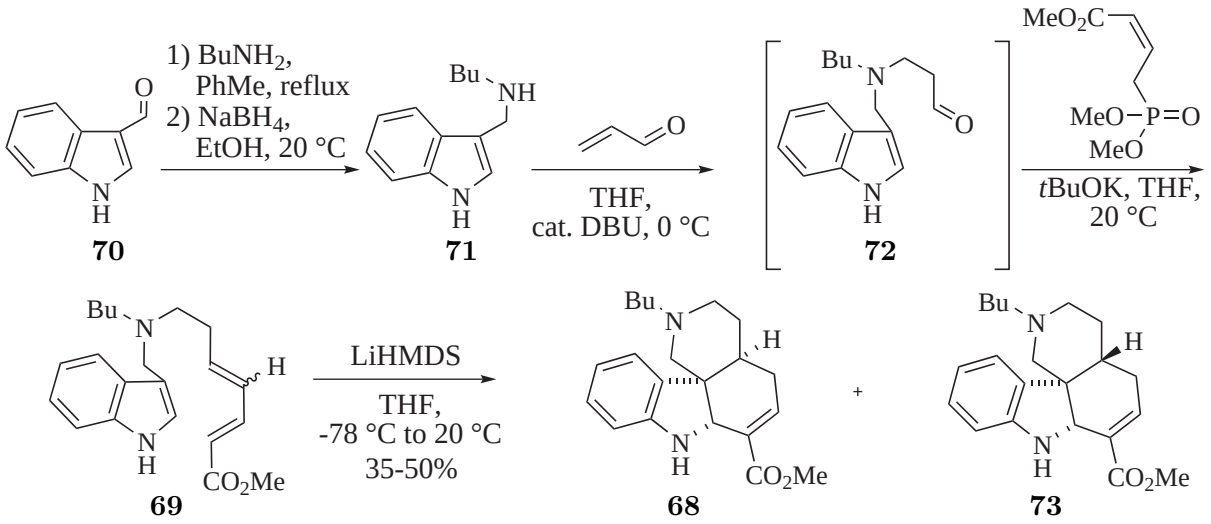
[36] Chesney, A.; Marco, I. E. *Synlett* **1992**, 275-278.

[37] Turet, L.; Marko, I. E.; Tinant, B.; Declercq, J.-P.; Touillaux, R. *Tetrahedron Lett.* **2002**, *43*, 6591-6595.



Scheme 1.22: Marko and co-workers' approach towards manzamine A (**1**).

afforded the protected amine **71**. Michael-like addition of amine **71** onto acrolein catalysed by DBU resulted in the unstable β-amino aldehyde **72**, which was immediately reacted with trimethylphosphonocrotonate to give the diene **69** as a 1:1 mixture of *E,E* and *Z,E* isomers. Various conditions were applied to induce diene **69** to undergo intermolecular Diels-Alder cycloaddition, but unfortunately the diene **69** refused to undergo the desired reaction. However, it was found that treatment with LiHMDS smoothly gave the expected tetracyclic adducts **68** and **73** in a 1:1 ratio.

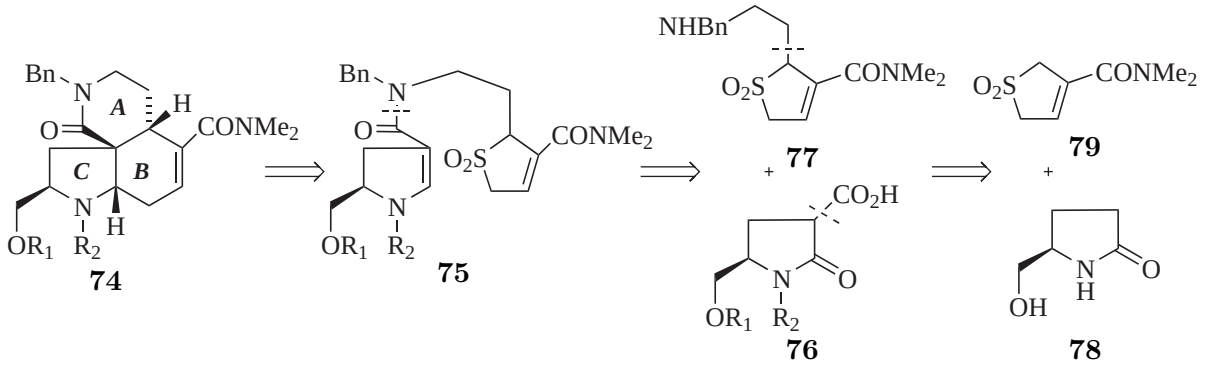


Scheme 1.23: Marko and co-workers' approach towards manzamine A (**1**).

Synthetic studies performed by Leonard and co-workers

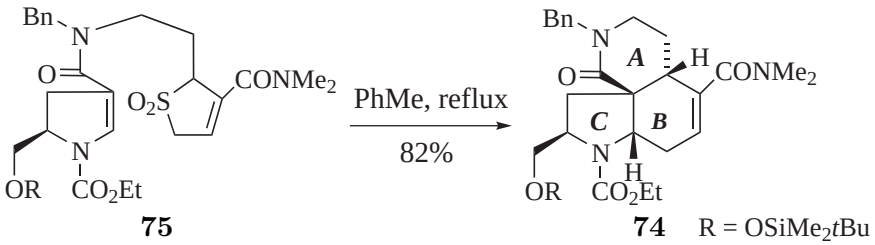
The group of Leonard synthesised the tricyclic system **74** as an intermediate during their attempts to prepare manzamine A (**1**).[38] The tricyclic ABC core **74** can be obtained from the sulfolene **75**, which when heated should undergo a tandem SO_2 extrusion and Diels-Alder cyclisation. The sulfolene **75** can be obtained from carbonyldiimidazole coupling of the amine **77** and the carboxylic acid **76**. The amine **77** can be obtained in four steps from the sulfone **79** and the carboxylic acid coupling partner **76** can be obtained in four steps from 5-(hydroxymethyl)-2-pyrrolidinone (**78**).

[38] Leonard, J.; Fearnley, S. P.; Hickey, D. M. B. *Synlett* **1992**, 272-274.



Scheme 1.24: Diels-Alder reaction to obtain the ABC ring system **74** of manzamine A (**1**).

Their strategy is based on an intramolecular inverse electron demand Diels-Alder reaction and uses a sulpholene derivative as a masked diene, and methyl pyroglutamate derived as the dienophile (Scheme 1.24).[39] The group of Leonard has used this strategy to synthesise the tricyclic core using an intramolecular Diels-Alder cycloaddition according to Scheme 1.25.[38,39]

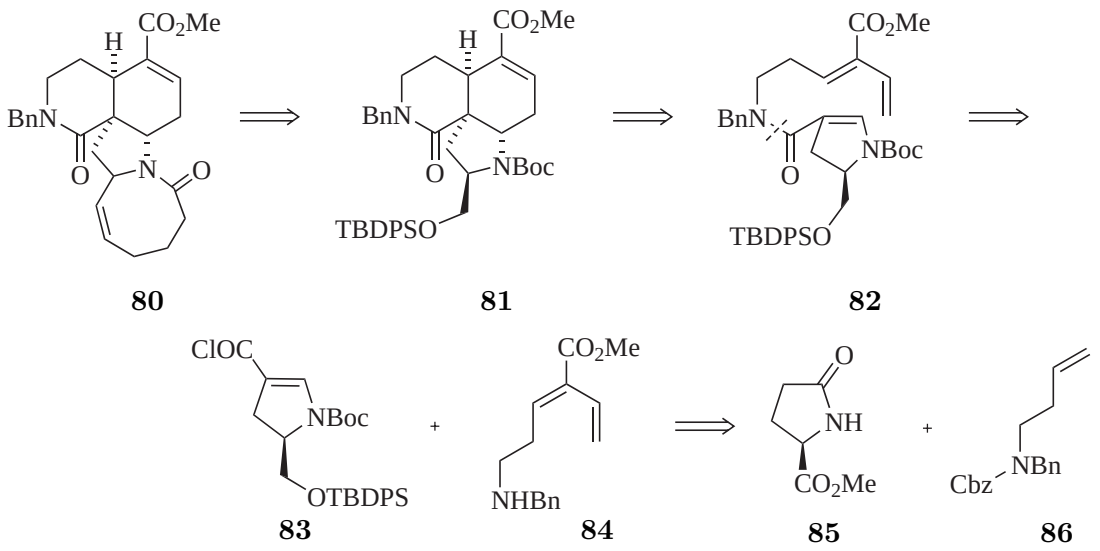


Scheme 1.25: Diels-Alder reaction to obtain the ABC ring system **74** of manzamine A (**1**).

The work of Martin and co-workers

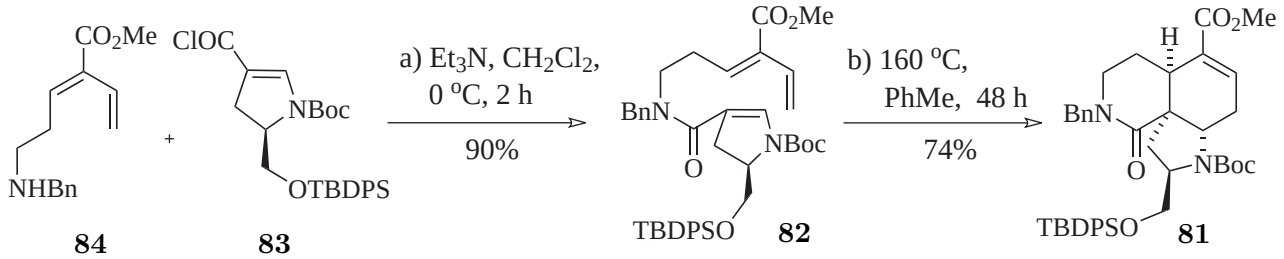
Independently, Martin and co-workers studied the same type of strategy as Leonard and co-workers. The strategy is a variant of the intramolecular Diels-Alder reaction which involves the use of the vinylogous amide **82** as the dienophile, leading to an effective entry to the ABCD core subunit **80** of manzamine A (**1**) (Scheme 1.26). The tetracyclic core **80** can be obtained from the tricyclic core **81** by a sequence involving RCM, to incorporate the D ring. The tricyclic core can be obtained using the Diels-Alder cycloaddition reaction of the vinylogous imide **82**. The imide **82** can be synthesised by *N*-acylation of the amine **84** with the acid chloride **83**. The acid chloride **83** can be obtained in seven steps starting from methyl pyroglutamate **85**; the diene **84** could be obtained in four steps from *N,N*-disubstituted aminobutene **86** (Scheme 1.26).[22] The cyclisation of substrates such as **82** would proceed to yield the cycloadduct **81**, thereby creating the tricyclic core of manzamine A (**1**) in a single step. The synthesis of the ABCD ring system requires the complete stereoselective assembly of the tricyclic ABC ring core.[21]

[39] Leonard, J.; Fearnley, S. P.; Finlay, M. R.; Knight, J. A.; Wong, G. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2359-2361.



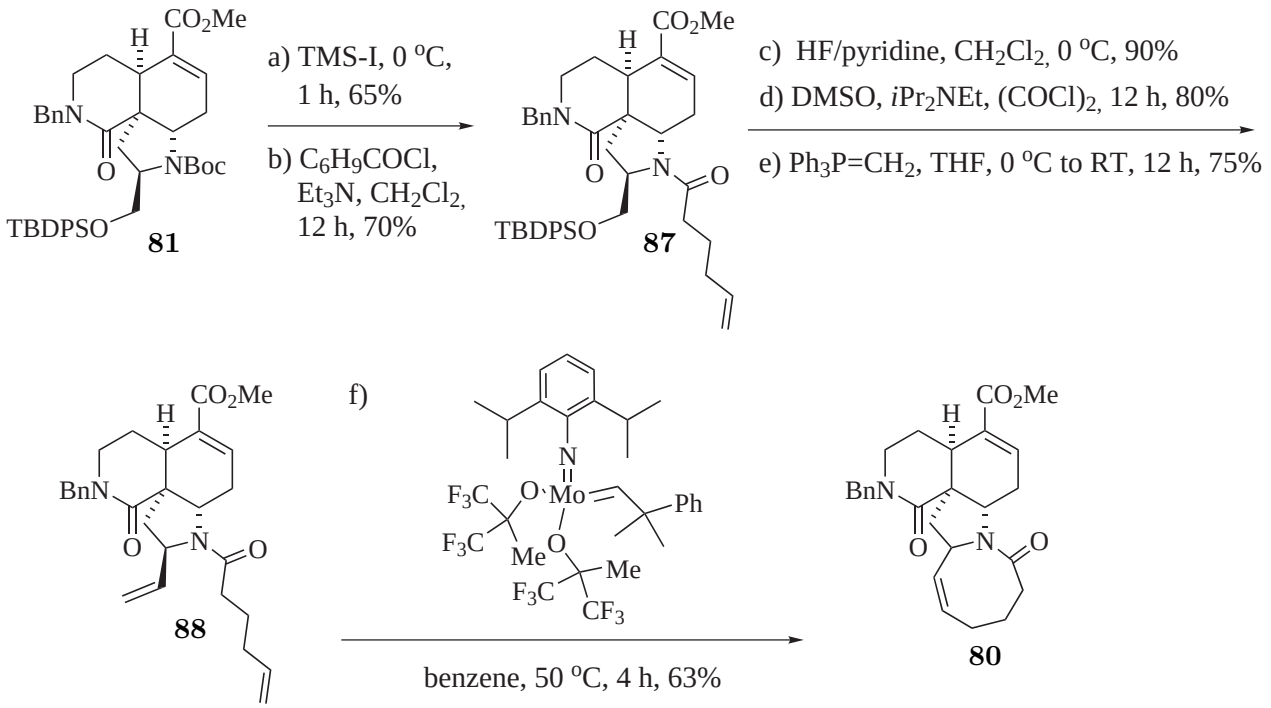
Scheme 1.26: Intramolecular Diels-Alder reaction to obtain the ABCD ring system **80** of manzamine A (**1**).

Union of the diene **83** and dienophile **84** by amide formation to give the intramolecular Diels-Alder precursor **82**. Execution of the Diels-Alder reaction under mild conditions afforded the tricyclic core **81** (Scheme 1.27).



Scheme 1.27: Synthesis of the ABCD ring of manzamine A (**1**) by Martin and co-workers.[5]

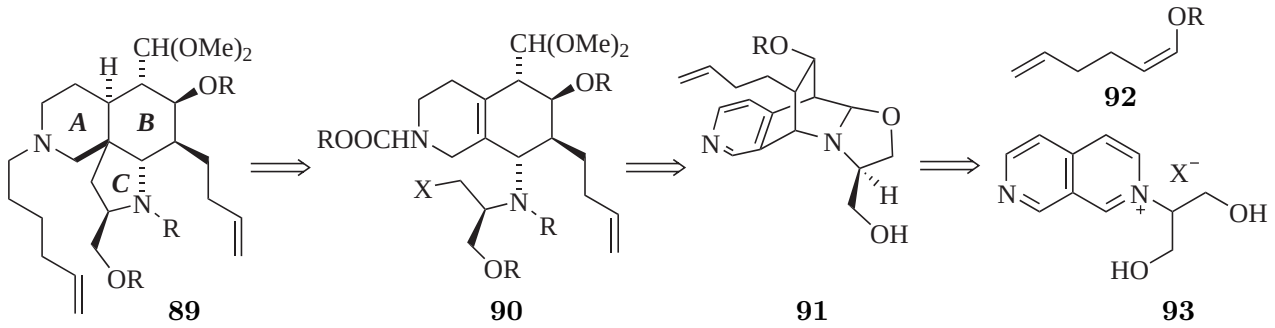
Conversion of the Diels-Alder cycloadduct **81** into the diene **88** was accomplished in five steps (Scheme 1.28). Deprotection of the amine and amide formation afforded the amide **87**. Alcohol deprotection, oxidation and olefination gave the desired diene **88**. Ring-closing metathesis in the presence of Schrock molybdenum catalyst delivered the tetracyclic product **80** in 65% yield.[22] Investigations performed by Martin and co-workers established the applicability of intramolecular Diels-Alder reactions of vinylogous imides to the construction of the pyrrolo[2,3-j]hydroisoquinoline ring system that constitutes the central tricyclic core of manzamine A (**1**) (Scheme 1.28).



Scheme 1.28: Synthesis of the ABCD ring of manzamine A (**1**) by Martin and co-workers.[5]

The approach of Langlois and co-workers

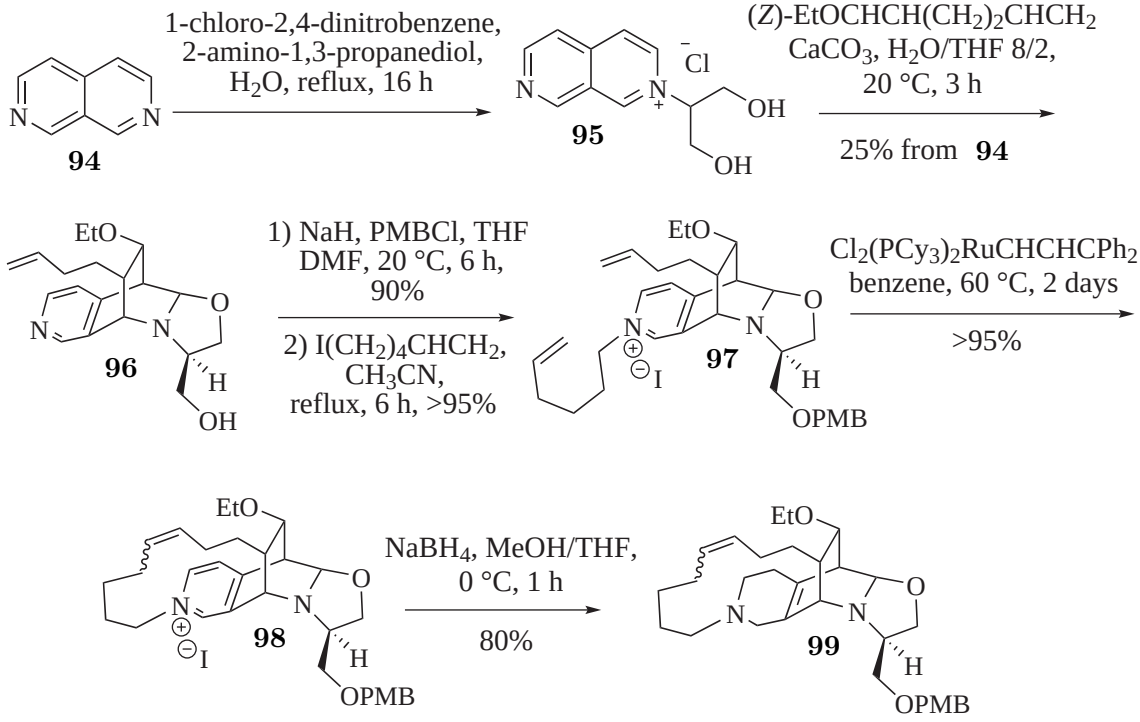
The group of Langlois synthesised the tricyclic core **89** of manzamine A (**1**) using an inverse electron-demand Diels-Alder cycloaddition reaction, also known as the Bradsher cycloaddition reaction. The tricyclic core **89** of manzamine A (**1**) can be obtained from octahydroisoquinoline **90** by introduction of the five membered C ring. The octahydroisoquinoline **90** can be obtained from a Bradsher cycloaddition reaction of naphthyridinium salt **93** and vinyl ether **92** (Scheme 1.29).[40,41] The strategy of Langlois and co-workers was designed to allow for short and convergent access to the functionalised octahydroquinoline **90**. The octahydroquinoline **90** bears all the appendages for further elaboration of the five (C ring), eight (D ring), and thirteen-membered (E ring) rings (Schemes 1.29 and 1.30).[40,41]



Scheme 1.29: Retrosynthetic analysis of Langlois and co-workers' synthetic route to the ABC ring **89**.[40,41]

[40] Urban, D.; Duval, E.; Langlois, Y. *Tetrahedron Lett.* **2000**, *41*, 9251-9256.
[41] Magnier, E.; Langlois, Y. *Tetrahedron Lett.* **1998**, *39*, 837-840.

Condensation of serinol with 2,7-naphthyridine resulted in the salt **95** followed by a Bradsher cycloaddition to afford the tricyclic intermediate **96**. Protection of the alcohol, and further alkylation of the protected alcohol with 6-iodo-1-hexene gave the pyridinium salt **97** nearly quantitatively. Ring closing metathesis of the pyridinium salt **97** resulted in an almost quantitative yield of the pentacyclic pyridinium salt **98** as an inseparable 7:3 mixture of *Z* and *E* isomers. Sodium borohydride reduction of the pyridinium salt **98** yielded the anticipated tetrahydropyridine derivative **99**, in 18% overall yield from **94**.[40,41]



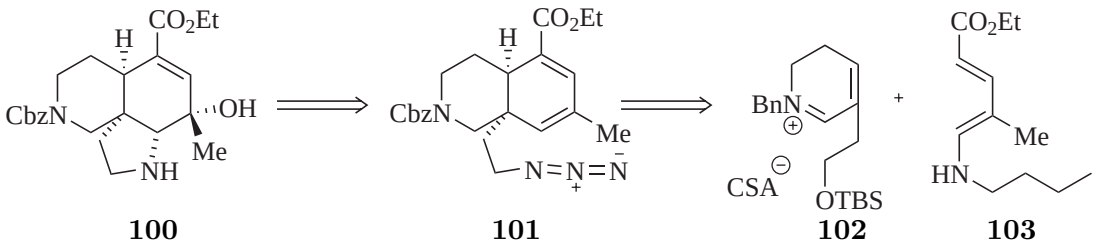
Scheme 1.30: The approach from Langlois and co-workers[40,41] to the ABE core system **99** of manzamine A (**1**).

Synthetic studies performed by Marazano and co-workers

Among the numerous cycloaddition strategies used to construct the central AB rings of manzamine A (**1**), the approach published by Marazano and co-workers is one of the most efficient because the synthesis brings together all the important functionalities in a single step.[42,43] Retrosynthetically, the ABC ring system **100** can be obtained from the AB ring system **101**, *via* intramolecular triazole formation and subsequent decomposition to give the imine. The AB ring **101** can be obtained *via* Diels-Alder cycloaddition of diene **103** and dienophile **102** (Scheme 1.31).

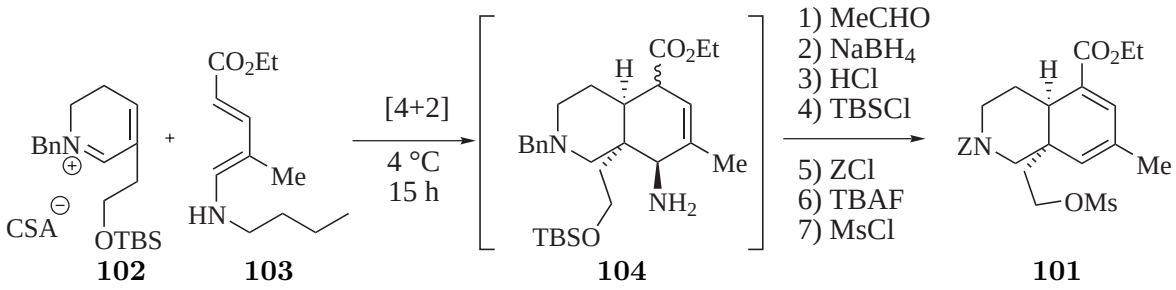
[42] Herdemann, M.; Al-Mourabit, A.; Martin, M.-T.; Marazano, C. *J. Org. Chem.* **2002**, *67*, 1890-1897.

[43] Jakubowicz, K.; Abdeljelil, K. B.; Herdemann, M.; Martin, M.-T.; Gateau-Olesker, A.; Mourabit, A. A.; Marazano, C.; Das, B. C. *J. Org. Chem.* **1999**, *64*, 7381-7387.



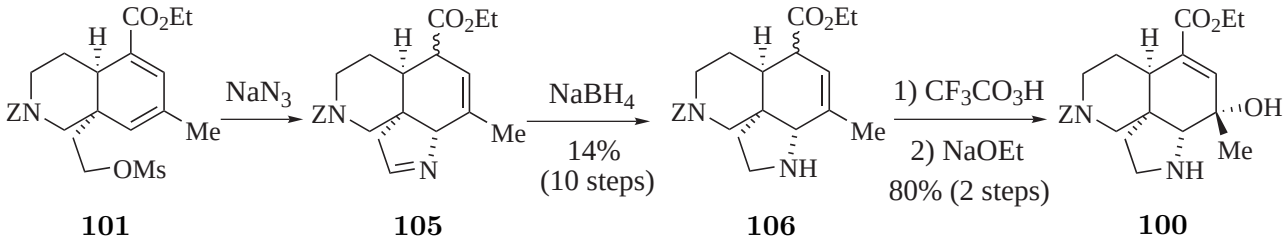
Scheme 1.31: Marazano and co-workers' retrosynthetic analysis of the ABC ring system **100** of manzamine A (**1**).

Condensation of the dihydropyridinium salt **102** with the diene **103** gave Diels-Alder adduct **104**. Reductive amination and elimination along with protecting group manipulation afforded the mesylate **101** (Scheme 1.32).



Scheme 1.32: Marazano and co-workers' synthesis of the ABC core system **100** of manzamine A (**1**).

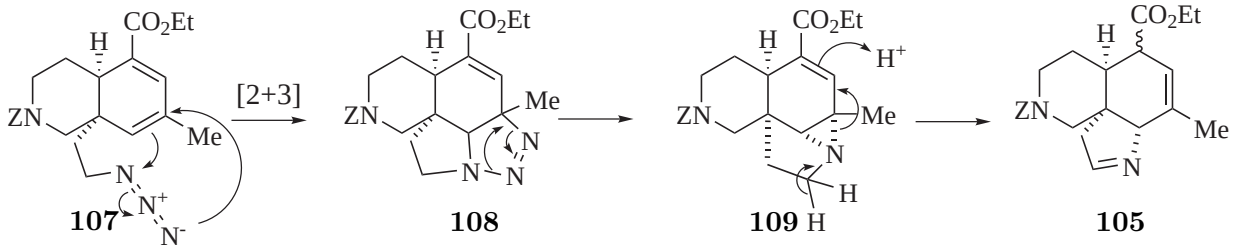
Displacement of the mesylate using sodium azide with subsequent imine formation, *via* an aziridine intermediate, gave the imine **105**.[42,43] Sodium borohydride reduction of the imine **105** afforded isomeric amines **106**. Oxidation to the epoxides and subsequent treatment with base resulted in the alcohol **100** (Scheme 1.33).



Scheme 1.33: Marazano and co-workers for to the ABC core system **100** of manzamine A (**1**).

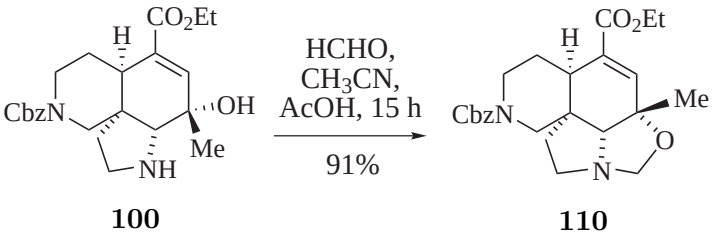
A plausible mechanism to explain this remarkable consecutive reaction sequence can be deduced by comparison on this work with related results previously reported by Hudlicky.[44] The azido group of unstable intermediate **107** may first add to the diene function, giving the triazole derivative **108**, a process that would be followed by spontaneous nitrogen elimination to produce the aziridine **109**, which ring opens to give imine **105** (Scheme 1.34).[42]

[44] Hudlicky, T.; Frazier, J. O.; Seoane, G.; Tiedje, A.; Seoane, A.; Kwart, L. D.; Beal, C. *J. Am. Chem. Soc.* **1986**, *108*, 3755-3762.



Scheme 1.34: Proposed mechanism for the consecutive reaction sequence.

The stereochemistry of the key derivative **100** possesses the essential features of the ABC ring of manzamine A (**1**). This fact was verified by the observation that **100** forms the oxazolidine **110** in the presence of formaldehyde (Scheme 1.35).[42]



Scheme 1.35: Formation of oxazolidine **110** in the presence of formaldehyde.

1.6.4 Pauson-Khand and [3+2] cycloaddition reactions

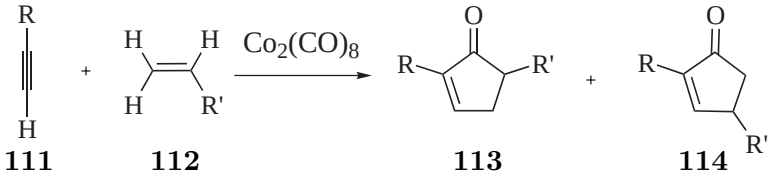
The Pauson-Khand and [3+2] cycloaddition reactions have not been as widely used as the Diels-Alder reaction in the synthetic endavours towards manzamine A (**1**). The only group to have examined the Pauson-Khand reaction is the group of Magnus, where their synthesis concerned the tricyclic core structure of manzamine A (**1**).[45] The groups of Coldham and Williams are the only groups to have studied the [3+2] cycloaddition reactions in the context of a total synthesis of manzamine A (**1**). Both syntheses involved construction of the tricyclic core, but they are distinct in their inter- and intramolecular character.[46,47]

Pauson-Khand reaction

The Pauson-Khand reaction is an interesting and useful [2+2+1] cycloaddition process in which an alkyne **111**, an alkene **112** and carbon monoxide react to form the cyclopentenones **113** and **114** (Scheme 1.36).[48] Pauson and Khand first reported the reaction in detail in 1973,[49] and it has proven

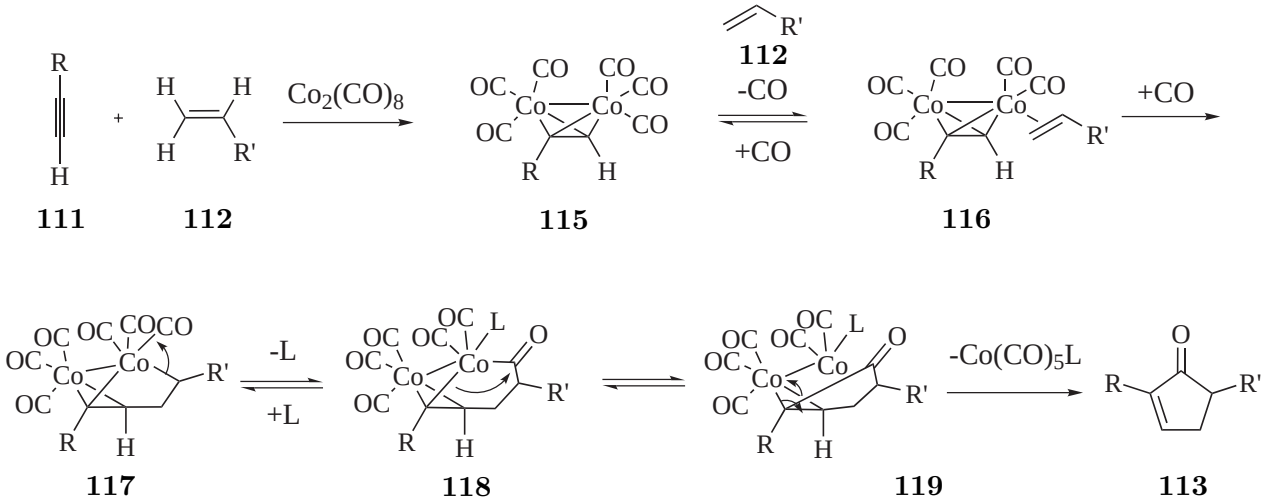
[45] Magnus, P.; Fielding, M. R.; Wells, C.; Lynch, V. *Tetrahedron Lett.* **2002**, *43*, 947-950.
[46] Coldham, I.; Pih, S. M.; Raboti, R. *Synlett* **2005**, 1743-1745.
[47] Ahrendt, K. A.; Williams, R. M. *Org. Lett.* **2004**, *6*, 4539-4541.
[48] Hegedus, L. S. *Transitions Metals in the Synthesis of Complex Organic Molecues;* University Science Books: 1999.
[49] Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I. *J. Chem. Soc., Perkin Trans. 1* **1973**, 977-981.

to be tolerant of a wide variety of functional groups such as esters, ethers, thioethers, tertiary amines, amides, sulfonamides, nitriles and alcohols, making it an attractive reaction for organic synthesis.



Scheme 1.36: The Pauson-Khand reaction.

The cyclopentenone **113** is formed by cyclisation of an alkyne **111**, an alkene **112** and carbon monoxide in the presence of $Co_2(CO)_8$. While there is no consistent mechanistic data for the Pauson-Khand reaction, a mechanism has been proposed based on regio- and stereochemical observations from many related examples.[50] The only intermediate that has been isolated is the initial, stable alkyne-$Co_2(CO)_6$ complex **115**. It is assumed that the next step involves dissociation of a CO ligand and coordination of the alkene to give **116**. The alkene then irreversibly inserts into one of the cobalt-carbon bonds forming **117**. This step is thought to be irreversible and rate-determining as well as product-determining. Migratory insertion of a CO ligand bound to cobalt to form the carbonyl moiety in **119** followed by reductive elimination of the $Co(CO)_3$ fragment. Loss of the $Co_2(CO)_5L$ fragment liberates the cyclopentenone **113** (Scheme 1.37).

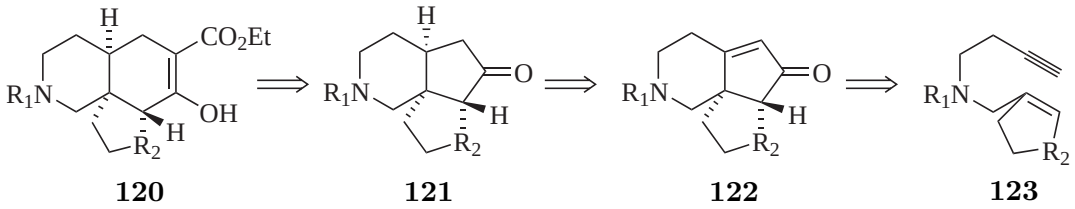


Scheme 1.37: Proposed mechanism for the Pauson-Khand reaction.[50]

[50] Magnus, P.; Principe, L. M. *Tetrahedron Lett.* **1985**, *26*, 4851-4854.

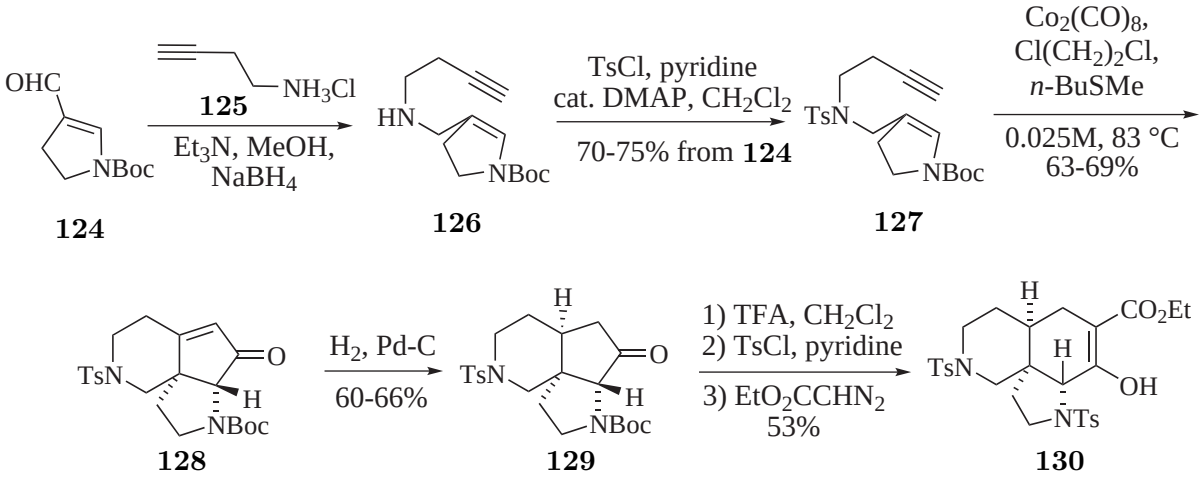
The work of Magnus and co-workers

Magnus and co-workers centered their studies around the tricyclic ABC rings of manzamine A (**1**) (Scheme 1.38). The central core **122** can in principle be constructed by an intramolecular Pauson-Khand reaction of **123** and conjugate reduction of the cyclopentenone to give tricyclic ketone **121**. Ring expansion of the B ring would result in formation of the tricyclic core structure of manzamine A (**1**).



Scheme 1.38: Magnus and co-workers' tricyclic intermediate **123**.[45]

Reductive amination of **124** with 1-amino-3-butyne hydrochloride (**125**) gave the secondary amine **126**. Subsequent protection using *para*-toluenesulfonyl chloride afforded the sulfonamide derivative **127**. Optimisation of the Pauson-Khand reaction using a variety of different conditions led to the Sugihara procedure[51] and the desired Pauson-Khand product in a 63-69% yield. Reduction of the cyclopentenone **128** to the cyclopentanone **129** was needed in order to ring expand the B ring. After protecting group interconversion, treatment of the ketone with ethyl diazoacetate and $BF_3.OEt_2$ resulted in formation of β-keto ester **130** in 53% overall yield from **129**. The Pauson-Khand reaction provides a resonably concise route to the manzamine A (**1**) core structure.

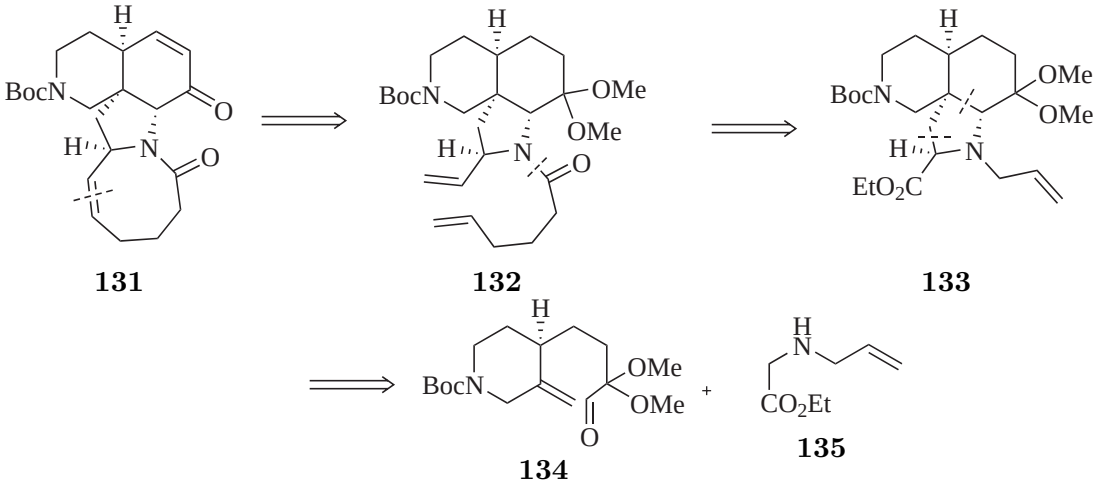


Scheme 1.39: Magnus and co-workers' tricyclic intermediate **130**.[45]

[51] Sugihara, T.; Yamada, M.; Yamaguchi, M.; Nishizawa, M. *Synlett* **1999**, 771-773.

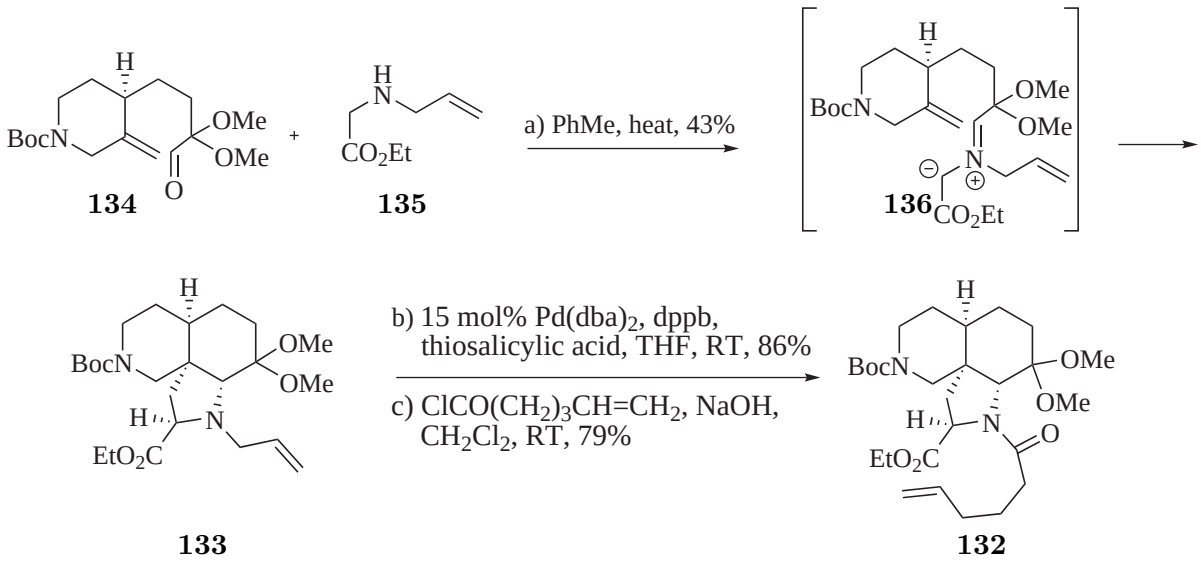
Synthetic studies performed by Coldham and co-workers

Coldham and co-workers have focused their study on the tetracyclic ABCD ring system of manzamine A (**1**) *via* intramolecular dipolar cycloaddition followed by RCM.[46] The tetracyclic ABCD ring **131** can be obtained from the diene **132** by sequential ring-closing metathesis, deprotection and oxidation. Diene **132** can be obtained from the tricyclic intermediate **133** which in turn can be obtained from aldehyde **134** using a [3+2] dipolar cycloaddition with the dialkylamine **135** (Scheme 1.40).[46]



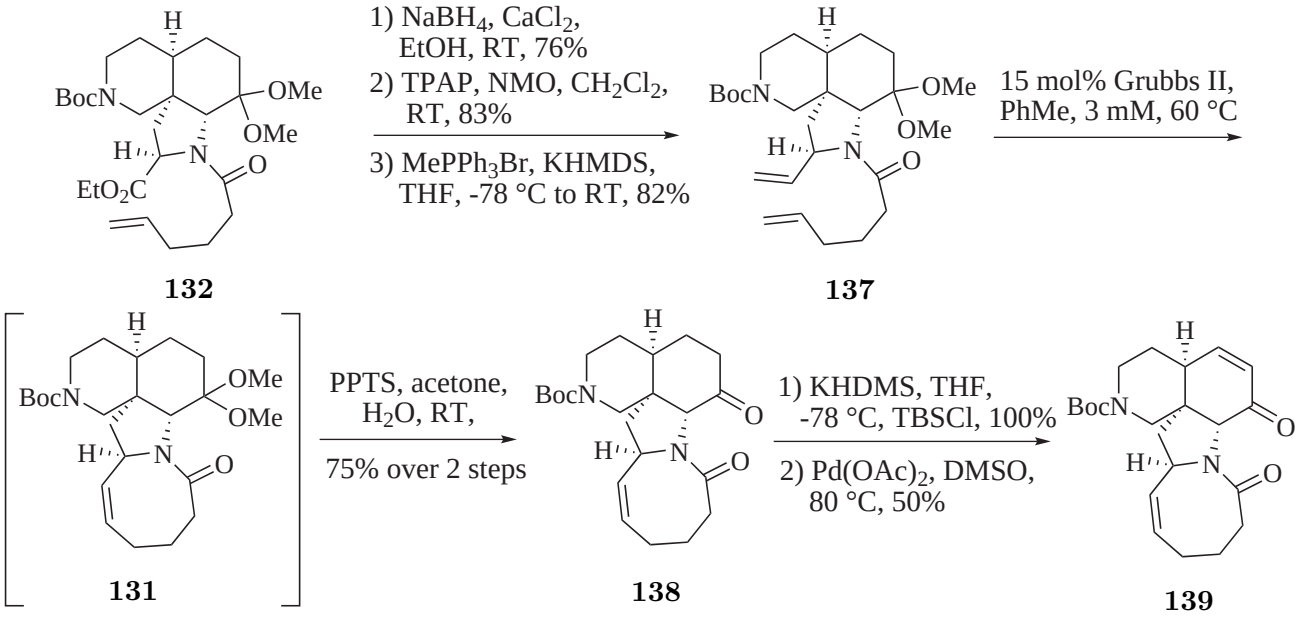
Scheme 1.40: Coldham and co-workers' retrosynthesis of the tricyclic core **131**.[46]

The aldehyde **134** was employed in the [3+2] dipolar cycloaddition reaction with secondary amine **135** and resulted in the tricyclic core **133** in a reasonable yield. Deallylation with palladium(0) provided the secondary amine in 86% yield, which was *N*-acylated with 5-hexenoyl chloride to afford amide **132** in a 79% yield (Scheme 1.41).



Scheme 1.41: Coldham and co-workers' tricyclic core **138**.[46]

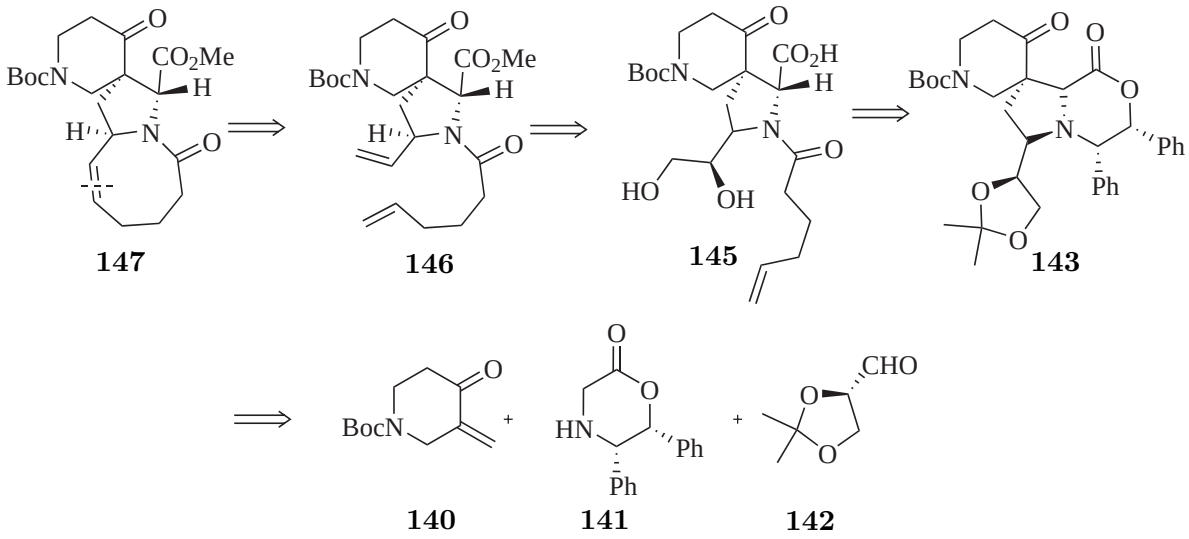
Reduction of the carboxylic ester, oxidation of the resulting alcohol to the aldehyde using TPAP and subsequent Wittig olefination yielded the diene **137**. Ring-closing metathesis using Grubbs ruthenium second generation catalyst followed by acid hydrolysis afforded the anticipated ketone **138** in 75% yield over two steps (Scheme 1.42). Further elaboration of ketone **138** to the unsaturated enone **139** was also accomplished. Deprotonation of the ketone **138** proceeded easily with KHMDS and trapping of the enolate as the silyl enol ether. Treatment of the silyl enol ether with $Pd(OAc)_2$ gave the desired enone **139** in 50% yield. Conjugate addition to the enone **139** would allow further functionalisation to incorporate the β-carboline unit.[46]



Scheme 1.42: Coldham and co-workers' tricyclic core **138**.[46]

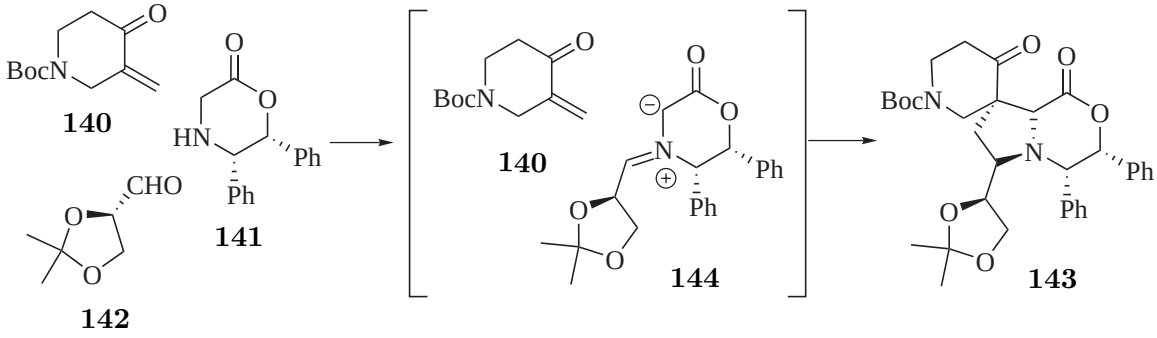
The work of Williams and co-workers

Williams and co-workers used an intermolecular [3+2]-dipolar cycloaddition reaction to synthesise the ACD fragment **147** of manzamine A (**1**) and nakadomarin A (**2**).[47] The retrosynthesis of the key intermediate **147** is predicted from ring-closing metathesis of the spirocyclic diene **146**. The diene **146** was envisioned to come from the amino acid **145**, which could be assembled using a stereoselective three-component [3+2]-dipolar cycloaddition reaction of the fragments **140**, **141** and **142**.



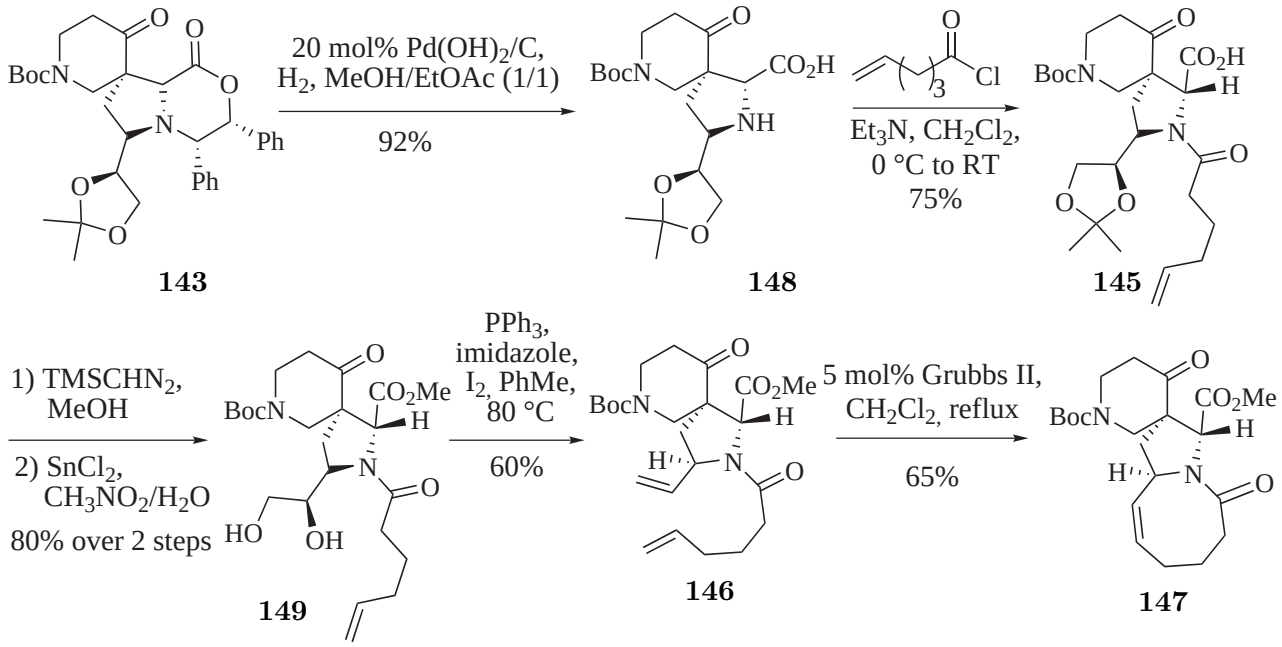
Scheme 1.43: William and co-workers' retrosynthesis of the tetracyclic core **147**.[47]

Three-component condensation of enone **140**, morpholinone **141** and aldehyde **142** yielded the 2,5-*trans*-cycloadduct **143** as a single diastereomer. Initial formation of the azomethine ylide **144** followed by cycloaddition with the enone **140** affords the desired cycloadduct **143** (Scheme 1.44).



Scheme 1.44: Williams and co-workers' retrosynthesis of the tetracyclic core **147**.[47]

Removal of the chiral template by hydrogenolysis with Pearlman's catalyst yielded the pyrrolidine **148** in 92%. *N*-Acylation with 5-hexenoyl chloride afforded the amide **145** in 75% yield. Treatment of **145** with TMS diazomethane followed by $SnCl_2$ resulted in protection of the acid and deprotection of the diol to give **149**, which was subsequently converted into the olefin **146**. Ring-closing metathesis using Grubbs second generation ruthenium catalyst gave the ACD intermediate **147** (Scheme 1.45).



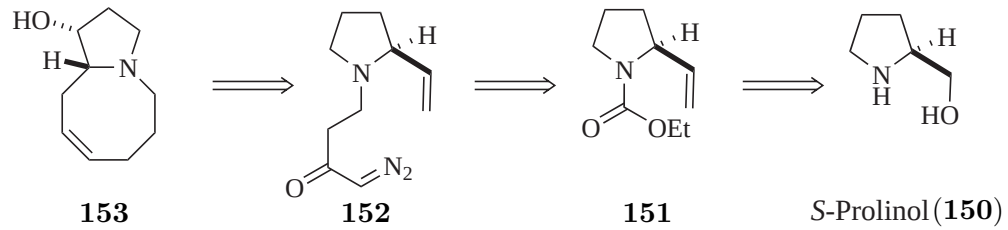
Scheme 1.45: Williams and co-workers' synthesis of the tricyclic ACE core **147**.[47]

1.6.5 Contributions from the Clark group

Among the many synthetic studies towards the total synthesis of manzamine A (**1**) several fragments, sub-units and advanced intermediates have been published. Within the Clark group, routes towards two sub-units, i.e., the CE ring fragment as well as the AB ring fragment of manzamine A (**1**) have been developed.[52,53]

Synthesis of the CD ring fragment

The first endeavours from the Clark group resulted in a very efficient enantioselective route to the CD ring system of manzamine A (**1**), E, F as well as ircinal A (**19**). The CD ring fragment can be obtained from the key intermediate, the diazo ketone **152**, which can be prepared from vinyl pyrrolidinone **151**, synthesised in 3 steps from (*S*)-prolinol (**150**) (Scheme 1.46).

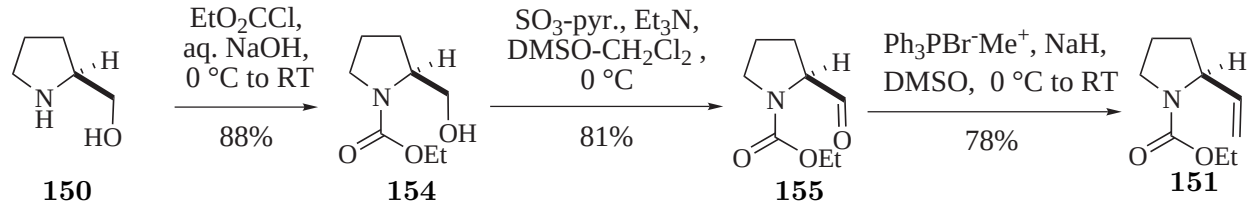


Scheme 1.46: Retrosynthesis of the CD ring fragment of manzamine A (**1**).

[52] Clark, J. S.; Hodgson, P. B. *Tetrahedron Lett.* **1995**, *36*, 2519-2522.

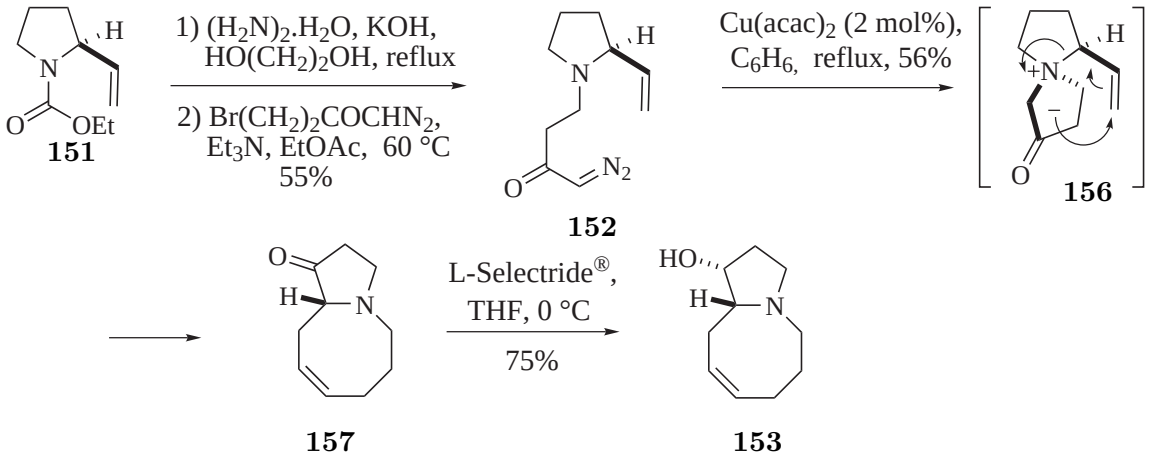
[53] Clark, J. S.; Townsend, R. J.; Blake, A. J.; Teat, S. J.; Johns, A. *Tetrahedron Lett.* **2001**, *42*, 3235-3238.

Protection of the secondary amine **150** as the carbamate afforded alcohol **154** in 88% yield. Oxidation of the alcohol **154** to the aldehyde **155** and subsequent methylenation delivered the vinyl pyrrolidine **151** in 78% yield (Scheme 1.47).



Scheme 1.47: Synthesis of the CE ring fragment of manzamine A (**1**).

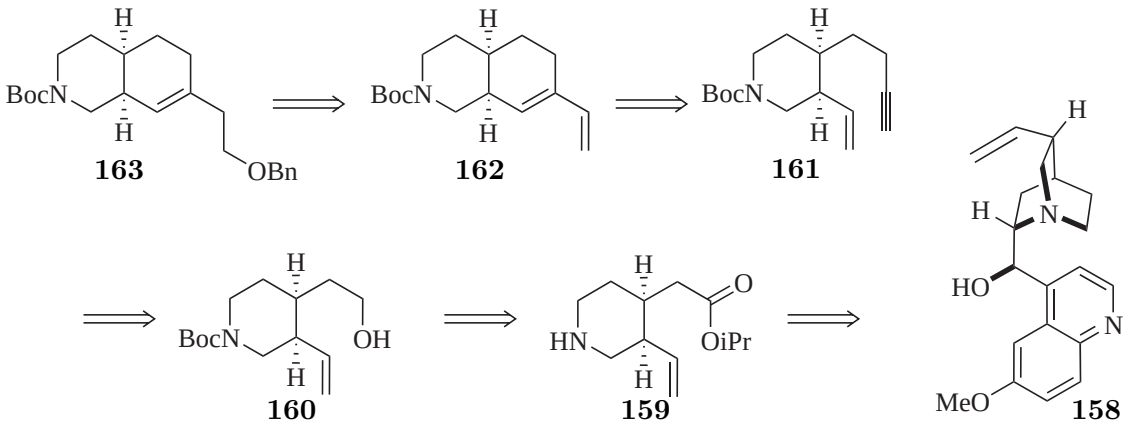
The vinyl pyrrolidine **151** was deprotected using hydrazine and the resulting amine was immediately treated with 4-bromo-1-diazobutan-2-one to give the cyclisation precusor **152** in 55% over two steps. Treatment of the cyclisation precusor **152** with $Cu(acac)_2$ (2 mol%) afforded the fused bicyclic system **157** as the only isolable product in 56% yield. It is thought that the reaction occured by [2,3]-sigmatropic rearrangement of the spiro-fused bicyclic ammonium ylide intermediate **156**, resulting in three-carbon ring-expansion of the pyrrolidine. Reduction of the ketone **157** using L-Selectride® afforded the alcohol **153** with an optical purity of > 98% *ee* (Scheme 1.48).[52]



Scheme 1.48: Synthesis of the CD ring fragment of manzamine A (**1**).

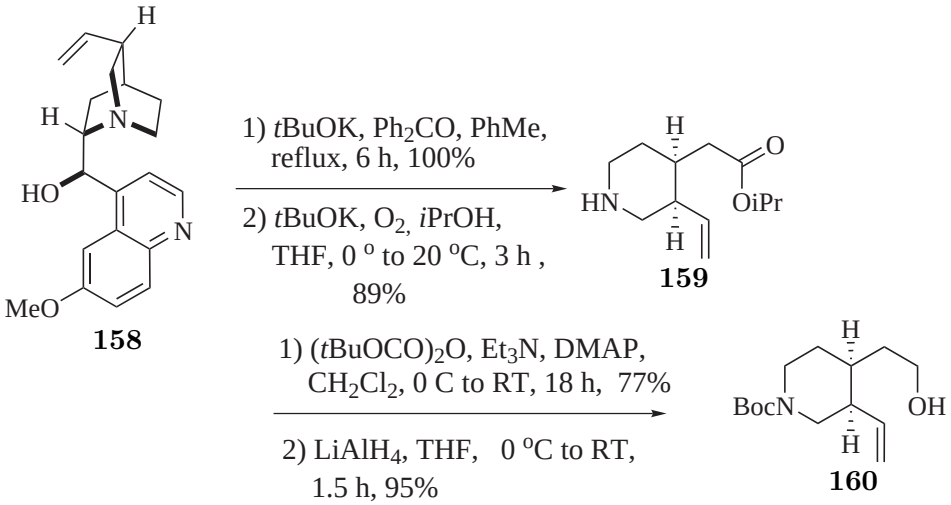
Synthesis of the AB ring fragment

In addition to the enantioselective route to the CD ring system **153**, the Clark group has also developed a short enantioselective synthesis of the AB ring system **163**. Hydroboration of the terminal alkene in **162** gives the partly functionalised AB ring system **163**. Diene **162** is a result of RCM of the key enyne **161**. Removal of the alkyne from **161** reveals alcohol **160**, which can be obtained from meroquinene ester **159**. Retrosynthetic autoxidation of **159** leads to (–)-quinine (Scheme 1.49).



Scheme 1.49: Retrosynthetic analysis of the AB ring fragment of manzamine A (**1**).

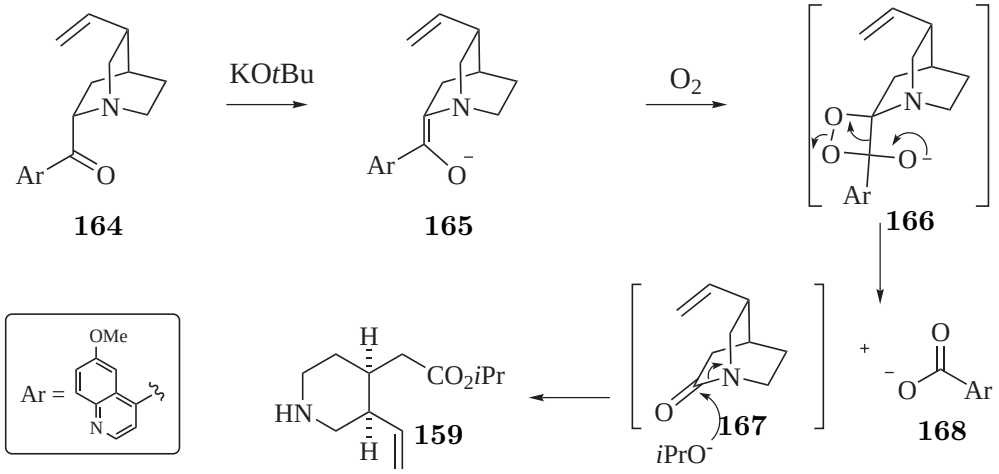
The synthesis commenced with the conversion of (–)-quinine (**158**) into the meroquinene ester **159**, by oxidation to the quininone and subsequent ring cleavage.[54,55] Protection of the amine as the *t*-butyl carbamate and subsequent ester reduction afforded the alcohol **160** in good yield.



Scheme 1.50: Synthesis of the meroquinene ester **159**.

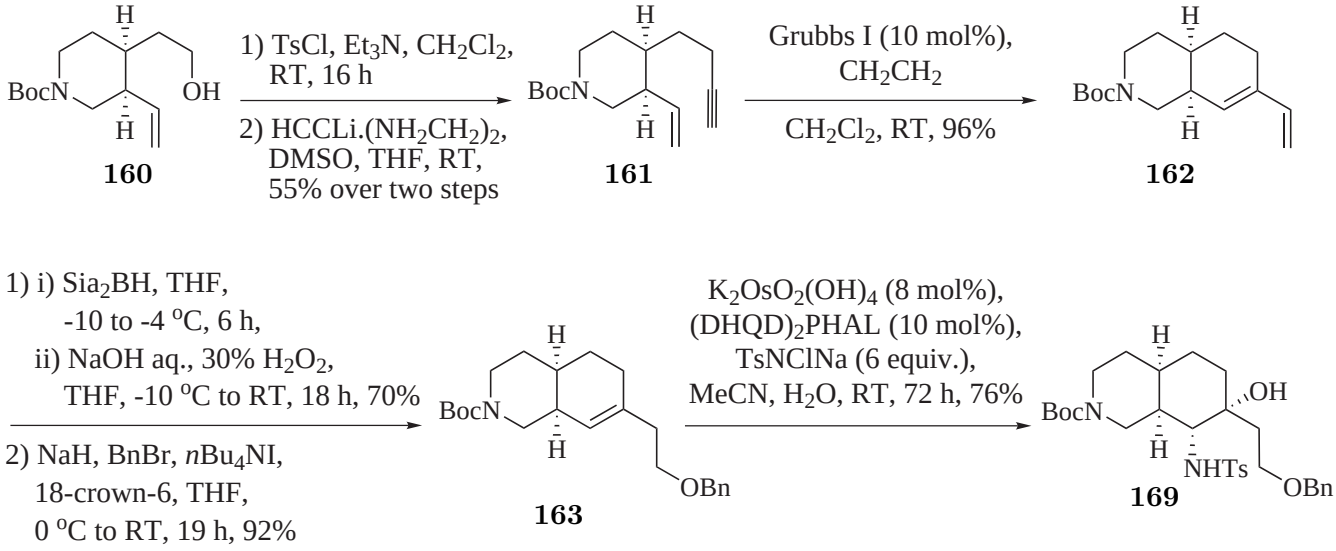
The mechanism for the autoxidation of meroquinene isopropyl ester **159** to quininone (**164**) is given in Scheme 1.51. Deprotonation of quininone (**164**) affords the enolate **165**, which combines with molecular oxygen to give the dioxo-adduct **166**. Ring opening of the 4-membered dioxo ring **166** is accompanied by C-C bond scission of the bicyclic lactam **167** and the carboxylate **168** is formed. Finally, ring opening of the lactam **167** with *i*-propanol yields the desired meroquinine ester **159** (Scheme 1.51).[54]

[54] Doering, W. E.; Chanley, J. D. *J. Am. Chem. Soc.* **1946**, *68*, 586-588.
[55] Woodward, R. B.; Wendler, N. L.; Brutschy, F. J. *J. Am. Chem. Soc.* **1945**, *67*, 1425-1429.



Scheme 1.51: Proposed mechanism for the autoxidation.[54]

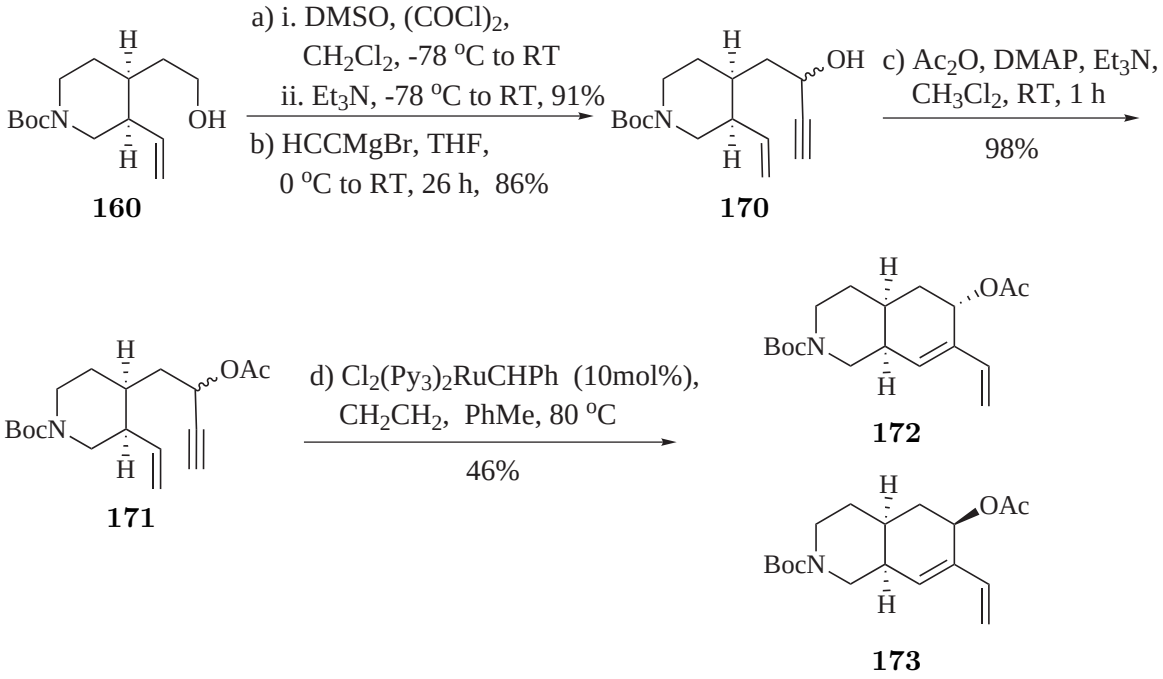
Tosylation of the alcohol and displacement with lithium acetylide ethylene diamine complex afforded the alkyne **161** in 55% yield over two steps. The enyne **161** was then treated with Grubbs ruthenium catalyst $[Cl_2(PCy_3)_2RuCHPh]$, resulting in efficient ring-closing metathesis to deliver the diene **162** in 96% yield. Regioselective hydroboration at the terminal position of the diene gave the homoallylic alcohol, which upon alkylation provided the benzyl ether **163**. The amino and hydroxyl groups were introduced simultaneously by employing a highly diastereoselective and regioselective Sharpless aminohydroxylation reaction affording the AB ring system **169** (Scheme 1.52).



Scheme 1.52: Further elaboration to the AB ring systems **169**.

Incorporation of an additional B ring oxygen substituent to facilitate introduction of the β-carboline ring system later in the synthesis was also explored (Scheme 1.53). The alcohol **160** was converted into the corresponding aldehyde, and subsequent addition of ethynylmagnesium bromide resulted in a 1:1 mixture of the diastereoisomeric propargylic alcohols **170**. Acetylation of these alcohols

delivered a diastereoisomeric mixture (1:1) of the acetates **171**. Ring-closing enyne metathesis using sub-stoichiometric amount of Grubbs ruthenium catalyst [$Cl_2(PCy_3)_2RuCHPh$] afforded the dienes **172** and **173** as a mixture of diastereoisomers (**172**/**173**) in 46% yield.



Scheme 1.53: Introduction of a B ring oxygen substituent.

In most published routes to the AB sub-unit of manzamine A (**1**), a Diels-Alder reaction has been employed to build up the reduced isoquinoline core. The Clark group has developed a synthesis using sequential ruthenium-catalysed ring-closing metathesis and aminohydroxylation reactions to construct the functionalised AB ring system.[53]

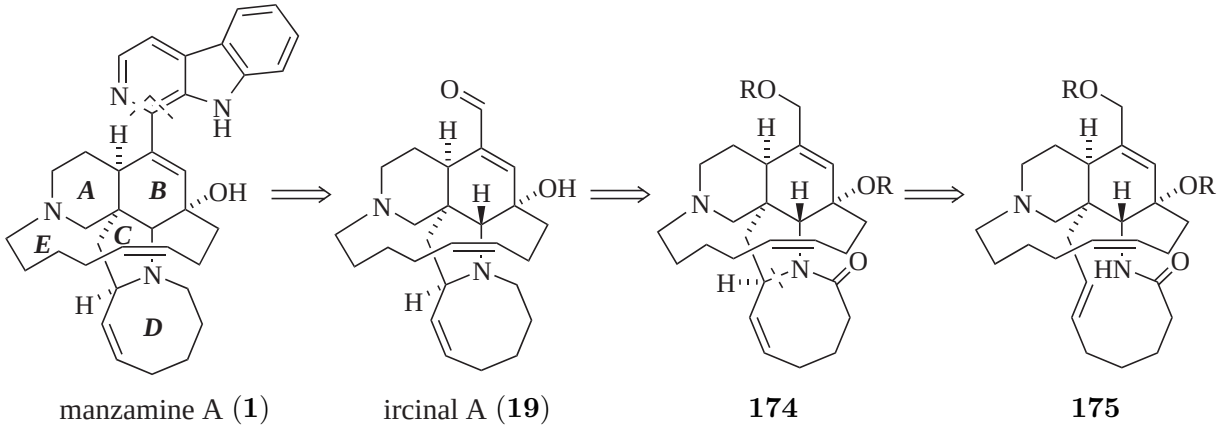
Chapter 2

Diels-Alder Approach Towards Manzamine A

This Chapter presents the application of Diels-Alder cycloaddition reaction to the synthesis of manzamine A (**1**). The Chapter is divided into two main sections starting with the proposed retrosynthetic analysis and followed by presentation of the synthetic progress.

2.1 Retrosynthetic analysis

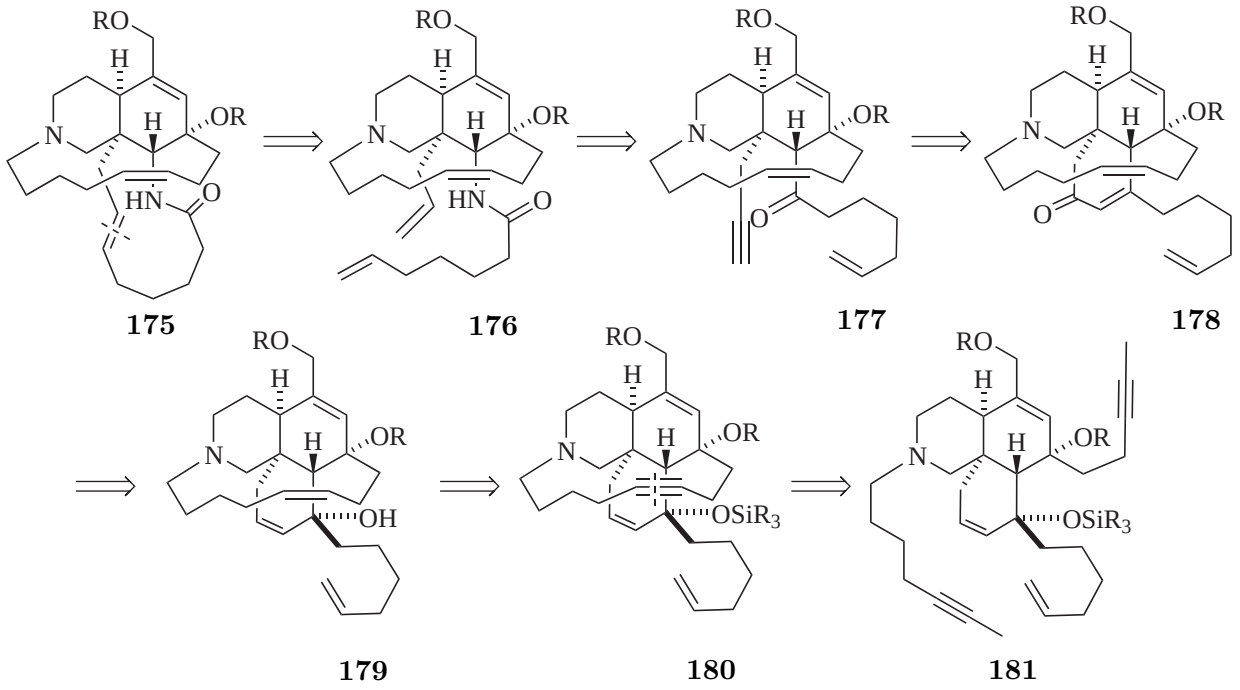
As discussed in Section 1.3, the alkaloid natural product ircinal A (**19**) can be converted into manzamine A (**1**) in two steps,[19] hence, ircinal A (**19**) was chosen as the starting point for retrosynthetic analysis. Functional group interconversion involving aldehyde reduction, hydroxyl group protection and conversion of the D ring amine into a lactam gives **174**. The fused pentacyclic compound **174** may then be further simplified by opening of the fused CD ring system, giving the tetracyclic ring system **175**, which contains an 11-membered lactam (Scheme 2.1).



Scheme 2.1: Retrosynthetic analysis - disconnection of the CD ring.

Retrosynthetic ring-closing metathesis disconnection, to cleave the alkene in the lactam, affords the

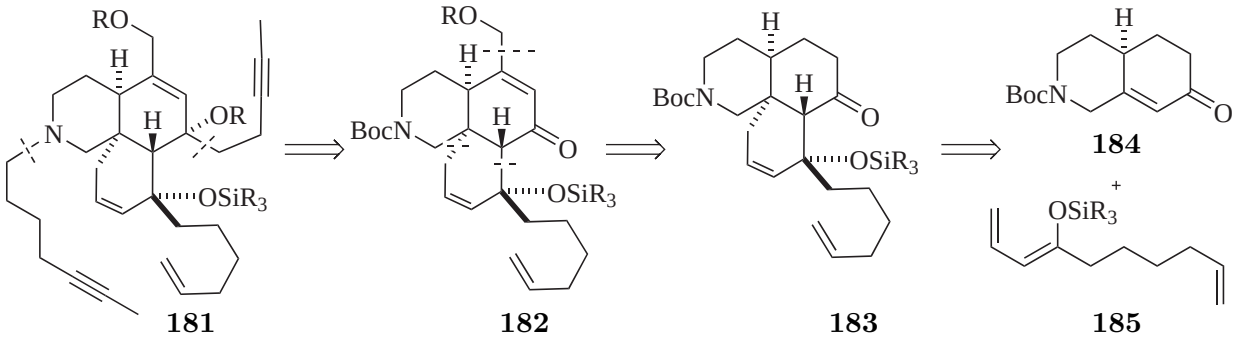
amide **176**. The alkene can be converted into an alkyne and the amide group into a ketone (retrosynthetic Beckmann rearrangement)[56] which yields the tricyclic intermediate **177**. Reconnection of the alkyne and ketone by a retrosynthetic Eschenmoser fragmentation[57] reaction will then give the tricyclic intermediate **178** and transposition of this enone affords the tertiary allylic alcohol **179** (Scheme 2.2). Conversion of the E ring alkene into an alkyne and hydroxyl group protection delivers the alkyne **180**. Retrosynthetic ring opening alkyne metathesis of the alkyne will give the diyne **181** (Scheme 2.2).



175 **176** **177** **178** **179** **180** **181**

Scheme 2.2: Retrosynthetic analysis - disconnection of the E ring.

Removal of the alkyne-containing side chains from the A and B rings affords the enone **182**, and further removal of the substituents from the B ring yields the tricyclic ketone **183**. A final Diels-Alder disconnection leads to the simple AB fragment **184** and the siloxydiene **185** (Scheme 2.3).



181 **182** **183** **184** **185**

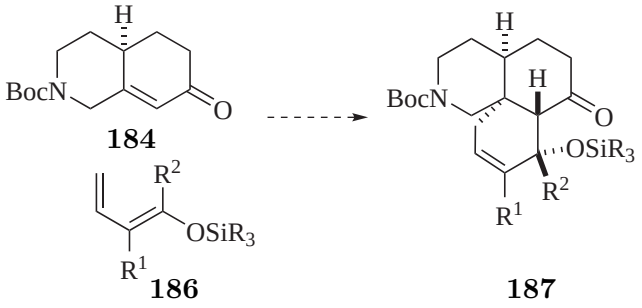
Scheme 2.3: Retrosynthetic analysis - disconnection to the AB ring fragment.

[56] Kametani, T.; Honda, T. Ishizone, H. Kanada, K. Naito, K. Suzuki, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 646-647.

[57] Mander, L. N.; McLachlan, M. M. *J. Am. Chem. Soc.* **2003**, *125*, 2400-2401.

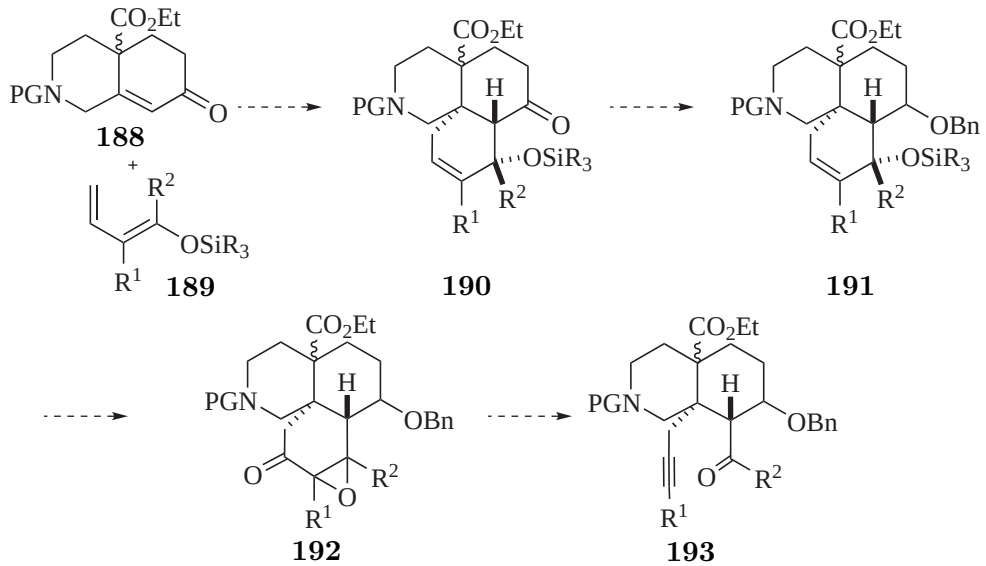
2.2 Project outline

According to the retrosynthetic analysis the first goal was the synthesis of the AB ring system **184**. This compound would then be required to undergo a Diels-Alder cycloaddition reaction to form the ABC ring system precursor **187** (Scheme 2.4).



Scheme 2.4: Diels-Alder reaction to obtain the ABC ring system **187** of manzamine A (**1**).

In order to validate the Diels-Alder reaction and the subsequent Eschenmoser fragmentation reaction, a model system resembling the AB ring system **188** was prepared in racemic from. With the synthesis of the AB ring system **188**, construction of the ABC ring precursor **190**, and hence construction of the CE ring system, was to be verified as outlined in Scheme 2.5. Following the successful Diels-Alder reaction, ketone reduction and protection of the resulting alcohol will give the benzylated alcohol **191**. Removal of the silicon protecting group followed by subsequent oxidative rearrangement would then be required to provide the epoxy ketone **192**. Eschenmoser fragmentation with ring scission should result in formation of ketone **193**.

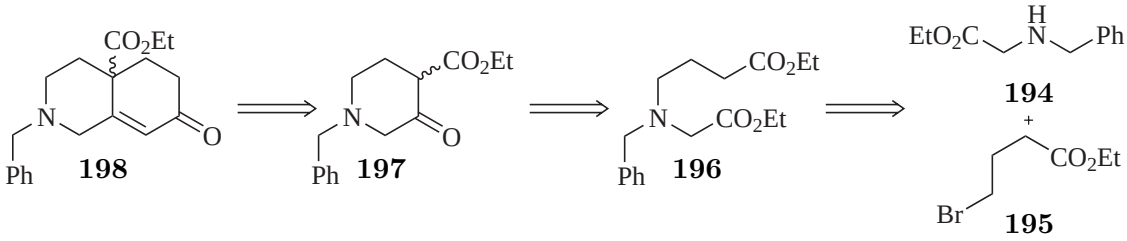


Scheme 2.5: The reaction pathway to validate if the proposed approach towards manzamine A (**1**) is feasible.

2.3 A model system - racemic synthesis of AB ring system

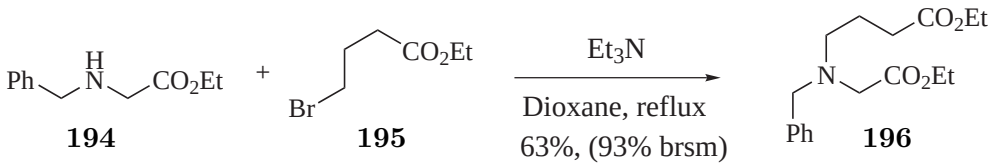
Synthesis of the AB ring system

In order to test the viability of the intermolecular Diels-Alder cycloaddition reaction to obtain the ABC ring precursor **187**, the AB ring system **198** had to be synthesised. According to the retrosynthetic pathway given in Scheme 2.6, the AB ring system **198** can be obtained from the cyclic ketone **197**, by Robinson annulation using methyl vinyl ketone (**202**).[58] The cyclic ketone **197** can be obtained from the diester **196** using a Dieckmann cyclisation reaction. Finally, the diester **196** can be obtained from alkylation of *N*-benzylglycine ester (**194**) with ethyl 4-bromobutyrate (**195**).



Scheme 2.6: Retrosyntheis of the AB ring system **198**.

With the reaction pathway in hand, the first synthetic step was to form the diester **196**. Treatment of *N*-benzylglycine ester (**194**) and ethyl 4-bromobutyrate (**195**) with triethylamine in dioxane under reflux yielded the desired diester **196** in a 63% yield, corresponding to a 93% yield based on recovered starting material (Scheme 2.7).

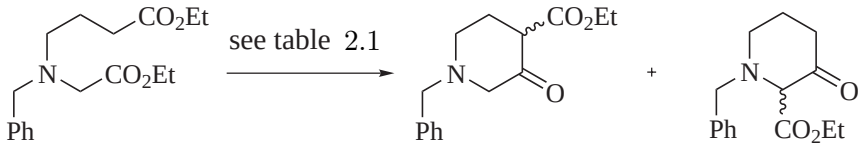


Scheme 2.7: Synthesis of the diester **196**.

Following the synthesis of the diester **196**, the Dieckmann cyclisation procedure, using NaOEt in toluene, was employed to obtain the A ring fragment **197** (Entry 1, Table 2.1). Unfortunately, problems were encountered and several attempts were needed in order to obtain the desired A ring fragment **197**. In an effort to overcome these problems, *t*BuOK was used as the base and the solvent, temperature and reaction time were varied, but all these reactions gave a mixture of inseparable products (Entries 2 and 3, Table 2.1).[58,59] To improve the reaction conditions, the solvent was replaced with acetonitrile, which is more polar and allows enhanced stability of the anion (Entry 3, Table 2.1). Successive attempts to optimise the reaction conditions further were not successful and also delivered mixtures of products (Scheme 2.3).

[58] Scalone, M.; Waldmeier, P. *Org. Proc. Res. and Devel.* **2003**, *7*, 418-425.

[59] Bit, R. A.; Davis, P. D.; Hill, C. H.; Keech, E.; Vesey, D. R. *Tetrahedron* **1991**, *47*, 4645-4664.

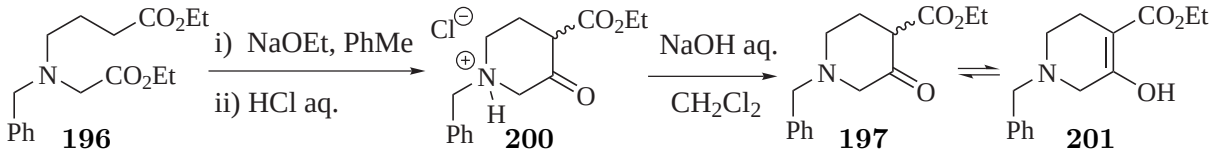


196 **197** : **199**

Entry	Base	Temperature	Reaction time	Solvent	Ratio (**197**:**199**)
1	NaOEt	RT→Reflux	Overnight	Toluene	-
2	*t*BuOK	RT	Overnight	CH_2Cl_2	1:1.3 (65%)
3	*t*BuOK	RT	1 h	MeCN	2:1
4	Na/EtOH	RT→ 85 °C	Overnight	Toluene	**197** only (84%)
5	NaOEt	RT→ 85 °C	3 h	Toluene	**197** only (87%)

Table 2.1: Different reaction conditions for the Dieckmann cyclisation.[58,59]

With reference to the method described by Scalone and co-workers[58] and appropriate variants, it was considered that the formation of the hydrochloride salt **200** was the problematic step (Scheme 2.8). Similar conditions to those described in Entry 1 (Entries 6 and 7, Table 2.1) were developed to afford the hydrochloride salt **200**. However, instead of isolating the hydrochloride salt, the resulting residue was diluted with a sodium hydroxide solution (1 M) and extracted with CH_2Cl_2 to provide the desired β-keto ester **197**, which is found in equilibrium with its enol **201** form, as the only product in 87% yield. It is worth mentioning that the desired ring formation is quite sensitive to the concentration of reactants as well as the rate of addition of the base. However, with this knowledge in mind, the A ring fragment **197** can be synthesised in good yield.

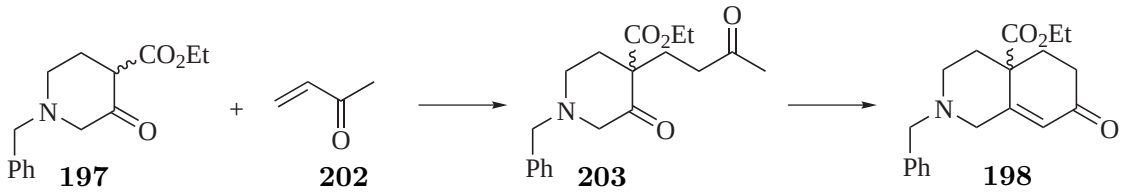


Scheme 2.8: Dieckmann cyclisation to obtain the A ring **197**.[58]

Having successfully synthesised the A ring fragment **197**, the next step was elaboration to give the AB ring system **198** in a single-step by Robinson annulation as outlined in Scheme 2.9.

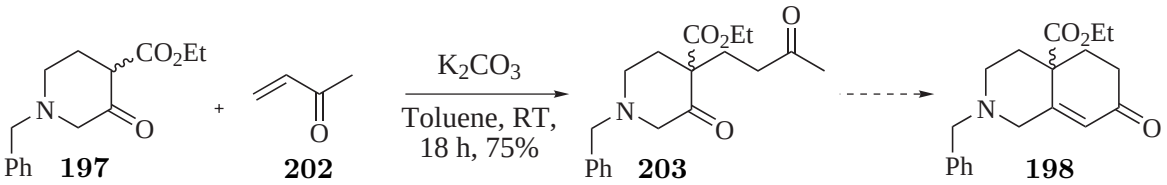
Scheme 2.9: Single-step process to obtain the AB ring **198**.

Performing the Robinson annulation reaction in a single-step had been shown to be unsuccessful[60] and instead of a single reaction, a two-step sequence with an initial Michael addition to methyl vinyl ketone (**202**) followed by an aldol condensation was proposed to yield the AB ring **198** (Scheme 2.10).[61]



Scheme 2.10: Two-step reaction sequence to obtain the AB ring system **198**.

With the appropriate synthetic pathway in hand, the Michael addition was performed and the adduct **203** was obtained in a good yield. Attention was then turned towards the second cyclisation reaction in order to obtain the required AB ring system **198**, as illustrated in Scheme 2.11.



Scheme 2.11: Michael addition to yield the Michael addition adduct **203**.

The first attempt to cyclise **203** involved successive enamine formation and subsequent hydrolysis (Entry 1, Table 2.2). However, this reaction was not successful and the AB ring system **198** did not form. It was speculated that **203** may be sensitive to the relatively high reaction temperature employed, and a change of solvent from toluene to benzene was explored (Entry 2, Table 2.2). Although consumption of the starting material was observed, reactions involving enamine formation and subsequent hydrolysis were not successful.[61,62] Following the failure of enamine formation, a search through the literature revealed several different methods in which the B ring could be formed. These included treatment with potassium hydroxide in methanol (not shown) and NaOEt in ethanol (Entries 4 and 5, Table 2.2).[63,64] After several attempts, in which the temperature and the source of NaOEt were varied, a 2:1 mixture of the desired compound **198** and the alcohol **204** was obtained (Entry 4, Table 2.2 and Scheme 2.3). However, the yield of products was too low and further optimisation of the reaction conditions was undertaken in order to improve this. Optimisation of the reaction conditions resulted in a lower yield of the product **198** but an increased yield (77%) of the alcohol **204** (Entry 5, Table 2.2). Although the yield of the desired AB ring system **198** was lowered dramatically, the

[60] Hunter, T. "A Novel Approach Towards the Total Synthesis of Manzamine A", MSci Project Report, University of Glasgow, 2007.

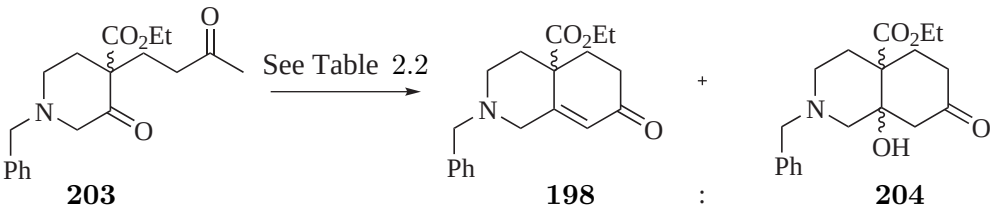
[61] Trudeau, S.; Deslongchamps, P. *J. Org. Chem.* **2004**, *69*, 832-838.

[62] Muskopf, J. W.; Robert, C. M. *J. Org. Chem.* **1985**, *50*, 69-76.

[63] Zheng, G.; Chen, J.; Fang, L.; Guan, Y.; Li, Y. *Chirality* **2004**, *16*, 483-485.

[64] Blay, G.; Collado, A. M.; Garcia, B.; Pedro, J. R. *Tetrahedron* **2005**, *61*, 10853-10860.

overall yield for the reaction was nevertheless improved.



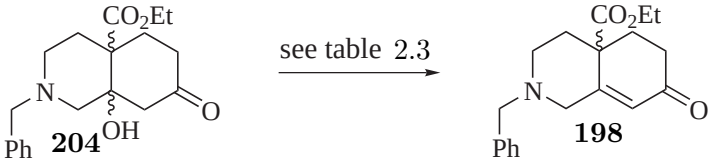
203 **198** : **204**

Entry	Base	Temperature	Solvent	Yield (**198**:**204**)
1	Pyrrolidine	Reflux	Toluene†	-
2	Pyrrolidine	Reflux	Benzene‡	-
3	Pyrrolidine	Reflux	CH_2Cl_2/AcOH	-
4	NaOEt	RT, 15 h	EtOH	34% (2:1)
5	NaOEt	0 °C →RT, 3 h	EtOH	77% (1:9)

† Dean-Stark apparatus employed.
‡ Dean-Stark apparatus and 4 Å molecular sieves employed.

Table 2.2: Different reaction conditions for construction of the B ring.[59–62]

Having optimised the aldol condensation reaction, the next step was to convert the alcohol **204** into the desired AB ring system **198**. The dehydration reaction was attempted in several ways as illustrated in Table 2.3.[63–65] However, only treatment with a solution of either hydrochloric acid or trifluoroacetic acid resulted in the AB ring system with an acceptable yield, (Entries 6 and 7, Table 2.3).



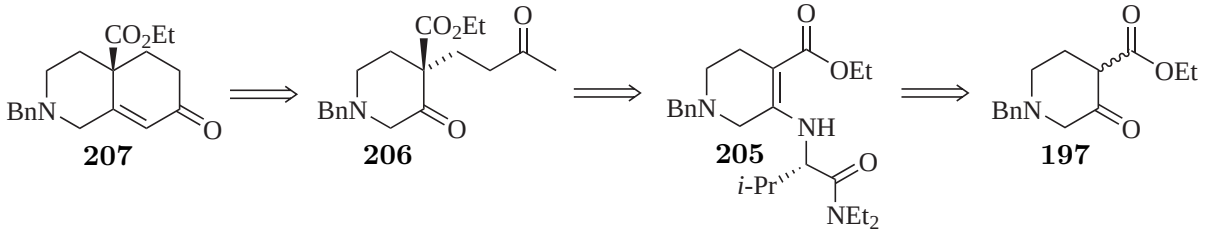
Entry	Conditions	Result
1	$MsCl/Et_3N/CH_2Cl_2$/0 °C	Decomposed
2	Oxalic acid/EtOH/RT	Recovered starting material
3	NaOEt/EtOH/RT	Decomposed
4	NaOMe/MeOH/RT	Decomposed
5	$SOCl_2$/Pyridine/0 °C →RT	Decomposed
6	AcOH/EtOH, 24 h	Approx. 1:1 mixture (68%) (**198**:**204**)
7	TFA/0 °C →RT, 24 h	4:1 (**198**:**204** (98%))

Table 2.3: Reaction conditions employed for the aldol condensation reaction.[63–65]

[65] Kato, M.; Matsumura, Y.; Heima, K.; Fukamiya, N.; Kabuto, C.; Yoshikoshi, A. *Tetrahedron* **1987**, *43*, 711-722.
[66] Ngo, K.-S.; Brown, G. D. *Tetrahedron* **1999**, *55*, 15099-15108.
[67] Davidson, J. P.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 13486-13489.

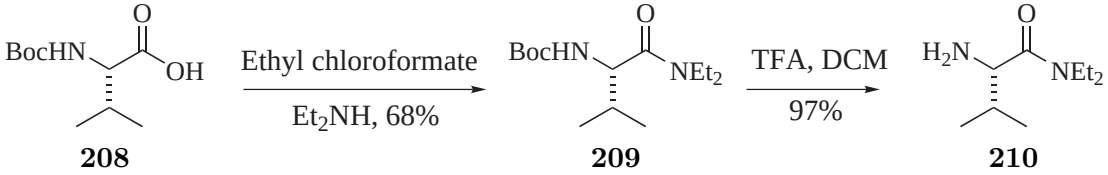
2.4 An alternative route to the AB ring system

Parallel to the synthesis of the AB ring system in racemic form given in the previous section, an alternative route to the AB ring system was explored. Retrosynthetic aldol condensation of the AB ring fragment **207** leads to the methyl vinyl ketone adduct **206**. Retrosynthetic Michael addition to methyl vinyl ketone (**202**) delivers enamino ester **205** which can be obtained from acid catalysed condensation of the the A ring fragment **197** with the auxiliary L-valine diethylamide **210**. The synthetic route given commences from the same A ring fragment **197** used for the synthesis of racemic material. If this route proved successful it would give access to the enantiomerically enriched AB ring system **207** (Scheme 2.12).



Scheme 2.12: Alternative route to the AB ring system **207**.

Before embarking on the alternative route, the chiral auxiliary **210** had to be synthesised. As outlined in Scheme 2.13, the chiral auxiliary **210** was easily obtained in two steps and 66% overall yield, commencing from Boc protected valine **208**.[68]



Scheme 2.13: Synthesis of the chiral auxiliary **210**.

Following the successful synthesis of the chiral auxillary **210**, the initial step to form the enamine **205** was carried out.[69] Despite several attempts to from the enamine by varying the solvent and temperature, the enamine **205** was not isolated.

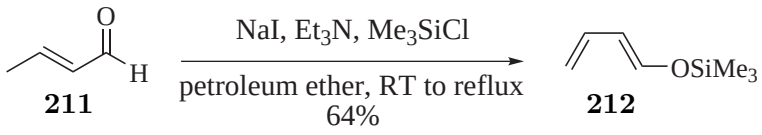
2.5 Intermolecular Diels-Alder reaction

Following preparation of the dieneophile **198**, attention turned to the synthesis of the simple siloxydiene **212**. The simple siloxydiene **212** can easily be synthesised from crotonaldehyde (**211**) (Scheme 2.14).[70]

[68] Anderson, J. C.; Skerratt, S. *J. Chem. Soc., Perkin Trans. 1* **2002**, *24*, 2871-2879.

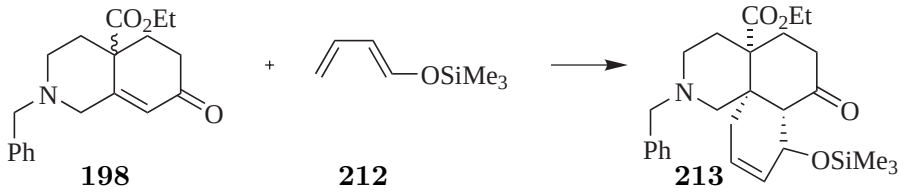
[69] Christoffers, J.; Scharl, H. *Eur. J. Org. Chem.* **2002**, 1505-1508.

[70] Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron* **1987**, *43*, 2089-2100.



Scheme 2.14: Synthesis of the siloxydiene **212**.

Preparation of the siloxy diene **212** was followed by initial attempts to perform the intermolecular Diels-Alder cycloaddition reaction (Table 2.4). The Diels-Alder cycloaddition reaction with the siloxydiene **212** should provide the tricyclic intermediate **213**; facial selectivity, arising from the bowl shaped conformation adopted by the AB ring system **198**, should be high. The facial selectivity of the diene is not important due to the fact that the quaternary stereocenter bearing the silyl ether is destroyed later in the synthesis. Treatment of the AB ring system **198** and the diene **212** in toluene under reflux did not yield the desired tricyclic system **213** (Entry 1), and performing the reaction without solvent in a sealed tube to allow a higher reaction temperature to be used did not improve the outcome of the reaction (Entry 2). In order to increase the reactivity, the addition of a Lewis acid was investigated (Entries 3 and 4). However, none of these reactions yielded the desired tricyclic system **213**.[69–72]



Entry	Temperature	Time	Additive	Solvent	Yield
1	60 °C → 120 °C	24 h	-	Toluene†	-
2	140 °C	24 h	-	Neat†	-
3	0 °C	1 min	$BF_3{\cdot}OEt_2$	*o*-Xylene‡	-
4	−78 °C →RT	24 h	$AlCl_3$	Toluene‡	-

† Recovered starting material.
‡ Consumption of both starting materials.

Table 2.4: Diels-Alder cyclisation attempts.

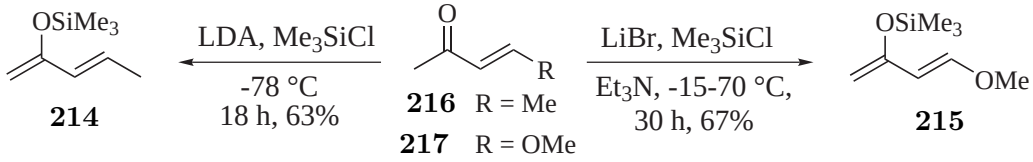
[71] Krohn, K.; Agocs, A.; Baeuerlein, C. *J. Carbohydr. Chem.* **2003**, *22*, 579-592.
[72] Fujita, R.; Oikawa, K.; Yoshisuji, T.; Okuyama, Y.; Nakano, H.; Matsuzaki, H. *Chem. Pharm. Bull.* **2003**, *51*, 295-300.
[73] Lanfranchi, D.; Hanquet, G. *J. Org. Chem.* **2006**, *71*, 4854-4861.
[74] He, J.; Tchabanenko, K.; Adlington, R. M.; Cowley, A. R.; Baldwin, J. E. *Eur. J. Org. Chem.* **2006**, 4003-4013.

In order to further investigate the Diels-Alder reaction and the proposed reaction sequence (Scheme 2.5), two additional siloxydienes were selected (Figure 2.1).

214 **215**

Figure 2.1: Selected siloxydienes.

The siloxydiene **214**, was obtained from 3-penten-2-one (**216**) using LDA and TMSCl at −78 °C, resulting in the diene **214** in 63% yield (Scheme 2.15).[75] The siloxydiene **215** was easily obtained from *trans*-4-methoxy-but-3-en-2-one (**217**) upon treatment with LiBr, TMSCl, and triethylamine to yield the diene **215** (Danishefsky's diene) in 67% yield.[76]

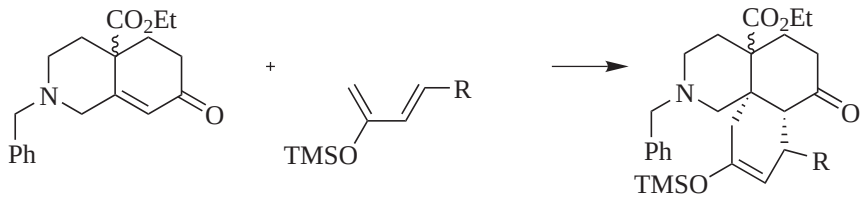


214 **216** R = Me **217** R = OMe **215**

Scheme 2.15: Synthesis of the siloxydiene **214** and **215**.

With the target dienes synthesised, attention turned again to the Diels-Alder reaction (Table 2.5).[71,72] Reaction of the enone **198** and the diene **214** or **215** under reflux did not yield any of the desired tricyclic system **219** (Entries 2 and 6, Table 2.5). Performing the reaction without solvent in a sealed tube to allow for a higher reaction temperature did not improve the outcome of the reaction (Entry 1, Table 2.5). Even the use of microwave irradiation to allow even higher temperatures and pressures was not successful (Entries 4 and 7, Table 2.5).[73,74] Since neither of the attempts yielded the tricyclic system **198**, it was speculated that the ester group may be in a position which does not allow the intermolecular Diels-Alder reaction to take place.

[75] Liu, H.-J.; Ngooi, T. K.; Browne, E. N. *Can. J. Chem.* **1988**, *66*, 3143-3152.
[76] Sax, M.; Berning, S.; Wünsch, B. *Tetrahedron* **2005**, *61*, 205-211.



198 **218** **219**

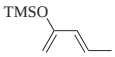
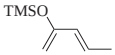
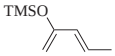
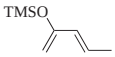
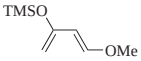
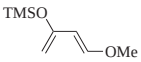
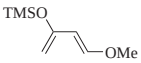
Entry	Solvent	Diene	Temperature	Reaction time	Yield
1	Neat		RT	18 h	-
2	Toluene		110 °C	18 h	-
3	o-Xylene		160 °C	18 h	decomposition
4	o-Xylene		150 °C/190 °C	40 min @ 150 °C/40 min @ 190 °C	-
5	Toluene		RT	18 h	-
6	Toluene		110 °C	18 h	-
7	o-Xylene		210 °C	4 × 30 min	-

Table 2.5: Diels-Alder reactions performed with dienes **214** and **215**.

2.6 Decarboxylation attempts

In order to verify that the carboxyl group was problematic, attempts to hydrolyse the ester functionality followed by decarboxylation to give **220** were then carried out (Table 2.6). Although various methods for the hydrolysis and decarboxylation of ester functionalities exist, attempts to remove the ester group were not successful, giving a complex mixture of compounds from decomposition of the AB ring system **198**.[75–80]

[77] Krapcho, A. P.; Weimaster, J. F.; Eldridge, J. M.; Jahngen, E. G. E.; Lovey, A. J.; Stephens, W. P. *J. Org. Chem.* **1978**, *43*, 138-147.

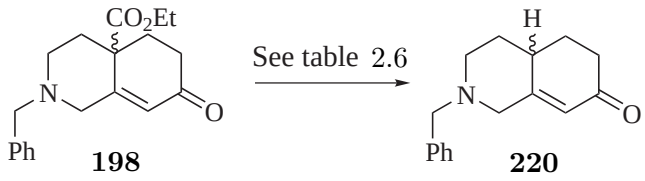
[78] Pal, S.; Mukhopadhyaya, J. K.; Ghatak, U. R. *J. Org. Chem.* **1994**, *59*, 2687-2694.

[79] Banerjee, M.; Mukhopadhyay, R.; Achari, B.; Banerjee, A. *J. Org. Chem.* **2006**, *71*, 2787-2796.

[80] Banik, B. K.; Ghosh, S.; Ghatak, U. R. *Tetrahedron* **1988**, *44*, 6947-6955.

[81] Mal, S. K.; Kar, G. K.; Ray, J. K. *Tetrahedron* **2004**, *60*, 2805-2811.

[82] Maiti, S.; Drew, M.; Mukhopadhyay, R.; Achari, B.; Banerjee, A. K. *Synthesis* **2005**, 3067-3078.



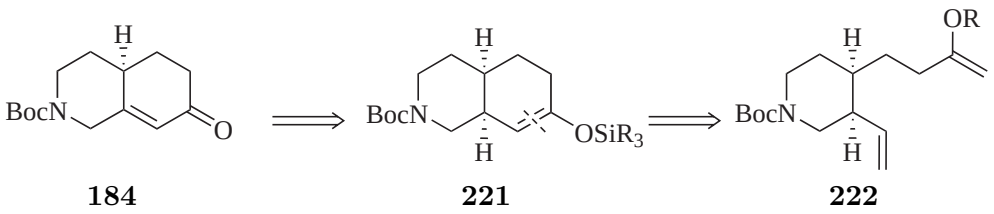
Entry	Reaction conditions	Temperature	Reaction time	Yield
1	LiCl/DMSO	reflux	overnight	decomposed
2	$KOH/H_2O/EtOH$	reflux	4 hours	decomposed
3	$LiOH/MeOH/H_2O$	RT	overnight	decomposed
4	6 N HCl	reflux	5 hours	decomposed
5	$NaOH/H_2O/DMSO$	160 °C	Overnight	decomposed

Table 2.6: Decarboxylations attempts.

Since the attempts to hydrolyse and decarboxylate the AB ring system **198** was unsuccessful, the synthesis of the AB ring system by a different approach was envisaged, in order to verify that the ester group did play a role in hindering the Diels-Alder reaction.

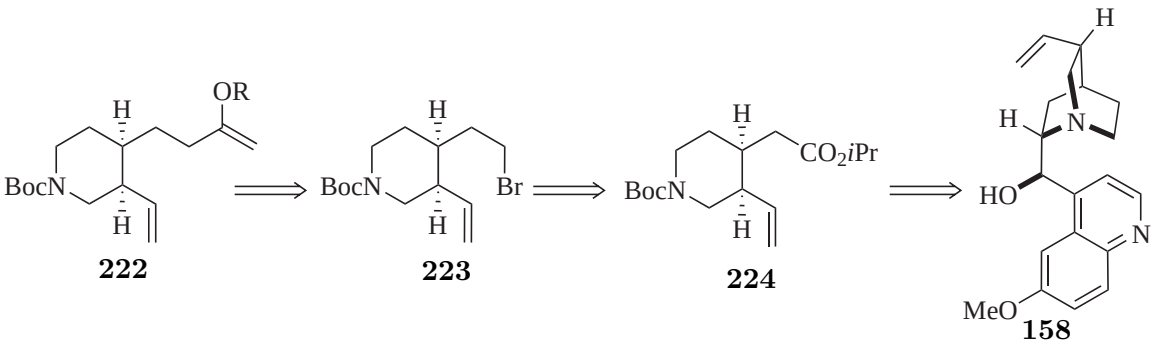
2.7 An enantioselective approach towards the AB ring system

In order to investigate the effect of the ester group in **198** on the outcome of the Diels-Alder reaction, an enantioselective route towards the AB ring **184** has been pursued, as outlined in Scheme 2.16. The AB ring system **184** can be obtained from silyl enol ether **221** by treatment with palladium acetate. Retrosynthetic ring-closing metathesis disconnection of the enol ether **221** leads to vinyl ether **222**.



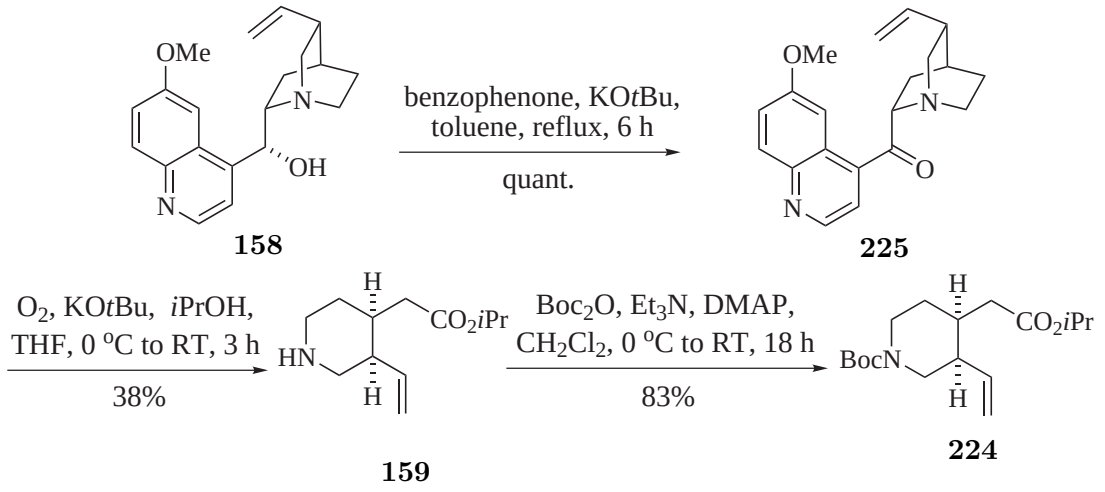
Scheme 2.16: Retrosynthesis for the enatioselective approach towards the AB ring system **184**.

Vinyl ether **222** can be obtained by displacement of the bromide in **223**. Retrosynthetic Appel reaction converts the bromide **223** into alcohol **160** that can be obtained by reduction of the ester **224**. Retrosynthetic autoxidation and oxidation of quinine **158** into quininone sets the starting point for the enantioselective synthesis (Scheme 2.17).



Scheme 2.17: Retrosynthesis for the enantioselective approach towards the AB ring system **184**.

The merquinine ester **158** was obtained from quinine **158** through a two-step oxidation sequence developed by Martinelli and co-workers.[83,84] The preferred oxidizing agent for this particular oxidation reaction is a combination of benzophenone and potassium *tert*-butoxide as described by Woodward, (for details on the mechanism see Scheme 1.51). Oxidation of quinine (**158**) to quininone (**225**) occurs by an Oppenauer-like oxidation reaction in which a hydrogen atom is transferred from quinine to benzophenone.[55] The secondary amine was protected using di*tert*-butyl dicarbonate to give the Boc-protected merquinine ester **224**.[85]



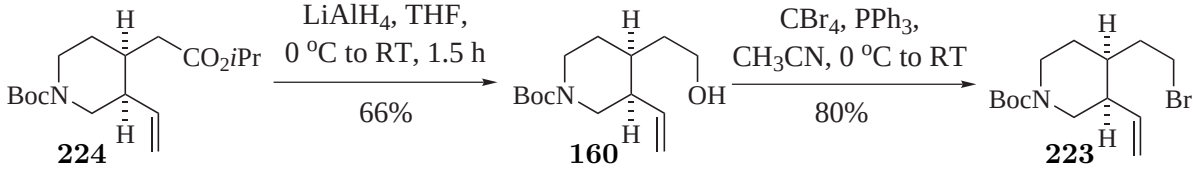
Scheme 2.18: Synthesis of the merquinine ester **224**.

Following Boc-protection of the meroquinine ester **159**, the ester functionality was reduced to the corresponding alcohol **160** (Scheme 2.19).[53] Conversion of the alcohol **160** into the bromide **223** was achieved using standard Appel conditions affording the bromide **223** in good yield (Scheme 2.19). With the bromide in hand focus was turned to formation of the vinyl ether **226**.

[83] Martinelli, M. J.; Peterson, B. C.; Khau, V. V.; Hutchinson, D. R.; Sullivan, K. A. *Tetrahedron Lett.* **1993**, *34*, 5413-16.

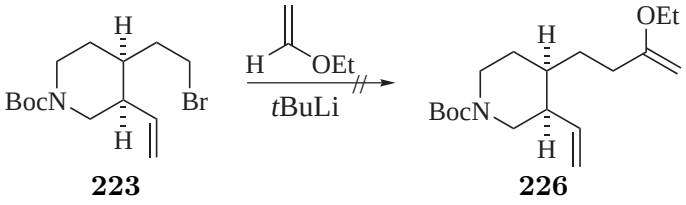
[84] Martinelli, M. J.; Peterson, B. C.; Huff, B. E.; Khau, V. V.; Torneau, M. L. *United States Patent* **1994**, 851.

[85] Li, L.; Thomas, S. A.; Klein, L. L.; Yeung, C. M.; Maring, C. J.; Grampovnik, D. J.; Lartey, P. A.; Plattner, J. J. *J. Med. Chem.* **1994**, *37*, 2655-2663.



Scheme 2.19: Synthesis of bromide **223**.

Displacement of the bromide using lithium di(α-methoxyvinyl)cuprate to obtain the vinyl ether **226** was attempted.[84–89] As outlined in Table 2.7, various attempts to displace the bromide have been carried out. Varying the copper source (Entries 1, 2, 4 and 8) and the addition of additives (Entry 7) did not improve the outcome of the reaction. Varying the reaction conditions as well as the temperature did not result in formation of the desired vinyl ether **226**.



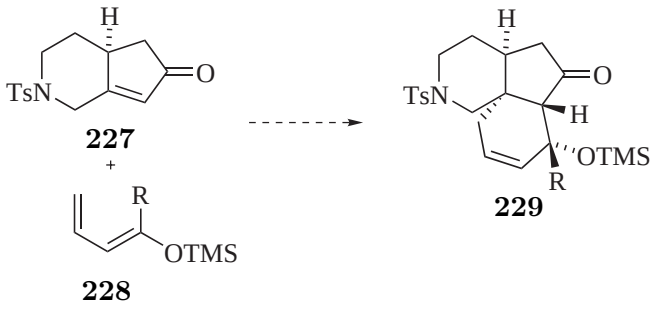
Entry	Copper source	Temperature	Yield
1	CuI	−78 °C	-
2	CuBr·SMe_2	−78 °C	-
3	CuI	−78 °C → 5 °C → −78 °C → RT	-
4	CuCN, DMS	−78 °C → RT	-
5	CuI, DMS	−78 °C → RT	-
6	CuCN, DMS	−78 °C → RT	-
7	CuCN, LiCl,	−45 °C → 0 °C	-
8	(2-Thienyl)Cu(CN)Li	−40 °C → 0 °C	-

Table 2.7: Displacement of the bromide to yield vinyl ether **223**.[84–89]

2.8 Synthesis of the bicyclic enone

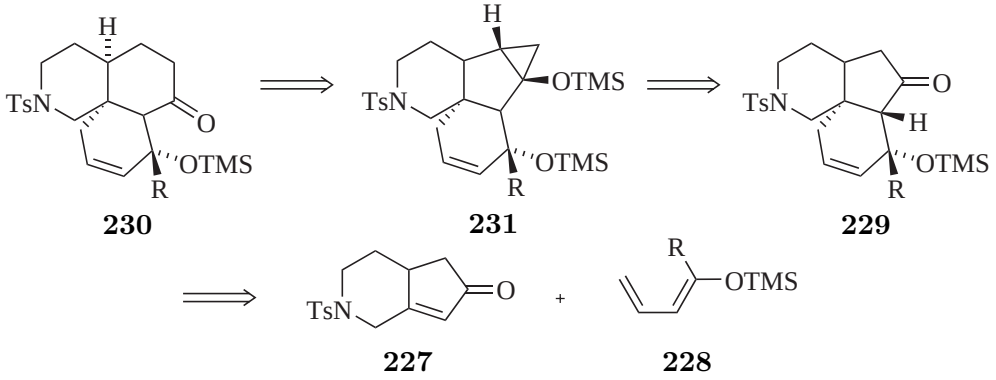
As a result of the unsuccessful approach towards the enantioselective synthesis of the AB ring system **184**, the bicyclic enone **227** was believed to be more accessible as a bicyclic system to test the viability of the Diels-Alder reaction (Scheme 2.20).

[86] Boeckman, R. K.; Bruza,; Bruza, J. K. *J. Org. Chem.* **1979**, *44*, 4781-4788.
[87] Chavdarian, C. G.; Heathcock, C. H. *J. Am. Chem. Soc.* **1975**, *97*, 3822-3823.
[88] Back, T. G.; Collins, S.; Krishna, M. V.; Law, K. W. *J. Org. Chem.* **1987**, *52*, 4258-4264.
[89] Crisp, G. T.; Meyer, A. G. *Tetrahedron* **1995**, *51*, 5585-5596.
[90] Miller, A.; Hughes, C.; Kennedy-Smith, J.; Gradl, S.; Trauner, D. *J. Am. Chem. Soc.* **2006**, *128*, 17057-17062.
[91] Boger, D. L.; Zhu, Y. *J. Org. Chem.* **1994**, *59*, 3453-3458.



Scheme 2.20: Diels-Alder reaction to obtain the ABC ring system **229** of manzamine A (**1**).

The connection to the previously proposed synthesis given in Schemes 2.1, 2.2 and 2.3 is outlined in Scheme 2.21. Retrosynthetic ring contraction affords the tetracyclic intermediate **231**, which can be obtained from retrosynthetic cyclopropanation of the Diels-Alder adduct **229**. A final Diels-Alder disconnection leads to the simple bicyclic enone **227** and the siloxydiene **228** (Scheme 2.21). The tricyclic intermediate **230** is equivalent to the tricyclic intermediate **183** (see Scheme 2.3), with the only difference being the nitrogen protecting group.

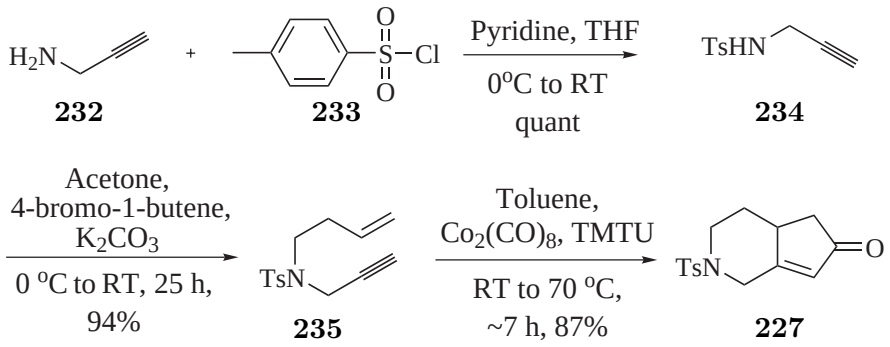


Scheme 2.21: Retrosynthetic analysis.

Synthesis of the bicyclic enone

The synthesis of the bicyclic enone **227** was easily accomplished as outlined in Scheme 2.22, commencing with propargylamine (**232**).[92] Introduction of the tosyl protecting group was performed using *para*-toluenesulfonyl chloride in THF at 0 °C and yielded the protected propargylamine **234** quantitatively. Following the amine protection, the olefin was introduced using 4-bromo-1-butene and potassium carbonate in acetone to afford the Pauson-Khand precursor **235**, in 94% yield. Following preparation of the desired precursor **235** for the bicyclic system **227**, the next step was the Pauson-Khand reaction that yielded the bicyclic enone **227** in 87% yield, after optimisation (Scheme 2.22).[92,93]

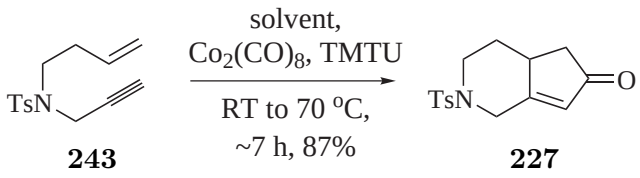
[92] Tang, Y.; Deng, L.; Zhang, Y.; Dong, G.; Chen, J.; Yang, Z. *Org. Lett.* **2005**, *7*, 593-595.
[93] Kobayashi, T.; Koga, Y.; Narasaka, K. *J. Organomet. Chem.* **2001**, *624*, 73-87.



Scheme 2.22: Synthesis of the bicyclic enone **227**.[92,93]

Optimisation of the Pauson-Khand reaction

Due to problems encountered when scaling up the Pauson-Khand reaction[92] an optimisation study was undertaken (Table 2.8). An initial attempt was successful on small scale using benzene and heating to 70 °C (Entry 1). However, problems were encountered when scaling up the reaction and the yield was considerably reduced (Entry 2). To overcome this problem, benzene was replaced by toluene as an alternative (Entry 3). The change of solvent along with performing the reaction at high dilution resulted in good reproducible yields (77-87%) (Entries 4 and 5).



See table 2.8

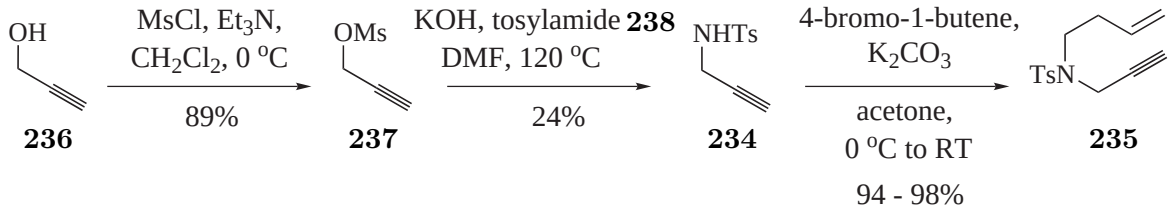
Entry	Conditions	Scale	Yield
1	Benzene, 100 mL	200 mg	85%
2	Benzene, 40-300 mL	1-10 g	40-57%
3	Toluene, 200 mL	500 mg	75%
4	Toluene, 500 mL	7 g	77%
5	Toluene, 700 mL	7 g	87%

Table 2.8: Optimisation of the Pauson-Khand reaction.

Alternative routes towards the Pauson-Khand precursor

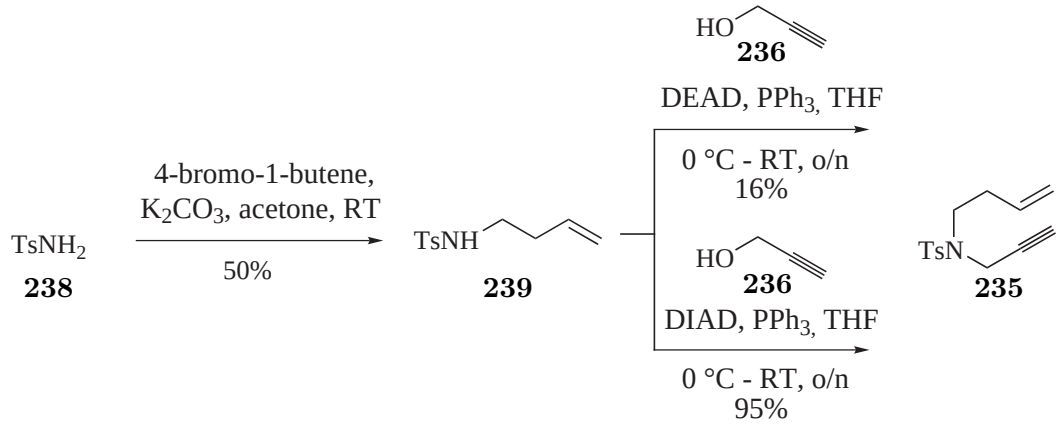
The Pauson-Khand reaction precursor **243** can easily be synthesised in two steps commencing from propargylamine (**232**) (Scheme 2.22).[92,93] Although this sequence to *N*-(3-butenyl)-4-methyl-*N*-(2-propynyl)benzenesulfonamide (**235**) is efficient, the cost of propagylamine (**232**) meant that cheaper alternative routes were required. Two routes were explored as shown in Scheme 2.23 and 2.24. The first route commenced with mesylate activation of propargyl alcohol (**236**) utilizing methanesulfonyl

chloride and triethylamine in CH_2Cl_2 yielding the mesylated alcohol **237** in 93% yield. Following mesylation, conversion to the tosylamide **234** was performed by treatment with KOH and the tosylamide (**238**) in DMF to afford **234** in 24% yield.[94,95]



Scheme 2.23: Alkylation approach towards the Pauson-Khand precursor **235**.

Another alternative route to enyne **235** involved alkylation of tosylamide (**238**) with 4-bromo-1-butene. This reaction yielded the desired alkylated tosylamide **239** in a moderate yield (Scheme 2.24).[94] Employing the alkylated tosylamide under Mitsunobu reaction conditions afforded the desired precursor **235** for the Pauson-Khand reaction in only 16% yield. However, changing from DEAD to DIAD increased the yield dramatically and the precursor was obtained in 95% yield. Although the starting materials used in both alternative routes to the Pauson-Khand precursor **235** are fairly cheap, the poor yields and excessive purification issues on large scale, makes the first route the preferred one (Scheme 2.22).



Scheme 2.24: Mitsunobu approach towards the Pauson-Khand precursor **235**.

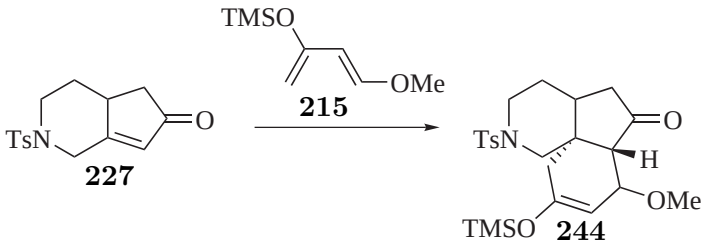
Attempted Diels-Alder cycloaddition

Inter-molecular Diel-Alder reaction

Following optimisation of the Pauson-Khand reaction, attention turned once again to the Diels-Alder reaction. Treatment of the bicyclic system **227** and the diene **215** in toluene at reflux overnight did

[94] Handa, S.; Kachala, M. S.; Lowe, S. R. *Tetrahedron Lett.* **2004**, *45*, 253-256.
[95] Patel, M. C.; Livinghouse, T.; Pagenkopf, B. L. *Org. Synth.* **2003**, *80*, 93-98.

not result in formation of the Diels-Alder product **244** (Entry 1). Performing the reaction neat and in a sealed tube at 180 °C or in the prescence of aluminium trichloride as a Lewis acid catalyst did not improve the outcome either (Entries 2 and 3, Table 2.9).



Entry	Solvent	Temperature	Reaction time	Yield
1	Toluene	reflux	Overnight	-
2	Neat	180 °C	1 h	-†
3	Neat, $AlCl_3$	100 °C	Overnight	-†

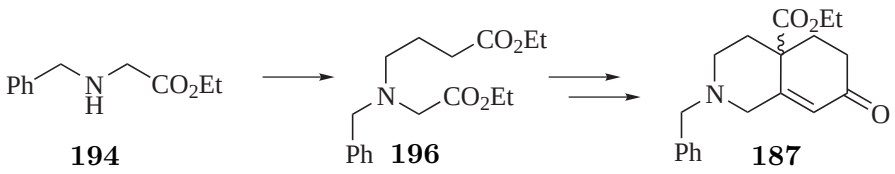
† Purified by column chromatography. Possible cleavage of the tosyl group.

Table 2.9: Diels-Alder reactions performed between the bicyclic system **227** and the diene **215**

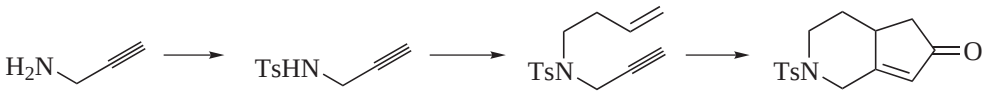
The initial results of the Diels-Alder reaction combined with those obtained from the previous study (Tables 2.4 and 2.5) prompted the termination of the Diels-Alder study.

2.9 Summary and outlook

In summary, the first approach incorporating the Diels-Alder reaction as one of the key steps, to the total synthesis of manzamine A (**1**) has been presented. The first goal was the synthesis of the AB ring system **187** and the sequence commenced from *N*-benzylglycine ester (**194**).



The synthetic route proposed encountered difficulties and the intermolecular Diels-Alder reaction was unsuccessful under the conditions applied. Further investigations led to the syntheis of the bicyclic enone **227**, which was easily synthesised commencing from commercially available propargylamine (**232**) in just three steps.



232 **227**

In addition to the unsuccessful Diels-Alder reaction, it is also speculated that introduction of the β-carboline unit later on in the synthesis may cause problems. Thus, another approach towards manzamine A (**1**) in which a cuprate 1,4-addition reaction to enone **227** is a key step, has been proposed and will be presented in Chapter 3.

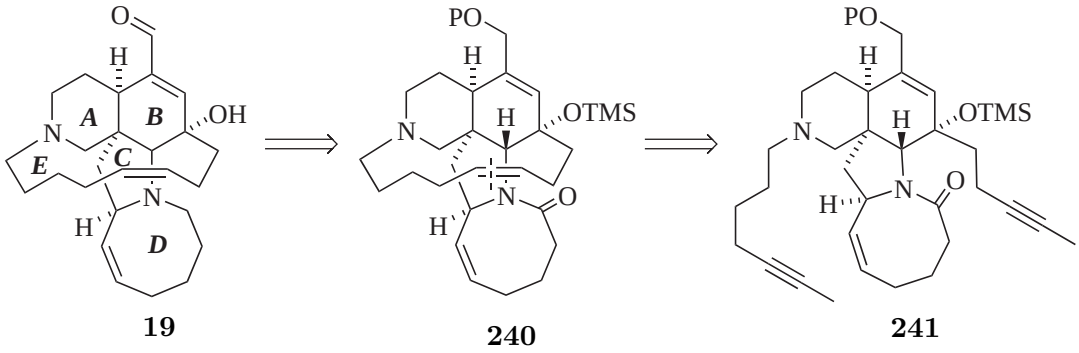
Chapter 3

Cuprate 1,4-Addition Approach Towards Manzamine A

This Chapter presents the application of cuprate conjugate addition to the total synthesis of manzamine A (**1**). The Chapter is divided into two main sections starting with the proposed retrosynthetic analysis and followed by presentation of the synthetic progress.

3.1 Retrosynthetic analysis

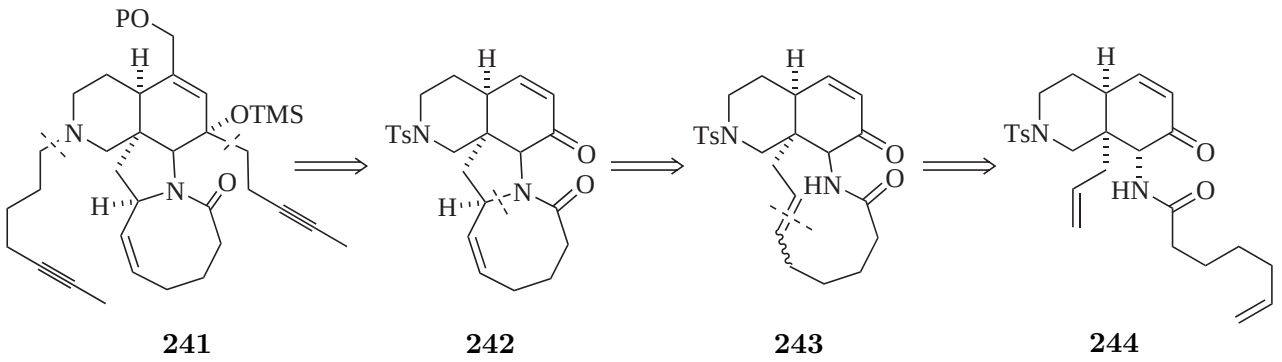
The retrosynthetic analysis commences from natural product ircinal A (**19**), which has been converted into manazamine A (**1**) in two steps by Kobayashi and co-workers (see Section 1.3).[19] Reduction of the aldehyde, protection of the hydroxyl groups and introduction of carbonyl group onto the E ring delivers the lactam **240**. Retrosynthetic ring-closing enyne metathesis along with partial alkyne reduction allows disconnection to give the tetracyclic *bis*-alkyne **241** (Scheme 3.1).



19 **240** **241**

Scheme 3.1: Retrosynthetic analysis - disconnection of ring E.

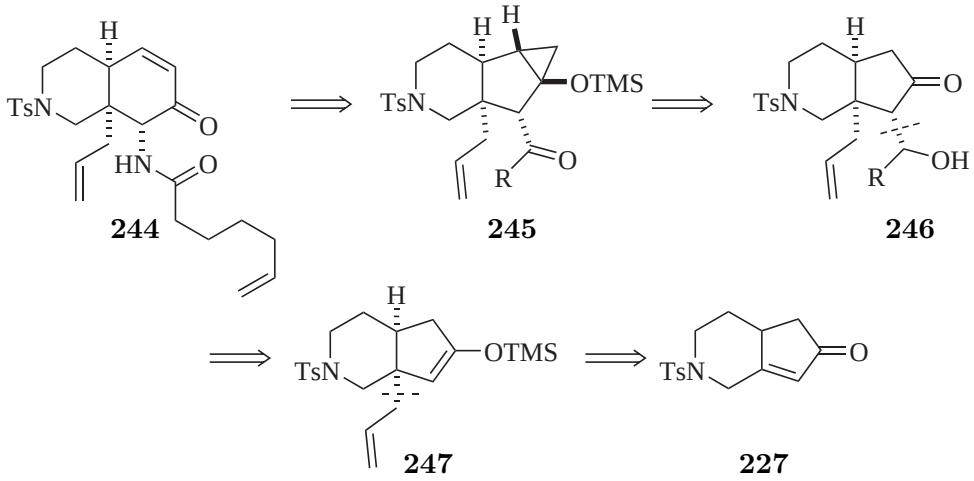
Removal of both alkyne-containing side chains along with the side chain at the alkene in ring B affords enone **242**. Scission of the C-N bond between the C and D rings provides the macrocyclic lactam **243**. Opening of the macrocyclic lactam **243** by retrosynthetic ring-closing metathesis gives the amide **244** (Scheme 3.2).



241 **242** **243** **244**

Scheme 3.2: Retrosynthetic analysis - disconnetction of the CE ring system.

Conversion of the amide into the ketone by retrosynthetic Beckmann rearrangement and conversion of the alkene into an alkyne along with contraction of the B ring gives the tricyclic lactam **245**. Retrosynthetic cyclopropanation yields the Mukaiyama aldol product **246**. A final disconnection of the allyl group leads to the simple enone fragment **227** (Scheme 3.3).



244 **245** **246**

247 **227**

Scheme 3.3: Retrosynthetic analysis - disconnection to the simple enone fragment **227**.

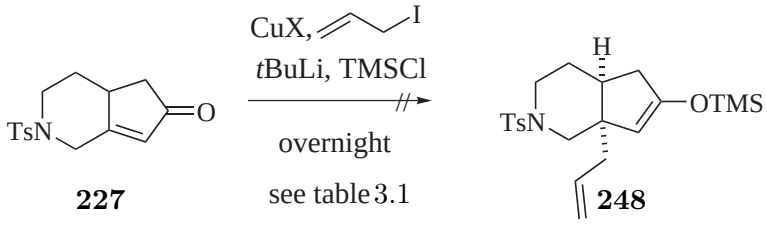
3.2 Project outline

Despite the fact that the Diels-Alder reaction was not investigated exhaustively, initial results were not encouraging and so an alternative approach towards the intermediate **244** was needed. As depicted in the retrosynthetic analysis given above, addition of a cuprate to the bicyclic enone **227** followed by a Mukaiyama aldol reaction of the formed TMS enol ether **247** would provide the tertiary alcohol **246**. Further elaboration to **244** involves oxidation of the alcohol and a Simmons-Smith-type cyclopropanation and expansion to give a 6-membered cyclic enone **244**.

3.3 Cuprate 1,4-addition approach

Cuprate 1,4-addition

With the change of approach, the conjugate addition reaction was investigated as summarised in Table 3.1. Lithium halogen exchange provided the lithiated product, that upon treatment with copper iodide resulted in formation of the cuprate. A few of the initial attempts to promote the cuprate addition are given below. Varying the source of copper and the number of equivalents did not result in the 1,4-addition product **248**. It should be mentioned that in Entry 3 a commercially available copper source was utilised. The "cuprate in a bottle" method was used to form the cuprate reagent (R_2CuLi).[90,96]



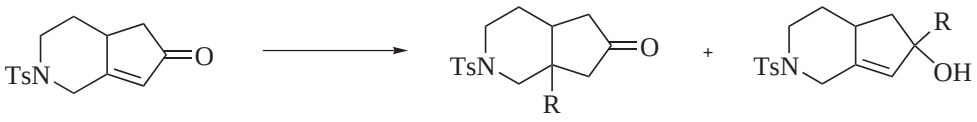
227 **248**

Entry	CuX	Solvent	Temperature	Eq. RCuXLi
1	CuCN	Ether	-78 °C $\rightarrow$ RT	1.5 eq. RCu(CN)Li
2	CuCN	THF	-45 °C $\rightarrow$ RT	1.5 eq. RCu(CN)Li
3	CuI	THF/DMS, 1/1	-78 °C $\rightarrow -40$ °C	1.5 eq. R_2CuLi
4	(2-Thienyl)Cu(CN)Li	THF	-78 °C $\rightarrow -40$ °C	1.2 eq. (2-Thienyl)Cu(CN)Li

Table 3.1: Initial attempted cuprate 1,4-additions.

Further investigations using the "cuprate in a bottle" to perfom the conjugate addition reaction to the bicyclic system **227** were undertaken (Table 3.2). Instead of focusing on the TMS enol ether, obtaining the 1,4-addition product **249** was the inital target. Following the establishment of the conjugate addition reaction, further elaboration to obtain the TMS enol ether was investigated. However, varying the temperature, the solvent, the source of copper, and the nucleophile did not allow the isolation of the desired product **249**. The only major product observed was the 1,2-addition product **250**.

[96] Iimura, S.; Overman, L.; Paulini, R.; Zakarian, A. *J. Am. Chem. Soc.* **2006**, *128*, 13095-13101.



227 **249** **250**

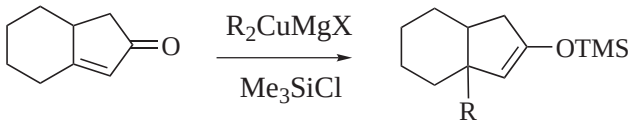
Entry	R	CuX	Solvent	Temperature	Reaction time	Yield
1	3-butenylMgBr	(2-Thienyl)Cu(CN)Li	Et_2O	$-10\ ^\circ C \rightarrow 0\ ^\circ C$	6 h	-[†]
2	allylI, *t*BuLi	(2-Thienyl)Cu(CN)Li	THF/Et_2O	$-45\ ^\circ C \rightarrow 0\ ^\circ C$	3 h	-[†]
3	allylMgCl	(2-Thienyl)Cu(CN)Li	THF	$-10\ ^\circ C \rightarrow 0\ ^\circ C$	3 h	-[†]
4	allylMgCl	CuCN	THF	$-78\ ^\circ C$	3 h	-[‡]

[‡] yielded the 1,2-addition as the major product determined by NMR.
[†] recovered starting material.

Table 3.2: Attempted 1,4-addition reactionss using the commercially available "cuprate in a bottle".

Further investigation of the 1,4-addition reaction

Despite the fact that the 1,4-addition of an organocopper reagents to α,β-unsaturated ketones is well established,[88,94–98] the failure of the reaction led to the investigation of the reaction on a model system **251** as depicted in Scheme 3.4.

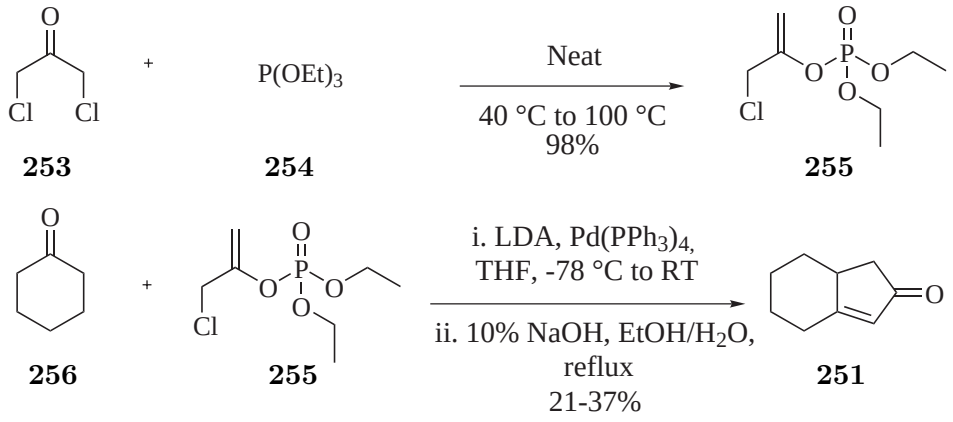


251 **252**

Scheme 3.4: Cuprate 1,4-addition using the model system **251**.

First, the synthesis of the model system **251** had to be carried out as shown in Scheme 3.5. Commencing from 1,3-dichloro acetone (**253**) and triethyl phosphite (**254**), the enol phosphate **255** was formed using a Perkow reaction in 97% yield. This was followed by a one-pot cyclopentenone annelation process and was conducted as follows: the enolate anion of cyclohexanone (**256**) was generated with LDA, followed by the addition of phosphate **255** in THF containing 5 mol% of $Pd(Ph_3P)_4$. Subsequent treatment with 10% NaOH in $EtOH/H_2O$ and heating at reflux for 24 h, afforded the desired bicyclic system **251** in 37% yield (Scheme 3.5).[99–101]

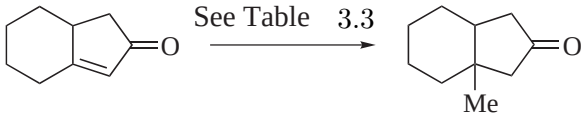
[97] Hughes, C.; Miller, A.; Trauner, D. *Org. Lett.* **2005**, *7*, 3425-3428.
[98] Taylor, R. J. K., Ed.; *Organocopper reagents. A pratical approach;* Oxford University Press: 1994.
[99] Piers, E.; Renaud, J. *J. Org. Chem.* **1993**, *58*, 11-13.
[100] Nagumo, S.; Suemune, H.; Sakai, K. *Tetrahedron Lett.* **1988**, *29*, 6927-6930.
[101] Welch, S. C.; Assercq, J. M.; Loh, J. P.; Glase, S. A. *J. Org. Chem.* **1987**, *52*, 1440-1450.
[102] Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802-5803.
[103] Polo, E.; Bellabarba, R. M.; Prini, G.; Traverso, O.; Green, M. L. *J. Organomet. Chem.* **1999**, *577*, 211-218.



253 **254** **255** **256** **255** **251**

Scheme 3.5: Synthesis of the model system **251**.

Following the synthesis of the model system, attention turned again to the 1,4-addition reaction. As shown in Table 3.3, various changes to variables such as reaction temperature, the copper source, and solvent did not give rise to the anticipated 1,4-addition product. The selected results presented in Table 3.3 were not encouraging but due to the considerable body of literature evidence[88,94–98] concerning organocopper addition of a methyl to α,β-substituted compounds, further investigations were undertaken.



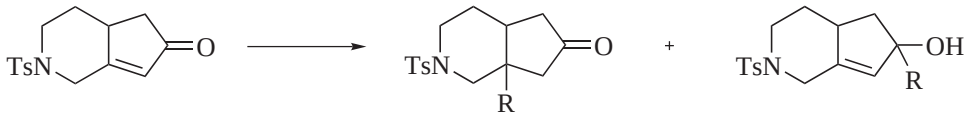
251 **257**

Entry	Temperature	Reaction time	CuX/RLi	Solvent	Yield
1	0 °C → RT	o/n	CuI/MeLi	THF	-
2	−20 °C → 0 °C	o/n	CuI/MeLi	Et_2O	-
3	−78 °C → 0 °C	o/n	CuI/MeLi	Et_2O	-
4	−78 °C → RT	o/n	CuCN/MeLi	Et_2O	-
5	−78 °C → RT	1 h	CuI/MeLi	Et_2O	-
6	−78 °C → RT	o/n	CuI/MeLi	THF	-
7	0 °C → RT	o/n	CuI/MeLi	THF	-
8	−78 °C	2 h	CuI/MeLi	THF	-

Table 3.3: Attempted cuprate 1,4-addition reactions.

Based on literature evidence concerning the use of Grignard reagents in cuprate addition reactions,[90,96] an initial attempt to form the cuprate using methyl magnesium bromide at −78 °C was made, but resulted in 1,2-addition (Entry 1, Table 3.4). In order to overcome the lack of reactivity, the temperature was changed to room temperature and revealed the desired cuprate 1,4-addition product **258** as the only product in a 85% yield (Entry 2, Table 3.4). Following successful identification of reaction conditions that gives exclusively the addition product **258**, the incorporation of the desired allyl

group was attempted. Unfortunately, this reaction gave a mixture of 1,2- and 1,4-addition products (Entry 3).



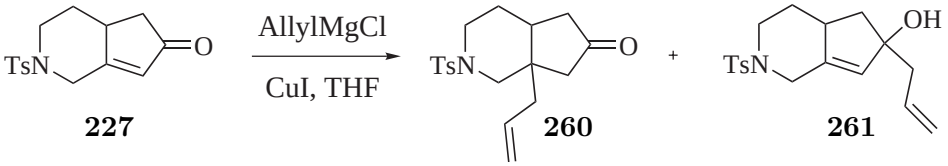
227 **258** **259**

Entry	R/Source	CuX	Solvent	Temperature	Reaction time	Yield (**258**/**259**)
1	Me/MeMgBr	CuI	Et_2O/THF	−78 °C → RT	o/n	**259**
2	Me/MeMgBr	CuI	Et_2O	RT	48 h	**258** only (85%)
3	Allyl/AllylMgCl	CuI	THF	−10 °C → 0 °C	o/n	Mixture (75%)

Table 3.4: Attempted cuprate 1,4-additions[90,96]

Optimisation of the cuprate addition reaction

Having established conditions that result in formation of the desired 1,4-addition product, optimisation (performed using compound **227**) to control the ratio of 1,2- to 1,4-addition product was investigated (Table 3.5). Applying the same reaction conditions as with the successful addition of the methyl group resulted in no reaction of the starting material (Entry 1, Table 3.5). Lowering the temperature to 0 °C changed the outcome and a 5:1 ratio of 1,4-addition to 1,2-addition products was observed (Entry 2, Table 3.5). Formation of the higher order cuprate at lower temperature resulted in a mixture of the starting material, the 1,2-addition product, and to some extent the 1,4-addition product (Entries 3 and 4, Table 3.5). The best ratio (5.8:1, 40%) was obtained by cooling the cuprate to −5 °C followed by the addition of the pre-cooled enone **227** (−10 °C) (Entry 5, Table 3.5).



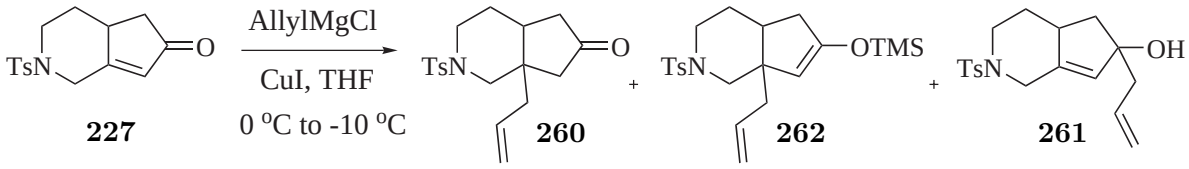
227 **260** **261**

Entry	Temperature	Reaction time	Ratio (**260**:**261**)
1	RT	o/n	No conversion
2	0 °C → RT	o/n	(5:1)
3	−40 °C → RT	o/n	Mixture (SM:**261**)
4	−40 °C → −5 °C	6 h	(1:1)
5	0 °C → −10 °C	6 h	(5.8:1)

Table 3.5: Optimisation of the 1,4-addition reaction

In summary the cuprate 1,4-addition reaction has been optimised and isolation of the TMS enol ether **262** has been achieved in a modest 37% yield along with the hydrolysed TMS enol ether **260** and the

1,2-addition product **261** (Scheme 3.6).



Scheme 3.6: Summary of the 1,4-addition reaction optimisation.

The ketone **260** resulting from either hydrolysis of the TMS enol ether **262** or the direct addition was obtained as a crystalline solid and X-ray analysis verified the *cis* relative stereochemistry of ketone **260**. As can be seen from the crystal structure, the observed relative stereochemistry of the newly formed centre is the desired one (Figure 3.3 and Scheme 3.3).

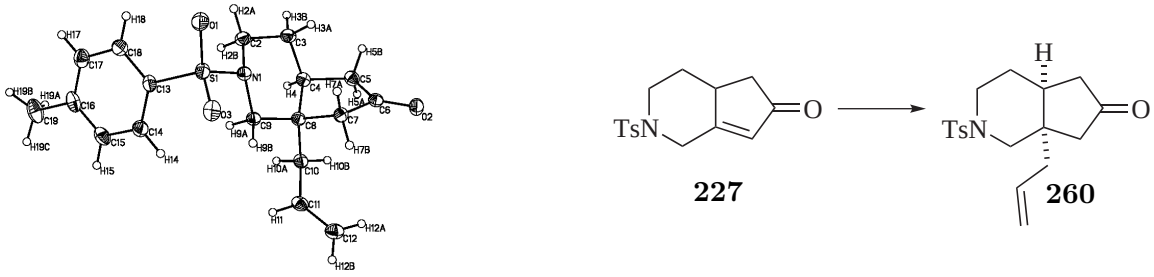
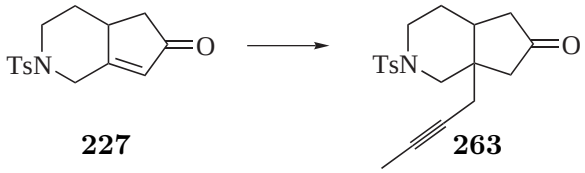


Figure 3.1: (a) X-ray structure of the 1,4-addition product **260** and (b) the relative stereochemistry of the newly formed centre in **260**.

3.4 Extension of the cuprate 1,4-addition reaction

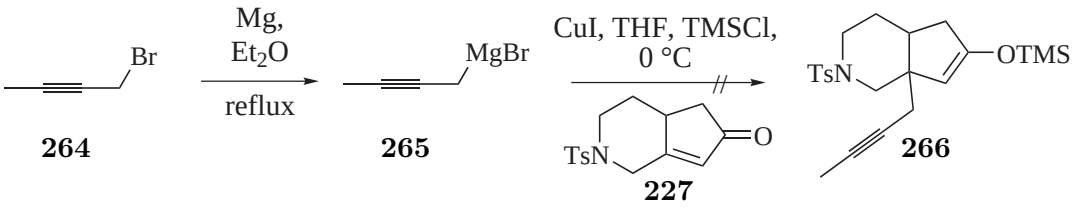
In order to perform alkyne metathesis, extension of the cuprate 1,4-addition reaction to introduce an alkyne-containing side-chain had to be accomplished (Scheme 3.7).



Scheme 3.7: Introduction of the alkyne side-chain.

Initial attempts to introduce the alkyne side-chain were performed utilising 1-bromo-2-butyne (**264**) (Scheme 3.8). Formation of the Grignard reagent was not as straightforward as expected and although repeated, formation of the 1,4-addition product was not observed. According to the literature, formation of the Grignard reagent is not easily accomplished and as a consequence, the cuprate and the

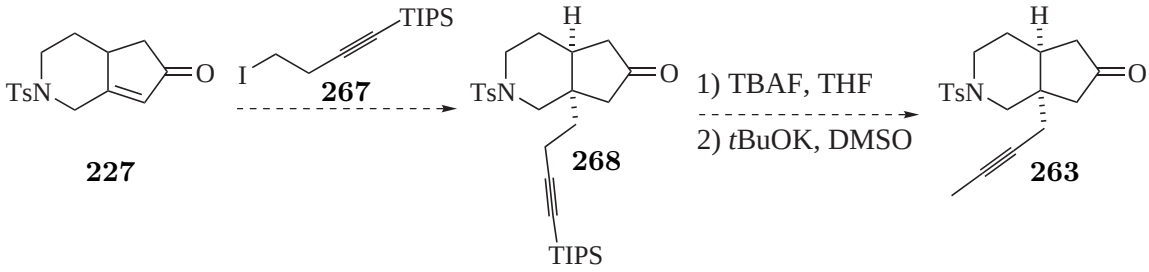
following 1,4-addition product were not obtained.[104]



Scheme 3.8: Attempt to introduce the alkyne side-chain.

Alternative approach to introduce the alkyne side-chain

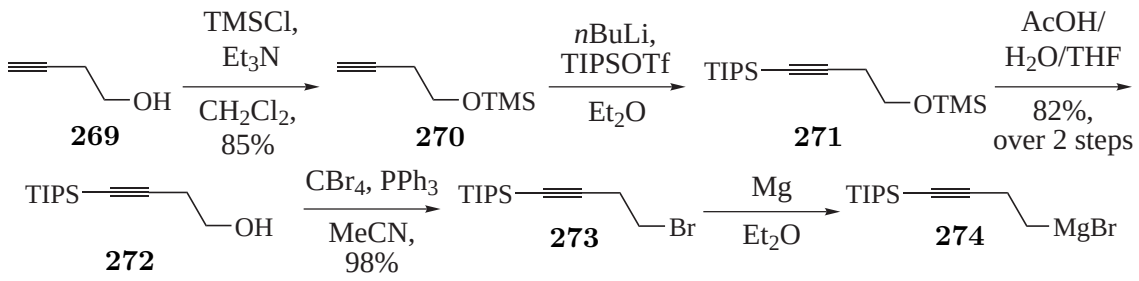
Instead of a procedure involving the unstable and unreliable reagent 2-butynylmagnesium bromide (**265**), an alternative three-step procedure to install the alkyne side-chain was employed (Scheme 3.9).[105,106] The key step is again a cuprate 1,4-addition reaction, but this time the Grignard reagent derived from iodide **267** was to be used for the formation of the cuprate. Following the 1,4-addition reaction, removal of the silyl protecting group and reverse alkyne Zipper reaction would lead to **263** (Scheme 3.9).[105,106,107]



Scheme 3.9: Alternative approach to install the alkyne side-chain.[105,106,107]

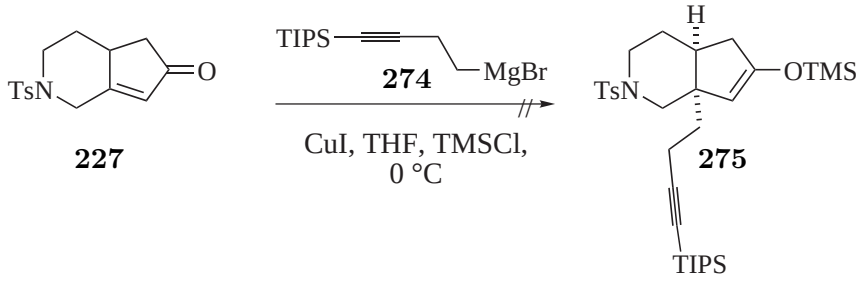
Due to the success of the introduction of the allyl group using allyl magnesium chloride, introduction of the alkyne side-chain by use of Grignard reagents inspired the synthesis of the brominated compound **273** (Scheme 3.10). Bromide **273** was easily obtained in five steps from 3-butynol (**269**). The synthesis commenced with TMS protection of 3-butynol (**269**) to afford the TMS protected alcohol **270** in 85% yield. Introduction of the TIPS group employing *n*BuLi and TIPSOTf, resulted in the TIPS protected alkyne **271**. Subsequent hydrolysis of the TMS ether yielded the alcohol **272** in 82% over 2 steps. The alcohol **272** was easily converted into the bromide **273**, using carbon tetrabromide and triphenylphosphine.[89] Further conversion to the Grignard reagent **274** was attempted using magnesium in ether (Scheme 3.10).[108]

[104] Acharya, H. P.; Miyoshi, K.; Kobayashi, Y. *Org. Lett.* **2007**, *9*, 3535-3538.
[105] Kedar, T.; Miller, M.; Hegedus, L. *J. Org. Chem.* **1996**, *61*, 6121-6126.
[106] Chan, J.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 10682-10691.
[107] Chan, J.; Jamison, T. *J. Am. Chem. Soc.* **2003**, *125*, 11514-11515.
[108] Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165-168.



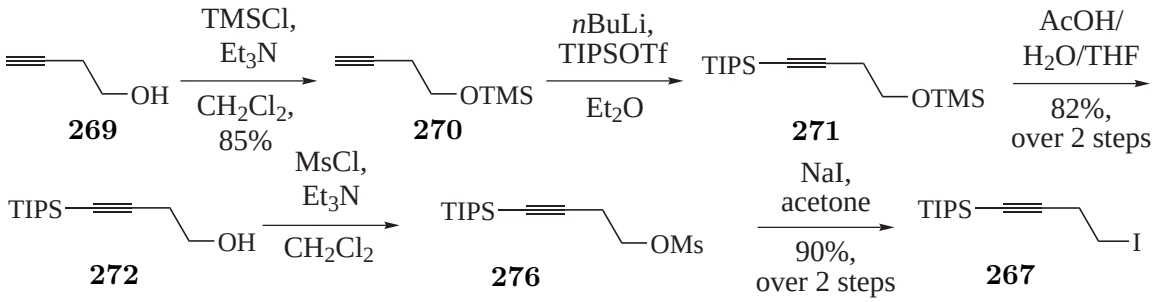
Scheme 3.10: Synthesis of 4-(triisopropylsilyl)-3-butyne-1-magnesium bromide (**274**).[105]

With the desired Grignard reagent **274** now available, the 1,4-addition reaction was attempted employing the optimised reaction conditions established in Tables 3.2 & 3.5, (Scheme 3.11). However, using these conditions the 1,4-addition product was not observed. Repeating the reaction and taking particular care during formation of the Grignard reagent, did not improve the outcome of the reaction.



Scheme 3.11: Cuprate 1,4-addition utilising 4-(triisopropylsilyl)-3-butyne-1-magnesiumbromide.[105]

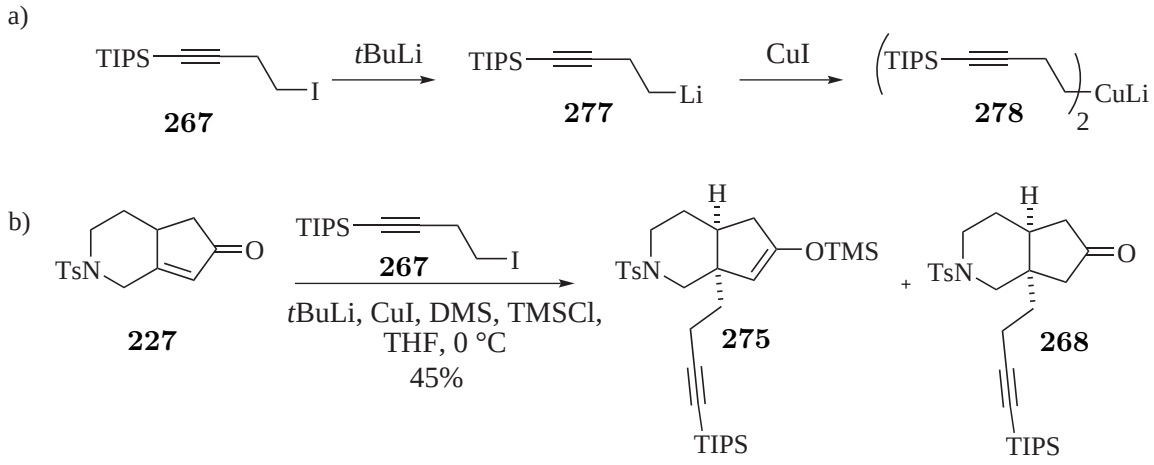
Following the failure of the reaction shown in Scheme 3.11, attention turned again to 1,4-addition reaction using the lithium cuprate reagent. Iodide **267** was easily obtained in five steps from 3-butynol (**269**). From alcohol **272** mesylation the alcohol gave **270** that upon treatment with sodium iodide afforded the iodinated compound **267** in 90% yield over 2 steps (Scheme 3.12).



Scheme 3.12: Synthesis of 1-iodo-4-(triisopropylsilyl)-3-butyne (**267**).[105]

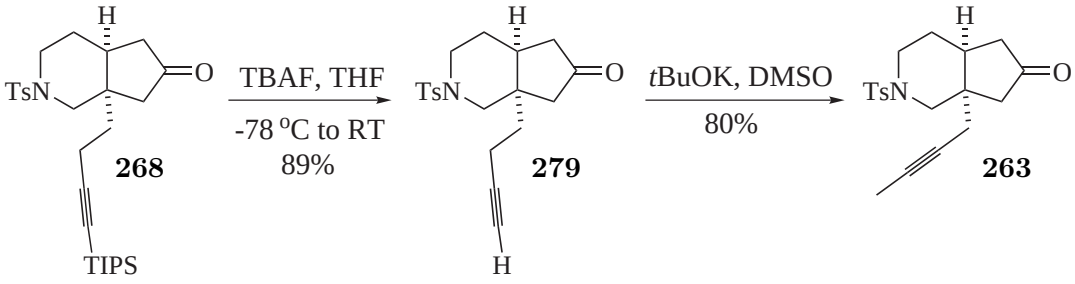
Halogen-lithium exchange with *t*BuLi furnished the lithiated compound **277**, which upon treatment with copper iodide resulted in formation of the dialkyl cuprate **278** (Scheme 3.13 a).[105,106] The bicyclic enone **227** was added to the dialkyl cuprate in the presence of DMS and TMSCl. The reaction

resulted in formation of the 1,4-addition product **275** in a 45% yield (Scheme 3.13 b).



Scheme 3.13: 1,4-Addition using the lithium cuprate reagent.[105,107]

It is worth mentioning that the isolated yield of **275** is somewhat lower than expected due to hydrolysis of the TMS enol ether **275** upon column chromatography. In order to prevent hydrolysis, the crude material should be employed directly in the next step. From the ketone **268**, efforts towards isomerisation of the alkyne were investigated. Removal of the TIPS group using TBAF afforded the terminal acetylene **279** in 89% yield. To place the triple bond in the position required for enyne ring-closing metathesis, the terminal acetylene **279** was isomerised with *t*BuOK in DMSO to afford **263** in 80% yield (Scheme 3.14).



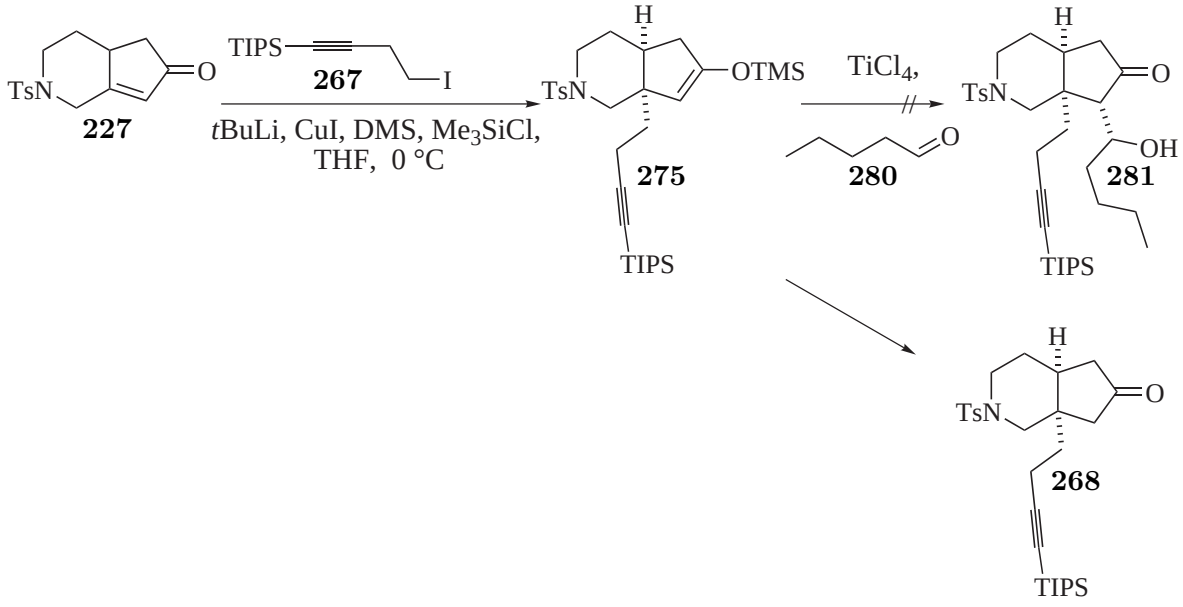
Scheme 3.14: Isomerisation of the alkyne.[105,107]

3.5 Aldol condensation reactions

Mukaiyama aldol condensation

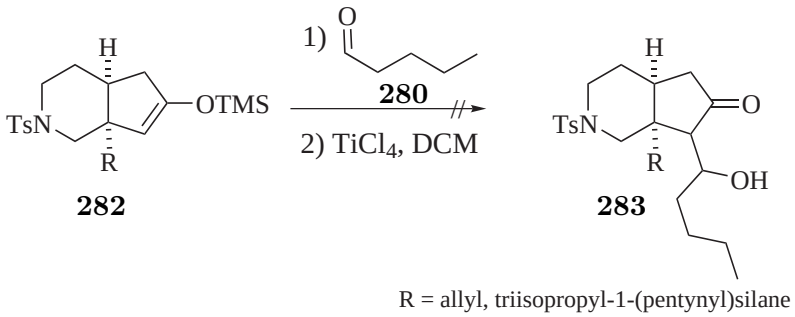
Following the successful 1,4-addition to form **275**, efforts were directed towards introduction of the third stereocentre. Initial experiments were carried out using methyllithium to generate the lithium enolate and these resulted in isolation of the corresponding ketone **268** or the TMS enol ether **275**.[109,110] The crude material from the 1,4-addition reaction was employed in a Mukaiyama aldol type addition reaction with valeraldehyde (**280**) and $TiCl_4$ at −78 °C. Unfortunately, the Mukaiyama

aldol type condensation reaction did not result in formation of the aldol product **281** and a 79% yield of the ketone **268** was isolated instead (Scheme 3.15).



Scheme 3.15: Aldol condensation.[105,107]

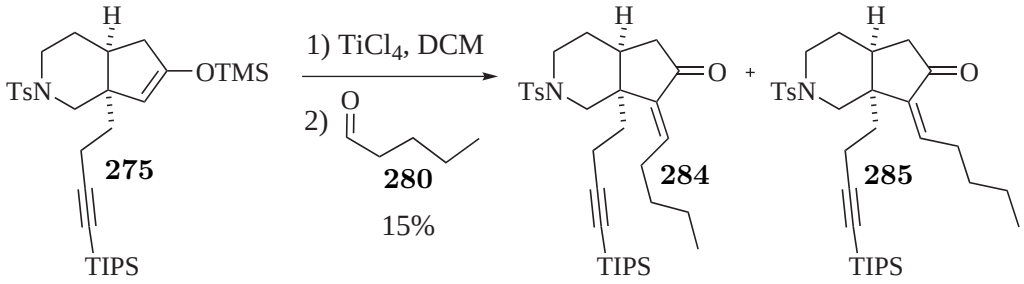
Following initial attempts to perform an aldol condensation reaction using $TiCl_4$, further investigations were undertaken. Treatment of a mixture of the TMS enol ether **282** and valeraldehyde (**280**) at −78 °C with titanium tetrachloride resulted in isolation of the ketone **268** and **260** instead of the required aldol product **283**, Scheme 3.16.



Scheme 3.16: Aldol condensation.

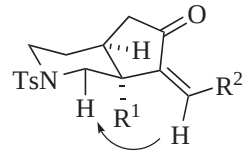
However, reversing the order of addition,[111] i.e., formation of the titanium enolate preceding the addition of the aldehyde **280**, resulted in formation of aldol condensation products. Unfortunately, the initial hydroxyketone product underwent dehydration and resulted in formation of the enones **284** and **285** as a 1:1 mixture in 15% yield which upon standing isomerised **284** to **285** (Scheme 3.17).

[111] Drège, E.; Tominiaux, C.; Morgant, G.; Desmale, D. *Eur. J. Org. Chem.* **2006**, 4825-4840.



Scheme 3.17: Mukaiyama aldol condensation.[111]

^{1}H-^{1}H NOE experiments of the *Z*-alkene confirmed the configuration as depicted in Figure 3.2



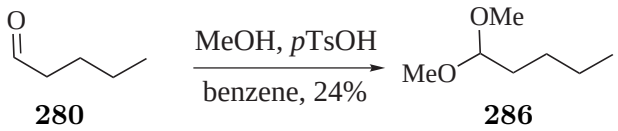
nOe 2.4%

285

R^1 = triisopropyl-1-(pentynyl)silane

Figure 3.2: NOE experiment of the *Z*-alkene.

In order to circumvent the dehydration problem, the enolate adddition to an acetal was attempted (Scheme 3.19). The dimethylacetal **286** was obtained in 24% yield by treatment of valeraldehyde (**280**) in benzene with methanol and a catalytic amount of *para*-toluenesulfonic acid. Optimisation of this low yielding reaction ws not been pursued (Scheme 3.18).[111,112]

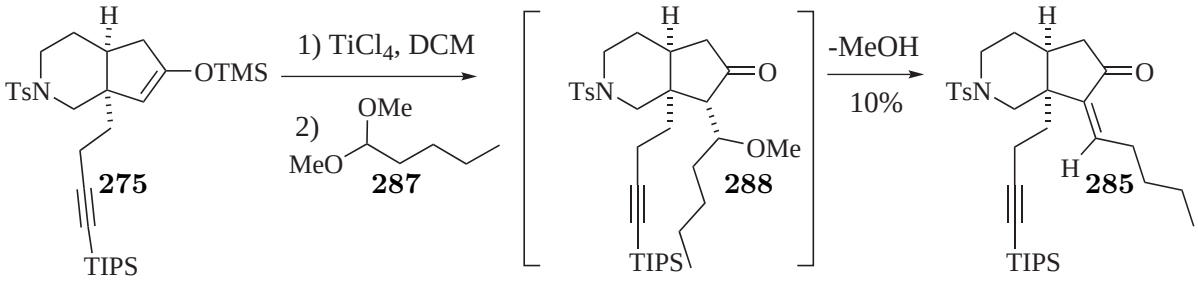


280 **286**

Scheme 3.18: Synthesis of the acetal protected aldehyde **286**.[111,112]

Initial attempts to form the titanium enolate led to hydrolysis of the TMS enol ether and the desired aldol condensation product **288** was not obtained. Reversing the order of addition, as well as pre-treating the TMS enol ether and acetal with titanium tetrachloride before mixing, resulted in lower levels of conversion and did not resolve the problem of dehydration.

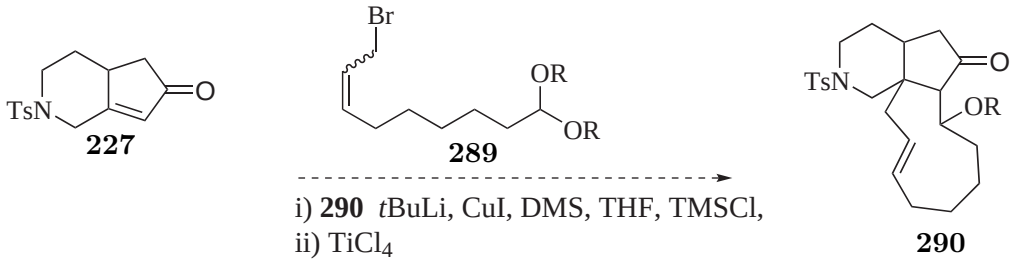
[112] Iwasaki, G.; Sano, M.; Sodeoka, M.; Yoshida, K.; Shibasaki, M. *J. Org. Chem.* **1988**, *53*, 4864-4867.



Scheme 3.19: Mukaiyama type aldol addition with acetal **287**.

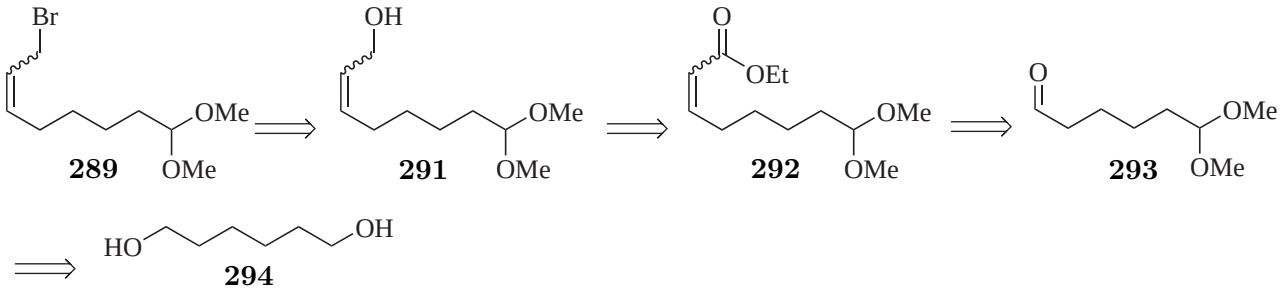
Intramolecular Mukaiyama aldol condensation

As an alternative approach to intermolecular Mukaiyama aldol addition, the intramolecular version of the reaction was explored. The intramolecular version could possibly prevent the dehydration reaction from taking place by providing more strain into the system (Scheme 3.20).



Scheme 3.20: Intramolecular Mukaiyama aldol condensation.

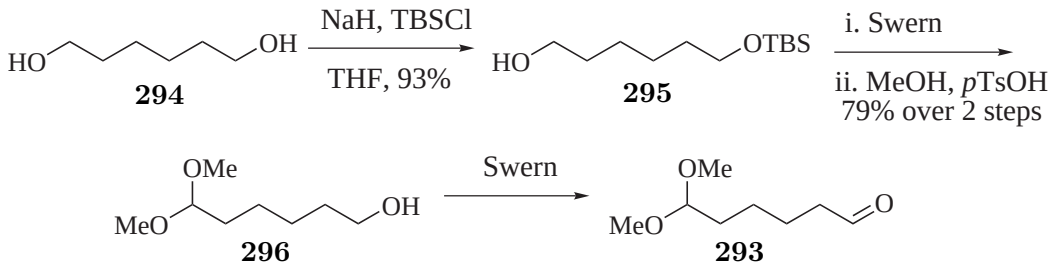
In order to investigate the intramolecular Mukaiyama aldol addition, the bromide **289** had to be synthesised. The retrosynthetic plan to obtain the allylic bromide **289** is given in Scheme 3.21.[113,114] Bromide **289** can be simplified to alcohol **291**. DIBAL-H reduction of ester **292** results in alcohol **291**, and the former can be prepared by a Horner-Wadsworth-Emmons reaction with aldehyde **293**. Aldehyde **293** can be obtained from commercially available 1,6-hexanediol (**294**) (Scheme 3.21).



Scheme 3.21: Retrosynthetic analysis of bromide **289**.

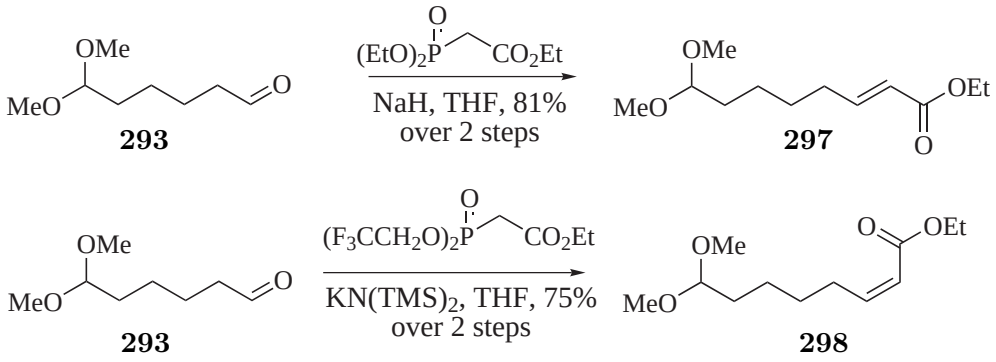
[113] Bihelovic, F.; Matovic, R.; Vulovic, B.; Saicic, R. N. *Org. Lett.* **2007**, *9*, 5063-5066.
[114] Schreiber, S. L.; Kelly, S. E.; Porco, J. A.; Sammakia, T.; Suh, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 6210-6218.

Mono-protection of 1,6-hexanediol (**294**) was accomplished using sodium hydride and TBSCl yielding the siloxy ether **295** in 93% yield.[115] Swern oxidation and subsequent treatment with methanol and catalytic amount of *para*-toluenesulfonic acid resulted in formation of the acetal **296** in 79% yield. The alcohol was oxidised to the aldehyde **293** using Swern conditions and the product was used directly in the olefination step without further purification (Scheme 3.22).



Scheme 3.22: Synthesis of aldehyde **293**.

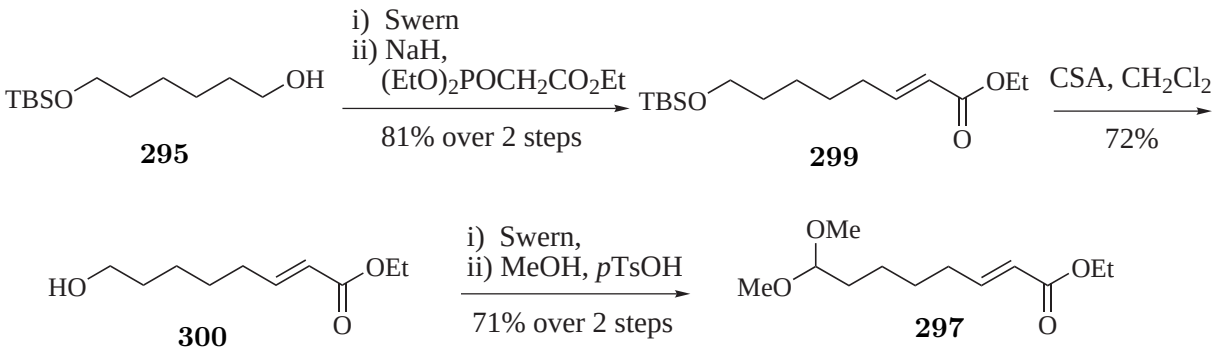
The aldehyde **293** was then converted into the *E* alkene **297** *via* Horner-Wadsworth-Emmons olefination in 81% yield (Scheme 3.23).[113] Aldehyde **293** was also subsequently converted into the *Z* alkene **298** in 75% yiled using a modified Still-Gennari olefination reaction (Scheme 3.23).[113]



Scheme 3.23: Horner-Wadsworth-Emmons olefinations to give **297** and **298**.

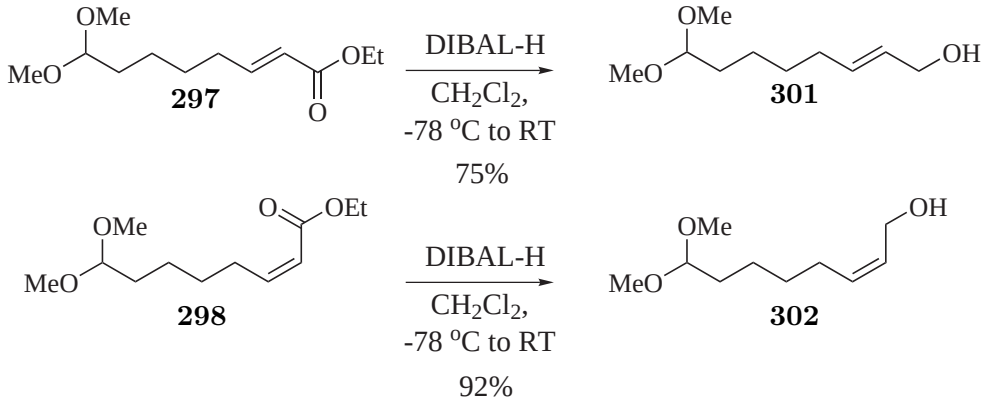
Alternatively, ester **297** can be obtained from alcohol **295** in four steps starting with Swern oxidation of alcohol **295** and followed by a Horner-Wadsworth-Emmons olefination to yield the *E* alkene **299** in 81% yield. Removal of the TBS group using camphorsulfonic acid gave the alcohol **300** in 72% yield. Further oxidation and acetal formation led to **297** in 71% yield (Scheme 3.24).

[115] McDougal, P. G.; Rico, J. G.; Oh, Y. I.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388-3390.



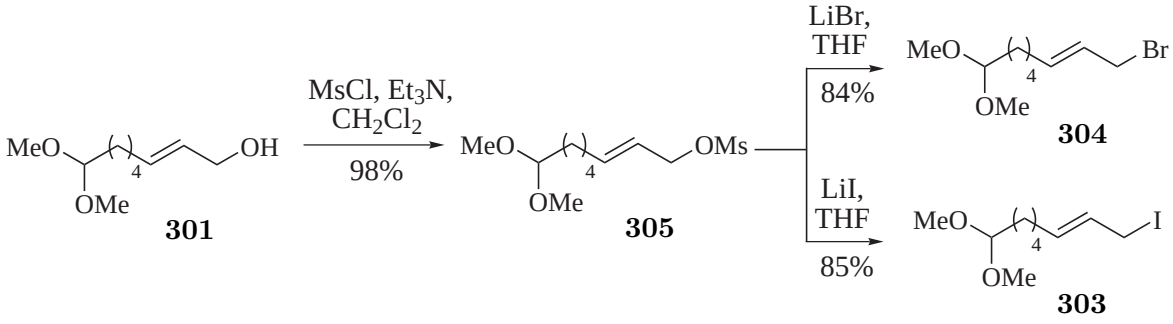
Scheme 3.24: Alternative synthesis of olefin **297**.

With the two esters **297** and **298** in hand, DIBAL-H reduction afforded the alcohols **301** and **302** in 75% and 92% yield, respectively (Scheme 3.25).



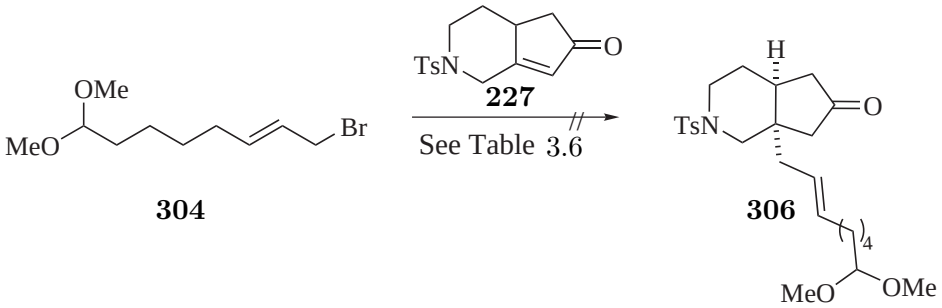
Scheme 3.25: DIBAL-H reduction of esters **297** and **298**.

To be able to perform the 1,4-addition reaction, alcohol **301** was converted into either the bromide **304** or the iodide **303** (Scheme 3.26). Initial attempts using standard Appel conditions, resulted in decomposition of the starting alcohol **301**. However, the bromide **304** was obtained in 84% yield by displacement of the mesylate **305** using LiBr.[113] Likewise, the iodide **303** was obtained in 85% yield when displacing the mesylate using LiI.[113] The iodide **303** was very unstable and so the use of the bromide **304** in the 1,4-addition reaction was preferred (Scheme 3.26).



Scheme 3.26: Synthesis of bromide **304** and ioide **303**.

Lithium halogen exchange on allylic bromide **304** led to the lithiated compound which upon treatment with CuI gave the higher order cuprate. Initial attempts to accomplish 1,4-addition were performed using the same conditions as when introducing the alkyne side chain (Entry 1, Table 3.5) However, the 1,4-addition product was not obtained from this reaction and lowering the temperature to −78 °C did not change the outcome (Entry 2, Table 3.5). Replacing DMS with tributylphosphine changed the outcome to what is believed to be the 1,2-addition mode instead of the desired 1,4-addition mode of reaction (Entries 4 and 5, Table 3.6).[116,117]

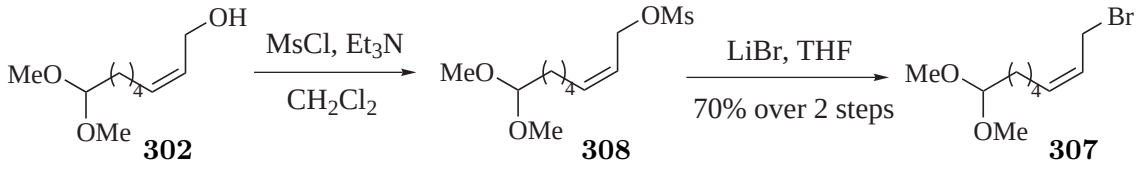


Entry	Conditions	Result
1	*t*BuLi, CuI, DMS, TMSCl, −40 °C	SM
2	*t*BuLi, CuI, DMS, TMSCl, −78 °C	SM
3	*t*BuLi, CuI, Bu_3P, TMSCl, −78 °C	1,2-addition†
4	*t*BuLi, CuI, Bu_3P, TMSCl, −78 °C	1,2-addition†

† Determined by ^{1}H-NMR analysis.

Table 3.6: Attempted cuprate 1,4-addition.[116,117]

In a further attempt to perfrom 1,4-addition, the *Z* alkene was converted into the bromide and utilised in the reaction (Scheme 3.27).

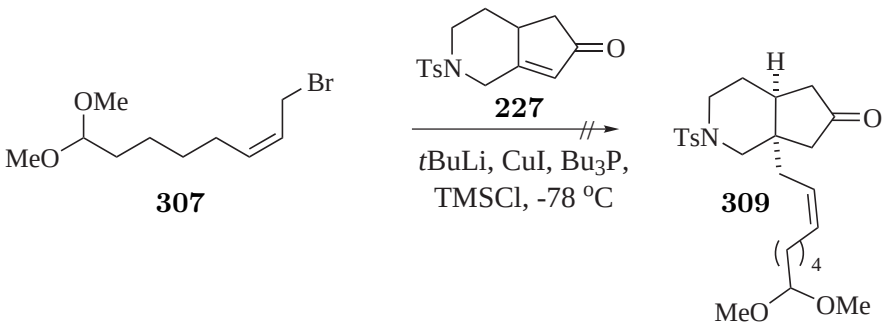


Scheme 3.27: Synthesis of bromide **307**.

The cuprate 1,4-addition reaction was attempted using bromide **307** However, the *Z* alkene showed the same reactivity characteristics as the *E* alkene and the required 1,4-addition product was not obtained from this reaction either (Scheme 3.28).

[116] Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 4718-4726.

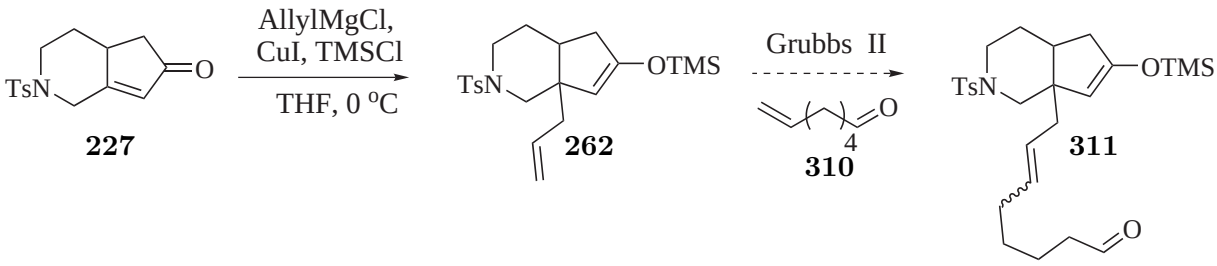
[117] Suzuki, M.; Kawagishi, T.; Yanagisawa, A.; Suzuki, T.; Okamura, N.; Noyori, R. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1299-1312.



Scheme 3.28: Attempted 1,4-addition using bromide **307**.

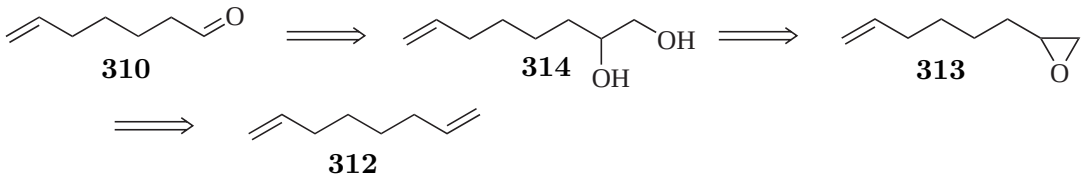
Intramolecular aldol condensation using cross-metathesis to prepare the substrate

In another attempt to overcome the dehydration problem it was thought that initial 1,4-addition of allylmagnesium chloride to enone **227** followed by cross-metathesis with an appropriate aldehyde would deliver a substrate suitable for intramolecular aldol condensation (Scheme 3.29).



Scheme 3.29: Cross-metathesis attempt towards the aldol precursor **311**.

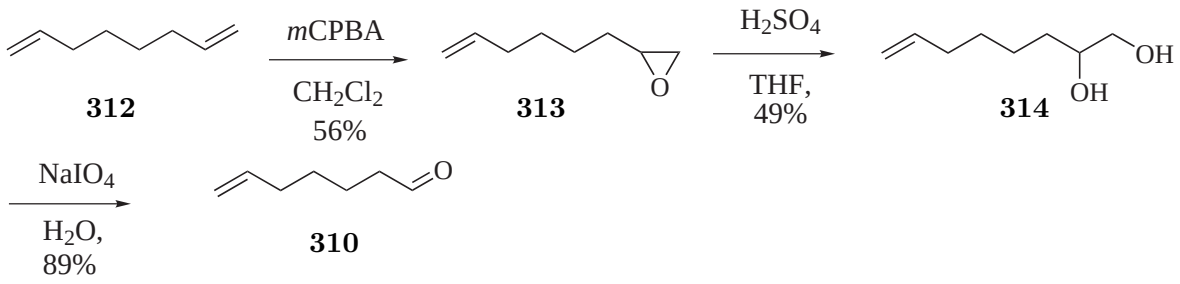
The aldehyde **310** required for cross-metathesis was synthesised using two synthetic routes. Retrosynthetically, the aldehyde **310** can be obtained from the diol **314**, and the diol **314** can be synthesised in two steps from 1,7-octadiene (**312**).



Scheme 3.30: Retrosynthesis of the aldehyde **310**.

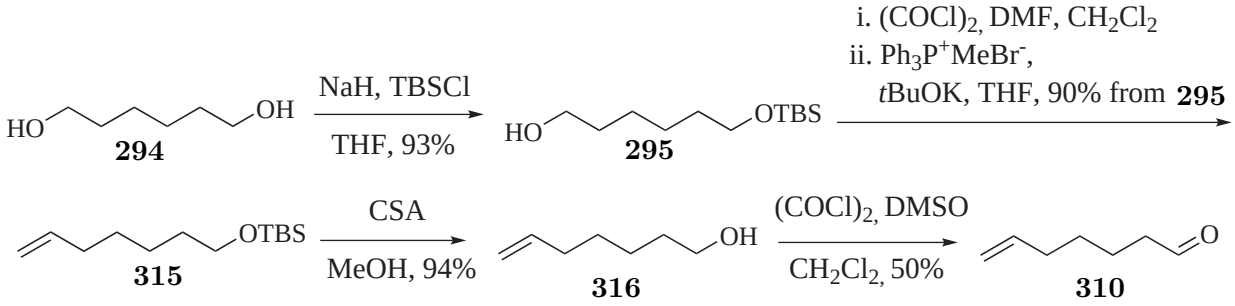
Mono-epoxidation of 1,7-octadiene **312** with *m*CPBA gave the epoxide **313** in 56% yield. Opening of the epoxide **313** with an aqueous solution of sulphuric acid resulted in isolation of the diol **314** in 49% yield. Diol **314** was then converted into the aldehyde **310** in 89% yield using an aqueous suspension of sodium periodate (Scheme 3.31).[118]

[118] Byrom, N. T.; Grigg, R.; Kongkathip, B.; Reimer, G.; Wade, A. R. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1643-1653.



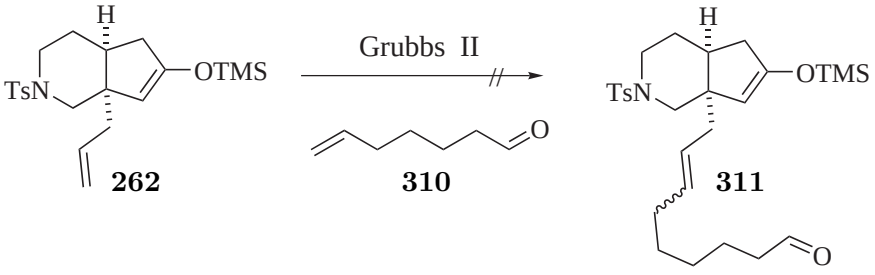
Scheme 3.31: Synthesis of the aldehyde **310**.

In an alternative but slightly longer route, the aldehyde can be obtained from 1,6 hexanediol (**294**) in five steps (Scheme 3.32). Monoprotection of the diol **294** afforded the TBS protected alcohol **295** in 93% yield. Swern oxidation and subsequent olefination afforded the alkene in **315** in 90% yield from the alcohol **295**. TBS deprotection using CSA provided in the alcohol **316** in 94% yield and final oxidation resulted in a 50% yield of the aldehyde **310** (Scheme 3.32).



Scheme 3.32: Alternative synthesis of the aldehyde **310**.

Following syntheis of the aldehyde **310**, attention turned to the cross-metathesis reaction (Scheme 3.33). Following the 1,4-addition reaction, the crude TMS enol ether **262**, which was contaminated with some 1,2-addition prodcut, was employed in the cross metathesis reaction along with the aldehyde **310** and 5 mol% Grubbs II catalyst. Despite several attempts to perfom the reaction, the cross metathesis product **311** was not obtained. It was speculated that the approach might not be viable as starting with a mixture of 1,4- and 1,2-addition products increases the number of possible products.

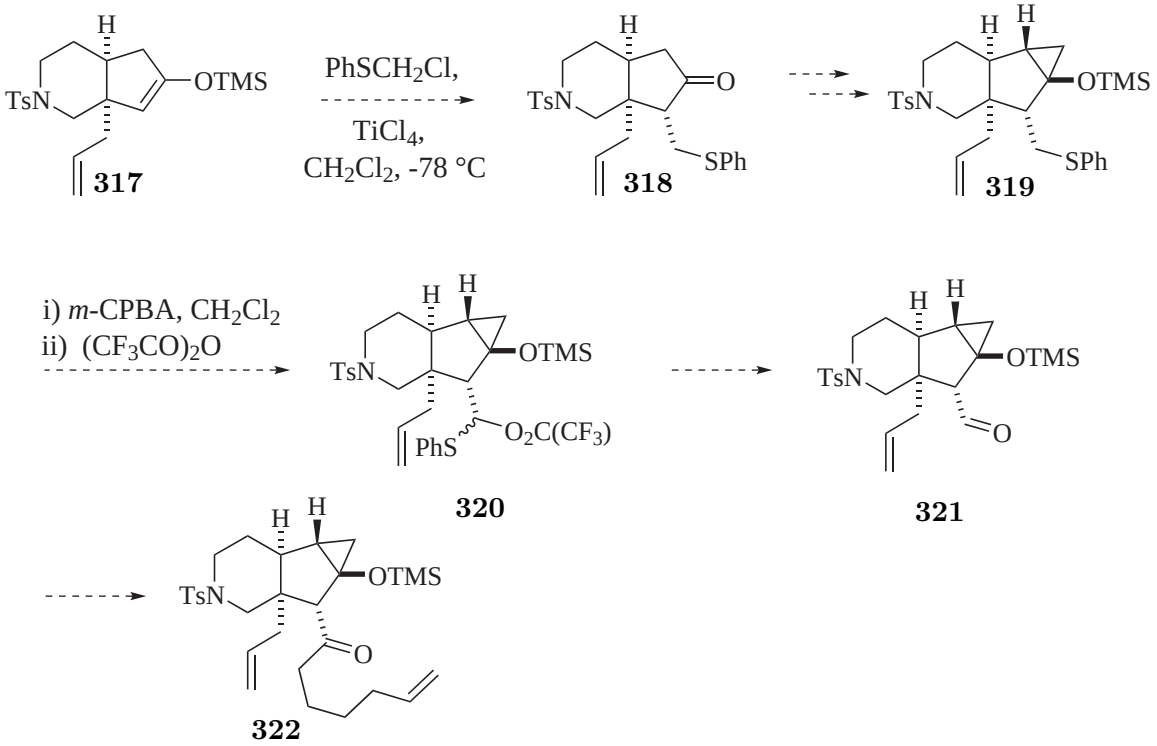


Scheme 3.33: Attempts to prepare the aldol precursor **311** by cross metathesis.

3.6 Ketone functionalisation by alkylation, halogenation or Rubottom oxidation

Attempted alkylation using chloromethyl phenylsulfide

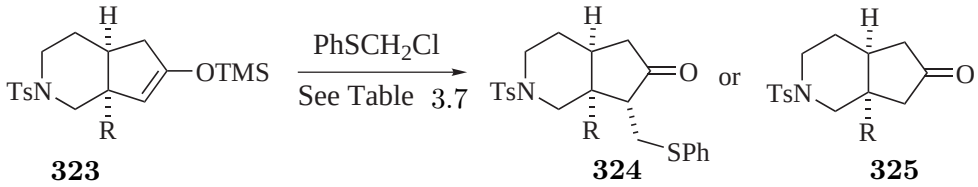
To avoid the dehydration problem encountered during the Mukaiyama aldol condensation, it was suggested that alkylation of the TMS enol ether **317** with chloro methyl phenyl sulfide could be performed (Scheme 3.34).[117−119] Following successful alkylation, cyclopropanation would give the tricyclic intermediate **319** which upon oxidation and Pummerer rearrangement would yield **320**. The thioacetal **320** could be hydrolysed to give the aldehyde **321** which would be further converted into the diene **322** (Scheme 3.34).



Scheme 3.34: Approach to circumvent dehydration reaction to take place.[117−119]

Unfortunately, attempts to alkylate substrates containing either side chain did not deliver the alkylated product (Table 3.7). It was speculated that the use of crude TMS enol ether would influence the outcome of the alkylation reaction, and so the TMS enol ether was prepared from the corresponding ketone (LDA and TMSCl) and used in the alkylation reaction (Table 3.7, Entry 4). However, this reaction did not give rise to the required product **324**.

[119] Paterson, I. *Tetrahedron* **1988**, *44*, 4207-4219.
[120] Solladie, G.; Wilb, N.; Bauder, C. *Eur. J. Org. Chem.* **1999**, 30212-3026.
[121] Gravel, D.; Bordeleau, J. *Tetrahedron Lett.* **1998**, *39*, 8035-8038.



323 **324** **325**

Entry	R	Temperature	Result
1		−20 °C	**325**
2		−78 °C	**325**
3		−78 °C	**325**†
4		−78 °C	**325**

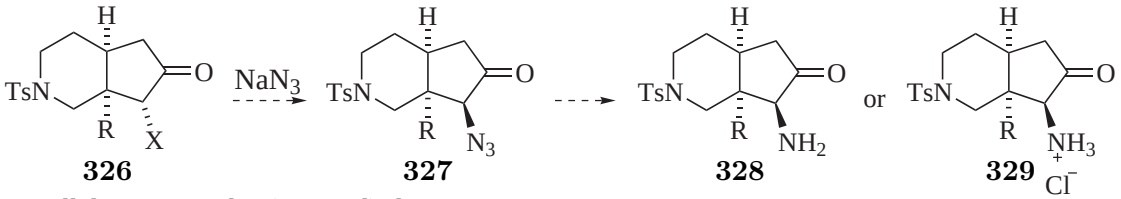
† TMS enol ether obtained from the ketone.

Table 3.7: Alkylation attempts.[119]

Despite the fact that the route involving alkylation of enol ether **323** with chloromethyl phenyl sulfide would lead to the rapid synthesis of an advance intermediate, the alkylation route was abandoned.

Halogenation of TMS enol ether

The literature evidence, that TMS enol ethers can be α-halogenated using *N*-iodosuccinimide, prompted exploration of the halogenation of the TMS enol ether obtained from 1,4-addition to the enone **227**. This was envisaged to allow indirect introduction of the nitrogen substituent, *via* either initial halogenation and subsequent substitution, or direct introduction of the nitrogen. This would circumvent the key Beckmann rearrangement reaction initially proposed in Scheme 3.3. Displacement of the halogen could deliver the α azide **327** which could be converted into either the amine **328** or its hydrochloride salt **329** (Scheme 3.35).



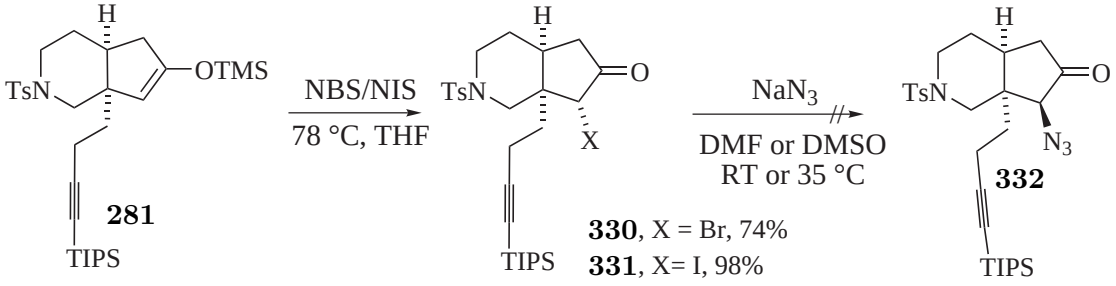
326 **327** **328** **329**

R = allyl, triisopropyl-1-(pentynyl)silane
X = I or Br

Scheme 3.35: Suggested route to aminoketones **328** and **329**.

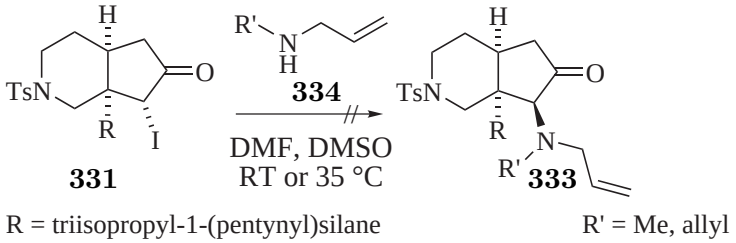
Halogenation using *N*-iodosuccinimide or *N*-bromoosuccinimide resulted in isolation of the coresponding bromide **330** in 74% yield over 2 steps and the iodide **331** in 98% yield over 2 steps (Scheme 3.36). With the halogenated compound available, synthesis of the amine **328** or its hydrochloride salt

329 should be possbile (Scheme 3.35).[122,123] Following halogenation, displacement of the halogen was attempted using sodium azide in either DMF or DMSO (Scheme 3.36). However, it appeared that the displacement is not favored and it is speculated that this is caused by steric factors due to the fact that S_N2 displacement would be required to occur from the sterically hindered face of the ring. As a result, the desired azide was not obtained.[122]



Scheme 3.36: Halogenation of TMS enol ether **281** and further conversion to the azide.[120−122]

The lack of reactivity of haloketones **330** and **331** to nucleophilic displacement was further confirmed when attempting halogen displacement with the allylic amines **334**. The displacement reactions resulted in consumption of the starting material, but the required product (**333**) was not obtained (Scheme 3.37).[124]



Scheme 3.37: Displacement of the iodide using secondary amines **334**.[124]

Preparation of α-hydroxy ketones by Rubottom type oxidation

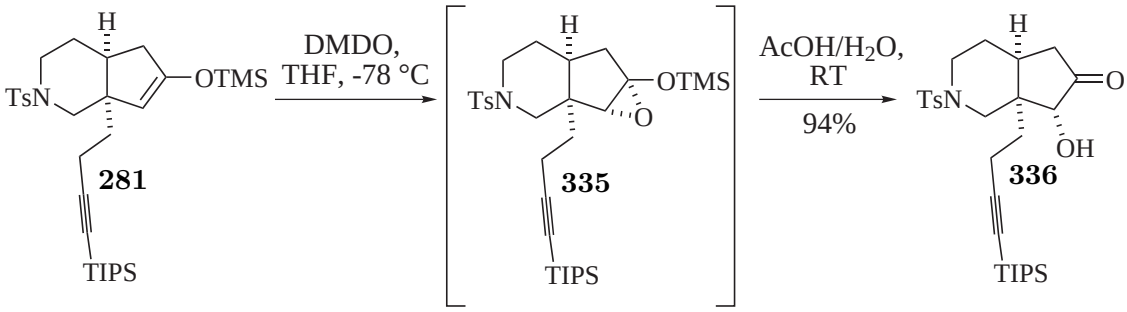
In an additional attempt to install a heteroatom next to the carbonyl group, Rubottom type oxidation using dimethyldioxirane was attempted (Scheme 3.38).[125] Initially, the epoxide **335** was formed, but isolation was not attempted and instead hydrolysis of the TMS enol ether generated the desired α-hydroxy ketone **336** in 94% yield over 2 steps.

[122] Taillier, C.; Hameury, T.; Bellosta, V.; Cossy, J. *Tetrahedron* **2007**, *63*, 4472-4490.

[123] Salunke, D. B.; Hazra, B. G.; Gonnade, R. G.; Bhadbhade, M. M.; Pore, V. S. *Tetrahedron* **2005**, *61*, 3605-3612.

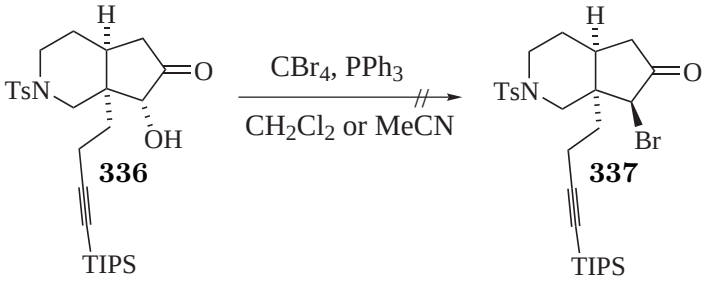
[124] Peglion, J.-L.; Goument, B.; Despaux, N.; Charlot, V.; Giraud, H.; Nisole, C.; Newman-Tancredi, A.; Dekeyne, A.; Bertrand, M.; Genissel, P.; Millan, M. J. *J. Med. Chem.* **2002**, *45*, 165-176.

[125] Thompson, C. F.; Jamison, T. F.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2000**, *122*, 10482-10483.



Scheme 3.38: Synthesis of α-hydroxy ketone **336**.[125]

Following formation of the α-hydroxy ketone **336**, attention was now turned towards further functionalisation α to the carbonyl group (Scheme 3.39). Interconversion of the hydroxyl group to a bromide using standard Appel conditions, would result in inversion of stereochemistry.[126] Displacing the introduced bromide with an azide or secondary amine would invert the stereochemistry once again to deliver the desired *cis*-stereochemistry.[122,123] However, several attempts to introduce the bromide resulted in no reaction of the starting alcohol (Scheme 3.39).

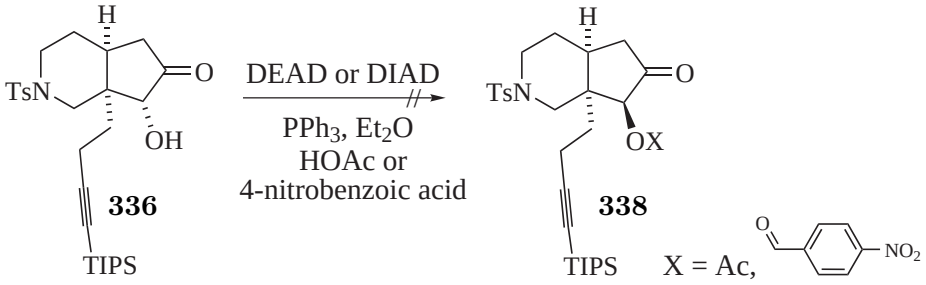


Scheme 3.39: Appel reaction to generate the bromide **337**.

As an alternative to the Appel reaction, the Mitsunobu reaction was considered. A Mitsunobu reaction should invert the stereochemistry in the same mannner as the Appel reaction. Following hydrolysis of the resulting ester functionality, the alcohol bearing the *trans* configuration could then be activated and displaced with a nucleophile.[127] When the Mitsunobu reaction was performed using DEAD with either HOAc or 4-nitrobenzoic acid starting material was recovered instead of the required ester **336** (Scheme 3.40). In an analogous fashion, the Mitsunobu reaction was attempted using DIAD as the coupling reagent, but the desired ester **338** was not obtained from the reaction either (Scheme 3.40).

[126] Tidgewell, K.; Groer, C. E.; Harding, W. W.; Lozama, A.; Schmidt, M.; Marquam, A.; Hiemstra, J.; Partilla, J. S.; Dersch, C. M.; Rothman, R. B.; Bohn, L. M.; Prisinzano, T. E. *J. Med. Chem.* **2008**, *51*, 2421-2431.

[127] Pereira, C. L.; Chen, Y.-H.; McDonald, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 6066-6067.

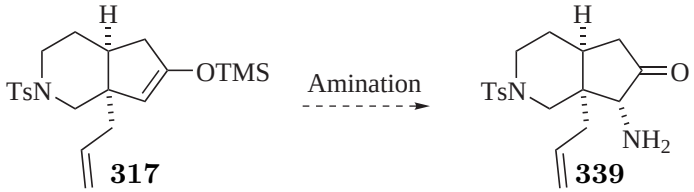


Scheme 3.40: Mitsunobu reaction with α-hydroxy ketone **336**.

3.7 Amination, azidation or aziridination of TMS enol ethers

Amination reaction using electrophilic nitrogen

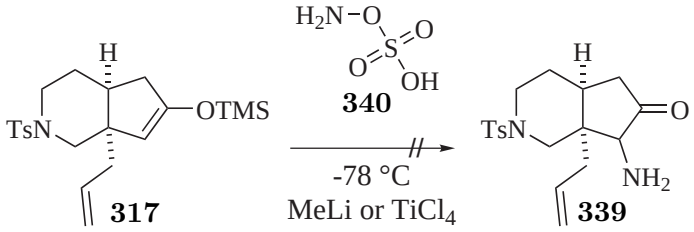
Electrophilic amination is an important strategy for CN bond formation in organic synthesis and provides a potentially powerful method for the direct introduction of a nitrogen functionality to carbanions.[127–129] The use of an electrophilic aminating reagent to functionalise the TMS enol ether **317** was attempted (Scheme 3.41).



Scheme 3.41: Amination reaction using electrophilic nitrogen.

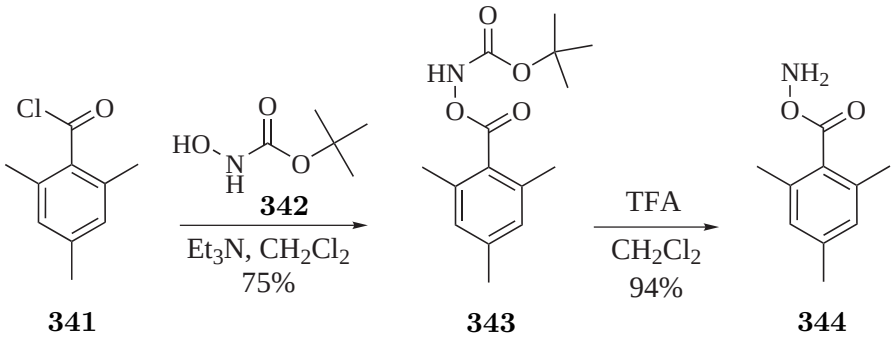
Initial reactions were carried out using commercially available hydroxylamine-*O*-sulfonic acid (**340**)[131] at −78 °C and either MeLi or $TiCl_4$ was used to generate the enolate from the enol ether. These reactions resulted in hydrolysis of the TMS enol ether, without formation of the aminated product **339** (Scheme 3.42).

[128] Erdik, E.; Ay, M. *Chem. Rev.* **1989**, *89*, 1947-1980.
[129] Erdik, E. *Tetrahedron* **2004**, *60*, 8747-8782.
[130] Dembech, P.; Seconi, G.; Ricci, A. *Chem. Eur. J.* **2000**, *6*, 1281-1286.
[131] Somei, M.; Natsume, M. *Tetrahedron Lett.* **1974**, *14*, 461-462.



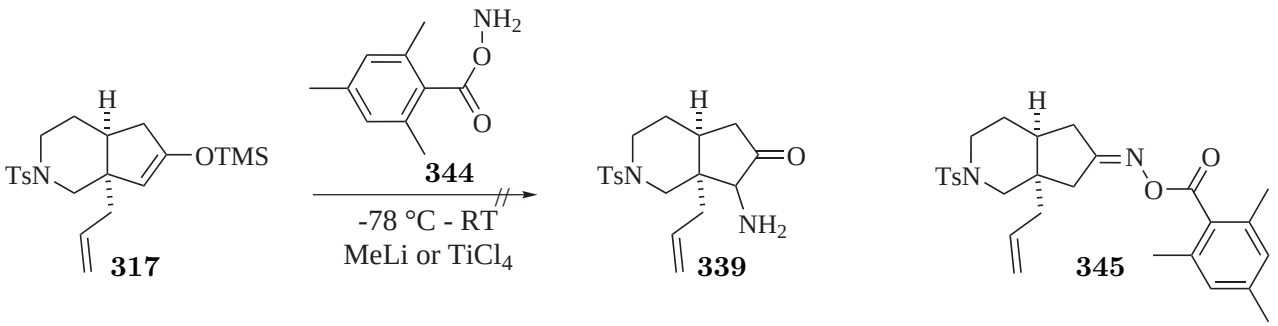
Scheme 3.42: Amination attempt using hydroxylamine-*O*-sulfonic acid (**340**).

As an alternative to the commercially available hydroxylamine **340**, *O*-(2,4,6-trimethylbenzoyl) - hydroxylamine (**344**) was synthesised. Starting from commercially available 2,4,6-trimethylbenzoyl chloride (**341**) the Boc protected hydroxylamine **343** was obtained in a 75% yield. *N*-Deprotection by removal of the Boc group using TFA resulted in the desired hydroxylamine **344** in a 94% yield (Scheme 3.43).



Scheme 3.43: Synthesis of *O*-(2,4,6-trimethylbenzoyl)hydroxylamine (**344**).

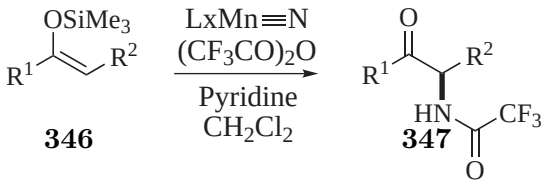
Following preparation of the hydroxylamine **344**, amination reaction was investigated (Scheme 3.44). After several attempts, varying the reaction conditions, the amination product was not obtained. Varying the Lewis acid and temperature in order to obtain the amination product, led only to the imine **345**. The imine **345** was probably obtained due to the acidic conditions used when performing the amination reaction (Scheme 3.44).



Scheme 3.44: Amination attempt of **317**.

Amination of silyl enol ethers unsing nitromanganese(V) complexes

Following the failure to perform amination using the reagents **340** and **344**, introduction of a *N*-trifluoroacetyl amino group in α position with respect to the ketone was investigated. The utilisation of a nitromanganese(V) complex relies on the fact that, when activated with trifluoroacetic anhydride, the complex can act as a nitrogen transfer reagent, allowing direct introduction of an *N*-trifluoroacetyl group (Scheme 3.45).[132]



Scheme 3.45: Formation of *N*-trifluoroacetyl α-amino ketone **347**.[132]

Before the nitrogen-transfer reaction was attempted, the appropriate nitromanganese(V) complexes had to be synthesised. Both the (salen)Mn(N) complex (**348**) and the (saltmen)Mn(N) complex (**349**) were prepared, because results published by Carreira and co-workers suggested that both of these complexes could deliver the aminated product (Scheme 3.3).[132,133]

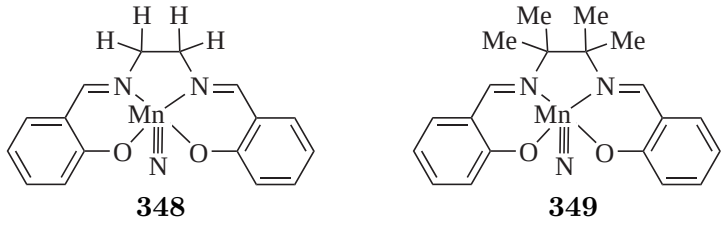
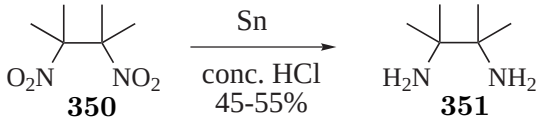


Figure 3.3: The salen **348** and saltmen **349** complexes.[132]

In order to synthesise the (saltmen)Mn(N) complex, reduction of commercially available 2,3-dimethyl-2,3-dinitrobutane to obtain the diamine **351** was carried out as outlined in Scheme 3.46. This reaction resulted in isolation of the required diamine **351** in acceptable yield.[134,135]



Scheme 3.46: Reduction of 2,3-dimethyl-2,3-dinitrobutane (**350**) to 2,3-diamino-2,3-dimethylbutane (**351**).[134,135]

Formation of the H_2saltmen ligand was accomplished by condensing the diamine **351** with salicylalde-

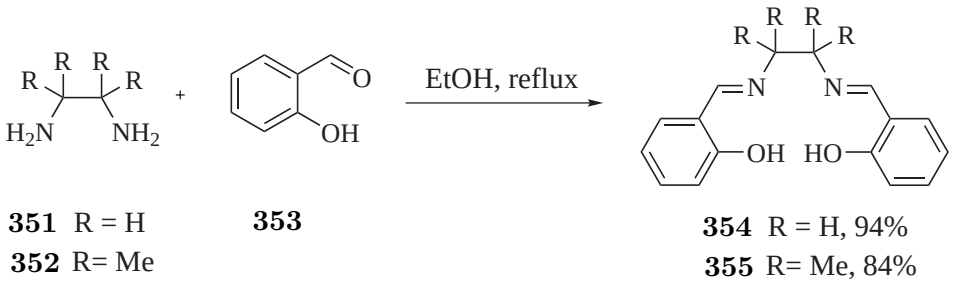
[132] Du Bois, J.; Hong, J.; Carreira, E. M.; Day, M. W. *J. Am. Chem. Soc.* **1996**, *118*, 915-916.

[133] Fallis, I. A.; Murphy, D. M.; Willock, D. J.; Tucker, R. J.; Farley, R. D.; Jenkins, R.; Strevens, R. R. *J. Am. Chem. Soc.* **2004**, *126*, 15660-15661.

[134] Che, C.-M.; Wong, K.-Y.; Lam, H.-W.; Chin, K.-F.; Zhou, Z.-Y.; Mak, T. C. W. *J. Chem. Soc., Dalton Trans.* **1993**, 857-861.

[135] Sayre, R. *J. Am. Chem. Soc.* **1955**, *77*, 6689-6690.

hyde (**353**); the ligand **355** was obtained as bright yellow crystals in 84% yield.[132] In a similar manner fashion the H_2salen ligand was obtained by condensing 1,2-diaminoethane with salicylaldehyde (**353**), providing the ligand **354** in 94% yield.



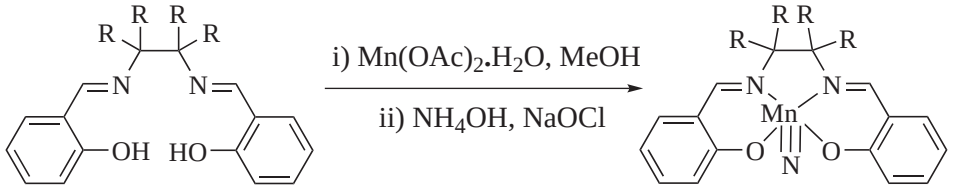
351 R = H
352 R= Me

353

354 R = H, 94%
355 R= Me, 84%

Scheme 3.47: Synthesis of H_2salen (**354**) and H_2saltmen (**355**).[132,133]

Following the synthesis of both salen ligands, the nitrido-Mn(V) complexes **348** and **349** were obtained in a single operation by reacting $Mn(OAc)_2.4H_2O$ with a solution of the ligand in methanol to give the air-oxidized (salen)Mn(N) and (saltmen)Mn(N) intermediates. Subsequent treatment with aqueous NH_4OH and aqueous NaOCl afforded the required Mn(V) nitrido complex in yields of 66-87%. The complexes are easily prepared on large scale and are stable to both air and H_2O.[132]

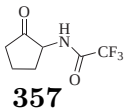
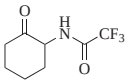
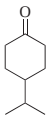
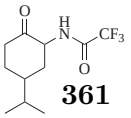
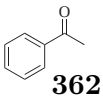
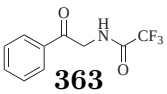
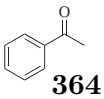
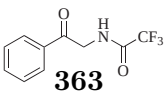
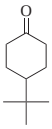
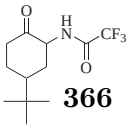
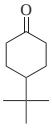
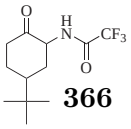
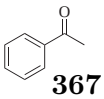
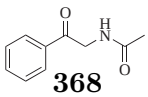


354 R = H
355 R= Me

348 R = H, 66%
349 R= Me, 87%

Scheme 3.48: Synthesis of Mn(V) nitrido.[132]

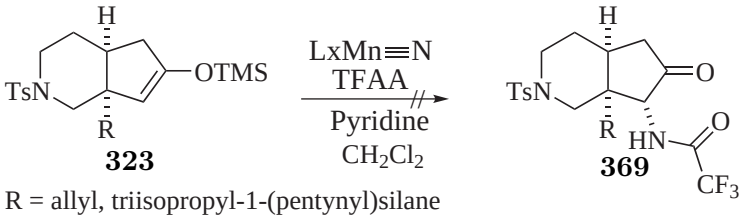
To test the Mn(V) complexes, a range of ketones were converted into their corresponding TMS enol ethers, using freshly made LDA and TMSCl, and then tested in the amination reaction (Table 3.8). The lack of amination product in Entries 1-6 can be explained by the volatility of the TMS enol ethers. Entries 7 and 8 confirmed that the complexes did indeed react to give the desired aminated products, which were obtained in moderate yields (not optimised or repeated). Following the success with acetophenone (Entries 4 and 5), 4-*tert*-butylcyclohexanone was tested, (Entries 6 and 7). In this case the aminated product was obtained in moderate yield as a 1:1 mixture of diastereoisomers. Finally, the final entry shows an attempt to use acetic anhydride as an alternative to TFAA.

Entry	Substrate	Complex	Product	Yield
1	 **356**	**348/349**	 **357**	traces
2	 **358**	**348/349**	 **359**	-
3	 **360**	**348/349**	 **361**	-
4	 **362**	**348**	 **363**	15%
5	 **364**	**349**	 **363**	50%
6	 **365**	**348**	 **366**	34%, *dr* 1:1
7	 **365**	**349**	 **366**	32% *dr* 1:1
8	 **367**	**349** †	 **368**	-

† In the presence of acetic anhydride.

Table 3.8: Attempted amination reactions using Mn(V) nitrido using TFAA.[132]

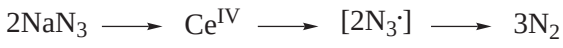
After establishing that the use of acetic anhydride was not successful, amination of the TMS enol ether obtained from the 1,4-addition was attempted using trifluoroacetic anhydride (Scheme 3.49). Despite encouraging results obtained using model systems, amination of the desired TMS enol ether **317** was not observed.



Scheme 3.49: Amination of the TMS enol ether **317** obtained from the 1,4-addition reaction.

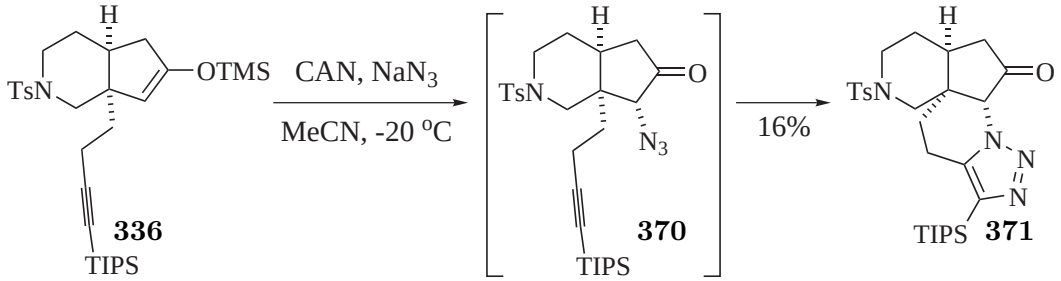
Azidation of silyl enol ethers using sodium azide and CAN

Although introduction of the nitrogen substituent by nucleophilic displacement of an α-hydroxy ketone with sodium azide was not successful, other possibilities for the direct introduction of a nitrogen substituent were considered. In 1915, oxidation of sodium azide with CAN to give nitrogen was reported (Scheme 3.50) However, it was not until 1979 that this method was extended to azidation of silyl enol ethers.[136,137] In 1990, the formation of an α-azido ketone from oxidative azidation of a *tert*-butyl dimethyl silyl enol ether was reported.[137–139] This report inspired us to attempt of formation of the α-azido ketone.



Scheme 3.50: Oxidation of sodium azide with CAN.

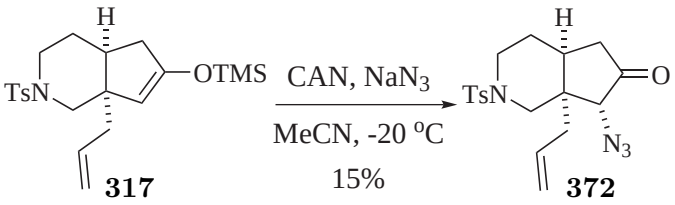
The initial attempts were made using the crude TMS enol ether obtained from the 1,4-addition of the alkyne containing side chain (Scheme 3.51). Treatment of the TMS enol ether with sodium azide followed by dropwise addition of a solution of CAN resulted in complete reaction of the TMS enol ether. Unfortunately, purification of the crude mixture did not result in isolation of the required α-azido ketone **370** and the 1,2,3-triazole **371** was obtained instead (Scheme 3.51).



Scheme 3.51: Azidation of enol ether **336**.

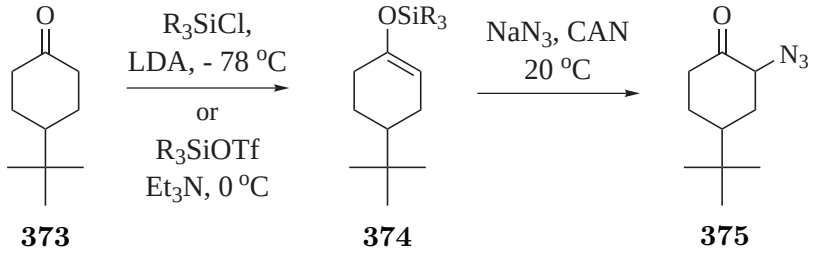
[136] Sommer, E.; Pincas, H. *Chem. Ber.* **1915**, *48*, 1963.
[137] Lemieux, R. U.; Ratcliffe, R. M. *Can. J. Chem.* **1979**, *57*, 1244-1251.
[138] Auberson, Y.; Vogel, P. *Tetrahedron* **1990**, *46*, 7019-7032.
[139] Magnus, P.; Barth, L. *Tetrahedron Lett.* **1992**, *33*, 2777-2780.
[140] Magnus, P.; Barth, L. *Tetrahedron* **1995**, *51*, 11075-11086.

In an attempt to prevent the 1,2,3-triazole formation, the TMS enol ether **317** was treated with sodium azide and CAN. However, the α-azido ketone **372** was isolated along with the ketone as a 1:4 in 15% yield (Scheme 3.52).



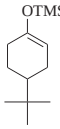
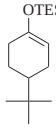
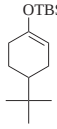
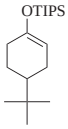
Scheme 3.52: Azidation of TMS enol ether **317**.

Due to the literature evidence[139,140] that silyl enol ethers can be converted into α-azido ketones it was decided to investigate the influence of the size and stability of the silyl group. 4-*tert*-Butylcyclohexanone was chosen as a suitable model for this study (Scheme 3.53 and Table 3.9).



Scheme 3.53: Model study to test the size and stability of the silyl protecting group.

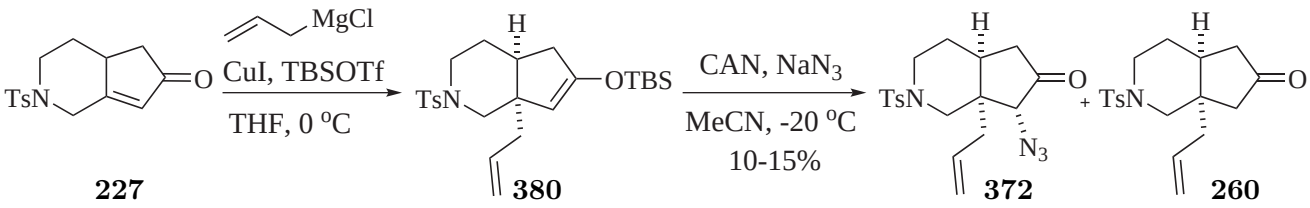
Four silyl protecting groups (TMS, TES, TBS and TIPS) were selected as candidates to carry out the model study as listed in Table 3.9. The silyl enol ethers were obtained using either LDA and TMSCl or TESCl to afford silyl enol ethers **376** and **377**, or Et_3N and TBSOTf or TIPSOTf to yield **378** and **379**. Following the synthesis of the enol ethers, further transformation to the α-azido ketones were investigated. As can be seen from Table 3.9 Entry 1, the TMS enol ether reacted to from only trace amounts of the α-azido ketone. The bulk of the material was the ketone **373**, resulting from hydrolysis of the TMS enol ether (Entry 1, Table 3.9). Moving to a slightly larger and more stable protecting group also resulted in detection of trace amounts of the desired α-azido ketone (Entry 2, Table 3.9). However, when changing to the bigger and more stable TBS group, formation of the α-azido ketone was observed as a 1:8 mixture in favour of the ketone (Entry 3). Finally, as predicted from the literature, the TIPS group proved the best delivering a mixture of **373** and **375** in an isolated yield of 65% (1:1 mixture of diastereomers), with a ratio of 6.7/1 in favour of the α-azido ketone **375** (Entry 4, Table 3.9).

Entry	Substrate	Ratio (Azide **375**:ketone **373**)
1	 **376**	traces of azide
2	 **377**	traces of azide
3	 **378**	1:8
4		6.7:1†

† Isolated yield 65%.

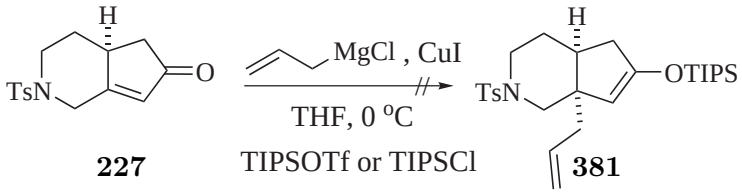
Table 3.9: Attempted azidation reactions using CAN and sodium azide.[132]

Although this study showed that the TIPS enol ether was more stable under azidation conditions and gave better conversion to the α-azido ketone, the substrate containing a TBS group was used in initial studies to establish whether the transformation was successful. Initially, the trapping of the copper enolate was pursued and resulted in an easy conversion to the enol ether **380**. TBSOTf was used instead of TBSCl because use of the latter resulted in hydrolysis to ketone (Scheme 3.54). Azidation of enol ether **380** to obtain the α-azido ketone **372** was investigated (Scheme 3.54). After several attempts, formation of the anticipated α-azido ketone was achieved and confirmed by IR analysis of the isolated matrial. It proved very difficult to improve the yield and in addtion separation of the α-azido ketone **372** from the starting ketone **260** gave rise to additional problems. Based on these observations, it was concluded that in order to achieve the synthesis of the α-azido ketone, an introduction of the more robust TIPS protecting group was essential (Scheme 3.54).



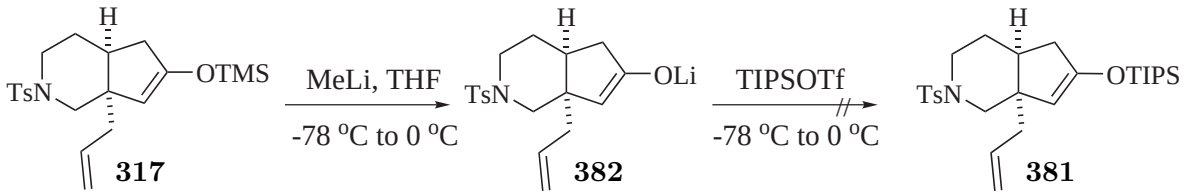
Scheme 3.54: Synthesis of the TBS enol ether **380**.

Incorporation of the TIPS protecting group was attempted by analogy with the installation of the TMS and the TBS groups. However, after numerous attempts to obtain the TIPS protected enol ether it was concluded that the reaction was not viable (Scheme 3.55).



Scheme 3.55: Trapping of the copper enolate to afford TIPS enol ether **381**.

Instead of attempting to trap the enolate directly as the TIPS enol ether after the 1,4-addition, it was thought that re-generation of the lithium enolate from the TMS enol ether and trapping with TIPSOTf might resolve the problem and allow the isolation of the TIPS enol ether **381**.[141] Synthesis of the TMS enol ether **317** was performed and the crude product was treated with MeLi to generate the lithium enolate **382** over a prolonged time. The lithium enolate **382** was cooled to −78 °C and treated with TIPSOTf. However, formation of the lithium enolate **382** and the subsequent trapping with TIPSOTf did not deliver the anticipated TIPS enol ether **381** (Scheme 3.56).[141]

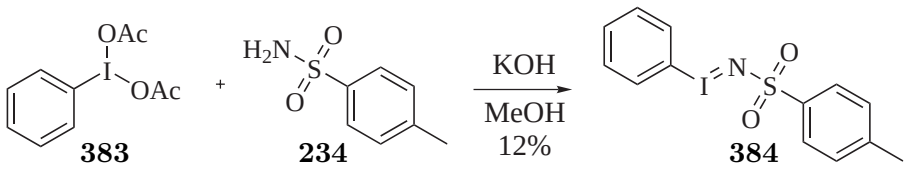


Scheme 3.56: Alternative route to achieve the TIPS enol ether **381**.[141]

Aziridination of silyl enol ethers using PhI=NTs

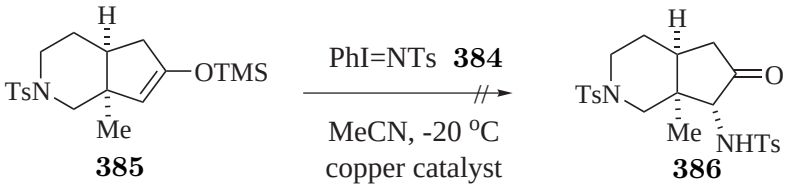
Finally, in analogy to the the Rubottom oxidation, aziridination of the silyl enol ether was attempted. Aziridination reactions are among the most useful transformations in organic chemistry and have been used widely because the resulting products are important building blocks for a variety of nitrogen-containing compounds, *i.e.* the preparation of amino acids, β-lactams and pyrrolidines.[142,143] The compound [*N*-(*p*-toluenelsulfonyl)imino]phenyliodinane (**384**), serves as a nitrenoid precursor and has been used for the direct aziridination of sily enol ethers to provide 2-aminoketones.[144] Before attempting the aziridination reaction, [*N*-(*p*-toluenelsulfonyl)imino]-phenyliodinane **384** was synthesised as outlined in Scheme 3.57. Treatment of *p*-toluenesulfonamide (**234**) with iodobenzene diacetate (**383**) in methanol and KOH yielded the nitrene precursor **384** in 12% yield (Scheme 3.57).

[141] Cesati. III, R. R.; de Armas, J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 96-101.
[142] Heuss, B. D.; Mayer, M. F.; Dennis, S.; Hossain, M. M. *Inorg. Chim. Acta.* **2003**, *342*, 301-304.
[143] Nakanishi, M.; Salit, A.-F.; Bolm, C. *Adv. Synth. Catal.* **2008**, *350*, 1835-1840.
[144] Evans, D. A.; Margaret M. Fau and, M. T. B. *J. Org. Chem.* **1991**, *56*, 6744-6746.



Scheme 3.57: Synthesis of [*N*-(*p*-toluenelsulfonyl)imino]phenyliodinane **384**.

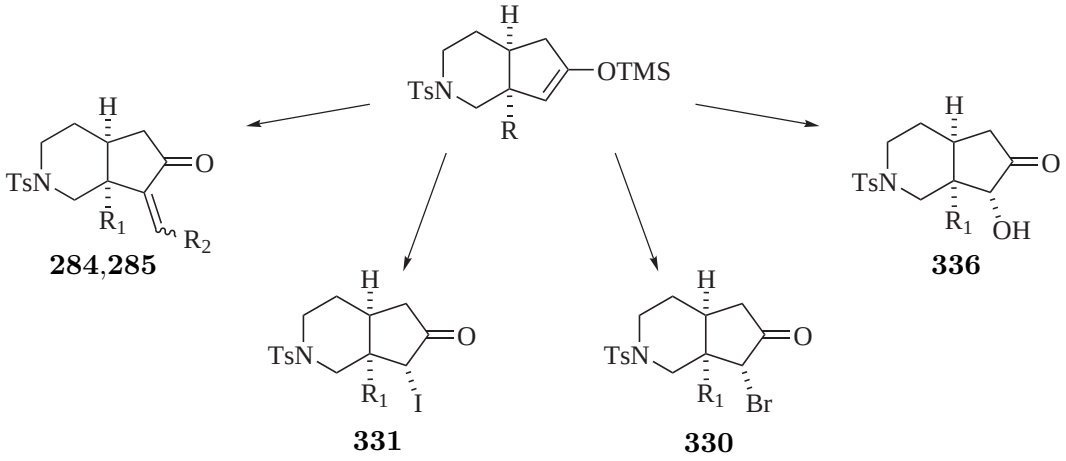
The TMS enol ether **385**, possessing a methyl substituent, was chosen to establish whether aziridination would allow the introduction of the second stereocentre. Due to time constraints, only two test reactions were carried out using $Cu(MeCN)PF_6$ and $Cu(acac)_2$ as catalysts. The reaction catalysed by $Cu(MeCN)PF_6$ resulted in isolation of the hydrolysed TMS enol ether, whereas the use of $Cu(acac)_2$ resulted in hydrolysis of the TMS enol ether along with another compound, which remains uncharacterised but is not the ketone (Scheme 3.58). More reactions have to be performed to establish whether the aziridination of TMS enol ethers is a feasible approach to progress the synthesis towards manzamine A (**1**).



Scheme 3.58: Aziridination of TMS enol ether **385**.

3.8 Summary and outlook

In summary, the 1,4-addition strategy for the total synthesis of the core manazmine A (**1**) has been examined, incorporating the conjugate addition reaction as one of the key steps. Further exploration of the synthesis of manzamine A (**1**) has been undertaken and has resulted in the examination of various methods by which the core structure could be synthesised. The 1,4-addition reaction was preferred to the initial approach based on the Diels-Alder reaction. Following successful 1,4-addition to the enone **227**, efforts were directed towards the introduction of the amine side chain. Several approaches were explored, including Mukaiyama aldol condensation, Rubottom oxidation, halogenation and amination of TMS enol ethers. These approaches resulted in the introduction of a carbon-carbon double bond **284** and **285**, iodine **331**, bromine **330** as well as a hydroxyl group **336**. However, despite the successful introduction of several groups in the α position of the ketone, further functionalisation to install the required nitrogen substituent remains an unsolved problem.


H
TsN
OTMS
R
H
TsN
O
R1
R2
284,285
H
TsN
O
R1
OH
336
H
TsN
O
R1
I
331
H
TsN
O
R1
Br
330

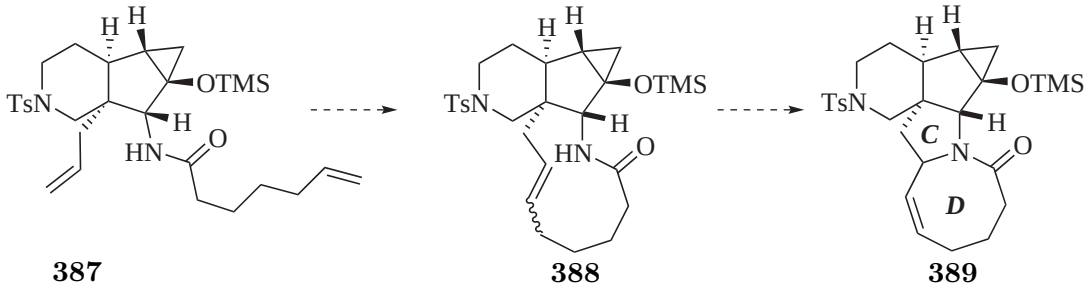
Chapter 4

Model Study on the CD Ring System of Manzamine A

This Chapter presents the efforts to construct the 11-membered macrocycle that would serve as a precursor for the CD ring system and would participate in the oxidative ring closure reaction. The Chapter is divided into three sections where the first section will focus on the project outline as well as the retrosynthetic analysis, the second section will present progress towards construction of the CD ring system and the final section will summarise progress and outlook.

4.1 Project outline

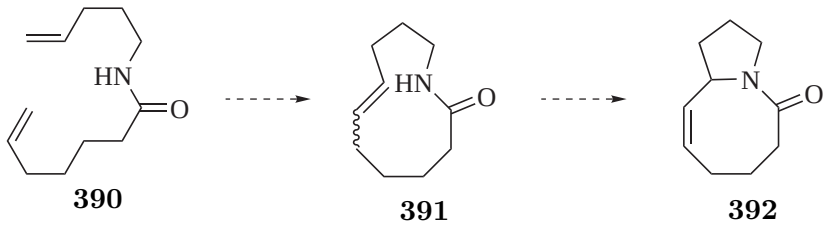
In order to test the viability of the RCM and oxidative ring closure sequence to form the CD ring system, a model system that could provide information about the construction of the CD ring system was investigated (Scheme 4.1).



387 **388** **389**

Scheme 4.1: Project outline.

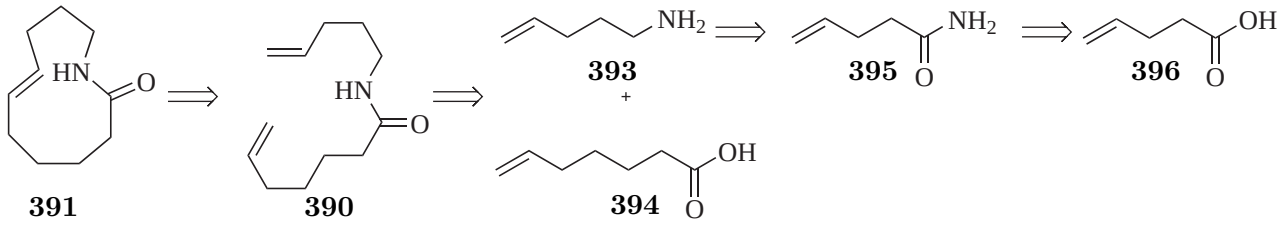
In order to model the CD ring system, the diene **390** was selected as an appropriate precursor for the 11-membered macrocycle **391**. Oxidative ring closure of the 11-membered macrocycle would afford the CD ring system **392** (Scheme 4.2).



Scheme 4.2: Model system to resemble the CD ring system.

4.2 Retrosynthetic analysis

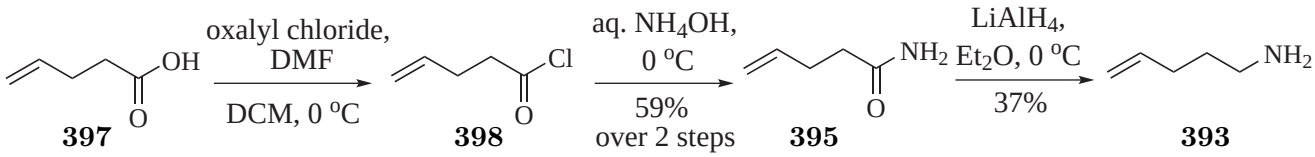
Retrosynthetically, the 11-membered macrocycle **391** can be obtained from the diene **390**, which can be synthesised from the amine **393** and the commercially available carboxylic acid **394**. Synthesis of the amine **393** can be accomplished by reduction of the amide **395** derived from the acid chloride which can be obtained from the commercially available carboxylic acid **396**.



Scheme 4.3: Retrosynthetic analysis of the CD ring system.

4.3 Synthesis of the diene

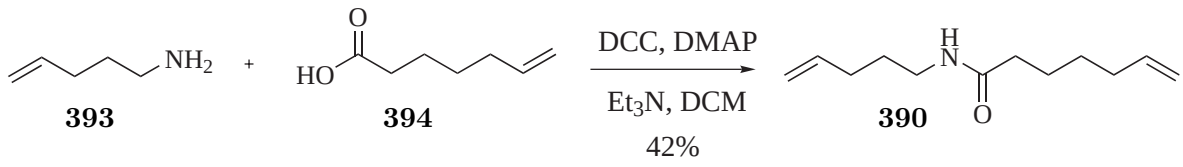
Before the diene **390** could be synthesised, the coupling partner for the carboxylic acid **394** - the amine **393** - was prepared. Synthesis of the amine **393** commenced with formation of the acid chloride **398**, using oxalyl chloride and a catalytic amount of DMF. The acid chloride **398** was used without any further purification and converted to the amide **395**, using an aqueous solution of ammonia, resulting in a 59% yield over the two steps. Reduction of the amide **395** employing lithium aluminium hydride provided the amine **393** in 37% yield.[145,146]



Scheme 4.4: Synthesis of amine **393**.

[145] Yang, Q.; Ney, J. E.; Wolfe, J. P. *Org. Lett.* **2005**, *7*, 2575-2578.
[146] Perlmutter, P.; Selajerern, W.; Vounatsos, F. *Org. Biomol. Chem.* **2004**, *2*, 2220-2228.

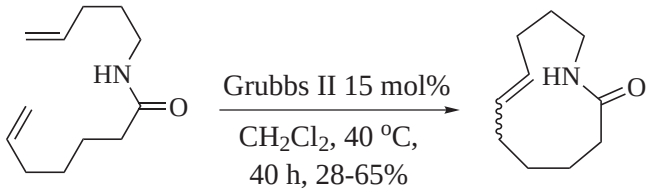
With the desired amine **393** in hand, attention turned to the coupling reaction to obtain the diene **390**. Standard peptide coupling conditions, employing DCC as the coupling reagent, yielded the diene **390** in 42% yield.[122]



393 **394** **390**

Scheme 4.5: Synthesis of diene **390**.

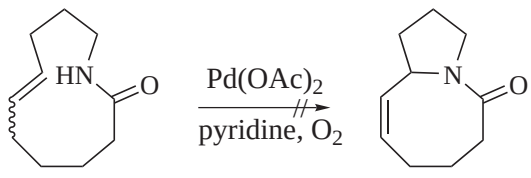
RCM of diene **390** using Grubbs' second generation catalyst afforded the 11-membered macrocycle **391** as a 1:1 mixture of *Z* and *E* alkene isomers. The low yield (28%) was improved to 65% by portionwise addition of the catalyst over a prolonged time. Purification of the product gave rise to a few problems, since ruthenium by-products were not separable from the product. To overcome this problem, the product was treated with the water soluble ruthenium coordinating ligand tris(hydroxymethyl)phosphine.[147] The amounts of ruthenium by-products were somewhat lowered but they were still present in the product (Scheme 4.6).



390 **391**

Scheme 4.6: RCM of diene **390**.

From the 11-membered macrocycle, attention turned towards the oxidative ring closure to give the CD ring system **392**. Initial attempts were performed using $Pd(OAc)_2$ in pyridine under an oxygen atmosphere. Despite the literature precedent for the oxidative ring closure under these conditions,[148,149] the desired bicyclic system **392** was not obtained (Scheme 4.7).



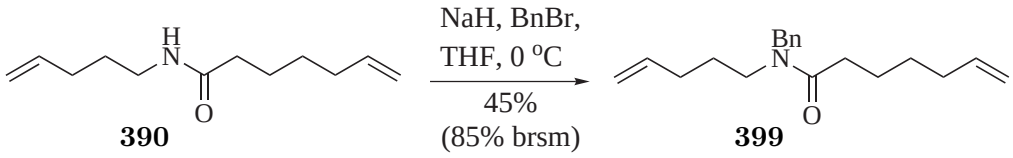
391 **392**

Scheme 4.7: Oxidative ring closing using $Pd(OAc)_2$.

[147] Maynard, H. D.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 4137-4140.
[148] Fix, S. R.; Brice, J. L.; Stahl, S. S. *Angew. Chem. Int. Ed.* **2002**, *41*, 164-166.
[149] Rogers, M. M.; Wendlandt, J. E.; Guzei, I. A.; Stahl, S. S. *Org. Lett.* **2006**, *8*, 2257-2260.

4.4 Alternative precursor for the oxidative ring closure

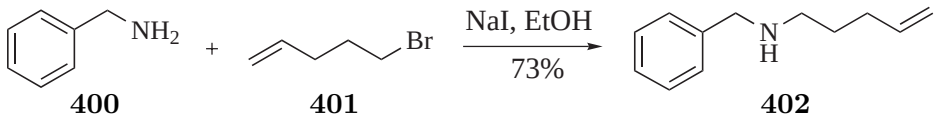
In an attempt to overcome the lack of reactivity of **391** in the oxidative ring closure reaction, protection of the amide with a benzyl group was expected to confer two advantages. Firstly, the polarity of the macrocycle would be different, and so removal of ruthenium by-products should be easier. Secondly the benzyl group has shown to have a positive effect when performing oxidative ring closure.[150]



390 **399**

Scheme 4.8: Benzylation of the amide **390**.[151]

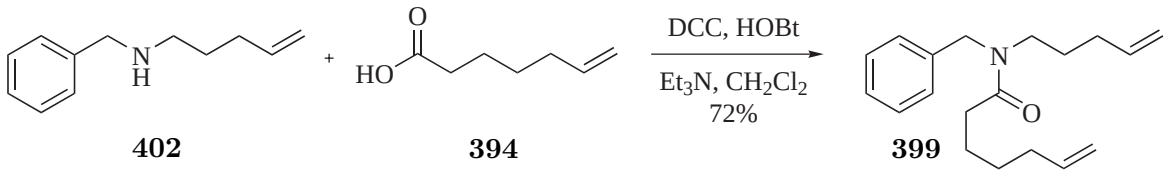
Benzylation of amide **390** yielded the protected amide **399** in 45% yield (Scheme 4.8).[151] Alternatively the benzylated amide **399** can be obtained starting from benzylamine (**400**) as depicted in Schemes 4.9 and 4.10. Alkylation of benzylamine (**400**) using 5-bromopentene (**401**) and sodium iodide in ethanol resulted in secondary amine **402** in 73% yield (Scheme 4.9).[122]



400 **401** **402**

Scheme 4.9: Synthesis of secondary amine **402**.[122]

Standard peptide coupling conditions, employing DCC and HOBt, afforded the diene **399** in 72% yield (Scheme 4.10).[122]

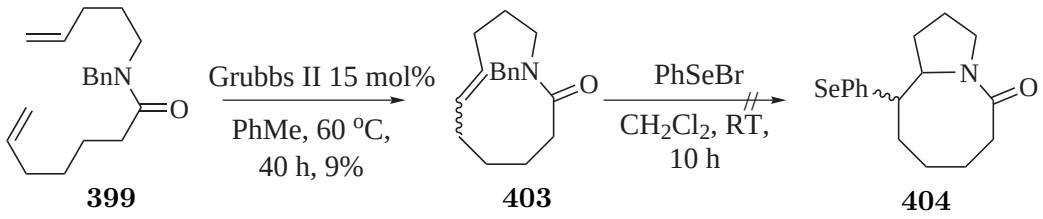


402 **394** **399**

Scheme 4.10: Synthesis of diene **399**.[122]

With the succesful synthesis of diene **399**, attention turned once again towards the key RCM reaction (Scheme 4.11). Despite several attempts to improve the yield, the cyclised product **403** was only obtained in only 9% yield (1:1 mixture of *Z* and *E* alkenes). With the anticipated macrocyclic amide **403** in hand electrophilic selenium-induced ring closure was explored.[150] Although the reaction time was increased no conversion to the CD ring system **404** was observed.

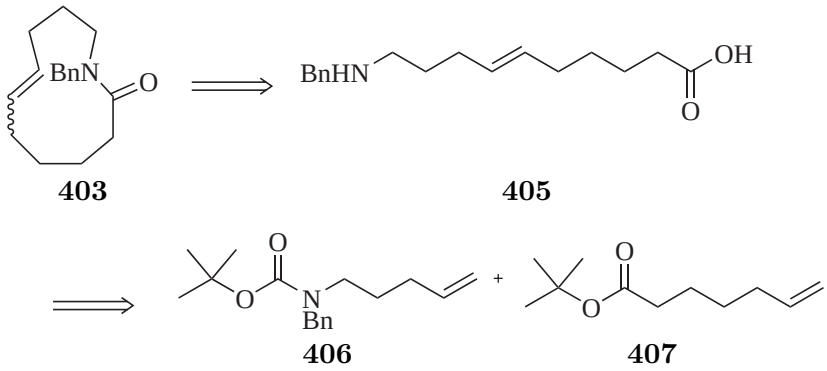
[150] Sudan, A.; Münch, W.; Nubbenmeyer, U. *J. Org. Chem.* **2000**, *65*, 1710-1720.



Scheme 4.11: RCM and oxidative ring closing to form macrocycle **404**.[122]

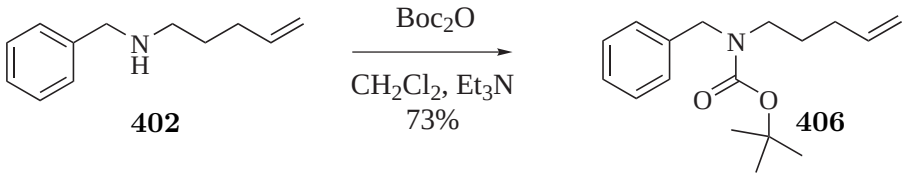
4.5 Cross-metathesis approach towards the macrocyclic amide

It was thought that the macrocycle **403** could be obtained from macrolactamisation of **405**. Cross-metathesis between the alkenes **406** and **407** would afford the precursor required for this macrolactamisation reaction (Scheme 4.12).



Scheme 4.12: Retrosynthetic analysis for the cross-metathesis approach.

Initially the amine **402** was protected with a Boc group affording the amide **406** in 73% yield (Scheme 4.13).[152]

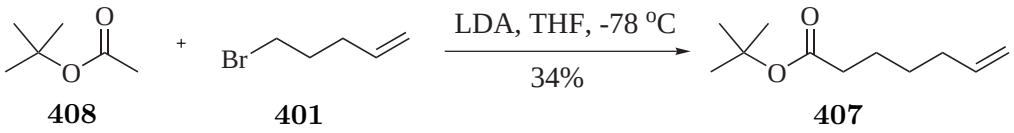


Scheme 4.13: Boc protection of amine **402**.[152]

The coupling partner **407** required for the cross-metathesis reaction was obtained from *tert*-butyl acetate. Treatment of *tert*-butyl acetate (**408**) with LDA followed by addition of 5-bromopentene (**401**) delivered **407** in 34% yield (Scheme 4.14).[153]

[152] Fischer, D.; Xin, Z.; Peters, R. *Angew. Chem. Int. Ed.* **2007**, *46*, 7704-7707.

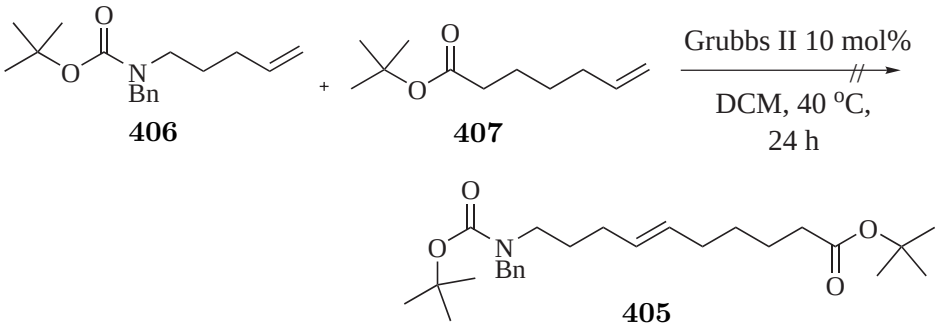
[153] Hester, J. B.; Gibson, J. K.; Buchanan, L. V.; Cimini, M. G.; Clark, M. A.; Emmert, D. E.; Glavanovich, M. A.; Imbordino, R. J.; LeMay, R. J.; McMillan, M. W.; Perricone, S. C.; Squires, D. M.; Walters, R. R. *J. Med. Chem.* **2001**, *44*, 1099-1115.



408 **401** **407**

Scheme 4.14: Synthesis of *tert*-butyl 6-heptenoate (**407**).[153]

After synthesis of the two coupling partners, the cross-metathesis reaction was investigated. Utilising an excess of *tert*-butyl 6-heptenoate (**407**), *tert*-butyl *N*-benzyl-(*N*-4-pentenyl)carbamate **406** and 10 mol% Grubbs' second generation catalyst, were added portionwise over 6 h, which resulted in an complex mixture of starting materials and products (Scheme 4.15).

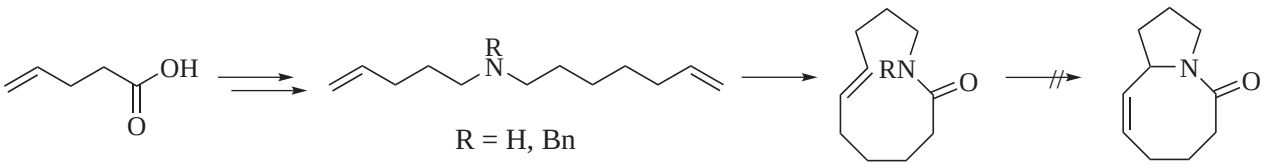


406 **407** **405**

Scheme 4.15: Cross-metathesis attempt to deliver **391**.

4.6 Summary and outlook

In summary, the synthesis of model systems required to study the oxidative ring closure reaction to obtain the CD ring system **392** has been presented. Synthesis of the macrocycle has been explored utilising two different routes and has resulted in preparation of the macrocycles **390** and **399**. In an attempt to overcome purification issues, an alternative approach relying on sequential cross-metathesis and macrolactamisation has been attempted. Initial studies on the oxidative ring closure reaction to obtain the CD ring **392** has been carried out. However, the ring-closed product has not been obtained using this route. Further investigations to study the oxidative ring closure are required to establish the viability of this reaction.

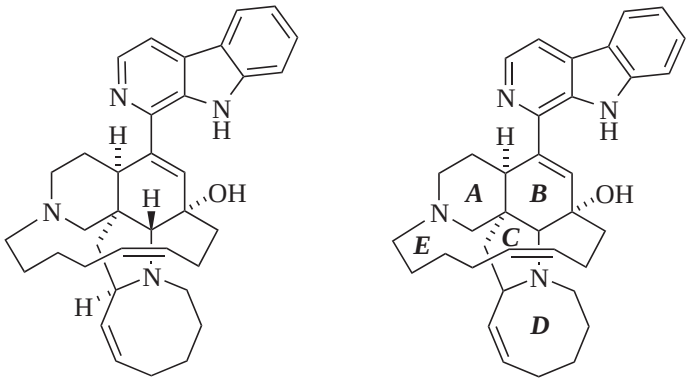


396 **390**,**399** **391**,**403** **392**

Chapter 5

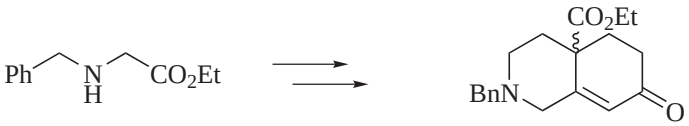
Conclusions

The objective of the work presented in this thesis has been a novel approach towards the total synthesis of manzamine A (**1**) with the main focus on the synthesis of ABC ring fragments as advanced intermediates.



manzamine A(1)

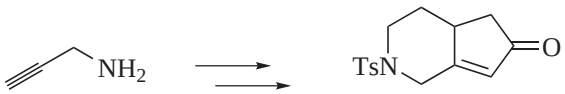
In Chapter 2 a Diels-Alder approach to the total synthesis of manzamnine A (**1**) was presented. The first intermediate goal was the construction of the bicyclic enone **183** that would serve as a model system to validate the proposed intermolecular Diels-Alder reaction. The AB ring **183** system was accessed commencing from *N*-benzylglycine ester **194** in just 5 steps.



198 **183**

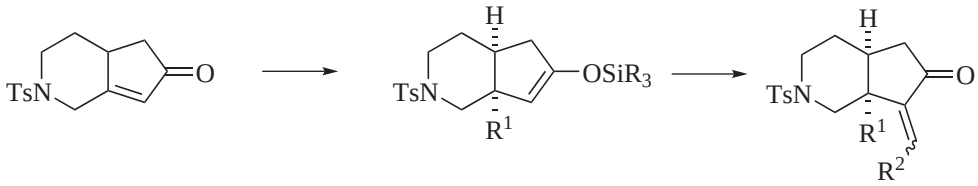
Parallel to an enantioselective route towards the synthesis of the bicyclic enone was explored. Following the successful synthesis of the bicyclic enone **183**, the Diels-Alder reaction was examined. Despite several attempts utilising various dienes, the Diels-Alder adduct was not obtained and an alternative bicyclic system was investigated. After accomplishing the synthesis of the simple AB fragment **227** from propargylamine (**232**), the Diels-Alder reaction was yet again investigated. Due to the failure of

the Diels-Alder reaction, this route towards the total synthesis of manzamine A (**1**) was abandoned.



232 **227**

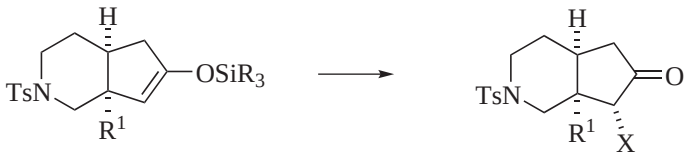
Chapter 3 introduced the conjugate addition approach to the total synthesis of manzamine A (**1**). This approach started off relying on the same intermolecular Diels-Alder reaction to access an advanced intermediate in the synthesis. Instead of the Diels-Alder approach, a 1,4-addition reaction followed by an aldol condensation reaction would afford an advanced intermediate of the total synthesis in fewer steps. Initial attempts to perform the 1,4-addition reaction and subsequent aldol condensation reaction afforded the dehydrated aldol condensation products **284** and **285**. Additional investigations to prevent the dehydration reaction taking place proved unsuccessful.



227 **284**,**285**

R^1 = allyl, triisopropyl-1-(pentynyl)silane R^2= C_4H_9

Thereafter, various methods for the introduction of a substituent in the α position to the ketone were investigated. These included alkylation using chloromethyl phenyl sulfide, halogenation using NBS or NCS, Rubottom oxidation using DMDO, direct amination using manganese(V) complexes, azidation using sodium azide and CAN as well as aziridination using PhI=NTs. Further investigations to synthesise α-amino ketones from TMS enol ethers are required to establish the use of PhI=NTs as amination reagent.

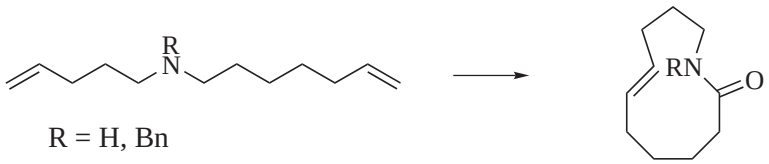


R = Me
R^1 = allyl, triisopropyl-1-(pentynyl)silane

330, X = Br, 74%
331, X = I, 98%
336, X = OH, 94%

Finally, Chapter 4 describes the efforts made towards the synthesis of a model system resembling the CD ring-system. The macrocyles **391** and **399** were easily synthesised commencing from 6-heptenoic acid. The RCM of diene **390** gave rise to isolation problems and it was decided to protect the amide with a benzyl group. Protecting the nitrogen should allow the oxidative ring-closing to take place, but the fused CD ring-system was not obtained. Due to time constraints, no further investigations to

form the CD ring-system were undertaken.



390,**399** **391**,**403**

Chapter 6

Experimental Section

6.1 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). Chemical shifts are reported in ppm. ^{1}H NMR spectra were recorded with $CDCl_3$ as solvent using ($\delta = 7.26$) as internal standard, and for ^{13}C NMR spectra, the chemical shifts are reported relative to the central resonance of $CDCl_3$ ($\delta = 77.16$). Signals in NMR spectra are described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), septet (sept), multiplet (m), broad (b) or combination of these, which refers to the spin-spin coupling pattern observed. DEPT 135, DEPT 90 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 recorded using a JASCO FT/IR 4100 using NaCl plates or KBr. Some 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 analyses were carried out on an Exeter Analytical Elemental Analyser EA 440. Melting points were recorded with an Electrothermal IA 9100 apparatus.

6.2 Chromatography

Column chromatography was performed under pressure using silica gel (Fluorochem LC60A, 35-70 micron) as solid support and HPLC-graded solvents 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).

6.3 Solvents and Reagents

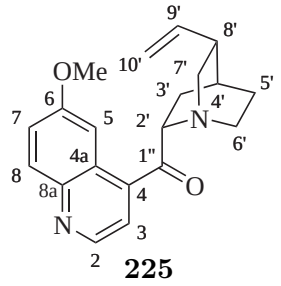
Liquid reagents were distilled prior to use if needed. All reagents were purchased from commercial suppliers and used without further purification unless otherwise stated.

6.4 General Reaction Conditions

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

6.5 Experimental Details

Quininone (225)



225

$C_{20}H_{22}N_2O_2$

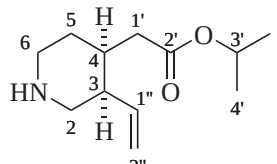
Mol. Wt.: 322.40

Anhydrous quinine (**158**) (1.00 g, 3.08 mmol), benzophenone (1.12 g, 7.72 mmol) and potassium *tert*-butoxide (866 mg, 6.16 mmol) were dissolved in toluene (20 mL) and heated to reflux for 6 h. The mixture was cooled to 0 °C and 2 M aqueous solution of hydrochloric acid (10 mL) was added to the orange viscous reaction mixture at such a rate that the temperature was maintained below 30 °C. The layers were separated and the organic phase was extracted with additional 2 M hydrochloric acid (3 × 20 mL). The combined aqueous extracts were cooled to 0 °C and basified by dropwise addition of concentrated ammonia solution. The aqueous phase was saturated with solid sodium chloride and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product. The crude compound was used directly in the synthesis of (3*R*, 4*S*)-4-isopropoxycarbonylmethyl-3-vinyl-piperidine **159** with no further purification. $R_f = 0.38$, Et_2O:acetone, 4:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.82 (d, 1H, $J = 5.5$ Hz, CH-C2), 8.02 (d, 1H, $J = 9.3$ Hz, CH-C8), 7.62-7.58 (m, 2H, CH-C6, CH-C3), 7.36 (1H, dd, $J = 9.3$, 2.8 Hz, CH-C7), 5.95 (1H, ddd, $J = 17.5$, 10.5, 7.4 Hz, CH-C9'), 5.04 (1H, d, $J = 10.5$ Hz, CH_2-C10'), 5.01 (1H, d, $J = 17.5$ Hz, CH_2-C10'), 4.16 (1H, dd, $J = 18.2$, 9.0 Hz, CH-C2'), 3.91 (3H, s, CH_3), 3.06 (1H,

m, CH_2-C6'), 2.89 (2H, m, CH_2-C7'), 2.60 (1H, dd, J = 14.0, 7.4 Hz, CH_2-C6'), 2.30 (2H, m, CH-C18, CH_2-C3'), 1.86 (1H, s, CH-C4'), 1.64 (3H, m, CH_2-C3', CH_2-C5'). IR (thin film) 3075 (w), 2937 (m), 2869 (m), 2858 (m), 1691 (s), 1618 (m) cm^{-1}. HRMS (EI) exact mass calculated for $C_{20}H_{22}N_2O_2$ $[M]^+$ m/z 322.1681, found m/z 322.1682.

The observed are in accordance with literature values.[154]

(3*R*, 4*S*)-4-isopropoxycarbonylmethyl-3-vinyl-piperidine (159)



159

$C_{12}H_{21}NO_2$

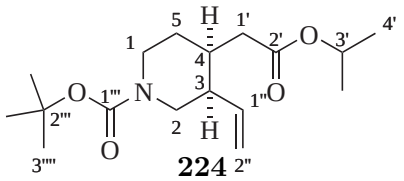
Mol. Wt.: 211.30

Potassium *tert*-butoxide (838 mg, 7.47 mmol) and isopropanol (3.2 mL, 4.2 mmol) were dissolved in THF (15 mL) and cooled to 0 °C. Oxygen gas was bubbled through the solution followed by dropwise addition of the quininone **225** (1.02 g, 2.99 mmol) at such a rate that the temperature was maintained below 20 °C. The reaction mixture was allowed to warm to room temperature over 3 h with continuous oxygen bubbling. The reaction mixture was cooled to 0 °C, glacial acetic acid (2 mL) was added and the yellow slurry was concentrated *in vacuo*. Water was added and the reaction mixture was basified by addition of a concentrated aqueous ammonia solution. The reaction mixture was extracted with ether (3 × 20 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude compound. The compound was purified by distillation (bp 124 − 126 °C at 22 mmHg) to yield the title compound **159** as a colorless oil (1.46 g, 38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.06 (1H, ddd, J = 17.5, 10.5, 10.5 Hz, CH-C1"), 5.14 (1H, dd, J = 10.5, 2.0 Hz, CH_2-C2"), 5.06 (1H, dd, J = 17.5, 2.0 Hz, CH_2-C2"), 5.02 (1H, sep, J = 6.3 Hz, CH-C3'), 3.02-2.95 (1H, m, CH_2-C2), 2.90-2.80 (2H, m, CH_2-C6), 2.67-2.58 (1H, m, CH_2-C2), 2.27-2.21 (1H, m, CH-C1'), 2.25-2.10 (4H, m, CH_2-C7, NH, CH-C3), 1.55-1.40 (2H, br m, CH_2-C5), 1.22 (6H, d, J = 6.3 Hz, CH_3-C4'). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 172.0 (C-C2'), 136.7 (CH-C1"), 116.5 (CH_2-C2"), 67.0 (CH-C3'), 50.9 (CH_2-C2), 45.6 (CH_2-C1'), 42.6 (CH-C4), 38.2 (CH_2-C1"), 35.3 (CH-C3), 28.5 (CH_2-C5), 21.5 (2 × CH_3-C10). IR (thin film) 3481 (br m), 2974 (m), 2929 (m), 2858 (m), 1685 (s), 1421 (m) cm^{-1}. HRMS (CI/Isobutane) exact mass calculated for $C_{12}H_{22}NO_2$ $[M+H]^+$ m/z 212.1651, found m/z 212.1650.

The observed data are in accordance with literature values.[154]

[154] Townsend, R. J. *Synthetic Studies Towards Manzamine A*, Thesis, University of Nottingham, 1999.

(3*R*, 4*S*) 4-Isopropoxycarbonylmethyl-3-vinyl-piperidine-1-carboxylic acid *tert*-butyl ester (224)



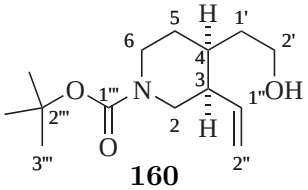
$C_{17}H_{29}NO_4$

Mol. Wt.: 311.42

The meroquinine ester **159** (7.9 g, 37 mmol) was dissolved in CH_2Cl_2 (40 mL) and cooled to 0 °C followed by the addition of triethylamine (6.7 mL, 48 mmol) and DMAP (45 mg, 0.37 mmol, 5 mol%). The mixture was allowed to stir at 0 °C for 15 min. after which di-*tert*-butyl dicarbonate (10.6 g, 48.6 mmol) was added. The reaction mixture was allowed to warm to room temperature over 18 h, then concentrated *in vacuo* to yield the crude compound. Purification by flash chromatography (petroleum ether:Et_2O, 2:1) yielded the title compound **224** as a pale yellow solid (10.8 g, 93%). R_f = 0.32, petroleum ether:Et_2O, 2:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.81 (ddd, 1H, J = 17.5, 10.5, 10.5 Hz, CH-C4'), 5.19-5.08 (2H, m, CH_2-C1"'), 5.01 (1H, sep, J = 6.3 Hz, CH-C2'), 4.09 (1H, br s, CH_2-C2), 3.93 (1H, br d, J = 13.5 Hz, CH_2-C1'), 3.04 (1H, dd, J = 13.5, 3.1 Hz, CH_2-C1'), 2.84 (1H, br s, CH_2-C2), 2.40-2.35 (1H, m, CH-C3), 2.30-2.05 (3H, m, CH-C4, CH_2-C1"), 1.52-1.49 (2H, m, CH-C5), 1.44 (9H, br s, 3 × CH_3-C3"'), 1.22 (6H, d, J = 6.3 Hz, 2 × CH_3-C3'). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 172.0 (C-C2'), 154.9 (C-C2"'), 135.1 (CH-C1"), 117.4 (CH_2-C2"), 79.3 (C-C2"'), 67.4 (CH-C3'), 48.8 (CH_2-C2), 43.4 (CH_2-C6), 42.3 (CH-C4), 38.1 (CH_2-C1"), 35.6 (CH-C3), 28.3 (3 × CH_3-C3"'), 27.2 (CH_2-C5), 21.7 (2 × CH_3-C4"). IR (thin film) 3440 (br m), 2978 (s), 2932 (m), 2861 (m), 1729 (s), 1694 (s), 1421 (m) cm^{-1}. HRMS (EI) exact mass calculated for $C_{17}H_{29}NO_4$ $[M]^+$ m/z 311.2097, found m/z 311.2098.

The observed data are in accordance with literature values.[154]

(3*R*, 4*S*)-4-(2-hydroxy-ethyl)-3-vinyl-piperidine-1-carboxylic acid *tert*-butyl ester (160)



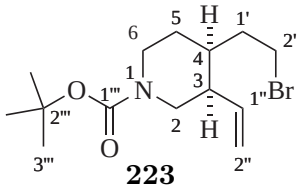
$C_{14}H_{25}NO_3$

Mol. Wt.: 255.35

A solution of the Boc protected meroquinine ester **224** (3.97 g, 12.7 mmol) in THF (30 mL) was added to a suspension of lithium aluminum hydride (724 mg, 19.0 mmol) in THF (5 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature over 1.5 h, then cooled to 0 °C and treated successively with water (2 mL) and aqueous 2 M sodium hydroxide solution (2 mL). The precipitated salts were filtered and washed with EtOAc (15 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to yield the crude compound. Purification by flash chromatography (petroleum ether:ether, 4:1) yielded the title compound **160** as a colorless oil (1.76 g, 66%). R_f = 0.29, petroleum ether:ether, 4:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.78 (1H, ddd, J = 17.5, 10.5, 10.5 Hz, CH-C1"), 5.10 (2H, m, CH_2-C1"), 4.11 (1H, br m, CH_2-C2), 3.95 (1H, br d, J = 13.5 Hz, CH_2-C6), 3.67 (2H, s, CH_2-C2'), 3.00 (1H, dd, J = 13.5, 3.1 Hz, CH_2-C6), 2.80 (1H, br s, CH_2-C2), 2.30 (1H, br s, CH-C3), 1.81 (1H, m, CH-C4), 1.46 (5H, m, CH_2-C5, CH_2-C1' OH), 1.44 (9H, s, 3 × CH_3-C3"'). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 155.1 (C-C1"'), 135.9 (CH-C1"), 118.8 (CH_2-C2"), 79.3 (C-C2"'), 60.3 (CH_2-C2'), 49.2 (CH_2-C2), 43.4 (CH_2-C6), 42.6 (CH-C3), 35.7 (CH_2-C1'), 35.1 (CH-C4), 28.4 (3 × CH_3-C3"'), 27.6 (CH_2-C5). IR (thin film) 3481 (br m), 2974 (m), 2929 (m), 2858 (m), 1685 (s), 1421 (m) cm^{-1}. HRMS (CI/Isobutane) exact mass calculated for $C_{14}H_{26}NO_3$ $[M+H]^+$ m/z 256.1913, found m/z 256.1910.

The observed data are in accordance with literature values.[154]

(3*R*, 4*S*-(4-(2-Bromo-ethyl)-3-vinyl-piperidine-1-carboxylic acid *tert*-butyl ester (223)



223

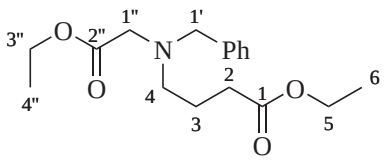
$C_{14}H_{24}BrNO_2$

Mol. Wt.: 318.25

To a solution of **160** (1.0 g, 3.9 mmol) and carbon tetrabromide (2.6 g, 7.8 mmol) in acetonitrile (15 mL) cooled to 0 °C, was added portionwise triphenylphosphine (2.0 g, 7.8 mmol). The solution was then left to warm to room temperature. The resulting mixture was filtered using EtOAc:petroleum ether (8 mL, 5:95), concentrated *in vacuo* to yield the crude compound. Purification by flash chromatography (petroleum ether:ether, 4:1) yielded the title compound **223** as a colorless oil (1.00 g, 81%).[89] R_f = 0.37, petroleum ether:ether, 4:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.78 (1H, ddd, J = 16.7, 14.9, 7.9 Hz, CH-C1"), 5.07 (2H, m, CH_2-C2"), 4.12-4.09 (1H, br m, CH_2-C6), 3.95 (1H, d, J = 12.2 Hz, CH_2-C2), 3.49-3.36 (2H, m, CH_2-C2'), 3.00 (1H, d, J = 12.2 Hz, CH_2-C2), 2.77 (1H, br s, CH_2-C6), 2.27 (1H, br s, CH-C3), 1.90-1.82 (1H, m, CH-C4), 1.78-1.65 (4H, m, CH_2-C5, CH_2-C1'), 1.39 (9H, s, 3 × CH_3-C13) ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 154.1 (C-C1"'), 135.3 (CH-C1"), 117.2 (CH_2-C2"), 79.3 (C-C2"'), 65.8 (CH_2-C2'), 49.4 (CH_2-C2), 43.3 (CH_2-C6), 42.1 (CH-C3), 37.0 (CH_2-C1'),

35.9 (CH-C4), 28.4 (3 × CH_3-C3"'), 26.8 (CH_2-C5). IR (thin film) 3005 (m), 2975 (s), 2857 (s), 1738 (s), 1693 (m) cm^{-1}. HRMS (EI) exact mass calculated for $C_{14}H_{24}BrNO_2$ $[M]^+$ m/z 317.0990, found m/z 317.0985

Ethyl 4-[benzyl(2"-ethoxy-2"-oxoethyl)amino]butanoate (196)



196

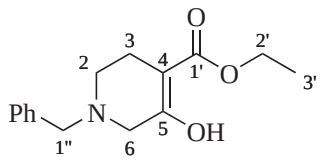
$C_{17}H_{25}NO_4$

Mol. Wt.: 307.38

To a solution of *N*-benzylglycine ethyl ester (**194**) (5.00 mL, 26.6 mmol) in 1,4-dioxane (60 mL) heated to 110 °C was added ethyl 4-bromobutyrate (**195**) (3.25 mL, 22.7 mmol). Et_3N (8.20 mL, 58.0 mmol) was subsequently added dropwise and the solution was stirred overnight at reflux. The mixture was cooled to 50 °C and toluene (20 mL) was added. The reaction mixture was further cooled 0 °C and left stirring for 1 h. The resulting precipitate was filtered and the filtrate was evaporated *in vacuo* to yield the crude product as a yellow oil. Purification by flash chromatography (petroleum ether:EtOAc, 5:1) yielded the title compound as a yellow oil (4.40 g, 63%; 93% based on recovered *N*-benzylglycine ethyl ester (**194**)).[61] R_f = 0.3, 8:1, petroleum ether:EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.37−7.23 (5H, m, CH-Ar), 4.17 (2H, q, J = 7.2 Hz, CH_2-C5), 4.13 (2H, q, J = 7.2 Hz, CH_2-C3"), 3.80 (2H, s, CH_2-C1"), 3.32 (2H, s, CH_2-C1'), 2.69 (2H, t, J = 6.8 Hz, CH_2-C4), 2.38 (2H, t, J = 7.2 Hz, CH_2-C2), 1.83 (2H, tt, J = 7.2, 6.8 Hz, CH_2-C3), 1.28 (3H, t, J = 7.2 Hz, CH_3-C6), 1.26 (3H, t, J = 7.2 Hz, CH_2-C4"). ^{13} C NMR (100 MHz, $CDCl_3$) δ (ppm): 173.8 (C-C1), 171.5 (C-C1'), 139.0 (C-Ar), 128.9 (2 × CH-Ar), 128.3 (2 × CH-Ar), 127.1 (CH-Ar), 60.3 (CH_2-C1'), 60.2 (CH_2-C5), 58.2 (CH_2-C3"), 54.0 (CH_2-C1"), 52.8 (CH_2-C4), 31.8 (CH_2-C2), 22.8 (CH_2-C3), 14.3 (CH_3-C6), 14.3 (CH_3-C4"). IR (thin film) 2981 (s), 1721 (s), 1603 (m), 1494 (m) cm^{-1}. HRMS (CI/Isobutane) exact mass calculated for $C_{17}H_{25}NO_4$ $[M+H]^+$ m/z 307.1784, found m/z 307.1786.

The data observed are in accordance with literature values.[58]

Ethyl 1-benzyl-5-hydroxy-1,2,3,6-tetrahydropyridine-4-carboxylate (201)



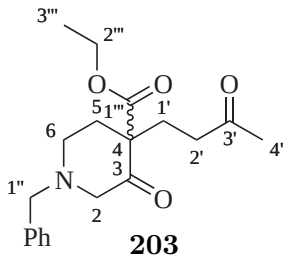
201

$C_{15}H_{19}NO_3$

Mol. Wt.: 261.32

To a solution of ethyl 4-[benzyl(2-ethoxy-2-oxoethyl)amino]butanoate (**196**) (4.0 g, 13 mmol) in toluene (40 mL) was added portionwise NaOEt (1.3 g, 20 mmol). The solution was heated to 85 °C and stirred for 2 h, after which it was left to cool to room temeprature followed by addition of toluene (20 mL) and Celite® (5 g). Acetic acid was added dropwise to neutralise the mixture, and the mixture was subsequently filtered. The filtrate was concentrated to half the volume after which a saturated solution of HCl in ethanol (15 mL) was added. The resultant residue was dissolved in 1 M NaOH (20 mL) solution and extracted with CH_2Cl_2 (5 × 20 mL). The combined organic layers were dried ($MgSO_4$), and evaporated *in vacuo* to yield the crude product (2.80 g, 82%) as a brown oil. Further purification was not necessary and the crude compound was used in the next reaction.[58] $R_f = 0.35$, 8:1, petroleum ether:EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.86 (1H, s, OH), 7.28−7.16 (5H, m, CH-Ar), 4.15 (2H, q, J = 7.0 Hz, CH_2-C2'), 3.53 (2H, s, CH_2-C1"), 3.03 (2H, s, CH_2-C6), 2.52 (2H, t, J = 5.6 Hz, CH_2-C2), 2.29-2.25 (2H, m, CH_2-C3), 1.22 (3H, t, J = 7.0 Hz, CH_3-C3'). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 171.0 (C-C5), 167.6 (C-C1'), 136.5 (C-Ar), 127.9 (2 × CH-Ar), 127.3 (2 × CH-Ar), 126.3 (CH-Ar), 95.2 (C-C4), 61.1 (CH_2-C2'), 59.3 (CH_2-C6), 53.2 (CH_2-C1"), 48.9 (CH_2-C2), 21.6 (CH_2-C3), 13.2 (CH_3-C3'). IR (thin film) 2927 (s), 1735 (s), 1664 (s), 1495 (m) cm^1. HRMS (CI/Isobutane) exact mass calculated for $C_{15}H_{19}NO_3$ $[M+H]^+$ m/z 262.1443, found m/z 262.1441. The data observed are in accordance with literature values.[58]

Ethyl 1-Benzyl-3-oxo-4-(3-oxo-butyl)-piperidine-4-carboxylate (203)



203

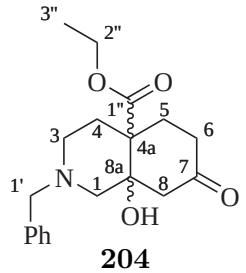
$C_{19}H_{25}NO_4$

Mol. Wt.: 331.41

To a solution of 1-benzyl-5-hydroxy-1,2,3,6-tetrahydro-pyridine-4-carboxylic acid ethyl ester (**201**) (1.0 g, 3.8 mmol) in toluene (20 mL) was added K_2CO_3 (735 mg, 5.32 mmol) followed by methyl vinyl

ketone (**202**) (450 μL, 5.32 mmol) and the solution was left stirring overnight at room temperature. Water (5 mL) was added the reaction and the resulting solution was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude compound. Purification by flash chromatography (petroleum ether:EtOAc 4:1 → 2:1) yielded the title compound as a colorless oil (942 mg, 75%). R_f = 0.33, petroleum ether:EtOAc, 4:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.26−7.15 (5 × CH, m, CH-Ar), 4.11 (2H, q, J = 7.2 Hz, CH_2-C2"'), 3.50 (1H, d, J = 13.2 Hz, CH_2-C2), 3.42 (1H, d, J = 13.2 Hz, CH_2-C2), 3.12 (1H, d, J = 15.7 Hz, CH_2-C1"), 2.90 (1H, d, J = 15.7 Hz, CH_2-C1"), 2.66 (1H, m, CH_2-C6), 2.55 (1H, dd, J = 10.0, 5.2 Hz, CH_2-C6), 2.52−2.46 (2H, m, CH_2-C5), 2.32 (1H, ddd, J = 16.4, 10.0, 5.6 Hz, CH_2-C2'), 2.05 (3H, s, CH_3-C4'), 2.00 (1H, ddd, J = 16.4, 10.0, 5.2 Hz, CH_2-C2'), 1.80 (1H, ddd, J = 15.4, 10.0, 5.6 Hz, CH_2-C1'), 1.59−1.50 (1H, m, CH_2-C1'), 1.14 (3H, t, J = 7.2 Hz, CH_3-C3"'). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 207.5 (C-C12), 204.7 (C-C4), 171.0 (C-C7), 137.1 (C-Ar), 128.9 (2 × CH-Ar), 128.4 (2 × CH-Ar), 127.4 (CH-Ar), 62.4 (CH_2-C6), 61.5 (CH_2-C8), 56.6 (CH_2-C5), 53.5 (C-C3), 48.7 (CH_2-C1), 38.6 (CH_2-C11), 31.7 (CH_2-C2), 29.7 (CH_3-C13), 27.2 (CH_2-C10), 14.1 (CH_3-C9). IR (thin film) 2934 (s), 1750 (s), 1496 (m) cm^{-1}. HRMS (EI) exact mass calculated for $C_{19}H_{25}NO_4$ $[M]^+$ m/z 331.1784, found m/z 331.1783.

Ethyl 2-Benzyl-8a-hydroxy-7-oxo-octahydro-isoquinoline-4a-carboxylate (204)



204

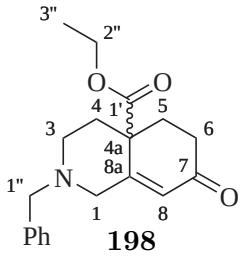
$C_{19}H_{25}NO_4$

Mol. Wt.: 331.41

A solution of ethyl 1-benzyl-3-oxo-4-(3-oxo-butyl)-piperidine-4-carboxylate (**203**) (1.8 g, 5.4 mmol) in dry ethanol (25 mL) was cooled to 0 °C and then NaOEt (100 mg, 1.47 mmol) was added. The resulting mixture was left stirring overnight. Addition of a saturated aqueous NH_4Cl solution (5 mL) was followed by extraction with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude compound. Purification by flash chromatography (petroleum ether: EtOAc 2:1 → 1:1) yielded the title compound **204** as a brown oil (1.39 g, 77%) as a single diastereomer. R_f = 0.54, petroleum ether:EtOAc, 2:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.17−7.09 (5H, m, 5 × CH-Ar), 4.42 (1H, br s, OH), 4.15−4.05 (2H, m, CH_2-C2"), 3.38−3.30 (2H, m, CH_2-C1'), 2.87−2.77 (1H, m, CH_2-C3), 2.53−2.43 (2H, m), 2.38−2.08 (7H, m), 1.91−1.80 (2H, m), 1.14 (t, 3H, J = 7.1 Hz, CH_3-C3"). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 209.4 (C-C6), 176.7 (C-C13), 137.9 (C-C11), 128.8 (2 × CH-C11), 128.4 (2 × CH-C11), 127.3 (CH-C11), 65.9 (CH_2-C14), 62.2 (CH_2-C9), 61.5 (C-C8), 61.4 (CH_2-C10), 58.4 (CH_2-C1) 50.1 (C-C3), 49.9 (CH_2-C7), 48.5

(CH_2-C5), 36.8 (CH_2-C2), 29.3 (CH_2-C4), 12.1 (CH_3-C15). IR (thin film) 3464 (br m), 3028 (m), 2958 (m), 2808 (m), 1718 (s), 1453 (m) cm^{-1}. HRMS (CI/Isobutane) exact mass calculated for $C_{19}H_{26}NO_4$ $[M+H]^+$ m/z 332.1862, found m/z 332.1865.

Etyl 2-Benzyl-7-oxo-1,3,4,5,6,7-hexahydro-2*H*-isoquinoline-4a-carboxylate (198)



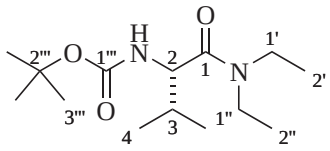
198

$C_{19}H_{23}NO_3$

Mol. Wt.: 313.39

Ethyl 2-Benzyl-8a-hydroxy-7-oxo-octahydro-isoquinoline-4a-carboxylate (**204**) (0.1 g, 0.30 mmol) was dissolved in CH_2Cl_2 (5 mL) followed by the addition of CF_3CO_2H (58 μL, 0.75 mmol). The mixture was left stirring overnight after which the reaction was quenched by the addition of a saturated aqueous solution of K_2CO_3 (10 mL) followed by extraction with ether (3 × 20 mL). The combined organic phases were dried ($MgSO_4$), and concentrated *in vacuo* to yield the crude compound. Purification by flash chromatography (petroleum ether: EtOAc 3:1 → 2:1) yielded the title compound **198** as a brown oil (27.6 mg, 29%, 99% based on recovered starting material). $R_f = 0.29$, petroleum ether:EtOAc, 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.26−7.19 (5H, m, 5 × CH-Ar), 5.92 (s, 1H, CH-C8), 4.21−4.14 (m, 2H, CH_2-C2'), 3.58 (1H, d, J = 13.0 Hz, CH_2-C1"), 3.51 (1H, d, J = 13.0 Hz, CH_2-C1"), 3.39 (1H, dd, J = 13.8, 1.5 Hz, CH_2-C1), 3.01 (1H, dd, J = 13.8, 1.4 Hz, CH_2-C1), 2.85 (1H, br d, J = 12.0 Hz, CH_2-C6), 2.36−2.20 (4H, m, 2 × CH_2-C3, CH_2-C4, CH_2-C5), 2.15 (1H, dt, J = 12.0, 2.2 Hz, CH_2-C6), 1.93−1.86 (m, 1H, CH_2-C4), 1.60 (1H, dt, J = 13.1, 4.1 Hz, CH_2-C5), 1.22−1.17 (3H, m, CH_3-C3'). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 198.8 (C-C7), 172.9 (C-C1'), 163.7 (C-C8a), 137.0 (C-Ar), 129.1 (2 × CH-Ar), 128.4 (2 × CH-Ar), 127.4 (CH-Ar), 126.9 (CH-C8), 62.7 (CH_2-C1"), 61.7 (CH_2-C2'), 58.5 (CH_2-C1), 50.4 (CH_2-C6), 47.2 (C-C4a), 38.9 (CH_2-C3), 34.4 (CH_2-C4), 29.7 (CH_2-C5), 14.3 (CH_3-C3'). IR (thin film) 2925 (s), 2853 (m), 2802 (m), 1725 (s), 1680 (S) cm^{-1}. HRMS (EI) exact mass calculated for $C_{19}H_{24}NO_3$ $[M]^+$ m/z 314.1756, found m/z 314.1756.

(*S*)-*tert*-Butyl 1-(diethylamino)-4-methyl-1-oxopentan-2-ylcarbamate (209)



$C_{14}H_{28}N_2O_3$

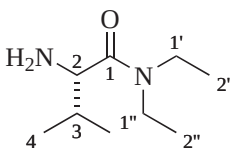
Mol. Wt.: 272.38

209

To a solution *N*-Boc-valine (**208**) (1.0 g, 4.6 mmol) in THF (10 mL) at room temperature was added Et_3N (0.43 mL, 4.6 mmol). The resulting mixture was cooled to −30 °C and ethyl chloroformate was added dropwise (0.43 mL, 4.6 mmol) and left stirring at −30 °C. After 40 min. the resulting white suspension was treated with Et_2NH (0.95 mL, 9.2 mmol) and the mixture was left at −30 °C for 30 min. after which it was allowed to warm to room temperature. The solvent was removed *in vacuo* after which the residue was redissolved in CH_2Cl_2 and washed with 0.1 M HCl, 7% aqueous K_2CO_3 solution (15 mL), water (15 mL), and brine (15 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude compound. Purification by flash chromatography (petroleum ether:EtOAc, 5:1 → 1:1) yielded the title compound **209** as a colorless oil (2.56 g, 68%).[68] R_f = 0.8, petroleum ether:EtOAc, 1:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.25 (1H, d, J = 9.2 Hz, NH), 4.30 (1H, dd, J = 9.4, 6.6 Hz, CH-C2), 3.58 (1H, dq, J = 14.1, 7.1 Hz, CH_2-C1'), 3.44 (1H, dq, J = 14.4, 7.2 Hz, CH_2-C1"), 3.36 (1H, dq, J = 14.4, 7.2 Hz, CH_2-1"), 3.16 (1H, dq, J = 14.1, 7.1 Hz, CH_2-C1'), 1.86 (1H, sep, J = 6.7 Hz, CH-C3), 1.36 (9H, s, 3 × CH_3-C3"'), 1.17 (3H, t, J = 7.2 Hz, CH_3-C2'), 1.05 (3H, t, J = 7.2 Hz, CH_3-C2'), 0.87 (3H, d, J = 6.7 Hz, CH_3-C4), 0.85 (3H, d, J = 6.7 Hz, CH_3-C4). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 174.4 (C-C1), 155.8 (C-C1"'), 79.4 (C-C2"'), 55.0 (CH-C2), 42.0 (CH_2-C1'), 40.2 (CH_2-C1"), 32.2 (CH-C3), 28.4 (3 × CH_3-C3"'), 19.6 (CH_3-C4), 17.5 (CH_3-C4), 14.6 (CH_3-C2'), 13.0 (CH_3-C2"). IR (thin film) 3438 (m), 3303 (m), 2972 (s), 2874 (s), 1715 (s), 1637 (s) cm^{-1}. HRMS (CI/Isobutane) exact mass calculated for $C_{15}H_{29}N_2O_3$ $[M+H]^+$ m/z 273.2178, found m/z 273.2179

The data observed are in accordance with literature values.[68]

(*S*)-2-Amino-*N,N*-diethyl-3-methylpentanamide (210)



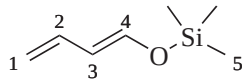
$C_9H_{20}N_2O$

Mol. Wt.: 172.27

210

To a solution (*S*)-*tert*-butyl 1-(diethylamino)-4-methyl-1-oxopentan-2-ylcarbamate (**209**) (62 mg, 0.23 mmol) in CH_2Cl_2 (5 mL) was added CF_3CO_2H (26 μL, 0.34 mmol). After stirring overnight the reaction was diluted with CH_2Cl_2 (15 mL) and washed with an aqueous 7% K_2CO_3 solution (2 × 25 mL), dried ($MgSO_4$), and concentrated *in vacuo* to yield the crude compound. The crude compound (38.1 mg, 97%) was ≥98% pure by ^{1}H NMR and was used without further purification.[68] R_f = 0.3, EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.61 (1H, dq, J = 14.1, 7.0 Hz, CH_2-C1'), 3.38 (1H, dq, J = 14.3, 7.1 Hz, CH_2-C1"), 3.23 (1H, d, J = 6.0 Hz, CH-C2), 3.15 (1H, dq, J = 14.3, 7.1 Hz, CH_2-C1"), 3.07 (1H, dq, J = 14.1, 7.0 Hz, CH_2-C1'), 1.80 (1H, sep, J = 6.7 Hz, CH-C3), 1.48 (2H, s, NH_2), 1.11 (3H, t, J = 7.0 Hz, CH_3-C2'), 1.02 (3H, t, J = 7.1 Hz, CH_3-C2"), 0.85 (3H, d, J = 6.7 Hz, CH_3-C4), 0.84 (3H, d, J = 6.7 Hz, CH_3-C4). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 174.4 (C-C2), 56.6 (CH-C1), 41.7 (CH-C8), 40.4 (CH_2-C3), 32.5 (CH_2-C5), 20.1 (CH_3-C9), 17.2 (CH_3-C9), 14.8 (CH_3-C4), 13.0 (CH_3-C6). IR (thin film) 3375 (m), 3303 (m), 2968 (s), 1709 (s) cm^{-1}. HRMS (CI/Isobutane) exact mass calculated for $C_9H_{21}N_2O$ $[M+H]^+$ m/z 173.1654, found m/z 173.1655. The data observed are in accordance with literature values.[68]

(*E*)-(Buta-1,3-dienyloxy)trimethylsilane (212)



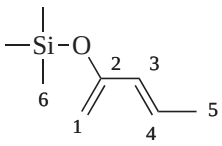
212

$C_7H_{14}OSi$

Mol. Wt.: 142.27

To a solution of sodium iodide (15.2 g, 102 mmol) in acetonitrile (10 mL) was added dropwise to a solution of crotonaldehyde (6.8 mL, 82 mmol), chlorotrimethylsilane (13.0 mL, 102 mmol) and triethylamine (14.2 mL, 102 mmol) in dry petroleum ether (40 mL) at room temperature. The resulting mixture was left to stir overnight and then heated to 40 °C for 4 h. The mixture was poured onto ice water (100 mL) and extracted with petroleum ether (3 × 25 mL). The combined organic layers were washed with aqueous saturated NH_4Cl until neutral, dried (Na_2SO_4) and distilled. (bp 59 − 62 °C at 60 mmHg; lit. 56 °C at 60 mmHg) to yield the title compound **212** as a colorless liquid (5 mL, 62%).[70] ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.53 (1H, d, J = 11.7 Hz, CH-C4), 6.21 (1H, ddd, J = 16.9, 11.0, 10.3 Hz, CH-C2), 5.71 (1H, dd, J = 11.7, 11.0 Hz, CH-C3), 4.98 (1H, dd, J = 16.9, 1.8 Hz, CH_2-C1), 4.81 (1H, dd, J = 10.3, 1.8 Hz, CH_2-C1), 0.21 (9H, s, CH_3-C5). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 143.1 (CH-C4), 132.7 (CH-C2), 113.8 (CH_2-C1), 111.5 (CH-C3), 1.0 (3 × CH_3-C5). The data observed are in accordance with literature values.[70]

(*E*)-(Penta-1,3-dien-2-yloxy)trimethylsilane (214)



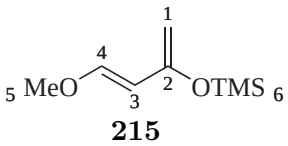
$C_8H_{16}OSi$

Mol. Wt.: 156.30

214

At −78 °C under an atmosphere of argon, *n*-butyllithium in hexane (2.6 mL, 2.5 M, 6.5 mmol) was added to a solution of diisopropylamine (908 μL, 6.47 mmol) in THF (10 mL). After stirring for 30 min., chlorotrimethylsilane (1.50 mL, 12.0 mmol) was added, followed by dropwise addition of 3-penten-2-one (**216**). The resulting solution was left stirring at −78 °C for 30 min. after which the reaction was quenched by the addition of NEt_3 and a saturated aqueous solution of $NaHCO_3$ (15 mL). The mixture was allowed to warm to room temperature and extracted with cold petroleum ether (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and the solvents were distilled off (bp 40 − 60 °C at 200 mmHg) to yield the title compound **214** as a colorless liquid (5 mL, 62%).[75] ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.92 (2H, m, CH-C4, CH-C3), 4.20 (2H, s, CH_2-C1), 1.76 (3H, d, J = 5.8 Hz, CH_3-C5), 0.22 (9H, s, 3 × CH_3-C6). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 154.9 (C-C2), 128.9 (CH-C4), 126.5 (CH-C3), 93.7 (CH_2-C1), 17.5 (CH_3-C5), 0.49 (3 × CH_3-C6).
The data observed are in accordance with literature values.[75]

(*E*)-(4-Methoxybuta-1,3-dien-2-yloxy)trimethylsilane (215)



215

$C_8H_{16}O_2Si$

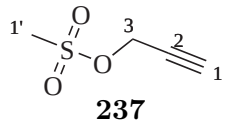
Mol. Wt.: 172.30

Anhydrous LiBr (8.85 g, 102 mmol) was dissolved in THF (20 mL) and cooled to −15 °C. Chlorotrimethylsilane (9.70 mL, 76.4 mmol) and *E*-4-methoxy-but-3-en-2-one (**217**) (5.0 mL, 51 mmol) were added gradually and the mixture was stirred for 15 min. Triethylamine (10.6 mL, 76.4 mmol) was added to the solution, and stirring was continued for another hour. The mixture was heated to 40 °C for 24 h. The mixture was then transferred with 30 mL of cold (4 °C) petroleum ether into a separating funnel loaded with ice (15 g), a cold aqueous solution of $NaHCO_3$ (15 mL), cold brine (15 mL), and another 30 mL cold petroleum ether. The organic layer was separated and the aqueous layer was

extracted with cold petroleum ether (2 × 30 mL). The combined organic layers were washed with cold brine (15 mL), cold water (5 × 15 mL) and dried ($MgSO_4$). After filtration, concentration (400 mmHg at 40 °C) afforded the crude compound. The compound was purified by distillation (bp 65 – 67 °C at 10 mmHg; lit.[76] bp 65 – 70 °C 7 mmHg), to yield the title compound **215** as a colorless liquid (4.9 g, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.83 (1H, d, J = 12.4 Hz, CH-C4), 5.35 (1H, d, J = 12.4 Hz, CH-C3), 4.11 (1H, s, CH_2-C1), 4.07 (1H, s, CH_2-C1), 3.58 (3H, s, CH_3-C5), 0.23 (9H, s, 3 × CH_3-C6). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 153.9 (C-C2), 150.3 (CH-C4), 103.0 (CH-C3), 91.9 (CH_2-C1), 56.4 (CH_3-C5), 0.03 (3 × CH_3-C6). IR (thin film) 2973 (m), 2942 (m), 963 (s), 933 (m), 920 (m) cm^{-1}. HRMS (CI/Isobutane) exact mass calculated for $C_8H_{17}O_2Si$ $[M+H]^+$ m/z 173.0920, found m/z 173.0999.

These data observed are in accordance with literature values.[70]

Methanesulfonic acid 2-propynyl ester (237)



237

$C_4H_6O_3S$

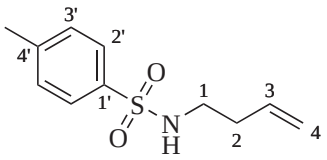
Mol. Wt.: 134.15

Methanesulfonyl chloride (1.70 mL, 22.3 mmol) was added slowly to a pre-cooled solution of 2-propynol (**236**) (1.00 mL, 17.2 mmol) and triethylamine (3.6 mL, 26 mmol) in CH_2Cl_2 (10 mL) at 0 °C and the mixture was left stirring for 2 h. Aqueous HCl (10 mL, 1 M) was added and the organic solution was washed with a 1 M aqueous HCl solution (2 × 10 mL), saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL), then dried ($MgSO_4$), and concentrated *in vacuo* to yield the crude compound. NMR analysis of the crude compound revealed that this was relatively pure and so it was used directly for the synthesis of *N*-(but-3-enyl)-4-methyl-*N*-(prop-2-ynyl)benzenesulfonamide (**235**).[159] ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.84 (2H, d, J = 2.5 Hz, CH_2-C3), 3.12 (3H, s, CH_3-C1'), 2.69 (1H, t, J= 2.5 Hz, CH-C1). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 78.0 (C-C2), 75.8 (CH-C1), 57.3 (CH_2-C3), 39.1 (CH_3-C1').

These data observed are in accordance with literature values.[159]

[159] Jackson, W. R.; Perlmutter, P.; Smallridge, A. J. *Aust. J. Chem.* **1988**, *41*, 1201-1208.

N-(3-Butenyl)-4-methylbenzenesulfonamide (239)



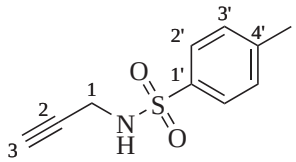
239

$C_{11}H_{15}NO_2S$

Mol. Wt.: 225.31

To a solution of tosylamide (**239**) (2.00 g, 11.7 mmol) and K_2CO_3 (1.60 g, 11.7 mmol) in acetone (20 mL) was added 4-bromo-1-butene (0.6 mL, 6 mmol), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo*. EtOAc (20 mL) and water (10 mL) were added and the aqueous was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine, then dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude compound. Purification by flash chromatography (petroleum ether:EtOAc, 6:1) yielded the title compound **239** as a colorless oil (662 mg, 50%).[94,95] R_f = 0.4, petroleum ether:EtOAc, 6:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.77 (2H, d, J = 8.2 Hz, CH-C3'), 7.35 (2H, d, J = 8.2 Hz, CH-C2'), 5.65 (1H, ddt, J = 17.1, 10.3, 6.9 Hz, CH-C3) 5.08-4.95 (2H, m, CH_2-C4) 4.37 (1H, t, J = 5.5 Hz, NH), 3.05 (2H, dt, J = 6.7, 6.6 Hz, CH_2-C1), 2.47 (3H, s, CH_3), 2.23-2.15 (2H, m, CH_2-C2). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 143.5 (C-C4'), 136.8 (C-C1'), 134.2 (CH-C3), 129.8 (2 × CH-C2'), 127.2 (2 × CH-C3'), 118.1 (CH_2-C4), 42.1 (CH_2-C1), 33.6 (CH_2-C2), 17.7 (CH_3). IR (Neat) 3582, 3280, 1215 cm^{-1}. HRMS (EI) exact mass calculated for $C_{11}H_{15}NO_2S$ $[M]^+$ m/z 225.0823, found m/z 225.0824.

4-Methyl-*N*-(prop-2-ynyl)benzenesulfonamide (234)



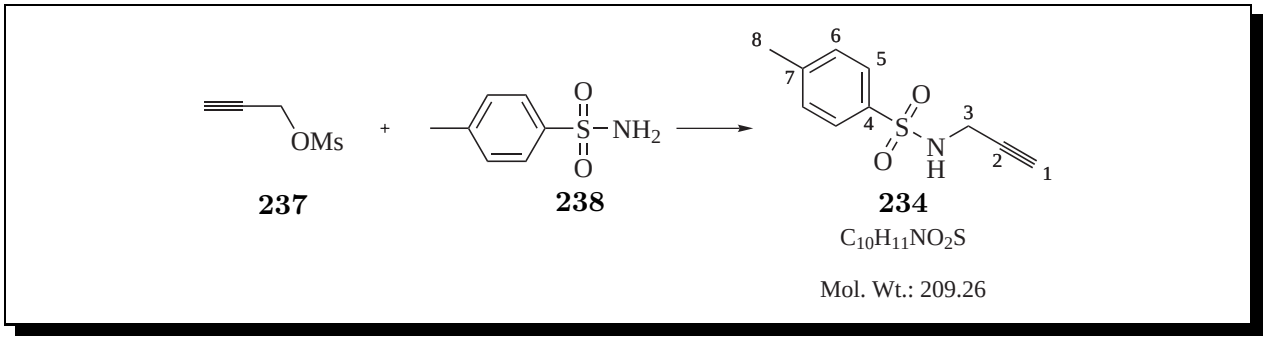
234

$C_{10}H_{11}NO_2S$

Mol. Wt.: 209.26

1st method: *para*-Toluenesulfonyl chloride (284 mg, 1.49 mmol) was dissolved in THF (3 mL) and pyridine (125 μL, 1.54 mmol) was added. The solution was cooled to 0 °C followed by dropwise addition of propargylamine (**232**) (100 μL, 1.45 mmol, at such a rate that the temperature was maintained below 15 °C. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. A 2 M aqueous NaOH (5 mL) solution was added and stirring was continued for another 2 h. The resulting solution was extracted with EtOAc (3 × 20 mL), the combined organic layers were washed

with brine (15 mL), dried ($MgSO_4$ and activated carbon), filtered through silica gel, and concentrated *in vacuo* to yield the crude compound. Purification by flash chromatography (petroleum ether:EtOAc, 4:1) yielded the title compound **234** as a colorless solid (307 mg, quant).[95]



237 **238** **234**

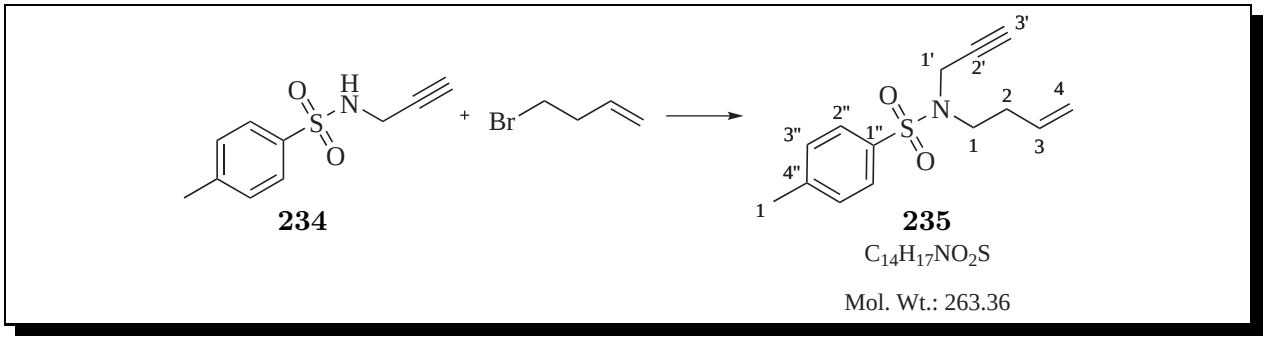
$C_{10}H_{11}NO_2S$

Mol. Wt.: 209.26

2nd method: KOH (1.30 g, 23.5 mmol) was dissolved in DMF (30 mL) at 120 °C and tosylamide (**238**) (4.00 g, 23.5 mmol) dissolved in DMF was added to the resulting solution. After 30 min a solution of the mesylate **237** (2.1 g, 16 mmol) in DMF (10 mL) was added. After 3 h the reaction mixture was cooled to room temperature, diluted with H_2O (10 mL) and extracted with Et_2O (4 × 10 mL). The combined organic layers were washed with H_2O (3 × 10 mL) and brine (3 × 10 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude compound. Purification by flash chromatography (petroleum ether:EtOAc, 5:1 → 4:1) yielded the title compound **234** as a colorless oil (282 mg, 9%).[155] R_f = 0.4, petroleum ether:EtOAc, 4:1. M.p. 74 − 76 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.77 (2H, d, J = 8.1 Hz, CH-C2'), 7.35 (2H, d, J = 8.1 Hz, CH-C3'), 4.56 (1H, br s, NH), 3.83 (2H, br dd, J = 2.5, 6.0 Hz, CH_2-C1), 2.43 (3H, s, CH_3), 2.11 (1H, t, J = 2.5 Hz, CH-C3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 143.8 (C-C4'), 136.5 (C-C1'), 129.7 (2 × CH-C3'), 127.4 (2 × CH-C2'), 77.9 (C-C2), 73.0 (CH-C3), 32.9 (CH_2-C1), 21.5 (CH_3). IR (thin film) 3747 (w), 3261 (m), 2360 (m), 1540 (m), 1521 (m), 1321 (s), 1159 (s) cm^{-1}. HRMS (CI/Isobutane) exact mass calculated for $C_{10}H_{12}NO_2S$ $[M+H]^+$ m/z 210.0589, found m/z 210.0588.

These data observed are in accordance with literature values.[156]

N-(But-3-enyl)-4-methyl-*N*-(prop-2-ynyl)benzenesulfonamide (235)



234 **235**

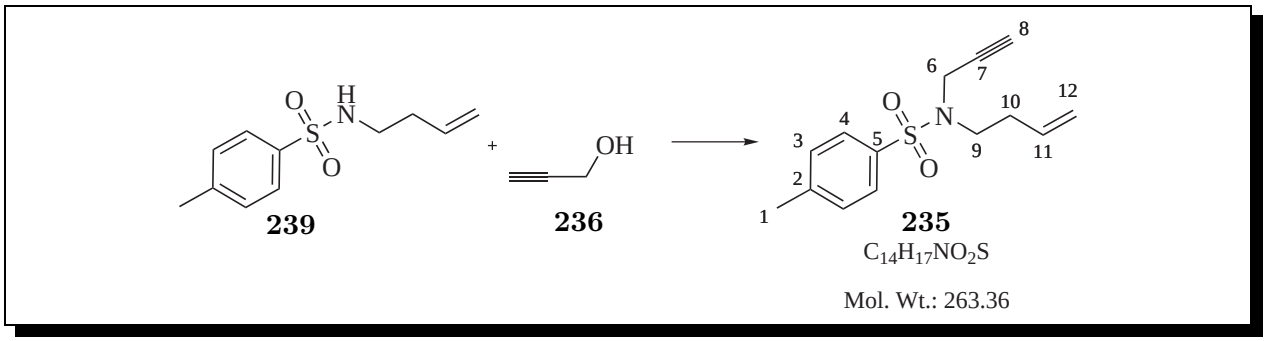
$C_{14}H_{17}NO_2S$

Mol. Wt.: 263.36

[155] Marcotullio, M. C.; Campagna, V.; Sternativo, S.; Costantino, F.; Curini, M. *Synthesis* **2006**, *16*, 2760-2766.

[156] Inamoto, K.; Yamamoto, A.; Ohsawa, K.; Hiroya, K.; Sakamoto, T. *Chem. Pharm. Bull.* **2005**, *53*, 1502-1507.

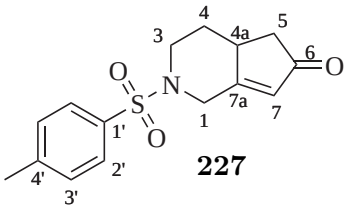
1st method: 4-Methyl-*N*-(prop-2-ynyl)benzenesulfonamide (**234**) (285 mg, 1.36 mmol) and K_2CO_3 (225 mg, 1.63 mmol) were dissolved in acetone (5 mL) was added 4-bromo-1-butene (167 μL, 1.63 mmol), and the mixture was heated to reflux and stirred overnight. The reaction mixture was cooled to room temperature, and concentrated *in vacuo*. EtOAc (20 mL) and water (10 mL) were added and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine, then dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude compound. Purification by flash chromatography (petroleum ether:EtOAc, 6:1) yielded the title compound **235** as a colorless oil (337 mg, 94%).[95]



2nd method: *N*-(3-Butenyl)-4-methylbenzenesulfonamide (**239**) (660 mg, 2.93 mmol), 2-propynol (**236**) (205 μL, 3.52 mmol), and triphenylphosphine (1.08 g, 4.10 mmol) were dissolved in THF (15 mL). The solution was cooled to 0 °C and then treated with DEAD (612 mg, 3.52 mmol) to give a bright yellow solution. The mixture was left to warm to room temperature overnight and concentrated *in vacuo* to yield the crude compound. Purification by flash chromatography (petroleum ether:EtOAc, 6:1) yielded the title compound **235** as a colorless oil (126 mg, 16%).[157] R_f = 0.4, petroleum ether:EtOAc, 6:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.71 (2H, d, J = 8.1 Hz, CH-C2"), 7.27 (2H, d, J = 8.1 Hz, CH-C3"), 5.75 (1H, ddt, J = 17.1, 6.8, 10.2 Hz, CH-C3), 5.09 (1H, ddd, J = 17.1, 3.0, 1.6 Hz, CH_2-C4), 5.04 (1H, ddd, J = 10.2, 3.0, 1.2 Hz, CH_2-C4), 4.13 (2H, d, J = 2.5 Hz, CH_2-C1'), 3.24 (2H, br t, J = 7.4 Hz, CH_2-C1), 2.43 (3H, s, CH_3), 2.33 (2H, dt, J = 14.6, 7.4 Hz, CH_2-C2), 2.11 (1H, t, J = 2.5 Hz, CH-C3'). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 143.5 (C-C4'), 136.5 (C-C1'), 134.3 (CH-C3), 129.4 (2 × CH-C3"), 127.7 (2 × C-C2"), 117.3 (CH_2-C4), 77.2 (C-C2'), 73.7 (CH-C3'), 45.7 (CH_2-C1'), 36.7 (CH_2-C1), 32.2 (CH_2-C2), 21.6 (CH_3). IR (KBr) 3277 (S), 3076 (m), 2978 (m), 2924 (m), 2869 (m), 1348 (s), 1159 (s) cm^{-1}. HRMS (CI/Isobutane) exact mass calculated for $C_{14}H_{18}NO_2S$ $[M+H]^+$ m/z 264.1058, found m/z 264.1060.
These data observed are in accordance with literature values.[158]

[157] Keith, J.; Gomez, L. *J. Org. Chem.* **2006**, *71*, 7113-7116.
[158] Watanabe, D.; Tsuda, M.; Kobayashi, J. *J. Nat. Prod.* **1998**, *61*, 689-692.

N-Tosyl-1,2,3,4,4a,5-hexahydrocyclopenta[c]pyridin-6-one (227)



227

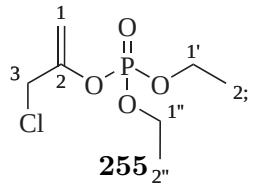
$C_{15}H_{17}NO_3S$

Mol. Wt.: 291.37

A solution of **235** (7.0 g, 26 mmol) in toluene (100 mL) was added dropwise to a solution of $Co_2(CO)_8$ (909 mg, 2.66 mmol) and TMTU (2.1 g, 16 mmol) in dry toluene (450 mL) charged with a ballon of carbon monoxide. The mixture was heated to 70 °C and stirred for 4 h (the color of the reaction mixture changed from orange/red to black). The solvent was removed *in vacuo* to yield the crude compound. Purification by flash chromatography (petroleum ether:EtOAc, 6:1 → 1:1) yielded the title compound **227** as a colorless solid (6.0 g, 87%).[92] R_f = 0.3, petroleum ether:EtOAc, 1:1. M.p. 124 − 126 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.66 (2H, d, J = 8.0 Hz, CH-C2'), 7.34 (2H, d, J = 8.0 Hz, CH-C3'), 6.00 (1H, br s, CH-C7), 4.71 (1H, d, J = 13.3 Hz, CH_2-C1), 3.93 (1H, d, J = 12.3 Hz, CH_2-C3), 3.18 (1H, d, J = 13.3 Hz, CH_2-C1), 2.59-2.52 (3H, m, CH_2-C3, CH-C4, CH_2-C4a), 2.43 (3H, s, CH_3), 2.12-1.97 (2H, m, CH_2-C5, CH_2-C4), 1.45 (d, 1H, 12.3 Hz, CH_2-C5). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 207.2 (C-C6) 172.2 (C-C4') 144.3 (C-C1'), 133.5 (C-C7a), 129.9 (2 × CH-C3'), 129.2 (2 × CH-C2'), 127.7 (CH-C7), 47.5 (CH_2-C1), 45.9 (CH_2-C3), 41.4 (CH_2-C5), 36.5 (CH-C4a), 32.0 (CH_2-C4), 22.3 (CH_3). IR (thin film) 3423 (m), 2980 (m), 2870 (m), 1710 (s), 1331 (m), 1159 (s), 788 (m) cm^{-1}. HRMS (CI/Isobutane) exact mass calculated for $C_{15}H_{18}NO_3S$ $[M+H]^+$ m/z 292.1007, found m/z 292.1006.

These data observed are in accordance with literature values.[92]

3-Chloro-2-[(diethoxyphosphoryl)oxy]-1-propene (255)



255

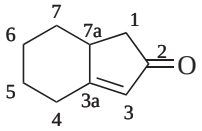
$C_7H_{14}ClO_4P$

Mol. Wt.: 228.61

1,3-Dichloroacetone (5.00 g, 39.4 mmol) was heated to 40 °C and triethyl phosphite (6.75 mL, 39.4 mmol) was added dropwise, under vigorous stirring, at such a rate that the temperature was maintained between 40 °C and 50 °C. The reaction mixture was then stirred for 3 h at 100 °C, and left to cool

to room temperature. The compound was purified by distillation (bp 133 °C at 11 mmHg; lit.[101] bp 85 °C at 1.4 mmHg) to yield the title compound **255** as a colorless oil (8.50 g, quant). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.07 (1H, dd, J = 2.5, 2.0 Hz, CH_2-C1), 4.89 (1H, dd, J = 2.5, 2.0 Hz, CH_2-C1), 4.22 (2H, dq, J = 15.3, 7.1 Hz, CH_2-C1') 4.18 (2H, dq, J = 15.3, 7.1 Hz, CH_2-C1"), 4.04 (2H, s, CH_2-C3), 1.49 (3H, t, J = 7.1 Hz, CH_3-C2'), 1.42 (3H, t, J = 7.1 Hz, CH_3-C2"). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 150.2 (d, J_{CP} = 7.8 Hz, C-C2), 101.3 (d, J_{CP} = 4.0 Hz, CH_2-C1), 64.7 (2 × C, d, J_{CP} = 6.2 Hz, CH_2-C1', CH_2-C1"), 44.1 (d, J_{CP} = 6.6 Hz, CH_2-C3), 16.1 (2 × C, d, J_{CP} = 6.8 Hz, CH_3-C2', CH_3-C2"). IR (Neat) 1279 (s), 1011 (s), 820 (m), 799 (s) cm^{-1}. HRMS (CI/Isobutane) exact mass calculated for $C_7H_{15}ClO_4P$ $[M+H]^+$ m/z 229.0396, found m/z 229.0397. These data observed are in accordance with literature values.[101]

1,4,5,6,7,7a-Hexahydro-inden-2-one (251)



251

$C_9H_{12}O$

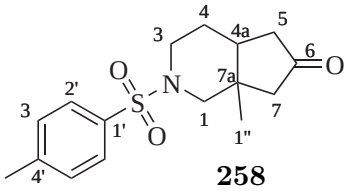
Mol. Wt.: 136.19

To a solution of diisopropylamine (1.63 mL, 11.6 mmol) in THF (10 mL) at −78 °C was added dropwise *n*-butyllithium (7.2 mL, 1.6 M in hexane, 11 mmol). After 15 min at −78 °C and additional 30 min at 0 °C, the mixture was cooled again to −78 °C and cyclohexanone (1.27 mL, 10.6 mmol) was added dropwise. The reaction mixture was then allowed to warm to 0 °C and after 30 min at this temperature a solution of tetrakis(triphenylphosphine)palladium(0) (734 mg, 0.635 mol) and 3-chloro-2-[(diethoxyphosphoryl)oxy]-l-propen (**255**) (2.5 g, 11 mmol) in THF (20 mL) was added. After stirring for 15 min at 0 °C and 3 h at room temperature, a mixture of 10% aqueous NaOH solution (8 mL) and ethanol (2 mL) was added. The resulting mixture was heated at reflux for 24 h and then cooled to room temperature and extracted with Et_2O (5 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to yield the crude compound. Purification by flash chromatography (petroleum ether:EtOAc, 4:1) yielded the title compound **251** as a colorless oil (576 mg, 37%).[101] R_f = 0.3, petroleum ether:EtOAc, 4:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.86 (1H, s, CH-C3), 2.87-2.81 (1H, m, CH_2-C4), 2.72-2.63 (1H, m, CH-C7a), 2.60-2.56 (1H, m, CH_2-C1), 2.32-2.16 (2H, m, CH_2-C7, CH_2-C5), 2.09-1.98 (2H, m, CH_2-C5, CH_2-C1), 1.91-1.83 (1H, m, CH_2-C5), 1.59-1.36 (2H, m, CH_2-C6), 1.21-1.09 (1H, m, CH_2-C7). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 209.3 (C-C2), 185.0 (C-C3a), 126.8 (CH-C3), 42.4 (CH_2-C1), 41.8 (CH-C7a), 35.1 (CH_2-C4), 31.1 (CH_2-C7), 27.1 (CH_2-C5), 25.3 (CH_2-C6). IR (Neat) 1705 (s), 1620 (m) cm^{-1}. HRMS (EI) exact mass calculated

for $C_9H_{12}O$ $[M]^+$ m/z 136.0888, found m/z 136.0880.

These data observed are in accordance with literature values.[101,102,103]

7a-Methyl-2-(toluene-4-sulfonyl)-octahydro-2-pyrindin-6-one (258)



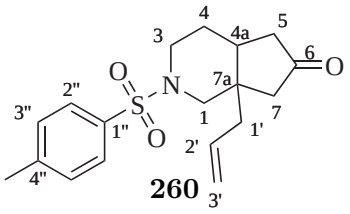
258

$C_{16}H_{21}NO_3S$

Mol. Wt.: 307.41

To a suspension of copper iodide (37 mg, 0.20 mmol) in THF (2 mL) was added dropwise methylmagnesium bromide (0.28 mL, 1.4 M in THF, 0.39 mmol). After the addition of one equivalent of the Grignard reagent the solution turned colorless, and following the second equivalent a yellow precipitate was observed. The mixture was stirred for 30 min and then a solution of 2-tosyl-1,2,3,4,4a,5-hexahydrocyclopenta[c]pyridin-6-one (**227**) (25.0 mg, 0.085 mmol) in THF (1.5 mL) was added. The reaction mixture was left stirring at room temperature for 2 h, after which the reaction was quenched by addition of a 10% NH_4OH/NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 15 mL), and the combined organic layers was washed with brine (15 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude compound. Purification by flash chromatography (petroleum ether:EtOAc, 3:1 → 1:1) yielded the title compound **258** as a colorless oil (22.3 mg, 85%). R_f = 0.3, petroleum ether:EtOAc, 3:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.66 (2H, d, J = 8.2 Hz, CH-C2'), 7.37 (2H, d, J = 8.2 Hz, CH-C3'), 3.16 (1H, m, CH_2-C3), 2.95 (1H, d, J = 12.0 Hz, CH_2-C1), 2.69 (1H, t, J = 8.9 Hz, CH_2-C3), 2.52 (1H, d, J = 12.0 Hz, CH_2-C1), 2.43-2.32 (2H, m, CH_2-C7), 2.38 (3H, s, CH_3-C6), 1.89 (4H, m, CH_2-C5, CH_2-C4a, CH_2-C4), 1.44 (1H, m, CH_2-C5), 1.09 (3H, s, CH_3-C1"). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 217.2 (C-C6), 143.9 (C-C4'), 133.0 (C-C1'), 129.8 (2 × CH-C3'), 127.6 (2 × CH-C2'), 52.3 (CH_2-C1), 47.6 (CH_2-C3), 44.0 (CH_2-C7), 42.4 (CH_2-C5), 39.0 (CH-C4a), 38.5 (C-C7a), 26.9 (CH_2-C4), 24.9 (CH_3), 21.6 (CH_3-C1"). IR (thin film) 2923 (m), 2850 (m), 1741 (s), 1340 (s), 1163 (s) cm^{-1}. HRMS (CI/Isobutane) exact mass calculated for $C_{16}H_{22}NO_3S$ $[M+H]^+$ m/z 308.1320, found m/z 308.1319.

7a-Allyl-2-(toluene-4-sulfonyl)-octahydro-[2]pyrindin-6-one (260)

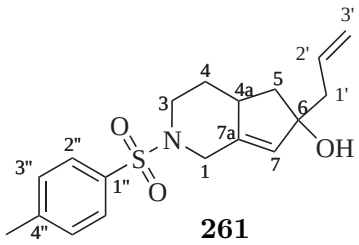


$C_{18}H_{23}NO_3S$

Mol. Wt.: 333.44

To a suspension of copper iodide (131 mg, 0.689 mmol) in THF (5 mL) at 0 °C was added dropwise allylmagnesium chloride (0.68 mL, 2 M in THF, 1.37 mmol). The mixture was left stirring for 5 min followed by the addition of 2-tosyl-1,2,3,4,4a,5-hexahydrocyclopenta[c]pyridin-6-one (**227**) (100 mg, 0.343 mmol) and chlorotrimethylsilane (174 μL, 1.37 mmol) dissolved in THF (3 mL). The reaction mixture was left stirring at 0 °C for 2 h, after which the reaction was quenched by the addition of 10% NH_4Cl/NH_4OH solution (5 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL), and the combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude compound. Purification by flash chromatography (petroleum ether:CH_2Cl_2, 1:1 with increasing percentage of Et_2O, 5-10%), yielded the titel compound **260** as a colorless solid (39.4 mg, 34%). M.p. 136 – 139 °C. R_f = 0.3, petroleum ether:CH_2Cl_2:Et_2O, 1:1:0.05). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.66 (2H, d, J = 8.1 Hz, CH-C2"), 7.37 (2H, d, J = 8.1 Hz, CH-C3"), 5.67 (1H, ddt, J = 17.8, 10.4, 7.5 Hz, CH-C2') 5.09 (2H, m, CH_2-C3'), 3.05 (1H, m, CH_2-C3), 2.93 (1H, d, J = 12.1 Hz, CH_2-C1), 2.79 (1H, t, J = 8.8 Hz, CH_2-C3), 2.49 (1H, d, J = 12.1 Hz, CH_2-C1), 2.38-2.42 (1H, m, CH_2-C3), 2.41 (3H, s, CH_3), 2.29 (1H, dd, J = 18.6, 7.6 Hz, CH_2-C5), 2.20 (1H, dd, J = 14.0, 7.6 Hz, CH_2-C1'), 2.17-2.15 (2H, m, CH_2-C7), 2.13-2.08 (1H, m, CH_2-C4a), 2.05-1.95 (2H, m, CH_2-C5, CH_2-C4), 1.57-1.51 (1H, m, CH_2-C4). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 216.6 (C-C9), 143.8 (C-C2), 132.9 (C-C5), 132.6 (CH-C15), 129.9 (2 × CH-C4), 127.6 (2 × CH-C3), 119.8 (CH_2-C16) 50.0 (CH_2-C6), 46.6 (CH_2-C8), 42.7 (CH_2-C13), 41.6 (C-C7), 41.1 (CH_2-C10), 40.5 (CH_2-C14), 37.0 (CH-C11), 25.4 (CH_2-C12), 21.6 (CH_3-C1). IR (thin film) 2922 (m), 2854 (m), 1732 (s), 1597 (w), 1332 (m), 1155 (s) cm^{-1}. HRMS (EI) exact mass calculated for $C_{18}H_{23}NO_3S$ $[M]^+$ m/z 333.1399, found m/z 333.1401. Microanalysis calculated for $C_{18}H_{23}NO_3S$ C 64.84%, H 6.95% and N 4.20%, found C 64.76%, H 6.88% and N 4.16%. Further elucidation resulted in:

6-Allyl-2-(toluene-4-sulfonyl)-2,3,4,4a,5,6-hexahydro-1*H*-[2]pyrindin-6-ol (261)



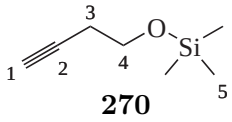
261

$C_{18}H_{23}NO_3S$

Mol. Wt.: 333.45

Obtained as a colourless oil (25 mg, 21%). R_f = 0.18, petroleum ether:EtOAc, 4:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.61 (2H, d, J = 8.1 Hz, CH_2-C2"), 7.26 (2H, d, J = 8.1 Hz, CH_2-C3"), 5.72-5.62 (1H, m, CH-C2'), 5.43 (1H, t, J = 1.7 Hz, CH-C7), 5.05-4.99 (2H, m, CH_2-C3'), 4.33 (1H, dd, J = 13.0, 1.1 Hz, CH_2-C1), 3.80 (1H, dt, J = 12.0, 4.0 Hz, CH_2-C3), 2.85 (1H, dt, J = 13.0, 1.6 Hz, CH_2-C1), 2.36 (3H, s, CH_3), 2.32-2.12 (5H, m, CH-C4a, CH_2-C4, CH_2-C3, CH_2-C1'), 1.61 (1H, s, OH), 1.90-1.82 (1H, m, CH_2-C5), 1.40-1.28 (2H, m, CH_2-C5, CH_2-C4). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 143.7 (C-C7a), 139.8 (C-C4"), 133.5 (CH-C2'), 133.2 (C-C1"), 130.7 (CH-C7), 129.7 (2 × CH_2-C3"), 127.8 (2 × CH_2-C2"), 118.7 (CH_2-C3'), 84.1 (C-C6), 46.9 (CH_2-C1), 46.0 (CH_2-C1'), 45.2 (CH_2-C3), 45.0 (CH_2-C5), 41.5 (CH-C4a), 33.1 (CH_2-C4), 21.6 (CH_3). IR (Neat) 3466 (br m), 3072 (m), 2926 (m), 2852 (m), 1350 (s), 1161 (s) cm^{-1}. HRMS (FAB/NOB + NaI) exact mass calculated for $C_{18}H_{23}NNaO_3S$ $[M+Na]^+$ m/z 356.1296, found m/z 356.1297.

4-(Trimethylsiloxy)-1-butyne (270)



270

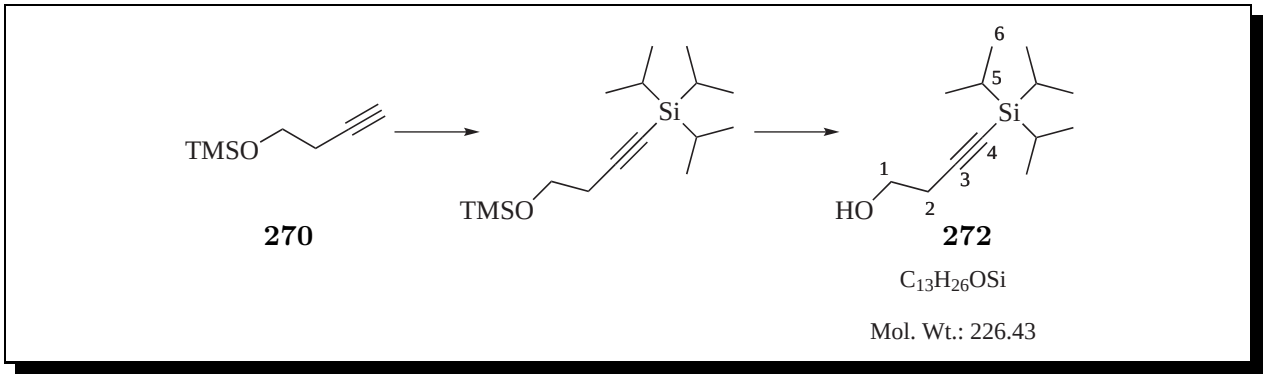
$C_7H_{14}OSi$

Mol. Wt.: 142.27

To a solution of 3-butyn-1-ol (**269**) (6.7 g, 95 mmol) and triethylamine (15 mL, 0.10 mol) in CH_2Cl_2 (50 mL) at 0 °C was added dropwise chlorotrimethylsilane (13.0 mL, 100 mmol). The resulting slurry was allowed to warm to room temperature, and left stirring overnight. The mixture was washed with saturated aqueous $NaHCO_3$ (3 × 15 mL), H_2O (3 × 15 mL), and then dried over Na_2SO_4. Filtration and purification by distillation at ambient pressure yielded the silyl ether **270** (11 g, 85%) as a colorless oil (bp 125 – 128 °C).[105] ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.71 (2H, t, J = 7.1 Hz, CH_2-C1), 2.42 (2H, dt, J = 7.1, 2.6 Hz, CH_2-C2), 1.98 (1H, t, J = 2.6 Hz, CH-C4), 0.13 (9H, s, 3 × CH_3-C5). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 81.9 (C-C3), 69.9 (CH-C4), 61.6 (CH_2-C1), 23.2 (CH_2-C2),

0.03 (3 × CH_3-C5). IR (thin film) 3347 (m), 2942 (m), 2865 (m), 2173 (s), 1028 (m) cm^{-1}. HRMS (CI/Isobutane) exact mass calculated for $C_7H_{15}OSi$ $[M+H]^+$ m/z 143.0892, found m/z 143.0896. These data observed are in accordance with literature values.[105]

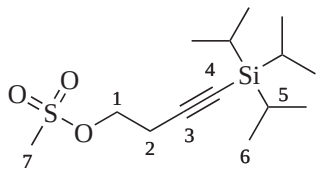
4-(Triisopropylsilyl)-3-butyn-1-ol (272)



To a solution of 1-(trimethylsiloxy)-3-butyne (**270**) (1.20 g, 8.43 mmol) in Et_2O (15 mL) at −40 °C, was added dropwise *n*-butyllithium (4.70 mL, 1.6 M in hexanes, 7.52 mmol). The mixture was stirred at −40 °C for 30 min, followed by dropwise addition of triisopropylsilyl trifluoromethanesulfonate (2.29 mL, 8.43 mmol). The reaction mixture was then allowed to warm to room temperature and stirred for 7 h. The reaction mixture was washed with H_2O (2 × 10 mL), and the combined aqueous layer were extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with aqueous 5% $NaHCO_3$ solution (15 mL) and brine (15 mL), and dried over Na_2SO_4. Filtration and concentration under reduced pressure yielded the crude material which was then taken up in a mixture of THF (8 mL), H_2O (5 mL) and glacial acetic acid (5 mL), and stirred at room temperature for 6 h. The mixture was then neutralized with a concentrated aqueous NH_4OH solution. The aqueous layer was extracted with Et_2O (3 × 20 mL), and the combined organic layers were washed with saturated aqueous NH_4Cl solution (15 mL) and brine (15 mL), then dried over $MgSO_4$. Filtration and concentration *in vacuo* gave the crude compound as a yellow oil. Purification by flash chromatography (petroleum ether:EtOAc, 7:1 → 6:1) yielded the title compound **272** as a colorless oil (1.2 g, 62% from 1-(trimethylsiloxy)-3-butyne).[105] R_f = 0.7, petroleum ether:EtOAc, 7:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.72 (2H, t, J = 6.2 Hz, CH_2-C1), 2.54 (2H, t, J = 6.2 Hz, CH_2-C2), 1.79 (1H, br s, OH), 1.07 (21H, m, CH-C5, CH_3-C6). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 104.9 (C-C4), 83.1 (C-C3), 61.2 (CH_2-C1), 24.4 (CH_2-C2), 18.6 (6 × CH_3-C6), 11.2 (3 × CH-C5). IR (thin film) 3341 (br m), 2942 (s), 2865 (s), 2173 (m), 1028 (m) cm^{-1}. HRMS (CI/Isobutane) exact mass calculated for $C_{13}H_{27}OSi$ $[M+H]^+$ m/z 227.1831, found m/z 227.1827.

These data observed are in accordance with literature values.[105]

4-(Triisopropylsilyl)but-3-ynyl methanesulfonate (276)



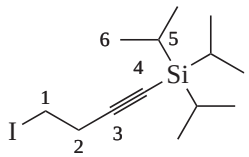
276

$C_{14}H_{28}O_3SSi$

Mol. Wt.: 304.52

Methanesulfonyl chloride (725 μL, 9.39 mmol) was added dropwise at 0 °C to a solution of 4-(triisopropylsilyl)-3-butynol (**272**) (1.95 g, 8.61 mmol) and triethylamine (1.30 mL, 9.39 mmol) in CH_2Cl_2. The mixture was allowed to warm to room temperature and left for 2 h. The reaction mixture was then washed with saturated aqueous NH_4Cl (2 × 10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting crude material was used in the synthesis of 1-iodo-4-(triisopropylsilyl)-3-butyne (**267**) without further purification.[105] ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.30 (2H, t, J = 7.0 Hz, CH_2-C1) 3.04 (3H, s, CH_3-C7) 2.73 (2H, t, J = 7.0 Hz, CH_2-C2) 1.06 (21H, m, CH-C6, CH_3-C6). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 102.0 (C-C4), 83.2 (C-C3), 67.4 (CH_2-C1), 37.7 (CH_3-C7), 21.1 (CH_2-C2), 18.6 (6 × CH_3-C6), 11.2 (3 × CH-C5). IR (thin film) 2943 (s), 2865(s), 2178 (m), 1359 (m), 1177 (s), 993 (m), 963 (m) cm^{-1}. HRMS (CI/Isobutane) exact mass calculated for $C_{14}H_{29}O_3SSi$ $[M+H]^+$ m/z 305.1607, found m/z 305.1605.
These data observed are in accordance with literature values.[105]

1-Iodo-4-(triisopropylsilyl)-3-butyne (267)



267

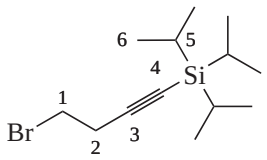
$C_{13}H_{25}ISi$

Mol. Wt.: 336.33

4-(Triisopropylsilyl)but-3-ynyl methanesulfonate (**276**) (2.9 g, 8.6 mmol) and NaI (6.4 g, 43 mmol) were dissolved in acetone (20 mL) and heated to reflux for 24 h. The mixture was cooled to room temperature and partitioned between hexanes (15 mL) and water (15 mL). The aqueous layer was extracted with hexanes (2 × 15 mL), and the combined organic layers were washed with aqueous 10% $Na_2S_2O_3$ (20 mL), brine (20 mL), and dried over Na_2SO_4 solution. Filtration and concentration *in vacuo* afforded the title compound (2.59 g, 90% from 4-(triisopropylsilyl)-3-butynol (**272**)) as a yellow oil. This material was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.27

(2H, t, J = 7.3 Hz, CH_2-C1), 2.86 (2H, t, J = 7.3 Hz, CH_2-C2), 1.09 (21H, m, CH-C5, CH_3-C6). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 107.2 (C-C4), 83.5 (C-C3), 25.7 (CH_2-C1), 19.2 (6 × CH_3-C6), 11.8 (3 × CH-C5), 2.4 (CH_2-C2). IR (thin film) 2941 (s), 2922 (s), 2172 (m), 1170 (m) cm^{-1}. HRMS (EI) exact mass calculated for $C_{13}H_{25}ISi$ m/z 336.0770, found 336.0771.
These data observed are in accordance with literature values.[105]

1-Bromo-4-(triisopropylsilyl)-3-butyne (273)



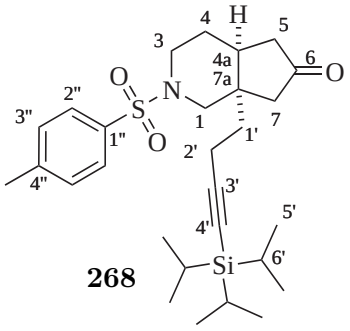
273

$C_{13}H_{25}BrSi$

Mol. Wt.: 289.33

To a solution of 4-(triisopropylsilyl)-3-butynol (**272**) (500 mg, 2.21 mmol) and carbon tetrabromide (1.46 g, 4.42 mmol) in acetonitrile (15 mL) cooled to 0 °C was added portionwise triphenylphosphine (1.16 g, 4.42 mmol). The solution was then subsequently left to warm to room temperature and the resulting mixture was filtered using EtOAc:petroleum ether (5:95) (20 mL), concentrated *in vacuo* to yield the crude compound. Purification by flash chromatography (petroleum ether) yielded the title compound **273** as a colorless oil (625 mg, 98%).[89] ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.45 (2H, t, J = 7.3 Hz, CH_2-C1), 2.81 (2H, t, J = 7.3 Hz, CH_2-C2), 1.07 (21H, m, CH-C5, CH_3-C6). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 105.3 (C-C4), 83.6 (C-C3), 30.3 (CH_2-C1), 24.8 (CH_2-C2), 11.7 (6 × CH_3-C6), 19.1 (3 × CH-C5). IR (thin film) 2942 (s), 2891 (s), 2175 (m), 1211 (m) cm^{-1}. HRMS (EI$^+$) exact mass calculated for $C_{13}H_{25}BrSi$ m/z $[M]^+$ 288.0909, found m/z 288.0904.

2-(Toluene-4-sulfonyl)-7a-(4-triisopropylsilanyl-but-3-ynyl)-octahydro -[2]pyrindin-6-one (268)



268

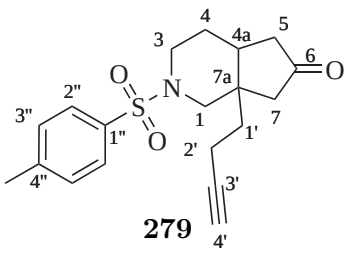
$C_{28}H_{43}NO_3SSi$

Mol. Wt.: 501.80

To a solution of iodide **267** (808 mg, 2.40 mmol) in ether (10 mL) at −78 °C was added *tert*-butyllithium (3.0 mL, 1.6 M in hexane, 4.8 mmol) and stirred 20 min. The reaction mixture was

warmed to room temperature and allowed to stir for 20 min. Meanwhile, dimethylsulfide (2.20 mL, 30.3 mmol) was added to a solution of copper iodide (229 mg, 1.20 mmol) in THF (20 mL). After all the copper iodide had dissolved, the solution was cooled to −40 °C and the organolithium solution was added by syringe to afford a black slurry which was stirred for 15 min. A pre-cooled solution of the enone **227** (200 mg, 0.69 mmol) and chlorotrimethylsilane (0.23 mL, 1.8 mmol) in THF (10 mL) was added dropwise and the mixture was allowed to warm to room temperature overnight. The reaction was quenched with a 10% NH_4OH/NH_4Cl solution. The biphasic mixture was extracted with EtOAC (3 × 30 mL) and the organic extracts were washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to yield the crude compound. Purification by flash chromatography (petroleum ether:EtOAc, 8:1 → 2:1) yielded the title compound **268** as a colorless gum (265 mg, 79%).[106] R_f = 0.21, petroleum ether:EtOAc, 8:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.62 (2H, d, J = 8.1 Hz, CH-C2"), 7.33 (2H, d, J = 8.1 Hz, CH-C3"), 3.25 (1H, dd, J = 16.0, 4.5 Hz, CH_2-C3), 3.10 (1H, d, J = 12.4 Hz, CH_2-C1), 2.75 (1H, dd, J = 16.0, 3.2 Hz, CH_2-C3), 2.44 (3H, s, CH_3), 2.43-2.33 (3H, m, CH_2-C1, CH_2-C2'), 2.31-2.19 (4H, m, CH_2-C7, CH_2-C5, CH-C4a), 2.11-1.98 (3H, m, CH_2-C5, CH_2-C4, CH_2-C1'), 1.76-1.69 (1H, m, CH_2-C1'), 1.61-1.54 (1H, m, CH_2-C4), 1.06 (21H, s, CH_3-C6', CH-C5'). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 215.9 (C-C6), 143.8 (C-C4"), 133.1 (C-C1"), 129.8 (2 × CH-C3"), 127.6 (2 × CH-C2"), 107.8 (C-C3'), 81.4 (C-C4'), 48.9 (CH_2-C1), 47.6 (CH_2-C7), 42.2 (CH_2-C3), 41.5 (C-C7a), 40.4 (CH_2-C5), 37.2 (CH-C4a), 35.0 (CH_2-C1'), 24.9 (CH_2-C4), 21.5 (CH_3), 18.6 (6 × CH_3-C6'), 15.2 (CH_2-C2'), 11.3 (3 × CH-C5'). IR (thin film) 2922, 1735, 1339 cm^{-1}. HRMS (FAB/NOBA) exact mass calculated for $C_{28}H_{44}NO_3SSi$ $[M+H]^+$ m/z 502.2811, found m/z 502.2816. Microanalysis calculated for $C_{28}H_{43}NO_3SSi$ C 67.02%, H 8.64%, and N 2.79%, found C 66.87%, H 8.68%, and N 2.93%.

7a-(But-3-ynyl-2-(toluene-4-sulfonyl)-octahydro-[2]pyrindin-6-one (279)



279

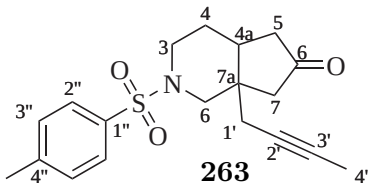
$C_{19}H_{23}NO_3S$

Mol. Wt.: 345.46

A solution of ketone **268** (85 mg, 0.17 mmol) in THF was cooled to −78 °C. TBAF (0.2 mL, 1.0 M in THF, 0.2 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature over 16 h. Water (10 mL) was added and the mixture was extracted with diethyl ether (3 × 30 mL). The organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude compound. Purification by flash chromatography (petroleum ether:EtOAc, 3:1 → 1:1) yielded the title compound **279** as a colorless gum (52 mg, 89%).[106] R_f = 0.18, 4:1 petroleum

ether:EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.62 (2H, d, J = 8.1 Hz, CH-C2"), 7.33 (2H, d, J = 8.1 Hz, CH-C3"), 3.26 (1H, dd, J = 16.1, 4.3 Hz, CH_2-C3), 3.13 (1H, d, J = 14.5 Hz, CH_2-C1), 2.74 (1H, dd, J = 16.1, 3.5 Hz, CH_2-C3), 2.45 (3H, s, CH_3), 2.43 (1H, d, J = 14.5 Hz, CH_2-C1), 2.37-2.28 (4H, m, CH_2-C7, CH_2-C5, CH_2-C2'), 2.25-2.06 (3H, m, CH_2-C4a, CH_2-C1', CH_2-C2'), 2.08-1.99 (2H, m, CH_2-C5, CH_2-C4), 1.98 (1H, t, J = 2.5 Hz, CH-C4'), 1.73-1.66 (1H, m, CH_2-C1'), 1.62-1.55 (1H, m, CH_2-C4). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 215.9 (C-C6), 143.9 (C-C4"), 133.1 (C-C1"), 129.9 (2 × CH-C3"), 127.6 (2 × CH-C2"), 83.7 (C-C3'), 69.3 (CH-C4'), 48.7 (CH_2-C1), 47.4 (CH_2-C7), 42.3 (CH_2-C3), 41.5 (C-C7a), 40.3 (CH_2-C5), 37.7 (CH-C4a), 34.9 (CH_2-C1'), 24.8 (CH_2-C4), 21.5 (CH_3), 13.8 (CH_2-C2'). IR (Neat) 3281 (m), 2924 (m), 2848 (m), 2100 (m), 1737 (s) cm^{-1}. HRMS (EI) exact mass calculated for $C_{19}H_{23}NO_3S$ $[M]^+$ m/z 345.1399, found m/z 345.1385. Microanalysis calculated for $C_{19}H_{23}NO_3S$ C 66.06%, H 6.71%, and N 4.05%, found C 65.62%, H 6.79%, and N 4.04%.

7a-But-2-ynyl-2-(toluene-4-sulfonyl)-octahydro-[2]pyrindin-6-one (263)



263

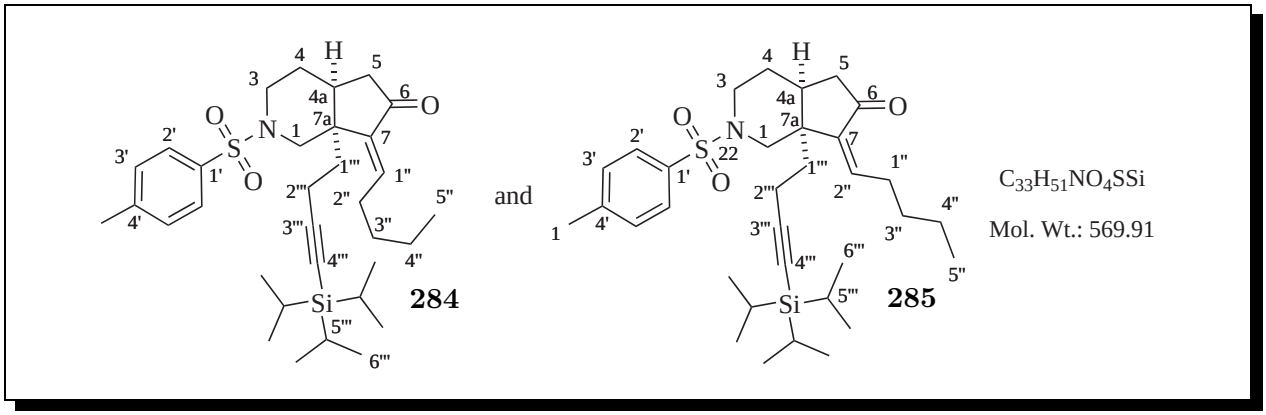
$C_{19}H_{23}NO_3S$

Mol. Wt.: 345.46

To a degassed solution of potassium *tert*-butoxide (40 mg, 0.36 mmol) in DMSO (5 mL), was added **279** (44 mg, 0.12 mmol) and the mixture was stirred for 15 min. The reaction mixture was quenched with water (15 mL) and 1 M HCl (15 mL). Ether (50 mL) was added, the organic layer was separated and the aqueous layer was extracted with ether (2 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 6:1) yielded the title compound **263** as a colorless oil (18 mg, 40%).[106] R_f = 0.29, petroleum ether:EtOAc, 4:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.62 (2H, d, J = 8.1 Hz, CH-C2"), 7.33 (2H, d, J = 8.1 Hz, CH-C3"), 3.72-3.63 (1H, m, CH_2-C1), 3.53 (1H, br d, J = 11.9 Hz, CH_2-C3), 3.05 (1H, quint, J = 7.2 Hz, CH_2-C5), 2.55 (1H, m, CH_2-C5), 2.45 (3H, s, CH_3), 2.43-2.31 (3H, m, CH_2-C7, CH-C4a, CH_2-C1'), 2.30-2.22 (1H, m, CH_2-C1), 2.22-2.12 (1H, m, CH_2-C7), 2.04 (3H, s, CH_3-C4'), 2.08-1.99 (2H, m, CH_2-C4, CH_2-C3), 1.73-1.66 (1H, m, CH_2-C1'), 1.62 (1H, d, J = 12.3 Hz, CH_2-C4). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 200.7 (C-C6), 152.8 (C-C2'), 143.7 (C-C1"), 142.5 (C-C3'), 132.9 (C-C4"), 129.8 (2 × CH-C2"), 129.6 (2 × CH-C3"), 55.4 (C-C7a), 48.6 (CH_2-C3), 44.3 (CH_2-C7), 41.7 (CH_2-C5), 41.5 (CH_2-C1), 39.1 (CH-C4a), 35.9 (CH_2-C1'), 24.3 (CH_2-C14), 21.6 (CH_3), 15.5 (CH_3-C4'). IR (Neat) 2922 (m), 2847 (m), 1703 (m), 1651 (s), 1329 (m), 1159 (s) cm^{-1}. HRMS (EI) exact mass calculated for $C_{19}H_{24}NO_3S$ $[M+H]^+$ m/z 346.1477, found

m/z 346.1479. Microanalysis calculated for $C_{19}H_{23}NO_3SSi$ C 66.06%, H 6.71%, and N 4.05%, found C 65.93%, H 7.15%, and N 3.82%.

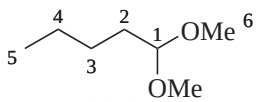
7a-Allyl-7-pent-(*Z*)-ylidene-2-(toluene-4-sulfonyl)-octahydro-[2]pyrindin-6-one (285)



To a solution of 1-iodo-4-(triisopropylsilyl)-3-butyne (**267**) (808 mg, 2.40 mmol) in ether (40 mL) at −78 °C was added *tert*-butyllithium (3.0 mL, 1.6 M in hexane, 5 mmol) and stirred 20 min. The reaction mixture was warmed to room temperature and allowed to stir for an additional 20 min. Meanwhile, dimethylsulfide (2.2 mL, 30 mmol) was added to a solution of copper iodide (229 mg, 1.20 mmol) in THF (40 mL). After all the copper iodide had dissolved, the solution was cooled to −40 °C and the organolithium solution was added by syringe to afford a black slurry and stirred for 15 min. A pre-cooled (0 °C) solution of the enone **227** (200 mg, 0.686 mmol) and chlorotrimethylsilane (0.27 mL, 1.8 mmol) in THF (10 mL) was added dropwise and the mixture was allowed to warm to room temperature overnight. The reaction was quenched with a 10% NH_4OH/NH_4Cl solution (10 mL). The biphasic mixture was extracted with EtOAc (3 × 30 mL), washed with brine (30 mL), then dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield the crude compound. The crude material was used without further purification. The silyl enol ether (0.69 mmol) was dissolved in CH_2Cl_2 (7 mL), cooled to −78 °C and treated with $TiCl_4$ (75 μL, 0.68 mmol) to afford a deep red solution. Valeraldehyde (**280**) (291 μL, 2.75 mmol) was added and the solution allowed to warm to room temperature. $NaHCO_3$ solution (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 8:1) yielded the title compound **285** as a colorless oil (58 mg, 15%). R_f = 0.33, petroleum ether:EtOAc, 8:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) *Z*-isomer: 7.62 (2H, d, J = 8.1 Hz, CH-C2'), 7.33 (2H, d, J = 8.1 Hz, CH-C3'), 5.95 (1H, t, J = 7.5 Hz, CH-C1"), 3.15-3.02 (2H, m, CH_2-C3, CH_2-C1), 2.88-2.79 (1H, m, CH_2-C3), 2.68-2.80 (2H, m, CH_2-C2"), 2.62 (1H, d, J = 12.3 Hz, CH_2-C CH_2-C1), 2.44 (3H, s, CH_3), 2.45-2.37 (1H, m, CH_2-C5), 2.18-2.08 (3H, m, CH-C4a, CH_2-C2"'), 2.08-1.88 (3H, m, CH_2-C4, CH_2-C5, CH_2-C1"'), 1.71-1.58 (1H, m, CH_2-C1"'), 1.52-1.34 (5H, m, CH_2-C4, CH_2-C3", CH_2-C4"), 1.12-0.98 (m, 21H, CH-C5"', CH_3-C6"'), 0.92 (3H, t, J = 7.2 Hz, CH_3-C5"). ^{13}C NMR

(100 MHz, $CDCl_3$) δ *Z*-isomer: 206.5 (CH-C6), 144.6 (CH-C7), 143.7 (CH-C1"), 136.6 (C-C4'), 133.2 (C-C1'), 129.8 (2 × CH-C3'), 127.6 (2 × CH-C2'), 107.7 (C-C14"'), 80.9 (C-C2"), 50.7 (CH_3-C1), 46.6 (CH-C7a), 43.5 (CH_3-C3), 41.1 (CH_3-C5), 34.9 (CH_2-C1"'), 34.4 (CH-C4a), 31.4 (CH_2-C3"'), 27.7 (CH_2-C4"'), 26.8 (CH_2-C4), 22.4 (CH_2-C2"), 21.6 (CH_3), 18.6 (6 × CH_3-C6"'), 14.7 (CH_2-C2"'), 13.9 (CH_3-C5"), 11.3 (3 × CH-C5"). $R_f = 0.28$, petroleum ether:EtOAc, 8:1 - which quickly isomerised to the *Z*-isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) *E*-isomer: 7.63 (2H, d, J = 8.2 Hz, CH-C2'), 7.35 (2H, d, J = 8.2 Hz, CH-C3'), 6.75 (1H, t, J = 7.7 Hz, CH-C1"), 3.26-3.18 (1H, m, CH_2-C3), 3.16 (1H, d, J = 12.3, CH_2-C1), 2.86 (1H, d, J = 12.3, CH_2-C1), 2.77-2.70 (1H, m, CH_2-C3), 2.46 (3H, s, CH_3), 2.44-2.17 (6H, m, CH-C4a, CH_2-C5, CH_2-C2"', CH_2-C2"), 2.12-2.09 (4H, m, CH_2-C4, CH_2-C5, CH_2-C1"'), 1.58-1.46 (3H, m, CH_2-C4, CH_2-C3"), 1.45-1.37 (2H, m, CH_2-C4"), 1.12-1.01 (m, 21H, CH-C5"', CH_3-C6"'), 0.97 (3H, t, J = 7.2 Hz, CH_3-C5"). ^{13}C NMR (100 MHz, $CDCl_3$) δ *E*-isomer: 206.5 (CH-C6), 144.6 (CH-C7), 141.9 (CH-C1"), 136.6 (2 × C-C4'), 133.2 (2 × C-C1'), 129.8 (CH-C3'), 127.6 (CH-C2'), 107.7 (C-C4"'), 80.9 (C-C3"'), 50.7 (CH_3-C1), 46.6 (CH-C7a), 43.5 (CH_3-C3), 41.1 (CH_3-C5), 34.9 (CH_2-C1"'), 34.4 (CH-C4a), 32.2 (CH_2-C2"), 31.4 (CH_2-C3"), 27.7 (CH_2-C4"), 26.8 (CH_2-C4), 21.6 (CH_3), 18.6 (6 × CH_3-C6"'), 14.7 (CH_2-C2"'), 13.9 (CH_3-C5"), 11.3 (3 × CH-C5"'). IR (thin film) 2941 (s), 2863 (s), 2170 (m), 1715 (s), 1637 (m), 1493 (m), 1165 (s), 1093 (m), 1039 (m) cm^{-1}.

1,1-Dimethoxypentane (286)



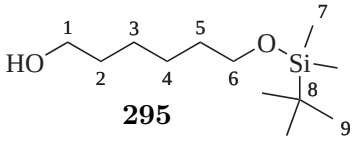
286

$C_7H_{16}O_2$

Mol. Wt.: 132.20

To a solution of valeraldehyde (**280**) (8.0 mL, 0.08 mol) and MeOH (15 mL, 0.4 mol) in benzene (20 mL) was added one drop of concentrated sulfuric acid. The resulting mixture was heated to reflux using Dean-Stark apparatus. After 16 h, the resulting mixture was cooled to room temperature, washed with $NaHCO_3$ (20 mL), brine (20 mL), dried (Na_2SO_4), and the residue was distilled (bp 128 – 130 °C at ambient pressure) to yield the title compound **286** as a colorless liquid (2.4 g, 24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.36 (1H, t, J = 5.8 Hz, CH-C1), 3.31 (6H, s, CH_3-C6), 1.57 (2H, m, CH_2-C2), 1.33 (4H, m, CH_2-C4, CH_2-C3), 0.90 (3H, t, J = 7.1 Hz, CH_3-C5). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 104.5 (CH-C1), 52.6 (2 × CH_3-C6), 32.1 (CH_2-C2), 26.8 (CH_2-C4), 22.5 (CH_2-C3), 14.0 (CH_3-C5). HRMS (CI/Isobutane) exact mass calculated for $C_7H_{17}O_2$ m/z $[M+H]^+$ 133.1229, found m/z 133.0865.

6-(*tert*-Butyldimethylsilyloxy)hexan-1-ol (295)



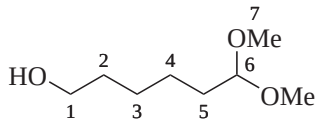
295

$C_{12}H_{28}O_2Si$

Mol. Wt.: 232.44

Sodium hydride (1.33 g, 30.5 mmol) was suspended in THF, and 1,6-hexanediol (**294**) (3.0 g, 25 mmol) was added at 0 °C. The mixture was stirred for 45 min, after which time a large amount of a white precipitate had formed. *tert*-Butyldimethylsilyl chloride (5.0 g, 31 mmol) was then added portionwise, and vigorous stirring was continued for 2 h. The mixture was poured into Et_2O (100 mL), washed with 10% aqueous K_2CO_3 solution (30 mL) and brine (30 mL), then dried (Na_2SO_4) and concentrated *in vacuo* to yield the crude material. Purification by flash chromatography (petroleum ether:EtOAc, 9:1 → 7:1) yielded the title compound **295** as a colorless oil (5.50 g, 93%).[115] R_f = 0.3, petroleum ether:EtOAc, 9:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.60 (2H, t, J = 6.6 Hz, CH_2-C6), 3.56 (2H, t, J = 6.6 Hz, CH_2-C1), 2.00 (1H, s, OH), 1.53 (4H, m, CH_2-C3, CH_2-C5), 1.34 (4H, m, CH_2-C4, CH_2-C4), 0.87 (9H, s, CH_3-C9), 0.03 (6H, s, CH_3-C7). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 63.2 (CH_2-C6), 63.0 (CH_2-C1), 32.8 (CH_2-C5), 32.7 (CH_2-C2), 26.0 (3 × CH_3-C9), 25.6 (CH_2-C3), 25.5 (CH_2-C4), 18.4 (C-C8), 4.95 (2 × CH_3-C7). IR (thin film) 3338 (br), 2931 (s), 2830 (m), 1473 (m) cm^{-1}. HRMS (CI/Isobutane) exact mass calculated for $C_{12}H_{29}O_2Si$ $[M+H]^+$ m/z 233.1937, found m/z 233.1938.

6,6-Dimethoxyhexan-1-ol (296)



296

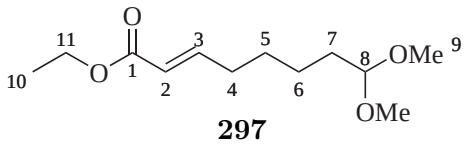
$C_8H_{18}O_3$

Mol. Wt.: 162.23

Oxalyl chloride (3.5 mL, 17 mmol) was dissolved in CH_2Cl_2 (40 mL) and cooled to −78 °C, followed by dropwise addition of DMSO (6.8 mL, 96 mmol). The resulting solution was left stirring at −78 °C and after 15 min a solution of alcohol **295** (4.0 g, 17 mmol) in CH_2Cl_2 (15 mL) was added and the mixture was allowed to stir additional 1.5 h at −78 °C and then Et_3N (30 mL) was added and the resulting slurry was allowed to warm to room temperature. CH_2Cl_2 was added and the organic

layer was washed with a saturated aqueous solution of NH_4Cl (60 mL) and brine (50 mL), then dried (Na_2SO_4) and concentrated *in vacuo* to yield the crude aldehyde. The crude aldehyde was dissolved in MeOH (10 mL) and a catalytic amount of *para*-toluenesulfonic acid (60 mg, 0.31 mmol) was added and the resulting mixture was left stirring overnight. Aqueous saturated $NaHCO_3$ solution (20 mL) was added, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), and concentrated *in vacuo* to yield the crude acetal. Purification by flash chromatography (petroleum ether:EtOAc, 1:1) yielded the title compound **296** as a colorless oil (2.2 g, 79%, from alcohol **295**). R_f = 0.3, petroleum ether:EtOAc, 1:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.32 (1H, t, J = 5.7 Hz, CH-C6), 3.65 (2H, t, J = 6.6 Hz, CH_2-C1), 3.32 (6H, s, CH_3-C7), 2.05 (1H, s, OH), 1.65-1.58 (4H, m, CH_2-C5, CH_2-C5), 1.42-1.35 (4H, m, CH_2-C3, CH_2-C3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 104.5 (CH-C6), 62.9 (CH_2-C1), 52.7 (2 × CH_3-C7), 32.7 (CH_2-C5), 32.5 (CH_2-C2), 25.6 (CH_2-C3), 24.4 (CH_2-C4). IR (thin film) 3417 (br), 2942 (s), 2830 (m), 1695 (m) cm^{-1}. HRMS (CI/Isobutane) exact mass calculated for $C_7H_{15}O_2$ [M-OMe]$^+$ m/z 131.1072, found m/z 131.1071.

(*E*)-Ethyl 8,8-dimethoxyoct-2-enoate (297)



297

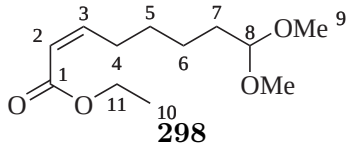
$C_{12}H_{22}O_4$

Mol. Wt.: 230.30

1st method: To a solution of oxalyl chloride (929 μL, 17.0 mmol) in CH_2Cl_2 (20 mL) at −78 °C, was added dropwise DMSO (1.8 mL, 25 mmol). The resulting solution was left stirring at −78 °C and after 15 min a solution of 6,6-dimethoxyhexan-1-ol (**296**) (840 mg, 4.51 mmol) in CH_2Cl_2 (7 mL) was added. The mixture was allowed to stir additional 1.5 h at −78 °C and Et_3N (10 mL) was added; the resulting slurry was allowed to warm to room temperature. CH_2Cl_2 (15 mL) was added and the organic layer was washed with a sat. aqueous solution of NH_4Cl (30 mL) and brine (25 mL), then dried (Na_2SO_4) and concentrated *in vacuo* to yield the crude aldehyde. The crude aldehyde was dissolved in MeOH (10 mL) and *para*-toluenesulfonic acid (15 mg, 0.081 mmol) was added. The resulting mixture was left stirring overnight. Aqueous saturated $NaHCO_3$ (20 mL) was added, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers was washed with brine (30 mL) and dried ($MgSO_4$), then concentrated *in vacuo* to yield the crude acetal. Purification by flash chromatography (petroleum ether:EtOAc, 10:1) yielded the title compound **297** as a colorless oil (737 mg, 71%, from alcohol **296**. **2nd method:** To a solution of oxalyl chloride (1.9 mL, 22 mmol) in CH_2Cl_2 (40 mL) at −78 °C was added dropwise DMSO (3.7 mL, 52 mmol). The resulting

solution was left stirring at −78 °C, and after 15 min a solution of alcohol **300** (1.5 g, 9.3 mmol) in CH_2Cl_2 (15 mL) was added. The mixture was allowed to stir additional 1.5 h at −78 °C and Et_3N (20 mL) was added; the resulting slurry was allowed to warm to room temperature. CH_2Cl_2 (15 mL) was added and the organic layer was washed with a sat. aqueous solution of NH_4Cl (40 mL) and brine (40 mL), then dried (Na_2SO_4), and concentrated *in vacuo* to yield the crude aldehyde. Ethyl 2-(diethoxyphosphoryl)acetate (1.8 mL, 9.3 mmol) was added dropwise at 0 °C to a suspension of sodium hydride (407 mg, 60%, 10.2 mmol). After 30 min a solution of the newly formed aldehyde (9.3 mmol) in THF (10 mL) was added dropwise to the ylide solution, and the resulting mixture was allowed to warm to room temperature for 14 h. The mixture was diluted with water (20 mL) and extracted with EtOAc (3 × 40 mL). The combined organic extracts were washed with brine (40 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the crude compound. Purification by flash chromatography (petroleum ether:EtOAc, 12:1 → 10:1) yielded the title compound **297** as a colorless oil (1.7 g, 81% from alcohol **300**).[113] R_f = 0.24, petroleum ether:EtOAc, 12:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.96 (1H, m, CH-C3), 5.81 (1H, ddt, J = 15.6, 3.2, 1.5 Hz, CH-C2), 4.35 (1H, t, J = 5.7 Hz, CH-C8), 4.18 (2H, q, J= 7.1 Hz, CH_2-C11), 3.31 (6H, s, CH_3-C9), 2.20 (2H, dq, J = 7.3, 1.5 Hz, CH_2-C4), 1.60 (2H, m, CH_2-C7), 1.48 (2H, m, CH_2-C5), 1.36 (2H, m, CH_2-C6), 1.28 (3H, t, J = 7.1 Hz, CH_3-C10). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.6 (C-C1), 148.8 (CH-C3), 121.3 (CH-C2), 104.2 (CH-C8), 60.0 (CH_2-C11), 52.6 (2 × CH_3-C9), 32.1 (CH_2-C7), 31.9 (CH_2-C4), 27.7 (CH_2-C5), 24.0 (CH_2-C6), 14.1 (CH_3-C10). IR (thin film) 2945 (s), 2830 (m), 1717 (s) cm^{-1}. HRMS (CI/Isobutane) exact mass calculated for $C_{11}H_{19}O_3$ m/z [M-OMe]$^+$ 199.1334, found m/z 199.1335.

(*Z*)-Ethyl 8,8-dimethoxyoct-2-enoate (298)



298

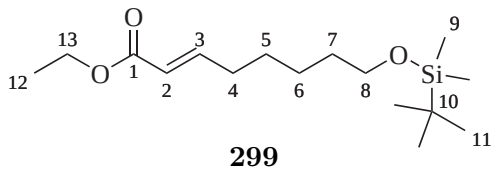
$C_{12}H_{22}O_4$

Mol. Wt.: 230.30

To a solution of oxalyl chloride (636 μL, 7.37 mmol) in CH_2Cl_2 (20 mL) at −78 °C, was added dropwise DMSO (1.2 mL, 17 mmol). The resulting solution was left stirring at −78 °C and after 15 min a solution of alcohol **296** (500 mg, 3.09 mmol) in CH_2Cl_2 (15 mL) was added and the mixture was allowed to stir additional 1.5 h at −78 °C and Et_3N (10 mL) was added; the resulting slurry was allowed to warm to room temperature. CH_2Cl_2 (15 mL) was added and the organic layer was washed with a sat. aqueous solution of NH_4Cl (20 mL) and brine (20 mL), then dried (Na_2SO_4) and concentrated *in vacuo* to yield the crude aldehyde. Meanwhile, a solution of trifluoroethylphosphonoester (730 μL, 3.09 mmol), 18-crown-6 (4.0 g, 15 mmol) in THF (20 mL) was cooled to −78 °C and treated with KHMDS (6.0

mL, 0.5 M in toluene, 3.1 mmol). The newly formed aldehyde (3.09 mmol) was then added and the resulting mixture was stirred for 30 min at −78 °C. Saturated aqueous NH_4Cl solution (10 mL) was added and the product was extracted with ether (3 × 40 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield the crude compound. Purification by flash chromatography (petroleum ether:EtOAc, 10:1) yielded the title compound **298** as a colorless oil (534 mg, 75% from alcohol **296**).[160] R_f = 0.4, petroleum ether:EtOAc, 10:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.20 (1H, dt, J = 11.5, 7.6 Hz, CH-C3), 5.76 (1H, d, J = 11.5 Hz, CH-C2), 4.35 (1H, t, J = 5.8 Hz, CH-C8), 4.13 (2H, q, J = 7.1 Hz, CH_2-C11), 3.31 (6H, s, CH_3-C9), 2.66 (2H, q, J = 7.6 Hz, CH_2-C4), 1.62 (2H, m, CH_2-C7), 1.40 (4H, m, CH_2-C5, CH_2-C6), 1.28 (3H, t, J = 7.1 Hz, CH_3-C10). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.4 (C-C1), 150.1 (CH-C3), 119.8 (CH-C2), 104.4 (CH-C8), 59.8 (CH_2-C11), 52.6 (2 × CH_3-C9), 32.3 (CH_2-C7), 28.9 (CH_2-C4), 28.8 (CH_2-C5), 24.3 (CH_2-C6), 14.3 (CH_3-C10).

(*E*)-Ethyl 8-(*tert*-butyldimethylsilyloxy)oct-2-enoate (299)



299

$C_{16}H_{32}O_3Si$

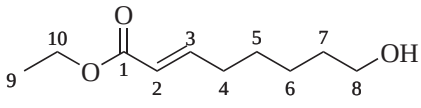
Mol. Wt.: 300.51

To a solution of oxalyl chloride (1.8 mL, 21 mmol) in CH_2Cl_2 (40 mL) at −78 °C, was added dropwise DMSO (3.4 mL, 48 mmol). The resulting solution was left stirring at −78 °C, after 15 min a solution of alcohol **300** (2.0 g, 8.6 mmol) in CH_2Cl_2 (15 mL) was added. The mixture was allowed to stir additional 1.5 h at −78 °C and Et_3N (20 mL, 14 mmol) was added and the resulting slurry was allowed to warm to room temperature. CH_2Cl_2 (15 mL) was added and the organic layer was washed with a sat. aqueous solution of NH_4Cl (40 mL) and brine (40 mL), then dried (Na_2SO_4), and concentrated *in vacuo* to yield the crude aldehyde. Meanwhile, ethyl 2-(diethoxyphosphoryl)acetate (1.7 mL, 8.6 mmol) was added dropwise to a cold 0 °C suspension of sodium hydride (227 mg, 60% in oil, 9.46 mmol). After 30 min the newly formed aldehyde (8.6 mmol) dissolved in THF (10 mL) was added dropwise and the resulting mixture was allowed to warm to room temperature for 14 h. The mixture was diluted with water (20 mL) and extracted with EtOAc (3 × 40 mL). The combined organic extracts were washed with brine (40 mL) and dried ($MgSO_4$), then filtered, and concentrated *in vacuo* to yield the crude compound. Purification by flash chromatography (petroleum ether:EtOAc, 20:1 → 15:1) yielded the title compound **299** as a colorless oil (2.1 g, 82% from alcohol **295**.[113] R_f = 0.6,

[160] Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405-4408.

petroleum ether:EtOAc, 15:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.96 (1H, td, J = 7.4, 15.5 Hz, CH-C3), 5.81 (1H, d, J = 15.5 Hz, CH-C2), 4.18 (2H, q, J = 7.1 Hz, CH_2-C13), 3.60 (2H, t, J = 6.5 Hz, CH_2-C8), 2.20 (2H, q, J = 7.4 Hz, CH_2-C4), 1.52-1.48 (4H, m, CH_2-C5, CH_2-C6), 1.28-1.34 (2H, m, CH_2-C7), 1.28 (3H, t, J = 7.1 Hz, CH_3-C12), 0.89 (9H, s, 3 × CH_3-C11), 0.04 (6H, s, 2 × CH_3-C9). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 165.6 (C-C1), 148.1 (CH-C3), 120.1 (CH-C2), 61.8 (CH_2-C8), 59.9 (CH_2-C13), 31.4 (CH_2-C4), 31.0 (CH_2-C7), 26.6 (CH_2-C5), 24.7 (3 × CH_3-C11), 24.1 (CH_2-C6), 17.1 (C-C10), 13.1 (CH_3-C12), 6.5 (2 × CH_3-C9). IR (thin film) 2931 (s), 2857 (m), 1724 (s), 1654 (m) cm^{-1}. HRMS (EI) exact mass calculated for $C_{16}H_{33}O_3Si$ $[M+H]^+$ m/z 301.2199, found m/z 301.2196.

(*E*)-Ethyl 8-hydroxyoct-2-enoate (300)



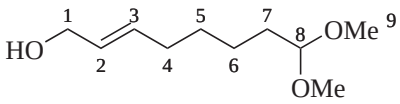
300

$C_{10}H_{18}O_3$

Mol. Wt.: 186.25

To a solution of the TBS protected alcohol **299** (2.1 g, 7.3 mmol) in MeOH (20 mL) was added camphorsulfonic acid (850 mg, 3.66 mmol). The resulting solution was left stirring at room temperature for 15 h. Et_3N (5 mL) was added and the mixture was concentrated *in vacuo* to yield the crude compound. Purification by flash chromatography (petroleum ether:EtOAc, 7:1 → 5:1) yielded the title compound **300** as a colorless oil (937 mg, 72%). R_f = 0.15, petroleum ether:EtOAc, 7:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.94 (1H, m, CH-H3), 5.79 (1H, d,t J = 15.6, 1.6 Hz, CH-C2), 4.16 (2H, q, J = 7.1 Hz, CH_2-C10), 3.73 (1H, s, OH), 3.62 (2H, t, J= 6.5 Hz, CH_2-C8), 2.19 (2H, dq, J = 7.2, 1.6 Hz, CH_2-C4), 1.56 (2H, m, CH_2-C7), 1.47 (2H, m, CH_2-C6), 1.38 (2H, m, CH_2-C5), 1.26 (3H, t, J = 7.1 Hz, CH_3-C9). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 167.4 (C-C1), 149.3 (CH-C3), 121.2 (CH-C2), 63.1 (CH_2-C8), 60.4 (CH_2-C10), 37.3 (CH_2-C4), 36.5 (CH_2-C7), 29.2 (CH_2-C5), 25.3 (CH_2-C6), 14.6 (CH_3-C9). IR (thin film) 3417 (br), 2935 (s), 2861 (m), 1719 (s) cm^{-1}. HRMS (CI/Isobutane) exact mass calculated for $C_{10}H_{19}O_3$ $[M+H]^+$ m/z 187.1334, found m/z 187.1331.

(*E*)-8,8-Dimethoxyoct-2-en-1-ol (301)



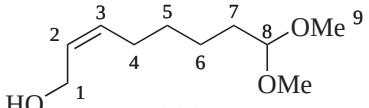
301

$C_{10}H_{20}O_3$

Mol. Wt.: 188.26

DIBAL-H (13.6 mL, 20 wt% in PhMe, 19.1 mmol) was added dropwise to solution of ester **297** (2.0 g, 8.7 mmol) at −78 °C in CH_2Cl_2 (20 mL) and the resulting mixture was allowed to warm to room temperature. The solution was cooled to 0 °C and a sat. aqueous solution of NH_4Cl (10 mL) was added and the mixture was allowed to warm to room temperature. The precipitate was filtered off through a pad of Celite® and the organic layer was concentrated *in vacuo* to yield the title compound **301** as a colorless oil (1.51 g, 92%).[113] ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.54-5.48 (m, 2H, CH-C3, CH-C3), 4.28 (1H, t, J = 5.9 Hz, CH-C8), 4.01 (2H, t, J = 5.4 Hz, CH_2-C1), 3.23 (6H, s, 2 × CH_3-C9), 1.98 (2H, q, J = 6.3 Hz, CH_2-C4), 1.52 (2H, q, J = 5.9 Hz, CH_2-C7), 1.29 (4H, m, CH_2-C5, CH_2-C6), 1.18 (1H, t, J = 5.4 Hz, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 133.4 (CH-C3), 129.4 (CH-C2), 104.7 (CH-C8), 64.1 (CH_2-C1), 52.9 (2 × CH_3-C9), 32.6 (CH_2-C7), 32.6 (CH_2-C4), 29.2 (CH_2-C5), 24.4 (CH_2-C6). IR (thin film) 3410 (br), 2993 (m), 2830 (s), 1762 (s), 1696 (s) cm^{-1}.

(*Z*)-8,8-Dimethoxyoct-2-en-1-ol (302)



302

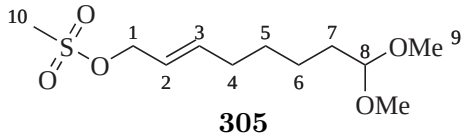
$C_{10}H_{20}O_3$

Mol. Wt.: 188.26

DIBAL-H (3.5 mL, 20 wt% in PhMe, 5.0 mmol) was added dropwise to a solution of ester **298** (520 mg, 2.26 mmol) at −78 °C in CH_2Cl_2 (20 mL) and the resulting mixture was allowed to warm to room temperature. The solution was cooled to 0 °C and a saturated aqueous solution of NH_4Cl (10 mL) was added and allowed to warm to room temperature. The precipitate was filtered off through a pad of Celite® and the organic layer was concentrated *in vacuo* to yield the title compound **302** as a colorless oil (308 mg, 72%).[113] ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.59 (2H, m, CH-C3, CH-C3), 4.35 (1H, t, J = 6.0 Hz, CH-C8), 4.19 (2H, t, J = 6.1 Hz, CH_2-C1), 3.32 (6H, s, 2 × CH_3-C9), 2.10 (2H, q, J = 6.9 Hz, CH_2-C4), 1.60 (2H, dd, J= 6.0, 13.9 Hz, CH_2-C7), 1.38 (5H, m, CH_2-C5, CH_2-C6,

OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 132.4 (CH-C3), 128.7 (CH-C2), 104.4 (CH-C8), 58.3 (CH_2-C1), 52.6 (2 × CH_3-C9), 32.2 (CH_2-C7), 29.2 (CH_2-C4), 27.1 (CH_2-C5), 23.9 (CH_2-C6).

(*E*)-8,8-Dimethoxyoct-2-enyl methanesulfonate (305)



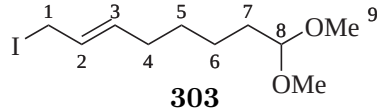
305

$C_{11}H_{22}O_5S$

Mol. Wt.: 266.35

Methanesulfonyl chloride (107 μL, 1.38 mmol) was added dropwise to a solution of alcohol **301** (200 mg, 1.06 mmol) and triethylamine (222 μL, 1.59 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The mixture was allowed to warmed to room temperature and left for 2 h. The reaction mixture was then washed with saturated an aqueous NH_4Cl (2 × 10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound **305** as a colorless oil (198 mg, 70%). The crude material was used in the synthesis of **304** and (**303** without further purification.[105] R_f = 0.1, petroleum ether:EtOAc, 10:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.89 (1H, m, CH-C3), 5.60 (1H, dtt, J = 15.2, 1.4, 6.8 Hz, CH-C2), 4.65 (2H, dd, J = 6.8, 0.8 Hz, CH_2-C1), 4.33 (1H, t, J = 5.7 Hz, CH-C8), 3.29 (6H, s, 2 × CH_3-C9), 2.98 (3H, s, CH_3-C10), 2.08 (2H, q, J = 6.8 Hz, CH_2-C4), 1.57 (2H, m, CH_2-C7), 1.36 (4H, m, CH_2-C5, CH_2-C6). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 134.9 (CH-C3), 128.1 (CH-C2), 104.4 (CH-C8), 65.4 (CH_2-C1), 52.7 (2 × CH_3-C9), 38.0 (CH_3-C10), 32.3 (CH_2-C7), 31.9 (CH_2-C4), 28.7 (CH_2-C5), 24.0 (CH_2-C6).

(*E*)-1-Iodo-8,8-dimethoxyoct-2-ene (303)



303

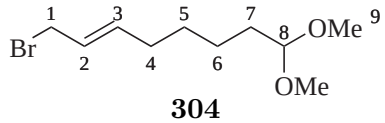
$C_{10}H_{19}IO_2$

Mol. Wt.: 298.16

A solution of LiI (2.5 g, 18 mmol) in THF (10 mL) was added to mesylate **305** (1.80 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The reaction mixture was stirred for 20 min at room temperature and then diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic extracts were washed with water (20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield the title compound **303** as a

colorless oil (454 mg, 85%).[113] ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.67 (2H, m, CH-C2, CH-C3), 4.31 (1H, t, J = 5.7 Hz, CH-C8), 3.83 (2H, m, CH_2-C1), 3.27 (6H, s, 2 × CH_3-C9), 2.04 (2H, q, J = 6.9 Hz, CH_2-C4), 1.59 (2H, m, CH_2-C7), 1.38 (4H, m, CH_2-C5, CH_2-C6). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 134.5 (CH-C3), 127.7 (CH-C2), 104.1 (CH-C8), 52.3 (2 × CH_3-C9), 31.9 (CH-C7), 31.6 (CH_2-C4), 28.3 (CH_2-C5), 23.7 (CH_2-C6), 6.5 (CH_2-C1).

(*E*)-1-Bromo-8,8-dimethoxyoct-2-ene (304)



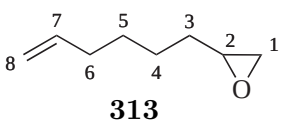
304

$C_{10}H_{19}BrO_2$

Mol. Wt.: 251.16

A solution of LiBr (2.83 g, 27.1 mmol) in THF (10 mL) was added at 0 °C solution of the mesylate **305** (2.71 mmol) in CH_2Cl_2 (15 mL). The reaction mixture was stirred for 20 min at room temperature and then diluted with water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL) and the organic extracts were washed with water (20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield the title compound **304** as a colorless oil (573 mg, 84%).[113] ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.87 (1H, m, CH-C3), 5.58 (1H, m, CH-C2), 4.64 (2H, dd, J = 6.8, 0.6 Hz, CH_2-C1), 4.31 (1H, t, J = 5.8 Hz, CH-C8), 3.25 (6H, s, CH_3-C9), 2.07 (2H, q, J = 6.7 Hz, CH_2-C4), 1.56 (2H, dt, J = 7.3, 5.8 Hz, CH_2-C7), 1.37 (4H, m, CH_2-C5, CH_2-C6). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 136.2 (CH-C3), 126.42 (CH-C2), 104.3 (CH-C8), 52.6 (2 × CH_3-C9), 33.4 (CH_2-C1), 32.2 (CH_2-C7), 31.9 (CH_2-C4), 28.5 (CH_2-C5), 24.9 (CH_2-C6). IR (thin film) 2934 (s), 2829 (m), 1460 (m), 1126 (m) cm^{-1}.

1,2-Epoxyoct-7-ene (313)



313

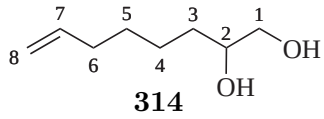
$C_8H_{14}O$

Mol. Wt.: 126.20

A solution of *m*-chloroperoxybenzoic acid (14.0 g, 81 mmol) in CH_2Cl_2 (90 mL) at room temperature was added dropwise to a stirred solution of 1,7-octadiene **312** (10 mL, 0.067 mol) in CH_2Cl_2 (200 mL).

The resulting mixture was stirred at ambient temperature for 24 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (50 mL), the layers were separated, and the organic layer was washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The compound was purified by distillation (bp 64 – 68 °C at 30 mmHg; Lit.[118] bp 76 – 78 °C at 29 mmHg) to yield the title compound **313** as a colorless liquid (4.76 g, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.80 (1H, ddt, J = 16.9, 10.1, 6.7 Hz, CH-C7), 4.96 (2H, m, CH_2-C8), 2.90 (1H, m, CH_2-C1) 2.75 (1H, t, J = 4.6 Hz, CH-C2), 2.47 (1H, dd, J = 4.6, 2.7 Hz, CH_2-C1), 2.05 (2H, q, J = 6.7 Hz, CH_2-C6), 1.44 (6H, m, CH_2-C5, CH_2-C4 and CH_2-C3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 138.7 (CH-C7), 114.5 (CH_2-C8), 52.3 (CH-C2), 47.1 (CH_2-C1), 33.6 (CH_2-C6), 32.3 (CH_2-C3), 28.7 (CH_2-C5), 25.4 (CH_2-C4). IR (thin film) 2977 (m), 2932 (s), 2858 (m), 1640 (m), 1460 (m), 1410 (m) cm^{-1}. The data observed are in accordance with literature values.[118]

1,2-Dihydroxyoct-7-ene (314)



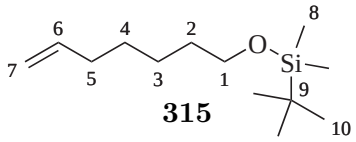
314

$C_8H_{16}O_2$

Mol. Wt.: 144.21

1,7-Epoxyoct-7-ene **313** (2.5 g, 19 mmol) was dissolved in THF (10 mL) and concentrated sulphuric acid (2 drops) in water (3.3 mL) was added. The mixture was stirred at room temperature for 15 h after which ether (20 mL) was added and the two layers separated. The aqueous phase was extracted with ether (3 × 30 mL) and the organic layers were combined, washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to yield the crude compound. The compound was purified by distillation (bp 66 – 68 °C at 3 mmHg; Lit.[118] bp 98 – 100 °C at 0.5 mmHg) *in vacuo* to yield the title compound **314** as a colorless liquid (1.4 g, 49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.80 (1H, ddt, J = 17.0, 10.2, 6.7 Hz, CH-C7), 5.00 (1H, ddd, J = 17.0, 3.6, 1.4 Hz, CH_2-C8), 4.95 (1H, ddt, J = 10.2, 2.2, 1.4 Hz, CH_2-C8), 3.78-3.61 (2H, m, CH_2-C1), 3.46-3.38 (1H, m, CH_2-C2), 2.55-2.40 (2H, m, OH) 2.07 (2H, q, J = 6.9 Hz, CH_2-C6), 1.49-1.35 (6H, m, CH_2-C5, CH_2-C5, CH_2-C3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 138.7 (CH-C7), 114.5 (CH_2-C8), 72.2 (CH-C2), 66.8 (CH_2-C1), 33.6 (CH_2-C3), 32.9 (CH_2-C6), 28.8 (CH_2-C5), 25.0 (CH_2-C4). IR (thin film) 3386 (br), 2930 (s), 2857 (m), 1640 (m), 992 (m), 909 (m) cm^{-1}. HRMS (CI/Isobutane) exact mass calculated for $C_8H_{17}O_2$ m/z $[M+H]^+$ 145.1229, found m/z 145.1227.

tert-Butyl(hept-6-enyloxy)dimethylsilane (315)



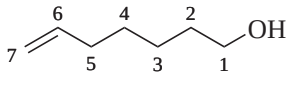
315

$C_{13}H_{28}OSi$

Mol. Wt: 228.45

To a solution of oxalyl chloride (887 μL, 10.3 mmol) in CH_2Cl_2 (20 mL) at −78 °C, was added dropwise DMSO (1.7 mL, 24 mmol). The resulting solution was left stirred at −78 °C for 15 min and a solution of alcohol **295** (1.0 g, 4.3 mmol) in CH_2Cl_2 (7 mL) was added. The mixture was then stirred for an additional 1.5 h at −78 °C and triethylamine (8 mL) was added; the resulting slurry was allowed to warm to room temperature. CH_2Cl_2 (15 mL) was added and the organic layer was washed with a sat. aqueous solution of NH_4Cl (40 mL) and brine (40 mL), then dried (Na_2SO_4) and concentrated *in vacuo* to yield the crude aldehyde. Meanwhile, potassium *tert*-butoxide (1.2 g, 11 mmol) was added to methyltriphenylphosphonium bromide (3.9 g, 11 mmol) in THF (15 mL) and the mixture was stirred at room temperature for 30 min to yield a bright yellow solution. The aldehyde (4.3 mmol), dissolved in THF (5 mL), was added dropwise and the resulting mixture was stirred at room temperature for 14 h. The mixture was diluted with water (15 mL) and extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the crude compound. Purification by flash chromatography (petroleum ether) yielded the title compound **315** as a colorless oil (888 mg, 90% from alcohol **295**). R_f = 0.28, petroleum ether. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.78 (1H, ddt, J = 17.0, 10.2, 6.7 Hz, CH-C6), 4.97 (1H, ddd, J = 17.0, 3.7, 1.4 Hz, CH_2-C7), 4.91 (1H, ddt, J = 10.2, 2.3, 1.4 Hz, CH_2-C7), 3.57 (2H, t, J = 6.7 Hz, CH_2-C1), 2.03 (2H, q, J = 6.8 Hz, CH_2-C5), 1.50 (2H, m, CH_2-C2), 1.35 (4H, m, CH_2-C4, CH_2-C3), 0.87 (9H, s, CH_2-C10), 0.02 (6H, s, CH_2-C8). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 136.6 (CH-C6), 111.8 (CH_2-C7), 60.8 (CH_2-C1), 31.4 (CH_2-C5), 30.3 (CH_2-C2), 26.3 (CH_2-C4), 23.7 (3 × CH_3-C10), 22.9 (CH_2-C3), 16.0 (C-C9), 7.7 (2 × CH_3-C8).

6-Hepteneol (316)



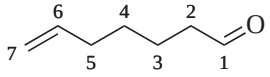
316

$C_7H_{14}O$

Mol. Wt.: 114.19

The TBS protected alcohol **295** (1.2 g, 5.3 mmol) was dissolved in MeOH (20 mL) and camphorsulfonic acid (610 mg, 2.63 mmol) was added. The resulting solution was left stirring at room temperature for 15 h. Trietylamine (2 mL) was added and the mixture was concentrated *in vacuo* to yield the crude compound. Purification by flash chromatography (petroleum ether:ether, 3:2) yielded the title compound **316** as a colorless oil (564 mg, 94%). $R_f = 0.36$, petroleum ether:ether, 3:2. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.81 (1H, ddt, J = 16.9, 10.1, 6.8 Hz, CH-C6), 4.98 (2H, m, CH_2C-7), 3.64 (2H, t, J = 6.8 Hz, CH_2-C1), 2.07 (2H, q, J = 6.8 Hz, CH_2-C5), 1.58 (2H, m, CH_2-C2), 1.39 (4H, m, CH_2-C4, CH_2-C3), 1.25 (1H, br s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 138.9 (CH-C6), 114.4 (CH_2-C7), 63.0 (CH_2-C1), 33.7 (CH_2-C5), 32.6 (CH_2-C2), 28.7 (CH_2-C4), 25.2 (CH_2-C3).

6-Heptenal (310)



310

$C_7H_{12}O$

Mol. Wt.: 112.17

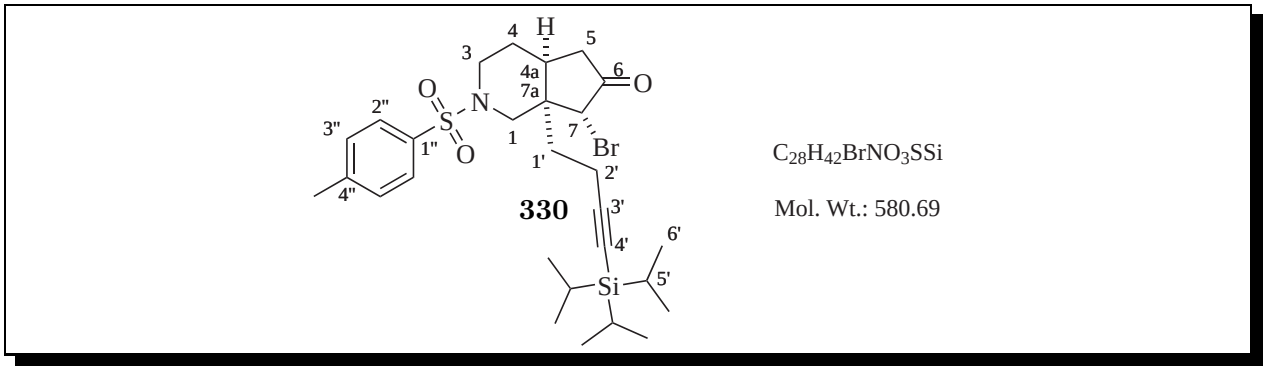
1st method: To a solution of 7-octene-1,2-diol (**314**) (98 mg, 6.8 mmol) in water (5 mL) was added an aqueous solution (5 mL) of $NaIO_4$ (1.6 g, 7.5 mmol) over a period of 10 min, a slight exotherm was observed. The resulting mixture was stirred at room temperature for an additional 1.5 h. The mixture was then decanted into a separatory funnel and the layers were separated. The organic fraction was dried (Na_2SO_4) and filtered to give the title compound **310** as a colorless liquid (678 mg, 89%).[161]
2nd method: Oxalyl chloride (887 μL, 10.3 mmol) was dissolved in CH_2Cl_2 (20 mL) and cooled to −78 °C, followed by dropwise addition of DMSO (1.7 mL, 24 mmol). The resulting solution was left stirring at −78 °C and after 15 min a solution of alcohol **316** (1.0 g, 4.3 mmol) in CH_2Cl_2 (7 mL) was added. The mixture was allowed to stir additional 1.5 h at −78 °C and triethylamine (8 mL) was added; the resulting slurry was allowed to warm to room temperature. CH_2Cl_2 (10 mL) was added and the organic layer was washed with a sat. aqueous solution of NH_4Cl (40 mL) and brine (40 mL), then dried (Na_2SO_4) and concentrated *in vacuo* to yield the aldehyde **310** as a colorless liquid (100 mg, 50%) without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.77 (1H, t, J = 1.8 Hz, CH-C1), 5.79 (1H, ddt, J = 17.1, 10.3, 6.9 Hz, CH-C6), 5.02 (1H, ddd, J = 17.1, 3.6, 1.4 Hz, CH_2-C7), 4.97 (1H, ddt, J = 10.3, 2.2, 1.4 Hz, CH_2-C7), 2.45 (2H, m, CH_2-C2), 2.08 (2H, q, J = 6.9 Hz, CH_2-C5), 1.65 (2H, m, CH_2-C3), 1.44 (2H, quint, J = 7.5 Hz, CH_2-C4). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 200.3 (CH-C1), 135.8 (CH-C6), 112.5 (CH_2-C7), 41.3 (CH_2-C2), 31.0

[161] Faucher, A.-M.; Bailey, M.; Beaulieu, P.; Brochu, C.; Duceppe, J.-S.; Ferland, J.-M.; Ghiro, E.; Gorys, V.; Halmos, T.; Kawai, S.; Poirier, M.; Simoneau, B.; Tsantrizos, Y.; Llinas-Brunet, M. *Org. Lett.* **2004**, *6*, 2901-2904.

(CH_2-C5), 25.9 (CH_2-C4), 19.1 (CH_2-C3). IR (Neat) 3422 (br), 2931 (s), 2859 (m), 1725 (s) cm^{-1}. HRMS (CI/Isobutane at low temperature) exact mass calculated for $C_7H_{13}O$ m/z $[M+H]^+$ 113.0966, found m/z 113.0954.

The data observed are in accordance with literature values.[118]

7-Bromo-2-(toluene-4-sulfonyl)-7a-(4-triisopropylsilanyl-but-3-ynyl)-octahydro -[2]pyrindin-6-one (330)



$C_{28}H_{42}BrNO_3SSi$

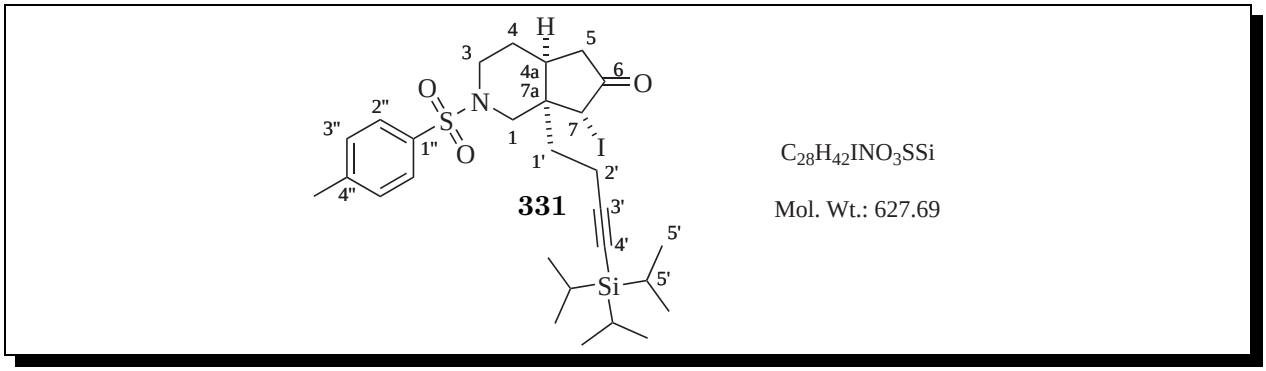
Mol. Wt.: 580.69

To a solution of 1-iodo-4-(triisopropylsilyl)-3-butyne (**267**) (500 mg, 1.49 mmol) in ether (10 mL) at −78 °C was added *tert*-butyllithium (1.9 mL, 1.6 M in hexane, 3.0 mmol) and stirred 20 min. The reaction mixture was warmed to room temperature and allowed to stir for an additional 20 min. Meanwhile, dimethylsulfide (1.30 mL, 18.8 mmol) was added to a solution of copper iodide (142 mg, 0.745 mmol) in THF (20 mL). After all the copper iodide had dissolved, the solution was cooled to −40 °C and the organolithium solution was added by syringe to afford a black slurry and stirred for 15 min. A pre-cooled (0 °C) solution of the enone **227** (124 mg, 0.426 mmol) and chlorotrimethylsilane (0.13 mL, 1.1 mmol) in THF (10 mL) was added dropwise and the mixture was allowed to warm to room temperature overnight. The reaction was quenched with a 10% NH_4OH/NH_4Cl solution (10 mL). The biphasic mixture was extracted with EtOAc (3 × 30 mL), washed with brine (30 mL), then dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield the crude compound. The crude material was used without further purification. The silyl enol ether (0.42 mmol) was dissolved in THF and the solution was cooled to −78 °C. A solution of *N*-bromosuccinimide (90 mg, 0.51 mmol) in THF (7 mL) was added dropwise and the mixture was allowed to stir for 2 h. The mixture was then allowed to warm to room temperature and concentrated *in vacuo* to afford the crude product. Purification by flash chromatography (petroleum ether:EtOAc, 4:1) yielded the title compound **330** as a colorless foam (182 mg, 74%).[162] $R_f = 0.24$, petroleum ether:EtOAc, 4:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.61 (2H, d, $J = 7.8$ Hz, CH-C2"), 7.33 (2H, d, $J = 7.8$ Hz, CH-C3"), 4.41 (1H, br s, CH-C7), 3.29-3.22 (1H, m, CH_2-C3), 3.16-3.06 (1H, m, CH_2-C1), 2.78-2.69 (1H, m, CH_2-C3), 2.56-2.31 (5H, m, CH-C4, CH_2-C1, CH_2-C5 and CH_2-C2'), 2.45 (3H, s, CH_3), 2.12-1.97 (3H, m, CH_2-C4, CH_2-C5 and CH_2-C1'), 1.65-1.54 (2H, m, CH_2-C4, CH_2-C1'), 1.10-1.00 (21H, m, CH-C5' and CH_3-C6'). ^{13}C NMR (100

[162] Carson, C. A.; Kerr, M. A. *Org. Lett.* **2009**, *11*, 777-779.

MHz, $CDCl_3$) δ (ppm): 216.2 (C-C7), 143.9 (C-C4"), 132.9 (C-C1"), 130.0 (2 × CH-C2"), 127.5 (2 × CH-C3"), 107.8 (C-C4'), 81.6 (C-C3'), 57.1 (CH-C7), 48.9 (CH_2-C1), 42.3 (CH_2-C3), 41.5 (C-C7a), 40.4 (CH_2-C5), 37.2 (CH-C4a), 34.9 (CH_2-C1'), 24.8 (CH_2-C4), 21.6 (CH_3), 18.7 (6 × CH_3-C6'), 15.3 (CH_2-C2'), 11.3 (3 × CH_2-C5'). IR (Neat) 2941 (m), 2926 (m), 2169 (s), 1745 (m), 1464 (m), 1161 (s), 1091 (m) cm^{-1}. HRMS (FAB/NOBA) exact mass calculated for $C_{28}H_{42}{}^{79}BrNO_3SSi$ $[M]^+$ m/z 580.1916, found m/z 580.1920.

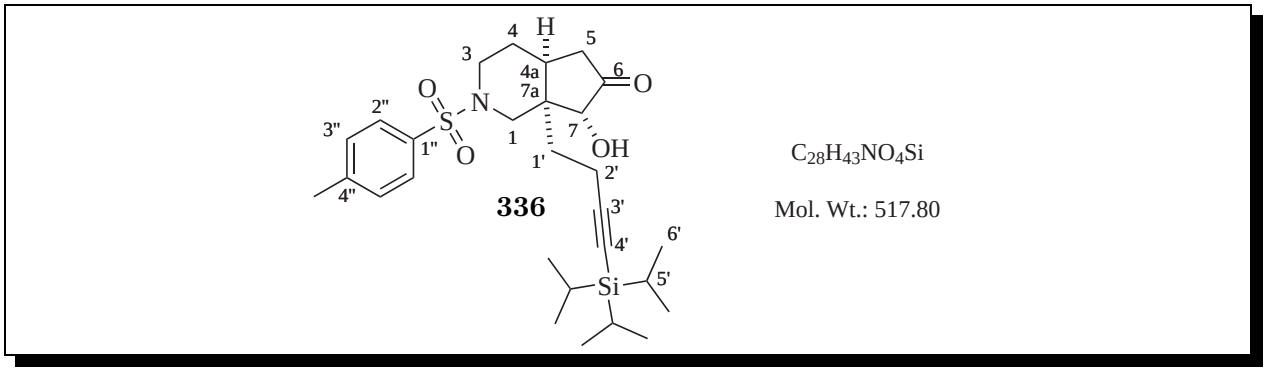
7-Iodo-2-(toluene-4-sulfonyl)-7a-(4-triisopropylsilanyl-but-3-ynyl)-octahydro -[2]pyrindin-6-one (331)



To a solution of 1-iodo-4-(triisopropylsilyl)-3-butyne (**267**) (1.2 g, 3.3 mmol) in ether (30 mL) at −78 °C was added *tert*-butyllithium (4.1 mL, 1.6 M in hexane, 6.6 mmol) and stirred 20 min. The reaction mixture was warmed to room temperature and allowed to stir for an additional 20 min. Meanwhile, dimethylsulfide (3.0 mL, 42 mmol) was added to a solution of copper iodide (317 mg, 1.67 mmol) in THF (30 mL). After all the copper iodide had dissolved, the solution was cooled to −40 °C and the organolithium solution was added by syringe to afford a black slurry and stirred for 15 min. A pre-cooled (0 °C) solution of the enone **227** (277 mg, 0.952 mmol) and chlorotrimethylsilane (0.3 mL, 2 mmol) in THF (15 mL) was added dropwise and the mixture was allowed to warm to room temperature overnight. The reaction was quenched with a 10% NH_4OH/NH_4Cl solution (15 mL). The biphasic mixture was extracted with EtOAc (3 × 30 mL), washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to yield the crude compound. The crude material was used without further purification. The silyl enol ether (0.95 mmol) was dissolved in THF (10 mL) and cooled to −78 °C. A solution of *N*-iodosuccinimide (256 mg, 1.15 mmol) in THF (10 mL) was added dropwise and the mixture was allowed to stir for 2 h. After 2 h the mixture was allowed to warm to room temperature and concentrated *in vacuo* to afford the crude product. Purification by flash chromatography (petroleum ether:EtOAc, 9:1 → 4:1) yielded the title compound **331** as a colorless foam (442 mg, 74%).[162] R_f = 0.5, petroleum ether:EtOAc, 4:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.66 (2H, d, J = 8.1 Hz, CH-C2"), 7.35 (2H, d, J = 8.1 Hz, CH-C3"), 4.51 (1H, br s, CH-C7), 3.78-3.68 (1H, m, CH_2-C3), 3.55 (1H, dd, J = 1.3, 16.0 Hz, CH_2-C1), 2.69-2.64 (1H, m, CH_2-C3), 2.60-2.15 (5H, m, CH_2-C5, CH-C4a, CH_2-C1' and CH_2-C2') 2.45 (3H, s, CH_3), 2.22 (1H, d, J = 16.0 Hz, CH_2-

C1), 2.18-2.05 (1H, m, CH_2-C4) 2.05-1.95 (1H, m, CH_2-C5), 1.74-1.55 (2H, m, CH_2-C4, CH_2-C1'), 1.10-0.90 (21H, m, CH-C5' and CH_3-C6'). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 209.2 (C-C76), 144.2 (C-C1"), 133.6 (C-C4"), 129.9 (2 × C, CH-C3"), 127.5 (2 × C, CH-C2"), 107.9 (C-C4'), 81.3 (C-C3'), 44.4 (C-C7a), 43.9 (CH_2-C1), 42.2 (CH_2-C3), 39.6 (CH-C7), 36.5 (CH_2-C5), 35.1 (CH-C4a), 34.8 (CH_2-C1'), 24.4 (CH_2-C4), 21.6 (CH_3), 18.6 (6 × CH_3-C6'), 15.1 (CH_2-C2'), 11.3 (3 × CH_2-C5'). IR (Neat) 2941 (m), 2864 (m), 2175 (s), 1739 (m), 1354 (m), 1161 (s)cm^{-1}. HRMS (CI/Isobutane) exact mass calculated for $C_{28}H_{43}NO_3SSi$ 628.1778 $[M+H]^+$ m/z, found 628.1776 m/z. Microanalysis calculated for $C_{28}H_{43}NO_4SSi$: C, 53.58%; H, 6.74%; N, 2.23%. Found C 53.60%, H 6.87%, N 2.31%.

7-Hydroxy-2-(toluene-4-sulfonyl)-7a-(4-triisopropylsilanyl-but-3-ynyl)-octahydro -[2]pyridin-6-one (336)

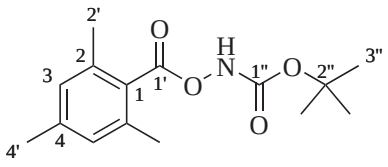


To a solution of 1-iodo-4-(triisopropylsilyl)-3-butyne (**267**) (1.4 g, 4.2 mmol) in ether (15 mL) at −78 °C was added *tert*-butyllithium (5.2 mL, 1.6 M in hexane, 8.3 mmol) and the mixture was stirred 20 min. The reaction mixture was warmed to room temperature and allowed to stir for an additional 20 min. Meanwhile, dimethylsulfide (3.8 mL, 52 mmol) was added to a solution of copper iodide (396 mg, 2.08 mmol) in THF (20 mL). After all the copper iodide had dissolved, the solution was cooled to −40 °C and the organolithium solution was added by syringe to afford a black slurry which was stirred for a further 15 min. A pre-cooled (0 °C) solution of the enone **227** (346 mg, 1.18 mmol) and chlorotrimethylsilane (0.38 mL, 3.0 mmol) in THF (10 mL) was added dropwise and the mixture was allowed to warm to room temperature overnight. The reaction was quenched with a 10% NH_4OH/NH_4Cl solution (10 mL). The biphasic mixture was extracted with EtOAc (3 × 30 mL), washed with brine (30 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield the crude compound. The crude material was used without further purification. The silyl enol ether **281** (1.18 mmol) was dissolved in THF (5 mL) and cooled to 0 °C. DMDO[163] (16.0 mL, 0.085 M, 1.4 mmol) in acetone was added dropwise and the mixture was allowed to stir for 2 h. After 2 h the mixture was concentrated *in vacuo* and re-dissolved in THF (16 mL). Acetic acid (6 mL) and H_2O (6 mL) were added and the mixture allowed to stand. After 2 h, saturated aqueous $NaHCO_3$ (15 mL) was added carefully along with EtOAc (20 mL). The biphasic system was separated and the organic layer

[163] Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377.

washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), then dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield the crude material. Purification by flash chromatography (petroleum ether:EtOAc, 4:1 → 1:3) yielded the title compound as a colorless oil (407 mg, 66%).[125] R_f = 0.23, petroleum ether:EtOAc, 4:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.66 (2H, d, J = 8.0 Hz, CH-C2"), 7.35 (2H, d, J = 8.0 Hz, CH-C3"), 4.51 (1H, br s, CH-C7), 3.75 (1H, d, J = 12.0 Hz, CH_2-C3), 3.60 (1H, d, J = 16.0 Hz, CH_2-C1), 2.60-2.15 (6H, m, CH-C4a, CH_2-C3, CH_2-C1, CH_2-C5, CH_2-C1' and CH_2-C2'), 2.45 (3H, s, CH_3), 2.10-2.00 (1H, m, CH_2-C5), 1.95-1.87 (1H, m, CH_2-C4), 1.75-1.55 (3H, m, CH_2-C4, CH_2-C2' and OH), 1.50-1.40 (1H, m, CH_2-C2'), 1.10-0.90 (21H, m, CH-C5' and CH_3-C6'). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 215.6 (C-C6), 143.8 (C-C4"), 133.6 (C-C1"), 129.9 (2 × CH-C2"), 127.5 (2 × CH-C3"), 107.9 (C-C3'), 81.3 (C-C4'), 76.9 (CH-C7) 47.9 (CH_2-C3), 45.3 (CH_2-C1), 43.6 (C-C7a), 39.4 (CH_2-C5), 31.9 (CH-C4a), 30.4 (CH_2-C1'), 29.2 (CH_2-C4), 21.6 (CH_3), 18.8 (6 × CH_3-C6'), 14.8 (CH_2-C2'), 11.2 (3 × CH_2-C5'). IR (Neat) 3483 (m), 2941 (s), 2864 (m), 2169 (s), 1749 (m), 1464 (w), 1338 (m), 1163 (s) cm^{-1}. HRMS (CI+) exact mass calculated for $C_{28}H_{44}NO_4SSi$ $[M+H]^+$ m/z 518.2760, found m/z 518.2756. Microanalysis calculated for $C_{28}H_{43}NO_4SSi$ C, 64.95%, H, 8.37%, N, 2.71%, found C 64.48%, H 8.40%, N 2.88%.

tert-Butyl 2,4,6-trimethylbenzoyloxycarbamate (343)



$C_{15}H_{21}NO_4$

Mol. Wt.: 279.33

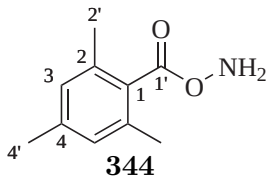
343

To a solution of *N*-Boc-hydroxylamine (**342**) (7.68 g, 57.7 mmol) in CH_2Cl_2 (300 mL) at 0 °C was added Et_3N (8.79 mL, 63.2 mmol), followed by slow addition of 2,4,6-trimethylbenzoyl chloride (**341**) (10 g, 55 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was allowed to warm to room temperature and stirred for additional 18 h. The resulting mixture was washed with water (50 mL), saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to yield the crude material as an yellow oil. Purification by flash chromatography (CH_2Cl_2) yielded the title compound **343** as a colorless solid (10.0 g, 90%). M.p. 76 − 78 °C; lit.[164] m.p. 75 − 76 °C. R_f = 0.2, CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.09 (1H, br s, NH), 6.91 (2H, s, CH-C3), 2.37 (6H, s, CH_3-C2'), 2.26 (3H, s, CH_3-C4'), 1.60 (9H, s, CH_3-C3"). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 169.3 (C-C1'), 155.6 (C-C1"), 140.8 (C-C4), 136.7 (2 × C-C2), 129.1 (2 × CH-C3), 126.7 (C-C1), 83.3 (C-C2"), 28.1 (3 × CH_3-C3"), 21.0 (CH_3-C4'), 19.3 (2 × CH_3-C2'). IR (thin film) 3277

[164] Marmer, W. N.; Maerker, G. *J. Org. Chem.* **1972**, *37*, 3520-3523.

(m), 2984 (m), 1772 (s), 1751 (s) cm^{-1}. HRMS (FAB/NOBA) exact mass calculated for $C_{15}H_{22}NO_4$ $[M+H]^+$ m/z 280.1549, found m/z 280.1545.

O-(2,4,6-Trimethylbenzoyl)-hydroxylamine (344)



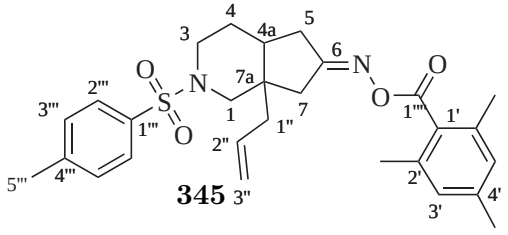
344

$C_{10}H_{13}NO_2$

Mol. Wt.: 179.22

tert-Butyl 2,4,6-trimethylbenzoyloxycarbamate (**342**) (2.0 g, 7.2 mmol) was dissolved in CH_2Cl_2 at 0 °C and CF_3CO_2H (503 μL, 71.6 mmol) was added in one portion. The mixture was stirred at 0 °C for 30 min and then allowed to warm to room temperature. The solvent and excess CF_3CO_2H were evaporated without heat *in vacuo*, and the resulting residue was dissolved in CH_2Cl_2 (50 mL) and washed carefully with a saturated aqueous $NaHCO_3$ solution (30 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* (room temperature to afford the title product **344** as an off white oil (1.1 g, 86%).[165] ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.85 (2H, s, CH-C3), 6.45 (2H, br s, NH_2), 2.29 (9H, s, CH_3-C4', CH_3-C2'). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 173.6 (C-C1'), 139.6 (C-C4), 135.7 (2 × C-C2), 128.2 (2 × CH-C3) 127.9 (C-C1), 20.3 (CH_3-C4'), 19.9 (CH_3-C2'). IR (thin film) 2961 (m), 2922 (m), 1729 (s) cm^{-1}. HRMS (CI/Isobutane) exact mass calculated for $C_{10}H_{14}NO_2$ m/z 180.1025, found m/z 180.1024.

7a-Allyl-2-(toluene-4-sulfonyl)-*N*-2,4,6-trimethyl-benzyloxy-octahydro-[2]prindin -ylideneamine (345)



345

$C_{28}H_{34}N_2O_4S$

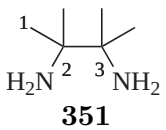
Mol. Wt.: 494.65

To a suspension of copper iodide (326 mg, 1.72 mmol) in THF (15 mL) at 0 °C was added dropwise allylmagnesium chloride (1.7 mL, 2 M in THF, 3.4 mmol). The mixture was left stirring for 5 min

[165] Boche, G. *Encyclopedia of Reagents for Organic Synthesis; O-Mesitoylhydroxylamine;* John Wiley & Sons, Ltd.: 2001.

followed by the addition of 2-tosyl-1,2,3,4,4a,5-hexahydrocyclopenta[c]pyridin-6-one (**227**) (200 mg, 0.686 mmol) and chlorotrimethylsilane (226 μL, 1.78 mmol) dissolved in THF (5 mL). The reaction mixture was left stirring at 0 °C for 2 h, after which the reaction was quenched by the addition of 10% NH_4Cl/NH_4OH solution (5 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL), and the combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) then concentrated *in vacuo* to yield the crude compound. The silyl enol ether (0.69 mmol) was dissolved in THF (7 mL), cooled to −78 °C and treated with $TiCl_4$ (75 μL, 0.68 mmol) to afford a deep red solution. *O*-(2,4,6-Trimethylbenzoyl)-hydroxylamine (**344**) (246 mg, 1.37 mmol) in THF (5 mL) was added and the solution allowed to warm to room temperature. $NaHCO_3$ solution (10 mL) was added and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 3:1) yielded the title compound **345** as a colorless oil (45 mg, 13%). R_f = 0.6, petroleum ether:EtOAc, 2:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.55 (2H, d, J = 8.1 Hz, 2 × CH-C2"'), 7.25 (2H, d, J = 8.1 Hz, 2 × CH-C3"'), 6.92 (2H, s, CH-C3') 5.67 (1H, ddt, J = 17.8, 10.3, 7.3 Hz, CH-C2"), 5.09 (2H, m, CH_2-C3"), 3.01-2.92 (1H, m, CH_2-C3), 2.86-2.78 (2H, m, CH_2-C3, CH_2-C1), 2.67 (1H, dd, J = 16.8, 7.2 Hz, CH_2-C1"), 2.54-2.46 (1H, m, CH_2-C4a), 2.45-2.23 (2H, m, CH-C7, CH_2-C1), 2.38 (3H, s, CH_3-C4"'), 2.33-2.20 (2H, m, CH_2-C7, CH_2-C5), 2.26 (6H, s, CH_3-C2'), 2.23 (3H, s, CH_3-C4'), 2.07 (1H, dd, J = 13.8, 7.3 Hz, CH_2-C1"), 1.94-1.82 (2H, m, CH_2-C4, CH_2-C5), 1.56-1.44 (1H, m, CH_2-C4). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 172.1 (C-C6), 167.4 (C-C1""") 143.8 (C-C3"'), 139.9 (C-C4') 135.7 (2 × C-C2'), 132.9 (C-C1"'), 132.4 (CH-C1") 129.8 (2 × CH-C3"'), 128.9 (C-C1'), 128.5 (2 × CH-C3') 127.6 (2 × CH-C2"'), 119.7 (CH_2-C3"), 60.5 (C-C7a) 49.4 (CH_2-C1), 42.8 (CH_2-C7), 40.4 (CH_2-C3), 38.4 (CH-C4a), 37.3 (CH_2-C5), 33.5 (CH_2-C1"), 25.1 (CH_2-C4), 21.5 (CH_3-C4') 21.2 (CH_3-C4"'), 19.9 (2 × CH_3-C22). IR (thin film) 3072 (m), 2923 (m), 2851 (m), 1747 (s), 1639 (m), 1442 (m), 1338 (m), 1184 (s) cm^{-1}. HRMS (FAB/NOBA) exact mass calculated for $C_{28}H_{35}N_2O_4S$ $[M]^+$ m/z 495.2318, found m/z 495.2313.

2,3-Diamino-2,3-dimethylbutane (351)



351

$C_6H_{16}N_2$

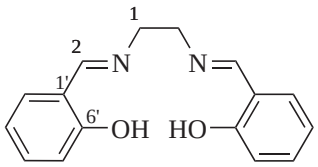
Mol. Wt.: 116.20

To a suspension of 2,3-dimethyl-2,3-dinitrobutane (**350**) (5.00 g, 28.4 mmol) in concentrated hydrochloric acid (75 mL) was added granular tin (30.0 g) portionwise. Following the addition of granular tin the mixture was heated to reflux for 3 h (the mixture became clear and pale yellow upon heating).

The mixture was allowed to cool slowly to room temperature over night. The mixture was basidified (pH = 14) by slow addition of ice-cold 20% NaOH solution. The mixture was steam distilled and the resulting mixture was extracted with $CHCl_3$ (5 × 50 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to yield the title compound **351** as a colorless solid (1.8 g, 55%).[134] ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.24 (4H, br s, NH_2), 1.15 (12H, s, CH_3-C1). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 54.6 (2 × C-C2, C-C3), 26.4 (4 × CH_3-C1). IR (thin film) 3400 (m), 3300 (m), 2967, (m), 2917 (m), 1570 (s), 1461 (m), 1371 (m) cm^{-1}.

The observed values are in accordance with literature values.[134,135]

H_2Salen (354)



354

$C_{16}H_{16}N_2O_2$

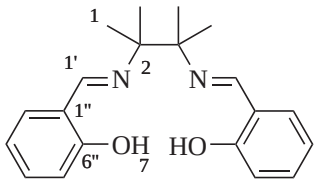
Mol. Wt.: 268.31

To a solution of salicylaldehyde (**353**) (16.8 mL, 0.157 mol) in ethanol (100 mL) was added 1,2-diaminoethane (5.0 mL, 75 mmol) dropwise over 10 min and the mixture was brought to reflux. After 24 h the solution cooled to 0 °C. After one hour at 0 °C, the yellow precipitate was filtered and washed with ethanol (2 × 15 mL) cooled to 0 °C. The filtered material required no further purification and the title compound **354** was obtained as yellow crystals (18.8 g, 94%). M.p. 125 − 127 °C; lit.[167] 126 − 127 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 13.21 (2H, s, OH), 8.39 (2H, s, CH-C2), 7.34-7.29 (2H, m, CH-Ar), 7.25 (2H, dd, J = 7.6, 1.6 Hz, CH-Ar), 6.96 (2H, br d, J = 8.4 Hz, CH-Ar), 6.88 (2H, dt, J = 7.6, 1.2 Hz, CH-Ar), 3.97 (4H, s, CH_2-C1). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.5 (2 × CH-C2), 161.0 (2 × C-C6'), 132.4 (2 × CH-Ar), 131.5 (2 × CH-Ar), 118.7 (2 × CH-Ar), 118.6 (2 × C-C1'), 116.9 (2 × CH-Ar), 59.8 (2 × CH_2-C1). IR (Neat) 2904 (m), 1628 (s), 1574 (s), 1496 (s), 1452 (s), 1416 (m), 1282 (s), 1149 (s), 1042 (s), 1021 (s), 856 (s), 748 (s) cm^{-1}. HRMS (FAB/NOBA) exact mass calculated for $C_{16}H_{16}N_2O_2$ m/z 268.1212, found m/z 268.1214.

The observed values are in accordance with literature values.[133]

[167] Chen, F.-X.; Liu, X.; Qin, B.; Zhou, H.; Feng, X.; Zhang, G. *Synthesis* **2004**, 2266-2272.

H_2Saltmen (355)



355

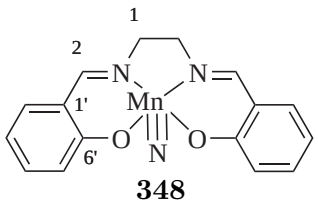
$C_{20}H_{24}N_2O_2$

Mol. Wt.: 324.42

To a solution of salicylaldehyde (**353**) (755 μL, 7.06 mmol) in ethanol (10 mL) was added 2,3-diamino-2,3-dimethylbutane (**351**) (400 mg, 3.44 mmol) in a single portion. The resulting yellow mixture was heated at reflux. After 12 h, water (4 mL) was added and reflux continued for an additional 5 min. Heating was discontinued and the solution was cooled slowly to room temperature. The flask, which contained yellow precipitate was placed in a freezer at -20 °C and allowed to stand at this temperature for 4 h. The crystalline product was filtered and washed with cold ethanol (2×15 mL). The filtered material required no further purification and the title compound **355** was obtained as yellow crystals (934 mg, 84%). M.p. $114 - 117$ °C; lit.[168] 117 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 14.08 (2H, s, OH), 8.38 (2H, s, CH-C8), 7.32-7.25 (4H, m, CH-Ar), 6.95 (2H, br d, $J = 8.8$ Hz, CH-Ar), 6.86 (2H, dt, $J = 7.5$, 1.0 Hz, CH-Ar), 1.40 (12H, s, CH_3-C1). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 161.6 ($2 \times$ CH-C1'), 161.5 ($2 \times$ C-C6"), 132.3 ($2 \times$ CH-Ar), 131.7 ($2 \times$ CH-Ar), 118.9 ($2 \times$ CH-Ar), 118.4 ($2 \times$ C-C1"), 117.1 ($2 \times$ CH-Ar), 65.2 ($2 \times$ C-C2), 23.1 ($4 \times$ CH_3-C1). IR (Neat) 2982 (m), 2947 (m), 2868 (m), 1623 (s), 1580 (m), 1496 (m), 1379 (m), 1277 (s), 1217 (m), 1109 (m), 945 (m), 891 (m), 829 (m), 749 (m), 738 (m) cm^{-1}. HRMS (FAB/NOBA) exact mass calculated for $C_{20}H_{25}N_2O_2$ $[M+H]^+$ m/z 325.1916, found m/z 325.1912.

The observed values are in accordance with literature given.[132]

(Salen)Mn(N) (348)



348

$C_{16}H_{14}MnN_3O_2$

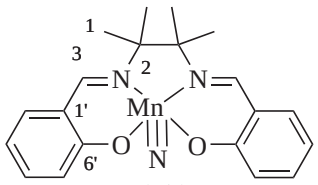
Mol. Wt.: 335.24

H_2salen (**354**) (4.0 g, 15 mmol) was suspended in MeOH (200 mL) and the mixture was heated to $55 - 60$ °C. To the yellow solution was added $Mn(OAc)_2.4H_2O$ (3.86 g, 15.8 mmol) portionwise. The

[168] Averill, D. F.; Broman, R. F. *Inorg. Chem.* **1978**, *17*, 3389.

resulting dark solution was heated to reflux for one hour and then 30 min at room temperature. Concentrated NH_4OH (8 M, 28.0 mL, 225 mmol) was then added dropwise over a 5 min period. To the vigorously stirring mixture was added bleach (225 mL, 0.4 M aq. NaOCl, 90 mmol) over 40 min. During the addition, the evolution of a white gas was observed. When addition was complete, the reaction mixture was cooled to 0 °C and CH_2Cl_2 (200 mL) was cautiously added and stirred at 0 °C for additional 30 min. The resulting biphasic misture was transferred to a separatory funnel with additional H_2O (100 mL). The dark green organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with H_2O (6 × 150 mL) and concentrated *in vacuo* to afford the crude compound. The crude material was suspended in EtOAc and petroleum ether was added. The mixture was cooled to room temperature and then placed in a freezer at −20 °C for 10 h. The dark green precipiate was collected to yield the title compound **348** (3.28 g, 66%). M.p. > 200 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.08 (2H, s, CH-C2), 7.40 (2H, br t, J = 7.5 Hz, CH-Ar), 7.18 (4H, br t, J = 6.7 Hz, CH-Ar), 6.70 (2H, br t, J = 7.3 Hz, CH-Ar), 3.95-3.85 (2H, m, CH_2-C1), 3.80-3.75 (2H, m, CH_2-C1). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 168.1 (2 × C-C5'), 166.7 (2 × CH-C2), 136.2 (2 × CH-Ar), 133.6 (2 × CH-Ar), 122.8 (2 × C-C1'), 120.2 (2 × CH-Ar), 116.5 (2 × CH-Ar), 61.2 (2 × CH_2-C2). IR (Neat) 2943 (m), 2909 (m), 2855 (m), 1623 (s), 1537 (s), 1469 (m), 1440 (s), 1384 (m), 1302 (m), 1202 (m), 1149 (m), 1125 (m), 1088 (m), 1047 (s, MnN), 905 (m), 849 (m), 798 (m), 769 (m), 740 (m) cm $^{-1}$. HRMS (FAB/NOBA) exact mass calculated for $C_{16}H_{15}MnN_3O_2$ $[M+H]^+$ m/z 336.0545, found m/z 336.0544.
The observed values are in accordance with literature given.[132,166]

(Saltmen)Mn(N) (349)



349

$C_{20}H_{22}MnN_3O_2$

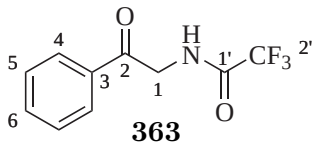
Mol. Wt.: 391.35

H_2saltmen (**355**) (800 mg, 2.46 mmol) was suspended in MeOH (40 mL) and the mixture was heated to 55 − 60 °C. To the yellow solution was added $Mn(OAc)_2.4H_2O$ (634 mg, 2.59 mmol) portionwise. The resulting dark solution was heated to reflux for one hour and then 30 min at room temperature. Concentrated NH_4OH (8 M, 4.60 mL, 36.9 mmol) was then added dropwise over a 5 min period. To the vigorously stirring mixture was added bleach (36.9 mL, 0.4 M aq. NaOCl, 14.7 mmol) over 40 min. During the addition, the evolution of a white gas was observed. When addition was complete, the

[166] Chang, C. J.; Connick, W. B.; Low, D. W.; Day, M. W.; Gray, H. B. *Inorg. Chem.* **1998**, *37*, 3107-3110.

reaction mixture was cooled to 0 °C and CH_2Cl_2 (50 mL) was added cautiously at 0 °C for additional 30 min. The resulting biphasic mixture was transferred to a separatory funnel with additional H_2O (50 mL). The dark green organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with H_2O (6 × 50 mL) and concentrated *in vacuo* to afford the crude compound. The crude material was suspended in EtOAc and petroleum was added. The solution was cooled to room temperature and then placed in a freezer at −20 °C for 10 h. The dark green precipitate was collected, yielding the title compound **349** (843 mg, 87%). M.p. > 200 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.09 (2H, s, CH-C3), 7.38 (2H, ddd, J = 8.6, 6.9, 1.8 Hz, CH-Ar) 7.23 (2H, dd, J = 7.8, 1.7 Hz, CH-Ar), 7.17 (2H, br d, J = 8.5 Hz, CH-Ar), 6.73-6.68 (2H, m, CH-Ar), 1.50 (12H, s, 4 × CH_3-C1). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 168.0 (2 × CH-C3), 162.9 (2 × C-C6'), 135.9 (2 × CH-Ar), 134.0 (2 × CH-Ar), 122.5 (2 × CH-Ar), 120.5 (2 × C-C1'), 116.5 (2 × CH-Ar), 72.5 (2 × C-C2), 26.7 (2 × CH_3-C1), 24.0 (2 × CH_3-C1). IR (Neat) 2977 (m), 1609 (m), 1532 (m), 1463 (s), 1441 (m), 1393 (m), 1304 (m), 1203 (s), 1141 (m), 1124 (m), 1053 (m), 1043 (MnN) (s), 906 (m), 848 (m), 799 (m), 764 (m), 746 (m) cm^{-1}. HRMS (FAB/NOBA) exact mass calculated for $C_{20}H_{23}MnN_3O_2$ $[M+H]^+$ m/z 392.1171, found m/z 392.1168.
The observed values are in accordance with literature given.[132,166]

2,2,2-Trifluoro-*N*-(2-oxo-2-phenyl-ethyl)-acetamide (363)



363

$C_{10}H_8F_3NO_2$

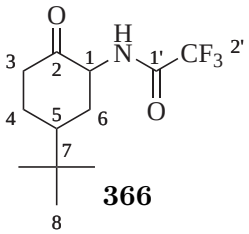
Mol. Wt.: 231.17

To a solution of diisopropylamine (130 μL, 0.921 mmol) in THF (5 mL) at −78 °C was added dropwise *n*BuLi (0.37 mL, 2.5 M in hexane, 0.94 mmol) and the mixture was stirred at −78 °C for 10 min. This was followed by the addition of chlorotrimethylsilane (0.22 mL, 1.7 mmol) and acetophenone (0.1 mL, 0.9 mmol). The resutlting mixture was left stirring for 2 h after which the reaction was quenched by the addition of a saturated aqueous $NaHCO_3$ (5 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried (Na_2SO_4), filtered, and concentrated *in vacuo* to yield the crude TMS enol ether that was used without purification. A solution of (Saltmen)Mn(N) (**349**) (670 mg, 1.71 mmol) in CH_2Cl_2 (3 mL) was cooled to −78 °C. Pyridine (2 drops) was added, followed by a solution of the silyl enol ether (0.86 mmol) in CH_2Cl_2 (4 mL) and TFAA (0.28 mL, 2.1 mmol). The solution was allowed to warm to room temperature overnight. During this time, the reaction mixture turned dark brown. Silica gel (800 mg) and Celite® (800 mg)

were added, along with petroleum ether (4 mL). The dark brown slurry was stirred for 30 min before being filtered through a pad of silica using Et_2O as the eluent. Concentration of the filtrate afforded the crude material as a pale yellow oil. Purification by flash chromatography (CH_2Cl_2:petroleum ether, 1:1) yielded the title compound as a colorless solid (108 mg, 50%). R_f = 0.2, CH_2Cl_2:petroleum ether, 1:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.20 (2H, d, J = 7.4 Hz, CH-C4), 7.73 (1H, t, J = 7.4 Hz, CH-C6), 7.58 (2H, t, J = 7.6 Hz, CH-C5), 7.53 (1H, br s, NH), 4.87 (2H, d, J = 4.0 Hz, CH_2-C1). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 192.0 (C-C2), 157.4 (q, J_{C-F} = 36.7 Hz, C-C1'), 134.8 (CH-C6), 133.6 (C-C3), 129.2 (2 × CH-C4), 128.0 (2 × CH-C5), 115.9 (q, J_{C-F} = 281.8 Hz, C-C2'), 46.3 (C-C1). IR (Neat) 3314 (m), 1711 (s), 1685 (s), 1558 (m), 1343 (m), 1175 (s), 1147 (s) cm^{-1}. HRMS (CI/Isobutane) exact mass calculated for $C_{10}H_9F_3NO_2$ 232.0585 $[M+H]^+$ m/z, found 232.0584 m/z.

The observed values are in accordance with literature values.[132]

N-(5-*tert*-Butyl-2-oxocyclohexyl)-2,2,2-trifluoroacetamide (366)



366

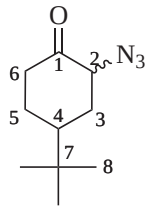
$C_{12}H_{18}F_3NO_2$

Mol. Wt.: 265.27

To a solution of diisopropylamine (0.1 mL, 0.7 mmol) in THF (5 mL) at −78 °C added dropwise *n*BuLi (0.3 mL, 2.5 M in hexane, 0.7 mmol) and the mixture was stirred at −78 °C for 10 min. This was followed by the addition of chlorotrimethylsilane (0.16 mL, 1.3 mmol) and 4-*tert*-butylcyclohexanone (100 mg, 0.648 mmol). The resulting mixture was left stirring for 2 h after which the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried (Na_2SO_4), filtered, and concentrated *in vacuo* to yield the crude TMS enol ether that was used without any further purification. A solution of (Salen)Mn(N) (**348**) (435 mg, 1.29 mmol) in CH_2Cl_2 (5 mL) was cooled to −78 °C. Pyridine (2 drops) was added, followed by a solution of the TMS enol ether (0.70 mmol) in CH_2Cl_2 (4 mL), and TFAA (0.21 mL, 1.6 mmol). The solution was allowed to warm to room temperature overnight. During this time, the reaction mixture turned dark brown. Silica gel (500 mg) and Celite® (500 mg) were added, along with petroleum ether (4 mL). The dark brown slurry was stirred for 30 min before being filtered through a pad of silica using Et_2O as the eluent. Concentration of the filtrate afforded the crude material as a pale yellow oil. Purification by flash chromatography (CH_2Cl_2:petroleum ether, 1:1) yielded the title compound as a colorless solid (58 mg, 34%) as a mixture of inseparable diastereomers (M:Major, m:minor, 1:1).[132] R_f = 0.42, CH_2Cl_2:petroleum ether, 1:1. ^{1}H

NMR (400 MHz, $CDCl_3$) δ (ppm): 7.34 (1H, br s, NH m), 7.28 (1H, br s, NH M), 4.57 (1H, q, $J = 9.0$ Hz, CH-C1 M), 4.49 (1H, dt, $J = 6.1$, 2.3 Hz, CH-C1 m), 2.75-2.70 (1H, m, CH_2-C6 m), 2.65-2.34 (5H, m, CH_2-C6 M, CH_2-C3 m, CH_2-C3 M), 2.23-2.18 (2H, m, CH_2-C4 m), 1.94-1.72 (3H, m, CH_2-C4 M, CH-C5 m), 1.56-1.45 (2H, m, CH_2-C6 M, CH_2-C5 M), 1.25 (1H, dd, $J = 24.7$, 12.4 Hz, CH_2-C6, m), 0.96 (9H, s, CH_3-C8 M), 0.94 (9H, s CH_3-C8 m) ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 208.5 (C-C2 m), 206.5 (C-C2 M), 156.7 (q, $J_{C-F} = 37.5$ Hz, C-C1' M and m), 115.9 (q, $J_{C-F} = 291.7$ Hz, C-C2' M and m), 57.7 (CH-C1 m), 54.9 (CH-C1 M), 45.5 (CH-C5 m), 42.8 (CH-C5 M), 39.8 (CH_2-C3 m), 37.4 (CH_2-C3 M), 35.6 (CH_2-C6 m), 33.3 (C-C7 m), 32.5 (C-C7 M), 29.2 (CH_2-C6 M), 28.8 (CH_2-C4 m), 27.6 ($3 \times CH_3$-C8 m), 26.8 ($3 \times CH_3$-C8 M), 21.4 (CH_2-C4 M). IR (Neat) 2963 (m), 2955 (s), 1733 (m), 1704 (s), 1549 (m), 1329 (w), 1207 (m), 1158 (s)cm^{-1}. HRMS (EI) exact mass calculated for $C_{12}H_{18}F_3NO_2$ $[M]^+$ m/z 265.1290, found m/z 265.1288. Microanalysis calculated for $C_{12}H_{18}F_3NO_2$: C, 54.33%; H, 6.84%; N, 5.28%, found C 54.34%, H 6.98%, N 5.27%.

2-Azido-4-*tert*-butyl-cyclohexanone (375)



375

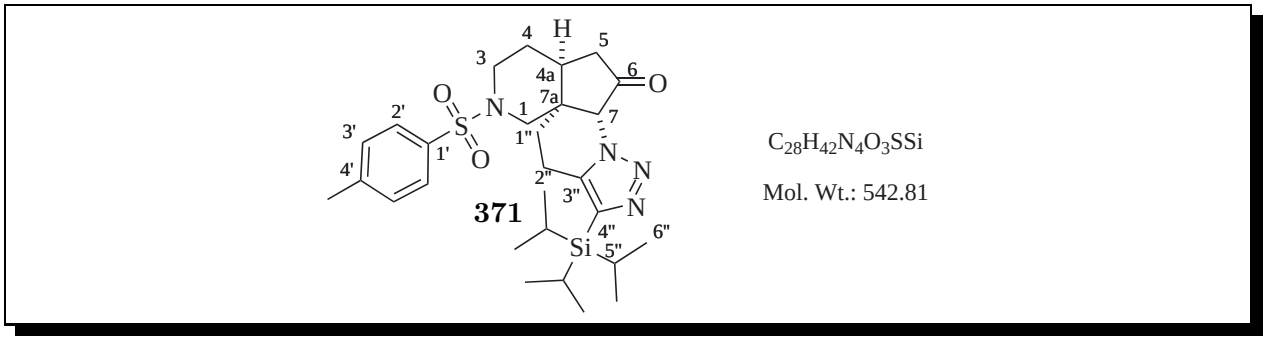
$C_{10}H_{17}N_3O$

Mol. Wt.: 195.26

A solution of 4-*tert*-butylcyclohexanone (100 mg, 0.648 mmol) in CH_2Cl_2 (5 mL) was cooled to 0 °C and Et_3N (0.18 mL, 1.3 mmol) was added dropwise. Triisopropylsilyl trifluoromethanesulfonate (0.18 mL, 0.68 mmol) was added dropwise and the resulting reaction mixture was stirred for one hour, after which the reaction was quenched by the addition of H_2O (10 mL). The layers were seperated and the organic layer washed with H_2O (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield the crude TIPS enol ether that was used without any further purification.[139,140] To a mixture of the triisopropylsilyl enol ether (0.65 mmol) in CH_3CN (2 mL) at −20 °C was added sodium azide (210 mg, 3.24 mmol), followed by dropwise addition of a solution of ceric ammonium nitrate (1.77 g, 3.24 mmol) in CH_3CN (8 mL). When the reaction was complete, the mixture was quenched by the addition of ice-cold water and the aqueous mixture was extracted with ice-cold Et_2O, the layers were separated and the organic layer was washed once with ice-cold water and the aqueous layers were extracted once with Et_2O. The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:Et_2O, 4:1) yielded the title compound **375** as a colorless oil (82 mg, 65%) $R_f = 0.7$, petroleum ether:Et_2O, 7:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1:1 mixture of inseparable diastereoisomers: 3.98-3.89 (1H, m, CH-C2), 2.65 (0.5H, dd, $J = 6.1$, 14.9 Hz, CH-C2), 2.55 (0.5H, dd, $J = 2.7$, 4.2 Hz, CH_2-C6), 2.41-2.30 (2H, m, $2 \times CH_2$-C6, $2 \times CH_2$-C3),

2.15-2.00 (1H, m, 2 × CH_2-C5), 1.75-1.60 (1.5H, m, 2 × CH_2-C4, CH_2-C6), 1.51-1.39 (1.5H, m, 2 × CH_2-C5, CH_2-C3), 0.94 (4.5H, s, CH_3-C8), 0.91 (4.5H, s, CH_3-C8). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 207.5 (C-C1), 205.8 (C-C1), 66.1 (CH-C2), 65.8 (CH-C2), 46.1 (CH_2-C6), 41.3 (CH_2-C6), 40.9 (CH_2-C3), 39.9 (CH_2-C3), 37.5 (CH_2-C4), 34.9 (CH_2-C4), 32.6 (C-C7), 32.5 (C-C7), 27.9 (CH_2-C5), 27.6 (3 × CH_3-C8), 27.4 (3 × CH_3-C8), 26.7 (CH_2-C5). IR (Neat) 2958 (m), 2866 (s), 2100 (s), 1720 (s), 1465 (m) cm^{-1}. HRMS (EI) exact mass calculated for $C_{10}H_{17}N_3O$ $[M]^+$ 195.1372 m/z, found m/z 195.1374.

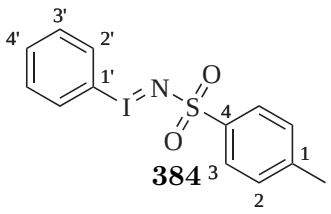
1,2,3-Triazole (371)



To a solution of 1-iodo-4-(triisopropylsilyl)-3-butyne (**267**) (500 mg, 1.49 mmol) in ether (30 mL) at −78 °C was added *tert*-butyllithium (1.9 mL, 1.6 M in hexane, 2.9 mmol) and stirred 20 min. The reaction mixture was warmed to room temperature and allowed to stir for an additional 20 min. Meanwhile, dimethylsulfide (1.3 mL, 18 mmol) was added to a solution of copper iodide (142 mg, 0.743 mmol) in THF (30 mL). After all the copper iodide had dissolved, the solution was cooled to −40 °C and the organolithium solution was added by syringe to afford a black slurry and stirred for 15 min. A pre-cooled (0 °C) solution of the enone **227** (124 mg, 0.425 mmol) and chlorotrimethylsilane (0.34 mL, 1.1 mmol) in THF (7 mL) was added dropwise and the mixture was allowed to warm to room temperature overnight. The reaction was quenched with a 10% NH_4OH/NH_4Cl solution (10 mL). The biphasic mixture was extracted with EtOAc (3 × 30 mL), washed with brine (30 mL), then dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield the crude compound. The crude material was used without further purification. The silyl enol ether (0.43 mmol) was dissolved in MeCN (7 mL), cooled to −15 °C and sodium azide (41 mg, 0.64 mmol) was added. Ceric ammonium nitrate (699 mg, 1.28 mmol) in MeCN was added and the solution allowed to warm to 0 °C. Water (10 mL) was added and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 2:1) yielded the title compound **371** as a colorless oil (36.5 mg, 16%). R_f = 0.2, petroleum ether:EtOAc, 2:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.51 (2H, d, J = 8.1 Hz, CH-C2'), 7.22 (2H, d, J = 8.1 Hz, CH-C3'), 5.09 (1H, s, CH-C7), 3.74 (1H, br d, J = 12.1 Hz, CH_2-C3), 3.38 (1H, d, J = 12.6 Hz, CH_2-C1), 2.84 (1H, dq, J = 17.4, 2.6 Hz, CH_2-C2"), 2.43-2.33 (4H, m, CH_2-C3, CH_2-C5, CH_2-C1, CH_2-C2"), 2.35 (3H, s, CH_3), 2.18-2.08 (2H, m, CH_2-

C4a, CH_2-C5), 2.03-1.94 (1H, m, CH_2-C4), 1.77 (1H, dq, J = 17.4 Hz, CH_2-C1") 1.69-1.58 (2H, m, CH_2-C4, CH_2-C1"), 1.41-1.32 (3H, m, CH-C5") 1.06 (18H, d, J = 7.5 Hz, CH_3-C6"). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 205.7 (C-C6), 143.3 (C-C4'), 136.5 (C-C3"), 135.1 (C-C4"), 132.1 (C-C1'), 130.0 (2 × CH-C3'), 127.6 (2 × CH-C2'), 63.3 (CH-C7), 48.6 (CH_2-C1), 44.5 (CH_2-C3), 41.1 (C-C7a), 40.4 (CH_2-C5), 34.8 (CH-C4a), 29.0 (CH_2-C4), 28.0 (CH_2-C1"), 21.6 (CH_3), 18.7 (6 × CH_3-C6"), 17.8 (CH_2-C2"), 11.4 (3 × CH-C5"). IR (thin film) 2939 (m), 2922 (m), 2862 (m), 1759 (s), 1338 (s), 1157 (s) cm^{-1}. HRMS (CI/Isobutane) exact mass calculated for $C_{28}H_{44}N_4O_3SSi$ $[M+H]^+$ m/z 543.2825, found m/z 502.2829.

[*N*-(*p*-Toluenesulfonyl)imino]phenyliodinane (384)



384

$C_{13}H_{12}INO_2S$

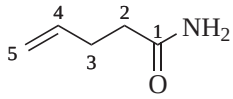
Mol. Wt.: 373.21

KOH (2.8 g, 0.049 mol) was dissolved in MeOH (80 mL) and cooled to 0 °C. *p*-Toluenesulfonamide (**239**) (3.4 g, 0.019 mol) and iodobenzene diacetate (6.4 g, 0.019 mol) were added portionwise. The resulting solution was stirred for 3 h at room temperature after which the reaction mixture was poured into distilled water (1 L) at 0 °C and kept at 4 °C overnight. The mixture was filtered and a solid was collected. The solid was crystalised from hot MeOH (20 mL) and afforded the title compound **384** as a pale yellow solid (919 mg, 12%). M.p. 100 − 102 °C; lit.[169] m.p. 102 − 104 °C. ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ (ppm): 7.71-7.67 (2H, m, 2 × CH-C2'), 7.49-7.42 (3H, m, 2 × CH-C3, CH-C3'), 7.33-7.27 (2H, m, 2 × CH-C3'), 7.07 (2H, d, J = 8.0 Hz, 2 × CH-C2), 2.28 (3H, s, CH_3-C1). ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ (ppm): 142.1 (C-C1), 140.1 (C-C4), 133.2 (2 × CH-C2'), 130.4 (CH-C4'), 130.1 (2 × CH-C3), 128.6 (2 × CH-C3'), 126.1 (2 × CH-C2), 117.2 (C-C1'), 20.8 (CH_3). IR (Neat) 3055 (w), 2927 (w), 1305 (m), 1131 (s) cm^{-1}.

The data observed are in accordance with literature values.[142]

[169] Evans, D. A. *Encyclopedia of Reagents for Organic Synthesis; [N-(p-Toluenesulfonyl)imino]phenyliodinane;* John Wiley & Sons, Ltd.: 2001.

N-4-Pentenoic acid amide (395)



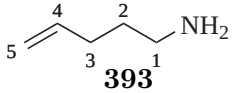
395

C_5H_9NO

Mol. Wt.: 99.13

A solution of 4-pentenoic acid (**394**) (5.0 g, 49 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C. Oxalyl chloride (4.5 mL, 52 mmol) was added dropwise followed by DMF (two drops). The mixture was allowed to warm to room temperature over 3 h and then added to saturated aqueous NH_4OH solution (200 mL) at 0 °C and stirred for additional 2 h. The mixture was extracted with EtOAc (3 × 150 mL) and the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the title compound **395**which was used without any further purification (2.0 g, 59%).[145,146] ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.85 (1H, ddt, J = 16.8, 10.2, 6.3 Hz, CH-C4), 5.49 (2H, br s, NH_2), 5.10 (1H, dq, J = 16.8, 1.6 Hz, CH_2-C5), 5.03 (1H, dq, J = 10.2, 1.3 Hz, CH_2-C5), 2.43-2.38 (2H, m, CH_2-C3), 2.35-2.31 (2H, m, CH_2-C2). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 174.7 (C-C1), 136.9 (CH-C4), 115.8 (CH_2-C5), 35.0 (CH_2-C2), 29.3 (CH_2-C3). IR (Neat) 3352 (m), 3174 (m), 2983 (w), 1658 (s), 1629 (s), 1415 (s) cm^{-1}. HRMS (CI) exact mass calculated for $C_5H_{10}NO$ $[M+H]^+$ m/z 100.0762, found m/z 100.0760.
The observed values are in accordance with literature given.[145,146]

4-Pentenylamine (393)



393

$C_5H_{11}N$

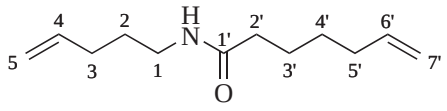
Mol. Wt.: 85.15

A solution of $LiALH_4$ (1.43 g, 37.8 mmol) in Et_2O (60 mL) was cooled to 0 °C and *N*-4-pentenoic acid amide (**395**) (2.5 mL, 25 mmol) was added portionwise. The mixture was allowed to warm to room temperature overnight (14 h). The reaction mixture was cooled to 0 °C, diluted with Et_2O (80 mL), and quenched slowly with aqueous 1 M NaOH until an insoluble material had precipitated. The organic supernatant was decanted in an Erlenmeyer flask and the precipitate was washed Et_2O (2 × 80 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *vacuo* to yield

the crude material. Fraction distillation from calcium hydride afforded the title compound **393** as a colorless liquid (785 mg, 37%).[145] ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.85 (1H, ddt, J = 17.0, 10.0, 6.4 Hz, CH-C4), 5.10 (1H, dq, J = 17.0, 1.6 Hz, CH_2-C5), 5.03 (1H, m, CH_2-C5), 2.70 (2H, t, J = 7.2 Hz, CH_2-C1), 2.14-2.06 (2H, m, CH_2-C3), 1.56 (2H, br s, NH_2), 1.55 (2H, quint, J = 7.2 Hz, CH_2-C2). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 138.5 (CH-C4), 114.7 (CH_2-C5), 41.7 (CH_2-C1), 32.9 (CH_2-C3), 31.1 (CH_2-C2).

The observed values are in accordance with literature given.[145]

N-(4-Pentenyl)hept-6-enamide (390)



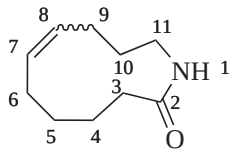
390

$C_{12}H_{21}NO$

Mol. Wt.: 195.30

To a solution of 6-heptenoic acid (**394**) (0.55 mL, 4.1 mmol) in CH_2Cl_2 (15 mL) at 0 °C, were added successively a catalytic amount of DMAP (11 mg, 0.090 mmol) and dicyclohexylcarbodiimide (837 mg, 4.06 mmol). 4-Pentenylamine (**393**) (345 mg, 4.06 mmol) was added dropwise and after 5 min at 0 °C, Et_3N (0.57 mL, 4.1 mmol) was added. The reaction mixture was stirred for 18 h at room temperature, then diluted with EtOAc (20 mL) and hydrolyzed with aqueous 1 M HCl (15 mL). The organic layer was separated and washed with a saturated aqueous K_2CO_3 solution (15 mL), water (15 mL), and brine (15 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to yield the crude compound. Purification by flash chromatography (petroleum ether:EtOAc, 4:1) yielded the title compound **390** as a colorless oil (333 mg, 42%).[122] R_f = 0.18, petroleum ether:EtOAc, 4:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.86-5.73 (2H, m, CH-C4, CH-C6'), 5.50 (1H, br s, NH), 5.07-4.91 (4H, m, CH_2-C5, CH_2-C7'), 3.25 (2H, dt, J = 7.0, 6.1 Hz, CH_2-C1), 2.17 (2H, t, J = 7.5 Hz, CH_2-C2'), 2.12-2.03 (4H, m, CH_2-C3, CH_2-C5'), 1.68-1.56 (4H, m, CH_2-C2, CH_2-C3'), 1.45-1.38 (2H, m, CH_2-C4'). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 172.9 (C-C7), 138.4 (CH-C12), 137.8 (CH-C2), 115.2 (CH_2-C1), 114.7 (CH_2-C13), 39.0 (CH_2-C5), 36.7 (CH_2-C8), 33.5 (CH_2-C11), 31.2 (CH_2-C3), 28.8 (CH_2-C4), 28.5 (CH_2-C10), 25.3 (CH_2-C9). IR (Neat) 3290 (m), 2976 (m), 2929 (m), 2858 (m), 1639 (s), 1548 (s), 908 (s) cm^{-1}. HRMS (CI/Isobutane) exact mass calculated for $C_{12}H_{22}NO$ m/z 196.1701, found m/z 196.1704.

(*Z*/*E*)-Azacycloundec-7-en-2-one (391)



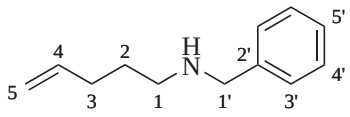
391

$C_{10}H_{17}NO$

Mol. Wt.: 167.25

To a solution of *N*-(4-pentenyl)hept-6-enamide (**390**) (96 mg, 0.64 mmol) in CH_2Cl_2 (200 mL) was added Grubbs' second generation catalyst (25 mg, 0.029 mmol). The resulting mixture was heated to reflux for 24 h after which another 5 mol% of the catalyst (25 mg, 0.029 mmol) was added. After another 24 h the reaction was cooled to room temperature and concentrated *in vacuo* to yield the crude material as a mixture of isomers. Purification by flash chromatography (EtOAc) yielded the title compound **391** as a colorless oil (56 mg, 65%).[170] $R_f = 0.2$, EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.45-5.25 (2H, m, CH-C7, CH-C8), 3.35-3.15 (2H, m, CH_2-C11), 2.20-2.10 (2H, m, CH_2-C3), 2.05-1.90 (4H, m, CH_2-C6, CH_2-C9), 1.70-1.45 (4H, m, CH_2-C4, CH_2-C10), 1.25-1.45 (2H, m, CH_2-C5). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 173.3 (C-C2), 130.7 (CH-C8), 130.0 (CH-C8), 130.6 (CH-C7), 130.2 (CH-C7), 38.4 (CH_2-C11), 37.9 (CH_2-C11), 37.0 (CH_2-C3), 36.8 (CH_2-C3), 31.9 (CH_2-C10), 31.7 (CH_2-C10), 29.4 (CH_2-C6), 29.3 (CH_2-C6), 29.1 (CH_2-C9), 28.7 (CH_2-C9), 28.5 (CH_2-C5), 28.2 (CH_2-C5), 24.8 (CH_2-C4), 24.7 (CH_2-C4). IR (Neat) 3293 (m), 2924 (m), 2854 (m), 1637 (s), 1552 (m) cm^{-1}. HRMS (CI/Isobutane) exact mass calculated for $C_{10}H_{18}NO$ $[M+H]^+$ m/z 168.1388, m/z found 168.1386.

N-Benzyl-*N*-pent-4-enylamine (402)



402

$C_{12}H_{17}N$

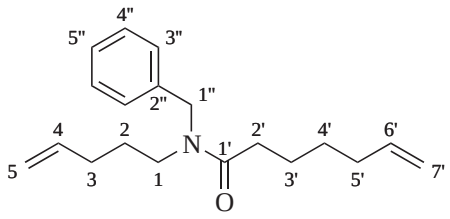
Mol. Wt.: 175.27

EtOH (20 mL) was degassed by passage of argon for 20 min, and benzylamine (**400**) (4.6 mL, 42 mmol), 4-bromobut-1-ene (1.25 mL, 8.44 mmol) and sodium iodide (ca. 40 mg) were added. The reaction mixture was heated at 75 °C for 4 h. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 (100 mL) and an aqueous solution of KOH (1 M, 100 mL) was added. The

[170] Gradillas, A.; Prez-Castells, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6086-6101.

aqueous layer was extracted with CH_2Cl_2 (3 × 70 mL) and the combined organic layers were dried over K_2CO_3, filtered, and and concentrated *in vacuo* to yield the crude compound. Purification by flash chromatography (petroleum ether:EtOAc, 5:1) yielded the title compound **402** as a colorless liquid (1.3 g, 73%).[122] R_f= 0.18, petroleum ether:EtOAc, 3:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.35-7.23 (m, 5H, CH-C3', CH-C4', CH-C5'), 5.81 (1H, ddt, J = 17.0, 10.2, 6.6 Hz, CH-C4), 5.01 (1H, dq, J = 17.0, 1.5 Hz, CH_2-C5), 4.95 (1H, ddt, J = 10.2, 2.2, 1.5 Hz, CH_2-C5), 3.78 (2H, s, CH_2-C1'), 2.65 (2H, t, J = 7.3 Hz, CH_2-C1), 2.13-2.06 (2H, m, CH_2-C3), 1.61 (2H, quint, J = 7.3 Hz, CH_2-C2), 1.40 (1H, br s, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 140.9 (C-C2'), 138.9 (CH-C4), 128.7 (2 × CH-C4'), 128.5 (2 × CH-C3'), 127.2 (CH-C5'), 114.9 (CH_2-C5), 54.4 (CH_2-C1'), 49.3 (CH_2-C1), 31.9 (CH_2-C3), 29.6 (CH_2-C2). IR (Neat) 3064 (m), 2926 (m), 2816 (m), 1452 (s), 1118 (m), 731 (s), 696 (s) cm^{-1}. HRMS (CI/Isobutane) exact mass calculated for $C_{12}H_{17}N$ 175.1361 m/z, found m/z.

N-(Benzyl)-*N*-(4-pentenyl)hept-6-amide (399)



399

$C_{19}H_{27}NO$

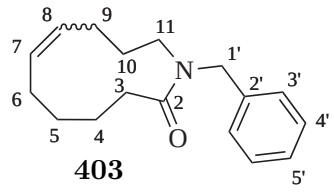
Mol. Wt.: 285.42

1st method: To a suspension of sodium hydride (39 mg, 0.98 mmol) in THF (5 mL) at 0 °C was added *N*-(4-Pentenyl)hept-6-enamide (**390**) (174 mg, 0.891 mmol) and the resulting solution was allowed to stir for 30 min. Benzyl bromide (137 μL, 1.16 mmol) was added dropwise and the mixture allowed to warm to room temperature. The reaction was quenched by the addition of H_2O (5 mL) and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combied organic layers were washed with brine (15 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield the crude compound. Purification by flash chromatography (petroleum ether:EtOAc, 12:1) yielded the title compound **399** as a colorless oil (803 mg, 72%).[171] **2nd method**: To a solution of hept-6-enoic acid (**394**) (0.43 mL, 3.7 mmol) in CH_2Cl_2 (15 mL) at 0 °C, were added successively HOBt (543 mg, 4.02 mmol) and dicyclohexylcarbodiimide (830 mg, 4.02 mmol) and the resulting mixture was stirred for 30 min. *N*-Benzyl-*N*-pent-4-enylamine (**398**) (711 mg, 4.06 mmol) in CH_2Cl_2 (10 mL) was added dropwise and after 5 min at 0 °C, Et_3N (1.0 mL, 7.4 mmol) was added and the reaction mixture was stirred for 18 h at room temperature. The reaction was quenched by the addition of aqueous saturated NH_4Cl (10 mL) and aqueous 1 M HCl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combied organic layers were washed with a saturated aqueous 1 M NaOH solution (15 mL), and brine (15 mL), dried

[171] Bélanger, G.; Larouche-Gauthier, R.; énard, F. M.; Nantel, M.; Barabé, F. *Org. Lett.* **2005**, *7*, 4431-4434.

(Na_2SO_4), filtered, and concentrated *in vacuo* to yield the crude compound. Purification by flash chromatography (petroleum ether:EtOAc, 12:1) yielded the title compound **399** as a colorless oil (803 mg, 72%).[171] R_f = 0.18, petroleum ether:EtOAc, 4:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) (Mixture of rotamers): 7.38-7.15 (10H, m, CH-Ar), 5.87-5.67 (4H, m, 2 × CH-C4, 2 × CH-C6'), 5.05-4.85 (8H, m, 2 × CH_2-C5, 2 × CH_2-C7'), 4.61 (2H, s, CH_2-C1"), 4.52 (2H, s, CH_2-C1"), 3.37 (2H, t, J = 7.6 Hz, CH_2-C1), 3.17 (2H, t, J = 7.6 Hz, CH_2-C1), 2.38 (2H, t, J = 7.5 Hz, CH_2-C2), 2.32 (2H, t, J = 7.5 Hz, CH_2-C2), 2.15-1.95 (8H, m, 2 × CH_2-C3, 2 × CH_2-C5'), 1.75-1.57 (8H, m, 2 × CH_2-C2, 2 × CH_2-C3'), 1.51-1.45 (2H, m, CH_2-C4') 1.45-1.35 (2H, m, CH_2-C4'). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) (Mixture of rotamers): 173.3 (C-C1'), 173.0 (C-C1'), 137.6 (CH-C4), 137.5 (CH-C4), 136.9 (CH-C6'), 136.8 (C-C2"), 136.1 (CH-C6'), 136.0 (C-C14), 128.9 (2 × CH-C4"), 128.5 (2 × CH-C4"), 127.9 (2 × CH-C3"), 127.5 (2 × CH-C3"), 127.2 (CH-C5"), 126.2 (CH-C5"), 114.7 (CH_2-C7'), 113.9 (CH_2-C7'), 113.6 (CH_2-C5), 113.5 (CH_2-C5), 51.1 (CH_2-C1"), 48.1 (CH_2-C1"), 46.5 (CH_2-C1), 45.8 (CH_2-C1), 33.6 (CH_2-C2'), 33.5 (CH_2-C2'), 33.1 (CH_2-C3), 32.9 (CH_2-C3), 31.2 (CH_2-C5'), 30.8 (CH_2-C5'), 28.8 (CH_2-C3), 28.6 (CH_2-C3), 27.6 (CH_2-C4'), 26.7 (CH_2-C4'), 25.0 (CH_2-C3'), 24.8 (CH_2-C3'). IR (Neat) 3076 (m), 2982 (m), 2858 (m), 1639 (s), 1419 (s), 908 (s) cm^{-1}. HRMS (EI) exact mass calculated for $C_{19}H_{27}NO$ $[M]^+$ 285.2093 m/z, found m/z 285.2094.

(*Z*/*E*)-1-Benzyl-azacycloundec-7-en-2-one (403)



403

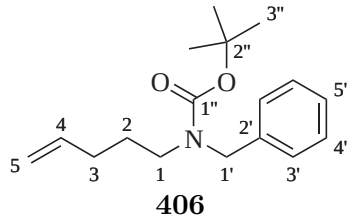
$C_{17}H_{23}NO$

Mol. Wt.: 257.37

To a solution of *N*-Benzyl-*N*-pent-4-enylamine (**399** (50 mg, 0.17 mmol) in PhMe (170 mL) was added Grubbs' second generation catalyst (5 mg, 0.01 mmol). The resulting mixture was heated to 60 °C for 10 h after which another 5 mol% of the catalyst (5 mg, 0.01 mmol) was added. After another 24 h the reaction was cooled to room temperature and concentrated *in vacuo* to yield the crude material. Purification by flash chromatography (petroleum ether:EtOAc, 6:1 → 4:1) yielded the title compound **403** as a colorless oil (4 mg, 9%). R_f = 0.39, petroleum ether:EtOAc, 4:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): Inseparable mixture of 1:1 E/Z isomers. 7.31-7.12 (5H, m, 2 × CH-C3', 2 × CH-C4', CH-C5'), 5.44-5.20 (3H m, CH-C7, CH-C8, CH_2-C1'), 3.77 (1H, d, J = 14.7 Hz, CH_2-C1'), 3.74-3.64 (1H, m, CH_2-C11), 2.94 (1H, br d, J = 13.4 Hz, CH_2-C11), 2.79-2.68 (1H, m, CH_2-C3), 2.24-2.08 (4H, m, CH_2-C4, CH_2-C5, CH_2-C6, CH_2-C9), 2.01-1.85 (4H, m, CH_2-C3, CH_2-C5, CH_2-C6, CH_2-C10), 1.82-1.74 (1H, m, CH_2-C9), 1.52-1.45 (1H, m, CH_2-C4), 1.34-1.28 (1H, m, CH_2-C10). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 174.3 (C-C2), 137.6 (C-C2'), 131.0 (CH-C7), 129.9 (CH-C8), 128.5

(2 × CH-C3'), 128.3 (2 × CH-C4'), 127.2 (CH-C5'), 45.5 (CH_2-C1'), 43.9 (CH_2-C11), (CH_2-6), 29.7 (CH_2-C3), 29.6 (CH_2-C4), 29.3 (CH_2-C10), 24.6 (CH_2-C5), 22.7 (CH_2-C6), 21.9 (CH_2-C9). IR (Neat) 3293 (m), 2924 (m), 2854 (m), 1637 (s), 1552 (m) cm^{-1}. HRMS (CI/Isobutane) exact mass calculated for $C_{10}H_{18}NO$ $[M+H]^+$ m/z 168.1388, found m/z 168.1386.

N-Benzyl-*N*-4-pentenyl-carbamic acid *tert*-butyl ester (406)



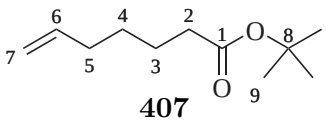
406

$C_{17}H_{25}NO_2$

Mol. Wt.: 275.39

Triethylamine (0.36 mL, 2.6 mmol) was added at 0 °C to a solution of *N*-benzyl-*N*-pent-4-enylamine **402** (300 mg, 1.71 mmol) and di-*tert*-butyl dicarbonate (448 mg, 2.05 mmol) in CH_2Cl_2 (15 mL). The solution was warmed to room temperature and stirred for 4 h before it was cooled again to 0 °C, followed by addition of saturated aqueous $NaHCO_3$ (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 12:1) yielded the title compound **406** as a colorless oil (480 mg, 99%).[152] R_f = 0.28, petroleum ether:EtOAc, 12:1. ^{1}H NMR (400 MHz, $(CD_3)_2CO$, 90 °C) δ (ppm): 7.37-7.30 (2H, m, CH-C4'), 7.28-7.21 (3H, m, CH-C8, CH-C5'), 5.79 (1H, ddt, J = 16.9, 10.1, 6.5 Hz, CH-C4), 5.03-4.92 (2H, m, CH_2-C5), 4.40 (2H, s, CH_2-C1'), 3.17 (2H, t, J = 7.4 Hz, CH_2-C1), 2.03-1.94 (2H, m, CH_2-C3), 1.56 (2H, q, J = 7.4 Hz, CH_2-C2) 1.43 (9H, s, CH_3-C3"). ^{13}C NMR (100 MHz, $(CD_3)_2CO$, 90 °C) δ (ppm): 155.0 (C-C1"), 138.8 (CH-C4), 137.9 (C-C2'), 128.2 (2 × CH-C4'), 127.2 (2 × CH-C3'), 126.8 (CH-C5'), 114.5 (CH_2-C5), 78.7 (C-C2"), 50.0 (CH_2-C1'), 46.2 (CH_2-C1), 30.3 (CH_2-C3), 28.6 (3 × CH_3-C3"), 27.0 (CH_2-C2). IR (Neat) 2976 (m), 2929 (m), 1689 (s) cm^{-1}. HRMS (EI) exact mass calculated for $C_{17}H_{26}NO_2$ $[M]^+$ m/z 276.1964, found m/z 276.1963.

6-Heptenoic acid *tert*-butyl ester (407)



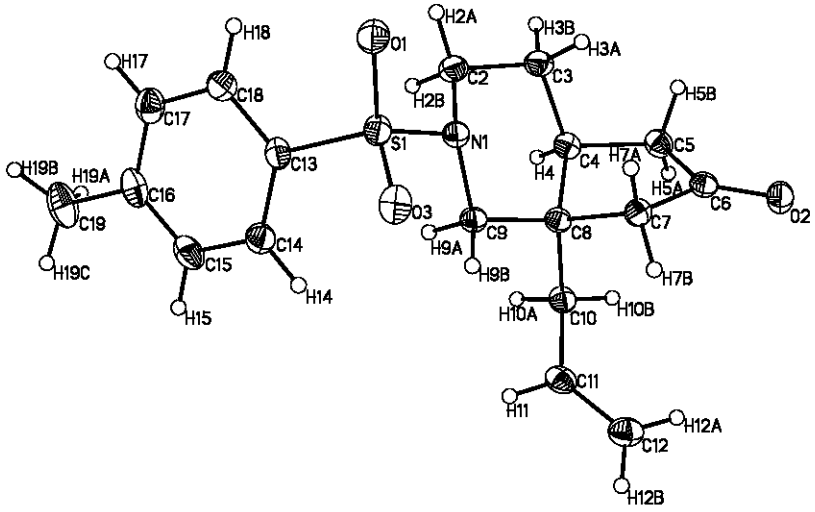
407

$C_{11}H_{20}O_2$

Mol. Wt.: 184.28

To a solution of diisopropylamine (1.0 mL, 7.7 mmol) in THF (7 mL) at −78 °C was added *n*-butyllithium (3.0 mL, 2.5 M in hexane, 7.7 mmol). After stirring for 30 min, the mixture was treated dropwise over 10 min with *tert*-butyl acetate (1.0 mL, 7.7 mmol). This mixture was allowed to stir for 45 min. and then treated dropwise during 15 min with a solution of 5-bromo-1-pentene (**401**) (1.0 mL, 8.4 mmol) in DMPU (0.92 mL, 7.7 mmol). The resulting mixture was allowed to warm to room temperature and treated with saturated aqueous NH_4Cl (10 mL) and diluted with Et_2O (20 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL) and the organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The compound was purified by distillation (45 − 50 °C at 1-2 mmHg; lit.[153] 45 − 56 °C at 0.09k Pa) to yield the title compound **407** as a colorless oil (429 mg, 34%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.79 (1H, ddt, J = 17.2, 10.4, 6.9 Hz, CH-C6) 4.92-4.78 (2H, m, CH_2-C7), 2.10 (2H, t, J = 7.4 Hz, CH_2-C2), 1.93 (2H, q, J = 6.9 Hz, CH_2-C5), 1.52-1.44 (2H, m, CH_2-C3), 1.31 (9H, s, CH_3-C8), 1.33-1.24 (2H, m, CH_2-C4). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 173.2 (C-C1), 138.6 (CH-C6), 114.6 (CH_2-C7), 80.0 (C-C8), 51.6 (CH_2-C2), 47.9 (CH_2-C5), 35.4 (CH_2-C4), 28.1 (3 × CH_3-C9), 24.6 (CH_2-C3). IR (Neat) 2978 (m), 2931 (m), 1728 (s), 1641 (m), 1147 (s), 993 (w) cm^{-1}. HRMS (CI/ISA) exact mass calculated for $C_{11}H_{21}O_2$ $[M+H]^+$ m/z 185.1542, found m/z 185.1543. The data observed are in accordance with literature values.[153]

Appendix A



X-ray crystal structure of ***260***

Identification code	shelxl
Empirical formula	$C_{18}H_{23}NO_3S$
Formula weight	333.43
Temperature	100(2) K
Wavelength	0.71075 Å
Crystal system	Triclinic
Space group	P -1
Unit cell dimensions	a = 6.3644(15) Å α = 77.334(7) °
	b = 7.4229(16) Å β = 79.607(6) °
	c = 18.238(4) Å γ = 81.558(7) °
Volume	821.7(3) $Å^3$
Z	2
Density (calculated)	1.348 Mg/m^3
Absorption coefficient	0.212 $mm^{-}1$
F(000)	356
Crystal size	0.43 × 0.30 × 0.12 mm^3
Theta range for data collection	3.26 to 27.48 °
Index ranges	-8⇐h⇐8, -9⇐k⇐9, -22⇐l⇐3
Reflections collected	14927
Independent reflections	3766 (R(int) = 0.297)
Observed reflections (>2(I))	3359
Completeness to theta = 27.48∞	99.8%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.000 and 0.870
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3766 / 0 / 209
Goodness-of-fit on F^2	1.059
Final R indices (I>2sigma(I))	R1 = 0.0403, wR2 = 0.1031
R indices (all data)	R1 = 0.0450, wR2 = 0.1064
Largest diff. peak and hole	0.576 and -0.296 e Å-3

Table 1: Crystal data and structure refinement.

Table 2: Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	-0.15276(6)	-0.20714(5)	-0.68772(2)	0.01976(11)
O(1)	0.05150(17)	-0.13652(17)	-0.70314(7)	0.0274(3)
O(2)	-0.20492(18)	-0.59992(16)	-0.98221(7)	0.0276(3)
O(3)	-0.17380(18)	-0.38990(16)	-0.64368(6)	0.0249(2)
N(1)	-0.22161(19)	-0.20604(17)	-0.76997(7)	0.0183(3)
C(2)	-0.2058(2)	-0.0337(2)	-0.82755(9)	0.0219(3)
C(3)	-0.1915(2)	-0.0813(2)	-0.90525(8)	0.0211(3)
C(4)	-0.3823(2)	-0.1780(2)	-0.91150(8)	0.0187(3)
C(5)	-0.3290(2)	-0.2763(2)	-0.97963(8)	0.0215(3)
C(6)	-0.2549(2)	-0.4766(2)	-0.94650(9)	0.0203(3)
C(7)	-0.2637(2)	-0.4974(2)	-0.86210(8)	0.0183(3)
C(8)	-0.4318(2)	-0.3384(2)	-0.84255(8)	0.0170(3)
C(9)	-0.4218(2)	-0.2865(2)	-0.76707(8)	0.0183(3)
C(10)	-0.6602(2)	-0.3908(2)	-0.83978(8)	0.0194(3)
C(11)	-0.7193(2)	-0.5547(2)	-0.77915(9)	0.0227(3)
C(12)	-0.7422(3)	-0.7181(2)	-0.79211(10)	0.0277(3)
C(13)	-0.3407(2)	-0.0506(2)	-0.64325(8)	0.0197(3)
C(14)	-0.5433(2)	-0.1021(2)	-0.61053(9)	0.0237(3)
C(15)	-0.6928(3)	0.0239(2)	-0.57783(9)	0.0271(3)
C(16)	-0.6432(3)	0.1983(2)	-0.57584(8)	0.0261(3)
C(17)	-0.4392(3)	0.2454(2)	-0.60785(9)	0.0265(3)
C(18)	-0.2878(3)	0.1236(2)	-0.64234(9)	0.0238(3)
C(19)	-0.8083(3)	0.3343(3)	-0.54066(10)	0.0367(4)

Table 3: Bond lengths [Å] and angles [°]. Symmetry transformations used to generate equivalent atoms:

S(1)-O(3)	1.4283(12)	C(11)-C(12)	1.319(2)
S(1)-O(1)	1.4309(12)	C(11)-H(11)	0.9500
S(1)-N(1)	1.6349(13)	C(12)-H(12A)	0.9500
S(1)-C(13)	1.7589(15)	C(12)-H(12B)	0.9500
O(2)-C(6)	1.2100(19)	C(13)-C(18)	1.387(2)
N(1)-C(2)	1.4698(19)	C(13)-C(14)	1.389(2)
N(1)-C(9)	1.4726(18)	C(14)-C(15)	1.384(2)
C(2)-C(3)	1.518(2)	C(14)-H(14)	0.9500
C(2)-H(2A)	0.9900	C(15)-C(16)	1.386(3)
C(2)-H(2B)	0.9900	C(15)-H(15)	0.9500
C(3)-C(4)	1.532(2)	C(16)-C(17)	1.385(2)
C(3)-H(3A)	0.9900	C(16)-C(19)	1.505(2)
C(3)-H(3B)	0.9900	C(17)-C(18)	1.384(2)
C(4)-C(5)	1.537(2)	C(17)-H(17)	0.9500
C(4)-C(8)	1.552(2)	C(18)-H(18)	0.9500
C(4)-H(4)	1.0000	C(19)-H(19A)	0.9800
C(5)-C(6)	1.517(2)	C(19)-H(19B)	0.9800
C(5)-H(5A)	0.9900	C(19)-H(19C)	0.9800
C(5)-H(5B)	0.9900	O(3)-S(1)-O(1)	119.59(7)
C(6)-C(7)	1.505(2)	O(3)-S(1)-N(1)	106.16(7)
C(7)-C(8)	1.5299(19)	O(1)-S(1)-N(1)	106.85(7)
C(7)-H(7A)	0.9900	O(3)-S(1)-C(13)	108.05(7)
C(7)-H(7B)	0.9900	O(1)-S(1)-C(13)	107.86(7)
C(8)-C(9)	1.5228(19)	N(1)-S(1)-C(13)	107.82(7)
C(8)-C(10)	1.5485(19)	C(2)-N(1)-C(9)	111.73(11)
C(9)-H(9A)	0.9900	C(2)-N(1)-S(1)	117.04(10)
C(9)-H(9B)	0.9900	C(9)-N(1)-S(1)	115.81(9)
C(10)-C(11)	1.496(2)	N(1)-C(2)-C(3)	108.23(12)
C(10)-H(10A)	0.9900	N(1)-C(2)-H(2A)	110.1
C(10)-H(10B)	0.9900	C(3)-C(2)-H(2A)	110.1

Table 3: *Continued*: Bond lengths [Å] and angles [°]. Symmetry transformations used to generate equivalent atoms:

N(1)-C(2)-H(2B)	110.1	C(9)-C(8)-C(7)	114.13(12)
C(3)-C(2)-H(2B)	110.1	C(9)-C(8)-C(10)	108.09(11)
H(2A)-C(2)-H(2B)	108.4	C(7)-C(8)-C(10)	109.82(12)
C(2)-C(3)-C(4)	112.72(12)	C(9)-C(8)-C(4)	112.56(12)
C(2)-C(3)-H(3A)	109.0	C(7)-C(8)-C(4)	102.59(11)
C(4)-C(3)-H(3A)	109.0	C(10)-C(8)-C(4)	109.53(11)
C(2)-C(3)-H(3B)	109.0	N(1)-C(9)-C(8)	111.11(11)
C(4)-C(3)-H(3B)	109.0	N(1)-C(9)-H(9A)	109.4
H(3A)-C(3)-H(3B)	107.8	C(8)-C(9)-H(9A)	109.4
C(3)-C(4)-C(5)	110.56(12)	N(1)-C(9)-H(9B)	109.4
C(3)-C(4)-C(8)	112.32(12)	C(8)-C(9)-H(9B)	109.4
C(5)-C(4)-C(8)	103.48(12)	H(9A)-C(9)-H(9B)	108.0
C(3)-C(4)-H(4)	110.1	C(11)-C(10)-C(8)	114.34(12)
C(5)-C(4)-H(4)	110.1	C(11)-C(10)-H(10A)	108.7
C(8)-C(4)-H(4)	110.1	C(8)-C(10)-H(10A)	108.7
C(6)-C(5)-C(4)	105.13(12)	C(11)-C(10)-H(10B	108.7
C(6)-C(5)-H(5A)	110.7	C(8)-C(10)-H(10B)	108.7
C(4)-C(5)-H(5A)	110.7	H(10A)-C(10)-H(10B)	107.6
C(6)-C(5)-H(5B)	110.7	C(12)-C(11)-C(10)	124.52(15)
C(4)-C(5)-H(5B)	110.7	C(12)-C(11)-H(11)	117.7
H(5A)-C(5)-H(5B)	108.8	C(10)-C(11)-H(11)	117.7
O(2)-C(6)-C(7)	126.04(14)	C(11)-C(12)-H(12A)	120.0
O(2)-C(6)-C(5)	125.07(14)	C(11)-C(12)-H(12B)	120.0
C(7)-C(6)-C(5)	108.83(12)	H(12A)-C(12)-H(12B)	120.0
C(6)-C(7)-C(8)	103.24(11)	C(18)-C(13)-C(14)	120.60(14)
C(6)-C(7)-H(7A)	111.1	C(18)-C(13)-S(1)	120.08(12)
C(8)-C(7)-H(7A)	111.1	C(14)-C(13)-S(1)	119.31(12)
C(6)-C(7)-H(7B)	111.1	C(15)-C(14)-C(13)	119.06(15)
C(8)-C(7)-H(7B)	111.1	C(15)-C(14)-H(14)	120.5
H(7A)-C(7)-H(7B)	109.1	C(13)-C(14)-H(14)	120.5

Table 3: *Continued*: Bond lengths [Å] and angles [°]. Symmetry transformations used to generate equivalent atoms:

C(14)-C(15)-C(16)	121.34(15)	C(17)-C(18)-C(13)	119.10(15)
C(14)-C(15)-H(15)	119.3	C(17)-C(18)-H(18)	120.5
C(16)-C(15)-H(15)	119.3	C(13)-C(18)-H(18)	120.5
C(17)-C(16)-C(15)	118.52(15)	C(16)-C(19)-H(19A)	109.5
C(17)-C(16)-C(19)	120.78(16)	C(16)-C(19)-H(19B)	109.5
C(15)-C(16)-C(19)	120.69(16)	H(19A)-C(19)-H(19B)	109.5
C(18)-C(17)-C(16)	121.36(15)	C(16)-C(19)-H(19C)	109.5
C(18)-C(17)-H(17)	119.3	H(19A)-C(19)-H(19C)	109.5
C(16)-C(17)-H(17)	119.3	H(19B)-C(19)-H(19C)	109.5

Table 4: Anisotropic displacement parameters (Å2×10^3). The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	0.01472(18)	0.0237(2)	0.02284(19)	-0.00962(14)	-0.00361(13)	-0.00022(13)
O(1)	0.0157(5)	0.0365(7)	0.0351(6)	-0.0178(5)	-0.0036(4)	-0.0031(5)
O(2)	0.0233(6)	0.0303(6)	0.0328(6)	-0.0167(5)	0.0002(5)	-0.0039(5)
O(3)	0.0252(6)	0.0253(6)	0.0251(5)	-0.0069(4)	-0.0087(4)	0.0028(4)
N(1)	0.0160(6)	0.0206(6)	0.0193(6)	-0.0058(5)	-0.0018(4)	-0.0035(5)
C(2)	0.0211(7)	0.0184(7)	0.0260(7)	-0.0046(6)	-0.0012(6)	-0.0043(6)
C(3)	0.0201(7)	0.0197(7)	0.0220(7)	-0.0018(5)	-0.0008(5)	-0.0040(6)
C(4)	0.0166(6)	0.0182(7)	0.0200(7)	-0.0021(5)	-0.0034(5)	0.0006(5)
C(5)	0.0208(7)	0.0256(8)	0.0180(7)	-0.0039(6)	-0.0030(5)	-0.0025(6)
C(6)	0.0128(6)	0.0241(7)	0.0254(7)	-0.0080(6)	-0.0011(5)	-0.0038(5)
C(7)	0.0153(6)	0.0171(7)	0.0225(7)	-0.0045(5)	-0.0033(5)	0.0002(5)
C(8)	0.0139(6)	0.0184(7)	0.0184(7)	-0.0032(5)	-0.0024(5)	-0.0014(5)
C(9)	0.0145(6)	0.0215(7)	0.0198(7)	-0.0055(5)	-0.0020(5)	-0.0037(5)
C(10)	0.0137(6)	0.0241(7)	0.0213(7)	-0.0062(6)	-0.0032(5)	-0.0019(5)
C(11)	0.0152(7)	0.0307(8)	0.0220(7)	-0.0042(6)	-0.0023(5)	-0.0049(6)
C(12)	0.0215(8)	0.0294(8)	0.0314(8)	-0.0038(7)	-0.0021(6)	-0.0060(6)
C(13)	0.0178(7)	0.0240(7)	0.0187(7)	-0.0085(6)	-0.0032(5)	0.0006(6)
C(14)	0.0201(7)	0.0278(8)	0.0245(7)	-0.0083(6)	-0.0018(6)	-0.0035(6)
C(15)	0.0186(7)	0.0391(9)	0.0225(7)	-0.0087(7)	0.0001(6)	0.0000(6)
C(16)	0.0284(8)	0.0311(8)	0.0168(7)	-0.0067(6)	-0.0051(6)	0.0081(6)
C(17)	0.0344(9)	0.0214(8)	0.0232(7)	-0.0055(6)	-0.0047(6)	0.0005(6)
C(18)	0.0226(7)	0.0272(8)	0.0221(7)	-0.0060(6)	-0.0019(6)	-0.0047(6)
C(19)	0.0391(10)	0.0381(10)	0.0281(8)	-0.0110(7)	-0.0035(7)	0.0152(8)

Table 5: Atomic coordinates and isotropic displacement parameters ($Å^2 \times 10^3$).

	x	y	z	U(eq)
H(2A)	-0.0765	0.0232	-0.8252	0.026
H(2B)	-0.3339	0.0563	-0.8180	0.026
H(3A)	-0.0568	-0.1633	-0.9156	0.025
H(3B)	-0.1850	0.0343	-0.9445	0.025
H(4)	-0.5125	-0.0856	-0.9169	0.022
H(5A)	-0.4577	-0.2687	-1.0041	0.026
H(5B)	-0.2139	-0.2193	-1.0179	0.026
H(7A)	-0.1223	-0.4843	-0.8496	0.022
H(7B)	-0.3088	-0.6194	-0.8345	0.022
H(9A)	-0.5466	-0.1955	-0.7550	0.022
H(9B)	-0.4301	-0.3987	-0.7261	0.022
H(10A)	-0.7660	-0.2824	-0.8316	0.023
H(10B)	-0.6710	-0.4175	-0.8897	0.023
H(11)	-0.7418	-0.5400	-0.7278	0.027
H(12A)	-0.7209	-0.7377	-0.8428	0.033
H(12B)	-0.7800	-0.8163	-0.7508	0.033
H(14)	-0.5785	-0.2220	-0.6106	0.028
H(15)	-0.8324	-0.0099	-0.5563	0.033
H(17)	-0.4024	0.3637	-0.6061	0.032
H(18)	-0.1496	0.1588	-0.6651	0.029
H(19A)	-0.8795	0.4187	-0.5805	0.055
H(19B)	-0.7376	0.4062	-0.5151	0.055
H(19C)	-0.9154	0.2666	-0.5035	0.055