Towards the Total Synthesis of Nakadomarin A

Chao Xu

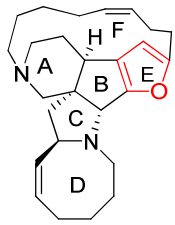
Thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

School of Chemistry
College of Science and Engineering
University of Glasgow

September 2015

Abstract

Nakadomarin A was first isolated from the sponge *Amphimedon sp.* by Kobayashi and co-workers in 1997. The structure showed a unique hexacyclic skeleton consisting of 5-, 6-, 8- and 13-membered rings. This natural product shows cytotoxicity, antimicrobial and inhibitory activities. The challenging structure, as well as the promising biological activity and limited availability make nakadomarin A an attractive target for total synthesis. The aim of the project was to design a synthesis of a common late-stage intermediate that could be used to prepare not only nakadomarin A, but also other members of the manzamine natural product family.



(–)-nakadomarin A

The concise preparation of the common intermediate ABCD tetracyclic core was achieved in only 7 steps (longest linear sequence). The key features of the synthetic route are asymmetric construction of the AB ring using an asymmetric Pauson-Khand reaction; installation of the azocine D ring through metathesis reactions (CM, RCM) and Overman rearrangement; and introduction of the C ring by *N*-alkylation. Finally, several side chains were prepared and evaluated to find the optimum method for installation of the furan. This resulted in two advanced intermediates which could be malipulated to form nakadomarin A in only 3 steps.

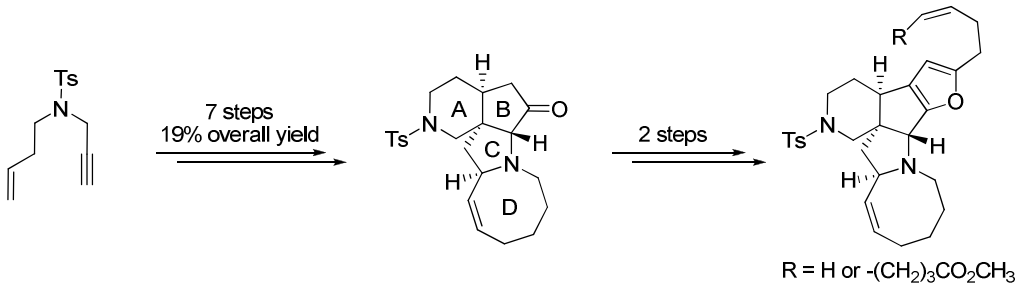


Table of Contents

Acknowledgements

I would like to express my gratitude to those who made the completion of this thesis possible. First and foremost, I would like to thank Professor J. Stephen Clark for giving me the opportunity to join his group and work on such a challenging and rewarding project. I appreciate all the advice, support and confidence he has given me over the past four years. I would also like to extend my gratitude to Dr Rudi Marquez for his help as my second supervisor. A special thanks goes to Dr Joëlle Prunet for her advice and encouragement, which helped me build up my confidence.

This PhD would not have been possible without fundings; I acknowledge the University of Glasgow, WestChem and CSC (中国留学基金委) for their financial support. I would also like to thank the staff members of the chemistry department: Ted, Bruce, Shawn and Kris (stores), Dr David Adam (NMR spectroscopy), Jim Tweedie and Harry Jackson (mass spectroscopy), Stuart Mackay (IT), Dr L. J. Farrugia and Dr Deliang Long (X-ray crystallography). Thank you all for providing amazing support and smiles when needed.

A particular note of thanks is due to Dr Alistair Boyer, Dr Andy Osnowski, Ludovic Decultot, Sam Alexander and Gregor Meier for spending time to proof read this thesis.

I would like to thank all the people I met in Glasgow, who have made these four years so lively and unforgettable. I would like to deeply thank Alistair for his intelligent insights and help in the lab. I extend my thanks to Dr David Lindsay for his patient help with all of my reports. I have been lucky to share this journey with two great colleagues: Filo, who was always there to solve chemistry problems and set up a good example of how to be a good chemist; Micha, who helped me stay fit, introduced me to climbing and took me on many nice trips. I want to thank all the lovely people I have met over these four years: Guang, for introducing me to the lab; Helen, for all the afternoon teas; Ian and Verena, for all the shows we watched together; Ludo and Michael P, for still talking to me even when I was grumpy and cheering me up with “funny” jokes. I

also want to thank all the past and present members of the Clark group and people in the chemistry department: Laura, Fred, Alex, Tony, Aurélien (junior), Kirsten, Gayle, Eeva, Haniti, Remy, Nicolai, Masha, Ewen, Aurélien (Weirdo) and Alex—thank you for the good moments we shared in and out the lab.

I would like to say a special thanks to Gregor for working together as team "NakadoManzamine" and Manuel Gemander (my first student) for his excellent work and the difficulties we conquered together!

Of the people I met over the last four years, I was lucky to make some friends I could share my happiness and sadness with, who were always there when I needed them. Paloma, thank you for helping me when I first started in the lab, all the nice dinners you cooked for me, all the artistic movies we watched, nice holidays we went on together and all the good memories we created. Laetitia, thank you for being a great fumehood mate and more importantly a reliable friend—I really appreciate all the help you gave to me and all the happiness you bring to me. Andy and Jane (the lady), thank you for making Glasgow feel like home. Alistair, thank you for all the time we spent together to get belly belly, talking about random stuff and enduring my bad mood. Thank you Sam and Joanna for the nice dinners, hiking and yoga classes. Justyna (pretty), thank you for all the lady night dinners, gossips and cute dog pictures. Svenja, thank you for being a great friend. I also want to thank: Jie, for all the help and encouragement; Xiaolu, for being an amazing flatmate and all the late night talks about life; Manman, for being a great friend; Nadine, for all the encouraging letters; Emilie (Madame), for the nice babysitting afternoons; Anna, for all the cake recipes and chat. Thank you guys for helping me through the difficulties and sharing the happy times with me, you made my four years in Glasgow enjoyable and memorable!

我要衷心的感谢我的硕士研究生导师姜申德教授，感谢他在我硕士期间的耐心教导和博士申请时的鼓励和支持！也感谢姜教授课题组所有成员这些年来对我的帮助。

最后，我要衷心感谢我的爸爸（许喜贵）妈妈（王九艳）。感谢他们对我毫无保留的奉献，对我所做出决定的全力支持，我感到十分幸运可以生在这样一个幸福的家庭。此外还要感谢我的亲戚们对我的鼓励和支持。

Declaration

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

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

Chao Xu

Professor J. S. Clark

Abbreviations

Ac	Acetyl
AIBN	2,2'-Azo *bis*isobutyronitrile
aq.	Aqueous
BHT	Butylhydroxytoluene
Bn	Benzyl
Bp	Boiling point
Brsm	Based on recovered starting material
Bu	Butyl
Bs	Butylsufonyl
Bz	Benzoyl
c.a	Circa
CBS	Corey-Bakshi-Shibata
CI	Chemical ionisation
COD	1,5-cyclooctadiene
COSY	Correlation spectroscopy
CSA	Camphorsulfonic acid
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	dichloromethane
DEPT	Distortionless enhancement by polarisation transfer
DET	Diethyl tartrate
DIBAL-H	Diisobutylaluminium hydride
DIPEA	Diisopropylethylamine
DMAP	*N*,*N*-4-Dimethylaminopyridine
DMDO	Dimethyl dioxirane
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
dppp	1,3-*Bis*(diphenylphosphino)propane
dr	Diastereomeric ratio
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	Enantiomeric excess

EI	Electron ionisation
ESI	Electrospray ionisation
Et	Ethyl
h	Hour
HMDS	1,1,1,3,3,3-Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HOBt	Hydroxybenzotriazole
HPLC	High pressure liquid chromatography
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence spectroscopy
hv	Irradiation with light
I	*iso*
i.e	Id est
IBX	*o*-Iodoxybenzoic acid
IC_{50}	Half maximal inhibitory concentration
IR	Infrared spectroscopy
IUPAC	International union of pure and applied chemistry
LDA	Lithium diisopropylamide
LRMS	Low resolution mass spectrometry
LUMO	Lowest unoccupied molecular orbital
M	*meta*
m-CPBA	*meta*-Chloroperbenzoic acid
Me	Methyl
Men	(2-Methoxyethoxy)methyl
min	Minute
MLn	Transition metal with ligands
Mp	Melting point
Ms	Methanesulfonyl
MS	Mass spectrometry
MVK	Methyl vinyl ketone
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine-*N*-oxide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
o	*ortho*
p	*para*
PCC	Pyridinium chlorochromate

Ph	Phenyl
PMB	*p*-Methoxybenzyl
PPTS	Pyridinium *p*-toluenesulfonate
Pr	Propyl
quant.	Quantitative
R_f	Retention factor in chromatography
rt	Room temperature
s	*sec*
t	*tert*
TBAF	tetra-*n*-Butylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBHP	*tert*-Butyl hydroperoxide
TBS	*tert*-Butyldimethylsilyl
Temp.	Temperature
TEMPO	2,2,6,6-Tetramethyl-1-piperinyloxy
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl (triflyl)
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
TPAP	Tetra-*n*-propylammonium perruthenate
Tr	Triphenylmethyl (trityl)
Ts	*p*-Toluenesulfonyl
WSC	Water soluble carbodiimide

1 Introduction

1.1 The Manzamine Family of Natural Products

Manzamine A (**3**) was first isolated in 1986 by Higa and co-workers from the marine sponge *Haliclona sp.*[1] To date, more than 70 natural products which are structurally related to manzamine A (**3**) have been isolated from various marine organisms,[2,3] including *Pachypellina*, *Xestospongia*, *Ircinia* and *Amphimedon* species, and their unprecedented molecular architectures have been elucidated by extensive spectroscopic studies.[4] The manzamine family of alkaloids features a wide variety of structures, from simple macrocyclic 3-alkylpyridinium salts, such as cyclostellettamine A (**5**), to highly functionalised complex structures, such as manzamine A (**3**), which possesses a diazapentacyclic core containing an array of 5-, 6-, 8- and 13-membered rings and possessing 5 stereogenic centres (Figure 1).[5]

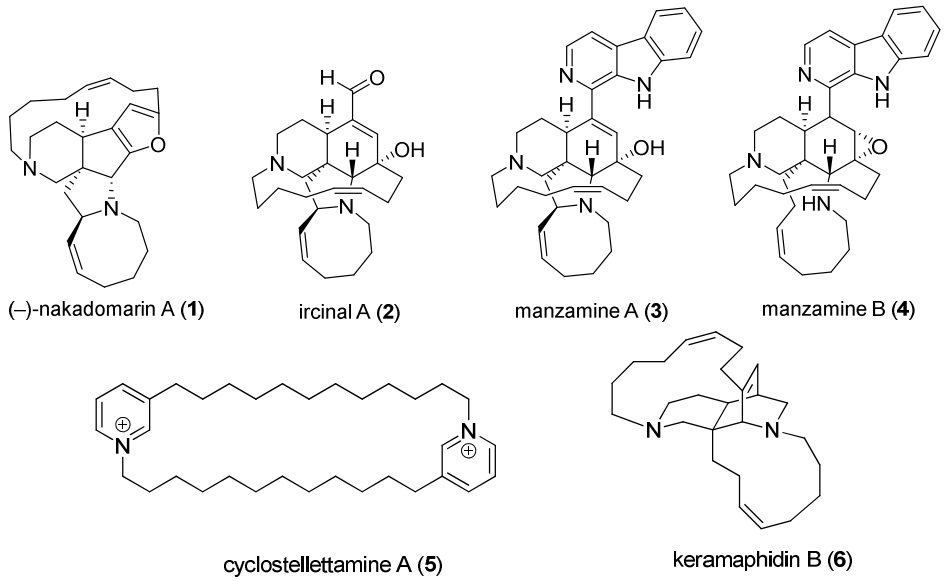


Figure 1 Representative members of the manzamine family of alkaloids

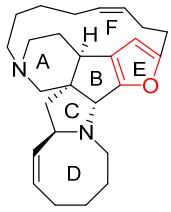
[1] Sakai, R.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *J. Am. Chem. Soc.* **1986**, *108*, 6404−6405
[2] Tsuda, M.; Kobayashi, J. *Heterocycles* **1997**, *46*, 765−794
[3] Watanabe, D.; Tsuda, M.; Kobayashi, J. *J. Nat. Prod.* **1998**, *61*, 689−692
[4] Magnier, E.; Langlois, Y. *Tetrahedron* **1998**, *54*, 6201−6258
[5] Duval, R.; Poupon, E. *Biomimetic Organic Synthesis* Wiley-VCH, **2011**

Members of the manzamine family of alkaloids possess a broad range of bioactivities, including cytotoxicity, antimicrobial activity,[6] antibacterial activity [7] and antimalarial activity.[8] Manzamine A (**3**) was found to have *in vitro* activity against cancer cells, 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). Consequently, the manzamine alkaloids also represent important lead structures for the development of novel anti-infective drugs.[9]

The unique molecular structures, including a complex array of rings, as well as their significant biological activities of manzamine A (**3**) and related alkaloids have held the attention of synthetic and medicinal chemists for the past three decades.

1.2 Nakadomarin A

1.2.1 Isolation and Biological Activity



(–)-nakadomarin A (**1**)

Figure 2

Nakadomarin A (**1**) was first isolated from the sponge *Amphimedon sp.* by Kobayashi and co-workers in 1997 (Figure 2).[10] This natural product exhibits cytotoxicity against murine lymphoma L1210 cells (IC_{50} = 1.3 µg/mL), antimicrobial activity, and inhibitory activity against cyclin-dependent kinase 4. The structure of nakadomarin A was elucidated by exhaustive spectroscopic

---

[6] 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

[7] Nakamura, H.; Deng, S.; Kobayashi, J.; Ohizumi, Y.; Tomotake, Y.; Matsuzaki, T.; Hirata, Y. *Tetrahedron Lett.***1987**, *28*, 621−624

[8] Ang, K. K. H.; Homnes, M. J.; Higa, T.; Hamann, M. T.; Kara, U. A. K. *Antimicrob. Agents Chemother.* **2000**, *44*, 1645−1649

[9] Winkler, J. D.; Londregan, A. T.; Hamann, M. T. *Org. Lett.* **2006**, *8*, 2591−2594

[10] Kobayashi, J.; Watanabe, D.; Kawasaki, N.; Tsuda, M.; *J. Org. Chem.* **1997**, *62*, 9236−9239

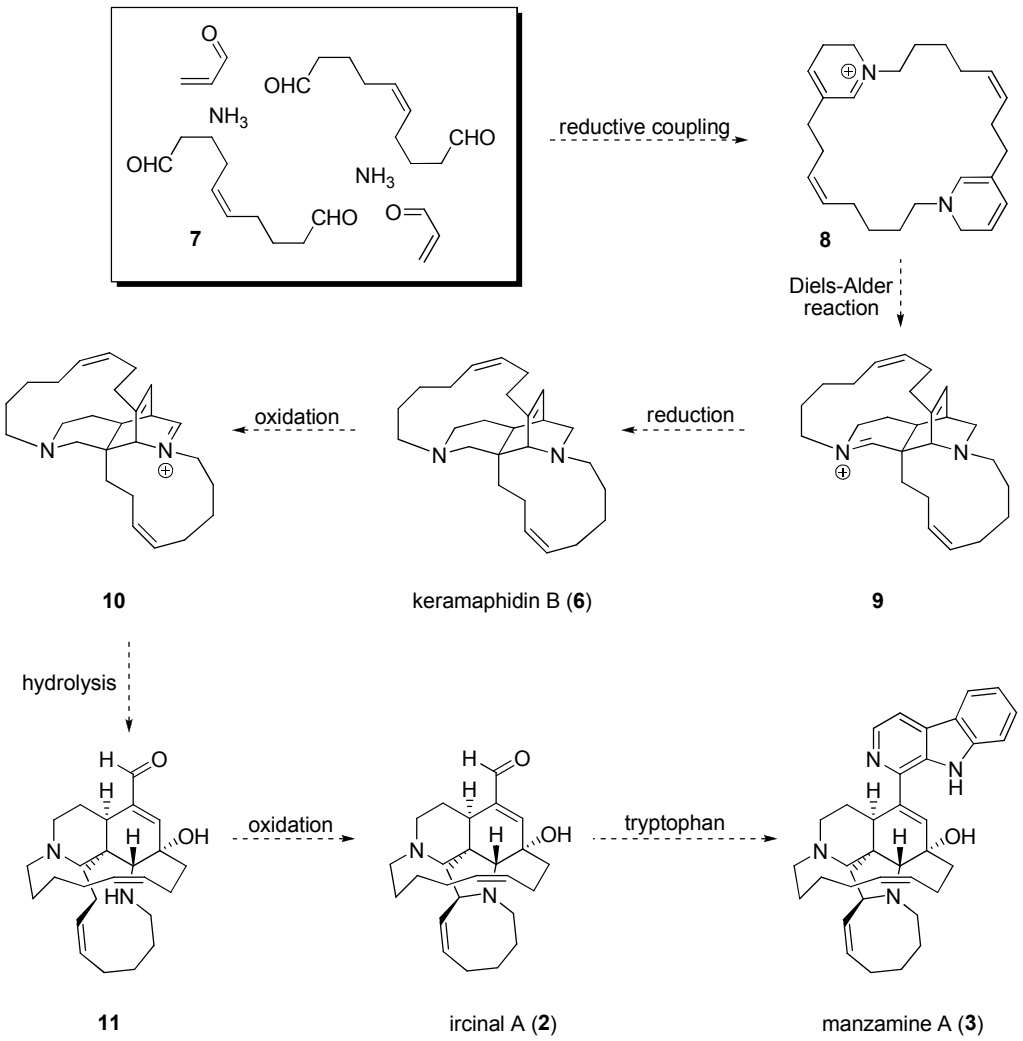
studies and was found to possess a unique hexacyclic skeleton consisting of fused 5-, 6-, 8- and 13-membered rings. More specifically, nakadomarin A (**1**) is the only member of the mazamine family that includes a furan ring. It also contains four stereogenic centres, two *Z*-alkenes and two tertiary amines. The challenging structure, as well as the promising biological activity and limited availability make nakadomarin A (**1**) a highly attractive target for total synthesis, a fact that is reflected by the number of synthetic studies that have been devoted to its synthesis (see section 1.3).

1.2.2 Biosynthesis

The development of an understanding of biosynthetic pathways is of great importance for total synthesis and numerous synthetic strategies have been inspired by nature.[11,12] Despite the fact that manzamine A (**3**) was isolated nearly 30 years ago, the complete biosynthetic route for the creation of these molecules still remains unclear. However, synthetic chemists have presented several credible hypotheses for the potential biosynthetic pathway towards manzamine A (**3**).

In 1992, Baldwin reported a biosynthetic proposal for manzamine alkaloid, which suggested manzamine A could be derived *in vivo* from four simple building blocks: 2 units of ammonia, 2 units of the symmetrical dialdehyde **7**, 2 units of acrolein and 1 unit of tryptophan (Scheme 1).[13]

[11] Breslow, R.; Dong, S. D. *Chem. Rev.* **1998**, *98*, 1997−2011
[12] Yoder. Y. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730−4756
[13] Baldwin, J. E.; Whitehead, R. C. *Tetrahedron Lett.* **1992**, *33*, 2059−2062

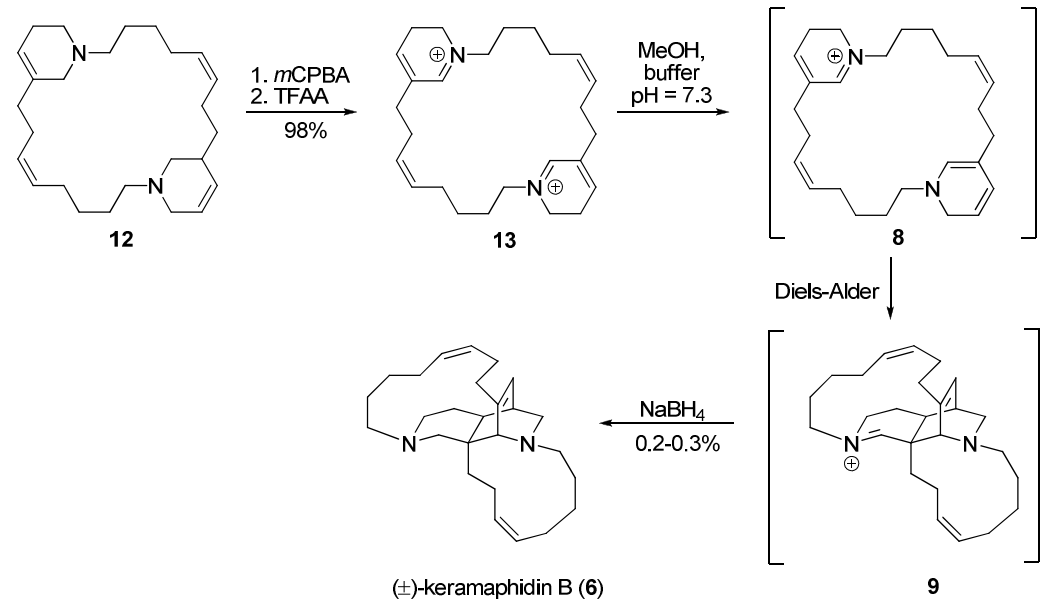


Scheme 1

As shown in Scheme 1, a reductive coupling reaction between ammonia, acrolein and dialdehyde **7** would lead to the formation of 3-alkylpyridinium intermediate **8**, which could undergo a transannular Diels-Alder reaction to afford polycyclic compound **9**. The iminium **9** could be converted into iminium ion **10** either by a redox process or by reduction to form the pentacyclic alkaloid karamaphidin B (**6**), followed by an oxidation reaction. Hydrolysis of iminium ion **10** and further oxidation would provide pentacyclic natural product iricinal A (**2**). Finally, condensation between iricinal A (**2**) and tryptophan would generate manzamine A (**3**).

The viability of this biogenetic pathway was confirmed by the biomimetic total synthesis of keramaphidin B (**6**) published by Baldwin and co-workers in 1999

(Scheme 2).[14] Keramaphidin B (**6**) is a pentacyclic alkaloid belonging to the manzamine family that was isolated by Kobayashi in 1994.[15] The key macrocylic diamine **12** was prepared in 8 steps from 3-*n*-propylpyridine with an overall yield of 37%. Oxidation of diamine **12** with *m*CPBA and subsequent treatment with TFAA afforded bis-iminium dication **13** in high yield. Extensive work was then carried out for the key transannular Diels-Alder reaction. After screening various solvents, temperatures and reducing reagents, the total synthesis of keramaphidin B (**6**) was accomplished by treating the dication **13** with buffered methanol (pH = 7.3) to generate the pyridium intermediate **8** required for the Diels-Alder reaction and subsequent reduction of the resulting iminium **9** with $NaBH_4$.



Scheme 2

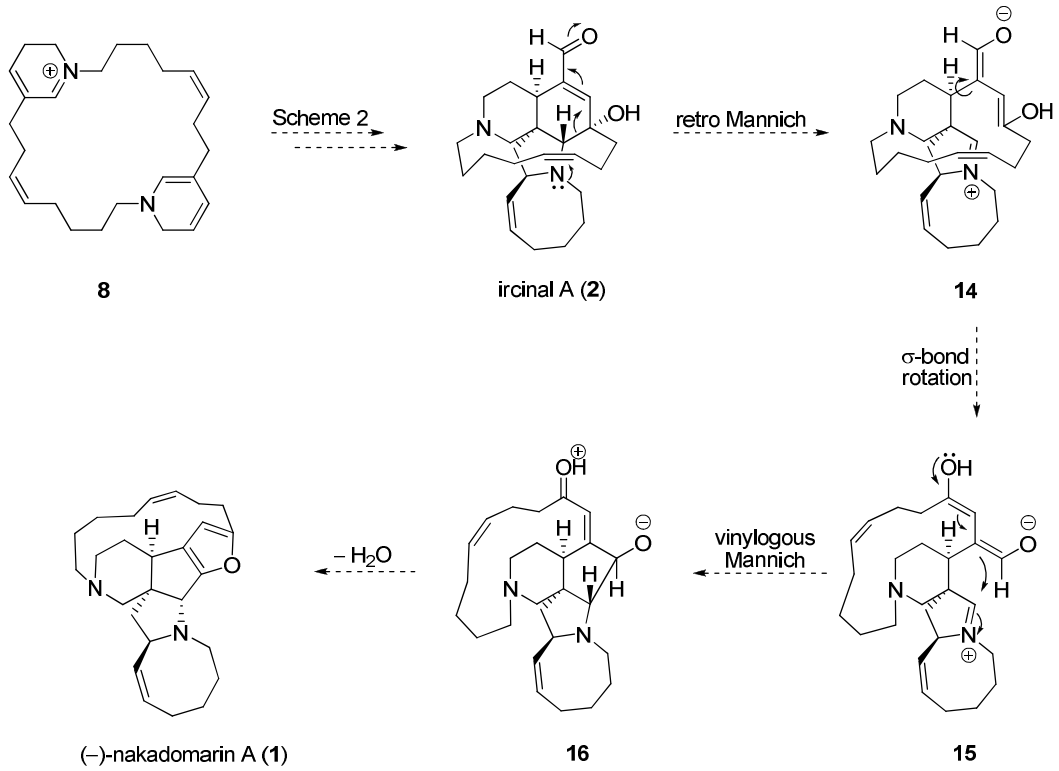
Although this biomimetic synthesis verified Baldwin's hypothesis, the Diels-Alder reaction and reduction sequence only produced a trace amount (0.2-0.3% yield) of the desired keramaphidin B (**6**) and the diamine **12** was recovered almost quantitatively**.** To account for this, Baldwin and co-workers proposed the existence of a "Diels-Alderase" directing enzyme capable of preorganising the substrate into a favourable conformation for the pericyclic reaction.

---

[14] 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

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

Based on Baldwin's hypothesis, Kobayashi proposed a biosynthetic pathway for (−)-nakadomarin A (**1**) from ircinal A (**2**, Scheme 3).[16] Ircinal A (**2**) could undergo a retro-Mannich reaction to generate the iminium ion **14**. σ-Bond rotation followed by a vinylogous Mannich reaction would afford the pentacyclic intermediate **16**. Final dehydrative furan formation would then generate (−)-nakadomarin A (**1**).



Scheme 3

1.3 Total Syntheses of Nakadomarin A

Due to its challenging molecular structure and promising biological activity, nakadomarin A has been a natural product target of great interest for the synthetic organic chemists over the past decade. The total syntheses of (−)-nakadomarin A (**1**) and/or its enantiomer (+)-nakadomarin A (*ent*-**1**) have been published by seven groups: those of Nishida,[17,18] Kerr,[19] Dixon,[20,21,22] Mukai,[23] Funk,[24] Zhai[25] and most recently Evans.[26]

[16] Kobayashi, J.; Tsuda, M.; Ishibashi, M. *Pure. Appl. Chem.* **1999**, *71*, 1123−1126
[17] Nagata, T.; Nakagawa, M.; Nishida, A. *J. Am. Chem. Soc.* **2003**, *125*, 7484−7485
[18] Ono, K.; Nakagawa, M.; Nishida, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 2020−2023

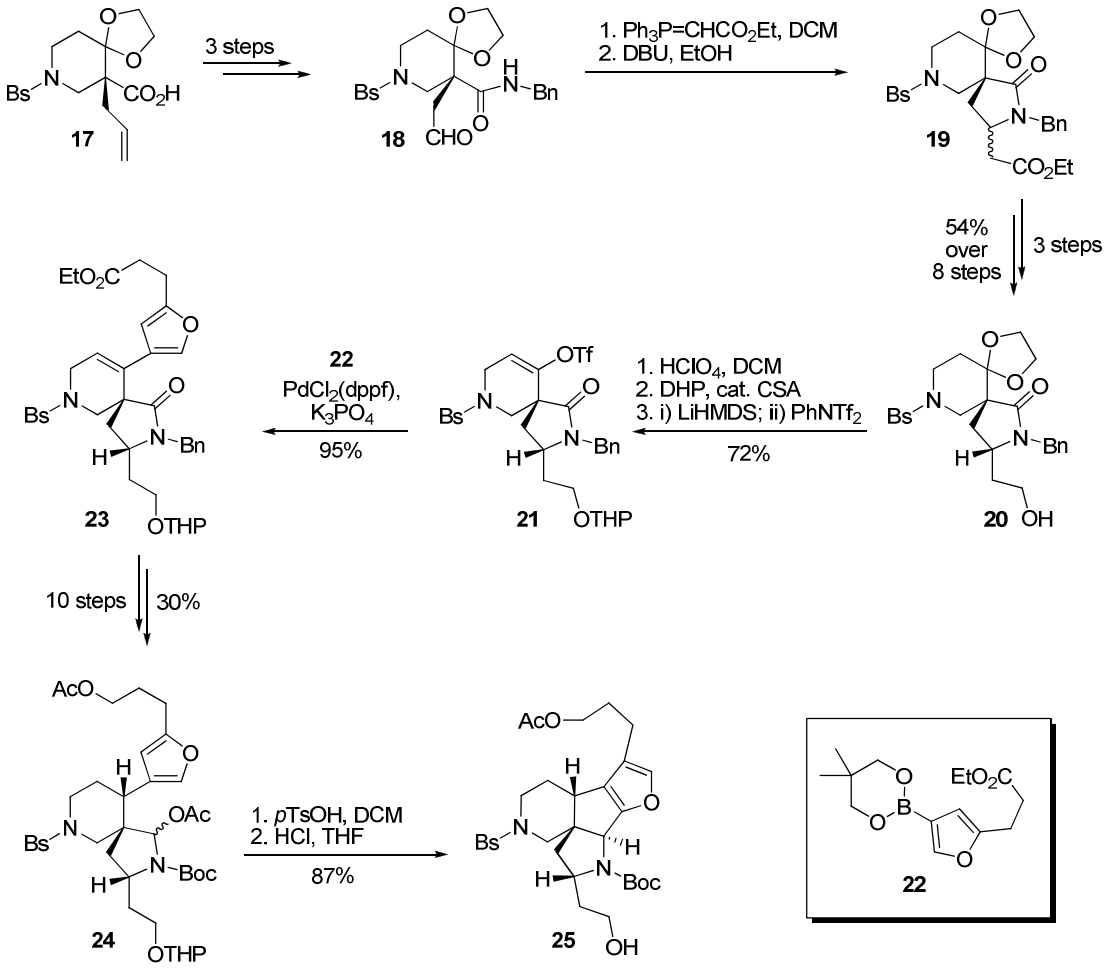
1.3.1 The Nishida's Strategy

1.3.1.1 The Total Synthesis of (+)-Nakadomarin A

Nishida and co-workers published the first total synthesis of (+)-nakadomarin A (*ent*-**1**) in 2003 (Scheme 4).[17] Their synthesis started with transformation of the relatively complex chiral acid **17** into the aldehyde **18** in three steps. Wittig olefination of aldehyde **18** and subsequent intramolecular Michael addition afforded the spirolactam **19** as an inseparable mixture of diastereoisomers (3.3:1) contaminated with triphenylphosphine oxide. Hydrolysis of ester **19** to its acid counterpart allowed the removal of non-polar impurities. Re-esterfication and reduction to the alcohol allowed the separation of diastereoisomers and delivered the enantiopure alcohol **20**. Acetal group cleavage followed by protection of the alcohol and enol triflate formation furnished the lactam **21**. Subsequently, the triflate **21** was coupled with furan-3-boronic ester **22** by Suzuki-Miyaura coupling, to deliver the tricyclic ester **23** in high yield. The subsequent 10-step synthetic sequence involving stereoselective hydrogenation and further functional group manipulation afforded hemiaminal **24**. Treatment of **24** with *p*TsOH led to the generation of an iminium ion which then underwent a stereoselective Pictet-Spengler reaction. The removal of the tetrahydropyranyl (THP) group afforded tetracyclic alcohol **25** in 87% yield.

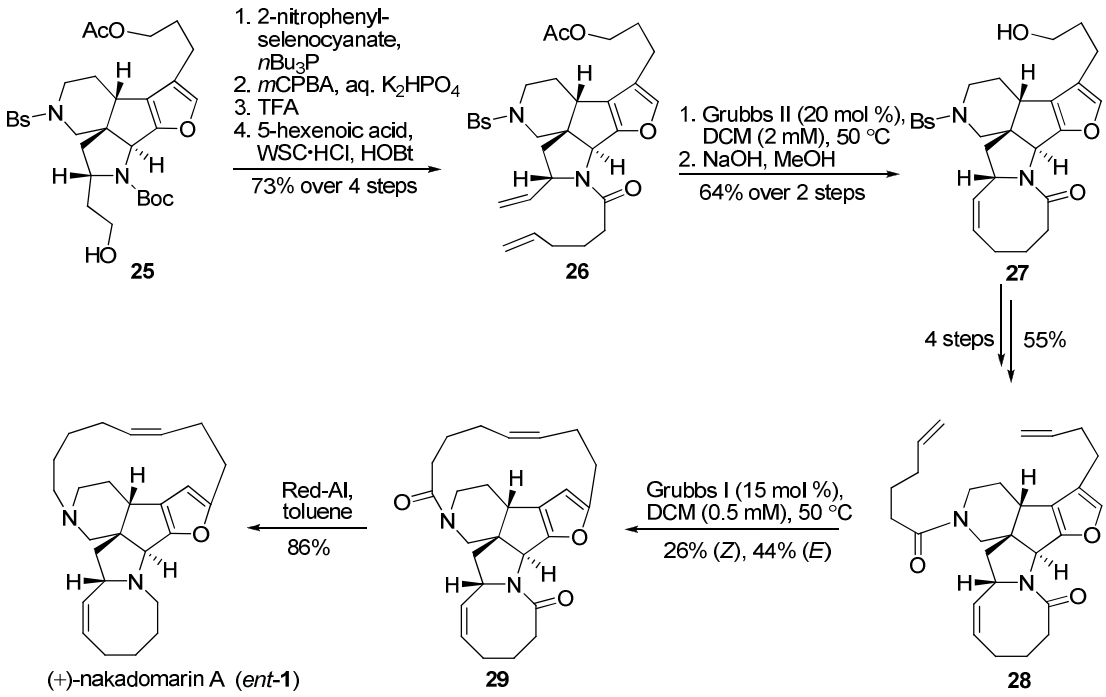
---

[19] Young, I. S.; Kerr, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 1465−1469
[20] Jakubec, P.; Cockfield, D. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 16632−16633
[21] Kyle, A. F.; Jakubec, P.; Cockfield, D. M.; Cleator, E.; Skidmore, J.; Dixon, D. J. *Chem. Commun.* **2011**, *47*, 10037−10039
[22] Jakubec, P.; Kyle, A. F.; Calleja, J.; Dixon, D. J. *Tetrahedron Lett.* **2011**, *52*, 6094−6097
[23] Inagaki, F.; Kinebuchi, M.; Miyakoshi, N.; Mukai, C. *Org. Lett.* **2010**, *12*, 1800−1803
[24] Nilson, M. G.; Funk, R. L. *Org. Lett.* **2010**, *12*, 4912−4915
[25] Cheng, B.; Wu, F. F.; Yang, X. B.; Zhou, Y. D.; Wan, X. L.; Zhai, H. B. *Chem. Eur. J.* **2011**, *17*, 12569−12572
[26] Bonazzi, S.; Cheng, B.; Wzorek, J.; Evans, D. A. *J. Am. Chem. Soc.* **2013**, *135*, 9338−9341



Scheme 4

Selenation of primary alcohol **25** followed by sequential oxidation, selenoxide elimination, Boc deprotection and *N*-alkylation formed diene **26** (Scheme 5). Treatment of this diene with the second-generation Grubbs catalyst to accomplish ring closing metathesis (RCM) followed by the hydrolysis of acetate gave the azocine **27** in good yield. The synthesis continued with conversion of the alcohol **27** into the bisamide **28** in 4 steps. The diene **28** then underwent another RCM reaction upon treatment with the first-generation Grubbs catalyst, to afford a separable mixture of *E* and *Z* isomers; the desired *Z* isomer **29** was the minor isomer and was isolated in 26% yield. Finally, reduction of the bislactam **29** with Red-Al, provided the target molecule in a total of 38 steps.



Scheme 5

Although the ^{1}H NMR data of the synthetic nakadomarin A matched with data reported by Kobayashi for the natural product, the opposite specific rotation suggested that (+)-nakadomarin A (*ent*-**1**) had been obtained. This result allowed assignment of the absolute configuration of natural (−)-nakadomarin A (**1**).

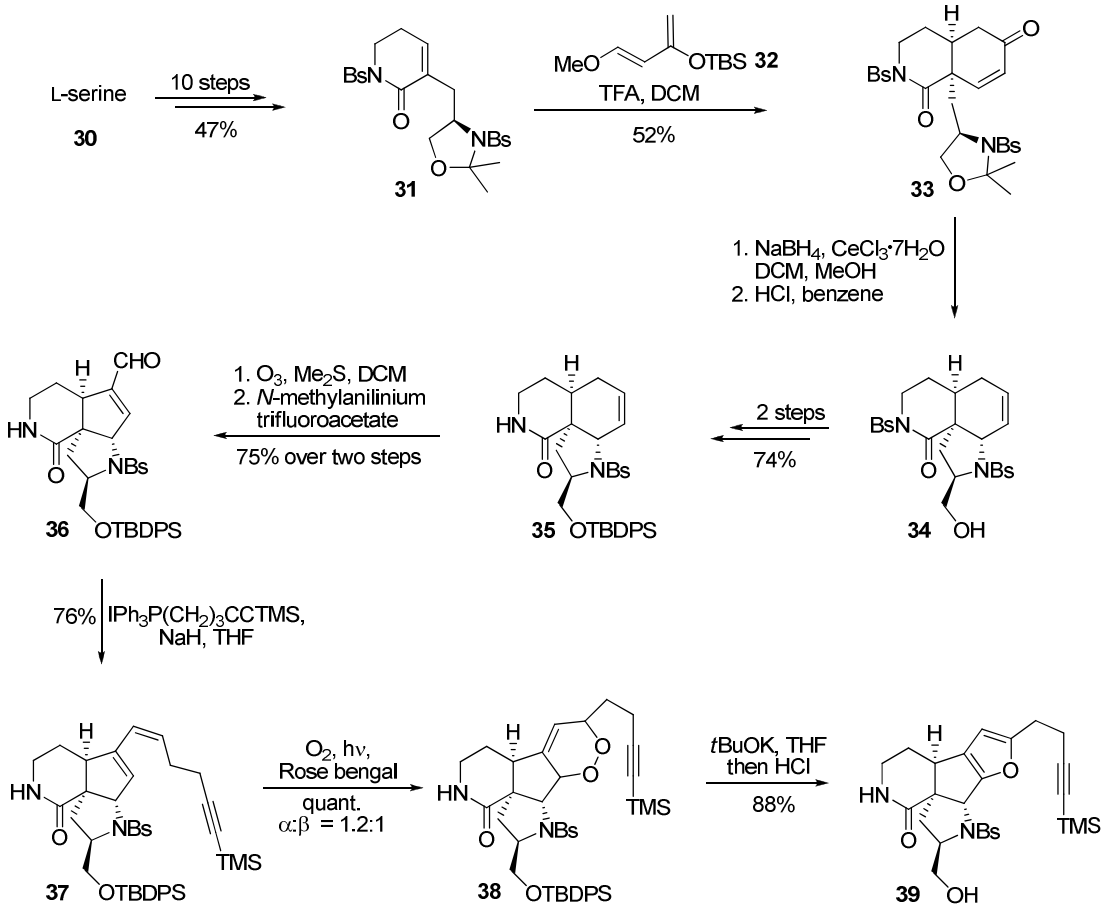
1.3.1.2 The Total Synthesis of (−)-Nakadomarin A

One year after the synthesis of (+)-nakadomarin A (*ent*-**1**), the Nishida group published the first total synthesis of (−)-nakadomarin A (**1**) in which a different route to the ABCD core was used (Scheme 6).[18]

The synthesis started from chiral amide **31** which was prepared from L-serine in 10 steps. Dienophile **31** underwent a Diels-Alder reaction with Danishefsky's diene **32**[27] to give enone **33**. Enone reduction under the Luche conditions[28] followed by actonide cleavage and S_N' cyclisation reaction afforded the fused tricyclic alcohol **34**. Subsequent selective protecting group removal provided alkene **35**. Double bond cleavage by ozonolysis and subsequent aldol

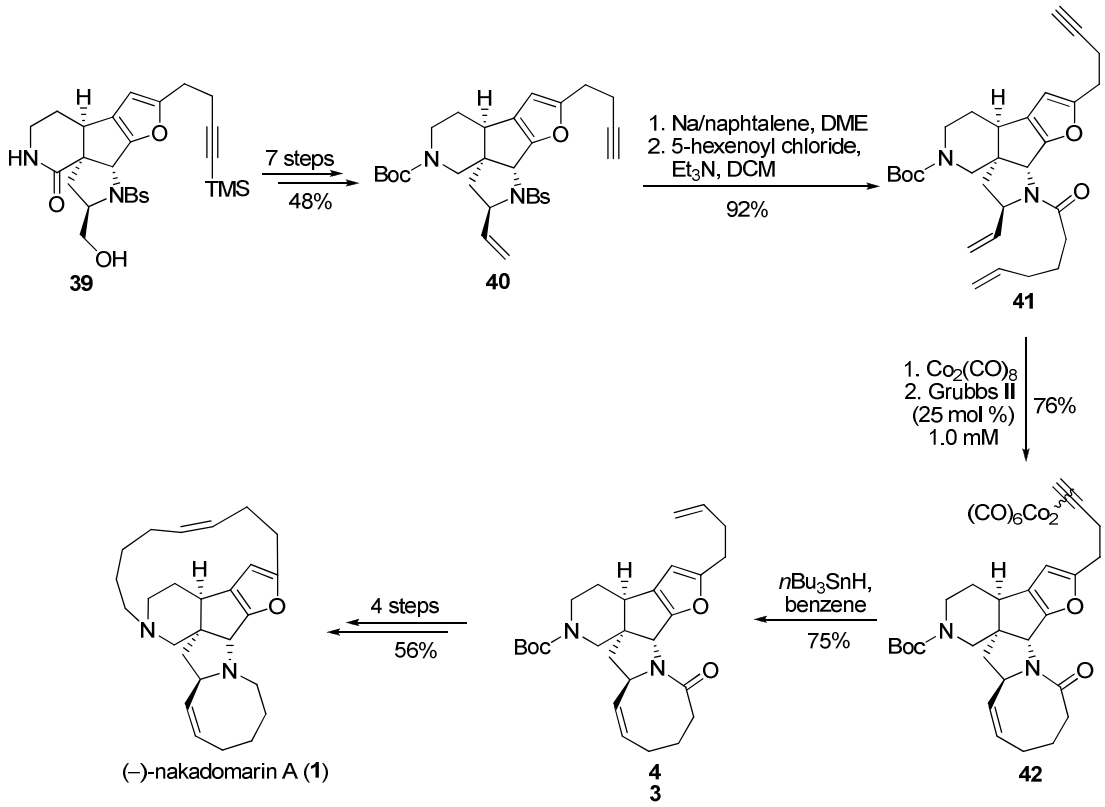
[18] Ono, K.; Nakagawa, M.; Nishida, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 2020−2023
[27] Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807−7808
[28] Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459

condensation delivered the desired aldehyde **36**, which then underwent a Wittig olefination to deliver the conjugated diene **37**. Oxidation of the diene **37** with singlet oxygen generated the peroxide **38** and furan formation was accomplished by base catalysed rearrangement. Removal of the TBDPS protecting group on workup then gave the primary alcohol **39**.



Scheme 6

Alcohol **39** was converted into the alkyne **40** in 7 steps and 48% yield. Reductive removal of the *N*-Bs group by treatment with sodium naphthalenide followed by acylation delivered diene **41**. Protection of the terminal alkyne with dicobalt octacarbonyl and subsequent RCM provided the pentacyclic lactam **42**. One-pot decomplexation and reduction afforded diene **43** and this was converted into (−)-nakadomarin A (**1**) in four steps using the strategy previously developed for the synthesis of (+)-nakadomarin A (*ent*-**1**).



Scheme 7

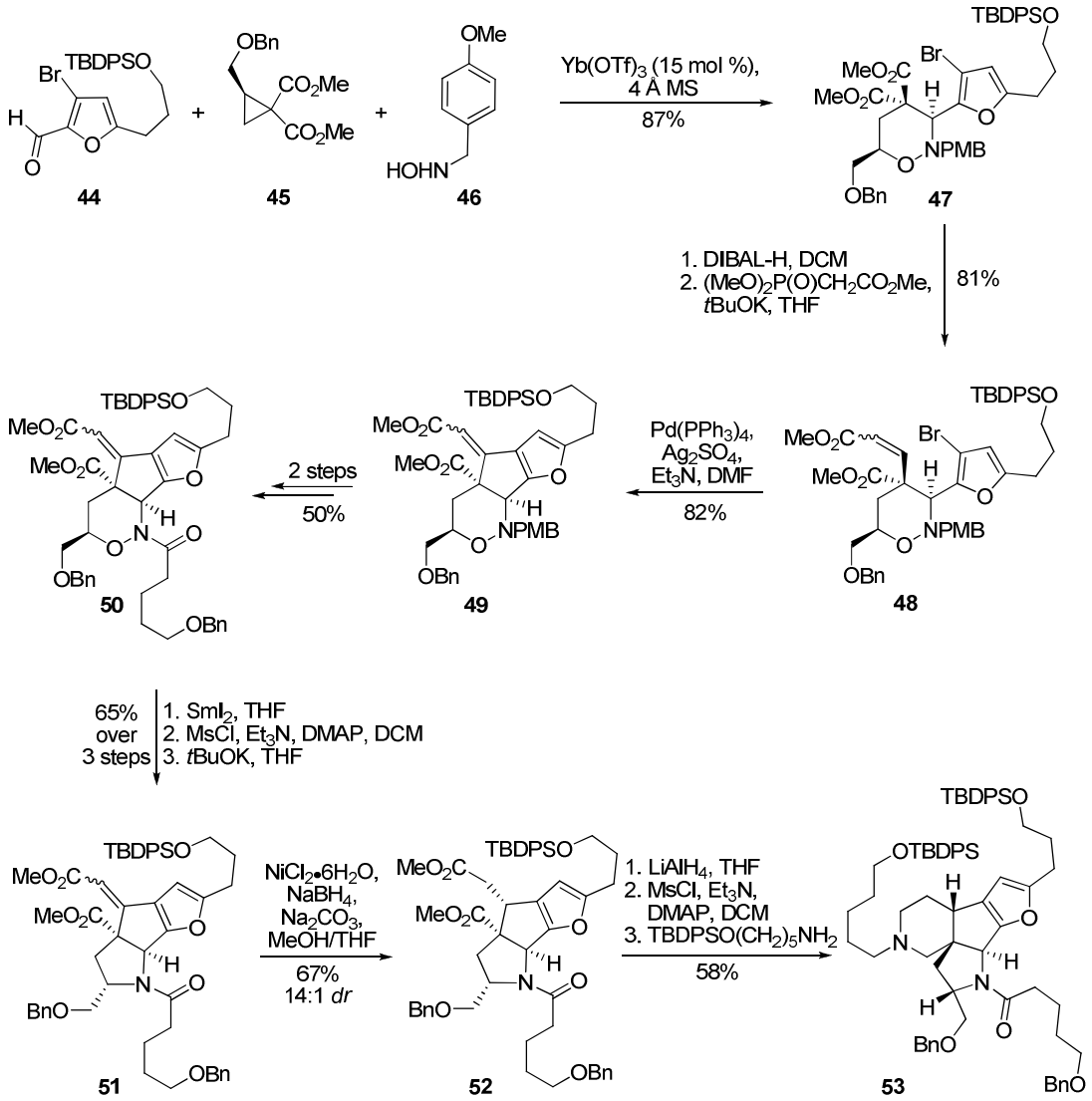
1.3.2 Kerr's Approach

The second total synthesis of (+)-nakadomarin A (*ent*-**1**) was reported by Kerr in 2007.[19] The key feature of this synthesis was the use of a three-component coupling reaction developed by Kerr and co-workers in 2005.[27]

The synthetic sequence commenced with the three-component reaction of aldehyde **44**, cyclopropane **45** and hydroxylamine **46** to give a highly functionalised tetrahydro-1,2-oxazine **47** (Scheme 8). Selective diisobutyl-aluminium hydride (DIBAL) reduction of the equatorial ester group in bicyclic intermediate **47**, followed by Horner-Wadsworth-Emmons (HWE) olefination and intramolecular Heck coupling provided tricyclic intermediate **49**. Removal of the PMB protecting group and *N*-acylation afforded the amide **50**. Cleavage of the N—O bond with SmI_2, followed by mesylate formation and subsequent S_N2 displacement with the amide delivered the desired pyrrolidine **51**. Stereoselective conjugate reduction of the α,ß-unsaturated ester with nickel

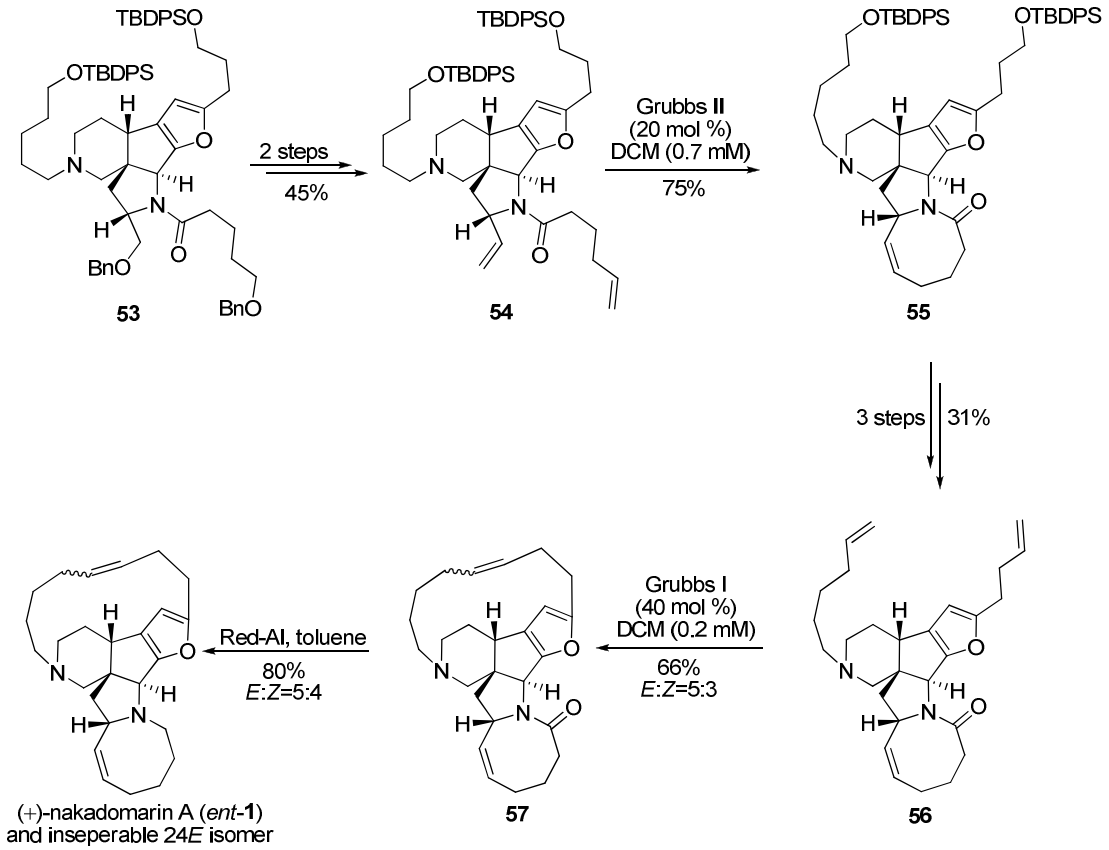
[19] Young, I. S.; Kerr, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 1465−1469
[27] Young, I. S.; Williams, J. L.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 953−955.

boride was carried out to give diester **52**. Thus, all the stereocentres required for (+)-nakadomarin A (*ent*-**1**) were installed correctly. Double ester reduction and mesylation generated a dimesylate that underwent a tandem S_N2 displacement with an amine to form a piperidine and deliver the tetracyclic amine **53**.



Scheme 8

The tetracyclic system **53** was readily converted to azocine **55** by sequential benzyl protecting group removal, oxidation, Wittig olefination and RCM. An analogous 4-step sequence was used to convert the bis-TBDPS-ether **55** into macrocycle **57**, the key RCM reaction delivering the macrocycle in moderate yield and as an inseparable mixture of *E* and *Z* isomers (*E*:*Z* = 5:3). The last step was the reduction of bis-lactam to afford (+)-nakadomarin A (*ent*-**1**).



Scheme 9

In conclusion, the Kerr group completed the total synthesis of (+)-nakadomarin A (*ent*-**1**) in 28 linear steps. Unfortunately, the *E* and *Z* isomers could not be separated at any stage and the final natural product was contaminated by its *E* isomer.

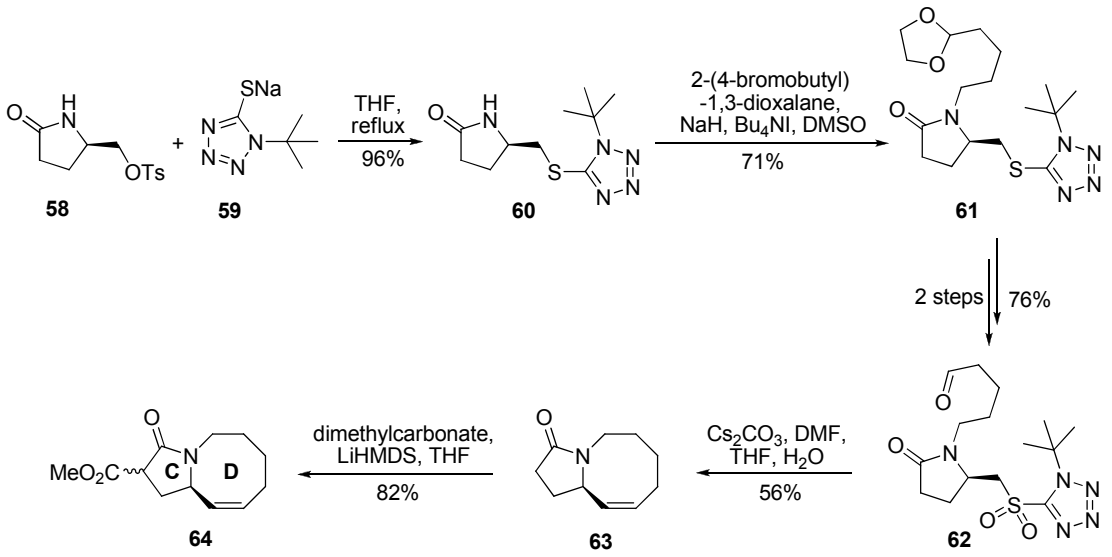
1.3.3 Dixon's Syntheses

In 2009, Dixon and co-workers published a convergent total synthesis of (−)-nakadomarin A (**1**).[20] The key features of this strategy were a diastereoselective Michael addition reaction and a three-component nitro-Mannich/lactamisation cascade developed within the group.

Dixon's sequence commenced with the synthesis of the CD ring fragment of (−)-nakadomarin A (**1**, Scheme 10). Nucleophilic substitution of the tosylate of pyroglutamol **58** by sodium thiolate **59** gave sulfide **60**, which underwent

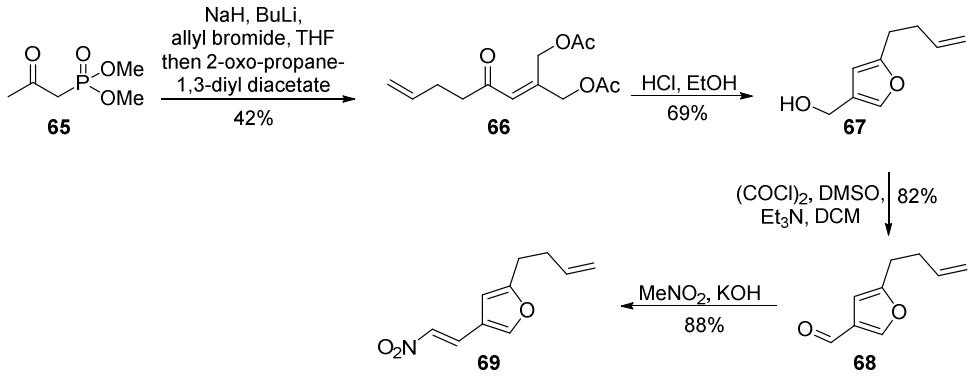
[20] Jakubec, P.; Cockfield, D. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 16632−16633

sequential *N*-alkylation, deprotection and oxidation to provide aldehyde **62**. Intramolecular Julia-Kocienski olefination[28,29] then took place to generate azocine **63**. Claisen condensation of amide **63** with dimethylcarbonate finished the synthesis of the CD fragment **64**.



Scheme 10

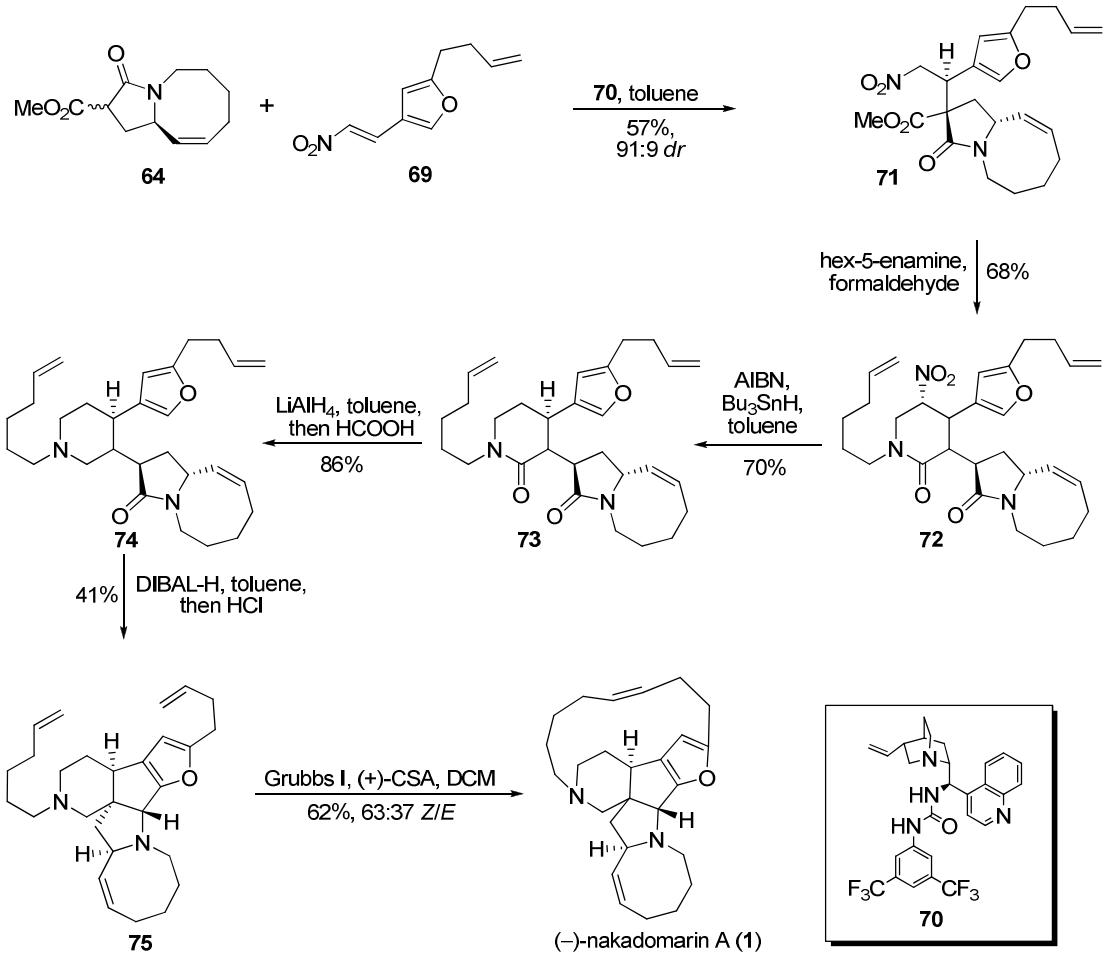
The synthesis of the furan fragment started with allylation of ketophosphonate **65** followed by a Horner-Wadsworth-Emmons olefination reaction using diacetyl dihydroxyacetone to give enone **66** (Scheme 11). Subsequent acid catalysed deprotection and dehydrative cyclisation provided furan **67**. Subsequent Swern oxidation followed by Henry condensation with nitromethane afforded the nitro olefin **69** in 4 steps and 21% overall yield.



Scheme 11

[28] Julia, M.; Paris, J. M. *Tetrahedron Lett.* **1973**, *14*, 4833−4836
[29] Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 829−834

Completion of both key fragments allowed the Michael addition reaction between CD ring system **64** and nitro olefin **69** to be investigated (Scheme 12). Unfortunately, an inseparable mixture of diastereoisomers (60:40, *dr*) was obtained. A chiral catalyst was then sought to increase the selectivity. By using the bifunctional cinchona catalyst **70**, the diastereomeric ratio was increased to 91:9 in favour of the desired isomer. Subjecting the resulting coupled product **71** to a stereoselective nitro-Mannich/lactamisation cascade sequence provided lactam **72** in good yield. Reduction of the nitro group by a modified Ono procedure[30] followed by selective reduction of the δ-lactam to the corresponding amine while the γ-lactam remained untouched, afforded amide **74**. Subsequent partial reduction generated an aminol intermediate, which underwent acid catalysed iminium formation and cyclisation to provide pentacyclic diamine **75**. A *Z*-selective olefin metathesis was achieved by using the first-generation Grubbs catalyst in the presence of an excess of camphor sulfonic acid (CSA) giving the final target (−)-nakadomarin A (**1**) in good yield (63:37 *Z*/*E* ratio; isomers were separable by semi-preparative HPLC).

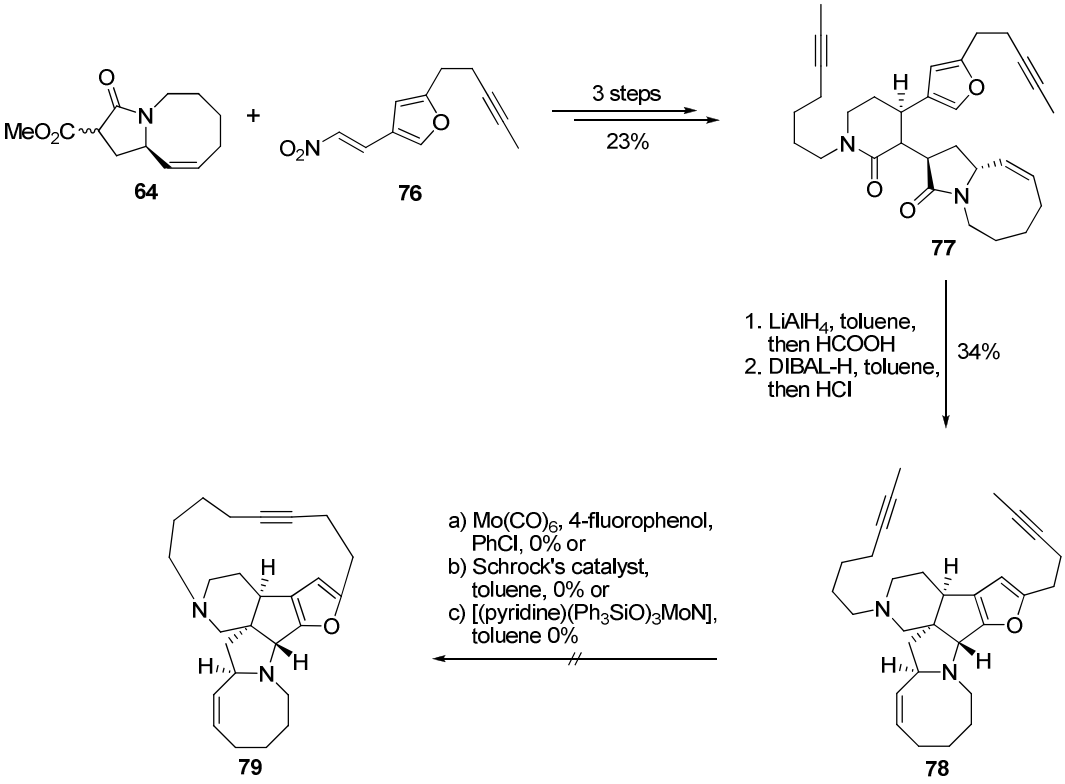


Scheme 12

[30] Ono, N.; Miyake, H.; Tamura, R.; Kaji, A. *Tetrahedron Lett.* **1981**, *22*, 1705−1708

In conclusion, Dixon and co-workers synthesised (−)-nakadomarin A (**1**) in 12 steps (longest linear sequence). Moderate *Z* selectivity in the final RCM reaction was achieved by using (+)-CSA as an additive.

In 2011, the Dixon group reported a modified synthesis of (−)-nakadomarin A (**1**).[22] In this paper, sequential alkyne ring closing metathesis and Lindlar reduction was employed to install the *Z* olefin moiety of the macrocycle in a highly stereoselective manner. The dialkyne **78** was prepared using a similar coupling strategy to that used originally (Scheme 13). Unfortunately, after extensive screening of various reaction conditions, it was found that the pentacyclic diyne **78** was unreactive towards alkyne RCM.

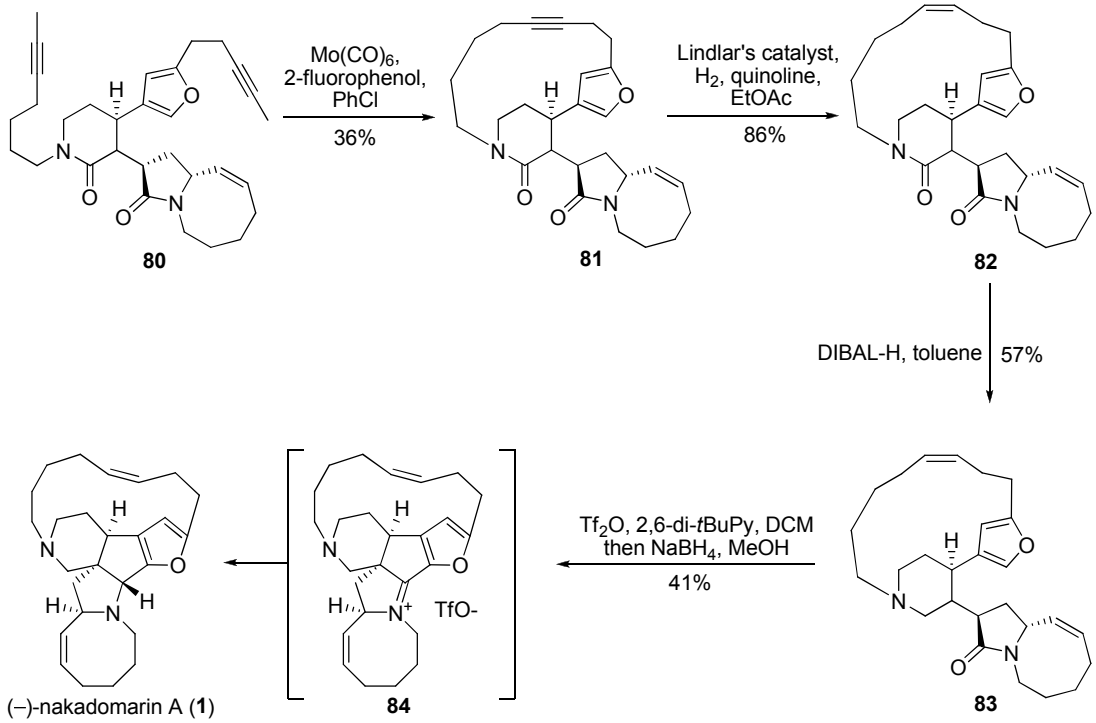


Scheme 13

This problem was solved by performing the alkyne RCM at an earlier stage in the synthesis. Thus, the intermediate **80** was converted into the desired alkyne RCM product **81** in moderate yield (Scheme 14). Subsequent Lindlar hydrogenation afforded *Z* alkene **82**. The synthesis was completed in a similar manner to their

[22] Jakubec, P.; Kyle, A. F.; Calleja, J.; Dixon, D. J. *Tetrahedron Lett.* **2011**, *52*, 6094−6097

first strategy led to the total synthesis of (−)-nakadomarin A (**1**) in 13 steps (longest linear sequence).



Scheme 14

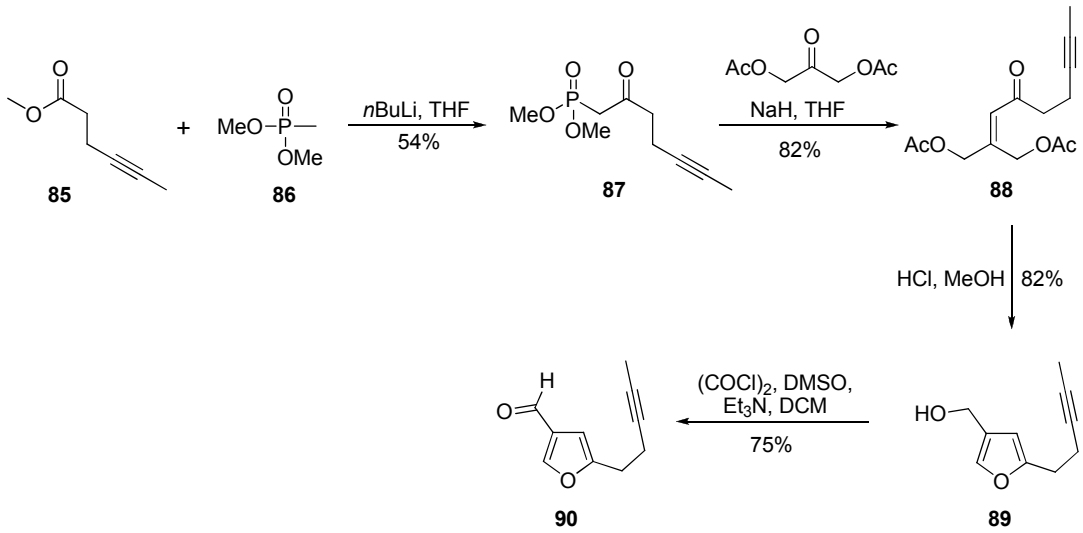
1.3.4 Funk's Total Synthesis

Funk and co-workers published their total synthesis of (−)-nakadomarin A (**1**) in 2010.[24] Their strategy was based on a retrosynthetic analysis that led to the furan **90** and the pyrrole **95** as early-stage intermediates. The key reaction in this route was a stereoselective Lewis acid catalysed iminium formation/conjugate addition cascade reaction previously developed within the group.[31]

The furan fragment was prepared following Maldonado's procedure (Scheme 15).[32] Condensation of ester **85** and dimethyl methylphosphonate **86** provided ketone **87,** which underwent Horner-Wadsworth-Emmons olefination with diacetoxyacetone to afford the enone **88**. Acid-catalysed deprotection and

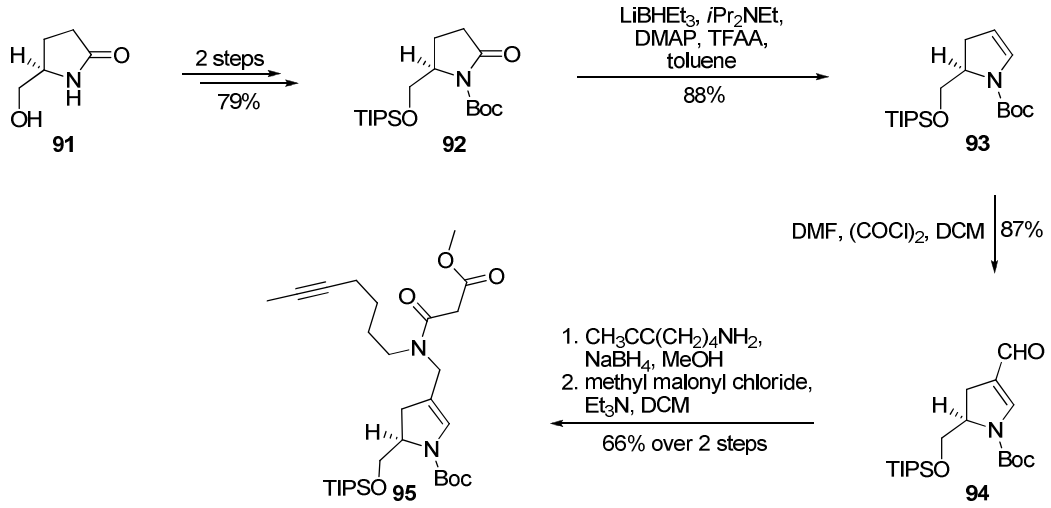
[24] Nilson, M. G.; Funk, R. L. *Org. Lett.* **2010**, *12*, 4912−4915
[31] Nilson, M. G.; Funk, R. L. *Org Lett.* **2006**, *8*, 3833−3836
[32] DiazCortes, R.; Silva, A. L.; Maldonado, L. A. *Tetrahedron Lett.* **1997**, *38*, 2207−2210

cyclisation of **88** gave furan **89**, which was then converted into the aldehyde **90** under standard Swern oxidation conditions.



Scheme 15

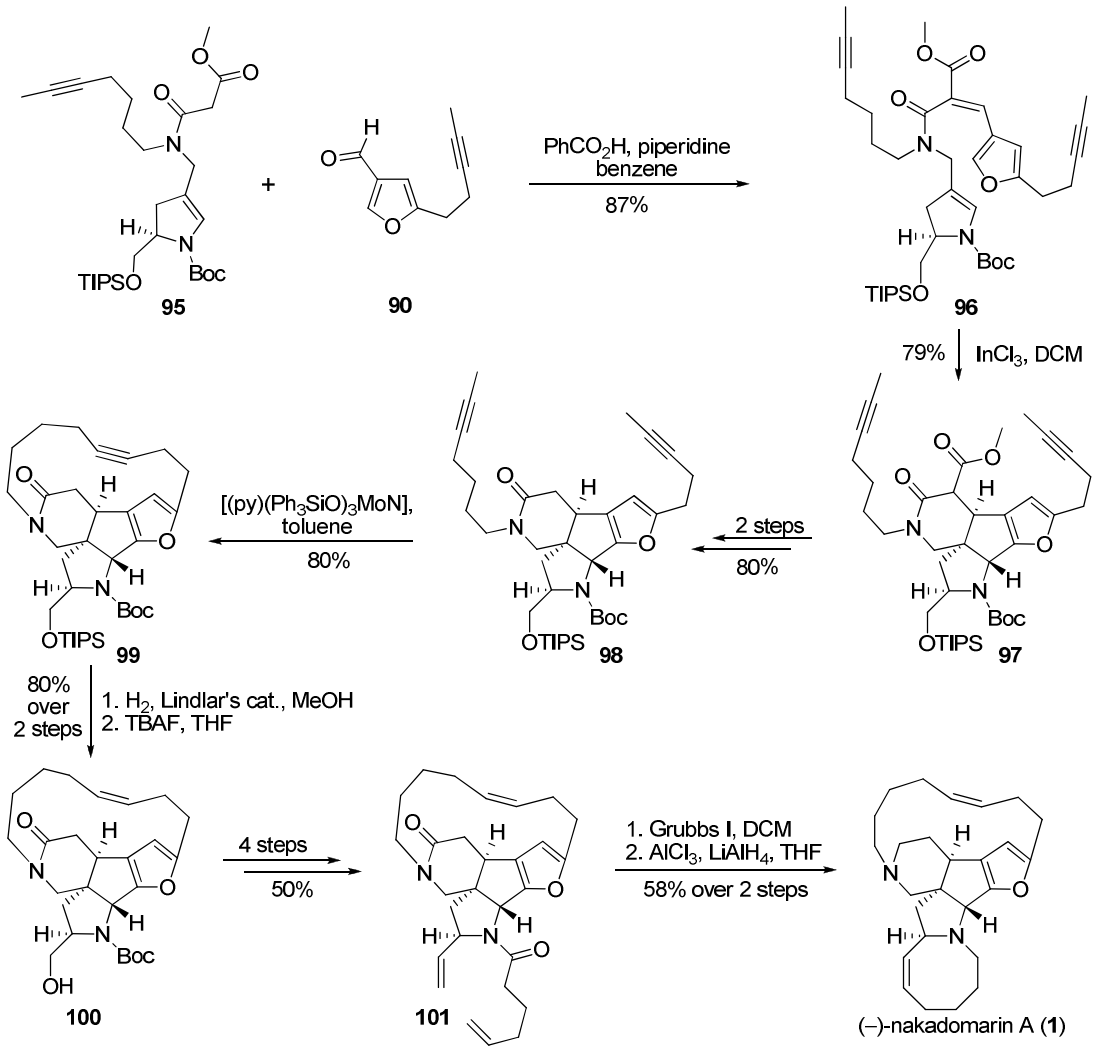
The synthesis of the dihydropyrrole fragment **95** started from the pyrrolidinone **91** (Scheme 16). Pyrrolidinone **91** was first protected to give the amide **92** which was reduced to the corresponding hemiaminal and further dehydrated by trifluoroacetic anhydride (TFAA) to yield the dihydropyrrole **93**.[33] Vilsmeier-Haack formylation of the enamine provided the aldehyde **94**. Subsequent reductive amination and *N*-acylation with methyl malonyl chloride afforded the desired pyrrole fragment **95** in 8 steps.



Scheme 16

[33] Yu, J. R.; Truc, V.; Riebel, P.; Hierl, E.; Mudryk, B. *Tetrahedron Lett.* **2005**, *46*, 4011−4013

Knoevenagel condensation of the aldehyde **90** with the 1,3-dicarbonyl compound **95** provided cyclisation precursor **96** in good yield (Scheme 17). The next step in the synthesis was a one pot Lewis acid ($InCl_3$) catalysed Michael addition/Pictet-Spengler cyclisation cascade reaction. This key reaction delivered the tetracyclic framework **97** in a stereoselective manner. Removal of the ester group in a two-step sequence provided the lactam **98** in good yield. Subsequent sequential alkyne metathesis using a molybdenum catalyst developed by Fürstner, [34] hydrogenation with Lindlar's catalyst and triisopropylsilyl (TIPS) deprotection provided the macrocyclic *Z* alkene **99**. Further installation of a diene and then RCM afforded the azocine ring. Finally, reduction of the bis-lactam led to the completion of (−)-nakadomarin A (**1**).



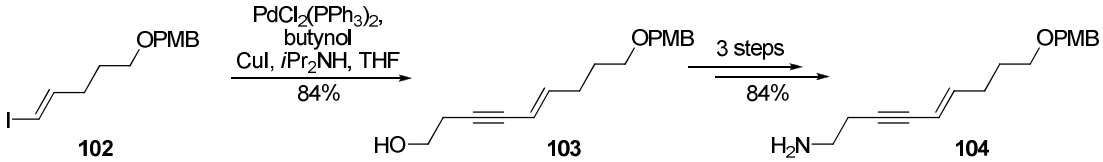
Scheme 17

[34] Bindl, M.; Stade, R.; Heilmann, E. K.; Picot, A.; Goddard, R.; Furstner, A. *J. Am. Chem. Soc.* **2009**, *131*, 9468−9470

1.3.5 Mukai's Formal Synthesis

In 2010, a formal synthesis of (+)-nakadomarin A (*ent*-**1**) was published by Mukai and co-workers.[23] Their synthetic strategy was based on the use of a stereoselective Pauson-Khand reaction to construct the ABC core.

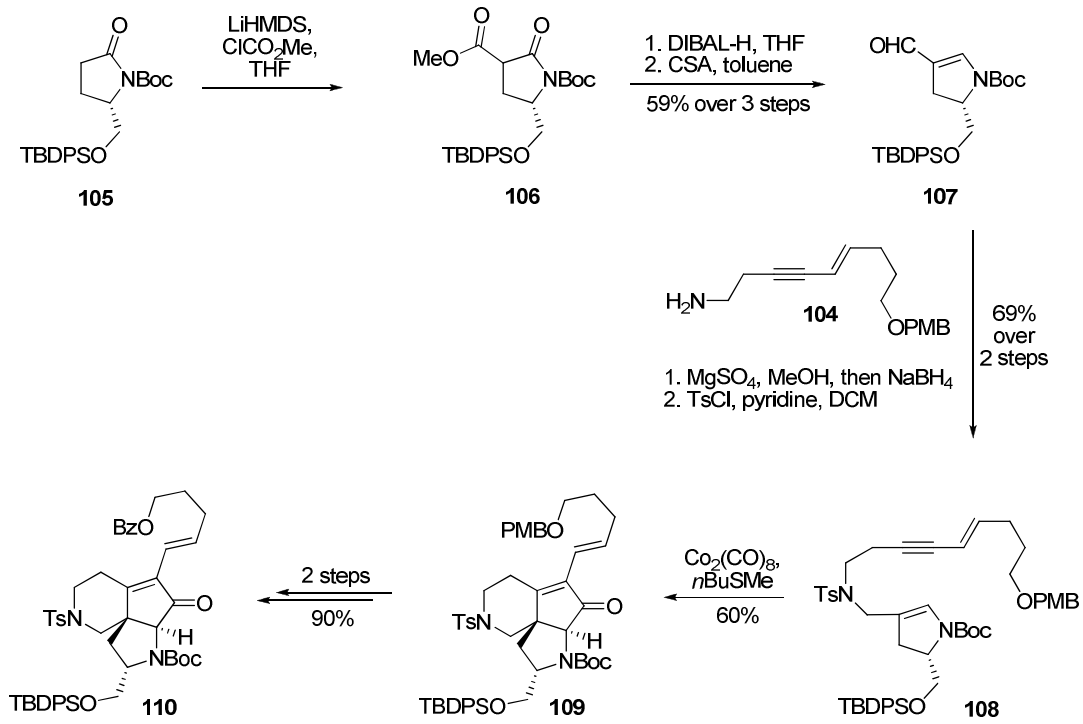
The synthesis started from the simple iodide **102** which was prepared in 2 steps from 4-pentyn-1-ol (Scheme 18). The iodide **102** underwent Sonogashira coupling with 3-butyn-1-ol to give alcohol **103**, which was further converted into primary amine **104** in high yield.[30]



Scheme 18

The coupling partner, aldehyde **107**, was prepared from the L-glutamic acid derivative **105** in 3 steps and in good yield (Scheme 19). Subsequent reductive amination of **107** with amine fragment **104** and tosyl protection of the resulting secondary amine afforded enyne intermediate **108**. Subjecting enyne **108** to the key intramolecular Pauson-Khand reaction generated enone **109** stereoselectively. Replacing the *p*-methoxybenzyl (PMB) protecting group with a benzoyl group provided tricyclic intermediate **110**.

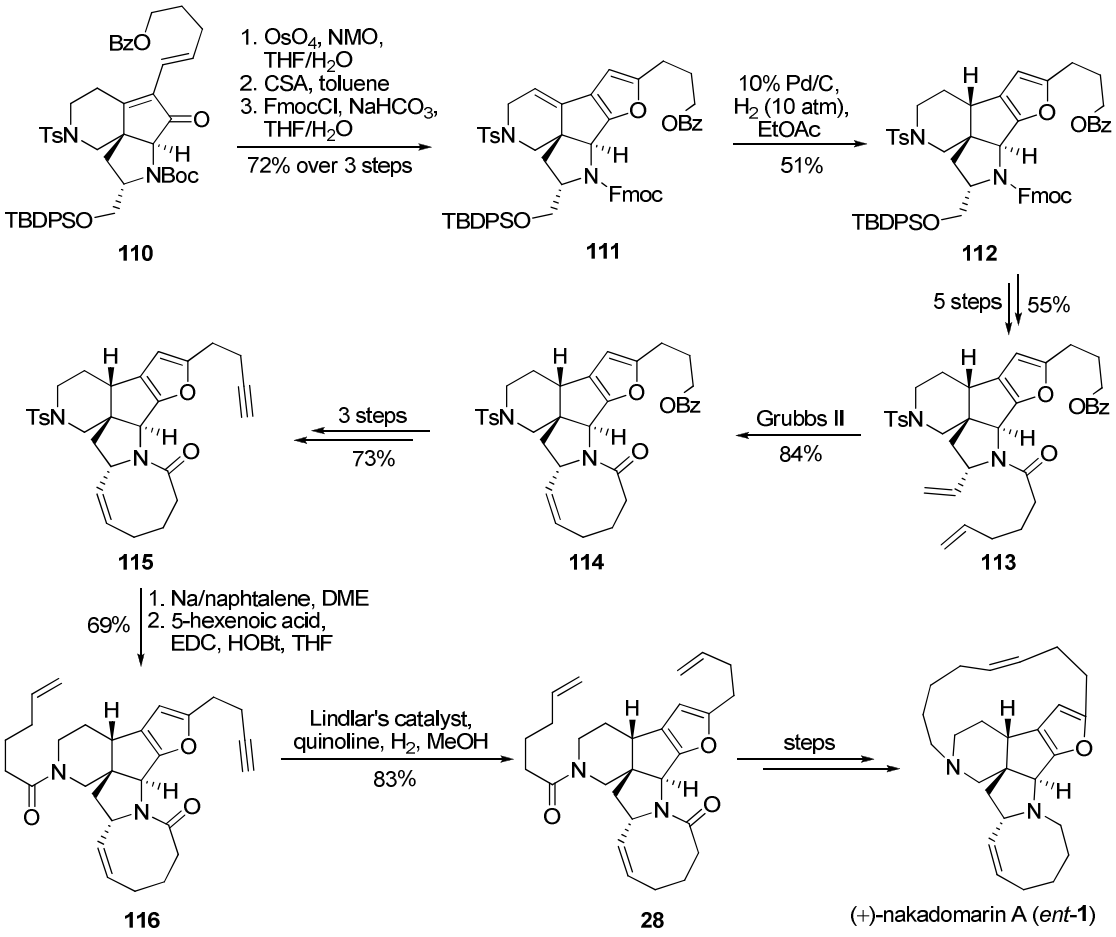
[23] Inagaki, F.; Kinebuchi, M.; Miyakoshi, N.; Mukai, C. *Org. Lett.* **2010**, *12*, 1800−1803



Scheme 19

The dienone **110** was converted to the fused tetracyclic system **111** by dihydroxylation, acid-catalysed dehydrative furan formation and fluorenylmethyloxycarbonyl (Fmoc) protection of the secondary amine (Scheme 20). Screening of conditions for the selective hydrogenation of the tetrahydropyridine showed the protecting group on the nitrogen had a crucial influence on the outcome of the reaction. Only a trace amount of the desired product was formed with free amine while its *tert*-butyloxycarbonyl (Boc) protected counterpart was hydrogenated in 32% yield. The Fmoc-protected intermediate **111** proved to give the highest conversion to piperidine **112** (51%). A similar strategy to that employed by Nishida was used to transform piperidine **112** to Nishida's intermediate **28**.[17]

[17] Nagata, T.; Nakagawa, M.; Nishida, A. *J. Am. Chem. Soc.* **2003**, *125*, 7484−7485



Scheme 20

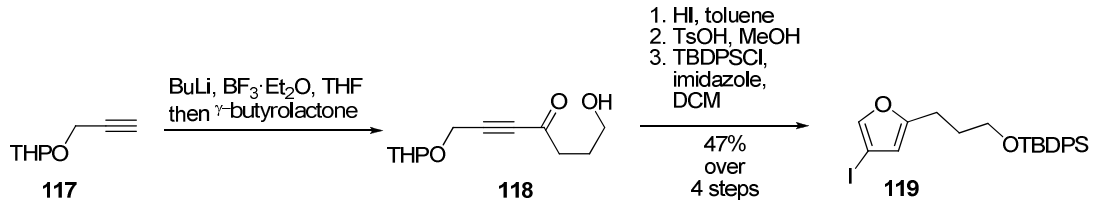
1.3.6 Zhai's Total Synthesis

In 2010, Zhai and co-workers accomplished the total synthesis of (−)-nakadomarin A (**1**) in 20 steps.[25] The key feature of the strategy was the use of a stereoselective Pt(II)-mediated cyclisation reaction that had been developed in Zhai's group to construct the ABCD core.[35]

The preparation of the iodide **119** for the key Sonogashira coupling reaction from THP protected propargyl alcohol **117** was accomplished in four steps (Scheme 21). Deprotonation of propargyl alcohol **117** with *n*-BuLi followed by nucleophilic attack of the lithium acetylide on γ-butyrolactone afforded ynone **118**. Addition of HI to the ynone **118** gave a vinyl iodide intermediate, which

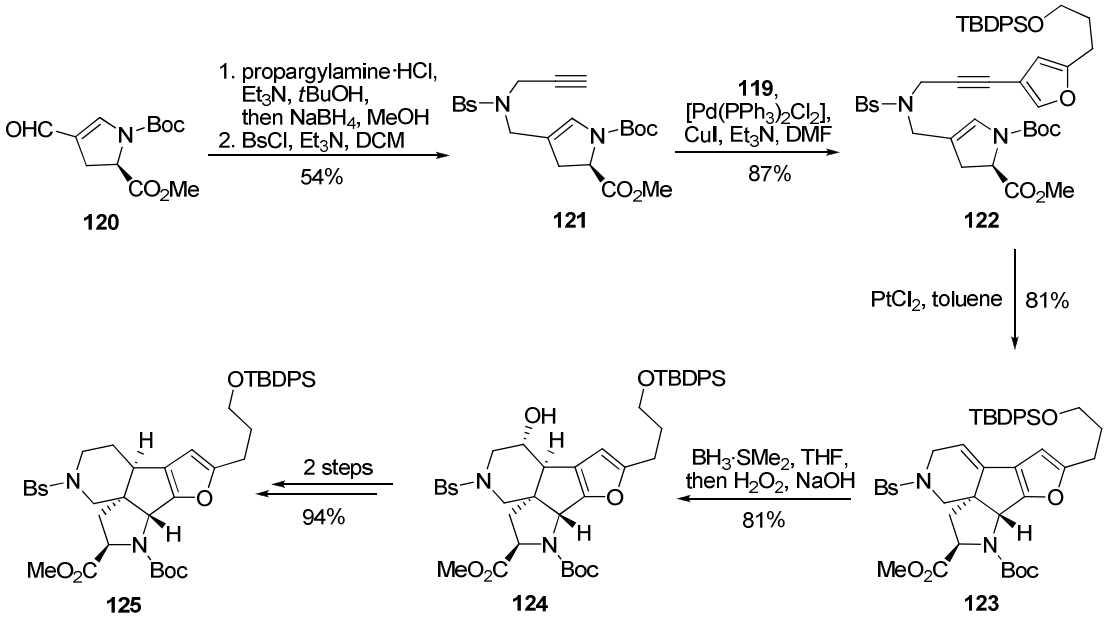
[25] Cheng, B.; Wu, F. F.; Yang, X. B.; Zhou, Y. D.; Wan, X. L.; Zhai, H. B. *Chem. Eur. J.* **2011**, *17*, 12569−12572
[35] Deng, H.; Yang, X.; Tong, Z.; Li, Z.; Zhai, H. *Org. Lett.* **2008**, *10*, 1791−1793

was subjected to THP deprotection, acid catalysed cyclisation and TBDPS protection to provide the desired furan **119** in good yield.



Scheme 21

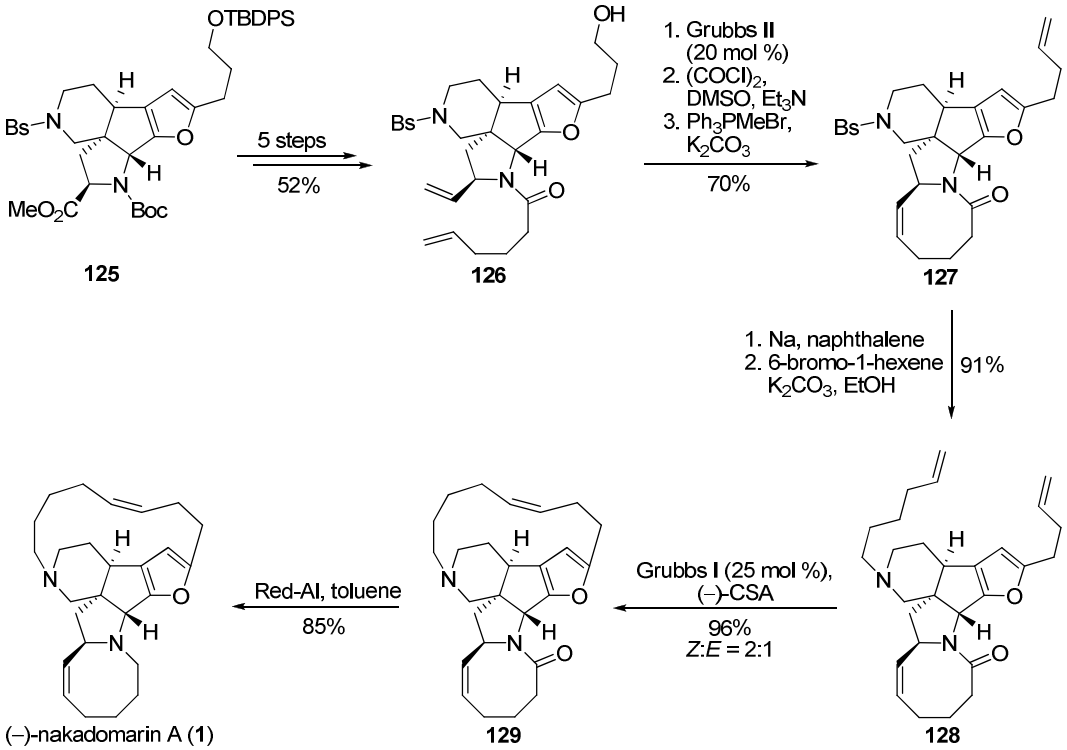
The aldehyde **120** was prepared from D-pyroglutamic acid in four steps (Scheme 22). Reductive amination and protection of the resulting secondary amine with a benzylsulfonyl group gave alkyne **121.**[36,37] Sonogashira coupling between the alkyne **121** and the iodide **119** afforded the furan **122.** Subsequently, the key Pt(II)-promoted stereoselective cascade cyclisation reaction converted alkyne **122** into the tetracyclic core **123.** The alkene moiety in compound **123** was inert to various hydrogenation conditions and so sequential hydroboration-oxidation and Barton-McCombie deoxygenation[38] was employed instead, which led to the formation of piperidine **125.**



Scheme 22

[36] Harrison, T. J.; Patrick, B. O.; Dake, G. R. *Org. Lett.* **2007**, *9*, 367−370
[37] Shono, T.; Matsumura, Y.; Inoue, K.; Ohmizu, H.; Kashimura, S. *J. Am. Chem. Soc.* **1982**, *104*, 5753−5757
[38] Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc. Perk. Trans. 1* **1975**, 1574−1585

The ester **125** was transformed into the diene **126** by a 5-step sequence (Scheme 23). Assembly of the azocine ring by RCM reaction, followed by Swern oxidation and Wittig olefination afforded the pentacyclic compound **127**. The alkene **127** was converted into (−)-nakadomarin (**1**) using a four-step sequence that is similar to that in previously established routes.

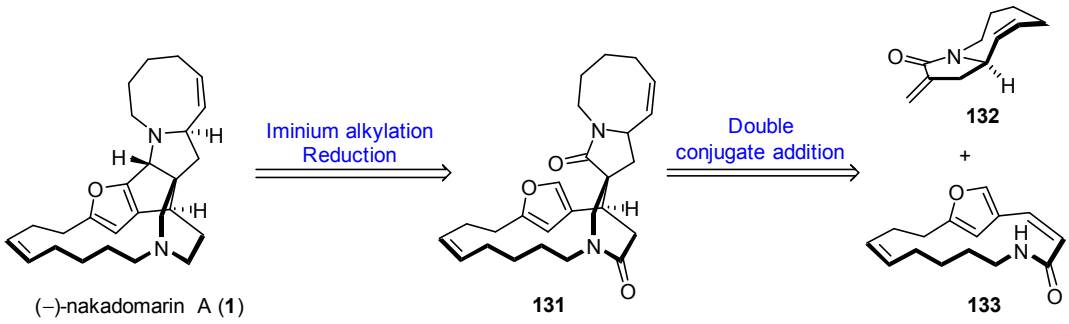


Scheme 23

1.3.6 Evans' total synthesis

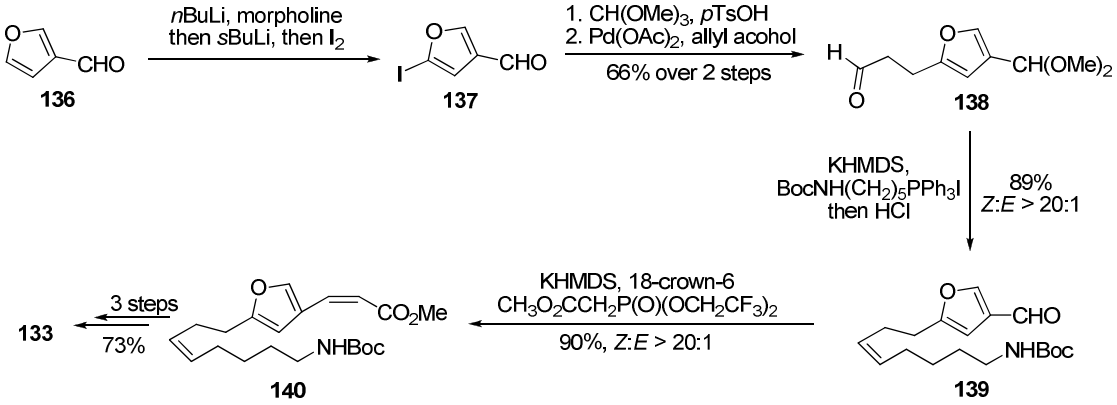
The most recent total synthesis of (−)-nakadomarin (**1**) was reported by the Evans group in 2013.[26] Retrosynthetic analysis (Scheme 24) revealed that (−)-nakadomarin (**1**) could be constructed from a lactam intermediate by reduction, iminium formation and Pictet-Spengler reaction. The requisite lactam would be made by preferential reduction of the δ-lactam over the γ-lactam in bis-lactam **131**. A key stereoselective double Michael addition reaction developed in the Evans group would deliver the pentacyclic intermediate **131** from the pyrrolidinone **132** and furan macrolactam **133**.

[26] Bonazzi, S.; Cheng, B.; Wzorek, J.; Evans, D. A. *J. Am. Chem. Soc.* **2013**, *135*, 9338−9341



Scheme 24

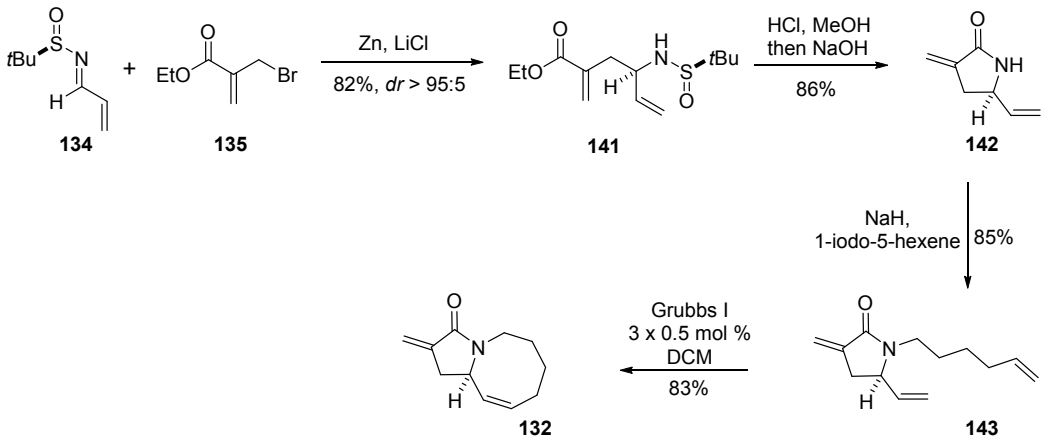
The synthesis of the furan fragment started with regioselective iodination of 3-furancarboxaldehyde (**136**) (Scheme 25). Acetal protection of the aldehyde in iodide **137** followed by Heck coupling with allyl alcohol under Jeffrey's conditions [39] delivered aldehyde **138**. Wittig olefination and removal of the dimethylacetal protecting group by acidic workup generated aldehyde **139**, which was converted into the furan fragment **133** by a sequence of *Z*-selective HWE reaction, saponification and macrolactam formation.



Scheme 25

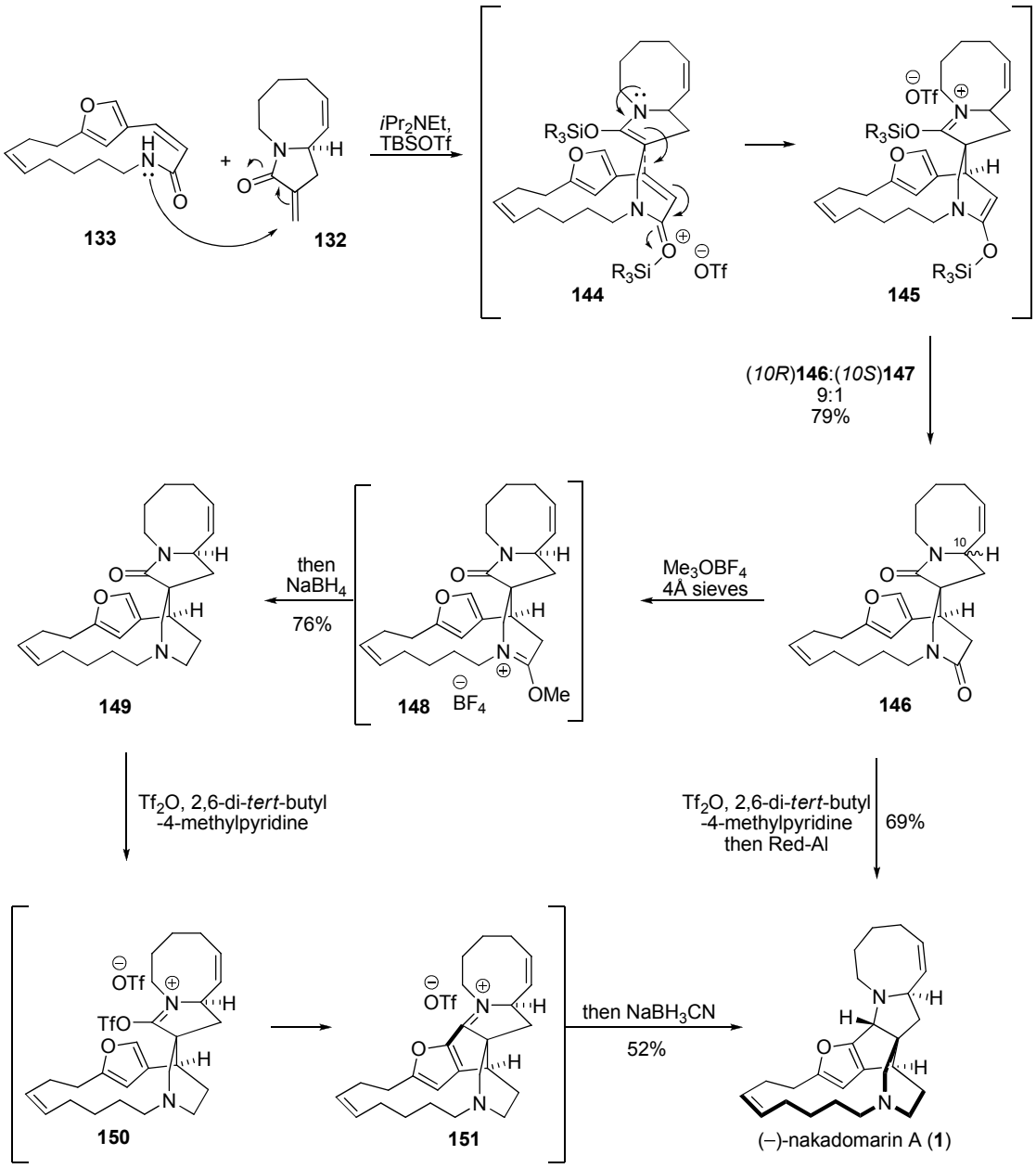
The synthesis of bicyclic lactam fragment **132** commenced with chiral imine **134** which was derived from the condensation between (*R*)-*tert*-butyl sulfinamide and acrolein (Scheme 26). Allylation of **134** with ethyl 2-(bromomethyl) acrylate under Barbier conditions provided sulfonamide **141** in good yield and with excellent diastereoselectivity (*dr* > 95:5). Removal of the chiral auxiliary followed by lactamisation afforded pyrrolidinone **142**. *N*-Alkylation and RCM medited by the first-generation Grubbs catalyst gave the desired bicyclic lactam **132** in excellent yield.

[39] Jeffrey, T. *Tetrahedron Lett.* **1991**, *32*, 2121−2124



Scheme 26

With the furan fragment **133** and the azocine fragment **132** available, the key double Michael addition was then investigated (Scheme 27). After various screening and optimisation reactions, it was found that slow addition of lactam **132** into a solution of Lewis acid pre-activated α,ß-unsaturated amide **133** afforded the desired coupling product **146** in good yield and diastereoselectivity (dr >9:1). More interestingly, only two of the four possible diastereomers were obtained and these compounds were readily separable by simple flash column chromatography on silica gel. Single-crystal X-ray diffraction was used to establish that the major product was **(10*R*)-146**, the diastereomer required for synthesis of (−)-nakadomarin A (**1**). It was proposed that the pentacyclic intermediate **146** was formed by the addition of the achiral unsaturated macrolactam **133** to the less hindered *convex* face of the bicyclic **132**. Subjecting the bis-lactam **146** to Meerwein's salt led to the selective electrophilic attack at the less hindered δ-lactam. Subsequent reduction of the activated iminium intermediate **148** provided the lactam **149**. The total synthesis of (−)-nakadomarin (**1**) was completed by sequential activation of the γ-lactam and cyclisation to afford the iminium intermediate **151** and reduction.



Scheme 27

A more efficient procedure to convert the bis-lactam **146** directly to (−)-nakadomarin A (**1**) was also developed (Scheme 27). Activation of bis-lactam **146** by triflic anhydride led to iminium formation and cyclisation, and one-pot reduction provided (−)-nakadomarin A (**1**).

In contrast to the previous synthetic strategies, the Evans' synthesis elegantly avoided the use of a late-stage RCM reaction. The synthesis of (−)-nakadomarin A (**1**) was completed in 9 steps (longest linear sequence) from 3-furaldehyde with 10% overall yield.

1.4 Fragment Syntheses towards Nakadomarin A

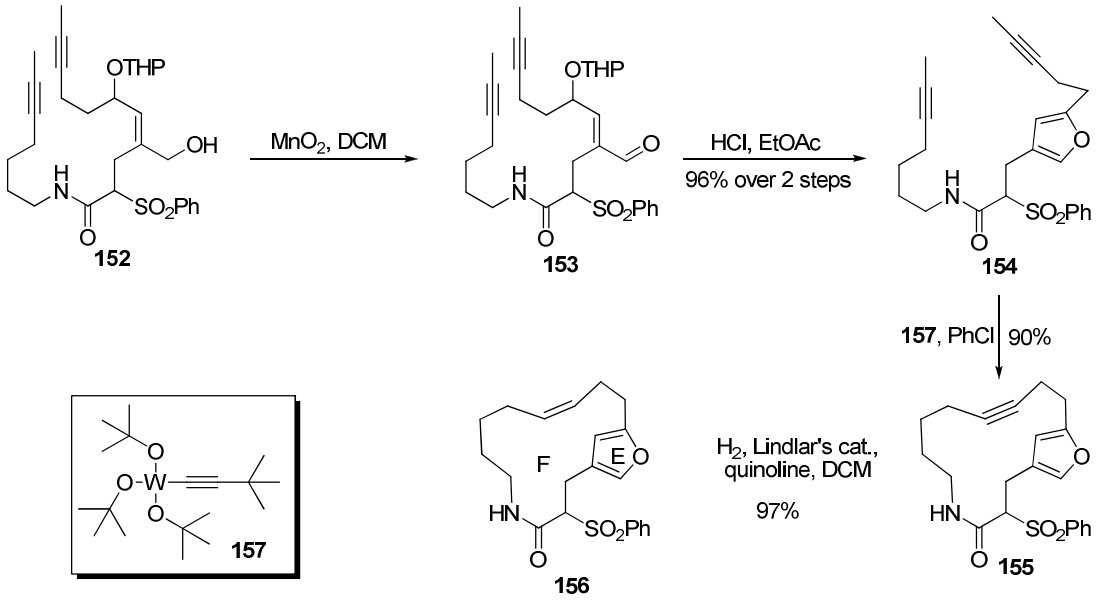
The potent biological activity of nakadomarin A combined with its alluring molecular architecture has made it an attractive target for total syntheses. Several other groups also worked on the total synthesis of this complex natural product and have reported the construction of various ring systems that are present in the target. The following section describes several representative elegant approaches.

1.4.1 Fürstner strategies: RCAM and RCM

The first effort towards the synthesis of (−)-nakadomarin A (**1**) was reported in 1999 by Fürstner and co-workers.[40] In their strategy, (−)-nakadomarin A (**1**) was disconnected into a 15-membered macrolactam EF ring fragment and a bicyclic azocine CD ring fragment.

The synthesis of 15-membered unsaturated lactam **156** started from the readily available diyne intermediate **153** (Scheme 28). Oxidation of allylic alcohol **153** followed by acid-catalysed dehydrative cyclisation gave furan **154**. Treatment of the diyne **154** with catalytic amount of the Schrock tungsten alkylidyne complex **157** [41] led to rapid formation of the desired macroalkyne **155** in excellent yield. Lindlar reduction of the resulting alkyne provided the target lactam EF ring fragment **156**.

[40] Fürstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc.* **1999**, *121*, 11108−11113
[41] Schrock, R. R.; Clark, D. N.; Sancho, J.; Wengrovius, J. H.; Rocklage, S. M.; Pedersen, S. F. *Organometallics* **1982**, *1*, 1645−1651

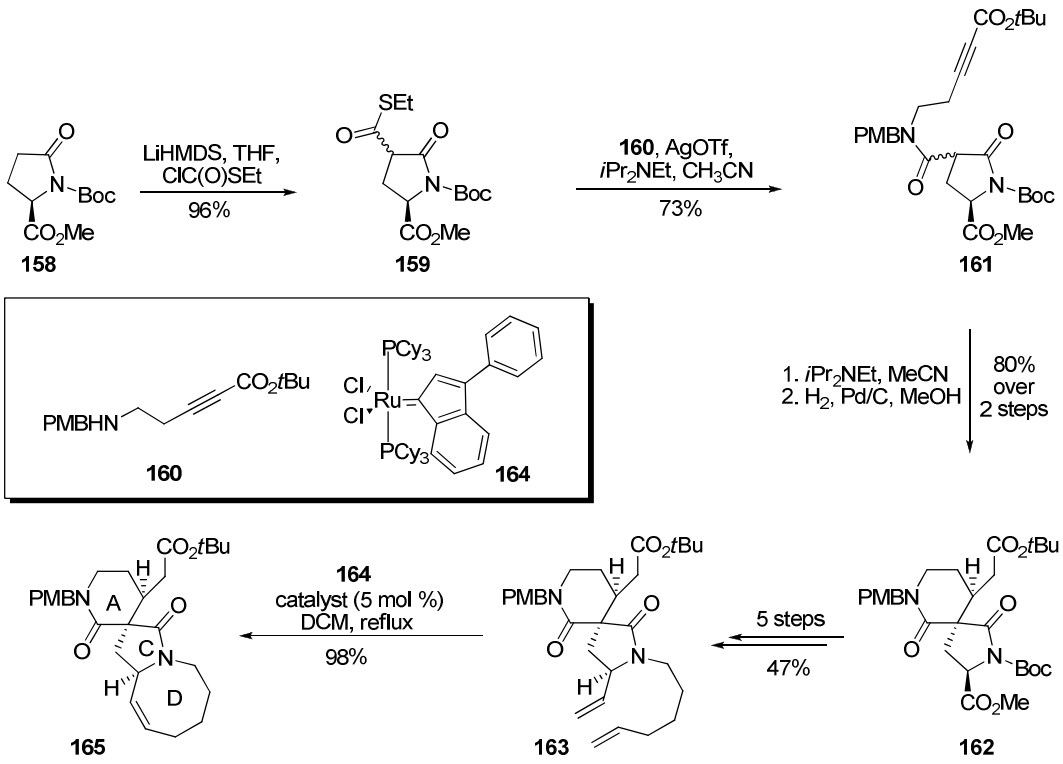


Scheme 28

The Fürstner group created a functionalised macrocycle corresponding to the EF ring system of (−)-nakadomarin A (**1**) in 9 steps with high overall yield. A highly convergent disconnection strategy for the synthesis of (−)-nakadomarin A (**1**) was presented, as well as various examples of diyne RCM for the first time. This approach was an efficient way to construct macrocyclic *Z*-alkenes.

In 2001, Fürstner and co-workers reported the synthesis of ACD ring fragment of (−)-nakadomarin A (**1**, Scheme 29).[42] Their synthesis commenced with the conversion of (*R*)-(+)-pyroglutaminic ester **158** into the thioester **159**, which underwent sequential amide formation, intramolecular Michael addition and stereoselective hydrogenation to afford spirobislactam **162**. The diene **163**, obtained from diester **162** in 5 steps and in high yield, was subjected to RCM by the treatment with a catalytic amount of ruthenium phenylinenylidene complex **164** to deliver the ACD fragment **165** in quantitative yield.

[42] Fürstner, A.; Guth, O.; Duffels, A.; Seidel, G.; Liebl, M.; Mynott, R. *Chem. Eur. J.* **2001**, *7*, 4811−4820



Scheme 29

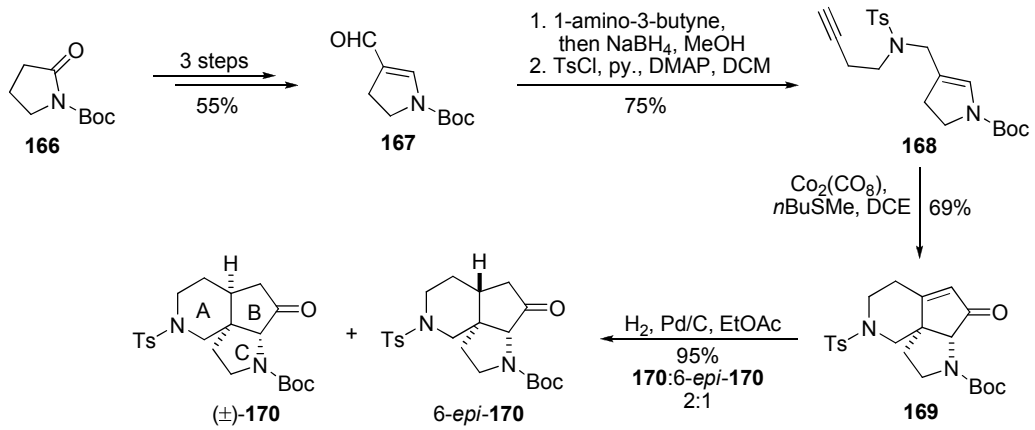
The ACD ring fragment **165** was completed in 10 steps and in high yield by Fürstner and co-workers. Three of the four stereogenic centres in (−)-nakadomarin A (**1**) had been introduced correctly. The utility of ruthenium phenylinenylidene complex **164** as a catalyst for olefin metathesis was well-demonstrated by applying to the highly functionalised substrate **163**.

1.4.2 Magnus Approach: Pauson-Khand Reaction

In 2002, Magnus and co-workers published a synthesis of the ABC ring system of (−)-nakadomarin A (**1**) featuring an intramolecular Pauson–Khand reaction.[43] The synthesis started from the Boc-protected 2-pyrrolidinone **166**, which was converted into the aldehyde **167** in 3 steps and in good yield (Scheme 30). Reductive amination of the aldehyde **167** with 1-amino-3-butyne hydrochloride followed by tosyl protection of the free amine provided the cyclisation precursor. Alkyne **168** was then subjected to the key Pauson-Khand reaction with a stoichiometric amount of dicobalt octacarbonyl to afford the tricyclic compound

[43] Magnus, P.; Fielding, M. R.; Wells, C.; Lynch, V. *Tetrahedron Lett.* **2002**, *43*, 947−950

169 in good yield. Finally, hydrogenation of the alkene delivered the desired ABC ring fragment **170** in 62% yield.



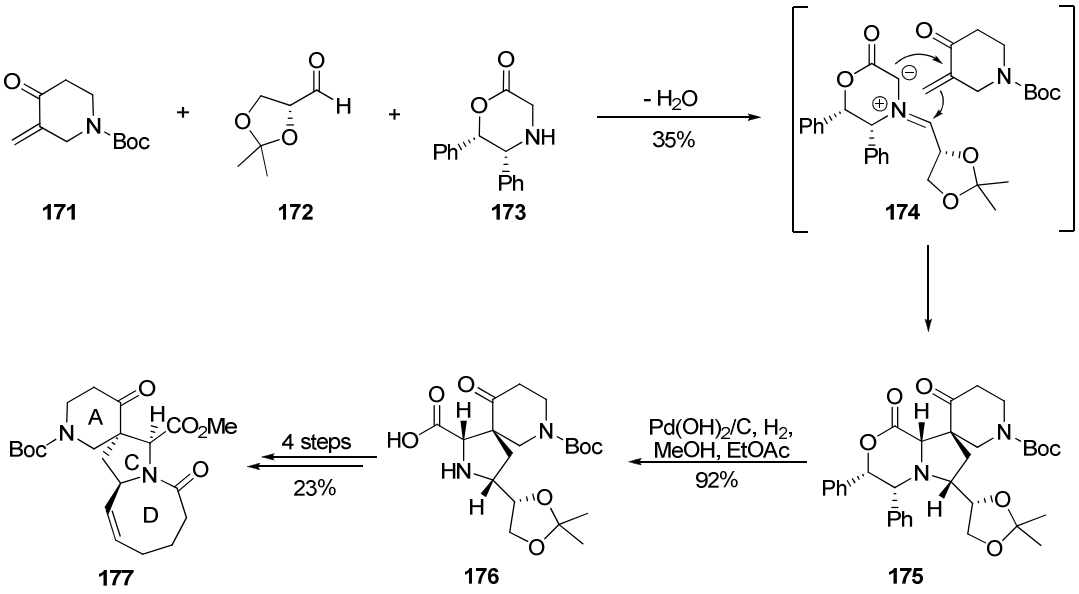
Scheme 30

Magnus had shown that it is possible to construct the five-membered B ring by Pauson-Khand reaction, but poor selectivity was observed for hydrogenation of the enone after screening of various conditions (the best result was 2:1 diastereomeric ratio in favour of the desired isomer **170**).

1.4.3 Williams' Strategy: Azomethine Ylide Cycloaddition

In 2004, an asymmetric synthesis of the ACD ring system of (−)-nakadomarin A (**1**) was reported by Williams and co-workers, employing an elegant azomethine ylide 1,3-dipolar cycloaddition reaction as the key step (Scheme 31).[44] The synthesis commenced with the key three-component condensation of enone **171**, aldehyde **172** and morpholinone **173** in a stereoselective manner. This transformation proceeded through the sequence of azomethine ylide formation between aldehyde **172** and morpholinone **173** and subsequent 1,3-dipolar cyclisation to provide the spirolactam **175** as a single diastereoisomer in 35% yield. Cleavage of the chiral template in bis-lactam **175** to provide amino acid **176** was accomplished by hydrogenolysis mediated by Pearlman's catalyst. Further functionalisation of the spiroamide **176** by alkylation and RCM led to the completion of the ACD fragment **177**.

[44] Ahrendt, K. A.; Williams, R. M. *Org. Lett.* **2004**, *6*, 4539−4541



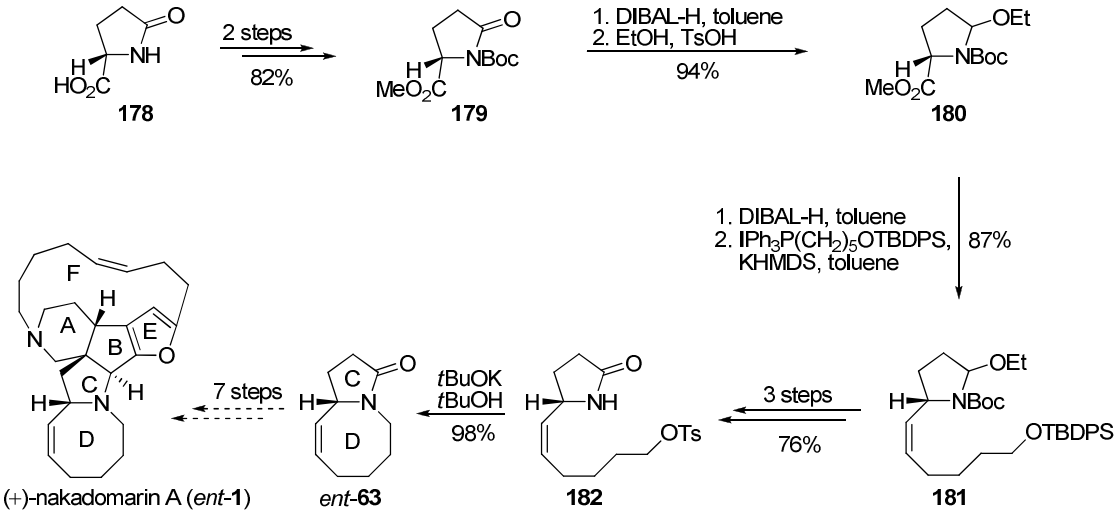
Scheme 31

Williams completed the asymmetric synthesis of the ACD ring fragment of (−)-nakadomarin A (**1**) in nine linear steps from commercially available materials using a stereoseletive three-component cyclisation reaction as the key transformation, although the yield was only modest.

1.4.4 Stockman strategy: Synthesis of the CD Ring

In 2012, Stockman published a synthesis of the CD ring fragment of (+)-nakadomarin A (*ent*-**1**).[45] The synthetic sequence started with esterification and Boc-protection of the L-pyroglutamic acid **178** to deliver the ester **179** in high yield (Scheme 32). Subsequent reduction of the lactam functionality led to an aminol which was protected to give the pyrrolidine **180**. The ethyl protection proved to be necessary in order to achieve a high yield from the subsequent Wittig olefination reaction (98% in comparison with 8% for the free aminol and 21% for the methyl ether). The alkene **181** was further subjected to sequential oxidation, deprotection and tosylation to provide the lactam **182**, which then underwent intramolecular nucleophilic substitution under basic conditions to produce the azocine ring.

[45] Stockman, R. A.; McDermott, P. J.; Newton, A. F.; Magnus, P. *Synlett* **2010**, 559−562



Scheme 32

Stockman completed the synthesis of CD ring fragment *ent*-**63** in 10 steps, which could be further converted (+)-nakadomarin A (*ent*-**1**) in 7 steps following Dixon's strategy.[20] This work demonstrated a simple and highly efficient methodology for the synthesis of chiral 5-substituted pyrrolidin-2-ones.

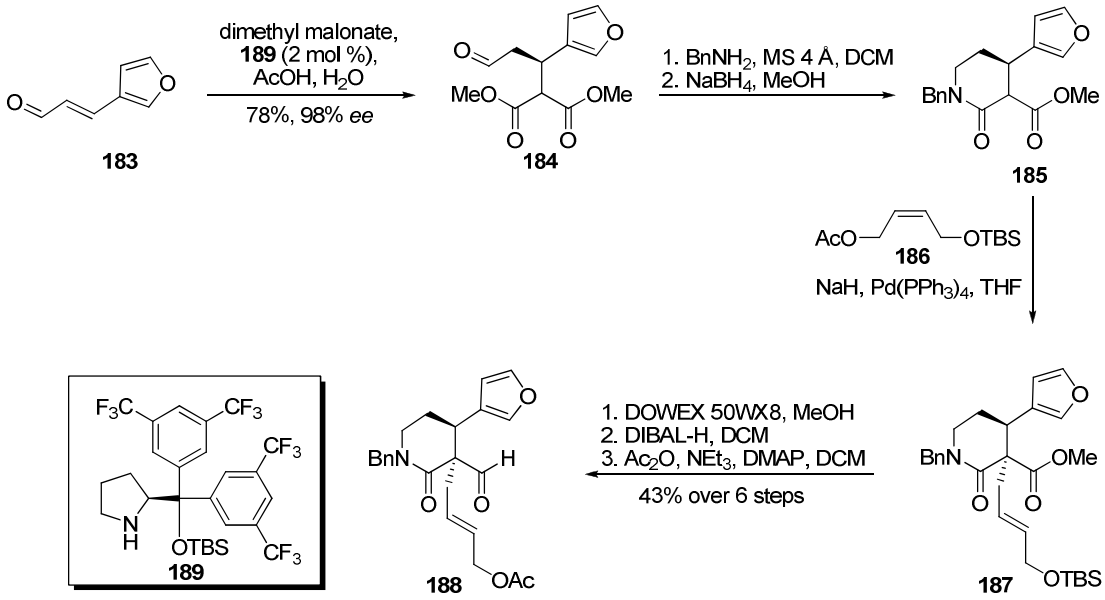
1.4.5 Takemoto's ABCDE Fragment Synthesis: Allylic Amination

In 2012, Takemoto and co-workers reported an asymmetric synthesis of ABCDE pentacyclic core of (−)-nakadomarin A (**1**).[46] The strategy featured a palladium catalysed allylic amination reaction and intramolecular Friedel-Crafts cyclisation *via* an oxazolidine intermediate.

Takemoto's synthesis commenced with α,ß-unsaturated aldehyde **183**, which underwent enantioselective Michael addition with dimethyl malonate (Scheme 33). After a screen of various organocatalysts, it was found that the Hayashi-Jørgensen catalyst **189**[47,48] showed the highest activity. Adduct **184** was formed in good yield (78%) and with high enantiomeric excess (97% *ee*) when a low loading (2 mol %) of the proline-derived catalyst **189** was employed. Reductive

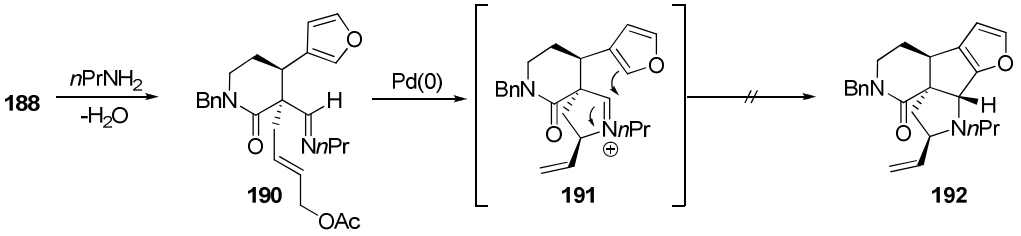
[20] Jakubec, P.; Cockfield, D. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 16632−16633
[46] Tsuji, N.; Stadler, M.; Kazumi, N.; Inokuma, T.; Kobayashi, Y.; Takemoto, Y. *Org. Biomol. Chem.* **2014**, *12*, 7919−7922
[47] Brandau, S.; Landa, A.; Franzøn, J.; Marigo, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2006**, *45*, 4305−4309
[48] Gotoh, H.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2007**, *9*, 5307−5309

amination and amide formation afforded the lactam **185**, which was subjected to standard Tsuji-Trost allylation[49,50] with the allylic acetate **186** to provide allylic TBS-ether **187** with correct configuration at the quaternary centre. Removal of the TBS protecting group, reduction of the ester to the aldehyde and reprotection of the primary alcohol as acetate gave key intermediate **188**.



Scheme 33

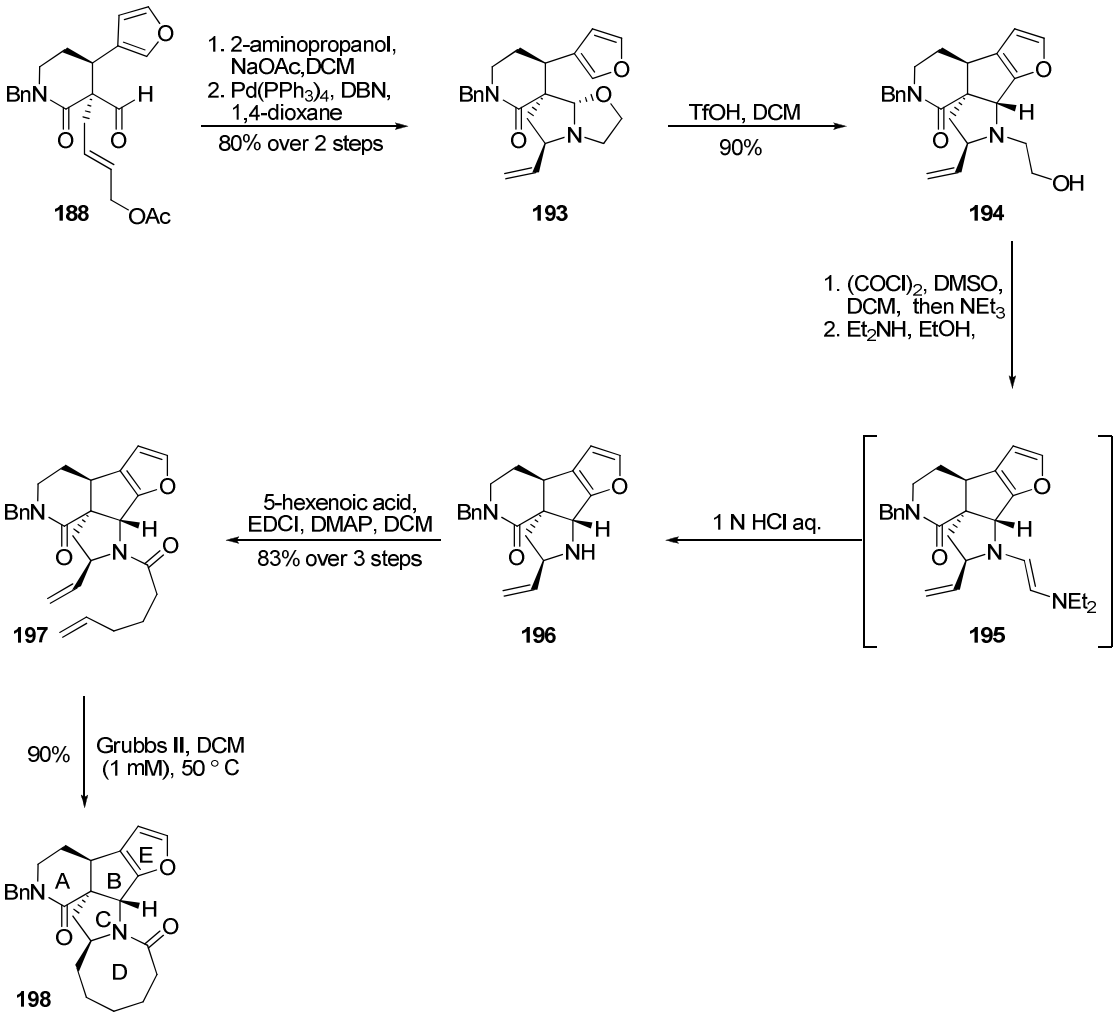
The first attempt to construct the ABCE tetracyclic core **192** from the aldehyde **188** started with imine formation, followed by the Pd-catalysed allylic amination to generate an iminium intermediate **190**, which was expected to undergo a one-pot Pictet-Spengler type reaction with the furan moiety (Scheme 34). Unfortunately, all the attempts to perform this transformation failed due to the instability of the iminium intermediate **191** under the reaction conditions.



Scheme 34

[49] Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, *6*, 4387−4388
[50] Trost, B. M.; Fullerton, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 292−294

The strategy was then revised by the introduction of a removable nucleophilic moiety to trap the unstable iminium cation. The oxazolidine **193** was prepared from the aldehyde **188** in good yield by applying this method (Scheme 35) and this compound was used as an iminium equivalent under acidic conditions allowing installation of the cyclopentane unit in a stereoselective manner and in high yield. Attempts to perform direct functionalisation of the hydroxyethyl group in the tetracyclic compound **194** to give the desired side chain were first investigated without success. Removal of the hydroxyethyl group by sequential Swern oxidation, enamine formation and hydrolysis afforded free amine **196**, which underwent *N*-acylation and RCM to provide the pentacyclic fragment **198**.



Scheme 35

In conclusion, Takemoto and co-workers described a facile and efficient asymmetric synthesis of the pentacyclic core of (−)-nakadomarin A (**1**) in 14 steps with the all four stereogenic centres installed with correct configurations.

Summary

To date, eight total syntheses of (−)-nakadomarin A (**1**) and/or its enantiomer (+)-nakadomarin A (*ent*-**1**) have been published as well as several fragment syntheses. The viability of constructing the azocine E-ring and 15-membered F-ring by alkene or alkyne RCM have been well-illustrated using various substrates. Installation of the 5-membered B-ring was achieved in various ways including the use of the Pauson-Khand reaction, Pictet-Spengler reaction and metal-catalysed cyclisations. Rings A, C and D were introduced mostly using building blocks derived from natural sources.

1.5 Furan Formation

1.5.1 Furan Moiety in Natural Products

Substituted furans appear in a variety of natural products, such as polyketides, phenylpropanoids, alkaloids, and terpenes.[51] Natural compounds containing a furan and or derivatives have been found in many classes of terrestrial and marine organisms. The target molecule (−)-nakadomarin A (**1**) is among those bioactive natural products (Figure 3). Other examples include the neurologically toxic marine furanocembranes, providencin (**199**) and pukalide (**200**),[52,53] the bacterial macrolide furanoephithilone B (**201**),[54] and furoscrobiculin B (**202**), which provide chemical defense against other organisms such as bacteria, fungi, animals and insects.[55]

Furan sub-units are also present in numerous biologically-active pharmaceuticals. Ranitidine (**203**, Zantac®, GSK) is an H2-receptor antagonist for the treatment of stomach ulcers and was one of the biggest-selling drugs in 1988 (Figure 3).[56] Vilazodone (**204**), consisting of an indole and a benzofuran, shows pharmacological activity against major depressive disorders and was approved by the FDA in 2011.[57]

[51] Boto, A.; Alvarez, L. *Heterocycles in Natural Product Synthesis*, Wiley-VCH Verlag & Co. KGaA, **2011** and references herein
[52] Donohoe, T. J.; Ironmonger, A.; Kershaw, N. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 7314−7316
[53] Kobayashi, J.; Watanabe, D.; Kawasaki, N.; Tsuda, M. *J. Org. Chem.* **1997**, *62*, 9236−9329
[54] Groebe, D. R.; Abramson, S. N. *J. Biol. Chem.* **1995**, *270*, 281−286
[55] Maki, S.; Toshihiro, S.; Hiroshi, S.; Kanematsu, K. *J. Chem. Soc., Perkin Trans. 1* **1997**, *11*, 1707−1714
[56] Wright, R. *J. Health Care Mark.* **1996**, *16*, 24−29
[57] Banerjee, R.; Banerjee, K. H. M. *Int. J. Rev. Life Sci.* **2012**, *2*, 7−16

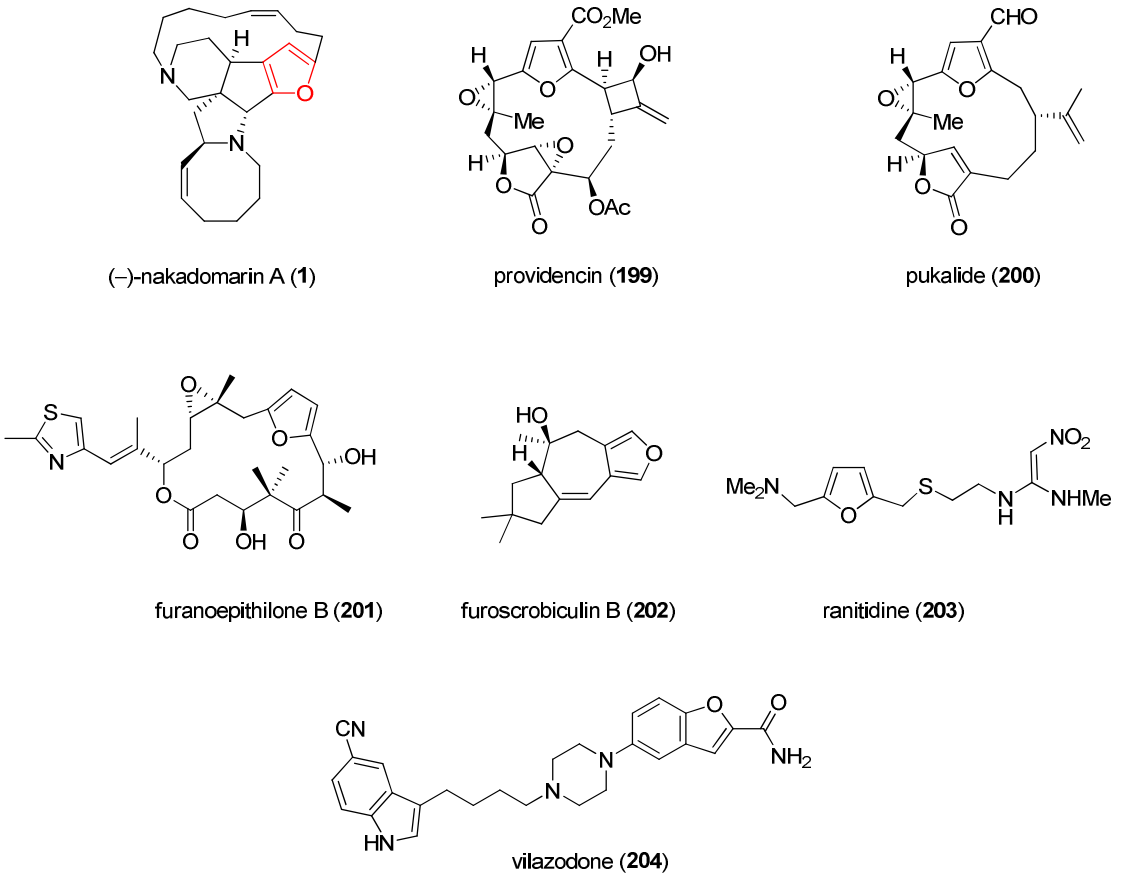


Figure 3 Representative Furan Containing Natural Product

1.5.2 Furan Synthesis

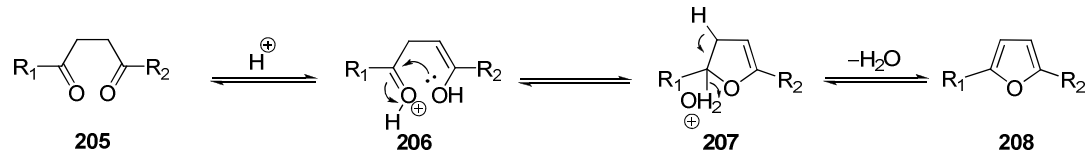
Due to the importance of furan motif, strategies for the synthesis of substituted furans attract extensive interest from synthetic chemists. In addition to classic approaches, methodologies for the furan construction by transition metal catalysis and organocatalysts have given ecellent results.[58]

1.5.2.1 Traditional Furan Synthesis

In 1884, Carl Paal and Ludwig Knorr, reported independently a synthetically valuable method for the preparation of furans from 1,4-diketones (Scheme 36).[59,60] In this most widely used approach, furans are formed by the acid catalysed dehydrative cyclisation of 1,4-diketones **205**. The mechanism shows that the first step of the Paal-Knorr reaction is protonation of the oxygen in one

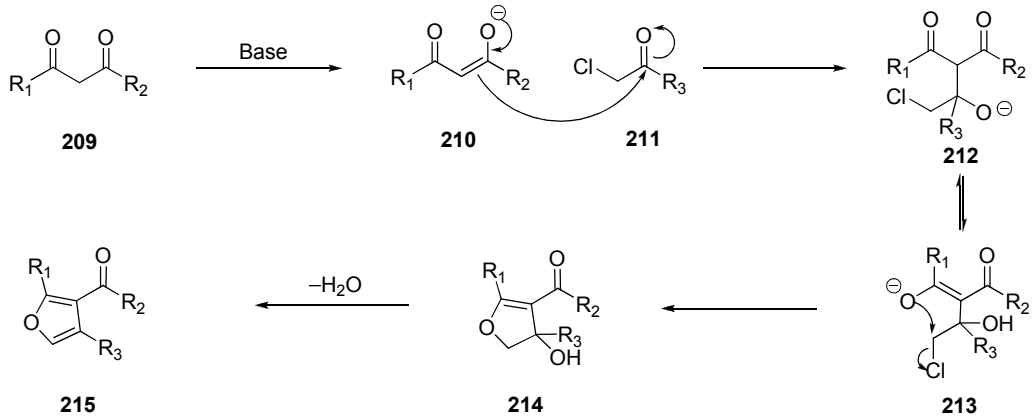
[58] Newkome, G. R.; Sauer, J. D.; Roper, J. M.; Hager, D. C. *Chem. Rev.* **1977**, *77*, 513−597
[59] Paal, C. *Chem. Ber.* **1884**, *17*, 2756−2767
[60] Knorr, L. *Chem. Ber.* **1884**, *17*, 2863−2870

of the carbonyl groups. This positively charged intermediate **206** can react through several pathways. In the generally accepted mechanism, protonation is followed by intramolecular nucleophilic attack of the protonated carbonyl group by the enol tautomer to deliver the dihydrofuran **207**. Subsequent dehydration of intermediate **207** provides the furan product **208**.[61]



Scheme 36

In 1902, Feist described methodology for the formation of highlysubstituted furans **215**.[62,63] Condensation of 1,3-dicarbonyl **209** with an α-chloroketone **211** takes place under basic condition to furnish the aldol adduct **212** (Scheme 37). Intramolecular nucleophilic substitution of chloride by the corresponding enolate **213** occurs, giving dihydrofuran **214** which undergoes dehydration to afford furan **215**.[64]



Scheme 37

Studies towards the synthesis of substituted furans have been an important research area since the 1990s. Most recently, research has focused on the transition metal and organocatalyst mediated formation of highly functionalised furans.

---

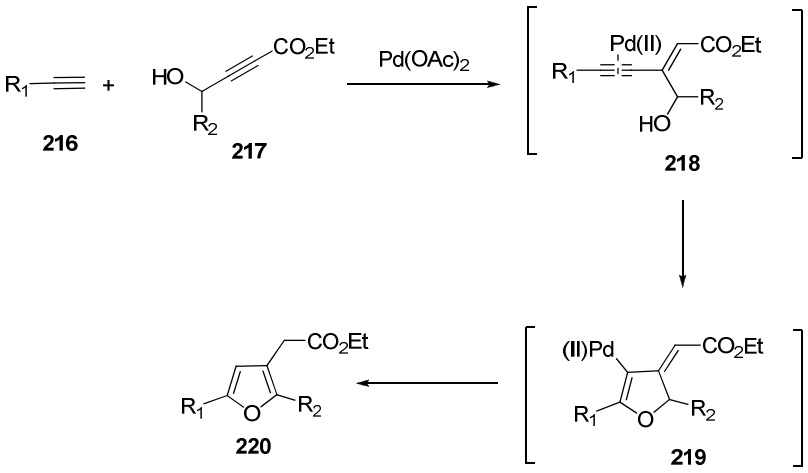
[61] Amarnath, V.; Amarnath, K. *J. Org. Chem.* **1995**, *60*, 301−307
[62] Feist, F. *Chem. Ber.* **1902**, *35,* 1537−1544
[63] Benary, E. *Chem. Ber.* **1911**, *44*, 489−493
[64] Calter, M. A.; Philips, R. M.; Flaschenriem, C. *J. Am. Chem. Soc.* **2005**, *127*, 14566−14567

1.5.2.2 Metal Catalysed Furan Formation

Developments in the area of transition metal-catalysed processes continue to lead to highly efficient and selective synthetic procedures.[65] Thus, metal catalysis is an important approach to the synthesis of valuable organic compounds. In recent years, metal catalysis has been well-developed for the synthesis of substituted furans from simple precursors under mild conditions. The use of complexes of many metals (e.g. palladium, copper, gold, silver and zinc) has been reported and some representative examples are described below.[66]

Palladium-Catalysed Synthesis of Furans

In 1995, Trost and co-workers reported a protocol for the Pd-catalysed construction of furans.[67] The synthesis commenced with conjugate addition of terminal alkynes **216** to *γ*-hydroxyalkynoates **217** to give enynols **218**, which underwent complexation with palladium and subsequent intramolecular nucleophilic attack by the hydroxyl group to provide the hydroxyfuran intermediate **219**. Decomplexation of palladium and isomerisation led to the desired furan product **220** (Scheme 38).



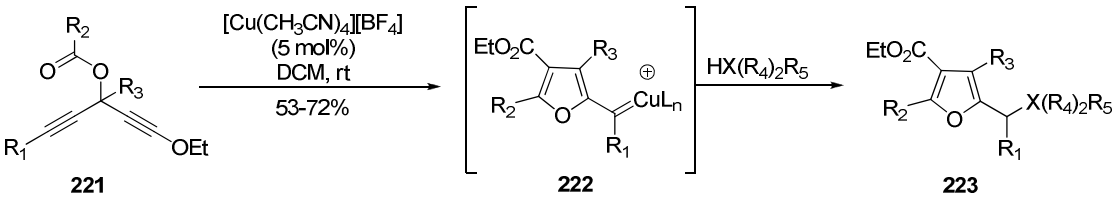
216 217 218 219 220

Scheme 38

[65] Moran, W. J.; Rodríguez, A. *Org. Prep. Proced. Int.* **2012**, *42*, 103−130
[66] Corma, A.; Leyva-Pérez, A.; Sabater, M.J. *Chem. Rev.* **2011**, *111*, 1657−1712
[67] Trost, B. M.; McIntosh, M. C. *J. Am. Chem. Soc.* **1995**, *117*, 7255−7256

Copper-Catalysed Synthesis of Furans

In 2008, the López group developed a copper(I)-catalysed regioselective synthesis of tri- and tetrasubstituted furans (Scheme 39).[68] The synthesis started from bispropargylic esters **221**, which underwent copper-catalysed cyclisation to form the 2-furyl copper(I)-carbene intermediates **222**. Further functionalisation of the copper carbenoids **222** led to formation of highly substituted furans. By investigating the scope of the reaction, it was found that the alkyne could be substituted with various groups (e.g. aryl, alkyl, trimethylsilyl and alkenyl) and that variation at R_2 did not affect the cyclisation process.



Scheme 39

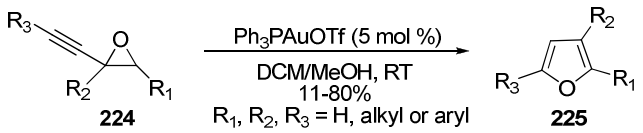
Gold-Catalysed Synthesis of Furans

Among the transition metals that are commonly employed in the construction of furans (Cu, Ag, Pd and Au), gold has proven to be particularly suitable given the strong π Lewis acidic property of cationic gold species and their ability to activate alkynes and allenes towards the addition of oxygen nucleophiles.[69] Four examples of gold-catalysed furan formation represented in the work of Pale,[70] Arcadi,[71] Hashmi[72] and Liu[73] are described in the following session.

In 2009, the Pale group reported a gold-catalysed isomerisation of alkynyl oxiranes **224**, using triphenylphosphine gold(I) triflate as catalyst (Scheme 40).[70] Trisubstituted furans **225** are generated in good yields and the presence of an alcohols as an external nucleophile is required for the reaction to proceed.

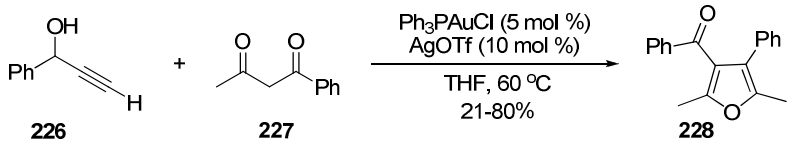
---

[68] Barluenga, J.; Riesgo, L.; Vicente, R.; López, L. A.; Tomás, L. *J. Am. Chem. Soc.* **2008**, *130*, 13528−13529.
[69] Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180−3211
[70] Blanc, A.; Tenbrink, K.; Weibel, J. M.; Pale, P. *J. Org. Chem.* **2009**, *74*, 5342−5348
[71] Arcadi, A.; Alfonsi, M.; Chiarini, M.; Marinelli, F. *J. Organomet. Chem.* **2009**, *694*, 576−582
[72] Hashmi, A. S. K.; Haffner, T.; Rudolph, M.; Rominger, F. *Eur. J. Org. Chem.* **2011**, *4*, 667−671
[73] Du, X.; Song, F.; Lu, Y.; Chen, H.; Liu, Y. *Tetrahedron* **2009**, *65*, 1839−1845



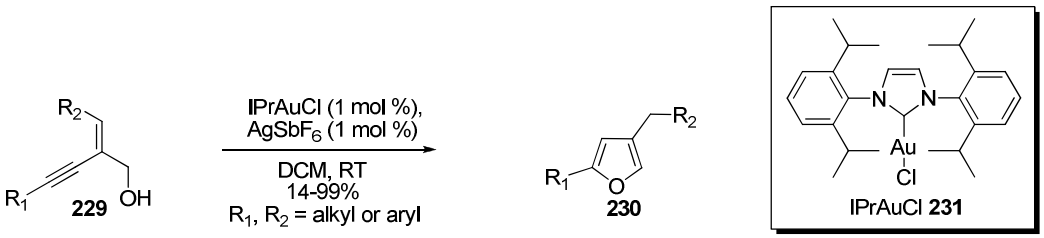
Scheme 40

In the same year, Arcadi illustrated another gold-catalysed reaction for furan formation (Scheme 41).[71] It was found that coupling between a propargylic alcohol **226** and a 1,3-dicarbonyl compound **227** took place in a tandem process to deliver tetrasubstituted furan **228** in good yield.



Scheme 41

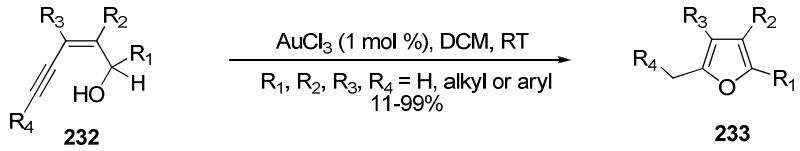
Hashmi and co-workers reported a new route for furan synthesis by gold-catalysed cyclisation of 2-alkynylallyl alcohols **229** under mild conditions (Scheme 42).[72] The cyclisation occurred at room temperature to form disubstituted furans **230** employing the gold-*N*-heterocyclic carbene (NHC) catalyst **231**.



Scheme 42

An interesting study concerning the construction of furan rings was reported by Liu and co-workers in 2009.[73] A wide range of substituted furans **233** were prepared by gold-catalysed cycloisomerisation of 2-en-4-yn-1-ols **232** (Scheme 43).

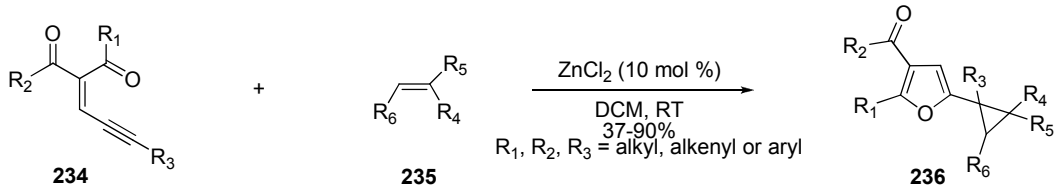
[72] Hashmi, A. S. K.; Haffner, T.; Rudolph, M.; Rominger, F. *Eur. J. Org. Chem.* **2011**, *4*, 667−671
[73] Du, X.; Song, F.; Lu, Y.; Chen, H.; Liu, Y. *Tetrahedron* **2009**, *65*, 1839−1845



Scheme 43

Zinc-Catalysed Synthesis of Furans

In 2012, the López group reported new methodology for the formation of cyclopropyl-substituted furans.[74] The reaction between enynones **234** and alkenes **235** in the presence of catalytic amount of zinc(II) chloride delivered the desired cyclopropyl furans **236** in good yield (Scheme 44). It was assumed the reaction proceeded through a Fischer-type 2-furyl zinc(II) carbene complex.



Scheme 44

It was also found that the reaction could be applied to a wide variety of alkene partners **235**, ranging from monosubstituted to disubstituted alkenes. Additionally, the R_1, R_2 and R_3 group in enynones **234** could bear aryl, alkyl and alkenyl groups.

1.5.2.3 Organocatalytic Furan Synthesis

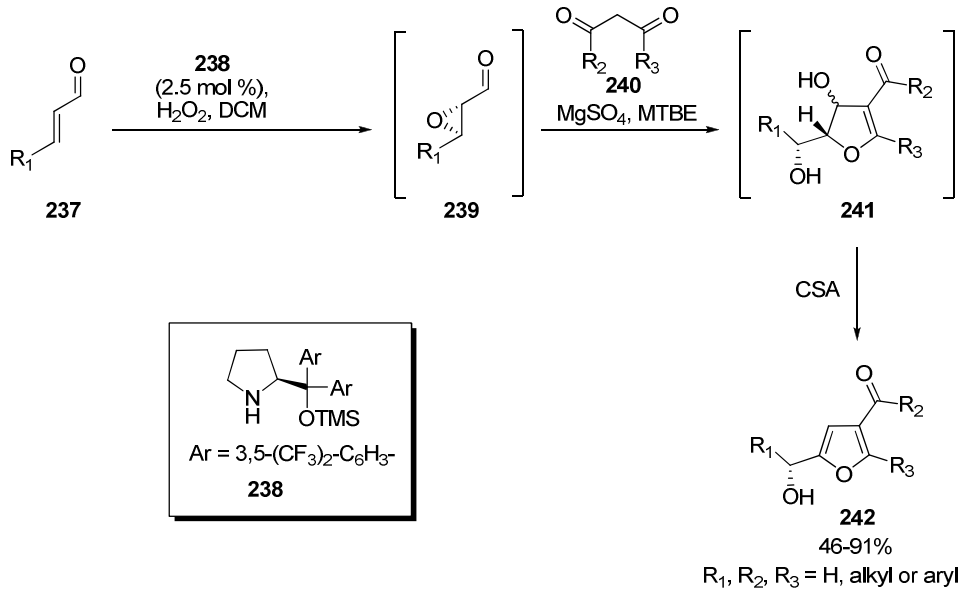
The term "organocatalysis" which was first used by MacMillan in 2000,[75] describes the acceleration of chemical reactions by employing a sub-stoichiometric amount of an organic compound. The interest in this field has increased enormously in the last decade as a result of its high efficiency and selectivity as well as the relatively low cost and toxicity of some catalysts.

[74] Vicente, R.; González, J.; Riesgo, L.; González, J.; López, L. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 8063−8067.
[75] Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244

Organocatalytic reactions are becoming powerful tools for the construction of complex molecules.[76]

Despite the fact that organocatalysis has become a thriving area and many of the reactions are widely applicable, it has rarely been used to construct furans in comparison to the metal-mediated methods. However, Jørgensen and co-workers have reported an enantioselective synthesis of 2-hydroxyalkyl- and 2-aminoalkyl furans based on a modified Feist-Benary synthesis.[77]

The synthetic sequence started from the epoxidation of enal **237** in the presence of catalytic amount of the Jørgensen catalyst **238**[78] to deliver the 2,3-epoxy aldehyde **239**, which underwent the Feist-Benary reaction with 1,3-dicarbonyl compounds **240** to provide dihydrofuran intermediate **241** (Scheme 45). Further dehydration by treating diol **241** with CSA led to the desired furan product **242** in moderate to good yield.

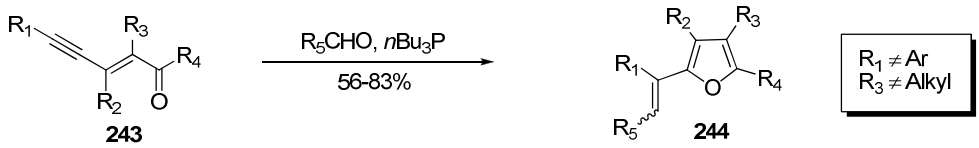


Scheme 45

[76] Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 3726–3748
[77] Albrecht, Ł.; Ransborg, L. K.; Gschwend, B.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 17886–17893
[78] Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 794–797

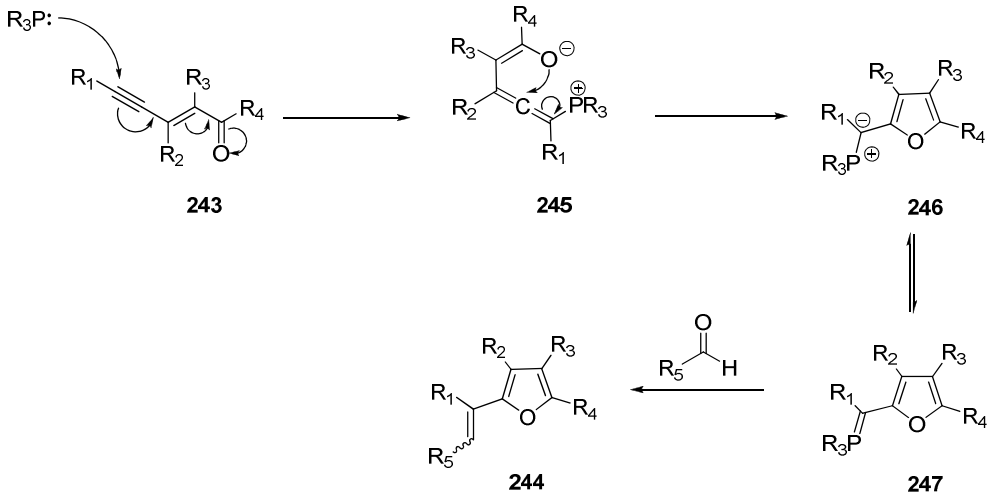
Phosphine-Mediated Furan Formation

In 1991, Kuroda and co-workers reported a protocol for the preparation of substituted furans **244** by phosphine-initiated cyclisation reactions of enynes **243** (Scheme 46).[79]



Scheme 46

It has been suggested that the mechanism proceeds through phosphine-initiated 1,6-addition to the enynone **243** (Scheme 47), followed by the cyclisation of allene intermediate **245** to afford the phosphonium ylide **247**. Subsequent Wittig reaction between the ylide **247** and an aldehyde delivers the furan **244**.



Scheme 47

In 2004, Kuroda applied this method to the synthesis of highly substituted furans.[80] In this paper, more details of the mechanism were given following a screen of reaction conditions and substrates.

The initial experiments were performed in the presence of a stoichiometric amount of tributylphosphine, which led to the formation of the furans **244** in

[79] Kuroda, H.; Hanaki, E.; Kawakami, M. *Tetrahedron Lett.* **1999**, *40*, 3753−3756
[80] Kuroda, H.; Hanaki, E.; Izawa, H.; Kano, M.; Itahashi, H. *Tetrahedron* **2004**, *60*, 1913−1920

good yield. Similar results were obtained with a slight drop in yield when triphenylphosphine was used (73% conversion of the desired furan product compared to 83% for tributylphosphine catalysed case). However, the use of triethylamine as a catalyst did not lead to formation of any furan product. It was suggested that the failure was possibly due to aza-ylide formation not taking place. Based on the proposed mechanism, it was noted that a stoichiometric amount of phosphine nucleophile is required. This was further confirmed when the amount of phosphine was reduced to half of the stoichiometric equivalent resulted in an approximate reduction in yield by half.

The versatility of the reaction was investigated by changing different substituents on enynone **243** and aldehyde partner. It was found that the yields are remarkably dependent on the nature of the R_1 substituent on the alkyne. Low yields were obtained with precursors possessing an aromatic substituent at this position. Additionally, the desired furan product was not observed in the cases where R_3 was an alkyl group.

Organosulfur-Catalysed Furan Formation

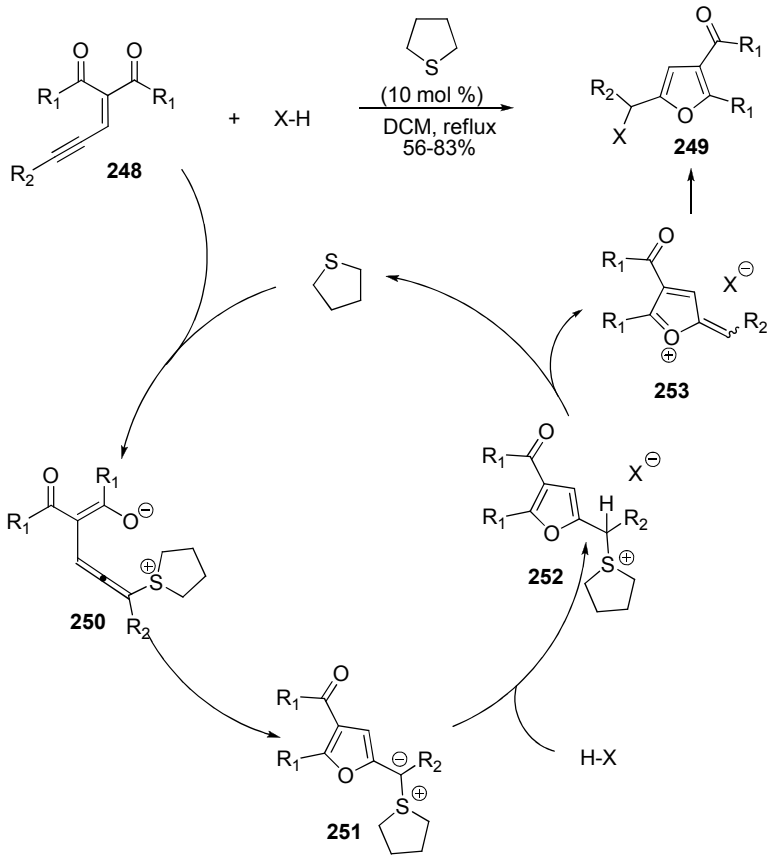
Inspired by Kuroda's work, the Clark group reported an organosulfur catalysed synthesis of furfuryl alcohols and amines in 2012.[81] It was proposed that the cyclisation could be carried out with a thioether catalyst, and the resulting sulfur ylide intermediate could be used to introduce new substituents to the α-position of the furan, leading to the synthesis of highly substituted furans.

In the work, a range of enynone substrates **248** was prepared with different R_1 and R_2 substituents (Scheme 48). Treatment of enynone **248** with catalytic amount (10 mol %) of tetrahydrothiophene (THT) provided an intermediate in which a sulfonium ylide lies α to the furan. Further reaction with a nucleophile (X-H) affords the furan product **249**.

The suggested mechanism commences with the 1,6-addition of the tetrahydrothiophene onto the reactive enynone **248** in a process similar to the

[81] Clark, J. S.; Boyer, A.; Aimon, A.; Garcia, P. E.; Lindsay, D. M.; Symington, A. D. F.; Danoy, Y. *Angew. Chem. Int. Ed.* **2012**, *51*, 12128−12131

phosphine-initiated reaction by Kuroda. The sulfur ylide **251** is formed by the intramolecular nucleophilic attack of the resulting enolate **250** onto the allene. The ylide **251** then undergoes protonation in the presence of an appropriate protonated nucleophile (X-H), giving a sulfonium salt **252**. Elimination of tetrahydrothiophene affords the oxocarbenium ion **253** and nucleophilic attack of X^- to **253** generates the desired furan product **249**.



Scheme 48

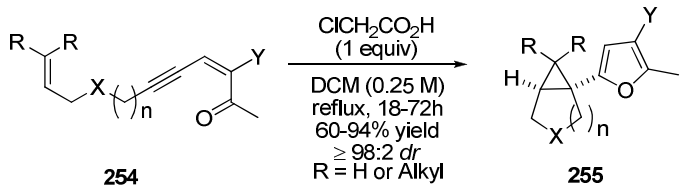
The initial experiment was carried out using tetrahydrothiophene as the catalyst and benzoic acid as the nucleophile, resulting in good yields while the use of other nitrogen (DMAP, DABCO) or phosphine (tributylphosphine) based catalysts only led to the decomposition of the starting enynones **248**. After careful screening of the reaction conditions, the highest yields of desired furans **249** were obtained using 10 mol % of THT in dichloromethane under reflux. The versatility of the reaction was explored by employing a diverse set of nucleophiles, including electron-rich and electron-poor aryl carboxylic acids, various alcohols and sulfonamides. Good to excellent yields were observed in

most case. This work demonstrated an elegant organocatalytic synthesis of highly functionalised furans under mild conditions in good yields.

Brønsted Acid Catalysed Furan Formation

Following the success of organosulfur-catalysed furan formation, it was of interest for Clark and co-workers to extend the methodology and investigate several aspects of the reaction.

In 2015, the Clark group published new methodology involving the synthesis of cyclopropyl-substitued furans by a Brønsted acid promoted cascade reaction.[82] A wide range of enynone susbtrates **254** with an alkene chain (3 or 4 carbons away from the alkyne moiety) were prepared with various R_1 substituents (Scheme 49). Treatment of enynone **254** with stoichiometric amount of chloroacetic acid provided the product **255** featuring a 2,3,5-trisubstituted furan bearing a fused cyclopropyl group at 5-position in good yield.



Scheme 49

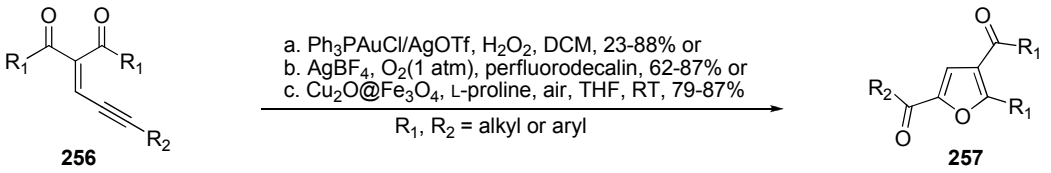
1.5.2.4 2-Acyl Furan Synthesis

Although various methodologies have been developed for the synthesis of substituted furans, few examples of the formation of 2-acyl furans have been reported.

In 2010, Zhang and co-workers reported an efficient approach to the construction of 2,4,5-trisubstituted 2-acyl furans (Scheme 50).[83] Treating

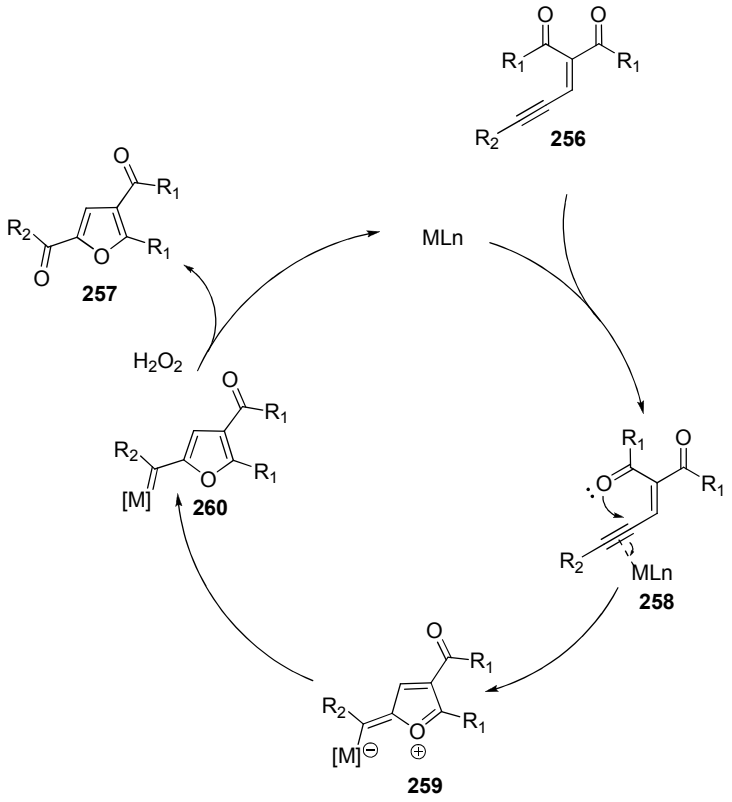
[82] Clark, J. S.; Romiti, F.; Hogg, K. F.; Hamid, M. H. S. A.; Richter, S.; Boyer, A.; Redman, J.; Farrugia, L. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 5744−5747
[83] Wang, T.; Zhang, J. *Dalton Trans.* **2010**, *39*, 4270−4273

enynones **256** with catalytic amount of gold catalyst in DCM at room temperature in the presence of hydrogen peroxide provided good yields of the 2-acyl furans **257**. Following Zhang's work, Liu[84] and Cui[85] also described similar transformations mediated by silver and copper catalysts respectively.



Scheme 50

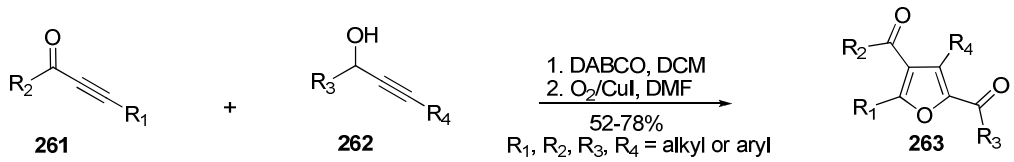
In the proposed mechanism, coordination of the metal catalyst to enynone **256** enhances the electrophicility of the alkyne moiety (Scheme 51). Subsequent intramolecular nucleophilic attack of the carbonyl oxygen onto the Lewis acid-activated alkyne provides the oxonium intermediate **259**, which further rearranges to generate the metal-carbenoid **260**. Subsequent oxidation with hydrogen peroxide affords the 2-acyl furan **257** and regenerates the catalyst ready for re-entry into the cycle.



Scheme 51

[84] Chen, Z.; Luo, M.; Ye, D.; Zhou, Z.; Ye, M.; Liu, L. *Synth. Commun.* **2014**, *44*, 1825−1831
[85] Liu, Y.; Liu, Z.; Cui, Y. *Chin. J. Chem.* **2015**, *33*, 175−180

In 2011, the Jiang group described a one-pot transition-metal catalysed domino reaction to form highly functionalised furans (Scheme 52).[86] The reaction proceeded through base-catalysed conjugate addition of alkynols **262** to ynones **261**, followed by copper-catalysed cyclisation in the presence of oxygen to generate target 2-acyl furans **263** in good yield.



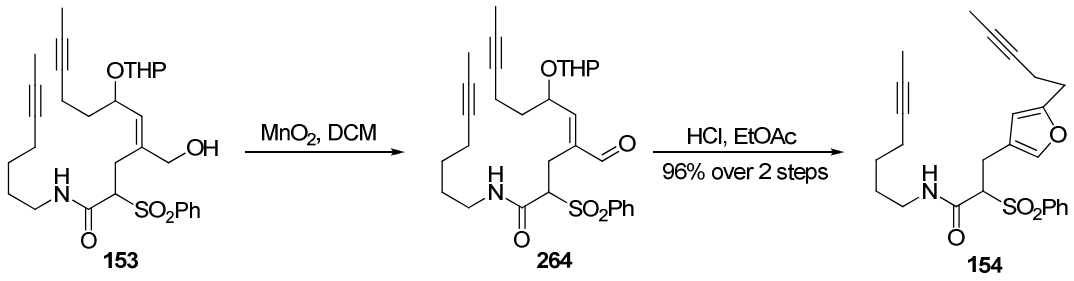
261 262 263

Scheme 52

1.5.2.5 Furan Synthesis in Nakadomarin A

Nakadomarin A is a unique member of the manzamine alkaloid family because it possesses a furan motif. In most of the syntheses of nakadomarin A and advanced intermediates, the furan has been introduced as a simple building block, but there are three examples in which a late-stage furan formation strategy has been employed on highly functionalised intermediates.

The first example was reported by Fürstner and co-workers during the construction of the EF fragment of nakadomarin A.[40] Alcohol **153** was oxidised to give the aldehyde **264** by manganese dioxide, which underwent acid-catalysed dehydrative cyclisation to deliver the furan product **154** in excellent yield (Scheme 53).

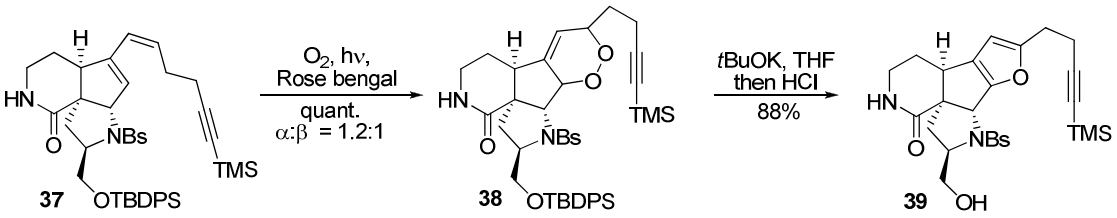


153 264 154

Scheme 53

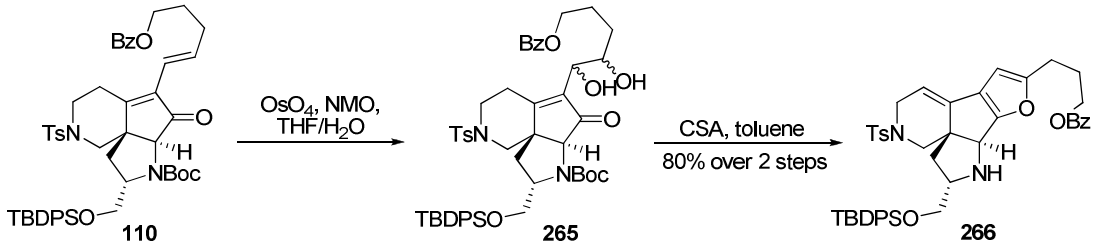
[86] Cao, H.; Jiang, H.; Huang, H. *Synthesis* **2011**, *7*, 1019−1036
[40] Fürstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc.* **1999**, *121*, 11108−11113

In Nishida's total synthesis of nakadomarin A, the diene **37** was converted into the desired fused furan intermediate **39** in good yield through a two-step sequence of peroxide **38** formation and dehydrative rearrangement (Scheme 54).[18]



Scheme 54

In 2010, Mukai and co-workers described a formal synthesis of nakadomarin A, in which a dihydroxylation reaction of the alkene **110** was employed to provide diol **265** as a mixture of diastereoisomers. The crude diol was directly subjected to the dehydrative cyclisation to afford furan **266** upon the treatment with CSA (Scheme 55).[23]



Scheme 55

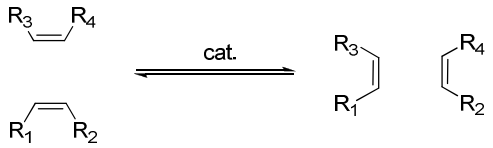
[18] Ono, K.; Nakagawa, M.; Nishida, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 2020−2023
[23] Inagaki, F.; Kinebuchi, M.; Miyakoshi, N.; Mukai, C. *Org. Lett.* **2010**, *12*, 1800−1803

1.6 Metathesis

1.6.1 Olefin Metathesis

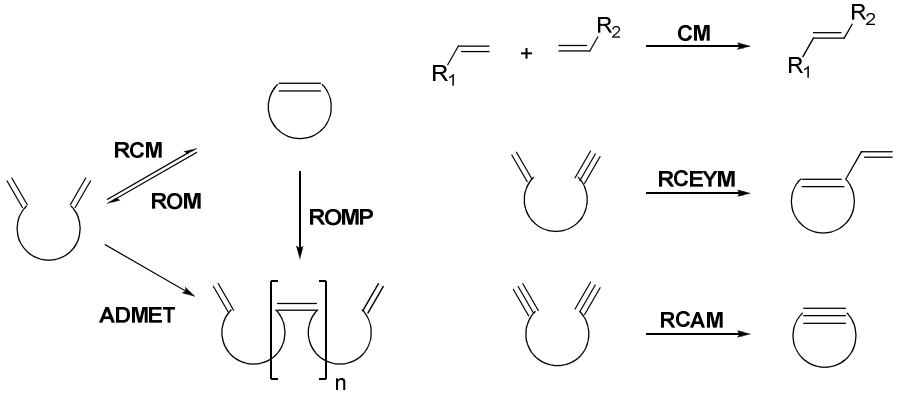
1.6.1.1 General Introduction

Over the past two decades olefin metathesis has been of great interest to synthetic chemists engaged in natural product synthesis. Olefin metathesis was discovered in the mid-1950s by Karl Ziegler during the study of ethylene polymerisation catalysis, [87] which involves two alkenes undergo bond reorganisation in the presence of metal catalysts, resulting in the redistribution of the alkene motifs (Scheme 56).[88]



Scheme 56

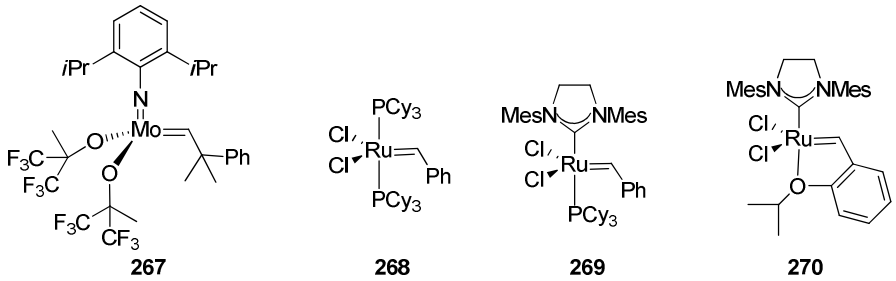
The scope of metathesis reaction has been extended to different π-systems: ring-opening metathesis polymerisation (ROMP), ring-closing metathesis (RCM), acyclic diene metathesis (ADMET), cross-metathesis (CM), ring-closing enyne metathesis (RCEYM) and ring-closing alkyne metathesis (RCAM, Scheme 57).



Scheme 57

[87] Fink, G.; Mülhaupt, R.; Brintzinger, H. H. *Ziegler Catalysts* **1995**, Eds. Springer: Berlin
[88] Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450

The design of metathesis catalysts has undergone a dramatic evolution since the early discovery of Ta-based metathesis catalysts.[89] To date, there are two main types of catalysts that are utilised practically, which are the molybdenum catalyst **267**, developed by Schrock and co-workers,[90] along with the ruthenium complexes **268** and **269**, developed within the Grubbs group (Scheme 58).[91]



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

Scheme 58

Molybdenum catalyst **267** is highly reactive towards a broad range of substrates and especially suitable for the sterically hindered cases.[92] However, its utility is limited by the poor functional group tolerance, as well as the high instability towards air, moisture and any impurities present in the solvent.[92]

In contrast, ruthenium catalysts **268** and **269** developed by Grubbs and co-workers have received great attention because of their improved stability and functional group tolerance. More recently, Hoveyda and co-workers have synthesised a series of ruthenium complexes such as **270** based on the Grubbs catalysts.[93] These modified catalysts have shown enhanced lifetimes and turnover rates.[94]

---

[89] Kotha, S.; Dipak, M. K. *Tetrahedron* **2012**, *68*, 397−421

[90] a) Schrock, R. R. *Acc. Chem. Res.* **1986**, *19*, 342−348; b) Feldman, J.; Murdzek, J. S.; Davis, W. M.; Schrock, R. R. *Organometallics* **1989**, *8*, 2260−2265

[91] a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **1995**, *34*, 2039−2041; b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956

[92] Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450

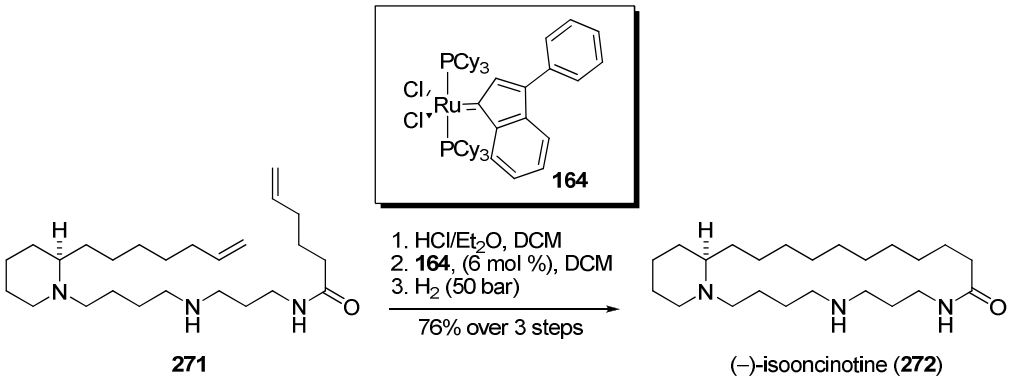
[93] Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791−799

[94] Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4592−4633

1.6.1.2 Macrolactam Formation Using RCM

As a consequence of the promising bioactivities and alluring chemical structures of natural alkaloids, nitrogen-containing heterocycles have been popular targets for synthetic chemistry community for many decades. Several successful cases proved RCM could be an effective method for macrolactam formation, though the Lewis basicity of nitrogen could be problematic for the outcome of reactions and for the lifetime and reactivity of the catalysts.[95,96]

In 2004, Fürstner and co-workers published an efficient total synthesis of (−)-isooncinotine (**272**), a spermidine alkaloid containing a 22-membered macrolactam motif (Scheme 59).[97] The synthesis featured an efficient one-pot RCM-hydrogenation sequence to deliver the desired macrocycle. It was found that the RCM reaction had to be performed in the presence of the ruthenium indenylidene catalyst **164** under acidic conditions to avoid the poisoning of the catalyst by amine.



Scheme 59

[95] a) De Clercq, B.; Verpoort, F. *Tetrahedron Lett.* **2001**, *42*, 8959-8963; (b) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H. J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204−2207

[96] Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199−2238

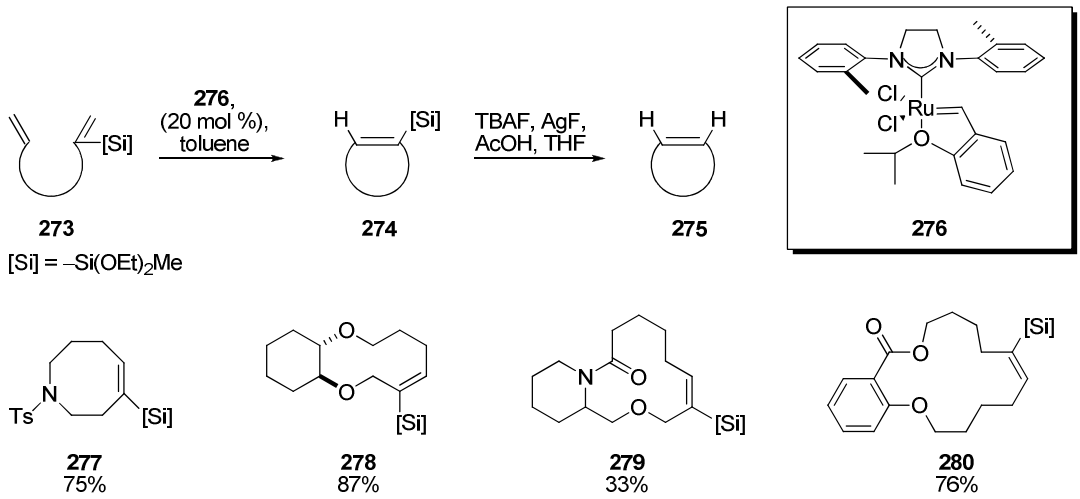
[97] Scheiper, B.; Glorius, F.; Leitner, A.; and Fürstner, A. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11960−11965

1.6.1.3 *Z*-Selective RCM

The stereoselectivity of RCM reactions in terms of macrocycle synthesis has remained problematic for synthetic chemists over the past two decades. In general, the ring size tends to dictate the selectivity for *Z* or *E*. However, significant progress has been made recently towards the stereoselective synthesis of macrocycles, which could be divided into two different approaches: substrate-controlled and catalyst-controlled *Z*-selective RCM.

Substrate-Controlled *Z*-Selective RCM

In 2011, Schreiber and co-workers reported an elegant strategy for the synthesis of macrocycles with *Z*-configured double bonds (Scheme 60).[98] The synthesis commenced with silyl-substituted substrates **273**, which underwent RCM reaction to provide the *E*-silylalkene intermediate **274**. Subsequent removal of the silyl group afforded the desired *Z*-cycloalkene product **275**. The scope of this methodology was demonstrated by the preparation of several *Z*-configured RCM products of various ring sizes (**277**–**280**) in moderate to good yield.

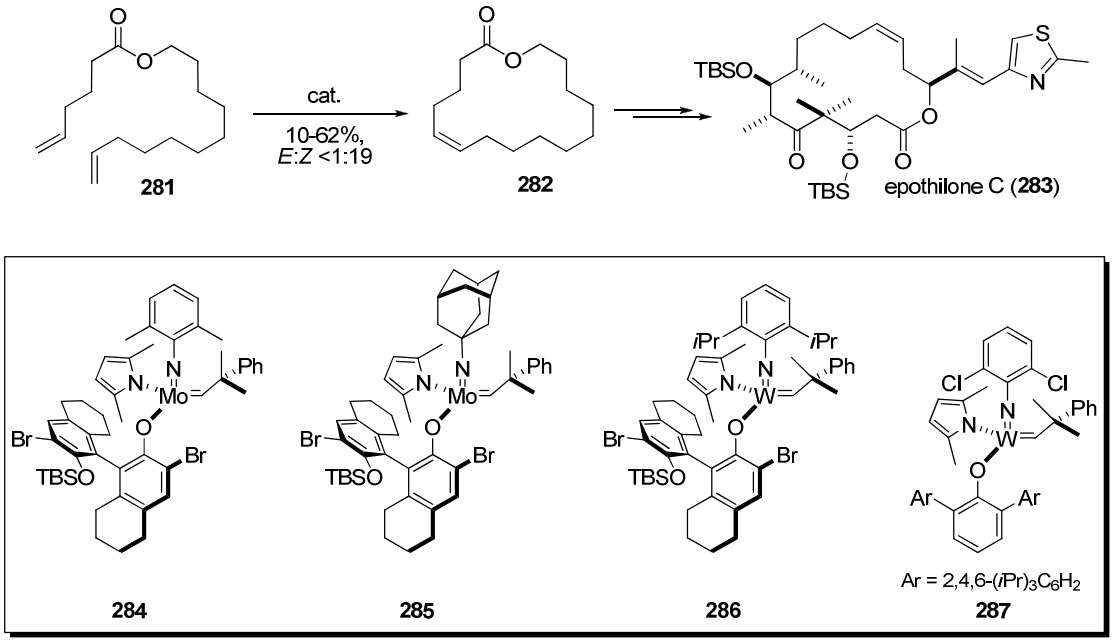


Scheme 60

[98] Wang, Y.; Jimenez, M.; Hansen, A. S.; Raiber, E. A.; Schreiber, S. L.; Young, D. W. *J. Am. Chem. Soc.* **2011**, *133*, 9196−9199

Catalyst-Controlled *Z*-Selective RCM

In 2011, Hoveyda and co-workers described the first example of a catalyst-controlled *Z*-selective RCM reaction and its application to the synthesis of macrocyclic natural products.[99,100] A series of tungsten or molybdenum based catalysts were synthesised and their reactivity and selectivity were explored with regard to various substrates. Acyclic compound **281** underwent RCM reaction in the presence of the *Z*-selective catalysts to provide the 16-membered macrocyclic lactone **282** in moderate to good yield (Scheme 61). Pleasingly, high yields and stereoselectivities were observed when W-alkylidene **286** was employed as the metathesis catalyst. This catalyst has the advantage that it can be manipulated in air unlike its molybdenum counterparts **284** and **285**.

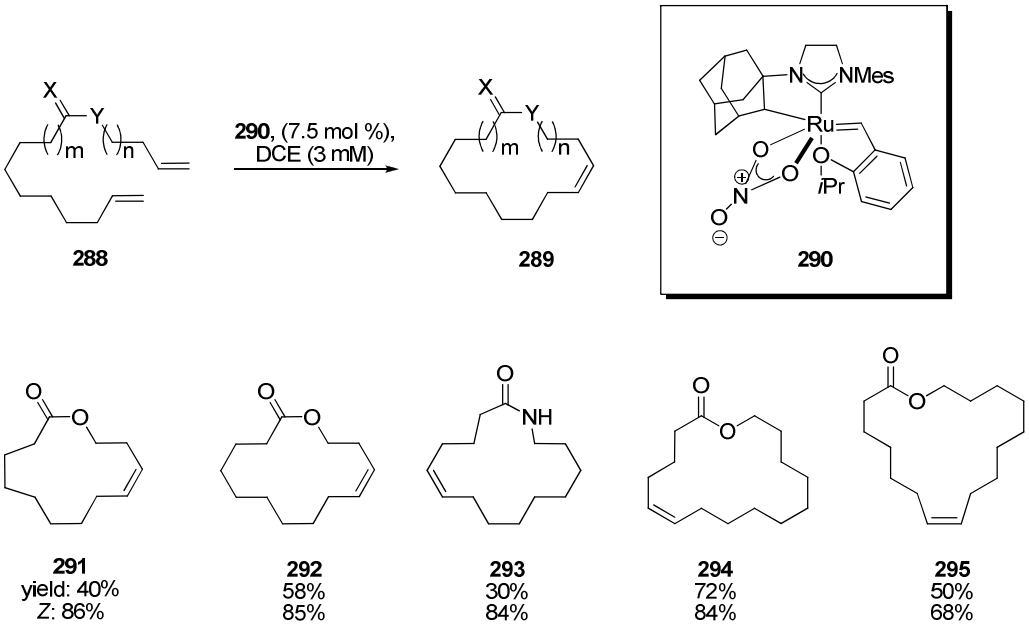


Scheme 61

In 2013, the Grubbs group reported the first *Z*-selective RCM reaction using the ruthenium catalyst **290**.[101] The catalyst **290** was used to prepare 13- to 17-membered macrocyclic compounds **289** from the dienes **288** in moderate to

[99] Yu, M.; Wang, C.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *479*, 88−93
[100] Wang, C.; Yu, M.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Chem. Eur. J.* **2013**, *19*, 2276−2740
[101] Marx, V. M.; Herbert, M. B.; Keitz, B. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2013**, *135*, 94−97

good yield and with excellent selectivity (Scheme 62). It is worth noting that catalyst **290** also promotes *Z*-selective homocoupling, cross-metathesis and ring-opening metathesis polymerisation. It was demonstrated that the adamantyl group is crucial for the high *Z*-selectivity, and the nitrato-type ligand significantly improves the reactivity of the catalyst.



288 **289** **290**

291 yield: 40% *Z*: 86%

292 58% 85%

293 30% 84%

294 72% 84%

295 50% 68%

Scheme 62

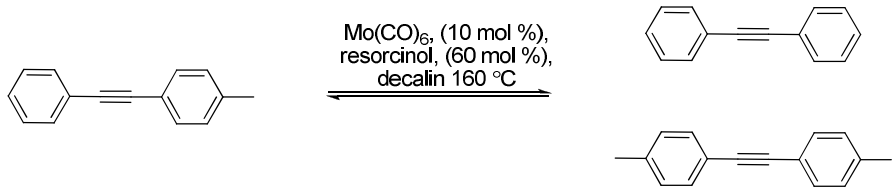
1.6.2 Alkyne Metathesis

Alkyne metathesis has gained significant importance recently, because it allows access to both *E*- and *Z*-configured olefins through the sequence of RCAM and stereoselective reduction. In particular, the utility of RCAM has been extended by the wide application in natural products synthesis.

The first example of an alkyne metathesis reaction was reported by Bailey and co-workers in 1968. In the study, WO_3/silica (6.8% w/w) was used as a heterogeneous catalyst in a continuous-flow system to initiate the disproportionation reaction of 2-pentyne at high temperatures.[102] Shortly after Bailey's discovery, Mortreux and Blanchard[103] found that the same type of

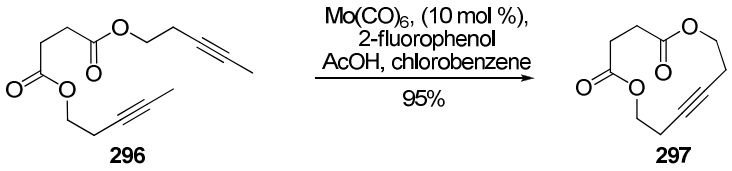
[102] Pennella, F.; Banks, R. L.; Bailey, G. C. *Chem. Commun.* **1968**, 1548−1549
[103] Mortreux, A.; Blanchard, M. *J. Chem. Soc., Chem. Commun.* **1974**, 786−787

transformation could also be promoted by the homogenous catalyst generated *in situ* from $Mo(CO)_6$ and resorcinol in decalin at 160 ° C(Scheme 63).



Scheme 63

In 2004, the Grela group published studies in which RCAM reaction conditions were optimized to improve the yield and the functional group tolerance.[104] In this work, RCAM reactions of various substrates were performed in the presence of various substituted phenols along with $Mo(CO)_6$. It was found that 2-fluorophenol was the most effective additive and the desired ring-closure product **297** was obtained in excellent yield (Scheme 64).



Scheme 64

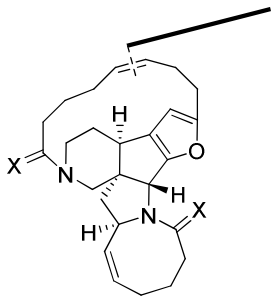
Alkyne metathesis has emerged as a powerful tool in synthesis and RCAM has been applied widely in natural products synthesis. There has been steadily increasing growth in this field in terms of catalyst development and substrate scope.[105]

[104] Grela, K.; Ignatowska, J. *Org. Lett.* **2002**, *4*, 3747−3749
[105] Fürstner, A. *Angew. Chem. Int. Ed.* **2013**, *52*, 2794−2819

1.6.3 Ring Closing Metathesis Strategy towards the Synthesis of Nakadomarin A

1.6.3.1 Olefin RCM

Nakadomarin A bears two *Z*-olefins within medium to large rings, which makes it a natural target for metathesis. The construction of the 8-membered ring through ring closing metathesis has proved to be successful, furnishing the desired azocine motif in good yield in several cases.[18,24] In contrast, the installation of the macrocycle by a late-stage alkene RCM was found to be problematic. The initial attempts by Nishida[18] and Kerr[19] only resulted in poor yield and low *E*/*Z* selectivity (Figure 4). Dixon[20] later improved the selectivity by employing a sub-stoichiometric amount of CSA during the metathesis process, but the conversion remained low. A similar result was obtained by Zhai[25] when applying Dixon's conditions on a slightly different substrate. In 2011, Hoveyda reported a series of tungsten or molybdenum metathesis catalysts for *Z*-selective RCM.[106] Good yields and excellent selectivities were obtained when Hoveyda's catalysts were applied to Dixon's intermediate.



(–)-nakadomarin A (**1**)

	Catalyst	Yield	*E*/*Z*
Nishida (2004)	Grubbs **I**	26%	1:1.5
Kerr (2007)	Grubbs **I**	66%	1:1.6
Dixon (2010)	Grubbs **I**	36%	1:1.7
Zhai (2011)	Grubbs **I**	31%	1:2.0
Dixon (2011)	Hoveyda's cat.	63%	**1:15.7**

X = O or H_2

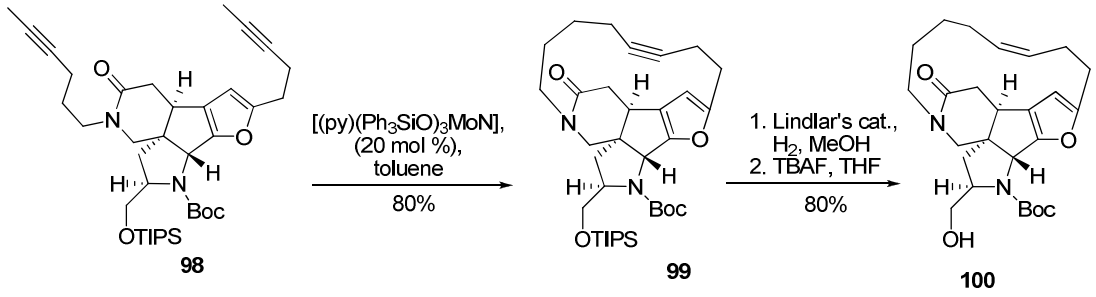
Figure 4

[18] Ono, K.; Nakagawa, M.; Nishida, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 2020−2023
[24] Nilson, M. G.; Funk, R. L. *Org. Lett.* **2010**, *12*, 4912−4915
[19] Young, I. S.; Kerr, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 1465−1469
[20] Jakubec, P.; Cockfield, D. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 16632−16633
[25] Cheng, B.; Wu, F. F.; Yang, X. B.; Zhou, Y. D.; Wan, X. L.; Zhai, H. B. *Chem. Eur. J.* **2011**, *17*, 12569−12572
[106] Yu, M.; Wang, C.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *479*, 88−93

1.6.3.2 Alkyne RCM

As a result of the problems encountered during the macrolactam formation by olefin metathesis, an alternate strategy was used in which RCAM was employed to close the ring and thereafter selective reduction of alkyne to give the *Z* alkene was performed using Lindlar conditions.

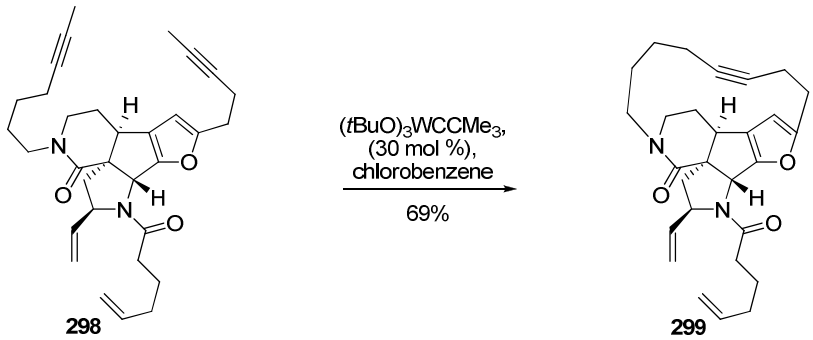
The first example of this approach was reported by Funk and co-workers,[24] who treated the diyne **98** with molybdenum nitride complex to deliver the cyclised product **99** (Scheme 65). Subsequent Lindlar reduction and TIPS protecting group cleavage afforded the *Z*-macrocycle **100** in good yield.



98 99 100

Scheme 65

The Dixon group employed the tungsten catalyst for the alkyne RCM of bis-alkyne **298**, which led to the desired cyclised product **299** with similar efficiency (Scheme 66).[107] Importantly, the catalyst proved to be highly compatible with the terminal alkene moieties.

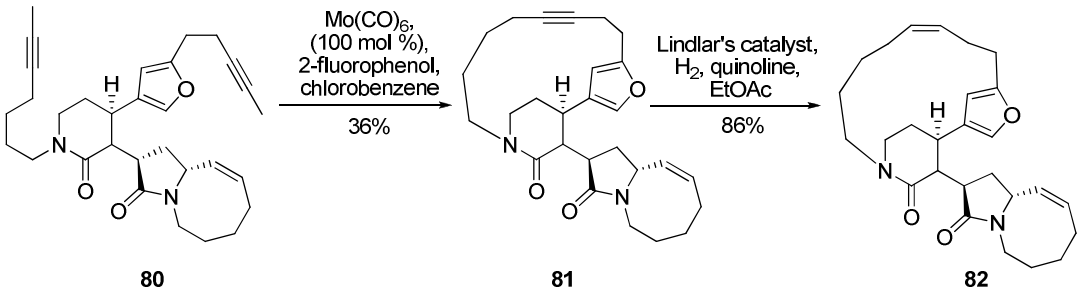


298 299

Scheme 66

[24] Nilson, M. G.; Funk, R. L. *Org. Lett.* **2010**, *12*, 4912−4915
[107] Kyle, A. F.; Jakubec, P.; Cockfield, D. M.; Cleator, E.; Skidmore, J.; Dixon, D. J. *Chem. Commun.* **2011**, 10037−10039

Later in the same year, Dixon further investigated the RCAM strategy on an earlier intermediate, diyne **80** (Scheme 67). A Mortreux-type[108] mixture was chosen as the metathesis catalyst, which led to the construction of the macrocycle in only modest yield.[22] Subsequent hydrogenation in the presence of Lindlar's catalyst provided *Z*-lactam **82** in good yield.



80 **81** **82**

Scheme 67

[108] Mortreux, A.; Blanchard, M. *J. Chem. Soc., Chem. Commun.* **1974**, 786−787
[22] Jakubec, P.; Kyle, A. F.; Calleja, J.; Dixon, D. J. *Tetrahedron Lett.* **2011**, *52*, 6094−6097

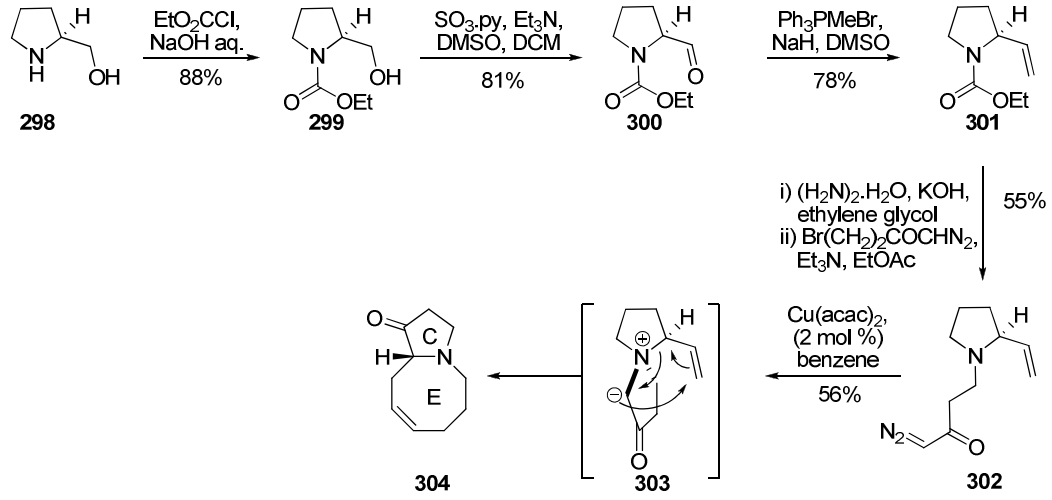
1.7 Previous Work within the Clark Group

1.7.1 Clark Syntheses of Fragments of Manzamine A

Among the studies towards the total synthesis of manzamine A (**3**), the syntheses of CE ring fragment as well as the AB ring fragment of manzamine A (**3**) have been developed within the Clark group.[109,110]

1.7.1.1 Synthesis of the CE Ring Fragment: [2,3]-Sigmatropic Rearrangement

The first effort from the Clark group resulted in a very efficient enantioselective synthesis of the CE ring system of manzamine A (**3**). The azocine fragment **304** was obtained from the key intermediate, the diazo ketone **302**, prepared from *(S)*-prolinol (**298**) in 4 steps (Scheme 68).[109]



Scheme 68

The synthesis started from the protection of the secondary amine **298** as an ethyl carbamate to afford alcohol **299** in high yield. Oxidation of the alcohol **299** to the aldehyde **300** and subsequent methylenation delivered the vinyl pyrrolidine **301**. The carbamate was deprotected using hydrazine and the resulting amine was immediately alkylated with 4-bromo-1-diazobutan-2-one to give the key diazoketone **302** in good yield over two steps. Treatment of the

[109] Clark, J. S.; Hodgson, P. B. *Tetrahedron Lett.* **1995**, *36*, 2519−2522
[110] Clark, J. S.; Townsend, R. J.; Blake, A. J.; Teat, S. J.; Johns, A. *Tetrahedron Lett.* **2001**, *42*, 3235−3238

cyclisation precursor **302** with catalytic amount of $Cu(acac)_2$ (2 mol %) afforded the fused bicyclic system **304**. It was thought that the reaction proceeded through a [2,3]-sigmatropic rearrangement of the spiro-fused bicyclic ammonium ylide 3**03**, resulting in the ring-expansion of the pyrrolidine.

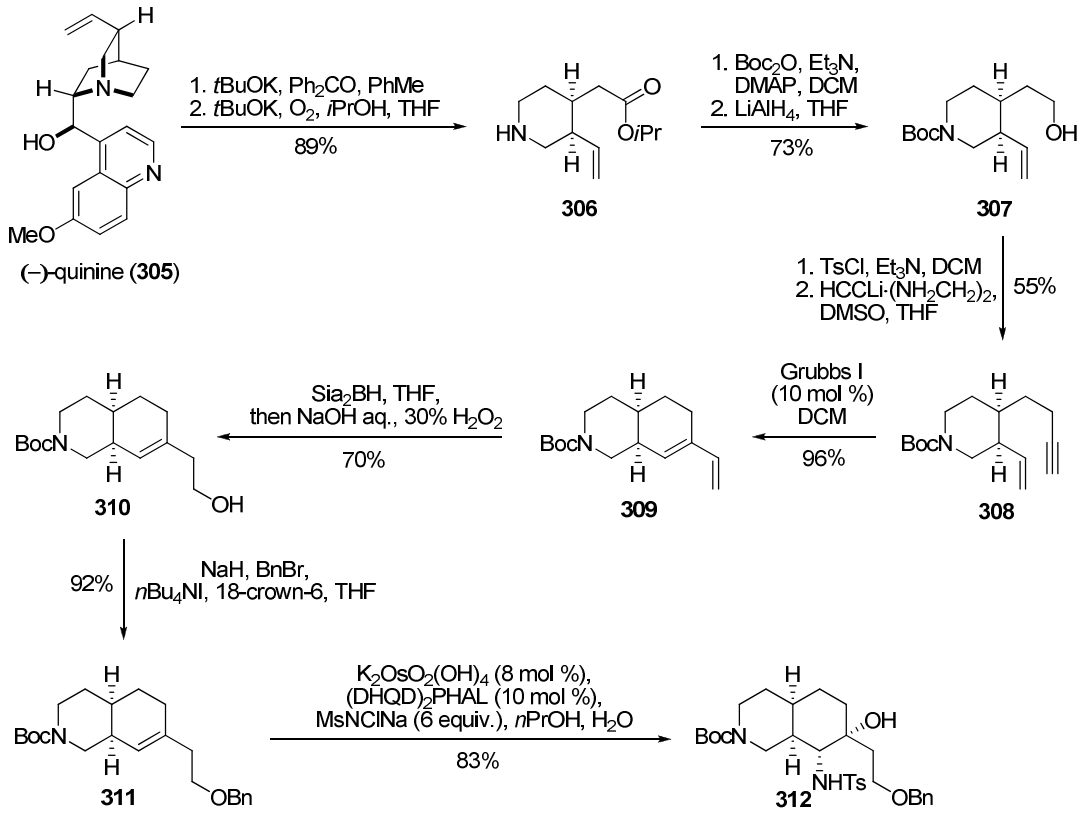
This synthesis of the CE ring fragment **304** was completed in 6 steps with 13% overall yield from *(S)*-prolinol (**298**). It provided an efficient and stereoselective method for accessing similarly fused bicycle system.

1.7.1.2 Synthesis of the AB Ring Fragment: Enyne Metathesis and Sharpless Aminohydroxylation

In addition to the stereoselective strategy for the synthesis of the CE ring system of manzamine A (**3**), the Clark group also developed a concise synthesis of the AB ring system in 2004.[110]

The synthesis commenced with the conversion of (−)-quinine (**305**) into the meroquinene ester **306** in high yield by sequential oxidation, [2+2] cyclisation and ring opening reaction (Scheme 69). Protection of the amine as the *t*-butyl carbamate and further ester reduction afforded the alcohol **307** which underwent tosylation and S_N2 substitution reaction with lithium acetylide to provide the alkyne **308**. Treating **308** with a catalytic amount of the Grubbs first-generation catalyst resulted in an efficient enyne metathesis delivering the diene **309** in good yield. A regioselective hydroboration-oxidation of the terminal double bond gave the alcohol **310**, which was further protected as benzyl ether **311**. A highly diastereoselective and regioselective Sharpless aminohydroxylation reaction was then carried out to complete the AB ring system **312**.

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



Scheme 69

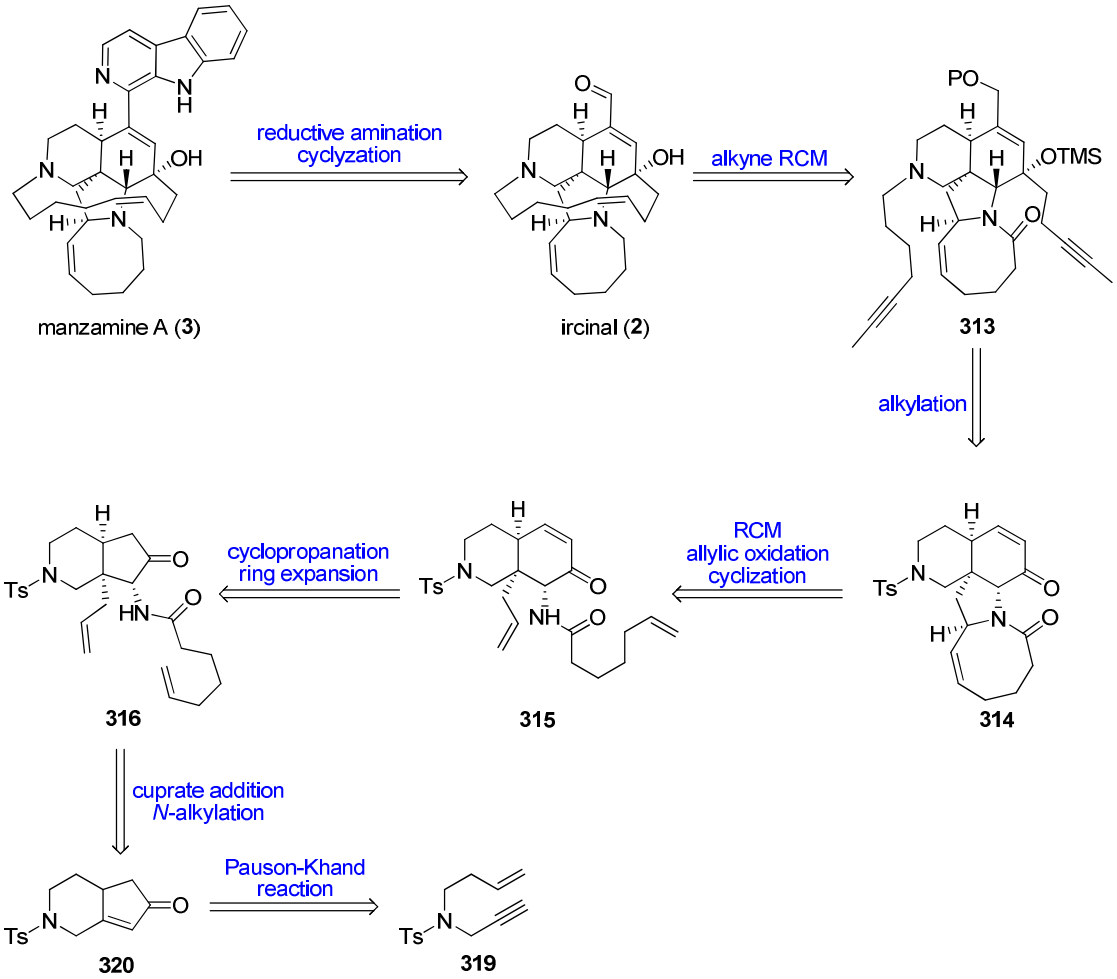
The Clark group's novel approach provided a new method for the synthesis of highly functionalised AB core using an enyne metathesis and Sharpless aminohydroxylation sequence.

1.7.2 Previous Work towards Total Syntheses of Manzamine A

Following the successful syntheses of the AB and CE fragments of manzamine A (**3**), studies towards the total synthesis of manzamine A (**3**) were then carried out in the Clark group.[111]

1.7.2.1 Retrosynthetic Analysis

The strategy developed by the Clark group featured the Pauson-Khand and ring closing metathesis as key reactions. The retrosynthetic analysis of mazanamine A (**3**) is depicted in Scheme 70.



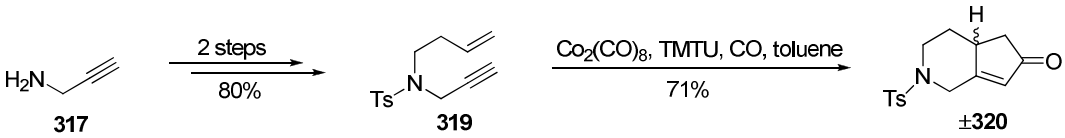
Scheme 70

[111] Hansen, A. M. *PhD thesis*, *University of Glasgow*, **2010**

Ircinal A (**2**) could be converted into manzamine A (**3**) in a two-step process involving reductive amination and cyclisation following Kobayashi's work.[15] Ircinal (**2**) could be prepared from the diyne **313** by alkyne metathesis and Lindlar reduction. The bis-alkyne **313** could be synthesised through alkylation of the tetracyclic intermediate **314**, which could be obtained by sequential ring closing metathesis, allylic oxidation and substitutive cyclisation of the diene **315** Cyclopropanation followed by ring expansion would convert the cyclopentanone **316** into the cyclohexenone **315**. The amide **316** could be prepared by conjugate addition and *N*-alkylation of the enone **320**, which could be constructed by Pauson-Khand reaction of the alkyne **319**.

1.7.2.2 Synthesis of the AB Core: Pauson-Khand

The proposed synthesis of manzamine A (**3**) commenced with Pauson-Khand reaction (Scheme 71). Commercially available propargylamine (**317**) was protected with tosyl chloride under basic conditions to afford a sulfonamide derivative which was subsequently alkylated with 4-bromo-1-butene to provide the enyne **319** in good yield.[112] The racemic bicyclic enone **320** was then prepared by a catalytic intramolecular Pauson-Khand reaction in 71% yield.



Scheme 71

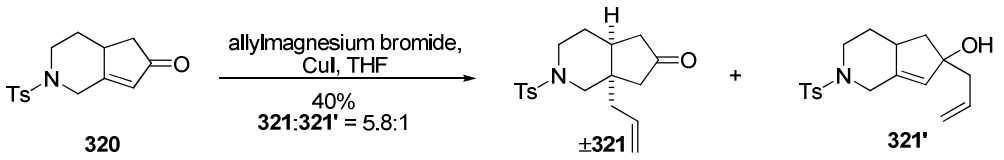
1.7.2.3 Efforts towards the Formation of the E Ring

After an efficient synthesis of the AB core of manzamine A (**3**) in 4 steps, studies towards the formation of the E ring were then explored.

Introduction of a functionalisable side chain by conjugate addition of a cuprate to the enone **320** was investigated first (Scheme 72). Treatment of the enone

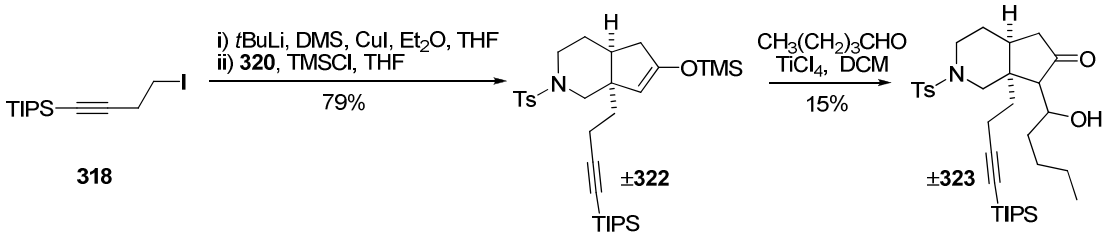
[15] Kobayashi, J.; Tsuda, M.; Ishibashi, M. *Pure. Appl. Chem.* **1999**, *71*, 1123−1126
[112] Patel, M. C.; Livinghouse, T.; Pagenkopf, B. L. *Org. Synth.* **2003**, *80*, 93−103

320 with allylmagnesium bromide and a sub-stochiometric of copper(I) iodide delivered the desired ketone **321** as well as the 1,2-addition by-product **321'**. Intensive work was carried out on screening reaction conditions to increase both the yield and regioselectivity, but with only moderate success (40% yield, **321**: **321'**, 5.8:1). It was found that the allylic side chain was added to the enone **320** in a diastereoselective manner (*cis* to the bridge-head proton) which was confirmed by single crystal X-ray diffraction studies of ketone **321**.



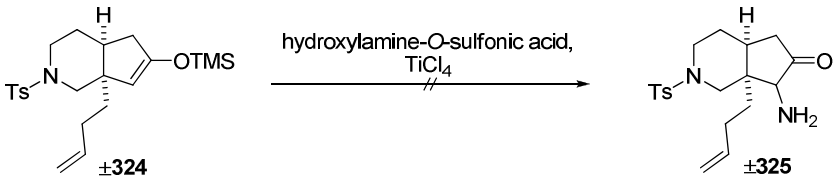
Scheme 72

Due to the poor yield of the allylation reaction, alkyne side chain **318** was then synthesised for the study of the conjugate addition (Scheme 73). Alkyl iodide **318** was submitted to a lithium-halogen exchange with *t*-BuLi, followed by transmetalation with copper iodide to form the dialkyl cuprate. Subjecting the resulting cuprate to the mixture of the enone **320** and TMSCl led to the formation of the desired 1,4-adduct **322** in good yield and regioselectivity. TMS enol ether **322** then went on nucleophilic addition to functionalise the α-position of the carbonyl group. Due to the instability of the intermediate **322**, it was used directly for the Mukaiyama aldol reaction without further purification. Unfortunately, ketone **323** was only isolated in low yield (15%).



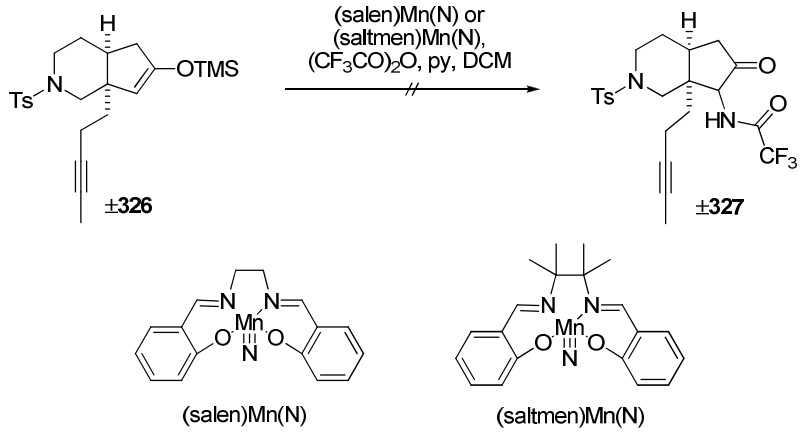
Scheme 73

Electrophilic amination was then explored by the Clark group in attempt to directly install an amino moiety α to the carbonyl group (Scheme 74). Hydroxylamine-*O*-sulfonic acid was employed as the electrophile in reaction with enol ether **324**. However, the desired amine **325** was never isolated.



Scheme 74

In an alternative route, the Clark group also investigated Carreira's methodology for the direct introduction of the *N*-trifluoroacetyl group to the α-position of the carbonyl group using manganese complexes, such as (salen)Mn(N) or (saltmen)Mn(N) (Scheme 75).[113] Activation of the nitromanganese complexes by trifluoroacetic anhydride resulted in the nitrogen transfer reaction. In the Clark group, both (salen)Mn(N) and (saltmen)Mn(N) complex were prepared, following the literature precedent. Unfortunately, the Clark group failed to replicate the amination reaction and compound **327** could not be prepared in this way.



Scheme 75

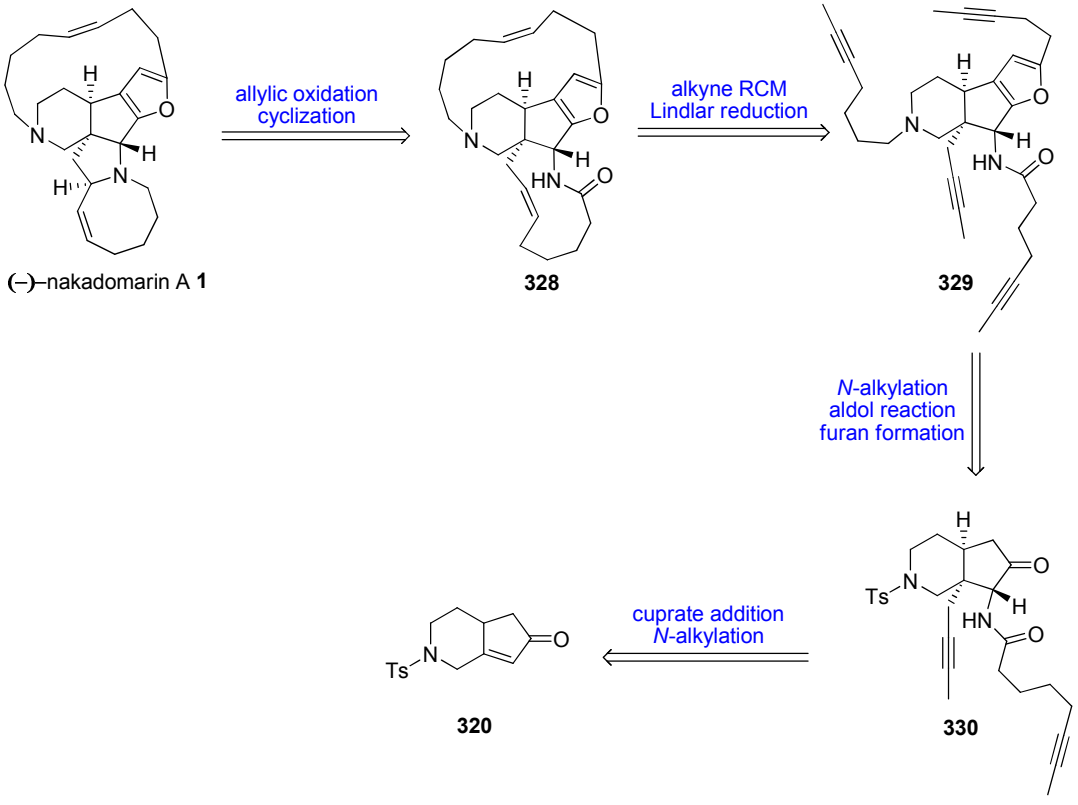
[113] DuBois, J.; Hong, J.; Carreira, E. M.; Day, M. W. *J. Am. Chem. Soc.* **1996**, *118*, 915−916

1.7.3 Previous Work towards Total Syntheses of Nakadomarin A

Due to the failure encountered during the study towards the synthesis of manzamine A (**3**), (−)-nakadomarin A (**1**) was chosen instead as a structurally less complicated target for developing a total synthesis strategy.[114]

1.7.3.1 Retrosynthetic Analysis

The retrosynthetic strategy started from allylic oxidation and cyclisation of amide **328**, was proposed to deliver the desired natural product (**1**) (Scheme 76). Diene **328** would be obtained by double alkyne ring closing metathesis of the tetra-alkyne **329** and subsequent Lindlar reduction. *N*-Alkylation followed by aldol reaction and furan formation could convert the ketone **330** to the furan **329**. Finally, bisalkyne **330** could be derived from conjugate addition and *N*-alkylation of enone **320**.

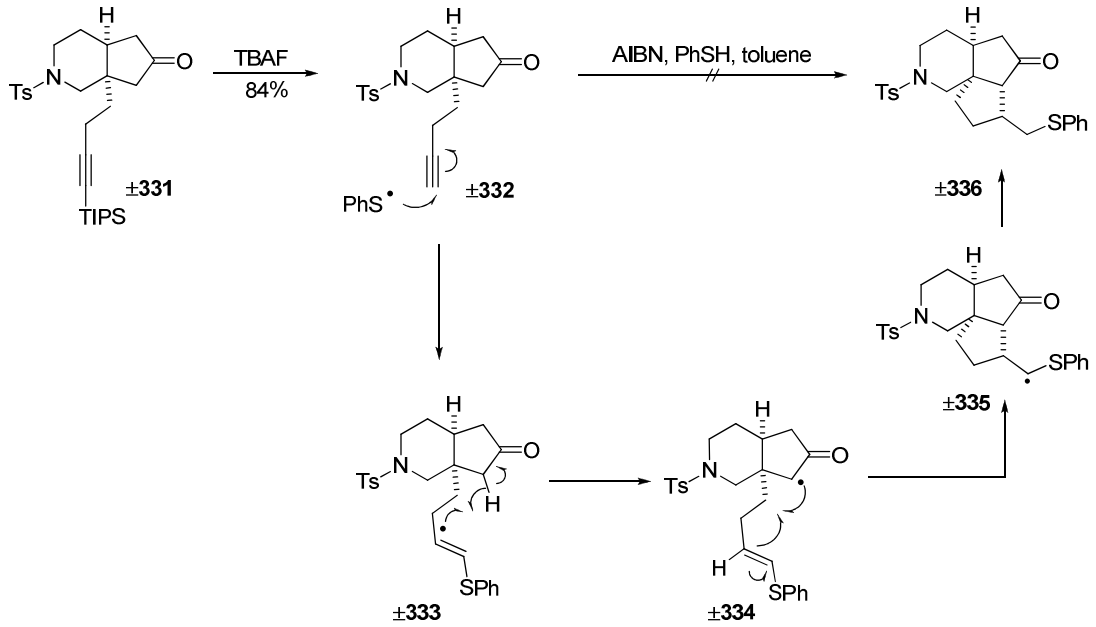


Scheme 76

[114] Poltronieri, E. M. *PhD thesis*, *University of Glasgow*, **2012**

1.7.3.2 Radical Cyclisation

Based on the previous work on delivering the E ring of manzamine A (**3**), a new strategy towards the synthesis of the tricyclic sulfide was investigated. It was believed that this could lead to the introduction of an α-amino carbonyl moiety through oxidative cleavage and Beckmann rearrangement. The initial strategy involved the cleavage of the TIPS protecting group to afford the terminal alkyne **332** (Scheme 77). The intermediate **332** would undergo a radical cyclisation by treatment with thiophenol and AIBN to provide the tricyclic system **336** employing the conditions reported by Roberston and co-workers.[115] Unfortunately, no formation of the tricycle **336** occurred.



Scheme 77

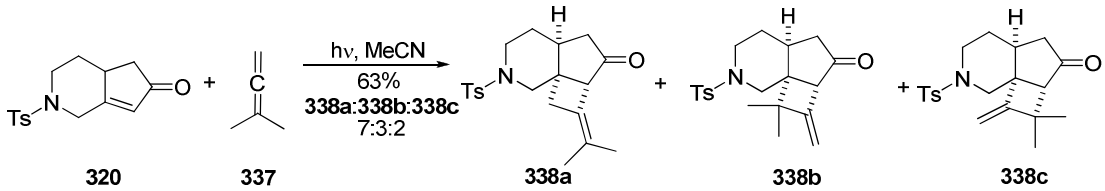
The mechanism of the proposed cyclisation is shown in Scheme 77. It was hoped that the addition of the phenylsulfide radical to the alkyne **332**, followed by a 1,5-hydrogen shift would lead to the thioenol ether **334**, which on undergoing a *5-exo-trig* radical cyclisation would generate tricyclic radical **335**. Finally, quenching of the radical would deliver the desired sulfide **336**.

[115] Robertson, J.; Pillai, J.; Lush, R. K. *Chem. Soc. Rev.* **2001**, *30*, 94−103

1.7.3.3 Photochemistry

Due to the difficulties encountered during the installation of the side chain on the B ring, attentions turned to the direct formation of the C ring by photocycloaddition. In 1964, Corey and co-workers described a [2+2] photochemical reaction between cyclohexenones and allenes to provide bicyclic compounds.[116]

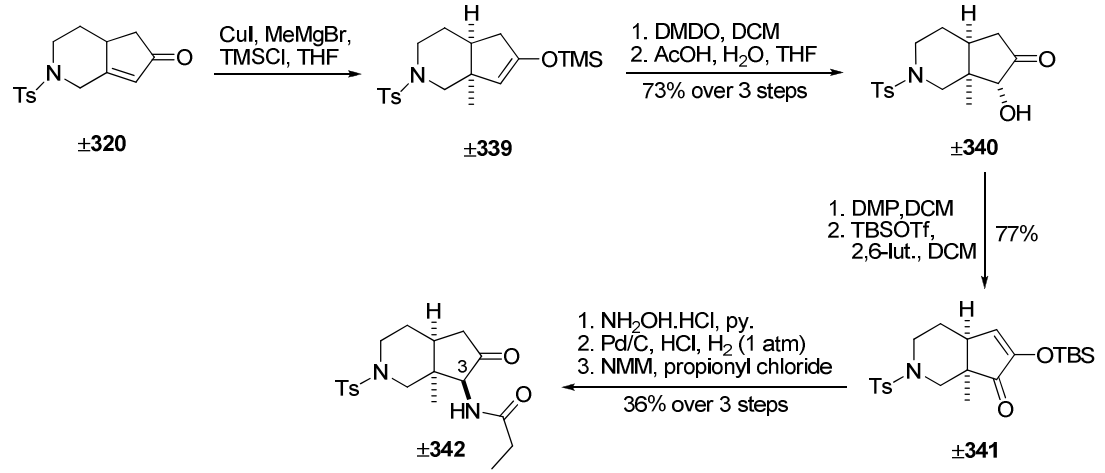
When applying this method to the reaction of the enone **320** with the allene **337**, the desired tricyclic compound **338a** was obtained along with regioisomers **338b** and **338c** (Scheme 78).[114] Various conditions including solvent, concentration and reaction time were screened, but the best yield observed was only 63% (**338a**:**338b**:**338c** as 7:3:2).



Scheme 78

1.7.3.4 Nucleophilic Introduction of Nitrogen to the C3 Position

Previous unsuccessful strategies of radical and photocyclisations led to a new investigation of nucleophilic introduction of a C3 amine.[114]



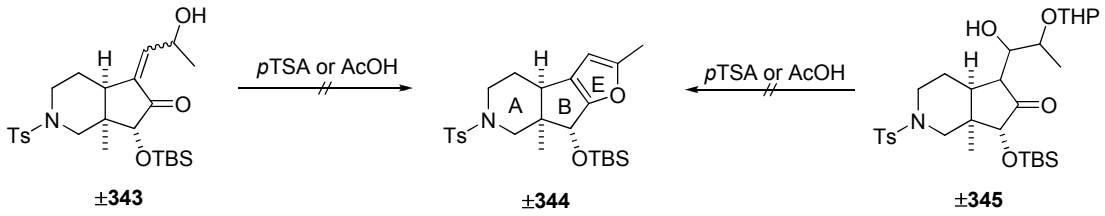
Scheme 79

[116] Corey, E. J.; Lemahieu, R.; Mitra, R. B.; Bass, J. D. *J. Am. Chem. Soc.* **1964**, *86*, 5570−5583
[114] Poltronieri, E. M. *PhD thesis*, *University of Glasgow*, **2012**

Model system **339** was first synthesised for the study of α-carbonyl amination by conjugate addition of methyl cuprate to the enone **320** (Scheme 79). The TMS enol ether then underwent Rubottom oxidation with dimethyldioxirane, which was followed by acidic opening of the epoxide intermediate to afford the α-hydroxyketone **340**. Oxidation of the alcohol **340** with Dess-Martin periodinane and subsequent TBS enol ether formation of C4 carbonyl group provided the ketone **341**. Sequential oxime formation, hydrogenation and amide coupling were carried out to deliver the desired C3 α-amino ketone **342** in moderate yield. The configuration at C3 position was confirmed by single crystal X-ray diffraction of amide **307** to be *trans* respect to the C2 methyl group, which proved to unfortrunately be the undesired diastereoisomer.

1.7.3.5 Studies towards the Furan Formation

The installation of the furan E ring on the AB bicyclic core was also explored in the Clark group. According to the proposed synthetic strategy, the furan moiety could be installed *via* an aldol condensation between AB ring fragment **320** and α-hydroxypropionaldehyde derivative, followed by the acid catalysed deprotection and/or dehydrative cyclisation to afford the tricycle **344** (Scheme 80).[114] Model system hydroxylenone **343** and ketone **345** were prepared in low yield, but proved unstable for the acidic conditions employed *p*TSA or acetic acid.



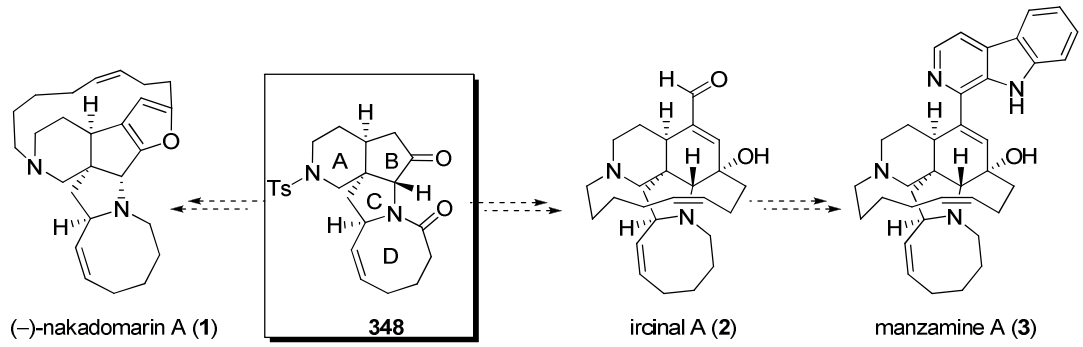
Scheme 80

[114] Poltronieri, E. M. *PhD thesis*, *University of Glasgow*, **2012**

2 Results and Discussion

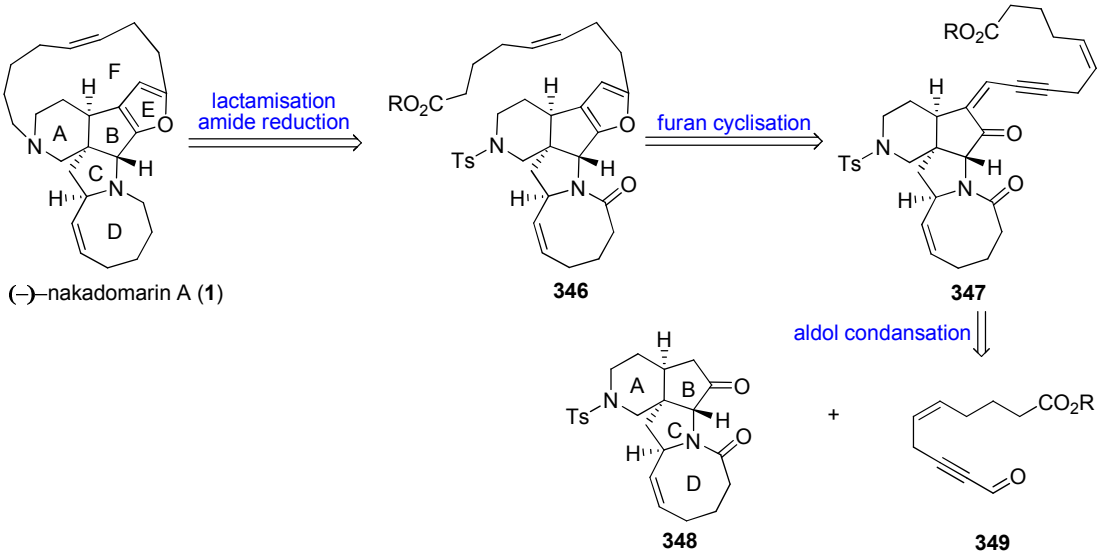
2.1 Evolution of the Strategy towards Nakadomarin A

Due to the structural similarity between (−)-nakadomarin A (**1**), ircinal (**2**) and manzamine A (**3**), the project focused on developing syntheses of all three natural products from a common late-stage intermediate (Scheme 81).



Scheme 81

(−)-Nakadomarin A (**1**) could be prepared from the pentacyclic intermediate **346** by macrolactam formation and amide reduction (Scheme 82). The furan intermediate **346** could be derived from the ynenone **347** by employing prior methodology developed within the Clark group. The ynenone **347** could be formed by aldol condensation between the ABCD tetracyclic ketone **348** and the propargylic aldehyde **349**, which provides the first stop towards the synthesis of nakadomarin A.

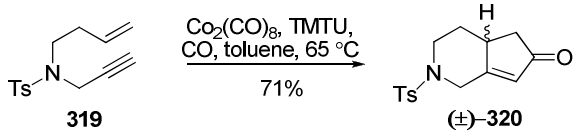


Scheme 82

2.2 Synthesis of the ABCD Core

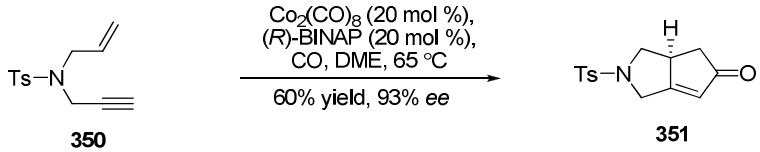
2.2.1 Asymmetric Synthesis of the AB Ring Fragment

Initial investigations towards the new strategy focused on the stereoselective synthesis of the AB ring system. As described before (Section 1.7.2.2, Scheme 71), the synthesis of (−)-nakadomarin A (**1**) started with Pauson-Khand reaction. Previous work had shown that the AB ring system **320** could be synthesised successfully as the racemate (Scheme 83) and so the initial goal was to access this product in an enantioselective manner. The Pauson–Khand reaction is well known for the preparation of 2-cyclopentenone derivatives.[117] However, only limited examples of asymmetric Pauson–Khand reactions, using chiral auxiliaries[118] and chiral ligands,[119] have been reported.



Scheme 83

In 2000, Hiroi and co-workers reported an enantioselective Pauson-Khand reaction in which catalytic amounts of dicobalt octacarbonyl and chiral phosphine ligands were used (Scheme 84).[120] Using this methodology, the fused bicyclic enone **351** had been formed in good yield and with an excellent enantiomeric ratio by treatment of the alkyne **350** with cobalt catalyst and (*R*)-BINAP in DME under a carbon monoxide atmosphere.

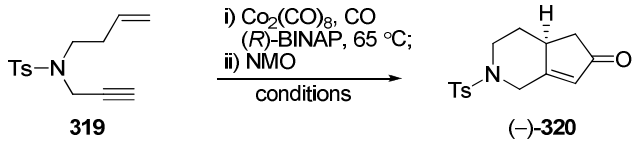


Scheme 84

[117] Pauson, P. L.; Khand, I. U. *Ann. N.Y. Acad. Sci.* **1977**, *295*, 2−14
[118] Castro, J.; Moyano, A.; Pericas, M. A.; Riera, A.; Greene, A. E. *Tetrahedron: Asymmetry* **1994**, *3*, 307–310
[119] Bladon, P.; Pauson, P. L.; Brunner, H.; Eder, R. *J. Organomet. Chem.* **1988**, *355*, 449−454
[120] Hiroi, K.; Watanabe, K.; Kawagishi, R.; Abe, I. *Tetrahedron: Asymmetry* **2000**, *11*, 797−808

The application of this reaction was first evaluated with the sulfonamide **319**. Moderate yield and enantioselectivity were observed when Hiroi's conditions were employed to cyclisation of the enyne **319** (Table 1, entry 1). Further studies were performed in order to optimize the outcome of the reaction through screening of solvents and varying the catalyst loading. The optimal result was achieved when 0.3 equivalent of cobalt catalyst and (*R*)-BINAP in toluene was used. In this case, the bicyclic enone **320** was oibtained in 76% yield and 97% *ee* (Table 1, entry 3).[121]

Table 1



319 (–)-**320**

Entry	$Co_2(CO)_8$ (equiv.)	(*R*)-BINAP (equiv.)	Solvent	Yield (%)	*ee* (%)[a]
1	0.2	0.2	DME	58	78
2	0.2	0.2	toluene	65	85
3	**0.3**	**0.3**	**toluene**	**76**	**97**
4	0.4	0.4	toluene	77	94

[a] The *ee* was determined by chiral HPLC.

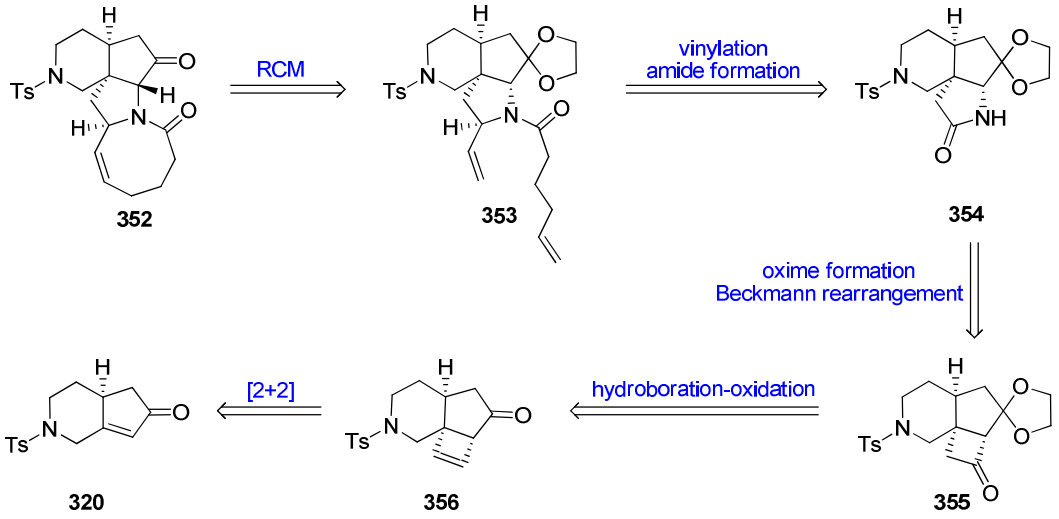
[121] Enantiomeric excess was determined by HPLC analysis of intermediate **320**. Column Chiralpak OD-H, temperature 25 °C, hexane: propan-2-ol 67:33, flowrate 0.5 mL.min^{-1}, retention time 17.2 min.

2.2.2 Synthesis of the CD Ring Fragment

2.2.2.1 First-Generation Retrosynthetic Analysis

The successful enantioselective synthesis of the AB ring system provided a promising starting point for the total synthesis of nakadomarin A. Our attention now turned to the construction of rings C and D.

In the initial retrosynthetic analysis of the ABCD ring system **352** it had been envisaged that formation of ring D would be accomplished by RCM of the diene **353**, which itself could be obtained from the lactam **354** by vinylation and amide coupling (Scheme 85). Oxime formation and Beckmann rearrangement[122] would convert the ketone **355** into the pyrrolidinone **354**, and the ketone **355** would be generated from a hydroboration-oxidation reaction of the alkene **356**. Finally, the tricyclic ketone **356** could be formed by [2+2] photocycloaddition of the enone **320** and trimethylsilylacetylene.

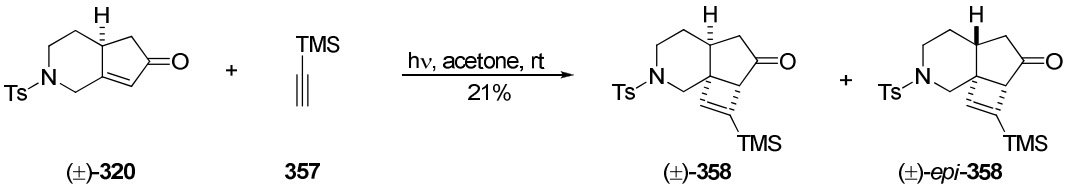


Scheme 85

[122] Beckmann, E. O. *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 988–993

2.2.2.2 Construction of the ABC Ring System: Photocycloaddition

As illustrated previously (Scheme 78, section 1.7.3.2), attempts had been made to introduce the C ring to the bicyclic AB system by photocyclisation.[114] However, low regio and stereoselectivity had been observed when using 1,1-dimethylallene. In order to solve the regioselectivity problem, trimethylsilylacetylene was chosen as a sterically hindered addition partner. Pleasingly, excellent regioselectivity was obtained, but unfortunately the photoaddition reaction proceeded slowly; ^{1}H NMR spectroscopic monitoring of the reaction mixture indicated only 10% conversion after 6 h under UV irritation. Prolonging reaction time resulted in an improvement in the level of conversion but without an increase in the isolated yield (18 h, 21% yield). Moreover, facial stereoselectivity proved to be problematic and an inseparable mixture of diastereoisomers **358** and *epi*-**358** was obtained in a ratio of 4:3 (Scheme 86).

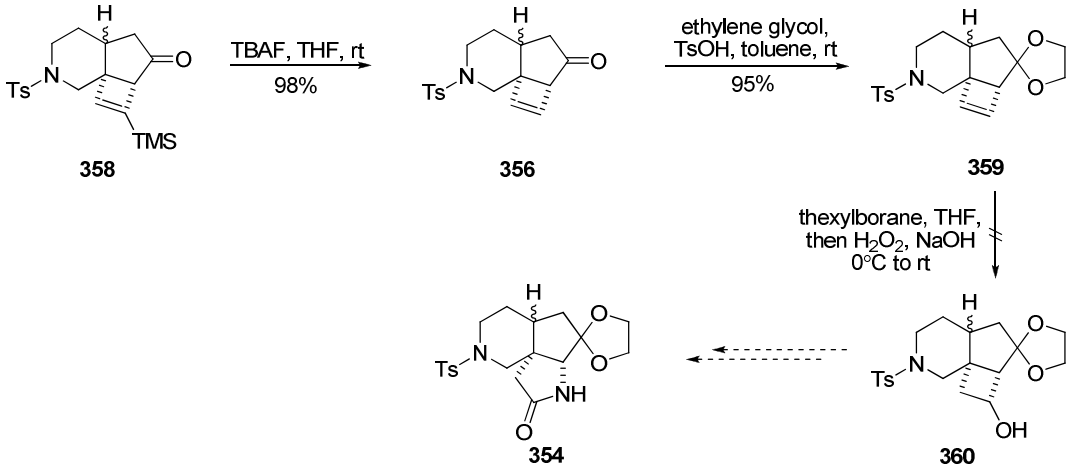


(±)-320 357 (±)-358 (±)-*epi*-358

Scheme 86

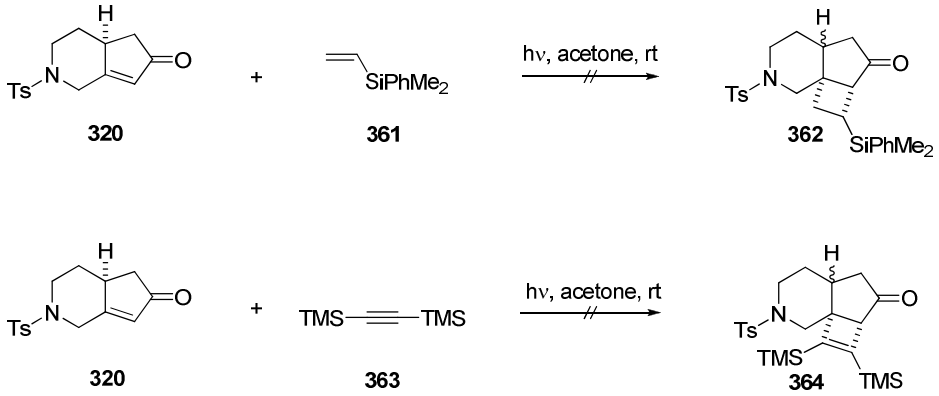
The isolated mixture of *cis*- and *trans*-photoaddition products **358** and *epi*-**358** was used to explore subsequent steps (Scheme 87). Removal of the TMS group with TBAF afforded the tricyclic ketone **356** in quantitative yield and the ketone was protected as a ketal to give the compound **359**. Hydroboration-oxidation of the alkene proved to be unsuccessful and resulted in decomposition of the starting material.

[114] Laloy, E. M. *PhD Thesis*, *University of Glasgow*, **2012**



Scheme 87

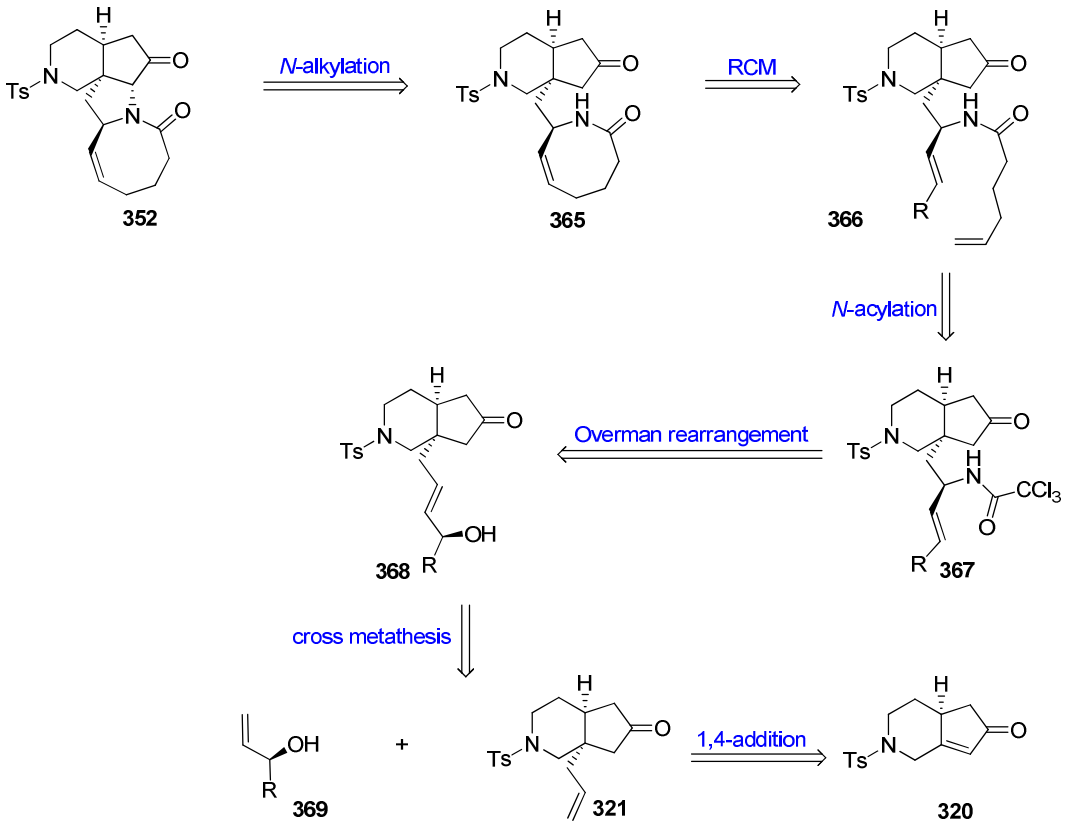
Photoaddition reactions were also performed between the enone **320** and various alternative partners, but all attempts failed to provide the required cyclic system (Scheme 88). Cyclisation between the enone **320** and the vinyl silane **361** as well as ethynyltrimethylsilane **363** resulted in the recovery of the starting material without product formation, an outcome that was assumed to be a consequence of steric hindrance.



Scheme 88

2.2.2.3 Second-Generation Retrosynthetic Analysis

Due to the failure of C ring formation through [2+2] photoaddition, an alternative synthetic route for the construction of rings C and D was explored. The second-generation strategy relied on intramolecular *N*-alkylation of the amide **365** as the key strategy to access the desired ABCD core **352** (Scheme 89). The alkene **365** could be synthesised by RCM of the diene **366**, which in turn could be obtained by deprotection and amide coupling of the alkene **367**. The trichloroacetamide **367** would be prepared by Overman rearrangement of the alcohol **368**. The allylic alcohol **368** could then be prepared by cross-metathesis of the chiral allylic alcohol **369** with the alkene **321**. Finally, the ketone **321** could be generated by conjugate addition of the core Pauson-Khand product **320**.



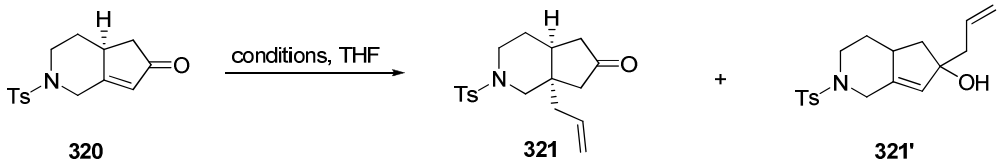
Scheme 89

2.2.2.4 Introduction of the Allyl Side Chain to C2 Position

As demonstrated previously (Section 1.7.2.3, Scheme 72), the introduction of an allyl side chain to the enone **320** through conjugate addition had been explored during studies directed towards the synthesis of manzamine A (**3**),[111] and problems of low yield and regioselectivity had been encountered.

In order to solve the regioselectivity problem and improve the reaction yield, various conditions were investigated (Table 2). The enone **320** was treated with a premixed solusion of copper(I) iodide, lithium chloride and allyl magnesium chloride to give the 1,4-addition product **321**. It was found that the quality of copper(I) iodide was critical to the success of this reaction and that it should be purified freshly before use (washed with water, ethanol and ether, then dried at 65 °C under vacuum overnight). The use of unwashed copper(I) iodide led to the formation of a significent amount of the 1,2-addition by-product **321'** (Table 2, Entry 1). The reaction temperature also had a dramatic influence on the outcome of this conjugate addition: when the reaction was performed at −78 °C, only a trace amount of the 1,4-adduct was formed (Table 2, Entry 2), but at −30°C, a moderate yield was observed (Table 2, Entry 3). The use of 3 equivalents of the organocuprate at −10 °C was found to be optimal and this set of conditions delivered the desired 1,4-addition product **321** in 82% yield (Table 2, Entry 5).

Table 2



320 **321** **321'**

Entry	CuI, LiCl (equiv.)	Grignard (equiv.)	T (°C)	321 (%)	321'(%)
1	2	2	−10	62	10[a]
2	2	2	−78	trace	–
3	2	2	−30	39	–
4	2	2	−10	73	–
5	**3**	**3**	**−10**	**82**	–
6	3	3	0	76	–

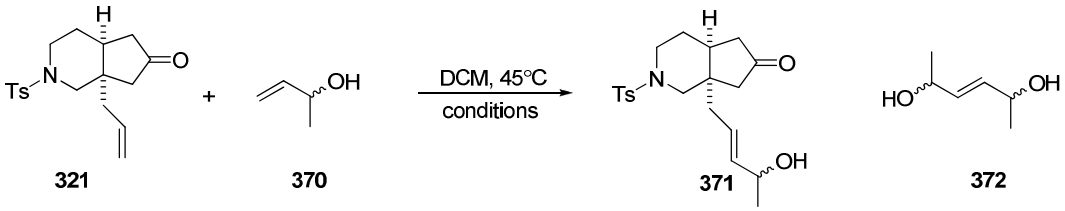
[a] unwashed copper iodide used

[111] Hansen, A. M. *PhD Thesis*, *University of Glasgow*, **2010**

2.2.2.5 Cross-Metathesis and Overman Rearrangement on C2 Side Chain

With alkene **321** in hand, attention was turned to the exploration of the sequence of cross-metathesis and Overman rearrangement for installation of the C10–N chiral centre. 3-Buten-2-ol (**370**) was selected as the cross-metathesis partner, and initially the racemic allylic alcohol was used to investigate reaction conditions. After treating the alkene **321** with 3 equivalents of the allylic alcohol **370** and 3 mol % of the Grubbs second-generation catalyst in DCM under reflux, the cross-metathesis product **371** was obtained in 50% yield, along with the homo-coupled by-product **372** (Table 3, Entry 1). Increasing the amount of the alcohol **370** to 10 equivalents marginally improved the yield (Table 3, Entry 2), although generation of a large amount of by-product **372** caused difficulties during purification. Higher catalyst loadings also proved to have a beneficial effect on the formation of the desired product (Table 3, Entry 3). Addition of 4 equivalents of the alcohol **370** to a mixture of **321** and catalyst (6 mol %) was found to be optimal and the allylic alcohol **371** was obtained in 72% yield using these conditions (Table 3, Entry 4).

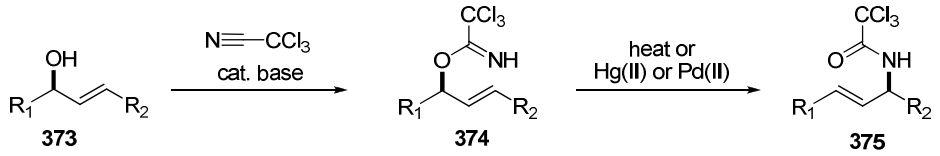
Table 3



Entry	370 (equiv.)	Grubbs II (mol %)	371 (%)[a]
1	3	3	50
2	10	3	63
3	5	6	70
4	**4**	**6**	**72**

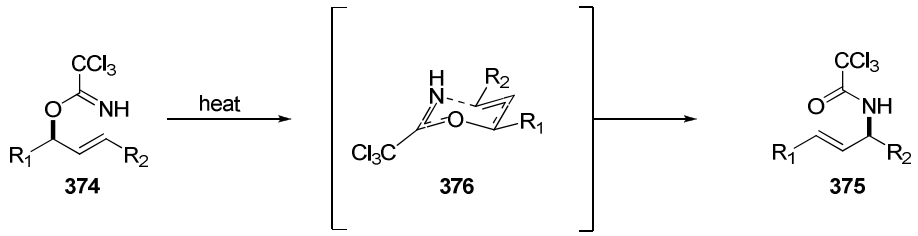
[a] Isolated yield for the alcohol **371**.

The successful preparation of alcohol **371** meant that the challenging imidate formation and Overman rearrangement sequence could be explored. In 1976, Overman and co-workers reported a general method for the synthesis of allylic amines by rearrangement of allylic trichloroacetimidates.[123] In this procedure, allylic alcohols **373** are treated with a sub-stoichiometric amount of base and trichloroacetonitrile to afford trichloroacetimidates of type **374**. These intermediates then undergo thermal or transition metal catalysed [3,3]-sigmatropic rearrangement to provide allylic amides **375** with transfer of stereochemical information (Scheme 90).



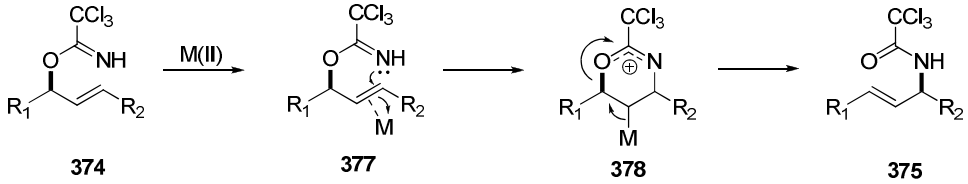
Scheme 90

Thermal [3,3]-sigmatropic rearrangement, which is driven by formation of an amide, proceeds through a 6-membered chair transition state **376**, similar to that observed in the Claisen rearrangement reaction (Scheme 91).



Scheme 91

Alternatively, rearrangement could be induced by a transition metal catalyst, such as Pd(II) or Hg(II).[124] This metal-catalysed reaction is a cyclisation-induced rearrangement process that proceeds through an iminometallation-deoxymetallation sequence (Scheme 92).

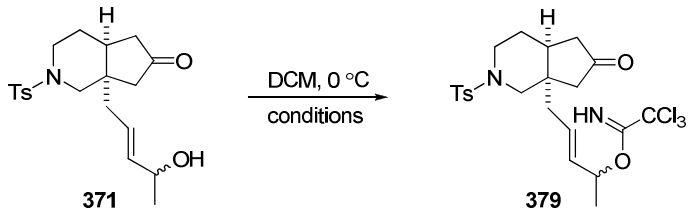


Scheme 92

[123] Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901−2910
[124] Overman, L. E. *Angew. Chem. Int. Ed.* **1984**, *23*, 579–586

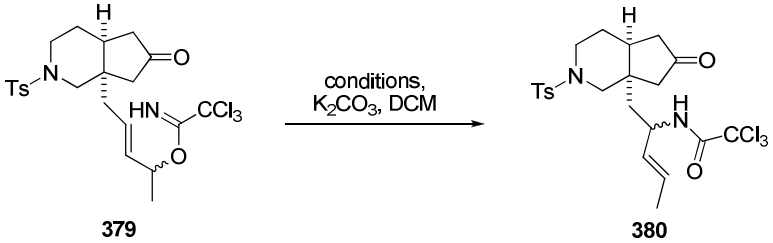
The use of the thermal Overman rearrangement reaction in our synthetic route required formation of the trichloroacetatimidate **379** by reaction of the alcohol **371** and trichloroacetonitrile. Initial screening of reaction conditions, which involved treating the alcohol **371** with 1.5 equivalents of trichloroacetonitrile and 0.5 equivalent of DBU, led to 50% conversion (Table 4, Entry 1). Only a trace amount of the desired product was formed when sodium hydride was employed as base (Table 4, Entry 2). The best result was obtained by increasing the amount of trichloroacetonitrile and DBU, giving the imidate **379** with a conversion level of 70% (Table 4, Entry 3).

Table 4



Entry	Trichloroacetonitrile (eq.)	DBU (eq.)	NaH (eq.)	Conversion (%)
1	1.5	0.5	–	50
2	1.5	–	0.3	trace
3	**3.0**	**1.0**	**–**	**70**

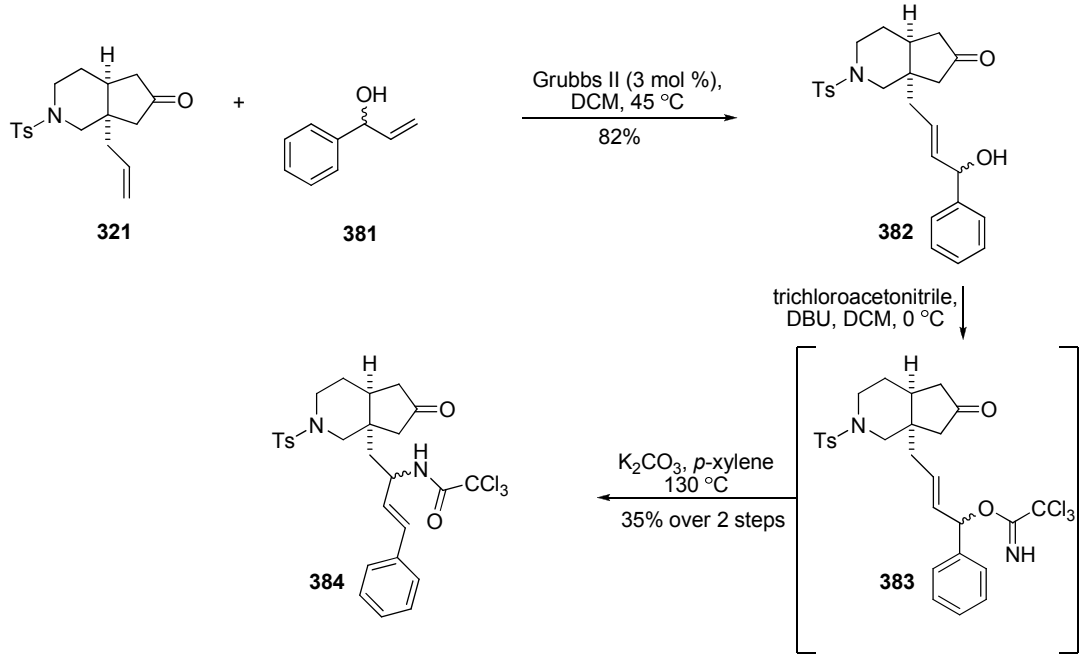
The imidate **379** was found to be unstable and was prone to decomposition back to the starting allylic alcohol **371** in the presence of water. Thus, the reaction mixture was passed through a short pad of silica, concentrated and used directly in the next step without further purification.



Scheme 93

The thermal Overman rearrangement reaction was then investigated (Scheme 93). Heating the imidate **379** in *p*-xylene at 160 °C under microwave irradiation gave the trichloroacetamide **380** in 18% yield over two steps. During the process, partial decomposition of the starting material was observed due to the high reaction temperature used. When the rearrangement was performed in a sealed tube at 140 °C, a slightly improved yield of 22% was obtained.

Sequential cross-metathesis and Overman rearrangement with a different metathesis partner, benzyl alcohol **381**, was also performed in parallel, leading to an improvement in the yields for both steps (Scheme 94). This result was believed to be a consequence of the increased stability of the imidate **383**.

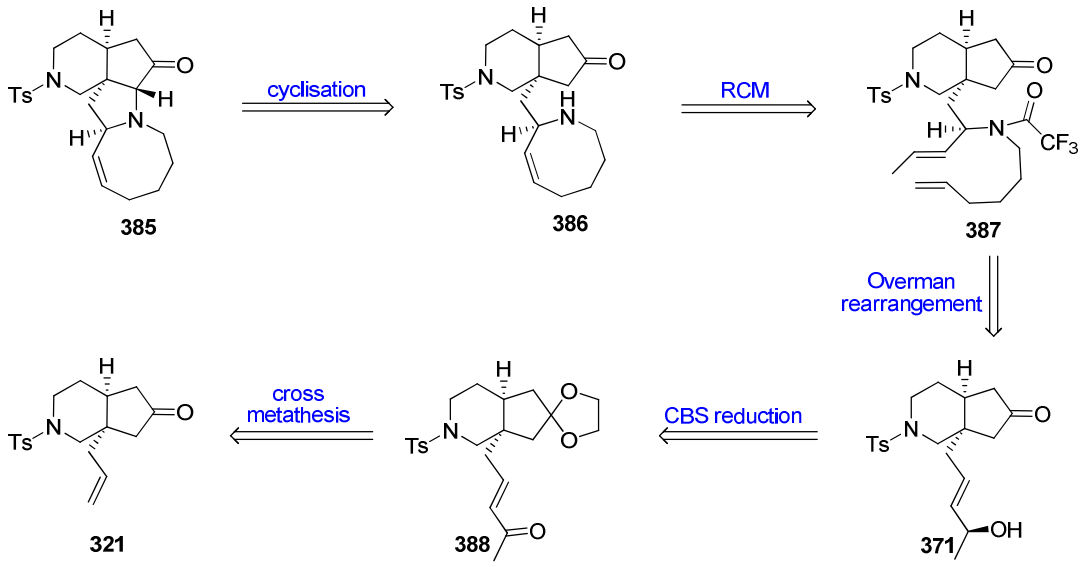


Scheme 94

In summary, introduction of an allylic side chain to the AB ring core was achieved in high yield and with excellent regioselectivity. The following cross-metathesis and Overman rearrangement sequence was investigated on two substrates but with limited success.

2.2.2.5 Third-Generation Retrosynthetic Analysis

As a consequence of the poor yields of the previous route, a modified retrosynthetic strategy was explored (Scheme 95). The revised ABCD core **385** could be delivered by α-bromination and intramolecular nucleophilic cyclisation of the amine **386**. The amide **387** could be converted into the tricyclic alkene **386** by sequential cleavage of the trifluoroacetyl group and RCM. The diene **387** would be derived from the allylic alcohol **371** through Overman rearrangement and the required starting material could be generated by stereoselective Corey-Bakshi-Shibata reduction[125] of the enone **388**. Finally, a cross-metathesis reaction between the alkene **321** and methyl vinyl ketone would provide the enone intermediate **388**.

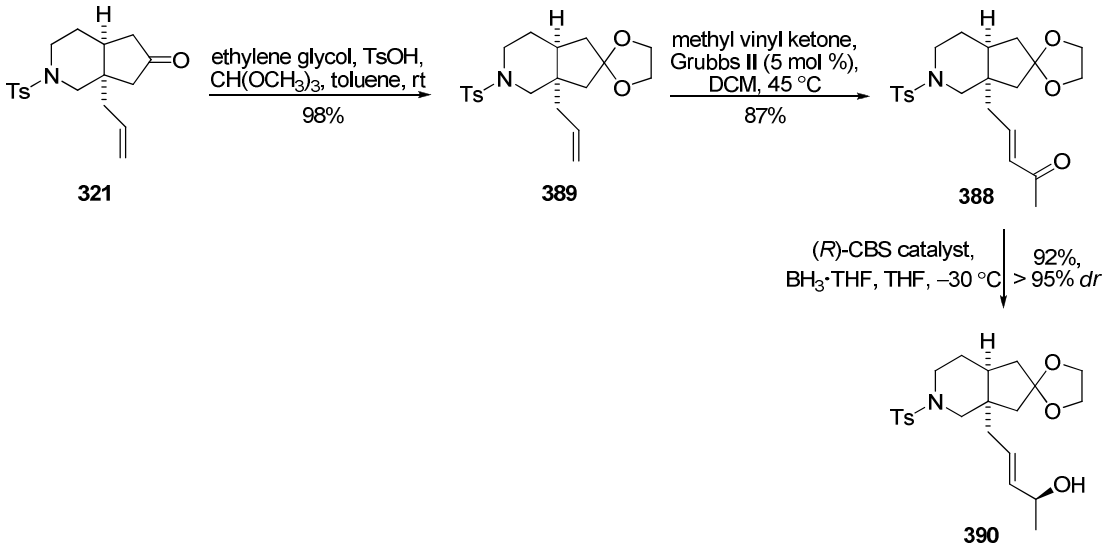


Scheme 95

Previous studies concerning the cross-metathesis reaction between the alkene **321** and racemic 3-buten-1-ol had been successful. However, enantiomerically pure 3-buten-1-ol is not commercially available and is difficult to prepare. Consequently, the plan was to circumvent this problem by employing methyl vinyl ketone as the cross-metathesis partner and introducing the required stereochemistry through CBS reduction. The synthesis commenced with protection of the ketone **321** as a ketal **389**. Cross-metathesis of this ketal with methyl vinyl ketone was successful and afforded the enone **388** in high yield.

[125] Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553

Subsequent asymmetric CBS reduction provided the allylic alcohol **390** in high yield and with an excellent diastereomeric ratio (Scheme 96).



Scheme 96

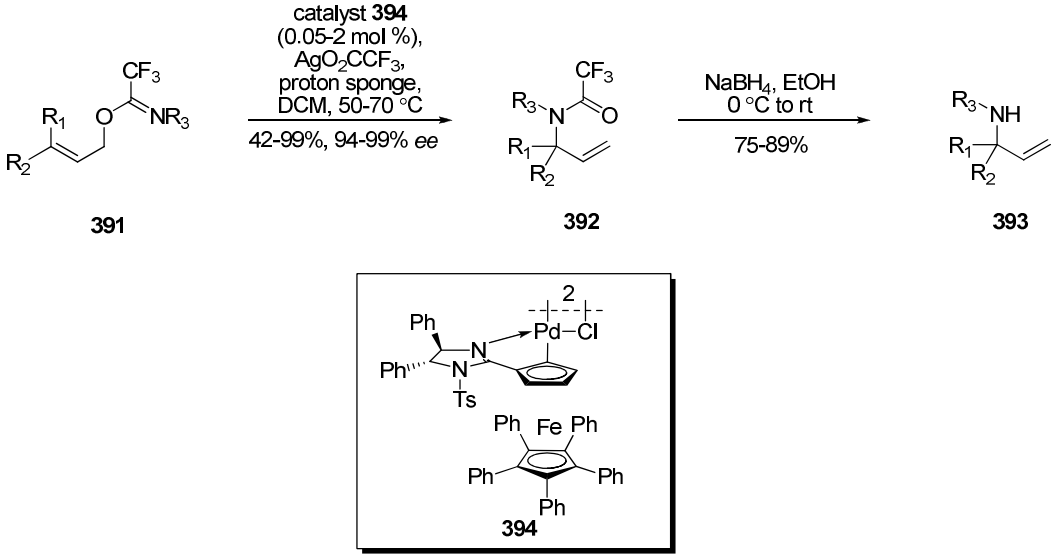
With the chiral allylic alcohol **390** in hand, the stage was set to investigate the key Overman rearrangement reaction. As described previously, rearrangement to form secondary allylic amides by Overman rearrangement is a well-developed reaction.[126] However, only a few examples of the tertiary equivalents have been reported.[127,128] In 2008, Peters and co-workers reported catalytic asymmetric formation of tertiary allylic amides by aza-Claisen rearrangement of trifluoroacetimidates (Scheme 97).[129] Treatment of trifluoroimidates **391** with a catalytic amount of the palladium complex **394** under basic conditions led to the formation of amides **392** in moderate to high yields. These amides were further converted into the corresponding secondary amines **393** by reductive cleavage of the trifluoroacetyl group. The influence of the R_3 substituent on the nitrogen was examined, and good yields were obtained for substrates bearing aryl or alkyl groups.

[126] Overman, L. E. *Angew. Chem. Int. Ed.* **1984**, *23*, 579–586

[127] Calter, M.; Hollis, T. K.; Overman, L. E.; Ziller, J.; Zipp, G. G. *J. Org. Chem.* **1997**, *62*, 1449–1456

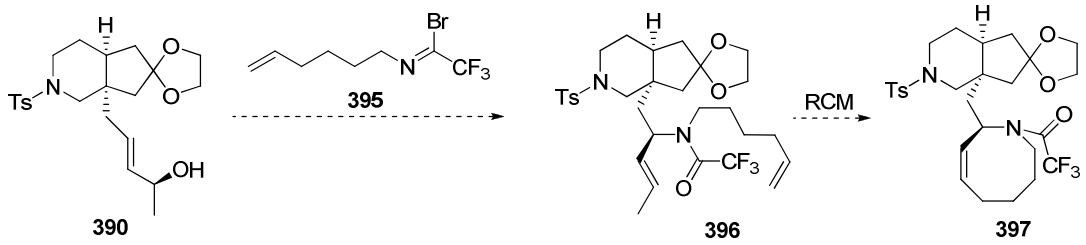
[128] Moyano, A.; Rosol, M.; Moreno, R. M.; López, C.; Maestro, M. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 1865–1869

[129] Xin, Z.; Fischer, D. F.; Peters, R. *Synlett.* **2008**, 1495–1499



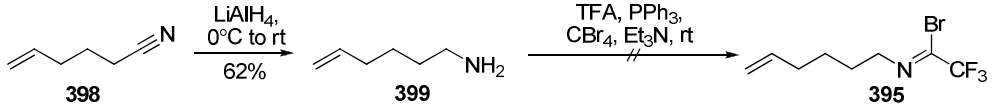
Scheme 97

Inspired by Peters' work, the acetimidoyl bromide **395,** which has the desired hexenyl side chain for the following RCM, was chosen as the *O*-alkylation partner (Scheme 98).



Scheme 98

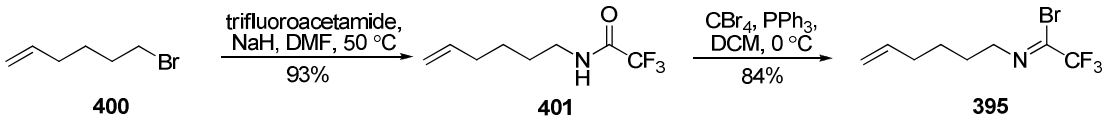
The synthesis of bromide **395** started with reduction of the nitrile **398** to afford the primary amine **399** in good yield (Scheme 99). Unfortunately, attempted formation of the trifluoroacetimidoyl bromide **395** using Uneyama's protocol[130] did not lead to the desired product.



Scheme 99

[130] Tamura, K.; Mizukami, H.; Maeda, K.; Watanabe, H.; Uneyama, K. *J. Org. Chem.* **1993**, *58*, 32–35

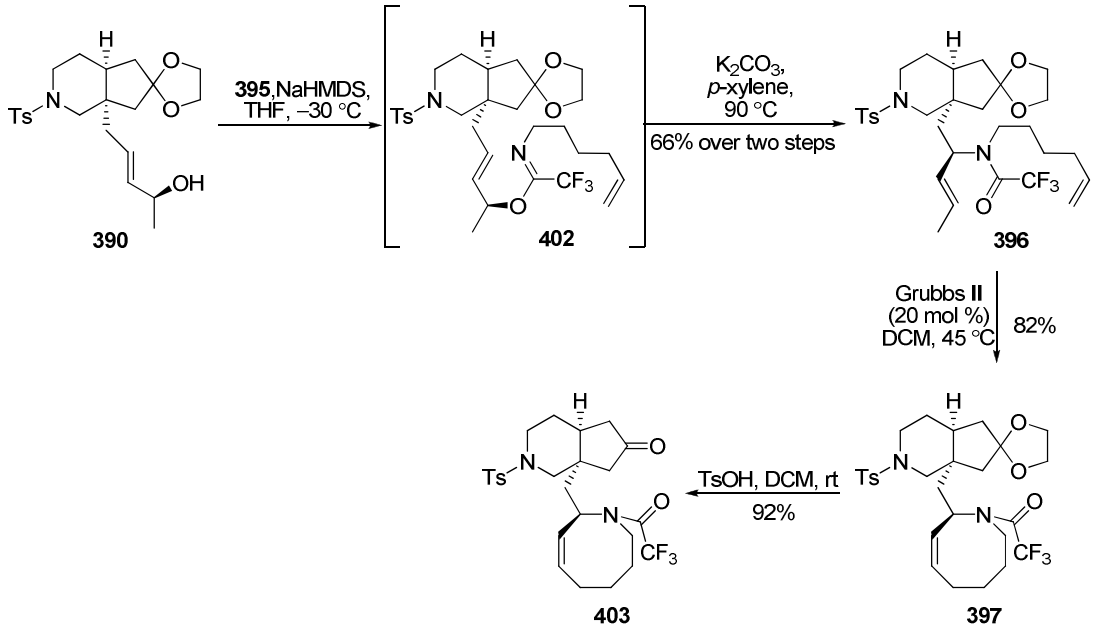
As an alternate, nucleophilic attack of trifluoroacetamide onto 6-bromo-1-hexene was investigated. This reaction delivered the amide **401** in quantitative yield and the compound was then converted into the target compound **395** by treatment with tetrabromomethane and triphenylphosphine (Scheme 100). Due to the instability of the bromide **395**, this compound was employed directly in the next reaction after filteration of the reaction mixture through a short pad of silica.



400 401 395

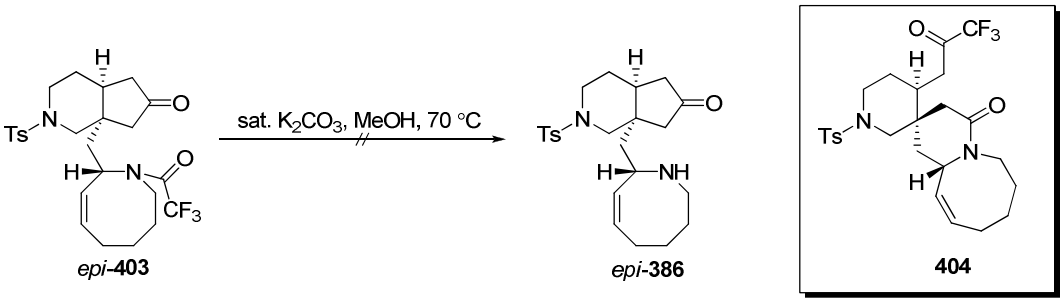
Scheme 100

With the allylic alcohol **390** and the trifluoroacetimidoyl bromide **395** in hand, the coupling of these two fragments could be explored. Nucleophilic substitution of the bromide **395** with the alcohol **390** took place in the presence of NaHMDS. However, the trifluoroimidate **402** was found to be prone hydrolytic cleavage, regenerating the trifluoroacetamide **401** and the starting alcohol **390**, and so a one-pot imidate formation and Overman rearrangement process was necessary (Scheme 101). On the formation of the intermediate **402**, the reaction mixture was treated with K_2CO_3 in *p*-xylene and heated to 90 ° C in a sealed tube for 2 days. Thermal rearrangement led to the complete consumption of the starting material and delivered the trifluoroacetamide **396** in good yield over two steps. Treatment of the diene with 20 mol % of the Grubbs second-generation catalyst in DCM under reflux resulted in RCM, which delivered the azocine **397** in 82% yield. Subsequent acid-mediated hydrolysis of the ketal **363** provided the ketone **403** in high yield.



Scheme 101

Removal of the trifluoroacetamide group under standard conditions proved to be problematic (Scheme 102). The deprotection was first attempted on the amide *epi*-**403** which was derived in three steps from *(S)*-CBS reduction of the enone **388**. When applying typical cleavage conditions (K_2CO_3 in MeOH at reflux)[131] to the amide *epi*-**403**, the expected product was not obtained and the unexpected spiroamide **404** was formed in quantitative yield instead.

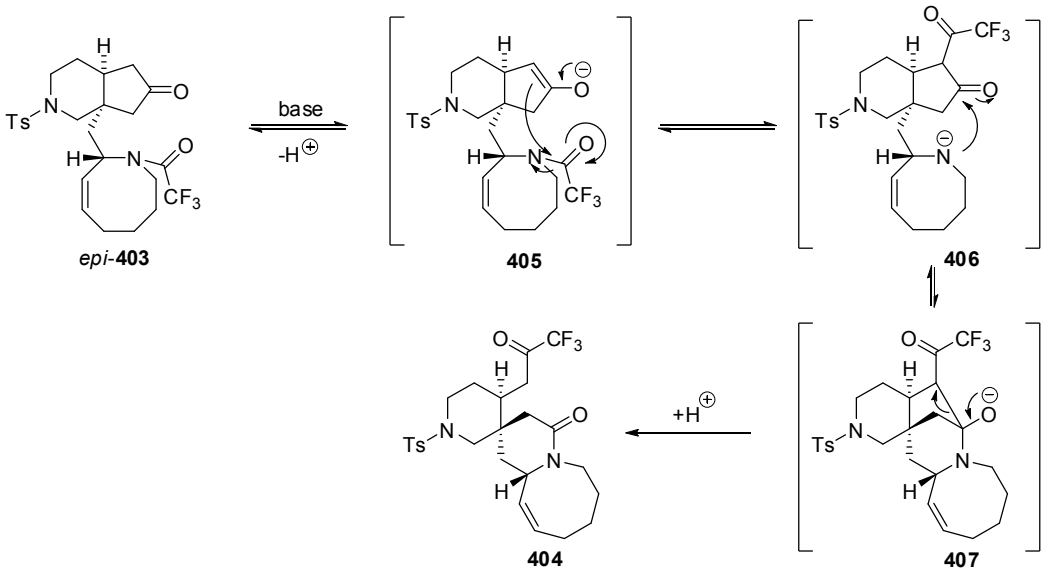


Scheme 102

The proposed mechanism for this transformation commences with a trifluoroacetyl group transfer under basic conditions from the nitrogen to the C5 position α to the carbonyl group to provide the diketone **406** (Scheme 103). The free secondary amine then participates in intramolecular nucleophilic attack of

[131] Bergerson, R. B.; McManis, J. J. *J. Org. Chem.* **1988**, *53*, 3108–3111

the ketone to afford the hemiaminal **407**, which undergoes a retro-aldol reaction to produce the δ-lactam **404**.



Scheme 103

The structure of the crystalline spiroamide **404** was elucidated by spectroscopic studies and stereochemical assignments were confirmed by single-crystal X-ray diffraction (Figure 4).

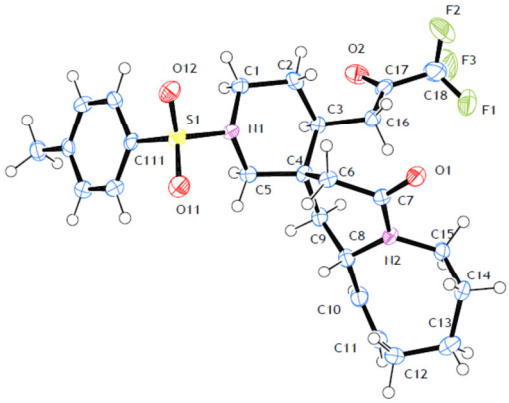
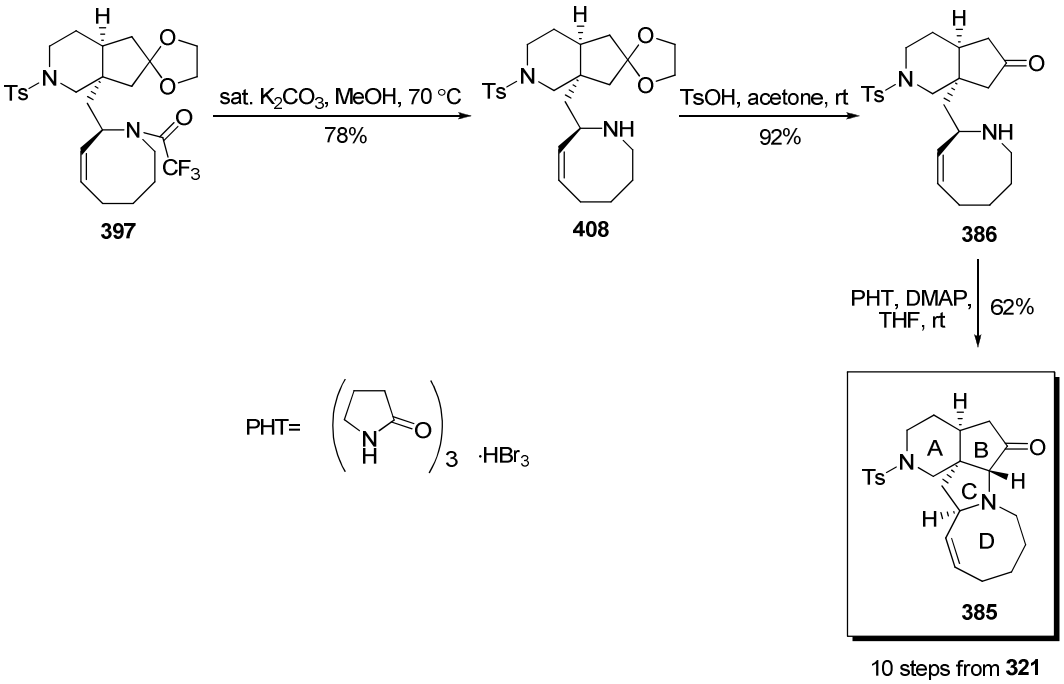


Figure 4

In order to avoid side-product formation, the deprotection sequence was reversed (Scheme 104). The trifluoroacetyl group was cleaved successfully under basic conditions in the presence of the ketal and the resulting intermediate **408** was subjected to acid hydrolysis to reveal the ketone **386** in high yield over two steps. Subsequent cyclisation employing a procedure developed by Carreira for

cyclisation of an analogous substrate[132] led to the formation of the tetracyclic ketone **385** in good yield.



Scheme 104

The structure of the tetracyclic core **385** was confirmed by spectroscopic studies and stereochemical assignments were confirmed by single-crystal X-ray diffraction (Figure 5). X-ray data showed that all four of the stereocentres required in (−)-nakadomarin A (**1**) had been installed correctly. Thus, the synthesis of the ABCD ring system had been performed in only 10 steps (longest linear sequence).

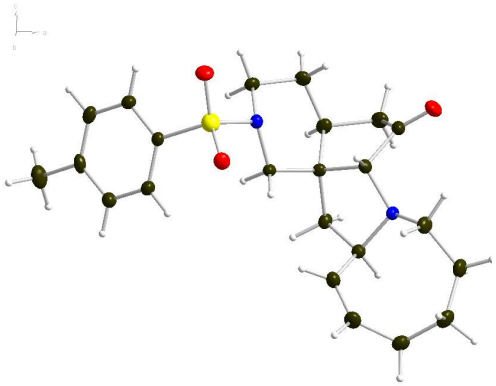
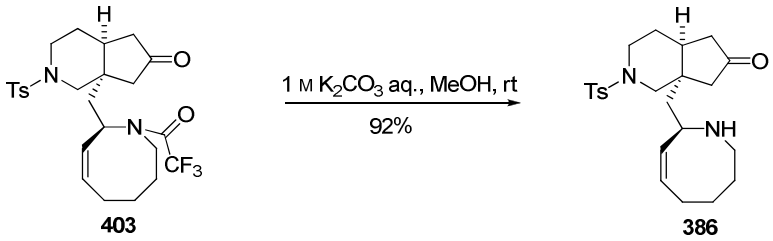


Figure 5

[132] Kreis, L. M.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2012**, *51*, 3436–3439

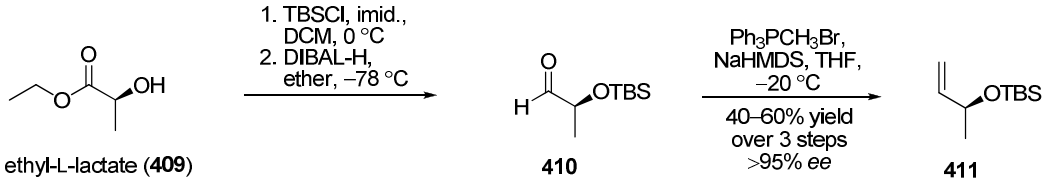
Following completion of the ABCD ring system, optimisation studies were undertaken to forge a more efficient route. The initial efforts were focused on reducing the number of protecting group manipulations. The trifluoroacetyl cleavage step, which was previously proven to be problematic with free ketone, was re-evaluated first. Careful tuning of the reaction conditions by alteration of the temperature and the concentration of the K_2CO_3 solution allowed optimisation of the reaction. The amide **403** was converted into the amine **386** in the presence of the ketone in good yield by treatment with 1 M aqueous K_2CO_3 solution in MeOH at room temperature for 2 days (Scheme 105).



403 **386**

Scheme 105

After demonstrating that ketal protection during trifluoroacetyl group cleavage was not crucial, the next challenge was to prepare the cross-metathesis partner as a single enantiomer, thereby avoiding the need for the CBS reduction of the ketone after metathesis. The silyl ether **411** was prepared from (−)-ethyl L-lactate (**409**) in good yield and excellent *ee*[133] by sequential TBS protection, partial ester reduction and Wittig olefination (Scheme 106).[134]



ethyl-L-lactate (**409**) **410** **411**

Scheme 106

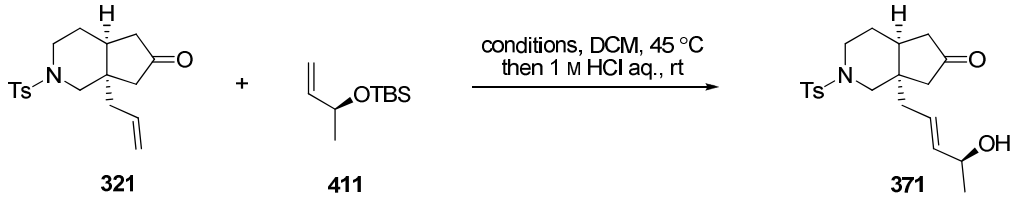
Exploration of the cross-metathesis reaction was then undertaken. The initial experiment was performed using 3 equivalents of the allylic alcohol **411** and 3

[133] Enantiomeric excess was determined by HPLC analysis of benzoyl allylic alcohol. Column Chiralpak AD-H, temperature 25 °C, hexane : (hexane: propan-2-ol [99.5: 0.5]) 90:10, flowrate 0.5 mL.min^{-1}, retention time 12.1 min.

[134] Uenishi, J.; Fujikura, Y.; Kawai, N. *Org. Lett.*, **2011**, *13*, 2350–2353

mol % of the Grubbs second-generation catalyst in DCM under reflux, providing the product **371** in 61% yield after an acidic work-up to promote the cleavage of the TBS ether (Table 6, Entry 1). Replacing the Grubbs second-generation catalyst with the Hoveyda-Grubbs second-generation catalyst resulted in a higher yield (Table 6, Entry 2), thus further optimisation studies were explored with this catalyst. The best result was obtained when the alkene **321** was treated with 4 equivalents of the allylic alcohol **411** and 5 mol % of Hoveyda-Grubbs second-generation catalyst to give the alcohol **371** in 88% yield (Table 6, Entry 4). It is also worth noting that the yield for the cross-metathesis reaction increased dramatically when the TBS ether **411** was employed as metathesis partner instead of 3-butene-2-ol. It is possible that the unprotected alcohol counterpart undergoes isomerisation in the presence of the ruthenium catalyst to generate butanone and deactivate the catalyst to the ruthenium hydride species.[135]

Table 6



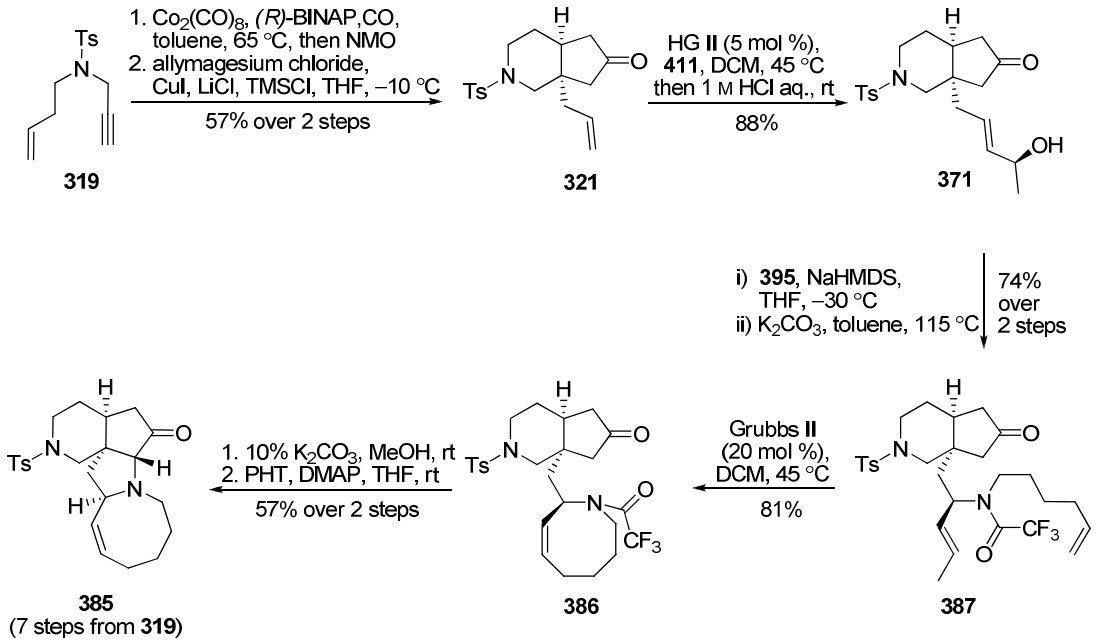
321 **411** **371**

Entry	411 (equiv.)	Catalyst	Yield (%)
1	3	G II (3 mol %)	61
2	3	HG II (3 mol %)	67
3	5	HG II (6 mol %)	86
4	**4**	**HG II (5 mol %)**	**88**

Careful consideration of the reaction sequence and optimisation of individual steps resulted in a shortened synthesis of the ABCD core of nakadomarin A (Scheme 107). The optimised strategy started with the Pauson-Khand reaction of alkyne **319** and then conjugate addition to deliver the ketone **321** in 57% yield over two steps. Subsequent cross-metathesis and Overman rearrangement

[135] Finnegan, D.; Seigal, B. A.; Snapper, M. L. *Org. Lett.* **2006**, *8*, 2603–2606

afforded the trifluoroamide **387** in good yield. It is worth noting that better result was achieved when preformed Overman rearrangement in refluxing toluene. Treatment of the diene **387** with 20 mol % of the Grubbs second-generation catalyst in DCM at reflux provided the azocine **386** in 82% yield, which underwent sequential trifluoroacetyl group removal and cyclisation to give the desired ABCD tetracyclic core **385** in only 7 steps (longest linear sequence) with good overall yield and stereoselectivity.



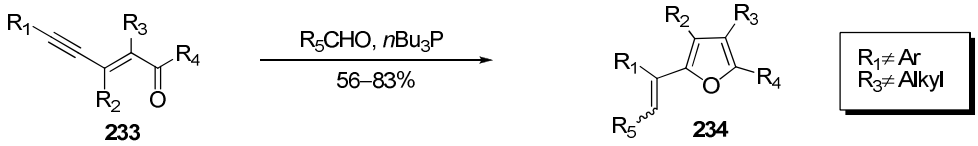
Scheme 107

2.3 Introduction of Furan E Ring to ABCD Core

Following the completion of the ABCD fragment using a concise 7-step strategy, attention was focused on installation of the furan E ring.

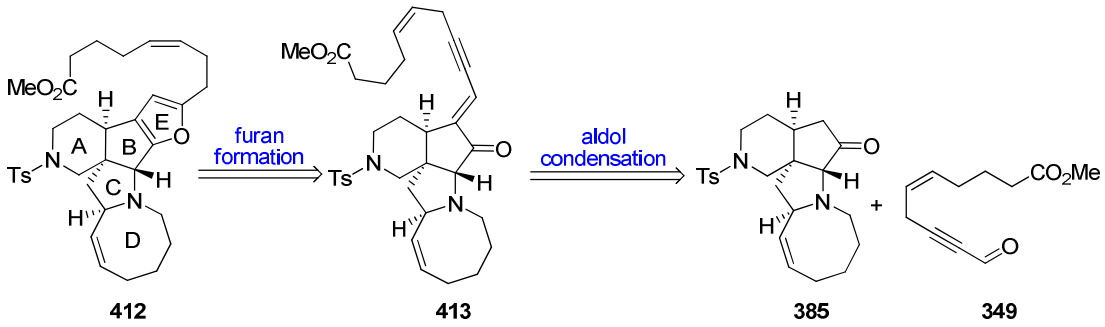
2.3.1 Phosphine-Mediated Furan Formation

The initial approach was inspired by the phosphine-initiated furan synthesis developed by Kuroda and co-workers as described in section 1.5.2.3 (Scheme 108).[79,80] It was reported that the ynenone **233** could be converted into the highly-substituted furan **234** by treatment with a stoichiometric amount of tributylphosphine and an aldehyde.



Scheme 108

The retrosynthetic analysis, incorporating Kuroda's methodology, is shown in Scheme 109. The pentacyclic core **412** could be delivered by furan formation from the ynenone **413**, which would be generated by aldol condensation between the tetracyclic ketone **385** and the propargylic aldehyde **349**.

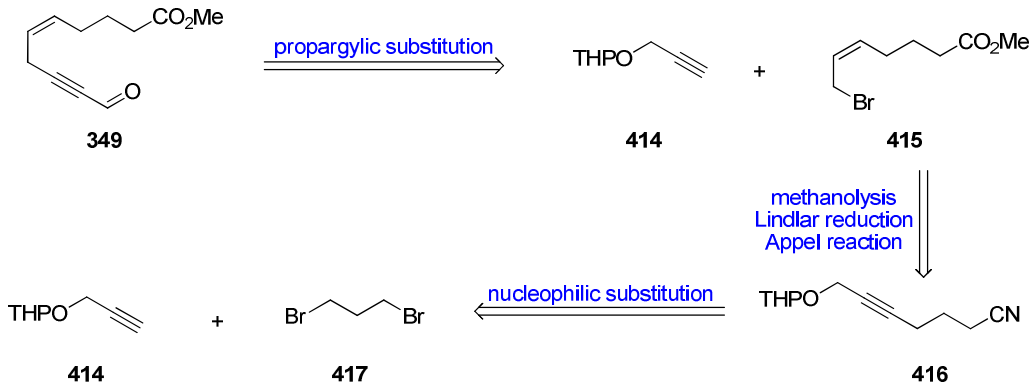


Scheme 109

[79] Kuroda, H.; Hanaki, E.; Kawakami, M. *Tetrahedron Lett.* **1999**, *40*, 3753–3756
[80] Kuroda, H.; Hanaki, E.; Izawa, H.; Kano, M.; Itahashi, H. *Tetrahedron* **2004**, *60*, 1913–1920

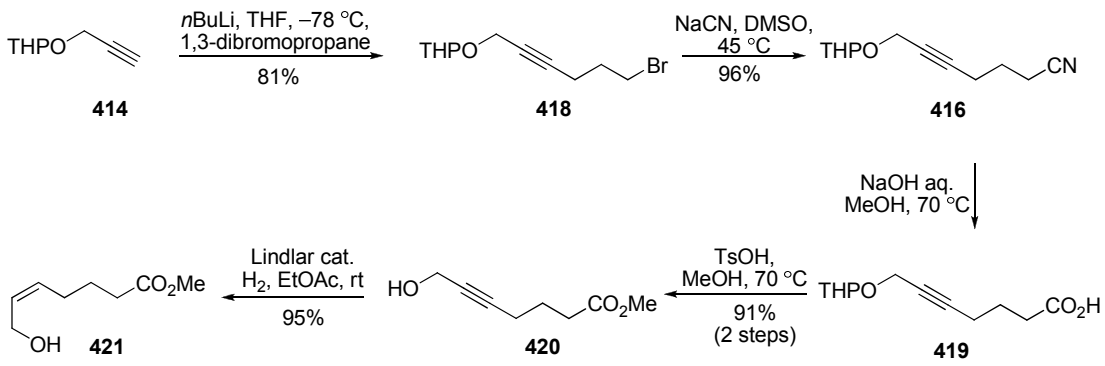
2.3.1.1 C17-C26 Side Chain Synthesis

The propargylic aldehyde **349** could be prepared by nucleophilic substitution of the allylic bromide **415** with THP protected propargyl alcohol **414**. The bromide **415** would be prepared from the alkyne **416** by Lindlar reduction and an Appel reaction (Scheme 110). Finally, nucleophilic substitution of dibromide **417** with alkyne **414** and subsequent substitution with NaCN would provide the nitrile **416**.



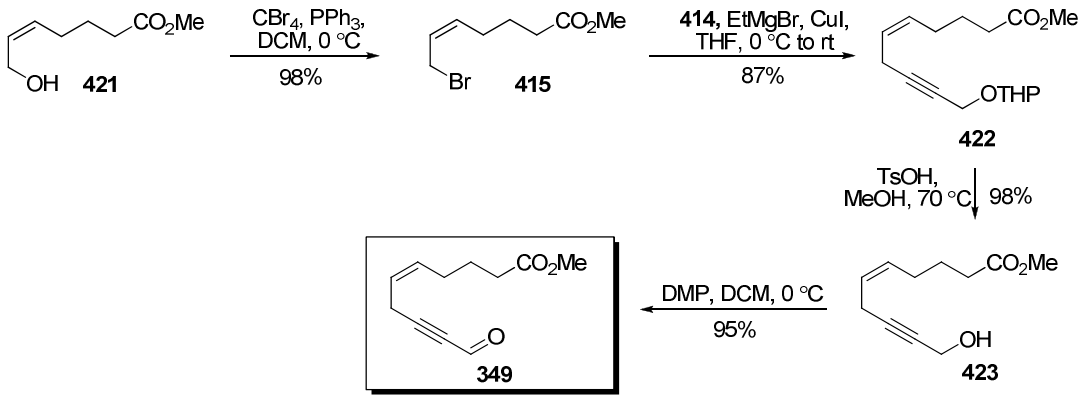
Scheme 110

The forward synthesis commenced with deprotonation of the alkyne **414** and subsequent alkylation of the anion with 1,3-dibromopropane to give the bromide **418** (Scheme 111). Pleasingly, the bromide **418** was obtained in good yield by slow addition of a stoichiometric amount of the lithiated alkyne into the solution of the 1,3-dibromopropane at −78 °C. This product was used in a second nucleophilic substitution reaction with NaCN to afford the nitrile **416**. Subsequent nitrile hydrolysis under basic conditions followed by a tandem esterification and THP cleavage sequence provided the alcohol **420** in high yield. Partial hydrogenation of the alkyne **420** using Lindlar catalyst delivered the desired allylic alcohol **421**.



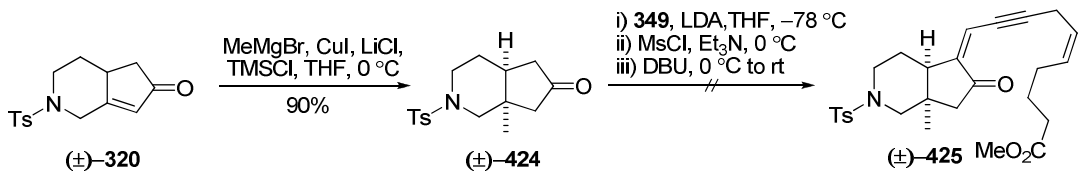
Scheme 111

The allylic alcohol **421** was converted into the bromide **415** by an Appel reaction (Scheme 112).[136] The bromide was then displaced with a copper acetylide prepared from the alkyne **414** to give the skipped enyne **422** in good yield. Subsequent THP group removal followed by oxidation with Dess-Martin periodinane provided the propargylic aldehyde **349** in good yield. Overall, the C17 to C26 side chain **349** was formed in nine high-yielding steps from readily available starting materials.



Scheme 112

Successful synthesis of the aldehyde **349** meant that the stage was set to investigate aldol condensation and furan formation reactions. The ketone **424** was synthesised for model studies by 1,4-addition of a methyl cuprate to the racemic enone **320** (Scheme 113). It was expected that the introduction of a methyl group at C2 position would allow the two α-carbonyl positions at C3 and C5 to be differentiated because of the increased steric hindrance at C3. Treatment of the ketone **424** with LDA provided an enolate, which then reacted with the aldehyde **349**. The resulting β-hydroxyketone was subjected to an one-pot mesylation and elimination sequence, but the desired ynenone **425** was not obtained and a complex mixture was formed instead.

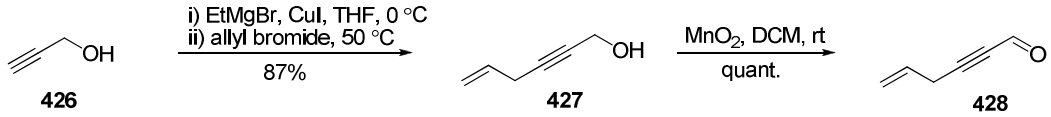


Scheme 113

[136] Appel, R. *Angew. Chem. Int. Ed.* **1975**, *14*, 801–811

2.3.1.2 Model Studies of Phosphine-Mediated Furan Formation

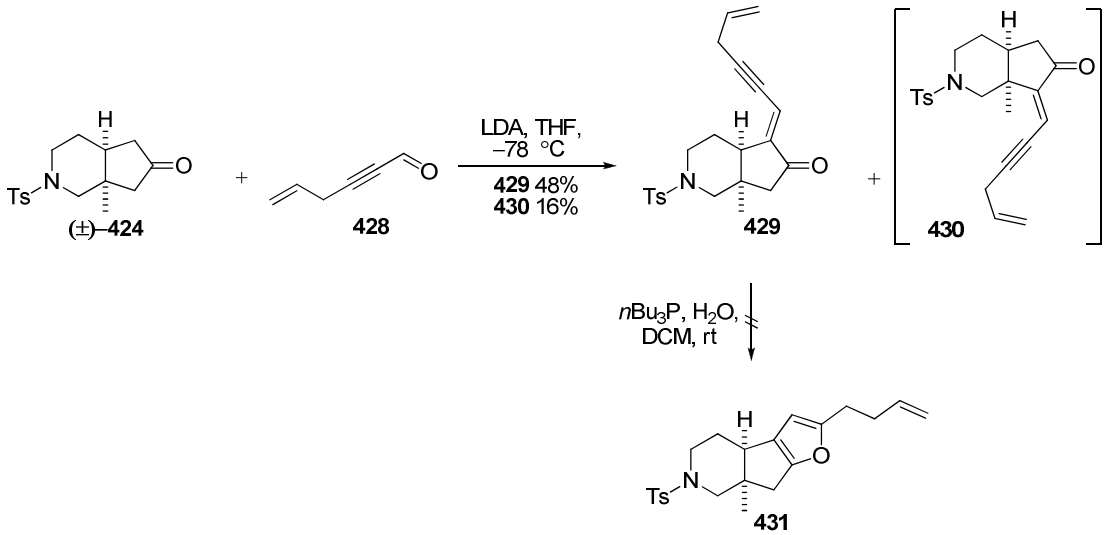
Owing to the failed attempt to install the side chain and cyclise the product to give the required furan, attention was turned to the introduction of a simpler side chain. Treatment of the propargyl alcohol **426** with a Grignard reagent and copper iodide provided a reactive copper acetylide intermediate, which on nucleophilic attack of allyl bromide afforded the alkene **427** (Scheme 114). Subsequent oxidation of the propargylic alcohol with manganese dioxide resulted in full conversion of the alcohol **427** into the desired aldehyde **428**. Due to the volatility and instability of the aldehyde **428**, it was used immediately following filtration through a short pad of Celite.



Scheme 114

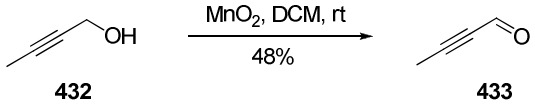
Coupling of the aldehyde **428** to the ketone **424** by aldol condensation was investigated next (Scheme 115). The enolate of ketone **424** was formed by deprotonation with LDA, and susbequent addition of the aldehyde **428** afforded a mixture of β-hydroxyketones that underwent dehydration to give the desired condensation product **429** in good yield, along with its C3 regioisomer **430**. Pleasingly, the isomers were readily separable by column chromatography. The ynenone **429** was then subjected to phosphine-mediated furan formation in the presence of a stoichiometric amount of tributylphosphine and excess water under Kuroda's conditions.[80] However, the target furan **431** was not obtained; instead, decomposition of the starting ynenone **429** was observed.

[80] Kuroda, H.; Hanaki, E.; Izawa, H.; Kano, M.; Itahashi, H. *Tetrahedron* **2004**, *60*, 1913−1920



Scheme 115

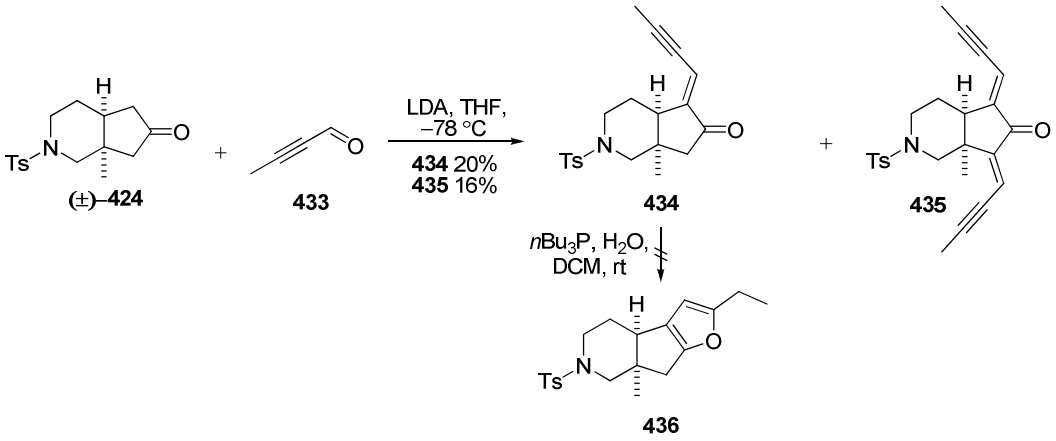
As a consequence of the failure of the ynenone **429** to undergo cyclisation, a model side chain **433** bearing a methyl substituent on the alkyne was prepared for studies of cycloisomerisation step. The propargylic aldehyde **433** was synthesised by direct oxidation of commercially available 2-butyn-1-ol (Scheme 116).[137] Owing to the very low boiling point (48–50 °C) of the aldehyde **433**, the isolated yield of this compound was modest.



Scheme 116

Aldol condensation between the ketone **424** and the aldehyde **433** gave a mixture of the desired C5 alkylation product **434** and bis-condensation product **435** in low yield (Scheme 117). Following isolation of the ynenone **434**, the phosphine-initiated cyclisation reaction was attempted employing Kuroda's conditions, unfortunately the starting material decomposed into a complex mixture of inseparable products.

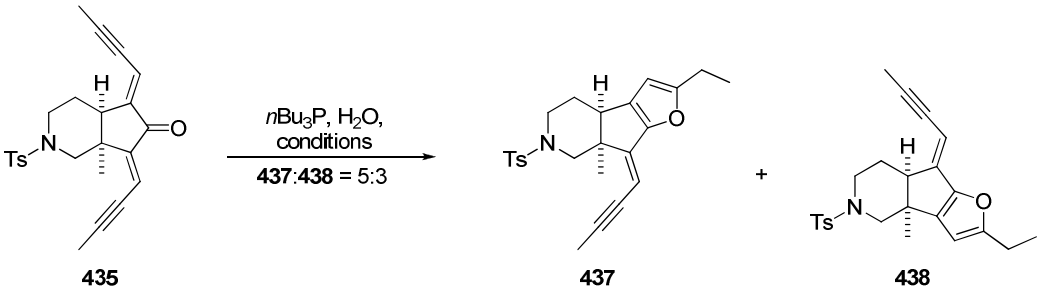
[137] Tietze, L. F.; Gericke, K. M.; Singidi, R. R.; Schuberth, I. *Org. Biomol. Chem.* **2007**, *5*, 1191–1200



Scheme 117

The by-product **435** was also used to investigate furan formation, and an initial experiment was performed following Kuroda's procedure but without success (Table 7, Entry 1). Lowering the reaction temperature to 0 °C led to the formation of furan products **437** and **438** as a separable mixture (5:3 ratio), albeit in poor yield and with formation of several by-products (Table 7, Entry 2). A slightly improved yield was obtained when the reaction was performed at a lower concentration (Table 7, Entry 3). It was proposed the low solubility of water in DCM was responsible for the formation of dimeric by-products. Hence, the ynenone **435** was converted into furans **437** and **438** in good yield when the reaction was peformed in THF (Table 7, entry 4).

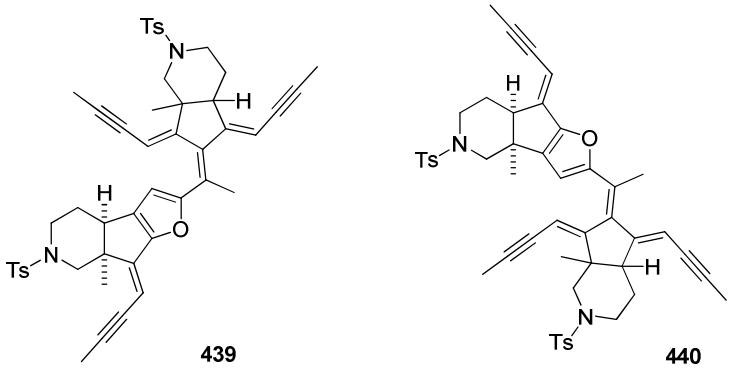
Table 7



435 437 438

Entry	Solvent	Concentration (mM)	T (˚C)	Yield (437+438)
1	DCM	25	rt	0%
2	DCM	25	0	31%
3	DCM	2.5	0	43%
4	**THF**	**2.5**	**0**	**80%**

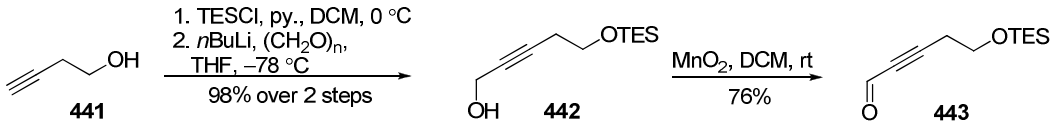
After careful NMR studies, it was found that the by-products such as **439** and **440** were generated from a Wittig reaction between the phosphonium ylide intermediate and the starting enone **435** (Scheme 118). This was further confirmed by mass spectrometry.



439 440

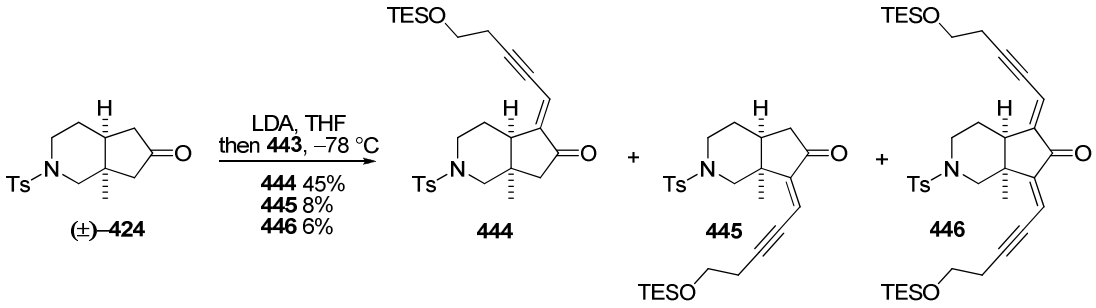
Scheme 118

Due to the promising results obtained during furan formation studies on the model system **435**, the modified side chain **443** was chosen because it could be further converted into the alkene required for a subsequent RCM reaction. The aldehyde **443** was prepared from 3-butyn-1-ol using a similar 3-step sequence to that described previously (Scheme 119).



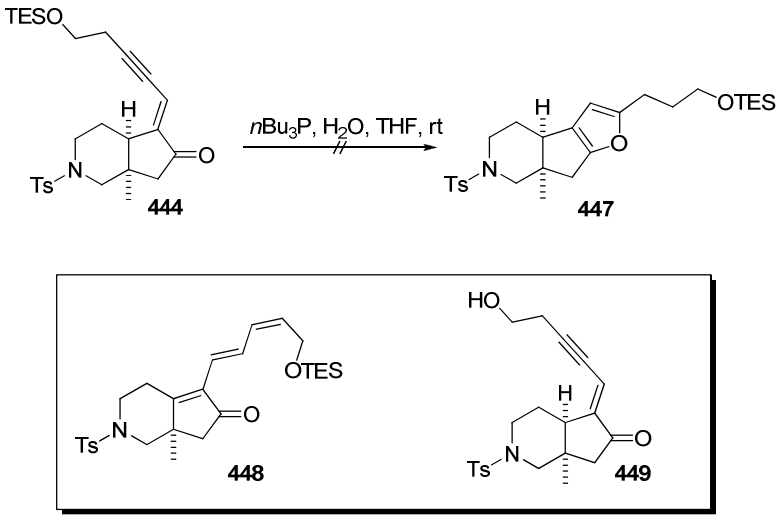
Scheme 119

Aldol condensation between the ketone **424** and the aldehyde **443** delivered the ynenone **444** in moderate yield along with a trace amount of the C3 regioisomeric compound **445** and bis-condensation product **446**, which were readily separable by column chromatography (Scheme 120).



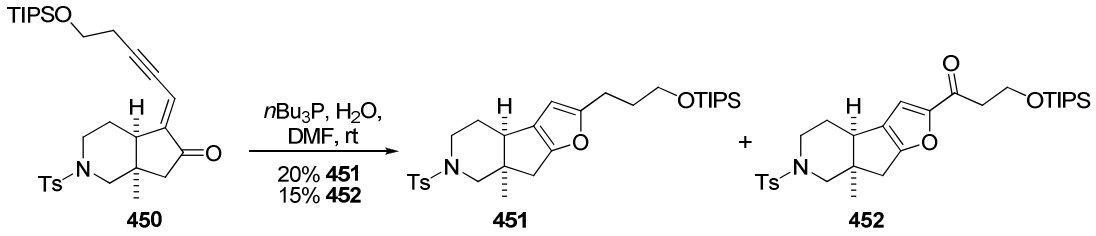
Scheme 120

With ynenone **444** in hand, furan formation was attempted under the optimised conditions described previously (Scheme 121), disappointingly, the furan product **447** was not obtained. Instead, the highly conjugated enone **448**, resulting from isomerisation of the starting material, was isolated in 37% yield along with 20% of the desilyated starting material **449**.



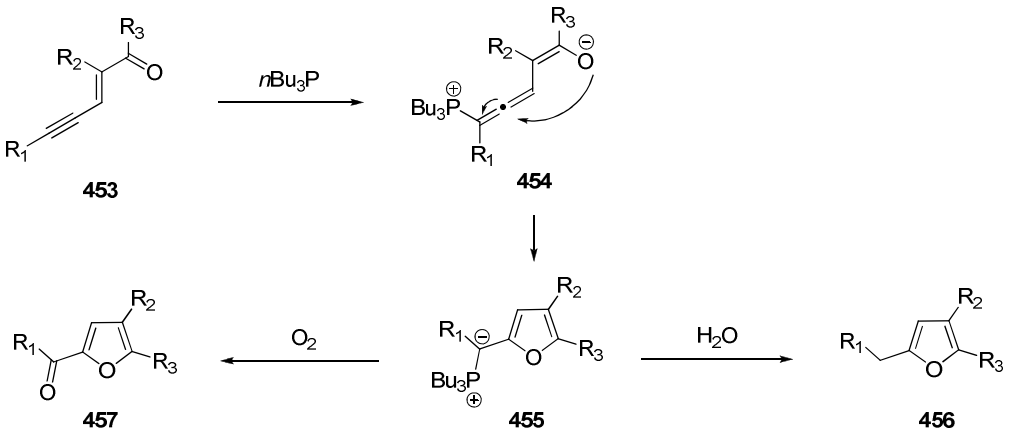
Scheme 121

The recovered alcohol **449** was reprotected as TIPS silyl ether **450** and this compound was subjected to furan-forming cyclisation reaction (Scheme 122). DMF was employed as a water miscible solvent to replace THF in this case. Pleasingly the desired furan **451** was obtained but in low yield (20%) along with a by-product. The two compounds could be separated and careful NMR analysis revealed that the by-product was in fact the 2-acyl furan **452**, the structure of which was further confirmed by mass spectrometry.



Scheme 122

Based on Kuroda's paper, the furan formation mechanism proceeds through a phosphine-initiated 1,6-addition to the ynenone **453** (Scheme 123), followed by the nucleophilic cyclisation of the allene intermediate **454** to afford the phosphonium ylide **455**. Subsequent quenching of the reaction with water leads to the formation of the furan **456**, and the by-product 2-acyl furan **457** is produced by reaction of the ylide **455** with oxygen present in the system.

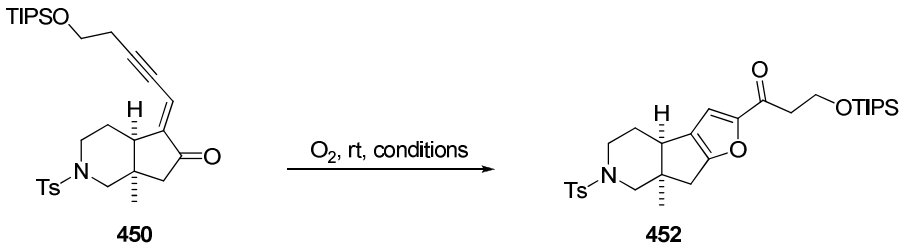


Scheme 123

This proposed cause for the generation of 2-acyl furans was further confirmed by the outcome of a reaction performed under an oxygen atmosphere. Pleasingly, the desired product **452** was obtained in excellent yield (Table 8, Entry 1). Moreover, it was found that changing solvent from DMF to DCM didn't affect the

outcome of the reaction (Table 8, Entry 2). Formation of the 2-carbonyl furan **452** was not observed when tributylphosphine was replaced with either triphenylphosphine or tetrahydrothiophene (Table 8, Entry 3 and 4).

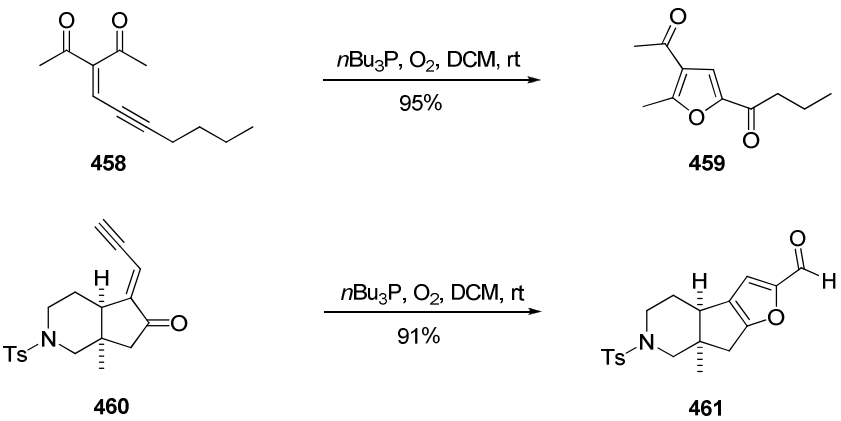
Table 8



450 **452**

Entry	Solvent	Initiator	Yield (%)
1	DMF	*n*-Bu_3P	93%
2	DCM	*n*-Bu_3P	95%
3	DCM	Ph_3P	**0%**
4	DCM	THT	0%

The scope of the reaction was expanded by performing it on the 1,3-dicarbonyl compound **458**, giving the diketone **459** in excellent yield (Scheme 124). It is worth noting that when this cyclisation reaction was performed on the terminal alkyne **460**, the furfural **461** was also obtained in high yield.



458 **459**

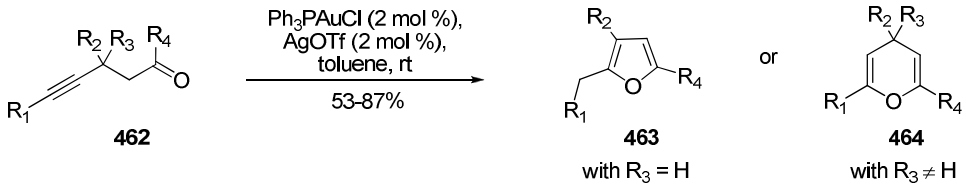
460 **461**

Scheme 124

2.3.2 Gold-Catalysed Furan Synthesis

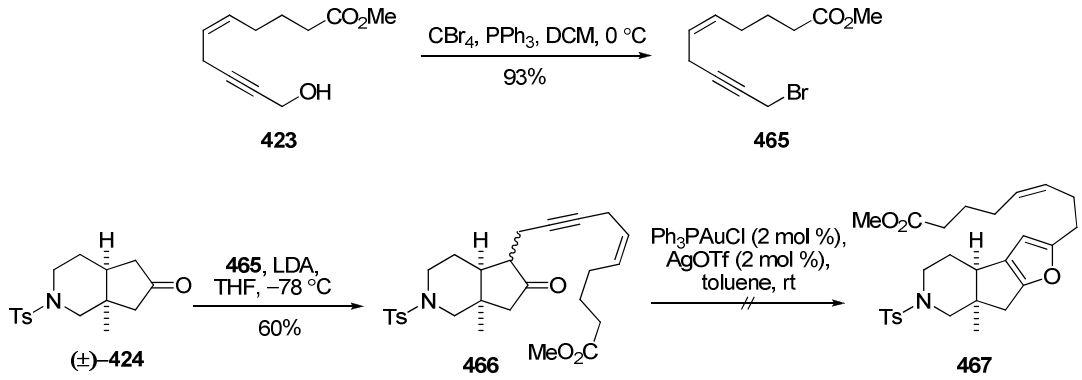
2.3.2.1 Furan Formation from Alk-4-yn-ones

As a consequence of the failure to obtain the required furan, an alternative strategy was required. In 2009, Krause and co-workers reported a gold-catalysed cycloisomerisation reaction of alk-4-yn-ones (Scheme 125).[138] Ketones of type **462** were converted into furans **463** or 4-*H*-pyrans **464** in good yield by reactions with sub-stoichiometric quantities of chloro(triphenylphosphine)gold(I) and silver(I) triflate.



Scheme 125

Inspired by Krause's work, it was proposed that this methodology could be used to install the furan E ring. The bromide **465** was synthesised by Appel reaction of the propargylic alcohol **423** in high yield (Scheme 126). The ketone **424** was deprotonated with LDA and the resulting enolate employed in a nucleophilic substitution reaction with bromide **465**, delivering the alk-4-yn-one **466** in moderate yield and as an inseparable mixture of diastereoisomers. Subsequent furan formation using Krause's protocol led only to decomposition of the starting material.

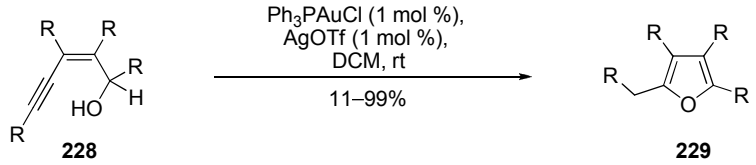


Scheme 126

[138] Belting, V.; Krause, N. *Org. Biomol. Chem.* **2009**, *7*, 1221–1225

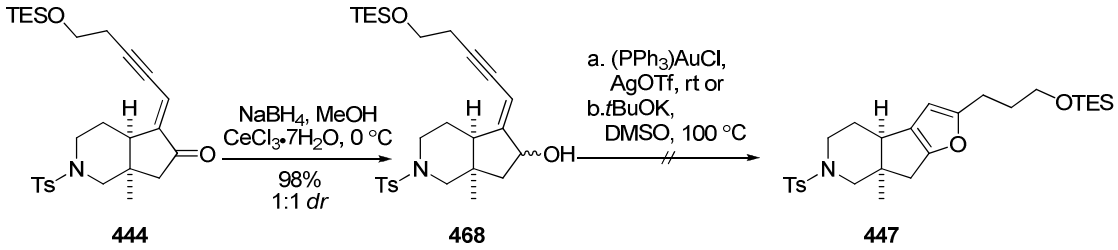
2.3.2.2 Furan Formation from 2-En-4-yn-1-ols

The failure of the gold-catalysed furan cyclisation reaction of alk-4-yn-ones led to the investigation of an alternative gold-catalysed reaction for furan formation. Liu and co-workers had reported new methodology for the synthesis of furans from 2-en-4-yn-1-ols in 2009.[73] Alcohols of type **228** were reported to undergo cycloisomerisation in the presence of a gold catalyst to deliver highly-substituted furans **229** in variable yield (Scheme 127).



Scheme 127

Inspired by this work, the ynenone **444** was reduced under Luche conditions, giving the allylic alcohol **468** as a separable mixture of diastereoisomers in good yield (Scheme 128). Further treatment with a sub-stoichiometric amount of chloro(triphenylphosphine)gold(I) and silver(I) triflate resulted in a complex mixture of products, but the desired furan was not obtained.

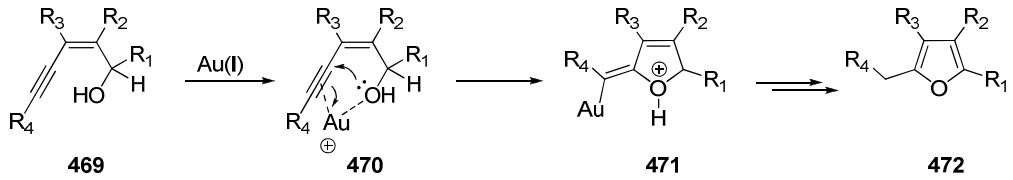


Scheme 128

One explanation of the failure of the reaction comes by considering the proposed mechanism. The reaction commences with the coordination of gold(I) catalyst to both hydroxyl group and alkyne moiety (Scheme 129). Subsequent nucleophilic attack of oxygen long-pair onto the Lewis acid activated alkyne gives the oxonium ion **471**, which further isomerises to afford the desired furan. It should be noted that the coordination of gold catalyst to substrate in order to

[73] Du, X.; Song, F.; Lu, Y.; Chen, H.; Liu, Y. *Tetrahedron* **2009**, *65*, 1839−1845

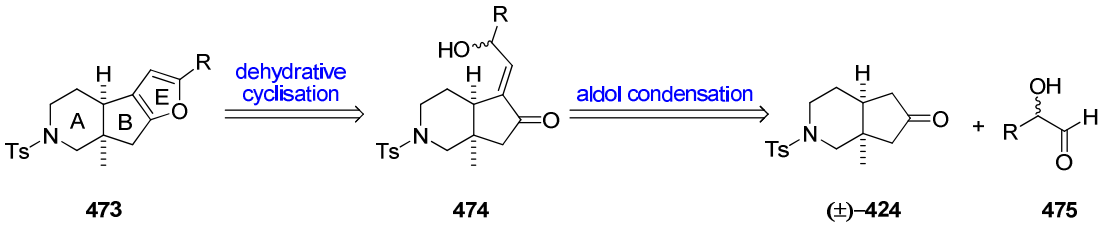
facilitate cyclisation is not possible with the *E*-isomer, which is found in the alcohol **468**.



Scheme 129

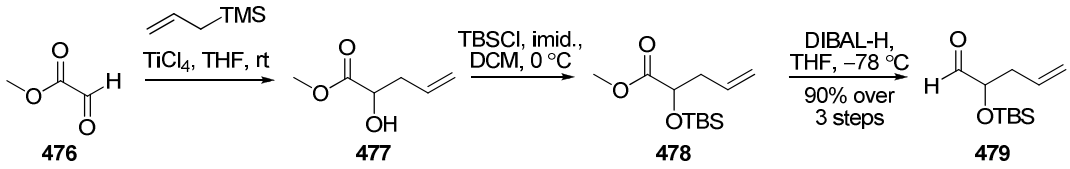
2.3.3 Acid-Catalysed Furan Formation

Undeterred by the disappointing failures of the phosphine and gold mediated cyclisation reactions, we decided to employ a dehydrative cyclisation strategy similar to that described in Mukai's formal total synthesis of nakadomarin A (Section 1.3.5, Scheme 20).[23] The revised strategy to install the furan E ring is illustrated in Scheme 130. It was anticipated that the furan **473** would be prepared from the hydroxyenone **474** through acid-catalysed dehydration. The intermediate **474** would, in turn, be obtained by using aldol condensation chemistry developed previously for the ketone **424**.



Scheme 130

Investigation of the new approach started with the synthesis of a model system. Methyl glyoxylate (**476**) underwent Hosomi-Sakurai allylation[139] to provide the alcohol **477** in quantitative yield (Scheme 131). Sequential TBS protection of the secondary alcohol and partial reduction of the methyl ester with DIBAL-H afforded the aldehyde **479**.

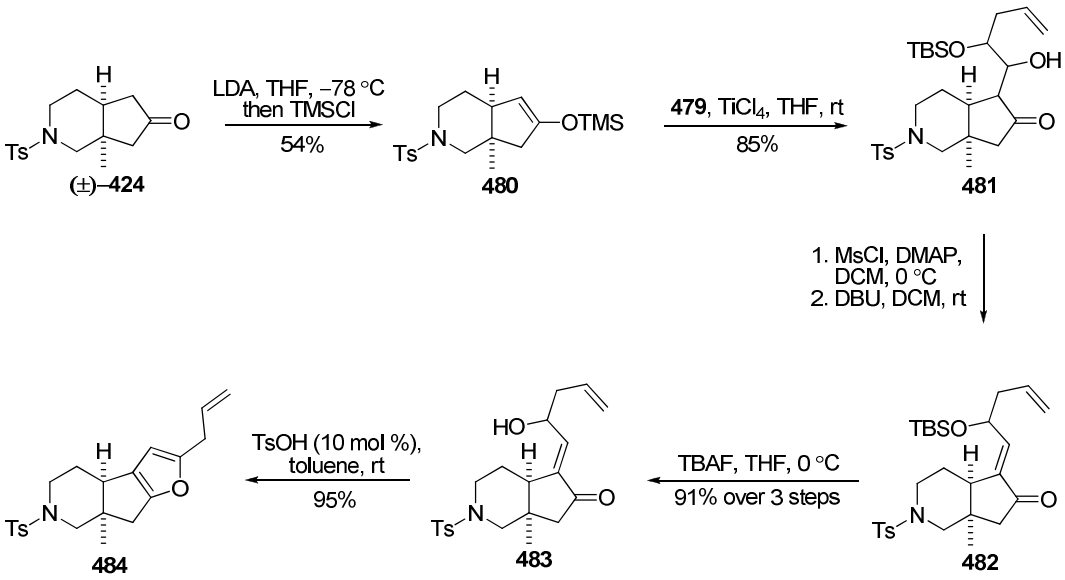


Scheme 131

Due to the unsatisfactory regioselectivity of aldol reaction, as demonstrated previously (Section 2.3.1.2, Scheme 112), a Mukaiyama aldol reaction[140] was employed to improve the regioselectivity. The ketone **424** was converted into

[23] Inagaki, F.; Kinebuchi, M.; Miyakoshi, N.; Mukai, C. *Org. Lett.* **2010**, *12*, 1800−1803
[139] Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, *17*, 1295–1298
[140] Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, *2*, 1011–1014

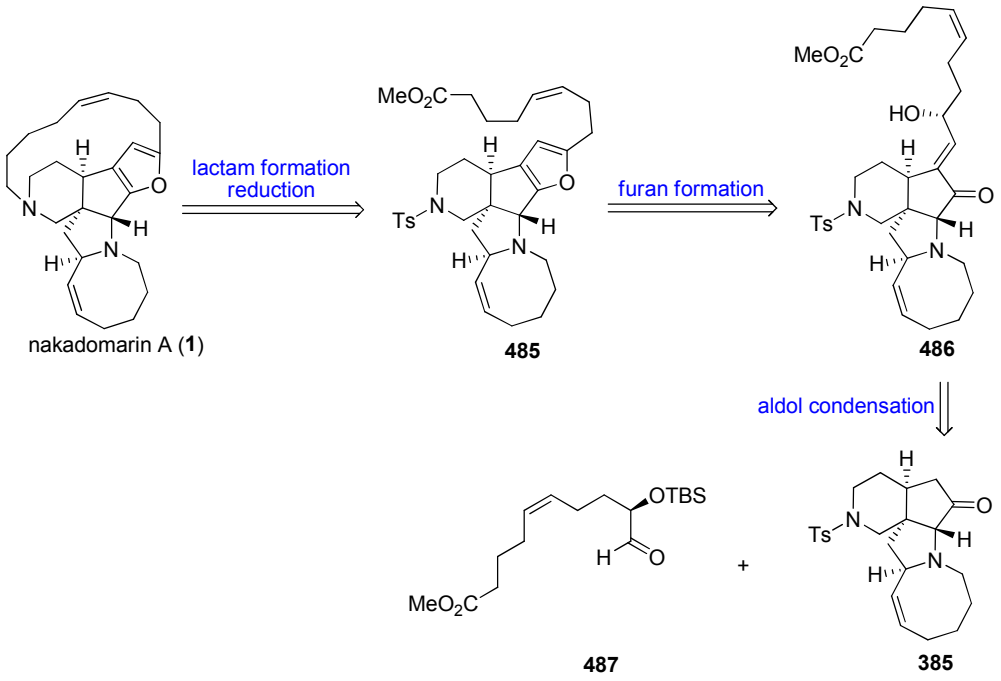
the TMS-enol ether **480** in moderate yield by treatment with LDA and TMSCl. The silyl enol ether was then subjected to Mukaiyama aldol condensation with the aldehyde **479**, in the presence of $TiCl_4$, to deliver the β-hydroxyketone **481** in good yield (Scheme 132). Sequential mesylate formation and elimination furnished the enone **482**, which was deprotected to give the secondary alcohol **483** in 91% yield over 3 steps. Finally, the furan **484** was formed in high yield by treatment of α-hydroxyenone **483** with sub-stoichiometric amount of *p*-toluenesulfonic acid.



Scheme 132

2.4 Fragment Coupling and 15-Membered Macrocycle Formation

After successful installation of the furan E ring on the model substrate **484**, the next challenge was to apply this protocol to the synthesis of the ABCD tetracyclic core **385**. The initial strategy was based on coupling of the ABCD fragment **385** with C17-C26 side chain **487**. The retrosynthetic analysis commenced with macrolactam formation from ester **485** and reduction of the resulting amide, which would deliver the final target (−)-nakadomarin A (Scheme 133). The furan **485** could be generated by acid-catalysed cyclisation of the alcohol **486**, while the enone of **486** would be derived from an aldol condensation reaction between the tetracyclic ketone **385** and the aldehyde **487**.

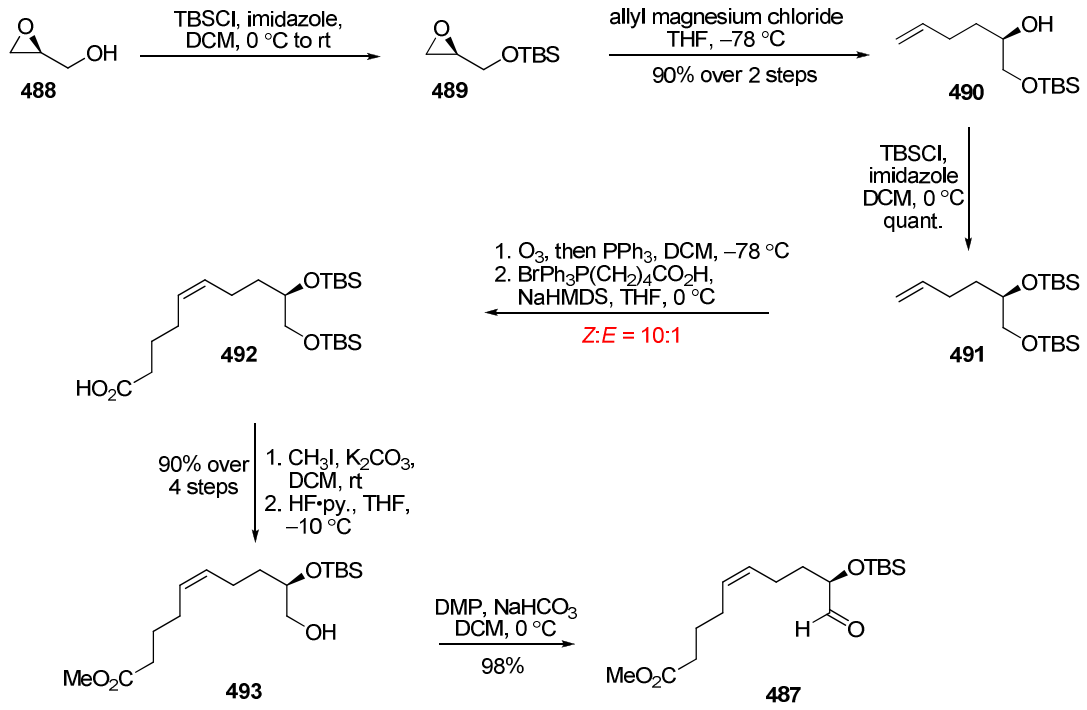


Scheme 133

2.4.1 Synthesis of C17-C26 Fragment

2.4.1.1 First-Generation Synthesis: Ozonolysis and Wittig Olefination

The initial sequence used to prepare the side chain **487** started with TBS protection of (*S*)-glycidol (**488**), followed by ring opening of the epoxide with an allyl Grignard reagent to provide the alcohol **490** in high yield over two steps (Scheme 134).[141] Sequential TBS protection, ozonolysis and Wittig olefination afforded the alkene **492** as a mixture of inseparable alkene isomers (*Z*:*E* = 10:1). The acid **492** was then converted into its methyl ester and subjected to selective deprotection of the primary hydroxyl group by treatment with HF•pyridine complex, giving the alcohol **493** in excellent yield. Finally, Dess-Martin periodinane oxidation delivered the required side chain **487**. Unfortunately, the desired *Z*-alkene isomer could not be separated from the unwanted *E*-isomer at any stage during this synthesis.

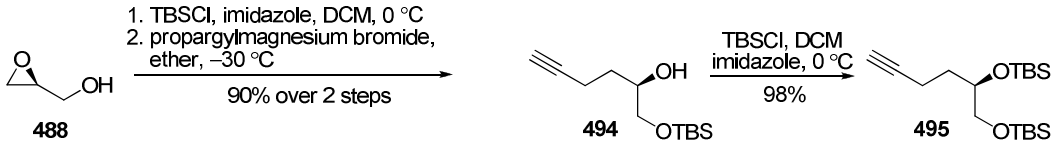


Scheme 134

[141] Florence, G. J.; Morris, J. C.; Murray, R. G.; Osler, J. D.; Reddy, V. R.; Smith, T. K. *Org. Lett.* **2011**, *13*, 514-517

2.4.1.2 Second-Generation Synthesis: Sonogashira Coupling

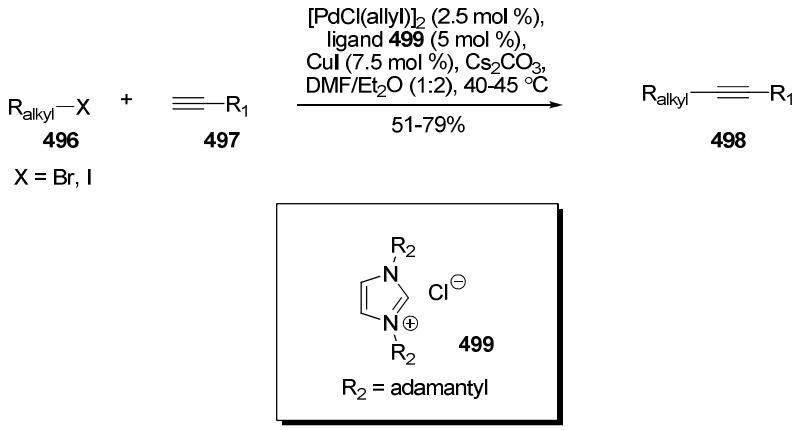
As a result of the unsatisfactory stereoselectivity during Wittig olefination, a sequence involving Sonogashira coupling and Lindlar reduction was explored to circumvent the problem (Scheme 135). The alkyne **495** was accessed in 3 steps in good yield from (*S*)-glycidol **488** using a similar strategy to that employed previously; the remaining requisite functionality was to be installed by Pd-catalysed cross-coupling methodology.



Scheme 135

Despite numerous modifications to the reaction since its discovery by Sonogashira and co-workers in 1975,[142] few examples have been published describing the coupling between terminal alkynes and alkyl halides.[143,144,145,146] Indeed, alkyl electrophiles are usually problematic substrates for the reaction because of their low reactivity as well as a tendency to undergo a β-hydride elimination side reaction. In 2003, Fu and co-workers published the first application of Sonogashira cross-coupling of terminal alkynes **497** with alkyl electrophiles **496** (Scheme 136). Moderate to good yields were obtained in most cases when the NHC precursor **499** was employed as a ligand. However, due to the instability of the reactive catalyst, it was necessary to perform the reaction in a glove box, thus severely limiting its application.

[142] Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470
[143] Eckhardt, M.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 13642–13643
[144] Altenhoff, G.; Wurtz, S.; Glorius, F. *Tetrahedron Lett.* **2006**, *47*, 2925−2928
[145] Vechorkin, O.; Barmaz, D.; Proust, V.; Hu, X. L. *J. Am. Chem.Soc.* **2009**, *131*, 12078−12079
[146] Yi, J.; Lu, X.; Sun, Y. Y.; Xiao, B.; Liu, L. *Angew. Chem. Int. Ed.* **2013**, *52*, 12409−12413



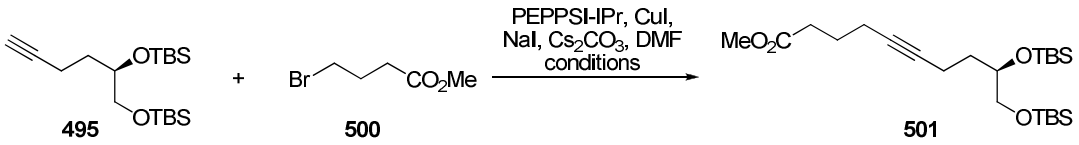
Scheme 136

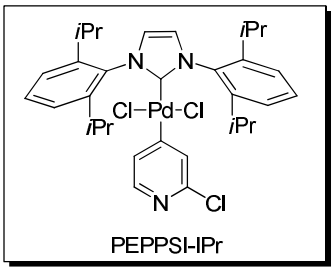
In 2005, the Organ group developed a series of Pd-NHC complexes (PEPPSI, **p**yridine-**e**nhanced **p**recatalyst **p**reparation, **s**tabilisation and **i**nitiation), which can be used to accelerate various cross-coupling reactions.[147] These catalysts feature increased stability towards air and moisture, as well as enhanced reactivity towards sp^3 carbons.

Inspired by the work of Fu and Organ, we explored the coupling of the alkyne **495** and methyl 4-bromobutyronate (**500**) in the presence of a commercially available PEPPSI catalyst. The initial attempt was performed under Fu's conditions (Table 9, Entry 1), but this reaction gave only trace amounts of the desired product **501**. On increasing the catalytic loading to 5 mol %, the desired cross-coupled product was generated in poor yield (Table 9, Entry 2). Reducing the amount of bromide and elevating the temperature to 50 ° C led to the highest conversion (Table 9, Entry 4). A higher loading of the PEPPSI catalyst (10 mol %) resulted in a slight drop in the conversion (Table 9, Entry 5) and the cross-coupled product **501** was isolated as an inseparable mixture of the product and the alkyl bromide **500**. The contaminant and the product could not be separated, so the mixture was taken on to Lindlar hydrogenation in the hope that the products could be separated at a later stage.

[147] Hadei, N.; Kantchev, E. A. B.; O'Brie, C. J.; Organ, M. G. *Org. Lett.* **2005**, *7*, 3805–3807

Table 9





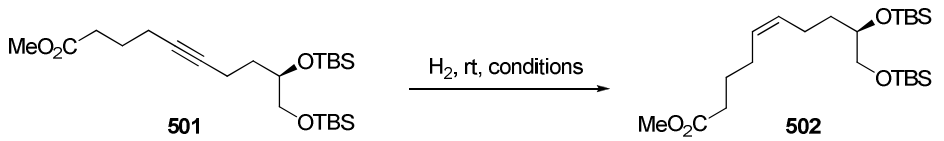
Entry	PEPPSI-IPr (mol %)	500 (equiv.)	T (°C)	Conversion (%)[a]
1	2.5	1.2	rt	trace
2	5.0	1.2	rt	11
3	5.0	0.9	rt	31
4	**5.0**	**0.9**	**50**	**66**
5	10.0	0.9	50	53

[a] Conversion based on alkyne **430**

When the hydrogenation reaction was attempted in hexane, the starting alkyne was fully recovered (Table 10, Entry 1). Changing solvent from hexane to MeOH resulted in only trace amounts of the *Z*-alkene **502** being isolated (Table 10, Entry 2). The optimal result was obtained when ethyl acetate was used as the solvent and the concentration was 0.25 M (Table 10, Entry 3). It was also found that a high catalyst loading led to the over-reduction of the starting material to the fully saturated product (Table 10, Entry 4). It was assumed that the poor yield was a result of the presence of a bromide impurity that could react with the Lindlar catalyst.[148]

[148] Coelho, A. V.; Souza, A. L. F.; Lima, P. G.; Wardell J. L.; Antunes, O. A. C. *Appl. Organometal. Chem.* **2008**, *22*, 39–42

Table 10

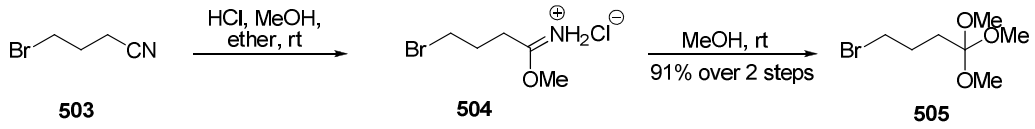


Entry	Solvent	Concentration (M)	Lindlar cat. (mol %)	Conversion (%)
1	hexane	0.05	5	0
2	MeOH	0.05	5	< 5
3	**EtOAc**	**0.25**	**5**	**41**
4	EtOAc	0.25	10	0[a]

[a] fully converted into saturated alkane by-product

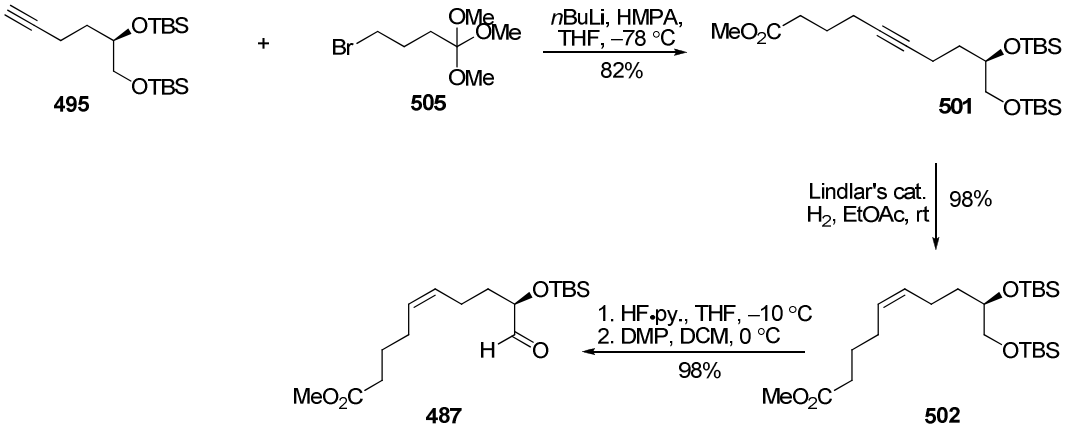
2.4.1.3 Third-Generation Synthesis: Lithium Acetylide Substitution

As a consequence of the problematic Sonogashira reaction, an alternative coupling strategy was sought. Using Taylor's procedure,[149] a new coupling partner **505** was synthesised from 4-bromobutyronitrile in high yield (Scheme 137). The trimethyl orthoformate group represents a protected ester and is stable towards alkyl lithium species.



Scheme 137

Trimethyl *ortho*-4-bromobutanoate **505** was subjected to bromide substitution with the lithium acetylide of **495**, providing the coupled product **501** in high yield (Scheme 112). Pleasingly, the alkyne **501** was readily separable from excess bromide **505** by silica gel chromatography, leading to an improved yield in the subsequent Lindlar reduction reaction. The *Z*-alkene **502** was then converted into the aldehyde **487** in two further steps using the sequence described previously (Scheme 138).

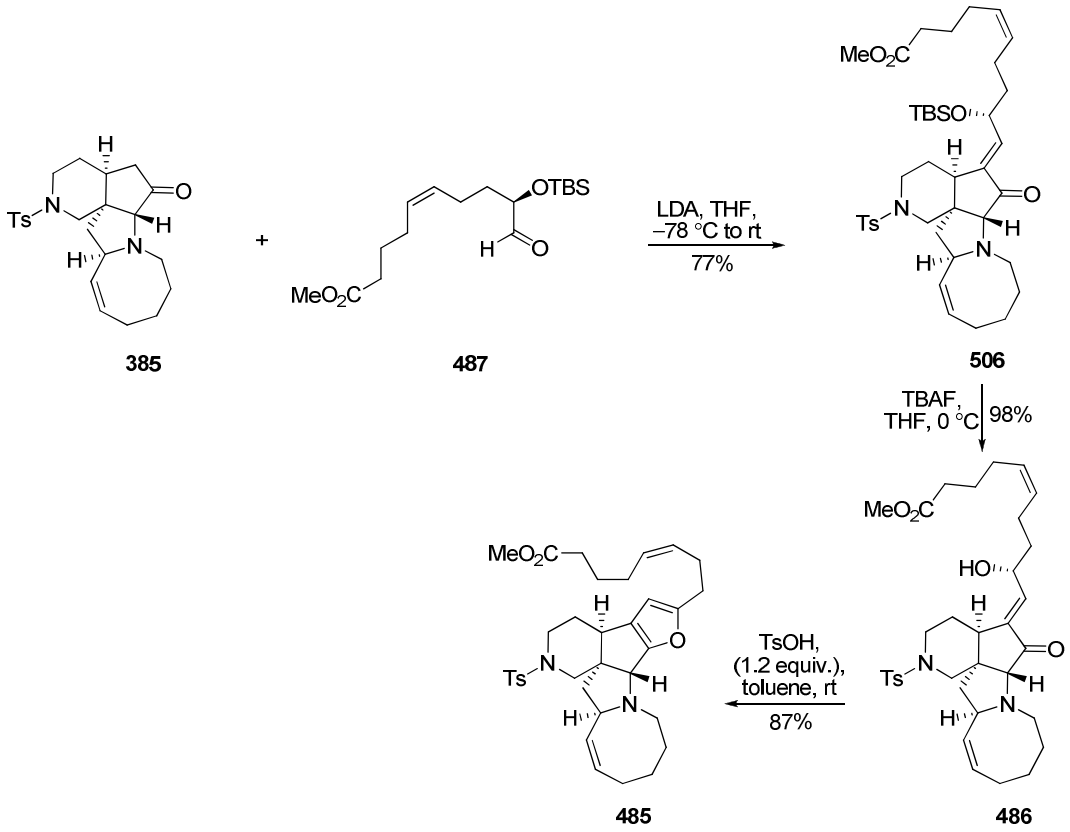


Scheme 138

[149] Casy, G.; Furber, M.; Richardson, K. A.; Stephenson, G. R.; Taylor, R. J. K. *Tetrahedron* **1986**, *42*, 5849–5956

2.4.2 Fragment Coupling and Macrolactam Formation

The successful synthesis of both the ABCD core **385** and the side chain **487** meant that the stage was set for coupling of the two fragments (Scheme 139). Regioselective enolate formation, through treatment of the ketone **385** with LDA at −78 ° C, followed by aldol condensation with the aldehyde **487** afforded the desired enone **506** in 77% yield. Cleavage of the TBS ether delivered the alcohol **486**, which underwent dehydrative cyclisation in the presence of TsOH to afford the furan **485** in good yield over two steps. It is noteworthy that 1.2 equivalents of acid were required to drive the reaction to completion due to protonation of the trialkylamine in the substrate.

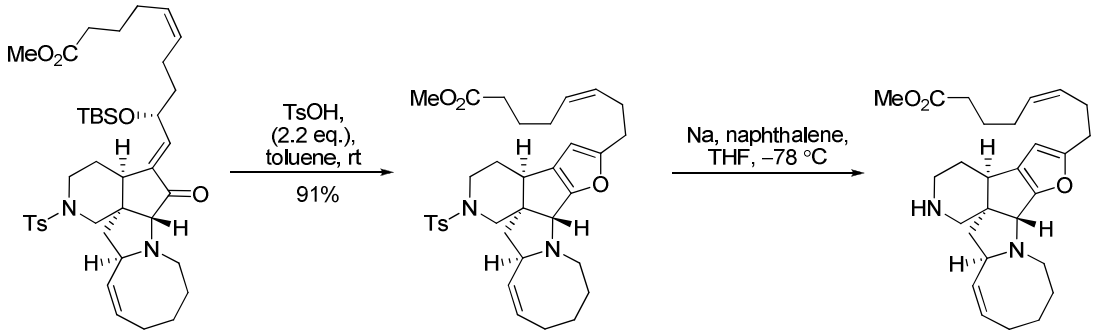


Scheme 139

TBS protecting groups can be removed under acidic conditions,[150] so direct transformation of the TBS-ether **506** to the furan **485** using excess tosic acid was investigated (Scheme 140). Pleasingly, the desired pentacyclic intermediate **485** was obtained in excellent yield and this protocol shortened the route. With the furan in place, the next challenge was the cleavage of tosyl protecting group to

[150] Thomas, E. J.; Williams, A. C. *J. Chem. Soc. Chem. Commun.* **1987**, 992–994

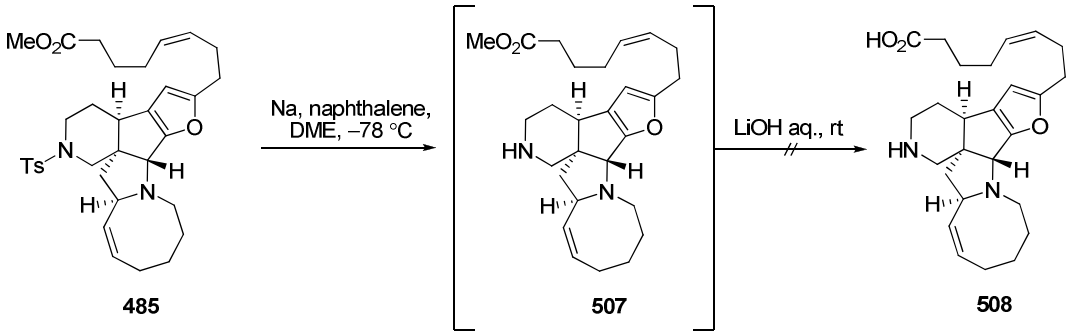
afford the piperidine substrate **507**. Treatment of the sulfonamide with a THF solution of sodium naphthalenide at −78 ° C led to rapid consumption of the starting material. However, the desired free amine was contaminated with a large amount of 1,4-butanediol generated from ring opening of THF.



506 **485** **507**

Scheme 140

Using DME as an alternative solvent successfully abolished the generation of the side-product (Scheme 141). However, subsequent purification of the product mixture was problematic as a consequence of the high polarity of the resulting amine along with its instability to light and open-atmosphere conditions. To address these problems, a one-pot sulfonamide deprotection and saponification sequence was examined. The tosyl-amine **485** was treated with sodium naphthalenide and then lithium hydroxide solution was added to cleave the ester. Unfortunately, the desired amino acid **508** was not isolated from this reaction sequence.



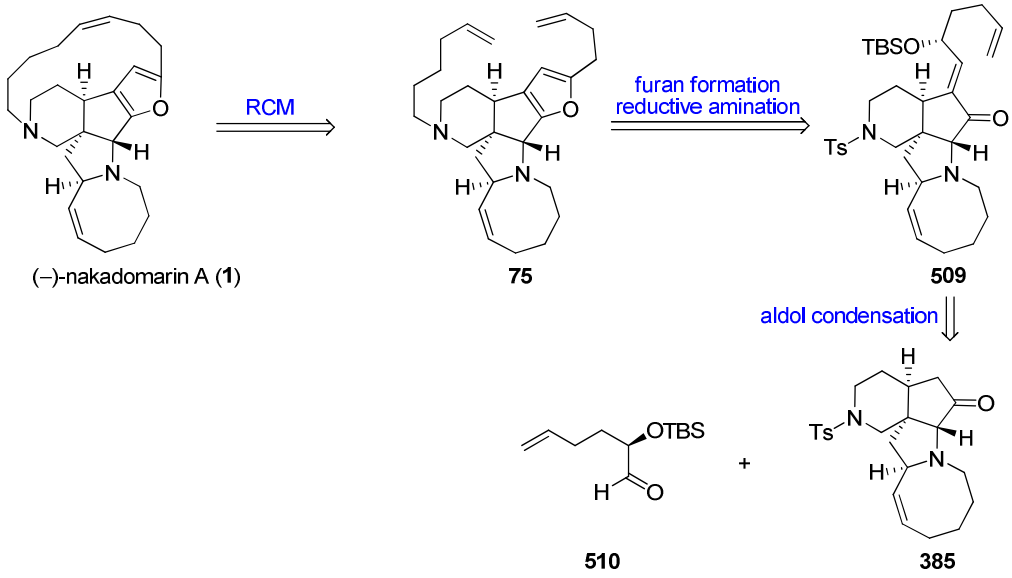
485 **507** **508**

Scheme 141

2.4.3 Fragment Coupling and Ring F Formation through Metathesis

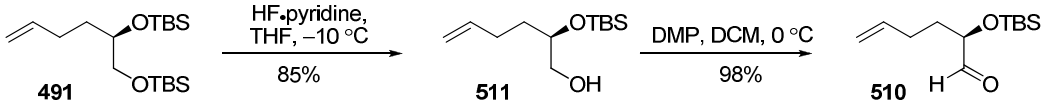
Direct installation of the complete side chain and closing the F ring through macrolactamisation was not successful and so a revised strategy was explored based on the introduction of a simple alkene chain which could be used to close the macrocycle by metathesis.

The target compound (−)-nakadomarin A (**1**) could be formed by RCM of the diene **75** (Scheme 142).[20] Acid-catalysed dehydrative furan formation, followed by sequential tosyl cleavage and reductive amination could afford the amine **75**. The enone **509** could be derived from aldol condensation between the tetracyclic ketone **385** and the aldehyde **510**.



Scheme 142

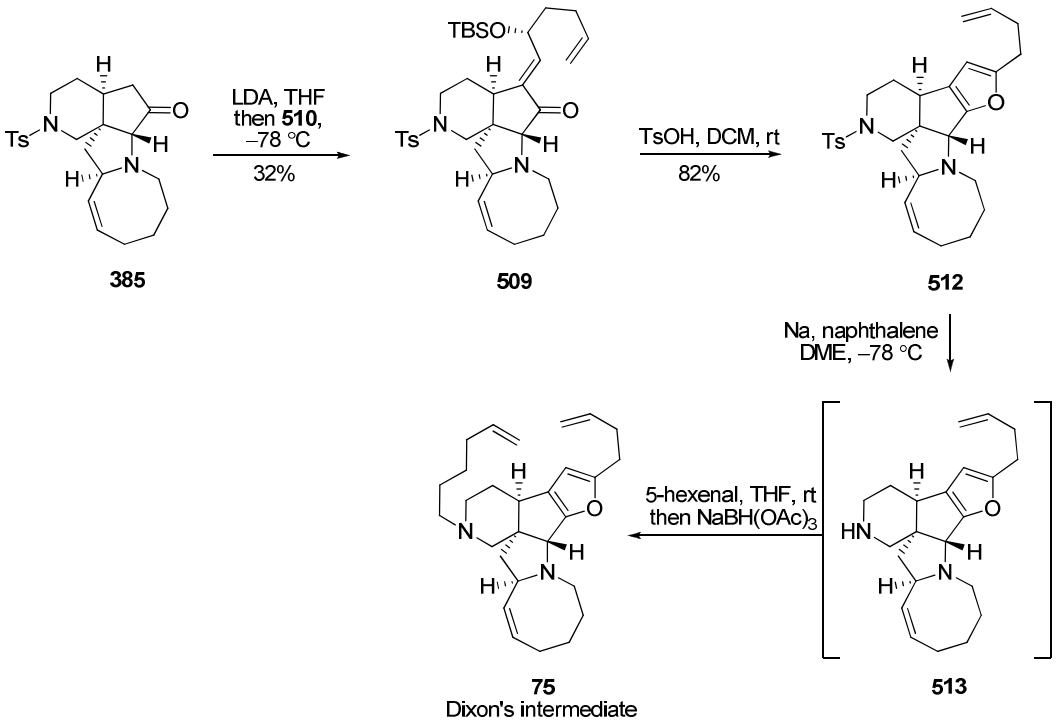
The aldehyde **510** was prepared from the protected diol **491** (synthesis described in Scheme 108) in two simple steps involving selective deprotection of the primary hydroxyl group followed by periodinane-mediated oxidation (Scheme 143).



Scheme 143

[20] Jakubec, P.; Cockfield, D. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 16632−16633

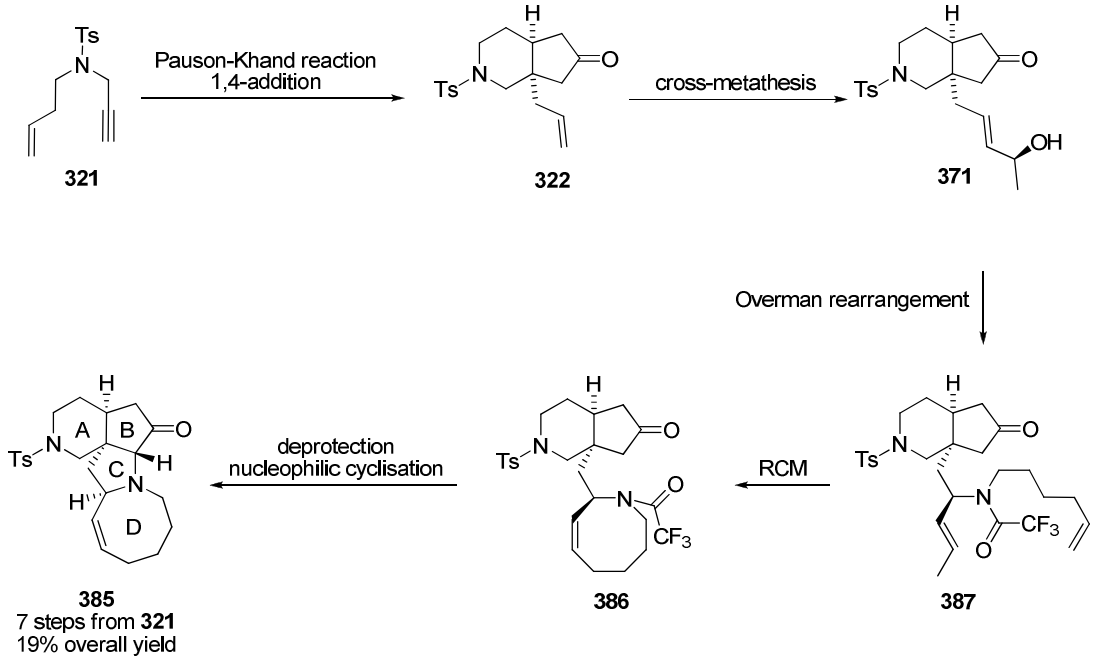
With the C17-C22 side chain **510** in hand, the familiar condensation reaction with enolate derived from the ketone **385** was undertaken to afford the enone **508** in moderate yield. Only small quantities of the ketone **385** were available at this point in the project, which meant that only a single reaction was carried out at 0.19 mmol scale (Scheme 144). The enone **508** was subjected to furan cyclisation in the presence of tosic acid to provide the furan **512** in good yield. Subsequent sulfonamide cleavage delivered the piperidine **513**, which was used directly without purification in the subsequent reductive amination reaction. The desired diene **75**, which had been prepared by Dixon during his total synthesis of nakadomarin A, was obtained but only a small amount. Unfortunately, NMR analysis failed to provide high quality spectra due to small amount of material that had been prepared. However, the mass analysis result was consistent with the formation of Dixon's intermediate **75**.



Scheme 144

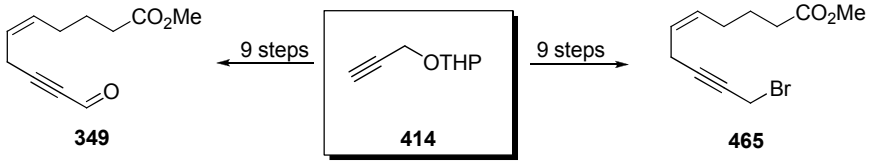
2.5 Conclusions

An efficient strategy for the total synthesis nakadomarin A and other manzamine alkaloids has been developed in which the tetracyclic ketone **385** serves as a common late-stage intermediate. The ABCD intermediate **385** was synthesised enantioselectively in 7 steps with high efficiency and overall yield (Scheme 145). The AB ring fragment was prepared stereoselectively employing an asymmetric Pauson-Khand reaction. Metathesis reactions (CM, RCM) and Overman rearrangement were employed to the construct the azocine C ring in good yield. The completion of the ABCD system was achieved by *N*-bromination and subsequent nucleophilic cyclisation.



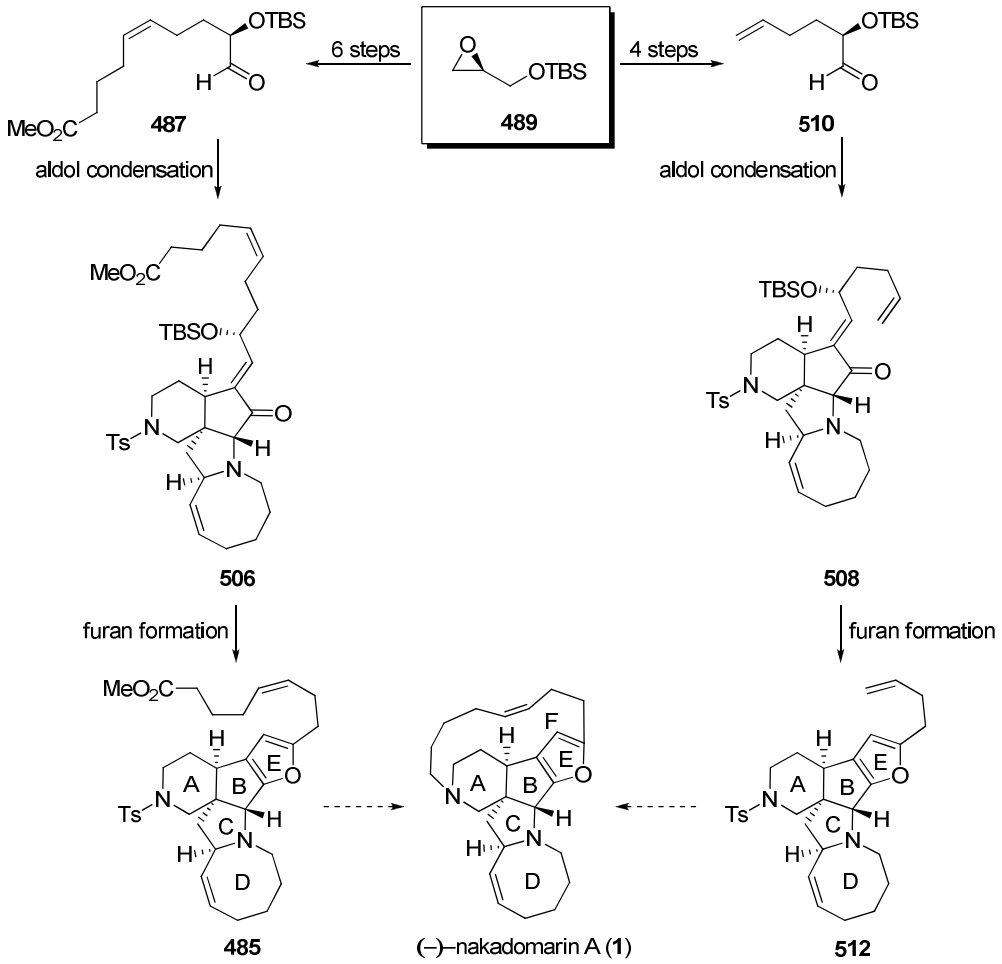
Scheme 145

The C17-C26 side chains **349** and **465** were synthesised in 9 steps from the propargylic alcohol **414** (Scheme 146). Unfortunately, further fragment coupling with the ABCD core **385** failed to deliver the desired product.



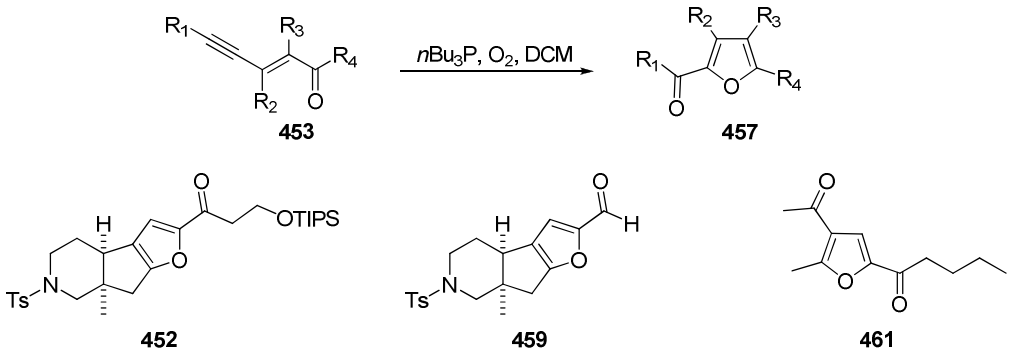
Scheme 146

The alternative side chains C17-C26 **487** and C17-C22 **510** were prepared from the epoxide **489** in 6 and 4 steps respectively (Scheme 147). Subsequent fragment coupling with the tetracyclic compound **385** through aldol condensation was successful, giving the condensation products **506** and **508**. Further installation of the furan E ring using an acid-catalysed dehydrative cyclisation reaction provided pentacyclic intermediates **485** and **512**, which could be manipulated to form the natural product in short order.



Scheme 147

Efficient methodology for the synthesis of substituted 2-acyl furans **457** by phosphine-mediated cyclisation of ynenones **453** was also developed (Scheme 148). Preliminary optimisation studies were performed using various solvents and initiators and these led to the formation of 2-acyl furans **452**, **459** and **461** in high yield.



Scheme 148

3 Experimental Section

General Reaction Conditions

Reactions involving air-sensitive reagents and dry solvents were performed in oven dried (125 °C) or flame dried glassware. These reactions were performed with the exclusion of air using an argon atmosphere.

Solvents and Reagents

Organic solvents were dried using a Pure Solv solvent purification system. Liquid reagents (DIPEA, Et_3N, $TiCl_4$, TMSCl) were distilled prior to use if needed. All reagents were purchased from commercial suppliers and used without further purification except where it is stated.

Chromatography

Column chromatography was performed under pressure using silica gel (Fluorochem LC60A, 35-70 micron or Merck Geduran Si60, 40-63 micron) as solid support and reagent-graded solvents as eluent. Petroleum ether used for column chromatography was the 40—60 °C fraction. The reactions were monitored by thin-layer chromatography (TLC) on Fisher and Merck silica gel 60 covered alumina plates.

The TLC plates were developed under UV light and/or with a $KMnO_4$ solution (3 g $KMnO_4$, 20 g K_2CO_3, 5 mL 5% NaOH aq. and 300 mL H_2O) or in an anisaldehyde solution (15 g anisaldehyde, 250 mL EtOH, 2.5 mL concentrated H_2SO_4).

Apparatus

Specific rotations of the chiral non-racemic compounds were recorded with an error ≤±0.1 using an automatic polarimeter Autopol V. The wavelength of the light was 589 nanometers.

IR spectra were recorded using a type IIa diamond single reflection element on a Shimadzu FTIR-8400S instrument. The IR spectrum of the compound was recorded directly on a thin film (liquid) or powder (solid) at ambient temperature.

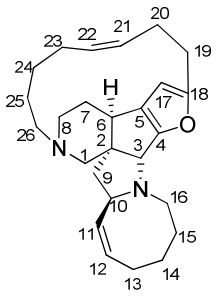
^{1}H NMR spectra were recorded on a Bruker Avance^{III} 400 MHz or Bruker Avance^{III} UltraShield 500 MHz spectrometer at ambient temperature. Data are reported as follows: chemical shift in ppm relative to $CDCl_3$ (7.26) on the δ scale, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, or a combination of these), coupling constant(s) *J* (Hz) and assignment. ^{13}C NMR spectra were recorded at 100 MHz or 126 MHz at ambient temperature. Data are reported as follows: chemical shift in ppm, relative to $CHCl_3$ (77.16) on the δ scale, and assignment.

High resolution mass spectra (HRMS) were obtained by the analytical services of the University of Glasgow on a Jeol MStation JMS-700 High Resolution Mass Spectrometer (EI, CI using isobutane) or a Bruker micro TOFq High Resolution Mass Spectrometer (ESI).

Melting points were recorded with an Electrothermal IA 9100 apparatus.

Nomenclature

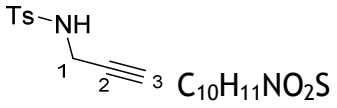
Compounds were named according to the IUPAC rules. Numbering of the carbon skeleton has been done independently according to the natural product numbering (Figure 9).



(–)-nakadomarin A (**1**)

Figure 9

4-Methyl-*N*-(prop-2-ynyl)benzenesulfonamide 319[151]



$C_{10}H_{11}NO_2S$

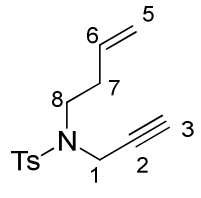
Pyridine (2.3 mL, 29 mmol) was added to a solution of *p*-toluenesulfonyl chloride (5.6 g, 29 mmol) in THF (100 mL). The solution was cooled to 0 °C and propargylamine (2.0 mL, 29 mmol) was added dropwise. The mixture was stirred for 12 h, before a 2.0 M aqueous solution of NaOH (100 mL) was added. The resulting solution was stirred for 2 h at rt and the phases were separated. The aqueous phase was then extracted with EtOAc (3 × 100 mL), and the combined organic phases were washed with brine (200 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 7:3) gave the title compound **319** (5.9 g, 94%) as a colourless solid.

R_f = 0.48 (petroleum ether: EtOAc, 8:2); m.p. 74–76 °C; ν_{max} (film) 3263, 3032, 2862, 2121, 1597, 1435, 1319, 1149 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (2H, d, *J* = 8.2 Hz, CH-Ts), 7.31 (2H, d, *J* = 8.2 Hz, CH-Ts), 4.72 (1H, br s, NH), 3.84 (2H, dd, *J* = 6.0, 2.4 Hz, CH_2-C1), 2.43 (3H, s, CH_3-Ts), 2.10 (1H, t, *J* = 2.4 Hz, CH-C3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9 (C-Ts), 136.5 (C-Ts), 129.8 (CH-Ts), 127.4 (CH-Ts), 77.9 (C-C2), 73.0 (CH-C3), 32.9 (CH_2-C1), 21.6 (CH_3-Ts); HRMS (CI, isobutane) for $C_{10}H_{12}NO_2S$ $[M+H]^+$ calcd. 210.0589, found 210.0587.

The analytical and spectroscopic data are in agreement with those reported in the literature.

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

_N_-(But-3-enyl)-4-methyl-_N_-(prop-2-ynyl)benzenesulfonamide 321[152]



$C_{14}H_{17}NO_2S$

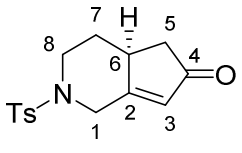
Potassium carbonate (4.4 g, 32 mmol) and 4-bromo-1-butene (3.6 mL, 32 mmol) were added to a solution of the alkyne **319** (5.5 g, 26 mmol) in acetone (150 ml) and the mixture was heated under reflux for 12 h. The reaction mixture was then cooled to rt and concentrated *in vacuo*. EtOAc (100 mL) and water (100 mL) were added and the phases were separated. The aqueous phase was extracted with EtOAc (2 × 100 mL). The combined organic phases were washed with brine (200 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 8:1) provided the title compound **321** (6.3 g, 91%) as a colourless oil.

R_f = 0.51 (petroleum ether: EtOAc, 6:1); ν_{max} (film) 3279, 3070, 2924, 2121, 1597, 1442, 1342, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (2H, d, *J* = 8.2 Hz, CH-Ts), 7.28 (2H, d, *J* = 8.2 Hz, CH-Ts), 5.75 (1H, ddt, *J* = 17.3, 10.3, 7.0 Hz, CH-C6), 5.08 (1H, dd, *J* = 17.3, 1.2 Hz, CH_2-C5), 5.06 (1H, dd, *J* = 10.3, 1.2 Hz, CH_2-C5), 4.14 (2H, d, *J* = 2.2 Hz, CH_2-C1), 3.26 (2H, t, *J* = 7.2 Hz, CH_2-C8), 2.41 (3H, s, CH_3-Ts), 2.33 (2H, td, *J* = 7.2, 7.0 Hz, CH_2-C7), 2.02 (1H, t, *J* = 2.2 Hz, CH-C3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5 (C-Ts), 135.9 (C-Ts), 134.5 (CH-C6), 129.5 (CH-Ts), 127.7 (CH-Ts), 117.3 (CH_2-C5), 76.5 (C-C2), 73.8 (CH-C3), 45.7 (CH_2-C8), 36.4 (CH_2-C1), 32.2 (CH_2-C7), 21.6 (CH_3-Ts); HRMS (CI, isobutane) for $C_{14}H_{18}NO_2S$ $[M+H]^+$ calcd. 264.1058, found 264.1054.

The analytical and spectroscopic data are in agreement with those reported in the literature.

[152] Patel, M. C.; Livinghouse, T.; Pagenkopf, B. L. *Org. Synth.* **2003**, *80*, 93−103

(*S*)-2-Tosyl-3,4,4a,5-tetrahydro-cyclopenta[c]pyridin-6-one 320[153]



$C_{15}H_{17}NO_3S$

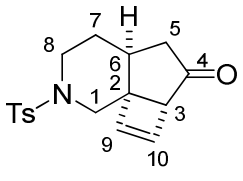
To a stirred solution of dicobalt octacarbonyl (2.3 g, 6.9 mmol) in toluene (100 mL) was added *(R)*-BINAP (4.3 g, 6.9 mmol) in one portion. The mixture was sparged with carbon monoxide for 15 min and stirred under a carbon monoxide atmosphere for 1 h at 65 °C. A solution of the alkene **321** (6.0 g, 23 mmol) in toluene (20 mL) was added dropwise to the reaction. The mixture was stirred at 65 °C for 6 h and then concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 6:4) provided the title compound **320** (4.8 g, 72%, 97% *ee*) as a pale yellow solid. Enantiomeric excess was determined by HPLC analysis of intermediate **320**. Column Chiralpak OD-H, temperature 25 °C, hexane: propan-2-ol 67:33, flowrate 0.5 mL.min^{-1}, retention time 17.2 min.

R_f = 0.18 (petroleum ether: EtOAc, 5:5); $[\alpha]_D^{28}$ −97.3 (c = 5.00, $CHCl_3$); m.p. 124−126 °C; ν_{max} (film) 2980, 2870, 1708, 1342, 1155, 788 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (2H, d, *J* = 8.0 Hz, CH-Ts), 7.34 (2H, d, *J* = 8.0 Hz, CH-Ts), 6.00 (1H, s, CH-C3), 4.72 (1H, d, *J* = 13.3 Hz, CH_2-C1), 3.97−3.94 (1H, m, CH_2-C8), 3.20 (1H, d, *J* = 13.3 Hz, CH_2-C1), 2.60−2.50 (3H, m, CH_2-C8, CH_2-C5, CH-C6), 2.44 (3H, s, CH_3-Ts), 2.13−2.10 (1H, m, CH_2-C7), 2.01 (1H, dd, *J* = 16.2, 2.7 Hz, CH_2-C5), 1.46 (1H, ddt, *J* = 12.4, 11.7, 3.6 Hz, CH_2-C7); ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.2 (C-C4), 172.2 (C-C2), 144.2 (C-Ts), 133.0 (C-Ts), 129.9 (CH-Ts), 129.2 (CH-Ts), 127.8 (CH-C3), 47.5 (CH_2-C1), 45.7 (CH_2-C8), 41.4 (CH_2-C5), 39.2 (CH-C6), 32.1 (CH_2-C7), 21.6 (CH_3-Ts); HRMS (EI) for $C_{15}H_{17}NO_3S$ $[M]^+$ calcd. 291.0929, found 291.0932.

The analytical and spectroscopic data are in agreement with those reported in the literature.

[153] Tang, Y. F.; Deng, L. J.; Zhang, Y. D.; Dong, G. B.; Chen, J. H.; Yang, Z. *Org. Lett.* **2005**, *7*, 593−595

(4a*S,6a*R**,8a*R**)-2-tosyl-1,2,3,4,4a,5-hexahydrocyclobuta[1,5]cyclopenta [1,2-c]pyridin-6-one 356**



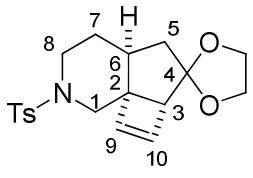
$C_{17}H_{19}NO_3S$

Trimethylsilyl acetylene (2.7 g, 25 mmol) was added to a solution of the enone **320** (2.0 g, 6.9 mmol) in acetone (150 mL). The solution was stirred and subjected to UV (125 W Hanovia mercury lamp) irradiation for 18 h and then concentrated *in vacuo*. The resulting crude silane **358** was used directly in the next step without purification.

TBAF (2.0 mL of a 1.0 M solution in THF, 2.0 mmol) was added to a solution of silane **358** (0.40 g, 1.0 mmol) in THF (50 mL). The mixture was stirred at rt for 3 h then concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 6:1) gave the title compound **356** (251 mg, 18% over 2 steps) as a colourless foam.

R_f = 0.48 (petroleum ether: EtOAc, 1:1); ν_{max} (film) 3032, 2360, 1723, 1373, 1218 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.59 (2H, d, *J* = 8.0 Hz, CH-Ts), 7.29 (2H, d, *J* = 8.0 Hz, CH-Ts), 6.22 (1H, d, *J* = 2.7 Hz, CH-C9), 6.12 (1H, dd, J = 2.7, 1.3 Hz, CH-C10), 3.80–3.64 (2H, m, CH_2-C1, CH_2-C8), 3.16 (1H, dd, *J* = 16.9, 6.6 Hz, CH_2-C5), 3.03 (1H, d, *J* = 1.3 Hz, CH-C3), 2.48 (3H, s, CH_3-Ts), 2.46–2.39 (1H, m, CH_2-C1), 2.12 (1H, m, ddd, *J* = 12.6, 11.7, 2.2 Hz, CH_2-C8), 1.92–1.70 (3H, m, CH_2-C5, CH_2-C7, CH-C6), 1.38–1.15 (1H, m, CH_2-C7); ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.0 (C-C4), 143.2 (C-Ts), 138.3 (CH-C10), 138.4 (CH-C9), 133.2 (C-Ts), 129.7 (CH-Ts), 127.7 (CH-Ts), 56.7 (CH-C3), 54.4 (C-C2), 49.9 (CH_2-C1), 45.5 (CH_2-C8), 41.9 (CH_2-C5), 31.8 (CH-C6), 29.4 (CH_2-C7), 21.6 (CH_3-Ts); HRMS (ESI) for $C_{17}H_{19}NNaO_3S$ $[M+Na]^+$ calcd. 340.0978, found 340.0983.

(4a*S,6a*R**,8a*R**)-2-tosyl-1,2,3,4,4a,5-hexahydro-spiro[cyclobuta[1,5] cyclopenta[1,2-c]pyridine-6,2'-[1,3]dioxolane] 359**

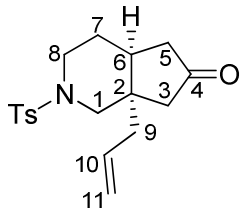


$C_{19}H_{23}NO_4S$

To a solution of the ketone **356** (0.20 g, 0.63 mmol) in dry toluene (30 mL) was added ethylene glycol (0.48 mL, 8.4 mmol), trimethyl orthoformate (0.62 mL, 6.0 mmol) and *p*-toluenesulfonic acid monohydrate (34 mg, 0.18 mmol). The mixture was heated at 55 °C for 2 h with vigorous stirring. After cooling to rt, the mixture was neutralised by addition of saturated aqueous $NaHCO_3$ solution. The phases were separated and the aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic phases were washed with brine (100 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 4:1 to 2:1) afforded the title compound **359** (216 mg, 95%) as a colourless oil.

R_f = 0.55 (petroleum ether: EtOAc, 1:1); ν_{max} (film) 3030, 2358, 1354, 1211 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.58 (2H, d, *J* = 8.0 Hz, CH-Ts), 7.25 (2H, d, *J* = 8.0 Hz, CH-Ts), 6.12 (1H, d, *J* = 2.7 Hz, CH-C9), 5.98 (1H, dd, *J* = 2.7, 1.3 Hz, CH-C10), 3.97–3.70 (5H, m, CH_2-C8, OCH_2CH_2O), 3.66 (1H, d, *J* = 11.4 Hz, CH_2-C1), 2.78 (1H, d, *J* = 1.3 Hz, CH-C3), 2.52 (1H, dd, *J* = 13.9, 6.3 Hz, CH_2-C5), 2.36 (3H, s, CH_3-Ts), 2.32 (1H, d, *J* = 11.4 Hz, CH_2-C1), 2.22–1.94 (2H, m, CH_2-C7, CH_2-C8), 1.59–1.46 (3H, m, CH_2-C5, CH_2-C7, CH-C6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.3 (C-Ts), 140.7 (CH-C10), 138.4 (CH-C9), 133.3 (C-Ts), 129.6 (CH-Ts), 127.8 (CH-Ts), 114.9 (C-C4), 64.4 (OCH_2), 64.0 (OCH_2), 56.2 (CH-C3), 56.1 (C-C2), 50.4 (CH_2-C1), 46.0 (CH_2-C8), 39.6 (CH_2-C5), 32.7 (CH-C6), 27.2 (CH_2-C7), 21.6 (CH_3-Ts); HRMS (ESI) for $C_{19}H_{23}NNaO_4S$ $[M+Na]^+$ calcd. 384.1240, found 384.1251.

(4a*S*,7a*R*)-7a-Allyl-2-tosylhexahydro-cyclopenta[c]pyridin-6-one 322

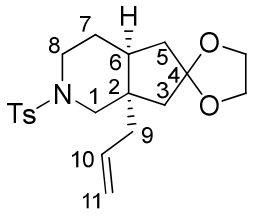


$C_{18}H_{23}NO_3S$

Allylmagnesium chloride (1.7 mL of a 1.6 M solution in THF, 2.7 mmol) was added dropwise to a solution of copper(I) iodide (0.50 g, 2.7 mmol) and lithium chloride (0.11 g, 2.7 mmol) in THF (30 mL) at −10 °C. This was followed by the rapid addition of a solution of the ketone **320** (0.26 g, 0.91 mmol) and chlorotrimethylsilane (0.12 mL, 1.0 mmol) in THF (10 mL). The mixture was stirred at −10 °C for 1 h and then allowed to reach rt. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (30 mL), saturated aqueous Na_2CO_3 solution (30 mL) and EtOAc (50 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with water (150 mL) and brine (150 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography on silica gel (petroleum ether: EtOAc, 8:1 to 4:1) provided the title compound **322** (0.27 g, 93%) as a colourless solid.

R_f = 0.29 (petroleum ether: EtOAc, 4:1); $[\alpha]_D^{22}$ +32.3 (c = 1.80, $CHCl_3$); m.p. 134−137 °C; ν_{max} (film) 2901, 2856, 1728, 1597, 1334, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (2H, d, *J* = 7.8 Hz, CH-Ts), 7.32 (2H, d, *J* = 7.8 Hz, CH-Ts), 5.72 (1H, ddt, *J* = 17.8, 10.3, 7.4 Hz, CH-C10), 5.17−5.11 (2H, m, CH_2-C11), 3.13−3.08 (1H, m, CH_2-C8), 3.00 (1H, d, *J* = 12.1 Hz, CH_2-C1), 2.89−2.83 (1H, m, CH_2-C8), 2.58 (1H, d, *J* = 12.1 Hz, CH_2-C1), 2.48−2.38 (1H, m, CH_2-C9), 2.43 (3H, s, CH_3-Ts), 2.31 (1H, dd, *J* = 18.5, 7.9 Hz, CH_2-C5), 2.23 (1H, dd, *J* = 14.0, 7.4 Hz, CH_2-C9), 2.22−2.18 (2H, m, CH_2-C3), 2.12 (1H, ddd, *J* = 13.7, 7.9, 5.7 Hz, CH-C6), 2.05−1.97 (2H, m, CH_2-C5, CH_2-C7), 1.55 (1H, ddt, *J* = 14.2, 5.7, 3.6 Hz, CH_2-C7); ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.7 (C-C4), 143.9 (C-Ts), 133.0 (C-Ts), 132.6 (CH-C10), 129.9 (CH-Ts), 127.7 (CH-Ts), 119.8 (CH_2-C11), 49.6 (CH_2-C1), 46.5 (CH_2-C3), 42.7 (CH_2-C8), 41.6 (C-C2), 41.2 (CH_2-C5), 40.5 (CH_2-C9), 37.0 (CH-C6), 25.4 (CH_2-C7), 21.6 (CH_3-Ts); HRMS (ESI) for $C_{18}H_{23}NNaO_3S$ $[M+Na]^+$ calcd. 356.1477, found 356.1479.

(4a*S*,7a*R*)-7a-Allyl-2-tosyloctahydrospiro[cyclopenta[c]pyridine-6,2'-[1,3] dioxolane] 389

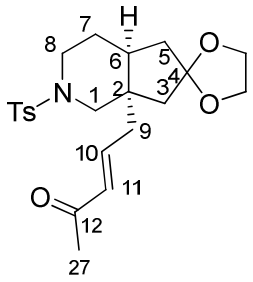


$C_{20}H_{27}NO_4S$

To a solution of the ketone **322** (0.20 g, 0.60 mmol) in dry toluene (20 mL) was added ethylene glycol (0.24 mL, 4.2 mmol), trimethyl orthoformate (0.31 mL, 3.0 mmol) and *p*-toluenesulfonic acid monohydrate (17 mg, 90 μmol). The mixture was heated at 55 °C for 2 h with vigorous stirring. After cooling to rt, the mixture was neutralised by addition of saturated aqueous $NaHCO_3$ solution. The phases were separated and the aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic phases were washed with brine (100 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 4:1 to 2:1) afforded the title compound **389** (212 mg, 94%) as a pale yellow oil.

R_f = 0.59 (petroleum ether: EtOAc, 1:1); ν_{max} (film) 2925, 2853, 1471,1338, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (2H, d, *J* = 8.2 Hz, CH-Ts), 7.31 (2H, d, *J* = 8.2 Hz, CH-Ts), 5.76 (1H, ddt, *J* = 17.6, 10.2, 7.3 Hz, CH-C10), 5.16−5.06 (2H, m, CH_2-C11), 3.99−3.76 (4H, m, OCH_2CH_2O), 3.22 (1H, dt, *J* = 9.6, 4.0 Hz, CH_2-C8), 3.07 (1H, d, *J* = 12.1 Hz, CH_2-C1), 2.73−2.64 (1H, m, CH_2-C8), 2.60 (1H, d, *J* = 12.1 Hz, CH_2-C1), 2.46−2.40 (1H, m, CH_2-C9), 2.43 (3H, s, CH_3-Ts), 2.15 (1H, dd, *J* = 14.0, 7.3 Hz, CH_2-C9), 1.92−1.86 (3H, m, CH_2-C5, CH-C6, CH_2-C7), 1.87 (1H, d, *J* = 14.7 Hz, CH_2-C3), 1.80−1.75 (1H, m, CH_2-C5), 1.73 (1H, d, *J* = 14.7 Hz, CH_2-C3), 1.65−1.52 (1H, m, CH_2-C7); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.3 (C-Ts), 133.9 (C-Ts), 133.7 (CH-C10), 129.6 (CH-Ts), 127.5 (CH-Ts), 118.6 (CH_2-C11), 116.0 (C-C4), 64.3 (OCH_2), 63.8 (OCH_2), 49.2 (CH_2-C1), 45.2 (CH_2-C3), 42.7 (C-C2), 42.3 (CH_2-C8), 40.4 (CH_2-C9), 39.6 (CH_2-C5), 38.9 (CH-C6), 24.2 (CH_2-C7), 21.5 (CH_3-Ts); HRMS (EI) for $C_{20}H_{27}NO_4S$ $[M]^+$ calcd. 377.1661, found 377.1645.

(*E*)-5-((4a*S*,7a*R*)-2-Tosyloctahydrospiro[cyclopenta[c]pyridine-6,2'-[1,3] dioxolane]-7a-yl)pent-3-en-2-one 388

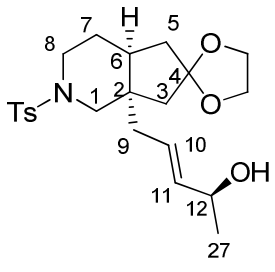


$C_{22}H_{29}NO_5S$

Methyl vinyl ketone (67 mg, 0.95 mmol) was added to a solution of the alkene **389** (126 mg, 0.32 mmol) and the Grubbs second-generation catalyst (5.4 mg, 2 mol %) in DCM (10 mL). The mixture was heated at 50 °C for 24 h and was concentrated *in vacuo*. Purification of the residue by column chromatography on silica gel (petroleum ether: EtOAc, 3:1 to 1:1) afforded the title compound **388** (112 mg, 81%) as a colourless foam.

R_f = 0.45 (petroleum ether: EtOAc, 1:2); $[\alpha]_D^{24}$ +30 (c = 0.53, $CHCl_3$); ν_{max} (film) 2928, 2885, 1672, 1339, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (2H, d, *J* = 8.2 Hz, CH-Ts), 7.30 (2H, d, *J* = 8.2 Hz, CH-Ts), 6.76 (1H, dt, *J* = 15.7, 7.8 Hz, CH-C10), 6.16 (1H, d, *J* = 15.7 Hz, CH-C11), 3.87–3.76 (4H, m, OCH_2CH_2O), 3.34 (1H, dt, *J* = 9.6, 4.0 Hz, CH_2-C8), 3.10 (1H, d, *J* = 12.3 Hz, CH_2-C1), 2.66 (1H, dd, *J* = 13.9, 7.8 Hz, CH_2-C9), 2.63–2.56 (1H, m, CH_2-C8), 2.55 (1H, d, *J* = 12.3 Hz, CH_2-C1), 2.37 (3H, s, CH_3-Ts), 2.26–2.17 (1H, m, CH_2-C9), 2.20 (3H, s, CH_3-C27), 1.96–1.85 (3H, m, CH_2-C7, CH_2-C5, CH-C6), 1.84 (1H, d, *J* = 14.3 Hz, CH_2-C3), 1.82–1.76 (1H, m, CH_2-C5), 1.73 (1H, d, *J* = 14.3 Hz, CH_2-C3), 1.65–1.55 (1H, m, CH_2-C7); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.3 (C-C12), 143.5 (C-Ts), 142.9 (CH-C10), 134.2 (CH-C11), 133.5 (C-Ts), 129.7 (CH-Ts), 127.5 (CH-Ts), 115.5 (C-C4), 64.5 (OCH_2), 64.0 (OCH_2), 49.1 (CH_2-C1), 45.8 (CH_2-C3), 43.1 (C-C2), 42.0 (CH_2-C8), 39.4 (CH_2-C5), 39.3 (CH-C6), 39.1 (CH_2-C9), 27.4 (CH_3-C27), 24.0 (CH_2-C7), 21.5 (CH_3-Ts); HRMS (ESI) for $C_{22}H_{29}NNaO_5S$ $[M+Na]^+$ calcd. 442.1659, found 442.1666.

(*R*,*E*)-5-((4a*S*,7a*R*)-2-Tosyloctahydrospiro[cyclopenta[c]pyridine-6,2'-[1,3] dioxolane]-7a-yl)pent-3-en-2-ol 390

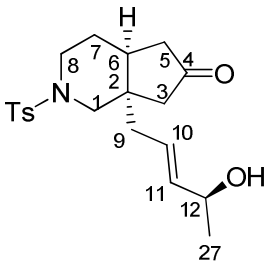


$C_{22}H_{31}NO_5S$

To a solution of the enone **388** (200 mg, 0.475 mmol) in dry THF (20 mL) was added (*S*)-CBS catalyst (0.07 mL of a 1 M solution in THF, 0.07 mmol). The mixture was cooled to −30 °C and borane-THF complex (0.58 mL of a 1 M solution in THF, 0.58 mmol) was added. After the mixture had been strirred at −30 °C for 2 h, the reaction was quenched by addition of saturated aqueous ammonium chloride solution (10 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with brine (50 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 2:1 to 1:1) afforded the title compound **390** (199 mg, 99%) as a colourless foam.

R_f = 0.40 (petroleum ether: EtOAc, 1:2); ν_{max} (film) 3502 (br), 2957, 2924, 2856, 1468, 1337, 1161, 1092 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (2H, d, *J* = 8.2 Hz, CH-Ts), 7.32 (2H, d, *J* = 8.2 Hz, CH-Ts), 5.66 (1H, dd, *J* = 14.6, 6.4 Hz, CH-C11), 5.55 (1H, ddd, *J* = 14.6, 8.1, 6.8 Hz, CH-C10), 4.28 (1H, qd, *J* = 6.6, 6.4 Hz, CH-C12), 3.88–3.75 (4H, m, CH_2-ketal), 3.34–3.25 (1H, m, CH_2-C8), 3.16 (1H, d, *J* = 12.8 Hz, CH_2-C1), 2.66–2.43 (3H, m, CH_2-C8, CH_2-C1, CH_2-C9), 2.43 (3H, s, CH_3-Ts), 2.09–2.02 (1H, m, CH_2-C9), 1.96–1.85 (4H, m, CH_2-C3, CH_2-C5, CH-C6, CH_2-C7), 1.79–1.72 (2H, m, CH_2-C3, CH_2-C5), 1.59–1.51 (1H, m, CH_2-C7), 1.25 (3H, d, *J* = 6.6 Hz, CH_3-C27); ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.5 (C-Ts), 143.9 (CH-C11), 133.5 (C-Ts), 129.8 (CH-Ts), 127.6 (CH-Ts), 125.5 (CH-C10), 115.9 (C-C4), 69.0 (CH-C12), 64.4 (OCH_2), 64.0 (OCH_2), 49.0 (CH_2-C1), 45.9 (CH_2-C3), 42.8 (C-C2), 42.2 (CH_2-C8), 39.5 (CH_2-C5), 39.2 (CH-C6), 39.1 (CH_2-C9), 24.1 (CH_2-C7), 23.5 (CH_3-C27), 21.6 (CH_3-Ts); HRMS (ESI) for $C_{22}H_{31}NNaO_5S$ $[M+Na]^+$ calcd. 444.1815, found 444.1819.

(4a*S*,7a*R*)-7a-((*S*,*E*)-4-Hydroxypent-2-enyl)-2-tosylhexahydro-cyclopenta[c] pyridin-6-one 371



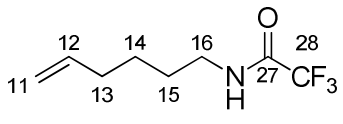
$C_{20}H_{27}NO_4S$

The TBS ether **411**[154] (1.4 g, 7.5 mmol) was added to a solution of the alkene **322** (0.50 g, 1.5 mmol) and the Hoveyda-Grubbs second-generation catalyst (47 mg, 5 mol %) in DCM (50 mL). The mixture was then heated at 50 °C for 12 h and then a 1 M aqueous solution of HCl (20 mL) was added. The biphasic mixture was stirred for 2 h and then neutralised by addition of saturated aqueous $NaHCO_3$ solution (40 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 50 mL). The organic phases were combined and washed with brine (100 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 3:1 to 1:1) afforded the title compound **371** (481 mg, 85%) as a colourless foam.

R_f = 0.26 (petroleum ether: EtOAc, 1:2); $[\alpha]_D^{22}$ +40 (c = 0.50, $CHCl_3$); ν_{max} (film) 3492 (br), 2969, 2926, 2851, 1738, 1337, 1161, 1092 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.60 (2H, d, *J* = 8.0 Hz, CH-Ts), 7.33 (2H, d, *J* = 8.0 Hz, CH-Ts), 5.71−5.65 (1H, m, CH-C11), 5.59−5.50 (1H, m, CH-C10), 4.29 (1H, dq, *J* = 6.5, 6.5 Hz, CH-C12), 3.25−3.18 (1H, m, CH_2-C8), 3.09 (1H, d, *J* = 12.1 Hz, CH_2-C1), 2.73 (1H, dt, *J* = 10.3, 5.3 Hz, CH_2-C8), 2.50 (1H, dd, *J* = 13.9, 8.2 Hz, CH_2-C9), 2.44 (3H, s, CH_3-Ts), 2.39 (1H, d, *J* = 12.1 Hz, CH_2-C1), 2.30 (1H, dd, *J* = 18.7, 8.2 Hz, CH_2-C5), 2.20−2.00 (3H, m, CH_2-C9, CH-C6, CH_2-C7), 2.16 (2H, s, CH_2-C3), 2.02 (1H, dd, *J* = 18.7, 8.2 Hz, CH_2-C5), 1.58 (1H, dtd, *J* = 14.2, 5.3, 3.5 Hz, CH_2-C7), 1.27 (3H, d, *J* = 6.5 Hz, CH_3-C27); ^{13}C NMR (126 MHz, $CDCl_3$) δ 216.3 (C-C4), 144.0 (C-Ts), 139.8 (CH-C11), 133.0 (C-Ts), 130.0 (CH-Ts), 127.7 (CH-Ts), 124.1 (CH-C10), 68.7 (CH-C12), 49.5 (CH_2-C1), 47.3 (CH_2-C3), 42.5 (C-C2), 41.8 (CH_2-C8), 40.9 (CH_2-C5), 39.1 (CH_2-C9), 37.3 (CH-C6), 25.1 (CH_2-C7), 23.7 (CH_3-C27), 21.7 (CH_3-Ts); HRMS (ESI) for $C_{20}H_{27}NNaO_4S$ $[M+Na]^+$ calcd. 400.1535, found 400.1553.

[154] Uenishi, J.; Fujikura, Y.; Kawai, N. *Org. Lett.* **2011**, *13*, 2350-2353

2,2,2-Trifluoro-*N*-(hex-5-enyl)acetamide 401[155]



$C_8H_{12}F_3NO$

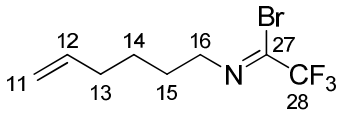
To a solution of trifluoroacetamide (1.13 g, 10.0 mmol) in DMF (50 mL) was added NaH (480 mg of a 60% dispersion in mineral oil, 12.0 mmol) and the mixture was stirred at rt for 15 min. 6-Bromo-1-hexene (1.70 g, 10.5 mmol) was added and the mixture was heated at 50 °C for 12 h. The mixture was then cooled to rt, diluted with EtOAc (100 mL) and the reaction was quenched by the addition of saturated aqueous NH_4Cl solution (100 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with water (3 × 100 mL) and brine (100 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 10:1) afforded the title compound **401** (1.26 g, 93%) as a colourless oil.

R_f = 0.38 (petroleum ether: EtOAc, 10:1); ν_{max} (film) 3304, 2938, 2862, 1701, 1560, 1157 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 6.27 (1H, brs, NH), 5.78 (1H, ddt, *J* = 16.9, 10.2, 6.7 Hz, CH-C12), 5.03 (1H, ddt, *J* = 16.9, 2.0, 1.5 Hz, CH_2-C11), 4.98 (1H, ddt, *J* = 10.2, 2.0, 1.5 Hz, CH_2-C11), 3.37 (2H, dt, *J* = 7.0, 6.6 Hz, CH_2-C16), 2.09 (2H, tdd, *J* = 7.0, 6.7, 1.5, CH_2-C13), 1.63 (2H, tt, *J* = 8.4, 6.6 Hz, CH_2-C15), 1.46 (2H, tt, *J* = 8.4, 7.0 Hz, CH_2-C14); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.1 (q, J^2_{C-F} = 36.6 Hz, C-C27), 137.8 (CH-C12), 115.7 (q, J^1_{C-F} = 287.7 Hz, C-C28), 114.6 (CH_2-C11), 39.5 (CH_2-C16), 33.0 (CH_2-C13), 28.0 (CH_2-C15), 25.6 (CH_2-C14).

The analytical and spectroscopic data are in agreement with those reported in the literature.

[155] Teichert, J. F.; Fananas-Mastral, M.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 688−691

2,2,2-Trifluoro-*N*-(hex-5-enyl)acetimidoyl bromide 395

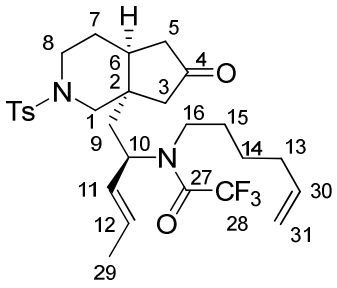


$C_8H_{11}BrF_3N$

To a stirred solution of CBr_4 (13.2 g, 40.0 mmol) in DCM (50 mL) at 0 °C was added PPh_3 (10.5 g, 40.0 mmol) in DCM (25 mL) in one portion. The resulting mixture was stirred at 0 °C for 5 min before the addition of a solution of the acetamide **401** (1.95 g, 10.0 mmol) in DCM (5 mL). The reaction mixture was stirred at 0 °C for 1 h and then allowed to reach rt. The mixture was concentrated; the residue was suspended in pentane, filtered through a short pad of Celite and the filter cake washed with pentane (50 mL). The filtrate was concentrated and the residue was purified by flash column chromatography on silica gel (pentane) to afford the title product **395** (47% w/w, 4.58 g, 84%) as a colourless solution in pentane.

R_f = 0.43 (pentane); ν_{max} (film) 2924, 2855, 1705, 1643, 1458, 1273, 1157 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 5.60 (1H, ddt, *J* = 17.2, 10.2, 6.9 Hz, CH-C12), 4.96–4.93 (1H, m, CH_2-C11), 4.92–4.91 (1H, m, CH_2-C11), 3.06 (2H, ddd, *J* = 8.5, 5.4, 1.6 Hz, CH_2-C16), 2.08 (2H, dt, *J* = 6.9, 2.2 Hz, CH_2-C13), 1.33–1.26 (2H, m, CH_2-C15), 1.16–1.10 (2H, m, CH_2-C14); ^{13}C NMR (126 MHz, C_6D_6) δ 138.3 (CH-C12), 125.2 (q, J^2_{C-F} = 43.3 Hz, C-C27), 116.4 (q, J^1_{C-F} = 277.0 Hz, C-C28), 115.1 (CH_2-C11), 57.5 (CH_2-C16), 33.6 (CH_2-C13), 28.3 (CH_2-C15), 26.7 (CH_2-C14).

2,2,2-Trifluoro-*N*-(hex-5-enyl)-*N*-((*R*,*E*)-1-((4a*S*,7a*R*)-6-oxo-2-tosyloctahydro-cyclopenta[c]pyridin-7a-yl)pent-3-en-2-yl)acetamide 387



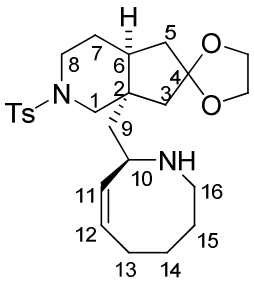
$C_{28}H_{37}F_3N_2O_4S$

To a solution of the allylic alcohol **371** (4.0 g, 10.5 mmol) in THF (40 mL) at −30 °C was added NaHMDS (9.5 mL of 1 M solution in THF, 11.5 mmol). To the solution was added the bromide **395** (6.3 g of a 47% w/w solution in pentane, 11.5 mmol) over 5 min. After stirring at −30 °C for 1 h, the reaction mixture was added anhydrous K_2CO_3 (1.6 g, 11.5 mmol) and toluene (80 mL). The resulting mixture was heated at 115 °C for 2 d with vigorous stirring. After cooling to rt, the mixture was filtered through a short pad of Celite and the filter cake was washed with EtOAc (100 mL). The combined filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (petroleum ether: EtOAc, 4:1 to 2:1) to afford the title compound **387** (4.3 g, 74% yield over two steps) as a colourless gum.

R_f = 0.66 (petroleum ether: EtOAc, 1:1); ν_{max} (film) 2928, 2856, 1741, 1684, 1445, 1337, 1184, 1161, 1092, 980 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50 (2H, d, *J* = 8.0 Hz, CH-Ts), 7.24 (2H, d, *J* = 8.0 Hz, CH-Ts), 5.91 (1H, ddq, *J* = 15.7, 8.7, 1.5 Hz, CH-C11), 5.79–5.65 (2H, m, CH-C12, CH-C30), 4.93 (1H, ddt, *J* = 17.0, 2.4, 1.5 Hz, CH-C31), 4.88–4.84 (1H, m, CH-C31), 3.98 (1H, dd, *J* = 8.7, 8.7 Hz, CH-C10), 3.45 (1H, d, *J* = 11.2 Hz, CH_2-C1), 3.34–3.24 (3H, m, CH_2-C16, CH_2-C8), 2.36–2.30 (1H, m, CH_2-C9), 2.34 (3H, s, CH_3-Ts), 2.26 (1H, d, J = 11.2 Hz, CH_2-C1), 2.17–1.97 (8H, m, CH_2-C3, CH_2-C5, CH-C6, CH_2-C7, CH_2-C9, CH_2-C13), 1.90–1.82 (2H, m, CH_2-C5, CH_2-C8), 1.73–1.64 (2H, m, CH_2-C15), 1.62 (3H, dd, *J* = 6.4, 1.5 Hz, CH_3-C29), 1.56–1.49 (1H, m, CH_2-C7), 1.34 (2H, tt, *J* = 7.9, 7.8 Hz, CH_2-C14); ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.2 (C-C4), 156.2 (q, J^2_{C-F} = 35.0 Hz, C-C27), 144.1 (C-Ts), 138.4 (CH-C30), 132.5 (C-Ts), 131.2 (CH-C12), 130.0 (CH-Ts), 129.9 (CH-C11), 128.9 (CH-Ts), 116.5 (q, J^1_{C-F} = 270.1 Hz, C-C28), 114.8 (CH_2-C31), 61.4 (CH-C10), 50.1 (CH_2-C3), 49.3 (CH_2-C16), 47.7 (CH_2-C8), 41.8 (CH_2-C1),

40.5 (C-C2), 38.7 (CH_2-C5), 38.2 (CH-C6), 36.9 (CH_2-C9), 33.2 (CH_2-C13), 28.7 (CH_2-C15), 26.0 (CH_2-C14), 23.4 (CH_2-C7), 21.6 (CH_3-Ts), 17.9 (CH_3-C29); HRMS (ESI) for $C_{28}H_{37}F_3N_2NaO_4S$ $[M+Na]^+$ calcd. 554.2426, found 554.2429.

(4a*S*,7a*R*)-7a-(((*R*,*Z*)-1,2,5,6,7,8-Hexahydroazocin-2-yl)methyl)-2-tosylocta hydrospiro[cyclopenta[c]pyridine-6,2'-[1,3]dioxolane] 408

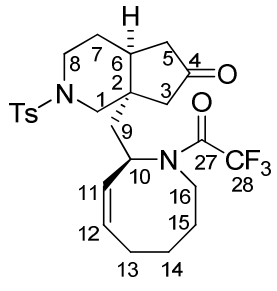


$C_{25}H_{36}N_2O_4S$

To a stirred solution of the trifluoroamide **397** (200 mg, 0.360 mmol) in MeOH (50 mL) was added saturated aqueous K_2CO_3 solution (10 mL). The mixture was heated at 70 °C for 3 h with vigorous stirring. After cooling to rt, the mixture was dried over anhydrous sodium sulfate, filtered through a short pad of Celite and the filter cake was washed with EtOAc (2 × 50 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (EtOAc, to EtOAc: MeOH, 10:1) to give the title compound **408** (204 mg, 81%) as a colourless gum.

R_f = 0.30 (EtOAc: MeOH: Et_3N, 87:10:3); ν_{max} (film) 3464 (br), 2924, 2853, 1740, 1468, 1447, 1335, 1161, 754 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.72 (2H, d, *J* = 8.0 Hz, CH-Ts), 6.79 (2H, d, *J* = 8.0 Hz, CH-Ts), 5.72 (1H, dd, *J* = 9.4, 8.1 Hz, CH-C12), 5.26 (1H, dd, *J* = 9.4, 9.4 Hz, CH-C11), 5.21 (1H, brs, NH), 4.11–4.00 (1H, m, CH-C10), 3.79 (1H, d, *J* = 12.1 Hz, CH_2-C1), 3.45–3.24 (5H, m, CH_2-C8, OCH_2CH_2O), 3.12–3.04 (1H, m, CH_2-C8), 2.91–2.84 (1H, m, CH_2-C16), 2.88–2.80 (1H, m, CH_2-C16), 2.69 (1H, d, *J* = 12.1 Hz, CH_2-C1), 2.53–2.40 (2H, m, CH_2-C8, CH_2-C13), 2.34 (1H, d, *J* = 11.4 Hz, CH-C9), 2.12 (1H, d, *J* = 14.5 Hz, CH_2-C3), 2.03 (1H, d, *J* = 14.5 Hz, CH_2-C3), 2.02–1.95 (1H, m, CH_2-C13), 1.84 (3H, s, CH_3-Ts), 1.82–1.59 (6H, m, CH_2-C9, CH_2-C5, CH_2-C7, CH_2-C15, CH-C6), 1.37–1.26 (2H, m, CH_2-C14), 1.14–1.08 (2H, m, CH_2-C5, CH_2-C7); ^{13}C NMR (126 MHz, C_6D_6) δ 144.2 (C-Ts), 137.6 (C-Ts), 132.4 (CH-C11), 131.2 (CH-Ts), 129.5 (CH-C12), 128.0 (CH-Ts), 116.1 (C-C4), 64.3 (OCH_2), 63.6 (OCH_2), 50.0 (CH-C10), 49.9 (CH_2-C1), 48.7 (CH_2-C3), 45.1 (CH_2-C16), 41.9 (CH_2-C8), 41.5 (CH_2-C9), 40.7 (C-C2), 39.9 (CH-C6), 38.6 (CH_2-C15), 30.0 (CH_2-C14), 28.3 (CH_2-C5), 26.4 (CH_2-C13), 23.5 (CH_2-C7), 20.7 (CH_3-Ts); HRMS (ESI) for $C_{25}H_{37}N_2O_4S$ $[M+H]^+$ calcd. 461.2462, found 461.2469.

(4a*S*,7a*R*)-2-Ts-7a-(((*R*,*Z*)-1-(2,2,2-trifluoroacetyl)-1,2,5,6,7,8-hexahydro azocin-2-yl)methyl)octahydro-cyclopenta[c]pyridin-6-one 397

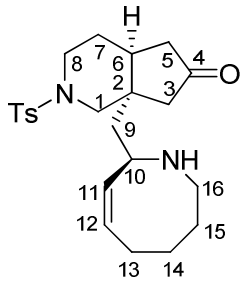


$C_{25}H_{31}F_3N_2O_4S$

The diene **387** (1.3 g, 2.3 mmol) in DCM (20 mL) was added to a solution of the Grubbs second-generation catalyst (0.20 g, 0.23 mmol) in DCM (1 L). The resulting solution was heated at reflux for 4 h. The solution was cooled to rt, MeOH (10 mL) was added and the mixture was concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 2:1) afforded the title compound **397** (0.97 g, 81%) as a colourless foam.

R_f = 0.52 (petroleum ether: EtOAc, 1:1); ν_{max} (film) 2926, 2860, 2257, 1744, 1681, 1450, 1337, 1196, 1160, 1092 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (2H, d, *J* = 8.3 Hz, CH-Ts), 7.25 (2H, d, *J* = 8.3 Hz, CH-Ts), 5.76–5.53 (2H, m, CH-C11, CH-C12), 4.54 (1H, dt, *J* = 5.3, 4.3 Hz, CH-C10), 3.76 (1H, dt, *J* = 14.5, 5.1 Hz, CH_2-C16), 3.52–3.35 (2H, m, CH_2-C16, CH_2-C8), 3.38 (1H, d, *J* = 12.1 Hz, CH_2-C1), 2.37–2.27 (2H, m, CH_2-C8, CH_2-C13), 2.35 (3H, s, CH_3-Ts) 2.30 (1H, d, *J* = 8.1 Hz, CH_2-C3), 2.23 (1H, d, *J* = 8.1 Hz, CH_2-C3), 2.16–1.99 (7H, m, CH_2-C1, CH_2-C9, CH_2-C5, CH-C6, CH_2-C7, CH_2-C13), 1.92–1.78 (3H, m, CH_2-C5, CH_2-C14, CH_2-C15), 1.71–1.59 (2H, m, CH_2-C14, CH_2-C15), 1.57–1.50 (1H, m, CH_2-C7); ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.5 (C-C4), 156.5 (q, J^2_{C-F} = 35.3 Hz, C-C27), 144.0 (C-Ts), 132.5 (C-Ts), 131.0 (CH-C12), 130.2 (CH-C11), 129.9 (CH-Ts), 127.4 (CH-Ts), 116.5 (q, J^1_{C-F} = 288.5 Hz, C-C28), 54.7 (CH-C10), 48.7 (CH_2-C3), 48.4 (CH_2-C1), 47.9 (CH_2-C16), 41.8 (CH_2-C8), 40.9 (C-C2), 39.1 (CH_2-C5), 37.9 (CH-C6), 37.5 (CH_2-C9), 28.1 (CH_2-C15), 26.4 (CH_2-C13), 24.8 (CH_2-C14), 23.7 (CH_2-C7), 21.4 (CH_3-Ts); HRMS (EI) for $C_{25}H_{31}F_3N_2O_4Si$ $[M]^+$ calcd 512.1957, found 512.1960.

(4a*S*,7a*R*)-7a-(((*R*,*Z*)-1,2,5,6,7,8-Hexahydroazocin-2-yl)methyl)-2-Tsocta hydro-cyclopenta[c]pyridin-6-one 386

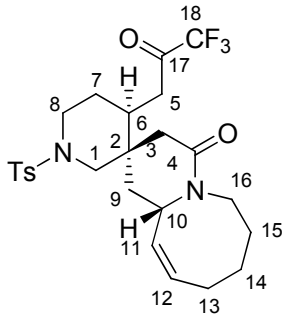


$C_{23}H_{32}N_2O_3S$

To a stirred solution of the amide **397** (475 mg, 1.14 mmol) in MeOH (40 mL) at rt was added 2 M aqueous K_2CO_3 solution (20 mL). The mixture was stirred at rt for 2 d. The reaction was diluted with EtOAc (80 mL) and then 1 M aqueous HCl solution (40 mL) was added. The phases were separated and the aqueous phase was extracted with EtOAc (3 × 60 mL). The combined organic extracts were washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 2:1) gave the title compound **386** (341 mg, 92%) as a pale yellow oil.

R_f = 0.28 (EtOAc: MeOH: Et_3N, 87:10:3); $[\alpha]_D^{22}$ +83 (c = 0.47, $CHCl_3$); ν_{max} (film) 3464 (br), 2924, 2853, 1740, 1468, 1447, 1335, 1161, 754 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.66 (2H, d, *J* = 8.3 Hz, CH-Ts), 6.85 (2H, d, *J* = 8.3 Hz, CH-Ts), 5.71 (1H, td, *J* = 12.2, 9.9 Hz, CH-C12), 5.27 (1H, dd, *J* = 9.9, 9.9 Hz, CH-C11), 4.51 (1H, brs, NH), 4.16–4.04 (1H, m, CH-C10), 3.34 (1H, d, *J* = 12.7 Hz, CH_2-C1), 3.32–3.23 (1H, m, CH_2-C16), 3.12–3.04 (1H, m, CH_2-C8), 2.91–2.84 (1H, m, CH_2-C16), 2.60 (1H, d, *J* = 12.0 Hz, CH_2-C9), 2.36–2.34 (1H, m, CH_2-C13), 2.28–2.18 (2H, m, CH_2-C1, CH_2-C8), 2.15 (1H, d, *J* = 18.0 Hz, CH_2-C3), 2.02 (1H, d, *J* = 18.0 Hz, CH_2-C3), 1.96–1.88 (1H, m, CH_2-C5), 1.86 (3H, s, CH_3-Ts), 1.85–1.69 (6H, m, CH_2-C9, CH_2-C13, CH_2-C7, CH_2-C15, CH-C6), 1.54–1.47 (1H, m, CH_2-C14), 1.47 (1H, dd, *J* = 18.6, 9.8 Hz, CH_2-C5), 1.06–0.91 (2H, m, CH_2-C14, CH_2-C7); ^{13}C NMR (126 MHz, C_6D_6) δ 215.0 (C-C4), 143.1 (C-Ts), 135.6 (C-Ts), 133.9 (CH-C11), 129.6 (CH-Ts), 128.2 (CH-C12), 127.6 (CH-Ts), 49.1 (CH_2-C3), 48.8 (CH-C10), 48.7 (CH_2-C1), 44.2 (CH_2-C16), 42.0 (CH_2-C8), 40.6 (C-C2), 39.3 (CH_2-C9), 39.0 (CH_2-C5), 37.3 (CH-C6), 28.1 (CH_2-C14), 26.2 (CH_2-C13), 25.6 (CH_2-C15), 23.8 (CH_2-C7), 20.8 (CH_3-Ts); HRMS (ESI) for $C_{23}H_{33}N_2O_3S$ $[M+H]^+$ calcd. 417.2175, found 417.2182.

(2'*R*,4*S*,11a'*R*,*Z*)-1-Tosyl-4-(3,3,3-trifluoro-2-oxopropyl)-1',6',7',8',9',11a'-hexahydrospiro[piperidine-3,2'-pyrido[1,2-a]azocin]-4'-one 404

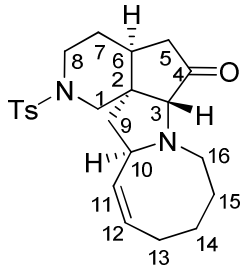


$C_{25}H_{31}F_3N_2O_4S$

To a solution of the trifluoroamide *epi*-**403** (78 mg, 0.15 mmol) in MeOH (20 mL) was added saturated aqueous K_2CO_3 (2 mL) and the mixture was heated at 70 °C for 3 h with vigorous stirring. After cooling to rt, the mixture was filtered through a short pad of Celite and washed with DCM (2 × 50 mL). The organic phases were concentrated *in vacuo*. Purification of the residue by column chromatography on silica gel (petroleum ether: EtOAc, 5:1 to 2:1) afforded the title compound **404** (72 mg, 92%) as a colourless solid.

R_f = 0.55 (petroleum ether: EtOAc, 1:1); $[\alpha]_D^{26}$ +108 (c = 0.24, $CHCl_3$); m.p. 170–175 °C; ν_{max} (powder) 2926, 2854, 1763, 1631, 1454, 1338, 1207, 1149, 1091, 979, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.55 (2H, d, *J* = 8.0 Hz, CH-Ts), 7.29 (2H, d, *J* = 8.0 Hz, CH-Ts), 5.89 (1H, dt, *J* = 10.7, 8.4 Hz, CH-C12), 5.22 (1H, dd, *J* = 10.7, 7.7 Hz, CH-C11), 4.36–4.25 (1H, m, CH-C10), 4.07 (1H, dd, *J* = 13.7, 10.1 Hz, CH_2-C16), 3.17 (1H, dd, *J* = 13.7, 7.0 Hz, CH_2-C16), 3.24–3.15 (1H, m, CH_2-C8), 3.01 (1H, d, *J* = 12.0 Hz, CH_2-C1), 2.71–2.64 (1H, m, CH_2-C8), 2.62 (1H, dd, *J* = 18.5, 2.8 Hz, CH_2-C5), 2.49 (1H, d, *J* = 12.0 Hz, CH_2-C1), 2.48–2.42 (1H, m, CH_2-C5), 2.39 (3H, s, CH_3-Ts), 2.36–2.17 (3H, m, CH_2-C9, CH_2-C13), 2.26 (1H, d, *J* = 16.9 Hz, CH_2-C3), 2.14 (1H, d, *J* = 16.9 Hz, CH_2-C3), 2.08–1.92 (4H, m, CH-C6, CH_2-C7, CH_2-C15), 1.68–1.59 (1H, m, CH_2-C14), 1.46–1.33 (3H, m, CH_2-C7, CH_2-C9, CH_2-C14); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.3 (q, J^2_{C-F} = 36.8 Hz, C-C17), 168.1 (C-C4), 144.1 (C-Ts), 134.9 (CH-C12), 132.9 (C-Ts), 130.0 (CH-Ts), 128.6 (CH-C11), 127.6 (CH-Ts), 116.8 (q, J^1_{C-F} = 287.9 Hz, C-C18), 49.9 (CH-C10), 49.8 (CH_2-C1), 43.0 (CH_2-C8), 42.6 (CH_2-C16), 38.9 (CH_2-C3), 37.2 (CH_2-C9), 36.2 (CH-C6), 34.8 (C-C2), 34.6 (CH_2-C5), 27.7 (CH_2-C7), 26.5 (CH_2-C13), 26.3 (CH_2-C14), 25.7 (CH_2-C15), 21.2 (CH_3-Ts); HRMS (ESI) $C_{25}H_{30}F_3N_2O_4S$ $[M\text{-}H]^-$ calcd. for 511.1880, found 511.1884.

(4a*R*,7*R*,5*S*,11*R*,*Z*)-*N*-Tosyl-1,2,3,4,4a,5,8,9,10,11,13a,14-dodecahydro pyrido [3'',4'':1',5']cyclopenta[1',2':4,5]pyrrolo[1,2-a]azocin-6-one 385

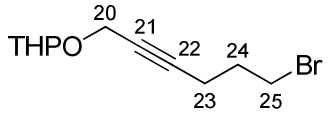


$C_{23}H_{30}N_2O_3S$

To a stirred solution of the amine **386** (437 mg, 1.05 mmol) in THF (40 mL) at 0 °C was added pyrrolidone hydrotribromide (550 mg, 1.10 mmol) in one portion. The mixture was stirred overnight before addition of DMAP (250 mg, 2.02 mmol). The reaction mixture was stirred at rt for 12 h and then washed with saturated aqueous $Na_2S_2O_3$ solution (30 mL), saturated aqueous Na_2CO_3 solution (30 mL) and brine (30 mL). The phases were separated and the organic phase was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 2:1) afforded the title compound **385** (288 mg, 66%) as a pale yellow solid.

R_f = 0.42 (petroleum ether: EtOAc, 1:1); $[\alpha]_D^{24}$ −47 (c = 0.48, $CHCl_3$); m.p. 128−132 °C; ν_{max} (powder) 2953, 2925, 2857, 1739, 1467, 1160, 935 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.63 (2H, d, *J* = 8.2 Hz, CH-Ts), 6.80 (2H, d, *J* = 8.2 Hz, CH-Ts), 5.55 (1H, ddd, *J* = 10.9, 7.9, 4.4 Hz, CH-C12), 5.27 (1H, dd, *J* = 10.9, 6.5 Hz, CH-C11), 3.49 (1H, td, *J* = 6.5, 6.5 Hz, CH-C10), 3.41 (1H, d, *J* = 11.9 Hz, CH_2-C1), 3.25 (1H, dt, *J* = 13.3, 4.7 Hz, CH_2-C16), 3.20−3.06 (1H, m, CH_2-C8), 2.96 (1H, s, CH-C3), 2.95−2.87 (1H, m, CH_2-C16), 2.49−2.35 (2H, m, CH_2-C1, CH_2-C13), 2.30 (1H, dd, *J* = 10.6, 9.8 Hz, CH_2-C8), 2.04 (1H, dtd, *J* = 13.1, 9.0, 4.4 Hz, CH_2-C13), 1.90 (3H, s, CH_3-Ts), 1.89−1.83 (1H, m, CH_2-C5), 1.72−1.62 (1H, m, CH_2-C9), 1.62−1.53 (3H, m, CH_2-C15, CH_2-C5), 1.45−1.24 (4H, m, CH-C6, CH_2-C14, CH_2-C9), 1.18 (1H, ddt, *J* = 14.6, 4.3, 2.5 Hz, CH_2-C7), 0.80 (1H, ddt, *J* = 14.6, 9.8, 4.7 Hz, CH_2-C7); ^{13}C NMR (126 MHz, C_6D_6) δ 215.0 (C-C4), 143.1 (C-Ts), 134.9 (C-Ts), 132.5 (CH-C11), 130.5 (CH-Ts), 129.7 (CH-C12), 128.6 (CH-Ts), 72.3 (CH-C3), 59.7 (CH-C10), 52.3 (CH_2-C1), 49.3 (CH_2-C16), 48.8 (C-C2), 44.8 (CH_2-C5), 44.7 (CH_2-C9), 44.2 (CH_2-C8), 36.9 (CH-C6), 28.3 (CH_2-C7), 27.4 (CH_2-C14), 26.5 (CH_2-C15), 26.0 (CH_2-C13), 21.2 (CH_3-Ts); HRMS (ESI) for $C_{23}H_{31}N_2O_3S$ $[M+H]^+$ calcd. 415.2037, found 415.2050.

2-(6-Bromohex-2-ynyloxy)tetrahydro-pyran 418[156]



$C_{11}H_{17}BrO_2$

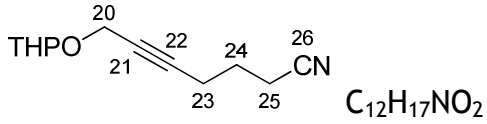
To a stirred solution of 2-(2-propynyloxy)-tetrahydro-2H-pyran **414** (100 mg, 0.713 mmol) in THF (20 mL) at −30 °C was added *n*-BuLi (0.33 mL of a 2.38 M solution in THF, 0.79 mmol). The mixture was stirred at −30 °C for 10 min and a solution of 1,3-dibromo-propane **417** (174 mg, 0.862 mmol) in THF (20 mL) was added. The mixture was stirred at −30 °C for 1 h and allowed to reach rt over 1 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution (50 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 5:1) gave the title compound **418** (150 mg, 81%) as a pale yellow oil.

R_f = 0.56 (petroleum ether: EtOAc, 4:1); ν_{max} (film) 2955, 2911, 2876, 2211, 1694, 1607, 1354, 1250, 1165, 1094, 907, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.81 (1H, t, *J* = 3.4 Hz, CH-THP), 4.35−4.18 (2H, m, CH_2-C20), 3.89−3.82 (1H, m, CH_2-THP), 3.60−3.56 (1H, m, CH_2-THP), 3.53 (2H, t, *J* = 6.3 Hz, CH_2-C25), 2.44 (2H, tt, *J* = 6.7, 2.1 Hz, CH_2-C23), 2.06 (2H, tt, *J* = 6.7, 6.3 Hz, CH_2-C24), 1.90−1.51 (6H, m, CH_2-THP); ^{13}C NMR (101 MHz, $CDCl_3$) δ 96.7 (CH-THP), 84.1 (C-C21), 77.2 (C-C22), 62.0 (CH_2-THP), 54.4 (CH_2-C20), 32.1 (CH_2-C25), 31.1 (CH_2-C24), 30.4 (CH_2-THP), 25.1 (CH_2-THP), 19.1 (CH_2-THP), 17.5 (CH_2-C23).

The analytical and spectroscopic data are in agreement with those reported in the literature.

[156] Danishefsky, S.; McKee, R.; Singh, R. K. *J. Am. Chem. Soc.* **1977**, *99*, 4783−4788

7-(Tetrahydro-2H-pyran-2-yloxy)hept-5-ynenitrile 416[157]



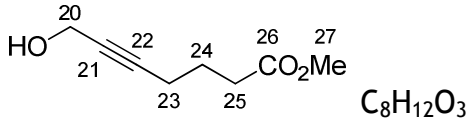
To a stirred solution of the bromide **418** (3.70 g, 15.0 mmol) in DMSO (30 mL) at rt was added NaCN (810 mg, 16.5 mmol). This mixture was stirred at 50 °C for 12 h and then poured into water (100 mL). The mixture was extracted with Et_2O (4 × 100 mL) and the combined organic phases were washed with brine (200 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 6:1) gave the title compound **416** (2.83 g, 96%) as a colourless oil.

R_f = 0.32 (4:1 petroleum ether: EtOAc); ν_{max} (film) 2948, 2242, 2215, 1446, 1345, 1118, 1023 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.76 (1H, t, *J* = 3.4 Hz, CH-THP), 4.32−4.13 (2H, m, CH_2-C20), 3.86−3.77 (1H, m, CH_2-THP), 3.55−3.45 (1H, m, CH_2-THP), 2.48 (2H, t, *J* = 7.2 Hz, CH_2-C25), 2.40 (2H, tt, *J* = 6.8, 2.1 Hz, CH_2-C23), 1.96 (2H, tt, *J* = 7.2, 6.8 Hz, CH_2-C24), 1.91−1.48 (6H, m, CH_2-THP); ^{13}C NMR (101 MHz, $CDCl_3$) δ 118.5 (C-C26), 96.0 (CH-THP), 82.9 (C-C21), 77.2 (C-C22), 61.2 (CH_2-THP), 53.4 (CH_2-C20), 29.7 (CH_2-C25), 24.8 (CH_2-C24), 23.8 (CH_2-THP), 18.3 (CH_2-THP), 17.1 (CH_2-THP), 15.5 (CH_2-C23).

The analytical and spectroscopic data are in agreement with those reported in the literature.

[157] Luo, F. T.; Negishi, E. *J. Org. Chem.* **1985**, *50*, 4762−4766

Methyl 7-hydroxyhept-5-ynoate 420[157]



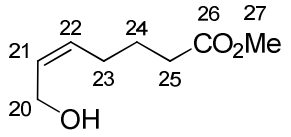
To a stirred solution of the nitrile **418** (3.00 g, 14.5 mmol) in MeOH (80 mL) at rt was added 10% aqueous NaOH solution (20 mL). The resulting mixture was heated at reflux for 12 h. The mixture was then cooled to rt and poured into ice-water (100 mL), acidified with aqueous concentrated HCl solution and extracted with Et_2O (4 × 100 mL). The combined organic extracts were washed with brine (300 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The acid **419** (3.18 g, 97%) was sufficient pure to be used directly into the next step without further purification.

To a stirred solution of the carboxylic acid **419** (3.00 g, 13.3 mmol) in MeOH (60 mL) at rt was added *p*-toluenesulfonic acid monohydrate (250 mg, 1.33 mmol). The resulting mixture was heated at reflux for 12 h. The mixture was cooled to rt, neutralised by the addition of saturated aqueous $NaHCO_3$ solution (30 mL) and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine (200 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 4:1) gave the title compound **420** (1.95 g, 94%) as a colourless oil.

R_f = 0.31 (petroleum ether: EtOAc, 1:1); ν_{max} (film) 3442 (br), 2948, 2911, 2872, 2221, 1740, 1444, 1163, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.24–4.22 (2H, m, CH_2-C20), 3.67 (3H, s, CH_3-C27), 2.42 (2H, t, *J* = 7.3 Hz, CH_2-C25), 2.28 (2H, tt, *J* = 6.8, 2.1 Hz, CH_2-C23), 1.83 (2H, tt, *J* = 7.3, 6.8 Hz, CH_2-C24); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6 (C-C26), 84.9 (C-C21), 79.2 (C-C22), 51.5 (CH_2-C20), 51.0 (CH_3-C27), 32.7 (CH_2-C25), 23.8 (CH_2-C24), 18.1 (CH_2-C23).

The analytical and spectroscopic data are in agreement with those reported in the literature.

(*Z*)-Methyl 7-hydroxyhept-5-enoate 421[157]



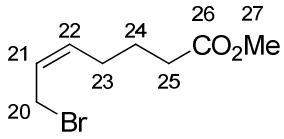
$C_8H_{14}O_3$

To a solution of the alkyne **420** (200 mg, 1.28 mmol) in EtOAc (10 mL) at rt was added Lindlar catalyst (10 mg, 0.13 mmol). This mixture was sparged with hydrogen for 10 min then stirred under a static hydrogen atmosphere at rt for 2 h. The reaction was filtered through a short pad of Celite and the filter cake waswashed with EtOAc (50 mL).The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (petroleum ether: ether, 10:1) to afford the title compound **421** (192 mg, 95%) as a colourless oil.

R_f = 0.31 (petroleum ether: EtOAc, 1:1); ν_{max} (film) 3412 (br), 3015, 2952, 2860, 2240, 1740, 1434, 1161, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.67 (1H, dtt, *J* = 10.8, 6.8, 1.4, Hz, CH_2-C21), 5.50 (1H, dtt, *J* = 10.8, 7.4, 1.3 Hz, CH_2-C22), 4.17 (2H, dd, *J* = 6.8, 1.3 Hz, CH_2-C20), 3.67 (3H, s, CH_3-C27), 2.32 (2H, t, *J* = 7.3 Hz, CH_2-C25), 2.14 (2H, dtd, *J* = 7.4, 7.2, 1.4 Hz, CH_2-C23), 1.72 (2H, tt, *J* = 7.3, 7.2 Hz, CH_2-C24); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8 (C-C26), 130.3 (C-C21), 129.8 (C-C22), 57.5 (CH_2-C20), 51.0 (CH_3-C27), 32.8 (CH_2-C25), 26.4 (CH_2-C24), 24.5 (CH_2-C23).

The analytical and spectroscopic data are in agreement with those reported in the literature.

(*Z*)-Methyl 7-bromohept-5-enoate 415[158]



$C_8H_{13}BrO_2$

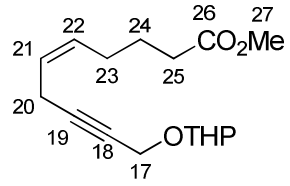
To a stirred solution of the alcohol **421** (1.2 g, 7.6 mmol) in DCM (50 mL) at 0 °C was added a solution of CBr_4 (2.8 g, 8.4 mmol) in DCM (15 mL) and a solution of PPh_3 (2.3 g, 8.7 mmol) in DCM (20 mL). This mixture was stirred at 0 °C for 1 h, filtered through a short pad of silica and the filter cake was washed with DCM (50 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (petroleum ether: EtOAc, 10:1) to give the title compound **415** (1.64 g, 98%) as a pale yellow oil.

R_f = 0.71 (petroleum ether: EtOAc, 2:1); ν_{max} (film) 3022, 2949, 2862, 2242, 1740, 1434, 1370, 1201, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.77 (1H, dtt, *J* = 10.5, 6.8, 1.4 Hz, CH_2-C21), 5.58 (1H, dtt, *J* = 10.5, 7.4, 1.3 Hz, CH_2-C22), 3.99 (2H, dd, *J* = 6.8, 1.3 Hz, CH_2-C20), 3.67 (3H, s, CH_3-C27), 2.33 (2H, t, *J* = 7.3 Hz, CH_2-C25), 2.18 (2H, dtd, *J* = 7.4, 7.2, 1.4 Hz, CH_2-C23), 1.74 (2H, tt, *J* = 7.3, 7.2 Hz, CH_2-C24); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6 (C-C26), 134.4 (C-C21), 129.8 (C-C22), 57.5 (CH_2-C20), 51.0 (CH_3-C27), 32.8 (CH_2-C25), 26.4 (CH_2-C24), 24.5 (CH_2-C23).

The analytical and spectroscopic data are in agreement with those reported in the literature.

[158] Johnson, C. R.; Penning, T. D. *J. Am. Chem. Soc.* **1988**, *110*, 4726−4735

(*Z*)-Methyl 10-(tetrahydro-2H-pyran-2-yloxy)dec-5-en-8-ynoate 422

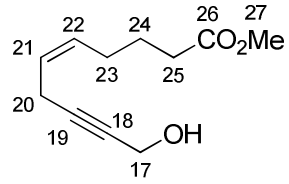


$C_{16}H_{24}O_4$

To a stirred solution of the alkyne **414** (1.00 g, 7.13 mmol) in THF (50 mL) at −78 °C was added EtMgBr (10.0 mL of a 0.70 M solution in THF, 7.2 mmol) and CuI (450 mg, 2.37 mmol). The mixture was stirred at −78 °C for 10 min and a solution of the bromide **415** (1.05 g, 4.75 mmol) in THF (10 mL) was added. The mixture was stirred at −78 °C for 1 h and allowed to reach rt over 2 h. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (50 mL). The aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic phases were washed with brine (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 10:1 to 4:1) gave the title compound **422** (1.16 g, 87%) as a colourless oil.

R_f = 0.68 (petroleum ether: EtOAc, 2:1); ν_{max} (film) 3020, 2950, 2861, 2241, 2212, 1740, 1354, 1250, 1165, 1094 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 5.47−5.40 (1H, m, CH_2-C21), 5.22−5.15 (1H, m, CH_2-C22), 4.94 (1H, t, *J* = 3.3 Hz, CH-THP), 4.36−4.23 (2H, m, CH_2-THP), 3.71 (1H, td, *J* = 10.6, 3.0 Hz, CH_2-C17), 3.35 (1H, td, *J* = 10.6, 1.4 Hz, CH_2-C17), 3.33 (3H, s, CH_3-C27), 2.81−2.74 (2H, m, CH_2-20), 2.00 (2H, t, *J* = 7.4 Hz, CH_2-C25), 1.78 (2H, dtd, *J* = 8.2, 7.3, 1.4 Hz, CH_2-C23), 1.76−1.54 (3H, m, CH_2-THP), 1.48 (2H, tt, *J* = 7.4, 7.3 Hz, CH_2-C24), 1.38−1.13 (3H, m, CH_2-THP); ^{13}C NMR (126 MHz, C_6D_6) δ 173.0 (C-C26), 130.6 (C-C22), 125.5 (C-C21), 96.5 (CH-THP), 84.5 (C-C18), 76.5 (C-19), 61.4 (CH_2-C17), 54.6 (CH_2-THP), 51.0 (CH_3-C27), 33.3 (CH_2-C25), 30.7 (CH_2-THP), 26.6 (CH_2-C23), 25.8 (CH_2-THP), 24.7 (CH_2-C24), 19.3 (CH_2-THP), 17.5 (CH_2-C20); HRMS (ESI) for $C_{16}H_{24}NaO_4$ $[M+Na]^+$ calcd. 303.1553, found 303.1524.

(*Z*)-Methyl 10-hydroxydec-5-en-8-ynoate 423

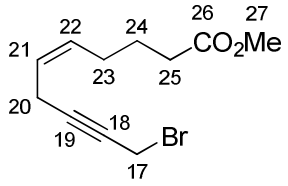


$C_{11}H_{16}O_3$

To a stirred solution of the protected alcohol **422** (710 mg, 2.54 mmol) in MeOH (40 mL) at rt was added *p*-toluenesulfonic acid monohydrate (22 mg, 0.12 mmol) and the mixture was heated under reflux for 12 h. The mixture was cooled to rt, neutralised by addition of saturated aqueous $NaHCO_3$ solution (30 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 4:1) gave the title compound **423** (495 mg, 98%) as a colourless oil.

R_f = 0.14 (petroleum ether: EtOAc, 2:1); ν_{max} (film) 3450 (br), 3020, 2950, 2912, 2861, 2241, 1740, 1354, 1250, 1165, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.52−5.39 (2H, m, CH_2-C21, CH_2-C22), 4.31−4.17 (2H, m, CH_2-C17), 3.68 (3H, s, CH_3-C27), 3.00−2.94 (2H, m, CH_2-20), 2.33 (2H, t, *J* = 7.0 Hz, CH_2-C25), 2.08 (2H, dtd, *J* = 7.9, 7.3, 1.4 Hz, CH_2-C23), 1.74 (2H, tt, *J* = 7.3, 7.0 Hz, CH_2-C24); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3 (C-C26), 130.9 (C-C22), 128.8 (C-C21), 85.9 (C-C18), 77.5 (C-19), 54.5 (CH_2-C17), 50.0 (CH_3-C27), 33.9 (CH_2-C25), 31.8 (CH_2-C23), 26.9 (CH_2-C24), 17.8 (CH_2-C20); HRMS (ESI) for $C_{11}H_{16}NaO_3$ $[M+Na]^+$ calcd. 219.0991, found 219.0992.

(*Z*)-Methyl 10-bromodec-5-en-8-ynoate 465

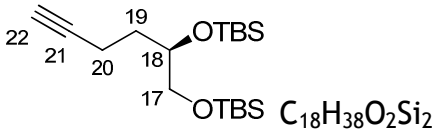


$C_{11}H_{15}BrO_2$

To a stirred solution of the alcohol **423** (300 mg, 1.53 mmol) in DCM (40 mL) at 0 °C was added a solution of CBr_4 (1.26 g, 3.83 mmol) in DCM (10 mL) and a solution of PPh_3 (1.00 g, 3.83 mmol) in DCM (10 mL). The mixture was stirred at 0 °C for 1 h, then filtered through a short pad of silica and the filter cake washed with DCM (50 mL). The filtrate was concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 10:1) gave the title compound **465** (367 mg, 93%) as a pale yellow oil.

R_f = 0.41 (petroleum ether: EtOAc, 4:1); ν_{max} (film) 3022, 2949, 2910, 2859, 2240, 1742, 1436, 1354, 1211, 1163 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 5.08–4.82 (2H, m, CH_2-C21, CH_2-C22), 3.15 (2H, t, *J* = 2.4 Hz, CH_2-C17), 3.12 (3H, s, CH_3-C27), 2.44–2.38 (2H, m, CH_2-20), 1.76 (2H, t, *J* = 7.0 Hz, CH_2-C25), 1.49 (2H, dtd, *J* = 7.9, 7.3, 1.4 Hz, CH_2-C23), 1.22 (2H, tt, *J* = 7.3, 7.0 Hz, CH_2-C24); ^{13}C NMR (126 MHz, C_6D_6) δ 173.6 (C-C26), 131.2 (C-C22), 124.0 (C-C21), 85.6 (C-C18), 77.3 (C-19), 57.5 (CH_2-C17), 49.9 (CH_3-C27), 33.0 (CH_2-C25), 28.3 (CH_2-C23), 23.0 (CH_2-C24), 16.1 (CH_2-C20); HRMS (ESI) for $C_{11}H_{15}NaO_2Br$ $[M+Na]^+$ calcd. 281.0135, found 281.0148.

(*R*)- 5,6-di(*tert*-butyldimethylsilyloxy)-1-hexyne 495[159]



$C_{18}H_{38}O_2Si_2$

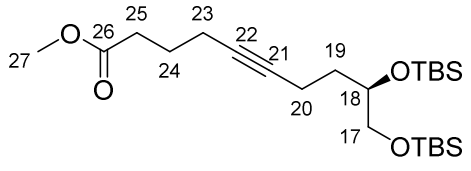
To a stirred solution of the alcohol **494** (3.42 g, 15.0 mmol) and imidazole (2.10 g, 30.0 mmol) in DCM (40 mL) at 0 °C was added TBSCl (3.40 g, 22.5 mmol). The mixture was stirred at 0 °C for 1.5 h and then allowed to reach rt over 30 min. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (50 mL) and extracted with Et_2O (3 × 100 mL). The organic extracts were washed with brine (80 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (100% petroleum ether to 50:1 petroleum ether: Et_2O) afforded the title compound **495** (4.80 g, 94%) as a colourless oil.

R_f = 0.91 (petroleum ether: Et_2O, 10:1); $[\alpha]_D^{27}$ +21.2 (c = 1.44, $CHCl_3$); ν_{max} (film) 3316, 2957, 2859, 1473, 1257, 1123, 836, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.78–3.75 (1H, m, CH-C18), 3.55 (1H, dd, *J* = 10.0, 5.2 Hz, CH_2-C17), 3.39 (1H, dd, *J* = 10.0, 6.8 Hz, CH_2-C17), 2.27–2.26 (2H, m, CH_2-C19), 1.93 (1H, t, *J* = 2.6 Hz, CH-C22), 1.84–1.80 (1H, m, CH_2-C20), 1.63–1.61 (1H, m, CH_2-C20), 0.89 (9H, s, CH_3-TBS), 0.88 (9H, s, CH_3-TBS), 0.08 (3H, s, CH_3-TBS), 0.07 (3H, s, CH_3-TBS), 0.05 (3H, s, CH_3-TBS), 0.04 (3H, s, CH_3-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 84.6 (C-C21), 71.6 (CH-C18), 68.2 (CH-C22), 67.1 (CH_2-C17), 33.2 (CH_2-C19), 25.9 (CH_3-TBS), 25.9 (CH_3-TBS), 18.3 (C-TBS), 18.1 (C-TBS), 14.4 (CH_2-C20), −4.3 (CH_3-TBS), −4.8 (CH_3-TBS), −5.3 (CH_3-TBS), −5.4 (CH_3-TBS).

The analytical and spectroscopic data are in agreement with those reported in the literature.

[159] Trost, B. M.; Sieber, J. D.; Qian, W.; Dhawan, R.; Ball, Z. T. *Angew. Chem. Int. Ed.* **2009**, *48*, 5478–5481

(*R*)-Methyl 9,10-bis(*tert*-butyldimethylsilyloxy)dec-5-ynoate 501

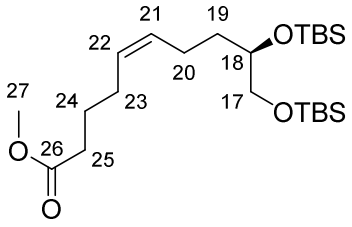


$C_{23}H_{46}O_4Si_2$

To a stirred solution of the alkyne **495 (**2.5 g, 7.3 mmol) in THF (60 mL) at −78 °C was added *n*-BuLi (3.8 mL of a 2.32 M solution in THF, 8.8 mmol). The mixture was stirred at −78 °C for 30 min before addition of HMPA (5.0 mL, 29 mmol) and the bromide **505** (1.5 mL, 8.8 mmol). The reaction mixture was then stirred at −78 °C for 1 h and allowed to reach rt overnight. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (50 mL) and the mixture was extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: Et_2O, 100:1 to 50:1) afforded the title compound **501** (2.6 g, 82%) as a colourless oil.

R_f = 0.45 (petroleum ether: Et_2O, 10:1); $[\alpha]_D^{27}$ +25.3 (c = 1.70, $CHCl_3$); ν_{max} (film) 2955, 2928, 2856, 1738, 1472, 1252, 1121, 835, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.74 (1H, m, CH-C18), 3.64 (3H, s, CH_3-C27), 3.52 (1H, dd, *J* = 10.0, 5.2 Hz, CH_2-C17), 3.39 (1H, dd, *J* = 10.0, 6.5 Hz, CH_2-C17), 2.41 (2H, t, *J* = 7.5, CH_2-C25), 2.23−2.15 (4H, m, CH_2-C20, CH_2-C23), 1.81−1.70 (3H, m, CH_2-C19, CH_2-C24), 1.50−1.49 (1H, m, CH_2-C19), 0.87 (9H, s, CH_3-TBS), 0.86 (9H, s, CH_3-TBS), 0.05 (3H, s, CH_3-TBS), 0.04 (3H, s, CH_3-TBS), 0.03 (3H, s, CH_3-TBS), 0.02 (3H, s, CH_3-TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.6 (C-C26), 81.0 (C-C22), 78.9 (C-C21), 71.8 (CH-C18), 67.3 (CH_2-C17), 51.4 (CH_3-C27), 33.7 (CH_2-C19), 32.8 (CH_2-C25), 25.9 (CH_3-TBS), 25.9 (CH_3-TBS), 24.2 (CH_2-C24), 18.3 (C-TBS), 18.2 (C-TBS), 18.1 (CH_2-C20), 14.7 (CH_2-C23), −4.3 (CH_3-TBS), −4.8 (CH_3-TBS), −5.3 (CH_3-TBS), −5.4 (CH_3-TBS); HRMS (ESI) for $C_{23}H_{46}NaO_4Si_2$ $[M+Na]^+$ calcd. 465.2805, found 465.2827.

(*R*,*Z*)-Methyl 9,10-bis(*tert*-butyldimethylsilyloxy)dec-5-enoate 502

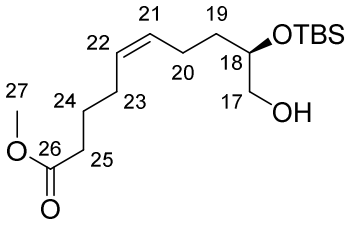


$C_{23}H_{48}O_4Si_2$

To a stirred solution of the alkyne **501** (1.5 g, 3.4 mmol) in EtOAc (20 mL) at rt was added Lindlar catalyst (722 mg, 0.34 mmol) and quinoline (44 mg, 0.34 mmol). The mixture was sparged with hydrogen for 10 min, and then stirred under a static hydrogen atmosphere at rt for 1h. The reaction was then filtered through a short pad of Celite and the filter cake was washed with EtOAc (100 mL). The filtrate was concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: Et_2O, 50:1) afforded the title compound **502** (1.5 g, 98%) as a colourless oil.

R_f = 0.51 (petroleum ether: Et_2O, 10:1); $[\alpha]_D^{21}$ +14 (c = 0.63, $CHCl_3$); ν_{max} (film) 2953, 2928, 2857, 1742, 1472, 1462, 1252, 1101, 831, 773 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.45–5.36 (1H, m, CH-C21), 5.36–5.27 (1H, m, CH-C22), 3.68–3.63 (1H, m, CH-C18), 3.65 (3H, s, CH_3-C27), 3.46 (1H, dd, *J* = 10.0, 5.5 Hz, CH_2-C17), 3.36 (1H, dd, *J* = 10.0, 6.2 Hz, CH_2-C17), 2.22 (2H, t, *J* = 7.6, CH_2-C25), 2.01 (2H, td, *J* = 7.5, 6.2 Hz, CH_2-C23), 2.13–1.91 (2H, m, CH_2-C20), 1.61 (2H, tt, *J* = 7.6, 7.5 Hz, CH_2-C24), 1.56–1.49 (1H, m, CH_2-C19), 1.40–1.32 (1H, m, CH_2-C19), 0.83 (18H, s, CH_3-TBS), 0.05 (6H, s, CH_3-TBS), 0.04 (3H, s, CH_3-TBS), 0.03 (3H, s, CH_3-TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.0 (C-C26), 130.9 (C-C21), 128.5 (C-C22), 72.8 (CH-C18), 67.2 (CH_2-C17), 51.4 (CH_3-C27), 34.4 (CH_2-C19), 33.5 (CH_2-C25), 26.6 (CH_2-C23), 25.9 (CH_3-TBS), 25.9 (CH_3-TBS), 24.9 (CH_2-C24), 23.0 (CH_2-C20), 18.4 (C-TBS), 18.1 (C-TBS), −4.3 (CH_3-TBS), −4.8 (CH_3-TBS), −5.3 (CH_3-TBS), −5.4 (CH_3-TBS); HRMS (ESI) for $C_{23}H_{48}NaO_4Si_2$ $[M+Na]^+$ calcd. 467.2967, found 467.2983.

(*R*,*Z*)-Methyl 9-(*tert*-butyldimethylsilyloxy)-10-hydroxydec-5-enoate 493

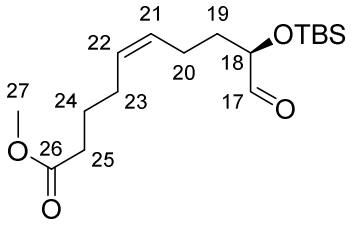


$C_{17}H_{34}O_4Si$

To a stirred solution of the bis-TBS ether **502** (2.5 g, 7.3 mmol) in THF (60 mL) at −10 °C was added HF•pyridine (23 mL of a 4.81 M solution in THF, 110 mmol). The mixture was stirred at −10 °C for 2 d. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution (100 mL) and the resulting mixture was extracted with Et_2O (3 × 100 mL). The combined organic phases were washed with brine (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: Et_2O, 10:1 to 5:1) afforded the title compound **493** (1.5 g, 90%) as a colourless oil.

R_f = 0.31 (petroleum ether: Et_2O, 4:1); $[\alpha]_D^{23}$= −1.8 (c = 0.73, $CHCl_3$); ν_{max} (film) 3499 (br), 2951, 2930, 2857, 1740, 1472, 1252, 1107, 835, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.36−5.18 (2H, m, CH-C21, CH-C22), 3.65 (1H, tt, *J* = 6.2, 3.2 Hz, CH-C18), 3.57 (3H, s, CH_3-C27), 3.50−3.42 (1H, m, CH_2-C17), 3.38 (1H, ddd, *J* = 11.2, 6.2, 5.7 Hz, CH_2-C17), 2.22 (2H, t, *J* = 7.6, CH_2-C25), 2.08−1.86 (4H, m, CH_2-C20, CH_2-C23), 1.60 (2H, tt, *J* = 7.6, 7.5 Hz, CH_2-C24), 1.53−1.37 (2H, m, CH_2-C19), 0.82 (9H, s, CH_3-TBS), 0.00 (6H, s, CH_3-TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.0 (C-C26), 130.3 (CH-C21), 128.8 (CH-C22), 72.5 (CH-C18), 66.0 (CH_2-C17), 51.4 (CH_3-C27), 33.9 (CH_2-C19), 33.4 (CH_2-C25), 26.5 (CH_2-C23), 25.8 (CH_3-TBS), 24.8 (CH_2-C24), 23.1 (CH_2-C20), 18.0 (C-TBS), −4.5 (CH_3-TBS), −4.6 (CH_3-TBS); HRMS (ESI) for $C_{17}H_{34}NaO_4Si$ $[M+Na]^+$ calcd. 353.2108, found 353.2119.

Methyl (*R*,*Z*)-9-((*tert*-butyldimethylsilyl)oxy)-10-oxodec-5-enoate 487

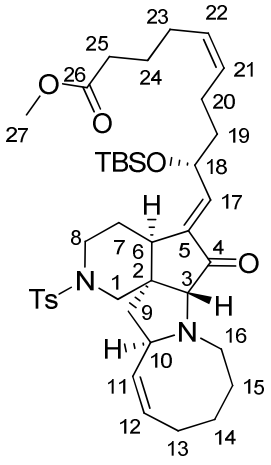


$C_{17}H_{32}O_4Si$

To a stirred solution of the alcohol **493 (**500 mg, 1.51 mmol) in DCM (30 mL) at 0 °C was added $NaHCO_3$ (378 mg, 4.52 mmol) and Dess-Martin periodinane (1.27 g, 3.02 mmol) in one portion. The mixture was stirred overnight before addition of saturated aqueous $Na_2S_2O_3$ solution (30 mL). The reaction was then stirred for 10 min and the phases were separated. The organic phase was washed with saturated aqueous Na_2CO_3 solution (30 mL), brine (30 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: ether, 4:1) afforded the title compound **487** (488 mg, 98%) as a colourless oil.

R_f = 0.42 (petroleum ether: Et_2O, 4:1); $[\alpha]_D^{23}$ +28 (c = 0.89, $CHCl_3$); ν_{max} (film) 2953, 2930, 2857, 1736, 1437, 1252, 1155, 1117, 837, 777 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.60 (1H, d, *J* = 1.6 Hz, CH-C17), 5.40–5.35 (2H, m, CH-C21, CH-C22), 3.99 (1H, ddd, *J* = 6.9, 5.4, 1.6 Hz, CH-C18), 3.67 (3H, s, CH_3-C27), 2.53 (2H, t, *J* = 7.5, CH_2-C25), 2.23–2.15 (4H, m, CH_2-C20, CH_2-C23), 1.81–1.70 (3H, m, CH_2-C19, CH_2-C24), 1.51 (1H, m, CH_2-C19), 0.87 (9H, s, CH_3-TBS), 0.05 (3H, s, CH_3-TBS), 0.04 (3H, s, CH_3-TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.1 (CH-C17), 173.6 (C-C26), 129.8 (CH-C22), 129.5 (CH-C21), 71.8 (CH-C18), 51.5 (CH_3-C27), 33.5 (CH_2-C19), 32.8 (CH_2-C25), 26.6 (CH_3-TBS), 25.8 (CH_2-C24), 24.8 (C-TBS), 22.3 (CH_2-C20), 18.7 (CH_2-C23), −4.6 (CH_3-TBS), −4.9 (CH_3-TBS); HRMS (ESI) for $C_{17}H_{32}NaO_4Si$ $[M+Na]^+$ calcd. 351.1969, found 351.1962.

Methyl(*R*,5*Z*,10*E*)-9-((*tert*-butyldimethylsilyl)oxy)-10-((4a*R*,6a*R*,13a*R*,14a*R*,*Z*)-6-oxo-2-tosyl-2,3,4,4a,6,6a,8,9,10,11,13a,14-dodecahydropyrido[3'',4'':1',5']cyclopenta[1',2':4,5]pyrrolo[1,2-a]azocin-5-ylidene)dec-5-enoate 506



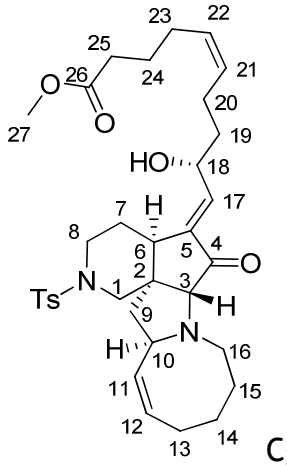
$C_{40}H_{60}N_2O_6SSi$

To a stirred solution of diisopropylamine (26 µL, 0.19 mmol) in THF (2 mL) at −78 °C was added *n*-BuLi (88 µL of a 2.16 M solution in THF, 0.19 mmol). The mixture was stirred at −78 °C for 10 min and a solution of the ketone **385** (70 mg, 0.17 mmol) in THF (1 mL) was added. The mixture was then stirred at −78 °C for 30 min and then a solution of the aldehyde **487** (61 mg, 0.19 mmol) in THF (1 mL) was added. The mixture was stirred at −78 °C for 2 h and allowed to reach rt over 12 h. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (5 mL) and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (gradient, petroleum ether: EtOAc, 10:1 to 2:1) afforded the title compound **506** (56 mg, 77%) as a yellow gum.

R_f = 0.78 (petroleum ether: EtOAc, 2:1); $[\alpha]_D^{21}$ −23.7 (c = 1.06, $CHCl_3$); ν_{max} (film) 2951, 2928, 2855, 1738, 1462, 1358, 1252, 1165, 982, 835, 775 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.71 (2H, d, *J* = 8.2 Hz, CH-Ts), 6.83 (2H, d, *J* = 8.2 Hz, CH-Ts), 6.67 (1H, dd, *J* = 8.9, 1.5 Hz, CH-C17), 5.53−5.29 (4H, m, CH-C12, CH-C21, CH-C11, CH-C22), 4.27−4.12 (2H, m, CH-C18, CH_2-C1), 3.80−3.66 (2H, m, CH_2-C8, CH_2-C16), 3.54 (1H, s, CH-C3), 3.49−3.42 (1H, m, CH-C10), 3.39 (3H, s, CH_3-C27), 3.26−3.16 (2H, m, CH_2-C16, CH_2-C13), 2.26−1.87 (11H, m, CH-C6, CH_2-C20, CH_2-

C13, CH_2-C25, CH_2-C23, CH_2-C8, CH_2-C1, CH_2-C9), 1.92 (3H, s, CH_3-Ts), 1.66–1.20 (10H, m, CH_2-C19, CH_2-C24, CH_2-C7, CH_2-C14, CH_2-C9, CH_2-C15), 1.09–1.03 (1H, m, CH_2-C7), 0.93 (9H, s, CH_3-TBS), 0.05 (3H, s, CH_3-TBS), 0.00 (3H, s, CH_3-TBS); ^{13}C NMR (101 MHz, C_6D_6) δ 206.8 (C-C4), 172.8 (C-C26), 142.7 (C-Ts), 139.8 (C-C5), 137.3 (CH-C17), 134.7 (CH-C11), 134.6 (C-Ts), 129.7 (CH-C21), 129.6 (CH-C22), 129.3 (CH-Ts), 127.8 (CH-Ts), 127.6 (CH-C12), 71.4 (CH-C3), 69.5 (CH-C10), 59.4 (CH-C18), 51.5 (CH_2-C1), 50.7 (CH_3-C27), 50.6 (CH_2-C16), 49.9 (C-C2), 46.0 (CH_2-C8), 44.1 (CH_2-C9), 39.5 (CH-C6), 37.0 (CH_2-C20), 32.9 (CH_2-C7), 30.1 (CH_2-C14), 26.8 (CH_2-C23), 25.8 (CH_3-TBS), 25.6 (CH_2-C15), 25.1 (CH_2-C13), 24.8 (CH_2-C25), 24.7 (CH_2-C19), 23.0 (CH_2-C24), 20.8 (CH_3-C27), 17.9 (C-TBS), −4.1 (CH_3-TBS), −4.9 (CH_3-TBS); HRMS (ESI) for $C_{40}H_{61}N_2O_6SSi$ $[M+H]^+$ calcd. 725.3961, found 725.4014.

Methyl(*R*,5*Z*,10*E*)-9-hydroxy-10-((4a*R*,6a*R*,13a*R*,14a*R*,*Z*)-6-oxo-2-tosyl-2,3,4,4a,6,6a,8,9,10,11,13a,14-dodecahydropyrido[3'',4'':1',5'] cyclopenta[1',2':4,5]pyrrolo[1,2-a]azocin-5-ylidene)dec-5-enoate 486



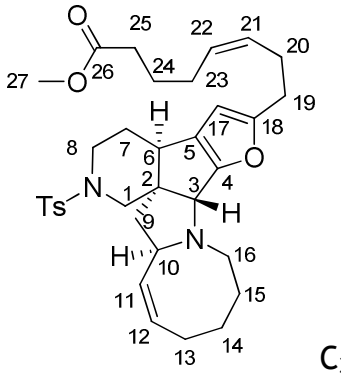
$C_{34}H_{46}N_2O_6S$

To a stirred solution of the TBS ether **506** (10 mg, 14 μmol) in THF (5 mL) at 0 °C was added TBAF (21 μL of a 1 M solution in THF, 21 μmol). The mixture was stirred at 0 °C for 1 h and allowed to reach rt over 2 h. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (20 mL) and the resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatograph on silica gel (petroleum ether: EtOAc, 3:1) afforded the title compound **486** (7 mg, 82%) as a pale yellow oil.

R_f = 0.41 (petroleum ether: EtOAc, 1:1); $[\alpha]_D^{22}$ −58 (c = 0.81, $CHCl_3$); ν_{max} (film) 3507 (br), 2924, 2853, 1734, 1719, 1651, 1458, 1354, 1163, 1096, 980, 816 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.69 (2H, d, *J* = 8.3 Hz, CH-Ts), 6.81 (2H, d, *J* = 8.3 Hz, CH-Ts), 6.53 (1H, dd, *J* = 7.8, 1.5 Hz, CH-C17), 5.49 (1H, dddd, *J* = 10.7, 9.0, 7.5, 1.5 Hz, CH-C12), 5.42−5.28 (3H, m, CH-C21, CH-C11, CH-C22), 4.12 (1H, dd, *J* = 11.9, 1.9 Hz, CH_2-C1), 4.02 (1H, dt, *J* = 7.8, 4.2 Hz, CH-C18), 3.75−3.68 (2H, m, CH-C16, CH_2-C8), 3.52 (1H, s, CH-C3), 3.42 (1H, dt, *J* = 9.8, 4.7 Hz, CH-C10), 3.33 (3H, s, CH_3-C27), 3.22 (1H, dt, *J* = 12.4, 2.4 Hz, CH_2-C16), 3.08 (1H, ddt, *J* = 12.9, 9.0, 4.9 Hz, CH_2-C13), 2.31 (1H, ddd, *J* = 12.0, 6.3, 1.5 Hz, CH_2-C6), 2.17−1.92 (7H, m, CH_2-C13, CH_2-C20, CH_2-C8, CH_2-C1, CH_2-C23), 1.91 (3H, s, CH_3-Ts), 1.83−1.76 (2H, m, CH_2-C15, CH_2-C9), 1.64−1.42 (7H, m, CH_2-C25, CH_2-

C14, CH_2-C15, CH_2-C7, CH_2-C19), 1.36−1.24 (3H, m, CH_2-C19, CH_2-C24), 1.18−1.06 (2H, m, CH_2-C9, CH_2-C7); ^{13}C NMR (126 MHz, C_6D_6) δ 207.4 (C-C4), 173.3 (C-C26), 142.7 (C-Ts), 141.2 (C-C5), 136.3 (CH-C17), 134.8 (CH-C11), 134.6 (C-Ts), 129.7 (CH-C21), 129.6 (CH-C22), 129.3 (CH-Ts), 128.2 (CH-Ts), 127.1 (CH-C12), 71.2 (CH-C3), 68.3 (CH-C10), 59.7 (CH-C18), 51.5 (CH_2-C1), 50.8 (CH_3-C27), 50.0 (CH_2-C16), 45.9 (C-C2), 44.8 (CH_2-C8), 44.1 (CH_2-C9), 39.5 (CH-C6), 37.0 (CH_2-C20), 32.9 (CH-C7), 30.1 (CH_2-C14), 26.8 (CH_2-C23), 26.4 (CH_2-C15), 25.1 (CH_2-C13), 24.8 (CH_2-C25), 24.7 (CH_2-C19), 23.0 (CH_2-C24), 20.8 (CH_3-Ts); HRMS (ESI) for $C_{34}H_{47}N_2O_6S$ $[M+H]^+$ calcd. 611.3120, found 611.3149.

Methyl (*Z*)-8-((4a*R*,7b*R*,14a*R*,15a*R*,*Z*)-2-tosyl-1,2,3,4,4a,7b,9,10,11,12,14a,15-dodecahydrofuro[2'',3'':3',4']pyrido[3'',4'':1',5']cyclopenta[1',2':4,5]pyrrolo[1,2-a]azocin-6-yl)oct-5-enoate 485



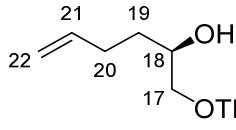
$C_{34}H_{44}N_2O_5S$

To a stirred solution of the alcohol **486** (10 mg, 16 µmol) in toluene (3 mL) at rt was added *p*-toluenesulfonic acid monohydrate (3.8 mg, 20 µmol). The mixture was stirred vigorously at rt for 12 h. The reaction was quenched by addition of saturated aqueous Na_2CO_3 solution (10 mL) and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 4:1 to 2:1) afforded the title **485** compound (7.8 mg, 82%) as a pale yellow oil.

R_f = 0.21 (petroleum ether: EtOAc, 3:2); $[\alpha]_D^{27}$ −7.3 (c = 0.70, $CHCl_3$); ν_{max} (film) 2924, 2855, 1736, 1445, 1346, 1260, 1163, 1092, 812 cm^{-1}; ^1H NMR (400 MHz, MeOD) δ 7.66 (2H, d, *J* = 8.3 Hz, CH-Ts), 7.40 (2H, d, *J* = 8.3 Hz, CH-Ts), 5.93 (1H, s, CH-C17), 5.79 (1H, ddd, *J* = 10.7, 9.0, 7.5 Hz, CH-C12), 5.48−5.31 (3H, m, CH-C21, CH-C11, CH-C22), 4.11 (1H, s, CH-C3), 3.65 (3H, s, CH_3-C27), 3.55 (1H, ddd, *J* = 10.7, 9.3, 4.5 Hz, CH-C10), 3.51 (1H, d, *J* = 12.1 Hz, CH_2-C1), 3.13−3.02 (4H, m, CH_2-C16, CH_2-C8, CH_2-C1), 2.95 (1H, dt, *J* = 13.9, 6.9 Hz, CH_2-C16), 2.84 (1H, dd, *J* = 5.5, 1.7 Hz, CH-C6), 2.66 (2H, t, *J* = 7.3 Hz, CH_2-C19), 2.44 (3H, s, CH_3-Ts), 2.41−2.28 (4H, m, CH_2-C20, CH_2-C25), 2.22−2.18 (2H, m, CH_2-C13), 2.10−1.94 (3H, m, CH_2-C9, CH_2-C23), 1.71−1.54 (9H, m, CH_2-C9, CH_2-C24, CH_2-C7, CH_2-C14, CH_2-C15); ^{13}C NMR (101 MHz, MeOD) δ 174.3 (C-C26), 163.4 (C-C4), 152.9 (C-C18), 143.6 (C-Ts), 134.8 (C-Ts), 133.0 (CH-C12), 131.8 (C-C5), 130.0 (CH-C11), 129.5 (CH-Ts), 129.3 (CH-C21), 129.0 (CH-C22), 126.9 (CH-Ts), 102.4

(CH-C17), 70.2 (CH-C3), 58.0 (C-C2), 56.6 (CH-C10), 50.6 (CH_3-C27), 49.5 (CH_2-C1), 49.3 (CH_2-C16), 45.6 (CH_2-C9), 41.5 (CH-C6), 40.8 (CH_2-C8), 32.7 (CH_2-C25), 28.4 (CH_2-C19), 27.8 (CH_2-C14), 27.6 (CH_2-C7), 26.1 (CH_2-C23), 25.7 (CH_2-C20), 24.8 (CH_2-C13), 24.5 (CH_2-C24), 24.4 (CH_2-C15), 20.1 (CH_3-Ts); HRMS (ESI) for $C_{34}H_{45}N_2O_5S$ $[M+H]^+$ calcd. 593.3033, found 593.3044.

(*R*)-1-(*tert*-Butyldimethylsilyloxy)hex-5-en-2-ol 490[160]



$C_{12}H_{26}O_2Si$

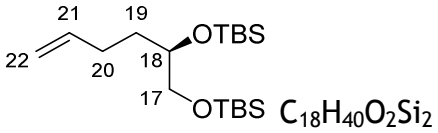
To a stirred solution of the epoxide **489** (2.5 g, 7.3 mmol) in Et_2O (60 mL) at −30 °C was added allyl magnesium chloride (3.8 mL of a 2.32 M solution in THF, 8.8 mmol). The mixture was stirred at −30 °C for 1 h and allowed to reach rt over 2 h. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (50 mL) and the resulting mixture was extracted with Et_2O (3 × 100 mL). The combined organic phases were washed with brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: Et_2O, 100:1 to 50:1) gave the title compound **490** (2.60 g, 82%) as a colourless oil.

R_f = 0.52 (petroleum ether: EtOAc, 10:1); ν_{max} (film) 3520 (br), 3314, 2956, 2928, 2852, 1473, 1257, 1123, 1087, 836, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.76 (1H, ddt, *J* = 16.9, 10.2, 6.6 Hz, CH-C21), 5.03−4.85 (2H, m, CH_2-C22), 3.64−3.51 (2H, m, CH_2-C17, CH-C18), 3.34 (1H, dd, *J* = 9.7, 7.2 Hz, CH_2-C17), 2.37 (1H, d, *J* = 3.5 Hz, OH), 2.21−1.97 (2H, m, CH_2-C20), 1.51−1.37 (2H, m, CH_2-C19), 0.83 (9H, s, CH_3-TBS), 0.00 (6H, s, CH_3-TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.5 (CH_2-C22), 114.7 (CH-C21), 71.4 (CH-C18), 67.3 (CH_2-C17), 32.1 (CH_2-C20), 30.0 (CH_2-C19), 26.0 (CH_3-TBS), 18.4 (C-TBS), −5.2(CH_3-TBS), −5.3(CH_3-TBS).

The analytical and spectroscopic data are in agreement with those reported in the literature.

[160] Matsuura, F.; Peters, R.; Anada, M.; Harried, S. S.; Hao, J.; Kishi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 7463−7465

(*R*)-5,6-Di(*tert*-butyldimethylsilyloxy)hex-1-ene 491[161]



$C_{18}H_{40}O_2Si_2$

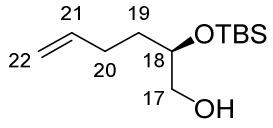
To a stirred solution of the alcohol **490** (7.20 g, 31.3 mmol) in DCM (300 mL) was added imidazole (3.13 g, 46.0 mmol), DMAP (719 mg, 5.89 mmol) and TBSCl (5.70 g, 37.8 mmol). The mixture was stirred at rt for 16 h. The reaction was quenched with saturated aqueous NH_4Cl solution (100 mL) and phases were separated. The aqueous phase was extracted with DCM (3 × 100 mL) and the combined organic extracts were washed with brine (100 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 97.5:2.5) provided bis-TBS ether **491** (10.6 g, 98%) as a colourless oil.

R_f = 0.91 (petroleum ether: Et_2O, 10:1); $[\alpha]_D^{27}$ +21 (c = 1.44, $CHCl_3$) {Lit.[11] $[\alpha]_D^{20}$ +9.2 (c = 2.1, $CHCl_3$)}; ν_{max} (film) 3316, 2957, 2930, 2859, 1473, 1257, 1123, 1087, 835, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.77 (1H, ddt, *J* = 16.9, 10.2, 6.5 Hz, CH-C21), 5.01−4.84 (2H, m, CH_2-C22), 3.62 (1H, dtd, *J* = 6.5, 5.4, 4.3 Hz, CH-C18), 3.47 (1H, dd, *J* = 9.9, 5.4 Hz, CH_2-C17), 3.35 (1H, dd, *J* = 9.9, 6.5 Hz, CH_2-C17), 2.16−1.94 (2H, m, CH_2-C20), 1.70−1.62 (1H, m, CH_2-C19), 1.46−1.39 (1H, m, CH_2-C19), 0.90 (9H, s, CH_3-TBS), 0.89 (9H, s, CH_3-TBS), 0.07−0.04 (12H, m, CH_3-TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.0 (CH_2-C21), 114.2 (CH-C22), 72.6 (CH-C18), 67.3 (CH_2-C17), 33.6 (CH_2-C20), 29.4 (CH_2-C19), 26.0 (CH_3-TBS), 25.9 (CH_3-TBS), 18.4 (C-TBS), 18.2 (C-TBS), −4.2 (CH_3-TBS), −4.7 (CH_3-TBS), −5.3 (CH_3-TBS), −5.4 (CH_3-TBS).

The analytical and spectroscopic data are in agreement with those reported in the literature.

[161] Florence, G. J.; Morris, J. C.; Murray, R. J.; Osler, J. D.; Reddy, V. R.; Smith, T. K. *Org. Lett.* **2011**, *13*, 514−517

(*R*)-2-(*tert*-Butyldimethylsilyloxy)hex-5-en-1-ol 511

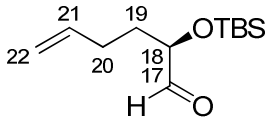


$C_{12}H_{26}O_2Si$

To a stirred solution of the bis-TBS ether **491** (2.5 g, 7.3 mmol) in THF (60 mL) at −10 °C was added HF•pyridine (23 mL of a 4.81 M solution in THF, 110 mmol). The mixture was stirred at −10 °C for 2 d. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution (100 mL) and the resulting mixture was extracted with Et_2O (3 × 100 mL). The combined organic phases were washed with brine (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: Et_2O, 100:1 to 50:1) gave the title compound **511** (1.5 g, 90%) as a colourless oil.

R_f = 0.48 (petroleum ether: EtOAc, 10:1); $[\alpha]_D^{21}$ −8.2 (c = 0.85, $CHCl_3$); ν_{max} (film) 3395 (br), 2953, 2930, 2857, 1472, 1254, 1105, 1045, 910, 833, 773 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.81 (1H, ddt, *J* = 16.9, 10.2, 6.5 Hz, CH-C21), 5.10–4.89 (2H, m, CH_2-C22), 3.76 (1H, dtd, *J* = 6.5, 5.1, 3.7 Hz, CH-C18), 3.58 (1H, ddd, *J* = 11.1, 5.8, 3.7 Hz, CH_2-C17), 3.47 (1H, ddd, *J* = 11.1, 6.5, 5.1 Hz, CH_2-C17), 2.11–2.05 (2H, m, CH_2-C20), 1.86 (1H, dd, *J* = 5.8, 5.1 Hz, OH), 1.65–1.56 (2H, m, CH_2-C19), 0.91 (9H, s, CH_3-TBS), 0.09 (3H, s, CH_3-TBS), 0.08 (3H, s, CH_3-TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.3 (CH_2-C21), 114.7 (CH-C22), 72.3 (CH-C18), 66.1 (CH_2-C17), 33.1 (CH_2-C20), 29.5 (CH_2-C19), 25.9 (CH_3-TBS), 18.1 (C-TBS), −4.4 (CH_3-TBS), −4.5 (CH_3-TBS); HRMS (ESI) for $C_{12}H_{26}NaO_2Si$ $[M+Na]^+$ calcd. 253.1587, found 253.1594.

(*R*)-2-(*tert*-Butyldimethylsilyloxy)hex-5-enal 510

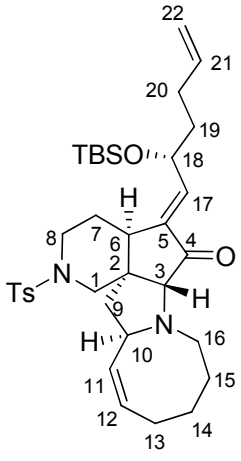


$C_{12}H_{24}O_2Si$

To a stirred solution of the alcohol **511** (1.4 g, 6.1 mmol) in DCM (50 mL) at 0 °C was added $NaHCO_3$ (1.5 g, 18 mmol) and Dess-Martin periodinane (6.1 g, 12 mmol) in one portion. The mixture was stirred at 0 °C for 2 h, then allowed to reach rt over 1 h and saturated aqueous $Na_2S_2O_3$ solution (60 mL) was added. The reaction was then stirred for 30 min and the phases were separated. The organic phase was washed with saturated aqueous Na_2CO_3 (60 mL), brine (60 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: Et_2O, 4:1) gave the title compound **510** (1.3 g, 95%) as a colourless oil.

R_f = 0.88 (petroleum ether: EtOAc, 4:1); $[\alpha]_D^{21}$ +34 (c = 0.99, $CHCl_3$); ν_{max} (film) 2955, 2930, 2857, 1736, 1472, 1254, 1107, 837, 777 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.57 (1H, d, *J* = 1.6 Hz, CH-C17), 5.75 (1H, ddt, *J* = 16.9, 10.2, 6.5 Hz, CH-C21), 5.06–4.82 (2H, m, CH_2-C22), 3.97 (1H, ddd, *J* = 7.0, 5.2, 1.6 Hz, CH-C18), 2.24–2.05 (2H, m, CH_2-C20), 1.79–1.62 (2H, m, CH_2-C19), 0.90 (9H, s, CH_3-TBS), 0.06 (3H, s, CH_3-TBS), 0.05 (3H, s, CH_3-TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.0 (CH-C17), 137.5 (CH_2-C21), 115.4 (CH-C22), 77.0 (CH-C18), 32.0 (CH_2-C20), 28.7 (CH_2-C19), 25.7 (CH_3-TBS), 18.1 (C-TBS), −4.6 (CH_3-TBS), −5.0 (CH_3-TBS); HRMS (ESI) for $C_{12}H_{24}NaO_2Si$ $[M+Na]^+$ calcd. 251.1426, found 251.1438.

(4a*R*,5*E*,6a*R*,12*Z*,13a*R*,14a*R*)-5-((*R*)-2-(*tert*-Butyldimethylsilyloxy)hex-5-en-1-ylidene)-2-tosyl-1,2,3,4,4a,5,8,9,10,11,13a,14-dodecahydropyrido[3'',4'':1',5'] cyclopenta [1',2':4,5]pyrrolo[1,2-a]azocin-6-one 508



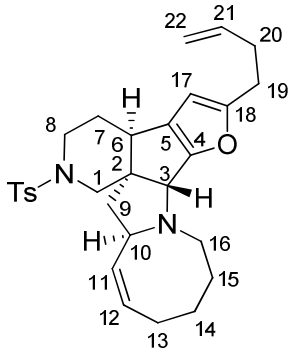
$C_{35}H_{52}N_2O_4SSi$

To a stirred solution of diisopropylamine (32 µL, 0.21 mmol) in THF (2 mL) at −78 °C was added *n*-BuLi (96 µL of a 2.16 M solution in THF, 0.21 mmol). The mixture was stirred at −78 °C for 10 min before addition of the ketone **385** (78 mg, 0.19 mmol) in THF (1 mL). The mixture was then stirred at −78 °C for 30 min before addition of the aldehyde **510** (51 mg, 0.19 mmol) in THF (1 mL). The mixture was stirred at −78 °C for 2 h and allowed to reach rt overnight. The reaction was quenched by addition of saturated aqueous NH_4Cl (5 mL) and the resulting mixture extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 10:1 to 2:1) gave the title compound **508** (33 mg, 32%) as a yellow gum.

R_f = 0.31 (petroleum ether: EtOAc, 2:1); $[\alpha]_D^{27}$ −40 (c = 1.78, $CHCl_3$); ν_{max} (film) 2953, 2926, 2855, 1721, 1449, 1256, 1163, 1086, 835, 775 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 7.65 (2H, d, *J* = 8.2 Hz, CH-Ts), 7.37 (2H, d, *J* = 8.2 Hz, CH-Ts), 6.37 (1H, dd, *J* = 8.9, 1.5 Hz, CH-C17), 5.79 (1H, ddt, *J* = 17.0, 10.2, 6.5 Hz, CH-C21), 5.56−5.46 (1H, m, CH-C12), 5.41 (1H, dd, *J* = 11.2, 4.7 Hz, CH-C11), 5.04−4.94 (2H, m, CH_2-C22), 4.23 (1H, td, *J* = 8.9, 4.0 Hz, CH-C18), 3.85 (1H, dd, *J* = 12.1, 1.9 Hz, CH_2-C1), 3.73 (1H, d, *J* = 12.2 Hz, CH_2-C8), 3.47−3.33 (2H, m, CH_2-C16, CH-C10), 3.41 (1H, s, CH-C3), 3.10 (1H, dt, *J* = 12.2, 2.4 Hz, CH_2-C16), 2.78 (1H, ddt, *J* = 13.2, 6.8, 4.2 Hz, CH_2-C13), 2.53 (1H, ddd, *J* = 11.9, 6.0, 1.5

Hz, CH-C6), 2.44 (3H, s, CH_3-Ts), 2.33 (1H, dt, *J* = 12.2, 2.5 Hz, CH_2-C8), 2.21 (1H, d, *J* = 12.1 Hz, CH_2-C1), 2.19–2.04 (3H, m, CH_2-C13, CH_2-C20), 1.94 (1H, dd, *J* = 13.8, 9.8 Hz, CH_2-C9), 1.84–1.47 (6H, m, CH_2-C7, CH_2-C14, CH_2-C15, CH_2-C19), 1.45–1.33 (3H, m, CH_2-C7, CH_2-C9, CH_2-C19), 0.85 (9H, s, CH_3–TBS), 0.01 (3H, s, CH_3–TBS), –0.05 (3H, s, CH_3–TBS); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 208.1 (C-C4), 143.8 (C-Ts), 139.4 (C-C5), 138.1 (CH-C17), 138.0 (CH-C21), 134.4 (CH-C11), 133.5 (C-Ts), 129.7 (CH-Ts), 127.9 (CH-C12), 127.6 (CH-Ts), 114.7 (CH_2-C22), 71.5 (CH-C3), 69.1 (CH-C18), 59.0 (CH-C10), 51.6 (CH_2-C1), 49.8 (CH_2-C16), 46.1 (C-C2), 45.0 (CH_2-C8), 44.2 (CH_2-C9), 39.9 (CH-C6), 37.4 (CH_2-C19), 30.7 (CH_2-C7), 29.3 (CH_2-C20), 27.0 (CH_2-C14), 25.5 (CH_3-TBS), 25.2 (CH_2-C15), 24.6 (CH_2-C13), 21.3 (CH_3-Ts), 17.9 (C-TBS), –4.4 (CH_3-TBS), –5.0 (CH_3-TBS); HRMS (ESI) for $C_{35}H_{53}N_2O_4SSi$ $[M+H]^+$ calcd. 625.3460, found 625.3490.

(4a*R*,7b*R*,14a*R*,15a*R*,*Z*)-6-(But-3-en-1-yl)-2-tosyl-1,2,3,4,4a,7b,9,10,11,12,14a,15-dodecahydrofuro[2'',3'':3',4']pyrido[3'',4'':1',5']cyclopenta[1',2':4,5]pyrrolo[1,2-a]azocine 512

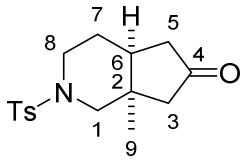


$C_{29}H_{36}N_2O_3S$

To a stirred solution of TBS ether **508** (10 mg, 16 μmol) in toluene (3 mL) at rt was added *p*-toluenesulfonic acid monohydrate (3.8 mg, 20 μmol). The mixture was stirred vigorously overnight at rt. The reaction was quenched by addition of saturated aqueous Na_2CO_3 (10 mL) and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 4:1 to 2:1) gave the title compound **512** (7.8 mg, 82%) as a pale yellow oil.

R_f = 0.45 (petroleum ether: Et_2O, 10:1); $[\alpha]_D^{26}$ + 36 (c = 0.23, $CHCl_3$); ν_{max} (film) 2924, 2855, 1447, 1348, 1163, 1094, 912, 731 cm^{-1}; ^1H NMR (500 MHz, MeOD) δ 7.55 (2H, d, *J* = 8.1 Hz, CH-Ts), 7.30 (2H, d, *J* = 8.1 Hz, CH-Ts), 5.83 (1H, s, CH-C17), 5.79–5.66 (2H, m, CH-C12, CH-C21), 5.38–5.32 (1H, m, CH-C11), 4.97–4.85 (2H, m, CH_2-C22), 4.01 (1H, s, CH-C3), 3.49–3.43 (1H, m, CH-C10), 3.42 (1H, d, *J* = 12.6 Hz, CH_2-C1), 3.00–2.93 (4H, m, CH_2-C1, CH_2-C8, CH_2-C16), 2.85 (1H, dt, *J* = 13.8, 7.2 Hz, CH_2-C16), 2.75 (1H, dd, *J* = 5.4, 1.7 Hz, CH-C6), 2.61 (2H, t, *J* = 7.4 Hz, CH_2-C19), 2.33 (3H, s, CH_3-Ts), 2.31–2.25 (2H, m, CH_2-C20), 2.14–2.04 (2H, m, CH_2-C13), 1.91–1.89 (2H, m, CH_2-C9, CH_2-C7), 1.67–1.25 (6H, m, CH_2-C7, CH_2-C9, CH_2-C14, CH_2-C15); ^{13}C NMR (126 MHz, MeOD) δ 161.9 (C-C17), 143.6 (C-Ts), 137.2 (CH-C21), 134.8 (C-Ts), 133.2 (CH-C12), 129.8 (CH-C11), 129.5 (CH-Ts), 127.8 (C-C4), 126.9 (CH-Ts), 121.0 (C-C18), 114.4 (CH_2-C22), 102.3 (CH-C17), 70.3 (CH-C3), 58.0 (C-C2), 56.5 (CH-C10), 49.4 (CH_3-C1), 49.2 (CH_2-C16), 45.5 (CH_2-C7), 41.5 (CH-C6), 40.7 (CH_2-C8), 32.1 (CH_2-C20), 29.4 (CH_2-C14), 28.0 (CH_2-C19), 25.1 (CH_2-C15), 24.7 (CH_2-C13), 24.3 (CH_2-C9), 20.1 (CH_3-Ts); HRMS (ESI) for $C_{29}H_{37}N_2NaO_3S$ $[M+Na]^+$ calcd. 493.2507, found 493.2495.

(4a*S,7a*R**)-7a-Methyl-2-tosylhexahydro-1H-cyclopenta[c]pyridin-6-one 424**

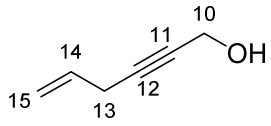


$C_{16}H_{21}NO_3S$

To a stirred solution of CuI (1.4 g, 7.5 mmol) and LiCl (0.35 g, 8.2 mmol) in THF (40 mL) at 0 °C was added methyl magnesium bromide (6 mL of a 2.85 M solution in THF, 17.1 mmol). The mixture was stirred at 0 °C for 10 min and a solution of the enone **320** (2.00 g, 6.8 mmol) in THF (10 mL) was added. The mixture was then stirred at 0 °C for 2 h and the reaction was quenched with saturated aqueous NH_4Cl solution (30 mL). The aqueous phase was extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 6:1 to 3:1) gave the title compound **424** (1.95 g, 93%) as a colourless foam.

R_f = 0.21 (petroleum ether: EtOAc, 4:1); ν_{max} (film) 2924, 1735, 1458, 1334, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (2H, d, *J* = 8.0 Hz, CH-Ts), 7.33 (2H, d, *J* = 8.0 Hz, CH-Ts), 3.24–3.19 (1H, m, CH_2-C8), 3.30 (1H, d, *J* = 12.0, CH_2-C1), 2.77 (1H, dd, *J* = 12.0, 0.6, CH_2-C1), 2.59 (1H, d, *J* = 12.0, CH_2-C8), 2.46 (1H, d, *J* = 18.7 Hz, CH_2-C3), 2.44 (3H, s, CH_3-Ts), 2.39–2.44 (1H, m, CH_2-C5), 2.01–1.94 (2H, m, CH-C6, CH_2-C5), 1.97 (1H, d, *J* = 18.7 Hz, CH_2-C3), 1.94–1.91 (1H, m, CH_2-C7), 1.52–1.48 (1H, m, CH_2-C7), 1.14 (3H, s, CH_3-C9); ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.1 (C-C4), 143.7 (C-Ts), 133.0 (C-Ts), 129.8 (CH-Ts), 127.6 (CH-Ts), 52.3 (CH_2-C1), 47.6 (CH_2-C3), 43.9 (CH_2-C8), 42.4 (CH_2-C5), 38.9 (C-2), 38.4 (CH-C6), 26.8 (CH_2-C7), 24.8 (CH_3-Ts), 21.5 (CH_3-C9); HRMS (EI) for $C_{16}H_{21}NO_3S$ ($[M]^+$) calcd.307.1242, found 307.1244.

Hex-5-en-2-yn-1-ol 427

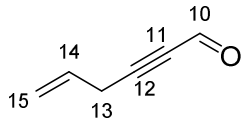


C_6H_8O

To a solution of propargyl alcohol (3.0 mL, 54 mmol) in THF (60 mL) at 0 °C was added ethylmagnesium bromide (38.0 mL of a 3.0 M solution in Et_2O, 112 mmol). The mixture was heated under reflux for 1 h. The mixture was then cooled to 0 °C and CuI (1.0 g, 5.3 mmol) was added in one portion. The mixture was stirred at 0 °C for 30 min before addition of allyl bromide (7.1 g, 59 mmol), and the resulting mixture was stirred at 0 °C for 5 h. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (100 mL). The phases were separated and the aqueous phase was extracted with Et_2O (2 × 100 mL). The combined organic extracts were washed with brine (200 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 5:1 to 3:1) gave the title compound **427** (4.5 g, 87%) as a colourless oil.

R_f = 0.32 (petroleum ether: EtOAc, 3:1); ν_{max} (film) 3440 (br), 3055, 3005, 2994, 2923, 2223, 1642, 1579, 1560, 1465, 1260, 1180, 922, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (1H, ddt, *J* = 17.1, 8.8, 7.6 Hz, CH-C14), 5.31(1H, ddt, *J* = 17.1, 1.7, 1.7 Hz, CH_2-C15), 5.11 (1H, ddt, *J* = 8.8, 1.7, 1.5 Hz, CH_2-C15), 4.28 (2H, t, *J* = 2.4 Hz, CH_2-C10), 3.00 (2H, dtdd, *J* = 7.6, 2.4, 1.7, 1.5 Hz, CH_2-C13), 2.74 (1H, s, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.2 (CH-C14), 116.9 (CH_2-C15), 82.6 (C-C11), 80.6 (C-C12), 50.9 (CH_2-C10), 22.9 (CH_2-C13); HRMS (ESI) for C_6H_8NaO ($[M+Na]^+$) calcd.119.0743, found 119.0737.

Hex-5-en-2-ynal 428

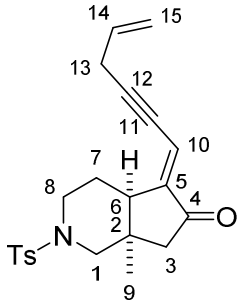


C_6H_6O

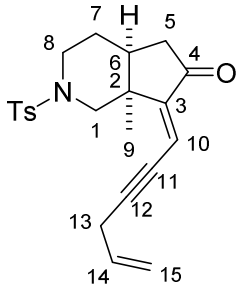
To a stirred solution of the alcohol **427** (500 mg, 5.21 mmol) in DCM (50 mL) at 0 °C was added manganese dioxide (4.5 g, 52 mmol) in one portion. The mixture was stirred at rt for 12 h. The mixture was then filtered through a short pad of Celite, washed with DCM (50 mL) and the filterate was concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (DCM: Et_2O, 30:1) gave the title compound **428** (432 mg, 86%) as a pale yellow oil.

R_f = 0.62 (petroleum ether: EtOAc, 9:1); ν_{max} (film) 2953, 2930, 2857, 1736, 1437, 1252, 1155, 1117, 837, 777 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.22 (1H, s, CH-C10), 5.80 (1H, ddt, *J* = 17.0, 10.0, 5.4 Hz, CH-C14), 5.36 (1H, dtd, *J* = 17.0, 1.8, 1.1 Hz, CH_2-C15), 5.22 (1H, ddt, *J* = 10.0, 1.1, 1.0 Hz, CH_2-C15), 3.20 (2H, ddd, *J* = 5.4, 1.8, 1.0 Hz, CH_2-C13); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.6 (C-C10), 130.6 (CH-C14), 115.8 (CH_2-C15), 87.7 (C-C12), 75.8 (C-C11), 26.6 (CH_2-C13); HRMS (ESI) for C_6H_6NaO $[M+Na]^+$ calcd. 117.0311, found 117.0298.

(4a*R,7a*R**,*E*)-5-(Hex-5-en-2-ynylidene)-7a-methyl-2-tosylhexahydro-cyclopenta[c]pyridin-6-one 429 and (4a*S**,7a*S**,*E*)-7-(Hex-5-en-2-ynylidene)-7a-methyl-2-tosylhexahydro-cyclopenta[c]pyridin-6-one 430**



$C_{22}H_{25}NO_3S$



$C_{22}H_{25}NO_3S$

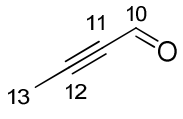
To a stirred solution of diisopropylamine (0.34 mL, 2.2 mmol) in THF (6 mL) at −78 °C was added *n*-BuLi (1.0 mL of a 2.2 M solution in THF, 2.2 mmol). The mixture was stirred at −78 °C for 10 min before addition of the ketone **320** (615 mg, 2.02 mmol) in THF (4 mL). The resulting mixture was further stirred at −78 °C for 30 min and a solution of the aldehyde **428** (226 mg, 2.41 mmol) in THF (2 mL) was added. The mixture was stirred at −78 °C for 2 h, then allowed to reach rt over 1 h. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (10 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 9:1) gave the title compound **429** (368 mg, 48%) and its C3 alkylation isomer **430** (124 mg, 16%) as pale yellow gums.

429: R_f = 0.91 (petroleum ether: EtOAc, 7:3); ν_{max} (film) 2955, 2926, 2855, 1717, 1618, 1339, 1163, 1034, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.55 (2H, d, *J* = 8.2 Hz, CH-Ts), 7.26 (2H, d, *J* = 8.2 Hz, CH-Ts), 6.38 (1H, dt, *J* = 2.3, 2.3 Hz, CH-C10), 5.72 (1H, ddt, *J* = 17.0, 10.3, 3.8 Hz, CH-C14), 5.19 (1H, dtd, *J* = 17.0, 2.0, 1.7 Hz, CH-C15), 5.07 (1H, dtd, *J* = 10.3, 1.7, 1.6 Hz, CH-C15), 3.35−3.28 (1H, m, CH_2-C8), 3.13 (1H, d, *J* = 12.1 Hz, CH_2-C1), 3.08 (2H, dddd, *J* = 3.8, 2.3, 2.0, 1.6 Hz, CH_2-C13), 2.61 (1H, d, *J* = 17.9 Hz, CH_2-C3), 2.58−2.50 (2H, m, CH-C6, CH_2-C8), 2.40 (1H, d, *J* = 12.1 Hz, CH_2-C1), 2.37 (3H, s, CH_3-Ts), 2.06−1.98 (1H, m, CH_2-C7), 2.02 (1H, d, *J* = 17.9 Hz, CH_2-C3), 1.79 (1H, dtd, *J* = 13.9, 10.0, 4.2 Hz,

CH_2-C7), 0.97 (3H, s, CH_3-C9); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.5 (C-C4), 149.0 (C-Ts), 143.8 (C-Ts), 133.3 (C-C5), 131.5 (CH-C14), 130.0 (CH-Ts), 127.6 (CH-Ts), 116.8 (CH_2-C15), 114.3 (CH-C10), 100.1 (CH-C12), 79.6 (C-C11), 52.8 (CH_2-C1), 46.8 (CH_2-C3), 45.3 (CH-C6), 44.8 (CH_2-C8), 36.4 (C-C2), 25.9 (CH_2-C7), 25.6 (CH_3-C9), 24.3 (CH_2-C13), 21.6 (CH_3-Ts); HRMS (ESI) for $C_{22}H_{25}NNaO_3S$ $[M+Na]^+$ calcd. 406.1415, found 406.1447

430: R_f = 0.88 (petroleum ether: EtOAc, 7:3); ν_{max} (film) 2948, 2927, 2850, 1717, 1620, 1339, 1160, 1032, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (2H, d, *J* = 8.2 Hz, CH-Ts), 7.31 (2H, d, *J* = 8.2 Hz, CH-Ts), 6.57 (1H, t, *J* = 2.5 Hz, CH-C10), 5.88 (1H, ddt, *J* = 17.0, 10.3, 5.3 Hz, CH-C14), 5.35 (1H, dtd, *J* = 17.0, 1.7, 1.5 Hz, CH-C15), 5.20 (1H, dtd, *J* = 10.3, 1.6, 1.5 Hz, CH-C15), 3.29–3.24 (2H, m, CH_2-C13), 3.18 (1H, d, *J* = 12.3 Hz, CH_2-C1), 3.16–3.13 (1H, m, CH_2-C8), 3.11 (1H, d, *J* = 12.3 Hz, CH_2-C1), 2.79–2.73 (1H, m, CH_2-C8), 2.43 (3H, s, CH_3-Ts), 2.38–2.32 (1H, m, CH_2-C5), 2.07 (1H, dd, *J* = 18.0, 8.3 Hz, CH_2-C5), 2.04–1.91 (2H, m, CH_2-C7, CH-C6), 1.53–1.45 (1H, m, CH_2-C7), 1.20 (3H, s, CH_3-C9); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.8 (C-C4), 149.3 (C-Ts), 143.3 (C-Ts), 133.3 (C-C3), 131.5 (CH-C14), 129.7 (CH-Ts), 127.7 (CH-Ts), 117.0 (CH_2-C15), 115.9 (CH-C10), 104.0 (CH-C12), 78.7 (C-C11), 50.4 (CH_2-C1), 43.6 (C-C2), 42.9 (CH_2-C8), 40.7 (CH_2-C5), 39.7 (CH-C6), 37.3 (CH_2-C7), 25.6 (CH_2-C13), 24.5 (CH_3-C9), 21.5 (CH_3-Ts); HRMS (ESI) for $C_{22}H_{25}NNaO_3S$ $[M+Na]^+$ calcd. 406.1415, found 406.1453.

But-2-ynal 433[162]



C_4H_4O

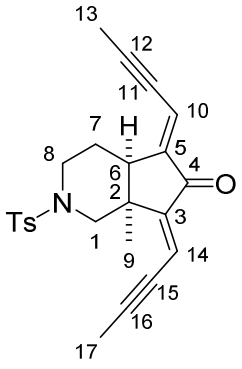
To a stirred solution of 2-butyn-1-ol (350 mg, 5.01 mmol) in DCM (40 mL) at 0 °C was added manganese dioxide (4.30 g, 50.2 mmol) in one portion. The mixture was stirred at rt for 12 h. The reaction mixture was then filtered through a short pad of Celite and the filter cake was washed with DCM (100 mL). The filterate was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (DCM: Et_2O, 30:1) to give the title compound **433** (162 mg, 48%) as a volatile, pale yellow oil.

R_f = 0.78 (petroleum ether: EtOAc, 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.13 (1H, q, *J* = 1.1 Hz, CH-C10), 2.05 (1H, d, *J* = 1.1 Hz, CH_3-C13); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.1 (C-C10), 95.2 (C-C12), 80.9 (C-C11), 4.1 (CH_3-C13).

The analytical and spectroscopic data are in agreement with those reported in the literature.

[162] Persich, P.; Llaveria, J.; Lhermet, R.; Haro, T.; Stade, R.; Kondoh, A.; Fürstner, A. *Chem. Eur. J.* **2013**, *19*, 13047−13058

(4a*R,5*E*,7*E*,7a*S**)-5,7-Di(but-2-ynylidene)-7a-methyl-2-tosylhexahydro-1H-cyclopenta[c]pyridin-6-one 435**



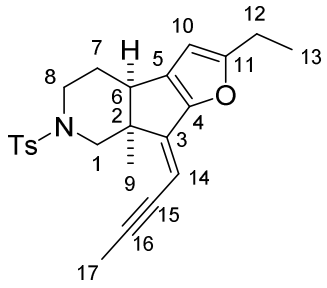
$C_{24}H_{25}NO_3S$

To a stirred solution of diisopropylamine (0.17 mL, 1.1 mmol) in THF (2 mL) at −78 °C was added *n*-BuLi (0.45 mL of a 2.4 M solution in THF, 1.1 mmol). The mixture was stirred at −78 °C for 10 min and a solution of the ketone **320** (0.30 g, 1.0 mmol) in THF (2 mL) was added. The mixture was stirred for 30 min at −78 °C and a solution of the aldehyde **433** (80 mg, 1.2 mmol) in THF (1 mL) was then added. The resulting mixture was stirred at −78 °C for 2 h, then allowed to reach rt over 1 h. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (10 mL). The aqueous phase was extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 9:1 to 3:1) gave the title compound **435** (200 mg, 45%) as a pale yellow gum.

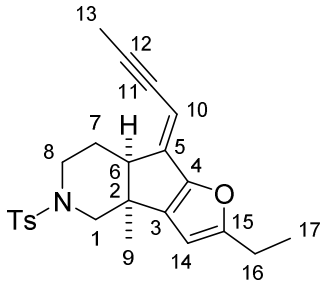
R_f = 0.40 (petroleum ether: EtOAc, 3:1); ν_{max} (film) 2945, 2922, 2853, 2212, 1694, 1607, 1462, 1350, 1256, 1163, 1094, 656 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (2H, d, *J* = 8.2 Hz, CH-Ts), 7.29 (2H, d, *J* = 8.2 Hz, CH-Ts), 6.59 (1H, q, *J* = 2.5 Hz, CH-C14), 6.50 (1H, q, *J* = 2.7 Hz, CH-C10), 3.47 (1H, d, *J* = 12.3 Hz, CH_2-C1), 3.19 (1H, d, *J* = 12.3 Hz, CH_2-C1), 3.09−3.02 (1H, m, CH_2-C8), 2.98 (1H, dt, *J* = 11.0, 5.3 Hz, CH_2-C8), 2.66−2.59 (1H, m, CH-C6), 2.41 (3H, s, CH_3-Ts), 2.14 (3H, d, *J* = 2.7 Hz, CH_3-C13), 2.09−2.02 (1H, m, CH_2-C7), 2.03 (3H, d, *J* = 2.5 Hz, CH_3-C17), 1.80 (1H, dddd, *J* = 18.2, 9.0, 5.3, 4.4 Hz, CH_2-C7), 1.34 (3H, s, CH_3-C9); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.3 (C-C4), 150.5 (C-C3), 148.1 (C-C5), 143.6 (C-Ts), 133.8 (C-Ts), 129.7 (CH-Ts), 127.7 (CH-Ts), 117.1 (CH-C10), 116.3 (CH-C14),

104.2 (C-C11), 101.3 (C-C15), 77.2 (C-C12), 76.8 (C-C16), 50.4 (CH_2-C1), 44.2 (CH-C6), 43.6 (CH_2-C8), 42.7 (C-C2), 25.4 (CH_2-C7), 24.5 (CH_3-C9), 21.6 (CH_3-Ts), 5.4 (CH_3-C13), 5.2 (CH_3-C17); HRMS (ESI) for $C_{24}H_{25}NNaO_3S$ $[M+Na]^+$ calcd. 430.1431, found 430.1447.

(4a*S,7a*R**,*E*)-3-(But-2-yn-1-ylidene)-11-ethyl-7a-methyl-8-tosyl-3b,5,6, 7,7a,8-hexahydro-furo[3',2':3,4]cyclopenta[1,2-c]pyridine 437 and *(*4a*R**,7a*S**,*E)*-5-(But-2-yn-1-ylidene)-15-ethyl-7a-methyl-8-tosyl-3b,5,6, 7,7a,8-hexahydro-furo[2',3':4,5]cyclopenta[1,2-c]pyridine 438**



$C_{24}H_{27}NO_3S$



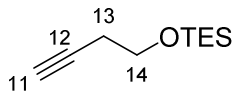
$C_{24}H_{27}NO_3S$

To a stirred solution of tributylphosphine (12 µL, 40 µmol) in DCM (10 mL) at 0 °C was added water (5.0 µL, 0.28 mmol) and a solution of the enyne **435** (20 mg, 40 µmol) in DCM (2 mL). The mixture was stirred at rt for 6 h. The solution was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 6:1 to 3:1) gave the title compound **437** (9.9 mg, 49%) as a pale yellow oil and its C3 isomer **438** (5.9 mg, 29%) as a pale yellow oil.

437: R_f = 0.65 (petroleum ether: EtOAc, 3:1); ν_{max} (film) 2963, 2924, 2855, 2216, 1618, 1456, 1335, 1261, 1161, 1090 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (2H, d, *J* = 8.3 Hz, CH-Ts), 7.26 (2H, d, *J* = 8.3 Hz, CH-Ts), 5.95 (1H, s, CH-C10), 5.33 (1H, q, *J* = 2.5 Hz, CH-C14), 3.86 (1H, d, *J* = 12.5 Hz, CH_2-C1), 3.71 (1H, ddd, *J* = 6.7, 6.1, 1.9 Hz, CH-C6), 3.24 (1H, d, *J* = 12.5 Hz, CH_2-C1), 3.15−3.11 (1H, m, CH_2-C8), 3.01−2.97 (1H, m, CH_2-C8), 2.62 (2H, q, *J* = 7.6 Hz, CH_2-C12), 2.42 (3H, s, CH_3-Ts), 2.21−2.14 (1H, m, CH_2-C7), 2.09 (3H, d, *J* = 2.5 Hz, CH_3-C17), 2.06−2.00 (1H, m, CH_2-C7), 1.25 (3H, s, CH_3-C9), 1.21 (3H, t, *J* = 7.6 Hz, CH_3-C13); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.0 (C-C11), 156.2 (C-C4), 144.7 (C-C5), 143.6 (C-Ts), 139.4 (C-C3), 133.8 (C-Ts), 129.7 (CH-Ts), 127.6 (CH-Ts), 107.2 (CH-C10), 107.1 (CH-C14), 98.8 (C-C16), 74.6 (C-C15), 58.5 (CH_2-C1), 49.2 (CH-C6), 43.6 (C-C2), 43.4 (CH_2-C8), 25.0 (CH_2-C7), 24.6 (CH_3-C9), 22.4 (CH_2-C12), 21.6 (CH_3-Ts), 9.6 (CH_3-C17), 5.2 (CH_3-C13); HRMS (ESI) for $C_{24}H_{27}NNaO_3S$ $[M+Na]^+$ calcd. 432.1583, found 432.1604.

438: R_f = 0.68 (petroleum ether: EtOAc, 3:1); ν_{max} (film) 2953, 2920, 2853, 2214, 1616, 1456, 1333, 1261, 1165, 1091 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.59 (2H, d, *J* = 8.2 Hz, CH-Ts), 7.26 (2H, d, *J* = 8.2 Hz, CH-Ts), 5.85 (1H, s, CH-C14), 5.39 (1H, q, *J* = 2.5 Hz, CH-C10), 3.31–3.27 (1H, m, CH_2-C8), 3.26 (1H, d, *J* = 12.2 Hz, CH_2-C1), 3.17 (1H, d, *J* = 12.2 Hz, CH_2-C1), 3.15–3.11 (1H, m, CH_2-C8), 3.01 (1H, dd, *J* = 7.3, 5.5 Hz, CH-C6), 2.62 (2H, q, *J* = 7.6 Hz, CH_2-C16), 2.41 (3H, s, CH_3-Ts), 2.21–2.14 (1H, m, CH_2-C7), 2.06–2.00 (1H, m, CH_2-C7), 1.99 (3H, d, *J* = 2.5 Hz, CH_3-C13), 1.25 (3H, s, CH_3-C9), 1.22 (3H, t, *J* = 7.6 Hz, CH_3-C17); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3 (C-C15), 158.0 (C-C4), 144.8 (C-C5), 143.6 (C-Ts), 136.8 (C-C3), 133.8 (C-Ts), 129.7 (CH-Ts), 127.6 (CH-Ts), 109.1 (CH-C14), 108.3 (CH-C10), 79.1 (C-C12), 74.4 (C-C11), 52.2 (CH_2-C1), 45.8 (CH-C6), 45.5 (C-C2), 43.4 (CH_2-C8), 25.0 (CH_2-C7), 24.6 (CH_3-C9), 22.4 (CH_2-C16), 21.6 (CH_3-Ts), 9.6 (CH_3-C17), 5.4 (CH_3-C13); HRMS (ESI) for $C_{24}H_{27}NNaO_3S$ $[M+Na]^+$ calcd. 432.1583, found 432.1594.

(But-3-yn-1-yloxy)triethylsilane 441[163]



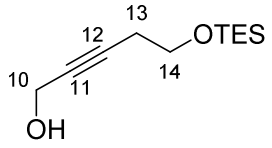
$C_{10}H_{20}OSi$

To a stirred solution of 3-butyn-1-ol (2.00 g, 28.5 mmol) in DCM (100 mL) at 0 °C was added TESCl (5.30 g, 34.5 mmol) and pyridine (2.90 g, 37.0 mmol). The mixture was stirred for 4 h at 0 °C and saturated aqueous NH_4Cl solution (60 mL) was added. The aqueous phase was extracted with DCM (2 × 60 mL) and the combined organic extracts were washed with brine (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: DCM, 3:1) gave the title compound **441** (5.02 g, 96%) as a colourless oil.

R_f = 0.80 (petroleum ether: DCM, 3:2); ν_{max} (film) 3315, 2943, 2926, 2866, 1464, 1111 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.75 (2H, t, *J* = 7.3 Hz, CH_2-C14), 2.37 (2H, td, *J* = 7.3, 2.7 Hz, CH_2-C13), 1.89 (1H, t, *J* = 2.7 Hz, CH-C11), 0.88 (9H, t, *J* = 8.1 Hz, CH_3-TES), 0.53 (6H, q, *J* = 8.1 Hz, CH_2-TES); ^{13}C NMR (126 MHz, $CDCl_3$) δ 81.5 (CH_2-C14), 69.4 (C-C12), 61.6 (C-C11), 23.0 (CH-C13), 6.8 (CH_2-TES), 4.5 (CH_3-TES).

[163] Tanabe, Y.; Okumura, H.; Maeda, A.; Murakami, M. *Tetrahedron Lett.* **1994**, *35*, 8413-8414

5-(Triethylsilyloxy)pent-2-yn-1-ol 442

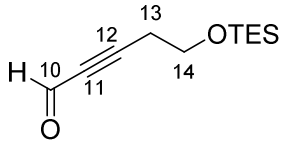


$C_{11}H_{22}O_2Si$

To a stirred solution of the alkyne **441** (4.60 g, 25.0 mmol) in THF (80 mL) at −78 °C was added *n*-BuLi (10 mL of a 2.75 M solution in THF, 27.5 mmol). The mixture was stirred at −78 °C for 30 min, then at 0 °C for 30 min and paraformaldehyde (2.25 g, 75.0 mmol) was added. The reaction mixture was stirred at 0 °C for 1 h, then allowed to reach rt over 2 h. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (100 mL) and the aqueous phase was extracted with EtOAc (2 × 80 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 1:5) gave the title compound **442** (5.13 g, 96%) as a colourless oil.

R_f = 0.44 (petroleum ether: EtOAc, 4:1); ν_{max} (film) 3372 (br), 2955, 2913, 2876, 1414, 1238, 1098, 829, 725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.14–4.11 (2H, m, CH_2-C10), 3.64 (2H, t, *J* = 7.2 Hz, CH_2-C14), 3.23 (1H, s, OH), 2.36 (2H, tt, *J* = 7.2, 2.1 Hz, CH_2-C13), 0.88 (9H, t, *J* = 8.1 Hz, CH_3-TES), 0.53 (6H, q, *J* = 8.1 Hz, CH_2-TES); ^{13}C NMR (126 MHz, $CDCl_3$) δ 82.5 (C-C12), 80.0 (C-C11), 61.5 (CH_2-C14), 50.8 (CH_2-C10), 23.0 (CH_2-C13), 6.6 (CH_3-TES), 4.3 (CH_2-TES); HRMS (ESI) for $C_{11}H_{22}NaO_2Si$ $[M+Na]^+$ calcd. 237.1287, found 237.1281.

5-(Triethylsilyloxy)pent-2-ynal 443

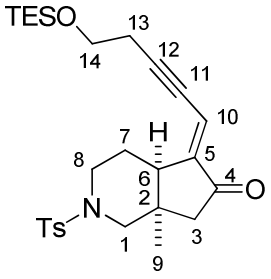


$C_{11}H_{20}O_2Si$

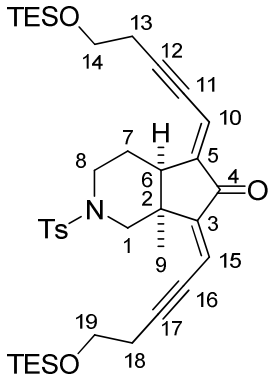
To a stirred solution of the alcohol **442** (1.3 g, 6.0 mmol) in DCM (50 mL) at 0 °C was added manganese dioxide (5.2 g, 60 mmol) in one portion. The mixture was stirred for 12 h at rt. The reaction was then filtered through a short pad of Celite, washed with DCM (100 mL) and the filtrate was concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 10:1) gave the title compound **443** (980 mg, 76%) as a pale yellow oil.

R_f = 0.91 (petroleum EtOAc, 4:1); ν_{max} (film) 3372 (br), 2955, 2913, 2876, 2205, 1668, 1238, 1136, 1101, 749 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.10 (1H , t, *J* = 0.8 Hz, CH-C10), 3.73 (2H, t, *J* = 6.8 Hz, CH_2-C14), 2.57 (2H, td, *J* = 6.8, 0.8 Hz, CH_2-C13), 0.88 (9H, t, *J* = 8.1 Hz, CH_3-TES), 0.54 (6H, q, *J* = 8.1 Hz, CH_2-TES); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.8 (CH-C10), 95.9 (C-C12), 82.2 (C-C11), 60.3 (CH_2-C14), 23.5 (CH_2-C13), 6.6 (CH_3-TES), 4.3 (CH_2-TES); HRMS (ESI) for $C_{11}H_{20}NaO_2Si$ $[M+Na]^+$ calcd. 235.1134, found 235.1125.

(4a*R,7a*R**,*E*)-7a-Methyl-2-tosyl-5-(5-triethylsilyloxypent-2-ynylidene) hexahydro-cyclopenta[c]pyridin-6-one 444 and (4a*R**,7a*R**,*E*)-7a-Methyl-2-tosyl-5-7-bis(5-triethylsilyloxypent-2-ynylidene)hexahydro-cyclopenta [c]pyridin-6-one 446**



$C_{27}H_{39}NO_4SSi$



$C_{38}H_{57}NO_5SSi_2$

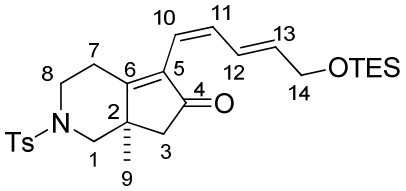
To a stirred solution of diisopropylamine (0.42 mL, 2.9 mmol) in THF (6 mL) at −78 °C was added *n*-BuLi (1.2 mLof a 2.38 M solution in THF, 2.9 mmol). The mixture was stirred for 10 min at −78 °C and a solution of ketone **320** (0.80 g, 2.6 mmol) in THF (2 mL) was added. The resulting mixture was stirred at −78 °C for 30 min and a solution of the aldehyde **443** (0.66 mg, 3.1 mmol) in THF (2 mL) was added. The mixture was stirred at −78 °C for 2 h and then allowed to reach rt over 1 h. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (10 mL). The aqueous phase was extracted with EtOAc (2 × 20 mL) and the combined organic extracts were washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 5:1) gave the title compound **444** (538 mg, 45%) as a colourless oil and bis-alkylated compound **446** (102 mg, 6%) as a pale yellow oil.

444: R_f = 0.41 (petroleum ether: EtOAc, 3:1); ν_{max} (film) 2955, 2911, 2876, 2212, 1719, 1616, 1354, 1341, 1161, 1096 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (2H, d, *J* = 8.2 Hz, CH-Ts), 7.31 (2H, d, *J* = 8.2 Hz, CH-Ts), 6.39 (1H, dt, *J* = 4.4, 2.2 Hz, CH-C10), 3.71 (2H, t, *J* = 6.8 Hz, CH_2-C14), 3.40−3.27 (1H, m, CH_2-C8), 3.16 (1H, d, *J* = 12.0 Hz, CH_2-C1), 2.65 (1H, d, *J* = 17.8 Hz, CH_2-C3), 2.61−2.52 (4H, m, CH_2-C8, CH_2-C13, CH-C6), 2.45 (1H, d, *J* = 12.0 Hz, CH_2-C1), 2.42 (3H, s, CH_3-Ts), 2.05 (1H, d, *J* = 17.8 Hz, CH_2-C3), 2.09−2.04 (1H, m, CH_2-C7), 1.90−1.78 (1H, m, CH_2-C7), 1.02 (3H, s, CH_3-C9), 0.92 (9H, t, *J* = 8.0 Hz, CH_3-TES), 0.57 (6H, q, *J* =

8.0 Hz, CH_2-TES); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.5 (C-C4), 148.9 (C-C5), 143.8 (C-Ts), 133.1 (C-Ts), 129.9 (CH-Ts), 127.7 (CH-Ts), 114.5 (CH-C10), 101.1 (C-C11), 78.4 (C-C12), 61.2 (CH_2-C14), 52.9 (CH_2-C1), 46.8 (CH_2-C3), 45.2 (CH-C6), 44.8 (CH_2-C8), 36.3 (C-C2), 25.7 (CH_2-C7), 25.6 (CH_3-C9), 24.5 (CH_2-C13), 21.6 (CH_3-Ts), 6.8 (CH_3-TES), 4.5 (CH_2-TES); HRMS (ESI) for $C_{27}H_{39}NNaO_4SSi$ $[M+Na]^+$ calcd. 524.2238, found 524.2261.

446: R_f = 0.61 (petroleum ether: EtOAc, 3:1); ν_{max} (film) 2955, 2911, 2876, 2211, 1694, 1607, 1354, 1250, 1165, 1094 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.60 (2H, d, *J* = 8.2 Hz, CH-Ts), 7.28 (2H, d, *J* = 8.2 Hz, CH-Ts), 6.61 (1H, t, *J* = 2.5 Hz, CH-C15), 6.52 (1H, dt, *J* = 2.3, 2.2 Hz, CH-C10), 3.84 (2H, t, *J* = 7.1 Hz, CH_2-C19), 3.72 (2H, t, *J* = 6.8 Hz, CH_2-C14), 3.48 (1H, d, *J* = 12.3 Hz, CH_2-C1), 3.17 (1H, d, *J* = 12.3 Hz, CH_2-C1), 3.07−2.94 (2H, m, CH_2-C8), 2.73 (2H, td, *J* = 7.1, 2.5 Hz, CH_2-C18), 2.65−2.61 (1H, m, CH-C6), 2.60 (2H, td, *J* = 6.8, 2.3 Hz, CH_2-C13), 2.42 (3H, s, CH_3-Ts), 2.09−2.02 (1H, m, CH_2-C7), 1.87−1.77 (1H, m, CH_2-C7), 1.35 (3H, s, CH_3-C9), 0.95 (9H, t, *J* = 8.0 Hz, CH_3-TES), 0.93 (9H, t, *J* = 8.0 Hz, CH_3-TES), 0.61 (6H, q, *J* = 8.0 Hz, CH_2-TES), 0.58 (6H, q, *J* = 8.0 Hz, CH_2-TES); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.2 (C-C4), 150.7 (C-C3), 148.4 (C-C5), 143.8 (C-Ts), 133.9 (C-Ts), 129.7 (CH-Ts), 127.7 (CH-Ts), 117.0 (CH-C15), 116.2 (CH-C10), 105.5 (C-C16), 102.8 (C-C11), 78.9 (C-C17), 78.5 (C-C12), 61.2 (CH_2-C19), 61.1 (CH_2-C14), 50.3 (CH_2-C1), 44.3 (CH-C6), 43.5 (CH_2-C8), 42.9 (C-C2), 25.3 (CH_2-C7), 24.9 (CH_3-C18), 24.6 (CH_2-C13), 21.6 (CH_3-Ts), 20.9 (CH_3-C9), 6.8 (CH_3-TES), 6.7 (CH_3-TES), 4.5 (CH_2-TES), 4.5 (CH_2-TES); HRMS (ESI) for $C_{38}H_{57}NNaO_5SSi_2$ $[M+Na]^+$ calcd. 718.3327, found 718.3388.

(*R)-7a-Methyl-2-tosyl-5-((1*E*,3*Z*)-5-(triethylsilyloxy)penta-1,3-dienyl)-3,4,7,7a-tetrahydro-1H-cyclopenta[c]pyridin-6-one 448**

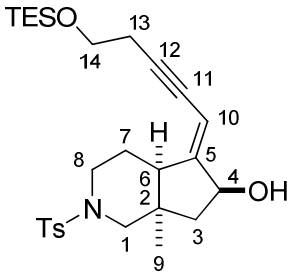


$C_{27}H_{39}NO_4SSi$

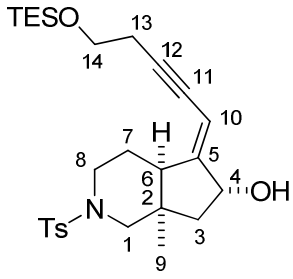
To a stirred solution of tributylphosphine (11 µL, 40 µmol) in DCM (10 mL) at 0 °C was added water (3.6 µL, 0.20 mmol) and the enyne **444** (20 mg, 40 µmol). The mixture was stirred at rt for 12 h. The solution was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 4:1) gave the title compound **448** (13.0 mg, 66%) as a pale yellow oil.

R_f = 0.32 (petroleum ether: EtOAc, 4:1); ν_{max} (film) 2953, 2930, 2857, 1736, 1437, 1252, 1155, 1117, 1005, 837, 777 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.62 (2H, d, *J* = 8.2 Hz, CH-Ts), 7.32 (2H, d, *J* = 8.2 Hz, CH-Ts), 6.29 (1H, dd, *J* = 11.3, 11.3 Hz, CH-C11), 6.07 (1H, dd, 15.1, 11.3 Hz, CH-12), 5.88 (1H, dt, *J* = 15.1, 4.5 Hz, CH-C13), 5.75 (1H, d, *J* = 11.3 Hz, CH-C10), 4.21 (2H, d, *J* = 4.5 Hz, CH_2-C14), 4.07−3.98 (1H, m, CH_2-C8), 3.90 (1H, dd, *J* = 11.1 Hz, CH_2-C1), 2.75−2.64 (1H, m, CH_2-C7), 2.59 (1H, dd, *J* = 13.1, 3.3 Hz, CH_2-C7), 2.42 (3H, s, CH_3-Ts), 2.36 (1H, d, *J* = 18.5 Hz, CH_2-C3), 2.22 (1H, dd, *J* = 11.9, 3.3 Hz, CH_2-C8), 2.16 (1H, d, *J* = 18.5 Hz, CH_2-C3), 2.14 (1H, d, *J* = 11.1 Hz, CH_2-C1), 1.48 (3H, s, CH_3-C9), 0.95 (9H, t, *J* = 8.0 Hz, CH_3-TES), 0.59 (6H, q, *J* = 8.0 Hz, CH_2-TES); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.1 (C-C4), 173.9 (C-C6), 143.8 (C-Ts), 141.8 (C-C5), 136.3 (CH-C13), 135.3 (CH-C11), 133.5 (C-Ts), 129.8 (CH-Ts), 127.4 (CH-Ts), 125.5 (CH-C12), 117.6 (CH-C10), 62.6 (CH_2-C14), 57.6 (CH_2-C1), 47.1 (CH_2-C3), 46.5 (CH_2-C8), 41.8 (C-C2), 26.5 (CH_2-C7), 25.6 (CH_3-C9), 21.6 (CH_3-Ts), 6.8 (CH_3-TES), 4.5 (CH_2-TES); HRMS (ESI) for $C_{27}H_{39}NNaO_4SSi$ $[M+Na]^+$ calcd. 524.7426, found 524.7432.

(4a*R,6*S*,7a*R**,*E*)-7a-Methyl-2-tosyl-5-(5-(triethylsilyloxy)pent-2-ynylidene) octahydro-cyclopenta[c]pyridin-6-ol 468 and (4a*R**,6*R*,7a*R**,*E*)-7a-Methyl-2-tosyl-5-(5-(triethylsilyloxy)pent-2-ynylidene)octahydro-cyclopenta[c] pyridin-6-ol *epi*-468**



$C_{27}H_{41}NO_4SSi$



$C_{27}H_{41}NO_4SSi$

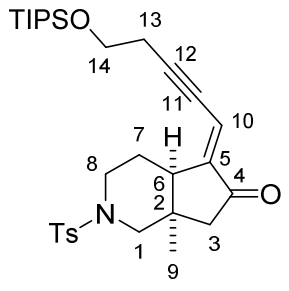
To a stirred solution of the enone **320** (138 mg, 0.248 mmol) in MeOH (20 mL) at 0 °C was added cerium chloride heptahydrate (134 mg, 0.361 mmol) and sodium borohydride (23 mg, 0.60 mmol) in one portion. The mixture was stirred overnight at rt before the reaction was quenched with saturated aqueous NH_4Cl solution (20 mL). The aqueous phase was extracted with Et_2O (2 × 30 mL) and the combined organic extracts were washed with brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 4:1 to 2:1) gave the title compound **468** (64 mg, 46%) and ***epi*-468** (67 mg, 47%) as colourless oils.

468: R_f = 0.38 (petroleum ether: EtOAc, 2:1); ν_{max} (film) 3495 (br), 2953, 2933, 2874, 1460, 1339, 1161, 1092 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (2H, d, *J* = 8.0 Hz, CH-Ts), 7.26 (2H, d, *J* = 8.0 Hz, CH-Ts), 5.60 (1H, td, *J* = 2.3, 2.0 Hz, CH-C10), 4.57 (1H, t, *J* = 7.8 Hz, CH-C4), 3.62 (2H, t, *J* = 6.8 Hz, CH_2-C14), 3.58−3.48 (1H, m, CH_2-C8), 3.39 (1H, d, *J* = 11.9 Hz, CH_2-C1), 2.44 (2H, td, *J* = 6.8, 2.3 Hz, CH_2-C13), 2.37 (3H, s, CH_3-Ts), 2.31−2.20 (2H, m, CH_2-C8, CH-C6), 2.13 (1H, d, *J* = 11.9 Hz, CH_2-C1), 2.09−1.95 (2H, m, CH_2-C3, CH_2-C7), 1.83−1.64 (2H, m, CH_2-C3, CH_2-C7), 1.54 (1H, s, OH), 0.87 (9H, t, *J* = 7.9 Hz, CH_3-TES), 0.79 (3H, s, CH_3-C9), 0.52 (6H, q, *J* = 7.9 Hz, CH_2-TES); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.9 (C-C5), 143.6 (C-Ts), 133.5 (C-Ts), 129.8 (CH-Ts), 127.8 (CH-Ts), 107.0 (CH-C10), 92.3 (C-C11), 78.5 (C-C12), 73.5 (CH-C4), 61.7 (CH_2-C14), 53.1 (CH_2-C1), 47.0 (CH-C6), 45.7 (CH_2-C8), 42.5 (CH_2-C3), 39.3 (C-C2), 26.8 (CH_2-C7), 26.3

(CH_3-C9), 24.2 (CH_2-C13), 21.7 (CH_3-Ts), 6.9 (CH_3-TES), 4.6 (CH_3-TES); HRMS (ESI) for $C_{27}H_{41}NNaO_4SSi$ $[M+Na]^+$ calcd. 526.2400, found 526.2415.

***epi*-468**: R_f = 0.35 (petroleum ether: EtOAc, 2:1); ν_{max} (film) 3490 (br), 2952, 2924, 2861, 1455, 1335, 1162, 1092 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.62 (2H, d, *J* = 8.3 Hz, CH-Ts), 7.31 (2H, d, *J* = 8.3 Hz, CH-Ts), 5.66 (1H, dt, *J* = 2.2, 2.0 Hz, CH-C10), 4.60–4.58 (1H, m, CH-C4), 3.69 (2H, t, *J* = 7.1 Hz, CH_2-C14), 3.17 (1H, dd, *J* = 11.0, 5.0 Hz, CH_2-C8), 3.39 (1H, d, *J* = 11.9, CH_2-C1), 2.63 (1H, ddd, *J* = 11.0, 8.2, 4.2 Hz, CH_2-C8), 2.55–2.45 (3H, m, CH_2-C13, CH-C6), 2.43 (3H, s, CH_3-Ts), 2.38 (1H, dd, *J* = 14.0, 8.2 Hz, CH_2-C3), 2.13 (1H, d, *J* = 11.9 Hz, CH_2-C1), 1.92–1.83 (2H, m, CH_2-C7), 1.72–1.59 (1H, brs, OH), 1.46–1.39 (1H, m, CH_2-C3), 1.09 (3H, s, CH_3-C9), 0.94 (9H, t, *J* = 7.9 Hz, CH_3-TES), 0.59 (6H, q, *J* = 7.9 Hz, CH_2-TES); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.9 (C-C5), 143.6 (C-Ts), 133.5 (C-Ts), 129.8 (CH-Ts), 127.8 (CH-Ts), 106.2 (CH-C10), 92.9 (C-C11), 78.3 (C-C12), 73.1 (CH-C4), 61.7 (CH_2-C14), 53.2 (CH_2-C1), 47.5 (CH-C6), 44.7 (CH_2-C8), 44.0 (CH_2-C3), 39.8 (C-C2), 26.3 (CH_2-C7), 25.3 (CH_3-C9), 24.2 (CH_2-C13), 21.7 (CH_3-Ts), 6.9 (CH_3-TES), 4.5 (CH_2-TES); HRMS (ESI) for $C_{27}H_{41}NNaO_4SSi$ $[M+Na]^+$ calcd. 526.2400, found 526.2418.

(4a*R,7a*R**,*E*)-7a-Methyl-2-tosyl-5-(5-triisopropylsilyloxypent-2-ynylidene) hexahydro-cyclopenta[c]pyridin-6-one 450**

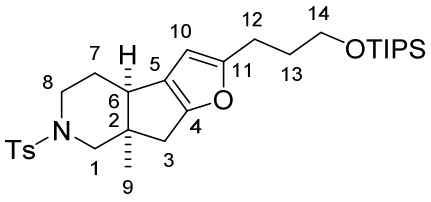


$C_{30}H_{45}NO_4SSi$

To a stirred solution of diisopropylamine (0.43 mL, 3.1 mmol) in THF (6 mL) at −78 °C was added *n*-BuLi (1.4 mL of a 2.38 M solution in THF, 3.1 mmol). The mixture was stirred at −78 °C for 10 min and a solution of the ketone **320** (900 mg, 2.93 mmol) in THF (2 mL) was added. The resulting mixture was stirred at −78 °C for 30 min and a solution of the aldehyde **445** (820 mg, 3.22 mmol) in THF (2 mL) was added. The mixture was stirred at −78 °C for 2 h, then allowed to reach rt over 1 h. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (10 mL). The aqueous phase was extracted with EtOAc (2 × 20 mL) and the combined organic extracts were washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 5:1) gave the title compound **450** (608 mg, 39%) as a colourless oil.

R_f = 0.74 (petroleum ether: EtOAc, 4:1); ν_{max} (film) 2943, 2928, 2866, 2214, 1719, 1618, 1356, 1163, 1098 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.63 (2H, d, *J* = 8.2 Hz, CH-Ts), 7.33 (2H, d, *J* = 8.2 Hz, CH-Ts), 6.41 (1H, dt, *J* = 2.3, 2.1 Hz, CH-C10), 3.80 (2H, t, *J* = 6.7 Hz, CH_2-C14), 3.34 (1H, dt, *J* = 10.9, 4.6 Hz, CH_2-C8), 3.17 (1H, d, *J* = 12.1 Hz, CH_2-C1), 2.66 (1H, d, *J* = 17.8 Hz, CH_2-C3), 2.63−2.57 (4H, m, CH_2-C8, CH_2-C13, CH-C6), 2.46 (1H, d, *J* = 12.1 Hz, CH_2-C1), 2.44 (3H, s, CH_3-Ts), 2.12−2.05 (1H, m, CH_2-C7), 2.07 (1H, d, *J* = 17.8 Hz, CH_2-C3), 1.86 (1H, dtd, *J* = 14.0, 9.9, 4.6 Hz, CH_2-C7), 1.04 (18H, d, *J* = 5.3 Hz, CH_3-TIPS), 1.02 (3H, s, CH_3-C9), 1.03−1.01 (3H, m, CH-TIPS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.6 (C-C4), 148.9 (C-C5), 143.8 (C-Ts), 133.4 (C-Ts), 129.9 (CH-Ts), 127.8 (CH-Ts), 114.6 (CH-C10), 101.4 (C-C11), 78.6 (C-C12), 61.9 (CH_2-C14), 52.9 (CH_2-C1), 46.9 (CH_2-C3), 45.3 (CH-C6), 44.8 (CH_2-C8), 36.4 (C-C2), 25.8 (CH_2-C7), 25.6 (CH_3-C9), 24.7 (CH_2-C13), 21.7 (CH_3-Ts), 16.9 (CH_3-TIPS), 12.1 (CH-TIPS); HRMS (ESI) for $C_{30}H_{45}NNaO_4SSi$ $[M+Na]^+$ calcd. 566.2711, found 566.2731.

(4a*R,7a*R**)-7a-Methyl-2-tosyl-5-(3-triisopropylsilyloxypropyl)-3b,5,6,7,7a, 8-hexahydro-furo[3',2':3,4]cyclopenta[1,2-c]pyridine 451**

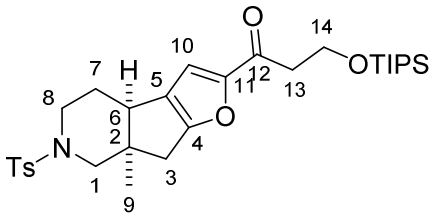


$C_{30}H_{47}NO_4SSi$

To a stirred solution of tributylphosphine (11 µL, 40 µmol) in DMF (1.5 mL) at rt was added water (1 mL) and a solution of the enyne **450** (20 mg, 40 µmol) in DMF (1.5 mL). The mixture was stirred at rt for 6 h and the solution was then dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 20:1 to 10:1 to 4:1) gave the title compound **451** (4.2 mg, 21%) as a pale yellow oil.

R_f = 0.76 (petroleum ether: EtOAc, 3:1); ν_{max} (film) 2943, 2928, 2866, 1356, 1163, 1098 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (2H, d, *J* = 8.2 Hz, CH-Ts), 7.29 (2H, d, *J* = 8.2 Hz, CH-Ts), 5.75 (1H, s, CH-C10), 3.69 (2H, t, *J* = 6.2 Hz, CH_2-C14), 3.33−3.27 (1H, m, CH_2-C8), 3.12 (1H, d, *J* = 11.8 Hz, CH_2-C1), 2.75 (1H, d, *J* = 11.8 Hz, CH_2-C1), 2.64 (2H, t, *J* = 7.7 Hz, CH_2-C12), 2.52 (1H, d, *J* = 14.7 Hz, CH_2-C3), 2.44 (3H, s, CH_3-Ts), 2.43 (1H, d, *J* = 14.7 Hz, CH_2-C3), 2.05−1.98 (2H, m, CH-C6, CH_2-C8), 1.84−1.77 (2H, m, CH_2-C13), 1.75−1.68 (1H, m, CH_2-C7), 1.45−1.38 (1H, m, CH_2-C7), 1.25 (3H, s, CH_3-C9), 1.03 (18H, d, *J* = 5.1 Hz, CH_3-TIPS), 1.03-1.01 (3H, m, CH-TIPS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.9 (C-C11), 151.0 (C-C4), 142.9 (C-C5), 142.7 (C-Ts), 133.4 (C-Ts), 129.8 (CH-Ts), 127.6 (CH-Ts), 107.1 (CH-C10), 66.3 (CH_2-C14), 58.6 (CH_2-C1), 43.4 (CH_2-C3), 43.2 (CH-C6), 42.5 (CH_2-C8), 40.0 (C-C2), 33.3 (CH_2-C12), 26.4 (CH_2-C7), 25.8 (CH_3-C9), 23.3 (CH_2-C13), 21.2 (CH_3-Ts), 17.6 (CH_3-TIPS), 12.6 (CH-TIPS); HRMS (ESI) for $C_{30}H_{47}NNaO_4SSi$ $[M+Na]^+$ calcd. 568.2863, found 568.2887.

1-((4a*R,7a*R**)-7a-Methyl-2-tosyl-3b,5,6,7,7a,8-hexahydro-4H-furo[3',2':3,4] cyclopenta[1,2-c]pyridin-2-yl)-3-(triisopropylsilyloxy)propan-12-one 452**

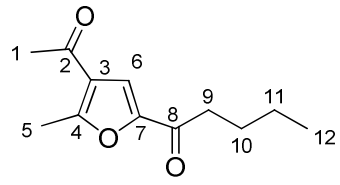


$C_{30}H_{45}NO_5SSi$

To a stirred solution of tributylphosphine (0.18 mL, 0.74 mmol) in DMF (25 mL) at rt was added a solution of the enyne **450** (0.10 g, 0.18 mmol) in DMF (1.5 mL). The mixture was sparged with oxygen and stirred under a static oxygen atmosphere at rt for 6 h. The mixture was then diluted with EtOAc (100 mL) and washed with water (2 × 50 mL), brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 10:1 to 4:1) gave the title compound **452** (95 mg, 95%) as a colourless oil.

R_f = 0.41 (petroleum ether: EtOAc, 3:1); ν_{max} (film) 2942, 2928, 2866, 1663, 1499, 1344, 1163, 1094 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.58 (2H, d, *J* = 8.0 Hz, CH-Ts), 7.27 (2H, d, *J* = 8.0 Hz, CH-Ts), 6.96 (1H, s, CH-C10), 4.04 (2H, t, *J* = 6.4 Hz, CH_2-C14), 3.25 (1H, dd, *J* = 10.8, 4.9 Hz, CH_2-C8), 3.03 (1H, d, *J* = 11.8 Hz, CH_2-C1), 2.90 (2H, t, *J* = 6.4 Hz, CH_2-C13), 2.71 (1H, dd, *J* = 5.3, 5.1 Hz, CH-C6), 2.59 (1H, d, *J* = 11.8 Hz, CH_2-C1), 2.56 (1H, d, *J* = 14.7 Hz, CH_2-C3), 2.55−2.52 (1H, m, CH_2-C8), 2.48 (1H, d, *J* = 14.7 Hz, CH_2-C3), 2.38 (3H, s, CH_3-Ts), 2.08 (1H, dddd, *J* = 14.6, 10.3, 5.3, 4.9 Hz, CH_2-C7), 1.76 (1H, ddd, *J* = 14.6, 5.1, 3.5 Hz, CH_2-C7), 1.34 (3H, s, CH_3-C9), 0.95 (18H, d, *J* = 6.5 Hz, CH_3-TIPS), 1.01−0.95 (3H, m, CH-TIPS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.6 (C-C12), 163.8 (C-C4), 157.2 (C-C11), 143.6 (C-Ts), 133.9 (C-Ts), 129.9 (CH-Ts), 129.7 (C-C5), 127.6 (CH-Ts), 115.5 (CH-C10), 60.0 (CH_2-C14), 53.4 (CH_2-C1), 48.4 (CH_2-C8), 43.2 (CH_2-C13), 41.7 (CH-C6), 41.3 (C-C2), 37.5 (CH_2-C3), 26.4 (CH_2-C7), 25.8 (CH_3-C9), 21.7 (CH_3-Ts), 17.4 (CH_3-TIPS), 12.0 (CH-TIPS); HRMS (ESI) for $C_{30}H_{45}NNaO_5SSi$ $[M+Na]^+$ calcd. 582.2656, found 582.2680.

1-(4-Acetyl-5-methylfuran-2-yl)pentan-1-one 459



$C_{12}H_{16}O_3$

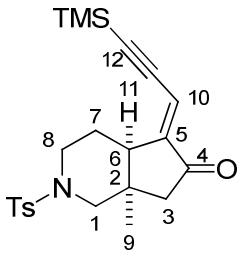
To a stirred solution of tributylphosphine (0.51 mL, 2.1 mmol) in DMF (25 mL) at rt was added a solution of the enyne **458** (0.10 mg, 0.52 mmol) in DMF (1.5 mL). The mixture was sparged with oxygen and stirred under a static oxygen atmosphere at rt for 3 h. The mixture was then diluted with EtOAc (100 mL) and washed with water (2 × 50 mL), brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 10:1 to 4:1) gave the title compound **459** (92 mg, 92%) as a pale yellow oil.

R_f = 0.28 (petroleum ether: EtOAc, 4:1); ν_{max} (film) 2959, 2932, 2874, 1672, 1576, 1528, 1234, 1151, 950 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (1H, d, *J* = 0.6 Hz, CH-C6), 2.81 (2H, t, *J* = 7.5 Hz, CH_2-C9), 2.69 (3H, s, CH_3-C5), 2.47 (3H, s, CH_3-C1), 1.70 (2H, tt, *J* = 7.5, 7.3 Hz, CH_2-C10), 1.40 (2H, qt, *J* = 7.4, 7.3 Hz, CH_2-C11), 0.95 (3H, t, *J* = 7.4 Hz, CH_3-C12); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.4 (C-C2), 189.4 (C-C8), 162.2 (C-C4), 150.1 (C-C7), 123.1 (C-C3), 117.1 (CH-C6), 38.1 (CH_2-C9), 29.1 (CH_3-C1), 26.4 (CH_2-C10), 22.4 (CH_2-C11), 14.9 (CH_3-C5), 13.9 (CH_3-C12); HRMS (ESI) for $C_{12}H_{16}NaO_3$ $[M+Na]^+$ calcd. 231.0984, found 231.0992.

The analytical and spectroscopic data are in agreement with those reported in the literature.[164]

[164] Wang, T.; Zhang, J. *Dalton Trans.* **2010**, *39*, 4270−4273

(4a*R,7a*R**,*E*)-7a-Methyl-2-tosyl-5-(3-trimethylsilylprop-2-ynylidene)hexa hydro-cyclopenta[c]pyridin-6-one 462**

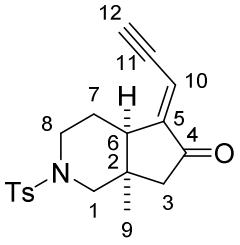


$C_{22}H_{29}NO_3SSi$

To a stirred solution of diisopropylamine (0.10 mL, 0.72 mmol) in THF (6 mL) at −78 °C was added *n*-BuLi (0.30 mL of a 2.38 M solution in THF, 0.72 mmol). The mixture was stirred at −78 °C for 10 min and a solution of the ketone **320** (0.20 g, 0.65 mmol) in THF (2 mL) was added. The resulting mixture was stirred at −78 °C for 30 min and a solution of 3-(trimethylsilyl)-2-propynal (98 mg, 0.78 mmol) in THF (2 mL) was added. The mixture was stirred for 2 h at −78 °C, then allowed to reach rt over 1 h. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (10 mL). The aqueous phase was extracted with EtOAc (2 × 20 mL) and the combined organic extracts were washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 6:1 to 4:1) gave the title compound **462** (136 mg, 51%) as a colourless oil.

R_f = 0.71 (petroleum ether: EtOAc, 2:1); ν_{max} (film) 2957, 2926, 2853, 1721, 1614, 1356, 1165, 1097, 904 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.62 (2H, d, *J* = 8.2 Hz, CH-Ts), 7.33 (2H, d, *J* = 8.2 Hz, CH-Ts), 6.39 (1H, d, *J* = 2.1 Hz, CH-C10), 3.41 (1H, dt, *J* = 10.8, 4.7 Hz, CH_2-C8), 3.12 (1H, d, *J* = 12.1 Hz, CH_2-C1), 2.65 (1H, d, *J* = 17.9 Hz, CH_2-C3), 2.69−2.59 (2H, m, CH_2-C8, CH-C6), 2.52 (1H, d, *J* = 12.1 Hz, CH_2-C1), 2.43 (3H, s, CH_3-Ts), 2.09 (1H, d, *J* = 17.9 Hz, CH_2-C3), 2.12−2.05 (1H, m, CH_2-C7), 1.93 (1H, ddt, *J* = 14.6, 9.7, 4.7 Hz, CH_2-C7), 1.06 (3H, s, CH_3-C9), 0.18 (9H, s, CH_3-TMS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.6 (C-C4), 150.6 (C-C5), 144.1 (C-Ts), 133.5 (C-Ts), 130.2 (CH-Ts), 127.9 (CH-Ts), 113.8 (CH-C10), 108.9 (C-C11), 101.4 (C-C12), 53.1 (CH_2-C1), 47.1 (CH_2-C3), 45.7 (CH-C6), 44.9 (CH_2-C8), 36.7 (C-C2), 25.7 (CH_2-C7), 25.6 (CH_3-C9), 21.9 (CH_3-Ts), −0.2 (CH_3-TMS); HRMS (ESI) for $C_{22}H_{29}NNaO_3SSi$ $[M+Na]^+$ calcd. 438.1512, found 438.1530.

(4a*R,7a*R**,*E*)-7a-Methyl-5-(prop-2-ynylidene)-2-tosylhexahydro-cyclopenta [c]pyridin-6-one 460**

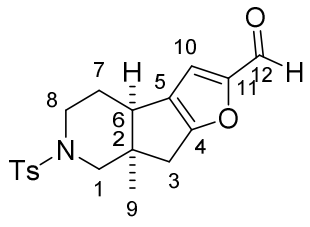


$C_{19}H_{21}NO_3S$

To a stirred solution of the enynone **462** (35 mg, 0.12 mmol) in THF (5 mL) at 0 °C was added TBAF (0.18 mL of a 1.0 M solution in THF, 0.18 mmol). The mixture was stirred at 0 °C for 1 h and allowed to reach rt over 2 h. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (5 mL). The aqueous phase was extracted with EtOAc (2 × 20 mL) and the combined organic extracts were washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 5:1) gave the title compound **460** (28 mg, 97%) as a pale yellow oil.

R_f = 0.26 (petroleum ether: EtOAc, 4:1); ν_{max} (film) 2957, 2926, 2853, 1721, 1614, 1356, 1165, 1097, 904 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.62 (2H, d, *J* = 8.2 Hz, CH-Ts), 7.33 (2H, d, *J* = 8.2 Hz, CH-Ts), 6.37 (1H, dd, *J* = 2.4, 2.2 Hz, CH-C10), 3.42 (1H, d, *J* = 2.4 Hz, CH-C12), 3.46–3.37 (1H, m, CH_2-C8), 3.24 (1H, d, *J* = 12.2 Hz, CH_2-C1), 2.72 (1H, d, *J* = 18.1 Hz, CH_2-C3), 2.67–2.61 (1H, m, CH-C6), 2.57 (1H, dt, *J* = 10.9, 4.1 Hz, CH_2-C8), 2.44 (1H, d, *J* = 12.2 Hz, CH_2-C1), 2.43 (3H, s, CH_3-Ts), 2.08 (1H, d, *J* = 18.1 Hz, CH_2-C3), 2.12–2.05 (1H, m, CH_2-C7), 1.93 (1H, ddt, *J* = 14.3, 10.2, 4.1 Hz, CH_2-C7), 1.03 (3H, s, CH_3-C9); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.1 (C-C4), 151.7 (C-C5), 143.8 (C-Ts), 133.1 (C-Ts), 129.8 (CH-Ts), 127.6 (CH-Ts), 112.3 (CH-C10), 88.8 (C-C11), 79.9 (C-C12), 52.7 (CH_2-C1), 46.4 (CH_2-C3), 45.3 (CH-C6), 44.7 (CH_2-C8), 36.3 (C-C2), 25.7 (CH_2-C7), 25.6 (CH_3-C9), 21.6 (CH_3-Ts); HRMS (EI^+) for $C_{19}H_{21}NO_3S$ $[M]^+$ calcd. 343.1242, found 343.1239.

(4a*R,7a*R**)-7a-Methyl-2-tosyl-3b,5,6,7,7a,8-hexahydro-furo[3',2':3,4] cyclopenta[1,2-c]pyridine-11-carbaldehyde 461**

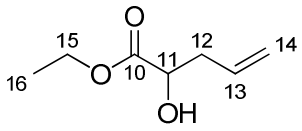


$C_{19}H_{21}NO_4S$

To a stirred solution of tributylphosphine (6.0 µL, 0.24 mmol) in DMF (5 mL) at rt was added a solution of the enynone **460** (21 mg, 60 µmol) in DMF (1.5 mL). The mixture was sparged with oxygen and stirred under a static oxygen atmosphere at rt for 8 h. The mixture was then diluted with EtOAc (20 mL), washed with water (2 × 10 mL) and brine (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 6:1 to 3:1) gave the title compound **461** (19 mg, 92%) as a pale yellow oil.

R_f = 0.19 (petroleum ether: EtOAc, 3:1); ν_{max} (film) 2959, 2924, 2853, 1672, 1503, 1344, 1331, 1163, 1092 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.43 (1H, s, CH-C12), 7.60 (2H, d, *J* = 8.2 Hz, CH-Ts), 7.30 (2H, d, *J* = 8.2 Hz, CH-Ts), 6.99 (1H, s, CH-C10), 3.26 (1H, dd, *J* = 10.4, 4.8 Hz, CH_2-C8), 3.10 (1H, d, *J* = 12.0 Hz, CH_2-C1), 2.75 (1H, t, *J* = 5.4 Hz, CH-C6), 2.71 (1H, d, *J* = 12.0 Hz, CH_2-C1), 2.68−2.64 (1H, m, CH_2-C8), 2.67 (1H, d, *J* = 13.7 Hz, CH_2-C3), 2.60 (1H, d, *J* = 13.7 Hz, CH_2-C3), 2.42 (3H, s, CH_3-Ts), 2.15−2.08 (1H, m, CH_2-C7), 1.79 (1H, ddd, *J* = 14.1, 4.8, 2.7 Hz, CH_2-C7), 1.36 (3H, s, CH_3-C9); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.6 (CH-C12), 149.4 (C-C11), 146.9 (C-C4), 143.5 (C-Ts), 133.7 (C-C5), 133.5 (C-Ts), 130.0 (CH-Ts), 127.6 (CH-Ts), 123.1 (CH-C10), 53.2 (CH_2-C1), 48.5 (C-C2), 43.2 (CH_2-C8), 41.1 (CH-C6), 37.4 (CH_2-C3), 25.9 (CH_2-C7), 25.0 (CH_3-C9), 21.7 (CH_3-Ts); HRMS (ESI) for $C_{19}H_{21}NNaO_4S$ $[M+Na]^+$ calcd. 382.1067, found 382.1083.

Ethyl 2-hydroxypent-4-enoate 477[165]



$C_7H_{12}O_3$

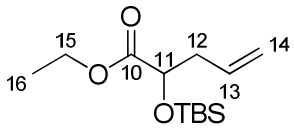
To a stirred solution of ethyl glyoxylate (2.00 mL of a 50% solution in toluene, 10.0 mmol) in DCM (40 mL) at rt was added freshly distilled $TiCl_4$ (1.90 mL, 12.0 mmol). The mixture was stirred at rt for 15 min and a solution of allyltrimethylsilane (2.10 g, 11.0 mmol) in DCM (10 mL) was added. The resulting mixture was stirred at rt for 1 h before addition of saturated aqueous $NaHCO_3$ solution (40 mL). The aqueous phase was extracted with DCM (3 × 50 mL) and the combined organic extracts were washed with brine (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 8:1 to 4:1) gave the title compound **477** (1.40 g, 96%) as a colourless oil.

R_f = 0.30 (petroleum ether: EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (1H, ddt, *J* = 17.2, 10.1, 7.1 Hz, CH-C13), 5.18−5.11 (2H, m, CH_2-C14), 4.30−4.18 (3H, m, CH-C11, CH_2-C15), 2.85 (1H, brs, OH), 2.62−2.54 (1H, m, CH_2-C12), 2.48−2.38 (1H, m, CH_2-C12), 1.29 (3H, t, *J* = 7.1 Hz, CH_3-C16); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6 (C-C10), 132.6 (CH-C13), 118.7 (CH_2-C14), 70.0 (CH-C11), 61.8 (CH_2-C15), 38.6 (CH_2-C12), 14.4 (CH_3-C16).

The analytical and spectroscopic data are in agreement with those reported in the literature.

[165] Boussonnière, A.; Bénéteau, R.; Zimmermann, N.; Lebreton, J.; Dénès, F. *Chem. Eur. J.* **2011**, *17*, 5613−5627

Ethyl 2-(*tert*-butyldimethylsilyloxy)pent-4-enoate 478[165]



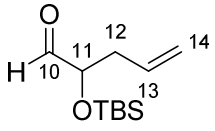
$C_{13}H_{26}O_3Si$

To a stirred solution of TBSCl (1.66 g, 11.0 mmol) and imidazole (1.02 g, 15.0 mmol) in DCM (50 mL) at 0 °C was added the alcohol **477** (1.40 g, 9.71 mmol). The mixture was stirred at 0 °C for 1 h then allowed to reach rt over 5 h. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (40 mL). The aqueous phase was extracted with DCM (3 × 50 mL) and the combined organic extracts were washed with brine (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (DCM: Et_2O, 10:1) gave the title compound **478** (2.48 g, 99%) as a colourless oil.

R_f = 0.92 (petroleum ether: EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (1H, ddt, *J* = 17.2, 10.1, 7.1 Hz, CH-C13), 5.16–5.04 (2H, m, CH_2-C14), 4.28–4.10 (3H, m, CH-C11, CH_2-C15), 2.54–2.39 (2H, m, CH_2-C12), 1.27 (3H, t, *J* = 7.1 Hz, CH_3-C16), 0.90 (9H, s, CH_3-TBS), 0.08 (3H, s, CH_3-TBS), 0.05 (3H, s, CH_3-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3 (C-C10), 133.8 (CH-C13), 118.1 (CH_2-C14), 72.3 (CH-C11), 60.9 (CH_2-C15), 39.9 (CH_2-C12), 25.9 (CH_3-TBS), 18.5 (C-TBS), 14.4 (CH_3-C16), −4.8 (CH_3-TBS), −5.1 (CH_3-TBS).

The analytical and spectroscopic data are in agreement with those reported in the literature.

2-(*tert*-Butyldimethylsilyloxy)pent-4-enal 479[165]



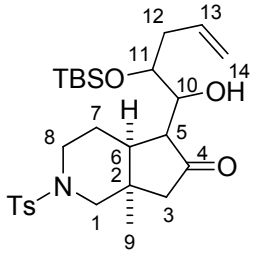
$C_{11}H_{22}O_2Si$

To a stirred solution of the ester **478** (1.0 g, 4.0 mmol) in Et_2O (40 mL) at −78 °C was added diisobutylaluminium hydride (4.0 mL of a 1.0 M solution in THF, 4.0 mmol) dropwise. The mixture was stirred at −78 °C for 2 h and then the reaction was quenched by addition of MeOH (1 mL). The mixture was allowed to reach rt before addition of saturated aqueous potassium sodium tartrate solution (50 mL). The mixture was then stirred vigorously for 30 min and the two phases were separated. The aqueous phase was extracted with Et_2O (3 × 50 mL) and the combined organic extracts were washed with brine (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: Et_2O, 98:2) gave the title compound **479** (751 mg, 88%) as a colourless oil.

R_f = 0.52 (petroleum ether: Et_2O, 50:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (1H, d, *J* = 1.6 Hz, CH-C10), 5.80 (1H, ddt, *J* = 17.3, 10.2, 7.1 Hz, CH-C13), 5.18−5.06 (2H, m, CH_2-C14), 4.31 (1H, ddd, *J* = 6.9, 5.1, 1.6 Hz, CH-C11), 2.51−2.31 (2H, m, CH_2-C12), 0.93 (9H, s, CH_3-TBS), 0.10 (3H, s, CH_3-TBS), 0.09 (3H, s, CH_3-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.2 (CH-C10), 132.9 (CH-C13), 118.3 (CH_2-C14), 77.3 (CH-C11), 37.4 (CH_2-C12), 25.7 (CH_3-TBS), 18.2 (C-TBS), −4.7 (CH_3-TBS), −4.9 (CH_3-TBS).

The analytical and spectroscopic data are in agreement with those reported in the literature.

(4a*S,7a*R**)-5-(2-(*tert*-Butyldimethylsilyloxy)-1-hydroxypent-4-enyl)-7a-methyl-2-tosylhexahydro-1H-cyclopenta[c]pyridin-6-one 481**

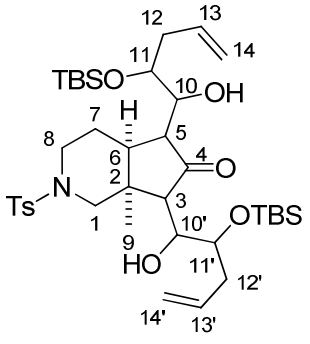


$C_{27}H_{43}NO_5SSi$

To a stirred solution of the aldehyde **479** (125 mg, 0.582 mmol) in DCM (20 mL) at −78 °C was added $TiCl_4$ (64 µL, 0.58 mmol). The mixture was stirred at −78 °C for 10 min and a solution of the enol ether **480** (200 mg, 0.534 mmol) in DCM (3 mL) was added. The mixture was stirred at −78 °C for 1 h and then allowed to reach rt over 1 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution (20 mL). The aqueous phase was extracted with EtOAc (2 × 30 mL) and the combined organic extracts were washed with brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 8:1 to 4:1) gave the title compound **481** (176 mg, 64%) as a colourless foam.

R_f = 0.42 (petroleum ether: Et_2O, 4:1); ν_{max} (film) 3557(br), 2953, 2928, 2857, 1740, 1337, 1252, 1163, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (2H, d, *J* = 8.2 Hz, CH-Ts), 7.34 (2H, d, *J* = 8.2 Hz, CH-Ts), 5.79 (1H, dddd, *J* = 17.3, 10.2, 8.3, 5.9 Hz, CH-C13), 4.88 (1H, ddt, *J* = 10.2, 2.2, 1.1 Hz, CH_2-C14), 4.78 (1H, ddt, *J* = 17.3, 2.2, 1.6 Hz, CH_2-C14), 4.25 (1H, ddd, *J* = 8.2, 5.4, 3.7 Hz, CH-C11), 3.71−3.62 (1H, m, CH_2-C8), 3.41 (1H, ddd, *J* = 8.2, 4.3, 2.1 Hz, CH-C10), 3.31 (1H, d, *J* = 12.0 Hz, CH_2-C1), 2.49 (1H, d, *J* = 4.3 Hz, OH), 2.45 (3H, s, CH_3-Ts), 2.37−2.26 (2H, m, CH_2-C12, CH-C6), 2.23 (1H, d, *J* = 17.9 Hz, CH_2-C3), 2.19−2.04 (5H, m, CH_2-C7, CH_2-C8, CH_2-C12, CH-C5, CH_2-C3), 1.91 (1H, d, *J* = 12.0 Hz, CH_2-C1), 1.55−1.51 (1H, m, CH_2-C7), 1.36 (3H, s, CH_3-C9), 0.88 (9H, s, CH_3-TBS), 0.09 (3H, s, CH_3-TBS), 0.07 (3H, s, CH_3-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.6 (C-C4), 143.9 (C-Ts), 134.3 (CH-C13), 133.1 (C-Ts), 129.9 (CH-Ts), 127.7 (CH-Ts), 117.1 (CH_2-C14), 73.0 (CH-C10), 71.6 (CH-C11), 52.6 (CH_2-C3), 51.8 (CH_2-C1), 48.7 (CH-C5), 41.5 (CH-C6), 41.3 (CH_2-C8), 38.5 (CH_2-C12), 36.7 (C-C2), 25.9 (CH_3-TBS), 23.5 (CH_3-C9), 22.2 (CH_2-C7), 21.7 (CH_3-Ts), 18.2 (C-TBS), −4.0 (CH_3-TBS), −4.6 (CH_3-TBS); HRMS (ESI) for $C_{27}H_{43}NNaO_5SSi$ $[M+Na]^+$ calcd. 544.2511, found 544.2523.

(4a*S*,7a*S***)-5,7-Bis(2-(*tert*-butyldimethylsilyloxy)-1-hydroxypent-4-enyl)-7a-methyl-2-tosylhexahydro-cyclopenta[c]pyridin-6-one 474**



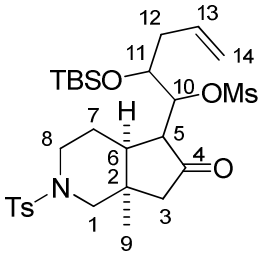
$C_{38}H_{65}NO_7SSi_2$

To a stirred solution of diisopropylamine (0.24 mL, 1.7 mmol) in THF (15 mL) at −78 °C was added *n*-BuLi (0.72 mL of a 2.38 M solution in THF, 1.7 mmol). The mixture was stirred at −78 °C for 10 min and a solution of the ketone **320** (0.50 g, 1.6 mmol) in THF (2 mL) was added. The reaction was stirred at −78 °C for 30 min and a solution of the aldehyde **479** (0.38 g, 1.8 mmol) in THF (2 mL) was added. The mixture was stirred at −78 °C for 2 h and then allowed to reach rt over 1 h. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (20 mL). The aqueous phase was extracted with EtOAc (2 × 30 mL) and the combined organic extracts were washed with brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 10:1 to 4:1) gave the title compound **474** (370 mg, 31%) as a colourless gum.

R_f = 0.44 (petroleum ether: Et_2O, 4:1); ν_{max} (film) 3457 (br), 2953, 2928, 2857, 1728, 1358, 1252, 1171, 1088 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (2H, d, *J* = 8.0 Hz, CH-Ts), 7.34 (2H, d, *J* = 8.0 Hz, CH-Ts), 5.88−5.61 (2H, m, CH-C13, CH-C13'), 5.05−4.85 (4H, m, CH_2-C14, CH_2-C14'), 4.16 (1H, dt, *J* = 8.8, 4.3 Hz, CH-C11), 3.98 (1H, dt, *J* = 8.5, 4.4 Hz, CH-C11'), 3.69 (1H, d, *J* = 8.5 Hz, CH-C10'), 3.54−3.41 (1H, m, CH_2-C8), 3.22 (1H, d, *J* = 8.8 Hz, CH-C10), 3.10 (1H, d, *J* = 11.5 Hz, CH_2-C1), 2.71 (1H, s, OH), 2.51 (1H, s, OH), 2.40−2.37 (1H, m, CH-C5), 2.29 (3H, s, CH_3-Ts), 2.26−2.14 (5H, m, CH_2-C12, CH_2-C12', CH-C6), 2.04−1.98 (2H, m, CH_2-C8, CH_2-C7), 1.97−1.94 (1H, m, CH-C3), 1.59 (1H, d, *J* = 11.5 Hz, CH_2-C1), 1.49−1.38 (1H, m, CH_2-C7), 1.30 (3H, s, CH_3-C9), 0.75 (9H, s, CH_3-TBS), 0.55 (9H, s, CH_3-TBS), 0.00 (3H, s, CH_3-TBS), −0.04 (3H, s, CH_3-TBS), −0.09 (3H, s,

CH_3-TBS), −0.51 (3H, s, CH_3-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 219.2 (C-C4), 143.6 (C-Ts), 134.3 (CH-C13), 134.1 (CH-C13'), 132.2 (C-Ts), 129.8 (CH-Ts), 127.6 (CH-Ts), 117.8 (CH_2-C14), 117.7 (CH_2-C14'), 75.4 (CH-C10), 73.6 (CH-C10'), 70.6 (CH-C11), 70.5 (CH-C11'), 56.5 (CH_2-C3), 52.8 (CH_2-C1), 48.4 (CH-C6), 40.9 (CH_2-C8), 40.0 (CH-C5), 39.2 (C-C2), 38.4 (CH_2-C12), 38.1 (CH_2-C12'), 25.9 (CH_3-TBS), 25.6 (CH_3-TBS), 21.9 (CH_2-C7), 21.5 (CH_3-Ts), 19.0 (CH_3-C9), 18.1 (C-TBS), 17.8 (C-TBS), −4.1 (CH_3-TBS), −4.5 (CH_3-TBS), −4.8 (CH_3-TBS), −5.2 (CH_3-TBS); HRMS (ESI) for $C_{38}H_{65}NNaO_7SSi_2$ $[M+Na]^+$ calcd. 758.3885, found 758.3912.

2-(*tert*-Butyldimethylsilyloxy)-1-((4a*S,7a*R**)-7a-methyl-6-oxo-2-tosylocta hydro-cyclopenta[c]pyridin-5-yl)pent-4-enyl methanesulfonate 475**

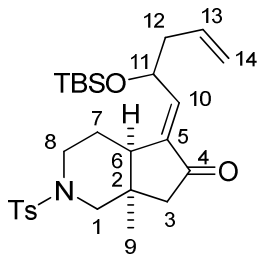


$C_{28}H_{45}NO_7S_2Si$

To a stirred solution of DMAP (74 mg, 0.60 mmol) and the alcohol **481** (80 mg, 0.15 mmol) in DCM (20 mL) at 0 °C was added MsCl (22 µL, 0.30 mmol). The mixture was stirred at 0 °C for 2 h, then allowed to reach rt over 1 h. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (20 mL). The aqueous phase was extracted with DCM (2 × 20 mL) and the combined organic extracts were washed with brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (DCM: Et_2O, 50:1) gave the title compound **475** (82 mg, 91%) as a colourless gum.

R_f = 0.27 (petroleum ether: Et_2O, 4:1); ν_{max} (film) 2955, 2930, 2857, 1744, 1344, 1256, 1169, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (2H, d, *J* = 8.2 Hz, CH-Ts), 7.35 (2H, d, *J* = 8.2 Hz, CH-Ts), 5.80–5.67 (1H, m, CH-C13), 5.07–4.96 (2H, m, CH_2-C14), 4.75 (1H, dd, *J* = 6.1, 4.4 Hz, CH-C10), 4.07 (1H, td, *J* = 6.2, 4.4 Hz, CH-C11), 3.50 (1H, dd, *J* = 11.8, 4.8 Hz, CH_2-C8), 3.19 (1H, d, *J* = 12.0 Hz, CH_2-C1), 2.99 (3H, s, CH_3-Ms), 2.52 (1H, ddd, *J* = 10.8, 6.1, 1.1 Hz, CH-C5), 2.42 (3H, s, CH_3-Ts), 2.37–2.05 (7H, m, CH_2-C12, CH_2-C3, CH_2-C7, CH_2-C8, CH-C6), 2.02 (1H, d, *J* = 12.0 Hz, CH_2-C1), 1.84–1.81 (1H, m, CH_2-C7), 1.34 (3H, s, CH_3-C9), 0.77 (9H, s, CH_3-TBS), 0.03 (3H, s, CH_3-TBS), −0.16 (3H, s, CH_3-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.6 (C-C4), 143.8 (C-Ts), 133.3 (CH-C13), 132.5 (C-Ts), 129.8 (CH-Ts), 127.6 (CH-Ts), 118.6 (CH_2-C14), 81.5 (CH-C10), 71.7 (CH-C11), 52.0 (CH_2-C3), 50.8 (CH_2-C1), 48.2 (CH-C5), 41.7 (CH-C6), 40.8 (CH_2-C8), 38.1 (CH_3-Ms), 37.9 (CH_2-C12), 36.6 (C-C2), 25.7 (CH_3-TBS), 23.8 (CH_3-C9), 23.7 (CH_2-C7), 21.5 (CH_3-Ts), 17.9 (C-TBS), −4.4 (CH_3-TBS), −4.6 (CH_3-TBS); HRMS (ESI) for $C_{28}H_{45}NNaO_7S_2Si$ $[M+Na]^+$ calcd. 622.2281, found 622.2299.

(4a*R,7a*R**,*E*)-5-(2-*tert*-Butyldimethylsilyloxypent-4-enylidene)-7a-methyl-2-tosylhexahydro-cyclopenta[c]pyridin-6-one 482**

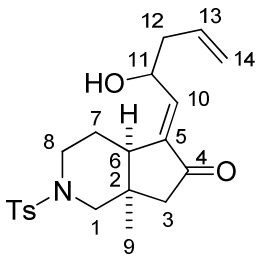


$C_{27}H_{41}NO_4SSi$

To a stirred solution of the mesylate **475** (67 mg, 0.11 mmol) in THF (20 mL) at 0 °C was added DBU (33 µL, 0.22 mmol). The mixture was stirred at 0 °C for 2 h, then allowed to reach rt over 1 h. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (20 mL). The aqueous phase was extracted with EtOAc (2 × 20 mL) and the combined organic phases were washed with brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 10:1 to 6:1) gave the title compound **482** (54 mg, 98%) as a colourless gum.

R_f = 0.68 (petroleum ether: Et_2O, 3:1); ν_{max} (film) 2955, 2928, 2857, 1724, 1659, 1356, 1343, 1252, 1163, 1097 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.64 (2H, d, *J* = 8.2 Hz, CH-Ts), 7.35 (2H, d, *J* = 8.2 Hz, CH-Ts), 6.45 (1H, dd, *J* = 9.0, 1.4 Hz, CH-C10), 5.71 (1H, ddt, *J* = 18.7, 9.4, 7.2 Hz, CH-C13), 5.07–4.99 (2H, m, CH_2-C14), 4.14 (1H, ddd, *J* = 9.0, 7.1, 5.2 Hz, CH-C11), 3.77 (1H, dd, *J* = 9.2, 2.6 Hz, CH_2-C8), 3.63 (1H, dd, *J* = 12.2, 1.6 Hz, CH_2-C1), 2.83 (1H, d, *J* = 17.9 Hz, CH_2-C3), 2.51 (3H, s, CH_3-Ts), 2.41–2.09 (5H, m, CH_2-C12, CH_2-C1, CH_2-C8, CH-C6), 1.98 (1H, dd, *J* = 17.9, 1.6 Hz, CH_2-C3), 1.74 (1H, ddd, *J* = 14.3, 5.6, 2.6 Hz, CH_2-C7), 1.55–1.47 (1H, m, CH_2-C7), 0.97 (3H, s, CH_3-C9), 0.82 (9H, s, CH_3-TBS), −0.02 (3H, s, CH_3-TBS), −0.07 (3H, s, CH_3-TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.9 (C-C4), 143.9 (C-Ts), 139.6 (C-C5), 137.9 (CH-C10), 133.9 (CH-C13), 133.1 (C-Ts), 129.8 (CH-Ts), 127.6 (CH-Ts), 117.8 (CH_2-C14), 70.3 (CH-C11), 52.8 (CH_2-C1), 45.4 (CH_2-C8), 45.2 (CH_2-C3), 43.7 (CH-C6), 42.9 (CH_2-C12), 36.6 (C-C2), 29.1 (CH_2-C7), 26.6 (CH_3-C9), 25.7 (CH_3-TBS), 21.6 (CH_3-Ts), 18.1 (C-TBS), −4.3 (CH_3-TBS), −4.7 (CH_3-TBS); HRMS (ESI) for $C_{27}H_{41}NNaO_4SSi$ $[M+Na]^+$ calcd. 526.2402, found 526.2418.

(4a*R,7a*R**,*E*)-5-(2-Hydroxypent-4-enylidene)-7a-methyl-2-tosylhexahydro-cyclopenta[c]pyridin-6-one 483**

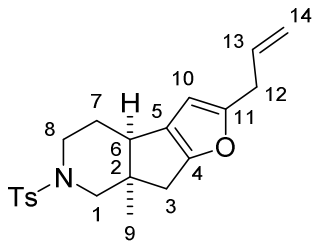


$C_{21}H_{27}NO_4S$

To a solution of the TBS ether **482** (20 mg, 40 μmol) in THF (10 mL) at 0 °C was added TBAF (80 μL, 1 M solution in THF, 80 μmol). The mixture was stirred at 0 °C for 1 h and allowed to reach rt over 2 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (10 mL) and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 3:1 to 1:1) gave the title compound **483** (13 mg, 81%) as a colourless oil.

R_f = 0.33 (petroleum ether: Et_2O, 1:1); ν_{max} (film) 3476 (br), 2955, 2924, 2857, 1724, 1655, 1341, 1163, 1097, 933, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (2H, d, *J* = 8.2 Hz, CH-Ts), 7.37 (2H, d, *J* = 8.2 Hz, CH-Ts), 6.47 (1H, dd, *J* = 7.3, 1.4 Hz, CH-C10), 5.71 (1H, ddt, *J* = 18.7, 9.4, 7.2 Hz, CH-C13), 5.22–5.12 (2H, m, CH_2-C14), 4.32 (1H, dd, *J* = 7.3, 5.3 Hz, CH-C11), 3.77 (1H, ddd, *J* = 11.3, 4.3, 2.3 Hz, CH_2-C8), 3.63 (1H, dd, *J* = 12.1, 1.5 Hz, CH_2-C1), 2.83 (1H, d, *J* = 18.0 Hz, CH_2-C3), 2.58 (1H, ddd, *J* = 11.9, 6.4, 1.4 Hz, CH-C6), 2.45 (3H, s, CH_3-Ts), 2.35–2.21 (3H, m, CH_2-C12, CH_2-C8), 2.18 (1H, d, *J* = 12.1 Hz, CH_2-C1), 2.00 (1H, dd, *J* = 18.0, 1.5 Hz, CH_2-C3), 1.87 (1H, ddd, *J* = 11.8, 6.4, 2.3 Hz, CH_2-C7), 1.57–1.46 (1H, m, CH_2-C7), 0.93 (3H, s, CH_3-C9); ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.1 (C-C4), 143.8 (C-Ts), 141.6(C-C5), 135.9 (CH-C10), 135.7 (CH-C13), 132.9 (C-Ts), 129.8 (CH-Ts), 127.7 (CH-Ts), 117.0 (CH_2-C14), 68.8 (CH-C11), 52.8 (CH_2-C1), 45.5 (CH_2-C8), 45.3 (CH_2-C3), 43.7 (CH-C6), 41.9 (CH_2-C12), 36.4 (C-C2), 28.8 (CH_2-C7), 26.5 (CH_3-C9), 21.6 (CH_3-Ts); HRMS (ESI) for $C_{21}H_{27}NNaO_4S$ $[M+Na]^+$ calcd. 412.1536, found 412.1553.

(4a*R,7a*R**)-11-Allyl-7a-methyl-2-tosyl-3b,5,6,7,7a,8-hexahydro-furo [3',2':3,4]cyclopenta [1,2-c]pyridine 484**



$C_{21}H_{25}NO_3S$

To a solution of the alcohol **483** (10 mg, 26 μmol) in toluene (3 mL) at rt was added *p*-toluenesulfonic acid monohydrate (0.5 mg, 3 μmol). The mixture was stirred vigorously at rt for 12 h. The reaction was quenched by addition of saturated aqueous Na_2CO_3 solution (10 mL) and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc 4:1 to 2:1) gave the title compound **484** (9.0 mg, 90%) as a pale yellow oil.

R_f = 0.63 (petroleum ether: Et_2O, 3:1); ν_{max} (film) 2954, 2924, 2856, 1614, 1341, 1163, 1097 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.62 (2H, d, *J* = 8.2 Hz, CH-Ts), 7.32 (2H, d, *J* = 8.2 Hz, CH-Ts), 5.89 (1H, ddt, *J* = 18.7, 9.4, 7.2 Hz, CH-C13), 5.72 (1H, s, CH-C10), 5.14–5.07 (2H, m, CH_2-C14), 3.29–3.17 (3H, m, CH_2-C12, CH_2-C8), 3.05 (1H, dd, *J* = 11.8, 1.4 Hz, CH_2-C1), 2.68 (1H, d, *J* = 11.8 Hz, CH_2-C1), 2.64–2.55 (2H, m, CH_2-C8, CH-C6), 2.46 (1H, dd, *J* = 15.2, 1.4 Hz, CH_2-C3), 2.35 (1H, d, *J* = 15.2 Hz, CH_2-C3), 2.34 (3H, s, CH_3-Ts), 1.95 (1H, ddd, *J* = 10.3, 5.8, 2.9 Hz, CH_2-C7), 1.68–1.61 (1H, m, CH_2-C7), 1.26 (3H, s, CH_3-C9); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.2 (C-C4), 155.5 (C-C11), 143.2 (C-Ts), 134.3 (C-Ts), 134.1 (CH-C13), 129.7 (CH-Ts), 127.4 (CH-Ts), 126.9 (C-C5), 116.8 (CH_2-C14), 103.2 (CH-C10), 53.4 (CH_2-C1), 47.7 (C-C2), 43.0 (CH_2-C8), 41.6 (CH-C6), 37.6 (CH_2-C3), 33.5 (CH_2-C12), 25.9 (CH_2-C7), 25.3 (CH_3-C9), 21.5 (CH_3-Ts); HRMS (ESI) for $C_{21}H_{25}NNaO_3S$ $[M+Na]^+$ calcd. 394.1429, found 394.1447.

References

1. Sakai, R.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *J. Am. Chem. Soc.* **1986**, *108*, 6404–6405
2. Tsuda, M.; Kobayashi, J. *Heterocycles* **1997**, *46*, 765–794
3. Watanabe, D.; Tsuda, M.; Kobayashi, J. *J. Nat. Prod.* **1998**, *61*, 689–692
4. Magnier, E.; Langlois, Y. *Tetrahedron* **1998**, *54*, 6201–6258
5. Duval, R.; Poupon, E. *Biomimetic Organic Synthesis* Wiley-VCH, **2011**
6. 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
7. Nakamura, H.; Deng, S.; Kobayashi, J.; Ohizumi, Y.; Tomotake, Y.; Matsuzaki, T.; Hirata, Y. *Tetrahedron Lett.***1987**, *28*, 621−624
8. Ang, K. K. H.; Homnes, M. J.; Higa, T.; Hamann, M. T.; Kara, U. A. K. *Antimicrob. Agents Chemother.* **2000**, *44*, 1645–1649
9. Winkler, J. D.; Londregan, A. T.; Hamann, M. T. *Org. Lett.* **2006**, *8*, 2591–2594
10. Kobayashi, J.; Watanabe, D.; Kawasaki, N.; Tsuda, M.; *J. Org. Chem.* **1997**, *62*, 9236–9239
11. Breslow, R.; Dong, S. D. *Chem. Rev.* **1998**, *98*, 1997–2011
12. Yoder. Y. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730–4756
13. Baldwin, J. E.; Whitehead, R. C. *Tetrahedron Lett.* **1992**, *33*, 2059–2062
14. 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
15. Kondo, K.; Shigemori, H.; Kikuchi, Y.; Ishibashi, M.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.* **1992**, *57*, 2480–2483
16. Kobayashi, J.; Tsuda, M.; Ishibashi, M. *Pure. Appl. Chem.* **1999**, *71*, 1123–1126
17. Nagata, T.; Nakagawa, M.; Nishida, A. *J. Am. Chem. Soc.* **2003**, *125*, 7484–7485
18. Ono, K.; Nakagawa, M.; Nishida, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 2020–2023
19. Young, I. S.; Kerr, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 1465–1469
20. Jakubec, P.; Cockfield, D. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 16632–16633
21. Kyle, A. F.; Jakubec, P.; Cockfield, D. M.; Cleator, E.; Skidmore, J.; Dixon, D. J. *Chem. Commun.* **2011**, *47*, 10037–10039
22. Jakubec, P.; Kyle, A. F.; Calleja, J.; Dixon, D. J. *Tetrahedron Lett.* **2011**, *52*, 6094–6097
23. Inagaki, F.; Kinebuchi, M.; Miyakoshi, N.; Mukai, C. *Org. Lett.* **2010**, *12*, 1800–1803
24. Nilson, M. G.; Funk, R. L. *Org. Lett.* **2010**, *12*, 4912–4915
25. Cheng, B.; Wu, F. F.; Yang, X. B.; Zhou, Y. D.; Wan, X. L.; Zhai, H. B. *Chem. Eur. J.* **2011**, *17*, 12569–12572

26. Bonazzi, S.; Cheng, B.; Wzorek, J.; Evans, D. A. *J. Am. Chem. Soc.* **2013**, *135*, 9338–9341
27. Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807–7808
28. Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459
29. Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 829–834
30. Ono, N.; Miyake, H.; Tamura, R.; Kaji, A. *Tetrahedron Lett.* **1981**, *22*, 1705–1708
31. Nilson, M. G.; Funk, R. L. *Org Lett.* **2006**, *8*, 3833–3836
32. DiazCortes, R.; Silva, A. L.; Maldonado, L. A. *Tetrahedron Lett.* **1997**, *38*, 2207–2210
33. Yu, J. R.; Truc, V.; Riebel, P.; Hierl, E.; Mudryk, B. *Tetrahedron Lett.* **2005**, *46*, 4011–4013
34. Bindl, M.; Stade, R.; Heilmann, E. K.; Picot, A.; Goddard, R.; Furstner, A. *J. Am. Chem. Soc.* **2009**, *131*, 9468–9470
35. Deng, H.; Yang, X.; Tong, Z.; Li, Z.; Zhai, H. *Org. Lett.* **2008**, *10*, 1791–1793
36. Harrison, T. J.; Patrick, B. O.; Dake, G. R. *Org. Lett.* **2007**, *9*, 367–370
37. Shono, T.; Matsumura, Y.; Inoue, K.; Ohmizu, H.; Kashimura, S. *J. Am. Chem. Soc.* **1982**, *104*, 5753–5757
38. Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc. Perk. Trans. 1* **1975**, 1574–1585
39. Jeffrey, T. *Tetrahedron Lett.* **1991**, *32*, 2121–2124
40. Fürstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc.* **1999**, *121*, 11108–11113
41. Schrock, R. R.; Clark, D. N.; Sancho, J.; Wengrovius, J. H.; Rocklage, S. M.; Pedersen, S. F. *Organometallics* **1982**, *1*, 1645–1651
42. Fürstner, A.; Guth, O.; Duffels, A.; Seidel, G.; Liebl, M.; Mynott, R. *Chem. Eur. J.* **2001**, *7*, 4811–4820
43. Magnus, P.; Fielding, M. R.; Wells, C.; Lynch, V. *Tetrahedron Lett.* **2002**, *43*, 947–950
44. Ahrendt, K. A.; Williams, R. M. *Org. Lett.* **2004**, *6*, 4539–4541
45. Stockman, R. A.; McDermott, P. J.; Newton, A. F.; Magnus, P. *Synlett* **2010**, 559–562
46. Tsuji, N.; Stadler, M.; Kazumi, N.; Inokuma, T.; Kobayashi, Y.; Takemoto, Y. *Org. Biomol. Chem.* **2014**, *12*, 7919–7922
47. Brandau, S.; Landa, A.; Franzøn, J.; Marigo, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2006**, *45*, 4305–4309
48. Gotoh, H.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2007**, *9*, 5307–5309
49. Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, *6*, 4387–4388
50. Trost, B. M.; Fullerton, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 292–294

51. Boto, A.; Alvarez, L. *Heterocycles in Natural Product Synthesis*, Wiley-VCH Verlag & Co. KGaA, **2011** and references herein
52. Donohoe, T. J.; Ironmonger, A.; Kershaw, N. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 7314–7316
53. Kobayashi, J.; Watanabe, D.; Kawasaki, N.; Tsuda, M. *J. Org. Chem.* **1997**, *62*, 9236–9329
54. Groebe, D. R.; Abramson, S. N. *J. Biol. Chem.* **1995**, *270*, 281–286
55. Maki, S.; Toshihiro, S.; Hiroshi, S.; Kanematsu, K. *J. Chem. Soc., Perkin Trans. 1* **1997**, *11*, 1707–1714
56. Wright, R. *J. Health Care Mark.* **1996**, *16*, 24–29
57. Banerjee, R.; Banerjee, K. H. M. *Int. J. Rev. Life Sci.* **2012**, *2*, 7–16
58. Newkome, G. R.; Sauer, J. D.; Roper, J. M.; Hager, D. C. *Chem. Rev.* **1977**, *77*, 513–597
59. Paal, C. *Chem. Ber.* **1884**, *17*, 2756–2767
60. Knorr, L. *Chem. Ber.* **1884**, *17*, 2863–2870
61. Amarnath, V.; Amarnath, K. *J. Org. Chem.* **1995**, *60*, 301–307
62. Feist, F. *Chem. Ber.* **1902**, *35*, 1537–1544
63. Benary, E. *Chem. Ber.* **1911**, *44*, 489–493
64. Calter, M. A.; Philips, R. M.; Flaschenriem, C. *J. Am. Chem. Soc.* **2005**, *127*, 14566–14567
65. Moran, W. J.; Rodríguez, A. *Org. Prep. Proced. Int.* **2012**, *42*, 103–130
66. Corma, A.; Leyva-Pérez, A.; Sabater, M.J. *Chem. Rev.* **2011**, *111*, 1657–1712
67. Trost, B. M.; McIntosh, M. C. *J. Am. Chem. Soc.* **1995**, *117*, 7255–7256
68. Barluenga, J.; Riesgo, L.; Vicente, R.; López, L. A.; Tomás, L. *J. Am. Chem. Soc.* **2008**, *130*, 13528–13529
69. Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180–3211
70. Blanc, A.; Tenbrink, K.; Weibel, J. M.; Pale, P. *J. Org. Chem.* **2009**, *74*, 5342–5348
71. Arcadi, A.; Alfonsi, M.; Chiarini, M.; Marinelli, F. *J. Organomet. Chem.* **2009**, *694*, 576–582
72. Hashmi, A. S. K.; Haffner, T.; Rudolph, M.; Rominger, F. *Eur. J. Org. Chem.* **2011**, *4*, 667–671
73. Du, X.; Song, F.; Lu, Y.; Chen, H.; Liu, Y. *Tetrahedron* **2009**, *65*, 1839–1845
74. Vicente, R.; González, J.; Riesgo, L.; González, J.; López, L. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 8063–8067
75. Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244
76. Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 3726–3748

77. Albrecht, Ł.; Ransborg, L. K.; Gschwend, B.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 17886–17893
78. Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 794–797
79. Kuroda, H.; Hanaki, E.; Kawakami, M. *Tetrahedron Lett.* **1999**, *40*, 3753–3756
80. Kuroda, H.; Hanaki, E.; Izawa, H.; Kano, M.; Itahashi, H. *Tetrahedron* **2004**, *60*, 1913–1920
81. Clark, J. S.; Boyer, A.; Aimon, A.; Garcia, P. E.; Lindsay, D. M.; Symington, A. D. F.; Danoy, Y. *Angew. Chem. Int. Ed.* **2012**, *51*, 12128–12131
82. Clark, J. S.; Boyer, A.; Aimon, A.; Garcia, P. E.; Lindsay, D. M.; Symington, A. D. F.; Danoy, Y. *Angew. Chem. Int. Ed.* **2012**, *51*, 12128–12131
83. Wang, T.; Zhang, J. *Dalton Trans.* **2010**, *39*, 4270–4273
84. Chen, Z.; Luo, M.; Ye, D.; Zhou, Z.; Ye, M.; Liu, L. *Synth. Commun.* **2014**, *44*, 1825–1831
85. Liu, Y.; Liu, Z.; Cui, Y. *Chin. J. Chem.* **2015**, *33*, 175–180
86. Cao, H.; Jiang, H.; Huang, H. *Synthesis* **2011**, *7*, 1019–1036
87. Fink, G.; Mülhaupt, R.; Brintzinger, H. H. *Ziegler Catalysts* **1995**, Eds. Springer: Berlin
88. Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450
89. Kotha, S.; Dipak, M. K. *Tetrahedron* **2012**, *68*, 397–421
90. a) Schrock, R. R. *Acc. Chem. Res.* **1986**, *19*, 342–348; b) Feldman, J.; Murdzek, J. S.; Davis, W. M.; Schrock, R. R. *Organometallics* **1989**, *8*, 2260–2265
91. a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **1995**, *34*, 2039–2041; b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956
92. Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450
93. Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791–799
94. Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4592–4633
95. a) De Clercq, B.; Verpoort, F. *Tetrahedron Lett.* **2001**, *42*, 8959-8963; (b) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H. J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204–2207
96. Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238
97. Scheiper, B.; Glorius, F.; Leitner, A.; and Fürstner, A. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11960–11965
98. Wang, Y.; Jimenez, M.; Hansen, A. S.; Raiber, E. A.; Schreiber, S. L.; Young, D. W. *J. Am. Chem. Soc.* **2011**, *133*, 9196–9199

99. Yu, M.; Wang, C.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *479*, 88–93

100. Wang, C.; Yu, M.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Chem. Eur. J.* **2013**, *19*, 2276–2740

101. Marx, V. M.; Herbert, M. B.; Keitz, B. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2013**, *135*, 94–97

102. Pennella, F.; Banks, R. L.; Bailey, G. C. *Chem. Commun.* **1968**, 1548–1549

103. Mortreux, A.; Blanchard, M. *J. Chem. Soc., Chem. Commun.* **1974**, 786–787

104. Grela, K.; Ignatowska, J. *Org. Lett.* **2002**, *4*, 3747–3749

105. Fürstner, A. *Angew. Chem. Int. Ed.* **2013**, *52*, 2794–2819

106. Yu, M.; Wang, C.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *479*, 88–93

107. Kyle, A. F.; Jakubec, P.; Cockfield, D. M.; Cleator, E.; Skidmore, J.; Dixon, D. J. *Chem. Commun.* **2011**, 10037–10039

108. Mortreux, A.; Blanchard, M. *J. Chem. Soc., Chem. Commun.* **1974**, 786–787

109. Clark, J. S.; Hodgson, P. B. *Tetrahedron Lett.* **1995**, *36*, 2519–2522

110. Clark, J. S.; Townsend, R. J.; Blake, A. J.; Teat, S. J.; Johns, A. *Tetrahedron Lett.* **2001**, *42*, 3235–3238

111. Hansen, A. M. *PhD thesis*, *University of Glasgow*, **2010**

112. Patel, M. C.; Livinghouse, T.; Pagenkopf, B. L. *Org. Synth.* **2003**, *80*, 93–103

113. DuBois, J.; Hong, J.; Carreira, E. M.; Day, M. W. *J. Am. Chem. Soc.* **1996**, *118*, 915–916

114. Poltronieri, E. M. *PhD thesis*, *University of Glasgow*, **2012**

115. Robertson, J.; Pillai, J.; Lush, R. K. *Chem. Soc. Rev.* **2001**, *30*, 94–103

116. Corey, E. J.; Lemahieu, R.; Mitra, R. B.; Bass, J. D. *J. Am. Chem. Soc.* **1964**, *86*, 5570–5583

117. Pauson, P. L.; Khand, I. U. *Ann. N.Y. Acad. Sci.* **1977**, *295*, 2–14

118. Castro, J.; Moyano, A.; Pericas, M. A.; Riera, A.; Greene, A. E. *Tetrahedron: Asymmetry* **1994**, *3*, 307–310

119. Bladon, P.; Pauson, P. L.; Brunner, H.; Eder, R. *J. Organomet. Chem.* **1988**, *355*, 449–454

120. Hiroi, K.; Watanabe, K.; Kawagishi, R.; Abe, I. *Tetrahedron: Asymmetry* **2000**, *11*, 797–808

121. Enantiomeric excess was determined by HPLC analysis of intermediate **320**. Column Chiralpak OD-H, temperature 25 °C, hexane: propan-2-ol 67:33, flowrate 0.5 $mL.min^{-1}$, retention time 17.2 min.

122. Beckmann, E. O. *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 988–993

123. Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901–2910

124. Overman, L. E. *Angew. Chem. Int. Ed.* **1984**, *23*, 579–586

125. Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553

126. Overman, L. E. *Angew. Chem. Int. Ed.* **1984**, *23*, 579–586

127. Calter, M.; Hollis, T. K.; Overman, L. E.; Ziller, J.; Zipp, G. G. *J. Org. Chem.* **1997**, *62*, 1449–1456

128. Moyano, A.; Rosol, M.; Moreno, R. M.; López, C.; Maestro, M. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 1865–1869

129. Xin, Z.; Fischer, D. F.; Peters, R. *Synlett.* **2008**, 1495–1499

130. Tamura, K.; Mizukami, H.; Maeda, K.; Watanabe, H.; Uneyama, K. *J. Org. Chem.* **1993**, *58*, 32–35

131. Bergerson, R. B.; McManis, J. J. *J. Org. Chem.* **1988**, *53*, 3108–3111

132. Kreis, L. M.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2012**, *51*, 3436–3439

133. Enantiomeric excess was determined by HPLC analysis of benzoyl allylic alcohol. Column Chiralpak AD-H, temperature 25 °C, hexane : (hexane: propan-2-ol [99.5: 0.5]) 90:10, flowrate 0.5 $mL.min^{-1}$, retention time 12.1 min.

134. Uenishi, J.; Fujikura, Y.; Kawai, N. *Org. Lett.*, **2011**, *13*, 2350–2353

135. Finnegan, D.; Seigal, B. A.; Snapper, M. L. *Org. Lett.* **2006**, *8*, 2603–2606

136. Appel, R. *Angew. Chem. Int. Ed.* **1975**, *14*, 801–811

137. Tietze, L. F.; Gericke, K. M.; Singidi, R. R.; Schuberth, I. *Org. Biomol. Chem.* **2007**, *5*, 1191–1200

138. Belting, V.; Krause, N. *Org. Biomol. Chem.* **2009**, *7*, 1221–1225

139. Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, *17*, 1295–1298

140. Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, *2*, 1011–1014

141. Florence, G. J.; Morris, J. C.; Murray, R. G.; Osler, J. D.; Reddy, V. R.; Smith, T. K. *Org. Lett.* **2011**, *13*, 514-517

142. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470

143. Eckhardt, M.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 13642–13643

144. Altenhoff, G.; Wurtz, S.; Glorius, F. *Tetrahedron Lett.* **2006**, *47*, 2925–2928

145. Vechorkin, O.; Barmaz, D.; Proust, V.; Hu, X. L. *J. Am. Chem.Soc.* **2009**, *131*, 12078–12079

146. Yi, J.; Lu, X.; Sun, Y. Y.; Xiao, B.; Liu, L. *Angew. Chem. Int. Ed.* **2013**, *52*, 12409–12413

147. Hadei, N.; Kantchev, E. A. B.; O'Brie, C. J.; Organ, M. G. *Org. Lett.* **2005**, *7*, 3805–3807

148. Coelho, A. V.; Souza, A. L. F.; Lima, P. G.; Wardell J. L.; Antunes, O. A. C. *Appl. Organometal. Chem.* **2008**, *22*, 39–42

149. Casy, G.; Furber, M.; Richardson, K. A.; Stephenson, G. R.; Taylor, R. J. K. *Tetrahedron* **1986**, *42*, 5849–5956

150. Thomas, E. J.; Williams, A. C. *J. Chem. Soc. Chem. Commun.* **1987**, 992–994

151. Inamoto, K.; Yamamoto, A.; Ohsawa, K.; Hiroya, K.; Sakamoto, T. *Chem. Pharm. Bull.* **2005**, *53*, 1502–1507

152. Patel, M. C.; Livinghouse, T.; Pagenkopf, B. L. *Org. Synth.* **2003**, *80*, 93–103

153. Tang, Y. F.; Deng, L. J.; Zhang, Y. D.; Dong, G. B.; Chen, J. H.; Yang, Z. *Org. Lett.* **2005**, *7*, 593–595

154. Uenishi, J.; Fujikura, Y.; Kawai, N. *Org. Lett.* **2011**, *13*, 2350-2353

155. Teichert, J. F.; Fananas-Mastral, M.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 688–691

156. Danishefsky, S.; McKee, R.; Singh, R. K. *J. Am. Chem. Soc.* **1977**, *99*, 4783–4788

157. Luo, F. T.; Negishi, E. *J. Org. Chem.* **1985**, *50*, 4762–4766

158. Johnson, C. R.; Penning, T. D. *J. Am. Chem. Soc.* **1988**, *110*, 4726–4735

159. Trost, B. M.; Sieber, J. D.; Qian, W.; Dhawan, R.; Ball, Z. T. *Angew. Chem. Int. Ed.* **2009**, *48*, 5478–5481

160. Matsuura, F.; Peters, R.; Anada, M.; Harried, S. S.; Hao, J.; Kishi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 7463–7465

161. Florence, G. J.; Morris, J. C.; Murray, R. J.; Osler, J. D.; Reddy, V. R.; Smith, T. K. *Org. Lett.* **2011**, *13*, 514–517

162. Persich, P.; Llaveria, J.; Lhermet, R.; Haro, T.; Stade, R.; Kondoh, A.; Fürstner, A. *Chem. Eur. J.* **2013**, *19*, 13047–13058

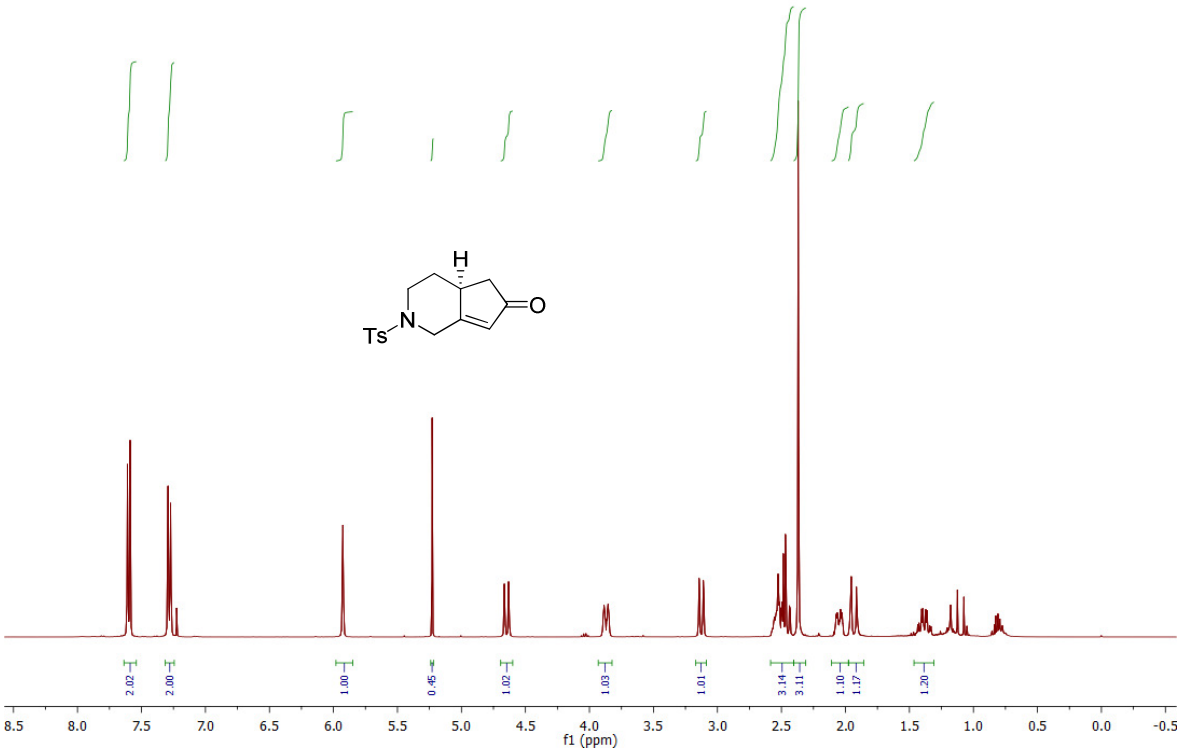
163. Tanabe, Y.; Okumura, H.; Maeda, A.; Murakami, M. *Tetrahedron Lett.* **1994**, *35*, 8413-8414

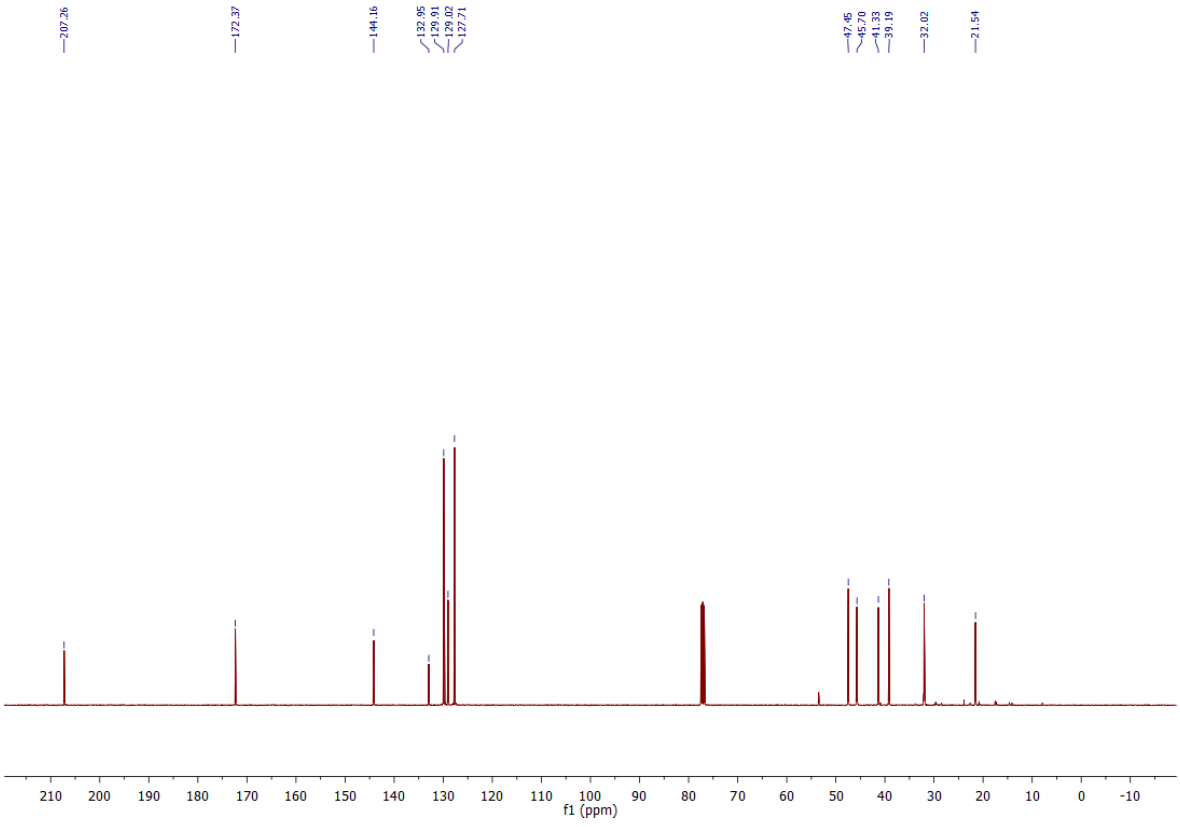
164. Wang, T.; Zhang, J. *Dalton Trans.* **2010**, *39*, 4270–4273

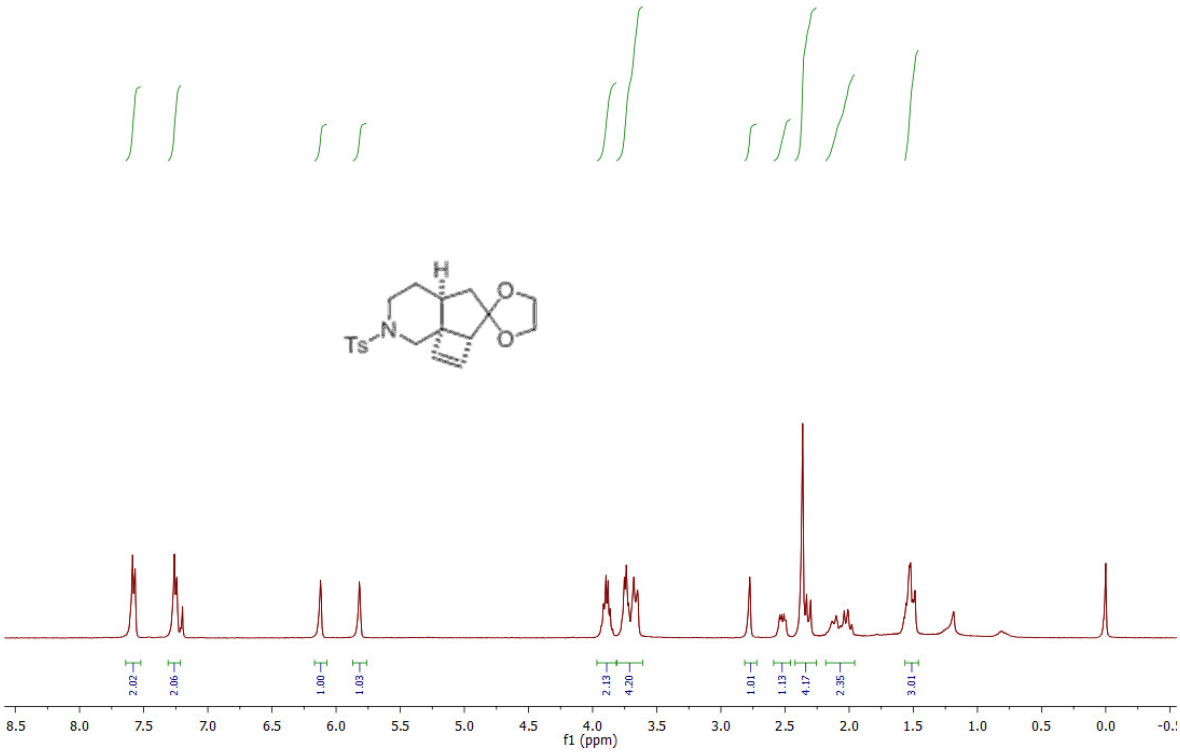
165. Boussonnière, A.; Bénéteau, R.; Zimmermann, N.; Lebreton, J.; Dénès, F. *Chem. Eur. J.* **2011**, *17*, 5613–5627

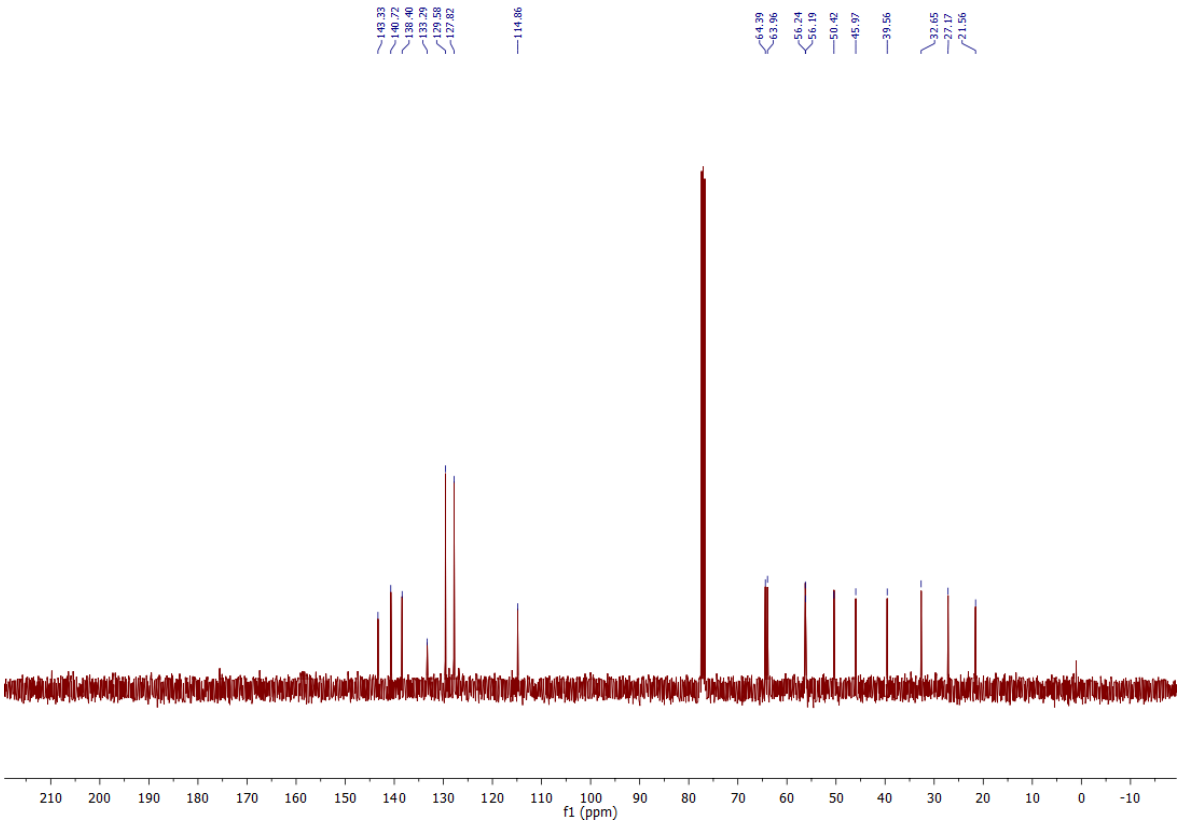
Appendices

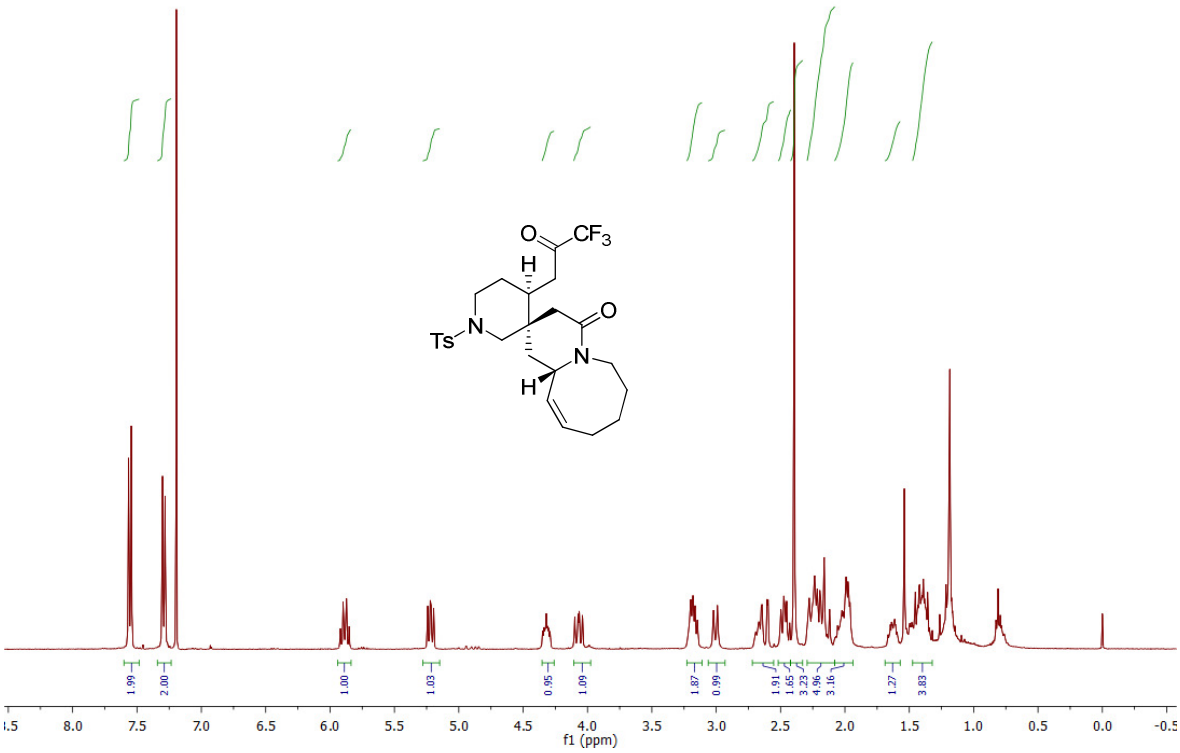
^{1}H and ^{13}C NMR Spectra of Selected Compounds

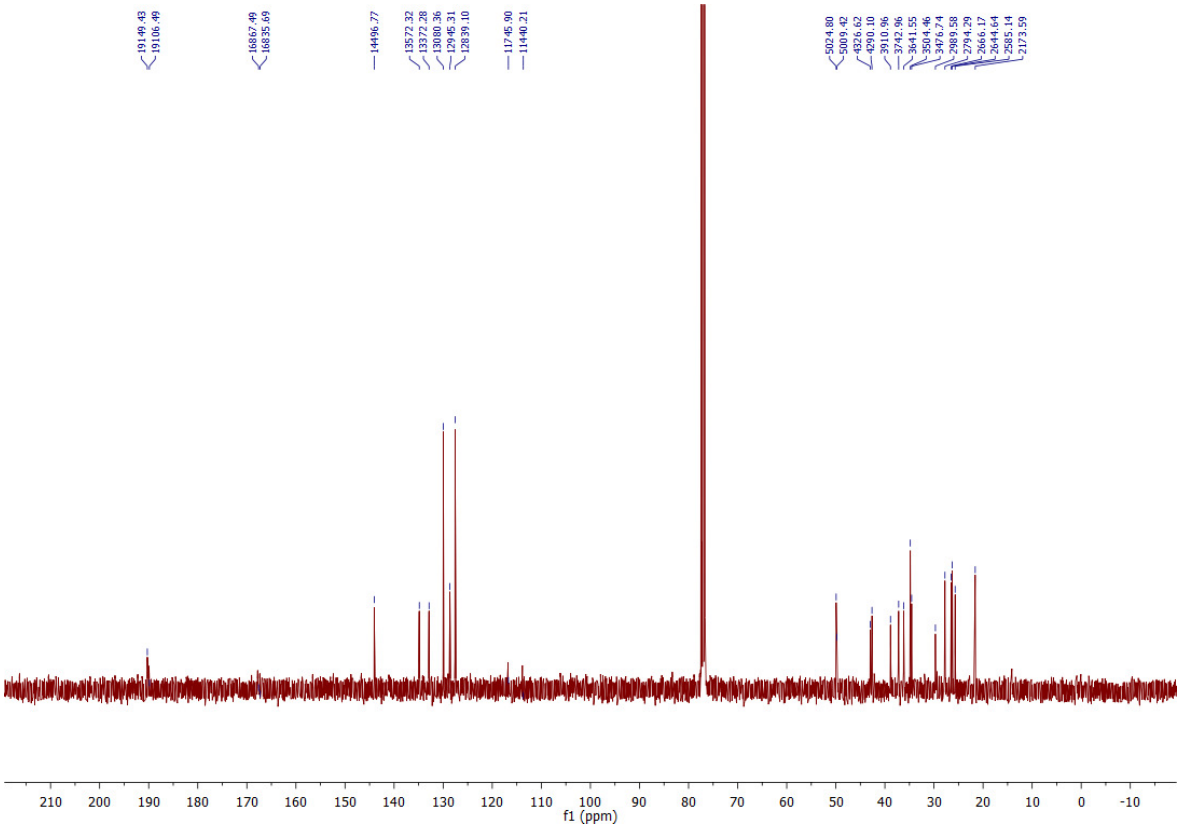


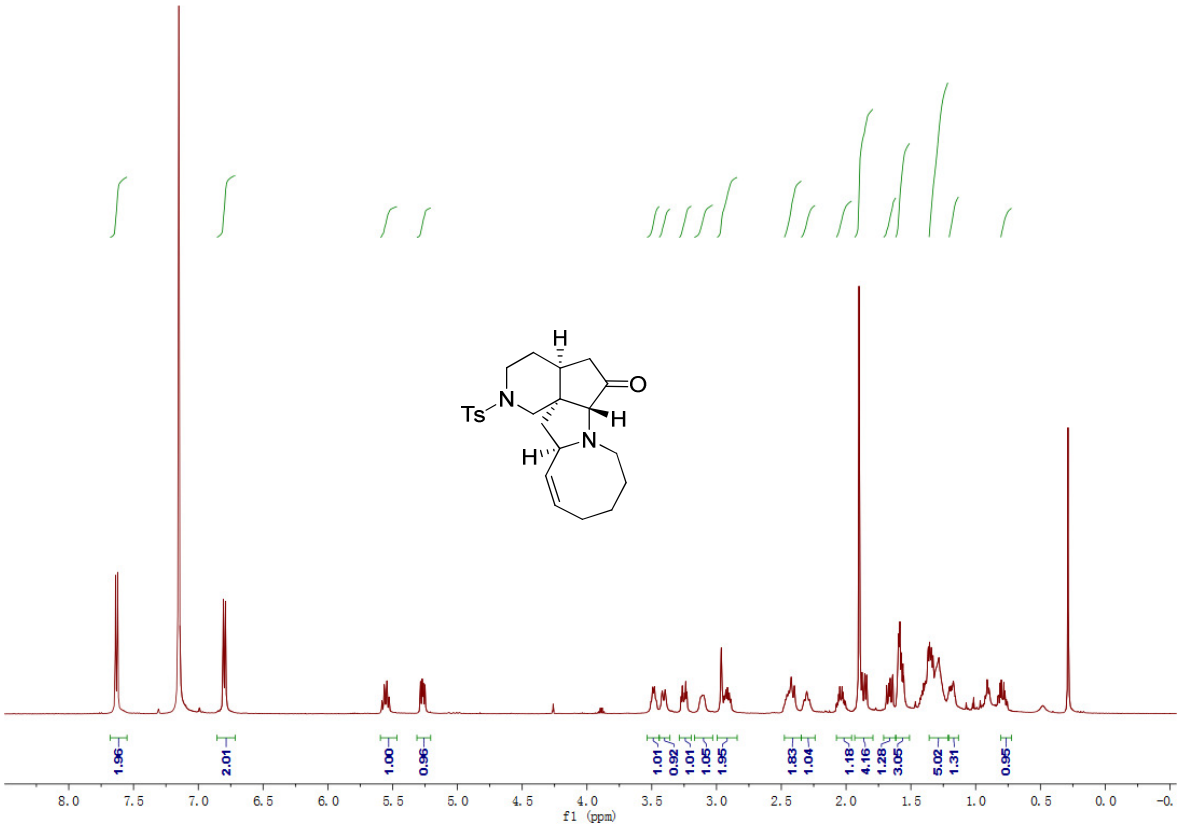


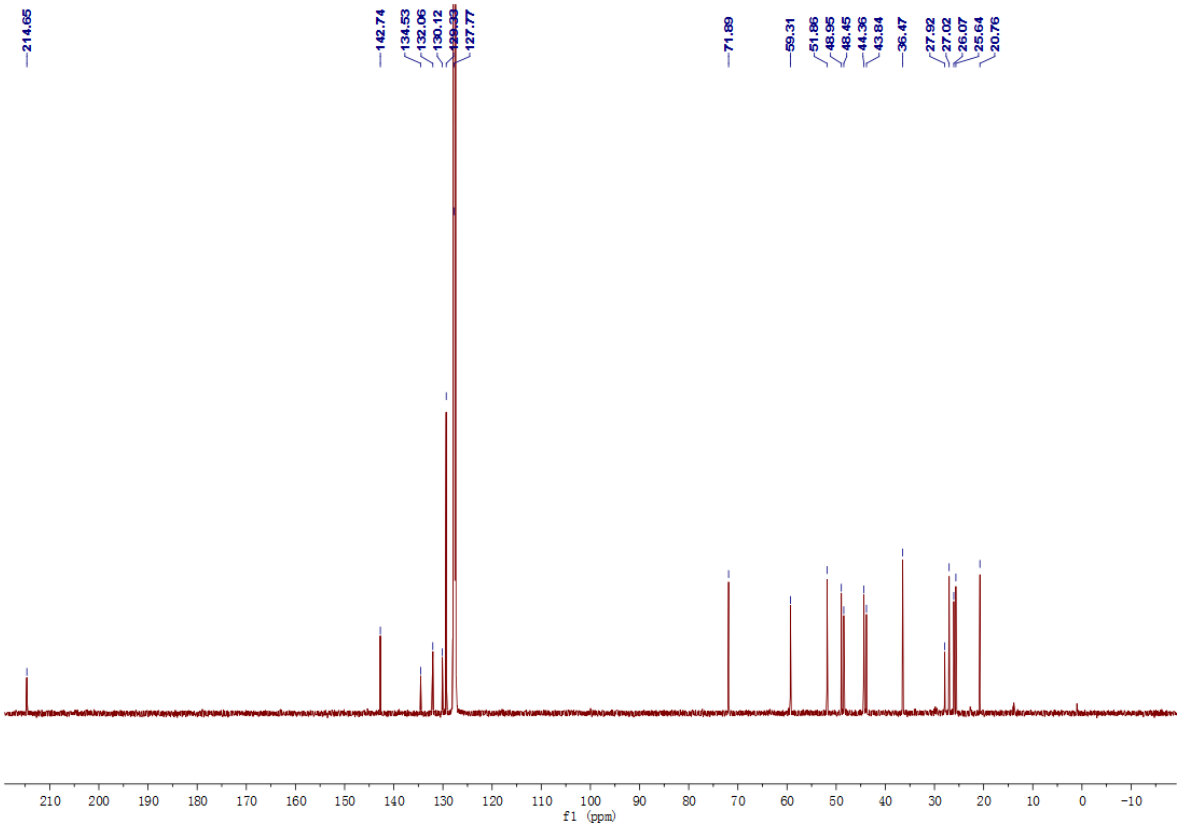

H
Ts
N
O
O
2.02
2.06
1.00
1.03
2.13
4.20
1.01
1.13
4.17
2.35
3.01
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

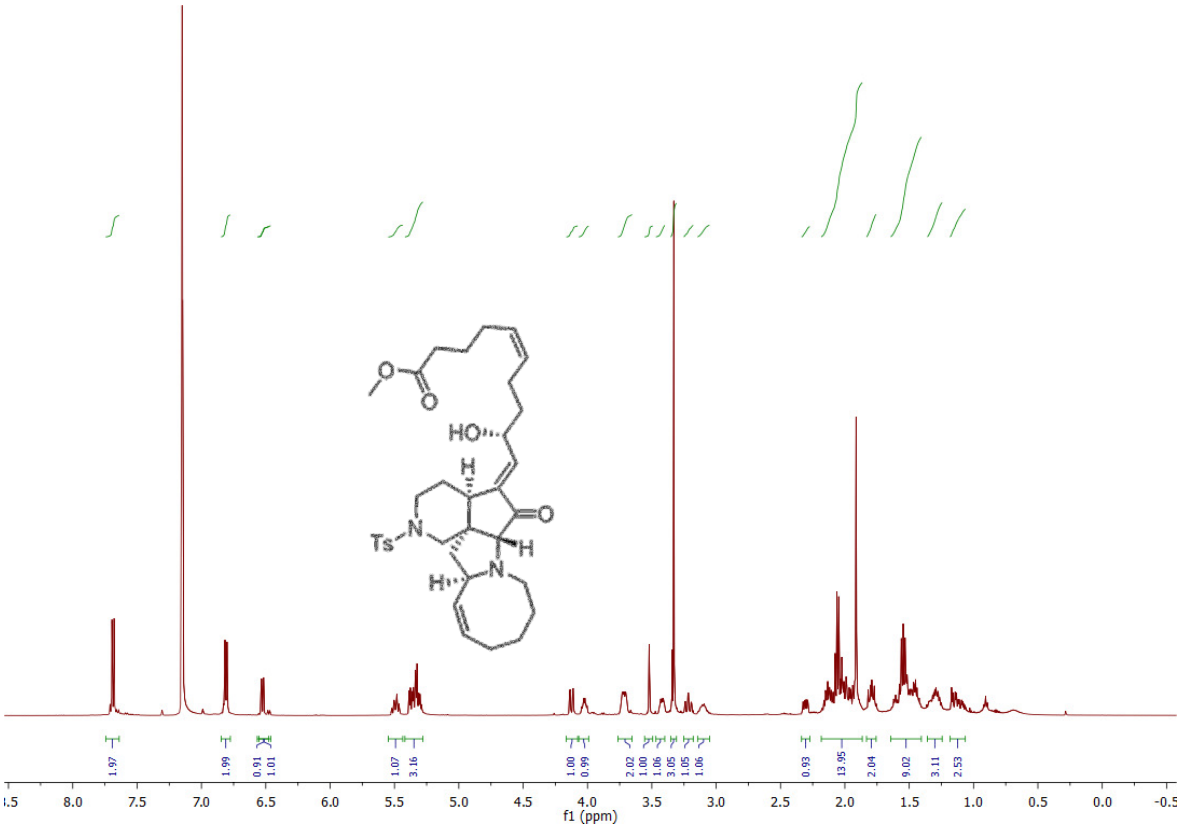

143.33
140.72
138.40
133.29
129.58
127.82
114.86
64.39
63.96
56.24
56.19
50.42
45.97
39.56
32.65
27.17
21.56
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

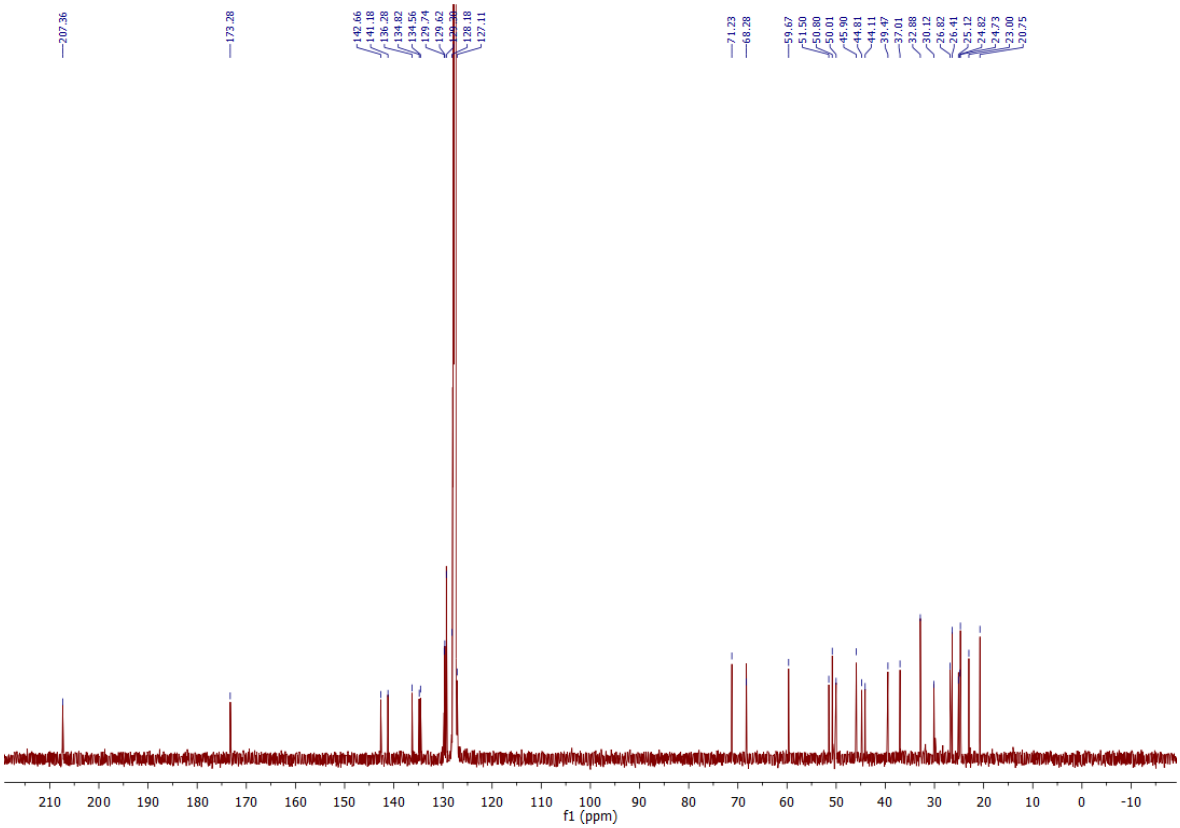

O
CF3
H
Ts
N
O
N
H
1.99
2.00
1.00
1.03
0.95
1.09
1.87
0.99
1.91
1.65
3.23
4.96
3.16
1.27
3.83
f1 (ppm)

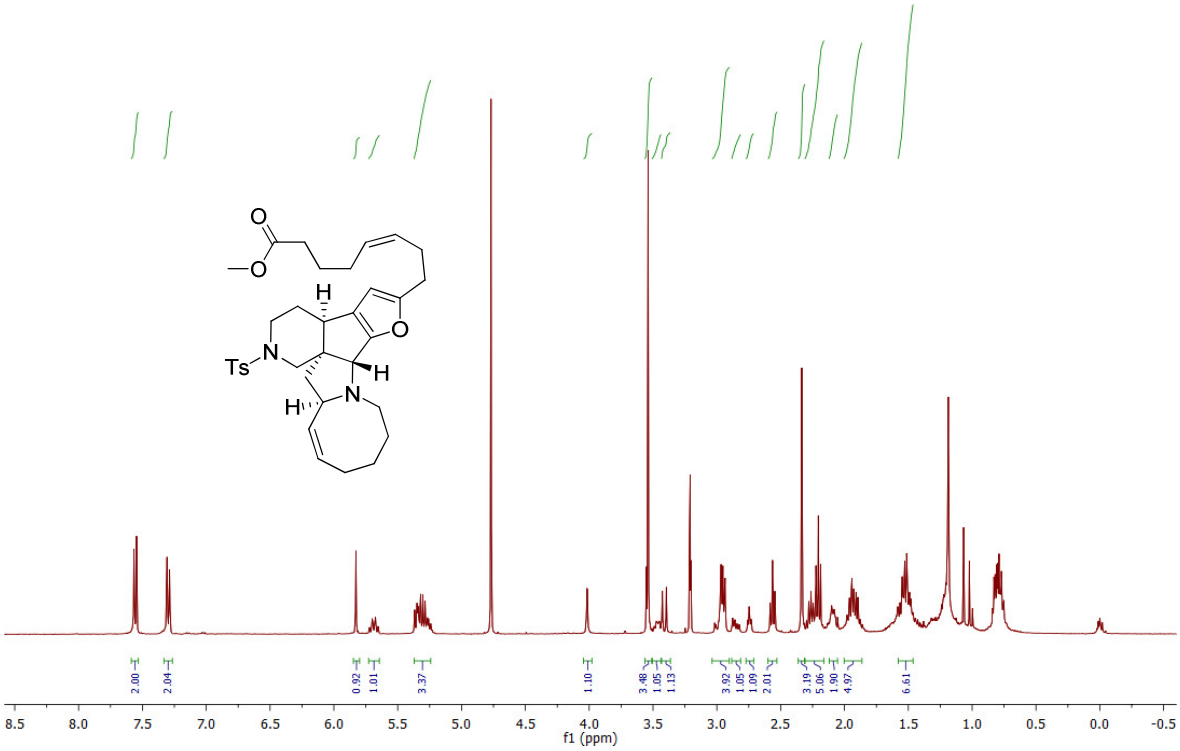

19149.43
19106.49
16867.49
16835.69
14496.77
13572.32
13372.28
13080.36
12945.31
12839.10
11745.90
11440.21
5024.80
5009.42
4826.62
4290.10
3910.96
3742.96
3641.55
3504.46
3476.74
2989.58
2794.29
2666.17
2644.64
2585.14
2173.59
f1 (ppm)

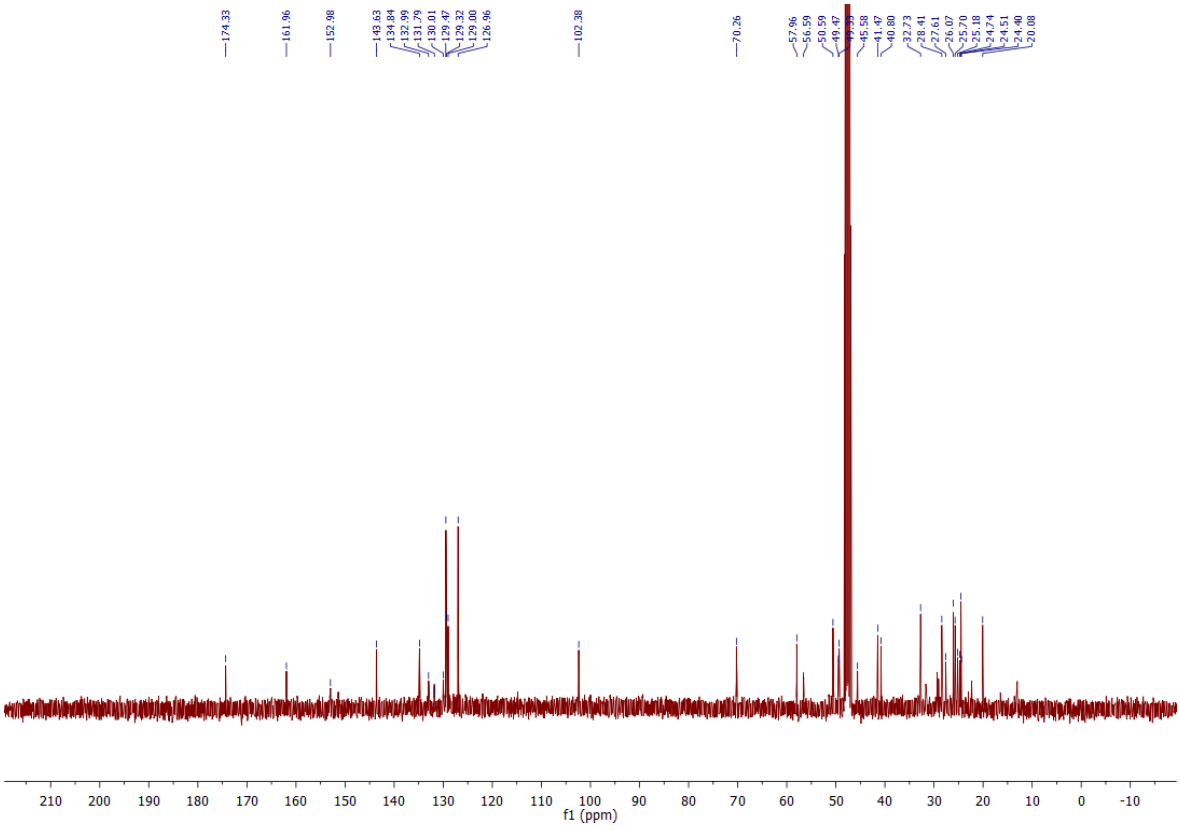

H
O
Ts
N
H
H
N
1.96
2.01
1.00
0.96
1.01
0.92
1.01
1.05
1.95
1.83
1.04
1.18
4.16
1.28
3.05
5.02
1.31
0.95
f1 (ppm)

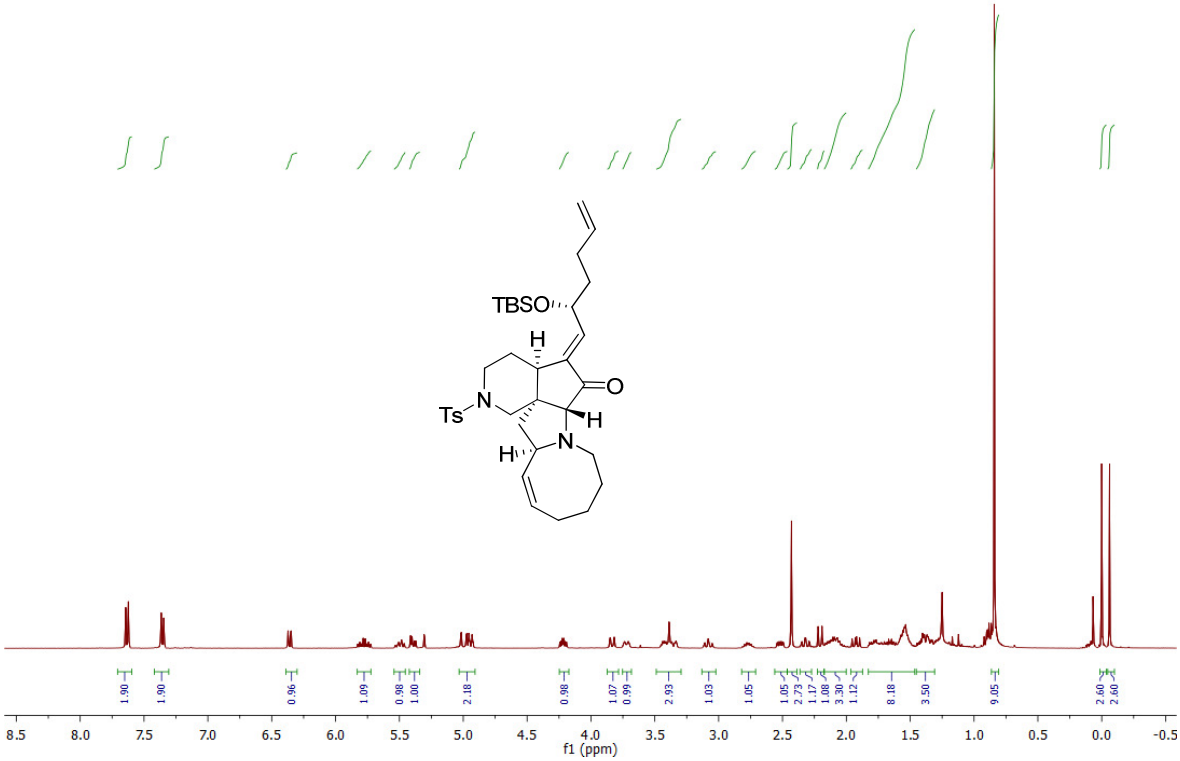

214.65
142.74
134.53
132.06
130.12
129.93
127.77
71.89
59.31
51.86
48.95
48.45
44.36
43.84
36.47
27.92
27.02
26.07
25.64
20.76
f1 (ppm)

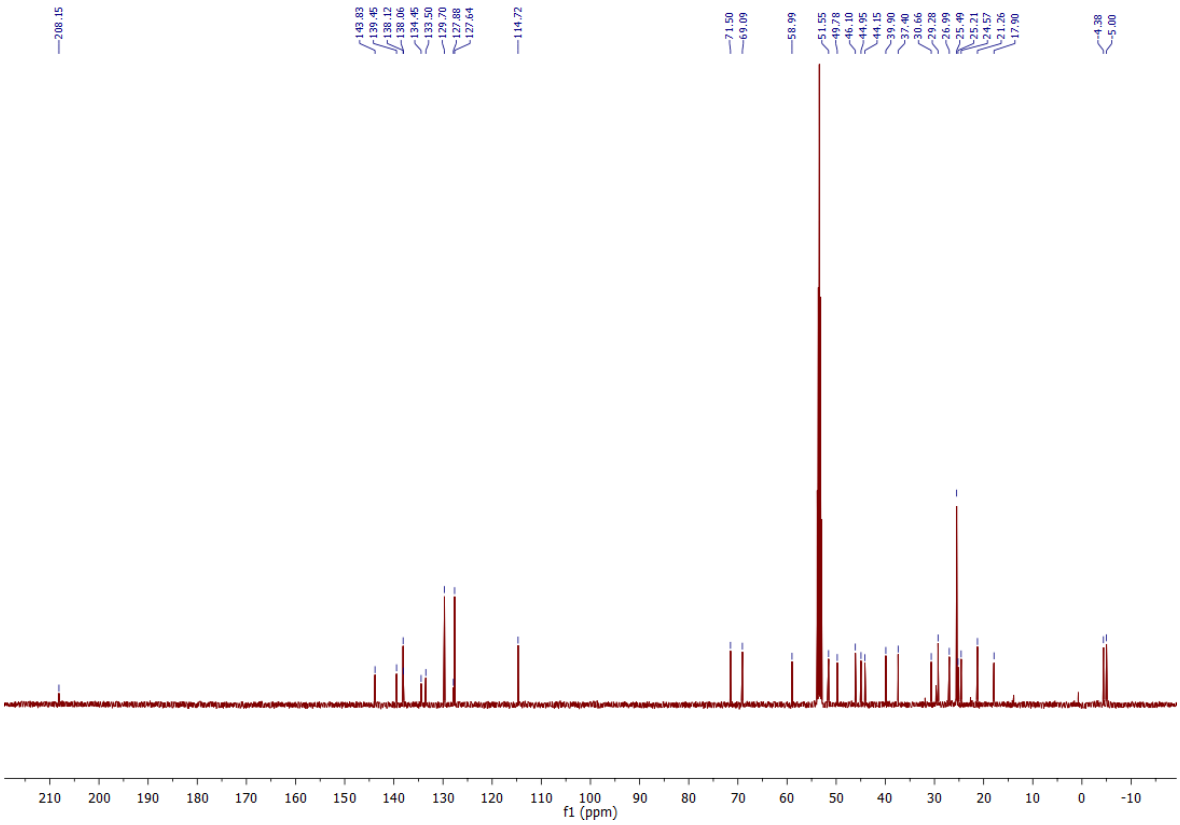

O
O
HO
H
O
Ts
N
H
H
N
1.97
1.99
0.91
1.01
1.07
3.16
1.00
0.99
2.02
1.00
1.06
3.05
1.05
1.06
0.93
13.95
2.04
9.02
3.11
2.53
f1 (ppm)

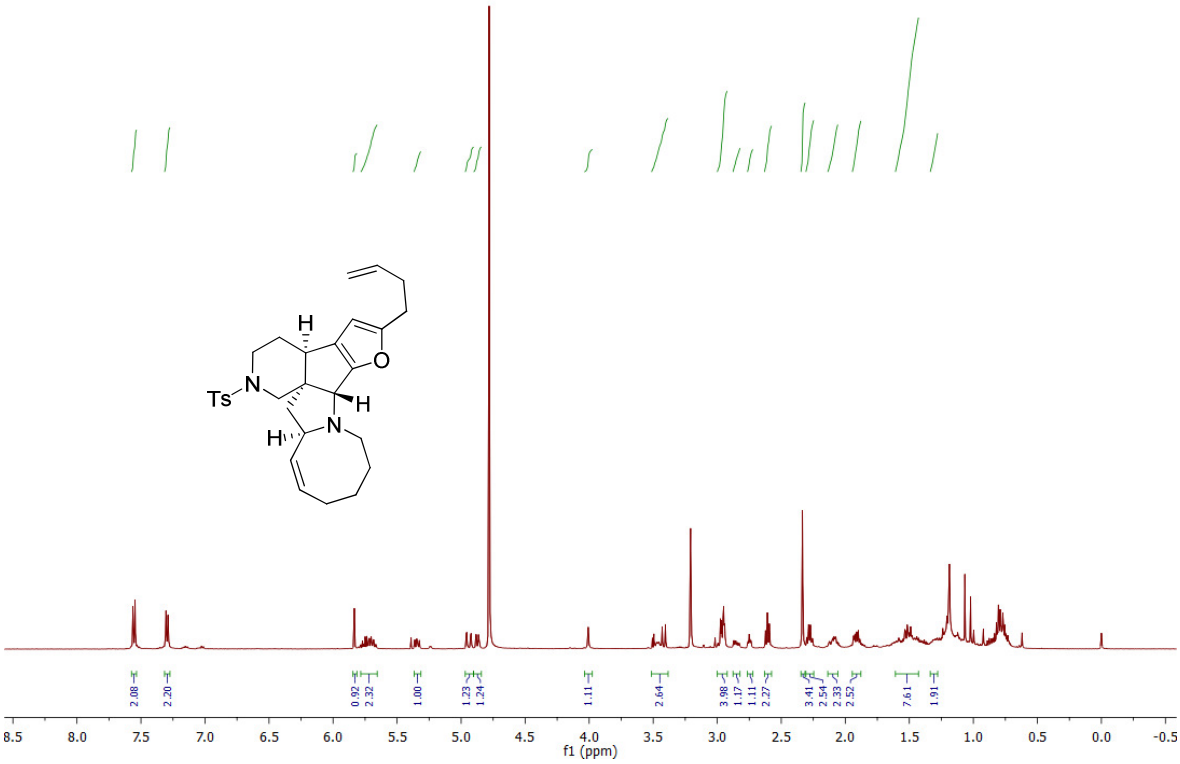

207.36
173.28
142.66
141.18
136.28
134.82
134.56
129.74
129.62
128.18
127.11
71.23
68.28
59.67
51.50
50.80
50.01
45.90
44.81
44.11
39.47
37.01
32.88
30.12
26.82
26.41
25.12
24.82
24.73
23.00
20.75
f1 (ppm)

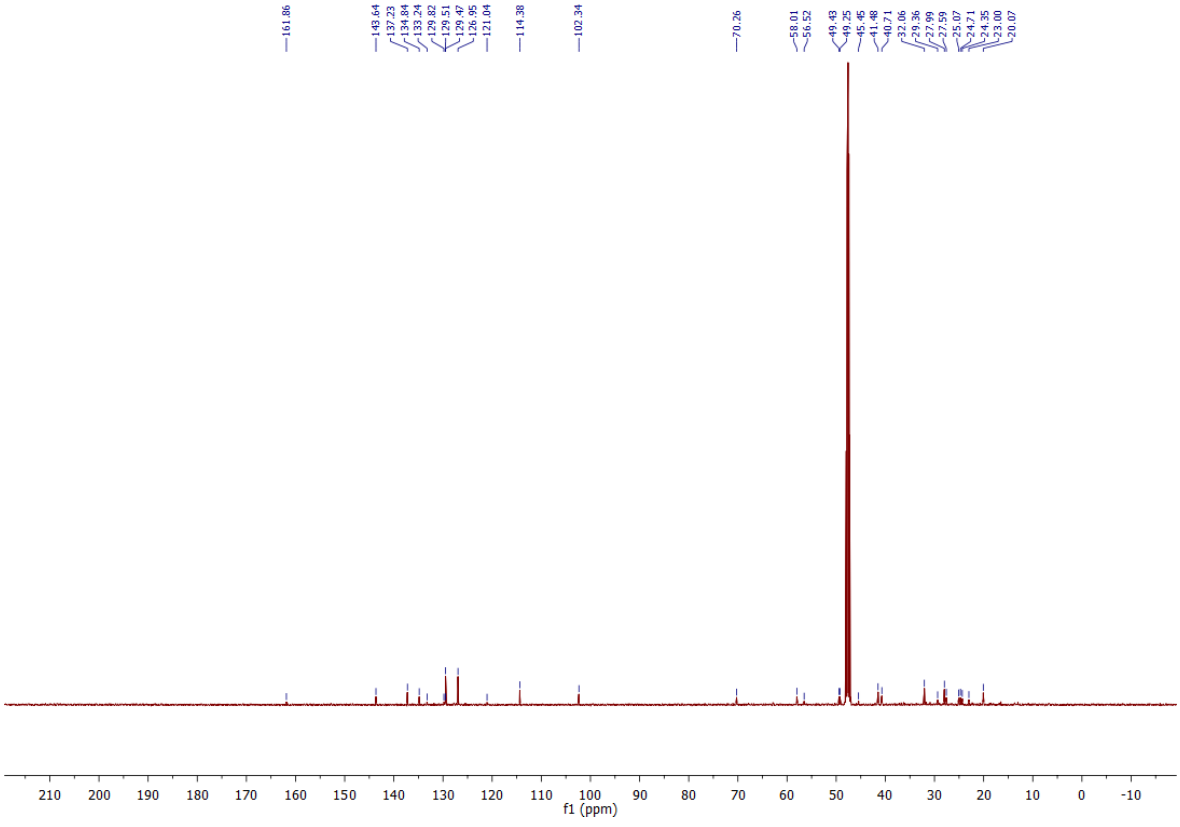

O
O
H
O
Ts
N
H
H
N
2.00
2.04
0.92
1.01
3.37
1.10
3.48
1.05
1.13
3.92
1.05
1.09
2.01
3.19
5.06
1.90
4.97
6.61
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

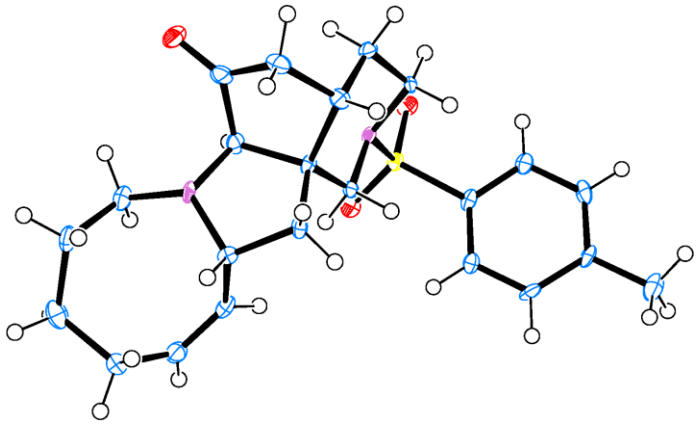

174.33
161.96
152.98
143.63
134.84
132.99
131.79
130.01
129.47
129.32
129.00
126.96
102.38
70.26
57.96
56.59
50.59
49.47
45.58
41.47
40.80
32.73
28.41
27.61
26.07
25.70
25.18
24.74
24.51
24.40
20.08
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


TBSO
H
O
Ts
N
H
N
H
1.90
1.90
0.96
1.09
0.98
1.00
2.18
0.98
1.07
0.99
2.93
1.03
1.05
1.05
2.73
1.17
1.08
3.30
1.12
8.18
3.50
9.05
2.60
2.60
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

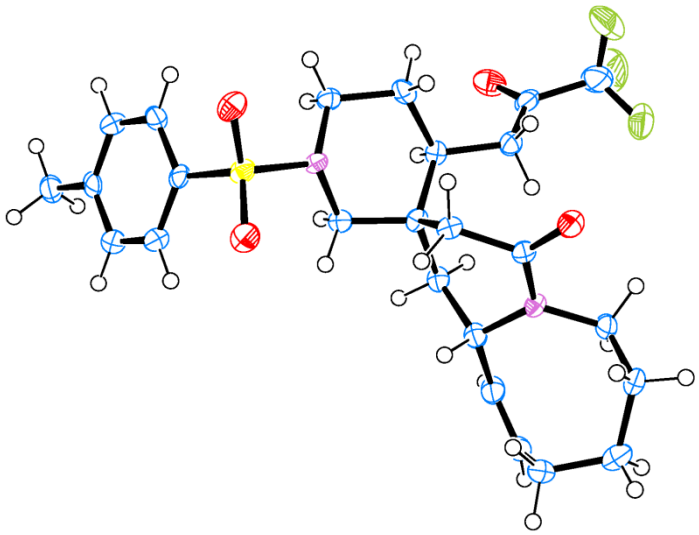

208.15
143.83
139.45
138.12
138.06
134.45
133.50
129.70
127.88
127.64
114.72
71.50
69.09
58.99
51.55
49.78
46.10
44.95
44.15
39.90
37.40
30.66
29.28
26.99
25.49
25.21
24.57
21.26
17.90
4.38
5.00
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


H
O
N
Ts
H
H
N
2.08
2.20
0.92
2.32
1.00
1.23
1.24
1.11
2.64
3.98
1.17
1.11
2.27
3.41
2.54
2.33
2.52
7.61
1.91
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


161.86
143.64
137.23
134.84
133.24
129.82
129.51
129.47
126.95
121.04
114.38
102.34
70.26
58.01
56.52
49.43
49.25
45.45
41.48
40.71
32.06
29.36
27.99
27.59
25.07
24.71
24.35
23.00
20.07
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



Empirical formula	$C_{23}H_{30}N_2O_3S$
Formula weight	414.55
Temperature	150(2) K
Wavelength	0.71073
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimension	a = 12.6438(12) Å α = 90 ° b = 17.2238(18) Å β = 90 ° c = 29.188(3) Å γ = 90 °
Volume	6356.4(11) $Å^3$
Z	12
Density (calculated)	1.300 mg/m^3
Radiation type	MoK\a
Absorption coefficient	0.180 µ/mm
F(000)	2664
Crystal size	0.512 × 0.120 × 0.048
θ range for data collection	1.373 to 25.070 °
Index ranges	−15 ≤ h ≤ +15, −20 ≤ k ≤ +20, −34 ≤ l ≤ +34
Number of reflections measured	74994
Number of independent reflections	11253
R_{int}	0.093
Completeness to θ = 25.242	0.981
Absorption correction type	Multi-scan
Max. and min. transmission	0.862 and 0.698
Refinement method	Full-matrix least-squares on F^2
Data / restraints/ parameters	11253 / 0 / 788
Goodness-of-fit on F^2	1.018
Final R indices [$I>2\sigma(I)$]	R_1 = 0.0608, wR_2 = 0.1060
R indices (all data)	R_1 = 0.0399, wR_2 = 0.0938
Largest diff. peak and hole	0.219 and −0.253 e.$Å^{-3}$



Empirical formula	$C_{25}H_{31}F_3N_2O_4S$
Formula weight	512.58
Temperature	100(2) K
Wavelength	0.71073
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimension	a = 5.6601(7) Å α = 90 °
	b = 16.842(2) Å β = 90 °
	c = 25.809(3) Å γ = 90 °
Volume	2460.3(5) $Å^3$
Z	4
Density (calculated)	1.384 mg/m^3
Radiation type	MoK\a
Absorption coefficient	0.085 μ/mm
F(000)	1080
Crystal size	0.6 × 0.2 × 0.02
θ range for data collection	2.54 to 25.05 °
Index ranges	−6 ≤ h ≤ +6, −20 ≤ k ≤ +20, −30 ≤ l ≤ +30
Number of reflections measured	22857
Number of independent reflections	4295
R_{int}	0.039
Completeness to θ = 25.242	0.973
Absorption correction type	Multi-scan
Max. and min. transmission	0.843 and 0.732
Refinement method	Full-matrix least-squares on F^2
Data / restraints/ parameters	4295 / 0 / 317
Goodness-of-fit on F^2	1.04
Final R indices [I>2σ(I)]	R_1 = 0.0849, wR_2 = 0.1446
R indices (all data)	R_1 = 0.0554, wR_2 = 0.1347
Largest diff. peak and hole	0.635 and −0.460 e.$Å^{-3}$