Studies towards the Total Synthesis of Nakadomarin A

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Thesis submitted in fulfillment of the requirements for the degree of

Doctor of Philosophy

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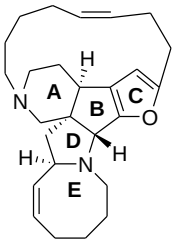
September 2012

Abstract

Nakadomarin A is a polycyclic marine alkaloid of the manzamine family. It was first isolated from the marine sponge *Haliclona sp*. collected off Manzamo, (Okinawa, Japan) and was characterised by Kobayashi and co-workers in 1997. The structure of this unprecedented compound was elucidated by exhaustive spectroscopic studies which showed that the natural product has a unique hexacyclic skeleton. In terms of biological activity, this natural product displays cytotoxicity against murine lymphoma L1210 cells (IC_{50} 1.3 μg/mL), inhibitory activity against cyclin-dependent kinase 4 (IC_{50} 9.9 μg/mL), anti-microbial activity against the fungus *Trichophyton mentagrophytes* (MIC 23 μg/mL) and anti-bacterial activity against the Gram-positive bacterium *Corynebacterium xerosis*.

The complex structure of nakadomarin A combined with its biological activities has made it a highly attractive synthetic target. The work described herein displays the most recent contribution to this field from our research group.



Nakadomarin A

The first chapter of this thesis gives a general introduction to nakadomarin A, its isolation and biological activities, followed by a summary of the efforts previously made towards its preparation.

The Clark group has been interested in the synthesis of manzamines, and the objective of the work described in the second chapter of this thesis is to carry on the strategy previously followed towards the formation of the ABD core of nakadomarin A. The second part of this chapter also describes the efforts towards the formation of the furan ring C.

Declaration

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

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

Emilie Laloy

Prof. J. Stephen Clark

Acknowledgements

I would like to express my gratitude to all those who made the completion of this thesis possible. First, I would like to thank Prof. J. Stephen Clark for giving me the opportunity to join his group. Prof. Clark not only served as my supervisor but also supported and challenged me throughout my PhD. I would also like to thank Pfizer Ltd. for financial support and my industrial supervisors, Dr Paul Fish and Dr David Pryde for all their help, especially during the three months I spent at Pfizer in Kent. Thank you to all the technical staff at the University of Glasgow who plays a vital role in the running of the department.

Of course, I would like to thank my parents who have supported me on so many levels for all these years. I should also thank BT for unlimited international phone calls, and Royal Mail for delivering my parcels of French delicacies. Both were really essential!

This thesis could not have been written without the help of Dr Laura Paterson, thank you for being so patient with me while reading and correcting my thesis. Thank you to Dr Alistair Boyer and Dr David Lindsay for their advices. Of course, I would also like to thank Dr Euan Fordyce who read all my previous reports. I have been fortunate to study in a country where people are so patient and polite (In France, I would have been yelled at more than once!).

In my daily work I have been blessed with a friendly and cheerful group of fellow students. I would like to thank in particular Dr Bora Sieng who helped me to settle in the lab, and answered all my questions for two years. We had a great time sharing a fumehood and lots of gossips. Thank you to Anthony Aimon, my second fumehood partner, not always in the best mood but always there for me.
My thanks to the rest of the “original” French Team: Dr Florence Szydlo, Dr Raphaelle Berger, Dr Frederick Nuter and Dr Alexandre Bayle who made Glasgow feel like home. In addition, it has been a pleasure working with the 2008-2011 male team: Flavien Labre, Derek Strowes, and Ralph Sigerson. I also would like to thank Laetitia Delion, Helen Gibbard and Chao Xu for their friendship and the chocolate breaks.

Am I missing someone? Obviously, I would like to thank Emelie Hansen, who shared so many things with me: from Wednesday Cookies to Dess-Martin Periodinate, from “The Rocky Horror Show” to a great week of conference. I know I made a friend for life.
An enormous thanks goes to everyone in the group, both past and present members, for the good atmosphere inside and outside the lab.

Finally, I would like to thank Romain Poltronieri, for his support over the last decade. I started my PhD as “Miss” and I will proudly finish it as “Mrs”.

List of Abbreviations

acac	acetylacetonate
AIBN	2,2'-azo*bis*(2-methylpropionitrile)
aq	aqueous
Ar	aromatic
Bn	benzyl
br	broad
Boc	*tert*-butoxycarbonyl
Cat	catalytic
CAN	ceric ammonium nitrate
CBz/Z	carboxybenzyl
CSA	camphorsulfonic acid
d	doublet
DBU	1,8-diazobicyclo-[5,4,0]-undec-7-ene
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
decomp.	decomposition
DET	diethyltartrate
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DHP	3,4-dihydro-2*H*-pyran-2-methanol
DIAD	di-*iso*-propyl azodicarboxylate
DIBAL-H	di-*iso*-butylaluminium hydride
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMEDA	*N*,*N'*-dimethylethylenediamine
DMF	*N*,*N*-dimethylformamide
DMM	dimethoxymethane
DMP	Dess-Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMS	dimethylsulfide

DMSO	dimethylsulfoxide
DMTSF	dimethyl(methylthio)sulfonium tetrafluoroborate
DPPA	diphenyl phosphoryl azide
dr	diastereomeric ratio
EDC	*N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide
ee	enantiomeric excess
i.e.	id est
h	hour(s)
HATU	*O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HMPA	hexamethylphosphoramide
HOBt	1-hydroxybenzotriazole
HRMS	high resolution mass spectrometry
IBX	2-iodoxybenzoic acid
IC_{50}	half maximal inhibitory concentration
imid.	imidazole
IR	infra red
isom.	isomerisation
KHMDS	potassium *bis*(trimethylsilyl)amide
LAH	Lithium aluminum hydride
LDA	lithium di-*iso*-propylamide
LiHMDS	lithium bis(trimethylsilyl)amide
liq.	liquid
M	molar
*m*CPBA	*meta*-chloroperbenzoic acid
MEM	methoxyethoxymethyl
Mes	1,3,5-trimethylbenzyl
MIC	minimum inhibitory concentration
min	minutes
ML*n*	metal and associated ligands
MOM	methoxymethyl
MS	molecular sieves
Ms	methanesulfonyl
MSH	*O*-mesitylenesulfonylhydroxylamine
n	normal

NaHMDS	sodium *bis*(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
nOe	nuclear overhauser effect
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
o/n	overnight
PE	petroleum ether (40-60 ◦C)
PG	protecting group
Ph	phenyl
PMB	*p*-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
*i*Pr	*iso*-propyl
*p*TSA	*para*-toluenesulfonic acid
pyr.	pyridine
quant.	quantitative
RCEM	ring-closing enyne metathesis
RCM	ring-closing metathesis
rt	room temperature
SM	starting material
t	*tert*
TBAF	tetra-*normal*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
*t*Bu	*tert*-butyl
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	tri-*iso*-propylsilyl
TLC	thin layer chromatography
TMEDA	*N,N,N',N'* -tetramethylethylenediamine

TMS	trimethylsilyl
TMTU	tetramethylthiourea
TPAP	tetra-*n*-propylammoniumperruthenate
Ts	*para*-toluenesulfonyl
UV	ultraviolet

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Chapter 1: Introduction to nakadomarin A

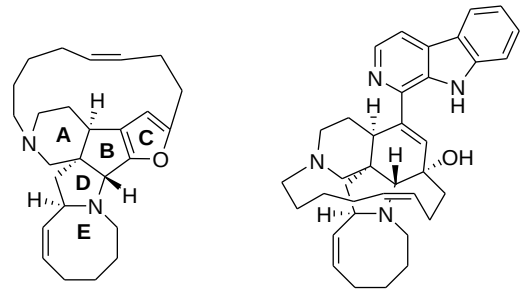
The total synthesis of natural products is one of the most challenging problems that chemists face because nature is a never-ending source of new and complex targets. Natural compounds are derived from plants, microorganisms, or marine organisms.[1] They are the subject of interest, not only in their natural forms, but also because they can serve as templates for synthetic modifications.[2] The most obvious proof of this is the number of well-known drug molecules derived from natural products. For millennia, natural products extracted from plants reigned supremely in medicine throughout the world as therapeutic agents (e.g. aspirin and morphine, which are two of the oldest drugs known to mankind).[3-4] Approximately 87% of all categorised human pathologies, including cancer and cardiovascular diseases, are treated using natural products and drugs related to them.[2]

The purpose of the work described in this thesis is the total synthesis of the polycyclic marine alkaloid nakadomarin A (**1**), a member of the manzamine family of natural products. This first chapter provides a general introduction to nakadomarin A — its isolation and biological activities — followed by a summary of the previous efforts to synthesise it. The second chapter will focus on the results achieved over the past three years and the final chapter will detail the experimental procedures carried out.

1.1 Nakadomarin A and members of the manzamine family

1.1.1 Nakadomarin A, a member of the manzamine family

Nakadomarin A (**1**) is a polycyclic marine alkaloid of the manzamine family (**Figure 1.1**).[5] The first manzanine alkaloid, manzamine A (**2**), was isolated from the marine sponge *Haliclona sp*. collected off Manzamo, (Okinawa, Japan) and characterised by Higa and co-workers in 1986.[6] Since then, more than 70 compounds of this family have been discovered.[7-10]



Nakadomarin A **(1)** Manzamine A **(2)**

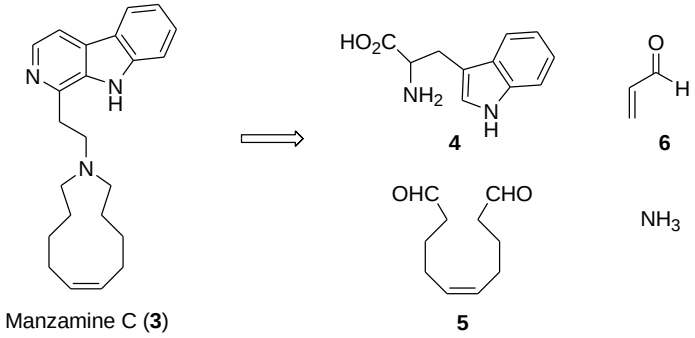
Figure 1.1: Selected compounds from the manzamine family

1.1.2 Isolation and biological activities of nakadomarin A

Nakadomarin A was first isolated from the sponge *Amphimedon sp.*, collected off the Kerama Islands (Okinawa, Japan), by Kobayashi and co-workers in 1997.[11] This natural product displays cytotoxicity against murine lymphoma L1210 cells (IC_{50} 1.3 μg/mL), inhibitory activity against cyclin-dependent kinase 4 (IC_{50} 9.9 μg/mL), anti-microbial activity against the fungus *Trichophyton mentagrophytes* (MIC 23 μg/mL) and anti-bacterial activity against the Gram-positive bacterium *Corynebacterium xerosis*.[11] The structure of this unprecedented compound was elucidated by exhaustive spectroscopic studies and shown to have a unique hexacyclic skeleton. Nakadomarin A contains 6 rings, one of which is a piperidine, and is the only compound of the mazamine family that contains a furan ring. It also possesses three different heterocycles and 4 stereogenic centres. Unfortunately, the limited availability of natural material (6 mg isolated from 1 kg of wet sponge) has prevented exhaustive screening of the compound.

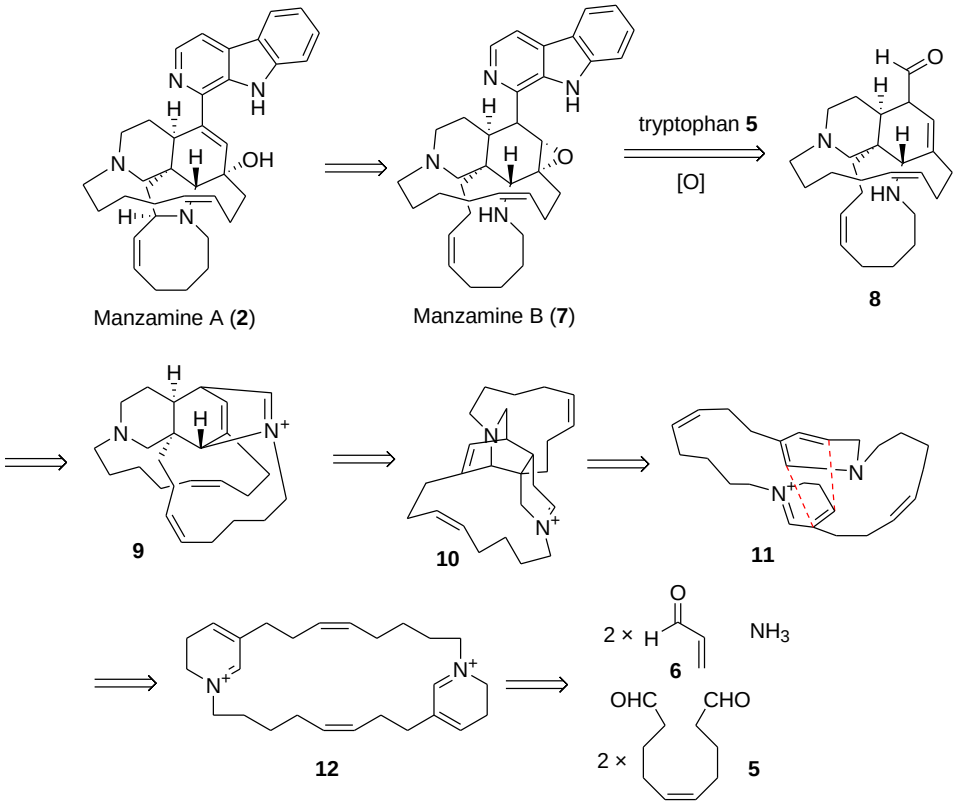
1.1.3 Biosynthesis of nakadomarin A

Knowledge of the biosynthesis is important when planning a total synthesis and an efficient biomimetic pathway can be a great source of inspiration when working on the total synthesis of complex molecules.[12] The complex structures of the manzamines were unprecedented in nature, making, as Higa said: "the provenance of manzamines B and C, like that of A, biogenetically problematic".[6] The preliminary sketch of the answer was made six years after the isolation of manzamine A (**Scheme 1.1**). This first theory was proposed by Baldwin and Whitehead in 1992 and is based on the assumption that the manzamines are derived *in vivo* from three simple building blocks: tryptophan (**4**), two units of a symmetrical dialdehyde **5** and two units of acrolein **6**.[1,13] With these three compounds in hand, a reductive coupling with ammonia gives the simple manzamine C (**3**).



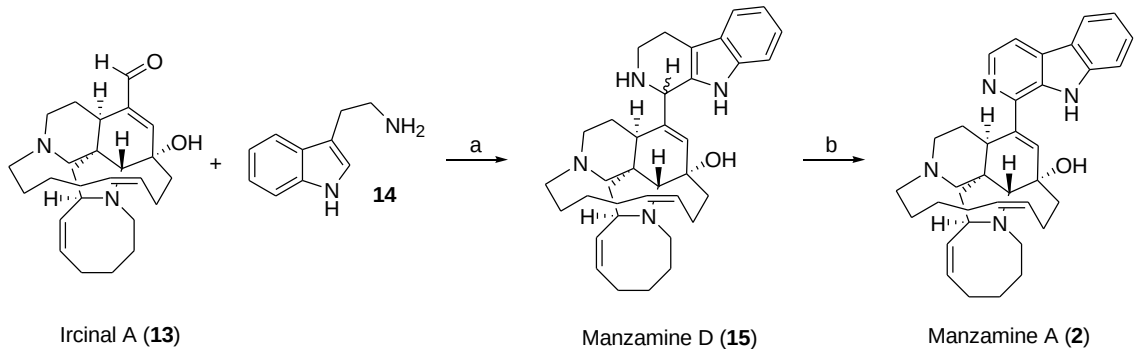
Scheme 1.1: Biosynthesis of manzamine C.

Baldwin and Whitehead were able to explain the biosynthesis of more complex manzamines, such as manzamine A (**2**) and B (**7**) (**Scheme 1.2**).[13] Indeed, manzamine A (**2**) could be derived from manzamine B (**7**) through a *trans*-eliminative opening of the epoxide, followed by allylic hydroxylation of a double bond and ring closure of the macrocycle. Manzamine B (**7**) is then obtained from aminoaldehyde **8** by oxygenation and introduction of the tryptophan unit **4**. Aldehyde **8** is simplified to **9** by hydrolysis, and redox exchange between the two piperidine rings gives **10**. Iminium ion **10** is clearly the product of an intramolecular *endo* Diels Alder reaction of **11**; its conjugate acid **12** could be easily obtained from the same units **5**, **6** and ammonia, as described for manzamine C (**3**).[13]



Scheme 1.2: The Baldwin-Whitehead hypothesis for the biosynthesis of manzamine A (**2**) and B (**7**).

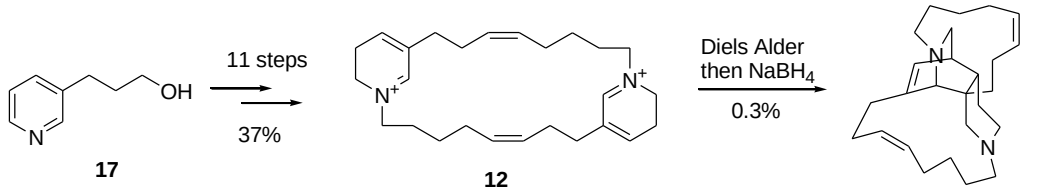
In 1992, Kobayashi and co-workers discovered and isolated another key compound of the manzamine family, ircinal A (**13**).[14] The Japanese group provided the first experimental proof of Baldwin's hypothesis by achieving the first semi-synthesis of manzamine A (**2**), converting ircinal A (**13**) to manzamine A (**2**) through a Pictet-Spengler cyclisation with tryptamine (**14**), which formed manzamine D (**15**) (**Scheme 1.3**). Subsequent DDQ oxidation of **15** led to manzamine A (**2**).[14-15]



Ircinal A (**13**) Manzamine D (**15**) Manzamine A (**2**)

Scheme 1.3: First semi synthesis of manzamine A. Conditions: a) TFA, toluene, rt, 37%; b) DDQ, $CHCl_3$, rt, 54%.

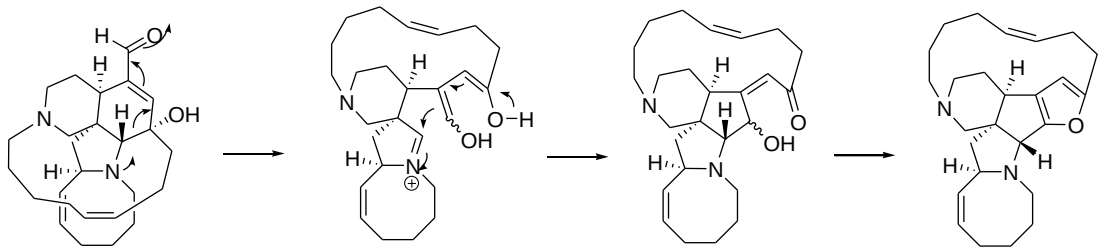
The validity of this proposed pathway was further re-affirmed, when Baldwin published his studies on the biomimetic synthesis of keramaphidin B (**16**),[16-17] a pentacyclic alkaloid, isolated independently by Kobayashi and Andersen (**Scheme 1.4**).[18-19] The macrocyle **12**, a common precursor to compounds of the manzamine family, was prepared not from the original four building blocks, but from the pyridine derivative **17** to achieve an efficient synthesis in 37% yield over 11 steps. Intermolecular Diels-Alder reaction of **12**, followed by treatment with sodium borohydride afforded a small quantity of keramaphidin B (**16**), confirming the validity of the proposal. However, the authors realise an enzymatic process is almost certainly involved in the Diels Alder reaction.[16,20]



17 **12** Keramaphidin B (**16**)

Scheme 1.4: Synthesis of keramaphidin B (**16**).

This proposed biogenetic route to manzamine A (**2**) and ircinal A (**13**) allowed a possible biosynthetic link to nakadomarin A (**1**). Indeed, nakadomarin A (**1**) is very likely to come from ircinal A (**13**) *via* a biotransformation process (**Scheme 1.5**).[21] The biosynthesis of nakadomarin A (**1**) could be explained mechanistically by ircinal A (**13**) undergoing a retro-Mannich reaction, leading to the tetracyclic compound **18**, followed by a Mannich reaction to close the cyclopentane ring (compound **19**) and dehydration then giving nakadomarin A (**1**).



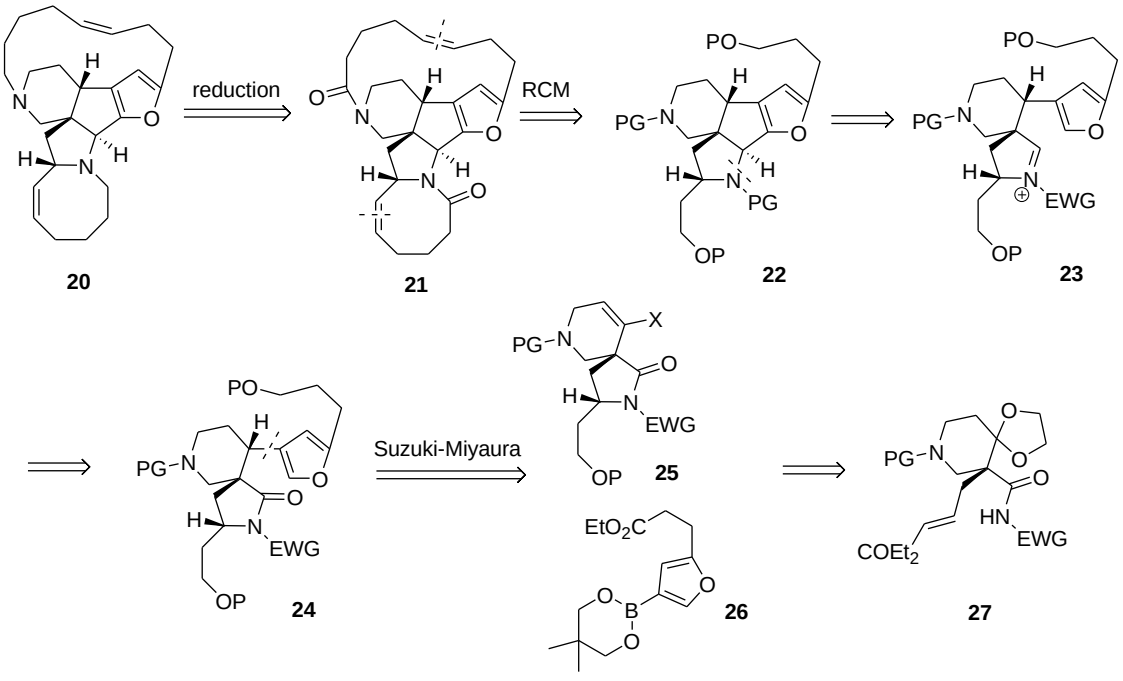
Scheme 1.5: Biosynthesis of nakadomarin A from ircinal A.

1.2 Total synthesis of nakadomarin A

Due to its unique structure and biological activity, nakadomarin A **(1)** has been the subject of much interest from the synthetic organic chemistry community over the last decade. Efforts have resulted in a total of 8 total syntheses of both natural (−) and non-natural (+) nakadomarin A. Nakagawa,[22-23] Kerr,[24] Dixon,[25-28] Funk,[29] and Zhai published the total synthesis of this natural product or its enantiomer,[30] and this list is completed by two formal syntheses, accomplished by Mukai and Magnus.[31-32] The synthesis of the natural product has also held the attention of several other groups, such as Fürstner,[33-34] Williams,[35] and Winkler,[36] and their work towards the target will be described at the end of the section.

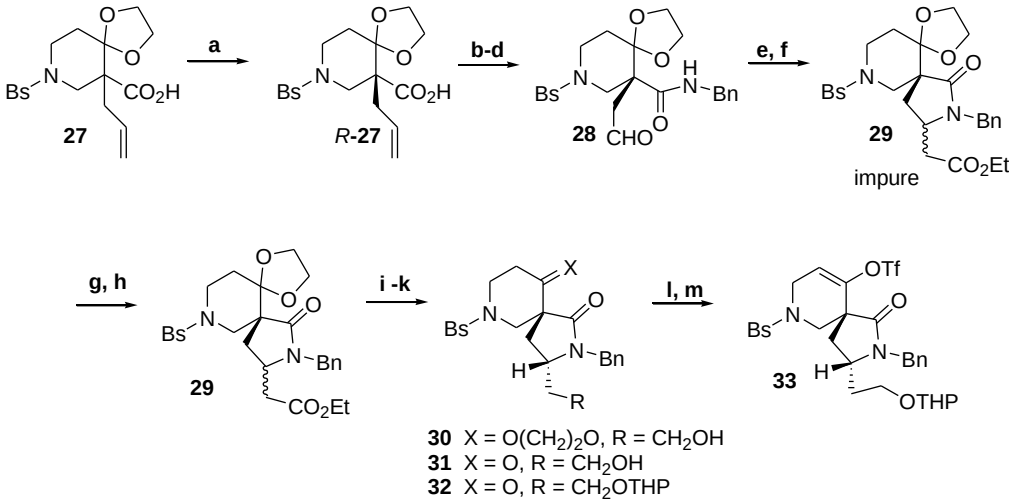
1.2.1 Nakagawa's strategy: the first total synthesis of nakadomarin A

Nakagawa and co-workers published their first work concerning nakadomarin A in 2001 with the synthesis of the central tetracyclic core of this natural product.[37] A novel intramolecular Mannich-type cyclisation was the key reaction, following the biogenetic pathway.[21] Using this approach, they described the first total synthesis of non-natural *ent*-(+)-nakadomarin A (**20**) in 2003, only six years after its isolation.[22] A year later they published the first asymmetric total synthesis of natural (−)-nakadomarin A.[23] The 2003 retrosynthetic analysis (**Scheme 1.6**) started with the reduction of the two amides of **21** to the corresponding amines, leading to *ent*-nakadomarin A (**20**). This compound could be obtained by employing ring-closing metathesis reactions to form both the 15- and 8-membered rings, the precursor of which was molecule **22**. At this point, the ABCD core could be obtained by an intramolecular Mannich-type cyclisation reaction, following in this respect their previous work regarding the elucidation of the biogenetic pathway,[37] and leading to **23**. The iminium compound **23** could be derived from spirolactam **24**, which could be prepared *via* Suzuki-Miyaura coupling from **25** and **26**. Finally, **25** could be prepared from the unsaturated ester **27**.[38]



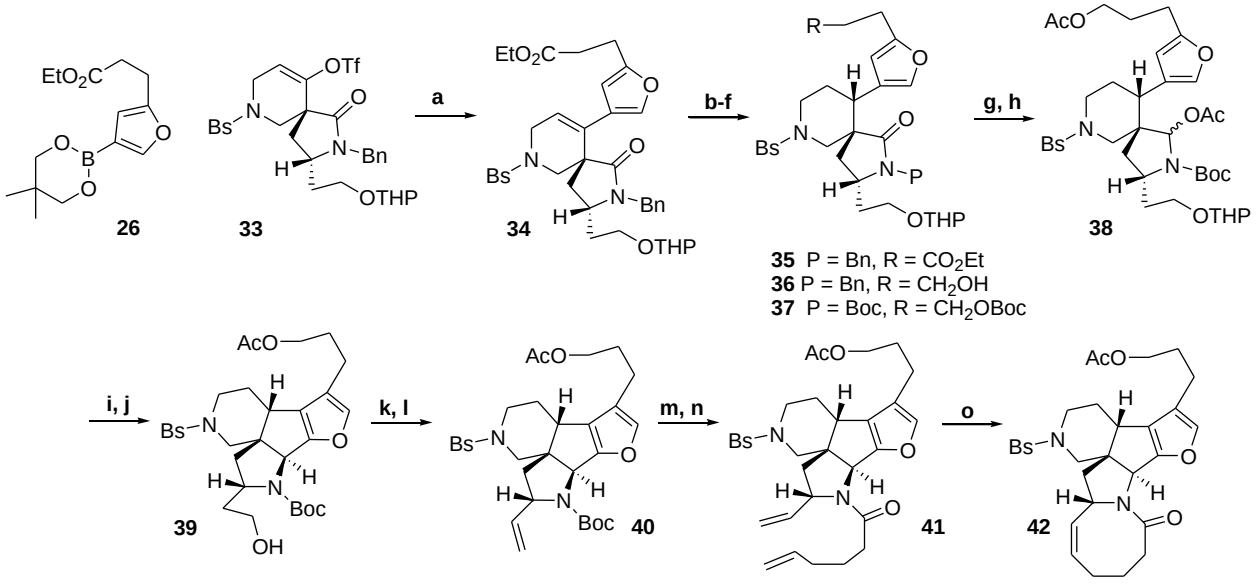
Scheme 1.6: Nakagawa's retrosynthesis analysis.

Their forward synthesis commenced with the use of readily available piperidine **27** (**Scheme 1.7**).[37] This compound was resolved to afford (*R*)-**27** in 99.6% *ee* using (+)-cinchonine. However, isolation of the opposite (*S*)-isomer, leading to the natural enantiomer, was not possible at this stage. Thus Nakagawa began with the racemic material and progressed to the enantioselective syntheses of the non-natural enantiomer but could not prepare (−)-nakadomarin A (**1**). Condensation of (*R*)-**27** with benzylamine was followed by catalytic dihydroxylation with osmium tetroxide to provide the corresponding diol, which was then cleaved to provide aldehyde **28**. Wittig olefination of aldehyde **28**, and subsequent intramolecular Michael addition provided the desired spirolactam **29**, as an inseparable 3.3:1 mixture of diastereoisomers.[39-40] Resolution and purification was performed by hydrolysis to the acids, allowing the removal of the phosphine oxide, and re-esterification to give back **29**. Subsequent reduction of **29** allowed the separation of the alcohols and the isolation of the desired isomer **30** in 58% yield from over 6 steps. The synthesis continued with the removal of the ketal group leading to keto alcohol **31**, which was subsequently protected using a THP group to prevent intermolecular acetal formation. Conversion of the ketone **32** into the enol triflate provided **33** in 87% yield.



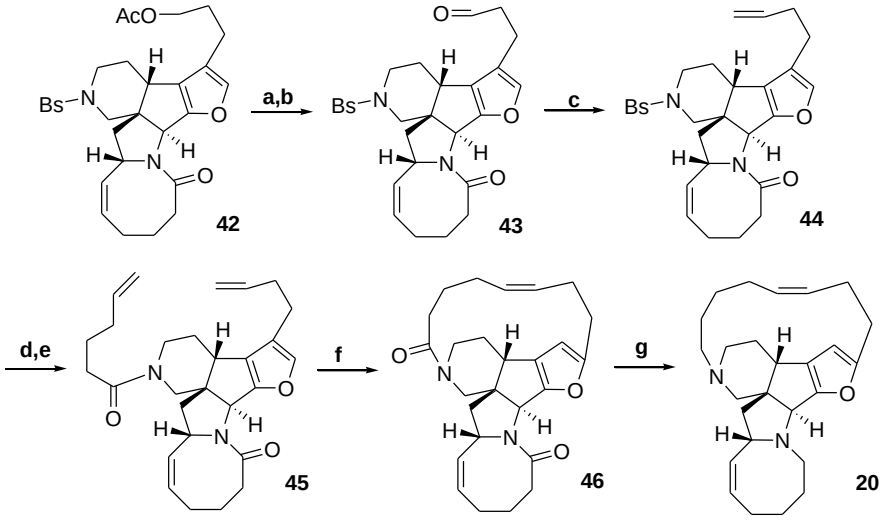
Scheme 1.7. Forward strategy. Conditions: a) resolution using (+)-cinchonine, MeOH, then HCl, 44%; b) $BnNH_2$, EDC, HOBt, DMF, 91%; c) cat. OsO_4, NMO, aq THF; d) $NaIO_4$, CH_2Cl_2, H_2O; e) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2; f) DBU, EtOH; g) NaOH, MeOH; h) AcCl, EtOH, 59% over 6 steps; i) $LiBH_4$, MeOH, THF, 99%; j) $HClO_4$, CH_2Cl_2, 91%; k) DHP, cat. CSA, 91%; l) LiHMDS, THF; m) $PhNTf_2$, 87% over 2 steps.

Suzuki-Miyaura coupling of **33** with furan-3-boronic ester **26**, provided the furan **34** in a 95% yield **(Scheme 1.8)**. Subsequent stereoselective hydrogenation occurred from the ß-side (in a 5.7:1 ratio) as expected from previous studies, and the two isomers of **35** were separated.[37] Subsequent reduction of the ester side chain with lithium borohydride afforded **36**, and a deprotection-protection procedure provided **37**. Reduction of the lactam with concomitant selective unmaking of the Boc protected alcohol, by treatment with DIBAL-H, was followed by alcohol acylation using Ac_2O/pyridine to yield ester **38** in 80% yield over these two steps. Treatment of **38** with *p*TSA, followed by removal of the THP group gave tetracyclic **39** in 87% yield. Selenation of **39** followed by oxidation of the selenide and thermal elimination of the resulting selenoxide formed **40**. Finally, removal of the Boc group followed by *N*-acylation using 5-hexenoic acid provided **41**, in a 73% yield over 4 steps. The diene **41** was treated with the Grubbs second generation metathesis catalyst to form **42** in 70% yield.[41]



Scheme 1.8: Nakagawa's approach. Conditions: a) **26**, $PdCl_2$(dppf), K_3PO_4, 95%; b) i) H_2, Pd-C, MeOH, 71%; ii) PPTS, EtOH; iii) sep diastereomers; iv) DHP, cat CSA, 69%; c) $LiBH_4$, MeOH, THF, 99%; d) Li, liq. NH_3; e) $PhSO_2Cl$, aq $NaHCO_3$, 80% over 2 steps; f) $(Boc)_2O$, Et_3N, cat. DMAP, 98%; g) DIBAL-H, CH_2Cl_2; h) Ac_2O, pyr., 80% over 2 steps; i) *p*TSA, CH_2Cl_2; j) HCl, THF, 87% over 2 steps; k) 2-nitrophenylselenocyanate, nBu_3P; l) *m*CPBA, aq K_2HPO_4; m) TFA, CH_2Cl_2; n) 5-hexenoic acid, EDC, HOBt, 73% over 4 steps, o) Grubbs II, CH_2Cl_2, 70%.

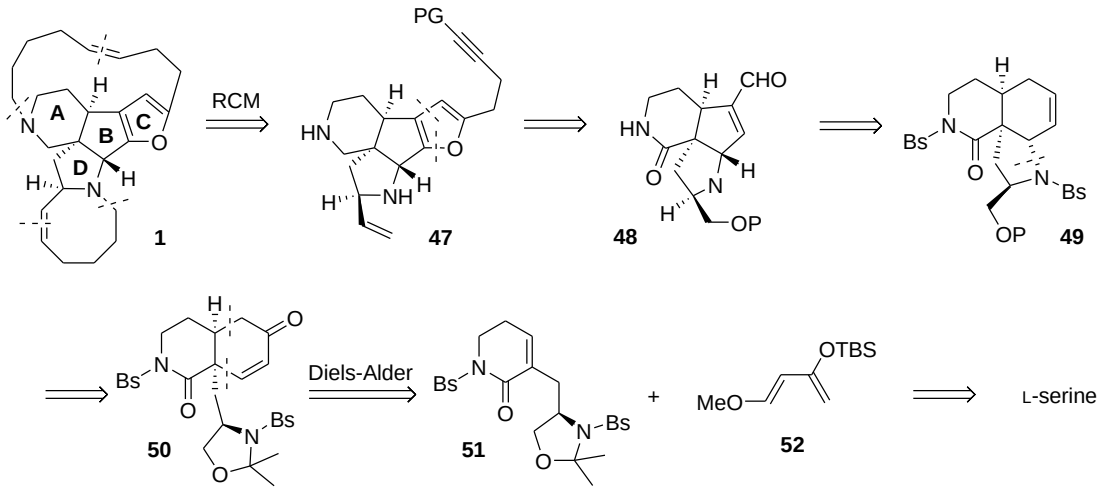
The synthesis continued with the removal of the acetate, in the furan side chain of **42**, followed by Dess-Martin oxidation of the resulting alcohol to form aldehyde **43**, which was then converted to **44** by a Wittig olefination in 53% yield (**Scheme 1.9**).[42] Removal of the sulfonamide protecting group, followed by *N*-acylation using 5-hexenoic acid gave **45** in two steps, in 77% yield. Triene **45** underwent RCM, with the Grubbs ruthenium catalyst, to give a separable mixture of *E* and *Z* products, from which the desired *Z* isomer **46** was isolated in 26% yield.[43] Finally, reduction of the *Z*-bislactam, using Red-Al, provided the target molecule **20** in 86% yield. This completed the first total synthesis of *ent*-(+)-nakadomarin A, from readily available carboxylic acid **27**, in 34 steps. The major drawbacks of this first synthesis were its length and the inability to form of the desired enantiopure starting material.



Scheme 1.9: Nakagawa's endgame. Conditions: a) NaOH, MeOH, 91%; b)DMP, 80%; c) $Ph_3P{=}CH_2$, 72%; d) Na, naphthalene; e) 5-hexenoic acid, EDC, 77% over 2 steps; f) Grubbs I (*Z*: 26% - *E*: 44%), g) Red Al, toluene, 86%.

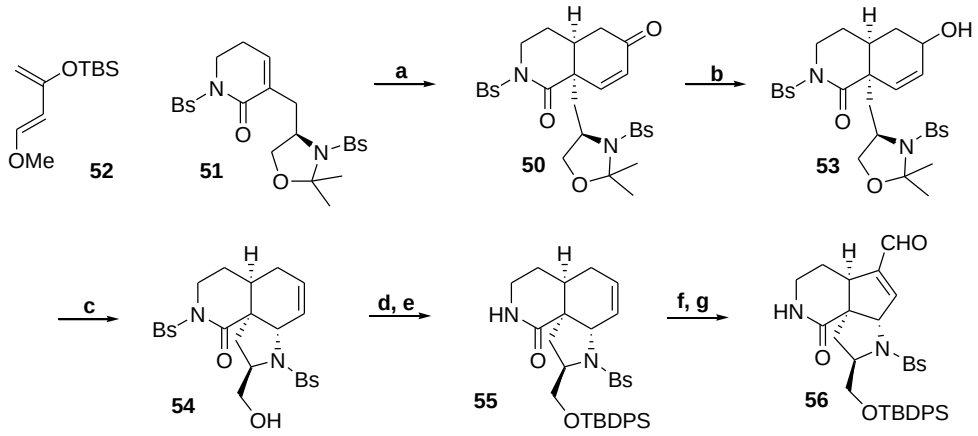
1.2.2 Strategy for the natural enantiomer

To achieve the first total synthesis of the naturally occurring enantiomer, (−)-nakadomarin A, Nakagawa and co-workers needed an appropriate starting material. They achieved this goal in 2004 and published a new route to the ABCD core, leading to the successful first total synthesis of (−)-nakadomarin A **(1)** (**Scheme 1.10**).[23] The starting point of this retrosynthetic analysis shows similarity with that of the non-natural compound.[22] Disconnection of both 15- and 8-membered macrocycles leads to **47**. The furan ring could be obtained from aldehyde **48**, itself prepared from ketone **49**.Tricyclic lactam **49** could be synthesised from bisketone **50**, which could be constructed from a Diels-Alder reaction between siloxydiene **52** and dienophile **51**. The unsaturated lactam **51** would be a derivative from natural amino acid L-serine.



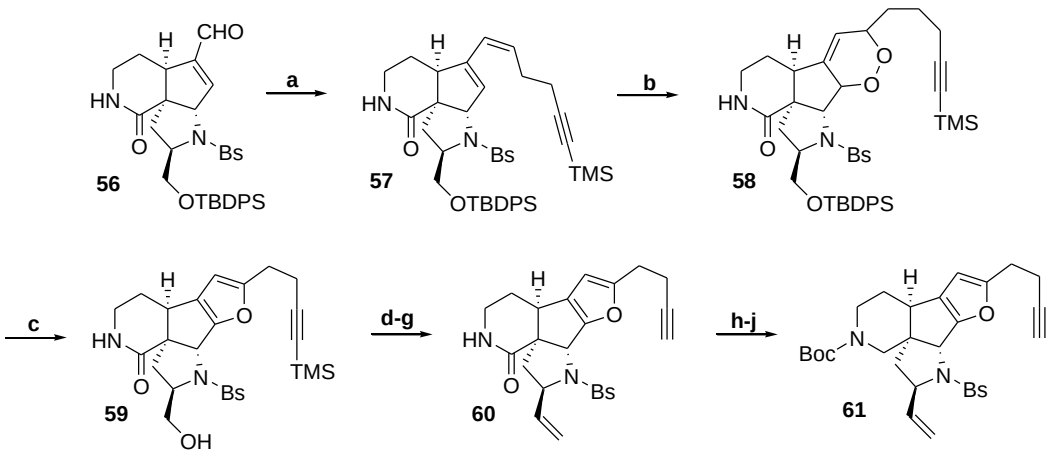
Scheme 1.10: Retrosynthesis – strategy for the natural enantiomer.

Nakagawa's synthesis started with the Diels-Alder reaction of diene **52** with the L-serine derived dienophile **51** (**Scheme 1.11**). This was followed by Luche reduction of the ketone to give a mixture of alcohols **53**, which were the intermediates for the key S_N2' reaction, performed in a 70% yield by treatment with HCl to remove the acetonide group, leading to **54**.[44] Subsequent protection of the hydroxyl group as a TBDPS ether allowed the removal of the *N*-benzenesulfonyl group, leading to **55** (74% over 2 steps). The six-membered ring was then cleaved by ozonolysis and recyclised by aldol condensation to give the desired 5-membered ring and deliver aldehyde **56** in 75% over 2 steps.[45]



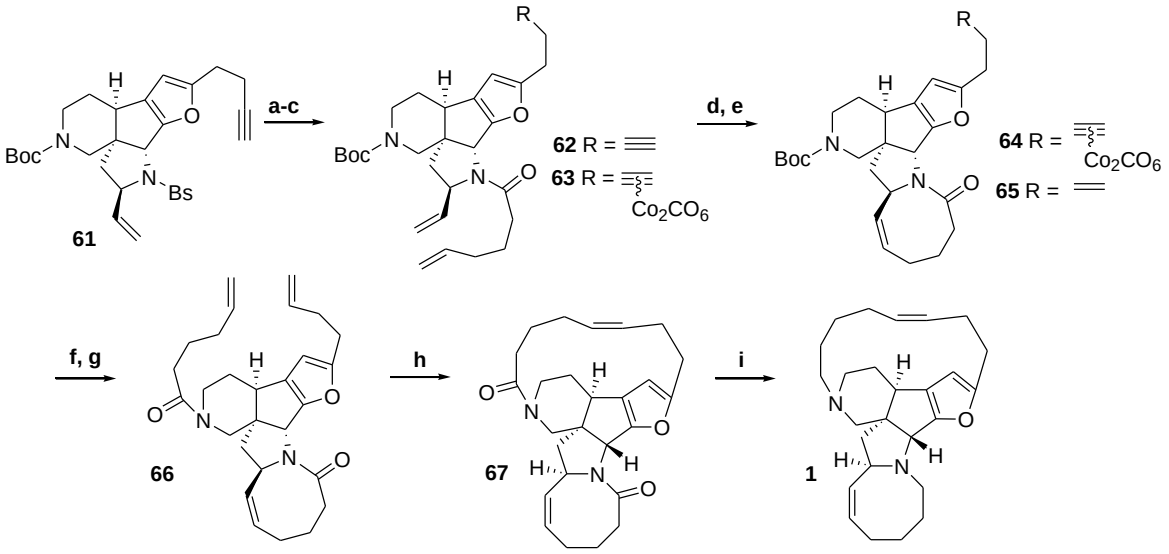
Scheme 1.11: Forward synthesis. Conditions: a) i) neat; ii) TFA, CH_2Cl_2, 52%; b) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, CH_2Cl_2, MeOH, 98% (d.r = 2:1); c) HCl, benzene, 70%; d) TBDPSCl, imidazole; e) Na/anthracene, 1,2-ethanediol, 74% over 2 steps; f) O_3, CH_2Cl_2, Me_2S; g) *N*-methylanilinium trifluoroacetate, THF, 75% over 2 steps.

The resulting aldehyde **56** underwent a Wittig olefination, to install the side chain necessary for the synthesis of the furan system (compound **57**) (**Scheme 1.12**). Treatment with singlet oxygen formed the peroxide **58**, which was treated with *t*BuOK, then with acid to provide furan **59** in a 88% yield (this sequence also removed the TBDPS group).[46] The tetracyclic compound **59** corresponded to the complete chiral ABCD-ring system of nakadomarin A. Oxidation of the alcohol to the aldehyde using the Dess-Martin-periodinane (90% yield) was followed by a Peterson olefination, and the TMS protecting group of the alkyne was removed, leading to the enyne **60**.[47] The protection of the nitrogen with a Boc group allowed the reduction of the lactam carbonyl group to give carbamate **61**.



Scheme 1.12: Towards **61**. Conditions: a) $Ph_3PCH_2CH_2CH_2CCTMS$, NaH, THF, 76%; b) O_2, Rose bengal, hν, CH_2Cl_2/MeOH, quant, (α/ß adducts = 1.2:1); c) *t*BuOK, THF, HCl, 88%; d) DMP, CH_2Cl_2 90%; e) $TMSCH_2MgCl$, Et_2O, 83% (d.r. = 2:1); f) $BF_3.Et_2O$, CH_2Cl_2; g) K_2CO_3, MeOH, 81% over 2 steps; h) Boc_2O, DMAP, Et_3N, 93%; i) DIBAL-H, toluene; j) Et_3SiH, $BF_3.Et_2O$, CH_2Cl_2, 84% over 2 steps.

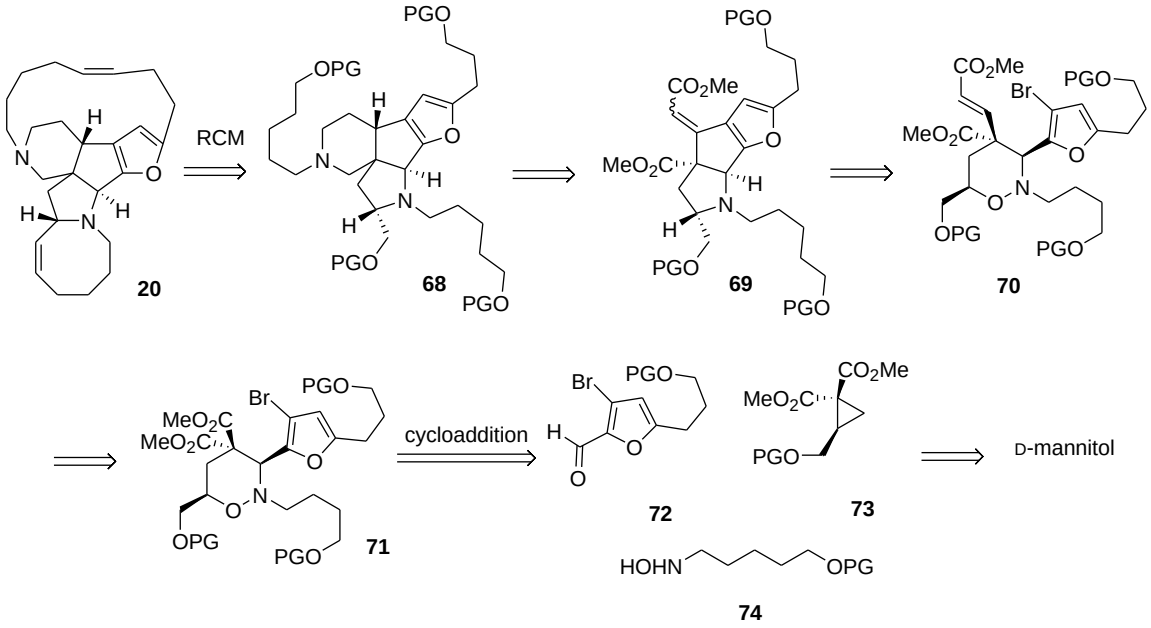
The final steps in this synthesis were similar to those employed for the preparation of the non-natural compound and allowed the first total synthesis of natural nakadomarin A (**Scheme 1.13**).[48] This sequence provided the natural (−)-nakadomarin A in 26 steps, from dienophile **51**.



Scheme 1.13: Endgame. Conditions: a) Na/naphtalene, DME; b) 5-hexenoyl chloride, Et_3N, CH_2Cl_2, 92% over 2 steps; c) $Co_2(CO)_8$, CH_2Cl_2, 91%; d) Grubbs II, CH_2Cl_2, 83%; e) *n*Bu_3SnH, benzene, 75%; f) TFA, CH_2Cl_2; g) 5-hexenoyl chloride, Et_3N, CH_2Cl_2 92%; h) Grubbs I, CH_2Cl_2, 83%, *Z* isomer: 26%, *E* isomer: 46%; i) Red-Al, toluene, 92%.

1.2.3 Kerr's approach (2007)

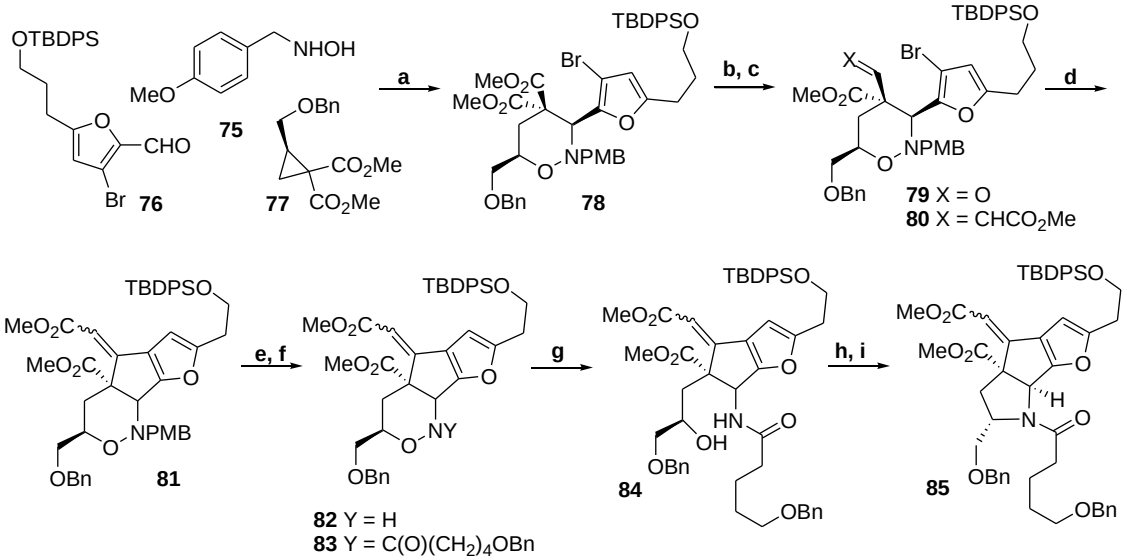
The second synthesis of nakadomarin A **(1)** was reported in 2007, when Kerr published his approach to the unnatural enantiomer **20**.[24] In this respect, he was able to improve his previous work published in 2005 regarding the synthesis of the tetracyclic core of this molecule using a nitrone/cyclopropane cycloaddition as the key step.[49-50] Kerr's retrosynthetic analysis began with the disconnection of the two macrocycles by RCM leading to **68**, followed by excision of the piperidine ring, leading to **69** (**Scheme 1.14**). In turn, this molecule could be prepared from **70** *via* a pyrrolidine synthesis including a *N-O* bond cleavage and ring closure.[49] This Heck substrate would derive from oxazine **71**, made from the three-component coupling of **72**, **73**, and **74**.[51] The chirality of **73**, establishing the stereogenicity of the target molecule, comes from D-mannitol. However, preparation of the corresponding enantiomer was difficult which meant that the natural product could not be accessed readily.[52]



Scheme 1.14: Kerr's retrosynthetic analysis.

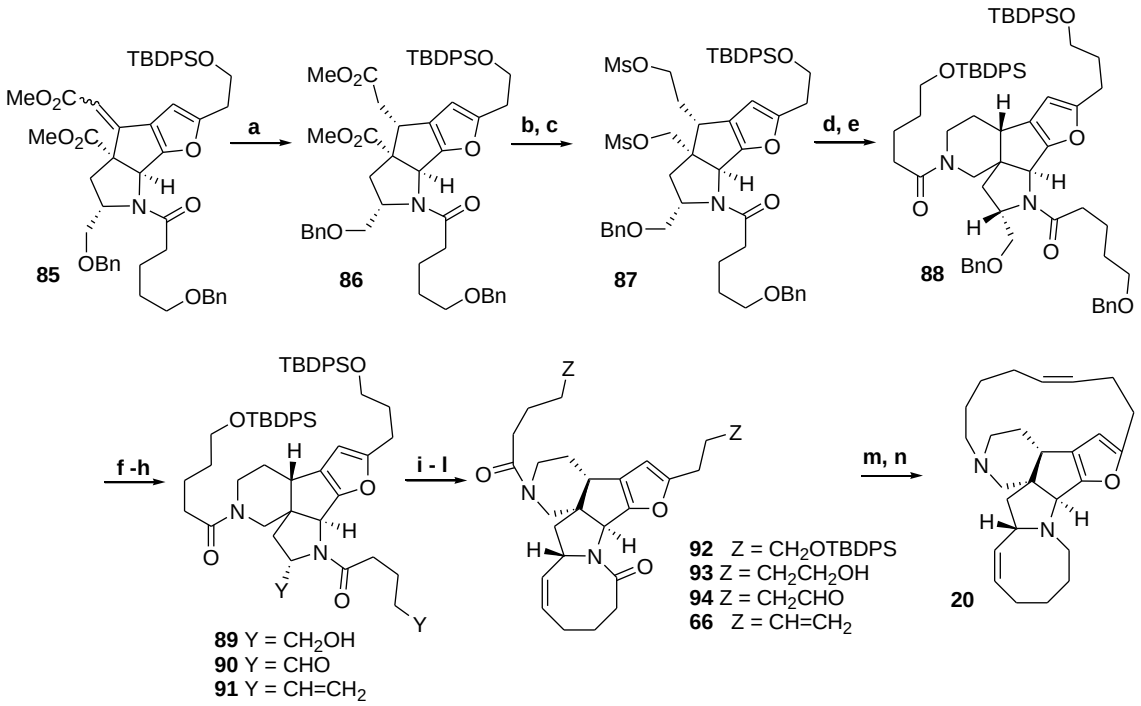
The key step in this synthesis was the three-component cycloaddition of the hydroxylamine **75**, aldehyde **76** and cyclopropane **77** to afford a highly functionalised tetrahydro-1,2-oxazine **78** (**Scheme 1.15**).[49] Mono-reduction of the equatorial ester in **78** using DIBAL-H (*via* an empirical method), followed by a Horner-Wadsworth-Emmons olefination afforded **80**.[53] Subsequent Heck cyclisation provided **81** as an undetermined, but single isomer around the alkene. Removal of the PMB protecting group and acylation of nitrogen afforded

83. Subsequent conversion of the oxazine to the pyrrolidine was the second key step in this synthesis: cleavage with SmI_2, followed by selective *O*-mesylation and subsequent treatment with base delivered the desired pyrrolidine **85**. It is interesting to note that this sequence had an unexpected consequence of isomerising the enoate moiety.[54-55] With intermediate **85** in hand, 14 further steps were required to complete the synthesis.



Scheme 1.15: Kerr's total synthesis. Conditions: a) Yb(OTf)3, 4 Å MS, 87%; b) DIBAL-H, CH_2Cl_2, 87%; c) $(MeO)_2P(O)CH_2CO_2Me$, *t*BuOK, THF, 93%; d) $Pd(PPh_3)_4$, Ag_2SO_4, Et_3N, DMF, 82%; e) DDQ, CH_2Cl_2/H_2O, 56%; f) $ClC(O)(CH_2)_4OBn$, Et_3N, CH_2Cl_2, 89%; g) SmI_2, THF; h) MsCl, Et_3N, DMAP, CH_2Cl_2; i) *t*BuOK, THF, 65% over 3 steps.

The α,ß-unsaturated ester in the tricyclic compound **85** was reduced with nickel boride, which afforded **86** (**Scheme 1.16**). Subsequent reduction of the carbomethoxy groups and mesylation of the resulting primary alcohols provided *bis* mesylate **87** in 79% yield over 2 steps. Subsequent formation of the piperidine ring in **88** was achieved by treatment of **87** with ammonia, followed by reaction the corresponding acyl chloride. Double debenzylation to the diol **89** was followed by oxidation to the bis aldehyde **90** and the subsequent double Wittig reaction provided diene **91**. Treatment of diene **91** with Grubbs' second generation catalyst resulted in RCM and afforded the pentacyclic compound **92**.[43] Removal of the silyl groups, oxidation to the *bis*-aldehyde and Wittig olefination provided Nishida's intermediate **66**. Analogous to Nakagawa's synthetic approach, treatment of **66** with Grubbs first generation catalyst, and subsequent reduction of the lactams to give the corresponding cyclic amines provided *ent*(+)-nakadomarin A **20**.[22]

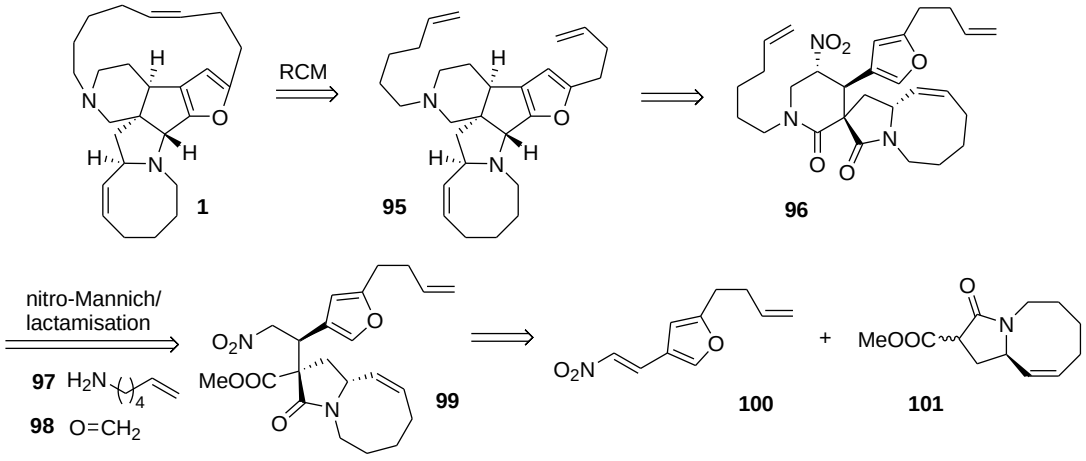


Scheme 1.16: Kerr's Endgame. Conditions: a) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, Na_2CO_3, MeOH/THF, 67% (14:1 *dr*); b) $LiAlH_4$, THF; c) MsCl, Et_3N, DMAP, CH_2Cl_2, 79% over 2 steps; d) NH_3, EtOH/THF, reflux; e) $ClC(O)(CH_2)_4OTBDPS$, Et_3N, CH_2Cl_2, 77% over 2 steps; f) BCl_3, CH_2Cl_2, 71%; g) IBX, DMSO; h) *t*BuOK, $MePPh_3I$, THF/toluene, 45% over 2 steps; i) Grubbs II, CH_2Cl_2, 84%; j) TBAF, THF; k) DMP, CH_2Cl_2, 70% over 2 steps; l) *t*BuOK, $MePPh_3Br$, THF/toluene; m) Grubbs I, CH_2Cl_2, 28% of *E*-isomer; n) Red-Al, toluene, 20% of *Z*-isomer over 2 steps.

Overall, this route yielded the unnatural nakadomarin A in 28 linear steps. Although shorter than Nakagawa's strategy, this route has the major drawback of only allowing access to (+)-nakadomarin A.

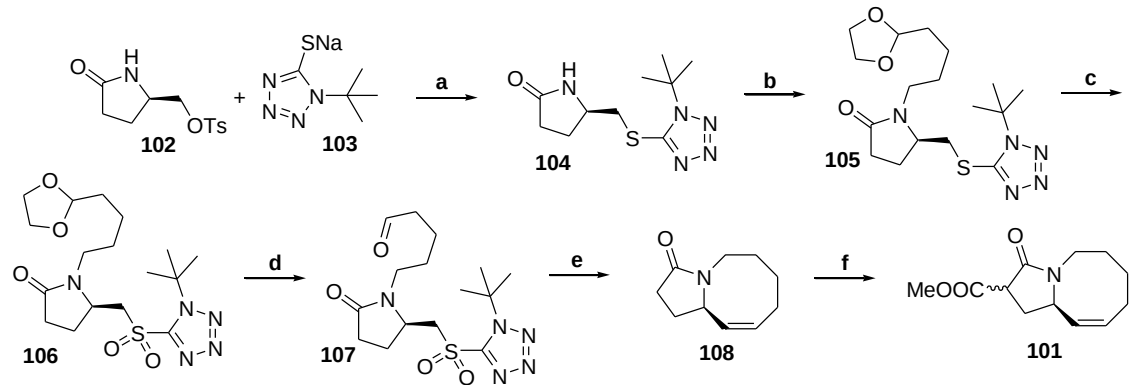
1.2.4 Dixon's syntheses of (−)-nakadomarin A (2009 & 2011)

In 2009, Dixon and co-workers published the second total synthesis of (−)-nakadomarin A.[25] Two years later, they published two further syntheses of this molecule and one modification, solving the major drawbacks of their first pathway.[26-28] Dixon's first retrosynthetic analysis shows that (−)-nakadomarin A (**1**) can be obtained by a ring-closing metathesis of **95** (**Scheme 1.17**). The triene **95** would by created by reduction of the nitro group and reductive manipulation of both carbonyl groups followed by a diastereoselective iminium ion cyclisation of **96**. Intermediate **96** would be constructed *via* a diastereoselective multicomponent nitro-Mannich/lactamisation cascade of nitro ester **99** and the imine formed *in situ* from commercial amine **97** and formaldehyde **98**. Finally, **99** could be obtained from nitro olefin **100** *via* a Michael addition with aza-bicyclic pro-nucleophile **101**.



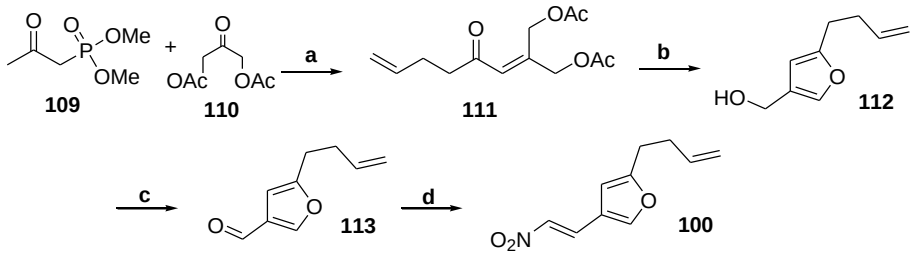
Scheme 1.17: Dixon's retrosynthetic analysis.

In Dixon's initial approach to the natural product, the first target was bicyclic compound **101**, which was prepared in 6 steps and in 24% overall yield (**Scheme 1.18**). Nucleophilic substitution of pyroglutamol **102**, with sodium thiolate **103** afforded sulfide **104**. This was followed by *N*-alkylation to afford **105** and oxidation of the sulfide to the sulfone **106**. Following deprotection to unveil aldehyde **107**, an intramolecular Julia-Kocienski olefination was used to provide the desired bicyclic lactam **108** in a good yield.[56] Finally, *C*-acylation with dimethyl carbonate provided the desired fragment **101** in 82% yield.



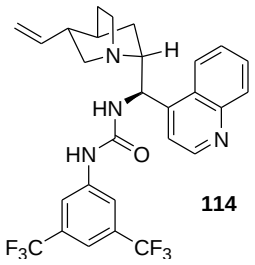
Scheme 1.18: Dixon's preparation of **101**. Conditions: a) THF, reflux, 96%; b) 2-(4-bromobutyl)-1,3-dioxalane, NaH, Bu_4NI, DMSO, 71%; c) *m*CPBA, CH_2Cl_2, 78%; d) HCl, THF, rt, 98%; e) $CsCO_3$, DMF, THF, H_2O, 56%; f) dimethylcarbonate, LHMDS, THF, 82%.

The second fragment, furanyl nitro olefin **100**, was synthesised in 4 steps and 21% yield (**Scheme 1.19**). Allylation of ketophosphonate **109**, followed by a Horner-Wadsworth-Emmons reaction using diacetyl dihydroxyacetone **110** afforded enone **111**. Subsequent acid hydrolysis provided alcohol **112**, which, after a Swern oxidation and Henry-type condensation, afforded the desired nitro olefin **100**.[57]



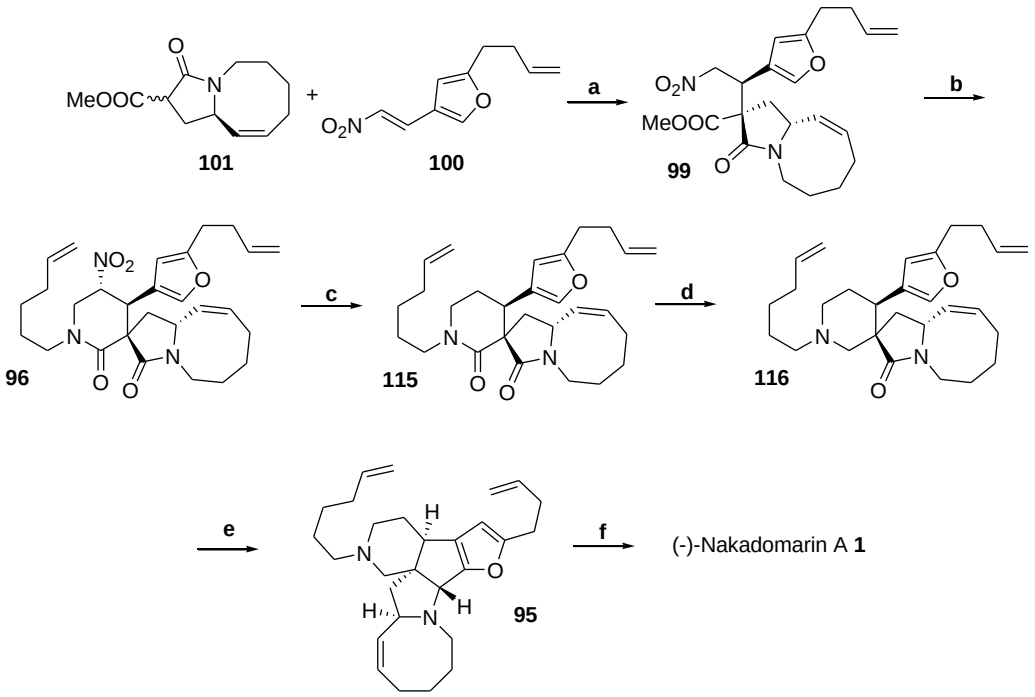
Scheme 1.19: Dixon's preparation of **100**. Conditions: a) NaH, BuLi, THF, allylbromide, then 2-oxopropane-1,3-diyl diacetate, THF, 42%; b) HCl, EtOH, 69%; c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 82%; d) $MeNO_2$, KOH, 88%.

With the two key fragments in hand, it was possible to combine them *via* a diastereoselective Michael addition, with the use of the bifunctional cinchona catalyst **114** (**Figure 1.2**). Submission of the resulting compound **99** to a three-component nitro-Mannich/lactamisation cascade provided **96** in 68% yield (**Scheme 1.20**).[58] Reduction of the nitro group was then achieved in 70% yield, and providing **115** as a single diastereoisomer.[59] The δ-lactam was reduced using lithium aluminium hydride at −20 °C, without reducing the less reactive γ-lactam. The piperidine **116** was thus isolated in 86% yield. Treatment of this compound with DIBAL-H, followed by acidification promoted cyclisation, which established the pentacyclic core of the natural target. Finally, olefin metathesis was achieved using Grubbs first generation catalyst, in the presence of camphor sulfonic acid, providing natural (−)-nakadomarin A (**1**) in 62% yield, and with a 63:37 *Z*/*E* ratio.[60]



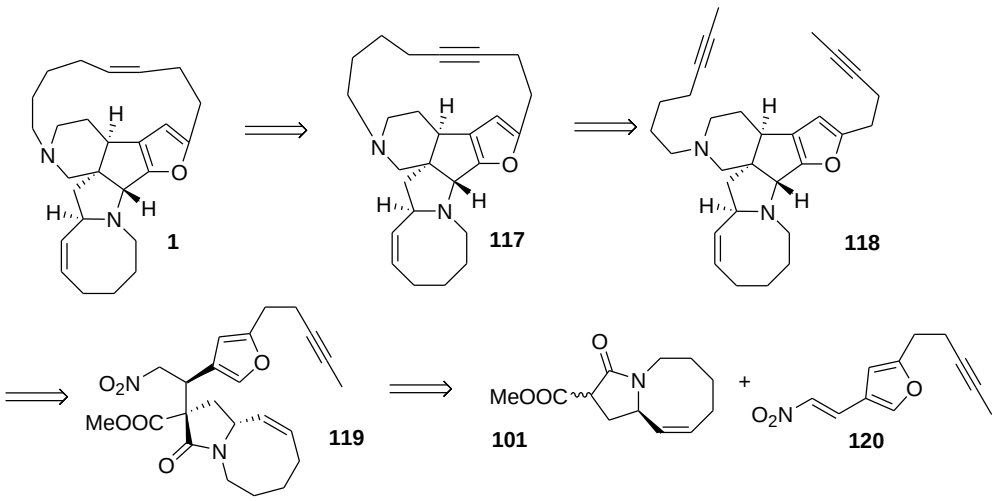
114

Figure 1.2: catalyst **114**



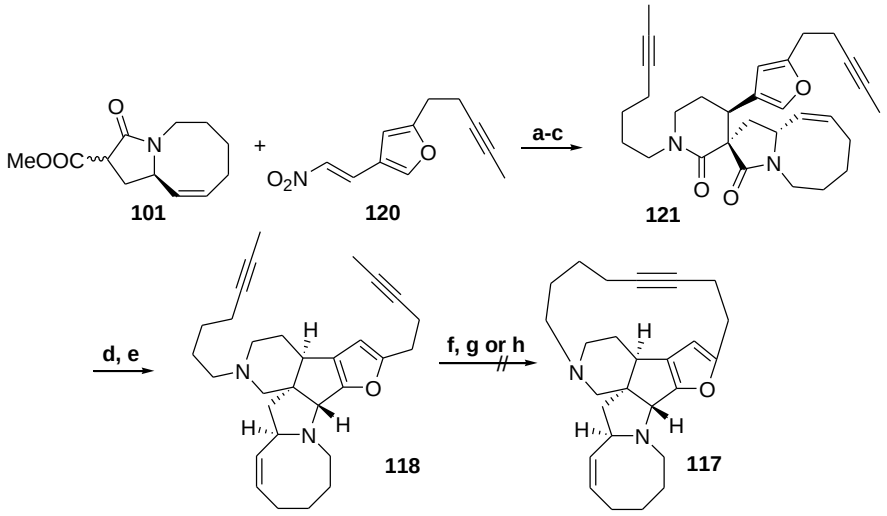
Scheme 1.20: Dixon's Endgame. Conditions: a) **114**, toluene, 57%, 91:9 *dr*; b) hex-5-enamine, CH_2=O, 68%; c) AIBN, Bu_3SnH, toluene, 70%; d) $LiAlH_4$, toluene, then HCOOH, 86%; e) DIBAL-H, toluene, HCl, 41%; f) Grubbs I, (+)-CSA, CH_2Cl_2, 62%, 63:37 *Z*/*E*.

This impressive 16-steps synthesis (longest linear sequence 12 steps) provided the natural enantiomer of nakadomarin A. Although the ratio of alkene isomers was better than Nakagawa's, the major drawback of this route was the poor selectivity (63:37 *Z*/*E*) in the final ring-closing metathesis reaction. To solve this issue, Dixon published two alternative routes to the natural product, employing diyne ring-closing metathesis.[26-27] The second synthesis, whilst containing an increased 19 synthetic steps, was a significant improvement: the ring closure was achieved using a diyne RCM/*syn*-reduction sequence thus avoiding the poor selectivity of the first diene RCM. The next improvement in Dixon's synthesis was highlighted in a further publication in the same year, which described a shorter third generation synthesis that built on the success of the two previous routes.[27] The initial retrosynthetic analysis of this final sequence deviated from the first generation synthesis mainly with regard to the initial disconnection. Nakadomarin A would be prepared from **118** *via* an alkyne RCM and a final hydrogenation step (**Scheme 1.21**). The continuation of the retrosynthesis is subsequently very similar to the group's earlier work.



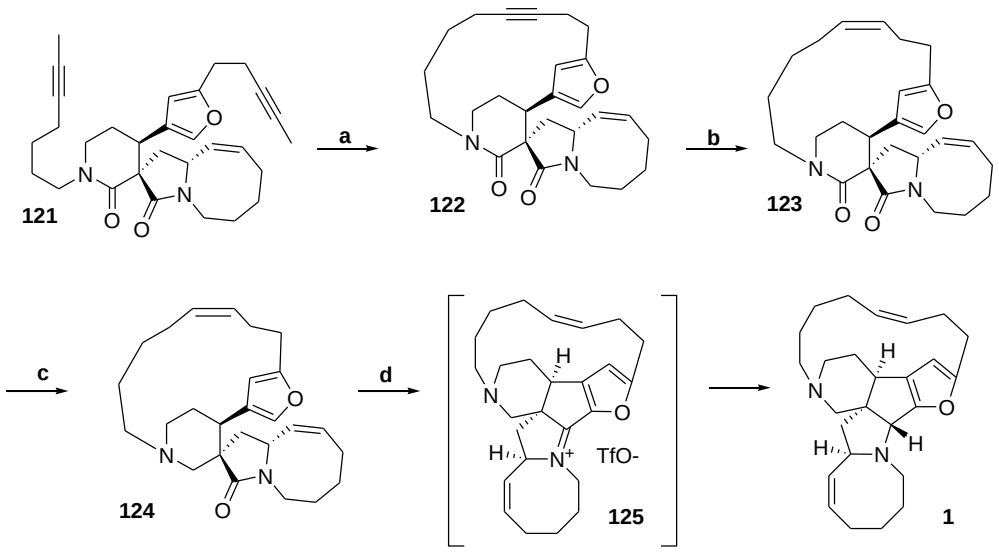
Scheme 1.21: Dixon's final retrosynthetic analysis

The bicyclic pro-nucleophile **101** was prepared using the route described in **Scheme 1.18**. The novel furanyl nitro olefin **120** was obtained in 22% yield over 4 steps, following a sequence that was similar to the pathway used to prepare **100**. As shown in **Scheme 1.22**, *bis*-alkyne **121** was obtained in 7% overall yield. Following preparation of **118**, Dixon observed a very low reactivity for the envisaged ring-closing metathesis reaction. This finding resulted in alteration of the originally proposed pathway.



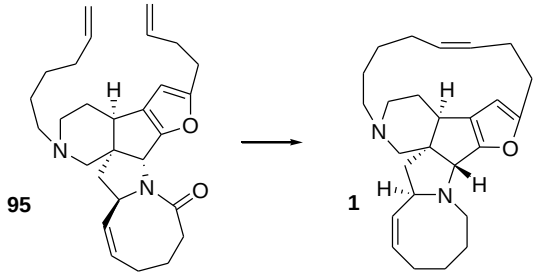
Scheme 1.22: Towards **117**. Dixon's Endgame. Conditions: a) **114**, toluene, 58%, 90:10 *dr*; b) hex-5-enamine, CH_2=O, MeOH, 63%; c) AIBN, Bu_3SnH, toluene, 64%; d) $LiAlH_4$, toluene, then HCOOH, 86%; e) DIBAL-H, toluene, HCl, 35%; f) $Mo(CO)_6$, 4-fluorophenol, PhCl, 0%; g) (*t*Buo)$_3$WCCMe$_3$, toluene, 0%; h) [(pyridine)(Ph_3SiO)$_3$MoN],toluene, 0%.

In order to solve the ring closure problem issue, the alkyne RCM reaction was performed earlier in the synthesis, by RCM of **121** to provide **122** (**Scheme 1.23**). This reaction was followed by a *syn*-selective partial hydrogenation leading to **123**. Subsequent reduction with DIBAL-H transformed the piperidinone to piperidine **124**. Lactam **124** was then treated with 2,6-di-*t*BuPy to form the desired final product. This short and highly stereoselective synthesis (13 steps longest linear sequence) allowed the preparation of (−)-nakadomarin A from commercially available starting materials.



Scheme 1.23: Conditions: a) $Mo(CO)_6$, 2-fluorophenol, PhCl, 36%; b) Lindlar's catalyst, H_2, quinoline, EtOAc, 86%; c) DIBAL-H, toluene, 57%; d) Tf_2O, 2,6-di-*t*BuPy, CH_2Cl_2, then $NaBH_4$, MeOH, 41%.

Finally, in 2011 Dixon published an ultimate improvement of his work toward Nakadomarin A. Indeed, using a tungsten based complex (**Figure 1.3**), he improved the Z/E ratio of the alkene RCM to 94:7.[28] This development also solved a major drawback of several previous syntheses, as Nakagawa and Kerr were facing the same challenge.



Scheme 1.24: Conditions: tungsten complex, toluene, 63%, 94:6 *Z*/*E*.

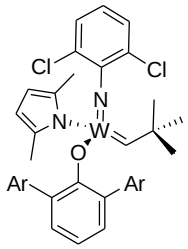
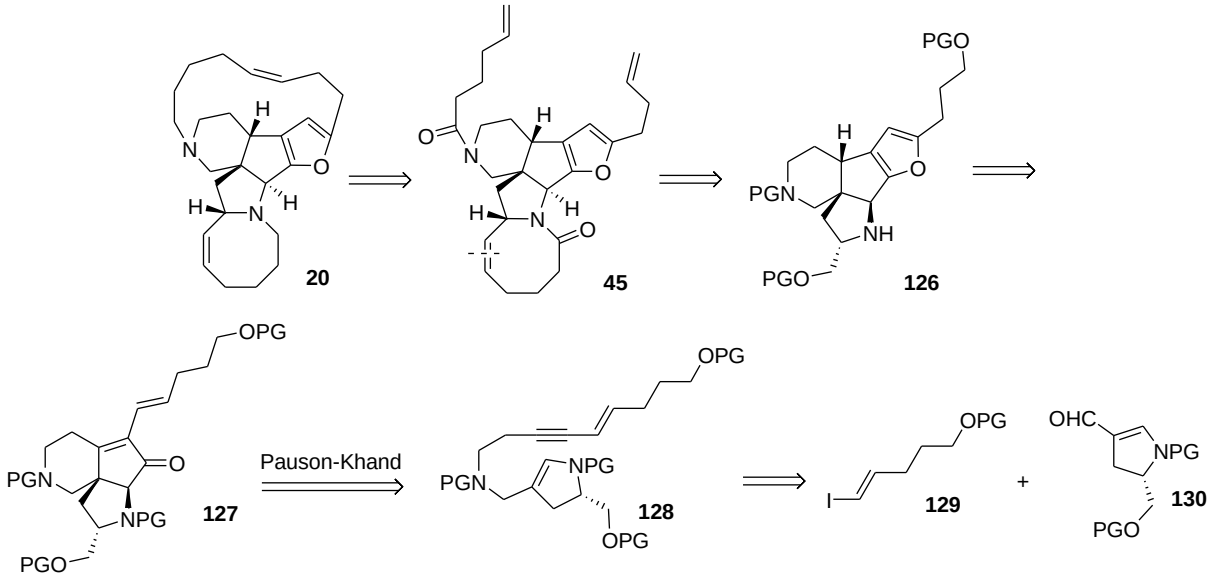


Figure 1.3: Hoveyda Schrock tungsten catalyst.

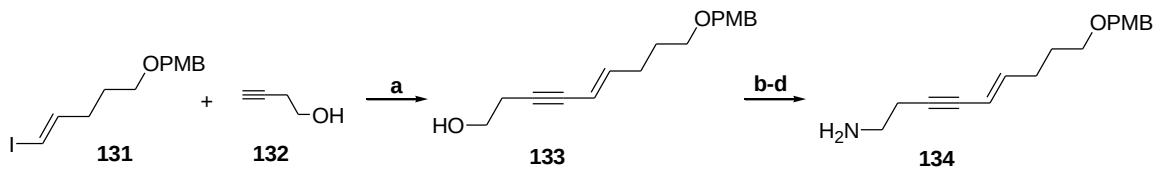
1.2.5 Mukai's formal synthesis of (+)-nakadomarin A (2010)

In 2010, the group of Mukai published the formal synthesis of (+)-nakadomarin A (**20**) using a strategy based on a Pauson-Khand reaction.[31] According to Mukai's reterosynthetic analysis, nakadomarin A would be prepared from **45**, as previously described by Nishida and Kerr (**Scheme 1.25**).[22,24] The triene **45** could be obtained from **126**, by *N*-acylation with the corresponding side chain, deprotection and RCM to form the E ring. The key synthetic intermediate, tetracyclic compound **126**, might be prepared from the tricyclic compound **127**, itself coming from a Pauson-Khand reaction of precursor the enyne **128**. Finally, **128** would be obtained from **129** and **130**.



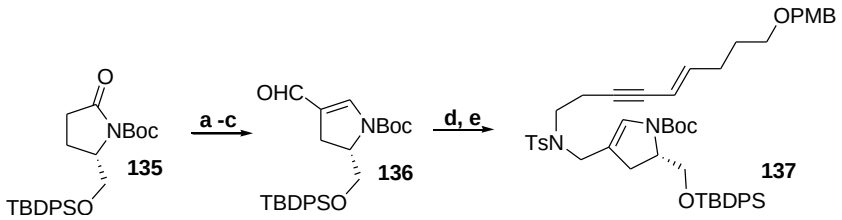
Scheme 1.25: Mukai's retrosynthetic analysis

The readily available vinyl iodide **131** was treated with 3-butyn-1-ol **132** to furnish the homopropargyl alcohol derivative **133** in 84% yield, through a Sonogashira coupling (**Scheme 1.26**).[61-62] This compound was subsequently converted to the primary amine **134** by treatment with sodium azide and reduction.



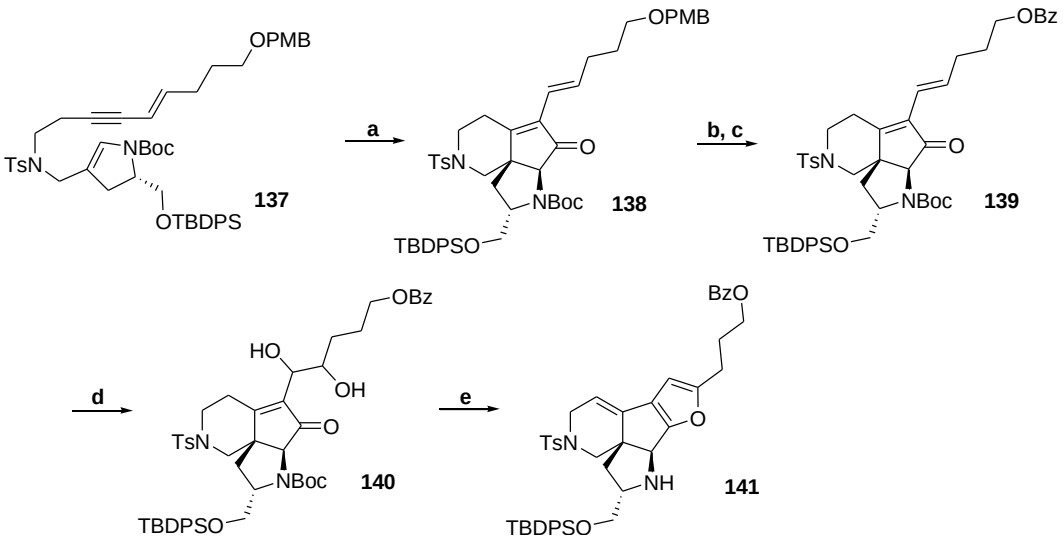
Scheme 1.26: Preparation of **134**. Conditions: a) $PdCl_2(PPh_3)_2$, CuI, *i*Pr_2NH, THF, 84%; b) MsCl, Et_3N, CH_2Cl_2; c) NaN_3, DMF; d) PPh_3, H_2O, Et_2O, 84% over 3 steps.

In addition to this, aldehyde **136** was prepared from the protected lactam **135** (derived from L-pyroglutamic acid),[63] in 3 steps and an with overall yield of 59% (**Scheme 1.27**). Subsequent reductive amination of **136** with the previously prepared amine **134**, followed by treatment with TsCl provided the enyne **137** in 69% yield.



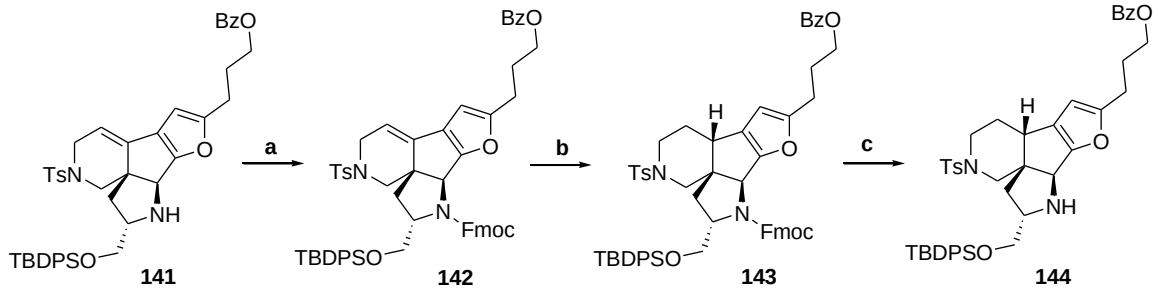
Scheme 1.27: Preparation of **137**. Conditions: a) LiHMDS, $ClCO_2Me$, THF; b) DIBAL-H, THF; c) CSA, toluene, 59% over 3 steps; d) **134**, $MgSO_4$, MeOH, then $NaBH_4$; e) TsCl, pyr., CH_2Cl_2, 69% over 2 steps.

The next step involved formation of the key tricyclic intermediate **138** *via* a Pauson-Khand reaction (**Scheme 1.28**). This was achieved in 60% yield by treatment of **137** with dicobalt octacarbonyl and *n*-butylmethyl sulfide, in a refluxing toluene/ether solution. In order to prepare the furan ring, exchange of the PMB group for a benzoyl group (molecule **139**) was followed by dihydroxylation to afford **140**. Subsequent ring closure, under acidic conditions, provided the desired tetracyclic compound **141**. The Boc protecting group was also cleaved under these conditions.



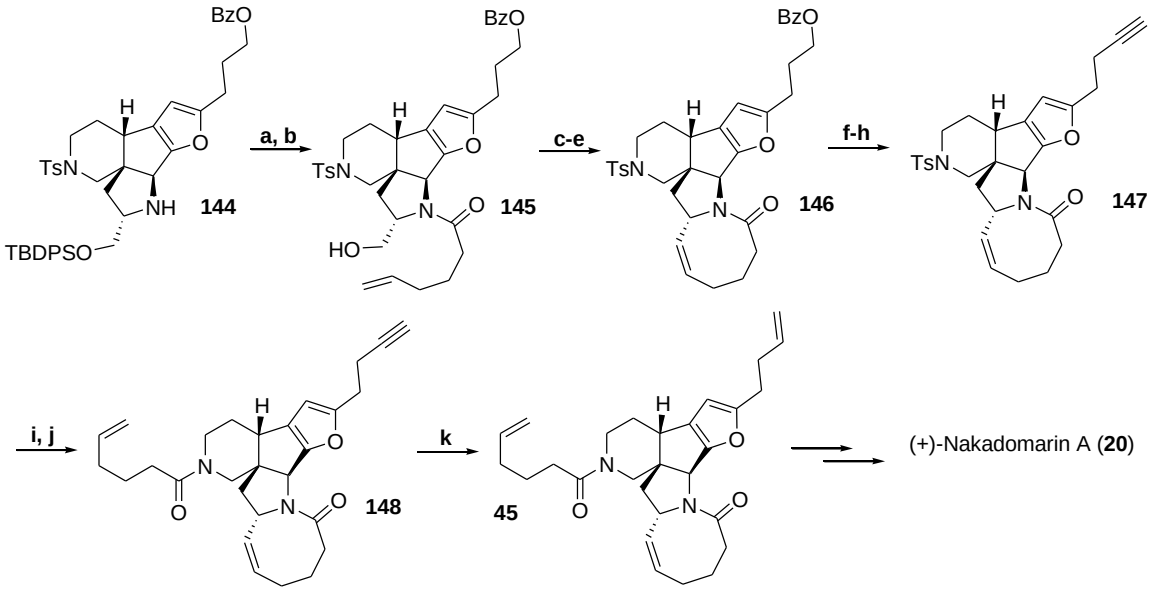
Scheme 1.28: Key Pauson-Khand reaction. Conditions: a) $Co_2(CO)_8$, Et_2O, toluene, *n*BuSMe, 100%; b) DDQ, CH_2Cl_2; c) BzCl, pyridine, CH_2Cl_2, 90% over 2 steps; d) OsO_4 aq, NMO, THF/H_2O; e) CSA, toluene, 80% over 2 steps.

In order to prepare the natural product, the double bond present in **141** required removal. Following Fmoc protection of the free amine, hydrogenation provided compound **143** as shown in **Scheme 1.29**. Finally, the Fmoc group was removed, to provide the desired tetracyclic amine **144**.



Scheme 1.29: Conditions: a) FmocCl, $NaHCO_3$, THF/H_2O, 90%; b) 20% Pd/C, H_2 (10 atm), EtOAc, 51%; c) piperidine, DMF, quant.

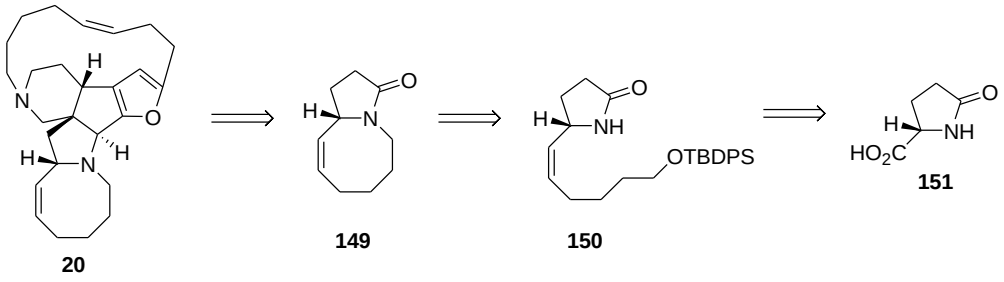
To prepare the southern 8-membered lactam, acylation of amine **144** was performed, followed by deprotection of the TBDPS group with TBAF afforded **145** in a 55% yield (**Scheme 1.30**). Subsequent Dess-Martin oxidation and Wittig olefination was followed by RCM using Grubbs 2nd generation catalyst to provide **146** in a 84% yield over 3 steps. Alkyne **147** was prepared from benzoate **148** in 73% yield *via* debenzoylation, oxidation and treatment with the Ohira-Bestmann reagent.[64] Removal of the tosyl group, followed by amide formation with 5-hexenoic acid provided **148**, in a 69% yield. Finally, hydrogenation of **148** with Lindlar's catalyst provided **45**.[65] This intermediate had been transformed to (+)-nakadomarin A by Nishida and Kerr.[22,24]



Scheme 1.30: Mukai's Endgame. Conditions: a) 5-hexenoyl chloride, Et_3N, CH_2Cl_2; b) TBAF, THF, 55% over 2 steps; c) DMP, CH_2Cl_2; d) *t*BuOK, $MePPh_3Br$, THF; e) Grubbs II, CH_2Cl_2, 84% over 3 steps; f) NaOH, MeOH; g) IBX, DMSO/THF; h) $PO(Me)_2CHN_2$, K_2CO_3, MeOH, 73% over 3 steps; i) Na/naphtalene, 1,2-ethandiol; j) 5-hexenoic acid, EDC, HOBt, THF, 69% over 2 steps; k) Lindlar's catalyst, quinoline, H_2, MeOH, 83%.

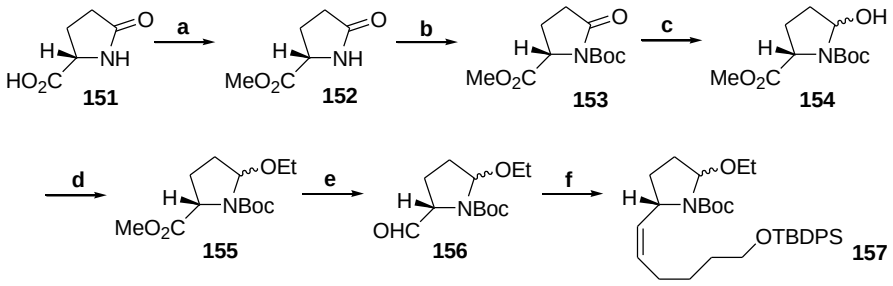
1.2.6 Magnus' strategy (2010): formal synthesis of ent-nakadomarin A

Magnus' 2010 approach towards nakadomarin A was a formal synthesis and involved synthesis of the *ent*-intermediate **149** in 49% yield form L-pyroglutamic acid **151** (**Scheme 1.31**).[32] In comparison to Dixon's approach towards the opposite enantiomer (29% of **108**), this was a much improved synthetic sequence in terms of overall yield.[25] In terms of the retrosynthetic analysis, Magnus proposed that **149** would be obtained from lactam **150**, which, in turn, would derive from L-pyroglutamic acid **151**.



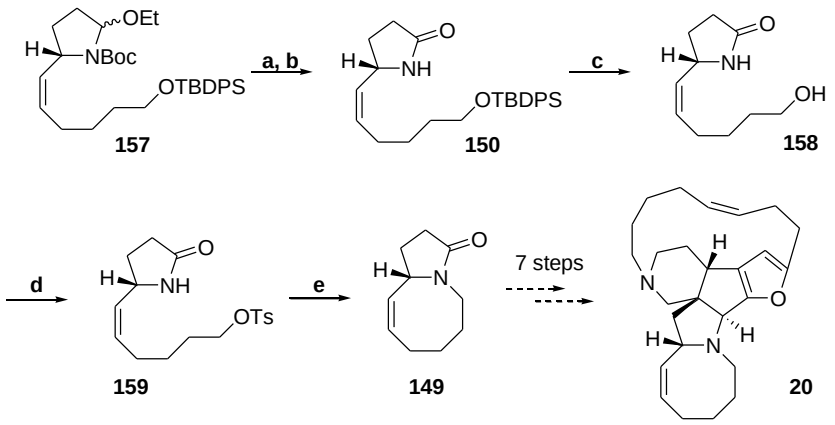
Scheme 1.31: Magnus' retrosynthetic analysis.

The synthetic sequence began with esterification of L-pyroglutamic acid **151**, followed by Boc protection of the free nitrogen to form **153** in 82% yield over 2 steps (**Scheme 1.32**). Subsequent reduction of the lactam functionality led to alcohol **154**. Treatment with ethanol, followed by reduction of the ester afforded the aldehyde **156**, which underwent a Wittig reaction to give the alkene **157** in an excellent 98% yield and with excellent stereoselectivity.



Scheme 1.32: Conditions : a) $SOCl_2$, MeOH, 92%; b) Boc_2O, DMAP, Et_3N, CH_2Cl_2, 89%; c) DIBAL-H, THF, toluene, 98%; d) EtOH, *p*TSA, 96%; e) DIBAL-H, toluene, 89%, f) $PPh_3CH(CH_2)_4OTBDPS$, KHMDS, toluene, 98%.

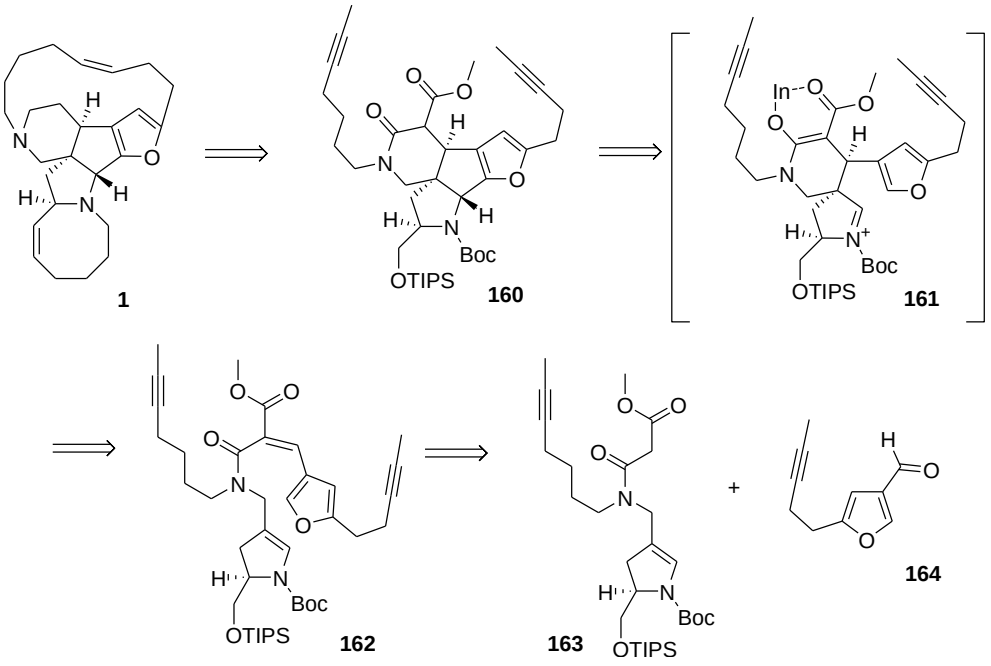
Subsequent Jones oxidation of **157** with chromium trioxide resulted in the formation of free lactam **150**, which, after TBDPS removal furnished compound **158** in an excellent yield over the two steps (**Scheme 1.33**). Conversion of the primary alcohol functionality of **158** into the tosylate **159** allowed the eight-membered ring-closure to the lactam **149** upon treatment with potassium *tert* butoxide in 98% yield. From **149**, only 7 steps are necessary, according to Dixon's synthesis, to prepare (−)-nakadomarin A.[25] Although Magnus only described an improvement in the synthesis of a fragment of nakadomarin A, his method would allow large amounts of non natural enantiomer to be prepared.



Scheme 1.33: Conditions : a) CrO_3, AcOH; b) TFA, CH_2Cl_2, 84% over 2 steps; c) HF, MeCN, 90%; d) TsCl, $Me_3N{\bullet}HCl$, Et_3N, CH_2Cl_2, 99%; e) *t*BuOH, THF, 98%.

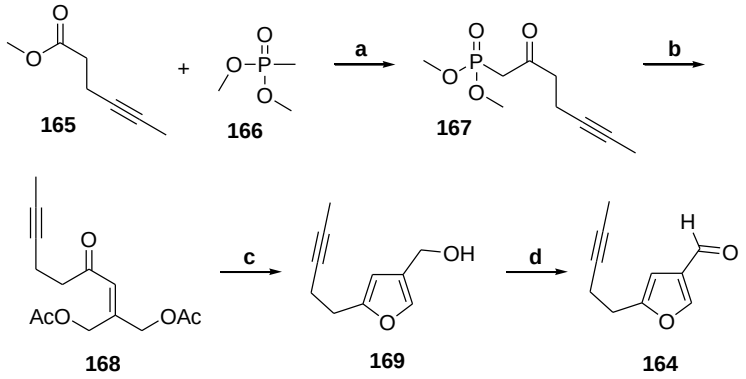
1.2.7 Funk's total synthesis (2010)

In 2010, Funk and co-workers published the synthesis of (−)-nakadomarin A, achieving in this regard the third total synthesis of the natural compound in 21 steps from D-pyroglutamic acid.[29] In his route, Funk employed previous methodology he had developed in 2006 involving the generation of an *N*-acyliminium ion *via* intramolecular conjugate addition.[66] His retrosynthetic analysis started with the disconnection of the macrocycles. He envisaged that a diene RCM reaction could provide the eight membered ring and a closure using diyne RCM/semihydrogenation strategy would be used to construct the *Z*-cycloalkene isomer (**Scheme 1.34**). Compound **160** is the product from the key cyclisation reaction previously described by Funk, where compound **162** is the starting precursor. In turn, **162** would be obtained as the product of a Knoevenagel condensation of furaldehyde **164** and amido-ester **163**.[67]



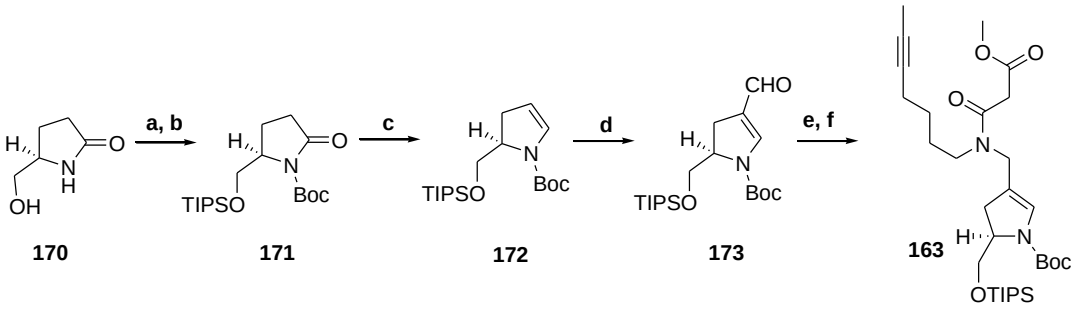
Scheme 1.34: Funk's retrosynthetic analysis.

The synthesis started with the preparation of the first fragment, furaldehyde **164**, which was prepared following Maldonado's methodology (**Scheme 1.35**).[68] Reaction between methyl 4-hexynoate **165** and dimethylphosphonate **166** provided **167** in 54% yield. Subsequent Horner-Wadsworth-Emmons olefination of diacetoxyacetone using phosphonate **167** afforded diacetoxyenone **168**. Acid-catalysed cyclisation of **168** formed furan **169**, which was in turn converted into the furaldehyde **164** using standard Swern oxidation conditions.



Scheme 1.35: Synthesis of furaldehyde **164**. Conditions: a) *n*BuLi, THF, 54%; b) NaH, 1,3-diacetoxyacetone, THF, 82%; c) HCl, MeOH, 82%; d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 75%

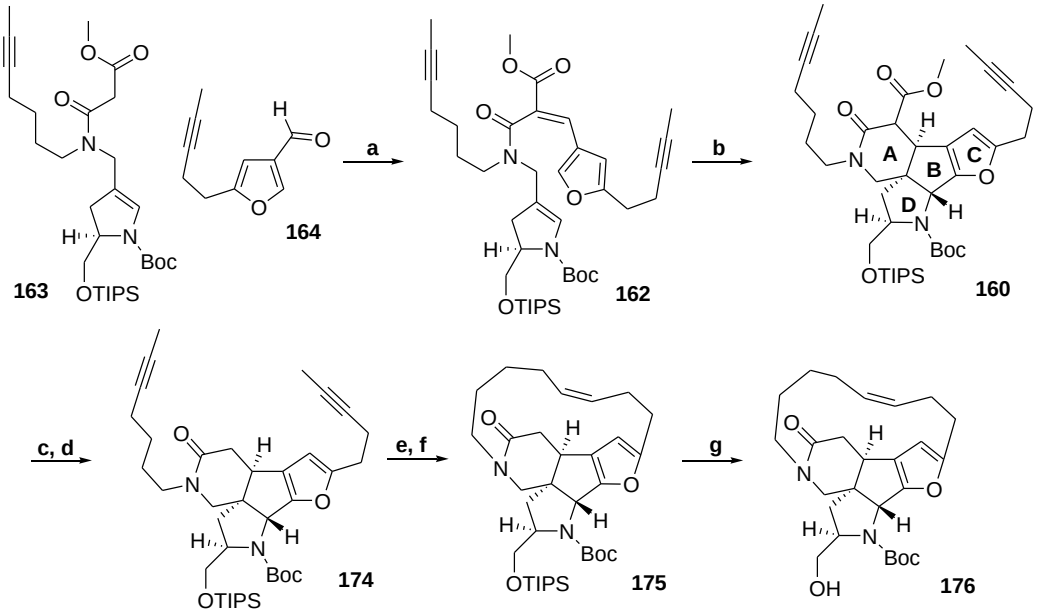
The second fragment, amido-ester **163**, was obtained in 8 steps from **170** (**Scheme 1.36**). The sequence started with the preparation of Boc-protected lactam **171** from D-pyroglutaminol **170**. Subsequent reduction of **171** following Yu's protocol, afforded to **172** in 88% yield.[69] Vilsmeier-Haack formylation of **172** provided **173**, from which reductive amination and *N*-acylation with methyl malonyl chloride afforded the desired 1,3-dicarbonyl compound **163**.[70]



170 **171** **172** **173** **163**

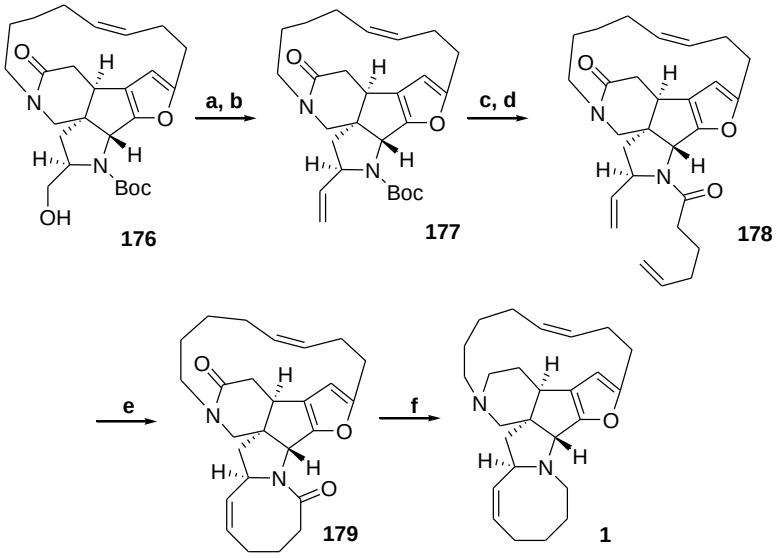
Scheme 1.36: Synthesis of fragment **163**. Conditions: a) imidazole, TIPSCl, CH_2Cl_2, DMF, 88%; b) Boc_2O, DMAP, MeCN, 90%; c) $LiBHEt_3$, *i*Pr_2NEt, DMAP, TFAA, toluene, 88%; d) DMF, $(COCl)_2$, CH_2Cl_2, 87%; e) $CHCC(CH_2)_4NH_2$, $NaBH_4$, MeOH; f) methyl malonyl chloride, Et_3N, CH_2Cl_2, 66% over 2 steps.

The sequence continued with the Knoevenagel condensation of aldehyde **164** and amido-ester **163** to provide **162**, with exclusively *E*-geometry, in 87% yield (**Scheme 1.37**).[71] Subsequent cyclisation of **162** to **160** using $InCl_3$ allowed the whole ABCD core of the molecule to be constructed in a single key step. Saponification and decarboxylation of **160** afforded lactam **174**. Diyne RCM, employing conditions developed by Fürstner, and alkyne reduction with Lindlar's catalyst provided **175**.[72] Subsequent TIPS deprotection led to the desired pentacyclic compound **176**. It is worth noting that Funk was the first chemist to successfully use the diyne RCM strategy, developed by Fürstner, to prepare nakadomarin A (see section 1.3.1).[33]



Scheme 1.37: Synthesis of pentacycle **176**. Conditions: a) $PhCO_2H$, piperidine, benzene, 87%; b) $InCl_3$, CH_2Cl_2, 79%; c) KOH, H_3O^+, MeOH; d) toluene, 80% over 2 steps; e) [(pyridine)$(Ph_3SiO)_3MoN$], toluene, 80%; f) H_2, Lindlar's cat., MeOH; g) TBAF, 80% over 2 steps.

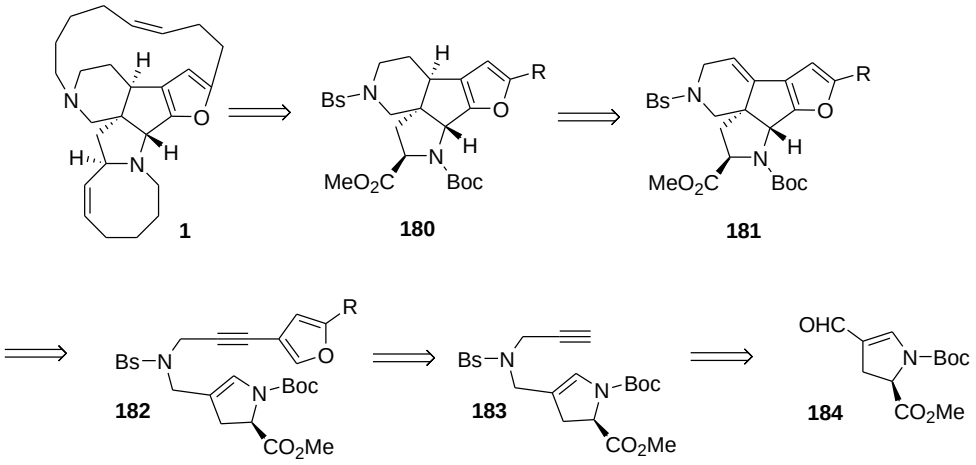
The synthesis concluded with the formation of the final E ring. Oxidation of the alcohol **176** with IBX was followed by Tebbe olefination to afford the alkene **177** (**Scheme 1.38**).[73] Subsequent removal of the Boc and *N*-acylation with 5-hexenoyl chloride provided **178**. Finally, RCM of **178** followed by reduction of the bis-lactam **179** afforded nakadomarin A (**1**).



Scheme 1.38: End game: a) IBX, DMSO; b) $Cp_2TiCH_2AlClMe_2$, THF, 68% over 2 steps; c) TFA, CH_2Cl_2; d) 5-hexenoyl chloride, Et_3N, benzene, 74% over 2 steps; e) Grubbs I, CH_2Cl_2; f) $AlCl_3$, $LiAlH_4$, THF, 58% over 2 steps.

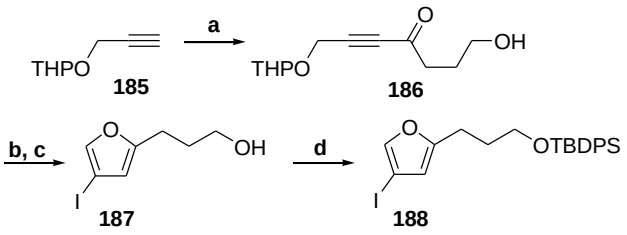
1.2.8 Zhai's total synthesis (2011)

In 2011, Zhai and co-workers accomplished the fourth total synthesis of natural nakadomarin A.[30] Zhai's retrosynthetic analysis started with the disconnection of both macrocycles, to provide the tetracyclic intermediate **180** (**Scheme 1.39**). This compound would come from the alkene **181**, the product of a Pt^{II}-promoted cascade reaction of the alkyne **182**.[74] Alkyne **182** would result from a Sonogashira coupling between **183** and the corresponding furan partner. Finally, **183** would be obtained from aldehyde **184**.



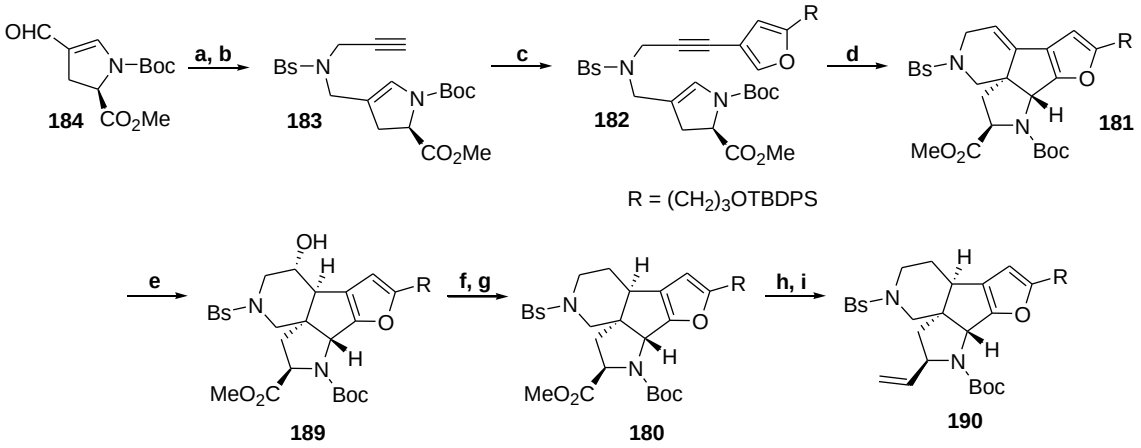
Scheme 1.39: Retrosynthetic analysis

The synthesis started with the preparation of the coupling partner for the Sonogashira coupling reaction, furan **188**, which was easily obtained in four steps (**Scheme 1.40**). The THP ether of propargyl alcohol (**185**) was deprotonated and treated with γ-butyrolactone to afford the ynone **186**. Subsequent iodination/cyclisation provided the alcohol **187**.[75] The desired furan (**188**) was finally obtained after TBDPS protection.



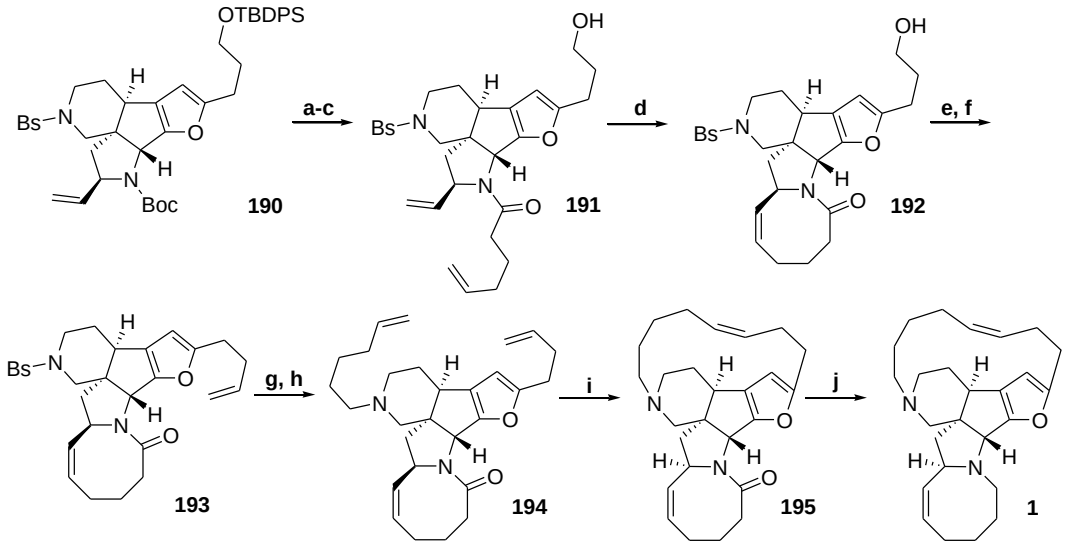
Scheme 1.40: Conditions: a) γ-butyrolactone, BuLi, $BF_3.Et_2O$, THF; b) HI, toluene; c) *p*TSA, MeOH, 53% over 3 steps; d) TBDPSCl, imidazole, CH_2Cl_2, 89%.

For the second fragment, readily available aldehyde **184** underwent reductive amination, followed by *N*-sulfonylation to provide the akyne **183** (**Scheme 1.41**).[69] A Sonogashira coupling with the previously prepared iodo furan **188** afforded **182**. Subsequent Pt^{II}-promoted cascade reaction, employing Dake's conditions, provided tetracyclic compound **181** in a regiospecific (6-*endo* vs. 5-*exo*) and stereospecific fashion.[76] This compound was then subjected to stereoselective hydroboration followed by oxidation to afford **189**. Subsequent Barton-McCombie deoxygenation, with prior xanthate ester formation, yielded **180**.[77] Finally, reduction of the ester within **180** to the aldehyde, followed by Wittig olefination afforded the alkene **190**.



Scheme 1.41: Conditions: a) propargylamine•HCl, Et_3N, *t*BuOH, $NaBH_4$, MeOH; b) BsCl, Et_3N, DCM, 54% over 2 steps; c) **188**, $[Pd(PPh_3)_2Cl_2]$, CuI, Et_3N, DMF, 87%; d) $PtCl_2$, MePh, 81%; e) BH_3•SMe_2, THF, H_2O_2, NaOH, 81%; f) NaH, CS_2, MeI, THF; g) Bu_3SnH, AIBN, toluene, 94% over 2 steps; h) DIBAL-H, DCM; i) CH_3PPh_3Br, *t*BuOK, THF, 74% over 2 steps.

Boc removal and *N*-acylation with 5-hexenoyl chloride of the resulting free amine was followed by removal of the TBDPS group, to provide **191** (**Scheme 1.42**). Subsequent RCM with Grubbs' second generation catalyst afforded pentacyclic compound **192**. Standard Swern oxidation and Wittig olefination led to compound **193**, from which the Bs group was removed and the resulting secondary amine was treated with 6-bromo-1-hexene to provide the triene **194**. Subsequent RCM and reduction of the lactam afforded the nakadomarin A (**1**) but only with a 2:1 ratio of *Z* and *E* isomers.



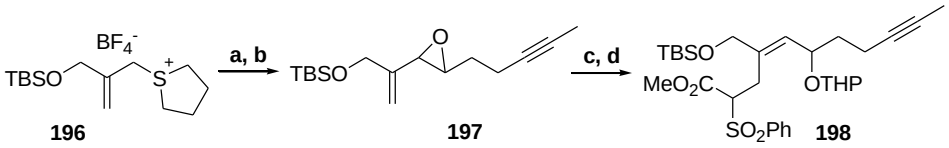
Scheme 1.42: Conditions: a) $ZnBr_2$, CH_2Cl_2; b) 5-hexenoyl chloride, Et_3N, DMAP, CH_2Cl_2; c) TBAF, THF, 70% over 3 steps; d) Grubbs II, CH_2Cl_2; e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, f) CH_3PPh_3Br, K_2CO_3, CH_2Cl_2, 70% over 3 steps; g) Na, naphthalene, THF; h) 6-bromo-1-hexene, K_2CO_3, EtOH, 91% over 2 steps; i) Grubbs I, CSA, CH_2Cl_2, *Z*/*E* 2:1, 65% (*E*+*Z*), 31% pure *Z*; j) Red-Al, toluene, 85%.

1.3 Other approaches towards nakadomarin A

Several other research groups have also been working toward the total synthesis of nakadomarin A and have developed the synthesis of various ring systems present within the target. The following paragraphs describe such approaches and highlight many elegant chemical transformations.

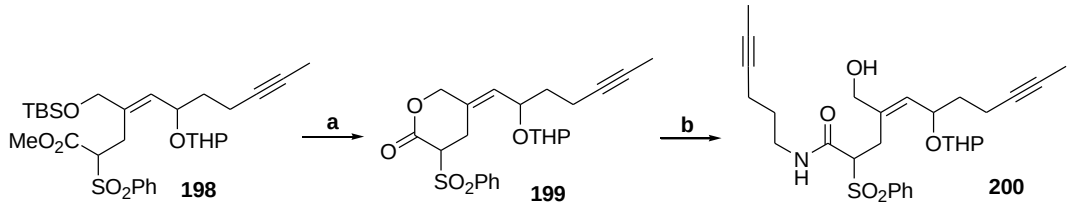
1.3.1 Fürstner strategies (1999 & 2001)

The first publication towards the synthesis of the main core of nakadomarin A was presented in 1999 by Fürstner and co-workers.[33] The Fürstner group developed an diyne RCM method, and tested it on the synthesis of the 15-membered ring of nakadomarin A. As previously described, this work was great inspiration to other groups working on the synthesis of this natural product. The synthesis of the model system started with the deprotonation of readily available **196**, followed by trapping of the resulting sulfur ylide with 4-hexynal to deliver vinylepoxide **197** (**Scheme 1.43**).[78] Subsequent treatment with methyl (phenylsulfonyl)acetate, in the presence of Pd(0), followed by THP protection of the hydroxyl group provided the alkyne **198**.



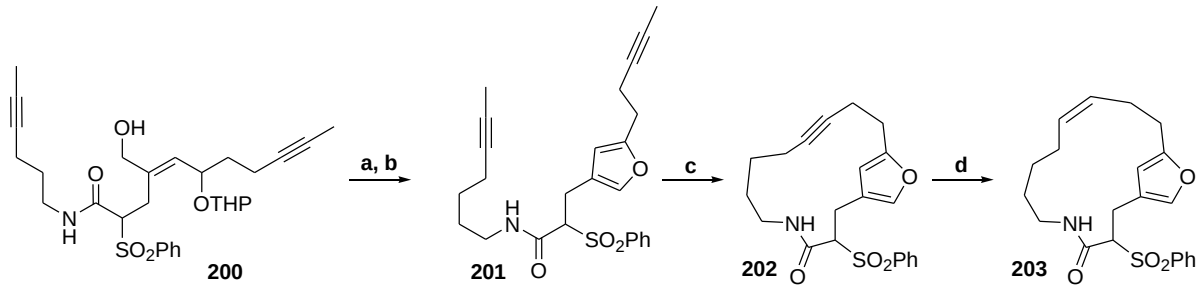
Scheme 1.43: Conditions: a) *t*BuLi, THF; b) $CH_3CCCH_2CH_2CHO$, THF, 70% over 2 steps; c) $PhSO_2CH_2COOMe$, $Pd(Ph_3)_4$, THF, 81%; d) DHP, PPTS, CH_2Cl_2, 89%.

The sequence continued with the TBAF removal of the TBS group which triggered spontaneous lactonisaton to afford **199** (**Scheme 1.44**). Treatment of this lactone with 1-amino-5-heptyne led to the formation of diyne **200**.



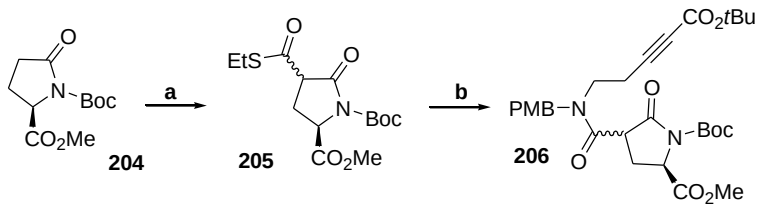
Scheme 1.44: Conditions: a) TBAF, NH_4F, THF, 81%; b) $CHCC(CH_2)_4NH_2$, NaCN, MeOH, 96%.

Oxidation of the primary alcohol **200**, followed by cleavage of the THP protecting group resulted in the formation of the 2,4-disubstituted furan **201** (**Scheme 1.45**). Subsequent treatment of diyne **201** with catalytic amounts of Schrock's tungsten alkylidyne complex resulted in the formation of the desired cycloalkyne **202** in 90% yield. Lindlar reduction of **202** provided (*Z*)-alkene **203** in 97% yield, which constituted the fully functionalised 15-membered ring of nakadomarin A.



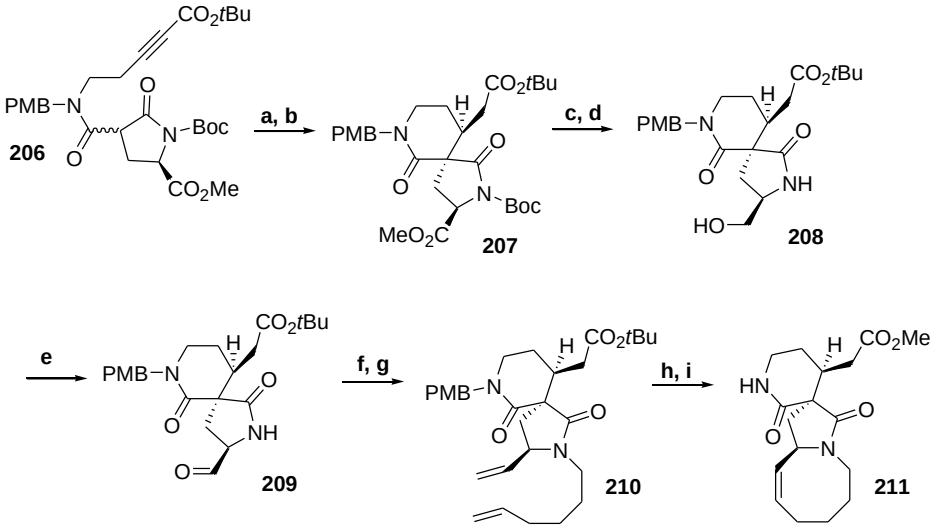
Scheme 1.45: Conditions: a) MnO_2, CH_2Cl_2; b) HCl, EtOAc, 96% over 2 steps; c) $(t\text{BuO})_3\text{WCCMe}_3$, PhCl, 90%; d) H_2, Lindlar's cat., quinoline, CH_2Cl_2, 97%.

In 2001, Fürstner and co-workers also reported the synthesis of a fully functionalised ADE ring system in which the quaternary centre was set with the correct absolute stereochemistry (**Scheme 1.46**).[34] Starting from (*R*)-(+)-pyroglutaminic ester **204**, conversion of this compound into the thioester **205** was followed by treatment with the corresponding amine to provide amide **206** in two steps and 70% yield.[79]

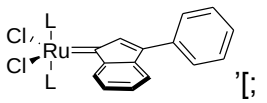


Scheme 1.46: Conditions: a) LiHMDS, THF, ClC(O)SEt, 96%; b) $\text{PMBNH(CH}_2)_2\text{CCCOO}t\text{Bu}$, AgOTf, $(i\text{Pr})_2\text{NEt}$, CH_3CN, 73%.

With **206** in hand, Fürstner performed an intramolecular Michael addition reaction. Subsequent hydrogenation provided spirocycle *bis*-lactam **207** in 80% yield as a single isomer (**Scheme 1.47**). Removal of the *N*-Boc group and selective reduction of the methyl ester delivered **208**. Oxidation of the resulting primary alcohol with Dess-Martin-periodinane afforded the required aldehyde **209**. Methylenation of this material followed by *N*-alkylation with 6-iodo-1-hexene provided the precursor **210** required for diene RCM. The phenylindenylidene complex **212** was employed as a pre-catalyst (**Figure 1.4**). The product was obtained in a nearly quantitative yield (98%). The final compound **211** was obtained by cleavage of the *t*butyl ester and conversion of the free acid to the methyl ester. This compound represents a fully functionalised ADE segment of nakadomarin A.



Scheme 1.47: Preparation of **220**. Conditions: a) $(i\text{Pr})_2\text{NEt}$, MeCN; b) H_2, Pd-C, MeOH, 80% over 2 steps; c) $Mg(ClO_4)_2$ MeCN, 99%; d) $LiBH_4$, THF, 82%; e) DMP, H_2O, CH_2Cl_2, 78%; f) CH_2I_2, $Ti(O i\text{Pr})_4$, Zn, THF, 84%; g) NaH, DMF, then 6-iodo-1-hexene, 88%; h) catalyst **212**, CH_2Cl_2, 98%; i) F_3CCOOH, then Me_3SiCHN_2, toluene, MeOH, 85%.

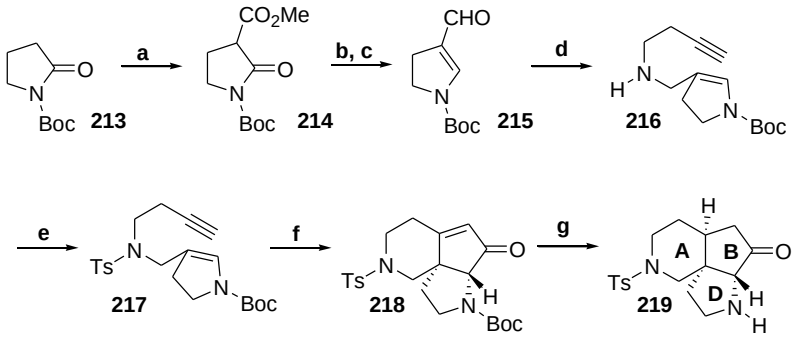


'[;

Figure 1.4: Complex **212**.

1.3.2 Magnus' original approach (2002)

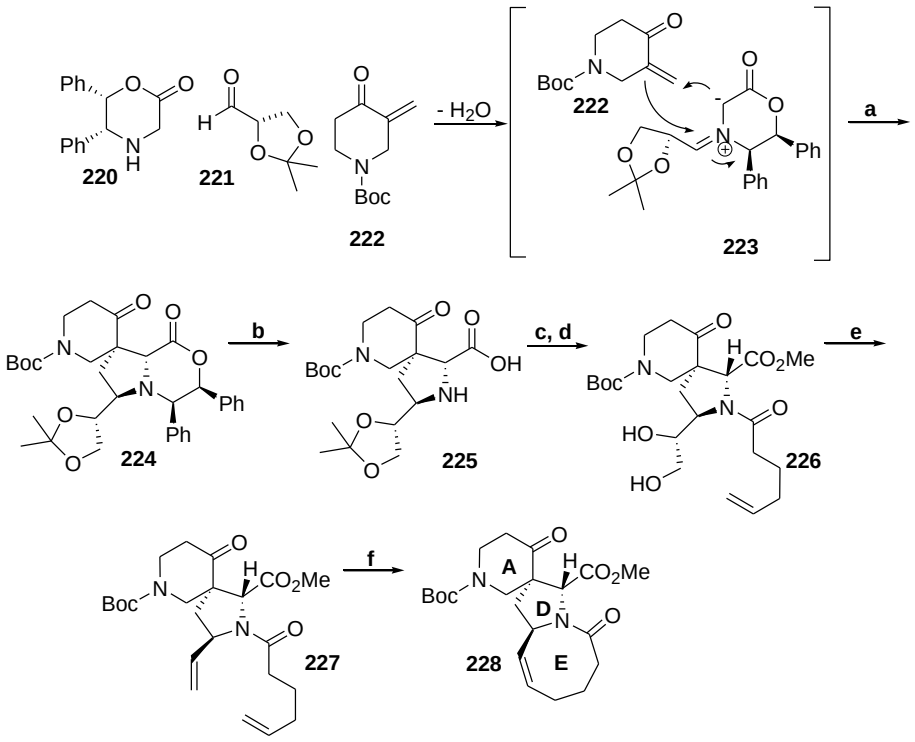
Before publishing the formal synthesis presented section 1.2.6, Magnus published a synthesis of the tricyclic ABD ring structure of nakadomarin A employing an intramolecular Pauson–Khand reaction as the key step.[80] The synthesis started with the treatment of lactam **213** with LiHMDS followed by treatment with methyl chloroformate (**Scheme 1.48**). Reduction of the resulting ester **214** with DIBAL-H followed by dehydration using quinolinium camphor sulfonic acid, provided **215** in 77% yield. Reductive amination of **215** with 1-amino-3-butyne afforded the alkyne **216** and was followed by protection of the free amine with TsCl to provide **217**, the precursor for the Pauson-Khand reaction. Enyne **217** was subsequently subjected to cobalt-mediated Pauson-Khand reaction conditions to afford **218** in 69% yield. Finally, hydrogenation of the double bond and removal of the Boc group provided the tricyclic ketone **219**, in 95% yield.



Scheme 1.48: Magnus' approach. Conditions: a) LiHMDS, THF, $ClCO_2Me$, 85%; b) *i*Bu_2AlH, THF, PhMe; c) quinolinium camphor sulfonic acid, 77% over 2 steps; d) $CC(CH_2)_2NH_3Cl$, Et_3N, MeOH, $NaBH_4$; e) TsCl, 75% over 2 steps; f) $Co_2(CO_8)$, *n*BuSMe, 1,2-DCE, 69%; g) H_2, Pd/C, 65%.

1.3.3 Williams' strategy (2004)

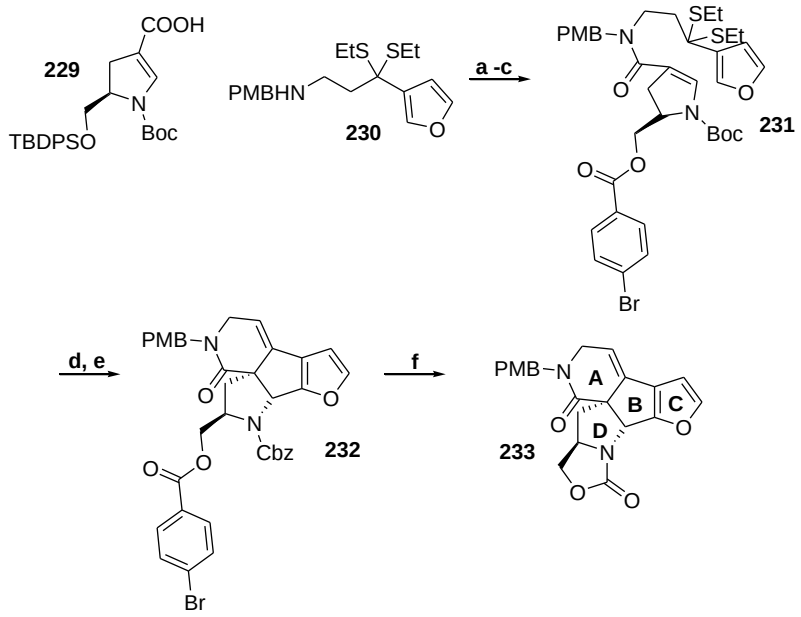
In 2004, Williams and co-workers reported an asymmetric synthesis of the ADE-ring system,[35] using an elegant azomethine ylide 1,3-dipolar cycloaddition reaction as the key step in the synthesis (**Scheme 1.49**). The key three component condensation of **220**, **221** and **222** allowed the formation of **224** as a single diastereomer in 35% yield. With compound **224** in hand, the removal of the chiral template was accomplished by hydrogenolysis using Pearlman's catalyst leading to **225** in 93% yield. The pyrrolidine was then *N*-acylated with 5-hexenoyl chloride in 75% yield. Treatment of the carboxylic acid with trimethylsilyl diazomethane followed by $SnCl_2$ yielded the diol **226** (80% yield over two steps), which was subsequently converted into the olefin **227.**[81] Ring-closing metathesis of **227** with Grubbs' second-generation catalyst afforded the ADE intermediate **228** in 65% yield. In this pathway, the asymmetric synthesis of the ADE fragment of nakadomarin A was accomplished in just nine steps from commercially available materials.



Scheme 1.49: Williams' approach. Conditions: a) **228**, **229**, **230**, toluene, 35%; b) H_2, $Pd(OH)_2/C$, MeOH, EtOAc, 92%; c) $CH_2CH(CH_2)_3COCl$, Et_3N, CH_2Cl_2, 75%; d) i) $TMSCHN_2$, MeOH ii) $SnCl_2$, CH_3NO_2/H_2O, 80%; e) PPh_3, imidazole, I_2, toluene, 60%; f) Grubbs II, CH_2Cl_2, 65%.

1.3.4 Winkler's approach (2010)

Finally, in 2010 Winkler published work towards nakadomarin A.[36] Reaction between the known acid **229** and amine **230**, followed by a deprotection/protection sequence provided benzoate **231** (**Scheme 1.50**).[82] Subsequent cyclisation using DMTSF and treatment with CbzCl to reprotect the amine functionality led to the lactam **232**. Finally, ester cleavage and cyclisation to give the cyclic urethane **233** was performed in 75% yield.



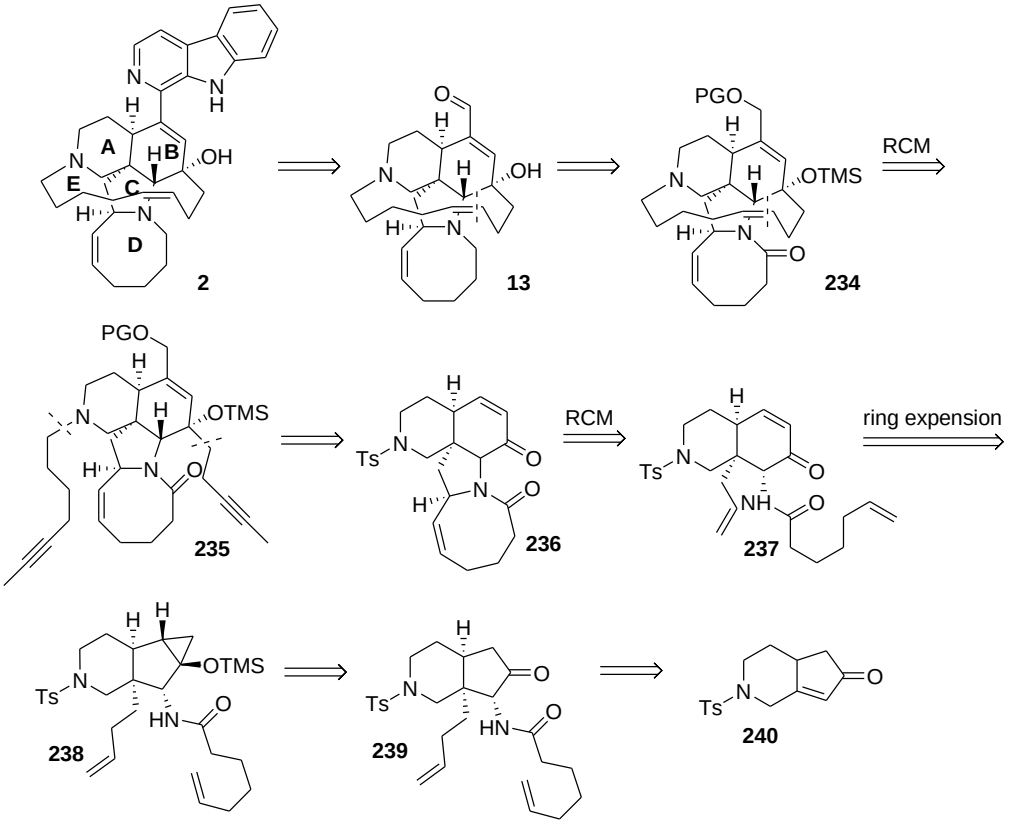
Scheme 1.50: Conditions: a) HATU, DIPEA, 83%; b) TBAF; c) *p*BrPhCOCl, Et_3N, DMAP, 89% over 2 steps; d) DMTSF, $MeNO_2$, 50%; e) CbzCl, DIPEA, DMAP, 62%; f) K_2CO_3, MeOH, 75%.

1.4 Contribution from the Clark group

As described in the preceding section, nakadomarin A (**1**) is a member of the manzanine family of marine alkaloids. The Clark research group has already targeted this class of compound and in particular manzamine A (**2**). The strategy is to develop a route for both the syntheses of manzamine A (**2**) and nakadomarin A (**1**). This section will present the relevant work achieved previously towards these targets.

1.4.1 Towards manzanine A

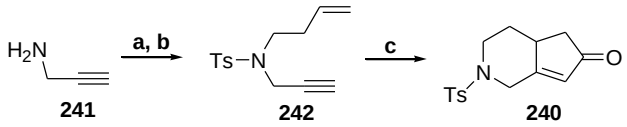
The strategy developed by the Clark group was based on a Pauson-Khand reaction and cuprate conjugate addition. The retrosynthetic analysis of mazanamine A (**2**) is depicted **Scheme 1.51**. Ircinal A **13** can be converted to manzamine A (**2**) in a two-step process, according to Kobayashi and co-workers.[14] Indeed, intermediate **13** could be derived from **234** by deprotection, oxidation of the aldehyde functionality and reduction of the lactam functionality. Retrosynthetic ring-closing diyne metathesis reveals **235**. Removal of the alkyne side chains along with the hydroxyl side chain provides **236**. The lactam **236** could be prepared by formation of the N-C bond and RCM of the bis-alkene. **237** would be formed by ring expansion of **238**. Finally, **238** would be obtained from cuprate addition to the Pauson-Khand product **240**.



Scheme 1.51: Clark's strategy towards manzamine A.

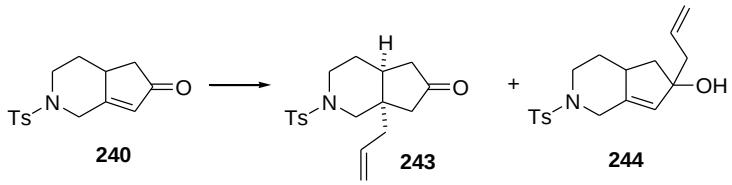
1.4.2 Development of the key steps

This approach started from commercially available propargylamine **241** (**Scheme 1.52**). Treatment of **241** with tosyl chloride followed by alkylation using 4-bromo-1-butene provided **242** in 95% yield over 2 steps. Subsequent Pauson-Khand reaction, using a catalytic amount of dicobalt octacarbonyl and under a carbon monoxide atmosphere, afforded the desired bicyclic enone **240** in high yield.[83]



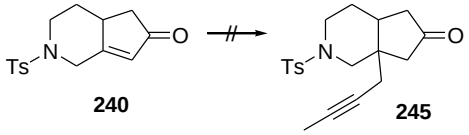
Scheme 1.52: Condition : a) TsCl, pyr., THF, 100%; b) 4-bromo-1-butene, K_2CO_3, acetone, 95%; c) $Co_2(CO)_8$, TMTU, toluene, CO, 70 °C, 6 h, 87%.

The next step in this synthesis was the introduction of the side chain between the A and B ring *via* a cuprate addition (**Scheme 1.53**). Extensive screening of conditions was performed, and variations in copper source, temperatures, and solvents were explored.[84] After solving problems such as the competitive 1,2-addition reaction, improved conditions were identified, which provided the desired 1,4-product **243** in a modest 37% yield.



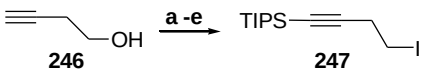
Scheme 1.53: Optimised conditions of the cuprate addition. Conditions: AllylMgBr, CuI, THF, 40%, 5.8:1 ratio of **243:244**.

In an attempt to obtain a more suitable substrate for the following synthetic steps, an alternative side chain was tested. However, employing 1-bromo-2-butyne failed to deliver the desired alkyne **245** (**Scheme 1.54**). Indeed, the formation of the Grignard reagent was not as straightforward as expected, thus, the 1,4 addition product was not observed.[85]



Scheme 1.54: Towards **245**. Conditions: 1-bromo-2-butyne, Mg, CuI, THF, 0%.

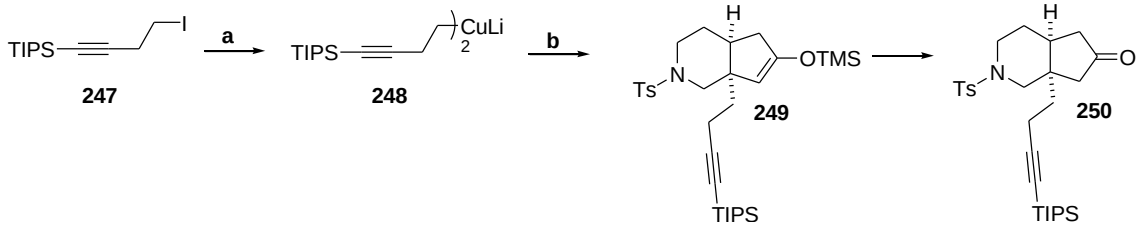
Instead of the unstable 2-butynylmagnesium bromide, the enyne side-chain was introduced using 1-iodo-4-(triisopropylsilyl)-3-butyne **247** (**Scheme 1.55**).[86] The desired alkyne species **247** was prepared from alcohol **246** in five steps and an excellent overall yield.



246 **247**

Scheme 1.55: Formation of the side chain. Conditions: a) TMSCl, Et_3N, CH_2Cl_2, 85%; b) *n*BuLi, Et_2O, TIPSOTf, used crude; c) AcOH, THF, H_2O, 82% over 2 steps; d) MsCl, Et_3N, CH_2Cl_2; e) NaI, acetone, reflux, 90% over 2 steps.

Alkyne **247** was submitted to a lithium-halogen exchange with *t*BuLi, and treatment with copper iodide resulted in the formation of dialkyl cuprate **248** (**Scheme 1.56**). Enone **240** was added in the presence of TMSCl and DMS which resulted in the formation of the desired enol ether **249**. Due to the sensitivity of this intermediate, it was used immediately without full characterisation. However, the corresponding ketone **250**, obtained after treatment of the crude enol ether **249** with acid, was fully characterised to confirm its structure. The expected *cis* configuration of the side chain was confirmed by X-ray studies of **250**.

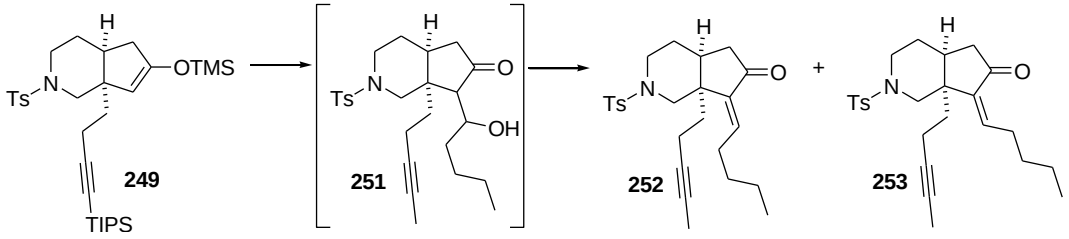


247 **248** **249** **250**

Scheme 1.56: Cuprate addition. Conditions: a) *t*BuLi, DMS, CuI, Et_2O, THF, −78 °C to 0 °C, 45 min, used directly; b) **240**, TMSCl, THF, 0 °C, 2 h, used crude or 79% of **250**.

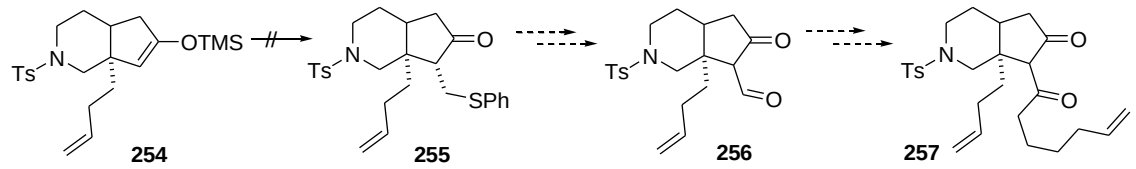
1.4.3 Attempted formation of the C ring

Studies directed towards the introduction of the second side chain using a Mukaiyama aldol condensation were explored with moderate success (**Scheme 1.57**). Treatment of silyl enol ether **249** with $TiCl_4$ and valeraldehyde did not provide the alcohol **251** as expected. Instead, alkenes **252** and **253** were obtained, resulting from the dehydration of the alcohol **251**. Despite extensive efforts to avoid this outcome, the desired product was never obtained.



Scheme 1.57: Towards **251**. Conditions: $TiCl_4$, CH_2Cl_2 then $(CH_2)_4CHO$, 1:1 of **252:253**, 15%.

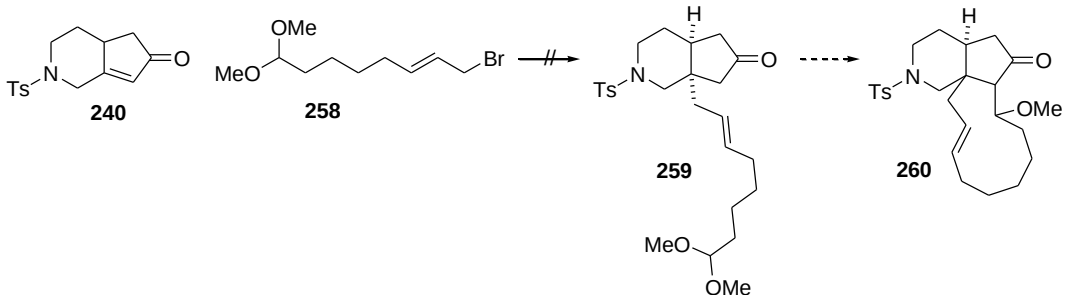
To avoid the dehydration problem encountered during Mukaiyama aldol condensation, a route involving the alkylation of the TMS enol ether **254** with chloromethyl phenyl sulfide to form **255** was investigated (**Scheme 1.58**). Aldehyde **256** could then be obtained through oxidation and Pummerer rearrangement, and would be converted to the desired diene **257**.[87] Unfortunately, attempts to alkylate **254** did not deliver the desired product.



Scheme 1.58: Towards **257**. Conditions: $PhSCH_2Cl$, $TiCl_4$, CH_2Cl_2, 0%.

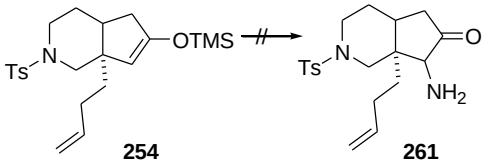
Alternatively, a pathway involving the intramolecular Mukaiyama aldol condensation was investigated. Starting from **240** and **258**, a 1,4-conjugated addition followed by an intramolecular Mukaiyama aldol condensation would have ultimately led to tricyclic compound **260** (**Scheme 1.59**). Unfortunately, the precursor for the condensation reaction, ketone **259**, was not obtained. Indeed, cuprate addition of allylic bromide **258** to enone

240 only resulted in an undesired 1,2-addition reaction. Introduction of various side chains was attempted but the desired compound could not be obtained.



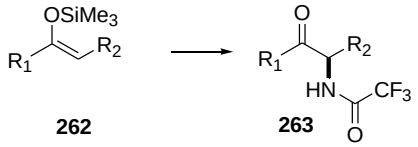
Scheme 1.59: Intramolecular Mukaiyama aldol condensation. Conditions: *t*BuLi, CuI, DMS, TMSCl.

In an additional attempt to form the C ring of manzamine A, electrophilic aminations were explored. An example is depicted in **Scheme 1.60** with the unsuccessful use of hydroxylamine-*O*-sulfonic acid.

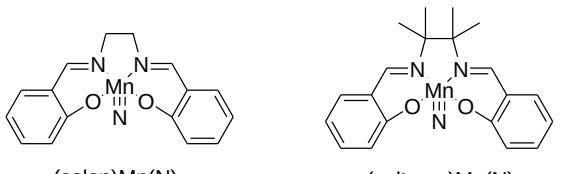


Scheme 1.60: Amination attempt. Conditions: hydroxylamine-*O*-sulfonic acid, $TiCl_4$.

In an alternative route, the Clark group also investigated Carreira's methodology towards the direct introduction of *N*-trifluoroacetyl group using a manganese complex, such as (salen)Mn(N) **262** or (saltmen)Mn(N) **263** (**Scheme 1.61** and **Figure 1.5**).[88] The employment of such nitromanganese (V) complexes can result in nitrogen transfer when activated with trifluoroacetic anhydride, allowing direct introduction of a *N*-trifluoroacetyl group.



Scheme 1.61: Carreira's strategy. Conditions: **264** or **265**, $(CF_3CO)_2O$, pyr., CH_2Cl_2.

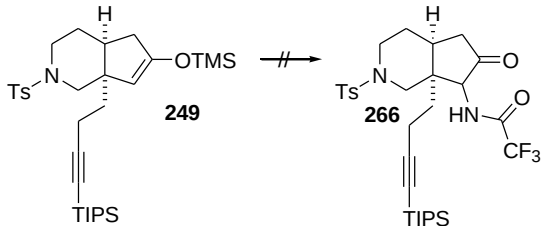


(salen)Mn(N)
264

(saltmen)Mn(N)
265

Figure 1.5: Manganese complexes.

Both (salen)Mn(N) **264** and (saltmen)Mn(N) **265** complex were prepared, following reported precedent.[88] Unfortunately, when employing these complexes on the TMS enol ether **249**, the reactions failed to deliver the desired product **266** (**Scheme 1.62**).



Scheme 1.62: Conditions: **264** or **265**, $(CF_3CO)_2O$, pyr., CH_2Cl_2, 0%

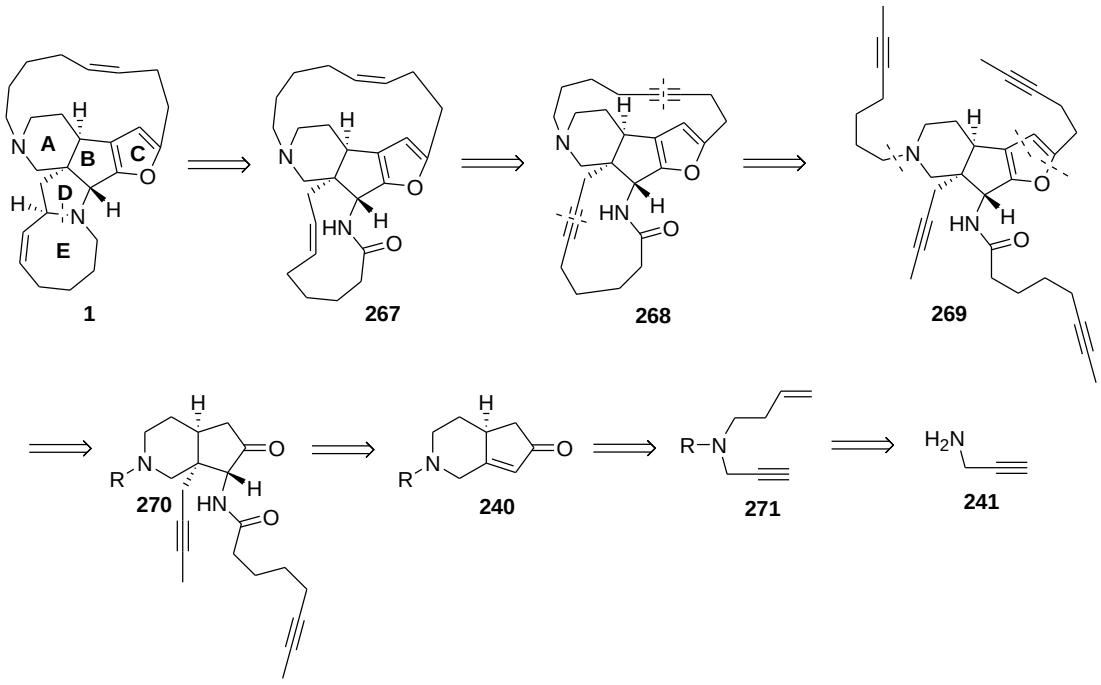
Although the success towards the synthesis of the manzamine family of natural products was modest, numerous strategies have been eliminated.

Chapter 2: Results and discussion

This chapter will focus on the approaches elaborated by the Clark group towards the synthesis of nakadomarin A. The chapter is divided into two main sections starting with the proposed retrosynthetic analysis followed by presentation of the synthetic progress.

2.1 Retrosynthetic analysis

As presented in an earlier section, the retrosynthetic approach taken by the Clark group towards nakadomarin A initially involved disconnection of the trisubstituted amine (ring D) leading to amide **267** (**Scheme 2.1**). This molecule could be accessed from the corresponding bisalkyne **268**, which itself could be formed by a double alkyne ring-closing metathesis reaction of **269**. Removal of the side chain on the trisubstituted nitrogen of the piperidine ring followed by disconnection of the furan ring leads to the bicyclic ketone **270**. Removal of the side chains, on both A and B rings, gives the simplied bicyclic enone **240**. This enone could then be obtained by the Pauson-Khand reaction of **271**, prepared from commercially available propargylamine **241**.

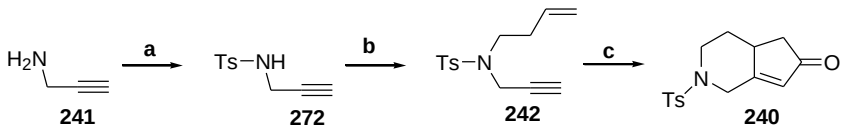


Scheme 2.1: Retrosynthetic analysis of nakadomarin A.

2.2 Results and discussion

*2.2.1 Towards the preparation of enone **240***

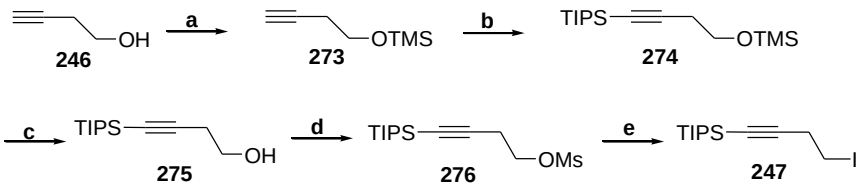
As depicted in section 1.4, the synthesis of nakadomarin A starts with the preparation of the enyne precursor **242** for the Pauson-Khand reaction (**Scheme 2.2**). Commercially available propargylamine **241** was treated with tosyl chloride under basic conditions to afford tosylated derivative **272** in 88% yield. Following this, treatment with 4-bromo-1-butene delivered the required enyne precursor **242** in excellent yield.[89] The bicyclic enone **240** was then prepared by a Pauson-Khand reaction in 71% yield, using a catalytic amount of dicobalt octacarbonyl and tetramethyl thiourea under a carbon monoxide atmosphere.[83]



Scheme 2.2: Formation of enone **240**. Condition: a) TsCl, THF, pyr, 0 ºC to rt, 16 h, 88%; b) 4-bromo-1-butene, K_2CO_3, acetone, reflux, 17 h, 91%; c) $Co_2(CO)_8$, TMTU, toluene, CO, 70 °C, 6 h, 71%.

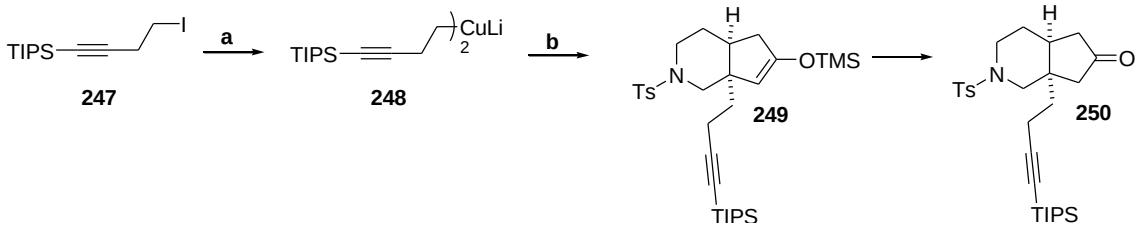
2.2.2 Synthesis of the side chain

With the synthesis of the AB core of nakadomarin A established, attention focused on preparation of the side chain required for the impending conjugate addition reaction. Following a literature protocol, this side chain was prepared from alcohol **246** (**Scheme 2.3**).[86] TMS protection of the hydroxyl group was followed by TIPS protection of the alkyne to provide **274**. Susequent deprotection of the hydroxyl group, mesylation and displacement with iodine provided the desired alkyne species **247** in an excellent overall yield.



Scheme 2.3: Preparation of the side chain. Conditions: a) TMSCl, Et_3N, CH_2Cl_2, 0 °C to rt, 15 h, 73%; b) *n*BuLi, Et_2O, TIPSOTf, −40 °C to rt, 16 h, used crude; c) AcOH, THF, H_2O, rt, 24 h, 85% over 2 steps; d) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 17 h, 98%; e) NaI, acetone, reflux, 24 h, 93%.

With the desired side chain in hand, conjugate addition, *via* the corresponding cuprate derivative, was attempted (**Scheme 2.4**). The 1,4 addition of **248** to enone **240** took place under anhydrous conditions and the resulting enolate was trapped using TMSCl to afford silyl enol ether **249**.[90] Due to the sensitivity of this intermediate, it was used immediately without full characterisation, although a characteristic peak at 4.5 ppm was observed in the crude ^{1}H NMR spectrum, corresponding to the enol ether hydrogen. Moreover, the corresponding ketone **250**, obtained after treatment of the crude enol ether **249** with acid, was fully characterised to confirm its structure. The relative configuration was established by comparison with previously acquired data.[84]

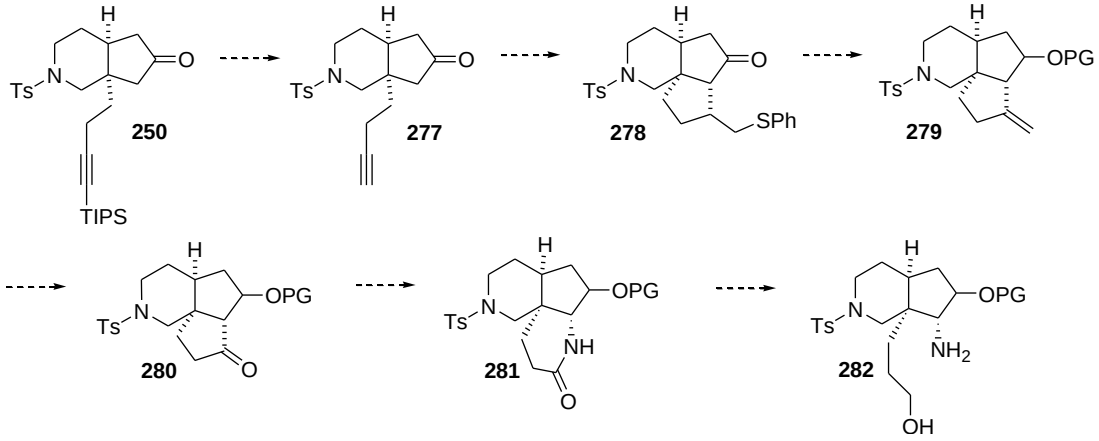


Scheme 2.4: Cuprate addition. Conditions: a) *t*BuLi, DMS, CuI, Et_2O, THF, −78 °C to 0 °C, 45 min, used directly; b) **240**, TMSCl, THF, 0 °C, 2 h, used crude or 96% of **250**.

With the required alkyne chain in place, the next step involved the introduction of a nitrogen-containing group α to the ketone moiety. Several studies to explore this functionalisation have been undertaken within the group, with moderate success.[84] The next section describes new strategies employed to install this requisite nitrogen atom.

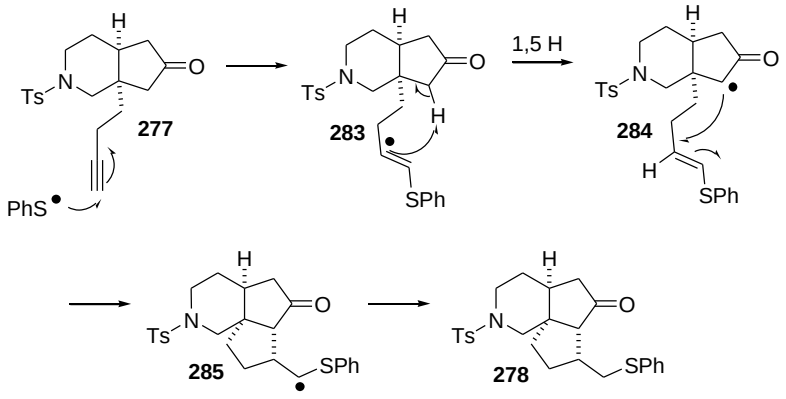
2.2.3 Radical cyclisation

The initial strategy involved the deprotection of alkyne **250**, followed by treatment with thiophenol and AIBN, to form the tricyclic ketone **278** (**Scheme 2.5**).[91] Elimination of phenyl sulfide followed by reduction and protection of the ketone functionality would provide compound **279**. Ozonolysis of the alkene would provide **280**, which is the precursor for a Beckmann rearrangement to afford lactam **281**. Further manipulation would then form the amino alcohol **282**, with the desired functionality in place.



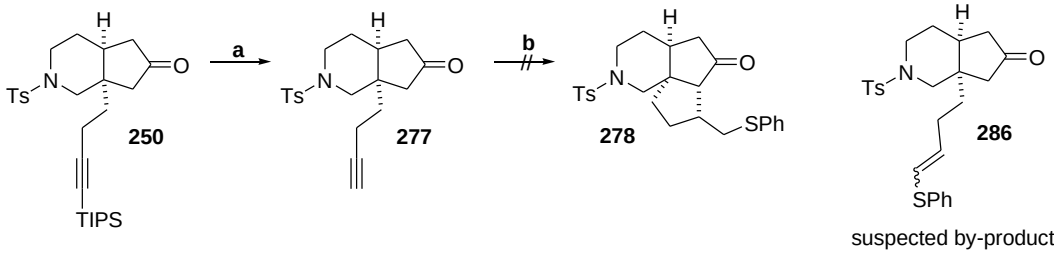
Scheme 2.5: Radical strategy.

The mechanism of the key cyclisation is depicted **Scheme 2.6**.[92] The addition of radical species PhS• to the alkyne **277** is followed by a 1,5-hydrogen transfer to deliver compound **284**. Subsequent *5-exo-trig* radical cyclisation would lead to the formation of the tricyclic system **285**. The radical formed will then be quenched to reveal the desired the tricyclic ketone **278**. The formation of the *cis* product would be expected because the newly formed 5-membered ring should be favoured compared to the *trans* fused product for ring-strain reasons.



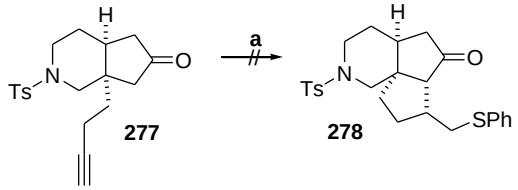
Scheme 2.6: Anticipated mechanism of the radical cyclisation.

The sequence commenced with removal of the TIPS group to afford bicyclic ketone **277** in 84% yield (**Scheme 2.7**). However, subsequent attempts to perform at the radical cyclisation reaction using this species proved unsuccessful and resulted in the formation of an undesired product.[91] Although the by-product formed under these conditions was not fully characterised, analysis of the ^{1}H NMR spectrum suggested that addition of thiophenol to the alkyne functionality (compound **286**), without continuing the radical cyclisation pathway, had occured.



Scheme 2.7: Attempts to perform the radical reaction. Conditions: a) TBAF, THF, −78 ºC to rt, 17 h, 84%; b) AIBN, PhSH, toluene, 70 ºC, 16 h, 0% (formation of a by-product).

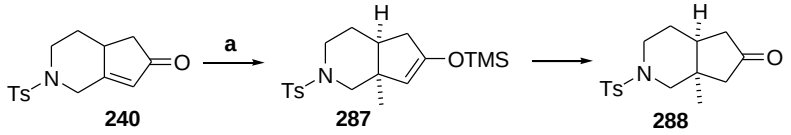
In addition to the above, alternative conditions, described by Beaufils *et al.*, were applied (**Scheme 2.8**).[93] Unfortunately this reaction was also unsuccessful and the starting material decomposed, and so an alternative approach was explored.



Scheme 2.8: Conditions: AIBN, PhSH, *t*BuOH, benzene, reflux, (decomposition of SM).

2.2.4 Alternative route

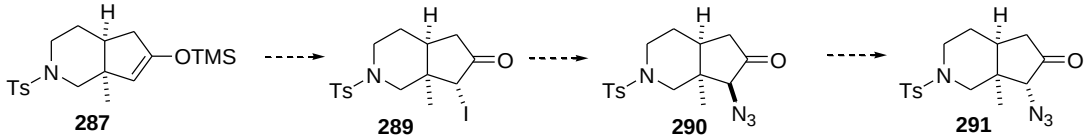
At this point, the synthesis of the desired α-amino ketone was explored using a simpler model substrate in order to test and optimise future steps. More specifically, a methyl cuprate addition was performed on enone **240** (**Scheme 2.9**). This reaction showed greater reproducibility and was more competitive in terms of cost, due to the commercial availability of the Grignard reagent. As encountered in the case of the initial target, the enol ether intermediate **287** could not be fully characterised due to its poor stability, and was directly used in the following reactions without purification. As before, the crude ^{1}H NMR spectrum showed the presence of the characteristic enol ether signal. Also, after an acidic treatment, the corresponding ketone **288** was isolated and fully characterised to confirm its structure.



Scheme 2.9: Model system. Conditions: MeMgBr, CuI, TMSCl, Et_2O, rt, 1 h, used crude or 96% yield of the corresponding ketone **288** after an acidic work up.

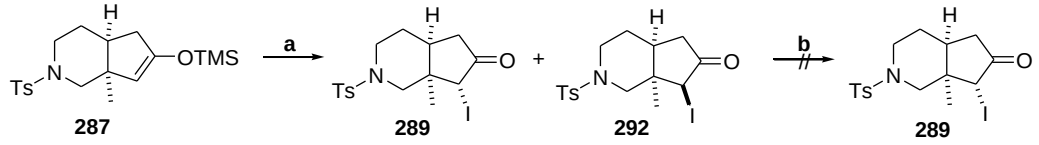
2.2.5 Introduction of an iodide

Given the difficulties encountered when attempting direct formation of a third ring, an alternative route was considered. Introduction of an iodide, using *N*-iodosuccinimide (NIS) would form the iodo ketone **289** and would be followed by displacement with sodium azide to install the nitrogen atom in a more direct fashion (**Scheme 2.10**). In terms of the configuration at the carbon centre bearing the iodine, it is anticipated that a *syn* relationship with the methyl group will be set up due to steric interactions. Subsequent displacement with sodium azide will therefore result in an inversion of configuration at this centre and undesired compound **290** would result. An epimerisation, under basic conditions, would be required to form **291**, if the molecule does not rearrange to give the *cis* configuration.



Scheme 2.10: Introduction of the iodide and displacement with NaN_3.

The reaction between enol ether **287** and NIS resulted in an inseparable 1:6 mixture of the two isomers **289** and **292** (**Scheme 2.11**). Unfortunately, the iodides were too unstable to be characterised fully and were used crude to the next reaction. The mixture of **289** and **292** was submitted to an epimerisation under basic conditions, in the hope of forming a single isomer, but this set of conditions only resulted in the decomposition of the starting material.

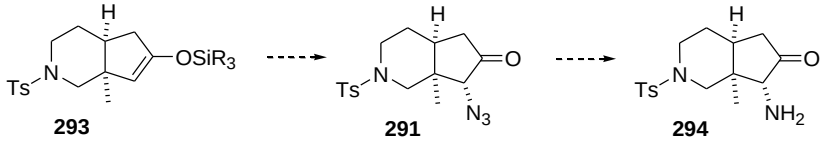


Scheme 2.11: Introduction of the iodide. Conditions: a) NIS, THF, −78 °C, 1 h, 20%, used crude; b) NaOH, H_2O, pyr., rt, 10 min (decomposition of the SM).

Moreover, the treatment of similar iodide substrates with sodium azide or various other amines, has been carried out within the group with little success.[84] It is speculated the S_N2 displacement of iodide with an amine would have to occur from the more sterically hindered top face of the ring, and as a result, the desired product would not have been obtained in any case. Following these negative results, this strategy was abandoned.

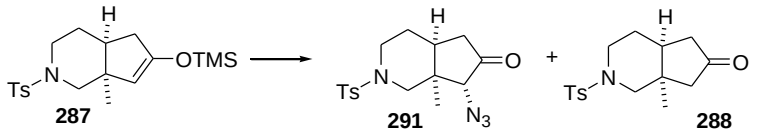
2.2.6 Reaction between sodium azide and the enol ether

Despite the lack of success with the approaches so far, another strategy was pursued. Indeed, the direct reaction between an enol ether and sodium azide in the presence of CAN is known to form the resulting α-azido ketone.[94-97] Applying this to our target, we envisaged the preparation of compound **291**, followed by a reduction to afford the desired amine **294** (**Scheme 2.12**).



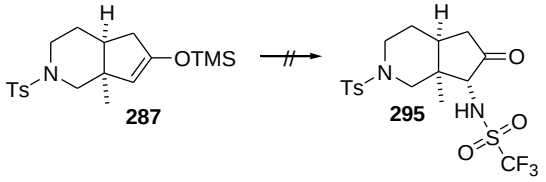
Scheme 2.12: Introduction of the azide and subsequent reduction.

Unfortunately, when applied to our substrate, the formation of α-azido ketone **291** proved to be difficult (**Scheme 2.13**). In fact, the best result obtained was the formation of an inseparable 6:1 mixture of both ketone **288** (the product of the hydrolysis of the silyl enol ether) and α-azido ketone **291**.



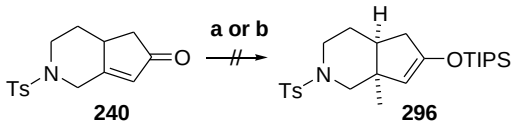
Scheme 2.13: Treatment of **287** with NaN_3 and CAN. Conditions: NaN_3, CAN, MeCN, −20 °C, 1h, 6:1 mixture of **288**:**291**.

As sodium azide did not seem to react rapidly enough, a new set of conditions involving the more reactive triflic azide were investigated (**Scheme 2.14**).[98] Triflyl azide was prepared from triflic anhydride and sodium azide directly before addition to the enol ether substrate **28**.[99] Unfortunately, this reaction did not provide any of the desired product, and only the ketone **37**, resulting from enol ether hydrolysis, was observed.



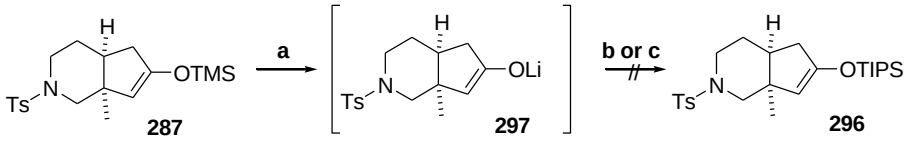
Scheme 2.14: Use of triflyl azide. Conditions: N_3OTf (formed from NaN_3, Tf_2O, MeCN, 0 °C, 2 h, used directly), MeCN, 0 °C, 2 h, (only formation of ketone **288**).

At the same time, work carried out within the group has showed that the formation of an α-azido ketone was more sucessful when a larger TIPS enol ether was used.[84] Thus, it was decided to use TIPSCl or TIPSOTf in order to trap the enol ether during the cuprate addition (**Scheme 2.15**). Unfortunately, the only product obtained with this reaction was the ketone **288**, suggesting the enolate was not trapped by the TIPS group.



Scheme 2.15: Preparation of compound **296**. Conditions: a) MeMgBr, CuI, TIPSCl, THF 0 ºC then rt, 2h, (only formation of ketone **288**); b) MeMgBr, CuI, TIPSOTf, THF 0 ºC then rt, 2h, (only formation of ketone **288**).

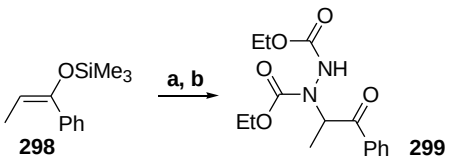
Undetered by these results, an alternative strategy was proposed to generate the TIPS enol ether **298** (**Scheme 2.16**). Instead of attempting to trap directly the enolate with the TIPS during the cuprate addition, the formation of a lithium enolate could be formed from the previously prepared TMS enol ether **287** using methyl lithium. Subsequent trapping of this lithium species with TIPSCl should form the desired compound **298**.[100] Unfortunately, despite using TIPSCl or the more reactive TIPSOTf, it was not possible to isolate the desired product **298**.



Scheme 2.16: Switching silyl groups. Conditions: a) MeLi, Et_2O, 0 ºC, used directly; b) TIPSCl, −78 ºC to 0 ºC, (only formation of the ketone **288**); c) TIPSOTf, −78 ºC to 0 ºC, (only formation of the ketone **288**).

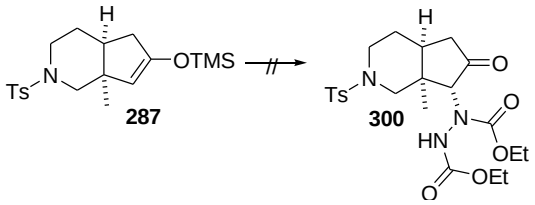
2.2.6 Other electrophilic sources of nitrogen

At this juncture, attention turned to the use of alternative amination methods. Kobayashi and co-workers have demonstrated that it is possible to introduce an amino group at the α position of a ketone starting from an enol ether, using the electrophilic DEAD reagent, as depicted in **Scheme 2.17** for one of their examples.[101]



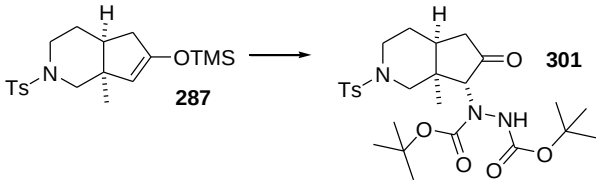
Scheme 2.17: Use of DEAD. Conditions: a) AgOTf (10%), DEAD, CH_2Cl_2, b) HF-THF, 90%.

Employing Kobayashi's conditions on our enol ether **287** in an attempt to form the desired compound **300** was unsuccessful (**Scheme 2.18**) and only ketone **288** was observed.



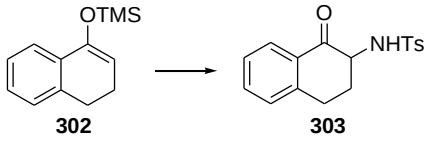
Scheme 2.18: Use of DEAD, AgOTf (10%), DEAD, CH_2Cl_2, (ketone **288** obtained as the only product).

In the same manner, another attempt to obtain the product by generation and reaction of the titanium enolate, following Gennari's conditions was unsuccessful (**Scheme 2.19**).[102] Thus, this strategy was abandoned and our attention focused on other types of electrophile.



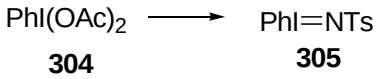
Scheme 2.19: Conditions: $TiCl_4$, DIAD, CH_2Cl_2, rt, 20h, (no reaction).

Despite the negative results obtained above, our attention turned to the use of another *N*-electrophile that could be used for the preparation of α amino ketone: *N*-tosyliminobenzyliodinane (PhI=NTs). This reagent has been used by Lim and co-workers to aminate cyclic ketones as depicted **Scheme 2.20**. For example, TMS enol ether **302** was treated with PhI=NTs to give the desired α-amino ketone **303** in 67% yield.[103]



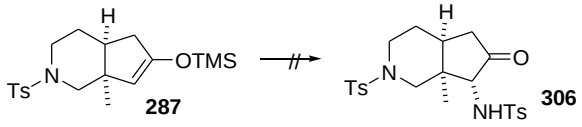
Scheme 2.20: Amination of silyl enol ether. Conditions: PhI=NTs, MeCN, rt, 67%.

N-Tosyliminobenzyliodinane (**305**) is not commercially available and so was prepared by treatment of *p*-toluenesulfonamide with iodobenzene diacetate **304** in methanol following the procedure of Heuss and co-workers.[104] The desired product was obtained in a 16% yield following this protocol (**Scheme 2.21**).



Scheme 2.21. Preparation of *N*-Tosyliminobenzyliodinane. Conditions: $TsNH_2$, KOH, MeOH, 0 °C to rt, 16%.

Despite the low yield obtained from the formation of the *N*-tosyliminobenzyliodinane, there was sufficient material to screen various sets of reaction conditions with our substrate (**Scheme 2.22** and **Table 2.1**). When the reaction was performed using Lim's conditions, it failed to deliver the desired product (Entry 1). Thus, our attention turned to other sets of conditions, particularly those employing copper catalysis, because numerous groups have employed this strategy with success.[104-107] The copper catalysts used in Entries 2—4 were commercially available,[106-107] but $Cu(MeCN)_4ClO_4$ (Entry 5) had to be prepared and was used directly.[105-106] Unfortunately, in every case, our attempt to prepare the amino ketone **306** led to hydrolysis of the enol ether and ketone **288** was isolated instead of the desired product. Thus, aziridination of the TMS enol ether **287** did not seem to be a feasible approach to progress the synthesis.



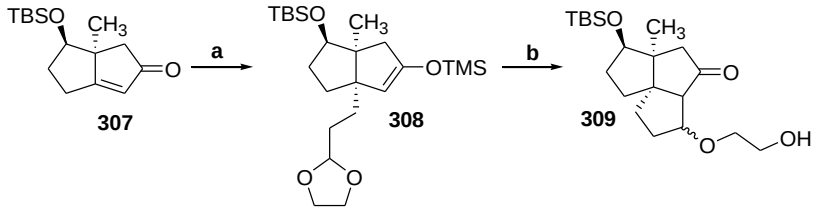
Scheme 2.22: Use of PhI=NTs. Conditions: PhI=NTs, catalyst, ligand, solvent, —20 °C to rt (see **Table 2.1**).

Entry	Catalyst	Ligand	Solvent	Time	Results
1	-	-	MeCN	17 h	SM + Ketone **288**
2	$Cu(acac)_2$	-	MeCN	20 h	SM + Ketone **288**
3	$Cu(MeCN)_4PF_6$	-	CH_2Cl_2	20 h	SM + Ketone **288**
4	$Cu(MeCN)_4PF_6$	TMEDA	CH_2Cl_2	20 h	SM + Ketone **288**
5	$Cu(MeCN)_4ClO_4$	-	MeCN	18 h	Ketone **288**

Table 2.1: Conditions used to install the tosyl amine.

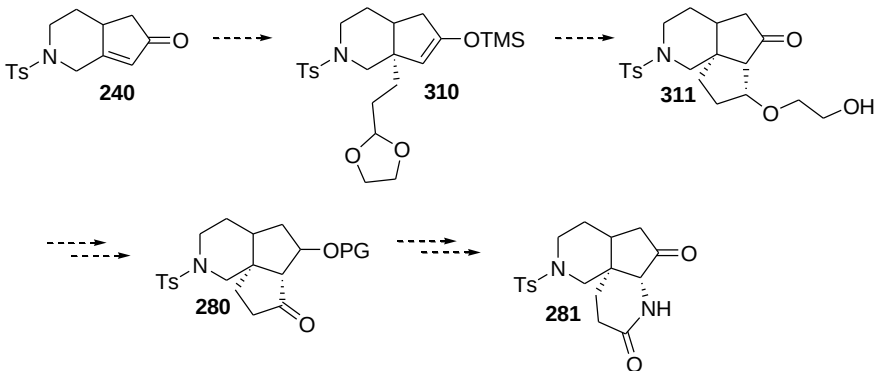
2.2.7 Titanium Chemistry

Due to the difficulties encountered at this stage, another pathway was investigated. In this case, an alternative reagent was employed for cuprate addition to the enone **240**. In 1993, Paquette and co-workers published the enantioselective total synthesis of (−)-subergorgic acid, in the course of which they perform the 1,4 addition of a dioxalane containing organocopper reagent to the enone **307**. Subsequent treatment of **308** with titanium tetrachloride formed the tricyclic ketone **309** as depicted in **Scheme 2.23**.[108]



Scheme 2.23: Paquette example. Conditions: a) Mg, 2-(2-Bromoethyl)-1,3-dioxolane, CuBr•SMe_2, TMSCl, DMAP, 90%; b) $TiCl_4$, CH_2Cl_2, 70% (1:1 mixture of diastereomers).

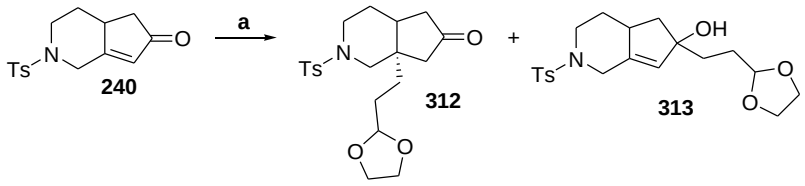
It was believed Paquette's ring construction methodology could be applied to the synthesis of the core of nakadomarin A by allowing us to prepare tricyclic ketone **311** (**Scheme 2.24**). From this compound, the ketone functionality would be reduced and protected, and the ether would be oxidised to form ketone **280** (a key intermediate from our original approach cf **Scheme 2.5**). Subsequent Beckmann rearrangement would reveal the desired lactam **281**.



Scheme 2.24: Strategy following Paquette's work.

Initial attempts to perform the reaction following Paquette's conditions failed to deliver the desired 1,4-addition compound **312** and so the reaction had to be modified (**Scheme 2.25** and **Table 2.2**). The use of CuBr.SMe_2 as the copper source, along with DMAP as

Paquette suggested, resulted in none of required product and led to the recovery of the starting material (Entries 1-3). However, when a catalytic amount of copper iodide was employed, reaction did occur, albeit to provide the product **313** arising from undesired 1,2-addition.[109] Upon switching to a super-stoichiometric amount of copper iodide, the desired product **312** was obtained in 55% yield (Entry 5).

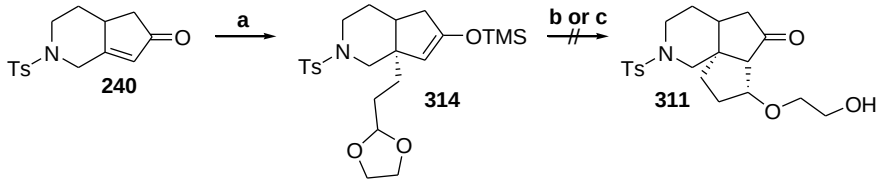


Scheme 2.25: An approach using Paquette's protocol. Conditions: a) Mg, 2-(2-Bromoethyl)-1,3-dioxolane, copper source, solvent, additive (see **Table 2.2**).

Entry	Copper source (eq)	Solvent	Additive	T	Results
1	$CuBr{\bullet}SMe_2$ (1.8)	THF	DMAP	−78 °C	No reaction
2	$CuBr{\bullet}SMe_2$ (1.8)	THF	-	−20 °C	No reaction
3	$CuBr{\bullet}SMe_2$ (1.8)	THF	DMAP	−20 °C	No reaction
4	CuI (0.2)	THF	-	−30 °C to −78 °C	**313** (62%)
5	CuI (1.2)	THF	-	−30 °C to−78 °C	**312** (55%)

Table 2.2: Optimisation of the cuprate addition.

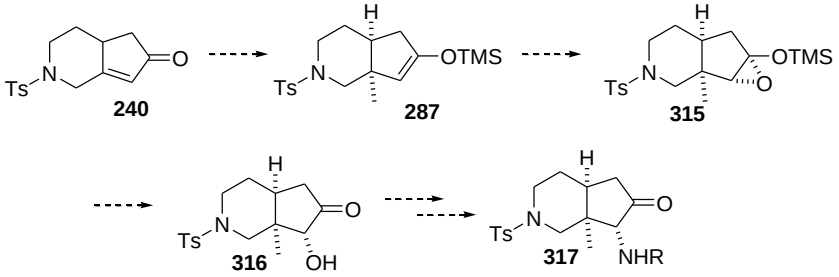
Following the successful conjugated addition reaction, conditions were modified in order to prepare enol ether **314**. TMSCl was added in order to trap the enolate (**Scheme 2.26**). However, subsequent treatment of **314** with titanium tetrachloride did not provide the corresponding tricyclic compound **311**. Only the formation of the ketone **312** was observed. Several attempts were made to accomplish the transformation using various temperatures and using $TiCl_4$ as either a 1 M solution in CH_2Cl_2 or in pure form (see conditions).[110]



Scheme 2.26: Conditions: a) Mg, 2-(2-bromoethyl)-1,3-dioxolane, CuI, TMSCl, THF, −30 °C to −78 °C, 2 h, used crude ; b) $TiCl_4$, CH_2Cl_2, −78 °C , 10 min, (obtained only ketone **312**, 53%); c) $TiCl_4$, CH_2Cl_2, −78 °C to 0 °C to −78 °C , 10 min, (obtained only ketone **312**, 54%).

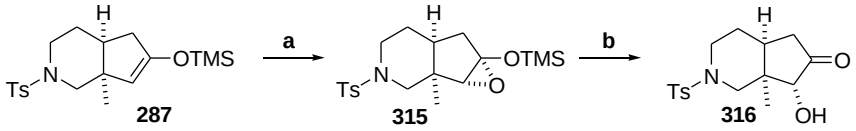
*2.2.8 Rubottom oxidation: formation of the hydroxyketone **316***

At this point in the project, it was clear that functionalisation of the TMS enol ether **287** was difficult; but another attempt was made to elaborate this compound using Rubottom oxidation.[111] As a result, our next approach was to prepare the hydroxyketone **316**, by epoxidation of the silyl enol ether **287**, followed by the opening of the epoxide to form hydroxyketone **316** (**Scheme 2.27**). This option would be a way to introduce a hetero functionality in the α-position of the ketone. The formation of the hydroxy ketone **316** would open a new avenue of potential reactions to allow the formation of the α-amino ketone **317**.



Scheme 2.27: Strategy to form the hydroxyketone **316**.

The initial set of conditions used to perform Rubottom oxidation, involved treatment of **287** with *m*CPBA. However this reaction led to decomposition of the starting material and only traces of the product **316** were observed. A significant improvement was achieved by treatment of the enol ether **287** with milder epoxidation reagent, dimethyldioxirane (DMDO).[112] The desired hydroxyketone **316** was isolated in 73% yield over 2 steps after opening of the epoxy acetal under acidic conditions (**Scheme 2.28**).



Scheme 2.28. Formation of the hydroxyketone. Conditions: a) DMDO, CH_2Cl_2, 0 °C, 5 min; b) AcOH, H_2O, THF, rt, 3 h, 73% over 2 steps.

Hydroxyketone **316** was obtained as a crystalline solid. In order to confirm its stereochemistry, this compound was submitted to X-Ray crystallography. The structure and the *cis* configuration of the methyl group compared to the hydroxyl group were validated (**Figure 2.1** and **Appendix 1**). It is worth noting this 3D structure shows a poor accessibility to the top face of the molecule.

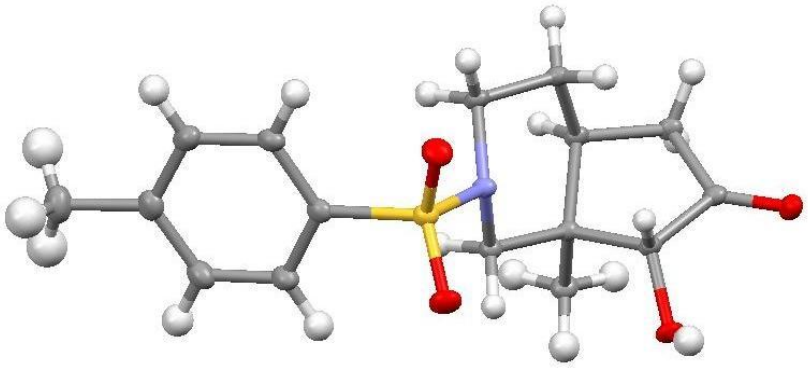
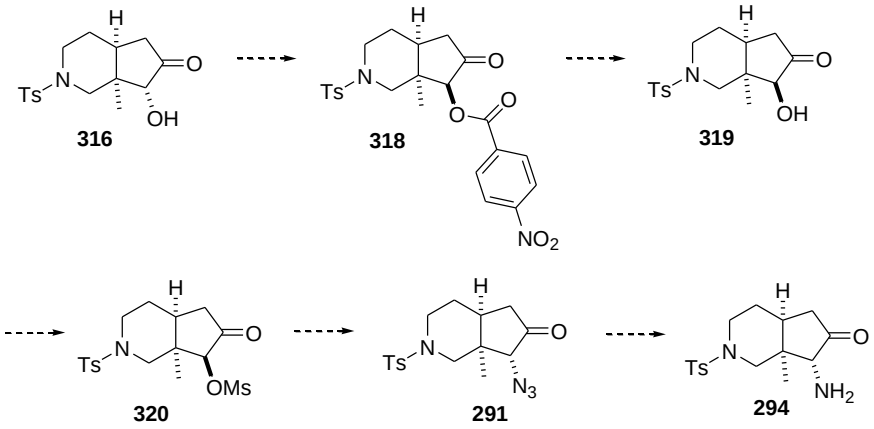


Figure 2.1: X-Ray Analysis of **316** (see **Appendix 1**).

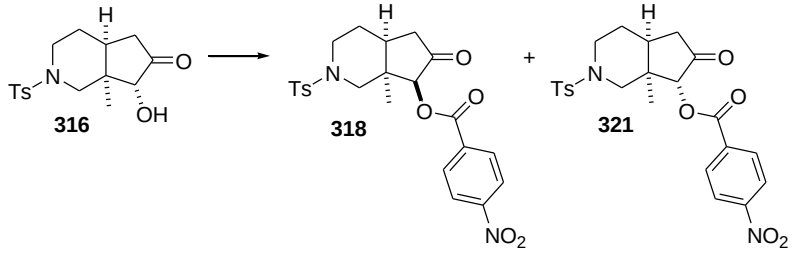
The outcome of the reaction was very gratifying and installation of functionality at the α-position of ketone **316** was a significant step forward. However, the *cis* stereochemistry obtained using the Rubottom conditions required inversion prior to a displacement with a nitrogen containing reagent; *i.e.* double inversion or net retention of configuration. It was

hoped under Mitsunobu conditions, the *trans* hydroxyketone **319** could be formed and mesylated to form the intermediate **320**. Subsequent displacement with a nitrogen containing nucleophilic reagent (i.e. sodium azide), would produce the desired *cis* product **291**, which, in turn, could be reduced to give product **294** (**Scheme 2.29**).[113]



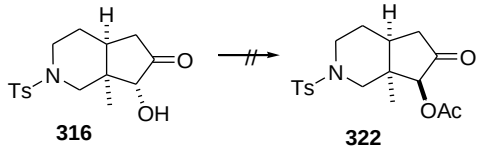
Scheme 2.29: Strategy for the formation of **294**.

Unfortunately, when applying the Mitsunobu strategy to our substrate, using 4-nitrobenzoic acid, the selectivity of the α-centre was lost and two inseparable isomers, **318** and **321,** were formed in 91% yield but only 10:9 *dr* (**Scheme 2.30**). Once again, it is suspected the problem occurred due to the S_N2 displacement being disfavoured when the approaching nucleophile comes from the less sterically accessible top face of the molecule.



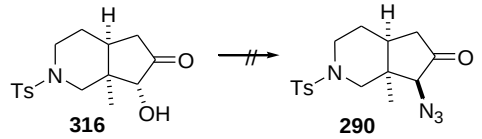
Scheme 2.30: Mitsunobu reaction. Conditions: 4-nitrobenzoic acid, DIAD, PPh_3, 0 °C to rt, 6 h, 91% yield, 10:9 *dr*.

To overcome this steric issue, the next set of conditions investigated for the Mitsunobu reaction involved attempted introduction of a smaller acetyl group to form **322** (**Scheme 2.31**).[114] Unfortunately, this reaction failed and the starting material was not consumed.



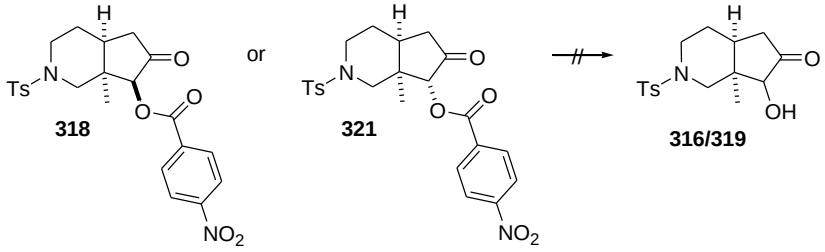
Scheme 2.31: AcOH in the Mitsunobu reaction. Conditions: AcOH, DIAD, PPh_3, Et_2O, 0 °C to reflux, 6 days (no reaction).

In the same manner, it seemed likely that a Mitsunobu reaction could be performed using diphenyl phosphoryl azide (DPPA), and thus the nitrogen could be introduced directly at this stage, forming **323**.[115] Regrettably this reaction led to the formation of an unknown byproduct and none of the required azide **290** was isolated (**Scheme 2.32**).



Scheme 2.32: DPPA in the Mitsunobu reaction. Conditions: DPPA, DEAD, PPh_3, THF, 0 °C to rt, 16 h (by-product).

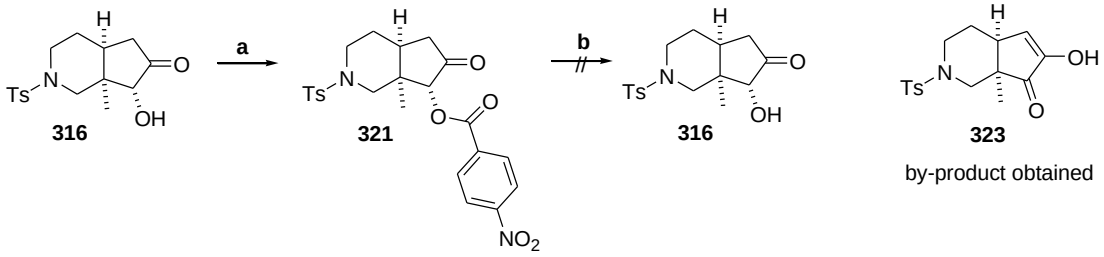
Parallel to this work, our attention focused on the hydrolysis of the diastereomeric mixture of ester **318** and **321**, to provide hydorxyketone **316** and **319**. Regrettably, hydrolysis led to an unknown by-product. More surprisingly, when submitting the mixture of both isomers **318** and **321**, the formation of a single compound was observed (**Scheme 2.33**).



Scheme 2.33: Attempted hydrolysis of esters **318** and **319**. Conditions: K_2CO_3 , MeOH, THF, rt, 17 h.

To elucidate the structure of the by-product, it was decided to esterify previously prepared alcohol **316** under standard conditions to form **321** (**Scheme 2.34**). This allowed us to work with a single isomer, compared to a mixture, in order to screen the conditions for the hydrolysis reaction. Several standard basic conditions were used to perform hydrolysis

(**Table 2.3**), but the same by-product, hydroxyketone **323**, was obtained in each case.[116-118]. The formation and use of the product will be discussed in section 2.2.12 of this chapter.

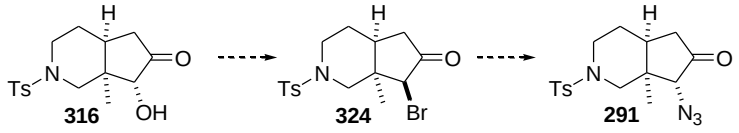


Scheme 2.34: Esterification and hydrolysis. Conditions: 4-nitrobenzoic chloride, DMAP, Et_3N, CH_2Cl_2, rt, 3 h, 95%; b) base, solvent (see **Table 3**).

Entry	Base (eq)	Solvent	Time	T	Results
1	K_2CO_3 (3.3)	MeOH/THF	16 h	rt	By-Product **316** (18%)
2	NaOHaq, (1.2)	MeCN	16 h	rt	By-Product **316** (45%)
3	TMSOK (5)	Et_2O	2 h	rt	By-Product **316** (12%)
4	Et_3N (3.1)	THF	16 h	rt	By-Product **316** (17%)

Table 2.3: Attempted formation of **316** *via* **321**.

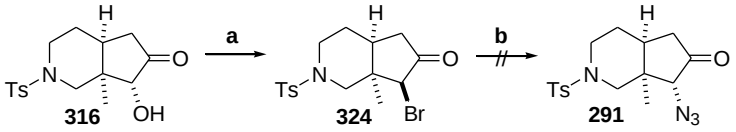
Despite the moderate success of the Mitsunobu reaction, another strategy, making use of the α-functionalised ketone **316**, involved the preparation of bromide **324** before displacement with sodium azide (**Scheme 2.35**).



Scheme 2.35: Bromination and displacement.

Accordingly, the formation of the brominated compound **324** was performed by displacement of the alcohol with carbon tetrabromide.[119] However, the poor stability of this product did not allow for full characterisation and so the crude compound was used

directly in the displacement with sodium azide. Unfortunately, this reaction was not successful after several attempts (**Scheme 2.36** and **Table 2.4**).[120-121] This route was eventually abandoned, due to the difficulty in characterising **324** and confirming its structure and also determining the stereochemical outcome of the reaction.

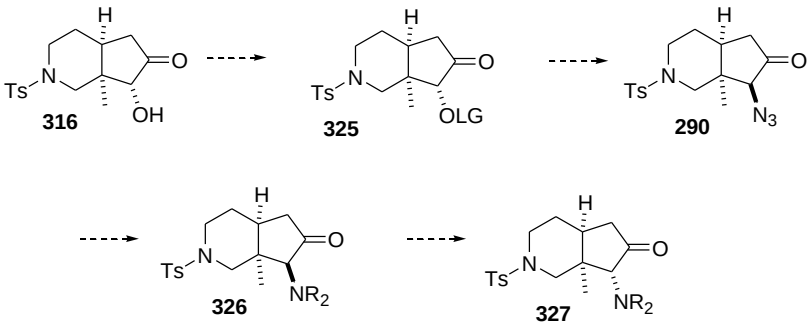


Scheme 2.36: Bromination and displacement with azide. Conditions: a) CBr_4, PPh_3, CH_2Cl_2, rt, 2 h, used crude, b) NaN_3, solvent, (see **Table 2.4).**

Entry	Solvent	Eq NaN_3	Time	Temperature	Results
1	DMSO	3	2 h	rt	No reaction
2	DMSO	3	16 h	35 °C	No reaction
3	DMSO	3	16 h	50 °C	No reaction
4	DMF	2	8 h	rt	No reaction
5	DMF	4	16 h	35 °C	No reaction

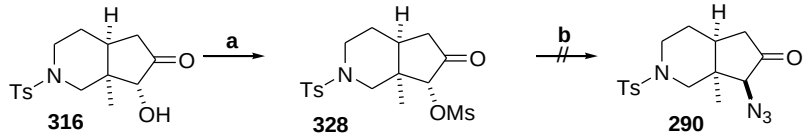
Table 2.4: Conditions used to displace the bromide

At this stage, attention turned to the direct displacement of the hydroxyl group in the hydroxyketone **316** with an azide source. The configuration of the hydroxyketone being *cis*, an S_N2 displacement should lead to the undesired *trans* configuration of the azide in compound **290** (**Scheme 2.37**). Despite this, it was hoped the molecule would undergo epimerisation to give the more stable *cis* configuration, otherwise the reduction of the azide to the amine, leading to **326**, would have to be followed by epimerisation to form the desired α-aminoketone **327**.



Scheme 2.37: Strategy involving S_N2 displacement of a leaving group.

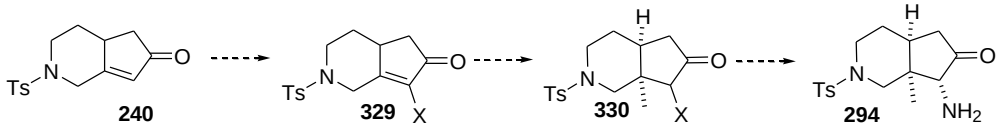
The first attempt to perform the transformation involved mesylation of the hydroxyl group, followed by displacement with sodium azide (**Scheme 2.38**).[113] The mesylation reaction proceeded well, as observed by TLC and analysis of the ^1H NMR spectrum showed the formation of the mesylate **328**, which was used crude because it was unstable. For the following displacement reaction, several sets of conditions were investigated, but no reaction occurred in any case, even when the reaction was heated to 65 ºC for 5 h. Because sodium azide can react violently when heated, the temperature was not increased further. As before, it can be assumed that attack from the top face of the molecule was not straightforward due to the steric encumbrance in this position, caused by the conformational preference of the bicyclic mesylate. Consequently, this strategy was abandoned.



Scheme 2.38: Mesylation and displacement. Condition: MsCl, Et_3N, rt, used crude; b) NaN_3, DMF, from 0 ºC over 2 h to 65 ºC over 5 h, no reaction.

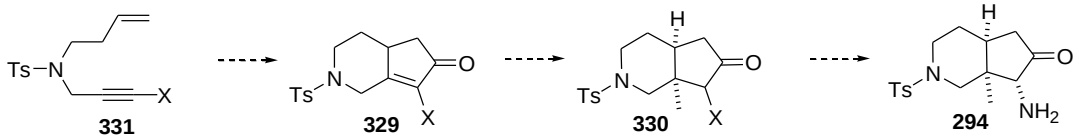
2.2.9 Functionalisation at an earlier stage

In all previous sections, the synthetic strategy has involved functionalisation of the α-position of the molecule after the cuprate reaction. Due to the lack of success regarding this approach, it was decided to explore a different route, in which functionalisation of the Pauson-Khand enone product was performed (Route A, **Scheme 2.39**), or the requisite functionality was installed during the Pauson-Khand reaction (Route B, **Scheme 2.40**). Following this idea of introducing a group α to the ketone before the cuprate addition, the thought of preparing functionalised enone **329** from **240** was explored (Route A). Subsequent cuprate addition to the functionalised enone **329** and displacement of the newly installed group with an amine would produce the amino ketone **294**.[122]



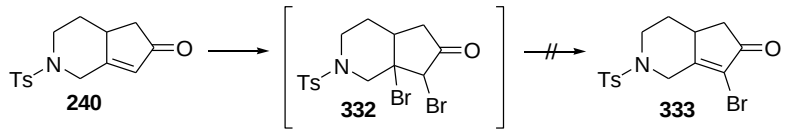
Scheme 2.39: Route A.

In Route B, the enone **329** would be obtained directly by the Pauson-Khand reaction of alkyne **331**. The group X would then be converted into the amino group in **294**.



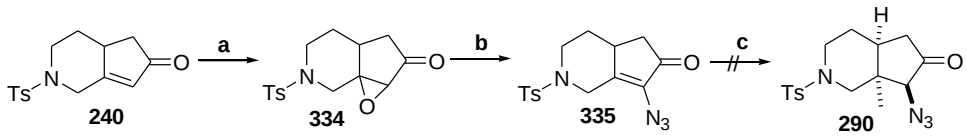
Scheme 2.40: Route B.

Attempts to perform direct bromination of compound **240** resulted only in the formation of an undesired by-product. Although it was not possible to isolate and characterise this compound, formation of the double bromination product was suspected, as it is an intermediate on the pathway to the final product. Increasing the reaction time did not change the outcome of the reaction and treatment of the by-product with $NaHCO_3$ resulted in the decomposition of the product (**Scheme 2.41**).[123]



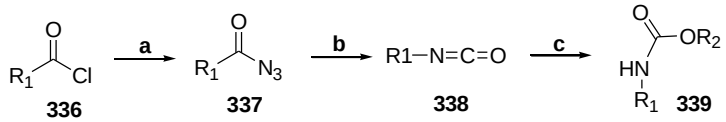
Scheme 2.41: Bromination. Conditions: NaBr, oxone, CH_2Cl_2, H_2O, Et_3N, 0 °C, 16h, then $NaHCO_3$, 16h, reflux (decomp).

Continuing with this new strategy, another set of conditions was explored (**Scheme 2.42**). Epoxidation of enone **240** was followed by treatment with DPPA, to form azide **335** in poor yield (12%).[124-125] Moreover, the subsequent cuprate addition failed to deliver the required keto azide **291**. It is also likely that the reaction would afford the non-desired isomer after the 1,4 addition, which would then require epimerisation. If the yield had been better reduction of the azide functionality in compound **335** to form the amine, and subsequent protection as an amide could have been explored, but this route was clearly problematic and so was abandoned.



Scheme 2.42: Conditions: a) H_2O_2, $NaHCO_3$; b) DPPA, DMAP, DMF, $LiClO_4$, 12%; c) MeMgBr, CuI, THF, rt, 3 h (decomp).

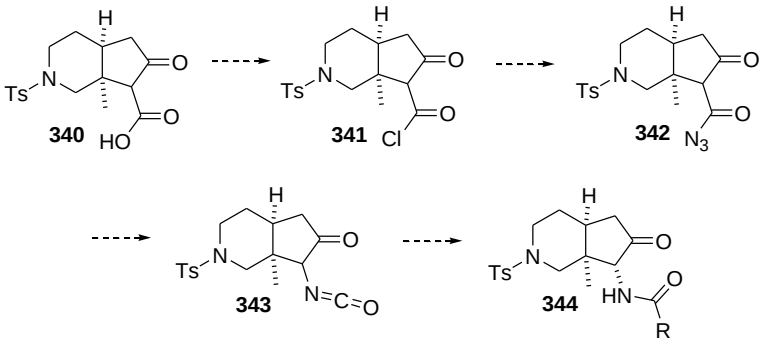
Despite the problems outlined above, another pathway was investigated, in which a Curtius rearrangement reaction was used to install the amine functionality. First described by Curtius in 1890, this reaction involves the thermal decomposition of an acyl azide formed from an acid chloride, to produce an isocyanate (**Scheme 2.43**).[126] The isocyanate intermediate may be isolated, or can be trapped by various nucleophiles to form an amide, such as **339**.



Scheme 2.43: Curtius rearrangement. Conditions: a) NaN_3; b) heat; c) R_2OH.

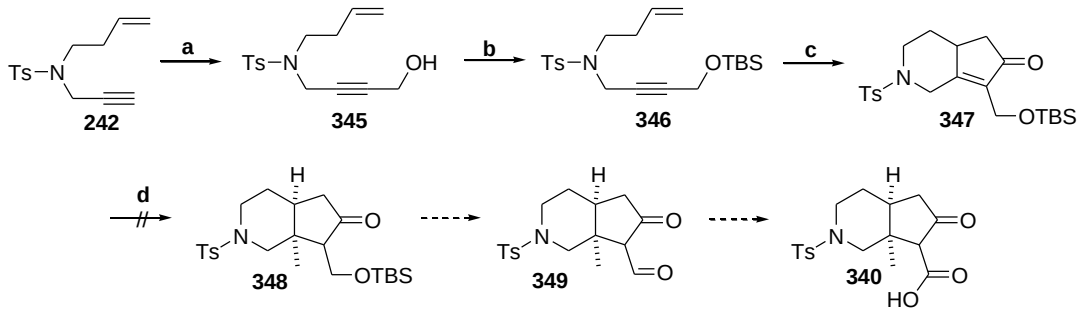
In an attempt to use this transformation to access our desired target, our first goal was to install a carboxyl group in place, α to the ketone (**340**). Subsequent manipulation to the

acid chloride **341**, followed by formation of the acyl azide **342** would allow the preparation of the amide **344** by isocyanide formation and rearrangement **(Scheme 2.44)**. It was hoped the acyl azide would rearrange to give the most thermodynamically stable isomer, with the *cis* configuration, otherwise epimerisation would be required.



Scheme 2.44: Curtius rearrangement strategy.

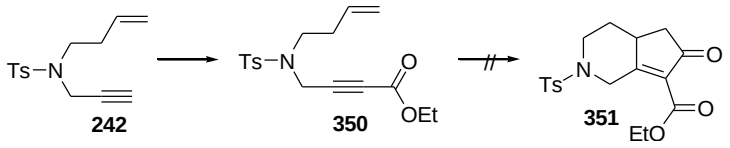
To form the desired compound **340**, the route began with reaction of the previously prepared enyne **242** with paraformaldehyde, followed by protection of the resulting alcohol with a TBS group to provide **346** in 57% yield over two steps (**Scheme 2.45**). The subsequent Pauson-Khand reaction to form the core of our target provided the bicyclic enone **347** in modest yield. Unfortunately, attempts to perform the 1,4-addition reaction on this enone to give **340** led only to an unidentified by-product.



Scheme 2.45: Towards **340**. Conditions: a) *n*BuLi, $OH(CH_2O)_nH$, THF, −78 °C to rt, 87%; b) TBSCl, DMAP, Et_3N, CH_2Cl_2, rt, 66%; c) $Co_2(CO)_8$, TMTU, CO, toluene, 70 °C, 48%; d) MeMgBr, CuI, THF.

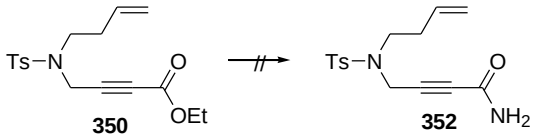
An alternative approach was explored, whereby an ester group was introduced prior to the Pauson-Khand reaction (**Scheme 2.46**). The ester cyclisation precursor **350** was prepared in 34% yield from **242** but the Pauson-Khand reaction of this enyne failed. This result is not

without precedent, as previous attempts to perform Pauson-Khand reactions using ynoates have delivered mediocre results.[127]



Scheme 2.46: Towards **351**. Conditions: ethylchloroformate, CH_2Cl_2, −78 ºC to rt, 34%; b) $Co_2(CO)_8$, TMTU, CO (unknown by-product).

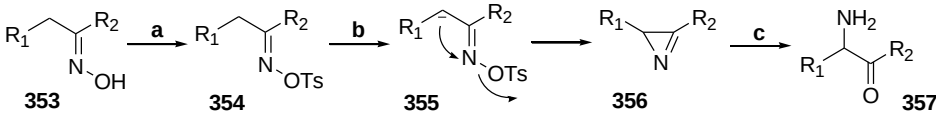
In a final attempt to utilise the Pauson-Khand reaction with a more highly functionalized substrate, ynamide **352** was targeted (**Scheme 2.47**). Unfortunately, treatment of **350** with aqueous ammonia failed to deliver the product and a by-product was obtained instead.



Scheme 2.47: Towards **352**. Conditions: NH_3/H_2O, THF, rt (by-product).

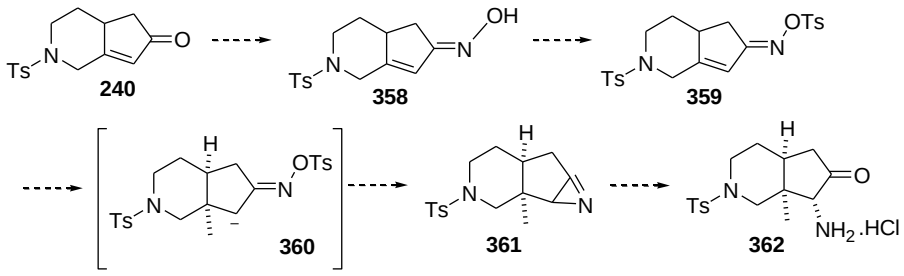
2.2.10 Neber rearrangement

At this stage, our attention turned to another strategy, employing the Neber rearrangement. The Neber reaction is a powerful reaction in which an oxime (**353**) is converted to an α-amino ketone (**357**), *via* the formation of an azirene **356**. It was first reported by Neber in 1926.[128] The general reaction scheme is depicted in **Scheme 2.48**.



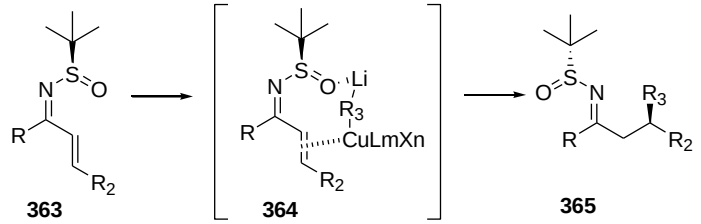
Scheme 2.48: Neber rearrangement. Conditions: a) TsCl; b) base; c) H_2O.

In our case, it was anticipated that formation of oxime **358** from enone **240**, and subsequent treatment with TsCl would deliver tosylated compound **359**. Subsequent 1,4-conjugate addition combined with a Neber rearrangement in presence of HCl would ultimately deliver α-amino ketone salt **362** (**Scheme 2.49**).



Scheme 2.49: Neber rearrangement.

This reaction sequence, in which cuprate addition is combined with a Neber rearrangement reaction, has never been described. Neither has a cuprate addition reaction starting from an α,ß-unsaturated tosylated oxime. However, cuprate addition reaction to *N*-sulfinyl-α,ß unsaturated imines has been reported by Ellman and McMahon (**Scheme 2.50**) with the aim of forming **365**, via intermediate **364**.[129]



Scheme 2.50: MacMahon and Ellman's model

In our case, the presence of the N-OTs functionality is crucial because is acts as the leaving group. Nevertheless, a similar intermediate to **364** could be reasonably formed in our case (**366**, **Figure 2.2**).

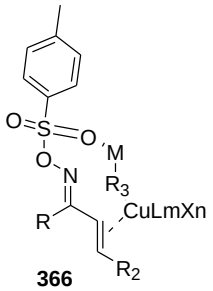
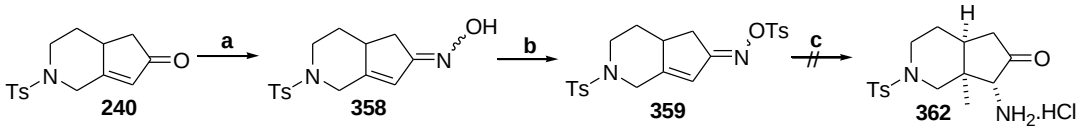


Figure 2.2: Possible intermediate.

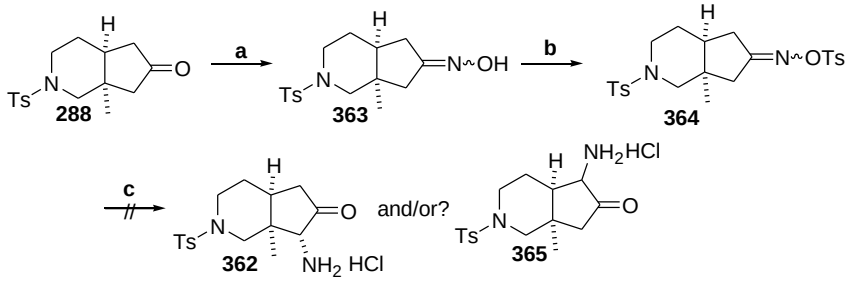
Thus, oxime **358** was prepared in 58% yield as a single isomer (**Scheme 2.51**). Whilst NOE experiments were unsuccessful in determining which isomer was formed, the subsequent steps were attempted directly. Protection of the oxime was performed and compound **359**

was used directly without further purification. Unfortunately, the subsequent cuprate addition and Neber reactions failed to deliver the desired product and led to decomposition of the starting material.[130]



Scheme 2.51: Conditions: $NH_2OH.HCl$, pyr, EtOH, rt, 24 h, 58%; b) TsCl, pyr, 0 °C to rt, 4 h, 24%; c) MeMgBr, CuI THF/Et_2O, then HCl(aq), rt, 1 h (decomp).

In order to probe the potential of this method, we decided to simplify the key reaction. Previously prepared ketone **288** was transformed into oxime **363**, which was tosylated, to form the precursor for the Neber rearrangement (**Scheme 2.52**). Carrying out the reactions in this order, we anticipated the formation of the regioisomers **362** and **365**, nevertheless the idea was explore the general feasibility of this strategy. The preparation of the oxime **363** from ketone **288** was performed in 95% yield. Subsequent tosylation was accomplished, providing **364**. The subsequent Neber reaction failed to deliver the product, and only decomposition of the starting material was observed. Consequently, this strategy was abandoned.

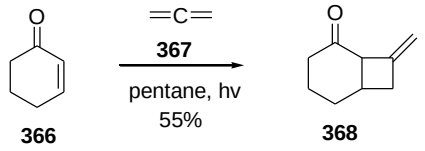


Scheme 2.52: Conditions: a) $NH_2OH.HCl$, pyr, EtOH, rt, 24 h, 95%; c) TsCl, pyr, 0 °C to rt, 4 h, used crude; d) *t*BuOK, EtOH, toluene, 0 °C to rt, 4 h, then HCl, rt (decomp).

2.2.11 Cycloaddition

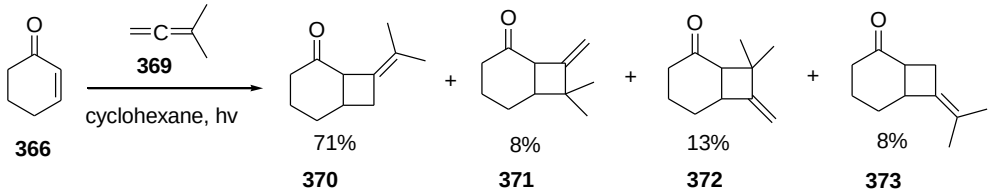
Regardless of these results, attention turned to the direct formation of the third cycle using photocycloaddition chemistry. As early as 1964, Corey and Bass described an enone photocyclisation reaction, to form bicyclic compound **368** (**Scheme 2.53**).[131] Cyclohexenone **366** was treated with allene **367** and irradiated with a mercury arc lamp, in pentane to form the product **368**. Since this initial study, other examples of reaction have

been described mostly with simple propadiene **367**, and the head-to-head (HH) regioisomers — where the ketone and alkene are syn — are generally formed in considerably higher yield than the head-to-tail isomers.[131-136]



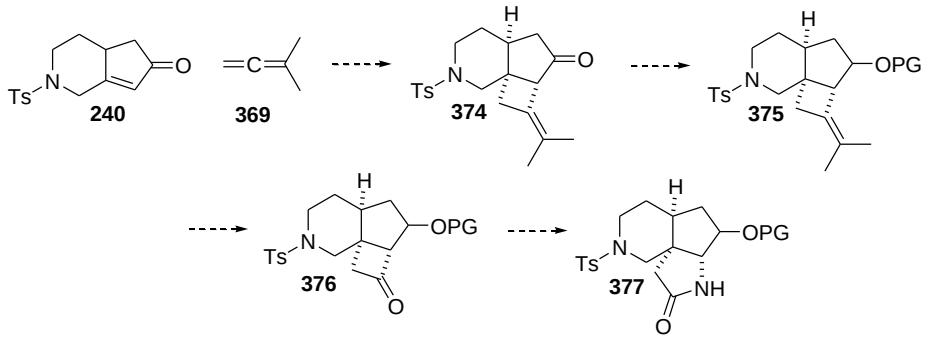
Scheme 2.53: Corey and Bass' conditions.

Moreover, in 1982, Becker and co-workers described the use of 3-methyl-1,2-butadiene **369** (**Scheme 2.54**).[137] The HH product **370** is also obtained as the major isomer in this case (71%), compared to the head-to-tail product **373**.



Scheme 2.54: Becker's conditions.

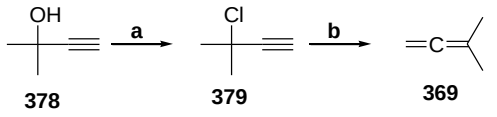
Applying this method to our substrate, the reaction of the enone **240** with allene **369** would form the tricyclic ketone **374** (**Scheme 2.55**). Subsequent reduction and protection of the ketone functionality would form **375**, which after ozonolysis of the alkene would form cyclobutanone **376**. Finally, Beckmann rearrangement of compound **376** would form the desired lactam **377**.



Scheme 2.55: Radical cyclisation strategy

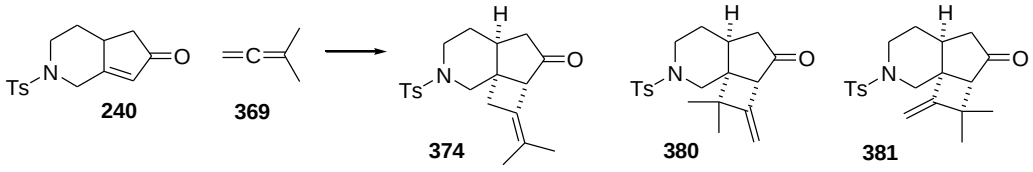
In a practical sense, the use of compound **378** is a good alternative to allene **367** which is a highly flammable gas. Whilst 3-methyl-1,2-butadiene (**378**) is commercially available, it

was formed in two steps (**Scheme 2.56**).[138] Treatment of **378** with HCl (conc), hydroquinone and $CaCl_2$ provided the desired chlorinated alkyne **379** in 73% yield, which was transformed into **369** in 19% yield.



Scheme 2.56: Preparation of **125a**. Conditions: a) $CaCl_2$, hydroquinone, HCl (conc), 73%, b) Zn (granules), *n*BuOH, 19%.

With **369** in hand, we screened various sets of conditions in order to form the desired tricyclic compound **374** in good yield (**Scheme 2.57**, **Table 2.5**). Irradiation of a solution of enone **240** and **369** for 2 h was first performed in cyclohexane (Entry 1), but the required reaction did not occur. By changing the solvent to a mixture of cyclohexane/acetone, traces of a new product were observed on TLC analysis (Entry 2). A dry state adsorption technique, using silica gel, was attempted, but this also proved unsuccessful (Entry 3).[132] A great improvement was achieved, when using a 125 W Hanovia mercuy lamp, and running the reaction in cyclohexane (Entry 4).[137] As predicted, and despite a decent overall yield (54%), the product was formed as an inseparable mixture of regioisomers. The ratio was determined by ^{1}H NMR analysis. The yield was increased when the reaction was carried out in acetonitrile (Entry 5), but the ratio did not change. The reaction was also performed at −30 °C, but this only resulted in a lower yield without altering the product ratio (Entry 6).



Scheme 2.57: Photocycloaddition. Conditions: see **Table 2.5**.

Entry	Solvent	Lamp Type[a]	Eq. Allene	Time	T	Yield	Ratio: **374**:**381**:**380**
1	Cyclohexane	1	1	2 h	rt	No reaction	-
2	Cyclohexane/acetone	1	1	2 h	rt	Traces	-
3	None	2	5	5 h	rt	No reaction	-
4	Cyclohexane	3	5	6 h	rt	54%	3.7:1.4:1
5	MeCN	3	5	6 h	rt	63%	3.5:1.4:1
6	MeCN	3	5	10 h	−30 °C	34%	4:1.5:1

[a] Type 1: LuzChem photoreactor, no cooling supply, 10x8W FL8BL-B lamps (UVA λ=360 nm), Type 2: LuzChem photoreactor, no cooling supply, 10x8 W low-pressure germicidal lamps (UVC λ=254 nm), Type 3: 125 W Hanovia Mercury Lamp, medium pressure, cooling supply (UVA λ=365 nm).

[b] reaction was performed under dry state absorption conditions (silica gel).

Table 2.5: Photocycloaddition.

In an attempt to improve the ratio of products, more sterically hindered allenes were considered as substrates. Indeed, a bulkier group on the allene functionality should lead the reaction to favor of a HH product. The three commercially available compounds shown **Figure 2.3** were tested. Unfortunately, as depicted **Scheme 2.58** and **Table 2.6**, the ratio of the product obtained using **382** could not be determined due to the difficulty in interpreting the complex ^{1}H NMR spectrum of the mixture (Entries 1 and 2). The use of allene **383** resulted in 2.9:1.1:1 ratio of **385/386/384** (Entry 3), a result that was poorer than that obtained using the optimised conditions described in **Table 2.5**. Finally, treatment of **240** with **384** resulted in the decomposition of the starting material (Entry 4) and no product was obtained. In this respect, this photocycloaddition pathway was abandoned.

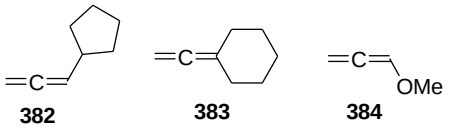
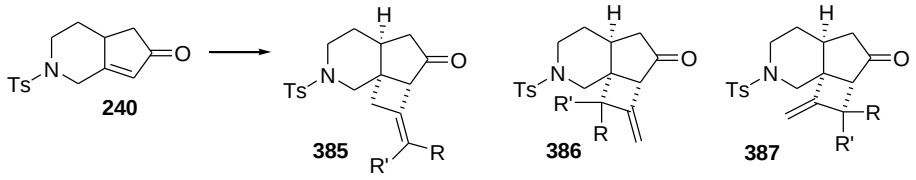


Figure 2.3: Allenes used.



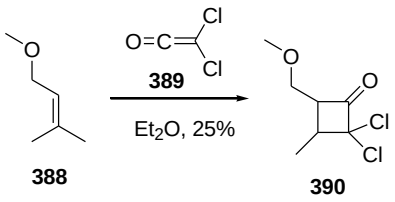
Scheme 2.58: Photocycloaddition. Conditions: see **Table 2.6**.

Entry[a]	Solvent	Allene (eq.)	Time	T	Results	Ratio **385/386/387**
1	MeCN	**382** (7)	6 h	rt	55%	could not be determined
2	1,2-DCE	**382** (7)	6 h	rt	60%	could not be determined
3	MeCN	**383** (7)	6 h	rt	61%	2.9:1.1:1
4	MeCN	**384** (7)	3 h	rt	Decomp.	-

[a] All experiments were carried out using 125 W Hanovia Mercury Lamp, cooling supply (UVA λ=365 nm).

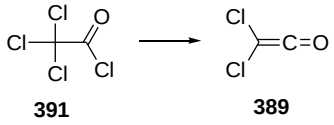
Table 2.6: Photocycloaddition reactions of enone **240** with allenes **382**-**384**.

Despite the moderate success using various allenes as photocycloadditions partners, an alternative cycloaddition reaction was considered. Indeed, the cycloaddition reaction of dichloroketene to allylic ethers was described as early as 1978, by Malherbe and Bellus (**Scheme 2.59**).[139] Simple allylic ether **388** was treated with dichloroketene **389** to form the dichlorocyclobutanone **390** in 25% yield.



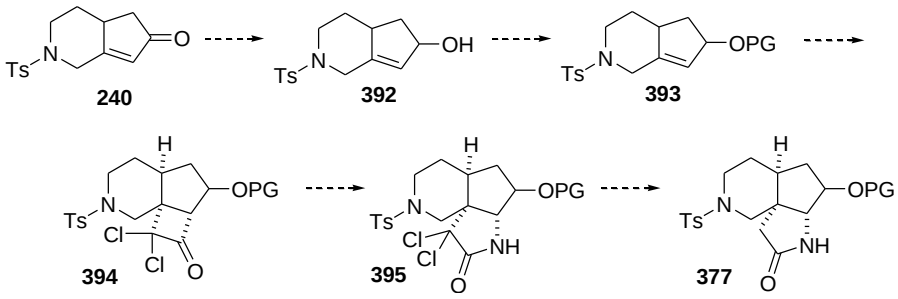
Scheme 2.59: Cycloaddition with dichloroketenes.

The reacting dichloroketene **389** was formed *in situ*, by dehalogenation of trichloroacetylchloride **391** with Zn-Cu couple, as depicted **Scheme 2.60**.[140]



Scheme 2.60: Formation of dichloroketene **389**. Conditions: Zn-Cu couple, Et_2O.

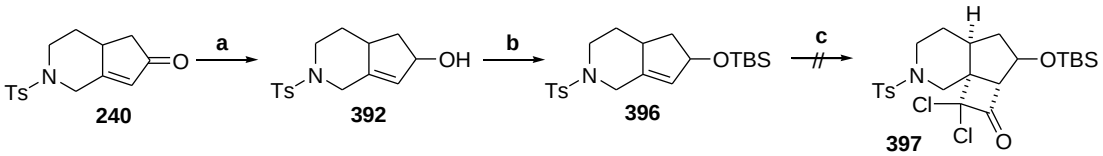
In an attempt to use this transformation to prepare our desired target, our first goal was the reduction and protection of the ketone functionality of **240**, to provide allylic ether **393** (**Scheme 2.61**). Subsequent cyclisation with dichloroketene **389** would be followed by a Beckmann rearrangement to form tricylic lactam **395**, from which dechlorination would provide the desired compound **377.**



Scheme 2.61: Cycloaddition pathway.

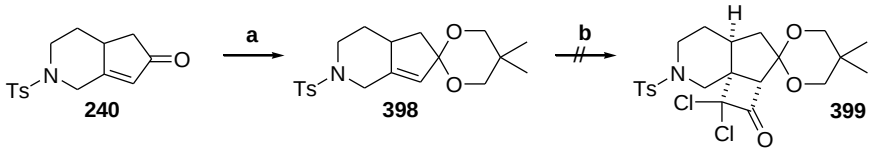
Thus, our strategy began with the reduction of the enone, using a Luche reduction,[44] to provide **392** in a 100% yield as a single but undetermined isomer (**Scheme 2.62**). Subsequent TBS protection of the resulting hydroxyl group formed the desired compound **396**. Unfortunately, when following Green's conditions,[140] treatment of **396** with the ketene formed *in situ* failed to deliver the desired tricyclic compound **397** and only an uncharacterised by-product was observed. Although it was not possible to fully identify this

resulting by-product, ^{1}H NMR spectrum analysis showed the disappearance of the entire OTBS group.



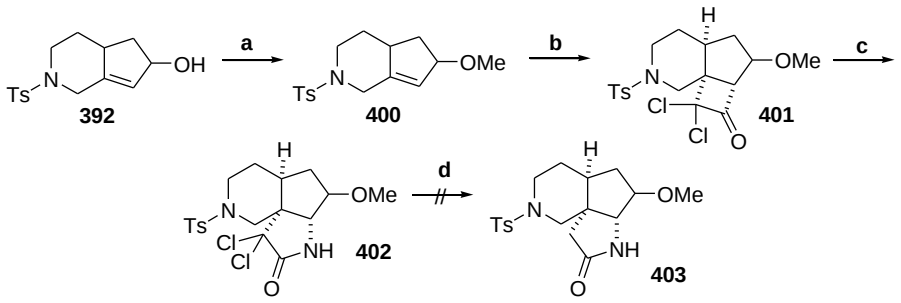
Scheme 2.62: Attempts to prepare ketone **397**. Conditions: a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 100%; b) TBSOTf, 2,6 lutidine, CH_2Cl_2, 100%; c) Cl_3COCl, Zn-Cu couple, Et_2O (by-product).

In order to avoid the elimination of the protecting group, the hydroxy group in **134** was protected as an acetal (**Scheme 2.63**). Thus, enone **6** was treated with dimethyl propanediol to provide the desired compound **145** in 54% yield. However, subsequent treatment of **145** with dichloroketene failed to deliver the desired product **146** and only decomposition of the starting material was observed.



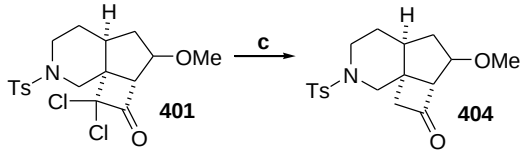
Scheme 2.63: Conditions: a) 2,2-Dimethyl-1,3-propanediol, oxalic acid, toluene, reflux, 4 h, 54%; b) Cl_3COCl, Zn-Cu couple, Et_2O (decomp).

In a final attempt to effect successful cycloaddition to the enone **240** with dichloroketene, the alcohol **392** was protected with a more robust methyl group (**Scheme 2.64**). This sequence was performed using standard methylation conditions, and provided **400** in 93% yield. Subsequent cycloaddition provided an extremely sensitive compound which could not be fully identified. However, analysis of the IR spectrum showed a peak at 1806 cm^{-1}, which is characteristic to a *bis*-chlorinated cyclobutanone.[140] This compound was treated with *O*-mesitylenesulfonylhydroxylamine (MSH),[140] in the aim of forming the corresponding amide **402** by Beckmann rearrangement pathway. The resulting compound was also very sensitive and again could not be fully identified. In the same manner, analysis of the IR spectrum showed a peak at 1735 cm^{-1}, characteristic to a *bis*-chlorinated 5 membered lactam. However, attempt to the dechlorination of **402** failed to produce the desired tricyclic compound **403**.



Scheme 2.64: Conditions: a) MeI, NaH, THF, 93%; b) Cl_3COCl, Zn-Cu couple, Et_2O, used crude; c) MSH, CH_2Cl_2, used crude; d) Zn-Cu couple, NH_4Cl, MeOH, rt, 3 h (decomp).

Following these somewhat promising results, we turned to the dechlorination of **401** (**Scheme 2.65**, **Table 2.7**). Unfortunately, attempts to perform this reaction proved unsuccessful, both when using Zn-Cu couple (Entry 1),[140] or zinc dust (Entry 2).[141] Treatment of **401** with Bu_3SnH in toluene also proved unsuccessful (Entry 3) and only led to the decomposition of the starting material.[142] As a consequence of these negative results, the cycloaddition strategy with dichloroketenes was terminated. The major drawback of this technique was the poor stability of the chlorinated products, thus it was necessary to use the crude product directly in the following steps. Not being able to determine which reaction failed within a 3-step sequence was obviously undesirable.



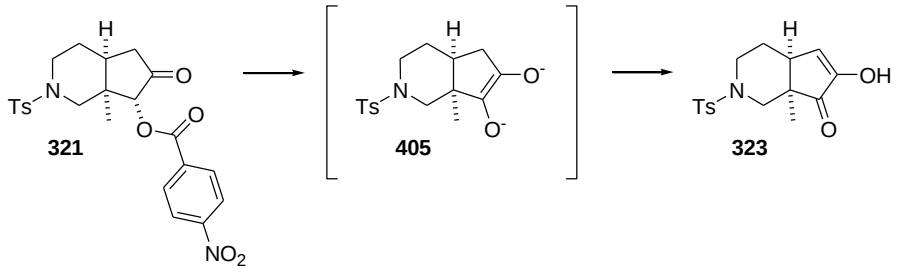
Scheme 2.65: Conditions: see **Table 2.7**.

Entry	Conditions (eq.)	Solvent	T	Time	Results
1	Zn-Cu (2.1), NH_4Cl (sat)	MeOH	rt	5 h	Decomp.
2	Zn dust (4)	AcOH	rt	3 h	Decomp.
3	Bu_3SnH (2.2), AIBN (0.1)	Toluene	rt	24 h	Decomp.

Table 2.7: Dechlorination.

2.2.12 Formation of the desired α-amidoketone

At this stage, our attention returned to a by-product discussed earlier in this chapter. We first observed the formation of by-product **323**, when treating ester **321** with base (**Scheme 2.66** and refer to **Scheme 2.33**). Upon reviewing the literature, this type of transformation was also observed by Magnus and co-workers.[143] The authors suggested that an oxidation mechanism - involving the oxygen of the air - *via* an intermediate such as **148** is possible. To confirm the structure of **323** an X-ray crystal analysis was obtained (**Figure 2.4** and **Appendix 2**).



Scheme 2.66: Formation of **323**. Conditions: $NaOH_{aq}$, MeCN, rt, 16 h, 45%

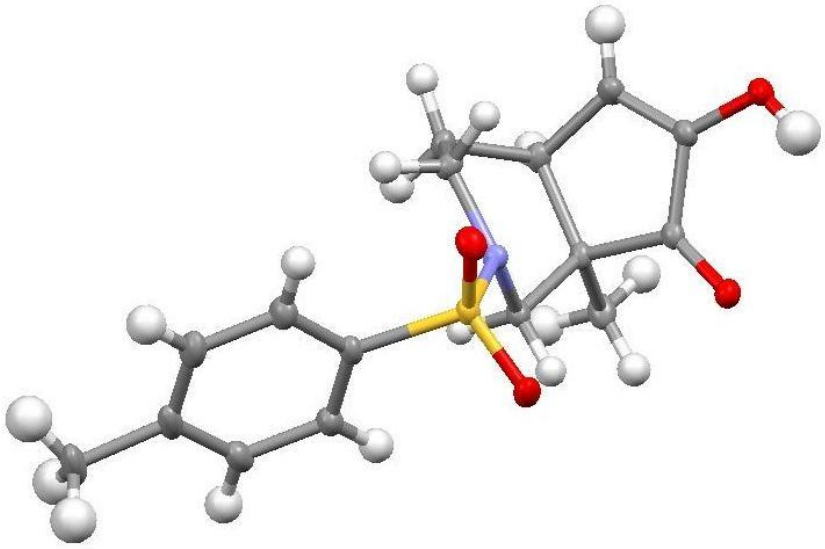
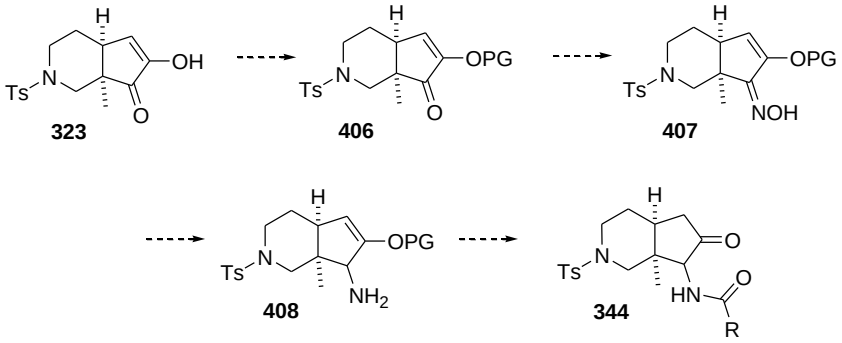


Figure 2.4: X-ray of **323** (see **Appendix 2**)

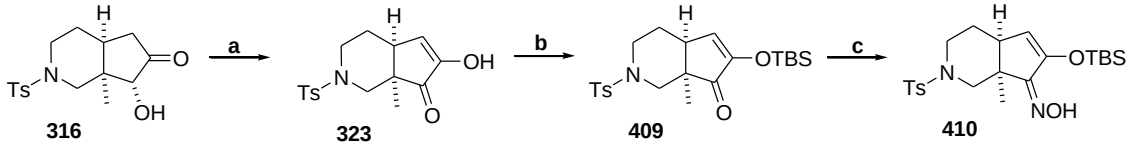
Whilst we were surprised the compound **323** was obtained, we decided to explore the possibility of making use of this intermediate in our synthesis. Consequently, our attention turned to the strategy depicted in **Scheme 2.67**. Starting from **323**, protection of the hydroxyl group would be followed by the transformation of the ketone functionality into an oxime, delivering compound **407**. Subsequent reduction of the oxime would afford the

amine **408** and we were aware of the possibility of a facial bias, leading to either the *cis* or *trans* product. A further reaction with a corresponding acid chloride would form the desired amide **344**.



Scheme 2.67: Final strategy to form the α-amidoketone **344**.

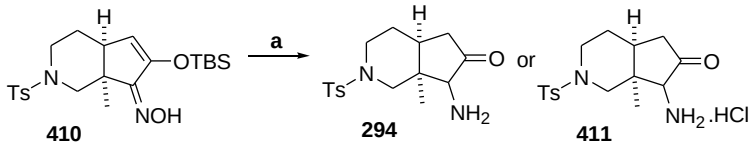
Our first goal was to prepare **323** in a higher yield (**Scheme 2.68**). This task was achieved by the use of DMP to oxidise hydroxyl ketone **316** and provided the enol form of the diketone (**323**) in excellent 99% yield.[42,144] Subsequent protection of the hydroxyl group was followed by the preparation of oxime **410**.[145] The reaction time of this transformation was long (7 days at 40 °C), and attempts to increase the reaction rate *via* a temperature increase resulted in a lower yield being obtained. Optimal yields were obtained when 2 equivalents of hydroxylamine hydrochloride were added every 24 h for a period of seven days.



Scheme 2.68: Successful preparation of oxime **410**. Conditions: a) DMP, CH_2Cl_2, rt, 2 h, 99%; b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 17 h, 78%; c) $NH_2OH.HCl$, pyr, 40 °C, 7 days, 72%.

Following the synthesis of the oxime **410** in good yield, attention was then focused on the reduction of **410** to give the amine **294** (**Scheme 2.69**). This step proved to be difficult, and deployment of standard conditions failed (**Table 2.8**). Indeed, attempts to reduce the oxime functionality with LAH in diethyl ether (Entry 1) resulted in decomposition of the starting material,[146] and the same result was obtained when treating **410** with ammonium acetate or ammonium formate and zinc (Entries 2 and 3).[147-148] Optimal conditions were

finally realised when using hydrogen gas and Pd/C, with hydrochloric acid, to trap the free amine **294** as its salt (Entry 4).[149] Salt **411** was used in further steps as the crude product. Although a single isomer was formed, it is important to note that the configuration at this newly formed stereocentre was not determined at this point.



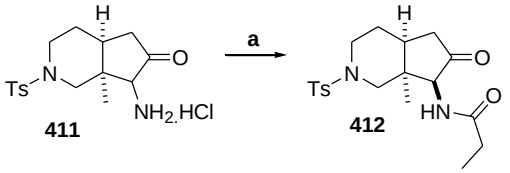
Scheme 2.69: Conditions: a) Pd/C, HCl, H_2 (1 atm), rt, 3 h, used crude (and see **Table 2.8**).

Entry	Conditions (eq)	Solvent	T	Time	Results
1	LAH (2)	Et_2O	reflux	5 h	Decomp.
2	$CH_3CO_2NH_4$ (1.7), Zn (4.5)	EtOH/H_2O/ NH_3(aq)	80 °C	20 h	Decomp.
3	HCO_2NH_4 (3), Zn dust (2)	MeOH	reflux	5 h	No reaction
4[b]	Pd/C, H_2, HCl(aq)	EtOH	0 °C	2 h	**411**

[b] The corresponding hydrochloride salt was obtained.

Table 2.8: Reduction of **410**.

With **411** in hand, subsequent treatment of this compound with propionyl chloride and NMM provided the corresponding crystalline amide **157** as a single isomer as depicted **Scheme 2.70**. The simple commercially available acyl chloride was used as a proof of concept for the preparation of the amide functionality. Regarding the configuration of **157**, submission of the crystalline compound to X-ray studies showed that it had the undesired *trans* configuration (**Figure 2.5** and **Appendix 3**).



Scheme 2.70: Conditions: a) NMM, propionyl chloride, THF, 0 ºC to rt, 24 h, 50% over 2 steps.

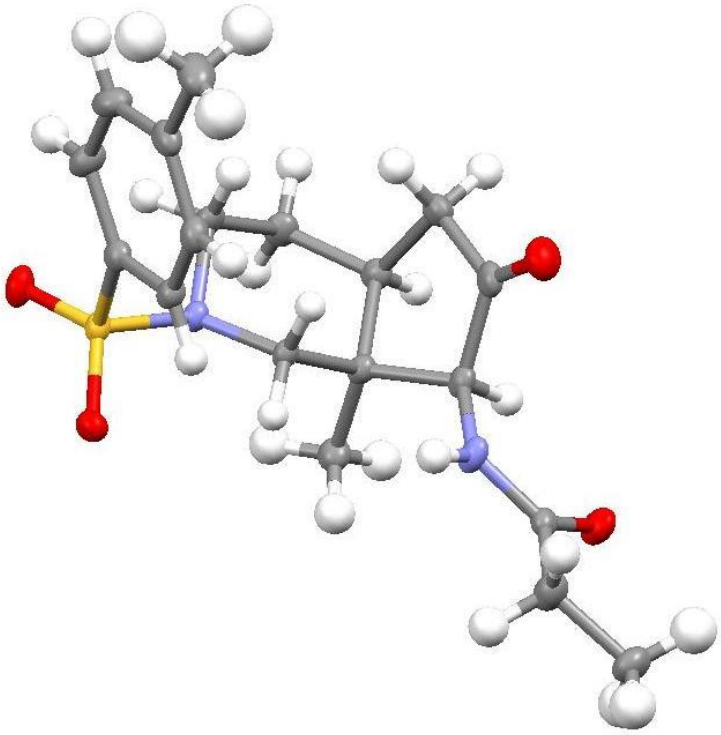
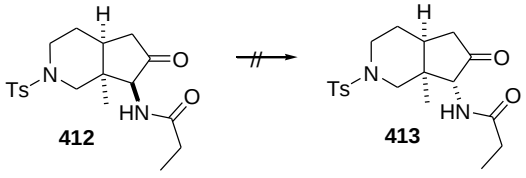


Figure 2.5: X-Ray of ketoamide **412** (see **Appendix 3**).

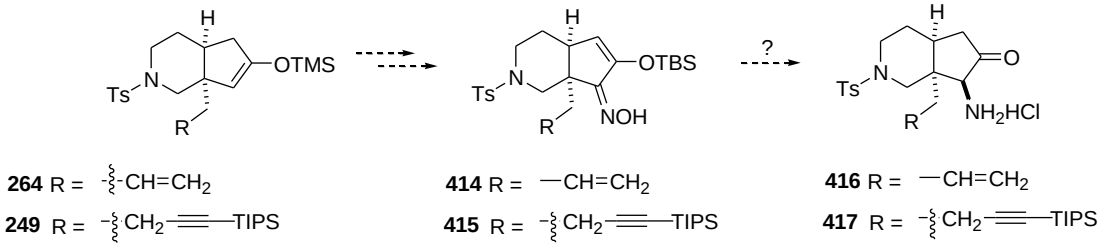
Considering all of our synthetic efforts it was very encouraging to have finally installed the desired amide functionality present in compound **157**. Although the configuration was the undesired (*trans*), we envisaged that an epimerisation reaction would address this issue (**Scheme 2.71**). Unfortunately, initial attempts to effect epimerisation were unsuccessful and we were unable to optimise the conditions due to time considerations.



Scheme 2.71: Epimerisation. Conditions: DBU, toluene, 0 ºC to rt, 16 h (no reaction).

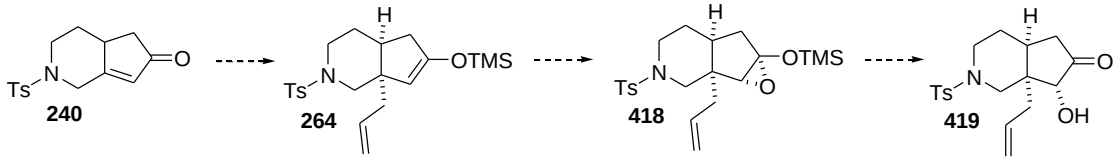
2.2.13 Ongoing work

Following the realisation of a strategy for the introduction of the amide functionality, the next step in our sequence required introduction of the correct side chain between the A and B ring (**Scheme 2.72**). Unfortunately, our strategy of reducing the oxime **410** to form the amide **411** involved hydrogenation with Pd/C. Of course, it is unlikely that such conditions would be compatible with a substrate, containing an alkyne or alkene.[84]



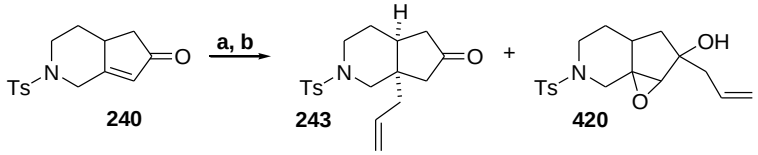
Scheme 2.72: Compatibility.

In this regard, it would be necessary to find a milder method to reduce the oxime functionality. In a preliminary experiment, commercially available allyl magnesium bromide was used for the 1,4-addition onto the enone **240** (**Scheme 2.73**). From there, a similar pathway would lead us to the preparation of hydroxyketone **419**.



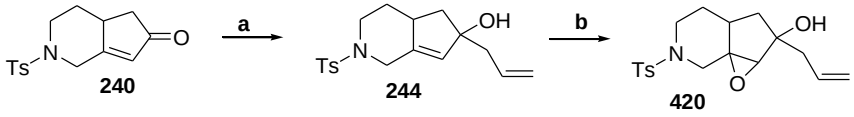
Scheme 2.73: Rubottom oxidation

Unfortunately this sequence was not successful, and two by-products were obtained instead of the required hydroxyketone **419**. After reactions with allyl magnesium bromide and DMDO, ketone **243** and epoxide **420** were isolated, respectively in 52% and 23% as depicted **Scheme 2.74**.



Scheme 2.74: By-products of the Rubottom oxidation. Conditions: a) allylMgBr, CuI, TMSCl, THF, used crude; b) DMDO, CH_2Cl_2, (2 by-products **243** (52%) and **420** (23%)).

While the formation of **243** was clearly the product of the conjugated addition followed by hydrolysis of the TMS enol ether, we believed **420** was obtained by a 1,2-addition of the allyl magnesium bromide to the enone **6**, followed by the epoxidation of the endo cyclic alkene with DMDO, as shown in **Scheme 2.75**. At this point, no further practical experiments were carried out on this part of the molecule.

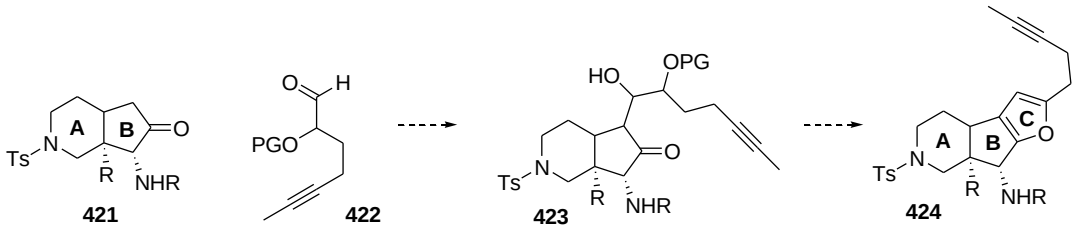


Scheme 2.75: Formation of **420**. Conditions: a) allylMgBr, CuI, TMSCl, THF, used crude; b) DMDO, CH_2Cl_2, 23%.

2.3 Construction of the furan ring

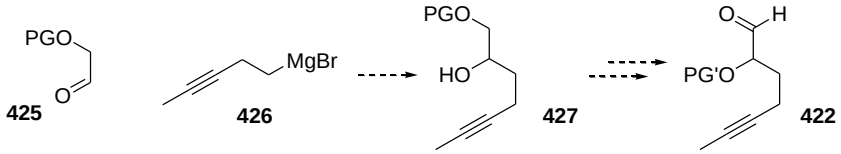
2.3.1 Initial strategy and model system

In order to explore the formation of additional ring system within nakadomarin A, our attention focused on the construction of the furan ring (ring C). This work was performed in parallel with the research on the AB system as previously discussed. According to our proposed synthesis, the furan could be installed *via* an aldol condensation between aldehyde **422** and α-amino ketone **421** to form the resulting hydroxyketone **423** (**Scheme 2.76**).[150] Subsequent removal of the protecting group (PG) would allow the formation of the furan ring, and provide tricyclic system **424**.[151]



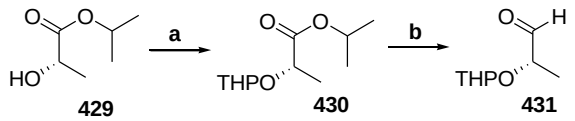
Scheme 2.76: Strategy to install the furan ring.

The aldehyde **422**, required for the aldol reaction could be obtained by a Grignard reaction between aldehyde **425** and alkyne **426** to form **427** (**Scheme 2.77**). Protecting group manipulation would be followed by oxidation to form the desired aldehyde **422**.



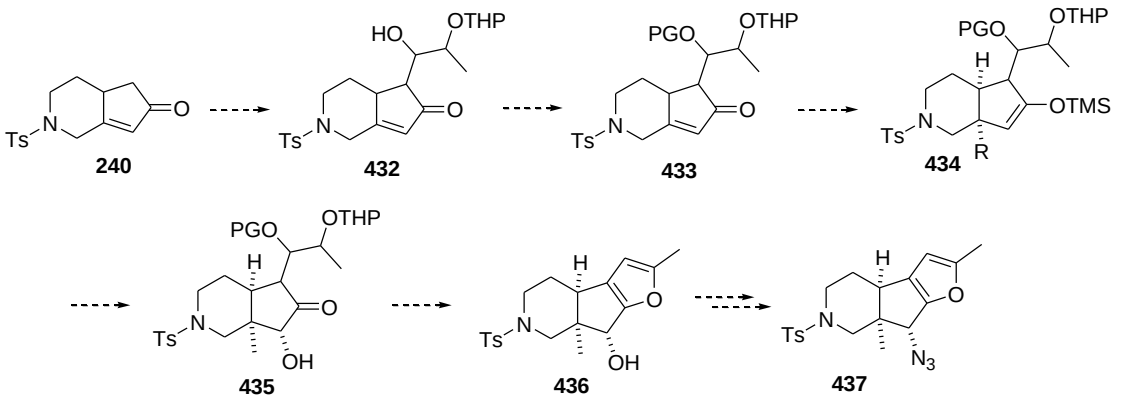
Scheme 2.77: Strategy to form aldehyde **422**.

We initially focused on a model system to validate this approach strategy. Thus, aldehyde **431** was prepared in two steps from commercially available L-*iso*propyl lactate **429** following literature procedures (**Scheme 2.78**).[152] First, L-*iso*propyl lactate **429** was protected with a THP group, in near quantitative yield. Subsequent reduction with DIBAL-H provided the desired aldehyde **431** in 63% yield. The main advantages of working with this model system were the low cost of the starting material and the easy scale-up.



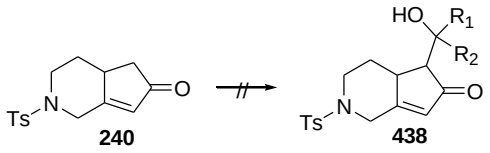
Scheme 2.78: Aldehyde **431**. Conditions: 3,4-dihydro-2*H*-pyran, PPTS, CH_2Cl_2, 98%; b) DIBAL-H, CH_2Cl_2, 63%.

It was possible to attempt the aldol condensation of aldehyde **431** and the subsequent cyclisation reaction. Because the α-amino ketone **421** had not been prepared at this point, it was thought that the enone **240** could be used as a starting substrate (**Scheme 2.79**). The aldol reaction to introduce the oxygenated side chain would be followed by the protection of the free hydroxyl group in hydroxyketone **432** to provide the enone **433**. Subsequent 1,4 addition and treatment with TMSCl should lead to compound **434**. After the Rubottom oxidation and the formation of the corresponding α-hydroxy ketone **435**, subsequent deprotection and cyclisation would provide tricyclic compound **436**. We were hoping that at this stage the formation of the corresponding azide **437** would be more facile because there would be activation of the leaving group from the adjacent furan ring.



Scheme 2.79: Strategy to install the furan ring.

The enone **6** proved to be unreactive towards an aldol reaction, and products of type **184** were never obtained (**Scheme 2.80**). Numerous conditions were explored using various electrophiles (**Table 2.9**) such as **174** (Entries 1-3), acetone (Entry 4),[153] or 3-methylbutanal (Entry 5). Bases were also screened, with the use of LDA (Entries 1, 4 and 5),[154] NaHMDS (Entry 2) or LiHMDS (Entry 3),[155] all proving to be unsuccessful in providing **184**.



Scheme 2.80: Attempts on the aldol reaction. Conditions: see **Table 2.9**.

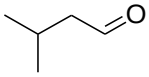
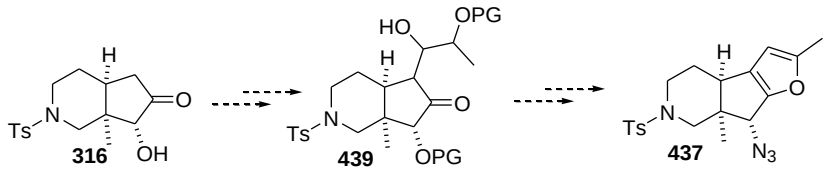
Entry	Carbonyl (eq.)	Eq. $ZnCl_2$	Base (eq.)	T	Results
1	**431** (2)	2.3	LDA (1.6)	−78 °C to 0 °C to rt	No reaction + decomp.
2	**431** (4)	6	NaHMDS (4)	−65 °C to 0 °C to rt	No reaction
3	**431** (4)	6	LiHMDS (4)	−65 °C to 0 °C	No reaction
4	Acetone (1.4)	1.5	LDA (1.2)	−50 °C to 0 °C to rt	No reaction
5	 (1.4)	1.5	LDA (1.2)	−50 °C to 0 °C to rt	No reaction

Table 2.9: Aldol reaction.

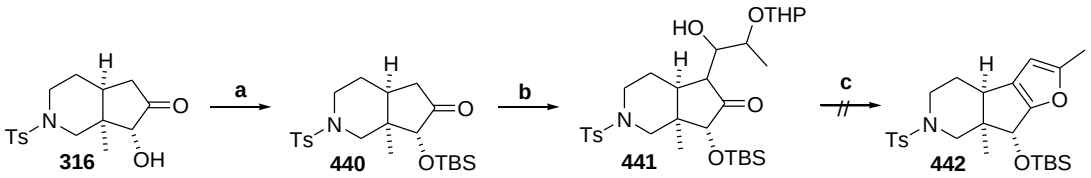
2.3.2 Aldol reaction of the hydroxyketone

Undaunted by these results, our attention focused on the use an alternative substrate in the aldol reaction. After synthesis of the hydroxyketone **316**, a new strategy was considered (**Scheme 2.81**). Starting from **316**, protection of the hydroxyl group could be followed by the aldol reaction to form **439**, which would subsequently provide azide **437** in a few steps.



Scheme 2.81: Tactic starting from the hydroxyketone **316**.

The sequence started with TBS protection of the α-hydroxy ketone **316**, to give the ketone **440** in 87% yield (**Scheme 2.82**). Following this, we were pleased to discover that the subsequent aldol reaction provided compound **441**. However, several diastereoisomers of **441** were formed, making NMR interpretation difficult. Moreover, deprotection and cyclisation with the aim of preparing **442**, did not work as expected (**Table 2.10**). In fact, treatment of **441** with *p*TSA, in THF/H_2O at 70 ºC resulted in no reaction (Entry 1),[150] and the use of a combination of acetic acid and *p*TSA at rt for 16 h did not change the outcome (Entry 2). The same result was obtained when reacting **441** with acetic acid for 5 h at 70 ºC (Entry 3), but increasing the reaction time to 36 h decomposed the product (Entry 4). Using methanol as the solvent, with *p*TSA also resulted in decomposition of the starting material (Entry 5).

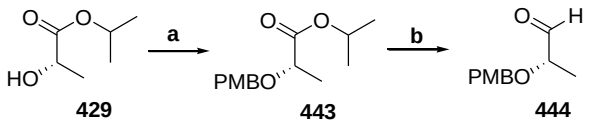


Scheme 2.82: Attempts to form **442**. Conditions: a) TBSCl, imid., DMF, 87%; b) aldehyde **431**, LDA, $ZnCl_2$, THF, −78 °C, 67%; c) acid, solvent (see **Table 2.10**).

Entry	Acid (eq.)	Solvent	T	Time	Results
1	*p*TSA (0.1)	THF/H_2O	70 °C	2 h	No reaction
2	*p*TSA (0.1)	AcOH/THF/H_2O	rt	16 h	No reaction
3	AcOH (solv)	THF/H_2O	70 °C	5 h	No reaction
4	AcOH (solv)	THF/H_2O	70 °C	36 h	Decomp.
5	*p*TSA (0.1)	MeOH	rt	1 h	Decomp.

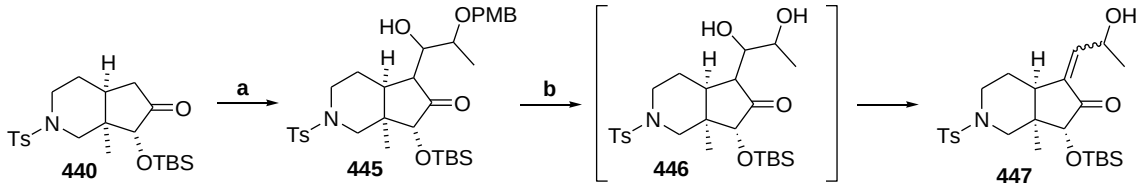
Table 2.10: Closure of the furan ring.

To overcome this deprotection issue, we decided to switch protecting groups and use the PMB-protected analogue of **431**. This new protecting group was expected to have two major advantages: firstly NMR interpretation would be easier (fewer isomers), and secondly deprotection and cyclisation would occur in a stepwise fashion under acidic conditions. Thus, the aldehyde precursor **444** was prepared from commercially available L-*iso*propyl lactate, in two steps (**Scheme 2.83**). Protection of the hydroxyl group in **429** was followed by reduction with DIBAL-H and affored the desired aldehyde **444.**



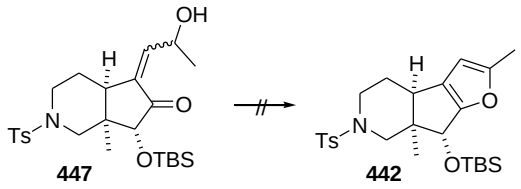
Scheme 2.83. Preparation of aldehyde **446**. Conditions: a) PMBCl, NaH, Bu_4NI, DMF, 0 °C to rt, 48%; b) DIBAL-H, DCM, −78 °C, 77%.

With the aldehyde **444** in hand, the aldol condensation with **440** was performed providing the product **445** in a 65% yield (**Scheme 2.84**). Subsequent deprotection using ceric ammonium nitrate (CAN), in aqueous acetonitrile, provided the desired enone **447** in 75% yield.[156] This compound, obtained as a mixture of isomers, was the result of PMB deprotection and dehydration of the adjacent alcohol of compound **446**. This dehydratation reaction was not regarded as a problem, as the dehydration product is an intermediate expected on the pathway towards formation of the furan.



Scheme 2.84: Aldol condensation. Conditions: a) **444**, LDA, $ZnCl_2$, THF, −78 °C, 65%; b) CAN, H_2O, MeCN, rt, 75%.

Following successful implementation of the aldol reaction, the next step was cyclisation to form the furan (**Scheme 2.85**). From enone **447**, several sets of acidic conditions were investigated (**Table 2.11**). The use of *p*TSA in THF proved to be unsuccessful, resulting in the recovery of the starting material only (Entry 1). When acetic acid was employed (Entry 2), the same outcome was observed and cyclisation did not occur. Upon switching solvent to dichloromethane, *p*TSA did not react (Entry 3).[157] However, by increasing the acidity and using sulfuric acid in dichloromethane (Entry 4), the unexpected by-product **448** was obtained (**Figure 2.6**). Treatment of **447** with acetic acid and hydrochloric acid in methanol at rt resulted in no reaction (Entry 5), and increasing the reaction temperature to 50 °C resulted in the formation of the by-product **449** (Entry 6) (**Figure 2.6**).



Scheme 2.85: Efforts to close the furan ring.

Entry	Acid (eq.)	Solvent	T	Time	Results
1	*p*TSA (0.1)	H_2O/THF	rt	24 h	No reaction
2	*p*TSA (0.1)	H_2O/THF/AcOH	70 °C	24 h	No reaction
3	*p*TSA (0.1)	CH_2Cl_2	rt	16 h	No reaction
4	HCl (0.5) + H_2SO_4 (0.5)	CH_2Cl_2	70 °C	3 h	By-product **448** (58%)
5	HCl (0.5)	MeOH/AcOH	rt,	3 h	No reaction
6	HCl (0.5)	MeOH/AcOH	50 °C	2 h	By-product **448** (68%)

Table 2.11: Conditions tried to form the furan ring.

The two by-products — **448** and **449 —** were obtained in good yield and their structures were deduced by extensive analysis. The by-products were unexpected but mechanisms could be proposed for their formation (**Scheme 2.86**). Removal of the TBS group in **447** could lead to **450.** Subsequent keto-enolic equilibrium in **450** could lead to the formation of **451**. From there, protonation of the hydroxyl group and dehydration would form enol **453**, which would rearrange to compound enone **454**. The ketone **448** or **449** would then be obtained by alkene migration. To the best of our knowledge this kind of reaction is without literature precedent.

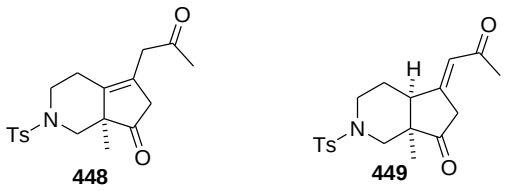
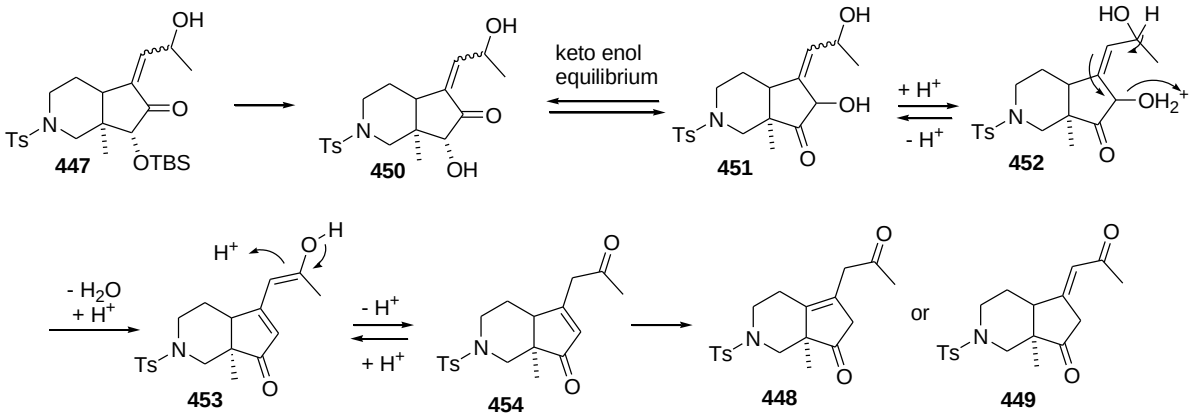
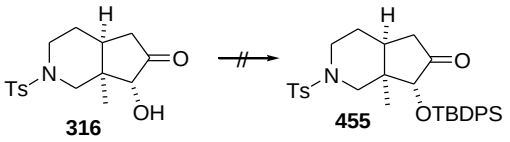


Figure 2.6: By-products.



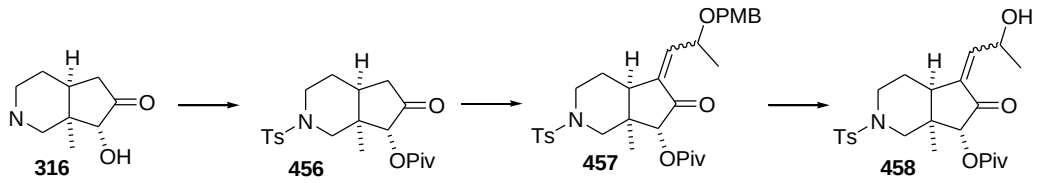
Scheme 2.86: Proposed Mechanism.

In the mechanism above, the starting point is the loss of the TBS group. Thus, our attention focused on the use of a protecting group which would be less sensitive to acidic conditions. First, the use of TBDPS group was examined, but reaction between **316** and TBDPSCl in DMF at rt for 70 h failed to provide the desired product **455**; only starting material was recovered from this reaction (**Scheme 2.87**). Different conditions — adding DMAP to promote the reaction, or heating to 60 °C — did not change the outcome.



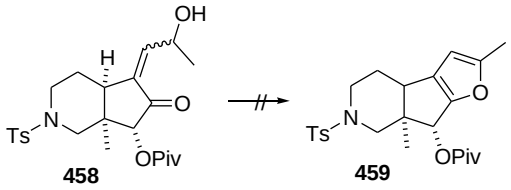
Scheme 2.87: Use of TBDPS as a protecting group. Conditions: TBDPSCl, imid, DMF, rt for 70 h or 60 °C for 6h. No reaction.

Despite the above, we decided to investigate the use of an alternative protecting group. The pivaloyl group seemed to be the group of choice as it is known to be fairly resistant to acid.[158] Protection of the hydroxyketone **316** with PivCl was achieved in a near quantitative yield (**Scheme 2.88**). Subsequent aldol reaction between **456** and aldehyde **444** provided the desired compound **457**, in 74% yield. Subsequent removal of the PMB group was achieved in a 71% yield, using ceric ammonium nitrate, forming the allylic alcohol **458**.



Scheme 2.88: Formation of **458**. Conditions: PivCl, pyr., rt to 40 ºC, 99%; b) aldehyde **444**, LDA, $ZnCl_2$, THF, −78 ºC, 74%; c) CAN, H_2O, MeCN, 71%.

Satisfactory removal of the PMB group meant a range of acidic conditions could be used to promote the formation of the furan ring (**Scheme 2.89, Table 2.12**). Following Mukai's conditions, [31] treatment of **458** with CSA in toluene at reflux failed to deliver the desired product and only provided the same by-product **448** obtained previously (Entry 1). Decreasing the temperature to 70 ºC led to the recovery of the starting material without product formation (Entry 2), and the same outcome was obtained when employing acetic acid (Entry 3). Finally, treatment of **458** with hydrochloric acid also provided by-product **449** (Entry 4).



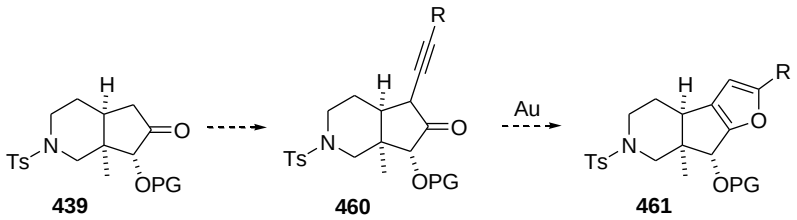
Scheme 2.89: Towards **459**.

Entry	Acid (eq.)	Solvent	T	time	results
1	CSA (2)	toluene	110 ºC	4 h	**448** (51%)
2	CSA (2)	toluene	70 ºC	16 h	No reaction
3	AcOH (0.1)	H_2O/THF	85 ºC	3 h	No reaction
4	HCl(aq) (0.1)	H_2O/THF	85 ºC	1h	**449** (54%)

Table 2.12: Towards **459.**

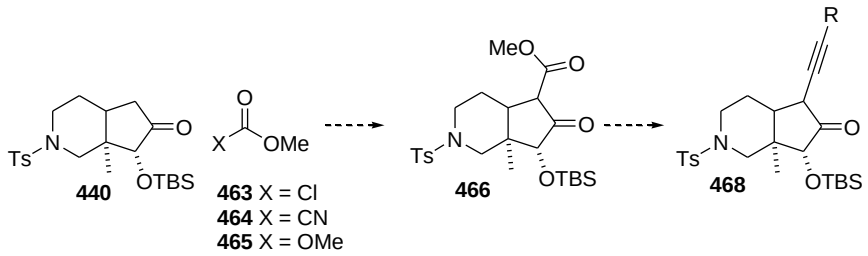
2.3.3 An alkyne as the precursor for the furan ring

It was at this juncture that Mukai and co-workers published their work on nakadomarin A (see section 1.2.5, Chapter 1). Their strategy was similar to ours with regards to the formation of the furan ring. Consequently, in order to deviate from their pathway, another route was proposed (**Scheme 2.90**). Starting from α-hydroxy ketone **439** our goal was to prepare alkyne **460**. Subsequent furan closure would be performed using a gold catalysed reaction to provide the tricyclic system **461**.[159]



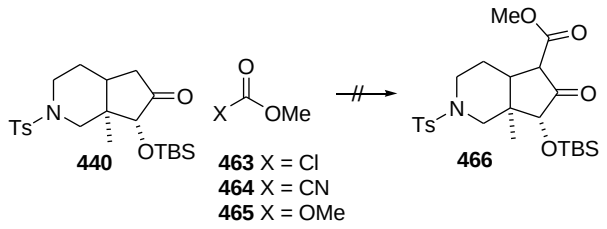
Scheme 2.90: New route.

Thus, our first aim was to install the alkyne functionality. The initial strategy we investigated involved the formation of keto ester **466**, as a precursor of alkyne **468** (**Scheme 2.91**).



Scheme 2.91: Proposed route to form the alkyne **468**.

Various sets of reagents and conditions were investigated in order to prepare keto-ester **466** from hydroxyketone **440** (**Scheme 2.92**). Regrettably, despite the use of reagents, such as methylchloroformate **463** (Entry 1), methylcyanoformate **464** (Entries 2-4),[136] or dimethyl carbonate **465** (Entry 5), no reaction occurred and the desired ß-keto ester **466** was not obtained (**Table 2.13**).[160]

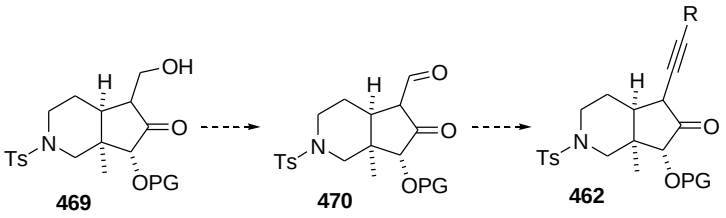


Scheme 2.92: Attempts to prepare the ß-keto ester **466**. Conditions: ester, base, solvent (see **Table 2.13**)

Entry	Ester	Base	Solvent	T	Time	Results
1	**463**	LDA	THF	−78 °C to −30 °C	3 h	No reaction
2	**464**	LDA	THF	−78 °C to −30°C	3 h	No reaction
3	**464**	LDA/HMPA	THF	−78 °C to rt	3 h	No reaction
4	**464**	LDA/$ZnCl_2$	THF	−78 °C to rt	3 h	No reaction
5	**465**	NaH	MeOH	reflux	4 h	No reaction

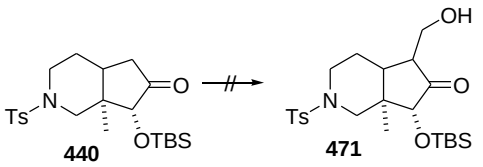
Table 2.13: Attempts to prepare ß-keto ester **466**.

Despite the failure above, attention turned to the discovery of an alternative pathway to prepare alkyne **462**. In this second approach, the aim was to prepare alkyne **462** from aldehyde **470** by a Corey Fuchs or Ohira Bestmann reaction (**Scheme 2.93**). Ultimately, alcohol **469** would be our required starting material.



Scheme 2.93: Corey Fuchs/Ohira Bestmann approach.

In order to prepare **471** the first route we envisaged was the direct introduction of the hydroxy group (**Scheme 2.94, Table 2.14**). To install this functionality, our attention focused on the use of paraformaldehyde and proline. Several solvents and temperatures were screened, such as water at rt or 70 ºC (Entries 1 and 4), water/methanol at 50 ºC (Entry 2), or DMSO at 70 ºC (Entry 3). However, all these protocols led only to the recovery of the starting material.[161-162]

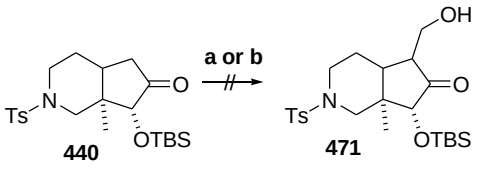


Scheme 2.94: Towards **471**. Conditions: $OH(CH_2O)_nH$, L-proline , solvent (see **Table 2.14**).

Entry	Solvent	T	Time	Results
1	H_2O	rt	1 h,	No reaction
2	H_2O/MeOH	50 ºC	5 h	No reaction
3	H_2O	100 ºC	5 h	No reaction
4	DMSO	70ºC	20 h	No reaction

Table 2.14: Conditions tested to form **471**.

In addition to the above reactions, another set of conditions were tried to form the hydroxyketone **471**, using hydroxymethylphtalimide (**Scheme 2.95**), but still no reaction occurred.[161]

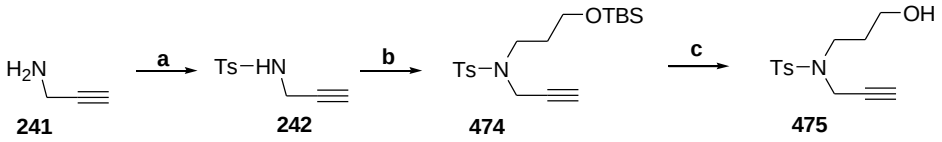


Scheme 2.95: Condition: a) hydroxymethylphtalimide, LDA, THF, −78 °C to rt, 3 h (no reaction); b) hydroxymethylphtalimide, 2,2,6,6-tetramethylpiperidine, THF, −78 °C to rt, 3 h (no reaction).

Dismayed by the outcome of the reactions described above, introduction of the required substituent in the original Pauson-Khand reaction (as used previously) was considered. The bicyclic ketone **473** would be prepared from enyne **472**, which itself would come from propargylamine **241** (**Scheme 2.96)**.

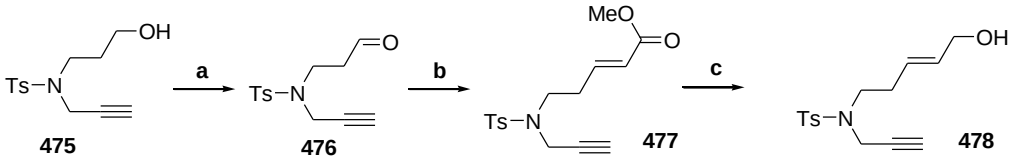
Scheme 2.96: Pathway to form **473**.

The new Pauson-Khand sequence commenced with propargylamine **241** being treated with tosyl chloride to afford tosylated derivative **242** (**Scheme 2.97**). Subsequent Mitsunobu reaction with the appropriate protected diol **476** to form **474** was followed by a removal of the TBS group to provide **475**.[163]



Scheme 2.97: Conditions: a) TsCl, pyr, 0 °C to rt, 16 h, 88%; b) DIAD, $HO(CH_2)_3OTBS$ **476**, PPh_3, THF, rt, 17 h, 96%; c) TBAF, THF, 0 °C to rt, 96%.

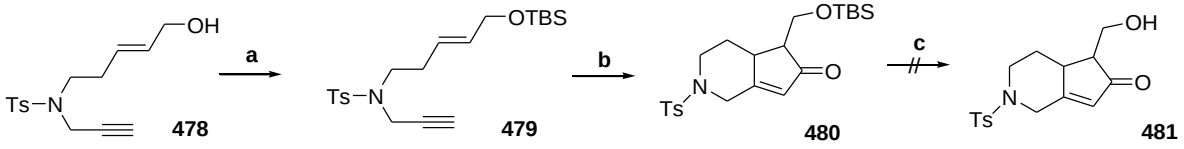
With the alcohol **475** in hand, the sequence continued with a Swern oxidation which provided aldehyde **476** in 88% yield. Subsequent Wittig reaction with the corresponding ylide [methyl (triphenylphosphoranylidene)acetate], provided the ester **477** in 89% yield (**Scheme 2.98**).[164] Finally, DIBAL-H reduction of the ester **477** delivered the desired alcohol **478** in 90% yield.



475 **476** **477** **478**

Scheme 2.98: Conditions: a) $(COCl)_2$, DMS, Et_3N, CH_2Cl_2, 88%; b) methyl (triphenylphosphoranylidene)acetate, CH_2Cl_2, rt, 17 h, 89%; c) DIBAL-H, CH_2Cl_2, –78 °C, 1 h, 90%.

With this material in hand, the protection of the hydroxyl group in **478** allowed the formation of the enyne **479**, precursor for the Pauson-Khand reaction (**Scheme 2.99**). When compound **479** was submitted to the set of Pauson-Khand reaction conditions used previously (catalytic amount of dicobalt octacarbonyl, 1 atm of CO, toluene), the product **480** was obtained in low yield (20%). However, treatment of **479** with a stoichiometric amount of the cobalt complex provided a much improved 78% yield.[165] It is worth noting that this reaction was difficult to scale up, as cobalt residues were not removed easily from the mixture. Unfortunately, subsequent removal of the TBS group in **480** failed to provide the hydroxyl ketone **481**, and instead resulted in decomposition of the starting material. It is most likely that the newly revealed hydroxyl group underwent elimination, allowing polymerisation of the molecule.

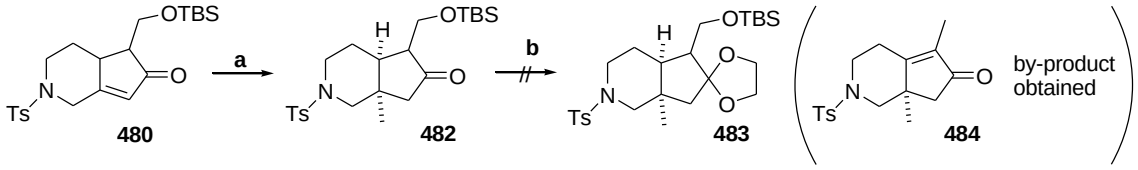


478 **479** **480** **481**

Scheme 2.99: Conditions: a) TBSCl, imid, CH_2Cl_2, rt, 17 h, 85%; b) $Co_2(CO)_8$, NMO, CH_2Cl_2, 78%; c) TBAF, THF, 0 °C, decomp.

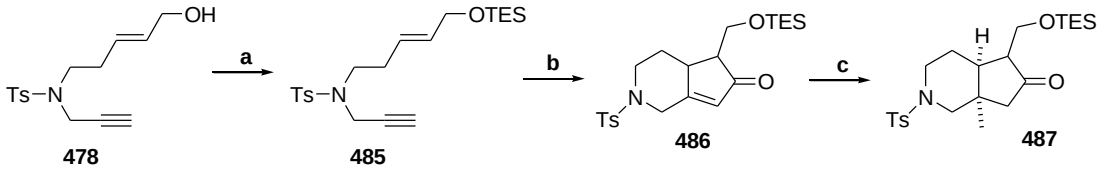
Thus, with the aim of avoiding the elimination of the hydroxyl group in **481**, we considered tuning the reactivity of the bicyclic core by masking the enone functionality, with the expectation that elimination would be less likely to occur (**Scheme 2.100**). Accordingly, enone **480** was submitted to 1,4-cuprate addition to form the ketone **482** in 53% yield.

Unfortunately, subsequent treatment of **482** with ethylene glycol and *p*TSA, in toluene, at reflux resulted in the formation of the by-product **484** through elimination and alkene isomerisation.



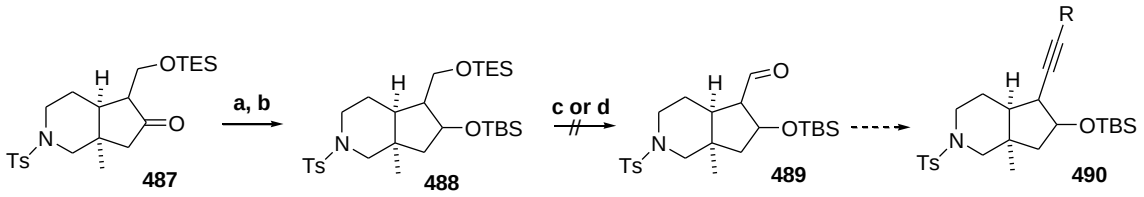
Scheme 2.100: Toward **483**. Conditions: a) MeMgBr, CuI, THF, rt, 1 h, 53%; b) ethylene glycol, *p*TSA, toluene, reflux, 6 h, Dean-Stark apparatus, 100% of **484**.

Alternatively, the same sequence could be performed replacing the TBS with a TES group (**Scheme 2.101**). Treatment of **478** with TESCl to provide **485** and this was followed by a Pauson-Khand reaction, forming **486** in a good overall yield. Compound **487** was the result of the subsequent 1,4-cuprate addition reaction using methyl magnesium bromide.



Scheme 2.101: Alternative protecting groups. Conditions: a) TESCl, imid., CH_2Cl_2, rt, 17 h, 100%; b) $Co_2(CO)_8$, NMO, CH_2Cl_2, 0 ºC, 64%; c) MeMgBr, CuI, THF, rt, 1 h, 64%.

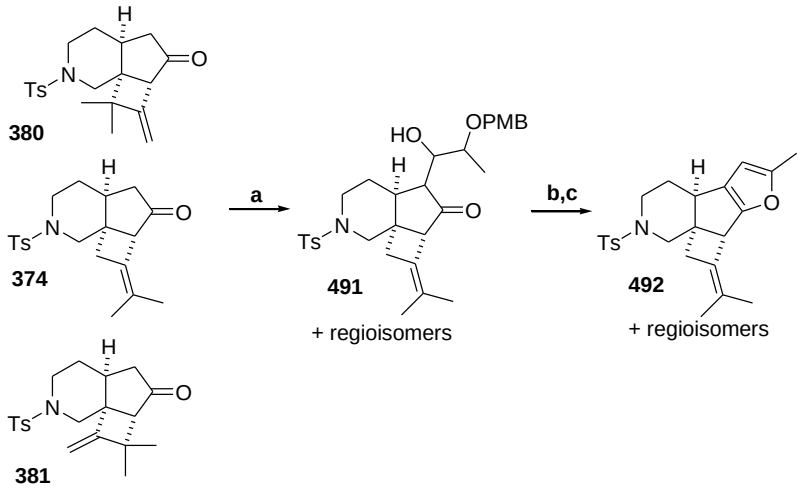
With bicyclic ketone **487** in hand, reduction of the ketone and TBS protection of the resulting alcohol provided compound **488** (**Scheme 2.102**). Unfortunately, the subsequent oxidation of the hydroxyl group under standard conditions (Swern or Dess Martin conditions) failed to deliver the desired aldehyde **489** and did not allow the formation of desired alkyne **490**. As a consequence this strategy was aborted in order to focus on another pathway.



Scheme 2.102: Attempts towards the formation of **490**. Conditions: a) $NaBH_4$, MeOH, 0 ºC, 1 h, 86%; b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 ºC to rt, 17 h, 100%; c) $(COCl)_2$, DMS, Et_3N, CH_2Cl_2, −78 ºC to rt, 4 h (decomp.); d) DMP, CH_2Cl_2, 0 ºC, 1 h (decomp.).

2.3.4 Photochemical Cycloaddition

Finally, our attention returned to the feasibility of our first aldol strategy using the mixture of compounds obtained from the cycloaddition reaction (**Scheme 2.103**). As previously described, regioisomers **374**, **380** and **381** were not separable. Aldol reaction of **374**, **380** and **381** provided **491** and was followed by removal of the PMB group. Finally, treatment of **491** with CSA in toluene at reflux provided a new compound again as a mixture of regioisomers. The products were not separable, however analysis of the ^1H NMR spectrum showed a peak at 5.76 ppm, characteristic of the C-H proton on the furan. Moreover, the IR spectrum showed the absence of the ketone and the mass spectrometry analysis was consistent with the formation of tetracyclic system **492**.

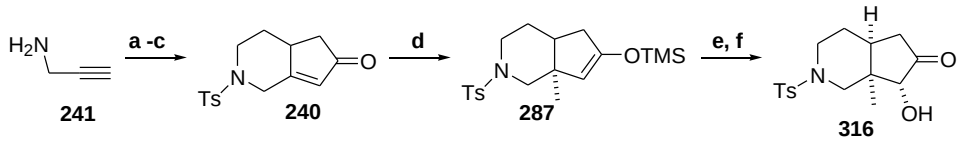


Scheme 2.103: Suspected formation of **492**. Conditions: a) **446**, LDA, $ZnCl_2$, THF, −78 ºC to rt, 18 h, 47%; b) CAN, $MeCN/H_2O$, rt, 3 h; c) CSA, toluene, reflux, 3 h.

2.4 Conclusions and outlook

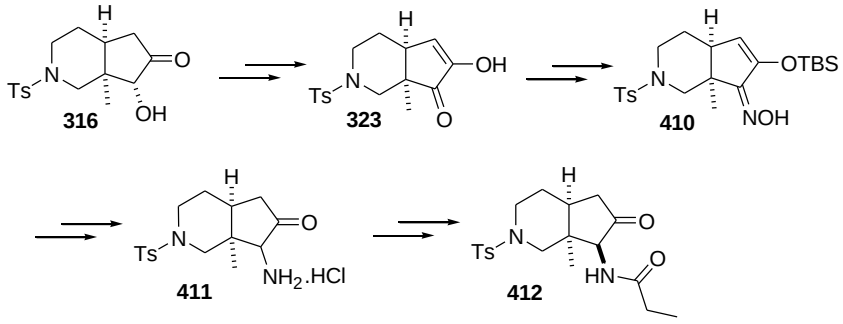
*2.4.1 Formation of aminoketone **316**.*

The AB core of nakadomarin A was formed through a Pauson-Khand reaction. Subsequent cuprate addition and Rubottom oxidation allowed us to functionalise the α-position of the ketone, with the formation of hydroxyketone **316** (**Scheme 2.104**).



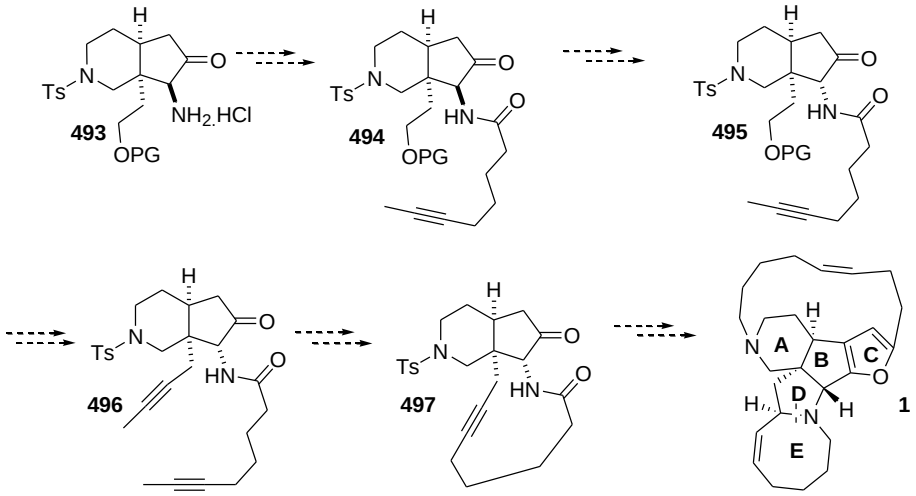
Scheme 2.104: Formation of hydroxyl ketone **316**.

We then demonstrated that it was possible to convert the hydroxyketone **316** into the oxidized product **323**. This compound was the starting point of a new synthetic pathway that was used to prepare **412** (**Scheme 2.105**). Following this method, we successfully installed the required nitrogen atom. In total, from the starting commercially available propargylamine **241**, 11 steps are required to prepare the amine.



Scheme 2.105: Formation of **412**.

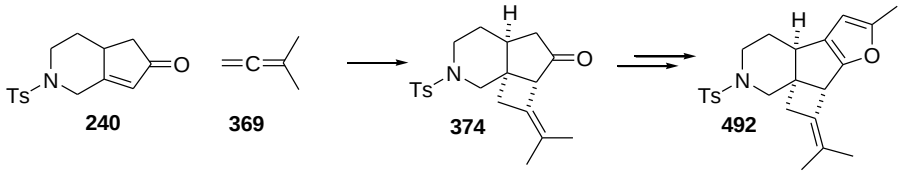
By applying this strategy to the fully functionalised precursor, we could expect to prepare amide **494**, (**Scheme 2.106**). Subsequent epimerisation and functionalisation would provide the diyne **496**, precursor for alkyne RCM. At this stage, the southern part of nakadomarin A (**1**) will be in place.



Scheme 2.106: Future work.

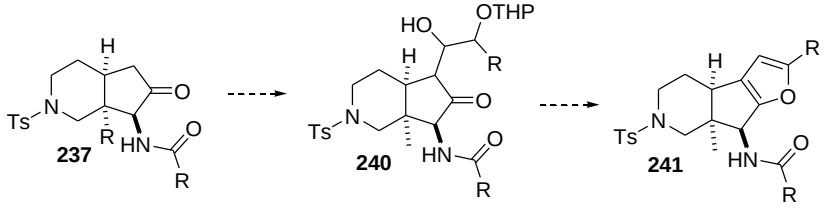
2.4.2 Formation of the furan ring

Regarding the northern part of the molecule, our strategy for the introduction of the furan used an aldol reaction as the key step. Even though furan **492** could not be isolated and fully characterised, the data collected were consistent with its formation.



Scheme 2.107: Furan formation.

By application of this strategy, amide **237** could be a potential starting point for furan formation (**Scheme 2.109**). Aldol reaction between **237** and a corresponding aldehyde would form **240** and subsequent removal of the THP group, followed by formation of the furan would deliver the desired amide **241**.



Scheme 2.108: Future work.

Experimental Section

General Reaction Conditions

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

Solvents and Reagents

Organic solvents were dried using a Pure Solv™ solvent purification system. Liquid reagents were distilled prior to use if needed.[166] 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, 60A) as solid support and HPLC-graded solvents as eluent. Petroleum ether used for column chromatography was 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 (anisaldehyde (15 g), EtOH (250 mL), concentrated H_2SO_4 (2.5 mL)).

Apparatus

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

^1H NMR spectra were recorded on a Bruker 400 MHz or 500 MHz spectrometer at ambient temperature. Data are reported as follows: chemical shift in ppm relative to $CDCl_3$ (7.27) 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 on a Bruker 400 MHz or 500 MHz Spectrospin spectrometer at 100 MHz or 126 MHz at ambient temperature and multiplicities were obtained using a DEPT sequence. Data are reported as follows: chemical shift in ppm relative to $CHCl_3$ (77.16) on the δ scale and assignment.

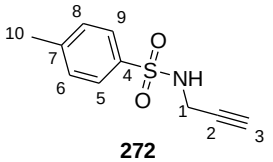
High resolution mass spectra (HRMS) were obtained under EI, FAB, CI and ES conditions by the analytical services of the University of Glasgow on a Jeol MStation JMS-700 instrument. Low resolution mass spectra (LRMS) were carried out on the same instrument; the intensity of each peak is quoted as a percentage of the largest, where this information was available.

Elemental analyses were carried out on an Exeter Analytical Elemental Analyser EA 440 by the analytical services of the University of Glasgow. Melting points were recorded with an Electrothermal IA 9100 apparatus.

Nomenclature

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

4-Methyl-*N*-(prop-2-ynyl) benzenesulfonamide 272:



272

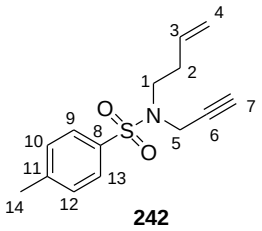
$C_{10}H_{11}NO_2S$

Molecular weight: 209.26 g.mol^{-1}

Pyridine (5.7 mL, 73 mmol) was added to a solution of *p*-toluenesulfonyl chloride (13.9 g, 73.0 mmol) in tetrahydrofuran (150 mL). The solution was cooled to 0 ºC and propargylamine (5.0 mL, 73 mmol) was added dropwise. The mixture was stirred for 16 h, before an aqueous solution of sodium hydroxide (0.25 L, 2.0 M) was added. The resulting solution was stirred for 2 h at rt and the phases were separated. The aqueous phase was then extracted with ethyl acetate (3 × 200 mL), and the combined organic phases were washed with brine (400 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 7:3) gave the title compound **272** (13.5 g, 64.5 mmol, 88%) as a colourless solid.

R_f: 0.48 (petroleum ether:ethyl acetate, 8:2); **m.p.:** 73—75 ºC (lit: 71—73 ºC); **IR:** ν_{max} 3263, 3032, 2862, 2121, 1597, 1435, 1319, 1149 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.77 (2H, d, *J* = 8.2 Hz, CH-C5, CH-C9), 7.31 (2H, d, *J* = 8.2 Hz, CH-C6, CH-C8), 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-C10), 2.10 (1H, t, *J* = 2.4 Hz, CH-C3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.9 (C-C7), 136.5 (C-C4), 129.8 (CH-C6, CH-C8), 127.4 (CH-C5, CH-C9), 77.9 (C-C2), 73.0 (CH-C3), 32.9 (CH_2-C1), 21.6 (CH_3-C10); **HRMS (CI, isobutane)** for $C_{10}H_{12}NO_2S$ ([M+H]$^+$) calculated: 210.0589, found 210.0587; **LRMS (CI, isobutane) *m/z* (intensity):** 210 (100), 113 (30), 97 (38), 71 (57); **Elemental analysis:** $C_{10}H_{11}NO_2S$ requires C: 57.41%, N: 6.70%, H: 5.26%, found C: 57.35%, N: 6.65%, H 5.27%. The data observed are in accordance with literature values.[167]

***N*-But-3-enyl-4-methyl-*N*-prop-2-ynyl-benzensulfonamide 242:**



242

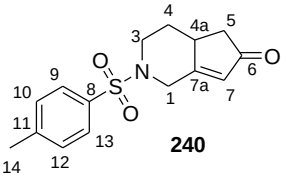
$C_{14}H_{17}NO_2S$

Molecular weight: 263.36 g.mol^{-1}

Potassium carbonate (11.1 g, 80.3 mmol) and 4-bromo-1-butene (8.1 mL, 80 mmol) were added to a solution of **272** (14.0 g, 66.9 mmol) in acetone (300 ml) and the mixture was heated to reflux for 17 h. The reaction mixture was then cooled to rt and concentrated *in vacuo*. Ethyl acetate (300 mL) and water (200 mL) were added and the phases were separated. The aqueous phase was extracted with ethyl acetate (2 × 300 ml), and the combined organic phases were washed with brine (300 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 8:1) provided the title compound **242** (16.1 g, 61.1 mmol, 91%) as a colourless oil.

R_f: 0.51 (petroleum ether:ethyl acetate, 6:1); **IR:** ν_{max} 3279, 3070, 2924, 2121, 1597, 1442, 1342, 1157 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.72 (2H, d, *J* = 8.2 Hz, CH-C9, CH-C13), 7.28 (2H, d, *J* = 8.2 Hz, CH-C10, CH-C12), 5.75 (1H, ddt, *J* = 17.3, 10.3, 7.0 Hz, CH-C3), 5.08 (1H, dd, *J* = 17.3, 1.2 Hz, CH_2-C4), 5.06 (1H, d, *J* = 10.3 Hz, CH_2-C4), 4.14 (2H, d, *J* = 2.2 Hz, CH_2-C5), 3.26 (2H, t, *J* = 7.2 Hz, CH_2-C1), 2.41 (3H, s, CH_3-C14), 2.33 (2H, dt, *J* = 7.2, 7.0 Hz, CH_2-C2), 2.02 (1H, t, *J* = 2.2 Hz, CH-C7); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 143.5 (C-C11), 135.9 (C-C8), 134.5 (CH-C3), 129.5 (CH-C10, CH-C12), 127.7 (CH-C9, CH-C13), 117.3 (CH_2-C4), 76.5 (C-C6), 73.8 (CH-C7), 45.7 (CH_2-C1), 36.4 (CH_2-C5), 32.2 (CH_2-C2), 21.6 (CH_3-C14); **HRMS (CI, isobutane)** for $C_{14}H_{18}NO_2S$ ($[M+H]^+$) calculated 264.1058, found 264.1054; **LRMS (CI, isobutane) *m/z* (intensity):** 264 (100), 222 (55), 157 (9), 110 (18); **Elemental analysis:** $C_{14}H_{17}NO_2S$ requires C: 63.85%, N: 5.32%, H 6.51%, found C: 63.64%, N: 5.27%, H: 6.65%. The data observed are in accordance with literature values.[89]

2-(Toluene-4-sulfonyl)-1,2,3,4a,5-hexahydro-[*2*]pyrindin-6-one 240:



240

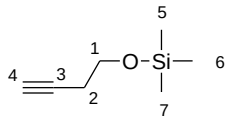
$C_{15}H_{17}NO_3S$

Molecular weight: 291.37 g.mol^{-1}

Tetramethylthiourea (2.1 g, 16 mmol) and dicobalt octacarbonyl (0.91 g, 2.7 mmol) were added to a flask, under argon atmosphere. This apparatus was evacuated and refilled with carbon monoxide (× 3), and toluene (400 ml) was added. A solution of **242** (7.0 g, 27 mmol) in toluene (100 mL) was added dropwise to the solution. The reaction mixture was stirred at 70 °C for 6 h, and then then solvent was removed *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 6:4) provided the product **240** (5.5 g, 19 mmol, 71%) as a pale yellow solid.

R_f: 0.18 (petroleum ether-ethyl acetate, 5:5); **m.p.** 124—126 °C (lit: 124—126 °C); **IR:** ν_{max} 1708, 1342, 1155 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.65 (2H, d, *J* = 8.0 Hz, CH-C9, CH-C13), 7.34 (2H, d, *J* = 8.0 Hz, CH-C10, CH-C12), 6.00 (1H, s, CH-C7), 4.72 (1H, d, *J* = 13.3 Hz, CH_2-C1), 3.94—3.97 (1H, m, CH_2-C3), 3.20 (1H, d, *J* = 13.3 Hz, CH_2-C1), 2.60—2.50 (3H, m, CH_2-C3, CH_2-C5, CH-C4a), 2.44 (3H, s, CH_3-C14), 2.13—2.10 (1H, m, CH_2-C4), 2.01 (1H, d, *J* = 16.2 Hz, CH_2-C5), 1.46 (1H, ddd, *J* = 12.4, 11.7, 3.6 Hz, CH_2-C4); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 207.2 (C-C6), 172.2 (C-C7a), 144.2 (C-C11), 133.0 (C-C8), 129.9 (CH-C10, CH-C12), 129.2 (CH-C9, CH-C13), 127.8 (CH-C7), 47.5 (CH_2-C1), 45.7 (CH_2-C3), 41.4 (CH_2-C5), 39.2 (CH-C4a), 32.1 (CH_2-C4), 21.6 (CH_3-C14); **HRMS (EI)** for $C_{15}H_{17}NO_3S$ ($[M]^+$) calculated 291.0929, found 291.0932; **LRMS (EI) *m/z* (intensity):** 291 (62), 263 (24), 249 (13), 136 (91), 108 (99), 91 (81); **Elemental analysis:** $C_{15}H_{17}NO_3S$ requires C: 61.83%, N: 4.81%, H: 5.88%, found C: 61.79%, N: 4.86%, H: 5.92%. The data observed are in accordance with literature values.[83-84]

But-3-ynyloxy-trimethylsilane 273:



273

$C_7H_{14}OSi$

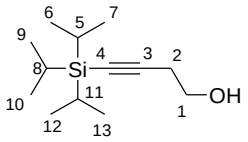
Molecular weight: 142.27 g.mol^{-1}

Trimethylsilylchloride (26.3 mL, 207 mmol) was added dropwise to a solution of 3-butyn-1-ol (15.0 mL, 198 mmol) and triethylamine (30.1 mL, 217 mmol) in dichloromethane (150 mL) at 0 °C. The mixture was stirred at rt for 15 h and then a saturated aqueous solution of sodium hydrogenocarbonate (150 mL) was added. The phases were separated and the aqueous phase was extracted with dichloromethane (3 × 150 mL). The combined organic phases were washed with water (150 mL) and brine (150 mL), then dried over magnesium sulfate. After filtration, the solution was reduced *in vacuo* to 35 mL, and the crude compound was distilled at 124—128 °C (1 atm) to provide the product **273** (20.5 g, 144 mmol, 73%) as yellow oil.

R_f: 0.71 (petroleum ether:ethyl acetate, 9:1); **b.p.**: 124—128 °C (lit: 125—128 °C); **IR:** ν_{max} 3313, 2956, 1251 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.71 (2H, t, *J* = 7.1 Hz, CH_2-C1), 2.40 (2H, td, *J* = 7.1, 2.6 Hz, CH_2-C2), 1.96 (1H, t, *J* = 2.6 Hz, CH-C4), 0.12 (9H, s, CH_3-C5, CH_3-C6, CH_3-C7); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 81.5 (C-C3), 69.5 (CH-C4), 61.2 (CH_2-C1), 22.8 (CH_2-C2), —0.4 (CH_3-C5, CH_3-C6, CH_3-C7); **HRMS (CI, isobutane)** for $C_7H_{15}OSi$ ($[M+H]^+$) calculated 143.0892, found 143.0893; **LRMS (CI, isobutane) *m/z* (intensity):** 143 (100), 103

(34), 85 (49), 69 (80); **Elemental analysis:** $C_7H_{14}OSi$ requires C: 59.09%, H: 9.92%, found C: 58.82%, H: 9.97%. The data observed are in accordance with literature values.[86]

4-Triisopropylsilanyl but-3-yn-1-ol 275:



275

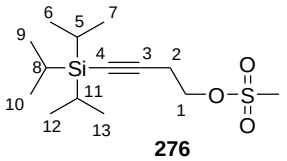
$C_{13}H_{26}OSi$

Molecular weight: 226.43 g.mol^{-1}

A solution of *n*-butyllithium (0.88 mL of a 2.5 M solution in hexane, 2.2 mmol), was added to a solution of **273** (300 mg, 2.11 mmol) in diethyl ether (10 ml), at −40 °C and the mixture was stirred at this temperature for 30 min. Tri*iso*propylsilyl trifluoromethanesulfonate (0.62 mL, 2.3 mmol) was added and the mixture was allowed to warm to rt, and stirred for 16 h. The reaction mixture was then washed with an aqueous solution of sodium hydrogenocarbonate (5%, 20 ml), and brine (20 mL), then dried over magnesium sulfate and concentrated in *vacuo*. The residue was dissolved in a mixture of tetrahydrofuran (5 mL), water (2 mL) and glacial acetic acid (2 mL). The mixture was stirred for 24 h and then neutralised by the addition of a saturated aqueous solution of ammonium hydroxide (20 mL). Ethyl acetate (30 mL) was added and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 30 mL), and the combined organic phases were washed with brine (30 mL), then dried over sodium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 7:1) provided the product **275** (408 mg, 1.8 mmol, 85%) as a colourless oil.

R_f: 0.63 (petroleum ether:ethyl acetate, 7:3); **IR:** ν_{max} 3335, 2943, 2866, 2173, 1464 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.72 (2H, t, *J* = 6.3 Hz, CH_2-C1), 2.52 (2H, t, *J* = 6.3 Hz, CH_2-C2), 1.94 (1H, br s, OH), 1.05—1.03 (21H, m, CH-C5, CH_3-C6, CH_3-C7, CH-C8, CH_3-C9, CH_3-C10, CH-C11, CH_3-C12, CH_3-C13). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 105.2 (C-C4), 83.1 (C-C3), 61.3 (CH_2-C1), 24.4 (CH_2-C2), 18.7 (CH_3-C6, CH_3-C7, CH_3-C9, CH_3-C10, CH_3-C12 CH_3-C13), 11.3 (CH-C5, CH-C11, CH-C8); **HRMS (CI, isobutane)** for $C_{13}H_{27}SiO$ ($[M+H]^+$) calculated 227.1831, found 227.1826; **LRMS (CI, isobutane) *m/z* (intensity):** 227 (42), 185 (100), 113 (14), 81 (31); **Elemental analysis:** $C_{13}H_{26}SiO$ requires C: 68.96%, H: 11.57%, found C: 68.84%, H: 11.63%. The data observed are in accordance with literature values.[86]

Methanesulfonic acid 4-tri*iso*propylsilanyl-but-3-ynyl ester 276:



276

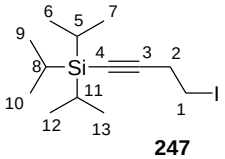
$C_{14}H_{28}O_3SSi$

Molecular weight: 304.52 g.mol^{-1}

Methanesulfonyl chloride (0.13 ml, 1.7 mmol) was added to a solution of **275** (340 mg, 1.50 mmol) and triethylamine (0.23 mL, 1.7 mmol) in dichloromethane (30 mL) at 0 °C. The solution was warmed to rt and stirred for 17 h. The mixture was then washed with a saturated aqueous solution of ammonium chloride (30 mL) and brine (30 mL), then dried over magnesium sulfate and concentrated *in vacuo* to provide **276** (0.45 g, 1.4 mmol, 98%) as a yellow oil. This product was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.30 (2H, t, *J* = 6.3 Hz, CH_2-C1), 3.03 (3H, s, CH_3-C14), 2.71 (2H, t, *J* = 6.3 Hz, CH_2-C2), 1.05—1.03 (21H, m, CH-C5, CH_3-C6, CH_3-C7, CH-C8, CH_3-C9, CH_3-C10, CH-C11, CH_3-C12, CH_3-C13). The data observed are in accordance with literature values.[86]

(4-Iodo *but*-1-ynyl)-tri*iso*propyl-silane 247:



247

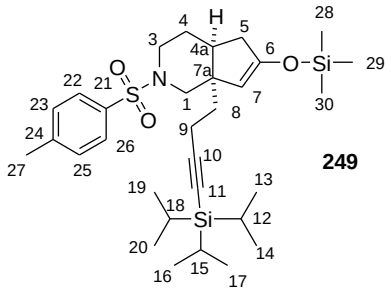
$C_{13}H_{25}ISi$

Molecular weight: 336.33 g.mol^{-1}

Sodium iodide (2.2 g, 1.5 mmol) was added to a solution of **276** (0.45 g, 1.5 mmol) in acetone (10 mL). The solution was heated to reflux for 24 h and was then cooled to rt and partitioned between petroleum ether (20 mL) and water (20 mL). The phases were separated and the aqueous phase was extracted with petroleum ether (2 × 50 mL) and the combined organic layers were washed with a saturated aqueous solution of sodium thiosulfate (100 mL) and brine (100 mL), then dried over magnesium sulfate and concentrated *in vacuo* to provide **247** (0.46 g, 1.4 mmol, 93%) as a yellow oil. This product was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.24 (2H, t, *J* = 7.3 Hz, CH_2-C1), 2.82 (2H, t, *J* = 7.3 Hz, CH_2-C2), 1.04—1.07 (21H, m, CH-C5, CH_3-C6, CH_3-C7, CH-C8, CH_3-C9, CH_3-C10, CH-C11, CH_3-C12, CH_3-C13). The data observed are in accordance with literature values.[86]

2-(Toluene-4-sulfonyl)-7a-(4-tri*iso*propylsilanyl-but-3-ynyl)-6-trimethylsilanyloxy-2,3,4,4a,5,7a-hexahydro-1*H*-[*2*]pyrindine 249:



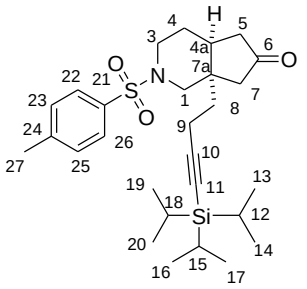
249

$C_{31}H_{51}NO_3SSi_2$

Molecular weight: 573.31 g.mol^{-1}

A solution of *t*-butyllithium (1.9 mL of a 1.6 M solution in heptane, 1.9 mL, 3.0 mmol,) was added dropwise to a solution of iodide **247** (0.51 g, 1.5 mmol), in diethyl ether (4 mL), at −78 ºC. The reaction was stirred at this temperature for 15 min, then allowed to warm at rt for 30 min. Meanwhile, dimethyl sulfide (0.8 mL, 0.01 mol) was added to a solution of copper (I) iodide (0.14 g, 0.75 mmol) in tetrahydofuran (4 mL), and the mixture was cooled at −42 ºC. Immediately after the cooling, the lithium reagent was added dropwise, *by* canula, to this mixture. Chlorotrimethylsilane (0.14 mL, 1.1 mmol) was added to a solution of enone **240** (125 mg, 0.429 mmol) in tetrahydrofuran (4 mL), cooled to 0 ºC and the resulting mixture was then added dropwise, *by* canula, to the previously formed cuprate compound. After 2 h, the mixture was quenched with a mixture of a saturated aqueous solution of ammonium chloride (10 mL), saturated aqueous solution of ammonium hydroxide (10 mL) and water (20 mL). Diethyl ether (20 mL) was added and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 20 ml), and the combined organic phases were washed with water (40 mL) and brine (40 mL), then dried over sodium sulfate and concentrated *in vacuo* to provide **249** as a colourless foam. Product **249** was used directly in the next step without further purification. ^{1}H NMR analysis showed a characteristic singlet at 4.5 ppm, corresponding to the enol CH-C7. The compound isolated after flash column chromatography on silica gel (petroleum ether:ethyl acetate, 7:3) was the corresponding ketone **250** (236 mg, 0.412 mmol, 96%) as a colourless oil.

Isolation and characterisation of the corresponding ketone 2-(toluene-4-sulfonyl)-7a-(4-tri*iso*propylsilanyl-but-3-ynyl)-octahydro-[*2*]pyrindin-6-one 250:



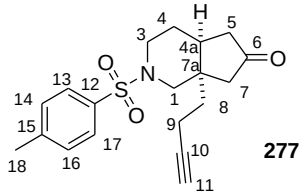
250

$C_{28}H_{43}NO_3SSi$

Molecular weight: 501.8 g.mol^{-1}

R_f: 0.60 (petroleum ether:ethyl acetate, 5:5); **IR:** ν_{max} 2941, 2864, 2360, 2169, 1745,1464, 1163 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.61 (2H, d, *J* = 7.7 Hz, CH-C22, CH-C26), 7.33 (2H, d, *J* = 7.7 Hz, CH-C23, CH-C25), 3.24—3.27 (1H, m, CH_2-C3), 3.09 (1H, d, *J* = 12.1 Hz, CH_2-C1), 2.73 (1H, dd, *J* = 9.8, 9.8 Hz, CH_2-C3), 2.44 (3H, s, CH_3-C27), 2.40—2.22 (6H, m, CH_2-C9, CH-C4a, CH_2-C5, CH_2-C7), 2.28 (1H, d, *J* = 12.1, CH_2-C1), 2.10—1.98 (2H, m, CH_2-C4, CH_2-C8), 2.02 (1H, dd, J = 18.7, 7.5 Hz, CH_2-C5), 1.71 (1H, ddd, 14.9, 7.4, 7.4 Hz, CH_2-C8), 1.56—1.61 (1H, m, CH_2-C4), 1.03—1.06 (21H, m, CH-C12, CH_3-C13, CH_3-C14, CH-C15, CH_3-C16, CH_3-C17, CH-C18, CH_3-C19, CH_3-C20); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 216.2 (C-C6), 143.9 (C-C24), 132.8 (C-C21), 129.9 (CH-C23, CH-C25), 127.5 (CH-C22, CH-C26), 107.7 (C-C10), 81.4 (C-C11), 48.8 (CH_2-C1), 47.6 (CH_2-C3), 42.2 (CH_2-C7), 41.4 (C-C7a), 40.4 (CH_2-C5), 37.2 (CH-C4a), 34.9 (CH_2-C8), 24.8 (CH_2-C4), 21.5 (CH_3-C27), 18.6 (CH_3-C13, CH_3-14, CH_3-C16, CH_3-C17, CH_3-C19, CH_3-C20), 15.2 (CH_2-C9), 11.2(CH-C12, CH-C15, CH-C18); **HRMS (CI, isobutane)** for $C_{28}H_{44}NO_3SSi$ ($[M+H]^+$) calculated 502.2811, found 502.2807; **LRMS (CI, isobutane) *m/z* (intensity):** 502 (100), 348 (35), 157 (31). The data observed are in accordance with literature values.[84]

7a-*But*-3-ynyl-2-(toluene-4-sulfonyl)-octahydro-[*2*]pyrindin-6-one 277:



277

$C_{19}H_{23}NO_3S$

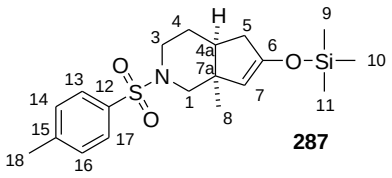
Molecular weight: 345.46 g.mol^{-1}

Tetrabutylammonium fluoride (1.4 mL of a 1.0 M solution in tetrahydrofuran, 1.4 mmol) was added dropwise to a solution of crude **249** (404 mg, 1.17 mmol) in tetrahydrofuran (15 mL), at —78 ºC. The reaction was allowed to warm at rt and stirred for 17 h. Diethyl ether

(15 mL) and a saturated aqueous solution of ammonium chloride (10 mL) were added and the phases were separated. The aqueous phase was extracted with diethyl ether (2 × 15 mL), and the combined organic phases were washed washed with brine (20 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 8:2) provided the product **277** (0.34 g, 0.98 mmol, 84%) as a colourless solid.

R_f: 0.57 (petroleum ether:ethyl acetate, 5:5); **m.p.:** 129—131 °C; **IR:** ν_{max} 3281, 2926, 1737 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.59 (2H, d, *J* = 8.4 Hz, CH-C13, CH-C17), 7.32 (2H, d, *J* = 8.4 Hz, CH-C14, CH-C16), 3.27—2.23 (1H, m, CH_2-C3), 3.11 (1H, d, *J* = 12.4 Hz, CH_2-C1), 2.71 (1H, dd, *J* = 9.6, 9.6 Hz, CH_2-C3), 2.42 (3H, s, CH_3-C18), 2.39 (1H, d, *J* = 12.4 Hz, CH_2-C1), 2.30—1.97 (10H, m, CH_2-C4, CH-C4a, CH_2-C5, CH_2-C7, CH-C11, CH_2-C8, CH_2-C9), 1.67 (1H, ddd, *J* = 14.3, 7.6, 6.6 Hz, CH_2-C8), 1.59—1.56 (1H, m, CH_2-C4); **^{13}C NMR** (101 MHz, $CDCl_3$): 216.1 (C-C6), 143.9 (C-C15), 132.8 (C-C12), 129.8 (CH-C14, CH-C16), 127.5 (CH-C13, CH-C17), 83.7 (C-C10), 69.3 (CH-C11), 48.6 (CH_2-C1), 47.5 (CH_2-C7), 42.2 (CH_2-C3), 41.5 (C-C7a), 40.3 (CH_2-C5), 37.6 (CH-C4a), 34.7 (CH_2-C8), 24.7 (CH_2-C4), 21.6 (CH_3-C18), 13.8 (CH_2-C9); **HRMS (CI, isobutane)** for $C_{19}H_{24}NO_3S$ ($[M+H]^+$) calculated 346.1477, found 346.1476; **LRMS (CI, isobutane) *m/z* (intensity):** 346 (16), 278 (7), 107 (27), 81 (70); **Elemental analysis:** $C_{19}H_{23}NO_3S$ requires C: 66.06%, N: 4.05 %, H: 6.71%, found C: 66.15%, N: 4.05%, H: 6.80%. The data observed are in accordance with literature values.[84]

7a-Methyl-2-(toluene-4-sulfonyl)-6-trimethylsilanyloxy-2,3,4,4a,5,7a-hexahydro-*1H*-[*2*]pyrindine 287:



287

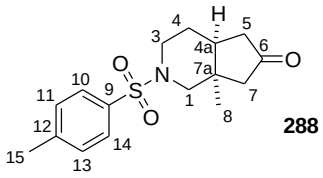
$C_{19}H_{29}NO_3SSi$

Molecular weight: 379.59 g.mol^{-1}

Methyl magnesium bromide (1.0 mL of a 1.4 M solution in tetrahydrofuran/toluene, 1.4 mmol) was added dropwise to a solution of copper(I) iodide (0.13 g, 0.69 mmol), in tetrahydrofuran (10 mL) at rt. This was followed by the dropwise addition of a solution of enone **240** (0.10 g, 0.34 mmol) and chlorotrimethylsilane (0.11 mL, 0.86 mmol), in tetrahydrofuran (5 mL). After 1h, the mixture was quenched by the addition of a mixture of saturated aqueous ammonium chloride solution (5 mL), saturated aqueous ammonium hydroxide solution (5 mL) and water (10 mL). Diethyl ether (20 mL) was added and the

phases were separated. The aqueous phase was extracted with diethyl ether (3 × 20 ml), and the combined organic phases were washed with water (30 mL), and brine (30 mL), then dried over sodium sulfate and concentrated *in vacuo* to provide **287**. This compound **287** was used directly in the next step without further purification. ^{1}H NMR analysis showed a characteristic singlet at 4.28 ppm, corresponding to the enol CH-C7. The compound isolated after flash column chromatography on silica gel (petroleum ether:ethyl acetate, 7:3) was the corresponding ketone **288** (0.10 g, 0.33 mmol, 96%) as a coulorless oil.

Isolation and characterisation of the corresponding ketone 7a-Methyl-2-(toluene-4-sulfonyl)-octahydro-[*2*]pyrindin-6-one 288:



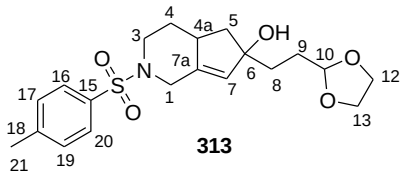
288

$C_{16}H_{21}NO_3S$

Molecular weight: 307.41 g.mol^{-1}

R_f: 0.24 (petroleum ether:ethyl acetate, 5:5); **IR:** ν_{max} 2924, 1735, 1458, 1334, 1157 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.63 (2H, d, *J* = 8.0 Hz, CH-C10, CH-C14), 7.33 (2H, d, *J* = 8.0 Hz, CH-C11, CH-C13), 3.24—2.19 (1H, m, CH_2-C3), 3.30 (1H, d, *J* = 12.0, CH_2-C1), 2.77 (1H, ddd, *J* = 10.2, 8.6, 0.6, CH_2-C3), 2.59 (1H, d, *J* = 12.0, CH_2-C1), 2.46 (1H, d, *J* = 18.7 Hz, CH_2-C7), 2.44 (3H, s, CH_3-C15), 2.39—2.44 (1H, m, CH_2-C5), 2.01—1.94 (2H, m, CH-C4a, CH_2-C5), 1.97 (1H, d, *J* = 18.7 Hz, CH_2-C7), 1.94—1.91 (1H, m, CH_2-C4), 1.52—1.48 (1H, m, CH_2-C4), 1.14 (3H, s, CH_3-C8); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 217.1 (C-C6), 143.7 (C-C12), 133.0 (C-C9), 129.8 (CH-C11, CH-C13), 127.6 (CH-C10, CH-C14), 52.3 (CH_2-C1), 47.6 (CH_2-C7), 43.9 (CH_2-C3), 42.4 (CH_2-C5), 38.9 (C-7a), 38.4 (CH-C4a), 26.8 (CH_2-C4), 24.8 (CH_3-C15), 21.5 (CH_3-C8); **HRMS (EI)** for $C_{16}H_{21}NO_3S$ ($[M]^+$) calculated 307.1242, found 307.1244; **LRMS (EI) *m/z* (intensity):** 307 (45), 198 (62), 152 (100), 91 (74); **Elemental analysis:** $C_{16}H_{21}NO_3S$ requires C: 62.51%, N: 4.56 %, H: 6.89%, found, C: 62.32%, N: 4.52%, H: 6.98%. The data observed are in accordance with literature values.[84]

6-(2-[1,3]Dioxolan-2-yl-ethyl)-2-(toluene-4-sulfonyl)-2,3,4,4a,5,6-hexahydro-1*H*-[*2*]pyrindin-6-ol 313:



313

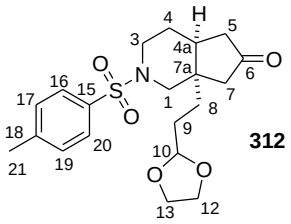
$C_{20}H_{27}NO_5S$

Molecular weight: 393.50 g.mol^{-1}

Copper(I) iodide (65 mg, 0.34 mmol) was introduced in a solid addition funnel, fitted on a flask containing magnesium (0.16 g, 6.8 mmol) and iodine (1 crystal), and tetrahydrofuran (14 mL) was then added. A solution of 2-(2-bromoethyl)-1,3-dioxolane (0.40 mL, 3.4 mmol) in tetrahydrofuran (4 mL) was added dropwise, while the reaction mixture was heated at 60 °C. This mixture was then cooled to rt and stirred for 30 min before further cooling to −15 °C, prior to the addition of the copper (I) iodide. After 15 min at this temperature, a solution of **240** (500 mg, 1.72 mmol) in tetrahydrofuran (4 mL) was added and the solution was stirred for a further 2 h. The mixture was quenched by addition of saturated aqueous ammonium chloride solution (5 mL), saturated aqueous ammonium hydroxide solution (5 mL) and water (10 mL). Diethyl ether (20 mL) was added and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 20 ml), and the combined organic phases were washed with water (30 mL) and brine (30 mL), then dried over sodium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 2:8) provided the product **313** (421 mg, 1.07 mmol, 62%) as a foam.

R_f: 0.38 (ethyl acetate); **IR:** ν_{max} 3464, 2928, 2854, 1597, 1446, 1334, 1161 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.64 (2H, d, *J* = 8.1 Hz, CH-C16, CH-C20), 7.31 (2H, d, *J* = 8.1 Hz, CH-C17, CH-C19), 5.48 (1H, s, CH-C7), 4.84—4.82 (1H, m, CH-C10), 4.36 (1H, d, *J* = 12.5 Hz, CH_2-C1), 3.95—3.80 (5H, m, CH_2-C3, CH_2-C12, CH_2-C13), 2.88 (1H, d, *J* = 12.5 Hz, CH_2-C1), 2.41 (3H, s, CH_3-C21), 2.34—2.28 (3H, m, CH_2-C3, CH-C4a, CH_2-C5), 1.92—1.88 (1H, m, CH_2-C4), 1.71—1.61 (4H, m, CH_2-C8, CH_2-C9), 1.44 (1H, dd, *J* = 12.7, 5.8 Hz, CH_2-C5), 1.42—1.32 (1H, m, CH_2-C4,); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 143.6 (C-C18), 139.3 (C-C15), 132.8 (C-C7a), 130.9 (CH-C7), 129.6 (CH-C17, CH-C19), 128.2 (CH-C16, CH-C20), 104.3 (CH-C10), 84.2 (C-C6), 64.8 (CH_2-C12, CH_2-C13), 46.9 (CH_2-C1), 46.0 (CH_2-C3), 45.5 (CH_2-C5), 41.3 (CH-C4a), 34.5 (CH_2-C9), 33.0 (CH_2-C4), 28.6 (CH_2-C8), 21.5 (CH_3-C21); **HRMS (CI, isobutane)** for $C_{20}H_{28}NO_5S$ ($[M+H]^+$) calculated 394.1688, found 394.1683; **LRMS (CI, isobutane) *m/z* (intensity):** 394 (14), 376 (100), 85 (49)**; Elemental analysis:** $C_{20}H_{27}NO_5S$ requires C: 61.05%, N: 3.56%, H: 6.92%, found C: 60.87%, N: 3.62%, H: 6.91%.

7a-(2-[*1,3*]Dioxolan-2-yl-ethyl)-2-(toluene-4-sulfonyl)-octahydro-[*2*]pyrindin-6-one 312:



312

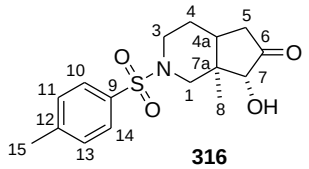
$C_{20}H_{27}NO_5S$

Molecular weight: 393.50 g.mol^{-1}

Copper(I) iodide (0.39 g, 2.1 mmol) was introduced in a solid addition funnel, fitted on a flask containing magnesium (0.16 g, 6.8 mmol) and iodine (1 crystal), and tetrahydrofuran (14 mL) was added. A solution of 2-(2-bromoethyl)-1,3-dioxolane (0.40 mL, 3.4 mmol), in tetrahydrofuran (4 mL) was added dropwise, while the reaction mixture was heated at 60 °C. This mixture was then cooled to rt and stirred for 30 min before further cooling to −30 °C, prior to the addition of the copper (I) iodide. The resulting mixture was cooled to −78 °C for 15 min prior to the addition of a solution of **240** (500 mg, 1.72 mmol) in tetrahydrofuran (4 mL). The solution was then stirred for a further 2 h at −78 °C and the reaction was quenched by the addition of a saturated aqueous of ammonium chloride solution (5 mL), saturated aqueous ammonium hydroxide solution (5 mL) and water (10 mL). Diethyl ether (20 mL) was added and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 20 ml) and the combined organic phases were washed with water (30 mL) and brine (30 mL), then dried over sodium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 8:2 to 7:3) provided the product **312** (380 mg, 0.966 mmol, 55%) as a colourless foam.

R_f: 0.45 (ethyl acetate); **IR:** ν_{max} 2924, 2885, 1743, 1303, 1141 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.58 (2H, d, *J* = 8.1 Hz, CH-C16, CH-C20), 7.29 (2H, d, *J* = 8.1 Hz, CH-C17, CH-C19), 4.81 (1H, dd, *J* = 4.5, 4.5 Hz, CH-C10), 3.95—3.91 (2H, m, CH_2-C12), 3.83—3.79 (2H, m, CH_2-C13), 3.73—3.70 (1H, m, CH_2-C3), 2.90 (1H, d, *J* = 12.2 Hz, CH_2-C1), 2.90—2.86 (1H, m, CH_2-C3), 2.56 (1H, d, *J* = 12.2 Hz, CH_2-C1), 2.40 (3H, s, CH_3-C21), 2.31 (1H, dd, *J* = 18.2, 7.4 Hz, CH_2-C5), 2.22 (1H, d, *J* = 18.5 Hz, CH_2-C7), 2.08 (1H, d, *J* = 18.5 Hz, CH_2-C7), 2.07—1.95 (3H, m, CH_2-C5, CH-C4a, CH_2-C4), 1.83 (1H, dd, *J* = 13.6, 3.8 Hz, CH_2-C8), 1.69 (1H, ddd, *J* = 12.3, 4.5, 3.8 Hz, CH_2-C9), 1.45—1.43 (3H, m, CH_2-C4, CH_2-C8, CH_2-C9); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 216.4 (C-C6), 143.7 (C-C18), 133.0 (C-C15), 129.8 (CH-C17, CH-C19), 127.5 (CH-C16, CH-C20), 104.1 (CH-C10), 64.9 (CH_2-C12, CH_2-C13), 49.1 (CH_2-C1), 46.6 (CH_2-C7), 42.7 (CH_2-C3), 41.1 (CH_2-C5), 41.0 (C-C7a),37.7 (CH-C4a), 30.2 (CH_2-C8), 28.5 (CH_2-C9), 25.4 (CH_2-C4), 21.5 (CH_3-C21); **HRMS (CI, isobutane)** for $C_{20}H_{28}NO_5S$

7-Hydroxy-7a-methyl-2-(toluene-4-sulfonyl)-octahydro-[*2*]pyrindin-6-one 316:



316

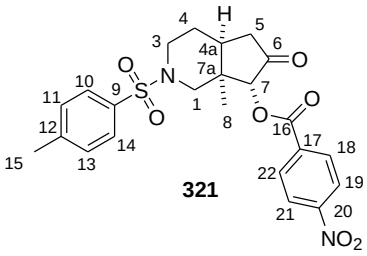
$C_{16}H_{21}NO_4S$

Molecular weight: 323.41 g.mol^{-1}

Dimethyldioxirane (4 mL of a 0.085 M solution in acetone, 0.47 mmol) was added to a solution of enol ether **287** (0.11 g, 0.34 mmol), in dichloromethane (1.5 mL), at 0 ºC. After 5 min, the solution was concentrated *in vacuo* and the resulting epoxide **315** was diluted in a mixture of tetrahydrofuran (5 mL), water (2 mL) and acetic acid (2 mL). The mixture was stirred at rt for 3 h. Solid sodium hydrogenocarbonate was added until the gas formation ceased. Ethyl acetate (10 mL) and water (10 mL) were added and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 20 ml) and the combined organic phases were washed with a saturated aqueous solution of sodium hydrogenocarbonate (10 mL), water (10 mL), and brine (10 mL), then dried over magnesium sulfate, and concentrated *in vacuo*. Purification of the residue by flash column chromatography (petroleum ether:ethyl acetate, 6:4 to 5:5) provided the product **316** (408 mg, 1.2 mmol, 73% over 3 steps) as a colourless crystalline solid allowing a crystal structure to be obtained (see **Appendix 1**).

R_f: 0.28 (petroleum ether:ethyl acetate, 5:5); **m.p.:** 163—164 ºC; **IR:** ν_{max} 3481, 2926, 1747, 1338 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.66 (2H, d, *J* = 8.0 Hz, CH-C10, CH-C14), 7.34 (2H, d, *J* = 8.0, CH-C11, CH-C13), 4.52 (1H, s, CH-C7), 3.86—3.84 (1H, m, CH_2-C3), 3.82 (1H, d, *J* = 12.1, CH_2-C1), 2.83 (1H, d, *J* = 3.2 Hz, OH), 2.53 (1H, dd, *J* = 19.7 Hz, *J* = 8.0 Hz, CH_2-C5), 2.43 (3H, s, CH_3-C15), 2.29 (1H, dd, *J* = 12.4, 11.5 Hz, CH_2-C3), 2.12 (1H, d, *J* = 12.1 Hz, CH_2-C1), 2.04 (1H, d, *J* = 19.7 Hz, CH_2-C5), 1.92—1.77 (2H, m, CH_2-C4, CH-C4a), 1.53—1.49 (1H, m, CH_2-C4), 0.80 (3H, s, CH_3-C8); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 216.0 (C-C6), 143.7 (C-C12), 133.4 (C-C9), 129.8 (CH-C11, CH-C13), 127.6 (CH-C10, CH-C14), 75.9 (CH-C7), 51.2 (CH_2-C1), 45.9 (CH_2-C3), 41.1 (C-C7a), 39.5 (CH_2-C5), 35.1 (CH-C4a), 29.9 (CH_2-C4), 21.6 (CH_3-C8), 18.8 (CH_3-C15); **HRMS (EI)** for $C_{16}H_{21}NO_4S$, ($[M]^+$) calculated 323.1191, found 323.1195; **LRMS (EI) *m/z* (intensity):** 323 (29), 295 (10), 185 (28), 168 (100), 155 (40), 82 (73); **Elemental analysis:** $C_{16}H_{21}NO_4S$: requires C: 59.42%, N: 4.33%, H: 6.54%, found C: 59.46%, N: 4.34%, H: 6.64%.

4-Nitro-benzoic acid 7a-methyl-6-oxo-2-(toluene-4-sulfonyl)-octahydro-[2]pyrindin-7-yl ester 321:



321

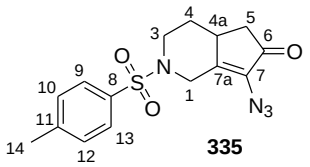
$C_{23}H_{24}N_2O_7S$

Molecular weight: 472.51 g.mol^{-1}

A solution of **316** (100 mg, 0.31 mmol), 4-nitrobenzoyl chloride (69 mg, 0.37 mmol), triethylamine (0.13 mL, 0.93 mmol), and dimethylaminopyridine (6 mg, 0.05 mmol) in dichloromethane (15 mL) was stirred at rt for 3h. This mixture was then washed with a aqueous 10% hydrochloric acid solution (3 × 10 mL) and brine, then dried with magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography (petroleum ether:ethyl acetate, 7:3) provided the product **321** (260 mg, 0.55 mmol, 95%) as a colourless solid, in a 95% yield.

R_f: 0.32 (petroleum ether:ethyl acetate, 5:5); **m.p.:** 179—182 ºC **IR:** ν_{max} 3063, 2924, 1759, 1735, 1527, 1342 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.28 (2H, d, *J* = 8.4 Hz, CH-C19, CH-C21), 8.12 (2H, d, *J* = 8.4 Hz, CH-C18, CH-C22), 7.63 (2H, d, *J* = 7.7 Hz, CH-C10), CH-C14), 7.29 (2H, d, J = 7.7 Hz, CH-C11, CH-C13), 5.96 (1H, s, CH-C7), 3.85 (1H, d, *J* = 11.4 Hz, CH_2-C3), 3.66 (1H, d, *J* = 12.4 Hz, CH_2-C1), 2.62 (1H, dd, *J* = 19.6, 7.6 Hz, CH_2-C5), 2.38 (3H, s, CH_3-C15), 2.28—2.26 (1H, m, CH_2-C3), 2.27 (1H, d, *J* = 12.4 Hz, CH_2-C1), 2.12 (1H, d, *J* = 19.6 Hz, CH_2-C5), 1.96—1.95 (2H, m, CH_2-C4, CH-C4a), 1.73—1.75 (1H, m, CH_2-C4), 1.06 (3H, s, CH_3-C8); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 209.2 (C-C6), 163.4 (C-C16), 150.7 (C-C20), 143.9 (C-C12), 134.9 (C-C9/C17), 133.3 (C-C9/C17), 131.5 (CH-Car, CH-Car), 129.9 (CH-Car, CH-Car), 127.8 (CH-Car, CH-Car), 123.6 (CH-Car, CH-Car), 77.7 (CH-C7), 50.7 (CH_2-C1), 45.6 (CH_2-C3), 40.6 (CH_2-C5), 39.9 (C-C7a), 35.8 (CH-C4a), 29.6 (CH_2-C4), 21.6 (CH_3-C15), 19.8 (CH_3-C8); **HRMS (FAB)** for $C_{23}H_{25}N_2O_7S$ ([M+H]$^+$) calculated 473.1382, found 473.1376; **LRMS (FAB) *m/z* (intensity):** 473 (54), 307 (94), 154 (100), 137 (95); **Elemental:** analysis calculated for $C_{23}H_{24}N_2O_7S$: requires C: 58.46%, N: 5.93%, H: 5.12% found C: 58.51%, N: 5.78%, H: 5.22%.

7-Azido-2-(toluene-4-sulfonyl)-1,2,3,4,4a,5-hexahydro-[*2*]pyrindin-6-one 335:



335

$C_{15}H_{16}N_4O_3S$

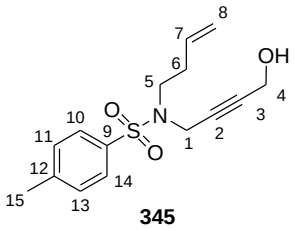
Molecular weight: 332.38 g.mol^{-1}

Water (40 mL) was added to a solution of enone **240** (0.30 g, 1.0 mmol) in tetrahydrofuran (40 mL). The solution was cooled to 0 ºC and sodium hydrogenocarbonate (1.5 g, 17 mmol) was added, followed by hydrogen peroxide (1.6 mL of a 27% solution in water, 26 mmol). The solution was stirred at 0 ºC for 6 h. Diethyl ether was added, the phases were separated and the aqueous phase was extracted with diethyl ether (2 × 80 mL). The combined organic phases were washed with and brine (100 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Due to poor stability, epoxide **334** was used directly in the next step without further purification.

Lithium perchlorate (11 mg, 0.10 mmol), 4-(dimethyamino)pyridine (0.15 g, 1.2 mmol), and diphenyl phosphoryl azide (0.27 mL, 1.2 mmol) were added to a solution of crude **334** in dimethylformamide (9 mL). The mixture was stirred at 50 ºC for 17 h, cooled to rt and diethyl ether (20 mL) and water (20 mL) were added. The phases were separated and the organic phase was washed with water (3 × 20 mL) and brine (10 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 8:2) provided the product **335** (40 mg, 0.12 mmol, 12% over 2 steps) as a colourless foam.

R_f: 2.0 (petroleum ether:ethyl acetate, 8:2); **IR:** ν_{max} 2924, 2126, 1709, 1654 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.69 (2H, d, *J* = 8.4 Hz, CH-C9, CH-C13), 7.34 (2H, d, *J* = 8.4 Hz, CH-C10, CH-C12), 4.72 (1H, d, *J* = 14.0 Hz, CH_2-C1), 3.97—3.95 (1H, m, CH_2-C3), 3.05 (1H, d, *J* = 14.0 Hz, CH_2-C1), 2.65 (1H, dd, *J* = 19.0, 6.3 Hz, CH_2-C5), 2.60 (1H, ddd, *J* = 12.5, 12.5, 2.3 Hz, CH_2-C3), 2.56—2.53 (1H, m, CH-4a), 2.44 (3H, s, CH_3-C14), 2.07—2.05 (1H, m, CH_2-C4), 2.04 (1H, dd, *J* = 19.0, 2.5 Hz, CH_2-C5), 1.39 (1H, ddd, *J* = 12.9, 12.5, 4.0 Hz, CH_2-C4); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 199.6 (C-C6), 148.3 (C-C11), 143.1 (C-C8), 132.2 (C-C7a), 128.8 (CH-C10, CH-C12), 126.7 (CH-C9, CH-C13), 44.6 (CH_2-C3), 43.1 (CH_2-C1), 38.7 (CH_2-C5), 33.9 (CH-C4a), 31.0 (CH_2-C4), 20.5 (CH_3-C14); **HRMS (CI, isobutane)** for $C_{15}H_{17}N_4O_3S$ ($[M+H]^+$) calculated 333.1021, found 333.1017; **LRMS (CI, isobutane) *m/z* (intensity):** 333 (17), 308 (100), 305 (78), 207 (70), 151 (85).

***N*-But-3-enyl-*N*-(4-hydroxy-but-2-ynyl)-4-methylbenzenesulfonamide 345:**



345

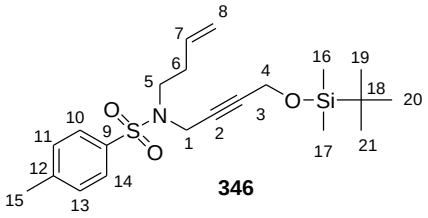
$C_{15}H_{19}NO_3S$

Molecular weight: 293.38 g.mol^{-1}

A solution of *n*-butyllithium (0.8 mL of a 2.5 M solution in hexanes, 2.0 mmol) was added dropwise to a solution of **242** (0.50 g, 1.9 mmol) in tetrahydrofuran (30 mL) at −78 °C. The mixture was stirred at this temperature for 1 h and then *p*-formaldehyde (0.11 g, 3.8 mmol) was added. The reaction mixture was slowly warmed to rt and stirred for 2 h, then water (100 mL) and dichloromethane (100 mL) were added. The phases were separated, the aqueous phase was extracted with dichloromethane (3 × 100 mL) and the combined organic phases were washed with brine (300 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 8:2) provided the product **345** (2.0 g, 6.8 mmol, 59%) as a colourless oil.

R_f: 0.38 (petroleum ether:ethyl acetate, 5:5); **IR:** ν_{max} 3474, 2926, 1598, 1450, 1341 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.73 (2H, d, *J* = 8.4 Hz, CH-C10, CH-C14), 7.30 (2H, d, *J* = 8.4 Hz, CH-C11, CH-C13), 5.72 (1H, dddd, *J* = 17.1, 10.2, 6.7, 6.7 Hz, CH-C7), 5.11 (1H, ddd, *J* = 17.1, 2.6, 1.5 Hz, CH_2-C8), 5.06 (1H, ddd, *J* = 10.2, 2.6, 1.2 Hz, CH_2-C8), 4.14 (2H, t, *J* = 1.9 Hz, CH_2-C1), 3.98 (2H, dt, *J* = 6.1, 1.9 Hz, CH_2-C4), 3.25 (2H, t, *J* = 7.8 Hz, CH_2-C5), 2.42 (3H, s, CH_3-C15), 2.32—2.27 (2H, m, CH_2-C6), 1.20 (1H, t, *J* = 6.1 Hz, OH); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 143.6 (C-C12), 135.8 (CH-C7), 134.5 (C-C9), 129.5 (CH-C11, CH-C13), 127.8 (CH-C10, CH-C14), 117.3 (CH_2-C8), 83.8 (C-C2), 78.3 (C-C3), 50.6 (CH_2-C4), 45.8 (CH_2-C5), 36.7 (CH_2-C1), 32.2 (CH_2-C6), 21.1 (CH_3-C15); **HRMS (CI, isobutane)** for $C_{15}H_{20}O_3NS$ ($[M+H]^+$) calculated 294.1164, found 294.1166; **LRMS (CI, isobutane) *m/z* (intensity):** 294.3 (100), 252.3 (39), 157.2 (21), 140.2 (19); **Elemental analysis:** $C_{15}H_{19}NO_3S$ requires C: 61.41%, N: 4.77%, H: 6.53%, found C: 61.28%, N: 4.73%, H: 6.56%.

***N*-But-3-enyl-*N*-[4-(*tert*-butyl-dimethyl-silanyloxy)-but-2-ynyl]-4-methyl-benzenesulfonamide 346:**



346

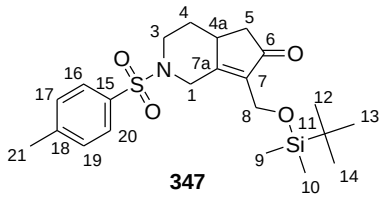
$C_{21}H_{33}NO_3SSi$

Molecular weight: 407.64 g.mol^{-1}

4-(Dimethylamino)pyridine (12 mg, 0.095 mmol), triethylamine (0.40 mL, 2.9 mmol) and *t*-butyldimethylsilyl chloride (0.22 g, 1.4 mmol) were added to a solution of 345 (0.28 g, 0.95 mmol) in dichloromethane (15 mL). The mixture was stirred at rt for 5 h, then water (15 mL) was added and the phases were separated. The aqueous phase was extracted with dichloromethane (3 × 15 mL) and the combined organic phases were washed with brine (50 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 95:5) provided the product 346 (0.28 g, 0.69 mmol, 72%) as a colourless oil.

R_f: 0.33 (petroleum ether:ethyl acetate, 9:1); **IR:** ν_{max} 2928, 2856, 1472, 1349, 1253, 1160 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.68 (2H, d, *J* = 8.2 Hz, CH-C10, CH-C14), 7.24 (2H, d, *J* = 8.2 Hz, CH-C11, CH-C13), 5.73 (1H, ddt, *J* = 17.1, 10.2, 6.8, Hz, CH-C7), 5.06 (1H, ddd, *J* = 17.1, 2.8, 1.5 Hz, CH_2-C8), 5.03 (1H, ddd, *J* = 10.2, 2.8, 1.5 Hz, CH_2-C8), 4.13 (2H, s, CH_2-C1), 4.01 (2H, s, CH_2-C4), 3.20 (2H, t, *J* = 7.2 Hz, CH_2-C5), 2.38 (3H, s, CH_3-C15), 2.31—2.28 (2H, m, CH_2-C6), 0.82 (9H, s, CH_3-C19, CH_3-C20, CH_3-C21), 0.00 (6H, s, CH_3-C16, CH_3-C17); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 142.3 (C-C12), 134.9 (CH-C7), 133.5 (C-C9), 128.3 (CH-C11, CH-C13), 126.7 (CH-C10, CH-C14), 116.2 (CH_2-C8), 83.1 (C-C2), 76.3 (C-C3), 50.3 (CH_2-C4), 44.7 (CH_2-C5), 35.7 (CH_2-C1), 31.2 (CH_2-C6), 24.7 (CH_3-C19, CH_3-C20, CH_3-C21), 20.5 (CH_3-C15), 17.2 (C-C18), —6.5 (CH_3-C16, CH_3-C17); **HRMS (FAB)** for $C_{21}H_{34}NO_3SSi$ ($[M+H]^+$) calculated 408.2029, found 408.2031**; LRMS (FAB) *m/z* (intensity):** 408 (100), 366 (81), 350 (99), 276 (44), 155 (24); **Elemental analysis:** $C_{21}H_{33}NO_3SSi$ requires C: 61.87%, N: 3.44%, H: 8.16%, found C: 62.03%, N: 3.36%, H: 8.34%.

7-(*tert*-Butyldimethylsilanyloxymethyl)-2-(toluene-4-sulfonyl)-1,2,3,4,4a,5-hexahydro-[2]pyrindin-6-one 347:



347

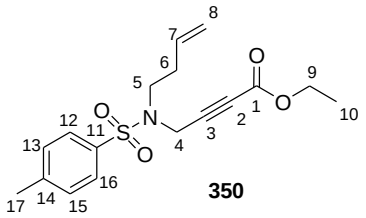
$C_{22}H_{33}NO_4SSi$

Molecular weight: 435.65 g.mol^{-1}

Tetramethylthiourea (19 mg, 0.15 mmol) and dicobalt octacarbonyl (8.4 mg, 0.025 mmol) were added in a flask, fitted with a condenser, under argon atmosphere. This apparatus was evacuated and refilled with carbon monoxide (× 3), and toluene (7 ml) was added. A solution of **346** (0.10 mg, 0.25 mmol) dissolved in toluene (1 mL) was added dropwise to the mixture. The reaction mixture was then stirred at 70 °C for 6 h, and the solvent was removed *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 6:4) provided the product **347** (51 mg, 12 mmol, 48%) as a colourless solid.

R_f: 0.40 (petroleum ether:ethyl acetate, 5:5); **m.p.:** 89—91 °C; **IR:** ν_{max} 2928, 2855, 1702, 1663, 1462, 1160 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.66 (2H, d, *J* = 8.3 Hz, CH-C16, CH-C20), 7.32 (2H, d, *J* = 8.3 Hz, CH-C17, CH-C19), 5.31 (1H, d, *J* = 14.0 Hz, CH_2-C1), 4.45—4.42 (2H, m, CH_2-C8), 3.94—3.92 (1H, m, CH_2-C3), 3.13 (1H, d, *J* = 14.0 Hz, CH_2-C1), 2.57 (1H, dd, *J* = 16.0, 3.5 Hz, CH_2-C5), 2.60—2.48 (2H, m, CH_2-C3, CH-C4a), 2.43 (3H, s, CH_3-C21), 2.08 (1H, dddd, *J* = 12.5, 5.0, 2.4, 2.4 Hz, CH_2-C4), 1.96 (1H, d, *J* = 16.0 Hz, CH_2-C5), 1.44 (1H, ddd, *J* = 12.5, 12.4, 4.0 Hz, CH_2-C4), 0.93 (9H, s, CH_3-C12, CH_3-C13, CH_3-C14), 0.14 (3H, s, CH_3-C9/C10), 0.08 (3H, s, CH_3-C9/C10); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 206.1 (C-C6), 166.4 (C-C7), 143.9 (C-C18), 138.4 (C-C15), 133.2 (C-C7a), 129.8 (CH-C17, CH-C19), 127.7 (CH-C16, CH-C20), 57.1 (CH_2-C8), 45.8 (CH_2-C1), 45.6 (CH_2-C3), 40.7 (CH_2-C5), 37.9 (CH-C4a), 31.7 (CH_2-C4), 25.9 (CH_3-C12, CH_3-C13, CH_3-C14), 21.6 (CH_3-C21), 18.3 (C-C11), —5.6 (CH_3-C9, CH_3-C10); **HRMS (FAB)** for $C_{22}H_{34}NO_4SSi$ ($[M+H]^+$) calculated 436.1978, found 436.1974; **LRMS (FAB) *m/z* (intensity):** 436 (100), 378 (42), 304 (50), 155 (92), 138 (56).

4-[But-3-enyl-(toluene-4-sulfonyl)-amino]-but-2-ynoic acid ethyl ester 350:



350

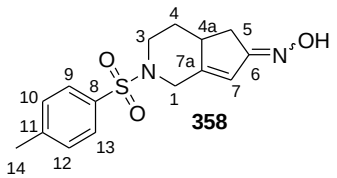
$C_{17}H_{21}NO_4S$

Molecular weight: 335.42 g.mol^{-1}

A solution of *n*-butyllithium (0.15 mL of a 2.5 M solution in hexanes, 0.38 mmol) was added dropwise to a solution of **242** (0.10 g, 0.38 mmol) in tetrahydrofuran (6 mL) at 0 °C and the mixture was cooled to −78 °C and stirred at this temperature for 1 h. Ethylchloroformate (0.04 mL, 0.4 mmol) was added dropwise and the reaction was stirred at rt for 5 h. The reaction was then quenched by the addition of a saturated aqueous solution of ammonium chloride (5 mL), dichloromethane (15 mL) was added and the phases were separated. The aqueous phase was extracted with dichloromethane (3 × 10 mL), and the combined organic phases were washed with water (30 mL) and brine (30 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 95:5) provided the product **350** (45 mg, 0.13 mmol, 35%) as a colourless oil.

R_f: 0.26 (petroleum ether:ethyl acetate, 8:2); **IR:** ν_{max} 2995, 2930, 2236, 1710, 1348, 1245 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.71 (2H, d, *J* = 8.1 Hz, CH-C12, CH-C16), 7.30 (2H, d, *J* = 8.1 Hz, CH-C13, CH-C15), 5.74 (1H, ddt, *J* = 17.1, 12.0, 6.9 Hz, CH-C7), 5.13 (1H, d, *J* = 17.1 Hz, CH_2-C8), 5.08 (1H, d, *J* = 12.0 Hz, CH_2-C8), 4.24 (2H, s, CH_2-C4), 4.14 (2H, q, *J* = 7.1 Hz, CH_2-C9), 3.24 (2H, t, *J* = 7.2 Hz, CH_2-C5), 2.40 (3H, s, CH_3-C17), 2.32 (2H, dt, *J* = 7.2, 6.9 Hz, CH_2-C6), 1.26 (3H, t, *J* = 7.1 Hz, CH_3-C10); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 152.6 (C-C1), 143.9 (C-C14), 135.3 (CH-C7), 134.2 (C-C11), 129.7 (CH-C13, CH-C15), 127.6 (CH-C12, CH-C16), 117.6 (CH_2-C8), 80.1 (C-C2), 77.2 (C-C3), 62.1 (CH_2-C9), 46.2 (CH_2-C5), 36.5 (CH_2-C4), 32.2 (CH_2-C6), 21.5 (CH_3-C17), 14.1 (CH_3-C10); **HRMS (CI, isobutane)** for $C_{17}H_{22}NO_4S$ ($[M+H]^+$) calculated 336.1270, found 336.1272; **LRMS (CI, isobutane) *m/z* (intensity):** 336 (100), 294 (20), 226 (16).

2-(Toluene-4-sulfonyl)-1,2,3,4,4a,5-hexahydro-[*2*]pyrindin-6-one oxime 358:



358

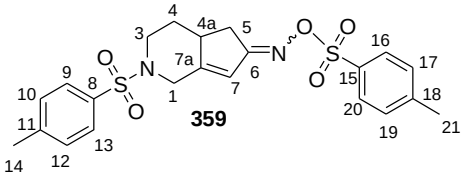
$C_{15}H_{18}N_2O_3S$

Molecular weight: 306.38 g.mol^{-1}

Pyridine (0.42 mL, 5.2 mmol) and hydroxylamine hydrochloride (0.24 g, 3.4 mmol) were added to a solution of enone **240** (500 mg, 1.72) in ethanol (7 mL) and the mixture was stirred for 24 h. The reaction mixture was then concentrated *in vacuo* and the residue was dissolved in dichloromethane (15 mL), washed with water (15 mL) and brine (15 mL), then dried over sodium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (heptane:ethyl acetate, 8:2 to 6:4) provided the product **358** (304 mg, 0.992 mmol, 58%) as a colourless solid.

R_f: 0.24 (petroleum ether:ethyl acetate, 5:5); **m.p.:** 90—92 °C; **IR:** ν_{max} 3232, 3109, 2924, 2854, 1296, 1157 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.37 (1H, s, OH), 7.68 (2H, d, *J* = 8.1 Hz, CH-C9, CH-C13), 7.34 (2H, d, *J* = 8.1 Hz, CH-C10, CH-C12), 6.05 (1H, s, CH-C7), 4.58 (1H, d, *J* = 12.9 Hz, CH_2-C1), 3.95—3.93 (1H, m, CH_2-C3), 3.10 (1H, d, *J* = 12.9 Hz, CH_2-C1), 2.98 (1H, dd, *J* = 18.6, 7.4 Hz, CH_2-C5), 2.51—2.49 (1H, m, CH_2-C3), 2.47—2.44 (1H, m, CH-C4a), 2.45 (3H, s, CH_3-C14), 2.24 (1H, dd, *J* = 18.6, 2.8 Hz, CH_2-C5), 2.07—2.04 (1H, m, CH_2-C4), 1.42—1.40 (1H, m, CH_2-C4); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.5 (C-C6), 153.7 (C-C11), 143.8 (C-C8), 133.3 (C-C7a), 129.7 (CH-C10, CH-C12), 127.7 (CH-C9, CH-C13), 123.2 (CH-C7), 47.2 (CH_2-C1), 45.7 (CH_2-C3), 41.4 (CH-C4a), 32.5 (CH_2-C4), 31.4 (CH_2-C5), 21.5 (CH_3-C14); **HRMS (CI, isobutane)** for $C_{15}H_{19}N_2O_3S$ ($[M+H]^+$) calculated 307.1116, found 307.1122; **LRMS (CI, isobutane) *m/z* (intensity):** 307 (100), 291 (59), 135 (91).

2-Tosyl-3,4,4a,5-tetrahydro-1*H*-cyclopenta[c]pyridin-6(*2H*)-one O-tosyl oxime 359



359

$C_{22}H_{24}N_2O_5S_2$

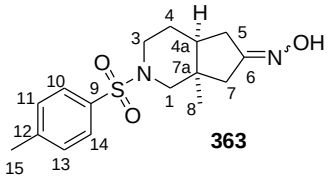
Molecular weight: 460.57 g.mol^{-1}

p-Toluenesulfonyl chloride (0.42 g, 2.2 mmol) was added to a solution of **358** (300 mg, 0.979 mmol) in pyridine (2 mL) at 10 °C and the mixture was stirred at this temperature for 2 h. This mixture was then poured into water (10 mL) and dichloromethane (10 mL) was

added. The phases were separated and the aqueous phase was extracted with dichloromethane (3 × 10 ml). The combined organic phases were washed with brine (30 mL), then dried over sodium sulfate and concentrated *in vacuo*. A short filtration on silica gel provided the crude product **359** as a brown solid (110 mg, 0.239 mmol, 24%), which was used directly in the next step due to its poor stability.

R_f: 0.51 (heptane:ethyl acetate, 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.85 (2H, d, *J* = 8.0 Hz, CH-C9, CH-C13/CH-C16, CH-C20), 7.64 (2H, d, *J* = 8.2 Hz, CH-C9, CH-C13/CH-C16, CH-C20), 7.33 (2H, d, *J* = 8.0 Hz, CH-C10, CH-C12/CH-C17, CH-C19), 7.31 (2H, d, *J* = 8.2 Hz, CH-C10, CH-C12/CH-C17, CH-C19), 6.02 (1H, s, CH-C7), 4.56 (1H, d, *J* = 12.6 Hz, CH_2-C1), 3.86—2.90 (1H, m, CH_2-C3), 3.07 (1H, dd, *J* = 12.6, 3.0 Hz, CH_2-C1), 2.54—2.41 (3H, m, CH_2-C3, CH_2-C5, CH-C4a), 2.44 (3H, s, CH_3-C14), 2.43 (3H, s, CH_3-C21), 2.31—2.27 (1H, m, CH_2-C4), 2.06-2.00 (1H, m, CH_2-C5), 1.34 (1H, ddd, *J* = 19.0, 12.8, 4.5 Hz, CH_2-C4).

7a-Methyl-2-(toluene-4-sulfonyl)-octahydro-[*2*]pyrindin-6-one oxime 363:



363

$C_{16}H_{22}N_2O_3S$

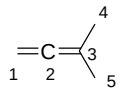
Molecular weight: 322.42 g.mol^{-1}

Pyridine (0.12 mL, 1.5 mmol) and hydroxylamine hydrochloride (68 mg, 0.98 mmol) were added to a solution of ketone **240** (150 mg, 0.488 mmol) in ethanol (1.5 mL) and the reaction mixture was stirred at rt for 24 h. The solution was then concentrated *in vacuo* and the residue was dissolved in dichloromethane (5 mL). The solution was washed with water (5 mL) and brine (5 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (heptane:ethyl acetate, 8:2 to 6:4) provided the product **363** (70 mg, 0.21 mmol, 45%) as a colourless solid.

R_f: 0.24 (petroleum ether:ethyl acetate, 5:5); **m.p.:** 192—193 °C; **IR:** ν_{max} 3269, 2943, 2872, 1338, 1161 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.62 (2H, d, *J* = 8.1 Hz, CH-C10, CH-C14), 7.43 (1H, s, N-OH), 7.32 (2H, d, *J* = 8.1 Hz, CH-C11, CH-C13), 3.13—3.09 (1H, m, CH_2-C3), 2.90 (1H, d, *J* = 11.8 Hz, CH_2-C1), 2.79—2.74 (1H, m, CH_2-C3), 2.65 (1H, d, *J* = 18.7 Hz, CH_2-C7), 2.59 (1H, d, *J* = 11.8 Hz, CH_2-C1), 2.53 (1H, ddd, *J* = 17.1, 7.2, 1.5 Hz, CH_2-C5), 2.43 (3H, s, CH_3-C15), 2.27 (1H, d, *J* = 18.7 Hz, CH_2-C7), 2.17 (1H, ddd, *J* = 17.1, 7.2, 1.5 Hz, CH_2-C5), 1.86—1.81 (1H, m, CH_2-C4), 1.72 (1H, ddd, *J* = 12.7, 7.2, 7.2 Hz, CH-C4a),

1.49—1.44 (1H, m, CH_2-C4), 1.09 (3H, s, CH_3-C8); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 163.9 (C-C6), 143.5 (C-C12), 133.3 (C-C9), 129.7 (CH-C11, CH-C13), 127.6 (CH-C10, CH-C14), 52.1 (CH_2-C1), 43.4 (CH_2-C3), 40.3 (CH-C4a), 39.4 (C-C7a), 36.8 (CH_2-C7), 33.8 (CH_2-C5), 26.0 (CH_2-C4), 24.2 (CH_3-C8), 21.5 (CH_3-C15); **HRMS (EI)** for $C_{16}H_{22}N_2O_3S$ ([M]$^+$) calculated 322.1351, found 322.1349; **LRMS (EI) *m/z* (intensity):** 322 (14), 305 (24), 167 (100), 151 (40), 91 (54).

3-methyl-1,2-butadiene 369:



369

C_5H_8

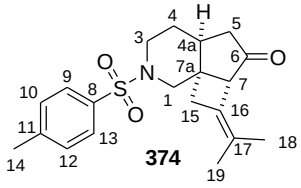
Molecular weight: 68.06 g.mol^{-1}

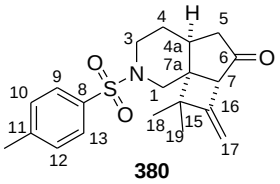
Calcium chloride (27 g, 0.24 mol) was added in portions to a mixture of concentrated hydrochloric acid (120 ml), 2-methyl-3-butyn-2-ol (20 g, 0.24 mol) and hydroquinone (0.2 g) at 0 ºC. The mixture was stirred at rt for 1 h. The top layer was separated, dried over sodium carbonate, and distilled under reduced pressure. All the material that distilled up to 40 °C under 110 mmHg was collected and distilled again. 3-Chloro-3-methyl-1-butyne was thus collected as a colourless liquid (18 g, 0.18 mol, 73%) which was used directly through the next step.

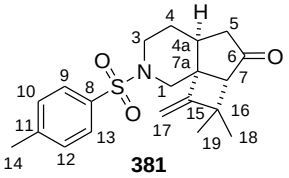
Zinc powder (23 g, 0.35 mol) was washed with aqueous 3% hydrochloric acid solution (2×20 ml), aqueous copper sulfate solution (30 ml), ethanol (30 ml), and *n*butanol (30 ml). 3-Chloro-3-methyl-1-butyne (18 g; 0.18 mol) was added dropwise to a mixture of the treated zinc in *n*butanol (45 mL). The mixture heated cautiously, with stirring, until the reaction started. Slow addition of the remaining propargyl chloride allowed the distillation of the desired 3-methyl-1,2-butadiene **369** at 37—45 ºC. The collected material was redistilled, providing the desired product **369** (3.3 g, 48 mmol, 27%) as a coulorless liquid.

b.p: 38—42 ºC (lit: 38—41 ºC); **^{1}H NMR** (400 MHz, $CDCl_3$): 4.59 (2H, m, CH_2-C1); 1.71 (6H, t, *J* = 3.2, CH_3-C4, CH_3-C5). The data observed are in accordance with literature values.[138]

2-Isopropylidene-7-(toluene-4-sulfonyl) octahydro-7-aza-cyclobuta[*c*]inden-3-one 374 and its regioisomers 380 and 381:







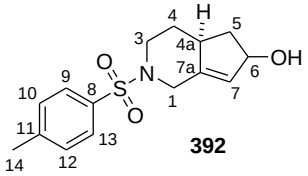
$C_{20}H_{25}NO_3S$

Molecular weight: 359.48 g.mol^{-1}

3-Methyl-1,2-butadiene (0.13 mL, 1.3 mmol) was added to a solution of enone **240** (75 mg, 0.25 mmol) in degassed acetronitrile (5 mL). This mixture was then irradiated using a 125 W Hanovia mercury lamp for 6 h at rt, and then concentrated *in vacuo*. Purification of the residue by flash column chromatography (petroleum ether:ethyl acetate, 8:2) provided the product as an inseparable mixture of regioisomers (63% overall yield). The ratio was determined by NMR; 3.5:1.4:1 of **374**:**380**:**381**

R_f: 0.72 (petroleum ether:ethyl acetate, 5:5); **IR:** ν_{max} 2926, 1735, 1336, 1161 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): Partial characterisation of **374**, δ 7.65 (2H, m, CH-C9, CH-C13), 7.33 (2H, d, *J* = 7.9 Hz, CH-C10, CH-C12), 3.87 (1H, dd, *J* = 12.1, 1.8 Hz, CH_2-C1), 3.26 (1H, s, CH-C7), 1.63 (3H, s, CH_3-C18/C19), 1.50 (3H, s, CH_3-C18/C19). Partial characterisation of **380**, δ 7.65 (2H, m, CH-C9, CH-C13), 7.33 (2H, d, *J* = 7.9 Hz, CH-C10, CH-C12), 4.93 (1H, dd, *J* = 2.5, 1.1 Hz, CH_2-C17), 4.91 (1H, dd, *J* = 3.0, 1.1 Hz, CH_2-C17), 3.62 (1H, dd, *J* = 12.7, 0.9 Hz, CH_2-C1), 3.18 (1H, s, CH-C7), 1.30 (3H, s, CH_3-C18/C19), 1.22 (3H, s, CH_3-C18/C19). Partial characterisation of **381**, δ 7.65 (2H, m, CH-C9, CH-C13), 7.33 (2H, d, *J* = 7.9 Hz, CH-C10, CH-C12), 5.00 (1H, d, *J* = 1.4 Hz, CH_2-C17), 4.90 (1H, d, *J* = 1.4 Hz, CH_2-C17), 4.05 (1H, dd, *J* = 12.6, 1.7 Hz, CH_2-C1), 1.38 (3H, s, CH_3-C18/C19), 1.01 (3H, s, CH_3-C18/C19); **HRMS (CI, isobutane)** for $C_{20}H_{26}NO_3S$ ($[M+H]^+$) calculated 360.1633, found 360.1632; **LRMS (CI, isobutane) *m/z* (intensity):** 360 (100), 206 (8), 69 (12).

2-(Toluene-4-sulfonyl)-2,3,4,4a,5,6-hexahydro-1*H*-[*2*]pyrindin-6-ol 392:



392

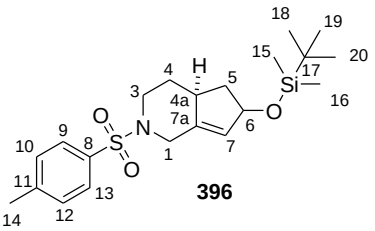
$C_{15}H_{19}NO_3S$

Molecular weight: 293.38 g.mol^{-1}

Sodium borohydride (0.78 g, 2.1 mmol) was added portionwise to a solution of **240** (300 mg, 1.03 mmol) and cerium(III) chloride heptahydrate (0.38 g, 1.0 mmol) in methanol (5 mL), at 0 °C. The mixture was stirred at this temprature for 1 h prior to the addition of water (5 mL). Diethyl ether (5 mL) was added and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 10 ml), the combined organic phases were washed with brine (30 mL), then dried over sodium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 5:5) provided the product **392** (301 mg, 1.03 mmol, 100%) as a colourless solid.

R_f: 0.30 (petroleum ether:ethyl acetate, 3:7); **IR:** ν_{max} 3356, 2920, 1354, 1334, 1159 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.66 (2H, d, *J* = 8.1 Hz, CH-C9, CH-C13), 7.32 (2H, d, *J* = 8.1 Hz, CH-10, CH-C12), 5.58 (1H, s, CH-C7), 4.79—4.78 (1H, m, CH-C6), 4.40 (1H, d, *J* = 12.9 Hz, CH_2-C1), 3.89—3.86 (1H, m, CH_2-C3), 2.92 (1H, d, *J* = 12.9 Hz, CH_2-C1), 2.59 (1H, ddd, *J* = 13.2, 7.7, 7.7 Hz, CH_2-C5), 2.43 (3H, s, CH_3-C14), 2.37 (1H, ddd, *J* = 12.4, 12.3, 2.3 Hz, CH_2-C3), 2.32—2.22 (1H, m, CH-C4a), 1.95—1.89 (1H, m, CH_2-C4), 1.40 (1H, ddd, *J* = 12.8, 12.3, 3.8 Hz, CH_2-C4), 1.20 (1H, ddd, *J* = 13.2, 6.3, 6.3 Hz, CH_2-C5); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 143.6 (C-C11), 141.0 (C-C7a), 133.3 (C-C8), 129.6 (CH-C7), 128.3 (CH-C10, CH-C12), 127.8 (CH-C9, CH-C13), 77.0 (CH-C6), 47.0 (CH_2-C1), 46.0 (CH_2-C3), 41.7 (CH-C4a), 40.9 (CH_2-C5), 33.3 (CH_2-C4), 21.5 (CH_3-C14); **HRMS (CI, isobutane)** for $C_{15}H_{18}NO_2S$ ([M-OH]$^+$) calculated 276.1058, found 276.1062; **LRMS (CI, isobutane) *m/z* (intensity):** 276 (100), 122 (13), 71 (22).

6-(*tert*Butyldimethylsilanyloxy)-2-(toluene-4-sulfonyl)-2,3,4,4a,5,6-hexahydro-1*H*-[*2*]pyrindine 396:



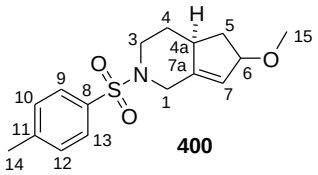
$C_{21}H_{33}NO_3SSi$

Molecular weight: 407.64 g.mol^{-1}

t-Butyldimethylsilyl trifluoromethanesulfonate (0.17 mL, 0.78 mmol) was added to a solution of 2,6-lutidine (0.19 mL, 1.6 mmol) and **392** (190 mg, 0.647 mmol) in dichloromethane (15 mL) at 0 °C. The resulting mixture was warmed to rt and stirred for 17 h before a saturated aqueous solution of ammonium chloride (15 ml) was added. The phases were separated and the aqueous phase was extracted with dichloromethane (3 × 15 ml). The combined organic phases were washed brine (45 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (heptane:ethyl acetate, 8:2) provided the product **396** (262 mg, 0.645 mmol, 100%) as a colourless oil.

R_f: 0.48 (petroleum ether:ethyl acetate, 8:2); **IR:** ν_{max} 2955, 1462, 1354, 1251, 1161 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.65 (2H, d, *J* = 8.1 Hz, CH-C9, CH-C13), 7.31 (2H, d, *J* = 8.1 Hz, CH-C10, CH-C12), 5.48 (1H, d, *J* = 1.6 Hz, CH-C7), 4.84—4.80 (1H, m, CH-C6), 4.40 (1H, d, *J* = 12.9 Hz, CH_2-C1), 3.86—3.83 (1H, m, CH_2-C3), 2.91 (1H, d, *J* = 12.9 Hz, CH_2-C1), 2.48—2.45 (1H, m, CH-C4a), 2.42 (3H, s, CH_3-C14), 2.36 (1H, ddd, *J* = 12.5, 12.3, 2.3 Hz, CH_2-C3), 2.26—2.19 (1H, m, CH_2-C5), 1.86 (1H, dddd, *J* = 10.2, 5.1, 2.4, 2.3 Hz, CH_2-C4), 1.40 (1H, ddd, *J* = 10.2, 12.3, 3.9 Hz, CH_2-C4), 1.24 (1H, ddd, *J* = 12.4, 7.3, 7.3 Hz, CH_2-C5), 0.88 (9H, s, CH_3-C18, CH_3-C19, CH_3-C20), 0.06 (3H, s, CH_3-C15/C16), 0.04 (3H, s, CH_3-C15/C16); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 143.5 (C-C11), 139.0 (C-C8), 133.4 (C-C7a), 129.6 (CH-C10, CH-C12), 129.1 (CH-C7), 127.5 (CH-C9, CH-C13), 76.8 (CH-C6), 46.8 (CH_2-C1), 45.9 (CH_2-C3), 41.9 (CH-C4a), 41.8 (CH_2-5), 32.8 (CH_2-4), 25.9 (CH_3-C18, CH_3-C19, CH_3-C20), 21.5 (CH_3-C14), 18.9 (C-C17), —4.6 (CH_3-C15, CH_3-C16); **HRMS (CI, isobutane)** for $C_{21}H_{34}NO_3SSi$ ($[M+H]^+$) calculated 408.2029, found 408.2030; **LRMS (CI, isobutane) *m/z* (intensity):** 408 (76), 350 (66), 276 (100), 133 (30).

6-Methoxy-2-(toluene-4-sulfonyl)-2,3,4,4a,5,6-hexahydro-1*H*-[*2*]pyrindine 400:



400

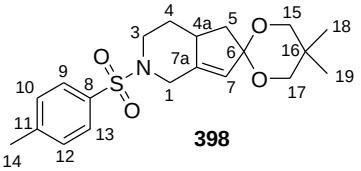
$C_{16}H_{21}NO_3S$

Molecular weight: 307.41 g.mol^{-1}

Sodium hydride (27 mg of a 60% dispersion in mineral oil, 0.68 mmol) was added portionwise to a solution of the alcohol **392** (100 mg, 0.341 mmol) in tetrahydrofuran (7 mL) at 0 °C. The mixture was stirred at this temperature for 10 min and methyl iodide (0.06 mL, 1 mmol) was added dropwise. This solution was then stirred at rt for 2 h and a saturated aqueous solution of ammonium chloride (7 mL) and ethyl acetate (10 mL) were added. The phases were separated and the aqueous phase was extracted with ethyl acetate (3 × 10 ml). The combined organic phases were washed with water (30 mL) and brine (30 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (heptane:ethyl acetate, 8:2) provided the product **400** (97 mg, 0.32 mmol, 93%) as a colourless solid.

R_f: 0.34 (petroleum ether:ethyl acetate, 6:4); **m.p.:** 88—91 °C; **IR:** ν_{max} 2924, 2823, 1450, 1342, 1157 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.66 (2H, d, *J* = 8.1 Hz, CH-C9, CH-C13), 7.31 (2H, d, *J* = 8.1 Hz, CH-C10, CH-C12), 5.62 (1H, d, *J* = 1.6 Hz, CH-C7), 4.44—4.40 (1H, m, CH-C6), 4.41 (1H, d, *J* = 13.1 Hz, CH_2-C1), 3.87—3.82 (1H, m, CH_2-C3), 3.30 (3H, s, CH_3-C15), 2.94 (1H, d, *J* = 13.1 Hz, CH_2-C1), 2.47 (1H, d, *J* = 13.1 Hz, CH_2-C5), 2.42 (3H, s, CH_3-C14), 2.38 (1H, ddd, *J* = 12.5, 12.1, 2.3 Hz, CH_2-C3), 2.27—2.19 (1H, m, CH-C4a), 1.94—1.82 (1H, m, CH_2-C4), 1.40 (1H, ddd, *J* = 12.6, 12.6, 12.1, 4.0 Hz, CH_2-C4), 1.28 (1H, ddd, *J* = 13.1, 6.6, 6.6 Hz, CH_2-C5); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 143.5 (C-C11), 141.2 (C-C8), 133.4 (C-C7a), 129.6 (CH-C10, CH-C12), 127.8 (CH-C9, CH-C13), 125.4 (CH-C7), 85.1 (CH-C6), 56.0 (CH_3-C15), 46.9 (CH_2-C1), 45.9 (CH_2-C3), 41.3 (CH-C4a), 36.8 (CH_2-C5), 33.0 (CH_2-C4), 21.5 (CH_3-C14); **HRMS (CI, isobutane)** for $C_{16}H_{22}NO_3S$ ($[M+H]^+$) calculated 308.1320, found 308.1315; **LRMS (CI, isobutane) *m/z* (intensity):** 308 (22), 276 (100), 122 (18); **Elemental analysis:** $C_{16}H_{21}NO_3S$: requires C: 62.51%, N: 4.56%, H: 6.89%, found C: 62.66%, N: 4.62%, H: 6.93%.

Tricyclic protected enone 398



398

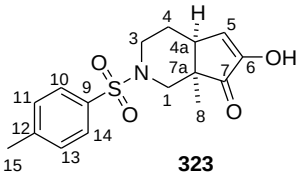
$C_{20}H_{27}NO_4S$

Molecular weight: 377.50 g.mol^{-1}

2,2-Dimethyl-1,3-propanediol (1.78 g, 17.2 mmol) and oxalic acid (62 mg, 0.68 mmol) were added to a solution of enone **240** (1.00 g, 34.3 mmol), in toluene (50 mL). The flask was fitted with a Dean-Stark apparatus and the mixture was heated at 110 °C for 4 h. The resulting solution was then concentrated *in vacuo*, and the residue was dissolved in ethyl acetate (50 mL), washed with water (50 mL) and brine (50 mL), then dried on magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 9:1) provided the product **398** (705 mg, 1.86 mmol, 54%) as a colourless solid.

R_f: 0.38 (petroleum ether:ethyl acetate, 7:3); **m.p.:** 100—102 °C **IR:** ν_{max} 2952, 1472, 1344, 1163 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.64 (2H, d, *J* = 8.1 Hz, CH-C9, CH-C13), 7.29 (2H, d, *J* = 8.1 Hz, CH-C10, CH-C12), 6.51 (1H, s, CH-C7), 3.87 (1H, ddd, *J* = 12.4, 3.0, 2.4 Hz, CH_2-C3), 3.48—3.44 (4H, m, CH_2-C15, CH_2-C17), 2.82 (1H, ddd, *J* = 12.8, 12.4, 2.6 Hz, CH_2-C3), 2.74 (1H, dd, *J* = 16.3, 2.4 Hz, CH_2-C1), 2.57 (1H, d, *J* = 16.3 Hz, CH_2-C1), 2.43 (3H, s, CH_3-C14), 2.39—2.29 (2H, m, CH-C4a, CH_2-C5), 1.98 (1H, dddd, *J* = 12.8, 3.0, 2.6, 2.7 Hz, CH_2-C4), 1.28—1.23 (1H, m, CH_2-C5), 1.17—1.07 (1H, m, CH_2-C4), 1.01 (3H, s, CH_3-C18/C19), 0.92 (3H, s, CH_3-C18/C19); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 143.5 (C-C11), 134.7 (C-C8), 129.6 (CH-C10, CH-C12), 127.6 (CH-C9, CH-13, 123.0 (C-C7a), 117.9 (CH-C7), 107.4 (C-C6), 72.5 (CH_2-C15/C17), 71.8 (CH_2-C15/C17), 43.5 (CH_2-C3), 41.9 (CH_2-C5), 37.8 (CH_2-C1), 34.9 (CH-C4a), 30.0 (C-C16), 26.7 (CH_2-C4), 22.4 (CH_3-C18, CH_3-C19), 21.5 (CH_3-C14); **HRMS (CI, isobutane)** for $C_{20}H_{28}NO_4S$ ($[M+H]^+$) calculated 378.1739, found 378.1743; **LRMS (CI, isobutane)** ***m/z*** **(intensity):** 378 (100), 224 (48), 157 (8); **Elemental analysis** $C_{20}H_{27}NO_4S$ requires C: 63.63%, N: 3.71%, H: 7.21%, found C: 63.91%, N: 3.79%, H: 7.63%.

6-Hydroxy-7a-methyl-2-(toluene-4-sulfonyl)-1,2,3,4,4a,7a-hexahydro-[*2*]pyrindin-7-one 323:



323

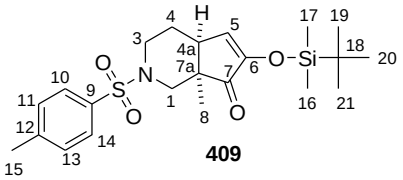
$C_{16}H_{19}NO_4S$

Molecular weight: 321.39 g.mol^{-1}

Dess-Martin periodinane (1.40 g, 3.30 mmol) was added to a solution of **316** (822 mg, 2.54 mmol), in dichloromethane (100 mL) at 0 °C and the solution was stirred for 2 h at rt. A saturated aqueous solution of sodium hydrogencarbonate (50 mL) and diethyl ether (50 mL) were added and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 50 ml), and the combined organic phases were washed with water (150 mL) and brine (150 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 8:2 to 6:4) provided the product **323** (810 mg, 2.52 mmol, 99%) as a colourless crystaline solid allowing a crystal structure to be obtained (appendix 2).

R_f: 0.37 (petroleum ether:ethyl acetate, 5:5); **m.p.:** 140—143 °C**; IR:** ν_{max} 3340, 2926, 1699, 1334, 1159 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.61 (2H, d, *J* = 8.1 Hz, CH-C10, C-C14), 7.28 (2H, d, *J* = 8.1 Hz, CH-C11, C-C13), 6.33 (1H, d, *J* = 3.0 Hz, CH-C5), 5.50 (1H, br s, OH), 3.33—3.31 (1H, m, CH_2-C3), 3.30 (1H, d, *J* = 12.4 Hz, CH_2-C1), 3.09 (1H, d, *J* = 12.4 Hz, CH_2-C1), 3.09—3.07 (1H, m, CH_2-C3), 2.56 (1H, ddd, *J* = 5.5, 5.4, 3.0 Hz, CH-C4a), 2.41 (3H, s, CH_3-C15), 2.02 (1H, dddd, *J* = 14.4, 10.7, 5.4, 5.4 Hz, CH_2-C4), 1.65 (1H, dddd, *J* = 14.4, 10.7, 5.5, 5.5 Hz, CH_2-C4), 1.15 (3H, CH_3-C8); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 205.9 (C-C7), 151.7 (C-C6), 143.4 (C-C12), 134.6 (C-C9), 130.3 (CH-C5), 129.6 (CH-C11, CH-C13), 127.2 (CH-C10, CH-C14), 48.1 (CH_2-C1), 46.5 (C-C7a), 40.8 (CH-C4a), 40.6 (CH_2-C3), 25.0 (CH_2-C4), 21.5 (CH_3-C15), 21.1 (CH_3-C8); **HRMS (CI, isobutane)** for **$C_{16}H_{20}NO_4S$** ([M+H]$^+$) calculated 322.1113, found 322.1115; **LRMS (CI, isobutane) *m/z* (intensity):** 322 (40), 266 (29), 172 (100),157 (89).

6-(*tert*Butyldimethylsilanyloxy)-7a-methyl-2-(toluene-4-sulfonyl)-1,2,3,4,4a,7a-hexahydro-[*2*]pyrindin-7-one 409:



409

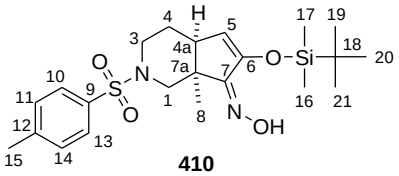
$C_{22}H_{33}NO_4SSi$

Molecular weight: 435.65 g.mol^{-1}

t-Butyldimethylsilyl trifluoromethanesulfonate (0.67 mL, 3.1 mmol) was added to a solution of 2,6-lutidine (0.83 mL, 7.2 mmol) and **323** (920 mg, 2.86 mmol) in dichloromethane (150 mL), at 0 °C. The mixture was stirred at rt for 17 h prior to the addition of a saturated aqueous solution of ammonium chloride (100 ml). The phases were separated and the aqueous phase was extracted with dichloromethane (3 × 100 ml), the combined organic phases were washed with brine (300 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 9:1 to 8:2) provided the product **409** (971 mg, 2.22 mmol, 78%) as a colourless solid.

R_f: 0.35 (petroleum ether:ethyl acetate, 8:2); **m.p.:** 134—136 °C; **IR:** ν_{max} 2929, 2856, 1711, 1616, 1330, 1157 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.62 (2H, d, *J* = 8.1 Hz, CH-C10, CH-C14), 7.28 (2H, d, *J* = 8.1 Hz, CH-C11, CH-C13), 6.40 (1H, d, *J* = 3.0 Hz, CH-C5), 3.31 (1H, ddd, *J* = 11.3, 5.9, 5.6 Hz, CH_2-C3), 3.15 (1H, d, *J* = 12.2 Hz, CH_2-C1), 3.07 (1H, d, *J* = 12.2 Hz, CH_2-C1), 3.06—3.00 (1H, m, CH_2-C3), 2.42 (1H, ddd, *J* = 5.5, 5.0, 3.0 Hz, CH-C4a), 2.40 (3H, s, CH_3-C15), 2.00 (1H, dddd, *J* = 14.3, 9.1, 5.6, 5.5 Hz, CH_2-C4), 1.55 (1H, dddd, *J* = 14.3, 6.2, 5.9, 5.0 Hz, CH_2-C4), 1.12 (3H, s, CH_3-C8), 0.92 (9H, s, CH_3-C19, CH_3-C20, CH_3-C21), 0.16 (6H, s, CH_3-16, CH_3-C17); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 206.0 (C-C7), 152.9 (C-C12), 143.3 (CH-C5), 137.6 (C-C6), 134.5 (C-C9), 129.6 (CH-C11, CH-C13), 127.3 (CH-C10, CH-C14), 48.2 (CH_2-C1), 46.3 (C-C7a), 41.1 (CH_2-C3), 40.2 (CH-C4a), 25.6 (CH_2-C4), 25.5 (CH_3-C19, CH_3-C20, CH_3-C21), 21.7 (CH_3-C8), 21.5 (CH_3-C15), 18.3 (C-C18), —4.6 (CH_3-16, CH_3-C17); **HRMS (CI, isobutane)** for $C_{22}H_{34}NO_4SSi$ ([M+H]$^+$) calculated 436.1978, found 436.1981; **LRMS (CI, isobutane) *m/z* (intensity):** 436 (100), 320 (26), 113 (48), 71 (94).

6-(*tert*Butyldimethylsilanyloxy)-7a-methyl-2-(toluene-4-sulfonyl)-1,2,3,4,4a,7a-hexahydro-[*2*]pyrindin-7-one oxime 410:



410

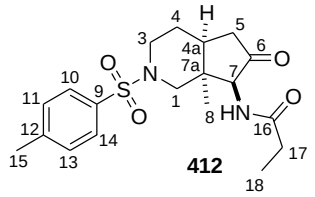
$C_{22}H_{34}N_2O_4SSi$

Molecular weight: 450.67 g.mol^{-1}

Hydroxylamine hydrochloride (11 mg, 0.16 mmol) was added to a solution of **409** (35 mg, 0.080 mmol) in pyridine (2 mL). The mixture was stirred at 40 °C and a further portion of hydroxylamine hydrochloride (11 mg, 0.16 mmol) was added every 24 h over a period of 7 days. The reaction mixture was then concentrated *in vacuo* and the residue was dissolved in ethyl acetate (10 mL), washed with water (10 mL) and brine (10 mL), then dried over sodium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 9:1) provided the product as a mixture of isomers **410** (26 mg, 0.057 mmol, 72%) as a colourless solid.

R_f: 0.58 (petroleum ether:ethyl acetate, 8:2); **m.p.:** 179—181 °C; **IR:** ν_{max} 3240, 3109, 2931, 2862, 1620, 1465, 1342, 1157 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.90 (0.75H, br s, OH), 8.62 (0.25H, br s, OH), 7.65 (2H, d, *J* = 8.5 Hz, CH-C10, CH-C13), 7.27 (2H, d, *J* = 8.5 Hz, CH-C11, CH-C14), 5.30 (1H, d, *J* = 2.9 Hz, CH-C5), 3.88 (1H, d, *J* = 12.7 Hz, CH_2-C1), 3.37 (1H, ddd, *J* = 10.5, 10.2, 5.6 Hz, CH_2-C3), 3.23 (1H, d, *J* = 12.7 Hz, CH_2-C1), 3.04 (1H, ddd, *J* = 10.5, 10.5, 5.3 Hz, CH_2-C3), 2.40 (3H, s, CH_3-C15), 2.26—2.20 (1H, m, CH-C4a), 1.86 (1H, ddd, *J* = 10.5, 10.1, 5.6, 5.2 Hz, CH_2-C4), 1.41 (3H, s, CH_3-C8), 1.34—1.27 (1H, m, CH_2-C4), 0.95 (9H, s, CH_3-C19, CH_3-C20, CH_3-C21), 0.18 (3H, s, CH_3-C16/C17), 0.16 (3H, s, CH_3-C16/C17); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 162.2 (C-C7), 149.3 (C-C6), 143.0 (C-C12), 135.0 (C-C9), 129.5 (CH-C11, CH-C14), 127.3 (CH-C10, CH-C13), 119.9 (CH-C5), 46.6 (CH_2-C1), 44.9 (C-C7a), 44.0 (CH-C4a), 41.6 (CH_2-C3), 26.9 (CH_2-C4), 25.5 (CH_3-C19, CH_3-C20, CH_3-C21), 22.0 (CH_3-C8), 21.5 (CH_3-C15), 18.2 (C-C17), —4.7 (CH_3-C16, CH_3-C17); **HRMS (CI, isobutane)** for $C_{22}H_{35}N_2O_4SSi$ ($[M+H]^+$) calculated 451.2087, found 451.2089; **LRMS (CI, isobutane) *m/z* (intensity):** 451 (32), 435 (58), 279 (36), 133 (74).

***N*-[7a-Methyl-6-oxo-2-(toluene-4-sulfonyl)-octahydro-[*2*]pyrindin-7-yl]-propionamide 412:**



412

$C_{19}H_{26}N_2O_4S$

Molecular weight: 378.49 g.mol^{-1}

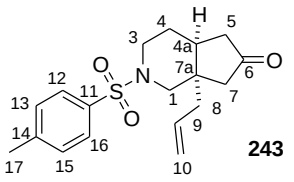
Palladium on carbon (16 mg, 0.15 mmol) was added to a solution of **410** (684 mg, 1.52 mmol) and hydrochloric acid (1.5 mL) in ethanol (15 mL) under hydrogen atmosphere ballon. The mixture was stirred at rt for 3 h, then filtered through Celite and concentrated *in vacuo*. The amine hydrochloric salt was obtained by trituration with ethanol, hydrochloric acid and diethyl ether, filtration, and subsequent driyng under vaccum. This product **411** was used directly in the next step (360 mg, 0.951 mmol, 62%).

N-Methyl morpholine (0.07 mL, 0.6 mmol) and propanoyl chloride (0.03 mL, 0.3 mmol) were added to a solution of **411** (90 mg, 0.25 mmol) in tetrahydrofuran (3 mL) at 0 °C The resulting mixture was warmed to rt and stirred for 24 h. Ethyl acetate (5 mL) and water (5 mL) were added and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 5 ml) and the combined organic phases were washed with a saturated aqueous solution of sodium hydrogencarbonate (5 mL) and brine (5 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (diethyl ether:ethyl acetate, 5:5) provided the product **412** (47 mg, 0.12 mmol, 50%) as a colourless crystalline solid allowing a crystal structure to be obtained (**Appendix 3**).

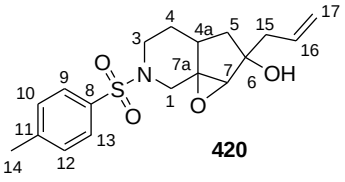
R_f: 0.47 (ethyl acetate, 10); **m.p.:** 189—182 °C; **IR:** ν_{max} 3410, 3286, 1751, 1681, 1512, 1327, 1157 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.62 (2H, d, *J* = 8.1 Hz, CH-C10, CH-C14), 7.31 (2H, d, *J* = 8.1 Hz, CH-C11, CH-C13), 5.45 (1H, d, *J* = 7.8 Hz, NH), 4.59 (1H, d, *J* = 7.8 Hz, CH-C7), 3.61 (1H, ddd, *J* = 11.5, 4.9, 2.5 Hz, CH_2-C3), 3.21 (1H, d, *J* = 12.2 Hz, CH_2-C1), 2.44 (3H, s, CH_3-C15), 2.42—2.26 (5H, CH_2-C3, CH_2-C5, CH-C4a, CH_2-C17), 2.13—2.21 (1H, m, CH_2-C4), 1.96 (1H, dd, *J* = 19.1, 9.8 Hz, CH_2-C5), 1.64—1.62 (1H, m, CH_2-C4), 1.87 (1H, d, *J* = 12.2 Hz, CH_2-C1), 1.39 (3H, s, CH_3-C8), 1.95 (3H, t, *J* = 7.5 Hz, CH_3-C18); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 212.8 (C-C6), 174.8 (C-C16), 143.9 (C-C12), 133.1 (C-C9), 129.9 (CH-C11, CH-C13), 127.4 (CH-C10, CH-C14), 66.3 (CH-C7), 47.4 (CH_2-C1), 42.5 (C-C7a), 41.1 (CH_2-C3), 35.6 (CH_2-C5), 34.3 (CH-C4a), 29.4 (CH_2-C17), 23.4 (CH_2-C4), 21.7 (CH_2-C8), 21.5 (CH_2-C15), 9.6 (CH_3-C18); **HRMS (CI, isobutane)** for $C_{19}H_{27}N_2O_4S$ ($[M+H]^+$) calculated 379.1692,

found 379.1696; **LRMS (CI, isobutane) *m/z* (intensity):** 379 (10), 225 (9), 113 (14), 89 (100).

7a-Allyl-2-(toluene-4-sulfonyl)-octahydro-[*2*]pyrindin-6-one 243 and 2-Allyl-6-(toluene-4-sulfonyl)-octahydro-1-oxa-6-aza-cyclopropa[*c*]inden-2-ol 420:



243



420

$C_{18}H_{23}NO_3S$

Molecular weight: 333.45 g.mol^{-1}

$C_{18}H_{23}NO_4S$

Molecular weight: 349.44 g.mol^{-1}

Allylmagnesium chloride (2.7 mL of a 1.0 M solution in tetrahydrofuran, 2.7 mmol) was added dropwise to a solution of copper (I) iodide (0.26 g, 1.4 mmol), in tetrahydrofuran (20 mL) at rt. This was followed by the dropwise addition of a solution of ketone **240** (200 g, 0.69 mmol) and chlorotrimethylsilane (0.21 mL, 1.7 mmol) in tetrahydrofuran (5 mL). After 1 h, the mixture was quenched by the addition of saturated aqueous ammonium chloride solution (10 mL), saturated aqueous ammonium hydroxide solution (10 mL) and water (20 mL), then diethyl ether (50 mL) was added. The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 50 ml). The combined organic phases were washed with water (150 mL) and brine (150 mL), then dried over sodium sulfate and concentrated *in vacuo*. Dimethyldioxirane (0.085 M in acetone, 9.6 mL) was added to a solution of the crude mixture, in dichloromethane (7.5 mL), at 0 ºC. After 5 min, the solution was concentrated *in vacuo* and the residue was dissolved in a mixture of tetrahydrofuran (10 mL), water (4 mL) and acetic acid (4 mL). The mixture was stirred at rt for 3 h. Solid sodium hydrogencarbonate was added until gas evolution ceased. Ethyl acetate (20 mL) and water (20 mL) were added and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 20 ml), the combined organic phases were successively washed with a saturated aqueous solution of sodium hydrogencarbonate (30 mL), water (30 mL), and brine (30 mL). The solution was then dried over magnesium sulfate, and concentrated *in vacuo*. Purification of the residue by flash column chromatography (petroleum ether-ethyl acetate, 8:2 to 3:7) provided the product **243** (119 mg, 0.357 mmol, 52%) and **420** (56 mg, 0.16 mmol, 23%) as colourless solids.

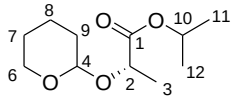
Data for **243**:

R_f: 0.29 (petroleum ether:ethyl acetate, 5:5); **m.p.:** 133—136 °C (lit: 136—139 °C); **IR:** ν_{max} 2901, 1728, 1334, 1157 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.61 (2H, d, *J* = 7.8 Hz, CH-C12, CH-C16), 7.32 (2H, d, *J* = 7.8 Hz, CH-C13, CH-C15), 5.72 (1H, dddd, *J* = 17.8, 10.3, 7.4, 7.4 Hz, CH-C9), 5.17—5.11 (2H, m, CH_2-C10), 3.13—3.08 (1H, m, CH_2-C3), 3.00 (1H, d, *J* = 11.5 Hz, CH_2-C1), 2.89—2.83 (1H, m, CH_2-C3), 2.58 (1H, d, *J* = 11.5 Hz, CH_2-C1), 2.43 (3H, s, CH_3-C17), 2.48—2.38 (1H, m, CH_2-C8), 2.31 (1H, dd, *J* = 18.5, 7.9 Hz, CH_2-C5), 2.26—2.19 (1H, m, CH_2-C8), 2.21 (2H, s, CH_2-C7), 2.15—2.10 (1H, m, CH-C4a), 2.05—1.97 (2H, m, CH_2-C4, CH_2-C5), 1.55 (1H, dddd, J = 14.2, 6.2, 6.1, 3.6 Hz, CH_2-C4); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 216.7 (C-C6), 143.9 (C-C11), 133.0 (C-14), 132.6 (CH-C9), 129.9 (CH-C12, CH-C16), 127.7 (CH-C13 CH-C15), 119.8 (CH_2-C10), 49.6 (CH_2-C1), 46.5 (CH_2-C7), 42.7 (CH_2-C3), 41.6 (C-C7a), 41.2 (CH_2-C5), 40.5 (CH_2-C8), 37.0 (CH-C4a), 25.4 (CH_2-C4), 21.6 (CH_3-C17); **HRMS (CI, isobutane)** for $C_{18}H_{24}NO_3S$ ($[M+H]^+$) calculated 346.1477, found 346.1479; **LRMS (CI, isobutane) *m/z* (intensity):** 346 (100), 192 (29), 71 (30); **Elemental analysis:** $C_{18}H_{23}NO_3S$ requires C: 64.84%, N: 4.20%, H: 6.95%, found C: 64.75%, N: 4.33%, H: 6.98%. The data observed are in accordance with literature values.[84]

Data for **420**:

R_f: 0.31 (petroleum ether:ethyl acetate, 3:7); **IR:** ν_{max} 3485, 2926, 2854, 1749), 1597, 1338, 1159 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.68 (2H, d, *J* = 8.2 Hz, CH-C9, CH-C13), 7.32 (2H, d, *J* = 8.2 Hz, CH-C10, CH-C12), 5.82 (1H, ddt, *J* = 17.2, 10.3, 7.3 Hz, CH-C16), 5.13 (1H, d, *J* = 10.3 Hz, CH_2-C17), 5.08 (1H, dd, *J* = 17.2, 1.5 Hz, CH_2-C17), 3.92—3.89 (1H, m, CH_2-C3), 3.71 (1H, d, *J* = 12.3 Hz, CH_2-C1), 3.41 (1H, s, CH-C7), 2.98 (1H, d, *J* = 12.3 Hz, CH_2-C1), 2.43 (3H, s, CH_3-C14), 2.44 (1H, m, CH_2-C3), 2.27 (1H, dd, *J* = 13.7, 7.0 Hz, CH_2-C5), 2.22 (1H, dd, *J* = 13.7, 7.0 Hz, CH_2-C5), 1.79—1.64 (4H, CH_2-C4, CH-C4a, CH_2-C15), 1.10—1.05 (1H, m, CH_2-C4); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 143.5 (C-C11), 133.5 (C-C8), 132.1 (CH-C16), 129.6 (CH-C10, CH-C12), 127.5 (CH-C9, CH-C13), 118.8 (CH_2-C17), 79.1 (C-C6), 65.7 (CH-C7), 63.8 (C-C7a), 48.8 (CH_2-C1), 45.8 (CH_2-C3), 40.6 (CH_2-C5), 37.4 (CH_2-C4), 37.1 (CH-C4a), 27.2 (CH_2-C15), 21.4 (CH_3-C14); **HRMS (CI, isobutane)** for $C_{18}H_{24}NO_4S$ ($[M+H]^+$) calculated 350.1426, found 350.1429; **LRMS (CI, isobutane) *m/z* (intensity):** 350 (19), 316 (36), 89 (100).

2-(Tetrahydropyran-2-yloxy)-propionic acid isopropyl ester 430:



430

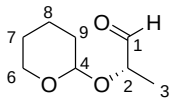
$C_{11}H_{20}O_4$

Molecular weight: 216.27 g.mol^{-1}

Pyridinium *p*-toluenesulfonate (0.19 g, 0.76 mmol) and 3,4-dihydro-2*H*-pyran (0.95 mL, 11 mmol) were added to a solution of L-isopropyl lactate (1.0 mL, 7.6 mmol) in dichloromethane (20 mL). The solution was stirred at rt for 3 h, then was washed with brine (20 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 9:1) provided the product **430** (1.6 g, 7.5 mmol, 98%) as a colourless oil. The product was isolated as an inseparable diastereomeric mixture (4:3) with respect to the stereogenic centre in the tetrahydropyranyl ring.

R_f: 0.57 (petroleum ether:ethyl acetate, 9:1); **IR:** ν_{max} 2940, 1743, 1454, 1374 cm^{-1}; **^{1}H NMR for the major isomer** (400 MHz, $CDCl_3$): δ 5.01 (1H, hept, *J* = 12.5, CH-C10), 4.68 (1H, t, *J* = 3.6 Hz, CH-C4), 4.34 (1H, q, *J* = 7.0 Hz, CH-C2), 3.95 (1H, ddd, *J* = 3.3, 5.9, 25.5, CH_2-C6), 3.37—3.52 (1H, m, CH_2-C6), 1.90—1.45 (6H, m, CH_2-C7, CH_2-C8, CH_2-C9), 1.40 (3H, d, *J* = 7.0, CH_3-C3), 1.23—1.20 (6H, m, CH_3-C11, CH_3-C12); **^{13}C NMR for the major isomer** (101 MHz, $CDCl_3$): 172.9 (C-C1), 97.6 (CH-C4), 70.1 (CH-C2), 68.3 (CH-C10), 62.4 (CH_2-C6), 30.4 (CH_2-C9), 25.5 (CH_2-C7), 21.9 (CH_3-C11, CH_3-C12), 19.2 (CH_3-C8), 18.7 (CH_2-C3); **^{1}H NMR for the minor isomer** (400 MHz, $CDCl_3$): δ 5.01 (1H, hept, *J* = 12.5, CH-C10), 4.65 (1H, t, *J* = 3.6 Hz, CH-C4), 4.09 (1H, q, *J* = 7.0 Hz, CH-C2), 3.85 (1H, ddd, *J* = 3.3, 5.9, 25.5, CH_2-C6), 3.37—3.52 (1H, m, CH_2-C6), 1.90—1.45 (6H, m, CH_2-C7, CH_2-C8, CH_2-C9), 1.34 (3H, d, *J* = 7.0, CH_3-C3), 1.23—1.20 (6H, m, CH_3-C11, CH_3-C12); **^{13}C NMR for the minor isomer** (101 MHz, $CDCl_3$): 172.8 (C-C1), 98.3 (CH-C4), 72.7 (CH-C2), 68.1 (CH-C10), 62.3 (CH_2-C6), 30.5 (CH_2-C9), 25.4 (CH_2-C7), 21.8 (CH_3-C11, CH_3-C12), 19.1 (CH_3-C8), 18.1 (CH_2-C3); **HRMS (CI, isobutane)** for $C_{11}H_{21}O_4$ ($[M+H]^+$) calculated 217.1440, found 217.1437; **LRMS (CI, isobutane) *m/z* (intensity):** 217 (8), 133 (18), 85 (100); **Elemental analysis:** $C_{11}H_{20}O_4$ requires C: 61.09%, H: 9.32% found, C: 61.23%, H: 9.40%.These data observed are in accordance with literature values.[152]

2-(Tetrahydropyran-2-yloxy)-propionaldehyde 431:



431

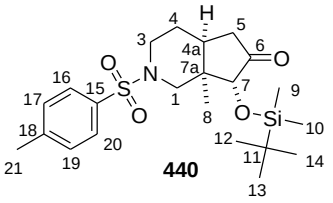
$C_8H_{14}O_3$

Molecular weight: 158.19 g.mol^{-1}

Diisobutylaluminum hydride (7.5 mL of a 1.0 M solution in dichloromethane, 7.5 mmol) was added dropwise to a solution of **430** (1.6 g, 7.5 mmol) in dichloromethane (200 mL) at −78 °C. The mixture was stirred at this temperature for 1 h and then quenched by the addition of a saturated aqueous solution of sodium potassium tartrate (200 mL), diluted with ethyl acetate (500 mL) and warmed to rt. The phases were separated and the aqueous phase was extracted with ethyl acetate (3 × 500 mL), the combined organic phases were washed with washed with water (1 L), and brine (1 L), then dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 9:1) provided the title compound **431** (0.75 g, 4.8 mmol, 63%) as a colourless oil. The product was isolated as an inseparable diastereomeric mixture (1:0.86) with respect to the stereogenic centre in the tetrahydropyranyl ring.

R_f: 0.47 (petroleum ether:ethyl acetate, 8:1); **IR:** ν_{max} 2940, 1743, 1454, 1374 cm^{-1}; **^{1}H NMR for the major isomer** (400 MHz, $CDCl_3$): δ 9.64 (1H, s, CHO-C1), 4.64 (1H, dd, *J* = 4.9, 2.5 Hz, CH-C4), 3.98 (1H, dq, *J* = 7.0, 2.5 Hz, CH-C2), 3.45—3.57 (1H, m, and m, CH_2-C6), 1.45—1.90 (6H, m, CH_2-C7, CH_2-C8, CH_2-C9), 1.31 (3H, d, *J* = 7.0 Hz, and d, *J* = 7.0, Hz CH_3-C3); **^{13}C NMR for the major isomer** (101 MHz, $CDCl_3$): δ 203.7 (C-C1), 99.5 (CH-C4), 76.8 (CH-C2), 63.7 (CH_2-C6), 30.8 (CH_2-C9), 25.3 (CH_2-C7), 20.1 (CH_2-C8), 15.3 (CH_3-C3); **^{1}H NMR for the minor isomer** (400 MHz, $CDCl_3$): δ 9.64 (1H, s, CHO-C1), 4.71 (1H, dd, *J* = 4.9, 2.5 Hz, CH-C4), 4.23 (1H, dq, *J* = 7.0, 2.5 Hz, CH-C2), 3.83—3.93 (1H, m, and m, CH_2-C6), 1.45—1.90 (6H, m, CH_2-C7, CH_2-C8, CH_2-C9), 1.35 (3H, d, *J* = 7.0 Hz, and d, *J* = 7.0, Hz CH_3-C3); **^{13}C NMR for the minor isomer** (101 MHz, $CDCl_3$): δ 203.3 (C-C1), 98.5 (CH-C4), 78.7 (CH-C2), 62.9 (CH_2-C6), 30.7 (CH_2-C9), 25.4 (CH_2-C7), 19.5 (CH_2-C8), 15.5 (CH_3-C3); **HRMS (CI, isobutane)** for $C_8H_{15}O_3$ ($[M+H]^+$) calculated 159.1021, found 159.1023; **LRMS (CI, isobutane) *m/z* (intensity):** 159 (18), 85 (100), 75 (61). These data observed are in accordance with literature values.[152]

7-(*tert*Butyldimethylsilanyloxy)-7a-methyl-2-(toluene-4-sulfonyl)-octahydro-[2]pyrindin-6-one 440:



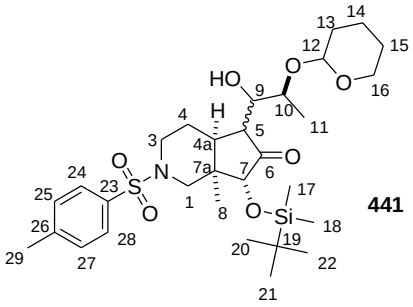
$C_{22}H_{35}NO_4SSi$

Molecular weight: 437.67 g.mol^{-1}

Imidazole (1.7 g, 25 mmol) and *t*-butyldimethylsilyl chloride (1.0 g, 6.8 mmol) were added to a solution of **316** (1.5 g, 4.5 mmol) in *N*,*N*-dimethylformamide (25 mL) and the mixture was stirred at 30 °C for 17 h. Diethyl ether (50 mL) and water (50 mL) were added, the phases were separated and the organic phase was washed with water (3 × 50 mL), and brine (50 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 95:5) provided the product **440** (1.7 g, 3.8 mmol, 83%) as a colourless solid.

R_f: 0.40 (petroleum ether:ethyl acetate, 6:4); **mp:** 171—172 °C; **IR:** ν_{max} 2929, 2856, 1749, 1462, 1340, 1161 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.64 (2H, d, *J* = 8.2 Hz, CH-C16, CH-C20), 7.34 (2H, d, *J* = 8.2 Hz, CH-C17, CH-C19), 4.39 (1H, s, CH-C7), 3.75—3.73 (1H, m, CH_2-C3), 3.64 (1H, dd, *J* = 11.9, 1.7 Hz, CH_2-C1), 2.47 (1H, dd, *J* = 19.4, 8.3 Hz, CH_2-C5), 2.43 (3H, s, CH_3-C21), 2.16 (1H, ddd, *J* = 12.4, 12.0, 2.5 Hz, CH_2-C3), 2.01 (1H, d, *J* = 11.9 Hz, CH_2-C1), 1.93 (1H, d, *J* = 19.4 Hz, CH_2-C5), 1.87—1.81 (1H, m, CH_2-C4), 1.81—1.73 (1H, m, CH-C4a), 1.57 (1H, ddd, *J* = 15.9, 12.4, 4.3 Hz, CH_2-C4), 0.93 (9H, s, CH_3-C12, CH_3-C13, CH_3-C14), 0.81 (3H, s, CH_3-C8), 0.20 (3H, s, CH_3-C9/C10), 0.19 (3H, s, CH_3-C9/C10); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 215.2 (C-C6), 143.7 (C-C18), 132.6 (C-C15), 129.7 (CH-C17, CH-C19), 127.9 (CH-C16, CH-C20), 76.4 (CH-C7), 51.1 (CH_2-C1), 46.0 (CH_2-C3), 41.6 (C-C7a), 39.7 (CH_2-C5), 34.8 (CH-C4a), 29.5 (CH_2-C4), 25.9 (CH_3-C12, CH_3-C13, CH_3-C14), 21.6 (CH_3-C21), 19.4 (CH_3-C8), 18.3 (C-C11), —5.1 (CH_3-C9, CH_3-C10); **HRMS (CI, isobutane)** for $C_{21}H_{36}NO_4SSi$ ($[M+H]^+$) calculated 438.2134, found 438.2138; **LRMS (CI, isobutane) *m/z* (intensity):** 438.5 (100), 284.5 (22), 107.2 (38); **Elemental analysis:** $C_{21}H_{35}NO_4SSi$ requires C: 60.37%, N: 3.20%, H: 8.06%, found C: 60.50%, N: 3.37 %, H: 8.10%.

7-(*tert*Butyldimethylsilanyloxy)-5-[1-hydroxy-2-(tetrahydropyran-2-yloxy)propyl]-7a-methyl-2-(toluene-4-sulfonyl)octahydro-[*2*]pyrindin-6-one 441:



441

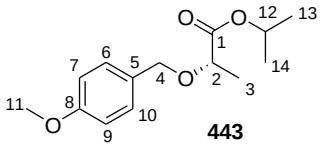
$C_{30}H_{49}NO_7SSi$

Molecular weight: 595.86 g.mol^{-1}

A solution of *n*-butyllithium (0.23 mL of a 2.5 M solution in hexanes, 0.57 mmol) was added dropwise to a solution of di*iso*propyl amine (77 µL, 0.55 mmol) in tetrahydrofuran (5 mL), at −78 °C. The solution was stirred at −78 °C for 10 min, then warmed to 0 °C for 10 min and finally cooled back to −78 °C. This solution of lithium di*iso*propyl amide was then added dropwise to a solution of **431** (0.20 g, 0.46 mmol) in tetrahydrofuran (10 mL) at −78 °C. The resulting mixture was stirred at this temperature for 30 min and a solution of zinc chloride (0.14 g, 1.1 mmol) in tetrahydofuran (2 mL) was added. After a further 5 min, a solution of **440** (0.14 g, 0.92 mmol) in tetrahydrofuran (2 mL) was added. The mixture was stirred at −78 °C for 2 h, then slowly warmed to rt, and stirred for a further 16 h. Diethyl ether (20 mL) and a saturated aqueous solution of ammonium chloride (20 mL) were added, the phases were separated and the aqueous phase was extracted with diethyl ether (2 × 20). The combined organic phases were washed with washed brine (50 mL) then dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 9:1 to 6:4) provided the product **441** (0.18 g, 0.30 mmol, 67%) as an inseparable mixture of diastereoisomers, which was used without further separation.

HRMS (FAB) for $C_{30}H_{49}NO_7SSiNa$ ($[M+Na]^+$) calculated 618.2897, found 618.2899; **LRMS (FAB) *m/z* (intensity):** 618 (100), 530 (21), 87 (60).

2-(4-Methoxy-benzyloxy)-propionic acid *iso*propyl ester 443:



443

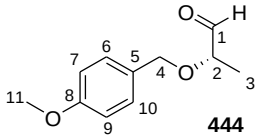
$C_{14}H_{20}O_3$

Molecular weight: 252.31 g.mol^{-1}

A solution of L-*iso*propyl lactate (2.0 mL, 15 mmol) in *N*,*N*-dimethylformamide (4 mL) was added dropwise to a solution of sodium hydroxide (0.67 g, 60% in mineral oil, 17 mmol) in *N*,*N*-dimethylformamide (50 mL) at 0 °C. The mixture was stirred for 1 h at rt and a solution of tetrabutylammonium iodide (0.28 g, 0.76 mmol) in *N*,*N*-dimethylformamide (8 mL) was added, followed by 4-methoxybenzyl chloride (2.5 mL, 18 mmol). The mixture was stirred at rt for 16 h, and diethyl ether (50 mL) and water (50 mL) were added. The organic phase was washed with water (3 × 50 mL) and brine (50 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 95:5) provided the product **443** (1.8 g, 7.2 mmol, 48%) as a colourless oil.

R_f: 0.65 (petroleum ether:ethyl acetate, 6:4); **IR:** ν_{max} 2982, 2937, 2837, 1737, 1587, 1514, 1246 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.29 (2H, d, *J* = 8.7 Hz, CH-C6, CH-C10), 6.87 (2H, d, *J* = 8.7 Hz, CH-C7, CH-C9), 5.09 (1H, hept, *J* = 6.2 Hz, CH-C12), 4.61 (1H, d, *J* = 11.2 Hz, CH_2-C4), 4.36 (1H, d, *J* = 11.2 Hz, CH_2-C4), 3.98 (1H, q, *J* = 6.8 Hz, CH-C2), 3.79 (3H, s, CH_3-C11), 1.39 (3H, d, *J* = 6.8 Hz, CH_3-C3), 1.27 (3H, d, *J* = 6.2 Hz, CH_3-C13/C14), 1.26 (3H, d, *J* = 6.2 Hz, CH_3-C13/C14); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 172.9 (C-C1), 159.6 (C-C8), 129.6 (C-C5), 129.3 (CH-C6, CH-C10), 113.9 (CH-C7, CH-C9), 73.8 (CH-C2), 71.6 (CH_2-C4), 66.1 (CH-C12), 55.6 (CH_3-C11), 22.1 (CH_3-C13, CH_3-C14), 18.7 (CH_3-C3).

2-(4-Methoxy-benzyloxy)propionaldehyde 444:



444

$C_{11}H_{14}O_4$

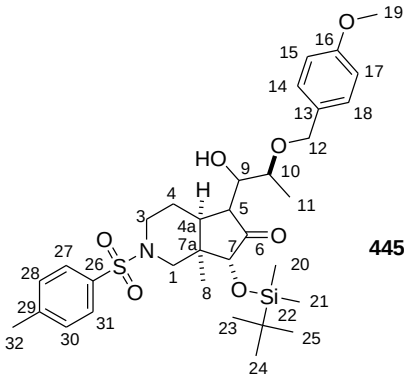
Molecular weight: 194.23 g.mol^{-1}

A solution of diisobutylaluminum hydride (6.8 mL of a 1.0 M solution in dichloromethane, 6.8 mmol) was added dropwise to a solution of **443** (1.7 g, 6.8 mmol), in dichloromethane (200 mL) at −78 °C. The mixture was stirred at this temperature for 1 h, quenched with a saturated aqueous solution of sodium potassium tartrate (300 mL), diluted with ethyl acetate (500 mL) and warmed to rt. The phases were separated and the aqueous phase was

extracted with ethyl acetate (3 × 500 mL). The combined organic phases were washed with water (500 mL) and brine (500 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 95:5) provided the title compound **444** (1.0 g, 5.2 mmol, 77%) as a colourless oil.

R_f: 0.65 (petroleum ether:ethyl acetate, 6:4); **IR:** ν_{max} 2982, 2908, 2837, 1737, 1464, 1514 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.63 (1H, d, *J* = 1.8 Hz, CHO-C1), 7.28 (2H, d, *J* = 8.5 Hz, CH-C6, CH-C10), 6.89 (2H, d, *J* = 8.5 Hz, CH-C7, CH-C9), 4.55 (1H, d, *J* = 3.7 Hz, CH_2-C4), 4.55 (1H, d, *J* = 3.7 Hz, CH_2-C4), 3.87 (1H, qd, *J* = 6.9, 1.8 Hz, CH-C2), 3.80 (3H, s, CH_3-C11), 1.30 (3H, d, *J* = 6.9 Hz, CH_3-C3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 203.3 (CHO-C1), 159.5 (C-C8), 130.4 (CH-C6, CH-C10), 129.4 (C-C5), 114.2 (CH-C7, CH-C9), 79.1 (CH-C2), 71.7 (CH_2-C4), 55.3 (CH_3-C11), 15.3 (CH_3-C3); **HRMS (EI)** for $C_{11}H_{14}O_3$ ([M]$^+$) calculated 194.0943, found 194.0945; **LRMS (EI) *m/z* (intensity):** 194 (8), 121 (100), 91 (10), 77 (19).

7-(*tert*Butyldimethylsilanyloxy)-5-[1-hydroxy-2-(4-methoxybenzyloxy)propyl]-7a-methyl-2-(toluene-4-sulfonyl)octahydro-[*2*]pyrindin-6-one 445:



445

$C_{33}H_{49}NO_7SSi$

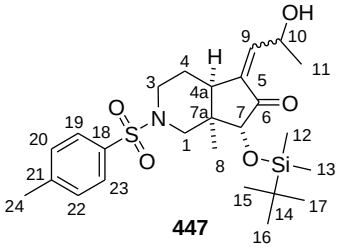
Molecular weight: 631.90 g.mol^{-1}

A solution of *n*-butyllithium (1.8 mL of a 2.5 M solution in hexanes, 4.4 mmol) was added dropwise to a solution of diisopropyl amine (0.58 mL, 4.1 mmol) in tetrahydrofuran (5 mL) at −78 °C. The solution was stirred at −78 °C for 10 min, then warmed to 0 °C for 10 min and finally cooled back to −78 °C. This solution of lithium diisopropyl amide was then added dropwise to a solution of **444** (1.13 g, 2.58 mmol) in tetrahydrofuran (50 mL) at −78 °C. The resulting mixture was stirred at this temperature for 30 min and a solution of zinc chloride (0.81 g, 5.9 mmol) in tetrahydofuran (10 mL) was added. After a further 5 min, a solution of **440** (1.0 g, 5.2 mmol) in tetrahydrofuran (10 mL) was added. The mixture was stirred at −78 °C for 2 h, then slowly warmed to rt and stirred for a further 16 h. Diethyl ether (50 mL) and a saturated aqueous solution of ammonium chloride (50 mL) were added

and the phases were separated. The aqueous phase was extracted with diethyl ether (2 × 50 ml), the combined organic phases were washed with brine (100 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate 9:1 to 6:4) provided the product **445** (1.1 g, 1.8 mmol, 69%) as a mixture of isomers, which was used without further separation. For data purposes, a fraction of the major isomer (16% of the mixture) was isolated and characterised.

R_f: 0.51 (petroleum ether:ethyl acetate, 6:4); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.61 (2H, d, *J* = 8.1 Hz, CH-C27, CH-C31), 7.33 (2H, d, *J* = 8.1 Hz, CH-C28, CH-C30), 7.15 (2H, d, *J* = 8.6 Hz, CH-C14, CH-C18), 6.79 (2H, d, *J* = 8.6 Hz, CH-C15, CH-C17), 4.45 (1H, d, *J* = 11.4 Hz, CH_2-C12), 4.34 (1H, d, *J* = 11.4 Hz, CH_2-C12), 4.14 (1H, s, CH-C7), 3.78 (3H, s, CH_3-C19), 3.63—3.51 (2H, m, CH-C9, CH-C10), 3.29—3.24 (1H, m, CH_2-C3), 3.13 (1H, d, *J* = 12.0 Hz, CH_2-C1), 2.46—2.44 (1H, m, CH_2-C3), 2.44 (3H, s, CH_3-C32), 2.28 (1H, d, *J* = 12.0 Hz, CH_2-C1), 2.22 (1H, ddd, *J* = 6.6, 5.1, 1.5 Hz, CH-C5), 1.90 (1H, dddd, *J* = 12.8, 5.6, 5.7, 3.3 Hz CH_2-C4), 1.81 (1H, ddd, J = 10.2, 5.6, 5.1 Hz, CH-C4a), 1.60 (1H, dddd, *J* = 12.8, 10.2, 9.4, 4.0 Hz, CH_2-C4), 1.19 (3H, d, *J* = 6.1 Hz, CH_3-C11), 0.93 (9H, s, CH_3-C23, CH_3-C24, CH_3-C25), 0.88 (3H, s, CH_3-C8), 0.15 (3H, s, CH_3-C2/C210), 0.14 (3H, s, CH_3-C20/C21); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 217.9 (C-C6), 159.2 (C-C16), 143.8 (C-C29), 132.7 (C-C13), 130.5 (C-C26), 129.8 (CH-C14, CH-C18), 129.4 (CH-C15, CH-C17), 127.8 (CH-Car, CH-Car), 113.8 (CH-Car, CH-Car), 77.8 (CH-C7), 76.4 (CH-C9), 75.5 (CH-C10), 70.5 (CH_2-C12), 55.3 (CH_3-C19), 51.0 (CH-C5), 50.5 (CH_2-C1), 44.8 (CH_2-C3), 40.8 (C-C7a), 38.6 (CH-C4a), 28.4 (CH_2-C4), 25.9 (CH_3-C23, CH_3-C24, CH_3-C25), 21.6 (CH_3-C32), 20.1 (CH_3-C8), 18.3 (C-C22), 15.5 (CH_3-C11), −4.1 (CH_3-C20/C21), −5.0 (CH_3-C20/C21); **HRMS (FAB)** for $C_{33}H_{50}NO_7SSi$ ($[M+H]^+$) calculated 632.3077, found 632.3071; **LRMS (FAB) *m/z* (intensity):** 632 (22), 530 (49), 380 (60), 122 (100).

7-(*tert*Butyldimethylsilanyloxy)-5-(2-hydroxypropylidene)-7a-methyl-2-(toluene-4-sulfonyl)octahydro-[*2*]pyrindin-6-one 447:



447

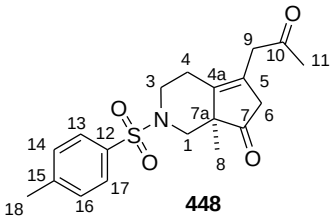
$C_{25}H_{39}NO_5SSi$

Molecular weight: 493.73 g.mol^{-1}

Ceric ammonium nitrate (0.95 g, 1.7 mmol) was added to a solution of **445** (0.55 g, 0.87 mmol) in acetonitrile (20 mL) and water (2 mL). The mixture was stirred at rt for 3 h and ethyl acetate (20 mL) and water (20 mL) were added. The phases were separated and the aqueous phase was extracted with ethyl acetate (3 × 20 mL), the combined organic phases were washed with water (20 mL), and brine (50 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: ethyl acetate 95:5 to 6:4) provided the product **447** (0.32 g, 0.65 mmol, 75%) as an inseparable mixture of *E*/*Z* isomers (2.3:1).

R_f: 0.37 (petroleum ether:ethyl acetate, 5:5); **IR:** ν_{max} 3700—3300, 2956, 2929, 2855, 1735, 1657, 1356, 1246 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.63 (2H, d, *J* = 8.1 Hz, CH-C19, CH-C23), 7.33 (2H, d, *J* = 8.1 Hz, CH-C20, CH-C22), 6.53—6.49 (1H, m, CH-C9), 4.54 (1H, s, CH-C7), 4.47—4.45 (1H, m, CH-C10), 3.74 (1H, d, *J* = 11.8 Hz, CH_2-C3), 3.74 (1H, d, *J* = 12.1 Hz, CH_2-C1), 2.35—2.33 (1H, m, CH-C4a), 2.43 (3H, s, CH_3-C24), 2.13—2.11 (1H, m, CH_2-C3), 2.01—1.99 (1H, m, CH_2-C4), 2.00 (3H, s, CH_3-C8), 1.95 (1H, d, *J* = 12.1 Hz, CH_2-C1), 1.55—1.53 (1H, m, CH_2-C4), 1.25 (3H, d, *J* = 7.2 Hz, CH_3-C11), 0.94 (9H, s, CH_3-C15, CH_3-C16, CH_3-C17), 0.22 (3H, s, CH_3-C12/C13), 0.19 (3H, s, CH_3-C12/C13); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 204.3 (C-C6), 143.8 (C-C21), 138.8 (CH-C9), 136.9 (C-C5), 132.5 (C-C18), 129.8 (CH-C20, CH-C22), 127.9 (CH-C19, CH-C23), 76.6 (CH-C7), 65.7 (CH-C10), 50.8 (CH_2-C1), 45.9 (CH_2-C3), 40.1 (CH-C4a), 40.1 (C-C7a), 28.8 (CH_2-C4), 25.9 (CH_3-C15, CH_3-C16, CH_3-C17), 23.4 (CH_3-C11), 21.6 (CH_3-C24), 20.1 (CH_3-C8), 18.3 (C-C14), —3.8 (CH_3-C12/C13), —5.0 (CH_3-C12/C13); **HRMS (CI, isobutane)** for $C_{25}H_{40}NO_5SSi$ ($[M+H]^+$) calculated 494.2396, found 494.2403; **LRMS (CI, isobutane) *m/z* (intensity):** 494 (8), 478 (15), 133 (100).

7a-Methyl-5-(2-oxo-propyl)-2-(toluene-4-sulfonyl)-1,2,3,4,6,7a-hexahydro-[*2*]pyrindin-7-one 448:



448

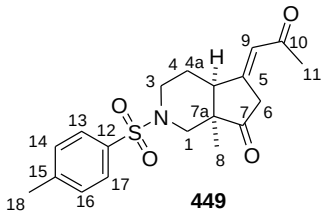
$C_{19}H_{23}NO_4S$

Molecular weight: 361.46 g.mol^{-1}

p-Toluenesulfonic acid monohydrate (3 mg, 0.01 mmol) was added to a solution of **447** (80 mg, 0.16 mmol) in chloroform (2 mL) and the solution was stirred at rt for 17 h. Analysis by TLC showed only starting material present, therefore sulphuric acid (0.2 mL) was added and the mixture was stirred at 70 °C for 2 h. At this time, TLC analysis showed complete consumption of **447** so dichloromethane (3 mL) and a saturated aqueous solution of sodium hydrogenocarbonate (3 mL) were added. The phases were separated and the aqueous phase was extracted with dichloromethane (3 × 5 mL). The combined organic phases were washed with water (15 mL), and brine (15 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate 5:5 to 7:3 provided the product **448** (33 mg, 0.092 mmol, 58%) as a colourless oil.

R_f: 0.46 (petroleum ether:ethyl acetate, 3:7); **IR:** ν_{max} 2961, 2926, 1705, 1659, 1344, 1114 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.61 (2H, d, *J* = 8.1 Hz, CH-C13, CH-C17), 7.31 (2H, d, *J* = 8.1 Hz, CH-C14, CH-C16), 4.08 (1H, dddd, *J* = 11.0, 6.1, 1.9, 1.9 Hz, CH_2-C3), 3.87 (1H, dd, *J* = 11.0, 1.9 Hz, CH_2-C1), 3.36 (1H, d, *J* = 16.9 Hz, CH_2-C9), 3.13 (1H, d, *J* = 16.9 Hz, CH_2-C9), 2.71 (1H, ddd, *J* = 13.5, 12.8, 6.1 Hz, CH_2-C4), 2.54 (1H, ddd, *J* = 13.5, 2.9, 1.9 Hz, CH_2-C4), 2.42 (3H, s, CH_3-C18), 2.36—2.26 (2H, m, CH_2-C3, CH-C6), 2.16 (1H, d, *J* = 11.0 Hz, CH_2-C1), 2.16 (3H, s, CH_3-C11), 2.18—2.11 (1H, m, CH_2-C6), 1.43 (3H, s, CH_3-C8); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 204.8 (C-CO), 203.9 (C-CO), 176.8 (C-C4a), 143.9 (C-C15), 133.4 (C-C5), 131.4 (C-C12), 129.9 (CH-C14, CH-C16), 127.3 (CH-C13, CH-C17), 57.5 (CH_2-C1), 46.7 (CH_2-C3), 46.6 (CH_2-C6), 42.0 (C-C7a), 37.0 (CH_2-C9), 30.1 (CH_3-C11), 25.7 (CH_2-C4), 23.8 (CH_3-C8), 21.5 (CH_3-C18); **HRMS (CI, isobutane)** for $C_{19}H_{24}NO_4S$ ($[M+H]^+$) calculated 362.1426, found 362.1423; **LRMS (CI, isobutane) *m/z* (intensity):** 362 (8), 157 (30), 89 (95), 79 (100).

7a-Methyl-5-[2-oxoprop-(E)-ylidene]-2-(toluene-4-sulfonyl)-octahydro-[*2*]pyrindin-7-one 451:



449

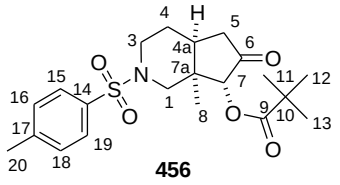
$C_{19}H_{23}NO_4S$

Molecular weight: 361.46 g.mol^{-1}

Acetic acid (0.2 mL) was added to a solution of **447** (40 mg, 0.08 mmol) in methanol (2 mL) and the solution was stirred at rt for 3 h. Analysis by TLC showed that only starting material was present, therefore hydrochloric acid (0.2 mL) was added and the mixture was stirred at 50 °C for 2 h. At this time, TLC analysis showed complete consumption of **447**, so the solution was concentrated *in vacuo* and the residue was dissolved in ethyl acetate (10 mL). The solution was washed with a saturated aqueous solution of sodium hydrogenocarbonate (5 mL) and brine (15 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate 8:2) provided the product **449** (19 mg, 0.05 mmol, 68%) as a colourless oil.

R_f: 0.54 (petroleum ether:ethyl acetate, 6:4); **IR:** ν_{max} 2924, 1732, 1690, 1339, 1163 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.64 (2H, d, *J* = 8.1 Hz, CH-C13, CH-C17), 7.35 (2H, d, *J* = 8.1 Hz, CH-C14, CH-C16), 6.82 (1H, d, *J* = 1.5 Hz, CH-C9), 3.81 (1H, dddd, *J* = 11.9, 4.4, 2.2, 1.8 Hz, CH_2-C3), 3.67 (1H, dd, *J* = 12.1, 1.8 Hz, CH_2-C1), 3.08 (1H, dd, *J* = 11.9, 4.2 Hz, CH-C4a), 2.91 (1H, d, *J* = 18.2, CH_2-C6), 2.45 (3H, s, CH_3-C18), 3.32 (3H, s, CH_3-C11), 2.28 (1H, ddd, *J* = 11.9, 12.7, 2.5 Hz, CH_2-C3), 2.15 (1H, d, *J* = 12.1 Hz, CH_2-C1), 2.16—2.11 (1H, m, CH_2-C4), 2.07 (1H, dd, *J* = 18.2, 1.5 Hz, CH_2-C6), 1.44—1.36 (1H, m, CH_2-C4), 0.87, (3H, s, CH_3-C8); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 206.3 (C-CO), 199.1 (C-CO), 151.7 (C-C5), 143.8 (C-C15), 133.0 (C-C12), 129.8 (CH-C14, CH-C16), 127.6 (CH-C13, CH-C17), 124.7 (CH-C9), 52.4 (CH_2-C1), 45.5 (CH_2-C3), 45.1 (CH-C4a), 44.8 (CH_2-C6), 36.5 (C-C7a), 32.2 (CH_3-C11), 26.7 (CH_3-C8), 26.2 (CH_2-C4), 21.5 (CH_3-C18); **HRMS (CI, isobutane)** for $C_{19}H_{24}NO_4S$ ($[M+H]^+$) calculated 362.1426, found 362.1424; **LRMS (CI, isobutane) *m/z* (intensity):** 362 (5), 89 (100), 79 (29).

2,2-Dimethylpropionic acid 7a-methyl-6-oxo-2-(toluene-4-sulfonyl)octahydro-[*2*]pyrindin-7-yl ester 456:



456

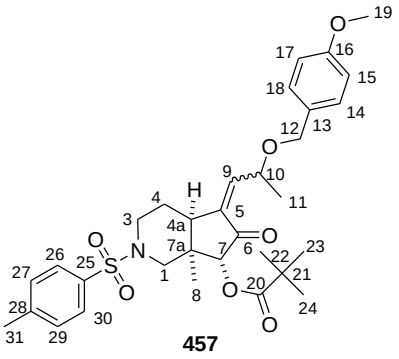
$C_{21}H_{29}NO_5S$

Molecular weight: 407.52 g.mol^{-1}

Trimethylacetyl chloride (0.46 mL, 3.7 mmol) was added to a solution of **316** (0.60 g, 1.6 mmol) in pyridine (3 mL). The mixture was stirred at rt for 16 h, then warmed to 40 ºC and stirred for a further 4 h. The mixture was then concentrated *in vacuo* and the residue was dissolved in diethyl ether (5 mL). An aqueous solution of hydrochloric acid (3 mL, 1 M) was added and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 5 mL) and the combined organic phases were washed with a saturated aqueous solution of sodium bicarbonate (3 mL) and brine (3 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: ethyl acetate, 9:1 to 7:3) provided the product **456** (0.65 g, 1.6 mmol, 86%) as a colourless solid.

R_f: 0.38 (petroleum ether:ethyl acetate, 4:6); **m.p.:** 157—160 ºC; **IR:** ν_{max} 2966, 2934, 2846, 1763, 1735, 1344 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.64 (2H, d, *J* = 8.2 Hz, CH-C15, CH-C19), 7.31 (2H, d, *J* = 8.2 Hz, CH-C16, CH-C18), 5.56 (1H, s, CH-C7), 3.76—3.74 (1H, m, CH_2-C3), 3.47 (1H, dd, *J* = 12.2, 1.7 Hz, CH_2-C1), 2.50 (1H, dd, *J* = 19.5, 7.8 Hz, CH_2-C5), 2.41 (3H, s, CH_3-C20), 2.33 (1H, ddd, *J* = 12.1, 12.1, 3.5 Hz, CH_2-C3), 2.21 (1H, d, *J* = 12.2 Hz, CH_2-C1), 2.01 (1H, d, *J* = 19.5 Hz, CH_2-C5), 1.92—1.84 (2H, m, CH-C4a, CH_2-C4), 1.65 (1H, ddd, *J* = 12.4, 3.5, 1.8 Hz, CH_2-C4), 1.22 (9H, s, CH_3-C11, CH_3-C12, CH_3-C13), 0.98 (3H, s, CH_3-C8); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 209.8 (C-C6), 176.9 (C-C9), 143.8 (C-C17), 133.3 (C-C14), 129.9 (CH-C16, CH-C18), 127.8 (CH-C15, CH-C19), 76.1 (CH-C7), 50.5 (CH_2-C1), 45.3 (CH_2-C3), 40.8 (CH_2-C5), 40.2 (C-C7a), 39.1 (C-C10), 35.5 (CH-C4a), 29.7 (CH_2-C4), 27.1 (CH_3-C11, CH_3-C12, CH_3-C13), 21.0 (CH_3-C20), 19.6 (CH_3-C8); **HRMS (CI, isobutane)** for $C_{21}H_{30}NO_5S$ ($[M+H]^+$) calculated 408.1845, found 408.1843; **LRMS (CI, isobutane) *m/z* (intensity):** 408 (46), 308 (100), 103 (32); **Elemental analysis:** $C_{21}H_{29}NO_5S$ requires C: 61.89%, N: 3.44%, H: 7.17%, found C: 61.94%, N: 3.50%, H: 7.20%.

2,2-Dimethyl-propionic acid 5-[2-(4-methoxybenzyloxy)propylidene]-7a-methyl-6-oxo-2-(toluene-4-sulfonyl)-octahydro-[*2*]pyrindin-7-yl ester 457.



457

$C_{32}H_{41}NO_7S$

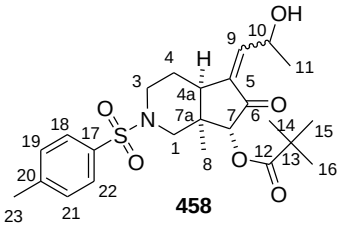
Molecular weight: 583.74 g.mol^{-1}

A solution of *n*-butyllithium (1.1 mL of a 2.5 M solution in hexanes, 2.7 mmol) was added dropwise to a solution of diisopropyl amine (0.36 mL, 2.6 mmol) in tetrahydrofuran (7 mL), at −78 ºC. The solution was stirred at −78 ºC for 10 min, then warmed to 0 ºC for 10 min and finally cooled to −78 ºC. This solution of lithium diisopropyl amide was then added dropwise to a solution of **443** (0.65 g, 1.6 mmol), in tetrahydrofuran (35 mL) at −78 ºC. The resulting mixture was stirred at this temperature for 30 min, and a solution of zinc chloride (0.50 g, 3.7 mmol), in tetrahydofuran (7 mL) was added. After a further 5 min, a solution of **456** (0.65 g, 3.4 mmol) in tetrahydrofuran (7 mL) was added. The mixture was stirred at −78 ºC for 2 h, then slowly warmed to rt, and stirred for a further 16 h. Diethyl ether (50 mL) and a saturated aqueous solution of ammonium chloride (50 mL) were added and the phases were separated. The aqueous phase was extracted with diethyl ether (2 × 50), and the combined organic phases were washed with brine (100 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate 9:1 to 6:4) provided the product **457** (0.69 g, 1.2 mmol, 74%) as a mixture of diastereoisomers (0.73:1), which was used without further separation. For characterisation purposes, a fraction of the major isomer was isolated and characterised.

R_f: 0.42 (petroleum ether:ethyl acetate, 7:3); **IR:** ν_{max} 2978, 2932, 2855, 1748, 1732, 1654, 1342, 1247, 1161 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.64 (2H, d, *J* = 8.1 Hz, CH-C26, CH-C30), 7.31 (2H, d, *J* = 8.1 Hz, CH-C27, CH-C29), 7.14 (2H, d, *J* = 8.6 Hz, CH-C14, CH-C18), 6.81 (2H, d, *J* = 8.6 Hz, CH-C15, CH-C17), 6.59 (1H, dd, *J* = 8.2, 1.4 Hz, CH-C9), 5.67 (1H, s, CH-C7), 4.36 (1H, d, *J* = 11.3 Hz, CH_2-C12), 4.20 (1H, d, *J* = 11.3 Hz, CH_2-C12), 4.12—4.05 (1H, m, CH-C10), 3.82—3.76 (1H, m, CH_2-C3), 3.75 (3H, s, CH_3-C19), 3.57 (1H, d, *J* = 12.3 Hz, CH_2-C1), 2.41 (3H, s, CH_3-C31), 2.40—2.35 (1H, m, CH-C4a), 2.25 (1H, ddd, *J* = 12.5, 12.4, 2.0 Hz, CH_2-C3), 2.17 (1H, d, *J* = 12.3 Hz, CH_2-C1), 1.81—1.73 (1H, m, CH_2-C4), 1.63

(1H, ddd, *J* = 13.5, 12.4, 4.3 Hz, CH_2-C4), 1.26 (3H, d, *J* = 6.6 Hz, CH_3-C11), 1.24 (9H, s, CH_3-C22, CH_3-C23, CH_3-C24), 0.89 (3H, s, CH_3-C8); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 198.3 (C-C6), 176.8 (C-C20), 159.2 (C-C16), 143.8 (C-C5), 139.4 (CH-C9), 137.9 (C-C28), 133.2 (C-C25), 129.9 (C-C13), 129.8 (CH-C27, CH-C29), 129.2 (CH-C26, CH-C30), 127.8 (CH-C14, CH-C18), 113.8 (CH-C15, CH-C17), 75.8 (CH-C7), 70.5 (CH-C10), 70.3 (CH_2-C12), 55.2 (CH_3-C19), 50.1 (CH_2-C1), 44.8 (CH_2-C3), 41.2 (CH-C4a), 39.1 (C-C7a), 38.9 (C-C21), 28.8 (CH_2-C4), 27.2 (CH_3-C22, CH_3-C23, CH_3-C24), 21.5 (CH_3-C11), 20.9 (CH_3-31), 20.4 (CH_3-C8); **HRMS (FAB)** for $C_{32}H_{42}NO_7S$ ($[M+H]^+$) calculated 584.2682, found 584.2674; **LRMS (FAB) *m/z* (intensity):** 584 (19), 362 (20), 121 (100).

2,2-Dimethylpropionic acid 5-(2-hydroxypropylidene)-7a-methyl-6-oxo-2-(toluene-4-sulfonyl)-octahydro-[*2*]pyrindin-7-yl ester 458:



458

$C_{24}H_{33}NO_6S$

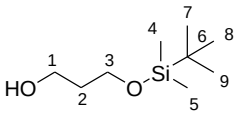
Molecular weight: 463.59 g.mol^{-1}

Ceric ammonium nitrate (0.34 g, 0.62 mmol) was added to a solution of **457** (0.18 g, 0.31 mmol) in acetonitrile (7 mL) and water (0.7 mL). The mixture was stirred at rt for 3 h, and ethyl acetate (7 mL) and water (7 mL) were added. The phases were separated and the aqueous phase was extracted with ethyl acetate (3 × 7 ml), and the combined organic phases were washed with brine (20 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate 9.5:0.5 to 6:4 provided the product **458** (0.10 g, 0.22 mmol, 71%) as an inseparable mixture of *E*/*Z* isomers (0.23:1).

R_f: 0.24 (petroleum ether:ethyl acetate, 5:5); **IR:** ν_{max} 3453, 2972, 1746, 1721, 1279, 1158 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.64 (2H, d, *J* = 8.1 Hz, CH-C18, CH-C22), 7.31 (2H, d, *J* = 8.1 Hz, CH-C19, CH-C21), 6.57-6.55 (1H, m, CH-C9), 5.67 (1H, s, CH-C7), 4.52—4.46 (1H, m, CH-C10), 3.81—3.77 (1H, m, CH_2-C3), 3.56 (1H, dd, *J* = 12.3, 1.6 Hz, CH_2-C1), 2.63 (1H, dd, *J* = 12.8, 6.3 Hz, CH_2-C4a), 2.41 (3H, s, CH_3-C23), 2.30 (1H, ddd, *J* = 12.7, 12.8, 2.5 Hz, CH_2-C3), 2.17 (1H, d, *J* = 12.3 Hz, CH_2-C1), 2.13—2.08 (1H, m, CH_2-C4), 1.65 (1H, ddd, *J* = 17.1, 12.8, 4.5 Hz, CH_2-C4), 1.27 (3H, d, *J* = 7.0 Hz, CH_3-C11), 1.23 (9H, s, CH_3-C14, CH_3-C15, CH_3-C16), 0.84 (3H, s, CH_3-C8); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 199.2 (C-C6), 177.2 (C-

C12), 143.9 (C-C20), 140.5 (CH-C9), 136.1 (C-C5), 133.2 (C-C17), 129.8 (CH-C19, CH-C21), 127.8 (CH-C18, CH-C22), 76.0 (CH-C7), 65.7 (CH-C10), 50.2 (CH_2-C1), 45.1 (CH_2-C3), 41.0 (C-C7a), 39.0 (CH-C4a), 38.9 (C-C13), 28.7 (CH_2-C4), 27.2 (CH_3-C14, CH_3-C15, CH_3-C16), 23.3 (CH_3-C11), 21.6 (CH_3-23), 20.3 (CH_3-C8); **HRMS (FAB)** for $C_{24}H_{34}NO_6S([M+H]^+)$ calculated 464.2107, found 464.2101; **LRMS (FAB)** ***m/z*** **(intensity):** 463 (63), 361 (100), 153 (68), 57 (81).

3-(*tert*Butyldimethylsilanyloxy)propan-1-ol 476:



476

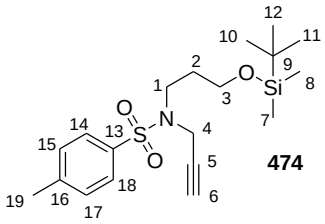
$C_9H_{22}O_2Si$

Molecular weight: 190.14 g.mol^{-1}

t-Butyldimethylsilyl chloride (6.9 g, 46 mmol) and triethylamine (9.6 mL, 69 mmol) were added to a solution of 1,3-propanediol (5.2 g, 69 mmol), in dichloromethane (300 mL). The mixture was stirred at rt for 20 h, and the reaction was then quenched with a saturated aqueous solution of ammonium chloride (200 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (3 × 200 ml). The combined organic phases were washed with brine (500 mL) then dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 8:2 to 6:4) provided the product **476** (7.8 g, 41 mmol, 90%) as a colourless oil.

R_f: 0.26 (petroleum ether:ethyl acetate, 8:2); **IR:** ν_{max} 3357, 2929, 2857, 1472, 1255, 1084 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.82 (2H, t, *J* = 5.6 Hz, CH_2-C3), 3.78 (2H, dt, *J* = 5.2, 5.6 Hz, CH_2-C1), 2.56 (1H, t, *J* = 5.2 Hz, OH), 1.77 (2H, tt, *J* = 5.6, 5.2 Hz, CH_2-C2), 0.89 (9H, s, CH_3-C7, CH_3-C8, CH_3-C9), 0.07 (6H, s, CH_3-C4, CH_3-C5); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 63.0 (CH_2-C1), 62.5 (CH_2-C3), 34.3 (CH_2-C2), 26.0 (CH_3-C7, CH_3-C8, CH_3-C9), 18.3 (C-C6), −5.3 (CH_3-C4, CH_3-C5); **HRMS (CI, isobutane)** for $C_9H_{23}O_2Si$ ($[M+H]^+$) calculated 191.1467, found 191.1468; **LRMS (CI, isobutane)** ***m/z*** **(intensity):**191.3 (100), 133.2 (26).

***N*-(3-(*tertB*utyldimethylsilyloxy)propyl)-4-methyl-*N*-(prop-2-ynyl)benzenesulfonamide 474:**



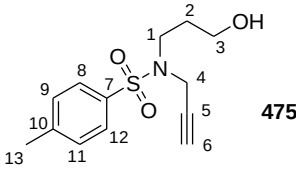
$C_{19}H_{31}NO_3SSi$

Molecular weight: 381.60 g.mol^{-1}

Diisopropyl azodicarboxylate (16.7 mL, 86.2 mmol) was added dropwise to a solution of **476** (10.4 g, 49.5 mmol), **242** (8.20 g, 43.0 mmol) and triphenylphosphine (22.6 g, 86.2 mmol) in tetrahydrofuran (500 mL), at 0 °C. The mixture was stirred at rt for 17 h, and then concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 9:1 to 8:2) provided the product **474** (15.8 g, 41 mmol, 96%) as a pink solid.

R_f: 0.60 (heptane:ethyl acetate, 7:3); **m.p.:** 36—39 °C; **IR:** ν_{max} 3308, 2928, 2884, 1446, 1348, 1160 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.71 (2H, d, *J* = 8.2 Hz, CH-C14, CH-C18), 7.26 (2H, d, *J* = 8.2 Hz, CH-C15, CH-C17), 4.12 (2H, d, *J* = 1.9 Hz, CH_2-C4), 3.63 (2H, t, *J* = 5.8 Hz, CH_2-C3), 3.27 (2H, t, *J* = 5.8 Hz, CH_2-C1), 2.40 (3H, s, CH_3-C19), 1.99 (1H, t, *J* = 1.9 Hz, CH-C6), 1.76 (2H, tt, *J* = 5.8, 5.8 Hz, CH_2-C2), 0.86 (9H, s, CH_3-C10, CH_3-C11, CH_3-C12), 0.02 (6H, s, CH_3-C7, CH_3-C8); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 143.5 (C-C16), 136.1 (C-C13), 129.5 (CH-C15, CH-C17), 127.9 (CH-C14, CH-C18), 77.1 (C-C5), 73.6 (CH-C6), 60.3 (CH-C3), 43.9 (CH-C1), 36.9 (CH_2-C4), 31.2 (CH_2-C2), 26.0 (CH_3-C10, CH_3-C11, CH_3-C12), 21.6 (CH_3-C19), 18.3 (C-C9), —5.2 (CH_3-C7, CH_3-C8); **HRMS (CI, isobutane)** for $C_{19}H_{32}NO_3SSi$ ($[M+H]^+$) calculated 382.1872, found 382.1871; **LRMS (CI, isobutane) *m/z* (intensity):** 382 (100), 324 (16), 252 (12); **Elemental analysis:** $C_{19}H_{31}NO_3SSi$ requires C: 59.80%, N: 3.67%, H: 8.19%, found C: 59.77%, N: 3.79%, H: 8.20%.

***N*-(3-Hydroxypropyl)-4-methyl-*N*-prop-2-ynyl-benzenesulfonamide 475:**



475

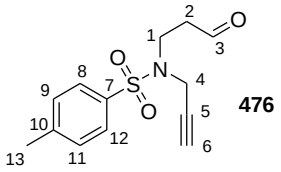
$C_{13}H_{17}NO_3S$

Molecular weight: 267.34 g.mol^{-1}

A solution of tetrabutylammonium fluoride (62.9 mL of a 1 M solution in tetrahydrofuran, 62.9 mmol) was added dropwise to a solution of **474** (20.2 g, 52.9 mmol) in tetrahydrofuran (200 mL), at 0 ºC. The reaction was allowed to warm at rt and stirred for 17 h. Diethyl ether (100 mL) and a saturated aqueous solution of ammonium chloride (100 mL) were added and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 1000 ml) and the combined organic phases were washed with brine (150 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 8:2 to 6:4) provided the product **475** (13.8 g, 51.6 mmol, 98%) as a colourless solid.

R_f: 0.28 (heptane:ethyl acetate, 5:5); **m.p.:** 57—60 °C; **IR:** ν_{max} 3493, 3232, 2956, 2827, 1597, 1328 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.75 (2H, d, *J* = 8.0, CH-C8, CH-C12), 7.31 (2H, d, *J* = 8.0, CH-C9, CH-C11), 4.16 (2H, d, *J* = 2.4, CH_2-C4), 3.75 (2H, dt, *J* = 6.2, *J* = 5.8, CH_2-C3), 3.35 (2H, t, *J* = 6.4, CH_2-C1), 2.44 (3H, s, CH_3-C13), 2.28 (1H, t, *J* = 6.2, OH), 2.05 (1H, t, *J* = 2.4, CH_2-C6), 1.79 (2H, tt, *J* = 6.4, *J* = 5.8, CH_2-C2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 143.8 (C-C10), 135.7 (C-C7), 129.7 (CH-C9, CH-C11), 127.8 (CH-C8, CH-C12), 77.1 (C-C5), 74.0 (CH-C6), 58.8 (CH_2-C3), 42.8 (CH_2-C1), 36.6 (CH_2-C4), 29.8 (CH_2-C2), 21.6 (CH_3-C13); **HRMS (CI, isobutane)** for $C_{13}H_{18}NO_3S$ ($[M+H]^+$) calculated 268.1007, found 268.1007; **LRMS (CI, isobutane) *m/z* (intensity):** 268 (100), 233 (11), 157 (32), 114 (49); **Elemental analysis:** $C_{13}H_{17}NO_3S$ requires C: 58.40%, N: 5.24%, H: 6.41%, found C: 58.49%, N: 5.28%, H: 6.40%.

4-Methyl-*N*-(3-oxo-propyl)-*N*-prop-2-ynyl-benzenesulfonamide 476:



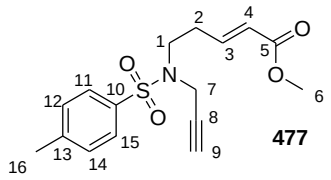
$C_{13}H_{15}NO_3S$

Molecular weight: 265.33 g.mol^{-1}

A solution of dimethyl sulfoxide (11.7 mL, 165 mmol) in dichloromethane (100 mL) was added dropwise *by* canula to a solution of oxalyl chloride (3.9 mL, 43 mmol), in dichloromethane (500 mL) at −78 °C and the mixture was stirred at for 30 min. A solution of **475** (11.6 g, 43.4 mmol) in dichloromethane (100 mL) was then added by canula and the resulting solution was stirred at −78 °C for 2 h. Triethylamine (30.1 mL, 217 mmol) was added and the reaction mixture was allowed to warm at rt. Water (500 mL) was added and the phases were separated. The aqueous phase was extracted with dichloromethane (3 × 500 mL) and the combined organic phases were washed with brine (1 L), then dried over magnesium sulfate and concentrated *in vacuo*. Filtration through silica gel provided the product **476** (11.5 g, 43.3 mmol, 88%) as a colourless oil, which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.80 (1H, s, CH-C3), 7.74 (2H, d, *J* = 8.0 Hz, CH-C8, CH-C12), 7.32 (2H, d, *J* = 8.0 Hz, CH-C9, CH-C11), 4.14 (2H, d, *J* = 2.6 Hz, CH_2-C4), 3.52 (2H, t, *J* = 7.1 Hz, CH_2-C1), 2.87 (2H, t, *J* = 7.1 Hz, CH_2-C2), 2.44 (3H, s, CH_3-C13), 2.07 (1H, t, *J* = 2.6 Hz, CH-C6).

(*E*)-5-[Prop-2-ynyl-(toluene-4-sulfonyl)-amino]pent-2-enoic acid methyl ester 477:



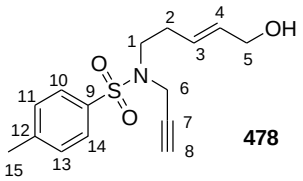
$C_{16}H_{19}NO_4S$

Molecular weight: 321.39 g.mol^{-1}

Methyl (triphenylphosphoranylidene)acetate (18.0 g, 53.8 mmol) was added to a solution of **476** (10.2 g, 38.4 mmol) in dichloromethane (300 mL), and the resulting mixture was stirred for 17 h. The reaction mixture was then concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (heptane:ethyl acetate, 8:2 to 7:3) provided the product **477** (11.0 g, 34.2 mmol, 89%) as a colourless solid.

R_f: 0.26 (heptane:ethyl acetate, 7:3); m.p.: 54—56 °C; **IR:** ν_{max} 3255, 2957, 1708, 1659, 1327, 1159 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.71 (2H, d, *J* = 8.2 Hz, CH-C11, CH-C15), 7.29 (2H, d, *J* = 8.2 Hz, CH-C12, CH-C14), 6.88 (1H, dt, *J* = 15.7, 7.0 Hz, CH-C3), 5.91 (1H, dt, *J* = 15.7, 1.4 Hz, CH-C4), 4.11 (2H, d, *J* = 2.4 Hz, CH_2-C7), 3.72 (3H, s, CH_3-C6), 3.31 (2H, t, *J* = 7.0 Hz, CH_2-C1), 2.54—2.48 (2H, m, CH_2-C2), 2.42 (3H, s, CH_3-C16), 2.06 (1H, t, *J* = 2.4 Hz, CH-C9); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.6 (C-C5), 144.6 (CH-C3), 143.8 (C-C13), 135.6 (C-C10), 129.7 (CH-C12, CH-C14), 127.8 (CH-C11, CH-C15), 123.3 (CH-C4), 76.4 (C-C8), 74.1 (CH-C9), 51.6 (CH_3-C6), 45.1 (CH_2-C1), 36.9 (CH_2-C7), 30.9 (CH_2-C2), 21.6 (CH_3-C16); **HRMS (FAB)** for $C_{16}H_{20}NO_4S$ ($[M+H]^+$) calculated 322.1113, found 322.1111; **LRMS (FAB) *m/z* (intensity):** 322 (100), 289 (57), 221 (98), 154 (28); **Elemental analysis:** $C_{16}H_{19}NO_4S$ requires C: 59.79%, N: 4.36%, H: 5.96%, found C: 59.73%, N: 4.52%, H: 5.61%.

***N*-((E)-5-Hydroxypent-3-enyl)-4-methyl-*N*-prop-2-ynyl benzenesulfonamide 478:**



478

$C_{15}H_{19}NO_3S$

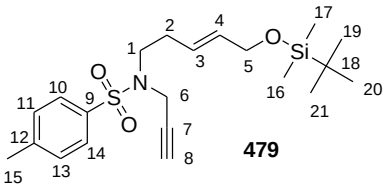
Molecular weight: 293.38 g.mol^{-1}

A solution of diisobutylaluminum hydride (71 mL of a 1 M solution in dichloromethane, 71 mmol) was added dropwise to a solution of **477** (9.1 g, 28 mmol) in dichloromethane (600 mL) at —78 °C. The mixture was stirred at this temperature for 1 h and then quenched by the addition of a saturated solution of sodium potassium tartrate (500 mL), diluted with ethyl acetate (1 L) and warmed to rt. The phases were separated and the aqueous phase was extracted with ethyl acetate (2 × 700 mL). The combined organic phases were washed with water (1 L) and brine (1 L), then dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 95:5) provided the title compound **478** (7.5 g, 25 mmol, 90%) as a colourless oil.

R_f: 0.28 (petroleum ether:ethyl acetate, 5:5); **IR:** ν_{max} 3514, 3281, 1599, 1448, 1346 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.72 (2H, d, *J* = 8.1 Hz, CH-C10, CH-C14), 7.28 (2H, d, *J* = 8.1 Hz, CH-C11, CH-C13), 5.73 (1H, dt, *J* = 15.4, 5.2 Hz, CH-C4), 5.64 (1H, dt, *J* = 15.4, 6.9 Hz, CH-C3), 4.12 (2H, d, *J* = 2.5 Hz, CH_2-C6), 4.09 (2H, d, *J* = 5.2 Hz, CH_2-C5), 3.27 (2H, t, *J* = 7.1 Hz, CH_2-C1), 2.42 (3H, s, CH_3-C15), 2.34 (2H, td, *J* = 7.1, 6.9 Hz, CH_2-C2), 2.03 (1H, t, *J* = 2.5 Hz, CH-C8), 1.42 (1H, s, OH); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 143.5 (C-C12), 135.8 (C-

C9), 131.7 (CH-C4), 129.5 (CH-C11, CH-C13), 128.3 (CH-C3), 127.6 (CH-C10, CH-C14), 76.5 (C-C7), 73.8 (CH-C8), 63.4 (CH_2-C5), 45.8 (CH_2-C1), 36.5 (CH_2-C6), 30.5 (CH_2-C2), 21.5 (CH_3-C15); **HRMS (CI, isobutane)** for $C_{15}H_{20}NO_3S$ ($[M+H]^+$) calculated 294.1164, found 294.1167; **LRMS (CI, isobutane) *m/z* (intensity):** 294 (15), 276 (56), 22 (56), 79 (100); **Elemental analysis:** $C_{15}H_{19}NO_3S$ requires C: 61.41%, N: 4.77%, H: 6.53%, found C: 60.96%, N: 4.83%, H: 6.56%.

***N*-[(E)-5-(*tert*Butyldimethylsilanyloxy)-pent-3-enyl]-4-methyl-*N*-prop-2-ynyl benzenesulfonamide 479:**



479

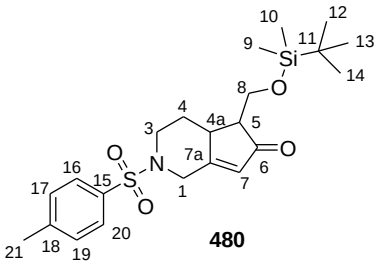
$C_{21}H_{33}NO_3SSi$

Molecular weight: 407.64 g.mol^{-1}

Imidazole (6.25 g, 91.9 mmol) and *t*-butyldimethylsilyl chloride (4.53 g, 30.1 mmol) were added to a solution of **478** (4.9 g, 17 mmol) in dichloromethane (150 mL) and the mixture was stirred at rt for 17 h. Water (150 mL) was added and the phases were separated. The organic phase was washed with water (150 mL), and brine (150 mL) then dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (heptane:ethyl acetate, 9:1) provided the product **479** (5.9 g, 14 mmol, 85%) as a colourless oil.

R_f: 0.44 (heptane:ethyl acetate, 7:3); **IR:** ν_{max} 3275, 2928, 2854, 1462, 1350, 1161 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.73 (2H, d, *J* = 8.2 Hz, CH-C10, CH-C14), 7.30 (2H, d, *J* = 8.2 Hz, CH-C11, CH-C13), 5.68—5.55 (2H, m, CH-C3, CH-C4), 4.14 (2H, d, *J* = 2.5 Hz, CH_2-C6), 4.11 (2H, d, *J* = 3.7 Hz, CH_2-C5), 3.26 (2H, t, *J* = 7.9 Hz, CH_2-C1), 2.43 (3H, s, CH_3-C15), 2.34 (2H, td, *J* = 7.9, 6.3 Hz, CH_2-C2), 2.05 (1H, t, *J* = 2.5 Hz, CH-C8), 0.92 (9H, s, CH_3-C19, CH_3-C20, CH_3-C21), 0.08 (6H, s, CH_3-C16, CH_3-C17); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 143.5 (C-C12), 136.0 (C-C9), 132.1 (CH-C4), 129.5 (CH-C11, CH-C13), 127.7 (CH-C10, CH-C14), 126.4 (CH-C3), 77.1 (C-C7), 73.7 (CH-C8), 63.7 (CH_2-C5), 46.0 (CH_2-C1), 36.5 (CH_2-C6), 30.8 (CH_2-C2), 26.0 (CH_3-C19, CH_3-C20, CH_3-C21), 21.6 (CH_3-C15), 18.5 (C-C18), —5.0 (CH_3-C16, CH_3-C17); **HRMS (CI, isobutane)** for $C_{21}H_{34}NO_3SSi$ ($[M+H]^+$) calculated 408.2029, found 408.2025; **LRMS (CI, isobutane) *m/z* (intensity):** 408 (69), 276 (52), 157 (55), 79 (100); **Elemental analysis:** $C_{21}H_{33}NO_3SSi$ requires C: 61.87%, N: 3.44%, H: 8.16%, found C: 61.94%, N: 3.57%, H: 8.24%.

5-(*tert*Butyldimethylsilanyloxymethyl)-2-(toluene-4-sulfonyl)-1,2,3,4,4a,5-hexahydro-[2]pyrindin-6-one 480:



480

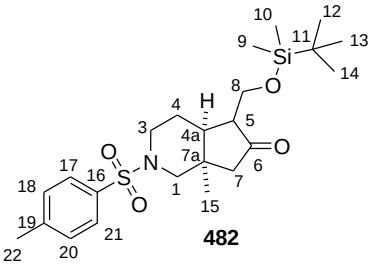
$C_{22}H_{33}NO_4SSi$

Molecular weight: 435.65 g.mol^{-1}

Dicobalt octacarbonyl (0.47 g, 1.4 mmol) was added to a solution of **479** (0.47 g, 1.2 mmol), in dichloromethane (20 mL) at 0 °C. The mixture was warmed to rt and stirred for 2 h. A solution of 4-methylmorpholine *N*-oxide (1.35 g, 1.15 mmol) in dichloromethane (10 mL) was added dropwise at 0 °C, and the resulting mixture was stirred at rt for 30 min before being filtrated through Celite and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 9:1 to 7:3) provided the product **480** (0.39 g, 0.90 mmol, 78%) as a colourless foam.

R_f: 0.47 (heptane:ethyl acetate, 7:3); **IR:** ν_{max} 2951, 2854, 1708, 1635, 1354, 1165 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.68 (2H, d, *J* = 8.2 Hz, CH-C16, CH-C20), 7.34 (2H, d, *J* = 8.2 Hz, CH-C17, CH-C19), 5.96 (1H, s, CH-C7), 4.73 (1H, d, *J* = 13.4 Hz, CH_2-C1), 3.98—3.95 (1H, m, CH_2-C3), 3.82 (1H, dd, *J* = 10.1, 4.0 Hz, CH_2-C8), 3.76 (1H, dd, *J* = 10.1, 5.9 Hz, CH_2-C8), 3.19 (1H, d, *J* = 13.4 Hz, CH_2-C1), 2.63—2.51 (2H, m, CH_2-C3, CH-C4a), 2.43 (3H, s, CH_3-C21), 2.09—2.18 (2H, m, CH_2-C4, CH-C5), 1.49 (1H, dddd, *J* = 12.6, 12.6, 12.6, 4.0 Hz, CH_2-C4), 0.79 (9H, s, CH_3-C12, CH_3-C13, CH_3-C14), 0.02 (3H, s, CH_3-C9/C10), 0.01 (3H, s, CH_3-C9/C10); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 207.0 (C-C6), 171.6 (C-C7a), 144.1 (C-C18), 133.2 (C-C15), 129.9 (CH-C17, CH-C19), 128.6 (CH-C7), 127.8 (CH-C16, CH-C20), 61.3 (CH_2-C8), 55.2 (CH-C5), 47.6 (CH_2-C1), 45.8 (CH_2-C3), 43.1 (CH-C4a), 31.5 (CH_2-C4), 25.8 (CH_3-C12, CH_3-C13, CH_3-C14), 21.6 (CH_3-C21), 18.2 (C-C11), —5.3 (CH_3-C9/C10), —5.4 (CH_3-C9/C10); **HRMS (CI, isobutane)** for $C_{22}H_{34}NO_4SSi$ ($[M+H]^+$) calculated 436.1978, found 436.1977; **LRMS (CI, isobutane) *m/z* (intensity):** 436 (100), 280 (22), 198 (45), 133 (32).

5-(*tert*Butyldimethylsilanyloxymethyl)-7a-methyl-2-(toluene-4-sulfonyl)-octahydro-[*2*]pyrindin-6-one 482:



482

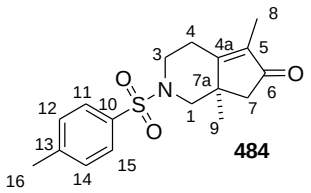
$C_{23}H_{37}NO_4SSi$

Molecular weight: 451.69 g.mol^{-1}

Methyl magnesium bromide (5.6 mL of a 1.4 M solution in tetrahydrofuran/toluene, 7.9 mmol) was added dropwise to a solution of copper iodide (0.75 g, 3.9 mmol), in tetrahydrofuran (50 mL) at rt. This was followed by the dropwise addition of a solution of ketone **480** (0.855 g, 1.96 mmol), in tetrahydrofuran (10 mL). After 1h, the mixture was quenched with a mixture of a saturated aqueous solution of ammonium chloride (20 mL), saturated aqueous solution of ammonium hydroxide (20 mL) and water (40mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 80 ml), the combined organic phases were washed with water (150 mL), and brine (150 mL), then dried over sodium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (heptane:ethyl acetate, 9:1 to 7:3) provided the product **482** (0.455 g, 1.01 mmol, 53%) as a colourless foam.

R_f: 0.47 (heptane:ethyl acetate, 7:3); **IR:** ν_{max} 2931, 2854, 1743, 1465, 1334, 1157 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.58 (2H, d, *J* = 8.1 Hz, CH-C17, CH-C21), 7.29 (2H, d, *J* = 8.1 Hz, CH-C18, CH-C20), 3.83 (1H, dd, *J* = 10.5, 4.0 Hz, CH_2-C8), 3.65—3.69 (1H, m, CH_2-C3), 3.55 (1H, dd, *J* = 10.5, 3.0 Hz, CH_2-C8), 3.32 (1H, d, *J* = 11.9 Hz, CH_2-C1), 2.41 (3H, s, CH_3-C22), 2.26—2.24 (1H, m, CH-C4a), 2.24—2.20 (1H, m, CH_2-C3), 2.13—2.18 (1H, m, CH_2-C4), 2.04 (2H, s, CH_2-C7), 2.00 (1H, ddd, *J* = 11.2, 4.0, 3.0 Hz, CH-C5), 1.94 (1H, d, *J* = 11.9 Hz, CH_2-C1), 1.71—1.65 (1H, m, CH_2-C4), 1.36 (3H, s, CH_3-C15), 0.82 (9H, s, CH_3-C12, CH_3-C13, CH_3-C14), —0.01 (3H, s, CH_3-C9/C10), —0.02 (3H, s, CH_3-C9/C10); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 216.4 (C-C6), 143.5 (C-C19), 133.0 (C-C16), 129.7 (CH-C18, CH-C20), 127.4 (CH-C17, CH-C21), 60.3 (CH_2-C8), 51.8 (CH_2-C1), 51.7 (CH_2-C7), 51.1 (CH-C5), 41.2 (CH_2-C3), 40.1 (CH-C4a), 38.1 (C-C7a), 25.7 (CH_3-C12, CH_3-13, CH_3-14), 23.5 (C-C11), 22.4 (CH_3-C22), 21.4 (CH_2-C4), 18.0 (CH_3-C15), —5.7 (CH_3-C9, CH_3-C10); **HRMS (CI, isobutane)** for $C_{23}H_{38}NO_4SSi$ ($[M+H]^+$) calculated 452.2291, found 452.2295; **LRMS (CI, isobutane) *m/z* (intensity):** 452 (5), 320 (100), 133 (28).

5,7a-Dimethyl-2-(toluene-4-sulfonyl)-1,2,3,4,7,7a-hexahydro-[*2*]pyrindin-6-one 484:



484

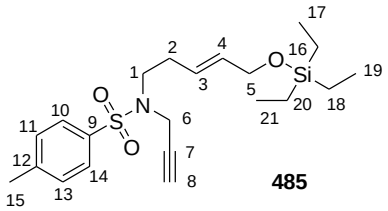
$C_{17}H_{21}NO_3S$

Molecular weight: 319.42 g.mol^{-1}

p-Toluenesulfonic acid (22 mg, 0.12 mmol) and ethylene glycol (54 mg, 0.86 mmol) were added to a solution of **482** (260 mg, 0.576 mmol) in toluene (7 mL). The flask was fitted with a Dean-Stark apparatus and the mixture was heated to 110 °C for 6 h. The solution was cooled to rt and a saturated aqueous solution of sodium hydrogenocarbonate (5 mL) was added. The phases were separated and the organic phase was washed with brine (5 mL) then dried over sodium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (heptane:ethyl acetate, 5:5) provided the product **484** (184 mg, 0.58 mmol, 100%) as a colourless solid.

R_f: 0.35 (petroleum ether:ethyl acetate, 5:5); **m.p.:** 128—129 °C; **IR:** ν_{max} 2924, 2847, 1705, 1658, 1334, 1157 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.61 (2H, d, *J* = 8.1 Hz, CH-C11, CH-C15), 7.31 (2H, d, *J* = 8.1 Hz, CH-C12, CH-C14), 4.12—4.08 (1H, m, CH_2-C3), 3.84 (1H, dd, *J* = 9.2, 2.0 Hz, CH_2-C1), 2.69 (2H, m, CH_2-C7), 2.42 (3H, s, CH_3-C16), 2.27—2.24 (2H, m, CH_2-C4), 2.11—2.05 (1H, m, CH_2-C3), 2.05 (1H, d, *J* = 9.2 Hz, CH_2-C1), 1.62 (3H, s, CH_3-C8), 1.40 (3H, s, CH_3-C9); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 206.2 (C-C6), 172.4 (C-C4a), 143.8 (C-C5), 137.0 (C-C13), 133.3 (C-C10), 130.1 (CH-C12, CH-C14), 127.3 (CH-C11, CH-C15), 57.6 (CH_2-C1), 46.8 (CH_2-C3), 46.6 (CH_2-C7), 41.5 (C-C7a), 24.9 (CH_2-C4), 23.7 (CH_3-C9), 21.5 (CH_3-C16), 7.7 (CH_3-C8); **HRMS (EI)** for $C_{17}H_{21}NO_3S$ ($[M]^+$) calculated 319.1242, found 319.1245; **LRMS (EI) *m/z* (intensity):** 319 (80), 198 (28), 164 (100), 91 (44).

4-Methyl-*N*-prop-2-ynyl-*N*-((E)-5-triethylsilanyloxypent-3-enyl)benzenesulfonamide 485:



485

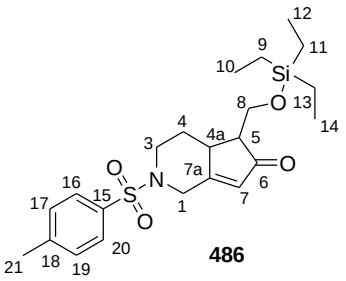
$C_{21}H_{33}NO_3SSi$

Molecular weight: 407.64 g.mol^{-1}

Imidazole (1.2 g, 17 mmol) and chlorotriethylsilane (1.1 mL, 6.8 mmol) were added to a solution of **478** (1.00 g, 3.41 mmol) in dichloromethane (30 mL) and the mixture was stirred at rt for 17 h. Water (30 mL) was added and the phases were separated. The organic phase was washed with brine (30 mL), dried over magnesium sulfate and then concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 9:1) provided the product **485** (1.40 g, 3.43 mmol, 100%) as a colourless oil.

R_f: 0.28 (petroleum ether:ethyl acetate, 9:1); **IR:** ν_{max} 3279, 2955, 2877, 1458, 1350, 1157 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.70 (2H, d, *J* = 8.1 Hz, CH-C10, CH-C14), 7.27 (2H, d, *J* = 8.1 Hz, CH-C11, CH-C13), 5.67—6.55 (2H, m, CH-C3, CH-C4), 4.12 (2H, d, *J* = 2.4 Hz, CH_2-C6), 4.09—4.08 (2H, m, CH_2-C5), 3.23 (2H, t, *J* = 7.6 Hz, CH_2-C1), 2.41 (3H, s, CH_3-C15), 2.34—2.29 (2H, m, CH_2-C2), 2.01 (1H, t, *J* = 2.4 Hz, CH-C8), 0.95 (9H, t, *J* = 7.9 Hz, CH_3-C17, CH_3-C19, CH_3-C21), 0.60 (6H, q, *J* = 7.9 Hz, CH_2-C16, CH_2-C18, CH_2-C20); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 143.5 (C-C12), 135.9 (C-C9), 132.0 (CH-C4), 129.4 (CH-C11, CH-C13), 127.7 (CH-C10, CH-C14), 126.7 (CH-C3), 76.6 (C-C7), 73.8 (CH-C8), 63.4 (CH_2-C5), 46.0 (CH_2-C1), 36.5 (CH_2-C6), 30.8 (CH_2-C2), 21.6 (CH_3-C15), 6.8 (CH_3-C17, CH_3-C19, CH_3-C21), 4.5 (CH_2-C16, CH_2-C18, CH_2-C20); **HRMS (CI, isobutane)** for $C_{21}H_{34}NO_3SSi$ ($[M+H]^+$) calculated 408.2029, found 408.2025; **LRMS (CI, isobutane) *m/z* (intensity):** 408 (100), 276 (75), 222 (85), 133 (53); **Elemental analysis:** $C_{21}H_{33}NO_3SSi$ requires C: 61.87%, N: 3.44%, H: 8.16% found, C: 61.84%, N: 3.52%, H: 8.12%.

2-(Toluene-4-sulfonyl)-5-triethylsilanyloxymethyl-1,2,3,4,4a,5-hexahydro-[*2*]pyrindin-6-one 486:



486

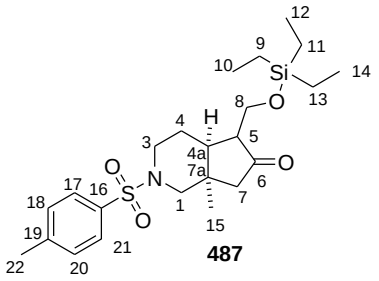
$C_{22}H_{33}NO_4SSi$

Molecular weight: 435.65 g.mol^{-1}

Dicobalt octacarbonyl (2.5 g, 7.4 mmol) was added to a solution of **485** (2.51 g, 6.16 mmol), in dichloromethane (50 mL) at 0 ºC. The resulting mixture was warmed to rt and stirred for 2 h. A solution of 4-methylmorpholine *N*-oxide (7.21 g, 61.5 mmol), in dichloromethane (15 mL) was added dropwise at 0 ºC, and the resulting mixture was stirred at rt for 30 min before being filtrated through Celite and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 9:1 to 7:3) provided the product **486** (1.72 g, 39.4 mmol, 64%) as a colourless solid.

R_f: 0.47 (petroleum ether:ethyl acetate, 8:2); **m.p.:** 75—77 °C **IR:** ν_{max} 2955, 1712, 1342, 1165 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.67 (2H, d, *J* = 8.0 Hz, CH-C16, CH-C20), 7.34 (2H, d, *J* = 8.0 Hz, CH-C17, CH-C19), 5.96 (1H, s, CH-C7), 4.73 (1H, d, *J* = 13.4 Hz, CH_2-C1), 3.98—3.95 (1H, m, CH_2-C3), 3.82 (1H, dd, *J* = 10.1, 4.0 Hz, CH_2-C8), 3.79 (1H, dd, *J* = 10.1, 6.0 Hz, CH_2-C8), 3.21 (1H, d, *J* = 13.4 Hz, CH_2-C1), 2.65—2.63 (1H, m, CH-C4a), 2.55 (1H, ddd, *J* = 12.4, 12.4, 3.0 Hz, CH_2-C3), 2.43 (3H, s, CH_3-C21), 2.17—2.09 (2H, m, CH_2-C4, CH-C5), 1.49 (1H, dddd, *J* = 12.6, 12.6, 12.4, 4.0 Hz, CH_2-C4), 0.86 (9H, t, *J* = 7.9 Hz, CH_3-C10, CH_3-C12, CH_3-C14), 0.51 (6H, q, *J* = 7.9 Hz, CH_2-C9, CH_2-C11, CH_2-C13); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 207.1 (C-C6), 171.6 (C-C7a), 144.2 (C-C18), 133.2 (C-C15), 130.0 (CH-C17, CH-C19), 128.6 (CH-C7), 127.8 (CH-C16, CH-C20), 61.1 (CH_2-C8), 55.3 (CH-C5), 47.6 (CH_2-C1), 45.9 (CH_2-C3), 43.0 (CH-C4a), 31.5 (CH_2-C4), 21.6 (CH_3-C21), 6.8 (CH_3-C10, CH_3-C12, CH_3-C14), 4.3 (CH_2-C9, CH_2-C11, CH_2-C13); **HRMS (EI)** for **$C_{22}H_{33}NO_4SSi$** ($[M]^+$) calculated 435.1900, found 435.1893; **LRMS (EI) *m/z* (intensity):** 406 (100), 250 (98), 91 (66); **Elemental analysis:** $C_{22}H_{33}NO_4SSi$ requires C: 60.65%, N: 3.22%, H: 7.63%, found C: 60.57%, N: 3.31%, H: 7.65%.

7a-Methyl-2-(toluene-4-sulfonyl)-5-triethylsilanyloxymethyloctahydro-[*2*]pyrindin-6-one 487:



487

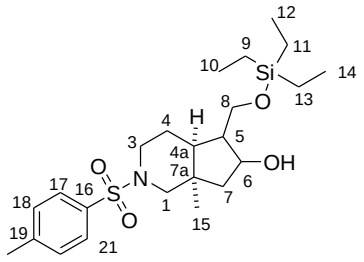
$C_{23}H_{37}NO_4SSi$

Molecular weight: 451.69 g.mol^{-1}

Methyl magnesium bromide (7.7 mL of a 1.4 M solution in tetrahydrofuran/toluene, 11 mmol) was added dropwise to a solution of copper iodide (1.0 g, 5.4 mmol) in tetrahydrofuran (75 mL) at rt. This was followed by the dropwise addition of a solution of ketone **486** (1.17 g, 2.69 mmol), in tetrahydrofuran (15 mL). The mixture was quenched by the addition of a mixture of saturated aqueous solution of ammonium chloride (40 mL), saturated aqueous ammonium hydroxide solution (40 mL) and water (80 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 100 ml). The combined organic phases were washed with water (200 mL), and brine (200 mL), then dried over sodium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 9:1) provided the product **487** (782 mg, 1.73 mmol, 64%) as a colourless oil.

R_f: 0.47 (petroleum ether:ethyl acetate, 8:2); **IR:** ν_{max} 2931, 2839, 1735, 1350, 1165, 1087 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.58 (2H, d, *J* = 8.2 Hz, CH-C17, CH-C21), 7.29 (2H, d, *J* = 8.2 Hz, CH-C18, CH-C20), 3.83 (1H, dd, *J* = 10.0, 4.2 Hz, CH_2-C8), 3.69—3.65 (1H, m, CH_2-C3), 3.58 (1H, dd, *J* = 10.0, 3.1 Hz, CH_2-C8), 3.32 (1H, d, *J* = 11.9 Hz, CH_2-C1), 2.42 (3H, s, CH_3-C22), 2.29—2.10 (3H, m, CH_2-C3, CH-C4, CH-C4a), 2.06—2.05 (2H, m, CH_2-C7), 2.02 (1H, ddd, *J* = 11.0, 4.2, 3.1 Hz, CH-C5), 1.94 (1H, d, *J* = 11.9 Hz, CH_2-C1), 1.72—1.68 (1H, m, CH_2-C4), 1.37 (3H, s, CH_3-C15), 0.89 (9H, t, *J* = 7.8 Hz, CH_3-C10, CH_3-C12, CH_3-C14), 0.54 (6H, q, *J* = 7.8 Hz, CH_2-C9, CH_2-C11, CH_2-C13); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 216.8 (C-C6), 143.7 (C-C19), 133.0 (C-C16), 129.8 (CH-C18, CH-C20), 127.6 (CH-C17, CH-C21), 60.3 (CH_2-C8), 52.0 (CH-C5), 51.9 (CH_2-C1), 51.2 (CH_2-C7), 41.4 (CH_2-C3), 40.3 (CH-C4a), 36.6 (C-C7a), 23.6 (CH_2-C15), 22.6 (CH_3-C4), 21.6 (CH_3-C22), 6.7 (CH_3-C10, CH_3-C12, CH_3-C14), 4.3 (CH_2-C9, CH_2-C11, CH_2-C13); **HRMS (CI, isobutane)** for $C_{23}H_{38}NO_4SSi$ ($[M+H]^+$) calculated 452.2291, found 452.2289; **LRMS (CI, isobutane) *m/z* (intensity):** 452 (5), 320 (100), 133 (30); **Elemental analysis:** $C_{23}H_{37}NO_4SSi$ requires C: 61.16%, N: 3.10%, H: 8.26%, found C: 61.38%, N: 3.13%, H: 8.39%.

7a-Methyl-2-(toluene-4-sulfonyl)-5-triethylsilanyloxymethyloctahydro-[*2*]pyrindin-6-ol 487':



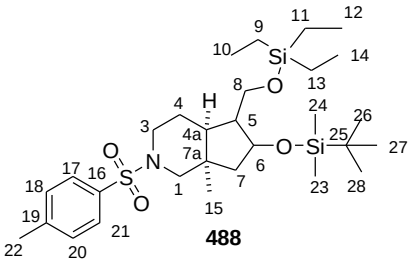
$C_{23}H_{39}NO_4SSi$

Molecular weight: 453.71 g.mol^{-1}

Sodium borohydride (0.19 g, 5.1 mmol) was added portionwise to a solution of **487** (772 mg, 1.71 mmol) in methanol (15 mL), at 0 °C. The mixture was stirred at this temprature for 1 h before water (15 mL) was added dropwise. Dichloromethane (20 mL) was added and the phases were separated. The aqueous phase was extracted with dichloromethane (3 × 20 ml) and the combined organic phases were washed with brine (100 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate, 9:1 to 8:2) provided the product **487'** (456 mg, 1.00 mmol, 86%) as a colourless solid.

R_f: 0.48 (petroleum ether:ethyl acetate, 6:4); **m.p.:** 94—96 °C; **IR:** ν_{max} 3525, 2924, 2862, 1597, 1465, 1327, 1157, 1087 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.62 (2H, d, *J* = 8.2 Hz, CH-C17, CH-C21), 7.30 (2H, d, *J* = 8.2 Hz, CH-C18, CH-C20), 4.04 (1H, ddd, *J* = 9.1, 6.7, 4.9 Hz, CH-C6), 3.72 (1H, dd, *J* = 8.8, 4.7 Hz, CH_2-C8), 3.56—3.51 (1H, m, CH_2-C3), 3.46 (1H, d, *J* = 8.8, Hz, CH_2-C8), 3.24 (1H, dd, *J* = 11.8, 1.7 Hz, CH_2-C1), 2.55 (1H, d, *J* = 11.8 Hz, CH_2-C1), 2.47 (1H, ddd, *J* = 12.0, 12.0, 2.9 Hz, CH_2-C3), 2.42 (3H, s, CH_3-C22), 1.83 (1H, d, *J* = 9.1 Hz, CH_2-C7), 1.95—1.82 (2H, m, CH-C5, CH_2-C4), 1.48 (1H, dddd, *J* = 14.2, 3.0, 2.9, 2.9 Hz, CH_2-C4), 1.41—1.36 (2H, m, CH_2-C7, CH_2-C4a), 1.17 (3H, s, CH_3-C15), 0.92 (9H, t, *J* = 7.9 Hz, CH_3-C10, CH_3-C12, CH_3-C14), 0.56 (6H, q, *J* = 7.9 Hz, CH_2-C9, CH_2-C11, CH_2-C13); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 143.3 (C-C19), 133.8 (C-C16), 129.6 (CH-C18, CH-20 127.4 (CH-C17, CH-C21), 75.94 (CH-C6), 65.1 (CH_2-C8), 53.0 (CH_2-C1), 50.5 (CH-C5), 45.4 (CH_2-C7), 43.1 (CH-C4a), 41.8 (CH_2-C3), 39.9 (C-C7a), 25.8 (CH_3-15), 22.5 (CH_2-C4), 21.5 (CH_3-C22), 6.7 (CH_3-C10, CH_3-C12, CH_3-C14), 4.2 (CH_2-C9, CH_2-C11, CH_2-C13); **HRMS (CI, isobutane)** for $C_{23}H_{40}NO_4SSi$ ($[M+H]^+$) calculated 454.2447, found 454.2445; **LRMS (CI, isobutane) *m/z* (intensity):** 454 (100), 320 (28), 298 (18), 133 (20); **Elemental analysis:** $C_{23}H_{39}NO_4SSi$ requires C: 60.89%, N: 3.09%, H: 8.66%, found C: 60.84%, N: 3.12%, H: 8.68%.

6-(*tert*Butyldimethylsilanyloxy)-7a-methyl-2-(toluene-4-sulfonyl)-5-triethylsilanyloxymethyloctahydro-[*2*]pyrindine 488:



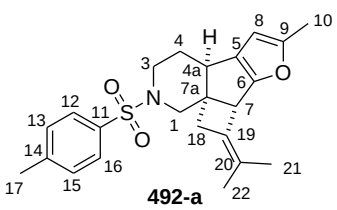
$C_{29}H_{53}NO_4SSi_2$

Molecular weight: 567.97 g.mol^{-1}

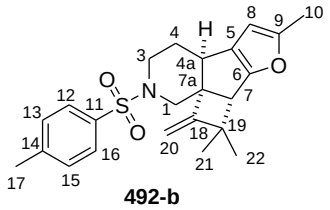
t-Butyldimethylsilyl trifluoromethanesulfonate (0.05 mL, 0.3 mmol) was added to a solution of 2,6-lutidine (0.06 mL, 0.6 mmol) and **487'** (100 mg, 0.22 mmol) in dichloromethane (10 mL) at 0 °C. The mixture was stirred at rt for 17 h, and a saturated aqueous solution of ammonium chloride (10 ml) was added. The phases were separated and the aqueous phase was extracted with dichloromethane (3 × 10 ml). The combined organic phases were washed with brine (30 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (heptane:ethyl acetate, 9.5:0.5) provided the product **488** (128 mg, 0.22 mmol, 100%) as a colourless solid.

R_f: 0.46 (petroleum ether:ethyl acetate, 9:1); **IR:** ν_{max} 2951, 1469, 1354, 1338, 1161, 1091 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.61 (2H, d, *J* = 8.1 Hz, CH-C17, CH-C21), 7.28 (2H, d, *J* = 8.1 Hz, CH-C18, CH-C20), 4.01—3.95 (1H, m, CH-C6), 3.57—3.46 (3H, m, CH_2-C3, CH_2-C8), 3.17 (1H, d, *J* = 11.6 Hz, CH_2-C1), 2.68 (1H, d, *J* = 11.6, CH_2-C1), 2.41 (3H, s, CH_3-C22), 2.35 (1H, ddd, *J* = 12.1, 11.8, 2.8 Hz, CH_2-C3), 1.97—1.88 (1H, m, CH_2-C4), 1.74—1.70 (1H, m, CH-C5), 1.66 (1H, dd, *J* = 13.8, 7.7 Hz, CH_2-C7), 1.61—1.50 (2H, m, CH_2-C4, CH-C4a), 1.36 (1H, ddd, *J* = 13.8, 5.6, 2.8 Hz, CH_2-C7), 1.15 (3H, s, CH_3-C15), 0.91 (9H, t, *J* = 7.9 Hz, CH_3-10, CH_3-C12, CH_3-C14), 0.85 (9H, s, CH_3-C26, CH_3-C27, CH_3-C28), 0.54 (6H, q, *J* = 7.9 Hz, CH_2-C9, CH_2-C11, CH_2-C13), 0.00 (3H, s, CH_3-C23/C24), —0.01 (3H, s, CH_3-C23/C24); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 143.1 (C-C19), 133.5 (C-C16), 129.5 (CH-C18, CH-C20), 127.5 (CH-C17, CH-C21), 73.0 (CH-C6), 62.4 (CH_2-C8), 52.6 (CH-C5), 52.4 (CH_2-C1), 47.7 (CH_2-C7), 43.2 (CH-C4a), 42.1 (CH_2-C3), 40.5 (C-C7a), 25.8 (CH_3-C26, CH_3-C27, CH_3-C28), 25.7 (CH_3-C15), 24.8 (C-C25), 22.7 (CH_2-C4), 21.5 (CH_3-C22), 6.8 (CH_3-10, CH_3-C12, CH_3-C14), 4.7 (CH_2-C9, CH_2-C11, CH_2-C13), —5.5 (CH_3-C23, CH_3-C24); **HRMS (CI, isobutane)** for $C_{29}H_{54}NO_4SSi_2$ ($[M+H]^+$) calculated 568.3312, found 568.3309; **LRMS (CI, isobutane) *m/z* (intensity):** 569 (100), 413 (10), 113 (19), 71 (35); **Elemental analysis:** $C_{29}H_{54}NO_4SSi_2$ requires C: 61.33%, N: 2.47%, H: 9.41%, found C: 61.22%, N: 2.54%, H: 9.50%.

Furans 492-a and 492-b



492-a



492-b

$C_{23}H_{27}NO_3S$

Molecular weight: 397.53 g.mol^{-1}

A solution of *n*-butyllithium (0.26 mL of a 2.5 M solution in hexanes, 0.66 mmol) was added dropwise to a solution of di*iso*propyl amine (0.09 mL, 0.6 mmol) in tetrahydrofuran (5 mL), at −78 °C. The solution was stirred at −78 °C for 10 min, then warmed to 0 °C for 10 min and finally cooled back to −78 °C. The solution of lithium di*iso*propyl amide was then added dropwise to a mixture of **374** and its regioisomers (0.20 g, 0.46 mmol) in tetrahydrofuran (10 mL) at −78 °C. The resulting mixture was stirred at this temperature for 30 min and a solution of zinc chloride (0.14 g, 1.1 mmol) in tetrahydofuran (2 mL) was added. After a further 5 min reaction time a solution of **431** (0.14 g, 0.92 mmol) in tetrahydrofuran (2 mL) was added. The mixture was stirred at −78 °C for 2 h, then warmed slowly to rt, and stirred for a further 16 h. Diethyl ether (10 mL) and a saturated aqueous solution of ammonium chloride (10 mL) were added and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 10 ml), and the combined organic phases were washed with and brine (20 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate 8:2) provided the product **491** (102 mg, 0.184 mmol, 47%) as a mixture of diastereo and regioisomers, which was used without further separation.

Ceric ammonium nitrate (0.12 g, 0.22 mmol) was added to a solution of crude **491** (102 mg, 0.184 mmol) in acetonitrile (2 mL) and water (0.2 mL). The mixture was stirred at rt for 3 h, and ethyl acetate (5 mL) and water (5 mL) were added. The phases were separated and the aqueous phase was extracted with ethyl acetate (3 × 5 mL). The combined organic phases were washed with brine (10 mL), then dried over magnesium sulfate and concentrated *in vacuo*. After a short filtration on silica gel, the residue was dissolved in toluene (5 mL) and camphorsulfonic acid (85 mg, 0.36 mmol) was added. After stirring for 3 h at 110 °C, the mixture was quenched with a saturated aqueous solution of sodium

hydrogencarbonate (5 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 5 ml) and the combined organic phases were washed with and brine (10 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether:ethyl acetate 95:5 to 6:4) provided the product as a mixture of regioisomers **492-a** and **492-b** (15 mg, 0.38 mmol, 10%).

R_f: 0.42 (petroleum ether:ethyl acetate, 5:5); **IR:** ν_{max} 2953, 2922, 1599, 1346, 1161 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): partial interpretation of isomer **492-b**; δ 7.68 (2H, d, *J* = 8.1 Hz, CH-C12, CH-C16), 7.31 (2H, d, *J* = 8.1 Hz, CH-C13, CH-C15), 5.76 (1H, d, *J* = 0.9 Hz, CH-C8), 4.95 (1H, d, *J* = 0.9 Hz, CH_2-C20), 4.84 (1H, d, *J* = 0.9 Hz, CH_2-C20), 3.80 (1H, d, *J* = 12.8 Hz, CH_2-C1), 3.31 (1H, d, *J* = 12.8 Hz, CH_2-C1), 2.43 (3H, s, CH_3-C17), 2.25 (3H, s, CH_3-C10), 1.26 (3H, CH_3-C21/C22), 0.83 (3H, CH_3-C21/C22); **HRMS (CI, isobutane)** for $C_{23}H_{28}NO_3S$ ($[M+H]^+$) calculated 398.1790, found 398.1788; **LRMS (CI, isobutane) *m/z* (intensity):** 398 (100), 260 (10), 85 (12).

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Appendices

Appendix 1: X-ray crystallography of compound 316

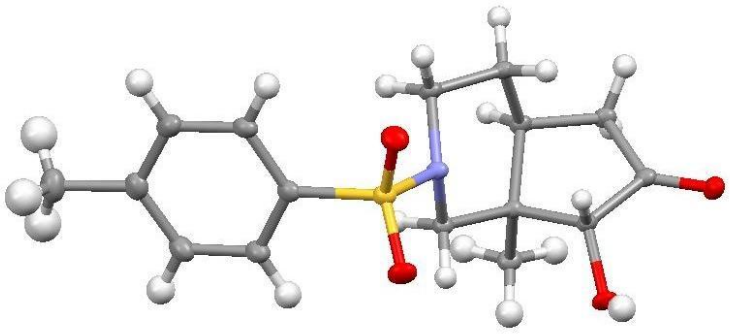


Table 1: Crystal data and structure refinement for **316**

Empirical formula	$C_{16}H_{21}NO_4S$
Formula weight	323.4
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P2(1)/c
Unit cell dimensions	a = 14.145(3) Å α = 90 °
	b = 7.8662(16) Å ß = 95.96(3) °
	c = 14.172(3) Å γ = 90 °
Volume	1568.3(5) A^3
Z, Calculated density	4, 1.370 Mg/m^3
Absorption coefficient	0.224 mm^{-1}
F(000)	688
Crystal size	0.40 x 0.30 x 0.25 mm
Theta range for data collection	2.89 to 30.12 °
Limiting indices	-19≤h≤19, -11≤k≤11, -19≤1<19
Reflections collected / unique	32641 / 4573 [R(int) = 0.346]
Completeness to theta = 30.12	99.20%
Max. and min. transmission	0.9461 and 0.9157
Refinement method	Full-matrix least-squares on F^2

Data / restraints / parameters	4573 / 0 / 202
Goodness-of-fit on F^2	1.056
Final R indices [I>2sigma(I)]	R1 = 0.0336, wR2 = 0.0852
R indices (all data)	R1 = 0.0412, wR2 = 0.092
Largest diff. peak and hole	0.501 and -0.422 $e.A^{-3}$

Table 2: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **316** U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
S(1)	7614(1)	2126(1)	4490(1)	15(1)
O(1)	10197(1)	-2879(1)	7509(1)	20(1)
O(2)	8522(1)	-735(1)	7496(1)	17(1)
O(3)	8322(1)	2971(1)	4009(1)	21(1)
O(4)	7284(1)	2883(1)	5316(1)	21(1)
N(1)	8045(1)	263(1)	4814(1)	14(1)
C(1)	9609(1)	-2759(1)	6821(1)	14(1)
C(2)	8875(1)	-1335(1)	6664(1)	13(1)
C(3)	8105(1)	-2117(1)	5948(1)	12(1)
C(4)	7485(1)	-763(1)	5421(1)	14(1)
C(5)	8452(1)	-770(1)	4082(1)	16(1)
C(6)	9158(1)	-2019(1)	4580(1)	15(1)
C(7)	8703(1)	-3150(1)	5291(1)	14(1)
C(8)	9477(1)	-3978(1)	5991(1)	16(1)
C(9)	7459(1)	-3298(1)	6452(1)	17(1)
C(10)	6617(1)	1794(1)	3653(1)	16(1)
C(11)	5738(1)	1404(2)	3965(1)	21(1)
C(12)	4954(1)	1172(2)	3304(1)	23(1)
C(13)	5026(1)	1334(2)	2333(1)	22(1)
C(14)	5915(1)	1695(2)	2037(1)	22(1)
C(15)	6711(1)	1924(2)	2688(1)	19(1)
C(16)	4160(1)	1191(2)	1620(1)	31(1)

Table 3: Bond lengths [Å] and angles [°] for **316**

S(1)-O(3)	1.4317(9)
S(1)-O(4)	1.4345(9)
S(1)-N(1)	1.6348(10)
S(1)-C(10)	1.7654(13)
O(1)-C(1)	1.2178(14)
O(2)-C(2)	1.4083(12)
O(2)-H(2)	0.8400
N(1)-C(4)	1.4700(13)
N(1)-C(5)	1.4800(13)
C(1)-C(8)	1.5143(15)
C(1)-C(2)	1.5275(14)
C(2)-C(3)	1.5384(15)
C(2)-H(2A)	1.000
C(3)-C(4)	1.5249(15)
C(3)-C(9)	1.5305(14)
C(3)-C(7)	1.5516(14)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-C(6)	1.5205(15)
C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900
C(6)-C(7)	1.5346(15)
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-C(8)	1.5429(15)
C(7)-H(7A)	1.0000
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800
C(10)-C(15)	1.3920(16)
C(10)-C(11)	1.3955(16)
C(11)-C(12)	1.3879(17)
C(11)-H(11A)	0.9500
C(12)-C(13)	1.3960(18)
C(12)-H(12A)	0.9500
C(13)-C(14)	1.3951(17)

C(13)-C(16)	1.5090(18)
C(14)-C(15)	1.3912(17)
C(14)-H(14A)	0.9500
C(15)-H(15A)	0.9500
C(16)-H(16A)	0.9800
C(16)-H(16B)	0.9800
C(16)-H(16C)	0.9800

O(3)-S(1)-O(4)	119.91(6)
O(3)-S(1)-N(1)	106.92(5)
O(4)-S(1)-N(1)	106.65(5)
O(3)-S(1)-C(10)	107.40(5)
O(4)-S(1)-C(10)	107.73(6)
N(1)-S(1)-C(10)	107.72(5)
C(2)-O(2)-H(2)	109.5
C(4)-N(1)-C(5)	112.42(9)
C(4)-N(1)-S(1)	116.67(7)
C(5)-N(1)-S(1)	117.15(7)
O(1)-C(1)-C(8)	126.31(10)
O(1)-C(1)-C(2)	124.78(10)
C(8)-C(1)-C(2)	108.92(9)
O(2)-C(2)-C(1)	114.72(9)
O(2)-C(2)-C(3)	113.42(8)
C(1)-C(2)-C(3)	103.09(8)
O(2)-C(2)-H(2A)	108.4
C(1)-C(2)-H(2A)	108.4
C(3)-C(2)-H(2A)	108.4
C(4)-C(3)-C(9)	108.14(8)
C(4)-C(3)-C(2)	112.08(8)
C(9)-C(3)-C(2)	110.59(8)
C(4)-C(3)-C(7)	113.16(8)
C(9)-C(3)-C(7)	110.57(9)
C(2)-C(3)-C(7)	102.25(8)
N(1)-C(4)-C(3)	110.66(8)
N(1)-C(4)-H(4A)	109.5
C(3)-C(4)-H(4A)	109.5
N(1)-C(4)-H(4B)	109.5
C(3)-C(4)-H(4B)	109.5
H(4A)-C(4)-H(4B)	108.1
N(1)-C(5)-C(6)	108.33(8)
N(1)-C(5)-H(5A)	110

C(6)-C(5)-H(5A)	110
N(1)-C(5)-H(5B)	110
C(6)-C(5)-H(5B)	110
H(5A)-C(5)-H(5B)	108.4
C(5)-C(6)-C(7)	112.30(9)
C(5)-C(6)-H(6A)	109.1
C(7)-C(6)-H(6A)	109.1
C(5)-C(6)-H(6B)	109.1
C(7)-C(6)-H(6B)	109.1
H(6A)-C(6)-H(6B)	107.9
C(6)-C(7)-C(8)	110.44(9)
C(6)-C(7)-C(3)	112.49(8)
C(8)-C(7)-C(3)	103.28(8)
C(6)-C(7)-H(7A)	110.1
C(8)-C(7)-H(7A)	110.1
C(3)-C(7)-H(7A)	110.1
C(1)-C(8)-C(7)	104.73(8)
C(1)-C(8)-H(8A)	110.8
C(7)-C(8)-H(8A)	110.8
C(1)-C(8)-H(8B)	110.8
C(7)-C(8)-H(8B)	110.8
H(8A)-C(8)-H(8B)	108.9
C(3)-C(9)-H(9A)	109.5
C(3)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
C(3)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
C(15)-C(10)-C(11)	120.44(11)
C(15)-C(10)-S(1)	119.84(9)
C(11)-C(10)-S(1)	119.72(9)
C(12)-C(11)-C(10)	119.37(11)
C(12)-C(11)-H(11A)	120.3
C(10)-C(11)-H(11A)	120.3
C(11)-C(12)-C(13)	121.24(11)
C(11)-C(12)-H(12A)	119.4
C(13)-C(12)-H(12A)	119.4
C(14)-C(13)-C(12)	118.36(11)
C(14)-C(13)-C(16)	120.56(11)
C(12)-C(13)-C(16)	121.04(12)
C(15)-C(14)-C(13)	121.30(11)

C(15)-C(14)-H(14A)	119.4
C(13)-C(14)-H(14A)	119.4
C(14)-C(15)-C(10)	119.26(11)
C(14)-C(15)-H(15A)	120.4000
C(10)-C(15)-H(15A)	120.4000
C(13)-C(16)-H(16A)	109.5000
C(13)-C(16)-H(16B)	109.5000
H(16A)-C(16)-H(16B)	109.5000
C(13)-C(16)-H(16C)	109.5000
H(16A)-C(16)-H(16C)	109.5000
H(16B)-C(16)-H(16C)	109.5000

Symmetry transformations used to generate equivalent atoms.

Table 4: Anisotropic displacement parameters ($A^2 \times 10^3$) for **316**. The anisotropic displacement factor exponent takes the form: $-2\ pi^2\ [\ h^2\ a^{*2}\ U11 + ... + 2\ h\ k\ a^*\ b^*\ U12]$

	U11	U22	U33	U23	U13	U12
S(1)	18(1)	11(1)	17(1)	1(1)	4(1)	1(1)
O(1)	22(1)	24(1)	14(1)	1(1)	0(1)	6(1)
O(2)	23(1)	16(1)	14(1)	-5(1)	5(1)	1(1)
O(3)	22(1)	16(1)	26(1)	4(1)	7(1)	-3(1)
O(4)	29(1)	15(1)	21(1)	-4(1)	7(1)	3(1)
N(1)	17(1)	12(1)	13(1)	1(1)	4(1)	2(1)
C(1)	18(1)	13(1)	13(1)	1(1)	4(1)	1(1)
C(2)	16(1)	12(1)	11(1)	-1(1)	3(1)	0(1)
C(3)	14(1)	11(1)	12(1)	-1(1)	3(1)	-1(1)
C(4)	14(1)	14(1)	14(1)	1(1)	3(1)	-1(1)
C(5)	21(1)	16(1)	12(1)	-1(1)	4(1)	3(1)
C(6)	18(1)	14(1)	13(1)	-1(1)	5(1)	2(1)
C(7)	18(1)	11(1)	13(1)	-2(1)	3(1)	0(1)
C(8)	21(1)	12(1)	16(1)	-1(1)	4(1)	3(1)
C(9)	19(1)	15(1)	18(1)	1(1)	5(1)	-3(1)
C(10)	18(1)	14(1)	18(1)	3(1)	4(1)	4(1)
C(11)	20(1)	23(1)	20(1)	4(1)	6(1)	3(1)
C(12)	19(1)	24(1)	27(1)	5(1)	5(1)	2(1)
C(13)	23(1)	18(1)	24(1)	1(1)	-1(1)	5(1)
C(14)	26(1)	22(1)	17(1)	2(1)	3(1)	6(1)
C(15)	20(1)	19(1)	20(1)	2(1)	7(1)	5(1)
C(16)	29(1)	29(1)	32(1)	2(1)	-6(1)	1(1)

Appendix 2: X-ray crystallography of compound 409

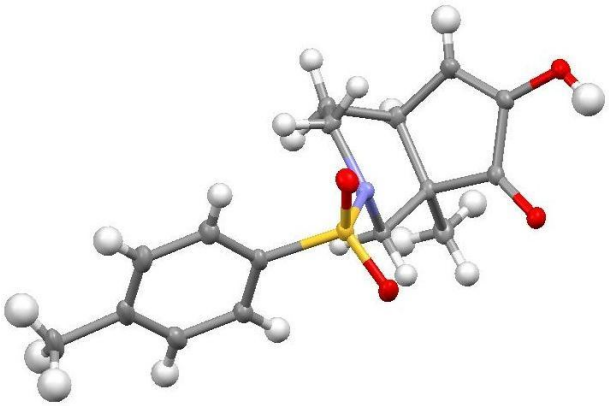


Table 1: Crystal data and structure refinement for **409**

Empirical formula	$C_{16}H_{19}NO_4S$
Formula weight	321.38
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	*C* 2/*c*
Unit cell dimensions	*a* = 26.9907(4) Å
	b = 10.4583(2) Å
	c = 12.2099(2) Å
Volume	3147.67(9) $Å^3$
Z	8
Density (calculated)	1.356 Mg/m^3
Absorption coefficient	0.223 mm^{-1}
F(000)	1360
Crystal size	0.69 x 0.26 x 0.17 mm^3
Theta range for data collection	2.12 to 29.97°.
Index ranges	-37≤h≤37, -14≤k≤14, -17≤l≤17
Reflections collected	67065
Independent reflections	4581 [*R*(int) = 0.0301]
Completeness to theta = 29.97°	100.00%
Absorption correction	Gaussian
Max. and min. transmission	0.9631 and 0.8613
Refinement method	Full-matrix least-squares on *F*2
Data / restraints / parameters	4581 / 0 / 221

Goodness-of-fit on *F*2	1.053
Final *R* indices [I > 2σ(I)]	*R*1 = 0.0289, w*R*2 = 0.0810
R indices (all data)	*R*1 = 0.0326, w*R*2 = 0.0832
Largest diff. peak and hole	0.409 and -0.369 e.Å^{-3}

Table 2: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **409** U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
S(1)	7775(1)	283(1)	7941(1)	15(1)
O(8)	9935(1)	2072(1)	9458(1)	22(1)
O(9)	9492(1)	-499(1)	8698(1)	19(1)
O(11)	7956(1)	-988(1)	8365(1)	21(1)
O(12)	7746(1)	1229(1)	8766(1)	21(1)
N(1)	8184(1)	825(1)	7376(1)	14(1)
C(2)	8385(1)	-61(1)	6708(1)	15(1)
C(3)	8926(1)	440(1)	6755(1)	15(1)
C(4)	8886(1)	1869(1)	6370(1)	17(1)
C(5)	8310(1)	2403(1)	6005(1)	17(1)
C(6)	8104(1)	2185(1)	6983(1)	17(1)
C(7)	9296(1)	2538(1)	7447(1)	21(1)
C(8)	9549(1)	1750(1)	8377(1)	17(1)
C(9)	9344(1)	443(1)	8051(1)	15(1)
C(31)	9127(1)	-443(1)	6017(1)	21(1)
C(111)	7117(1)	155(1)	6776(1)	17(1)
C(112)	7021(1)	-766(1)	5887(1)	20(1)
C(113)	6496(1)	-924(1)	5019(1)	24(1)
C(114)	6066(1)	-189(1)	5034(1)	25(1)
C(115)	6174(1)	745(1)	5915(1)	26(1)
C(116)	6699(1)	927(1)	6788(1)	22(1)
C(117)	5494(1)	-423(1)	4125(1)	35(1)

Table 3: Bond lengths [Å] and angles [°] for **409**

S(1)-O(12)	1.4367(7)
S(1)-O(11)	1.4390(7)
S(1)-N(1)	1.6250(7)
S(1)-C(111)	1.7704(9)
O(8)-C(8)	1.3499(11)
O(8)-H(8)	0.8400
O(9)-C(9)	1.2231(11)
N(1)-C(2)	1.4752(11)
N(1)-C(6)	1.4887(11)
C(2)-C(3)	1.5318(12)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-C(9)	1.5244(12)
C(3)-C(31)	1.5353(12)
C(3)-C(4)	1.5570(12)
C(4)-C(7)	1.5025(13)
C(4)-C(5)	1.5387(12)
C(4)-H(4)	1.0000
C(5)-C(6)	1.5248(12)
C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-C(8)	1.3421(12)
C(7)-H(7)	0.9500
C(8)-C(9)	1.4676(12)
C(31)-H(31A)	0.9800
C(31)-H(31B)	0.9800
C(31)-H(31C)	0.9800
C(111)-C(116)	1.3925(13)
C(111)-C(112)	1.3936(13)
C(112)-C(113)	1.3920(12)
C(112)-H(112)	0.9500
C(113)-C(114)	1.3968(15)
C(113)-H(113)	0.9500
C(114)-C(115)	1.3935(16)

C(114)-C(117)	1.5106(14)
C(115)-C(116)	1.3965(13)
C(115)-H(115)	0.9500
C(116)-H(116)	0.9500
C(117)-H(11A)	0.9800
C(117)-H(11B)	0.9800
C(117)-H(11C)	0.9800

O(12)-S(1)-O(11)	119.42(4)
O(12)-S(1)-N(1)	107.34(4)
O(11)-S(1)-N(1)	106.53(4)
O(12)-S(1)-C(111)	107.05(4)
O(11)-S(1)-C(111)	107.59(4)
N(1)-S(1)-C(111)	108.55(4)
C(8)-O(8)-H(8)	109.5
C(2)-N(1)-C(6)	117.41(7)
C(2)-N(1)-S(1)	118.82(6)
C(6)-N(1)-S(1)	115.81(6)
N(1)-C(2)-C(3)	108.92(7)
N(1)-C(2)-H(2A)	109.9
C(3)-C(2)-H(2A)	109.9
N(1)-C(2)-H(2B)	109.9
C(3)-C(2)-H(2B)	109.9
H(2A)-C(2)-H(2B)	108.3
C(9)-C(3)-C(2)	109.29(7)
C(9)-C(3)-C(31)	108.76(7)
C(2)-C(3)-C(31)	109.41(7)
C(9)-C(3)-C(4)	104.06(7)
C(2)-C(3)-C(4)	111.65(7)
C(31)-C(3)-C(4)	113.47(7)
C(7)-C(4)-C(5)	112.41(8)
C(7)-C(4)-C(3)	104.26(7)
C(5)-C(4)-C(3)	111.97(7)
C(7)-C(4)-H(4)	109.4
C(5)-C(4)-H(4)	109.4
C(3)-C(4)-H(4)	109.4
C(6)-C(5)-C(4)	111.49(7)
C(6)-C(5)-H(5A)	109.3
C(4)-C(5)-H(5A)	109.3
C(6)-C(5)-H(5B)	109.3
C(4)-C(5)-H(5B)	109.3

H(5A)-C(5)-H(5B)	108
N(1)-C(6)-C(5)	110.10(7)
N(1)-C(6)-H(6A)	109.6
C(5)-C(6)-H(6A)	109.6
N(1)-C(6)-H(6B)	109.6
C(5)-C(6)-H(6B)	109.6
H(6A)-C(6)-H(6B)	108.2
C(8)-C(7)-C(4)	113.24(8)
C(8)-C(7)-H(7)	123.4
C(4)-C(7)-H(7)	123.4
C(7)-C(8)-O(8)	126.74(9)
C(7)-C(8)-C(9)	109.68(8)
O(8)-C(8)-C(9)	123.58(8)
O(9)-C(9)-C(8)	126.01(8)
O(9)-C(9)-C(3)	125.27(8)
C(8)-C(9)-C(3)	108.70(7)
C(3)-C(31)-H(31A)	109.5
C(3)-C(31)-H(31B)	109.5
H(31A)-C(31)-H(31B)	109.5
C(3)-C(31)-H(31C)	109.5
H(31A)-C(31)-H(31C)	109.5
H(31B)-C(31)-H(31C)	109.5
C(116)-C(111)-C(112)	121.00(9)
C(116)-C(111)-S(1)	119.89(7)
C(112)-C(111)-S(1)	119.04(7)
C(113)-C(112)-C(111)	118.91(9)
C(113)-C(112)-H(112)	120.5
C(111)-C(112)-H(112)	120.5
C(112)-C(113)-C(114)	121.20(10)
C(112)-C(113)-H(113)	119.4
C(114)-C(113)-H(113)	119.4
C(115)-C(114)-C(113)	118.84(9)
C(115)-C(114)-C(117)	120.66(10)
C(113)-C(114)-C(117)	120.49(11)
C(114)-C(115)-C(116)	120.87(10)
C(114)-C(115)-H(115)	119.6
C(116)-C(115)-H(115)	119.6
C(111)-C(116)-C(115)	119.13(10)
C(111)-C(116)-H(116)	120.4
C(115)-C(116)-H(116)	120.4
C(114)-C(117)-H(11A)	109.5

C(114)-C(117)-H(11B)	109.5
H(11A)-C(117)-H(11B)	109.5
C(114)-C(117)-H(11C)	109.5
H(11A)-C(117)-H(11C)	109.5
H(11B)-C(117)-H(11C)	109.5

Symmetry transformations used to generate equivalent atoms.

Table 4: Anisotropic displacement parameters ($A^2 \times 10^3$) for **409**. The anisotropic displacement factor exponent takes the form: $-2\ pi^2\ [\ h^2\ a^{*2}\ U11 + ... + 2\ h\ k\ a^*\ b^*\ U12]$

	U11	U22	U33	U23	U13	U12
S(1)	13(1)	19(1)	12(1)	2(1)	4(1)	-1(1)
O(8)	20(1)	19(1)	20(1)	0(1)	-1(1)	-2(1)
O(9)	19(1)	19(1)	17(1)	2(1)	4(1)	1(1)
O(11)	19(1)	21(1)	20(1)	7(1)	5(1)	-1(1)
O(12)	21(1)	27(1)	15(1)	-2(1)	9(1)	-2(1)
N(1)	14(1)	15(1)	15(1)	1(1)	7(1)	0(1)
C(2)	13(1)	17(1)	15(1)	-2(1)	5(1)	0(1)
C(3)	13(1)	19(1)	12(1)	0(1)	4(1)	1(1)
C(4)	15(1)	21(1)	15(1)	4(1)	6(1)	1(1)
C(5)	16(1)	20(1)	14(1)	4(1)	5(1)	2(1)
C(6)	18(1)	16(1)	18(1)	3(1)	9(1)	2(1)
C(7)	17(1)	20(1)	23(1)	4(1)	5(1)	-3(1)
C(8)	14(1)	18(1)	18(1)	0(1)	4(1)	-1(1)
C(9)	12(1)	18(1)	14(1)	0(1)	5(1)	1(1)
C(31)	18(1)	29(1)	18(1)	-4(1)	7(1)	3(1)
C(111)	13(1)	20(1)	16(1)	4(1)	4(1)	-2(1)
C(112)	17(1)	20(1)	19(1)	2(1)	5(1)	-2(1)
C(113)	22(1)	24(1)	20(1)	3(1)	2(1)	-6(1)
C(114)	16(1)	29(1)	23(1)	12(1)	1(1)	-5(1)
C(115)	15(1)	31(1)	31(1)	9(1)	8(1)	2(1)
C(116)	17(1)	25(1)	24(1)	3(1)	9(1)	0(1)
C(117)	18(1)	42(1)	33(1)	15(1)	-3(1)	-8(1)

Appendix 3: X-ray crystallography of compound 412

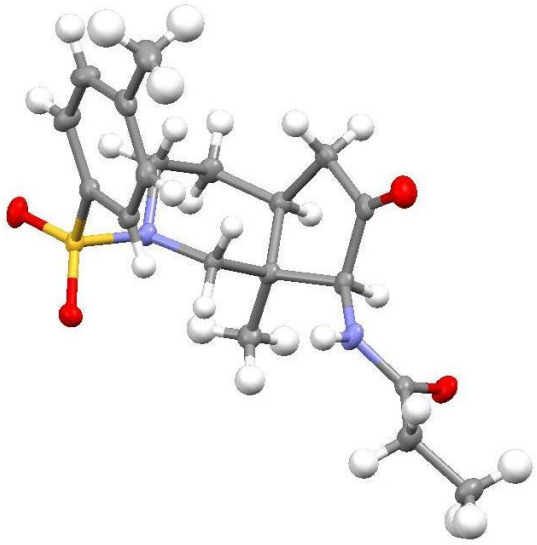


Table 1: Crystal data and structure refinement for **412**

Empirical formula	$C_{19}H_{26}N_2O_4S$
Formula weight	378.48
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P2(1)/c
Unit cell dimensions	a = 11.2667(3) Å α = 90 °.
	b = 15.2906(4) Å ß = 110.9560(10) ° .
	c = 11.5112(3) Å γ = 90 °.
Volume	1851.92(8) $Å^3$
Z, Calculated density	4, 1.357 Mg/m^3
Absorption coefficient	0.202 mm^{-1}
F(000)	808
Crystal size	0.12 x 0.10 x 0.05 mm
Theta range for data collection	1.94 to 26.00 deg.
Limiting indices	-13≤h≤13, -16≤k≤18, -9≤l≤14
Reflections collected /unique	14272 / 3621 [R(int) = 0.0294]
Completeness to theta = 26.00	99.60%
Absorption correction	Empirical

Max. and min. Transmission	0.9900 and 0.9761
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3621 / 0 / 238
Goodness-of-fit on F^2	1.042
Final R indices [I>2sigma(I)]	R1 = 0.0338, wR2 =0.082
R indices (all data)	R1 = 0.0407, wR2 = 0.0869
Extinction coefficient	none
Largest diff. peak and hole	0.32 and -0.34 $e.A^{-3}$

Table 2: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **412**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	4003(1)	-162(1)	7659(1)	20(1)
C(2)	3336(1)	723(1)	7239(1)	17(1)
C(3)	2329(1)	637(1)	5925(1)	17(1)
C(4)	2742(2)	1070(1)	8141(1)	24(1)
C(5)	2997(1)	2004(1)	5220(1)	21(1)
C(6)	4027(2)	2141(1)	6488(2)	23(1)
C(7)	4465(1)	1285(1)	7190(1)	19(1)
C(8)	5210(1)	667(1)	6637(2)	24(1)
C(9)	4885(1)	-245(1)	6924(1)	22(1)
C(10)	3434(1)	-1428(1)	8636(1)	18(1)
C(11)	2578(2)	-2218(1)	8443(2)	29(1)
C(12)	2872(2)	-2788(1)	9591(2)	31(1)
C(13)	809(1)	948(1)	3007(1)	18(1)
C(14)	679(1)	43(1)	3006(1)	20(1)
C(15)	970(2)	-451(1)	2133(1)	23(1)
C(16)	1407(2)	-57(1)	1276(2)	25(1)
C(17)	1510(2)	850(1)	1280(2)	28(1)
C(18)	1217(2)	1355(1)	2137(2)	25(1)
C(19)	1768(2)	-606(1)	367(2)	37(1)
N(1)	3216(1)	-913(1)	7624(1)	22(1)
N(2)	1930(1)	1515(1)	5390(1)	17(1)
O(1)	5233(1)	-925(1)	6611(1)	33(1)
O(2)	4267(1)	-1265(1)	9631(1)	27(1)
O(3)	-357(1)	1124(1)	4571(1)	22(1)
O(4)	388(1)	2461(1)	3828(1)	26(1)
S(1)	582(1)	1562(1)	4205(1)	17(1)

Table 3: Bond lengths [Å] and angles [°] for **412**

C(1)-N(1)	1.442(2)
C(1)-C(9)	1.523(2)
C(1)-C(2)	1.540(2)
C(2)-C(4)	1.518(2)
C(2)-C(3)	1.5381(19)
C(2)-C(7)	1.553(2)
C(3)-N(2)	1.4783(18)
C(5)-N(2)	1.4869(19)
C(5)-C(6)	1.520(2)
C(6)-C(7)	1.524(2)
C(7)-C(8)	1.545(2)
C(8)-C(9)	1.508(2)
C(9)-O(1)	1.211(2)
C(10)-O(2)	1.2189(18)
C(10)-N(1)	1.354(2)
C(10)-C(11)	1.511(2)
C(11)-C(12)	1.517(2)
C(13)-C(18)	1.389(2)
C(13)-C(14)	1.392(2)
C(13)-S(1)	1.7616(16)
C(14)-C(15)	1.387(2)
C(15)-C(16)	1.388(2)
C(16)-C(17)	1.392(2)
C(16)-C(19)	1.506(2)
C(17)-C(18)	1.383(2)
N(2)-S(1)	1.6405(12)
O(3)-S(1)	1.4368(11)
O(4)-S(1)	1.4351(12)
N(1)-C(1)-C(9)	115.78(13)
N(1)-C(1)-C(2)	117.74(12)
C(9)-C(1)-C(2)	103.89(12)
C(4)-C(2)-C(3)	110.58(12)
C(4)-C(2)-C(1)	112.18(13)
C(3)-C(2)-C(1)	109.81(12)
C(4)-C(2)-C(7)	113.50(13)

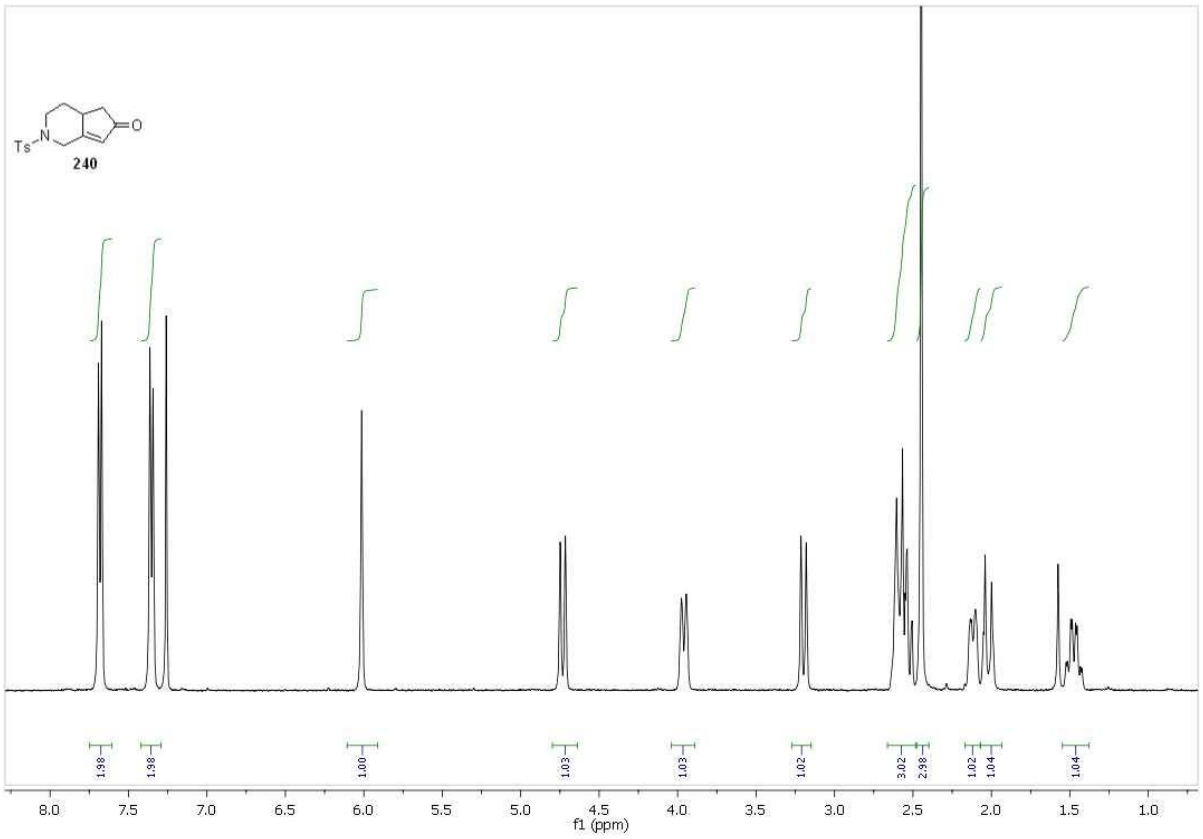
C(3)-C(2)-C(7)	109.73(12)
C(1)-C(2)-C(7)	100.63(12)
N(2)-C(3)-C(2)	109.82(12)
N(2)-C(5)-C(6)	108.57(12)
C(5)-C(6)-C(7)	112.46(13)
C(6)-C(7)-C(8)	115.34(13)
C(6)-C(7)-C(2)	112.36(12)
C(8)-C(7)-C(2)	104.41(12)
C(9)-C(8)-C(7)	105.38(13)
O(1)-C(9)-C(8)	126.74(16)
O(1)-C(9)-C(1)	125.59(15)
C(8)-C(9)-C(1)	107.65(13)
O(2)-C(10)-N(1)	122.07(14)
O(2)-C(10)-C(11)	122.59(14)
N(1)-C(10)-C(11)	115.34(13)
C(10)-C(11)-C(12)	113.69(14)
C(18)-C(13)-C(14)	120.54(15)
C(18)-C(13)-S(1)	120.21(12)
C(14)-C(13)-S(1)	119.03(12)
C(15)-C(14)-C(13)	119.29(15)
C(14)-C(15)-C(16)	120.98(15)
C(15)-C(16)-C(17)	118.71(15)
C(15)-C(16)-C(19)	120.30(16)
C(17)-C(16)-C(19)	120.99(16)
C(18)-C(17)-C(16)	121.22(16)
C(17)-C(18)-C(13)	119.23(15)
C(10)-N(1)-C(1)	121.21(12)
C(3)-N(2)-C(5)	111.82(12)
C(3)-N(2)-S(1)	116.04(9)
C(5)-N(2)-S(1)	114.86(10)
O(4)-S(1)-O(3)	119.19(7)
O(4)-S(1)-N(2)	106.79(6)
O(3)-S(1)-N(2)	107.20(6)
O(4)-S(1)-C(13)	108.82(7)
O(3)-S(1)-C(13)	108.03(7)
N(2)-S(1)-C(13)	106.09(7)

Symmetry transformations used to generate equivalent atoms

Table 4: Anisotropic displacement parameters ($A^2 \times 10^3$) for **412**. The anisotropic displacement factor exponent takes the form: $-2\ pi^2\ [\ h^2\ a^{*2}\ U11 + ... + 2\ h\ k\ a^*\ b^*\ U12]$

	U11	U22	U33	U23	U13	U12
C(1)	19(1)	19(1)	16(1)	2(1)	1(1)	0(1)
C(2)	19(1)	16(1)	15(1)	0(1)	4(1)	-1(1)
C(3)	19(1)	14(1)	16(1)	1(1)	5(1)	0(1)
C(4)	26(1)	26(1)	18(1)	-1(1)	7(1)	2(1)
C(5)	23(1)	17(1)	21(1)	4(1)	6(1)	-4(1)
C(6)	22(1)	19(1)	25(1)	-1(1)	6(1)	-6(1)
C(7)	18(1)	21(1)	16(1)	-2(1)	2(1)	-4(1)
C(8)	17(1)	29(1)	23(1)	2(1)	6(1)	1(1)
C(9)	18(1)	25(1)	17(1)	1(1)	0(1)	4(1)
C(10)	18(1)	19(1)	18(1)	2(1)	7(1)	5(1)
C(11)	28(1)	26(1)	27(1)	5(1)	4(1)	-4(1)
C(12)	39(1)	24(1)	30(1)	6(1)	15(1)	-1(1)
C(13)	17(1)	20(1)	15(1)	-1(1)	2(1)	0(1)
C(14)	20(1)	20(1)	17(1)	2(1)	5(1)	0(1)
C(15)	23(1)	21(1)	21(1)	0(1)	3(1)	3(1)
C(16)	20(1)	33(1)	18(1)	-2(1)	4(1)	5(1)
C(17)	30(1)	36(1)	22(1)	2(1)	12(1)	-5(1)
C(18)	30(1)	22(1)	20(1)	1(1)	7(1)	-6(1)
C(19)	38(1)	48(1)	26(1)	-3(1)	12(1)	13(1)
N(1)	24(1)	20(1)	16(1)	3(1)	0(1)	-3(1)
N(2)	18(1)	16(1)	15(1)	1(1)	3(1)	-1(1)
O(1)	36(1)	29(1)	35(1)	-1(1)	12(1)	9(1)
O(2)	29(1)	31(1)	18(1)	4(1)	2(1)	-3(1)
O(3)	19(1)	25(1)	22(1)	-1(1)	7(1)	0(1)
O(4)	30(1)	17(1)	24(1)	2(1)	3(1)	4(1)
S(1)	18(1)	16(1)	15(1)	0(1)	3(1)	1(1)

Appendix 4: Spectrum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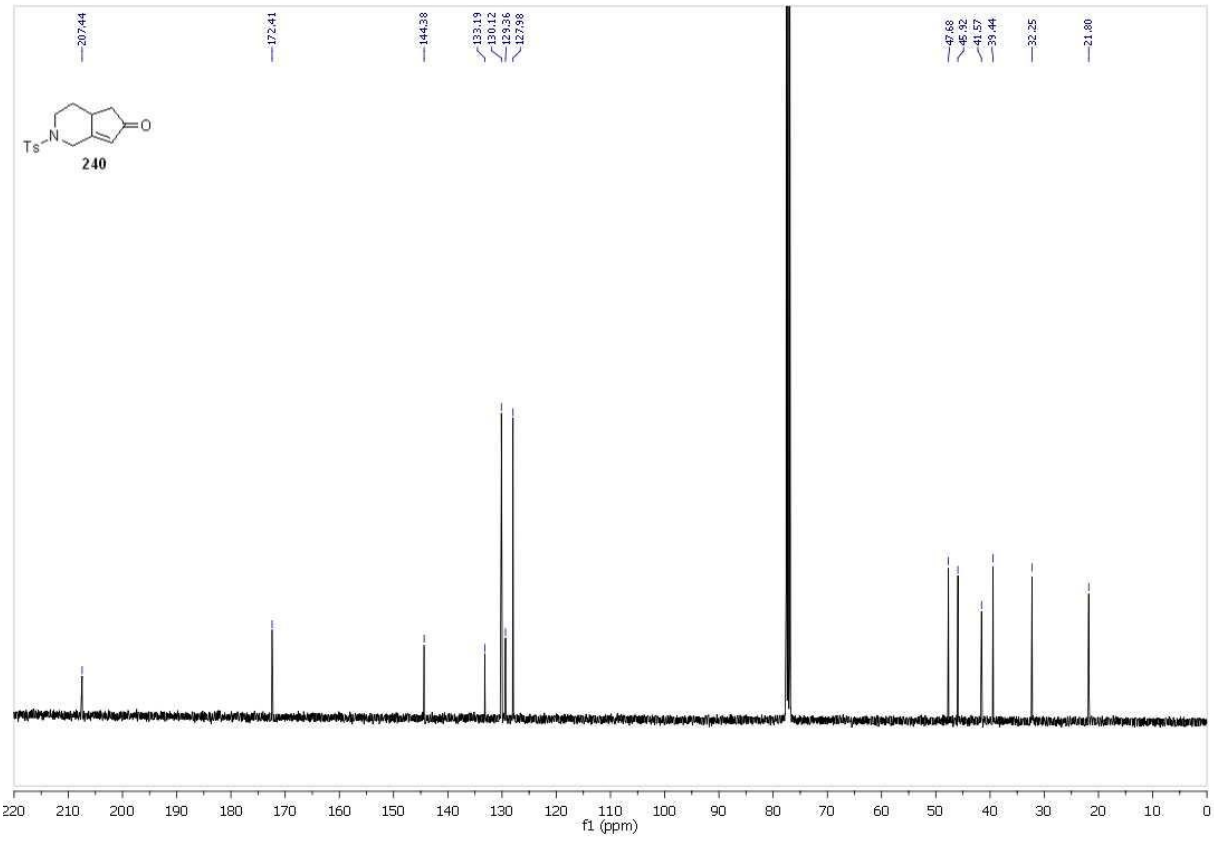
1.98
1.00
1.03
1.03
1.02
3.02
2.98
1.02
1.04
1.04
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)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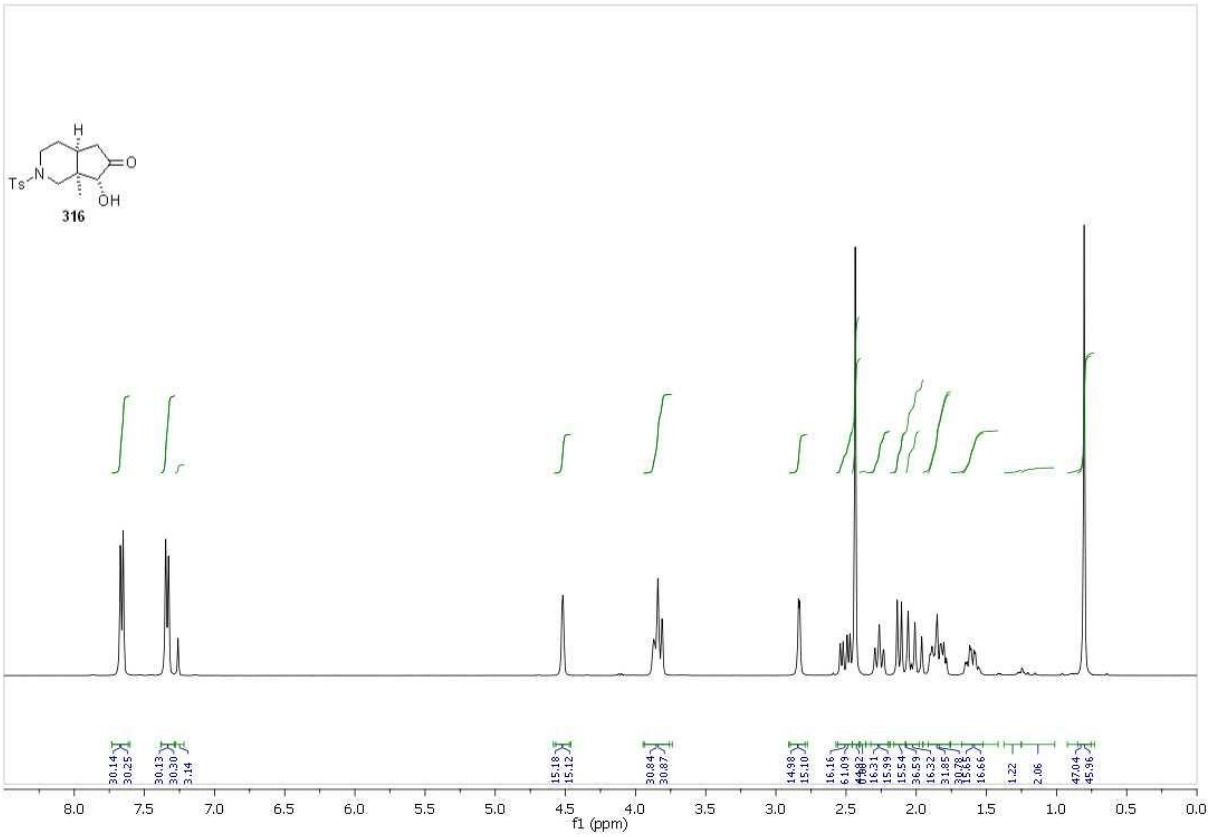
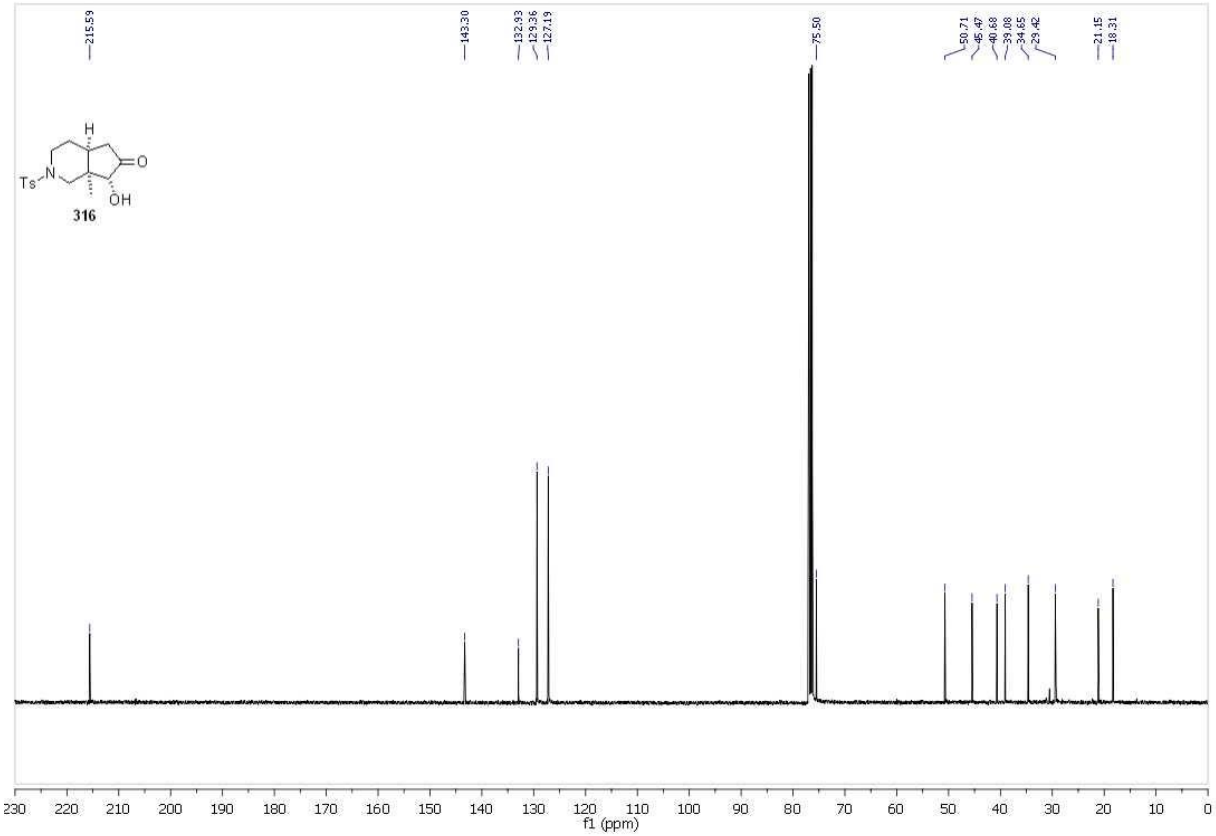
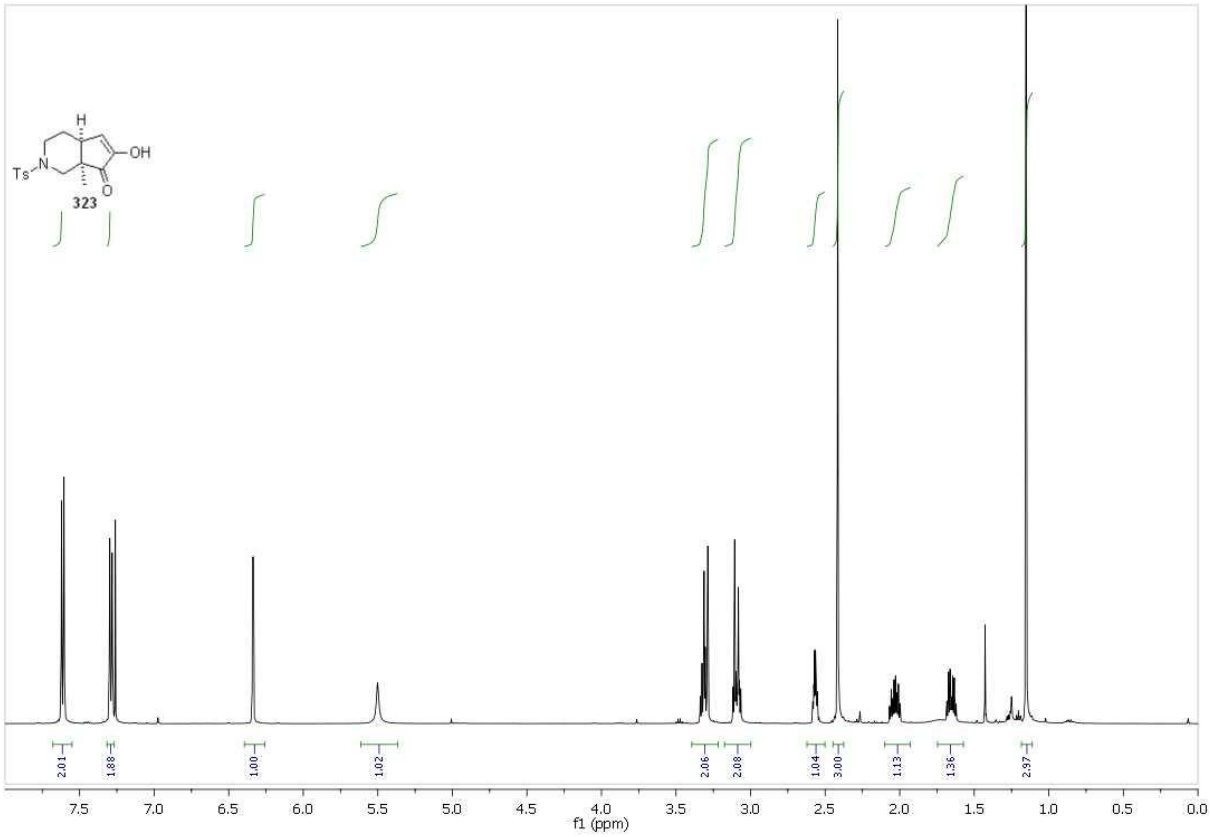
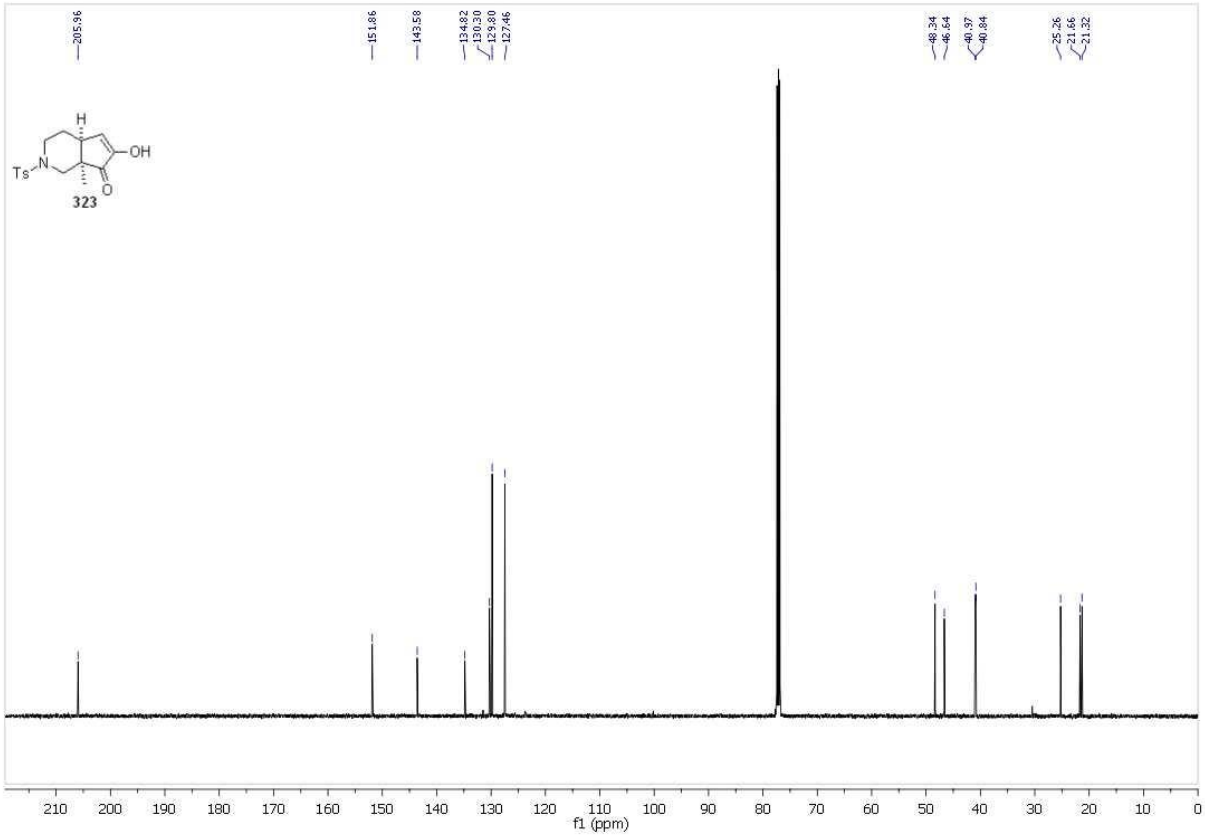
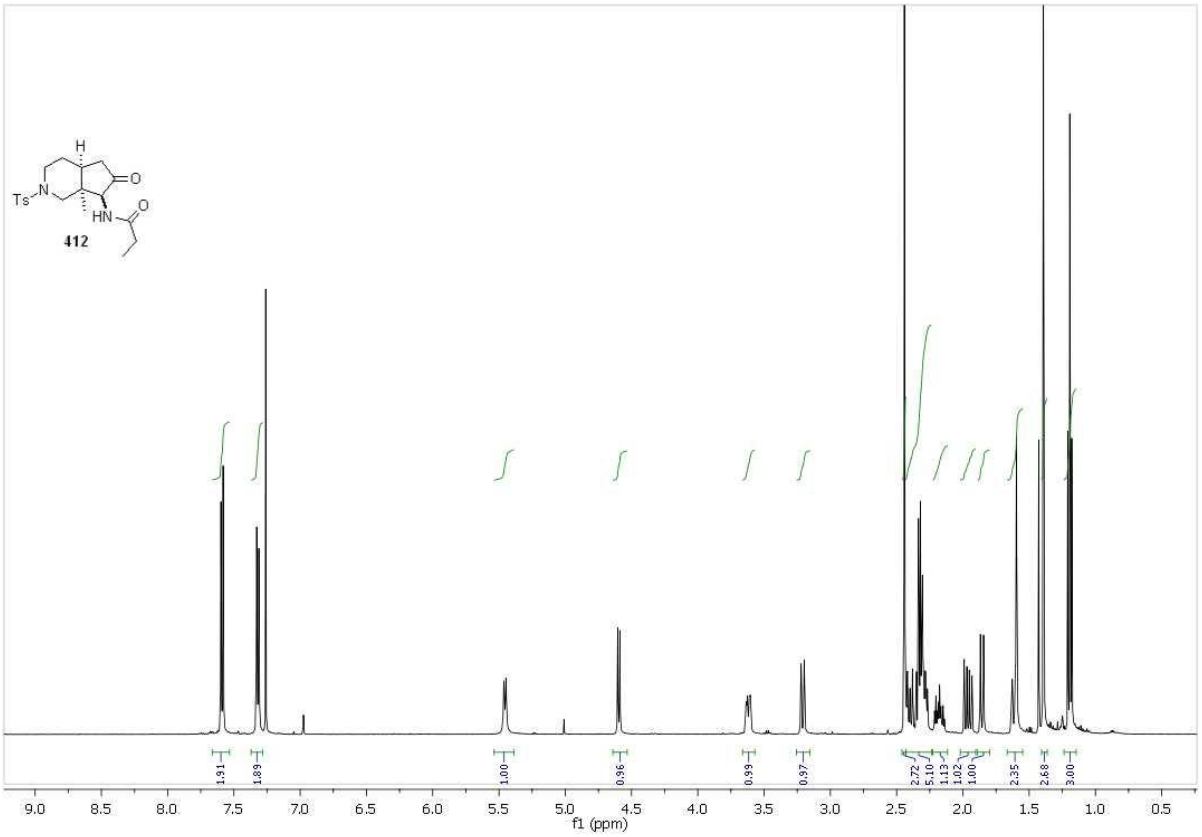
172.41
144.38
133.19
130.12
129.36
127.98
47.68
46.92
41.57
39.44
32.25
21.80
Ts
N
O
240
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

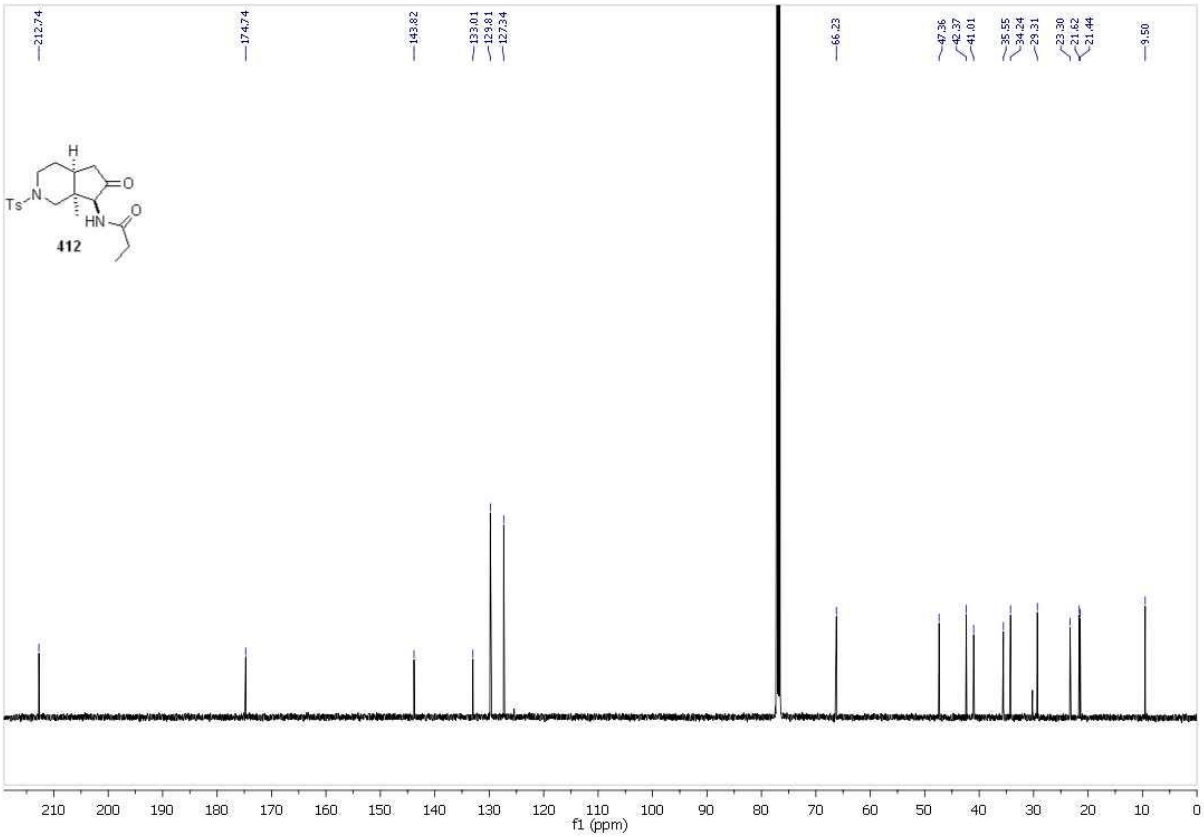

316
f1 (ppm)

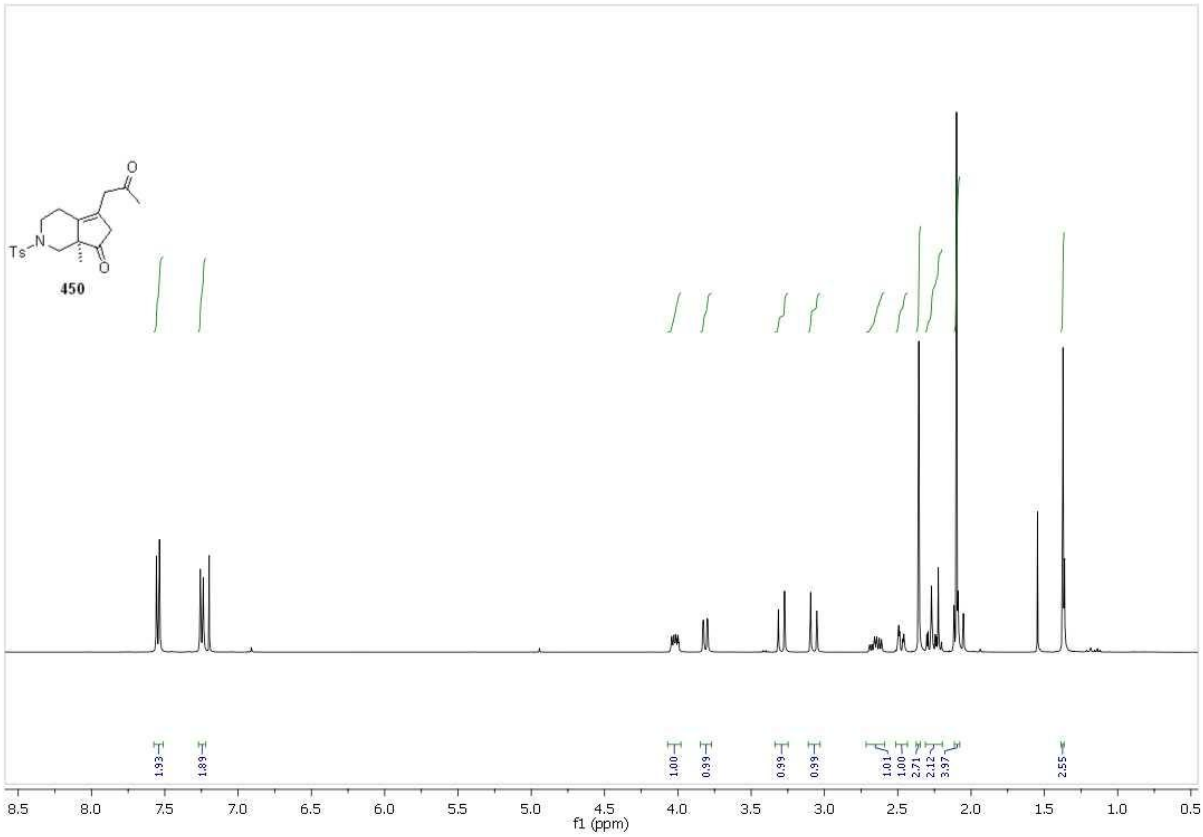

316
f1 (ppm)

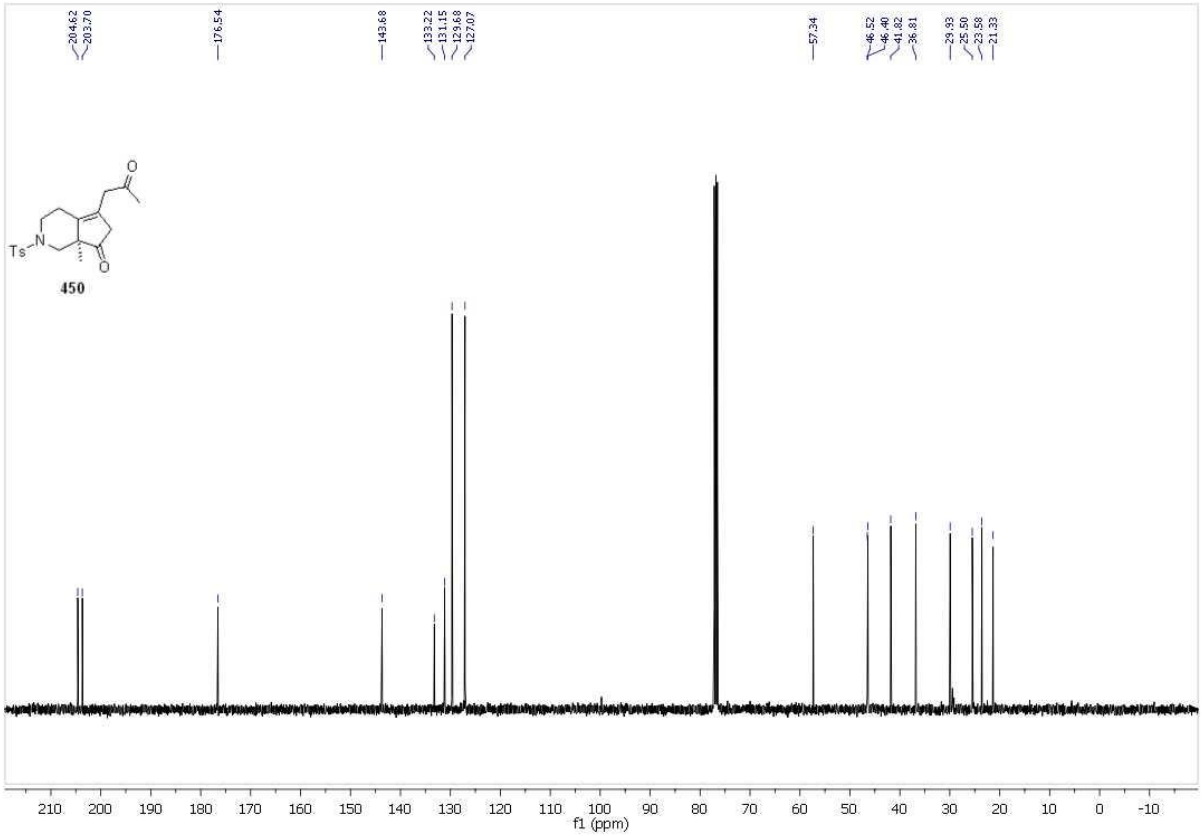

H
OH
Ts
N
O
323
2.01
1.88
1.00
1.02
2.06
2.08
1.04
3.00
1.13
1.36
2.97
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

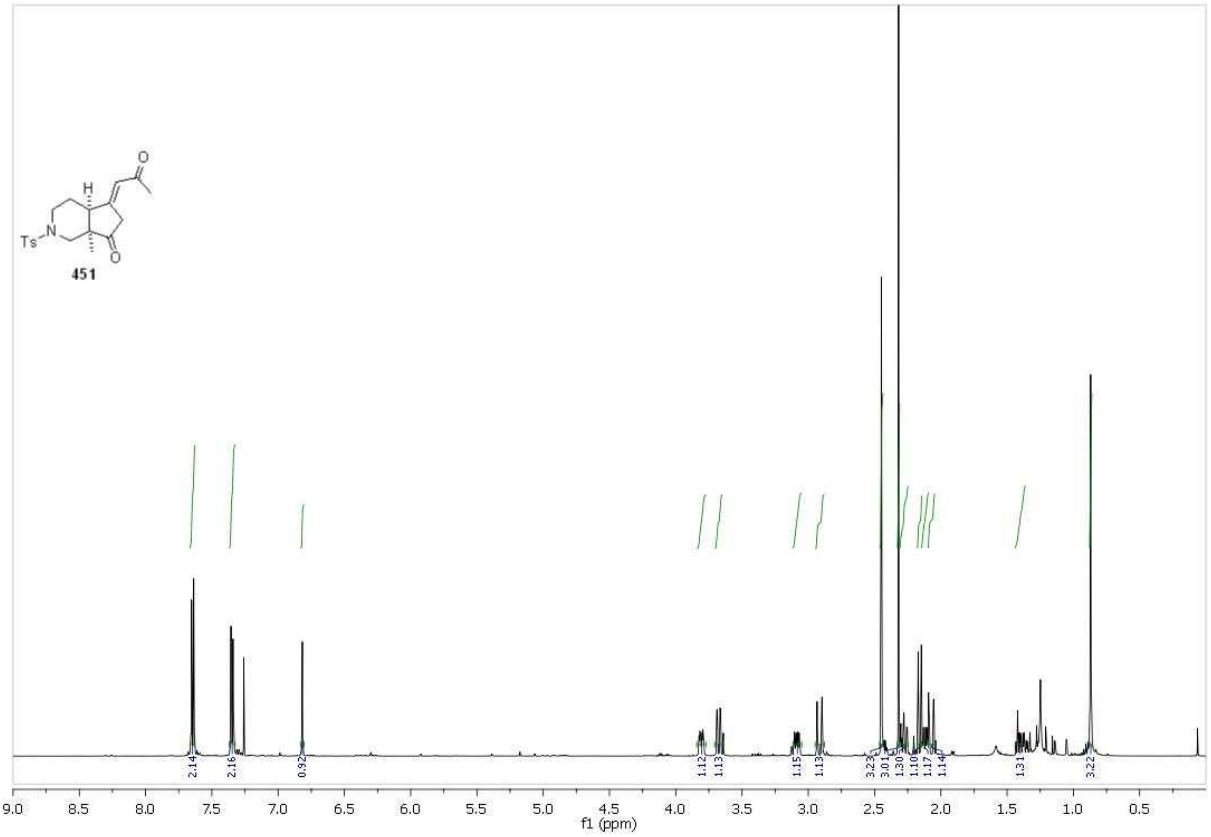

205.96
151.86
143.58
134.82
130.30
129.80
127.46
48.34
46.64
40.37
40.04
25.26
21.66
21.32
H
OH
Ts
N
O
323
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

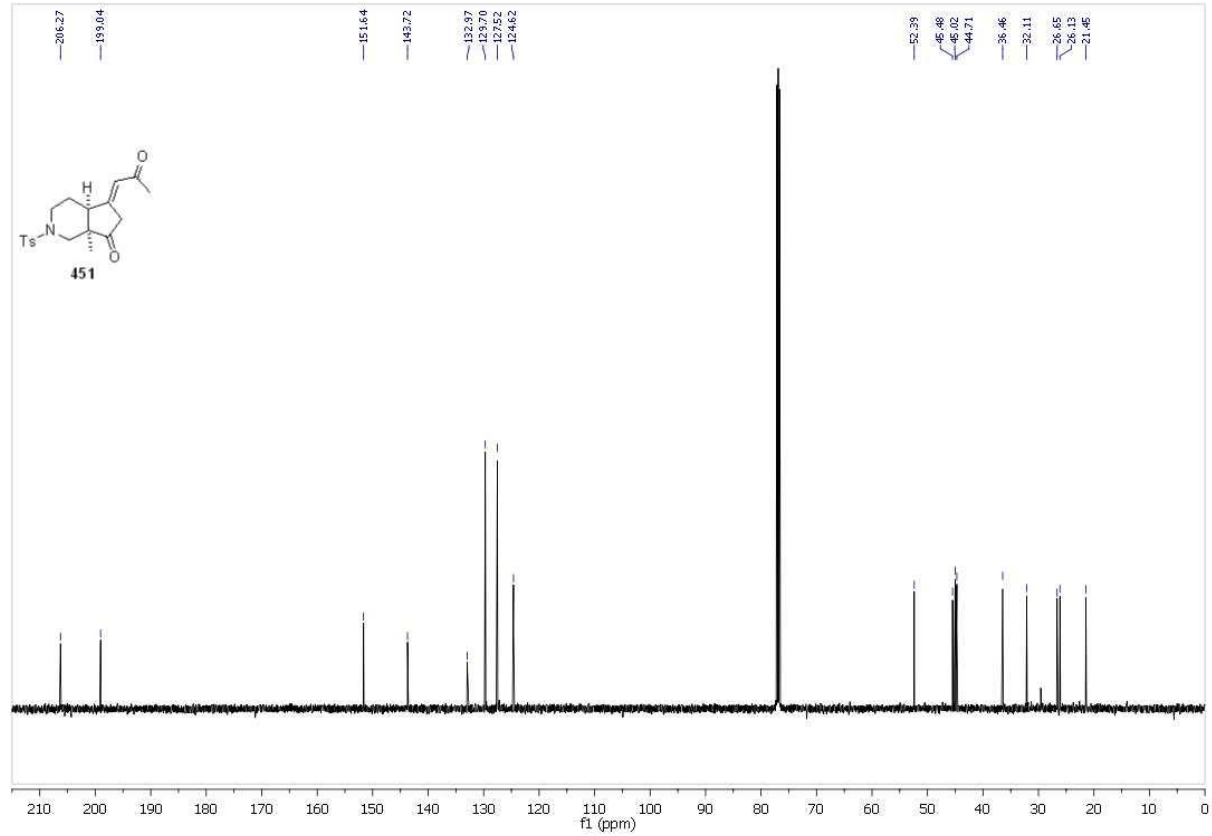

412
1.91
1.89
1.00
0.96
0.99
0.97
2.72
5.10
1.13
1.02
1.00
2.35
2.68
3.00
f1 (ppm)


412
212.74
174.74
143.82
133.01
129.81
127.34
66.23
47.36
42.37
41.01
35.55
34.24
29.31
23.30
21.62
21.44
9.50
f1 (ppm)


Ts
N
O
O
450
1.93
1.89
1.00
0.99
0.99
0.99
1.01
1.00
2.71
2.12
3.97
2.55
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
f1 (ppm)


204.62
203.70
176.54
143.68
133.22
131.15
129.68
127.07
57.34
46.52
46.40
41.82
36.81
29.93
25.50
23.58
21.33
Ts
N
O
O
450
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)


Ts
N
H
O
O
451
2.14
2.16
0.92
1.12
1.13
1.15
1.13
3.23
3.01
1.30
1.10
1.17
1.14
1.31
3.22
9.0
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
f1 (ppm)


206.27
199.04
151.64
143.72
132.97
129.70
127.52
124.62
52.39
46.48
46.02
44.71
36.46
32.11
26.65
26.13
21.46
Ts
N
H
O
O
451
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)