Total synthesis of bistramide D

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**NANYANG
TECHNOLOGICAL
UNIVERSITY**

**TOTAL SYNTHESIS OF
BISTRAMIDE D**

LI LU

**SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES
DIVISION OF CHEMISTRY AND
BIOLOGICAL CHEMISTRY**

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D

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ABBREVIATIONS:

Å	Angstrom unit
Ac	acetyl
App	apparent
aq.	aqueous
Ar	aryl
Bn	benzyl
Boc	<i>tert</i> -butyloxycarbonyl
BOM	benzyloxymethyl
b.p.	boiling point
Bu	butyl
Bz	benzoyl
CBS	Corey-Bakshi-Shibata
CM	cross metathesis
COSY	correlated spectroscopy
conc.	concentrated
CSA	camphorsulfonic acid
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undecane
DIBAL	diisobutylaluminium hydride
DIPEA	<i>N,N</i> -Diisopropylethylamine
DCC	1,3-dicyclohexylcarbodiimide
DDQ	dichlorodicyanoquinine
DMF	dimethyl formide

DMP	Dess-Martin periodinane
DMAP	4- <i>N,N</i> -dimethylamino pyridine
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dr	diastereoisomeric ratio
EA	ethyl acetate
EDA	ethylene diamine
e.e	enantiomeric excess
eq.	equivalent
GC	gas chromatography
HMPA	hexamethylphosphoramide
hr	hour
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
<i>i</i>	iso
IBX	2-iodoxybenzoic acid
IR	infra-red spectroscopy
<i>J</i>	coupling constant
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazane
Lit.	literature
m	multiplet
mCPBA	3-chloroperoxybenzoic acid
Me	methyl

m.p.	melting point
MS	mass spectrometry
NaHMDS	Sodium bis(trimethylsilyl)amide
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
NMR	nuclear magnetic resonance
NMO	<i>N</i> -methylmorpholine N-oxide
NIS	<i>N</i> -iodosuccinimide
NOESY	nuclear overhauser effect spectroscopy
<i>n</i> -Bu	butyl
<i>n</i> -Pr	propyl
N.D.	not determined
Nu	nucleophile(s)
<i>p</i>	para
PCC	pyridinium chlorochromate
PG	protecting group(s)
Ph	phenyl
PMB	<i>p</i> -methoxybenzyl
ppm	parts per million
PPTS	pyridinium <i>p</i> -toluenesulfonate
PTSA	<i>p</i> -toluenesulfonic acid
Pr	propyl
Py	pyridine
q	quartet
quant.	quantitative

R	undefined alkyl or aryl group
r.t.	room temperature
RCM	ring closing metathesis
Red-Al	sodium bis(2-methoxyethoxy)aluminium hydride
ROM	ring opening metathesis
s	singlet
Sat.	saturated
t	triplet
TBDMS/TBS	<i>tert</i> -butyldimethylsilyl
<i>tert</i>	tertiary
TBAF	tetrabutylammoniumfluoride
Tf	triflyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMG	tetramethylguanidine
TMS	trimethylsilyl
Ts	tosyl

ABSTRACT

Fig 1 Structure of bistramide D

The bistramides are a class of natural products isolated from the marine ascidian *Lissoclinum bistratum*. These molecules demonstrate significant bioactive properties, such as cytotoxicity, antiproliferative and neurotoxic activities.

This thesis describes synthetic studies towards the development of the total asymmetric synthesis of one of the members, bistramide D. The structure of this natural product comprises 12 stereogenic centres and consists of three units, a tetrahydropyran (THP), an amino acid and a [6,6]-spiroketal.

Building upon prior studies in our group, the synthesis of the tetrahydropyran ring has been achieved using a combination of selective cross-metathesis and an intramolecular Michael addition under kinetic control. Five different approaches were studied for the synthesis of a key intermediate, the sulfone fragment.

The synthesis of the spiroketal fragment features an Au-mediated dehydrative cyclisation via a propargylic triol. The [6,6]-spiroketal unit has been successfully constructed in enantiomerically highly enriched form.

Scheme 2 Retrosynthesis of bistramide D

Chapter One:

Introduction to Bistramide D

//

1.1 Introduction to Bistramides

1.1.1 Isolation and biological activities

The bistramides are a family of natural products isolated from *Lissoclinum bistratum* sluter, an ascidian which is a marine organism.¹ Since the discovery of bistramide A, in New Caledonia and in Australia,² four additional members (bistramide B-D and K) have been reported.³ More recently, bistramides A, D and a new member, named 39-oxobistramide K, have also been isolated from the marine invertebrate tunicate *Trididemnum Cyclops* Michaelsen in Madagascar.⁴

Bistramides display numerous biological properties, such as antiproliferative, antiparasitic, neurotoxic and immunomodulatory activities.^{3, 5} They also play an important role in cell cycle regulation, differentiation and apoptosis.^{5a, 5c} Bistramide A has been shown to exhibit cytotoxic properties towards various tumor cell lines including the human non-small cell lung carcinoma (NSCLC-N6).⁶ Recently, Kozmin *et al.* showed that actin is the primary cellular receptor of bistramide A.⁷ This activity provides a molecular explanation for the potent antiproliferative effects of bistramide A.

Among the members, bistramide D is least toxic, probably due to the absence of a Michael acceptor. To the best of our knowledge, no total synthesis of this compound has been reported, although a hemi-synthesis of bistramide D by stereoselective reduction of bistramide A has been reported.⁸

1.1.2 Structure Elucidation of Bistramides

The first structural elucidation of bistramide A was conducted by Gouiffes *et. al* in 1988.¹ Their study involved the application of nuclear magnetic resonance spectroscopy in solution using a combination of several 2D NMR techniques. However, due to the limitation of the techniques the results only allowed the unequivocal proposal of a linear carbon backbone of bistramide A. Four years later, a revised structure of the same molecule was reported by Ireland and co-workers.⁹ By means of a 2D INADEQUATE experiment, the unambiguous structural determination of bistramide A was proposed.

In 2000, Biard's group carried out a hemisynthesis of bistramide D by stereoselective reduction of bistramide A. This work allowed the partial assignment of the absolute and relative configurations of the molecules by combining NMR analysis and a synthetic correlation of natural bistramide A and bistramide D.¹⁰ They later reported a crystalline derivative of bistramide D synthesized from natural bistramide A and its absolute configuration was determined by crystallographic analysis.¹¹ Around the same time, the X-ray crystallographic structure of the bistramide A-actin complex was also reported.¹²

The structural assignment of bistramide C, reported by Wipf *et al.*, was based on an elegant spectroscopic and computational method.¹³ They performed the total synthesis of the natural product, providing the key segments for a chiroptical analysis, which was crucial for the assignment of the relative and absolute configuration.

On the other hand, Kozmin and co-workers studied the unambiguous structural assignment of bistramide A through a convergent and fully diastereocontrolled total synthesis and comparison with the natural product.¹⁴

1.1.3 Molecular Structures of the Bistramide family

Bistramides A, B, C and D share a common structure, consisting of a spiroketal unit (C19-

C40), a central amino acid fragment (C14-C18), and a tetrahydropyran ring (C1-C13). Bistramides A and C are differentiated by the oxidation level at the C-39 position, where a hydroxyl group or a ketone group is attached respectively. Bistramide B differs by having a saturated C2-C3 bond, whilst the others all contain a double bond at this position. The structure of bistramide D is unique by having two hydroxyl groups at both the C4 and C39 positions. Bistramide K and oxobistramide K differ from all the other members of the bistramide family in that the tetrahydropyran subunit (C6-C11) is replaced by an unsaturated, linear moiety (Fig. 1.1).

Figure 1.1

1.2 Recent synthetic studies of Bistramides

A detailed review of the previous synthetic studies of the bistramide members has been discussed by the predecessor student of this project, Kalpana Palani.¹⁵ Therefore this section will only deal with the more recent publications on this topic.

1.2.1 Yadav's synthesis of the THP fragment of Bistramide A:

In 2013, Yadav *et al.* reported a stereoselective synthesis of *trans* 2,6-disubstituted tetrahydro-pyran rings via iodine catalyzed allylation of tetrahydro-2*H*-pyranol in favor of the *trans* isomer.¹⁶

Scheme 1.2

The proposed mechanism involves activation of the oxocarbenium ion by the TMS group followed by an axial attack of the allyl group under stereoelectronic control. The *in-situ* generated Me_3SiI is probably the active catalyst. Good yield and diastereoselectivities were obtained with a wide range of substrates. Based on this success, they applied the methodology to the synthesis of the C1-C13 THP unit of bistramide A.

C1-C13 fragment of Bistramide A

Scheme 1.3

Reagents and conditions: (i) TiCl_4 , $i\text{-Pr}_2\text{NEt}$, CH_2Cl_2 , -20°C , 90%; (ii) NaBH_4 , MeOH , r.t., 88%; (iii) BAIB, TEMPO; (iv) $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$, benzene, 85% over 2 steps; (v) Mg , MeOH , r.t., 86%; (vi) DIBAL-H, CH_2Cl_2 , -78°C , 82%; (vii) allyl TMS, I_2 , CH_2Cl_2 , 0°C , 85%, *de* (9:1); (viii) O_3 , CH_2Cl_2 ; (ix) allyl bromide, Zn , THF, r.t., 86% over 2 steps; (x) COCl_2 , DMSO, CH_2Cl_2 , triethyl amine, 75%; (xi) TiCl_4 , CH_2Cl_2 , 0°C , 82%.

The synthesis started from the $\text{TiCl}_4/\text{DIPEA}$ mediated aldol reaction which led to a non Evans *syn* aldol adduct (1.3.3). The subsequent reductive cleavage of the auxiliary, followed by a selective oxidation using TEMPO and a one-pot Wittig reaction afforded the α,β -unsaturated

ester (1.3.5). The double bond was then reduced by Mg/MeOH and the saturated ester (1.3.6) was subjected to tandem DIBAL-H reduction/cyclisation, leading to the key intermediate lactol (1.3.7) in 82% yield. The I₂ catalyzed allylation of lactol (1.3.7) furnished the desired C-allylated cyclized product (1.3.8) in 85% with *de* of 9:1. The subsequent ozonolysis followed by a Barbier reaction gave rise to alcohol (1.3.9) in 86% yield over 2 steps. The allylic alcohol was then oxidized under Swern's conditions then excess triethyl amine was used to effect the isomerization which led to the enone (1.3.10). The final benzyl deprotection was carried out using TiCl₄ in DCM, furnishing the C1-C13 fragment of bistramide A (1.3.11) in 82% yield.

A related addition has been used by Kozmin in the synthesis of the THP fragment of bistramide A.¹⁴ Their approach involved a ZnCl₂ mediated C-glycosidation with a silyl dienol ether, giving the desired enone with high diastereoselectivity and efficiency.

Scheme 1.4

In comparison, Yadav's method is less efficient while giving similar diastereoselectivity, as multiple steps are required to build up the side chain. Nevertheless, the iodine catalyzed C-allylation of tetrahydro-2H-pyranol represents an alternative method towards *trans*-disubstituted THP ring. Their approach provided the C1-C13 fragment of Bistramide A in a total of 11 steps with 21.4% overall yield.

1.2.2 Goekjian's total synthesis of Bistramide A and its 36(Z) isomers:

Following the first total synthesis of Bistramide A by Kozmin and co-workers in 2004,¹⁴ Crimmins',¹⁷ Panek's¹⁸ and Yadav's groups¹⁹ have also performed total syntheses of this natural product. Recently, Goekjian *et al.* reported another total synthesis study of bistramide A and its 36(Z), 39(S) and 36(Z), 39(R) isomers.²⁰ They also showed that these compounds have different effects on cell division and apoptosis.

Synthesis of the spiroketal fragment:

The synthesis of the spiroketal C19-C40 fragment features a novel formation of exocyclic enol ethers from lactones, based upon Julia chemistry.

Scheme 1.5

Reagents and conditions: (i) NaIO₄, H₂O/NaHCO₃, (EtO)₂POCH₂CO₂Et, K₂CO₃, 92%; (ii) LiHMDS, BF₃.Et₂O, THF, -78°C; (iii) DBU, THF, r.t.; (iv) *p*-TsOH, CH₂Cl₂, 69%; (v) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78°C to r.t.; (vi) LiHMDS, THF, (1.5.7), -78°C then 60°C, 72% over 2 steps; (vii) TBAF, THF, r.t.; (viii) (COCl)₂, DMSO, Et₃N, THF, -78°C to r.t.; (ix) (EtO)₂POCH₂CO₂Et, NaH, THF, 0°C to r.t., 73% over 3 steps; (x) H₂, Pd/C, EtOH, 76%; (xi) TBDPSCl, imidazole, DMAP, DMF, 0°C to r.t.; (xii) LiAlH₄, THF, 0°C to r.t., 97% over 2 steps.

The synthesis of the spiroketal fragment commenced from the preparation of lactone (1.5.3) and benzothiazolyl sulfone (1.5.4), which can be formed from a common precursor (1.5.2), that in turn can be derived from dicyclohexylidene D-mannitol (1.5.1). The coupling of the two fragments proceeded via Julia olefination, followed by *ipso* substitution and spontaneous reductive elimination by DBU provided the key enol ether (1.5.5), which led to the spiroketal (1.5.6) upon treatment with *p*-TSA. Further elaboration via Swern oxidation followed by a Horner-Emmons reaction and a deprotection/protection sequence afforded intermediate (1.5.10).

Scheme 1.6

Reagents and conditions: (i) I₂, imidazole, PPh₃, THF, 0°C to r.t.; (ii) Potassium phthalimide, DMF, 40°C; (iii) Et₃N.3HF, THF, 60°C, 63% over 3 steps; (iv) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78°C to r.t.; (v) (EtO)₂POCH(Me)COMe₂, Ba(OH)₂, BaO, THF, r.t.; (vi) (*R*)-Methyl-CBS, catecholborane, toluene, -78°C, 50% over 3 steps; (vii) (CF₃CH₂O)₂POCH(Me)COMe, Ba(OH)₂, BaO, THF, r.t., 60% over 2 steps; (viii) (*R*) or (*S*)-Methyl-CBS, catecholborane, toluene, -78°C.

Further elongation from intermediate (1.5.10) was carried out by generally following the route reported by Crimmins and DeBaillie.¹⁷ The *E* enone (1.6.4) was prepared via a BaO/Ba(OH)₂ mediated Horner-Emmons reaction, whereas the *Z* isomer (1.6.3) was obtained selectively via a Still-Gennari reaction using (CF₃CH₂O)₂POCH(Me)COMe. The final CBS reduction on (1.6.4) and (1.6.3) led to the natural bistramide A spiroketal fragment (1.6.5) and

the C36(Z) analogues with both configurations at C39 (1.6.6a/b) respectively.

Synthesis of the tetrahydropyran fragment:

The tetrahydropyran fragment was accessed by a kinetically controlled oxa-Michael cyclisation reaction.

Scheme 1.7

Reagents and conditions: (i) (COCl)₂, DMF cat.; (ii) (1.7.2), *n*-BuLi, -78°C to 20°C; (iii) LDA, MeI, 0°C to 20°C, 77%; (iv) LiAlH₄, Et₂O, r.t.; (v) PMB-trichloroacetimidate, CSA cat., 0°C to 20°C; (vi) NMO, OsO₄ cat.; (vii) NaIO₄, 80%; (viii) (1.7.5), NaOH, 91%, d.r. 4:1; (ix) TBSCl, imidazole, CH₂Cl₂, r.t.; (x) DDQ, CH₂Cl₂/H₂O; (xi) Dess-Martin periodinane, CH₂Cl₂; (xii) (1.8.1), CH₂Cl₂, 0°C to 20°C, 70%; (xiii) CSA cat. CH₂Cl₂/MeOH, quant.; (xiv) *t*BuOK, THF, -78°C, 96%; (xv) NMO, OsO₄ cat.; (xvi) NaIO₄; (xvii) allyl bromide, Zn, THF/NH₄Cl aq., 92%; (xviii) NaOH (5%), MeOH; (xix) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78°C; (xx) MgBr₂.Et₂O, Et₂O, r.t.; (xxi) *N*-hydroxysuccinimide, EDCI, CH₂Cl₂, r.t., 40% over 4 steps.

The synthesis started from 5-hexenoic acid (1.7.1), an asymmetric alkylation and methylation afforded intermediate (1.7.3). The subsequent reductive removal of the auxiliary, protection of alcohol and oxidative cleavage led to aldehyde (1.7.4), which was subjected to an allylation reaction mediated by the Roush chiral diisopropyl tartrate allylboronate ²¹ to provide alcohol (1.7.6) in 91% yield with d.r. of 4:1.

The key step of this part of the synthesis is the intramolecular oxa-Michael cyclization reaction of (1.8.2). By using 1.1 equivalent of *t*BuOK in THF at -78°C, the desired kinetic Michael adduct (1.8.4) was obtained as the major product in 3:1 ratio. In comparison, much better selectivities were obtained for the intramolecular oxa-Michael addition, which is the key step during the synthesis of the THP fragment of bistramide D conducted by our group.²²

Scheme 1.8

For our system, with the des-methyl substrate (1.8.1) and the methyl substrate (1.8.2), treatment with KO^t-Bu under Banwell's conditions²³ gave a 85:15 and 90:10 mixture of *trans*:*cis* diastereoisomers of THP ring respectively. However, the reason for the difference is unclear.

Goekjian's synthesis involved further elaboration of the THP ring (1.8.4) to the THP fragment precursor (1.8.6), which was subsequently functionalized to the ethyl ester of the natural THP fragment (1.8.8) in 3 more steps.

Synthesis of the amino acid unit and the final assembly:

The amino acid linker was prepared in five steps from the protected aminoacetaldehyde (1.9.1) via an asymmetric crotyltitanation in a modified procedure reported by Kozmin *et al.*

Scheme 1.9

Reagents and conditions: (i) (1.9.2), -78°C, 57%; (ii) DMP, *p*-TSA, acetone; (iii) NaIO₄, RuCl₃, CCl₄, CH₃CN, H₂O; (iv) HCl (3M), EtOAc, r.t.; (v) Fmoc-OSu, Na₂CO₃, dioxane/H₂O, quant.

Comparing to Kozmin's approach,¹⁴ Goekjian's method avoided the use of the boron reagent which is sensitive and hard to handle. The rest of the steps are very similar. Furthermore, the titanium reagent (TADDOL) (1.9.2) has previously been used by Cossy *et al.* in the synthesis of bistramide K.²⁴

Scheme 1.10

Reagents and conditions: (i) MeNH_2 (40% in H_2O); (ii) PyBOP, DIPEA, (1.9.5), DMF, r.t., 78%; (iii) Et_2NH , DMF, r.t.; (iv) (1.8.8), DMF, r.t., 97%.

In the final assembly, the spiroketal fragment (1.6.5) first underwent cleavage of the phthalimide group, and then was subjected to PyBOP mediated condensation with the amino acid unit (1.9.5). Removal of the Fmoc group followed by condensation with the activated ester of the THP fragment furnished the natural bistramide A. The 36(*Z*), 39(*R*) isomer (1.10.4a) and the 36(*Z*), 39(*S*) isomer (1.10.4b) analogues were prepared by the same

sequence.

In conclusion, Goekjian's route is less convergent (29 steps, 2% overall yield). However, it is convenient and most of the steps are robust. Moreover, the use of the novel spiroketalization via enol ethers allows the access to other analogues of the natural product.

1.2.3 Bauder's synthesis of the C1-C13 fragment of Bistramide K:

Compared to other bistramide members, Bistramide K contains a linear C1-C13 fragment which has three stereogenic centres and two supplementary (*E*)-olefins. In 2010, Bauder reported the first asymmetric synthesis of the C1-C13 fragment of Bistramide K, featuring a Julia-Kocienski reaction between an aldehyde and a benzothiazolesulfone.²⁵

Scheme 1.11

Reagents and conditions: (i) Bu₂BOTf, Et₃N, CH₂Cl₂, crotonaldehyde, -78°C to 0°C, 70%, 75:25 for (1.11.2a)/(1.11.2b); (ii) TBSCl, DMF, imidazole, 98%; (iii) LiBH₄, MeOH/THF, 82%; (iv) Py•SO₃, Et₃N, DMSO, CH₂Cl₂, 91%.

The synthesis began with the preparation of aldehyde (1.11.4). Use of a chiral auxiliary and

the Evans aldol strategy allowed the introduction of the chiral centre at the C4 position, affording the aldol adduct as a mixture of two epimers (*anti:syn* of 75:25). Acetyl derivatives usually give poor selectivity in this reaction. The subsequent protection, reductive cleavage and oxidation under the Parikh-Doering protocol led to the volatile aldehyde (1.11.4) in good yield.

Scheme 1.12

Reagents and conditions: (i) Bu₂BOTf, Et₃N, CH₂Cl₂, -78°C to 0°C, BnOCH₂CH₂CHO, 79%; (ii) TBSCl, DMF, imidazole, 92%; (iii) LiBH₄, MeOH, THF, 82%; (iv) Ph₃P, I₂, imidazole, Et₂O/MeCN, 87%; (v) for (1.12.5a): (MeO)₂P(O)Me, *n*-BuLi, HMPA/THF, -78°C, 63%; for (1.12.5b): PhSO₂Me, *n*-BuLi, THF, 0°C, 67%; for (1.12.5c): BT-SMe, LDA, HMPA/THF, 70.5% then EtOH, (NH₄)₆Mo₇O₂₄•4H₂O, H₂O₂, 0°C, 73%.

To optimize the key Julia-Kocienski olefination, three different coupling partners, including phosphonate (1.12.5a), sulfonate (1.12.5b) and benzothiazolesulfone (1.12.5c), were prepared according to scheme 1.12. A modified Julia-Lythgoe-Kocienski olefination between aldehyde (1.11.4) and benzothiazolesulfone (1.12.5c) turned out to be most successful, providing the key intermediate olefin in 81% yield as a 1:1 mixture of (*E*) and (*Z*) isomers. Finally, the (*E*)-isomer was debenzylated under Birch conditions, furnishing the desired C1-C13 fragment of

bistramide K in 68% yield.

Scheme 1.13

Reagents and conditions: (i) LiHMDS (2.3 eq.), -78°C, 81%, (*E*:*Z* 1:1); (ii) Na, NH₃, -78°C to r.t., 68.7%.

This work represents the first stereoselective synthesis of the C1-C13 fragment of Bistramide K, with the highlight being a satisfactory Julia-Kocienski olefination. However, the stereoselectivities obtained on several steps were rather poor. Nevertheless, the obtained free alcohol (1.13.2) can be further manipulated for peptide coupling for further elongation.

1.2.4 Cossy's Synthesis Towards 39-oxobistramide K:

Cossy's group has studied a diastereoselective synthesis of *cis*-2,6-tetrahydropyran rings via FeCl₃ catalyzed cyclization of ζ-hydroxy allylic alcohol derivatives. The high diastereoselectivities are attributed to the thermodynamic equilibration of the produced 2-alkenyl 6-substituted tetrahydropyrans, allowing the most stable *cis*-isomer to be obtained. Furthermore, the mild reaction conditions provide high tolerance of functional groups.

Scheme 1.14

They extended the study to the synthesis of spiroketals from unsaturated lactols via FeCl_3 catalysis and later applied this method to the synthesis of 39-oxobistramide K.²⁴

Synthesis of the amino acid fragment:

Scheme 1.15

Reagents and conditions: (i) Boc_2O , DMAP, CH_3CN , r.t. -78°C to 60°C , 70%; (ii) O_3 , CH_2Cl_2 , -78°C , then Me_2S , -78°C to r.t., 80%; (iii) (1.15.3), Et_2O , -78°C , 18 h, dr > 95:5, ee > 95%; (iv) TESCl , DMAP, imidazole, CH_2Cl_2 , 0°C to r.t., 97% over 2 steps; (v) NaIO_4 , RuCl_3 , CCl_4 , CH_3CN , H_2O , r.t.; (vi) HCl (3M), EtOAc , r.t.; (vii) FmocOSu , Na_2CO_3 , 1,4-dioxane, H_2O , r.t., 71% over 3 steps.

The preparation of the amino acid fragment was achieved in seven steps from allylamine (1.15.1). Double protection followed by ozonolysis afforded aldehyde (1.15.2) which was

treated with the highly face-selective reagent, crotyltitanium complex (1.15.3), to give the homoallylic alcohol (1.15.4) with excellent diastereoselectivity and enantioselectivity. Compound (1.15.4) was then further elaborated via 4 steps to furnish the amino acid fragment in 71% overall yield.

Synthesis of the spiroketal fragment:

Scheme 1.16

Reagents and conditions: (i) TBDPSCl, $i\text{Pr}_2\text{NEt}$, CH_2Cl_2 , r.t., 93%; (ii) $(\text{COCl})_2$, DMSO, CH_2Cl_2 , -78°C , Et_3N ; (iii) (1.15.3), Et_2O , -78°C , 97% over 2 steps; (iv) Hoveyda Grubbs II catalyst (HG-II) (5-8 mol%), methyl acrylate, MW, CH_2Cl_2 , 80°C , 2 h, 83%; (v) H_2 , Pd/C (10 mol%), EtOAc, 2 h; (vi) CSA, CH_2Cl_2 , r.t., quant.; (vii) (1.16.5), Et_2O , -20°C , 16 h, 93%; (viii) (1.16.6), HG-II, CH_2Cl_2 , MW, 80°C , 2 h; (ix) cat. CSA, THF/ H_2O , r.t., 2 h, 84% over 2 steps; (x) $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (5 mol%), CH_2Cl_2 , r.t., 59%.

The synthesis of the spiroketal fragment started from the commercially available 1,4-butanediol (1.16.1) which led to the protected hydroxyaldehyde (1.16.2) in 2 steps. The subsequent treatment with crotyltitanium complex (1.15.3) established the chiral centers at the C22 and C23 positions, giving homoallylic alcohol (1.16.3) in excellent yield and stereoselectivity. Further transformation via cross metathesis, hydrogenation and acid catalyzed cyclisation furnished lactone (1.16.4). Subsequent alkylation using a Grignard reagent, a second cross metathesis and hydration gave the key intermediate lactol (1.16.7) which was treated with $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ to give the spiroketal (1.16.8) in 59% yield.

Scheme 1.17

Reagents and conditions: (i) TPAP, NMO, MS 4 Å, CH_2Cl_2 , r.t., 1 h; (ii) $\text{Ba(OH)}_2 \cdot 8\text{H}_2\text{O}$, THF, r.t., (1.17.2); (iii) DCC, CH_2Cl_2 , 0°C to r.t., 1 h; (iv) MeNHNH_2 , THF, -10°C, 10 min; (v) PyBOP, $i\text{Pr}_2\text{NEt}$, DMF, (1.15.5), r.t., 48 h, 27% over 5 steps.

Spiroketal (1.16.8) was further transformed to alcohol (1.17.1) via 5 steps, including ozonolysis, a Wittig reaction and desilylation, followed by a Mitsunobu reaction and a hydrogenation. The following oxidation and Ba(OH)₂ mediated olefination afforded the unsaturated ketone (1.17.3). Under these conditions, an unexpected opening of the phthaloyl group was observed. However, this was recoverable by using DCC for ring re-closure and after treatment with methylhydrazine, the free amine was directly coupled with the amino acid fragment (1.15.5) to furnish (1.17.4).

Cossy's synthetic route accomplished the C14-C40 fragment of 39-oxobistramide K in 19 steps with a total yield of 6.2%, featuring the FeCl₃ catalyzed spiroketalization from an ω-unsaturated lactol. Compound (1.17.4) can be further manipulated into the natural 39-oxobistramide K and bistramide C.

1.3 Conclusion:

The bistramide family has attracted considerable attention owing to their intriguing molecular architecture and significant biological activities. Over the last decade, the bistramide members and their analogues have been intensively studied. Bistramide D was reported to be least toxic in vivo compared to their congeners but far less abundant in nature. We are interested in this natural product and decided to carry out a study on the total synthesis of this molecule.

Chapter Two:

Synthesis of the THP fragment of Bistramide D

2

2.1 Retrosynthetic Approach to THP Unit:

Scheme 2.1

Our retrosynthetic plan called for disconnection of the THP ring via the C-O bond in the heterocyclic ring, for which we planned to utilize an intramolecular oxa-Michael addition under kinetic control. The α , β -unsaturated ester can be constructed by regioselective cross metathesis of methyl acrylate with the terminal alkene which comes from a protected epoxy alcohol (fragment A) and optically pure olefin (fragment B).

2.2 Background: Introduction to the Previous Studies

2.2.1 Palani's Model Study of the THP Ring of Bistramide D

In 2008 our group reported a model study towards the synthesis of the tetrahydropyran moiety of bistramide D, utilizing a stereoselective kinetic intramolecular Michael addition.^{22a} This strategy is a facile pathway to construct a heterocyclic ring and has been demonstrated in the synthesis of diospongin A.²⁶ In these cases, the *cis*- isomer, which is the more stable one, has been formed as the major product. On the other hand, Banwell has shown that under carefully controlled conditions, the *trans*-isomer can also be isolated.²³ This strategy was used as the key step in Palani's model study.

The only difference between the model molecule and the natural target is that the methyl group at the C9 position is absent. The synthesis started from the ring opening of the commercially available (*S*)-(+)-epichlorohydrin (3.2.1) using lithiobutynes and BF₃·OEt₂. The alcohol was then converted to a *t*-butyl carbonate and the alkyne (2.2.2) was reduced to alkene (2.2.3) using P2-nickel.²⁷ The following construction of the *syn*-1,3-diol (2.2.4) was achieved in an expeditious fashion using the cycloiodination chemistry of Barlett and Cardillo.²⁸ The pure *cis* cyclic carbonate (2.2.4) was subjected to *meta*-chloroperbenzoic acid (*m*CPBA) to effect iodoso elimination²⁹ and carbonate opening, the protected epoxy alcohol (2.2.5) was obtained as a single diastereoisomer.

Scheme 2.2

The Michael acceptor was introduced by ring opening of the epoxide (2.2.5) with a Grignard reagent, followed by selective cross-metathesis. It was shown that cross-metathesis with methyl acrylate occurred exclusively at the terminal alkene, however, some cross-metathesis had also occurred between the internal alkene and the ethylene by-product from the first metathesis, leading to the formation of an inseparable mixture of compounds (2.3.3) and (2.3.4). This problem was simply solved by passing a stream of nitrogen gas through the reaction mixture to expel the ethylene by-product.

Scheme 2.3

The final intramolecular Michael addition was carried out using sodium hydride in THF at -78°C .²³ The *trans*-isomer (2.4.1) was obtained as the major product, in a ratio of 7:3 with the *cis*-isomer (2.4.2). On the other hand, the ratio could be further improved to 85:15 when KO*t*-Bu was used as the base.

Scheme 2.4

Our model study has demonstrated that the combination of selective cross-metathesis and intramolecular Michael addition is a facile pathway to construct a THP ring. Upon this success we turned our attention to the synthesis of the natural THP ring of bistramide D.

2.2.2 Previous Synthesis of the natural THP ring, part I: synthesis of fragment B

The first and major challenge in the synthesis of the real molecule was to establish a pathway to effectively construct the methyl group at the C9 position in a stereoselective fashion. There are a number of possible methodologies such as asymmetric catalysis, use of chiral auxiliaries and bio-catalysis for asymmetric synthesis. However it turned out that the formation of this stereocentre was not trivial at all. To achieve the best result, extensive optimization has been carried out throughout the project. To lay a full picture, a summary of the studies which were done by previous PhD student Kalpana Palani is given below.

She initially chose to use the chiral auxiliary strategy as many reports have proven that this is an attractive, well established and reliable methodology for enantioselective transformations.

Chiral oxazolidinone chemistry:

Evans chiral oxazolidinone was first studied owing to its high level of selectivity and ease of synthesis. The chiral oxazolidinone was prepared from the commercially available D-

phenylalanine. The amino acid (2.5.1) was first reduced using borane which was generated *in situ* from sodium borohydride and boron trifluoride diethyletherate complex. The alcohol (2.5.2) was then subjected to cyclisation with diethyl carbonate using a standard protocol³⁰ and treated with crotonyl chloride to afford the desired crotonyl oxazolidinone (2.5.4).

Scheme 2.5

Reagents and conditions: (i) NaBH₄, BF₃.Et₂O, THF, 0°C to RT, 95%; (ii) diethyl carbonate, K₂CO₃, 135°C, 93%; (iii) *n*-BuLi, crotonyl chloride, THF, -78°C, 98%

The first attempt to methylate the oxazolidinone (2.5.4) was carried out using LDA and MeI in THF at -78°C. Surprisingly, the reaction afforded the Michael adduct (2.6.2) instead as a single diastereomer. She then tried KHMDS and LiHMDS as bases, however, both gave unsatisfactory results. Trials with KHMDS afforded the methylated product (2.6.1) and its separable diastereomer (2.6.4) in good yield but with poor selectivity of only 2:1 ratio. When LiHMDS was used, dimerisation (2.6.3) of the starting oxazolidinone was observed occasionally during repeated trials. The best result was obtained using NaHMDS to give a 9:1 diastereoselectivity ratio with moderate yield. However, it was later found that when using this method, the yield would drop significantly on scale up.

Scheme 2.6

It was proposed that the difference in stereoselectivity is probably due to the different cation size. The small Li atom induces strong chelation, activating the crotonyl moiety for Michael addition, whereas the potassium atom is larger, hence has a weaker chelation effect and lower selectivity. Sodium possesses the most appropriate size, resulting in tight chelation and high stereoselectivity.

Prolinol chemistry:

Palani then moved on to use the Evans proline derived chiral auxiliary which has been employed in many enantiotopic alkylation reactions. It is suggested that the alkylation is directed by the hydroxyl moiety of the prolinol.³¹

Scheme 2.7

The prolinol (2.8.2) was synthesized from L-proline (2.8.1) using borane reduction. Crotylation of the prolinol with triethyl amine provided the isomerised terminal alkene (2.8.3) as the major product. That is probably due to the formation of a vinyl ketene which comes from the elimination of HCl from crotonyl chloride, followed by α -protonation of the enolate that subsequently formed. This problem was overcome by using a weaker base, such as sodium carbonate. The following stereoselective methylation was carried out with LDA and MeI in THF and mixture of THF and DMPU. Unfortunately, no reaction occurred in THF and in THF/DMPU the reaction afforded the *O*-methylated (2.8.6) compound instead.

Scheme 2.8

Reagents and conditions: (i) NaBH_4 , $\text{BF}_3 \cdot \text{Et}_2\text{O}$, THF, 0°C to RT, 52%; (ii) (a) Et_3N , crotonyl chloride, only (b) aq. Na_2CO_3 , crotonyl chloride, 98%; (iii) (a) LDA, MeI, THF, -78°C , 0% (b) LDA, MeI, THF/DMPU, -78°C , only (3.8.6).

Sulfoxide chemistry:

After considering the unsuccessful trials, Palani decided to modify the strategy by introducing the alkene functionality later as it was proposed that the difficulty in methylation could possibly arise from the presence of the double bond. To this end, they employed sulfoxide elimination strategy³². It was expected that the alkene could be obtained by a base induced β -elimination or a simple pyrolysis. The methylation precursor (2.9.4) was prepared by a ring opening reaction between thiocresol (2.9.1) and γ -butyrolactone (2.9.2), followed by treatment with oxazolidinone. Gratifyingly, methylation on this substrate (2.9.4) provided the desired methylated compound (2.9.5) as a single diastereomer in excellent yield. The chiral amide was then directly reduced to the alcohol (2.9.6) using lithium aluminium hydride and the sulfide was oxidized to sulfoxide (2.9.7) with mCPBA. However, the subsequent sulfoxide elimination turned out to be very problematic. Neat pyrolysis, reflux in DCM and thermal elimination with mild bases all resulted in no reaction. The use of higher temperature led to decomposition of starting material. Alternatively, the sulphone elimination strategy³³ and Matsuo's mesitylene sulfonylhydroxylamine (MSH) induced elimination³⁴ were also tried, however, none of the conditions gave the desired product.

Scheme 2.9

Reagents and condition: (i) NaOEt, 98%; (ii) (a) oxalyl chloride, CH₂Cl₂, DMF; (b) oxazolidinone, *n*-BuLi, THF, -78°C, 84%; (iii) LDA, MeI, THF, -78°C, 91%; (iv) LiAlH₄, THF, 5°C; (v) mCPBA, -78°C to 0°C, CH₂Cl₂, 99%; (vi) mCPBA, 0°C, CH₂Cl₂, 99%; (vii) (a) CH₂Cl₂, reflux, 48h, 0%; (b) CH₂Cl₂, NaHCO₃, reflux, 16h, 0%; (c) Toluene, K₂CO₃, 110°C, 36h, 0%; (d) Toluene, CaCO₃, reflux, 30h, 0%; (e) Neat, NaHCO₃, 160°C, 3h, 0%; (viii) (a) KO^tBu, DMSO, 0%; (b) KO^tBu, THF, 0%; (ix) K₂CO₃, CH₂Cl₂, 0%.

Selenoxide chemistry:

Since attempts to synthesis fragment B from sulfide, sulfoxide and sulfone analogs were unsuccessful, Palani carried out her final trial using selenoxide chemistry. Selenoxides are less commonly used due to their high toxicity, however, the β-elimination of selenoxides are known to be more facile than that of their sulfoxide analogs. The selenoxide analog was

synthesized from diphenyldiselenide (2.10.1) using a similar procedure to the sulfoxide derivative (2.9.5). The enantioselective methylation of the amide (2.10.3) afforded the desired product (2.10.4) as a single diastereomer in excellent yield. The selenoxide (2.10.6) was obtained by ozonolysis, while this compound was stable at room temperature, heating in dichloroethane led to the formation of the alkene alcohol (2.9.10).

Scheme 2.10

Reagents and condition: (i) NaBH_4 , DMF, 99%; (ii) oxalyl chloride, CH_2Cl_2 ; oxazolidinone (3.5.3), $n\text{BuLi}$, THF, -79°C , 98%; (iii) LDA, MeI, THF, -78°C to -40°C , 82%; (iv) lithium aluminium hydride, THF, 0°C to r.t., 99%; (v) O_3 , dichloroethane, -20°C , 99%; (vi) reflux, dichloroethane.

2.2.3 Previous Synthesis of the natural THP ring, part II:

With the alcohol in hand, Palani converted it to the corresponding Grignard reagent (2.11.1) using LiBr in THF. However, unlike in the model study, the Grignard reagent formed for fragment B refused to ring open the epoxide. Under standard conditions, only the bromo compound (2.11.3) and a small amount of starting material were isolated.

Scheme 2.11

She then modified this approach by using the sulfone analog of fragment B instead of the bromide. The sulfone was prepared from the alkene alcohol (2.9.10) via mesylate formation (2.12.1) and sulfide (2.12.2) oxidation.

Scheme 2.12

Reagents and condition: (i) MsCl , Et_3N , 0°C , CH_2Cl_2 ; (ii) thiocresol, NaH , THF/DMF , 70°C ; (iii) $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}$, H_2O_2 , EtOH , 88% (over 2 steps).

The epoxide ring opening reaction between fragment A and the lithio derivative of the sulfone (2.12.3) did proceed, however, a mixture of the desired product and its BOM migrated isomer was obtained. It was later realized that this side reaction can be minimized by reducing the amount of the Lewis acid and quenching the reaction at low temperature. To further modify the reaction and complete the study, it was also proposed at that time that other protecting groups should be tested for this reaction.

Scheme 2.13

Scheme 2.14

Reagents and condition: (i) *n*-BuLi, BF₃.OEt₂, THF, -78°C, 85%; (ii) Mg, MeOH, TMEDA, 95%; (iii) Hoveyda-Grubbs catalyst, methyl acrylate, N₂ flow, Toluene, 76%; (iv) KO^{*t*}-Bu, THF, -78°C, 92%, 90:10.

Following epoxide ring opening, desulfonylation was carried out using the same procedure described in the model study. In the subsequent cross metathesis of the terminal alkene (2.14.2) with methyl acrylate, prolonged reaction times resulted in epimerization at the C-4 position, leading to the formation of an inseparable mixture of the desired product and an isomer. It was proposed that this epimerization arose from the Ru-H catalysed alkene isomerisation. At this stage, Kalpana minimized the side reaction by stopping the reaction at 3h, however, incomplete reaction resulted.

Scheme 2.15

With the unsaturated ester in hand, Kalpana went on to test the crucial intermolecular Michael addition. By using KO^tBu in THF at low temperature, the reaction proceeded smoothly to afford the desired *trans* THP (2.14.4) in 90:10 ratio in total yield of 92%. Compared to the model system, the *trans:cis* ratio has improved by having the additional methyl group.

2.2.4 Conclusions and problems of the previous studies:

Kalpana's studies demonstrated that the combination of the regioselective cross metathesis and the intramolecular oxa-Michael addition under kinetic control can be a viable approach to complex tetrahydropyrans. However, there are still several issues that need to be addressed to complete the synthesis.

Problem I: Synthesis of fragment B

The synthesis of fragment B is still unsatisfactory. Previously Kalpana obtained the best result for the methylation reaction using a selenoxide chemistry strategy, however, the toxicity of selenoxide compounds as well as the issue of atom efficiency make them unsuitable especially on preparative scales. Secondly, the chiral oxazolidinone method led to a significant drop in yield as we scaled up the reaction. Despite testing several reaction conditions, the best yield obtained on gram scale was only around 35%. In order to improve the efficiency, studies on alternative methods are needed for the synthesis of fragment B.

Problem II: BOM group migration during epoxide opening:

As mentioned previously, the epoxide ring opening reaction between fragment A and fragment B caused BOM group migration, leading to the formation of the desired product and its isomer. To further modify the reaction and complete the study, other protecting groups could be tested for this reaction.

Problem III: Epimerization during cross metathesis

The epimerization caused by Ru-H catalyzed alkene isomerisation can be problematic as it leads to the formation of an inseparable mixture of products. Other modifications, such as use of additives, alternative catalysts should be tested for the cross metathesis. It is also worthy testing whether a different protecting group has any effect on this side reaction.

Scheme 2.16

2.3 New Studies on the Synthesis of the Natural THP Ring of Bistramide D

2.3.1 Synthesis of fragment B: on preparative scale and other methodologies

Strategy A:

Based on careful consideration, we decided to continue our study of the synthesis of fragment B by moving onto asymmetric metal catalysis. This category of methods shows advantages in many aspects, such as mild reaction conditions, high atom economy, high yields and good selectivity, as well as easy purifications. The first strategy studied was based on Tsuji's reaction involving palladium-catalyzed hydrogenolysis of a disubstituted epoxide³⁵. The palladium-catalyzed displacement reaction of an allylic substrate with various nucleophiles is a well-established reaction and useful tool in organic synthesis³⁶. Tsuji and co-workers reported a method for the preparation of 1-alkenes from terminal allylic carbonates and acetates by palladium-catalyzed hydrogenolysis with formic acid-triethylamine.

Scheme 2.17

As shown in Scheme 2.17, regioselectivity is a major problem for the nucleophilic addition with monosubstituted allylic substrates (such as 2.17.1). Carbo-nucleophiles usually attack the less substituted site of the π -allyl intermediate (2.17.3) formed with the Pd complex.

Similarly, if hydride acts as the nucleophile, attack at the less substituted site leads to the formation of internal alkenes (path B). Terminal alkenes are formed by hydride attack at the more substituted side. Tsuji reported that only the hydride generated from formates tend to give terminal alkenes as the major product³⁷. They found that the regioselectivity also depends on the structure of the allylic compound and the type of phosphine ligands. The combination of a disubstituted allylic substrate and the use of tri(*n*-butyl)phosphine as a ligand would significantly favor the formation of 1-alkenes. Based on this idea, we proposed the following reaction scheme:

The substituted epoxide (2.18.1) was prepared from isoprene (2.19.1) via a bromohydrin intermediate (2.19.3).³⁸ The first step proceeded with good yield. For the epoxidation, the literature method was modified so that powder sodium hydroxide and ether were used to improve the difficulty on workup due to the high volatility of the product.

Reagents and condition: (i) H₂O, 87%; (ii) NaOH powder, Et₂O, 80%

Several catalyst systems were tested for this reaction and the best result was obtained using Pd(PPh₃)₂Cl₂ and Et₃N/HCO₂H as the hydride donor. The selectivity for terminal over internal alkene was found to be 45:1 which is comparable to Tsuji's result.³⁵ However, unlike Tsuji's report, we found that PPh₃, not P(*n*-Bu)₃ was the best ligand.

Table 2.1

Catalyst	Loading	Solvent	[H ⁺]	Terminal:Internal (2.18.3):(2.18.4)
Pd(PPh ₃) ₂ Cl ₂	0.4%	THF	HCOOH\Et ₃ N	45:1
Pd(PPh ₃) ₂ Cl ₂	0.4%	CH ₂ Cl ₂	HCOOH\Et ₃ N	2:1
Pd(PPh ₃) ₂ Cl ₂	0.4%	THF	NH ₄ ⁺ HCOO ⁻	10:1
Pd(PBu ₃) ₂ Cl ₂	0.4%	THF	HCOOH\ Et ₃ N	2:1
Pd(P ^t Bu ₃) ₂ Cl ₂	0.4%	THF	HCOOH\ Et ₃ N	Only (2.18.4)
Pd(dppf)Cl ₂	0.4%	THF	HCOOH\ Et ₃ N	1:2
Pd(dba) ₃ CHCl ₃ /P(n-C ₄ H ₉) ₃	0.4%	THF	HCOOH\ Et ₃ N	4:1

After optimizing the regioselectivity, we turned our attention to establishing the asymmetric synthesis by means of palladium catalysis in the presence of one of the Trost ligands.³⁹ Pioneered by Barry Trost for the palladium catalyzed asymmetric allylic alkylation, these are a series of C₂-symmetric chiral ligands derived from *trans*-1,2-diaminocyclohexane. We first carried out the study by employing the Trost ligand (2.20.2) directly in the Tsuji reaction under the optimized conditions. Unfortunately, preliminary reactions gave a complex mixture of products.

Scheme 2.20

We then decided to try an alternative reaction route, going via a cyclic carbonate under the conditions reported by Trost³⁹. In the presence of 1 mol% (dba)₃Pd₂•CHCl₃, 3 mol% of Trost ligand, sodium bicarbonate in DCM-water, isoprene monoepoxide (2.21.1) gave, at room temperature, the cyclic carbonate (2.21.5 or 2.21.6) at 93% ee in 56% yield.

Scheme 2.21

As shown in Scheme 2.21, this reaction system is enantioconvergent via fast π - σ - π inversion with HCO_3^- being the source of CO_2 . According to Trost, the cyclisation must be slower than the interconversion between the isomers to ensure high ee, therefore rate of formation of the π -allyl system from the isoprene monoepoxide and competing racemisation of the product must be accomplished for satisfactory results.

We employed Trost's optimized conditions for the cyclisation and the yield was rather low even after a prolonged reaction time. The cyclic carbonate (2.22.1) was then ring opened using Tsuji's reaction conditions described earlier. An excellent ee was obtained, determined as the Mosher's acid derivative of the alcohol,⁴⁰ however, the yield was again very poor. The low yield is probable due to the fact that both the starting material and product are very volatile therefore difficult to handle. Furthermore, the heterogeneous nature of the reaction means that the conversion rate is sensitive to variables such as mixing rate, solubility and reaction temperatures.

Reagents and conditions: (i) 1 mol% $(\text{dba})_3\text{Pd}_2\cdot\text{CHCl}_3$, 3 mol% Trost ligand, NaHCO_3 , $\text{H}_2\text{O}/\text{CH}_2\text{Cl}_2$, 24h, 25%; (ii) 0.4% $(\text{dba})_3\text{Pd}_2\cdot\text{CHCl}_3$, Formic acid, Et_3N , 98% ee.

Strategy B:

Among the stereoselective metal-catalyzed alkylation reactions, catalytic allylic substitution has recently shown significant developments.⁴¹ However, such asymmetric alkylations are usually done with soft carbon nucleophiles such as malonates or other stabilized carbanions. Copper-based catalysis provides the possibility of using hard organometallic nucleophiles, allowing the construction of simple fragments at the γ -position.⁴² This can afford the branched chiral molecules which contain the terminal alkene functionality.

In 2006, Feringa and co-workers reported an enantioselective copper-catalyzed alkylation of allylic bromides (2.23.1) with a protected hydroxyl or amine moiety using Grignard reagents and Taniaphos (2.23.4) as a ligand.⁴³

Scheme 2.23

With 1 mol% CuBr.SMe₂ and the commercially available Taniaphos (1.1 mol%), excellent regioselectivity (branched *vs* linear product) and enantioselectivity (up to 98% e.e.) were achieved. One advantage of this system is that the compatibility of substrates containing a protected hydroxyl group can provide the chiral primary alcohol in high optical purity.

We were inspired by this strategy and decided to use it in the synthesis of our chiral sulfone fragment. We first chose a sulfone as the functional group as this can lead directly to the sulfone fragment we need. To our disappointment, alkylation of this substrate resulted in no regioselectivity despite an increase of catalyst loading. The two isomers were formed as an inseparable mixture.

When we changed to the methyl ester, the direct S_N2 product was obtained as the major product and the reaction proceeded much more slowly. After 24h only about 50% conversion was seen by NMR. We then tried another substrate which bears a benzyl ester group. An excellent regioselectivity of more than 95% was obtained and the reaction fully converted after stirring overnight. However, in this case the ee was found to be poor. Even at a very low reaction temperature (-78°C) and with slow addition of the substrate, the ee was only around 50%.

Scheme 2.24

Table 2.2

Substrate	Catalyst Loading	Conversion ^[2]	Selectivity	
			(2.22.2):(2.22.3) ^[2]	ee
ArSO ₂ -CH ₂ -CH=CH-CH ₂ -Br	1 mol%	full	40:60	—
ArSO ₂ -CH ₂ -CH=CH-CH ₂ -Br	5 mol%	full	50:50	—
MeO-C(=O)-CH=CH-CH ₂ -Br	5 mol%	50%	5:95	—
BnO-C(=O)-CH=CH-CH ₂ -Br	5 mol%	full	>95%	45% ^[3]

^[1] Conditions: Substrates were added via syringe pump @ -78°C

^[2] Conversion and regioselectivity were determined by ¹H NMR

^[3] ee was determined by chiral HPLC

Strategy C:

While studying the metal catalyzed alkylation, we also investigated another method for the synthesis of our sulfone fragment. Strategy C was inspired by the method described by Hoye.⁴⁴ The Reaction scheme is very similar to the oxazolidinone strategy studied previously by Palani, involving the use of Evans auxiliary. The enantiomeric oxazolidinone (2.25.1) was used as we swapped the order of addition of the substituents. Instead of methylation, we carried out an allylation with allyl bromide and NaHMDS. Further transformations including alkene isomerisation and the cleavage of the additional methyl group via ethenolysis are also involved.

Scheme 2.25

Reagents and conditions: (i) NaHMDS, allyl bromide, 73%; (ii) $\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$, EtOH/ H_2O , quantitative; (iii) LiAlH_4 , Et_2O ; (iv) MsCl , Et_3N , 62% over 2 steps; (v) Ethylene, 5 mol% Grubbs II, toluene, 45°C , 90%.

The allylation step afforded the product in a much better yield than did the methylation. In Hoyer's original report, allyl iodide was used but we found that distilled allyl bromide is also fine. The better result is probably due to the more effective proton abstraction of the starting material. It was found that pre-cooling of the base and slow addition helped to improve the yield as well. Furthermore, the allylation product **(2.25.2)** was obtained as a single diastereomer. The bulkier alkyl halides are better directing than their sterically less demanding counterparts, such as MeI , hence better stereoselectivity can be achieved. We also carried out the reaction at preparative scales (*ca.* 10 mmol) and with the above precautions, the yield of about 70% could still be obtained. The following isomerization proceeded smoothly in the presence of $\text{RhCl}_3/\text{EtOH}$. No over-isomerisation was observed under the reaction conditions. One possible explanation is that the coordination of the Rh to monosubstituted alkene (terminal alkene) is much easier than to disubstituted ones (internal alkene). Therefore once the olefin migrates to internal position, the Rh would easily dissociate from the substrate hence the reaction stops.

Scheme 2.26

The subsequent cross metathesis was carried out with the Grubbs II and Hoveyda-Grubbs catalysts under a continuous flow of ethylene gas. Interestingly, cross-metathesis of the oxazolidinone derivative (2.25.3) with ethylene failed to proceed to more than 50% conversion, even when higher pressures, up to 50 psi, of ethylene were used.

Scheme 2.27

Table 2.3

Substrate	Conditions	Pressure of ethylene gas	Conversion
(2.25.3)	Grubbs II, r.t.	balloon	10%
(2.25.3)	Hoveyda-Grubbs, r.t.	50 psi	50%
(2.25.5)	Grubbs II, 45°C	balloon	>90%
(2.25.5)	Hoveyda-Grubbs, r.t.	50 psi	50%

This reluctance can probably be attributed to the presence of the oxazolidinone carbonyl group, which can coordinate to the Ru metal hence deactivating the catalyst by forming an

unreactive chelate.⁴⁵

Fig 2.28

Gratifyingly, no such problem was observed when the mesylate derivative (2.25.5) was used. With the corresponding mesylate, the cross metathesis proceeded smoothly with an ethylene balloon and gentle heating, giving the product in quantitative yield. Noticeably, under high pressure of ethylene gas, neither the oxazolidinone derivative (2.25.3) nor the mesylate derivative (2.25.5) gave satisfactory results. This is probably because high concentration of the gas would increase the reaction rate between the ethylene molecules, promoting the formation of [Ru=] which is unstable, and therefore increase the decomposition rate of the catalyst. Nevertheless, a gentle and effective ethylene cross-metathesis has been established. The 1-alkene mesylate (2.12.1) can then be easily converted to the desired sulfone (2.12.3) by the methods described previously.

Strategy D:

Strategy D is based on metal mediated decarboxylative alkylation. In recent years, transition-metal-catalyzed asymmetric allylic alkylation has become one of the most efficient ways to construct chiral compounds with high degrees of regio- and enantioselectivity from monosubstituted allylic carbonates.⁴⁶

Scheme 2.29

The regioselectivity depends on many factors, such as the central metal, ligand, incoming nucleophile, and substituent on the π -allyl system. The monosubstituted palladium complex system is generally under steric control and leads to preferential alkylation at the unsubstituted allylic terminus. On the other hand, iridium,⁴⁷ molybdenum,⁴⁸ tungsten⁴⁹ and ruthenium⁵⁰ tend to lead to alkylation preferentially at the substituted allylic terminus. While Mo and Ru complexes furnished good results only in special cases, Ir catalysts are applicable to alkylations, aminations⁵¹ and etherifications.⁵²

As reported by Takeuchi^{47a} and You,^{47b} iridium complexes have been found to be efficient catalysts for allylic esters with a stabilized carbon nucleophile. The reaction with dialkyl sodiomalonate in the presence of $[\text{Ir}(\text{COD})\text{Cl}]_2/\text{P}(\text{OPh})_3$ has been shown to give a product alkylated at the substituted allylic terminus with good selectivity. We initially employed this system with the α -sulfonyl acetate (2.30.4) as the nucleophile.

Scheme 2.30

Reagents and conditions: (i) Pyridine, CH_2Cl_2 , 0°C , quantitative; (ii) (a) 2 mol% $[\text{Ir}(\text{COD})\text{Cl}]_2$, 8 mol% $\text{P}(\text{OPh})_3$, NaH, THF, rt, 0%; (b) 2 mol% $[\text{Ir}(\text{COD})\text{Cl}]_2$, 8 mol% $\text{P}(\text{OPh})_3$, NaH, THF, reflux, 0%; (c) 2 mol% $[\text{Ir}(\text{COD})\text{Cl}]_2$, 8 mol% $\text{P}(\text{OPh})_3$, K^tOBu , THF, reflux, 0%.

Unfortunately, the reaction did not proceed even upon reflux. This is probably due to the low solubility of the sodium salt of tosylmalonate (2.30.4) as it quickly turned into solid when treated with base. We then reconstructed our substrate and inserted the sulfone functional group into the starting material, therefore allowing *in situ* generation of the nucleophile.

Scheme 2.31

Reagents and conditions: (i) K_2CO_3 , DMAP, CH_2Cl_2 , quantitative; (ii) $(n\text{-Bu})_4\text{NBr}$, Sodium *p*-toluenesulfonate, DME, quantitative; (iii) 2 mol% $[\text{Ir}(\text{COD})\text{Cl}]_2$, 8 mol% $\text{P}(\text{OPh})_3$, THF, reflux, 0%.

Again no desired product was obtained using the iridium complex. We then carried out the reaction with the Pd complex. Interestingly, in the presence of $\text{Pd}(\text{OAc})_2$ and PPh_3 isomerisation occurred under reflux.

Scheme 2.32

Reagents and conditions: (i) 4 mol% $\text{Pd}(\text{OAc})_2$, 16 mol% PPh_3 , THF, reflux, 75%.

We suspected that the resistance towards decarboxylation is probably due to the high energy of the sulfone carbanion (2.32.4). One solution to overcome this problem is to add an

electron-withdrawing group, such as an ester group, onto the carbon next to the sulfone moiety to stabilize the carbanion. We therefore further modified the substrate to the α -sulfonyl malonate (2.33.5) which can be made from addition of the alcohol (2.33.3) and the carboxylic acid (2.33.2), followed by a tosylation following the method of Craig.⁵³

Scheme 2.33

Reagents and conditions: (i) 0.25M KOH solution, THF/H₂O; (ii) DCC, DMAP, CH₂Cl₂, overnight, 88%; (iii) *t*-BuOK, DMSO, TsF, r.t., 67%.

Table 2.4

Catalyst/Ligand	Catalyst Loading	Condition	Yield	Internal:Terminal (2.33.6): (2.33.7)
Pd(OAc) ₂ /PPh ₃	4 mol%	Reflux/THF	86%	(2.33.7) only
[Ir(COD)Cl] ₂ /P(OPh) ₃	4 mol%	Reflux/THF	trace	Alkene region messy
[Ir(COD)Cl] ₂ /L1/TBD/CuI	2 mol%	r.t./THF	75%	3:2

Using this system, efficient decarboxylative allylation occurred. However, the Ir catalyzed alkylation led to a mixture of products resulting from both terminal and internal attacks. The poor regioselectivity probably arose from the bulky size of the nucleophile which reduced the electronic control by the metal and enhanced the steric-hindrance effect. However, we were delighted to see that the Palladium catalyzed reaction gave only the terminal attacked product (2.33.7) with an excellent yield.

We were inspired by this result and decided to further modify our substrate into compound (2.34.4) which contains an extra methyl group. In this case, a C₂ symmetric pi-allyl system

will be generated and there is equal chance for attack from either sides, leading to the formation of the internal product only. However, an additional ethylene metathesis will be needed to convert the internal alkene to terminal.

Scheme 2.34

Reagents and conditions: (i) MeMgBr, Et₂O, quant.; (ii) *t*-BuOK, DMSO, TsF, r.t., 67%; (iii) Pd₂dba₃.CHCl₃, (*S,S*)-DACH-phenyl Trsot ligand, THF, 65%; (iv) NaCl, DMSO, 76%.

We constructed an extra methyl group in the further modified substrate following a similar procedure described for (2.33.5). Carbonate (2.34.4) was subjected to Pd catalyzed alkylation and the product (2.34.6) was decarboxylated under Krapcho's conditions.⁵⁴ We anticipated that, by using a chiral ligand, we would be able to control the enantioselectivity as well. A number of Pd complexes and ligands were screened for this system.

Table 2.5

Catalyst/Ligand	Loading mol% (cat/ligand)	Condition	Yield	ee ^[1]
Pd(OAc) ₂ /PPh ₃	4/16	THF, reflux	90%	N.A.
(η^3 -C ₃ H ₅ PdCl) ₂ /L1 ^[2] (Trost)	2/6	THF, reflux	No reaction	N.A.
Pd ₂ dba ₃ .CHCl ₃ /L1 (Trost)	2.5/7.5	THF, reflux	65%	67%
Pd ₂ dba ₃ .CHCl ₃ /L1 (Trost)	2.5/7.5	THF, 40°C	60%	68%
Pd ₂ dba ₃ .CHCl ₃ /L1 (Trost)	2.5/7.5	Dioxane, 50°C	No reaction	N.A.
Pd ₂ dba ₃ .CHCl ₃ /L1 (Trost)	2.5/7.5	Toluene, 50°C	37%	56%
Pd ₂ dba ₃ .CHCl ₃ /L2 ^[3] (Pfaltz)	2.5/6.25	THF, 40°C	94%	42%
Pd ₂ dba ₃ .CHCl ₃ /L3 ^[4] (ANDEN)	2.5/7.5	THF, reflux	51%	67%

^[1] ee were determined by chiral HPLC on Daicel ID column

^[2] L1: (S,S)-DACH-phenyl Trost ligand, CAS: 169689-05-8

^[3] L2: (S)-(-)-2-[2-(Diphenylphosphino)phenyl]-4-isopropyl-2-oxazoline, CAS: 148461-14-7

^[4] L3: (S,S)-ANDEN-Phenyl Trost Ligand, CAS: 138517-65-4

The reaction was first carried out in a racemic system, using Pd(OAc)₂ and PPh₃. The reaction worked nicely in refluxing THF to give the desired product in excellent yield. We then tested the system with several chiral ligands. The Pd₂dba₃.CHCl₃ complex and Trost ligand L1⁵⁵ afforded the product in 65% yield and 67% ee. Changing the solvent to dioxane and toluene resulted in either no reaction or significant drop in yield. We also tried to lower the reaction temperature to 40°C, however, this led to a 5% decrease in yield and only 1% increase in ee. When Pd₂dba₃.CHCl₃ and Pfaltz ligand⁵⁶ L2 were used, the reaction proceeded with a quantitative yield at 40°C in THF. Unfortunately, the ee was rather too low. When a bulkier Trost ligand L3⁵⁵ was used, the reaction only proceeded in refluxing THF. In this case, a lower yield was obtained while maintaining the same ee. From the above experimental data, we can draw the following conclusions: firstly, the reaction works the best in THF, other solvent result in a decrease in both yield and ee; secondly, lower reaction temperature does not improve the ee significantly; thirdly, the symmetrical Trost ligands tend to give higher ee than the non-symmetrical Pfaltz ligand; finally, the use of a bulkier ligand does not help to improve the ee, but leads to a decrease in reaction yield. Nevertheless, it should be noted that most literature examples use substrates with aromatic substituents, clearly the results cannot be extended to substrates with smaller substituent.

Undoubtedly, this strategy showed advantages in many aspects such as its easy protocol, mild reaction conditions and high atom economy. However, to our disappointment, the best ee obtained was around 68%, which is too low for our synthesis.

Strategy E:⁵⁷

Strategy E is a revised methodology of strategy D, aiming to improve the ee outcome of the decarboxylative alkylation. We propose to control the stereo-outcome through an existing chiral center. The polar substituent would direct the nucleophile to the opposite terminus of the π -allyl complex.

Scheme 2.35

The initial stereo-center could be introduced by enantioselective reduction of the α,β -unsaturated ketone (2.35.1). During the key step, a η^3 -allyl complex will be formed by allylic substitution. With the commonly used palladium-phosphine systems, the terminus distant from the electron withdrawing group is attacked. The stereochemical results of such reactions have been carefully studied⁵⁸. If a chiral carbonate is used, then the alkylated product is found to exert retention of stereochemistry.⁵⁹ Retention is a result of two inversions- inversion during formation of the η^3 -allyl complex, and a second inversion during attack by the nucleophile. Furthermore, no expensive chiral ligands would be required for this system, hence

it can bring down the cost as well.

Scheme 2.36

Reagents and conditions: (i) NaClO_2 , NaH_2PO_4 , $t\text{BuOH-H}_2\text{O}$, 75%; (ii) CHCl_3 , 0°C , overnight (iii) K_2CO_3 , CH_3I , $(\text{CH}_3)_2\text{CO}$, 72%; (iv) (S)-CBS, BMS, CH_2Cl_2 , -30°C , 85%, e.e. > 99%; (v) ClCO_2Me , Pyridine, CH_2Cl_2 , 89%; (vi) $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$, PPh_3 , (3.33.5), THF, r.t.; (vii) ethylene, 5 mol% Grubbs II, Toluene, 70°C , 22% over 2 steps; (viii) NaCl , $\text{H}_2\text{O/DMSO}$, quantitative.

The α,β -unsaturated ketone (2.35.1) was prepared from the commercially available 2-methylfuran (2.36.1) in 75% yield using the procedure for furan oxidation.⁶⁰ Interestingly, the following isomerization took place spontaneously upon leaving the crude product in chloroform at 0°C overnight. The process is probably catalyzed by the trace amount of H^+ in chloroform. The asymmetric reduction was carried out with (S)-(-)-2-methyl-CBS-oxazolidinone and borane dimethyl sulfide complex in DCM at -30°C . The enantiomeric excess of the asymmetric reduction product was measured on the derivatives of the enantiopure (2.35.2) and the racemic alcohols (2.37.1) with p-toluenesulfonyl isocyanate.

Scheme 2.37

An excellent e.e. of > 99% was obtained by this protocol, ensuring a good chiral platform for the following key step.

Fig 2.38 HPLC peaks for the racemic ketone reduction product (derivatized with p-toluenesulfonyl isocyanate)⁶¹

Fig 2.39 HPLC peaks for the asymmetric ketone reduction product (derivatized with *p*-toluenesulfonyl isocyanate)⁶¹

We carried out the subsequent decarboxylative allylic alkylation in a base-free fashion. Carbonates are widely used leaving groups⁶². They enjoy an advantage that where the nucleophile must be generated by deprotonation, that the leaving group itself can act as a base. The allylic carbonate underwent facile decarboxylation to form (π -allyl)palladium methoxide. The methoxide acted as a base, generating the nucleophile internally. 100% regioselectivity was achieved as the product was obtained by attack preferentially at the terminus away from the electron withdrawing group. However, due to the fact that the alkylated product is inseparable from the sulphone nucleophile on a column and that an extra stereogenic center is present in the molecule, we were unable to measure either yield or e.e. at this stage.

Scheme 2.40

The ester group was then cleaved by cross metathesis with ethylene gas. However, only 22% conversion (over 2 steps) was observed, despite increasing the reaction temperature to 70°C. This could be attributed to the steric hindrance caused by the methyl 2-tosylacetate group. After the final Krapcho decarboxylation, the sulfone (2.36.4) (Fig 2.36) was subjected to e.e. measurement. To our great disappointment, this time an e.e. of around 0% was obtained, suggesting that racemisation must have occurred during the alkylation. To further investigate the reaction, a series of metal catalysts and phosphorus ligands which exhibit different electronic and steric properties were screened.

Table 2.6

Metal	Catalysts	Loading (mol%) (metal/ligand)	Reaction conditions ^[1]	Result
Pd	Pd ₂ (dba) ₃ •CHCl ₃ P(2-furyl) ₃	2.5/20	r.t., overnight	Formation of (3.32.4)
Pd	Pd ₂ (dba) ₃ •CHCl ₃ P(C ₆ F ₅) ₃	2.5/20	r.t., overnight	No reaction
Pd	Pd ₂ (dba) ₃ •CHCl ₃ dppe	2.5/20	r.t., overnight	Formation of (3.32.4)
Pd	Pd ₂ (dba) ₃ •CHCl ₃ PCy ₃	2.5/20	r.t., overnight	No reaction
Rh	(Ph ₃ P) ₃ Rh	2.5	r.t., overnight	No reaction
Mo	Mo(CO) ₆	2.5	Reflux, overnight	No reaction
Ir	[Ir(COD)Cl] ₂ (PhO ₃)P	2.5/20	r.t., overnight	No reaction

^[1] All reactions were carried in anhydrous THF

Among the metals that have been screened, only Pd was found to be active in this reaction. In terms of the ligand, both the mono-dentate P(2-furyl)₃ and bi-dentate dppe gave the desired product, suggesting that electron rich ligands are probably preferred for the alkylation regardless of their cone angles. However, the e.e. value was again disappointing. Only around 20% e.e. was obtained for the compound afforded using Pd and dppe, suggesting that the use of electron rich ligands does not have any significant effect on racemisation.

2.3.2 Modifications on other steps

As mentioned previously, synthesis of fragment A led to the formation of the BOM protected epoxy alcohol (2.2.5). However the BOM group migration occurred during epoxide opening, leading to a mixture of the desired product and its isomer. To improve this, several different protecting groups were tested.

Scheme 2.41

The secondary alcohol was protected with several groups prior to the epoxide opening. Attempts to protect as the PMB ether were unsuccessful. On the other hand, TMS and TES groups were found labile during epoxide opening, whereas TBS group protection resulted in no opening reaction even in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$. BOM was found to be the only workable protecting group.

In the subsequent cross metathesis of the terminal alkene with methyl acrylate, prolonged reaction times resulted in epimerization at the C-4 position, leading to the formation of an inseparable mixture of the desired protect and an isomer. It was proposed that this epimerization arose from the Ru-H catalysed alkene isomerisation.

Scheme 2.42

Table 2.7

Catalyst	Loading ^[1]	Additive	Reaction time	Yield	Ratio (2.14.3): (2.15.1)
Grubbs II	6mol%	No	Overnight	81%	7:1
Hoveyda-Grubbs II	5.5mol%	No	8 h	76%	4:1
Hoveyda-Grubbs II	5.5mol%	1,4-Benzoquinone ^[2]	8 h	60%	4:1
Hoveyda-Grubbs II	5.5mol%	No	3 h	64% ^[3]	Only (2.14.3)
Hoveyda-Grubbs II	5.5mol%	Phenol ^[2]	7 h	75%	Only (2.14.3)

^[1] Catalyst was added in portions

^[2] Additives were added in 50 mol% eq.

^[3] S.M. was recovered

During the attempt of addressing this issue, we firstly tried 1,4-benzoquinone as an additive in the reaction mixture since Grubbs reported that 1,4-benzoquinone can be used to stop the unwanted isomerization by oxidizing the Ru-H species. However, our trial resulted in no improvement.

We then tried another additive, phenol. Phenol has been shown to have several positive roles in cross metathesis reactions, including altering the relative rates of phosphine loss and rebinding, promoting the formation of the activated form of the catalyst as well as hemilabile stabilization of the key intermediate species⁶³. Therefore, the activity and lifetime of certain CM reactions catalyzed by Grubbs catalyst may be enhanced by the simple addition of phenol.

Scheme 2.43

From the proposed mechanism, it is believed that the added phenol can slow phosphine loss to afford the 14-electron intermediate (2.43.1). As suggested by Forman and co-workers, excess phenol may be capable of sequestering dissociated phosphine so as to form species of the type $(PhOH)_nPCy_3$. Furthermore, Schmidt has demonstrated the use of phenol in difficult cross-metathesis reactions during the total synthesis of (-)-Cleistenolide.⁶⁴ We were encouraged by these results and tried this additive in our cross-metathesis reaction. To our delight, in the presence of 50 mol% eq. of phenol, complete reaction is possible and higher yield can be achieved. More importantly, no epimerization occurred even after a prolonged reaction time.

2.4 Conclusion:

Based on Palani's previous studies, several synthetic issues have been further addressed. In particular, a number of alternative methods have been studied for the synthesis of the key intermediate, the sulphone fragment. Strategy A, B, D and E are based on transition metal catalyzed alkylation. These approaches showed advantages including mild reaction conditions, high atom economy and easy purifications. However, strategy A led to a low yield and strategy B, D and E suffered from low stereoselectivity. In comparison, strategy C which was via Evans' chiral oxazolidinone is less atom efficient. However, under Hoye's conditions, the key step proceeded with good yield and excellent stereoselectivity. Furthermore, the overall synthetic route is more reliable and scalable. This is by far the most feasible synthesis of the sulfone fragment.

Other key steps including epoxide opening and cross metathesis have also been further modified for improvement. In conclusion, the natural THP moiety of bistramide D has been prepared in 11 linear steps and in 16% overall yield. Highlights of our synthesis are the use of a regioselective cross-metathesis followed by an intramolecular Michael addition under kinetic control.

3.1 Scope of the review:

This is not a comprehensive review on spiroketals and spiroketal related chemistry. The main scope will focus on recently developed metal mediated spiroketalization methods.

3.2 Introduction to spiroketals:

Spiroketals are polycyclic ether ring systems where the rings are fused together at the alpha carbon to the oxygen of the cyclic ether. Generally, the term “spiroketal” refers to bicyclic systems and the term “bis-spiroketal” refers to tricyclic systems.

Spiroketals enjoy widespread occurrence as a common structural element in naturally occurring substances from a variety of sources, such as insects, microbes, fungi and marine organism.⁶⁵ The increasing biological importance of such compounds has evoked intense interest in both their synthesis and chemical reactivity.^{65a, 66} In general, 1,7-dioxaspiro[5.5]undecanes (3.1.1), 1,6-dioxaspiro[4.5]decanes (3.1.2) and 1,6-dioxaspiro[4.4]nonanes (3.1.3) are the most commonly occurring ring systems. Most of the natural products fall into these structural categories. Other ring sizes are also found but far less frequently.

Fig 3.1

3.2.1 Examples of naturally occurring spiroketals

Steroidal Saponins and Sapogenins

The steroidal saponins and sapogenins are probably the earliest recorded examples of naturally occurring spiroketal structures. They were originally isolated from plants found in southwestern America and Mexico during 1930s-1940s. This class of molecule usually contains a steroidal nucleus bearing a spiroketal moiety fused to the D ring. Rare variation in the spiroketal subunit has been found (e.g. Tomatidine)

Fig 3.2

The structures of the majority of the saponin aglycones were described in the 1940s, however, at that time, the steroid nucleus drew more attention to the synthetic chemistry, whereas spiroketal chemistry was relatively neglected.

This family of molecules shows a range of biological and pharmaceutical activities. Saponins,

in general, have been found to lower surface tension and possess emulsifying properties, making them good emulsion stabilizers.⁶⁷ They were also found to display hemolytic and antilipemic activities. Furthermore, general pharmacological behaviors of saponins have been studied. It has been shown that ingested saponins of alfalfa show effects on cardiovascular, central nervous systems and various parts of the digestive tract.⁶⁸

Insect Secretions or Pheromones

A number of species of flying insects, such as fruit flies, bees and wasps, have been found to elaborate simple volatile spiroketals which exhibit pheromonal activity. A series of spiroketals of the [6,6], [6,5] and [5,5] types have been described. Three typical examples are given in fig 3.3 with the source organisms listed below.

Fig 3.3

These compounds are usually very simple in structure, containing an unbranched carbon skeleton with few functional groups. However, they played an important role in the synthesis work during the early days, providing simple target molecules on which to test synthetic methodologies.

Polyether Inophores

The polyketide-derived polyether antibiotics, produced by filamentous branching bacteria,

represent another large class of naturally occurring spiroketals. These molecules are usually more highly functionalized with the spiroketal subunit often being only a small part of the structure. The [5,6] type ring system predominates in this series, with the main variations being due to the presence or absence of methyl, hydroxyl and alkoxy groups.

One illustrative example of this category is monensin which is a polyether antibiotic isolated from *Streptomyces cinnamonensis*. The structure of monensin was first described by Agtarap *et al.* in 1967.⁶⁹ The structural description followed by the discovery of its ionophoric properties triggered extensive interest in polyethers.

Monensin A

Fig 3.4

Monensin has been found to be a potent chelator of alkali metal cations such as Li^+ , Na^+ , K^+ , Rb^+ , Ag^+ and Ti^+ . It blocks intracellular protein transport and has broad-spectrum anticoccidial activity. Monensin is used extensively in dairy industries to prevent coccidiosis. Monensin and its derivatives are also widely used in ion selective electrodes.

Spiroketal of Marine Origin

The discovery of spiroketals from marine sources is a relatively recent phenomenon. Okadaic acid was one of the first polyether carboxylic acids described from a marine origin.⁷⁰ Even

though originally isolated from sea sponges, *Halichondria okadai* and *H. melanodicia*, the compound is believed to be a metabolite of an epiphytic microorganism and is the causative agent of diarrhetic shellfish poisoning. Furthermore, Okadaic acid has been found to be an inhibitor of protein serine/threonine phosphatase (PP), which are important regulators of many cellular processes.⁷¹

Okadaic Acid

Fig 3.5

Another representative example of marine origin is the Spongistatin family. This class of macrolide was first isolated from genus *spongia* and *spirastrella* in 1993.⁷² These compounds possess a remarkable general structure which contains a 51-carbon chain, 2 spiroketal rings and a 42-membered lactone ring. The complete structure of spongistatin 1 was proposed by Kitagawa,⁷³ and later, in 1998, Kishi's group reported the first total synthesis of this compound, establishing its relative and absolute configuration.⁷⁴ The members of the Spongistatin family exhibit extraordinarily potent growth inhibitory activity against a range of human tumor cells including a subset of highly chemoresistant tumor types.

(Spongistatin 1)

Fig 3.6

Milbemycin-Avermectins

The discovery of milbemycin and the closely related avermectins has brought the most activity in spiroketal synthesis. Most synthetic studies on spiroketals to date have been concerned with this series of molecules. These structurally related macrolides were isolated from *Streptomyces* bacteria found in soils.⁷⁵ As a class, they display potent anthelmintic, insecticidal and acaricidal activity with low mammalian toxicity, demonstrating significant potential for the treatment of parasitic infections. In particular, Ivermectin, which is derived from Avermectin B₁ by selective hydrogenation using Wilkinson's catalyst, has been shown to be effective in the treatment of onchocerciasis, a parasitic disease that may lead to permanent blindness.⁷⁶ Moreover, it is also widely used in veterinary medicine.

Milbemycin

Avermectin B_{1a}

Fig 3.7

3.2.2 Conformational aspects of 6,6-spiroketal

The 6,6-spiroketal are the most easily and widely studied spiroketal ring system for conformational aspects. Generally, there are three factors which can affect conformational preferences in this system: (1) steric factors, (2) anomeric and related effects, and (3) chelation effects such as intramolecular hydrogen bonding.

As expected, the most stable conformer tends to accommodate its substituents in equatorial positions, to minimize unfavorable steric clashes. This is especially important and normally an overriding factor in carbocyclic systems. However, for tetrahydropyrans, this must be balanced against another stabilizing effect, which is the thermodynamic preference for the polar substituent at the anomeric position of the heterocycle to reside at an axial position, known as the anomeric effect.

In the case of unsymmetrical substitution, there are four possible chair-chair conformers as illustrated in scheme 3.8. They are interconvertible by inversion of each ring. According to Deslongchamps *et al.*,⁷⁷ conformer (3.8.2) is most stable due to maximization of the anomeric effect and minimization of steric repulsions.

Scheme 3.8

There have been many postulated theories raised to rationalize the origin of the anomeric effect, such as syn-axial 1,3-repulsions of lone-pair orbitals⁷⁸, dipolar interactions⁷⁹, electrostatic repulsions⁸⁰ and $n-\sigma^*$ stabilization.⁸¹ The last theory had become most widely accepted and it suggests that there is a stabilizing interaction between the non-bonding electrons on the oxygen and the empty σ^* non-bonding orbital of the adjacent C-O bond. Furthermore, this stabilization is maximized when the two orbitals are antiperiplanar to each other. The effect can be characterized as two components: an *exo* component (3.9.1 and 3.9.2), where the donor electron pair originates from the *exo* cyclic heteroatom, and an *endo* component where the donor originates from the *endo* cyclic heteroatom. These effects can be reinforcing or opposing, and has been shown to have a profound influence on the conformation of spiroketals.

Scheme 3.9A Dipole-dipole interactions of the heteroatom and C-X bond

Fig 3.9B The *exo*- and *endo*- anomeric effect in axial and equatorial conformers

Furthermore, other stereoelectronic factors, such as dipole-dipole interactions and electrostatic repulsions can also have significant contributions to the overall configuration of the molecule.

3.3 General Methods for the Synthesis of Spiroketal

3.3.1 Overview

Over the course of the last several decades, a number of strategies have evolved for spiroketal synthesis. They differ depending on the structure, stereoselectivities and functionalities of the desired ring systems. There are several reviews in the literature that covered this topic.^{65a, 66, 82} Traditionally, strategies for spiroketal synthesis have tended to focus on common routes to a spiroketal precursor via a key bond forming step, with the final cyclisation step being rather trivial. However, as more diverse synthetic methods became available, greater variations and more efficient approaches have been seen. The synthetic strategies in this area can be phenomenologically divided into categories based on which bond is formed to produce the precursors to cyclisation reactions. Each category also includes a number of methods and variations.

Scheme 3.10

Synthesis by Formation of Two C-O bonds:

Disconnection of the spiroketal unit through the two C-O bonds is probably the most commonly employed retrosynthetic step to the open-chain precursor. This category includes methods such as: (method A) cyclisation of hydroxyketones or their equivalent; (method B) intramolecular *hetero-Michael* addition; and (method G) metal mediated cyclisation.

Method A is the predominant ring-forming process and most early approaches have taken this course. Both methods B and G are anomerically driven processes which means that the thermodynamically more stable spiroketals are formed. Development of method G is a rather recent phenomenon. However, it draws more and more attention due to a number of advantages. More detailed discussions on this topic will be covered in the next section.

Synthesis by Formation of One C-O bond and One C-C bond:

This represents another general approach to the synthesis of spiroketals, containing firstly a C-C bond forming reaction with a cyclic ether fragment, followed by the ring closure through C-O bond formation. This category demonstrates the potential for controlling the C-O ring closure in a stereoselective fashion. Methods that fall into this category usually involve alkylation followed by cyclisation of the sequentially formed cyclic vinyl ether or pyrone. Representative examples include: (method I) synthesis from cyclic vinyl ethers via sulfone alkylation or acylation; and (method E) cyclisation by *hetero-Diels-Alder* reaction.

Exceptionally, the C-C bond and C-O bond formation during the *Diels-Alder* reaction, where the cyclic ethers act as the electron-rich diene, can be considered to occur simultaneously. Furthermore, when subjected to kinetic conditions, this method is particularly useful for preparing the thermodynamically less stable isomer.

Synthesis by Formation of One C-O bond:

Methods in this category typically involve elaboration of complex tetrahydropyran or dihydropyran derivatives. There have been many protocols reported, such as: (method C) reductive cyclisation; (method D) cyclisation of enol ethers and glycal; (method H) intramolecular hydrogen abstraction; and (method J) oxidative ring expansion.

Method C and H usually lead to the formation of the mono-anomerically stabilised isomer. Under acidic conditions, method D tends to afford the thermodynamically stable spiroketal, however, this approach also provides the opportunity to synthesise the less thermodynamically stable isomer when a stereo-directing group is used.

The oxidative ring expansion method is rather different compared to other approaches, since the bicyclic structure is formed prior to the spiroketal forming step. However, this strategy is rarely used because of the low tolerance of functional groups.

Synthesis by Formation of One C-C bond:

In comparison, there are much fewer reported procedures which involve C-C bond formation as the last step of the spiroketal synthesis. One well-known example is the ring-closing metathesis. This simple yet powerful approach has generated much interest in the synthetic community. The easy and mild protocol allows high tolerance of functionalities and usually proceeds with no loss of stereochemical integrity at the spiro centre.

Other examples from this category include use of photochemical reactions and synthesis from alkylidenecarbene complexes, however, these methods are rarely used. Nevertheless, the development of new and diverse approaches for C-C bond formation in spiroketal synthesis represents an opportunity for discovery.

3.3.2 Metal Mediated Spiroketalizations:

Homogeneous catalysis using transition metals has emerged as a powerful tool in organic synthesis, with many diverse and useful new transformations appearing at a rapid pace. Being important structural elements, the synthesis of spiroketals involving metal catalysis has received considerable attention. Compared with the conventional approaches, metal mediated spiroketalizations enjoy a number of advantages, such as 100% atom efficiency, high yield and fast reaction times, mild reaction conditions, high functional group tolerance and high regio- and diastereo-selectivities. Furthermore, synthesis via metal catalysis avoids some potential sensitivity issues associated with highly functionalized ketones which are often elaborated in the conventional methods. A number of transition metals have been reported to be active for catalyzing spiroketalization. This section will review the use of some representative metals in spiroketal synthesis. Selected synthetic examples will also be discussed.

Pt(II) catalysts:

Hydration of unactivated alkynes represents a useful means of functionalization in organic synthesis. In principle, use of alkyne simplifies the synthesis of starting materials. Platinum(II) in the form of Zeise's dimer and simple Pt(II) halides have been shown to act as excellent hydration catalysts for unactivated alkynes to form ketones.⁸³

Scheme 3.11

In a paper by Hartman, it was reported that with unsymmetrical alkynes, modest to excellent regioselectivity was observed, resulting from steric effects or chelation control.⁸⁴

Table 3.1

	A(%)	B(%)	T _{1/2} (h)
Zeise's Dimer	71	29	4.0
PtCl ₂	64	36	3.8
PtBr ₂	74	26	
PtI ₂	78	22	14.8

It is suggested by the author that regiochemistry is derived from the fact that the metal atom is unsymmetrically bound to the alkyne due to steric reasons. This leads to the accumulation

of more positive charge on the carbon nearest the steric bulk and hence the bonding of water to that carbon. Furthermore, this system shows chemoselectivity for water over alcohols. It was suggested that this phenomenon is probably due to the fact that step (2) is reversible when tautomerization is prevented, as in the case of ROH addition.

Later, Hartman and co-worker produced another paper dealing with platinum (II)-catalyzed addition of alcohols to alkynes using anhydrous sodium sulphate or potassium sulphate as co-catalysts.⁸⁵

Scheme 3.12

A base is needed to abstract the acidic proton from the intermediate and drive the equilibrium forward. In the presence of Na₂SO₄, high conversion of alkynes to the corresponding acetals was observed. However, only modest regioselectivity was obtained with this system.

Table 3.2

R	A(%)	B(%)
Me	54	46
Et	56	44
<i>n</i> -Pr	62	38
<i>i</i> -Pr	59	41

The oxy-functionalization of internal alkynes represents an attractive route, and one of the mainstays for constructing spiroketal substructure. From the pioneering studies, addition of

water or alcohol to nonactivated and unbiased internal alkynes suffers from low regioselectivity.

de Brabander *et al.* have worked extensively on the oxy-functionalization of internal alkynes.⁸⁶ In the case of non-4-yne-1, 9-diol, a mixture of the [6,6] and [5,7]-spiroketals have been obtained using 1% PdCl₂.

Scheme 3.13

In the attempt of addressing this regioselectivity problem, they screened a series of catalysts using mono-hydroxyalkynes as substrates. Mixtures resulting from 6-*exo-dig* and 7-*endo-dig* cyclizations were obtained depending on the catalyst. Low yields (36-52%) and regioselectivities were observed when palladium(I), gold(I) and gold(III) catalysts were used. Platinum(II) catalysts, on the other hand, formed spiroketals in high yields and good selectivities with the 6-*exo-dig* product as the major product. Although PtCl₂ gave the best regioselectivity (entry 5, 116:1), Zeise's dimer [Cl₂Pt(CH₂CH₂)₂]₂ led to a much shorter reaction time while still keeping a good regioselectivity (30:1). This is likely to be due to better catalyst solubility. Changing the protecting group from THP to TBS resulted in a decrease in regioselectivity but a higher overall yield.

Table 3.3

Entry	R	mol% catalyst	Time (h)	Yield (%)	Ratio ^[1]
1 ^[2]	THP	1% PdCl ₂	1.5	52	2:1
2	THP	1% MeAuPPh ₃ , 10% TfOH	0.5	40	1.3:1
3	THP	5% AuClPPh ₃ /AgOTf (1:1)	0.5	36	2:1
4	THP	5% AuCl ₃	0.5	41	2.2
5	THP	2% PtCl ₂	24 ^[3]	64	116:1
6	THP	1% [Cl ₂ Pt(CH ₂ CH ₂) ₂] ₂	0.5	75	30:1
7	TBS	1% [Cl ₂ Pt(CH ₂ CH ₂) ₂] ₂	0.5	83	20:1

^[1] Yields (at >95% conversion) and ratios (6-*exo*: 7-*endo*) determined by GC with an external standard

^[2] MeCN was used instead of Et₂O

^[3] <5% conversion at 30 min

Having found the best conditions for 6-*exo* selective hydroalkoxylation, de Brabander *et al.* next studied the 5-*exo*/6-*endo* selectivity associated with the hydroalkoxylation of 4-alkynols. They found with these substrates, Pt(II)-catalyzed cyclization favored the 6-*endo* derived products, whereas Pd(II) and Au(I) catalysts systems led to 5-*exo* selectivities ranging from 4:1 to 6.6:1. Furthermore, substrates bearing THP protecting groups tended to afford higher *endo*-selectivity in comparison to TBS protected substrates.

Table 3.4

Entry	R	mol% catalyst	Solvent	Time (h)	Yield (%)	Ratio ^[1]
1	THP	1% [Cl ₂ Pt(CH ₂ CH ₂) ₂] ₂	dioxane	0.5	70	11:1
2	THP	1% [Cl ₂ Pt(CH ₂ CH ₂) ₂] ₂	Et ₂ O	0.5	60	9:1
3	TBS	1% [Cl ₂ Pt(CH ₂ CH ₂) ₂] ₂	Et ₂ O	0.5	58	3.7:1
4	H	3% PdCl ₂ (PhCN) ₂	Et ₂ O	3	>95	1:2
5	H	1% MeAuPPh ₃ /AgPF ₆	ⁱ Pr ₂ O	0.5	92	1:3.7
6	TBS	1% [Cl ₂ Pt(CH ₂ CH ₂) ₂] ₂	ⁱ Pr ₂ O	13	73	1:6.6

^[1] Determined by GC

The authors also proposed a mechanistic hypothesis which involves the initial coordination of the alkynol to Pt(II), activating intramolecular attack by the alcohol to form *endo*-(3.16.4) or *exo*-(3.16.5) adducts. Subsequent tautomerization afforded the platinated oxocarbenium species (3.16.6) and (3.16.7), which undergo another intramolecular attack by the pendant alkoxy group followed by metallation to yield the spiroketals.

This work demonstrates nicely the Pt(II)-catalyzed oxy-functionalization of unactivated internal alkynes. Zeise's dimer ([Cl₂Pt(CH₂=CH₂)₂]₂) has been shown to be an efficient and selective catalyst for the intramolecular hydroalkoxylation of 5-alkynols and 3-alkynols.

Scheme 3.14

Gold(I) and Gold(III) catalysts:

Spiroketalization of Monopropargylic Triols:

The application of cationic gold catalysts in organic synthesis has been of great interest in recent years, and a variety of gold-catalyzed transformations have been reported.⁸⁷

In 2008, Aponick and co-workers reported the dehydrative cyclization of monopropargylic triols to form olefin-containing spiroketals using a cationic gold complex.⁸⁸ The reactions were found to be rapid and high yielding with 2 mol% $Au[P(t-Bu)_2(o-biphenyl)]Cl/AgOTf$ in

Table 3.5

entry	Substrate ^[1]	product	Time(min)	Yield
1			60	81
2			40	83
3			25	81
4			35	99
5 ^[2]			80	80
6 ^{[3],[4]}			60	75

^[1] All triols were in racemic form

^[2] Reaction temperature 23°C

^[3] Catalyst loading 5 mol%

^[4] Reaction temperature 45°C

The reaction was found to be tolerant of different substitution patterns (table 3.5) and the predicted spiro systems were the sole products in all cases. Furthermore, Aponick reported that the relative 1,3-stereochemistry of the propargylic and nucleophilic hydroxyls within triols influenced the spiroketalisation regioselectivity. It was found that with substrate (3.16.1) the relative configuration of the propargyl alcohol had no influence over the course of the reaction since both diastereomers (3.16.1 a/b) gave the same product. In contrast, the *syn*-diastereomer (3.16.3) gave a mixture of the desired spiroketal and additional anomers (3.16.5) and (3.16.6). It was suggested that the order of the cyclization events may play a significant

role in the outcome of the reaction.

Scheme 3.16

To further explore the steric factors in more substituted substrates and to demonstrate the utility of the method, Aponick and co-workers prepared a naturally occurring 1,6-dioxaspiro[4,4]-non-3-ene which was identified after extraction from a Japanese hop oil in 1967.⁸⁹

Scheme 3.17

The synthesis begins from the alkyne alcohol (3.17.1), prepared from the corresponding ethyl ester. Protection followed by reaction of the lithio-derivative of the alkyne with the aldehyde (3.17.2) afforded the cyclisation precursor (3.17.3). As expected, the Au-catalyzed spiroketalization afforded the desired product as a single isomer. However, as for the more sterically hindered substrate, harsher reaction conditions were required to obtain a good yield. In 2010, Forsyth and co-workers performed another example of the Au-catalyzed spiroketalization of monopropargylic triols.⁹⁰ During the total synthesis of okadaic acid, they prepared the C34 spiroketal domain using this method and the resulting double bond was later removed by hydrogenation.

Fig 3.18

Scheme 3.19

The diastereomers (3.19.2) and (3.19.6) were prepared as the cyclisation precursors during the course of the total synthesis. In agreement with Aponick's result, they found that the stereo outcome of the cyclisation relates to the relative configuration of the 1,3-diol. The *syn*-diol (2.19.2) afforded the desired unsaturated spiroketal (2.19.3) as a minor product in only 13% yield. The major products, anomers (3.19.4) and (3.19.5), resulted from the cyclisation onto C33 instead of the expected dehydrative cyclisation via addition to C34. In contrast, the *anti*-diol (3.19.6) afforded the desired spiroketal as a single product.

Spiroketalisation through alkyne hydroalkoxylation:

In 2007, Li and co-workers reported a gold-catalyzed double intermolecular alkyne hydroalkoxylation and employed this method in the synthesis of the bisbenzannelated spiroketal core of natural bioactive rubromycins.

γ -rubromycin (1): $R_1 = H$; $R_2 = H$; $R_3 = H$
 purpuromycin (2): $R_1 = H$, $R^2 = H$; $R^3 = OH$
 heliquinomycin (3): $R^1 = O$ -cymarose; $R^2 = OH$, $R^3 = H$

Fig 3.20

The basic structural motif of these natural products consists of a 5,6-spiroketal core fused to aromatic naphthoquinone and isocoumarin moieties. The cyclisation precursors were prepared from the corresponding alkyne and various *o*-iodophenol acetates by a Sonogashira coupling reaction. The spiroketalization reaction was performed using 10 mol% $Ph_3PAuCl/AgOTf$ in DCM at room temperature.

Scheme 3.21

Table 3.6

Entry ^[1]	Substrates	R ¹	R ²	Time (d)	Yield (%) ^[2]	Yield of by-pdt ^[3]
1	a	Me	H	5	64	26
2	b	<i>t</i> -Bu	H	4	68	30
3	c	Ph	H	4	62	30
4	d	COMe	H	7	48	14
5	e	Cl	H	5	50	41
6	f	H	OMe	7	45	42

^[1] All reactions were performed on a 0.2 mmol scale

^[2] Isolated yields of the corresponding spiroketals

^[3] Yields of the by-product benzofurans (3.23.5) a-f

Using the optimal conditions, the expected corresponding bisbenzannelated spiroketals were formed in all cases in moderate to good yields along with the benzofuran side products. The by-products are probably stabilized by aromaticity. Substrates containing electron-donating groups at the *para* position of the phenyl ring tend to give better yields (entry 1-3). However, the reaction times were rather too long. Nevertheless, the mild reaction conditions and wide substrate scope allow for the synthesis of various substituted 5,6-aromatic spiroketal skeletons.

Spiroketalization of Propargyl Vinyl Ether:

Toste *et al.* reported a Au(I)-catalyzed stereoselective synthesis of 2-hydroxy-3,6-

dihydropyrans from propargyl vinyl ethers through tandem Claisen rearrangement /heterocyclization.⁹¹

Scheme 3.22

The reaction proceeded in good yield and with excellent diastereocontrol and chirality transfer from the precursor. By replacing water with a pendant alcohol as the nucleophile, the reaction also provides a stereoselective entry into spiroketal structures.

Scheme 3.23

When (3.23.1a) and (3.23.1b) were treated with 1 mol% of Au(I) catalyst, 5,6- (3.23.2a) and 6,6-spiroketal (3.23.2b) were formed in good yield and with excellent diastereoselectivity. Furthermore, the enantiopure propargyl vinyl ether (3.23.3) gave the corresponding spiroketal

(3.23.4) without loss of optical activity.

The reaction is believed to proceed via the oxocarbenium intermediate (3.24.2) followed by nucleophilic trapping by the pendant alcohol.

Scheme 3.24

This method allows the formation of a bicyclic spiroketal framework from a linear precursor with complete stereocontrol. Furthermore, the reaction is tolerant of a wide range of functional groups.

Intramolecular Reaction of Epoxy Alkynes:

Shi and co-workers have previously worked on an Au-catalyzed cascade cyclization of epoxy alkynes to form a ketal which provides an alternative strategy in the construction of the C-O bond.⁹² They proposed two reaction pathways involving the coordination of the cationic gold catalyst to either the epoxy alkyne (3.25.2) or the oxirane (3.25.5), followed by an intramolecular nucleophilic attack.

Scheme 3.25

The method was extended to the intramolecular reaction of propargylic/homo-propargylic alcohols with oxiranes to yield spiroketals.⁹³ It was found that in the presence of [AuClPPh₃]/AgSbF₆ (5 mol%) and *p*-TsOH (30 mol%), epoxy alcohol (3.26.1) can afford the desired spiroketal (3.26.2 a-f) in moderate yield and diastereoselectivity, along with the free alcohol (3.26.3 a,e,f) as the by-product.

Scheme 3.26

p-Toluenesulfonic acid acts as a co-catalyst and is believed to facilitate epoxide ring opening.

The diastereoselectivity decreased with increasing bulkiness of the alcohol nucleophile increase (scheme 3.26). With extremely bulky alcohols such as 2-methylpropan-2-ol or 2,2-dimethylpropan-1-ol were used, only the by-products were formed, however in low yield.

Scheme 3.27

Furthermore, use of secondary epoxy homopropargylic alcohol (3.27.1) favors the formation of the free alcohol (3.27.3); whereas when a 1', 2'-disubstituted epoxide bearing a phenyl group (3.27.4) was employed, the reaction yielded the desired spiroketal (3.27.5) exclusively in good yield and high diastereoselectivity.

A plausible mechanism was proposed based on the assumption that the tandem process proceeded via dihydrofuran (3.28.3). The activated alkyne (3.28.1) succumbs to nucleophilic attack by the pendant OH to give intermediate (3.28.2). Subsequent ethanol elimination and intermolecular attack on the oxirane activated by $p\text{-TsOH}$ or the cationic gold catalyst provided oxonium ion conformers (3.28.5) and (3.28.7). Intramolecular nucleophilic attack gives rise to (3.28.6) and (3.28.8), between which spiroisomerisation can proceed via intermediate (3.28.9). Diastereoisomer (3.28.8) is preferably obtained due to the anomeric effect.

Scheme 3.28

Hg(II) catalysts:

In 2010 Deslongchamps' group reported the use of $Hg(OTf)_2$ catalyzed spiroketalization from a semiprotected alkyne diol in the synthesis of the natural product hippuristanol and its analogues.⁹⁴ They further studied the scope and limitations of this catalytic system and identified it as a highly efficient catalyst for the versatile construction of spiroketals from alkyne diols in aqueous conditions.

Table 3.7

Entry	Substrate	Product ^[1]	Time (min)	Yield (%) ^[2]
1			45	90
2			45	92
3			45	90
4			45	94
5			45	90
6			10	92
7			10	90
8			10	94
9			10	90

^[1] All the products were prepared as racemic mixture

^[2] Isolated yields

As reported by de Brabander, the THP protected alkyne diol (table 3.7, entry 1 and 3) gave a mixture of 6-*exo* and 7-*endo* products when treated with PdCl₂ and AuCl₃.⁹⁵ Pt catalysis would improve the yields and regioselectivities, however, a Brønsted acid is needed for both deprotection of the THP ether group and spiroketalization. Deslongchamps used the same substrate for comparison. When the alkyne diol was subject to 10 mol% Hg(OTf)₂ in aqueous CH₃CN, the 6-*exo* product was yielded exclusively in excellent yield and shorter reaction time. Moreover, no additional acid was needed for THP acetal deprotection or to facilitate cyclisation, indicating that acid is generated *in situ*. The same result was observed with substrates from entries 3, 4, and 5. This catalyst system seems to favour the 6-*exo-dig* cyclisation rather than 6-*endo*- or 5-*exo-dig* cyclisations. The [5,6] and [5,5] spiroketal systems were also formed smoothly in even shorter reaction times. This is probably because

the transition state energy of the 5-*endo-dig* process is lower than that of the 6-*exo-dig* process.

Scheme 3.29

This catalyst system was also found active for spiroketalization from propargylic triols. With the optimal conditions, all substrates gave the corresponding monounsaturated products except (3.29.7), where a hydroxyl ketal (3.29.8) was yielded instead of the dehydration product. It is suggested that a preferred 5-*endo* or 5-*exo* cyclisation pathway took place in this case. Interestingly, anhydrous conditions are not needed for this reaction system in contrast with Aponick's protocol.⁸⁸

Deslongchamps' group also demonstrated the use of this catalyst system in natural product synthesis. They performed a synthesis of the potent antiproliferative agent Hippuristanol, featuring a rapid construction of a spiroketal unit via $\text{Hg}(\text{OTf})_2$ catalyzed spiroketalization of the 3-alkyn-1,7-diol motif.⁹⁴

Scheme 3.30

Intermediate (3.30.3) was prepared from the commercially available 11-ketotigogenin. Subsequent reaction with the THP protected alkyne alcohol provided the cyclization precursor (3.30.5). Exposure of the semiprotected 3-alkyn-1,7-diol (3.30.5) to Hg(OTf)₂ in aqueous acetonitrile at room temperature afforded the desired spiroketal (3.30.6), which on debenzoylation afforded 22-*epi*-hippuristanol as the major diastereomer (22S:22R, 99.9:0.1) in 82% over 2 steps. The 22-*epi*-hippuristanol was then converted to hippuristanol using PPTS in chloroform at ambient temperature.

Fe(III) catalysts:

Another example of the metal-catalyzed carbon-oxygen bond formation in spiroketalization processes utilized an Fe(III) salt as the catalyst. In 2010, Cossy's group reported a diastereoselective synthesis of substituted tetrahydropyrans from allylic acetates using iron (III) chloride.⁹⁶

Scheme 3.31

When an ω-unsaturated lactol (3.31.5) was used as the substrate, treatment with FeCl₃ led to the corresponding spiroketal (3.31.6). The reactions proceeded smoothly with 5 mol% of FeCl₃ at ambient temperature in good yield and high diastereoselectivity. The mild conditions allow use of a wide scope of substrates bearing alkyl or ester groups. It was proposed that the cyclisation occurred via a carbocation intermediate and the high diastereoselectivities resulted from the thermodynamic epimerization of the produced tetrahydropyrans.

Cossy and co-workers demonstrated the utility of this methodology in the synthesis of 39-oxobistramide K.²⁴

Scheme 3.32

The synthesis started from the commercially available 1,4-butanediol (3.31.1), which was converted to the corresponding TBDPS protected hydroxyaldehyde (3.32.2). The subsequent alkylation using crotyltitanium complex (3.32.7) selectively installed the chiral centers at C22 and C23. The sequential cross-metathesis, hydrogenation and acid treatment afforded lactone (3.32.4) which was further transformed into the spiroketalization precursor, the lactol (3.32.5). The key cyclisation step proceeded with 5 mol% of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ in CH_2Cl_2 at room temperature, accomplishing the key spiroketal unit of 39-oxobistramide K in 59% yield.

Cu(I) and Cu(II) catalysts:

The hetero-Diels-Alder reaction has proven to be a convergent and efficient strategy for the formation of spiroketal systems. This versatile method allows many modifications to be made. Jørgenson and colleagues have studied the catalytic and highly enantioselective approach for

the synthesis of optically active carbohydrate derivatives. In 2000, they reported an inverse-electron demand hetero-Diels-Alder reaction of α , β -unsaturated carbonyl compounds with electron-rich alkenes in the presence of chiral bisoxazolines and the Lewis acid $\text{Cu}(\text{OTf})_2$.⁹⁷

Scheme 3.33

The enantioselective HDA reaction can also be used for the preparation of optically active spiroketal structures. Compared to other methods, this approach offers access to the spiroacetal functionality in a convergent way, avoiding a stepwise process.

Scheme 3.34

Reaction of β,γ -unsaturated α -keto ester (3.34.1) and (3.34.2) with α -methylenefuran catalyzed by *t*-Bu-Box-Cu(OTf)₂ led to the formation of *endo*-spiroketals (3.34.4) and (3.34.6) as the major diastereomers in moderate ee. Further transformations provided the carbohydrate derivative (3.34.8) as an optically pure compound with the alcohol introduced on carbon-4 being *anti* to the substituents on carbon-3 and 5.

Based on the X-ray study on the products and isolation of a chiral bisoxazoline copper (II) hydrolyzed enone complex, it was suggested that the enantioselectivity arises from such a reaction mechanism where the α -keto ester coordinates to the metal centre in a bidentate fashion, directing the alkene to the *si*-face of the carbonyl group.

Alternatively, Cu(I) catalysts have also shown activity for the hetero-Diels-Alder reaction. Li and co-workers studied a domino process for the diastereoselective synthesis of a series of multifunctionalized aromatic spiroketals using copper iodide as the catalyst.⁹⁸

Scheme 3.35

As shown in Scheme 3.35, cyclisation of (3.35.2) affords the exocyclic enol ethers (3.35.3), which can subsequently undergo an asymmetric hetero-Diels-Alder reaction with *o*-quinone methides (3.35.6) to accomplish the aromatic spiroketal unit. The entire process is in a cascade fashion and both building blocks are easily accessible from commercially available salicylaldehydes.

The scope and generality of this methodology was tested with a wide range of substrates.

Table 3.8

Entry	Product	Yield (%)	dr
1		78	>20:1
2		76	>20:1
3		(X=Cl) 72 (X=Br) 86	(X=Cl) >20:1 (X=Br) >20:1
4		67	>20:1
5		79	>20:1
6		76	>20:1

Under the optimal conditions, substrates bearing both electron-donating and electron-withdrawing substituents provide the corresponding spiroketals in good yields and high diastereoselectivities (>20:1 in all cases). Furthermore, the sterically hindered bis(ortho-methoxy)-substituted spiroketal (entry 5) was also obtained smoothly.

It is believed that the excellent diastereoselectivities are achieved due to a transition state that involves a hydrogen-bonding interaction between the two reacting units, which results in formation of a single diastereoisomer as the major product.

Fig 3.36

Eu(III) catalysts:

Europium(III) catalysts have also shown activity in spiroketalization via the hetero-Diels-Alder approach. In the synthesis of (-)-Reveromycin A, Rizzacasa and co-workers utilized an $\text{Eu}(\text{fod})_3$ catalyzed inverse electron demand hetero-Diels-Alder reaction followed by hydroboration/oxidation to afford the [6,6]-spiroketal core in a stereoselective fashion.⁹⁹ The [4+2] cycloaddition was envisioned to proceed via the $\text{TS}^\ddagger$ where the diene approaches the dienophile from an axial direction.

Fig 3.37

Scheme 3.38

Table 3.9

Entry	Additives (loading mol%)	Solvent	Temp (°C)	Time (d)	Yield (%)	Ratios (3.38.8):(3.38.7)
1	K_2CO_3 (50)	toluene	110	1	11	1:0
2	K_2CO_3 (50)	neat	110	1	26	1:0
3	$\text{Eu}(\text{fod})_3$ (15)	MeCN	0	2	35	1:1.3
4	$\text{Eu}(\text{fod})_3$ (15)	neat	0	3	59	2:1

Potassium carbonate was tested as an additive when examining the conditions as it was previously shown to be effective in suppressing the *exo* to *endo* isomerisation of the dienophile (3.38.6). They found that the basic additives led to the formation of only one spiroketal stereoisomer, however, in very low yields. They then turned to Lewis acids and found that when 15 mol% of $\text{Eu}(\text{fod})_3$ was used, the spiroketal (3.38.8) was formed along with the ene product (3.38.7) as a mixture of diastereoisomers. The best yield was obtained when the reaction was then at 0°C without solvent. Even though it was not possible to completely suppress the formation of the by product, this protocol allowed the desired

spiroketal to be made in large scales and in a stereoselective manner. The spiroketal core (3.38.8) was then further manipulated to afford (-)-Reveromycin A.

Pd(II) catalysts:

Spiroketalization via oxycarbonylation of dienones:

In addition to alkyne functionality, olefins serve as an alternative precursor to spiroketal structures via π -bond activation. To this end, Yadav and colleagues reported a method towards synthesizing bifunctional spiroketals via palladium catalyzed oxycarbonylation of dienones.¹⁰⁰

Scheme 3.39¹⁰¹

When dienones (3.39.1/2/5) were subject to carbonylation using catalytic amounts of palladium chloride, CuCl_2 , CO , methanol and trimethylorthoformate at room temperature, double cyclisation with concomitant introduction of methoxy groups in the side chain occurs to provide the corresponding spiroketal in moderate to good yield. The reaction is believed to proceed via dimethyl acetals that are formed *in situ* from the dienones.

Spiroketalization via Tandem Wacker Cyclization:

Intramolecular Wacker cyclization has been shown to be effective for the synthesis of pyrans,¹⁰² furans¹⁰³ and chromans.¹⁰⁴ During continuing research on the synthesis of rubromycins, Li and co-workers studied a Pd(II)/Cu(II) catalyzed chemoselective tandem Wacker cyclisation.¹⁰⁵

Scheme 3.40

When treated with O₂ under PdCl₂/CuCl₂ catalysis in MeOH, the phenolic olefin (3.40.1) led to the desired [5,6]-bisbenzannelated spiroketal (3.40.2) along with the 5-*endo*-trig cyclization product (3.40.3). The use of copper salt as a co-catalyst was found essential to this oxidative transformation. Interestingly, when a base such as Cs₂CO₃ was used as an additive, the chroman (3.40.4) was exclusively formed via 6-*exo*-trig cyclisation in good yield and short reaction time. This base-oriented chemoselectivity was observed in all cases.

Scheme 3.41

The substrate screening showed that the substituents on the phenol ring had a significant effect on this Wacker cyclisation. Electron-donating substituents on ring (1) (3.41.1a/2a) might benefit the formation of the spiroketal product by activating the double bonds in benzofuran for nucleophilic attack by the second phenolic OH group. On the other hand, the electron-withdrawing substituents (3.41.3a/4a) on ring (1) would reduce the reactivity of the double bond toward Pd(II) catalyzed olefin activation.

Furthermore, a control study showed that the by-product benzofuran (3.42.1) can be converted to the desired spiroketal (3.42.2) with PdCl₂ in MeOH after 18 hours, demonstrating that the 5-*endo*-trig cyclization product was the precursor of the biscyclized spiroketal.

Scheme 3.42

Ru(II) catalysts:

Alkene Ring-Closing Metathesis:

Transition metal catalyzed ring-closing metathesis [RCM] represents a powerful strategy for

the construction of carbo- and heterocyclic compounds. This approach differs from the methods described above whereby a carbon-carbon double bond is formed during the key step.

In 1998, van Boom and co-workers reported a novel and flexible synthesis of pyranose spiroketal derivatives using the Grubbs' I catalyst mediated ring-closing metathesis.¹⁰⁶ The metathesis precursors were readily prepared from D-Glucono-1,5-lactone by vinyl- Grignard reagent addition followed by stereoselective *O*-glycosidation using Montmorillonite K-10 clay with different allyl alcohols.

Scheme 3.43

RCM of the diene substrates (3.43.1a-b) and (3.43.4a-c) in the presence of 6 mol% Grubbs I catalyst gave the corresponding spiroketals at 60°C in excellent yields. The stereochemistry at the spirocenter was firmly established. The only exception was diene (3.43.1c) which, upon the same treatment, did not yield the expected spiroketal but a dimer product. Furthermore, the undesired dimerisation could not be prevented by decreasing the substrate concentration or increasing the catalyst loading.

Harrity and colleagues exploited the RCM using a different approach where the spirocycles were assembled through the employment of two tandem ring closing metatheses on a tetraalkene.¹⁰⁷

Scheme 3.44

It was observed that this spirocyclisation process favours the formation of a 5-membered ring (3.44.2) over a 7-membered ring. Cyclic acetal (3.44.3) can also lead to the [5,5]-spiroketal (3.44.2) after 36 hours. However, formation of butenolide (3.44.5) was sluggish even after portionwise addition of the catalyst over a prolonged reaction time.

Scheme 3.45

It was postulated that the catalyst coordinates to the less hindered alkene to form alkylidene (3.45.4). Subsequently, the 5-membered ring closure (3.45.5) can compete with the 7-membered ring formation (3.45.3). However, the obtained selectivity and the observation of substrate (3.44.3) being unreactive suggest that the 5-membered ring closure is kinetically favoured.

In 2004, Hsung and co-workers reported an unconventional approach to construct spiroketals using a ketal-tethered RCM strategy.¹⁰⁸ The metathesis precursor cyclic ketals were prepared from dihydropyran in 65% overall yield. The two separable isomers (3.46.4s) and (3.46.4a) (*anti* and *syn* relationship between the C1-*O*-allyl and C2-OAc groups) were obtained in a 1.6:1 ratio.

Scheme 3.46

The RCM of diene (3.46.4a) using Grubbs' I catalyst in DCM afforded the desired spiroketal (3.46.5) in 83% yield with no erosion of stereochemical integrity at the C1 spiro centre. More

substrates were screened under the same conditions.

Table 3.10

Entry	Ketals	Product	Solvent	Ru-catalyst ^[1]	Yield (%) ^[2]
1			CH ₂ Cl ₂	Grubbs' I	83
2 ^[3]			C ₆ H ₆	Grubbs' II	88
3			C ₆ H ₆	Grubbs' I	27 ^{[4], [5]}
			CH ₂ Cl ₂	Grubbs' II	5
4			C ₆ H ₆	Grubbs' II	79
5			CH ₂ Cl ₂	Grubbs' I	90
6			C ₆ H ₆	Grubbs' II	78

^[1] All reactions were carried out at r.t. for 30 min. Catalyst loading is 10 mol% and ketal concentration is 0.01M in all cases

^[2] Isolated yields

^[3] Same reaction condition and yield for both *syn* and *anti* isomers

^[4] Reaction temperature is 60°C, substrate loading is 0.004 M

^[5] Reaction time was 14-48 h

Under the optimal RCM conditions, all substrates led to the desired spiroketals in high yields except the ketal from entry 3. The author postulated that the acetoxy group shuts down the catalytic cycle by internally coordinating to the Ru metal in the Ru-alkylidene complex generated *in situ*. Furthermore, it was not necessary to protect the C-2 hydroxyl group for the RCM process to occur (entry 5). Lastly, Grubbs' II catalyst seemed more effective in the cyclisation of larger rings (entry 4, 6).

Hsung and co-workers applied this methodology to the total synthesis of (+)-aigialospirol.¹⁰⁹

Their work features a cyclic ketal-tethered RCM in constructing the spiroketal core and a facile epimerization of the benzylic hydroxyl group.

Scheme 3.47

The synthesis started from the commercially available (*S*)-glycidol (3.47.1), preparing the known dihydro- α -pyrone (3.47.2) in 4 steps. Dihydroxylation of (3.47.2), followed by acetonide formation and addition of vinyl magnesium bromide afforded lactol (3.47.6). Treatment with 1 eq. of Tf_2NH and the chiral homoallylic alcohol (3.47.7) provided the key cyclic ketal (3.47.8). In the presence of 12.5 mol% of Grubbs' I catalyst, which is surprisingly high loading, the ring-closing metathesis proceeded smoothly to afford spiroketal (3.47.9) in 86% yield. However, the stereoisomer obtained at this stage is actually the epimer of the natural product. The authors postulated that the configuration of the natural product was due to the H-bonding between the C4-OH and the spiroketal oxygen in the natural product. The spiroketal (3.47.9) was further converted to the lactone (3.47.10), which was subjected to

actonide removal concomitant with C6 epimerization to accomplish (+)-aigialospirol in a total of 15-steps.

Ring-rearrangement metathesis:

Ring rearrangement metathesis (RRM) of strained heterobicycles is an alternative strategy to construct complex molecular scaffolds in a single step. Blanchard and co-workers reported a novel approach to spiro- and dispiroketal via a metathesis rearrangement of oxabicyclic derivatives under neutral conditions.¹¹⁰

The RRM precursors were accessed through cycloaddition reactions of the corresponding α -alkoxyfurans with selected dienophiles.

Scheme 3.48

The RRM of the corresponding [2.2.1]-oxabicycles bearing sulfone (3.48.1) or ester groups (3.48.5) proceeded smoothly in the presence of 10 mol% Grubbs' II catalyst in DCM at 45°C to yield the desired spiroketal products in excellent yield after 1 h. (6,6)-Spiroketal (3.48.4) can also be accessed from [3.2.1]-oxabicyclo (3.48.3) under the same reaction condition in 70% yield. However, when the oxabicycles bearing a cyclopentenyl moiety were used, only the ring opening of the oxa-bridge of (3.48.7) was observed, even under harsher conditions.

The sequence of events of this RRM strategy is believed to be an initiation at the mono-substituted exo-olefin followed by a RCM/ROM reaction.

3.4 Conclusion:

As a consequence of the important biological activities of spiroketal containing natural products, together with their intriguing and challenging molecular structure, many synthetic studies have been made on these heterocyclic systems. Compared with conventional approaches, metal mediated spiroketalization demonstrates a number of advantages. These methodologies allow oxygen-carbon or carbon-carbon bonds to be formed under mild conditions and in a stereoselective fashion. Over the past few years, they have been applied and shown to be effective in the synthesis of many complex natural products. The stereocontrolled synthesis of spiroketals, especially non-anomeric spiroketals, will continue to present a stimulating challenge in target- and diversity-oriented synthesis.

Chapter Four:

Synthesis of the Spiroketal fragment of Bistramide D

4

4.1 Introduction:

In general, spiroketals show a common structure in which the two oxygen atoms are axial to each other due to the anomeric effect. By far, the most common disconnection for a spiroketal would be through the two C-O bonds where the stereogenic centre is thermodynamically controlled. For the synthesis of the spiroketal fragment of bistramide D, we prepared two different approaches to construct the bicyclic O-C-O ketal bonding system.

The first approach involves acid catalyzed dehydrative cyclization of oxo diol precursors, which will be prepared via bidirectional elongation. The cyclization of dihydroxy ketones is a simple and useful method when the desired spiroketal is required in its thermodynamically most stable form.

Our second approach will utilize transition metal facilitated spiroketalization of monopropargylic triol. This method is particularly attractive due to its mild reaction conditions and high regio- and diastereo-selectivities.

4.2 Preliminary Study of the Spiroketal Fragment:

4.2.1 Approach A:

Retrosynthetic analysis

Scheme 4.1

Disconnection at the O-C-O system leads to a dihydroxyketone precursor. A common way to synthesize such a molecule can be complex as it involves lots of protection group chemistry. In approach A, we are interested in a two directional synthesis that allows parallel construction of the two sides, minimizing steps and use of protecting groups. As shown in Fig 4.1, disconnection at the double bonds of the two unsaturated ketones leads to dialdehyde (4.1.4), with which we plan to perform a bidirectional homologation via olefination.

Hoye *et al* have reported a protocol for the *in situ* generation and nucleophilic capture of 1,n-dial equivalents from 1,n-dioates.¹¹¹ They use DIBAL-H reduction of the corresponding 1,n-

dioates followed by nucleophilic trapping, allowing for one-pot, bidirectional homologation.

Scheme 4.2

When the succinate (4.2.1) and glutarate (4.2.3) were treated with DIBAL-H followed by addition of the phosphonate anion, the corresponding dienoate esters (4.2.2) and (4.4.4) were afforded in good yield and regioselectivity. For its easy handling and high efficiency, we decided to use this methodology as the key step to construct our cyclisation precursor.

Proposed synthesis of the spiroketal unit:

Scheme 4.3

The synthesis of the spiroketal fragment of bistramide D will start from the protected ketone (4.3.1), which can be made from the commercially available ethyl formate via allylation, oxidation and protection. Subsequent ozonolysis and Horner-Emmons olefination with the two phosphonates (4.3.2) and (4.3.3) will provide the key intermediate (4.3.4). After the asymmetric ketone reduction, the two internal alkenes will be stereoselectively reduced via directed hydrogenation, possibly using the cationic rhodium catalyst [Rh(NBD)(DIPHOS-4)]BF₄, to establish C27 stereogenic centre. It has been demonstrated that the proximal hydroxyl groups can be employed to direct the stereochemical course of selected transition-metal catalyzed olefin hydrogenation.¹¹² The linear precursor (4.1.2) will be subject to acid catalyzed cyclization. After construction of the spiroketal skeleton, the side chain will be

elongated, again using oxidation followed by olefination. Finally, the ketone will be stereoselectively reduced via CBS reduction to furnish the spiroketal unit.

Model Study Of Approach A:

We started this part of the synthesis by carrying out a model study to construct two simple spiroketals using the bidirectional strategy. The target molecules are natural products isolated from rectal gland secretions of adult male cucumber flies.¹¹³

Fig 4.4

The first challenge was to synthesize the diketone intermediate (4.4.4) efficiently. A Barbier reaction on ethyl formate¹¹⁴ followed by PCC mediated oxidation¹¹⁵ and ketone protection afforded the protected diallyl ketone (4.3.1) in good yield. We initially subjected (4.3.1) to ozonolysis, followed by Ba(OH)₂ mediated Horner-Emmons reaction,¹¹⁶ hoping the elongation would occur in a one-pot and bidirectional fashion.

Scheme 4.5

Reagents and conditions: (i) (4.5.2), Mg, THF, reflux, 95%; (ii) PCC, CH₂Cl₂, r.t.; (iii) HO(CH₂)₂OH, PTSA, hexane, reflux, 63% over 2 steps; (iv) O₃, Me₂S, CH₂Cl₂, -78°C; (v) (4.5.4), Ba(OH)₂, THF/H₂O, 16% over 2 steps.

Despite numerous attempts, we were unable to obtain a good yield for the formation of the diketone. This is probably due to cyclisation of the dialdehyde intermediate which would affect the subsequent olefination reaction, or other condensation reaction of the labile dialdehyde.

Scheme 4.6

We then turned to another approach in which a protected diester (4.7.2) was treated with DIBAL, was then subjected to a Wittig reaction.¹¹⁷ Again only a moderate yield was obtained. Alternatively, we reduced the diester to a diol, and then carried out a one-pot Swern Oxidation and Wittig reaction. This strategy led to the formation of a mixture of the desired product (4.4.4) and a half reacted ketone alcohol (4.7.4). The formations of these compounds were confirmed by ¹H NMR. For diketone (4.4.4), a doublet at 6.1 ppm and a doublet of

triplet at 6.7 ppm indicate the success of the olefinatinon. The singlet at 3.9 ppm corresponds to the CH₂ next to the double bond and suggests the molecule is symmetrical. Whereas for the half reacted ketone alcohol (4.7.4), there is an extra triplet at 4.2 ppm, corresponding to the CH₂ adjacent to the hydroxyl group.

Scheme 4.7

Despite increasing the amount of oxidizing reagents, the ketone alcohol (4.7.4) would not to react further. This is probably due to the formation of the dioxolane (4.8.2) via intramolecular cyclization, preventing the reaction from going to completion. Nevertheless, a much better yield could be obtained using this method.

Scheme 4.8

The rest of the synthesis was performed smoothly. Asymmetric ketone reduction of (4.4.4) followed by hydrogenation and tandem deprotection cyclisation afforded the spiroketal

product (4.4.1) as a single diastereoisomer in good yield.

Scheme 4.9

Reagents and conditions: (i) (R)-CBS-Me, $\text{BH}_3\cdot\text{SMe}_2$, THF, -10°C to 0°C ; (ii) 5 mol% Pd/C, H_2 balloon, r.t., 68% over 2 steps; (iii) 10% amberlyst-15, Et_2O , molecular sieves, 80%.

Table 4.1

NMR signals ^[1]	Obtained (ppm)	Literature (ppm)
^{13}C	95.9	96.1
	64.9	65.2
	35.4	35.7
	33.0	33.3
	22.0	22.3
	19.1	19.4

^[1] NMR experiment was done in C_6D_6

The spiroketal (4.4.1) was analyzed by NMR. As listed in table 4.1, all ^{13}C NMR signals match very well with that of the literature value, suggesting the obtained product is the (*E,E*)-diastereoisomer.¹¹⁸

We then proceeded to synthesize the other natural spiroketal containing the unsymmetrical side chains. In this case, the dialdehyde intermediate will be treated with two different ylides (or phosphonates) to elongate the main skeleton. It is expected that the dialdehyde will react with the two phosphonates respectively to give rise to the diketone intermediate.

Scheme 4.10

Reagents and conditions: (i) LiAlH₄, Et₂O, 0°C, quantitative; (ii) oxalyl chloride, DMSO, Et₃N, CH₂Cl₂; (iii) (4.7.3), (4.10.2), CH₂Cl₂, trace amount.

For the unsymmetrical model, we used one ylid (4.10.2) in excess of the other (4.7.3), hoping to drive the statistics of the olefination reaction. To our great disappointment, the reaction was sluggish. With stepwise addition of the ylids (Table 4.2), the desired unsaturated ketone (4.10.4) was only obtained in trace amount along with many other by products including the half reacted ketone (4.10.3) and double olefination product (4.10.5).

Table 4.2

Entry	eq. of diol (4.10.1)	eq. of ylid (4.7.3)	eq. of ylid (4.10.2)	Result
1 ^[1]	1	1	2	Trace amount of (4.10.4) and (4.10.5)
2 ^[2]	2	1	2	Formation of (4.10.3) and trace amount of (4.10.4)

^[1] Ylid (4.7.3) was added followed by (4.10.2)

^[2] Ylid (4.10.2) was added first then (4.7.3)

Furthermore, it was difficult to separate the by-product from the desired product using flash chromatography due to their similar polarities. Changing the equivalents of the ylids (Table

4.1, entry 2), or using excess of the diol (4.10.1), also did not help to improve the results. Considering the great difficulty in performing this bidirectional elongation of the unsymmetrical unsaturated ketone which will be the key intermediate in our real molecule synthesis, we decided to turn to approach B.

4.2.2 Approach B:

Retrosynthetic analysis

Scheme 4.11

In approach B, disconnection of the O-C-O system leads to a propargylic triol (4.11.1) with which we plan to perform the transition metal catalyzed spiroketalization. Further disconnection at the propargylic position leads to (i) fragment A, a terminal alkyne (4.11.2), which takes direction to sulfone (4.11.4) and epoxide (4.11.6); (ii) fragment B, a thioester or the corresponding aldehyde (4.11.3).

Aponick and co-workers studied the dehydrative cyclization of monopropargylic triols to

form unsaturated spiroketals using $\text{Au}[\text{P}(t\text{-Bu})_2(o\text{-biphenyl})\text{Cl}]/\text{AgOTf}$ in THF.⁸⁸ The reaction was found to be rapid, high yielding and highly selective.

Scheme 4.12

Whereas Pt catalyzed dihydroalkoxylation of alkyne diols can lead to the formation of a mixture of spiroketals resulting from either 6-*endo* or 5-*exo* attack,⁹⁵ cyclization of monopropargylic triols were found to be highly regioselective as the propargylic hydroxyl group drives the regioselectivity. There the olefin would be precisely placed (scheme 4.14), leaving no ambiguity in the sizes of the rings formed.

Scheme 4.13

A plausible catalytic cycle is illustrated in Scheme 4.14. In pathway A, intermediate (4.13.1) is formed by complexation with the gold complex. Nucleophilic addition of the pendent C9 hydroxy group followed by water elimination gives rise to cyclic alkoxyallene (4.13.3) which leads to intermediate (4.13.4) after electrophilic addition. Subsequent addition of the C-1 hydroxyl group to the oxocarbenium ion affords the product via (4.23.5). Alternatively, the

C1 hydroxyl group attacks first to give intermediate (4.13.7), which can undergo proton transfer to provide β -hydroxy Au complex (4.13.8). Subsequent elimination followed by cyclization resulting from attack by the other hydroxyl group provided the product after deprotonation. Control experiments suggested both pathways are operative in the catalytic cycle.

This Au-catalyzed cyclization is carried out in mild conditions, allowing high tolerance of functional groups. Moreover, the cyclisation precursor is relatively easy to prepare using different approaches and the double bond inside the spiroketal unit can be easily removed by hydrogenation. We were inspired by this method and decided to use it as the key step in our synthesis of the spiroketal fragment of bistramide D. Moreover, we anticipate that the involvement of an alkyne intermediate would simplify the synthesis.

Model Study Of Approach B:

Proposed synthesis:

To test the feasibility of the Au-catalyzed spiroketalization, a model study was carried out using a simplified alkyne partner (4.14.1). The proposed synthesis is illustrated in Scheme 4.14.

Scheme 4.14

The first challenge was the construction of fragment B in an expeditious fashion. We opted to employ the Evans aldol reaction to establish the two chiral centers in a *syn* relationship. Chiral auxiliary-mediated asymmetric aldol additions have been studied extensively and have become one of the most valuable tools for asymmetric carbon-carbon bond formation.¹¹⁹ In particular, boron enolates of acyl oxazolidinones, pioneered by Evans, are highly effective for *syn*-addition.¹²⁰ However, boron reagent such as $\text{Bu}_2\text{B}(\text{OTf})$ is unstable and causes difficulty in reproducibility. It was later discovered that tetrachlorotitanium enolates can also participate in highly selective aldol reactions. The stereoselectivity in these reactions has been found to be highly comparable to that of the analogous boron-mediated processes. Moreover, the yields of *syn* aldol adducts are often higher with the chlorotitanium enolates.¹²¹

Scheme 4.15

It was noted the stereoselectivity of the titanium reactions is modestly dependent on the structure of the amine base. Experimental results suggest that these enolates probably exist as aggregated complexes with the amine closely through ion pairing. Depending on the substrate, several amine bases such as, Et_3N , $i\text{-Pr}_2\text{NEt}$ and TMEDA have been employed in the tetrachlorotitanium mediated asymmetric aldol addition.

A steric model for the auxiliary-based asymmetric aldol reaction is illustrated in Scheme 4.16. The stereocontrol arises from the favored transition state (4.16.3) where the small hydrogen (as opposed to the benzyl group) is projected towards the sterically demanding centre of the transition state.

Scheme 4.16¹²²

For the coupling of the thiol ester (4.11.3) with 1-alkyne (4.14.1), we planned to employ the palladium-catalyzed coupling protocol reported by Fukuyama and co-workers.¹²³ Conventional methods for making α,β -acetylenic ketones would involve the use of metal acetylides with carboxylic acid derivatives¹²⁴ or palladium-catalyzed coupling of acyl halides with terminal alkynes in the presence of copper(I) and amines.¹²⁵ However, these protocols have limitations in terms of functional group tolerance since they require the use of strongly basic or acidic conditions for generating acid halides. In 2003, Fukuyama and colleagues reported a mild and general method for synthesizing α,β -acetylenic ketones by palladium-mediated coupling of thiol esters with 1-alkynes.

Scheme 4.17

In the presence of $[\text{PdCl}_2(\text{dppf})]$, $\text{P}(2\text{-furyl})_3$ and CuI , various thiol esters and terminal alkynes can couple together to give the desired ynone product (4.17.3) in moderate to

excellent yield. The reaction was found to be highly chemoselective and can be applied to thiol esters containing aromatic bromides and ketones with functionalized terminal acetylenes. It was speculated that the reaction pathway probably involves transmetalation between an acylpalladium species and the cuprous acetylide.

Synthesis of fragment B:

For the formation of the chlorotitanium enolate, we decided to use the same oxazolidinone that has been employed in the synthesis of the THP fragment. This Evans auxiliary can be readily prepared from the commercially available L-phenyl alanine on a multi-gram scale. The aldol adducts are easily removed and can be directly converted to a thioester or aldehyde.

Scheme 4.18

Reagents and conditions: (i) NaBH₄, BF₃·Et₂O, 0°C, quantitative; (ii) diethyl carbonate, K₂CO₃, 150°C, quantitative; (iii) propionyl chloride, *n*-BuLi, THF, -78°C, 93%.

Synthesis of the aldehyde partner is shown in Scheme 4.19. The method was previously used in this lab for Swainsonine.¹²⁶ Ring-opening of THF in the presence of NaI led to the iodo ester (4.19.3) in quantitative yield.¹²⁷ Subsequent azide conversion and LiOH mediated hydrolysis gave rise to the azide alcohol (4.19.5), which could be easily oxidized to aldehyde (4.19.5) when needed. The route is economical and easily handled, providing the desired substrate in large scale with excellent yield.

Scheme 4.19

Reagents and conditions: (i) NaI, acetonitrile, quantitative; (ii) NaN₃, DMF, 85%; (iii) LiOH, THF/H₂O/MeOH, 83%; (iv) IBX, DMSO, 79%.

The Evans aldol reaction was carried out with several amine bases under different conditions.

TiCl₄ was used in all cases due to the ease of handling as well as high stability.

Scheme 4.20

Table 4.3

Entry	Enolization	Addition (eq. of aldehyde)	Yield ^[1]	d.r. ^[2]
1	TiCl ₄ ^[3] (1.1 eq), Et ₃ N (1.2 eq), 0°C	-78°C, 1.5 h (1.2 eq)	trace	N.A.
2	TiCl ₄ (1.1 eq), i-Pr ₂ NEt (1.2 eq), 0°C	-78°C, 1.5 h (1.2 eq)	40%	92:8
3	TiCl ₄ (1.1 eq), i-Pr ₂ NEt (1.2 eq), 0°C	-78°C to 0°C, 1.5 h (1.2 eq)	60%	91:9
4	TiCl ₄ (1.1 eq), TMEDA (1.2 eq), 0°C	-78°C, 1.5 h (1.2 eq)	46%	96:4
5	TiCl ₄ (2 eq), TMEDA (2 eq), 0°C	-78°C to 0°C, 3 h (2 eq)	65%	96:4

^[1] Combined isolated yield of all diastereomers

^[2] Diastereoselectivity was determined by ¹H NMR spectroscopy

^[3] TiCl₄ used as 1M solution in toluene

The desired Evans aldol reaction between oxazolidinone (4.18.4) and aldehyde (4.11.5) did

not occur in the presence of TiCl_4 and Et_3N , however, it proceeded smoothly with *i*- Pr_2NEt and TMEDA as the bases. The yield was found to be highly dependent on the temperature. When the addition temperature was increased from -78°C to 0°C , the yield improved significantly (entry 2 vs 3, entry 4 vs 5). The diastereoselectivity was determined by ^1H NMR spectroscopy and comparing with that of Evans' result. The same oxazolidinone has been used by Evans *et al* in the aldol reaction with isobutyraldehyde where the *syn* adduct was isolated as the major product.¹²¹ In agreement with Evans' results, the diastereoselectivity is modestly dependent on the amine base. As for our model, TMEDA gave a better d.r. than *i*- Pr_2NEt , probably due to a chelation effect. Moreover, the stereoselectivity was not affected greatly by the change of reaction temperature or the number of equivalents used of the amine base.

Having established the optimal conditions for the *syn* adduct, we continued our synthesis by protecting the free alcohol with a TBS group using TBSOTf and 2,6-lutidine. This protocol seemed to be much more effective in protecting secondary alcohols in comparison to the usual TBSCl and imidazole combination. The auxiliary was subsequently cleaved and converted to thio ester (4.21.2) using *n*-BuLi and ethanethiol. It is noteworthy that this conversion is highly sensitive to the reaction temperature. If too low (-78°C throughout), incomplete reaction would result; if the temperature was elevated to 0°C , a large amount of an unknown impurity was formed. The best conditions were to carry out the deprotonation and addition at -78°C then slowly warming the mixture to -40°C and quenching the reaction at the same temperature to give the desired thio ester as the only product in excellent yield. The following Zn mediated azide reduction and amine protection with trifluoroacetic anhydride proceeded smoothly to afford the intermediate (4.21.4) in 75% yield over two steps. The trifluoroacetyl group was chosen as the protecting group since it is robust to acidic conditions but can be easily cleaved under basic conditions. The quartet at around $\delta = 155$

ppm in ^{13}C NMR confirmed the success of the protection as the carbon next to the carbonyl couples to the three fluorine atoms.

Scheme 4.21

Reagents and conditions: (i) lutidine, TBSOTf, CH_2Cl_2 , 0°C , quantitative; (ii) *n*-BuLi, EtSH, THF, -78°C to -40°C , 95%; (iii) Zn, acetic acid, THF, r.t.; (iv) $(\text{CF}_3\text{CO})_2\text{O}$, Et_3N , CH_2Cl_2 , 0°C , 75% over 2 steps.

With the thiol ester in hand, we attempted to carry out the subsequent coupling reaction according to Fukuyama's procedure. We decided to use the commercially available 5-hexyn-1-ol as a model. The alcohol was protected as a TBS group then subjected to the coupling conditions.

Scheme 4.22

Reagents and conditions: (i) (4.22.1) (2 eq.), $\text{PdCl}_2(\text{dppf})$ (0.1 eq.), $\text{P}(2\text{-furyl})_3$ (0.25 eq.), CuI (1.7 eq.), DMF- Et_3N , 50°C , 0%; (ii) (4.22.1) (2 eq.), $\text{PdCl}_2(\text{dppf})$ (0.2 eq.), $\text{P}(2\text{-furyl})_3$ (0.5 eq.), CuI (2.5 eq.), DMF- Et_3N , 50°C , 0%; (iii) (4.22.1) (2 eq.), $\text{Pd}_2(\text{dba})_3$ (0.2 eq.), $\text{P}(2\text{-furyl})_3$ (0.25 eq.), CuI (2.5 eq.), DMF- Et_3N , 50°C , 0%.

furyl)₃ (0.5 eq.), CuI (2.5 eq.), DMF-Et₃N, 50°C, 0%.

To our disappointment, the coupling reaction did not occur under the conditions described by Fukuyama. Changing the Pd catalyst or increasing the loading of catalyst and ligands did not help to improve the situation. Both starting materials were recovered even after a prolonged reaction time. Since no competitive Glaser coupling was observed, the inactivity is probably due to the steric hindrance around the thioester and not due to contamination of oxygen.

Alternatively, we can convert fragment B into an aldehyde then carry out an alkylation with the lithio or other organo-metallic derivative of the terminal alkyne. There are many possible ways to inter-convert between aldehydes and other functional groups. However, mild conditions would be desirable since our substrate is prone to epimerization. We tested several methods and the results are summarized in table 4.4.

Scheme 4.23

Table 4.4

Entry	Starting material	Reagents	Conditions	Yield	Racemization ^[1]
1	(4.21.1)	DIBAL	CH ₂ Cl ₂ , -78°C	20% messy	Partially
2	(4.21.1)	Et ₃ SiH, 	Toluene, r.t.	0% ^[2]	N.A.
3	(4.21.2)	DIBAL	CH ₂ Cl ₂ , -78°C	40%	Partially
4	(4.21.2)	Et ₃ SiH, Pd/C	CH ₂ Cl ₂ , r.t.	10% ^[2]	No
5	(4.21.2)	Et ₃ SiH, Pd/C, MgSO ₄	CH ₂ Cl ₂ , r.t.	86%	No

^[1] Racemization determined by ¹H NMR spectroscopy

^[2] Starting material recovered

We first attempted the direct conversion of the oxazolidinone (4.21.1) to the corresponding aldehyde (4.23.1). The reaction was found to be very sluggish with use of 1 equivalent of DIBAL at -78°C , giving the aldehyde in only 20% yield with partial epimerization observed by ^1H NMR spectroscopy. Two singlets, which correspond to the carbonyl proton, are present at $\delta = 9.8$ ppm with integral of 1:0.4. We then tested a catalytic reduction mediated by a borane complex and triethyl silane.¹²⁸ This combination has been found to be able to convert esters to aldehydes without over reducing. Moreover, the milder reaction conditions might slim down the possibility of epimerization. Unfortunately, the catalytic system was not active for our substrate and overnight treatment only led to the recovery of starting material.

We then moved on to investigate the conversion of thiol ester (4.21.4) to aldehyde (4.23.2). Again, reaction with DIBAL at low temperature led to low yield and epimerization. We suspect that the low yield is probably due to the presence of the acidic proton on the nitrogen which might inactivate DIBAL. However, increasing the number of equivalents of the reducing agent did not improve the yield, but resulted in more epimerization.

Scheme 4.24

Having realized the sensitivity of our substrate towards epimerization, we turned to a much milder system involving the use of triethylsilane and a catalytic amount of Pd on carbon. Originally reported by Fukuyama and co-workers, this essentially neutral reduction method has been found suitable for the conversion of optically active amino acids to amino aldehyde derivatives, which are known to racemize even under mild conditions.¹²⁹ The versatility and the exceptionally high chemoselectivity of this reaction system have been demonstrated in the total synthesis of a number of complex natural products.¹³⁰

Scheme 4.25¹³¹

The proposed mechanism involves initial oxidative addition of Pd(0) to form the acylpalladium species (4.25.2) which then undergoes transmetalation with Et₃SiH. Reductive elimination of the resulting hydride (4.25.5) gives rise to the corresponding aldehyde (4.25.6) and the regeneration of the Pd(0) species.

We carried out our initial trial using 5 mol% of Pd/C and 3 eq. of Et₃SiH in CH₂Cl₂. Surprisingly, the reaction was very slow and the consumption of the starting thiol ester stopped after some point. After 48 h, the desired aldehyde was obtained in only 10% yield. It later came to our attention that it was mentioned in Fukuyama's unpublished work that such a problem can be solved by introducing anhydrous MgSO₄ to the reaction mixture.¹³¹⁻¹³² Gratifyingly, when we used 2 eq. of MgSO₄ with 5 mol% of Pd/C and 0.5M of thiol ester (4.21.4) in CH₂Cl₂, the reaction proceeded nicely to provide the desired aldehyde (4.23.2) in excellent yield. More importantly, the product was obtained without epimerization even after a prolonged reaction time. However, the role of MgSO₄ remains unknown. Nevertheless, we have established an efficient synthesis for fragment B.

The subsequent coupling of the TBS protected alkyne alcohol (4.22.1) with fragment B (4.23.1) proceeded smoothly to yield propargylic triol (4.24.1 a/b) as a 1:1 mixture of two diastereoisomers. An excellent yield of 83% was obtained for this step in the model study.

Excess alkyne (4.22.1) and *n*-BuLi were used to effect complete consumption of the aldehyde. A global deprotection was then carried out using amberlyst-15 with easy workup, to afford the cyclization precursor (4.24.2) in 87% yield.

Scheme 4.26

Reagents and conditions: (i) *n*-BuLi, THF, 83%; (ii) amberlyst-15, MeOH, 40°C, 87%.

The final cyclization was examined using Aponick's protocol. A range of transition metals were screened.

Scheme 4.27

Table 4.5

Catalysts	Loading ^[1]	Solvent ^[2]	Rxn Temp	Rxn Time	Yield ^[3]
Ph ₃ PAuCl/AgOTf	2 mol%	THF	r.t.	overnight	35%
Ph ₃ PAuCl/AgOTf	5 mol%	THF	45°C	overnight	65%
Ph ₃ PAuCl/AgBF ₄	5 mol%	THF	45°C	overnight	Trace
Ph ₃ PAuCl/AgSbF ₆	5 mol%	THF	45°C	overnight	44%
AuCl ₃	5 mol%	THF	45°C	overnight	53%
AgOTf	5 mol%	THF	45°C	overnight	24%
PtCl ₂	5 mol%	THF	45°C	overnight	No rxn ^[4]
PtCl ₂ /COD	5 mol%	THF	45°C	overnight	No rxn ^[4]

^[1] Loading of both catalyst and co-catalyst

^[2] All reactions were done in anhydrous THF with molecular sieves

^[3] Product obtained as single diastereomer in all entries

^[4] Starting material recovered

The cyclisation proceeded with the catalyst system generated from a number of cationic gold(I) and silver additives. However, no reaction was observed when the triol was treated with Pt(II) catalyst. Interestingly, and in contrast to Aponick's result, we found that silver catalyst on its own also catalyzed the reaction, even though the yield was much poorer. Increasing the catalyst loading and reaction temperature improved the yield significantly. The best result was obtained with 5 mol% of $\text{Ph}_3\text{PAuCl/AgOTf}$ and MS 4Å in anhydrous THF at 45°C, providing the desired spiroketal in 65% yield as a single diastereoisomer. The structure was confirmed by ^1H NMR spectroscopy. The doublet at $\delta = 5.6$ ppm and the doublet of doublet at $\delta = 5.9$ ppm correspond to the double bond formed during the cyclisation process. The peaks at $\delta = 3.6$ to $\delta = 3.9$ ppm correspond to the protons at the position α to the oxygen atoms, confirming the formation of the spiroketal unit. Furthermore, the peak at $\delta = 94.2$ ppm in ^{13}C NMR confirms the presence of the acetal carbon.

During the model study, we have established an efficient synthetic route for fragment B which is also a key intermediate for the real molecule. The model spiroketal has been successfully synthesized, demonstrating the feasibility of this gold-catalyzed spiroketalisation reaction.

4.3 Synthesis of the Natural Spiroketal Fragment of Bistramide D:

4.3.1 Retrosynthetic analysis of the Bistramide D spiroketal unit:

Scheme 4.28

Based on the success of the model study, we turned our attention to the synthesis of the real spiroketal fragment of Bistramide D. Our retrosynthetic approach starts with cleavage of the two C-O bonds in the bicyclic ring, for which we planned to utilize the gold-catalyzed cyclisation. Disconnection at the propargylic position of the cyclisation precursor leads to fragment A and fragment B.

We planned to construct fragment A from sulfone (4.11.4) and TMS protected alkyne epoxide (4.11.6) using the ring opening strategy. Epoxides are versatile building blocks in organic synthesis. They demonstrate high synthetic potential due to the presence of electrophilic carbons and the nucleophilic oxygen atom. Many related synthons can be easily prepared on large scales using simple and well-established methodologies.

Fig 4.29¹³³

The nucleophilic ring opening of epoxides is a powerful tool in organic synthesis since a favorable release of ring strain energy is involved. Such reactions are usually regioselective as the nucleophiles preferably attack the less-hindered site of the three-membered ring. We have successfully demonstrated the versatility of this strategy in the synthesis of the THP fragment of Bistramide D where a hydroxyl epoxide (2.32.5) was ring opened by a sulfone fragment (2.32.6) in the presence of $\text{BF}_3 \cdot \text{OEt}_2$.

Scheme 4.30

In another example conducted by Yoon and co-workers, an epoxide (4.31.2) bearing a TMS protected terminal alkyne was ring opened using the lithio derivative of propynoate to furnish the bisalkynyl ester (4.31.3), which is the key intermediate in the synthesis of the natural product Tarchonanthulactone (4.31.5 & 4.31.6).¹³⁴

Scheme 4.31

Reagents and conditions: (i) TMSCLi, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, THF; (ii) NaOH, CH_2Cl_2 , 72% over 2 steps; (iii) LiCCCOOMe , $\text{BF}_3 \cdot \text{OEt}_2$, THF, 67%.

4.3.2 Synthesis of fragment A:

Scheme 4.32

Reagents and conditions: (i) $\text{en.LiC}\equiv\text{CH}$, DMSO, quantitative; (ii) $n\text{BuLi}$, Me_3SiCl , THF, 90%; (iii) mCPBA, CH_2Cl_2 , 0.5M NaHCO_3 , 57%; (iv) (S,S)- Co^{II} catalyst, AcOH, H_2O , 46%.

The TMS-protected alkyne epoxide (4.11.6) was prepared from the commercially available 5-bromo-1-pentene in 3 steps, including alkyne conversion, TMS protection and mCPBA mediated epoxidation. Hydrolytic kinetic resolution was then carried out to furnish the (S)-epoxide (4.11.6)¹³⁵ in 46% yield.

The sulfone fragment (4.11.4) was prepared using the same method described for (2.32.6) in chapter two.

Scheme 4.33

Reagents and conditions: (i) NaHMDS, allyl bromide, 73%; (ii) $\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$, $\text{EtOH}/\text{H}_2\text{O}$, quantitative; (iii) LiAlH_4 , Et_2O ; (iv) MsCl , Et_3N , 62% over 2 steps; (vi) NaH , *p*-thiocresol, DMF/THF , 70°C , 86%; (vii a) *n*BuLi, $\text{BF}_3 \cdot \text{OEt}_2$, THF, -78°C , 0%; (vii b) *n*BuLi, $\text{BF}_3 \cdot \text{OEt}_2$, THF, -78°C to 0°C , SM decomposed; (vii c) *n*BuLi, $\text{BF}_3 \cdot \text{THF}$, THF, -78°C , 0%.

The subsequent epoxide opening reaction was tested using *n*BuLi in the presence of the Lewis acid boron trifluoride. Surprisingly, no reaction occurred with *n*BuLi and $\text{BF}_3 \cdot \text{OEt}_2$ at -78°C and both starting materials were recovered. When we increased the temperature to 0°C , the epoxide (4.11.6) was found to slowly decompose. The same reaction was repeated with $\text{BF}_3 \cdot \text{THF}$ ¹³⁶ as the Lewis acid, but again no desired product was obtained but the sulfone fragment was recovered.

Scheme 4.34

A proposed mechanism that leads to the decomposition is illustrated in scheme 4.34. We hypothesize that in the presence of BF_3 , an intramolecular cyclisation may preferably occur to give rise to (4.34.2). The resulted cyclosilane could further react in two different pathways. Path A would lead to a cyclic allene (4.34.3) and path B would give a cyclohexyne (4.34.4). However, neither substrate can be stabilized and easily collapse and fall to decomposition. Considering the problem caused by alkynyl silane, we decided to turn to an epoxy chloride, so change the order to introduce the alkyne functionality at a later stage.

Scheme 4.35(a)

Reagents and conditions: (i) SOCl_2 , pyridine, CH_2Cl_2 , quantitative; (ii) mCPBA, CH_2Cl_2 , 0°C to r.t., quantitative; (iii) (S,S)- Co^{II} catalyst, AcOH, H_2O , 41%, 99% e.e.; (iv) $n\text{BuLi}$, (4.11.4), $\text{BF}_3\cdot\text{OEt}_2$, 85%.

The non-racemic epoxy chloride (4.35.4) was prepared from 4-penten-1-ol through chlorination by SO_2Cl and mCPBA mediated epoxidation. The racemic epoxide was subjected to hydrolytic kinetic resolution under Jacobsen's conditions.¹³⁷ The enantiomeric excess of the epoxide was measured by performing a derivatization using *p*-thiocresol.

Scheme 4.35(b)

Table 4.6

Entry	Conditions ^[1]	Yield	e.e. ^[2]
1	(<i>S,S</i>)-Co(II)(salen) (0.5 mol%), 16 h	48%	32%
2	(<i>S,S</i>)-Co(II)(salen) (1.2 mol%), 43 h	41%	99%

^[1] All reactions were done in THF with AcOH and H_2O

^[2] ee were determined by chiral HPLC on chiralcel OD-H column

Figure 4.35(c)

Figure 4.35(d)

The kinetic resolution was analyzed at different time intervals. The resolved epoxides were then ring opened using *p*-thiocresol and subjected to e.e. measurement by chiral HPLC. The best result was obtained at 43 hr, giving the desired chiral epoxide in 41% yield with 99% e.e. The vital epoxide opening reaction was carried out with the lithio derivative of sulfone (4.11.4) in the presence of $\text{BF}_3 \cdot \text{OEt}_2$. Gratifyingly, the reaction proceeded smoothly in THF at -78°C to afford the alcohol (4.35.5) as a diastereoisomeric mixture in excellent yield. Furthermore, the reaction was quenched at low temperature, so tetrahydrofuran was not formed by substitution of the chloride.

Scheme 4.36

Reagents and conditions: (i) 3,4-Dihydro-2*H*-pyran, amberlyst-15, CH_2Cl_2 , 86%; (ii) Mg, TMEDA, MeOH, 79%; (iii) NaI, NaHCO_3 , $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$, acetone; (iv) *n*BuLi, TMS-acetylene, THF/DMPU, 76% over 2 steps; (v) K_2CO_3 , MeOH, 84%.

The alcohol (4.35.5) was subsequently protected as a THP ether then subjected to Mg/MeOH mediated desulphonylation and a subsequent Finkelstein reaction to afford the iodide (4.36.3). NaHCO₃ and Na₂S₂O₃ were added as buffers to quench any HI and I₂ that might form during the reaction. THP ring was chosen as the protecting group due to its stability towards basic conditions and strong nucleophiles, despite the complexity it brings to the NMR analysis. The following displacement of iodide was carried out in THF and DMPU. DMPU (*N, N'*-dimethyl-*N, N'*-propylene urea) is shown to exhibit unique properties as a dipolar aprotic solvent and has been used as a safe substitute of the carcinogenic HMPT (hexamethylphosphoric triamide) as a cosolvent in diverse types of reactions.¹³⁸ The substituted alkyne could then undergo deprotection to provide fragment A (4.36.5) in 84% yield.

4.3.2 Synthesis of spiroketal unit

Having established the synthetic routes for both fragment A and fragment B, we proceeded to couple the two parts together. As in the model study, fragment B could easily react with the TBS protected 5-hexyn-1-ol using *n*BuLi to afford the propargylic alcohol. We decided to apply the same conditions for the synthesis of the real molecule.

Scheme 4.37

Table 4.7

Entry	Base	Solvent	Temp.	Yield of (4.37.1)	Yield of (4.37.2)
1	<i>n</i> BuLi	THF	-78°C	22%	5%
2	<i>n</i> BuLi	THF	-78°C to -40°C	31%	12%
3	<i>n</i> BuLi	THF/DMPU	-78°C	trace	50%
4	LiHMDS	THF	-78°C to -40°C	34%	9%

Unexpectedly, the reaction of the acetylide (4.36.4) with the aldehyde (4.11.3) turned out to be sluggish. With *n*BuLi in THF, the desired product was only obtained in 22% yield accompanied by a side product (4.37.2) resulting from elimination reaction of the aldehyde fragment. The side reaction is probably induced by the strong base, leading to a stabilized conjugated system (4.37.2), which structure was confirmed by ¹H NMR. First of all, the aldehyde peak shifted from $\delta = 9.7$ ppm to $\delta = 9.4$ ppm; secondarily, a new triplet appeared at about $\delta = 6.5$ ppm, corresponding to the olefinic proton H_b; thirdly, the previous methylene peak, which appears as a doublet at $\delta = 1.2$ ppm, is now replaced by a singlet at $\delta = 1.7$ ppm, shifting down field due to H_c which is now at the allylic position.

Scheme 4.38

Several variations were examined and summarized in table 4.7. Increasing the temperature seemed to improve the yield slightly, however, this led to more side product as well. Use of DMPU as a co-solvent resulted in no desired product but a significant increase in the amount of side product obtained. Lastly, with the bulkier base LiHMDS, it was still impossible to prevent the formation of the side product.

The problem could come from either the deprotonation or the nucleophilic addition step. The experimental results suggest that the deprotonation step is exceptionally slow hence the unreacted *n*BuLi attacks the aldehyde instead. To further investigate the problem, we decided

to study the deprotonation in more details. A series of deuteration experiments were performed. The alkyne was deprotonated under various conditions (eg. different base, temperature, time) then quenched with D₂O and subjected to NMR analysis, looking for reduction of the size of the signal at $\delta = 1.8$ ppm.

Scheme 4.39

Table 4.8

Entry	Base	Temp.	Deprotonation time	Percentage of deprotonation
1	LiHMDS	-78°C	2 h	34%
2	LiHMDS	-78°C to 0°C	40 min	70%
3	<i>n</i> BuLi	-78°C	2 h	38%
3	<i>n</i> BuLi	-78°C to 0°C	40 min	78%
4	<i>n</i> BuLi	-78°C to 0°C	2 h	91%

The deuteration experiments suggested that deprotonation of fragment A using either LiHMDS or *n*BuLi was somehow very inefficient, especially at low temperature. Degree of deprotonation is positively correlated to the temperature and reaction time. Moreover, *n*BuLi seems to be more effective in deprotonating the alkyne compared to LiHMDS. A satisfactory deprotonation required stirring with *n*BuLi at 0°C for as long as 2 hours. This is remarkable compared to normal alkynes for which the metallations with the various basic reagents are extremely fast, even at very low temperatures¹³⁹ (eg. deprotonation of butyne in the THP chapter). Based on these observations, we hypothesized that fragment A may adopt a folded conformation in a polar solvent such as THF, hence the acidic proton is shielded from the base. Such molecular conformation apparently has significant influence on the course of the reaction. To test our hypothesis, we carried out the same reaction using a non-polar solvent.

Scheme 4.40

Reagents and conditions: (i) *n*BuLi, toluene, -78°C to -40°C, 67%.

To our great delight, when we switched the solvent to toluene, the desired propargylic alcohol (4.37.1) formed smoothly in 67% yield and no elimination of the aldehyde was observed even when the temperature was raised to -40°C. Excess alkyne and base were used to ensure completion of the reaction. In addition, the result was reproducible from small scale (eg. 0.1 mmol) to relatively large scale (eg. 1 mmol).

To gain an insight of this interesting phenomenon and to further confirm our hypothesis, a series of NOE experiments were carried out on fragment A using different solvents.

The nuclear overhauser effect (NOE) is a phenomenon observed by NMR spectroscopy. It measures the transfer of nuclear spin polarization from one nucleus to another. NOE occurs through space but not through chemical bonds hence atoms which are in close proximity to each other can give a NOE signal. The inter-atomic distance derived from an NOE experiment can help one to determine the precise molecular conformation.

We ran the NOE experiment in a polar solvent (d⁸-THF) and a non-polar solvent (C₆D₆) by irradiating the characteristic protons peaks.

Fig 4.41

In d^8 THF, when the olefinic protons H_a and H_b were irradiated (Figure 4.42), NOE enhancements could be observed for the THP and the propargylic proton H_d . Hence the double bond is in close proximity to both the THP ring and the terminal alkyne, suggesting the molecule must be in a folded conformation.

Figure 4.42

Similarly, when the THP proton H_c was irradiated (Figure 4.43), NOE enhancement can be seen for H_a/H_b and the propargylic H_d .

Figure 4.43

On the other hand, when the experiment was run in the non-polar d_6 benzene, quite different spectra were obtained. As shown in Figure 4.44, when the double bond signals were irradiated, no obvious NOE enhancement can be observed for the THP moiety or the terminal alkyne, indicating the molecule is in an extended conformation.

Figure 4.44

When the THP proton H_c was irradiated (Figure 4.45), NOE enhancement can only be seen for the nearby H_e but not for the olefin or the terminal alkyne protons.

Figure 4.45

The NOE experiment has clearly shown that fragment A tends to adapt a folded conformation in polar solvent and an extended conformation in non-polar solvent. Unlike in model, one end of the long chain probably hinders the other hence deprotonation of the terminal alkyne are difficult. However, the reason for such phenomenon is still unknown.

Nevertheless, an efficient synthesis for the propargylic triol (4.37.1) has been established. We moved forward and carried out a global deprotection, affording the cyclisation precursor in 88% yield.

Scheme 4.46a

Reagents and conditions: (i) amberlyst-15, MeOH, 43°C, 88%; (ii) 5 mol% AuCl(PPh₃), 5 mol% AgOTf, 4 Å MS, THF, 45°C, 68%; (iii) 5 mol% Au[P(*t*-Bu)₂(*o*-biphenyl)]Cl, 5 mol%

AgOTf, 4Å MS, THF, 45°C, 84%.

As anticipated, the key cyclisation step proceeded nicely with 5 mol% of AgCl(PPh₃)/AgOTf to yield the desired spiroketal (4.46.2) as a single diastereoisomer in 68% yield. To further improve the yield, we also tried a more complex catalyst, Au[P(*t*-Bu)₂(*o*-biphyl)]Cl (4.46.3) that has been used in Aponick's work.

The ligand used in catalyst (4.46.3) was first introduced by Buchwald, and named Johnphos.¹⁴⁰ The biphenyl moiety in these ligands have a significant effect as the second aryl ring, twisted at an angle to the first ring, may affect the metal directly by coordination.¹⁴¹

Scheme 4.46b

In particular, the Johnphos types of ligands have been widely studied by Echavarren *et al.* in gold catalysis for their ability in effecting various C–C, C–N, and C–O bond formations.¹⁴²

In agreement with Aponick's result, a better yield of 84% can be obtained when we switched to Au[P(*t*-Bu)₂(*o*-biphyl)]Cl (4.46.3). Moreover, the reaction time can be shortened to 1 hr. Gentle heating was applied to ensure a satisfactory result.

The mono-unsaturated spiroketal (4.46.3) was then taken for regio-selective hydrogenation mediated by Wilkinson's catalyst. The complex RhCl(PPh₃)₃ was the first active homogeneous hydrogenation catalyst. It is well known for its great compatibility with a range of functional groups since the mechanism does not involve hydride transfer.

Scheme 4.47

The rate of the Wilkinson's catalyst mediated hydrogenation depends on the steric environment of an olefin as well as the degree of substitution of the C=C bond. Compared to heterogeneous hydrogenation catalysts such as Pd/C, Wilkinson's catalyst shows high site selectivity where the least sterically hindered double bond will be preferentially hydrogenated. In an example demonstrated by Fisher *et al*, the highly effective antiparasitic agent, ivermectin, was derived from avermectin B₁ via selective hydrogenation using Wilkinson's catalyst.^{76b} The double bond within the spiroketal ring, which is the only *cis* substituted olefin in the molecule, was selectively hydrogenated using Wilkinson's catalyst under 1.1 atm of hydrogen to furnish ivermectin in 85% yield.

Scheme 4.48

Reagents and conditions: (i) 1.1 atm H₂, Rh(PPh₃)Cl, toluene, r.t., 20 h, 85%.

For our target molecule, it was anticipated that the olefin in the spiroketal ring would undergo selective hydrogenation since (a) it is a *cis* alkene and (b) it is more strained compared to the other olefin on the side chain.

Scheme 4.49

Table 4.9

Entry	Catalyst loading	Condtions ^[1]	Duration	Result
1	10 mol%	Toluene, r.t., 1 atm H ₂	3 h	(1) Reaction complete (2) Over hydrogenation occurred ^[2]
2	4 mol%	Toluene, r.t., 1 atm H ₂	overnight	(1) Reaction incomplete (2) Less over hydrogenation ^[2]

^[1] H₂ balloon was used

^[2] Over hydrogenation observed by ¹H NMR spectroscopy

Unfortunately, the hydrogenation did not proceed as expected. With 10 mol% of Wilkinson's catalyst and a H₂ balloon, the targeted olefin was hydrogenated in 3 h, however, over hydrogenation on the side chain was also observed and the two products are inseparable. When the catalyst loading was reduced to 4 mol%, incomplete reaction resulted even after overnight stirring.

At this stage, how to differentiate of the two olefins had become a formidable challenge. After careful consideration, we decided to employ dihydroxylation.¹⁴³ The oxidative functionalization of double bonds is of great importance for organic synthesis since the product 1, 2-diols can be used in a wide variety of applications. In general, dihydroxylations of olefins can be catalyzed by osmium, ruthenium or manganese oxo species.¹⁴⁴ Among these

methods, the osmium-catalyzed variant is the most reliable and efficient protocol for the preparation of *cis*-1,2-diols. In particular, Tsuji's modification using $\text{K}_3[\text{Fe}(\text{CN})_6]$ as the cooxidant allows dramatic reduction of the amount of the highly toxic and expensive OsO_4 needed.¹⁴⁵ The modified protocol has also been found active to prevent overoxidation or inertness towards hindered olefins. Furthermore, OsO_4 is an electrophilic reagent and reacts only slowly with electron deficient alkenes. Therefore, the Osmium catalyst system displays regio selectivity toward electron rich olefins.

Scheme 4.50

McDonald *et al.* have demonstrated the utility of this method in a convergent synthesis of Fostriecin.¹⁴⁶ As illustrated in Fig 4.51, the allylic ester characteristic of the lactone (4.51.2) deactivates the C6-C7 alkene. Therefore, the C8-C9 alkene underwent preferential dihydroxylation using $\text{K}_2\text{OsO}_2(\text{OH})_4$, $\text{K}_3\text{Fe}(\text{CN})_6$, K_2CO_3 and the monomeric ligand DHQD-4-MEQ, providing diol (4.51.3) as the major product.

Scheme 4.51

In the case of our spiroketal fragment (4.46.2), we surmised that the cyclic olefin should be more electron deficient owing to its proximity to the two electron-withdrawing oxygen atoms. Hence oxidation of the other olefin on the side chain should be favored. Moreover, the diol will later be cleaved and converted to an aldehyde, therefore the stereochemical course of the dihydroxylation is not an issue.

We were delighted to find that Tsuji's dihydroxylation procedure ultimately provided great chemoselectivity, giving the desired diol (4.52.1) as the only product and as an inseparable mixture of diastereoisomers in 76% yield. No overoxidation occurred on the other olefin even after a prolonged reaction time.

Scheme 4.52

Reagents and conditions: (i) $\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}$, $\text{K}_3\text{Fe}(\text{CN})$, K_2CO_3 , $t\text{BuOH}/\text{H}_2\text{O}$, 76%; (ii) Pd/C , ethyl acetate, quantitative; (iii) $\text{SiO}_2\text{-NaIO}_4$, CH_2Cl_2 ; (iv) $\text{Ba}(\text{OH})_2$, (4.52.4), $\text{THF}/\text{H}_2\text{O}$, overnight, 0%; 1.5 h, 50% over two steps; (v) CH_2Cl_2 , Et_3N , overnight, 58%; (vi) diethyl phosphite, NaH , THF , 0°C , quantitative.

Subsequent hydrogenation of the cyclic alkene proceeded smoothly in the presence of 10% Pd/C under ambient pressure of hydrogen (balloon), affording intermediate (4.52.2) in quantitative yield. The diol was then subjected to oxidative cleavage using sodium periodate on silica to yield the corresponding aldehyde,¹⁴⁷ which was taken immediately for olefination. Due to the presence of the α -proton, which is prone to epimerization, we employed the $\text{Ba}(\text{OH})_2$ mediated Horner-Wadsworth-Emmons (HWE) reaction introduced by Sinisterra. $\text{Ba}(\text{OH})_2$ has proven to be a mild yet effective base for HWE olefination.¹⁴⁸ In another project

(-)-2-methyl-CBS-oxazaborolidine was used as the catalyst in all attempts.

Scheme 4.54

Table 4.10

Entry	Borane	Solvent ^[3]	Condition	Yield	Remark
1 ^[1]	Catechol borane	Toluene	-78°C, 20 hr	63% ^{[4][5]}	Product inseparable from catecholborane
2 ^[1]	BH ₃ .SMe ₂	THF	-10°C to 0°C, 1.5 hr	91%	Epimerisation occurred ^[6]
3 ^[1]	BH ₃ .SMe ₂	CH ₂ Cl ₂	-30°C, 16 hr	58% ^[4]	Reaction incomplete, but no epimerisation
4 ^[2]	BH ₃ .SMe ₂	CH ₂ Cl ₂	-30°C, 24 hr	75%	Reaction complete, no epimerisation

^[1] 0.1 eq. of (R)-(-)-2-methyl-CBS-oxazaborolidine was used

^[2] 0.2 eq. of (R)-(-)-2-methyl-CBS-oxazaborolidine was used

^[3] All solvents were used as anhydrous

^[4] Yield included catecholborane

^[5] Starting material recovered

^[6] Epimerisation determined by ¹H NMR spectroscopy

From the initial screening, we found that reaction with 0.1 eq. (*R*)-CBS catalyst and 1 eq. of catechol borane in toluene at -78°C led to an inseparable mixture of the desired product and the remaining catecholborane. When BH₃.SMe₂ was used as the borane source, the reaction proceeded rapidly in THF at -10°C to 0°C, however epimerisation was observed as the doublet at around $\delta = 6.4$ ppm changed to a multiplet. With the same borane source, when we cooled the reaction temperature to -30°C, the reaction proceeded much more slowly. But the desired product can be isolated cleanly without epimerisation. To further improve the reaction, we increased the catalyst loading to 0.2 eq. and the reaction time to 24 h. To our delight,

under this condition, the reaction can go to completion and gave the desired product as a single diastereoisomer in 75% yield.

As we expected, the final deprotection of the trifluoroacetyl group went smoothly with potassium carbonate in refluxing MeOH, affording the spiroketal fragment (4.54.2) in quantitative yield.

4.4 Conclusion:

In summary, the natural spiroketal fragment of bistramide D has been successfully synthesized from the readily available 4-penten-1-ol and an easily prepared Evans' oxazolidinone, through 14 linear steps in 8% overall yield. The epoxide ring opening, the highly diastereo-selective Evans' aldol reaction and the gold(I) catalysed dehydrative cyclization are the highlights of the synthesis.

4.5 Future work:

Firstly, to further improve the olefination step (scheme 4.52), other mild protocols, such as the Masamune-Roush modification should be further tested.¹⁵¹ The use of a milder and less nucleophilic base (eg. DBU) might help to reduce the possibility of loss of the trifluoroacetyl group.

Secondarily, finally assembling of the three fragments will also be carried out. One possibility is to couple the THP ring firstly with the amino acid linker using the Staudinger reaction.¹⁵² The spiroketal fragment can be subsequently attached via condensation. On the other hand, the spiroketal might first be coupled with the amino acid fragment, followed by Staudinger coupling with the THP fragment. Finally, a global deprotection of the BOM and Benzyl group through reduction will be carried out to accomplish the synthesis of bistramide D.

Experimental Section

General Methods

All anhydrous and oxygen sensitive reactions were carried out under an inert atmosphere of nitrogen in oven dried (120°C) glassware. Anhydrous toluene was distilled from sodium metal under nitrogen. Anhydrous THF and Et₂O were distilled from sodium metal and benzophenone under nitrogen. Acetonitrile, DMSO (under reduced pressure) and CH₂Cl₂ were distilled from CaH₂ under nitrogen. Methanol and ethanol were distilled from activated magnesium. All the other solvents and reagents were commercial and used as received.

¹H NMR spectra were recorded on Bruker Advance DPX at 300, 400, or 500 MHz or JEOL ECA 400 MHz using deuterated solvents (CDCl₃ or CD₃OD). ¹³C NMR spectra were recorded on the same instruments at 75, 100 or 125 MHz respectively. Chemical shifts are reported in δ units using CDCl₃ as an internal standard (δ 7.26 ppm ¹H, δ 77.00 ppm ¹³C). Chemical Shifts (δ) were recorded in ppm and coupling constants *J* were recorded in Hz.

Mass spectra were recorded out on a Finnigan LCQ DECA XP MAX Ultra instrument or a Finnigan Polaris Q, GCMS XP mass spectrometer. High Resolution Mass Spectroscopy (HRMS) experiments were carried on a Waters Q-ToF premier instrument.

Infrared spectra were recorded either neat, or as nujol mull on NaCl or KBr plate on a Shimadzu IR Prestige-21 FTIR or a Bruker Alpha-E FTIR.

Specific optical rotations were recorded on a Jasco-1030 polarimeter and are given with units of 10⁻¹degcm²g⁻¹. The angles of rotations were measured at wavelength of 589 nm.

Enantiomeric excess was determined by chiral HPLC analysis which was performed on a Agilent HPLC using Daicel ID column and chiralcel OD-H column, eluting with IPA/hexane. Conversion determined by HPLC was performed on a Agilent HPLC using Agilent Poroshell EC C18 column, eluting with acetonitrile and water.

Part one: Procedures for synthesis of the sulfone fragment using Hove's method:

Synthesis of (*R*)-4-benzyl-3-propionyloxazolidin-2-one (2.25.1):

n-BuLi (1.6M in hexane, 3.57 ml, 5.71 mmol) was added dropwise to a solution of the oxazolidinone (1.0 g, 5.65 mmol) in THF (19 ml) at -78°C. The mixture was stirred for 10 minutes followed by addition of propionyl chloride (0.55 ml, 6.21 mmol). The reaction mixture was stirred for 1 h at -78°C, and then quenched with sat. aq. ammonium chloride. The volatiles were evaporated and the residue was diluted with dichloromethane. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine and dried over Na₂SO₄. The solvent was evaporated *in vacuo*, the residue was purified by column chromatography (hexane: ethyl acetate = 85:15) on silica gel to give the title compound as a colourless oil (1.23 g, 93%).

¹H NMR (400MHz, CDCl₃): δ 1.21 (t, 3H, *J* = 7.36 Hz), 2.76 (dd, 1H, *J* = 13.3, 9.6 Hz), 2.87-3.02 (m, 2H), 3.32 (dd, 1H, *J* = 13.4, 3.2 Hz), 4.15-4.22 (m, 2H), 4.65-4.70 (m, 1H), 7.20-7.35 (m, 5H).

¹³C NMR (100MHz, CDCl₃): δ 8.3, 29.2, 37.9, 55.1, 66.2, 127.3, 128.9, 129.4, 135.3, 153.5, 174.1

GC-LRMS: *t_R* = 12.14 min; *m/z*: 233 [M]⁺, 204 [M-C₂H₅]⁺, 160.06, 148.06, 134.05, 91.09

Data is consistent with that of the literature.¹⁵³

Synthesis of (*R*)-4-benzyl-3-((*R*)-2-methylpent-4-enoyl)oxazolidin-2-one (2.25.2):

The literature procedure⁴⁴ was modified as follows: a solution of the imide (2.25.1) (1.0 g, 4.27 mmol, azeotropically pre-dried with anhydrous toluene) in THF (8.5 ml) was cooled down to -78°C. NaHMDS (1M solution in THF, 4.70 ml, 4.70 mmol) was then added dropwise by sliding down the flask wall. The reaction mixture was stirred for 30 minutes. Allyl bromide (1.10 ml, 12.80 mmol) was added slowly and the mixture was stirred for further 10 minutes at -78°C. The solution was allowed to warm up to -40°C and stirred overnight. The reaction mixture was quenched with sat. aq. ammonium chloride at -40°C then warmed up to room temperature. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane: ethyl acetate = 92:8) on silica gel to give the title compound as a colourless oil (854 mg, 73%).

¹H NMR (400MHz, CDCl₃): δ 1.19 (d, 3H, *J* = 6.8 Hz), 2.20-2.23 (m, 1H), 2.49-2.56 (m, 1H), 2.70 (dd, 1H, *J* = 13.3, 9.8 Hz), 3.30 (dd, 1H, *J* = 13.3, 3.2 Hz), 3.84-3.89 (m, 1H), 4.16-4.21 (m, 2H), 4.65-4.71 (m, 1H), 5.05-5.13 (m, 2H), 5.82 (ddt, 1H, *J* = 17.1, 10.2, 7.0 Hz, 1H), 7.21-7.35 (m, 5H).

¹³C NMR (100MHz, CDCl₃): δ 16.4, 37.1, 38.0, 38.1, 55.4, 66.0, 117.2, 127.3, 128.9, 129.4, 135.2, 135.3, 153.1, 176.5

GC-LRMS: *t_R*=13.39 min; *m/z*: 273 [M]⁺, 244 [M-C₂H₅]⁺, 182, 178 [M-

$\text{COCHCH}_3\text{CH}_2\text{C}_2\text{H}_5]^+$, 117, 97 $[\text{COCHCH}_3\text{CH}_2\text{C}_2\text{H}_5]^+$.

Synthesis of (R)-4-benzyl-3-((R,E)-2-methylpent-3-enoyl)oxazolidin-2-one (2.25.3):⁴⁴

The allylated imide (2.25.2) (854 mg, 3.13 mmol) was placed in a round bottom flask and the system was purged with nitrogen gas. Into the flask was added a solution of $\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$ (17 mg, 0.078 mmol) in ethanol (5 ml) and distilled water (0.45 ml). The reaction mixture was heated to 80°C for 7.5 h. Upon completion of the reaction, most of the organic volatiles were removed under reduced pressure. The residue was diluted with ethyl acetate and washed with water. The solvent was evaporated *in vacuo* to give the crude product as a brown oil which was used directly in the next step without further purification (850 mg, quantitative).

^1H NMR (400MHz, CDCl_3): δ 1.27 (d, 3H, $J=6.84$ Hz), 1.72 (d, 3H, $J=6.44$ Hz), 2.77 (dd, 1H, $J=13.5, 9.2$ Hz), 3.23 (dd, 1H, $J=13.4, 3.3$ Hz), 4.14-4.22 (m, 1H), 4.42-4.45 (m, 1H), 4.66-4.69 (m, 1H), 5.57-5.74 (m, 2H), 7.19-7.28 (m, 5H).

^{13}C NMR (100MHz, CDCl_3): δ 17.2, 18.0, 37.7, 40.5, 55.1, 65.9, 127.3, 127.8, 128.8, 129.5, 129.6, 135.2, 152.9, 175.2.

HRMS: m/z calculated for $\text{C}_{16}\text{H}_{19}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 274.1443 found: 274.1441

GC-LRMS: $t_R=13.51$ min; m/z : 273 $[\text{M}]^+$, 244 $[\text{M}-\text{C}_2\text{H}_5]^+$, 174, 117, 96 $[\text{COCHCH}_3\text{C}_2\text{H}_2\text{CH}_3]^+$

IR: 3028, 2976, 1771, 1694, 1454, 1360, 1211, 976 cm^{-1} .

$[\alpha]_D^{22} = -18.1$ (CHCl_3 , $c = 1.4$).

Synthesis of (*R,E*)-2-methylpent-3-en-1-ol (2.25.4):

LiAlH₄ (38 mg, 1.0 mmol) was added in two portions to a mixture of the imide (2.25.3) (136 mg, 0.50 mmol) in anhydrous ether (4ml) at 0°C. The mixture was stirred for 2 h then water was added until effervescence cease. The solution was filtered through celite and taken directly into next step.

Synthesis of (*R,E*)-2-methylpent-3-enyl methanesulfonate (2.25.5):

Dry dichloromethane (4 ml) was added to a solution of the alkene alcohol (2.25.4) in ether. The solution was cooled to 0°C. Et₃N (139.12 µl, 1.0 mmol) was added, followed by methanesulfonyl chloride (77 µl, 1.0 mmol) dropwise. A white precipitate was formed and the mixture was stirred at 0°C for 2 h. The reaction was quenched with water and satd. aq. NH₄Cl solution. The organic layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over anhydrous MgSO₄ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexane: ethyl acetate = 95:5) on silica gel to give the title compound as a colourless oil (55 mg, 62% over 3 steps).

¹H NMR (400MHz, CDCl₃): δ 1.05 (d, 3H, *J* = 6.7 Hz), 1.66 (d, 3H, *J* = 6.2 Hz), 2.51-2.58

(m, 1H), 2.97 (s, 3H), 3.96-4.09 (m, 2H), 5.28-5.34 (m, 1H), 5.51-5.58 (m, 1H).

¹³C NMR (100MHz, CDCl₃): δ 16.6, 17.9, 36.4, 37.3, 74.0, 127.0, 131.0

HRMS: m/z calculated for C₇H₁₅O₃S [M+H]⁺: 179.0750 found: 179.0742

GC-LRMS: t_R=6.07 min; m/z: 179 [M]⁺, 123 [CH₃SO₂OCH₂]⁺, 82, 67.

IR: 3028, 2968, 1454, 1354, 1175, 970, 958, 825 cm⁻¹.

[α]_D²² = -3.9 (CHCl₃, c = 2.0).

Synthesis of (R)-(2-methylbut-3-enyl)(p-tolyl)sulfane (4.33.1):

NaH (0.18 g, 4.57 mmol) was added to a solution of *p*-thiocresol (0.5 g, 4.02 mmol) in a mixture of dry DMF (2 ml) and THF (2 ml) at room temperature. The mixture was stirred for 5 minutes then a solution of mesylate (2.25.5) (0.3 g, 1.83 mmol) in THF (2 ml) was added dropwise via a cannula. The mixture was heated to 70°C for 12 h, and then quenched with aq. NaOH solution, and extracted with diethyl ether. The combined organic layers were washed with water and brine and dried over anhydrous MgSO₄. The solvents were removed under reduced pressure to give the title compound as a colourless oil (0.35 g, 86 %) which was used in next step without purification.

¹H NMR (400 MHz, CDCl₃): δ 1.12 (d, 3H, *J* = 6.7 Hz), 1.68 (d, 3H, *J* = 6.1 Hz), 2.33 (s, 3H), 2.37-2.43 (m, 1H), 2.79 (dd, 1H, *J* = 12.5, 7.3 Hz), 2.94 (dd, 1H, *J* = 12.5, 6.7 Hz), 5.41-5.52 (m, 2H), 7.09 (d, 2H, *J* = 8.2 Hz), 7.26 (d, 2H, *J* = 8.2 Hz).

¹³C NMR (100 MHz, CDCl₃): δ 17.9, 19.9, 20.9, 36.4, 41.6, 124.5, 129.5, 129.7, 133.4, 135.2, 135.7.

m/z: 207 [M+H]⁺, 123 [*p*-TolS]⁺.

HRMS calculated for C₁₃H₁₈S [M+H]⁺: 207.1207 found: 207.1205.

IR: 3418, 3020, 2959, 2868, 1639, 1493, 1454, 1375, 1092, 966, 802 cm⁻¹.

[α]_D²² = +26.5 (CHCl₃, c = 2.1).

Synthesis of (*R*)-1-methyl-4-(2-methylbut-3-enylsulfonyl) benzene (4.11.4):

Ammonium heptamolybdate (1.54 g, 1.25 mmol) was added to a solution of hydrogen peroxide (30% in water, 2.5 ml, 24.79 mmol) at 0°C, the mixture was stirred for 10 minutes, then 1 ml of the mixture was added to a solution of the sulphide (4.33.1) (0.1 g, 0.52 mmol) in ethanol (5 ml) at 0°C. The mixture was stirred for 4 h at 0°C, then was diluted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous Na₂SO₄. Solvents were evaporated *in vacuo*, the residue was purified by column chromatography (hexane: ethyl acetate = 95: 5) on silica gel to give the title compound as a colourless oil (0.12 g, 98 %).

¹H NMR (400 MHz, CDCl₃): δ 1.12 (d, 3H, *J* = 6.8 Hz), 1.54 (d, 3H, *J* = 6.4 Hz), 2.43 (s, 3H), 2.69-2.73 (m, 1H), 3.01 (dd, 1H, *J* = 14.1, 6.8 Hz), 3.13 (dd, 1H, *J* = 14.2, 6.3 Hz), 5.18-5.24 (m, 1H), 5.34-5.41 (m, 1H), 7.33 (d, 2H, *J* = 8.0 Hz), 7.75 (d, 2H, *J* = 8.2 Hz).

¹³C NMR (100 MHz, CDCl₃): 17.7, 20.6, 21.5, 32.1, 62.4, 125.2, 128.0, 129.7, 133.6, 137.1, 144.4.

m/z: 239 [M+H]⁺

HRMS calculated for $C_{13}H_{19}O_2S$ $[M+H]^+$: 239.1106 found: 239.1103.

IR: 3028, 2965, 1597, 1452, 1311, 1145, 968 cm^{-1} .

$[\alpha]_D^{22} = +6.4$ ($CHCl_3$, $c = 2.2$).

Synthesis of (*R*)-2-methylbut-3-enyl methanesulfonate (2.12.1):¹⁵⁴

A solution of the mesylate (2.25.5) (40 mg, 0.22 mmol) in toluene (3.5 ml) was saturated by bubbling through ethylene gas for 10 minutes. The system was then heated to 45 °C and maintained under a continuous ethylene flow. Into the solution was added a solution of Grubbs II catalyst (11.5 mg, 0.013 mmol) in toluene (1.5 ml) over three portions at an interval of 2 h. The resulted mixture was then stirred overnight while maintaining ethylene flow. Upon completion of the reaction, solvent was removed under reduced pressure and the residue was purified by column chromatography (hexane: ethyl acetate = 90:10) on silica gel to give the title compound as a colourless oil (32.5 mg, 90%).

1H NMR (400MHz, $CDCl_3$): δ 1.09 (d, 3H, $J = 6.8$ Hz), 2.64-2.57 (m, 1H), 2.99 (s, 3H), 4.05 (dd, 1H, $J = 9.6, 6.6$ Hz, 1H), 4.12 (dd, 1H, $J = 9.7, 6.6$ Hz, 1H), 5.15 (dd, 2H, $J = 17.3, 1.3$ Hz), 5.74 (ddd, 1H, $J = 17.4, 10.4, 7.0$ Hz).

^{13}C NMR (100MHz, $CDCl_3$): δ 16.0, 37.2, 37.3, 73.3, 116.2, 138.3

m/z : 187 $[M+Na]^+$, 165 $[M+H]^+$, 117, 102.

HRMS calculated for $C_6H_{13}O_3S$ $[M+H]^+$: 165.0585 found: 165.0581

IR: 3085, 1350, 1171, 957 cm^{-1} .

$[\alpha]_D^{22} = +5.0$ ($CHCl_3$, $c = 0.6$).

Part two: Modified procedure for the regioselective cross-metathesis with phenol:

Synthesis of (2*E*,4*S*,7*R*,9*R*,10*E*)-methyl 9-(benzyloxymethoxy)- 7-hydroxy-4- methyl-dodeca- 2,10-Dienoate (2.14.3):

The literature procedure⁶³⁻⁶⁴ was modified as follows: into a solution of the diene (2.14.2) (20 mg, 0.06 mmol) and methyl acrylate (11.94 μ l, 0.13 mmol) in toluene (1.5 ml) was added phenol (1.53 μ l, 0.017 mmol). The system was degassed by bubbling through N₂ gas for 30 minutes. Into the mixture was added a solution of Hoveyda-Grubbs catalyst (2.96 mg, 0.004 mmol) in toluene (0.5 ml) in three portions at intervals of 0.5 h. The mixture was then stirred for 7 h while maintaining continuous N₂ flow. Upon completion of the reaction, solvent was removed under reduced pressure and the residue was purified by column chromatography (hexane: ethyl acetate =85:15) on silica gel to give the title compound as a colourless oil (18 mg, 75%).

¹H NMR (400 MHz, CDCl₃) δ 1.05 (d, 3H, J = 6.7 Hz), 1.39-1.78 (m, 6H), 1.70 (dd, 3H, J = 6.6, 1.6 Hz), 2.27-2.34 (m, 1H), 3.26 (br. s, 1H), 3.72 (s, 3H), 3.74-3.78 (m, 1H), 4.29 (dt, 1H, J = 9.0, 4.4 Hz), 4.52 (d, 1H, J = 11.2 Hz), 4.67 (d, 1H, J = 7.0 Hz), 4.71 (d, 1H, J = 11.1 Hz), 4.83 (d, 1H, J = 7.0 Hz), 5.21-5.31 (m, 1H), 5.69 (dq, 1H, J = 15.6, 6.5 Hz), 5.78 (d, 1H, J = 15.1 Hz), 6.86 (dd, 1H, J = 15.1, 8.0 Hz), 7.27-7.37 (m, 5H).

¹³C NMR (100 MHz, CDCl₃): 17.6, 19.5, 31.6, 35.0, 36.5, 42.6, 51.4, 69.7, 70.9, 77.4, 90.9, 119.5, 127.8, 127.9, 128.4, 130.2, 130.4, 137.6, 154.6, 167.2.

m/z : 399.16 [M+Na]⁺.

HRMS calculated for C₂₂H₃₃O₅ [M+H]⁺: 377.2328 found: 377.2326.

IR: 2924, 1720, 1272, 1169, 1098, 1025 cm^{-1}

$[\alpha]_{\text{D}}^{22} = +109.2$ (CHCl_3 , $c = 0.9$).

Part three: Procedures for asymmetric palladium catalyzed decarboxylative allylation:

Synthesis of (*E*)-but-2-enal compound with (*E*)-pent-3-en-2-ol (1:1) (2.34.1):

To a stirred solution of MeMgBr (7.13 ml, 21.40 mmol) in dry Et_2O (10 ml) was added a solution of crotonaldehyde (1.18 ml, 14.27 mmol) in dry Et_2O (7.5 ml) over 30 minutes at 0°C . The mixture was heated at reflux for 2 h, then left to stir at r. t. overnight. The reaction was quenched with aq. sat. NH_4Cl solution. The mixture was extracted with diethyl ether. The combined organic layers were washed with aq. NaHCO_3 , water and then dried over anhydrous MgSO_4 . The solvents were removed by distillation to give the title compound as a colourless oil (1.22g, quantitative).

^1H NMR (400 MHz, CDCl_3) δ 1.23 (d, 3H, $J = 6.4$ Hz), 1.66 (d, 3H, $J = 6.4$ Hz), 4.21-4.24 (m, 1H), 5.48-5.66 (m, 2H)

^{13}C NMR (100 MHz, CDCl_3): 17.5, 23.3, 68.8, 125.7, 135.4.

m/z : 87 $[\text{M}+\text{H}]^+$

Data is consistent with that of the literature.¹⁵⁵

Synthesis of 3-methoxy-3-oxopropanoic acid (2.33.2):

Dimethyl malonate (4 g, 30.28 mmol) was dissolved in THF (50.4 ml) and H₂O (504 ml). The mixture was cooled to 0°C. At this temperature, 0.25 M KOH solution (121.1 ml, 30.28 mmol) was added dropwise. The mixture was stirred for 1 h. The solution was then acidified to *ca.* pH 2 using 1M HCl, saturated with NaCl and extracted with ethyl acetate. The combined layers were dried over anhydrous MgSO₄ and concentrated *in vacuo* to give the title compound as colourless oil (3.5 g, quantitative).

¹H NMR (400 MHz, CDCl₃) δ 3.44 (s, 2H), 3.76 (s, 3H), 10.87 (br. s, OH)

¹³C NMR (100 MHz, CDCl₃): 40.7, 52.7, 167.0, 171.8.

m/z: 119 [M+H]⁺, 108.

Data is consistent with that of the literature.¹⁵⁶

Synthesis of (E)-methyl pent-3-en-2-yl malonate (2.34.3):

N,N-Dicyclohexylcarbodiimide (11.78 g, 57.07 mmol) was added to a mixture of the carboxylic acid (2.33.2) (6.74 g, 57.07 mmol), alcohol (2.34.1) (2.45 g, 28.53 mmol) and DMAP (0.45 g, 3.71 mmol) in CH₂Cl₂ (80 ml) at 0°C. The flask was fitted with a drying tube and the resulting mixture was stirred overnight. The solution was diluted with CH₂Cl₂ and the mixture was filtered through a pad of celite. The filtrate was washed with aq. NaHCO₃ and then dried over anhydrous MgSO₄. The solvents were removed *in vacuo*. The residue was purified by flash column chromatography (hexane: ethyl acetate = 85 : 15) to give the title compound as a colourless oil (4.67 g, 88%).

¹H NMR (400 MHz, CDCl₃) δ 1.31 (d, 3H, *J* = 6.4 Hz), 1.69 (d, 3H, *J* = 6.4 Hz), 3.36 (s, 2H), 3.74 (s, 3H), 5.34-5.44 (m, 1H), 5.45-5.50 (m, 1H), 5.70-5.79 (m, 1H).

¹³C NMR (100 MHz, CDCl₃): 17.6, 20.1, 41.7, 52.4, 72.6, 128.8, 130.1, 165.8, 167.1.

IR: 2955, 1751, 1736, 1439, 1337, 1151, 1020, 970 cm⁻¹.

m/z: 209 [M+Na]⁺, 181.

Data is consistent with that of the literature.⁵³

Synthesis of (*E*)-1-methyl 3-pent-3-en-2-yl 2-tosylmalonate (2.34.4):

t-BuOK (1M solution in THF, 7.17 ml, 7.17 mmol) was added slowly to a solution of the allylic methyl malonate (2.34.3) (1.5 g, 8.06 mmol) in DMSO (4.5 ml) under N₂ at room temperature. The mixture was stirred for 15 minutes, then a solution of TsF (312 mg, 1.79 mmol) in DMSO (3 ml) was added slowly. The mixture was stirred for 20 h at room temperature. The mixture was poured into 10% HCl and extracted with diethyl ether. The combined organic layers were washed with brine then dried over anhydrous MgSO₄. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (hexane: ethyl acetate = 65: 35) on silica gel to give the title compound as a colourless oil (411 mg, 67 %).

¹H NMR (400 MHz, CDCl₃) δ 1.26 (dd, 3H, *J* = 6.3, 3.6 Hz), 1.70 (t, 3H, *J* = 6.6 Hz), 2.47 (s,

3H), 3.76 (s, 3H), 4.95 (s, 1H), 5.33-5.45 (m, 2H), 5.70-5.78 (m, 1H), 7.36 (d, 2H, $J = 8.3$ Hz), 7.87 (d, 2H, $J = 8.3$ Hz).

^{13}C NMR (100 MHz, CDCl_3): 17.6, 19.9, 21.7, 53.5, 74.6, 74.8, 129.2, 129.4, 129.7, 129.8, 130.2, 145.9, 160.1, 161.6.

IR: 2955, 1744, 1732, 1597, 1435, 1337, 1151, 1084, 1033, 968, 816, 673 cm^{-1} .

m/z : 363 $[\text{M}+\text{Na}]^+$, 304.

Data is consistent with that of the literature.⁵³

Synthesis of (*R,E*)-methyl 3-methyl-2-tosylhex-4-enoate (2.34.6):¹⁵⁷

$\text{Pd}_2\text{dba}_3 \cdot \text{CHCl}_3$ (4.56 mg, 0.0044 mmol) and (*S,S*)-DACH-phenyl Trost ligand (9.13 mg, 0.0132 mmol) were placed in a 2-necked RBF. The RBF was placed under vacuum for 15 minutes then purged with N_2 . THF (1 ml) was added to the reaction and the mixture was stirred for 30 minutes at room temperature. A solution of the carbonate (2.34.4) (60 mg, 0.17 mmol) in THF (1 ml) was added to the above mixture. The solution was heated at reflux overnight under N_2 . The mixture was filtered through a short pad of celite and silica and concentrated in *in vacuo*. The residue was purified by column chromatography (hexane: ethyl acetate = 80: 20) on silica gel to give the title compound as a colourless oil (33 mg, 65%).

^1H NMR (400 MHz, CDCl_3) δ 1.03 (d, $J = 6.8\text{Hz}$, one isomer), 1.28 (d, $J = 6.8$ Hz, other isomer), 1.56 (dd, $J = 6.4, 1.4$ Hz), 1.60 (dd, $J = 6.0, 1.3$ Hz), 2.43 (s, 3H), 2.93-2.98 (m, 1H), 3.48 (s, 1.5H, one isomer), 3.65 (s, 1.5H, other isomer), 3.83 (d, $J = 9.4$ Hz, one isomer),

3.87 (d, $J = 8,8$ Hz, other isomer), 5.19-5.24 (m, 1H), 5.43-5.51 (m, 1H), 7.30-7.33 (m, 2H), 7.72-7.77 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): 17.8, 18.9, 19.3, 21.6, 36.4 and 36.8, 52.3 and 52.6, 75.7 and 76.2, 127.1 and 127.7, 129.3, 129.5, 130.7 and 131.4, 135.3 and 135.6, 145.0 and 145.1, 166.2.

IR: 2953, 1745, 1597, 1454, 1435, 1323, 1263, 1144, 1084, 1034, 966, 816, 663 cm^{-1} .

m/z: 297 $[\text{M}+\text{Na}]^+$

Synthesis of (*R,E*)-1-methyl-4-(2-methylpent-3-enylsulfonyl)benzene (2.34.7):

The sulfone ester (2.34.6) (31 mg, 0.10 mmol) was dissolved in DMSO (0.5 ml) and H_2O (8 μl). NaCl (6.4 mg, 0.11 mmol) was added under N_2 . The mixture was heated at 185°C for 6 h. The mixture was diluted with diethyl ether, washed with H_2O and Brine. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (hexane: ethyl acetate = 80: 20) on silica gel to give the title compound as a colourless oil (19 mg, 76 %).

^1H NMR (400 MHz, CDCl_3): δ 1.12 (d, 3H, $J = 6.8$ Hz), 1.54 (d, 3H, $J = 6.4$ Hz), 2.43 (s, 3H), 2.69-2.73 (m, 1H), 3.00 (dd, 1H, $J = 14.1, 6.8$ Hz), 3.11 (dd, 1H, $J = 14.2, 6.3$ Hz), 5.18-5.24 (m, 1H), 5.34-5.41 (m, 1H), 7.33 (d, 2H, $J = 8.0$ Hz), 7.75 (d, 2H, $J = 8.2$ Hz).

^{13}C NMR (100 MHz, CDCl_3): 17.7, 20.6, 21.5, 32.1, 62.4, 125.2, 128.0, 129.7, 133.6, 137.1, 144.4.

m/z: 239 $[\text{M}+\text{H}]^+$

HRMS calculated for $C_{13}H_{19}O_2S$ $[M+H]^+$: 239.1106; found: 239.1103.

IR: 3028, 2965, 1597, 1452, 1311, 1145, 968 cm^{-1} .

Part four: Procedures for the synthesis of the spiroketal fragment of bistramide D:

Synthesis of 4-azidobutanal (4.11.5):

IBX (7.96 g, 28.43 mmol) was added to a solution of the azido alcohol (4.19.5) in DMSO (30 ml) at room temperature. The mixture was stirred overnight. The mixture was then diluted with water and filtered through a pad of celite. The cake was washed with ethyl acetate. The aqueous layer was saturated with NaCl and extracted with ethyl acetate. The combined organic layers were washed with aq. $NaHCO_3$, aq. Na_2CO_3 , water, brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give the title compound as a pale yellow oil (2.11, 79%).

1H NMR (400 MHz, $CDCl_3$): δ 1.89 (m, 2H), 2.56 (t, 2H, $J = 7.1$ Hz), 3.34 (t, 2H, $J = 6.7$ Hz), 9.75 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): 21.4, 40.7, 50.5, 200.9.

Data is consistent with that of the literature.¹²⁶

Synthesis of (S)-3-((2S,3R)-6-azido-3-hydroxy-2-methylhexanoyl)-4-benzylloxazolidin-2-

one (4.20.1):

The literature procedure¹²¹ was modified as follows: TiCl_4 (1 M in toluene, 4.43 ml, 4.43 mmol) was added dropwise to a solution of the oxazolidinone (4.18.4) (518 mg, 2.21 mmol) in CH_2Cl_2 (10 ml) at 0°C . Into the mixture was added TMEDA (633.4 μl , 4.42 mmol) slowly. The mixture was stirred at 0°C for 40 min. The solution was then cooled to -78°C and the aldehyde (4.11.5) (500 mg, 4.42 mmol) was added dropwise. The mixture was allowed to warm up to 0°C and stirred for further 2 h at this temperature. The reaction was quenched with aq. NH_4Cl solution. The aqueous layer extracted with dichloromethane. The combined organic layers were dried over anhydrous MgSO_4 . The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (hexane: ethyl acetate = 65: 35) on silica gel to give the title compound as a colourless oil (327 mg, 65 %).

^1H NMR (400 MHz, CDCl_3) δ 1.27 (d, 2H, $J = 7.1$ Hz), 1.51-1.92 (m, 4H), 2.36-2.79 (m, 1H), 3.23-3.38 (m, 1H), 3.75-3.78 (m, 1H), 3.96-4.17 (m, 1H), 4.20-4.24 (m, 1H), 4.68-4.73 (m, 1H), 7.19-7.36 (m, 5H).

^{13}C NMR (100 MHz, CDCl_3): δ 10.59, 14.20, 25.64, 30.91, 37.81, 42.33, 51.34, 55.07, 66.25, 71.03, 127.49, 129.00, 129.42, 134.96, 152.97.

m/z : 369 $[\text{M}+\text{Na}]^+$, 367 $[\text{M}+\text{H}]^+$, 196, 164.

HRMS calculated for $\text{C}_{17}\text{H}_{23}\text{N}_4\text{O}_4$ $[\text{M}+\text{H}]^+$: 347.1719; found: 347.1726.

IR: 3520, 2941, 2098, 1770, 1693, 1454, 1385, 1209, 1111, 912, 733 cm^{-1} .

$[\alpha]_D^{22} = +43.5$ (CHCl_3 , $c = 1.1$).

Synthesis of (S)-3-((2S,3R)-6-azido-3-((tert-butyldimethylsilyl)oxy)-2-methylhexanoyl)-4-benzyl-oxazolidin-2-one (4.21.1):

Lutidine (3.84 ml, 32.93 mmol) was added dropwise to a solution of the alcohol (4.20.1) (5.93 g, 16.46 mmol) in dichloromethane (72 ml) at 0°C. The mixture was stirred for 5 min, then TBSOTf (4.54 ml, 19.76 mmol) was followed dropwise. The mixture was stirred for 1 h at 0°C and quenched with aq. NH₄Cl solution. The aqueous layer was extracted with dichloromethane. The combined organic layers were dried over anhydrous MgSO₄. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (hexane: ethyl acetate = 90: 10) on silica gel to give the title compound as colourless solid (7.45 g, quantitative).

¹H NMR (400 MHz, CDCl₃) δ 0.01 (s, 3H), 0.05 (s, 3H), 0.90 (s, 9H), 1.23 (d, 3H, *J* = 6.8 Hz), 1.62-1.64 (m, 4H), 2.77 (dd, 1H, *J* = 13.3, 9.6 Hz), 3.23-3.32 (m, 3H), 3.86-3.87 (m, 1H), 3.89-4.04 (m, 1H), 4.17-4.20 (m, 2H), 4.60-4.64 (m, 1H), 7.20-7.36 (m, 5H).

¹³C NMR (100 MHz, CDCl₃): δ -4.9, -4.2, 12.2, 18.0, 24.2, 25.6, 25.8, 32.4, 37.6, 42.6, 51.5, 55.7, 66.1, 72.3, 127.4, 128.9, 129.4, 135.3, 153.1, 175.1.

m/z : 483 [M+Na]⁺, 461 [M]⁺, 431, 196.

HRMS calculated for C₂₃H₃₆N₄O₄SiNa [M+Na]⁺: 483.2404; found: 483.2401.

IR: 2922, 2853, 2091, 1761, 1703, 1462, 1377 cm⁻¹.

[α]_D²² = +51.0 (CHCl₃, *c* = 0.6).

Melting point: 72 - 74°C

Synthesis of S-ethyl (2*S*,3*R*)-6-azido-3-((*tert*-butyldimethylsilyl)oxy)-2-methylhexane-thioate (4.21.2):

The literature procedure¹⁵⁸ was modified as follows: *n*-BuLi (1.6M in hexane, 3.39 ml, 5.43 mmol) was added dropwise to a solution of ethane thiol (0.48 ml, 6.52 mmol) in THF (20 ml) at -78°C. The mixture was stirred for 10 min then a solution of the oxazolidinone (Fig. 28) (1.0 g, 2.17 mmol) in THF (4 ml) was added slowly. The mixture was allowed to warm up to -40°C slowly and quenched with aq. NH₄Cl solution. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous MgSO₄. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (hexane: ethyl acetate = 95: 5) on silica gel to give the title compound as a colourless oil (900 mg, 95 %).

¹H NMR (400 MHz, CDCl₃) δ 0.05 (s, 3H), 0.07 (s, 3H), 0.90 (s, 9H), 1.18 (d, 3H, *J* = 7.0 Hz), 1.24 (t, 4H, *J* = 7.4 Hz), 1.53-1.70 (m, 4H), 2.71-2.74 (m, 1H), 2.87 (q, 2H, *J* = 7.5 Hz), 3.26 (t, 2H, *J* = 6.4 Hz), 3.97 (app. q, 1H, *J* = 5.3 Hz).

¹³C NMR (100 MHz, CDCl₃): δ -4.6, -4.4, 13.4, 14.6, 18.0, 23.1, 24.1, 25.8, 32.1, 51.6, 53.4, 72.9, 202.1.

m/z : 368 [M+Na]⁺, 345 [M]⁺, 288, 196.

HRMS calculated for C₁₅H₃₂N₃O₂SiS [M+H]⁺: 346.1985; found: 346.2012.

IR: 2930, 2096, 1684, 1462, 1362, 1256, 1107, 957, 837 cm⁻¹.

[α]_D²² = -4.7 (CHCl₃, *c* = 0.7).

Synthesis of S-ethyl (2S,3R)-6-amino-3-((*tert*-butyldimethylsilyl)oxy)-2-methylhexanethioate (4.21.3):

Acetic acid (4.48 ml, 78.22 mmol) was added to a solution of the azide (4.21.2) (4.5 g, 13.03 mmol) in THF (24 ml). Into the mixture was added activated Zn (4.3 g, 65.18 mmol) in 3 portions. The reaction solution was stirred for 2 h at room temperature and then filtered through celite. THF was removed on rotary evaporator under reduced pressure. The residue was diluted with ethyl acetate and washed with aq. NaHCO₃ solution. The combined organic layers were dried over anhydrous MgSO₄ and the solvent was removed under reduced pressure. The crude product was taken directly into next step.

Synthesis of S-ethyl (2S,3R)-3-((*tert*-butyldimethylsilyl)oxy)-2-methyl-6-(2,2,2-trifluoroacet-amido) hexanethioate (4.21.4):

To a solution of the amine (4.21.3) (13.03 mmol) in dichloromethane was added Et₃N (3.63 ml, 26.07 mmol) and trifluoroacetic anhydride (2.72 ml, 19.55 mmol) at 0°C. The reaction mixture was stirred for 1.5 h and quenched with aq. NH₄Cl solution. The aqueous layer was extracted with dichloromethane. The combined organic layers were dried over anhydrous MgSO₄. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (hexane: ethyl acetate = 85: 15) on silica gel to give the title compound as a

colourless oil (4.02 g, 75% over two steps).

^1H NMR (400 MHz, CDCl_3) δ 0.05 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 1.18 (d, 3H, $J = 6.9$ Hz), 1.24 (t, 4H, $J = 7.4$ Hz), 1.53-1.68 (m, 4H), 2.71-2.74 (m, 1H), 2.87 (q, 2H, $J = 7.4$ Hz), 3.38 (m, 2H), 3.94 (app. q, 1H, $J = 4.9$ Hz), 6.47 (br. s, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ -4.6, -4.3, 14.0, 14.5, 18.1, 23.2, 23.8, 25.7, 25.8, 32.0, 39.9, 53.3, 72.9, 114.4, 117.3, 157.0 (q, $J = 36.7$ Hz), 202.2.

m/z : 416 $[\text{M}+\text{H}]^+$.

HRMS calculated for $\text{C}_{17}\text{H}_{33}\text{NO}_3\text{SiSF}_3$ $[\text{M}+\text{H}]^+$: 416.1903; found: 416.1911.

IR: 3315, 2932, 1703, 1556, 1454, 1257, 1182, 959, 837, 775 cm^{-1} .

$[\alpha]_D^{22} = -1.4$ (CHCl_3 , $c = 0.5$).

Synthesis of N-((4*R*,5*S*)-4-((*tert*-butyldimethylsilyl)oxy)-5-methyl-6-oxohexyl)-2,2,2-trifluoro-acetamide (4.23.1):¹²⁹

Pd (10% on carbon, 22 mg, 0.02 mmol) was added to a mixture containing the thioester (4.21.4) (168 mg, 0.40 mmol) and MgSO_4 (*ca.* 93 mg) in anhydrous dichloromethane (1 ml) under N_2 . Triethylsilane (194 μl , 1.21 mmol) was added in one portion and the mixture was stirred overnight at room temperature. The solution was filtered through a short pad of celite. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (hexane: ethyl acetate = 75: 25) on silica gel to give the title compound as a colourless oil (124 mg, 86%).

¹H NMR (400 MHz, CDCl₃) δ 0.05 (s, 3H), 0.07 (s, 3H), 0.87 (s, 9H), 1.18 (d, 3H, *J* = 6.9 Hz), 1.43-1.72 (m, 4H), 2.45-2.51 (m, 1H), 3.36-3.39 (m, 1H), 4.09 (app. q, 1H, *J* = 4.5 Hz), 6.40 (br. s, 1H), 9.76 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ -4.6, -4.4, 8.2, 17.9, 25.1, 25.7, 31.5, 39.7, 51.3, 71.5, 114.4, 117.2, 157.5 (q, *J* = 36.7 Hz), 204.8.

m/z : 372, 356 [M+H]⁺.

HRMS calculated for C₁₅H₂₈NO₃F₃SiNa [M+Na]⁺: 378.1688; found: 378.1690.

IR: 3313, 2934, 1715, 1556, 1464, 1375, 1254, 1182, 1163, 1045, 837, 775 cm⁻¹.

[α]_D²² = +32.4 (CHCl₃, *c* = 0.2).

Synthesis of *tert*-butyldimethyl(pent-4-yn-1-yloxy)silane (4.22.1):

To a solution of 5-hexyn-1-ol (3.00 g, 30.57 mmol) in dichloromethane (140 ml) was added imidazole (4.16 g, 61.14 mmol) followed by TBSCl (6.91 g, 45.85 mmol). The reaction was stirred overnight at room temperature. The reaction was quenched with 1M HCl and extracted with dichloromethane. The combined organic layers were dried over anhydrous MgSO₄. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (pentane: diethyl ether = 85: 15) on silica gel to give the title compound as a colourless oil (5.8 mg, 89 %).

¹H NMR (400 MHz, CDCl₃) δ 0.04 (s, 6H), 0.89 (s, 9H), 1.61 (m, 4H), 1.93 (t, 1H, *J* = 2.6 Hz), 2.19-2.21 (m, 2H), 3.63 (t, 2H, *J* = 5.8 Hz).

¹³C NMR (100 MHz, CDCl₃): δ -4.6, -4.4, 18.2, 18.3, 24.9, 25.9, 31.8, 62.5, 68.2, 84.4.

IR: 3311, 2930, 1472, 1256, 1107, 1007, 974, 835, 775 cm⁻¹.

Data is consistent with that of the literature.¹⁵⁹

Synthesis of N-((4*R*,5*R*)-4,11-bis((*tert*-butyldimethylsilyl)oxy)-6-hydroxy-5-methylundec-7-yn-1-yl)-2,2,2-trifluoroacetamide (4.24.1):

n-BuLi (1.6M in hexane, 1.55 ml, 2.48 mmol) was added dropwise to a solution of the alkyne (4.22.1) (554 mg, 2.61 mmol) in THF (6.0 ml) at -78°C. The mixture was stirred for 30 min, then a solution of the aldehyde (4.23.1) (420 mg, 1.18 mmol) in THF (3.0 ml) was added slowly. The resulting mixture was stirred for further 2 h at -78°C. The reaction was quenched with aq. NH₄Cl solution and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous MgSO₄. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (hexane: ethyl acetate = 75: 25) on silica gel to give the title compound as an inseparable mixture of diastereomers (555 mg, 83 %).

2 diastereoisomers:

¹H NMR (400 MHz, CDCl₃) δ 0.07 (s, 3H), 0.09 (s, 3H), 0.11 (s, 3H), 0.12 (s, 3H), 0.90 (s, 9H), 0.91 (s, 9H), 0.95 (d, 3H, *J* = 7.0 Hz), 1.00 (d, 3H, *J* = 7.0 Hz), 1.55-1.79 (m, 18H), 2.25 (app. t, 4H, *J* = 6.7 Hz), 3.33-3.42 (m, 4H), 3.62 (app. t, 4H, *J* = 5.8 Hz), 3.91-3.99 (m, 2H), 4.29-4.38 (m, 1H), 4.50-4.54 (m, 1H), 6.49 (br. s, 1H), 6.55 (br. s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ -5.4, -4.8, -4.5, -4.4, -4.3, 11.4, 11.7, 17.9, 18.3, 18.5, 23.6, 25.1, 25.5, 25.8, 25.9, 30.3, 31.0, 32.0, 39.8, 39.9, 42.0, 43.5, 62.6, 64.2, 65.0, 73.1, 74.4, 80.1, 80.7, 85.8, 85.9, 114.8, 117.6, 157.4 (q, *J* = 36.7 Hz).

m/z : 568 $[M]^+$, 569 $[M+H]^+$.

HRMS calculated for $C_{27}H_{53}NO_4Si_2F_3$ $[M+H]^+$: 568.3465; found: 568.3481.

IR: 3306, 2953, 2859, 1713, 1564, 1472, 1385, 1256, 1163, 1026, 837 cm^{-1} .

Synthesis of 2,2,2-trifluoro-N-((4*R*,5*S*)-4,6,11-trihydroxy-5-methylundec-7-yn-1-yl)acetamide (4.24.2):

Amberlyst-15 (*ca.* 6 mg, 0.04 mmol) was added to a solution of the protected triol (4.24.1) (230 mg, 0.4 mmol) in methanol (6 ml). The reaction mixture was heated to 40°C and stirred overnight at this temperature. The mixture was filtered through celite and the volatile was evaporated under reduced pressure. The residue was purified by column chromatography (hexane: ethyl acetate = 20: 80) on silica gel to give the title compound as a mixture of diastereomers (120 mg, 87 %).

2 diastereoisomers:

1H NMR (400 MHz, MeOD) δ 0.96 (d, 3H, J = 6.8 Hz), 1.04 (d, 3H, J = 6.9 Hz), 1.51-1.80 (m, 18H), 2.29 (app. t, 4H, J = 6.9 Hz), 3.32-3.35 (m, 4H), 3.60 (app. t, 4H, J = 6.2 Hz), 3.89-3.93 (m, 2H), 4.32-4.35 (m, 1H), 4.61-4.63 (m, 1H).

^{13}C NMR (100 MHz, MeOD): δ 7.7, 9.8, 17.8, 24.6, 24.8, 24.9, 25.3, 30.6, 31.3, 31.9, 39.4, 44.7, 45.4, 61.0, 63.9, 64.8, 71.9, 72.3, 79.3, 80.7, 84.8, 85.3, 114.8, 117.6, 157.4 (q, J = 36.3 Hz).

m/z : 340 $[M+H]^+$, 362 $[M+Na]^+$.

HRMS calculated for $C_{15}H_{25}NO_4F_3$ $[M+H]^+$: 340.1736; found: 340.1732.

IR: 3323, 2941, 1713, 1566, 1454, 1184, 1159, 1057 cm^{-1} .

Synthesis of 2,2,2-trifluoro-N-(3-((2*R*,3*S*,6*S*)-3-methyl-1,7-dioxaspiro[5.5]undec-4-en -2-yl) pro- pyl)acetamide (4.14.4):⁸⁸

Anhydrous THF (0.75 ml) was added to an aluminium foil covered RBF containing AuCl(PPh₃) (3.3 mg, 0.006 mmol), AgOTf (1.54 mg, 0.006 mmol) and molecular sieves (*ca.* 26 mg). The mixture was stirred for 10 min then a solution of the triol (4.24.2) (100 mg, 0.30 mmol) in THF (2.25 ml) was added slowly. The resulted mixture was heated to 45°C and stirred overnight. The mixture was filtered through a short pad of celite and silica. The volatiles were evaporated under reduced pressure and the residue was purified by column chromatography (hexane: ethyl acetate = 75: 25) on silica gel to give the title compound as a colourless oil (63 mg, 65%).

¹H NMR (400 MHz, CDCl₃) δ 0.87 (d, 3H, J = 7.0 Hz), 1.41-1.68 (m, 9H), 1.70-1.94 (m, 4H), 3.41-3.46 (m, 2H), 3.59-3.63 (m, 1H), 3.76-3.78 (m, 1H), 3.91-3.95 (m, 1H), 5.55 (d, 1H, J = 8.9 Hz), 5.90 (dd, 1H, J = 9.9, 4.2 Hz), 6.68 (br. s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 12.5, 18.7, 25.0, 25.8, 29.3, 32.3, 35.1, 40.0, 61.0, 69.4, 94.2, 128.9, 134.1, 157.1 (q, J = 36.4 Hz).

m/z : 322 [M+H]⁺.

HRMS calculated for C₁₅H₂₂NO₃F₃Na [M+Na]⁺: 344.1449; found: 344.1447.

IR: 3306, 2945, 1713, 1556, 1454, 1184, 997, 733 cm^{-1} .

$[\alpha]_D^{22} = +16.4$ (CHCl_3 , $c = 0.59$).

Synthesis of 5-chloropent-1-ene (4.35.2):

To a solution of 4-penten-1-ol (10 ml, 96.83 mmol) in dichloromethane (27 ml) was added anhydrous pyridine (2 ml, 0.03 mmol) and SOCl_2 (11.6 ml, 160.73 mmol) at 10°C . When effervescence ceased, the reaction mixture was allowed to warm up to room temperature and stirred overnight. The solution was poured into ice-water. The layers were separated and the organic layer was washed with aq. NaHCO_3 solution. Solvent was removed by distillation to give the crude product as a yellow oil (10 g, quantitative).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 1.83-1.90 (quin, 2H, $J = 6.8$ Hz), 2.18-2.24 (m, 2H), 3.54 (t, 2H, $J = 6.6$ Hz), 5.00-5.10 (m, 2H), 5.73-5.83 (m, 1H).

$^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 30.8, 31.6, 44.3, 115.7, 136.9.

Data is consistent with that of literature.¹⁶⁰

Synthesis of 2-(3-chloropropyl)oxirane (4.35.3):

To a solution of the chloride (4.35.2) (10g, 96.83 mmol) in dichloromethane (350 ml) was added mCPBA (55%, 31 g, 96.83 mmol) in 3 portions at 0°C . The mixture was slowly warmed up to room temperature and stirred overnight. The reaction mixture was cooled in ice-bath for 30 min then filtered through celite. The filtrate was washed with aq. $\text{Na}_2\text{S}_2\text{O}_5$, aq.

NaHCO₃ and brine. The crude product was purified by distillation under reduced pressure to give the title compound as a colourless oil (11 g, quantitative).

¹H NMR (400 MHz, CDCl₃) δ 1.55-1.63 (m, 1H), 1.77-1.88 (m, 1H), 1.90-2.01 (m, 2H), 2.49-2.51 (m, 1H), 2.76-2.78 (m, 1H), 2.92-2.85 (m, 1H), 3.55-3.65 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 29.0, 29.6, 44.4, 46.8, 51.4.

Data is consistent with that of the literature.¹⁶¹

Synthesis of (*S*)-2-(3-chloropropyl)oxirane (4.35.4):

The racemic epoxide (4.35.3) (11 g, 96.83 mmol) was treated with the (*S,S*)-Co(II)(salen) (293 mg, 0.48 mmol) and acetic acid solution (966 μl, 12% in THF). The mixture was cooled to 0°C then H₂O (996 μl) was added in one portion. The solution was warmed to room temperature and stirred for 43 h. The mixture was distilled under reduced pressure to give the title compound as a colourless oil (4.5 g, 41%).

¹H NMR (400 MHz, CDCl₃) δ 1.55-1.63 (m, 1H), 1.77-1.88 (m, 1H), 1.90-2.01 (m, 2H), 2.49-2.51 (m, 1H), 2.76-2.78 (m, 1H), 2.92-2.85 (m, 1H), 3.55-3.65 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 29.0, 29.6, 44.4, 46.8, 51.4.

IR: 3479, 2947, 1445, 1259, 1049, 920, 862 cm⁻¹.

[α]_D²² = -11.8 (CHCl₃, c = 2.6).

Synthesis of (S)-5-chloro-1-(p-tolylthio)pentan-2-ol (4.35.8):

To an oven-dried round bottomed flask was added *p*-thiocresol (4.35.6) (74.5 mg, 0.6 mmol) and anhydrous methanol (2.0 ml) under N₂ atmosphere. The mixture was cooled to 0°C then a solution of the epoxide (4.35.4) (36 mg, 0.3 mmol) in methanol (0.5 ml) was added dropwise over 5 mins, followed by the addition of Et₃N (41.8 μl, 0.3 mmol). After 2 h stirring, the mixture was warmed to room temperature and stirred for 30 mins. The volatile was evaporated under reduced pressure and the residue was purified by column chromatography (hexane: ethyl acetate = 20: 80) on silica gel to give the title compound as a colourless oil (61 mg, 83%).

¹H NMR (400 MHz, CDCl₃) δ 1.55-1.63 (m, 1H), 1.66-1.74 (m, 1H), 1.79-1.88 (m, 1H), 1.92-2.01 (m, 1H), 2.32 (s, 3H), 2.53 (br. s, 1H), 2.80 (dd, 1H, *J* = 13.7, 9.0 Hz), 3.09 (dd, 1H, *J* = 13.7, 3.4 Hz), 3.52-3.58 (m, 2H), 3.60-3.67 (m, 1H), 7.11 (d, 2H, *J* = 8.0 Hz), 7.30 (d, 2H, *J* = 8.0 Hz).

¹³C NMR (100 MHz, CDCl₃): δ 21.0, 28.9, 33.2, 43.1, 45.0, 68.5, 129.9, 130.9, 131.1, 137.2.

IR: 3416, 2953, 2918, 2866, 1493, 1443, 1263, 1090, 920, 804, 650 cm⁻¹.

m/z : 246 [M]⁺ ³⁷Cl, 244 [M]⁺ ³⁵Cl.

HRMS calculated for C₁₈H₂₈O₃S³⁵Cl [M+H]⁺: 245.0767; found: 245.0772.

C₁₈H₂₈O₃S³⁷Cl [M+H]⁺: 247.0737; found: 247.0736.

[α]_D²² = +31.6 (CHCl₃, *c* = 1.8).

Synthesis of (4*S*,7*R*,*E*)-1-chloro-7-methyl-6-tosyldec-8-en-4-ol (4.35.5):

n-BuLi (1.6M in hexane, 2.62 ml, 4.20 mmol) was added dropwise to a solution of the sulfone (4.11.4) (1.0 g, 4.20 mmol) in THF (25 ml) at -78°C. The mixture was stirred for 30 min. A solution of the epoxide (4.35.4) (252 mg, 2.10 mmol) in THF (5 ml) was added slowly followed by dropwise addition of BF₃·OEt₂ (0.53 ml, 4.20 mmol). The resulted mixture was stirred for 2 h at -78°C then quenched with aq. NH₄Cl. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous MgSO₄. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (hexane: ethyl acetate = 65: 35) on silica gel to give the title compound as a colourless oil (639 mg, 85 %).

2 diastereoisomers:

¹H NMR (400 MHz, CDCl₃) δ 1.10 (d, 3H, *J* = 6.9 Hz), 1.51-1.68 (m, 5H), 1.79-2.04 (m, 4H), 2.46 (s, 3H), 2.64-2.67 (m, 1H), 3.23-3.26 (m, 1H), 3.55 (t, 2H, *J* = 6.4 Hz), 3.58-3.63 (m, 1H), 5.25 (dd, 1H, *J* = 14.6, 5.6 Hz), 5.36-5.42 (m, 1H), 7.36 (d, 2H, *J* = 8.0 Hz), 7.77 (d, 2H, *J* = 8.2 Hz).

¹³C NMR (100 MHz, CDCl₃): δ 13.7, 17.8, 21.6, 28.6, 31.3, 35.2, 35.1, 44.9, 66.2, 69.6, 126.3, 128.7, 129.8, 132.8, 135.1, 144.7.

m/z : 361 [M+H]⁺ ³⁷Cl, 359 [M+H]⁺ ³⁵Cl.

HRMS calculated for C₁₈H₂₈O₃S³⁵Cl [M+H]⁺: 359.1448; found: 359.1448.

C₁₈H₂₈O₃S³⁷Cl [M+H]⁺: 361.1418; found: 361.1426.

IR: 3501, 2961, 1597, 1454, 1373, 1286, 1142, 1084, 815, 671 cm⁻¹.

Synthesis of 2-(((4*S*,7*R*,*E*)-1-chloro-7-methyl-6-tosyldec-8-en-4-yl)oxy)tetrahydro-2H-pyran (4.36.1):

To a suspension of amberlyst-15 (13 mg, 0.19 mmol) in dichloromethane (2.5 ml) was added a solution containing the alcohol (4.35.5) (672 mg, 1.88 mmol), dihydropyran (0.21 ml, 2.25 mmol) and dichloromethane (5 ml). The mixture was stirred for 1 h at room temperature. The solution was filtered through celite and the volatile was evaporated under reduced pressure. The residue was purified by column chromatography (hexane: ethyl acetate = 80: 20) on silica gel to give the title compound as a colourless oil (716 mg, 86 %).

4 diastereoisomers:

¹H NMR (400 MHz, CDCl₃) δ 1.10-1.17 (m, 3H), 1.24-1.30 (m, 2H), 1.49-2.07 (m, 11H), 1.65 (d, 3H, *J* = 5.2 Hz), 2.02-2.06 (m, 1H), 2.44 (two s, 3H), 2.94-3.04 (m, 1H), 3.36-3.39 (m, 1H), 3.43-3.50 (m, 2H), 3.63-3.75 (m, 1H), 3.83-3.87 (m, 1H), 4.40-4.48 (m, 1H), 5.40-5.46 (m, 2H), 7.31-7.36 (m, 2H), 7.75-7.79 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 14.1, 15.2, 17.8, 17.9, 18.8, 20.4, 20.6, 20.7, 21.6, 22.6, 25.3, 26.9, 27.8, 28.0, 28.8, 30.0, 31.0, 31.1, 31.2, 31.5, 31.7, 34.6, 34.9, 35.4, 35.7, 44.9, 45.0, 63.6, 63.8, 64.0, 64.5, 65.1, 74.0, 74.3, 74.4, 98.7, 98.8, 98.9, 125.8, 126.1, 126.3, 128.5, 128.7, 129.0, 129.4, 129.5, 129.7, 129.8, 130.8, 130.9, 131.7, 133.1, 133.3, 136.1, 136.2.

m/z : 445 [M+H]⁺ ³⁷Cl, 443 [M+H]⁺ ³⁵Cl, 361 [M-THP]⁺ ³⁵Cl, 359 [M-THP]⁺ ³⁷Cl.

HRMS calculated for C₂₃H₃₆O₄SCl [M+H]⁺: 443.2023; found: 443.2027.

C₂₃H₃₆O₄S³⁷Cl [M+H]⁺: 445.1993; found: 445.1996.

IR: 2941, 1597, 1443, 1373, 1242, 1144, 1076, 1031, 673 cm⁻¹.

Synthesis of 2-(((4*R*,7*S*,*E*)-1-chloro-7-methyldec-8-en-4-yl)oxy)tetrahydro-2*H*-pyran (4.36.2):

The literature procedure¹⁶² was modified as follows: a suspension of activated Mg flakes (158 mg, 6.48 mmol) in anhydrous MeOH (15 ml) was sonicated until the solution turned slightly cloudy. Into this was added anhydrous TMEDA (4.8 ml, 32.38 mmol) and a solution of the protected alcohol (4.36.1) (716 mg, 1.62 mmol) in MeOH (5 ml). The mixture was sonicated until all the Mg had been consumed (*ca.* 40 min). The reaction was monitored by TLC. More portions of Mg and TMEDA were added when necessary. Upon completion of the reaction, MeOH was removed by evaporation under reduced pressure. The mixture was diluted with ethyl acetate and washed with water, aq. NH₄Cl solution and brine. The organic layers were dried over anhydrous MgSO₄. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (hexane: ethyl acetate = 90: 10) on silica gel to give the title compound as a colourless oil (368 mg, 79 %).

2 diastereoisomers:

¹H NMR (400 MHz, CDCl₃) δ 0.96 (d, 3H, *J* = 6.7 Hz), 1.53-1.72 (m, 10H), 1.63 (d, 3H, *J* = 6.0 Hz), 1.75-1.89 (m, 4H), 1.91-2.09 (m, 1H), 3.46-3.66 (m, 4H), 3.88-3.89 (m, 1H), 4.61-4.63 (m, 1H), 5.24-5.39 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 17.9, 19.9, 20.1, 20.7, 20.8, 25.4, 25.5, 28.1, 28.2, 28.8, 30.5, 30.6, 31.1, 31.2, 32.0, 32.1, 32.5, 32.6, 36.7, 36.8, 45.3, 62.7, 63.0, 75.8, 76.1, 97.6, 123.0, 123.1, 137.2, 137.3.

m/z : 291 [M+H]⁺ ³⁷Cl, 289 [M+H]⁺ ³⁵Cl.

HRMS calculated for C₁₆H₃₀O₂SCl [M+H]⁺: 289.1934; found: 289.1941.

C₁₆H₃₀O₃S³⁷Cl [M+H]⁺: 291.1905; found: 291.1917.

IR: 2939, 1454, 1377, 1199, 1132, 1076, 1024, 995 cm⁻¹.

Synthesis of 2-(((4R,7S,E)-1-iodo-7-methyldec-8-en-4-yl)oxy)tetrahydro-2H-pyran (4.36.3):

NaI (594 mg, 3.96 mmol), NaHCO₃ (34 mg, 0.39 mmol) and Na₂S₂O₃·5H₂O (98 mg, 0.39 mmol) were added to a solution of the chloride (4.36.2) (570 mg, 1.98 mmol) in acetone (3 ml). The reaction mixture was protected from light and heated overnight at reflux. The volatile was removed on rotatory evaporator. The residue was diluted with diethyl ether and filtered through celite. The solvent was evaporated *in vacuo* to give the crude product as yellow oil (748 mg, quantitative) which was used directly in the next step.

2 diastereoisomers:

¹H NMR (400 MHz, CDCl₃) δ 0.95 (d, 3H, *J* = 6.7 Hz), 1.30-1.69 (m, 10H), 1.63 (d, 3H, *J* = 6.1 Hz), 1.80-1.85 (m, 4H), 2.02-2.03 (m, 1H), 3.17-3.25 (m, 2H), 3.46-3.48 (m, 1H), 3.61-3.64 (m, 1H), 4.59-4.63 (m, 1H), 5.28-5.39 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 17.9, 19.9, 20.1, 20.8, 25.4, 25.5, 28.9, 29.0, 29.6, 31.1, 31.2, 32.2, 32.5, 32.6, 32.7, 34.0, 34.1, 35.6, 35.7, 36.7, 36.8, 62.7, 63.0, 75.5, 75.7, 97.5, 97.7, 123.0, 123.1, 137.2, 137.3.

m/z : 381 [M+H]⁺, 279.

HRMS calculated for C₁₆H₃₀O₂I [M+H]⁺: 381.1291; found: 381.1290.

IR: 2937, 1454, 1377, 1199, 1132, 1076, 1024, 989 cm⁻¹.

Synthesis of trimethyl((6*S*,9*S*,*E*)-9-methyl-6-((tetrahydro-2*H*-pyran-2-yl)oxy)dodec- 10-en-1-yn-1 -yl)silane (4.36.4):¹³⁸

n-BuLi (1.6M in hexane, 1.62 ml, 2.58 mmol) was added dropwise to a solution of TMS acetylene (392 μ l, 2.77 mol) in THF (4.2 ml) cooled in an ice-salt bath. The temperature was kept below 0°C. The mixture was stirred for 40 min then cooled to -78°C. Freshly distilled DMPU (2.10 ml) was added slowly. 10 min later, a solution of the iodide (4.36.3) (702 mg, 1.85 mmol) in DMPU (2.10 ml) was followed dropwise. The reaction mixture was allowed to warm up to room temperature over 6 h and stirred overnight. The reaction was quenched with aq. NH₄Cl solution and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over anhydrous MgSO₄. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (hexane: ethyl acetate = 95: 5) on silica gel to give the title compound as a colourless oil (480 mg, 76%).

2 diastereoisomers:

¹H NMR (400 MHz, CDCl₃) δ 0.14 (app. two s, 9H), 0.94-0.97 (app. two d, 3H, *J* = 6.7, 6.6 Hz), 1.24-1.72 (m, 13H), 1.63 (d, 3H, *J* = 6.0 Hz), 1.80-1.83 (m, 1H), 1.93-2.07 (m, 1H), 2.21-2.24 (m, 2H), 3.46-3.49 (m, 1H), 3.61-3.63 (m, 1H), 3.89-3.90 (m, 1H), 4.62-4.65 (m, 1H), 5.28-5.39 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 17.9, 19.9, 20.0, 20.8, 23.9, 24.6, 25.5, 31.2, 32.2, 32.2, 32.4,

32.6, 32.8, 33.0, 33.9, 36.7, 36.9, 62.7, 62.8, 68.2, 68.3, 76.0, 76.1, 84.4, 84.7, 97.4, 97.5, 107.3, 107.61, 123.0, 123.1, 137.3, 137.4.

m/z : 351 $[M+H]^+$, 279 $[M-TMS]^+$.

HRMS calculated for $C_{21}H_{39}O_2Si$ $[M+H]^+$: 351.2719; found: 351.2730.

IR: 2951, 2868, 2174, 1454, 1377, 1248, 1132, 1024, 843 cm^{-1} .

Synthesis of 2-(((6*S*,9*S*,*E*)-9-methyldodec-10-en-1-yn-6-yl)oxy)tetrahydro-2*H*-pyran (3.36.5):

The TMS protected alkyne (4.36.4) (166 mg, 0.47 mmol) was dissolved in MeOH (4.5 ml). Into this was added anhydrous K_2CO_3 (196 mg, 1.42 mmol) at room temperature and the mixture was stirred overnight. MeOH was removed by evaporation under reduced pressure. The residue was diluted with dichloromethane and washed with water. The organic layer was dried over anhydrous $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (hexane: ethyl acetate = 95: 5) on silica gel to give the title compound as a colourless oil (111 mg, 84%).

2 diastereoisomers:

1H NMR (400 MHz, $CDCl_3$) δ 0.94-0.97 (app. two d, 3H, J = 6.7, 6.6 Hz), 1.24-1.72 (m, 13H), 1.63 (d, 3H, J = 6.0 Hz), 1.80-1.83 (m, 1H), 1.93-1.94 (m, 1H), 2.04-2.07 (m, 1H), 2.20-2.21 (m, 2H), 3.46-3.49 (m, 1H), 3.61-3.63 (m, 1H), 3.89-3.90 (m, 1H), 4.63-4.65 (m, 1H), 5.29-5.37 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 17.8, 18.3, 18.5, 19.8, 19.9, 20.7, 20.7, 23.8, 23.8, 24.5, 25.4,

31.1, 32.1, 32.1, 32.2, 32.3, 32.4, 32.5, 32.6, 32.8, 33.7, 33.8, 36.6, 36.8, 36.8, 62.5, 62.6, 68.1, 68.3, 75.7, 75.8, 76.1, 76.2, 84.2, 84.4, 97.3, 97.4, 122.8, 122.8, 122.9, 123.0, 137.1, 137.3.

m/z : 279 $[M+H]^+$, 217, 196.

HRMS calculated for $C_{18}H_{31}O_2$ $[M+H]^+$: 279.2324; found: 279.2327.

IR: 3310, 2939, 2174, 1454, 1377, 1199, 1134, 1076, 1024, 631 cm^{-1} .

Synthesis of N-((4*R*,5*R*,12*S*,15*S*,*E*)-4-((*tert*-butyldimethylsilyl)oxy)-6-hydroxy-5,15-dimethyl-12-((tetrahydro-2*H*-pyran-2-yl)oxy)octadec-16-en-7-yn-1-yl)-2,2,2-trifluoroacetamide (4.37.1):

n-BuLi (1.6M in hexane, 554 μ l, 0.89 mmol) was added dropwise to a solution of the alkyne (4.36.5) (258 mg, 0.93 mmol) in anhydrous toluene (4.5 ml) at $-78^{\circ}C$. The mixture was stirred for 1 h. A solution of the aldehyde (4.23.1) (150 mg, 0.42 mmol) in toluene (2 ml) was added slowly and the resulted solution was stirred for further 2 h at $-78^{\circ}C$. The reaction was then allowed to warm up to $-40^{\circ}C$ and stirred overnight. The reaction was quenched with aq. NH_4Cl solution and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (hexane: ethyl acetate = 75: 25) on silica gel to give the title compound as a colourless oil (180 mg, 67%).

4 possible diastereoisomers:

¹H NMR (400 MHz, CDCl₃) δ 0.04 (s, 3 H), 0.06 (s, 3 H), 0.87 (s, 9H), 0.88 (s, 9H), 0.93 (d, 3 H, *J* = 6.8 Hz), 0.99 (d, 3 H, *J* = 6.8 Hz), 1.21-1.53 (m, 20 H), 1.62 (d, 3H, *J* = 5.9 Hz), 1.95-2.05 (m, 1H), 2.22-2.24 (m, 2H), 3.35-3.40 (m, 4H), 3.48-3.50 (m, 1H), 3.60-3.62 (m, 1H), 3.89-3.97 (m, 2H), 4.27-4.34 (m, 1H), 4.62-4.67 (m, 1H), 5.24-5.39 (m, 2H), 6.58-6.70 (two br. s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 6.7, 9.2, 9.3, 11.3, 14.0, 17.9, 18.0, 18.8, 19.0, 19.7, 19.9, 20.8, 22.7, 24.0, 24.6, 25.0, 25.5, 25.8, 28.3, 30.5, 31.1, 31.2, 31.6, 31.7, 32.2, 32.6, 32.8, 32.9, 34.1, 35.2, 36.8, 36.9, 39.9, 40.0, 40.4, 43.4, 43.5, 62.5, 62.7, 64.9, 65.3, 73.0, 73.6, 73.9, 76.1, 76.2, 80.8, 85.8, 97.1, 97.2, 97.7, 123.0, 123.1, 137.2, 137.4, 157.2 (q, *J* = 37.0 Hz),.

m/z : 656 [M+Na]⁺, 550 [M-THP]⁺.

IR: 3312, 2951, 2245, 1715, 1557, 1456, 1376, 1254, 1182, 1024, 837 cm⁻¹.

HRMS calculated for C₃₃H₅₉NO₅SiF₃ [M+H]⁺: 634.4115; found: 634.4098.

Synthesis of 2,2,2-trifluoro-N-((4*R*,5*S*,12*S*,15*S*,*E*)-4,6,12-trihydroxy-5,15-dimethyloctadec-16-en-7-yn-1-yl)acetamide (4.46.1):

The protected triol (4.37.1) (61 mg, 0.10 mmol) was dissolved in MeOH (2 ml). Into this solution was added amberlyst-15 (*ca.* 14 mg, 0.01 mmol) and two drops of water. The

reaction mixture was heated to 43°C and stirred overnight at this temperature. The mixture was filtered through celite and the volatile was evaporated under reduced pressure. The residue was purified by column chromatography (hexane: ethyl acetate = 25: 75) on silica gel to give the title compound as a mixture of diastereomers (37 mg, 88 %).

2 diastereoisomers:

¹H NMR (400 MHz, CDCl₃) δ 0.98 (d, 3H, *J* = 7.1 Hz), 1.01 (d, 3H, *J* = 7.0 Hz), 1.05 (d, 3H, *J* = 7.0 Hz), 1.21-1.74 (m, 14 H), 1.62 (d, 3H, 6.0 Hz), 1.95-2.05 (m, 1H), 2.22-2.24 (m, 2H), 3.27-3.32 (m, 2H), 3.37-3.44 (m, 2H), 3.56-3.68 (m, 2H), 3.92-3.94 (m, 1H), 4.08-4.09 (m, 1H), 4.35-4.36 (m, 1H), 4.51-4.52 (m, 1H), 5.24-5.34 (m, 2H), 7.55-7.62 (m, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 7.0, 10.3, 17.8, 18.6, 20.7, 20.9, 24.6, 24.7, 25.5, 25.6, 31.3, 32.2, 32.8, 33.0, 35.0, 35.1, 35.2, 36.2, 36.6, 36.7, 39.8, 43.2, 43.3, 66.4, 66.8, 71.5, 71.8, 73.8, 80.1, 80.6, 86.4, 86.6, 123.1, 123.2, 137.0, 137.1, 157.2 (q, *J* = 31.6 Hz).

IR: 3323, 2936, 2228, 1715, 1568, 1456, 1373, 1211, 1184, 968 cm⁻¹.

m/z : 458 [M+Na]⁺, 436 [M+H]⁺.

HRMS calculated for C₂₂H₃₇NO₄F₃ [M+H]⁺: 436.2675; found: 436.2666.

Synthesis of 2,2,2-trifluoro-N-(3-((2*R*,3*S*,6*S*,8*S*)-3-methyl-8- ((*S*,*E*)-3-methylhex-4- en-1-yl)- 1,7- dioxaspiro[5.5]undec-4-en-2-yl)propyl)acetamide (4.46.2):

Anhydrous THF (0.5 ml) was added to an aluminium foil covered RBF containing AuCl(PPh₃)

(1.64 mg, 0.0033 mmol), AgOTf (0.85 mg, 0.0033 mmol) and molecular sieves (*ca.* 26 mg). The mixture was stirred for 10 min then a solution of the triol (4.46.1) (36 mg, 0.08 mmol) in THF (1.5 ml) was added slowly. The resulted mixture was heated to 45°C and stirred overnight. The mixture was filtered through a short pad of celite and silica. The volatile was evaporated under reduced pressure and the residue was purified by column chromatography (hexane: ethyl acetate = 85: 15) on silica gel to give the title compound as a colourless oil (29 mg, 84%).

¹H NMR (400 MHz, CDCl₃) δ 0.65-1.05 (m, 2H), 0.85 (d, 3H, *J* = 6.5 Hz), 0.93 (d, 3H, *J* = 6.8 Hz), 1.15-1.52 (m, 9H), 1.53-1.79 (m, 3H), 1.62 (d, 3H, *J* = 5.6 Hz), 1.82-1.89 (m, 2H), 1.90-1.93 (m, 1H), 1.99-2.04 (m, 1H), 3.41-3.48 (m, 2H), 3.65-3.66 (m, 1H), 3.93-3.96 (m, 1H), 5.27-5.34 (m, 2H), 5.54 (d, 1H, *J* = 10.1 Hz), 5.88-5.92 (m, 1H), 6.39 (br. s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 12.6, 17.9, 19.1, 20.7, 25.9, 29.4, 30.7, 32.4, 33.1, 34.1, 34.8, 36.7, 40.1, 69.3, 70.2, 94.8, 123.0, 129.6, 133.9, 137.3, 157.2 (q, *J* = 36.7 Hz).

m/z : 418 [M+H]⁺.

HRMS calculated for C₂₂H₃₅NO₃F₃ [M+H]⁺: 418.2569; found: 418.2561.

IR: 3306, 2938, 1713, 1557, 1456, 1373, 1205, 1184, 1089, 991, 723 cm⁻¹.

[α]_D²² = -56.0 (CHCl₃, *c* = 0.6).

Synthesis of N-(3-((2*R*,3*S*,6*S*,8*S*)-8-((3*S*)-4,5-dihydroxy-3-methylhexyl)-3-methyl-1,7-dioxaspiro [5.5]undec- 4-en-2-yl)propyl)-2,2,2-trifluoroacetamide (4.52.1):

K₂OsO₄·2H₂O (0.35 mg, 0.00094 mmol) was added in one portion to a vigorously stirring solution of the alkene (4.46.2) (52 mg, 0.12 mmol), K₃Fe(CN)₆ (123 mg, 0.24 mmol), K₂CO₃ (33.8 mg, 0.37 mmol) in ^tBuOH (520 μl) and H₂O (520 μl). The reaction mixture was stirred for 24 h at room temperature then quenched with aq. Na₂SO₃ solution. The mixture was stirred for further 3 h and the solution turned into deep red. Upon the removal of ^tBuOH on rotary evaporator, the mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous MgSO₄. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (hexane: ethyl acetate = 40: 60) on silica gel to give the title compound as a colourless oil (43 mg, 76%).

4 possible diastereoisomers:

¹H NMR (400 MHz, CDCl₃) δ 0.80-0.95 (multiple d, 6H, *J* = 7.0 Hz), 1.10-1.20 (multiple d, 6H, *J* = 6.3 Hz), 1.32-1.65 (m, 17 H), 1.66-1.80 (m, 2H), 3.10 (app. t, 1H, *J* = 5.2 Hz), 3.28-3.48 (m, 2H), 3.65-3.75 (m, 1H), 3.78-3.88 (m, 1H), 3.89-3.96 (m, 1H), 5.52 (d, 1H, *J* = 10 Hz), 5.88-5.92 (m, 1H), 7.00-7.10 (two br. s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 12.5, 12.8, 14.1, 16.5, 19.0, 19.10, 20.2, 21.0, 25.6, 25.8, 27.5, 29.2, 29.3, 30.6, 30.7, 30.8, 32.5, 32.6, 33.5, 34.7, 34.8, 35.1, 40.1, 40.2, 60.4, 67.6, 68.6, 69.3, 70.5, 70.9, 78.4, 79.9, 94.9, 129.2, 129.4, 134.1, 134.3, 157.2 (q, *J* = 36.7 Hz).

m/z : 474 [M+Na]⁺, 452 [M+H]⁺, 434.

HRMS calculated for C₂₂H₃₇NO₅F₃ [M+H]⁺: 452.2624; found: 452.2616.

IR: 3451, 2938, 1715, 1557, 1454, 1373, 1186, 988 cm⁻¹.

Synthesis of N-(3-((2*R*,3*S*,6*S*,8*S*)-8-((3*S*)-4,5-dihydroxy- 3-methylhexyl)-3- methyl-1,7-dioxaspiro- [5.5]undecan-2-yl)propyl)-2,2,2-trifluoroacetamide (4.52.2):

A 10 ml RBF was charged with the unsaturated spiroketal (4.52.1) (43 mg, 0.09 mmol) and 10% Pd/C (20 mg, 0.019 mmol). The flask was purged with N₂ gas 3 times then fitted with a H₂ balloon. Degassed ethyl acetate (1.5 ml) was added. The resulted mixture was stirred overnight at room temperature. The mixture was filtered through celite and the volatile was evaporated under reduced pressure. The residue was purified by column chromatography (hexane: ethyl acetate = 40: 60) on silica gel to give the title compound as a colourless oil (43 mg, quantitative).

4 possible diastereoisomers:

¹H NMR (400 MHz, CDCl₃) δ 0.82-0.97 (multiple d, 6H, *J* = 7.0 Hz), 1.12-1.28 (multiple d, 6H, *J* = 6.3 Hz), 1.31-1.81 (m, 23 H), 1.66-1.80 (m, 2H), 3.11-3.13 (m, 1H), 3.28-3.44 (m, 2H), 3.67-3.68 (m, 1H), 3.70-3.72 (m, 1H), 3.85-3.86 (m, 1H), 6.80-7.00 (two br. s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 11.0, 11.6, 13.0, 13.3, 13.6, 13.9, 14.0, 16.5, 18.9, 19.0, 19.1, 19.2, 20.2, 21.5, 21.7, 21.8, 22.2, 22.4, 22.5, 22.6, 25.5, 25.6, 26.3, 26.8, 27.1, 27.2, 28.8, 29.1, 29.6, 30.0, 30.2, 30.4, 30.5, 31.0, 31.1, 31.2, 33.6, 33.8, 34.3, 34.7, 34.8, 35.2, 35.3, 39.7, 40.0, 40.1, 67.8, 67.9, 68.7, 69.0, 69.2, 69.6, 69.7, 78.6, 78.8, 79.8, 80.0, 95.7, 96.2, 114.5, 117.3, 157.2 (q, *J* = 36.1 Hz).

m/z : 476 [M+Na]⁺, 454 [M+H]⁺, 436.

HRMS calculated for $C_{22}H_{39}NO_5F_3$ $[M+H]^+$: 454.2780; found: 454.2773.

IR: 3306, 2924, 1713, 1462, 1454, 1377, 1161, 984 cm^{-1} .

Synthesis of 2,2,2-trifluoro-N-(3-((2*R*,3*S*,6*S*,8*S*)-3-methyl-8-((*S*)-3-methyl-4-oxobutyl)-1,7-dioxaspiro[5.5]undec-4-en-2-yl)propyl)acetamide (4.52.3):

Diol (4.52.2) (48 mg, 0.11 mmol) was added to a vigorously stirring suspension of SiO_2-NaIO_4 (*ca.* 200 mg) in DCM with external cooling. The mixture was stirred for 30 minutes at room temperature then filtered through celite. The cake was washed with chloroform and the volatile was removed by evaporation under reduced pressure. The colourless oil was taken directly into next step without purification.

1H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, 3H, $J = 7.0$ Hz), 1.11 (d, 3H, $J = 7.0$ Hz), 1.26-1.45 (m, 8H), 1.47-1.63 (m, 10H), 2.03-2.11 (m, 1H), 2.37 (q, 1H, $J = 6.6$ Hz), 3.35-3.51 (m, 3H), 3.65-3.68 (m, 1H), 6.62 (br. s, 1H), 9.63 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 11.1, 13.3, 18.9, 25.8, 26.3, 26.7, 30.2, 30.5, 31.0, 33.6, 35.2, 40.2, 46.4, 69.2, 70.7, 74.4, 96.2, 205.2.¹⁶³

m/z : 430 $[M+Na]^+$, 422, 408 $[M+H]^+$, 390.

HRMS calculated for $C_{20}H_{32}NO_4F_3Na$ $[M+Na]^+$: 430.2181; found: 430.2177.

IR: 3316, 2934, 2868, 1726, 1715, 1556, 1454, 1213, 1163, 982 cm^{-1} .

$[\alpha]_D^{22} = +32.5$ (CHCl_3 , $c = 0.5$).

Synthesis of *N*-methoxy-*N*-methylacetamide (4.52.7):

N,O-dimethylhydroxylamine hydrochloride (6.0 g, 61.51 mmol) was suspended in CH_2Cl_2 (64 ml) under nitrogen. Into the mixture was added acetyl chloride (2.2 ml, 30.76 mmol), followed by dropwise addition of Et_3N (17.2 ml, 123.03 mmol). The mixture was left to stir overnight at room temperature. Water was then added to dissolve the white precipitate. The reaction mixture was washed with with aq. NH_4Cl / aq. NaHCO_3 solutions. The combined organic layers were washed with brine then dried over anhydrous MgSO_4 . The volatile was evaporated *in vacuo* to give the title compound as a yellow oil (2.81 g, 88%) which was taken to next step without purification.

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 2.03 (s, 3H), 3.15 (s, 3H), 3.66 (s, 3H).

$^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 19.8, 32.0, 61.0, 171.9.

Data is consistent with that of the literature.¹⁶⁴

Synthesis of diethyl ethylphosphonate (4.52.8):

Diethyl phosphite (6.0 ml, 46.49 mmol) was added slowly to a suspension of NaH (2.24g,

55.78 mmol) in THF at 0°C. The mixture was stirred for 30 minute at room temperature. The mixture was then cooled to 0°C again and into this was added a solution of ethyl iodide (4.5 ml, 55.78 mmol). The resulted mixture was stirred for further 1 h at 0°C. The reaction was then quenched with H₂O and the aqueous layer was extraced with ethyl acetate. The combined organic layers were dried over anhydrous MgSO₄. The volatile was evaporated *in vacuo* to give the title compound as a yellow oil (5.57 g, 72%) which was taken to next step without purification.

¹H NMR (400 MHz, CDCl₃) δ 1.14 (dt, 3H, *J* = 19.9, 7.7 Hz), 1.31, (t, 3H, *J* = 7.1 Hz), 1.79 (dq, 2H, *J* = 18.5, 7.7 Hz), 4.0-4.3 (m, 2H).

³¹P NMR (121.5 MHz, CDCl₃): δ 34.3.

Data is consistent with that of the literature.¹⁶⁵

Synthesis of diethyl 3-oxobutan-2-ylphosphonate (4.52.9):

n-BuLi (1.6M in hexane, 18.75 ml, 29.99 mmol) was added dropwise to a solution of phosphonate (4.52.8) (4.98 g, 29.99 mmol) in THF (74 ml) at -78°C. The mixture was stirred for 0.5 h at this temperature. A solution of the amide (4.52.7) (2.81 g, 27.26 mmol) was then followed and the resulted solution was allowed to stir for further 2 h at -78°C. The reaction was quenched with 2M HCl. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous MgSO₄. The solvent was evaporated *in vacuo* to give the title compound as a colourless oil (5.47g, 96%) which was taken to next step without purification.

¹H NMR (400 MHz, CDCl₃) δ 1.30 (m, 6H), 1.34 (d, 3H, *J* = 6.9 Hz), 2.4 (s, 3H), 3.21 (dq, 1H, *J* = 22.5, 7.2 Hz), 4.0-4.3 (m, 4H).

³¹P NMR (121.5 MHz, CDCl₃): δ 24.0.

Data is consistent with that of the literature.¹⁶⁶

Synthesis of N-(3-((2*R*,3*S*,6*S*,8*S*)-8-((*S*,*E*)-3,5-dimethyl-6-oxohept-4-en-1-yl)-3-methyl-1,7-dioxaspiro[5.5]undec-4-en-2-yl)propyl)-2,2,2-trifluoroacetamide (4.52.4):

Ba(OH)₂ (90 mg, 0.53 mmol) was heated to 125°C under vacuum for 2 hr then cooled to room temperature. A solution of the phosphonate (4.52.9) (66 mg, 0.31 mmol) in THF (0.85 ml) was added. The mixture was stirred for 10 min followed by the addition of the aldehyde (4.52.3) (43 mg, 0.10 mmol) in a mixture of THF (0.85 ml) and H₂O (46 µl). The solution was stirred for further 1.5 h at room temperature. The reaction was quenched with aq. NH₄Cl solution and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous MgSO₄. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (hexane: ethyl acetate = 80: 20) on silica gel to give the title compound as a colourless oil (24 mg, 50%).

¹H NMR (400 MHz, CDCl₃) δ 0.82 (d, 3H, *J* = 6.5 Hz), 0.90 (d, 3H, *J* = 7.0 Hz), 1.33-1.46

(m, 8H), 1.48-1.64 (m, 10H), 1.78 (s, 3H), 2.04-2.13 (m, 1H), 2.31 (s, 3H), 2.48-2.56 (m, 1H), 3.37-3.46 (m, 3H), 3.65-3.68 (m, 1H), 6.39 (d, 1H, $J = 9.7$ Hz), 6.60 (br. s, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ 11.1, 11.4, 18.9, 20.0, 25.6, 25.8, 26.3, 30.2, 30.3, 30.5, 31.2, 32.9, 33.9, 34.3, 35.3, 40.2, 69.2, 70.6, 96.1, 136.2, 149.2, 155.7 (q, $J = 36.7$ Hz), 200.3.

m/z : 462 $[\text{M}+\text{H}]^+$.

HRMS calculated for $\text{C}_{24}\text{H}_{39}\text{NO}_4\text{F}_3$ $[\text{M}+\text{H}]^+$: 462.2831; found: 462.2824.

IR: 3445, 2936, 2870, 1715, 1651, 1557, 1456, 1373, 1182, 1159, 982, 733 cm^{-1} .

$[\alpha]_D^{22} = +19.2$ (CHCl_3 , $c = 0.8$).

Synthesis of 2,2,2-trifluoro-N-(3-((2*R*,3*S*,6*S*,8*S*)-8-((3*S*,6*S*,*E*)-6-hydroxy-3,5-dimethylhept-4-en-1-yl)-3-methyl-1,7-dioxaspiro[5.5]undecan-2-yl)propyl)acetamide (4.54.1):

To the enone (4.52.4) (24 mg, 0.05 mmol) under a nitrogen atmosphere was added (*R*)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrole-[1,2-*c*][1,2,3] oxazaborole (11 μl , 1M solution in toluene, 0.01 mmol) via syringe. The mixture was placed under high vacuum for 2 h to remove most of the toluene. The mixture was then purged with nitrogen, dry CH_2Cl_2 (0.6 ml) was added, and the reaction was cooled to -30°C . To this solution at -30°C was added borane dimethyl sulfide complex (52 μl , 2 M solution in THF, 0.10 mmol) over a period of 15 min. After complete addition, the reaction was allowed to stir at -30°C for 24 h. Upon completion of the reaction, a mixture of 1 M HCl (7.8 ml) in MeOH (620 μl) was added to

the mixture at -30°C dropwise. The reaction was then allowed to warm up to room temperature and stirred for 30 min. The resulting cloudy solution was filtered and the filtrate was extracted with ethyl acetate. The combined organic layers were dried over anhydrous MgSO_4 . The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (hexane: ethyl acetate = 75: 25) on silica gel to give the title compound as a colourless oil (18 mg, 75%).

^1H NMR (400 MHz, CDCl_3) δ 0.89 (d, 3H, $J = 6.5$ Hz), 0.94 (d, 3H, $J = 7.0$ Hz), 1.25 (d, 3H, 6.3 Hz), 1.04-1.46 (m, 8H), 1.45-1.70 (m, 10H), 1.62 (s, 3H), 2.04-2.13 (m, 1H), 2.28-2.39 (m, 1H), 3.37-3.46 (m, 3H), 3.65-3.70 (m, 1H), 4.18 (q, 1H, $J = 5.3$ Hz), 5.17 (d, 1H, $J = 9.7$ Hz), 6.57 (br. s, 1H).

^{13}C NMR (100 MHz, CDCl_3) δ 11.1, 11.7, 19.0, 20.9, 21.7, 25.7, 26.3, 30.2, 30.5, 31.2, 32.0, 33.6, 34.2, 35.2, 40.2, 69.3, 70.5, 73.3, 73.4, 96.1, 131.3, 137.2, 157.2 (q, $J = 36.4$ Hz).

m/z : 463 $[\text{M}]^+$

HRMS calculated for $\text{C}_{24}\text{H}_{39}\text{NO}_4\text{F}_3$ $[\text{M}+\text{H}]^+$: 464.2988; found: 464.2949.

IR: 3451, 3306, 2936, 2868, 1713, 1564, 1454, 1211, 1161, 972 cm^{-1} .

$[\alpha]_D^{22} = +10.9$ (CHCl_3 , $c = 1.6$).

Synthesis of (2*S*,5*S*,*E*)-7-((2*S*,6*S*,8*R*,9*S*)-8-(3-aminopropyl)-9-methyl-1,7- dioxaspiro[5.5] undecan-2-yl)-3,5-dimethylhept-3-en-2-ol (4.54.2):

To a mixture of the amide (4.54.1) (8.8 mg, 0.02 mmol) in MeOH (200 μ l) was added anhydrous K_2CO_3 (13 mg, 0.10 mmol) and one drop of water. The reaction mixture was heated under reflux overnight. Upon the removal of MeOH on rotary evaporator, the mixture was diluted with $CHCl_3$ and washed with water. The aqueous layer was extracted with $CHCl_3$ and the combined organic layers were dried over anhydrous $MgSO_4$. The solvent was evaporated *in vacuo* to give the crude product as a pale yellow oil (7 mg, quantitative).

1H NMR (400 MHz, $CDCl_3$) δ 0.89 (d, 3H, J = 6.5 Hz), 0.95 (d, 3H, J = 7.0 Hz), 1.24 (d, 3H, 6.3 Hz), 1.04-1.46 (m, 8H), 1.45-1.70 (m, 10H), 1.62 (s, 3H), 2.04-2.12 (m, 1H), 2.28-2.40 (m, 1H), 2.71 (t, 2H, J = 6.4), 3.42-3.49 (m, 1H), 3.63-3.70 (m, 1H), 4.18 (q, 1H, J = 5.3 Hz), 5.15 (d, 1H, J = 9.7 Hz), 7.30 (br. s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 11.1, 12.0, 19.1, 21.0, 21.8, 26.3, 26.5, 30.3, 30.5, 31.3, 31.9, 33.6, 33.8, 35.4, 42.3, 69.3, 70.4, 73.0, 73.3, 96.0, 131.0, 137.3.

m/z : 368 $[M+H]^+$.

HRMS calculated for $C_{24}H_{39}NO_4F_3$ $[M+H]^+$: 368.3165; found: 368.3163.

IR: 3364, 2934, 2866, 1661, 1454, 1385, 1221, 1078, 982 cm^{-1} .

$[\alpha]^{22}_D$ = +20.8 ($CHCl_3$, c = 0.6).

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