Synthesis of the ABC tricyclic fragment of the pectenotoxins *via* stereocontrolled cyclization of a γ-hydroxyepoxide appended to the AB spiroacetal unit†

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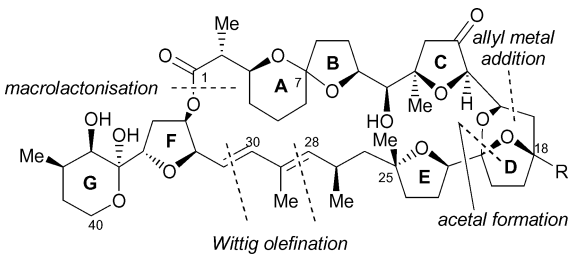
The stereocontrolled synthesis of the C1–C16 ABC spiroacetal-containing tricyclic fragment of pectenotoxin-7 **6** has been accomplished. The key AB spiroacetal aldehyde **9** was successfully synthesized *via* acid catalyzed cyclization of protected ketone precursor **28** that was readily prepared from aldehyde **12** and sulfone **13**. The *syn* stereochemistry in aldehyde **12** was installed using an asymmetric aldol reaction proceeding *via* a titanium enolate. The stereogenic centre in sulfone **13** was derived from (*R*)-(+)-glycidol. The absolute stereochemistry of the final spiroacetal aldehyde **9** was confirmed by NOE studies establishing the (*S*)-stereochemistry of the spiroacetal centre. Construction of the tetrahydrofuran C ring system began with Wittig olefination of the AB spiroacetal aldehyde **9** with (carbethoxyethylidene)triphenylphosphorane **10** affording the desired (*E*)-olefin **32**. Appendage of a three carbon chain to the AB spiroacetal fragment was achieved *via* addition of acetylene **11** to the unstable allylic iodide **39**. Epoxidation of (*E*)-enyne **8** *via in situ* formation of L-fructose derived dioxirane generated the desired *syn*-epoxide **36**. Semi-hydrogenation of the resulting epoxide **36** followed by dihydroxylation of the alkene effected concomitant cyclization, thus completing the synthesis of the ABC spiroacetal ring fragment **6**.

Introduction

The pectenotoxins are a family of polyether lactones that were first isolated in 1985 by Yasumoto *et al.*[1] They were named after the generic name of the scallop initially used for the toxin extraction, *Patinopecten yessoensis* and were originally produced by toxic dinoflagellate species of the genera *Dinophysis* (*D. acuta* and *D. fortii*). The first pectenotoxins to be isolated were pectenotoxin-1 (PTX1, **1**), −2 (PTX2, **2**), −3 (PTX3), −4 (PTX4 **3**) and −5 (PTX5) (Fig. 1). The absolute stereochemistry of PTX1 **1** was established by X-ray crystallography[1] and the remaining structure of the family was elucidated by comparison of NMR and mass spectroscopic data. Since then, more pectenotoxins have been isolated[2,3,4,5,6] and characterised and the most recent compound to be isolated from algae and mussels in Norway is PTX12.[6] The pectenotoxins comprise a macrolide structure containing a spiroacetal, three substituted tetrahydrofurans and 19 (or 20 in the case of PTX11) stereocentres embedded within a 40-carbon chain (Fig. 1). PTX2 **2** exhibited selective and potent cytotoxicity against several cancer cell lines at the nanomolar level.[7] PTX2 **2** and PTX6 **4** have also been shown to interact with the actin cytoskeleton at a unique site[8] thus providing an important research tool for the study of basic cellular behaviour.

The architecturally complex structure of the pectenotoxins together with their potent biological activity has attracted the attention of several research groups[9,10,11,12] however, only Evans *et al.*[13] have achieved the total synthesis of PTX4 **2** and PTX8. In light of this research group's interest in the synthesis of spiroacetal-containing natural products we herein report the full details[14] of our synthetic work focused on the synthesis of the ABC spiroacetal-containing tricyclic ring system.



1: PTX1(7*R*, R=CH_2OH)
2: PTX2 (7*R*, R=Me)
3: PTX4 (7*S*, R=CH_2OH)
4: PTX6 (7*R*, R=COOH)
5: PTX7 (7*S*, R=COOH)

Fig. 1 Structure of PTXs and the key disconnections used for their synthesis.

Results and discussion

Our retrosynthetic analysis of the key spiroacetal containing ABC tricyclic fragment **6** is depicted in Scheme 1. The ABC fragment **6** is constructed *via* a 5-*exo*-tet cyclisation of epoxy-diol **7**, in which all the necessary stereogenic centres of the C ring are already installed. Epoxy-diol **7** in turn is obtained from enyne **8** by asymmetric epoxidation followed by semi-hydrogenation and

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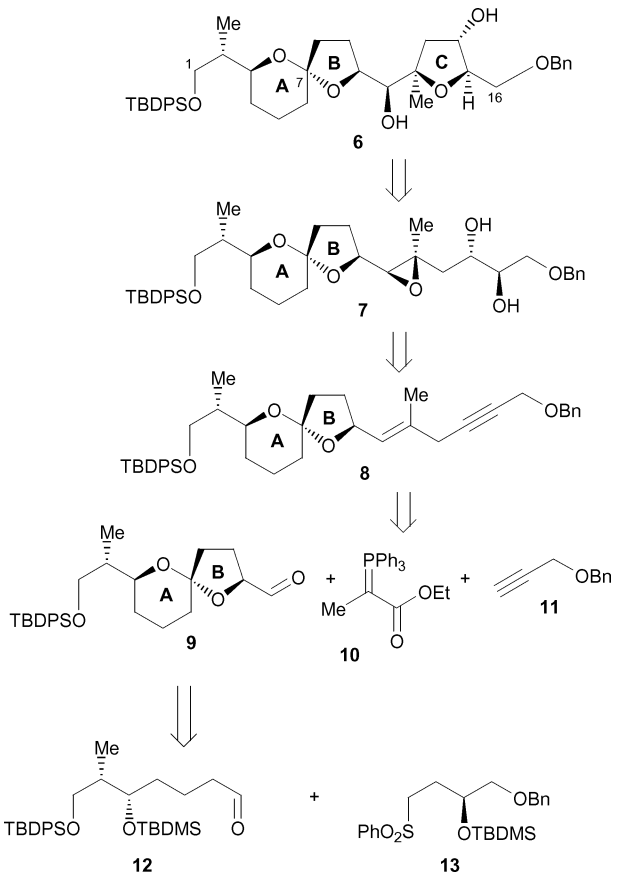


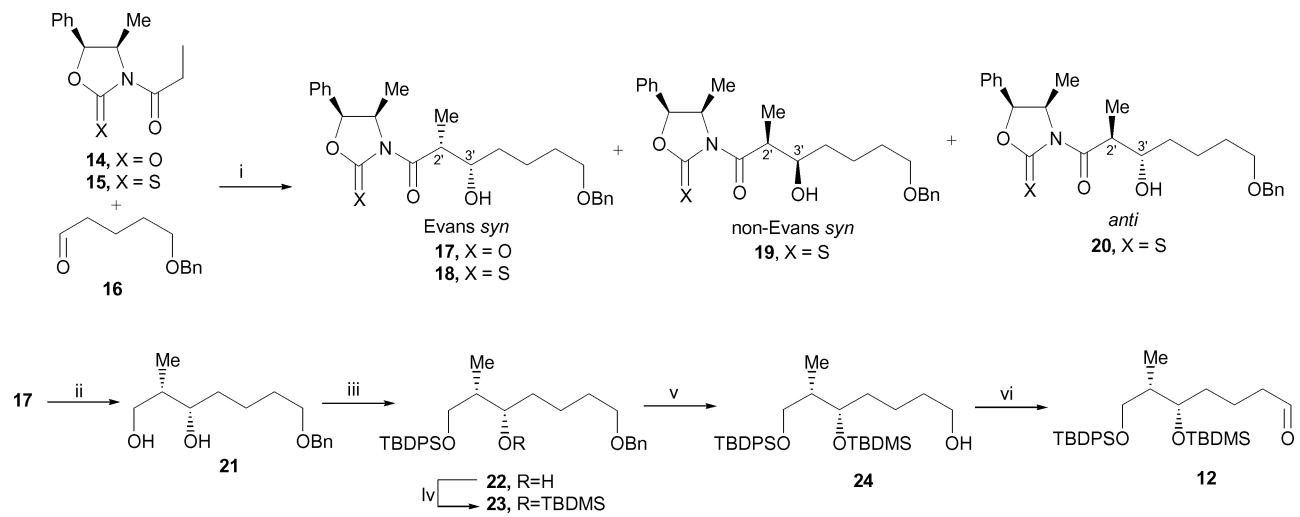
Scheme 1 Retrosynthetic analysis of ABC fragment **6**.

asymmetric dihydroxylation. Enyne **8** is prepared from spiroacetal aldehyde **9**, stabilised ylide **10** and acetylene **11**. Finally spiroacetal **9** is derived from the union of aldehyde **12** with sulfone **13**.

The synthesis of PTX2 **2** requires establishment of the (7*R*) configuration of the spirocentre. However, the (7*S*)-configuration as present in PTX4 **3** and PTX7 **5** is stabilized by the anomeric effect and is in fact thermodynamically favoured stereochemistry when the spiroacetal ring is not embedded in the macrocyclic structure. It was therefore planned to obtain the natural (7*R*)-isomer of PTX2 **2** at a later stage in the synthesis after assembly of macrolide ring based on the precedent reported by Sasaki and co-workers[4] for PTX4 **3**. Our initial attention was therefore directed towards the synthesis of spiroacetal **9** with the (7*S*)-configuration as present in PTX7 **5**.

The execution of our synthetic plan towards the synthesis of the ABC tricyclic system of PTX7 **5** commenced with the synthesis of the C1-C11 AB spiroacetal fragment starting from aldehyde **12** and sulfone **13**. The first issue to address was to install the *syn* stereochemistry in the aldehyde fragment **12** using an asymmetric aldol reaction (Scheme 2). Initial attempts to execute the aldol reaction between aldehyde **16**[15] and propanoyloxazolidinone **14**[16] using commercial (Aldrich®) dibutylboron triflate (Bu_2BOTf) as a 1 M solution in dichloromethane with diisopropylethylamine as the base to form the *Z*-enolate of propanoyloxazolidinone **14** followed by condensation with aldehyde **16** at 0 °C gave the desired *syn*-adduct **17** exclusively in only 43% yield. It was postulated that the quality of the boron reagent was responsible for the low yields observed in this reaction. Fuentes *et al.*[17] reported non-reproducible results in related aldol reactions using commercial dibutylboron triflate[18] as a solution in CH_2Cl_2 and diethyl ether.

In 1997, Crimmins and co-workers[19] reported the formation of titanium enolates of *N*-acyloxazolidinethiones rather than acyloxazolidinones using $TiCl_4$. The use of (−)-sparteine (2.5 equiv.) was found to be the most effective base, giving high rate enhancement and high selectivity for the Evans' *syn* adducts using only 1 equiv. of aldehyde and 1 equiv. of $TiCl_4$. Further investigation showed that there was minimal asymmetric induction provided by (−)-sparteine and the rate enhancement may be related to bidentate coordination of (−)-sparteine to the metal centre. The Evans *syn* adduct is the major product as coordination of the diamine to the metal centre prevents coordination of the imide or thioimide carbonyl group to the metal. Crimmins *et al.*[20] later found that use of *N*-methyl-2-pyrrolidinone (NMP, 1 equiv.)



Scheme 2 Reagents and conditions and yields: (i) **14**, $TiCl_4$ (1 M in CH_2Cl_2), (−)-sparteine, CH_2Cl_2, 0 °C then NMP, **16**, CH_2Cl_2, −78 °C to 0 °C, **17**, 90%; or **15**, $TiCl_4$ (1 M in CH_2Cl_2), (−)-sparteine, CH_2Cl_2, 0 °C then NMP, **16**, CH_2Cl_2, −78 °C to 0 °C, **18** : **19** : **20** (4.6 : 2 : 1), 76%; (ii) $LiBH_4$, THF, 0 °C, 5 min, 87%; (iii) TBDPSCl, imidazole, CH_2Cl_2, 20 h, 77%; (iv) TBDMSOTf, 2,6-lutidine, DMAP, DMF, 20 h, 95%; (v) 10% Pd/C, MeOH, H_2, 99%; (vi) PCC, K_2CO_3, CH_2Cl_2, 3 h, 99%.

as a co-reagent proved to be compatible with the reaction and the amount of (−)-sparteine could be reduced to 1.0 equiv.

It was next decided to use propanoyloxazolidinethione **15**[21] rather than propanoyloxazolidinone **14** and form the titanium enolate in the presence of (−)-sparteine as the base. Attempts to perform the aldol reaction following the Crimmins' protocol using neat $TiCl_4$ and oxazolidinethione **15** were not successful. Using a 1 M solution of $TiCl_4$ in dichloromethane to form the enolate improved the yield of the reaction (76% yield) however, the diastereoselectivity observed was disappointing giving a 4.6 : 2 : 1 mixture of Evans *syn* isomer **18** : non-Evans *syn* isomer **19** : *anti* isomer **20**. The absolute stereochemistry of the Evans *syn* adduct **18** compared to the non-Evans *syn* adduct **19** was determined by cleaving the chiral auxiliary with lithium borohydride and comparing the optical rotation of the resulting diols with the diol **21** derived from *syn*-adduct **17** that was prepared using a boron enolate as discussed above. The diol derived from compound **18** has the same optical rotation as the diol derived from compound **17** and was therefore assigned as the Evans *syn* adduct. On the other hand, the diol derived from compound **19** had the opposite optical rotation and was assigned as the non-Evans *syn* adduct.

The reasons for the low selectivity using the Crimmins' procedure using propanoyloxazolidinethione **15** were not clear but the different substituents on the oxazolidinethione employed may play a role in the selectivity. In the Crimmins' experiments, an oxazolidinethione possessing a benzyl group at C4 was used[19,20] while in our case oxazolidinethione **15** only contains a methyl group at C4 and a phenyl group at C5.

The next attempt to generate the *syn* configuration involved the use of oxazolidinone **14** that had been prepared earlier for the aldol reactions using boron enolates. This study also probed whether the nature of the substituents attached to the chiral auxiliary was responsible for the low selectivity in the reaction of the titanium enolate of oxazolidinethione **15** with aldehyde **16**. Enolisation of **14** with 1.0 equiv. of 1 M $TiCl_4$ in CH_2Cl_2 in the presence of 1.0 equiv. of (−)-sparteine was carried out at 0 °C. The mixture was cooled to −78 °C, NMP was then added followed by the addition of 1.1 equiv. of aldehyde **16**. Pleasingly, this reaction afforded the desired Evans *syn* adduct **17** in 90% yield with the *anti* isomer only being observed in small quantities (<1% yield). This reaction was reproducible giving consistent and satisfactory results and was adopted as the method of choice for use in the subsequent steps towards the ABC ring of PTX7 **5**.

The fact that oxazolidinethione **15** was less selective for formation of the expected Evans *syn* adduct **18** than the analogous formation of Evans *syn* adduct **17** from oxazolidinone **14** might be attributed to the known higher affinity of sulfur for titanium than oxygen[22] resulting in a competitive pathway proceeding *via* a chelation transition state **TS I** rather than a non-chelation transition state **TS II** (Fig. 2). In the case of oxazolidinone **14**, where the oxygen of the oxazolidinone carbonyl group has less affinity to bind to titanium, reaction proceeds *via* the non-chelation transition state **TS II** affording the Evans *syn* adduct **17** especially in the presence of (−)-sparteine which coordinates to the titanium and prevents further coordination of the oxazolidinone carbonyl group.

Having finally fully ascertained the conditions required to execute the aldol reaction with the desired *syn* stereochemistry, the next step was to remove the chiral auxiliary and install a

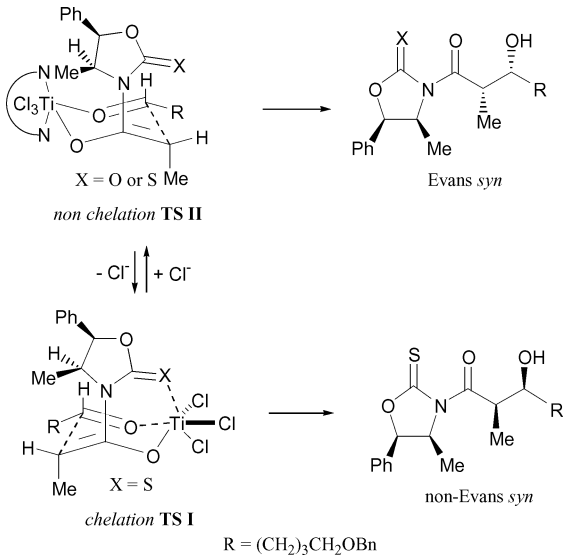


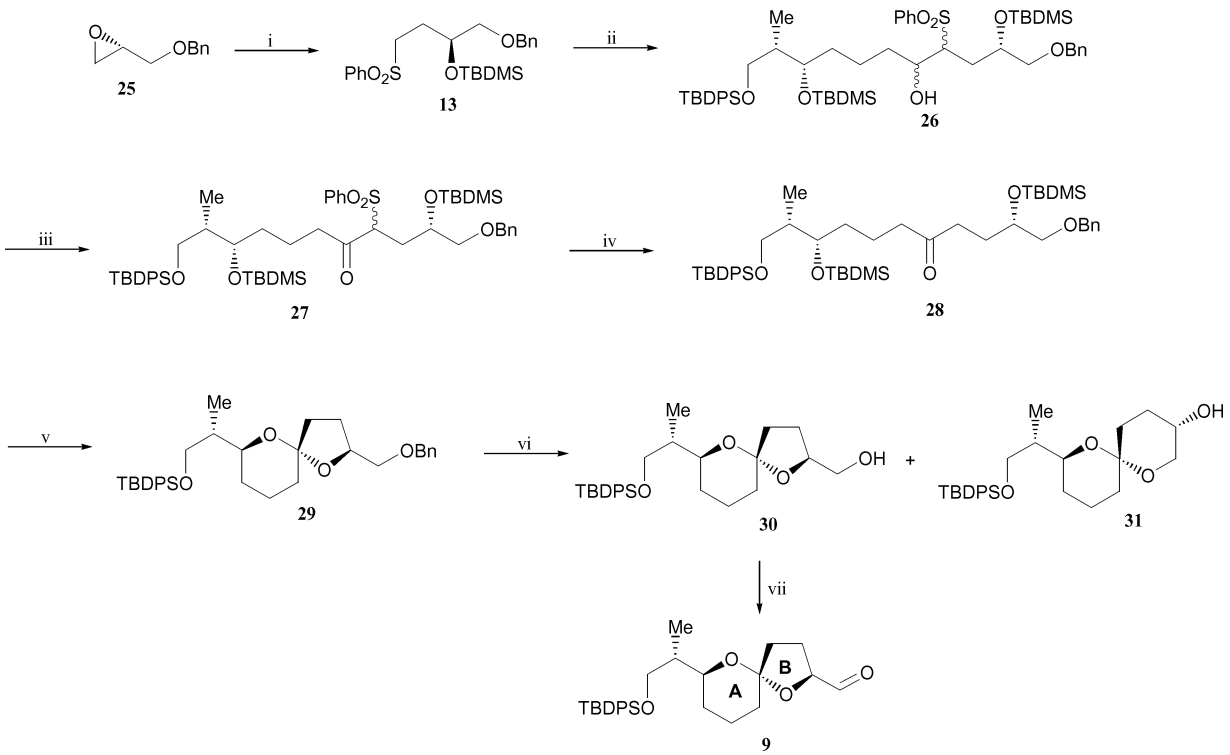
Fig. 2 Chelation and non-chelation transition states.

protecting group at the resulting terminal hydroxyl group. The chiral auxiliary in **17** was first removed using lithium borohydride to give diol **21**. The primary alcohol in diol **21** was then selectively protected as a TBDPS ether **22** and the secondary alcohol was also protected to give TBDMS ether **23** (Scheme 2). These steps proceeded smoothly giving an overall yield of 64% over three steps from the *syn* adduct **17**. The benzyl group was next removed by hydrogenolysis using palladium on carbon as catalyst to give a quantitative yield of alcohol **24**. Oxidation of **24** using pyridinium chlorochromate in the presence of potassium carbonate afforded the desired aldehyde **12** in 99% yield.

Sulfone **13** was prepared starting from (*R*)-(+)-benzylglycidol **25** (Scheme 3). Treatment of methyl phenyl sulfone with BuLi in a mixture of THF and hexamethylphosphoramide (HMPA) followed by addition of glycidol **25** effected regioselective ring opening of the epoxide. The resulting alkoxide was then trapped directly with a premixed solution of *tert*-butyldimethylsilyl trifluoromethanesulfonate and 2,6-lutidine in THF affording the required sulfone **13** in 97% yield. It was also crucial to use two molar equivalents of HMPA in this reaction in order to obtain a high yield.[23]

With sulfone **13** efficiently in hand, the next step was to effect its union with aldehyde **12**. The union of aldehyde **12** with sulfone **13** in THF using BuLi as base proceeded smoothly giving a mixture of the four diastereomeric alcohols **26** (Scheme 3). Oxidation of the resulting alcohols **26** to the two diastereomeric ketones **27** was next effected using Dess–Martin reagent[24] in dichloromethane with pyridine as base proceeding in 82% yield over 2 steps. Excess unreacted sulfone **13** could be recovered from the coupling reaction and reused in the synthesis. The mixture of sulfone diastereomers **27** was then exposed to sodium mercury amalgam in methanol to give ketone **28** as a single isomer in 68% yield.

Selective deprotection of the TBDMS groups in the presence of the benzyl and TBDPS groups was achieved by heating ketone **28** at reflux with *p*-toluenesulfonic acid in toluene for several hours. This method resulted in clean cyclisation of the resulting diol to give the 5,6-spiroacetal **29** as a single isomer in 84% yield. The next step after formation of spiroacetal **29** required removal of



Scheme 3 Reagents and conditions and yields: (i) $MeSO_2Ph$, BuLi, HMPA, **25**, THF, then premixed solution of TBDMSOTf and 2,6-lutidine, THF, 97%; (ii) BuLi, THF, then **12**, −78 °C, 88%; (iii) Dess–Martin periodinane, py, CH_2Cl_2, 93%; (iv) 10% Na/Hg, Na_2HPO_4, MeOH, 68%; (v) p-TsOH, toluene, 80 °C, 4 h, 84%; (vi) Raney Ni, EtOH, 35 °C, 2 d, **30**, 82%; or 10% Pd/C, EtOAc, 4.5 h, **30** : **31** (3 : 1), 100%; (vii) Dess–Martin periodinane, py, CH_2Cl_2, 95%.

the terminal benzyl group to the primary alcohol **30**. Initially, the deprotection step was carried out using 10% palladium on carbon under a hydrogen atmosphere in ethyl acetate. Unfortunately these conditions also effected ring opening of the spiroacetal resulting in formation of a 3 : 1 mixture of the desired 5,6-spiroacetal **30** and the more thermodynamically favoured 6,6-spiroacetal system **31**. Changing the nature of the palladium catalyst to palladium hydroxide also afforded substantial quantities of the undesired 6,6-spiroacetal **31** and use of lithium aluminium hydride afforded a low yield of 5,6-spiroacetal **30** together with several other by-products. Finally, use of Raney nickel in ethanol at 35 °C for 48 h gave exclusively the desired 5,6-spiroacetal **30** in 82% yield and no 6,6-spiroacetal **31** was detected.

The formation of 6,6-spiroacetal **31** was confirmed by the ^{13}C NMR spectrum that exhibited a spiroacetal carbon at δ_C 94.6 ppm, similar to the 6,6-spiroacetal carbon observed in the natural products PTX8 or PTX9[4] (Fig. 3). The methine carbon assigned to C-3 in **31** was observed at δ_C 69.6 ppm, considerably upfield

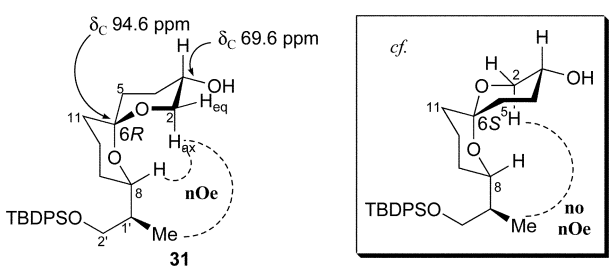


Fig. 3 NOE correlations for spiroacetal **31**.

from the corresponding methine carbon in 5,6-spiroacetal systems (*cf.* 78–85 ppm).[25,26] Further support for structure **31** comes from the coupling pattern observed for H-2_{ax} (dd, J_{gem} 10.3, $J_{2ax,3ax}$ 10.3 Hz), consistent with the presence of an axial proton at C-3 with the hydroxyl group at C-3 being assigned to an equatorial position. The absolute configuration of the spiroacetal centre was determined from NOE studies. As depicted in Fig. 3, the isomer with the (6*R*)-configuration at the spirocentre shows a correlation between H-2_{ax} and the methyl group at C-1′. A similar NOE effect was not expected in the spiroacetal with the (6*S*)-configuration. An additional correlation was expected between H-2_{ax} and H-8_{ax}. However, the resonance for H-8 in the ^1H NMR spectrum overlapped with other signals, namely H-3 and H-2′B. However, given the correlation observed between H-2 and the methyl group, spiroacetal **31** was assigned the (6*R*)-configuration. The (6*R*)-isomer was also expected to be the major product due to operation of the anomeric effect. Similar observations were also reported for PTX8 and PTX9 that also contain a 6,6-spiroacetal ring system.[4]

The structure of the 5,6-spiroacetal ring system in **30** was established from the resonance assigned to the spirocarbon at δ_C 106.4 ppm in the ^{13}C NMR spectrum similar to the spirocarbon observed at δ_C 106.2 ppm in PTX7 **5**.[4] The methine proton H-2 in 5,6-spiroacetal **30** was observed at δ_C 77.6 ppm. A summary of the characteristic ^{13}C NMR resonances is given in Table 1.

Once the debenzylation step had been successfully achieved, oxidation of the alcohol to the corresponding aldehyde **9** was required in preparation for the Wittig olefination step (see retrosynthesis, Scheme 1). The oxidation step was effected using Dess–Martin reagent[24] in pyridine affording aldehyde **9** in

Table 1 Characteristic ^{13}C NMR resonances for spiroacetals **31** and **30** compared to PTX9 and PTX7, respectively

	31	PTX9 (*R*)-6,6-spiroacetal	**30**	PTX7 (*R*)-5,6-spiroacetal
spirocarbon centre (δ_C)	94.6 ppm	96.6 ppm	106.4 ppm	106.2 ppm
CHO of B ring (δ_C)	C3 = 69.6 ppm	C3 = 67.4 ppm	C2 = 77.6 ppm	C2 = 79.7 ppm

quantitative yield (Scheme 3). The aldehyde thus obtained was not stable upon prolonged storage and was therefore freshly prepared immediately before use in the subsequent step. NOE correlations were observed for spiroacetal **9** (Fig. 4) between H-2 and H-7 and also between H-2 and the methyl group, thus suggesting that O1 and O6 are axial to each other and that C4 adopts an equatorial position on the A ring. These observations established the (5*S*)-configuration of the 5,6-spiroacetal ring system as was expected due to anomeric stabilization dominating the thermodynamically controlled cyclization process. This conclusion was also consistent with the NOE studies carried out for PTX7 **5** that also contains a 5,6-spiroacetal core system with the (*S*)-configuration at the spirocentre.[4] Furthermore these NOE studies also established that no epimerisation had occurred during the debenzylation and oxidation steps.

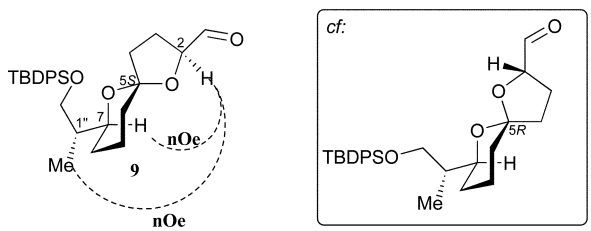
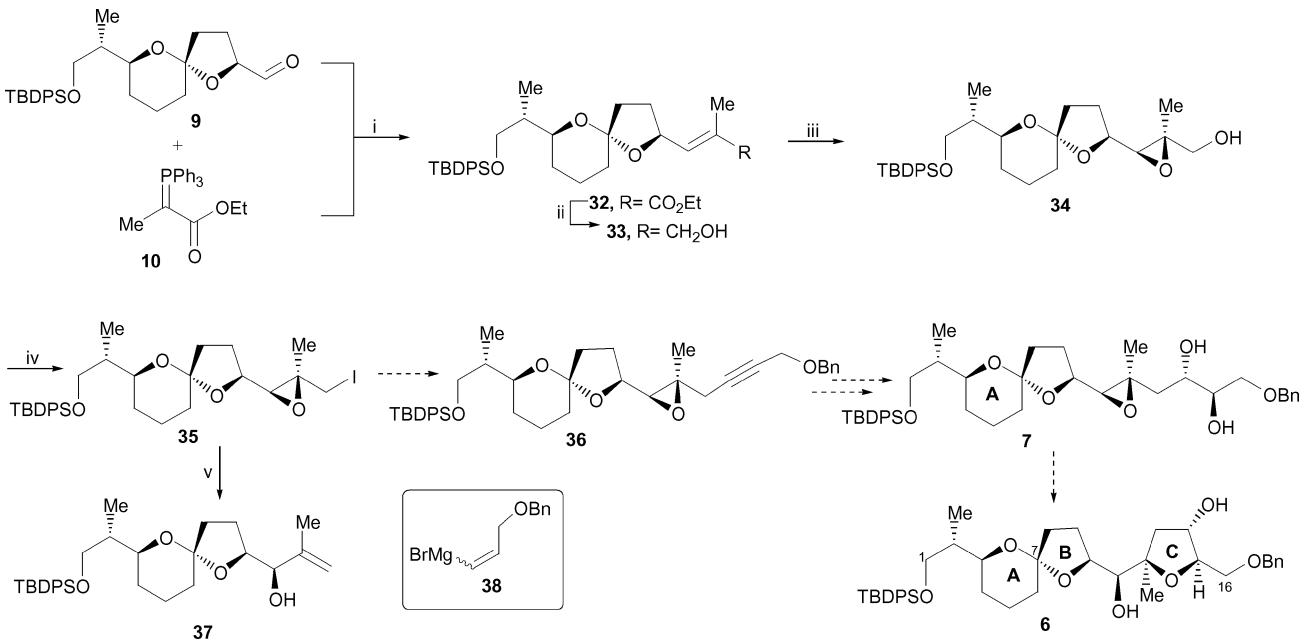


Fig. 4 NOE correlations for spiroacetal **9**.

Assembly of the ABC tricyclic ring system began with Wittig olefination of spiroacetal aldehyde **9** with ylide **10** (Scheme 4) affording olefin **32** ($E:Z = 100:1$ by ^1H NMR) in quantitative yield. Reduction of ester **32** to alcohol **33** was then achieved in 91% yield using di-*iso*-butylaluminium hydride in CH_2Cl_2 at −78 °C. With our sights set on epoxydiol **7** as the immediate precursor to the desired tricyclic fragment **6** (see retrosynthesis, Scheme 1) it was decided to install the epoxide functionality at this stage by taking advantage of the allylic alcohol which can be used to effect a Sharpless asymmetric epoxidation. Treatment of allylic alcohol **33** with Ti(O-*i*Pr)$_4$, (+)-diethyl L-tartrate, *tert*-butylhydroperoxide afforded epoxy alcohol **34** in 71% yield with the required (*S*,*S*)-stereochemistry in accordance with the Sharpless mnemonic. The ^1H NMR spectra established the diastereomeric ratio to be >100 : 1. Conversion of the primary alcohol **34** to an iodide **35** was successfully carried out in 83% yield *via* formation of the mesylate. Iodide **35** was isolated as a yellow oil and was able to be stored in the freezer for a few days before subsequent use.

With iodide **35** in hand, the next step was to install the remaining three carbons required for subsequent assembly of the tetrahydrofuran ring. Attempts to displace iodide **35** with the lithium acetylide generated from acetylene **11**[27] in THF only afforded recovered starting material. Use of hexamethylphosphoramide (HMPA) as an additive to improve the reactivity of the acetylide[28] only led to the formation of allylic alcohol **37** (86% yield) presumably resulting from lithium–halogen exchange of



Scheme 4 Reagents and conditions and yields: (i) CH_2Cl_2, 0 °C to 20 °C, 20 h, 99%; (ii) 1 M DIBAL-H, CH_2Cl_2, −78 °C, 91%; (iii) Ti(OiPr)$_4$ (10 mol%), L-(+)-DET (12 mol%), ^{t}BuOOH, 4 Å MS, CH_2Cl_2, 71%; (iv) MsCl, Et_3N, DMAP, THF, 0 °C, 1 h, then NaI, $NaHCO_3$, acetone, 50 °C, 24 h, 83%; (v) acetylene **11**, BuLi, THF, −78 °C, then HMPA, **35**, THF, −78 °C to 20 °C, 86%.

the epoxy iodide **35** followed by rapid elimination of the β-epoxy bond. None of the desired displacement product **36** was observed. Formation of the acetylenic Grignard reagent of **11** followed by reaction with iodide **35** in the presence of copper iodide (0.1 equiv.) and HMPA in THF also only afforded allylic alcohol **37**.

At the time this work was being carried out, Millar and Underhill[29] reported that the addition of 1-iodo-*cis*-2,3-epoxides to alkynyl-lithium or alkynyl-Grignard reagents in THF–HMPA, with or without CuI catalysis, afforded the allylic alcohol products in preference to the displacement product. This study confirmed that reductive elimination as a result of metal halogen exchange was a common issue faced when attempting to displace halides in a halo epoxide, by an acetylide. An alternative method involving addition of 1-halo or 1-tosyl-*cis*-2,3-epoxides to divinylcuprates[30,31] in either THF, ether, or a THF–ether mixture with varying proportions of HMPA and/or triethyl phosphite, also afforded the elimination product rather than the desired displacement product. In order to overcome this problem, Millar and Underhill used methodology initially reported by Nicolaou *et al.*[32] whereby inverse addition of a substituted vinylmagnesium bromide to preformed solutions of 1-iodo-2,3-epoxides with a catalytic amount of copper iodide in THF–HMPA afforded good yields of the nucleophilic substitution products.[29] In our case, however, attempts to displace iodide **35** with either (*E*)- or (*Z*)-vinylmagnesium bromide **38** were unsuccessful.

In light of the fact that nucleophilic substitution of AB spiroacetal epoxy iodide **35** by the derived-from acetylene **11** was not successful, it was decided to pursue an alternative strategy involving epoxidation at a later stage. It was postulated that the remaining carbon chain of the C1–C16 fragment **8** could be installed *via* nucleophilic substitution of allylic iodide **39** rather than epoxy iodide **35** (Scheme 5).

AB spiroacetal-containing allylic alcohol **33** was converted to the corresponding iodide **39** *via* the mesylate. Treatment of the mesylate with sodium iodide at room temperature for 2 h afforded iodide **39**, which was used in the next step without any purification. Addition of the iodide **39** in THF to the acetylide formed from acetylene **11** with BuLi in THF at −78 °C followed by warming the mixture to 0 °C afforded the (*E*)-enyne **8** in 56% yield together with (*Z*)-enyne **40** in 18% yield. The formation of two diastereomers of the coupled product was unexpected given that the starting allylic alcohol used was a pure single isomer therefore only a single isomer of the coupled product was expected. The NOESY spectra for the major (*E*)-alkene **8** showed a correlation between H-1′ and H-3′ and no correlation between H-3′ and H-2 (Fig. 5). For the minor alkene **40**, an NOE correlation was observed between H-2 and H-3′ and no NOE correlation was observed between H-1′ and H-3′, thereby establishing the (*Z*)-stereochemistry of alkene **40**.

Having finally fully assembled the C1–C16 carbon chain fragment of PTX7 **5**, in the form of spiroacetal enyne **8**, our attention next focused on the conversion of the enyne unit to the required epoxy diol fragment **7** which could be transformed into the target ABC ring fragment **6** by acid catalysed cyclization (Scheme 5). The *syn*-epoxide was envisaged to be formed *via* asymmetric epoxidation and the diol by asymmetric dihydroxylation of the olefin formed upon subsequent semi-hydrogenation of the triple bond.

The first attempts to effect epoxidation of alkene **8** were carried out using achiral epoxidation reagents *m*-CPBA and dimethyldioxirane (DMDO) hoping that the neighbouring C–O bond on the adjacent chiral centre may influence the stereochemical outcome of epoxidation. Epoxidation of (*E*)-enyne **8** using *m*-CPBA in CH_2Cl_2 afforded a 1.2 : 1 mixture of the *syn*-epoxide **36** and *anti*-epoxide **42** in 76% yield. Epoxidation of (*E*)-enyne **8** using freshly prepared DMDO[33,34,35] in acetone for 36 h afforded a 1.8 : 1 mixture of the *syn*-epoxide **36** and *anti*-epoxide **42** in 78% yield.

Disappointed by the lack of selectivity in the epoxidation of (*E*)-enyne **8** using achiral epoxidation agents, it was decided to use a chiral dioxirane generated *in situ* from potassium peroxomonosulfate (Oxone®) and a chiral fructose-derived ketone, a method reported by Shi *et al.*[36] to effect epoxidation of unfunctionalised (*E*)-olefins in a highly enantioselective fashion. Based on the predictive model, invoking the spiro transition state model[36] it was envisaged that use of ketone **41**, derived from L-fructose, would generate the desired *syn*-epoxide **36** whilst use of the enantiomeric D-fructose derived ketone would result in predominant formation of the undesired *anti*-epoxide **42**.

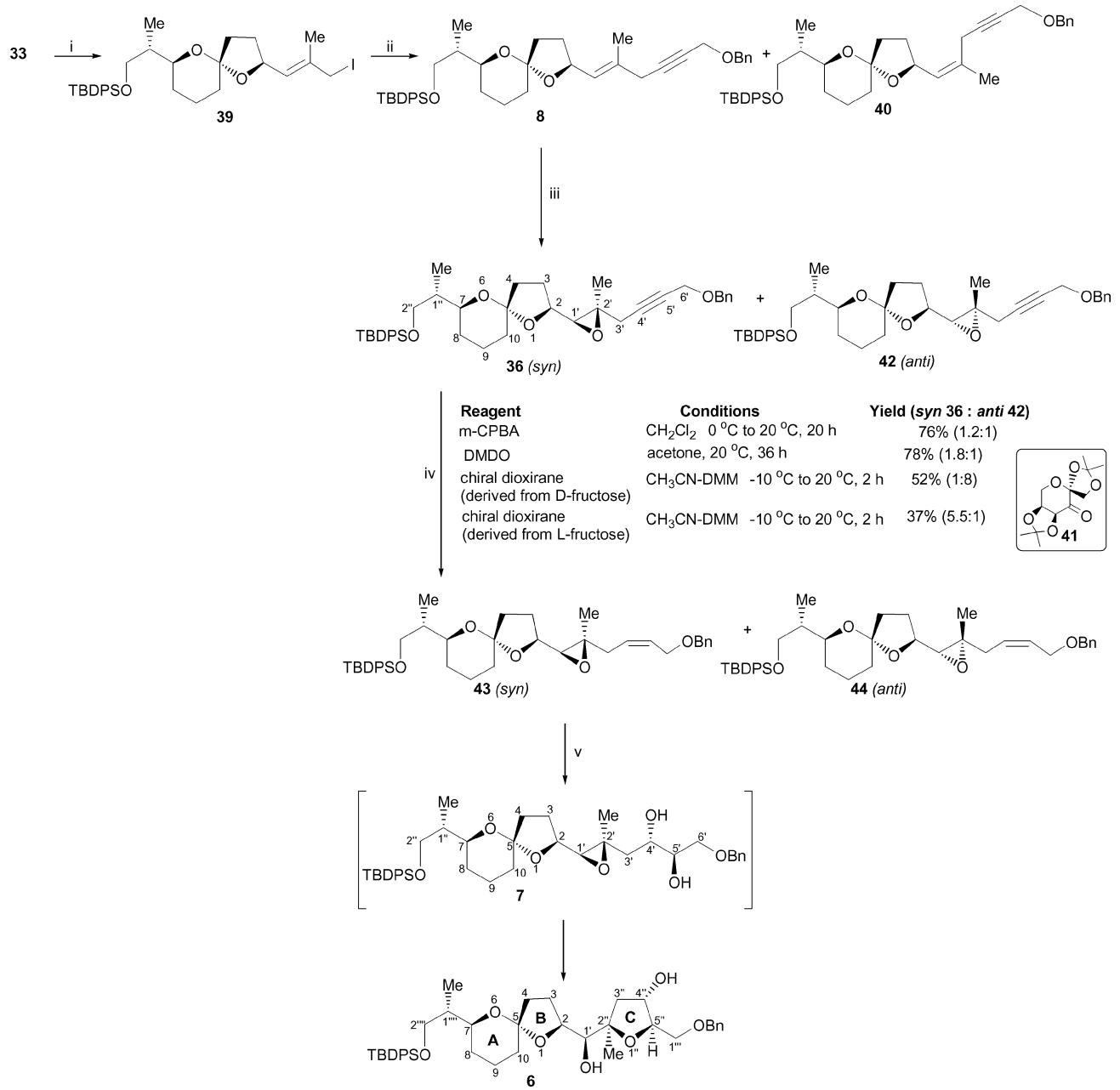
The chiral ketone ent-**41**, derived from naturally occurring D-fructose, was commercially available whereas the ketone **41**, derived from L-fructose, was not commercially available and was prepared from L-sorbose.[37] Reaction of (*E*)-enyne **8** with the more readily available chiral dioxirane prepared *in situ* from D-fructose derived ketone ent-**41** (3 equiv.) and oxone® (3 equiv.) at −10 to 20 °C in acetonitrile and dimethoxymethane (DMM) (1 : 2 *v*/*v*) for 2 h afforded an inseparable 1 : 8 mixture of the *syn*-epoxide **36** : *anti*-epoxide **42** in 52% yield (see Table in Scheme 5). In this case the major epoxide formed had the opposite configuration to the major epoxide formed using *m*-CBPA and DMDO.

Epoxidation of (*E*)-enyne **8** with the chiral dioxirane formed from L-fructose derived ketone **41** was then attempted in an effort to produce more of the desired *syn*-epoxide **36**. Epoxidation of (*E*)-enyne **8** using chiral ketone **41** and oxone® was carried out using the same conditions as those described above using D-fructose derived ketone ent-**41**. However, in this case (see Table in Scheme 5) conversion to the epoxide proceeded in a lower 37% yield. Encouragingly the stereoselectivity observed was promising with a 5.5 : 1 ratio of the desired *syn*-epoxide **36** to *anti*-epoxide **42** being observed.

Although the epoxides **36** and **42** obtained were in fact an inseparable mixture of two isomers, the two isomers were distinguishable by ^{1}H NMR, with the epoxide resonance, H-1′,‡ providing a diagnostic tool. H-1′ in *syn*-epoxide **36** resonated as a doublet at δ_H 2.89 ppm with coupling constant, *J* 8.0 Hz whereas H-1′ in *anti*-epoxide **42** resonated as a doublet further downfield at δ_H 2.92 ppm with *J* 7.6 Hz.

The 5.5 : 1 mixture of *syn*-epoxide **8** : *anti*-epoxide **41** was subjected to semi-hydrogenation over Lindlar catalyst affording a 5.5 : 1 mixture of (*Z*)-olefin **43**: (*Z*)-olefin **44** in 88% yield in preparation for the subsequent asymmetric dihydroxylation[38] (AD) step. High enantioselectivity in the AD of (*Z*)-olefins is usually observed when the size of the two olefinic substituents is significantly different. In the case of (*Z*)-olefin **43**, we hoped that high enantioselectivity would be observed given that it contains two sterically different substituents. High enantioselectivity in

‡ The numbering system based on a 1,7-dioxaspiro[5.5]undecane ring system is used rather than PTX numbering system.



Scheme 5 Reagents and conditions and yields: (i) MsCl, Et_3N, THF, 0 °C, 20 min, then NaI, THF, 20 °C, 2 h, filter; (ii) acetylene **11**, BuLi, THF, −78 °C, then iodide **39**, THF, −78 °C to 0 °C, 20 h, **8**: 56%, **40**: 18%; (iii) see Table in Scheme; (iv) H_2, $Pd/CaCO_3$ (5% Pb), Et_3N, hexane, 50 min, **43**, 88%; (v) DHQ-IND, $K_3Fe(CN)_6$, $MeSO_2NH_2$, OsO_4, $^tBuOH–H_2O$ (1 : 1), 20 h, **6**, 38%; or OsO_4, acetone–H_2O (5 : 1), 18 h, **6**, 70%.

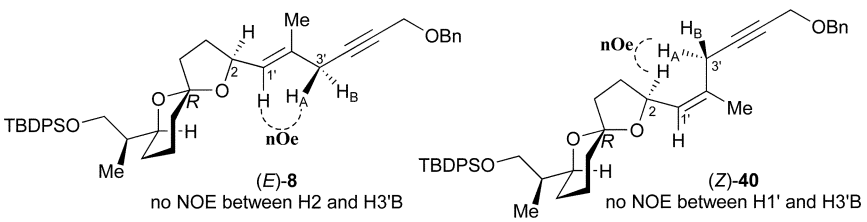


Fig. 5 NOE correlations for (*E*)-**8** and (*Z*)-**40**.

the AD of (*Z*)-olefins can be achieved by using an indoline type of ligand (DHQ-IND or DHQD-IND)[39] and application of the mnemonic developed for predicting stereoselectivity in AD reactions predicts that using DHQ-IND, the hydroxyl group would be predominantly delivered to (*Z*)-olefin **43** from the α-face affording diol **7** that would undergo cyclization to the desired spiroacetal-containing tetrahydrofuran **6**.

AD reaction of the 5.5 : 1 mixture of (*Z*)-olefins **43** : **44** using DHQ-IND as the chiral ligand afforded the ABC ring fragment **6** in 38% yield together with a complex diastereomeric mixture of diols (43% yield). The exact stereochemistry of the diol mixture obtained was not established and the lack of diastereoselectivity observed in this reaction was disappointing.

The low yield of the desired tricyclic fragment **6** obtained using DHQ-IND as the chiral ligand prompted us to investigate the use of OsO_4 without the asymmetric catalyst to see whether the neighbouring chiral centres in the olefin substrate might influence the stereoselectivity in the dihydroxylation step. Somewhat surprisingly treatment of the 5.5 : 1 mixture of (*Z*)-olefins **43** : **44** with OsO_4 afforded the desired tricyclic fragment **6** as the major product in 70% yield together with a mixture of diols (<10% yield). Thus, the neighbouring chiral centres in this system clearly play a role in the hydroxylation which may contribute to the lower diastereoselectivity being observed in the above reaction using DHQ-IND as the chiral ligand.

The NOESY spectrum for tricyclic fragment **6** showed a clear correlation between C2″-Me and H-5″ thus establishing the desired *syn* relationship between these two groups on the tetrahydrofuran C ring system. The ^{13}C NMR data for the ABC tricyclic fragment **6** was compared to the ^{13}C NMR data reported for the ABC fragment of PTX7 **5** since both of these compounds contain a spiroacetal ring system with the (*S*)-configuration at the spiroacetal centre (*cf.* PTX2 **2** has the (*R*)-configuration at the spirocentre). The ^{13}C NMR data obtained for both tricyclic fragments were in fact similar rendering support for the successful synthesis of the ABC tricyclic fragment **6** of PTX7 **5** (Fig. 6). Synthetic efforts towards the synthesis of the E and FG fragments of the pectenotoxins are now underway in preparation for union with the ABC fragment **6** reported herein.

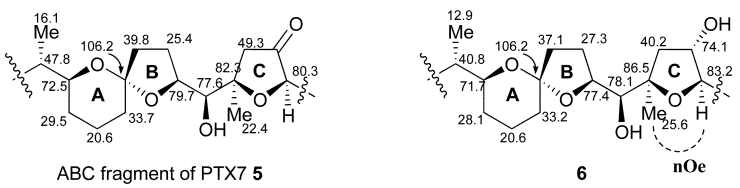
Experimental

(2*S*, 9*S*, 10*S*)-(−)-1-Benzyloxy-2,9-bis-(*tert*-butyldimethylsilyloxy)-11-(*tert*-butyldiphenylsilyloxy)-10-methylundecane-5-one (28)

To a solution of sulfone **13** (0.1 g, 0.23 mmol) in dry THF (1 mL) at −78 °C was added a solution of BuLi (0.15 mL, 1.6 M solution in hexane, 0.24 mmol). After 30 min, a solution of aldehyde **12** (0.11 g, 0.21 mmol) in dry THF 1.5 mL) was added and the mixture was stirred for 2.5 h at −78 °C. The reaction was quenched with saturated NH_4Cl solution (1 mL), warmed to room temperature and extracted with Et_2O (3 × 5 mL). The combined organic phase was washed with brine (2 × 3 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give the crude mixture that was purified by flash chromatography using hexane–ethyl acetate (9 : 1) as eluent to afford alcohols **26** as a mixture of four diastereomers (0.185 g, 88%) as a pale yellow oil.

The mixture of alcohols **26** (0.176 g, 0.19 mmol), Dess–Martin periodinane[24] (0.15 g, 0.37 mmol) and pyridine (0.06 mL, 0.74 mmol) in dry CH_2Cl_2 (3 mL) was stirred at room temperature for 5 h. Saturated NH_4Cl solution (2 mL) was added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by flash chromatography using hexane–ethyl acetate (95 : 5) as eluent to afford sulfones **27** (0.163 g, 93%) as a mixture of diastereomers.

To a stirred solution of sulfones **27** (0.13 g, 0.14 mmol) and anhydrous Na_2HPO_4 (0.078 g, 0.55 mmol) in MeOH (2 mL) was added 10% Na/Hg amalgam (0.1 g) at room temperature. The reaction mixture was vigorously stirred for 1 h then poured into saturated NH_4Cl solution (4 mL). Residual amalgam was removed by decantation and the mixture extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (2 × 15 mL) and dried over $NaSO_4$. The solvent was removed under reduced pressure. The crude mixture was purified by flash chromatography using hexane–ethyl acetate (95 : 5) as eluent to afford the title compound **28** (75 mg, 68%) as a pale yellow oil; $[\alpha]_D$ −2.5° (c = 1.4, $CHCl_3$); found: MH^+, 805.5079, $C_{47}H_{77}O_5Si_3$ requires 805.5079; ν_{max} (cm^{-1}) 1604s (C=O), 1495s, 1460m, 1250w (Si–O–C); δ_H (300 MHz, $CDCl_3$) −0.001 (3H, s, Me_2^{t}BuSi), 0.02 (3H, s, Me_2^{t}BuSi), 0.05 (6H, s, Me_2^{t}BuSi), 0.83 (3H, d, J 7.5 Hz, Me), 0.85 (9H, s, Me_2^{t}*Bu*Si), 0.89 (9H, s, Me_2^{t}*Bu*Si), 1.07 (9H, s, ^{t}*Bu*Ph_2Si), 1.20–1.98 (7H, m, H-3, H-7, H-8, H-10), 2.37 (2H, t, J 7.0 Hz, H-6), 2.46 (2H, m, H-4), 3.34–3.41 (2H, m, H-1), 3.48 (1H, dd, J 6.6, 9.8 Hz, H-11A), 3.62 (1H, dd, J 6.6, 9.8 Hz, H-1B), 3.79–3.82 (2H, m, H-2 and H-9), 4.52 (2H, s, CH_2Ph), 7.26–7.43 (11H, m, Ph), 7.64–7.70 (4H, m, Ph); δ_C (75 MHz, $CDCl_3$) −4.8 (CH_3, Me_2^{t}BuSi), −4.6 (CH_3, Me_2^{t}BuSi), −4.4 (CH_3, Me_2^{t}BuSi), −4.2 (CH_3, Me_2^{t}BuSi), 10.7 (CH_3, Me), 18.0 (C, Me_2^{t}*Bu*Si), 18.1 (C, Me_2^{t}*Bu*Si), 19.2 (C, Ph_2^{t}*Bu*Si), 20.1 (CH, C-7), 25.7 (CH_3, Me_2^{t}*Bu*Si), 25.8 (CH_3, Me_2^{t}*Bu*Si), 26.9 (CH_3, Ph_2^{t}*Bu*Si), 28.4 (CH_2, C-3), 34.1 (CH_2, C-8), 38.1 (CH_2, C-4), 39.9 (CH, C-10), 42.8 (CH_2, C-6), 66.1 (CH_2, C-1), 70.4 (CH, C-2), 71.9 (CH, C-9), 73.3 (CH_2, CH_2Ph), 74.4 (CH_2, C-11), 127.55 (CH, Ph), 127.57 (CH, Ph), 127.6 (CH, Ph), 128.3 (CH, Ph), 128.47 (CH, Ph), 128.5 (CH, Ph), 133.9 (C, Ph), 134.0 (C, Ph), 135.6 (CH, Ph), 138.3 (C, Ph), 210.5 (C, C-5); m/z (FAB) 806 (MH^+, 0.24%), 748 (M–^{t}Bu, 0.48%), 269 (5%), 135 (CH_2CH_2OBn, 34%), 91 (CH_2Ph, 100%), 73 (76%).



ABC fragment of PTX7 **5** **6**

Fig. 6 Comparison of ^{13}C NMR data for **6** and the ABC fragment of PTX7 **5**.

(2*S*, 5*S*, 7*S*, 1″*S*)-(+)-2-(1′-Benzyloxymethyl)-7-{2″-(*tert*-butyldiphenylsilyloxy)-1″-methylethyl}-1,6-dioxaspiro[4.5]decane (29)

A mixture of ketone **28** (0.91 g, 1.13 mmol) and *p*-toluenesulfonic acid monohydrate (0.43 g, 2.26 mmol) in toluene (10 mL) was heated under reflux for 4 h. The brown solution was cooled to room temperature, diluted with Et_2O (20 mL) and washed with brine (3 × 20 mL). The organic phase was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude mixture was purified by flash chromatography using hexane–ethyl acetate (95 : 5) as eluent to afford the title compound **29** (0.53 g, 84%) as a pale yellow oil; $[\alpha]_D$ +21.5° ($c = 0.9$, $CHCl_3$) [lit.[10] $[\alpha]_D$ +13.9° ($c =$ 0.9, $CHCl_3$)]; found: $M^{+\bullet}$, 558.3160; $C_{35}H_{46}O_4Si$ requires 558.3165; ν_{max} (cm^{-1}) 1427w, 1265s (Si–O–C); δ_H (300 MHz, $CDCl_3$) 0.94 (3H, d, *J* 6.8 Hz, Me), 1.04 (9H, s, $^tBuPh_2Si$), 1.28 (1H, m, H-8A), 1.45–1.69 (7H, m, H-3A, H-4A, H-8B, H-9A, H-10, H-1″), 1.82 (2H, m, H-4B and H-9B), 2.04 (1H, m, H-3A), 3.48 (3H, m, H-1′ and H-2″A), 3.66 (1H, dd, *J* 5.5, 9.9 Hz, H-2″B), 3.76 (1H, m, H-7), 4.18 (1H, m, H-2), 4.56 (2H, s, CH_2Ph), 7.25–7.43 (11H, m, Ph), 7.64–7.68 (4H, m, Ph); δ_C (75 MHz, $CDCl_3$) 12.6 (CH_3, Me), 19.3 (C, $^tBuPh_2Si$), 20.5 (CH_2, C-9), 26.4 (CH_2, C-3), 26.9 (CH_3, $^tBuPh_2Si$), 28.1 (CH_2, C-8), 32.9 (CH_2, C-10), 37.3 (CH_2, C-4), 40.8 (CH, C-1″), 66.1 (CH_2, C-2″), 71.1 (CH, C-7), 72.6 (CH_2, C-1′), 73.2 (CH_2, CH_2Ph), 106.3 (C, C-5), 127.4 (CH, Ph), 127.5 (CH, Ph), 127.6 (CH, Ph), 128.3 (CH, Ph), 129.5 (CH, Ph), 134.1 (C, Ph), 135.6 (CH, Ph), 138.6 (C, Ph); *m*/*z* 558 (M^+, 0.1%), 501 (M–^{t}Bu, 501), 437 (M–OBn, 9%), 91 (CH_2Ph, 100%).

(2*S*, 5*S*, 7*S*, 1″*S*)-(+)-7-{2″-(*tert*-Butyldiphenylsilyloxy)-1″-methylethyl}-2-hydroxymethyl-1,6-dioxaspiro[4.5]decane (30)

To a slurry of Raney nickel (washed twice with absolute EtOH) in absolute EtOH (2 mL) was added a solution of benzyl ether **29** (130 mg, 0.23 mmol) in absolute EtOH (2 mL) and the mixture was stirred vigorously at 35 °C for 2 d. The mixture was then filtered under nitrogen and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography using ethyl acetate–hexane (4 : 1) as eluent to afford the title compound **30** (89 mg, 82%) as a colourless oil; $[\alpha]_D$ +31.0° ($c = 0.75$, $CHCl_3$); found: MH^+, 469.2768, $C_{28}H_{41}O_4Si$ requires 469.2774; ν_{max} (cm^{-1}) 3434br (OH), 1463m, 1428m,1215s (Si–O–C); δ_H (300 MHz, $CDCl_3$) 0.93 (3H, d, *J* 6.8 Hz, 1″-Me), 1.05 (9H, s, $^tBuPh_2Si$), 1.26 (1H, m, H-8A), 1.53–2.10 (10H, m, H-3, H-4, H-8B, H-9, H-10, H-1″), 3.50 (2H, m, H-1′A and H-2″A), 3.65 (2H, m, H-1′B and H-2″B), 3.79 (1H, m, H-7), 4.09 (1H, m, H-2), 7.39 (6H, m, Ph), 7.65 (4H, m, Ph); δ_C (75 MHz, $CDCl_3$) 12.4 (CH_3, Me), 19.3 (C, $^tBuPh_2Si$), 20.6 (CH_2, C-9), 25.3 (CH_2, C-3), 26.9 (CH_3, $^tBuPh_2Si$), 28.0 (CH_2, C-8), 32.8 (CH_2, C-10), 37.9 (CH_2, C-4), 40.7 (CH, C-1″), 65.0 (CH_2, C-1′), 66.0 (CH_2, C-2″), 70.9 (CH, C-7), 77.6 (CH, C-2), 106.4 (C, C-5), 127.5 (CH, Ph), 129.5 (CH, Ph), 134.1 (C, Ph), 135.59 (CH, Ph), 135.6 (CH, Ph); *m*/*z* (CI) 486 ($MH + NH_3$, 12%), 469 (MH^+, 100%), 391 (M–Ph, 53%), 313 (54%), 195 (44%), 127 (41%).

(3*S*, 6*R*, 8*S*, 1′*S*)-(+)-8-{(2′-*tert*-Butyldiphenylsilyloxy)-1′-methylethyl}-3-hydroxy-1,7-dioxaspiro[5.5]undecane (31)

A solution of benzyl ether **29** (130 mg, 0.23 mmol) in ethyl acetate was stirred with 10% palladium on charcoal (10 mg) under a balloon of hydrogen for 4.5 h. After removal of the catalyst by filtration the solvent was evaporated and the residue purified by flash chromatography using ethyl acetate–hexane (4 : 1) as eluent to afford 5,6-spiroacetal **30** (80 mg, 75%) for which the spectroscopic data was in agreement with that reported above and 6,6-spiroacetal **31** (26 mg, 25%) as a colourless oil; $[\alpha]_D$ +25.5° ($c = 0.59$, $CHCl_3$); found: MH^+, 469.2778, $C_{28}H_{42}O_4Si$ requires 469.2774; ν_{max} (cm^{-1}) 3413br (OH), 1427m, 1216s (Si–O–C); δ_H (300 MHz, $CDCl_3$) 0.99 (3H, d, *J* 6.8 Hz, 1′-Me), 1.04 (9H, s, $^tBuPh_2Si$), 1.15–1.82 (12H, m, H-4, H-5, H-9, H-10, H-11, H-1′, OH), 3.35 (1H, dd, *J* 10.3, 10.3 Hz, H-2A), 3.50–3.58 (2H, m, H-2B and H-2′A), 3.64–3.72 (3H, m, H-3, H-8, H-2′B), 7.24–7.42 (6H, m, Ph), 7.62–7.68 (4H, m, Ph); δ_C (75 MHz, $CDCl_3$) 12.5 (CH_3, Me), 19.1 (CH_2, C-10), 19.3 (C, $^tBuPh_2Si$), 26.9 (CH_3, $^tBuPh_2Si$), 28.1 (CH_2, C-9), 28.4 (CH_2, C-4), 34.3 (CH_2, C-5 or C-11), 35.0 (CH_2, C-11 or C-5), 40.9 (CH, C-1′), 64.7 (CH_2, C-2), 65.9 (CH_2, C-2′), 66.5 (CH, C-8), 69.6 (CH, C-3), 94.6 (C, C-6), 127.58 (CH, Ph), 127.60 (CH, Ph), 129.5 (CH, Ph), 133.9 (C, Ph), 135.6 (CH, Ph); *m*/*z* (CI) 486 ($MH^+ + NH_3$, 8%), 469 (MH^+, 100%), 411 (M–^{t}Bu, 33%), 391 (M–Ph, 56%), 313 (51%), 195 (64%), 127 (57%).

(2*S*, 5*S*, 7*S*, 1″*S*)-(+)-7-{2″-(*tert*-Butyldiphenylsilyloxy)-1″-methylethyl}-2-formyl-1,6-dioxaspiro[4.5]decane (9)

A mixture of alcohol **30** (68 mg, 0.14 mmol), dry pyridine (0.18 mL, 2.18 mmol) and Dess–Martin periodinane[24] (120 mg, 0.29 mmol) was stirred in dry CH_2Cl_2 (4 mL) at room temperature for 3 h. Saturated NH_4Cl solution (2 mL) was added and the mixture was extracted with Et_2O (3 × 10 mL). The organic layer was washed with brine (3 × 10 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude mixture was purified by flash chromatography using ethyl acetate–hexane (4 : 1) as eluent to afford the title compound **9** (64 mg, 95%) as a pale yellow oil; $[\alpha]_D$ +8.8° ($c = 0.66$, $CHCl_3$) [lit.[10] $[\alpha]_D$ +10.0° ($c = 0.16$, $CHCl_3$)]; found: MH^+, 467.2618, $C_{28}H_{39}O_4Si$ requires 467.2618; ν_{max} (cm^{-1}) 1735s (C=O), 1463m,1255s (Si–O–C); δ_H (300 MHz, $CDCl_3$) 0.91 (3H, d, *J* 6.8 Hz, 1″-Me), 1.05 (9H, s, $^tBuPh_2Si$), 1.28 (1H, m, H-8A), 1.45–1.79 (6H, m, H-4A, H-8B, H-9A, H-10, H-1″), 1.80–1.98 (3H, m, H-3A, H-4B, H-9B), 2.25 (1H, m, H-3B), 3.50 (1H, dd, *J* 6.1, 9.9 Hz, H-2″A), 3.63 (1H, dd, *J* 6.1, 9.9 Hz, H-2″B), 3.87 (1H, m, H-7), 4.29 (1H, m, H-2), 7.39 (6H, m, Ph), 7.65 (4H, m, Ph), 9.67 (1H, d, *J* 1.2 Hz, H-1′); δ_C (75 MHz, $CDCl_3$) 12.1 (CH_3, Me), 19.2 (C, $^tBuPh_2Si$), 20.4 (CH_2, C-9), 25.8 (CH_2, C-3), 26.8 (CH_3, $^tBuPh_2Si$), 27.8 (CH_2, C-8), 32.4 (CH_2, C-10), 37.0 (CH_2, C-4), 40.5 (CH, C-1″), 65.8 (CH_2, C-2″), 71.1 (CH, C-7), 81.6 (CH, C-2), 107.4 (C, C-5), 127.5 (CH, Ph), 129.5 (CH, Ph), 133.9 (C, Ph), 135.52 (CH, Ph), 135.53 (CH, Ph), 202.5 (CH, C-1′); *m*/*z* 437 (M–CHO, 13%), 409 (M–CHO–CO, 46%), 253 (41%), 199 (100%), 125 (65%).

(1′*E*, 2*S*, 5*R*, 7*S*, 1″*S*)-(+)-7′-{2″-(*tert*-Butyldiphenylsilyloxy)-1″-methylethyl}-2-(2′-ethoxycarbonyl-2′-methyl-1′-propenyl)-1,6-dioxaspiro[4.5]decane (32)

To a solution of aldehyde **9** (115 mg, 0.25 mmol) in dry CH_2Cl_2 (3 mL) at 0 °C was added ylide **10** (270 mg, 0.74 mmol).

The yellow solution was stirred at room temperature overnight. Et_2O (10 mL) was added and the solution was washed with brine (2 × 7 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude mixture was purified by flash chromatography using ethyl acetate–hexane (1 : 9) as eluent to afford the title compound **32** (130 mg, 99%) as a pale yellow oil; $[\alpha]_D$ +13.7° (c = 1.22, $CHCl_3$) [lit.[10] $[\alpha]_D$ +11.9° (c = 0.16, $CHCl_3$)]; found: $M^{+\bullet}$, 550.3117, $C_{33}H_{46}O_5Si$ requires 550.3115; ν_{max} (cm^{-1}) 1713s (C=O), 1428m, 1247s (Si–O–C), 1111s; δ_H (300 MHz, $CDCl_3$) 0.98 (3H, d, J 6.8 Hz, 1″-Me), 1.04 (9H, s, $^tBu$$Ph_2Si$), 1.29 (4H, m, OCH_2CH_3 and H-8A), 1.40–1.95 (12H, m, H-3A, H-4, H-8B, H-9, H-10, H-1″, 2′-Me), 2.24 (1H, m, H-3B), 3.52 (1H, dd, J 6.5, 9.9 Hz, H-2″A), 3.67 (1H, dd, J 5.3, 9.9 Hz, H-2″B), 3.76 (1H, ddd, J 1.7, 5.1, 11.5 Hz, H-7), 4.18 (2H, q, J 7.1 Hz, OCH_2CH_3), 4.72 (1H, q, J 7.6 Hz, H-2), 6.74 (1H, dq, J 1.4, 7.6 Hz, H-1′), 7.37 (6H, m, Ph), 7.65 (4H, m, Ph); δ_C (75 MHz, $CDCl_3$) 12.5 (CH_3, 1″-Me), 12.9 (CH_3, OCH_2CH_3), 14.3 (CH_3, 2′-Me), 19.3 (C, $^tBu$$Ph_2Si$), 20.5 ($CH_2$, C-9), 26.9 ($CH_3$, $^tBu$$Ph_2Si$), 28.0 ($CH_2$, C-8), 30.4 ($CH_2$, C-3), 33.0 ($CH_2$, C-10), 37.9 ($CH_2$, C-4), 40.8 (CH, C-1″), 60.6 (CH_2, OCH_2CH_3), 66.2 (CH_2, C-2″), 71.4 (CH, C-7), 73.8 (CH, C-2), 106.5 (C, C-5), 127.6 (CH, Ph), 128.7 (C, C-2′), 129.5 (CH, Ph), 134.1 (C, Ph), 135.58 (CH, Ph), 135.60 (CH, Ph), 141.9 (CH, C-1′), 167.9 (C, C-3′); m/z 550 ($M^{+\bullet}$, 100%), 493 (M–^{t}Bu, 34%), 415 (14%), 277 (46%), 199 (100%).

(1′*E*, 2*S*, 5*R*, 7*S*, 1″*S*)-(+)-7′-{2″-(*tert*-Butyldiphenylsilyloxy)-1″-methylethyl}-2-(3′-hydroxy-1′-propenyl)-1,6-dioxaspiro[4.5]decane (33)

To a solution of ester **32** (120 mg, 0.22 mmol) in dry CH_2Cl_2 (3 mL) at −78 °C was added a solution of di-*iso*-butylaluminium hydride (0.36 mL, 20% solution in toluene, 0.44 mmol) and the resulting solution was stirred at −78 °C for 45 min. An aqueous solution of potassium sodium tartrate tetrahydrate (2 mL) was added and the mixture was warmed to room temperature and stirred until both phases became clear. The aqueous phase was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by flash chromatography using ethyl acetate–hexane (4 : 1) as eluent afforded the title compound **33** (100 mg, 91%) as a colourless oil; $[\alpha]_D$ +29.1 (c = 0.95, $CHCl_3$) [lit.[10] $[\alpha]_D$ +9.0° (c = 0.19, $CHCl_3$)]; found: $M^{+\bullet}$, 508.3003, $C_{31}H_{44}O_4Si$ requires 508.3009; ν_{max} (cm^{-1}) 3411br (OH), 1427m, 1221m (Si–O–C), 1112s; δ_H (300 MHz, $CDCl_3$) 1.01 (3H, d, J 6.8 Hz, 1″-Me), 1.05 (9H, s, $^tBu$$Ph_2Si$), 1.26 (1H, m, H-8A), 1.50–1.95 (12H, m, H-3A, H-4, H-8B, H-9, H-10, H-1″, 2′-Me), 2.10 (1H, m, H-3B), 3.56 (1H, dd, J 6.6, 9.9 Hz, H-2″A), 3.67 (1H, dd, J 5.0, 9.9 Hz, H-2″B), 3.76 (1H, ddd, J 1.7, 5.1, 11.5 Hz, H-7), 3.99 (2H, s, H-3′), 4.69 (1H, q, J 7.6 Hz, H-2), 5.49 (1H, dq, J 1.4, 7.6 Hz, H-1′), 7.37 (6H, m, Ph), 7.66 (4H, m, Ph); δ_C (75 MHz, $CDCl_3$) 12.8 (CH_3, 1″-Me), 14.0 (CH_3, 2′-Me), 19.3 (C, $^tBu$$Ph_2Si$), 20.5 ($CH_2$, C-9), 26.9 ($CH_3$, $^tBu$$Ph_2Si$), 28.1 ($CH_2$, C-8), 30.7 ($CH_2$, C-3), 33.1 ($CH_2$, C-10), 38.1 ($CH_2$, C-4), 40.8 (CH, C-1″), 66.3 (CH_2, C-2″), 68.0 (CH_2, C-3′), 71.5 (CH, C-7), 73.4 (CH, C-2), 106.0 (C, C-5), 126.0 (CH, C-1′), 127.5 (CH, Ph), 129.4 (CH, Ph), 134.0 (C, Ph), 135.56 (CH, Ph), 135.58 (CH, Ph), 138.1 (C, C-2′); m/z 508 ($M^{+\bullet}$, 0.8%), 451 (M–^{t}Bu, 14%), 433 (M–^{t}Bu–H_2O, 12%), 309 (22%), 199 (100%).

(2*S*, 5*S*, 7*S*, 1′*S*, 2′*S*, 1″*S*)-(+)-7-{2″-(*tert*-Butyldiphenylsilyloxy)-1″-methylethyl}-2-(1′,2′-epoxy-3′-hydroxy-2′-methylprop-1′-yl)-1,6-dioxaspiro[4.5]decane (34)

To a suspension of activated 4 Å molecular sieves (*ca.* 50 mg) in dry CH_2Cl_2 (0.5 mL) at −20 °C was added (+)-diethyl L-tartrate (0.8 μL, 4.7 μmol) followed by titanium(IV) tetraisopropoxide (1 μL, 3.9 μmol). After 5 min, anhydrous *tert*-butylhydroperoxide (16 μL, 0.08 mmol) was added dropwise maintaining the temperature of the mixture at −20 °C. The resulting complex was stirred at −20 °C for 30 min then a solution of allylic alcohol **33** (20 mg, 0.04 mmol) in dry CH_2Cl_2 (0.5 mL) was slowly added. The mixture was stirred for 4 h at −20 °C then warmed to 0 °C for 5 min. Water (*ca.* 0.2 mL) was added and the mixture was stirred at room temperature for 30 min. 30% NaOH saturated with NaCl (*ca.* 1 mL) was added and the mixture was vigorously stirred for 15 min to hydrolyze the tartrate. The mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the excess peroxide removed azeotropically with toluene. The crude mixture was purified by flash chromatography using hexane–ethyl acetate (3 : 1) as eluent to give the title compound **34** (15 mg, 71%) as a pale yellow oil; $[\alpha]_D$ +16.5° (c = 0.98, $CHCl_3$) [lit. $[\alpha]_D$ +13.2° (c = 0.42, $CHCl_3$)]; found: MH^+, 525.3050, $C_{31}H_{45}O_5Si$ requires 525.3036; ν_{max} (cm^{-1}) 3436br (OH), 1427m, 1112s (Si–O–C); δ_H (300 MHz, $CDCl_3$) 0.97 (3H, d, J 6.8 Hz, 1″-Me), 1.04 (9H, s, $^tBu$$Ph_2Si$), 1.25 (1H, m, H-8A), 1.29 (3H, s, 2′-Me), 1.48–1.95 (9H, m, H-3A, H-4, H-8B, H-9, H-10, H-1″), 2.24 (1H, m, H-3B), 2.98 (1H, d, J 8.0, H-1′), 3.53 (1H, dd, J 6.1, 9.9 Hz, H-2″A), 3.62 (2H, m, H-3′A and H-2″B), 3.67 (2H, m, H-3′B and H-7), 3.82 (1H, m, H-2), 7.39 (6H, m, Ph), 7.64 (4H, m, Ph); δ_C (75 MHz, $CDCl_3$) 12.9 (CH_3, 1″-Me), 14.3 (CH_3, 2′-Me), 19.3 (C, $^tBu$$Ph_2Si$), 20.5 ($CH_2$, C-9), 26.9 ($CH_3$, $^tBu$$Ph_2Si$), 28.1 ($CH_2$, C-8), 28.2 ($CH_2$, C-3), 32.8 ($CH_2$, C-10), 37.3 ($CH_2$, C-4), 40.8 (CH, C-1″), 61.2 (CH, C-1′), 61.4 (C, C-2′), 65.2 (CH_2, C-3′), 66.1 (CH_2, C-2″), 71.6 (CH, C-7), 75.0 (CH, C-2), 106.5 (C, C-5), 127.6 (CH, Ph), 129.5 (CH, Ph), 134.0 (C, Ph), 135.6 (C, Ph); m/z (CI) 525 (MH^+, 4%), 507 (M–OH, 32%), 467 (M–^{t}Bu, 100%).

(2*S*, 5*S*, 7*S*, 1′*S*, 2′*S*, 1″*S*)-(+)-7-{2″-(*tert*-Butyldiphenylsilyloxy)-1″-methylethyl}-2-(1′,2′-epoxy-3′-iodo-2′-methylprop-1′-yl)-1,6-dioxaspiro[4.5]decane (35)

To a solution of alcohol **34** (10 mg, 0.02 mmol) in dry THF (1 mL) at 0 °C was added dry triethylamine (3 μL, 0.02 mmol) followed by methanesulfonyl chloride (2 μL, 0.02 mmol). After 1 h, the mixture was filtered, NaI (4 mg, 0.03 mmol) and $NaHCO_3$ (6 mg, 0.08 mmol) were added to the filtrate. The resulting yellow mixture was heated under reflux for 24 h. The mixture was filtered to remove the precipitate and the filtrate was concentrated under reduced pressure. The residue was dissolved in Et_2O (10 mL), washed with saturated $Na_2S_2O_3$ (5 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. The crude mixture was purified by flash chromatography using hexane–ethyl acetate (9 : 1) as eluent to give the title compound **35** (10 mg, 83%) as a yellow oil; $[\alpha]_D$ +21.3° (c = 1.1, $CHCl_3$); found: MH^+, 635.2052, $C_{31}H_{44}IO_4Si$ requires 635.2054; ν_{max} (cm^{-1}) 1427m, 1387m, 1265s

(Si–O–C); δ_H (300 MHz, $CDCl_3$) 0.96 (3H, d, *J* 6.8 Hz, 1″-Me), 1.04 (9H, s, $^tBuPh_2Si$), 1.25 (1H, m, H-8A), 1.42 (3H, s, 2′-Me), 1.48–1.95 (9H, m, H-3A, H-4, H-8B, H-9, H-10, H-1″), 2.24 (1H, m, H-3B), 2.88 (1H, d, *J* 7.8, H-1′), 3.14 (1H, d, *J* 10.1 Hz, H-3′A), 3.28 (1H, d, *J* 10.1 Hz, H-3′B), 3.51 (1H, dd, *J* 6.1, 9.9 Hz, H-2″A), 3.61 (1H, dd, *J* 5.1, 9.9 Hz, H-2″B), 3.65–3.77 (2H, m, H-2 and H-7), 7.34–7.44 (6H, m, Ph), 7.64 (4H, m, Ph); δ_C (100 MHz, $CDCl_3$) 12.8 (CH_3, 1″-Me), 14.1 (CH_2, C-3′), 16.6 (CH_3, 2′-Me), 19.3 (C, $^tBuPh_2Si$), 20.5 (CH_2, C-9), 26.9 (CH_3, $^tBuPh_2Si$), 28.0 (CH_2, C-8), 28.04 (CH_2, C-3), 32.9 (CH_2, C-10), 37.3 (CH_2, C-4), 40.7 (CH, C-1″), 60.2 (C, C-2′), 66.0 (CH_2, C-2″), 67.9 (CH, C-1′), 71.6 (CH, C-7), 75.7 (CH, C-2), 106.6 (C, C-5), 127.6 (CH, Ph), 129.5 (CH, Ph), 133.9 (C, Ph), 135.6 (CH, Ph); *m/z* (CI) 635 (MH^+, 17%), 577 (M–^{t}Bu, 11%), 437 (100%), 379 (67%), 199 (96%), 181 (68%).

(2*S*, 5*S*, 7*S*, 1′*R*, 1″*S*)-(+)-7-{2″-(*tert*-Butyldiphenylsilyloxy)-1″-methylethyl}-2-(1′-hydroxy-2′-methyl-2′-propen-1′-yl)-1,6-dioxaspiro[4.5]decane (37)

To a solution of acetylene **11**[27] (17 mg, 0.12 mmol) in dry THF (1.5 mL) at −78 °C was added BuLi (0.07 mL, 1.6 M solution in hexane, 0.11 mmol). After 45 min, hexamethylphosphoramide (0.02 mL, 0.11 mmol) was added followed by a solution of iodide **35** (15 mg, 0.02 mmol) in dry THF (1 mL). The mixture was stirred at −78 °C for 15 min and then at room temperature overnight. Saturated NH_4Cl solution (1 mL) was added and the mixture was extracted with Et_2O (3 × 5 mL). The combined organic phase was washed with brine (2 × 5 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude mixture was purified by flash chromatography using hexane–ethyl acetate (9 : 1) as eluent to give the title compound **37** (8.7 mg, 86%) as a pale yellow oil; $[\alpha]_D$ +34.4° (*c* = 0.8, $CHCl_3$); found: MH^+, 509.3093, $C_{31}H_{45}O_4Si$ requires 509.3087; ν_{max} (cm^{-1}) 3468br (OH), 1428s, 1224m; δ_H (400 MHz, $CDCl_3$) 0.94 (3H, d, *J* 6.8 Hz, 1″-Me), 1.05 (9H, s, $^tBuPh_2Si$), 1.25 (1H, m, H-8A), 1.48–1.87 (13H, m, H-3, H-4, H-8B, H-9, H-10, H-1″, 2′-Me), 2.17 (1H, br, OH), 3.51 (1H, dd, *J* 6.1, 9.9 Hz, H-2″A), 3.67 (1H, dd, *J* 5.1, 9.9 Hz, H-2″B), 3.82 (1H, ddd, *J* 1.9, 5.6, 11.6 Hz, H-7), 4.16 (1H, m, H-2), 4.25 (1H, br, H-1′), 4.89 (1H, d, *J* 1.3 Hz, H-3′A), 5.08 (1H, br, H-3′B), 7.34–7.44 (6H, m, Ph), 7.64 (4H, m, Ph); δ_C (100 MHz, $CDCl_3$) 12.3 (CH_3, 1″-Me), 19.3 (C, $^tBuPh_2Si$), 19.7 (CH_3, 2′-Me), 20.5 (CH_2, C-9), 22.5 (CH_2, C-3), 26.9 (CH_3, $^tBuPh_2Si$), 28.0 (CH_2, C-8), 32.9 (CH_2, C-10), 38.0 (CH_2, C-4), 40.7 (CH, C-1″), 66.0 (CH_2, C-2″), 70.9 (CH, C-7), 74.5 (CH, C-1′), 78.7 (CH, C-2), 106.5 (C, C-5), 111.0 (CH_2, C-3′), 127.6 (CH, Ph), 129.5 (CH, Ph), 133.9 (C, Ph), 135.6 (CH, Ph), 143.3 (C, C-2′); *m/z* 508 ($M^{+\bullet}$, 0.05%), 451 (M–^{t}Bu, 40%), 437 (M–^{t}Bu–CH_2, 31%), 199 (100%).

(1′*E*, 2*S*, 5*R*, 7*S*, 1″*S*)-(+)-2-(6′-Benzyloxy-2′-methyl-1′-hexen-4′-yn-1′-yl)-7-{2″-(*tert*-butyldiphenylsilyloxy)-1″-methylethyl}-1,6-dioxaspiro[4.5]decane 8 and (1′*Z*, 2*S*, 5*R*, 7*S*, 1″*S*)-(+)-2-(6′-benzyloxy-2′-methyl-1′-hexen-4′-yn-1′-yl)-7-{2″-(*tert*-butyldiphenylsilyloxy)-1″-methylethyl}-1,6-dioxaspiro[4.5]decane (40)

To a solution of alcohol **33** (96 mg, 0.19 mmol) in dry THF (2 mL) at 0 °C was added dry triethylamine (0.028 mL, 0.20 mmol) followed by methanesulfonyl chloride (0.015 mL, 0.19 mmol). After stirring for 20 min at 0 °C, the mixture was filtered and washed with dry THF. To the filtrate was added sodium iodide (31 mg, 0.21 mmol) and the yellow mixture was stirred at room temperature for 2 h. The mixture was then filtered to remove the precipitate and the solvent was removed under reduced pressure. The resulting unstable iodide **39** (110 mg) was used directly without further purification.

To a solution of acetylene **11**[27] (57 mg, 0.39 mmol) in dry THF (1.5 mL) at −78 °C was added BuLi (0.27 mL, 1.6 M solution in hexane, 0.43 mmol). After 45 min, iodide **39** (110 mg) in dry THF (2 mL) was added. The mixture was stirred at −78 °C for 1 h then transferred to an ice-bath and stirred overnight. Saturated NH_4Cl (1 mL) was added and the mixture extracted with Et_2O (3 × 5 mL). The combined organic phase was washed with brine (3 × 5 mL) and dried over $MgSO_4$. The solvent was evaporated at reduced pressure and the mixture was purified by flash chromatography using hexane–ethyl acetate (95 : 5) as eluent to give (*E*)-enyne **8** (68 mg, 56%) and (*Z*)-enyne **40** (22 mg, 18%) both as colourless oils; **8**: $[\alpha]_D$ +12.8° (*c* = 1.38, $CHCl_3$); found: $M^{+\bullet}$, 636.3627, $C_{41}H_{52}O_4Si$ requires 636.3635; ν_{max} (cm^{-1}) 1455m, 1427s; δ_H (300 MHz, $CDCl_3$) 1.02 (3H, d, *J* 6.9 Hz, 1″-Me), 1.04 (9H, s, $^tBuPh_2Si$), 1.21 (1H, m, H-8A), 1.50–1.91 (12H, m, H-3A, H-4, H-8B, H-9, H-10, 2′-Me, H-1″), 2.11 (1H, m, H-3B), 2.96 (2H, s, H-3′), 3.54 (1H, dd, *J* 6.5, 9.9 Hz, H-2″A), 3.67 (1H, dd, *J* 4.8, 9.9 Hz, H-2″B), 3.78 (1H, ddd, *J* 1.7, 5.1, 11.5 Hz, H-7), 4.19 (2H, t, *J* 1.9 Hz, H-6′), 4.60 (2H, s, CH_2Ph), 4.67 (1H, q, *J* 7.6 Hz, H-2), 5.52 (1H, dq, *J* 1.1, 7.6 Hz, H-1′), 7.24–7.43 (11H, m, Ph), 7.65 (4H, m, Ph); δ_C (75 MHz, $CDCl_3$) 12.9 (CH_3, 1″-Me), 16.6 (CH_3, 2′-Me), 19.3 (C, $^tBuPh_2Si$), 20.5 (CH_2, C-9), 26.8 (CH_3, $^tBuPh_2Si$), 28.0 (CH_2, C-8), 28.9 (CH_2, C-3′), 30.7 (CH_2, C-3), 33.1 (CH_2, C-10), 38.1 (CH_2, C-4), 40.8 (CH, C-1″), 57.7 (CH_2, C-6′), 66.2 (CH_2, C-2″), 71.3 (CH_2, CH_2Ph), 71.5 (CH, C-7), 73.6 (CH, C-2), 78.3 (C, C-4′), 83.9 (C, C-5′) 106.0 (C, C-5), 127.1 (CH, C-1′), 127.5 (CH, Ph), 127.8 (CH, Ph), 128.1 (CH, Ph), 128.4 (CH, Ph), 129.5 (CH, Ph), 133.7 (C, Ph), 134.0 (C, Ph), 135.56 (CH, Ph), 135.58 (CH, Ph), 137.6 (C, C-2′); *m/z* 636 ($M^{+\bullet}$, 0.4%), 579 (M–^{t}Bu, 8%), 199 (68%), 91 (CH_2Ph, 100%).

40: $[\alpha]_D$ +47.8° (*c* = 0.97, $CHCl_3$); found: $M^{+\bullet}$, 636.3636, $C_{41}H_{52}O_4Si$ requires 636.3635; ν_{max} (cm^{-1}) 1428m, 1220m; δ_H (300 MHz, $CDCl_3$) 1.01 (3H, d, *J* 6.8 Hz, 1″-Me), 1.05 (9H, s, $^tBuPh_2Si$), 1.26 (1H, m, H-8A), 1.45–1.92 (12H, m, H-3A, H-4, H-8B, H-9, H-10, 2′-Me, H-1″), 2.13 (1H, m, H-3B), 2.88 (1H, m, H-3′A), 3.10 (1H, m, H-3′B), 3.53 (1H, dd, *J* 6.5, 9.9 Hz, H-2″A), 3.64–3.77 (2H, m, H-7 and H-2″B), 4.14 (2H, t, *J* 2.0 Hz, H-6′), 4.57 (2H, s, CH_2Ph), 4.63 (1H, m, H-2), 5.31 (1H, d, *J* 8.4 Hz, H-1′), 7.24–7.41 (11H, m, Ph), 7.66 (4H, m, Ph); δ_C (75 MHz, $CDCl_3$) 13.0 (CH_3, 1″-Me), 19.3 (C, $^tBuPh_2Si$), 20.5 (CH_2, C-9), 22.0 (CH_2, C-3′), 26.9 (CH_3, $^tBuPh_2Si$), 28.0 (CH_2, C-8), 28.9 (CH_2, C-3′), 30.9 (CH_2, C-3), 33.2 (CH_2, C-10), 38.1 (CH_2, C-4), 40.8 (CH, C-1″), 57.7 (CH_2, C-6′), 66.1 (CH_2, C-2″), 71.3 (CH_2, CH_2Ph), 71.7 (CH, C-7), 73.5 (CH, C-2), 76.3 (C, C-4′), 84.3 (C, C-5′), 106.0 (C, C-5), 127.2 (CH, C-1′), 127.5 (CH, Ph), 127.7 (CH, Ph), 127.9 (CH, Ph), 128.0 (CH, Ph), 128.37 (CH, Ph), 128.43 (CH, Ph), 129.5 (CH, Ph), 134.0 (C, Ph), 134.03 (C, Ph), 135.6 (CH, Ph), 137.6 (C, C-2′); *m/z* 636 ($M^{+\bullet}$, 0.6%), 579 (M–^{t}Bu, 4%), 199 (64%), 91 (CH_2Ph, 100%).

(2*S*, 5*S*, 7*S*, 1′*S*, 2′*S*, 1″*S*)-2-(6′-Benzyloxy-1′,2′-epoxy-2′-methylhex-4′-yn-1′-yl)-7-{2″-(*tert*-butyldiphenylsilyloxy)-1″-methylethyl}-1,6-dioxaspiro[4.5]decane (*syn*-epoxide 36) and (2*S*, 5*S*, 7*S*, 1′*R*, 2′*R*, 1″*S*)-2-(6′-benzyloxy-1′-epoxy-2′-methylhex-4′-yn-1′yl)-7-{2″-(*tert*-butyldiphenylsilyloxy)-1″-methylethyl}-1,6-dioxaspiro[4.5]decane (*anti*-epoxide 42)

(*E*)-Enyne **8** (0.02 mmol) was dissolved in a mixture of CH_3CN–DMM (0.3 mL, 1 : 2 *v*/*v*). A solution of buffer [0.05 M of $Na_2B_4O_7{\cdot}10H_2O$ in 4×10^{-4} M of Na_2(EDTA)] (0.2 mL) was added followed by tetrabutylammonium sulfate (0.02 mmol) and ketone **41** or ent-**41** (0.06 mmol). After cooling to −10 °C, a solution of oxone (0.1 mmol) in 4×10^{-4} M Na_2(EDTA) (0.3 mL) and a solution of K_2CO_3 (0.3 mmol) in water (0.3 mL) were added dropwise simultaneously over 40 min. After the last addition, the mixture was stirred for 1 h. Water was added and the mixture was extracted with diethyl ether (3 × 3 mL). The combined organic extracts were washed with brine (3 × 1 mL) and dried over $MgSO_4$. The solvent was evaporated and the mixture was purified by flash chromatography using hexane–ethyl acetate (9 : 1) as eluent.

Using ketone ent-**41** derived from D-fructose afforded a 1 : 8 mixture of *syn*-epoxide **36** : *anti*-epoxide **42** in 52% yield.

Using ketone **41** derived from L-fructose afforded a 5.5 : 1 mixture of *syn*-epoxide **36** : *anti*-epoxide **42** in 37% yield.

syn-Epoxide **36** and *anti*-epoxide **42**, colourless oil; found: $M^{+\bullet}$, 652.3589, $C_{41}H_{52}O_5Si$ requires 652.3584; ν_{max} (cm^{-1}) 1428m, 1265m (Si–O–C); δ_H (300 MHz, $CDCl_3$)§ 0.94 (1.35H, d, *J* 6.7 Hz, 1″-Me*), 0.96 (1.65H, d, *J* 6.7 Hz, 1″-Me), 1.036 (4.95H, s, ^{t}*Bu*Ph_2Si), 1.043 (4.05H, s, ^{t}*Bu*Ph_2Si*), 1.20 (1H, m, H-8A), 1.35 (1.65H, s, 2′-Me), 1.37 (1.35H, s, 2′-Me*), 1.59–1.90 (9H, m, H-3A, H-4, H-8B, H-9, H-10, H-1″), 2.18 (1H, m, H-3B), 2.59 (2H, m, H-3′), 2.89 (0.55H, d, *J* 8.0 Hz, H-1′), 2.92 (0.45H, d, *J* 7.7 Hz, H-1′*), 3.48 (1H, m, H-2″A), 3.58–3.84 (3H, m, H-2, H-7, H-2″B), 4.17 (2H, m, H-6′), 4.58 (1.1H, s, CH_2Ph), 4.59 (0.9H, s, CH_2Ph*), 7.26–7.42 (11H, m, Ph), 7.65 (4H, m, Ph); δ_C (75 MHz, $CDCl_3$) 12.6 (CH_3, 1″-Me), 12.9 (CH_3, 1″-Me*), 16.9 (CH_3, 2′-Me), 17.3 (CH_3, 2′-Me), 19.3 (C, ^{t}*Bu*Ph_2Si), 20.36 (CH_2, C-9), 20.42 (CH_2, C-9*), 26.85 (CH_3, ^{t}*Bu*Ph_2Si), 26.87 (CH_3, ^{t}*Bu*Ph_2Si*), 27.0 (CH_2, C-3), 27.9 (CH_2, C-3*), 28.05 (CH_2, C-8), 28.09 (CH_2, C-8*), 28.6 (CH_2, C-3′), 29.1 (CH_2, C-3′*), 32.8 (CH_2, C-10), 32.9 (CH_2, C-10*), 37.3 (CH_2, C-4), 37.5 (CH_2, C-4*), 40.7 (CH, C-1″), 57.6 (CH_2, C-6′), 58.1 (C, C-2′), 59.5 (C, C-2′*), 63.8 (CH, C-1′), 64.6 (CH, C-1′*), 66.03 (CH_2, C-2″), 66.07 (CH_2, C-2″*), 71.36 (CH_2, CH_2Ph), 71.44 (CH_2, CH_2Ph*), 71.6 (CH, C-7), 75.2 (CH, C-2), 76.7 (CH, C-2*), 78.4 (C, C-4′), 78.5 (C, C-4′*), 81.8 (C, C-5′), 81.9 (C, C-5′*), 106.5 (C, C-5), 106.8 (C, C-5*), 127.5 (CH, Ph), 127.6 (CH, Ph), 127.80 (CH, Ph), 127.84 (CH, Ph), 128.0 (CH, Ph), 128.1 (CH, Ph), 128.4 (CH, Ph), 128.42 (CH, Ph), 129.4 (CH, Ph), 129.5 (CH, Ph), 133.9 (C, Ph), 133.95 (C, Ph), 134.0 (C, Ph), 134.1 (C, Ph), 135.6 (CH, Ph), 137.5 (C, Ph); *m*/*z* 652 ($M^{+\bullet}$, 0.2%), 595 (M–^{t}Bu, 5%), 379 (20%), 199 (81%), 181 (57%), 135 (41%), 91 (CH_2Ph, 100%).

(4′*Z*, 2*S*, 5*S*, 7*S*, 1′*S*, 2′*S*, 1″*S*)-2-(6′-Benzyloxy-1′,2′-epoxy-2′-methylhex-4′-en-1′-yl)-7-{2″-(*tert*-butyldiphenylsilyloxy)-1″-methylethyl}-1,6-dioxaspiro[4.5]decane (*syn*-epoxide 43) and (4′*Z*, 2*S*, 5*S*, 7*S*, 1′*R*, 2′*R*, 1″*S*)-2-(6′-benzyloxy-1′,2′-epoxy-2′-methylhex-4′-en-1′-yl)-7-{2″-(*tert*-butyldiphenylsilyloxy)-1″-methylethyl}-1,6-dioxaspiro[4.5]decane (*anti*-epoxide 44)

A mixture of epoxides **36** and **42** (14 mg, 0.04 mmol, *syn*-epoxide **36** : *anti*-epoxide **42** = 5.5 : 1), Lindlar catalyst (1–2 mg) and triethylamine (0.1 mL) in hexane (1.5 mL) was stirred under an atmosphere of hydrogen (balloon pressure) for 50 min. The progress of the reaction was monitored by ^{1}H NMR. The mixture was filtered through a pad of Celite® and the solvent was evaporated under reduced pressure. The crude mixture was purified by flash chromatography using hexane–ethyl acetate (9 : 1) as eluent to give the title compounds (12 mg, 91%) as an inseparable 5.5 : 1 mixture of *syn*-epoxide **43** : *anti*-epoxide **44**; found: MH^+, 655.3821, $C_{41}H_{55}O_5Si$ requires 655.3819; ν_{max} (cm^{-1}) 1458m, 1265s (Si–O–C); δ_H (300 MHz, $CDCl_3$)¶ 0.94 (1.07H, d, *J* 6.7 Hz, 1″-Me*), 0.96 (1.93H, d, *J* 6.7 Hz, 1″-Me), 1.03 (5.79H, s, ^{t}*Bu*Ph_2Si), 1.04 (3.21H, s, ^{t}*Bu*Ph_2Si*), 1.18–1.27 (4H, m, H-8A, 2′-Me), 1.45–1.93 (9H, m, H-3A, H-4, H-8B, H-9, H-10, H-1″), 2.04–2.42 (3H, m, H-3B and H-3′), 2.69 (0.64H, d, *J* 8.0 Hz, H-1′), 2.74 (0.36H, d, *J* 7.7 Hz, H-1′*), 3.45–3.82 (4H, m, H-2, H-7, H-2″), 4.06 (2H, m, H-6′), 4.51 (2H, s, CH_2Ph), 5.53–5.67 (1H, m, H-5′), 5.71–5.82 (1H, m, H-4′), 7.26–7.42 (11H, m, Ph), 7.65 (4H, m, Ph); δ_C (75 MHz, $CDCl_3$) 12.7 (CH_3, 1″-Me), 12.9 (CH_3, 1″-Me*), 17.0 (CH_3, 2′-Me), 17.5 (CH_3, 2′-Me*), 19.3 (C, ^{t}*Bu*Ph_2Si), 20.3 (CH_2, C-9), 20.4 (CH_2, C-9*), 26.85 (CH_3, ^{t}*Bu*Ph_2Si), 26.87 (CH_3, ^{t}*Bu*Ph_2Si*), 26.9 (CH_2, C-3), 27.9 (CH_2, C-3*), 28.08 (CH_2, C-8), 28.10 (CH_2, C-8*), 32.9 (CH_2, C-10), 36.1 (CH_2, C-3′), 36.6 (CH_2, C-3′*), 37.3 (CH_2, C-4), 37.5 (CH_2, C-4*), 40.7 (CH, C-1″), 59.2 (C, C-2′), 60.9 (C, C-2′*), 63.9 (CH, C-1′), 64.5 (CH, C-1′*), 65.7 (CH_2, C-6′), 66.03 (CH_2, C-2″), 66.09 (CH_2, C-2″*), 71.49 (CH, C-7), 71.53 (CH, C-7*), 72.2 (CH_2, CH_2Ph), 72.3 (CH_2, CH_2Ph*), 75.3 (CH, C-2), 76.8 (CH, C-2*), 106.4 (C, C-5), 106.7 (C, C-5*), 127.49 (CH, Ph), 127.54 (CH, Ph), 127.55 (CH, Ph), 127.6 (CH, C-4′), 127.6 (CH, C-4′*), 127.80 (CH, Ph), 128.4 (CH, Ph), 129.0 (CH, C-5′), 129.2 (CH, C-5′*), 129.3 (CH, Ph), 129.4 (CH, Ph), 129.5 (CH, Ph), 133.9 (C, Ph), 133.96 (C, Ph), 134.1 (C, Ph), 135.6 (CH, Ph), 138.16 (C, Ph), 138.24 (C, Ph); *m*/*z* (FAB) 655 (MH^+, 3%), 437 (16%), 199 (25%), 91 (CH_2Ph, 82%).

(2*S*, 5*S*, 7*S*, 1′*S*, 2″*R*, 4″*S*, 5″*R*, 1‴*S*)-(+)-2-[5″-Benzyloxymethyl-4″-hydroxy-2″-methyltetrahydrofur-2″-yl)-hydroxymethyl]-7-{2‴-(*tert*-butyldiphenylsilyloxy)-1‴-methylethyl}-1,6-dioxaspiro[4.5]decane (6)

To a 5.5 : 1 mixture of *syn*-epoxide **43** : *anti*-epoxide **44** (10 mg, 15.2 μmol) in acetone–H_2O (0.5 mL, 5 : 1 *v*/*v*) at room temperature was added OsO_4 (50 μL, 2.5wt% in ^{t}BuOH). The mixture was left at room temperature for 18 h. Saturated $Na_2S_2O_3$ solution (0.5 mL) was added and the mixture stirred vigorously for 45 min at room temperature. The mixture was extracted with CH_2Cl_2 (5 × 1 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude mixture was purified by flash chromatography using hexane–ethyl acetate (7 : 3) as eluent to give

§ Resonances assigned with the *anti*-epoxide **42** are designated with an asterisk *.

¶ Resonances assigned with the *anti*-epoxide **44** are designated with an asterisk *.

ABC spiroacetal **6** (5.8 mg, 70%) as a colourless oil; $[\alpha]_D$ +23.5° (c = 0.13, $CHCl_3$); found: $M^{+\bullet}$, 688.3792, $C_{41}H_{56}O_7Si$ requires 688.3795; ν_{max} (cm^{-1}) 3444 br (OH), 1427m, 1362s, 1262s; δ_H (300 MHz, $CDCl_3$) 0.99 (3H, d, J 6.7 Hz, 1‴-Me), 1.05 (9H, s, $^tBuPh_2Si$), 1.25 (1H, m, H-8A), 1.42 (3H, s, 2″-Me), 1.44–2.21 (11H, m, H-3, H-4, H-8B, H-9, H-10, H-3″A, H-1⁗), 2.41 (1H, dd, J 7.6, 13.3 Hz, H-3″B), 3.45 (1H, d, J 7.6 Hz, H-1′), 3.48–3.65 (5H, m, H1‴, H-7, H-2⁗), 3.80 (1H, q, J 7.0 Hz, H-2), 3.97 (1H, q, J 3.7 Hz, H-5″), 4.32 (1H, m, H-4′), 4.56 (2H, AB, J_{AB} 12.3 Hz, CH_2Ph), 7.27–7.42 (11H, m, Ph), 7.64–7.67 (4H, m, Ph); δ_C (75 MHz, $CDCl_3$) 12.9 (CH_3, 1⁗-Me), 19.4 (C, $^tBuPh_2Si$), 20.6 (CH_2, C-9), 25.6 (CH_3, 2″-Me), 26.9 (CH_3, $^tBuPh_2Si$), 27.3 (CH_2, C-3), 28.1 (CH_2, C-8), 33.2 (CH_2, C-10), 37.1 (CH_2, C-4), 40.2 (CH_2, C-3″), 40.8 (CH, C-1⁗), 66.2 (CH_2, C-1‴), 69.7 (CH_2, C-2⁗), 71.7 (CH, C-7), 73.4 (CH_2, CH_2Ph), 74.1 (CH, C-4″), 77.4 (CH, C-2), 78.1 (CH, C-1′), 83.2 (CH, C-5″), 86.5 (C, C-2″), 106.2 (C, C-5), 127.6 (CH, Ph), 127.8 (CH, Ph), 127.82 (CH, Ph), 128.5 (CH, Ph), 129.5 (CH, Ph), 134.1 (C, Ph), 135.6 (CH, Ph), 137.6 (C, Ph); m/z 688 ($M^{+\bullet}$, 0.2%), 631 (9%), 221 (52%), 199 (49%), 91 (CH_2Ph, 100%).

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References

1 T. Yasumoto, M. Murata, Y. Oshima, G. K. Sano and J. Matsumoto, *Tetrahedron*, 1985, **41**, 1019.
2 M. Murata, M. Sano, T. Iwashita, H. Naoki and T. Yasumoto, *Agric. Biol. Chem.*, 1986, **50**, 2693.
3 T. Yasumoto, M. Murata and J.-S. Lee, in *Bioactive Molecules: Mycotoxins and Phycotoxins '88, vol. 10*, ed. S. Natori, K. Hashimoto and Y. Ueno, Elsevier, New York, 1989 p. 375.
4 K. Sasaki, J. L. C. Wright and T. Yasumoto, *J. Org. Chem.*, 1998, **63**, 2475.
5 T. Suzuki, V. Beuzenberg, L. Mackenzie and M. A. Quilliam, *J. Chromatogr., A*, 2003, **992**, 141.
6 C. O. Miles, A. L. Wilkins, I. A. Samdal, M. Sandvik, D. Petersen, M. A. Quilliam, L. J. Naustvoll, T. Rundberget, T. Torgersen, P. Hovgaard, D. J. Jensen and J. M. Cooney, *Chem. Res. Toxicol.*, 2004, **17**, 1423.
7 J. H. Jung, C. J. Sim and C.-O. Lee, *J. Nat. Prod.*, 1995, **58**, 1722.
8 I. Spector, F. Braet, N. R. Shochet and M. R. Bubb, *Microsc. Res. Tech.*, 1999, **47**, 18; F. Leira, A. G. Cabado, M. R. Vieytes, Y. Roman, A. Alfonso, L. M. Botana, T. Yasumoto, C. Malaguti and G. P. Rossini, *Biochem. Pharmacol.*, 2002, **63**, 1979.
9 S. Amano, K. Fujiwara and A. Murai, *SYNLETT*, 1997, 1300; D. Awakura, K. Fujiwara and A. Murai, *SYNLETT*, 2000, 1733; K. Fujiwara, M. Kobayashi, F. Yamamoto, A. Fuyuki, K. Yu-ichi, M. Kawamura, A. Mariko, Awakura, A. Daisuke, O. Seiji, A. Murai, H. Kawai and T. Suzuki, *Tetrahedron Lett.*, 2005, **46**, 5067.
10 L. A. Paquette, X. Peng and D. Bondar, *Org. Lett.*, 2002, **4**, 937; X. Peng, D. Bondar and L. A. Paquette, *Tetrahedron*, 2004, **60**, 9589; D. Bondar, J. Liu, T. Mueller and L. A. Paquette, *Org. Lett.*, 2005, **7**, 1813.
11 G. C. Micalizio and W. R. Roush, *Org. Lett.*, 2001, **3**, 1949.
12 P. M. Pihko and J. E. Aho, *Org. Lett.*, 2004, **6**, 3849.
13 D. A. Evans, H. A. Rajapakse and D. Stenkamp, *Angew. Chem., Int. Ed.*, 2002, **41**, 4569; D. A. Evans, H. A. Rajapakse, A. Chiu and D. Stenkamp, *Angew. Chem., Int. Ed. Engl.*, 2002, **41**, 4573.
14 For preliminary communication of this work see: R. Halim, M. A. Brimble and J. Merten, *Org. Lett.*, 2005, **7**, 2659.
15 L. Borjesson, I. Csoregh and C. J. Welch, *J. Org. Chem.*, 1995, **60**, 2989.
16 D. A. Evans, J. Bartroli and T. L. Shih, *J. Am. Chem. Soc.*, 1981, **103**, 2127.
17 L. M. Fuentes, I. Shinkai and T. N. Salzmann, *J. Am. Chem. Soc.*, 1986, **108**, 4675.
18 T. Inoue and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 174.
19 M. T. Crimmins, B. W. King and E. A. Tabet, *J. Am. Chem. Soc.*, 1997, **119**, 7883.
20 M. T. Crimmins, B. W. King, E. A. Tabet and K. Chaudhary, *J. Org. Chem.*, 2001, **66**, 894.
21 Y. Nagao, T. Kumagi, S. Yamada and E. Fujita, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2361.
22 G. W. A. Fowles, D. A. Rice and J. D. Wilkins, *J. Chem. Soc. A*, 1971, 1920.
23 D. Craig and A. M. Smith, *Tetrahedron Lett.*, 1990, **31**, 2631.
24 D. B. Dess and J. C. Martin, J. C., *J. Org. Chem.*, 1983, **48**, 4155.
25 D. Uemura, K. Takahashi, T. Yamamoto, C. Katayama, J. Tanaka, Y. Okumura and Y. Hirata, *J. Am. Chem. Soc.*, 1985, **107**, 4796.
26 G. R. Pettit, Y. Ichihara, G. Wurzel, M. D. Williams, J. M. Schmidt and J. Chapuis, *J. Chem. Soc., Chem. Commun.*, 1995, 383.
27 R. E. Sammelson, R. B. Miller and M. J. Kurth, *J. Org. Chem.*, 2000, **65**, 2225.
28 R. Matsumura, T. Suzuki, K. Sato, T. Inotsume, H. Hagiwara, T. Hoshi, V. P. Kamat and M. Ando, *Tetrahedron Lett.*, 2000, **41**, 7697.
29 J. G. Millar and E. W. Underhill, *J. Org. Chem.*, 1986, **51**, 4726.
30 A. Alexakis, G. Cahiez and J. F. Normant, *Synthesis*, 1979, 826.
31 M. Gardette, A. Alexakis and J. F. Normant, *J. Chem. Ecol.*, 1983, **9**, 225.
32 K. C. Nicolau, M. E. Duggan and T. Ladduwahetty, *Tetrahedron Lett.*, 1984, **25**, 2069.
33 W. Adam, Y.-Y. Chan, D. Cremer, J. Gauss, D. Scheutzow and M. Schindler, *J. Org. Chem.*, 1987, **52**, 2800.
34 R. W. Murray and R. J. Jeyaraman, *J. Org. Chem.*, 1985, **50**, 2847.
35 R. W. Murray and M. Singh, *Org. Synth.*, 1997, **74**, 91.
36 Z.-X. Wang, T. Tu, M. Frohn, J.-R. Zhang and Y. Shi, *J. Am. Chem. Soc.*, 1997, **119**, 11224.
37 C. C. Chen and R. L. Whistler, *Carbohydr. Res.*, 1988, **175**, 265.
38 H. C. Kolb, P. G. Andersson and K. B. Sharpless, *J. Am. Chem. Soc.*, 1994, **116**, 1278.
39 L. Wang and K. B. Sharpless, *J. Am. Chem. Soc.*, 1992, **114**, 7568.