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Synthesis of the 1,6,8-trioxadispiro[4.1.5.2]tetradec-11-ene ring system present in the spirolide family of shellfish toxins and its conversion into a 1,6,8-trioxadispiro[4.1.5.2]-tetradec-9-en-12-ol *via* base-induced rearrangement of an epoxide†

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The synthesis of the 1,6,8-trioxadispiro[4.1.5.2]tetradec-11-enes **12** present in the shellfish toxins spirolides B **1** and D **2**, is reported. The two spirocentres were constructed *via* iterative radical oxidative cyclization of hydroxyalkyl dihydropyran **14** and hydroxyalkyl spiroacetal **13** using iodobenzene diacetate and iodine. This procedure initially afforded a 1 : 1 : 1 : 1 mixture of bis-spiroacetals **12a** : **12b** : **12c** : **12d**, however subsequent acid catalysed equilibration afforded a 3 : 1 : 0.9 thermodynamic mixture of **12a** : **12b** : **12c**. The major bis-spiroacetal **12a** underwent stereoselective epoxidation using dimethyldioxirane to α-epoxide **33a**. Subsequent base induced rearrangement of this epoxide **33a** using lithium diethylamide in pentane afforded allylic alcohol **34a**, that was converted to the more thermodynamically favoured homoallylic alcohol **11a** upon treatment with lithium pyrrolidinylamide in tetrahydrofuran. Homoallylic alcohol **11a** possesses a hydroxyl group at C-12 as required for introduction of the tertiary alcohol group present at this position in spirolides B **1** and D **2**.

Introduction

Spirolides B **1** and D **2** are toxic metabolites of the marine dinoflagellate *Alexandrium ostenfeldii* that were isolated from the digestive glands of mussels (*Mytilus edulis*) and scallops (*Placopecten magellanicus*) during routine monitoring for diarrhetic shellfish toxins in Nova Scotia, Canada, in 1995.[1,2] Further investigations afforded spirolides A **3**, C **4**, 13-desmethyl-C **5**[3] and biologically inactive spirolides E **6** and F **7**.[4] Spirolides A–D contain an unusual 5,5,6-bis-spiroacetal moiety, together with a rare 6,7-spirocyclic imine. Spirolides E **6** and F **7** are keto amine hydrolysis derivatives resulting from ring opening of the cyclic imine, suggesting that this functionality is the pharmacophore responsible for toxicity. Although the absolute stereochemistry of the spirolide family of toxins has not been established to date, a computer-generated relative assignment of 13-desmethyl spirolide C **5** showing the same relative stereochemistry as the related toxins pinnatoxin A **8** and D **9**[5] in the region of their common structure, was later reported.[6] Preliminary pharmacological research into the mode of action of the spirolides suggested that they are antagonists of the muscarinic acetylcholine receptor.[7]

A total synthesis of the spirolides has not been reported to date, however, an elegant total synthesis of pinnatoxin A **8** has been reported by Kishi *et al.*[8] Partial syntheses of the bis-spiroacetal moiety of the pinnatoxins are also discussed in a recent review on the synthesis of bis-spiroacetal ring systems.[9]

Our continued interest in the synthesis of natural products containing bis-spiroacetal ring systems led us to pursue the synthesis of the bis-spiroacetal ring system present in the spirolides using a radical oxidative cyclization strategy that we have previously applied to the synthesis of several polyether antibiotics.[10] In the present case, it was envisaged that radical oxidative cyclizations would provide an ideal method to construct the two five membered rings in the 5,5,6-bis-spiroacetal unit of the spirolides. Therefore, herein we report the full details[11] of this synthetic work, addressing the stereochemical issues associated with the assembly of bis-spiroacetals **12** and the base-induced rearrangement of the derived epoxides.

Results and discussion

The key disconnection in our proposed retrosynthesis of spirolides B **1** and D **2** (Scheme 1) involves Ni(II)/Cr(II)-mediated Kishi–Nozaki coupling[12] between an aldehyde and a vinyl iodide to form the C-9–C-10 bond of the macrocyclic ring in a similar fashion to that used by Kishi *et al.* in the synthesis of pinnatoxin A **8**. The substituted allyl group at C-22 can be introduced *via* Lewis acid-mediated addition of an allyl stannane to bis-spiroacetal **10** that possesses an acetate functionality at the anomeric position. Precedent for this latter step has been demonstrated by this research group[13] using a simpler 6,6-spiroacetal. Acetate **10** is available *via* hydration and acetylation of alkene **11**, that in turn can be synthesised from alkene **12** by epoxidation followed by a base-induced rearrangement. The C-19 tertiary alcohol group in spirolides B **1** and D **2** is then accessible by oxidation of the hydroxyl group introduced in the rearrangement step, followed by addition of a methyl group.

Our earlier successful application of radical chemistry to the synthesis of bis-spiroacetal ring systems suggested that an iterative oxidative radical cyclization strategy might provide a valuable route to the key bis-spiroacetal intermediate **12**. This synthetic approach forms the basis of the current study. Thus, bis-spiroacetal **12** can be derived from spiroacetal alcohol **13** using a radical oxidative cyclization mediated by hypervalent iodine. The spirocentre in **13** can, in turn, be formed using a similar cyclization of dihydropyran **14**, that is available from aldehyde **15**, and the Grignard reagent, prepared from dihydropyranyl bromide **16**. The Brown and Bhat crotyl metallation methodology can be used to prepare aldehyde **15** in a flexible approach that also allows access to varying configurations at the two stereogenic centres by the appropriate choice of (*Z*)- or (*E*)-2-butene and (−)- or (+)-diisopinocampheylborane starting materials.[14]

† Electronic supplementary information (ESI) available: General experimental details together with full experimental procedures, ^{1}H NMR, ^{13}C NMR and mass spectral data for compounds **15**–**31**. See http://www.rsc.org/suppdata/ob/b4/b412883d/

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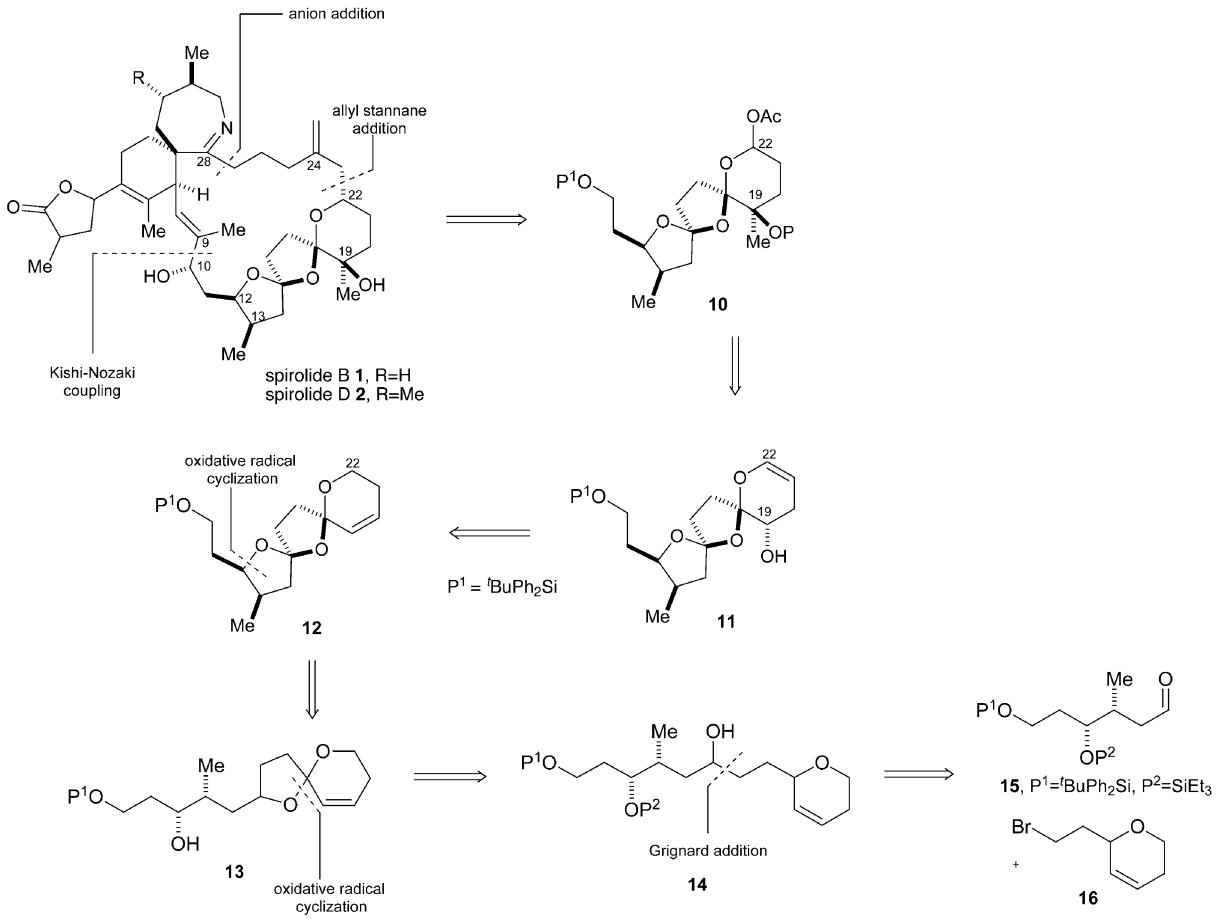
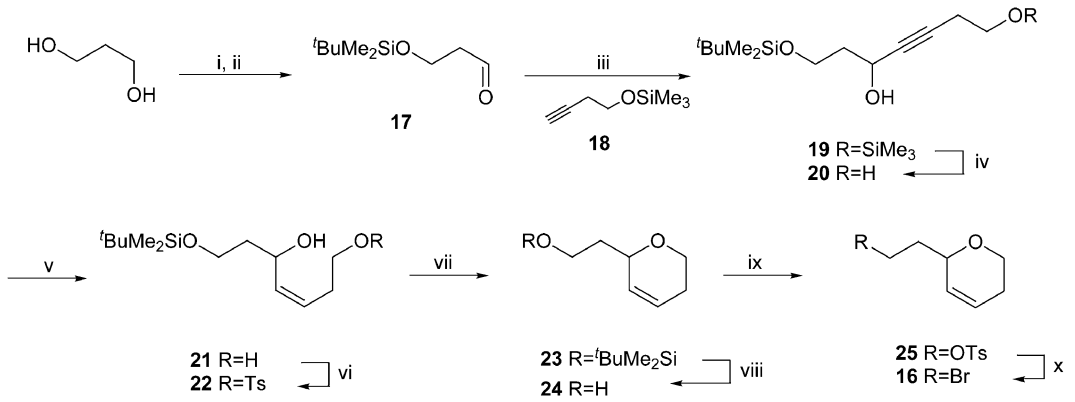


Scheme 1 Proposed retrosynthesis of spirolides B **1** and D **2**.

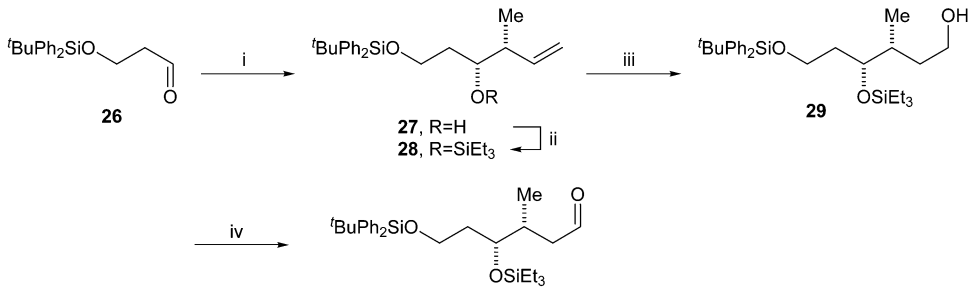


Scheme 2 *Reagents and conditions and yields:* (i) ^{t}BuMe$_2$SiCl, Et$_3$N, CH$_2$Cl$_2$, room temp., 16 h, 76%; (ii) PCC, NaOAc, CH$_2$Cl$_2$, rt, 4 h, 78%; (iii) **18**, BuLi, THF, −78 °C, 25 min then **17**, warm to room temp., 86%; (iv) MeOH, cat. K$_2$CO$_3$, 30 min, 97%; (v) Lindlar, H$_2$, THF, 1.5 h, 96%; (vi) TsCl, Et$_3$N, CH$_2$Cl$_2$, rt, 16 h, 82%; (vii) NaH, THF, 0 °C then room temp., 16 h, 75%; (viii) Bu$_4$NF, THF, rt, 4 h, 80%; (ix) TsCl, NEt$_3$, DMAP, CH$_2$Cl$_2$, room temp., 16 h, 89%; (x) LiBr, acetone, heat, 1.5 h, 91%.

The most practical preparative route to dihydropyran **16** (Scheme 2) involved addition of the lithium acetylide of **18** to aldehyde **17** (available in two steps from propane-1,3-diol). The trimethylsilyl ether in the resultant alcohol **19** was selectively cleaved to alcohol **20** using K$_2$CO$_3$ (catalytic) in methanol, followed by careful partial hydrogenation of the acetylene over a Lindlar catalyst to give (*Z*)-alkene **21** in high yield. Conversion of the primary alcohol **21** into the tosylate **22**, followed by treatment with sodium hydride (1.0 equiv.) in THF afforded dihydropyran **23**. After cleavage of the silyl ether, alcohol **24** was converted to bromide **16** *via* displacement of the corresponding tosylate **25**.

Aldehyde **15** was prepared *via* stereocontrolled crotyl metallation of aldehyde **26** (Scheme 3) using (*Z*)-2-butene and (−)-*β*-methoxydiisopinocampheylborane to give (3*R*,4*R*)-**27** in 82% yield and 90% ee.[14,15] The (3*R*,4*R*) configuration was selected by both analogy with pinnatoxin A **8** and the relative stereochemistry of the spirolides proposed by Falk *et al.*[6] The ^{1}H NMR spectrum of the known Mosher ester derivative prepared by treatment of **27** with (*R*)-2-methoxy-2-trifluoromethyl-2-phenylacetyl chloride, exhibited a methoxy group singlet at *δ* 3.46 ppm and a methyl group doublet at *δ* 0.98 ppm (*J* 6.9 Hz), as reported previously. The ^{19}F NMR spectrum of the Mosher ester derivative contained two resonances for the trifluoromethyl group at *δ* −72.47 and −72.28 ppm, in the ratio of 19.2 : 1, corresponding to an enantiomeric excess of 90%.

The secondary hydroxyl group in alcohol **27** was subsequently protected as a triethylsilyl ether **28**. Subsequent hydroboration



Scheme 3 *Reagents and conditions and yields*: (i) (*Z*)-$CH_3CH{=}CHCH_2$(−)-B(iPc)$_2$, BF_3OEt_2, THF, −78 °C, then NaOH, H_2O_2, heat, 1 h, 84%; (ii) Et_3SiCl, 2,6-lutidine, DMAP, CH_2Cl_2, room temp., 16 h, 95%; (iii) $BH_3{\cdot}SMe_2$, THF, 0 °C, 30 min, then room temp., 2 h, then MeOH, NaOH, H_2O_2, 82%; (iv) Dess–Martin periodinane, py, CH_2Cl_2, room temp., 0.5 h, 92%.

to alcohol **29** followed by Dess–Martin oxidation afforded aldehyde **15**, required for union with bromide **16**.

With both the required coupling partners in hand, addition of aldehyde **15** to the Grignard reagent prepared from dihydropyran bromide **16** was investigated. It was initially disappointing to find that the use of standard Grignard conditions in either diethyl ether or tetrahydrofuran at room temperature or reflux afforded none of the desired product **14** (Scheme 4). Pre-activation of the magnesium metal, the use of iodine, or prolonged dry stirring of the magnesium under an inert atmosphere, only led to the formation of the undesired Wurtz coupling of bromide **16**.

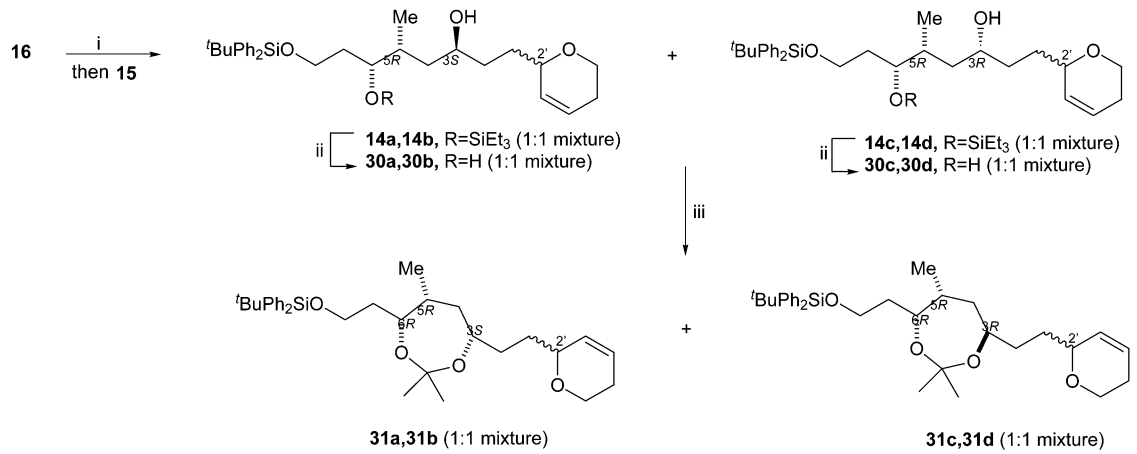
The one-step Barbier reaction[16], in which the halide and aldehyde are introduced to the magnesium concomitantly, has proven successful in cases where formation of the Grignard reagent is troublesome or leads to high levels of dimerisation.[17] Thus, a Barbier mixture of aldehyde **15** and an excess of bromide **16** was slowly added to a slurry of magnesium powder in THF at 0 °C. Standard work-up and flash column chromatography afforded alcohols **14** as a 1 : 1 : 1 : 1 mixture of diastereomers in 64% yield. Prolonged vigorous dry stirring of the magnesium powder under an inert atmosphere or a high vacuum in a pear-shaped flask, addition of a crystal of iodine and entrainment with 1,2-dibromoethane were necessary to ensure consistent yields.

Use of the analogous dihydropyran iodide in the Barbier reaction or the generation of an organolithium reagent *via* lithium–iodide exchange[18] using *tert*-butyllithium (2.0 equiv.) did not improve the yield of **14**.

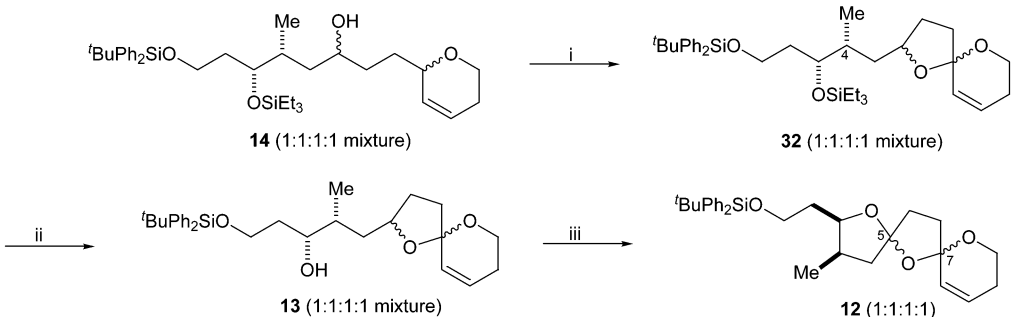
The 1 : 1 : 1 : 1 mixture of Barbier coupled products **14** could be further separated by flash chromatography into two fractions. The ^{13}C NMR spectra of each of these fractions established the presence of two diastereomers in each fraction that were later assigned as **14a**, **14b** (less polar fraction) and **14c**, **14d** (more polar fraction). The alcohols **14a**, **14b** and **14c**, **14d** were converted to the diols **30a**, **30b** and **30c**, **30d** and then to the seven-membered acetonides **31a**, **31b** and **31c**, **31d** in order to establish the stereochemistry of these two fractions. The strong NOE observed between H-3 and H-6 in acetonides **31a**, **31b** (derived from less polar **14a**, **14b**) established that acetonides **31a**, **31b** possessed the (3*S*)-configuration. The absence of a similar correlation in acetonides **31c**, **31d** (derived from more polar **14c**, **14d**) established that **31c**, **31d** had the (3*R*)-configuration. Both **31a**, **31b** and **31c**, **31d** were 1 : 1 mixtures as the stereogenic centre at C-2′ was not controlled during the synthesis. This position is transformed into a quaternary spirocentre and its configuration was later determined by the outcome of the oxidative radical cyclization step and the thermodynamically controlled isomerisation of the 5,5,6-bis-spiroacetal ring system (*vide infra*).

With the Barbier coupling products **14** in hand, attention turned to formation of the bis-spiroacetal system *via* iterative oxidative radical cyclization. Although the pairs of diastereomers **14a**, **14b** and **14c**, **14d** could be separated and cyclized independently for spectroscopic purposes, the 1 : 1 mixture resulting from the Barbier coupling was routinely used for the preparation of bis-spiroacetals **12** (Scheme 5). Towards this end, a 1 : 1 : 1 : 1 mixture of alcohols **14a**, **14b**, **14c**, **14d** was stirred with iodobenzene diacetate (2.0 equiv.) and iodine (2.0 equiv.) in cyclohexane with irradiation using a standard 40 W tungsten filament desk lamp. The iodobenzene produced as a by-product from this reaction was easily separated by flash chromatography affording spiroacetals **32** as a 1 : 1 : 1 : 1 mixture of diasteromers in 90% yield.

Selective deprotection of the triethylsilyl group in **32** using HF·pyridine resulted in significant loss of the *tert*-butyldiphenylsilyl ether, possibly attributed to the steric influence of



Scheme 4 *Reagents and conditions and yields*: (i) Mg, Et_2O, 0 °C, 64%; (ii) HF·py, THF, room temp., 3 h, **14a**, **14b**, 58% or **14c**, **14d**, 46%; (iii) 2,2-dimethoxypropane, toluene, room temp., 1 h, **31a**, **31b**, 84% or **31c**, **31d**, 80%.



Scheme 5 *Reagents and conditions and yields*: (i) $PhI(OAc)_2$, I_2, cyclohexane, 40 W tungsten *hv*, 90%; (ii) HCL·py, py, 48 h, 87%; (iii) $PhI(OAc)_2$, I_2, cyclohexane, 40 W tungsten *hv*, 83%.

the C-4 methyl substituent hindering access to the secondary triethylsilyl ether. Alcohols **13** were therefore best prepared by deprotection of bis-silyl ethers **32** using hydrogen chloride in pyridine[19] for 48 h. (2*R*,3*R*)-5,5,6-Bis-spiroacetals **12** were then successfully obtained as an equimolar mixture of four diastereomers in 83% yield upon further irradiation with iodobenzene diacetate and iodine.

The possibility of a direct one-step formation of bis-spiroacetals **12** from diols **30** was also investigated. Treatment of diols **30** with iodobenzene diacetate and iodine afforded a complex mixture in line with the findings of Suarez *et al.*[20] who were unable to effect the formation of a 6,6,5-spiroacetal system in one-step from a diol precursor that contained the central ring.

The four diastereomers of the 5,5,6-bis-spiroacetal system **12a**, **12b**, **12c**, **12d** result from the stereogenic spiroacetal centres at C-5 and C-7. These can be designated *cis* or *trans* based on the disposition of oxygen atoms across the central tetrahydrofuran ring. These two pairs of diastereomers can be further classified as *syn* or *anti*, defined in this case by the relationship of the central ring C-5–O-6 bond and the hydroxyalkyl substituent at C-2 (Scheme 6). Bis-spiroacetal systems exhibit a thermodynamic preference for particular configurations at the spiroacetal centres based on stereoelectronic, steric and hydrogen bonding effects. It was therefore decided to equilibrate the 1 : 1 : 1 : 1 mixture of bis-spiroacetals **12a**, **12b**, **12c**, **12d** obtained from the final radical cyclization with the idea of obtaining a simpler mixture of thermodynamically favoured diastereomers.

Accordingly, the equimolar mixture of bis-spiroacetals **12a**, **12b**, **12c**, **12d** was dissolved in dichloromethane and stirred at room temperature for 24 h with a catalytic quantity of *p*-toluenesulfonic acid. Analysis of the crude product mixture by ^1H and ^{13}C NMR spectroscopy indicated that only three of the four possible diastereomers (Scheme 6) were now present, in a ratio of 3 : 1 : 0.9. This equilibrium product distribution proved largely independent of the choice of reaction solvent or acid catalyst, although the use of trifluoroacetic acid or camphorsulfonic acid resulted in substantial destruction of the bis-spiroacetal ring system. The mixture was partially separable by careful preparative layer chromatography on glass-backed plates using hexane–diethyl ether (9 : 1) as eluant that also contained *ca.* 0.1% triethylamine to prevent epimerisation. After several consecutive elutions, a less polar minor band and a more polar major band were isolated. The ^1H and ^{13}C NMR spectra of the less polar minor band indicated that a single diastereomer was present, while the ^1H and ^{13}C NMR spectra of the more polar major band indicated that two further diastereomers were present in a 3 : 0.9 ratio. Further separation of these latter two diastereomers proved elusive.

In an effort to unambiguously assign the stereochemistry of the individual bis-spiroacetals using X-ray crystallography, the *tert*-butyldiphenylsilyl ethers **12** were deprotected with tetrabutylammonium fluoride and converted to their bromobenzoate esters. Disappointingly, none of the bromobenzoate derivatives yielded crystals suitable for X-ray analysis and the stereochemistry of bis-spiroacetals **12a**, **12b**, **12c** was assigned using extensive two-dimensional NMR studies in conjunction with molecular modelling studies.

Close examination of NOESY correlations involving H-2, H-4a, H-4b, H-12 and the methyl group provided the most useful information about the relative disposition of the rings of the bis-spiroacetal system (Fig. 1). The bis-spiroacetal ring system in the less polar minor band was assigned as *trans syn* **12b** in the following manner. The *trans* stereochemistry of the bis-spiroacetal rings was established from the NOE correlation observed between H-14 and both H-2 and H-12. Nicolaou *et al.*[21] reported similar correlations as evidence for the assignment of *trans* stereochemistry to the bis-spiroacetal moiety of azaspiracid. The absence of a correlation between H-4 and the methylene protons H-13 and H-14 indicated that this diastereomer also possessed a *syn* relationship between the C-2 alkyl substituent and the central C-5–O-6 bond.

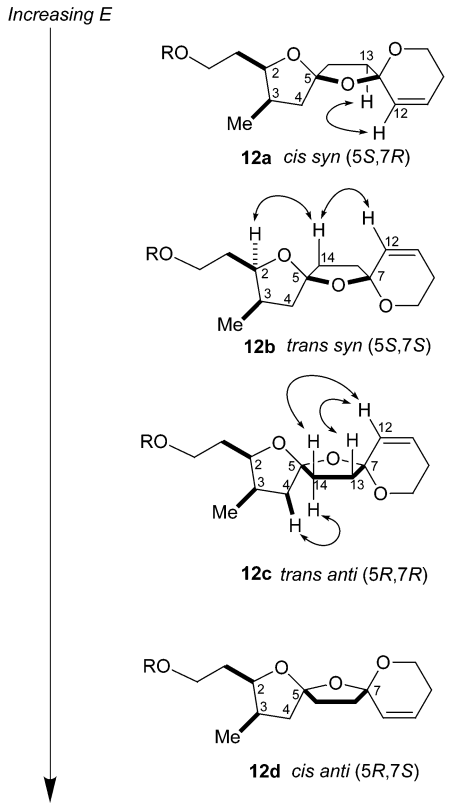
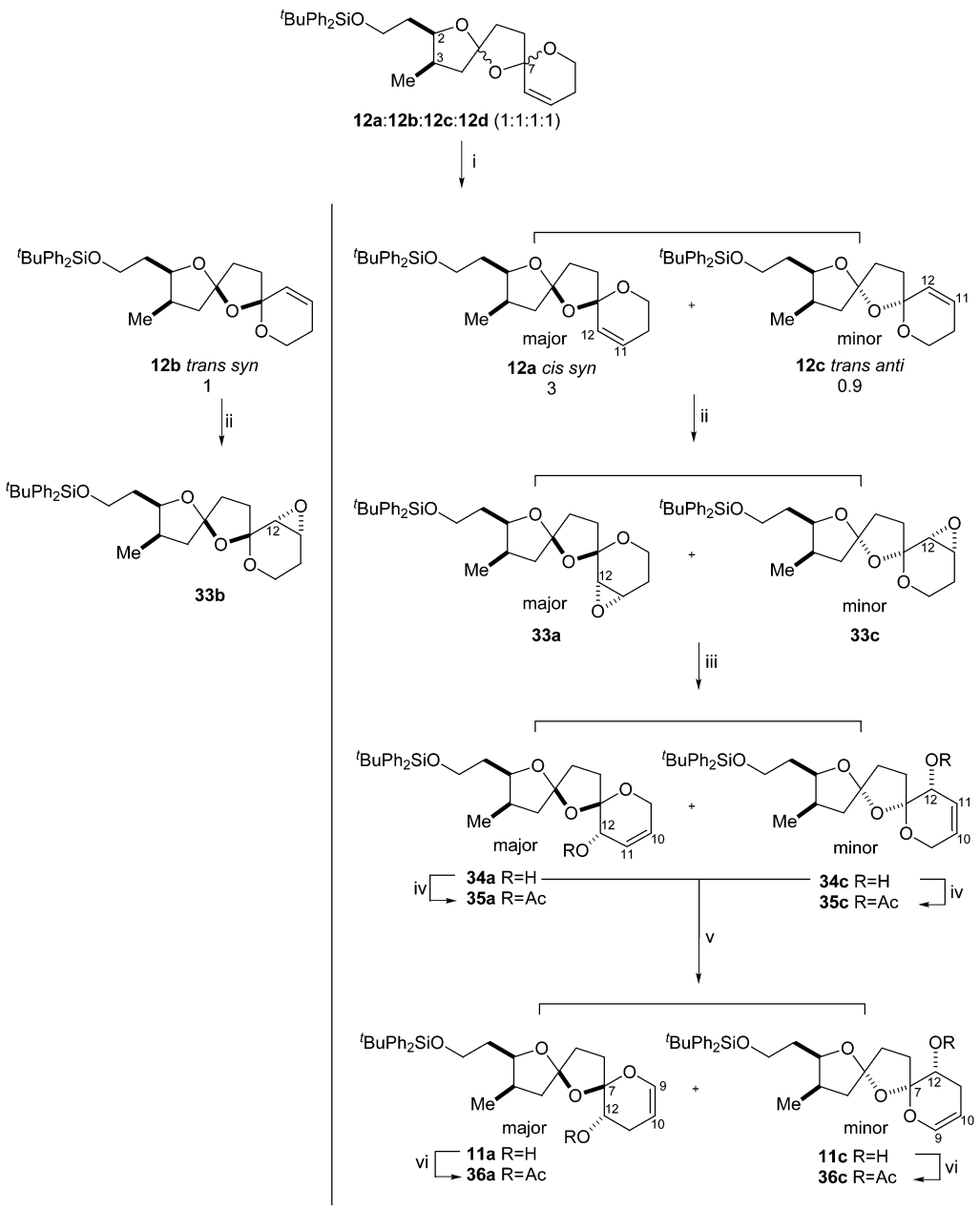


Fig. 1 Putative assignments for bis-spiroacetals **12a**, **12b** and **12c** showing selected NOEs.

The major component **12a**, of the 3 : 0.9 mixture of diastereomers present in the more polar major band, was also assigned as *syn* due to the lack of an NOE correlation between H-14 and H-4, whereas the stereochemistry of the minor



Scheme 6 *Reagents and conditions and yields:* (i) *p*-TsOH, CH_2Cl_2, room temp., 24 h, **12b**, 80%, **12a** : **12c** (3 : 1), 68%; (ii) dimethyldioxirane, acetone, K_2CO_3, 0 °C, 16 h, **33a** : **33c** (3 : 1), 78%, **33b**, 74%; (iii) $LiEt_2$ (10 equiv.), pentane, −78 °C then room temp., 16 h, **34a** : **34c** (3 : 1), 74%; (iv) Ac_2O, py, DMAP, room temp., 1 h, **35a** : **35c** (3 : 1), 75%; (v) lithium pyrrolidinylamide, THF, −78 °C then room temp., 16 h, **11a** : **11c** (3 : 1), 50%; (vi) Ac_2O, py, DMAP, room temp., 1 h, **36a** : **36c** (3 : 1), 67%.

component **12c** was established as having an *anti* relationship between the C-2 alkyl substituent and the C-5–O-6 bond due to the strong NOE correlation observed between H-4a and the unresolved methylene protons H-13 and H-14. Assignment of these latter two diasteromers as *cis* or *trans* was more difficult. For the *anti* diastereomer **12c**, NOEs were observed between the vinylic proton H-12 and one of the geminal methylene protons H-14a, as well as between the other geminal proton H-14b and H-4, suggesting that H-12 and H-4 were on opposite faces of the central five-membered ring, thus establishing the stereochemistry of the terminal rings to be *trans*. The minor component of the more polar band was therefore assigned as *trans anti* **12c**. The lack of similar NOEs being observed in the case of the major component of the more polar major band suggested assignment of this bis-spiroacetal diastereomer as *cis syn* **12a**.

In an effort to gain more information about the thermodynamic preferences of the 5,5,6-bis-spiroacetal ring system, each of the four diastereomers **12a**, **12b**, **12c**, **12d** were examined using computer-based molecular modelling (*tert*-butyldiphenylsilyl ether replaced by trimethylsilyl ether for calculations). Relative energies were calculated at the *ab initio* level (Hartree–Fock, 3–21 G* basis set), using semi-empirical optimized geometries (AM1) for all molecular mechanics conformers (MMFF94) within 3 $kcal^{-1}$ mol^{-1} of the global minimum. The calculated energies followed the trend: *cis syn* **12a** < *trans syn* **12b** < *trans anti* **12c** ≪ *cis anti* **12d** (Fig. 1), thus further supporting the assignment of the major component of the more polar band as *cis syn* **12a** and the minor component as *trans anti* **12c**. The major isomer formed in the present work is the most stable *cis syn* diastereomer **12a** and this isomer has the same configuration as the bis-spiroacetal ring system present in spirolides B **1** and D **2**.

With bis-spiroacetals **12a**, **12b**, **12c** in hand, epoxidation of the alkene and subsequent base-induced rearrangement of the resultant epoxides **33** to allylic alcohols **34** and homoallylic alcohols **11** was next investigated (Scheme 6). The more polar major

band, containing alkenes **12a** and **12c** (3 : 1), was treated with a solution of dimethyldioxirane in acetone[22] to afford epoxides **33a** and **33c** (3 : 1) in 78% yield. H-12 of the predominant component of the product mixture **33a** resonated as a doublet at δ 3.02 ppm in the ^{1}H NMR spectrum ($CDCl_3$), while H-12 of the remaining component **33c** resonated as a doublet at δ 2.87 ppm. Both doublets exhibited coupling constants of 3.9 Hz. It was interesting to note that when the NMR spectrum was recorded in deuterated benzene, these two H-12 doublets resonated at δ 3.10 and 2.69 ppm, respectively. Analogous treatment of the minor band **12b** with dimethyldioxirane afforded a single epoxide **33**, exhibiting a doublet assigned to H-12 with a coupling constant of 3.9 Hz, at δ 2.92 in $CDCl_3$ or 3.12 ppm in C_6D_6 respectively.

Due to the fact that a single alkene gave rise to a single epoxide, it appeared that the epoxidation with dimethyldioxirane proceeded with high facial selectivity, as previously observed[13] in related 1,7-dioxaspiro[5,5]undec-4-ene ring systems. This can be rationalised by significant steric interactions involving the bulky *tert*-butyldiphenylsilyl ether which disfavour the approach of dimethyldioxirane from the β face. Dipole–dipole repulsions, which would also disfavour β approach,[23] reinforce the steric influence upon facial selectivity for the *syn* configurations *cis syn* **12a** and *trans syn* **12b**, due to the β disposition of the central ring oxygen with respect to the C-11=12 double bond. Epoxides **33a**, **33b**, **33c** were therefore all assigned as α and this assignment was later verified by the successful execution of the base-induced rearrangement reaction. Due to the small amount of epoxide **33b** available, the rearrangement studies were only carried out on epoxides **33a** and **33c** derived from the more predominant 3 : 1 mixture of bis-spiroacetal alkenes **12a** and **12c**.

Exposure of the 3 : 1 mixture of epoxides **33a** and **33c** to lithium diethylamide (10 equiv.) in tetrahydrofuran at −78 °C disappointingly did not effect the desired rearrangement and returned only the unreacted starting material. The reaction also failed to proceed either at room temperature or under reflux for periods of up to 24 h. It was concluded that the Lewis basicity of the tetrahydrofuran solvent disrupted the required coordination of lithium diethylamide and the epoxide oxygen. The 3 : 1 mixture of epoxides **33a** and **33c** was therefore treated with lithium diethylamide (10 equiv.) in the non-coordinating solvent pentane at −78 °C (Scheme 6). The reaction mixture was then allowed to warm slowly to room temperature and stirred for a further 16 h, to afford a 3 : 1 mixture of allylic alcohols **34a** and **34c** in 74% yield.

The ^{1}H NMR spectrum of the 3 : 1 mixture of alcohols **34a** and **34c** lacked the doublets at δ 3.02 and 2.87 ppm corresponding to H-12 of epoxides **33a** and **33c**, respectively. A new two proton multiplet was observed at δ 5.8 ppm indicating the presence of a double bond. In the ^{13}C NMR spectrum, the methine resonances at δ 51.3 and 53.6 ppm corresponding to the epoxide carbons C-11 and C-10 were no longer present. Two new vinylic carbons assigned to C-10 and C-11 were observed at δ 126.0 and 128.0 ppm together with a methine resonance at δ 67.5 ppm assigned to C-12. The C-7 spiro carbon also shifted downfield from δ 103.4 ppm in the epoxide to δ 107.2 ppm. Alcohols **34a**, **34c** were also converted to their acetate derivatives **35a**, **35c** under standard conditions in order to aid the interpretation of the NMR spectra.

The outcome of this base-induced rearrangement confirmed that **33a** and **33c** were in fact α-epoxides, as only the α-epoxides possess a pseudo-axial proton required for base-induced rearrangement to proceed successfully (Fig. 2).

With allylic alcohols **34a**, **34c** in hand, attention focussed on their rearrangement to homoallylic alcohols **11**. Our earlier studies on base-induced rearrangements of epoxides using bicyclic spiroacetal systems established that better yields of the homoallylic alcohols were obtained using tetrahydrofuran as solvent rather than hexane or hexane–diethyl ether mixtures. In the present work isomerisation of allylic alcohols **34a**, **34c** to the more thermodynamically favoured homoallylic alcohols **11a**, **11c** was investigated using tetrahydrofuran as solvent. Thus, a 3 : 1 mixture of allylic alcohols **34a**, **34c** was added to a solution of lithium diethylamide (10 equiv.) in tetrahydrofuran at −78 °C and the mixture was warmed slowly to room temperature. After 16 hours, subsequent work-up and purification by flash chromatography afforded recovered starting materials **34a**, **34c**, together with the desired homoallylic alcohols **11a**, **11c** (3 : 1 mixture) in 35% yield.

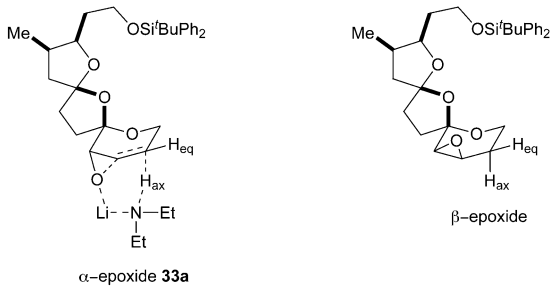


Fig. 2 Transition states required for base-induced rearrangement of α-epoxide **33a**. The β-epoxide does not react due to the lack of an axial *syn*-hydrogen atom.

In the course of their investigations into the rearrangement of epoxides with lithium amide bases, Rickborn and Kissel[24] found that the secondary amine used to generate the amide base also influenced the relative amounts of allylic alcohols and homoallylic alcohols formed in these reactions. In particular, the lithium amide of pyrrolidine was found to be the most effective base to maximise the formation of the homoallylic alcohols. Accordingly, allylic alcohols **34a**, **34c** (3 : 1) were treated with the lithium amide base derived from pyrrolidine and *n*-butyllithium (10 equiv.) at −78 °C and the mixture was allowed to warm slowly to room temperature over 16 hours. Subsequent work-up and purification by flash chromatography afforded homoallylic alcohols **11a**, **11c** (3 : 1) in an improved 50% yield.

The ^{1}H NMR spectrum of the mixture of homoallylic alcohols **11a**, **11c** (3 : 1) showed significant differences in the resonances due to the alkene protons, in comparison to the allylic alcohol starting materials. In the mixture of allylic alcohols **34a**, **34c**, H-10 and H-11 resonated as a single multiplet at δ 5.8 ppm, however the spectrum of homoallylic alcohols **11a**, **11c** exhibited multiplets at δ 4.64 and 6.17 ppm corresponding to H-10 and H-9 respectively. This large difference in chemical shifts observed for the vinylic protons reflects the fact that honoallylic alcohols **11a**, **11c** are in fact cyclic enol ethers. In the ^{13}C NMR spectrum, the resonance due to C-9 appeared significantly downfield at δ 141.2 ppm.

Alcohols **11a**, **11c** were also converted to their acetate derivatives **36a**, **36c** under standard conditions in order to aid in the interpretation of the NMR spectra. Acetylation of the secondary alcohol caused a large downfield shift in the resonance of H-12, from δ 3.8 ppm in homoallylic alcohols **11a**, **11c**, to δ 4.9 ppm in homoallylic acetates **36a**, **36c**. More importantly, separate resonances were now observed for C-10 and C-7, at δ 98.0 and 105.0 ppm respectively, which were previously coincidental at δ 98.7 ppm in the homoallylic alcohols **11a**, **11c**.

In summary, the first synthesis of the 5,5,6-bis-spiroacetal ring system present in spirolides B **1** and D **2** has been achieved using a novel iterative oxidative radical cyclization strategy. The mild conditions used, and the high yields obtained for the cyclization steps, suggest that this approach is a practical method for the construction of this ring system. The stereogenic centres at C-2 and C-3 on the bis-spiroacetal ring were assembled using the Brown and Bhat crotyl metallation methodology. Unsaturated bis-spiroacetals **12a**, **12c** were successfully elaborated to homoallylic alcohols **11a**, **11c** *via* epoxidation and base-induced rearrangement, however the synthetic utility of this approach is limited by the presence of inseparable diastereomers due to the stereogenic spirocentres at C-5 and C-7.

Experimental

(2′*R*,3*S*,5*R*,6*R*)- and (2′*S*,3*S*,5*R*,6*R*)-8-(*tert*-Butyldiphenylsilyloxy)-1-(5,6-dihydro-2*H*-pyran-2-yl)-5-methyl-6-(triethylsilyloxy)octan-3-ol (14a,14b) (2′*R*,3*R*,5*R*,6*R*)- and (2′*S*,3*S*,5*R*,6*R*)-8-(*tert*-butyldiphenylsilyloxy)-1-(5,6-dihydro-2*H*-pyran-2-yl)-5-methyl-6-(triethylsilyloxy)octan-3-ol (14c,14d)

Flame-dried magnesium powder (150 mg, 6.3 mmol) was vigorously stirred in a pear-shaped flask under a nitrogen atmosphere for 4 h, after which time diethyl ether (1.0 mL), a single crystal of iodine (5 mg) and 1,2-dibromoethane (50 μL, 0.2 mmol) were added. When decolourisation had occurred the flask was cooled to 0 °C in an ice bath and a mixture of bromide **16** (0.69 g, 3.63 mmol), aldehyde **15** (1.45 g, 2.91 mmol) and diethyl ether (2.0 g) was added slowly dropwise over 60 min *via* syringe. After stirring for a further 60 min at room temperature, saturated aqueous sodium bicarbonate (1.0 mL) was added and the reaction mixture extracted with diethyl ether (60 mL). The organic layer was washed with water (15 mL) and brine (15 mL) and was dried over $MgSO_4$. Removal of the solvent under a reduced pressure, followed by flash column chromatography using hexane–ethyl acetate (19 : 1–1 : 1) gave a 1 : 1 : 1 : 1 mixture of the *title compounds* **14a**, **14b**, **14c**, **14d** (1.12 g, 64%) as a colourless oil. **14a**, **14b** and **14c**, **14d** were separable by careful chromatography if desired, but the 1 : 1 : 1 : 1 mixture was routinely used for the preparation of spiroacetals **32**.

Alcohols **14a**, **14b** [Found (CI, NH_3): MH^+, 611.3960; $C_{36}H_{59}O_4Si_2$ requires M_r, 611.3952]; ν_{max}/cm^{-1} ($CDCl_3$): 3400, 3053, 2958, 2932, 2305, 1461, 1427, 1265, 1111, 1082, 895, 738, 705; δ_H (300 MHz, $CDCl_3$): 0.59 (6H, q, *J* 8.2, $SiCH_2CH_3$), 0.84 (3H, d, $J_{Me,5}$ 7.0, Me), 0.93 (9H, t, *J* 8.2, $SiCH_2CH_3$), 1.05 (9H, s, Si′*Bu*Ph_2), 1.43–1.70 (8H, m, H-1, H-2, H-4 and H-7), 1.79–1.97 (2H, H-5 and H-5′a), 2.19–2.32 (1H, m, $CH{=}CHCH_2$, H-5′b), 3.54–3.73 (4H, m, H-3, H-6′$_{ax}$ and H-8), 3.84–3.91 (1H, m, C*H*OSi, H-6), 3.93–4.03 (1H, m, $CH_{ax}H_{eq}O$, H-6′$_{eq}$), 4.05–4.14 (1H, m, C*H*O, H-2′), 5.57–5.66 (1H, m, $CH{=}CHCH_2$, H-3′), 5.79–5.87 (1H, m, $CH{=}CHCH_2$, H-4′), 7.33–7.45 (6H, m, ArH, *m* and *p*), 7.60–7.69 (4H, m, ArH, *o*); δ_C (75 MHz, $CDCl_3$): 5.8 ($SiCH_2CH_3$), 6.6 ($SiCH_2CH_3$), 15.8 (CH_3, Me), 15.9 (CH_3, Me*), 19.0 (quat., Si′*Bu*Ph_2), 25.18 (CH_2, $CH_2CH{=}CH$, C-5′), 25.21 (CH_2, $CH_2CH{=}CH$, C-5′*), 26.8 (CH_3, Si′*Bu*Ph_2), 31.7 (CH_2, CH_2CH_2O, C-7), 31.8 (CH_2, CH_2CH_2O, C-7*), 34.2 (CH_2, CH_2CHO, C-1), 34.3 (CH_2, CH_2CHO, C-1*), 34.5 (CH_2, CH_2CHO, C-2), 34.6 (CH_2, CH_2CHO, C-2*), 36.6 (CH, *C*HMe, C-5), 40.9 (CH_2, CH_2CHMe, C-4), 41.0 (CH_2, CH_2CHMe, C-4*), 63.6 (CH_2, CH_2O, C-6′), 63.7 (CH_2, CH_2O, C-6′*), 63.9 (CH_2, CH_2OSi, C-8), 64.0 (CH_2, CH_2OSi, C-8*), 70.2 (CH, *C*HOH, C-3), 70.5 (CH, *C*HOH, C-3*), 74.1 (CH, *C*HO, C-2′), 74.2 (CH, *C*HO, C-2′*), 75.1 (CH, *C*HOSi, C-6), 75.2 (CH, *C*HOSi, C-6*), 124.8 (CH, $CH{=}CHCH_2$, C-4′), 127.7 (CH, ArH, *m*), 129.8 (CH, ArH, *p*), 130.2 (CH, $CH{=}CHCH_2$, C-3′), 133.0 (quat., ArSi), 135.6 (CH, ArH, *o*); *m*/*z* (CI, NH_3): 611 (MH^+, 4%), 501 (3), 485 (5), 479 (4), 455 (10), 291 (22), 216 (24), 199 (20), 196 (32), 132 (27), 120 (34), 78 (100).

Alcohols **14c**, **14d** as a colourless oil [Found (CI, NH_3): MH^+, 611.3944. $C_{36}H_{59}O_4Si_2$ requires M_r, 611.3952]; ν_{max}/cm^{-1} ($CDCl_3$): 3400, 3053, 2958, 2932, 2305, 1461, 1427, 1265, 1111, 1082, 895, 738, 705; δ_H (400 MHz, $CDCl_3$): 0.57 (6H, q, *J* 8.2, $SiCH_2CH_3$), 0.84–0.93 (12H, m, $SiCH_2CH_3$ and Me), 1.05 (9H, s, Si′*Bu*Ph_2), 1.43–1.70 (8H, m, H-1, H-2, H-4 and H-7), 1.81 (1H, m, H-5), 1.88 (0.5H, br s, $CH{=}CHCH_aH_b$ H-5′a), 1.92 (0.5H, br s, $CH{=}CHCH_aH_b$ H-5′a*), 2.22–2.34 (1H, m, $CH{=}CHCH_2$, H-5′b), 2.85 (0.5H, br s, OH), 3.05 (0.5H, br s, OH*), 3.62–3.73 (4H, m, H-3, H-6′$_{ax}$ and H-8), 3.84–3.89 (1H, m, C*H*OSi, H-6), 3.95–4.01 (1H, m, H-6′$_{eq}$), 4.12 (1H, br s, C*H*O, H-2′), 5.61 (1H, br d, $J_{3',4'}$ 10.0, $CH{=}CHCH_2$, H-3′), 5.78–5.85 (1H, m, $CH{=}CHCH_2$, H-4′), 7.34–7.44 (6H, m, ArH, *m* and *p*), 7.61–7.69 (4H, m, ArH, *o*); δ_C (100 MHz, $CDCl_3$): 5.1 ($SiCH_2CH_3$), 6.9 ($SiCH_2CH_3$), 16.5 (CH_3, Me), 16.6 (CH_3, Me*), 19.1 (quat., Si′*Bu*Ph_2), 25.2 (CH_2, $CH_2CH{=}CH$, C-5′), 25.3 (CH_2, $CH_2CH{=}CH$, C-5′*), 26.8 (CH_3, Si′*Bu*Ph_2), 31.7 (CH_2, CH_2CH_2O, C-7), 33.1 (CH_2, CH_2CHO, C-1), 33.2 (CH_2, CH_2CHO, C-1*), 35.37 (CH, *C*HMe, C-5), 35.43 (CH, *C*HMe, C-5*), 35.55 (CH_2, CH_2CHO, C-2), 35.64 (CH_2, CH_2CHO, C-2*), 40.0 (CH_2, CH_2CHMe, C-4), 61.1 (CH_2, CH_2OSi, C-8), 63.6 (CH_2, CH_2O, C-6′), 70.0 (CH, *C*HOH, C-3), 70.1 (CH, *C*HOH, C-3*), 72.65 (CH, *C*HOSi, C-6), 72.69 (CH, *C*HOSi, C-6*), 74.0 (CH, *C*HO, C-2′), 74.1 (CH, *C*HO, C-2′*), 124.8 (CH, $CH{=}CHCH_2$, C-4′), 127.6 (CH, ArH, *m*), 129.6 (CH, ArH, *p*), 130.29 (CH, $CH{=}CHCH_2$, C-3′), 130.34 (CH, $CH{=}CHCH_2$, C-3′*), 133.9 (quat., ArSi), 135.6 (CH, ArH, *o*); *m*/*z* (CI, NH_3): 611 (MH^+, 13%), 479 (19), 461 (9), 455 (12), 401 (14), 283 (12), 216 (26), 205 (27), 199 (30), 196 (32), 132 (29), 120 (35), 91 (48), 83 (48), 78 (100).

(2*S*,2′*R*,3′*R*,5*R*)- and (2*S*,2′*R*,3′*R*,5*S*)-2-[5′-(*tert*-Butyldiphenylsilyloxy)-2′-methyl-3′-(triethylsilyloxy)pentyl]-1,6-dioxaspiro[4.5]dec-9-ene (32a,32b)

Iodine (60 mg, 0.24 mmol) and iodobenzene diacetate (70 mg, 0.22 mmol) were added to a 1 : 1 solution of alcohols **14a**, **14b** (60 mg, 0.10 mmol) in cyclohexane (10 mL). After stirring for 1 h under 40 W irradiation at room temperature, the reaction mixture was diluted with diethyl ether (50 mL) and shaken with saturated aqueous sodium thiosulfate–sodium bicarbonate (1 : 1, 10 mL) until colourless. The organic layer was washed with brine (10 mL) and dried over anhydrous potassium carbonate. Removal of the solvent under a reduced pressure, followed by flash column chromatography using hexane–diethyl ether (9 : 1) as eluant afforded a 1 : 1 mixture of the *title compounds* **32a**, **32b** (54 mg, 90%) as a colourless oil [Found (CI, NH_3): MH^+, 609.3791. $C_{36}H_{57}O_4Si_2$ requires M_r, 609.3795]; ν_{max}/cm^{-1} ($CDCl_3$): 3053, 2986, 2959, 2876, 2305, 1422, 1265, 1111, 1079, 1018, 895, 736; δ_H (300 MHz, $CDCl_3$): 0.57 (6H, q, *J* 8.0, $SiCH_2CH_3$), 0.82–0.91 (12H, m, Me and $SiCH_2CH_3$), 1.05 (9H, s, Si′*Bu*Ph_2), 1.48–2.29 (11H, m, H-1′, H-2′, H-3, H-4, H-4′ and H-8), 3.64–3.77 (3H, m, H-5′ and H-7$_{ax}$), 3.80–3.84 (1H, m, C*H*OSi, H-3′), 3.92–4.01 (1H, m, $CH_{ax}H_{eq}O$, H-7$_{eq}$), 4.17–4.26 (1H, m, C*H*O, H-2), 5.60 (1H, br d, $J_{10',9'}$ 11.3, $CH{=}CHCH_2$, H-10), 5.93–6.02 (1H, m, $CH{=}CHCH_2$, H-9), 7.36–7.44 (6H, m, ArH, *m* and *p*), 7.64–7.70 (4H, m, ArH, *o*); δ_C (100 MHz, $CDCl_3$): 5.2 (CH_3, $SiCH_2CH_3$), 7.0 (CH_3, $SiCH_2CH_3$), 14.1 (CH_3, Me), 14.5 (CH_3, Me*), 19.2 (quat., Si′*Bu*Ph_2), 24.54 (CH_2, $CH_2CH{=}CH$, C-8), 24.59 (CH_2, $CH_2CH{=}CH$, C-8*), 26.8 (CH_3, Si′*Bu*Ph_2), 31.1 (CH_2, CH_2CH_2O, C-4′), 31.4 (CH_2, CH_2CH_2O, C-4′*), 35.4 (CH, *C*HMe, C-2′), 36.2 (CH_2, CH_2CHO, C-3), 36.7 (CH_2, CH_2CHO, C-3*), 37.3 (CH_2, CH_2CHO, C-4), 38.4 (CH_2, CH_2CHO, C-4*), 41.6 (CH_2, CH_2CHMe, C-1′), 58.5 (CH_2, CH_2O, C-7), 59.1 (CH_2, CH_2O, C-7*), 61.2 (CH_2, CH_2OSi, C-5′), 72.9 (CH, *C*HOSi, C-3′), 73.3 (CH, *C*HOSi, C-3′*), 76.4 (CH, *C*HO, C-2), 78.8 (CH, *C*HO, C-2*), 102.2 (quat., C-5), 102.5 (quat., C-5*), 127.6 (CH, ArH, *m*), 128.9 (CH, $CH{=}CHCH_2$, C-9), 129.5 (CH, ArH, *p*), 130.2 (CH, $CH{=}CHCH_2$, C-10), 134.0 (quat., ArSi), 135.6 (CH, ArH, *o*); *m*/*z* (CI, NH_3): 609 (MH^+, 11%), 593 (6), 579 (11), 551 (6), 477 (54), 455 (23), 397 (12), 283 (16), 221 (20), 216 (25), 199 (26), 196 (28), 139 (35), 78 (100).

(2*R*,2′*R*,3′*R*,5*R*)- and (2*R*,2′*R*,3′*R*,5*S*)-2-[5′-(*tert*-Butyldiphenylsilyloxy)-2′-methyl-3′-(triethylsilyloxy)pentyl]-1,6-dioxaspiro[4.5]dec-9-ene (32c,32d)

Iodine (60 mg, 0.24 mmol) and iodobenzene diacetate (69 mg, 0.22 mmol) were added to a 1 : 1 solution of alcohols **14c**, **14d** (60 mg, 0.10 mmol) in cyclohexane (10 mL). After stirring for 1 h under 40 W irradiation at rt, the reaction mixture was diluted with diethyl ether (50 mL) and shaken with saturated aqueous sodium thiosulfate–sodium bicarbonate (3 : 1, 10 mL) until colourless. The organic layer was washed with brine (10 mL) and dried over anhydrous potassium carbonate. Removal of the solvent under a reduced pressure, followed by flash column

chromatography using hexane–diethyl ether (9 : 1) as eluant afforded a 1 : 1 mixture of the *title compounds* **32c**, **32d** (54 mg, 90%) as a colourless oil [Found (CI, NH_3): MH^+, 609.3791; $C_{36}H_{57}O_4Si_2$ requires M_r, 609.3795]; ν_{max}/cm^{-1} ($CDCl_3$): 3053, 2986, 2959, 2876, 2305, 1422, 1265, 1111, 1079, 1018, 895, 736; δ_H (300 MHz, $CDCl_3$): 0.55 (6H, q, J 8.0, $SiCH_2CH_3$), 0.84–0.93 (12H, m, Me and $SiCH_2CH_3$), 1.04 (9H, s, Si^t*Bu*Ph_2), 1.40–2.30 (11H, m, H-1′, H-2′, H-3, H-4, H-4′ and H-8), 3.68–3.76 (3H, m, H-7_{ax} and H-5′), 3.78–3.83 (1H, m, C*H*OSi, H-3′), 3.93–4.02 (1H, m, $CH_{ax}H_{eq}O$, H-7_{eq}), 4.12–4.20 (1H, m, C*H*O, H-2), 5.61 (1H, br d, $J_{10',9'}$ 11.2, C*H*=$CHCH_2$, H-10), 5.95–6.01 (1H, m, CH=C*H*CH_2, H-9), 7.36–7.44 (6H, m, ArH, *m* and *p*), 7.64–7.70 (4H, m, ArH, *o*); δ_C (100 MHz, $CDCl_3$): 5.2 (CH_3, $SiCH_2CH_3$), 7.0 (CH_3, $SiCH_2CH_3$), 15.0 (CH_3, Me), 15.3 (CH_3, Me*), 19.2 (quat., Si^t*Bu*Ph_2), 24.5 (CH_2, CH_2CH=CH, C-8), 24.6 (CH_2, CH_2CH=CH, C-8*), 26.9 (CH_3, Si^t*Bu*Ph_2), 30.4 (CH_2, CH_2CH_2O, C-4′), 30.9 (CH_2, CH_2CH_2O, C-4′*), 35.8 (CH_2, CH_2CHO, C-3), 36.0 (CH_2, CH_2CHO, C-3*), 36.49 (CH, CHMe, C-2′), 36.52 (CH, CHMe, C-2′*), 37.2 (CH_2, CH_2CHO, C-4), 37.4 (CH_2, CH_2CHO, C-4*), 38.4 (CH_2, CH_2CHO, C-1′), 40.3 (CH_2, CH_2CHO, C-1′*), 58.5 (CH_2, CH_2O, C-7), 59.2 (CH_2, CH_2O, C-7*), 61.17 (CH_2, CH_2OSi, C-5′), 61.21 (CH_2, CH_2OSi, C-5′*), 72.7 (CH, CHOSi, C-3′), 72.8 (CH, CHOSi, C-3′*), 77.5 (CH, CHO, C-2), 80.2 (CH, CHO, C-2*), 102.3 (quat., C-5), 127.6 (CH, ArH, *m*), 128.2 (CH, CH=$CHCH_2$, C-9), 128.8 (CH, CH=$CHCH_2$, C-9*), 129.0 (CH, CH=$CHCH_2$, C-10), 129.2 (CH, CH=$CHCH_2$, C-10*), 129.5 (CH, ArH, *p*), 133.98 (quat., ArSi), 134.04 (quat., ArSi*), 135.6 (CH, ArH, *o*); m/z (CI, NH_3): 609 (MH^+, 11%), 593 (6), 579 (11), 551 (6), 477 (54), 455 (23), 397 (12), 283 (16), 221 (20), 216 (25), 199 (26), 196 (28), 139 (35), 78 (100).

(2*S*,2′*R*,3′*R*,5*R*)- and (2*S*,2′*R*,3′*R*,5*S*)-2-[5′-(*tert*-Butyldiphenylsilyloxy)-3′-hydroxy-2′-methylpentyl]-1,6-dioxaspiro[4.5]dec-9-ene (13a,13b) (2*R*,2′*R*,3′*R*,5*R*)- and (2*R*,2′*R*,3′*R*,5*S*)-2-[5′-(*tert*-butyldiphenylsilyloxy)-3′-hydroxy-2′-methylpentyl]-1,6-dioxaspiro[4.5]dec-9-ene (13c,13d)

A solution of pyridinium hydrochloride was prepared by bubbling freshly prepared hydrogen chloride gas through pyridine (100 mL) with the formation of a crystalline precipitate. Further pyridine was added portionwise until the precipitate just redissolved. An equimolar mixture of bis-silyl ethers **13a**, **13b**, **13c**, **13d** (150 mg, 0.25 mmol) was dissolved in an aliquot of this HCl–pyridine solution (5.0 mL) and stirred for 48 h at 50 °C. Saturated aqueous sodium bicarbonate (1.0 mL) was then added and the reaction mixture extracted with ethyl acetate (2 × 15 mL). The organic extracts were washed with brine (5 mL) and dried over magnesium sulfate. Removal of the solvent under a reduced pressure afforded an oil which was purified by flash column chromatography using hexane–diethyl ether (9 : 1–0 : 1) as eluant to afford a 1 : 1 : 1 : 1 mixture of the *title compounds* **13a**, **13b**, **13c**, **13d** (105 mg, 87%) as a colourless oil.

Alcohols **13a**, **13b** [Found (CI, NH_3): MH^+, 495.2910; $C_{30}H_{43}O_4Si$ requires M_r, 495.2931]; ν_{max}/cm^{-1} ($CDCl_3$): 3460, 2958, 2930, 2857, 1471, 1462, 1427, 1213, 1111, 1078, 1027, 997, 702; δ_H (400 MHz, $CDCl_3$): 0.92 (1.5H, d, $J_{Me,2'}$ 6.8, Me), 0.94 (1.5H, d, $J_{Me,2'}$ 6.8, Me*), 1.05 (9H, s, Si^t*Bu*Ph_2), 1.40–2.08 (10H, m, H-1′a, H-2′, H-3, H-4, H-4′ and H-8), 2.12–228 (1H, m, CH_aH_bCHO, H-1′b), 3.12 (0.5H, br s, OH), 3.17 (0.5H, br s, OH*), 3.73 (1H, m, $CH_{ax}H_{eq}O$, H-7_{ax}), 3.80–3.96 (4H, m, H-3′, H-5′ and H-7_{eq}), 4.19–4.28 (1H, m, C*H*O, H-2), 5.57–5.63 (1H, m, C*H*=$CHCH_2$, H-10), 5.95–6.01 (1H, m, CH=C*H*CH_2, H-9), 7.37–7.44 (6H, m, SiArH, *m* and *p*), 7.65–7.69 (4H, m, SiArH, *o*); δ_C (100 MHz, $CDCl_3$): 14.2 (CH_3, Me), 19.1 (quat., Si^t*Bu*Ph_2), 24.4 (CH_2, CH_2CH=CH, C-8), 24.5 (CH_2, CH_2CH=CH, C-8*), 26.8 (CH_3, Si^t*Bu*Ph_2), 31.3 (CH_2, CH_2CHO, C-4′), 31.4 (CH_2, CH_2CHOSi, C-4′*), 35.7 (CH_2, CH_2CH_2, C-4), 36.6 (CH, CHMe, C-2′), 37.3 (CH_2, CH_2CH_2, C-3), 38.4 (CH_2, CH_2CH_2, C-3*), 39.5 (CH_2, CH_2CH_2, C-1′), 41.9 (CH_2, CH_2CHMe, C-1′*), 58.8 (CH_2, CH_2O, C-7), 59.2 (CH_2, CH_2O, C-7*), 63.3 (CH_2, CH_2OSi, C-5′), 73.6 (CH, CHOH, C-3′), 74.2 (CH, CHOH, C-3′*), 76.9 (CH, CHO, C-2), 79.1 (CH, CHO, C-2*), 102.6 (quat., C-5), 127.7 (CH, ArH, *m*), 128.8 (CH, CH=$CHCH_2$, C-9), 128.9 (CH, CH=$CHCH_2$, C-10), 129.7 (CH, ArH, *p*), 133.4 (quat., ArSi), 135.6 (CH, ArH, *o*); m/z (CI, NH_3): 495 (MH^+, 2%), 479 (14), 477 ($MH^+ - H_2O$, 28), 274 (35), 216 (41), 199 (24), 196 (72), 98 (44), 94 (38), 78 (100).

Alcohols **13c**, **13d** [Found (CI, NH_3): MH^+, 495.2903; $C_{30}H_{43}O_4Si$ requires M_r, 495.2931]; ν_{max}/cm^{-1} ($CDCl_3$): 3460, 2958, 2930, 2857, 1471, 1462, 1427, 1213, 1111, 1078, 1027, 997, 702; δ_H (400 MHz, $CDCl_3$): 0.94 (1.5H, d, $J_{Me,2'}$ 6.7, Me), 0.95 (1.5H, d, $J_{Me,2'}$ 6.7, Me*), 1.04 (9H, s, Si^t*Bu*Ph_2), 1.48–2.30 (10.5H, m, H-1′, H-2′, H-3, H-4, H-4′ and H-8), 2.40 (0.5H, dd, $J_{1',2} = J_{1',2'}$ 7.4, CH_aH_bCHO, H-1′b*), 3.41 (0.5H, d, $J_{OH,3'}$ 2.1, OH), 3.43 (0.5H, d, $J_{OH,3'}$ 2.1, OH*), 3.74 (1H, ddd, $J_{7ax,7eq} = J_{7ax,8ax}$ 10.3 and $J_{7ax,8eq}$ 5.7, $CH_{ax}H_{eq}O$, H-7_{ax}), 3.80–3.98 (4H, m, H-3′, H-5′ and H-7_{eq}), 4.24–4.30 (1H, m, C*H*O, H-2), 5.57–5.63 (1H, m, C*H*=$CHCH_2$, H-10), 5.95–6.02 (1H, m, CH=C*H*CH_2, H-9), 7.36–7.43 (6H, m, SiArH, *m* and *p*), 7.66–7.69 (4H, m, SiArH, *o*); δ_C (100 MHz, $CDCl_3$): 13.9 (CH_3, Me), 14.2 (CH_3, Me*), 19.1 (quat., Si^t*Bu*Ph_2), 24.4 (CH_2, CH_2CH=CH, C-8), 24.5 (CH_2, CH_2CH=CH, C-8*), 26.8 (CH_3, Si^t*Bu*Ph_2), 30.6 (CH_2, CH_2CHO, C-4′), 31.1 (CH_2, CH_2CHOSi, C-4′*), 35.5 (CH_2, CH_2CH_2, C-4), 35.9 (CH_2, CH_2CH_2, C-4*), 36.1 (CH, CHMe, C-2′), 36.3 (CH, CHMe, C-2′*), 37.3 (CH_2, CH_2CH_2, C-3), 38.4 (CH_2, CH_2CH_2, C-3*), 38.9 (CH_2, CH_2CHO, C-1′), 41.8 (CH_2, CH_2CHO, C-1′*), 58.7 (CH_2, CH_2O, C-7), 59.3 (CH_2, CH_2O, C-7*), 63.5 (CH_2, CH_2OSi, C-5′), 63.6 (CH_2, CH_2OSi, C-5′*), 73.8 (CH, CHOH, C-3′), 74.0 (CH, CHOH, C-3′*), 76.4 (CH, CHO, C-2), 79.7 (CH, CHO, C-2*), 102.5 (quat., C-5), 127.7 (CH, ArH, *m*), 128.4 (CH, CH=$CHCH_2$, C-9), 128.7 (CH, CH=$CHCH_2$, C-9*), 128.9 (CH, CH=$CHCH_2$, C-10), 129.0 (CH, CH=$CHCH_2$, C-10*), 129.7 (CH, ArH, *p*), 133.2 (quat., ArSi), 133.3 (quat., ArSi*), 135.6 (CH, ArH, *o*); m/z (CI, NH_3): 495 (MH^+, 1%), 477 (2), 447 (1), 399 (1), 274 (2), 216 (4), 199 (5), 139 (2), 102 (100), 86 (47).

(2*R*,3*R*,5*S*,7*R*)-, (2*R*,3*R*,5*R*,7*S*)-, (2*R*,3*R*,5*S*,7*S*)- and (2*R*,3*R*,5*R*,7*R*)-2-[2′-(*tert*-Butyldiphenylsilyloxy)ethyl]-3-methyl-1,6,8-trioxadispiro[4.1.5.2]tetradec-11-ene (12a,12b,12c,12d)

Iodine (230 mg, 0.91 mmol) and iodobenzene diacetate (280 mg, 0.87 mmol) were added to a 1 : 1 : 1 : 1 mixture of spiroacetal alcohols **13a**, **13b**, **13c**, **13d** (205 mg, 0.41 mmol) in cyclohexane (10 mL). After stirring for 1 h under 40 W irradiation at room temperature, the reaction mixture was diluted with diethyl ether (50 mL) and shaken with saturated aqueous sodium thiosulfate–sodium bicarbonate (3 : 1, 10 mL) until colourless. The organic layer was washed with brine (10 mL) and dried over anhydrous potassium carbonate. Removal of the solvent under a reduced pressure, followed by flash column chromatography using hexane–diethyl ether (9 : 1) as eluant afforded a 1 : 1 : 1 : 1 mixture of four diastereomers **12a**, **12b**, **12c**, **12d** (165 mg, 83%) as a colourless oil [Found (CI, NH_3): MH^+, 493.2782. $C_{30}H_{41}O_4Si$ requires M_r, 493.2774]; ν_{max}/cm^{-1} ($CDCl_3$): 2958, 2931, 2877, 2857, 1472, 1462, 1427, 1111, 1078, 994, 975, 702; δ_H (400 MHz, $CDCl_3$): 0.85–0.91 (3H, m, Me), 1.60–2.61 (11H, m, H-1′, H-3, H-4, H-10, H-13 and H-14), 3.58–4.29 (5H, m, H-2, H-2′ and H-9), 5.53–5.66 (1H, m, C*H*=$CHCH_2$, H-12), 5.85–5.99 (1H, m, CH=C*H*CH_2, H-11), 7.33–7.44 (6H, m, SiArH, *m* and *p*), 7.62–7.70 (4H, m, SiArH, *o*); δ_C (100 MHz, $CDCl_3$): 14.1 (CH_3, Me), 14.3 (CH_3, Me*), 14.5 (CH_3, Me**), 14.6 (CH_3, Me***), 19.17 (quat., Si^t*Bu*Ph_2), 19.22 (quat., Si^t*Bu*Ph_2*), 24.3 (CH_2, CH_2CH=CH, C-10), 24.4 (CH_2, CH_2CH=CH, C-10*), 24.5 (CH_2, CH_2CH=CH, C-10**), 26.9 (CH_3, Si^t*Bu*Ph_2), 33.3 (CH_2, CH_2CH_2O, C-1′), 33.49 (CH_2, CH_2CH_2O, C-1′*), 33.56 (CH_2, CH_2CH_2O, C-1′**), 33.64 (CH_2, CH_2CH_2O, C-1′***), 34.5 (CH,

*C*HMe, C-3), 34.6 (CH, *C*HMe, C-3*), 35.3 (CH, *C*HMe, C-3**), 35.7 (CH_2, CH_2CHO, C-13 or C-14), 36.2 (CH_2, CH_2CHO, C-13* or C-14*), 36.4 (CH_2, CH_2CHO, C-13** or C-14**), 36.6 (CH_2, CH_2CHO, C-13*** or C-14***), 37.0 (CH_2, CH_2CHO, C-14 or C-13), 37.2 (CH_2, CH_2CHO, C-14* or C-13*), 37.4 (CH_2, CH_2CHO, C-14** or C-13**), 37.5 (CH_2, CH_2CHO, C-14*** or C-13***), 44.97 (CH_2, CH_2CHO, C-4), 45.01 (CH_2, CH_2CHO, C-4*), 45.2 (CH_2, CH_2CHO, C-4**), 45.9 (CH_2, CH_2CHO, C-4***), 59.20 (CH_2, CH_2O, C-9), 59.26 (CH_2, CH_2O, C-9*), 59.31 (CH_2, CH_2O, C-9**), 59.3 (CH_2, CH_2O, C-9***), 61.5 (CH_2, CH_2O, C-2′), 61.6 (CH_2, CH_2O, C-2′*), 61.69 (CH_2, CH_2O, C-2′**), 61.71 (CH_2, CH_2O, C-2′***), 78.0 (CH, *C*HO, C-2), 78.8 (CH, *C*HO, C-2*), 79.3 (CH, *C*HO, C-2**), 102.6 (quat., C-7), 102.9 (quat., C-7*), 114.3 (quat, C-5), 114.8 (quat, C-5*), 115.3 (quat, C-5**), 127.6 (CH, ArH, *m*), 127.8 (CH, CH=*C*HCH_2, C-11), 128.2 (CH, CH=*C*HCH_2, C-11*), 128.4 (CH, CH=*C*HCH_2, C-11**), 128.98 (CH, CH=*C*HCH_2, C-11***), 129.03 (CH, *C*H=$CHCH_2$, C-12), 129.4 (CH, *C*H=$CHCH_2$, C-12*), 129.5 (CH, ArH, *p*), 129.8 (CH, *C*H=$CHCH_2$, C-12**), 130.1 (CH, *C*H=$CHCH_2$, C-12***), 133.9 (quat., ArSi), 134.1 (quat., ArSi*), 135.6 (CH, ArH, *o*); *m*/*z* (EI): 492 (M^+, 1%), 474 ($M^+ - H_2O$, 83), 447 (1), 435 ($M^+ - {}^t$Bu, 55), 417 (13), 337 (6), 219 (14), 199 (69), 136 (56), 109 (100).

(2*R*,3*R*,5*S*,7*R*)-, (2*R*,3*R*,5*S*,7*S*)- and (2*R*,3*R*,5*R*,7*R*)-2-[2′-(*tert*-Butyldiphenylsilyloxy)ethyl]-3-methyl-1,6,8-trioxadispiro[4.1.5.2]tetradec-11-ene 12a,12b,12c

A 1 : 1 : 1 : 1 mixture of the four diastereomers **12a**, **12b**, **12c**, **12d** (165 mg, 0.33 mmol) was dissolved in dichloromethane (10 mL) and stirred with *p*-toluenesulfonic acid (5 mg, 0.03 mmol) at room temperature. After 24 h, triethylamine (50 μL) was added and the solution filtered through a plug of silica. Removal of the solvent under a reduced pressure afforded a colourless oil which was purified by preparative layer chromatography (8 sweeps, hexane–diethyl ether (9 : 1) containing 0.1% triethylamine) to give band A containing the less polar *trans syn* bis-spiroacetal **12b** (30 mg, 18%) and band BC containing an inseparable 3 : 1 mixture of the more polar bis-spiroacetals *cis syn* **12a** and *trans anti* **12c** (113 mg, 68%).

trans syn Bis-spiroacetal **12b** (minor band A), colourless oil [Found (CI, NH_3): MH^+, 493.2782; $C_{30}H_{41}O_4Si$ requires M_r, 493.2774]; $[\alpha]_D^{20} = +10.0\ 10^{-1}$ deg cm^2 g^{-1} (c = 1.8, $CDCl_3$); ν_{max}/cm^{-1} ($CDCl_3$): 2958, 2931, 2877, 2857, 1472, 1462, 1427, 1111, 1078, 994, 975, 702; δ_H (400 MHz, $CDCl_3$): 1.01 (3H, d, $J_{Me,3'}$ 6.8, Me), 1.04 (9H, s, Si^t*Bu*Ph_2), 1.67–1.75 (1H, m, H-1′a), 1.82–2.06 (6H, m, H-1′b, H-4a, H-10a, H-13a, H-14), 2.13–2.26 (4H, m, H-3, H-4b, H-10b and H-13b), 3.74 (1H, dddd, J_{gem} 11.2, $J_{9eq,10ax}$ 5.6 and $J_{9eq,10eq} = J_{9eq,11}$ 1.2, C$H_{eq}H_{ax}$O, H-9$_{eq}$), 3.77–3.82 (2H, m, CH_2OSi, H-2′), 3.91 (1H, ddd, $J_{gem} = J_{9ax,10ax}$ 11.2 and $J_{9ax,10eq}$ 3.8, C$H_{eq}H_{ax}$O, H-9$_{ax}$), 4.09 (1H, m, C*H*O, H-2), 5.57 (1H, ddd, $J_{12,11}$ 10.0, $J_{12,10a}$ 2.6 and $J_{12,10b}$ 1.4, C*H*=$CHCH_2$, H-12), 5.89 (1H, dddd, $J_{11,12}$ 10.0, $J_{11,10a}$ 5.4, $J_{11,10b}$ 2.2 and $J_{11,9a}$ 1.2, CH=C*H*CH_2, H-11), 7.36–7.42 (6H, m, SiArH, *m* and *p*), 7.65–7.70 (4H, m, SiArH, *o*); δ_C (100 MHz, $CDCl_3$): 14.3 (CH_3, Me), 19.2 (quat., Si^t*Bu*Ph_2), 24.4 (CH_2, *C*H_2CH=CH, C-10), 26.9 (CH_3, Si^t*Bu*Ph_2), 33.7 (CH_2, *C*H_2CH_2O, C-1′), 35.3 (CH, *C*HMe, C-3), 36.5 (CH_2, *C*H_2CH_2, C-13 or C-14), 36.6 (CH_2, *C*H_2CH_2, C-14 or C-13), 45.0 (CH_2, *C*H_2CHO, C-4), 59.4 (CH_2, *C*H_2O, C-9), 61.5 (CH_2, *C*H_2OSi, C-2′), 78.8 (CH, *C*HO, C-2), 102.9 (quat., C-7), 114.8 (quat., C-5), 127.6 (CH, ArH, *m*), 127.8 (CH, CH=*C*HCH_2, C-11), 129.5 (CH, ArH, *p*), 130.1 (CH, *C*H=$CHCH_2$, C-12), 134.1 (quat., ArSi), 135.6 (CH, ArH, *o*); *m*/*z* (EI): 492 (M^+, 1%), 474 ($M^+ - H_2O$, 83), 447 (1), 435 ($M^+ - {}^t$Bu, 55), 417 (13), 337 (6), 219 (14), 199 (69), 136 (56), 109 (100).

cis syn Bis-spiroacetal **12a** *and trans anti bis-spiroacetal* **12c** (major band BC), colourless oil [Found (CI, NH_3): MH^+, 493.2782. $C_{30}H_{41}O_4Si$ requires M_r, 493.2774]; $[\alpha]_D^{20} = +17.2\ 10^{-1}$ deg cm^2 g^{-1} (c = 1.8, $CDCl_3$); ν_{max}/cm^{-1} ($CDCl_3$): 2958, 2931, 2877, 2857, 1472, 1462, 1427, 1111, 1078, 994, 975, 702; δ_H (400 MHz, $CDCl_3$): 0.87 (0.75H, d, $J_{Me,3'}$ 6.8, Me*), 0.89 (2.25H, d, $J_{Me,3'}$ 6.8, Me), 1.04 (9H, s, Si^t*Bu*Ph_2), 1.54–1.73 (3H, m, H-1′ and H-4a), 1.82–2.31 (7H, m, H-4b, H-10, H-13 and H-14), 2.38–2.52 (1H, m, C*H*Me, H-3), 3.7 (3H, m, H-2′ and H-9$_{eq}$), 3.87–3.98 (1H, m, C$H_{ax}H_{eq}$OSi, H-9$_{ax}$), 4.19–4.28 (1H, m, C*H*O, H-2), 5.57 (0.25H, br d, $J_{12,11}$ 10, C*H*=$CHCH_2$, H-12*), 5.64 (0.75H, br d, $J_{12,11}$10, C*H*=$CHCH_2$, H-12), 5.96 (1H, m, CH=C*H*CH_2, H-11), 7.34–7.42 (6H, m, SiArH, *m* and *p*), 7.65–7.71 (4H, m, SiArH, *o*); δ_C (100 MHz, $CDCl_3$): 14.5 (CH_3, Me), 14.6 (CH_3, Me*), 19.2 (quat., Si^t*Bu*Ph_2), 24.3 (CH_2, *C*H_2CH=CH, C-10*), 24.4 (CH_2, *C*H_2CH=CH, C-10), 26.9 (CH_3, Si^t*Bu*Ph_2), 33.56 (CH_2, *C*H_2CH_2O, C-1′), 35.4 (CH, *C*HMe, C-3), 35.6 (CH, *C*HMe, C-3*), 35.7 (CH_2, *C*H_2CH_2, C-13 or C-14), 36.2 (CH_2, *C*H_2CH_2, C-13* or C-14*), 37.0 (CH_2, *C*H_2CH_2, C-14 or C-13), 37.4 (CH_2, *C*H_2CH_2, C-14* or C-13*), 45.2 (CH_2, *C*H_2CHMe, C-4), 45.9 (CH_2, *C*H_2CHMe, C-4*), 59.27 (CH_2, *C*H_2O, C-9), 61.71 (CH_2, *C*H_2OSi, C-2′), 78.0 (CH, *C*HO, C-2), 79.3 (CH, *C*HO, C-2*), 102.6 (quat., C-7), 114.3 (quat., C-5), 127.6 (CH, ArH, *m*), 128.2 (CH, CH=*C*HCH_2, C-11), 128.4 (CH, CH=*C*HCH_2, C-11*), 129.5 (CH, ArH, *p*), 129.0 (CH, *C*H=$CHCH_2$, C-12*), 129.8 (CH, *C*H=$CHCH_2$, C-12), 134.1 (quat., ArSi), 135.6 (CH, ArH, *o*); *m*/*z* (EI): 492 (M^+, 1%), 474 ($M^+ - H_2O$, 83), 447 (1), 435 ($M^+ - {}^t$Bu, 55), 417 (13), 337 (6), 219 (14), 199 (69), 136 (56), 109 (100).

(2*R*,3*R*,5*S*,7*R*,11*S*,12*S*)- and (2*R*,3*R*,5*R*,7*R*,11*R*,12*R*)-2-[2′-(*tert*-Butyldiphenylsilyloxy)ethyl]-3-methyl-1,6,8-trioxadispiro[4.1.5.2]-11,12-epoxy-tetradecanes (33a,33c)

Dimethyldioxirane (2.0 mL of a *ca.* 0.1 M solution in acetone, 0.2 mmol) was added dropwise to a stirred solution of the major bis-spiroacetal band BC containing a 3 : 1 mixture of *cis syn* **12a** and *trans anti* **12c** (50 mg, 0.10 mmol), potassium carbonate (20 mg, 0.14 mmol) and activated 4 Å molecular sieves in acetone (2.0 mL) at 0 °C. After stirring for 16 h at room temperature, further dimethyl dioxirane (1.0 mL, 0.1 mmol) was added and stirring continued for 8 h. The reaction mixture was then filtered and the solvents removed under a reduced pressure to afford a pale yellow oil which was purified by flash column chromatography using hexane–diethyl ether (9 : 1–1 : 1) as eluant to afford the *title compounds* **33a**, **33c** (40 mg, 3 : 1, 78%) as a colourless clear oil [Found (CI, NH_3): MH^+, 509.2718; $C_{30}H_{41}O_5Si$ requires M_r, 507.2723]; ν_{max}/cm^{-1} ($CDCl_3$): 2955, 2929, 2856, 1471, 1427, 1359, 1272, 1111, 1083, 999, 885, 840, 822, 739, 702, 614; δ_H (400 MHz, $CDCl_3$): 0.90 (0.75H, d, J 6.9, Me*), 0.91 (2.25H, d, J 6.9, Me), 1.05 (9H, s, Si^t*Bu*Ph_2), 1.58–1.72 (3H, m, H-1′ and H-4a), 1.79–2.36 (7H, m, H-4b, H-10, H-13 and H-14), 2.40–2.50 (1H, m, C*H*Me, H-3), 2.87 (0.25H, d, $J_{12,11}$ 3.9, C*H*OCHCH_2, H-12*), 3.02 (0.75H, d, $J_{12,11}$ 3.9, C*H*OCHCH_2, H-12*), 3.35 (0.75H, dd, $J_{11,12} = J_{11,10a}$ 3.9, CHOC*H*CH_2, H-11), 3.39 (0.25H, dd, $J_{11,12} = J_{11,10a}$ 3.9, CHOC*H*CH_2, H-11*), 3.42–3.48 (1H, m, C$H_{ax}H_{eq}$O, H-9$_{eq}$), 3.70–3.82 (3H, m, H-2′ and H-9$_{ax}$), 4.25–4.32 (1H, m, C*H*O, H-2), 7.34–7.43 (6H, m, SiArH, *m* and *p*), 7.67–7.70 (4H, m, SiArH, *o*); δ_C (100 MHz, $CDCl_3$): 14.6 (CH_3, Me), 19.2 (quat,. ^{t}*Bu*Ph_2), 22.7 (CH_2, *C*H_2CH_2O, C-10*), 23.1 (CH_2, *C*H_2CH_2O, C-10), 26.9 (CH_3, ^{t}*Bu*Ph_2), 33.4 (CH_2, *C*H_2CH_2O, C-1′), 34.5 (CH, *C*HMe, C-3), 34.6 (CH_2, *C*H_2CHO, C-13 or C-14), 34.9 (CH_2, *C*H_2CHO, C-14 or C-13), 35.4 (CH_2, *C*H_2CHO, C-14* or C-13*), 44.4 (CH_2, *C*H_2CHMe, C-4), 51.3 (CH, CHO*C*HCH_2, C-11), 53.4 (CH, *C*HOCHCH_2, C-12), 56.7 (CH_2, *C*H_2O, C-9), 61.5 (CH_2, *C*H_2OSi, C-2′), 77.9 (CH, *C*HO, C-2), 78.1 (CH, *C*HO, C-2*), 103.4 (quat., C-7), 115.4 (quat., C-5), 127.6 (CH, ArH, *m*), 129.5 (CH, ArH, *p*), 134.0 (quat., ArSi), 135.6 (CH, ArH, *o*); *m*/*z* (EI): 508 (M^+, 1%), 490 (M^+-H_2O, 10), 451 (21), 433 (10), 325 (32), 199 (100), 149 (63), 91 (65), 57 (78), 42 (67), 41 (68); *m*/*z* (CI, NH_3): 509 (MH^+, 41%), 491 ($MH^+ - H_2O$, 35), 475 (27), 325 (30), 216 (42), 199 (79), 109 (46), 91 (52), 78 (100), 75 (51).

(2*R*,3*R*,5*S*,7*S*,11*R*,12*R*)-2-[2′-(*tert*-Butyldiphenylsilyloxy) ethyl]-3-methyl-1,6,8-trioxadispiro[4.1.5.2]-11,12-epoxy-tetradecane (33b)

Using a similar procedure to that described for **33a**, **33c** above, band A containing *trans syn* bis-spiroacetal **12b** (18 mg, 0.037 mmol) was reacted with dimethyldioxirane (2.0 mL, 0.2 mmol) to give the *title compound* **33b** (14 mg, 74%) as a colourless oil [Found (CI, NH_3): MH^+, 509.2718; $C_{30}H_{41}O_5Si$ requires M_r, 507.2723]; ν_{max}/cm^{-1} ($CDCl_3$): 2955, 2929, 2856, 1471, 1427, 1359, 1272, 1111, 1083, 999, 885, 840, 822, 739, 702, 614; δ_H (400 MHz, $CDCl_3$): 0.96 (3H, d, $J_{Me,3'}$ 7.0, CH_3, Me), 1.05 (9H, s, Si^t*Bu*Ph_2), 1.65–2.32 (11H, m, H-1′, H-3, H-4, H-10, H-13 and H-14), 2.92 (1H, d, $J_{12,11}$ 3.9, C*H*OCHCH$_2$, H-12), 3.31 (1H, dd, $J_{11,12} = J_{11,10a}$ 3.9, CHOC*H*CH$_2$, H-11), 3.42–3.50 (1H, m, CH$_{ax}H_{eq}$O, H-9$_{eq}$), 3.70–3.86 (3H, m, H-2′ and H-9$_{ax}$), 4.11–4.19 (1H, m, C*H*O, H-2), 7.34–7.43 (6H, m, SiArH, *m* and *p*), 7.67–7.70 (4H, m, SiArH, *o*); δ_C (100 MHz, $CDCl_3$): 14.3 (CH$_3$, Me), 19.2 (quat,. ^{t}*Bu*Ph_2), 23.1 (CH$_2$, *C*H$_2$CH$_2$O, C-10), 26.9 (CH$_3$, ^{t}*Bu*Ph_2), 33.8 (CH$_2$, *C*H$_2$CH$_2$O, C-1′), 34.5 (CH, *C*HMe, C-3), 35.3 (CH$_2$, *C*H$_2$CHO, C-13 or C-14), 35.4 (CH$_2$, *C*H$_2$CHO, C-14 or C-13), 44.2 (CH$_2$, *C*H$_2$CHMe, C-4), 51.3 (CH, CHO*C*HCH$_2$, C-11), 53.5 (CH, *C*HOCHCH$_2$, C-12), 56.7 (CH$_2$, *C*H$_2$O, C-9), 61.5 (CH$_2$, *C*H$_2$OSi, C-2′), 79.2 (CH, *C*HO, C-2), 103.4 (quat., C-7), 115.4 (quat., C-5), 127.6 (CH, ArH, *m*), 129.5 (CH, ArH, *p*), 133.9 (quat., ArSi), 135.6 (CH, ArH, *o*); *m*/*z* (EI): 508 (M^+, 1%), 490 (M^+-H_2O, 10), 451 (21), 433 (10), 325 (32), 199 (100), 149 (63), 91 (65), 57 (78), 42 (67), 41 (68); *m*/*z* (CI, NH_3): 509 (MH^+, 41%), 491 ($MH^+ - H_2O$, 35), 475 (27), 325 (30), 216 (42), 199 (79), 109 (46), 91 (52), 78 (100), 75 (51).

(2*R*,3*R*,5*S*,7*R*,12*S*)- and (2*R*,3*R*,5*R*,7*R*,12*R*)-2-[2′-(*tert*-Butyldiphenylsilyloxy)ethyl]-3-methyl-1,6,8-trioxadispiro[4.1.5.2] tetradec-10-en-12-ol (34a,34c)

n-Butyllithium (0.36 mL of a 1.6 M solution in hexanes, 0.58 mmol) was added dropwise to a solution of freshly distilled diethylamine (60 μL, 0.58 mmol) in pentane (3.0 mL) at −40 °C. The resultant slurry was stirred for 25 min then cooled to −78 °C and a solution of bis-spiroacetal epoxides *cis syn* **33a** and *trans anti* **33c** (38 mg, 3 : 1, 0.075 mmol) in pentane (1.5 mL) was added *via* syringe. After 25 min the reaction was allowed to warm to room temperature and stirred for a further 2 h. Saturated aqueous sodium bicarbonate (1.0 mL) was added after 2 h and the reaction mixture extracted with diethyl ether (2 × 5 mL). The organic layer was washed with water (3 mL), brine (3 mL) and dried over potassium carbonate. Removal of the solvent under a reduced pressure gave an orange oil which was purified by flash column chromatography using hexane–diethyl ether (4 : 1–1 : 1) as eluant to afford the *title compounds* **34a**, **34c** (28 mg, 74%) as a colourless oil [Found (CI, NH_3): MH^+, 509.2747; $C_{30}H_{41}O_5Si$ requires M_r, 509.2723]; ν_{max}/cm^{-1} ($CDCl_3$): 3435, 2961, 2931, 2857, 1468, 1462, 1260, 1111, 1088, 988, 742, 703; δ_H (400 MHz, $CDCl_3$): 0.88 (2.25H, d, *J* 6.9, Me), 0.98 (0.75H, d, *J* 6.9, Me*), 1.04 (9H, s, Si^t*Bu*Ph_2), 1.59–1.75 (3H, m, H-1′ and H-4a), 1.88–2.45 (6H, m, H-3, H-4b, H-13 and H-14), 3.71–3.87 (3H, m, H-2′ and H-12), 4.09–4.11 (0.25H, m, CH_aH_bO, H-9a*), 4.12–4.16 (0.75H, m, CH_aH_bO, H-9a), 4.20–4.27 (1H, m, C*H*O, H-2), 4.28–4.31 (0.75H, m, CH$_a$*H*$_b$O, H-9b), 4.32–4.35 (0.25H, m, CH$_a$*H*$_b$O, H-9b*), 5.76–5.99 (2H, m, C*H*=C*H*, H-10 and H-11), 7.35–7.43 (6H, m, SiArH, *m* and *p*), 7.63–7.69 (4H, m, SiArH, *o*); δ_C (100 MHz, $CDCl_3$): 14.3 (CH$_3$, Me*), 14.6 (CH$_3$, Me), 19.2 (quat., Si^t*Bu*Ph_2), 26.9 (CH$_3$, Si^t*Bu*Ph_2), 31.4 (CH$_2$, *C*H$_2$CH$_2$O, C-1′), 33.3 (CH$_2$, *C*H$_2$CH$_2$, C-13 or C-14), 34.5 (CH, *C*HMe, C-3), 34.9 (CH$_2$, *C*H$_2$CH$_2$, C-14 or C-13), 35.2 (CH, *C*HMe, C-3*), 35.4 (CH$_2$, *C*H$_2$CH$_2$, C-14* or C-13*), 43.7 (CH$_2$, *C*H$_2$CHMe, C-4*), 44.0 (CH$_2$, *C*H$_2$CHMe, C-4), 61.4 (CH$_2$, *C*H$_2$O, C-9), 61.7 (CH$_2$, *C*H$_2$O, C-9*), 62.5 (CH$_2$, *C*H$_2$OSi, C-2′), 62.8 (CH$_2$, *C*H$_2$OSi, C-2′), 67.5 (CH, *C*HOH, C-12), 67.6 (CH, *C*HOH, C-12*), 77.8 (CH, CH$_2$*C*HO, C-2), 79.3 (CH, CH$_2$*C*HO, C-2*), 107.2 (quat., C-7), 107.6 (quat., C-7*), 115.2 (quat., C-5), 115.5 (quat., C-5*), 125.0 (CH, CH=*C*HCH$_2$, C-10*), 126.0 (CH, CH=*C*HCH$_2$, C-10), 127.6 (CH, ArH, *m*), 128.0 (CH, *C*H=CHCH$_2$, C-11), 129.5 (CH, ArH, *p*), 129.8 (CH, *C*H=CHCH$_2$, C-11*), 133.8 (quat., ArSi), 134.0 (quat., ArSi*), 135.6 (CH, ArH, *o*); *m*/*z* (CI, NH_3): 509 (MH^+, 11%), 491 ($MH^+ - H_2O$, 100), 216 (47), 199 (55), 196 (40), 78 (48).

(2*R*,3*R*,5*S*,7*R*,12*S*)- and (2*R*,3*R*,5*R*,7*R*,12*R*)-12-Acetoxy-2-[2′-(*tert*-butyldiphenylsilyloxy)ethyl]-3-methyl-1,6,8-trioxadispiro [4.1.5.2]tetradec-10-ene (35a,35c)

A mixture of allylic alcohols **34a**, **34c** (3 : 1, 14 mg, 0.029 mmol), pyridine (1.5 mL), acetic anhydride (0.25 mL, 2.6 mmol) and a catalytic quantity of DMAP was stirred at room temperature for 60 min. Saturated aqueous sodium bicarbonate (1.0 mL) was added and the reaction mixture extracted with dichloromethane (2 × 10 mL). The organic layer was washed with brine, dried over a mixture of potassium carbonate and magnesium sulfate and eluted through a short column of silica. Removal of the solvent under a reduced pressure afforded a 3 : 1 mixture of the *title compounds* **35a**, **35c** (11 mg, 75%) as a pale yellow oil [Found (CI, NH_3): MH^+, 551.2825; $C_{32}H_{43}O_6Si$ requires M_r, 551.2830]; ν_{max}/cm^{-1}(neat): 3584, 2966, 2928, 2863, 1737, 1642, 1598, 1428, 1369, 1260, 1110, 1093, 1020, 799; δ_H (400 MHz, $CDCl_3$): 0.90 (2.25H, d, *J* 6.9, Me), 0.97 (0.75H, d, *J* 6.9, Me*), 1.04 (9H, s, Si^t*Bu*Ph_2), 1.58–1.75 (3H, m, H-1′ and H-4a), 1.81–2.42 (9H, m, H-3, H-4b, H-13, H-14 and OAc), [2.07 (2.25H, s, OAc) and 2.09 (0.75H, s, OAc*)],‡ 3.72–3.82 (2H, m, CH$_2$OSi, H-2′), 4.05–4.37 (3H, m, H-2 and H-9), 4.90 (0.25H, dd, $J_{12,11}$ 4.9 and $J_{12,10}$ 1.9, C*H*OAc, H-12*), 4.90 (0.75H, dd, $J_{12,11}$ 5.0 and $J_{12,10}$ 1.8, C*H*OAc, H-12), 5.80–6.05 (2H, m, C*H*=C*H*, H-10 and H-11), 7.35–7.43 (6H, m, SiArH, *m* and *p*), 7.63–7.69 (4H, m, SiArH, *o*); δ_C (100 MHz, $CDCl_3$): 14.2 (CH$_3$, Me*), 14.6 (CH$_3$, Me), 19.2 (quat., Si^t*Bu*Ph_2), 21.0 (CH$_3$, OAc), 21.1 (CH$_3$, OAc*), 26.9 (CH$_3$, Si^t*Bu*Ph_2), 33.4 (CH$_2$, *C*H$_2$CH$_2$O, C-1′), 34.3 (CH$_2$, *C*H$_2$CH$_2$, C-13 or C-14), 34.4 (CH, *C*HMe, C-3), 34.5 (CH$_2$, *C*H$_2$CH$_2$, C-14* or C-13*), 34.7 (CH$_2$, *C*H$_2$CH$_2$, C-14 or C-13), 44.4 (CH$_2$, *C*H$_2$CHMe, C-4), 46.1 (CH$_2$, *C*H$_2$CHMe, C-4*), 61.2 (CH$_2$, *C*H$_2$O, C-9), 61.4 (CH$_2$, *C*H$_2$O, C-9*), 62.6 (CH$_2$, *C*H$_2$OSi, C-2′), 67.9 (CH, *C*HOAc, C-12*), 69.0 (CH, *C*HOAc, C-12), 77.2 (CH, CH$_2$*C*HO, C-2), 78.0 (CH, CH$_2$*C*HO, C-2*), 104.7 (quat., C-7), 115.5 (quat., C-5), 120.9 (CH, CH=*C*HCH$_2$, C-10*), 121.5 (CH, CH=*C*HCH$_2$, C-10), 127.6 (CH, ArH, *m*), 129.5 (CH, ArH, *p*), 131.2 (CH, *C*H=CHCH$_2$, C-11), 132.1 (CH, *C*H=CHCH$_2$, C-11*), 133.9 (quat., ArSi), 135.6 (CH, ArH, *o*), 170.1 (quat., OAc); *m*/*z* (CI, NH_3): 568 ($M^+ + NH_3$, 18%), 551 (MH^+, 100), 553, ($MH^+ - H_2O$, 34), 475 (28), 381 (52), 274 (38), 263 (35), 216 (44), 196 (78), 94 (63), 78 (71).

(2*R*,3*R*,5*S*,7*R*,12*S*)- and (2*R*,3*R*,5*R*,7*R*,12*R*)-2-[2′-(*tert*-Butyldiphenylsilyloxy)ethyl]-3-methyl-1,6,8-trioxadispiro [4.1.5.2]tetradec-9-en-12-ol (11a,11c)

n-Butyllithium (0.120 mL of a 1.6 M solution in hexanes, 0.19 mmol) was added dropwise to a stirred solution of freshly distilled pyrrolidine (20 μL, 0.19 mmol) in THF (1.0 mL) at −40 °C. The resultant slurry was stirred for 25 min then cooled to −78 °C before a solution of allylic alcohols **34a**, **34c** (18 mg, 3 : 1, 0.035 mmol) in THF (1.0 mL) was added *via* syringe. After 30 min the reaction was allowed to warm slowly to room temperature and stirred for a further 16 h. Saturated aqueous sodium bicarbonate (2 mL) was added and the reaction mixture extracted with diethyl ether (2 × 5 mL). The organic layer was washed with water (2 mL), brine (2 mL) and dried over potassium carbonate. Removal of the solvent under

‡ These two acetate methyl group resonances were contained within the multiplet at δ 1.81–2.42 ppm.

a reduced pressure, followed by flash column chromatography using hexane–diethyl ether (9 : 1) as eluant afforded a 3 : 1 mixture of the *title compounds* **11a**, **11c** (9 mg, 50%) as a colourless oil [Found (EI): MH^+, 508.2633; $C_{30}H_{40}O_5Si$ requires M_r, 509.2645]; ν_{max}/cm^{-1}($CDCl_3$): 3435, 2956, 2927, 2853, 1650, 1428, 1260, 1111, 1085, 1025, 742, 702; δ_H (400 MHz, $CDCl_3$): 0.87 (0.75H, d, *J* 6.9, Me*), 0.89 (2.25H, d, *J* 6.9, Me), 1.04 (9H, s, Si^t*Bu*Ph_2), 1.73–2.52 (11H, m, H-1′, H-3, H-4, H-11, H-13, H-14), 2.86 (1H, br s, OH), 3.74–3.82 (3H, m, H-2′ and H-12), 4.12–4.17 (0.25H, m, C*H*O, H-2*), 4.26–4.34 (0.75H, m, C*H*O, H-2), 4.64 (1H, m, OCH=C*H*, H-10), 6.17 (1H, m, OC*H*=CH, H-9), 7.36–7.42 (6H, m, SiArH, *m* and *p*), 7.64–7.69 (4H, m, SiArH, *o*); δ_C (100 MHz, $CDCl_3$): 14.5 (CH_3, Me), 19.2 (quat., Si^t*Bu*Ph_2), 26.9 (CH_3, Si^t*Bu*Ph_2), 27.2 (CH_2, CH=CH*C*H_2, C-11), 29.2 (CH_2, CH_2CH_2, C-13), 33.2 (CH_2, *C*H_2CH_2O, C-1′), 34.7 (CH, *C*HMe, C-3), 34.9 (CH_2, CH_2CH_2, C-14), 43.5 (CH_2, *C*H_2CHMe, C-4), 61.2 (CH_2, *C*H_2OSi, C-2′), 67.2 (CH, *C*HOH, C-12), 77.2 (CH, CH_2*C*HO, C-2), 78.2 (CH, CH_2*C*HO, C-2*), 98.7 (quat., C-7 and CH, OCH=*C*H, C-10), 115.2 (quat., C-5), 127.6 (CH, ArH, *m*), 129.5 (CH, ArH, *p*), 133.9 (quat., ArSi), 135.6 (CH, ArH, *o*), 141.2 (CH, O*C*H=CH, C-9); *m*/*z* (EI): 508 (MH^+, 1%), 490 ($M^+ - H_2O$, 1), 451 (52), 433 (27), 235 (42), 199 (100), 183 (25), 135 (38), 85 (33).

(2*R*,3*R*,5*S*,7*R*,12*S*)- and (2*R*,3*R*,5*R*,7*R*,12*R*)-12-Acetoxy-2-[2′-(*tert*-Butyldiphenylsilyloxy)ethyl]-3-methyl-1,6,8-trioxadispiro[4.1.5.2]tetradec-9-ene (36a,36c)

Using a similar procedure to that described for **35a**, **35c**, a 3 : 1 mixture of homoallylic alcohols **11a**, **11c** (4.0 mg, 7.9 μmol) was reacted with pyridine (1.0 mL), acetic anhydride (0.1 mL, 1.0 mmol) and a catalytic quantity of DMAP. The resultant pale yellow semi-solid was purified by flash column chromatography in a Pasteur pipette using hexane–diethyl ether (4 : 1) as eluant to afford a 3 : 1 mixture of the *title compounds* **36a**, **36c** (2.9 mg, 67%) as a colourless oil [Found (CI, NH_3): MH^+, 551.2825; $C_{32}H_{43}O_6Si$ requires M_r, 551.2830]; ν_{max}/cm^{-1}(neat): 3585, 2955, 2929, 2870, 1737, 1658, 1511, 1455, 1265, 1240, 1110, 1018, 737; 702; δ_H (400 MHz, $CDCl_3$): 0.87 (3H, br d, *J* 6.9, Me), 1.04 (9H, s, Si^t*Bu*Ph_2), 1.59–1.74 (3H, m, H-1′ and H-4a), 1.88–2.02 (2H, m, H-13a and H-14a), 2.03 (2.25H, s, OAc), 2.04 (0.75H, s, OAc*), 2.06–2.41 (5H, m, H-3, H-4b, H-11a, H-13b and H-14b) 2.43–2.47 (1.5H, m, CH=CHC*H*$_2$, H-11), 2.49–2.54 (0.5H, m, CH=CHC*H*$_2$, H-11*), 3.75 (2H, t, $J_{2',1'}$ 6.7, C*H*$_2$O, H-2′), 4.04–4.12 (0.25H, m, C*H*O, H-2*), 4.14–4.22 (0.75H, m, C*H*O, H-2), 4.63–4.72 (1H, m, OCH=C*H*, H-10), 4.98–5.03 (1H, m, C*H*OAc, H-12), 6.17–6.24 (1H, m, OC*H*=CH, H-9), 7.33–7.42 (6H, m, SiArH, *m* and *p*), 7.63–7.69 (4H, m, SiArH, *o*); δ_C (100 MHz, $CDCl_3$): 14.6 (CH_3, Me), 19.2 (quat., Si^t*Bu*Ph_2), 21.2 (CH_3, OAc), 24.3 (CH_2, CH=CH*C*H_2, C-11), 26.9 (CH_3, Si^t*Bu*Ph_2), 33.2 (CH_2, CH_2CH_2, C-13), 33.5 (CH_2, *C*H_2CH_2O, C-1′), 33.8 (CH_2, *C*H_2CH_2O, C-1′*), 34.3 (CH, *C*HMe, C-3), 34.6 (CH_2, CH_2CH_2, C-14), 44.4 (CH_2, *C*H_2CHMe, C-4), 61.4 (CH_2, *C*H_2OSi, C-2′), 69.2 (CH, *C*HOAc, C-12), 78.0 (CH, CH_2*C*HO, C-2), 79.6 (CH, CH_2*C*HO, C-2*), 98.0 (CH, OCH=*C*H, C-10), 105.0 (quat., C-7), 115.4 (quat., C-5), 127.6 (CH, ArH, *m*), 129.5 (CH, ArH, *p*), 133.9 (quat., ArSi), 135.6 (CH, ArH, *o*), 140.9 (CH, O*C*H=CH, C-9), 170.2 (quat., OAc); *m*/*z* (CI, NH_3): 568 ($M^+ + NH_3$, 4%), 551 (MH^+, 83), 493 (15), 381 (44), 274 (44), 263 (35), 216 (37), 196 (84), 94 (100), 78 (89).

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