

Synthesis of the bis-spiroacetal moiety of the shellfish toxins spiroolides B and D using an iterative oxidative radical cyclization strategy†

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The enantioselective synthesis of the *bis*-spiroacetal fragment of the shellfish toxins, spiroolides B **1** and D **2**, is reported. The carbon framework was constructed *via* a Barbier reaction of dihydropyran **10** with aldehyde **11**, followed by two oxidative radical cyclizations to construct the *bis*-spiroacetal ring system. A silyl-modified Prins cyclization and enantioselective crotylation successfully installed the stereocenters in the cyclization precursor **21**. The initial unsaturated *bis*-spiroacetals **9a–d** underwent equilibration during epoxidation to *trans*-epoxide **24** that was converted to tertiary alcohol **7**.

Introduction

The spiroolides A–D **1–5** (Fig. 1) comprise a novel family of pharmacologically active macrocyclic imines found in the polar lipid fraction obtained from the digestive glands of contaminated mussels (*Mytilus edulis*), scallops (*Placopecten magellanicus*) and toxic plankton from the eastern coast of Nova Scotia, Canada. Spiroolides A–D **1–5** contain an unusual 5,5,6-bis-spiroacetal moiety together with a rare 6,7-spirocyclic imine.¹ Spiroolides E and F are keto amine hydrolysis derivatives resulting from the ring opening of the cyclic imine suggesting that this functionality is the pharmacophore responsible for toxicity.² Recently, isolation and culture of a toxic clone of the dinoflagellate *Alexandrium ostenfeldii* obtained from the same aquaculture site allowed the structural elucidation of three more congeners, spiroolides A **1**, C **3** and 13-desmethyl C **5**.³ The spiroolides A–D (**1–5**) cause potent and characteristic symptoms in the mouse bioassay (spiroolide

A: LD₅₀ 250 µg kg⁻¹) and are activators of L-type calcium channels. These macrocycles contain a novel 6,5,5-bis-spiroacetal ring system as well as an unusual 7,6-spiroimine moiety and bear close resemblance to pinnatoxin A **6** (LD₅₀ 180 µg kg⁻¹) which was isolated from toxic extracts of the clam *Pinna muricata* and has been linked to several major shellfish poisoning events in Japan and China.^{4,5} The absolute stereochemistry of the spiroolide family of toxins has not been established to date, however, a computer-generated relative assignment of 13-desmethyl spiroolide C **5** indicating the same relative stereochemistry as the related toxin pinnatoxin A **6**⁵ in the region of their common structure, was later reported.⁶ Preliminary pharmacological research into the mode of action of the spiroolides suggests that they are antagonists of the muscarinic acetylcholine receptor.⁷

A total synthesis of the spiroolides has not been reported to date, however, an elegant total synthesis of pinnatoxin A **6** has been reported by Kishi *et al.*⁸ wherein the BCD bis-spiroacetal ring system was assembled *via* acid-catalyzed cyclization of a dione precursor. A synthesis of the bis-spiroacetal core of spiroolide B **2** *via* acid-catalyzed cyclization of an acyclic triketone has been communicated⁹ whilst 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.¹⁰ Our interest in the synthesis of natural products containing bis-spiroacetal ring systems¹¹ led us to pursue the synthesis of the bis-spiroacetal ring system present in the spiroolides using an oxidative radical cyclization to construct the two five-membered rings in the 5,5,6-bis-spiroacetal unit of the spiroolides. In addition to our work on the synthesis of model spiroimines¹² related to the spiroolides, we have previously also reported the synthesis of a C10–C22 *bis*-spiroacetal fragment lacking the C19 tertiary alcohol group, using a double oxidative radical cyclization.¹³ However, problems were encountered during the introduction of functionality at C19 and the extension of the carbon framework at C22, thus prompting the adoption of a modified synthetic plan in which disconnection of the C23–C24 bond rather than the C22–C23 bond was a pivotal step. The full details¹⁴ of this revised strategy are presented herein providing rapid access to the fully functionalized C10–C23 *bis*-spiroacetal fragment of spiroolides B and D that is homologous to our previous fragment.

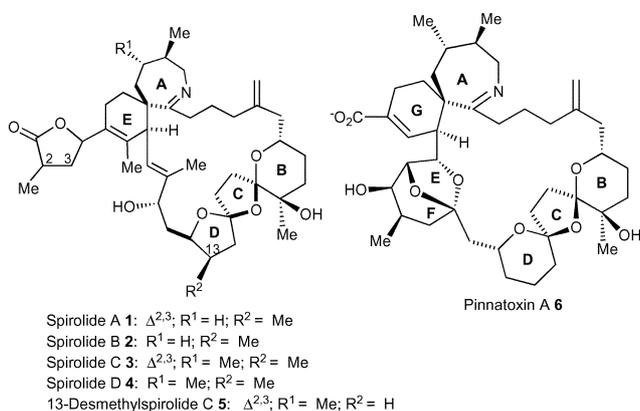
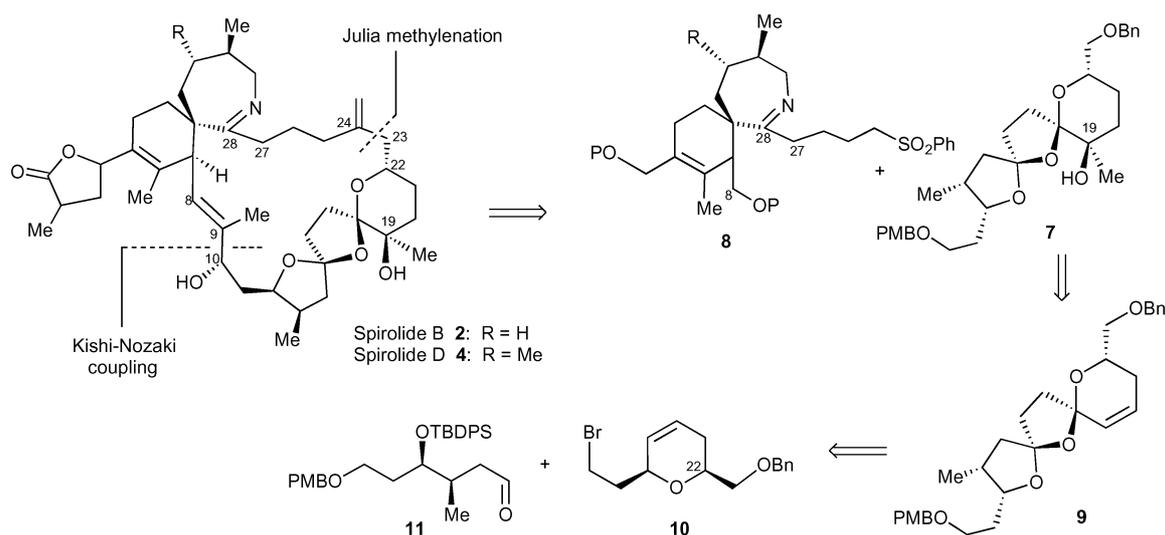


Fig. 1 Structure of the spiroolides and pinnatoxins.

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† Electronic supplementary information (ESI) available: General experimental details together with full experimental procedures, ¹H NMR, ¹³C NMR and mass spectral data for compounds **10–14** and **17–20**. See DOI: 10.1039/b604334h

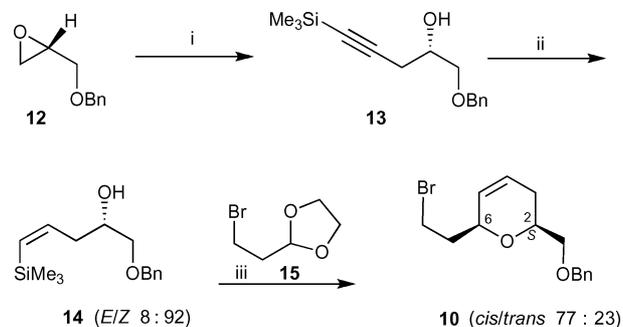


Scheme 1 Retrosynthesis of spiroolides B 2 and D 4.

Results and discussion

The key disconnection in our proposed retrosynthesis of spiroolides B 2 and D 4 (Scheme 1) involves Ni^{II}/Cr^{II}-mediated Kishi–Nozaki coupling¹⁵ between an aldehyde and a vinyl iodide to form the C9–C10 bond of the macrocyclic ring in a similar fashion to that used by Kishi *et al.*⁸ in the synthesis of pinnatoxin A 6. Given that our revised synthetic plan relied on the disconnection of the C23–C24 bond rather than the C22–C23 bond, use of a Julia coupling to effect the construction of the C23–C24 bond was envisaged as a key step. Our attention therefore focused on the synthesis of bis-spiroacetal 7, making use of a Julia methylenation¹⁶ for the subsequent union with spiroimine sulfone 8. This new approach required access to dihydropyran 9 with the required (*S*)-configuration at C22 using a silyl-modified Prins cyclization. The two spiroacetal centres in unsaturated spiroacetal 9 are then formed by oxidative radical cyclization of the alcohol resulting from the Barbier coupling of this dihydropyran 10 with aldehyde 11, followed by deprotection of the *tert*-butyldiphenylsilyl ether and execution of a second oxidative radical cyclization. The *syn* stereochemistry in aldehyde 11 is available from an enantioselective crotylation. The alkene in *bis*-spiroacetal 9 provides functionality for subsequent installation of the tertiary alcohol. It is also envisaged that the *cis* stereochemistry between the terminal rings of the *bis*-spiroacetal will be established by equilibration after incorporation into the macrocyclic ring. Thus, the initial synthesis of *trans*-*bis*-spiroacetals 7 and 9 was required.

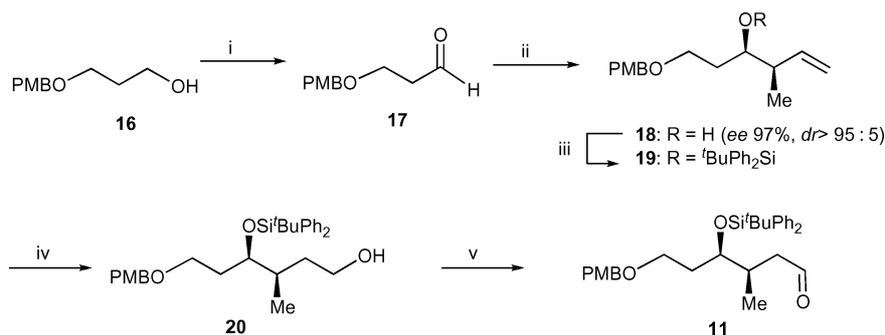
The synthesis of the dihydropyran fragment 10 was carried out in 3 steps (51% overall yield), starting from enantiomerically pure *O*-benzyl protected¹⁷ (*R*)-(+)-glycidol 12 (Scheme 2). Ring opening of epoxide 12 with lithium trimethylsilylacetylide in the presence of a catalytic amount of trimethylaluminum¹⁸ afforded homopropargyl alcohol 13 in a higher yield than when using a stoichiometric amount of boron trifluoride diethyl etherate.¹⁹ Vinylsilane 14 was initially prepared by semi-hydrogenation of the corresponding acetylene 13 in the presence of a poisoned catalyst. Use of the Rosenmund catalyst (Pd/BaSO₄) gave moderate *E/Z* selectivities and poor yields, while Lindlar's catalyst



Scheme 2 Reagents and conditions and yields: (i) Me₃SiC≡CH, BuLi, Me₃Al (cat.), toluene, –78 °C to room temp., 98%; (ii) DIBALH, Et₂O, room temp. then reflux, 24 h, 72%; (iii) InCl₃, CH₂Cl₂, room temp., 48 h, 73%.

(Pd/CaCO₃/Pb) gave variable selectivities. The optimum solvent using Lindlar's catalyst was found to be THF affording vinylsilane 14 as a 15 : 85 mixture of *E/Z* isomers in 69% yield when carried out on a 200 mg scale. Somewhat surprisingly, scaling up of this reaction to a 2 g scale afforded a reversed *E/Z* selectivity of 100 : 0. Similar selectivity issues when effecting the semi-hydrogenation of alkynes bearing a trimethylsilyl substituent have been reported by others.²⁰ The (*Z*)-configuration of vinylsilane 14 is crucial for the formation of dihydropyran 10, as elimination of the trimethylsilyl group from the resultant 6-membered ring formed from the (*E*)-isomer is very slow (<10% conversion after 12 hours).

Fortunately, after the frustrating attempts to effect the stereoselective semi-hydrogenation of acetylene 13, hydroalumination²¹ of 13 in ether using DIBALH (1 M in hexane) gave the desired vinylsilane 14 with high (*Z*)-selectivity (92 : 8). The desired dihydropyran 10 was then prepared in low yield using a silyl-modified Prins cyclization developed by Marko *et al.*²² by the reaction of vinylsilane 14 with acetal 15 in dichloromethane using trimethylsilyl triflate. The desired dihydropyran 10 was later formed more efficiently using the Lewis acids indium trichloride (72%) or iron trichloride (52%) in dichloromethane at room temperature. For the indium trichloride-catalyzed reaction



Scheme 3 Reagents and conditions and yields: (i) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 °C, 96%; (ii) (*Z*)-butene, *t*-BuOK, *n*-BuLi, (-)-(Ipc)₂B(OMe), BF₃·Et₂O, THF, -78 °C, NaOH, H₂O₂, 72%; (iii) *t*-BuPh₂SiCl, imid, DMF, 100 °C, 99%; (iv) BH₃-DMS, THF, room temp., then H₂O₂, NaOH, 78%; (v) Dess–Martin periodinane, py, CH₂Cl₂, room temp., 84%.

the 1,3-*cis* isomer was the major product (*cis*–*trans* 77 : 23), however this was of minor importance given that both isomers of the dihydropyran can be used in the radical oxidative cyclization step as an allylic oxocarbenium ion is formed at C6. The relative configuration between C2 and C6 of the major isomer of dihydropyran **10** was assigned as 1,3-*cis* due to the observation of a strong correlation between H2 and H6 in the NOESY spectrum.

Aldehyde **11** was prepared in five steps from monoprotected 1,3-propanediol **16**^{23,24} via reagent-controlled enantioselective crotylation²⁵ of aldehyde **17** using (*Z*)-2-butene and (-)-β-methoxydiisopinocampheylborane to give (3*R*,4*R*)-alcohol **18** in 97% optical purity and *dr* >95 : 5 (Scheme 3). The absolute configuration of *ent*-**18** was assigned by X-ray diffraction of the derived camphanic ester.²⁶ The enantiomeric excess was measured by ¹⁹F NMR after the formation of the Mosher ester using similar methodology to an analogous aldehyde.¹³ After protection as a *tert*-butyldiphenylsilyl ether **19**, hydroboration with borane-dimethylsulfide followed by oxidative work-up, afforded alcohol **20** that was oxidized with Dess–Martin periodinane to the desired aldehyde **11**.

With aldehyde **11** and bromide **10** in hand, attention next turned to their union via the generation of a Grignard reagent from bromide **10**. Previous studies in our group¹³ have shown that the coupling of similar substrates works best with the use of Barbier's conditions. Magnesium powder was dried under high vacuum with a heat gun and after activation with iodine and 1,2-dibromoethane, a solution of bromide **10** and aldehyde **11** in diethyl ether was added dropwise. After heating for 3 hours under reflux the coupled product **21** was isolated in 88% yield as a ~1 : 1 mixture of the diastereomers at C3' (Scheme 4). The two diastereomers could be easily separated by flash chromatography, but usually the mixture was used throughout the synthesis, as equilibration of the bis-spiroacetal ring system was carried out at a later stage. Activation of the magnesium powder was deemed to be a crucial step before the addition of the iodine and 1,2-dibromoethane.

With the basic carbon skeleton fully assembled, use of iterative radical oxidative cyclizations then allows the formation of the bis-spiroacetal. Irradiation of the mixture of alcohols **21** with a 60 W standard desk lamp in the presence of iodobenzene diacetate and iodine²⁷ in cyclohexane afforded spiroacetal **22** as a mixture of diastereomers in 86% yield. Spirocyclization takes place via the formation of an alkoxy radical (generated from a hypoiodite), 1,5-

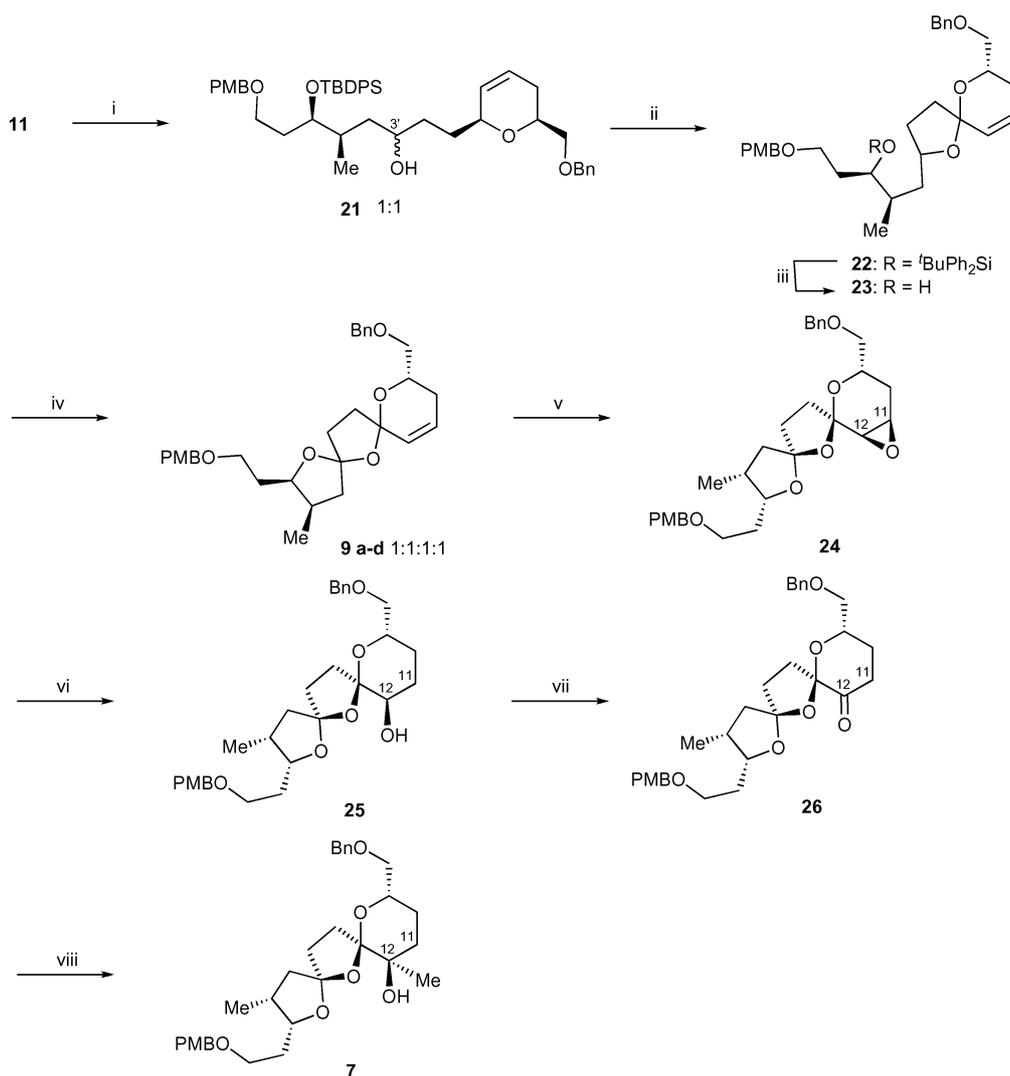
hydrogen transfer to generate a carbon-centred radical, oxidation of the radical to a cation and finally intramolecular trapping of the cation by the hydroxyl group. The *tert*-butyldiphenyl silyl ether in spiroacetal **22** was removed using tetrabutylammonium fluoride with gentle heating at 80 °C resulting in the formation of alcohol **23**. The final bis-spiroacetal ring system was then formed upon execution of a second oxidative radical cyclization providing bis-spiroacetals **9a–d** in 81% yield as a 1 : 1 : 1 : 1 mixture of diastereomers.

Acid-catalyzed spiroacetalisation of the 1 : 1 : 1 : 1 mixture of **9a–d** gave a ~4 : 1 mixture of the two major isomers (**9a** and **9b**) together with trace quantities (<5%) of two other minor isomers (Table 1). Interestingly, use of indium trichloride gave better results than the commonly used reagents such as HF-py, PPTS, ZnBr₂ or ZnCl₂ affording a 87 : 13 mixture of the thermodynamically favoured isomers **9a** and **9b** (entry 5). This is the first example of the use of indium trichloride as a Lewis acid to effect the equilibration of a mixture of spiroacetals allowing convergence to one major diastereomer. The absolute configuration at C5 and C7 in isomer **9a** was assigned unambiguously using 2D NMR NOESY experiments, that showed clear correlations between H9 and H4, and between 3-CH₃ and H14, respectively (Table 1). Use of a 600 MHz spectrometer was essential in order to see the splitting of the H2 and H9 resonances.

Introduction of the tertiary alcohol at C12 onto the unsaturated bis-spiroacetals **9a–d** was initially investigated using a hydroboration–oxidation sequence. Treatment of the unsaturated

Table 1 Equilibration of bis-spiroacetals **9a** and **9b**

Entry	Conditions	9a : 9b (yield)
1	HF-Pyr, MeCN, room temp., 12 h	76 : 24 (81%)
2	PPTS (0.2 equiv), MeCN, room temp., 18 h	~81 : 19 (89%)
3	ZnBr ₂ (0.2 equiv), CH ₂ Cl ₂ , room temp., 19 h	76 : 24 (95%)
4	ZnCl ₂ (0.2 equiv), CH ₂ Cl ₂ , room temp., 24 h	~83 : 17 (88%)
5	InCl ₃ (0.2 equiv), MeCN, room temp., 1 h	87 : 13 (85%)



Scheme 4 Reagents and conditions and yields: (i) **10**, Mg, $\text{Br}(\text{CH}_2)_2\text{Br}$, I_2 , Et_2O , room temp., 88%; (ii) $\text{PhI}(\text{OAc})_2$, I_2 , hv, cyclohexane, room temp., 86%; (iii) Bu_4NF , DMF, 80 °C, 82%; (iv) $\text{PhI}(\text{OAc})_2$, I_2 , hv, cyclohexane, room temp., 81%; (v) *m*-CPBA, CH_2Cl_2 , 0 °C to room temp., 63%; (vi) DIBALH, hexane, 0 °C, 54%; (viii) Dess–Martin periodinane, CH_2Cl_2 , room temp., 88%; (viii) MeMgBr , Et_2O , –78 °C, 86%.

bis-spiroacetals **9a–d** with either $\text{BH}_3 \cdot \text{SMe}_2$ or $\text{BH}_3 \cdot \text{THF}$ resulted in the complete disappearance of any starting material, but after oxidation of the resultant alcohol using Dess–Martin periodinane only low yields of the undesired C11 ketone could be isolated. Use of different procedures known to be mild for the oxidation of alkylboranes (H_2O_2 , AcONa ;²⁸ oxone;²⁹ or NaBO_3 ³⁰) did not result in improved yields.

Attempts to direct the formation of a ketone at C12 by the use of a Wacker oxidation³¹ only afforded recovered starting material (using PdCl_2 , CuCl and O_2) or an intractable complex mixture of products (using PdCl_2 and 1,4-benzoquinone) in which oxypalladation appeared to be directed towards the formation of the undesired C11 ketone. Notably, starting with a 1 : 1 : 1 : 1 mixture of unsaturated bis-spiroacetals **9a–d**, palladium-catalyzed equilibration of the bis-spiroacetals was also observed to give predominantly bis-spiroacetal **9a**.

Finally, treatment of the 1 : 1 : 1 : 1 mixture of bis-spiroacetals **9** with *m*CPBA afforded β -epoxide **24** as a single diastereomer together with recovered starting material. Remarkably, the presence

of *meta*-chlorobenzoic acid and water in the *m*CPBA (*m*CPBA purchased from Fluka contains ~10% *m*-chlorobenzoic acid and ~20% H_2O) effected equilibration of the mixture of bis-spiroacetals **9a–d** to the most thermodynamically favoured isomer **9a**, that then underwent stereoselective epoxidation from the β -face presumably due to the involvement of the neighbouring oxygens in hydrogen bonding to the *m*CPBA.

Epoxide **24** underwent regioselective reductive opening with DIBALH in hexane and the resultant alcohol **25** was oxidized to ketone **26** upon treatment with Dess–Martin periodinane. Use of hexane as the solvent was crucial for the reductive opening of epoxide **24**. Additionally, the reaction was difficult to carry to completion with starting material also being recovered from the reaction. Addition of methylmagnesium bromide to ketone **26** proceeded stereoselectively from the axial direction affording the desired tertiary alcohol **7** with the same stereochemistry as that present in the spirocyclics. Ishiara and coworkers have similarly reported the use of MeLi in THF to effect the stereoselective axial introduction of the methyl group.⁹

The stereochemistries of epoxide **24** and tertiary alcohol **7** were assigned unambiguously by 2D NMR NOESY (Fig. 2). For epoxide **24**, correlations between H9 and H4, between H12 and H13 and between 3-CH₃ and H14 established the stereochemistry as indicated. No correlations were observed between H9 and H11 or H12 as would be expected if epoxidation had taken place from the *a*-face. For tertiary alcohol **7**, clear correlations between H9 and H4 and between H2 and H11 clearly established the *trans* arrangement of the oxygen atoms about the central ring. The absolute configuration of the CH₃ group at C12 was assigned by the observed correlation with H13.

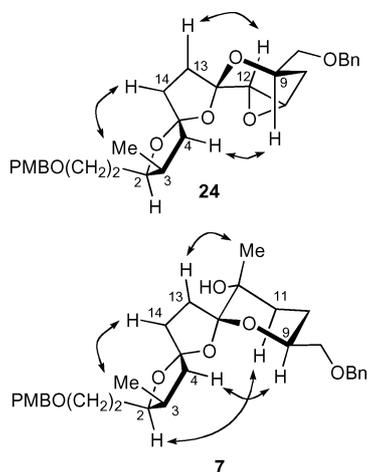


Fig. 2 Characteristic NOESY correlations for the assignment of the absolute configuration of epoxide **24** and alcohol **7**.

The *trans* stereochemistry of the bis-spiroacetal ring system adopted by tertiary alcohol **7** represents the thermodynamically favoured isomer and it is hoped that re-equilibration of the bis-spiroacetal to the desired *cis* stereochemistry as found in the spirolides will take place upon the incorporation of this moiety into the larger macrocyclic system. A comparison of the ¹H NMR and ¹³C NMR chemical shifts recorded for *trans* bis-spiroacetal **7** with the analogous resonances in the *cis* bis-spiroacetal moiety of natural product spirolide **B 2** is summarized in Table 2.

The present work demonstrates the efficient construction of the bis-spiroacetal ring system present in the spirolides using an iterative oxidative radical cyclization strategy. Use of InCl₃ and *m*-CPBA to effect the equilibration of the 6,5,5-bis-spiroacetal ring system provides further examples of reagents to effect spiroacetalizations in a stereoselective fashion. Furthermore, the use of a silyl-modified Prins cyclization provides an efficient entry to the dihydropyran unit of the cyclization precursor. Further synthetic work towards the synthesis of spirolides **B 2** and **D 4** awaits the synthesis of the spiroimine unit of these marine biotoxins.

Experimental

Electronic supplementary material

General experimental details together with full experimental procedures, ¹H NMR, ¹³C NMR and mass spectral data for compounds **10–14** and **17–20** have been deposited as ESI.†

Table 2 Comparison of ¹H NMR and ¹³C NMR data for *trans* bis-spiroacetal **7** with the *cis* bis-spiroacetal moiety of spirolide **B 2**

Carbon no. for spirolide B 2	¹³ C chemical shift (δ _c) for spirolide B 2 ^a	Carbon no. for alcohol 7	¹³ C chemical shift (δ _c) for alcohol 7 ^b	¹ H chemical shift (δ _H) for spirolide B 2 ^c	¹ H chemical shift (δ _H) for alcohol 7 ^d
10	75.1	2'	67.7	4.25	3.58
11	37.1	1'	30.8	1.77, 2.02	1.56
12	81.5	2	78.0	4.38	4.23
13	35.1	3	34.8	2.46	2.42
14	42.5	4	44.0	2.24, 1.93	2.37, 1.75
15	116.3	5	114.9	—	—
16	35.4	14	35.4	2.38, 2.04	2.21, 1.94
17	30.8	13	35.0	2.16, 1.81	2.40, 1.76
18	111.1	7	110.4	—	—
19	69.8	12	68.9	—	—
20	35.8	11	30.8	1.65 (2x)	1.89, 1.67
21	29.0	10	26.9	1.62, 1.25	1.63, 1.54
22	68.3	9	69.5	3.96	4.04
39	15.1	CH ₃ C(3)	14.6	1.18	0.92
40	20.9	CH ₃ C(12)	21.2	1.23	1.26

^a Measured at 125 MHz in CDCl₃. ^b Measured at 100 MHz in CDCl₃. ^c Measured at 500 MHz in CDCl₃. ^d Measured at 600 MHz in CDCl₃.

(3*R*,5*R*,6*R*)-1-(2*S*,6*S*)-6-[(Benzyloxy)methyl]-5,6-dihydro-2*H*-pyran-2-yl-6-[(*tert*-butyl(diphenyl)silyl)oxy]-8-[(4-methoxybenzyl)oxy]-5-methyl-3-octanol 21a and (3*S*,5*R*,6*R*)-1-(2*S*,6*S*)-6-[(benzyloxy)methyl]-5,6-dihydro-2*H*-pyran-2-yl-6-[(*tert*-butyl(diphenyl)silyl)oxy]-8-[(4-methoxybenzyl)oxy]-5-methyl-3-octanol 21b. Magnesium powder (100 mg, 4.1 mmol) was dried under high vacuum for one day. Diethyl ether (5 mL) was added, followed by iodine (one crystal) and 1,2-dibromoethane (25 μ L, 0.28 mmol, 0.3 equiv). The mixture was stirred until the iodine colour disappeared, then a solution of aldehyde **11** (430 mg, 0.85 mmol) and dihydropyran **10** (529 mg, 1.70 mmol) in Et₂O (6 mL) was added dropwise over one hour. After 3 hours diethyl ether (20 mL) was added followed by sat. NaHCO₃ (20 mL). If the reaction was not complete after 3 hours, the solution was heated under reflux. The aqueous phase was further extracted with diethyl ether (3 \times 50 mL) and the organic extracts were dried over MgSO₄. Flash chromatography of the residue obtained after concentration of the solvent using hexane–diethyl ether (90 : 10 to 1 : 1) as the eluent afforded the title compounds **21** (555 mg, 88%) as a mixture of diastereomers and as a viscous colourless oil.

Spectroscopic data for less polar diastereomer 21a. ν_{\max} (film)/cm⁻¹ 3445, 3070, 3030, 2930, 2855, 1613, 1585, 1515, 1465, 1425, 1365, 1305, 1245, 1175, 1110, 935, 820, 740, 700, 615; δ_{H} (400 MHz; CDCl₃) 7.66–7.70 (m, 4H, PhSi), 7.26–7.45 (m, 11H, PhSi and ArH), 7.11 (d, 2H, *J* 8.6, ArH), 6.84 (d, 2H, *J* 8.6, ArH), 5.83 (tdd, 1H, *J* 1.7, 5.3 and 10.0, 5'-H), 5.62 (tdd, 1H, *J* 1.2, 2.2 and 10.0, 4'-H), 4.64 (d, 1H, *J* 12.3, CH₂Bn), 4.58 (d, 1H, *J* 12.3, CH₂Bn), 4.19–4.21 (m, 1H, 6'-H), 4.16 (s, 2H, CH₂PMBn), 3.81–3.88 (m, 2H, 6-H, 2'-H), 3.81 (s, 3H, CH₃O), 3.57–3.62 (m, 1H, 3-H), 3.57 (dd, 1H, *J* 6.4 and 10.8, 1''-H_a), 3.49 (dd, 1H, *J* 5.4 and 10.8, 1''-H_b), 3.33 (td, 1H, *J* 7.5 and 15.0, 8-H_a), 3.20 (td, 1H, *J* 7.3 and 15.0, 8-H_b), 1.93–2.10 (m, 2H, 3'-H), 1.93–2.09 (m, 2H, 4-H), 1.82–1.96 (m, 2H, 2-H), 1.72–1.82 (m, 2H, 7-H), 1.55–1.70 (m, 2H, 1-H), 1.46–1.55 (m, 1H, 5-H), 1.07 (s, 9H, (CH₃)₃CSi) and 0.84 (d, 3H, *J* 6.8, CH₃); δ_{C} (100 MHz; CDCl₃) 158.9 (C, C_{arom}(PMBn)), 138.3 (C, C_{arom}(PMBn)), 136.1, 136.0 (4 \times CH, PhSi), 134.5 (C, PhSi), 134.0 (C, PhSi), 130.6 (C, C_{arom}(Bn)), 130.2 (CH, C_{arom}(Bn)), 129.6 (2 \times CH, PhSi), 129.5 (CH, C-5'), 129.1 (2 \times CH, C_{arom}(PMBn)), 128.3 (2 \times CH, C_{arom}(Bn)), 127.7 (CH, C_{arom}(Bn)), 127.6 (CH, C_{arom}(Bn)), 127.5 (CH, PhSi), 127.4 (CH, PhSi), 124.2 (CH, C-4'), 113.6 (2 \times CH, C_{arom}(PMBn)), 75.3 (CH, C-3), 74.8 (CH, C-6), 73.4 (CH₂, CH₂Bn), 73.3 (CH, C-6'), 73.0 (CH₂, C-1''), 72.2 (CH₂, CH₂PMBn), 69.3 (CH, C-2'), 67.3 (CH₂, C-8), 55.2 (CH₃, CH₃O), 40.5 (CH₂, C-4), 35.0 (CH, C-5), 34.4 (CH₂, C-2), 34.2 (CH₂, C-7), 31.8 (CH₂, C-3'), 27.6 (CH₂, C-1), 27.1 (3 \times CH₃, (CH₃)₃CSi), 19.5 (C, (CH₃)₃CSi) and 14.7 (CH₃, CH₃); MS (FAB) *m/z* (%) 737 (0.5, [M + H]⁺), 481 (0.5), 359 (1), 197 (4), 135 (11), 121 (100), 105 (2) and 91 (19, [Bn]⁺); HRMS (CI) *m/z* 737.4237 calcd for C₄₆H₆₁O₆Si 737.4235.

Spectroscopic data for more polar diastereomer 21b. [α]_D²⁰ -1 (*c* = 0.15, CHCl₃); ν_{\max} (film)/cm⁻¹ 3435, 3030, 2930, 2855, 1960, 1890, 1830, 1610, 1590, 1515, 1455, 1430, 1365, 1300, 1170, 1110, 1040, 820, 740, 700, 615; δ_{H} (400 MHz; CDCl₃) 7.65–7.69 (m, 4H, PhSi), 7.26–7.43 (m, 11H, PhSi, ArH), 7.09 (d, 2H, *J* 8.6, ArH), 6.83 (d, 2H, *J* 8.6, ArH), 5.83 (m, 1H, 5'-H), 5.58 (bd, 1H, *J* 10.3, 4'-H), 4.62 (d, 1H, *J* 12.2, CH₂Bn), 4.55 (d, 1H, *J* 12.2, CH₂Bn), 4.15–4.18 (m, 1H, 6'-H), 4.13 (s, 2H, CH₂PMBn), 3.81–3.89 (m, 2H, 6-H, 2'-H), 3.80 (s, 3H, CH₃O), 3.55 (dd, 1H, *J* 6.4 and 10.2, 1''-H_a), 3.44 (dd, 1H, *J* 6.0 and 10.2, 1''-H_b), 3.40–3.47 (m, 1H,

3-H), 3.28 (td, 1H, *J* 6.8 and 9.3, 8-H_a), 3.17 (td, 1H, *J* 7.0 and 9.3, 8-H_b), 2.63 (d, 1H, *J* 3.8, OH), 1.90–1.97 (m, 1H, 3'-H_a), 2.01–2.11 (m, 1H, 3'-H_b), 1.73–1.78 (m, 2H, 7-H), 1.23–1.69 (m, 7H, 1-H, 2-H, 4-H, 5-H), 1.05 (s, 9H, (CH₃)₃CSi) and 0.90 (d, 3H, *J* 6.9, CH₃); δ_{C} (100 MHz; CDCl₃) 158.9 (C, C_{arom}(PMBn)), 138.3 (C, C_{arom}(PMBn)), 136.0 (CH, PhSi), 135.9 (CH, PhSi), 134.7 (C, PhSi), 133.9 (C, PhSi), 130.5 (C, C_{arom}(Bn)), 130.0 (CH, C_{arom}(Bn)), 129.6 (CH, PhSi), 129.4 (CH, PhSi), 129.1 (2 \times CH, C_{arom}(PMBn)), 128.3 (2 \times CH, C_{arom}(Bn)), 127.7 (2 \times CH, C_{arom}(Bn)), 127.6 (CH, C-4'), 127.5 (2 \times CH, PhSi), 127.4 (2 \times CH, PhSi), 124.4 (CH, C-5'), 113.6 (2 \times CH, C_{arom}(PMBn)), 74.7 (CH, C-3), 73.6 (CH, C-6), 73.4 (CH₂, CH₂Bn), 73.3 (CH, C-6'), 73.0 (CH₂, C-1''), 72.1 (CH₂, CH₂PMBn), 69.9 (CH, C-2'), 67.3 (CH₂, C-8), 55.2 (CH₃, CH₃O), 40.0 (CH₂, C-4), 34.8 (CH, C-5), 33.6 (CH₂, C-2), 33.0 (CH₂, C-7), 31.7 (CH₂, C-3'), 27.6 (CH₂, C-1), 27.1 (CH₃, (CH₃)₃CSi), 19.5 (C, (CH₃)₃CSi) and 14.7 (CH₃, CH₃); MS (FAB) *m/z* 737 (0.8, [M + H]⁺), 481 (0.5), 359 (1), 197 (5), 135 (11), 121 (100, [PMBn]⁺) and 91 (26). HRMS (CI) *m/z* 737.4256 (calcd for C₄₆H₆₁O₆Si 737.42352).

(2*SR*,3*R*)-Benzyl-(2-methyl-3-[(*tert*-butyl(diphenyl)silyl)oxy]-5-[(5*RS*,7*S*)-(4-methoxybenzyl)oxy]-2-methylpentyl-1,6-dioxaspiro-[4.5]dec-9-en-7-yl)methyl ether 22. A 1 : 1 mixture of alcohols **21** (90 mg, 0.12 mmol), with PhI(OAc)₂ (78 mg, 0.24 mmol) and iodine (68 mg, 0.27 mmol) in cyclohexane (10 mL) was degassed with argon and irradiated with a desk lamp (60 W). After 2 hours the mixture was diluted with diethyl ether (10 mL) then sat. Na₂S₂O₃ (5 mL) and sat. NaHCO₃ (5 mL) were added. After extraction with diethyl ether (3 \times 20 mL), the organic extracts were dried over MgSO₄. Purification of the residue obtained after concentration of the solvents at reduced pressure by flash chromatography using hexane–diethyl ether (80 : 20) as the eluent afforded the title spiroacetals **22** (92 mg, 86%) as a colourless oil and as a 1 : 1 mixture of two diastereomers; ν_{\max} (film)/cm⁻¹ 3400, 3035, 2930, 2860, 1740, 1610, 1590, 1515, 1455, 1425, 1360, 1302, 1250, 1170, 1110, 1040, 820, 740, 700, 610; δ_{H} (400 MHz; CDCl₃) 7.65–7.70 (m, 4H, PhSi), 7.26–7.43 (m, 11H, PhSi, ArH), 7.08 (d, 2H, *J* 8.7, ArH), 6.82 (d, 2H, *J* 8.7, ArH), 5.94 (ddd, 1H, *J* 1.9, 5.6 and 9.9, 9-H), 5.57 (ddd, 1H, *J* 1.3, 2.6 and 9.9, 10-H), 4.62 (d, 1H, *J* 12.4, CH₂Bn), 4.59 (d, 1H, *J* 12.4, CH₂Bn), 4.11–4.23 (m, 2H, 7-H, 2-H), 4.13, 4.11 (each d, 2H, *J* 11.9, CH₂(PMBn)), 3.80 (s, 3H, CH₃O), 3.75 (dt, 1H, *J* 2.7 and 6.1, 3'-H), 3.58 (dd, 1H, *J* 5.5 and 10.4, 1''-H_a), 3.52 (dd, 1H, *J* 4.7 and 10.4, 1''-H_b), 3.26 (td, 1H, *J* 6.8 and 9.1, 5'-H_a), 3.11 (td, 1H, *J* 7.2 and 9.1, 5'-H_b), 1.81–2.36 (m, 10H, 4'-H_a, 2'-H, 3-H, 4-H, 8-H, 1'-H), 1.71 (bq, 2H, *J* 6.8, 4'-H_b) 1.04 (s, 9H, (CH₃)₃CSi) and 0.86 (d, 3H, *J* 6.8, CH₃); δ_{C} (100 MHz; CDCl₃) 158.8 (C, C_{arom}(PMBn)), 138.4 (C, C_{arom}(PMBn)), 136.1 (2 \times CH, PhSi), 135.9 (2 \times CH, PhSi), 134.7, 134.0 (each C, PhSi), 130.5 (C, C_{arom}(Bn)), 129.4, 129.3, 129.1 (each CH, PhSi, C_{arom}(Bn)), 129.0 (2 \times CH, C_{arom}(PMBn)), 128.2 (CH, C-9), 127.5 (2 \times CH, C_{arom}(Bn)), 127.4 (2 \times CH, C_{arom}(Bn)), 127.4 (CH, C-10), 127.4 (2 \times CH, PhSi), 127.3 (2 \times CH, PhSi), 113.5 (2 \times CH, C_{arom}(PMBn)), 103.3 (C, C-5), 76.2 (CH, C-2), 74.6 (CH, C-3'), 73.0 (CH₂, C-1''), 72.6, 72.1 (each CH₂, CH₂(Bn), CH₂(PMBn)), 67.6 (CH, C-7), 67.3 (CH₂, C-5'), 55.1 (CH₃, CH₃O), 38.3 (CH₂, C-1'), 37.3 (CH₂, C-4), 35.1 (CH, C-2'), 33.5 (CH₂, C-3), 31.2 (CH₂, C-4'), 26.9 (CH₂, C-8), 27.1 (CH₃, (CH₃)₃CSi), 19.5 (C, (CH₃)₃CSi) and 14.2 (CH₃, CH₃); MS (FAB) *m/z* (%) 735 (1.5, [M + H]⁺), 479 (1.5), 211 (1), 197 (5),

135 (12), 121 (100), 107 (3) and 91 (25, [Bn]⁺). HRMS (CI) *m/z* 735.4073 (calcd for C₄₆H₅₉O₆Si 735.4081).

(2R,3R)-1-[(5R,7S)-7-[(Benzyloxy)methyl]-1,6-dioxaspiro[4.5]dec-9-en-2-yl]-5-[(4-methoxybenzyl)oxy]-2-methyl-3-pentanol 23. A solution of spiroacetals **22** (60 mg, 0.081 mmol, 1 equiv) in DMF (2 mL) containing tetrabutylammonium fluoride (213 mg, 0.81 mmol) was heated to 80 °C overnight. The cooled reaction mixture was diluted with diethyl ether (5 mL) and water (10 mL). The aqueous phase was extracted with diethyl ether (3 × 5 mL) and the organic layers were dried over MgSO₄. After concentration of the solvents at reduced pressure purification by flash chromatography using hexane–diethyl ether (1 : 1) as the eluent afforded the title spiroacetals **23** (34 mg, 82%) as a colourless oil and as a 1 : 1 mixture of diastereomers.

Spectroscopic data for less polar diastereomer 23a. [*a*]_D²⁰ –32 (*c* = 0.18, CHCl₃); *v*_{max} (film)/cm⁻¹ 3450, 2860, 1720, 1610, 1510, 1455, 1360, 1300, 1250, 1090, 1030, 990, 870, 820, 740, 700; *δ*_H (400 MHz; CDCl₃) 7.24–7.34 (m, 5H, ArH), 7.23 (d, 2H, *J* 8.7, ArH), 6.85 (d, 2H, *J* 8.7, ArH), 5.95 (ddd, 1H, *J* 1.9, 5.6 and 9.8, 9-H), 5.62 (ddd, 1H, *J* 1.3, 2.6 and 9.8, 10-H), 4.60 (d, 1H, *J* 12.2, CH₂Bn), 4.56 (d, 1H, *J* 12.2, CH₂Bn), 4.43 (s, 2H, CH₂(PMBn)), 4.28 (dtd, 1H, *J* 3.5, 7.2 and 10.3, 2-H), 4.12–4.19 (m, 1H, 7-H), 3.77 (s, 3H, CH₃O), 3.73 (dt, 1H, *J* 2.5 and 9.9, 3'-H), 3.57–3.78 (m, 2H, 5'-H), 3.56 (dd, 1H, *J* 5.7 and 10.5, 1''-H_a), 3.50 (dd, 1H, *J* 4.3 and 10.5, 1''-H_b), 1.94–2.03 (m, 2H, 4-H), 1.78 (m, 1H, 2'-H), 1.69–2.09 (m, 2H, 8-H), 1.66–1.78 (m, 2H, 4'-H), 1.54–2.22 (m, 2H, 3-H), 1.46–1.69 (m, 2H, 1'-H) and 0.90 (d, 3H, *J* 6.8, CH₃); *δ*_C (100 MHz; CDCl₃) 159.1 (C, C_{arom}(PMBn)), 138.4 (C, C_{arom}(PMBn)), 130.2 (C, C_{arom}(Bn)), 129.2 (2 × CH, C_{arom}(PMBn)), 128.6 (CH, C-10), 128.2 (2 × CH, C_{arom}(Bn)), 128.0 (CH, C-9), 127.4 (2 × CH, C_{arom}(Bn)), 127.3 (CH, C_{arom}), 113.7 (2 × CH, C_{arom}(PMBn)), 103.6 (C, C-5), 76.6 (CH, C-2), 73.6 (CH, C-3'), 73.0 (CH₂, CH₂(Bn)), 72.8 (CH₂, CH₂(PMBn)), 72.5 (CH₂, C-1''), 69.1 (CH₂, C-5'), 67.9 (CH, C-7), 55.1 (CH₃, CH₃O), 39.2 (CH₂, C-1'), 37.2 (CH₂, C-4), 36.4 (CH, C-2'), 33.3 (CH₂, C-4'), 31.3 (CH₂, C-3), 26.7 (CH₂, C-8) and 14.3 (CH₃, CH₃); MS (EI) *m/z* (%) 496 (1, [M]⁺), 478 (1, [M – H₂O]⁺), 425 (2), 384 (5), 320 (12), 307 (9), 266 (4), 199 (3), 157 (6), 121 (100) and 91 (56); HRMS (EI) *m/z* 496.2819 (calcd for C₃₀H₄₀O₆ 496.2825).

Spectroscopic data for more polar diastereomer 23b. [*a*]_D²⁰ –34 (*c* = 0.07, CHCl₃); *v*_{max} (film)/cm⁻¹ 3450, 2860, 1720, 1610, 1510, 1455, 1360, 1300, 1250, 1090, 1030, 990, 870, 820, 740, 700; *δ*_H (400 MHz; CDCl₃) 7.26–7.34 (m, 5H, ArH), 7.23 (d, 2H, *J* 8.5, ArH), 6.85 (d, 2H, *J* 8.5, ArH), 5.90 (ddd, 1H, *J* 1.8, 4.4 and 9.9, 9-H), 5.60 (ddd, 1H, *J* 2.0, 3.0 and 9.9, 10-H), 4.56 (s, 2H, CH₂Bn), 4.41 (s, 2H, CH₂(PMBn)), 4.24–4.30 (m, 1H, 2-H), 4.15–4.21 (m, 1H, 7-H), 3.77 (s, 3H, CH₃O), 3.73 (dt, 1H, *J* 2.6 and 10.1, 3'-H), 3.55–3.68 (m, 2H, 5'-H), 3.54 (dd, 1H, *J* 5.8 and 10.5, 1''-H_a), 3.48 (dd, 1H, *J* 5.0 and 10.5, 1''-H_b), 1.96–2.07 (each m, 2H, 8-H), 1.90–2.09 (each m, 2H, 3-H), 1.85–2.09 (each m, 2H, 4-H), 1.70–1.88 (each m, 2H, 1'-H), 1.69 (m, 1H, 2'-H), 1.63–1.77 (each m, 2H, 4'-H) and 0.90 (d, 3H, *J* 6.5, CH₃); *δ*_C (100 MHz; CDCl₃) 159.1 (C, C_{arom}(PMBn)), 138.4 (C, C_{arom}(PMBn)), 130.1 (C, C_{arom}(Bn)), 129.2 (2 × CH, C_{arom}(PMBn)), 128.5 (CH, C-9), 128.3 (CH, C-10), 128.2 (2 × CH, C_{arom}(Bn)), 127.4 (2 × CH, C_{arom}(Bn)), 127.3 (CH, C_{arom}), 113.7 (2 × CH, C_{arom}(PMBn)), 103.4 (C, C-5), 78.5 (CH, C-2), 73.5 (CH, C-3'), 73.0 (CH₂, CH₂(Bn)), 72.8 (CH₂, CH₂(PMBn)), 72.6 (CH₂, C-1''), 69.3 (CH₂, C-5'), 67.2 (CH, C-7),

55.1 (CH₃, CH₃O), 41.7 (CH₂, C-1'), 38.2 (CH₂, C-4), 36.2 (CH, C-2'), 33.7 (CH₂, C-4'), 30.9 (CH₂, C-3), 26.8 (CH₂, C-8) and 13.8 (CH₃, CH₃); MS (FAB) *m/z* (%) 497 (12, [M + H]⁺), 479 (8, [M + H – H₂O]⁺), 357 (2), 121 (100), 91 (39, [Bn]⁺); HRMS (FAB) *m/z* 497.2895 (calcd for C₃₀H₄₁O₆ 497.2903).

(2R,3R,5R,7R,9S)-9-[(Benzyloxy)methyl]-2-[(4-methoxybenzyl)oxy]ethyl-3-methyl-1,6,8-trioxadisp[4.1.5.2]tetradec-11-ene 9a. A mixture of spiroacetals **23** (34 mg, 0.068 mmol), PhI(OAc)₂ (44 mg, 0.13 mmol) and iodine (38 mg, 0.15 mmol) in cyclohexane (5 mL) was degassed with argon and irradiated with a desk lamp (60 W). After 2 hours the mixture was diluted with diethyl ether (5 mL) and sat. Na₂S₂O₃ (3 mL) and sat. NaHCO₃ (3 mL) were added. After extraction with diethyl ether (3 × 10 mL), the combined organic extracts were dried over MgSO₄. Purification by flash chromatography using hexane–diethyl ether (80 : 20) as eluent afforded the title bis-spiroacetals **9** (28 mg, 81%) as a 1 : 1 : 1 : 1 mixture of diastereomers and as a colourless oil. Subsequent equilibration using the conditions summarized afforded two diastereomers **9a** and **9b** with varying ratios as reported in Table 1.

Spectroscopic data for major diastereomer 9a. [*a*]_D²⁰ –23 (*c* = 0.25, CHCl₃); *v*_{max} (film)/cm⁻¹ 3495, 2930, 2860, 2060, 1880, 1735, 1655, 1610, 1585, 1515, 1500, 1455, 1300, 1245, 1205, 1175, 1095, 1035, 1005, 980, 875, 820, 735, 700; *δ*_H (600 MHz; CDCl₃) 7.26–7.35 (m, 5H, ArH), 7.26 (d, 2H, *J* 8.5, ArH), 6.87 (d, 2H, *J* 8.5, ArH), 5.97 (ddd, 1H, *J* 2.2, 5.5 and 9.9, 11-H), 5.70 (brd, 1H, *J* 9.9, 12-H), 4.59 (s, 2H, CH₂Ph), 4.35 (s, 3H, CH₂(PMBn)), 4.14–4.25 (m, 2H, 2-H, 9-H), 3.80 (s, 3H, CH₃O), 3.38–3.64 (m, 4H, 2'-H, 1''-H), 2.50 (dq, 1H, *J* 14.1 and 7.4, 3-H), 2.28–2.40 (m, 2H, 4-H_a, 13-H_a), 1.89–2.11 (m, 5H, 13-H_b, 14-H, 10-H), 1.62–1.70 (m, 3H, 1'-H, 4-H_b) and 0.90 (d, 3H, *J* 7.0, CH₃); *δ*_C (100 MHz; CDCl₃) 159.0 (C, C_{arom}(PMBn)), 138.5 (C, C_{arom}(PMBn)), 130.8 (C, C_{arom}(Bn)), 129.3 (2 × CH, C_{arom}(PMBn)), 129.2 (CH, C12), 128.3 (2 × CH, C_{arom}(Bn)), 128.1 (CH, C-11), 127.5 (3 × CH, C_{arom}(Bn)), 114.6 (C, C-5), 113.7 (2 × CH, C_{arom}(PMBn)), 103.4 (C, C-7), 78.6 (CH, C-2), 73.1 (CH₂, CH₂Ph), 72.8 (CH₂, CH₂Ar), 72.7 (CH₂, C-1''), 68.0 (CH, C-9), 67.8 (CH₂, C-2'), 55.3 (CH₃, CH₃O), 45.5 (CH₂, C-4), 35.6, 36.9 (each CH₂, C-13, C-14), 34.5 (CH, C-3), 31.1 (CH₂, C-1'), 26.8 (CH₂, C-10), 14.3 (CH₃, CH₃); MS (EI) *m/z* (%) 494 (1, [M]⁺), 477 (9, [M – OH]⁺), 476 (25, [M – H₂O]⁺), 403 (1, [M – Bn]⁺), 485 (1, [M – Bn – H₂O]⁺), 373 (8, [M – PMBn]⁺), 358 (8), 355 (3, [M – PMBn – H₂O]⁺), 229 (6), 203 (6), 157 (11), 137 (10), 121 (100), 91 (65); HRMS (EI) *m/z* 494.2668 (calcd for C₃₀H₃₈O₆ 494.26684).

Spectroscopic data for minor diastereomer 9b. *δ*_H (600 MHz; CDCl₃) 7.28–7.32 (m, 5H, ArH), 7.22 (d, 2H, *J* 8.5, ArH), 6.83 (d, 2H, *J* 8.5, ArH), 5.92–5.96 (m, 1H, 11-H), 5.58 (brd, 1H, *J* 9.9, 12-H), 4.44 (s, 2H, CH₂Ph), 4.30 (s, 2H, CH₂(PMBn)), 4.10–4.16 (m, 2H, 2-H, 9-H), 3.79 (s, 3H, CH₃O), 3.38–3.42 (m, 4H, 2'-H, 1''-H), 2.50 (m, 1H, 3-H), 2.20–2.33 (m, 2H, 4-H_a, 13-H_a), 1.72–2.01 (m, 5H, 13-H_b, 14-H, 10-H), 1.61–1.69 (m, 3H, 1'-H, 4-H_b) and 0.89 (m, 3H, CH₃).

(2R,3R,5S,7R,9S,11R,12R)-9-[(Benzyloxy)methyl]-11,12-epoxy-2-2-[(4-methoxybenzyl)oxy]ethyl-3-methyl-1,6,8-trioxadisp[4.1.5.2]tetradecane 24. To a 1 : 1 : 1 : 1 mixture of bis-spiroacetals **9a–d** (60 mg, 0.12 mmol) in dichloromethane (2 mL) at 0 °C was added *m*-CPBA (84 mg, 0.48 mmol). The solution was allowed to warm to room temperature and left to stir overnight. After 24 h the solution was cooled to 0 °C, filtered through a

Celite pad and washed with cold dichloromethane. The organic phase was washed with sat. NaHCO_3 and dried (Na_2SO_4). After concentration by removal of the solvents at reduced pressure the residue was purified by flash chromatography using hexane–ethyl acetate (2 : 1) as the eluent to afford recovered starting material (22 mg) and the title epoxide **24** (35 mg, 63%) as a colourless oil; $[\alpha]_{\text{D}}^{20} +7$ ($c = 0.21$, CHCl_3); ν_{max} (film)/ cm^{-1} 2955, 2925, 2855, 1725, 1615, 1585, 1515, 1455, 1360, 1300, 1250, 1210, 1175, 1100, 1035, 1010, 980, 830, 735, 700; δ_{H} (400 MHz; CDCl_3) 7.27–7.34 (m, 5H, ArH), 7.26 (d, 2H, J 8.6, ArH), 6.87 (d, 2H, J 8.6, ArH), 4.54 (s, 2H, CH_2Ph), 4.44 (s, 2H, CH_2Ar), 4.24 (ddd, 1H, J 4.9, 7.2 and 8.6, 2-H), 4.06 (tdd, 1H, J 4.7, 6.0 and 9.4, 9-H), 3.80 (s, 3H, CH_3O), 3.56 (m, 2H, 2'-H), 3.43 (dd, 2H, J 10.4, and 5.3, 1''-H), 3.33–3.41 (m, 1H, 11-H), 3.00 (d, 1H, J 3.9, 12-H), 2.49 (sept, 1H, J 7.2, 3-H), 2.36 (m, 1H, 4-H_a), 2.33–2.05 (m, 4H, 13-H, 14-H), 1.75–1.91 (m, 2H, 10-H), 1.68 (m, 3H, 4-H_b, 1'-H), 0.91 (d, 3H, J 6.9, CH_3); δ_{C} (100 MHz; CDCl_3) 159.1 (C, C_{arom} (PMBn)), 138.3 (C, C_{arom} (PMBn)), 130.6 (C, C_{arom} (PMBn)), 129.2 (2 \times CH, C_{arom} (PMBn)), 128.3 (2 \times CH, C_{arom} (Bn)), 127.6 (CH, C_{arom} (Bn)), 127.5 (CH, C_{arom} (Bn)), 115.6 (C, C(5)), 113.7 (CH, C_{arom} (PMBn)), 103.5 (C, C-7), 78.4 (CH, C-2), 73.2 (CH_2 , C-1''), 72.8 (CH_2 , CH_2Ph), 72.4 (CH_2 , CH_2Ar), 67.8 (CH_2 , C-2), 66.1 (CH, C-9), 55.3 (CH_3 , CH_3O), 52.5 (CH, C-12), 51.0 (CH, C-11), 44.7 (CH_2 , C-4), 35.2, 34.7 (each CH_2 , C-13, C-14), 34.5 (CH, C-3), 31.0 (CH_2 , C-1'), 25.2 (CH_2 , C-10) and 14.3 (CH_3 , CH_3); MS (FAB) m/z (%) 511 (8, $[\text{M} + \text{H}]^+$), 493 (6, $[\text{M} - \text{H}_2\text{O}]^+$), 373 (5), 121 (100) and 91 (42, $[\text{Bn}]^+$); HRMS (FAB) m/z 511.2696 (calcd for $\text{C}_{30}\text{H}_{39}\text{O}_7$ 511.2685).

(2R,3R,5S,7R,9S,12R)-9-[(Benzyloxy)methyl]-2-2-[(4-methoxybenzyl)oxy]ethyl-3-methyl-1,6,8-trioxadispiro[4.1.5.2]tetradecan-12-ol 25. To a solution of epoxide **24** (13 mg, 26.0 μmol) in dry hexane (500 μL) at 0 °C was added DIBALH (1 M in hexane, 77 μL , 77.0 μmol). After 1 hour 1 M HCl (1 mL) was added and the aqueous phase extracted with diethyl ether (3 \times 2 mL). After concentration by removal of the solvents at reduced pressure the residue was purified by flash chromatography using hexane–ethyl acetate (1 : 1) as the eluent to afford the title compound **25** (8.4 mg, 63%) as a colourless oil; $[\alpha]_{\text{D}}^{20} +2$ ($c = 0.11$, CHCl_3); ν_{max} (film)/ cm^{-1} 3435, 2925, 2855, 1725, 1615, 1515, 1455, 1360, 1300, 1245, 1175, 1100, 1035, 980, 870, 820, 745, 700, 620; δ_{H} (400 MHz; CDCl_3) 7.26–7.35 (m, 5H, ArH), 7.26 (d, 2H, J 8.4, ArH), 6.88 (d, 2H, J 8.4, ArH), 4.57 (s, 2H, CH_2Ph), 4.44 (s, 2H, CH_2Ar), 4.18 (ddd, 1H, J 4.9, 6.7 and 8.9, 2-H), 4.06 (dtd, 1H, J 2.7, 5.2 and 7.7, 9-H), 3.81 (s, 3H, CH_3O), 3.57 (m, 1H, 12-H), 3.55 (m, 2H, 2'-H), 3.48 (m, 2H, 1''-H), 2.47 (dq, 1H, J 14.2 and 7.2, 3-H), 2.34 (dd, 1H, J 7.2 and 13.1, 4-H_a), 1.94–2.25 (m, 5H, 11-H_a, 13-H, 14-H), 1.79 (ddd, 1H, J 3.2, 6.7 and 13.8, 11-H_b), 1.69 (m, 2H, 1'-H), 1.68 (m, 1H, 4-H_b), 1.62 (m, 1H, 10-H_a), 1.43 (m, 1H, 10-H_b) and 0.92 (d, 3H, J 7.0, CH_3); δ_{C} (100 MHz; CDCl_3) 159.1 (C, C_{arom} (PMBn)), 138.4 (C, C_{arom} (PMBn)), 130.6 (C, C_{arom} (Bn)), 129.3 (2 \times CH, C_{arom} (PMBn)), 128.3 (2 \times CH, C_{arom} (Bn)), 127.5 (3 \times CH, C_{arom} (Bn)), 115.3 (C, C-5), 113.7 (2 \times CH, C_{arom} (PMBn)), 106.8 (C, C-7), 78.0 (CH, C-2), 73.3 (CH_2 , C-1''), 73.2 (CH_2 , CH_2Ph), 72.8 (CH_2 , CH_2Ar), 69.8 (CH, C-9), 69.7 (CH, C-12), 67.8 (CH_2 , C-2), 55.3 (CH_3 , CH_3O), 44.6 (CH_2 , C-4), 35.0, 34.8 (each CH_2 , C-13, C-14), 34.4 (CH, C-3), 30.9 (CH_2 , C-1'), 26.6 (CH_2 , C-11), 21.3 (CH_2 , C-10) and 14.5 (CH_3 , CH_3); MS (FAB) m/z (%) 513 (2, $[\text{M} + \text{H}]^+$), 495 (22, $[\text{M} - \text{H}_2\text{O}]^+$),

391 (4), 219 (4), 178 (3), 165 (6), 121 (100) and 91 (42); HRMS (FAB) m/z 512.2774 (calcd for $\text{C}_{30}\text{H}_{40}\text{O}_7$ 512.2773).

(2R,3R,5S,7R,9S)-9-[(Benzyloxy)methyl]-2-2-[(4-methoxybenzyl)oxy]ethyl-3-methyl-1,6,8-trioxadispiro[4.1.5.2]tetradecan-12-one 26. To a solution of bis-spiroacetal alcohol **25** (5 mg, 9.70 μmol) and pyridine (2.4 μL , 29.25 μmol) in dichloromethane (500 mL) was added Dess–Martin periodinane (8.3 mg, 19.5 μmol) at room temperature. After 1 h more Dess–Martin periodinane (8.3 mg) was added. After 3 hours, the solution was diluted with dichloromethane (1 mL) and a sat. NaHCO_3 –sat. Na_2SO_3 (1 : 1) solution (1 mL) was added. The aqueous phase was extracted with dichloromethane (3 \times 2 mL), dried over MgSO_4 and the solvent was removed under reduced pressure. The residue was purified by flash chromatography using hexane–diethyl ether (5 : 4) as the eluent to afford the title compound (4.5 mg, 88%) as a colourless oil; $[\alpha]_{\text{D}}^{20} +27$ ($c = 0.41$, CHCl_3); ν_{max} (film)/ cm^{-1} 2920, 2850, 1735, 1615, 1585, 1515, 1455, 1360, 1300, 1245, 1095, 1030, 995, 865, 825, 735; δ_{H} (400 MHz; CDCl_3) 7.28–7.37 (m, 5H, ArH), 7.26 (d, 2H, J 8.7, ArH), 6.88 (d, 2H, J 8.6, ArH), 4.59 (s, 2H, CH_2Ph), 4.44 (ddd, 1H, J 2.5, 5.1, 7.5 and 11.7, 9-H), 4.42 (s, 2H, CH_2Ar), 4.17 (ddd, 1H, J 4.2, 6.7 and 10.7, 2-H), 3.81 (s, 3H, CH_3O), 3.56 (m, 1H, 2'-H_a), 3.55 (dd, 1H, J 5.1 and 10.1, 1''-H_a), 3.48 (td, 1H, J 6.1 and 10.2, 2''-H_b), 3.45 (m, 1H, 1''-H_b), 2.87 (dt, 1H, J 6.1, 14.0 and 14.0, 11-H_a), 2.80 (ddd, 1H, J 8.6, 10.9 and 13.0, 13-H_a), 2.49 (m, 1H, 3-H), 2.44 (ddd, 1H, J 14.0, 2.5 and 4.8, 11-H_b), 2.39 (dd, 1H, J 7.3 and 13.1, 4-H_a), 2.18 (ddd, 1H, J 8.2, 11.1 and 12.4, 14-H_a), 2.12 (tdd, 1H, J 2.5, 6.1 and 13.3, 10-H_a), 2.03 (ddd, 1H, J 2.8, 7.7 and 12.4, 14-H_b), 1.95 (dddd, 1H, J 4.8, 11.7, 14.0 and 14.0, 10-H_b), 1.74 (ddd, 1H, J 2.8, 8.2 and 13.0, 13-H_b), 1.71 (dd, 1H, J 7.7 and 13.1, 4-H_b), 1.65 (m, 2H, 1'-H) and 0.92 (d, 1H, J 7.0, CH_3); δ_{C} (100 MHz; CDCl_3) 202.0 (C, C-12), 159.1 (C, C_{arom} (PMBn)), 138.2 (C, C_{arom} (Bn)), 130.7 (C, C_{arom} (PMBn)), 129.3 (2 \times CH, C_{arom} (PMBn)), 128.4 (2 \times CH, C_{arom} (Bn)), 127.6 (CH, C_{arom} (Bn)), 127.5 (2 \times CH, C_{arom} (Bn)), 115.9 (C, C-5), 113.7 (2 \times CH, C_{arom} (PMBn)), 106.1 (C, C-7), 78.3 (CH, C-2), 73.4 (CH_2 , $\text{CH}_2\text{(Bn)}$), 72.8 (CH_2 , $\text{CH}_2\text{(PMBn)}$), 72.3 (CH_2 , C-1''), 69.4 (CH, C-9), 67.7 (CH_2 , C-2), 55.3 (CH_3 , CH_3O), 45.0 (CH_2 , C-4), 35.5 (CH_2 , C-11), 34.6 (CH_2 , C-14), 34.4 (CH, C-3), 30.9 (CH_2 , C-1'), 30.5 (CH_2 , C-13), 30.3 (CH_2 , C-10) and 14.5 (CH_3 , CH_3); MS (FAB) m/z (%) 511 (9, $[\text{M} + \text{H}]^+$), 493 (5, $[\text{M} - \text{H}_2\text{O}]^+$), 391 (6), 373 (5, $[\text{M} - \text{PMBnO}]^+$), 273 (3), 219 (3), 121 (76) and 91 (35); HRMS (FAB) m/z 511.2696 (calcd for $\text{C}_{30}\text{H}_{39}\text{O}_7$ 511.26824).

9-[(Benzyloxy)methyl]-2-2-[(4-methoxybenzyl)oxy]ethyl-3,12-dimethyl-1,6,8-trioxadispiro[4.1.5.2]tetradecan-12-ol 7. To a solution of bis-spiroacetal ketone **7** (5 mg, 9.79 μmol) in diethyl ether (500 μL) at –78 °C was added dropwise a solution of MeMgBr (3 M in ether, 6.52 μL , 19.58 mmol). After 2 hours, a solution of sat. NH_4Cl in MeOH was added (500 μL) and the solution allowed to warm to room temperature. After evaporation to dryness, the residue was purified by flash chromatography using hexane–diethyl ether (80 : 20) as the eluent to afford the title compound **7** (4.5 mg, 87%) as a colourless oil; $[\alpha]_{\text{D}}^{20} +38$ ($c = 0.29$, CHCl_3); ν_{max} (film)/ cm^{-1} 2930, 2850, 1730, 1615, 1585, 1515, 1455, 1360, 1300, 1250, 1210, 1175, 1100, 1035, 1001, 980, 865, 820, 750, 700; δ_{H} (600 MHz; CDCl_3) 7.28–7.37 (m, 5H, ArH), 7.26 (d, 2H, J 8.6, ArH), 6.88 (d, 2H, J 8.6, ArH), 4.57 (s, 2H, CH_2Ar), 4.45 (d, 1H, J 11.3, CH_2Ph), 4.41 (d, 1H, J 11.3, CH_2Ph), 4.23 (ddd, 1H, J 4.1, 5.9 and 9.8, 2-H), 4.04 (dtd, 1H, J 3.4, 5.2 and

8.0, 9-H), 3.81 (s, 3H, CH₃O), 3.58 (m, 1H, 2'-H_a), 3.53 (m, 1H, 2'-H_b), 3.50 (dd, 1H, *J* 5.2 and 10.3, 1''-H_a), 3.42 (dd, 1H, *J* 5.2 and 10.3, 1''-H_b), 2.42 (m, 1H, 3-H), 2.40 (m, 1H, 13-H_a), 2.37 (m, 1H, 4-H_a), 2.21 (ddd, 1H, *J* 7.6, 12.2 and 12.2, 14-H_a), 1.94 (dd, 1H, *J* 7.6 and 12.2, 14-H_b), 1.89 (dt, 1H, *J* 4.6, and 13.3, 11-H_a), 1.76 (m, 1H, 13-H_b), 1.75 (m, 1H, 4-H_b), 1.67 (m, 1H, 11-H_b), 1.63 (ddd, 1H, *J* 2.5, 4.6 and 13.7, 10-H_a), 1.56 (m, 2H, 1'-H), 1.54 (m, 1H, 10-H_b), 1.26 (s, 3H, CH₃) and 0.92 (d, 3H, *J* 6.9, CH₃); δ_H (100 MHz, CDCl₃) 159.1 (C, C_{arom}(PMBn)), 138.5 (C, C_{arom}(Bn)), 130.6 (C, C_{arom}(PMBn)), 129.4 (2 × CH, C_{arom}(PMBn)), 128.3 (2 × CH, C_{arom}(Bn)), 127.5 (3 × CH, C_{arom}(Bn)), 114.9 (C, C-5), 113.7 (2 × CH, C_{arom}(PMBn)), 110.4 (C, C-7), 78.0 (CH, C-2), 73.3, 73.2 (each CH₂, CH₂Ar, C-1''), 72.2 (CH₂, CH₂Ph), 69.5 (CH, C-9), 68.9 (C, C-12), 67.7 (CH₂, C-2'), 55.3 (CH₃, CH₃O), 44.0 (CH₂, C-4), 35.4, 35.0 (each CH₂, C-13, C-14), 34.8 (CH, C-3), 30.8 (2 × CH₂, C-1', C-11), 26.9 (CH₂, C-10), 21.2 (CH₃, CH₃) and 14.6 (CH₃, CH₃); MS (FAB) *m/z* (%) 527 (3, [M + H]⁺), 509 (11, [M - H₂O]⁺), 493 (2), 391 (26), 279 (9), 205 (8), 167 (12), 149 (58), 137 (21), 121 (100) and 91 (42). HRMS (FAB) *m/z* 527.30221 (calcd for C₃₁H₄₃O₇ = 527.3009).

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