Addition of a Grignard reagent to bis-spiroacetal aldehydes: appendage of a tetrahydrofuran ring

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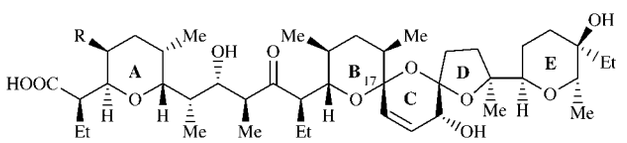
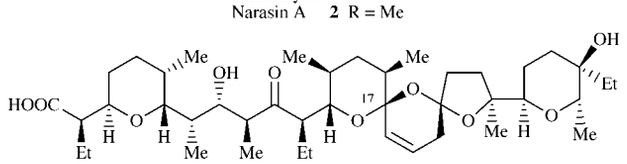
The synthesis of tetracyclic polyethers **16** and **17**, which are closely related to the polyether antibiotics *epi*-17-deoxy-(*O*-8)-salinomycin **3** and CP44,161 **4**, is described. The key step involved Barbier–Grignard addition of bromide **8** to bis-spiroacetal aldehyde **7a** which proceeded *via* chelation control to provide *erythro* alcohol **9a** as the major product. Addition of the Grignard reagent derived from bromide **8** to the isomeric bis-spiroacetal aldehydes **7b**,**7c**,**7d** also afforded *erythro* alcohols **9b**,**9c**,**9d**, respectively as the major products. A rationale for this observed stereoselectivity is provided. Attempts to effect iodoetherification of alkene **9a** resulted in decomposition of the sensitive bis-spiroacetal ring system, however, epoxidation followed by acid catalyzed cyclization of the resultant epoxides **14**,**15** afforded bis-spiroacetal tetrahydrofurans **16**,**17**. Attempts to effect ring expansion of tetrahydrofuran alcohols **16**,**17** to tetrahydropyrans **18**,**19** were unsuccessful.

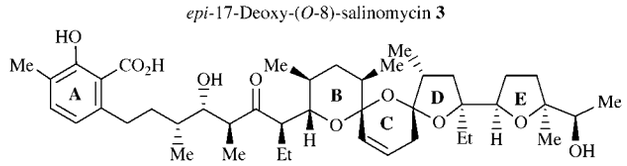
The polyether antibiotics salinomycin **1**,[1] narasin A **2**,[2] *epi*-17-deoxy-(*O*-8)-salinomycin **3**,[3] noboritomycin,[4] CP44,161 **4**[5] and X-14766A,[6] many of which have anticoccidial properties and are used as growth promotants for ruminants, all possess the characteristic 1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene bis-spiroacetal ring system. These complex synthetic targets have provided most of the impetus for synthetic work directed towards the construction of bis-spiroacetal ring systems.[7]



Salinomycin **1** R = H
Narasin A **2** R = Me



epi-17-Deoxy-(*O*-8)-salinomycin **3**



CP44,161 **4**

The synthetic approaches to salinomycin **1** by Kishi,[8] Yonemitsu[9–12] and Kocienski[13–15] have all focused on late assembly of the C ring after appending the D,E rings to the B ring whereas our synthetic endeavours[16,17] towards *epi*-17-deoxy-(*O*-8)-salinomycin **3** have focused on the construction of a tricyclic bis-spiroacetal core containing the B,C,D rings with the idea of appending the A and E rings at a later stage in the synthesis.

Towards this end we reported[17] the synthesis of bis-spiroacetal aldehyde **7** *via* oxidative cyclisation of a hydroxy spiroacetal **5** wherein the acetate group served as a latent aldehyde group (Scheme 1). The acetate group also controlled the outcome of the key oxidative cyclisation preventing undesired fragmentation of the alkoxy radical from occurring. Aldehyde **7** is an important compound for the development of methodology (albeit on a model system) to append a substituted tetrahydropyran ring with the same stereochemistry as that present in *epi*-17-deoxy-(*O*-8)-salinomycin **3** to a bis-spiroacetal framework. Our synthetic efforts towards this goal are reported herein together with a detailed study of the addition of the Grignard reagent derived from bromide **8** to the four isomeric bis-spiroacetal aldehydes **7a**,**7b**,**7c**,**7d**.

Based on earlier model work[18] performed on a bicyclic system, it was proposed that the E ring could be appended to a B,C,D fragment using an iodoetherification–ring expansion strategy. We therefore focussed on the stereoselective formation of iodoether **10** from *erythro* alcohol **9c** (Scheme 2) with the view that silver-assisted ring expansion would provide the required tetrahydropyran **11**. A critical factor was the compatibility of the bis-spiroacetal ring system with the iodoetherification and ring expansion reactions. It transpires that the work described herein prompted a change in the target molecule under investigation such that our more recent synthetic endeavours have focused on the synthesis of a tetracyclic fragment of the polyether antibiotic CP44,161.[19]

Initial work focussed on the addition of the Grignard reagent derived from bromide **8** to bis-spiroacetal aldehyde **7**. Given the fact that all four isomers of aldehyde **7** were available, an investigation was undertaken as to whether the stereochemistry of the bis-spiroacetal (*cis* or *trans*) or the stereochemistry at the carbon α to the aldehyde group, affected the stereoselectivity of the Grignard reaction. Bromide **8** was readily prepared as a 9 : 1 mixture of *E* : *Z* isomers using the procedure described previously[20] as were *trans* bis-spiroacetal aldehydes **7a** and **7b**.[17] The *cis* bis-spiroacetal aldehydes **7c** and **7d** proved to be unstable and were therefore prepared from the corresponding acetates **6c** and **6d** and immediately reacted with the Grignard reagent derived from bromide **8**.

The experimental conditions for execution of the above Grignard reaction required careful experimentation. The difficulties observed in forming homoallylic Grignard reagents from trisubstituted alkenes have been reported by Henrick *et al.*[21] who eventually overcame these barriers by slow addition of the homoallylic bromides to metallic magnesium to afford the desired Grignard reagents. Repetition of this procedure in the present case afforded substantial quantities of the diene

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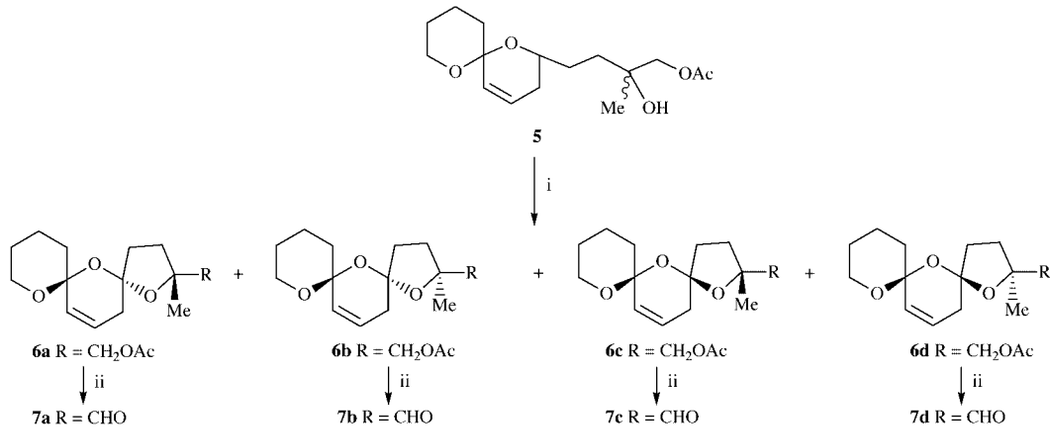
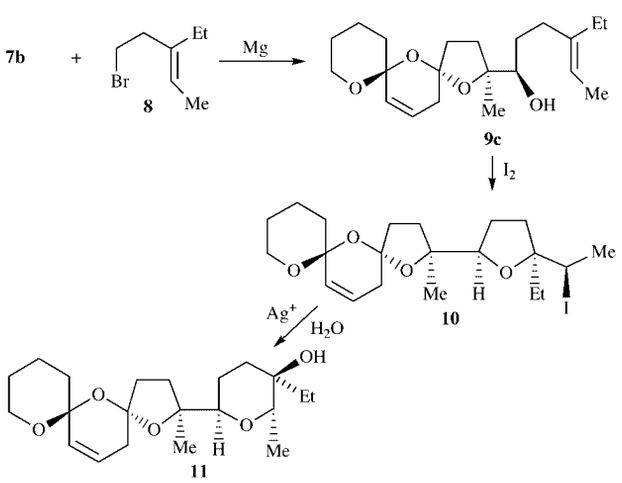


Scheme 1 *Reagents, conditions and yields*: (i) $PhI(OAc)_2$ (3 equiv.), I_2 (2 equiv.), cyclohexane, hν, 24 h, **6a**:**6b**:**6c**:**6d** 1.3:1.3:1:1, 69%; (ii) K_2CO_3, MeOH, room temp. then TPAP, NMO, CH_2Cl_2, room temp., 81%.



Scheme 2

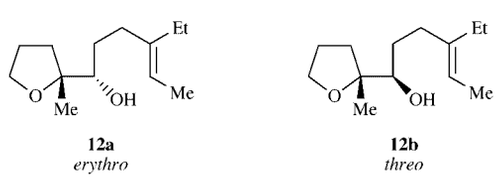
formed by reaction of the Grignard reagent with unreacted bromide. The use of 1,2-dibromoethane as an entrainment reagent[22] and the magnesium–anthracene complex[23,24] were ineffective.

The Barbier reaction[25] in which the carbonyl compound and the alkyl halide are introduced to the magnesium concomitantly, offers a viable alternative in situations where the generation of the Grignard is particularly difficult. The best method to prepare alcohol **9** involved dry stirring magnesium powder under an atmosphere of nitrogen for 18 h followed by initiation of the reaction with a crystal of iodine to obtain sufficiently activated magnesium. To this, the Barbier mixture [bromide **8** (4.8 equiv.), aldehyde **7** (1 equiv.) in ether[21]] was added dropwise with gentle heating (maintaining the temperature of the reaction at 35 °C) followed by stirring the reaction for 2 h affording alcohol **9** in 53–73% yield. This method not only provided a successful means of connecting aldehyde **7** with *E*-bromide **8** but also ensured that reaction only occurred with *E*-alkene **8** thereby avoiding generation of isomeric products since unreacted alkene **8** recovered from the reaction was enriched in the *Z*-isomer. This result suggested that the reactivity of the *E*-bromide **8** was greater than the *Z*-bromide.

Modifications to this procedure including the use of Rieke magnesium,[27] sublimed magnesium,[28] and sonication[29] to activate the magnesium in the Barbier reaction described above, afforded no improvement. Generation of the organolithium reagent from bromide **8** using *tert*-butyllithium afforded only low yields of the coupled product with little stereoselectivity. Transmetallation of the organolithium to an organozinc species also met with little success as did prior complexation of the aldehyde with titanium tetrachloride and the generation of a titanium reagent by treatment of the organolithium reagent with chlorotriisopropoxytitanium.[30]

Table 1 Selected ^{1}H NMR chemical shifts (δ) and coupling constants of alcohols **12**, **9**

Alcohol	$\delta_{H\text{-}1}$ (ppm), multiplicity	*J*/Hz *erythro*
12a	3.52, dd	$J_{1,2A}$ 10.4, $J_{1,2B}$ 2.0
12b	3.35–3.41, m	—
9a	3.58, dd	$J_{1',2'A}$ 9.9, $J_{1',2'B}$ 2.2
9b	3.44, ddd	$J_{1',2'A}$ 10.2, $J_{1',OH}$ 7.8, $J_{1',2'B}$ 2.4
9c	3.48, dd	$J_{1',2'A}$ 10.0, $J_{1',2'B}$ 2.0
9d	3.36, dd	$J_{1',2'A}$ 9.4, $J_{1',2'B}$ 3.0
9e	3.57, dd	$J_{1',2'A}$ 10.4, $J_{1',2'B}$ 2.3
9f	3.34–3.39, m	—
9g	3.48, dd	$J_{1',2'A}$ 10.4, $J_{1',2'B}$ 1.8
9h	3.32–3.37, m	—

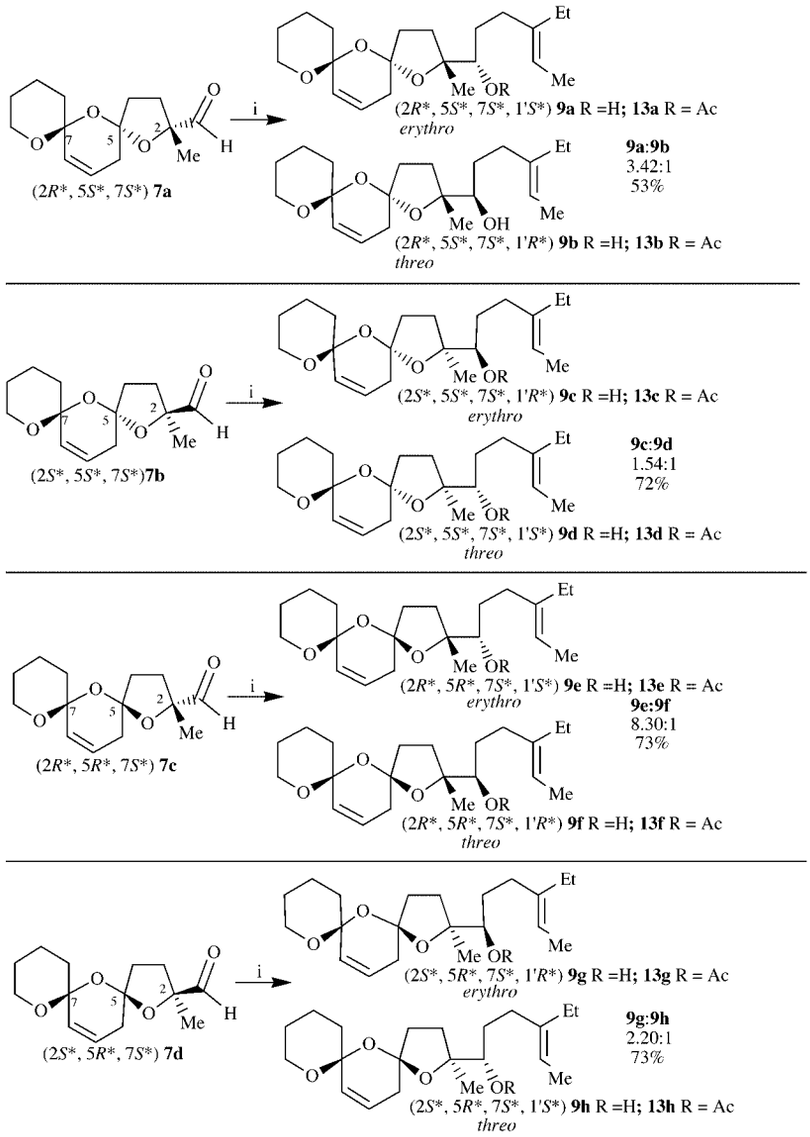


12a *erythro* **12b** *threo*

Barbier–Grignard addition of bromide **8** to *trans* bis-spiroacetal aldehyde **7a** afforded a 3.42:1 mixture of alcohols **9a**:**9b** which were separated by flash chromatography. The stereochemistry of alcohols **9a** and **9b** was assigned by comparison[18] with alcohols **12a** and **12b** in which the resonance for H-1 appeared as a double doublet at δ_H 3.52 ($J_{1,2A}$ 10.4, $J_{1,2B}$ 2.0 Hz) for the *erythro* product while a multiplet at δ_H 3.35–3.41 was observed for the *threo* product (Table 1). In the present work, H-1′ in *erythro* alcohol **9a** resonated as a double doublet at δ_H 3.58 ($J_{1',2'A}$ 9.9, $J_{1',2'B}$ 2.2 Hz) whilst this same proton in *threo* alcohol **9b** resonated as a double double doublet at δ_H 3.44 ($J_{1',2'A}$ 10.2, $J_{1',OH}$ 7.8, $J_{1',2'B}$ 2.4 Hz).

Having successfully united tricyclic aldehyde **7a** with bromide **8**, the chelation controlled addition of bromide **8** to the isomeric aldehydes **7b**,**7c**,**7d** was next examined. Repetition of the Barbier reaction for aldehydes **7b**,**7c**,**7d** using the same procedure described above for aldehyde **7a** resulted in the formation of alcohols **9c**,**9d**,**9e**,**9f**,**9g**,**9h** with significant *erythro* selectivity except for aldehyde **7b** in which a 1.54:1 inseparable mixture of alcohols **9c** and **9d** was observed (Scheme 3).

Separation of the *erythro* **9c** and *threo* **9d** alcohols [derived from aldehyde **7b**] by conversion to their acetate derivatives was unsuccessful in that treatment of alcohols **9c** and **9d** with triethylamine and acetic anhydride with a catalytic quantity of 4-dimethylaminopyridine afforded a 1.54:1 inseparable mixture of acetates **13c** and **13d**. This was a disappointing result



Scheme 3 *Reagents and conditions*: (i) Bromide **8** (4.8 equiv.), Mg, Et_2O, 35 °C.

since aldehyde **7b** and *erythro* alcohol **9c** derived from it, have the correct stereochemistry for the synthesis of *epi*-17-deoxy-(*O*-8)-salinomycin **3**.

The differences in the observed selectivity for *erythro* or *threo* alcohols **9a–9h** from the reaction of the Grignard reagent of bromide **8** with the isomeric bis-spiroacetal aldehydes **7a**,**7b**,**7c**,**7d** can be ascribed to the diversity in the stereochemistry of each bis-spiroacetal system. As summarised in Scheme 3, *cis* bis-spiroacetal aldehydes **7c** and **7d** undergo nucleophilic attack with greater *erythro* selectivity than their *trans* isomers **7a** and **7b** respectively. In turn, bis-spiroacetal aldehydes **7a** and **7c** which have the (2*R**,7*S**) configuration as drawn, exhibit greater *erythro* selectivity than the corresponding isomers **7b** and **7d** with the (2*S**,7*S**) configuration. Thus, bis-spiroacetal aldehyde **7c**, which contains a *cis* bis-spiroacetal ring system as well as the (2*R**,7*S**) configuration affords the greatest *erythro* selectivity.

Given that an excess of magnesium was used in the reaction, chelation to the α-alkoxy group was assumed in each case. The preference for the *erythro* product is therefore explained by chelation controlled nucleophilic addition. The pronounced *erythro* selectivity observed for *cis* bis-spiroacetal aldehyde **7c** is rationalised (Fig. 1 [**A**]) by nucleophilic attack from the side of the sterically less bulky C-3 methylene group rather than from the direction of the 2-Me group. The greater *erythro* selectivity observed for *cis* bis-spiroacetal aldehyde **7c** compared to *cis* bis-spiroacetal aldehyde **7d** is then explained by the observation that the trajectory (leading to the *erythro* product) of the approaching nucleophile in the latter case is in close proximity to the first ring (Fig. 1 [**B**]). In this case, the transition state leading to the *threo* isomer (by competitive attack from the direction of the 2-Me group) is more comparable in energy and the observed *erythro* selectivity is decreased relative to *cis* bis-spiroacetal aldehyde **7c**.

Similar effects are observed for *trans* bis-spiroacetal aldehydes **7a** and **7b**. As depicted in Fig. 1 [**C**], the direction of nucleophilic attack on *trans* bis-spiroacetal aldehyde **7a** from the side of the sterically less bulky C-3 methylene group is hindered by the first ring, therefore *erythro* selectivity is lower than that observed for *cis* isomers **7c** and **7d**. In the case of *trans* bis-spiroacetal aldehyde **7b** Fig. 1 [**D**], hindrance due to close proximity of the protons at C-15 to the incoming nucleophile lowers the observed *erythro* selectivity even further. From these observations it is evident that the unique three-dimensional structure of bis-spiroacetals **7a**,**7b**,**7c**,**7d** had a pronounced effect on the stereochemical outcome of the Grignard addition reactions.

Execution of the model work required for the appendage of the E ring to a B,C,D bis-spiroacetal fragment in the synthesis of *epi*-17-deoxy-(*O*-8)-salinomycin **3** required a study of the iodoetherification–ring expansion protocol using *erythro* alcohol **9c**. Alcohol **9c**, however, was unable to be separated from

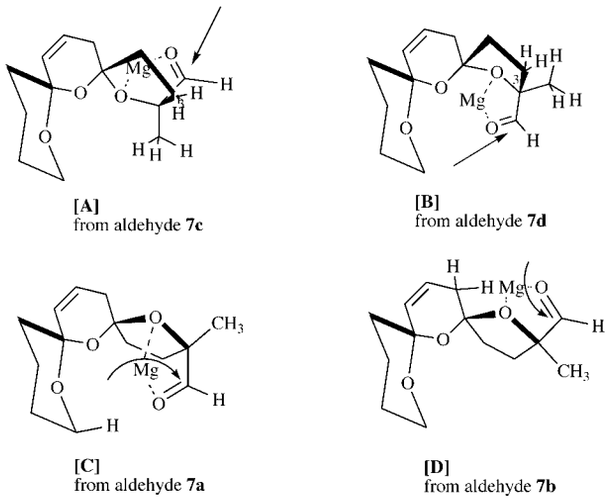
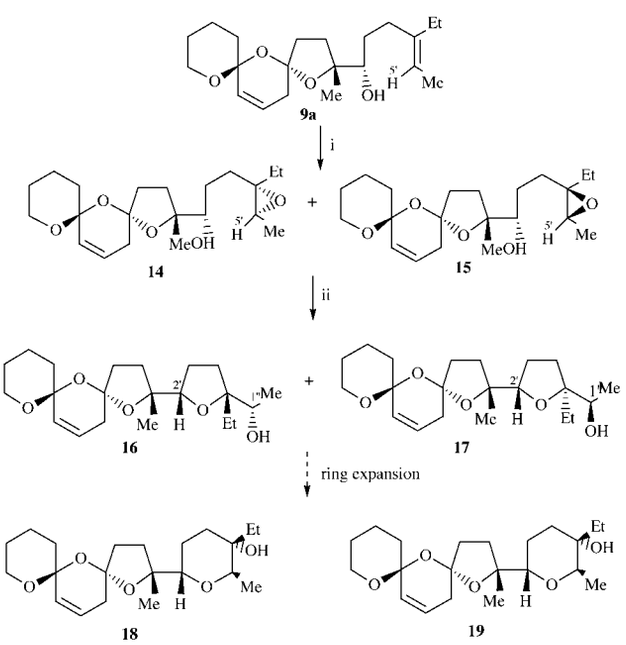


Fig. 1 In all cases the arrow depicts the projectory for formation of the erythro isomers of alcohol **7**.

the *threo* isomer **9d** hence it was decided to focus our attention on the alternative *erythro* alcohol **9a** in which the stereochemistry of the bis-spiroacetal system was also *trans*.

Attempted iodoetherification of alcohol **9a**, by treatment with iodine at 0 °C, resulted in the formation of a polar product which lacked the familiar spiroacetal colourisation when examined by TLC using vanillin as the visualisation agent. ^{1}H NMR analysis of the crude product also revealed the absence of the characteristic resonances for H-15$_B$, H-4$_A$, H-13 and H-14 present in the tricyclic bis-spiroacetal portion of alcohol **9a**. It was therefore concluded that attempted iodoetherification of alcohol **9a** led to destruction of the bis-spiroacetal ring system.

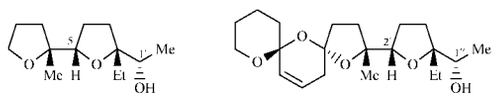
Since the iodoetherification reaction was incompatible with the bis-spiroacetal functionality, an alternative strategy for the appendage of the E ring was investigated using an epoxide cyclisation (Scheme 4). Treatment of bis-spiroacetal olefin **9a**



Scheme 4 *Reagents*, *conditions and yields*: (i) dimethyldioxirane, K_2CO_3, acetone, 0 °C, 96%; (ii) PPTS, CH_2Cl_2, 0 °C, 79%.

with freshly prepared dimethyldioxirane at 0 °C, afforded selective epoxidation of the trisubstituted bond of alcohol **9a** affording epoxides **14** and **15** as an inseparable 1:1 mixture of diastereomers in 96% yield. The preparation of epoxides **14** and **15** was confirmed by the characteristic upfield shift of the resonance assigned to H-5′ from δ_H 5.22 in alcohol **9a** to δ_H 3.79–4.10 in the ^{1}H NMR spectrum of epoxides **14** and **15**. Further evidence was obtained from the mass spectrum, which exhibited a molecular ion at *m*/*z* 367.2478 (M + H) corresponding to the molecular formula $C_{21}H_{35}O_5$.

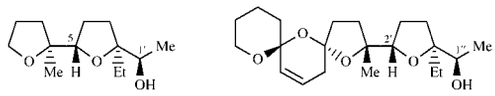
Table 2 Selected ^{1}H NMR chemical shifts (δ) and coupling constants of compounds **16**, **17**, **22**, **23**



22

16

H-5	δ_H 3.97, dd, $J_{5,4A}$ 10.6, $J_{5,4B}$ 5.1 Hz	H-2′	δ_H 3.91, t, $J_{2',3'}$ 6.8 Hz
H-1′	δ_H 3.93, q, $J_{1',2'}$ 6.6 Hz	H-1″	δ_H 3.88, q, $J_{1'',2''}$ 5.9 Hz



23

17

H-5	δ_H 3.71–3.96, m	H-2′	δ_H 3.82, t, $J_{2',3'}$ 8.0 Hz
H-1′	δ_H 3.71–3.96, m	H-1″	δ_H 3.76, q, $J_{1'',2''}$ 6.5 Hz

Cyclisation of epoxides **14** and **15** to bis-spiroacetal-bis tetrahydrofurans **16** and **17** required treatment with acid. Tricyclic bis-spiroacetal systems are very acid sensitive therefore epoxides **14** and **15** were treated with only a catalytic quantity of pyridinium toluene-*p*-sulfonate in dichloromethane at 0 °C for 4 h effecting successful cyclisation to a 1:1 mixture of tetrahydrofurans **16** and **17** in 79% yield. After separation of tetrahydrofurans **16** and **17** by flash chromatography, the stereochemistry of the products was confirmed by comparison of their ^{1}H NMR spectra with bis-tetrahydrofurans **22** and **23** (Table 2). As illustrated in Table 2, the resonances for *cis* tetrahydrofurans **22** and **16** occurred further downfield than the corresponding resonances for the *trans* tetrahydrofurans **23** and **17**. The ^{1}H NMR spectrum exhibited a characteristic downfield shift of the resonance assigned to H-1′ from δ_H 3.55 in epoxides **14** and **15** to δ_H 3.91 and 3.82 (H-2′) for tetrahydrofurans **16** and **17** respectively. Further evidence was obtained from the mass spectrum of tetrahydrofuran **16** which exhibited a molecular ion at *m*/*z* 367.2503 (M + H) corresponding to the molecular formula $C_{21}H_{35}O_5$.

Finally, all that remained was to effect ring expansion of the terminal tetrahydrofuran ring to a tetrahydropyran ring following literature precedent.[8,15] Tetrahydrofuran **16** was therefore treated with pyridine and methanesulfonyl chloride at −20 °C to afford an intermediate mesylate. Various attempts to perform a successful silver-assisted ring expansion of derived mesylate to tetrahydropyran **18** resulted in either no reaction occurring or a baseline product being observed by TLC. Although ^{1}H NMR analysis of the baseline material indicated the presence of a mesyl group, characteristic resonances due to the bis-spiroacetal portion (namely the olefinic resonances at δ_H 5.59 and 5.85 corresponding to H-13 and H-14) of the molecule were absent. The attempted conversion of alcohol **16** to a triflate using triflic anhydride and pyridine in dichloromethane at −30 °C resulted in collapse of the bis-spiroacetal system.

Due to the lack of success using silver cations to promote ring expansion of the mesylate derivative of tetrahydrofuran **16** to polyether **18**, the use of zinc was next examined. It was hoped that use of an alternative metal ion would avoid the undesired destruction of the bis-spiroacetal system. Zinc-mediated ring expansions have been reported wherein the mesylate is heated under reflux with zinc acetate in aqueous acetic acid.[31] Although this methodology was used in ring expansions of various cyclic compounds,[31,32] none of the compounds studied contained acid sensitive groups.

Tetrahydrofuran **17** was treated with acetic acid and water and after 3 h at room temperature, a polar baseline product was observed by TLC. ^{1}H NMR analysis of the crude material indicated the loss of the vinylic protons, implying that the spiroacetal ring system had been destroyed. At this point, changing the conditions required using zinc acetate to effect ring expansion was considered. Stirring the reaction mixture overnight at room temperature resulted in recovered mesylate. Heating the mesylate of alcohol **16** to 45–48 °C with zinc acetate in acetone–water (3:1 v/v) for 48 h only afforded a polar product (TLC) for which the crude ^{1}H NMR spectrum indicated that destruction of the bis-spiroacetal ring system had occurred.

These results clearly indicate that the metal-assisted ring expansion step is incompatible with the tricyclic bis-spiroacetal moiety of tetrahydrofurans **16** and **17**. This could be attributed to the high affinity of oxygen atoms in the bis-spiroacetal mesylate for the metal, which in turn may result in preferential ring opening of the bis-spiroacetal ring instead of ring expansion of the mesylate to a tetrahydropyran.

The successful conversion of aldehyde **7a** to tetrahydrofuran **16** using the epoxide cyclisation strategy described above, can be applied to the synthesis of a B,C,D,E tetracyclic fragment of a precursor to *epi*-17-deoxy-(*O*-8)-salinomycin **3**. The work reported herein, however, has clearly demonstrated that our original tetrahydrofuran ring expansion strategy to append a tetrahydropyran E ring to a bis-spiroacetal fragment is not viable.

The B,C,D and E rings of the tetrahydrofurans **16**, **17** resemble antibiotic CP44,161 **4** which contains an additional methyl group at C-4, an ethyl group at C-2 on ring D and a methyl group rather than an ethyl group at C-5′ on the E ring. The tricyclic bis-spiroacetal stereochemistry is the same as that present in salinomycin **1**. It was concluded that the synthetic methodology currently developed for appendage of a tetrahydrofuran fragment to the model bis-spiroacetal aldehyde **7a** can be more appropriately applied to the synthesis of antibiotic CP44,161 **4** which contains a tetrahydrofuran rather than a tetrahydropyran as the E ring.[19]

Experimental

Mps were determined on a Kofler hot-stage apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC 200 (200.13 MHz), a Bruker AM 200 (200.13 MHz), a Bruker AM360 (360 MHz), a Bruker AMX 400 (400.13 MHz) or a Bruker DRX 400 (400.12 MHz) spectrometer at ambient temperature. All *J* values are given in Hz. ^{13}C NMR spectra were recorded on a Bruker AC 200 (50.3 MHz), Bruker AM 400 (100.6 MHz), Bruker AMX 400 (100.4 MHz) or a Bruker DRX 400 (100.51 MHz) spectrometer at ambient temperature with complete proton decoupling. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard and reported in the order, position (δ_C), multiplicity (aided by DEPT 135 and DEPT 90 experiments) and assignment (aided by COSY and HETCOR experiments). Low resolution mass spectra were recorded on a VG70-250S, a VG70-SD or a AEI model MS902 double focusing magnetic sector mass spectrometer operating with an ionisation potential of 70 eV (EI, DEI, CI and DCI). High resolution mass spectra were recorded at a nominal resolution of 5000 or 10000 as appropriate. Major fragments are given as percentages relative to the base peak and assigned where possible. Ionisation methods employed were either electron impact or chemical ionisation with ammonia or methane as reagent gas (CI). Low resolution chemical ionisation mass spectra were also recorded on a Hewlett Packard 5989A mass spectrometer using ammonia as reagent gas with the sample dissolved in methanol. Flash chromatography was performed using Merck Kieselgel 60 (230–400 mesh) with the indicated solvents. Thin layer chromatography (TLC) was performed using 0.2 mm thick precoated silica gel plates (Merck Kieselgel 60 F_{254} or Riedel-de Haen Kieselgel S F_{254}). Compounds were visualised by ultraviolet fluorescence or by staining with iodine or vanillin in methanolic sulfuric acid. When NMR data is reported for isomeric mixtures, resonances for the minor isomer are denoted by an asterisk (*).

(*E*)-(2*R**,5*S**,7*S**,1′*S**)- and (*E*)-(2*R**,5*S**,7*S**,1′*R**)-2-(4-Ethyl-1-hydroxyhex-4-en-1-yl)-2-methyl-1,6,8-trioxadispiro-[4.1.5.3]pentadec-13-ene 9a, 9b [*erythro* and *threo*]

A suspension of magnesium powder (200 mg, 8.70 mmol) was stirred for 18 h under an atmosphere of nitrogen. Ether (0.75 mL) was added and the magnesium activated using a small crystal of iodine. Stirring was continued until the colour of the iodine disappeared and bromide **8** (109 mg, 0.53 mmol) was added to initiate formation of the alkyl metal reagent. To this, the Barbier mixture, a solution of bromide **8**[20] (109 mg, 0.53 mmol) and aldehyde **7a**[17] (27 mg, 0.11 mmol) in ether (0.25 mL) was added dropwise with gentle heating. The reaction mixture was heated gently under reflux for 2 h, cooled to room temperature then quenched using a water–ice mixture. The aqueous layer was extracted with ether (3 × 10 mL) and dichloromethane (2 × 10 mL) and the combined organic extracts dried over potassium carbonate. The solvent was removed under reduced pressure to afford a yellow oil, which was purified by flash chromatography using hexane–ethyl acetate (20:1) containing a drop of triethylamine, as eluent to afford the following.

(i) *(E)-(2R*,5S*,7S*,1′S*)-2-(4-Ethyl-1-hydroxyhex-4-en-1-yl)-2-methyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene* **9a** [*erythro*] (15 mg, 41%) as a colourless oil (Found: M^+, 350.2435. $C_{21}H_{34}O_4$ requires *M*, 350.2457); ν_{max}/cm^{-1} 3495 (br, OH), 2943s, 2872s, 1455s, 1343s, 1308s, 1196, 1114s (C–O–C asym.), 1092s (C–O–C asym.), 1065s (C–O–C asym.), 1045s, 1031s, 991s (C–O–C), 938s (C–O–C), 885s (C–O–C); δ_H (400 MHz; $CDCl_3$) 0.97 (3H, t, $J_{2'',1''}$ 7.6, CH_2CH_3), 1.18 (3H, s, 2-Me), 1.58 (3H, d, $J_{6',5'}$ 6.7, H-6′), 2.10 (1H, ddd, J_{gem} 17.1, $J_{15,14}$ 6.3 and $J_{15,13}$ 1.0, 15-H_A), 1.43–2.29 (15H, m, 3-H_A, 3-H_B, 4-H_B, 10_{ax}-H, 10_{eq}-H, 11_{ax}-H, 11_{eq}-H, 12_{ax}-H, 12_{eq}-H, 2′-H_A, 2′-H_B, 3′-H_A, 3′-H_B, 1″-H_A and 1″-H_B), 2.55 (1H, ddd, J_{gem} 17.1, $J_{15,14}$ 2.6 and $J_{15,13}$ 2.6, H-15$_B$), 2.80 (1H, dd, J_{gem} 12.7 and $J_{4,3}$ 7.6, H-4$_A$), 3.58 (1H, dd, $J_{1',2'A}$ 9.9 and $J_{1',2'B}$ 2.2, 1′-H), 3.65 (1H, ddd, $J_{9eq,9ax}$11.1, $J_{9eq,10ax}$ 2.0 and $J_{9eq,10eq}$ 2.0, 9_{eq}-H), 3.76 (1H, s, OH), 4.05 (1H, ddd, $J_{9ax,9eq}$11.1, $J_{9ax,10ax}$ 11.1 and $J_{9ax,10eq}$ 4.2, 9_{ax}-H), 5.22 (1H, q, $J_{5',6'}$ 6.7, 5′-H), 5.57 (1H, ddd, $J_{13,14}$ 10.0, $J_{13,15}$ 2.6 and $J_{13,15}$ 1.0, 13-H), 5.84 (1H, ddd, $J_{14,13}$ 10.0, $J_{14,15}$ 6.3 and $J_{14,15}$ 2.6 Hz, 14-H); δ_C (400 MHz; $CDCl_3$) 12.8 (CH_3, C-2″), 13.0 (CH_3, C-6′), 18.7 (CH_2), 23.0 (CH_2), 24.4 (CH_3, 2-Me), 24.9 (CH_2), 28.2 (CH_2), 30.6 (CH_2), 33.3 (CH_2), 34.8 (CH_2), 35.8 (CH_2), 36.4 (CH_2), 61.8 (CH_2, C-9), 75.0 (CH, C-1′), 89.5 (quat., C-2), 97.0 (quat., C-7), 106.0 (quat., C-5), 117.8 (CH, C-5′), 124.9 (CH, C-13), 130.0 (CH, C-14), 141.8 (quat., C-4′); *m/z* (EI) 350 (M^+, 26%), 253 (M − C_7H_{13}, 6), 235 (M − $C_7H_{15}O$, 3), 223 (M − $C_8H_{15}O$, 100), 166 (M − $C_{12}H_{14}O$, 21), 111 (M − $C_{15}H_{27}O_2$, 13), 99 (M − $C_{16}H_{27}O_2$, 36) and 85 (M − $C_{16}H_{27}O_3$, 50).

(ii) *(E)-(2R*,5S*,7S*,1′R*)-2-(4-Ethyl-1-hydroxyhex-4-en-1-yl)-2-methyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene* **9b** [*threo*] (4.5 mg, 12%) as a colourless oil (Found: M^+, 350.2435. $C_{21}H_{34}O_4$ requires *M*, 350.2457); ν_{max}/cm^{-1} 3495 (br, OH), 2943s, 2872s, 1455s, 1343s, 1308s, 1196, 1114s (C–O–C asym.), 1092s (C–O–C asym.), 1065 (C–O–C asym.), 1045s, 1031s, 991s (C–O–C), 938s (C–O–C), 885 (C–O–C); δ_H (400 MHz; $CDCl_3$) 0.98 (3H, t, $J_{2'',1''}$ 7.6, CH_2CH_3), 1.18 (3H, s, 2-Me), 1.58 (3H, d, $J_{6',5'}$ 6.6, 6′-H), 2.12 (1H, ddd, J_{gem} 17.2, $J_{15,14}$ 6.2 and $J_{15,13}$ 0.9, 15-H_A), 1.43–2.29 (15H, m, 3-H_A, 3-H_B, 4-H_B, 10_{ax}-H, 10_{eq}-H, 11_{ax}-H, 1_{eq}-H, 12_{ax}-H, 12_{eq}-H, 2′-H_A, 2′-H_B, 3′-H_A, 3′-H_B, 1″-H_A and 1″-H_B), 2.53 (1H, ddd, J_{gem} 17.2, $J_{15,14}$ 2.5 and $J_{15,13}$ 2.5,

15-H_B), 2.76 (1H, dd, J_{gem} 12.2 and $J_{4,3}$ 7.4, 4-H_A), 3.17 (1H, d, $J_{OH,1}$ 7.8, OH), 3.44 (1H, ddd, $J_{1',2'A}$ 10.2, $J_{1,OH}$ 7.8, and $J_{1',2'B}$ 2.4 Hz, 1′-H), 3.67 (1H, br d, $J_{9eq,9ax}$ 10.8, 9_{eq}-H), 4.03 (1H, ddd, $J_{9ax,9eq}$ 10.8, $J_{9ax,10ax}$ 10.8 and $J_{9ax,10eq}$ 4.2, 9_{ax}-H), 5.24 (1H, q, $J_{5',6'}$ 6.6, 5′-H), 5.64 (1H, ddd, $J_{13,14}$ 10.0, $J_{13,15}$ 2.5 and $J_{13,15}$ 0.9, H-13), 5.85 (1H, ddd, $J_{14,13}$ 10.0, $J_{14,15}$ 6.2 and $J_{14,15}$ 2.5, 14-H); *m/z* (EI) 350 (M^+, 26%), 253 (M − C_7H_{13}, 6), 235 (M − $C_7H_{15}O$, 3), 223 (M − $C_8H_{15}O$, 100), 166 (M − $C_{12}H_{14}O$, 21), 111 (M − $C_{15}H_{27}O_2$, 13), 99 (M − $C_{16}H_{27}O_2$, 36) and 85 (M − $C_{16}H_{27}O_3$, 50).

(*E*)-(2*S**,5*S**,7*S**,1′*R**)- and (*E*)-(2*S**,5*S**,7*S**,1′*S**)-2-(4-Ethyl-1-hydroxyhex-4-en-1-yl)-2-methyl-1,6,8-trioxadispiro-[4.1.5.3]pentadec-13-ene 9c, 9d [*erythro* and *threo*]

Using the procedure described for the synthesis of alcohols **9a** and **9b**, a suspension of magnesium powder (200 mg, 8.70 mmol) in ether (0.75 mL) was activated and bromide **8** (66 mg, 0.38 mmol) added to initiate formation of the alkyl metal reagent. To this, the Barbier mixture, a solution of bromide **8** (66 mg, 0.38 mmol) and aldehyde **7b**[17] (14 mg, 0.06 mmol) in ether (0.25 mL) was added dropwise with gentle heating. The reaction mixture was heated gently under reflux for 2 h, cooled to room temperature and worked up as before to afford an inseparable (1.54 : 1, ^{1}H NMR) mixture of *erythro* **9c** and *threo* **9d** *alcohols* (14 mg, 72%) as a colourless oil (Found: M^+, 350.2443. $C_{21}H_{34}O_4$ requires *M*, 350.2457); ν_{max}/cm^{-1} 3495 (br, OH), 2943s, 2872s, 1455s, 1343s, 1308s, 1196w, 1114 (C–O–C asym.), 1092s (C–O–C asym.), 1065s (C–O–C asym.), 1045s, 1031s, 991s (C–O–C), 938s (C–O–C), 885s (C–O–C); δ_H (400 MHz; $CDCl_3$) 0.96, 0.97* (3H, t, $J_{2'',1''}$ 7.6, CH_2CH_3), 1.25 (3H, s, 2-Me), 1.58 (3H, d, $J_{6',5'}$ 6.8, 6-H), 1.43–2.29 (16H, m, 3-H_A, 3-H_B, 4-H_B, 10_{ax}-H, 10_{eq}-H, 11_{ax}-H, 11_{eq}-H, 12_{ax}-H, 12_{eq}-H, 15-H_A, 2′-H_A, 2′-H_B, 3′-H_A, 3′-H_B, 1″-H_A and 1″-H_B), 2.51 (1H, ddd, J_{gem} 17.0, $J_{15,14}$ 2.6 and $J_{15,13}$ 2.6, 15-H_B), 2.65–2.76 (1H, m, 4-H_A), 3.36* (1H, dd, $J_{1',2'A}$ 9.4 and $J_{1',2'B}$ 3.0, 1′-H), 3.48 (1H, dd, $J_{1',2'A}$ 10.0 and $J_{1',2'B}$ 2.0, 1′-H), 3.69 (1H, ddd, $J_{9eq,9ax}$ 11.3, $J_{9eq,10ax}$ 2.0 and $J_{9eq,10eq}$ 2.0, 9_{eq}-H), 4.01 (1H, ddd, $J_{9ax,9eq}$ 11.3, $J_{9ax,10ax}$ 11.3 and $J_{9ax,10eq}$ 2.9, 9_{ax}-H), 5.22 (1H, q, $J_{5',6'}$ 6.8 Hz, 5′-H), 5.61 (1H, ddd, $J_{13,14}$ 10.0, $J_{13,15}$ 2.6 and $J_{13,15}$ 0.9, 13-H), 5.84, 5.84* (1H, ddd, $J_{14,13}$ 10.0, $J_{14,15}$ 6.3 and $J_{14,15}$ 2.6, H-14); *m/z* (EI) 350 (M^+, 26%), 253 (M − C_7H_{13}, 6), 235 (M − $C_7H_{15}O$, 3), 223 (M − $C_8H_{15}O$, 100), 166 (M − $C_{12}H_{14}O$, 21), 111 (M − $C_{15}H_{27}O_2$, 13), 99 (M − $C_{16}H_{27}O_2$, 36) and 85 (M − $C_{16}H_{27}O_3$, 50).

(*E*)-(2*R**,5*R**,7*S**,1′*S**)- and (*E*)-(2*R**,5*R**,7*S**,1′*R**)-2-(4-Ethyl-1-hydroxyhex-4-en-1-yl)-2-methyl-1,6,8-trioxadispiro-[4.1.5.3]pentadec-13-ene 9e, 9f [*erythro* and *threo*]

Using the procedure described for the synthesis of alcohols **9a** and **9b**, a suspension of magnesium powder (100 mg, 4.35 mmol) in ether (0.50 mL) was activated and bromide **8** (38 mg, 0.22 mmol) added to initiate formation of the alkyl metal reagent. To this, the Barbier mixture, a solution of bromide **8** (38 mg, 0.22 mmol) and aldehyde **7c** (prepared using the procedure for aldehydes **7a**,**7b**[17] and used directly without further purification) (11 mg, 0.04 mmol) in ether (0.25 mL) was added dropwise with gentle heating. The reaction mixture was heated gently under reflux for 2 h, cooled to room temperature and worked up as before to afford a 8.3 : 1 mixture of *erythro* **9e** and *threo* **9f** *alcohols* (11 mg, 73%, ^{1}H NMR) as a colourless oil (Found: M^+, 350.2455. $C_{21}H_{34}O_4$ requires *M*, 350.2457); ν_{max}/cm^{-1} 3495 (br, OH), 2943s, 2872s, 1455s, 1343s, 1308s, 1196, 1114s (C–O–C asym.), 1092s (C–O–C asym.), 1065s (C–O–C asym.), 1045s, 1031s, 991s (C–O–C), 938 (C–O–C), 885s (C–O–C); δ_H (400 MHz; $CDCl_3$) 0.94, 0.95* (3H, t, $J_{2'',1''}$ 7.6, CH_2CH_3), 1.26 (3H, s, 2-Me), 1.58 (3H, d, $J_{6',5'}$ 7.0, 6′-H), 1.30–2.07 (17H, m, 3-H_A, 3-H_B, 4-H_A, 4-H_B, 10-H_{ax}, 10-H_{eq}, 11-H_{ax}, 11-H_{eq}, 12-H_{ax}, 12-H_{eq}, 15-H_A, 2′-H_A, 2′-H_B, 3′-H_A, 3′-H_B, 1″-H_A and 1″-H_B), 2.47 (1H, ddd, J_{gem} 16.4, $J_{15,14}$ 2.6 and $J_{15,13}$ 2.6, 15$_B$-H), 3.34–3.39* (1H, m, 1′-H), 3.57 (1H, dd, $J_{1',2'A}$ 10.4 and $J_{1',2'B}$ 2.3, 1′-H), 3.61–3.73 (1H, m, 9_{eq}-H), 4.00–4.02 (1H, m, 9_{ax}-H), 5.18 (1H, q, $J_{5',6'}$ 7.0, 5′-H), 5.95 (1H, ddd, $J_{13,14}$ 10.0, $J_{13,15}$ 2.6 and $J_{13,15}$ 1.0, 13-H), 6.14 (1H, dd, $J_{14,13}$ 10.0 and $J_{14,15}$ 6.3, 14-H); *m/z* (EI) 350 (M^+, 26%), 253 (M − C_7H_{13}, 6), 235 (M − $C_7H_{15}O$, 3), 223 (M − $C_8H_{15}O$, 100), 166 (M − $C_{12}H_{14}O$, 21), 111 (M − $C_{15}H_{27}O_2$, 13), 99 (M − $C_{16}H_{27}O_2$, 36) and 85 (M − $C_{16}H_{27}O_3$, 50).

(*E*)-(2*S**,5*R**,7*S**,1′*R**)- and (*E*)-(2*S**,5*R**,7*S**,1′*S**)-2-(4-Ethyl-1-hydroxyhex-4-en-1-yl)-2-methyl-1,6,8-trioxadispiro-[4.1.5.3]pentadec-13-ene 9g, 9h [*erythro* and *threo*]

Using the procedure described for the synthesis of alcohols **9a** and **9b**, a suspension of magnesium powder (100 mg, 4.35 mmol) in ether (0.50 mL) was activated and bromide **8** (28 mg, 0.16 mmol) added to initiate formation of the alkyl metal reagent. To this, the Barbier mixture, a solution of bromide **8** (28 mg, 0.16 mmol) and aldehyde **9d** (8 mg, 0.03 mmol) in ether (0.25 mL) was added dropwise with gentle heating. The reaction mixture was heated gently under reflux for 2 h, cooled to room temperature and worked up as before to afford a 2.2 : 1 mixture of *erythro* **9g** and *threo* **9h** *alcohols* (8 mg, 73%, ^{1}H NMR) as a colourless oil (Found: M^+, 350.2435. $C_{21}H_{34}O_4$ requires *M*, 350.2457); ν_{max}/cm^{-1} 3495 (br, OH), 2943s, 2872s, 1455s, 1343s, 1308s, 1196, 1114 (C–O–C asym.), 1092s (C–O–C asym.), 1065s (C–O–C asym.), 1045s, 1031s, 991s (C–O–C), 938s (C–O–C), 885s (C–O–C); δ_H (400 MHz; $CDCl_3$) 0.95, 0.96* (3H, t, $J_{2'',1''}$ 7.6, CH_2CH_3), 1.26 (3H, s, 2-Me), 1.58 (3H, d, $J_{6',5'}$ 6.8, 6′-H), 1.40–2.20 (17H, m, 3-H_A, 3-H_B, 4-H_A, 4-H_B, 10-H_{ax}, 10-H_{eq}, 11-H_{ax}, 11-H_{eq}, 12-H_{ax}, 12-H_{eq}, 15-H_A, 2′-H_A, 2′-H_B, 3′-H_A, 3′-H_B, 1″-H_A and 1″-H_B), 2.45–2.55 (1H, m, 15$_B$-H), 3.32–3.37* (1H, m, 1′-H), 3.48 (1H, dd, $J_{1',2'A}$ 10.4 and $J_{1',2'B}$ 1.8, 1′-H), 3.63–3.69 (1H, m, 9_{eq}-H, 4.05 (1H, dd, $J_{9ax,9eq}$ 11.8 and $J_{9ax,10ax}$ 11.8 Hz, 9_{ax}-H), 5.20 (1H, q, $J_{5',6'}$ 6.8, 5′-H), 5.75 (1H, ddd, $J_{13,14}$ 10.0, $J_{13,15}$ 2.6 and $J_{13,15}$ 1.0, 13-H), 6.14 (1H, ddd, $J_{14,13}$ 10.0, $J_{14,15}$ 6.3 and $J_{14,15}$ 2.6, 14-H); *m/z* (EI) 350 (M^+, 26%), 253 (M − C_7H_{13}, 6), 235 (M − $C_7H_{15}O$, 3), 223 (M − $C_8H_{15}O$, 100), 166 (M − $C_{12}H_{14}O$, 21), 111 (M − $C_{15}H_{27}O_2$, 13), 99 (M − $C_{16}H_{27}O_2$, 36) and 85 (M − $C_{16}H_{27}O_3$, 50).

(*E*)-(2*S**,7*S**,1′*R**)- and (*E*)-(2*S**,5*S**,7*S**,1′*S**)-2-(1-Acetoxy-4-ethylhex-4-en-1-yl)-2-methyl-1,6,8-trioxadispiro[4.1.5.3]-pentadec-13-ene 13c, 13d

To a 1.54 : 1 mixture of alcohols **9c** and **9d** (7 mg, 0.02 mmol) in dry dichloromethane (1 mL) were added triethylamine (6 μL, 0.04 mmol), acetic anhydride (2 μL, 0.02 mmol) and a catalytic quantity of 4-dimethylaminopyridine (~1 mg). After 4 h the solvent was removed under reduced pressure and the residue purified by flash chromatography using hexane–ethyl acetate (20 : 1) containing triethylamine (1 drop) as eluent, to afford a mixture of *erythro* **13c** and *threo* **13d** *acetates* (6 mg, 77%) as a colourless oil (Found: M^+, 392.2561. $C_{23}H_{36}O_5$ requires *M*, 392.2563); ν_{max}/cm^{-1} 2940s, 2872s, 1739 (C=O), 1441s, 1371s, 1350s, 1236s (C–O–C asym.), 1201s, 1096s (C–O–C asym.), 1073 (C–O–C asym.), 1043s, 1006s (C–O–C), 943s (C–O–C), 890s (C–O–C); δ_H(200 MHz; $CDCl_3$) 0.94 (3H, t, $J_{2'',1''}$ 7.6, CH_2CH_3), 1.45 (3H, s, 2-Me), 1.46* (3H, s, 2-Me), 1.50–2.15 (19H, m, 3-H_A, 3-H_B, 4-H_B, 10_{ax}-H, 10_{eq}-H, 11_{ax}-H, 11_{eq}-H, 12_{ax}-H, 12_{eq}-H, 15-H_A, 2′-H_A, 2′-H_B, 3′-H_A, 3′-H_B, 6′-H, 1″-H_A and 1″-H_B), 2.06, 2.07* (3H, s, CH_3CO), 2.48 (1H, ddd, J_{gem} 17.1, $J_{15,14}$ 2.5 and $J_{15,13}$ 2.5, 15-H_B), 2.64–2.80 (1H, m, 4-H_A), 3.67 (1H, ddd, $J_{9eq,9ax}$ 10.2, $J_{9eq,10ax}$ 2.2 and $J_{9eq,10eq}$ 2.2, 9_{eq}-H), 3.98 (1H, ddd, $J_{9ax,9eq}$ 10.2, $J_{9ax,10ax}$ 10.2 and $J_{9ax,10eq}$ 4.1, 9_{ax}-H), 4.83–4.91 (1H, m, 1′-H), 5.15 (1H, q, $J_{5',6'}$ 6.7, 5′-H), 5.58 (1H, ddd, $J_{13,14}$ 10.1, $J_{13,15}$ 2.4 and $J_{13,15}$ 0.9, 13-H), 5.84 (1H, ddd, $J_{14,13}$ 10.1, $J_{14,15}$ 5.8 and $J_{14,15}$ 2.4, 14-H); *m/z* (EI) 392 (M^+, 23%), 364 (M − C_2H_9, 5), 235 (M − $C_9H_{17}O_2$, 5), 223 (M − $C_{10}H_{27}O_2$, 100), 169 (M − $C_{14}H_{23}O_2$, 13), 124 (M − $C_{29}H_{28}O_3$, 43) and 99 (M − $C_{31}H_{29}O_3$, 52).

(2*R,5*S**,7*S**,1′*S**,4′*R**,5′*R**)- and (2*R**,5*S**,7*S**,1′*S**,4′*S**, 5′*S**)-2-(4,5-Epoxy-4-ethyl-1-hydroxyhexan-1-yl)-2-methyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene 14, 15**

Freshly prepared dimethyl dioxirane[33] (3 mL) was added to a solution of alcohol **9a** (10 mg, 0.03 mmol) and potassium carbonate (2 mg) in acetone (0.5 mL) at 0 °C under an atmosphere of nitrogen. The reaction mixture was stirred for 1 h at 0 °C and the solvent removed under reduced pressure to afford a colourless oil. Purification by flash chromatography using hexane–ethyl acetate (20 : 1) containing triethylamine (1 drop) as eluent afforded a 1 : 1 mixture of *epoxides* **14**,**15** (10 mg, 96%) as a clear oil (Found: $(M + H)^+$, 367.2478. $C_{21}H_{34}O_5$ requires M + H, 367.2484); ν_{max}/cm^{-1} 3492 (br, OH), 2933s, 2869s, 1449s, 1376s, 1344s, 1312s, 1197s (C–O–C asym.), 1092s (C–O–C asym.), 1027s (C–O–C asym.), 987s (C–O–C), 936s (C–O–C), 886s (C–O–C); δ_H(200 MHz; $CDCl_3$) 0.99 (3H, t, $J_{2'',1''}$ 7.6, CH_2CH_3), 1.00* (3H, t, $J_{2'',1''}$ 7.6, CH_2CH_3), 1.19 (3H, s, 2-Me), 1.29 (3H, d, $J_{6',5'}$ 5.3, 6′-H), 2.10 (1H, br dd, J_{gem} 17.2 and $J_{15,14}$ 6.3, 15-H_A), 1.43–2.29 (15H, m, 3-H_A, 3-H_B, 4-H_B, 10_{ax}-H, 10_{eq}-H, 11_{ax}-H, 11_{eq}-H, 12_{ax}-H, 12_{eq}-H, 2′-H_A, 2′-H_B, 3′-H_A, 3′-H_B, 1″-H_A and 1″-H_B), 2.55 (1H, br d, J_{gem} 17.2, 15-H_B), 2.79 (1H, dd, J_{gem} 12.4 and $J_{4,3}$ 7.5, 4-H_A), 3.55 (1H, dd, $J_{1',2'A}$ 9.2 and $J_{1',2'B}$ 2.3, 1′-H), 3.65 (1H, br d, $J_{9eq,9ax}$ 10.2, 9_{eq}-H), 3.88 (1H, s, OH), 3.79–4.10 (2H, m, 9_{ax}-H, 5′-H), 5.57 (1H, br dd, $J_{13,14}$ 10.0 and $J_{13,15}$ 2.4, 13-H), 5.84 (1H, ddd, $J_{14,13}$ 10.0, $J_{14,15}$ 6.3 and $J_{14,15}$ 2.4, 14-H); *m*/*z* (CI) 367 (M + H, 100%), 349 (M − OH, 45), 323 (M − C_2H_3O, 10), 267 (M − $C_6H_{11}O$, 3), 223 (M − $C_8H_{15}O_2$, 8) and 125 (M − $C_{14}H_{25}O_3$, 18).

(2*R,5*S**,7*S**,2′*S**,5′*S**,1″*R**)- and (2*R**,5*S**,7*S**,2′*S**,5′*R**, 1″*S**)-2-{5-Ethyl-5-(1-hydroxyethyl)tetrahydro-2-furyl}-2-methyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene 16, 17**

To a solution of epoxides **14**,**15** (7 mg, 0.2 mmol) in dichloromethane (1.0 mL) at 0 °C was added pyridinium toluene-*p*-sulfonate (~ 1 mg). After stirring for 4 h at room temperature, the solvent was removed under reduced pressure and the residue was purified by flash chromatography using hexane–ethyl acetate (10 : 1) containing triethylamine (1 drop) as eluent to afford the following.

(i) *Tetracycle* **16** as a colourless oil (2.8 mg, 40%) (Found: $(M + H)^+$, 367.2503. $C_{21}H_{34}O_5$ requires M + H, 367.2484); ν_{max}/cm^{-1} 3464 (br, OH), 2938s, 2861s, 1463s, 1393s, 1372s, 1349s, 1284s, 1255s, 1223s, 1200s (C–O–C asym.), 1094s (C–O–C asym.), 1073s (C–O–C asym.), 1044s (C–O–C asym.), 1005s (C–O–C), 982s (C–O–C), 943s (C–O–C), 890s (C–O–C); δ_H (400 MHz; $CDCl_3$) (3H, t, $J_{2''',1'''}$ 7.4, CH_2CH_3), 1.07 (3H, d, $J_{2'',1''}$ 5.9, 2″-H), 1.25 (3H, s, 2-Me), 1.43–2.29 (16H, m, 3-H_A, 3-H_B, 4-H_B, 10_{ax}-H, 10_{eq}-H, 11_{ax}-H, 11_{eq}-H, 12_{ax}-H, 12_{eq}-H, 15-H_A, 3′-H_A, 3′-H_B, 4′-H_A, 4′-H_B, 1‴-H_A and 1‴-H_B), 2.48 (1H, ddd, J_{gem} 17.2, $J_{15,14}$ 2.7 and $J_{15,13}$ 2.7, 15-H_B), 2.68 (1H, ddd, J_{gem} 13.0, $J_{4,3}$ 8.6 and $J_{4,3}$ 2.0, 4-H_A), 3.63 (1H, br s, OH), 3.68 (1H, br d, $J_{9eq,9ax}$ 11.5, 9_{eq}-H), 3.88 (1H, q, $J_{1'',2''}$ 5.9, 1″-H), 3.91 (1H, t, $J_{2',3'}$ 6.8, 2′-H), 4.01 (1H, ddd, $J_{9ax,9eq}$ 11.5, $J_{9ax,10ax}$ 11.5 and $J_{9ax,10eq}$ 3.4, 9_{ax}-H), 5.59 (1H, ddd, $J_{13,14}$ 10.0, $J_{13,15}$ 2.7 and $J_{13,15}$ 1.2, 13-H), 5.85 (1H, br dd, $J_{14,13}$ 10.0 and $J_{14,15}$ 5.7, 14-H); *m*/*z* (CI) 367 (M + H, 100%), 349 (M − OH, 22), 321 (M − C_2H_5O, 6), 267 (M − $C_6H_{11}O$, 5), 223 (M − $C_8H_{15}O_2$, 7) and 125 (M − $C_{14}H_{25}O_3$, 12).

(ii) *Tetracycle* **17** (2.7 mg, 39%) as a colourless oil (Found: $(M + H)^+$, 367.2501. $C_{21}H_{34}O_5$ requires M + H, 367.2484); ν_{max}/cm^{-1} 3464 (br, OH), 2938s, 2861s, 1463s, 1393s, 1372s, 1349s, 1284s, 1255, 1223s, 1200s (C–O–C asym.), 1094s (C–O–C asym.), 1073s (C–O–C asym.), 1044s (C–O–C asym.), 1005s (C–O–C), 982s (C–O–C), 943s (C–O–C), 890s (C–O–C); δ_H(400 MHz; $CDCl_3$) 0.91 (3H, t, $J_{2''',1'''}$ 7.4, CH_2CH_3), 1.06 (3H, d, $J_{2'',1''}$ 6.5, 2″-H), 1.25 (3H, s, 2-Me), 2.19 (1H, br dd, J_{gem} 17.2 and $J_{15,14}$ 6.3, 15_A-H), 1.43–2.29 (15H, m, 3-H_A, 3-H_B, 4-H_B, 10_{ax}-H, 10_{eq}-H, 11_{ax}-H, 11_{eq}-H, 12_{ax}-H, 12_{eq}-H, $3'_A$-H, $3'_B$-H, $4'_A$-H, $4'_B$-H, 1‴-H_A and 1‴-H_B), 2.54 (1H, ddd, J_{gem} 17.2, $J_{15,14}$ 2.7 and $J_{15,13}$ 2.7, 15-H_B), 2.77 (1H, ddd, J_{gem} 13.0, $J_{4,3}$ 8.6 and $J_{4,3}$ 2.0, 4-H_A), 3.56 (1H, s, OH), 3.68 (1H, ddd, $J_{9eq,9ax}$ 11.2, $J_{9eq,10ax}$ 2.1 and $J_{9eq,10eq}$ 2.1, 9_{eq}-H), 3.76 (1H, q, $J_{1'',2''}$ 6.5, 1″-H), 3.82 (1H, t, $J_{2',3'}$ 8.0, 2′-H), 4.01 (1H, ddd, $J_{9ax,9eq}$11.2, $J_{9ax,10ax}$ 11.2 and $J_{9ax,10eq}$ 3.6, 9_{ax}-H), 5.58 (1H, ddd, $J_{13,14}$ 10.1, $J_{13,15}$ 2.7 and $J_{13,15}$ 1.3, 13-H), 5.83 (1H, ddd, $J_{14,13}$ 10.1, $J_{14,15}$ 5.8 and $J_{14,15}$ 2.7, 14-H); *m*/*z* (CI) 367 (M + H, 100%), 349 (M − OH, 22), 321 (M − C_2H_5O, 6), 267 (M − $C_6H_{11}O$, 5), 223 (M − $C_8H_{15}O_2$, 7) and 125 (M − $C_{14}H_{25}O_3$, 12).

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