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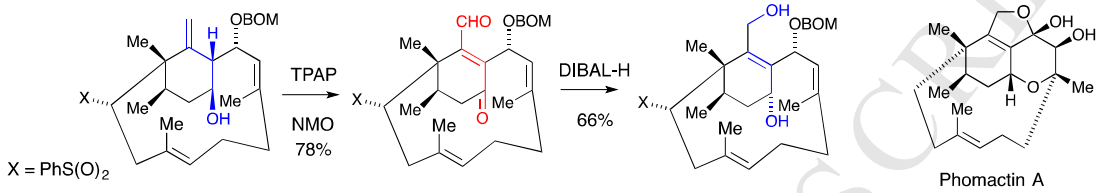

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Synthetic approaches to phomactins: novel oxidation of homoallylic alcohols using tetra-*n*-propylammonium perruthenate

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ABSTRACT

Previous studies of a synthesis of phomactin A had resulted in the synthesis of a 15-methylenebicyclo[9.3.1]pentadecadiene. The next step in the synthesis was to be the epoxidation of this methylenecyclohexane that was hoped would lead to a 1-(hydroxymethyl)cyclohexene by rearrangement of the exocyclic epoxide, but the epoxidation was difficult to carry out regioselectively on advanced intermediates. However, oxidation of a 15-methylenebicyclo[9.3.1]pentadeca-3,7-dien-14-ol using tetra-*n*-propylammonium perruthenate and *N*-methylmorpholine-*N*-oxide led to conversion of this homoallylic alcohol into the corresponding 14-oxobicyclo[9.3.1]pentadeca-1(15),3,7-triene-15-carboxaldehyde in one step. Reduction of this using DIBAL-H gave a promising intermediate for a synthesis of a phomactin. The scope of this oxidation of homoallylic alcohols was briefly investigated.

1. Introduction

The phomactins are a novel group of diterpenes originally isolated from the marine fungus *Phoma* sp. although other sources have since been identified. They are characterised by a bicyclo[9.3.1]pentadecenyl skeleton as exemplified by phomactins A, D, G and B2, **1** – **4**, see Figure 1, and show interesting biological activity including platelet activating factor antagonism.[1,2] They are recognised as challenging targets for synthesis with many synthetic approaches and six total syntheses reported to date.[3,4] Phomactin A **1**, in particular, has been the focus of many synthetic studies with three total syntheses now complete.

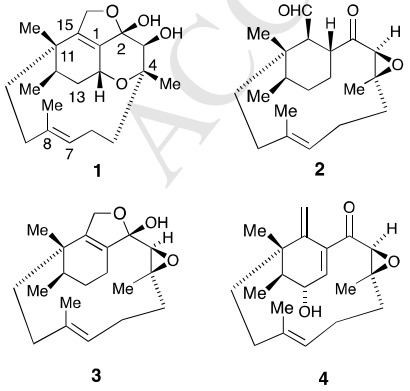

Figure 1 Structures of representative phomactins showing the numbering scheme used.

In our approach to phomactins, the cyclohexenylmethanol **5** was converted stereoselectively into the methylenecyclohexanol **6** using the Still variant of the 2,3-Wittig rearrangement. Development of the side chain using a ytterbium(III) triflate promoted vinyllithium addition to the corresponding aldehyde gave the alcohol **7**. Protection of this alcohol as its benzyloxymethyl ether, conversion of the *tert*-butyldimethylsilyl ether into the corresponding allylic bromide, and base mediated cyclisation, gave the macrocyclic sulphone **8**.[5,6] This has the bicyclo[9.3.1]pentadecadienyl structure found in the phomactins and would appear to be a useful advanced intermediate for their synthesis, see Figure 2.

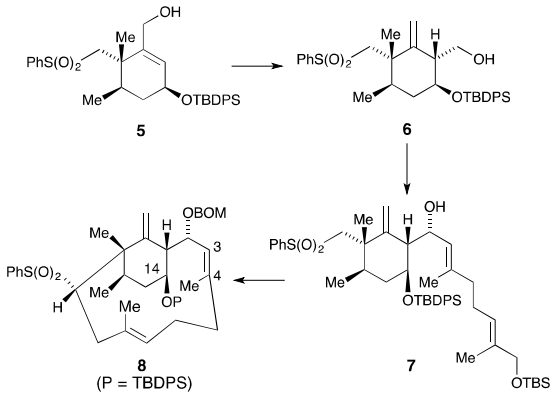

Figure 2 Synthesis of the bicyclo[9.3.1]pentadecenyl sulfone **8**.

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A possible synthetic route from the sulfone **8** to phomactin A **1** is outlined in Figure 3. Reductive deprotection of the BOM-protected hydroxysulfone **8** with concomittant loss of the sulfonyl moiety would give the alcohol **9**. Regioselective epoxidation directed by the alcohol at C2 should then deliver the bis-epoxide **10** possibly as a mixture of isomers.[2a] Oxidation of the alcohol would lead to the ketone **11** but this should be unstable with respect to isomerisation of the βγ-epoxide to the corresponding allylic alcohol that would be expected to equilibrate with the hemi-acetal **12** by analogy with the behaviour of phomactins A **1** and G **3**. Removal of the remaining silyl protecting group, inversion of configuration at C14, and intramolecular opening of the epoxide by the C14 alcohol,[2b] would then provide phomactin A **1**. We now describe studies of the early stages of this scheme together with an unexpected oxidation of homoallylic alcohols using tetra-*n*-propylammonium perruthenate.[7]

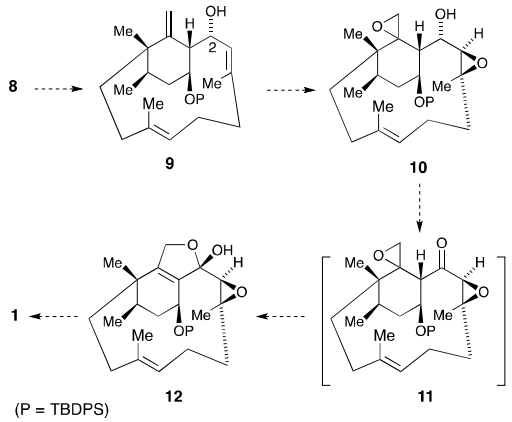


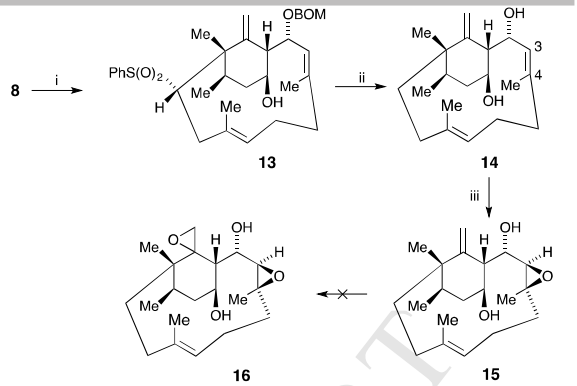
Figure 3 Proposed development of a synthetic approach to phomactin A **1** from the macrocyclic sulfone **8**.

2. Results and discussion

2.1 Epoxidation of a 2-hydroxy-15-methylene-bicyclo[9.3.1]pentadeca-3,7-diene and precursors

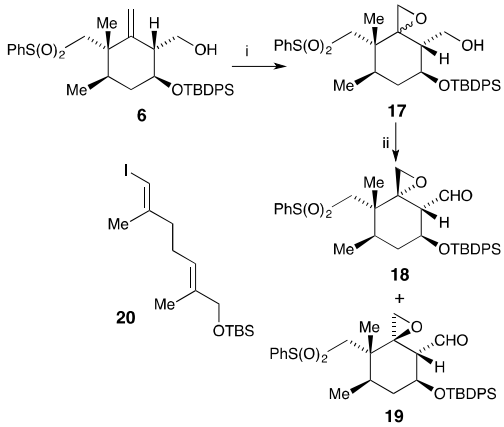
To avoid competing reduction of the benzene rings in the *tert*-butyldiphenylsilyl ether, the macrocycle **8** was first desilylated using tetra-*n*-butylammonium fluoride to give the alcohol **13** that was converted into the diol **14** using Birch conditions. Epoxidation of this dihydroxytriene using a small excess of *tert*-butyl hydroperoxide and $VO(acac)_2$ gave a good yield of a monoepoxide derived from the 3,4-alkene. This was identified as the stereoisomer **15** by analogy with previous work[8] and was consistent with a directed epoxidation on the more accessible face of the 3,4-double-bond as indicated by the X-ray crystal structure of the macrocyclic sulfone **8**.[5] However, attempts to prepare the bis-epoxide **16** using prolonged reaction times, an excess of the oxidant, or by using $Ti(^iPrO)_4$ or $Mo(CO)_6$ as the catalyst,[9] were unsuccessful. Lower yields of the monoepoxide **15** were formed in these reactions with none of the required bis-epoxide **16** being obtained, Scheme 1. It would appear that the exocyclic double-bond is too hindered in this system, perhaps by the 11-methyl group, for epoxidation to take place.

Epoxidation of the methylenecyclohexane moiety of earlier intermediates in the synthesis was considered as a way round this problem since for these compounds the exocyclic double-bond should be more accessible. Indeed epoxidation of the 2,3-Wittig



Scheme 1 Epoxidation of the hydroxytriene **14** Reagents and conditions i, TBAF, THF, rt, 16 h (95%); ii, Na, EtOH, NH_3, THF, 45 min (75%); iii, TBHP, $VO(acac)_2$ (cat.), benzene, rt, 30 min (85%).

product **6** using either *tert*-butyl hydroperoxide and $VO(acac)_2$ or *m*-chloroperoxybenzoic acid gave the hydroxyepoxide **17** as mixtures of diastereoisomers, ratio *ca*. 60 : 40 in both cases, albeit the major isomer from the *tert*-butyl hydroperoxide oxidation was the minor isomer from the per-acid epoxidation. These hydroxyepoxides were not easy to separate but after oxidation, the diastereoisomeric epoxyaldehydes **18** and **19** could be separated, Scheme 2. The *tert*-butyl hydroperoxide epoxidation should be directed by the homoallylic alcohol[9] and would be expected to give epoxyaldehyde **18** as the major product after oxidation. Approach of the peracid to the less hindered face of the alkene would give isomer **19** after oxidation. These assignments were consistent with ^1H NMR data and were confirmed by an X-ray crystal structure of the epoxyaldehyde **18**, see Figure 4. However, preliminary studies of the addition of the vinyllithium reagent derived from the vinylic iodide **20** to the separated epoxyaldehydes **18** and **19** gave mixtures of products. These were not properly characterised but, interestingly, side products that involved epoxide cleavage did not appear to predominate. However, the low stereoselectivity of epoxidation of the methylenecyclohexane **6** and the formation of mixtures of products from reactions of the aldehydes **18** and **19** with the vinyllithium reagent led to this study being discontinued in favour of studies of epoxidation of hydroxytriene **7**.



Scheme 2 Epoxidation of methylenecyclohexane **6** Reagents and conditions i, either (a) TBHP, $VO(acac)_2$, benzene, rt, 9 h (95%, ratio 60:40) or (b) *m*CPBA, DCM, rt, 3 h (85%, ratio 40:60); ii, **17** from TBHP epoxidation, py.SO_3, $^iPr_2NEt$, DMSO, DCM, 0 ^oC, 15 min (**18**, 40%; **19**, 25%).

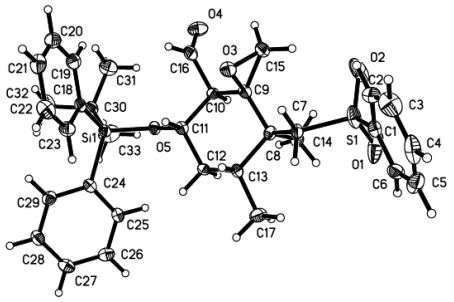
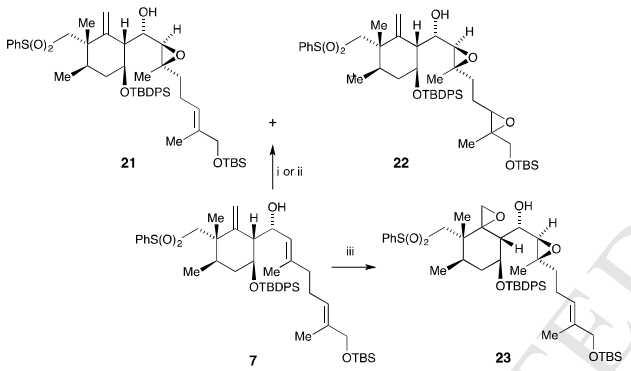


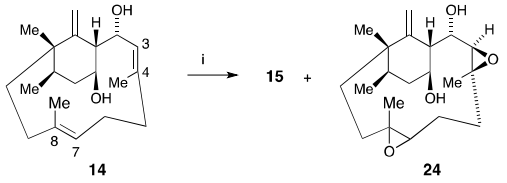
Figure 4 X-Ray crystal structure of epoxyaldehyde **18**

The products obtained from epoxidation of the hydroxytriene **7** varied significantly depending on the reaction conditions. Using *tert*-butyl hydroperoxide and $VO(acac)_2$ at room temperature, the monoepoxide **21** was obtained regioselectively as a 10:1 mixture of diastereoisomers, the threo-configuration being assigned to the major diastereoisomer **21** by analogy with the literature.[10] Initial studies using *m*-chloroperoxybenzoic acid gave the bis-epoxide **22** as a mixture of diastereoisomers, as well as the monoepoxide **21**. However, the use of *tert*-butyl hydroperoxide and $VO(acac)_2$ under microwave conditions[11] gave the bis-epoxide **23**, predominantly as one diastereoisomer, in which the methylenecyclohexane had been epoxidised as well as the 2,3-double-bond of the side-chain, Scheme 3.



Scheme 3 Epoxidation of the hydroxytriene **7** Reagents and conditions i, TBHP, $VO(acac)_2$, benzene, rt, 10 min (**21**, 78%); ii, *m*CPBA, DCM, rt, 1.5 h (**21**, 15%, **22**, 48%); iii, TBHP, $VO(acac)_2$, DCM, 60 °C microwave, 1 h (57%).

The formation of the bis-epoxide **23** from the microwave promoted epoxidation of the hydroxytriene **7** using *tert*-butyl hydroperoxide and $VO(acac)_2$ was encouraging and so the epoxidation of the macrocyclic dihydroxytriene **14** was examined under these more forcing conditions. However the major product was a 9:1 mixture of isomers of the bis-epoxide **24** in which the 7,8-double-bond had been epoxidised rather than the double-bond of the methylenecyclohexane, see Scheme 4.



Scheme 4 Epoxidation of the dihydroxytriene **14** under forcing conditions Reagents and conditions i, TBHP, $VO(acac)_2$, DCM, 60 °C microwave, 30 min (**15**, 13%; **24**, 31%).

Although these investigations into the epoxidation of 2-hydroxybicyclopentadecatrienes could have been continued, it was decided instead to look at a second aspect of the proposed synthesis of phomactin A **1**, namely the introduction of the C14 alcohol with the required configuration. Indeed alcohol **25** should be available by inverting the configuration of its epimer **13**. Following reductive desulfonylation and BOM-deprotection, epoxidation directed by the hydroxyl group at C2 would then give the epoxide **26**. This should be unstable with respect to isomerisation to the tetrahydropyran **27**,[8] a promising intermediate for a synthesis of phomactin A **1**, see Figure 5.

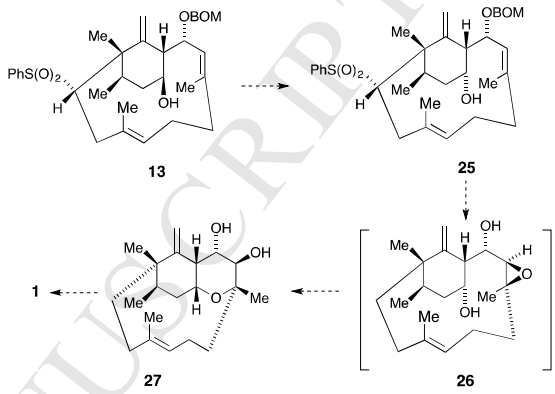
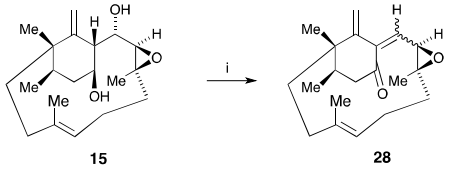


Figure 5 Proposed epoxidation of an inverted C14 alcohol

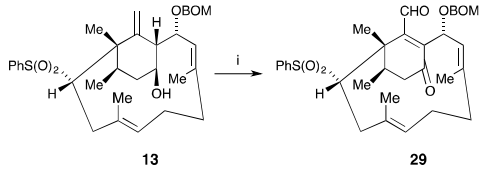
2.2 Oxidation of 14-alcohols using tetra-*n*-propylammonium perruthenate

Oxidation of the dihydroxyepoxide **15** was investigated first. In the event, Parikh-Doering conditions using the pyridine.SO_3 complex in dimethyl sulfoxide[12] did not give the expected diketone. Instead the major product was the dienone **28** identified from spectroscopic data. The geometry of the newly introduced double-bond was not confirmed, see Scheme 5.



Scheme 5 Oxidation of dihydroxyepoxide **15** Reagents and conditions i, $^{i}Pr_2NEt$, py.SO_3, DCM, DMSO, –7 °C, 5 min (50%).

Attempted oxidation of the conjugated diene **28** using singlet oxygen (O_2, Rose Bengal)[13] gave a mixture of products and reduction using several reagents was similarly inconclusive. Oxidation of the hydroxytriene **13** was therefore investigated since reduction of the resulting ketone away from the macrocyclic ring was expected to give the required inverted alcohol **25**, see Scheme 6. Oxidation of the alcohol **13** using pyridine.SO_3-DMSO gave unchanged starting material, the Dess Martin periodinane, pyridinium dichromate and pyridinium chlorochromate gave complex mixtures of products, and a Swern oxidation returned the starting material. However, oxidation using tetra-*n*-propylammonium perruthenate and *N*-methylmorpholine *N*-oxide[14] gave a single product isolated in a 78% yield and identified as the keto-aldehyde **29**, Scheme 6.



Scheme 6 Oxidation of the hydroxytriene **13** using TPAP Reagents and conditions i, TPAP (cat.), NMO, 4Å sieves, DCM, rt, 1 h (78%),

This oxidation of alcohol **13** has achieved several of the transformations needed for a synthesis of phomactin A **1**. Apart from the intended oxidation of the alcohol at C14, the double-bond migration and exocyclic carbon oxidation were the conversions it had been hoped to carry out by the elusive epoxidation of the methylenecyclohexane and isomerisation of the resulting epoxide. The only similar TPAP oxidations in the literature are the oxidations of derivatives of cholesterol **30** that give the enediones **31**.[15] However, good yields were only obtained for these reactions if they were promoted using ultrasound, see Figure 6.

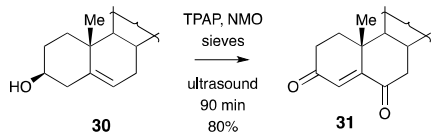
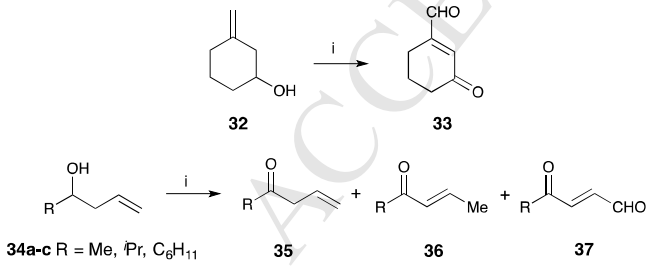


Figure 6 Ultrasound promoted oxidation of cholesterol using TPAP-NMO.

In our hands the efficient conversion of cholesterol **30** into the enedione **31** did not need ultrasound but was relatively slow (70% after 24 h). The oxidation of simpler homoallylic alcohols using TPAP-NMO was also very briefly investigated, Scheme 7. 3-Methylenecyclohexanol **32**[16] gave 3-formylcyclohex-2-enone **33**,[17] 54%, but only after 48 h. Oxidation of the open-chain homoallylic alcohols **34a-c** gave mixtures of the non-conjugated ketones **35**, together with the conjugated ketones **36** (for **24a**,**b**) and the ketoaldehydes **37**, when the reactions were carried out until no starting materials remained (8 – 94 h).



Scheme 7 TPAP-NMO oxidation of simple homoallylic alcohols Reagents and conditions i, TPAP, NMO, 4 Å sieves, DCM, rt (**33**, 48 h, 54%; **35a**, **36a**, **37a**, 8 h, 74%, 10%, 16%; **35b**, **36b**, **37b**, 24 h, 47%, 15%, 38%; **35c**, **36c**, **37c**, 94 h, 63%, 0%, 26%).

The oxidation of homoallylic alcohols to unsaturated ketoaldehydes using TPAP-NMO would seem to have some generality albeit better yields were obtained in our hands for the methylenecyclohexanols **13** and **32**. The mechanism of this reaction was not studied, but in the case of a 3-methylenecyclohexanol may involve the conversion of the initially formed non-conjugated ketone **38** into an enolate **39** that could be susceptible to further oxidation by ruthenium(VII) possibly *via* an intermediate **40** with final fragmentation to the ketoaldehyde **33**,[18] see Figure 7.

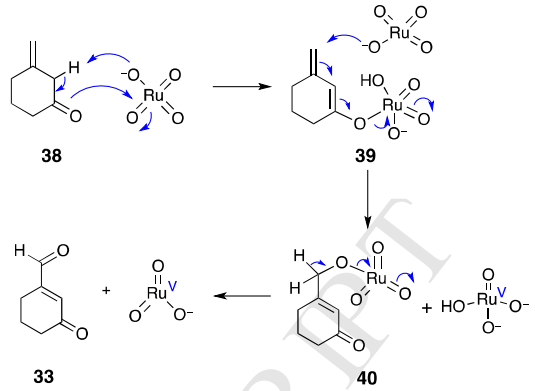


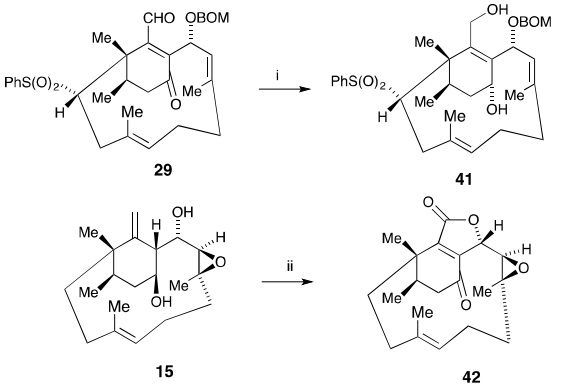
Figure 7 A rationalization of the TPAP-NMO oxidation of homoallylic alcohols.

To progress a synthesis of phomactin A **1**, the reduction of the ketoaldehyde **29** was investigated. A Luche reduction converted the aldehyde to the corresponding primary alcohol but only in a low yield. However, reduction with di-isobutylaluminium hydride was more efficient and gave the diol **41** that now has the required configuration at C14, in an acceptable yield of 66%. The configuration of the diol **41** at C14 was initially assigned on the basis that the hydride would approach the ketone on its less hindered face away from the phenylsulfonyl substituted macrocyclic ring. This assignment was supported by a significant nOe observed between the 12-methyl group and H-14 that suggested that the 14-hydroxyl group was on the opposite side of the six-membered ring from the 12-methyl group, Scheme 8.[19]

Deprotection of the BOM-protected dihydroxysulphone **41** followed by hydroxyl directed epoxidation would appear to be a useful way forward for a synthesis of phomactin A. However in his synthesis, Pattenden found that in some cases this epoxidation was accompanied by competing epoxidation of the tetrasubstituted 1,15-alkene.[8] Although by judicious choice of reaction conditions and substrate this side-reaction could be minimised, in our case, the 3,4-epoxide **15** had already been prepared and so its oxidation using TPAP-NMO was investigated. A single major product was isolated from this reaction but was identified as the ketolactone **42** not the expected ketoaldehyde, see Scheme 8. It would appear that the initially formed ketoaldehyde had suffered further oxidation, possibly of the hemiacetal derived from the 2-hydroxyl group and exocyclic aldehyde.[14a,20] Preliminary attempts to reduce this lactone led to mixtures of products that were not identified. To avoid formation of this lactone, the 2-hydroxyl group of the dihydroxyepoxide **15** would have to be protected before the TPAP-NMO oxidation is carried out. This work was more difficult than expected because of stereochemical issues and will be reported in full elsewhere.[7,21]

3. Summary and conclusions

This paper reports work on the later stages of a proposed synthesis of phomactin A **1**. Studies of the epoxidation of 2-hydroxy-15-methylenebicyclo[9.3.1]pentadeca-3,7-dienes confirmed the regio- and stereo-selective introduction of the 3,4-epoxide, but epoxidation of the exocyclic methylene group at C15 was only possible on earlier intermediates and gave rise to the formation of mixtures of stereoisomers during attempts to



Scheme 8 Further modification of advanced intermediates Reagents and conditions i, DIBAL-H, DCM, −78 °C, 1 h (66%); ii, TPAP (cat.), NMO, 4Å sieves, DCM, rt, 1 h (48%).

progress the synthesis. However, the oxidation of a 14-hydroxy-15-methylenebicyclo[9.3.1]pentadeca-3,7-diene using TPAP-NMO was very useful and gave a 14-oxobicyclo[9.3.1]pentadeca-1(15),3,7-triene-15-carboxaldehyde, a promising intermediate for the completion of the synthesis. The scope of this novel TPAP-NMO oxidation of homoallylic alcohols was briefly examined and found to be more useful for 3-methylenecyclohexanols than for open chain substrates. Its use may well depend on the propensity of the initally formed non-conjugated unsaturated ketone to undergo isomerisation to its enol tautomer although further work is required if the full potential of this reaction is to be realised. Nevertheless, this one-pot conversion of an unsaturated non-conjugated ketone into a conjugated keto-aldehyde is a novel reaction that may have other applications in synthesis. In the next phase of our work on the synthesis of phomactins, the TPAP-NMO oxidation was applied to other macrocyclic epoxides to avoid formation of lactones analogous to the ketolactone **42**.[21]

4. Experimental

4.1 General experimental details

Flash column chromatography was performed using Merck silica gel 60H. Light petroleum refers to the fraction boiling between 40 and 60 °C and was redistilled before use. Tetrahydrofuran was dried over sodium-benzophenone and distilled under nitrogen prior to use. Dichloromethane was dried over CaH_2 and distilled before use. Ether refers to diethyl ether. Reactions under non-aqueous conditions were carried out under an atmosphere of nitrogen or argon.

Mass spectra used electron impact ionisation (EI^+), chemical ionisation using ammonia (CI^+) or electrospray ionisation in the positive or negative modes (ES^+, ES^-). Low and high resolution mass spectra were recorded using Micromass Trio 200 and Kratos Concept IS spectrometers, respectively. Infra-red spectra were measured using a Genesis FTIR spectrometer on NaBr plates, either neat or as evaporated films. Nuclear magnetic resonance spectra were recorded using Bruker Ultrashield 500 (500 MHz) and Varian INOVA 400 (400 MHz) spectrometers. Coupling constants (*J*) are given in Hertz (Hz) and chemical shifts are relative to tetramethylsilane. Residual non-deuteriated solvent was used as the internal standard.

4.2 Experimental procedures

*4.2.1 (1*SR,*2*RS,*10*SR,*11*SR,*12*RS,*14*SR,*3*E,*7*E*)-10-Benzenesulfonyl-2-benzyloxymethoxy-4,8,11,12-tetramethyl-15-methylenebicyclo[9.3.1]pentadeca-3,7-dien-14-ol (**13**).* Tetra-*n*-butylammonium fluoride in THF (1 M, 16.6 mL, 16.6 mmol) was added to the *tert*-butyldiphenylsilyl ether **8** (0.67 g, 0.83 mmol) in THF (5.43 mL) at rt and the solution stirred at rt for 16 h. Water (13 mL) was added and the aqueous phase extracted with ethyl acetate (4 × 50 mL). The organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue (20:80 to 50:50 ether:light petroleum) gave the *title compound* **13** as a white foam (0.45 g, 95%), R_f = 0.13 (50:50 ether:light petroleum); ν_{max}/cm^{-1} 3513, 3063, 3030, 2932, 1662, 1620, 1448, 1383, 1301, 1268, 1143, 1024, 925, 736 and 697; δ_H (500 MHz, $CDCl_3$) 7.71-7.74 (2H, m, ArH), 7.19-7.46 (8H, m, ArH), 5.95 and 5.06 (each 1H, d, *J* 1.9, 15-CH), 4.98 (1H, dd, *J* 10.1, 2.2, 2-H), 4.81 (1H, d, *J* 10.1, 3-H), 4.63 and 4.62 (each 1H, d, *J* 6.6, OHC*H*O), 4.57 and 4.47 (each 1H, d, *J* 11.7, PhHC*H*), 4.13 (1H, m, 7-H), 3.54 (1H, m, 14-H), 3.25 (1H, m, 10-H), 3.11 (1H, dt, *J* 14.8, 8.8, 13-H), 3.01 (1H, dq, *J* 14.8, 7.3, 12-H), 2.72 (1H, dd, *J* 12.5, 2.2, 1-H), 2.30-2.38 (2H, m, 9-H_2), 1.73-1.90 (3H, m, 5-H_2, 6-H), 1.57 (1H, m, 6-H′), 1.54 (3H, s, 8-CH_3), 1.34 (3H, s, 11-CH_3), 1.25 (1H, m, 13-H′), 1.20 (1H, m, OH) 1.13 (3H, s, 4-CH_3) and 0.99 (1H, d, *J* 7.3, 12-CH_3); δ_C (125 MHz, $CDCl_3$) 145.9, 140.6, 138.4, 137.6, 133.2, 129.8, 128.7, 128.6, 128.4, 128.1, 127.6, 124.7, 120.4, 119.3, 92.2, 72.3, 69.6, 65.4, 62.7, 52.2, 49.4, 39.6, 38.8, 34.6, 34.3, 22.8, 22.2, 22.0, 17.3 and 16.2; *m/z* (ES^+) 587.5 (M^+ + 23, 100%); HRMS (ES^+): MNa^+, found 587.2798. $C_{34}H_{44}O_5SNa$ requires 587.2802.

*4.2.2 (1*SR,*2*RS,*11*SR,*12*RS,*14*SR,*3*E,*7*E*)-15-Methylene-4,8,11,12-tetramethylbicyclo[9.3.1]pentadeca-3,7-diene-2,14-diol (**14**).* The BOM-protected sulfone **13** (0.38 g, 0.68 mmol) in THF (8.09 mL) and anhydrous ethanol (55 μL) were added to liquid NH_3 (12.4 mL) at −78 ºC. Finely chopped sodium rinsed in light petroleum was added portionwise until the solution retained a blue colour. The cooling bath was then removed and the reaction allowed to reflux for 45 min. Solid NH_4Cl as added until the solution had lost the blue colour, the white residue was allowed to warm to rt, and the ammonia was allowed to evaporate. Tetrahydrofuran (5 mL) was added, the mixture was filtered through a pad of cotton wool and the filtrate was concentrated under reduced pressure. The solid residue was dissolved in water (5 mL) and the solution washed with ethyl acetate (5 × 2.5 mL) then added to the remaining residue from the filtration and the combined solution concentrated under reduced pressure. Chromatography of the residue (50:50 ether:light petroleum ether) gave the *title compound* **14** as an off white solid (0.16 g, 75%), R_f = 0.21 (100% ether), mp 147-149 ºC; ν_{max}/cm^{-1} 3368, 3082, 2961, 2920, 1660, 1624, 1447, 1381, 1074, 1020, 978, 903 and 733; δ_H (500 MHz, $CDCl_3$) 5.14 (1H, s, 15-CH), 5.07 (1H, d, *J* 8.5, 3-H), 5.00 (1H, s, 15-CH′), 4.60 (1H, m, 7-H), 4.14 (1H, m, 2-H), 4.04 (1H, m, 14-H), 2.34 (1H, br. s, 2-OH), 2.24 (1H, d, *J* 10.1, 1-H), 2.09-2.18 (2H, m, 6-H_2), 1.88-2.01 (3H, m, 5-H_2, 14-OH), 1.71-1.88 (3H, m, 9-H_2, 10-H), 1.58 (1H, dd, *J* 12.3, 6.6, 13-H), 1.47 (3H, s, 4-CH_3), 1.44 (3H, s, 8-CH_3), 1.28 (1H, dq, *J* 13.2, 6.6, 12-H), 1.17 (1H, m, 13-H′), 0.80 (3H, d, *J* 6.6, 12-CH_3), 0.73 (3H, s, 11-CH_3) 0.40 (1H, m, 10-H′); δ_C (125 MHz, $CDCl_3$) 149.4, 139.6, 136.7, 128.5, 125.2, 117.6, 71.4, 70.1, 64.3, 42.3, 39.2, 38.3, 37.0, 35.5, 33.3, 22.9, 16.6, 15.9(2) and 15.8; *m/z* (ES^+) 327.3 (M^+ + 23, 80%); HRMS (EI^+): M^+, found 304.2398. $C_{20}H_{32}O_2$ requires 304.2397.

*4.2.3 (1*SR,*2*SR,*3*RS,*5*RS,*12*SR,*13*RS,*15*SR,*8*E*)-5,9,12,13-Tetramethyl-16-methylene-4-oxatricyclo[10.3.1.0^{3,5}]hexadec-8-ene-2,15-diol (**15**). tert*-Butyl hydroperoxide (5.5 M in decane, 14 μL, 0.079 mmol) was added to dihydroxytriene **14** (20 mg, 0.065

mmol) and $VO(acac)_2$ (1.7 mg, 0.0065 mmol) in benzene (0.6 mL) at rt and the solution stirred at rt for 30 min. Saturated aqueous Na_2SO_3 (2-3 drops) was added and the mixture was stirred for 10 min, diluted with EtOAc (5 mL) and washed with saturated aqueous $NaHCO_3$ (5 mL). The aqueous phase was extracted with EtOAc (4 × 10 mL) and the organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue (70:30 ether:light petroleum) gave the *title compound* **15** as a white solid (18 mg, 85%), R_f = 0.43 (ether); ν_{max}/cm^{-1} 3430, 3082, 2960, 2924, 1622, 1450, 1384, 1244, 1204, 1077, 1037, 1015, 910, 872, 799, 731 and 678; δ_H (500 MHz, $CDCl_3$) 5.22 and 5.13 (each 1H, s, 16-CH), 4.78 (1H, dd, *J* 10.4, 1.3, 8-H), 4.14 (1H, m, 15-H), 3.47 (1H, br. d, *J* 11.0, 2-H), 2.99 (1H, s, 3-H), 2.60 (1H, s, 2-OH), 2.41 (1H, d, *J* 11.0, 1-H), 2.12 (1H, m, 7-H), 2.03 (1H, m, 6-H), 1.91-2.08 (2H, m, 7-H′, 15-OH), 1.83-1.91 (3H, m, 10-H_2, 11-H), 1.58 (1H, m, 14-H), 1.49 (3H, s, 9-CH_3), 1.32 (1H, m, 13-H), 1.18-1.27 (2H, m, 14-H′, 6-H′), 1.12 (3H, s, 5-CH_3), 0.87 (3H, d, *J* 6.9, 13-CH_3), 0.81 (1H, s, 12-CH_3) and 0.67 (1H, m, 11-H′); δ_C (125 MHz, $CDCl_3$) 148.4, 137.1, 124.0, 119.4, 71.1, 65.6, 63.8, 62.3, 42.6, 38.2, 37.8, 36.9, 36.5, 32.9, 29.7, 23.8, 19.2, 17.0, 16.0 and 15.7; *m/z* (ES^+) 343.3 (M^+ + 23, 60%); HRMS (EI^+): M^+, found 320.2346. $C_{20}H_{32}O_3$ requires 320.2346.

*4.2.4 (1*RS,*3*SR,*4*RS,*6*SR*)-3-Benzenesulfonylmethyl-6-*tert*-butyldiphenylsilyloxy-1-hydroxymethyl-3,4-dimethyl-2-oxiranylcyclohexane (**17**). meta*-Chloroperoxybenzoic acid (77% in mineral oil, 40 mg, 0.18 mmol) was added to the methylenecyclohexane **6** (50 mg, 0.088 mmol) in DCM (1.03 mL) at rt and the solution stirred at rt for 3 h. Dichloromethane (10 mL) was added and the solution washed with aqueous NaOH (0.1 M, 2 × 4 mL), water (8 mL) and brine (8 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue (60:40 ether:light petroleum) gave the *title compound* **17** as a glassy solid (45 mg, 85%), a 60:40 mixture of diastereoisomers (^{1}H NMR), R_f = 0.4 (70% ether in light petroleum); ν_{max}/cm^{-1} 3520, 3071, 2957, 2932, 2858, 1588, 1444, 1428, 1308, 1150, 1111, 911, 829, 735 and 704; δ_H (500 MHz, $CDCl_3$) 7.74-7.77 (2H, m, ArH), 7.60-7.66 (4H, m, ArH), 7.54 (1H, m, ArH), 7.43-7.47 (2H, m, ArH), 7.27-7.41 (6H, m, ArH), 3.84-3.90 (1.6H, m, 6-H, 1-CH), 3.71 (0.4H, m, 1-CH′), 3.70 (0.6H, dd, *J* 11.7, 2.4, 1-CH′), 3.64 (0.4H, m, 6-H), 3.36 (0.4H, m, OH), 3.21 (0.6H, d, *J* 2.4, 2-CH), 3.16 (0.4H, s, 2-CH), 3.15 (0.6H, d, *J* 2.4, 2-CH′), 2.88 (0.4H, d, *J* 2.0, 2-CH′), 2.84 (0.4H, d, *J* 15.3, 3-CH), 2.83 (0.6H, d, *J* 15.3, 3-CH), 2.78 (0.4H, d, *J* 15.3, 3-CH′), 2.55 (0.6H, d, *J* 15.3, 3-CH′), 2.34 (0.4H, m, 1-H), 2.17 (0.6H, m, 1-H), 1.90 (0.4H, m, 4-H), 1.61 (0.6H, br s, OH), 1.53 (0.4H, dt, *J* 13.3, 4.3, 5-H), 1.34-1.42 (4H, m, 5-H, 5-H′, 3-CH_3), 1.14-1.22 (1.2H, m 5-H′, 4-H), 0.97 [9H, s, $SiC(CH_3)_3$], 0.8 (1.2H, d, *J* 6.3, 4-CH_3) and 0.67 (1.8H, d, *J* 6.7, 4-CH_3); *m/z* (ES^+) 596.4 (M^+ + 18, 100%); HRMS (ES^+): MNH_4^+, found 596.2853. $C_{33}H_{46}O_5NSSi$ requires 596.2860.

*4.2.5 (1RS,2RS,3SR,4RS,6SR)- and (1RS,2SR,3SR,4RS,6SR)-3-Benzenesulfonylmethyl-6-*tert*-butyldiphenylsilyloxy-3,4-dimethyl-2-oxiranylcyclohexanecarbaldehydes (**18**) and (**19**).* Di-isopropylethylamine (0.205 mL, 1.17 mmol) was added to a mixture of isomers of the hydroxyepoxide **17** (140 mg, 0.27 mmol) in DCM (1 mL) at rt and the solution cooled to 0 ºC before the addition of the pyridine.SO_3 (0.127 mg, 0.803 mmol) in DMSO (1.1 mL). The solution was stirred at 0 ºC for 15 min and then poured into brine (3.5 mL). The aqueous phase was extracted into ethyl acetate (3 × 15 mL) and the organic extracts were washed with saturated aqueous $CuSO_4$ (50 mL), water (50 mL) and brine (50 mL), then dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue (50:50 ether:light petroleum) gave the *title compound* **18** as a white solid (55 mg, 40%), mp 154-156 ºC, R_f = 0.49 (50:50 ether:light petroleum); ν_{max}/cm^{-1} 3069, 2933, 2859, 1729, 1468, 1449, 1313, 1150, 1109, 1041, 912, 825 and 739; δ_H (500 MHz, $CDCl_3$) 9.22 (1H, d, *J* 4.4, CHO), 7.84-7.89 (2H, m, ArH), 7.63-7.72 (5H, m, ArH), 7.54-7.59 (2H, m, Ar-H), 7.39-7.49 (6H, m, ArH), 4.37 (1H, td, *J* 10.7, 4.8, 6-H), 3.24 (1H, d, *J* 2.4, 2-CH), 2.95 (1H, d, *J* 15.9, 3-CH), 2.89 (1H, dd, *J* 10.7, 4.4, 1-H), 2.67 (1H, d, *J* 15.9, 3-CH′), 2.60 (1H, d, *J* 2.4, 2-CH′), 1.69 and 1.54 (each 1H, m, 5-H), 1.48 (3H, s, 3-CH_3), 1.44 (1H, m, 4-H), 1.03 [9H, s, $SiC(CH_3)_3$] and 0.98 (3H, d, *J* 6.1, 4-CH_3); δ_C (125 MHz, $CDCl_3$) 203.4, 141.7, 136.2, 136.1, 134.2, 133.9, 133.1, 130.4, 130.1, 129.6, 128.1, 127.9, 127.7, 69.8, 61.8, 56.6, 56.0, 47.6, 42.4, 37.6, 37.0, 27.1, 19.4, 16.6 and 13.7. The second fraction was the *title compound* **19** as a white solid, (35 mg, 25%), R_f = 0.41 (50:50 ether:light petroleum); ν_{max}/cm^{-1} 3069, 2930, 2857, 1729, 1466, 1451, 1314, 1151, 1109, 1039, 911, 825 and 737; δ_H (500 MHz, $CDCl_3$) 9.51 (1H, d, *J* 3.0, CHO), 7.83-7.87 (2H, m, ArH), 7.68-7.74 (4H, m, ArH), 7.65 (1H, m, ArH), 7.55-7.60 (2H, m, ArH), 7.41-7.52 (6H, m, ArH), 4.38 (1H, td, *J* 8.9, 4.6, 6-H), 3.27 (1H, dd, *J* 2.4, 1.0, 2-CH), 2.96 (1H, d, *J* 13.5, 3-CH), 2.89 (1H, m, 1-H), 2.89 (1H, d, *J* 13.5, 3-CH′), 2.75 (1H, d, *J* 2.4, 2-CH′), 2.07 (1H, m, 4-H), 1.76 (1H, dt, *J* 13.5, 4.5, 5-H), 1.59 (1H, m, 5-H′), 1.23 (3H, s, 3-CH_3), 1.09 (3H, d, *J* 6.5, 4-CH_3) and 1.06 [9H, s, $SiC(CH_3)_3$]; δ_C (125 MHz, $CDCl_3$) 200.8, 142.0, 136.2, 136.1, 134.2, 133.9, 133.4, 130.3, 130.1, 129.7, 128.1, 127.9, 127.6, 69.0, 60.7, 59.1, 59.2, 49.0, 44.0, 37.8, 34.6, 27.1, 19.4, 17.7 and 17.5; *m/z* (ES^+) 599 (M^+ + 23, 80%) and 179 (100); HRMS (ES^+): MNa^+, found 599.2256. $C_{33}H_{40}O_5SSiNa$ requires 599.2258.

*4.2.6 (1*RS,*3*SR,*4*RS,*6*SR*)-1-[(1*SR,*2*RS,*3*RS,*6*E*)-8-*tert*-Butyldimethylsilyloxy-3,7-dimethyl-2,3-epoxy-1-hydroxyoct-6-en-1-yl]-3-benzenesulfonylmethyl-6-*tert*-butyldiphenylsilyloxy-3,4-dimethyl-2-methylenecyclohexane (**21**). tert*-Butyl hydroperoxide (5.5 M in decane, 20 μL, 0.108 mmol) was added to the hydroxytriene **7** (20 mg, 0.024 mmol) and $VO(acac)_2$ (1 mg, 0.004 mmol) in benzene (0.18 mL) at rt and the solution was stirred at rt for 10 min. Saturated aqueous Na_2SO_3 (2-3 drops) was added and the mixture was stirred for 10 min then diluted with EtOAc (5 mL) and washed with saturated aqueous $NaHCO_3$ (5 mL). The aqueous phase was extracted with EtOAc (4 × 10 mL) and the organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography of the residue (70:30 ether:light petroleum) gave the *title compound* **21** as a white foam (16 mg, 78%) containing 10% of a minor isomer (^{1}H NMR), R_f = 0.50 (50:50 ether:light petroleum); ν_{max}/cm^{-1} 3479, 3071, 2957, 2931, 1631, 1589, 1462, 1448, 1428, 1309, 1255, 1149, 1108, 1083, 910, 837, 776, 741 and 704; δ_H (500 MHz, $CDCl_3$) 7.76-7.79 (2H, m, ArH), 7.61-7.65 (4H, m, ArH), 7.52 (1H, m, ArH), 7.43-7.46 (2H, m, ArH), 7.28-7.37 (6H, m, ArH), 5.25 (1H, m, 6′-H), 5.19 and 5.04 (each 1H, s, 2-CH), 4.09 (1H, m, 6-H), 3.94 (2H, s, 8′-H_2), 3.70 (1H, m, 1′-H), 3.42 and 3.34 (each 1H, d, *J* 14.5, 3-CH), 2.66 (1H, d, *J* 6.3, 2′-H), 2.52 (1H, m, 1-H), 2.26 (1H, d, *J* 3.8, OH), 1.95 (2H, m, 5′-H_2), 1.75 (1H, m, 4-H), 1.67 (1H, dt, *J* 14.2, 4.41, 5-H), 1.51 (3H, s, 7′-CH_3), 1.45 (1H, m, 5-H′), 1.32 (3H, s, 3′-CH_3), 1.31-1.34 (2H, m, 4′-CH_2), 1.16 (3H, s, 3-CH_3), 0.95 and 0.84 [each 9H, s, $SiC(CH_3)_3$], 0.79 (3H, d, *J* 6.9, 4-CH_3) and 0.00 (6H, s, 2 × $SiCH_3$); δ_C (125 MHz, $CDCl_3$) 149.6, 142.5, 135.9(2), 134.9, 134.1, 133.7, 133.3, 129.8, 129.2, 127.7, 127.6, 127.3, 123.4, 71.4, 70.2, 68.5, 65.0, 62.4, 43.9, 38.1, 36.3, 27.0, 26.0, 23.1, 21.3, 19.2, 18.4, 17.1, 16.7, 13.5 and −5.2; *m/z* (ES^-) 867.5 ($[M + 35]^-$, 65%) and 865.5 ($[M + 35]^-$, 100): HRMS (ES^+): MNa^+, found 853.4335. $C_{48}H_{70}O_6SSi_2Na$ requires 853.4324.

*4.2.7 (1*RS,*3*SR,*4*RS,*6*SR*)-1-[(1*SR,*2*RS,*3*RS*)-8-*tert*-Butyldimethylsilyloxy-3,7-dimethyl-2,3,6,7-bisepoxy-1-hydroxyoct-1-yl]-3-benzenesulfonylmethyl-6-*tert*-

*butyldiphenylsilyloxy-3,4-dimethyl-2-methylenecyclohexane (**22**).* *meta*-Chloroperoxybenzoic acid (77% in mineral oil, 7 mg, 0.029 mmol) was added to the hydroxytriene **7** (20 mg, 0.025 mmol) in DCM (0.36 mL) at rt and the solution was stirred at rt for 1.5 h. More *meta*-chloroperoxybenzoic acid (77% in mineral oil, 3 mg, 0.013 mmol) was added and the solution stirred at rt for 1 h. Dichloromethane (5 mL) was added and the solution washed with aqueous NaOH (0.1 M, 2 × 4 mL), water (4 mL) and brine (4 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue (30:70 ether:light petroleum) gave the monoepoxide **21** (3.5 mg, 15%) followed by the *title compound* **22** as a white foam (9 mg, 48%), a 55:45 mixture of diastereoisomers with other very minor isomers (^{1}H NMR), R_f = 0.24 (70:30 ether: light petroleum); ν_{max}/cm^{-1} 3477, 3071, 2957, 2930, 2857, 1726, 1631, 1588, 1470, 1448, 1428, 1387, 1308, 1256, 1106, 1085, 909, 838, 778, 742 and 704; δ_H (500 MHz, $CDCl_3$) 7.77-7.80 (2H, m, ArH), 7.62-7.66 (4H, m, ArH), 7.54 (1H, m, ArH), 7.44-7.47 (2H, m, ArH), 7.30-7.38 (6H, m, ArH), 5.20 and 5.02 (each 1H, s, 2-CH), 4.10 (1H, m, 6-H), 3.74 (1H, m, 1′-H), 3.51-3.52 (2H, m, 8′-H_2), 3.41 and 3.35 (each 1H, d, *J* 14.5, 3-CH), 2.70-2.76 (2H, m, 2′-H, OH), 2.54 (1H, m, 1-H), 2.40 (0.55H, m, 6′-H), 2.34 (0.45H, m, 6′-H), 1.73 (1H, m, 4-H), 1.67 (1H, dt, 14.2, 4.7, 5-H), 1.35-1.51 (5H, m, 5-H′, 4′-H_2, 5′-H_2), 1.32 (3H, s, 3-CH_3), 1.18-1.20 (6H, m, 3′-CH_3, 7′-CH_3), 0.96 and 0.83 [each 9H, s, $SiC(CH_3)_3$], 0.78 (3H, d, *J* 6.6, 4-CH_3) and −0.01 and −0.02 (each 3H, s, $SiCH_3$); *m/z* (ES^+) 869.8 (M^+ + 23, 100%); HRMS (ES^+): MNa^+ found 869.4271. $C_{48}H_{70}O_7SSi_2Na$ requires 869.4273.

*4.2.8 (1*RS,*3*SR,*4*RS,*6*SR*)-1-[(1*SR,*2*RS,*3*RS,*6*E*)-8-*tert-*Butyldimethylsilyloxy-3,7-dimethyl-2,3-epoxy-1-hydroxyoct-6-en-1-yl]-3-benzenesulfonylmethyl-6-*tert-*butyldiphenylsilyloxy-3,4-dimethyl-2-oxiranylcyclohexane (**23**).* *tert*-Butyl hydroperoxide (5.5 M in decane, 44 μL, 0.245 mmol) was added to the hydroxytriene **7** (20 mg, 0.024 mmol) and $VO(acac)_2$ (1 mg, 0.004 mmol) in DCM (0.2 mL) at rt and the solution heated at 60 ºC in a microwave reactor for 1 h. Saturated aqueous Na_2SO_3 (2-3 drops) was added, the mixture was stirred at rt for 10 min, and EtOAc (5 mL) was added. The solution washed with saturated aqueous $NaHCO_3$ (5 mL) and the aqueous phase was extracted with EtOAc (4 × 10 mL). The organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography of the residue (20:80 to 30:70 ether:light petroleum) gave the *title compound* **23** as yellow gum (12 mg, 57%); R_f = 0.22 (50:50 ether:light petroleum); ν_{max}/cm^{-1} 3483, 3071, 2957, 2930, 2857, 1726, 1686, 1588, 1462, 1447, 1428, 1388, 1320, 1253, 1152, 1110, 1084, 837, 778, 741 and 704; δ_H (500 MHz, $CDCl_3$) 7.77-7.67 (6H, m, ArH), 7.53 (1H, m, ArH), 7.44-7.47 (2H, m, ArH), 7.41-7.31 (6H, m, ArH), 5.30 (1H, m, 6′-H), 4.12 (1H, dt, *J* 10.4, 4.4, 6-H), 3.95 (2H, s, 8′-H_2), 3.38 (1H, m, 1′-H), 3.32 (1H, m, 2′-H), 3.04 (1H, m, 2-CH), 2.91-2.95 (2H, m, 2-CH′, 3-CH), 2.84 (1H, d, *J* 14.8, 3-CH′), 2.05-2.11 (3H, m, 1-H, 5′-H_2), 1.74 (1H, m, 4-H), 1.53 (3H, s, 7′-CH_3), 1.39-1.60 (4H, m, 5-H_2, 4′-H_2), 1.24 (3H, s, 3′-CH_3), 0.98 and 0.85 [each 9H, s, $SiC(CH_3)_3$], 0.84 (3H, s, 3-CH_3), 0.76 (3H, d, *J* 6.9, 4-CH_3) and 0.00 (6H, s, 2 × $SiCH_3$); δ_C (125 MHz, $CDCl_3$) 142.2, 135.8, 135.7, 135.1, 134.5, 133.4, 133.0, 130.0, 129.7, 129.3, 127.9, 127.6, 127.3, 123.3, 68.5, 67.4, 66.7, 61.7, 61.1, 60.4, 49.1, 43.9, 38.7, 29.7, 27.1, 26.6, 26.0, 25.8, 25.7, 23.5, 19.3, 18.4, 17.2, 16.7, 13.5 and −5.2; *m/z* (ES^+) 906.2 (100%) and 869.7 (M^+ + 23, 82); HRMS (ES^+): MNa^+ found 869.4294. $C_{48}H_{70}O_7SSi_2Na$ requires 869.4273.

*4.2.9 (1SR,2SR,3*RS,*5*RS,*13SR,14RS,16SR)-5,10,13,14-Tetramethyl-17-methylene-4,9-bis-oxatetracyclo[11.3.1.0^{3,5}.0^{8,10}]heptadecane-2,16-diol (**24**).* Following the procedure outlined for the synthesis of the bis-epoxide **23**, the dihydroxytriene **14** (20 mg, 0.064 mmol), $VO(acac)_2$ (2.6 mg, 0.010 mmol) in DCM (0.53 mL) and *tert*-butyl hydroperoxide (5.5 M in decane, 0.12 mL, 0.66 mmol), after heating in a microwave reactor at 60 ºC for 0.5 h and chromatography (70:30 to 80:20 ether:light petroleum), gave firstly the monoepoxide **15** as a thin clear film (3 mg, 13%) containing *ca*. 25% of a minor diastereoisomer, R_f = 0.42 (ether); HRMS (EI^+): M^+, found 320.2346. $C_{20}H_{32}O_3$ requires 320.2346. The second fraction was the *title compound* **24** as a white foam (7 mg, 31%), a 9:1 mixture of diastereoisomers (^{1}H NMR), R_f = 0.24 (ether); ν_{max}/cm^{-1} 3436, 3082, 2960, 2929, 2360, 1722, 1625, 1453, 1422, 1387, 1304, 1249, 1075, 1027, 917, 796 and 732; δ_H (500 MHz, $CDCl_3$) major diastereoisomer 5.12 and 5.00 (each 1H, s, 17-CH), 4.30 (1H, dd, *J* 10.7, 7.2, 16-H), 3.56 (1H, dd, *J* 11.7, 4.4, 2-H), 2.96 (1H, d, *J* 4.4, 3-H), 2.65 (1H, s, 2-OH), 2.39 (1H, m, 1-H), 2.38 (1H, d, *J* 9.4, 8-H), 2.19 (1H, dt, *J* 13.6, 3.5, 15-H) 1.80-1.90 (3H, m, 11-H, 7-H_2), 1.63-1.68 (3H, m, 11-H′, 6-H_2), 1.52 (1H, s, 16-OH), 1.39 (1H, m, 14-H), 1.26 (1H, m, 15-H′), 1.19 (3H, s, 10-CH_3), 1.15 (3H, s, 5-CH_3), 0.97 (1H, dd, *J* 13.0, 9.8, 12-H), 0.84 (3H, d, *J* 6.9 14-CH_3), 0.74 (3H, s, 13-CH_3), 0.57 (1H, dd, *J* 13.0, 9.8, 12-H′); minor diastereoisomer 5.22 and 5.03 (each 1H, s, 17-CH), 4.20 (1H, m, 16-H) and 3.66 (1H, m, 2-H); *m/z* (ES^+) 359.4 (M^+ + 23, 100%); HRMS (ES^+): MNa^+, found 359.2201. $C_{20}H_{32}O_4Na$ requires 359.2193.

*4.2.10 (3RS,5RS,12SR,13RS,8E)-5,9,12,13-Tetramethyl-16-methylene-4-oxatricyclo[10.3.1.0^{3,5}]hexadeca-1,8-dien-15-one (**28**).* Di-isopropylethylamine (35 μL, 0.21 mmol) was added to the dihydroxyepoxide **15** (15 mg, 0.046 mmol) in DCM (0.17 mL) at rt, the solution was cooled to to −7 ºC, and the pyridine.SO_3 complex (30 mg, 0.19 mmol) was added in DMSO (0.19 mL). The reaction mixture was stirred at −7 º for 5 min then poured into brine (3 mL). The aqueous phase was extracted with EtOAc (4 × 6 mL) and the organic extracts washed with saturated aqueous $CuSO_4$ (10 mL), water (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (80:20 ether:light petroleum to ether) gave the *title compound* **28** as a clear colourless oil (7 mg, 50%); ν_{max}/cm^{-1} 2918, 2851, 1694, 1618, 1453, 1384, 1230, 1183, 1062, 908 and 863; δ_H (500 MHz, $CDCl_3$) 6.01 (1H, d, *J* 9.8, 2-H), 5.36 and 5.03 (each 1H, s, 16-CH), 4.85 (1H, m, 8-H), 3.61 (1H, d, *J* 9.8, 3-H), 2.72 (1H, dd, *J* 16.7, 5.7, 14-H), 2.22 (1H, dd, *J* 16.7, 3.2, 14-H′), 2.09-2.17 (2H, m, 7-H, 10-H), 2.05 (1H, dt, *J* 12.9, 3.5, 11-H), 1.98 (1H, m, 10-H′), 1.91 (1H, dt, *J* 10.1, 4.1, 7-H′) 1.78 (1H, dqd, *J* 13.6, 6.9, 3.2, 13-H), 1.71 (1H, dt, *J* 13.9, 4.1, 6-H), 1.50 (1H, m, 6-H′), 1.48 (3H, s, 9-CH_3), 1.14 (3H, s, 5-CH_3), 1.05 (1H, m, 11-H′), 1.05 (3H, s, 12-CH_3) and 0.84 (3H, d, *J* 6.9, 13-CH_3); δ_C (125 MHz, $CDCl_3$), 199.1, 144.2, 143.8, 134.9, 133.4, 123.8, 114.3, 62.7, 59.2, 43.2, 38.1, 37.8, 34.1, 33.2, 28.7, 23.4, 19.2, 16.0, 15.2 and 14.3; *m/z* (ES^+) 301 (M^+ + 1, 100%); HRMS (EI^+): M^+, found 300.2085. $C_{20}H_{28}O_2$ requires 300.2084.

*4.2.11 (2*RS,*10*SR,*11*SR,*12*RS,*3*E,*7*E*)-10-Benzenesulfonyl-2-benzyloxymethoxy-4,8,11,12-tetramethyl-14-oxobicyclo[9.3.1]pentadeca-1(15),3,7-triene-15-carbaldehyde (**29**).* *N*-Methylmorpholine-*N*-oxide (10 mg, 0.088 mmol) was added to a suspension of the alcohol **13** (10 mg, 0.017 mmol) and 4Å molecular sieves (8 mg) in DCM (0.41 mL) and the mixture was stirred for 10 min at rt. Tetra-*n*-propylammonium perruthenate (1 mg, 0.0026 mmol) in DCM (0.1 mL) was added and the mixture stirred for 1 h. Dichloromethane (1 mL) was added and the mixture was filtered through celite with copious washings of ether. The filtrate was washed with aqueous $Na_2S_2O_3$ (20 mL) and brine (20 mL), and the aqueous layer was extracted with ether (1 × 30 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the

residue (40:60 ether:light petroleum) gave the *title compound* **29** as a yellow viscous oil (8 mg, 78%), R_f = 0.39 (40:60 ether:light petroleum); ν_{max}/cm^{-1} 3066, 2923, 1675, 1449, 1303, 1146, 1026, 911 and 729; δ_H (500 MHz, $CDCl_3$) 10.58 (1H, s, 15-CHO), 7.8-7.82 (2H, m, ArH), 7.57 (1H, m, ArH), 7.47-7.50 (2H, m, ArH), 7.19-7.29 (5H, m, ArH), 5.76 (1H, d, *J* 9.5, 2-H), 4.98 (1H, d, *J* 9.5, 3-H), 4.69 and 4.63 (each 1H, d, *J* 6.9, OHC*H*O), 4.57 (1H, m, 7-H), 4.48 and 4.43 (each 1H, d, *J* 11.7, PhHC*H*), 3.61 (1H, m, 12-H), 3.43 (1H, d, *J* 6.6, 10-H), 3.13 (1H, dd, *J* 16.7, 7.3, 9-H), 3.08 (1H, dd, *J* 19.9, 5.7, 13-H), 2.44 (1H, d, *J* 16.7, 9-H′), 2.41 (1H, dd, *J* 19.9, 5.7,13-H′), 1.98 (1H, m, 6-H), 1.85-1.94 (2H, m, 5-H_2), 1.74 (1H, m, 6-H′), 1.53 (3H, s, 8-CH_3), 1.39 (3H, s, 4-CH_3), 0.98 (3H, d, *J* 7.0,12-CH_3) and 0.47 (3H, s, 11-CH_3); δ_C (125 MHz, $CDCl_3$) 197.8, 197.2, 151.0, 146.9, 139.9, 138.2, 137.5, 133.9, 131.2, 129.6, 129.3, 129.0, 128.4, 128.0, 127.8, 126.2, 92.8, 69.7, 67.7, 65.0, 46.34, 42.2, 38.1, 35.8, 35.4, 25.6, 21.0, 16.5, 15.7 and 13.5; *m/z* (ES$^+$) 594.5 (M$^+$ + 18, 100%); HRMS (ES$^+$): MNH_4^+, 594.2887. $C_{34}H_{44}O_6NS$ requires 594.2884.

*4.2.12 Cyclohex-2-en-1-one-3-carbaldehyde (**33**).*[17] 4Å Molecular sieves (450 mg), NMO (370 mg, 3.12 mmol) and TPAP (50 mg, 0.14 mmol) were added to 3-methylenecyclohexanol **32**[16] (100 mg, 0.89 mmol) in dichloromethane (10 mL) and the resulting mixture was stirred at rt for 84 h then filtered through a short pad of silica (DCM). After concentration under reduced pressure, chromatography of the residue (30:70 to 50:50 ether:light petroleum) gave the title compound **33**[17] as a white solid (60 mg, 0.48 mmol, 54%), R_f = 0.42 (25:75 EtOAc:light petroleum); δ_H (400 MHz, $CDCl_3$) 9.79 (1H, s, CHO), 6.56 (1H, t, *J* 1.7, 2-H), 2.53-2.57 (2H, m, 4-H_2), 2.50 (2H, m, 6-H_2) and 2.08 (2H, quintet, *J* 6.5, 5-H_2); δ_C (125 MHz, $CDCl_3$) 200.5, 194.5, 154.5, 139.5, 38.6, 21.8 and 21.5; *m/z* (EI$^+$) 124 (M$^+$, 100%).

The same procedure with reaction times as indicated in the text gave mixtures of products as outlined in Scheme 7; **37a** (16%); δ_H (400 MHz, $CDCl_3$) 9.81 (1H, d, *J* 7.1, 5-H), 6.85 (1H, d, *J* 16.6, 3-H), 6.76 (1H, dd, *J* 16.6, 7.1, 4-H) and 2.4 (3H, s, 1-H_3); **37b** (38%); δ_H (400 MHz, $CDCl_3$) 9.78 (1H, d, *J* 7.3, 6-H), 6.99 (1H, d, *J* 16.1, 4-H), 6.82 (1H, dd, *J* 16.1, 7.3, 5-H), 2.95 (1H, sept, *J* 6.8, 2-H) and 1.12 (6H, d, *J* 6.8, 1-H_3, 2-CH_3); **37c** (28 mg, 0.17 mmol, 26%) as a white solid, R_f = 0.32 (30:70 ether:light petroleum); ν_{max}/cm^{-1} 2927, 2854, 1705, 1692, 1449, 1375, 1061, 977, 734, 701, 684, 653 and 617; δ_H (400 MHz, $CDCl_3$) 9.79 (1H, d, *J* 7.3, 4-H), 6.99 (1H, d, *J* 15.9, 2-H), 6.83 (1H, dd, *J* 15.9, 7.6, 3-H), 2.69 (1H, tt, *J* 10.9, 3.3, 1′-H) and 1.2-1.9 (10H, m); *m/z* (EI$^+$) 166 (M$^+$, 100%).

*4.2.13 (2*RS,*10*SR,*11*SR,*12*RS,*14*RS,*3*E,*7*E*)-10-Benzenesulfonyl-2-benzyloxymethoxy-15-hydroxymethyl-4,8,11,12-tetramethylbicyclo[9.3.1]pentadeca-1(15),3,7-trien-14-ol (**41**).* Di-isobutylaluminium hydride (54 µL, 0.054 mmol) was added to the keto-aldehyde **29** (9 mg, 0.0156 mmol) in DCM (0.3 mL) at −78 ºC and the solution stirred at −78 °C for 1 h. Methanol was added and the mixture stirred at at −78 ºC for 10 min then allowed to warm to rt. Aqueous Rochelle's salt (5%, 0.5 mL) and EtOAc (0.5 mL) were added and the mixture was stirred for 20 min then diluted with water (1 mL). The aqueous phase was extracted with EtOAc (4 × 2 mL) and the organic extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue (30:70 to 80:20 ether:light petroleum) gave the *title compound* **41** as a viscous oil (6 mg, 66%), R_f = 0.48 (80:20 ether:light petroleum); ν_{max}/cm^{-1} 3500, 2916, 2848, 1446, 1386, 1295, 1146, 1083, 1023, 909 and 727; δ_H (500 MHz, $CDCl_3$) 7.80-7.82 (2H, m, ArH), 7.55 (1H, m, ArH),7.45-7.49 (2H, m, ArH), 7.24-7.31 (5H, m, ArH), 5.53 (1H, dd, *J* 8.5, 0.6, 3-H), 5.10 (1H, d, *J* 8.5, 2-H), 4.73 (1H, m, 7-H), 4.71 and 4.67 (each 1H, d, *J* 6.9, OHC*H*O), 4.67 (1H, m, 15-CH), 4.59 and 4.48 (each 1H, d, *J* 12.0, PhHC*H*), 4.09 (1H, m, 14-H), 3.93 (1H, t, *J* 12.0, OH) 3.63 (1H, d, *J* 6.6, 10-H), 3.45 (1H, dd, *J* 11.3, 1.6, 15-CH′), 3.19 (1H, m, 12-H), 2.44 (1H, d, *J* 17.0, 9-H), 2.14 (1H, dd, *J* 17.0, 7.9, 9-H′), 2.09 (1H, m, 6-H), 1.93-2.04 (4H, m, 5-H_2, 13-H_2), 1.82 (1H, m, 6-H′), 1.58 (3H, s, 8-CH_3), 1.49 (3H, s, 4-CH_3), 1.20 (1H, m, 14-OH), 0.92 (1H, d, *J* 6.9, 12-CH_3) and 0.66 (3H, s, 11-CH_3); δ_C (125 MHz, $CDCl_3$), 142.5, 141.9, 140.3, 137.8, 137.6, 133.5, 131.7, 129.2, 128.8, 128.6, 127.9, 127.8, 125.3(2), 92.4, 72.9, 69.9, 68.1, 66.0, 60.4, 45.9, 39.1, 37.0, 36.6, 26.2, 19.2, 16.2, 15.9 and 13.8; *m/z* (ES$^+$) 603.0 (M$^+$ + 23, 100%); HRMS (ES$^+$): MNa^+, 603.2760. $C_{34}H_{44}O_6SNa$ requires 603.2751.

*4.2.14 (4*SR,*5*RS,*7*RS,*14*SR,*15*RS,*10*E*)-7,11,14,15-Tetramethyl-3,6-bis-oxatetracyclo[12.4.0^{4,18}.0^{5,7}]octadeca-1(18),10-diene-2,17-dione (**42**).* Following the procedure outlined for the synthesis of the keto-aldehyde **29**, the epoxydiol **15** (10 mg, 0.031 mmol), 4Å molecular sieves (8 mg), TPAP (2 mg, 0.05 mmol) and NMO (18 mg, 0.16 mmol) in DCM (0.8 mL), after chromatography (40:60 ether:light petroleum), gave the *title compound* **42** as a white viscous oil (4 mg, 48%), R_f = 0.79 (50:50 ether:light petroleum); ν_{max}/cm^{-1} 2918, 2850, 1766, 1694, 1455, 1392, 1262, 1158, 1047, 912, 870, 792 and 731; δ_H (500 MHz, $CDCl_3$) 4.94 (1H, d, *J* 6.6, 4-H), 4.85 (1H, m, 10-H), 2.69 (1H, ddd, *J* 15.8, 13.6, 2.5, 12-H), 2.61 (1H, ddq, *J* 18.9, 13.2, 6.9, 15-H), 2.50 (1H, d, *J* 6.6, 5-H), 2.33-2.40 (2H, m, 16-H_2), 2.29 (1H, m, 12-H′), 1.90 (1H, m, 13-H), 1.89 (1H, ddd, *J* 15.8, 5.0, 2.5, 8-H), 1.77 and 1.67 (each 1H, m, 9-H), 1.54 (1H, dd, *J* 5.3, 2.2, 13-H′), 1.48 (4H, m, 8-H′, 11-CH_3), 1.33 (1H, s, 7-CH_3), 1.16 (1H, s, 14-CH_3) and 0.97 (1H, d, *J* 6.9, 15-CH_3); *m/z* (ES$^+$) 353.2 (M$^+$ + 23, 100%); HRMS (ES$^+$): MH$^+$, 331.1917. $C_{20}H_{27}O_4$ requires 331.1904.

4.3. X-ray data.

X-ray data for epoxyaldehyde **18** were collected at a temperature of 100 K using a using Mo-K_α radiation on an Oxford X'calibur diffractometer, equipped with an Oxford Cryosystems Cobra nitrogen flow gas system. Data were measured using CrysAlisPro suite of programs. Absorption correction was performed using empirical methods based upon symmetry-equivalent reflections combined with measurements at different azimuthal angles. The crystal structure was solved and refined against all F^2 values using the SHELXL and OLEX 2 suite of programs. Atoms were refined anisotropically. Hydrogen atoms were placed in calculated positions refined using idealized geometries (riding model) and assigned fixed isotropic displacement parameters.

Empirical formula	$C_{33}H_{40}O_5SSi$
Formula weight	576.80
Temperature/K	100
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	7.9940(9)
b/Å	16.6550(18)
c/Å	22.846(2)
α/°	90
β/°	93.232(2)
γ/°	90
Volume/Å^3	3036.9(6)
Z	4
ρ_{calc}g/cm^3	1.262
µ/mm^{-1}	0.186
F(000)	1232.0
Crystal size/mm^3	0.25 × 0.15 × 0.05

Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	3.572 to 50.698
Index ranges	$-9 \leq h \leq 9$, $-18 \leq k \leq 20$, $-27 \leq l \leq 24$
Reflections collected	16142
Independent reflections	5542 [R_{int} = 0.0830, R_{sigma} = 0.1672]
Data/restraints/parameters	5542/27/385
Goodness-of-fit on F^2	0.710
Final R indexes [I>=2σ (I)]	R_1 = 0.0436, wR_2 = 0.0550
Final R indexes [all data]	R_1 = 0.1070, wR_2 = 0.0641

CCDC 1830872 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

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6 References and notes

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Supplementary information

Copies of ^{1}H and ^{13}C NMR spectra have been deposited as supplementary data.