Novel squalestatin derivatives arising from reactions at the allylic centre of the C1-side chain

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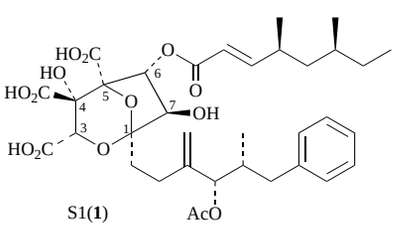
Reaction of 2 with Ac_2O–TMSOTf gives the triacetate 5, which on further reaction gives isomer 6, arising from an allylic rearrangement, whereas reaction of 2 with Et_3SiH–TMSOTf gives tricycle 7 arising from addition of the C7-OH to the allylic centre. Attempted ionic reduction of triacetate 5 gives benzocycloheptene 8, arising from Friedel-Crafts alkylation of the phenyl ring by the allylic centre. Similar alkylation has been obtained with analogue 9, and with the trifluoromethanesulfonate ester of the allylic alcohol 13. Attempted ionic reduction of 17, lacking the allylic centre, gives 20 arising from ester hydrolysis at C4.

In 1992 we described the isolation[1,2] and structure elucidation[3] of the squalestatins, a novel group of fungal metabolites isolated from a previously unknown *Phoma* species (*coelomycetes*). Squalestatin S1 (**1**) is a potent and selective inhibitor of both rat



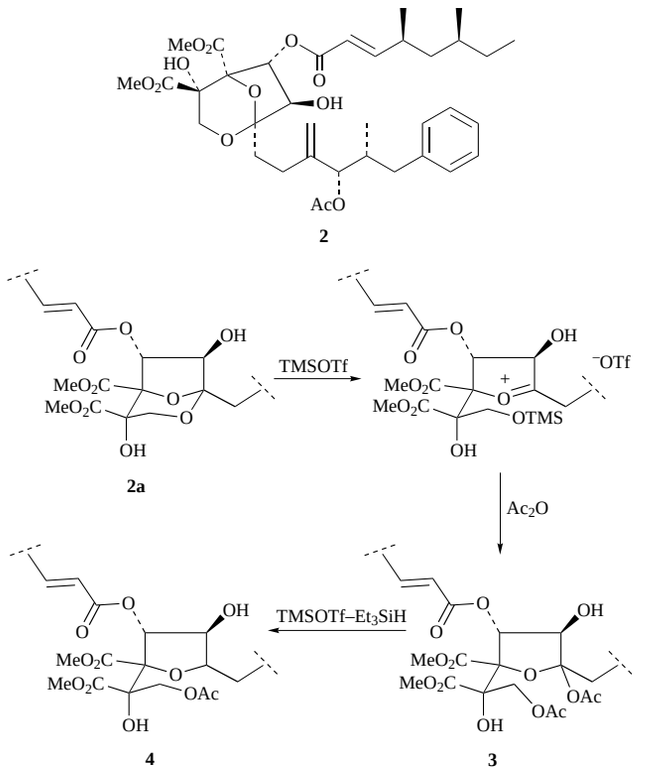
S1(**1**)

and *Candida* squalene synthase (SQS); 50% inhibition of rat liver microsomal SQS activity is observed *in vitro* at a concentration of 12 nmol dm^{-3}. Furthermore when S1 is administered orally to marmosets, a 50% reduction in serum cholesterol levels is observed at a dose of 10 mg kg^{-1} day^{-1} for 7 days.[4] S1 has a profound and extended effect on lipids (50–60% decrease in serum cholesterol levels during 7 days after a single intravenous dose of 1 mg kg^{-1} in marmosets).[5] At the end of 1992 a group at Merck published the isolation[6–9] of the zaragozic acids, the structure of zaragozic acid A being identical with that of S1. In 1993 a group at Tokyo Noko University-Mitsubishi[10] isolated S1 from another organism, *Setosphaeria khartoumensis*, and more recently a group at Pfizer have also isolated S1 from an unidentified fungus.[11]

As a part of our chemical programme aimed at the modification of the complex squalestatin structure and the identification of the key structural features responsible for the biological activity, we have reported on the C1 chain-length requirements;[5,12] on the role of the tricarboxylic acid moiety;[13] on C6 and C7 modifications,[14] on the C6,C7-dideoxy,[15] C3-decarboxy,[16,17] C4-decarboxy and C4-deoxy,[17] C4-carboxamide,[18] monocyclic,[19,20] acyclic,[21,22] C3-hydroxymethyl,[23] C3-heterocyclic[24] and other C3 modified analogues,[25] and on modifications at the allylic centre in the C1 side chain.[26] In addition a detailed review bringing together all the published structure-activity relationships of the squalestatins and the zaragozic acids has been published.[27] Apart from our own and Merck's studies there has been a tremendous flurry of activity by the scientific community on the squalestatins/zaragozic acids culminating in the total synthesis of S1 by the Nicolaou[28] and Heathcock[29] groups and of zaragozic acid C by the Carreira[30] and Evans[31] groups. A second review dealing with the chemistry and biology of these exciting molecules has been published by Nicolaou.[32]

In order to probe the role of the complex 2,8-dioxabicyclo-[3.2.1]octane core of the squalestatins in securing potent SQS activity, we were interested in cleaving of the C1–O2 bond to generate novel monocyclic tetrahydrofuran analogues. This was complementary to our studies on the preparation of monocyclic 1,3-dioxane analogues,[19] *via* fission of the C6–C7 bond, and on the cleavage of the 6,8-dioxabicyclo[3.2.1]octane ring system obtained by rearrangement of the S1 core.[22] In this paper, we report our attempts towards C1–O2 cleavage and the resulting novel squalestatin analogues modified in the C1-side chain.

In one of our earlier communications[16] we have reported on the preparation of the C3-decarboxy squalestatin **2** which provided a structurally simplified model substrate for this work. When compound **2** is redrawn as in structure **2a** it can be considered as an anhydro-sugar. Fraser-Reid has reported[33] the use of triethylsilyl trifluoromethanesulfonate and acetic anhydride as a powerful reagent for the ring opening of 1,6-anhydro-sugars providing diacetate esters. We envisaged reacting compound **2** with trimethylsilyl trifluoromethanesulfonate (TMSOTf) and acetic anhydride (Ac_2O) according to the above method to form ketal acetate **3**, followed by reduction with triethylsilane in the presence of a Lewis acid[34,35] to give tetrahydrofuran **4** (Scheme 1). The attempted acetolysis of **2** in Ac_2O as solvent at 0 °C and using a catalytic amount of TMSOTf (3.3 mol%) gave almost immediately the 4,7-diacetate squalestatin derivative **5** (94%; Scheme 2). A literature search revealed only two references from a French group[36,37] on the use of Ac_2O–TMSOTf for the selective cleavage of the ring carbon–oxygen bond of methyl β-D-glycopyranosides, and for the replacement of the anomeric methoxy group of α-D-pyranosides where these transformations were accompanied by peracetylation of all unprotected hydroxy groups. Taking advantage of the mildness, speed and efficiency of this reaction we have developed it into a very powerful esterification procedure for a variety of complex, functionalised and sterically hindered alcohols.[38] Further reaction of **5** under the same conditions at room temperature for 5 days led to the slow generation of a new product **6** (11%) which was regioisomeric with the starting



Scheme 1

material. In the ^{1}H NMR spectrum of **6** the two singlets corresponding to the olefinic protons in the C1 side chain of **5** (4.94 and 5.00 ppm) disappeared and were replaced by a single olefinic proton appearing as a doublet at 5.31 ppm. Furthermore a primary allylic acetate methylene was observed as a two proton AB quartet at 4.42 ppm instead of the usual secondary allylic acetate methine present in the starting material as a one proton doublet at 5.09. Other data (^{1}H and ^{13}C) were consistent with structure **6**. In particular the chemical shift of C2′ (29.3 ppm) was characteristic of the *Z* geometry of the C1 side-chain double bond observed in other naturally occurring squalestatins.[2] Key long range ^{1}H–^{13}C correlations are summarised in Fig. 1. The formation of compound **6** from **5** can be rationalised by an allylic rearrangement brought about by TMSOTf. However, the extent of the rearrangement (only 11% after 5 days) suggests that the new esterification procedure (Ac_2O–TMSOTf) will be of particular use in acid sensitive allylic alcohols.

In order to avoid esterification of the C7-hydroxy group we attempted an ionic reduction of the C1 ketal by treating **2** with TMSOTf and triethylsilane in dichloromethane.[39] A new product was generated, identified as the tricyclic product **7** (23%). Clearly the tricycle **7** is formed by intramolecular attack of the C7-hydroxy group onto the olefin in the C1 side chain, followed by elimination of acetic acid. A similar reaction has been reported by the Merck group[9] where S1 was heated in aqueous sulfuric acid and tetrahydrofuran at 40 °C for 1 h, followed by esterification of the tricarboxylic acid moiety to provide the crystalline tris-*tert*-butyl ester, whose structure was confirmed by an X-ray diffraction study. The geometry of the newly generated exocyclic olefin in **7** was assigned as *E* based on the chemical shift of C3 (23.5 ppm).[2] It is also noteworthy that one of the protons attached to C2 appeared at 0.27 ppm and this is consistent with the phenyl ring being in close proximity to this proton in solution as it is in the solid state.[9]

Ionic reduction using TMSOTf as the Lewis acid and triethylsilane as the reducing agent[39] was attempted once more, but this time the 4,7-diacetate derivative **5** was used in place of **2** in order to block participation of the hydroxy groups. After 23 h a new product **8** had formed and was isolated in 16% yield. The ^{1}H NMR spectrum of **8** indicated the presence of only 4 aromatic protons and a single olefinic proton which appeared as a singlet at 6.34 ppm and showed a strong NOE to an aromatic proton. Saturation transfer experiments showed no exchangeable protons to be present. The olefinic protons in the C1 side chain and allylic acetate were clearly

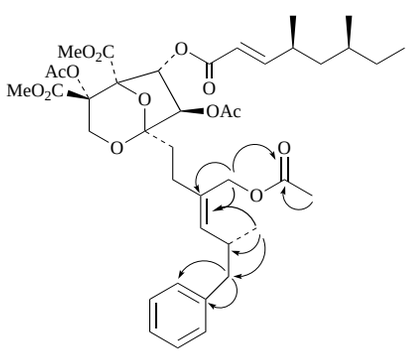
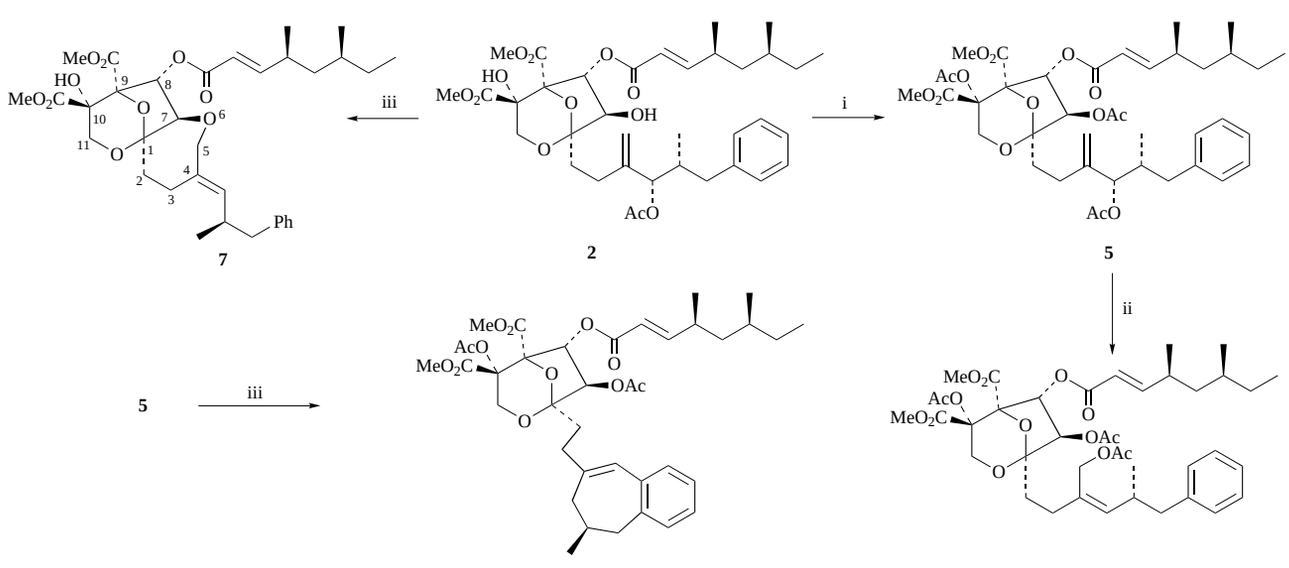


Fig. 1 Key long range ^{1}H–^{13}C correlations



Scheme 2 *Reagents and conditions*: i, TMSOTf, Ac_2O, 0 °C, 10 min, 94%; ii, TMSOTf, Ac_2O, 20 °C, 11%; iii, TMSOTf, Et_3SiH

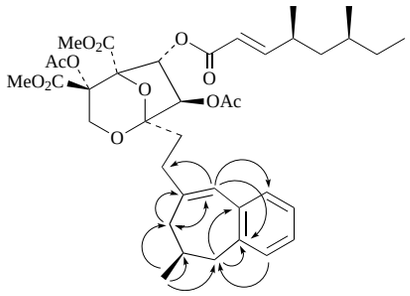
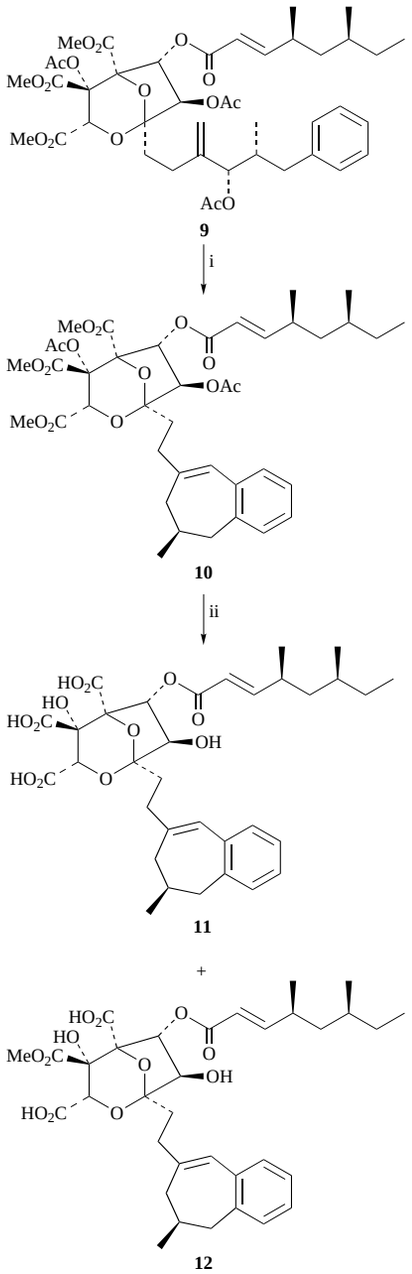


Fig. 2 Key long range $^{1}H–^{13}C$ correlations

absent, whereas the remainder of the molecule was intact. The molecular formula of $C_{38}H_{50}O_{12}$ was obtained from the high resolution mass spectrum and confirmed the loss of $C_2H_4O_2$ (acetic acid). The ^{13}C NMR and DEPT spectra confirmed the presence of an additional methylene, a disubstituted phenyl ring and a trisubstituted double bond. These data together with long range $^{1}H–^{13}C$ couplings (Fig. 2) established the structure as that of the benzocycloheptene **8**. Mechanistically, this is the result of electrophilic intramolecular attack by the phenyl ring of the C1-side chain onto an allylic cation generated by the TMSOTf, in a Friedel-Crafts fashion. The benzocycloheptene **8** was of sufficient novelty to warrant biological evaluation and thus preparation of the corresponding S1 analogue was undertaken. The previously described 4,7-diacetate-3,4,5-trimethyl ester of S1 **9**[3] was treated with TMSOTf in dichloromethane for 13 days to give a mixture which had a major component by HPLC (48%; Scheme 3). This was isolated in 25% yield and identified as the benzocycloheptene **10**. Deprotection of ester **10** with excess lithium iodide in 2,4,6-trimethylpyridine[40] at 45 °C for 24 h removed not only the methyl esters, but also resulted in cleavage of the O-acetyl ester at C7 together with partial cleavage of the C6-ester side chain. Purification of this reaction mixture by preparative HPLC gave the tricarboxylic acid **11** (4%) and the 3,5-dicarboxylic acid-4-methyl ester **12** (10%). The position of the methyl ester at the C4-carboxylic acid was assumed based on previous findings showing that the C4 ester was the most resistant ester to hydrolysis and dealkylation.[13,23–25]

It was of interest to investigate the formation of the benzocycloheptene ring under different conditions (non-Lewis acid catalysed) and from other substrates, for example using the trifluoromethanesulfonate ester of the allylic alcohol **13**. Allylic alcohol **13** which was previously used in the preparation of allylic ethers[26] was prepared from S1 according to Scheme 4. Reaction of S1 in methanol and in the presence of concentrated hydrochloric acid introduced the methyl ester at the C3-carboxylic acid and concurrently converted the allylic acetate to the allylic alcohol.[2] Esterification of this product with *N*,*N*-dimethylformamide di-*tert*-butyl acetal in toluene gave ester **14** (32% overall from S1). Acetylation of **14** with excess Ac_2O and triethylamine in dichloromethane gave predominantly ester **13** (54%) and diacetate **15** (14%), separable by chromatography. Treatment of the allylic alcohol **13** with trifluoromethanesulfonic anhydride in the presence of 2,4,6-trimethylpyridine in dichloromethane for 2 h at 20 °C gave benzocycloheptene **16** (26%). Interestingly the double bond in the cycloheptene ring of **16** was not conjugated with the phenyl ring, unlike that in benzocycloheptene **10**. This could be explained by the initial formation of the non-conjugated olefin as the kinetic product, followed by equilibration with time under the reaction conditions to the thermodynamic conjugated olefin (*cf*. formation of **16** 2 h; formation of **10** 13 days). However, we have not attempted deliberate equilibration of **16** to the corresponding conjugated olefin.

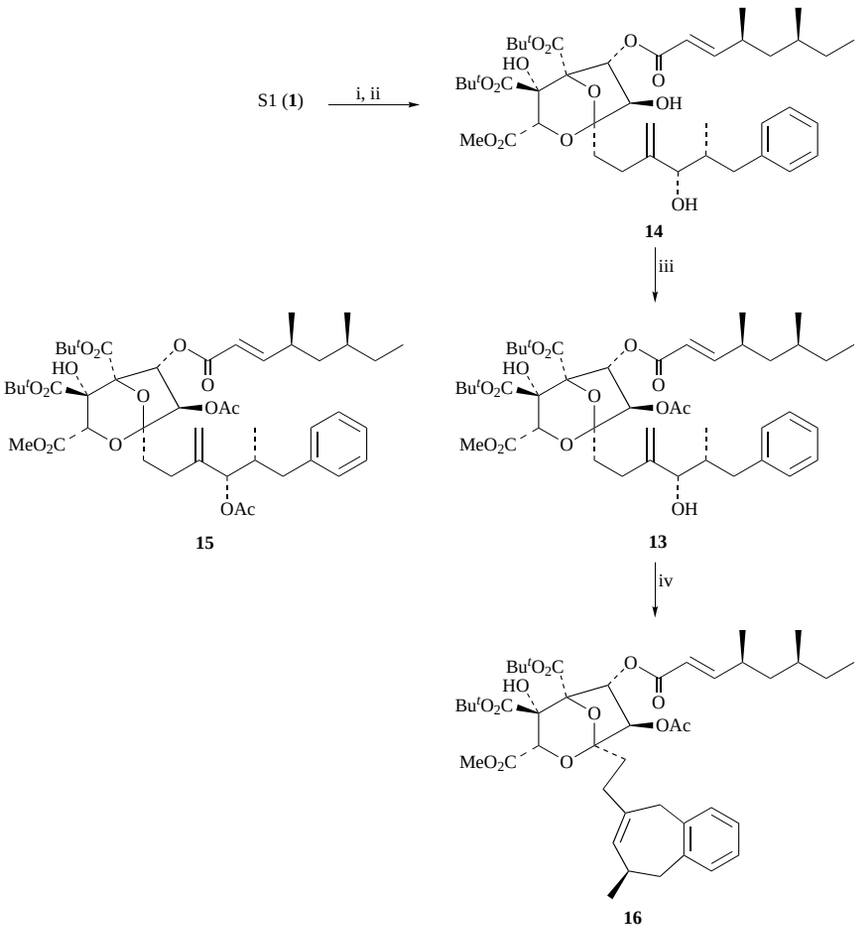
Given the incompatibility of the allylic centre to the reaction conditions employed for the cleavage of the C1–O2 bond, the tetrahydro-desacetoxy analogue **17** was identified as a more promising substrate for further work. This compound was readily prepared by converting the previously reported tricarboxylic acid[5] **18** (as a 1:1 mixture of diastereoisomers) into its trimethyl ester **19** (81%), followed by protection of the C4- and C7-hydroxy groups as the diacetate **17** (66%) using our newly developed acetylation procedure (Scheme 5).[38] Treatment of **17** with either triethylsilane and a catalytic amount of TMSOTf in dichloromethane at 20 °C for 7 days or with triethylsilane and a catalytic amount of boron trifluoride–diethyl ether in dichloromethane at 20 °C for 11 days, gave the partially deprotected analogue **20** (78%) as the only isolated product.



Scheme 3 *Reagents and conditions*: i, TMSOTf, CH_2Cl_2, 0 °C, 13 d, 25%; ii, LiI, 2,4,6-trimethylpyridine, 45 °C

Compounds **11** and **12** were tested in our mammalian squalene synthase inhibition screen and found to be considerably weaker inhibitors than S1 *in vitro*. Thus the IC_{50} value for the inhibition of cholesterol biosynthesis from [^{14}C]farnesyl diphosphate using male rat liver microsomes as enzyme source was 500 nmol dm^{-3} for both compounds.

In conclusion the present study has demonstrated the robustness of the squalestatin core to cleavage and has led to



Scheme 4 *Reagents and conditions*: i, HCl, MeOH; ii, *N*,*N*-dimethylformamide di-*tert*-butyl acetal, PhMe, 32%; iii, Ac_2O, Et_3N, CH_2Cl_2, 54%; iv, Tf_2O, 2,4,6-trimethylpyridine, CH_2Cl_2, 20 °C, 2 h, 26%

the identification of a powerful acetylation reaction of alcohols with Ac_2O–TMSOTf. In addition novel squalestatin derivatives were obtained, arising from allylic rearrangement or from intramolecular reaction of an allylic cation in the C1 side chain with either the C7-hydroxy group or with the phenyl ring when the C7-OH is protected. The intramolecular cycloaddition reactions of allylic cations have very recently been reviewed by Harmata.[41]

Experimental

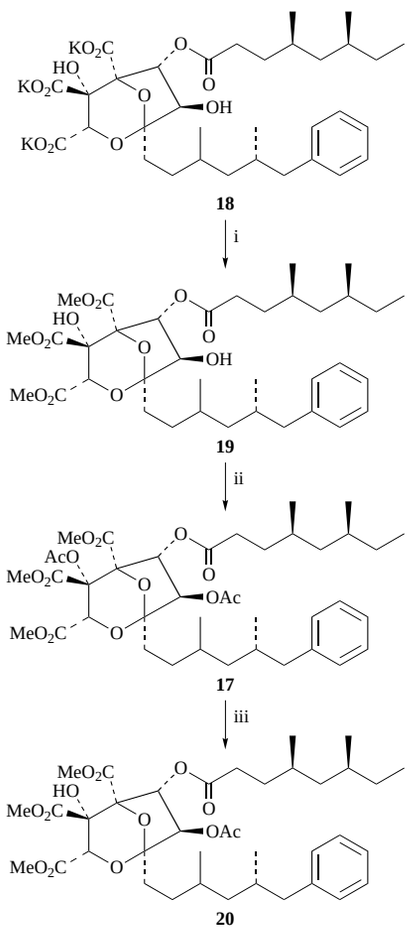
Organic solutions were dried over $MgSO_4$ and column chromatography was performed on silica gel 60 (Merck, Art no. 9385). Analytical HPLC was performed on a Spherisorb 5 ODS-2 column (15 × 0.46 cm) using MeCN–H_2O as eluent, at a flow rate of 2 cm^3 min^{-1} and detecting at 210 nm (column A) or on a Spherisorb 5 ODS-2 column (25 × 0.46 cm) using MeCN–H_2O as eluent, at a flow rate of 1.5 cm^3 min^{-1} and detecting at 210 nm (column B). Preparative HPLC was conducted on a Spherisorb 5 ODS-2 column (25 × 2.2 cm) using MeCN–H_2O as eluent, at a flow rate of 15 cm^3 min^{-1} and detecting at 210 nm. The appropriate fractions from each run were combined, the acetonitrile was removed under reduced pressure (bath temperature <40 °C), and the remainder extracted with ethyl acetate. The combined extracts were washed with brine, dried and evaporated to dryness. IR spectra were recorded on a Nicolet 5SXC or a Bio-Rad FTS-7 FTIR spectrometer. NMR spectra were recorded on a Bruker AM 500, AM 250 or Varian VXR 400 spectrometers using standard pulse sequences. Chemical shifts are expressed as parts per million downfield from internal tetramethylsilane. All *J* values are in Hz. Positive ammonia chemical-ionisation (CI), desorption chemical-ionisation (DCI), fast-atom-bombardment (FAB) or high resolution mass spectrometry were conducted on a VG Autospec spectrometer.

(1*S*,4*S*,5*R*,6*R*,7*R*)-Dimethyl 4,7-diacetoxy-1-{3-[(1*S*,2*R*)-1-acetoxy-2-methyl-3-phenylpropyl]but-3-enyl}-6-{[(4*S*,6*S*,2*E*)-4,6-dimethyloct-2-enoyl]oxy}-2,8-dioxabicyclo[3.2.1]octane-4,5-dicarboxylate 5

A solution of the dimethyl ester **2** (100 mg, 0.15 mmol) in acetic anhydride (2 cm^3) was treated with TMSOTf (0.001 cm^3, 0.005 mmol) at 0 °C for 5 min under nitrogen. The reaction mixture was treated with saturated aqueous sodium hydrogen carbonate (60 cm^3), stirred for 10 min and extracted with ethyl acetate (3 × 20 cm^3). The combined organic phases were washed with saturated aqueous sodium hydrogen carbonate (20 cm^3) and brine (20 cm^3), then dried and evaporated to a gum (106 mg, 95%) [Found: (CI) $(M + H)^+$, 759.3592. $C_{40}H_{55}O_{14}$ requires (*M* + H), 759.3596]; analytical HPLC t_r 4.98 min 94% (column A; 80% MeCN–H_2O); $\nu_{max}(CHBr_3)/cm^{-1}$ 1744, 1649, 1241 and 1228; δ_H(250 MHz; $CDCl_3$) 0.8–0.9 (9H, m, CH_3), 1.02 (3H, d, *J* 7, =CHCHCH_3), 2.09, 2.17 and 2.19 (3s, 3H each, AcO), 2.70 (1H, dd, *J* 13 and 5, CH_2Ph), 3.73 and 3.81 (2s, 3H each, CO_2CH_3), 4.58 and 4.89 (2d, 1H each, *J* 14, OCH_2), 4.94 and 5.00 (2s, 1H each, $=CH_2$), 5.09 (1H, d, *J* 5, C*H*OAc), 5.23 (1H, d, *J* 2, 7-H), 5.72 (1H, d, *J* 16, OCOC*H*=CH), 6.18 (1H, d, *J* 2, 6-H), 6.83 (1H, dd, *J* 16 and 8, OCOCH=C*H*) and 7.1–7.3 (5H, m, Ph); *m*/*z* (DCI–NH_3) 776 $(M + NH_4)^+$.

(1*S*,4*S*,5*R*,6*R*,7*R*)-Dimethyl 4,7-diacetoxy-1-[(5*R*,3*Z*)-3-acetoxymethyl-5-methyl-6-phenylhex-3-enyl]-6-{[(4*S*,6*S*,2*E*)-4,6-dimethyloct-2-enoyl]oxy}-2,8-dioxabicyclo[3.2.1]octane-4,5-dicarboxylate 6

A solution of triacetate **5** (22.7 mg, 0.03 mmol) in acetic anhydride (0.5 cm^3) was cooled to 0 °C under nitrogen and



Scheme 5 *Reagents and conditions*: i, MeI, $NaHCO_3$, DMF, 20 °C, 81%; ii, TMSOTf, Ac_2O, 0 °C, 5 min, 66%; iii, $BF_3{\cdot}OEt_2$, Et_3SiH, CH_2Cl_2, 20 °C, 11 d, 56%

treated with TMSOTf (0.001 cm^3, 0.005 mmol). The solution was allowed to warm to 20 °C and stirred for 5 days. The reaction mixture was stirred with saturated aqueous sodium hydrogen carbonate (20 cm^3) and extracted with ethyl acetate (3 × 7 cm^3). The combined organic extracts were washed with aqueous sodium hydrogen carbonate (7 cm^3), brine (7 cm^3), then dried and purified by preparative HPLC 73% MeCN–H_2O to give compound **6** as a colourless gum (2.5 mg, 11%) [Found: (CI) $(M + H)^+$, 759.3592. $C_{40}H_{55}O_{14}$ requires (M + H), 759.3596]; δ_H(500 MHz; $CDCl_3$) 0.81–0.84 (6H, m, CH_3), 0.98 [3H, d, J 7, CH(CH_3)Bn], 1.02 (3H, d, J 7, =CHCHCH_3), 1.06–1.17 (2H, m), 1.23–1.44 (4H, m), 1.73 (1H, m), 2.03 (1H, m), 2.07, 2.17 and 2.18 (3s, 3H each, AcO), 2.20 (1H, m), 2.41 (1H, m), 2.48–2.62 (2H, m, CH_2Ph), 2.73 (1H, m), 3.73 and 3.80 (2s, 3H each, CO_2CH_3), 4.37 and 4.46 (2d, 1H each, J 12.5, CH_2OAc), 4.55 and 4.88 (2d, 1H each, J 14, 3-H), 5.12 (1H, d, J 2.5, 7-H), 5.32 [1H, d, J 10, =CHCH(CH$_3$)Bn], 5.74 (1H, dd, J 15.5, 1, OCOCH=CH), 6.15 (1H, d, J 2.5, 6-H), 6.85 (1H, dd, J 15.5 and 8, OCOCH=CH), 7.11–7.16 (3H, m, Ph) and 7.23 (2H, t, J 7.5, Ph); δ_C(125 Hz, $CDCl_3$), 170.4 (CO), 169.5 (CO), 168.9 (CO), 166.0 (CO), 164.2 (CO), 163.9 (CO), 156.6 (d), 140.0 (s), 136.1 (d), 131.7 (s), 128.9 (d), 127.6 (d), 125.4 (d), 117.7 (d), 104.6 (s), 87.6 (s), 79.0 (d), 78.3 (s), 76.1 (d), 67.9 (t), 62.9 (t), 52.8 (q), 52.0 (q), 43.3 (t), 42.8 (t), 34.2 (t), 34.0 (d), 33.9 (d), 31.5 (d), 29.3 (t), 21.1 (q), 20.6 (q), 20.4 (q), 20.2 (q), 19.8 (q), 18.5 (q), 10.7 (q). Selected long range ^1H–^{13}C couplings are shown schematically in Fig. 1.

(1*S*,7*R*,8*R*,9*R*,10*S*)-Dimethyl 8-{[(4*S*,6*S*,2*E*)-4,6-dimethyloct-2-enoyl]oxy}-10-hydroxy-4-[(2*R*,*E*)-2-methyl-3-phenylpropylidene]-6,12,13-trioxatricyclo[7.3.1.0^{1,7}]tridecane-9,10-dicarboxylate 7

Triethylsilane (0.0065 cm^3, 0.041 mmol) was added to a solution of TMSOTf (0.002 cm^3, 0.01 mmol) in dichloromethane (0.5 cm^3) under nitrogen at 0 °C, followed by compound **2** (25 mg, 0.037 mmol). The resulting clear solution was stirred at 0 °C for 0.5 h and then allowed to warm to 20 °C and stirred for a further 96 h. The reaction mixture was treated with saturated aqueous sodium hydrogen carbonate (15 cm^3) and extracted with ethyl acetate (3 × 5 cm^3). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (5 cm^3), brine (5 cm^3), then dried and evaporated under reduced pressure. The residue was purified by preparative reversed-phase HPLC eluting with 73% MeCN–H_2O to give compound **7** (5.2 mg, 23%) as a colourless gum. Analytical HPLC t_r 9.80 min 98.2% (column A; 70% MeCN–H_2O) [Found: (CI) $(M + H)^+$, 615.3187. $C_{34}H_{47}O_{10}$ requires (M + H), 615.3169]; $\nu_{max}(CHBr_3)/cm^{-1}$ 3445, 1740 and 1650; δ_H(400 MHz; $CDCl_3$) 0.27 (1H, m, CH_2CH$_2$C=), 0.8–0.9 (6H, m, CH_3), 1.03 [3H, d, J 6, CH(CH_3)Bn], 1.05 (3H, d, J 7, =CHCHCH_3), 1.10–1.20 (2H, m), 1.25–1.47 (3H, m), 1.80–1.95 (2H, m), 2.35–2.52 (3H, m), 2.63 [1H, m, CH(CH$_3$)Bn], 2.73 (1H, dd, J 12 and 4, CH_2Ph), 3.70 (1H, d, J 2.5, 7-H), 3.78 and 3.86 (2s, 3H each, CO_2CH_3), 3.82 (1H, s, OH), 4.18 and 4.26 (2d, 1H each, J 8, OCH_2C=CH), 3.77 and 4.54 (2d, 1H each, J 12, 11-H), 5.33 (1H, d, J 10, OCH$_2$C=CH), 5.82 (1H, d, J 16, OCOCH=CH), 6.27 (1H, d, J 2.5, 8-H), 6.91 (1H, dd, J 16 and 8, OCOCH=CH), 7.06 (2H, m, Ph) and 7.2–7.3 (3H, m, Ph); δ_C(100 MHz, $CDCl_3$) 169.5 (CO), 165.4 (CO), 164.2 (CO), 156.2 (d), 140.4 (s), 139.1 (d), 133.3 (s), 128.4 (d), 128.1 (d), 126.0 (d), 118.2 (d), 106.0 (s), 89.0 (s), 82.7 (d), 76.9 (d), 76.8 (t), 73.8 (s), 68.0 (t), 53.1 (q), 52.1 (q), 43.5 (t), 42.9 (t), 35.9 (d), 34.1 (t), 33.9 (d), 31.6 (d), 29.4 (t), 23.5 (t), 20.8 (q), 20.0 (q), 18.4 (q) and 10.7 (q); m/z (CI–NH_3) 632 [$(M + NH_4)^+$, 100%], 615 [$(M + H)^+$, 20%].

(1*S*,4*S*,5*R*,6*R*,7*R*)-Dimethyl 4,7-diacetoxy-6-{[(4*S*,6*S*,2*E*)-4,6-dimethyloct-2-enoyl]oxy}-1-{2-[(6*S*)-6-methyl-6,7-dihydro-5*H*-benzocyclohepten-8-yl]ethyl}-2,8-dioxabicyclo[3.2.1]octane-3,5-dicarboxylate 8

Triethylsilane (0.0058 cm^3, 0.036 mmol) was added at 0 °C under nitrogen to a solution of TMSOTf (0.001 cm^3, 0.005 mmol) in dichloromethane (0.5 cm^3), followed by the triacetate **5** (25 mg, 0.033 mmol). The reaction mixture was stirred at 0 °C for 0.5 h and at 20 °C for 23 h. The reaction was then diluted with aqueous saturated sodium hydrogen carbonate (15 cm^3) and ethyl acetate (5 cm^3). The aqueous phase was extracted with ethyl acetate (2 × 5 cm^3) and the combined organic extracts were washed with aqueous saturated sodium hydrogen carbonate (5 cm^3), brine (5 cm^3), then dried and evaporated to a pale yellow gum (17.8 mg). This was purified by preparative reversed-phase HPLC eluting with 80% MeCN–H_2O collecting fractions with a t_r 25 min, to give a clear colourless gum (3.8 mg, 16%). Analytical HPLC t_r 5.075 min 95.6% (column A; 90% MeCN–H_2O) [Found: (CI) $(M + H)^+$, 699.3371. $C_{38}H_{51}O_{12}$ requires (M + H), 699.3380]; $\nu_{max}(CHBr_3)/cm^{-1}$ 1745, 1645 and 1220; δ_H(500 MHz; $CDCl_3$) 0.8–0.9 (6H, m, CH_3), 1.02 [3H, d, J 7, CH(CH_3)CH$_2$Ar], 1.03 (3H, d, J 7, =CHCHCH_3), 1.05–1.18 (2H, m), 1.23–1.41 (3H, m), 1.86 [1H, dd, J 16 and 9, =CCH_2CH(CH$_3$)], 2.05–2.21 (3H, m), 2.19 and 2.23 (2s, 3H each, AcO), 2.25–2.52 (5H, m), 2.69 (1H, dd, J 14 and 4, CH_2Ar), 3.74 and 3.82 (2s, 3H each, CO_2CH_3), 4.63 and 4.92 (2d, 1H each, J 14, 3-H), 5.31 (1H, d, J 2, 7-H), 5.72 (1H, d, J 16, OCOCH=CH), 6.20 (1H, d, J 2, 6-H), 6.34 (1H, s, C=CHAr), 6.85 (1H, dd, J 16 and 8, OCOCH=CH), 7.03–7.12 (3H, m, Ar) and 7.16 (1H, m, Ar); δ_C(125 MHz; $CDCl_3$) 170.0 (CO), 169.5 (CO), 166.4 (CO), 164.6 (CO), 164.3 (CO), 157.1 (d), 142.4 (s), 139.4 (s), 137.6 (s), 129.5 (d), 129.1 (d), 125.9 (d), 125.8 (d), 118.0 (d), 105.3 (s), 88.1 (s), 79.3 (d), 78.7 (s), 76.4 (d), 63.4 (t), 53.3 (q), 52.6 (q), 43.2 (t), 42.0 (t), 40.7 (t), 37.0 (d), 35.0 (t), 34.4 (d), 33.0 (t), 31.8 (d), 29.7 (t), 22.0 (q), 21.5 (q), 20.9 (q), 20.2 (q), 18.9 (q), 11.1 (q); m/z (DCI–NH_3) 716 $(M + NH_4)^+$. Selected long range ^1H–^{13}C couplings are shown schematically in Fig. 2.

(1*S*,3*S*,4*S*,5*R*,6*R*,7*R*)-Trimethyl 7-acetoxy-6-{[(4*S*,6*S*,2*E*)-4,6-dimethyloct-2-enoyl]oxy}-4-hydroxy-1-{2-[(6*S*)-6-methyl-6,7-dihydro-5*H*-benzocyclohepten-8-yl]ethyl}-2,8-dioxabicyclo-[3.2.1]octane-3,4,5-tricarboxylate 10

A solution of triacetate **9** (1.42 g, 1.74 mmol) in dichloromethane (25 cm^3) was treated with TMSOTf (0.057 cm^3, 0.31 mmol) under nitrogen at 0 °C. The reaction mixture was allowed to warm to 20 °C and stirred for 13 days. Saturated aqueous sodium hydrogen carbonate (150 cm^3) was added and the mixture was extracted with ethyl acetate (3 × 50 cm^3). The combined organic extracts were washed with further saturated aqueous sodium hydrogen carbonate (50 cm^3), brine (50 cm^3), then dried and evaporated under reduced pressure to a gum (1.161 g) which was purified by preparative reversed-phase HPLC eluting with 75% MeCN–H_2O collecting fractions with a t_r 22 min, to give the acetate **10** as a colourless gum (329 mg, 25%). Analytical HPLC t_r 16.82 min 97.9% (column B; 70% MeCN–H_2O) [Found: (CI) $(M + H)^+$, 715.3329. $C_{38}H_{51}O_{13}$ requires (M + H), 715.3333]; $\nu_{max}(CHBr_3)/cm^{-1}$ 1770, 1745, 1646 and 1222; δ_H(250 MHz, $CDCl_3$) 0.8–0.92 (6H, m, CH_3), 1.02 (6H, d, J 6, CH_3), 2.20 (3H, s, AcO), 2.69 (1H, dd, J 14 and 4, CH_2Ar), 3.74, 3.79 and 3.96 (3s, 3H each, CO_2CH_3), 5.14 (1H, s, 3-H), 5.35 (1H, d, J 2, 7-H), 5.70 (1H, d, J 16, OCOC*H*=CH), 6.35 (1H, d, J 2, 6-H), 6.36 (1H, s, C=*H*Ar), 6.82 (1H, dd, J 16 and 8, OCOCH=C*H*) and 7.00–7.2 (4H, m, Ar); *m*/*z* (DCI–NH_3) 732 $(M + NH_4)^+$.

(1*S*,3*S*,4*S*,5*R*,6*R*,7*R*)-6-{[(4*S*,6*S*,2*E*)-4,6-Dimethyloct-2-enoyl]oxy}-4,7-dihydroxy-1-{2-[(6*S*)-6-methyl-6,7-dihydro-5*H*-benzocyclohepten-8-yl]ethyl}-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic acid 11 and (1*S*,3*S*,4*S*,5*R*,6*R*,7*R*)-6-{[(4*S*,6*S*,2*E*)-4,6-dimethyloct-2-enoyl]oxy}-4,7-dihydroxy-4-methoxycarbonyl-1-{2-[(6*S*)-6-methyl-6,7-dihydro-5*H*-benzocyclohepten-8-yl]ethyl}-2,8-dioxabicyclo[3.2.1]octane-3,5-dicarboxylic acid 12

A mixture of ester **10** (320 mg, 0.45 mmol) and lithium iodide (3.25 g, 24.28 mmol) in 2,4,6-trimethylpyridine (15 cm^3) was heated to 45 °C under nitrogen for 24 h. The mixture was allowed to cool, filtered and the solid was washed with toluene (100 cm^3). The filtrate and washings were evaporated under reduced pressure. The residue was redissolved in toluene (100 cm^3) and re-evaporated under reduced pressure. The process of dissolving in toluene and evaporating was repeated three times to remove 2,4,6-trimethylpyridine. The residue was dissolved in ethyl acetate (150 cm^3), washed with dilute hydrochloric acid (3 × 100 cm^3), 5% aqueous sodium metabisulfite (2 × 100 cm^3), brine (100 cm^3), then dried and evaporated to dryness. The resulting orange foam was then purified by preparative reversed-phase HPLC (60% MeCN–H_2O containing 0.15 cm^3 concentrated H_2SO_4 dm^{-3}). The appropriate fractions were combined and the acetonitrile was removed under reduced pressure. The aqueous phase was extracted with ethyl acetate and the organic solution was dried and then evaporated under reduced pressure. The first compound to be eluted off the column was obtained as a white foam (12 mg, 4%) identified as the tricarboxylic acid **11**, analytical HPLC t_r 11.94 min 95% (column B; 60% MeCN–H_2O containing 1 cm^3 trifluoroacetic acid dm^{-3}) [Found: (LSIMS −ve) $(M - H)^-$, 629.2607. $C_{33}H_{41}O_{12}$ requires (M − H), 629.2598]; δ_H(250 MHz; $CDCl_3$ + CD_3OD) 0.8–0.9 (6H, m, CH_3) 1.02 (6H, d, J 6, CH_3) 2.69 (1H, dd, J 14 and 4, CH_2Ar), 4.17 (1H, s, 7-H), 5.32 (1H, s, 3-H), 5.78 (1H, d, J 16, OCOC*H*=CH), 6.09 (1H, s), 6.37 (1H, s), 6.88 (1H, dd, J 16 and 8, OCOCH=C*H*) and 7.02–7.19 (4H, m, Ar); *m*/*z* (FAB −ve) 629 $(M - H)^-$. The second compound to be eluted off the column was obtained as a white foam (28 mg, 10%) identified as the dicarboxylic acid **12**, analytical HPLC t_r 16.97 min, 89% (column B; 60% MeCN–H_2O containing 1 cm^3 trifluoroacetic acid dm^{-3}); δ_H(250 MHz; $CDCl_3$ + CD_3OD) 0.8–0.9 (6H, m, CH_3), 1.03 (6H, d, J 6, CH_3), 3.82 (3H, s, CO_2CH_3), 4.20 (1H, s, 7-H), 5.22 (1H, s, 3-H), 5.76 (1H, d, J 16, OCOC*H*=CH), 6.30 (1H, s), 6.41 (1H, s), 6.85 (1H, dd, J 16 and 9, OCOCH=C*H*) and 7.00–7.11 (4H, m, Ar); *m*/*z* (DCI–NH_3) 662 $(M + NH_4)^+$.

(1*S*,3*S*,4*S*,5*R*,6*R*,7*R*)-4,5-Di-*tert*-butyl 3-methyl 6-{[(4*S*,6*S*,2*E*)-4,6-dimethyloct-2-enoyl]oxy}-4,7-dihydroxy-1-{3-[(1*S*,2*R*)-1-hydroxy-2-methyl-3-phenylpropyl]but-3-enyl}-2,8-dioxabicyclo-[3.2.1]octane-3,4,5-tricarboxylate 14

A solution of tricarboxylic acid **1** (10 g, 14.5 mmol) in methanol (1 dm^3) and conc. hydrochloric acid (12.5 cm^3) was stood at 20 °C for 2 days. The solution was concentrated under reduced pressure to half volume and poured into water (2 dm^3). The resulting mixture was extracted with ethyl acetate (3 dm^3), the extracts were dried and evaporated under reduced pressure to a very pale brown foam (10.18 g). The residue was dissolved in toluene (100 cm^3) and heated to 80 °C under nitrogen. *N*,*N*-Dimethylformamide di-*tert*-butyl acetal (31 cm^3, 129 mmol) was added over 30 min and the mixture was heated to 80 °C for 3 h. The reaction mixture was allowed to cool to room temperature and diluted with diethyl ether (600 cm^3). The organic solution was washed with brine (500 cm^3), dried and evaporated to a brown gum (13.2 g), which was purified by column chromatography. Elution of the column with ethyl acetate–cyclohexane (1:5→2:1) gave the 3-methyl-4,5-di-*tert*-butyl ester **14** (3.596 g, 32%) as a yellow foam (Found: C, 64.6; H, 8.1. $C_{42}H_{62}O_{13}\cdot 0.25H_2O$ requires C, 64.72; H, 8.08%); $\nu_{max}(CHBr_3)/cm^{-1}$ 3535, 1770, 1741, 1706 and 1648; δ_H(250 MHz; $CDCl_3$) 0.8–0.9 (9H, m, CH_3), 1.03 (3H, d, J 7, =CHCHCH_3), 1.47 and 1.60 (2s, 9H each, *tert*-BuO), 2.78 (1H, dd, J 14 and 6, CH_2Ph), 3.17 (1H, d, J 5, 7-OH), 3.74 (3H, s, CO_2CH_3), 3.95 (1H, s, 4-OH), 4.06 (2H, m, 7-H, =CC*H*OH), 5.04 and 5.13 (2s, 1H each, =CH_2), 5.27 (1H, s, 3-H), 5.76 (1H, d, J 16, OCOC*H*=CH), 5.97 (1H, d, J 2, 6-H), 6.89 (1H, dd, J 16 and 9, OCOCH=C*H*) and 7.12–7.30 (5H, m, Ph); *m*/*z* (DCI–NH_3) 792 $(M + NH_4)^+$.

(1*S*,3*S*,4*S*,5*R*,6*R*,7*R*)-4,5-Di-*tert*-butyl 3-methyl 7-acetoxy-6-{[(4*S*,6*S*,2*E*)-4,6-dimethyloct-2-enoyl]oxy}-4-hydroxy-1-{3-[(1*S*,2*R*)-1-hydroxy-2-methyl-3-phenylpropyl]but-3-enyl}-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate 13 and (1*S*,3*S*,4*S*,5*R*,6*R*,7*R*)-4,5-di-*tert*-butyl 3-methyl 7-acetoxy-6-{[(4*S*,6*S*,2*E*)-4,6-dimethyloct-2-enoyl]oxy}-4-hydroxy-1-{3-[(1*S*,2*R*)-1-acetoxy-2-methyl-3-phenylpropyl]but-3-enyl}-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate 15

A solution of alcohol **14** (10.701 g, 13.8 mmol) in dichloromethane (107 cm^3) and triethylamine (30 cm^3, 214 mmol) was treated with acetic anhydride (17.12 cm^3, 181 mmol) at 20 °C and stirred for 20 h. The reaction mixture was diluted with diethyl ether and poured into dilute hydrochloric acid (200 cm^3). The organic phase was washed with aqueous sodium hydrogen carbonate (2 × 200 cm^3), brine (200 cm^3), then dried and concentrated under reduced pressure. The residue was chromatographed on silica gel eluting with ethyl acetate–cyclohexane (2:3) to give the diacetate **15** as a white foam (1.671 g, 14%) (Found: C, 64.5; H, 8.05. $C_{46}H_{66}O_{15}$ requires C, 64.32; H, 7.74%); $\nu_{max}(CHBr_3)/cm^{-1}$ 3540, 1770, 1733 and 1645; δ_H(250 MHz; $CDCl_3$) 0.8–0.9 (9H, m, CH_3), 1.03 (3H, d, J 7, =CHCHCH_3), 1.43 and 1.65 (2s, 9H each, *tert*-BuO), 2.10 (3H, s, AcO), 2.14 (3H, s, AcO), 2.73 (1H, dd, J 14 and 5, CH_2Ph), 3.76 (3H, s, CO_2CH_3), 4.05 (1H, s, 4-OH), 4.98 and 5.00 (2s, 1H each, =CH_2), 5.12 (1H, d, J 5, C*H*OAc), 5.16 (1H, s, 3-H), 5.20 (1H, d, J 2, 7-H), 5.77 (1H, d, J 16, OCOC*H*=CH), 6.45 (1H, d, J 2, 6-H), 6.92 (1H, dd, J 16 and 8, OCOCH=C*H*) and 7.1–7.3 (5H, m, Ph); *m*/*z* (DCI–NH_3) 876 $(M + NH_4)^+$; and the monoacetate **13** as a white foam (6.109 g, 54%) (Found: C, 64.8; H, 8.1. $C_{44}H_{64}O_{14}$ requires C, 64.69; H, 7.90%); $\nu_{max}(CHBr_3)/cm^{-1}$ 3530, 1765, 1740 and 1647; δ_H(250 MHz; $CDCl_3$) 0.8–0.9 (9H, m, CH_3), 1.03 (3H, d, J 7, =CHCHCH_3), 1.42 and 1.63 (2s, 9H each, *tert*-BuO), 2.14 (3H, s, AcO), 2.80 (1H, dd, J 14 and 6, CH_2Ph), 3.75 (3H, s, CO_2CH_3), 3.98 (1H, s, 4-OH), 4.10 (1H, d,

J 5, C*H*OH), 5.02 (1H, s, =CH_2), 5.13 (2H, s, 3-H, =CH_2), 5.22 (1H, d, *J* 2, 7-H), 5.76 (1H, d, *J* 16, OCOC*H*=CH), 6.44 (1H, d, *J* 2, 6-H), 6.90 (1H, dd, *J* 16 and 8, OCOCH=C*H*) and 7.1–7.3 (5H, m, Ph); *m*/*z* (DCI–NH_3) 834 $(M + NH_4)^+$.

(1*S*,3*S*,4*S*,5*R*,6*R*,7*R*)-4,5-Di-*tert*-butyl 3-methyl 7-acetoxy-6-{[(4*S*,6*S*,2*E*)-4,6-dimethyloct-2-enoyl]oxy}-4-hydroxy-1-{2-[(8*R*)-8-methyl-8,9-dihydro-5*H*-benzocyclohepten-6-yl]ethyl}-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate 16

A solution of allylic alcohol **13** (200 mg, 0.24 mmol) in dichloromethane (3 cm^3) was treated with dry 2,4,6-trimethylpyridine (0.14 cm^3, 1.06 mmol) and trifluoromethanesulfonic anhydride (0.12 cm^3, 0.71 mmol) at 20 °C under nitrogen. After 2 h stirring, the mixture was diluted with diethyl ether and washed with dilute hydrochloric acid, saturated sodium hydrogen carbonate, then dried and evaporated. The residue was chromatographed on silica gel eluting with ethyl acetate–light petroleum (1:3) to give compound **16** (50 mg, 26%), as a foam (Found: C, 65.9; H, 7.9. $C_{44}H_{62}O_{13}$ requires C, 66.14; H, 7.76%); δ_H(500 MHz; $CDCl_3$) 0.82–0.86 (6H, m, CH_3), 0.97 [3H, d, *J* 7, CH(C*H*$_3$)CH_2Ar], 1.02 (3H, d, *J* 7, CH=CHCHC*H*$_3$), 1.05–1.18 (2H, m), 1.20–1.50 (3H, m), 1.42 and 1.63 (2s, 9H each, *tert*-BuO), 2.05–2.20 (2H, m), 2.15 (3H, s, AcO), 2.30–2.48 (3H, m), 2.78 [1H, dd, *J* 16 and 9, CH(CH_3)C*H*$_2$Ar], 2.94 [1H, dd, *J* 16 and 4, CH(CH_3)C*H*$_2$Ar], 3.31 and 3.47 (2d, 1H each, *J* 16, =CC*H*$_2$Ar), 3.77 (3H, s, CO_2CH_3), 4.01 (1H, s, 4-OH), 5.16 (1H, s, 3-H), 5.17 (1H, d, *J* 4, C=C*H*CH_2), 5.26 (1H, d, *J* 2, 7-H), 5.75 (1H, d, *J* 16, OCOC*H*=CH), 6.44 (1H, d, *J* 2, 6-H), 6.92 (1H, dd, *J* 16 and 9, OCOCH=C*H*) and 7.06–7.15 (4H, m, Ar); δ_C(125 MHz; $CDCl_3$) 169.3 (CO), 167.9 (CO), 167.1 (CO), 164.5 (CO), 163.3 (CO), 157.0 (d), 141.4 (s), 139.9 (s), 134.4 (s), 129.7 (d), 128.9 (d), 127.7 (d), 126.2 (d), 125.9 (d), 118.4 (d), 104.4 (s), 89.6 (s), 86.0 (s), 84.4 (s), 80.4 (d), 75.9 (d), 75.7 (d), 74.0 (s), 52.3 (q), 43.2 (t), 39.4 (t), 36.9 (t), 34.5 (t), 34.5 (t), 34.4 (d), 33.5 (d), 31.8 (d), 29.7 (t), 28.0 (q), 27.8 (q), 22.3 (q), 20.7 (q), 20.2 (q), 18.9 (q) and 11.1 (q).

(1*S*,3*S*,4*S*,5*R*,6*R*,7*R*)-Trimethyl 6-{[(4*R*,6*S*)-4,6-dimethyloctanoyl]oxy}-1-[(3*RS*,5*S*)-3,5-dimethyl-6-phenylhexyl]-4,7-dihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate 19

A mixture of tripotassium salt **18** (150 mg, 0.20 mmol), sodium hydrogen carbonate (252 mg, 3.0 mmol) and methyl iodide (0.075 cm^3, 1.2 mmol) was stirred in DMF (2 cm^3) for 23 h at 20 °C. The suspension was poured into water (15 cm^3) and extracted with diethyl ether (50 cm^3). The organic phase was washed with aqueous sodium hydrogen carbonate (3 × 15 cm^3), water (15 cm^3), brine (15 cm^3), then dried and evaporated to a gum (112 mg). This was purified by column chromatography on silica gel eluting with ethyl acetate–cyclohexane (1:3) to give the trimethyl ester **19** as a white foam (110 mg, 81%) [Found: (CI) $(M + H)^+$, 679.3711. $C_{36}H_{55}O_{12}$ requires (*M* + H), 679.3693]; analytical HPLC t_r 5.23 min, 97.7% (column A; 80% MeCN–H_2O); $\nu_{max}(CHBr_3)/cm^{-1}$ 3550, 1769, 1736 and 1251; δ_H(250 MHz; $CDCl_3$) 0.76–0.95 (15H, m, CH_3), 2.57 (0.5H, dd, *J* 13 and 6, C*H*$_2$Ph), 2.68 (0.5H, dd, *J* 13 and 5, C*H*$_2$Ph), 3.13 (1H, t, *J* 2.5, 7-OH), 3.76, 3.80 and 3.92 (3s, 3H each, CO_2CH_3), 3.77 (1H, s, 4-OH), 4.00 (1H, m, 7-H), 5.23 (1H, s, 3-H), 5.75 (1H, m, 6-H) and 7.10–7.32 (5H, m, Ph); *m*/*z* (DCI–NH_3) 696 $(M + NH_4)^+$.

(1*S*,3*S*,4*S*,5*R*,6*R*,7*R*)-Trimethyl 4,7-diacetoxy-6-{[(4*R*,6*S*)-4,6-dimethyloctanoyl]oxy}-1-[(3*RS*,5*S*)-3,5-dimethyl-6-phenylhexyl]-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate 17

A solution of the diol **19** (94.9 mg, 0.14 mmol) in acetic anhydride (2 cm^3) was cooled to 0 °C under nitrogen and treated with TMSOTf (0.001 cm^3, 0.005 mmol). After 5 min at 0 °C the reaction was treated with saturated sodium hydrogen carbonate (75 cm^3), stirred for 10 min and extracted with ethyl acetate (3 × 25 cm^3). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (25 cm^3), brine (25 cm^3), then dried and evaporated to a gum (89.1 mg). This was purified by column chromatography on silica gel eluting with ethyl acetate–cyclohexane (1:4) to give the diacetate **17** as a colourless gum (70.1 mg, 66%) [Found: (CI) $(M + H)^+$, 763.3931. $C_{40}H_{59}O_{14}$ requires (*M* + H), 763.3904]; analytical HPLC t_r 11.042 min, 95.2% (column A; 80% MeCN–H_2O); $\nu_{max}(CHBr_3)/cm^{-1}$ 1770, 1749 and 1220; δ_H(250 MHz; $CDCl_3$) 0.76–0.93 (15H, m, CH_3), 2.10 and 2.16 (2s, 3H each, AcO), 2.58 (0.5H, dd, *J* 13 and 6, C*H*$_2$Ph), 2.68 (0.5H, dd, *J* 13 and 5, C*H*$_2$Ph), 3.77, 3.79 and 3.89 (3s, 3H each, CO_2CH_3), 5.07 (1H, s, 3-H), 5.20 (1H, m, 7-H), 6.43 (1H, d, *J* 2, 6-H) and 7.10–7.32 (5H, m, Ph); *m*/*z* (DCI–NH_3) 780 $(M + NH_4)^+$.

(1*S*,3*S*,4*S*,5*R*,6*R*,7*R*)-Trimethyl 7-acetoxy-6-{[(4*R*,6*S*)-4,6-dimethyloctanoyl]oxy}-1-[(3*RS*,5*S*)-3,5-dimethyl-6-phenylhexyl]-4-hydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate 20

Boron trifluoride–diethyl ether (0.001 cm^3, 0.008 mmol) was added to a solution of diacetate **17** (14.6 mg, 0.019 mmol) and triethylsilane (0.0022 cm^3, 0.014 mmol) in dichloromethane (0.5 cm^3) and the mixture was stirred for 0.5 h at 0 °C and 11 days at 20 °C. The mixture was then treated with aqueous sodium hydrogen carbonate (15 cm^3) and ethyl acetate (15 cm^3). The aqueous phase was extracted with ethyl acetate (3 × 5 cm^3) and the combined organic extracts were washed with aqueous sodium hydrogen carbonate (5 cm^3), brine (5 cm^3), then dried and evaporated to a gum. This was chromatographed on silica gel eluting with ethyl acetate–cyclohexane (1:2) to give alcohol **20** (7.7 mg, 56%), as a white foam (Found: C, 63.4; H, 7.9. $C_{38}H_{56}O_{13}$ requires C, 63.32; H, 7.83%); analytical HPLC t_r 3.124 min 96.7% (column A; 90% MeCN–H_2O); $\nu_{max}(CHBr_3)/cm^{-1}$ 3496, 1768, 1746 and 1222; δ_H(250 MHz; $CDCl_3$) 0.78–0.95 (15H, m, CH_3), 2.17 (3H, s, AcO), 2.58 (0.5H, dd, *J* 13 and 6, C*H*$_2$Ph), 2.68 (0.5H, dd, *J* 13 and 5, C*H*$_2$Ph), 3.76, 3.77 and 3.95 (3s, 3H each, CO_2CH_3), 5.08 (1H, s, 3-H), 5.21 (1H, m, 7-H), 6.28 (1H, d, *J* 2, 6-H) and 7.08–7.30 (5H, m, Ph); *m*/*z* (FAB +ve) 721 $[(M + H)^+$, 40%], 743 $[(M + Na)^+$, 20%].

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References

1 M. J. Dawson, J. E. Farthing, P. S. Marshall, R. F. Middleton, M. J. O'Neill, A. Shuttleworth, C. Stylli, R. M. Tait, P. M. Taylor, G. Wildman, A. D. Buss, D. Langley and M. V. Hayes, *J. Antibiot.*, 1992, **45**, 639.

2 W. M. Blows, G. Foster, S. J. Lane, D. Noble, J. E. Piercey, P. J. Sidebottom and G. Webb, *J. Antibiot.*, 1994, **47**, 740.

3 P. J. Sidebottom, R. M. Highcock, S. J. Lane, P. A. Procopiou and N. S. Watson, *J. Antibiot.*, 1992, **45**, 648.

4 A. Baxter, B. J. Fitzgerald, J. L. Hutson, A. D. McCarthy, J. M. Motteram, B. C. Ross, M. Sapra, M. A. Snowden, N. S. Watson, R. J. Williams and C. Wright, *J. Biol. Chem.*, 1992, **267**, 11 705.

5 P. A. Procopiou, E. J. Bailey, M. J. Bamford, A. P. Craven, B. W. Dymock, J. G. Houston, B. E. Kirk, A. D. McCarthy, M. Sareen, J. J. Scicinski, P. J. Sharratt, M. A. Snowden, N. S. Watson and R. J. Williams, *J. Med. Chem.*, 1994, **37**, 3274.

6 J. D. Bergstrom, M. M. Kurtz, D. J. Rew, A. M. Amend, J. D. Karkas, R. G. Bostedor, V. S. Bansal, C. Dufresne, F. L. VanMiddlesworth, O. D. Hensens, J. M. Liesch, D. L. Zink, K. E. Wilson, J. Onishi, J. A. Milligan, G. Bills, L. Kaplan, M. Nallin-Omstead, R. G. Jenkins, L. Huang, M. S. Meinz, L. Quinn, R. W. Burg, Y. L. Kong, S. Mochales, M. Mojena, I. Martin, F. Pelaez, M. T. Diez and A. W. Alberts, *Proc. Natl. Acad. Sci. USA*, 1993, **90**, 80.

7 O. D. Hensens, C. Dufresne, J. M. Liesch, D. L. Zink, R. A. Reamer and F. L. VanMiddlesworth, *Tetrahedron Lett.*, 1993, **34**, 399.

8 C. Dufresne, K. E. Wilson, D. Zink, J. Smith, J. D. Bergstrom, M. Kurtz, D. Rew, M. Nallin, R. Jenkins, K. Bartizal, C. Trainor, G. Bills, M. Meinz, L. Huang, J. Onishi, J. Milligan, M. Mojena and F. Pelaez, *Tetrahedron*, 1992, **48**, 10 221.
9 K. E. Wilson, R. M. Burk, T. Biftu, R. G. Ball and K. Hoogsteen, *J. Org. Chem.*, 1992, **57**, 7151.
10 K. Hasumi, K. Tachikawa, K. Sakai, S. Marakawa, N. Yoshikawa, S. Kumazawa and A. Endo, *J. Antibiot.*, 1993, **46**, 689.
11 T. T. Dabrah, H. J. Harwood Jr., L. H. Huang, N. D. Jankovich, T. Kaneko, J.-C. Li, S. Lindsey, P. M. Moshier, T. A. Subashi, M. Therrien and P. C. Watts, *J. Antibiot.*, 1997, **50**, 1.
12 P. A. Procopiou, E. J. Bailey, J. L. Hutson, B. E. Kirk, P. J. Sharratt, S. J. Spooner and N. S. Watson, *Bioorg. Med. Chem. Lett.*, 1993, **3**, 2527.
13 N. S. Watson, R. Bell, C. Chan, B. Cox, J. L. Hutson, S. E. Keeling, B. E. Kirk, P. A. Procopiou, I. P. Steeples and J. Widdowson, *Bioorg. Med. Chem. Lett.*, 1993, **3**, 2541.
14 G. M. P. Giblin, R. Bell, A. P. Hancock, C. D. Hartley, G. G. A. Inglis, J. J. Payne, P. A. Procopiou, A. H. Shingler, C. Smith and S. J. Spooner, *Bioorg. Med. Chem. Lett.*, 1993, **3**, 2605.
15 M. G. Lester, G. M. P. Giblin, G. G. A. Inglis, P. A. Procopiou, B. C. Ross and N. S. Watson, *Tetrahedron Lett.*, 1993, **34**, 4357.
16 C. Chan, G. G. A. Inglis, P. A. Procopiou, B. C. Ross, A. R. P. Srikantha and N. S. Watson, *Tetrahedron Lett.*, 1993, **34**, 6143.
17 C. Chan, D. Andreotti, B. W. Dymock, S. E. Keeling, P. A. Procopiou, B. C. Ross, M. Sareen, P. J. Sharratt, M. A. Snowden and N. S. Watson, *J. Med. Chem.*, 1996, **39**, 207.
18 C. Chan, J. J. Scicinski, A. R. P. Srikantha and N. S. Watson, *Tetrahedron Lett.*, 1996, **49**, 8925.
19 P. J. Sharratt, J. L. Hutson, G. G. A. Inglis, M. G. Lester, P. A. Procopiou and N. S. Watson, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 661.
20 R. E. Shaw, C. Burgess, R. P. C. Cousins, G. M. P. Giblin, D. G. H. Livermore, A. H. Shingler, C. Smith and P. M. Youds, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 2155.
21 D. Andreotti, P. A. Procopiou and N. S. Watson, *Tetrahedron Lett.*, 1994, **35**, 1789.
22 P. A. Procopiou, E. J. Bailey, C. Chan, G. G. A. Inglis, M. G. Lester, A. R. P. Srikantha, P. J. Sidebottom and N. S. Watson, *J. Chem. Soc., Perkin Trans. 1*, 1995, 1341.
23 B. Cox, J. L. Hutson, S. E. Keeling, B. E. Kirk, A. R. P. Srikantha and N. S. Watson, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 1931.
24 M. J. Bamford, C. Chan, A. P. Craven, B. W. Dymock, D. Green, R. A. Henson, B. E. Kirk, M. G. Lester, P. A. Procopiou, M. A. Snowden, S. J. Spooner, A. R. P. Srikantha, N. S. Watson and J. A. Widdowson, *J. Med. Chem.*, 1995, **38**, 3502.
25 P. A. Procopiou, B. Cox, B. E. Kirk, M. G. Lester, A. D. McCarthy, M. Sareen, P. J. Sharratt, M. A. Snowden, S. J. Spooner, N. S. Watson and J. Widdowson, *J. Med. Chem.*, 1996, **39**, 1413.
26 M. G. Lester, G. L. Evans, R. A. Henson, P. A. Procopiou, M. Sareen, M. A. Snowden, S. J. Spooner, A. R. P. Srikantha and N. S. Watson, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 2683.
27 N. S. Watson and P. A. Procopiou, Squalene Synthase Inhibitors: Their Potential as Hypocholesterolaemic Agents, in *Progress in Medicinal Chemistry*, eds. G. P. Ellis and D. K. Luscombe, Elsevier, Amsterdam, 1996, vol. 33, ch. 7, pp. 331–378.
28 (*a*) K. C. Nicolaou, A. Nadin, J. E. Leresche, E. W. Yue and S. La Greca, *Angew. Chem.*, *Int. Ed. Engl.*, 1994, **33**, 2190; (*b*) K. C. Nicolaou, E. W. Yue, Y. Naniwa, F. De Riccardis, A. Nadin, J. E. Leresche, S. La Greca and Z. Yang, *Angew. Chem.*, *Int. Ed. Engl.*, 1994, **33**, 2184; (*c*) K. C. Nicolaou, A. Nadin, J. E. Leresche, S. La Greca, T. Tsuri, E. W. Yue and Z. Yang, *Angew. Chem.*, *Int. Ed. Engl.*, 1994, **33**, 2187; (*d*) K. C. Nicolaou, E. W. Yue, S. La Greca, A. Nadin, Z. Yang, J. E. Leresche, T. Tsuri, Y. Naniwa and F. De Riccardis, *Chem. Eur. J.*, 1995, **1**, 467.
29 (*a*) D. Stoermer, S. Caron and C. H. Heathcock, *J. Org. Chem.*, 1996, **61**, 9115; (*b*) S. Caron, D. Stoermer, A. Kathryn Mapp and C. H. Heathcock, *J. Org. Chem.*, 1996, **61**, 9126.
30 (*a*) E. M. Carreira and J. Du Bois, *J. Am. Chem. Soc.*, 1994, **116**, 10 825; (*b*) E. M. Carreira and J. Du Bois, *J. Am. Chem. Soc.*, 1995, **117**, 8106.
31 D. A. Evans, J. C. Barrow, J. L. Leighton, A. J. Robichaud and M. J. Sefkow, *J. Am. Chem. Soc.*, 1994, **116**, 12 111.
32 A. Nadin and K. C. Nicolaou, *Angew. Chem.*, *Int. Ed. Engl.*, 1996, **35**, 1622.
33 M. Zottola, B. V. Rao and B. Fraser-Reid, *J. Chem. Soc.*, *Chem. Commun.*, 1991, 969.
34 D. N. Kursanov, Z. N. Parnes and N. M. Loim, *Synthesis*, 1974, 633.
35 D. D. Dhavale, E. Tagliavini, C. Trombini and A. Umani-Ronchi, *Tetrahedron Lett.*, 1988, **29**, 6163.
36 P. Angibeaud and J.-P. Utille, *J. Chem. Soc.*, *Perkin Trans. 1*, 1990, 1490.
37 P. Angibeaud, C. Bosso and J.-P. Utille, *Carbohydr. Res.*, 1990, **198**, 403.
38 P. A. Procopiou, S. P. D. Baugh, S. S. Flack and G. G. A. Inglis, *Chem. Commun.*, 1996, 2625.
39 T. Tsunoda, M. Suzuki and R. Noyori, *Tetrahedron Lett.*, 1979, **48**, 4679.
40 F. Elsinger, J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta*, 1960, **43**, 113.
41 M. Harmata, *Tetrahedron*, 1997, **53**, 6235.

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