An observation on the regioselectivity of ring-opening of some substituted cyclohexenyl epoxides

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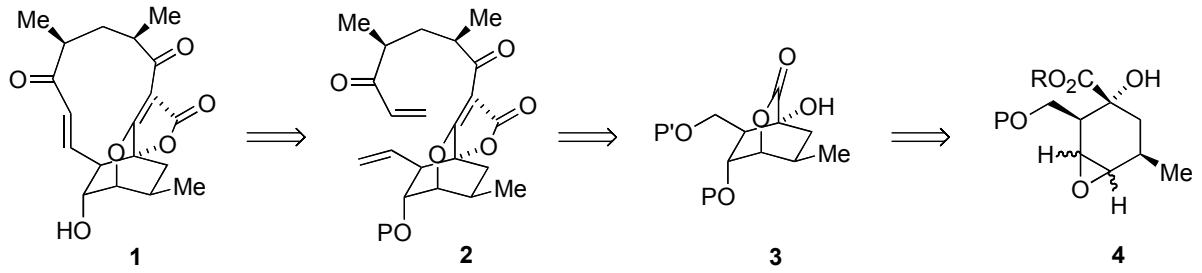
Dedicated to Professor Atta-ur-Rahman on the occasion of his 65th birthday

Abstract
Attempted epoxidation of the cyclohexenyl carboxylic acid **11** using *m*-chloroperoxybenzoic acid was accompanied by epoxide ring-opening and gave a mixture of lactones **13**, **14** and **15**, ratio 20 : 40 : 40, respectively. In contrast, treatment of the *cis*-hydroxyepoxide **18** of the methyl ester **12** with aqueous sulfuric acid in acetonitrile gave the lactone **14** with excellent regioselectivity together with the triol **22**. The *trans*-hydroxyepoxide **19** gave only the lactone **14** under these conditions.

Keywords: Epoxide ring-opening, lactone, regioselectivity, abyssomicin C

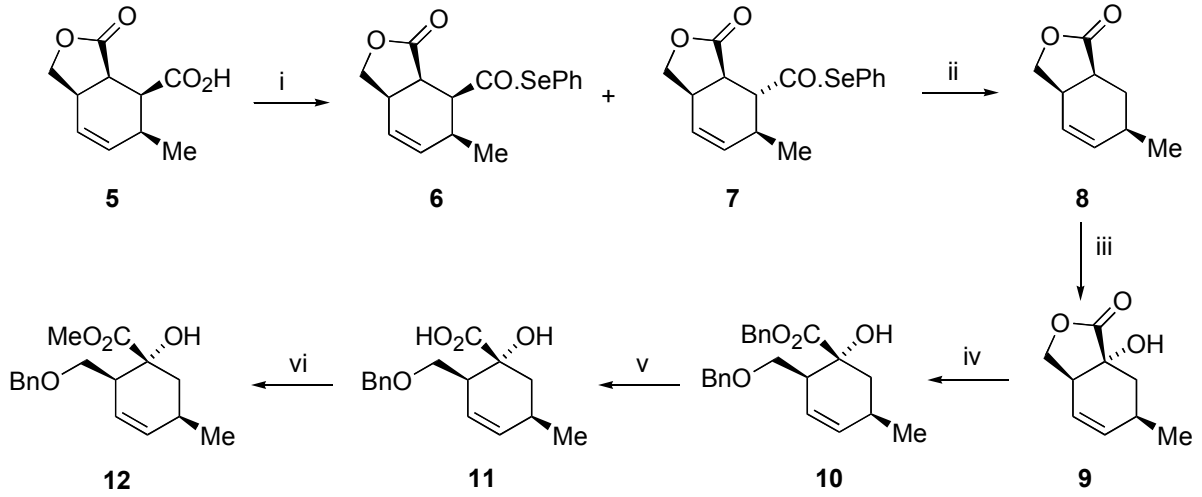
Introduction

The abyssomicins are a small group of antibacterial macrocyclic polyketides isolated from a marine *Verrucosispora* strain which exhibit biological activity as inhibitors of *p*-aminobenzoic acid biosynthesis.[1] Several approaches to the total synthesis of these compounds have been reported[2] and two total syntheses have already been described.[3] We independently[4] envisaged a strategy for the synthesis of abyssomicin C **1** in which the C8-C9 double-bond would be introduced by ring-closing metathesis, and the metathesis precursor **2** prepared by fusing the tetronic acid fragment onto the bicyclic lactone **3**. This lactone, in turn, was to be prepared by regioselective ring-opening of epoxides **4**. This approach to the tricyclic core of the abyssomicins differs from those already reported[2a,2b,3b] where preformed tetronic acids act as the nucleophile for intramolecular epoxide ring-opening. Since our approach is dependent on the ring-opening of epoxides **4** being regioselective, we report preliminary studies on the regioselectivity of ring-opening of these epoxides which were carried out in order to evaluate routes to lactones **3**.



Results and Discussion

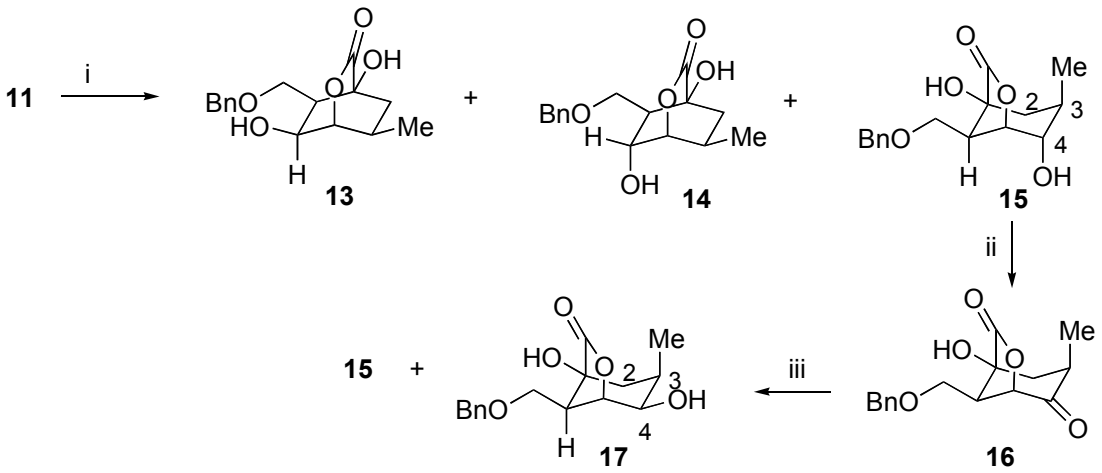
The bicyclic lactone **8** was identified as a precursor of epoxides **4**. It has been prepared by an intramolecular Diels Alder reaction of sorbyl acrylate[5] and by an intermolecular Diels Alder reaction of methyl acrylate and sorbyl alcohol mediated by methylmagnesium bromide.[6] In our hands, however, decarboxylation of the Diels Alder product **5**[7] of sorbyl alcohol and maleic anhydride by tributyltin hydride mediated decarbonylation[8] of the phenylselanyl esters **6** and **7**, was convenient and scaleable, see Scheme 1. Hydroxylation was achieved using the Davis oxaziridine[9] to give the hydroxy-lactone **9**,[2b] and treatment with potassium hydroxide in toluene in the presence of benzyl bromide gave the benzyl ester **10**.[2b,10] This was saponified to give the acid **11** and the acid converted into the methyl ester **12** using trimethylsilyl diazomethane.



Scheme 1. *Reagents and conditions*: i, (a) Et_3N, (b) Bu_3P, PhSeCl, THF, r.t. (**6**, 60%; **7**, 20%); ii, Bu_3SnH, AIBN (cat.) (95%); iii, KHMDS, -78 to –20 °C, 30 min, then (±)-3-phenyl-2-(phenylsulfonyl)oxaziridine, -78 °C, 3 h (70%); iv, KOH, BnBr, toluene, reflux, 48 h (83%); v, NaOH, MeCN (59%); vi, $TMSCHN_2$, toluene, methanol, 0 °C, 1 h (90%).

Having prepared esters **10** and **12**, and the acid **11**, the stereoselectivity of epoxidation of these compounds and the regioselectivity of epoxide ring-opening was investigated. First, a one-

step procedure of epoxidation and ring-opening was attempted on the acid **11**. After treatment of the acid **11** with *m*-chloroperoxybenzoic acid at room temperature in chloroform for 72 h, three products were isolated which were identified, in increasing order of polarity (tlc), as lactone **13** (15%), the required lactone **14** (30%) and the regioisomeric lactone **15** (30%).



Scheme 2. *Reagents and conditions:* i, *m*CPBA, $CHCl_3$, r.t., 72 h (**13**, 15%; **14**, 30%; **15**, 30%); ii, PCC, CH_2Cl_2 (85%); iii, $NaBH_4$, EtOH (81%, **17** : **15** = 50 : 50).

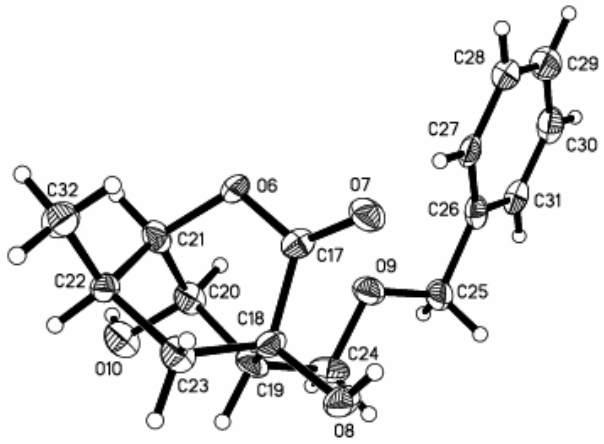
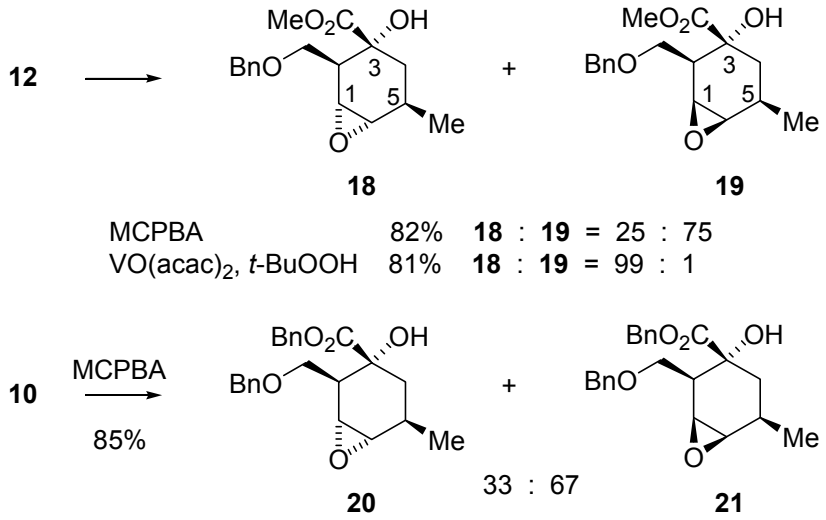


Figure 1. The structure of the lactone **14** as established by X-ray diffraction.

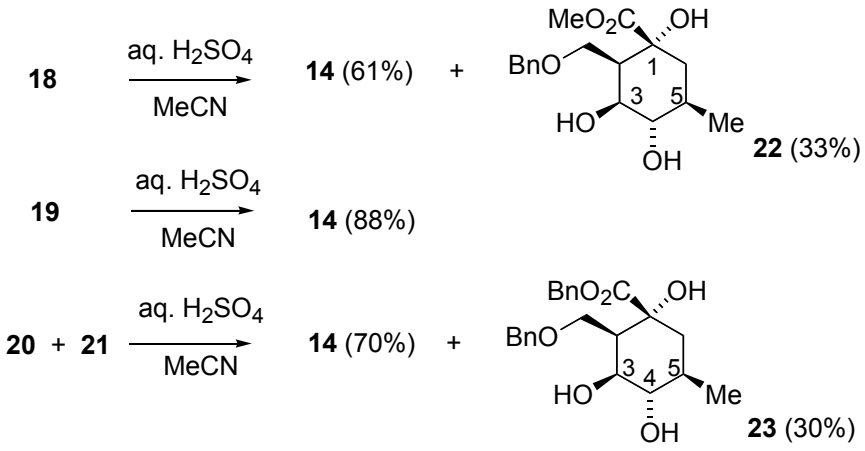
The structure of the crystalline lactone, which was the second product off the column, was identified as the required lactone **14** by X-ray diffraction, see Figure 1. The most polar lactone was shown to be the regioisomeric lactone **15** by oxidation to the ketone **16** followed by reduction which gave a mixture of the separable lactones **15** and **17**. Spin-decoupling experiments on lactone **17** indicated that the C*H*OH proton was coupled with the C*H*CH_3 proton so confirming the regiochemistry of lactones **15** and **17** as shown. The configuration of the

hydroxyl bearing carbon, C-4, in lactones **15** and **17** was provisionally assigned on the assumption that the hydroxyl group would be introduced *trans* with respect to the lactone bridge by epoxide opening. However, this assignment is tentative since the products may be the result of thermodynamic control. The structure of lactone **13** was assigned by comparison of the carbonyl stretching frequency in its IR with that of lactone **14**, from its ^{1}H NMR, and from the identification of lactones **14**, **15** and **17** as the other three possible regio- and stereo-isomers.

To see whether a regioselective synthesis of the lactone **14** could be achieved, rearrangements of the epoxides obtained from the ester **12** were investigated. Epoxidation of this ester using *m*-chloroperoxybenzoic acid gave a 25 : 75 mixture of the *cis*-hydroxyepoxide **18** and its *trans*-diastereoisomer **19** (82%) whereas epoxidation using *tert*-butyl hydroperoxide in the presence of vanadyl acetylacetonate gave the *cis*-isomer **18** (81%) only. The structures of epoxides **18** and **19** were assigned by analogy with the literature,[2b] and were consistent with nOe studies since enhancement of an epoxide proton was observed on irradiation of the 5-CH_3 group only for the *cis*-epoxide **18** and irradiation of H-2 and H-5 enhanced the epoxide protons only for the *trans*-isomer **19**. The benzyl ester **10** was also epoxidised using *m*-chloroperoxybenzoic acid to give a 33 : 67 mixture of the *cis*- and *trans*-hydroxyepoxides **20** and **21**, the stereochemistry of these epoxides being assigned by analogy with the literature[2b] and by comparison with methyl esters **18** and **19**.



Acid catalysed rearrangement of the *cis*-hydroxyepoxide **18** using aqueous sulfuric acid in acetonitrile gave the required bicyclic lactone **14** (61%) together with the trihydroxy-ester **22** (33%). Under these conditions, the *trans*-epoxide **19** gave only the lactone **14** (88%), and the mixture of benzyl ester epoxides **20** and **21** gave the lactone **14** (70%) and the trihydroxy-ester **23** (30%). The configuration of the triol **23** was assigned on the basis of the diaxial couplings of *ca*. 10 Hz observed between H-3 and H-4 and between H-4 and H-5, and the axial – equatorial coupling of 3 Hz observed between H-2 and H-3. The structure of the trihydroxy methyl ester **22** was assigned by analogy.



Conclusions

Since the ester and the epoxide are *cis*-disposed in the *trans*-hydroxyepoxide **19**, direct participation of the ester in epoxide ring-opening is not possible and so the epoxide ring-opening must involve a regioselective acid catalysed attack of water at C-1 (epoxide numbering), with subsequent lactonisation giving lactone **14**. For the *cis*-hydroxyepoxide **18**, the triol **22** must also have been formed by ring-opening of the epoxide initiated by attack of water at C-1. However, the mechanism of formation of the lactone **14** from the *cis*-hydroxyepoxide **18** is ambiguous since either hydrolysis of the epoxide followed by lactonisation or direct acid-catalysed epoxide ring-opening involving the ester carbonyl oxygen may be involved. Similar processes must be involved in the fomation of the lactones **13**, **14** and **15** during the reaction between the acid **11** and *m*-chloroperoxybenzoic acid with a double-inversion process giving the unexpected hydroxylactone **13** in which the hydroxyl group is *cis*-disposed with respect to the lactone bridge. However, notwithstanding mechanistic complexities, this work has resulted in a regio- and stereo-selective synthesis of lactone **14** which may be useful for a synthesis of the abyssomicins.

Experimental Section

General Procedures. Low resolution mass spectra were recorded on a Micromass Trio 200 spectrometer and high resolution mass spectra on a Kratos Concept IS spectrometer using electron impact ionisation (EI), chemical ionisation using ammonia (CI) or electrospray in the positive mode (ES). For selenium containing compounds, only peaks corresponding to isotope ^{80}Se are quoted although characteristic isotope patterns were seen. Infrared spectra were recorded on a Genesis FTIR as evaporated films on sodium chloride plates and nuclear magnetic

resonance (NMR) spectra using deuterated chloroform as solvent unless otherwise stated. Proton NMR spectra were recorded on Bruker (500 MHz) and Varian Unity 500 (500 MHz) spectrometers. Residual non-deuterated solvent was used as internal standar and coupling constants are in Hz. Flash column chromatography was carried out using silica gel 60H (40 – 60 nm, 230 – 300 mesh) from Merck. Light Petroleum refers to the fraction that boils between 40 ^{o}C and 60 ^{o}C and was distilled prior to use. Ether refers to diethyl ether which was used without purification.

(1*RS*,2*SR*,3*SR*,6*RS*)-3-Methyl-9-oxo-8-oxabicyclo[4.3.0]non-4-ene-2-carboselenoic acid Se-phenyl ester (6) and (1*RS*,2*RS*,3*SR*,6*RS*)-3-methyl-9-oxo-8-oxabicyclo[4.3.0]non-4-ene-2-carboselenoic acid Se-phenyl ester (7). A solution of triethylamine (4.74 mL, 34 mmol) in CH_2Cl_2 (55 mL) was added to a suspension of the acid **5**[7] (6.68 g, 34 mmol), in CH_2Cl_2 (165 mL) at r.t under N_2 and the mixture stirred at room temperature for 10 min before being concentrated under reduced pressure to give the triethylammonium carboxylate salt as an orange oil. Tributylphosphine (12.63 mL, 51.17 mmol) was separately added dropwise to phenyl selenenyl chloride (10 g, 51.17 mmol) in tetrahydrofuran (250 mL) under N_2 and the resulting yellow solution stirred for 15 min. The triethylammonium carboxylate salt was then added as a suspension in tetrahydrofuran (250 mL). The cloudy mixture was stirred at ambient temperature under N_2, for 48 h, added to ether (300 mL), and the mixture washed with water (2 x 500 mL) and dried ($MgSO_4$). After concentration under reduced pressure, the orange residue was chromatographed (1:1, ether: light petroleum) to give *title compound* **7** (2.27 g, 6.76 mmol, 20 %) as an oil (Found: M^++NH_4, 354.0605. $C_{16}H_{20}NO_3{}^{80}Se$ requires *M*, 354.0603); ν_{max} 1771, 1708, 1153, 1016, 986 and 739 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.45 (2 H, m, ArH), 7.32 (3 H, m, ArH), 5.71 (1H, ddd, *J* 2, 4, 10, 4-H), 5.51 (1 H, td, *J* 2.5, 10, 5-H), 4.35 (1 H, dd, *J* 7, 9, 7-H), 3.97 (1 H, dd, *J* 4, 9, 7-H'), 3.13 (1 H, m, 6-H), 3.12 (1 H, m, 1-H), 3.07 (1 H, dd, *J* 5.5, 8, 2-H), 2.60 (1 H, m, 3-H) and 1.12 (3 H, d, *J* 7, 3-CH_3); δ_C (75 MHz, $CDCl_3$), 202.6, 177.0, 136.3, 133.8, 129.9, 129.6, 126.4, 124.2, 72.0, 55.2, 39.8, 34.5, 31.8 and 21.4; Further elution gave the the *title compound* **6** (6.89 g, 20.5 mmol, 60 %) as a white solid, m.p : 88.6 - 91.4 ^{o}C (Found: C, 57.5; H, 4.8 %; $C_{16}H_{16}O_3Se$ requires C, 57.3, H, 4.8%; Found: M^+ + NH_4, 354.0605. $C_{16}H_{20}NO_3{}^{80}Se$ requires *M*, 354.0603); ν_{max} 1773, 1710, 1477, 1373, 1209, 1153, 1016, 986, 806 and 740 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.45 (2 H, m, ArH), 7.28 (3 H, m, ArH), 5.70 (1 H, ddd, *J* 2, 4, 12, 4-H), 5.54 (1 H, td, *J* 2, 12, 5-H), 4.34 (1 H, t, *J* 8.5, 7-H), 4.07 (1 H, dd, *J* 5, 8.5, 7-H'), 3.37 (1 H, t, *J* 5.5, 2-H), 3.21 (1 H, dd, *J* 5.5, 9.5, 1-H), 3.15 (1 H, m, 6-H), 2.69 (1 H, m, 3-H), 1.22 (3 H, d, *J* 7.5, 3-CH_3); δ_C (75 MHz, $CDCl_3$), 200.3, 176.7, 136.4, 133.6, 131.9, 129.8, 125.0, 124.9, 71.6, 54.3, 39.9, 35.8, 31.5 and 18.4; *m/z* (CI^+) 354 (M^++ 18, 100 %).

(1*SR*,3*RS*,6*RS*)-3-Methyl-9-oxo-8-oxabicyclo[4.3.0]non-4-ene (8).[2b,5] A solution of AIBN (30 mg, 0.19 mmol) and tributyltin hydride (3.2 mL, 11.24 mmol) in toluene (125 mL) was added dropwise over 30 min to a solution of the phenylselanyl esters **6** and **7** (2.51 g, 7.49 mmol) in toluene (125 mL) at reflux under nitrogen and the mixture stirred under reflux for 36 h. After cooling, the reaction mixture was added to aqueous potassium fluoride (250 mL) at 0 ^{o}C and the biphasic mixture stirred for 30 min. The aqueous layer was extracted with ether (250 mL) and

the combined organic layers dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography of the residue using light petroleum and ether (2 : 1) as eluent gave the *title compound* **8** (1.08 g, 7.1 mmol, 95 %) as a clear oil (Found: $M^+ + NH_4$, 170.1176. $C_9H_{16}NO_2$ requires *M*, 170.1176); ν_{max} 3021, 1765, 1484, 1457, 1374, 1329, 1300, 1208, 1151, 1086, 1037, 1011, 986, 901, 836, 771, 741 and 685; δ_H (500 MHz, $CDCl_3$) 5.69 (1 H, dd, *J* 5, 12, 4-H), 5.51 (1 H, ddd, *J* 2.5, 4, 12, 5-H), 4.40 and 3.85 (each 1 H, t, *J* 8.5, 7-H), 3.00 (1 H, m, 6-H), 2.64 (1 H, ddd, *J* 5, 7, 13, 1-H), 2.19 (1 H, m, 3-H), 1.97 and 1.29 (each 1 H, m, 2-H) and 1.00 (3 H, d, *J* 7, 3-CH_3); δ_C (75 MHz, $CDCl_3$) 179.6, 136.7, 122.8, 72.2, 38.4, 35.2, 29.2, 29.0, 21.4; *m/z* (CI) 170 ($M^+ + 18$, 100 %).

(1*RS*,3*RS*,6*SR*)-1-Hydroxy-3-methyl-9-oxo-8-oxabicyclo[4.3.0]non-4-ene (9).[2b] Potassium hexamethyldisilylazide (0.5 M in toluene, 4.2 mL, 2.11 mmol) was added to the lactone **8** (230 mg, 1.51 mmol) in tetrahydrofuran (15 mL) at – 78 °C under nitrogen and the solution stirred at -78 °C for 10 min and at – 20 °C for 30 min. After re-cooling to –78 °C, the 2-sulfonyloxaziridine (423 mg, 1.62 mmol) in tetrahydrofuran (3 mL) was added and the mixture stirred for 3 h at – 78 °C. After being allowed to warm to 0 °C, saturated aqueous ammonium chloride (20 mL) was added, and the aqueous layer acidified to pH 4 with aqueous hydrogen chloride (1 M, 2.3 mL). After extraction with ether (3 x 25 mL), the combined organic layers were dried (Na_2SO_4) and concentrated under reduced presure. Chromatography of the residue using light petroleum and ether (gradient ellution up to 1 : 2) gave the *title compound* **9** (177 mg, 1.05 mmol, 70 %), as a white crystalline solid, m.p: 72.9 -74.0 °C (Found: C, 63.75; H, 7.0%. $C_9H_{12}O_3$ requires C, 64.3; H, 7.2 %; Found: $M^+ + NH_4$, 186.1129. $C_9H_{16}NO_3$ requires *M*, 186.1125); ν_{max} 3427, 1769, 1331, 1221, 1146, 1105, 1012, 975 and 748 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 5.73 (1 H, dd, *J* 1, 10, 4-H), 5.52 (1 H, ddd, *J* 2.5, 4, 10, 5-H), 4.45 (1 H, t, *J* 9, 7-H), 3.65 (1H, dd, *J* 9, 10.5, 7-H'), 2.91 (1 H, m, 6-H), 2.59 (1 H, br. s, OH), 2.49 (1 H, m, 3-H), 1.79 (1 H, ddd, *J* 1, 5, 14, 2-H), 1.26 (1 H, dd, *J* 11.5, 14, 2-H') and 1.02 (3 H, d, *J* 7, 3-CH_3); δ_C (75 MHz, $CDCl_3$), 179.8, 136.5, 121.0, 72.9, 70.8, 42.3, 36.1, 52.9 and 20.9; *m/z* (CI) 186 (M^++18, 100%).

Benzyl (1*RS*,2*SR*,5*RS*)-2-benzyloxymethyl-1-hydroxy-5-methylcyclohex-3-ene-1-carboxylate (10).[2b] Benzyl bromide (6.14 mL, 52.36 mmol) was added to a suspension of lactone **9** (2.2 g, 13.09 mmol) and potassium hydroxide (3.16 g, 56.3 mmol) in toluene (20 mL) under nitrogen. The mixture was stirred under reflux for 48 h, cooled to room temperature, diluted with ethyl acetate (30 mL), washed with water (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography using light petroleum and ether (70 : 30) as eluent gave the *title compound* **10** (4.0 g, 10.92 mmol, 83 %) as a solid, m.p. 63-63.7 °C (Found: $M^+ + NH_4$, 384.2177. $C_{23}H_{30}NO_4$ requires *M*, 384.2169); ν_{max} 3497, 3030, 1728, 1497, 1454, 1223, 1162, 1117, 1026, 737 and 698 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.15 (10 H, m, ArH), 5.58 (1 H, dd, *J* 1.5, 10, 4-H), 5.37 (1 H, ddd, *J* 2.5, 4.5, 10, 3-H), 4.92 and 4.79 (each 1 H, d, *J* 12.5, PhHC*H*), 4.21 (2 H, s, $PhCH_2$), 3.26 (1 H, dd, *J* 3.5, 10, 2-CH), 3.19 (1 H, dd, *J* 9, 10, 2-CH'), 2.93 (1 H, br. s, OH), 2.43 (1 H, m, 2-H), 2.29 (1 H, m, 5-H), 1.79 (1 H, dd, *J* 5.5, 13.5, 6-H_{eq}), 1.55 (1 H, dd, *J* 11, 13.5, 6-H_{ax}) and 0.91 (3 H, d, *J* 7, 5-CH_3); δ_C (75 MHz, $CDCl_3$) 175.6. 138.2, 135.8, 135.3,

128.8, 128.6, 128.5, 128.4, 128.0, 127.9, 123.2, 74.7, 73.1, 71.1, 67.6, 47.4, 35.2, 27.5 and 21.1; *m/z* (CI) 384 (M^++18, 100%) and 367 (M^++1, 97).

(1*RS*,2*SR*,5*RS*)-2-Benzyloxymethyl-1-hydroxy-5-methylcyclohex-3-ene-1-carboxylic acid (11). Sodium hydroxide (3.3 g, 82.5 mmol) in water (22 mL) was added to the benzyl ester **10** (4.0 g, 11.13 mmol) in acetonitrile (110 mL) and the solution stirred under reflux for 24 h. After concentration under reduced pressure, the aqueous residue was washed with ether, cooled to 0 ^oC and diluted to 50 mL with water. Aqueous hydrogen chloride (1 M) added until the pH was between 1 and 2. The solution was then extracted with dichloromethane (3 x 50 mL) and the extracts dried (Na_2SO_4) and concentrated under reduced pressure. Recrystallization of the residue from toluene and methanol (50 : 1) gave the *title compound* **11** (1.80 g, 6.54 mmol, 59 %) as white crystals, m.p: 117.9 - 120.1 ^oC (Found : M^++NH_4, 294.1711. $C_{16}H_{24}NO_4$ requires *M*, 294.1700); ν_{max} 3524, 1679, 1453, 1320, 1261, 1174, 1113, 1084, 1047, 756, 730, 695 and 642 cm^{-1}; δ_H (500 MHz, $CDCl_3$), 7.23 (5 H, m, ArH), 5.65 (1 H, dd, *J* 10, 1, 4-H), 5.43 (1 H, ddd, *J* 10, 4, 2.5, 3-H), 4.40 and 4.32 (each 1 H, d, *J* 12, Ph*H*CH), 3.42 (1 H, dd, *J* 4, 10, 2-CH), 3.33 (1 H, dd, *J* 8.5, 10, 2-CH'), 2.47 (1 H, m, 2-H), 2.35 (1 H, m, 5-H), 1.77 (1 H, dd, *J* 14, 6, 6-H_{eq}), 1.58 (1 H, dd, *J* 14, 10.5, 6-H_{ax}) and 0.98 (3 H, d, *J* 7, 5-CH_3); δ_C (75 MHz, $CDCl_3$) 178.0, 138.5, 135.3, 128.8, 128.2, 128.0, 123.2, 74.9, 73.4, 71.3, 46.8, 36.2, 27.5 and 21.0; *m/z* (CI) 294 (M^++18, 10%) and 276 (M^+, 50).

Methyl (1*RS*,2*SR*,5*RS*)-2-benzyloxymethyl-1-hydroxy-5-methylcyclohex-3-ene-1-carboxylate (12). Trimethylsilyldiazomethane (0.8 mL, 1.6 mmol) was added to the acid **11** (139 mg, 0.5 mmol) in toluene (1.9 mL) and methanol (1.3 mL) at 0 ^oC under nitrogen until the yellow colour of the trimethylsilyldiazomethane persisted. The yellow solution was then stirred at 0 ^oC for 1 h, acetic acid (0.2 mL) was added and the mixture stirred for 10 min. After concentration under reduced pressure, the residue was chromatographed using light petroleum and ether (1 : 1) as eluent to give the *title compound* **12** (130 mg, 0.45 mmol, 90 %) as a white solid, m.p. 68.2-70.1 ^oC (Found: M^++NH_4, 308.1859. $C_{17}H_{26}NO_4$ requires *M*, 308.1856); ν_{max} 3492, 1731, 1454, 1258, 1164, 1119, 1080, 1028, 736 and 698 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.20 (5 H, m, ArH), 5.63 (1 H, dd, *J* 1, 10, 4-H), 5.40 (1 H, ddd, *J* 2.5, 4.5, 10, 3-H), 4.34 and 4.31 (each 1 H, d, *J* 12, Ph*H*CH), 3.54 (3 H, s, OCH_3), 3.32 (1 H, dd, *J* 3, 10, 2-CH), 3.23 (1 H, dd, *J* 9, 10, 2-CH'), 2.99 (1 H, br. s, OH), 2.45 (1 H, m, 2-H), 2.37 (1 H, m, 5-H), 1.81 (1 H, dd, *J* 5.5, 13.5, 6-CH_{eq}), 1.57 (1 H, dd, *J* 11, 13.5, 6-CH_{ax}) and 0.96 (3 H, d, *J* 7, 5-CH_3); δ_C (75 MHz, $CDCl_3$), 176.2, 138.1, 135.3, 128.6, 127.8, 123.1, 74.6, 73.2, 71.5, 52.8, 47.3, 35.3, 27.4 and 21.1; *m/z* (CI) 291 (M^++1, 100 %) and 308 (35).

(1*RS*,4*RS*,5*RS*,6*SR*,7*RS*)-5-Benzyloxymethyl-4,6-dihydroxy-7-methyl-2-oxabicyclo-[2.2.2]octan-3-one (13), (1*RS*,4*RS*,5*RS*,6*RS*,7*RS*)-5-benzyloxymethyl-4,6-dihydroxy-7-methyl-2-oxabicyclo[2.2.2]octan-3-one (14) and (1*RS*,3*RS*,4*SR*,5*SR*,8*RS*)-8-benzyloxymethyl-1,4-dihydroxy-3-methyl-6-oxabicyclo[3.2.1]octan-7-one(15). *meta*-Chloro- peroxybenzoic acid (190 mg, 0.77 mmol) in chloroform (0.8 mL) was added to the carboxylic acid **11** (178 mg, 0.64 mmol) in chloroform (4.2 mL) and the solution stirred at room temperature for 72 h. The reaction mixture was then washed with a saturated aqueous sodium bicarbonate and the

aqueous layer extracted with chloroform (5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography using light petroleum and ether (70 : 30) gave the *title compound* **13** (28 mg, 0.096 mmol, 15 %) as an oil (Found: M^++NH_4, 310.1651. $C_{16}H_{24}NO_5$ requires *M*, 310.1649); υ_{max} 3446, 1752, 1455, 1365, 1260, 1067, 798, 741 and 698 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.25 (5 H, m, ArH), 4.43 and 4.41 (each 1 H, d, *J* 12, Ph*H*CH), 4.25 (1 H, d, *J* 3.5, 1-H), 3.73 (1 H, t, *J* 4, 6-H), 3.61 (1 H, dd, *J* 4, 9, 5-CH), 3.42 (2 H, m, 5-CH', OH), 2.46 (1 H, m, 7-H), 2.22 (1 H, dd, *J* 10.5, 13, 8-H), 1.94 (1 H, q, *J* 4, 5-H), 1.25 (1 H, dd, *J* 13, 5, 8-H') and 1.03 (3 H, d, *J* 7.5, 7-CH_3); δ_C (75 MHz, $CDCl_3$) 177.5, 138.1, 128.8, 128.0, 127.9, 79.9, 75.9, 73.8, 70.9, 68.0, 65.9, 48.5, 26.6 and 19.6; *m/z* (CI) 310 (M^++18, 100%) and 293 (M^++1, 20). The second fraction was the *title compound* **14** (56 mg, 0.192 mmol, 30 %) as a crystalline solid, m.p. 123.7-124.3 ^oC (Found: M^+, 292.1305. $C_{16}H_{20}O_5$ requires *M*, 292.1305); ν_{max} 3434,1752, 1455, 1261, 1108, 1068, 799, 740 and 699 cm^{-1}; δ_H (500 MHz, $CDCl_3$), 7.27 (5 H, m, ArH), 4.45 and 4.43 (each 1 H, d, *J* 12, Ph*H*CH), 4.15 (1 H, d, *J* 5, 1-H), 4.08 (1 H, t, *J* 5, 6-H), 3.56 (1 H, dd, *J* 10, 5, 5-CH), 3.45 (1 H, dd, *J* 10, 7, 5-CH'), 3.29 (1 H, s, OH), 2.52 (1 H, m, 7-H), 2.26 (1 H, dd, *J* 15, 10, 8-H), 2.10 (1 H, br. s, OH), 1.99 (1 H, m, *J* 5-H), 1.25 (1 H, dd, *J* 15, 5, 8-H') and 1.05 (3 H, d, *J* 5, 7-CH_3); δ_C (75 MHz, $CDCl_3$) 177.3, 137.9, 128.7, 128.1, 127.9, 82.0, 73.7, 70.8, 69.4, 68.2, 49.6, 40.5, 26.0 and 19.3; *m/z* (CI) 310 (M^++18, 100%) and 293 (M^++1, 20). The third fraction was the *title compound* **15** (56 mg, 0.192 mmol, 30 %) as an oil (Found: M^+, 292.1302. $C_{16}H_{20}O_5$ requires *M*, 292.1305); ν_{max} 3432, 1774, 1454, 1161, 1101, 1023, 963, 740 and 698 cm^{-1}: δ_H (500 MHz, $CDCl_3$) 7.29 (5 H, m, ArH), 4.50 (1 H, d, *J* 4, 5-H), 4.48 and 4.45 (each 1 H, d, *J* 12, Ph*H*CH), 3.80 (1 H, t, *J* 3, 4-H), 3.67 (1 H, dd, *J* 5.5, 10, 8-CH), 3.58 (1 H, dd, *J* 7, 10, 8-CH'), 3.02 (1 H, br. s, OH), 2.81 (1 H, dd, *J* 7, 5.5, 8-H), 2.26 (1 H, dd, *J* 9, 13.5, 2-H), 2.08 (1 H, m, 3-H), 1.65 (1 H, dd, *J* 3.5, 13.5, 2-H'), 1.5 (1 H, br. s, OH) and 1.05 (3 H, d, *J* 7, 3-CH_3); δ_C (75 MHz, $CDCl_3$) 179.2, 137.6, 128.8, 128.3, 128.0, 80.8, 74.4, 71.4, 67.3, 44.5, 39.8, 34.5, 26.3 and 21.2; *m/z* (CI) 310 (M^++18, 100 %) .

(1*RS*,3*RS*,5*SR*,8*RS*)-8-Benzyloxymethyl-1-hydroxy-3-methyl-6-oxabicyclo[3.2.1]octane-4,7-dione (16). Pyridinium chlorochromate (301 mg, 1.37 mmol) in dichloromethane (4 mL) was added to a solution of the hydroxylactone **15** (200 mg, 0.68 mmol) in dichloromethane (4 mL) and the mixture stirred for 12 h. The reaction mixture was then washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum and ether (60 : 40) gave the *title compound* **16** (168 mg, 0.58 mmol, 85 %) as a clear oil (Found: M^++NH_4, 308.1491. $C_{16}H_{22}NO_5$ requires *M*, 308.1492); υ_{max} 3432, 1769, 1644, 1333, 1217, 1145, 1106, 1013, 976 and 749 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.25 (5 H, m, ArH), 4.53 (1 H, s, 5-H), 4.47 (2 H, s, $PhCH_2$), 3.69 (1 H, dd, *J* 4.5, 10, 8-CH), 3.63 (1 H, dd, *J* 6.5, 10, 8-CH'), 3.27 (1 H, br. s, OH), 2.75 (1 H, pent, *J* 7, 3-H), 2.55 (1 H, dd, *J* 4.5, 6.5, 8-H), 2.34 (1 H, dd, *J* 7.5, 13.5, 2-H), 1.89 (1 H, d, *J* 13.5, 2-H') and 1.24 (3 H, d, *J* 8, 3-CH_3); δ_C (75 MHz, $CDCl_3$) 204.4, 177.8, 137.3, 128.9, 128.2, 127.9, 82.1, 74.0, 73.7, 66.1, 49.4, 39.7, 39.2 and 20.5; *m/z* (CI) 308 (M^++18, 20%).

(1*RS*,3*RS*,4*SR*,5*SR*,8*RS*)-8-Benzyloxymethyl-1,4-dihydroxy-3-methyl-6-oxabicyclo-[3.2.1] octan-7-one (15) and (1*RS*,3*RS*,4*RS*,5*SR*,8*RS*)-8-benzyloxymethyl-1,4-dihydroxy-3-methyl-

6-oxabicyclo[3.2.1]octan-7-one (17). Sodium borohydride (2.5 mg, 0.066 mmol) was added to the ketone **16** (25 mg, 0.066 mmol) in ethanol (0.3 mL) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 1 h, water (1 mL) was added, the mixture was stirred for 5 min and then extracted with dichloromethane (2 x 5 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum and ether (3 : 7) gave the alcohol **15** (7.7 mg, 0.026 mmol, 40 %) and the *title compound* **17** (8 mg, 0.027 mmol, 41 %) as an oil (Found: M^++H, 293.1383. $C_{16}H_{21}O_5$ requires *M*, 293.1384); υ_{max} 3450, 1775, 1640, 1455, 1162, 1105, 1024, 964, 743 and 700 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.24 (5 H, m, ArH), 4.53 (1 H, d, *J* 5, 5-H), 4.59 and 4.45 (each 1 H, d, *J* 12, Ph*H*CH), 3.91 (1 H, q, *J* 5, 4-H), 3.67 and 3.59 (each 1 H, dd, *J* 6, 10, 8-CH), 2.80 (1 H, t, *J* 6, 8-H), 1.87 (1 H, m, 3-H), 1.68 (2 H, m, 2-H_2) and 0.98 (3 H, d, *J* 7, 3-CH_3); *m/z* (CI) 310 (M^++18, 100%).

Methyl (1*RS*,2*RS*,3*RS*,5*RS*,6*SR*)-2-benzyloxymethyl-3-hydroxy-5-methyl-7-oxabicyclo[4.1.0]heptane-3-carboxylate (18) and methyl (1*SR*,2*RS*,3*RS*,5*RS*,6*RS*)-2-benzyloxymethyl-3-hydroxy-5-methyl-7-oxabicyclo[4.1.0]heptane-3-carboxylate (19). *meta*-Chloroperoxybenzoic acid (930 mg, 3.77 mmol) in chloroform (30 mL) was added to the methyl ester **12** (910 mg, 3.14 mmol) in chloroform (30 mL) at room temperature and the mixture stirred at room temperature for 18 h. Saturated aqueous sodium bicarbonate (10 mL) was added and the aqueous phase washed with dichloromethane (2 x 10 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using dichloromethane and ether (4 : 1) gave the *title compound* **18** (200 mg, 0.65 mmol, 20 %) (Found: M^++NH_4, 324.1809. $C_{17}H_{26}NO_5$ requires *M*, 324.1805); ν_{max} 3451, 1738, 1455, 1366, 1252, 1108, 804, 739 and 700 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.26 (5 H, m, ArH), 4.41 and 4.37 (each 1 H, d, *J* 12, Ph*H*CH), 3.59 (3 H, s, OCH_3), 3.40 (2 H, m, 2-CH_2), 3.37 (1 H, dd, *J* 1, 4, 1-H or 6-H), 2.97 (1 H, d, *J* 4, 1-H or 6-H), 2.65 (1 H, t, *J* 6, 2-H), 2.30 (1 H, m, 5-H), 1.88 (1 H, dd, *J* 7, 14, 4-H_{eq}), 1.53 (1 H, dd, *J* 10, 14, 4-H_{ax}), 1.50 (1 H, br. s, OH) and 1.05 (3 H, d, *J* 7.5, 5-CH_3); δ_C (75 MHz, $CDCl_3$) 19.5, 26.0, 35.6, 42.6, 52.6, 57.4, 57.8, 68.6, 73.7, 75.8, 128.6, 128.6, 128.7, 137.8 and 173.3; *m/z* (CI) 324 (M^++18, 30 %) and 307 (M^++1, 100). The second fraction was the *title compound* **19** (600 mg, 1.96 mmol, 62 %) (Found: M^++NH_4, 324.1805. $C_{17}H_{26}NO_5$ requires *M*, 324.1805); ν_{max} 3477, 1733, 1455, 1364, 1258, 1167, 1112, 1025, 778, 740 and 700 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.20 (5 H, m, ArH), 4.39 (2 H, s, $PhCH_2$), 3.61 (1 H, dd, *J* 3.5, 10, 2-CH), 3.51 (3 H, s, OCH_3), 3.36 (1 H, dd, *J* 9, 10, 2-CH'), 3.25 (1 H, dd, *J* 4, 5, 1-H or 6-H), 3.09 (1 H, d, *J* 4, 1-H or 6-H), 3.01 (1 H, br. s, OH), 2.26 (2 H, m, 2-H, 5-H), 1.56 (1 H, dd, *J* 13, 14, 4-H_{ax}), 1.40 (1 H, ddd, *J* 1, 5, 14, 4-H_{eq}) and 1.05 (3 H, d, *J* 7, 5-CH_3); δ_C (75 MHz, $CDCl_3$) 176.1, 138.2, 128.7, 128.1, 127.9, 73.6, 73.4, 68.5, 57.2, 53.7, 53.1, 44.9, 31.9, 26.0 and 18.4; *m/z* (CI) 324 (M^++18, 90 %) and 307 (M^++1, 40).

Vanadyl acetylacetonate (5 mg, 0.016 mmol) in benzene (0.3 mL) was added to the methyl ester **12** (329 mg, 1.13 mmol) in benzene (1 mL). The brown solution was stirred under reflux and *tert*-butyl hydrogen peroxide (0.37 mL, 1.85 mmol) was added. The reaction mixture was stirred under reflux for 4.5 h then cooled to room temperature and washed with aqueous sodium sulphite (10 %) and brine. The organic extracts were dried ($MgSO_4$) and concentrated under reduced

pressure. Chromatography of the residue using dichloromethane and ether (4 : 1) as eluent gave the *cis*-hydroxyepoxide **18** (280 mg, 0.91 mmol, 81 %) as a colourless oil with spectroscopic data identical to those reported above.

Benzyl (1*RS*,2*RS*,3*RS*,5*RS*,6*SR*)-2-benzyloxymethyl-3-hydroxy-5-methyl-7-oxabicyclo-[4.1.0]heptane-3-carboxylate (20) and benzyl (1*SR*,2*RS*,3*RS*,5*RS*,6*RS*)-2-benzyloxy-methyl-3-hydroxy-5-methyl-7-oxabicyclo[4.1.0]heptane-3-carboxylate (21).[2b] *meta*-Chloroperoxybenzoic acid in dichloromethane (1 M, 7.4 mL) was added to the benzyl ester **10** (1.36 g, 3.71 mmol) in dichloromethane at 0 ^{o}C and the reaction mixture warmed to room temperature and stirred for 5 h. The mixture was then washed with aqueous sodium sulfite (10 %), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum and ether (3 : 2) gave a mixture of the *title compounds* **20** and **21** (1.2 g, 3.14 mmol, 85 %; **20** : **21** = 33 : 67) as a colourless oil (Found: M^++NH_4, 400.2117. $C_{23}H_{30}NO_5$ requires *M*, 400.2118); ν_{max} 3471, 3031, 1734, 1497, 1454, 1365, 1219, 1164, 1108, 1024, 737 and 698 cm^{-1}; δ_H (500 MHz, $CDCl_3$) (*cis*-isomer **20**) 7.35 (10 H, m, ArH), 5.20 and 5.15 (each 1 H, d, *J* 12.5, CO_2CHHPh), 4.38 and 4.34 (each 1 H, d, *J* 14.5, $OCHHPh$), 3.50 (2 H, m, 2-CH_2), 3.39 (1 H, dd, *J* 1, 4, 1-H or 6-H), 3.09 (1 H, d, *J* 4, 1-H or 6-H), 2.80 (1 H, m, 2-H), 2.42 (1 H, m, 5-H), 2.04 (1 H, dd, *J* 7, 14, 4-H), 1.68 (1 H, dd, *J* 10, 14, 4-H') and 1.18 (3 H, d, *J* 7, 5-CH_3); (*trans*-isomer **21**) 7.35 (10 H, m, ArH), 5.12 and 4.97 (each 1 H, d, *J* 12.5, CO_2CHHPh), 4.45 and 4.41 (each 1 H, d, *J* 12, $OCHHPh$), 3.72 (1 H, dd, *J* 5, 10, 2-CH), 3.45 (1 H, dd, *J* 10, 9, 2-CH'), 3.33 (1 H, t, *J* 4, 1-H or 6-H), 3.15 (1 H, d, *J* 4, 1-H or 6-H), 3.09 (1 H, br. s, OH), 2.43 (2 H, m, 5-H, 2-H), 1.73 (1 H, t, *J* 14, 4-H), 1.59 (1 H, dd, *J* 5, 14, 4-H') and 1.19 (3 H, d, *J* 7, 5-CH_3); *m/z* (CI) 400 (M^++18, 30 %) and 383 (M^++1, 20).

(1*RS*,4*RS*,5*RS*,6*RS*,7*RS*)-5-Benzyloxymethyl-4,6-dihydroxy-7-methyl-2-oxabicyclo-[2.2.2] octan-3-one (14) and methyl (1*RS*,2*RS*,3*SR*,4*SR*,5*RS*)-2-benzyloxymethyl-1,3,4-trihydroxy-5-methylcyclohexane-1-carboxylate (22). Sulfuric acid (0.2 M; 2 mL, 0.39 mmol) was added to the *cis*-hydroxyepoxide **18** (100 mg, 0.33 mmol) in acetonitrile (3.3 mL) and the reaction mixture stirred under reflux for 48 h. The mixture was then cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in dichloromethane (10 mL) and the solution washed with water (10 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. Chromatography of the residue using light petroleum and ether (40 : 60) with gradient elution to neat ether gave the lactone **14** (64 mg, 0.2 mmol, 61 %) followed by the *title compound* **22** (36 mg, 0.11 mmol, 33 %) as a white solid, m.p. 97.3-100 ^{o}C (Found: M^++H, 325.1641. $C_{17}H_{25}O_6$, requires *M*, 325.1646); ν_{max} 3411, 1727, 1641, 1454, 1367, 1264, 1062, 1029 and 739 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.23 (5 H, m, ArH), 4.36 (2 H, s, $PhCH_2$), 3.98 (1 H, m, 3-H), 3.71 (1 H, dd, *J* 10, 6, 2-CH), 3.56 (3 H, s, OCH_3), 3.36 (1 H, dd, *J* 10, 7, 2-CH'), 3.09 (1 H, t, *J* 10, 4-H), 3.05 and 2.83 (each 1 H, br. s, OH), 2.39 (1 H, m, 2-H), 2.28 (1 H, br. s, OH),1.77 (1 H, m, 5-H), 1.76 (1 H, t, *J* 12.5, 6-H), 1.64 (1 H, dd, *J* 10, 2, 6-H') and 0.99 (3 H, d, *J* 6, 5-CH_3); δ_C (75 MHz, $CDCl_3$) 175.1, 137.8, 128.7, 128.1, 127.9, 76.5, 76.0, 73.6, 72.9, 67.2, 52.9, 50.0, 36.7, 32.7 and 18.1; *m/z* (CI) 342 (M^++18, 100 %), 325 (50) and 307 (30).

Following the above procedure, the *trans*-hydroxyepoxide **19** (418 mg, 1.3 mmol) gave the lactone **14** (350 mg, 1.2 mmol, 88%) isolated from the crude product mixture by crystallisation.

(1*RS*,4*RS*,5*RS*,6*RS*,7*RS*)-5-Benzyloxymethyl-4,6-dihydroxy-7-methyl-2-oxabicyclo-[2.2.2]octan-3-one (14) and benzyl (1*RS*,2*RS*,3*SR*,4*SR*,5*RS*)-2-benzyloxymethyl-1,3,4-trihydroxy-5-methylcyclohexane-1-carboxylate (23). Aqueous sulfuric acid (18 mL, 3.6 mmol, 0.2 M) was added to a mixture of the epoxy esters **20** and **21** (**20** : **21** = 1 : 2; 1.15 g, 3.01 mmol) in acetonitrile (30 mL) and the solution stirred under reflux for 48 h. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure. The residue was taken up in dichloromethane and the solution washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum and ether (1 : 4) gave the lactone **14** (620 mg, 2.1 mmol, 70 %) followed by the *title compound* **23** (361 mg, 0.9 mmol, 30 %) as a white crystalline solid, m.p 127.7-129 ^oC (Found: M^++NH_4, 418.2219. $C_{23}H_{32}NO_6$ requires *M*, 418.2224); ν_{max} 3400, 1727, 1455, 1247, 1061, 1028, 737 and 697 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.28 (10 H, m, ArH), 5.05 and 4.96 (each 1 H, d, *J* 12, CO_2CHHPh), 4.32 and 4.30 (each 1 H, d, *J* 12, $OCHHPh$), 4.04 (1 H, dd, *J* 5, 10, 3-H), 3.73 (1 H, dd, *J* 6, 10, 2-CH), 3.65 (2 H, br. s. 2 x OH), 3.38 (1 H, dd, *J* 10, 8, 2-CH'), 3.15 (1 H, t, *J* 10, 4-H), 2.50 (1 H, m, 2-H), 1.86 - 1.73 (3 H, m, 5-H, 6-H_2) and 1.04 (3 H, d, *J* 5.5, 5-CH_3); δ_C (75 MHz, $CDCl_3$) 174.4, 138.1, 135.6, 128.8, 128.5, 128.6, 128.0, 76.4, 76.1, 73.4, 72.2, 67.6, 66.8, 50.2, 36.4, 32.6 and 18.3; *m/z* (CI) 418 (M^++18, 80 %).

Crystal data for lactone (14). $C_{16}H_{20}O_5$, *M* = 292.32, monoclinic, *a* = 11.755(3), *b* = 11.749(3), *c* = 11.929(3)Å, β = 116.464(3)°, *U* = 1474.8(5)$Å^3$, *T* = 100 K, space group *P2₁* (no. 4), *Z* = 4, μ(Mo-Kα) = 0.097 mm^{-1}, 9487 reflections measured, 2732 unique (*R*int = 0.089) which were used in all calculations. The final *R*(*F*) was 0.05238 using 1739 with $I > 2\sigma(I)$, wR2 = 0.11801 (all data). Data have been deposited with the Cambridge Crystallographic Data Centre, CCDC number 617539.

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