HETEROCYCLES, Vol. 52, No. 1, 2000, pp. 171 – 183, Received, 8th February, 1999

OXETANE FORMATION BY 1,3-MIGRATION OF BENZYLOXY GROUP IN 7-OXABICYCLO[2.2.1]HEPT-2-YL CATIONS: SYNTHESIS OF 4,7-DIOXA-TRICYCLO[3.2.1.$O^{3,6}$]OCTANE AND 2-OXABICYCLO[2.2.2]OCTANE ENCRUSTED IN THE 1,4:5,8-DIEPOXY-PERHYDROPHENANTHRENE RING SYSTEM

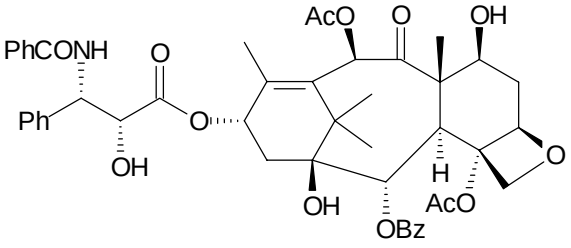
Hervé Mosimann and Pierre Vogel*

Section de chimie de l'Université, BCH, CH-1015-Lausanne-Dorigny, Switzerland

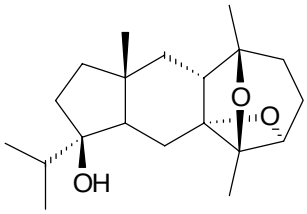
Abstract Epoxidation of (1RS,2SR,3SR,4RS,6RS,7RS,8RS,12RS,13RS)-6,13-bis(benzyloxy)-15,16-dioxapentacyclo[10.2.1.$1^{4.7}$.$0^{2,11}$.$0^{3.8}$]hexadec-10-en-8-yl-methanol (**12**) led to the stereoselective formation of (1RS,2RS,3RS,5RS,6SR,7RS,8RS,10RS,11SR,12SR,16SR)-3,10-bis(benzyloxy)-13,17,18-trioxahexacyclo[10.2.2.$1^{2,5}$.$1^{8,11}$.$0^{1,6}$.$0^{7,12}$]octadecan-16-ol (**13**). Epoxidation of the acetate (**19**) derived from **12** gave an epoxide (**20**) that generated (1RS,2SR,3RS,4RS,6RS,7SR,8RS,9SR,11RS,12RS,13RS)-13-benzyloxy-9-hydroxy-15,16,17-trioxahexacyclo[10.2.1.$1^{4,7}$.$1^{6,8}$.$0^{2,11}$.$0^{3,8}$]heptadecane-11-methyl acetate (**21**) under acidic conditions. These reactions imply the formation of 2-alkyl-6-endo-benzyloxy-7-oxabicyclo[2.2.1]hept-2-yl cation intermediates (e.g. **14**) that are quenched intramolecularly by the hydroxymethyl group to give the corresponding 2-oxabicyclo[2.2.2]octane systems (**12**→**13**). In the case of the acetoxymethyl containing intermediate, the latter cyclization is retarted and a facile 1,3-migration of the endo-benzyloxy group occurs leading to the corresponding 4,7-dioxatricyclo[3.2.1.$0^{3,6}$]octane derivative (**20**→**21**).

Taxol (**1**)[1] and dictyoxetane (**2**)[2] are rare natural compounds containing an oxetane moiety that confer to these products their extremely useful biological properties. Synthetic oxygenated 6,8-dimethyl-2,7-dioxatricyclo-[4.2.1.$0^{3,8}$]nonanes such as **3** have shown antitumor activity comparable to that of 5-fluorouracil.[3,4] Natural products with a 2-oxabicyclo[2.2.2]octane ethereal moiety are more common, among them 1,8-epoxy-p-

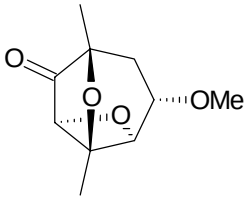
menthane (1,8-cineol: **4**) found in eucalyptus, lavender and many other essential oils,[5] 10,11-epoxyeremophilane (**5**), a metabolite of Hypomyces odoratus that is a phytotoxin,[6] or norsalvioxide (7,20-epoxy-13-methyl-8,11,13-podocarpatrien-12-ol: **6**), a constituent of Chinese drug Dan-Shen (Salvia miltiorrhiza).[7,8]



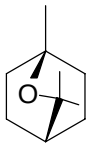
1



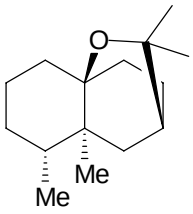
2



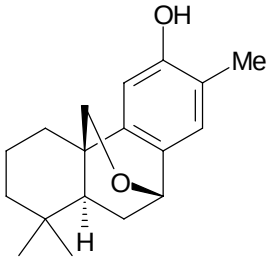
3



4



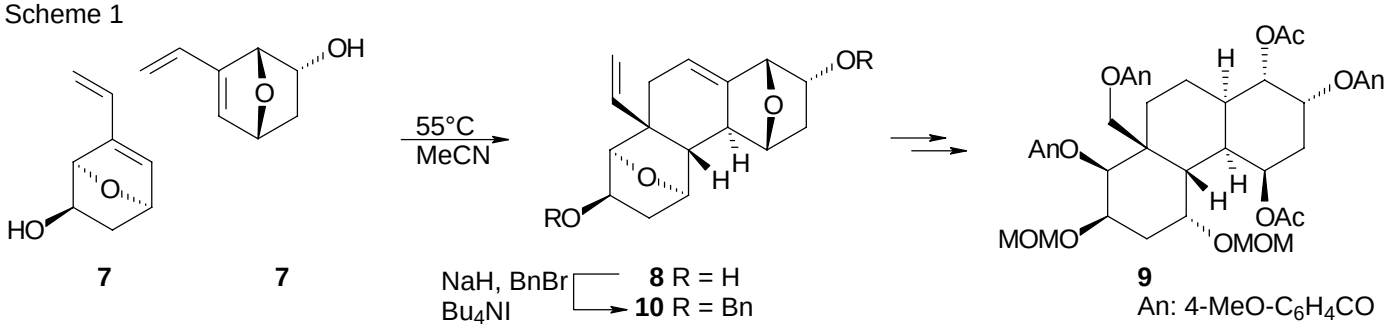
5



6

Diterpenes of the type tetradecahydrophenanthrene with cis,trans,cis ring junctions are very rare natural compounds, among them α-dictalediol and β-dictalediol monoacetate isolated from a brown algae of the genus Dictyota, the extracts of which exhibit cytotoxic, antibacterial, and antiviral activities.[9] We have presented recently an efficient synthesis of perhydro-8a-hydroxymethylphenanthrene-1,2,4,5,7,8-hexol and derivatives (e.g. **9**) based on the highly stereoselective cyclodimerization of dienol (**7**) into **8** (Scheme 1).[10] This Diels-Alder cycloaddition requires homochiral matching,[11] thus allowing one to prepare the polycyclic systems in both their enantiomeric forms as **7** can be obtained readily pure in both its enantiomeric forms starting from the Diels-Alder adducts of furan to 1-cyanovinyl esters ("naked sugars of the first generation").[12] We disclose here our efforts to generate polyoxygenated perhydrophenanthrene derivatives possessing either an oxetane or a 2-oxabicyclo[2.2.2]octane moiety.

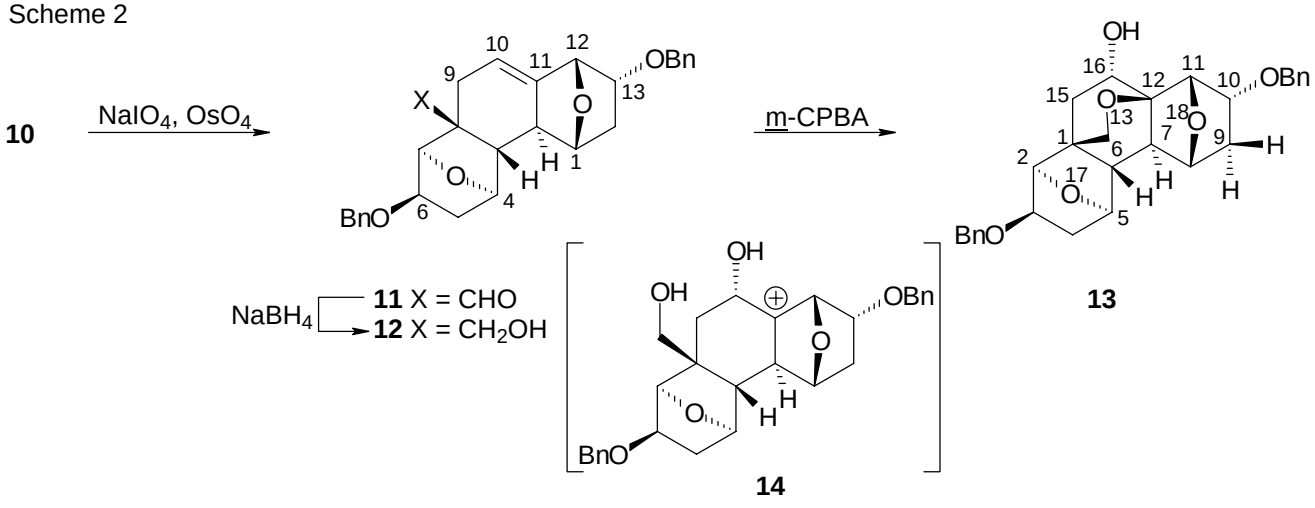
Scheme 1



7 **7** **9**

Diol (**8**)[10] was benzylated (NaH, BnBr, THF, Bu_4NI)[13] into the corresponding dibenzyl ether **10** (95%). Selective oxidative cleavage of the vinyl group in **10** was achieved on treatment with $NaIO_4$ and a catalytic amount of OsO_4. The produced aldehyde (**11**) (76%) was reduced with $NaBH_4$ (MeOH, CH_2Cl_2) into the primary alcohol (**12**) (89%). Because of the endo-13-benzyloxy substituent in **12** it was not clear from molecular models which face of the alkene moiety at C-10,11 would be attacked by a peracid. This question was answered immediately by a first epoxidation attempt using 90% m-chloroperbenzoic acid in $CHCl_3$ that did not furnish the expected epoxide but gave the hexacyclic product (**13**) in 81% yield (Scheme 2). The structure of **13** was given by its spectral data, in particular by its 2D-NOESY ^{1}H-NMR spectrum that showed NOE effects between the signals of the alcoholic proton (singulet at δ_H = 5.84 ppm) and Hendo-C(7) (doublet at δ_H = 1.65 ppm) and Hendo-C(9) (doublet x doublet at δ_H = 1.47 ppm). This suggested that the epoxidation had occurred on the face of the alkene unit of **12** syn with respect to the 13-endo benzyloxy group and that the acidity of m-CPBA and that of m-chlorobenzoic acid formed as co-product is sufficient to induce the epoxide ring opening with formation of a relatively stable tertiary carbenium ion intermediate (**14**) that is quenched intramolecularly by the primary hydroxy moiety of **12**, generating the observed 2-oxabicyclo[2.2.2]octane system (**13**). The latter cyclization must be a fast process as no product of rearrangement (hydride shifts, pinacolic rearrangements) was detected in the crude reaction mixture. It is possible also that the epoxide ring opening and the formation of the 2-oxabicyclo[2.2.2]octane moiety are concerted processes (anchimeric assistance by the hydroxymethyl group).

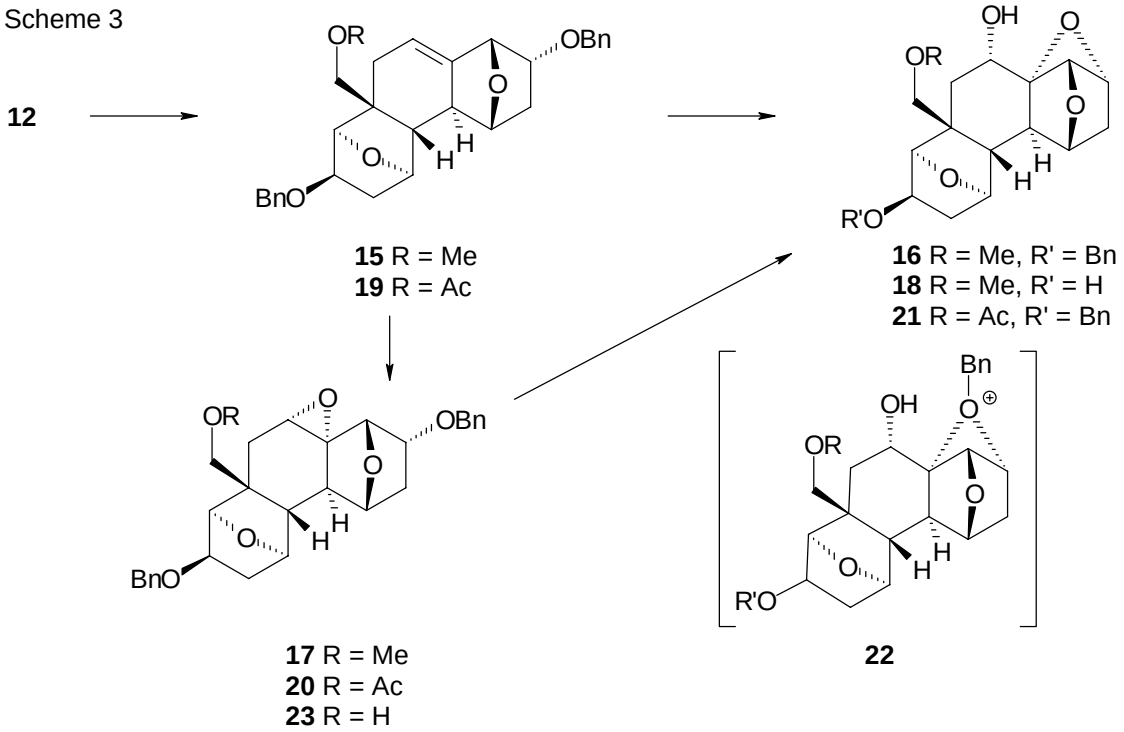
Scheme 2



In order to retard the formation of the 2-oxabicyclo[2.2.2]octane system from intermediate (**14**), we converted the primary alcohol (**12**) into the corresponding methyl ether (**15**) on treatment with NaH and MeI. To our surprise, when **15** was treated with m-CPBA in $CHCl_3$, a mixture was formed that contained oxetane (**16**) as major product. Repeating the epoxidation of **15** with m-CPBA and Na_2CO_3 ($CHCl_3$, 20°C) epoxide (**17**) was obtained in 50% yield. Hydrogenolysis of the benzyl ether of **17** produced a mixture containing oxetane (**18**) as major product (Scheme 3). In order to improve the yield of the conversion of **12** into a 4,7-

dioxatricyclo[3.2.1.$0^{3,6}$]octane derivative and because the methyl ether moiety is a protective group difficult to cleave, we explored the possibility to protect the hydroxymethyl group of **12** as an acetate as in **19** (Ac_2O, Py, DMAP, 88%). Treatment of **19** with 90% m-CPBA ($CHCl_3$, 20°C) provided the endo epoxide (**20**) in 96% yield, without rearrangement. Several acids were tried to induce the 1,3-migration of the endo-benzyloxy group with the hope to generate the expected oxetane as observed with reaction **15**→**16**. Mixtures of compounds were obtained except when $BF_3{\cdot}OEt_2$ was used as acid (CH_2Cl_2, -70°C, then at –50°C) that led to crystalline oxetane (**21**) isolated in 81% yield. These results demonstrate that the 1,3-migration of the endo-benzyloxy group with generation of oxonium ion intermediate[15] of type (**22**)[16] can compete with the quenching of the tertiary carbenium ion intermediate of type (**14**) by the acetoxymethyl group. This is a surprise as it was expected that the strain increase during the formation of the tricyclic oxonium ion intermediate of type (**22**) would make the formation of 2-oxabicyclo[2.2.2]octane intermediate favored as in the case of reaction **12**→**13**. This suggests that the strain in 4,7-dioxatricyclo[3.2.1.$0^{3,6}$]octane is lower than the sum of the strain of oxetane and 7-oxanorbornane. The structures of the new compounds were confirmed by 2D-^{1}H-NMR (NOESY, COSY) experiments. Furthermore, we have shown that saponification of the acetoxy-epoxide (**20**) (NaOH, THF, H_2O, 45°C) generates the 2-oxabicyclo[2.2.2]octane derivative (**13**), probably via the intermediacy of alcohol (**23**).[17]

Scheme 3



This work discloses efficient methods to generate yet unknown polyoxygenated cis,trans,cis-tetradecahydrophenanthrene derivatives including 13,17,18-trioxahexacyclo[10.2.2.$1^{2,5}$.1.^{8,11}.$0^{1,6}$.$0^{7,12}$]octadecane-3,10,16-triol and 9,13-dihydroxy-15,16,17-trioxahexacyclo[10.2.1.$1^{4,7}$.$1^{6,8}$.$0^{2,11}$.$0^{3,8}$]heptadecane-11-methanol derivatives from the Diels-Alder adducts of furan to 1-cyanovinyl esters. It presents a new method to generate oxetanes under electrophilic conditions involving 1,3-migration of benzyloxy group in a 2-alkyl-6-endo-

benzyloxy-7-oxabicyclo[2.2.1]hept-2-yl cation intermediate that does not undergo the expected pinacolic rearrangement (migration of the σC(1),C(6) bond).[18] All known examples of 1,3-migration of alkoxy groups involve their direct anchimeric assistance to the formation of the cationic intermediates,[16] which is not possible in the reactions **17**, **20**→**22** as the leaving group (protonated epoxide) is situated syn with respect to the migrating group. The facile formation of benzyloxonium ions of type (**22**) has allowed one to generate new types of 4,7-oxatricyclo[3.2.1.$0^{3,6}$]octane systems.

ACKNOWLEDGMENTS

We thank the Swiss National Science Foundation and the Fonds Herbette (Lausanne) for financial support.

EXPERIMENTAL SECTION

General, see ref. 19. ^{1}H-NMR assignments were confirmed by 2D-(COSY, NOESY)-NMR spectra.

(1RS,2SR,3SR,4RS,6RS,7RS,11SR,12RS,13RS)-6,13-Bisbenzyloxy-11-vinyl-15,16-dioxapentacyclo-[10.2.1.$1^{4,7}$.$0^{2,11}$.$0^{3,8}$]hexadec-8-ene (**10**). NaH (55% in oil; 0.3 g, 7 mmol), was added to a stirred solution of **8**[10] (0.4 g, 1.44 mmol) in anhydrous THF (12 mL) cooled to 0°C. After stirring at 0°C for 10 min, benzyl bromide (0.38 mL, 3.18 mmol) and tetrabutylammonium iodide (53 mg, 0.144 mmol) were added. The mixture was stirred at 20°C for 20 h and saturated aqueous solution of NH_4Cl (10 mL), than H_2O (10 mL) were added. After saturation with NaCl, the mixture was extracted with CH_2Cl_2 (10 mL, 6 times). The combined organic extracts were dried ($MgSO_4$), the solvent was evaporated and the residue purified by flash chromatography on silica gel (∅ = 2 cm, h = 15 cm, 1:3 EtOAc/light petroleum): 627 mg (95%) of **10**, colorless oil. UV (MeCN) λ_{max}: 212 nm (ε = 9200). IR (film) ν 3050, 2960, 2860, 1630, 1490, 1440, 1410, 1390, 1350, 1260, 1210, 1170, 1150, 1090, 1040, 1020, 990, 930, 900, 830, 800, 780, 740, 690, 660 cm^{-1}. ^{1}H-NMR (360 MHz, $CDCl_3$) δ_H 7.38-7.28 (m, Ph); 6.25 (dd, ^3J = 17.3, 10.7, H-C(α)); 5.76 (ddd, ^3J = 7.2, 3.8, ^4J = 2.3, H-C(9)); 4.91 (dd, ^3J = 17.3, ^2J = 0.8, H_Z-C(β)); 4.89 (dd, ^3J = 10.7, ^2J = 0.8, H_E-C(β)); 4.75 (d, ^3J = 4.8, H-C(7)); 4.54, 4.51, 4.46, 4.43 (4d, ^2J = 11.6, CH_2Ph); 4.38 (d, ^3J = 5.6, H-C(4)); 4.35 (d, ^3J = 6.2, H-C(1)); 4.15 (ddd, ^3J = 9.6, 4.8, 3.1, H-C(6)); 4.15 (ddd, ^3J = 10.4, 5.6, 4.2, H-C(13)); 4.07 (d, ^3J = 4.2, H-C(12)); 2.42 (dd, ^2J = 13.7, ^3J = 7.2, H_{eq}-C(10)); 2.36 (ddd, ^2J = 12.2, ^3J = 10.4, 6.2, H_{exo}-C(14)); 2.26 (ddd, ^2J = 12.5, ^3J = 9.6, 5.6, H_{exo}-C(5)); 2.17 (dd, ^2J = 13.7, ^3J = 3.8, H_{ax}-C(10)); 2.10 (dd, ^3J = 9.5, ^4J = 2.3, H-C(3)); 1.83 (d, ^3J = 9.5, H-C(2)); 1.45 (dd, ^2J = 12.2, ^3J = 5.6, H_{endo}-C(14)); 1.44 (dd, ^2J = 12.5, ^3J = 3.1, H_{endo}-C(5)). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ_C 143.0 (d, ^1J(C,H) = 156, C(9)); 141.5 (s, C(8)); 137.9, 137.8 (2s, Ph); 128.1, 128.0, 127.6, 127.5, 127.3, 127.2, (6d, ^1J(C,H) = 161, 160, 159, 159, 162, 164, Ph); 118.0 (d, ^1J(C,H) = 163, C(α)); 110.9 (t, ^1J(C,H) =156, C(β));

84.4, 84.2, 81.2, 80.0 (4d, ^{1}J(C,H) = 156, 156, 156, 160, C(1), C(4), C(7), C(12)); 80.9, 78.0 (2d, ^{1}J(C,H) = 147, 149, C(6), C(13)); 72.0, 71.5 (2t, ^{1}J(C,H) = 141, CH_2Ph); 54.6, 47.7 (2d, ^{1}J(C,H) = 133, 135, C(2), C(3)); 54.4 (s, C(11)); 37.3, 32.5 (2t, ^{1}J(C,H) = 133, C(5), C(14)); 32.5 (t, ^{1}J(C,H) = 131, C(10)). CI-MS (NH_3) m/z 457 (1, M + H^+), 366 (20), 365 (80), 275 (9), 259 (6), 231 (7), 215 (6), 137 (12), 105 (9), 91 (100). Elemental analysis, see **12**.

(1RS,2SR,3SR,4RS,6RS,7RS,8SR,12RS,13RS)-6,13-Bisbenzyloxy-15,16-dioxapentacyclo-[10.2.1.$1^{4,7}$.$0^{2,11}$.$0^{3,8}$]hexadec-10-ene-8-carbaldehyde (**11**). $NaIO_4$ (633 mg, 2.96 mmol), 0.1 M solution of OsO_4 in CCl_4 (1.48 mL, 0.148 μmol) were added to a stirred solution of **10** (676 mg, 1.48 mmol) in 9:5 dioxane/H_2O (28 mL). The mixture was stirred at 20°C for 19 h. The solvent was evaporated to half volume and the solution was saturated with NaCl and extracted with CH_2Cl_2 (10 mL, 7 times). The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated. The residue was purified by flash chromatography on silica gel (∅ = 2 cm, h = 20 cm, 1:2 EtOH/light petroleum): 518 mg (76%) of **11**, colorless foam. UV (MeCN) λ_{max}: 263 nm (ε = 400), 257 (500), 251 (450), 212 (9200). IR (CCl_4) ν 3020, 2960, 2850, 2730, 1710, 1440, 1390, 1340, 1310, 1250, 1200, 1170, 1090, 1040, 1030, 990, 940, 900, 690 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ_H 9.58 (s, CHO); 7.39-7.26 (m, Ph); 5.70 (ddd, ^{3}J = 7.3, 3.8, ^{4}J = 2.3, H-C(10)); 4.70 (d, ^{3}J = 4.6, H-C(12)); 4.47, 4.49 (2d, ^{2}J = 11.6, CH_2Ph); 4.44, 4.42 (2d, ^{3}J = 5.0, 5.1, H-C(1), H-C(4)); 4.39 (s, CH_2Ph); 4.33 (d, ^{3}J = 4.4, H-C(7)); 4.17-4.06 (m, H-C(6), H-C(13)); 2.91 (dd, ^{2}J = 14.0, ^{3}J = 7.3, H_{eq}-C(9)); 2.36 (d, ^{3}J = 9.7, H-C(3)); 2.35-2.22 (m, H_{exo}-C(5), H_{exo}-C(14)); 2.13 (dd, ^{3}J = 9.7, ^{4}J = 2.3, H-C(2)); 2.09 (dd, ^{2}J = 14.0, ^{3}J = 3.8, H_{ax}-C(9)); 1.48 (dd, ^{2}J = 12.6, ^{3}J = 4.0, H_{endo}-C(5)); 1.43 (dd, ^{2}J = 12.4, ^{3}J = 2.8, H_{endo}-C(14)). ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ_C 200.2 (d, ^{1}J(C,H) = 180, CHO); 143.8 (s, C(11)); 137.8, 137.1 (2s, Ph); 128.3, 128.2, 127.7, 127.5 (4d, ^{1}J(C,H) = 160, Ph); 116.8 (d, ^{1}J(C,H) = 164, C(10)); 85.6, 84.3, 80.5, 80.1 (4d, ^{1}J(C,H) = 159, 157, 163, 161, C(1), C(4), C(7), C(12)); 79.5, 78.1 (2d, ^{1}J(C,H) = 151, 148, C(6), C(13)); 72.2, 71.8 (2t, ^{1}J(C,H) = 142, CH_2Ph); 63.3 (d, ^{2}J(C,H) = 20, C(8)); 51.9, 47.2 (2d, ^{1}J(C,H) = 137, 136, C(2), C(3)); 37.4, 36.0 (2t, ^{1}J(C,H) = 133, 134, C(5), C(14)); 29.1 (t, ^{1}J(C,H) = 133, C(9)). CI-MS (NH_3) m/z 367 (6, M^+ -Bn), 323 (2), 277 (2), 259 (24), 147 (4), 92 (11), 91 (100). Elemental analysis, see **12**.

(1RS,2SR,3SR,4RS,6RS,7RS,8RS,12RS,13RS)-6,13-Bisbenzyloxy-15,16-dioxapentacyclo-[10.2.1.$1^{4,7}$.$0^{2,11}$.$0^{3,8}$]hexadec-10-en-8-ylmethanol (**12**). $NaBH_4$ (50 mg, 1.3 mmol) was added to a stirred solution of **11** (200 mg, 0.44 mmol) in 2:1 MeOH/CH_2Cl_2 (9 mL) cooled to 0°C. The mixture was allowed to warm up to 20°C and was stirred for 20 min. Aqueous 10% HCl was added until pH = 4 and the solvent was evaporated to half volume, the solution was saturated with NaCl and extracted with CH_2Cl_2 (10 mL, 7 times). The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated to dryness: 179 mg (89%) of **10**, colorless oil that crystallizes from EtOAc/hexane giving colorless prisms, mp 144-145°C. IR (KBr) ν 3505,

2945, 1720, 1655, 1495, 1455, 1355, 1205, 1175, 1090, 995, 945, 840, 740, 700, 660, 590 cm^{-1}. ^{1}H-NMR (360 MHz, $CDCl_3$) δ_H 7.40-7.28 (m, Ph); 5.83 (ddd, ^3J = 7.4, 3.0, ^4J = 2.9, H-C(10)); 4.74 (d, ^3J = 4.6, H-C(12)); 4.62, 4.53 (2d, ^2J = 11,6, CH_2Ph); 4.51, 4.44 (2d, ^2J = 11.5, CH_2Ph); 4.31, 4.30 (2d, ^3J = 7.8, 6.0, H-C(1), H-C(4)); 4.21-4.11 (m, H-C(6), H-C(13)); 4.04 (d, ^3J = 4.4, H-C(7)); 3.67 (br d, ^2J = 11.8, CH_2OH); 3.37 (br dd, ^2J = 11.8, ^3J = 9.1, CH_2OH); 3.26 (br d, ^3J = 9.1, OH); 2.59 (dd, ^2J = 14.0, ^3J = 7.4, H_{eq}-C(9)); 2.32-2.20 (m, H_{exo}-C(5), H_{exo}-C(14)); 2.05 (br d, ^3J = 9.6, H-C(2)); 1.91 (br d, ^2J = 14.0, ^3J = 3.0, H_{ax}-C(9)); 1.41, 1.40 (2dd, ^2J = 12.4, 10.5, ^3J = 2.8, 5.4, H_{endo}-C(5), H_{endo}-C(14)); 1.31 (d, ^3J = 9.6, H-C(3)). ^{13}C-NMR (90.6 MHz, $CDCl_3$) δ_C 142.7 (s, C(11)); 138.0, 136.9 (2s, Ph); 128.6, 128.3, 128.2, 127.8, 127.7 (5d, ^1J(C,H) = 158-160, Ph); 118.2 (d, ^1J(C,H) = 162, C(10)); 84.3, 81.3, 80.7, 80.3 (4d, ^1J(C,H) = 157, 160, 160, 160, C(1), C(4), C(7), C(12)); 84.2. 78.2 (2d, ^1J(C,H) = 150, C(6), C(13)); 73.4, 71.8 (2t, ^1J(C,H) = 144, 143, CH_2Ph); 67.0 (t, ^1J(C,H) = 143, CH_2OH); 54.7 (s, C(8)); 53.3, 47.5 (2d, ^1J(C,H) = 134, 135, C(2), C(3)); 37.5, 34.7 (2t, ^1J(C,H) = 133, 133, C(5), C(14)); 30.6 (t, ^1J(C,H) = 130, C(9)). CI-MS (NH_3) m/z 478 (100, M + NH_4^+), 461 (10, M + H^+), 370 (6), 369 (5), 108 (21), 106 (21), 91 (36). Anal. Calcd for $C_{29}H_{32}O_5$: C 75.63, H 7.00. Found: C 75.59, H 7.05.

(1RS,2RS,3RS,5RS,6SR,7RS,8RS,10RS,11SR,12SR,16SR)-3,10-Bisbenzyloxy-13,17,18-trioxahexacyclo-[10.2.2.1^{2,5}.1^{8,11}.0^{1,6}.0^{7,12}]octadecan-16-ol (**13**). A mixture of **12** (31 mg, 0.067 mmol), $CHCl_3$ (1.5 mL) and 90% m-chloroperbenzoic acid (32 mg, 0.168 mmol) was stirred at 20°C for 4 days. The solvent was evaporated and the residue purified by flash chromatography on silica gel (∅ = 1 cm, h = 12 cm; 2:3 EtOAc/light petroleum): 26 mg (81%) of **13**, colorless crystals, mp 55-56°C (Et_2O/light petroleum). IR (KBr) ν 3420, 2935, 2870, 1455, 1355, 1130, 1050, 995, 905, 860, 790, 735, 700, 615, 450 cm^{-1}. ^{1}H-NMR (360 MHz, $CDCl_3$) δ_H 7.39-7.24 (m, Ph); 5.84 (s, OH); 4.62, 4.57 (2d, ^2J = 11.4, CH_2Ph); 4.49, 4.42 (2d, ^2J = 11.6, CH_2Ph); 4.29 (d, ^3J = 5.6, H-C(8)); 4.26 (d, ^3J = 4.7, H-C(11)); 4.26 (ddd, ^3J = 10.1, 5.6, 4.1, H-C(3)); 4.17 (d, ^3J = 4.1, H-C(2)); 4.16 (ddd, ^3J = 9.8, 4.7, 2.7, H-C(10)); 4.07 (d, ^3J = 6.4, H-C(5)); 3.97, 3.69 (2d, ^2J = 7.7, H_2-C(14)); 3.68 (d, ^3J = 6.2, H-C(16)); 2.44 (ddd, ^2J = 12.5, ^3J = 10.1, 6.4, H_{exo}-C(4)); 2.18 (ddd, ^2J = 12.4, ^3J = 9.8, 5.6, H_{exo}-C(9)); 2.15 (d, ^2J = 11.6, H_{syn}-C(15)); 1.80 (d, ^3J = 8.7, H-C(6)); 1.79 (dd, ^2J = 11.6, ^3J = 6.2, H_{anti}-C(15)); 1.69 (dd, ^2J = 12.5, ^3J = 5.6, H_{endo}-C(4)); 1.65 (d, ^3J = 8.7, H-C(7)); 1.47 (dd, ^2J = 12.4, ^3J = 2.7, H_{endo}-C(9)). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ_C 137.8, 136.4 (2s, Ph); 128.6, 128.4, 128.3, 128.1, 127.6, 127.2 (6d, ^1J(C,H) = 158-160, Ph); 85.3 (s, C(12)); 83.9, 82.9, 81.9, 81.3 (4d, ^1J(C,H) = 157, 157, 156, 157, C(2), C(5), C(8), C(11)); 79.5, 77.6 (2d, ^1J(C,H) = 148, 150, C(3), C(10)); 75.8 (d, ^1J(C,H) = 157, C(16)); 74.1, 73.4 (2t, ^1J(C,H) = 148, 150, CH_2Ph); 72.7 (t, ^1J(C,H) = 141, C(14)); 55.6, 54.6 (2d, ^1J(C,H) = 130, 138, C(6), C(7)); 52.8 (s, C(1)); 39.0, 35.1, 34.0 (3t, ^1J(C,H) = 133, 134, 134, C(4), C(9), C(15)). CI-MS (NH_4) m/z 477 (5, M + H^+), 325 (3), 133 (3), 108 (7), 92 (53), 91 (100). Anal. Calcd for $C_{29}H_{32}O_6$: C 73.09, H 6.77. Found: C 72.80, H 6.92.

(1RS,2SR,3SR,4RS,6RS,7RS,11RS,12RS,13RS)-6,13-Bisbenzyloxy-11-methoxymethyl-15,16-dioxapentacyclo[10.2.1.1^{4,7}.0^{2,11}.0^{3,8}]hexadec-8-ene (**15**). A mixture of NaH (55% in oil, 50 mg, 1.14 mmol), **12** (86 mg, 0.187 mmol) and anhydrous THF (4 mL) was stirred at 20°C for 10 min. Methyl iodide (0.4 mL, 6.42 mmol) was added and the mixture stirred at 20°C for 6 h. Saturated aqueous solution of NH_4Cl (5 mL) was added and the mixture saturated with NaCl. The mixture was extracted with CH_2Cl_2 (5 mL, 6 times). The combined organic extracts were dried ($MgSO_4$), the solvent was evaporated and the oily residue purified by flash column chromatography on silica gel (∅ = 2 cm, h = 15 cm, 1:3 EtOAc/light petroleum): 82 mg (93%) of **15**, colorless foam. IR (KBr) ν 2970, 1455, 1355, 1205, 1135, 1100, 1045, 1000, 945, 840, 810, 735, 695, 585 cm^{-1}. ^{1}H-NMR (360 MHz, $CDCl_3$) δ_H 7.38-7.27 (m, Ph); 5.83 (ddd, ^3J = 7.4, 2.1, ^4J = 2.0, H-C(9)); 4.75, 4.51 (2d, ^2J = 11.9, CH_2Ph); 4.74 (d, ^3J = 3.9, H-C(7)); 4.52, 4.46 (2d, ^2J = 11.6, CH_2Ph); 4.31, 4.27 (2dd, ^3J = 5.5, 6.1, H-C(1), H-C(4)); 4.20-4.13 (m, H-C(6), H-C(12), H-C(13)); 3.77 (dd, ^2J = 8.7, ^4J = 1.5, CH_2OMe); 3.15 (d, ^2J = 8.7, CH_2OMe); 3.11 (s, Me); 2.72 (dd, ^2J = 13.8, ^3J = 7.4, H_{eq}-C(10)); 2.39 (ddd, ^2J = 12.3, ^3J = 11.9, 6.1, H_{exo}-C(5 ou 14)); 2.24 (ddd, ^2J = 12.5, ^3J = 9.6, 5.5, H_{exo}-C(5 ou 14)); 2.08 (dd, ^3J = 9.4, ^4J = 2.0, H-C(3)); 1.93 (ddd, ^2J = 13.8, ^3J = 2.1, ^4J = 1.5, H_{ax}-C(10)); 1.69-1.39 (m, H_{endo}-C(5), H_{endo}-C(14)); 1.15 (d, ^3J = 9.4, H-C(2)). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ_C 141.9 (s, C(8)); 138.6, 138.0 (2s, Ph); 128.3, 128.2, 127.8, 127.7, 127.4 (5d, ^1J(C,H) = 158-161, Ph); 118.4 (d, ^1J(C,H) = 162, C(9)); 83.8, 83.0, 80.9, 80.3 (4d, ^1J(C,H) = 156, 156, 157, 158, C(1), C(4), C(7), C(12)); 81.7, 78.2 (2d, ^1J(C,H) = 145, 150, C(6), C(13)); 75.3, 72.9, 71.8 (3t, ^1J(C,H) = 142, 141, 142, CH_2Ph, CH_2OMe); 58.4 (q, ^1J(C,H) = 140, Me); 54.0, 47.7 (2d, ^1J(C,H) = 132, 135, C(2), C(3)); 53.1 (s, C(11)); 37.4, 36.1 (2t, ^1J(C,H) = 136, C(5), C(14)); 30.0 (t, ^1J(C,H) = 132, C(10)). CI-MS (NH_3) m/z 475 (11, M + H$^+$), 474 (11, M$^+$), 444 (3), 443 (3), 384 (11), 383 (9), 92 (26), 91 (100). Anal. Calcd for $C_{30}H_{34}O_5$: C 75.92, H 7.22. Found: C 75.92, H 7.23.

(1RS,2SR,3RS,4RS,6RS,7SR,8RS,9SR,11RS,12RS,13RS)-6,13-Bisbenzyloxy-8,9-epoxy-11-methoxymethyl-15,16-dioxapentacyclo[10.2.1.1^{4,7}.0^{2,11}.0^{3,8}]hexadecane (**17**). A mixture of Na_2CO_3 (250 mg), **15** (37 mg, 0.078 mmol) and 90% m-chloroperbenzoic acid (60 mg, 0.31 mmol.) in $CHCl_3$ (3 mL) was stirred at 20°C for 35 h. The mixture was washed with 5% aqueous solution of Na_2CO_3 (10 mL, twice), then with brine (10 mL, twice). The aqueous layers were united and extracted with $CHCl_3$ (10 mL, 3 times). The combined organic phases were dried ($MgSO_4$), the solvent was evaporated and the residue purified by flash column chromatography on silica gel (∅ = 1 cm, h = 13 cm; 1:4 EtOAc/light petroleum): 19 mg (50%) of **17**, colorless oil that crystallizes form CH_2Cl_2/hexane, colorless needles, mp 154-155°C. IR (KBr) ν 2980, 290, 1450, 1360, 1205, 1140, 1115, 1005, 745, 735, 700, 540 cm^{-1}. ^{1}H-NMR (360 MHz, $CDCl_3$) δ_H 7.36-7.27 (m, Ph); 5.82 (ddd, ^3J = 7.3, 3.8, ^4J = 1.2, H-C(12)); 4.73 (d, ^3J = 4.6, H-C(14)); 4.51-4.47 (m, CH_2Ph, H-C(6)); 4.41 (dd, ^3J = 11.7, 7.0, H-C(6)); 4.35 (d, ^3J = 5.6, H-C(1)); 4.30 (d, ^3J = 4.6, H-C(4)); 4.15 (ddd, ^3J = 9.6, 4.6, 2.8, H-C(15)); 3.76, 3.60 (2d, ^2J = 8.2, H_2-C(9)); 2.32 (dd, ^2J = 14.7, ^3J = 3.8, H_{ax}-C(11)); 2.27 (ddd, ^2J = 12.5, ^3J =

9.6, 5.6, H_{exo}-C(16)); 2.22 (dd, ^2J = 14.7, ^3J = 7.3, H_{eq}-C(10)); 2.15 (dd, ^3J = 10.6, ^4J = 1.2, H-C(2)); 1.83 (ddd, ^2J = 11.7, ^3J = 7.0, 4.6, H_{exo}-C(18)); 1.57 (d, ^3J = 11.7, H_{endo}-C(18)); 1.57 (d, ^3J = 10.6, H-C(3)); 1.44 (dd, ^2J = 12.5, ^3J = 2.8, H_{endo}-C(16)). ^{13}C-NMR (90.6 MHz, $CDCl_3$) δ_C 142.7 (s, C(11)); 138.0, 136.9 (2s, Ph); 128.6, 128.3, 128.2, 127.8, 127.7 (5d, ^1J(C,H) = 158-160, Ph); 118.2 (d, ^1J(C,H) = 162, C(10)); 84.3, 81.3, 80.7, 80.3 (4d, ^1J(C,H) = 157, 160, 160, 160, C(1), C(4), C(7), C(12)); 84.2. 78.2 (2d, ^1J(C,H) = 150, C(6), C(13)); 73.4, 71.8 (2t, ^1J(C,H) = 144, 143 CH_2Ph); 67.0 (t, ^1J(C,H) = 143, CH_2OH); 54.7 (s, C(8)); 53.3, 47.5 (2d, ^1J(C,H) = 134, 135, C(2), C(3)); 37.5, 34.7 (2t, ^1J(C,H) = 133, 133, C(5), C(14)); 30.6 (t, ^1J(C,H) = 130, C(9)). CI-MS (NH_3) m/z 335 (1, M + H^+), 309 (1), 308 (1), 262 (22), 261 (100), 217 (2), 129 (5), 91 (56). Anal. Calcd for $C_{30}H_{34}O_6$: C 74.98, H 6.86. Found: C 75.07, H 6.78.

(1RS,2SR,3SR,4RS,6RS,7RS,8RS,12RS,13RS)-6,13-Bisbenzyloxy-15,16-dioxapentacyclo-[10.2.1.1^{4,7}.0^{2,11}.0^{3,8}]hexadec-10-ene-8-methyl acetate (**19**). $NaBH_4$ (40 mg) was added portionwise in 15 min to a stirred solution of **11** (152 mg, 0.338 mmol) in 5:2 MeOH/CH_2Cl_2 (7 mL) cooled to 0°C. After stirring at 0°C for 15 min, 10% aqueous HCl was added until pH = 4. The solvent was evaporated to one quarter of the volume, the mixture was saturated with NaCl and extracted with CH_2Cl_2 (10 mL, 7 times). The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated. The oily residue was taken in anhydrous pyridine (1 mL), acetic anhydride (1 mL) and 4-dimethylaminopyridine (5 mg) were added. The mixture was stirred at 20°C for 15 h. The solvents were evaporated in vacuo and the residue filtered through a pad of silica gel (1:2 EtOAc/light petroleum): 147 mg (88%) of **19**, colorless solid, can be recrystallized from EtOAc/hexane: colorless needles, mp 109-110°C. UV (MeCN) λ_{max}: 263 nm (ε = 540), 257 (660), 251 (590), 212 (11000). IR (KBr) ν 2975, 2900, 2880, 1725, 1495, 1455, 1380, 1360, 1305, 1260, 1245, 1130, 1115, 1075, 1045, 985, 940, 850, 820, 755, 735, 695, 605, 575, 540, 460 cm^{-1}. ^{1}H-NMR (360 MHz, $CDCl_3$) δ_H 7.30-7.20 (m, Ph); 5.72 (ddd, ^3J = 7.3, 3.1, ^4J = 2.1, H-C(10)); 4.68 (d, ^3J = 4.7, H-C(12)); 4.55, 4.47 (2d, ^2J = 12.0, CH_2Ph); 4.44, 4.41 (2d, ^2J = 11.6, CH_2Ph); 4.31 (dd, ^2J = 10.9, ^4J = 1.7, CH_2OAc); 4.27 (2d, ^3J = 5.9, H-C(1), H-C(4)); 4.07-4.15 (m, H-C(6), H-C(13)); 4.11 (d, ^3J = 3.0, H-C(7)); 4.04 (d, ^2J = 10.9, CH_2OAc); 2.41 (dd, ^2J = 14.0, ^3J = 7.3, H_{eq}-C(9)); 2.32 (ddd, ^2J = 12.5, ^3J = 12.3, 5.9, H_{exo}-C(5 ou 14)); 2.19 (ddd, ^2J = 15.3, ^3J = 9.6, 5.9, H_{exo}-C(5 ou 14)); 2.04 (dd, ^3J = 9.5, ^4J = 2.1, H-C(2)); 2.09 (ddd, ^2J = 14.0, ^3J = 3.1, ^4J = 1.7, H_{ax}-C(9)); 1.75 (s, Ac); 1.40-1.34 (m, H_{endo}-C(5), H-C(14)); 1.27 (d, ^3J = 9.5, H-C(3)). ^{13}C-NMR (90.6 MHz, $CDCl_3$) δ_C 170.8 (s, COO); 142.7 (s, C(11)); 138.2, 138.1 (2s, Ph); 128.3, 128.2, 127.8, 127.7, 127.4, 126.8 (6d, ^1J(C,H) = 154-160, Ph); 117.7 (d, ^1J(C,H) = 167, C(10)); 84.1, 82.8, 80.7, 80.2 (4d, ^1J(C,H) = 156, 156, 156, 159, C(1), C(4), C(7), C(12)); 81.6. 78.3 (2d, ^1J(C,H) = 149, 141, C(6), C(13)); 72.9, 71.9 (2t, ^1J(C,H) = 140, CH_2Ph); 67.5 (t, ^1J(C,H) = 150, CH_2OAc); 54.1, 47.8 (2d, ^1J(C,H) = 134, 136, C(2), C(3)); 51.9 (s, C(8)); 37.5, 35.7 (2t, ^1J(C,H) = 133, C(5), C(14)); 30.4 (t, ^1J(C,H) = 131, C(9)); 20.6 (q, ^1J(C,H) = 129, Ac). CI-MS (NH_3) m/z 503

(1, M$^+$), 411 (8), 307 (8), 261 (6), 105 (5), 92 (10), 91 (100). Anal. Calcd for $C_{31}H_{34}O_6$: C 74.08, H 6.82. Found: C 74.23, H 6.79.

(1RS,2RS,3SR,4RS,6RS,7RS,8RS,10SR,11RS,12SR,13RS)-6,13-Bisbenzyloxy-10,11-epoxy-15,16-dioxa-pentacyclo[10.2.1.1^{4,7}.0^{2,11}.0^{3,8}]hexadecane-8-methyl acetate (**20**). A mixture of **19** (215 mg, 0.427 mmol), 90% m-chloroperbenzoic acid (162 mg, 0.85 mmol) and $CHCl_3$ (8 mL) was stirred at 20°C for 15 h. The mixture was washed with a 5% aqueous solution of Na_2CO_3 (10 mL, twice), then with brine (10 mL, twice). The aqueous layers were combined and extracted with $CHCl_3$ (10 mL, twice). The combined organic extracts were dried ($MgSO_4$). The solvent was evaporated and the residue purified by flash chromatography on Florisil (∅ = 2 cm, h = 13 cm, 1:2 EtOAc/light petroleum): 213 mg (96%) of **20**, colorless foam that can be crystallized from EtOAc/hexane: colorless prisms, mp 142-143°C. UV (MeCN) λ_{max}: 257 nm (ε = 630), 209 (11100). IR (KBr) ν 2975, 1740, 1500, 1455, 1360, 1245, 1145, 1100, 1030, 915, 860, 785, 740, 700 cm^{-1}. ^{1}H-NMR (360 MHz, $CDCl_3$) δ_H 7.41-7.26 (m, Ph); 4.56, 4.51 (2d, ^2J = 12.0, CH_2Ph); 4.50, 4.44 (2d, ^2J = 11.4, CH_2Ph); 4.56, 4.35 (2d, ^2J = 11.3, CH_2OAc); 4.25 (d, ^3J = 6.1, H-C(1)); 4.23 (ddd, ^3J = 10.0, 4.2, 4.1, H-C(6)); 4.21 (d, ^3J = 6.5, H-C(4)); 4.14 (ddd, ^3J = 10.4, 5.3, 4.3, H-C(13)); 4.09 (d, ^3J = 4.2, H-C(7)); 3.94 (d, ^3J = 4.3, H-C(12)); 3.25 (dd, ^3J = 6.1, 4.8, H-C(10)); 2.46 (dd, ^2J = 14.3, ^3J = 6.1, H_{eq}-C(9)); 2.43 (ddd, ^2J = 12.7, ^3J = 10.0, 6.5, H_{exo}-C(5)); 2.33 (ddd, ^2J = 12.3, ^3J = 10.4, 6.1, H_{exo}-C(14)); 1.92 (s, Ac); 1.68 (dd, ^2J = 12.7, ^3J = 4.1, H_{endo}-C(5)); 1.64, 1.62 (d, ^3J = 9.2, H-C(2), H-C(3)); 1.41 (dd, ^2J = 12.3, ^3J = 5.3, H_{endo}-C(14)); 1.20 (dd, ^2J = 14.3, ^3J = 4.8, H_{ax}-C(9)). ^{13}C-NMR (90.6 MHz, $CDCl_3$) δ_C 170.8 (s, COO); 138.0, 137.9 (2s, Ph); 128.4, 128.0, 127.7, 127.1 (4d, ^1J(C,H) = 159-164, Ph); 84.3, 83.8, 82.5, 75.9 (4d, ^1J(C,H) = 167, 160, 161, 162, C(1), C(4), C(7), C(12)); 81.2, 80.1 (2d, ^1J(C,H) = 148, C(6), C(13)); 73.0, 72.5 (2t, ^1J(C,H) = 142, 143, CH_2Ph); 68.4 (t, ^1J(C,H) = 149, CH_2OAc); 64.9 (s, C(11)); 52.6, 47.8 (2d, ^1J(C,H) = 134, 130, C(2), C(3)); 50.9 (d, ^1J(C,H) = 179, C(10)); 50.0 (s, C(8)); 35.8, 33.6, 35.5 (3t, ^1J(C,H) = 136, 138, 130, C(5), C(9), C(14)); 20.8 (q, ^1J(C,H) = 130, Ac). CI-MS (NH_3) m/z 536 (7, M + NH_4^+), 519 (3, M + H^+), 411 (4), 370 (9), 369 (27), 277 (16), 261 (12), 106 (7), 92 (9), 91 (100). Anal. Calcd for $C_{31}H_{34}O_7$: C 71.80, H 6.61. Found: C 71.82, H 6.69.

(1RS,2SR,3RS,4RS,6RS,7SR,8RS,9SR,11RS,12RS,13RS)-13-Benzyloxy-9-hydroxy-15,16,17-trioxahexa-cyclo[10.2.1.1^{4,7}.1^{6,8}.0^{2,11}.0^{3,8}]heptadecane-11-methyl acetate (**21**). BF_3·Et_2O (85 μL, 0.67 mmol) was added to a stirred solution of **20** (50 mg, 0.096 mmol) in anhydrous CH_2Cl_2 (8 mL) cooled to –70°C. The temperature was allowed to reach –50°C and the mixture was stirred at that temperature for 2.5 h. A saturated aqueous solution of $NaHCO_3$ (10 mL) was added at once, the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (10 mL, 4 times). The combined organic extracts were dried ($MgSO_4$), the solvent was evaporated and the residue purified by flash column chromatography on Florisil (∅ = 1 cm, h = 12 cm; 2:3 EtOAc/light petroleum): 33 mg (81%), colorless oil. Crystallization from EtOAc/light petroleum: colorless needles, mp 132-

133°C. IR (KBr) ν 3480, 2975, 2935, 2870, 1745, 1375, 1350, 1235, 1145, 1065, 1040, 1015, 965, 755, 700 cm^{-1}. ^{1}H-NMR (360 MHz, C_6D_6) δ_H 7.18-7.10 (m, Ph); 5.93 (s, OH); 5.49 (d, ^3J = 4.5, H-C(4)); 4.34 (dd, ^3J = 7.5, 4.7, H-C(6)); 4.23 (d, ^3J = 4.5, H-C(12)); 4.21 (d, ^3J = 4.7, H-C(7)); 4.20, 3.61 (2d, ^2J = 8.8, CH_2OAc); 4.15, 4.07 (2d, ^2J = 11.6, CH_2Ph); 3.98 (ddd, ^3J = 10.3, 5.1, 4.5, H-C(13)); 3.74 (d, ^3J = 5.0, H-C(9)); 3.70 (d, ^3J = 6.3, H-C(1)); 2.33 (d, ^2J = 14.2, H_{syn}-C(10)); 2.03, 1.70 (2d, ^3J = 10.3, H-C(2), H-C(3)); 1.98 (ddd, ^2J = 12.6, ^3J = 10.3, 6.3, H_{exo}-C(14)); 1.73 (s, Ac); 1.71 (dd, ^2J = 14.2, ^3J = 5.0, H_{anti}-C(10)); 1.71 (ddd, ^2J = 12.9, ^3J = 7.5, 4.5, H_{exo}-C(5)); 1.41 (d, ^2J = 12.9, H_{endo}-C(5)); 1.30 (dd, ^2J = 12.6, ^3J = 5.1, H_{endo}-C(14)). ^{13}C-NMR (100.6 MHz, C_6D_6) δ_C 169.9 (s, Ac); 137.0 (s, Ph); 128.8, 128.4, 128.2 (3d, ^1J(C,H) = 158-160, Ph); 88.2, 83.0, 82.0, 81.5, 77.7, 76.2, 73.4 (7d, ^1J(C,H) = 156, 155, 154, 154, 156, 154, 154, C(1), C(4), C(6), C(7), C(9), C(12), C(13)); 82.2 (s, C(8)); 81.4 (t, ^1J(C,H) = 141, CH_2Ph); 73.2 (t, ^1J(C,H) = 141, CH_2OAc); 57.0, 54.1 (2d, ^1J(C,H) = 133, C(2), C(3)); 48.3 (s, C(11)); 40.2, 35.2, 30.3 (3t, ^1J(C,H) = 132, 132, 128, C(5), C(10), C(14)); 20.9 (q, ^1J(C,H) = 129, Ac). CI-MS (NH_3) m/z 446 (6, M + NH_4^+), 429 (54, M + H^+), 277 (20), 276 (37), 260 (20), 234 (27), 92 (35), 91 (100). Anal. Calcd for $C_{24}H_{28}O_7$: C 67.28, H 6.59. Found: C 67.31, H 6.64.

REFERENCES

1. M. C. Wani, H. L. Taylor, M. E. Wall, P. Coggon, and A. T. McPhail, J. Am. Chem. Soc., 1971, **93**, 2325; D. Guénard, F. Guéritte-Voegelein, and P. Potier, Acc. Chem. Res., 1993, **26**, 160; D. G. I. Kingston, A. A. Molinero, and J. M. Rimoldi, Prog. Chem. Org. Nat. Prod., 1993, **61**, 1.
2. K. C. Pullaiah, R. K. Surapaneni, C. Bheemasankara Rao, K. F. Albizati, B. W. Sullivan, D. J. Faulkner, H. Cun-heng, and J. Clardy, J. Org. Chem., 1985, **50**, 3665; C. Bheemasankara Rao, K. C. Pullaiah, R. K. Surapaneni, B. W. Sullivan, K. F. Albizati, D. J. Faulkner, H. Cun-heng, and J. Clardy, Ibid., 1986, **51**, 2736.
3. J. Wittenberg, W. Beil, and H. M. R. Hoffmann, Tetrahedron Lett., 1998, **39**, 8259.
4. Laureatin, a constituent of Laurencia nipponica contains a 3,8-dioxabicyclo[5.1.1]nonane moiety: T. Irie, M. Izawa, and E. Kurosawa, Tetrahedron, 1970, **26**, 851.
5. W. Karrer, in "Konstitution und Vorkommen der organischen Pflanzenstoffe", Birkhäuser Verlag, Basel & Stuttgart, 1976, 2nd edition, No. 570, p. 222; W. Karrer, H. Hürlimann, and E. Cherbuliez, Ibid., 1981, No. 570, p. 130.
6. B. Kühne, H.-P. Hanssen, W.-R. Abraham, and V. Wray, Phytochemistry, 1991, **30**, 1463.
7. H. Ginda, T. Kusumi, M. O. Ishitsuka, H. Kakisawa, Z. Weijie, C. Jun, and G. Y. Tian, Tetrahedron Lett., 1988, **29**, 4603; B. Li, F-D. Niu, Z-W. Lin, H-J. Zhang, D-Z. Wang, and H-D. Sun, Phytochemistry, 1991, **30**, 3815.

8. For other examples of natural products containing 2-oxabicyclo[2.2.2]octane moieties, see e.g.: G. Cuevas, O. Collera, F. García, J. Cárdenas, E. Maldonado, and A. Ortega, Phytochemistry, 1987, **26**, 2019; the granaticins: W. Keller-Schierlein, M. Brufani, and S. Barcza, Helv. Chim. Acta, 1968, **51**, 1257; M. Brufani and M. Dobler, *Helv. Chim. Acta* 1968, **51**, 1269; M. L. Gilpin, S. J. Box, and A. L. Elson, J. Antibiot., 1988, **41**, 512; heterocurvistone, constituent of Heterotropa curvistigma: M. Niwa, Y. Sugie, and S. Yamamura, Phytochemistry, 1981, **20**, 1137; spironippol a constituent of the red alga Laurencia nipponica Yamada: A. Fukuzawa, C. M. Shea, T. Masamune, A. Furusaki, C. Katayama, and T. Matsumoto, Tetrahedron Lett., 1981, **22**, 4087; sesquicineol, a bisabolene oxide found in plants with antiinflamatory activity: F. Bohlmann and C. Zdero, Phytochemistry, 1982, **21**, 1697; J. de Pascual-T., M. L. Hernández, J. R. Moran, C. Caballero, J. Anaya, and V. Alcazar, Tetrahedron, 1988, **44**, 5109; miltipolone, a constituent of Salvia miltiorrhiza Bunge ("Tanjin" folk medicine): G. Haro, M. Mori, M. O. Ishitsuka, T. Kusumi, Y. Inouye, and H. Kakisawa, Bull. Chem. Soc. Jpn., 1991, **64**, 3422; abietane diterpene derivatives from Salvia mellifera: J. C. Lius, L. San Andés, Phytochemistry, 1993, **33**, 635; pauciflorol acetate isolated from Sericostoma pauciflorum: S. A. M. Ayatollahi, Z. Ahmed, N. Afza, and A. Malik, Phytochemistry, 1992, **31**, 2899; (-)-dehydro-1,8-sesquicineole and derivatives, constituent of the essential oil of Artemisia sieberi: P. Weyerstahl, S. Schneider, H. Marschall, and A. Rustaiyan, Liebigs Ann. Chem., 1993, 111.
9. A. G. González, J. D. Martín, B. González, J. L. Ravelo, C. Pérez, S. Rafii, and J. Clardy, J. Chem. Soc., Chem. Commun., 1984, 669; J. Clardy, G. Van Duyne, A. Galardo, E. Manta, J. D. Martín, C. Pérez, R. Pérez, J. L. Ravelo, M. L. Rodríguez, and G. K. Schulte, Tetrahedron Lett., 1987, **28**, 6699.
10. H. Mosimann, P. Vogel, A. A. Pinkerton, and K. Kirschbaum, J. Org. Chem., 1997, **62**, 3002.
11. L. Meerpoel, M.-M. Vrahami, J. Ancerewicz, and P. Vogel, Tetrahedron Lett., 1994, **35**, 111.
12. E. Vieira and P. Vogel, Helv. Chim. Acta, 1983, **66**, 1865; J.-L. Reymond and P. Vogel, Tetrahedron: Asymmetry, 1990, **1**, 729; P. Vogel, D. Fattori, F. Gasparini, and C. Le Drian, Synlett, 1990, 173; see also: R. Saf, K. Faber, G. Penn, and H. Griengl, Tetrahedron, 1988, **44**, 389; B. Ronan and H. B. Kagan, Tetrahedron: Asymmetry, 1991, **2**, 75; E. J. Corey and T.-P. Loh, Tetrahedron Lett., 1993, **34**, 3979.
13. S. Czernecki, C. Georgoulis, and C. Provelenghiou, Tetrahedron Lett., 1976, 3535,
14. For the parent 4,7-dioxatricyclo[3.2.1.$0^{3,6}$]octane, see: C. Le Drian and P. Vogel, J. Org. Chem., 1993, **58**, 2328; A. A. Pinkerton, C. Le Drian, and P. Vogel, Acta Cryst., 1996, **C52**, 2927.
15. H. Perst, in "Carbonium Ions", ed. by G. A. Olah, P. von R. Schleyer, Wiley-Interscience, 1976, Vol. V, Chapter 34, p. 1961.
16. For rearrangement in which 1,3-migration of alkoxy groups have been reported, see e.g.: C. Le Drian and P. Vogel, Helv. Chim. Acta, 1987, **70**, 1703; P. G. Gassman and J. L. Marshall, Tetrahedron Lett., 1968, 2429; C. Nativi, J.-L. Reymond, and P. Vogel, Helv. Chim. Acta, 1989, **72**, 882; E. Reynard, J.-L.

Reymond, and P. Vogel, Synlett, 1991, 469; J.-L. Reymond, A. A. Pinkerton, and P. Vogel, J. Org. Chem., 1991, **56**, 2128.

17. Preliminary experiments with the analogue of **20** in which the benzyl ethers have been exchanged for (tert-butyl)dimethylsilyl ethers have shown that the treatment of the epoxide with $BF_3{\cdot}Et_2O$ also generates the corresponding oxetane.
18. J. C. Martin and P. D. Bartlett, J. Am. Chem. Soc., 1957, **79**, 2533; Yu. K. Yur'ev and N. S. Zefirov, Zh. Obschch. Khim., 1962, **32**, 773; N. S. Zefirov, R. A. Ivanova, K. M. Kecher, and Yu. K. Yur'ev, Ibid., 1965, **35**, 61; H. W. Gschwend, M. J. Hillman, and B. Kisis, J. Org. Chem., 1976, **41**, 104; P.-A. Carrupt and P. Vogel, J. Phys. Org. Chem., 1988, **1**, 287; G. P. Moss, O. C. Keat, and G. V. Bondar, Tetrahedron Lett., 1996, **37**, 2877; G. P. Moss and C. K. Ooi, J. Chem. Soc., Chem. Commun., 1992, 342; L.G. French, E. E. Fenion, and T. P. Charlton, Tetrahedron Lett., 1991, **32**, 851; L. G. French and T. P. Charlton, Heterocycles, 1993, **35**, 305; J. L. Reymond and P. Vogel, Chimia, 1990, **44**, 342; J. B. Lambert, E. G. Larson, and K. P. Steele, J. Am. Chem. Soc., 1985, **107**, 704.
19. K. Kraehenbuehl, S. Picasso, and P. Vogel, Helv. Chim. Acta, 1998, **81**, 1439.