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Synthesis of a Bicyclo[3.2.1]octane Analogue of Isocarbacyclin

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A new isocarbacyclin analogue (**1a**), containing a bicyclo[3.2.1]octane ring system, has been synthesized by means of a regioselective rearrangement of the cyclopropyl carbinol (**8**) to the homoallyl bromide (**9**) with hydrobromic acid. Compound **1a** showed very weak inhibitory activity against platelet aggregation.

Keywords——carbacyclin; isocarbacyclin; 3-oxaisocarbacyclin; bicyclo[3.2.1]octane; cyclopropyl'carbinol; homoallyl bromide

Many prostacyclin analogues have been synthesized with the aim of developing therapeutically useful agents.[1] Ring-modified carbacyclin analogues such as a bicyclo[4.3.0]nonane analogue (**2**),[2] a bicyclo[3.2.0]heptane analogue (**3**)[3] and a bicyclo[3.1.0]hexane analogue (**4**)[4] have already been synthesized, but no bicyclo[3.2.1]octane analogue has yet been reported.[5] In the course of our synthetic studies on stable prostacyclin analogues, we wished to synthesize a new bicyclo[3.2.1]octane analogue (**1a**) of 3-oxaisocarbacyclin (**5**), because 3-oxaisocarbacyclin showed fairly potent inhibitory activity against platelet aggregation.[6] We herein describe the synthesis of **1a** by using a regioselective rearrangement of the cyclopropyl carbinol (**8**) to the homoallyl bromide (**9**) with hydrobromic acid as a key step.

The starting tricyclic β-ketoester (**6**) was prepared as described in the previous report.[6] The ketone group in **6** was reduced with sodium borohydride ($NaBH_4$) to afford the unstable

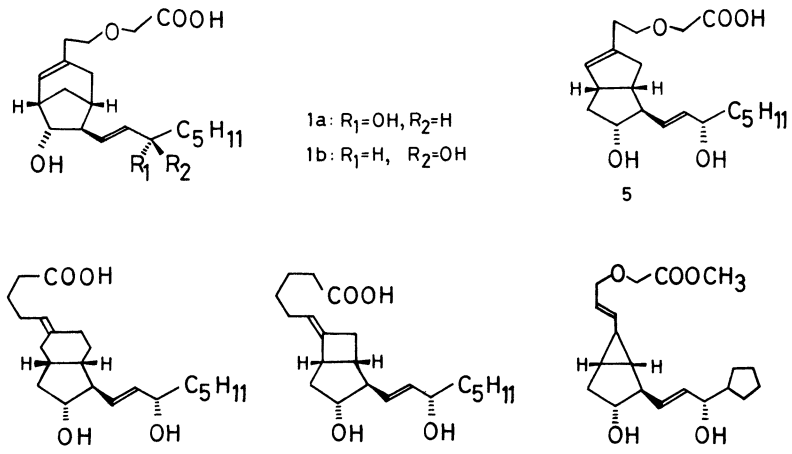


Chart 1

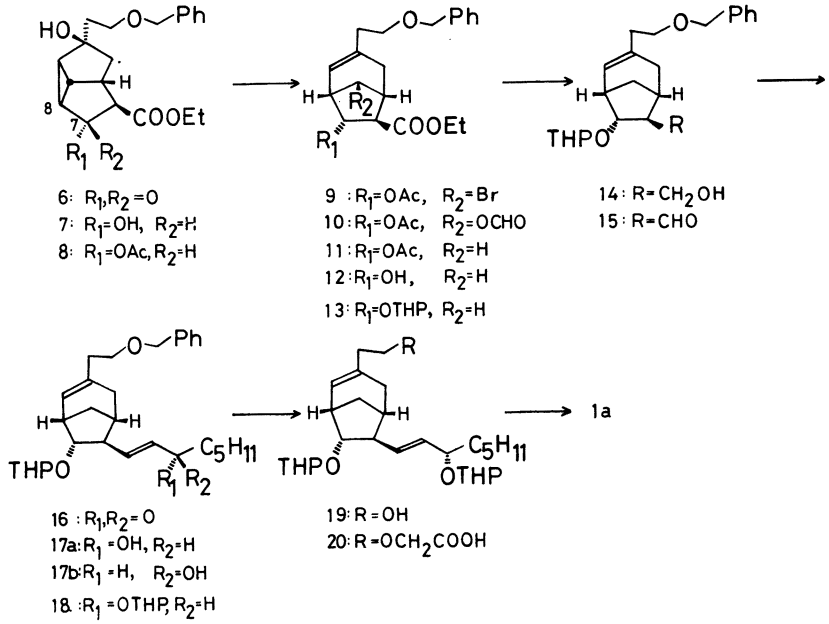
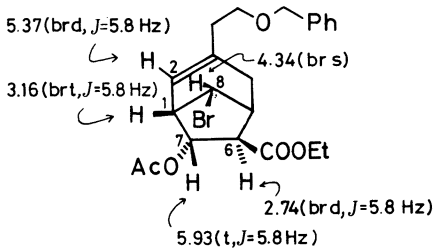


Chart 2

hydroxy ester (**7**), which was acetylated with acetic anhydride and pyridine to give the tricyclic acetate (**8**) in 55% yield from **6**. α-Stereochemistry of the acetoxy group in **8** was assigned on the basis of the steric effects on the $NaBH_4$ reduction and an analysis of the proton nuclear magnetic resonance (^{1}H-NMR) spectrum. The ^{1}H-NMR spectrum of **8** shows a signal due to the C_7 proton as a broad doublet with a coupling constant of $J_{7,8}=6$ Hz.

We then carried out the key reaction, the conversion of the cyclopropyl carbinol system in **8** to the homoallylic system in **9**. Treatment of **8** with excess 48% hydrobromic acid in ether under ice-cooling afforded the single bromide (**9**) in 63% yield. The structure of **9** was determined by ^{1}H-NMR assignment including a decoupling experiment, as summarized in Chart 3. Compound **9** still has an acetyl group, suggesting that the cyclopropyl carbinol moiety with the tertiary hydroxy group is, as expected, more reactive than the cyclopropyl carbinol acetate moiety with a secondary acetate function. However, there are two possible routes for the acid rearrangement of the cyclopropyl carbinol group in **8**; one yields a bicyclo[3.2.1]octane skeleton, such as **9**, and the other affords a bicyclo[3.3.0]octane skeleton. The ^{1}H-NMR spectrum of the product exhibits an olefinic proton signal at δ 5.37 as a broad



9

Chart 3

doublet with a coupling constant of $J=5.8$ Hz, which is coupled with the C_1 proton at δ 3.16 observed as a broad triplet ($J=5.8$ Hz). In bicyclo[3.3.0]octane compounds, the olefinic proton is observed as a broad singlet[6] instead of a doublet. The C_1 proton is further coupled with the C_7 proton at δ 5.93[7] observed as a triplet with $J=5.8$ Hz, and the C_7 proton is also coupled with the C_6 proton at δ 2.74 observed as a broad doublet with $J=5.8$ Hz. The proton at C_8 position is observed at δ 4.34 as a broad singlet ($W_{1/2}=5$ Hz), which changes to a sharp singlet ($W_{1/2}=3$ Hz) on irradiation of the C_1 proton at δ 3.16. These ^{1}H-NMR data coupled with molecular model inspection indicate that the bromide (**9**) has a bicyclo[3.2.1]octane skeleton. Similar treatment of **8** with hydrobromic acid in formic acid afforded the formate (**10**) in 79% yield.

We had thus obtained the desired compound **9**, which was converted into **1a** by means of the following sequence of reactions. Reductive debromination of **9** to **11** was easily accomplished by treatment with tributyltin hydride (n-Bu_3SnH)[8] and α,α'-bis(isobutyronitrile) (AIBN) in benzene at 60 °C in 97% yield. Treatment of **11** with anhydrous potassium carbonate in ethanol at room temperature afforded the hydroxy ester (**12**). The hydroxy group in **12** was protected with tetrahydropyranyl ether to give **13**. After reduction of the ester group in **13** with lithium aluminum hydride in tetrahydrofuran (THF), the obtained alcohol (**14**) was oxidized to the aldehyde (**15**) with excess sulfur trioxide (SO_3)–pyridine complex and triethylamine in dimethyl sulfoxide (DMSO). The Wittig reaction of **15** with tributyl 2-oxoheptylidenephosphorane (n-$Bu_3P=CHCOC_5H_{11}$) in ether at room temperature gave the α,β-unsaturated ketone (**16**) in 92% yield from the ester (**13**). Reduction of the ketone group in **16** with $NaBH_4$ in the presence of cerium (III) chloride ($CeCl_3$) in methanol gave the more polar 15α-alcohol (**17a**) (PG numbering) and the less polar 15β-alcohol (**17b**) in 49% and 44% yields, respectively. The stereochemistry at the C_{15} position was tentatively assigned on the basis of the relative thin layer chromatographic (TLC) mobilities (silica gel). In general in prostaglandin chemistry, the more polar alcohol is the 15α-hydroxy compound, and the less polar alcohol is the 15β-hydroxy compound. Protection of the hydroxy group in the 15α-alcohol (**17a**) with dihydropyran (DHP) and p-toluenesulfonic acid in methylene chloride, followed by treatment with excess sodium metal in liquid ammonia at -78 °C gave the alcohol (**19**) in 74% yield from **17a**. Alkylation of the alcohol (**19**) with lithium chloroacetate ($ClCH_2COOLi$) afforded the carboxylic acid (**20**). Finally, removal of the protective groups of **20** with camphorsulfonic acid in aqueous acetone gave the desired compound **1a** as a colorless viscous oil.

By using a sequence of reactions similar to that described for the synthesis of **1a**, the 15β-alcohol (**17b**) was led to the 15β-isomer (**1b**).

Compounds **1a** and **1b** exhibited very weak inhibitory activities (IC_{50}: 5.4 and 4.1 μg/ml, respectively) against adenosine diphosphate induced platelet aggregation using rabbit platelet-rich plasma.

Experimental

Infrared (IR) spectra were recorded with a JASCO A-102 spectrophotometer. ^{1}H-NMR spectra were recorded with a Varian T-60A (60 MHz) or EM-390 (90 MHz) instrument or with a JEOL JNM-DX-270 (270 MHz) spectrometer in deuteriochloroform, with tetramethylsilane as an internal reference. Low-resolution mass spectra (LR-MS) were obtained with a JEOL JMS-01SG or JMS-G300 mass spectrometer and high-resolution mass spectra (HR-MS) with a JEOL JMS-HX100 or JMS-G300 mass spectrometer. Removal of solvents *in vacuo* was accomplished with a rotating flash evaporator at 20—30 mmHg and usually at 35—50 °C. Plates for TLC were Silica gel 60 F-254 (E. Merck AG) and spots were visualized by spraying a solution of 0.5% vanillin in 20% ethanol in sulfuric acid (v/v), followed by heating. Columns for ordinary chromatography were prepared with Silica gel 60 (70—230 mesh or 230—400 mesh, E. Merck AG). In general, reactions were carried out under a nitrogen stream.

(1*R,2*R**,3*R**,5*S**,6*R**,7*R**,8*S**)-7-Acetoxy-3-[2-(benzyloxy)ethyl]-6-ethoxycarbonyl-3-hydroxytricyclo-[3.3.0.0^{2,8}]octane (8)**——$NaBH_4$ (0.712 g) was added to a stirred solution of **6** (3.012 g) in ethanol (30 ml) under

ice-cooling, and the whole was stirred for 2 h. The reaction mixture was poured into brine and extracted with AcOEt. The extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an unstable hydroxy ester (**7**), which was treated with Ac_2O (10 ml) in pyridine (20 ml) for 4 h at room temperature. The reaction mixture was poured into water and extracted with Et_2O. The extracts were washed with dil. HCl and brine, and dried over Na_2SO_4. Removal of the solvent gave an oily residue, which was purified by silica gel column chromatography. Elution with 20—35% AcOEt in hexane (v/v) afforded **8** (1.860 g) as a colorless oil. IR (neat): 3500, 1735, 1235 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.97 (3H, s, CH_3CO), 4.10 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.48 (2H, s, CH_2Ph), 5.67 (1H, br d, J=6 Hz, C_7-H), 7.30 (5H, s, arom.-H). LR-MS m/z: 370 ($M^+ - H_2O$), 329, 311. HR-MS m/z: Calcd for $C_{22}H_{26}O_5$ ($M^+ - H_2O$): 370.1780. Found: 370.1790.

(1*S,5*R**,6*R**,7*S**,8*S**)-7-Acetoxy-3-[2-(benzyloxyl)ethyl]-8-bromo-6-ethoxycarbonylbicyclo[3.2.1]oct-2-ene (9)**——A 48% aqueous solution of HBr (14 ml) was added to a stirred solution of **8** (1.430 g) in Et_2O (50 ml) under ice-cooling, and the whole was stirred for 20 min under the same conditions. The reaction mixture was poured into water and extracted with Et_2O. The extracts were washed with $NaHCO_3$ aq. and brine, and dried over Na_2SO_4. Removal of the solvent gave an oily residue, which was purified by silica gel column chromatography. Elution with 6—12% AcOEt in hexane (v/v) afforded **9** (1.050 g) as a colorless oil. IR (neat): 1735, 1240 cm^{-1}. ^{1}H-NMR (270 MHz) ($CDCl_3$) δ: 1.27 (3H, t, J=7.2 Hz, $OCH_2C\underline{H}_3$), 2.01 (3H, s, CH_3CO), 2.74 (1H, br d, J=5.8 Hz, C_6-H), 3.16 (1H, br t, J=5.8 Hz, C_1-H), 3.52 (2H, t, J=6.6 Hz, $OC\underline{H}_2CH_2$), 4.21 (2H, q, J=7.2 Hz, $OC\underline{H}_2CH_3$), 4.34 (1H, br s, C_8-H), 4.49 (2H, s, CH_2Ph), 5.37 (1H, br d, J=5.8 Hz, C_2-H), 5.93 (1H, t, J=5.8 Hz, C_7-H), 7.32 (5H, s, arom.-H). LR-MS m/z: 452 (M^++2), 450 (M^+), 344, 346. HR-MS m/z: Calcd for $C_{22}H_{27}BrO_5$ (M^++2): 452.1022. Found: 452.1012.

(1*S,5*R**,6*R**,7*S**,8*S**)-7-Acetoxy-3-[2-(benzyloxy)ethyl]-6-ethoxycarbonyl-8-formyloxybicyclo[3.2.1]oct-2-ene (10)**——A 48% aqueous solution of HBr (0.1 ml) was added to a stirred solution of **8** (192 mg) in 99% formic acid (2 ml) at room temperature, and the whole was stirred for 30 min under the same conditions. The reaction mixture was poured into water and extracted with Et_2O. The extracts were washed with $NaHCO_3$ aq. and brine, then dried over Na_2SO_4. Removal of the solvent gave an oily residue, which was purified by silica gel column chromatography. Elution with 14—18% AcOEt in hexane (v/v) afforded **10** (162 mg) as a colorless oil. IR (neat): 1730, 1240, 1165 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.99 (3H, s, CH_3CO), 3.50 (2H, t, J=6 Hz, $OC\underline{H}_2CH_2$), 4.11 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.46 (2H, s, CH_2Ph), 5.01 (1H, br s, C_8-H), 5.32 (1H, br d, J=6 Hz, C_2-H), 5.52 (1H, t, J=6 Hz, C_7-H), 7.26 (5H, s, arom.-H), 7.89 (1H, s, CHO). LR-MS m/z: 416 (M^+), 312, 220.

(1*S,5*S**,6*R**,7*R**)-7-Acetoxy-3-[2-(benzyloxy)ethyl]-6-ethoxycarbonylbicyclo[3.2.1]oct-2-ene (11)**——A mixture of **9** (1.050 g) and *n*-Bu_3SnH (1.0 ml) and AIBN (50 mg) in toluene (30 ml) was stirred for 30 min at 60 °C. The reaction mixture was concentrated to dryness. The residue obtained was purified by silica gel column chromatography. Elution with 6—9% AcOEt in hexane (v/v) afforded **11** (840 mg) as a colorless oil. IR (neat): 1735, 1240 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.97 (3H, s, CH_3CO), 3.51 (2H, t, J=6 Hz, $OC\underline{H}_2CH_2$), 4.13 (2H, q, J=6 Hz, $OC\underline{H}_2CH_3$), 4.48 (2H, s, CH_2Ph), 5.10 (1H, t, J=6 Hz, C_7-H), 5.52 (1H, br d, J=6 Hz, C_2-H), 7.30 (5H, s, arom.-H). LR-MS m/z: 372 (M^+), 312, 266. HR-MS m/z: Calcd for $C_{22}H_{28}O_5$ (M^+): 372.1937. Found: 372.1931.

(1*S,5*S**,6*R**,7*R**)-3-[2-(Benzyloxy)ethyl]-6-ethoxycarbonyl-7-hydroxybicyclo[3.2.1]oct-2-ene (12)**——A mixture of **11** (840 mg) and anhydrous K_2CO_3 (2.00 g) in ethanol (20 ml) was stirred for 3 h at room temperature. The reaction mixture was poured into water and extracted with AcOEt. The extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 12—18% AcOEt in hexane (v/v) afforded **12** (715 mg) as a colorless oil. IR (neat): 3440, 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 3.48 (2H, t, J=6 Hz, $OC\underline{H}_2CH_2$), 4.10 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.45 (2H, s, OCH_2Ph), 5.55 (1H, br d, J=6 Hz, C_2-H), 7.36 (5H, s, arom.-H). LR-MS m/z: 330 (M^+), 312. HR-MS m/z: Calcd for $C_{20}H_{26}O_4$ (M^+): 330.1836. Found: 330.1840.

(1*S,5*S**,6*R**,7*R**)-3-[2-(Benzyloxy)ethyl]-6-ethoxycarbonyl-7-(tetrahydropyran-2-yl)oxybicyclo[3.2.1]oct-2-ene (13)**——A mixture of **12** (714 mg), DHP (0.30 ml) and a catalytic amount of *p*-TsOH in CH_2Cl_2 (20 ml) was stirred under ice-cooling for 30 min. The reaction mixture was diluted with CH_2Cl_2, washed with 5% $NaHCO_3$ aq. and brine, and then dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 4—7% AcOEt in hexane (v/v) afforded **13** (839 mg) as a colorless oil. IR (neat): 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 4.12 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.48 (2H, s, OCH_2Ph), 4.60 (1H, br s, OCHO), 5.60 (1H, br t, J=6 Hz, C_2-H), 7.30 (5H, s, arom.-H). LR-MS m/z: 414 (M^+), 330. HR-MS m/z: Calcd for $C_{25}H_{34}O_5$ (M^+): 414.2406. Found: 414.2383.

(1*S,5*S**,6*S**,7*R**)-3-[2-(Benzyloxy)ethyl]-6-hydroxymethyl-7-(tetrahydropyran-2-yl)oxybicyclo[3.2.1]oct-2-ene (14)**——A solution of **13** (826 mg) in THF (8 ml) was added to a stirred suspension of $LiAlH_4$ (120 mg) in THF (15 ml) under ice-cooling, and the whole was stirred for 30 min, and then quenched with 4% NaOH aq. (0.5 ml). The reaction mixture was stirred at room temperature for another 1 h, and then the precipitate was filtered off. Removal of the solvent of the filtrate *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 15—25% AcOEt in hexane (v/v) afforded **14** (723 mg) as a colorless oil. IR (neat): 3470, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.47 (2H, s, OCH_2Ph), 5.57 (1H, br t, J=6 Hz, C_2-H), 7.28 (5H, s, arom.-H). LR-MS m/z: 372

(M^+), 354, 288. HR-MS *m/z*: Calcd for $C_{23}H_{32}O_4$ (M^+): 372.2301. Found: 372.2291.

(1*S,5*S**,6*R**,7*R**)-3-[2-(Benzyloxy)ethyl]-6-formyl-7-(tetrahydropyran-2-yl)oxybicyclo[3.2.1]oct-2-ene (15)**——A solution of sulfur trioxide–pyridine complex (2.10 g) in DMSO (15 ml) was added to a stirred mixture of **14** (720 mg) and Et_3N (6.7 ml) in DMSO (7 ml) at room temperature. After being stirred for 30 min, the reaction mixture was poured into ice-water and extracted with AcOEt. The extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave a practically pure aldehyde (**15**) (691 mg) as a pale yellow oil. The crude material was used for the subsequent step without purification. IR (neat): 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.46 (2H, s, OCH_2Ph), 4.58 (1H, br s, OCHO), 5.57 (1H, br t, J=6 Hz, C_2-H), 7.25 (5H, s, arom.-H), 9.70 (1H, d, J=4 Hz, CHO).

(1*S,5*S**,6*S**,7*R**)-3-[2-(Benzyloxy)ethyl]-6-[3-oxo-1(*E*)-octenyl]-7-(tetrahydropyran-2-yl)oxybicyclo[3.2.1]-oct-2-ene (16)**——Tributyl 2-oxoheptylidenephosphorane (840 mg) in Et_2O (5 ml) was added to a solution of **15** (688 mg) in Et_2O (15 ml), and the whole was stirred for 2.5 h at room temperature. The reaction mixture was concentrated to dryness. The resultant residue was purified by silica gel column chromatography. Elution with 6—9% AcOEt in hexane (v/v) afforded **16** (850 mg) as a colorless oil. IR (neat): 1690, 1670, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.48 (2H, s, OCH_2Ph), 5.60 (1H, br t, J=6 Hz, C_2-H), 6.09 (1H, dd, J=3, 16 Hz, olefinic-H), 6.60—7.10 (1H, m, olefinic-H), 7.30 (5H, s, arom.-H). LR-MS *m/z*: 382 (M^+-84), 364. HR-MS *m/z*: Calcd for $C_{25}H_{34}O_3$ ($M^+-C_5H_8O$): 382.2508. Found: 382.2505.

(1*S,5*S**,6*S**,7*R**)-3-[2-(Benzyloxy)ethyl]-6-[3(*S**)-hydroxy-1(*E*)octenyl]-7-(tetrahydropyran-2-yl)oxybicyclo-[3.2.1]oct-2-ene (17a) and (1*S**,5*S**,6*S**,7*R**)-3-[2-(Benzyloxy)ethyl]-6-[3(*R**)-hydroxy-1(*E*)-octenyl]-7-(tetra-hydropyran-2-yl)oxybicyclo[3.2.1]oct-2-ene (17b)**——$NaBH_4$ (100 mg) was added to a stirred solution of **16** (846 mg) and $CeCl_3 \cdot 7H_2O$ (812 mg) in methanol (16 ml) under ice-cooling. After 30 min of stirring, the excess reagent was decomposed by addition of AcOH, and the reaction mixture was diluted with brine and extracted with AcOEt. The extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 10% AcOEt in hexane (v/v) afforded **17b** (376 mg) as a colorless oil, and further elution with 12% AcOEt in hexane (v/v) afforded **17a** (420 mg) as a colorless oil. Compound **17a**: IR (neat): 3450 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.52 (2H, s, OCH_2Ph), 4.68 (1H, br s, OCHO), 5.30—5.90 (3H, m, olefinic-H), 7.35 (5H, s, arom.-H). LR-MS *m/z*: 366 (M^+-102), 276. HR-MS *m/z*: Calcd for $C_{25}H_{34}O_2$ ($M^+-C_5H_{10}O_2$): 366.2559. Found: 366.2542. Compound **17b**: IR (neat): 3450 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.52 (2H, s, OCH_2Ph), 4.70 (1H, br s, OCHO), 5.30—5.90 (3H, m, olefinic-H), 7.35 (5H, s, arom.-H). LR-MS *m/z*: 366 (M^+-102), 276. HR-MS *m/z*: Calcd for $C_{25}H_{34}O_2$ ($M^+-C_5H_{10}O_2$): 366.2559. Found: 366.2558.

(1*S,5*S**,6*S**,7*R**)-3-[2-(Benzyloxy)ethyl]-7-(tetrahydropyran-2-yl)oxy-6-[3(*S**)-(tetrahydropyran-2-yl)oxyoct-1(*E*)-enyl]bicyclo[3.2.1]oct-2-ene (18)**——A mixture of **17a** (410 mg), DHP (0.12 ml) and a catalytic amount of *p*-TsOH in CH_2Cl_2 (4 ml) was stirred under ice-cooling for 15 min. The reaction mixture was diluted with CH_2Cl_2, washed with 5% $NaHCO_3$ aq. and brine, and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 5—9% AcOEt in hexane (v/v) afforded **18** (410 mg) as a colorless oil. IR (neat): 2950, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.47 (2H, s, OCH_2Ph), 4.62 (2H, br s, OCHO), 5.10—5.90 (3H, m, olefinic-H), 7.27 (5H, s, arom.-H). LR-MS *m/z*: 366 ($M^+-102-84$), 285. HR-MS *m/z*: Calcd for $C_{25}H_{34}O_2$ ($M^+-C_5H_{10}O_2-C_5H_8O$): 366.2559. Found: 366.2533.

(1*S,5*S**,6*S**,7*R**)-3-(2-Hydroxyethyl)-7-(tetrahydropyran-2-yl)oxy-6-[3(*S**)-(tetrahydropyran-2-yl)oxyoct-1(*E*)-enyl]bicyclo[3.2.1]oct-2-ene (19)**——Excess sodium metal was added to a stirred solution of **18** (402 mg) in a mixture of liquid ammonia (20 ml) and THF (14 ml) at −78 °C until a blue color persisted, and the whole was stirred for 20 min. The reaction was quenched by the addition of NH_4Cl, and then ammonia was evaporated off at room temperature under a stream of N_2. Water was added to the residue and the mixture was extracted with Et_2O. The extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent gave an oily residue, which was purified by silica gel column chromatography. Elution with 12—16% AcOEt in hexane (v/v) afforded **19** (294 mg) as a colorless oil. IR (neat): 3500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.65 (2H, br s, OCHO), 5.10—5.90 (3H, m, olefinic-H). LR-MS *m/z*: 360 (M^+-102), 316. HR-MS *m/z*: Calcd for $C_{23}H_{36}O_3$ ($M^+-C_5H_{10}O_2$): 360.2664. Found: 360.2648.

(1*S,5*S**,6*S**,7*R**)-3-[2-(Carboxymethoxy)ethyl]-7-(tetrahydropyran-2-yl)oxy-6-[3(*S**)-(tetrahydropyran-2-yl)oxyoct-1(*E*)-enyl]bicyclo[3.2.1]oct-2-ene (20)**——A solution of 15% *n*-BuLi in hexane (0.53 ml) was added to a stirred solution of **19** (282 mg) in THF (7 ml) under ice-cooling. The mixture was stirred for 10 min, then dimethylformamide (1.0 ml), DMSO (1.0 ml), $ClCH_2COOLi$ (200 mg) and NaI (500 mg) were added, and the whole was stirred for 5 h at room temperature. The reaction mixture was diluted with water, acidified with 3% HCl aq. and extracted with AcOEt. The extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by acid-washed silica gel column chromatography. Elution with 20—30% AcOEt in hexane (v/v) afforded **20** (220 mg) as a colorless oil. IR (neat): 1755, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.06 (2H, s, OCH_2COOH), 4.66 (2H, br s, OCHO), 5.10—5.90 (3H, m, olefinic-H), 8.58 (1H, s, COOH). LR-MS *m/z*: 334 ($M^+-102-84$), 258, 154. HR-MS *m/z*: Calcd for $C_{20}H_{32}O_5$ ($M^+-C_5H_{10}O_2-C_5H_8O$): 334.2144. Found: 334.2154.

(1*S,5*S**,6*S**,7*R**)-3-[2-(Carboxymethoxy)ethyl]-7-hydroxy-6-[3(*S**)-hydroxyoct-1(*E*)-enyl]bicyclo[3.2.1]oct-2-ene (1a)**——A mixture of **20** (216 mg) and camphorsulfonic acid (20 mg) in acetone (8 ml) and water (4 ml) was stirred at 40 °C for 2 h. The reaction mixture was poured into water and extracted with AcOEt. The extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified

by acid-washed silica gel column chromatography. Elution with 70% AcOEt in hexane (v/v) to AcOEt afforded **1a** (97 mg) as a colorless viscous oil. IR (neat): 3400, 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.67 (2H, t, J=6 Hz, OCH_2CH_2), 4.07 (2H, s, OCH_2COOH), 5.40—5.85 (3H, m, olefinic-H). LR-MS m/z: 334 (M^+-18), 316, 290. HR-MS m/z: Calcd for $C_{20}H_{32}O_5$ (M^+-H_2O): 334.2144. Found: 334.2132. Rf=0.27 (benzene : AcOEt : MeOH : AcOH = 20 : 60 : 1 : 1).

(1*S,5*S**,6*S**,7*R**)-3-[2-(Carboxymethoxy)ethyl]-7-hydroxy-6-[3(*R**)-hydroxyoct-1(*E*)-enyl]bicyclo[3.2.1]oct-2-ene (1b)**——Similar treatment of the 15β-alcohol (**17b**) through the reaction sequence used for the synthesis of **1a** gave **1b** as a colorless viscous oil. IR (neat): 3400, 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.67 (2H, t, J=6 Hz, OCH_2CH_2), 4.09 (2H, s, OCH_2COOH), 5.40—5.85 (3H, m, olefinic-H). LR-MS m/z: 334 (M^+-18), 316, 290. HR-MS m/z: Calcd for $C_{20}H_{32}O_5$ (M^+-H_2O): 334.2144. Found: 334.2126. Rf=0.36 (benzene : AcOEt : MeOH : AcOH = 20 : 60 : 1 : 1).

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References and Notes

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