10-H), 7.19 (1 H, m, 10-H or 9-H); ^{13}C NMR δ ($CDCl_3$), 14.0 (C-18), 22.4 (C-17), 23.5 (C-5 or C-14), 24.0 (C-14 or C-5), 24.4 (C-3), 28.5 (C-15 or C-16), 28.8 (C-16 or C-15), 31.5 (C-4), 33.7 (C-2), 40.7 (C-6 or C-13), 41.6 (C-13 or C-6), 135.8 (C-8 or C-11), 136.1 (C-11 or C-8), 138.7 (C-9 or C-10), 139.0 (C-10 or C-9), 178.3 (C-1), 199.7 (C-7 or C-12), 200.2 (C-12 or C-7); MS *m/e* (rel intensity) 308 (M^+, 23), 290 (4), 237 (2), 223 (4), 207 (4), 205 (8), 165 (100), 138 (53), 125 (78), 123 (39), 95 (76), 85 (34), 81 (52), 55 (77), 43 (73), 41 (50); exact mass 308.1988 (calcd for $C_{18}H_{28}O_4$ 308.1986). Anal. Calcd for $C_{18}H_{28}O_4$: C, 70.13; H, 9.09. Found: C, 70.01; H, 9.06.

Acknowledgment. We thank the National Science Council of Taiwan, ROC, for the financial support of this research.

Supplementary Material Available: ^1H NMR spectra of synthetic and natural ostopanic acid (2 pages). Ordering information is given on any current masthead page.

Synthesis of Bicyclo[2.1.0]pentanoid-Containing Prostaglandins[1]

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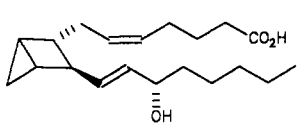
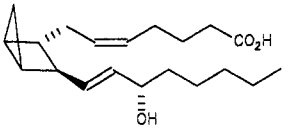
The synthesis of (5*Z*,13*E*,15*S*)-15-hydroxy-9α,11α-cycloprosta-5,13-dien-1-oic acid and its 9β,11β epimer was accomplished in 21 steps from cyclopentadiene with an efficiency of 0.75%. Although the strain (almost 48 kcal/mol of the 56 kcal/mol total by MMX calculation) in the 9,11 bridging bond renders its susceptible to electrophilic opening, these compounds were not found to inhibit platelet aggregation by blocking any of the prostaglandin biosynthetic pathways in the arachidonic acid cascade. Specific inhibition (IC_{50} at 3.2×10^{-6} M) of TXA_2-stimulated platelet aggregation, however, suggests that they are weak TXA_2 antagonists.

Prostaglandin endoperoxide (PGH_2) is the key member of the arachidonic acid cascade that leads to the formation (Scheme I) of prostacyclin (PGI_2) and thromboxane A_2 (TXA_2).[2] Since these natural compounds have been implicated to be intimately involved in many of the pulmonary–cardiovascular disorders that account for over a million deaths (USA) each year,[3] it is not surprising that they continue to be the focus of intensive study by synthetic organic chemists.

The ability to selectively modulate the biological conversion of PGH_2 into TXA_2 has important therapeutic value, and several analogues of PGH_2 have been investigated for this purpose.[2] Recent mechanistic studies[4] suggest that the synthetase enzymes involved in the arachidonic acid cascade are electrophilic in nature, and since the strain (almost 48 kcal/mol of the 56 kcal/mol total by MMX[5] calculation) in the bridging bond in bicyclo[2.1.0]pentane renders it susceptible to electrophilic opening,[6] we felt that the novel prostanoids **1** and **2**

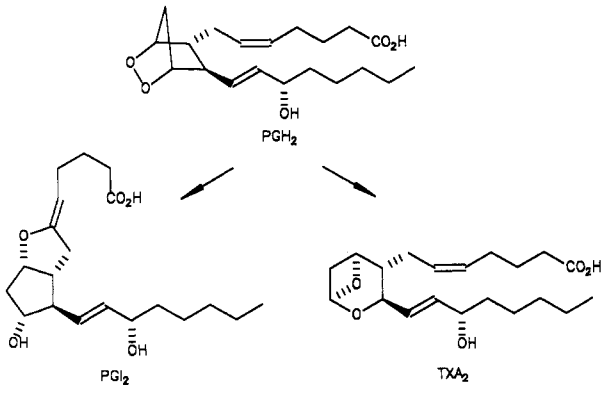


1



2

Scheme I



[(5*Z*,13*E*,15*S*)-15-hydroxy-9α,11α-cycloprosta-5,13-dien-1-oic acid and its 9β,11β epimer] would be suitably functionalized to intercept and block some of these enzymatic processes. Furthermore, since Gassman,[6a] Noyori,[6b] and others[6c] have shown that bicyclo[2.1.0]pentanoid intermediates (under controlled conditions) can be converted into bicyclo[2.2.1]heptanoids, **1** and **2** have the potential of being common precursors to many of the important PGH_2 analogues that presently are available only through independent multistep total syntheses. Herein, we describe the total synthesis of **1** and its epimer **2** and report on their biological properties.

Our strategy for the synthesis of **1** and **2** (Scheme II) was designed to profit from the elegant work outlined by Corey and his group in their total synthesis of the 9,11-azo analogue of PGH_2.[7] Early removal of the labile azo functionality and obtaining the appropriately fuctionalized chiral bicyclo[2.1.0]pentane derivatives **8a** and **8b**, both

(1) Dedicated to Prof. E. C. Taylor on the occasion of his 65th birthday.

(2) For an excellent description of prostaglandin chemistry, see: Taylor, R. K. In *Prostaglandins and Thromboxanes*; Newton, R. F., Roberts, S. M., Eds.; Butterworths: New York, 1982, and references cited therein; *Advances in Prostaglandin, Thromboxane, and Leukotriene Research*; Pike, J. E.; Morton, D. R., Jr., Eds.; Raven Press: New York, 1985; Vol. 14, and references cited therein. See also: Bhagwat, S. S.; Hamann, P. R.; Still, W. C. *J. Am. Chem. Soc.* **1985**, *107*, 6372 and references cited therein. Hall, S. E.; Han, W. C.; Haslanger, M. F.; Harris, D. N.; Ogletree, M. L. *J. Med. Chem.* **1986**, *29*, 2335.

(3) Taylor, M. D.; Sircar, I.; Steffen, R. P. In *Annual Reports in Medicinal Chemistry*; Bailey, D. M., Ed.; Academic Press: New York, 1987; Vol. 22, Chapter 9; *Time* **1987**, *130*(21), 58. Stinson, S. *Chem. Eng. News* **1988** October 3, p 35.

(4) Corey, E. J. *Pure Appl. Chem.* **1987**, *59*, 269.

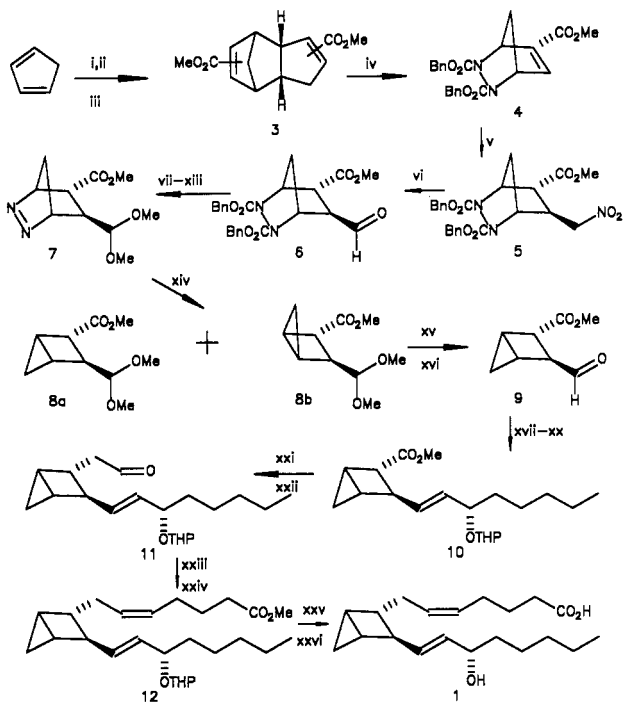
(5) Obtained from Serena Software, P.O. Box 3076, Bloomington, IN 47402-3076.

(6) See for example: (a) Gassman, P. G. *Acc. Chem. Res.* **1971**, *4*, 128 and references cited therein. (b) Suzuki, T.; Kumagai, Y.; Yamakawa, M.; Noyori, R. *J. Org. Chem.* **1981**, *46*, 2846 and references cited therein. (c) Bloodworth, A. J.; Hargreeves, N. *Tetrahedron Lett.* **1987**, *28*, 2783.

(7) Corey, E. J.; Narasaka, K.; Shibasaki, M. *J. Am. Chem. Soc.* **1976**, *98*, 6417.

0022-3263/89/1954-5128$01.50/0

Scheme II[a]



[a] (i) NaH/THF; (ii) CO_2/THF/0 °C; (iii) MeOH/5% H_2SO_4; (iv) DBAD/PhCl/125 °C 15 h; (v) CH_3NO_2/TMG/MeOH/H_2O; (vi) see ref 9; (vii) $(MeO)_3CH$/CSA/MeOH; (viii) H_2 (1 atm)/Pd(10%), C/MeOH; (ix) HgO/MeOH; (x) NaOH; (xi) ephedrine-*d*; (xii) 1 N HCl; (xiii) CH_2N_2; (xiv) *hν* 350 nm/Et_2O; (xv) HPLC; (xvi) PTSA/THF/H_2O; (xvii) $(MeO)_2P(O)CH_2C(O)(CH_2)_3CH_3$/NaH/DME; (xviii) see ref 11; (xix) chrom (silica); (xx) DHP/CSA/CH_2Cl_2; (xxi) DIBAL/toluene; (xxii) $Ph_3PCHOMe$; $Hg(OAc)_2$/Et_3N/THF/H_2O/KI; (xxiii) $Ph_3P(CH_2)_4CO_2Na$/DMSO/NaH; (xxiv) CH_2N_2; (xxv) CSA/MeOH; (xxvi) 1 N NaOH.

of which could serve as synthons to **1** or **2** by selective manipulation of the acetal–ester groups during chain homologation, was given high priority.

Thus, thermally (125 °C PhCl 15 h under argon) induced retro-Diels–Alder fragmentation of Thiele's ester **3** in the presence of dibenzyl azodicarboxylate followed by removal of the solvent and addition of ether (−20 °C) crystallized out the thermodynamically more stable Diels–Alder azo adduct **4**[8] (mp 87–88 °C) in 40% yield.[7] 1,1,3,3-Tetramethylguanadine[7] (10.5 mmol) catalyzed Michael addition of nitromethane to **4** (100 mmol) in a solvent mixture of nitromethane (167 mL), methanol (167 mL), and water (500 mL) for 6 h at 25 °C gave, after concentration of the solvent by rotary evaportion, addition of ether, washing with brine, drying the organic layer over $MgSO_4$, concentration, and filtration of the resulting residue through a pad of silica (10 g per g of residue) with use of CCl_4/ether (1:1) as the eluent, analytically pure **5**[8] (65% yield) as a light-sensitive, white amorphous solid that does not lend itself to crystallization.

Susceptibility of **5** to ring opening made the conversion into aldehyde **6**[8] far more challenging than anticipated. However, after considerable experimentation, we found that the potassium nitro enolate of **5** could be hydrolized into **6**, in high yield (95%), by carrying out the Nef reaction in methanol instead of water.[9] Protection of the aldehyde as its dimethyl acetal followed by hydrogenolysis of the benzyl appendages and oxidation of the resulting hydrazine with HgO gave the key racemic crystalline azo intermediate **7**[8] in 80% overall yield from **5**. The chiral material (white, low-melting, volatile solid, $[\alpha]^{23}_D$ −32.2° (c = 1.0, $CHCl_3$)) was obtained by first hydrolyzing the ester (1 equiv of NaOH in MeOH/H_2O, 9:1, at 0 °C), forming a salt with ephedrine-*d*, separating the diastereomers by fractional crystallization and then regenerting the free acid (1 M HCl) followed by reesterification with diazomethane.

Photolytically (350 nm in ether) induced extrusion of nitrogen from (−)-**7**[8] gave a 2:3 mixture of the enantiomerically pure epimeric esters (−)-**8a**[8] and (−)-**8b**[8] in 92% yield. Since the bicyclo[2.1.0]pentane moiety is often used in numerous studies concerning strained bonds,[10] these functionalized epimers, which are readily separable by HPLC, may now provide an easy access to other interesting derivatized bicyclo[2.1.0]pentanes that would be difficult to attain otherwise.

Removal of the dimethyl acetal protecting group (PTSA, THF/H_2O, 9:1, reflux for 17 h) from (−)-**8a** afforded the crucial aldehyde (−)-**9**[8] (85% yield), having all the required stereochemistry and functionality necessary for development into the target compounds set in place. Sequential ω and α chain homologation as described in Scheme II, using racemic material, afforded prostanoid **1**[8] in 21 steps from cyclopentadiene with an overall efficiency of 0.75%. In the same way, prostanoid **2**[8] was obtained from **8b** in similar yield. Use of Noyori's reagent[11] for high yield (97%) stereoselective reduction of the 15-keto functionality into the 15*S*-hydroxy group in these syntheses was most important. The ususal[2] chromatographic separating techniques for 15*S*/15*R* epimers are ineffective when substantial amounts of the unwanted 15*R* epimer of **2** is produced.

Compounds **1**, **2**, **8a**, and **8b** were tested for platelet aggregating properties, and all showed very weak inhibition (IC_{50} at 1.4×10^{-4} M) toward collagen-, U-46619-, ADP-, and A23187-stimulated platelet aggregation. However, since prostanoids **1** and **2** specifically inhibit (IC_{50} at 3.2×10^{-5} M) TXA_2-stimulated platelet aggregation, it suggests that they are TXA_2 antagonists rather than inhibitors.[12]

Experimental Section[8]

(−)-Methyl 2-*endo*-3-*exo*-3-(Dimethoxymethyl)-5,6-diazabicyclo[2.2.1]hept-5-ene-2-carboxylate [(−)-7]. Aldehyde **6**[9] (4.22 g, 10 mmol) was hydrogenated, at ambient pressure, in methanol (100 mL) over 10% Pd on charcoal (294 mg) for 3 h. The mixture was filtered through a pad of Celite, and the Celite was washed with 3 × 10 mL of methanol. The filtrate and washings were combined, and a mixture of $MgSO_4$ (1 g) and HgO (2.81 g, 13.0 mmol) was added with vigorous stirring. After being stirred for a total of 3 h, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated by rotary evaporation, and the residue was triturated with CH_2Cl_2 (5 × 25 mL). The CH_2Cl_2 extracts were combined and concentrated by rotary

(8) All compounds were fully characterized by spectroscopic means, and combustion analyses (Guelph Chemical Laboratories Ltd.) were satisfactorily performed on all key intermediates. "Chromatographed on silica" refers to "flash chromatography" as described by Still. See: Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923. Optical purity was established with the use of ^1H NMR spectroscopy (400 MHz) using shift reagents, and where combustion analysis is not given chemical purity was established by chromatography as one spot on TLC and ^1H NMR analysis. Spectral data for compounds **7**, **9**, **11**, and **12** are provided as supplementary material.

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(10) Adam. W.; Oppenlander, T. *Angew Chem., Int. Ed. Engl.* **1986**, *25*, 661. Wiberg, K. B.; Wadell, S. T. *Tetrahedron Lett.* **1987**, *28*, 151 and references cited therein. Wiberg, K. B.; Bader, R. F.; Lau, C. D. H. *J. Am. Chem. Soc.* **1987**, *109*, 1001 and references cited therein. See also ref 6.

(11) Noyori, R.; Tomono, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717. Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *Ibid.* **1984**, *106*, 6709.

(12) Bhagwat, S. S.; Hamann, P. R.; Still, W. C.; Bunting, S.; Fitzpatrick, F. A. *Nature (London)* **1985**, *315*, 511.

evaporation, and the resulting residue was doubly sublimed (70 °C, 0.5 mmHg) to give 2.37 g (88% yield) of racemic **7** as a crystalline solid: mp 60–62 °C; R_f (EtOAc) 0.44; IR ($CHCl_3$) 1740 (CO_2CH_3) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 (2 H, m), 2.05–2.10 (1 H, m), 2.72–2.80 (1 H, m), 3.35 (3 H, s), 3.39 (3 H, s), 3.71 (3 H, s), 4.28 (1 H, d, J = 6.2 Hz), 5.18 (1 H, br s), 5.45 (1 H, br s); ^{13}C NMR ($CDCl_3$) δ 39.3, 39.6, 42.6, 52.1, 53.8, 54.1, 77.7, 78.9, 104.6, 170.7; MS (IC) m/z (M^+ + 1) 229.

The chiral material was obtained as follows: Racemic **7** (1.33 g, 5.82 mmol) was hydrolyzed with 1 N NaOH in 50 mL of methanol/H_2O (9:1) at reflux for 2 h, cooled to 0 °C, and then acidified to pH 3 with 1 M HCl. The mixture was then transferred to a separatory funnel and extracted with 6 × 20 mL of EtOAc. The extracts were combined, dried ($MgSO_4$), and concentrated by rotary evaporation to give 1.12 g of the free acid as a white labile solid (90% yield) that can be kept in the freezer (−20 °C) for a few days: mp 132–142 °C; R_f (5% MeOH/H_2O) 0.23; ^1H NMR ($CDCl_3$) δ 1.48 (2 H, AB q, J_1 = 11.1 Hz, J_2 = 1.8 Hz), 1.99 (1 H, t, J = 5.6 Hz), 2.80 (1 H, m), 3.37 (3 H, s), 3.40 (3 H, s), 4.29 (1 H, d, J = 6.2 Hz), 5.20 (1 H, br s), 5.49 (1 H, br s), 8.43 (1 H, br s); ^{13}C NMR ($CDCl_3$) δ 39.3, 39.6, 42.8, 54.1, 77.6, 79.0, 85.1, 104.5, 174.9.

Without further purification, 4.07 g (19.0 mmol) of the above acid (from combined runs) and 3.14 g of ephedrine-*d* (19 mmol) were refluxed in methanol (100 mL) for 2 h. After rotary evaporation, the residue was crystallized (3 times) from $CHCl_3$/acetone to give 1.96 g (54% yield) of the diastereomeric salt: mp 172–173 °C; $[\alpha]^{23}$ D −7.03° (c = 1.0, $CHCl_3$). Anal. Calcd for $C_{19}H_{29}N_3O_6$: C, 60.14; H, 7.70; N, 11.07. Found: C, 59.98; H, 7.60; N, 10.68.

The above salt (1.59 g, 4.19 mmol) was dissolved in H_2O (5 mL), acidified to pH 3 with 1 M HCl, diluted with 30 mL of brine, and transferred to a separatory funnel. The resolved free acid was then extracted with EtOAc (6 × 20 mL), and the extracts were combined, dried ($MgSO_4$), and concentrated by rotary evaporation. Esterifiction in ether (0 °C) with excess diazomethane followed by rotary evaporation and sublimation (70 °C, 0.5 mmHg) of the residue gave the chiral material [(−)-**7**] analytically pure: $[\alpha]^{23}$ D − 32.2° (c = 1.0, $CHCl_3$).

Methyl (1α,2β,3α)-3-(Dimethoxymethyl)bicyclo[2.1.0]pentane-2-carboxylate [(−)-8a] and Its 1α,2α,3β Isomer [(−)-8b]. An argon-saturated ethereal (100 mL) solution of chiral azo **7** (1.45 g, 6.37 mmol) was irradiated (350 nm) for 3.5 h in a cooled Pyrex tube using a Rayonet apparatus. The ether was then rotary evaporated, and the resulting residue was distilled "bulb-to-bulb" (65 °C, 0.2 mmHg) to afford 1.17 g (92% yield) of a 60:40 mixture of chiral epimers (−)-**8a** and (−)-**8b**. HPLC (10% EtOAc/ether) separation gave analytically pure samples: (−)-**8a**: R_f (15% EtOAc/petroleum ether) 0.28; ^1H NMR ($CDCl_3$) δ 0.73–0.91 (2 H, m), 1.64 (1 H, t, J = 6.1 Hz), 1.78–1.89 (1 H, m), 2.28–2.40 (1 H, m), 2.97 (1 H, t, J = 4.0 Hz), 3.33 (3 H, s), 3.39 (3 H, s), 3.66 (3 H, s), 4.50 (1 H, d, J = 7.3 Hz); $[\alpha]^{23}$ D −119.3° (c = 1.32, $CHCl_3$). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.99; H, 8.01. (−)-**8b**: R_f (15% EtOAc/petroleum ether) 0.23; ^1H NMR ($CDCl_3$) δ 0.76–0.99 (2 H, m), 1.69–1.86 (2 H, m), 2.18 (1 H, m), 2.41 (1 H, d, J = 4.4 Hz), 2.88–3.06 (1 H, m), 3.27 (3 H, s), 3.35 (3 H, s), 3.75 (3 H, s), 4.23 (1 H, d, J = 8.2 Hz); $[\alpha]^{23}$ D −79.2° (c = 0.51, $CHCl_3$). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.99; H, 8.01.

Methyl (1α,2β,3α)-3-Formylbicyclo[2.1.0]pentane-2-carboxylate [(−)-9]. A mixture of (−)-**8a** (398 mg, 1.99 mmol) and PTSA (37.8 mg, 0.2 mmol) was refluxed in THF/H_2O (9:1, 25 mL) for 17 h, cooled to ambient temperature, diluted with 60 mL of EtOAc, and transferred to a separatory funnel. The organic layer was washed with saturated $NaHCO_3$ (3 × 20 mL), dried ($MgSO_4$), and rotary evaporated to give on oily residue that was further purified by slow condensation, under high vacuum, into a U tube sitting in a dry ice/acetone bath to afford 261 mg (85% yield) of the chiral aldehyde as a colorless oil: R_f (10% EtOAc/C_6H_6) 0.3; IR ($CHCl_3$) 2710 (CHO), 1720 (CO_2CH_3) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88–1.00 (2 H, m), 1.92–2.01 (2 H, m), 2.96 (1 H, d, J = 5.0 Hz), 3.33–3.48 (1 H, m), 3.69 (3 H, s), 9.84 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 11.5, 12.5, 14.1, 38.0, 50.9, 51.9, 172.1, 199.3; MS calcd for $C_8H_{10}O_3$ m/z 154.0627, found m/z 154.0634. The 1β,4β-epimeric aldehyde was similarly obtained from (−)-8b.

(15*S*)-Tetrahydropyranyl Ether 10. To a 60% oily suspension of NaH (95.6 mg, 2.39 mmol) in freshly prepared anhydrous DME (65 mL) was added dimethyl (2-oxoheptyl)-phosphonate (0.5 mL, 2.39 mmol). After being stirred for 0.5 h, the mixture was cooled to −23 °C (CO_2/CCl_4), and a solution of racemic **9** (261 mg, 1.70 mmol) in 2 mL of anhydrous DME was added dropwise under an atmosphere of argon. Upon complete addition of the aldehyde, the reaction mixture was let stir for 1 h at −23 °C, warmed to 0 °C for 2 h, quenched with 15% aqueous NH_4Cl (40 mL), and transferred to a separatory funnel. The aqueous phase was extracted with EtOAc (5 × 10 mL), and the combined extracts were dried over $MgSO_4$. Rotary evaporation followed by chromatography[8] of the residue over silica (4% EtOAc/toluene) gave 386 mg (91% yield) of the 15-oxo derivative as a colorless oil: R_f (5% EtOAc/toluene) 0.35; IR ($CHCl_3$) 1730 (CO_2CH_3), 1670 (C=O), and 1615 (C=C) cm^{-1}; ^1H NMr ($CDCl_3$) δ 0.82–0.95 (5 H, m), 1.22–1.38 (4 H, m), 1.55–1.96 (4 H, m), 2.57 (2 H, t, J = 6.7 Hz), 2.68–3.06 (2 H, m), 3.67 (3 H, s), 6.62 (2 H, center AB q, J_1 = 15.9 Hz, J_2 = 8.2 Hz); MS calcd for $C_{15}H_{23}O_2$ m/z 250.1566, found m/z 250.1567. The chiral material has $[\alpha]^{23}$ D −110.8° (c = 2.07, $CHCl_3$).

To an anhydrous THF (5 mL) solution of 1.33 mmol of Noyori's[11] reagent kept at −98 °C under an atmosphere of argon was added 90.3 mg (0.361 mmol) of the above ketone. The reaction mixture was let stir for 2 h at −98 °C and then for 2 h at −78 °C before quenching with 10 mL of a 15% aqueous solution of NH_4Cl. At ambient temperature, the mixture was transferred to a separatory funnel and extracted with 4 × 5 mL of EtOAc. The extracts were combined, dried ($MgSO_4$), and concentrated. The chiral binaphthol byproduct was recrystallized from $CHCl_3$/hexanes and collected (86% recovery) by filtration. The filtrate was then concentrated by rotary evaporation, and the residue was chromatographed on silica (15% ETOAc/toluene) to give 54.1 mg (59% yield) of the 15*S*-epimeric alcohol.[8] Using material from combined runs, a mixture of the above alcohol (134 mg, 0.53 mmol), freshly distilled dihydropyran (0.48 mL, 5.3 mmol), and anhydrous camphorsulfonic acid (12.3 mg, 0.053 mmol) in anhydrous CH_2Cl_2 kept under argon was stirred for 0.5 h and then transferred to a separatory funnel. The organic phase was washed with $NaHCO_3$ (3 × 5 mL), dried ($MgSO_4$), and then concentrated by rotary evaporation to give 185 mg of a residue that was further purified by chromatography on silica (2% EtOAc/toluene) to afford 166 mg (93% yield) of the (15*S*)-tetrahydropyranyl ether **10** as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.68–0.94 (5 H, m), 1.30–1.86 (16 H, m), 2.56 (1 H, br t, J = 5.0 Hz), 2.82 (1 H, br t, J = 3.4 Hz), 3.42–3.55 (1 H, m), 3.65 (3 H, s), 3.73–4.13 (2 H, m), 4.69 (1 H, br s), 5.24–6.03 (2 H, m). Anal. Calcd for $C_{26}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.43; H, 9.62.

9α,11α-Aldehyde 11. To a dry toluene (4 mL) solution of tetrahydropyranyl ether **10** (76.6 mg, 0.288 mmol) kept under argon at −78 °C was added 0.27 mL of a 0.83 M (0.228 mmol) solution of DIBAL-H. The reaction mixture was let stir for 45 min, quenched at ambient temperature with 3 mL of 15% aqueous NH_4Cl, and transferred to a separatory funnel. The organic phase was separated, and the aqueous phase was extracted with 4 × 5 mL of toluene. The organic extracts were then combined, dried ($MgSO_4$), and concentrated by rotary evaporation to give 67.8 mg (97% yield) of the corresponding aldehyde,[8] which was used without further purification in the next step.

To a suspension of (methoxymethyl)triphenylphosphonium chloride (172 mg, 0.502 mmol) in dry toluene (6 mL) kept under argon at 0 °C was added 0.228 mL of a 2 M (0.456 mmol) cyclohexane/ether solution of phenyllithium. After the mixtue was stirred for 20 min, a toluene (1 mL) solution of a freshly prepared batch of the above aldehyde (67.8 mg, 0.221 mmol) was added dropwise. The reaction mixture was stirred for 15 min and then quenched with 10 mL of 15% aqueous NH_4Cl and transferred to a separatory funnel. The organic phase was separated, and the aqueous phase washed with 4 × 4 mL of benzene. The organic extracts were combined, dried ($MgSO_4$), and concentrated by rotary evaporation to give an oily residue that was chromatographed on silica (2% EtOAc/toluene) to give 54.4 mg (71% yield from **10**) of the corresponding mixture of the vinyl methoxy ethers as a colorless oil: R_f (5% EtOAc/toluene) 0.44 and 0.48.[8]

To a suspension of a freshly prepared batch of the above methoxy ethers (54.4 mg, 0.163 mmol) in 5 mL of a 9:1 solution of THF/H_2O were added Et_3N (0.136 mL, 0.98 mmol) and Hg(OAc)$_2$ (156 mg, 0.489 mmol) at ambient temperature with stirring.

After the mixture was stirred for 3 h, 3 mL of a 10% aqueous solution of KI was added, and the mixture transferred to a separatory funnel and extracted with 4 × 3 mL of benzene. The benzene extracts were combined, washed with 3 × 2 mL of 10% aqueous KI, dried ($MgSO_4$), and concentrated by rotary evaporation. Chromatography on silica (4% EtOAc/toluene) gave a 57% yield (from **10**) of the homologated aldehyde as a colorless oil: R_f (5% EtOAc/toluene) 0.27; IR (CH_2Cl_2) 2700 (CHO), 1720 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.71 (2 H, m), 0.89 (3 H, t, J = 5.9 Hz), 1.3–1.61 (17 H), 1.93–2.03 (1 H, m), 2.31–2.55 (2 H, m), 3.44–3.56 (1 H, m), 3.83–4.13 (2 H, m), 4.69 (1 H, br s), 5.13–6.00 (2 H, m), 9.69 (1 H, d, J = 2.0 Hz).

Methyl Ester 12. To a solution of (4-carboxybutyl)triphenylphosphonium bromide (231 mg, 0.520 mmol) in freshly distilled anhydrous DMSO (4 Ml) kept under argon was added dropwise 0.52 mL (1.04 mmol) of a freshly prepared 2 M DMSO solution of dimsyl sodium. The mixture was stirred for 5 min, and a DMSO (0.5 mL) solution of the above aldehyde (41.7 mg, 0.130 mmol) was syringed in dropwise. After the mixture was stirred for 0.5 h at ambient temperature, the reaction was quenched with 1.04 mL (1.04 mmol) of a 1 M solution of acetic acid in anhydrous ether and then transferred with 30 mL of brine to a separatory funnel and extracted with 4 × 10 mL of ether. The ether extracts were combined, dried ($MgSO_4$), and concentrated by rotary evaporation to give 133 mg of a yellowish oily residue that was taken up in 10 mL of ether and treated with excess diazomethane at 0 °C for 15 min. The solvent was then removed by rotary evaporation, and the residue was chromatographed on silica (3% EtOAc/toluene) to give 43.3 mg (74% yield from **11**) of the methyl ester derivative **12** as a colorless oil: R_f (5% EtOAc/toluene) 0.43; ^1H NMR ($CDCl_3$) δ 0.52–0.72 (2 H, m), 0.75–1.01 (3 H, br t), 1.28–2.10 (24 H), 2.31 (2 H, t, J = 7.6 Hz), 3.23–3.70 (1 H, m), 3.67 (3 H, s), 3.75–4.13 (2 H, m), 4.69 (1 H, br s), 5.07–5.93 (4 H, m).

[1*R*[1α,2β,3α,3(*S)]]-7-[3-(3-Hydroxy-1(*E*)-octenyl)bicyclo[2.1.0]pentan-2-yl]hept-5(*Z*)-enoic Acid [(±)-1].** A mixture of **12** (16.2 mg, 0.0385 mmol), and anhydrous camphorsulfonic acid (1.4 mg, 0.007 mmol) was stirred, at ambient temperature, in anhydrous methanol (1 mL) under an atmosphere of argon for 24 h. The reaction mixture was then diluted with 10 mL of EtOAc, transferred to a separatory funnel, and washed with $NaHCO_3$ (3 × 3 mL). The organic phase was dried ($MgSO_4$), and the solvent was removed by rotary evaporation. Chromatography of the residue on silica (7% EtOAc/toluene) gave 9.6 mg of the free alcohol (75% yield) as a colorless oil: R_f (10% EtOAc/toluene) 0.26; ^1H NMR ($CDCl_3$) δ 0.61–0.67 (2 H, m), 0.71–0.89 (3 H, br t), 1.34–2.18 (19 H), 2.32 (2 H, t, J = 7.3 Hz), 3.67 (3 H, s), 4.10 (1 H, m), 5.27–5.98 (4 H, m).

To a 9:1 MeOH/H_2O (0.5 mL) solution of the above alcohol (9.6 mg, 0.0287 mmol) was added 57.4 μL (0.057 mmol) of a 1 M aqueous solution of NaOH. After stirring at ambient temperature for 72 h, the reaction mixture was cooled to 0 °C and acidified with 115 μL (0.115 mmol) of a 1 M solution of acetic acid in toluene. At ambient temperature, 4 mL of toluene was added, and the mixture was then transferred to a separatory funnel. The organic phase was washed with water (3 × 1 mL), dried ($MgSO_4$), and concentrated by rotary evaporation. Last traces of solvent were removed by high vacuum, leaving 8.5 mg (93% yield) of analytically pure material as a colorless oil: R_f (5% MeOH/$CHCl_3$) 0.3; ^1H NMR ($CDCl_3$) δ 0.66 (1 H, m), 0.74 (1 H, d, J = 4.6 Hz), 0.90 (3 H, t, J = 4.4 Hz), 1.31 (7 H, br s), 1.47–1.76 (6 H, m), 1.93 (2 H, m), 2.03 (2 H, m), 2.17 (1 H, m), 2.36 (2 H, br s), 4.10 (1 H, q, J = 6.8 Hz), 4.40–4.80 (2 H, m), 5.35 (2 H, m), 5.65 (2 H, dd, J_1 = 15.3 Hz, J_2 = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 11.6, 13.9, 14.1, 14.6, 22.5, 24.5, 25.0, 26.3, 27.8, 29.6, 31.6, 37.2, 42.7, 44.6, 73.3, 128.3, 128.9, 131.0, 135.8. Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 75.69; H, 10.27.

Similarly, the 9β,11β-epimer (±)-**2** was prepared: R_f (25% EtOAc/toluene) 0.49; ^1H NMR ($CDCl_3$) δ 0.63 (1 H, d, J = 5.1 Hz), 0.70 (1 H, m), 0.89 (3 H, t, J = 6.8 Hz), 1.29 (8 H), 1.41–1.57 (4 H, m), 1.63–1.75 (3 H, m), 2.12–2.23 (2 H, m), 2.25–2.39 (4 H, m), 2.47 (1 H, br s), 4.03 (1 H, q, J = 6.6 Hz), 5.33–5.48 (3 H, m), 5.53–5.58 (1 H, dd, J_1 = 15.5 Hz, J_2 = 5.9 Hz).

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Supplementary Material Available: ^1H NMR (400 MHz), ^{13}C NMR, IR, and mass spectra for **7**, **9**, **11**, and **12** and biological data for **1**, **2**, **8a**, and **8b** (15 pages). Ordering information is given on any current masthead page.