A Synthetic Approach to 15-D_{2c}-Isoprostane Ethyl Ester

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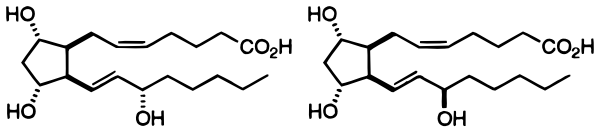
The preparation of ketone **10** is described. Oxidation of **10** to the sulfoxide followed by sigmatropic rearrangement gave not the expected 15-D_{2c}-isoprostane ethyl ester (**4**), but the *trans* diastereomer **11**. A ^{13}C NMR method for establishment of the relative configuration of the cyclopentane rings of the isoprostanes and prostaglandins is also reported.

In 1990, Roberts and co-workers reported that a series of prostaglandin-like compounds are produced in vivo in humans independent of the cyclooxygenase enzymes, by free radical-mediated oxidation of membrane-bound arachidonic acid.[1] These oxidation products have been named the isoprostanes.[2] In addition to F-ring isoprostanes (e.g., **1** and **2**), it was recently reported that E-ring (e.g., **3**) and D-ring isoprostanes (e.g., **4**) are also produced in abundance in vivo.



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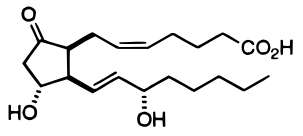

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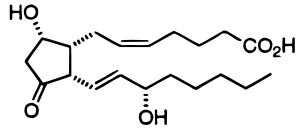

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While the detailed physiological investigation of these compounds has just begun,[3] it has already been shown that the kidney failure and death associated with severe liver disease is a consequence of the production and release of the isoprostanes.[4] It has also been demonstrated that the effects of 15-F_{2t}-isoprostane (**1** and **2**) on the renal vasculature result from specific receptor binding.[3ab,5] To investigate the physiological activity of the isoprostanes, it will be necessary to prepare each of these by chemical synthesis.[6−8]

While syntheses of 15-F_{2t}-isoprostane,[6] 15-F_{2c}-isoprostane,[7] and 15-E_{2t}-isoprostane[8] have been described, no synthesis of a D-ring isoprostane has yet been reported. The synthesis of a 15-D-isoprostane (e.g., **4**) appears to be truly challenging. It is anticipated that dehydration of the C-9 hydroxyl group, epimerization of the C-12 position and movement of the C-13 double bond into conjugation could easily occur under either acidic or alkaline conditions.

Starting from the alcohol **6**,[6c,d] we attempted the synthesis of 15-D_{2c}-isoprostane (**4**), as shown in Scheme 1. Protection of the alcohol with ethyl vinyl ether and a catalytic amount of PPTS gave the ethoxyethyl ether **7**, which on treatment with *n*-Bu_4NF in THF produced the alcohol **8**. Oxidation of the alcohol with Dess−Martin periodinate[9] produced the ketone **9**. Treatment of **9** with aqueous acetic acid cleanly produced the alcohol **10**. A portion of this material was chromatographed for spectroscopic characterization. The remainder of the crude **10** was carried on through sequential oxidation and Mislow rearrangement,[10] producing the allylic alcohol **11** in 70% yield from **9**.

Although the allylic alcohol **11** had been produced in good yield and as a single (^{13}C) diastereomer, the relative configuration at C-12 was not secure. Indeed, ^{13}C NMR studies (Table 1) suggested that epimerization had taken place at C-12, without conjugation or isomerization of the C-13 double bond, and that the product was in fact the ethyl ester (**11**) of 15-*epi*-prostaglandin D_2.

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(2) For a summary of isoprostane nomenclature, see: Taber, D. F.; Morrow, J. D.; Roberts, L. J., II. *Prostaglandins* **1997**, *53*, 63.

(3) Initial reports on isoprostane isolation and studies include: (a) Morrow, J. D.; Minton, T. A.; Roberts, L. J., II. *Prostaglandins* **1992**, *44*, 155. (b) Fukunaga, M.; Makita, N.; Roberts, L. J., II; Morrow, J. D.; Takahashi, K.; Badr, K. F. *Am. J. Physiol. (Cell Physiol. 33)* **1993**, *264*, C1619. (c) Morrow, J. D.; Badr, K. F.; Roberts, L. J., II. *Biochim. Biophys. Acta* **1994**, *1210*, 244. Also see: Parsons, W. G. I.; Roberts, L. J., II. In *Advances in Prostaglandin, Thromboxane, and Leukotriene Research*; Samuelsson, B., Wong, P. Y. K., Sun, F. F., Eds.; Raven Press: New York, 1988; Vol. 19, p 499.

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(5) (a) Takahashi, K.; Nammour, T. M.; Fukunaga, M.; Ebert, J.; Morrow, J. D.; Roberts, L. J., II; Hoover, R. L.; Badr, K. F. *J. Clin. Invest.* **1992**, *90*, 136. (b) Longmire, A. W.; Roberts, L. J., II; Morrow, J. D. *Prostaglandins* **1994**, *48*, 247. (c) Fukunaga, M.; Takahashi, K.; Badr, K. F. *Biochem. Biophys. Res. Commun.* **1993**, *195*, 507.

(6) For synthetic routes to 15-F_{2t}-isoprostane: (a) Corey, E. J.; Shih, C.; Shih, N.-Y.; Shimoji, K. *Tetrahedron Lett.* **1984**, *25*, 5013. (b) Hwang, S. W.; Adiyaman, M.; Khanapure, S.; Schio, L.; Rokach, J. *J. Am. Chem. Soc.* **1994**, *116*, 10829. (c) Taber, D. F.; Herr, R. J.; Gleave, D. M. *J. Org. Chem.* **1997**, *62*, 194.

(7) For synthetic routes to 15-F_{2c}-isoprostane: (a) Larock, R. C.; Lee, N. H. *J. Am. Chem. Soc.* **1991**, *113*, 7815. (b) Vionnet, J.-P.; Renaud, P. *Helv. Chim. Acta* **1994**, *77*, 1781. (c) Hwang, S. W.; Adiyaman, M.; Khanapure, S. P.; Rokach, J. *Tetrahedron Lett.* **1996**, *37*, 779.

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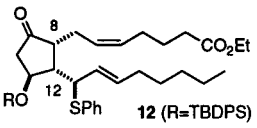
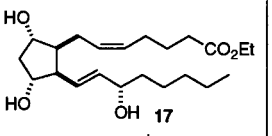
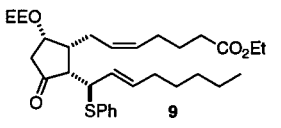
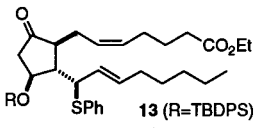
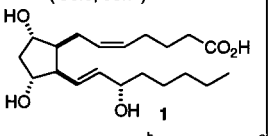
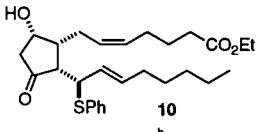
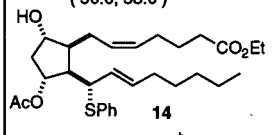
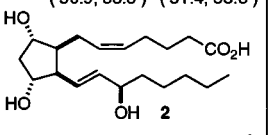
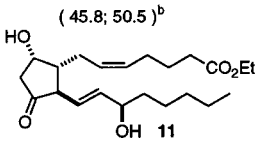
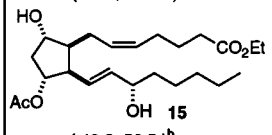
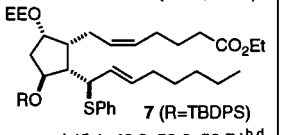
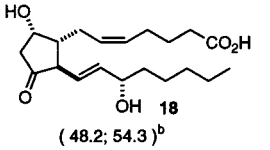
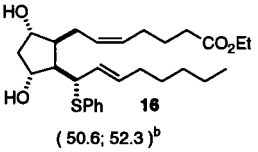
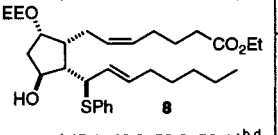
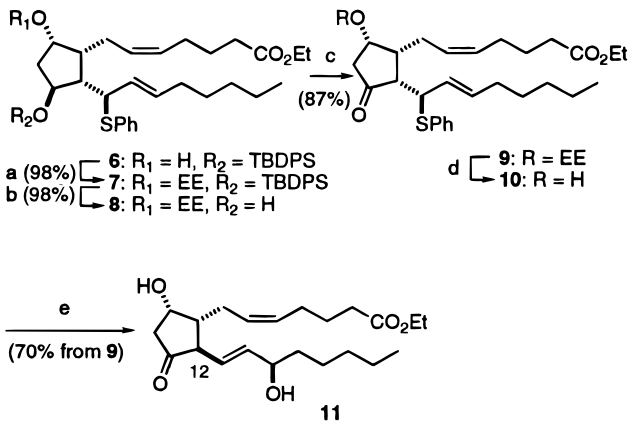
Table 1. ^{13}C Chemical Shifts of C-8 and C-12 Methines

Entry[a]	Chemical Shifts (ppm)	Entry[a]	Chemical Shifts (ppm)	Entry[a]	Chemical Shifts (ppm)
1[6c,6d]	 **12** (R=TBDPS) (50.3; 51.4)[b]	6[6c]	 **17** (50.8; 53.7)[b]	11	 **9** (45.0, 45.7; 49.6, 49.9)[b,d]
2[6c,6d]	 **13** (R=TBDPS) (50.0; 53.0)[b]	7[6b,6d]	 **1** (50.9; 53.5)[b] (51.4; 53.8)[c]	12	 **10** (45.8; 50.5)[b]
3[6d]	 **14** (48.7; 50.12)[b]	8[6d]	 **2** (51.4; 53.5)[c]	13	 **11** (48.4, 54.0)[b]
4[6d]	 **15** (49.8; 50.5)[b]	9	 **7** (R=TBDPS) (45.1, 46.3; 53.6, 53.7)[b,d]	14	 **18** (48.2; 54.3)[b]
5[6d]	 **16** (50.6; 52.3)[b]	10	 **8** (45.1, 46.3; 53.3, 53.4)[b,d]		

[a] References. [b] In $CDCl_3$. [c] In CD_3OD. [d] Unseparable mixture of two diastereomers.

Scheme 1[a]



[a] Reagents and conditions: (a) ethyl vinyl ether, PPTS, CH_2Cl_2, 0 °C to rt; (b) *n*-Bu_4NF, THF, 0 °C to rt; (c) Dess−Martin periodinate, rt; (d) AcOH−H_2O (2:1), rt; (e) *m*-CPBA, CH_2Cl_2, −78 °C; $(MeO)_3P$, EtOH, −78 °C to rt.

Table 1 focuses on the C-8 and C-12 methines of a series of isoprostane and prostaglandin derivatives. While an exact matching pair is only available for entries 1 and 2, this sets the stage for the discussion: the ^{13}C chemical shift of the C-12 methine of compound **13**, having trans side chains, is shifted downfield compared to its cis diastereomer **12**. The ^{13}C chemical shifts of the C-8 and C-12 methines of compound **11** (entry 13), from the Mislow rearrangement, in comparison to its precursors (entries 9−12), suggested that the side chain had in fact epimerized to trans. The chemical shift changes observed for both the C-8 and the C-12 methines of the allylic alcohol **11** were much larger than one would expect just from the Mislow rearrangement (entries 3 vs 4 and 5 vs 6).

If epimerization had occurred, the product would then have the structure (**11**) shown, the 15-epi diastereomer of PGD_2 **18**. We therefore recorded the ^{13}C spectrum of **18**, which had not previously been reported. While the C-8 and the C-12 methine chemical shifts for **11** and **18** were remarkably congruent, this might have been fortuitous, since one was the ethyl ester and the other was the free acid and they differed in relative configuration at C-15. We therefore compared the ester **17** and the acid **1** (entries 6 and 7) and the epimeric allylic alcohols **1** and **2** (entries 7 and 8). It is clear that these changes have very little impact on the C-8 and the C-12 methine chemical shifts. Our conclusion was that **11** was the correct structure and that epimerization had taken place at C-12. This conclusion was supported by the close spectroscopic (^{1}H and ^{13}C NMR) correlation between **11** and prostaglandin D_2 (**18**). The ^{13}C NMR correlations reported here should significantly facilitate work on the D- and E-isoprostanes.

We had shown that 15-E_{2t}-isoprostane methyl ester does not epimerize under the conditions of the Mislow rearrangement.[8] We also observed (TLC) that ketone **10** does not epimerize before it is oxidized to the sulfoxide. We hypothesize that epimerization is occurring after Mislow rearrangement, when the very labile β,γ-unsaturated ketone is exposed to residual 3-chlorobenzoic acid. The facile epimerization of 15-D_{2c}-isoprostane ethyl ester observed in this work raises the likelihood that endogenous 15-D_{2c}-isoprostane may be epimerized in vivo to the physiologically very active D-series prostaglandins.

Experimental Procedures[11]

Ethyl (5*Z*,8*R,9*S**,11*S**,12*S**,13*R**,14*E*)-11-[(*tert*-Butyldiphenylsilyl)oxy]-9-(ethoxyethoxy)-13-(phenylthio)prosta-5,14-dienoate (7).** To a stirred solution of the alcohol **6** (27 mg, 0.038 mmol) in CH_2Cl_2 (2 mL) at 0 °C were added ethyl vinyl ether (36 μL, 0.38 mmol) and PPTS (1.9 mg, 0.008 mmol). After an additional 30 min at rt, the reaction was partitioned between CH_2Cl_2 and, sequentially, saturated aqueous $NaHCO_3$ and brine. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to afford the ethoxyethyl ether **7** (29.5 mg, 98%) as a colorless oil: TLC R_f [petroleum ether/methyl *tert*-butyl ether (MTBE) = 9/1] = 0.44; ^{1}H NMR δ 7.70−7.73 (m, 2H), 7.65−7.68 (m, 2H), 7.34−7.44 (m, 6H), 7.12−7.24 (m, 5H), 5.21−5.31 (m, 3H), 4.81 (dt, J = 7.7, 15.1 Hz), 4.64 (ddd, J = 3.3, 6.8, 11.5 Hz), 4.50 and 4.51 (each q, each 0.5 H, J = 5.3 Hz), 4.04−4.18 (m, 1H), 4.10 and 4.11 (each q, each 1H, J = 7.2 Hz), 3.68 (dt, 1H, J = 9.6, 12.4 Hz), 3.25−3.53 (m, 2H), 2.44−2.49 (m, 1H), 2.13−2.30 (m, 5H), 2.04 (quint, 2H, J = 7.6 Hz), 1.62−1.94 (m, 6H), 1.23 and 1.24 (each t, each 1.5 H, J = 7.2 Hz), 1.14 and 1.16 (each d, each 1.5H, J = 5.3 Hz), 1.10 and 1.12 (each t, each 1.5 Hz, J = 7.2 Hz), 1.08−1.20 (m, 6H), 1.06 (s, 9H), 0.83 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ up 173.7, 173.6, 135.6, 135.4, 134.7, 134.6, 134.0, 60.2, 59.8, 41.5, 40.5, 33.88, 33.85, 32.1, 31.3, 28.9, 26.90, 26.86, 24.85, 24.83, 23.88, 19.17, 19.15; down 136.0, 135.8, 133.6, 133.4, 131.44, 131.40, 130.81, 130.29, 130.20, 129.54, 129.51, 129.45, 129.42, 128.6, 128.4, 128.32, 128.30, 127.53, 127.47, 127.46, 126.77, 126.72, 99.9, 97.4, 76.5, 76.3, 75.0, 53.8, 53.7, 53.6, 46.5, 46.3, 27.0, 20.6, 20.0, 153, 14.2, 14.0; IR (film) 2930, 1737, 1112, 702 cm^{-1}; FAB MS *m*/*z* (rel intensity) 807 (M^+ + Na, 49), 586 (45), 347 (39), 329 (85), 219 (84), 199 (50), 197 (41), 137 (44), 135 (100); FAB HRMS calcd for $C_{48}H_{68}O_5NaSiS$ 807.4454, found 807.4405.

Ethyl (5*Z*,8*R,9*S**,11*S**,12*S**,13*R**,14*E*)-9-(Ethoxyethoxy)-11-hydroxy-13-(phenylthio)prosta-5,14-dienoate (8).** To a stirred solution of the silyl ether **7** (17 mg, 0.022 mmol) in THF (1.5 mL) at 0 °C was added a 1 M THF solution of *n*-Bu_4NF (130 μL, 0.132 mmol). After an additional 24 h, the reaction mixture was partitioned between EtOAc and, sequentially, saturated aqueous NH_4Cl and brine. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to afford the alcohol **8** (11.5 mg, 98%) as a colorless oil: TLC R_f (petroleum ether/MTBE = 7/3) = 0.26; ^{1}H NMR δ 7.40−7.43 (m, 2H), 7.27−7.38 (m, 3H), 5.20−5.47 (m, 3H), 5.10 (dt, 1H, J = 6.7, 15.4 Hz), 4.65 and 4.69 (each q, each 0.5 H, J = 5.3 Hz), 4.32−4.43 (m, 2H), 4.11 (q, 2H, J = 7.2 Hz), 3.40−3.66 (m, 3H), 2.93 (br s, 1H), 2.27 (t, 2H, J = 7.6 Hz), 1.92−2.31 (m, 9H), 1.88 (q, 2H, J = 6.8 Hz), 1.65 (quint, 2H, J = 7.6 Hz), 1.25 and 1.27 (each d, each 1.5 H, J = 5.3 Hz), 1.25 (t, 3H, J = 7.2 Hz), 1.18 and 1.19 (each t, each 1.5 H, J = 7.2 Hz), 1.10−1.27 (m, 6H), 0.849 and 0.852 (each t, each 1.5 Hz, J = 7.2 Hz); ^{13}C NMR δ up 173.63, 173.59, 133.3, 138.2, 60.9, 60.21, 60.20, 59.4, 38.9, 38.6, 33.8, 32.1, 31.2, 28.9, 26.70, 26.68, 24.76, 24.74, 22.46, 22.36, 22.1; down 134.4, 134.4, 132.47, 132.40, 130.99, 130.82, 129.43, 129.30, 128.7, 128.1, 127.91, 127.90, 127.85, 98.75, 98.73, 75.4, 74.5, 74.2, 74.0, 54.9, 54.8, 53.4, 53.3, 46.3, 45.1, 20.7, 19.9, 15.36, 15.31, 14.24, 14.00; IR (film) 3457, 2928, 1737, 1094, 961, 692 cm^{-1}; FAB MS *m*/*z* (rel intensity) 547 (M^+ + 1, 2), 391 (23), 3365 (28), 348 (26), 347 (100), 329 (87), 303 (20), 301 (22), 293 (22), 257 (21), 221 (37), 219 (95); FAB HRMS calcd for $C_{32}H_{51}O_5Si$ 547.3457, found 547.3425.

Ethyl (5*Z*,8*R,9*S**,12*S**,13*R**,14*E*)-9-(Ethoxyethoxy)-11-oxo-13-(phenylthio)prosta-5,14-dienoate (9).** To a stirred solution of the alcohol **8** (12 mg, 0.022 mmol) in CH_2Cl_2 (1 mL) at rt was added Dess−Martin periodinate (18.6 mg, 0.044 mmol). After an additional 1 h, the reaction mixture was cooled to an ice bath. The resulting precipitate was filtered and washed with Et_2O. Evaporation of the filtrate gave a residue that was chromatographed to afford the ketone **9** (10.4 mg, 87%) as a colorless oil: TLC R_f (petroleum ether/MTBE = 7:3) = 0.45; ^{1}H NMR δ 7.20−7.46 (m, 5H), 5.10−5.33 (m, 3H), 4.74 and 4.75 (each q, each 0.5 H, J = 5.3 Hz), 4.35 and 4.45 (each dt, each 0.5 H, J = 5.5, 6.6 Hz), 4.12 (q, 2H, J = 7.2 Hz), 4.04 (dt, 1H, J = 7.8, 9.2 Hz), 3.43−3.68 (m, 2H), 2.15−2.64 (m, 8H), 2.29 (t, 2H, J = 7.6 Hz), 2.03−2.15 (m, 2H), 1.61−1.84 (m, 4H), 1.30 and 1.32 (each d, each 1.5 H, J = 5.3 Hz), 1.24 (t, 3H, J = 7.2 Hz), 1.19 and 1.20 (each t, each 1.5 H, J = 7.0 Hz), 1.06−1.25 (m, 6H), 0.84 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ up 213.7, 213.5, 174.03, 173.98, 134.9, 134.8, 60.9, 60.7, 59.9, 44.5, 43.7, 34.25, 34.23, 32.5, 31.6, 29.2, 27.25, 27.22, 25.16, 25.13, 23.4, 23.2, 22.9; down 134.4, 133.7, 133.5, 130.0, 129.8, 129.61, 129.59, 128.9, 128.7, 128.5, 127.82, 127.81, 99.8, 98.6, 73.4, 71.5, 56.6, 56.3, 49.9, 49.6, 45.7, 45.0, 20.7, 20.3, 15.7, 14.7, 14.4; IR (film) 2928, 1738, 1148, 1097, 957 cm^{-1}; FAB MS *m*/*z* (rel intensity) 567 (M^+ + Na, 1), 389 (24), 363 (30), 346 (26), 345 (100), 317 (21), 299 (26); FAB HRMS calcd for $C_{32}H_{48}O_4NaS$ 567.3120, found 567.3076.

15-*epi*-Prostaglandin D_2 Ethyl Ester (11). A solution of the ethoxyethyl ether **9** (10 mg, 0.018 mmol) in AcOH−H_2O (1.5 mL, 2:1) was stirred at rt for 1.5 h. The reaction mixture was partitioned between EtOAc and, sequentially, saturated aqueous $NaHCO_3$ and brine. The organic extract was dried (Na_2SO_4) and concentrated. A small amount of the crude product was chromatographed to afford the alcohol **10**; TLC R_f (petroleum ether/MTBE = 1/1) = 0.47; ^{1}H NMR δ 7.21−7.42 (m, 5H), 5.75 (dd, 1 H, J = 9.6, 15.2 Hz), 5.39−5.50 (m, 2H), 5.17 (dt, 1H, J = 6.9, 15.2 Hz), 4.20−4.44 (m, 1H), 4.13 (q, 2H, J = 7.2 Hz), 3.73 (dd, 1H, J = 4.2, 9.6 Hz), 3.14 (d, 1H, J = 9.3 Hz), 2.75 (dd, 1H, J = 4.2, 9.6 Hz), 2.30−2.65 (m, 6H), 2.27 (t, 2H, J = 7.4 Hz), 1.91−2.13 (m, 4H), 1.67 (quint, 2H, J = 7.4 Hz), 1.26 (t, 3H, J = 7.2 Hz), 1.11−1.29 (m, 6H), 0.86 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ up 216.1, 173.7, 133.9, 60.3, 48.4, 33.7, 31.9, 31.2, 28.9, 26.8, 24.7, 23.7, 22.5; down 133.4, 132.4, 130.6, 129.7, 128.9, 128.2, 128.0, 70.0, 54.2, 50.5, 45.8, 14.2, 14.0; IR (film) 3456, 2927, 1736, 1156, 1026, 748, 692 cm^{-1}; FAB MS *m*/*z* (rel intensity) 495 (M^+ + Na, 1), 364 (27), 363 (100), 345 (36), 317 (39), 299 (30), 219 (26); FAB HRMS calcd for $C_{28}H_{40}O_4NaS$ 495.2545, found 495.2541. The bulk of the crude thioether was carried on without further purification. Thus, to a stirred solution of the crude thioether **10** in CH_2Cl_2 (0.7 mL) at −78 °C was added a solution of *m*-CPBA (4.8 mg, 0.028 mmol) in CH_2Cl_2 (0.3 mL). The mixture was stirred for 1 h, after which time a solution of trimethyl phosphite (22 μL, 0.18 mmol) in EtOH (0.5 mL) was added. The mixture was stirred at −78 °C for 5 min and then warmed to rt. The reaction mixture was partitioned between EtOAc and, sequentially, saturated aqueous $NaHCO_3$ and brine. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to afford 15-*epi*-prostaglandin D_2 ethyl ester **11** (5 mg, 70% from **9**) as a colorless oil: TLC R_f (petroleum ether/MTBE = 1/3) = 0.44; ^{1}H NMR δ 5.66 (dd, 1H, J = 6.7, 15.8 Hz, 5.44−5.52 (m, 3H), 4.48 (br s, 1H), 4.13 (q, 2H, J = 7.2 Hz), 4.10−4.16 (m, 1H), 2.85 (dd, 1H, J = 8.0, 12.2 Hz), 1.94−2.44 (m, 8H), 1.51−1.85 (m, 5H), 1.22−1.48 (m, 6H), 1.26 (t, 3H, J = 7.2 Hz), 0.89 (t, 3H, J = 6.9 Hz); ^{13}C NMR δ up 216.3, 174.1, 60.6, 47.7, 37.2, 33.5, 31.7, 26.6, 25.6, 25.1, 24.7, 22.6; down 138.5, 130.8, 127.7, 125.5, 72.5, 67.9, 54.0, 48.4, 14.2, 14.0; IR (film) 3442, 2926, 1736, 1459, 1376, 1159, 1029, 969; 728 cm^{-1}; FAB MS *m*/*z* (rel intensity) 403 (M^+ + Na, 1), 364 (23), 363 (100), 362 (11), 161 (18), 345 (28), 317 (15); FAB HRMS calcd for $C_{22}H_{36}O_5Na$ 403.2460, found 403.2480.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all new compounds (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(11) For a summary of general experimental procedures, see: Taber, D. F.; Meagley, R. P.; Doren, D. J. *J. Org. Chem.* **1996**, *61*, 5723.