Enantioselective Synthesis of 12-*epi*-$PGF_{2\alpha}$ and 12,15-*diepi*-$PGF_{2\alpha}$

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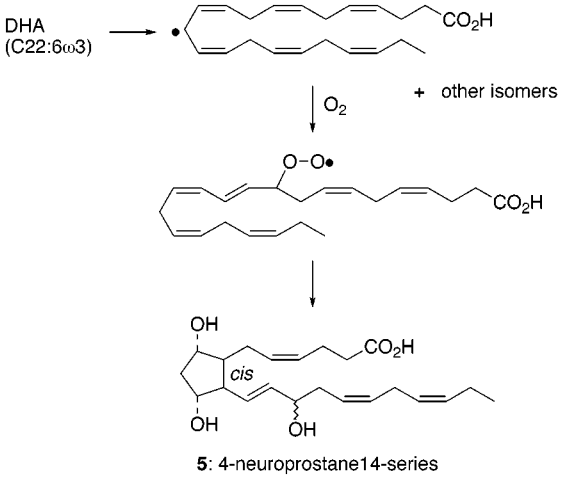
An enantioselective synthesis of 12-*epi*-$PGF_{2\alpha}$ (**3**) and 12,15-*diepi*-$PGF_{2\alpha}$ (**4**), PG-like compounds that are probably generated in vivo by nonenzymatic, free-radical-induced peroxidation of arachidonic acid, has been achieved starting from the commercially available Corey lactone (**9**). The key strategy involves SmI_2 reduction of the ç,ä-epoxy-α,â-unsaturated ester **7**, followed by in situ trapping with hexanal; subsequent hydrogenation and decarboxylation affords the stereoselective construction of the lower side chain. This new method is expected to provide a convenient access to various PG-like isoprostanes derived from oxidation of arachidonic acid and *cis*-4,7,10,13,16,19-docosahexaenoic acid.

Introduction

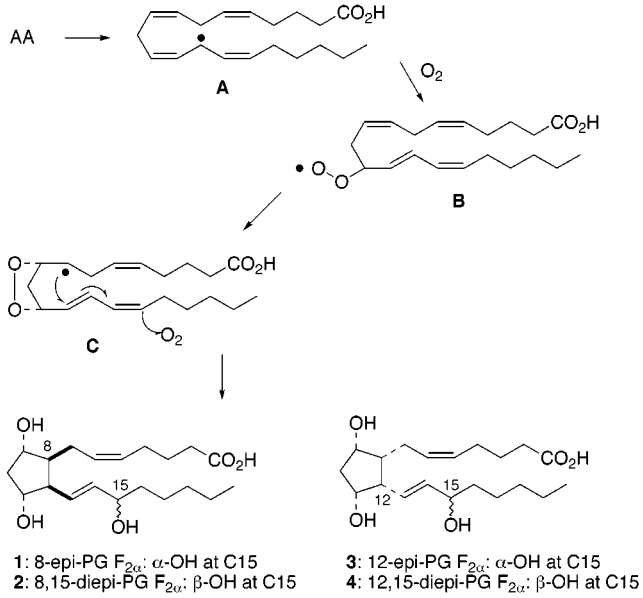
Prostaglandins (PGs) exhibit a wide range of potent pharmacological properties that have spurred the development of many elegant synthetic methods.[1] Roberts, Morrow, and colleagues recently discovered a new class of epimeric PGs, named isoprostanes, that are characterized by *cis*-dialkyl stereochemistry at the five-membered ring junction.[2] These PG-like compounds are produced in vivo by nonenzymatic, free-radical induced peroxidation of arachidonic acid (AA) (Scheme 1), independent of cyclooxygenase activity that produces the more familiar "primary" *trans*-dialkyl PGs. One of the compounds whose formation was anticipated by the proposed 5-exo radical cyclization, 8-*epi*-$PGF_{2\alpha}$ (**1**), was isolated and subsequently found to exert potent biological activity as a renal vasoconstrictor. More recently, the same group reported the formation of isoprostane-like compounds (i.e., **5**) from *cis*-4,7,10,13,16,19-docosahexaenoic acid (DHA), which is highly enriched in the brain, by a similar free-radical mechanism.[2d] These findings suggest that



5: 4-neuroprostane14-series

isoprostanes may provide a useful marker of oxidative injury such as kidney failure and Alzheimer's disease. Preparation of these structurally unique isoprostanes is

Scheme 1



1: 8-epi-PG $F_{2\alpha}$: α-OH at C15
2: 8,15-diepi-PG $F_{2\alpha}$: β-OH at C15
3: 12-epi-PG $F_{2\alpha}$: α-OH at C15
4: 12,15-diepi-PG $F_{2\alpha}$: β-OH at C15

warranted and timely for their identification and investigation of biological activities. Herein we report an enantioselective synthesis of 12-*epi*-$PGF_{2\alpha}$ (**3**) and 12,15-*diepi*-$PGF_{2\alpha}$ (**4**), which would also provide a general method for preparation of other possible stereoisomers and related compounds.

Results and Discussion

In the cyclization of radical **C**, preponderance of *cis*-dialkyl stereochemistry in the newly formed cyclopentane ring is consistent with the Beckwith−Houk model of hex-5-enyl cyclizations and typical for C1-substituted radicals

(1) For a recent review, see: Collins, P. W.; Djuric, S. W. *Chem. Rev.* **1993**, *93*, 1533.

(2) (a) Morrow, J. D.; Hill, K. E.; Burk, R. F.; Nammour, T. M.; Badr, K. F.; Roberts, L. J., II. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 9383. (b) Morrow, J. D.; Awad, J. A.; Boss, H. J.; Blair, I. A.; Roberts, L. J., II. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 10721. (c) Morrow, J. D.; Harris, T. M.; Roberts, L. J., II. *Anal. Biochem.* **1990**, *184*, 1. (d) Roberts, L. J., II; Montine, T. J.; Markesbery, W. R.; Tapper, A. R.; Hardy, P.; Chemtob, S.; Dettbarn, W. D.; Morrow, J. D. *J. Biol. Chem.* **1998**, *273*, 13605 and references therein. See also: (e) Praticò, D.; Barry, O. P.; Lawson, J. A.; Adiyaman, M.; Hwang, S.-W.; Khanapure, S. P.; Iuliano, L.; Rokach, J.; FitzGerald, G. A. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 3449.

10.1021/jo990906r CCC: $18.00
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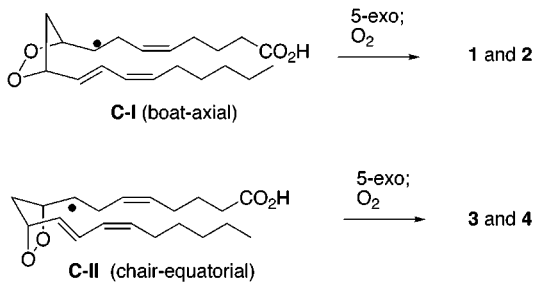
Scheme 2

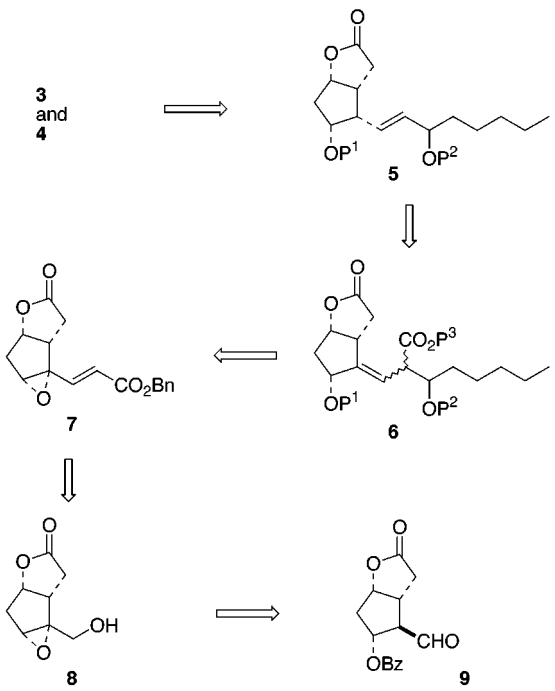


(Scheme 2).[3] A priori, it is difficult to predict the exo/endo selectivity between the two cis isomers: "boat-axial" transition structure **C-I** provides isoprostanes **1** and **2**, whereas all syn isomers **3** and **4** are expected from "chair-equatorial" transition structure **C-II**. Closely related model studies suggest that these two pathways are indeed competitive in the absence of overriding steric effects.[4,5] So far, **1** is the only isoprostane isolated from plasma and fully characterized. Independent syntheses of **3** and **4** will be useful for ascertaining their presence in biological fluids. Toward this end, 12-*epi*-$PGF_{2\alpha}$ (**3**) and 12,15-*diepi*-$PGF_{2\alpha}$ (**4**) were chosen as the target compounds to develop general synthetic methods for isoprostanes.[6,7]

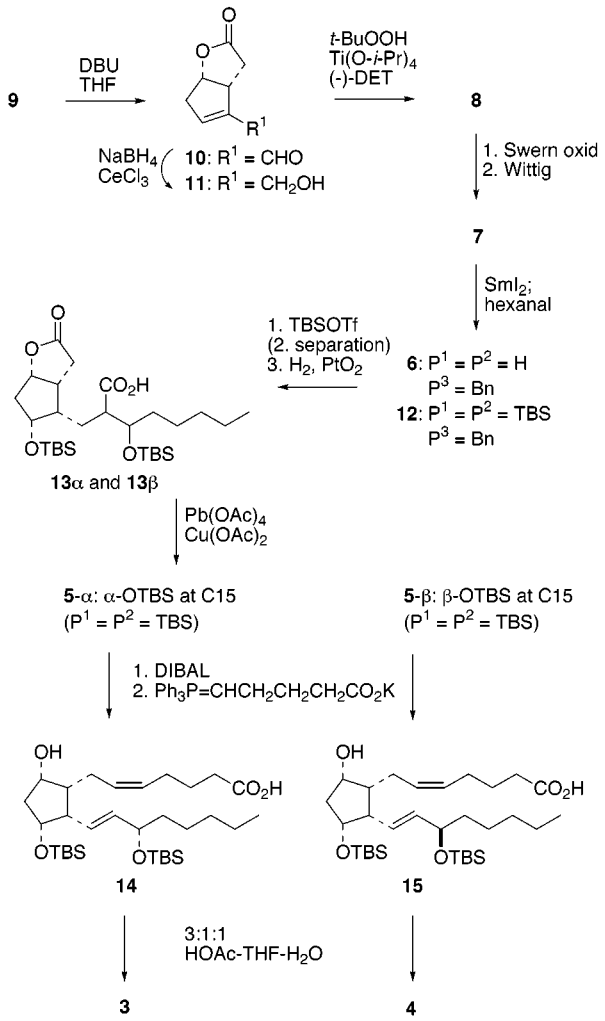
We chose the Corey lactone (**9**) as starting material in light of its commercial availability in enantiomerically pure form,[8] as well as several, well-optimized synthetic procedures for either antipode. Moreover, **9** is well-suited for the installation of various types of two cis side chains that could be formed in vivo from free-radical oxidation of AA and DHA. As outlined in the retrosynthetic analysis, our key strategy centers around SmI_2 reduction of ç,ä-epoxy-α,â-unsaturated ester **7** and in situ treatment with an appropriate aldehyde for the construction of the lower side chain (Scheme 3). The requisite cis stereochemistry can be conveniently established by stereoselective hydrogenation of **6** from the less-hindered convex face of the bicyclic lactone. Finally, the upper side chain should be readily prepared by standard Wittig olefination.

Treatment of **9** with DBU afforded the α,â-unsaturated aldehyde **10** in nearly quantitative yield (Scheme 4). The allylic alcohol **11** was then prepared by Luche reduction in 90−100% yield.[9] Subsequent epoxidation with *t*-BuOOH in the presence of $VO(acac)_2$, surprisingly, gave

Scheme 3



Scheme 4



a ≥10:1 mixture of the requisite α-epoxide **8** and the corresponding â-isomer. The stereoselective preparation of **8** was also achieved (75%) by means of the Sharpless

(3) For excellent reviews, see: (a) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions. Concepts, Guidelines, and Synthetic Applications*; VCH: New York, 1996. (b) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073.

(4) (a) Porter, N. A.; Funk, M. O. *J. Org. Chem.* **1975**, *40*, 3614. (b) O'Connor, D. E.; Mihelich, E. D.; Coleman, M. C. *J. Am. Chem. Soc.* **1981**, *103*, 223; **1984**, *106*, 3577. (c) Corey, E. J.; Shih, C.; Shih, N.-Y.; Shimoji, K. *Tetrahedron Lett.* **1984**, *25*, 5013. (d) Weinges, K.; Sipos, W. *Chem. Ber.* **1988**, *121*, 363. See also: (e) RajanBabu, T. V.; Fukunaga, T.; Reddy, G. S. *J. Am. Chem. Soc.* **1989**, *111*, 1759.

(5) See also: (a) Hwang, S.-W.; Adiyaman, M.; Khanapure, S.; Schio, L.; Rokach, J. *J. Am. Chem. Soc.* **1994**, *116*, 10829. (b) Hwang, S.-W.; Adiyaman, M.; Khanapure, S. P.; Rokach, J. *Tetrahedron Lett.* **1996**, *37*, 779.

(6) Total syntheses of **3** have been reported: (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) Reference 5b. (d) Roland, A.; Durand, T.; Rondot, B.; Vidal, J.-P.; Rossi, J.-C. *Bull. Soc. Chim. Fr.* **1996**, *133*, 1149. (e) A synthesis of (±)-**4** was also reported: ref 6b.

(7) Total syntheses of **1** have been reported: (a) Reference 5a. (b) Taber, D. F.; Herr, R. J.; Gleave, D. M. *J. Org. Chem.* **1997**, *62*, 194.

(8) Available in large quantities from Cayman Chemical, Ann Arbor, MI 48108.

(9) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

asymmetric epoxidation using diethyl D-tartrate.[10] Similiarly, use of diethyl L-tartrate afforded exclusively the â-epoxide in 80% yield. Swern oxidation of **8** and subsequent Wittig olefination ($Ph_3P{=}CHCO_2Bn$) afforded the ç,ä-epoxy-α,â-unsaturated ester **7** in 88% yield.

Now the stage was set for the introduction of the lower side-chain by reductive epoxide opening,[11] followed by in situ trapping of the resulting dienolate with hexanal.[12] Treatment of **7** with SmI_2 in THF at −78 °C and subsequent addition of excess hexanal afforded the condensation product **6** ($P^1 = P^2 = H$; $P^3 = Bn$) in 95% yield: upon protection of both hydroxyl groups, several isomers were generated, but ∼90% of the products consisted of two easily separable (by column chromatography) fractions of a nearly equal amount, each of which appeared to be a single diastereomer but epimeric at C-15.[13] In passing, we note that the stereoselective introduction of the C-15 (PG numbering) alcohol function would be achieved by use of a suitable chiral auxiliary in place of the benzyl ester. In the present study, however, stereorandom preparation of both epimers was pursued to secure both **3** and **4**. Subsequent hydrogenation (PtO_2, 60 psi) produced the free carboxylic acids **13**α and **13**â; *cis*-dialkyl stereochemistry at the cyclopentane ring was assigned on the basis of the expected hydrogenation from the less hindered, convex face. Oxidative decarboxyaltion by the procedure of Kochi then afforded *E*-olefins **5**-α and **5**-â, free from the *Z*-olefins, in overall (from **6**) 40% and 64% yields, respectively.[14] The stereochemistry at C-15, as well as that at C-12, was determined by ultimate conversion to **3** and **4** (vide infra).

With pure **5**-α and **5**-â in hand, the remaining task involved the construction of the other side chain, which was readily accomplished by standard PG chemistry. Each compound was subjected separately to DIBAL-H reduction, followed by olefination with (4-carboxybutyl)-triphenylphosphonium bromide and potassium *tert*-butoxide to furnish **14** and **15**, protected forms of **3** and **4**, respectively, in 81−89% yield. Finally, desilylation with 3:1:1 HOAc−THF−H_2O at room temperature yielded 12-*epi*-$PGF_{2\alpha}$ (**3**) and 12,15-*diepi*-$PGF_{2\alpha}$ (**4**) in 85% yield. The ^1H and ^{13}C NMR spectra of **3** and **4** were in excellent agreement with literature values.[6]

Conclusion

In summary, we have developed a convenient route to isoprostanes containing *cis*-dialkyl stereochemistry at the cyclopentane ring. The cornerstone of our approach involves SmI_2-induced reductive ring opening of a ç,ä-epoxy-α,â-unsaturated ester and in situ trapping of the resulting dienolate with an aldehyde, where the requisite *cis*-dialkyl stereochemistry is established by stereocontrolled hydrogenation from the less hindered, convex face of the bicyclic lactone. This new method would also offer a convenient access to other possible stereo- and structural isomers derived from oxidation of AA and DHA.

Experimental Section

(1*S*,5*R*)-6-Hydroxymethyl-2-oxabicyclo[3.3.0]oct-6-en-3-one (11). A solution of commercially available Corey lactone **9** (1.154 g, 4.0 mmol) in CH_2Cl_2 (10 mL) was treated at −78 °C with DBU (0.65 mL, 4.26 mmol). The reaction mixture was stirred at −78 °C for 1 h and concentrated in vacuo. Direct purification of the residue by flash silica gel column chromatography (using as eluant 1:2 and 1:3 hexanes−EtOAc) afforded **10** (608 mg, 100%) as pale yellow solids.

The α,â-unsaturated aldehyde was dissolved in 9 mL of 1:2 CH_2Cl_2−MeOH, and cerium(III) chloride heptahydrate (918 mg, 2.4 mmol) was then added. After the solution was cooled to −78 °C, sodium borohydride (93 mg, 2.4 mmol) was added. The resulting mixture was stirred at −78 °C for 90 min and acidified to pH 3 with an aqueous 1 N HCl solution. Most of the organic solvents were removed by evaporation. The residue was then dissolved in H_2O and extracted with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Purification by column chromatography (SiO_2, using EtOAc as eluant) provided alcohol **11** (592 mg, 96%) as white solids: mp 49−50 °C; $[\alpha]_D$ +12° (*c* 1.02, $CHCl_3$); IR (film) 3418, 1770, 1651, 1178 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) ä 5.65 (br s, 1 H), 5.15 (t, J = 6.0 Hz, 1 H), 4.22 (br d, J = 13.7 Hz, 1 H), 4.14 (br d, J = 13.7 Hz, 1 H), 3.52 (m, 1 H), 2.75 (ddd, J = 18.4, 6.0, 2.0 Hz, 1 H), 2.72 (dd, J = 18.2, 9.5 Hz, 1 H), 2.64 (br d, J = 18.4 Hz, 1 H), 2.59 (dd, J = 18.2, 2.2 Hz, 1 H), 2.22 (br s, −OH, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) ä 176.9, 142.3, 125.0, 83.7, 59.7, 45.4, 38.7, 31.6; HRMS (M^+) calcd for $C_8H_{10}O_3$ 154.0630, found 154.0632.

(1*S*,5*S*,6*R*,7*R*)-6,7-Epoxy-6-hydroxymethyl-2-oxabicyclo-[3.3.0]octan-3-one (8). A mixture of titanium tetraisopropoxide (0.24 mL, 0.78 mmol), (−)-D-diethyl tartrate (0.15 mL, 0.87 mmol), and molecular sieves 4Å (289 mg) in CH_2Cl_2 (2 mL) was stirred at −23 °C for 15 min. A solution of allylic alcohol **11** (100 mg, 0.65 mmol) in CH_2Cl_2 (2 mL), followed by a 2.0 M solution of *tert*-butylhydroperoxide in CH_2Cl_2 (0.68 mL, 1.36 mmol), was added. After the reaction mixture was stirred at −23 °C for 2.5 h, a 10% aqueous (−)-D-tartaric acid solution (2.5 mL) was added. The mixture was then stirred at −23 °C for 30 min and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (SiO_2, using as eluant 1:1 hexanes−EtOAc, followed by EtOAc) gave, along with a small amount of â-epoxide (2.8 mg, 2.5%), the desired α-epoxide **8** (82.5 mg, 75%) as white solids: mp 97−98 °C; $[\alpha]_D$ −27° (*c* 0.24, $CHCl_3$); IR (film) 3450, 1745, 1188 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) ä 5.03 (t, J = 7.1 Hz, 1 H), 3.94 (dd, J = 12.6, 5.0 Hz, 1 H), 3.84 (dd, J = 12.6, 7.1 Hz, 1 H), 3.67 (br s, 1 H), 3.04 (ddd, J = 7.8, 7.1, 3.2 Hz, 1 H), 2.75 (dd, J = 18.1, 3.2 Hz, 1 H), 2.69 (dd, J = 18.1, 7.8 Hz, 1 H), 2.47 (d, J = 16.2 Hz, 1 H), 2.17 (ddd, J = 16.2, 7.1, 1.3 Hz, 1 H), 2.10 (dd, J = 7.1, 5.0 Hz, −OH, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) ä 176.4, 84.1, 70.9, 64.1, 60.6, 40.3, 34.1, 30.0; HRMS (M^+ + H) calcd for $C_8H_{11}O_4$ 171.0657, found 171.0653.

(1*S*,5*S*,6*S*,7*R*)-6,7-Epoxy-6-[(*E*)-2′-carbobenzyloxy-1′-vinyl]-2-oxabicyclo[3.3.0]octan-3-one (7). To a solution of oxalyl chloride (0.12 mL, 1.4 mmol) in CH_2Cl_2 (1 mL) at −78 °C was added slowly a solution of DMSO (0.16 mL, 2.2 mmol) in CH_2Cl_2 (1 mL). After 10 min, a solution of alcohol **8** (71 mg, 0.42 mmol) in CH_2Cl_2 (1 mL) was added, and the resulting mixture was then stirred at −78 °C for an additional 1 h. Triethylamine (0.45 mL, 3.2 mmol) was added, and the mixture was stirred at −78 °C for 10 min and at 0 °C for 40 min. The mixture was then extracted with ether several times. The organic extracts were washed with brine and water, dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, using EtOAc as eluant) furnished the desired aldehyde in quantitative yield.

The aldehyde was dissolved in CH_2Cl_2 (3 mL) and treated with (carbobenzyloxymethylene)triphenylphosphorane (119

(10) Cf. Finn, M. G.; Sharpless, K. B. In *Asymmetric Synthesis—Chiral Catalysis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1985; Vol. 5, Chapter 8.

(11) Molander, G. A.; La Belle, B. E.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 5259. For a review on synthetic applications of SmI_2, see: Molander, G. A. *Chem. Rev.* **1992**, *92*, 29.

(12) Samarium enolates are known to react readily with aldehydes. For example, see: Enholm, E. J.; Jiang, S. *Tetrahedron Lett.* **1992**, *33*, 313.

(13) We thank Mr. Haizhong Tang for technical assistance with the initial preparation of **7**.

(14) (a) Sheldon, R. A.; Kochi, J. K. *Org. React.* **1972**, *19*, 279. (b) Ogibin, Y. N.; Katzin, M. I.; Nikishin, G. I. *Synthesis* **1974**, 889.

mg, 0.3 mmol) at room temperature for 2 h. After the solvent was removed by evaporation, the residue was purified by column chromatography (using 2:1, 1:1 hexanes−EtOAc as eluant) to give **7** (112 mg, 89%) as white solids: mp 125−126 °C; $[\alpha]_D$ +50.8° (*c* 1.0, $CHCl_3$); IR (film) 3064, 1771, 1717, 1657, 1498, 1173 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) ä 7.41−7.25 (m, 5 H), 6.88 (d, *J* = 15.8 Hz, 1 H), 6.14 (d, *J* = 15.8 Hz, 1 H), 5.20 (s, 2 H), 5.02 (t, *J* = 7.0 Hz, 1 H), 3.68 (br s, 1 H), 3.19 (ddd, *J* = 9.5, 7.0, 1.6 Hz, 1 H), 2.69 (dd, *J* = 18.0, 9.5 Hz, 1 H), 2.54 (dd, *J* = 18.0, 1.6 Hz, 1 H), 2.51 (d, *J* = 16.2 Hz, 1 H), 2.23 (ddd, *J* = 16.2, 7.0, 1.5 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) ä 175.4, 165.0, 141.3, 135.5, 128.6, 128.4, 128.3, 124.1, 83.2, 69.1, 68.7, 66.7, 40.9, 34.4, 29.6; HRMS (M^+ + H) calcd for $C_{17}H_{17}O_5$ 301.1076, found 301.1091.

(1*S*,5*R*,7*R*,2′*R*,*S*,3′*R*,*S*)-7-Hydroxy-6-[(*E*,*Z*)-3′-hydroxy-oct-2′-carbobenzyloxy-1′-ylidene]-2-oxabicyclo[3.3.0]octan-3-one (6). To a solution of samarium(II) iodide (26 mL of 0.1 M in THF) in THF at −78 °C was added dropwise a solution of **7** (219 mg, 0.73 mmol) and *n*-hexanal (0.4 mL, 3.3 mmol) in THF (10 mL). The reaction mixture was stirred at −78 °C for 50 min, quenched by addition of a pH 7.4 buffer solution, and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, using as eluant 10:1, 5:1, 2:1, 1:1 hexanes−EtOAc, followed by EtOAc) afforded **6** (294 mg, 100%) as a pale yellow oil: IR (film) 3417, 1770, 1732, 1183 cm^{-1}; MS *m*/*z* 277, 276 (M^+ − OBn − H_2O), 266, 234, 193. The ^1H NMR spectrum indicated the presence of 6 diastereomers, which can be most easily separated after silylation.

(1*S*,5*R*,7*R*,2′*R*,*S*,3′*R*,*S*)-7-[(*tert*-Butyl)dimethylsiloxy]-6-[(*E*,*Z*)-3′-(*tert*-butyl)dimethylsiloxyoct-2′-carbobenzyloxy-1′-ylidene]-2-oxabicyclo[3.3.0]octan-3-one (12). A solution of alcohol **6** (255 mg, 0.63 mmol) in CH_2Cl_2 (5 mL) was treated at 0 °C with 2,6-lutidine (0.8 mL, 6.8 mmol) and *tert*-butyldimethylsilyl trifluromethanesulfonate (0.8 mL, 3.4 mmol). After the resulting solution was stirred at room temperature for 45 min, 1 N HCl (20 mL) was added. The mixture was then extracted with CH_2Cl_2. The combined extracts were washed with H_2O and brine, dried (Na_2SO_4), and concentrated in vacuo to give **12** (391 mg, 98%) as a slightly yellow oil, whose ^1H NMR spectrum indicated the presence of 6 diastereomers [**a**, ä 5.78 (dd, *J* = 10.1, 1.0 Hz); **b**, ä 5.63 (dd, *J* = 10.1, 1.4 Hz); **c**, ä 5.56 (br d, *J* = 10.7 Hz); **d**, ä 5.47 (br d, *J* = 10.8 Hz); **e**, ä 5.46 (dd, *J* = 10.5, 1.2 Hz); **f**, ä 5.39 (dd, *J* = 10.1, 1.0 Hz)] in a ratio of 4:4:0.8:0.6:1.5:1. IR (film) 1774, 1736 cm^{-1}; HRMS (M^+ − *tert*-butyl) calcd for $C_{31}H_{49}O_6Si_2$ 573.3068, found 573.3078.

Most conveniently, these diastereomeric products were separated by column chromatography (SiO_2, using as eluant 15:1, 10:1, 8:1, and 4:1 hexanes−EtOAc) into three fractions **12**−**I** (pure **e**, 44 mg, 11%), **12-II** (a mixture of **b**, **c**, and **f**, 159 mg, 40%), and **12-III** (a miture of **a** and **d**, 158 mg, 40%).

The spectral data of the pure isomer **e** (**12-I**) were listed below: ^1H NMR (360 MHz, $CDCl_3$) ä 7.40−7.30 (m, 5 H), 5.46 (dd, *J* = 10.5, 1.2 Hz, 1 H), 5.07 (s, 2 H), 5.06 (t, *J* = 6.8 Hz, 1 H), 4.42 (br d, *J* = 4.4 Hz, 1 H), 4.16 (m, 1 H), 3.49 (m, 1 H), 3.28 (dd, *J* = 10.5, 8.5 Hz, 1 H), 2.81 (dd, *J* = 18.4, 11.8 Hz, 1 H), 2.38 (dd, *J* = 18.4, 3.9 Hz, 1 H), 2.17 (d, *J* = 15.0 Hz, 1 H), 1.80 (ddd, *J* = 15.0, 6.8, 4.4 Hz, 1 H), 1.48−1.35 (m, 3 H), 1.35−1.10 (m, 5 H), 0.85 (s, 9 H), 0.84 (t, *J* = 7.8 Hz, 3 H), 0.83 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H), 0.02 (s, 3 H), −0.03 (s, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) ä 176.5, 171.7, 150.2, 135.3, 128.7, 128.5, 120.8, 84.0, 76.6, 73.0, 66.9, 52.7, 41.5, 38.6, 36.7, 34.1, 31.9, 25.7, 25.6, 23.1, 22.4, 18.0, 17.9, 13.9, −4.3, −4.6, −4.9, −5.0; HRMS (M^+ − *tert*-butyl) calcd for $C_{31}H_{49}O_6Si_2$ 573.3068, found 573.3083.

(1*S*,5*R*,6*S*,7*R*,3′*S*)-7-[(*tert*-Butyl)dimethylsiloxy]-6-[(*E*)-3′-(*tert*-butyl)dimethylsiloxyoct-1′-en-1′-yl]-2-oxabicyclo-[3.3.0]octan-3-one (5-α). A solution of **12-II** (128.5 mg, 0.2 mmol) in EtOAc (6 mL) was hydrogenated under pressure (60 psi) overnight in the presence of PtO_2 (35 mg) and Li_2CO_3 (84.6 mg, 1.1 mmol). The solution was filtered through Celite, and the filter cake was rinsed thoroughly with EtOAc, followed by 5:1 CH_2Cl_2−MeOH. The combined filtrates were concentrated in vacuo to give 118 mg of the crude product, which was used for the next step without further purification.

The crude acid was treated with $Cu(OAc)_2$ (66 mg, 0.36 mmol) and pyridine (64 mg, 0.8 mmol) in chlorobenzene (3 mL). After the mixture was stirred for 35 min, a solution of $Pb(OAc)_4$ (288 mg, 0.62 mmol) in 3 mL of chlorobenzene was added. The resulting mixture was stirred in the dark at room temperature for 1 h and then was heated at 125 °C for 4 h. The reaction mixture was diluted with EtOAc, washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the crude product by flash column chromatography (SiO_2, using as eluant 20:1, 15:1, and 10:1 hexanes−EtOAc) gave **5**-α (44.5 mg, 44%) as a slightly yellow oil: $[\alpha]_D$ −2.4° (*c* 1.24, $CHCl_3$); IR (film) 1780, 1255, 1092 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) ä 5.79 (ddd, *J* = 15.5, 8.5, 1.0 Hz, 1 H), 5.54 (dd, *J* = 15.5, 5.8 Hz, 1 H), 5.07 (t, *J* = 7.0 Hz, 1 H), 4.17 (dd, *J* = 3.7, 3.4 Hz, 1 H), 4.10 (dq, *J* = 1.0, 5.8 Hz, 1 H), 3.03 (dddd, *J* = 11.7, 8.5, 7.0, 5.0 Hz, 1 H), 2.82 (dd, *J* = 18.5, 5.0 Hz, 1 H), 2.50 (dt, *J* = 3.4, 8.5 Hz, 1 H), 2.44 (dd, *J* = 18.5, 11.7 Hz, 1 H), 2.16 (d, *J* = 15.1 Hz, 1 H), 1.88 (ddd, *J* = 15.1, 7.0, 3.7 Hz, 1 H), 1.55−1.35 (m, 2 H), 1.35−1.20 (m, 6 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.87 (t, *J* = 7.3 Hz, 3 H), 0.059 (s, 3 H), 0.045 (s, 3 H), 0.040 (s, 3 H), 0.014 (s, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) ä 177.7, 137.4, 125.0, 84.7, 76.7, 73.0, 50.8, 42.3, 42.1, 38.2, 31.8, 31.1, 25.9, 25.7, 24.8, 22.6, 18.2, 18.0, 14.0, −4.3, −4.7, −4.8, −5.2; HRMS (M^+ − *tert*-butyl) calcd for $C_{23}H_{43}O_4Si_2$ 439.2700, found 439.2718.

(1*S*,5*R*,6*S*,7*R*,3′*R*)-7-[(*tert*-Butyl)dimethylsiloxy]-6-[(*E*)-3′-(*tert*-butyl)dimethylsiloxyoct-1′-en-1′-yl]-2-oxabicyclo-[3.3.0]octan-3-one (5-â). According to the experimental procedure described for the conversion of **12-II** to **5**-α, the epimer **5**-â (56 mg, 64%) was obtained as a slightly yellow oil from **12-III** (112 mg, 0.18 mmol). Similarly, **12-I** was also converted to **5**-â (66% overall): $[\alpha]_D$ −2.8° (*c* 0.75, $CHCl_3$); IR (film) 1772, 1092 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) ä 5.69 (dd, *J* = 15.6, 8.2 Hz, 1 H), 5.51 (dd, *J* = 15.6, 7.0 Hz, 1 H), 5.07 (t, *J* = 7.2 Hz, 1H), 4.17 (dd, *J* = 3.7, 3.4 Hz, 1 H), 4.04 (q, *J* = 7.0 Hz, 1 H), 3.06 (dddd, *J* = 11.8, 8.2, 7.2, 5.0 Hz, 1 H), 2.81 (dd, *J* = 18.5, 5.0 Hz, 1 H), 2.49 (dt, *J* = 3.4, 8.2 Hz, 1 H), 2.46 (dd, *J* = 18.5, 11.8 Hz, 1 H), 2.15 (d, *J* = 15.1 Hz, 1 H), 1.88 (ddd, *J* = 15.1, 7.2, 3.7 Hz, 1 H), 1.45 (m, 1 H), 1.40 (m, 1 H), 1.35−1.16 (m, 6 H), 0.87 (s, 9 H), 0.86 (s, 9 H), 0.85 (t, *J* = 6.6 Hz, 3 H), 0.044 (s, 3 H), 0.036 (s, 3 H), 0.024 (s, 3 H), 0.006 (s, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) ä 177.6, 137.7, 126.0, 84.7, 76.7, 74.0, 50.5, 42.3, 41.8, 38.2, 31.7, 31.1, 25.9, 25.7, 25.0, 22.6, 18.2, 18.0, 14.0, −4.2, −4.66, −4.74, −5.2; HRMS (M^+ − *tert*-butyl) calcd for $C_{23}H_{43}O_4Si_2$ 439.2700, found 439.2690.

11,15-Bis(*tert*-butyldimethylsilyl)-12-epi-$PGF_{2\alpha}$ (14). To a solution of **5**-α (50 mg, 0.1 mmol) in THF (5 mL) was added dropwise DIBAL-H (0.7 mL of 1 M in hexanes) at −78 °C. The reaction mixture was stirred at −78 °C for 5 h and then quenched by slow addition of MeOH, followed by EtOAc and H_2O. The resulting mixture was stirred at room temperature for 30 min, filtered through a pad of Celite−Na_2SO_4, and washed thoroughly with EtOAc. The combined filtrates were concentrated in vacuo. Purification by SiO_2 column chromatography (using as eluant 15:1, 10:1, and 5:1 hexanes−EtOAc) afforded 48.7 mg (97%) of the hemiacetal as a colorless oil, which was used immediately for the next step.

A solution of (4-carboxybutyl)triphenylphosphonium bromide (508 mg, 1.1 mmol) in THF (2 mL) was treated at 0 °C with a solution of potassium *tert*-butoxide (2.2 mL of 1 M in THF) in THF. After the mixture was stirred for 30 min, a solution of the hemiacetal in THF (2 mL) was added. The resulting mixture was then stirred at 0 °C for 1 h, quenched with addition of saturated aqueous NH_4Cl solution, diluted with water, adjusted to pH 3 with 1 N HCl, and then extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2, using as eluant 4:1, 2:1, 1:1, and 1:2 hexanes−EtOAc) yielded **14** (45 mg, 80%) as a colorless oil: $[\alpha]_D$ +8° (*c* 0.15, $CHCl_3$); IR (film) 3518, 3457, 1710 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) ä 5.72 (ddd, *J* = 15.4, 10.2, 1.0 Hz, 1 H), 5.51 (m, 1 H), 5.45 (dd, *J* = 15.4, 5.2 Hz, 1 H), 5.32 (m, 1 H), 4.24 (m, 1 H), 4.20−4.10 (m, 2 H), 2.64 (ddd,

J = 10.2, 10.0, 5.2 Hz, 1 H), 2.33 (t, J = 7.5 Hz, 2 H), 2.23 (m, 1 H), 2.14−2.07 (m, 2 H), 2.02 (m, 1 H), 1.96 (m, 1 H), 1.94−1.84 (m, 2 H), 1.74−1.64 (m, 2 H), 1.55−1.40 (m, 2 H), 1.40−1.20 (m, 6 H), 0.89 (s, 18 H), 0.88 (t, J = 6.9 Hz, 3 H), 0.068 (s, 3 H), 0.050 (s, 3 H), 0.048 (s, 3H), 0.041 (s, 3 H);^{13}C NMR (90 MHz, $CDCl_3$) ä 178.7, 136.4, 130.6, 128.6, 126.9, 77.5, 74.3, 72.9, 50.5, 47.9, 43.0, 38.6, 33.4, 31.9, 26.6, 25.9, 25.0, 24.9, 24.6, 22.6, 18.2, 18.1, 14.0, −4.3, −4.7, −4.80, −4.82; HRMS (M^+ − *tert*-butyl − H_2O) calcd for $C_{28}H_{51}O_4Si_2$ 507.3326, found 507.3309.

11,15-Bis(*tert*-butyldimethylsilyl)-12,15-di-*epi*-$PGF_{2\alpha}$ (15). Prepared from **5**-â in 88% yield as a colorless oil according to the procedure as described for **14**: $[\alpha]_D$ −5° (*c* 0.10, $CHCl_3$); IR (film) 3523, 3456, 1711 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) ä 5.65 (dd, J = 15.4, 10.2 Hz, 1 H), 5.52 (m, 1 H), 5.42 (dd, J = 15.4, 7.2 Hz, 1 H), 5.34 (m, 1 H), 4.20 (m, 1 H), 4.18 (m, 1 H), 4.07 (q, J = 7.2 Hz, 1 H), 2.61 (ddd, J = 10.2, 9.7, 5.5 Hz, 1 H), 2.33 (t, J = 7.5 Hz, 2 H), 2.26 (m, 1 H), 2.17−2.05 (m, 2 H), 2.08 (m, 1 H), 1.99 (m, 1 H), 1.97 (m, 1 H), 1.86 (m, 1 H), 1.76−1.63 (m, 2 H), 1.55−1.36 (m, 2 H), 1.36−1.18 (m, 6 H), 0.88 (s, 18 H), 0.87 (t, J = 6.6 Hz, 3 H), 0.063 (s, 3 H), 0.049 (s, 6 H), 0.016 (s, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) ä 179.1, 136.9, 130.3, 128.8, 128.2, 77.1, 74.0, 73.8, 50.5, 47.6, 43.0, 38.6, 33.5, 31.8, 26.6, 25.9, 25.8, 25.0, 24.6, 22.6, 18.2, 18.1, 14.1, −4.0, −4.7, −4.8, −4.9; HRMS (M^+ − *tert*-butyl − H_2O) calcd for $C_{28}H_{51}O_4Si_2$ 507.3326, found 507.3339.

12-*epi*-$PGF_{2\alpha}$ (3). The TBS-protected 12-*epi*-$PGF_{2\alpha}$ (**14**) (21 mg, 0.036 mmol) was stirred in HOAc−H_2O−THF (3:1:1) (5 mL) for 2 d at ambient temperature. After being diluted with H_2O, the reaction mixture was extracted with Et_2O. The organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using as eluant 1:4 hexanes−EtOAc, followed by EtOAc and 2% HOAc−EtOAc. Additional purification by preparative TLC (developed with 1:4 hexane−2% HOAc in EtOAc) afforded 10.8 mg (84%) of **3** as a colorless semisolid: $[\alpha]_D$ −4.2° (*c* 0.48, THF); $[\alpha]_D$ +7.5° (*c* 0.43, $CHCl_3$); IR (film) 3377, 3006, 1709 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) ä 5.83 (dd, J = 15.2, 10.3 Hz, 1 H), 5.51 (dd, J = 15.2, 6.1 Hz, 1 H), 5.45−5.30 (m, 2 H), 4.50−4.05 (br s, −OH, 3 H), 4.30−4.17 (m, 2 H), 4.12 (m, 1 H), 2.75 (m, 1 H), 2.31 (t, J = 5.6 Hz, 2 H), 2.28 (m, 1 H), 2.25−2.02 (m, 4 H), 1.98 (m, 1 H), 1.90 (m, 1 H), 1.72−1.58 (m, 2 H), 1.58−1.42 (m, 2 H), 1.40−1.24 (m, 6 H), 0.88 (t, J = 6.6 Hz, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) ä 177.7, 137.0, 129.9, 129.4, 128.5, 75.6, 73.8, 72.6, 50.0, 47.1, 42.5, 37.0, 33.1, 31.8, 26.4, 25.2, 24.5, 24.3, 22.6, 14.0; MS *m*/*z* 355 (M^+ + H), 336 (M^+ − H_2O), 300, 290, 277, 265, 245, 229, 207, 191. These spectral data were found to be in excellent agreement with literature values.[6b]

12,15-Di-*epi*-$PGF_{2\alpha}$ (4). By following the procedure for the preparation of **3**, desilylation of **15** (22 mg, 0.038 mmol) provided 11.4 mg (85%) of **4** as a colorless oil: $[\alpha]_D$ +3.2° (*c* 0.56, THF); $[\alpha]_D$ +27.6° (*c* 0.55, $CHCl_3$); IR (film) 3376, 3006, 1710 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) ä 5.89 (dd, J = 15.2, 10.7 Hz, 1 H), 5.56 (dd, J = 15.2, 6.0 Hz, 1 H), 5.47 (m, 1 H), 5.39 (m, 1 H), 4.30−4.12 (m, 3 H), 3.80−3.20 (br s, −OH, 3 H), 2.75 (m, 1 H), 2.32 (m, 1 H), 2.31 (t, J = 6.7 Hz, 2 H), 2.20−2.08 (m, 3 H), 2.05 (m, 1 H), 2.00 (m, 1 H), 1.90 (m, 1 H), 1.73−1.62 (m, 2 H), 1.60−1.45 (m, 2 H), 1.45−1.22 (m, 6 H), 0.88 (t, J = 6.6 Hz, 3 H);^{13}C NMR (90 MHz, $CDCl_3$) ä 178.6, 136.7, 130.0, 129.6, 127.8, 75.6, 73.7, 72.4, 50.2, 47.2, 42.3, 37.3, 33.3, 31.8, 26.3, 25.2, 24.6, 24.3, 22.6, 14.0; MS *m*/*z* 355 (M^+ + H), 336 (M^+ − H_2O), 300, 290, 277, 265, 245, 229, 207, 191. These spectral data were found to be in excellent agreement with literature values.[6b]

12-*epi*-$PGF_{2\alpha}$ Methyl Ester. For additional characterization of 12-*epi*-$PGF_{2\alpha}$ (**3**), the methyl ester was prepared: To a solution of **3** (7.0 mg, 0.02 mmol) in 1 mL of benzene−MeOH (4:1) was added dropwise a 2.0 M (trimethylsilyl)diazomethane solution in hexanes (0.1 mL, 0.2 mmol) at room temperature. The reaction mixture was stirred for 6 h and then concentrated in vacuo. The concentrate was purified by column chromatography on silica gel (using as eluant 1:1 hexanes−EtOAc, 10:1 CH_2Cl_2−MeOH, and 3:1, 2:1, 1:1 CH_2Cl_2−acetone) to give 6.3 mg (87%) of the methyl ester as a white solid: $[\alpha]_D$ +10.2° (*c* 0.29, $CHCl_3$); IR (film) 3383, 3004, 1742 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) ä 5.82 (dd, J = 15.3, 10.5 Hz, 1 H), 5.52 (dd, J = 15.3, 7.2 Hz, 1 H), 5.43 (m, 1 H), 5.35 (m, 1 H), 4.26−4.17 (m, 2 H), 4.10 (q, J = 7.2 Hz, 1 H), 3.66 (s, 3 H), 3.10−2.84 (br s, −OH, 2 H), 2.75 (ddd, J = 10.5, 10.0, 6.5 Hz, 1 H), 2.50 (br s, 1 H, OH), 2.31 (t, J = 7.4 Hz, 2 H), 2.27 (m, 1 H), 2.18−1.96 (m, 4 H), 1.93 (m, 1 H), 1.86 (m, 1 H), 1.73−1.63 (m, 2 H), 1.57 (m, 1 H), 1.47 (m, 1 H), 1.40−1.22 (m, 6 H), 0.88 (t, J = 6.6 Hz, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) ä 174.3, 137.5, 129.5, 129.4, 129.1, 75.6, 73.7, 73.0, 51.6, 50.0, 47.2, 42.7, 37.0, 33.4, 31.8, 26.7, 25.2, 24.8, 24.3, 22.6, 14.0; HRMS (M^+ − H_2O) calcd for $C_{21}H_{34}O_4$ 350.2457, found 350.2461.

12,15-Di-*epi*-$PGF_{2\alpha}$ Methyl Ester. For additional characterization of 12,15-di-*epi*-$PGF_{2\alpha}$ (**4**), its methyl ester was also prepared in 86% yield as a colorless oil, as described for the preparation of 12-*epi*-$PGF_{2\alpha}$ methyl ester: $[\alpha]_D$ +20° (*c* 0.27, $CHCl_3$); IR (film) 3382, 3005, 1738 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) ä 5.86 (dd, J = 15.4, 10.4 Hz, 1 H), 5.61 (dd, J = 15.4, 6.3 Hz, 1 H), 5.45 (m, 1 H), 5.37 (m, 1 H), 4.23 (t, J = 6.3 Hz, 1 H), 4.20−4.12 (m, 2 H), 3.67 (s, 3 H), 2.75 (ddd, J = 10.4, 9.0, 6.3 Hz, 1 H), 2.34 (br s, −OH, 2 H), 2.32 (t, J = 7.1 Hz, 2 H), 2.28 (m, 1 H), 2.16 (m, 1 H), 2.16−2.02 (m, 3 H), 1.96 (m, 1 H), 1.85 (m, 1 H), 1.74 (br s, −OH, 1 H), 1.73−1.63 (m, 2 H), 1.60−1.45 (m, 2 H), 1.45−1.24 (m, 6 H), 0.88 (t, J = 6.6 Hz, 3 H);^{13}C NMR (90 MHz, $CDCl_3$) ä 174.4, 138.0, 129.7, 129.5, 127.6, 75.5, 73.6, 72.5, 51.6, 50.2, 47.1, 42.8, 37.3, 33.3, 31.8, 26.7, 25.2, 24.7, 24.3, 22.6, 14.0; HRMS (M^+ − H_2O) calcd for $C_{21}H_{34}O_4$ 350.2457, found 350.2447.

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Supporting Information Available: Photocopies of the ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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