Total Synthesis of the Four Enantiomerically Pure Diastereomers of 8-F_{2t}-Isoprostane

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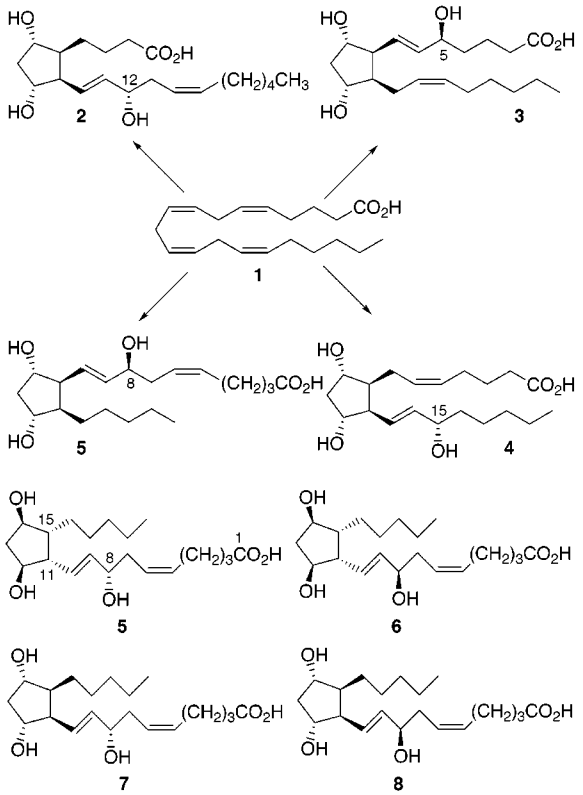
Syntheses of the four enantiomerically pure diastereomers of 8-F_{2t}-isoprostane (**5**−**8**) are described. The key to this approach was to prepare the racemic alcohol **9** in high diastereomeric purity and then resolve **9** by lipase-mediated acetylation to yield the enantiomerically pure alcohols **30** and **32**.

Introduction

In 1990, Roberts and Morrow reported that a series of prostaglandin-like compounds are produced in abundance in vivo independent of the cyclooxygenase enzymes, by free radical-mediated oxidation of membrane-bound arachidonic acid (**1**).[1] These oxidation products have been named the F_2-isoprostanes,[2] the D_2-isoprostanes, and the E_2-isoprostanes.[3] There are four different regioisomers of each of these classes of isoprostanes. Thus **2** is 12-F_{2t}-isoprostane, **3** is 5-F_{2t}-isoprostane, **4** is 15-F_{2t}-isoprostane, and **5** is 8-F_{2t}-isoprostane. 15-F_{2t}-Isoprostane (**4**), prepared by total synthesis,[4−11] has been shown to have hormonal activity, with a receptor in the kidney vasculature.[12] To investigate the physiological activity[4] of the other isoprostanes, it has been necessary to devise synthesis routes to each of them. We report herein the first preparation of each of the four enantiomerically pure diastereomers of 8-F_{2t}-isoprostane (**5**−**8**).



Results and Discussion

The 8-F_{2t}-isoprostanes are produced in vivo as racemic mixtures of C-8 diastereomers. To screen the bioactivity, it was necessary to prepare each of the four enantiomerically pure diastereomers. We envisioned (Scheme 1) a

(1) (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.

(2) (a) For a summary of isoprostane nomenclature, see: Taber, D. F.; Morrow, J. D.; Roberts, L. J., II. *Prostaglandins* **1997**, *53*, 63. (b) For an alternative nomenclature system for the isoprostanes, see Rokach, J.; Khanapure, S. P.; Hwang, S. W.; Adiyaman, M.; Lawson, J. A.; FitzGerald, G. A. *Prostaglandins* **1997**, *54*, 853.

(3) Morrow, J. D.; Minton, T. A.; Mukundan, C. R.; Campell, M. D.; Zackert, W. E.; Daniel, V. C.; Badr, K. F.; Blair, J. A.; Roberts, L. J., II. *J. Biol. Chem.* **1994**, *269*, 4317.

(4) Morrow, J. D.; Roberts, L. J., II. *Biochem. Pharmacol.* **1996**, *51*, 1.

(5) For a previous synthetic route to 8-F_{2t}-isoprostane, see: Adiyaman, M.; Li, H.; Lawson, J. A.; Hwang, S. W.; Khanapure, S. P.; FitzGerald, G. A.; Rokach, J. *Tetrahedron Lett.* **1997**, *38*, 3339.

(6) For synthetic routes to 15-F_{2t}-isoprostane, see: (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. (d) Taber, D. F.; Kanai, K. *Tetrahedron* **1998**, *54*, 11767.

(7) For synthetic routes to 15-F_{2c}-isoprostane, see: (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.

(8) For a synthetic route to 15-E_{2t}-isoprostane, see: (a) Taber, D. F.; Hoerrner, R. S. *J. Org. Chem.* **1992**, *57*, 441. (b) Reference 6d.

(9) For synthetic routes to 5-F_{2t}-isoprostane, see: (a) Adiyaman, M.; Lawson, J. A.; Hwang, S. W.; Khanapure, S. P.; FitzGerald, G. A.; Rokach, J. *Tetrahedron Lett.* **1996**, *37*, 4849. (b) Taber, D. F.; Kanai, K.; Pina, R. *J. Am. Chem. Soc.* **1999**, *121*, 7773.

(10) For a synthetic route to 5-F_{2c}-isoprostane, see: Adiyaman, M.; Lawson, J. A.; FitzGerald, G. A.; Rokach, J. *Tetrahedron Lett.* **1998**, *39*, 7039.

(11) For a synthetic route to 12-F_{2t}-isoprostane, see: Pudukulathan, Z.; Manna, S.; Hwang, S. W.; Khanapure, S. P.; Lawson, J. A.; FitzGerald, G. A.; Rokach, J. *J. Am. Chem. Soc.* **1998**, *120*, 11953.

(12) (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) 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. (d) Longmire, A. W.; Roberts, L. J., II; Morrow, J. D. *Prostaglandins* **1994**, *48*, 247. (e) Fukunaga, M.; Takahashi, K.; Badr, K. F. *Biochem. Biophys. Res. Commun.* **1993**, *195*, 507.

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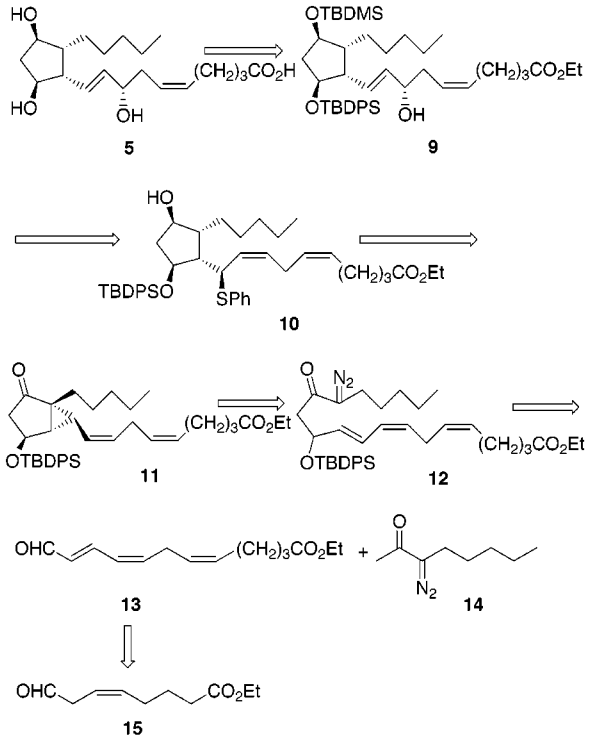
Scheme 1

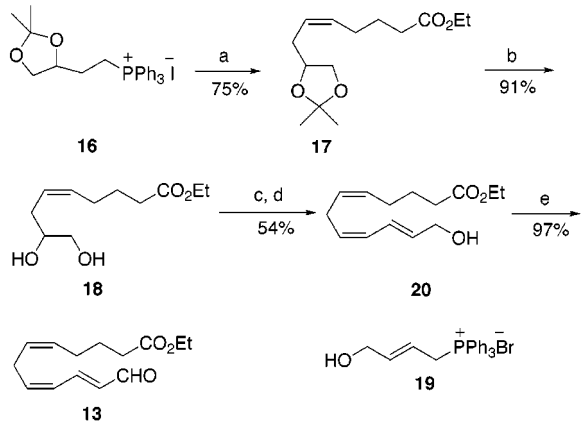


stereodivergent synthetic route which would lead to each of these four from a common intermediate, the racemic alcohol **9**. The diastereomerically pure alcohol **9** could be prepared from the thioether **10**, which could be produced by kinetic opening of the activated cyclopropane of the bicyclic ketone **11** with thiophenol and $BF_3{\cdot}OEt_2$. The bicyclic ketone **11** could be assembled by a rhodium-mediated cyclization of the diazoketone **12**, the product of aldol condensation between the diazoketone **14** and the aldehyde **13**. To establish this route, we had to develop an efficient procedure for the resolution of **9**, and we had to develop a method for the preparation and condensation of the unstable aldehyde **15**.

On the basis of the results we previously reported,[13] we anticipated that rather than attempting purification of the very reactive β,γ-unsaturated aldehyde **15**, it would be more sensible to prepare the precusor diol **18** (Scheme 2). To this end, Wittig reaction of the known phosphonium salt **16**[14] following a modification of the method of Kobayashi[15] with ethyl 5-oxopentanoate[16] proceeded smoothly to give the *cis*-alkene **17**, which was hydrolyzed by 80% acetic acid aqueous solution to furnish diol **18**.

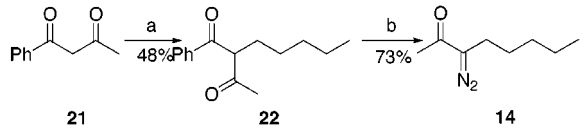
The key to this approach was the development of conditions for the cleavage of diol **18** such that the very unstable β,γ-aldehyde **15** would be generated in sufficient purity that it could be used directly in the subsequent Wittig condensation. In fact, the Vo-Quang[17] periodate cleavage (Scheme 2) gave a CH_2Cl_2 solution of **15** that could be directly used in the following modified Wittig

Scheme 2[a]



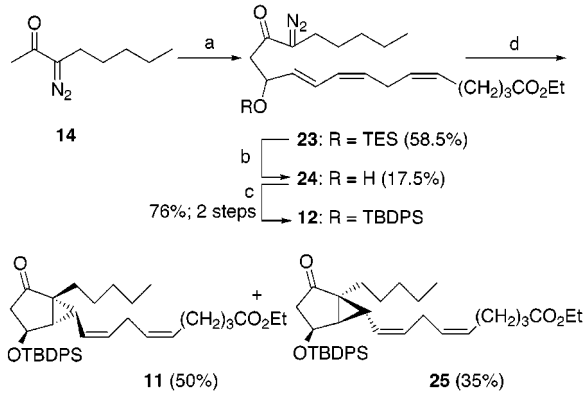
[a] Key: (a) KHMDS, THF, −78 °C; ethyl 5-oxopentanoate, −78 °C to 0 °C; (b) 80% HOAc (aq.), rt; (c) $NaIO_4/SiO_2$, CH_2Cl_2/H_2O, rt; (d) **19**, KHMDS, THF/CH_2Cl_2, −78 °C to room temperature; (e) Dess−Martin periodinane, CH_2Cl_2, rt.

Scheme 3[a]



[a] Key: (a) K_2CO_3, toluene, TBAI (cat.), Cu, reflux; 1-bromopentane, 50 °C; (b) *p*-NBSA, DBU, CH_2Cl_2, 0 °C.

Scheme 4[a]



[a] Key: (a) KHMDS, toluene, −78 °C; **13**, TESCl; (b) TBAF, NH_4Cl (solid), THF, 0 °C; (c) TBDPSCl, imidazole, DMAP (cat.), CH_2Cl_2, rt; (d) $Rh_2(Oct)_4$, CH_2Cl_2, rt.

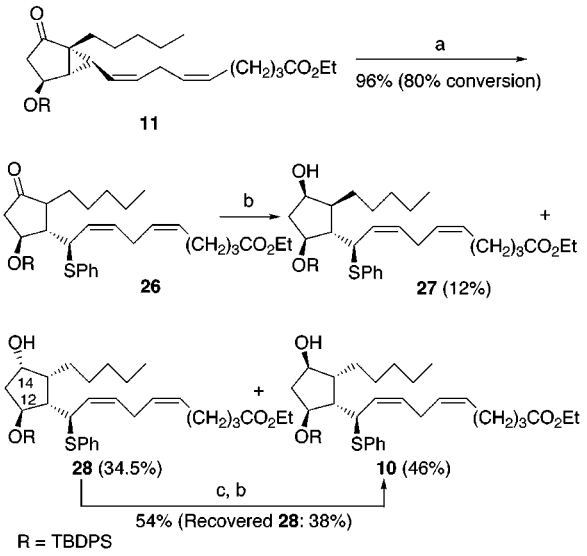
reaction[15] with phosphonium salt **19**[9b] to give the trienol **20**. Finally, oxidation of the trienol **20** with the Dess−Martin periodinane[18] produced the aldehyde **13**.

The diazoketone **14** was prepared (Scheme 3) by the approach we have previously reported.[19] Thus, alkylation of benzoylacetone (**21**) with 1-bromopentane gave the diketone **22**, which was smoothly converted to the diazoketone **14** on exposure to *p*-nitrobenzenesulfonyl azide (*p*-NBSA) and DBU.

Aldol condensation[6d] (Scheme 4) of the potassium enolate of the diazoketone **14** with the aldehyde **13** in the presence of triethylchlorosilane (TESCl) in toluene

(13) Taber, D. F.; You, K. *J. Org. Chem.* **1995**, *60*, 139.
(14) Mosset, P.; Pointeau, P.; Aubert, F.; Lellouche, J. P.; Beaucourt, J. P.; Grée, R. *Bull. Soc. Chim. Fr.* **1990**, *127*, 298.
(15) Hosoda, A.; Taguchi, T.; Kobayashi, Y. *Tetrahedron Lett.* **1987**, *28*, 65.
(16) Ethyl 5-oxopentanoate was prepared by ethanolysis of δ-valerolactone followed by PCC oxidation. For full characterization, see Penn, J. H.; Liu, F. *J. Org. Chem.* **1994**, *59*, 2608.
(17) Daumas, M.; Vo-Quang, Y.; Vo-Quang, L.; Le Goffic, F. *Synthesis* **1989**, 64.
(18) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.
(19) Taber, D. F.; Gleave, D. M.; Herr, R. J.; Moody, K.; Hennessy, M. J. *J. Org. Chem.* **1995**, *60*, 2283.

Scheme 5[a]



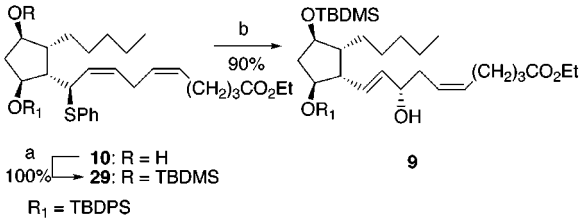
[a] Key: (a) PhSH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −30 °C; (b) $NaBH_4$, MeOH, 0 °C; (c) Dess−Martin periodinane, CH_2Cl_2, rt.

gave the TES-protected aldol **23** together with a small amount of the free aldol **24** (hydrolysis on workup). The TES group of **23** does not survive under the conditions for cyclopropane ring opening with thiophenol and $BF_3{\cdot}OEt_2$, so it was necessary to change the protecting group from TES to *tert*-butyldiphenylsilyl (TBDPS). The diazoketone **12** was then cyclized with the $Rh_2(oct)_4$ catalyst in CH_2Cl_2 to provide the desired bicyclic ketone **11** and the diastereomer **25**. The structures of the bicyclic ketones **13** and **25** were assigned by comparing the ^1H and ^{13}C NMR spectra to those for the analogous bicyclic ketones that are intermediates in the synthesis of the 5-F_{2t}-isoprostane.[9b] In particular, the oxygenated methine of **11** (^{13}C δ 69.3; ^1H δ 4.46, d, J = 4.9 Hz) is exactly congruent with the analogous 5-F_{2t}-isoprostane precusor (^{13}C δ 69.3; ^1H δ 4.46, d, J = 4.9 Hz), while the oxygenated methine of **25** (^{13}C δ 68.0; ^1H δ 4.59, dt, J = 5.1 and 10.8 Hz) is quite different.

Kinetic cyclopropane ring opening of **11** (Scheme 5) with thiophenol and $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at −30 °C gave the ketone **26** as a mixture of diastereomers. This was immediately reduced with $NaBH_4$ in methanol to produce the alcohols **27**, **28**, and **10**. Again, the relative configurations of **28** (^1H NMR δ 4.75, dt, J = 2.1 and 5.8 Hz, 1H; 4.30, m, 1H) and **10** (^1H NMR δ 4.48, dt, J = 2.5 and 6.5 Hz, 1H; 4.05, m, 1H) were assigned by analogy to the chemical shifts of the H's at C-12 and C-14 in the corresponding diastereomers of the 5-F_{2t}-isoprostane precusors (^1H NMR δ 4.74, dt, J = 2.6 and 6.2 Hz, 1H; 4.29, m, 1H) and (^1H NMR δ 4.44, dt, J = 3.6 and 6.6 Hz, 1H; 4.08, m, 1H).[9b] The undesired alcohol **28** was recycled by oxidation with Dess−Martin periodinane, followed by reduction with $NaBH_4$.

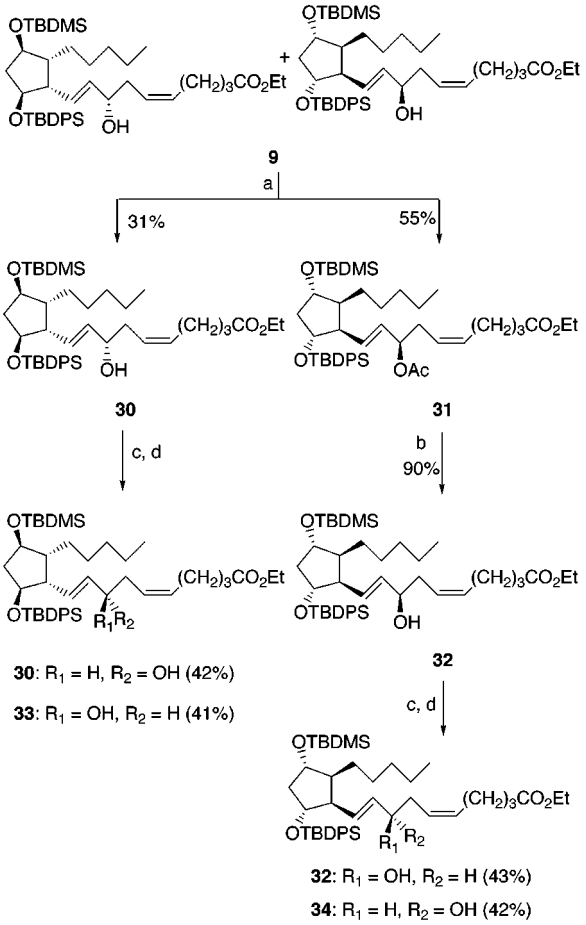
Before establishing the side-chain hydroxyl of **9**, we first protected the ring hydroxyl in **10** (Scheme 6) with TBDMSCl, to yield the disilyloxy thioether **29**. Oxidation of **29** with *m*CPBA followed by Mislow rearrangement[20]

Scheme 6[a]



[a] Key: (a) TBDMSCl, imidazole, DMAP (cat.), CH_2Cl_2, rt; (b) *m*CPBA, CH_2Cl_2, −78 °C; $(MeO)_3P$, EtOH, −78 °C to room temperature.

Scheme 7[a]



[a] Key: (a) Amano Lipase AK, vinyl acetate, 55 °C ~ 60 °C; (b) K_2CO_3, EtOH, rt; (c) Dess−Martin periodinane, CH_2Cl_2, rt; (d) $NaBH_4$, MeOH, 0 °C.

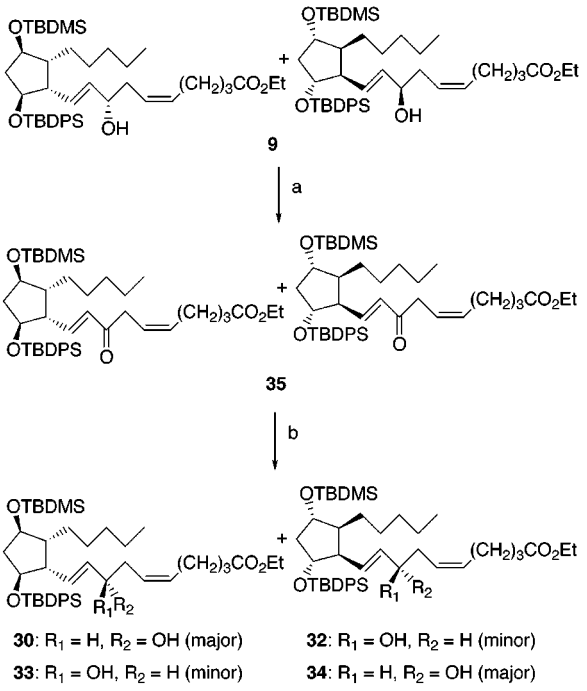
and reductive workup then gave the diastereromerically pure alcohol **9**.

With the racemic alcohol **9** in hand, we could proceed with the separation of the two enantiomers. At first, we tried the enzymatic resolution[21] of alcohol **9** (Scheme 7) with Amano lipase AK in neat vinyl acetate at room temperature. Unfortunately, the reaction was too slow. To speed up the reaction, the reaction temperature was then raised to 55 °C to 60 °C, giving the alcohol **30** [(*S*)-OH] and the acetate **31** after 13 days. The ee of the alcohol **30** was determined to be >99% by chiral HPLC

(20) (a) Bickart, P.; Carson, F. W.; Jacobus, J.; Miller, E. J.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4869. (b) Tang, R.; Mislow, K. *J. Am. Chem. Soc.* **1970**, *92*, 2100.

(21) Wong, C.-H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Pergamon Press: Oxford, U.K., 1994; and references therein.

Scheme 8[a]



[a] Key: (a) Dess−Martin periodinane, CH_2Cl_2, rt; (b) (*S*)-BINAL-H, THF, −78 °C.

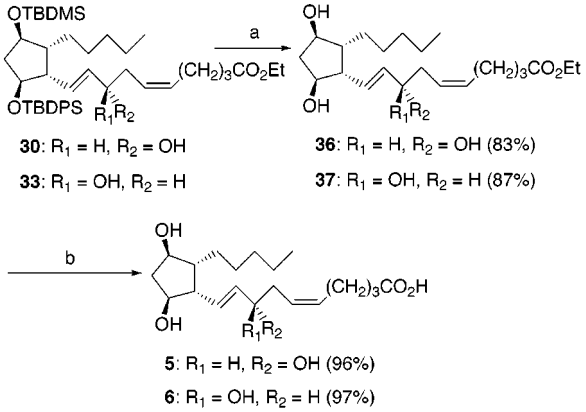
analysis.[22] Deacetylation of the acetate **31** provided the alcohol **32** [(*R*)-OH], the ee of which was determined to be 80% by chiral HPLC analysis. Oxidation of the alcohols **30** and **32**, respectively, with Dess−Martin periodinane followed by reduction with $NaBH_4$ yielded the epimeric alcohols **30**, **33** (>99% ee) and **32**, **34** (80% ee).

To investigate the biological activity of the isoprostanes, it is necessary to prepare each of these in high enantiomeric excess. Therefore, the enantiomerically enriched alcohols **32** and **34** (80% ee) were again subjected to the enzymatic resolution to give, respectively, the alcohol **34**, the ee of which was determined to be >99% by chiral HPLC analysis, and, after deacetylation, the alcohol **32**, the ee of which was determined to be >99% by chiral HPLC analysis.

The absolute configuration of the enzymatically resolved compounds was determined by comparison of the chiral HPLC retention time of the alcohols **30** and **32** with the products **30** and **32** of enantioselective (*S*)-BINAL-H reduction[9b] of the racemic ketone **35**, which was obtained by oxidation of the racemic alcohol **9** (Scheme 8). The ee's of alcohols **30** and **32** which were obtained from the (*S*)-BINAL-H reduction was determined to be 17% by chiral HPLC analysis. The major enantiomer of the alcohols **30** and **32** had a retention time of 9 min, and its minor enantiomer had a retention time of 13 min. The alcohols **30** and **32** derived by the enzymatic resolution had a retention time of 9 and 13 min, respectively. Thus, we established the absolute configurations of the enzymatically resolved alcohols **30** and **32** to be as shown in Scheme 7.

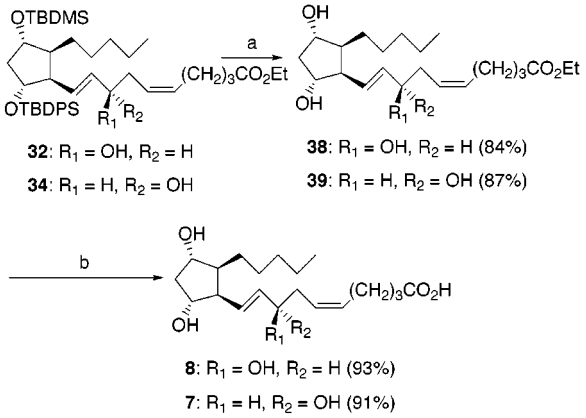
(22) The ee's were determined by HPLC analysis with a CHIRALCEL OD column (Daicel Chemical Industries Ltd.): detector, UV (254 nm); flow rate, 1 mL/min; mobile phase, hexanes/2-PrOH = 150/1. Retention time: **30**, 9 min; **32**, 13 min; **33**, 11 min; **34**, 9 min.

Scheme 9[a]



[a] Key: (a) TBAF, THF, rt; (b) LiOH·H_2O, THF/H_2O (1:1, v/v), rt.

Scheme 10[a]



[a] Key: (a) TBAF, THF, rt; (b) LiOH·H_2O, THF/H_2O (1:1, v/v), rt.

The alcohols **30**, **33**, **32**, and **34** were separately desilylated (Schemes 9 and 10) with TBAF in THF followed by hydrolysis with LiOH in THF/H_2O (1:1) to furnish 8-F_{2t}-isoprostane (**5**), 8-*epi*-8-F_{2t}-isoprostane (**6**), *ent*-8-*epi*-8-F_{2t}-isoprostane (**7**), and *ent*-8-F_{2t}-isoprostane (**8**). The ^1H and ^{13}C NMR data for **5** were identical with those reported.[5,23]

Conclusion

We have developed a practical synthesis of the four enantiomerically pure diastereomers of 8-F_{2t}-isoprostanes (**5**−**8**) using rhodium-mediated intramolecular cyclopropanation and enzymatic resolution as the key steps. This synthesis will make **5**−**8** available in sufficient quantity to allow the detailed assessment of their physiological activity.

Experimental Procedures.

General. ^1H NMR and ^{13}C NMR spectra were obtained as solutions in deuteriochloroform ($CDCl_3$). ^{13}C multiplicities were determined with the aid of a JVERT pulse sequence, differentiating the signals for methyl and methine carbons as "down" from methylene and quaternary carbons as "up". The infrared (IR) spectra were determined as neat oils. Optical rotations were determined as solutions in chloroform unless

(23) The previous report did not include $[\alpha]_D$, so no comparison could be made.

otherwise noted. R_f values indicated refer to thin-layer chromatography (TLC) on 2.5 × 10 cm, 250 μm analytical plates coated with silica gel GF and developed in the solvent system indicated. Silica gel (60 Å) was used for flash column chromatography. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium metal/benzophenone ketyl under dry nitrogen. Dichloromethane (CH_2Cl_2) and toluene were distilled from calcium hydride under dry nitrogen. All reaction mixtures were stirred magnetically, unless otherwise noted.

Alkene 17. To a stirred solution of the phosphonium salt **16** (24.40 g, 47.10 mmol) in THF (400 mL) was added a 0.55 M solution of KHMDS (81.70 mL, 44.90 mmol) in toluene at −78 °C under N_2. The reaction mixture was stirred for 1 h, and then a solution of ethyl 5-oxopentanoate (6.17 g, 42.8 mmol) in THF (20 mL) was added. After an additional 10 min at −78 °C, the reaction mixture was allowed to warm to room temperature over 1.5 h. It was then partitioned between Et_2O and, sequentially, saturated aqueous NH_4Cl and brine. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to produce the alkene **17** (8.18 g, 75% yield from **16**) as a colorless oil, TLC R_f = 0.78 (petroleum ether/MTBE = 1/1); CI MS *m*/*z* (rel intensity) 241 ($M^+ - CH_3$, 45); IR (film) 2984, 2936, 2872, 1735, 1456, 1370, 1244, 1214, 1157, 1062 cm^{-1}; ^1H NMR δ 5.29−5.44 (m, 2H), 4.00−4.06 (m, 3H), 3.93 (dd, J = 6.0 and 7.9 Hz, 1H), 3.46 (dd, J = 7.1 and 7.9 Hz, 1H), 2.15−2.35 (m, 4H), 2.01 (q, J = 7.3 Hz, 2H), 1.61 (quint, J = 7.4 Hz, 2H), 1.33 (s, 3H), 1.26 (s, 3H), 1.17 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ up 173.2, 108.7, 68.8, 60.0, 33.4, 31.3, 26.5, 24.5; down 131.3, 124.9, 75.3, 26.7, 25.4, 14.0; HRMS calcd for $C_{13}H_{21}O_4$ ($M - CH_3$) 241.1440, found 241.1442.

Diol 18. A solution of the alkene **17** (6.88 g, 26.88 mmol) in 80% aqueous HOAc (100 mL) was stirred for 42 h at room temperature. The reaction mixture was then concentrated and the residue was chromatographed to give the diol **18** (5.26 g, 91% yield from **17**) as a colorless oil, TLC R_f = 0.35 (petroleum ether/EtOAc = 1/3); CI MS *m*/*z* (rel intensity) 234 ($M^+ + NH_4$, 60), 217 ($M^+ + H$, 100); IR (film) 3404, 2935, 1733, 1458, 1374, 1313, 1244, 1187, 1150, 1074, 1032 cm^{-1}; ^1H NMR δ 5.35−5.45 (m, 2H), 4.06 (q, J = 7.1 Hz, 2H), 3.65 (ddd, J = 2.9, 7.1, and 13.7 Hz, 1H), 3.62 (brs, 2H), 3.55 (dd, J = 2.9 and 11.3 Hz, 1H), 3.38 (dd, J = 7.3 and 11.3 Hz, 1H), 2.24 (t, J = 7.4 Hz, 2H), 2.09−2.19 (m, 2H), 1.99−2.04 (m, 2H), 1.62 (quint, J = 7.4 Hz, 2H), 1.87 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ up 173.8, 66.0, 60.2, 33.5, 31.0, 26.4, 24.5; down 131.2, 125.7, 71.8, 14.0; HRMS calcd for $C_{11}H_{21}O_4$ (M + H) 217.1440, found 217.1436.

Trienol 20. A stirred mixture of $NaIO_4$ (3.98 g, 18.60 mmol) and H_2O (8 mL) was heated until the $NaIO_4$ was dissolved, and then SiO_2 (20 g) was added with vigorous stirring. After cooling to room temperature, CH_2Cl_2 (60 mL) was added, followed by a solution of diol **18** (2.00 g, 9.30 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred for 20 min at room temperature and was then filtered. The filter cake was washed with CH_2Cl_2 (30 mL). The filtrate, which was a solution of the aldehyde **15** in CH_2Cl_2, was used in the next step without further purification.

To a stirred solution of the phosphonium salt **19** (4.22 g, 10.20 mmol) in THF (150 mL) was added a 0.51 M solution of KHMDS in toluene (19.10 mL, 9.74 mmol) at −78 °C under N_2. After an additional 1 h at −78 °C, the solution of aldehyde **15** in CH_2Cl_2 was added, and the reaction mixture was then allowed to warm slowly to room temperature over 4 h. The reaction mixture was partitioned between Et_2O and, sequentially, saturated aqueous NH_4Cl and brine. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield the trienol **20** (1.19 g, 54% yield from **18**) as a colorless oil, TLC R_f = 0.41 (petroleum ether/MTBE = 1/1); CI MS *m*/*z* (rel intensity) 220 ($M^+ - H_2O$, 100); IR (film) 3435, 3009, 2934, 2866, 1734, 1458, 1374, 1313, 1244, 1188, 1156, 1087, 1029, 985, 952 cm^{-1}; ^1H NMR δ 6.51−6.58 (m, 1H), 5.98 (t, J = 10.9 Hz, 1H), 5.81 (dt, J = 5.7 and 15.2 Hz, 1H), 5.32−5.41 (m, 3H), 4.18 (d, J = 5.7 Hz, 2H), 4.09 (q, J = 7.2 Hz, 2H), 2.90 (t, J = 6.1 Hz, 2H), 2.28 (t, J = 7.4 Hz, 2H), 2.23 (brs, 1H), 2.06−2.11 (m, 2H), 1.67 (quint, J = 7.3 Hz, 2H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ up 173.8, 63.2, 60.3, 33.6, 26.5, 26.0, 24.7; down 132.5, 130.1, 129.2, 128.2, 127.7, 125.9, 14.1; HRMS calcd for $C_{14}H_{20}O_2$ ($M - H_2O$) 220.1464, found 220.1466.

Aldehyde 13. To a stirred solution of trienol **20** (2.38 g, 10.00 mmol) in CH_2Cl_2 (100 mL) was added Dess−Martin periodinane (6.30 g, 15.00 mmol). The reaction mixture was stirred for 50 min at room temperature under N_2 and was then concentrated. The residue was filtered through a short pad of silica gel. The filter cake was washed with Et_2O (100 mL). The filtrate was concentrated, and the residue was then chromatographed to furnish the aldehyde **13** (2.28 g, 97% yield from **20**) as a colorless oil, TLC R_f = 0.70 (petroleum ether/MTBE = 1/1); CI MS *m*/*z* (rel intensity) 236 (M^+, 80), 191 ($M^+ - CH_3CH_2O$, 65); IR (film) 2980, 2936, 2868, 1732, 1681, 1630, 1446, 1374, 1243, 1186, 1139, 1105, 1031, 964 cm^{-1}; ^1H NMR δ 9.63 (d, J = 7.9 Hz, 1H), 7.45−7.53 (m, 1H), 6.25−6.31 (m, 1H), 6.12−6.19 (m, 1H), 5.91−5.98 (m, 1H), 5.39−5.49 (m, 2H), 4.09−4.16 (m, 2H), 3.09 (t, J = 6.8 Hz, 2H), 2.29−2.38 (m, 2H), 2.14 (q, J = 7.2 Hz, 2H), 1.67−1.76 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ up 173.4, 60.2, 33.5, 26.6, 26.5, 24.6; down 193.9, 146.3, 141.0, 132.1, 130.6, 126.7, 126.5, 14.2; HRMS calcd for $C_{14}H_{20}O_3$ (M) 236.1413, found 236.1422.

Diketone 22. To a stirred solution of benzoylacetone (**21**) (16.20 g, 0.1 mol) in toluene (300 mL) were added K_2CO_3 (55.20 g, 0.4 mol), *tert*-butylammonium iodide (TBAI) (1.85 g, 5 mmol), and copper powder (0.32 g, 5 mmol). The reaction mixture was heated to reflux for 3 h under N_2 and was then cooled to 50 °C. A solution of 1-bromopentane (15.10 g, 0.1 mol) in toluene (60 mL) was then added over 40 min. The reaction mixture was stirred at 50 °C for 43 h and was then cooled to 0 °C. The reaction mixture was filtered through a short pad of silica gel, and the filter cake was washed with Et_2O (300 mL). Concentration of the filtrate followed by chromatography of the residue gave the diketone **22** (11.14 g, 48% yield from **21**) as a colorless oil, TLC R_f = 0.46 (petroleum ether/MTBE = 9/1); FAB MS *m*/*z* (rel intensity) 233 ($M^+ + H$, 100), 217 ($M^+ - CH_3$, 19); IR (film) 2956, 2929, 2859, 1723, 1677, 1596, 1581, 1448, 1357, 1275, 1215, 1182, 971, 770, 694 cm^{-1}; ^1H NMR δ 7.98−8.00 (m, 2H), 7.58−7.62 (m, 1H), 7.47−7.51 (m, 2H), 4.44 (t, J = 7.0 Hz, 1H), 2.14 (s, 3H), 1.93−2.05 (m, 2H), 1.30 (brs, 6H), 0.86 (brs, 3H); ^{13}C NMR δ up 204.5, 196.4, 136.4, 31.6, 29.0, 27.3, 22.3; down 133.6, 128.8, 128.6, 63.5, 27.7, 13.9; HRMS calcd for $C_{15}H_{21}O_2$ (M + H) 233.1542, found 233.1535.

Diazoketone 14. To a stirred solution of diketone **22** (2.32 g, 10 mmol) in CH_2Cl_2 (30 mL) was added a solution of DBU (3.04 g, 20 mmol) in CH_2Cl_2 (3 mL) at 0 °C under N_2. After 20 min, a solution of *p*-nitrobenzenesulfonyl azide (*p*-NBSA) (4.56 g, 20 mmol) in CH_2Cl_2 (20 mL) was added over 30 min. After an additional 3 h at 0 °C, the reaction mixture was diluted with CH_2Cl_2 (150 mL) and was then partitioned between CH_2Cl_2 and, sequentially, 10% aqueous NaOH, H_2O, and brine. The organic extract was dried (Na_2SO_4) and concentrated. The residue was distilled bulb-to-bulb (100 °C/0.5 mmHg) to yield the diazoketone **14** (1.12 g, 73% yield from **22**) as a yellow oil, TLC R_f = 0.28 (petroleum ether/MTBE = 9/1); IR (film) 2958, 2929, 2860, 2066, 1644, 1457, 1368, 1326, 1186, 1124, 963 cm^{-1}; ^1H NMR δ 2.32 (t, J = 7.3 Hz, 2H), 2.24 (s, 3H), 1.47 (brs, 2H), 1.32 (brs, 4H), 0.88 (brs, 3H); ^{13}C NMR δ up 191.0, 30.8, 26.5, 22.2, 22.0; down 25.2, 13.8.

TES-Protected Aldol 23 and Free Aldol 24. To a stirred solution of diazoketone **14** (1.56 g, 10.13 mmol) in toluene (150 mL) was added a 0.59 M solution of KHMDS in toluene (18.00 mL, 10.62 mmol) at −78 °C under N_2. The reaction mixture was stirred for 10 min, and a solution of aldehyde **13** (2.28 g, 9.66 mmol) and triethylsilyl chloride (TESCl) (1.75 g, 11.61 mmol) in toluene (30 mL) was then added. After an additional 1 h, the reaction mixture was partitioned between EtOAc and, sequentially, saturated aqueous NH_4Cl and brine. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to afford the TES-protected aldol **23** (2.85 g, 58.5% yield from **13**) as a pale yellow oil, TLC R_f = 0.85 (petroleum ether/MTBE = 2/1); IR (film) 2956, 2934, 2875, 2069, 1736, 1630, 1458, 1369, 1239, 1176, 1097, 1069, 1006, 743 cm^{-1}; ^1H NMR δ 6.50 (dd, J = 11.6 and 14.6 Hz, 1H), 5.94 (t, J = 10.8 Hz, 1H), 5.65 (dd, J = 6.4 and 15.0 Hz,

1H), 5.33−5.40 (m, 3H), 4.68 (brs, 1H), 4.11 (q, J = 7.1 Hz, 2H), 2.89 (brs, 2H), 2.73 (dd, J = 8.4 and 13.5 Hz, 1H), 2.45 (dd, J = 4.0 and 13.5 Hz, 1H), 2.22−2.37 (m, 4H), 2.09 (q, J = 6.9 Hz, 2H), 1.69 (quint, J = 7.4 Hz, 2H), 1.44 (brs, 2H), 1.30 (brs, 4H), 1.24 (t, J = 7.1 Hz, 3H), 0.87−0.97 (m, 12H), 0.55 (q, J = 7.9 Hz, 6H); ^{13}C NMR δ up 191.7, 173.6, 68.8, 60.2, 46.7, 33.6, 30.9, 26.6, 26.5, 26.0, 24.7, 22.4, 22.3, 4.7; down 135.5, 130.4, 129.4, 128.2, 127.7, 124.8, 71.0, 14.2, 13.9, 6.7. This was followed by the free aldol **24** (0.66 g, 17.5% yield from **13**) as a pale yellow oil, TLC R_f = 0.13 (petroleum ether/MTBE = 2/1); ^{1}H NMR δ 6.61 (dd, J = 11.2 and 15.1 Hz, 1H), 5.98 (t, J = 11.0 Hz, 1H), 5.70 (dd, J = 6.1 and 15.2 Hz, 1H), 5.35−5.44 (m, 3H), 4.70 (dd, J = 5.9 and 11.6 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 2.92 (t, J = 6.1 Hz, 2H), 2.66−2.70 (m, 2H), 2.26−2.36 (m, 4H), 2.11 (q, J = 7.2 Hz, 2H), 1.70 (quint, J = 7.4 Hz, 2H), 1.46−1.50 (m, 2H), 1.27−1.34 (m, 5H), 1.26 (t, J = 7.1 Hz, 3H), 0.90 (t, J = 6.8 Hz, 3H).

TBDPS-Protected Aldol 12. To a stirred mixture of TES-protected aldol **23** (2.57 g, 5.09 mmol) and solid NH_4Cl (1.36 g, 25.42 mmol) in THF (80 mL) was added a 1.0 M solution of tetrabutylammonium fluoride (TBAF) in THF (7.64 mL, 7.64 mmol) at 0 °C. The reaction mixture was stirred for 1 h and was then partitioned between EtOAc and, sequentially, saturated aqueous NH_4Cl and brine. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue which contained unpurified free aldol **24** was used in the next step without further purification.

To a stirred solution of the unpurified free aldol **24**, imidazole (1.04 g, 15.29 mmol), and DMAP (62 mg, 0.51 mmol) in CH_2Cl_2 (80 mL) was added *tert*-butyldiphenylsilyl chloride (TBDPSCl) (2.80 g, 10.18 mmol). The reaction mixture was stirred for 12 h at room temperature and was then partitioned between CH_2Cl_2 and, sequentially, saturated aqueous NH_4Cl and brine. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give the TBDPS-protected aldol **12** (2.43 g, 76% yield from **23**) as a pale yellow oil, TLC R_f = 0.89 (petroleum ether/MTBE = 2/1); IR (film) 2929, 2856, 2066, 1735, 1636, 1458, 1427, 1370, 1155, 1112, 1063, 822, 739, 702 cm^{-1}; ^{1}H NMR δ 7.62−7.65 (m, 4H), 7.32−7.43 (m, 6H), 6.02 (dd, J = 11.2 and 15.0 Hz, 1H), 5.74 (t, J = 10.8 Hz, 1H), 5.53 (dd, J = 7.3 and 15.0 Hz, 1H), 5.21−5.40 (m, 3H), 4.72 (dd, J = 6.9 and 13.1 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 2.80 (dd, J = 7.5 and 13.7 Hz, 1H), 2.67 (t, J = 7.1 Hz, 2H), 2.51 (dd, J = 5.6 and 13.7 Hz, 1H), 2.20−2.37 (m, 4H), 2.05 (q, J = 7.1 Hz, 2H), 1.68 (quint, J = 7.4 Hz, 2H), 1.38−1.43 (m, 2H), 1.26−1.30 (m, 4H), 1.25 (t, J = 7.1 Hz, 3H), 1.03 (s, 9H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR δ up 191.3, 173.6, 133.8, 133.5, 68.6, 60.2, 46.3, 33.6, 30.9, 26.6, 26.5, 25.8, 24.7, 22.3, 19.3; down 135.9, 134.3, 130.4, 129.6, 129.5, 129.2, 128.2, 127.6, 127.4, 127.3, 125.9, 72.2, 26.9, 14.2, 13.9.

Bicyclic Ketone 11 and 25. To a stirred solution of TBDPS-protected aldol **12** (5.90 g, 9.38 mmol) in CH_2Cl_2 (50 mL) was added a solution of $Rh_2(oct)_4$ (73 mg, 0.094 mmol) in CH_2Cl_2 (170 mL) over a period of 2 h at room temperature. After an additional 2 h, the reaction mixture was concentrated. The residue was chromatographed to yield the bicyclic ketone **25** (1.97 g, 35% yield from **12**) as a colorless oil, TLC R_f = 0.41 (petroleum ether/MTBE = 9/1); IR (film) 2956, 2930, 2858, 1728, 1463, 1428, 1372, 1156, 1112, 823, 742, 702 cm^{-1}; ^{1}H NMR δ 7.63−7.73 (m, 4H), 7.37−7.47 (m, 6H), 5.57 (dt, J = 7.4 and 10.6 Hz, 1H), 5.40−5.47 (m, 2H), 5.38 (dd, J = 9.1 and 10.6 Hz, 1H), 4.59 (dt, J = 8.0 and 15.1 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 2.97 (t, J = 7.0 Hz, 2H), 2.51 (dd, J = 3.7 and 8.8 Hz, 1H), 2.21−2.36 (m, 4H), 2.13 (q, J = 7.2 Hz, 2H), 1.80 (dd, J = 4.2 and 4.9 Hz, 1H), 1.68−1.77 (m, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.07−1.22 (m, 7H), 1.05 (s, 9H), 0.80 (t, J = 7.3 Hz, 3H); ^{13}C NMR δ up 210.8, 173.6, 133.8, 133.4, 60.2, 46.8, 42.1, 33.7, 31.8, 26.8, 26.6, 26.1, 24.8, 24.0, 22.4, 19.1; down 135.7, 135.5, 131.6, 129.9, 129.8, 129.5, 128.1, 127.8, 127.7, 125.4, 68.1, 39.9, 26.7, 25.9, 14.2, 14.0; HRMS calcd for $C_{38}H_{52}O_4Si$ (M) 600.3635, found 600.3628. This was followed by the bicyclic ketone **11** (2.80 g, 50% yield from **12**) as a colorless oil, TLC R_f = 0.28 (petroleum ether/MTBE = 9/1); IR (film) 2930,2858, 1727, 1428, 1156, 1113, 1063, 823, 740, 702 cm^{-1}; ^{1}H NMR δ 7.61−7.70 (m, 4H), 7.35−7.47 (m, 6H), 5.43−5.48 (m, 1H), 5.27−5.36 (m, 2H), 4.88−4.93 (m, 1H), 4.47 (d, J = 4.9 Hz, 1H), 4.08 (q, J = 7.1 Hz, 2H), 2.72 (t, J = 7.0 Hz, 2H), 2.22−2.33 (m, 3H), 2.00−2.14 (m, 5H), 1.60−1.71 (m, 3H), 1.38−1.45 (m, 2H), 1.27−1.33 (m, 4H), 1.16−1.25 (m, 4H), 1.06 (s, 9H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ up 212.9, 173.5, 133.7, 133.5, 60.2, 43.9, 42.9, 33.6, 31.7, 27.2, 26.5, 26.0, 24.7, 23.5, 22.6, 19.0; down 135.7, 131.7, 129.8, 129.5, 127.9, 127.8, 127.7, 125.1, 69.3, 41.5, 27.3, 26.9, 14.2, 14.0; HRMS calcd for $C_{38}H_{52}O_4Si$ (M) 600.3635, found 600.3617.

Thioether 26. To a stirred solution of bicyclic ketone **11** (1.47 g, 2.45 mmol) and thiophenol (0.81 g, 7.36 mmol) in CH_2Cl_2 (12 mL) was added BF_3·OEt_2 (1.39 g, 9.79 mmol) dropwise at −30 °C under N_2. After an additional 5.5 h, the reaction mixture was partitioned between CH_2Cl_2 and, sequentially, saturated aqueous $NaCO_3$ and brine. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to recover the starting material **11** (0.29 g) and provide the thioether **26** (1.35 g, 96% yield from **11** based on 80% conversion) as a colorless oil, TLC R_f = 0.46 (petroleum ether/CH_2Cl_2/MTBE = 70/25/5); CI MS m/z (rel intensity) 653 ($M^+ - C_4H_9$, 15); IR (film) 2956, 2930, 2857, 1740, 1472, 1400, 1167, 1112, 1060, 1026, 822, 740, 702 cm^{-1}; ^{1}H NMR δ 7.61−7.74 (m, 5H), 7.43−7.47 (m, 2H), 7.36−7.41 (m, 6H), 7.17−7.27 (m, 2H), 5.18−5.23 (m, 1H), 5.13 (t, J = 10.6 Hz, 1H), 5.01−5.06 (m, 1H), 4.79−4.86 (m, 1H), 4.62 (d, J = 5.8 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.66 (dd, J = 4.2 and 10.4 Hz, 1H), 2.81−2.86 (m, 1H), 2.68 (dd, J = 3.7 and 7.6 Hz, 1H), 2.55 (dd, J = 6.1 and 19.6 Hz, 1H), 2.34 (d, J = 19.6 Hz, 1H), 2.22 (t, J = 7.5 Hz, 3H), 1.95−2.04 (m, 2H), 1.86 (q, J = 7.2 Hz, 2H), 1.31−1.64 (m, 9H), 1.25 (t, J = 7.1 Hz, 3H), 1.06 (s, 9H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR δ up 217.3, 173.5, 135.2, 133.4, 133.3, 60.2, 46.9, 33.6, 31.9, 28.1, 26.4, 25.0, 24.6, 24.3, 22.5, 19.0; down 135.8, 135.7, 134.0, 129.9, 129.8, 129.3, 129.1, 128.8, 128.7, 127.8, 127.7, 127.6, 127.5, 70.4, 53.8, 52.6, 46.5, 26.9, 14.2, 14.1; HRMS calcd for $C_{40}H_{49}O_4SSi$ ($M - C_4H_9$) 653.3121, found 653.3133.

Alcohols 27, 28, and 10. To a stirred solution of thioether **26** (292 mg, 0.41 mmol) in MeOH (20 mL) was added $NaBH_4$ (156 mg, 4.11 mmol) at 0 °C. The reaction mixture was stirred for 30 min and was then partitioned between EtOAc and, sequentially, 5% aqueous HCl and brine. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield the alcohol **27** (35 mg, 12% yield from **26**) as a colorless oil, TLC R_f = 0.40 (petroleum ether/CH_2Cl_2/MTBE = 70/25/5); CI MS m/z (rel intensity) 655 ($M^+ - C_4H_9$, 8), 603 (M^+ − PhS, 25); IR (film) 3532, 2930, 2857, 1733, 1588, 1472, 1428, 1373, 1310, 1188, 1153, 1112, 1037, 822, 739, 702 cm^{-1}; ^{1}H NMR δ 7.67−7.74 (m, 4H), 7.33−7.47 (m, 6H), 7.18−7.22 (m, 5H), 5.04−5.17 (m, 3H), 4.71−4.74 (m, 1H), 4.22 (brs, 1H), 4.19 (d, J = 4.2 Hz, 1H), 4.10 (q, J = 7.1 Hz, 2H), 3.52 (dd, J = 5.7 and 10.3 Hz, 1H), 3.15 (d, J = 10.5 Hz, 1H), 2.20 (t, J = 7.4 Hz, 2H), 2.01−2.16 (m, 3H), 1.80−1.93 (m, 5H), 1.54−1.67 (m, 5H), 1.34−1.37 (m, 5H), 1.24 (t, J = 7.1 Hz, 3H), 1.07 (s, 9H), 0.90 (t, J = 6.8 Hz, 3H); ^{13}C NMR δ up 173.4, 134.5, 133.0, 132.9, 60.2, 42.6, 33.5, 32.1, 30.8, 28.1, 26.3, 25.0, 24.6, 22.7, 18.9; down 136.0, 135.8, 133.6, 129.9, 129.8, 129.3, 129.0, 128.5, 128.3, 127.8, 127.7, 127.5, 127.3, 80.1, 75.3, 57.7, 49.3, 47.6, 26.9, 14.2, 14.1; HRMS calcd for $C_{40}H_{51}O_4SSi$ ($M - C_4H_9$) 655.3277, found 655.3263. This was followed by the alcohol **28** (101 mg, 35% yield from **26**) as a colorless oil, TLC R_f = 0.30 (petroleum ether/CH_2Cl_2/MTBE = 70/25/5); CI MS m/z (rel intensity) 603 (M^+ − PhS, 15), 545 (M^+ − PhSH − C_4H_9, 100); IR (film) 3460, 2957, 2929, 2856, 1736, 1588, 1472, 1428, 1373, 1188, 1155, 1112, 822, 740, 702 cm^{-1}; ^{1}H NMR δ 7.62−7.69 (m, 4H), 7.35−7.45 (m, 6H), 7.29−7.33 (m, 2H), 7.19−7.24 (m, 3H), 5.16−5.24 (m, 2H), 4.98 (dt, J = 7.3 and 10.7 Hz, 1H), 4.83−4.91 (m, 1H), 4.74−4.76 (m, 1H), 4.29−4.31 (m, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.90 (dd, J = 6.4 and 10.7 Hz, 1H), 2.45−2.52 (m, 2H), 2.20−2.38 (m, 4H), 2.13 (ddd, J = 2.3, 7.0 and 15.2 Hz, 1H), 1.85−1.94 (m, 4H), 1.55−1.63 (m, 3H), 1.41−1.53 (m, 2H), 1.26−1.32 (m, 5H), 1.25 (t, J = 7.1 Hz, 3H), 1.05 (s, 9H), 0.89 (t, J = 6.6 Hz, 3H); ^{13}C NMR δ up 173.7, 134.3, 134.0, 133.9, 60.2, 45.2, 33.7, 32.2, 28.5, 26.4, 25.5, 25.1, 24.7, 22.6, 19.1; down 135.9, 135.8, 134.6,

131.5, 129.6, 129.5, 128.8, 128.7, 128.3, 127.9, 127.5, 126.8, 76.1, 73.4, 54.9, 47.7, 46.3, 27.0, 14.2, 14.1; HRMS calcd for $C_{44}H_{60}O_4SSiNa$ (M + Na) 735.3879, found 735.3896. This was followed by the alcohol **10** (134 mg, 46% yield from **26**) as a colorless oil, TLC R_f = 0.16 (petroleum ether/CH_2Cl_2/MTBE = 70/25/5); CI MS *m*/*z* (rel intensity) 603 (M^+ − PhS, 30), 545 (M^+ − PhSH − C_4H_9, 100); IR (film) 3455, 2929, 2857, 1734, 1647, 1473, 1427, 1374, 1186, 1111, 1026, 822, 740, 702 cm^{-1}; ^1H NMR δ 7.70−7.75 (m, 4H), 7.36−7.45 (m, 6H), 7.29−7.32 (m, 2H), 7.20−7.25 (m, 3H), 5.15−5.22 (m, 2H), 4.98 (dt, *J* = 7.4 and 10.7 Hz, 1H), 4.79−4.85 (m, 1H), 4.44−4.49 (m, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 4.05 (brs, 1H), 3.71 (dd, *J* = 6.9 and 10.6 Hz, 1H), 2.48−2.53 (m, 1H), 2.13−2.26 (m, 5H), 1.83−1.92 (m, 3H), 1.77 (d, *J* = 6.4 Hz, 1H), 1.48−1.67 (m, 4H), 1.20−1.30 (m, 7H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.08 (s, 9H), 0.86 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR δ up 173.5, 134.6, 134.3, 133.8, 60.2, 43.7, 33.7, 32.1, 28.5, 27.8, 26.4, 25.1, 24.7, 22.6, 19.1; down 136.1, 136.0, 134.8, 130.4, 129.6, 129.5, 129.0, 128.6, 128.5, 128.1, 127.7, 127.6, 127.5, 77.1, 76.4, 54.4, 50.6, 47.3, 27.1, 14.2, 14.1; HRMS calcd for $C_{44}H_{60}O_4SSiNa$ (M + Na) 735.3879, found 735.3907.

Alcohol 10 Obtained from Alcohol 28. To a stirred solution of alcohol **28** (15.7 mg, 0.022 mmol) in CH_2Cl_2 (3 mL) was added Dess−Martin periodinane (18.5 mg, 0.044 mmol) at room temperature. The reaction mixture was stirred for 30 min and was then filtered through a short pad of silica gel. The filter cake was washed with Et_2O, and the filtrate was concentrated. The residue was used in the next step without further purification.

To a stirred solution of the residue in MeOH (2 mL) was added $NaBH_4$ (8.4 mg, 0.22 mmol) at 0 °C. The reaction mixture was stirred for 30 min and was then partitioned between EtOAc and, sequentially, 5% aqueous HCl and brine. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to produce the alcohol **28** (6 mg, 38% yield from **28**) as a colorless oil, followed by the alcohol **10** (8.5 mg, 54% yield from **28**) as a colorless oil.

Disilyloxy Thioether 29. To a stirred solution of alcohol **10** (33.5 mg, 0.047 mmol), imidazole (9.6 mg, 0.14 mmol), and a catalytic amount of DMAP in CH_2Cl_2 (5 mL) was added TBDMSCl (14 mg, 0.093 mmol) at room temperature under N_2. The reaction mixture was stirred for 46 h and was then partitioned between CH_2Cl_2 and, sequentially, saturated aqueous NH_4Cl and brine. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give the disilyloxy thioether **29** (41 mg, 100% yield from **10**) as a colorless oil, TLC R_f = 0.52 (petroleum ether/CH_2Cl_2/MTBE = 70/28/2); CI MS *m*/*z* (rel intensity) 769 (M^+ − C_4H_9, 100), 716 (M^+ − PhSH, 90); IR (film) 2956, 2929, 2856, 1737, 1472, 1373, 1252, 1111, 1063, 836, 774, 740, 702 cm^{-1}; ^1H NMR δ 7.69−7.79 (m, 4H), 7.33−7.44 (m, 8H), 7.22−7.25 (m, 3H), 5.17−5.26 (m, 2H), 4.99 (dt, *J* = 7.2 and 10.7 Hz, 1H), 4.80−4.85 (m, 1H), 4.40 (quint, *J* = 3.7 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.97 (dd, *J* = 6.4 and 10.5 Hz, 1H), 3.81 (dd, *J* = 6.8 and 10.7 Hz, 1H), 2.49−2.50 (m, 1H), 2.27−2.32 (m, 1H), 2.23 (t, *J* = 7.8 Hz, 2H), 2.12−2.17 (m, 1H), 1.93−2.04 (m, 2H), 1.88 (q, *J* = 7.1 Hz, 2H), 1.57−1.68 (m, 2H), 1.53 (dt, *J* = 3.8 and 14.3 Hz, 1H), 1.16−1.43 (m, 8H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.08 (s, 9H), 0.89 (s, 9H), 0.86 (t, *J* = 6.9 Hz, 3H), 0.00 (s, 3H), −0.03 (s, 3H); ^{13}C NMR δ up 173.5, 134.9, 134.8, 134.2, 60.2, 44.3, 33.7, 32.1, 28.4, 27.2, 26.4, 25.1, 24.7, 22.6, 19.2, 18.0; down 136.2, 136.1, 134.8, 130.6, 129.4, 129.3, 128.9, 128.6, 128.3, 127.6, 127.4, 127.3, 127.2, 76.1, 75.7, 53.4, 50.0, 47.3, 27.1, 25.9, 14.2, 14.1, −4.4, −4.8; HRMS calcd for $C_{46}H_{65}O_4SSi_2$ (M − C_4H_9) 769.4142, found 769.4140.

Alcohol 9. To a stirred solution of disilyloxy thioether **29** (805 mg, 0.97 mmol) in CH_2Cl_2 (35 mL) was added a solution of *m*CPBA (336 mg, 1.95 mmol) in CH_2Cl_2 (6 mL) at −78 °C under N_2. After an additional 1 h, a solution of $P(OCH_3)_3$ (1.21 g, 9.76 mmol) in EtOH (10 mL) was added. After an additional 15 min at −78 °C, the reaction mixture was allowed to warm to room temperature and was then stirred for 30 min. The reaction mixture was partitioned between EtOAc and, sequentially, saturated aqueous $NaCO_3$ and brine. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to furnish the alcohol **9** (645 mg, 90% yield from **29**) as a colorless oil, TLC R_f = 0.30 (petroleum ether/MTBE = 80/20); CI MS *m*/*z* (rel intensity) 677 (M^+ − C_4H_9, 85), 659 (M^+ − C_4H_9 − H_2O, 100); IR (film) 3460, 2956, 2929, 2857, 1738, 1472, 1428, 1375, 1252, 1112, 1061, 836, 775, 702 cm^{-1}; ^1H NMR δ 7.63−7.66 (m, 4H), 7.34−7.43 (m, 6H), 5.44−5.50 (m, 1H), 5.29−5.36 (m, 1H), 5.17−5.22 (m, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.96 (brs, 1H), 3.93 (quint, *J* = 3.2 Hz, 1H), 3.72 (dd, *J* = 7.4 and 13.3 Hz, 1H), 2.64 (brs, 1H), 2.29 (t, *J* = 7.5 Hz, 2H), 2.10−2.22 (m, 4H), 2.04 (q, *J* = 7.3 Hz, 2H), 1.58−1.72 (m, 3H), 1.46 (d, *J* = 3.7 Hz, 1H), 1.19−1.29 (m, 11H), 1.05 (s, 9H), 0.89 (s, 9H), 0.87 (t, *J* = 7.0 Hz, 3H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR δ up 173.7, 134.4, 134.3, 60.3, 44.1, 35.1, 33.7, 32.1, 28.4, 27.5, 26.7, 24.7, 22.6, 19.1, 18.0; down 135.9, 135.8, 134.2, 131.2, 129.5, 129.1, 127.5, 125.8, 77.1, 76.5, 71.8, 52.7, 49.1, 26.9, 25.8, 14.2, 14.1, −4.4, −4.8; HRMS calcd for $C_{40}H_{61}O_5Si_2$ (M − C_4H_9) 677.4058, found 677.4047.

Alcohol 30 and Acetate 31. To a stirred solution of the racemic alcohol **9** (645 mg, 0.88 mmol) in vinyl acetate (15 mL) was added Amano lipase AK (1935 mg, 3 mass eq.) at room temperature. The reaction mixture was stirred at 55 °C to 60 °C for 13 days. The insoluble material was filtered, and the filtrate was concentrated. The residue was chromatographed to give the acetate **31** (374 mg, 55% yield from **9**) as a colorless oil, TLC R_f = 0.65 (petroleum ether/MTBE = 80/20); CI MS *m*/*z* (rel intensity) 799 (M^+ + Na, 25), 761 (M^+ − CH_3, 100), 719 (M^+ − C_4H_9, 30); IR (film) 2929, 2857, 1737, 1472, 1428, 1371, 1238, 1112, 1061, 835, 774, 740, 702 cm^{-1}; ^1H NMR δ 7.63−7.65 (m, 4H), 7.34−7.44 (m, 6H), 5.08−5.42 (m, 5H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.91 (quint, *J* = 3.1 Hz, 1H), 3.69 (dd, *J* = 7.5 and 13.5 Hz, 1H), 2.60−2.65 (m, 1H), 2.27−2.34 (m, 1H), 2.28 (t, *J* = 7.5 Hz, 2H), 2.00−2.18 (m, 5H), 1.99 (s, 3H), 1.67 (quint, *J* = 7.5 Hz, 2H), 1.60 (dt, *J* = 4.6 and 14.2 Hz, 1H), 1.16−1.27 (m, 11H), 1.05 (s, 9H), 0.88 (s, 9H), 0.87 (t, *J* = 7.1 Hz, 3H), 0.00 (s, 3H), −0.01 (s, 3H); ^{13}C NMR δ up 173.5, 170.1, 134.3, 134.2, 60.2, 44.1, 33.6, 32.2, 32.0, 28.3, 27.4, 26.6, 24.7, 22.5, 19.1, 18.0; down 135.8, 132.8, 131.2, 129.6, 129.5, 127.5, 125.0, 76.9, 76.5, 74.1, 52.8, 49.2, 26.9, 25.8, 21.2, 14.2, 14.1, −4.4, −4.8; HRMS calcd for $C_{46}H_{72}O_6Si_2Na$ (M + Na) 799.4765, found 799.4803. This was followed by the alcohol **30** (197 mg, 31% yield from **9**) as a colorless oil, TLC R_f = 0.30 (petroleum ether/MTBE = 80/20); $[\alpha]^{20}_D$ = −29.5° (*c* = 3.94, $CHCl_3$); ES MS *m*/*z* (rel intensity) 757 (M^+ + Na, 30); IR (film) 3456, 2956, 2929, 2857, 1737, 1472, 1428, 1374, 1252, 1112, 1060, 836, 775, 740, 702 cm^{-1}; ^1H NMR δ 7.64−7.68 (m, 4H), 7.34−7.44 (m, 6H), 5.44 (m, 1H), 5.29−5.37 (m, 1H), 5.21−5.24 (m, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.93−3.99 (m, 2H), 3.74 (dd, *J* = 7.4 and 13.4 Hz, 1H), 2.66 (brs, 1H), 2.30 (t, *J* = 7.5 Hz, 2H), 2.12−2.23 (m, 4H), 2.07 (q, *J* = 7.3 Hz, 2H), 1.69 (quint, *J* = 7.4 Hz, 2H), 1.63 (dt, *J* = 4.6 and 14.3 Hz, 1H), 1.57 (brs, 1H), 1.21−1.35 (m, 11H), 1.07 (s, 9H), 0.90 (s, 9H), 0.88 (t, *J* = 7.1 Hz, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR δ up 173.6, 134.4, 134.3, 60.2, 44.0, 35.1, 33.6, 32.0, 28.4, 27.5, 26.6, 24.7, 22.6, 19.1, 18.0; down 135.9, 135.8, 134.2, 131.5, 129.4, 129.0, 127.5, 127.4, 125.8, 77.1, 76.5, 71.8, 52.7, 49.1, 26.9, 25.8, 14.2, 14.1, −4.4, −4.8; HRMS calcd for $C_{44}H_{70}O_5Si_2Na$ (M + Na) 757.4660, found 757.4683. The ee of the alcohol **30** was determined to be >99% by HPLC with a CHIRALCEL OD column (Daicel Chemical Industries Ltd.) using hexanes/2-propanol (150/1, v/v) as a mobile phase; flow rate: 1 mL/min; monitoring at 254 nm. Alcohol **30** had a retention time of 9 min. Its enantiomer, alcohol **32** (see below), had a retention time of 13 min.

Alcohol 32. To a stirred solution of the acetate **31** (271 mg, 0.35 mmol) in EtOH (35 mL) was added K_2CO_3 (240 mg, 1.74 mmol) at room temperature. The reaction mixture was stirred for 16 h and was then concentrated. The residue was partitioned between CH_2Cl_2 and, sequentially, 5% HCl aqeouse solution and brine. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to provide the alcohol **32** (231 mg, 90% yield from **31**) as a colorless oil. The data of TLC, MS, IR, ^1H and ^{13}C NMR of alcohol **32** were the same as the alcohol **30**. HRMS calcd for

$C_{44}H_{70}O_5Si_2Na$ (M + Na) 757.4660, found 757.4682. The ee of the alcohol **32** was determined to be 80% by HPLC with a CHIRALCEL OD column (see above).

Alcohols 30 and 33. To a stirred solution of the alcohol **30** (197 mg, 0.27 mmol) in CH_2Cl_2 (20 mL) was added Dess−Martin periodinane (225 mg, 0.54 mmol) at room temperature under N_2. The reaction mixture was stirred for 2 h and was then concentrated. The residue was filtered through a short pad of silica gel, and the filter cake was washed with petroleum ether/MTBE (1/1, v/v). Concentration of the filtrate gave a residue which was used in the next step without further purification.

To a stirred solution of the residue in MeOH (20 mL) was added $NaBH_4$ (103 mg, 2.71 mmol) at 0 °C. After an additional 30 min, the reaction mixture was partitioned between EtOAc and, sequentially, 5% aqueous HCl and brine. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to produce the alcohol **30** (82 mg, 42% yield from **30**) as a colorless oil. This was followed by the alcohol **33** (80 mg, 41% yield from **30**) as a colorless oil, TLC R_f = 0.29 (petroleum ether/MTBE = 80/20); $[\alpha]^{20}_D$ = −26.4° (c = 3.48, $CHCl_3$); IR (film) 3464, 2956, 2929, 2857, 1731, 1472, 1428, 1374, 1253, 1111, 1061, 836, 775, 740, 702 cm^{-1}; ^1H NMR δ 7.64−7.69 (m, 4H), 7.35−7.44 (m, 6H), 5.44−5.50 (m, 1H), 5.30−5.36 (m, 1H), 5.13−5.24 (m, 2H), 4.12 (q, J = 7.1 Hz, 2H), 3.93−3.96 (m, 2H), 3.72 (dd, J = 7.5 and 13.6 Hz, 1H), 2.64 (t, J = 6.7 Hz, 1H), 2.30 (t, J = 7.5 Hz, 2H), 2.12−2.25 (m, 4H), 2.05 (q, J = 7.5 Hz, 2H), 1.69 (quint, J = 7.4 Hz, 2H), 1.64 (dt, J = 4.9 and 14.3 Hz, 1H), 1.41 (d, J = 2.9 Hz, 1H), 1.23−1.28 (m, 11H), 1.07 (s, 9H), 0.90 (s, 9H), 0.88 (t, J = 7.1 Hz, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR δ up 173.6, 134.4, 134.3, 60.2, 44.1, 35.1, 33.6, 32.0, 28.4, 27.4, 26.7, 24.7, 22.6, 19.1, 18.0; down 135.8, 134.3, 131.4, 129.7, 129.5, 129.4, 127.4, 125.8, 77.2, 76.5, 72.2, 52.8, 49.1, 26.9, 25.8, 14.2, 14.1, −4.4, −4.8; HRMS calcd for $C_{44}H_{70}O_5Si_2Na$ (M + Na) 757.4660, found 757.4675.

Alcohols 32 and 34. The reactions were performed with the alcohol **32** (231 mg, 0.31 mmol), Dess−Martin periodinane (264 mg, 0.63 mmol), CH_2Cl_2 (25 mL); $NaBH_4$ (119 mg, 3.13 mmol), and MeOH (30 mL) in the same manner as described for the preparation of the alcohols **30** and **33** to afford the alcohol **32** (99 mg, 43% yield from **32**) as a colorless oil and the alcohol **34** (97 mg, 42% yield from **32**) as a colorless oil. The data of TLC, IR, ^1H and ^{13}C NMR of the alcohol **34** were the same as the alcohol **33**. HRMS calcd for $C_{44}H_{70}O_5Si_2Na$ (M + Na) 757.4660, found 757.4698. The ee of the alcohol **34** was determined to be 80% by HPLC with a CHIRALCEL OD column (Daicel Chemical Industries Ltd.) using hexanes/2-propanol (150/1, v/v) as a mobile phase; flow rate: 1 mL/min; monitoring at 254 nm. Alcohol **34** had a retention time of 9 min. Its enantiomer, alcohol **33** (see above), had a retention time of 11 min.

Further Resolution of Alcohol 32. The reaction was performed with the enantiomerically enriched alcohol **32** (99 mg, 0.14 mmol, 80% ee), Amano lipase AK (396 mg, 4 mass equiv), and vinyl acetate (2.3 mL) in the same manner as described for the preparation of the alcohol **30** and acetate **31** to provide the alcohol (35 mg, 35% yield from **32**) and the enantiomerically pure acetate **31** (65 mg, 62% yield from **32**) as a colorless oil, $[\alpha]^{20}_D$ = +42.1° (c = 2.17, $CHCl_3$). The deacetylation was performed on the enantiomerically pure acetate **31** (65 mg, 0.084 mmol), K_2CO_3 (58 mg, 0.42 mmol), and EtOH (8 mL) in the same manner as described for the preparation of the alcohol **32** to give the enantiomerically pure alcohol **32** (56 mg, 91% yield from **31**) as a colorless oil, $[\alpha]^{20}_D$ = +30.2° (c = 2.80, $CHCl_3$). The ee of the enantiomerically pure alcohol **32** was determined to be >99% by HPLC with a CHIRALCEL OD column (see above).

Further Resolution of Alcohol 34. The reaction was performed with the enantiomerically rich alcohol **34** (97 mg, 0.13 mmol, 80% ee), Amano lipase AK (388 mg, 4 mass equiv), and vinyl acetate (2.2 mL) in the same manner as described for the preparation of the alcohol **30** and acetate **31** to furnish the acetate (29 mg, 28% yield from **34**) and the enantiomerically pure alcohol **34** (50 mg, 52% yield from **34**) as a colorless oil, $[\alpha]^{20}_D$ = +26.6° (c = 2.50, $CHCl_3$). The ee of the enantiomerically pure alcohol **34** was determined to be >99% by HPLC with a CHIRALCEL OD column (see above).

Racemic Ketone 35 and (*S*)-BINAL-H Reduction of 35. To a stirred solution of racemic alcohol **9** (12.5 mg, 0.017 mmol) in CH_2Cl_2 (3 mL) was added Dess−Martin periodinane (14 mg, 0.033 mmol) at room temperature under N_2. After an additional 1 h, the reaction mixture was filtered through a short pad of silica gel and the filter cake was washed with petroleum ether/MTBE (1/1, v/v). Concentration of the filtrate gave a residue which was chromatographed to afford the racemic ketone **35** (11 mg, 88% yield from **9**).

To a stirred 1 M solution of $LiAlH_4$ in THF (51 μL, 0.051 mmol) was added a 2 M solution of EtOH in THF (25.5 μL, 0.051 mmol) over a period of 5 min followed by a solution of (*S*)−(−)-1,1′-bi-2-naphthol (14.6 mg, 0.051 mmol) in THF (0.5 mL) at room temperature under N_2. After an additional 0.5 h, a solution of the racemic ketone **35** (11 mg, 0.015 mmol) in THF (0.5 mL) was added at −78 °C. After an additional 5 h at −78 °C, the reaction mixture was partitioned between EtOAc and, sequentially, saturated aqueous NH_4Cl and brine. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield the alcohols **30** and **32** (3.7 mg, 30% yield from **35**) as a inseparable mixture. This was followed by the alcohols **33** and **34** (3 mg, 24% yield from **35**) as a inseparable mixture. The ee of the alcohols **30** and **32** was determined to be 17% by HPLC with a CHIRALCEL OD column (see above).

Triol 36. To a stirred solution of the alcohol **30** (82 mg, 0.11 mmol) in THF (11 mL) was added a 1 M solution of tetrabutylammonium fluoride (TBAF) in THF (0.56 mL, 0.56 mmol) at room temperature under N_2. After an additional 40 h, the reaction mixture was partitioned between EtOAc and, sequentially, saturated aqueous NH_4Cl and brine. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to furnish the triol **36** (35.5 mg, 83% yield from **30**) as a colorless oil, TLC R_f = 0.31 (petroleum ether/acetone = 1/1); $[\alpha]^{20}_D$ = −8.2° (c = 1.10, $CHCl_3$); IR (film) 3355, 2926, 2856, 1735, 1459, 1375, 1153, 1033, 974 cm^{-1}; ^1H NMR δ 5.57 (dd, J = 6.1 and 15.4 Hz, 1H), 5.37−5.52 (m, 3H), 4.11 (q, J = 7.1 Hz, 2H), 4.09−4.11 (m, 1H), 3.92−4.01 (m, 2H), 2.71−2.76 (m, 2H), 2.40 (quint, J = 7.4 Hz, 2H), 2.03−2.33 (m, 8H), 1.68 (quint, J = 7.4 Hz, 2H), 1.62 (dt, J = 3.3 and 14.7 Hz, 1H), 1.19−1.30 (m, 11H), 0.86 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ up 173.9, 60.4, 42.4, 35.2, 33.7, 32.1, 29.0, 27.9, 26.7, 24.7, 22.6; down 134.7, 131.6, 128.9, 125.7, 76.8, 76.4, 71.9, 53.5, 50.4, 14.2, 14.1; HRMS calcd for $C_{22}H_{38}O_5Na$ (M + Na) 405.2618, found 405.2607.

Triol 37. The reaction was performed with the alcohol **33** (80 mg, 0.11 mmol), a 1 M solution of TBAF in THF (0.55 mL, 0.55 mmol), and THF (11 mL) in the same manner as described for the preparation of the triol **36** to give the triol **37** (36 mg, 87% yield from **33**) as a colorless oil, TLC R_f = 0.29 (petroleum ether/acetone = 1/1); $[\alpha]^{20}_D$ = −23.1° (c = 1.50, $CHCl_3$); IR (film) 3360, 2927, 2857, 1735, 1446, 1374, 1312, 1193, 1063, 972 cm^{-1}; ^1H NMR δ 5.55 (dd, J = 6.9 and 15.2 Hz, 1H), 5.36−5.51 (m, 3H), 4.11 (q, J = 7.1 Hz, 2H), 4.06−4.10 (m, 1H), 3.93−3.96 (m, 2H), 3.03 (brs, 3H), 2.72 (dd, J = 8.8 and 12.5 Hz, 1H), 2.31−2.45 (m, 2H), 2.29 (t, J = 7.5 Hz, 2H), 2.18−2.26 (m, 1H), 2.07 (q, J = 7.2 Hz, 2H), 2.02−2.05 (m, 1H), 1.68 (quint, J = 7.4 Hz, 2H), 1.61 (d, J = 14.4 Hz, 1H), 1.16−1.30 (m, 11H), 0.86 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ up 173.9, 60.4, 42.3, 35.3, 33.7, 32.1, 29.0, 27.9, 26.7, 24.7, 22.6; down 135.0, 131.5, 130.0, 125.7, 76.6, 76.3, 72.4, 53.5, 50.5, 14.2, 14.1; HRMS calcd for $C_{22}H_{38}O_5Na$ (M + Na) 405.2618, found 405.2613.

Triol 38. The reaction was performed with the alcohol **32** (56 mg, 0.076 mmol), a 1 M solution of TBAF in THF (0.38 mL, 0.38 mmol), and THF (7.6 mL) in the same manner as described for the preparation of the triol **36** to give the triol **38** (24.5 mg, 84% yield from **32**) as a colorless oil, $[\alpha]^{20}_D$ = +8.5° (c = 1.20, $CHCl_3$). The data of TLC, IR, ^1H and ^{13}C NMR of the triol **38** were the same as the triol **36**. HRMS calcd for $C_{22}H_{38}O_5Na$ (M + Na) 405.2618, found 405.2626.

Triol 39. The reaction was performed with the alcohol **34** (50 mg, 0.068 mmol), a 1 M solution of TBAF in THF (0.34 mL, 0.34 mmol), and THF (6.8 mL) in the same manner as described for the preparation of the triol **36** to give the triol **39** (22.5 mg, 87% yield from **34**) as a colorless oil, $[\alpha]^{20}_D$ = +23.2° (*c* = 1.13, $CHCl_3$). The data of TLC, IR, ^{1}H and ^{13}C NMR of the triol **39** were the same as the triol **37**. HRMS calcd for $C_{22}H_{38}O_5Na$ (M + Na) 405.2618, found 405.2637.

8-F_{2t}-Isoprostane (5). To a stirred solution of the triol **36** (22 mg, 0.058 mmol) in THF/H_2O (1:1, 2.4 mL) was added LiOH·H_2O (24 mg, 0.57 mmol) at room temperature. After an additional 2 h, the reaction mixture was acidified to pH 4 by adding 0.5% aqueous HCl at 0 °C. After addition of NaCl (1 g), the mixture was extracted with $CHCl_3$. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to afford 8-F_{2t}-isoprostane (**5**) (19.5 mg, 96% yield from **36**) as a colorless oil, TLC R_f = 0.33 (EtOAc/MeOH/AcOH = 80/20/0.1); $[\alpha]^{20}_D$ = −9.2° (*c* = 0.98, MeOH); IR (film) 3338, 2927, 2856, 1708, 1407, 1247, 1064, 973 cm^{-1}; ^{1}H NMR (CD_3OD) δ 5.48 (dd, *J* = 5.8 and 15.4 Hz, 1H), 5.34−5.42 (m, 3H), 3.98 (q, *J* = 6.1 Hz, 1H), 3.83 (dt, *J* = 4.2 and 6.7 Hz, 1H), 3.73−3.78 (m, 1H), 2.57 (dt, *J* = 3.9 and 12.4 Hz, 1H), 2.39 (quint, *J* = 7.0 Hz, 1H), 2.14−2.26 (m, 4H), 2.03 (q, *J* = 7.2 Hz, 2H), 1.91−1.95 (m, 1H), 1.59 (quint, *J* = 7.4 Hz, 2H), 1.45 (dt, *J* = 5.2 and 14.2 Hz, 1H), 1.18−1.35 (m, 8H), 0.83 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR δ up 177.9, 43.9, 36.6, 34.6, 33.5, 29.8, 29.1, 28.0, 26.2, 23.9; down 136.0, 131.8, 130.1, 127.6, 76.9, 76.6, 73.3, 54.0, 50.6, 14.7; HRMS calcd for $C_{20}H_{34}O_5Na$ (M + Na) 377.2305, found 377.2296.

8-*epi*-8-F_{2t}-Isoprostane (6). The reaction was performed with the triol **37** (30 mg, 0.079 mmol), LiOH·H_2O (33 mg, 0.79 mmol), and THF/H_2O (1:1, 3.2 mL) in the same manner as described for the preparation of 8-F_{2t}-isoprostane (**5**) to give 8-*epi*-8-F_{2t}-isoprostane (**6**) (27 mg, 97% yield from **37**) as a colorless oil, $[\alpha]^{20}_D$ = −14.4° (*c* = 1.35, MeOH); IR (film) 3346, 2926, 2858, 1709, 1410, 1242, 1064, 972 cm^{-1}; ^{1}H NMR (CD_3OD) δ 5.46 (dd, *J* = 6.6 and 15.3 Hz, 1H), 5.34−5.41 (m, 3H), 3.97 (q, *J* = 6.6 Hz, 1H), 3.85 (dt, *J* = 4.3 and 6.6 Hz, 1H), 3.74−3.79 (m, 1H), 2.57 (dt, *J* = 3.6 and 12.9 Hz, 1H), 2.40 (quint, *J* = 7.7 Hz, 1H), 2.13−2.29 (m, 4H), 2.05 (q, *J* = 7.1 Hz, 2H), 1.93−1.95 (m, 1H), 1.61 (quint, *J* = 7.4 Hz, 2H), 1.47 (dt, *J* = 5.0 and 14.1 Hz, 1H), 1.18−1.35 (m, 8H), 0.85 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR δ up 177.7, 43.8, 36.5, 34.5, 33.5, 30.0, 29.0, 28.0, 26.1, 23.9; down 136.1, 131.8, 131.1, 127.5, 77.0, 76.7, 73.8, 54.3, 50.6, 14.7; HRMS calcd for $C_{20}H_{34}O_5Na$ (M + Na) 377.2305, found 377.2304.

***ent*-8-*epi*-8-F_{2t}-Isoprostane (7).** The reaction was performed with the triol **39** (22.5 mg, 0.059 mmol), LiOH·H_2O (25 mg, 0.59 mmol), and THF/H_2O (1:1, 2.4 mL) in the same manner as described for the preparation of 8-F_{2t}-isoprostane (**5**) to give *ent*-8-*epi*-8-F_{2t}-isoprostane (**7**) (19 mg, 91% yield from **39**) as a colorless oil, $[\alpha]^{20}_D$ = +14.5° (*c* = 0.95, MeOH). The data of TLC, IR, ^{1}H and ^{13}C NMR of *ent*-8-*epi*-8-F_{2t}-isoprostane (**7**) were the same as 8-*epi*-8-F_{2t}-isoprostane (**6**). HRMS calcd for $C_{20}H_{34}O_5Na$ (M + Na) 377.2305, found 377.2295.

***ent*-8-F_{2t}-Isoprostane (8).** The reaction was performed with the triol **38** (24.5 mg, 0.064 mmol), LiOH·H_2O (27 mg, 0.64 mmol), and THF/H_2O (1:1, 2.6 mL) in the same manner as described for the preparation of 8-F_{2t}-isoprostane (**5**) to give *ent*-8-F_{2t}-isoprostane (**8**) (21 mg, 93% yield from **38**) as a colorless oil, $[\alpha]^{20}_D$ = +9.3° (*c* = 1.05, MeOH). The data of TLC, IR, ^{1}H and ^{13}C NMR of *ent*-8-F_{2t}-isoprostane (**8**) were the same as 8-F_{2t}-isoprostane (**5**). HRMS calcd for $C_{20}H_{34}O_5Na$ (M + Na) 377.2305, found 377.2302.

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Supporting Information Available: Copies of the ^{1}H and ^{13}C NMR spectra for compounds **5**−**14**, **17**, **18**, **20**, **22**, **23**, **25**−**34**, **36**−**39** and a copy of the ^{1}H NMR spectrum for compound **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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