J|A|C|S
ARTICLES
Published on Web 10/11/2002

Synthesis of the Eight Enantiomerically Pure Diastereomers of the 12-F_2-Isoprostanes

Douglass F. Taber,* Ming Xu, and John C. Hartnett[1]

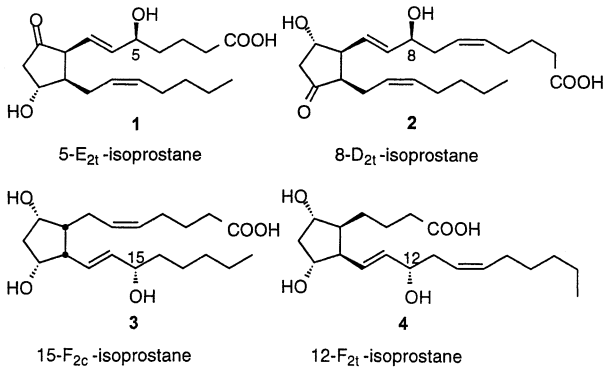
Contribution from the Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716

Received June 7, 2002

Abstract: Syntheses of the eight enantiomerically pure diastereomers of the 12-F_2-isoprostanes (**4**−**11**) are described. The key steps included rhodium-mediated intramolecular cyclopropanation and enzymatic resolution of the racemic diol **12**.

Introduction

The isoprostanes (e.g. **1**−**4**), a new family of prostaglandin-like compounds, were recently discovered to be produced in vivo in humans, independent of the cyclooxygenase enzymes, by free radical mediated oxidation of membrane-bound arachidonic acid.[2] There are D-ring, E-ring, and F-ring isoprostanes. Four different regioisomers of each of these classes of isoprostanes are formed.[3] Interestingly, levels of F_2-isoprostanes (**1**−**4**) in normal human biological fluids exceed levels of prostaglandins. Several synthesis routes to particular isoprostanes have been reported.[4−10] Since we are interested in the physiological activity of each of the isoprostanes,[11] we thought it more attractive to prepare, through a common advanced intermediate, the several diastereomers of an isoprostane family. Herein, we report the preparation of all eight of the enantiomerically pure diastereomers of the 12-F_2-isoprostanes (**4**−**11**) from the racemic diol **12** (Scheme 1). This is the first preparation of the 12-F_{2c} series.



Results and Discussion

The 12-F_2-isoprostanes were first identified in human plasma samples by Roberts.[11] To screen the physiological activity of the eight enantiomerically pure diastereomers of the 12-F_2-isoprostanes, it will be necessary to individually prepare each of them. One synthesis, specifically of 12-F_{2t}-isoprostane **4**, was reported by Rokach in 1998.[9]

It seemed more attractive to develop a stereodivergent synthesis scheme toward these targets from a common intermediate, rather than design different syntheses of each. We envisioned (Scheme 1) that the eight target molecules could be prepared from the same racemic intermediate **12**. The two enantiomers of **12**, which could be obtained by enzymatic resolution,[12] could each be converted to two of the four

* To whom correspondence should be addressed. E-mail taberdf@udel.edu.

(1) Undergraduate research participant, University of Delaware.

(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.; Kato. T.; Takahashi, K.; Badr, K. F.; Roberts, L. J., II; Burk, R. F. *J. Clin. Invest.* **1992**, *90*, 2502. (c) Morrow, J. D.; Awad, J. A.; Boss, H. J.; Blair, J. A.; Roberts, L. J., II. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 10721. (d) 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.

(3) 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.

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

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

(6) For synthetic routes to 8-F_{2t}-isoprostane, see: (a) Taber, D. F.; Jiang, Q. *J. Org. Chem.* **2001**, *66*, 1876. (b) Adiyaman, M.; Li, H.; Lawson, J. A.; Hwang, S. W.; Khanapure, S. P.; FitzGerald, G. A.; Rokach, J. *Tetrahedron Lett.* **1997**, *38*, 3339.

(7) 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. P.; 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. (e) Durand, T.; Guy, A.; Vidal, J.-F.; Rossi, J.-C. *J. Org. Chem.* **2002**, *67*, 3615.

(8) 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. (d) Lai, S.; Lee, D.; Sun U, J. Cha, J. K. *J. Org. Chem.* **1999**, *64*, 7213.

(9) For synthetic routes to 12-F_{2t}-isoprostane, see: (a) 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. (b) Hwang, S. W.; Adiyaman, M.; Lawson, J. A.; FitzGerald, G. A.; Rokach, J. *Tetrahedron Lett.* **1999**, *40*, 6167.

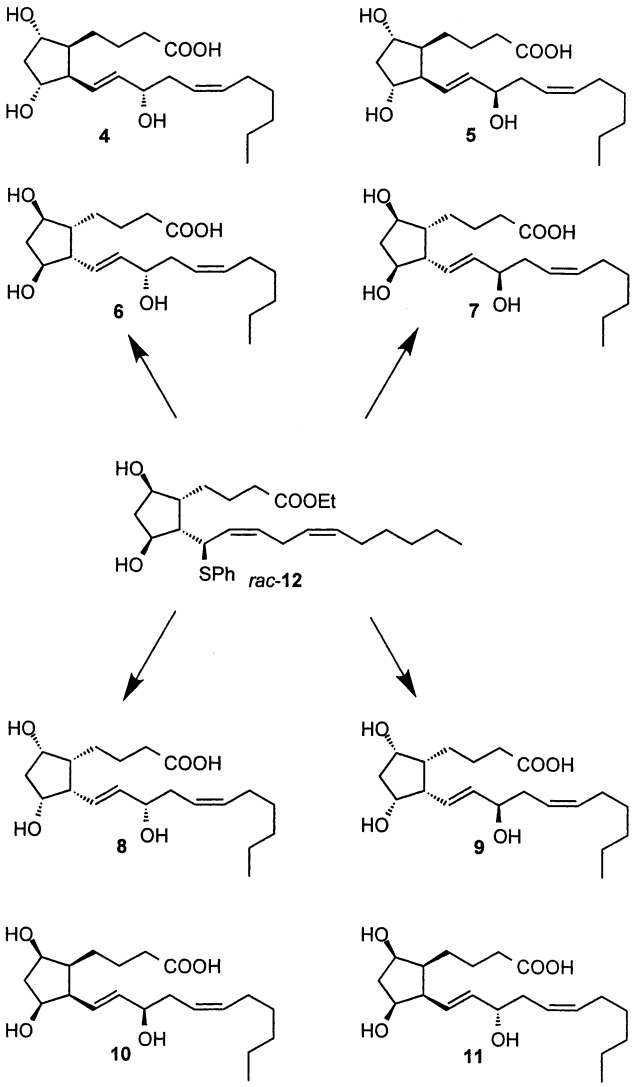
(10) For a synthetic route to 15-E_{2t}-isoprostane, see: Taber, D. F.; Hoerrner, R. S. *J. Org. Chem.* **1992**, *57*, 441.

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

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

10.1021/ja020816v CCC: $22.00

Scheme 1

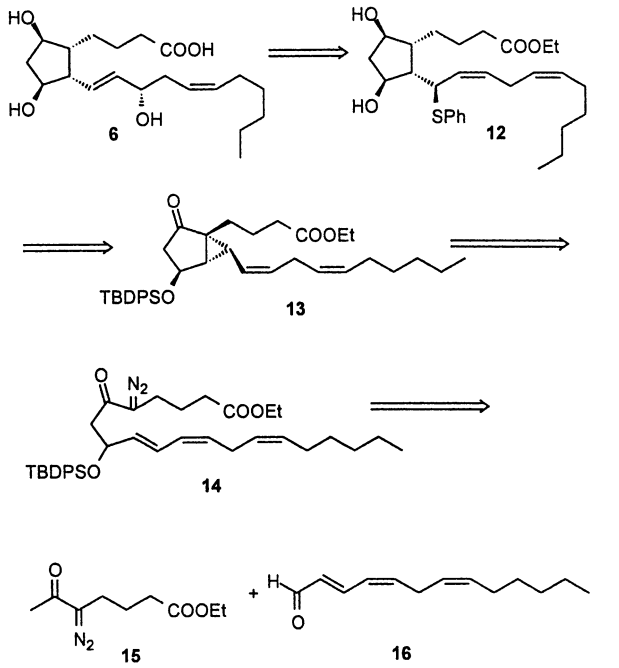


enantiomerically pure diastereomers **4**−**7**. Mitsunobu inversion[13] of the enantiomers of **12** would lead to the four enantiomerically pure cis isomers **8**−**11**.

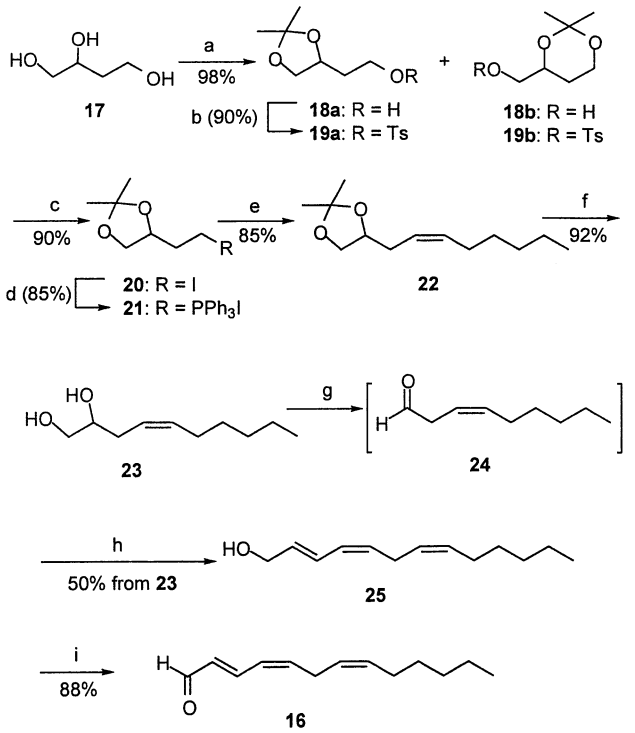
Pursuing the retrosynthetic analysis (Scheme 2), the key diol **12** could be generated by kinetic opening of the activated bicyclic ketone **13** with thiophenol and $BF_3{\cdot}OEt_2$. The bicyclic ketone **13** could be constructed by rhodium-mediated cyclopropanation of the diazoketone **14**. The aldol condensation of diazoketone **15** and aldehyde **16** would provide the desired diazoketone **14**.

The aldehyde **16**, a natural odorant,[14] was prepared from the commercially available 1,2,4-butanetriol **17** (Scheme 3). On exposure to acetone, **17** was converted to **18a** and **18b** (ratio **18a**/**18b** = 3:1) as a mixture, which was further transferred to the mixture of *p*-toluenesulfonates **19a** and **19b**. These were tedious to separate by column chromatography, especially on a large scale. Fortunately, on exposure to NaI in acetone, both **19a** and **19b** were converted smoothly to **20**. We also found that the ratio of **18a** to **18b** increased when the mixture was

Scheme 2



Scheme 3 [a]



[a] Reagents and conditions: (a) acetone, TsOH; (b) TsCl, Et_3N, CH_2Cl_2; (c) NaI, Cu, acetone; (d) PPh_3, $NaHCO_3$, CH_3CN; (e) KHMDS, THF, −78 °C, hexanal; (f) 80% HOAc (aq), room temp; (g) $NaIO_4/SiO_2$, CH_2Cl_2/H_2O, room temp; (h) $HOCH_2CH{=}CHCH_2PPh_3Br$, KHMDS, THF/CH_2Cl_2, −78 °C; (i) Dess−Martin periodinane, CH_2Cl_2, room temp.

stored at 5 °C for several weeks. Using this approach, substantial quantities of the valuable phosphonium salt **21**[15] could be conveniently prepared.

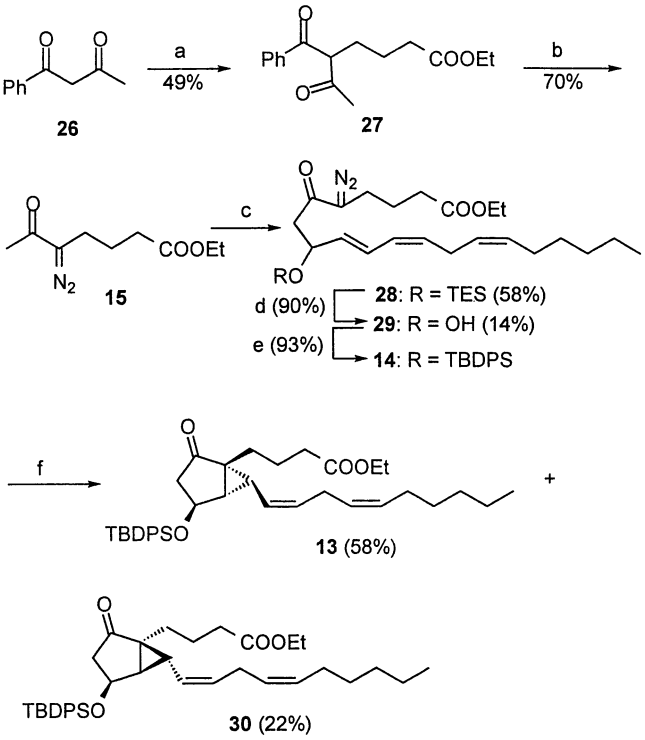
Wittig coupling of **21** with hexanal resulted in the *cis*-alkene **22**, which was hydrolyzed with 80% aqueous acetic acid to

(13) (a) Mitsunobu, O. *Synthesis* **1981**, 1 and references therein. (b) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017.

(14) For alternative syntheses of **16**, see: Blank, I.; Lin, J.; Vera, F. A.; Welti, D. H.; Fay, L. B. *J. Agric. Food. Chem.* **2001**, *49*, 2959 and references therein.

(15) Mosset, P.; Pointeau, P.; Aubert, F.; Lellouche, J. P.; Beaucourt, J. P.; Gree, R. *Bull. Soc. Chim. Fr.* **1990**, *127*, 298.

Scheme 4 [a]



[a] Reagents and conditions: (a) K_2CO_3, toluene, TBABr, ethyl 4-bromobutyrate, 60 °C; (b) p-NBSA, DBU, CH_2Cl_2, 0 °C; (c) KHMDS, toluene, −78 °C, **16**, (TES)Cl; (d) TBAF, THF, 0 °C; (e) (TBDPS)Cl, imidazole, DMAP, CH_2Cl_2, room temp; (f) Rh_2 (Oct) $_4$, toluene/ CH_2Cl_2, −20 °C.

Table 1. $Rh_2(Oct)_4$ Catalyzed Cyclization of Diazoketone **14**[a]

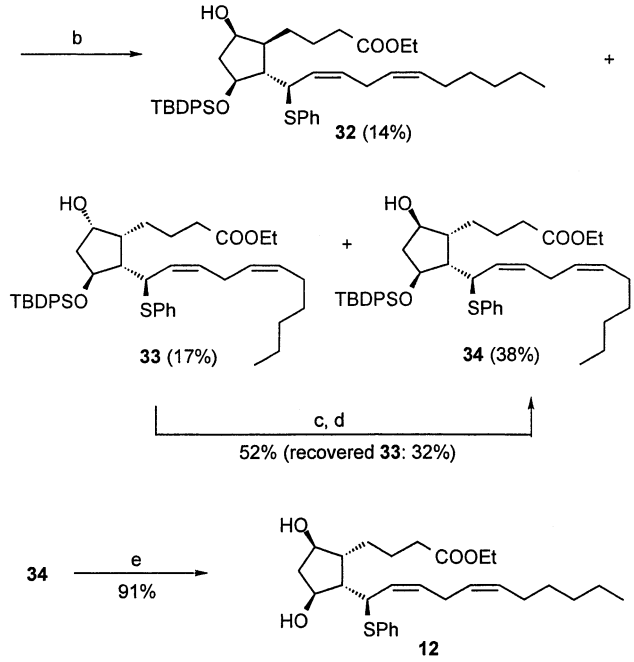
entry	solvent, concn (M)	temp (°C)	total yield[b] (**13** and **30**) (%)	ratio **13**/**30**
1	CH_2Cl_2, 0.01	0	48	3.0:1
2	CH_2Cl_2, 0.02	0	52	2.8:1
3	CH_2Cl_2, 0.03	0	63	3.0:1
4[c]	CH_2Cl_2, 0.03	0	36	3.5:1
5	CH_2Cl_2, 0.1	0	58	2.9:1
6	CH_2Cl_2, 0.03	rt	56	2.5:1
7	CH_2Cl_2, 0.1	78	61	3.3:1
8	CH_2Cl_2, 0.06	20	72	2.8:1
9	toluene, 0.06	20	62	2.9:1
10	hexane/CH_2Cl_2, 0.05	20	53	3.5:1
11	toluene/CH_2Cl_2, 0.05	20	80	2.7:1
12[d]	toluene/CH_2Cl_2, 0.05	20	73	3.0:1
13[e]	toluene/CH_2Cl_2, 0.05	20 to room temp	40[f]	2.8:1

[a] Unless otherwise indicated, all reactions were carried out with 1% of $Rh_2(Oct)_4$. The solution of $Rh_2(Oct)_4$ (3 mL/mg in CH_2Cl_2) was added to a solution of **14** over 1 h. [b] Isolated yield. [c] A solution of **14** in CH_2Cl_2 was added to a solution of $Rh_2(Oct)_4$ in CH_2Cl_2. [d] 0.5% of $Rh_2(Oct)_4$ was used. [e] 0.2% of $Rh_2(Oct)_4$ was used. [f] With 75% conversion.

provide the diol **23**. Expecting the β,γ-unsaturated aldehyde **24** to be unstable, we carried the crude product from the Vo−Quang periodate cleavage[16] directly into the modified Wittig reaction,[17] to afford the trienol **25**. Oxidation of the trienol **25** with the Dess−Martin periodinane[18] provided the aldehyde.

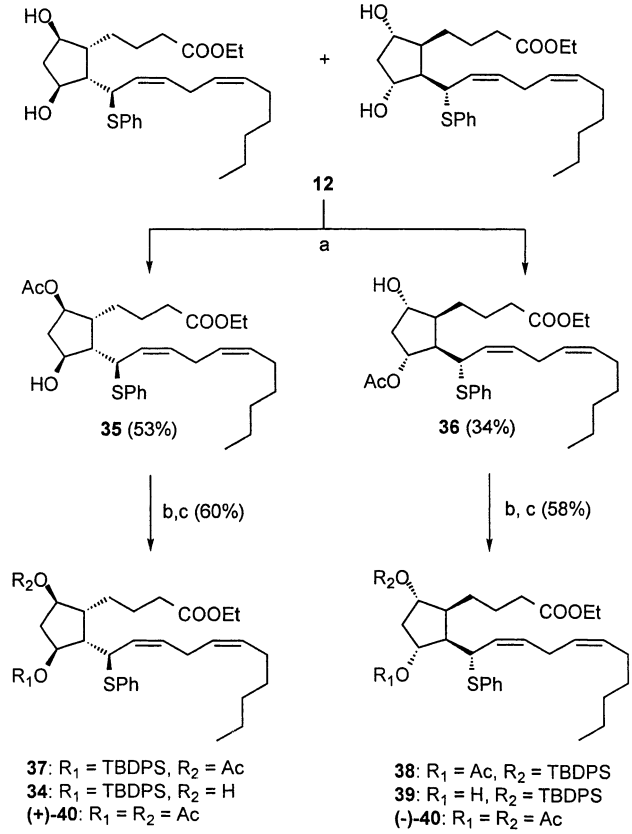
The diazoketone **15**[19] (Scheme 4) was prepared from the commercially available diketone **26** following the procedure we previously developed.[20] Alkylation of benzoylacetone **26** with ethyl 4-bromobutyrate gave the diketone **27**. The diazo transfer of **27** with *p*-nitrobenzenesulfonyl azide provided the diazoketone **15**.

Scheme 5 [a]



[a] Reagents and conditions: (a) PhSH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −30 °C, (b) $NaBH_4$, MeOH/ EtOH, 0 °C; (c) Dess−Martin periodinane, CH_2Cl_2, room temp; (d) $NaBH_4$, MeOH/EtOH, 0 °C; (e) TBAF, THF, 0 °C to room temp.

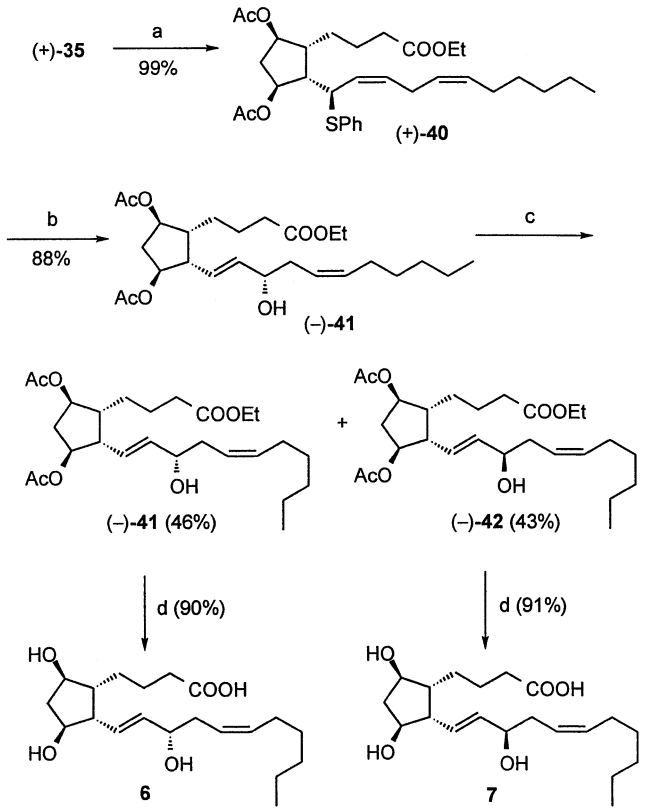
Scheme 6 [a]



[a] Reagents and conditions: (a) Amano lipase AK, vinyl acetate, 45 °C, 48 h; (b) (TBDPS)Cl, imidazole, DMAP, CH_2Cl_2, room temp; (c) K_2CO_3, EtOH, 60 °C.

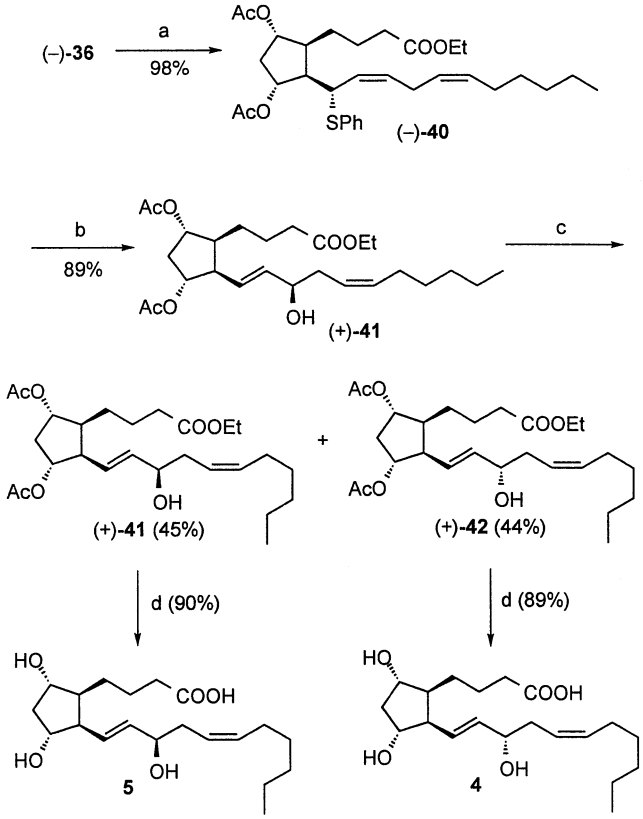
(16) Daumas, M.; Vo-Quang, Y.; Vo-Quang, L.; Le Goffic, F. *Synthesis* **1989**, 64.
(17) Hosoda, A.; Taguchi, T.; Kobayashi, Y. *Tetrahedron Lett.* **1987**, *28*, 65.
(18) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.
(19) Shinada, T.; Kawakami, T.; Sakai, H.; Takada, I.; Ohfune, Y. *Tetrahedron Lett.* **1998**, *39*, 3757. No preparation details or characterization data for diazoketone **15** were found in this reference.

Scheme 7 [a]



[a] Reagents and conditions: (a) Ac_2O, pyr. CH_2Cl_2, room temp; (b) (i) mCPBA, CH_2Cl_2, −78 °C; (ii) $(MeO)_3P$, EtOH, −78 °C to room temp; (c) (i)Dess−Martin periodinane, CH_2Cl_2, room temp; (ii) $NaBH_4$, EtOH, 0 °C; (d) LiOH, THF/H_2O, room temp.

Scheme 8 [a]



[a] Reagents and conditions: (a) Ac_2O, pyr. CH_2Cl_2, room temp; (b) (i) mCPBA, CH_2Cl_2, −78 °C; (ii) $(MeO)_3P$, EtOH, −78 °C to room temp; (c) (i)Dess−Martin periodinane, CH_2Cl_2, room temp; (ii) $NaBH_4$, EtOH, 0 °C; (d) LiOH, THF/H_2O, room temp.

Aldol condensation of the diazoketone **15** and the aldehyde **16** was carried out in toluene in the presence of triethylsilyl (TES) chloride with potassium bis(trimethylsilyl)amide at −78 °C.[7d] Apart from the desired TES-protected aldol **28** (58%), a small amount of the free aldol **29** (14%) was also found. Due to the instability of the TES group under the conditions for cyclopropane ring opening with thiophenol and $BF_3{\cdot}OEt_2$, we changed the protecting group to *t*-butyldiphenylsilyl (TBDPS), to give **14**.

The rhodium catalyzed cyclopropanation of diazoketone **14** afforded the bicyclic ketone **13** and its diastereomer **30**. To optimize this intramolecular cyclopropanation, we screened several variables of solvent, temperature, and catalyst loading. The results are summarized in Table 1. We found that the optimal concentration was around 0.05 M (entries 1−5). The yield decreased dramatically when the solution of **14** was added to the solution of $Rh_2(Oct)_4$ in CH_2Cl_2 (entry 4 vs 3). Temperature had a modest affect on the ratio of **13** to **30**. The mixed solvent of toluene and dichloromethane gave the best yield of **13** (58%) and **30** (22%) (entry 11). A catalyst loading of 0.5 mol % also gave good results (entry 12). The reaction did not go to completion with 0.2 mol % of $Rh_2(Oct)_4$, resulting in a low chemical yield (entry 13).

The structures of the bicyclic ketones **13** and **30** were assigned by comparing the ^1H and ^{13}C NMR spectra to those for analogous bicyclic ketones that were intermediates in the synthesis of the 5-F_{2t}-isoprostanes[4a] and the 8-F_{2t}-isoprostanes.[6a] In particular, the oxygenated methine of **13** (^{13}C δ 69.5; ^1H δ 4.47, d, J = 4.9 Hz) is congruent with the analogous 5-F_{2t}-isoprostane precursor (^{13}C δ 69.3; ^1H δ 4.46, d, J = 4.9 Hz) and 8-F_{2t}-isoprostane precursor (^{13}C δ 69.3; ^1H δ 4.46, d, J = 4.9 Hz), while the oxygenated methine of **30** (^{13}C δ 68.1; ^1H δ 4.60, dt, J = 5.1, 7.9 Hz) is quite different.

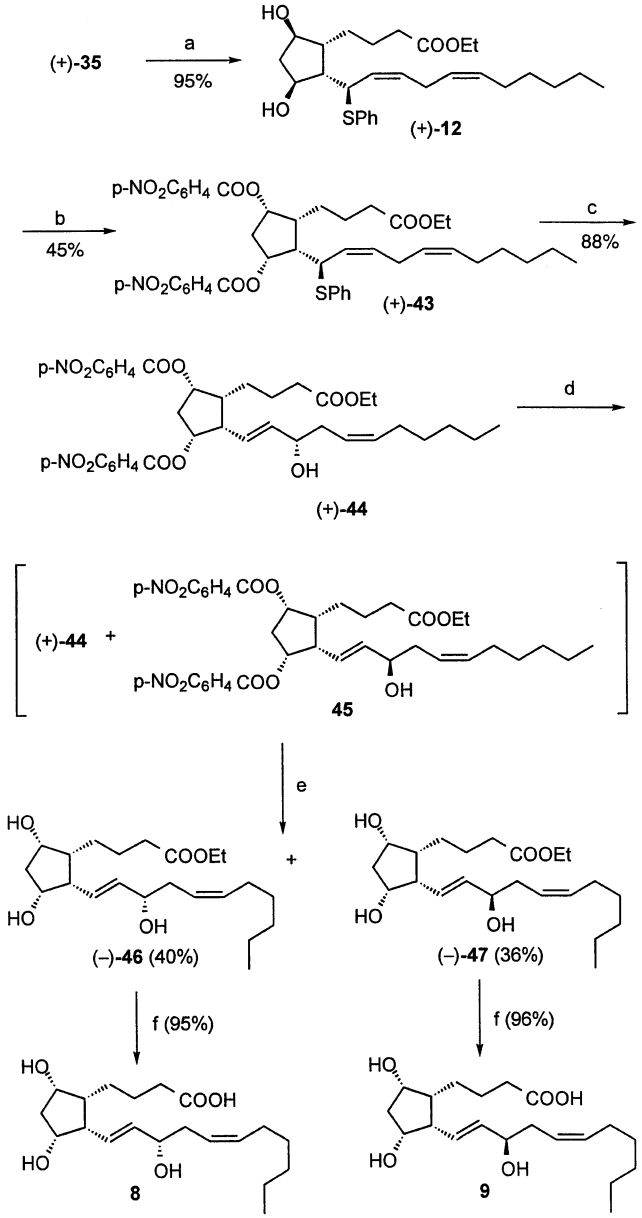
Initially, difficulties were encountered in the cyclopropane ring opening of **13** (Scheme 5) with thiophenol and $BF_3{\cdot}OEt_2$.[21] Low temperature (<−30 °C) or low concentration (<0.1 M) resulted in incomplete reaction. Warmer temperatures (0 °C) generated several side products. We found that treatment of **13** with 3 equiv of thiophenol and 4 equiv of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 (0.2 M) at −30 to −20 °C for 6 h gave smooth conversion to the ketone **31**, which was used directly in the subsequent reduction. We found that some deprotection of the TBDPS group occurred when the reduction was carried out in MeOH or EtOH over 1 h. Fortunately, this reaction could be finished in a mixed solvent system of MeOH/EtOH (1:1) with $NaBH_4$ within 20 min without causing silyl group deprotection.

The undesired alcohol **33** could be transferred to the mixture of **33** and **34** by oxidation with Dess−Martin periodinane,[18] followed by reduction. The relative configuration of **34** (^1H NMR δ 4.47, dt, J = 2.5, 6.4 Hz, 1H, 4.08, m, 1H) was also

(20) Taber, D. F.; Gleave, D. M.; Herr, R. J.; Moody, K.; Hennessy, M. *J. Org. Chem.* **1995**, *60*, 2283.

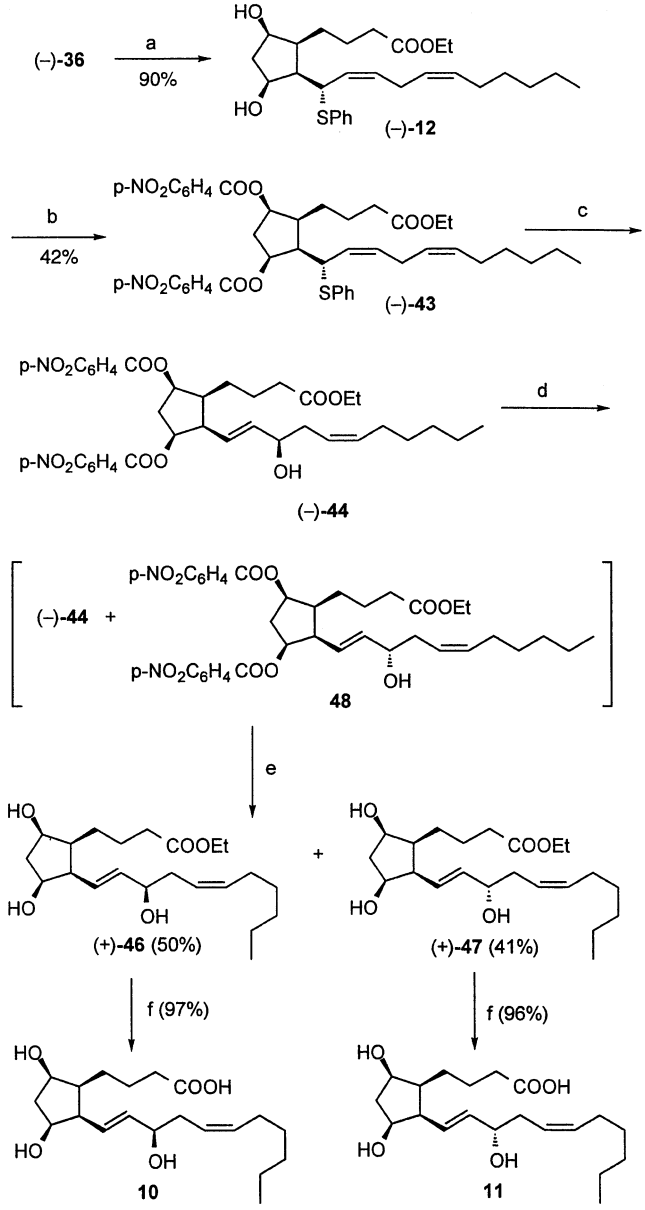
(21) From ketone **13** on, all reactions (except for the enzymatic resolution and the final hydrolysis steps) were run in the presence of a trace amount of methylene blue to inhibit isomerization of the side chain. For the use of methylene blue to stabilize 1,4-dienes, see: Taber, D. F.; Phillips, M. A.; Hubbard, W. C. *Prostaglandins* **1981**, *22*, 349.

Scheme 9 [a]



[a] Reagents and conditions: (a) K_2CO_3, EtOH, 60 °C, 1.5 h; (b) PPh_3, DEAD, *p*-$NO_2C_6H_4COOH$, benzene; (c) mCPBA, CH_2Cl_2, −78 °C; (ii) $(MeO)_3P$, EtOH, −78 °C to room temp; (d) (i) Dess−Martin periodinane, CH_2Cl_2, room temp; (ii) $NaBH_4$, EtOH, 0 °C; (e) K_2CO_3, EtOH; (f) LiOH, THF/H_2O, room temp.

Scheme 10 [a]



[a] Reagents and conditions: (a) K_2CO_3, EtOH, 60 °C, 1.5 h; (b) PPh_3, DEAD, *p*-$NO_2C_6H_4COOH$, benzene; (c) mCPBA, CH_2Cl_2, −78 °C; (ii) $(MeO)_3P$, EtOH, −78 °C to room temp; (d) (i) Dess−Martin periodinane, CH_2Cl_2, room temp; (ii) $NaBH_4$, EtOH, 0 °C; (e) K_2CO_3, EtOH; (f) LiOH, THF/H_2O, room temp.

assigned by comparing the ^1H and ^{13}C NMR spectra to those precursors for the 5-F_{2t}-isoprostanes (^1H NMR δ 4.44, dt, J = 3.6, 6.6 Hz, 1H, 4.08, m, 1H) and the 8-F_{2t}-isoprostanes (^1H NMR δ 4.48, dt, J = 2.5, 6.5 Hz, 1H, 4.05, m, 1H). Desilylation of **34** with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) provided the key intermediate **12**.

The racemic diol **12** (Scheme 6) when treated with Amano lipase AK in neat vinyl acetate at 40 °C for 48 h provided monoacetates (+)-**35** (53% yield) and (−)-**36** (34% yield) along with the diacetate (−)-**40** (8% yield with 86% ee). The monoacetates (+)-**35** and (−)-**36** were converted to their diacetates (+)-**40** and (−)-**40** in quantitative yield. Their ee values were determined to be 85 and >98% respectively, by chiral HPLC.[22] The enantiomerically enriched monoacetate (+)-**35** was hydrolyzed to diol **12** and subjected to enzyme resolution again to give the monoacetate (+)-**35** with >98% ee in 41% overall yield (82% of theoretical) from the racemic diol **12**.

The structure of the monoacetate (+)-**35** was established by conversion to **34** by protection followed by hydrolysis. The same transformation converted the monoacetate (−)-**36** to **39**. Since the same enzyme and a very similar substrate were employed in this resolution, the absolute configurations of (+)-**35** and (−)-**36** were assigned by analogy to our recent synthesis of the enantiomerically pure diastereomers of 15-F_{2t}-isoprostane.[7d]

With the requisite enantiomerically pure acetates (+)-**35** and (−)-**36** in hand, the four enantiomerically pure trans isomers

(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, hexane/2-PrOH = 9:1. Retention time: (+)-40, 6.3 min; (−)-40, 8.0 min.

of 12-F_{2t}-isoprostane were prepared. The diacetate (+)-**40** (Scheme 7) was obtained in quantitative yield by treating the monoacetate (+)-**35** with acetic anhydride. Oxidation and Mislow rearrangement[23] of (+)-**40** provided the allylic alcohol (−)-**41**, which on treatment with Dess−Martin periodinane, followed by reduction with $NaBH_4$, afforded the epimeric allylic alcohol (−)-**41** and (−)-**42**. These were readily separated by column chromatography. They were separately hydrolyzed with LiOH in THF−H_2O (1:1) to furnish *ent*-12-F_{2t}-isoprostane **6** and its 12-epimer **7** in 90 and 91% yields, respectively. The same procedures were carried out (Scheme 8) with the monoacetate (−)-**36** to complete the preparation of 12-F_{2t}-isoprostane **4** and its 12-epimer **5**. The spectroscopic data for **4** (^{1}H and ^{13}C NMR) were consistent with those previously reported.[9,24]

We thought that perhaps Mitsunobo inversion[13] of **12** could lead to the all-cis 12-F_2-isoprostane derivatives. In fact, Mitsunobo coupling of the diol (+)-**12** (Scheme 9) afforded the 12-F_{2c}-isoprostane derivative (+)-**43** in 45% yield, accompanied by elimination products. That the reaction had proceeded with inversion at each of the reacting stereogenic centers was confirmed by comparing the ^{13}C NMR chemical shifts of the non-oxygenated methines of (+)-**43** (δ 43.1, 44.6, 49.4) with those of (+)-**12** (δ 49.6, 50.5, 53.1). As can be seen by comparing **33** (δ 46.3, 47.9, 55.2) with **34** (δ 47.3, 50.4, 54.6), the methine adjacent to a cis OH resonates at higher field than the methine adjacent to a trans OH. Since both the methines of (+)-**43** were shifted upfield, both of the reacting centers must have inverted. This assignment was confirmed by comparing the ^{13}C NMR chemical shifts of the non-oxygenated methines of **6** (δ 50.1, 54.2) with those of **8** (δ 46.9, 50.1).

Oxidation and Mislow rearrangement[22] of (+)-**43** provided the allylic alcohol (+)-**44**. Oxidation of (+)-**44** followed by reduction gave an inseparable mixture of (+)-**44** and **45**. Fortunately, transesterification of (+)-**44** and **45** with K_2CO_3 at room temperature in EtOH gave (−)-**46** and (−)-**47**, which could be separated by column chromatography. Hydrolysis of (−)-**46** or (−)-**47** individually with LiOH furnished the 12-F_{2c}-isoprostane diastereomers **8** and **9**. The same strategy was applied to the enantiomerically pure monoacetate (−)-**36** (Scheme 10), leading to the two other 12-F_{2c}-isoprostane diastereomers **10** and **11**. The 12-F_{2c} diastereomers had never previously been prepared.[25]

Conclusion

A stereodivergent and practical synthesis of the eight enantiomerically pure diastereomers of the 12-F_2-isoprostanes has been developed. The key steps include rhodium-mediated intramolecular cyclopropanation and enzymatic resolution. This approach has provided a sufficient quantity of **4**−**11** to assess their physiological activity.

Acknowledgment. We thank the National Institutes of Health (Grant GM42056) for support for this work.

Supporting Information Available: Text giving detailed experimental procedures and figures showing spectra for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA020816V

(23) (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.
(24) The previous report did not include $[\alpha]_D$, so no comparison could be made.
(25) For a recent synthesis of each of the eight enantiomerically pure diastereomers of the 15-F_2-isoprostanes, see: Schrader, J. O.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 10998.