

## Synthesis of the Eight Enantiomerically Pure Diastereomers of the 12-F<sub>2</sub>-Isoprostanes

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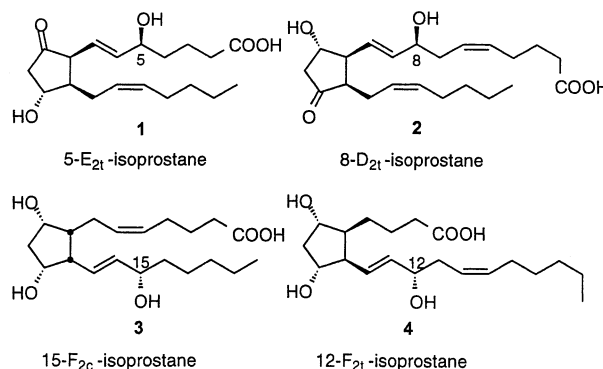
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**Abstract:** Syntheses of the eight enantiomerically pure diastereomers of the 12-F<sub>2</sub>-isoprostanes (**4–11**) are described. The key steps included rhodium-mediated intramolecular cyclopropanation and enzymatic resolution of the racemic 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.<sup>2</sup> There are D-ring, E-ring, and F-ring isoprostanes. Four different regioisomers of each of these classes of isoprostanes are formed.<sup>3</sup> Interestingly, levels of F<sub>2</sub>-isoprostanes (**1–4**) in normal human biological fluids exceed levels of prostaglandins. Several synthesis routes to particular isoprostanes have been reported.<sup>4–10</sup> Since we are interested in the physiological activity of each of the isoprostanes,<sup>11</sup> 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<sub>2</sub>-isoprostanes (**4–11**) from the racemic diol **12** (Scheme 1). This is the first preparation of the 12-F<sub>2</sub>c series.



### Results and Discussion

The 12-F<sub>2</sub>-isoprostanes were first identified in human plasma samples by Roberts.<sup>11</sup> To screen the physiological activity of the eight enantiomerically pure diastereomers of the 12-F<sub>2</sub>-isoprostanes, it will be necessary to individually prepare each of them. One synthesis, specifically of 12-F<sub>21</sub>-isoprostane **4**, was reported by Rokach in 1998.<sup>9</sup>

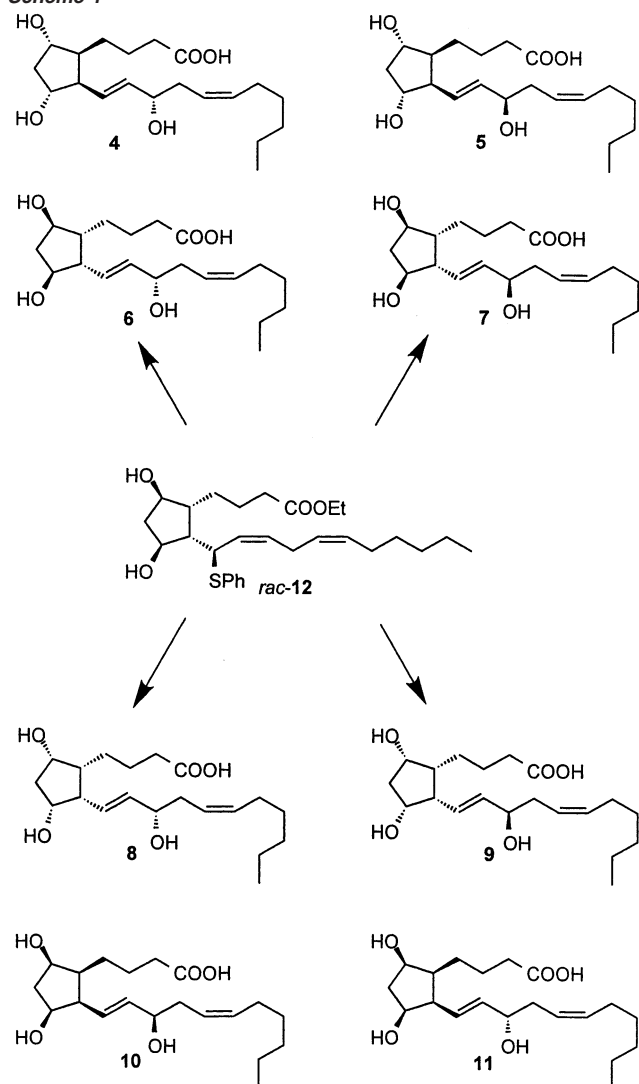
It seemed more attractive to develop a stereodivergent synthesis scheme toward these targets from a common intermediate, rather than design different syntheses of each. We envisioned (Scheme 1) that the eight target molecules could be prepared from the same racemic intermediate **12**. The two enantiomers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

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- (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<sub>21</sub>-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<sub>2c</sub>-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<sub>21</sub>-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<sub>21</sub>-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<sub>2c</sub>-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<sub>21</sub>-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<sub>21</sub>-isoprostane, see: Taber, D. F.; Hoermer, 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.

Scheme 1

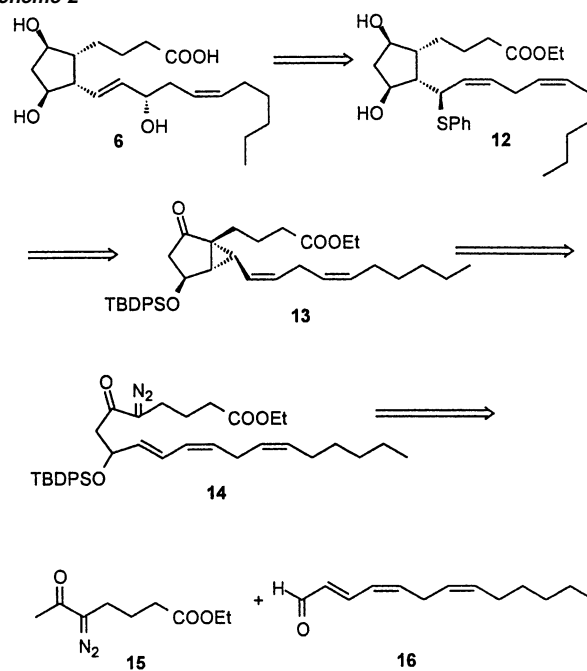
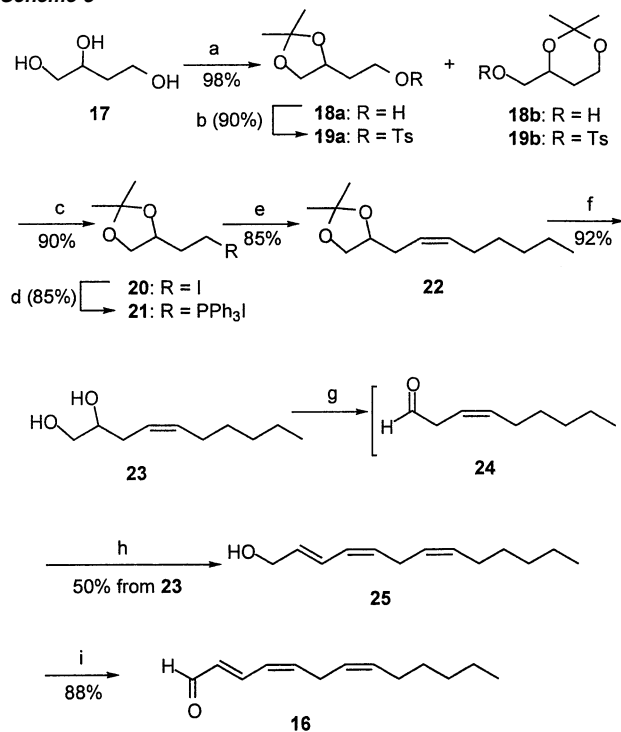


enantiomerically pure diastereomers **4–7**. Mitsunobu inversion<sup>13</sup> of the enantiomers of **12** would lead to the four enantiomerically pure *cis* isomers **8–11**.

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  $\text{BF}_3 \cdot \text{OEt}_2$ . 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,<sup>14</sup> 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<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a) acetone, TsOH; (b) TsCl,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ; (c) NaI, Cu, acetone; (d)  $\text{PPh}_3$ ,  $\text{NaHCO}_3$ ,  $\text{CH}_3\text{CN}$ ; (e) KHMDS, THF,  $-78^\circ\text{C}$ , hexanal; (f) 80% HOAc (aq), room temp; (g)  $\text{NaIO}_4/\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ , room temp; (h)  $\text{HOCH}_2\text{CH}=\text{CHCH}_2\text{PPh}_3\text{Br}$ , KHMDS, THF/ $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ ; (i) Dess–Martin periodinane,  $\text{CH}_2\text{Cl}_2$ , room temp.

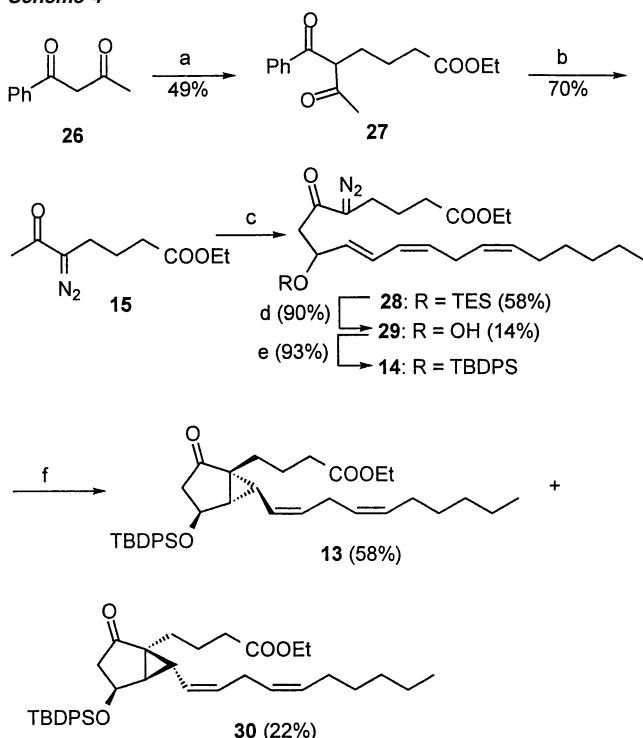
stored at  $5^\circ\text{C}$  for several weeks. Using this approach, substantial quantities of the valuable phosphonium salt **21**<sup>15</sup> could be conveniently prepared.

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.; Poiteau, P.; Aubert, F.; Lellouche, J. P.; Beaucourt, J. P.; Gree, R. *Bull. Soc. Chim. Fr.* **1990**, 127, 298.

Scheme 4<sup>a</sup>

<sup>a</sup> 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.

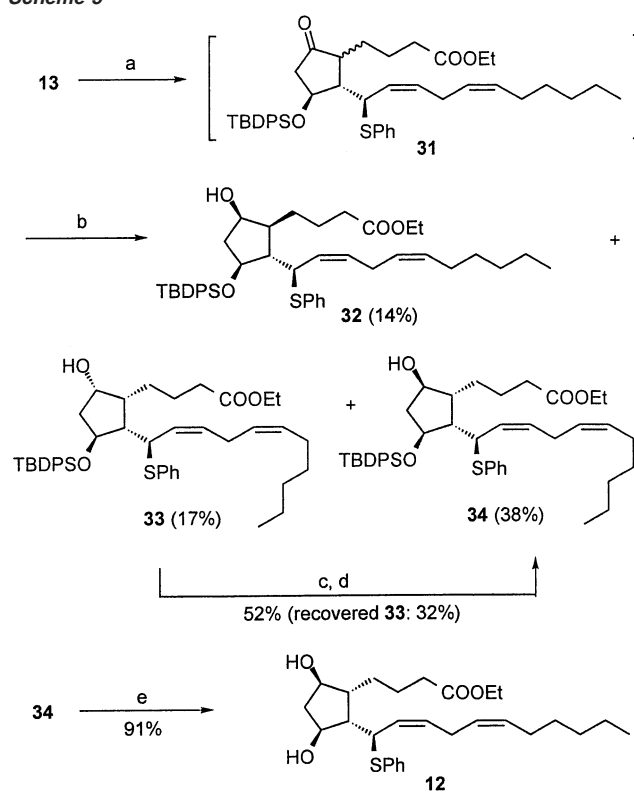
Table 1.  $Rh_2(Oct)_4$  Catalyzed Cyclization of Diazoketone **14**<sup>a</sup>

entry	solvent, concn (M)	temp (°C)	total yield <sup>b</sup> ( <b>13</b> and <b>30</b> ) (%)	ratio <b>13/30</b>
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 <sup>c</sup>	$CH_2Cl_2$ , 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 <sup>d</sup>	toluene/ $CH_2Cl_2$ , 0.05	-20	73	3.0:1
13 <sup>e</sup>	toluene/ $CH_2Cl_2$ , 0.05	-20 to room temp	40 <sup>f</sup>	2.8:1

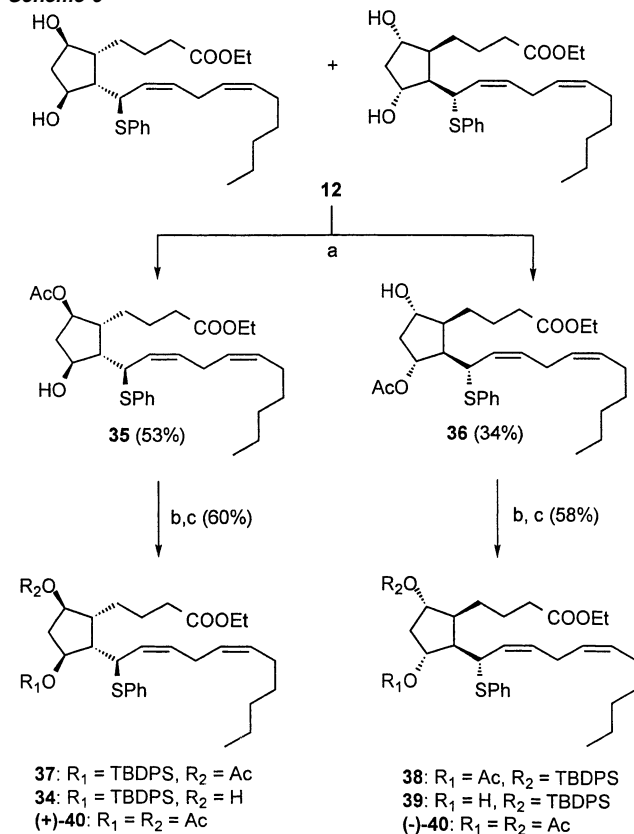
<sup>a</sup> Unless otherwise indicated, all reactions were carried out with 1% of  $Rh_2(Oct)_4$ . The solution of  $Rh_2(Oct)_4$  (3 mL/mg in  $CH_2Cl_2$ ) was added to a solution of **14** over 1 h. <sup>b</sup> Isolated yield. <sup>c</sup> A solution of **14** in  $CH_2Cl_2$  was added to a solution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

provide the diol **23**. Expecting the  $\beta,\gamma$ -unsaturated aldehyde **24** to be unstable, we carried the crude product from the Vo-Quang periodate cleavage<sup>16</sup> directly into the modified Wittig reaction,<sup>17</sup> to afford the trienol **25**. Oxidation of the trienol **25** with the Dess-Martin periodinane<sup>18</sup> provided the aldehyde.

The diazoketone **15**<sup>19</sup> (Scheme 4) was prepared from the commercially available diketone **26** following the procedure we

Scheme 5<sup>a</sup>

<sup>a</sup> 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<sup>a</sup>

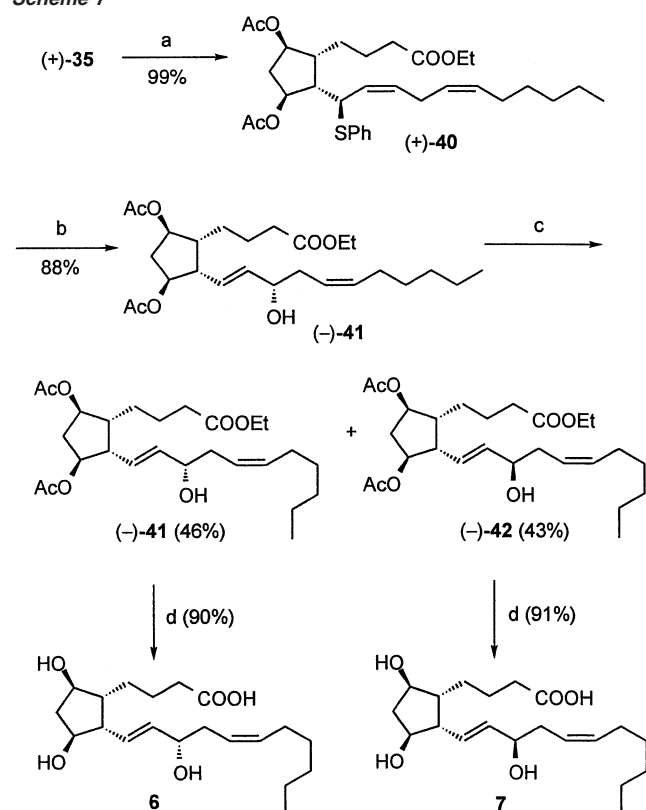
<sup>a</sup> Reagents and conditions: (a) Amano lipase AK, vinyl acetate, 45 °C, 48 h; (b) (TBDPS)Cl, imidazole, DMAP,  $CH_2Cl_2$ , room temp; (c)  $K_2CO_3$ , EtOH, 60 °C.

(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.; Ohfuné, Y. *Tetrahedron Lett.* **1998**, 39, 3757. No preparation details or characterization data for diazoketone **15** were found in this reference.

Scheme 7<sup>a</sup>

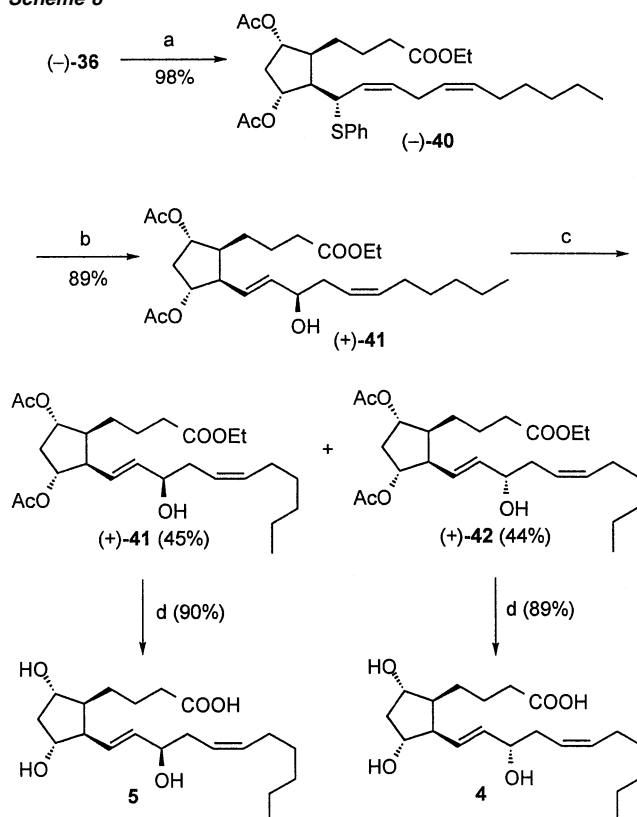
<sup>a</sup> Reagents and conditions: (a) Ac<sub>2</sub>O, pyr, CH<sub>2</sub>Cl<sub>2</sub>, room temp; (b) (i) mCPBA, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C; (ii) (MeO)<sub>3</sub>P, EtOH, -78 °C to room temp; (c) (i) Dess–Martin periodinane, CH<sub>2</sub>Cl<sub>2</sub>, room temp; (ii) NaBH<sub>4</sub>, EtOH, 0 °C; (d) LiOH, THF/H<sub>2</sub>O, room temp.

previously developed.<sup>20</sup> 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**.

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.<sup>7d</sup> 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<sub>3</sub>·OEt<sub>2</sub>, 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<sub>2</sub>(Oct)<sub>4</sub> in CH<sub>2</sub>Cl<sub>2</sub> (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<sub>2</sub>(Oct)<sub>4</sub>, resulting in a low chemical yield (entry 13).

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

Scheme 8<sup>a</sup>

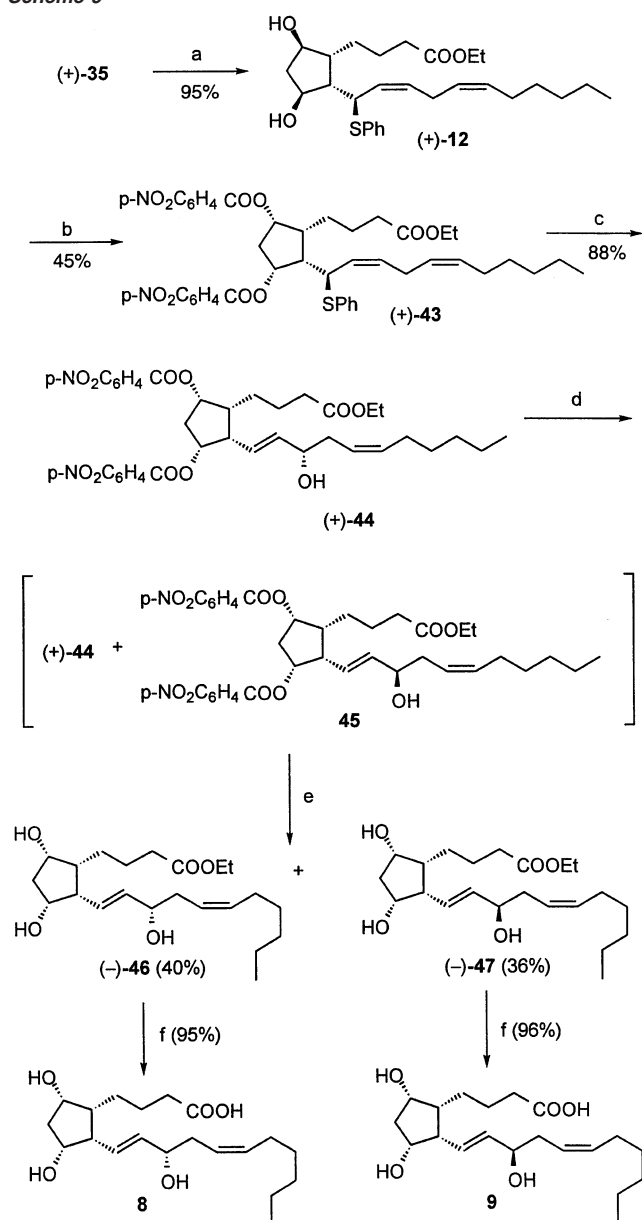
<sup>a</sup> Reagents and conditions: (a) Ac<sub>2</sub>O, pyr, CH<sub>2</sub>Cl<sub>2</sub>, room temp; (b) (i) mCPBA, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C; (ii) (MeO)<sub>3</sub>P, EtOH, -78 °C to room temp; (c) (i) Dess–Martin periodinane, CH<sub>2</sub>Cl<sub>2</sub>, room temp; (ii) NaBH<sub>4</sub>, EtOH, 0 °C; (d) LiOH, THF/H<sub>2</sub>O, room temp.

The structures of the bicyclic ketones **13** and **30** were assigned by comparing the <sup>1</sup>H and <sup>13</sup>C NMR spectra to those for analogous bicyclic ketones that were intermediates in the synthesis of the 5-F<sub>21</sub>-isoprostanes<sup>4a</sup> and the 8-F<sub>21</sub>-isoprostanes.<sup>6a</sup> In particular, the oxygenated methine of **13** (<sup>13</sup>C δ 69.5; <sup>1</sup>H δ 4.47, d, *J* = 4.9 Hz) is congruent with the analogous 5-F<sub>21</sub>-isoprostane precursor (<sup>13</sup>C δ 69.3; <sup>1</sup>H δ 4.46, d, *J* = 4.9 Hz) and 8-F<sub>21</sub>-isoprostane precursor (<sup>13</sup>C δ 69.3; <sup>1</sup>H δ 4.46, d, *J* = 4.9 Hz), while the oxygenated methine of **30** (<sup>13</sup>C δ 68.1; <sup>1</sup>H 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<sub>3</sub>·OEt<sub>2</sub>.<sup>21</sup> 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<sub>3</sub>·OEt<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub> (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<sub>4</sub> 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,<sup>18</sup>

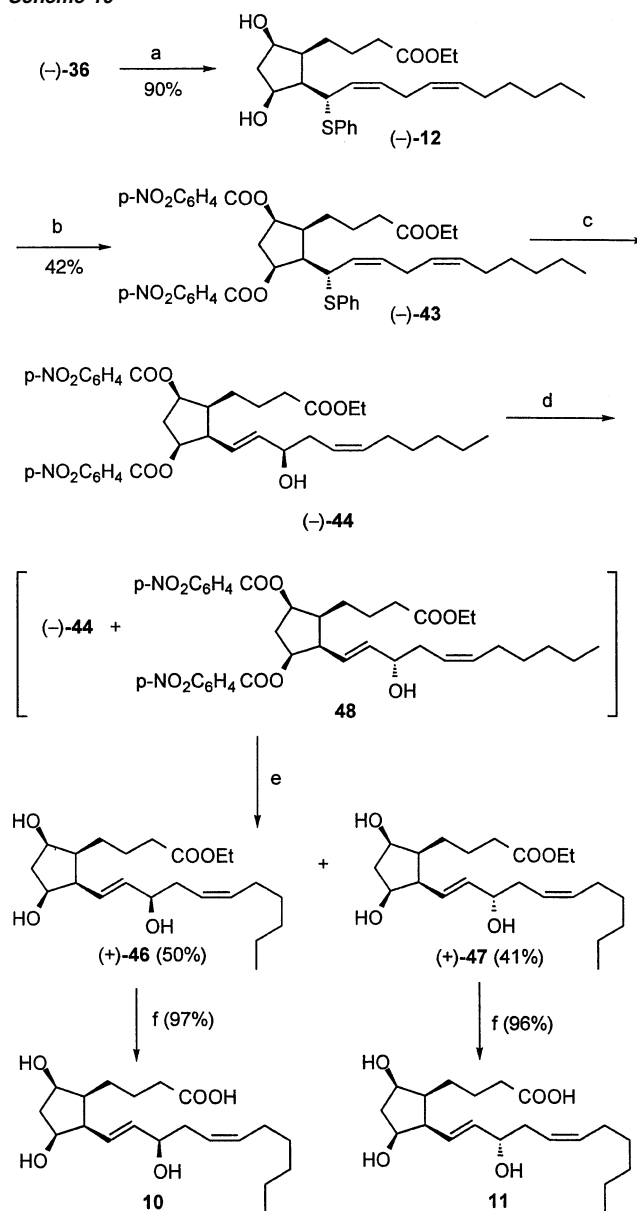
(21) From ketone **13** on, all reactions (except for the enzymatic resolution and the final hydrolysis steps) were run in the presence of a trace amount of methylene blue to inhibit isomerization of the side chain. For the use of methylene blue to stabilize 1,4-dienes, see: Taber, D. F.; Phillips, M.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

Scheme 9<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a)  $K_2CO_3$ , EtOH, 60 °C, 1.5 h; (b)  $PPh_3$ , DEAD, *p*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>COOH, benzene; (c) mCPBA, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C; (ii) (MeO)<sub>3</sub>P, EtOH, -78 °C to room temp; (d) (i) Dess–Martin periodinane, CH<sub>2</sub>Cl<sub>2</sub>, room temp; (ii) NaBH<sub>4</sub>, EtOH, 0 °C; (e)  $K_2CO_3$ , EtOH; (f) LiOH, THF/H<sub>2</sub>O, room temp.

followed by reduction. The relative configuration of **34** (<sup>1</sup>H NMR  $\delta$  4.47, dt,  $J$  = 2.5, 6.4 Hz, 1H, 4.08, m, 1H) was also assigned by comparing the <sup>1</sup>H and <sup>13</sup>C NMR spectra to those precursors for the 5-*F*<sub>2</sub>-isoprostanes (<sup>1</sup>H NMR  $\delta$  4.44, dt,  $J$  = 3.6, 6.6 Hz, 1H, 4.08, m, 1H) and the 8-*F*<sub>2</sub>-isoprostanes (<sup>1</sup>H NMR  $\delta$  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

Scheme 10<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a)  $K_2CO_3$ , EtOH, 60 °C, 1.5 h; (b)  $PPh_3$ , DEAD, *p*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>COOH, benzene; (c) mCPBA, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C; (ii) (MeO)<sub>3</sub>P, EtOH, -78 °C to room temp; (d) (i) Dess–Martin periodinane, CH<sub>2</sub>Cl<sub>2</sub>, room temp; (ii) NaBH<sub>4</sub>, EtOH, 0 °C; (e)  $K_2CO_3$ , EtOH; (f) LiOH, THF/H<sub>2</sub>O, room temp.

chiral HPLC.<sup>22</sup> 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*<sub>2</sub>-isoprostane.<sup>7d</sup>

(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.

With the requisite enantiomerically pure acetates (+)-**35** and (-)-**36** in hand, the four enantiomerically pure trans isomers 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<sup>23</sup> of (+)-**40** provided the allylic alcohol (-)-**41**, which on treatment with Dess–Martin periodinane, followed by reduction with  $\text{NaBH}_4$ , afforded the epimeric allylic alcohol (-)-**41** and (-)-**42**. These were readily separated by column chromatography. They were separately hydrolyzed with LiOH in THF– $\text{H}_2\text{O}$  (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** ( $^1\text{H}$  and  $^{13}\text{C}$  NMR) were consistent with those previously reported.<sup>9,24</sup>

We thought that perhaps Mitsunobo inversion<sup>13</sup> 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  $^{13}\text{C}$  NMR chemical shifts of the non-oxygenated methines of (+)-**43** ( $\delta$  43.1, 44.6, 49.4) with those of (+)-**12** ( $\delta$  49.6, 50.5, 53.1). As can be seen by comparing **33** ( $\delta$  46.3, 47.9, 55.2) with **34** ( $\delta$  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  $^{13}\text{C}$  NMR chemical shifts of the non-oxygenated methines of **6** ( $\delta$  50.1, 54.2) with those of **8** ( $\delta$  46.9, 50.1).

Oxidation and Mislow rearrangement<sup>22</sup> 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  $\text{K}_2\text{CO}_3$  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.<sup>25</sup>

## 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.

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**Note Added after Print Publication:** Due to a production error, Table 1 and Scheme 5 contained errors in the version published on the Web 10/11/2002 (ASAP) and in the November 6, 2002 issue (Vol. 124, No. 44, pp 13121–13126); the correct electronic version of the paper was published on 11/27/2002 and an Addition and Correction appears in the December 25, 2002 issue (Vol. 124, No. 51).

**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>.

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(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.