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A Cross-Metathesis Route to the 5-F_2-Isoprostanes

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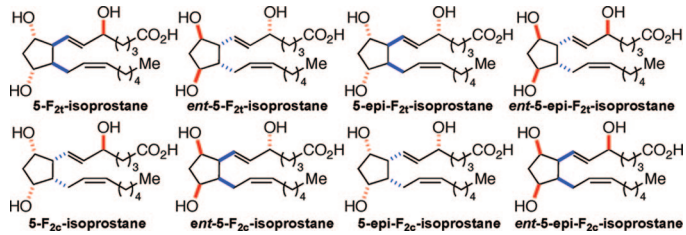

A library of eight 5-F_2-isoprostanes was prepared through a ring-opening metathesis/cross-metathesis protocol between functionalized bicyclo[3.2.0]heptenes, ethylene, and α,β-unsaturated ketones. This sequence provided racemic enones in a regio- and stereoselective fashion that could be converted to enantiomerically enriched allylic alcohols through a catalyst-controlled asymmetric reduction. Completion of the sidechains, followed by global deprotection, resulted in a stereodivergent route to eight enantiomerically enriched 5-F_2 isoprostanes. Overall, the synthesis of this library of known and anticipated lipid oxidation metabolites was achieved in 10 steps from commercially available 4-hydroxy-2-cyclopentenone.

Introduction

Reactive oxygen species have been implicated in a variety of human diseases.[1] These free radical intermediaries are believed to be able to transform common lipid components into a variety of potent secondary messengers. A well-known example of this phenomenon is the conversion of arachidonic acid into the prostaglandins (e.g., **2**, Figure 1).[2] A lesser known example is the formation of the isoprostanes and isoprostanyl esters[3] from arachidonic esters (**1**).[4] Since their discovery by Morrow and Roberts,[4] clinicians have used the levels of certain isoprostanes in bodily fluids as quantitative markers of disease-related oxidative stress.[5] In addition, the isoprostanes have also been linked to inflammatory events as well as smooth muscle regulation.[6] The role of these lipid metabolites in normal, as

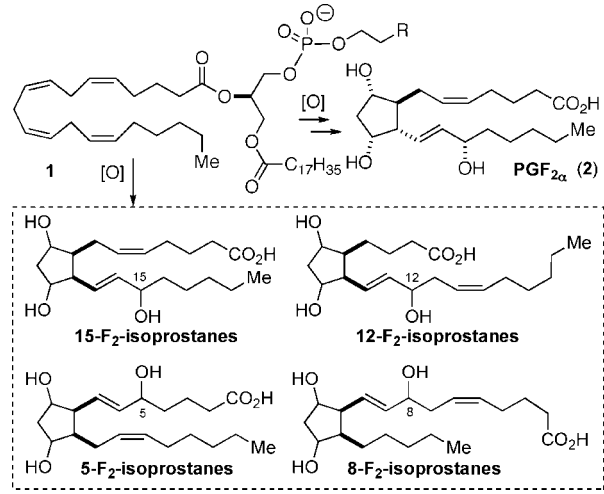

FIGURE 1. Arachidonic acid metabolites.

(1) For heptatorenal syndrome, see: (a) Morrow, J. D.; Moore, K. P.; Awad, J. A.; Raveenscraft, M. D.; Marini, G.; Badr, K. F.; Williams, R.; Roberts, L. J, II. *Lipid Mediators* **1993**, *6*, 417. For alcohol induced-liver disease, see: (b) Lands, W. E. *Alcohol.: Clin. Exp. Res.* **1995**, *19*, 928. For pulmonary hypertension, see: (c) Kang, H. K.; Morrow, J. D.; Roberts, L. J., II; Newman, J. H.; Banerjee, M. *J. Appl. Physiol.* **1993**, *74*, 460. For myocardial infarction, see: (d) Sing, N.; Dhalla, A. K.; Seneviratne, C.; Singal, P. K. *Mol. Cell. Biochem.* **1995**, *147*, 77. For atherosclerosis, see: (e) Gopaul, N. K.; Nourooz-Zadeh, J.; Mallet, A. I.; Anggard, E. E. *Biochem. Biophys. Res. Commun.* **1994**, *200*, 338. (f) Cracowski, J.-L. *Chem. Phys. Lipids* **2004**, *128*, 75.

(2) For example, see: (a) *Prostaglandins, Leukotrienes and Essential Fatty Acids*; Horrobin, D. F., Manku, M. S., Sirois, P., Borgeat, P., Eds.; Churchill Livingstone: Edinburgh, UK, 2002. (b) *Prostaglandins, leukotrienes and other eicosanoids: from biogenesis to clinical application*, Marks, F., Furstenberger, G., Eds.; Wiley-VCH: Weinheim, Germany, 1999. Also see: (c) Helmer, M. E.; Lands, W. E. M. *Lipids* **1997**, *12*, 591. (d) Porter, N. A.; Funk, M. O. *J. Org. Chem.* **1975**, *40*, 3614.

(3) Shizuka, M.; Schrader, T. O.; Snapper, M. L. *J. Org. Chem.* **2006**, *71*, 1330.

(4) 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.

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well as disrupted, physiological processes may be critical to uncovering relationships between radical-mediated oxidative damage and human disease.[7]

Unlike the prostaglandins, the isoprostanes may be generated in the absence of any initial enzymatic control.[8] Depending on the regioselectivity of the initial oxidation of the arachadonic ester (**1**), four regioisomeric classes of the isoprostanes are possible (Figure 1, 15-F_2-isoprostane, 12-F_2-isoprostane, 8-F_2-isoprostane, and 5-F_2-isoprostane).[9] Preliminary studies suggest that each of these isoprostanoidal families may have unique physiological activities.[10]

In an effort to learn more about the formation and physiological functions of these lipid oxidation metabolites, we have begun to develop concise, stereospecific entries into the specific families of the isoprostanes. Previously, we reported the preparation of a stereodefined library of 15-F_2-isoprostanes using a ring-opening cross-metathesis (ROCM)[11] on a common cyclobutene precursor.[12] Herein, we describe a modified metathesis strategy that allows for the preparation of a stereodiverse library of the 5-F_2-isoprostanes (**3**−**6**, Figure 2).[13] Although members of this class are among the most abundant of the isoprostanes found in human urine, relatively little is known about their biological activities and possible intra- and extracellular interactions.[14]

Like the 15-F_2-isoprostanes, a ROCM of functionalized cyclobutenes was envisioned as an effective entry into the 5-F_2-isoprostanyl series. Given the low degree of olefin stereochemical control observed in our earlier cross-metathesis studies, we were particularly keen on using α,β-unsaturated ketones as reaction partners to install the upper side chain of the 5-F_2 isoprostanes. Cross-metatheses of electron-deficient olefins are known to generate *E*-disubstituted olefins, at times almost exclusively.[15] Moreover, the robust ruthenium benzylidenes **8** and **9** have shown to be particularly useful in these transformations.[16]

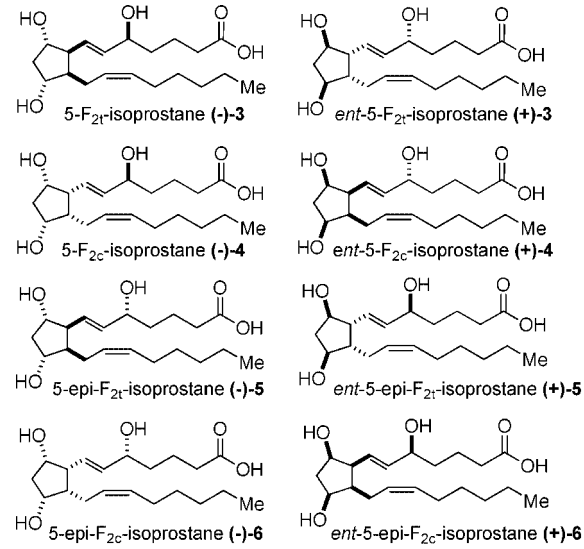
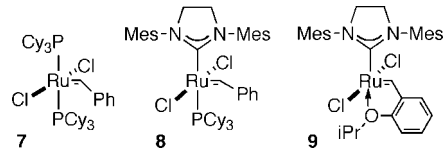


FIGURE 2. Known and predicted 5-F_2-isoprostanes.



Results and Discussion

In the retrosynthetic analysis of the 5-F_2 isoprostanes, we considered two metathesis-based strategies for elaborating the functionalized cyclobutenes into the appropriate *cis*-dialkyl substituted cyclopentandiols. These strategies are summarized in Figure 3 (Pathways A and B). Pathway A involves a selective ring-opening cross-metathesis of a bicyclo[3.2.0]heptene with an suitably functionalized olefin. Given our experience with the

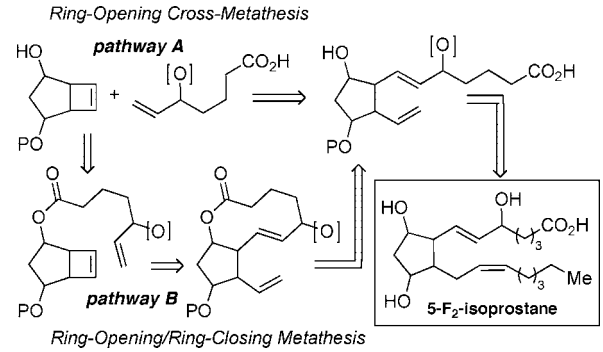


FIGURE 3. ROM routes to the 5-F_2-isoprostanes.

(5) (a) Garret, A. F.; Rokach, J.; Lawson, J. A.; Patrico, D. *Chem. Phys. Lipids* **2004**, *128*, 165. (b) Morrow, J. D.; Roberts, L. J., II. *Cell. Mol. Life Sci.* **2002**, *59*, 808. (c) Lawson, J. A.; Rokach, J.; Fitzgerald, G. A. *J. Biol. Chem.* **1999**, *274*, 2441. (d) Lawson, J. A.; Li, H.; Rokach, J.; Adiyaman, M.; Hwang, S. W.; Khanapure, S. P.; Fitzgerald, G. A. *J. Biol. Chem.* **1998**, *273*, 29295. (e) Kadiiska, M. B.; Morrow, J. D.; Awad, J. A.; Roberts, L. J., II; Mason, R. P. *Chem. Res. Toxicol.* **1998**, *11*, 1516. (f) Morrow, J. D.; Minton, T. A.; Mukundan, C. R.; Campbell, M. D.; Zackert, W. E.; Daniel, V. C.; Badr, K. F.; Blair, I. A.; Roberts, L. J., II. *J. Biol. Chem.* **1994**, *269*, 4317.

(6) Hou, X.; Roberts, L. J., II; Gobeil, F., Jr.; Taber, D. F.; Kanai, K.; Abran, D.; Brault, S.; Daniella, C.; Sennlaub, F.; LaChapelle, P.; Varma, D. R.; Chemtob, S. *Free Radical Bio. Med.* **2004**, *36*, 163.

(7) Adiyaman, M.; Lawson, J. A.; Hwang, S.-W.; Khanapure, S. P.; FitzGerald, G. A.; Rokach, J. *Tetrahedron Lett.* **1996**, *37*, 4849.

(8) (a) Morrow, J. D.; Awad, J. A.; Boss, H. J.; Blair, I. A.; Roberts, L. J., II. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 10721. (b) Kayganich-Harrison, K. A.; Rose, D. M.; Murphy, R. C.; Morrow, J. D.; Roberts, L. J., II. *J. Lipid Res.* **1993**, *34*, 1229. A small percentage of isoprostane production may be attributed to the action of the COX enzymes. (c) Practicó, D.; Lawson, J. A.; FitzGerald, G. A. *J. Biol. Chem.* **1995**, *270*, 9800. (d) Practicó, D.; FitzGerald, G. A. *J. Biol. Chem.* **1996**, *271*, 8919. (e) Patrignani, P.; Santini, G.; Panara, M. R.; Sciulli, M.; Greco, A.; Rotondo, M. T.; Giamberardino, M.; Maclouf, J.; Ciabttoni, G.; Patrono, C. Br. *J. Pharmacol.* **1996**, *118*, 1285.

(9) (a) Patrono, C.; Davi, G.; Falco, A. *Chem. Phys. Lipids* **2004**, *128*, 149. For a summary of isoprostane nomenclature, see: (b) Roberts, L. J., II; Taber, D. F.; Morrow, J. D. *Prostaglandins* **1997**, *53*, 63. For an alternative nomenclature system, see: (c) Rokach, J.; Khanapure, S. P.; Hwang, S. W.; Adiyaman, M.; Lawson, J. A.; FitzGerald, G. A. *Prostaglandins* **1997**, *54*, 853.

(10) For a recent synopsis of the pharmacology of isoprostanes and other lipid peroxidation products, see: Chem. Phys. Lipids 2004, *128*, 1−193.

(11) (a) Randall, M. L.; Tallarico, J. A.; Snapper, M. L. *J. Am. Chem. Soc.* **1995**, *117*, 9610. For lead references on ring-opening cross-metathesis applications in total synthesis, see: (b) Grubbs, R. H., Ed.; *Handbook of Metathesis*; Wiley-VCH: New York, 2003; Vol. 2, Sec. 2.6, and references therein.

(12) (a) Schrader, T. O.; Snapper, M. L. *Tetrahedron Lett.* **2000**, *41*, 9685. (b) Schrader, T. O.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 10998.

(13) For lead references on the syntheses of 5-F_2-isoprostanes, see: (a) Taber, D. F.; Kanai, K.; Pina, R. *J. Am. Chem. Soc.* **1999**, *121*, 7773. (b) Adiyaman, M.; Lawson, J. A.; Khanapure, S. P.; FitzGerald, G. A.; Rokach, J. *Anal. Biochem.* **1998**, *262*, 45. (c) Adiyaman, M.; Lawson, J. A.; FitzGerald, G. A.; Rokach, J. *Tetrahedron Lett.* **1998**, *39*, 7039. (d) Durand, T.; Cracowski, J.-L.; Guy, A.; Rossi, J.-C. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2495. (e) Also, see ref 7.

(14) For example, see: (a) Marliere, S.; Cracowski, J.-L.; Durband, T.; Chavanon, O.; Bessard, J.; Guy, A.; Stank-Labesque, F.; Ross, J.-C.; Bessard, G. *Br. J. Pharmacol.* **2002**, *135*, 1276. (b) Arnaud, C.; Cracowski, J.-L.; Hakim, A.; Durand, T.; Guy, A.; Godin-Ribuot, D.; Bessard, G.; Ribuot, C. *Clin. Exp. Pharmacol. Physiol.* **2005**, *32*, 350. (c) Hou, X.; Roberts, L. J.; Gobeil, F., Jr.; Taber, D. F.; Kanai, K.; Abran, D.; Brault, S.; Checchin, D.; Sennlaub, F.; Lachapelle, P.; Varma, D. R.; Chemtob, S. *Free Radical Bio. Med.* **2004**, *36*, 163.

(15) Choi, T.-L.; Lee, C. W.; Chatterjee, A. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 10417.

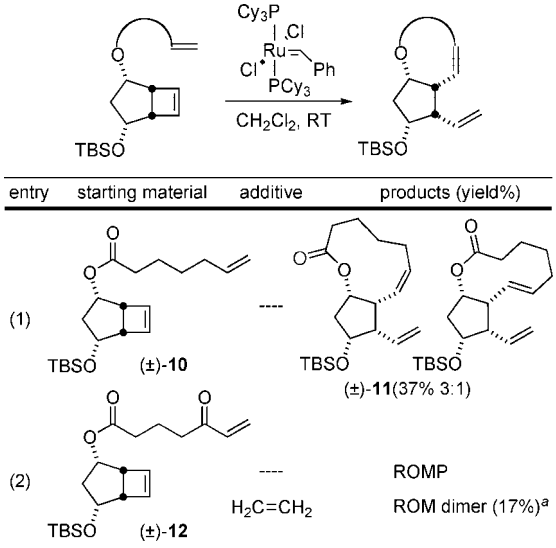
(16) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.

15-F_2-isoprostanes, there were some concerns over establishing the correct olefin stereochemistry in this cross-metathesis route. Alternatively, as illustrated in pathway B, an intramolecular ring-opening/ring-closing metathesis (RO/RCM) route could be used to influence the stereochemistry of the newly established disubstituted olefin. In this case, esterification of the bicyclo[3.2.0]-heptene would provide an intermediate with an appended side chain that contained a terminal olefin and appropriate substitution at the allylic position. Ring-opening/ring-closing metathesis of this functionalized cyclobutene could generate a 10-membered lactone with control over the newly formed olefin geometry.[17] Hydrolysis of the lactone, followed installation of the lower side chain, would then complete the synthesis of the 5-F_2-isoprostane.

From the onset, we opted to examine both of these strategies concurrently since the requisite starting materials were available from known compounds in short order. Although multiple precatalysts were evaluated for either approach, the most productive were the Grubbs' first generation complex **7** and Hoveyda-Grubbs complex **9**.

Ring-Opening/Ring-Closing Metathesis (RO/RCM). Our preliminary evaluation of the RO/RCM strategy using functionalized cyclobutenes **10** and **12** is summarized in Table 1. Cyclobutene **10** participated in a sequential ring-opening/ring-closing metathesis with alkylidene **7** to provide lactone **11** as a mixture of olefin isomers (3:1) in a modest 37% yield (entry 1). When the appended alkene contained an α,β-unsaturated ketone at the terminus, such as **12**, the ring-closed product was not observed (Entry 2). The substrate did provide ring-opened product under ethylene atmosphere in low yield, but further reaction resulted only in homodimerization of the triene. Given these shortcomings, attention was focused on the intermolecular ROCM strategy (pathway A, Figure 3).

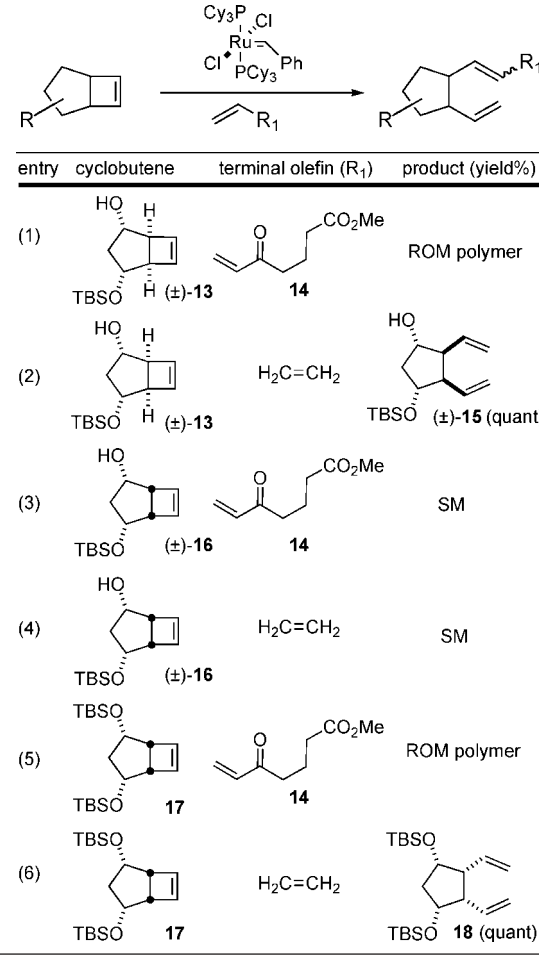
TABLE 1. Ring-Opening/Ring-Closing Metatheses



[a] Hoveyda-Grubbs catalyst 9 (5 mol%).

Ring-Opening Cross-Metathesis (ROCM). The results for the ring-opening cross-metathesis studies on cyclobutenes **13**, **16**, and **17** with keto-ester **14**[18] and/or ethylene are summarized in Table 2. As shown in entry 1, ROCM of cyclobutene **13** with enone **14** using the first generation Grubbs' catalyst **7** provided intractable products that were ascribed to rapid ring-opening polymerization of the cyclobutene. Despite modifications to the reaction conditions, such as changes to reaction concentration, solvent, temperature, catalyst loading, and olefin addition rates, this polymerization process could not be suppressed. Initiation of ruthenium benzylidene with electron deficient alkenes is not likely, and in our case, propagation with the enone must be slower than reaction of the alkylidene with another molecule of cylcobutene. Ring-opening of cyclobutene **13** with ethylene to provide the protected divinylcyclopentandiol **15**, however, did proceed without incident (entry 2).[19]

TABLE 2. Ring-Opening Cross-Metatheses (ROCM)



Interestingly, cyclobutene **16** was inert to reaction conditions optimized for the diastereomeric cyclobutene **13** (entries 3 and 4). Rather than recover cyclobutene polymer when reacted with enone **14**, the major product obtained was the starting cyclobutene. This was peculiar considering the ring strain of these molecules. Careful examination of the mass balance suggested that the catalyst was being sequestered by the substrate thus

(17) (a) Fürstner, A.; Radkowski, K.; Wirtz, C.; Goddard, R.; Lehmann, C. W.; Mynott, R. *J. Am. Chem. Soc.* **2002**, *124*, 7061.

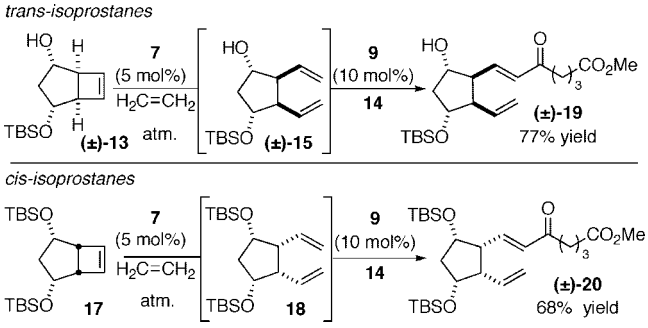
(18) (b) Fürstner, A.; Schlede, M. *Adv. Synth. Cat.* **2002**, *344*, 657. (c) Banwell, M. G.; Loong, D. T. J. *Org. Biomol. Chem.* **2004**, *2*, 2050. (d) Kaul, R.; Surprenant, S.; Lubell, W. D. *J. Org. Chem.* **2005**, *70*, 3838. (e) Davoli, P.; Fava, R.; Morandi, S.; Spaggiari, A.; Prati, F. *Tetrahedron* **2005**, *61*, 4427. Milstein, D.; Stille, J. K. *J. Org. Chem.* **1979**, *44*, 1613.

(19) Yields for these reactions were dependent on the protocol used to separate ruthenium byproducts from the desired material. For optimal results, see: (a) Kim, B. M.; Cho, J. H. *Org. Lett.* **2003**, *5*, 531.

preventing turnover.[20] This problem was solved by silylation of the free alcohol to provide *meso*−**17**. Ring-opening cross-metathesis or polymerization activity was then restored with fully protected cyclobutene **17** (entries 5 and 6).

On the basis of these observations, a stepwise metathesis-based functionalization of cyclobutenes **13** and **17** was examined (Scheme 1). ROCM of cyclobutene **13** with ethylene, followed by a cross-metathesis (CM) of the resulting diene **15** with enone **14**, provided racemic ketone **19** as single regio- and (*E*)-stereoisomer in 77% isolated yield in a single reaction vessel.[21]

SCHEME 1. ROCM/CM Entry into 5-F_2-Isoprostanes

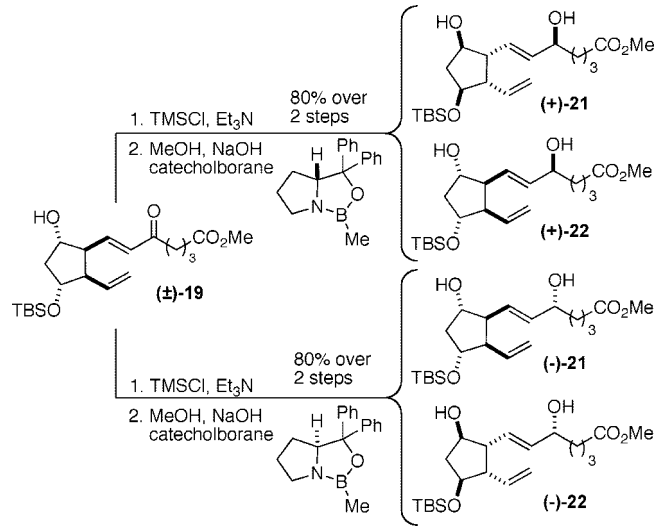


Although cyclobutene **17** undergoes a quantitative ROCM with ethylene, the selectivity for the cross metathesis of the resulting diene **18** with enone **14** was difficult to control. To avoid consuming the desired ketone **20** to a second facile cross-metathesis with enone **14**, the reaction was run to partial conversion and the recovered *meso*-diene **18** was recycled in the cross-metathesis (3×) to provide the desired (*E*)-enone (±)-**20** in an overall yield of 68%.

5-F_{2t}-Isoprostane Syntheses. Having established a reliable pathway to ketone (±)-**19**, synthesis of the four trans 5-F_{2t}-isoprostanes proceeded with TMS protection of the secondary alcohol and enantioselective reduction/resolution of the resulting unsaturated ketone with catecholborane in the presence of the (*R*)-CBS catalyst (Scheme 2).[22] In situ removal of the TMS ether provided the chromatographically distinct diastereomers (+)-**21** and (+)-**22** in 82 and 78% ee, respectively, in an average 80% yield for the two steps. The optical purity of these diols could be enhanced further by oxidation of these products to the corresponding optically enriched α,β-unsaturated ketones (+)- and (−)-**19** and then resubjection of each enantiomerically enriched ketone to the two-step TMS protection/enantioselective reduction to provide diols (+)-**21** and (+)-**22** in 97% ee[23] and 66% yield for the three-step sequence.

Alternatively, using the (*S*)-Methyl CBS catalyst and catecholborane on racemic ketone **19** allowed access to the diastereomeric diols (−)-**21** (77% ee) and (−)-**22** (78% ee) in approximately 80% yield. The optical purity of these compounds

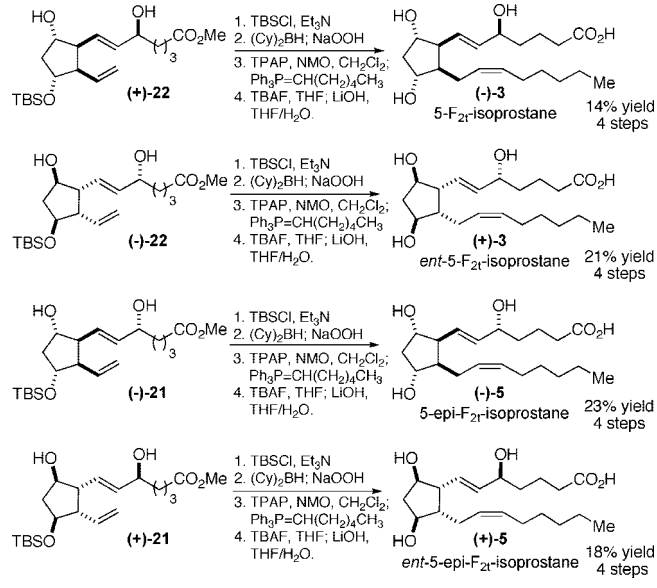
SCHEME 2. Resolution of 5-F_{2t}-Isoprostane Precursors



were also enhanced by recycling them through the oxidation/asymmetric reduction sequence described above to give both diols (−)-**21** and (−)-**22** in 96% ee.

Global protection of the secondary alcohols in (+)-**21** and (+)-**22** as TBS ethers increased the selectivity of the subsequent reactions (Scheme 3). Hydroboration of the terminal olefin was accomplished with dicyclohexylborane to provide a primary alcohol, which was then subjected to a one-pot oxidation-Wittig olefination protocol.[24] Fluoride-mediated deprotection of the silyl groups and saponification of the ester yielded *ent*-5-epi-F_{2t}-isoprostane (+)-**5** (from diol (+)-**21**) and 5-F_{2t}-isoprostane (−)-**3** (from diol (+)-**22**) in overall yields of 18% and 14%, respectively for the final four steps. Likewise, the final steps in the synthesis (c-f, Scheme 3) were repeated to provide 5-epi-F_{2t}-isoprostane (−)-**5** and *ent*-5-F_{2t}-isoprostane (+)-**3** in 17% and 16% overall yield for the six-step sequence.

SCHEME 3. Preparation of 5-F_{2t}-Isoprostanes



5-F_{2c}-Isoprostane Syntheses. Ketone (±)-**20** provides the launching point for the preparation of the cis 5-F_{2c}-isoprostanes

(20) For early examples of this type of interaction, see: (a) Snapper, M. L.; Tallarico, J. A.; Randall, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 1478. (b) Tallarico, J. A.; Bonitatebus, P. J., Jr.; Snapper, M. L. *J. Am. Chem. Soc.* **1997**, *1197*157.

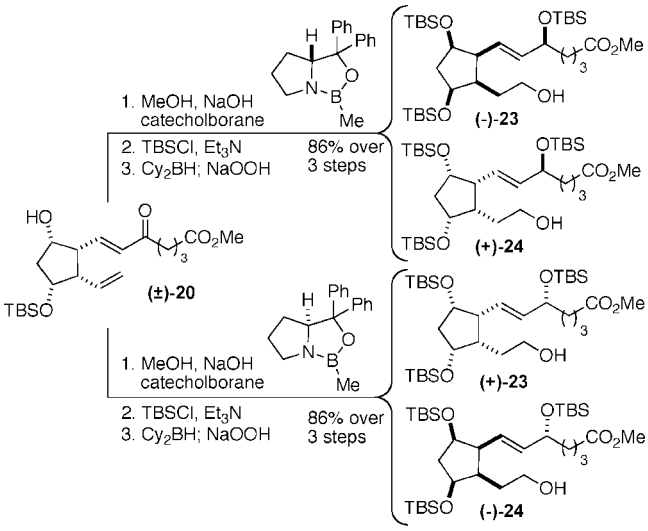
(21) For a related CM strategy to install a similar sidechain, see: (a) Jacobo, S. H.; Chang, C.-T.; Lee, G.-J.; Lawson, J. A.; Powell, W. S.; Praticó, D.; FitzGerald, G. A.; Rokach, J. *J. Org. Chem.* **2006**, *71*, 1370. For a discussion of selective issues in cross-metatheses, see: (b) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360. Catalyst **13** was inefficient in performing the CM either in tandem or separate operations. Conversely, catalyst **15** provided only cyclobutene polymer when subjected to optimal ring-opening under ethylene atmosphere.

(22) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1987.

(23) Enantiomeric excess determined by HPLC of corresponding ketone. See Supporting Information for details.

(24) MacCoss, R. N.; Balskus, E. P.; Ley, S. V. *Tetrahedron Lett.* **2003**, *44*, 7779.

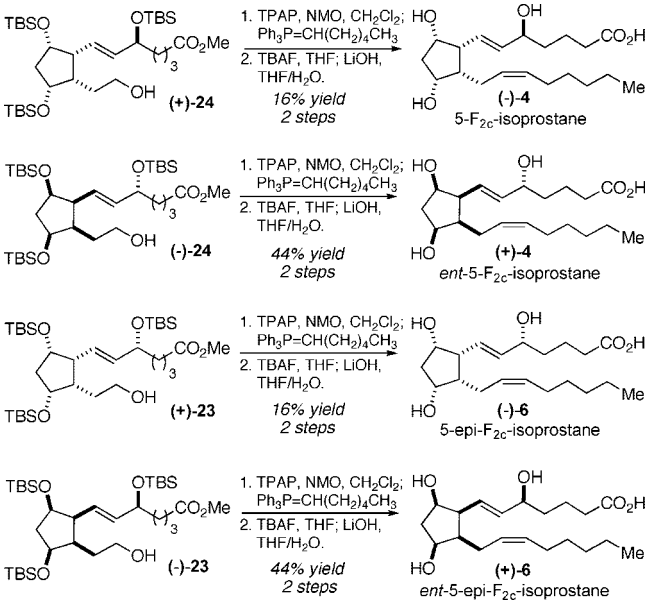
SCHEME 4. Resolution of 5-F_{2c}-Isoprostane Precursors



(Scheme 4). Reduction of the carbonyl with the (*R*)-CBS catalyst, followed by protection and hydroboration yields the primary alcohols (−)-**23** and (+)-**24**, in approximately 50% ee and 86% yield over three steps.[25] Employing the opposite antipode of the reduction-resolution catalyst, (*S*)-methyl-CBS, gives alcohols (+)-**23** and (−)-**24** in similar yield and selectivity after the analogous three-step sequence.

As shown in Scheme 5, the separable enantiomerically enriched intermediates (+)-**23** and (−)-**24** were carried forward to their respective isoprostanes (+)-**6** and (−)-**4** in a fashion similar to the previously described isomers (Scheme 3). Using this strategy, the four *cis*-isoprostanes, 5-epi-F_{2c}-isoprostane (−)-**6**, *ent*-5-F_{2c}-isoprostane (+)-**4**, *ent*-5-epi-F_{2c}-isoprostane (+)-**6**, and 5-F_{2c}-isoprostane (−)-**4** were obtained in an average 26% yield over 5 steps.

SCHEME 5. Preparation of 5-F_{2c}-Isoprostanes



Conclusions

Modifications to the ROCM strategy that was used to generate the 15-F_2-isoprostanes has allowed for a concise preparation of a library of 5-F_2-isoprostanes. ROCM of appropriately functionalized cyclobutenes with ethylene, followed by a cross-metathesis with α,β-unsaturated ketone **14** provided isoprostane precursors with high regio- and stereocontrol. Additional key steps in the synthesis include an enantioselective reduction/resolution strategy to generate enantiomerically enriched products and an oxidation/olefination protocol to complete the 5-F_2-isoprostane framework. These transformations offer in a longest linear sequence of ten steps[26] from commercially available 4-hydroxy-2-cyclopentenone, a concise, stereodivergent route to eight enantiomerically enriched 5-F_2-isoprostanes.

Experimental Section

Representative Procedure for the Cyclobutene Ring-Opening Metathesis/Cross-Metathesis Sequence. (*E*)-Methyl-7-(-3-(*t*-butyldimethylsilyloxy)-2-vinylcyclopentyl)-5-oxohept-6-noate (±)-19. To a solution of Grubbs' catalyst **7** (131 mg, 0.159 mmol) in benzene (25 mL), ethylene gas was bubbled using a balloon and outlet needle for 5 min. A violet-to-amber color change of the catalyst solution was observed. To a solution of cyclobutene **13** (766 mg, 3.19 mmol) in benzene (70 mL) in a separate flask was added this catalyst solution (25 mL, 0.006 M) by syringe with continuous introduction of ethylene gas by balloon and outlet needle. Saturation of the reaction medium with ethylene gas was continued for an additional minute, after which the outlet needle was removed and the balloon needle was raised from its immersion in solvent. The balloon atmosphere of ethylene was maintained for 12 h, after which the reaction was judged to be complete by TLC and GC with internal standard (decane). The ethylene balloon was then replaced with a cold water condenser containing a nitrogen inlet. The flask was charged with enone **14** (6.4 mmol) as a solution in benzene (8 mL) followed by Hoveyda-Grubbs' II catalyst **9** (200 mg, 0.320 mmol). The reaction was heated to a gentle reflux under a N_2 atmosphere for 18 h. The reaction was cooled to rt at which time silica gel (10 g) was added to the dark solution along with ethyl vinyl ether (3 mL). The suspension was stirred open to air for 10 min before being loaded directly on to a silica gel column prewet (10% EtOAc/hexanes). Enone (±)-**19** was obtained as a yellow oil (969 mg, 2.45 mmol, 77% yield). TLC R_f 0.30 (33% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.67 (dd, J = 15.6, 9.6 Hz, 1H), 6.13 (d, J = 15.6 Hz, 1H), 5.48 (dt, J = 16.4, 10.4 Hz, 1H), 5.08 (s, 1H), 5.05 (d, J = 7.6 Hz, 1H), 4.12 (dt, J = 7.8, 4.8 Hz, 1H), 4.07 (dt, J = 6.0, 3.2 Hz, 1H), 3.67 (s, 3H), 3.01 (dt, J = 8.4, 5.6 Hz, 1H), 2.85 (t, J = 8.0 Hz, 1H), 2.59 (t, J = 7.2 Hz, 2H), 2.43−2.34 (m, 3H), 1.93 (qt, J = 14.4, 7.2 Hz, 2H), 1.76 (t, J = 3.4 Hz, 2H), 1.72 (t, J = 3.4 Hz, 1H), 0.88 (s, 9H), 0.05 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.7, 173.4, 145.3, 135.6, 130.9, 117.6, 76.3, 56.8, 54.0, 51.6, 43.3, 39.5, 33.2, 25.9, 19.3, 18.1, −4.5, −4.6. IR (thin film, NaCl): 3444, 2955, 2926, 2852, 1741 (s), 1673, 1623, 1255, 1093 cm^{-1}. Anal. Calcd for $C_{20}H_{34}O_5Si$: C, 62.79; H, 8.96; Found: C, 63.44; H, 9.38.

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Supporting Information Available: Experimental procedures and spectroscopic characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) Optical purity in this series was determined by ^{1}H-NMR analysis of the corresponding secondary alcohol Mosher esters. See Supporting Information for details.

(26) The step count doesn't include the recycling steps that were used to enhance the optical purity of these isoprostanes.