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Stereocontrolled Access to Isoprostanes via a Bicyclo[3.3.0]octene Framework

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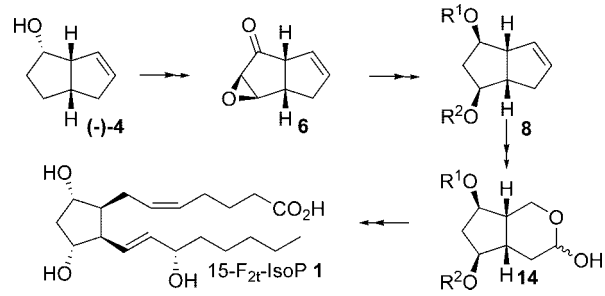
ABSTRACT



We report a simple and highly stereocontrolled strategy toward the total synthesis of isoprostanes based on a bicyclic α,β-epoxy ketone intermediate 6. Bicyclo[3.3.0]octene scaffold permitted stereodirection of reagents allowing stereoselective epoxidation, diastereoselective ketone reduction, and regioselective epoxide opening otherwise not accessible with a simple cyclopentene framework.

Discovered in 1990 by Roberts, Morrow, et al., the nonenzymatic in vivo synthesis of isoprostanes (IsoPs) questioned the apparently clear picture of cyclic polyunsaturated fatty acid (PUFA) metabolites.[1] Since then, joint efforts of biologists, biochemists, and analytical and synthetic organic chemists has revealed the multiple roles of a large variety of cyclic PUFA metabolites.[2] Isomeric to prostaglandins (lateral side chains are cis in relation to the plane of the prostane ring), IsoPs are produced by free-radical-catalyzed peroxidation of arachidonic acid (AA) leading to four racemic isomers (5-, 8-, 12-, and 15-series of IsoPs).[3] The F-type of these compounds is used as marker of oxidative stress in vivo.[4] These lipid metabolites have also been shown to be potent vasoconstrictors, to act as smooth muscle growth factors, and to possess platelet aggregation properties.[5] From a synthetic point of view, efforts still have to be made in developing divergent strategies which allow access to the E- and D-types of IsoPs.[6] These strategies should also permit the synthesis of structurally related neuroprostanes (NeuroPs)[7] and phytoprostanes (PhytoPs)[8] (Figure 1).

In this paper, we report our results concerning the synthesis of E,D,F-IsoPs[9] possessing syn-anti-syn stereochemistry using a bicyclo[3.3.0]octane scaffold.

In the literature, other bicyclic synthetic intermediates (bicyclo[4.3.0]nonane,[9d] bicyclo[3.2.0]heptane,[9g] and bicyclo[3.1.0]hexane[9c] skeletons) have been used in the total synthesis of IsoPs. The cis ring fusion of these systems

(1) 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) For a recent review, see: Jahn, U.; Galano, J.-M.; Durand, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5894.
(3) Taber, D. F.; Morrow, J. D.; Roberts, L. J., II. *Prostaglandins* **1997**, *53*, 63.
(4) (a) Musiek, E. S.; Yin, H.; Milne, G. L.; Morrow, J. D. *Lipids* **2005**, *40*, 987. (b) Montuschi, P.; Barnes, P. J.; Roberts, L. J., II. *FASEB J.* **2004**, *18*, 1791.
(5) (a) Morrow, J. D. *Curr. Pharm. Des.* **2006**, *12*, 895. (b) Cracowski, J. L.; Durand, T. *Fundam. Clin. Pharmacol.* **2006**, *20*, 417.
(6) We recently reported a strategy to access E-type isoprostane isomers: Pinot, E.; Guy, A.; Fournial, A.; Balas, L.; Rossi, J. C.; Durand, T. *J. Org. Chem.* **2008**, *73*, 3063.
(7) Nourooz-Zadeh, J.; Liu, E. H.; Anggärd, E.; Halliwell, B. *Biochem. Biophys. Res. Commun.* **1998**, *242*, 338.
(8) Imbusch, R.; Mueller, M. *J. Plant Physiol.* **2000**, *124*, 1293.

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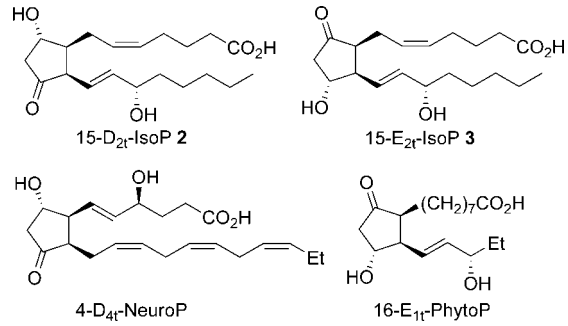


Figure 1. Examples of different metabolites belonging to E,D-IsoPs, NeuroPs, and PhytoPs.

permits adequate control over stereochemistry of isoprostane side chains. However, a clear limitation of the previous systems is the need for the early introduction of 1,3-diol or 1,3-ketohydroxyl functionalities prior to bicycle formation—impeding flexibility and leading to low diastereoselectivities in bicycle formation and ketone reduction. We envisaged that a bicyclic intermediate would not only serve to lock side-chain stereochemistry but also solve the inherent problem of introducing *cis*-1,3-hydroxyl groups on a cyclopentane system.

Bicyclo[3.3.0]octene systems are easily available by transannular C−H insertion of cyclooctene oxide;[10] therefore, we considered that alcohol **4** may be used to address the above issues and provide an attractive entry point to IsoPs (Scheme 1).

Precedent shows that the envelope shape of such systems can efficiently bias the approach of reagents from the convex face[11] and that when this face is inaccessible, the more accessible carbon from the concave face is the β carbon from the fused ring.[12] Therefore, we anticipated that epoxidation of enone **5** obtained by oxidation of **4** should occur selectively from the convex face. The newly introduced epoxide functionality in **6** should then bias reduction of the ketone from the concave face to afford *exo*-alcohol **7**. Moreover, the envelope shape of **7** should lead to regioselective opening of the epoxide affording *cis*-1,3-diol **8**. An interesting feature of this approach is the possible chemoselective ketone reduction of **6**, allowing orthogonal protection of diol **8** in order to access to E- and D-series of IsoPs.

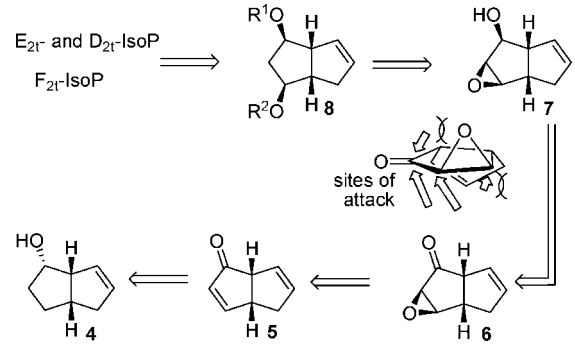
(9) For leading strategies towards IsoPs, see: (a) Corey, E.; Shih, C.; Shih, N.; Shimoji, K. *Tetrahedron Lett.* **1984**, *25*, 5013. (b) Larock, R. C.; Lee, N. H. *J. Am. Chem. Soc.* **1991**, *113*, 7815. (c) Rondot, B.; Durand, T.; Girard, J. P.; Rossi, J. C.; Schio, L.; Khanapure, S. P.; Rokach, J. *Tetrahedron Lett.* **1993**, *34*, 8245. (d) Taber, D. F.; Herr, R. J.; Gleave, D. M. *J. Org. Chem.* **1997**, *62*, 194. (e) 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. (f) Durand, T.; Guy, A.; Henry, O.; Vidal, J.-P.; Rossi, J.-C.; Rivalta, C.; Valagussa, A.; Chiabrando, C. *Eur. J. Org. Chem.* **2001**, 809. (g) Zanoni, G.; Porta, A.; Vidari, G. *J. Org. Chem.* **2002**, *67*, 4346. (h) Schrader, T. O.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 10998. (i) Quan, L. G.; Cha, J. K. *J. Am. Chem. Soc.* **2002**, *124*, 12424. (j) Rodriguez, A. R.; Spur, B. W. *Tetrahedron Lett.* **2002**, *43*, 4575.

(10) Crandall, J. K.; Chang, L. H. *J. Org. Chem.* **1967**, *32*, 532.

(11) Hodgson, D. M.; Galano, J.-M.; Christlieb, M. *Tetrahedron* **2003**, *59*, 9719.

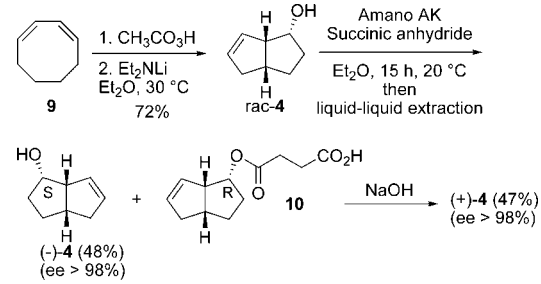
(12) Tanaka, M.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1985**, *26*, 3035.

Scheme 1. Retrosynthetic Analysis of IsoPs Based on a Bicyclo[3.3.0]octene Framework



Alcohol **4** was prepared following a previously described two-step route from 1,3-cyclooctadiene (1,3-COD) **9** (Scheme 2).[10] Monoepoxidation of **9** was achieved with peracetic acid

Scheme 2. Multigram-Scale Preparation of Enantiopure Bicyclo[3.3.0]oct-7-en-2-ol **4**



in CH_2Cl_2 at 0 °C for 3 h leading to the corresponding monoepoxide. Subsequent treatment with Et_2NLi in Et_2O at 30 °C gave, after transannular C−H insertion, the bicyclic alcohol **4** (40 g of **4** can be routinely prepared).

Ikegami et al. described an enzymatic resolution procedure of **4** on a 5 g scale using a lipase from *Pseudomonas fluorescens* (Amano AK) in the presence of vinyl acetate as a solvent. Both enantiomers have been obtained with excellent yields and ee's >99% after only one enzymatic resolution.[13] Nevertheless, we wished to apply a procedure that does not implicate purification by chromatography, thereby allowing an easy scale-up of this step.[14,15]

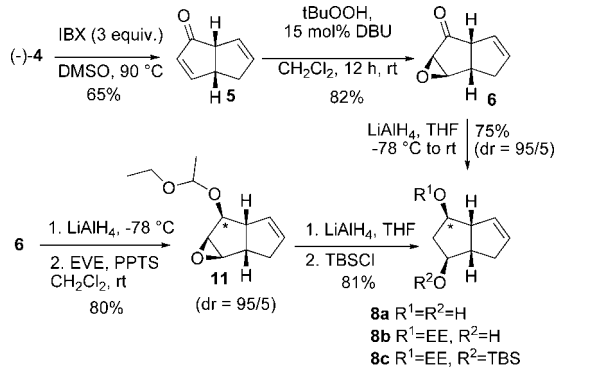
Best results were obtained by using Amano AK and succinic anhydride in dry Et_2O at room temperature (routinely run on a 20 g scale of **4**). At the stage of 50% of conversion, unreacted (−)-(*S*)-alcohol **4** and monosuccinate **10** were separated by basic ($NaHCO_3$) aqueous−organic solvent liquid−liquid extraction. Ester hydrolysis of **10** gave (+)-(*R*)-alcohol **4**. Both enantiomers were obtained in high yields

(13) Iimori, T.; Azumaya, I.; Hayashi, Y.; Ikegami, S. *Chem. Pharm. Bull.* **1997**, *45*, 207.

and high ee's ((*S*)-**4** in 48% yield; ee >98%, (*R*)-**4** in 47% yield; ee >98%) with no need for any additional purification.[16]

Recent studies by Nicolaou et al.[17] led us to consider that alcohol **4** might be oxidized in one step to enone **5**[18] by treatment with *o*-iodoxybenzoic acid (IBX). We were pleased to find that reaction of alcohol (*S*)-**4** (8 g) with IBX (3.0 equiv) in DMSO (0.8 M) at 90 °C for 15 h afforded enone **5** in 65% yield (Scheme 3). At this stage of the synthesis,

Scheme 3. Functionalization of Bicyclic Intermediate **5**



nucleophilic epoxidation was investigated in order to introduce the epoxide from the convex face of **5**. After extensive investigation, α,*β*-epoxy ketone **6** was reproducibly obtained on a gram scale with complete *exo*-stereoselectivity in 82% yield using *t*-BuOOH−15 mol % DBU[19] in CH_2Cl_2 at 20 °C for 12 h. Treatment of **6** with $LiAlH_4$ (1.9 equiv) in THF or Et_2O from −78 °C to rt led to ketone reduction and subsequent epoxide ring opening in one pot. The desired *cis*-1,3-diol **8a** was obtained with high diastereoselectivity (75%, dr = 95/5). Easy separation from *trans*-**8a**[20] was realized by flash chromatography.

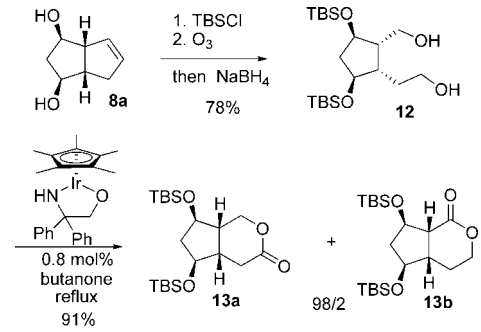
This six-step sequence from 1,3-COD is routinely performed with only one column chromatography at the last stage and affords up to 3 g of enantiopure *cis*-diol **8a** starting from 8 g of alcohol (*S*)-**4**.

In order to access to E,D-IsoPs, our strategy foresees orthogonal protection of the 1,3-*cis*-diol functionality, allowing at a later stage of the synthesis selective deprotection of one of the two hydroxyls.

Indeed, chemoselective reduction of ketone **6** was achieved with $LiAlH_4$ (0.58 equiv) in THF at −78 °C for 20 min providing α,*β*-epoxy alcohols **7** (95/5 dr in favor of the desired compound **7**). Protection of the alcohol functionality was carried out by treatment of **7** with ethylvinyl ether (EVE) in CH_2Cl_2 in the presence of a catalytic amount of PPTS at rt providing **11** in 80% yield, after chromatographic separation of the undesired *endo*-epimer of **11**. Subsequent epoxide opening with $LiAlH_4$ (1.0 equiv, −78 °C to rt) afforded alcohol **8b** as a single regioisomer. Formation of the *tert*-butyldimethylsilyl (TBS) ether under classical conditions gave rise to orthogonally protected diol **8c** in 81% yield (two steps), confirming the feasibility of our strategy for orthogonal protection.

Carrying on the synthesis toward 15-F_{2t}-IsoP, **8a** was protected as its bis-TBS ether. Ozonolysis in CH_2Cl_2/MeOH at −78 °C followed by $NaBH_4$ reduction afforded diol **12** in 78% yield (two steps) (Scheme 4). We next investigated the

Scheme 4. Synthesis of Suitable Precursor **13** for Side-Chain Introduction



possibility of selective lactonization of diol **12** to **13a** taking advantage of the relative steric hindrance of primary alcohols. Unfortunately, treatment of **12** with PDC or IBX (1.2 equiv) only provided 20% of unseparable lactones **13a** and **13b** in a 1:1 ratio and a separable mixture of the corresponding lactols **15a** and **15b** in a 1:1 ratio in good yields.[21] We next turned our attention to a specifically designed reagent for selective oxidation, Cp*Ir[$OCH_2C(C_6H_5)_2NH$].[22] Ir catalysis (0.8 mol %) in refluxing butanone afforded the corresponding lactones **13** in 91% yield with an impressive 98/2 ratio in favor of lactone **13a**.[23]

Continuing the synthetic sequence toward our target molecule, lactones **13** were reduced by DIBAL-H in CH_2Cl_2 at −78 °C to the corresponding lactols **15a** and **15b**. Desired **15a** was obtained in 89% yield after flash chromatography (Scheme 5). Introduction of the α-side chain was achieved

(14) ter Halle, R.; Bernet, Y.; Billard, S.; Bufferne, C.; Carlier, P.; Delaitre, C.; Flouzat, C.; Humblot, G.; Laigle, J. C.; Lombard, F.; Wilmouth, S. *Org. Process Res. Dev.* **2004**, *8*, 283.

(15) Bouzemi, N.; Debbeche, H.; Aribi-Zouioueche, L.; Fiaud, J. C. *Tetrahedron Lett.* **2004**, *45*, 627.

(16) The ee's were determined by converting alcohols into their corresponding 2,4-dinitrobenzoate derivatives and by chiral HPLC analysis (see the Supporting Information).

(17) Nicolaou, K. C.; Zhong, Y. L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596.

(18) Enone **5** was previously obtained in three steps from **4** by palladium-induced oxidation of the silyl enol ether obtained from the corresponding ketone in 55% yield; see: Parkes, K. E. B.; Pattenden, G. *J. Chem. Soc., Perkin Trans.* **1988**, 1119.

(19) Yadav, V. K.; Kapoor, K. K. *Tetrahedron* **1995**, *51*, 8573.

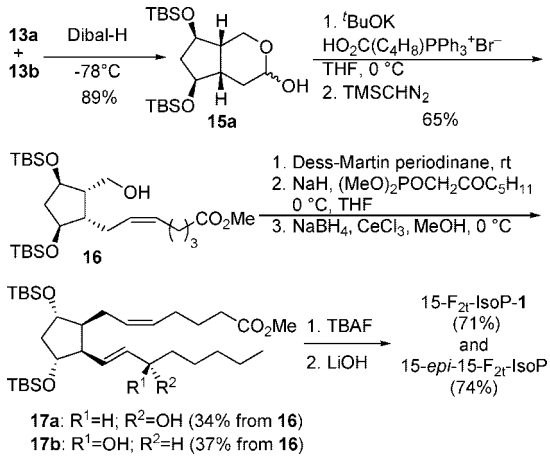
(20) The stereochemistry of *cis*- and *trans*-1,3-diols **8a** was confirmed by NMR experiments and by reported NMR data of *trans*-**8a**; see: Weinges, K.; Haremsa, S. *Liebigs Ann. Chem.* **1987**, 679.

(21) It is reported that oxidation of diols by IBX afforded only lactols. For 1,4-diol to lactol oxidation by IBX, see: Corey, E. J.; Palani, A. *Tetrahedron Lett.* **1995**, *36*, 3485.

(22) Suzuki, T.; Morita, K.; Tsuchida, M.; Hiroi, K. *Org. Lett.* **2002**, *4*, 2361.

(23) Lactone **13** has already been described in the total synthesis of 15-F_{2t}-IsoP **1** based on an approach developed by Rokach; see: Hwang, S. W.; Adiyaman, M.; Khanapure, S.; Schio, L.; Rokach, J. *J. Am. Chem. Soc.* **1994**, *116*, 10829.

Scheme 5. Total Synthesis of 15-F_{2t}-IsoP **1** and its 15-Epimer



by Wittig reaction of **15a** and (4-carboxybutyl)triphenylphosphonium bromide using *t*-BuOK as base in THF at 0 °C. Esterification of the crude carboxylic acid ($TMSCHN_2$ in Et_2O/MeOH) provided ester **16** in 65% yield.[24] Introduction of the ω-side chain was performed after Dess−Martin periodinane oxidation into the aldehyde by Horner−Wadsworth−Emmons (HWE) chain elongation in 82% yield (only the *E* isomer was observed, within the limits of NMR detection). Subsequent Luche reduction of the enone functionality provided allylic alcohols epimers **17a** and **17b** as an ∼1:1 mixture. These epimers were easily separated by flash chromatography in 34% and 37% yields from **16**.[25]

(24) Two side products were also isolated; a coeluting compound with **16** attributed to the *E* isomer and a compound corresponding to a silyl migration to the primary alcohol (see the Supporting Information).

n-Bu_4NF (TBAF) deprotection of the silyl groups in THF[26] afforded triols in 91% yield.[27] Finally, ester saponification in the presence of LiOH in water/THF afforded 15-F_{2t}-IsoP **1** and 15-*epi*-F_{2t}-IsoP in 78% and 81% yields from **17a** and **17b**, respectively.

In summary, the total synthesis of 15-F_{2t}-IsoP **1** and its 15 epimer validated the feasibility of our strategy to access isoprostane derivatives from a readily available bicyclo[3.3.0]-octene scaffold. The bicyclic shape allowed an easy and highly selective introduction of the four stereocenters of the target compounds through a series of simple synthetic transformations. Currently, the total syntheses of unreported E, D-IsoPs and PhytoPs are in progress, and results will be reported in due course.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) Absolute configurations were determinated after completion of the synthesis to known 15-F_{2t}-IsoP **1** and its 15-epimer and by NMR correlation of known **17a** (see ref 23).

(26) Kaburagi, Y.; Kishi, Y. *Org. Lett.* **2007**, *9*, 723.

(27) Yield given from a 1:1 mixture **17a** and **17b** after separation of triol epimers (see the Supporting Information).