ORGANIC LETTERS

2012
Vol. 14, No. 1
299–301

Formal Synthesis of Antiplatelet Drug, Beraprost

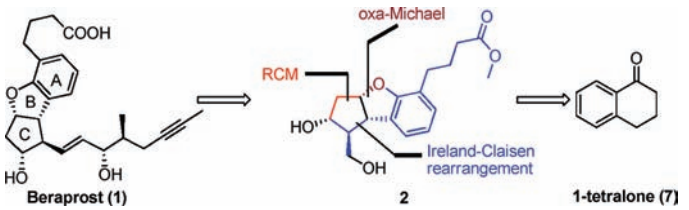
Naredla Kesava Reddy, Bodduri Venkata Durga Vijaykumar, and Srivari Chandrasekhar*

Division of Natural Products Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad, India 500 007

**srivaric@iict.res.in*

Received November 14, 2011

ABSTRACT

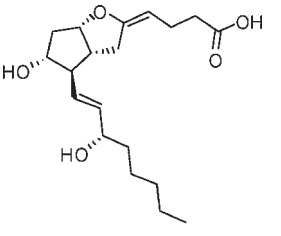


The first stereocontrolled and enantiospecific formal synthesis of antiplatelet drug beraprost has been achieved from readily available 1-tetralone.

Prostacyclin (PGI_2, Figure 1) has been a prime synthetic target for researchers, ever since its discovery, due to its excellent ability to inhibit platelet aggregation and vasodilation.[1] The biggest problem associated with handling these classes of compounds is their very labile nature, even in neutral media, due to the 'enol' functionality, let alone the acidic medium of the gastrointestinal tract.[2] Thus, the design, synthesis, and evaluation of stable analogs of PGI_2 has been a primary objective of scientists engaged in this field. Toray industries have come up with a very stable form of PGI_2 and named it beraprost (**1**).

The researchers from Toray have developed beraprost as a drug for the treatment of platelet aggregation.[3] It is less toxic and more stable than other PGI_2 analogs and sold in the market as Careload (sodium salt of beraprost).[4] The commercial route used to manufacture this drug involves bromination−debromination steps and resolution for obtaining the chiral tricyclic cyclopenta[*b*] benzofuran core.[5] Other approaches have also been reported in literature for the construction of this core for beraprost synthesis.[6]

The profound clinical use, the difficulty associated with construction of the tricyclic core with full enantiocontrol, and the synthetic challenges posed by the beraprost structure encouraged us to take up its total synthesis.



Prostacyclin (PGI_2)

Figure 1. Structure of prostacyclin (PGI_2).

Our retrosynthesis of beraprost (Scheme 1) used an oxa-Michael reaction to dissect the AB ring system.[7] This was allied with a stereoselective Ireland−Claisen rearrangement[8] and a Grubbs metathesis based enone

(1) (a) Moncada, S.; Grygleski, S.; Bunting, S.; Vane, J. R. *Nature* **1976**, *263*, 663. (b) Johnson, R. A.; Morton, D. R.; Kinner, J. H.; Gorman, R. R.; McGuire, J. C.; Sun, F. F.; Whittaker, N.; Bunting, S.; Salmon, J.; Moncada, S.; Vane, J. R. *Prostaglandins* **1976**, *12*, 915. (c) Johnson, R. A.; Lincoln, F. H.; Nidy, E. G.; Schneider, W. P.; Thompson, J. L.; Axen, U. *J. Am. Chem. Soc.* **1978**, *100*, 7690. (d) Moncada, S.; Higgs, G. A.; Vane, J. R. *Lancet* **1977**, *1*, 18.

(2) Cho, M. J.; Allen, M. A. *Prostaglandins* **1978**, *15*, 9453.

(3) (a) Collins, P. W.; Djuric, S. W. *Chem. Rev.* **1993**, *93*, 1533. (b) Nickolson, R. C.; Town, M. H.; Vorbruggen, H. *J. Med. Res. Rev.* **1985**, *5*, 1. (c) Ansoff, P. A. *Adv. Prostaglandin Thromboxane Leukotriene Res.* **1985**, *14*, 309.

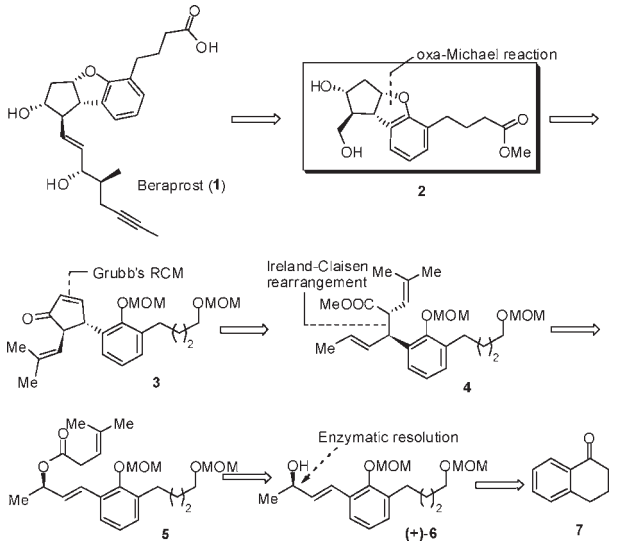
(4) Nagase, H.; Matsumo, K.; Nishiya, H. *J. Synth. Org. Chem.* **1996**, *54*, 1055.

(5) Wakita, H.; Matsumoto, K.; Yoshiwara, H.; Hosono, Y.; Hayashi, R.; Nishiyama, H.; Nagase, H. *Tetrahedron* **1999**, *55*, 2449.

10.1021/ol203060v
Published on Web 12/14/2011

construction to build the C ring. Lipase catalyzed asymmetric induction was also conceived as a key step toward the target.[9,10]

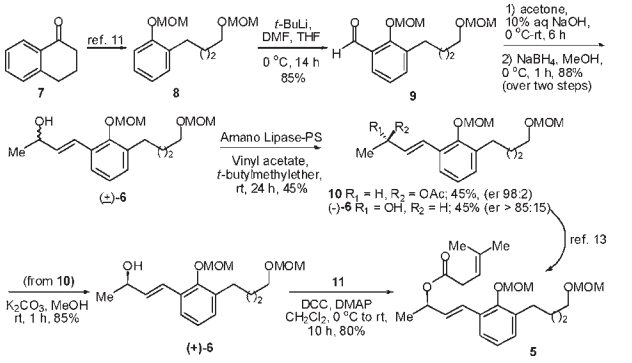
Scheme 1. Retrosynthetic Analysis of Beraprost



The forward strategy started from commercially available 1-tetralone (**7**), which was converted to the di-MOM derivative **8** in decent yields, in a process amenable to scaleup.[11] Classical formylation of **8** using DMF and *t*-BuLi smoothly afforded the di-MOM protected aldehyde **9**. Aldehyde **9** was subjected to aldol reaction with acetone in the presence of 10% aqueous NaOH, furnishing the enone which was reduced with $NaBH_4$ into racemic allyl alcohol **6** in 88% yield over two steps (Scheme 2). Attention was then directed to introduction of the chiral hydroxyl group via *Burkholderia cepacia* lipase-mediated (Amano Lipase PS, Sigma-Aldrich) resolution.[10]

After successful enzymatic resolution, using lipase and vinyl acetate in *tert*-butylmethyl ether at room temperature, (*R*)-acetate **10** was obtained in 45% yield and ~97% ee as confirmed by HPLC analysis.[12] The hydrolysis of the acetyl group in **10** resulted in chiral alcohol (+)-**6** in 85% yield. 4-Methyl 3-pentenoic acid **11** was coupled with (+)-**6** in the presence of DCC/DMAP to furnish ester **5**. The other enantiomer (−)-**6** was also converted to the desired **5** *via* esterification with **11** under Mitsunobu conditions[13] (total 51% yield of **5** from *rac*-**10**).

Scheme 2. Preparation of Intermediate **5**



The desired Ireland−Claisen rearrangement was performed on **5** with LDA/TBSCl and HMPA; this resulted in selective formation of the (*Z*)-silyl ketene acetal prior to rearrangement at −78 °C and furnished the required stereoisomer **12** (Scheme 3). This can be explained by invoking the chairlike transition state TS-1. A steady increase in temperature to 25 °C followed by an acidic workup, gave the desired rearrangement product **12** which was further derivatized as the methyl ester **4**

(6) (a) Review: Saibal, D.; Chandrasekhar, S.; Yadav, J. S.; Gree, R. *Chem. Rev.* **2007**, *107*, 3286. (b) Review: Collins, P. W.; Djuric, S. W. *Chem. Rev.* **1993**, *93*, 1533. (c) Jahn, U.; Galano, J. M.; Durand, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5894. (d) Nagase, H.; Matsumoto, K.; Nishiyama, H. *Yuki Gousei Kagaku Kyoukaishi* **1999**, *57*, 1116. (e) Nishino, S.; Nagase, H.; Kanou, K.; Aoki, S.; Kanabayashi, Y. *Yakugaku Zasshi* **1997**, *117*, 509. Synthesis of (±)-Beraprost:(f) Ohno, K.; Nagase, H.; Matsumoto, K. European Patent EP84,-856, 1983; European patent specification EP 1 519 930 B1; *Chem. Abstr.* **1984**, *100*, 51356m. (g) Ohno, K.; Nishiyama, H.; Nagase, H.; Matsumoto, K.; Ishikawa, M. *Tetrahedron Lett.* **1990**, *31*, 4489. Synthesis of optically active Beraprost:(h) Nagase, H.; Yoshiwara, H.; Tajima, A.; Ohno, K. *Tetrahedron Lett.* **1990**, *31*, 4493. (i) Wakita, H.; Yoshiwara, H.; Tajima, A.; Kitano, Y.; Nagase, H. *Tetrahedron: Asymmetry* **1999**, *10*, 4099. (i) Wakita, H.; Yoshiwara, H.; Nishiyama, H.; Nagase, H. *Heterocycles* **2000**, *53*, 1085. (j) Wakita, H.; Yoshiwara, H.; Kitano, Y.; Nishiyama, H.; Nagase, H. *Tetrahedron: Asymmetry* **2000**, *11*, 2981. (k) Yukio, Y.; Yoshitaka, S.; Sentaro, O.; Fumie, S. *J. Chem. Soc., Chem. Commun.* **1995**, 811. (l) Richard, C. L.; Nam, H. L. *J. Org. Chem.* **1991**, *56*, 6253. (m) Kazuhiro, H.; Kazuyuki, S.; Hisanori, N.; Takeshi, S.; Yasuyuki, K. *Org. Lett.* **2003**, *5*, 3703.

(7) (a) Tatjana, G. K.; Martina, P.; Svjetlana, K.; Damjan, M.; Janez, P.; Tobias, L. R.; Simon, M. A.; Silvana, R. M. *Molecules* **2011**, *16*, 5113. (b) Carl, F. N.; Stefan, B. *Chem. Soc. Rev.* **2008**, *37*, 1218.

(8) (a) Hyojin, K.; Eunkyung, K.; Jae Eun, p.; Deukjoon, K.; Sanghee, K. *J. Org. Chem.* **2004**, *69*, 112. (b) Yanling, S.; Soonho, H.; Ping, G.; Deukjoon, K.; Sanghee, K. *Org. Lett.* **2008**, *10*, 269.

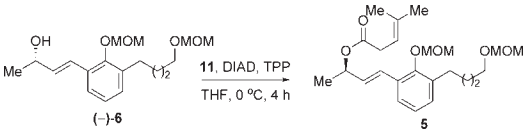
(9) (a) Thomas, R. H.; Hongyu, Z. *Org. Lett.* **1999**, *1*, 1123. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2037. (d) Ulman, M.; Grubbs, R. H. *Organometallics* **1998**, *17*, 2484. (c) Thomas, N.; Michael, B.; Kai, D.; Paul, K. *Org. Process Res. Dev.* **2005**, *9*, 513. (d) Nathan, K. Y.; Vittorio, F.; Ioannis, N. H.; Nizar, H.; Rogelio, P. F.; Fabrice, G.; Xiao-jun, W.; Xudong, W.; Robert, D. S.; Xuwu, F.; Victor, F.; Yibo, X.; Jonathan, T.; Li, Z.; Jinghua, X.; Lana, L. S. K.; Jana, V.; Michael, D. R.; Earl, M. S.; Michael, J. *J. Org. Chem.* **2006**, *71*, 7133.

(10) Brenna, E.; Fuganti, C.; Galli, F. G.; Passoni, M.; Serra, S. *Tetrahedron: Asymmetry* **2003**, *14*, 2401.

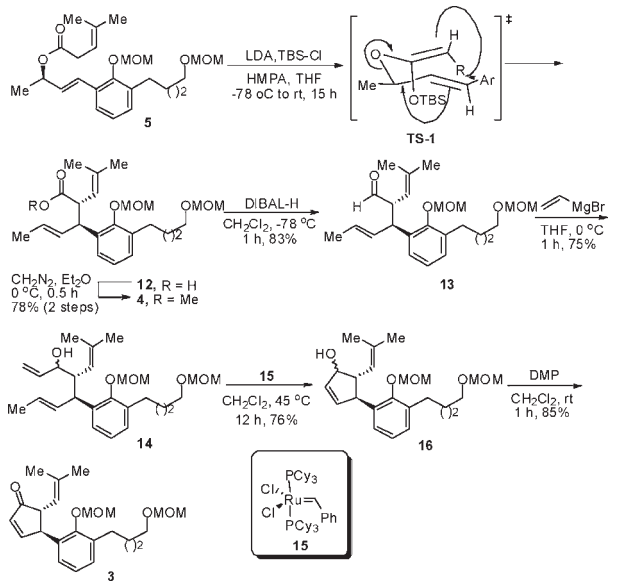
(11) (a) Quinkert, G.; Billhardt, U. M.; Jakob, H.; Fischer, G.; Glenneberg, J. *Helv. Chim. Acta* **1987**, *70*, 822. (b) Cambie, R. C.; MitchellLorna, H.; Rutledge, P. S. *Aust. J. Chem.* **1998**, *51*, 1167. (c) Youssefyeh, R. D.; Campbell, H. F.; Klein, S.; Airey, J. E.; Darkes, P. *J. Med. Chem.* **1992**, *35*, 895. (d) Masahiko, I.; Yoshiyuki, N.; Kakuzo, I. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1163.

(12) See the Supporting Information for details.

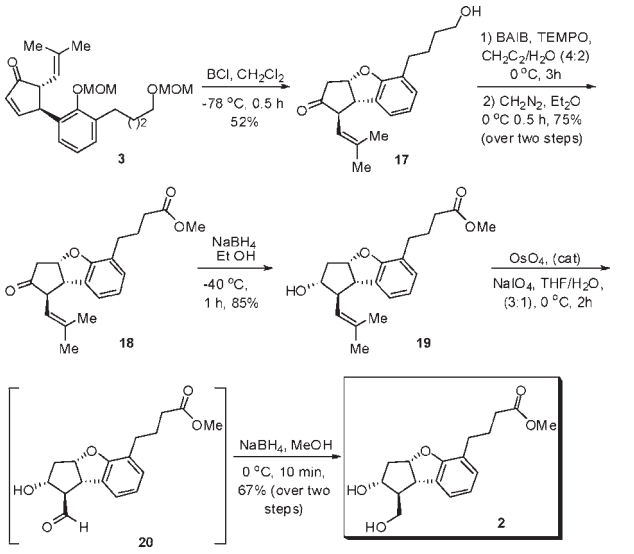
(13) The enantiomeric purity of (*S*)-isomer (−)-**6** was improved by repeated resolution (twice), which was subjected to esterification with **11** under Mitsunobu inversion reaction conditions to realize compound **5** in 65% yield.



Scheme 3. Preparation of Intermediate **3**



Scheme 4. Synthesis of **2**



(78% yield over two steps) with >15:1 diastereoselectivity.[12] The relative stereochemistry was tentatively assigned for the two newly generated stereocenters of **4** on the basis of literature precedent and was solvent dependent, with 20% HMPA being critical to obtaining high levels of diastereoselectivity.[8]

DIBAL-H reduction of **4** yielded aldehyde **13** which was reacted with vinyl magnesium bromide in THF at 0 °C to furnish a diastereomeric mixture (1:1) of allylic alcohol **14** in 75% yield. Ring-closing metathesis[9] was facile with the first generation Grubbs catalysis and gave **16**. Oxidation of **16** with Dess-Martin reagent produced enone **3**. This enone required exposure to BCl_3 not only for deprotection of two MOM protecting groups but also to induce an *in situ* oxa-Michael cyclization to provide the cyclopenta[*b*]benzofuran **17** having all the required functionalities to arrive at the target (Scheme 4). Thus, oxidation of **17** was achieved with BAIB, TEMPO. The acid formed was isolated as methyl ester **18** by diazomethane treatment. The keto functionality in **18** was reduced with $NaBH_4$ to produce alcohol **19** as a single diastereomer, as anticipated. The osmylative cleavage of olefin **19** to unstable aldehyde **20** was followed by reduction with $NaBH_4$. It resulted in a late-stage fully functional core **2** of beraprost in enantiopure form.[14]

In summary, the present stereospecific formal synthesis of beraprost was successfully achieved using enzymatic resolution, Ireland–Claisen rearrangement, Grubbs' metathesis, and oxa-Michael reaction as key transformations starting from commercially available 1-tetralone.

Acknowledgment. N.K.R. and B.V.D.V. thank UGC and CSIR-New Delhi respectively for the award of a research fellowship.

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

(14) Wakita, H.; Yoshiwara, H.; Nishiyama, H.; Nagase, H. *Heterocycles* **2000**, *53*, 1085.