ORGANIC LETTERS

2000
Vol. 2, No. 16
2543−2544

A Short Catalytic Enantioselective Synthesis of the Proinflammatory Eicosanoid 12(*R*)-Hydroxy-5(*Z*),8(*Z*),10(*E*),14(*Z*)-eicosatetraenoic Acid (12(*R*)-HETE)

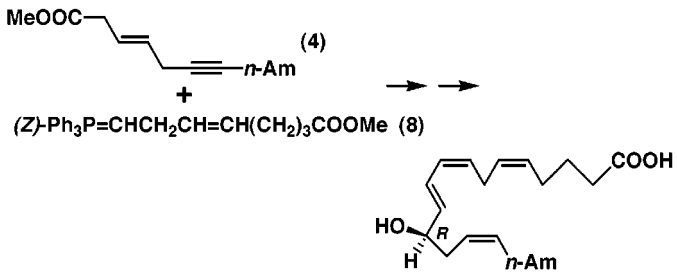
Xiaojun Han and E. J. Corey*

Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138

corey@chemistry.harvard.edu

Received June 21, 2000

ABSTRACT



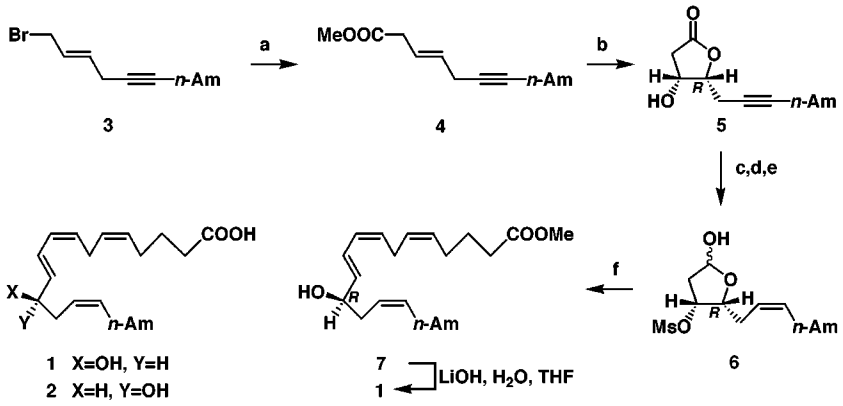
A new and effective pathway is described for the synthesis of 12(*R*)-HETE and the 12(*S*)-enantiomer from the common intermediates 4 and 8.

The understanding of the cyclooxygenase (CO) pathway to prostanoids (PG's) and of the 5-lipoxygenase (5-LO) pathway to leukotrienes from arachidonic acid has had profound effects on biology and medicine and represents a major contribution of chemistry to these fields. Recently, it has become clear that the 12-LO pathway from arachidonic to 12-hydroxy-5(*Z*),8(*Z*),10(*E*),14(*Z*)-eicosatetraenoic acid (12-HETE), discovered over a quarter of a century ago by Hamberg and Samuelsson in human platelets[1] and epidermis of psoriasis,[2] also plays a critical role in human health and disease. The 12-LO pathway and 12-HETE have been implicated, inter alia, in angiogenesis,[3] the viability and metastatic potential of tumor cells,[4] atherogenesis,[5] coronary thrombosis,[6] type I diabetes induction,[7] inflammation and psoriasis,[2,8] and inhibition of apoptosis.[9] It has been established that 12(*R*)-HETE is present in psoriatic tissue rather than the more common 12(*S*)-enantiomer.[10] It also has been

(1) Hamberg, M.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 3400.
(2) Hammarström, S.; Hamberg, M.; Samuelsson, B.; Duell, E. A.; Stawiski, M.; Voorhees, J. J. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*, 5130.
(3) (a) Nie, D.; Tang, K.; Diglio, C.; Honn, K. V. *Blood* **2000**, *95*, 2304. (b) Tang, K.; Finley, R. L.; Nie, D.; Honn, K. V. *Biochemistry* **2000**, *39*, 3185. (c) Nie, D.; Hillman, G. G.; Geddes, T.; Tang, K.; Pierson, C.; Grignon, D. J.; Honn, K. V. *Adv. Exptl. Med. Biol.* **1999**, *469*, 623.
(4) (a) Ding, X. Z.; Iversen, P.; Cluck, M. W.; Knezetic, J. A.; Adrian, T. E. *Biochem. Biophys. Res. Commun.* **1999**, *261*, 218. (b) Chen, L. C.; Chen, B. K.; Liu, Y. W.; Chang, W. C. *FEBS Lett.* **1999**, *455*, 105. (c) Tang, K.; Honn, K. V. *Adv. Exptl. Med. Biol.* **1999**, *447*, 181. (d) Yamamoto, S.; Suzuki, H.; Ueda, N. *Prog. Lipid Res.* **1997**, *36*, 23. (e) Herbertsson, H.; Hammarström, S. *Adv. Exptl. Med. Biol.* **1997**, *400A*, 287. (f) Nie, D.; Hillman, G. G.; Geddes, T.; Tang, K.; Pierson, C.; Grignon, D. J.; Honn, K. V. *Cancer Res.* **1998**, *58*, 4047.
(5) Cyrus, T.; Witztum, J. L.; Rader, D. J.; Tangirala, R.; Fazio, S.; Linton, M. F.; Funk, C. D. *J. Clin. Invest.* **1993**, *103*, 1597.
(6) Katoh, A.; Ikeda, H.; Murohara, T.; Haramaki, N.; Ito, H.; Imaizumi, T. *Circulation* **1998**, *98*, 2891.
(7) Bleich, D.; Chen, S.; Zipser, B.; Sun, D.; Funk, C. D.; Nadler, J. L. *J. Clin. Invest.* **1999**, *103*, 1431.
(8) (a) Ziboh, V. A. *Lipids* **1996**, *31*, S249. (b) Natarajan, R.; Pei, H.; Gu, J. L.; Sarma, J. M.; Nadler, J. *Cardiovasc. Res.* **1999**, *41*, 489.
(9) Tang, D. G.; Chen, Y. Q.; Honn, K. V. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 5241.
(10) (a) Woolard, P. M. *Biochem. Biophys. Res. Commun.* **1986**, *136*, 169. (b) Cunningham, F. M.; Woolard, P. M. *Prostaglandins* **1987**, *34*, 71.
(11) (a) Boeglin, W. E.; Kim, R. B.; Brash, A. R. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 6744. (b) Sun, D.; McDonnell, M.; Chen, X. S.; Lakkis, M. M.; Li, H.; Isaacs, S. N.; Elsea, S. H.; Patel, P. I.; Funk, C. D. *J. Biol. Chem.* **1998**, *273*, 33540.

10.1021/ol0062392 CCC: $19.00
Published on Web 07/08/2000

Scheme 1



(a) 2 mol % $Pd(PPh_3)_4$, 1 eq $KHCO_3$, 65 atm CO, MeOH, 36 h at 23 °C (70%). (b) AD-mix-β, 1 eq $CH_3SO_2NH_2$, 1 : 1 *t*-BuOH–H_2O, 36 h at 0 °C (72%, 95% ee). (c) 1 atm H_2, Pd–$CaCO_3$ (Lindlar), THF, 40 min at 23 °C (99%). (d) 1.4 eq CH_3SO_2Cl, 1.4 eq Et_3N, CH_2Cl_2, 1 h at 0 °C. (e) *i*-Bu_2AlH, C_7H_8, 1 h at -78 °C (70% overall from **5**). (f) (*Z*)-$Ph_3P{=}CHCH_2CH{=}CH(CH_2)_3COOMe$ (**8**), 1 : 0.3 THF–HMPA, 1 h at -25 °C (72%).

discovered that humans possess genes encoding the 12(*R*)-LO[11] as well as genes for the longer known 12(*S*)-LO enzymes.[4d,12] Interestingly, 12(*R*)-HETE (**1**) appears to be an order of magnitude more proinflammatory than 12(*S*)-HETE (**2**).[10]

The growing importance of 12(*S*)- and 12(*R*)-HETE in biological regulation and disease underscores the need for adequate supplies of these enantiomeric substances for fundamental studies. This paper reports an efficient and short synthetic route to the enantiomers **1** and **2** using modern catalytic asymmetric methodology. The route is illustrated specifically for the 12(*R*)-HETE (**1**) but clearly can be applied equally well to the enantiomer **2**. Since the original synthesis of 12(*S*)-HETE,[13] a number of other syntheses of racemic and chiral 12-HETEs have been described, none being of the modern catalytic enantioselective type.[14]

The pathway of synthesis of **1** is summarized in Scheme 1. The allylic bromide **3**, synthesized in 65% yield by coupling of 1 equiv of 1-heptynylmagnesium bromide with (*E*)-1,4-dibromo-2-butene in the presence of 10 mol % of CuBr in THF at 0 → 50 °C[15] was converted to (*E*)-β,γ-unsaturated ester **4** by Pd(0)-catalyzed carbonylation in methanol.[16] Sharpless asymmetric dihydroxylation of **4** using the dihydroquinidine-based biscinchona catalyst/reagent AD-mix-β (Aldrich) occurred with in situ lactonization to give the chiral β-hydroxy lactone **5**, $[\alpha]_D^{22}$ +45.4 (*c* 0.8, Me_2CO), of 95% ee[17] as determined by HPLC analysis using a Whelk O-1 column with 1:9 isopropyl alcohol−hexane as eluent (retention times: 21.7 min for *S*,*S*-enantiomer of **5** and 26.1 min for **5**). Selective Lindlar reduction of the triple bond of **5** gave the corresponding *Z*-olefin, which was converted to the methanesulfonate and reduced with DIBAL-H in toluene at −78 °C to form lactol mesylate **6**. Reaction of **6** with the ylide $(Z)\text{-}Ph_3P{=}CHCH_2CH{=}CH(CH_2)_3COOMe$ (**8**)[18] in 1:0.3 THF−HMPA at −25 °C for 1 h produced the methyl ester (**7**) of 12(*R*)-HETE, $[\alpha]_D^{22}$ −14.8 (*c* 0.9, acetone), which was spectroscopically identical with an authentic sample. Saponification of the methyl ester **7** with 1:1 1 N LiOH(aq)−THF affords 12(*R*)-HETE (**1**).

Modification of the synthesis shown in Scheme 1 by replacing AD-mix-β by AD-mix-α in the synthesis allows formation of *ent*-**5** and therefore 12(*S*)-HETE (**2**).

The synthetic process described herein thus allows the preparation of both 12(*R*)- and 12(*S*)-HETE from the common building blocks **4** and **8** in a remarkably simple and effective way.

Acknowledgment. This research was assisted by a grant from the National Science Foundation. We are very grateful to Dr. Sheldon Crane for experimental assistance.

OL0062392

(12) (a) Izumi, T.; Hoshiko, S.; Rådmark, O.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 7477. (b) Funk, C. D.; Furci, L.; Fitzgerald, G. A. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 5638.

(13) Corey, E. J.; Niwa, H.; Knolle, J. *J. Am. Chem. Soc.* **1978**, *100*, 1942.

(14) (a) Corey, E. J.; Marfat, A.; Falck, J. R.; Albright, J. O. *J. Am. Chem. Soc.* **1980**, *102*, 1433. (b) Corey, E. J.; Kyler, K.; Raju, N. *Tetrahedron Lett.* **1984**, *25*, 5115. (c) Russell, S. W.; Pabon, H. J. J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 545. (d) Just, G.; Wang, Z. Y. *Tetrahedron Lett.* **1985**, *26*, 2993. (e) Just, G.; Wang, Z. Y. *J. Org. Chem.* **1986**, *51*, 4796. (f) Yadagiri, P.; Lumin, S.; Mosset, P.; Capdevila, J.; Falck, J. R. *Tetrahedron Lett.* **1986**, *27*, 6039. (g) Shimazaki, T.; Kobayashi, Y.; Sato, F. *Chem. Lett.* **1988**, 1785. (h) Nagata, R.; Kawakami, M.; Matsuura, T.; Saito, I. *Tetrahedron Lett.* **1989**, *30*, 2817. (i) Nicolaou, K. C.; Ramphal, J. Y.; Abe, Y. *Synthesis* **1989**, 898. (j) Mosset, P.; Pointeau, P.; Aubert, F.; Lellouche, J. P.; Beaucourt, J. P.; Grée, R. *Bull. Soc. Chim. Fr.* **1990**, *127*, 298. (k) Lumin, S.; Falck, J. R.; Schwartzman, M. L. *Tetrahedron Lett.* **1991**, *32*, 2315.

(15) Nicolaou, K. C.; Ladduwahetty, T.; Elisseou, E. M. *J. Chem. Soc., Chem. Commun.* **1985**, 1580.

(16) Kiji, J.; Okano, T.; Higashimae, Y.; Fukui, Y. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1029. Increased pressure of CO minimizes methanolysis of allylic bromide **3** to the corresponding methyl ether.

(17) (a) Sharpless, K. B.; Amberg, W.; Bennani, Y.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768. (b) Wang, Z.; Zhang, X.; Sharpless, K. B.; Sinha, S. C.; Sinha-Bagchi, A.; Keinan, E. *Tetrahedron Lett.* **1992**, *33*, 6407.

(18) Ylide **8** was prepared from the corresponding phosphonium salt by reaction with sodium hexamethyldisilazide in THF at −25 °C, see: (a) Zamboni, R.; Milette, S.; Rokach, J. *Tetrahedron Lett.* **1983**, *24*, 4899. (b) Sandri, J.; Viala, J. *J. Org. Chem.* **1995**, *60*, 6627.