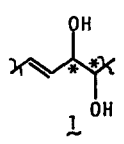
Tetrahedron Letters,Vol.29,No.48,pp 6297-6300,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

A HIGHLY PRACTICAL SYNTHESIS OF CHIRAL (E)-1-TRIMETHYLSILYL-1-ALKEN-3,4-DIOLS VIA THE SHARPLESS ASYMMETRIC EPOXIDATION OF 1,5-BIS(TRIMETHYLSILYL)-1,4-PENTADIEN-3-OL. FORMAL TOTAL SYNTHESIS OF LIPOXIN B

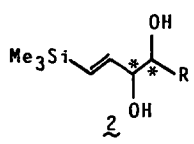
Yuichi Kobayashi, Norihiro Kato, Toshiyuki Shimazaki, and Fumie Sato*
Department of Chemical Engineering, Tokyo Institute of Technology,
Meguro, Tokyo 152, Japan

Summary: The Sharpless asymmetric epoxidation of the alcohol 4 proceeds with an extremely high efficiency to afford the epoxide 5 from which the title chiral alcohol 2 is synthesized in good overall yield. By using the alcohol 2, the Nicolaou's lipoxin B intermediates 18 and 20 are prepared in a stereoselective way.

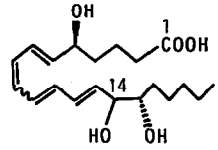
In the last several years, a family of linear oxygenated metabolites of arachidonic acid has been implicated in immediate hypersensitivity reactions, inflammation, and a number of other health-problems.[1] Because of the low availability of these compounds from natural sources, their total syntheses have attracted much interests for further biological investigations.[2] Among these metabolites, several compounds such as lipoxin A, lipoxin B, 5,6-diHETE, 11,12-diHETE, and 14,15-diHETE possess 1-substituted (E)-1-alken-3,4-diol unit 1 as a common substructure. Herein we report a highly efficient and general method for preparation of chiral (E)-1-trimethylsilyl-1-alken-3,4-diols (2) which are useful compounds for construction of the unit 1, and the formal total synthesis of lipoxin B (3) by using 2.[3]



1

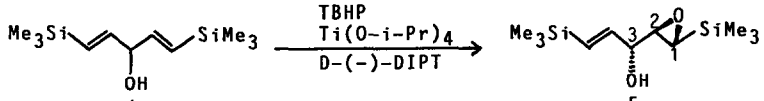


2



lipoxin B (3)

The present method for synthesis of 2 is based on the new finding that the Sharpless asymmetric epoxidation of 1,5-bis(trimethylsilyl)-1,4-pentadien-3-ol (4) which possesses the symmetry σ-plane proceeds with a high efficiency to afford the 1R,2R,3R epoxide 5 as a sole product (eq 1).

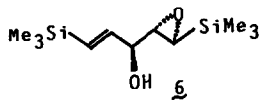


4 5 (1)

The starting alcohol 4 was conveniently prepared in a large quantity by the reaction of ethyl formate with (E)-Me_3SiCH=CHLi in 83% yield (>99% chemical purity) or with Me_3SiCH=CHMgBr in 70% yield (ca 95% chemical

purity). The epoxidation of 4 using t-BuOOH (TBHP) (1.5 equiv), $Ti(O\text{-}i\text{-}Pr)_4$ (0.2 equiv), and D-(-)-DIPT (0.24 equiv) in the presence of 4A molecular sieves provided the epoxide 5 ($[\alpha]_D^{25}$ -24.0° (c 1.35, $CHCl_3$)) in 92% yield as a sole product (>99% ds by ^{13}C NMR) after 3.5 h at -21 °C (eq 1).[4] The optical purity of 5 thus prepared was found to be more than 98% ee by ^1H NMR spectroscopy of the corresponding MTPA ester (detection limit ca 98% ee). Noteworthy here is the fact that the epoxide 5 with >98% ee was obtained even at 30% conversion of the reaction. This result is in much contrast to the reported finding that the asymmetric epoxidation of 1,4-pentadien-3-ol (protodesilylated compound of 4) afforded the corresponding epoxy alcohol with rather low ee at low conversion.[5,6]

Similarly 1S,2S,3S epoxide 6 (>98% ee), the antipode of 5, was obtained in 92% yield by using L-(+)-DIPT instead of D-(-)-DIPT in the reaction of eq (1).



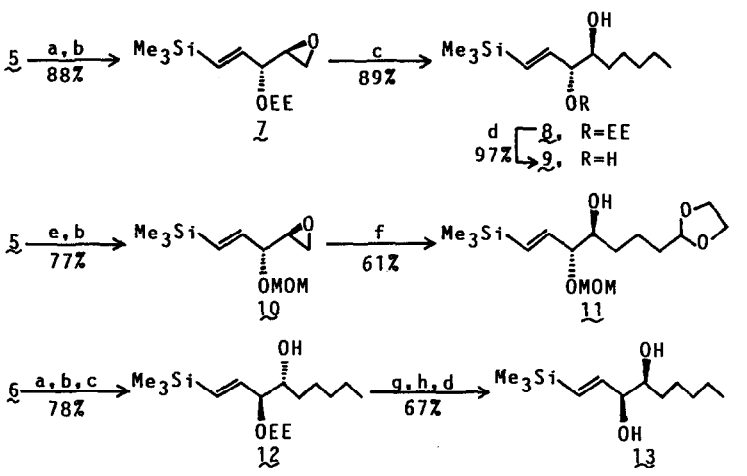
6

Starting with the epoxy alcohols 5 and 6, the corresponding diols 2 were readily prepared by the sequence of simple reactions. Thus, the diol 9 which can be used as an intermediate for synthesis of 14(R)-lipoxin B (3) and 14(R),15(S)-diHETE was synthesized from 5 as detailed in Scheme I. The alcohol 5 was protected as the ethoxyethyl ether which upon selective desilylation (Bu_4NF) afforded 7 in 88% yield. Epoxide ring opening reaction of 7 with n-BuMgBr in the presence of a catalytic amount of CuI furnished the alcohol 8, deprotection of which with aqueous HCl afforded 9 in 86% yield from 7. The diol derivative 11 which is corresponding to C(1)-C(8) portion of 6(R)-lipoxin A and 5(S),6(R)-diHETE was prepared from 5 in 47% overall yield by a similar sequence of reactions. The diol 13 corresponding to C(12)-C(20) portion of 14(S)-lipoxin B (3) and 14(S),15(S)-diHETE was also synthesized starting from 6 via the Mitsunobu inversion of 12 (the antipode of 8).[7]

With (E)-1-trimethylsilyl-1-alken-3,4-diols such as 9 and 13 in hand, we have carried out the synthesis of the Nicolaou's lipoxin B intermediates 18 and 20 as shown in Scheme II.[3a,b] Oxidation of 9 with mCPBA afforded the epoxide as a mixture of diastereoisomers which upon treatment with Bu_3SnLi yielded 14 in 40% yield. Reaction of 14 with excess (E)-ClCH=CHCl in the presence of Pd(0) catalyst afforded 15 in 61% yield.[8] Coupling reaction of 15 with the C(1)-C(9) fragment 16[9,10] (>99% ee) was effected by Pd(0)-Cu(I) catalyst to give 17 in 70% yield.[11] Finally, desilylation of 17 and subsequent SiO_2-column chromatography furnished 18[12] ($[\alpha]_D^{27}$ +11.9° (c 0.41, $CHCl_3$)) in 61% yield along with the corresponding lactone in 10% yield. In the same manner, 20 ($[\alpha]_D^{25}$ -21.1° (c 0.25, $CHCl_3$); lit.[3b] $[\alpha]_D^{20}$ -21.72° (c 1.0, $CHCl_3$)) was synthesized from 13 and 16 via 19. The spectroscopic data (^1H NMR and IR) of 20 thus prepared were in good agreement with those reported by Nicolaou.[3b]

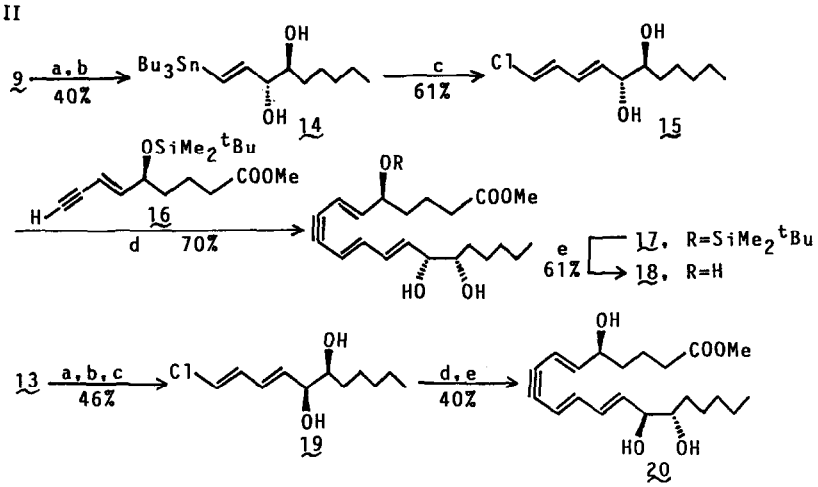
Investigation for the stereoselective transformation of 18 and 20 into the corrisponding lipoxin B (3), and synthesis of lipoxin A and 5,6- and

Scheme I



a, CH_2=CHOEt, PPTS (cat), CH_2Cl_2; b, n-Bu_4NF, DMSO; c, n-BuMgBr, CuI (cat), THF/Et_2O; d, 3N HCl, MeOH/H_2O; e, MOMCl, NaH, THF; f,  MgBr, CuI (cat), THF; g, DEAD, p-NO_2-C_6H_4COOH, PPh_3, THF; h, NaOH, THF/MeOH/H_2O.

Scheme II



a, mCPBA, CH_2Cl_2; b, n-Bu_3SnLi, THF/HMPA; c, (E)-ClCH=CHCl, $Pd(PPh_3)_4$ (cat), DMF; d, 16, n-$PrNH_2$, $Pd(PPh_3)_4$ (cat), CuI (cat), PhH; e, n-Bu_4NF, THF.

14,15-diHETE are now in progress.

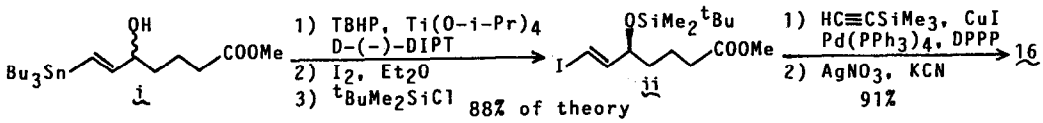
A part of this work was supported by the Grant-in-Aid for Special Project Research from the Ministry of Education, Science and Culture.

References and Notes

1. (a) L. W. Chakrin and D. M. Bailey, Eds., "The Leukotrienes. Chemistry and Biology", Academic Press, New York, 1984; (b) B. Samuelsson, Science,

220, 568 (1983); (c) C. N. Serhan, M. Hamberg, B. Samuelsson, J. Morris, and D. G. Wishka, Proc. Natl. Acad. Sci. USA, 83, 1983 (1986); (d) C. N. Serhan, K. C. Nicolaou, S. E. Webber, C. A. Veale, S.-E. Dahlén, T. J. Puustinen, and B. Samuelsson, J. Biol. Chem., 261, 16340 (1986), and references cited therein.

2. R. H. Green and P. F. Lambeth, Tetrahedron, 39, 1687 (1983); J. Rokach and J. Adams, Acc. Chem. Res., 18, 87 (1985); E. J. Corey, D. A. Clark, and A. Marfat, ref. 1a, Chapter 2.
3. Total synthesis of lipoxin B reported thus far: (a) K. C. Nicolaou and S. E. Webber, J. Chem. Soc., Chem. Commun., 297 (1985); (b) Idem, Synthesis, 453 (1986); (c) Y. Leblanc, B. Fitzsimmons, J. Adams, and J. Rokach, Tetrahedron Lett., 26, 1399 (1985); (d) E. J. Corey, M. M. Mehrotra, and W. Su, ibid., 26, 1919 (1985); (e) J. Morris and D. G. Wishka, ibid., 27, 803 (1986); (f) Idem, Adv. Prostaglandin, Thromboxane, Leukotriene Res., 16, 99 (1986).
4. Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, K. B. Sharpless, J. Am. Chem. Soc., 109, 5765 (1987).
5. S. L. Schreiber, T. S. Schreiber, and D. B. Smith, J. Am. Chem. Soc., 109, 1525 (1987).
6. Far higher efficiency of the kinetic resolution of γ-trimethylsilyl-allylic alcohols compared to the corresponding protodesilylated allylic alcohols, see: Y. Kitano, T. Matsumoto, and F. Sato, J. Chem. Soc., Chem. Commun., 1323 (1986); Idem, Tetrahedron, 44, 4073 (1988); P. R. Carlier, W. S. Mungall, G. Schröder, and K. B. Sharpless, J. Am. Chem. Soc., 110, 2978 (1988).
7. O. Mitsunobu, Synthesis, 1 (1981).
8. J. K. Stille and B. L. Groh, J. Am. Chem. Soc., 109, 813 (1987).
9. The optically pure fragment 16 (>99% ee) was readily prepared as shown below starting with the racemic alcohol i via the kinetic resolution using the Sharpless reagent.[10]



10. Y. Kitano, T. Matsumoto, S. Okamoto, T. Shimazaki, Y. Kobayashi, and F. Sato, Chem. Lett., 1523 (1987).
11. K. Sonogashira, Y. Tohda, and N. Hagihara, Tetrahedron Lett., 4467 (1975); V. Ratovelomanana and G. Linstrumelle, ibid., 22, 315 (1981); Idem, Synth. Commun., 11, 917 (1981).
12. IR(neat) 3410, 1725, 1110, 988 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.87 (t, J = 6 Hz, 3H), 1.20-1.82 (m), 2.04 (br s, 3H), 2.36 (t, J = 7.5 Hz, 2H), 3.67 (s, 3H), 3.66-3.78 (m, 1H), 4.11-4.26 (m, 2H), 5.68-5.98 (m, 3H), 6.12 (dd, J = 5.5, 16 Hz, 1H), 6.34 (dd, J = 11, 15 Hz, 1H), 6.59 (dd, J = 11, 15 Hz, 1H).

(Received in Japan 12 September 1988)