Tetrahedron Letters,Vol.31,No.1,pp 27-30,1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

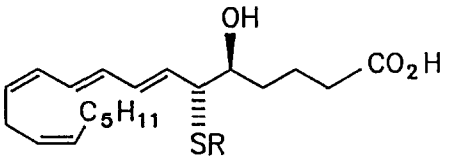
CONFORMATIONALLY RESTRICTED LEUKOTRIENE ANTAGONISTS. ASYMMETRIC SYNTHESIS OF A NOR-LEUKOTRIENE D_4 ANALOG. II[1].

Jeffrey S. Sabol*
Merrell Dow Research Institute
2110 East Galbraith Road, Cincinnati, Ohio 45215, U.S.A.

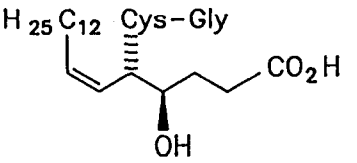
Robert J. Cregge
Merrell Dow Research Institute
9550 North Zionsville Road, Indianapolis, Indiana 46268, U.S.A.

Summary: Chiral diol 5 is prepared from cyclohexanone and used in the asymmetric synthesis of nor-leukotriene D_4 analog 1.

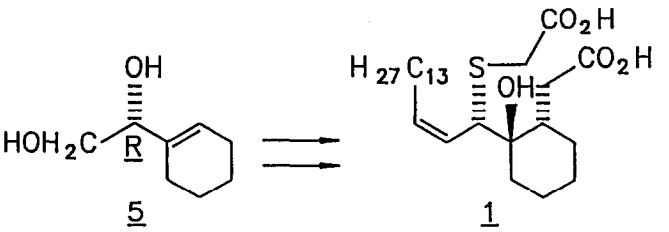
Inspired by a recent report that 2-nor-leukotriene analogs, such as SKF 101132[2], possess significant LTD_4 antagonist activity, we have extended our conformationally restricted approach to the design of new LTD_4 antagonists based upon nor-LTD_4 analogs. The molecule 1, in which two of the three contiguous asymmetric centers are confined to the cyclohexane ring, was considered to be a particularly attractive target.



LTD_4 SR=Cysteinylglycine



SKF 101132

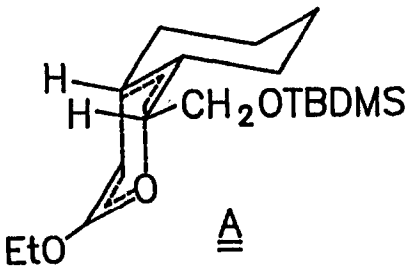


While considering approaches to this problem, the potential of the Sharpless asymmetric epoxidation[3] of allylic alcohols was appealing in that 2,3-epoxy alcohols are versatile intermediates in the enantio- and stereoselective syntheses of polyfunctional organic molecules.[4] In this letter, we report the asymmetric synthesis of the chiral diol 5 and its conversion to 1 (Scheme I).

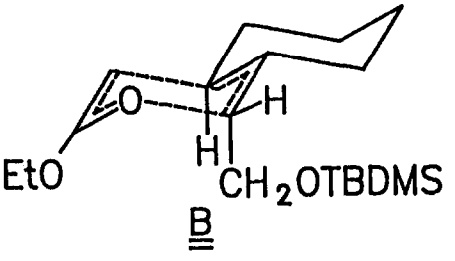
The first substrate for asymmetric epoxidation in this reaction scheme was the allylic alcohol 3. This substance was prepared in two steps from 2 by a Wadsworth-Emmons homologation [5] followed by reduction with DIBAL in 65% overall yield. Catalytic asymmetric epoxidation[6] of 3, employing a non-acidic aqueous workup, afforded epoxy alcohol 4($[\alpha]_D^{20}$= -16.1(c=1.0, $CHCl_3$)) as an oil in 80% yield and 82% enantiomeric excess (ee), determined by ^1H and ^{19}F NMR (C_6D_6, 300 MHz[7]) analyses of the (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid [(+)-MTPA]ester[8]. The (S)-absolute configuration, resulting from delivery of oxygen from the bottom enantioface of the olefin using L-(+)-DET, is predicted by the Sharpless model[3].

With the acid-sensitive epoxy-alcohol 4 in hand, careful isomerization to the chiral diol 5 was accomplished by stirring in a two-phase mixture of 10% aqueous tartaric acid-methylene chloride at room temperature. In this way, 5 was produced in 40% yield after chromatography[9]. Recrystallization from hexane-chloroform produced analytically pure 5 (m.p. 72-73°C; $[\alpha]_D^{20}$=-28.1°(c=1.02, $CHCl_3$)). The R absolute configuration was confirmed by analogy to the reported optical rotation for R-2-cyclohexyl-1,2-ethanediol($[\alpha]_D^{20}$=-4.17°(c=1.73, $CHCl_3$))[10]. Diol 5 was selectively converted to the tert-butyldimethylsilyl (TBDMS)ether 6 in 84% yield by 4-dimethylaminopyridine catalyzed silylation[11]. At this point, the enantiomeric purity of 6 was determined by ^1H and ^{19}F NMR analyses of the (+)-MTPA ester. Within the detection limits, 6 was judged to be optically pure (>95% ee).

In the next phase of the synthesis, the acetic acid side chain was introduced via an ortho-ester Claisen rearrangement[12]. Treatment of 6 with triethyl orthoacetate in the normal way resulted in complete transfer of chirality from the side chain in 6 to the bottom face of the olefin affording 7 in good yield. Upon examination of the possible transition states A



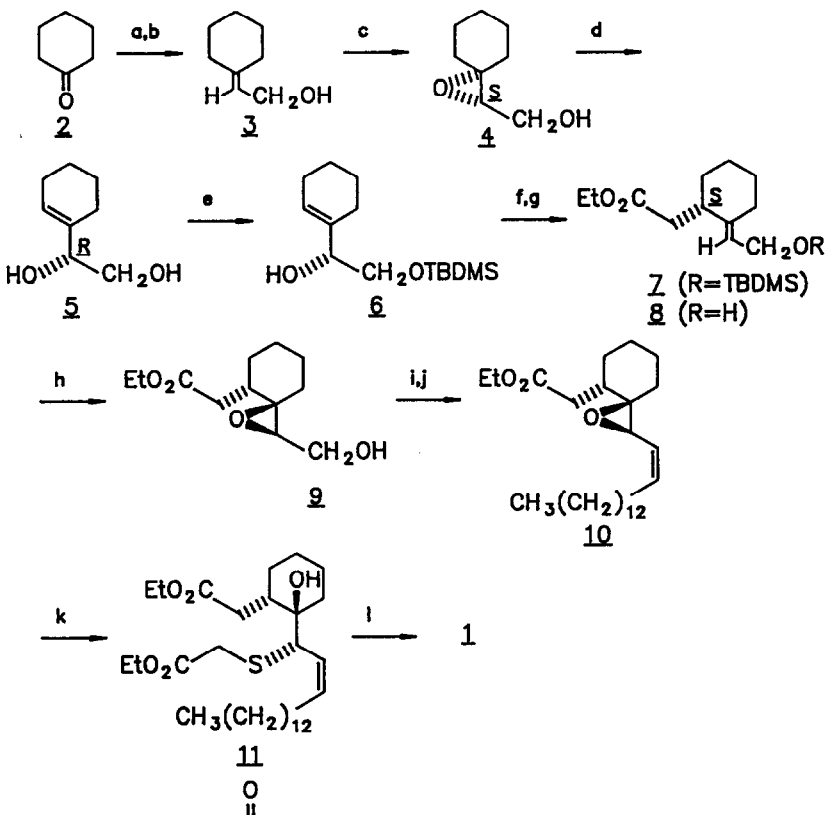
A



B

and B, the formation of 7 occurs presumably via A, the most stable chair-like transition state with the bulky substituent in the equatorial position. Assignment of the E-olefin geometry was made from spectral analyses and supported by comparison with an analogous recent literature report.[13]. Deprotection of 7 with fluoride ion afforded allylic alcohol 8 ($[\alpha]_D^{20}$ =-18.2°(c=1.18, $CHCl_3$); NMR (300 MHz, $CDCl_3$) δ 5.31 ppm (t, 1H, J=6.5 Hz)). The yield for the two-step transformation of 6 to 8 was 80%.

SCHEME I



CONDITIONS: a) $(EtO)_2PCH_2CO_2Et$,NaH,benzene; b) DIBAL(2.1), toluene,rt(2h); c) $Ti(OiPr)_4$,L-(+)-DET,$(CH_3)_3COOH$,4Å sieves, CH_2Cl_2,-25°(2h); d) 1:1 CH_2Cl_2-10%aq.tartaric acid rt(0.5h); e) TBDMS-Cl,Et_3N,DMAP,CH_2Cl_2,rt(18h); f) $CH_3C(OEt)_3$,o-xylene,propionic acid(cat.),135°(2h); g) $(n\text{-}Bu)_4\overset{\oplus}{N}\overset{\ominus}{F}$,THF,rt(1h); h) D-(-)-DET,$(CH_3)_3COOH$,$TiO(iPr)_4$, CH_2Cl_2,-25°(20h); i) DMSO,$(COCl)_2$,CH_2Cl_2,Et_3N; j) $CH_3(CH_2)_{12}CH_2\overset{\oplus}{P}Ø_3\overset{\ominus}{Br}$,THF,n-BuLi,-78°→0°; k) $HSCH_2CO_2Et$,Et_3N,EtOH,rt(18h); l) KOH,EtOH,H_2O,rt(18h).

To further elaborate the molecule with complete control of stereochemistry, a second asymmetric epoxidation was employed at this stage of the synthesis. Thus, treatment of 8 with tert-BuOOH and $Ti(OiPr)_4$ in the presence of D-(-)-DET produced 9 ($[\alpha]_D^{20}$=-13.3°(c=1.05, $CHCl_3$)) in 77% yield with delivery of oxygen from the top enantioface as predicted by the Sharpless mnemonic[3]. With all asymmetric centers now in place and well-defined, the completion of the synthesis was straightforward and followed our previously published sequence[1]. Swern oxidation[14] of 9 followed by Wittig olefination[15] afforded the Z-olefin (J=11.29 Hz) 10 ($[\alpha]_D^{20}$=-21.6°(c=1.05, $CHCl_3$)) in 48% yield for the 2 steps. Regiospecific opening of vinyl oxirane 10 with ethyl 2-mercaptoacetate produced the di-ester 11 ($[\alpha]_D^{20}$= -33.2°(c=1.60, $CHCl_3$)) in 60% yield. The regiochemistry of the substitution was clearly seen in the ^1H NMR (300 MHz, $CDCl_3$); the sulfur methine resonance at δ 3.94 (d, 1H, J=9.93 Hz) clearly excluding any S_N2' derived product. Saponification of 11 in 55% yield afforded 1 ($[\alpha]_D^{20}$=-66.8°(c=1.41, $CHCl_3$)). When tested in a guinea pig ileum model, this conformationally-restricted nor-LTD_4 analog showed moderate activity as an antagonist, comparable to that reported for SKF 101132.[16]

Acknowledgements: We thank Dr. Michael Whalon (MDRI-Indianapolis) and Robert J. Barbuch (MDRI-Cincinnati) for their assistance in obtaining analytical data, and Dr. Edward Huber (MDRI-Cincinnati) for ^1H and ^{19}F NMR spectra.

REFERENCES AND NOTES

1) Part I; Sabol, J.S.; Cregge, R.J. Tetrahedron Lett. 1989, 30, 3377.

2) Ku, T.W.; McCarthy, M.E., Weichman, B.W.; Gleason, J.G. J. Med. Chem. 1985, 28, 1847.

3) Katsuki, T.; Sharpless, K.B. J. Am. Chem. Soc. 1980, 102, 5974.

4) (a) Behrens, C.H.; Sharpless, K.B. Aldrichimica Acta. 1983, 16, 67. (b) Pfenninger, A. Synthesis 1986, 89.

5) Wadsworth, W.S.; Emmons, W.D. Org. Synthesis Coll. 1973, Vol. 5, 547..

6) Gao, Y.; Hanson, R.M.; Klunder, J.M., Ko, S.Y.; Masamune, H.; Sharpless, K.B. J. Am. Chem. Soc. 1987, 109, 5765.

7) ^1H and ^{19}F NMR spectra were run on a Varian 300 MHz spectrometer by Dr. Edward Huber of MDRI, Cincinnati.

8) Dale, J.A.; Dull, D.L.; Mosher, H.S. J. Org. Chem. 1969, 34, 2543.

9) A two-phase mixture of 5% aq. H_2SO_4 - ether was equally effective, however, efforts were not made to optimize the formation of 5.

10) Ko, K.Y.; Frazee, W.J.; Eliel, E.L. Tetrahedron 1984, 40, 1333.

11) Chaudhary, S.K.; Hernandez, O. Tetrahedron Lett. 1979, 20, 99.

12) Johnson, W.S., et. al. J. Am. Chem. Soc. 1970, 92, 741.

13) Uskokovic, M.R.; Lewis, R.L.; Partrige, J.J.; Despreaux, C.W., Prues, D.L. J. Am. Chem. Soc. 1979, 101, 6742.

14) Omura, K.; Swern, D. Tetrahedron 1978, 34, 1651.

15) Koreeda, M.; Patel, P.D.; Brown, L. J. Org. Chem. 1985, 50, 5910.

16) Dr. T.H. Gieske (MDRI-Cincinnati), unpublished results.

(Received in USA 3 October 1989)