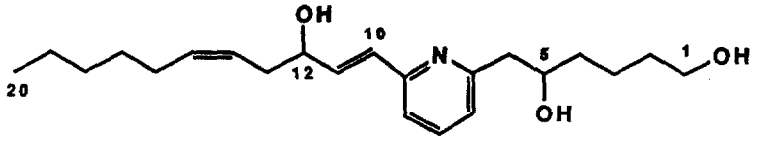
Tetrahedron Letters,Vol.30,No.38,pp.5081-5084,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

ASYMMETRIC SYNTHESIS OF THE DIASTEREOISOMERS OF THE LEUKOTRIENE B_4 ANTAGONIST, U-75302

Carmen E. Burgos, Eldon G. Nidy, and Roy A. Johnson*
Pharmaceutical Research and Development
The Upjohn Company
Kalamazoo, Michigan 49001

Summary: A synthesis of the four diastereoisomers of U-75302 has been completed using (R) and (S)-glycidol as the precursors to the C_5 chiral centers and asymmetric reductions of a ketone to generate the C_{12} centers.

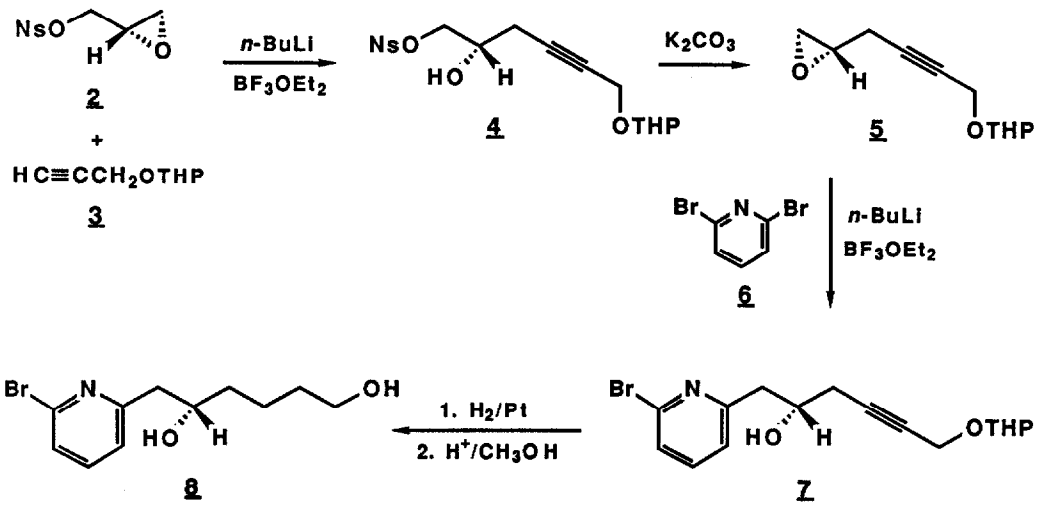
In 1988, Morris and Wishka described the synthesis of a series of 2,6-disubstituted pyridine analogs of leukotriene B_4 (LTB_4) which were found to bind competitively to LTB_4 receptors in human neutrophils.[1,2] One of the compounds (1, U-75302) was described as an effective antagonist to LTB_4-induced contraction of guinea pig lung parenchyma strips at a concentration (0.3 μM) where it is devoid of agonist activity.[1,3] Other work has shown that 1 blocks antigen-induced eosinophil migration into the lungs of sensitized guinea pigs.[4] The synthesis of 1 was designed to give a racemic mixture of the four diastereoisomers of 1. With the finding of desirable biological properties for 1, the question arises naturally as to whether the agonist and antagonist properties of this substance might be split among the diastereoisomers. To address this question, we have carried out the asymmetric synthesis of the four diastereoisomers of 1 as described in this communication.



1, U-75302

The synthetic approach we have developed takes advantage of several aspects of the original synthesis[1] of 1. In that synthesis, 1 was constructed by elaboration of a C_1-C_9 fragment (numbering of atoms is by analogy to the numbering of LTB_4) and coupling of this to a C_{10}-C_{20} fragment. The coupling reaction was the penultimate step of the synthesis and was followed by an efficient reduction as the final step. Application of this approach to suitable enantiomerically pure fragments offered an attractive route for assembly of the four diastereoisomers. We therefore undertook asymmetric synthesis of the two needed fragments by methods that could be used to generate both enantiomers of each fragment.

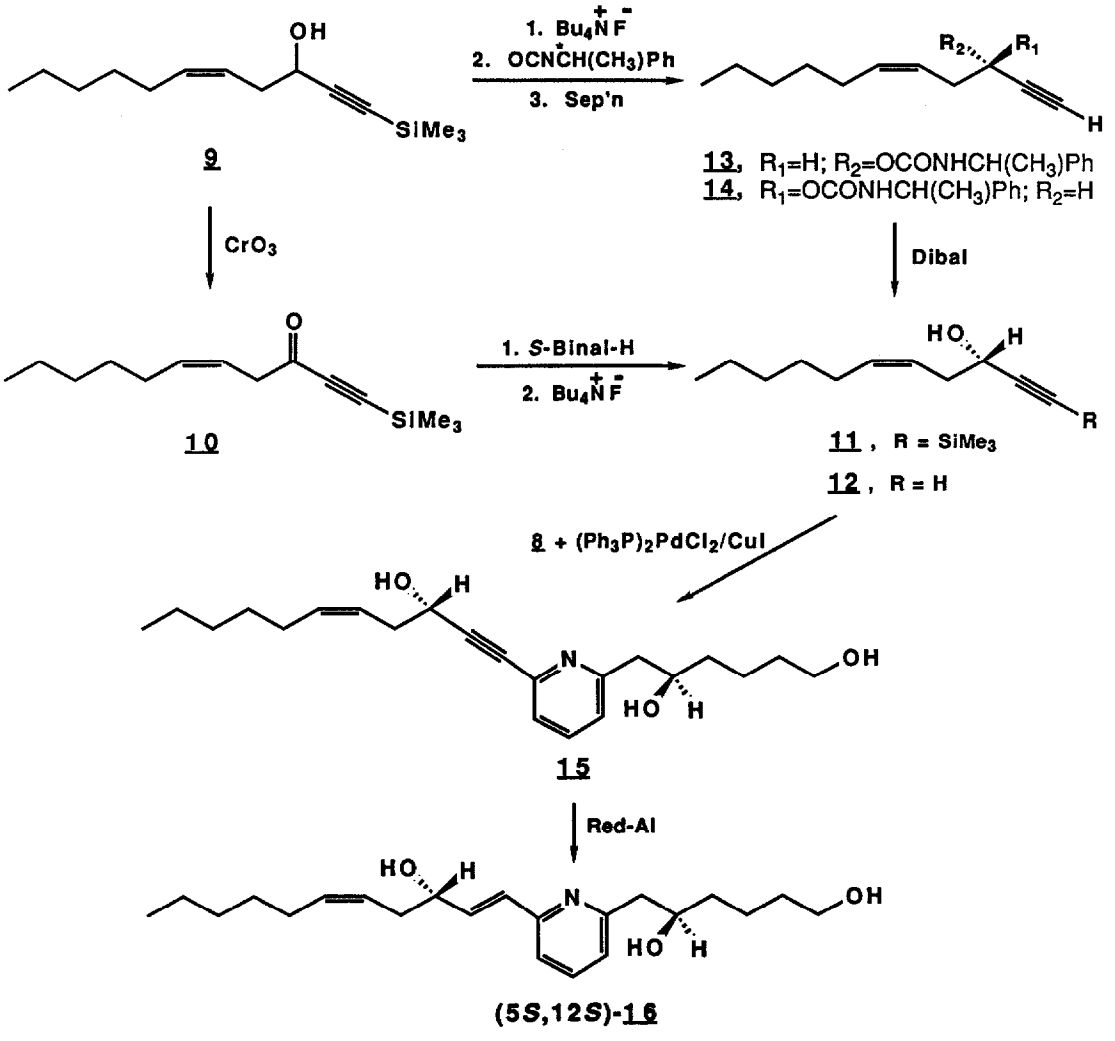
Scheme 1



For the C_1-C_9 fragment, the synthesis outlined in Scheme 1 was developed. (S)-Glycidol 3-nitrobenzenesulfonate (2), readily available from the asymmetric epoxidation of allyl alcohol,[5] provided the asymmetric carbon for the eventual C_5 position. The epoxide ($[a]_D$ +22.35°) was subjected to boron trifluoride etherate assisted[6] opening at the 3-position by nucleophilic attack[7] of the anion of propargyl-THP (3),[8] giving a six-carbon chain (4) corresponding to C_1-C_6 of the desired fragment. This hydroxy-nosylate (4) can be isolated and purified but the crude product is conveniently transformed into epoxide 5 (71% yield) by reaction in the presence of potassium carbonate-methanol. Boron trifluoride assisted ring opening of epoxide 5 with the anion derived from 2,6-dibromopyridine[9] (6) gives 7 (48%) accompanied by a side reaction that produces 1,6-dihydroxyhex-2-en-4-yne 6-THP (~10%) and recovered 5 (17%). Catalytic reduction of the acetylenic bond of 7 (90%) and subsequent removal of the THP group (92%) both proceed smoothly to give a C_1-C_9 fragment, (S)-8,[10] suitable for the coupling process. Repetition of the steps of Scheme 1 using (R)-glycidyl 3-nitrobenzenesulfonate in place of the (S)-enantiomer leads to the synthesis of the epimeric (R)-8. The enantiomeric purity of (S)-8 and (R)-8 was determined from the NMR spectra of the bis-Mosher esters and was > 98% ee for both isomers.

A number of alternatives exist for preparation of the C_{10}-C_{20} side chain in optically active form.[11] With alcohol 9 available from the synthesis of 1, we decided to examine asymmetric reduction of ketone 10, derived from 9, as a route to the (R) and (S)-enantiomers of this side chain (Scheme 2). Oxidation of 9 with Jones reagent provided a satisfactory route to ketone 10. Reduction of 10 with (S)-Binal-H[12,13] at -100°C generated (S)-11 with an ee of 90% as determined from the NMR spectrum of the acetate derivative in the presence of $Eu(hfc)_3$. Removal of the silyl group provided the C_{10}-C_{20}

Scheme 2



fragment (S)-12 (47% yield overall from 9) needed for the coupling reaction. In a similar way, reduction of 10 with (R)-Binal-H followed by desilylation gave the epimeric (R)-12. Correlation of the sign of rotation of (S)-12, $[a]_D$ -10.9°, with a sample of known absolute configuration[11] confirmed the assignment of configuration. We also have found that the diastereomeric urethans[14] 13 and 14, derived from 9, are separable by chromatography. Reductive removal of the urethan group from the pure diastereoisomers with Dibal provides an alternate route to (S)-12 and (R)-12 with ee >95%.

Palladium-copper promoted coupling[1] of the two fragments, (S)-8 and (S)-12, gave 15 in 97% yield. Finally, Red-Al reduction of 15 produced (5S,12S)-16, (70% yield), mp 75-76°C, $[a]_D$ -51.47° (c = 5.25, $CHCl_3$), a diastereoisomer of 1. Three repetitions of the coupling-reduction reaction sequence using the remaining three combinations of fragment 8 and 12 enantiomers gave (5R,12S)-16, (70%), an oil, $[a]_D$ +1.29° (c = 5.12, $CHCl_3$); (5R,12R)-16, (60%), mp 77-78°C, $[a]_D$ +51.16° (c = 5.02, $CHCl_3$); and (5S,12R)-16, (83%), an oil, $[a]_D$ -0.95°C (c = 5.50, $CHCl_3$). Attempts to derivatize the diastereoisomers as acetates or Mosher esters were unsuccessful, so the compounds were first reduced catalytically over platinum to remove the C_{10} and C_{14} double bonds. Then derivatization as the tris-Mosher esters was possible and high field NMR spectra of these esters confirmed that the same degree of optical purity was present in the final products as had been observed in the fragments 8 and 12. Biological evaluation of the four diastereoisomers will be reported separately.[16]

REFERENCES AND NOTES

1. Morris, J., Wishka, D.G. Tetrahedron Lett. **1988**, 29, 143.
2. Lin, A.H., Morris, J., Wishka, D.G., Gorman, R.R. Ann. N.Y. Acad. Sci. **1988**, 524, 196.
3. Lawson, C.F., Wishka, D.G., Morris, J., Fitzpatrick, F.A. J. Lipid Mediators **1989**, 1, 3.
4. (a) Richards, I.M., Dunn, C.J., Gorman, R.R., Lin, A.H., Morris, J., Oostveen, J.A., Wishka, D.G. Br. J. Pharmacol., **1988**, 95, 769P. (b) Richards, I.M., Griffin, R.L., Morris, J., Oostveen, J.A., Wishka, D.G., Dunn, C.J. Amer. Rev. Respir. Dis., in press.
5. Klunder, J.M., Onami, T., Sharpless, K.B.J. Org. Chem., **1989**, 54, 1295.
6. (a) Yamaguchi, M., Hirao, I. Tetrahedron Lett. **1983**, 24, 391. (b) Eis, M.J., Wrobel, J.E., Ganem, B. J. Am. Chem. Soc. **1984**, 106, 3693. (c) Mohr, P., Tamm, C. Tetrahedron Lett. **1987**, 28, 391. (d) Guivisdalsky, P.N., Bittman, R. J. Am. Chem. Soc., **1989**, 111, 3077.
7. (a) McClure, D.E., Arison, B.H., Baldwin, J.J. J. Am. Chem. Soc. **1979**, 101, 3666. (b) Bell, T.W., Ciaccio, J.A. Tetrahedron Lett. **1988**, 29, 865.
8. White, J.D., Kang, M., Sheldon, B.G. Tetrahedron Lett. **1983**, 24, 4539.
9. Parks, J.E., Wagner, B.E., Holm, R.H. J. Organometal. Chem. **1973**, 56, 53.
10. Satisfactory ^1H NMR, elemental analysis and/or high resolution mass spectral data were obtained for all new compounds in this report.
11. (+)-(R)-3-Hydroxyundec-5Z-en-1-yne [(+)-(R) 12] has been prepared from the D-mannitol-derived benzoate aldehyde, (R,Z)-$C_5H_{11}CH=CHCH(OB_Z)CHO$[15] (J. Morris and D. G. Wishka, unpublished results, The Upjohn Company, 1986).
12. Noyori, R., Tomino, I., Yamada, M., Nishizawa, M. J. Am. Chem. Soc. **1984**, 106, 6709, 6717.
13. We thank J. H. Symonds, Chemical Process Research and Development, The Upjohn Company, for supplies of (S) and (R)-binaphthol.
14. Henderson, M. A., Heathcock, C. H. J. Org. Chem. **1988**, 53, 4736.
15. LeMerrer, Y., Duréault, A., Gravier, C., Languin, D., Depezay, J.C. Tetrahedron Lett. **1985**, 26, 319.
16. The IC_{50} values for inhibition of 1nM $[^3H]LTB_4$ binding to human neutrophil membranes are: (5S,12S)-16, >10μM; (5R,12S)-16, 9μM; (5R,12R)-16, 0.7μM; (5S,12R)-16, 0.5μM; U-75302 (1), 1.0μM. We thank Alice H. Lin and Robert R. Gorman for these neutrophil binding data.

(Received in USA 19 June 1989)