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ASYMMETRIC EPOXIDATION OF ALLYLIC ALCOHOLS EMPLOYING 4,5-DIPHENYLOXAZOLE AS A MASKED ESTER FUNCTIONALITY

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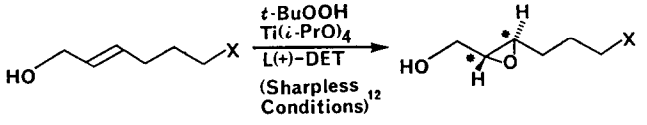
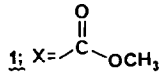
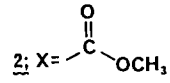
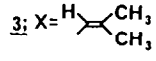
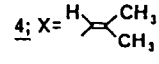
Summary: The 4,5-diphenyloxazolyl moiety has been found to be a masked ester functionality fully compatible with the Sharpless epoxidation of allylic alcohols within the same molecule.

Laboratory syntheses of optically active, slow-reacting substances (SRS) leukotrienes A-E have generally been based on (-)-methyl (5,S),(6,S)-oxido-7-hydroxyheptanoate (2) or its aldehydic derivative as the principal intermediate.[1] Conceptually, a convenient and highly enantiospecific approach for a synthesis of 2 can be envisioned via the Sharpless epoxidation procedure [2,3] on suitably substituted allylic alcohols. However, experiments in our laboratory, as well as another published report[3] indicate that the terminal methyl ester (and t-butyl ester)[4] functionality in allylic alcohol 1 interferes with the course of the reaction. Allylic alcohol 3 containing a terminal olefin as a masked ester functionality was found by Corey[3] to be a successful alternative. The utility of 3 is greatly reduced, however, by the number of additional steps its transformation to 2 requires. This study was undertaken to identify carboxyl equivalents or protecting groups that would: (1) permit the



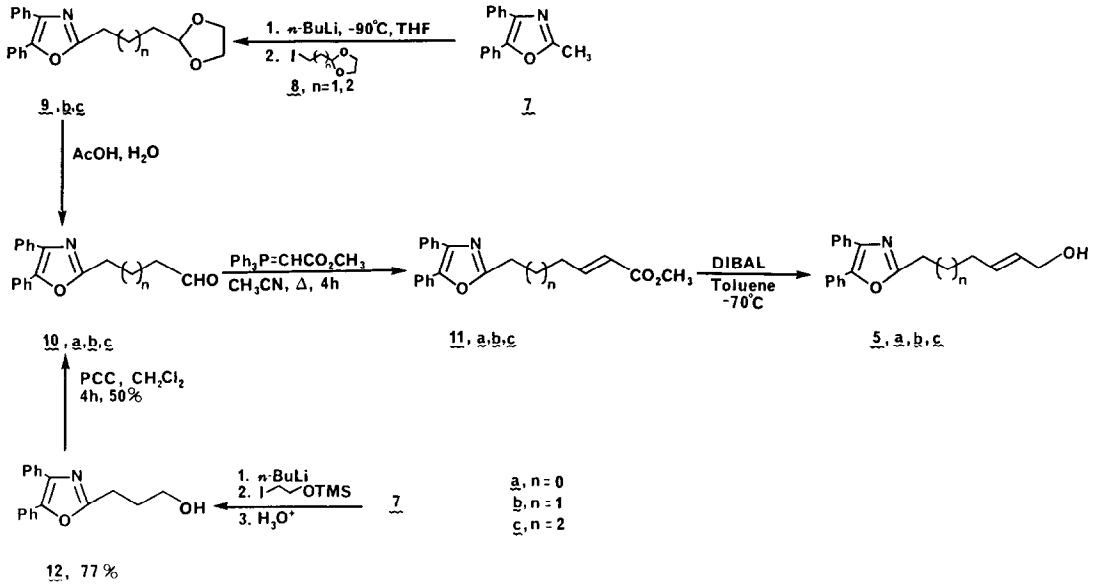
1; X=  2; X= 

3; X=  4; X= 

5; X=4,5-Diphenyloxazole 6; X=4,5-Diphenyloxazole

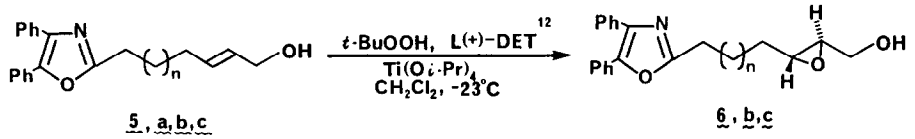
Sharpless epoxidation to proceed on a suitably functionalized allylic alcohol derivative without loss of chirality transfer; and (2) be readily unmasked to the terminal ester under mild conditions. The 4,5-diphenyloxazolyl moiety has been found by Wasserman and co-workers to be a versatile carboxyl equivalent in a variety of applications. The mild singlet oxygen conditions employed by his laboratory for conversion of the oxazole ring to carboxylic derivatives appeared suited to these objectives.[5-7]

Scheme 1:

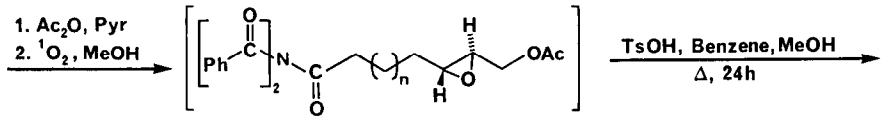


Syntheses of the prerequisite oxazole allylic alcohols 5 a,b,c (n=0,1,2 respectively) are outlined in Scheme 1. The following conversions typify the experimental for 5b and 5c. 2-Methyl-4,5-diphenyloxazole (7) (Aldrich) was alkylated at -90°C in THF with 2-(2-iodoethyl)-1,3-dioxolane 8(n=1)[5,8,9] to give 9b in 84% yield after flash chromatography (petroleum ether/ether, 1:1). Conceivably, 9b could also be prepared by cross-coupling the Grignard of 8(n=2) with 2-methylthio-4,5-diphenyloxazole.[10] Conversion of acetal 9b to aldehyde 10b [HOAc-H_2O (2:1), 50°C, 16hr, 78%] was followed by treatment with methyl (triphenylphosphoranylidene)acetate (CH_3CN, 4hr, Δ, 95%) to yield α,β-unsaturated ester 11b. Ester 11b was reduced to allylic alcohol 5b on treatment with DIBAL (toluene, -70°C, 1.25hr, 68%). Purification of the product was carried out using either radial or flash chromatography (ethyl acetate/hexanes, 7:3).[11] For the synthesis of aldehyde 10a and hence 5a, 7 was alkylated as described above with 2-trimethylsilyloxy-iodoethane in 77% yield. The resulting alcohol was oxidized to the aldehyde 10a using PCC (4 hr, CH_2Cl_2, 50%) and elaborated on to 5a as described above in 75% and 64% yields for the Wittig and DIBAL reduction steps respectively.

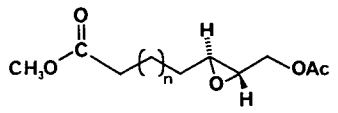
Scheme 2:



5, a,b,c 6, b,c



13, b,c



14, b ; 51% $[\alpha]_D^{23}$ -36.6°(c 2.1, $CHCl_3$); % ee> 99[16]

14, c ; 78% $[\alpha]_D^{23}$ -29.5°(c 2.3, $CHCl_3$); % ee> 99

Asymmetric epoxidations of the oxazole allylic alcohols 5b and 5c were conducted and worked up as described by Sharpless and Katsuki[12] providing, after flash chromatography (ethyl acetate/hexanes, 65/35), enantiomerically pure epoxy oxazoles 6b and 6c[13] [75% yield, $[\alpha]_D^{23}$ -16.8° (C 0.3, $CHCl_3$); 66% yield, $[\alpha]_D^{23}$ -11.1 (C 0.5, $CHCl_3$)], respectively. Acetylated (Ac_2O, pyridine, 0°C, 95%) alcohols 6b and 6c were treated with singlet oxygen in methanol for 2hr as described by Wasserman[6]. The methanolic solution (50 ml) of the intermediate triamide 13 was reduced to 10-15 ml and 50 ml of benzene was added along with 2-3 mg of p-TsOH. The solution was heated under reflux for 24hr while being monitored by tlc (pentane/ether, 1:1)[15] to yield the optically active methyl esters 14b and 14c after flash chromatography (51% and 78%, respectively). The oxazole allylic alcohol 5a (n=0) did not yield the desired epoxide 6. Only a complex mixture that included starting material was obtained from the reaction.

We conclude that the oxazolyl moiety may be employed as a masked ester functionality in the asymmetric Sharpless epoxidation of allylic alcohols without interference in the reaction as long as it is sufficiently removed from the site of reaction. The necessary distance in our studies is three methylene groups.

Acknowledgements: We thank Dr. H. Wasserman and particularly Mr. R. Gambale of Yale University, New Haven, CT for their technical assistance in carrying out the singlet oxygen cleavages and Mr. D. Staiger of this laboratory for his help in determining optical purities.

References and Notes

1. For a comprehensive review of leukotriene syntheses employing 2 see: N. Cohen, B.L Banner, R. J. Lopresti, F. Wong, M. Rosenberger, Yu-Ying Liu, E. Thom, and A. A. Liebman, J. Amer. Chem. Soc., 105, 3661 (1983).
2. B.E. Rossiter, T. Katsuki, and K.B. Sharpless, Ibid. 103, 464 (1981). During the preparation of this manuscript, Baker[17] reported the successful utilization of the Sharpless procedure to prepare (-)-methyl (8S),(9S)-oxido-10-hydroxydecanoate.
3. E.J. Corey, S. Hashimoto, and A.E. Barton, Ibid. 103, 721 (1981).
4. The t-butyl ester analog of 1 was satisfactorily synthesized and fully characterized (IR, ^{1}H NMR, MS). When used in the Sharpless epoxidation procedure[12] none of the desired epoxide could be detected by GC/Methane Gas Chemical Ionization Spectroscopy.
5. H.H. Wasserman, R.J. Gambale, and M.J. Pulwer, Tetrahedron, Symposium in Print, "New General Synthetic Methods", Edited by E.J. Corey, 37, 4059 (1981).
6. H.H. Wasserman, R.J. Gambale, and M.J. Pulwer, Tetrahedron Lett. 22, 1737 (1981).
7. For a recent review see: H.H. Wasserman and B.H. Lipshultz, Chapter 9, in Singlet Oxygen, (Edited by H.H. Wasserman and R.W. Murray), Academic Press, New York (1979).
8. B.H. Lipshultz and R.W. Hungate, J. Org. Chem. 46, 1410 (1981).
9. This iodoacetal was formed in 84% yield by heating 2-(2-bromoethyl)-1,3-dioxolane (Aldrich) under reflux in acetone containing NaI. IR, ^{1}H NMR and MS were satisfactory; b.p. 45° (0.1 torr).
10. L.N. Pridgen, submitted to Synthesis. The Grignard actually used in this instance was derived from 2-bromoethyl-1,3-dioxane [76%, using $NiCl_2$(dppe) as catalyst].
11. All new compounds exhibited expected IR, ^{1}H NMR, and high-resolution mass spectral data.
12. T. Katsuki and K.B. Sharpless, J. Amer. Chem. Soc. 102, 5974 (1980). DET represents diethyl tartrate.
13. Optical purities were determined on epoxy acetates 14b and 14c using a JEOL GX-270 MHz NMR employing Eu(hfc)$_3$ as the chiral shift reagent. Chemical shift assignments of the diastereomeric protons were determined first on a racemic mixture of 14b. The (R,R) enantiomeric acetoxy methyl ester of 14b was synthesized from trans-1-hydroxy-2,7-octadiene employing exactly the same epoxidation procedure[2], ruthenium tetraoxide olefin cleavage[14], and diazomethane esterification conditions reported by Sharpless: $[\alpha]_D^{23}$+37.1° (C 4, $CHCl_3$). Using this technique, none of the (R,R) enantiomer could be detected in optically active 14b and 14c. The optical purities of 6b and 6c were not directly determined but both may be inferred to be optically clean through their conversion to epoxides 14b and 14c in excellent optical yields.
14. Per. H.J. Carlson, T. Katsuki, V.S. Martin, K.B. Sharpless, J. Org. Chem. 46, 3936 (1981).
15. A ceric sulfate-ammonium molybdate -10% sulfuric acid (1g: 25g: 500ml) spray was used as visual indicator.
16. The rotation of 14b has been reported to be $[\alpha]_D^{23}$ -44.3° (C 2.24, $CHCl_3$) by Prof. Corey[3]. However, Cohen[1] has observed wide fluctuations in rotation values for the enantiomerically clean precursor alcohol to 14b and concluded that the rotation of these compounds is highly sensitive to impurities.
17. S.R. Baker, J.R. Boot, S.E. Morgan, Tetrahedon Lett. 24, 4469 (1983). Apparently the success enjoyed by Baker in asymmetrically epoxidizing methyl trans-10-hydroxy-8-decenoate was due to the increased distance, two methylene units, between the ester and olefin functionalities as compared to the unsuccessful epoxidation attempts on methyl trans-7-hydroxy-5-heptenoate[3].

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