Tetrahedron Letters No. 37, pp 3415 - 3418.

0040-4039/78/0908-3415$02.00/0

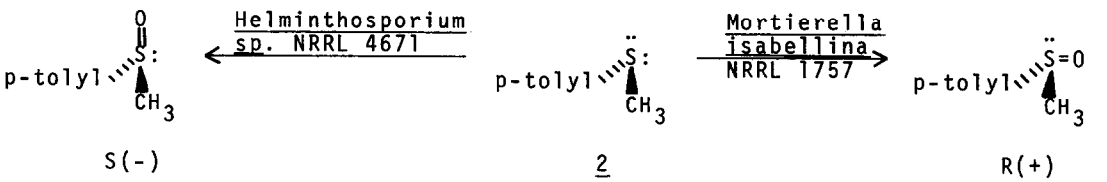
STEREOSPECIFIC MICROBIAL OXIDATION OF THIOETHERS TO SULFOXIDES. APPLICATION TO THE SYNTHESIS OF R-MEVALONOLACTONE.

Elie Abushanab[1], Douglas Reed, Fumio Suzuki and Charles J. Sih*
School of Pharmacy, University of Wisconsin, Madison, Wisconsin 53706

A variety of chemical methods have been used for the preparation of sulfoxides in various states of optical purity.[2] The most widely used synthetic method involves the reaction of a resolved sulfinate ester with a Grignard reagent furnishing sulfoxides of high optical purity.[3] However, it was reported[4] that the yields of sulfoxides varied greatly with the structure of both sulfinate ester and Grignard reagent. Also, the reaction conditions must be carefully selected, otherwise considerable quantities of sulfides and other impurities are produced. Since these impurities are often difficult to separate from the desired sulfoxide, the synthetic utility of this method is limited.

It is well documented that microorganisms are capable of oxidizing thioethers into sulfoxides.[5] In most instances however, chemical and optical yields are low except with certain benzyl sulfides where high enantiomeric excesses were reported.[5a] The increasing use of chiral sulfoxides in asymmetric syntheses[6] prompted us to develop a convenient microbiological method for the preparation of R and S methyl p-tolyl sulfoxides, (1), compounds that serve as synthons for a variety of other chiral sulfoxides.

Methyl p-tolyl sulfide (2) was selected as the model substrate for our microbiological investigations, for chiral methyl p-tolyl sulfoxides[6] and other derivatives[7] have been widely used in synthetic applications. Although numerous fungi are capable of catalyzing the oxidation of 2, the yields and the optical purities of the resulting sulfoxide were found to be low. However, after an exhaustive study, it was found that Mortierella isabellina NRRL 1757[8] converted 2 into (+)R-1 in 60% yield, m.p. 73-75°, $[\alpha]_D^{25}$ +141° (c, 10.1 EtOH) 100% optical purity.[9] Whereas Helminthosporium sp. NRRL 4671 stereospecifically oxidized 2 into (-)S-1 in 50% yield, m.p. 73-75° $[\alpha]_D^{25}$ -141° (c, 12 EtOH); 100% optical purity. Although the substrate specificities of these microbial oxidations have not been examined in detail, ethyl p-tolyl sulfide was similarly oxidized to yield the respective sulfoxide in similar yields and optical purity.



S(-) 2 R(+)

In the course of these investigations, the French workers reported the condensation of the anion of chiral α-sulphinyl ester, 3 with aldehydes and ketones leading to β-hydroxy acids of high chemical and optical yields. This observation aroused an interest to examine the possibility of devising an asymmetric synthesis of mevalonolactone using the chirality of the sulfoxide functionality.

(+)-R-t-Butyl-α-p-tolyl sulphinyl acetate (3), $[\alpha]_D^{25}$ +149° (EtOH, c, 20.2, 25°C); reported[10] $[\alpha]_D^{25}$ +149° (EtOH, c, 2.25, 20°C); was prepared in 91% yield by reacting a solution of LDA (2 eq) in THF at -78°C, with R-methyl p-tolyl sulfoxide 1 (1 eq) followed by di-t-butyl-dicarbonate (1 eq). Reaction of the anion, prepared by treating (R)-3 with (Bu^tMgCl) in THF-DME (2:1) at -78°C[11], with the ketone, 4 afforded 6 in 75% yield. When the tetrahydropyranoxy protecting group was replaced by a t-butyldimethylsilyl group, no addition products were formed with recovery of the starting material. This unexpected difference in reactivity may be interpreted in terms of a complexation of the tetrahydropyranoxy oxygen with the Mg counterion thereby accelerating the addition reaction.[12] Such interactions are severely interrupted in 5 by the sterically bulky t-bultydimethylsilyl

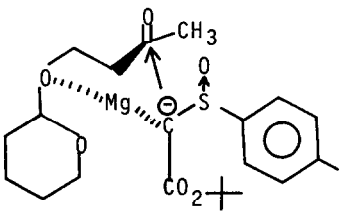
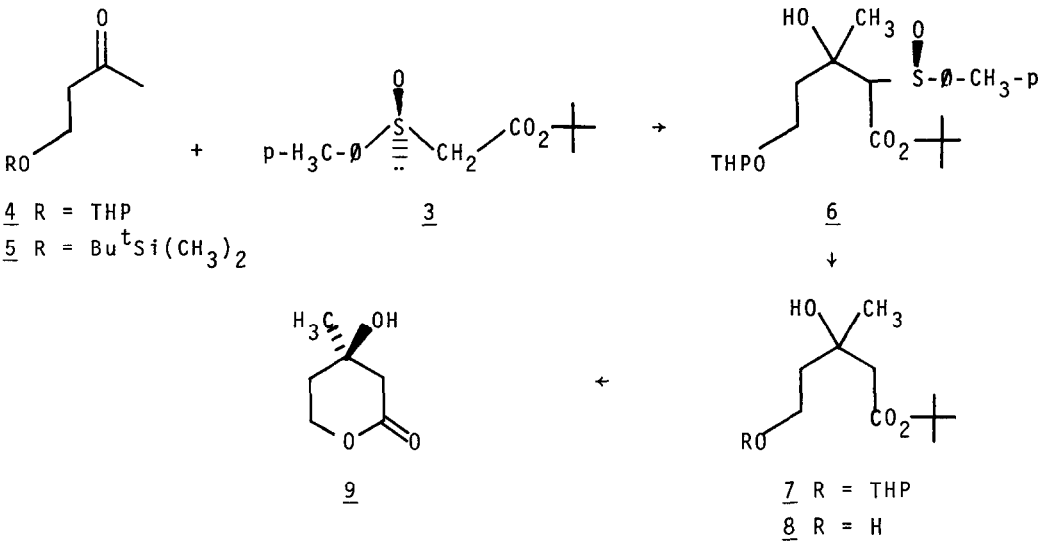


Figure 1

group. After silica gel chromatography, 6 was obtained as a mixture of diasteromers, pmr, δ 1.28 (s, 5H), 1.29 (s, 4H), 1.1-1.9 (m, 9H), 2.15 (m, 2H), 2.38 (s, 3H), 3.5-4.2 (m, 5H), 4.55 (m, 1H), 7.28 (m, 2H), 7.51 (m, 2H).[13] The sulfoxide group was removed by treating 6 with aluminum foil[14] in 3% aq $HgCl_2$-THF (1:3) at 60°C to afford 7, (87%) δ 1.29 (s, 3H), 1.49 (s, 9H), 1.4-1.8 (m, 6H), 1.89 (m, 2H), 2.49 (bs, 2H), 3.3-4.1 (m, 4H), 4.59 (m, 1H). Stirring 7 in an acidic medium (AcOH-H_2O-THF, 1:1:1) at 50°C gave 8, δ 1.32 (s, 3H), 1.49 (s, 9H), 1.77 (m, 2H), γ_A = 2.36, γ_B = 2.56 (AB, q, JAB = 16.2 Hz, 2H), 3.86 (m, 2H), (98%). Treatment of 8 with 15% aq. NaOH at 100°C for 3 hours afforded 9[15] (61%), $[\alpha]_D^{25}$ -4.04° (EtOH) (17% enantiomeric excess[16]). Attempts to further improve optical induction by varying solvents (ethyl ether, THF, DME) and temperatures (-78° to -20°C) were unsuccessful (Scheme 1).

The (-)-R-mevalonolactone, thus prepared from (+)R-methyl p-tolyl sulfoxide in 17% optical yield suggest that the enolate anion of 3 preferentially attack 4 as shown in Figure 1. Unfortunately, the difference of steric effects proximal



4 R = THP
5 R = $Bu^tSi(CH_3)_2$

Scheme 1

to the reaction site between the methyl and the 2-tetrahydropyranoxylethyl groups are insufficient to allow high optical induction. Further application of the optically-active sulfoxide in asymmetric synthesis are currently being explored.

Acknowledgment

Financial support from National Institutes of Health Grant No. AM4874 is gratefully acknowledged.

References and Notes

1. Visiting professor on sabbatical leave from the University of Rhode Island, College of Pharmacy, 1976-77.

2. a) U. Folli and D. Iarossi, Gazz. Chim. Ital., 99, 1306(1969); b) T. Higuchi, I. H. Pitman and K. H. Gensch, J. Amer. Chem. Soc., 88, 5676(1966); c) H. B. Kagan, G. Balavoine and A. Moradpour, J. Mol. Evol., 4, 41(1974); d) M. Mikolajczyk and J. Drabowicz, J. Amer. Chem. Soc., 100, 2510(1978).

3. a) H. Gilman, J. Robinson and N. Beaber, J. Amer. Chem. Soc., 48, 2715(1926); b) K. K. Anderson, Tetrahedron Lett., 93(1962); c) K. K. Anderson, J. Foley, R. Perkins, W. Gaffield and N. Papanikolaou, J. Amer. Chem. Soc., 86, 5637 (1964).

4. D. N. Harpp, S. M. Vines, J. P. Montillier and T. H. Chan, J. Org. Chem., 41, 3987(1976).

5. a) B. J. Auret, D. R. Boyd, H. B. Henbest and S. Ross, J. Chem. Soc. C, 2371 (1968); b) B. J. Auret, D. R. Boyd, H. B. Henbest, C. G. Watson, K. Balenovix, V. Polak, V. Johanides and S. Divjak, Phytochem., 13, 65(1974); c) R. M. Dodson, N. Newman and H. M. Tsuchiya, J. Org. Chem., 27, 2707(1962).

6. a) G. I. Tsuchihashi, S. Iriuchijima and M. Ishibashi, Tetrahedron Lett., 4605(1962); b) G. I. Tsuchihashi, S. Iriuchijima and K. Maniva, ibid., 3389 (1973); c) C. R. Johnson and C. W. Schroeck, J. Amer. Chem. Soc., 95, 7418 (1973); d) C. Mioskowski and G. Solladie, J. Chem. Soc., Chem. Commun., 162 (1977).

7. a) V. Reutrakul and W. Kanghae, Tetrahedron Lett., 1377(1977);
b) S. Tsutsumi, Tetrahedron Lett., 3883(1977).

8. The medium composition, conditions for the cultivation of microorganisms and workup are the same as that described by J. Rosazza, P. Foss, M. Lemberger and C. J. Sih, J. Pharm. Sci., 63, 544(1974) except 40 g/l of glucose was used. Methyl p-tolyl sulfide was exposed to M. isobellina for 40 hours and H. sp. for 48 hours.

9. The reported value for R methyl p-tolyl sulfoxide is $[\alpha]_D$ +141° (EtOH). K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons and A. L. Ternay, Jr., J. Amer. Chem. Soc., 87, 1958(1965).

10. C. Mioskowski and G. Solladie, Tetrahedron Lett., 3341(1975).

11. N. Kunieda, N. Nokami and M. Kinoshita, Tetrahedron Lett., 3997(1974).

12. S. Danishefsky and A. Zimmer, J. Org. Chem., 41, 4059(1976). They alluded to the possibility that the ketal oxygen may stabilize the enolate in their system.

13. Pmr were recorded on an EM390 Varian Spectrometer in $CDCl_3$ with TMS as internal standard.

14. The sulfoxide, 6 failed to undergo reduction using the conventional aluminum amalgam method [E. J. Corey and Chayhovsky, J. Amer. Chem. Soc., 86, 1639 (1964)].

15. Acidic hydrolyses (CF_3COOH; 10% H_2SO_4) failed to yield 9.

16. a) R. H. Cornforth, J. W. Cornforth and G. Popjak, Tetrahedron, 18, 1351 (1962); b) F. C. Huang, L. F. H. Lee, R. S. D. Mittal, P. R. Ravikumar, J. A. Chan, C. J. Sih, E. Caspi and C. R. Eck, J. Amer. Chem. Soc., 97, 4144 (1975).

(Received in USA 30 May 1978; received in UK for publication 7 July 1978)