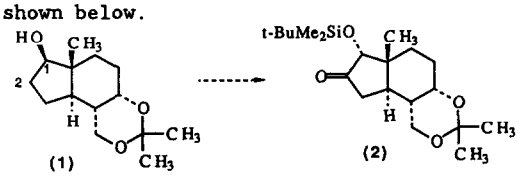
Tetrahedron Letters,Vol.29,No.18,pp 2163-2166,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

STUDIES DIRECTED TOWARD TAXANES. PREPARATION OF α-KETOLS BY OXIDATIVE RING-OPENING OF EPOXIDES.

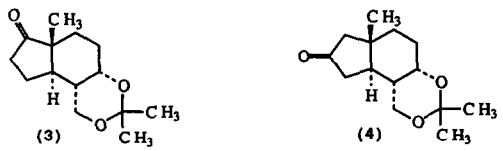
Barry M. Trost* and M. Jonathan Fray[1]
Departments of Chemistry
University of Wisconsin, Madison, WI 53706
Stanford University, Stanford, CA 94305

Summary: Protonic acid promoted ring-opening of epoxides by dimethyl sulphoxide at room temperature followed by treatment with diisopropylethylamine at -78°, affords α-ketols in modest to good yields.

During our studies directed towards the total synthesis of taxane group diterpenes,[2] we desired a short, selective method for converting alcohol (1)[3] into the protected hydroxy-ketone (2), as shown below.

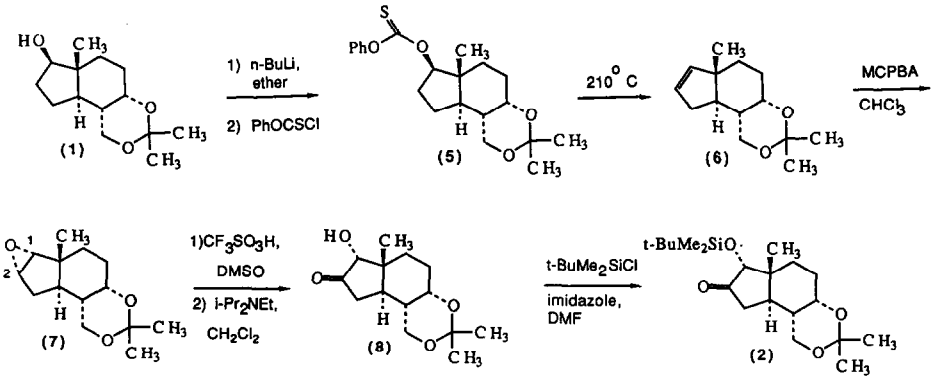


This transformation required the introduction of a carbonyl group at C-2, and inversion of the alcohol stereochemistry adjacent to a fully substituted bridgehead carbon. Of the many literature methods which might accomplish this task, carbonyl transpositions[4] of ketone (3), for example, were considered unsatisfactory due to their length, and the anticipated difficulties involved with the regio- and stereoselective hydroxylation of ketone (4). We have, therefore, developed a concise method with full stereochemical

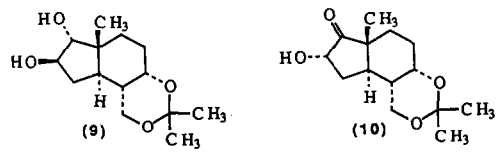


control for circumventing this problem, based on the ring-opening of epoxides by dimethyl sulphoxide, a reaction that heretofore has proven to be of little synthetic value.[5,6] The use of boron trifluoride at elevated temperatures[6] is not compatible with acid sensitive groups as required. The milder conditions of Swern,[5] however, only gave minor amounts of the ketol.

The enantiomerically pure alcohol (1)[7] was first converted to its thionocarbonate derivative (5)[7] (n-BuLi in hexane, 1.05 eq., ether, 0°C then PhOCSCl,[8] 1.05 eq., 20°C, 5h) in 93% yield after chromatography. Thermolysis of (5) (Kugelrohr, 210°C, 760 mm Hg) afforded a mixture of the alkene (6)[7] (90%), and phenol which could be removed by washing with aqueous potassium hydroxide. Epoxidation of (6) (MCPBA, 1.05 eq., $CHCl_3$, 0°C, 16h), proceeded smoothly to give the epoxide (7)[7] as a single isomer.[9]



The key transformation of (7) into ketol (8) was achieved by first treating (7) (1M in dimethyl sulphoxide) with a solution of trifluoromethanesulphonic acid (1.05 eq., ca. 6M in dimethyl sulphoxide) at room temperature for 2h, then diluting the mixture with dichloromethane (ca. 2 vol.), cooling to -78°C and adding diisopropylethylamine (5 eq.). After warming to room temperature, the solution was partitioned between brine and dichloromethane, and the crude product was purified by flash chromatography to afford the hygroscopic (8)[7] (60%), together with 10% of the diol (9). This reaction proceeded equally well on scales of 0.2 to 35 mmol. Interestingly, the epoxide was regioselectively cleaved at C(2); none of the regioisomeric ketol (10) was detected. Presumably, the neopentyl nature of C(1) of 7 disfavors attack at this position. Finally, the alcohol (8) was protected as its t-butyldimethylsilyl ether (2)[7] (84%) using the standard conditions.[10]

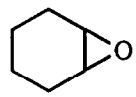
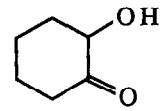
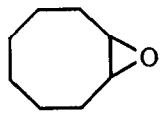
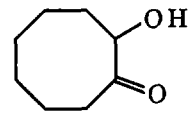
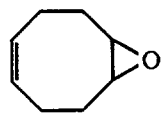
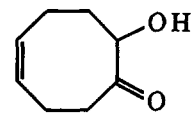
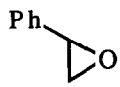
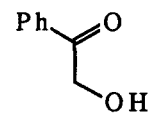
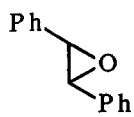
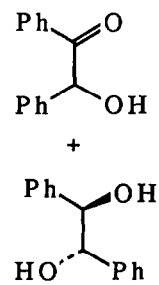


Although this methodology was designed to solve a particular synthetic problem, these conditions for the oxidative ring-opening of epoxides may be applied in other instances, as shown by the examples in the Table. The fact that only stoichiometric amounts of acid need be employed at room temperature or below allows acid labile functions like ketals to survive. The absence of transannular cyclization products in the example of entry 3 of the table reveals the transition state of the DMSO opening of the protonated epoxide normally has little carbonium ion character. This modification should prove useful for the formation of α-hydroxyketones.

Acknowledgements

M.J.F. wishes to thank the S.E.R.C. for the award of a N.A.T.O. postdoctoral fellowship. We also wish to thank the National Institutes of Health for their generous support of our programs.

Table. Oxidative Ring Opening of Epoxides[a]

Entry	Epoxide	Ketol[b]	Yield[c]
1			61%
2			56%
3			71%
4			34%
5			70% 17%

(a) A general experimental procedure follows: A solution of trifluoromethanesulphonic acid (0.18 mL, 2.0 mmol) in 0.5 mL of DMSO was added to a stirred solution of 2.0 mmol of the epoxide in 1.5 mL of DMSO with cold water cooling. The mixture was stirred at 23° until t.l.c. analysis indicated complete consumption of the epoxides (generally 30-45 min except for entry 2 which required 1.5 eq of trifluoromethanesulphonic acid and 48h). After adding 3 mL of dichloromethane and cooling to -78°, 10.0 mmol of diisopropylethylamine was added. The mixture was warmed to room temperature and then poured into 30 mL of 10% aqueous sodium bisulfate and extracted with 3x25 mL of dichloromethane. After drying ($MgSO_4$) and evaporating the solution *in vacuo*, purification of the residue by flash chromatography gave the pure products in the stated yields. (b) Products identified spectroscopically. (c) Yields refer to chromatographed products.

References and Notes

1. Present address: Pfizer Central Research, Sandwich, Kent CT13 9NJ, U.K.
2. For a comprehensive list of references, see Berkowitz, W.F.; Amarasekara, A.S.; Perumattan, J.J. *J. Org. Chem.*, **1987**, *52*, 1119.
3. Trost, B.M.; Walsh, T.F. unpublished results.
4. Kane, V.V.; Singh, V.; Martin, A.; Doyle, D.L. *Tetrahedron*, **1983**, *39*, 345.
5. Khuddus, M.A.; Swern, D. *J. Am. Chem. Soc.*, **1973**, *95*, 8393; Santosusso, T.M.; Swern, D. *J. Org. Chem.*, **1975**, *40*, 2764.
6. Cohen, T.; Tsuji, T. *J. Org. Chem.*, **1961**, *26*, 1681.
7. Compounds fully characterized by spectroscopic means and combustion analysis, except (6) and (8) (accurate mass determination). Spectroscopic data: (1) m.p. 84-86°C (hexane), $[\alpha]_D$ = +9.7° (c - 5.0, $CHCl_3$) IR 3200-3575, 2860-3020, 1210 cm^{-1} ^1H nmr (200 MHz, $CDCl_3$) 0.72 (3H, s), 1.35 (3H, s), 1.42 (3H, s), 1.10-1.81 (9H, m), 1.99-2.18 (2H, m), 3.61 (1H, dd, *J* 1.2, 12 Hz), 3.74 (1H, t, *J* 8.4 Hz), 3.99 (1H, dd, *J* 3, 12 Hz), 4.09 (1H, q, *J* 2.8 Hz); ^{13}C nmr (15 MHz, $CDCl_3$) 97.7, 81.0, 66.5, 61.4, 42.5, 37.8, 35.8, 31.4, 29.7, 29.5, 27.7, 22.8, 18.71, 10.0
   (5) m.p. 115°C (hexane), $[\alpha]_D$ = +2.0° (c = .85, $CHCl_3$) IR ($CHCl_3$) 1587, 1487, 1453, 1430, 1063 cm^{-1}; ^1H nmr (270 MHz, $CDCl_3$) 0.87 (3H, s), 1.34-1.49 (2H, m), 1.39 (3H, s), 1.45 (3H, s), 1.58-1.78 (5H, m), 1.89 (1H, m), 2.25 (1H, dt, *J* 8, 12.3 Hz), 2.49 (1H, dtd, *J* 13.7, 9.4, 6.5 Hz), 3.66 (1H, d, *J* 11.8 Hz), 4.04 (1H, dd, *J* 2.7, 11.8 Hz), 4.12 (1H, m), 5.21 (1H, dd, *J* 7.5, 9 Hz), 7.11 (2H, m), 7.29 (1H, m), 7.43 (2H, m); ^{13}C nmr (15 MHz, $CDCl_3$) 194.2, 153.0, 129.0 (2C), 126.0, 121.6 (2C), 97.9, 92.0, 66.4, 61.4, 42.9, 37.4, 35.6, 31.7, 29.8, 27.5, 26.2, 23.0, 18.8, 11.5
   (6) $[\alpha]_D$ = +6.07° (c = 2.84, $CHCl_3$); ^1H nmr (270 MHz, $CDCl_3$) 0.75 (3H, s), 1.36 (3H, s), 1.43 (3H, s), 1.46 (3H, m), 1.59-1.91 (3H, m), 2.27 (1H, ddd, *J* 2.5, 6.5, 14.5 Hz), 2.46 (1H, dt, *J* 8, 6.7 Hz), 3.70 (1H, d, *J* 12 Hz), 4.05 (1H, dd, *J* 3, 12 Hz), 4.13 (1H, m), 5.72 (1H, ddd, *J* 1.4, 3, 5.7 Hz), 5.87 (1H, dd, *J* 1.3, 5.7 Hz); ^{13}C nmr (15 MHz, $CDCl_3$) 143.4, 128.6, 97.8, 67.2, 62.4, 45.5, 43.3, 34.7, 31.6, 31.3, 30.0, 28.4, 19.0, 16.2
   (7) m.p. 58-59°C (hexane), $[\alpha]_D$ = +7.54° (c = 1.04, $CHCl_3$); IR ($CHCl_3$) 1265, 902, 840 cm^{-1}; ^1H nmr (270 MHz, $CDCl_3$) 0.72 (3H, s), 1.11 (1H, dt, *J* 1, 12 Hz), 1.23-1.44 (2H, m), 1.35 (3H, s), 1.40 (3H, s), 1.64-1.89 (3H, m), 2.06 (1H, dd, *J* 6.5, 13 Hz), 2.19 (1H, dt, *J* 7, 12 Hz), 3.12 (1H, d, *J* 3 Hz), 3.35 (1H, m), 3.57 (1H, dd, *J* 1, 12 Hz), 4.01 (1H, dd, *J* 3, 12 Hz), 4.08 (1H, m); ^{13}C nmr (15 MHz, $CDCl_3$) 97.8, 66.6, 62.0 (2C), 52.9, 40.6, 34.5, 32.1, 29.7, 28.0 (2C), 26.9, 18.9, 14.6
   (8) IR ($CHCl_3$) 3595, 3450, 1747 cm^{-1}; ^1H nmr (270 MHz, $CDCl_3$) 0.82 (3H, s), 1.26 (1H, m), 1.40 (3H, s), 1.44 (3H, s), 1.48 (1H, m), 1.84 (2H, m), 1.88 (1H, dd, *J* 9.5, 18 Hz), 2.11 (1H, dt, *J* 5.3, 12.8 Hz), 2.39 (1H, d, *J* 3 Hz), 2.45 (1H, dd, *J* 8, 18 Hz), 3.11 (1H, dd, *J* 7.5, 12.8 Hz), 3.42 (1H, d, *J* 3 Hz), 3.55 (1H, dd, *J* 0.5, 12 Hz), 4.07 (1H, dd *J* 2.6, 12 Hz), 4.16 (1H, m); ^{13}C nmr (15 MHz, $CDCl_3$) 216.6, 98.2, 80.3, 66.5, 62.3, 42.2, 36.8, 35.4, 34.1, 29.8, 27.1, 25.1, 18.9, 15.9
   (2) m.p. 114-115°C, (hexane), $[\alpha]_D$ = +179° (c = 0.57, $CHCl_3$); IR ($CDCl_3$) 1750, 1089, 838 cm^{-1} ^1H nmr (270 MHz, $CDCl_3$) 0.04 (3H, s), 0.07 (3H, s), 0.74 (3H, s), 0.87 (9H, s), 1.11 (1H, ddd, *J* 3, 4.3, 12.3 Hz), 1.38 (3H, s), 1.40 (1H, m), 1.43 (3H, s), 1.70-1.84 (3H, m), 2.10 (1H, dt, *J* 6, 12.6 Hz), 2.40 (1H, dd, *J* 8, 18 Hz), 3.19 (1H, dt, *J* 8, 12.6 Hz), 3.30 (1H, s), 3.55 (1H, dd, *J* 1, 12 Hz), 4.05 (1H, dd, *J* 2.7, 12 Hz), 4.13 (1H, q, 2.7 Hz); ^{13}C nmr (15 MHz, $CDCl_3$) 214.7, 98.2, 81.3, 66.7, 62.6, 43.0, 36.2, 35.5, 33.6, 29.9, 27.4, 25.9 (3C), 25.5, 19.0, 18.5, 15.4, -4.4, -4.8
8. Gerlach, H.; Huong, T.T.; Miller, W. *J. Chem. Soc. Chem. Commun.*, **1972**, 1215; Rivier, H. *Bull. Soc. Chim. Fr.*, **1907**, *1*, 733.
9. Schnoenecker, B.; Ponsold, K.; Neuland, P. *Z. Chem.*, **1971**, *10*, 221 or *Ger. Pat.* 79,730 (1971).
10. Corey, E.J.; Venkateswarlu, A. *J. Amer. Chem. Soc.*, **1972**, *94*, 6190.

(Received in USA 3 February 1988)