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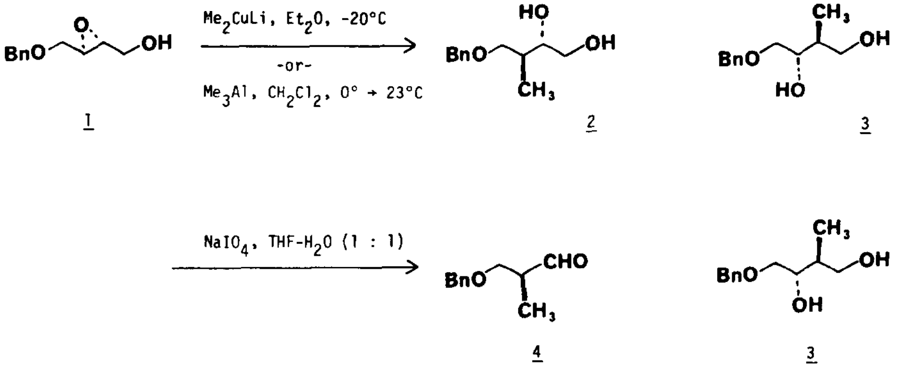
REGIOSELECTIVITY OF THE REACTIONS OF TRIALKYLALUMINUM REAGENTS WITH 2,3-EPOXYALCOHOLS: APPLICATION TO THE SYNTHESIS OF α-CHIRAL ALDEHYDES

William R. Roush,*[1] Michael A. Adam, and Steven M. Peseckis
Department of Chemistry, Massachusetts Institute of Technology,
Cambridge, MA 02139

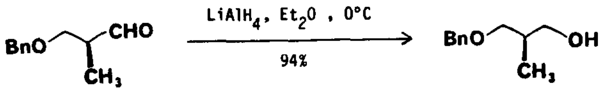
Summary: Treatment of optically active 2,3-epoxyalcohols with trialkylaluminum reagents followed by periodate cleavage constitutes a convenient synthesis of α-chiral aldehyde derivatives, especially when the branching alkyl group is methyl.

We recently required a convenient source of either 1,2-diol 2 or 1,3-diol 3 for use in a natural product synthesis. Indeed, treatment of (R,R)-epoxide 1[2] ($[\alpha]_D^{21}$ + 21.4°, c=1.40, $CHCl_3$, >95% ee) with Me_2CuLi (1.2 equiv.) in Et_2O at -20°C[3] for 1 h afforded a mixture of 2 and 3 (ca. 1:6 by NMR analysis), whereas complimentary regioselectivity was realized when 1 was treated with Me_3Al (3 equiv.) in CH_2Cl_2 (0° to 23°C over 10 h; ca. 5:1 mixture of 2:3).[4] These mixtures were inseparable by conventional chromatographic techniques. Purification of 1,3-diol 3, however, was accomplished after treating these mixtures with $NaIO_4$ in aqueous THF, which transformed 1,2-diol 2 to aldehyde 4. In this manner diol 3[5a,b] ($[\alpha]_D^{30}$ + 16.5°, c=1.18, $CHCl_3$) was obtained in 74-79% yield via the cuprate sequence.



	4	3
Me_2CuLi experiment:	10-12%	74-79%
Me_3Al experiment:	69-73%	13-14%

We recognized, however, that the sequence involving the Me_3Al reaction could also prove useful in synthesis. Aldehyde 4 and its enantiomer are well-known intermediates usually prepared from (S)- β-hydroxyisobutyric acid,[6] and have been used in a number of recent natural product syntheses.[7] Indeed, aldehyde 4 ($[\alpha]_D^{21}$ + 28.4°, c=1.56, $CHCl_3$) prepared as outlined above was shown to be at least 95% ee by conversion to alcohol 5[8] ($[\alpha]_D^{21}$ + 16.5°, c=1.05, $CHCl_3$; lit.[7b]



4 (+)-5

$[\alpha]_D$ + 17.2°, c=3.24, $CHCl_3$); $[\alpha]^{21}_D$ + 5.2°, c=1.46, EtOH; lit.[8] $[\alpha]_D$ + 5.3°, c=2.2, EtOH).

These results encouraged us to study the reactions of trialkylaluminum reagents with a number of 2,3-epoxyalcohols (Table I).[9] Each of the substrates examined underwent substitution preferentially at the position furthest removed from the hydroxyl substituent. No product of attack at the α position (C.2) was realized with substrates 11, 13, and 15.[10] With 1 and 6, however, a lesser degree of regioselectivity was realized owing to the benzyloxy substituent at C.4 which inductively deactivates C.3 towards nucleophilic attack.

One can imagine a number of uses for the 1,2-diols produced in these reactions. We concentrate here, however, on the application of these compounds as intermediates in the synthesis of α-chiral aldehydes.[11] Chiral epoxides 1 (>95% ee), 6[2] ($[\alpha]^{19}_D$ + 22.2°,c=3.86, $CHCl_3$; 82% ee), and 11[12]($[\alpha]^{19}_D$ + 23.1°, c=0.48, $CHCl_3$; 92% ee) were transformed to 4 (>95% ee), (-)-5 ($[\alpha]^{19}_D$- 14.2°, c=3.12, $CHCl_3$; 82% ee) and 12 ($[\alpha]^{26}_D$+ 15.4°, c=1.77, CH_2Cl_2; 92% ee (determined after $LiAlH_4$ reduction to the corresponding alcohol[5a,b])), respectively, with no detectable racemization. Thus, at least in these examples, the optical purity of the α-chiral aldehydes produced is determined by the optical purity of the starting epoxyalcohols.[13]

This two step sequence coupled to the Sharpless asymmetric epoxidation reaction[14] constitutes a convenient synthesis of α-chiral aldehyde derivatives, especially when the branching alkyl group is methyl. One problem which remains to be solved, however, is the proclivity of alkylaluminum reagents such as Et_3Al to serve as hydride donors (see the second and seventh entries of Table I). Possible solutions to this problem are under current investigation.[15]

Representative Experimental Procedure: Synthesis of Aldehyde 4: To a 0°C solution of 2.63 g (13.6 mmol) of epoxide 1 ($[\alpha]^{21}_D$ + 21.4°, c=1.40, $CHCl_3$; >95% ee) in 20 mL of CH_2Cl_2 under argon was added dropwise 17.2 mL (40.6 mmol, 3 equiv.) of 2.36 M Me_3Al in hexane. The reaction mixture was stirred at room temperature for 10 h and then cooled to 0°C and quenched with 40 mL of 3N HCl. After extractive workup the crude mixture of 2 and 3 (83:17 ratio by 270 MHz ^1H NMR) was treated with 4.35 g (20.3 mmol) of $NaIO_4$ in 70 mL of 1:1 aqueous THF. This mixture was stirred for 2 h at room temperature and then was worked up by extraction. The crude product was purified by flash chromatography (silica gel, 19:1 hexane-ether) to give 408 mg (14%) of 3 and 1.76 g (73%) of 4: $[\alpha]^{21}_D$ + 28.4° (c=1.56, $CHCl_3$); NMR (270 MHz, $CDCl_3$) δ 9.74 (d, J=1.6 Hz, 1 H), 7.34 (m, 5 H), 4.54 (s, 2 H), 3.67 (m, 2 H), 2.69 (m, 1 H), 1.15 (d, J=6.9 Hz, 3 H); IR (neat) 3090, 3070, 3040, 2980, 2940, 2870, 2720, 1725 cm^{-1}. The optical purity of 4 was determined to be at least 95% ee by reduction to (+)-5 (see text).

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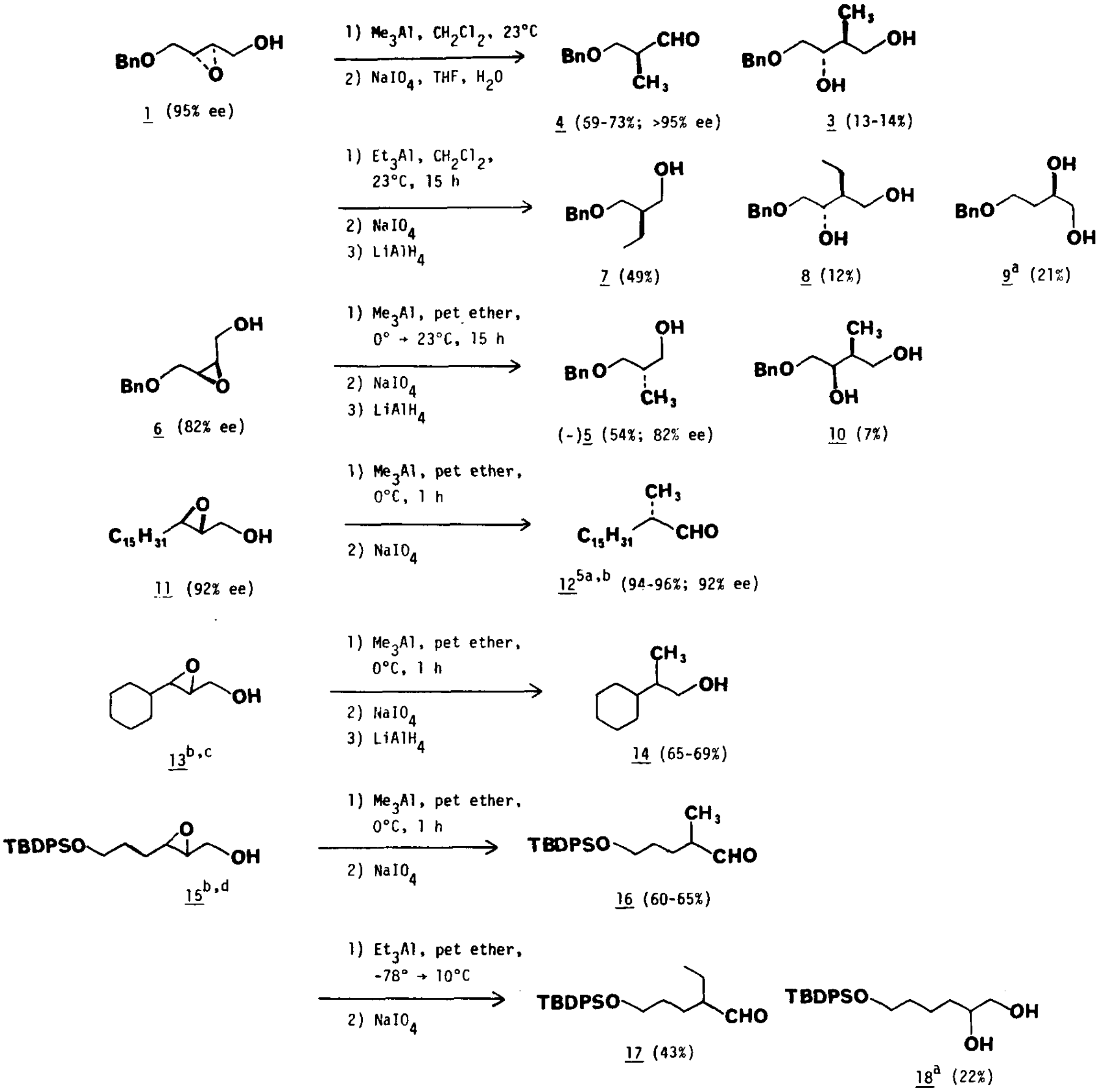
Scheme I[5a]



(a) This compound was separated by chromatography before the periodate cleavage step.

(b) Racemic epoxide was used.

(c) An unidentified mixture of by-products (12-13%) was isolated from this sequence.

(d) An unidentified mixture of by-products (ca. 25%) was also obtained.

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5. (a) The spectroscopic properties (NMR, IR, mass spectrum) of all new compounds were fully consistent with the assigned structures. (b) A satisfactory combustion analysis (± 0.3 for C,H) was obtained for this compound or a derivative.

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10. Authentic samples of the unobserved 1,3-diols were prepared by treating 11, 13 and 15 with Me_2CuLi and then $NaIO_4$. In none of these cases was the regioselectivity as high as observed with 1. The 1,3-diol was favored from 13, but only by a ratio of 70:30. The ratios for the other substrates ranged from 60:40 (1,3 : 1,2) for 6 to 40:60 for 11.

11. Such intermediates are usually prepared by enantioselective alkylation of chiral enolate derivatives. For recent reviews, see: (a) Evans, D.A.; Takacs, J.M.; McGee, L.R.; Ennis, M.D.; Mathre, D.J.; Bartroli, J. Pure Appl. Chem. 1981, 53, 1109; (b) Meyers, A.I. Ibid. 1979, 51, 1255; (c) ApSimon, J.W.; Seguin, R.P. Tetrahedron 1979, 35, 2797.

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