Enantioselective Syntheses using Chiral Epoxy-alcohols

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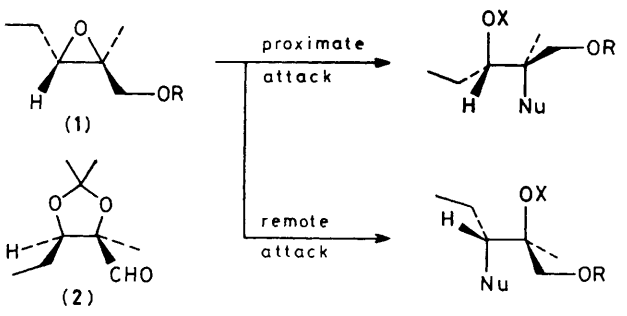
The epoxy-alcohol (**1**, R=CH_2Ph) opens under acid catalysis by attack at the proximate carbon atom.

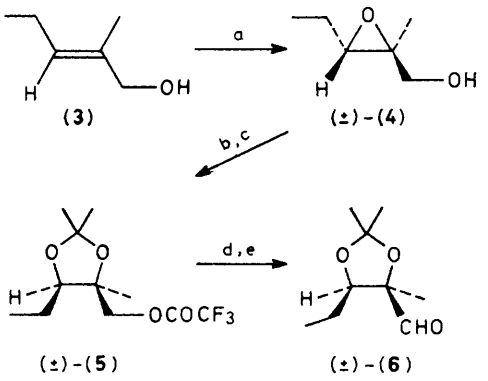
Current interest and intense activity in the synthetic potential of chiral epoxy-alcohols prompt us to disclose our observations on the regiochemistry of acid-catalysed nucleophilic ring-opening of epoxides. Under such conditions, the epoxide (**1**, R=CH_2Ph) undergoes selective attack at the proximate carbon atom (Scheme 1). On the basis of a bimolecular reaction pathway, and of consideration of the inductive substituent effects which are believed[1] to govern the regiochemistry of opening, this result is the *opposite* of that predicted. This observation has implications on the employment of the sophisticated techniques now available for the chiral construction[2] of polyhydroxylated natural products utilising the controlled regiospecific ring opening of chiral epoxy-alcohols.

In a synthetic approach to the macrolide methymycin, the *erythro* acetonidoaldehyde (**2**) has obvious attractions as a building block. It was planned to construct the primary alcohol precursor, in protected form, directly from a chiral epoxy-alcohol derivative (**1**). Acid-catalysed attack by acetone

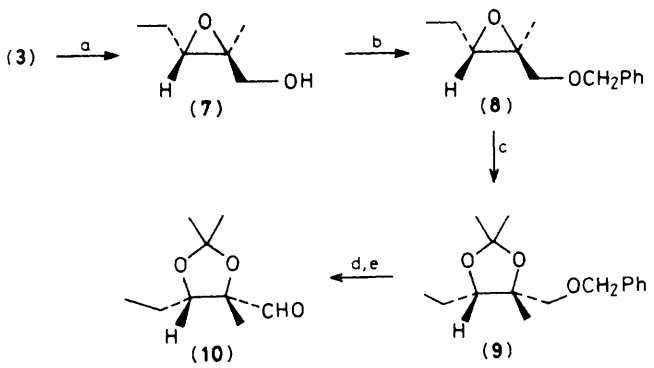


Scheme 1

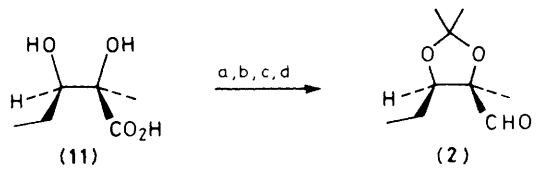
on an epoxide has been shown[3] to result in inversion of configuration at the epoxide carbon atom being attacked; bond rotation followed by ring closure then produces an acetonide directly. For success in the present case, two requirements



Scheme 2. *Reagents:* a, *m*-chloroperbenzoic acid, Na_2HPO_4, CH_2Cl_2, 0 °C; b, $(CF_3CO)_2O$, pyridine; c, 20 equiv. acetone, BF_3–Et_2O (catalytic), 0 to 22 °C, 24 h; d, Na_2CO_3, H_2O; e, CrO_3.2-pyridine



Scheme 3. *Reagents:* a, 2.2 equiv. Bu^tOOH, 1 equiv. $Ti(OPr^i)_4$, 1 equiv. diethyl (+)-tartrate, CH_2Cl_2, −20 °C; b, NaH, $PhCH_2Br$, tetrahydrofuran;; c, 20 equiv. acetone, BF_3–Et_2O (catalytic), 0 to 20 °C, 24 h; d, H_2, 10% Pd/C, 90 lb in^{-2}, AcOEt, 20 h; e, CrO_3.2-pyridine.



Scheme 4. *Reagents:* a, CH_2N_2, Et_2O; b, acetone, $CuSO_4$ (anhydrous); c, $LiAlH_4$, Et_2O; d, CrO_3.2pyridine.

must be fulfilled. First, the epoxide ring must cleave in a concerted manner, to ensure diastereoisomeric integrity; secondly, the ring must open by attack, and hence inversion of configuration, specifically at the remote carbon atom, to ensure production of the correct enantiomer. Ample precedent[1] would seem to satisfy this second requirement. Addressing attention to diastereoisomeric integrity, the (*E*)-epoxy-alcohol (**4**) was prepared in racemic form from the corresponding (*E*)-allylic alcohol[4] (**3**). Treatment of the derived trifluoroacetate with acetone and a catalytic amount of BF_3–Et_2O produced a single acetonide (**5**). This acetonide was assigned the *erythro*-configuration, as shown by a nuclear Overhauser effect (n.O.e.) integrated enhancement[5] of 15% between the protons of the quaternary methyl group and the lone acetonide proton; W-coupling was not detected, confirming the absence of the *threo*-diastereoisomer. Hydrolysis followed by oxidation gave the acetonidoaldehyde (**6**) (Scheme 2); addition of Eu(hfc)$_3$† produced separate signals[6] for the enantiomeric aldehyde protons in the ^1H n.m.r. spectrum.

Epoxidation of the allylic alcohol (**3**) in the presence of diethyl (+)-tartrate[7] produced the chiral epoxy-alcohol‡ (**7**). This was converted§ into its benzyl ether (**8**) under non-isomerising conditions.[8] Treatment with acetone as before gave an acetonide (**9**) (Scheme 3), which underwent smooth hydrogenolysis to an alcohol. Oxidation gave an acetonidoaldehyde (**10**), $[\alpha]_D^{22}$ +7.2° (*c* 1, $CHCl_3$), which displayed an n.O.e. of 12%. An aldehyde of this diastereoisomeric structure, but prepared[9] by a different route, has been converted into natural (+)-methynolide, thus defining its absolute stereochemistry as that of (**2**). Its specific rotation, $[\alpha]_D^{25}$ −9.8° (*c* 0.82, EtOH), demands that the aldehyde (**10**) be of the enantiomeric structure shown.

In confirmation, epoxidation of the allylic alcohol (**3**) in the presence of diethyl (−)-tartrate,[7] and subsequent transformations as above, produced a series of compounds (**7a**—**10a**). These had physical properties identical to those of the corresponding compounds in the series (**7**—**10**), including specific rotations of approximately equal magnitude but of opposite sign. The acetonidoaldehyde (**10a**) possessed a specific rotation of $[\alpha]_D^{22}$ −7.4° (*c* 0.73, $CHCl_3$) and an n.O.e. of 8%. It proved to be identical in all respects, including, within experimental error, specific rotation, to the aldehyde (**2**), prepared unambiguously (Scheme 4) from the acid[10] (**11**), of known[11] absolute configuration. The enantiomeric purities of the aldehydes (**10**), (**10a**), and (**2**) were confirmed using Eu(hfc)$_3$.

From these results, acid-catalysed nucleophilic opening of the epoxide (**1**, R=CH_2Ph) with acetone occurs by attack at the proximate carbon atom. In addition, reaction of the chiral epoxide (**8**) with dilute aqueous H_2SO_4 gave a diol, $[\alpha]_D^{22}$ −3° (*c* 1, $CHCl_3$); treatment of this diol with acetone and $CuSO_4$ gave an acetonide, $[\alpha]_D^{22}$ +4° (*c* 1, $CHCl_3$), identical in all respects to acetonide (**9**).

Many examples exist of remote carbon opening of epoxyketones and aldehydes under acid catalysis. Masamune's landmark synthesis[12] of methymycin employs such regiospecificity. Several highly regiospecific proximate or remote nucleophilic openings[2b],[13] of benzyloxymethyl epoxides are known. Most, if not all, of these involve some degree of complexation and/or intramolecularity, and hence cyclic transition states, which will govern the regiochemistry of opening; such effects are unlikely in the present case.

† Tris-[3-(heptafluoropropylhydroxymethylene)-(−)-camphorato]-europium(III).

‡ Compound (**7**): $[\alpha]_D^{22}$ −13.5 (*c* 0.84, $CHCl_3$); δ($CDCl_3$) 1.05 (t, 3H, *J* 7 Hz), 1.26 (s, 3H), 1.3—1.8 (m, 2H), 2.6 (s, 1H, exchanges with D_2O), 3.05 (t, 1H, *J* 7 Hz), and 3.65 (ABq, 2H, *J* 13 Hz); (**7a**): $[\alpha]_D^{22}$ −14.3° (*c* 1.02, $CHCl_3$); (**8**): $[\alpha]_D^{22}$ +5° (*c* 0.9, $CHCl_3$), δ($CDCl_3$) 2.82 (t, 1H, *J* 6 Hz), 3.45 (s, 2H), 4.55 (s, 2H), and 7.32 (br. s, 5H); (**8a**): $[\alpha]_D^{22}$ −2° (*c* 1.1, $CHCl_3$); (**9**): $[\alpha]_D^{22}$ +4° (*c* 1, $CHCl_3$); δ($CDCl_3$) 1.3 (s, 3H), 1.33 (s, 3H), 1.38 (s, 3H), 3.34 (ABq, 2H, *J* 9 Hz), 3.68 (dd, 1H, *J* 9 and 7 Hz), 4.53 (s, 2H), and 7.30 (br. s, 5H); (**9a**): $[\alpha]_D^{22}$ −2.2° (*c* 0.82, $CHCl_3$); (**10**): $[\alpha]_D^{22}$ +7.2° (*c* 1, $CHCl_3$); δ($CDCl_3$) 1.0 (t, 3H, *J* 7 Hz), 1.28 (s, 3H), 1.42 (s, 3H), 1.55 (s, 3H), 3.82 (t, 1H, *J* 8 Hz), and 9.60 (s, 1H); irradiation of the signal at δ 1.28 caused an increase in the integrated intensity of the triplet at δ 3.82 of 15%; (**10a**): $[\alpha]_D^{22}$ −7.4° (*c* 0.73, $CHCl_3$); similar irradiation of the signal at δ 1.28 resulted in an n.O.e. of 8% on the signal at δ 3.82; (**2**): $[\alpha]_D^{22}$ −10° (*c* 0.99, $CHCl_3$).

§ The corresponding trifluoroacetate proved to be unsuitable in this sequence, with enantiomeric integrity being lost. The reasons for this are under current investigation.

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