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## Unusual stereochemical course of epoxide rearrangement in a carvone-derived series

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## Abstract

Carvone-derived 2,3-epoxy alcohol derivatives rearrange with stereoselective formation of ring-contracted ketones. In contrast to previously described similar processes, the stereochemical result seems to be independent of epoxide configuration. © 1999 Published by Elsevier Science Ltd. All rights reserved.

The acid-catalyzed rearrangement of appropriately substituted 2,3-epoxy alcohol derivatives represents a valuable method of forming quaternary carbon centers in a stereocontrolled fashion.<sup>1</sup> The regioselectivity of the process is, however, critically dependent on the proper choice of the Lewis acid catalyst and the nature of the alcohol protecting group.<sup>2</sup> Neighboring group effects were shown to account for regioand stereoselectivity in the rearrangement of various epoxy acylates, but it remains difficult to formulate general rules that would reliably predict the type of bond migration (e.g. 1,2-hydride shift versus carbon migration).<sup>3</sup>

The stereochemical course of the process that converts an epoxy alcohol derivative I into an aldol II (Scheme 1) has been the subject of several reports.<sup>4</sup> The observed stereospecificity was interpreted to arise from the *anti*-migration of the oxygen-substituted carbon to the epoxide moiety. A rigorous transfer of chirality could be demonstrated for a wide range of type I epoxy alcohol derivatives.



When we started to make use of the above transformation and extended it to the rearrangement of carvone derived epoxide 1, the result seemed to be in perfect agreement with the mechanistic conclusions drawn by others.

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The BF<sub>3</sub>-etherate treatment of benzyl ether-protected epoxy alcohol 1 proceeded with clean and highyield formation of a single ring-contracted ketone 2 (Scheme 2).



Scheme 2.

In order to obtain the isomeric product with the oppositely configured quaternary center, we synthesized epoxy alcohol derivative 3 and subjected it to the same reaction conditions. To our surprise, the rearrangement resulted again in exclusive formation of ketone 2 with no detectable trace of the expected diastereomer 4 (Scheme 3).



Scheme 3.

Clearly, the experimental outcome was incompatible with a concerted mechanism and rather suggested the intermediacy of a long-lived benzylic cation. A confirmation of this assumption was expected from the rearrangement and product analysis of the remaining two possible diastereomers 5 and 7 (Scheme 4).



Scheme 4.

The Lewis acid treatment of epoxides 5 and 7 resulted in the formation of isomer mixtures. In both cases, rearrangement yielded ketone 6a as the preferred diastereomer but product analysis revealed a small but significantly different 6a/6b composition. The stereochemical assignment for the main isomer 6a was confirmed by X-ray crystal structure analysis.

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Again, the result excludes a concerted mechanism, but also the assumption of a long-lived benzylic carbenium intermediate cannot fully account for the experimental outcome.

Being unable at this point to suggest a common single mechanism for the products obtained from the rearrangement of epoxides 1, 3, 5 and 7, we concentrated upon the unambiguous assignment of educt and product configuration by crystal structure analysis and chemical interconversion. The  $\alpha$ -epoxides 1 and 5 can be obtained from known (–)-carvone oxide<sup>5</sup> by reaction with phenyl magnesium bromide (Scheme 5). The primary adduct 9 undergoes a Payne rearrangement<sup>6</sup> in situ to give a 51.1% yield of epoxy alcohol 10 which is benzylated under standard conditions. Mitsunobu reaction<sup>7</sup> and saponification cleanly transforms the alcohol 10 into its epimer 11. Again crystal structure analysis was used to prove the assignment for epoxy-benzyl ether 5.



Scheme 5. (a) PhMgBr, THF (51%); (b) PhCH<sub>2</sub>Br, NaH, DMF (96%); (c) Ph<sub>3</sub>P, DIAD, THF, PhCOOH (92%); (d) KOH, MeOH (97%)

The epimeric  $\beta$ -epoxides 3 and 7 are prepared by reacting (+)-carvone with phenyl magnesium bromide and subsequent pyridinium chlorochromate oxidation to give unsaturated ketone 13 (Scheme 6). A benzyl trimethylammonium hydroxide catalyzed hydrogen peroxide epoxidation proceeds with high stereoselectivity to yield epoxy-ketone 14. Lithium tri-*t*-butoxyaluminum hydride reduction of 14 results in the formation of a 3:1 mixture of diastereomeric alcohols from which the preferred isomer 15 is separated by either chromatography or fractionate crystallization. Epoxy alcohol 15 formed nice crystals that allowed structure determination by X-ray measurements.

Alternatively, unsaturated ketone 13 can be reduced (Li(*t*-buO)<sub>3</sub>AlH, THF) to give the alcohol 17 as major isomer [ $\alpha$ : $\beta$  (7:3)] which is subjected to Sharpless epoxidation (Scheme 7).<sup>8</sup> The resulting epoxy alcohol is identical with the product 11 obtained via the carvone oxide route.

Mitsunobu inversion of allyl alcohol 17 and subsequent epoxidation of epimer 18 provide an additional route for the preparation of epoxide 16.9

In summary, we presented another example of a process which, in spite of its high stereoselectivity, does not allow to draw straightforward mechanistic conclusions. The rearrangement of tetrasubstituted cyclic epoxy alcohol derivatives remains a transformation for which both regioselectivity and stereo-chemical outcome are difficult to predict.





Scheme 6. (a) PhMgBr, THF (78%); (b) PCC, MeCl<sub>2</sub> (79%); (c) Triton B, 30% H<sub>2</sub>O<sub>2</sub>, 60°C, 6 h (62%); (d) Li(*t*-BuO)<sub>3</sub>AlH, THF (75%); (e) Ph<sub>3</sub>P, DIAD, PhCOOH (95%); (f) KOH, MeOH (97%); (g) PhCH<sub>2</sub>Br, NaH, DMF (96%)



Scheme 7.

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- 9. Selected spectroscopic and physicochemical properties: 1, colorless oil, <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ=1.08 ppm (s, 3H, Me); 1.72 (s, 3H, Me); 3.95 (t, J=2.5 Hz, 1H, H-1); 4.51 (d, J=11 Hz, 1H, benzyl-H); 4.70 (d, J=11 Hz, 1H, benzyl-H); 4.73 (s, 2H, vinyl-H). 2, colorless oil,  $[\alpha]_{20}^{20}$  +160.3 (MeOH, c=0.524), <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$ =1.76 ppm (s, 3H, Me); 1.97 (s, 3H, COMe); 4.30 (d, J=11 Hz, 1H, benzyl-H); 4.48 (d, J=11 Hz, 1H, benzyl-H); 4.66 (dd, J=5 and 1.5 Hz, 1H, H-1); 4.75 (s(br), 2H, vinyl-H); 6.95–7.05 (m, 2H, arom.-H); 7.16–7.43 (m, 8H, arom.-H). 3, oil, <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ=1.01 ppm (s, 3H, Me); 1.72 (s, 3H, Me); 3.83 (dd, J=2.5 and 5 Hz, 1H, H-1); 4.60 (d, J=11 Hz, 1H, benzyl-H); 4.75 (s(br), 2H, vinyl-H); 4.75 (d, J=11 Hz, 1H, benzyl-H). 5, mp 91–92°C (from hexane),  $[\alpha]_D = -26.2$ (CHCl<sub>3</sub>, c=0,5), <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ=1.07 ppm (s, 3H, Me); 1.71 (s, 3H, Me); 3.83 (dd, J=5 and 10 Hz, 1H, H-1); 4.57 (d, J=11 Hz, 1H, benzyl-H); 4.72 and 4.75 (2s, 1H each, vinyl-H); 4.78 (d, J=11 Hz, 1H, benzyl-H). 6a, mp 77-78°C (from hexane/diethyl ether),  $[\alpha]_D - 271.4$  (CHCl<sub>3</sub>, c=0,5), <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta = 1.71$  (s, 3H, Me); 1.87 (s, 3H, COMe); 4.45 (d, J=11 Hz, 1H, benzyl-H); 4.64-4.78 (m, 4H, H-1, benzyl-H, vinyl-H); 7.20-7.42 (m, 10H, arom.-H). **6b**, oil,  $[\alpha]_D - 226.3$  (MeOH, c=0,516), <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta = 1.76$  ppm (s, 3H, Me); 1.97 (s, 3H, COMe); 4.15 (d, J=11 Hz, 1H, benzyl-H); 4.40 (d, J=11 Hz, 1H, benzyl-H); 4.60 (d, J=0 5 Hz, 1H, H-1); 4.75 and 4.83 (2s, 1H each, vinyl-H); 6.85–6.95 (m, 2H, arom.-H); 7.15–7.41 (m, 8H, arom.-H). 7, oil, <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$ =1.11 ppm (s, 3H, Me); 1.72 (s, 3H, Me); 3.78 (dd, J=5 and 11 Hz, 1H, H-1); 4.60 (d, J=11 Hz, 1H, benzyl-H); 4.71 (d, J=11 Hz, 1H, benzyl-H); 4.74 (s, 2H, vinyl-H). 10, oil, <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ=1.10 ppm (s, 3H, Me); 1.72 (s, 3H, Me); 4.26–4.32 (m, 1H, H-1); 4.73 (s, 2H, vinyl-H). 11, mp 125–126°C (from hexane/ethyl acetate),  $[\alpha]_{\rm D}$  +20.1 (MeOH, c=0.5), <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ=1.10 ppm (s, 3H, Me); 1.71 (s, 3H, Me); 3.89-4.01 (m, 1H, H-1); 4.73 (s, 2H, vinyl-H). 14, mp 71°C (from hexane),  $[\alpha]_D$  +59.4 (CHCl<sub>3</sub>, c=0.5). 15, mp 122°C (from hexane/ethyl acetate),  $[\alpha]_D$  -61.8 (MeOH, c=0.516), <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ=1.09 ppm (s, 3H, Me); 1.72 (s, 3H, Me); 4.00–4.10 (m, 1H, H-1); 4.74 (s, 2H, vinyl-H). 16, oil, <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$ =1.12 ppm (s, 3H, Me); 1.73 (s, 3H, Me); 3.98–4.07 (m, 1H, H-1); 4.73 and 4.75 (2s, 1H each, vinyl-H).