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

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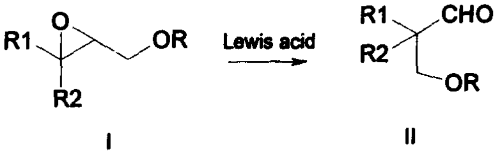
Abstract

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.[1] 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.[2] Neighboring group effects were shown to account for regio- and 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).[3]

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.[4] 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.



Scheme 1.

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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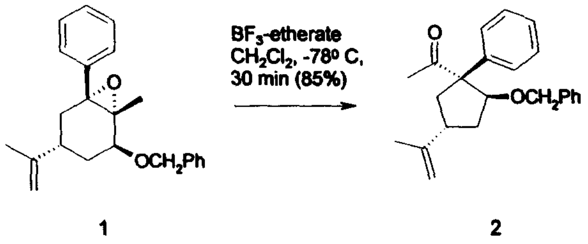
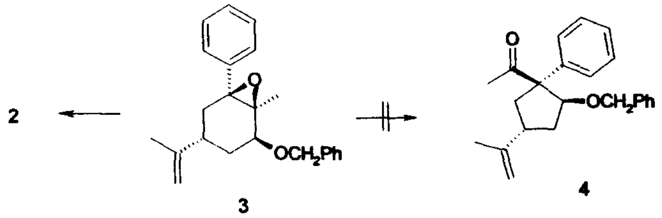
The BF_3-etherate treatment of benzyl ether-protected epoxy alcohol **1** proceeded with clean and high-yield formation of a single ring-contracted ketone **2** (Scheme 2).



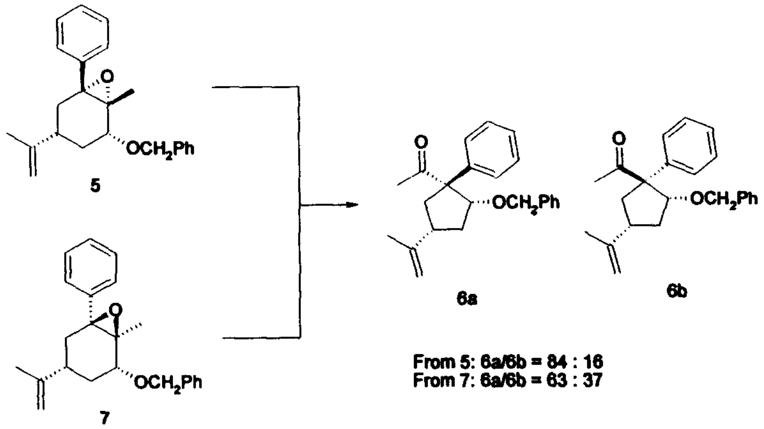
Scheme 2.

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).

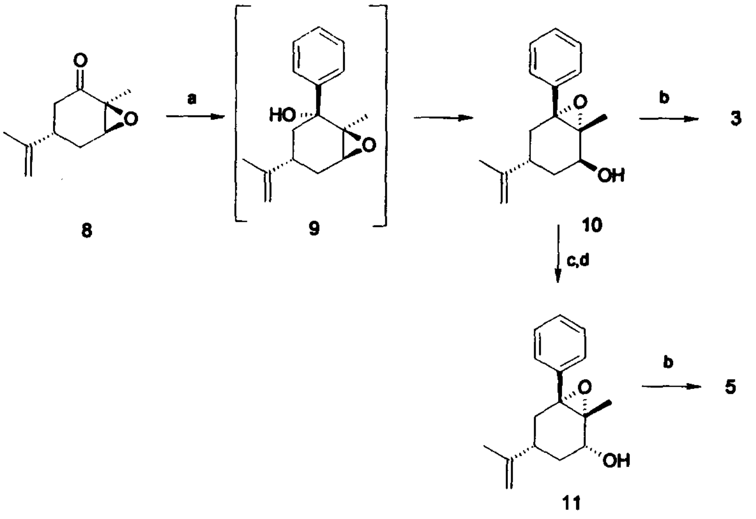


Scheme 4.

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.

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 α-epoxides **1** and **5** can be obtained from known (−)-carvone oxide[5] by reaction with phenyl magnesium bromide (Scheme 5). The primary adduct **9** undergoes a Payne rearrangement[6] in situ to give a 51.1% yield of epoxy alcohol **10** which is benzylated under standard conditions. Mitsunobu reaction[7] 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**.



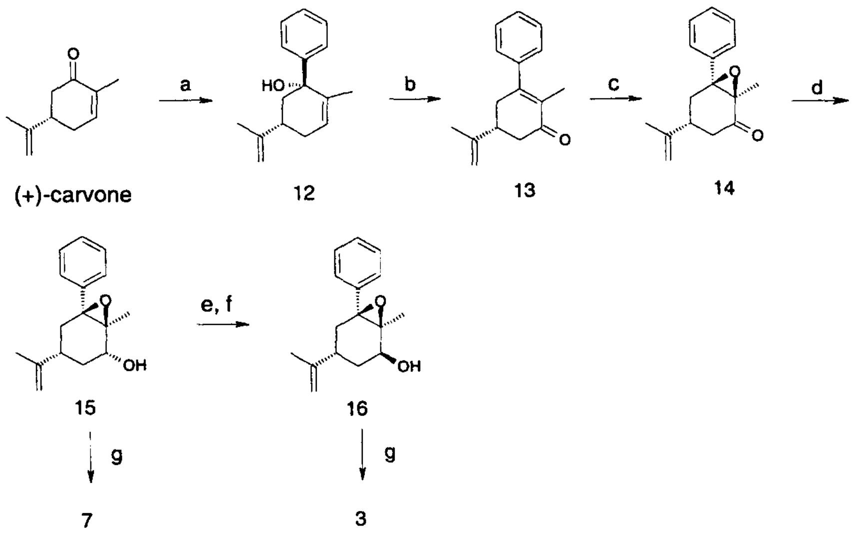
Scheme 5. (a) PhMgBr, THF (51%); (b) $PhCH_2Br$, NaH, DMF (96%); (c) Ph_3P, DIAD, THF, PhCOOH (92%); (d) KOH, MeOH (97%)

The epimeric β-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.

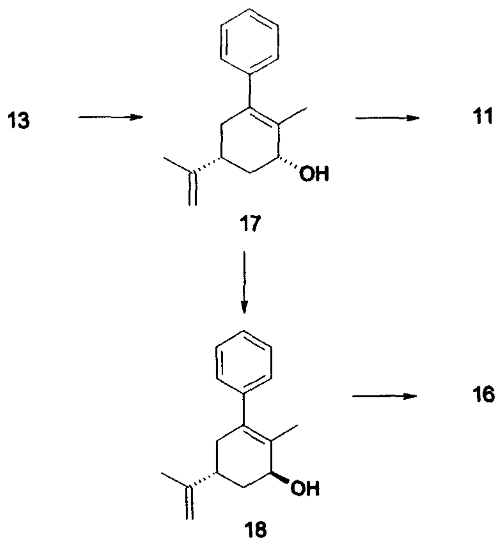
Alternatively, unsaturated ketone **13** can be reduced (Li(*t*-buO)$_3$AlH, THF) to give the alcohol **17** as major isomer [α:β (7:3)] which is subjected to Sharpless epoxidation (Scheme 7).[8] The resulting epoxy alcohol is identical with the product **11** obtained via the carvone oxide route.

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 stereochemical outcome are difficult to predict.



Scheme 6. (a) PhMgBr, THF (78%); (b) PCC, $MeCl_2$ (79%); (c) Triton B, 30% H_2O_2, 60°C, 6 h (62%); (d) Li(*t*-BuO)$_3$AlH, THF (75%); (e) Ph_3P, DIAD, PhCOOH (95%); (f) KOH, MeOH (97%); (g) $PhCH_2Br$, NaH, DMF (96%)



Scheme 7.

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9. Selected spectroscopic and physicochemical properties: **1**, colorless oil, ^{1}H NMR ($CDCl_3$, 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, $[\alpha]_D^{20}$ +160.3 (MeOH, c=0.524), ^{1}H NMR ($CDCl_3$, 300 MHz): δ=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, ^{1}H NMR ($CDCl_3$, 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 ($CHCl_3$, c=0,5), ^{1}H NMR ($CDCl_3$, 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 ($CHCl_3$, c=0,5), ^{1}H NMR ($CDCl_3$, 300 MHz): δ=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), ^{1}H NMR ($CDCl_3$, 300 MHz): δ=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, ^{1}H NMR ($CDCl_3$, 300 MHz): δ=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, ^{1}H NMR ($CDCl_3$, 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), $[\alpha]_D$ +20.1 (MeOH, c=0.5), ^{1}H NMR ($CDCl_3$, 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 ($CHCl_3$, c=0.5). **15**, mp 122°C (from hexane/ethyl acetate), $[\alpha]_D$ −61.8 (MeOH, c=0.516), ^{1}H NMR ($CDCl_3$, 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, ^{1}H NMR ($CDCl_3$, 300 MHz): δ=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).