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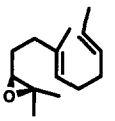
Remarkably Complex and Unpredictable Cyclization and Rearrangement Reactions of Cations Derived from Unsaturated Oxiranes

E. J. Corey* and Bryan E. Roberts

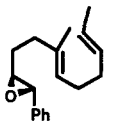
Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138

Abstract: *Lewis-acid catalyzed reactions of unsaturated epoxides 1 and 2 afford the unprecedented products 3 and 5, respectively. Mechanistic pathways for these reactions are presented (Schemes 2 and 4) along with a more fundamental analysis.* © 1997 Elsevier Science Ltd.

Cation-olefin cyclization reactions are a major resource for the synthesis of polycyclic structures ranging from steroids to sesqui-, di- and triterpenoids. Their importance has steadily increased over the past three decades, especially with the advent of better routes to the polyolefinic precursors, methods of asymmetric synthesis of the initiating species and application of aprotic Lewis acids at low temperatures.[1,2] However, major gaps remain in this area of synthesis stemming from the lack of methods for controlling the folding of the substrate during cyclization and for limiting alternative reaction pathways. Such competing pathways for highly reactive cationic intermediates are all of quite low activation energy and their control or prediction is at present highly problematic. We describe herein some extraordinary results from the study of cyclization reactions of two substrates (**1** and **2**) which *a priori* would seem to be good candidates for conventional double annulation to form *trans*-decalin systems. Substrates **1** and **2** were readily available by the three component coupling reactions described in the accompanying papers.[3]



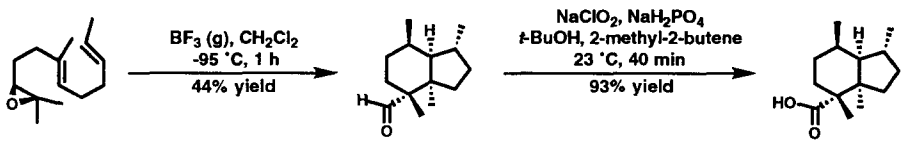
1



2

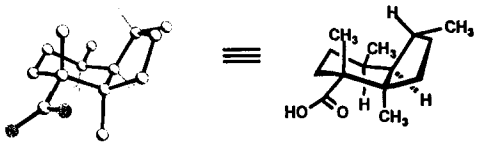
As shown in Scheme 1, treatment of the chiral epoxide **1** with anhydrous BF_3(g) in CH_2Cl_2 at -95 °C provided the [4.3.0]-bicyclic aldehyde **3** as the major product in 44% yield. Sodium chlorite oxidation of **3** afforded carboxylic acid **4** which was converted to the corresponding (*S*)-(-)-α-methylbenzylamine salt (crystallized from a CH_2Cl_2-heptane bilayer at 23 °C). Single crystal X-ray diffraction analysis of this salt unambiguously demonstrated the bond connectivity and absolute stereochemistry shown in **4** (Figure 1) and, by extension, **3**.[4]

Scheme 1. Cyclization of 1 to form aldehyde 3 and subsequent derivatization.



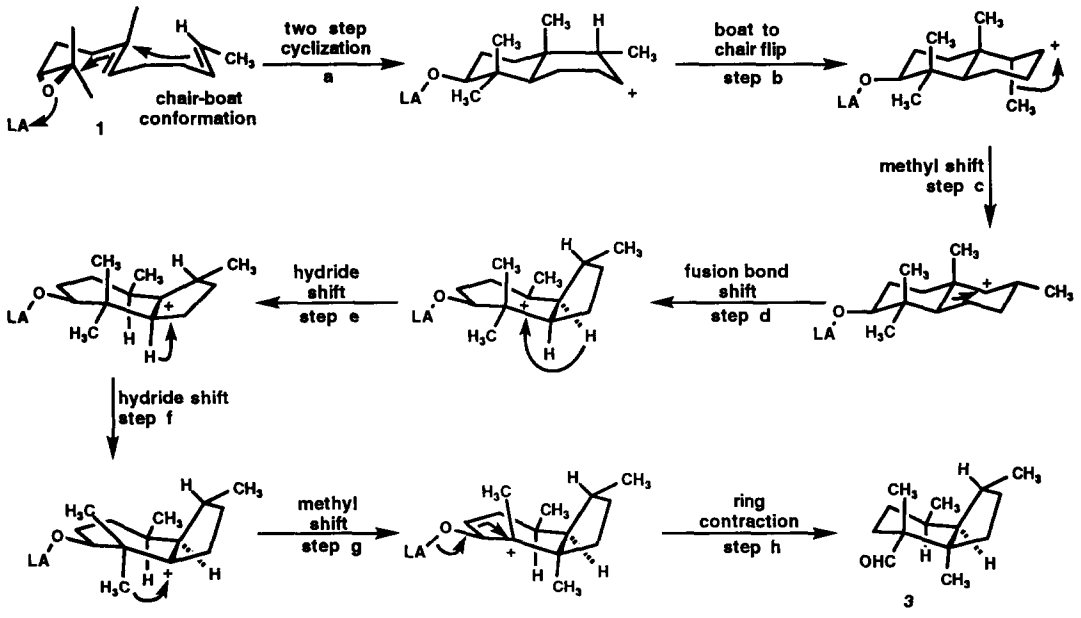
1 **3** **4**

Figure 1. X-ray crystal structure of carboxylic acid 4.[5]



Aldehyde **3** is believed to result from epoxide **1** by the series of cyclization and [1,2]-suprafacial rearrangement steps shown in Scheme 2. The critical step leading to formation of **3** rather than a [4.4.0]-bicyclic alcohol (via conventional cyclization and immediate elimination) is closure of the second ring from a boat conformation (Scheme 2, a). Rapid boat to chair flip (Scheme 2, step b) allows migration of the resulting axial α-methyl group (Scheme 2, step c). The [1,2]-suprafacial shift of the fusion bond (Scheme 2, step d) followed by two sequential hydride shifts (Scheme 2, steps e and f) and migration of a methyl group (Scheme 2, step g) affords a cation which undergoes ring contraction (Scheme 2, step h) to terminate the reaction and produce aldehyde **3**. The formation of a boat-formed bicyclic cation from **1** is both surprising and without close precedent.[6]

Scheme 2. Rearrangement pathway for the transformation of 1 to 3.



Methyl aluminum dichloride-induced cyclization of epoxide **2** in CH_2Cl_2 at -95 °C for 1 h also afforded a product of further rearrangement, the bicyclo[5.3.0]decene **5** in 50% yield (Scheme 3). Esterification of **5** with 3,5-dinitrobenzoyl chloride afford the ester **6** as a solid which crystallized from a CH_2Cl_2-pentane bilayer at 4 °C. Single crystal X-ray diffraction analysis of **6** confirmed the structure and stereochemistry of the rearrangement product **5** which is indicated in Figure 2.[4]

Scheme 3. Cyclization of 2 to form alcohol 5 and subsequent derivatization.

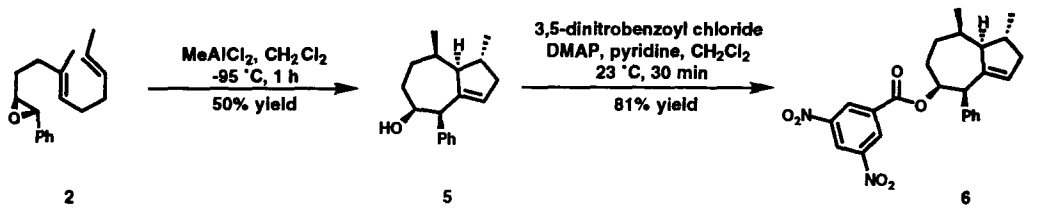
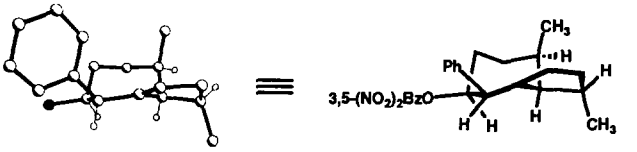
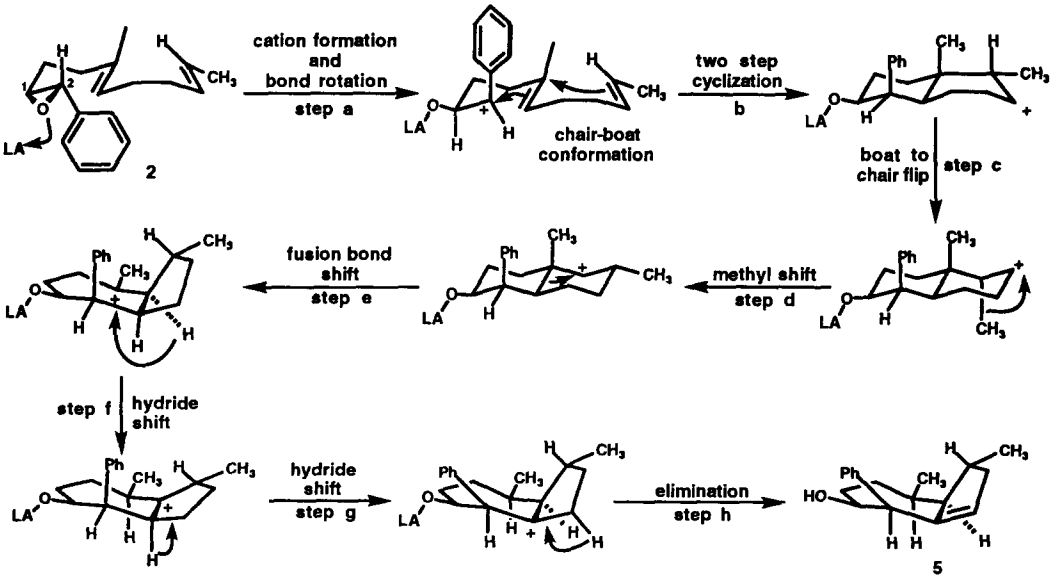


Figure 2. X-ray crystal structure of 3,5-dinitrobenzoate 6.[7]



It seems reasonable that alcohol **5** results from the rearrangement process outlined in Scheme 4. The initiation of cyclization must occur via oxirane cleavage to form a stabilized benzylic cation which undergoes C(1)-C(2) bond rotation prior to ring closure.[8b] That ring closure evidently occurs most readily via the conformation which leads to the axial phenyl arrangement. The subsequent cation-induced closure of the second ring again appears to produce that ring in the boat form,[6] which flips to the chair form prior to methyl rearrangement (step d, the formation of one secondary carbocation from another). Migration of the fusion bond, two subsequent 1,2-hydride shifts (steps e through g, all involving tertiary carbocations) and deprotonation then produce the observed product, **5**. The series of steps shown in Scheme 4, although credible in retrospect, were totally unexpected.

Scheme 4. Rearrangement pathway for the transformation of 2 to 5.



The unexpected reaction pathways for the Lewis acid catalyzed cationic transformations of substrates **1** and **2**, as detailed in Schemes 2 and 4, may be of broader consequence, since their analysis could reveal subtle and hitherto unappreciated factors which can influence the outcome of such processes. The initial step of the reaction of substrate **2**, in which the first ring is formed, for instance seems so bizarre that there is the temptation to regard it as inexplicable because almost any explanation may seem to a degree implausible and inconsistent with conventional thinking. However, in our view, there is one novel explanation for that first step that is not easily dismissed and which may, therefore, be deserving of serious consideration. Mechanistic studies in these laboratories have provided strong evidence that the first cyclization of oxiranes such as in **1** occurs with concerted oxirane C-O cleavage and ring formation, i.e. with nucleophilic assistance by the nearby double bond which is involved in ring closure.[8a] Clearly, this cannot be the case in the cyclization of **2**.[8b] The reason may be that the steric bulk of the phenyl group slows the rate of cyclization relative to back side attack by solvent CH_2Cl_2 to form a weak covalent bond, i.e. chloronium ion (R^+-$ClCH_2Cl$) intermediate,[9] with inversion. Cyclization of this intermediate with inversion would then close the first ring to form an axial phenyl appendage as shown in Scheme 4.

There is also a possible explanation for the formation of the initial boat-formed bicyclic cation from substrates **1** and **2** in the second ring closure step (see Schemes 2 and 4, respectively). If the closure of the second ring leads to a delocalized 3-center carbocation, instead of an open cyclohexyl type cation, two diastereomeric geometries are possible (involving the two different π-faces of the *E*-$RCH{=}CHCH_3$ olefinic terminator). Examination of molecular models reveals that the one leading to the *boat formed* open ion might well be favored in each case (**1** and **2**) because of lesser steric repulsions involving the terminal methyl group. Thus, with substrates **1** and **2**, because the terminator double bond is 1,2-disubstituted, in contrast to the usual trisubstituted situation, the six-membered open cation is not generated directly, but via a three-center precursor whose formation is product determining. Time will tell whether these conjectures have merit.[10]

References and Notes:

1. See Sutherland, J. K. in *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I. Eds.; Pergamon Press: Oxford, 1991; Vol. 3, p. 341.
2. (a) Corey, E. J.; Lee, J. *J. Am. Chem. Soc.* **1993**, *115*, 8873. (b) Corey, E. J.; Lee, J.; Liu, D. R. *Tetrahedron Lett.* **1994**, *35*, 9149. (c) Corey, E. J.; Lin, S. *J. Am. Chem. Soc.* **1996**, *118*, 8765.
3. Corey, E. J.; Roberts, B. E. *Tetrahedron Lett.* preceding papers in this issue.
4. We are indebted to Dr. Mark C. Noe and Dr. Marcus Semones for carrying out the X-ray crystallographic analyses. Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.
5. The (*S*)-(-)-α-methylbenzylammonium group has been omitted from the X-ray structure of **4** for clarity.
6. See however: Corey, E. J.; Wood, H. B., Jr. *J. Am. Chem. Soc.* **1996**, *118*, 11982.
7. The 3,5-dinitrobenzoyl group has been omitted from the X-ray structure of **6** for clarity.
8. (a) Corey, E. J.; Daley, D. C. manuscript in preparation. (b) Another explanation for the observed stereochemistry in **5** is that the starting material **2** was actually the *cis* epoxide. This possibility was ruled out by comparison of the ^1H and ^{13}C NMR spectra of **2** with the NMR spectra of both the *trans* and *cis* isomers of **2** prepared by a different route, namely stereospecific *m*-CPBA epoxidation of the corresponding olefins.
9. See Jenson, C; Jorgensen, W. L. *Synlett.* **1997**, 518 for the CH_2Cl_2-*t*-Bu^+ complex (binding energy 8.2 kcal/mole at 3.77Å C^+-$ClCH_2Cl$ distance).
10. This research was supported by the National Science Foundation and the National Institutes of Health.

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