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An Effective System for Epoxide-Initiated Cation-Olefin Cyclization

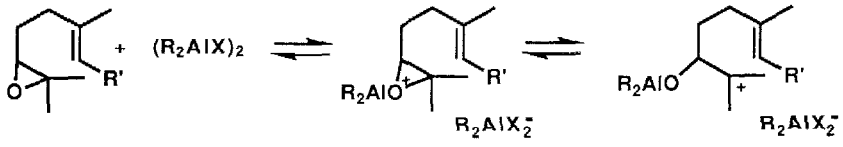
E. J. Corey and Mikiko Sodeoka

Department of Chemistry, Harvard University, Cambridge, Massachusetts, 02138

Summary: *Aprotic, Lewis-acid-catalyzed cyclization of epoxy diene **1**, e.g. using $MeAlCl_2$ in CH_2Cl_2, affords bis-cyclization product **3** in good yield (75-79%).*

Epoxide-initiated cation-olefin cyclization plays a key role in the biosynthesis of triterpenes and steroids.[1] Of all the known biosynthetic processes it is among the most powerful with regard to rapid development of molecular complexity. Thus, only one step is required for the conversion of 2,3-oxidosqualene to lanosterol, but an additional eighteen steps (and numerous enzymes) are needed to complete the biosynthesis of cholesterol. Nonetheless, attempts to utilize epoxides as initiators for synthetic cation-olefin polycyclization have met with poor yields, on the average about 20%.[2,3] We were especially interested in improving the synthetic methodology in this area because of its potentially great value when coupled to reactions for enantioselective epoxide synthesis. Recent studies in this laboratory have led to the successful development of enantioselective routes to chiral epoxides such as 2,3-oxidosqualene,[4] adding urgency to the development of superior cyclization methodology. In this note we report a much improved process for *bis*-cyclization of an epoxy diene which is a good prototype for many interesting cyclizations and which involves especially mild conditions.

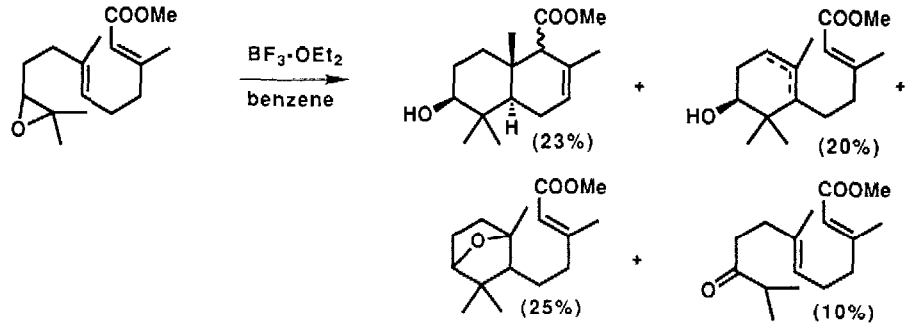
The use of the epoxide function as the initiating unit in cation-olefin cyclizations is plagued by several problems in chemical systems in which the olefinic acceptor unit is not held in proximity to the electrophilic oxirane carbon. The most important of these are (1) facile pinacol rearrangement to a carbonyl compound and (2) formation of 1,2-diol or halohydrin derivatives, in lieu of cyclization. Protic-acid catalysts and many Lewis acids can be very effective in promoting such non-cyclization pathways. There is also a problem with cyclization reactions which are terminated by deprotonation, since the protic acid which is formed as a result of cyclization can destroy the initiating epoxide function. We reasoned that the ideal catalyst for epoxide-initiated cyclization would be a species of the type Me_2AlX that would activate the epoxide by the following process:



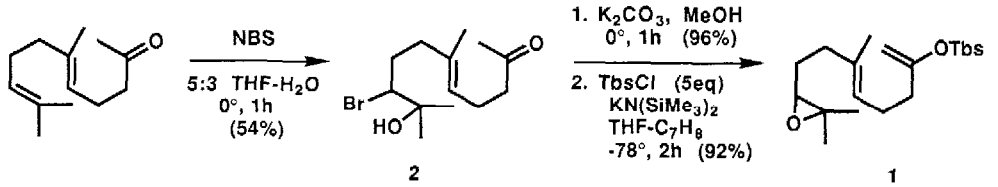
a *b* *c*

It was expected that pinacol rearrangement would be minimized at the critical stage of species *c*, since multiple bonding between oxygen and aluminum would remove the driving force for such rearrangement. The group X should in principle either be non-C-nucleophilic or removed by another pathway, for example, silyl transfer. The unit R' = $CH_2CH_2C(OSiR_3)=CH_2$ was chosen for the substrate (**1**) because it promotes the nucleophilicity of the terminating olefinic linkage, while leading to an innocuous product, R_3SiX. The results of our study as reported below may be compared to those of a previous study[5] which is shown in Scheme I.

Scheme 1



Scheme 2

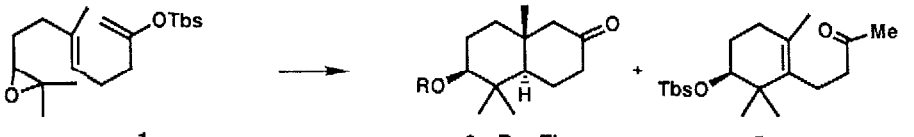


2

Tbs = Me_2t-BuSi

1

Scheme 3

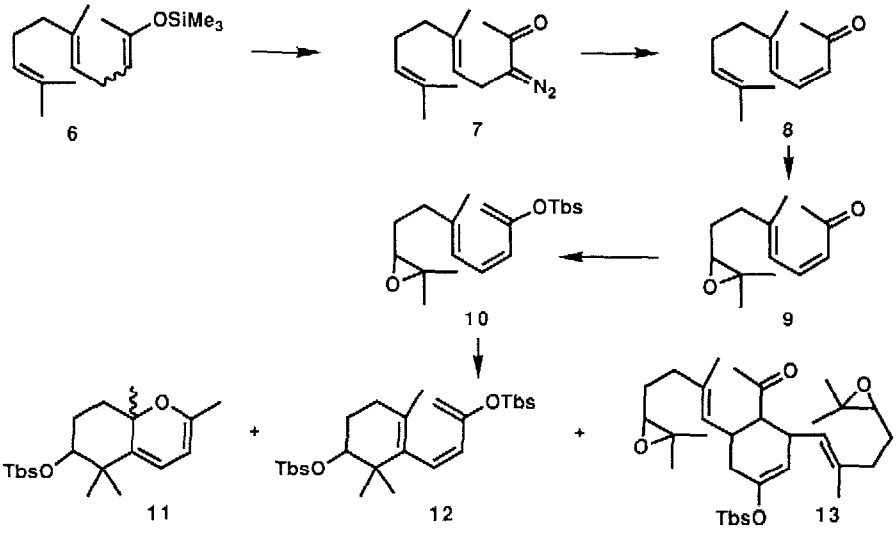


1

3, R = Tbs
4, R = H

5

Scheme 4



6 7 8 9 10

11 12 13

Substrate **1** was synthesized from commercial geranylacetone as shown in Scheme 2. Under optimized conditions bromohydrin **2** was obtained in 54% yield after column chromatography on silica gel (SG) and conversion to the corresponding epoxide was very clean (96% isolated yield). *t*-Butyldimethylsilyl (Tbs) enol ether **1** could be formed in 92% yield under special conditions which involved *in situ* trapping of the initially formed terminal enolate by TbsCl, as indicated in Scheme 2.[6] Prior formation of the enolate and subsequent addition of TbsCl was unsatisfactory, since a mixture of the two isomeric silyl enol ethers was invariably obtained.

A number of experiments were performed to determine optimum conditions for the *bis*-cyclization of **1** with results that can be summarized as follows. Under optimal conditions the yields of bicyclic product in several experiments were in the range 75-79%, using methylaluminum dichloride (0.3 to 0.5 equiv) as catalyst in methylene chloride[7] at -78 °C with a reaction time of 1 h. The rate of reaction was found to vary with the Lewis acid in the order $MeAlCl_2 > Me_2AlCl > Me_2AlOSO_2CF_3$,[8] but the yields of bicyclic product were comparable with all three Lewis acids. The principal products of the cyclization of **1** under optimal conditions were the bicyclic silyloxy ketone **3**, the bicyclic hydroxy ketone **4** and the monocyclic silyloxy methyl ketone **5**, as shown in Scheme 3. In practice, the crude cyclization product was obtained by addition of 5% aqueous hydrochloric acid to the reaction mixture and extractive isolation and the resulting mixture was silylated ($TbsOSO_2CF_3$–2,6-lutidine in CH_2Cl_2 at 23 °C) and subjected to SG column chromatography. In addition to **3** (75-79%), the monocyclic methyl ketone **5** was isolated in 10-15% yield.[9] The ratio of **3** to **4** in the cyclization mixture prior to isolation and silylation varied from 10 : 1 to 3 : 1 in different experiments.[10] A number of attempts to minimize the formation of the monocyclic product **5** were to no avail. Thus, lower temperature (-95 °C), the use of tribenzylsilyl or trimethylsilyl analogs of **1**, or larger quantities of Lewis acid failed to decrease the formation of **5** or to increase the yield of **3**.

A study was made of the cyclization of substrate **10**, a *Z*-dehydroderivative of epoxide **1**, under optimal conditions for the *bis*-cyclization of **1**. The synthesis of **10** was accomplished as outlined in Scheme 4. Geranylacetone upon treatment sequentially with KH in THF and then trimethylsilyl chloride gave silyl enol ether **6** (*E* and *Z*) admixed with the terminal silyl enol ether (*ca.* 5 : 1 ratio). The mixture was formylated by reaction with 3 equiv of methyl formate and 3 equiv of sodium methoxide in MeOH–THF at 23 °C for 16 h, and the resulting mixture was allowed to react with 3.6 equiv of TsN_3 at 0 to 23 °C for 4 h to give diazo ketone **7** (45% overall) and the isomeric diazomethyl ketone (17%) after separation by SG chromatography. Reaction of **7** with 2.5 mole% of $Rh_2(OAc)_4$ in THF at 23 °C for 40 min gave the *Z*-α,β-unsaturated ketone **8** as a colorless oil in 53% yield.[11] Epoxidation of **8** (*m*-chloroperoxy benzoic acid in CH_2Cl_2–sat. aq. $NaHCO_3$ at 0 °C for 1 h) gave **9** (65%) which was silylated, as described above for the synthesis of **1**, to give 91% of **10**. Cyclization experiments with epoxy triene **10** and Me_2AlCl in CH_2Cl_2 at -78 °C gave many products, including **11** (4%), **12** (8%) and **13** (12%). However, no bicarbocyclic compounds could be isolated. The bimolecular product **13** presumably results from a Lewis-acid-catalyzed Diels-Alder pathway. From these results, it is clear that the extra olefinic function of **10** is deleterious to the desired cation-olefin cyclization.

In conclusion, conditions have been developed which lead to good yields of the bicyclic ketone **3** by cation-olefin cyclization of **1** and which probably will prove effective for other substrates.[12]

References and Notes

1. Sukh Dev, *CRC Handbook of Terpenoids;* CRC Press, Inc.; Boca Raton, FL; 1989; Vol. I, pp. 7-61.
2. See, (a) van Tamelen, E. E.; Storni, A.; Hessler, E. J.; Schwartz, M. *J. Am. Chem. Soc.* **1963**, *85*, 3295-3296. (b) van Tamelen, E. E.; McCormick, J. P. *J. Am. Chem. Soc.* **1969**, *91*, 1847-1848. (c) Sharpless, K. B.; van Tamelen, E. E. *J. Am. Chem. Soc.* **1969**, *91*, 1848-1849. (d) van Tamelen, E. E.; Leiden, T. M. *J. Am. Chem. Soc.* **1982**, *104*, 2061-2062. (e) Sharpless, K. B. *J. Am. Chem. Soc.* **1970**, *92*, 6999-7001. (f) Goldsmith, D. J.; Phillips, C. F. *J. Am. Chem. Soc.* **1969**, *91*, 5862-5870.

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3. For a recent exceptional case involving a yield of 72%, see Tanis, S. P.; Chuang, Y-H.; Head, D. B. *J. Org. Chem.* **1988**, *53*, 4929-4938.
4. Corey, E. J.; Yi, K. Y. manuscript in preparation.
5. See van Tamelen, E. E. *Acc. Chem. Res.* **1968**, *1*, 111-120.
6. The following procedure was used for the preparation of enol ether **1**. A solution of potassium bis(trimethylsilyl)amide in toluene (0.5 M, 1.2 ml, 0.6 mmol) was added to a solution of *t*-butyldimethylsilyl chloride (302 mg, 2.0 mmol) in THF (2.0 ml) at -78 °C. To the resulting mixture was added dropwise a solution of the epoxy methyl ketone (84 mg, 0.4 mmol) in toluene (2.0 ml) at -78 °C over 30 min. After stirring for 80 min at -78 °C, triethylamine (0.6 ml) was added followed by saturated aqueous sodium bicarbonate. The mixture was stirred at 23 °C for 20 min and extracted with petroleum ether. The organic layer was washed with water, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by SG (1% triethylamine) flash chromatography with 1 : 100 : 5 triethylamine–hexane–ether for elution to afford the silyl enol ether **1** (119 mg, 92%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 270 MHz): δ 5.18 (t, *J*=5.9 Hz, 1H), 4.02 (s, 2H), 2.71 (t, *J*=6.3 Hz, 1H), 1.96-2.24 (m, 6H), 1.55-1.80 (m, 2H), 1.63 (s, 3H), 1.30 (s, 3H), 1.26 (s, 3H), 0.93 (s, 9H), 0.16 (s, 6H); ^{13}C NMR ($CDCl_3$, 65 MHz): δ 159.4, 134.6, 124.6, 90.0, 64.2, 58.3, 36.9, 36.5, 27.7, 26.4, 25.9, 25.7, 25.0, 18.9, 16.2, 0.51 ppm.; IR (film): 1662, 1634, 1254 cm^{-1}. The ratio of the two position-isomeric enol ethers can be determined by integration of the vinyl proton signals in the ^{1}H NMR spectrum: δ 4.02 (terminal enol ether, s, 2H) *vs* 4.38 and 4.62 (internal enol ether, *t*, 1H).
7. Methylene chloride was found to be a superior solvent to 1,2-dichloroethane, nitroethane, toluene or hexane, with respect to the rate and efficiency of *bis*-cyclization.
8. In the case of $Me_2AlOSO_2CF_3$ as catalyst (prepared from Me_3Al and 1 equiv of CF_3SO_3H) 1.2 equiv of reagent was required for maximum yield.
9. A solution of methylaluminum dichloride in hexane (1.0 M, 77 μl, 0.077 mmol) was added to a stirred solution of **1** (50 mg, 0.154 mmol) in methylene chloride (2.5 ml) at -78 °C, and the resulting solution was stirred at -78 °C for 1 h. The reaction was quenched by the addition of 8 ml of 5% aqueous hydrochloric acid at -78 °C and stirred for 20 min as the mixture warmed to 0 °C. The mixture was extracted with ether, and the organic layer was washed with saturated aqueous sodium bicarbonate and brine, dried over calcium sulfate, and concentrated. The residue was dissolved in methylene chloride (0.3 ml). To this solution was added 2,6-lutidine (55 μl, 0.47 mmol) and *t*-butyldimethylsilyl trifluoromethanesulfonate (70 μl, 0.31 mmol), and the mixture was stirred at 23 °C for 2 h. After addition of 5% aqueous hydrochloric acid and stirring for 30 min, the mixture was extracted with ether. The organic layer was washed with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, and concentrated. The residue was purified by SG flash chromatography (1 : 40 ethyl acetate–hexane) to afford the monocyclic silyl ether **5** (5.7 mg, 11%) as a colorless oil and the bicyclic silyl ether **3** (37.4 mg, 75%) as a colorless solid, mp 99-100 °C (from hexane). Data for **3**: ^{1}H NMR ($CDCl_3$, 270 MHz): δ 3.30 (dd, *J*=10.9, 4.7 Hz, 1H), 2.40 (m, 1H), 2.27 (m, 1H), 1.90-2.15 (m, 3H), 1.20-1.85 (m, 6H), 1.00 (s, 3H), 0.89 (s, 12H), 0.79 (s, 3H), 0.06 (s, 6H). Data for **5** : ^{1}H NMR ($CDCl_3$, 270 MHz): δ 3.43 (t, *J*=6.6 Hz, 1H), 2.48 (t, *J*=8.2 Hz, 2H), 2.20-2.40 (m, 2H), 2.14 (s, 3H), 1.80-2.10 (m, 2H), 1.50-1.80 (m, 2H), 1.55 (s, 3H), 0.98 (s, 3H), 0.91 (s, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H).
10. We surmise that the formation of bicyclic silyl ether **3** in the cyclization mixture is the result of an intermolecular silylation of an aluminum alkoxide of **4** by the initial *bis*-cyclized intermediate ROTbs$^+$. At -78 °C there is no reaction between the *i*-Bu_2Al alkoxide of **4** (from **4** and *i*-Bu_2AlH) and TbsCl in CH_2Cl_2.
11. Spectral data for **8**: ^{1}H NMR ($CDCl_3$, 270 MHz): δ 7.19 (d, *J* = 11.5 Hz, 1H), 6.73 (t, *J* = 11.5 Hz, 1H), 5.93 (d, *J* = 11.5 Hz, 1H), 5.09 (br s, 1H), 2.23 (s, 3H), 2.18 (m, 4H), 1.86 (s, 3H), 1.68 (s, 3H), 1.61 (s, 3H). IR (film): 1684, 1624, 1571 cm^{-1}.
12. This research was assisted financially by a grant from the National Science Foundation. We are grateful to Dr. Robert Burk for preliminary studies in this area which showed that epoxide **1** could be converted to **3** in *ca.* 50% yield using as reagent Tbs triflate–2,6-di-*t*-butylpyridine.

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