Pergamon

Tetrahedron Letters 43 (2002) 2687–2690

TETRAHEDRON LETTERS

$FeCl_3$ and $ZrCl_4$ regiochemically controlled biomimetic-like cyclizations of simple isoprenoid epoxyolefins

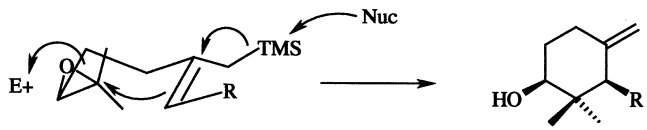
Giovanni Vidari,* Stephen Beszant, Jamal El Merabet, Marcella Bovolenta and Giuseppe Zanoni

Dipartimento di Chimica Organica, Via Taramelli 10, 27100 Pavia, Italy

Received 12 February 2002; accepted 25 February 2002

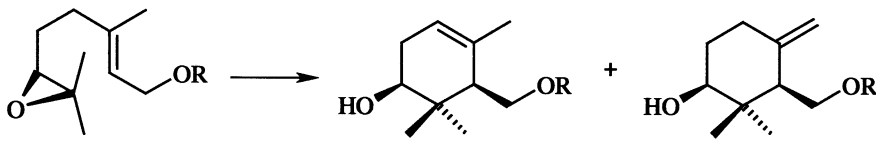
Abstract—$FeCl_3 \cdot 6H_2O$ and $ZrCl_4$ efficiently promote the biomimetic-like cyclization of geraniol and farnesol epoxides, yielding the corresponding *endo* mono- and bicyclic olefins, respectively, in reasonable yields and with complete positional control.

Following the seminal studies of Goldsmith[1] and van Tamelen,[2] Lewis acid promoted electrophilic cyclizations of terminal polyene epoxides have been employed in many syntheses of carbocyclic compounds in the past 40 years.[3,4] Geraniol and farnesol epoxides are readily available and inexpensive starting materials; however, despite their appeal, their biomimetic cyclizations are seldom used in the synthesis of cyclic terpenoids. In fact, such annulations of simple acyclic alkenes are usually inefficient and poorly regioselective, due to the absence of regiocontrol in quenching the carbonium ion produced in the cyclization, thus resulting in unproductive mixtures of regioisomeric olefins. Several terminating units, among which acetylenic, styryl, allyltin and allylsilyl groups are the most used, have therefore been introduced in the starting alkenes to exert the required regiocontrol.[3,4] As a consequence, ad hoc preparation of such substrates usually requires additional lengthy synthetic steps; moreover, loss of the allylsilyl or the allyltin group during the cyclization step (Scheme 1), severely impairs the overall atom economy of the synthesis.[5]



Scheme 1.

In the case of geraniol epoxide **1a**, a survey of the literature[6] clearly indicates that, besides other parameters, the nature of the C(1)-alcohol substituent and the choice of Lewis acid exert important roles in determining the reaction efficiency and the product distribution. For example, reaction of acetate **1b** with $BF_3 \cdot Et_2O$ or with BBr_3 afforded neither **2b** nor **3b**,[7] whereas $SnCl_4$ in CH_2Cl_2 at −10°C gave a mixture of *endo*-/*exo*-olefin in 4.4% yield,[7] and reaction of **1c** with the same Lewis acid in toluene at 0°C produced an ca. 85:15 mixture of **2a** and **3a** in 60% yield (Scheme 2).[6]



1a R= H
1b R= Ac
1c R= TMS

2a R= H
2b R= Ac

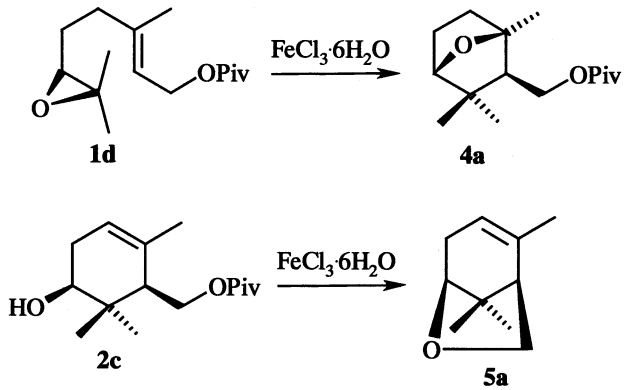
3a R= H
3b R= Ac

Scheme 2.

Keywords: biomimetic reactions; cyclization; terpenes; epoxides; regiocontrol.
* Corresponding author. Fax: +39 0382507323; e-mail: vidari@chifis.unipv.it

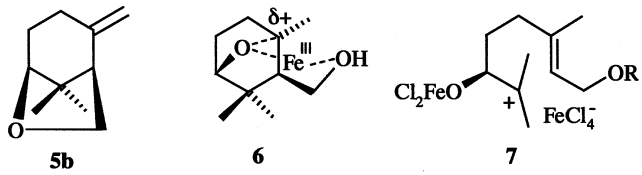
0040-4039/02/$ - see front matter
PII: S0040-4039(02)00394-5

Among the several Lewis acids screened to induce epoxide-initiated cation-polyene cyclizations, $FeCl_3 \cdot 6H_2O$ appears to have seldom been used as a cyclization promoter. Indeed, it showed variable efficiency in the cyclization of allylsilane[8] or alkoxyarene[9,10] terminating polyenes; however, to our knowledge, no example in the annulation of simple epoxy-polyenes has been reported so far. This prompted us to examine the ability of $FeCl_3 \cdot 6H_2O$ to cyclize **1a** esters. In the event, pivalate **1d** was directly converted into internal ether **4a** in 30 min in 41% yield upon exposure to $FeCl_3 \cdot 6H_2O$ (3 equiv.) in CH_2Cl_2 at room temperature (Scheme 3). Monocyclic compounds such as **2c** were not detected nor were intermediates in the formation of **4a**. Indeed, by submitting **2c** to $FeCl_3 \cdot 6H_2O$ in a separate experiment (Scheme 3), we obtained, as the sole product, the highly volatile cyclic ether **5a**, identical with the literature data.[11] Noteworthy, compound **5a** has never been obtained before free of the naturally occurring *exo* olefin karahana ether (**5b**).[7,11]



Scheme 3.

In contrast with these results, exposure of free alcohol **1a** to $FeCl_3 \cdot 6H_2O$ rapidly afforded an ca. 1:1 mixture of **2a** and **4b** (Scheme 4), whereas prolonged reaction time (24 h) afforded the sole *endo* olefin (±)-**2a** in 40% isolated yield.[12] In separate experiments, $FeCl_3 \cdot 6H_2O$ promoted 37% conversion (GC) of **4b** into **2a** in 1 h, whereas, under the same conditions, the *exo* olefin **3a** rapidly degraded without isomerization either to the *endo* isomer **2a** or to ether **4b**. These results clearly indicated that **1a** afforded the monocyclic *endo* olefin **2a** either directly or through the intermediacy of **4b** and that the regiochemistry of the cyclization was controlled by the Lewis acid and not by thermodynamic factors. Conversion of **4b** into **2a** could be promoted by traditional Lewis acid coordination of the ether oxygen and a double coordination with the alcohol oxygen might facilitate formation of such complex (see formula **6** as a proposed transition state of the reaction).



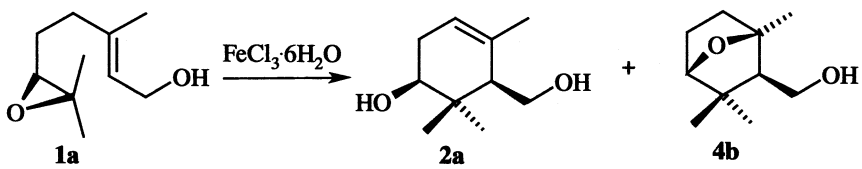
5b **6** **7**

In both $FeCl_3 \cdot 6H_2O$ promoted cyclizations of **1a** and **1d** we observed minor formation of 1,2-diol or halohydrin derivatives, and carbonyl compounds which usually plague several epoxide-initiated cation-olefin cyclizations.[4,6,7,13] In our opinion, this result was due to a threefold beneficial effect of $FeCl_3 \cdot 6H_2O$: (i) the modest protic acidity[14] and (ii) the Cl^- sequestering property of this compound, so that undesired acid promoted epoxide opening and rearrangement reactions were prevented; (iii) the strong bond between oxygen and Fe^{III} which very likely furnished a highly electrophilic cation species, i.e. **7**, and removed the driving force for pinacol rearrangement.

A number of attempts to improve the yields of **2a**, i.e. by lowering the temperature (−10°C), or by using a higher concentration of $FeCl_3 \cdot 6H_2O$ or the salt supported[15] on SiO_2, were to no avail.

Considering the mechanism of the cyclization of **1a** to **2a** outlined above, and the species **7** and **6** presumably involved, we reasoned that a Lewis acid more oxophilic than ferric chloride would further improve the cyclization of **1a**. In fact, we expected that a stronger coordination of a metal to the oxirane oxygen of **1a** would speed up the formation of electrophilic cation species analogous to **7** and prevent the subsequent ring closure to **4b** by the oxygen bonded to the metal. For the same reason, conversion of **4b** into **2a** through the intermediacy of species similar to **6** would be facilitated.

After some experimentation, we found that $ZrCl_4$ was the Lewis acid of choice. Under optimal conditions the yields of the conversion of **1a** into the monocyclic diol **2a** were in the range 50–55% on an $\leq$1.5 g scale, whereas a 5–10% erosion of the yields occurred on multigram scale. As expected, the reaction was much faster than with $FeCl_3 \cdot 6H_2O$, conversion of **1a** to **2a** being completed in less than 10 min.[†] When the reaction was quenched after ca. 2 min, internal ether **4b** was

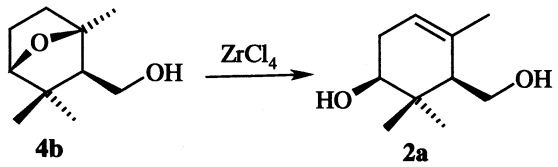


1a **2a** **4b**

Scheme 4.

[†] To our knowledge, this is the first example of cationic cyclization of polyene epoxides promoted by $ZrCl_4$.

detected in the cyclization mixture; however, at the end of the reaction, neither **4b** nor the *exo* olefin **3a** were detectable among the products (GC and NMR). Moreover, upon exposure to $ZrCl_4$, **4b** was quantitatively converted into **2a** in ca. 5 min (Scheme 5).



4b **2a**

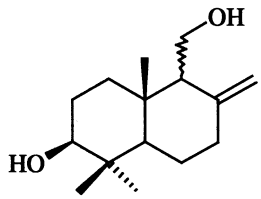
Scheme 5.

General cyclization procedure using $ZrCl_4$: Commercially available $ZrCl_4$ (6.16 g, 3 equiv.) was added to a solution of epoxide **1a** (1.5 g, 8.81 mmol) in anhydrous CH_2Cl_2 (1.2 L) at rt. The resulting whitish suspension was stirred for 10 min, then 1 M HCl (ca. 200 mL) was added and the two layers were separated in a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (3×25 mL) and the combined organic layers were washed with saturated aq. $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel flash chromatography (1:4→2:3 EtOAc–hexane gradient) to afford diol (±)-**2a** (0.78 g, 52%) as a white solid, mp 89–90°C. Spectroscopic data of **2a** were identical with the literature data.[6]

Yields of the reaction were dramatically dependent on the concentration of $ZrCl_4$ and the temperature. At concentrations higher than ca. 0.007 M, even in the presence of minor quantities of the Lewis acid, unidentified degradation products increased in comparison with **2a**, whereas lower temperature (–20°C) favored the formation of halohydrin derivatives. Addition of a base (pyridine or NEt_3) to buffer protic acidity was to no avail; ZrF_4 or $Zr(acac)_4$ instead of $ZrCl_4$ proved to be completely inert as promoters of the **1a** cyclization.

Gratifyingly, $ZrCl_4$ was also an efficient promoter of the bis-cyclization of farnesol epoxide **8**. Under the general procedures reported above, this Lewis acid afforded the C-9 epimeric $\Delta^{7,8}$-*trans*-bicyclofarnesyl derivatives **9a**[16,17] and **9b**[16–18] (Scheme 6), uncontaminated by the exocyclic alkene **10**,[18] in a ratio of 2:1 and in 40% yield.

Isolated yields of **9a**–**b**, though unexceptional, were significantly better than those reported in the literature for analogous cationic *bis*-cyclizations of farnesol epoxide derivatives, which merely exceeded 25%.[2,16,17,19,20]



10

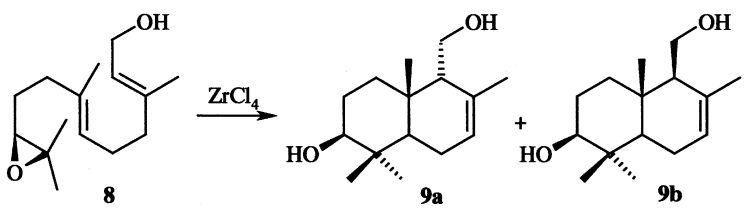
In conclusion, $FeCl_3 \cdot 6H_2O$ and $ZrCl_4$ have been proved to efficiently promote the biomimetic-like cyclization of geraniol and farnesol epoxides which are valuable starting materials in terpenoid synthesis. A notable feature of this new methodology is the complete control exerted by the Lewis acid on the regiochemistry of the formed olefin product. Thus, no additional directional group on starting polyenes is required. Moreover, this methodology can, in principle, readily afford both enantiomers of **2a** and **9** from enantiomerically enriched epoxides **1a** and **8**.[21] In addition, the advantages such as non-toxicity, stability, and cheapness of the compounds, mild reaction condition and ease of workup make this method attractive also for the cyclization of other substrates.

Acknowledgements

The Italian MIUR (funds COFIN 2001), the University of Pavia (funds FAR), and the EU Commission (Contract No. ERBFAIRCT961781) are acknowledged for financial support. We thank Professor Mariella Mella and Dr. Marina Ricci for the NMR and MS spectra.

References

1. Goldsmith, D. J. *J. Am. Chem. Soc.* **1962**, *84*, 3913–3918.
2. van Tamelen, E. E. *Acc. Chem. Res.* **1968**, *1*, 111–120.
3. Sutherland, J. K. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp. 341–377.
4. Taylor, S. K. *Org. Prep. Proc. Int.* **1992**, *24*, 245–284.
5. Trost, B. M. *Science* **1991**, *254*, 1471–1477.
6. Alcaraz, L.; Harnett, J. J.; Mioskowski, C.; Le Gall, T.; Shin, D.-S.; Falck, J. R. *J. Org. Chem.* **1995**, *60*, 7209–7214 and Refs. 13, 15, and 17 cited therein.
7. Barrero, A. F.; Alvarez-Manzaneda, E. J.; Linares Palomino, P. *Tetrahedron* **1994**, *50*, 13239–13250.
8. Sen, S. E.; Roach, S. L.; Smith, S. M.; Zhang, Y.z. *Tetrahedron Lett.* **1998**, *39*, 3969–3972.



8 **9a** **9b**

Scheme 6.

9. van Tamelen, E. E.; Zawacky, S. R.; Rusell, R. K.; Carlson, J. G. *J. Am. Chem. Soc.* **1983**, *105*, 142–143.
10. Bogenstatter, M.; Limberg, A.; Overman, L. E.; Tomasi, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 12206–12207.
11. Yamada, Y.; Sanjoch, H.; Iguchi, K. *Tetrahedron Lett.* **1979**, *20*, 1323–1326.
12. Spectral data of **2a** were identical to the literature data.[6]
13. Corey, E. J.; Sodeoka, M. *Tetrahedron Lett.* **1991**, *32*, 7005–7008.
14. Nicholls, D. In *Comprehensive Inorganic Chemistry*; Bailar, J. C.; Emeléus, H. J.; Nyholm, R.; Trotman-Dickenson, A. F., Eds.; Pergamon: Oxford, 1973; Vol. 3, pp. 1038–1049.
15. Iranpoor, N.; Tarrian, T.; Movahedi, Z. *Synthesis* **1996**, 1473–1476.
16. van Tamelen, E. E.; Storni, A.; Hessler, E. J.; Schwartz, M. *J. Am. Chem. Soc.* **1963**, *85*, 3295–3296.
17. van Tamelen, E. E.; Schwartz, M.; Hessler, E. J.; Storni, A. *Chem. Commun.* **1966**, 409–411.
18. Breslow, R.; Olin, S. S.; Groves, J. T. *Tetrahedron Lett.* **1968**, 1837–1840.
19. van Tamelen, E. E.; Coates, R. M. *Chem. Commun.* **1966**, 413–415.
20. van Tamelen, E. E.; Coates, R. M. *Bioorg. Chem.* **1982**, *11*, 171–196.
21. Vidari, G.; Dapiaggi, A.; Garlaschelli, L.; Zanoni, G. *Tetrahedron Lett.* **1993**, *34*, 6485–6488.