ORGANIC LETTERS

2002
Vol. 4, No. 3
451−454

A Facile C–C Bond Cleavage in the Epoxides and Its Use for the Synthesis of Oxygenated Heterocycles by a Ring Expansion Strategy

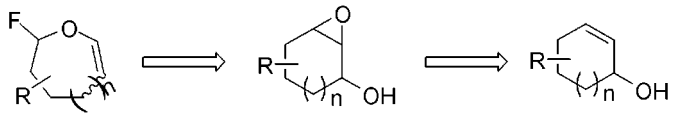
Pandarinathan Lakshmipathi, Danielle Grée, and René Grée*

ENSCR, Laboratoire de Synthèses et Activations de Biomolécules, CNRS UMR 6052, Avenue du Général Leclerc, 35700 Rennes, France

rene.gree@ensc-rennes.fr

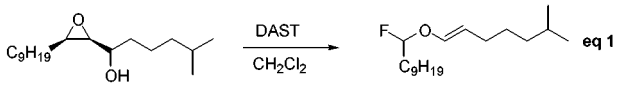
Received December 3, 2001

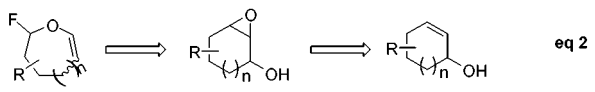
ABSTRACT



The bicyclic epoxy alcohols when treated with DAST gave a new class of rearranged organofluorine compounds, by a ring expansion via C–C bond cleavage of the oxirane ring. The outcome of this reaction with respect to ring size and stereochemical relation between the functionalities is presented here.

Epoxides are highly versatile intermediates in organic synthesis due to their easy access and their susceptibility to ring opening by facile C−O bond cleavage.[1] Ring opening by C−C bond cleavage is rare and has found only limited applications in synthesis. Such an example was the formation of carbonyl ylides at high temperatures from the appropriately substituted epoxides and their further utilization in 1,3-dipolar cycloadditions.[2] It has also been reported that the oxiranyl carbinyl radicals can lead to products from C−C bond cleavage,[3] and in a few cases ring-expanded heterocycles have been synthesized.[4] Elegant mechanistic studies have been reported for the oxiranyl carbinyl cations, both from the theoretical[5] and experimental points of view.[6] These intermediates, which are usually generated under solvolytic conditions, follow different reaction pathways to give a complex mixture of products via C−O or C−C bond cleavage.[6d] However, to the best of our knowledge, only one example of oxocene[7] and two examples of the bicyclic oxepenes[6g] have been synthesized via ring expansion of the corresponding oxiranyl cations. During the synthesis of a monofluorinated analogue of a pheromone, we observed recently that the reaction of diethylaminosulfur trifluoride (DAST) with epoxy alcohol **1** exhibited an unusually easy C−C bond cleavage, leading exclusively to vinyl ether **2** (eq 1).[8] Taking into account the mechanism of fluorination





by DAST,[9] the ring-opened form of the oxiranyl carbinyl cation can be envisaged as an intermediate for such a product formation. Extension of this reaction appeared very attractive to us, especially in the case of bicyclic epoxyalcohols, since it could lead to a new ring expansion methodology (eq 2).

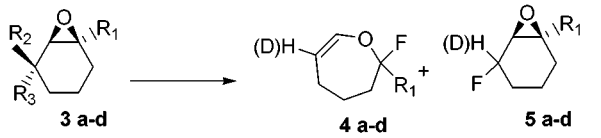
(1) Rickborn, B. In *Comprehensive Organic Synthesis*; Trost, B M., Fleming, I., Pattenden, G., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, Chapter 3.3, pp 733−76.
(2) Padwa, A. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 2, p 341.
(3) Marples, B. A.; Rudderham, J. A.; Slawin, A. M. Z.; Edwards, A. J.; Hird, N. W. *Tetrahedron Lett.* **1997**, *38*, 3599−3602 and references therein.
(4) Corser, D. A.; Marlpes, B. A.; Dar, R. K. *Synlett* **1992**, 987−9.
(5) Danen, W. C. *J. Am. Chem. Soc*. **1972**, *94*, 4835−45

10.1021/ol017164k CCC: $22.00
Published on Web 01/15/2002

The purpose of this Letter is to report our preliminary studies on the scope and limitations of this reaction for medium and large ring heterocycles. We chose to study the effects of certain factors such as ring size, nature of substituents, and role of stereochemical relation (*syn*/*anti*) between the oxirane ring and vicinal carbinol center. Further, in the case of larger ring compounds, the influence of the *cis*/*trans* stereochemistry of epoxide on the product formation has been studied.

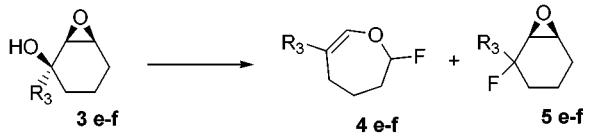
The initial experiments were performed with the easily accessible cyclohexene oxide derivatives **3a** and **3b** (Scheme 1). The *syn* epoxy alcohol **3a** reacted smoothly with DAST

Scheme 1



3 a-d **4 a-d** **5 a-d**

substrate	products ratio[a] (**4**:**5**)	yield (%)[b]
a: R_1= H, R_2= OH, R_3= H(D)	63:37	58
b: R_1= H, R_2= H(D), R_3= OH	31:69	61
c: R_1= Me,R_2= OH, R_3= H	83:17	c
d: R_1= Me, R_2= H, R_3= OH	80:20	c



3 e-f **4 e-f** **5 e-f**

	substrate	products ratio[a] (**4**:**5**)	yield (%)[d]
e	R_3= Me	**5e** only	73
f	R_3= CF_3	**4f** only	70

[a] Ratios were determined by ^{19}F NMR analysis of the crude reaction mixtures. [b] Isolated total yield of **4** and **5**. [c] Compounds decomposed rapidly. [d] Isolated yield.

to give quantitatively a 63:37 ratio of ring-expanded fluorovinyl ether **4a** and fluoro epoxides **5a** (*syn*:*anti* 2:1), which could not be separated. High-field NMR was employed to monitor the reaction, and the product ratios were calculated from the ^1H and ^{19}F NMR spectra of the crude reaction mixture. Although **4a** was not isolated in pure form due to its sensitivity to hydrolysis, its structure could be unambiguously deduced from the ^1H, ^{13}C, and ^{19}F NMR spectral data. Particularly relevant data were the peaks corresponding to the olefinic protons at 4.98 and 6.13 ppm with $^3J_{HH} = 6.9$ Hz. The first indication on the role of stereochemistry of the precursor was shown by the result obtained with *anti* epoxy alcohol **3b**, which gave only 31% of the seven-membered heterocycle and 69% of fluoroepoxides (*anti*/*syn* 90:10). To determine the mechanistic basis of this reaction, the corresponding deuterated compounds were reacted under the same conditions. The deuterium was detected exclusively on the olefinic carbon for oxepene **4** and geminal to fluorine in the epoxides **5**. These data clearly exclude the occurrence of oxobicyclobutoniums as intermediates.[6b]

When the cyclopropane derivatives corresponding to **3a** and **3b** were treated with DAST, the reaction gave exclusively the corresponding fluorocyclopropanes and showed no evidence for ring-expanded products. This could be attributed to the participation of oxygen (with its lone pair of electrons) in stabilizing the intermediates of the rearrangement products. Thus we felt a need to consider the effects of the substituents on the epoxide ring. The reaction with the methyl-substituted derivatives **3c** and **3d** gave high ratios (>80%) of ring expansion products versus fluoro epoxides. The stereochemical relation between the functionalities was only of minor influence in the product selectivity. However, when the methyl group was located on the carbinol carbon (as in tertiary alcohol **3e**), a reverse product selectivity was observed, and only fluorinated epoxides **5e** were identified in the crude reaction mixtures. The electronic effect of the substituents at the position vicinal to the oxirane ring was further evidenced by the result obtained by treating trifluoromethyl derivative **3f**, which led exclusively to oxepene **4f**.

These results encouraged us to extend the study to the more challenging system of medium-sized heterocycles. For the cycloheptane-derived epoxides, the results were similar to the preceding six-membered case: *syn* epoxy alcohol **6a** gave a 70:30 mixture of fluoro oxocene **7a** and fluoroepoxides **8a** (1:1 mixture of *syn* and *anti* isomers). As we anticipated, the *anti* epoxy alcohol **6b** showed a reverse selectivity in giving the products **7b** and **8b** (only *anti* fluoroepoxide was detected).

As we extended the study further to the bicyclic oxiranyl cycloalkanols derived from eight-membered cyclic allylic alcohols, the results obtained were very interesting since the *syn* isomer **9** gave exclusively the ring-expanded product **10**, while the *anti* isomer **11** gave a 1:1 mixture of fluoro epoxide **12** and bicyclic oxetane **13** (Scheme 2). The structure of this Meerwein rearrangement type product was established by subjecting both **13** and its deuterated derivative to extensive NMR studies.

It has been well documented that the solvolysis of brosylates of **9** and **11**[6d] led to complex mixtures of products, but they clearly indicate a similar stereochemical trend in the product distribution and the same effect of the stereochemistry of the starting oxiranes. Furthermore, it gave evidence for the formation of four-membered intermediates.[6d]

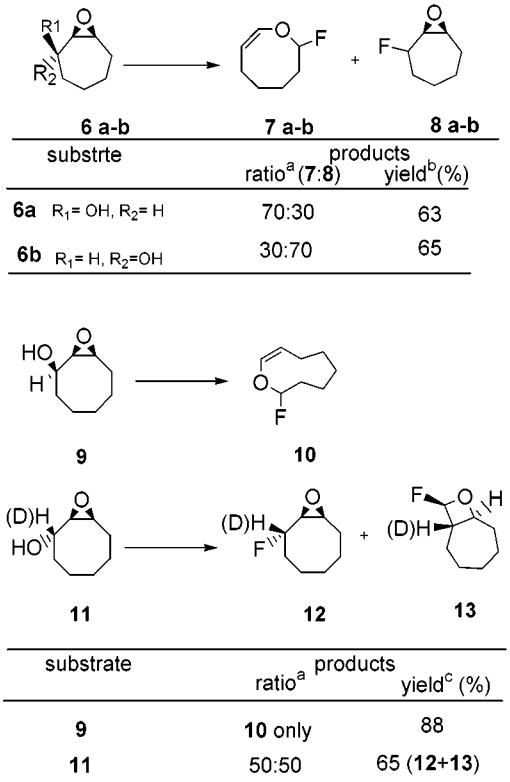
(6) (a) Morita, H.; Oae, S. *Tetrahedron Lett*. **1969**, 1347−9. (b) Richey, H. G., Jr; Kinsman, D. V. *Tetrahedron Lett*. **1969**, 2505−8. (c) Santelli, M.; Viala, J. *Tetrahedron* **1979**, *34*, 2327−2330. (d) Whalen, D. L.; Brown, S.; Ross, A. M.; Russel, H. M. *J. Org. Chem*. **1978**, *43*, 428−32. Whalen, D. L.; Cooper, J. D. *J. Org. Chem*. **1978**, *43*, 432−7. (e) Peters, E. N. *J. Org. Chem*. **1978**, *43*, 4006−7. (f) Whalen D. L.; Ross, A. M.; Montemarano, J. A.; Thakker, D. R.; Yagi, H.; Jerina, D. M. *J. Am. Chem. Soc*. **1979**, *101*, 5086−8 (g) Clark, G. R. *Tetrahedron Lett*. **1984**, *25*, 2839−42.

(7) Cooper, J. D.; Vitullo, V. P.; Whalen, D. L. *J. Am. Chem. Soc*. **1971**, *93*, 6294−6.

(8) Filmon, J.; Gree, D.; Gree, R. *J. Fluorine Chem*. **2001**, *107*, 271−3.

(9) Hudlicky, M. *Org. React*. **1988**, *34*, 513.

Scheme 2



substrte	products ratio[a] (7:8)	yield[b](%)
6a R_1= OH, R_2= H	70:30	63
6b R_1= H, R_2=OH	30:70	65

substrate	products ratio[a]	yield[c] (%)
9	**10** only	88
11	50:50	65 (**12**+**13**)

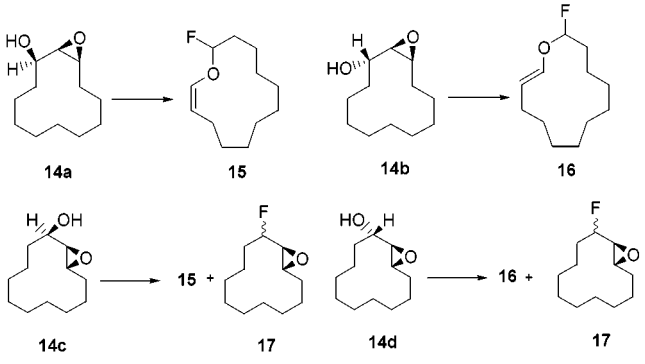
[a] Ratios were determined by ^{19}F NMR analysis of the crude reaction mixture. [b] Isolated yield of **7** and **8**. [c] Isolated yield.

It should be noted that the results obtained in the above experiments were in good agreement[10] with the cationic rearrangements of the cyclopropane analogues of **9** and **11**: the *syn* isomer gave mostly or exclusively ring-expanded product, while the *anti* isomer led to mixtures of bicyclic cyclobutane derivatives.

The cyclododecene oxides appeared to be very attractive substrates since we could study both the effects of the epoxide ring stereochemistry and the *syn*−*anti* relation between the epoxy and alcohol groups. Therefore, we prepared all four diastereomers **14a**−**d** on the same basic model using literature procedures. The *cis* epoxides gave very clean results since the *syn* alcohol **14a** gave exclusively the *Z* enol ether **15** ($^3J_{HH}$ = 6.4 Hz), while the *anti* derivative **14 b** gave only *E* enol ether **16** ($^3J_{HH}$ = 12.1 Hz). As far as the *trans* epoxides are concerned, the reaction gave far fewer ring expansion products and showed similar stereospecificity. The *syn* alcohol gave **15** and the *anti* alcohol gave **16**. However, in both the cases, the formation of fluoroepoxides became predominant (Scheme 3).

From a mechanistic point of view, it is interesting to note that reaction with DAST generates the oxiranylcarbinyl cation at much lower temperatures than the solvolysis conditions and with a single nucleophile (F^-) in the reaction

Scheme 3

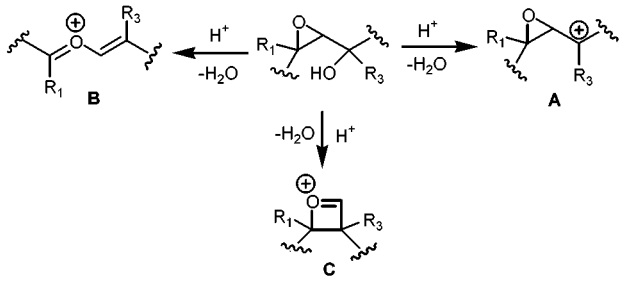


substrate	products ratio[a]	yield[b] (%)
14a	**15** only	86
14b	**16** only	90
14c	10:90 (**15**:**17**)	78 (**15**+**17**)
14d	26:74 (**16**:**17**)	82 (**16**+**17**)

[a] Ratios were determined by ^{19}F NMR analysis of the crude reaction mixture. [b] Isolated yield.

mixture. Therefore, the reactions[11] are easier to analyze since only three carbocationic intermediates, **A**, **B**, and **C**, have to be considered (Scheme 4).[12] The choice of the reaction

Scheme 4



pathway involves a delicate balance between steric and electronic factors, and several points are worthy of discussion here.

The experimental outcome with the examples of cyclohexene oxides **3** has unambiguously shown that the electronic effects of the substituents are in full agreement with the above proposed mechanistic scheme: (i) the methyl group on the epoxy ring carbon (R_3 = H, R_1 = Me) stabilized the oxonium ion **B** and gave the ring-expanded product, (ii) when the same methyl group was placed on the vicinal carbinol carbon (R_3 = Me, R_1 = H), a type **A** oxiranyl cation was stabilized and gave mostly fluoro epoxides, and (iii) on the contrary, intermediate **A** was destabilized by the presence of a CF_3 group on the carbinol carbon (R_3 = CF_3, R_1 = H), and this led to exclusive formation of oxepene **4f**.

(10) Poulter, C. D.; Friedrich, E. C.; Winstein, S. *J. Am. Chem. Soc.* **1970**, *92*, 4274−841.

(11) It is also important to note that the ^{19}F NMR spectroscopy presents a very convenient way to monitor these reactions.

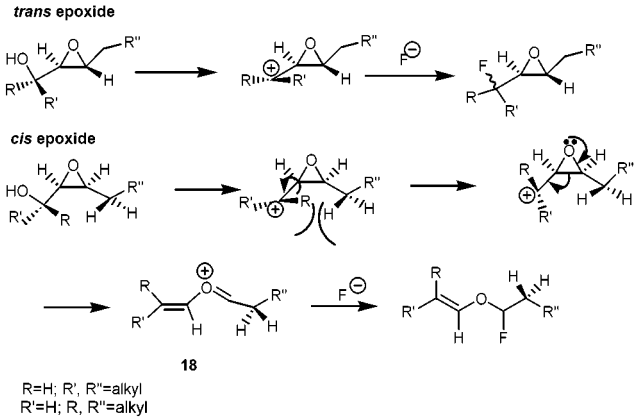
(12) Under these conditions we did not observe any 2,6-hydride shift such as reported previously in the solvolytic studies (see ref 6d).

The most novel and intriguing results are the different reaction pathways followed by the *cis* and *trans* epoxides of the large ring systems. By analogy with the previous solvolytic studies, we envisaged that each alcohol gives stereoselectively a single cation (cisoid from *syn* alcohol and transoid from the *anti* derivative).[6d,g] Then, on the basis of theoretical calculations,[5] we should also conclude that structures close to bisected conformations are highly favored for such cations. On the basis of these hypotheses, molecular model studies indicate that the corresponding structures are relatively easily accessible to cations derived from *trans* epoxides. This is due to the limited steric interaction around the epoxide ring, and therefore, fluoroepoxides are essentially obtained (Scheme 5).[13]

On the contrary, the intermediates from *cis* epoxides showed strong steric interactions between the substituents on the carbocationic center and the vicinal epoxy carbon. These destabilizing steric interactions could be removed by a slight upward rotation around the C^+-C bond: this makes the C−C epoxide bond almost perpendicular to the carbocationic center, and therefore in a favorable position for C−C double bond formation in a stereospecific manner (Scheme 5). But, in the case of *anti* cyclooctene oxide **11**, the formation of a nine-membered heterocycle with a *trans* double bond, **18** [R = H, R′, R″ = $(CH_2)_5$], is strongly disfavored. The carbonium ion is now very well aligned for a Wagner−Meerwein shift and gave the bicyclic oxetane **13**.

In conclusion, we have successfully demonstrated that the DAST-mediated fluorination of bicyclic epoxy alcohols often occurs with ring expansion and exhibits stereocontrol in product formation. It is noteworthy to mention here that the new class of organofluorine compounds is easily obtained by a two-step sequence from cyclic allylic alcohols. A plausible mechanism has been proposed with some special emphasis on the conformation of oxiranyl carbinyl cations. We are currently studying the use of these fluorinated heterocycles in synthesis and the extension of such methodology to constructing C−C and C−heteroatom bonds.

Scheme 5



Acknowledgment. We thank MENRT for a fellowship to P.L. and Dr. P. Guenot (CRMPO, Rennes) for mass spectral analysis.

Supporting Information Available: General experimental procedures and spectral data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL017164K

(13) It should be noted that during the hydrolysis of acyclic *trans* epoxy carbinyl brosylates, only epoxy alcohols were isolated and no trace of products from the C−C bond cleavage (see ref 6d, p 428).