# Mechanism of the Boron Trifluoride Etherate-catalysed Rearrangement of an Acyclic Trisubstituted Epoxide to a Carbonyl Compound

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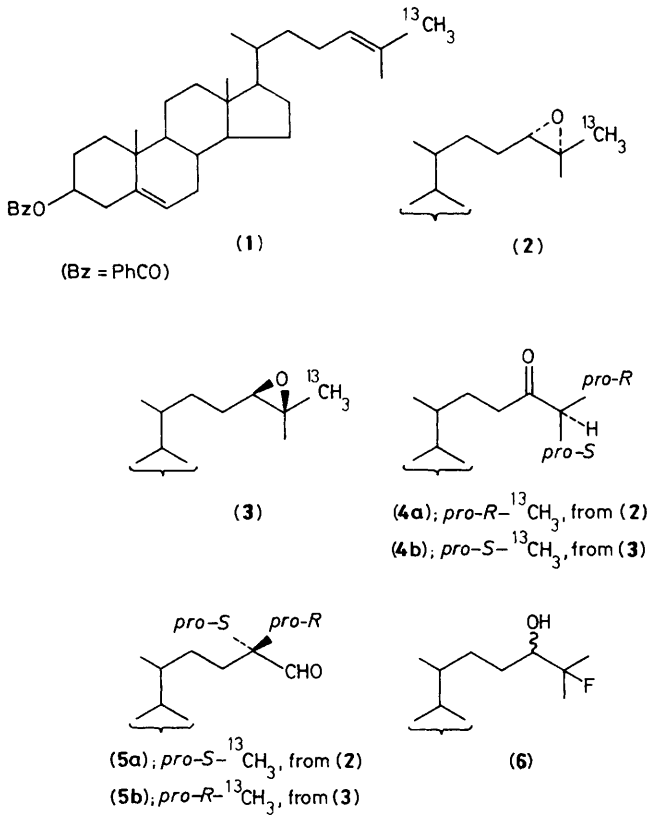
The mechanism of the $BF_3$-catalysed rearrangement of an acyclic trisubstituted epoxide to a carbonyl compound has been studied using (24*S*,25*S*)-[26-$^{13}$C] and (24*R*,25*R*)-[26-$^{13}$C]-desmosterol benzoate 24,25-epoxides (**2**) and (**3**), demonstrating that C-24 hydrogen migration leading to the 24-oxo compound (**4**) occurs with retention of configuration at the migration terminus (C-25), whereas C-23 alkyl group migration leading to aldehyde (**5**) proceeds with inversion of configuration at C-25.

Lewis acid-catalysed rearrangement of epoxides to carbonyl compounds involves the 1,2-shift of a hydride, alkyl, or aryl substituent to an adjacent carbon atom. *A priori* the electron-deficient carbon centre generated by the co-ordination of a Lewis acid to the oxygen atom of an epoxide may either become a discrete carbonium ion or rearrange by a more-or-less concerted mechanism (this implies stereochemical inversion at the migration terminus) into a more stable structure, depending on the particular environment of the epoxide ring. It has been suggested on the basis of the stereochemistry of the products that a discrete carbonium ion plays an intermediary role in the $BF_3$ etherate-catalysed rearrangement, which involves a tertiary cationic centre.[1] Examples of rearrangements involving migration of a substituent *cis* to the departing epoxide oxygen atom have been noted earlier.[2,3] Further, the possible intermediary role of fluorohydrin as well as the isolation of fluorohydrin products has been reported in a few cases.[4] However, these results have been obtained with epoxides on carbocyclic ring systems such as steroidal epoxides and must be interpreted taking into account factors inherent in cyclic systems, *i.e.*, axial–equatorial preference and ring strain. In contrast, few studies have been done on the mechanism of rearrangement of acyclic epoxides,[5] probably because of difficulty in preparing chiral epoxides and in determining the chirality of the resulting carbonyl products. We describe here our results on the mechanism of and, in particular, the stereochemical course at the migration terminus of the $BF_3$-catalysed rearrangement of acyclic trisubstituted epoxides.

Two steroidal epoxides, (24*S*,25*S*)-[26-$^{13}$C] and (24*R*,25*R*)-[26-$^{13}$C]-desmosterol benzoate 24,25-epoxides, (**2**) and (**3**), were used in our study. We selected these epoxides for the following reasons. (i) $BF_3$-Catalysed rearrangement of similar epoxides has been reported.[6] (ii) The epoxides could be prepared easily from desmosterol benzoate and their C-24 stereochemistry has been well established.[7] (iii) The stereochemistry at C-25 of the product ketone (**4**) and at C-24 of the aldehyde (**5**) could be determined by the preparation of appropriate compounds having a defined stereochemistry at these prochiral centres. (iv) The diastereotopic methyl groups at C-25 of (**4**) and at C-24 of (**5**) were expected to be differentiated by the chirality of the steroidal skeleton, yet this might not dictate the stereochemical course of the reactions at the remote terminal of the steroidal side chain. (v) Labelling with $^{13}$C at the diastereotopic methyl group made it possible to follow the fate of the methyl group in the rearranged products.

The isomeric epoxides (**2**) and (**3**) [labelled 92% at the *pro-S* and 8% at the *pro-R* methyl for (**2**), and *vice versa* for (**3**)] were prepared by *m*-chloroperbenzoic acid (*m* CPBA) treatment of [26-$^{13}$C] desmosterol benzoate,[8] followed by separation of the isomers by preparative t.l.c. Treatment of (24*S*,25*S*)-epoxide (**2**) with $BF_3$ etherate (2 equiv. benzene,



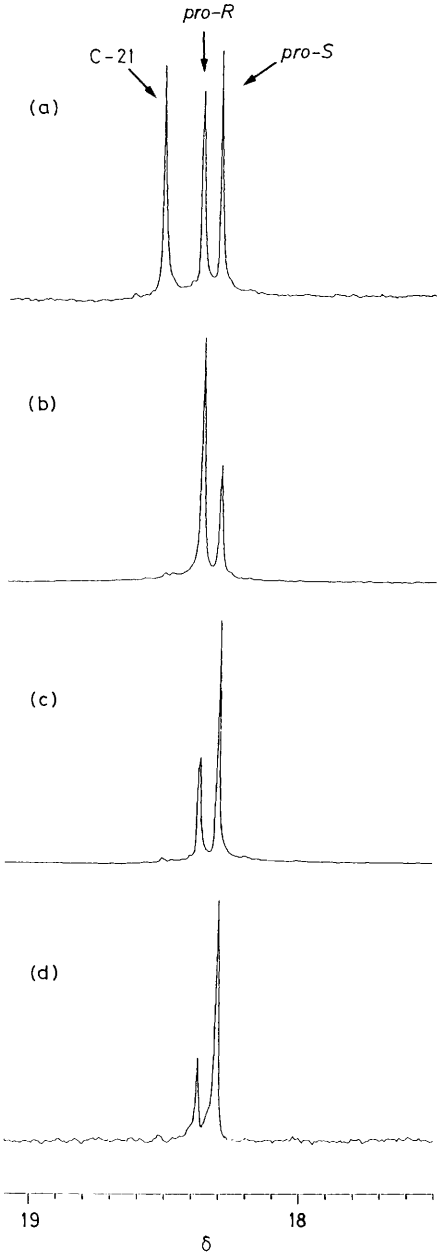




**Figure 1.** $^{13}C$ N.m.r. spectra of the rearranged ketone (**4**). (a) Non-labelled sample (**4**), (b) rearranged product (**4a**) obtained from (**2**), (c) rearranged product (**4b**) obtained from (**3**), (d) *pro-S* methyl $^{13}C$-labelled reference sample (**4**).

room temperature, 40 min) produced, as reported for lanosterol 24,25-epoxide acetate,[6] 24-oxocholesterol benzoate (**4a**) (60%) and aldehyde (**5a**) (25%) after chromatographic separation. The parallel reaction starting with the isomeric epoxide (**3**) similarly afforded (**4b**) and (**5b**).

The $^{13}C$ n.m.r. spectra of the 24-oxo compounds (**4a**) and (**4b**) are illustrated in Figure 1. Since the $^{13}C$ chemical shifts of the diastereotopic methyl groups of (**4**), *i.e.*, *pro-R* and *pro-S* at δ 18.37 and 18.30,† respectively, were assigned by the preparation of *pro-S* methyl $^{13}C$-labelled 24-oxocholesterol benzoate (Figure 1d),‡ it was found that (**4a**) derived from (**2**) was predominantly labelled at the *pro-R* methyl (*pro-R*:*pro-S* 67:33), whereas (**4b**) derived from (**3**) was predominantly labelled at the *pro-S* methyl (*pro-R*:*pro-S* 35:65). Based on the peak intensity ratio of the signals at δ 18.37 and 18.30, it was estimated that approximately 70% of the reaction proceeded by a mechanism involving retention of configuration at C-25. Further treatment of (**4a**) under the rearrangement conditions recovered starting material labelled with $^{13}C$ in the original ratio (*pro-R*:*pro-S* 67:33).

The aldehydes (**5a**) and (**5b**) were similarly analysed by $^{13}C$ n.m.r. (Figure 2). The diastereotopic $^{13}C$ methyl groups were assigned by synthesizing the *pro-R* methyl $^{13}C$-labelled aldehyde,§ whose *pro-R* methyl carbon resonated at δ 21.41 (Figure 2d). Thus, it is clear that (**5a**) from (**2**) was labelled predominantly at the *pro-S* methyl group (*pro-S*:*pro-R* 77:23), whereas (**5b**) from (**3**) was labelled mainly at the *pro-R* methyl (*pro-S*:*pro-R* 22:78). It is estimated from the peak intensity ratio of the signals at δ 21.20 and 21.41, that approximately 83% of the reaction occurs with inversion of configuration at the migration terminus.

† All n.m.r. spectra were measured in $CDCl_3$ ($Me_4Si$ reference).

‡ The stereochemically defined compound was prepared from [26-$^{13}C$]desmosterol t-butyldimethylsilyl ether (ref. 8) in four steps, initiated with hydroboration. For stereochemical assignment of an intermediate, 24-alcohol, see: Y. Fujimoto, Y. Ikuina, and K. Kakinuma, *J. Chem. Soc., Chem. Commun.*, 1989, 464; K. Koizumi, M. Morisaki, and N. Ikekawa, *Tetrahedron Lett.*, 1975, 2203.

§ The stereochemically defined compound was prepared from compound (**A**), which was in turn obtained by stepwise alkylation of des-methyl lactone (for the lactone, see E. Nakamura and I. Kuwajima, *J. Am. Chem. Soc.*, 1985, **107**, 2138). Nuclear Overhauser enhancement (n.O.e.) was observed between 22-H and the α-methyl group of compound (**A**).

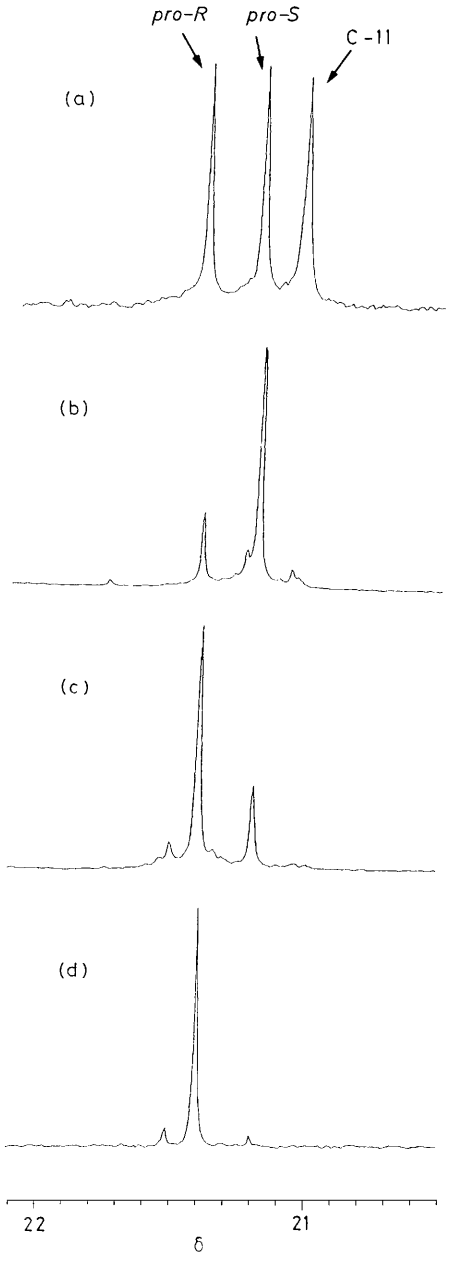
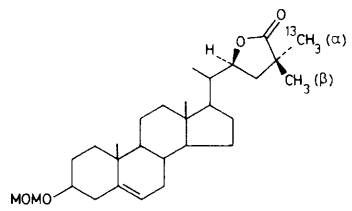



**Figure 2.** $^{13}C$ N.m.r. spectra of the rearranged aldehyde (**5**). (a) Non-labelled sample (**5**), (b) rearranged product (**5a**) obtained from (**2**), (c) rearranged product (**5b**) obtained from (**3**), (d) *pro-R* methyl $^{13}C$-labelled reference sample (**5**).




**A**

MOM = methoxymethyl

Complementary stereochemical behaviour in the rearrangement of (**2**) and (**3**) excludes, as originally expected, the possibility that the steroidal moiety plays a role in the stereochemical course of the rearrangement. The observed stereochemical diversity in the transfer of hydride and alkyl group should be noted. The retention of configuration is particularly surprising, since previously reported cases in acyclic systems generally require a neighbouring group which can stabilize an adjacent positive carbon centre.[3] There are no such groups in the present case.

Critical monitoring of the reaction in benzene showed the transient formation of a polar compound. The decay of the compound (lifetime, a few minutes) was accompanied by the formation of (**4**) and (**5**). The formation and conversion of the polar intermediate(s) became slow in ether or dioxane solvent, as previously noted.[4,9] The intermediate was isolated in 38% yield by carrying out the reaction in dioxane for 10 min at room temperature and its structure was established as that of fluorohydrin (**6**)¶ on the basis of spectral data and elemental analysis. Further, when (**6**) was subjected to the rearrangement condition, (**4**) and (**5**) were obtained. This finding suggests that the formation of the ketone proceeds *via* the fluorohydrin intermediate (**6**). It is inferred that both introduction of the fluorine atom at C-25 and subsequent replacement of the fluorine atom with hydride proceed *via* an $S_N2$ mechanism; thus the observed stereochemical course (net retention) is rationalized.

The present work emphasizes the general importance of a fluorohydrin intermediate in the migration of hydride in the $BF_3$-catalysed rearrangement of acyclic trisubstituted epoxides.

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¶ The reaction was performed starting with a mixture of non-labelled (24*R*)- and (24*S*)-epoxides, thus affording a C-24 epimeric fluorohydrin (**6**), which is separable by preparative t.l.c. A separate experiment starting with the (24*R*)-epoxide gave a fluorohydrin identical to the more polar one. Data for the less polar epimer: $^1H$ n.m.r., δ 3.53 (1H, t, *J* 10 Hz, 24-H); $^{13}C$ n.m.r., δ 77.8 (C-24, $^2J_{C-F}$ 22 Hz), 98.2 (C-25, $^1J_{C-F}$ 165 Hz); fast atom bombardment (f.a.b.) m.s., *m/z* 403 ($M^+$ + H − $PhCO_2H$), 383 ($M^+$ + H − $PhCO_2H$ − HF). Data for the more polar epimer: $^1H$ n.m.r. δ 3.53 (1H, t, *J* 10 Hz, 24-H); $^{13}C$ n.m.r. δ 77.0 (C-24, $^2J_{C-F}$ 22 Hz), 98.2 (C-25, $^1J_{C-F}$ 165 Hz); f.a.b.-m.s., *m/z* 403 ($M^+$ + H − $PhCO_2H$), 383 ($M^+$ + H − $PhCO_2H$ − HF).