MECHANISM OF BF_3·ETHERATE-CATALYZED REARRANGEMENT OF FUCOSTEROL EPOXIDE

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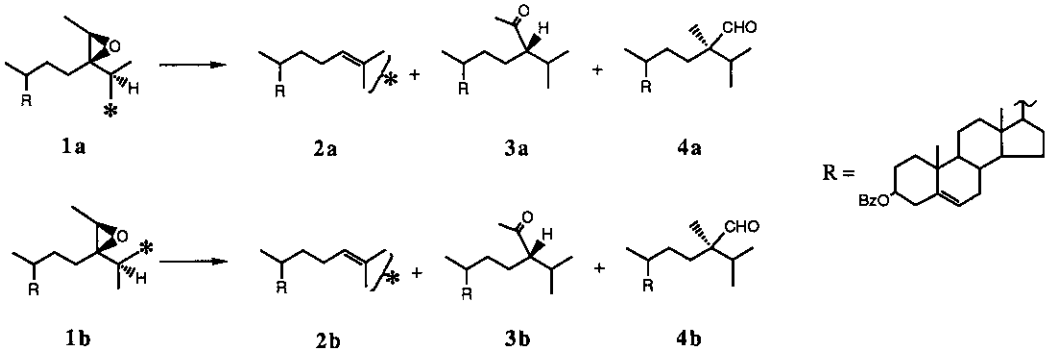
Abstract——The mechanism of the BF_3·etherate-catalyzed rearrangement of fucosterol benzoate 24,28-epoxide (**1**) leading to desmosterol benzoate (**2**) and two carbonyl compounds (**3**) and (**4**) was investigated.

A fragmentation reaction of fucosterol epoxide to desmosterol, which proceeds with the migration of hydrogen from C-25 to C-24, is a crucial step in the biological dealkylation of sitosterol into cholesterol in phytophagous insects.[1] We have recently demonstrated that the reaction catalyzed by a fucosterol epoxide lyase from guts of the silkworm, Bombyx mori, is stereospecific in terms of the C-25 prochirality, i.e., the isopropyl (pro-R)- and (pro-S)- methyl groups of the epoxide become isopropylidene (E)- and (Z)- methyl groups of desmosterol, respectively.[2] Interestingly, a similar fragmentation reaction can be achieved in a chemical manner; treatment of fucosterol epoxide (3-ester) with BF_3 etherate affords three products, desmosterol (3-ester), a ketone (arising from migration of hydrogen), and an aldehyde (arising from migration of methyl group).[3] We have investigated the mechanism of this chemical rearrangement and describe herein i) stereochemical fates of the diastereotopic methyl groups in the formation of desmosterol (3-benzoate) and ii) stereochemistry at the C-24 position (migration terminus of the transferring group) during the formation of two carbonyl products. To investigate the behavior of the prochiral C-25 center, (pro-S)-methyl-^{13}C-labeled (**1a**)[4] and (pro-R)-methyl-^{13}C-labeled (**1b**)[4] fucosterol benzoate (24R,28R)-epoxides were employed. Synthesis and utilization of these labeled epoxides were reported in our previous paper.[2] Treatment of the epoxide (**1a**) (4.0 mg) with BF_3·etherate (2.0 eq) in benzene at room temperature for 5 min afforded three products, desmosterol benzoate (**2a**), a ketone (**3a**) and an aldehyde (**4a**) in ca. 2:3:1 ratio. The same treatment of the epoxide (**1b**) afforded desmosterol benzoate (**2b**), a ketone (**3b**) and an aldehyde (**4b**) in a similar ratio.



The location of the ^{13}C label at the isopropylidene groups of the desmosterol benzoates (**2a**) and (**2b**) was determined by ^{13}C-nmr spectroscopy (Figure 1). On the basis of the signal (δ 25.7 and 17.6) intensity ratio, the distribution of ^{13}C was estimated as 55 : 45 for (E)-methyl:(Z)-methyl in **2a** and 47 : 53 in **2b**. These values were normalized with the intensity ratio (1.8) of the (E)-methyl/(Z)-methyl signals of the non-labeled standard. These values are beyond those expected for a stereospecific reaction, and suggest that the formation of **2a** and **2b** involves a carbonium ion intermediate. This scrambling of the label is in remarkable contrast to the case of the above mentioned enzymatic reaction.

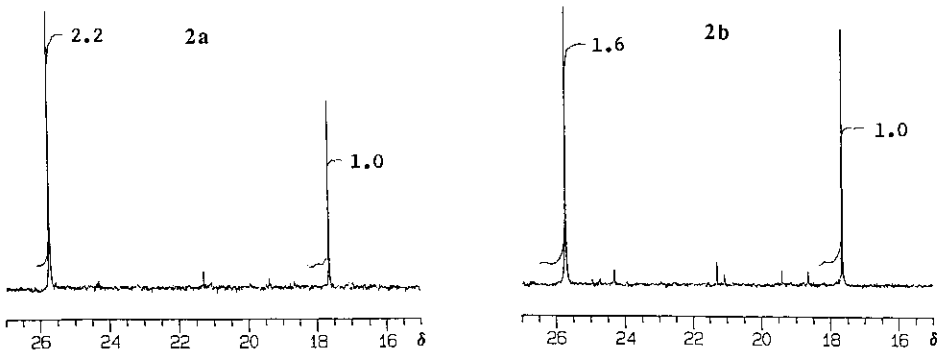


Figure 1. Partial ^{13}C-nmr spectra (125 MHz, in $CDCl_3$) of the desmosterol benzoates (**2a**) and (**2b**).

Stereochemistry at the C-24 position of the ketones (**3a**) and (**3b**) was determined by tlc and hplc comparison with the authentic (24R)- and (24S)-compounds. The reference samples were prepared from the known (24R,28S)- and (24S,28R)-28-alcohols[5] in three steps, i.e., PCC oxidation, treatment with p-TsOH in refluxing dioxane-water, and benzoylation. Hplc analysis (shown in Figure 2) of the ketones revealed that the ketone (**3a**) contained 76% of (24S)-isomer and 24% of (24R)-isomer, and the ketone (**3b**) contained 81% of the former and 19% of the latter.

These results indicate migration of the hydrogen proceeds predominantly with retention of configuration at the migration terminus.

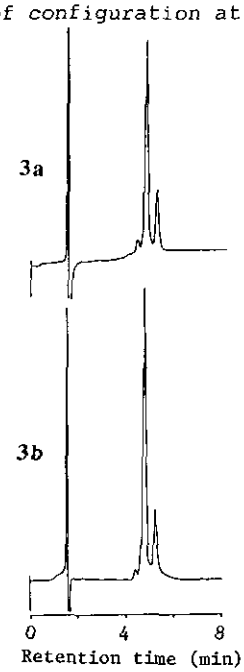


Figure 2. Hplc chart of the ketones (**3a**) and (**3b**). The authentic (24S)- and (24R)-ketones were eluted at 6.8 and 7.3 min, respectively. Conditions: column, Zorbax SIL; solvent, hexane-CH_2Cl_2 (2:1); flow rate, 2 ml/min; detection, UV at 254 nm.

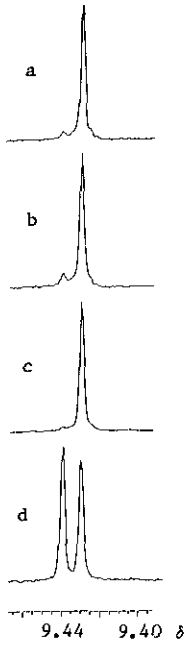
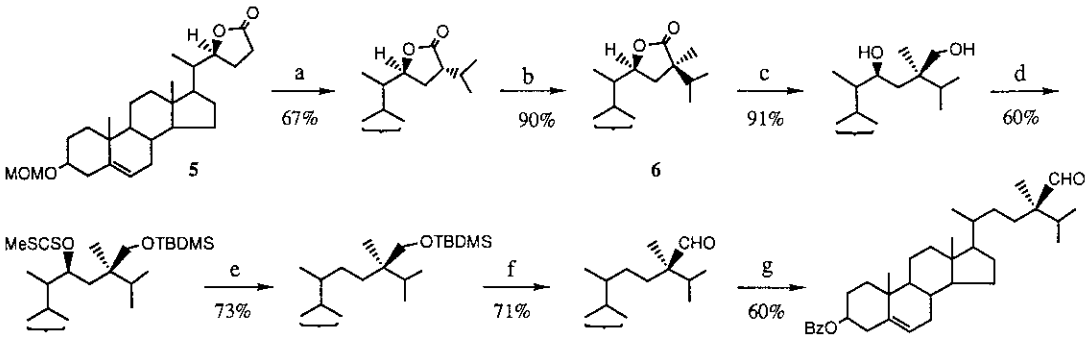


Figure 3. Partial ^{1}H-nmr (500 MHz, in $CDCl_3$) of the aldehydes (**4a**) and (**4b**). a, aldehyde (**4a**); b, aldehyde (**4b**); c, authentic (24R)-aldehyde; d, a mixture of (24R)- and (24S)-aldehyde.

Stereochemistry at the C-24 position of the aldehydes (**4a**) and (**4b**) was established as 24R by comparative study of the ^{1}H-nmr spectra of **4a** and **4b** with an authentic (24R)-aldehyde (shown in Figure 3). The authentic (24R)-aldehyde was synthesized from the (22R)-lactone (**5**)[6] in ten steps according to Scheme 1. The C-24 stereochemistry of the intermediate (**6**) was predicted by the generally accepted stereochemical course of the sequential alkylation of 5-membered lactones,[7] and was confirmed by NOE experiments in ^{1}H-nmr, in which the signal of 22-H was intensified by irradiation upon the 24-methyl signal. Further manipulations of **6** afforded the (24R)-aldehyde as a sole product.

The stereochemical courses in the formation of the ketone (**3**) and the aldehyde (**4**) are in good agreement with our recent findings[8] on a trisubstituted epoxide system that in the BF_3·etherate-catalyzed rearrangement of desmosterol benzoate 24,25-epoxide migration of hydrogen takes place with retention of configuration at the migration terminus, whereas migration of alkyl group proceeds with inversion

of configuration at the migration terminus.



a) LDA, i-PrI, b) LDA, MeI, c) $LiAlH_4$, d) TBDMSCl, imidazole; NaH, CS_2, MeI, e) $(n\text{-}Bu)_3SnH$, f) $(n\text{-}Bu)_4NF$; PCC, g) 6N-HCl; BzCl, pyridine.

Scheme 1. Synthetic route for the authentic (24R)-aldehyde.

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