

MECHANISM OF  $\text{BF}_3$ ·ETHERATE-CATALYZED REARRANGEMENT OF FUCOSTEROL EPOXIDE

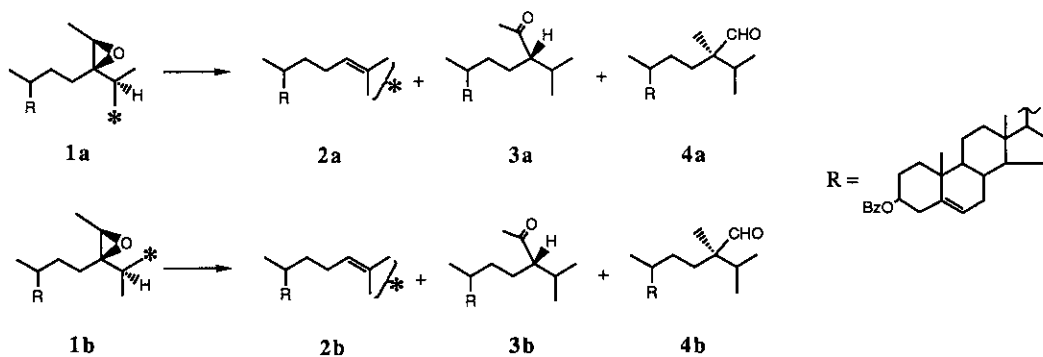
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**Abstract**—The mechanism of the  $\text{BF}_3$ ·etherate-catalyzed rearrangement of fucosterol benzoate 24,28-epoxide (**1**) leading to desmosterol benzoate (**2**) and two carbonyl compounds (**3**) and (**4**) was investigated.

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.<sup>1)</sup> 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.<sup>2)</sup> Interestingly, a similar fragmentation reaction can be achieved in a chemical manner; treatment of fucosterol epoxide (3-ester) with  $\text{BF}_3$  etherate affords three products, desmosterol (3-ester), a ketone (arising from migration of hydrogen), and an aldehyde (arising from migration of methyl group).<sup>3)</sup> 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-<sup>13</sup>C-labeled (**1a**)<sup>4)</sup> and (*pro-R*)-methyl-<sup>13</sup>C-labeled (**1b**)<sup>4)</sup> fucosterol benzoate (24*R*,28*R*)-epoxides were employed. Synthesis and utilization of these labeled epoxides were reported in our previous paper.<sup>2)</sup> Treatment of the epoxide (**1a**) (4.0 mg) with  $\text{BF}_3$ ·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  $^{13}\text{C}$  label at the isopropylidene groups of the desmosterol benzoates (**2a**) and (**2b**) was determined by  $^{13}\text{C}$ -nmr spectroscopy (Figure 1). On the basis of the signal ( $\delta$  25.7 and 17.6) intensity ratio, the distribution of  $^{13}\text{C}$  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.

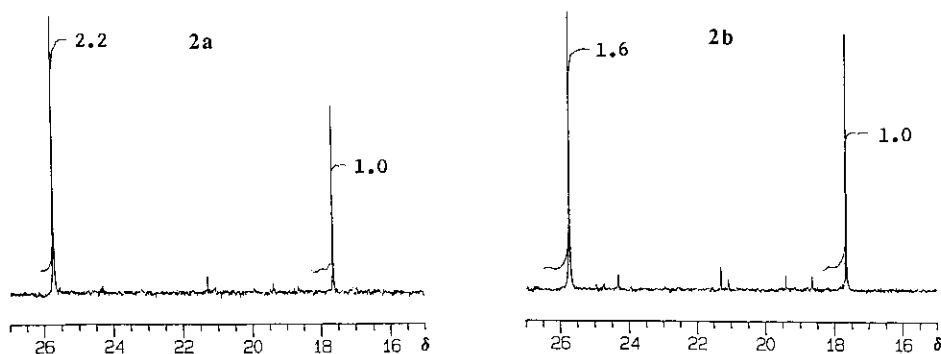


Figure 1. Partial  $^{13}\text{C}$ -nmr spectra (125 MHz, in  $\text{CDCl}_3$ ) of the desmosterol benzoates (**2a**) and (**2b**).

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<sup>5)</sup> in three steps, *i.e.*, PCC oxidation, treatment with *p*-TsOH in refluxing dioxane-water, and benzylation. 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.

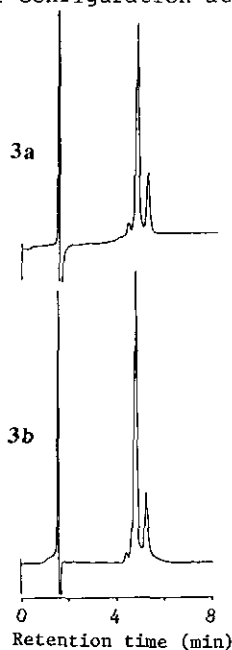


Figure 2. Hplc chart of the ketones (**3a**) and (**3b**). The authentic (24S)- and (24R)-ketones were eluted at 6.8 and 7.3 min, respectively. Conditions: column, Zorbax SIL; solvent, hexane-CH<sub>2</sub>Cl<sub>2</sub> (2:1); flow rate, 2 ml/min; detection, UV at 254 nm.

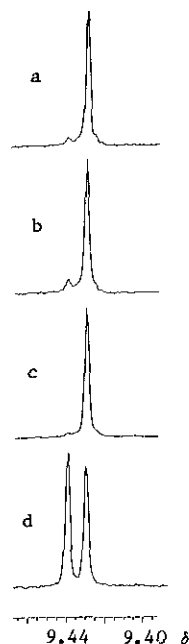
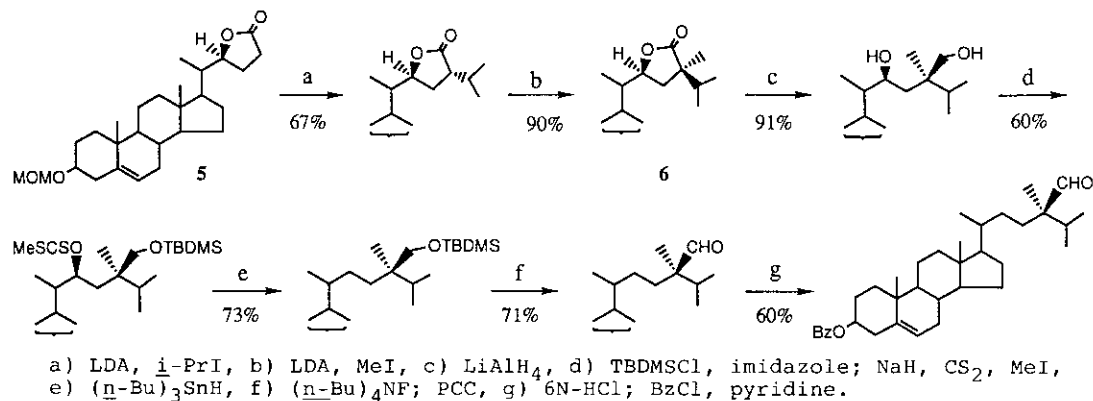


Figure 3. Partial <sup>1</sup>H-nmr (500 MHz, in CDCl<sub>3</sub>) of the aldehydes (**4a**) and (**4b**). a, aldehyde (**4a**); b, aldehyde (**4b**); c, authentic (24R)-aldehyde; d, a mixture of (24R)- and (24S)-aldehyde.

Stereochemistry at the C-24 position of the aldehydes (**4a**) and (**4b**) was established as 24R by comparative study of the <sup>1</sup>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**)<sup>6)</sup> 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,<sup>7)</sup> and was confirmed by NOE experiments in <sup>1</sup>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<sup>8)</sup> on a trisubstituted epoxide system that in the BF<sub>3</sub>·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.



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

#### ACKNOWLEDGMENTS

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4. The <sup>13</sup>C label was located 85% at (*pro-S*)-methyl and 15% at (*pro-R*)-methyl in **1a**, and *vice versa* in **1b**.
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