Further Investigations of the Stereochemistry of Electrophilic Addition Reactions of the Steroidal C-22 Double Bond [1]

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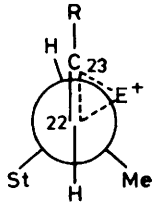
Three kinds of electrophilic addition reactions, *viz.* peracid epoxidation, hydroboration, and iodoacetoxylation, of both the *trans*- and *cis*-isomers of 6β-methoxy-3α,5-cyclo-5α-cholest-22-enes (**1**) and (**2**) were examined. The observed stereoselectivity can be explained on the basis of the product-like model for the transition states. The preferred conformation of the transition state is determined by the difference in steric interaction between the C-16 hydrogens and reacting species or C-23 alkyl moiety.

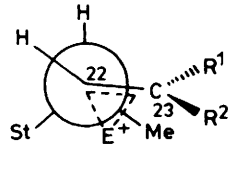
A number of biologically active steroids possessing an oxygen function at the C-22 and/or C-23 position, *e.g.* ecdysones, withanolides, vitamin D_3 metabolites, and brassinolides, have been encountered in nature. For the synthesis of these steroids, the introduction of an oxygen function with the required stereochemistry is of great importance. One method to achieve this is an electrophilic reaction with a *trans*- or *cis*-Δ^{22}-double bond. Several electrophilic reactions to *trans*-Δ^{22}-double bonds have been reported.[2] Barton *et al.*[3] interpreted the stereoselectivity of iodo- and bromo-acetoxylation to the *trans*-Δ^{22}-double bond of an ergosterol derivative on the basis of the results of *X*-ray analysis of ergocalciferol, which shows the ground-state conformation [conformation (**I**)]. In this model,



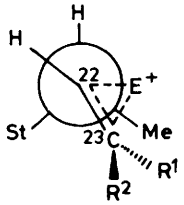
(**I**)

E^+ = electrophile

the Δ^{22}-double bond is eclipsed with the C-20 hydrogen and an electrophile would approach the Δ^{22}-system predominantly from the side of the C-20 methyl group. However, this model cannot rationalize the stereochemical course of some other electrophilic reactions.[4] We have proposed an alternative model from the results of electrophilic reactions of a dinorchol-22-ene derivative.[1] It was inferred that, in the transition state, the C-22 hydrogen is placed between the steroid nucleus and the C-20 hydrogen, and either conformation (**II**) or conformation (**III**) is preferred depending on the size of the electrophile. The presence of such a conformation in the ground state is evidenced from ^1H n.m.r., ^{13}C n.m.r., and *X*-ray data of several C-22 substituted steroids.[5]



(**II**)



(**III**)

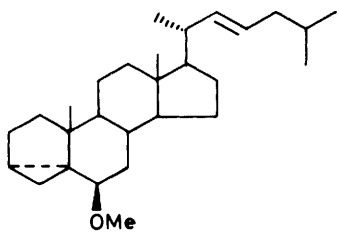
Table 1. H.p.l.c. mobility of 22- and 23-hydroxycholesterol dibenzoates

Compound	Retention time (min)	
	Normal phase[a]	Reverse phase[a]
(**5**)	9.2	18.9
(**6**)	14.2	17.2
(**7**)	14.2	19.9
(**8**)	10.6	18.1

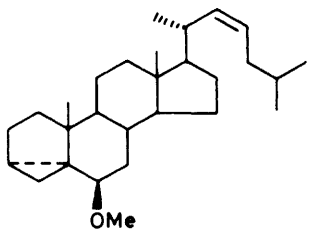
[a] The following conditions were used: normal phase; Zorbax SIL column, 15 cm × 4.6 mm i.d.; hexane–methylene dichloride (10:1), 2 ml min^{-1}. Reverse phase; Zorbax ODS column, 25 cm × 4.6 mm i.d.; methanol, 2 ml min^{-1}.

On the other hand, the stereochemistry of electrophilic reactions with a *cis*-Δ^{22}-double bond is little known. Therefore, we have further investigated the stereochemical course of electrophilic reactions with both a *trans*- and a *cis*-Δ^{22}-double bond of the cholest-22-ene derivatives (**1**) and (**2**).

Three kinds of electrophilic reactions, *viz. m*-chloroperbenzoic acid (*m*-CPBA) oxidation, hydroboration, and iodoacetoxylation, were examined. The olefinic substrates (**1**) and (**2**) were synthesized according to the published methods[6] and their homogeneity was fully confirmed by h.p.l.c. after conversion into their rearranged 3-benzoates (**3**) and (**4**). The stereochemistry at C-22 and C-23 of the reaction products was unequivocally determined by correlating the products with the dibenzoate derivatives (**5**)—(**8**) of (22*R*)-22-, (22*S*)-22-, (23*R*)-23-, and (23*S*)-23-hydroxycholesterol.[7] The chromatographic mobility of the four authentic dibenzoates is listed in Table 1. The (22*S*)-dibenzoate (**6**) and (23*R*)-dibenzoate (**7**) were not separable by normal-phase h.p.l.c., but were separable by reverse-phase h.p.l.c. Therefore, the fraction corresponding to the (22*S*)-(**6**) and the (23*R*)-dibenzoate (**7**) in normal-phase h.p.l.c. was collected and then re-analysed by reverse-phase h.p.l.c. The stereoselectivity of the peracid oxidation was determined by the weight of the stereoisomeric epoxides isolated by preparative t.l.c. In order to determine their C-22,23-stereochemistry, the separated epoxides were successively treated with lithium aluminium hydride, toluene-*p*-sulphonic acid–aqueous dioxane, and benzoyl chloride–pyridine to give a mixture of 22- and 23-hydroxycholesterol dibenzoates which was analysed by h.p.l.c. The iodoacetoxylation products were treated with sodium carbonate and the resulting epoxides were examined as described above. The stereoselectivity of the hydroboration was determined by h.p.l.c. analysis of the 3,22- and 3,23-dibenzoates. The results are summarized in Table 2,



(1)



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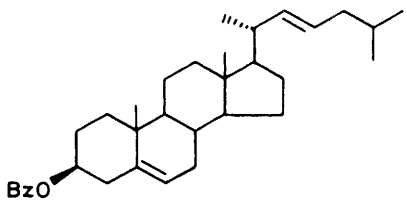
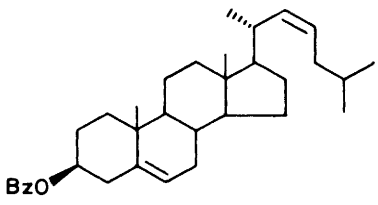


(3)



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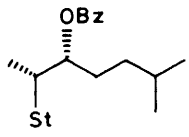

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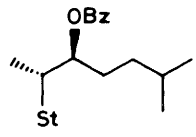
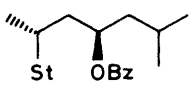


(6)



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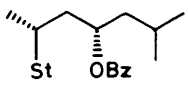
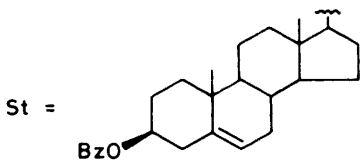


(8)



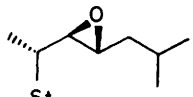
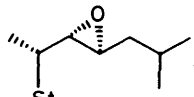
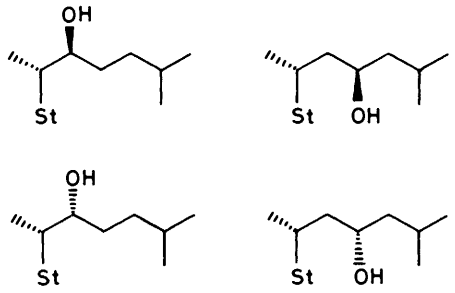
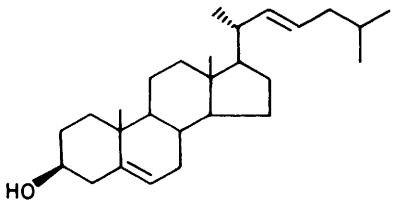
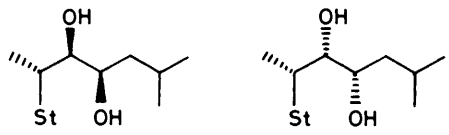
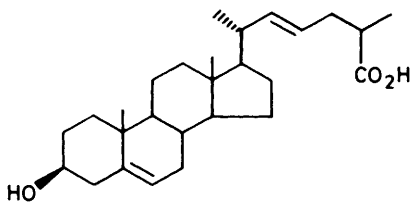
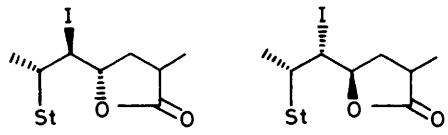
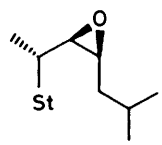
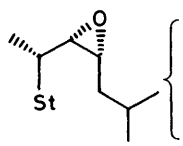
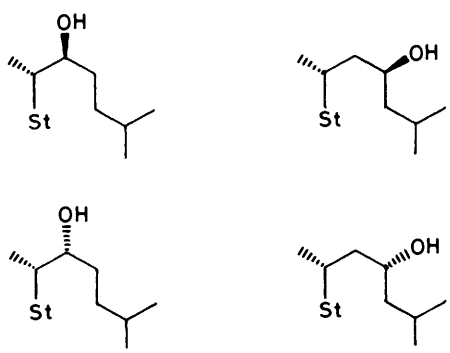
together with those of the previously described osmium tetraoxide oxidation, iodolactonization, and phenylselenenyl-lactonization.[6a,8]

The differing stereoselectivity observed with peracid oxidation and osmium tetraoxide oxidation of the *trans*-Δ^{22}-double bond is reminiscent of the previous results of a dinorchol-22-ene derivative.[1] The effective molecular size of *m*-CPBA may be smaller than that of the C-23 alkyl moiety so that conformation (**II**; R^1 = H, R^2 = Bu^i) where the C-23 alkyl moiety is located in the less crowded position will be preferable to conformation (**III**; R^1 = H, R^2 = Bu^i). On the other hand, the effective molecular size of osmium tetraoxide may be larger than that of the C-23 alkyl moiety so that conformation (**III**) becomes more favourable than conformation (**II**). The stereoselectivity of the hydroboration of the *trans*-Δ^{22}-double bond is analogous to that of the osmium tetraoxide oxidation, indicating that the effective molecular size of borane is similar to that of osmium tetraoxide. In the case of iodoacetoxylation, the rate-determining step might be an attack of the acetoxy anion on an iodonium ion. Conformation (**IV**; R^1 = H, R^2 = Bu^i) is thus more stable than conformation (**V**; R^1 = H, R^2 = Bu^i) which has a steric interaction between the incoming acetoxy anion and the C-16 hydrogens. A similar concept could be applied to the explanation of the stereoselectivity of the iodolactonization of a (22*E*)-cholest-22-en-26-oic acid derivative [conformations (**VI**) and (**VII**)].

In the case of the *cis*-Δ^{22}-double bond, all the electrophilic reactions examined here showed the same tendency in their stereoselectivity. The stereoisomers produced through the conformation (**II**; R^1 = Bu^i, R^2 = H) predominate over those produced through the conformation (**III**; R^1 = Bu^i, R^2 = H). Because the double bond would not take a position between the steroid nucleus and the C-21 methyl group, due to an intolerable steric interaction between the *cis*-substituted alkyl group at C-23 and the C-16 hydrogens, conformation (**II**) becomes preferable to conformation (**III**) in electrophilic reaction of the *cis*-Δ^{22}-double bond. In iodoacetoxylation and phenylselenenyl-lactonization, conformations (**IV**; R^1 = Bu^i, R^2 = H) and (**VIII**) are more favourable than conformations (**V**; R^1 = Bu^i, R^2 = H) and (**IX**), respectively, for the same reason as described for the *trans*-Δ^{22}-double bond.

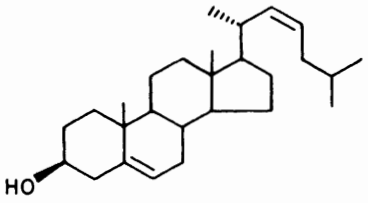
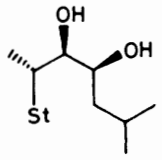
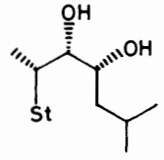
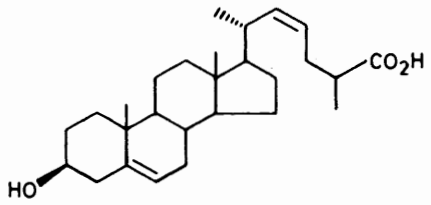
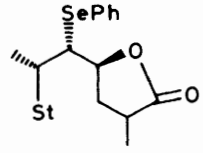
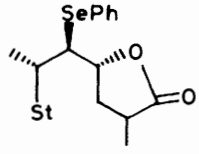
In summary, the stereoselectivity of electrophilic reactions of the Δ^{22}-double bond is determined by the difference in steric interaction between the C-16 hydrogens and reacting species or the C-23 alkyl moiety. Based on the observed stereoselectivity in this study, the effective molecular size can be estimated to decrease in the order $C^{23}HR$ (*cis*), OsO_4, BH_3, $C^{23}HR$ (*trans*), *m*-CPBA. The stereochemistry at C-24 of the C-24 alkylated Δ^{22}-steroids also influences the stereochemical course of electrophilic reactions to some extent.[2] The stereoselectivity of osmium tetraoxide oxidation of an ergosterol-like side-chain has been reported to be significantly affected by the C-24 stereochemistry.[9] The effect of C-24 alkyl substituents on these reactions remains to be explored. Recently, Houk *et al.* have employed the perpendicular model to rationalize the stereoselectivity of a hydroboration of simple olefins.[10] It is not yet established at the present time that this perpendicular model can be applied to more complex olefins such as the compounds studied here. Our model is based on a product ratio but the concept discussed above might be useful for the prediction of a reaction product in the synthesis of steroids.

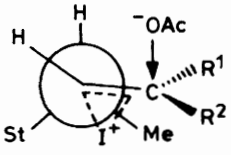
Table 2. Stereoselectivity of electrophilic reactions with some Δ^{22}-steroids

Substrate	Reagent	Product and stereoselectivity
(1)	*m*-CPBA	 (9)  (10) 2:1
(1)	i, I_2–AgOAc; ii, Na_2CO_3	0:100
(1)	i, BH_3; ii, H_2O_2–NaOH	 23:19:27:31 *
	OsO_4	 2:5
	I_2	 1:10
(2)	*m*-CPBA	 (11)  (12) 5:1
(2)	i, I_2–AgOAc; ii, Na_2CO_3	1:4
(2)	i, BH_3; ii, H_2O_2–NaOH	 46:31:10:13 *

* Analysed as the dibenzoates. St is the basic steroidal ring system of the substrate.

Table 2. (*contd*)

Substrate	Reagent	Product and stereoselectivity	
	OsO_4		 7:1
	PhSeCl		 1:10



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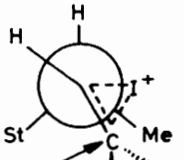

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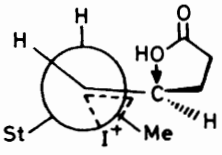

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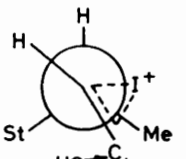

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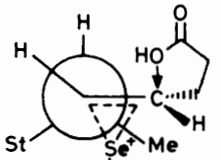

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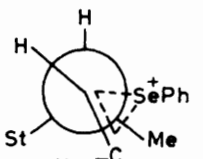

(IX)

Experimental

M.p.s were determined with a hot-stage microscope apparatus and are uncorrected. ^1H N.m.r. spectra were recorded in deuteriochloroform solution on a Hitachi R-24A or JEOL JNM-PS-100 spectrometer with tetramethylsilane as internal reference. Low-resolution mass spectra were obtained with a Shimadzu LKB-9000S instrument and high-resolution mass spectra were recorded on a Hitachi M-80 spectrometer. H.p.l.c. was carried out with a Shimadzu LC-3A liquid chromatograph with a Shimadzu SPD-1 spectrophotometric detector, using a Zorbax SIL normal-phase column or Zorbax ODS reverse-phase column. T.l.c. was performed on Merck precoated Kieselgel 60 F_{254} (0.5 mm thickness) plates and column chromatography was effected on Merck Kieselgel 60.

(22E)-6β-*Methoxy*-3α,5-*cyclo*-5α-*cholest*-22-*ene* (**1**).—(22*E*)-22,23-Dehydrocholesterol[6a] (172 mg) was treated with toluene-*p*-sulphonyl chloride (128 mg) and pyridine (2 ml) for 16 h, followed by potassium acetate (110 mg) and methanol (5 ml) at reflux for 1 h. The crude product (170 mg) was chromatographed on silica gel. Elution with benzene gave the *methyl ether* (**1**) (119 mg, 67% from the alcohol), m.p. 65—66 °C (from hexane) (Found: C, 84.4; H, 11.4. $C_{28}H_{46}O$ requires C, 84.34; H, 11.63%); δ 0.74 (3 H, s, 18-H_3), 0.86 (6 H, d, *J* 6 Hz, 26- and 27-H_3), 1.00 (3 H, d, *J* 6 Hz, 21-H_3), 1.03 (3 H, s, 19-H_3), 2.76 (1 H, m, 6-H), 3.32 (3 H, s, OMe), and 5.22 (2 H, m, 22- and 23-H); *m/z* 398 (M^+), 383 (M^+ − Me), 366 (M^+ − MeOH), 351 (M^+ − Me − MeOH), and 343 (M^+ − 55).

(22E)-22,23-*Dehydrocholesterol Benzoate* (**3**).—(22*E*)-22,23-Dehydrocholesterol (60 mg) was treated with benzoyl chloride (50 μl) and pyridine (1 ml) at 0 °C for 1 h to give the (22E)-*benzoate* (**3**) (70 mg, 92%), m.p. 141—142.5 °C (from acetone–methanol) (Found: C, 83.7; H, 9.8. $C_{34}H_{49}O_2$ requires C, 83.55; H, 9.90%); δ 0.70 (3 H, s, 18-H_3), 0.98 (6 H, d, *J* 6 Hz, 26- and 27-H_3), 1.07 (3 H, s, 19-H_3), 4.50—5.10 (1 H, m, 3-H), 5.20—5.60 (3 H, m, 6-, 22-, and 23-H), and 7.30—7.70 and 7.90—8.30 (5 H, m, COPh); h.p.l.c. R_f 13.8 min [normal phase; hexane–methylene dichloride (20:1)] and 28.6 min (reverse phase; methanol).

(22Z)-22,23-*Dehydrocholesterol Benzoate* (**4**).—The (22*Z*)-methyl ether (**2**) (60 mg), prepared from (20*S*)-6β-methoxy-3α,5-cyclo-5α-pregnane-20-carbaldehyde according to the published method,[6c] was treated with a catalytic amount of toluene-*p*-sulphonic acid and aqueous dioxane (2 ml) at reflux for 1 h, followed by benzoyl chloride (50 μl) and pyridine (1 ml) at 0 °C for 1 h to afford the (22Z)-*benzoate* (**4**) [60 mg, 82% from (**2**)], m.p. 174—176 °C (from acetone–methanol) (Found: C, 83.8; H, 9.9. $C_{34}H_{49}O_2$ requires C, 83.55; H, 9.90%); δ 0.71 (3 H, s, 18-H_3), 0.98 (6 H, d, *J* 6 Hz, 26- and 27-H_3), 1.07 (3 H, s, 19-H_3), 4.50—5.10 (1 H, m, 3-H), and 5.10—5.50 (3 H, m, 6-, 22-, and 23-H); h.p.l.c. R_f 15.5 min [normal phase; hexane–methylene dichloride (20:1)] and 25.8 min (reverse phase; methanol).

Epoxidation of the (22E)-*Methyl Ether* (**1**).—A solution of the (22*E*)-methyl ether (**1**) (100 mg) and *m*-CPBA (65 mg) in chloroform (2 ml) was stirred for 1 h. After dilution with water, the reaction mixture was extracted with ethyl acetate and the extract was washed successively with saturated aqueous Na_2CO_3 and brine, and dried over $MgSO_4$. Evaporation of the solvent gave a crude product (98 mg) which showed two spots on t.l.c. Preparative t.l.c. of the crude product (90 mg) afforded the *less polar epoxide* (**9**) as an oil (48 mg, 51%) (Found: M^+,

414.3518. $C_{28}H_{46}O_2$ requires *M*, 414.3496); δ 0.70 (3 H, s, 18-H_3), 0.98 (6 H, d, *J* 6 Hz, 26- and 27-H_3), 1.02 (3 H, s, 19-H_3), 2.20—2.50 (1 H, m, 22-H), 2.70—2.90 (2 H, m, 6- and 23-H), and 3.34 (3 H, s, OMe); *m/z* 414 (M^+), 399 (M^+ − Me), 382 (M^+ − MeOH), 359 (M^+ − 55), 356, 255, 253, and 213; t.l.c. R_F 0.57 [hexane–ethyl acetate (10:1), developed three times] and the *more polar epoxide* (**10**) as an oil (24 mg, 26%) (Found: M^+, 414.3523. $C_{28}H_{46}O_2$ requires *M*, 414.3496); δ 0.72 (3 H, s, 18-H_3), 0.97 (6 H, d, *J* 6 Hz, 26- and 27-H_3), 1.03 (3 H, s, 19-H_3), 2.40—2.56 (1 H, m, 22-H), 2.65 (1 H, ddd, *J* 6, 6, and 2 Hz, 23-H), 2.76 (1 H, m, 6-H), and 3.32 (3 H, s, OMe); t.l.c. R_F 0.51. The mass spectrum of (**10**) was identical with that of (**9**).

The C-22,23 stereochemistry of the epoxides (**9**) and (**10**) was established as follows. The less polar epoxide (**9**) (6 mg) was treated with lithium aluminium hydride (5 mg) in tetrahydrofuran (THF) (2 ml) at reflux for 10 h. The resulting product was treated with a catalytic amount of toluene-*p*-sulphonic acid and aqueous dioxane (2 ml) followed by benzoyl chloride (50 μl) and pyridine (0.5 ml). Normal-phase h.p.l.c. analysis of the reaction product showed the fraction corresponding to (22*S*)-22-hydroxycholesterol dibenzoate (**6**) and its (23*R*)-isomer (**7**). This fraction was collected and analysed by reverse-phase h.p.l.c. which showed the presence of (**6**) and (**7**) in the ratio 2:1. Hence, the less polar epoxide (**9**) has the 22*R*,23*R*-configuration and the more polar epoxide (**10**) has the 22*S*,23*S*-configuration.

Epoxidation of the (22Z)-*Methyl Ether* (**2**).—The (22*Z*)-methyl ether (**2**) (100 mg) was oxidized under the same conditions as described for the (22*E*)-olefin (**1**). A part of the crude product (70 mg) was separated by preparative t.l.c. to give the *less polar epoxide* (**11**) as an oil (47 mg, 65%) (Found: M^+, 414.3504. $C_{28}H_{46}O_2$ requires *M*, 414.3496); δ 0.70 (3 H, s, 18-H_3), 1.02 (6 H, d, *J* 6 Hz, 26- and 27-H_3), 1.05 (3 H, s, 19-H_3), 2.59 (1 H, dd, *J* 8 and 2 Hz, 22-H), 2.78 (1 H, m, 6-H), 3.02 (1 H, ddd, *J* 9, 4, and 2 Hz, 23-H), and 3.34 (3 H, s, OMe); t.l.c. R_F 0.62 [hexane–ethyl acetate (10:1), developed three times] and the *more polar epoxide* (**12**) as an oil (10 mg, 14%) (Found: M^+, 414.3458. $C_{28}H_{46}O_2$ requires *M*, 414.3496); δ 0.72 (3 H, s, 18-H_3), 0.99 (6 H, d, *J* 6 Hz, 26- and 27-H_3), 1.03 (3 H, s, 19-H_3), 2.50—2.94 (3 H, m, 6-, 22-, and 23-H), and 3.31 (3 H, s, OMe); t.l.c. R_F 0.56. The mass spectra of (**11**) and (**12**) were identical with that of (**9**).

The less polar epoxide (**11**) (10 mg) was converted into a mixture of dibenzoates in the same way as described for the epoxide (**9**). Normal-phase h.p.l.c. analysis showed the presence of the (23*S*)-dibenzoate (**8**) and the fraction corresponding to the (22*S*)-dibenzoate (**6**) and the (23*R*)-dibenzoate (**7**) in the ratio 9:1. This fraction was analysed by reverse-phase h.p.l.c. which showed the presence of the (22*S*)-dibenzoate (**6**). Hence, the less polar epoxide (**11**) has the 22*R*,23*S*-configuration and the more polar epoxide (**12**) has the 22*S*,23*R*-configuration.

Hydroboration of the (22E)-*Methyl Ether* (**1**).—A solution of the (22*E*)-methyl ether (**1**) (50 mg) and 1M BH_3THF complex (0.2 ml) in dry THF (2 ml) was stirred at ambient temperature for 2 d. After the mixture has been cooled to 0 °C, 3M sodium hydroxide (1 ml) and 30% hydrogen peroxide (1 ml) were added and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a crude product (42 mg). A part of the product (10 mg) was treated with toluene-*p*-sulphonic acid and aqueous dioxane followed by benzoyl chloride. The resulting mixture of the dibenzoates was analysed by h.p.l.c. as described above, which showed the presence of the (22*R*)- (**5**), (22*S*)- (**6**), (23*R*)- (**7**), and (23*S*)-dibenzoate (**8**) in the proportions 27:23:19:31, respectively.

Hydroboration of the (22Z)-*Methyl Ether* (**2**).—The (22*Z*)-methyl ether (**2**) (50 mg) was treated with 1M BH_3–THF complex followed by alkaline hydrogen peroxide as described for the (22*E*)-methyl ether (**1**). A part of the crude product was converted into a mixture of the dibenzoates which was then analysed by h.p.l.c. which showed the presence of the (22*R*)- (**5**), (22*S*)- (**6**), (23*R*)- (**7**), and (23*S*)-dibenzoate (**8**) in the proportions 10:46:13:31, respectively.

Iodoacetoxylation of the (22E)-*Methyl Ether* (**1**).—To the (22*E*)-methyl ether (**1**) (45 mg) and silver acetate (50 mg) in acetic acid (1 ml) was added iodine (40 mg) and the mixture was stirred for 3 h. Chloroform (2 ml) was added and the mixture was filtered. The filtrate was washed successively with water, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, and evaporated to give a crude product (59 mg) which was treated with anhydrous Na_2CO_3 (30 mg) in methanol (2 ml) at reflux for 2 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined extracts were washed with brine, dried over $MgSO_4$, and evaporated to afford a crude product (40 mg). T.l.c. analysis of this product showed a single spot corresponding to the more polar 22*S*,23*S*-epoxide (**10**).

Iodoacetoxylation of the (22Z)-*Methyl Ether* (**2**).—The (22*Z*)-methyl ether (**2**) (50 mg) was treated with silver acetate and iodine in acetic acid followed by sodium carbonate in methanol in the same way as described for the (22*E*)-isomer (**1**) to give a mixture of epoxides (45 mg). A part of this crude mixture (35 mg) was separated by preparative t.l.c. to yield the less polar 22*R*,23*S*-epoxide (**11**) (5 mg) and the more polar 22*S*,23*R*-epoxide (**12**) (21 mg).

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