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Differential behavior of (25*R*)-5,6-epoxyspirostan-22α-*O*-3β-ol and (25*R*)-5,6-epoxyspirostan-22α-*O*-3β,4β-diol toward Dowex

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The acid-catalyzed hydrolytic cleavage of the 5,6-epoxyspirostane derivatives by the cation exchange resin Dowex 50W X8 has been exploited with the goal of developing synthetic protocols toward 3,4,5,6-polyhydroxyspirostane analogs that can serve as intermediates to potential biologically active compounds. Whereas the diastereomers (25R)-5α,6α-epoxyspirostan-22α-O-3β-ol and (25R)-5β,6β-epoxyspirostan-22α-O-3β-ol yield two products, (25R)-6β-methoxyspirostan-22α-O-3β,5α-diol and (25R)-spirostan-22α-O-3β,5α,6β-triol on Dowex treatment in water-methanol, the α- and β-diastereomers of the 5,6-epoxy derivative of 3β,4β-diol provide a single product, (25R)-3β,6β-dihydroxy-5α-spirostan-4-one, in good yields. The structures of these products have been confirmed using ^{1}H NMR, ^{13}C NMR, and ^{1}H-^{1}H J-correlated spectroscopies. Multifunctional product formation suggests tremendous utility of Dowex in steroid synthesis. The product formation has been rationalized on the basis of differential conformational constraints of the A/B rings of the different epoxides in directing the reaction course. The reaction shows an interesting example of stereoelectronic effect of a single hydroxy group in discriminating solvent participation. (*Steroids* **61**:290–295, 1996)

Keywords: polyhydroxy; 5,6-epoxy sterol; cation exchange resin; nuclear magnetic resonance

Introduction

Marine species such as sponges, coelenterates, mollusks, and echinoderms are a rich source of a large variety of polyhydroxy steroids.[1–5] The 3β,5α,6β-hydroxylation pattern is found in several polyhydroxy sterols of marine origin.[6–10] Similarly a number of 4-oxygenated steroids are known to occur and possess biological activities.[11–14] Granulotoside A (**1**) occurs in an echinoderm species, *Choriaster granulotus*,[1] while the polyhydroxy sterol **2** was extracted from a species of coelenterates, *Sarcophylum glaucum*.[2] Other examples of the A/B ring functionalized sterols are that of (24*S*)-24-methylcholestan-3β,4β,5β,25-tetrol-6-one-25-acetate (**3**)[4] derived from coelenterate, *Lobophytum pauciflorum*, and the heptol **4** isolated from a sponge, *Dysidea etheria*[5] (Fig. 1). Many of these naturally occurring sterols exhibit cytotoxic and/or antibacterial activities.[15–17]

The synthesis and stereochemical studies of polyhydroxy sterols have been a challenging subject for synthetic chemists for several years now.[18–22] Of the steroid drug precursors, diosgenin is very important and versatile and is used for the synthesis of nearly 50% of the total steroid drugs in the world. In addition, diosgenin possesses functionalized intact E and F rings that can be manipulated to a desired hydroxy side chain.[23] We sought to prepare 3,4,5,6-tetrahydroxy derivative **17** of diosgenin as a model intermediate to potential biologically active compounds. A trihydroxy derivative of diosgenin, spirostan-3β,5α,6β-triol (**8**), has been synthesized by routine oxidation.[24,25] We reasoned that preparing the tetrahydroxy derivative should be relatively easy since the additional hydroxyl group could be introduced through the well studied preparation of 4-acetoxy derivatives.[26] Thus the epoxidation of Δ^5-steroidal 3β,4β-diol followed by hydrolytic cleavage would be ex-

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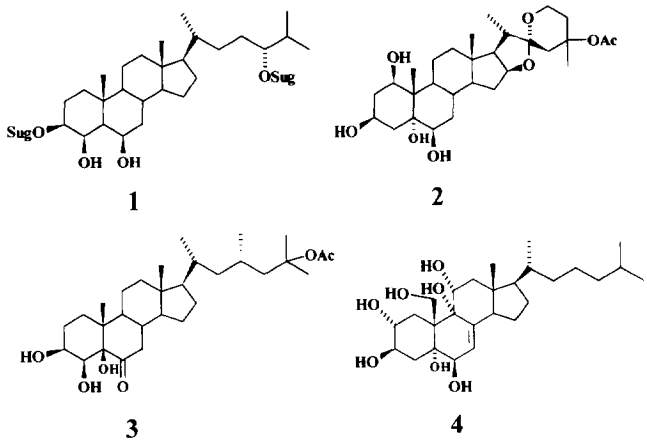


Figure 1 Naturally occurring polyhydroxy steroids.

pected to yield the required multihydroxysteroid derivative. Since the E and F rings of diosgenin are susceptible to strong mineral acids, a cation exchange resin, Dowex 50W X8, that is known to be compatible with acid-sensitive functional groups,[27] was chosen for the acid-catalyzed epoxide cleavage. It is important to note that Dowex 50W X8 together with sodium chloride has been successfully exploited in the cleavage of 5,6-epoxides to provide halohydrins.[28] In this work, we present Dowex 50W X8-mediated cleavage of 5,6-epoxides to yield some unexpected multifunctional steroid products in high yields and a plausible mechanism that can explain the product formation. The results highlight the exceptional hydrolytic utility of Dowex for the first time.

Experimental

Diosgenin was obtained from Glaxo Laboratories, India, and recrystallized before use. Dowex 50W X8 was purchased from Fluka and used after activating with 2 M HCl followed by washing with methanol. 4-Hydroxydiosgenin was prepared according to the procedure reported earlier.[29] IR spectra were recorded on a Perkin-Elmer 681 spectrophotometer in KBr or in Nujol. Ultraviolet spectra were obtained from a Shimadzu UV160 spectrophotometer while a Shimadzu QP 1000 spectrometer was used to record the mass spectra. The elemental analyses were performed on a CEST model 110 analyzer. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR 300S or a Bruker AM360 or AM600 MHz spectrometer at ambient temperatures. About 10 mg of the sample was dissolved in 0.6 mL of the solvent for ^{1}H NMR studies, and about 10 times that concentration was used for ^{13}C NMR studies. The magnitude model COSY experiments were carried out using the pulse sequence Δ–$\pi/2$–t_1–$\pi/2$-FID with 256 data points in f_1 and 1024 data points in f_2 dimensions with 16 transients each. The FIDs were processed using sine bell window function, zero filled to 1K × 1K and plotted as contours.

Epoxidation of diosgenin (5)

A solution of (25*R*)-spirost-5-en-22α-*O*-3β-ol **(5)** (1.7 g, 4.08 mmol) in dichloromethane (25 mL) was cooled to 0°C and treated with *m*-chloroperbenzoic acid (1.5 g, 8.14 mmol). The reaction mixture was stirred vigorously at room temperature for 23 h. It was then successively washed with solutions of Na_2SO_3 (10%), $Na_2S_2O_3$ (5%), saturated $NaHCO_3$, and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography over silica gel to yield 85% of (25*R*)-5,6-epoxy spirostan-22α-*O*-3β-ol **(6).** M.p. = 182–184°C. The diastereomeric mixture **6a,b** was characterized as such. MS: m/z 430 (M^+, 10%), 412 (M^+-18, 5%), 139 ($[C_9H_5O]^+$, 100%). IR(KBr): $\bar{\nu}$ 3450 (OH), 1460, 1380, 1250, 1180, 1100, 1060 cm^{-1}. Elemental analysis: calculated for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83%. Found C, 75.15, H, 9.81%.

*5α,6α-Isomer **6a***

^{1}H NMR ($CDCl_3$): δ 4.35(dt, J = 7.5, 8.4 Hz, 1H, 16α-H), 3.8(m, 1H, 3α-H), 3.45–3.50(m, 1H, 26α-H), 3.30(t, J = 10.8 Hz, 1H, 26β-H), 2.81(d, J = 4.34 Hz, 1H, 6β-H), 0.98(s, 3H, 19-H_3), 0.86(d, J = 6.9 Hz, 3H, 21-H_3), 0.69(d, J = 6.3 Hz, 3H, 27-H_3), 0.63(s, 3H, 18-H_3). ^{13}C NMR ($CDCl_3$): δ 109.2(C-22), 80.6(C-16), 68.3(C-3), 66.8(C-26), 65.7(C-5), 59.0(C-6), 16.2(C-18), 15.9(C-19).

*5β,6β-Isomer **6b***

^{1}H NMR ($CDCl_3$): δ 4.34(dt, J = 7.5,8.4 Hz, 1H, 16α-H), 3.4(m, 1H, 3α-H), 3.35–3.50(m, 1H, 26α-H), 3.30(t, J = 10.8 Hz, 1H, 26β-H), 2.98(d, J = 2.94 Hz, 1H, 6α-H), 0.91(s, 3H, 19-H_3), 0.86(d, J = 6.9 Hz, 3H, 21-H_3), 0.69(d, J = 6.3 Hz, 3H, 27-H_3), 0.66(s, 3H, 18-H_3). ^{13}C NMR ($CDCl_3$): δ 109.2(C-22), 80.6(C-16), 69.1(C-3), 66.8(C-26), 62.9(C-5), 63.5(C-6), 17.9(C-19), 16.0(C-18).

Hydrolytic cleavage of (25R)-5,6-epoxyspirostan-22α-O-3β-ol (6)

To a solution of (25*R*)-5,6-epoxyspirostan-22α-*O*-3β-ol **(6)** (300 mg, 0.72 mmol) in aqueous methanol (20 mL, 1:1 v/v ratio), Dowex 50W X8 (150 mg) was added and refluxed with vigorous stirring for 4 h. The reaction mixture was then filtered, concentrated, and extracted with chloroform. The extract was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. On column chromatography using silica gel, the products **7** and **8** were eluted with ethyl acetate/petroleum ether and could be isolated in yields of 130 mg (40%) and 170 mg (54%), respectively.

(25R)-6β-Methoxyspirostan-22α-O-3β,5α-diol (7)

M.p. = 206–207°C. MS: m/z = 462 (M^+, 4%), 139 ($[C_9H_5O]^+$, 100%). IR(KBr): $\bar{\nu}$ 3450 (OH), 1380, 1240, 1160, 1110, 1060 cm^{-1}. Elemental analysis: calculated for $C_{28}H_{46}O_5$: C, 72.69; H, 10.02%. Found C, 72.69, H, 9.98%. ^{1}H NMR ($CDCl_3$): δ 4.38(m, 1H, 16α-H), 4.06(m, 1H, 3α-H), 3.43–3.52(m, 1H, 26α-H), 3.38(t, J = 10.8 Hz, 1H, 26β-H), 3.28(s, 1H, OCH_3), 2.95(m, 1H, 6α-H), 1.10(s, 3H, 19-H_3), 0.96(d, J = 6.9 Hz, 3H, 21-H_3), 0.79(d, J = 6.3 Hz, 3H, 27-H_3), 0.76(s, 3H, 18-H_3). ^{13}C NMR ($CDCl_3$): δ 109.2(C-22), 85.5(C-6), 80.8(C-16), 76.2(C-5), 67.6(C-3), 66.8(C-26), 16.5(C-18), 16.3(C-19).

(25R)-Spirostan-22α-O-3β,5α,6β-triol (8)

M.p. = 270–271°C. MS: m/z = 448 (M^+, 0.2%), 139 ($[C_9H_5O]^+$, 100%). IR(KBr): $\bar{\nu}$ 3400, 3320 (OH), 1460, 1380, 1240, 1160, 1110, 1060 cm^{-1}. Elemental analysis: calculated for $C_{27}H_{44}O_5$: C, 72.28; H, 9.89%. Found C, 72.28, H, 9.84%. ^{1}H NMR ($CDCl_3$ + CD_3OD (9:1 v/v)): δ 4.40(m, 1H, 16α-H), 4.00(m, 1H, 3α-H), 3.46(m, 1H, 6α-H), 3.43–3.47(m, 1H, 26α-H), 3.38(t, J = 10.8 Hz, 1H, 26β-H), 1.16(s, 3H, 19-H_3), 0.98(s, 3H, 18-H_3), 0.96(d, J = 6.9 Hz, 3H, 21-H_3), 0.79(d, J = 6.3 Hz, 3H, 27-H_3). ^{13}C NMR ($CDCl_3$ + CD_3OD (9:1 v/v)): δ 109.3(C-22), 80.8(C-16), 75.5(C-5), 75.2(C-6), 67.1(C-3), 66.7(C-26), 16.4(C-19), 16.3(C-18).

Epoxidation of (25R)-spirost-5-en-22α-O-3β,4β-diol (10)

The epoxidation reaction of the diol **10** was performed by the same procedure as that for (25*R*)-spirost-5-en-22α-*O*-3β-ol (**5**). 85% of the product **11** was obtained. The diastereomeric mixture of **11a,b** was characterized as such. M.p. = 176–178°C. MS: m/z 446 (M^+, 2%), 428 (M^+-18, 1%), 139 ($[C_9H_5O]^+$, 50%), 83 ($[C_4H_3O_2]^+$, 100%). IR(KBr): $\bar{\nu}$ 3450 (OH), 1460, 1380, 1240, 1180, 1110, 1060 cm^{-1}. Elemental analysis: calculated for $C_{27}H_{42}O_5$: C, 72.61; H, 9.48%. Found C, 72.51, H, 9.47%.

5α,6α-Isomer 11a

^1H NMR ($CDCl_3$): δ 4.39(dt, *J* = 7.5, 8.4 Hz, 1H, 16α-H), 3.85(m, 1H, 3α-H), 3.45–3.50(m, 1H, 26α-H), 3.30(t, *J* = 10.8 Hz, 1H, 26β-H), 3.24(d, *J* = 3.36 Hz, 1H, 4α-H), 3.04(d, *J* = 4.2 Hz, 1H, 6β-H), 1.24(s, 3H, 19-H_3), 0.95(d, *J* = 6.9 Hz, 3H, 21-H_3), 0.79(d, *J* = 6.3 Hz, 3H, 27-H_3), 0.72(s, 3H, 18-H_3). ^{13}C NMR ($CDCl_3$): δ 109.2(C-22), 80.6(C-16), 77.4(C-4), 69.9(C-3), 66.8(C-26), 64.8(C-5), 59.1(C-6), 16.2(C-18), 15.3(C-19).

5β,6β-Isomer 11b

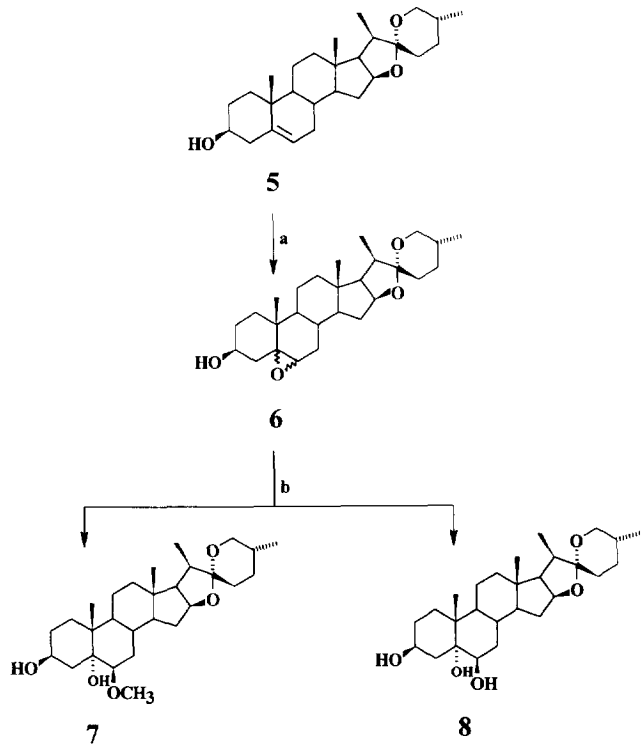
^1H NMR ($CDCl_3$): δ 4.39(dt, *J* = 7.5, 8.4 Hz, 1H, 16α-H), 3.75(m, 1H, 3α-H), 3.45–3.50(m, 1H, 26α-H), 3.36(br s, 1H, 4α-H), 3.30(t, *J* = 10.8 Hz, 1H, 26β-H), 3.19(d, *J* = 3.4 Hz, 1H, 6α-H), 1.14(s, 3H, 19-H_3), 0.95(d, *J* = 6.9 Hz, 3H, 21-H_3), 0.79(d, *J* = 6.3 Hz, 3H, 27-H_3), 0.74(s, 3H, 18-H_3). ^{13}C NMR ($CDCl_3$): δ 109.2(C-22), 80.6(C-16), 77.2(C-4), 71.1(C-3), 66.8(C-26), 65.4(C-5), 63.5(C-6), 17.8(C-19), 16.0(C-18).

Dowex-mediated cleavage of epoxides 11a,b

The cleavage of (25*R*)-5,6-epoxyspirostan-22α-*O*-3β,4β-diol (**11**) (100 mg, 0.23 mmol) was carried out using the same procedure as adopted for the epoxidation of (25*R*)-5,6-epoxyspirostan-22α-*O*-3β-ol (**6**). The product (25*R*)-3β,6β-dihydroxy-5α-spirostan-22α-*O*-4-one (**12**) was obtained as a white crystalline solid with a yield of 95 mg (92%). M.p. = 183°C. MS: m/z 446 (M^+, 2%), 431 (M^+-15, 1%), 139 ($[C_9H_5O]^+$, 100%). IR(Nujol): $\bar{\nu}$ 3480, 3370 (OH), 2840, 1710 (C=O), 1450, 1380, 1120, 1060 cm^{-1}. Elemental analysis: calculated for $C_{27}H_{42}O_5$: C, 72.61; H, 9.48%. Found C, 72.39, H, 9.51%. ^1H NMR ($CDCl_3$): δ 4.39 (dt, *J* = 7.5, 8.4 Hz, 1H, 16α-H), 4.32–4.37(br m, 1H, 6α-H), 4.16(dd, *J* = 8.54, 11.29 Hz, 1H, 3α-H), 3.43–3.51(m, 1H, 26α-H), 3.30(t, *J* = 10.8 Hz, 1H, 26β-H), 2.43(br d, 1H, 5α-H), 1.00(s, 3H, 19-H_3), 0.96(d, *J* = 6.9 Hz, 3H, 21-H_3), 0.80(s, 3H, 18-H_3), 0.79(d, *J* = 6.4 Hz, 3H, 27-H_3). ^{13}C NMR ($CDCl_3$): δ 215.0(C-4), 109.2(C-22), 80.6(C-16), 74.8(C-6), 65.1(C-3), 66.8(C-26), 58.4(C-5), 17.1(C-19), 16.5(C-18).

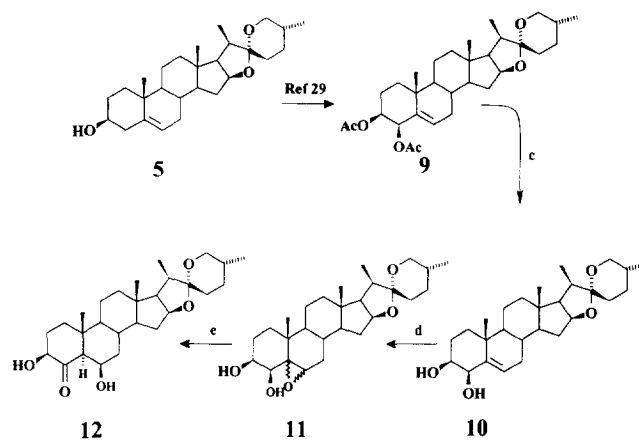
Results and discussion

The reaction of *m*-chloroperbenzoic acid (MCPBA) with Δ^5-steroids produces both the 5α,6α- as well as 5β-6β-epoxides with the epoxidation taking place predominantly from the α-face of the molecule (product ratio 4:1).[30] In the present study, when compounds **5** and **10** were individually treated with MCPBA for 24 h, diastereomeric mixtures of α- and β-epoxides (**6a,b** and **11a,b,** respectively) were obtained in the same proportion (viz. 4:1) in each case (Schemes 1 and 2). This indicated that the 4β-OH group of the sterol **10** did not affect the proportion. The two diastereomers in both cases could not be purified using preparative silica gel chromatography, and hence the stereochemical analysis was performed with the mixtures.



Scheme 1 Conditions: a) MCPBA, dichloromethane, room temperature; b) Dowex 50W X8, H_2O:CH_3OH (1:1 v/v).

Noticeable differences in the chemical shift of the 19-H_3 and 6-H for the α- and β-epoxides have been used as criteria to determine the stereochemical assignments.[31,32] The ^1H NMR spectrum of the mixture of **6a** and **6b** showed a doublet at 2.81 ppm that could be assigned to the 6β-H of the 5α,6α-epoxide **6a** while that at 2.98 ppm was assigned to the 6α-H of the 5β,6β-epoxide **6b.** The 19-H_3 signals of **6a** and **6b** appeared at 0.98 and 0.91 ppm, respectively. In the case of **11a,** the 19-H_3 signal appeared downfield at 1.24 ppm while that of **11b** resonated at 1.14 ppm. The 6β-H proton resonated at 3.04 ppm while the 6α-H signal was



Scheme 2 Conditions: c) KOH, methanol, reflux; d) MCPBA, dichloromethane, room temperature; e) Dowex 50W X8, H_2O:CH_3OH (1:1 v/v).

deshielded by 0.15 ppm. In addition to these differences, the spectrum also showed a difference in the chemical shifts of the 4-H signals of **11a,b.** The signal at 3.24 ppm was assigned to 4α-H of **11a** while it was deshielded by 0.05 ppm in **11b.**

The utility of Dowex 50W X8 toward preparation of polyhydroxy steroids was first tested with the diastereomeric mixture **6a,b.** When the mixture was refluxed in aqueous methanol with Dowex 50W X8, two compounds could be isolated after silica gel column chromatography in approximately 40 and 54% yields (Scheme 1). The elemental analysis and the M^+ ion peak (m/z = 462) in the mass spectrum of the minor compound indicated a molecular formula of $C_{28}H_{46}O_5$. The IR spectrum showed a broad band at 3450 cm^{-1} characteristic of OH group. The ^1H NMR spectrum exhibited five methyl signals at 0.78, 0.79, 0.96, 1.10, and 3.28 ppm corresponding to 27-H_3, 18-H_3, 21-H_3, 19-H_3, and OCH_3, respectively. In the downfield region, besides 16α-H and 26-H_2 protons, there were two additional signals at 4.06 and 2.95 ppm. The multiplet centered at 4.06 ppm had a complexity normally seen for the 3α-H with a 3β-OH group. Hence the remaining signal at 2.95 ppm with a small coupling constant (4 Hz) was assigned to the proton bearing the methoxy group. The small value of *J* is consistent with an equatorial proton and indicated the presence of an axial methoxy group. Since no other proton could be observed in the downfield region, the fifth oxygen atom was located on a tertiary carbon. A comparison of the ^{13}C chemical shifts of the minor product with that of its underivatized counterpart[33] showed changes in carbons C-1 to C-10 and C-19 only. The signal at 57.88 ppm substantiated the presence of a methoxy group while the quaternary carbon signal at 76.19 ppm indicated the presence of a tertiary hydroxy group at C-5. The C-19 signal at 16.32 ppm was typical of a transfused A/B ring system.[33] The upfield shift of the C-8 resonance by about 5 ppm indicated the presence of an axial methoxy group, thus confirming the minor compound as (25*R*)-6β-methoxyspirostan-22α-*O*-3β,5α-diol **(7).**

The elemental analysis and the molecular ion peak (m/z = 448) in the mass spectrum of the major compound indicated the presence of an extra oxygen atom and two protons as compared with that of the starting material. The ^1H NMR spectrum of compound **8** showed that besides 3α-H, 16α-H, and 26-H_2 protons, there was only one signal at 3.46 ppm with a small coupling constant (4.4 Hz). This could be assigned to the 6-H proton. Since no other deshielded proton signal was observed, the remaining oxygen atom could be that of a tertiary hydroxy group at C-5. The downfield shift of the 3α-H by 0.64 ppm from that in **6** suggested the presence of a 5α-OH group. Similarly the downfield shift of 19-H_3 from 1.00 to 1.16 ppm indicated the presence of a 6β-OH group. This was further confirmed from the ^{13}C NMR spectrum of major compound. The C-19 signal at 16.38 ppm corroborated the transfusion of rings A and B. This suggested that the major product was (25*R*)-spirostan-22α-*O*-3β,5α,6β-triol **(8).** It is worthwhile to note that similar stereochemistry was observed in the synthesis of halohydrins using Dowex.[28]

Since Dowex 50W X8-mediated cleavage of epoxides **6a,b** provided the desired triol, albeit in low yields, epoxides **11a,b** were similarly treated (Scheme 2). However, this diastereomeric mixture gave a single product in 92% yield. The mass spectrum of the product showed the M^+ peak at m/z = 446. This along with the elemental analysis indicated a molecular formula identical to its starting material ($C_{27}H_{42}O_5$). The IR spectrum showed bands corresponding to hydroxyl and carbonyl groups. Two downfield signals at 4.35 and 4.16 ppm were observed in the ^1H NMR spectrum, besides the 16α-H and 26-H_2 protons. These could be due to protons on two carbons bearing a hydroxy group each. The ^1H-^1H COSY plot of this compound did not show any cross-peaks between these two signals, indicating that the two hydroxy groups are not vicinally located. The signal at 4.16 ppm could be assigned to 3α-H proton that is deshielded by the presence of a carbonyl group at C-4. This was also substantiated by a distinct simplification in the coupling pattern of the 3α-H. The other downfield signal at 4.35 ppm could be assigned as 6-H. This signal appeared as a broad singlet suggesting a 6β-OH configuration. The carbonyl carbon at 4-position of the product resonated at 215.04 ppm. The signal at 17.1 ppm for C-19 confirmed the existence of a transfused A/B ring system. The upfield shift of C-8 at 29.39 ppm by 5.2 ppm[34] supported the β-orientation of the OH group at C-6, thus confirming the product being (25*R*)-3β,6β-dihydroxy-5α-spirostan-22α-*O*-4-one **(12).**

Thus, while the sterol without the 4β-OH group provided the expected epoxide opening product, the one with 4β-OH differed completely in its reaction. An attractive aspect of the latter epoxide cleavage is that a single product in high yields is generated from both diastereomers. In addition, whereas solvent methanol participates in the opening of epoxides **6a,b** it is completely non-participating in the cleavage of **11a,b.**

The formation of **7** and **8** from diastereomeric **6a,b** can be rather easily rationalized (Fig. 2). The protonation of the α- and β-epoxides **6a** and **6b** will lead to the formation of oxonium intermediates **13** and **14,** respectively, which are susceptible to nucleophilic attack. Intermediate **13** is expected to be particularly reactive at its relatively unhindered 6-position by both nucleophilic components, H_2O and CH_3OH, of solvent and hence will lead to the two products, **7** and **8,** respectively. The approach of the nucleophile in the intermediate **14** has to be from the α-face. Ball and stick model studies suggest that due to cage formation by 2α-H, 4α-H, 7α-H, and 9α-H in the A/B cis geometry, the attack of bulkier CH_3OH may be sterically restricted, while the attack by H_2O will lead to the formation of compound **8** only.

Since the yield in the cleavage of **11a,b** is nearly quantitative and because of the fact that a single product **12** is formed, it is expected that both diastereomers evolve from a common intermediate (Fig. 3). As with the previous epoxides, the protonation of **11a,b** will lead to the formation of oxonium intermediates **15** and **16.** Model studies suggest that steric crowding of the 4β-OH group and the 10-CH_3 in **15** may lead to the deformed chair conformation of B-ring resulting in 6-position becoming inaccessible to the bulkier CH_3OH. This will lead to the formation of **17,** which under acidic conditions will provide intermediate **18.** At this stage,

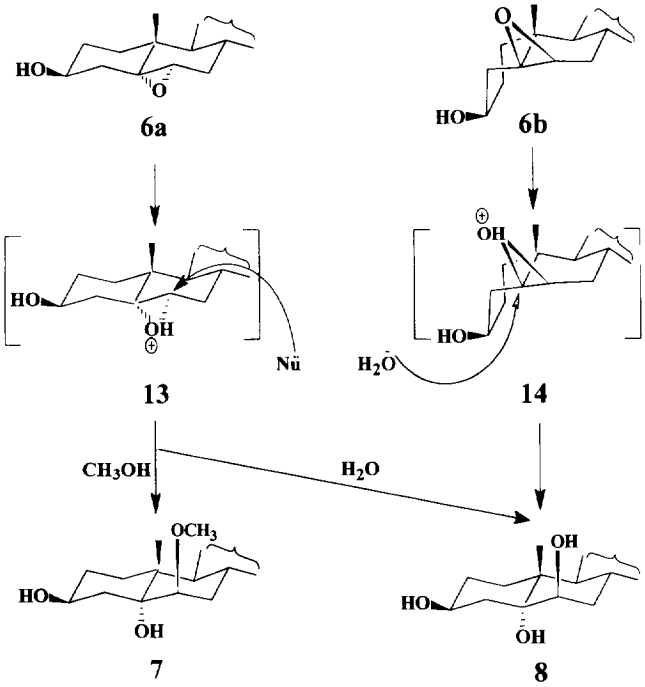


Figure 2 Epoxide cleavage of diastereomers **6a** and **6b**. Only rings A and B are shown.

either the 4β-OH or the 6β-OH group may drive away the leaving group leading to the formation of 4β,5β- or 5β,6β-epoxide, respectively. However, models show that the formation of 4β,5β-epoxy derivative will increase the steric interaction between the 10-methyl group and the 6β-OH group. This derivative may also not be feasible because the constraint introduced by the fused epoxide ring will reduce the conformational flexibility of A-ring. Such constraints are partially reduced in the formation of 5β,6β-epoxy group due to the somewhat flexible ring A. Under acidic conditions, therefore, oxonium intermediate **16** is preferred, essentially implying the conversion of 5α,6α-epoxide to 5β,6β-epoxide.[35] This is also the expected intermediate from diastereomer **11b.** Oxonium ion **16** is A/B cis fused, and model studies suggest that conformational mobility of the ring B is much reduced. Moreover, ring B cannot retain chair conformation; rather a twist (distorted) chair is more likely. Under these circumstances, the 6α-H is synclinal to the C-O bond of the epoxy ring, whereas the 4α-H is almost antiperiplanar. This leads to a familiar 1,2-hydride shift[36] from position 4 to 5 explaining the formation of **12.**

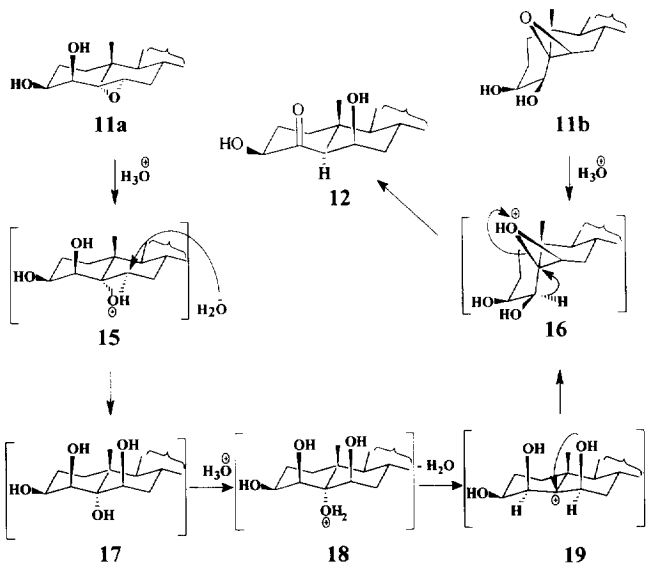


Figure 3 Stereoelectronic effect of the 4-hydroxy group on the cleavage of epoxides **11a** and **11b.** Only rings A and B are shown.

In conclusion, whereas Dowex-mediated synthesis of polyhydroxy steroids is feasible and attractive, the synthesis of 3,4,5,6-tetrahydroxy spirostane derivative failed. However, the specificity for the synthesis of multifunctional steroid **12** was observed to be high. This provides an opportunity for further exploration of the synthetic utility of Dowex.

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