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SYNTHESIS AND DEHYDROHALOGENATION OF 3β-CHLORO-5α,7α-DIBROMO-6-KETOSTEROIDS OF THE STIGMASTANE AND CHOLESTANE SERIES

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*3β-Chloro-5α,7α-dibromo-6-ketosteroids **5a** and **5b** are synthesized from β-sitosterol (**1a**) and cholesterol (**1b**). Dehydrohalogenation of these forms 7α-bromo-2,4-dien-6-ones (**6a-b**), 2,4-dien-6-ones (**7a-b**), and 14α-hydroperoxy-2,4,7-trien-6-ones (**8a-b**). Woodward hydroxylation of dienone **6a** produces 2β-iodo-7α-bromo-3α-acetoxy-Δ^4-6-ketone **9** and 7α-bromo-2α,3α-diacetoxy-Δ^4-6-ketone **10**. 2β-Iodo-3α-acetoxy-$\Delta^{4,7,14}$-trien-6-one **11** is prepared analogously from trienone **8a**.*

Key words: 3β-chloro-5α,7α-dibromo-6-ketosteroids, dehydrohalogenation, synthesis.

Natural ecdysteroids include a small group of molecules with the 2,3-dihydroxy-4,7-dien-6-ketone group [1]. These compounds include, in particular, 4-dehydroecdysterone [2], diaulusterols A and B [3], and phytoecdysteroids of the red alga *Laurentia pinnata* [4, 5]. In our opinion, one of the chemical syntheses of this class of compounds could be hydroxylation of the 2(3)-double bond in steroidal 2,4,7-trien-6-ketones. The preparation of these compounds was studied previously [6] using dehydration of the corresponding 5α-hydroxy-2,7-dien-6-ketones. It was found that such a synthetic route encounters several difficulties, for example, a low yield of a required product, although 14α-hydroperoxy-2,4,7-trien-6-ketosteroids are formed.

We searched for an alternative method to synthesize 2,4,7-trien-6-ketosteroids from β-sitosterol (**1a**) and cholesterol (**1b**). The key step was the use of a single-step dehydrohalogentaion of the corresponding 3β-chloro-5,7-dibromo-6-ketosteroids.

In the first step of the reaction of starting **1a** and **1b** with neat thionylchloride by the literature method [7], 3β-chloroderivatives **2a** and **b** are obtained in yields of 89 and 96%, respectively. Addition of hypobromous acid (formed by reacting N-bromoacetamide and aqueous perchloric acid) to the 5(6)-double bond in **2a** in aqueous THF and subsequent oxidation of the resulting bromohydrin by chromic acid without isolating it gave 3β-chloro-5α-bromo-6-ketosteroid **3a** in overall yield of ~40%. The structure of **3a** was established by comparing its IR and ^{1}H NMR spectra with those of an authentic sample that was prepared earlier [8]. It was also found that 3β-chloro-5α-hydroxy-6-ketone **4** is a side product of this reaction (10% yield). Its structure was proved by comparing its IR and ^{1}H NMR spectra with those of the compound synthesized by a different method [9]. This 5α-hydroxy-6-ketosteroid is most probably formed via cyclization of the 5α-bromo-6β-hydroxysteroid obtained from addition of hypobromous acid to the 5β,6β-epoxide, acid hydrolysis of the epoxide to the 5α,6β-diol, and oxidation of the secondary 6β-hydroxy of the diol by chromic acid. It should be noted that analogous transformations of 5α-bromo-6β-hydroxysteroids to 5β,6β-epoxides and then to 5α,6β-diols under conditions of hypobromous acid addition to the Δ^5-bond have been reported for the androstane series [10].

In the same way 3β-chloro-5α-bromo-6-ketone **3b** was synthesized in 73% overall yield by reacting **2b** with hypobromous acid in aqueous dioxane and subsequent oxidation of the resulting bromohydrin. It should be pointed out that this method of preparing **3a** and **b** from 3β-chloro-Δ^5-steroids **2a** and **b** without isolating the intermediate bromohydrins has a certain advantage over the previously published one [8].

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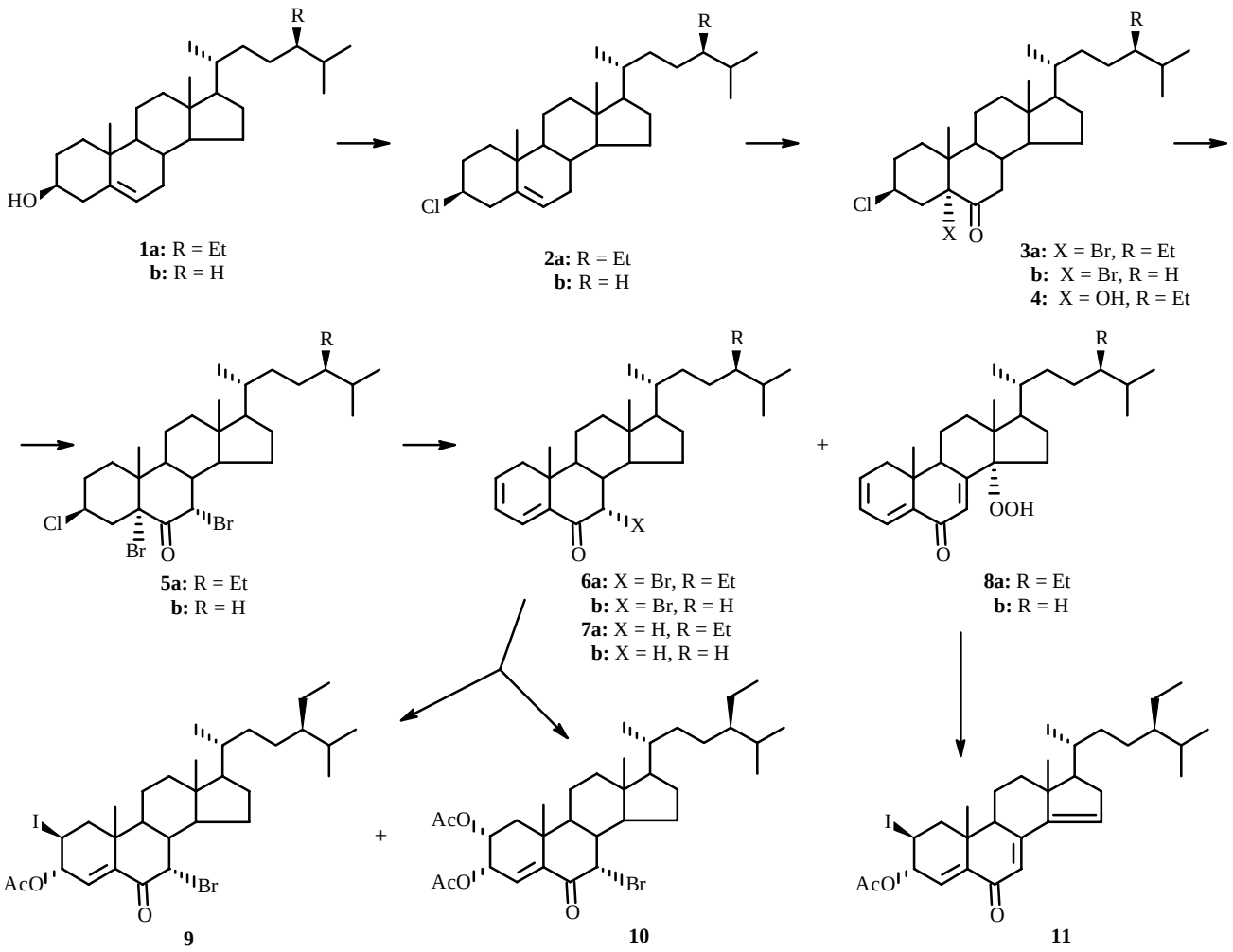

In the next step, bromination with heating of a mixture of acetic acid and $CHCl_3$ in the presence of hydrobromic acid produces 3β-chloro-5α,7α-dibromo-6-ketone **5a** in 71% yield from 3β-chloro-5α-bromo-6-ketosteroid **3a**. The structure of this compound was determined using spectral data. In particular, its ^{1}H NMR spectrum contains a doublet for methine proton H-7 geminal to the Br at δ 4.36 ppm, among other signals. This signal is split by geminal coupling with axial proton H-8β. The splitting constant (J = 6 Hz) is consistent with an equatorial—axial alignment of protons H-7 and H-8 and indicates that the Br atom on C-7 has the α-orientation. It should be noted that the signal for H-7 in the ^{1}H NMR spectra of 7β-bromo-6-ketosteroids also appears as a doublet. However, its splitting constant is due to axial—axial coupling with methine proton H-8β and is larger (~10 Hz) [11-13]. Additional confirmation of the structure of **5a** can be obtained by analyzing its ^{13}C NMR spectrum (Table 1). The signals for C-7, C-14, and C-15 have chemical shifts characteristic of 7α-bromo-6-ketosteroids and not their 7β-isomers [14]. The significant shift to weak field of the signals for C-5, C-9, and C-14 compared with their positions in the spectrum of starting 5α-bromo-6-ketone **3a** is also interesting. Such a shift certainly occurs as a result of a *γ-gauche*-effect of the 7α-bromo atom situated axial in dibromide **5a**.

Bromination of 3β-chloro-5α-bromo-6-ketosteroid **3b**, which belongs to the cholestane series, under analogous conditions produced a mixture of the starting material and 5α,7α-dibromo-6-ketone **5b** that could not be separated despite several attempts. However, signals of protons of the separate components can be reliably identified in the ^{1}H NMR spectrum of this mixture, enabling their structures to be proved. Pure 5α,7α-dibromo-6-ketone **5b** was obtained in ~80% yield from a longer bromination.

TABLE 1. Chemical Shifts in ^{13}C NMR Spectra (CD_2Cl_2, δ, ppm) of steroids **3a**, **3b**, **5a**, **5b**, and **6a**

Atom	**3a**	**3b**	**5a**	**5b**	**6a**
C-1	32.2	32.2	31.7	31.7	38.1
C-2	31.9	31.9	31.6	31.5	133.8
C-3	57.0	57.1	56.0	56.0	123.3
C-4	40.0	40.0	40.0	40.0	131.8
C-5	81.1	81.2	75.1	75.1	139.3
C-6	203.7	203.7	199.6	199.6	193.4
C-7	40.8	40.8	53.4	53.4	64.2
C-8	36.4	36.1	38.4	38.4	37.8
C-9	47.7	47.8	40.8	40.8	42.8
C-10	42.8	42.8	41.4	41.9	
C-11	22.0	22.0	21.4	21.4	21.4
C-12	39.6	39.8	38.6	38.6	39.2
C-13	43.3	43.4	43.2	43.2	42.8
C-14	56.6	56.6	50.6	50.6	50.8
C-15	24.1	24.2	23.8	23.7	23.6
C-16	28.4	28.7	28.2	28.1	28.3
C-17	56.3	56.4	55.8	55.7	56.2
C-18	12.1	12.2	12.9	12.8	12.2
C-19	14.8	14.8	15.6	15.6	18.9
C-20	36.4	36.1	36.4	36.0	36.4
C-21	18.7	18.8	19.0	18.7	18.9
C-22	34.2	36.5	34.2	36.4	34.2
C-23	26.4	24.2	26.4	24.1	26.3
C-24	46.2	39.7	46.2	39.8	46.2
C-25	29.5	28.4	29.6	28.4	29.5
C-26	19.2	22.7	19.2	22.7	19.2
C-27	19.9	22.9	20.0	22.9	20.0
C-28	23.4		23.5		23.4
C-29	12.1		12.2		12.0

Next, **5a** was dehydrohalogenated by lithium carbonate and lithium bromide in boiling DMF to give 7α-bromo-2,4-dien-6-one **6a**, 2,4-dien-6-one **7a**, and 14α-hydroperoxy-2,4,7-trien-6-one **8a** in yields of 25, 21, and 23%, respectively. The structures of these compounds were proven by comparing their spectra with those of the corresponding cholestane derivatives **6b**, **7b**, and **8b**, which were synthesized earlier [6]. We note that **6a** and **8a** are the expected products of the corresponding partial and full dehydrohalogenation of 3β-chloro-5α,7β-dibromo-6-ketone **5a**. However, dienone **7a**, which lacks a Br on C-7 or a 7(8)-double bond, is obtained via reductive dehydrobromination. It should be noted that this type of reduction products has been formed before via dehydrobromination of 7-bromo-6-ketosteroids [6, 12].

Dehydrohalogenation of the mixture of 3β-chloro-5α-bromo-6-ketone **3b** and 3β-chloro-5α,7α-dibromo-6-ketone **5b** under the same conditions proceeds analogously. We isolated 7α-bromo-2,4-dien-6-one **6b**, 2,4-dien-6-one **7b**, and 14α-hydroperoxy-2,4,7-trien-6-one **8b** in moderate yields. Compound **7b** is formed from starting steroids **3b** and **5b**. Therefore, its yield in this reaction is naturally higher than for dehydrohalogenation of the corresponding stigmastane derivative **5a**. Dehydrohalogenation of pure 3β-chloro-5α-bromo-6-ketone **3b** also yields **6b**-**8b**.

An important structural element of ecdysteroids is the 2,3-dihydroxy group that can be introduced by hydroxylation of the 2,3-double bond in the starting steroids. The *cis*-hydroxylation of **6b** and **7b** by silver acetate and iodine in aqueous acetic acid (Woodward reaction) to introduce the 2α,3α-dihydroxy group was investigated earlier [6]. We performed the same procedure for **6a** and **7a** and found that Woodward hydroxylation of 7α-bromo-2,4-dien-6-ketosteroid **6a** followed by acetylation produces mainly 2β-iodo-7α-bromo-3α-acetoxy-Δ^4-6-ketone **9** and 7α-bromo-2α,3α-diacetoxy-Δ^4-6-ketone **10** in yields of 22

and 30%, respectively. Compounds of this same structure were prepared earlier [6] via Woodward hydroxylation of **6b**. Therefore, the structures of **9** and **10** were easily proved by comparing their IR, UV, and ^{1}H and ^{13}C NMR spectra with those of the corresponding cholestane derivatives.

Woodward hydroxylation of 2,4,7-trien-6-ketone **8a** and subsequent acetylation produces mainly 2β-iodo-3α-acetoxy-$\Delta^{4,7,14}$-trien-6-one **11**, which was isolated from the reaction products in 23% yield. The structure of **11** was determined by comparing its IR, UV and ^{1}H NMR spectra with those of a compound of analogous structure that was prepared in the same manner from 2,4,7-trien-6-ketone **8b** [6].

Thus, we found that dehydrohalogenation of 3β-chloro-5α,7α-dibromo-6-ketosteroids can be used to prepare 2,4,7-trien-6-ketosteroids.

EXPERIMENTAL

Melting points were measured on a Kofler block. IR spectra were recorded (if not noted otherwise) in KBr pellets on a UR-20 instrument in the range 700-3600 cm^{-1}. UV spectra of ethanol solutions were taken on a Specord M-400 instrument. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AC-200 NMR-spectrometer at working frequencies 200 and 50.32 MHz, respectively. Chemical shifts are given relative to TMS internal standard.

(24R)-3β-Chloro-5-bromo-5α-stigmastan-6-one (3a). A solution of **2a** {from β-sitosterol (**1a**) by the literature method [7]} (23.5 g) in THF (350 mL) was treated with water (20 mL) and $HClO_4$ (30 mL, 32%), stirred, treated in portions with N-bromoacetamide (15.0 g) over 1.5 h and with chromic acid (45 mL, 8 N) after 0.5 h, and stirred for 2.5 h. The excess of oxidant was neutralized by isopropanol (80 mL). The solution was filtered through a layer of aluminum oxide. Most of the solvent was removed in a rotary evaporator. The remainder was diluted with water and extracted with petroleum ether. The organic layer was washed with water and evaporated in vacuum. The solid was chromatographed over a silica-gel column with elution by petroleum ether—THF (75:1) to give bromoketone **3a**, 12.4 g, 37%, mp 122-132°C (hexane) (lit. [8] mp 135-137°C). IR spectrum (ν, cm^{-1}): 1720 (C=O). ^{1}H NMR spectrum (CD_2Cl_2, δ, ppm, J/Hz): 0.67 (3H, s, 18-Me), 0.94 (3H, d, J = 6.5, 21-Me), 1.00 (3H, s, 19-Me), 4.48 (1H, m, W/2 = 21, H-3α).

Then, elution by petroleum ether—THF (40:1) gave **4**, 2.4 g, 10%, mp 157-159°C (hexane) (lit. [9] mp 152-155°C). IR spectrum (ν, cm^{-1}): 1720 (C=O). ^{1}H NMR spectrum (CD_2Cl_2, δ, ppm, J/Hz): 0.66 (3H, s, 18-Me), 0.82 (3H, s, 19-Me), 1.92 (3H, d, J = 6.5, 21-Me), 4.44 (1H, m, W/2 = 20, H-3α).

3β-Chloro-5-bromo-5α-cholestan-6-one (3b). A solution of **2b** {from cholesterol (**1b**) by the literature method [7]} (8.0 g) in dioxane (300 mL) was treated with water (20 mL) and $HClO_4$ (20 mL, 32%), stirred, treated in portions with N-bromoacetamide (4.6 g), treated after 0.5 h with chromic acid (12 mL, 8 N), and stirred for another 0.5 h. The excess of oxidant was neutralized by ethanol (50 mL). The solution was filtered through a layer of aluminum oxide. Most of the solvent was removed in a rotary evaporator. The remainder was diluted with water and extracted with benzene. The organic layer was washed with water and evaporated in vacuum. The solid was chromatographed over a silica-gel column with elution by petroleum ether—ethylacetate (60:1) to give bromoketone **3b**, 7.2 g, 73%, mp 128-129°C (hexane) (lit. [8] mp 128-130°C). IR spectrum (ν, cm^{-1}): 1720 (C=O). ^{1}H NMR spectrum (CD_2Cl_2, δ, ppm, J/Hz): 0.66 (3H, s, 18-Me), 0.87 (6H, d, J = 6.5, 26/27-Me), 0.92 (3H, d, J = 6, 21-Me), 1.00 (3H, s, 19-Me), 4.48 (1H, m, W/2 = 19, H-3α).

(24R)-3β-Chloro-5,7α-dibromo-5α-stigmastan-6-one (5a). A heated (40°C) solution of bromoketone **3a** (5.5 g) in the mixture of glacial acetic acid (100 mL) and 1,2-dichloroethane (45 mL) was stirred, treated with bromine in acetic acid (15 mL, 1 M) and hydrobromic acid (1.2 mL, 40%), stirred at 41-44°C for 4 h 20 min, cooled to room temperature, stirred, treated with sodium sulfite (8 mL, 2 M), and poured after 5 min into water. The organic and aqueous layers were separated. The aqueous layer was extracted with dichloroethane. The combined organic extract was washed successively with water, sodium carbonate (5%), and water and evaporated in a rotary evaporator. The solid was chromatographed over a silica-gel column with elution by hexane—THF (100:1) to give dibromoketone **5a**, 4.5 g, 71%, mp 110-112°C (dec.) (hexane). IR spectrum (ν, cm^{-1}): 1720 (C=O). ^{1}H NMR spectrum (CD_2Cl_2, δ, ppm, J/Hz): 0.71 (3H, s, 18-Me), 0.96 (3H, d, J = 6.5, 21-Me), 1.04 (3H, s, 19-Me), 4.36 (1H, d, J = 6, H-7β), 4.57 (1H, m, W/2 = 26, H-3α).

3β-Chloro-5,7α-dibromo-5α-cholestan-6-one (5b). A. A heated (40°C) solution of bromoketone **3b** (4.1 g) in the mixture of glacial acetic acid (50 mL) and 1,2-dichloroethane (20 mL) was stirred, treated with bromine (0.9 mL) and aqueous hydrobromic acid (1.2 mL, 40%). The reaction and work-up were performed as above. The solid was chromatographed over

a silica-gel column with elution by hexane—ethylacetate (100:1) to give a mixture (3.1 g) of dibromoketone **5b** and starting bromoketone **3b**. The mixture was chromatographed repeatedly over a silica-gel column with elution by hexane—ethylacetate (200:1) to give a mixture of **5b** and **3b** in a 3:1 (**5b**:**3b**) ratio. IR spectrum (ν, cm^{-1}): 1725 (C=O). ^1H NMR spectrum (CD_2Cl_2, δ, ppm, J/Hz): for **5b**: 0.72 (s, 18-Me), 0.96 (d, J = 6.5, 21-Me), 1.05 (s, 19-Me), 4.36 (d, J = 6, H-7β), 4.40-4.62 (m, H-3α); for **3b**: 0.66 (s, 18-Me), 0.92 (d, J = 6.5, 21-Me), 1.01 (19-Me), 4.40-4.62 (m, H-3α).

B. A heated (40°C) solution of **3b** (1.5 g) in the mixture of glacial acetic acid (30 mL) and dichloroethane (10 mL) was stirred, treated with bromine (0.35 mL) and aqueous hydrobromic acid (0.2 mL, 40%), stirred at 43-45°C for 7 h, cooled to room temperature, left for 19 h, stirred, treated with sodium sulfite (2 M) until it became colorless, and poured into water. The organic layer was separated. The aqueous layer was extracted with dichloroethane. The combined organic extract was washed with water, sodium carbonate (5%), and water and evaporated in a rotary evaporator. The solid was chromatographed over a silica-gel column with elution by petroleum ether—ethylacetate (120:1) to give **5b**, 1.38 g, 79%, mp 147-150°C (dec.) (petroleum ether). IR spectrum (ν, cm^{-1}): 1725 (C=O). ^1H NMR spectrum (CD_2Cl_2, δ, ppm, J/Hz): 0.72 (s, 18-Me), 0.88 (6H, d, J = 6.5, 26/27-Me), 0.94 (d, J = 6, 21-Me), 1.04 (s, 19-Me), 4.36 (d, J = 6, H-7α), 4.58 (m, H-3α).

Dehydrohalogenation of 5a. A solution of **5a** (4.2 g) in DMF (30 mL) was treated with Li_2CO_3 (3.0 g) and LiBr (2.2 g), boiled under argon for 10 min, rapidly cooled to room temperature, and filtered through a layer of silica gel. The filtrate was diluted with water and extracted with hexane. The organic layer was thoroughly washed with water and evaporated in vacuum. The solid was chromatographed over a silica-gel column with elution by hexane:THF (120:1) to give **6a**, 0.84 g, 25%, mp 118-120°C (hexane). IR spectrum (ν, cm^{-1}): 1690 (C=O), 1645, 1570 (C=O), UV spectrum (λ_{max}, nm): 328 (ε 6200). ^1H NMR spectrum (CD_2Cl_2, δ, ppm, J/Hz): 0.74 (3H, s, 18-Me), 0.93 (3H, d, J = 6.5, 21-Me), 0.99 (3H, s, 19-Me), 4.20 (1H, d, J = 3, H-7β), 6.11 (2H, m, W/2 = 9, H-2, H-3), 6.83 (1H, m, W/2 = 9, H-4).

Continued elution by hexane:THF (90:1) gave **7a**, 0.60 g, 21%, mp 105-106°C (acetone) (lit. [8] mp 116-118°C). IR spectrum (ν, cm^{-1}): 1690 (C=O), 1560, 1640 (C=C). UV spectrum (λ_{max}, nm): 234 (ε 2800), 316 (ε 10900). ^1H NMR spectrum (CD_2Cl_2, δ, ppm, J/Hz): 0.72 (3H, s, 18-Me), 0.97 (3H, d, J = 6.5, 21-Me), 1.00 (3H, s, 19-Me), 6.07 (2H, m, W/2 = 8, H-2, H-3), 6.76 (1H, br.t, J = 3, H-4).

Further elution by hexane:THF (4:1) gave **8a**, 0.71 g, 23%, mp 153-154°C (dec.) (hexane). IR spectrum (ν, cm^{-1}): 3440, 3220 (OH), 1665 (C=O), 1640, 1620, 1560 (C=C), 865 (O–O). UV spectrum (λ_{max}, nm): 270 (ε 9600), 335 (ε 9800). ^1H NMR spectrum (C_5D_5N, δ, ppm, J/Hz): 0.82 (3H, s, 18-Me), 0.88 (3H, d, J = 6.5, 21-Me), 1.00 (3H, s, 19-Me), 2.80 (1H, m, W/2 = 22, H-9α), 5.92-6.04 (1H, m, H-2), 6.04-6.17 (1H, m, H-3), 6.56 (1H, d, J = 2, H-7), 7.20 (1H, d, J_1 = 5.5, J_2 = 1, H-4).

Dehydrohalogenation of 5b. A. A solution of **5b** and **3b** (2.3 g, 3:1) in DMF (30 mL) was treated with Li_2CO_3 (1.0 g) and LiBr (0.8 g), boiled under argon for 15 min, rapidly cooled to room temperature, and filtered through a layer of silica gel. The filtrate was diluted with water and extracted with hexane. The organic layer was thoroughly washed with water and evaporated in vacuo. The solid was treated with petroleum ether (20 mL) and left for three days at 0°C. The crystalline solid was filtered off, washed with petroleum ether, and dried in vacuum to give **8b**, 0.150 g, 13%, mp 155-156°C (dec.) (hexane). IR spectrum (ν, cm^{-1}): 3440, 3220 (OH), 1665 (C=O), 1640, 1620, 1560 (C=C), 865 (O–O). UV spectrum (λ_{max}, nm): 270 (ε 9600), 335 (ε 9800). ^1H NMR spectrum (C_5D_5N, δ, ppm, J/Hz): 0.82 (3H, s, 18-Me), 0.88 (3H, d, J = 6.5, 21-Me), 1.00 (3H, s, 19-Me), 2.80 (1H, m, W/2 = 22, H-9α), 5.92-6.04 (1H, m, H-2), 6.04-6.17 (1H, m, H-3), 6.56 (1H, d, J = 2, H-7), 7.20 (1H, d, J_1 = 5.5, J_2 = 1, H-4).

The mother liquor was evaporated in vacuo. The solid was placed on a silica-gel column and eluted by hexane:ethylacetate (120:1) to give **6b**, 0.36 g, 26%.

Continued elution by hexane:ethylacetate (60:1) gave **7b**, 0.61 g, mp 128-130°C (hexane) (lit. [8] mp 126-128°C). IR spectrum (ν, cm^{-1}): 1690 (C=O), 1640, 1560 (C=C). UV spectrum (λ_{max}, nm): 234 (ε, 2800), 316 (ε 10900). ^1H NMR spectrum (CD_2Cl_2, δ, ppm, J/Hz): 0.72 (3H, s, 18-Me), 0.97 (3H, d, J = 6.5, 21-Me), 1.00 (3H, s, 19-Me), 6.07 (2H, m, W/2 = 8, H-2, H-3), 6.76 (1H, br.t, J = 3, H-4).

B. A solution of **5b** (1.07 g) in DMF (30 mL) was treated with Li_2CO_3 (0.8 g) and LiBr (0.5 g), boiled under argon for 15 min, rapidly cooled to room temperature, and filtered through a layer of silica gel. The filtrate was diluted with water and extracted with hexane. The organic layer was thoroughly washed with water and evaporated in vacuum. The solid was treated with petroleum ether (10 mL) and left for one day at 0°C. The crystalline solid was filtered off, washed with petroleum ether, and dried in vacuo to give **8b**, 0.23 g, 30%.

The mother liquor was evaporated in vacuo. The solid was placed on a silica-gel column and eluted by

hexane:ethylacetate (120:1) to give **6b**, 0.31 g, 36%, mp 73-75°C (petroleum ether). IR spectrum (ν, cm^{-1}): 1685 (C=O), 1650, 1570 (C=C). UV spectrum (λ_{max}, nm): 320 (ε 6100). ^{1}H NMR spectrum (CD_2Cl_2, δ, ppm): 0.74 (3H, s, 18-Me), 0.87 (6H, d, J = 6.5, 26/27-Me), 0.93 (3H, d, J = 6, 21-Me), 0.99 (3H, s, 19-Me), 4.20 (1H, d, J = 3, H-7β), 6.11 (2H, m, W/2 = 9, H-2, H-3), 6.83 (1H, m, W/2 = 9, H-4).

Continued elution by hexane:ethylacetate (90:1) gave **7b**, 0.12 g, 17%.

Woodward Hydroxylation of 6a A heated (40°C) solution of **6a** (0.84 g) in the mixture of acetic acid (25 mL), THF (20 mL), and water (1 mL) was stirred, treated with silver acetate (0.70 g) and iodine (0.70 g), stirred at 40-45°C for 2 h 20 min, cooled to room temperature, and treated with sodium thiosulfate (2 M) until the iodine was neutralized. The solid was filtered off by a layer of silica gel. The filtrate was evaporated in vacuo to half its volume. The remainder was diluted with water and extracted with 1,2-dichloroethane. The organic layer was washed with water. The solvent was removed in vacuum. The solid was dissolved in benzene and evaporated in a rotary evaporator. The resulting oil was dissolved in the mixture of pyridine (4 mL) and acetic anhydride (2 mL), held at room temperature for 19 h, treated with water, and extracted with benzene. The benzene extract was washed with water and evaporated in a rotary evaporator. The solid was chromatographed over a silica-gel column with elution by hexane:THF (15:1) to give amorphous **9**, 0.26 g, 22%. IR spectrum (film, ν, cm^{-1}): 1755, 1235 (AcO), 1720 (C=O), 1650 (C=C). UV spectrum (λ_{max}, nm): 242 (ε 9700). ^{1}H NMR spectrum (CD_2Cl_2, δ, ppm, J/Hz): 0.74 (3H, s, 18-Me), 0.96 (3H, d, J = 6.5, 21-Me), 1.06 (3H, s, 19-Me), 2.14 (3H, s, AcO), 2.80 (1H, dd, J_1 = 15.0, J_2 = 3.5, H-1α), 4.16 (1H, d, J = 3, H-7β), 4.10-4.20 (1H, m, H-2α), 5.51 (1H, dd, J_1 = 9, J_2 = 1.5, H-3β), 5.85 (1H, d, J = 1.5, H-4).

Elution by hexane:THF (10:1) gave an oily product (0.39 g) that was rechromatographed over a silica-gel column with elution by hexane:ethylacetate (15:1) to give **10**, 0.31 g, 30%. IR spectrum (film, ν, cm^{-1}): 1755, 1250, 1235 (AcO), 1715 (C=O), 1645 (C=C). UV spectrum (λ_{max}, nm): 240 (ε 9700). ^{1}H NMR spectrum (CD_2Cl_2, δ, ppm, J/Hz): 0.74 (3H, s, 18-Me), 0.96 (3H, d, J = 6.5, 21-Me), 1.09 (3H, s, 19-Me), 2.02 (3H, s, 2α-AcO), 2.08 (3H, s, 3α-AcO), 4.22 (1H, d, J = 3, H-7β), 5.09 (1H, dt, J_1 = 12, J_2 = 4, H-2β), 5.52 (1H, t, J_1 = 4.5, H-3β), 6.12 (1H, d, J = 5.5, H-4).

Woodward Hydroxylation of 8a. A solution of **8a** (0.39 g) in the mixture of acetic acid (40 mL) and THF (20 mL) at room temperature was stirred, treated successively with water (2 mL), silver acetate (0.29 g), and iodine (0.29 g), and stirred for 35 min at room temperature. The precipitate (AgI) was filtered off. The filtrate was evaporated in vacuum to half the volume. The remainder was diluted with water and extracted with benzene. The extract was washed with sodium thiosulfate (0.2 M) and water. The solvent was removed in vacuo. The solid was chromatographed over a silica-gel column with elution by hexane:ethylacetate (20:1) to give **11**, 0.12 g, 23%, mp 127-130°C (dec.) (hexane). IR spectrum (ν, cm^{-1}): 1760, 1225 (AcO), 1670 (C=O), 1640, 1620, 1590 (C=C). UV spectrum (λ_{max}, nm): 259 (ε 6600), 312 (ε 22300). ^{1}H NMR spectrum (CD_2Cl_2, δ, ppm, J/Hz): 0.88 (6H, d, J = 6.5, 26-Me, 27-Me), 0.92 (3H, s, 18-Me), 0.95 (3H, d, J = 6, 21-Me), 1.12 (3H, s, 19-Me), 2.13 (3H, s, AcO), 2.51 (1H, m, W/2 = 22, H-9α), 2.75 (1H, dd, J_1 = 15, J_2 = 3.5, H-1β), 4.09 (1H, ddd, J_1 = 14, J_2 = 9.5, J_3 = 3.5, H-2α), 5.62 (1H, dd, J_1 = 9.5, J_2 = 1.5, H-3β), 5.99 (1H, m, W/2 = 7, H-15), 6.13 (1H, d, J = 1.5, H-4), 6.24 (1H, d, J = 2.5, H-7).

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