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SYNTHESIS OF 2β,3β,14α-TRIHYDROXY-$\Delta^{4,7}$-6-KETOSTEROIDS AND THEIR DERIVATIVES

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A scheme using β-sitosterol as an example for synthesizing 2β,3β,14α-trihydroxy-$\Delta^{4,7}$-6-ketosteroids and their derivatives from 3β-hydroxy-Δ^{5}-steroids was developed.

Key words: synthesis, β-sitosterol, 2β,3β,14α-trihydroxy-$\Delta^{4,7}$-6-ketosteroids.

Ecdysteroids are a rather large group of natural compounds that have not only common biological activity as shedding and metamorphosis insect hormones but also similar structures [1, 2]. Despite the fact that the chemical structures of ecdysteroids are quite similar, separate groups of compounds among them with certain common structural fragments can be distinguished. Thus, compounds that contain the usual set of functional groups and an additional 4-double bond are clearly distinguished among the numerous natural ecdysteroids. For example, this type of ecdysteroids includes 4-dehydroecdysterone (**1**) [3], diaulusterol A (**2a**) and B (**2b**) [4], and acetylpinnasterol (**3**) [5, 6]. It should be noted that chemical syntheses of 4-dehydroecdysteroids are poorly developed. Only isolated studies have been reported [7-9] for the preparation of simple derivatives of 4,7-dien-6-ketosteroids that do not have the 2β,3β-diol group in their structure.

The goal of the present investigation was to develop a method for introducing into steroids the 2β,3β,14α-trihyhdroxy-4,7-dien-6-keto group, which is a characteristic structural fragment of the cyclic part of 4-dehydroecdysterone. Then, if successful, this system can be used to synthesize both 2α,3α-dihydroxy- and 2β,3α-dihydroxy-4,7-dien-6-ketosteroids, which include ecdysteroids (**2a-b**) and (**3**).

We selected β-sitosterol as the starting compound. It was converted by the previously developed method [10] in five steps into 5α-hydroxy-2,7-dien-6-one (**4**). *cis*-Hydroxylation of the more accessible 2-double bond in **4** with silver acetate and iodine in aqueous acetic acid (Woodward reaction) and subsequent acetylation produced two compounds. The structure of the main product (**5**), which was isolated in 48% yield, was established by spectral analysis. In particular, a strong absorption at 250 nm in the UV spectrum suggests that **5** contains a Δ^{7}-6-ketone.

An analogous conclusion is reached by examining the IR spectrum, which contains stretching vibrations of a 6-ketone and a 7-double bond conjugated to it at 1680 and 1630 cm^{-1}, respectively. Furthermore, the IR spectrum suggests that **5** has acetoxy groups. The ^{1}H NMR spectrum of **5** has a triplet at 5.68 ppm, which is characteristic of the H-7 vinyl proton and lacks signals for H-2 and H-3 vinyl protons, which were present in the spectrum of **4**. Instead of them, the spectrum of **5** exhibits signals for methine protons H-2 and H-3, which are geminal to the acetoxy groups, with δ 5.33 and 5.28, respectively. The half-width of these signals (W/2 = 3.5 and 20 Hz) indicates axial and equatorial orientations of the acetoxy groups, respectively. Of the two most probable structures, the 2β,3β structure is favored over the 2α,3α structure based on literature data for similar compounds that are *cis*-hydroxylated using the Woodward reaction [11, 12].

The second product of the reaction is a 3α-acetoxy-2α,5α epoxysteroid (**6**) that is isolated in 31% yield. Its structure was proven by us using spectral analysis. The similarity in the ^{1}H NMR spectra of **6** and the analogous derivative without a 7-double bond that was previously reported [12] was especially useful. Judging from the literature [12], compounds like **6** are typically formed via *cis*-hydroxylation of a Δ^{2}-bond in steroids containing an additional 5α-hydroxyl. A possible explanation for their formation was also presented, which enables us to move on without discussing the details.

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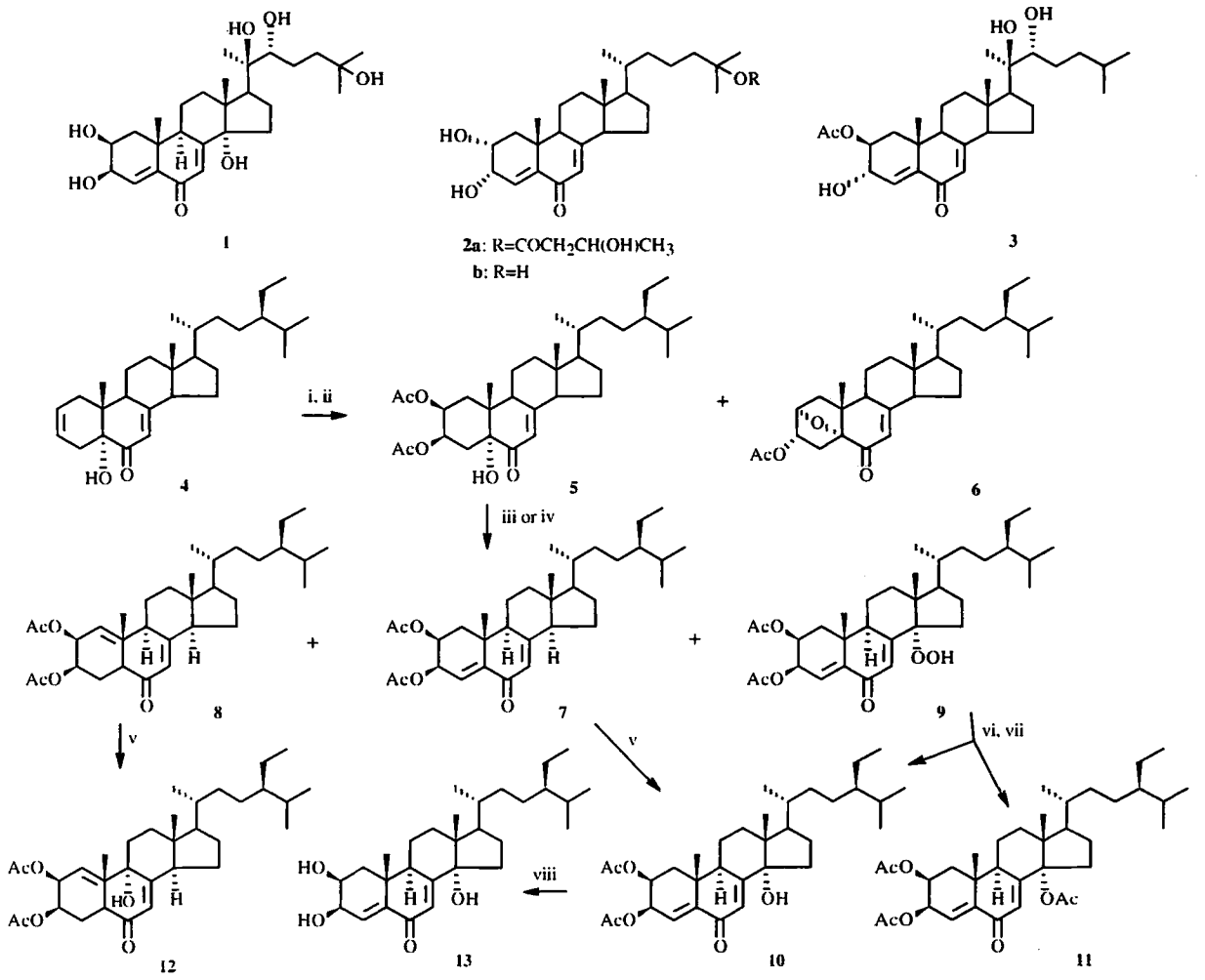

i: AcOAg, I_2, aq AcOH; ii: Ac_2O, Py; iii: $SOCl_2$, Py; iv: MsCl, SO_2, DMF, Py; v: SeO_2, dioxane; vi: NaI, AcOH; vii: Ac_2O, Py, DMAP; viii: R_2CO_3, MeOH

Next, **5** was dehydrated by thionylchloride in pyridine to introduce the required 4-double bond. As it turned out, the 1(10),7-dien-6-one (**8**) and 14α-hydroperoxide (**9**), which were isolated in 7 and 51% yield, respectively, were produced along with the desired 4,7-dien-6-one (**7**), which was obtained in 18% yield. Dehydration of **5** by methanesulfonylchloride and SO_2 in a mixture of pyridine and DMF under carefully controlled conditions produced **7** and **8** in yields of 38 and 28%, respectively.

The structures of **7-9** were proven using spectral data. Thus, the mass spectrum of **7** lacks a peak for the molecular ion. The peak with the highest mass has *m/z* 466. It forms by loss from the molecular ion of acetic acid. A strong absorption band in the UV spectrum at 264 nm indicates that **7** has the 4,7-dien-6-one structure [7]. This same conclusion is reached by examining the ^{1}H NMR spectrum, which contains characteristic signals for vinyl protons, a doublet for H-4 (δ 6.22 ppm) and a triplet for H-7 (δ 5.82 ppm).

The mass spectra suggest that the second product from dehydration (**8**) is an isomer of the 4,7-dien-6-one (**7**). The UV spectrum of **8** contains an absorption band at 242 nm, which excludes the 4-position for the newly formed double bond. The structure of **8** as a Δ^7-6-ketone is confirmed by the ^{1}H NMR spectrum, which contains a signal characteristic of the vinyl proton H-7 with δ 5.71 ppm. Furthermore, the spectrum contains yet another signal for a vinyl proton as a doublet with δ 5.60 ppm and splitting constant J = 4.5 Hz.

Use of double resonance established that the splitting is caused by a vicinal coupling to the methine proton with δ 5.41 ppm, which in turn is geminal to the 2β-acetoxy group. Because **8** is not a 4,7-dien-6-one, it can be assigned only as a

1(10),7-dien-6-one. This is possible if **8** results from a Westphalen—Lettre rearrangement [13]. This is also consistent with the magnitude of the chemical shift of the 5β-methyl group (δ 1.46 ppm) in the ^{1}H NMR of **8**. The position of this signal at weak field agrees well with literature data for the Westphalen—Lettre rearrangement products [14]. It is noteworthy that these compounds usually have a tetrasubstituted 9(10)-double bond. Apparently the simultaneous presence in our case of 7- and 9(10)-double bonds and a 6-ketone would thoroughly flatten ring *B*, which makes this position for the additional double bond unfavorable.

The third compound isolated from dehydration of the 5α-hydroxy-6-ketone (**5**) by thionylchloride has the 4,7-dien-6-one (**9**) structure according to the UV spectrum, which contains an absorption band at 258 nm. This is confirmed by signals in the ^{1}H NMR spectrum for vinyl protons H-4 (δ 6.21 ppm) and H-7 (δ 6.04 ppm). The large shift to weak field of the H-7 signal compared with its position in the spectrum of **7** is interesting. This change may be caused by an electron-accepting substituent on C-14 in **9**, for example, a hydroxyl. Because the H-7 signal appears as a doublet, it can be assumed that it experiences allyl coupling with only one proton. In fact, application of double resonance established that the splitting of the H-7 signal into a doublet is caused by allylic coupling to the methine proton with δ 2.84 ppm, which can therefore be assigned as the resonance of H-9α.

Direct comparison of **9** with the previously prepared 14α-hyhdroxy-4,7-dien-6-ketone (**10**) showed that they are not identical. Therefore, it was assumed that **9** has the 14α-hydroperoxide structure. In fact, it turned out that **9** gives a qualitative reaction for peroxide with KI. Very important data were obtained from analysis of the ^{13}C NMR spectrum. The position of the signal for C-14 at δ 96.4 ppm is interesting. Such a chemical shift for C-14 is highly characteristic of spectra of 14α-hydroperoxy-Δ^7-6-ketosteroids [15]. We note that the formation of this type of compounds via auto-oxidation of Δ^7-6-ketosteroids is rather common [15]. We found that **9** also accumulates if solutions of **7** are stored.

The 14α-hydroxyl was introduced in the next step via allylic hydroxylation of **7** by selenium dioxide in dioxane. This produced in 51% yield the corresponding 14α-hydroxyl derivative (**10**). The structure of **10** was proven using ^{1}H NMR spectra. In particular, the presence of a 14α-hydroxyl was confirmed by the shift to weak field (δ 6.01 ppm) of the signal for vinyl proton H-7. Furthermore, this signal appears not as a triplet, like in the starting steroid (**7**), but as a doublet with splitting constant J = 1.5 Hz that is due to allylic coupling to only one proton (H-9α). Furthermore, the presence of the 14α-hydroxyl in **10** shifts the signal of the H-9α methine proton that is situated 1,3-diaxially to it to δ 2.93 ppm.

We also found that **10** can be prepared in 32% yield via reduction of **9** by NaI in acetic acid. We used acetylation by acetic anhydride in pyridine with 4-dimethylaminopyridine to simplify the separation of products in this synthesis. Thus, the second compound, isolated in 25% yield, is the 2β,3β,14α-triacetate (**11**). The presence of signals in the ^{1}H NMR for the three acetoxy groups at 1.95, 2.06, and 2.08 ppm is very important for proving the structure of **11**. Furthermore, the signal for H-9α shifts slightly to weak field compared with its position in the spectrum of the 14α-alcohol (**10**).

The reaction of 1(10),7-dien-6-one (**8**) with selenium dioxide in dioxane produced the 9α-hydroxyderivative (**12**) in 44% yield. The UV spectrum of **12** has an absorption band at 240 nm, which is characteristic of Δ^7-6-ketosteroids. Of the two possible allylic positions for the hydroxy group, i.e., 9α or 14α, the former is favored based on the shift to weak field to δ 6.16 ppm for H-1 in the ^{1}H NMR spectrum compared with its position in the spectrum of the starting compound **8**. These chemical shifts for the vinylic protons are characteristic of the spectra of allylic alcohols.

The signal for the vinyl proton H-7 in the ^{1}H NMR spectrum of **12** appears as a doublet at δ 5.68 ppm with splitting constant J = 1.5 Hz. Double resonance showed that the splitting of this signal is due to allylic coupling with the proton that resonates as a complicated multiplet at δ 3.02 ppm. Therefore, the latter should be assigned to absorption of the allylic proton H-14α.

The final synthesis step was hydrolysis of **10** by K_2CO_3 in CH_3OH to give 2β,3β,14α-trihydroxy-4,7-dien-6-one (**13**) in 46% yield. The cyclic part of this compound contains a set of functional groups that is characteristic of a 4-dehydroecdysterone (**1**). The ^{1}H NMR spectrum of **13** agrees well with analogous data reported in the literature [3] for 4-dehydroecdysterone (**1**).

Thus, the reaction sequence developed by us makes it possible to introduce into the cyclic portion of steroids the 2β,3β,14α-trihydroxy-4,7-dien-6-ketone group. The reactions can be used to synthesize 4-dehydroecdysteroids.

EXPERIMENTAL

Melting points were determined on a Kofler block. IR spectra were recorded on a UR-20 instrument in the range 700-3600 cm^{-1} in KBr pellets. UV spectra of ethanol solutions were taken on a Spekord M-400 instrument. ^1H and ^{13}C NMR spectra of solutions in $CDCl_3$ (unless specifically stated) were obtained on a Bruker AC-200 NMR spectrometer at 200 and 50 MHz, respectively. Chemical shifts are given relative to TMS as an internal standard. Mass spectra (electron-impact) were recorded on a Shimadzu QP-5000 instrument at ionization-electron energy 70 eV.

***cis*-Hydroxylation (Woodward) of (24R)-5-Hydroxy-5α-stigmasta-2,7-dien-6-one (4).** A solution of hydroxydienone (**4**, 0.31 g) (prepared by the literature method [10]), silver acetate (0.37 g), and water (0.2 ml) in glacial acetic acid (30 ml) was heated to 60 C under an Ar stream and treated over 3 h with several portions of iodine (0.33 g) in acetic acid (10 ml). The solution was cooled to 25 C. The precipitate of AgI was filtered off. The filtrate was treated with $CHCl_3$ (50 ml), washed with water (2×35 ml), saturated Na_2CO_3 (2×20 ml), and water (2×20 ml), and dried over $MgSO_4$. The desiccant was filtered off. The filtrate was evaporated under vacuum. The solid was dissolved in a mixture of pyridine (4 ml) and acetic anhydride (1 ml). After 17 h the solution was evaporated under vacuum. The residual solvent was removed by evaporation with toluene. The solid was chromatographed on a silica-gel column with elution by a mixture of cyclohexane and ethylacetate of increasing polarity (from 15:1 to 2:1). Two fractions were obtained.

Fraction 1: (24R)-2α,5-epoxy-3α-acetoxy-5α-stigmast-7-en-6-one (**6**), yield 0.11 g (31%), mp 184-187 C (dec.) (hexane—ethylacetate). IR spectrum (ν, cm^{-1}): 1740 (AcO), 1670 (C=O), 1630 (C=C). UV spectrum (λ_{max}, nm): 253 (ε 11,000). ^1H NMR spectrum (δ, ppm): 0.64 (18-Me, s), 0.95 (21-Me, d, J = 5.5 Hz), 1.03 (19-Me, s), 2.07 (AcO, s), 4.60 (H-2β, d, J = 6.5 Hz), 4.76 (H-3β, dd, J_1 = 2.5 Hz, J_2 = 7 Hz), 5.91 (H-7, t, J = 2 Hz).

Fraction 2: (24R)-2β,3β-diacetoxy-5-hydroxy-5α-stigmast-7-en-6-one (**5**), yield 0.19 g (48%), mp 155-165 C (ether—hexane). IR spectrum (ν, cm^{-1}): 1760, 1730, 1260, 1240 (AcO), 1700, 1680 (C=O), 1630 (C=C). UV spectrum (λ_{max}, nm): 250 (ε 11,000). ^1H NMR spectrum (δ, ppm): 0.58 (18-Me, s), 0.94 (21-Me, d, J = 5.0 Hz), 1.08 (19-Me, s), 2.02 (AcO, s), 2.08 (AcO, s), 5.28 (H-3α, m, W/2 = 20 Hz), 5.33 (H-2α, m, W/2 = 8.5 Hz), 5.68 (H-7, t, J = 2 Hz).

Dehydration of (24R)-2β,3β-Diacetoxy-5-hydroxy-5α-stigmast-7-en-6-one (5). A. A solution of **5** (0.2 g) in pyridine (5 ml) cooled to -19 C was treated with thionylchloride (0.16 ml). Water (5 ml) was added after 10 ml. The resulting mixture was extracted with ethylacetate (3×10 ml). The extracts were washed with HCl (2 N, 3×30 ml) and water (1×10 ml) and dried over $MgSO_4$. The desiccant was filtered off. The filtrate was evaporated under vacuum. The solid was chromatographed on a silica-gel column with elution by a mixture of hexane and ethylacetate of increasing polarity (from 10:1 to 2:1). Three fractions were obtained.

Fraction 1: (24R)-2β,3β-diacetoxy-5-methyl-19-nor-5β-stigmasta-1(10),7-dien-6-one (**8**), yield 0.013 g (7%), mp 158-162 C (methanol). IR spectrum (ν, cm^{-1}): 1760, 1270, 1240 (AcO), 1690, 1670 (C=O), 1650 (C=C). UV spectrum (λ_{max}, nm): 206 (ε 8400), 242 (ε 10,000). ^1H NMR spectrum (δ, ppm): 0.66 (18-Me, s), 1.46 (19-Me, s), 2.06 (AcO, s), 2.09 (AcO, s), 5.07 (H-3α, m, W/2 = 15 Hz), 5.41 (H-2α, t, J = 3.5 Hz), 5.60 (H-1, d, J = 4.5 Hz), 5.71 (H-7, br. s, W/2 = 4 Hz). Mass spectrum, *m/z* (%): 466 (0.6) (M^+ - AcOH), 424 (13) (446 - CH_2CO), 406 (5) (M^+ - 2AcOH), 265 (8) (M^+ - AcOH - side chain), 43 (100).

Fraction 2: (24R)-2β,3β-diacetoxystigmasta-4,7-dien-6-one (**7**), yield 0.035 g (18%), mp 142-145 C (methanol). IR spectrum (ν, cm^{-1}): 1760, 1260, 1230 (AcO), 1690 (C=O), 1650 (C=C). UV spectrum (λ_{max}, nm): 264 (ε 12,900). ^1H NMR spectrum (δ, ppm): 0.64 (18-Me, s), 1.23 (19-Me, s), 2.06 (AcO, s), 2.08 (AcO, s), 5.23 (H-2α, m, W/2 = 16 Hz), 5.54 (H-2α, m, W/2 = 9 Hz), 5.82 (H-7, t, J = 2 Hz), 6.22 (H-4, d, J = 4 Hz). Mass spectrum, *m/z* (%): 466 (0.6) (M^+ - AcOH), 424 (7) (M^+ - AcOH - CH_2CO), 406 (6), 406 (1) (M^+ - 2AcOH), 265 (1) (M^+ - 2 AcOH - side chain), 43 (100).

Fraction 3: (24R)-2β,3β-diacetoxy-14α-hydroperoxystigmasta-4,7-dien-6-one (**9**), yield 0.105 g (51%), mp 144-148 C (methanol). IR spectrum (ν, cm^{-1}): 1755, 1250, 1240 (AcO), 1685 (C=O), 1640 (C=C). UV spectrum (λ_{max}, nm): 258 (ε 9400). ^1H NMR spectrum (δ, ppm): 0.77 (18-Me, s), 1.24 (19-Me, s), 2.05 (AcO, s), 2.06 (AcO, s), 2.84 (H-9α, m, W/2 = 20 Hz), 5.26 (H-2α, m, W/2 = 12 Hz), 5.52 (H-3α, t, J = 3.5 Hz), 6.04 (H-7, d, J = 2 Hz), 6.21 (H-4, d, J = 3.5 Hz). ^{13}C NMR spectrum (δ, ppm): 66.9 (C-2), 67.1 (C-3), 127.5 (C-4), 146.5 (C-5), 189.0 (C-6), 124.6 (C-7), 162.2 (C-8), 96.4 (C-14).

B. A solution of **5** (0.15 g) in pyridine (1 ml) and DMF (3 ml) at 0 C was treated with methanesulfonylchloride (0.17 ml) containing 9% anhydrous SO_2. The mixture was diluted after 1 h 15 min with water (10 ml) and extracted with ethylacetate (3×5 ml). The extracts were washed successively with water (1×10 ml), HCl (2 N, 2×5 ml), and water (1×5 ml) and evaporated under vacuum. Traces of solvent were removed by evaporation with benzene. The solid was chromatographed on a silica-gel column and eluted with a mixture of cyclohexane and ethylacetate of increasing polarity (from 10:1 to 7:1). Two

fractions were obtained.

Fraction 1: (24R)-2β,3β-diacetoxy-5-methyl-19-nor-5β-stigmasta-1(10),7-dien-6-one (**8**), yield 0.041 g (28%).

Fraction 2: (24R)-2β,3β-diacetoxystigmasta-4,7-dien-6-one (**7**), yield 0.055 g (38%).

(24R)-2β,3β-Diacetoxy-14α-hydroxystigmasta-4,7-dien-6-one (10). A solution of **7** (0.070 g) in dioxane (10 ml) was treated with stirring with selenium dioxide (0.050 g) and four drops of water. The mixture was heated for 1 h at 60-65 C and another 2.5 h at 65-70 C and cooled to room temperature. The precipitated selenium was filtered off through a layer of silica gel. The filtrate was treated with ethylacetate (40 ml) and washed successively with water (3×10 ml), saturated Na_2SO_4 (4×5 ml), and water (2×10 ml). The ethylacetate was evaporated under vacuum. The solid was separated by preparative TLC on silica-gel plates with elution by a mixture of cyclohexane and ethylacetate (3:1). Yield 0.037 g (51%) of the 14α-hydroxyderivative of **10**. ^{1}H NMR spectrum (δ, ppm): 0.71 (18-Me, s), 0.94 (21-Me, d, J = 6.5 Hz), 1.22 (19-Me, s), 2.05 (AcO, s), 2.07 (AcO, s), 2.93 (H-9α, m, W/2 = 22 Hz), 5.25 (H-2α, m, W/2 = 13 Hz), 5.57 (H-3α, t, J = 3.5 Hz), 6.01 (H-7, d, J = 1.5 Hz), 6.21 (H-4, d, J = 3.5 Hz).

Reduction of 14α-Hydroperoxide (9). A solution of **9** (0.086 g) in glacial acetic acid (3 ml) was treated with NaI (0.023 g) in glacial acetic acid (2 ml). After 2 min the reaction mixture was treated with water (20 ml) and extracted with ethylacetate (2×10 ml). The organic layer was washed successively with water (10 ml), 5% $NaHCO_3$ (8×10 ml), 5% sodium thiosulfate and water (2×10 ml). The solution was diluted with toluene and evaporated under vacuum. The solid was dissolved in a mixture of pyridine (1.5 ml) and acetic anhydride (1 ml) and treated with 4-dimethylaminopyridine (2 mg). The reaction mixture was evaporated under vacuum after seven days. The solid was chromatographed on a silica-gel column with elution by a mixture of cyclohexane and ethylacetate of increasing polarity (from 6:1 to 3:1). Two fractions were obtained.

Fraction 1: (24R)-2β,3β-14α-triacetoxystigmasta-4,7-dien-6-one (**11**), yield 0.022 g (25%) (amorph.). UV spectrum (λ_{max}, nm): 256.5 (ε 6400). ^{1}H NMR spectrum (δ, ppm): 0.81 (18-Me, s), 1.25 (19-Me, s), 1.95 (AcO, s), 2.06 (AcO, s), 2.08 (AcO, s), 2.99 (H-9α, m, W/2 = 22 Hz), 5.30 (H-2α, m, W/2 = 16 Hz), 5.58 (H-3α, t, W/2 = 9 Hz), 6.04 (H-7, d, J = 2 Hz), 6.27 (H-4, d, J = 3.5 Hz)..

Fraction 2: (24R)-2β,3β-diacetoxy-14α-hydroxystigmasta-4,7-dien-6-one (**10**). Yield 0.026 g (32%).

(24R)-2β,3β-Diacetoxy-9α-hydroxy-5-methyl-19-nor-5β-stigmasta-1(10),7-dien-6-one (12). A solution of **8** (0.0615 g) in dioxane (10 ml) was treated with stirring with selenium dioxide (0.045 g) and four drops of water and heated at 80-85 C for 6 h. The precipitated selenium was filtered off through a layer of silica gel. The filtrate was diluted with ethylacetate and washed successively with water (2×10 ml), saturated Na_2SO_4 solution (4×5 ml), and water (2×10 ml) and evaporated under vacuum. Residual solvent was removed by evaporation with benzene. The solid was separated by preparative TLC on silica-gel plates with elution by a mixture of cyclohexane and ethylacetate (3:1). Yield of **12** 0.028 g (44%) (amorph.). UV spectrum (λ_{max}, nm): 210.0 (ε 6900), 240 (ε 9000). ^{1}H NMR spectrum (δ, ppm): 0.65 (18-Me, s), 0.94 (21-Me, d, J = 6.0 Hz), 1.50 (19-Me, s), 2.05 (AcO, s), 2.07 (AcO, s), 3.02 (H-14α, m, W/2 = 21 Hz), 5.12 (H-2α, m, W/2 = 15 Hz), 5.43 (H-3α, t, J = 3.5 Hz), 5.68 (H-7, d, J = 1.5 Hz), 6.16 (H-1, d, J = 4.0 Hz).

(24R)-2β,3β,14α-Trihydroxystigmasta-4,7-dien-6-one (13). A solution of **10** (0.064 g) in methanol (10 ml) was treated with stirring with K_2CO_3 (0.098 g). After 2 h 15 min the K_2CO_3 was neutralized with glacial acetic acid (0.081 ml). The reaction mixture was evaporated under vacuum. The solid was chromatographed on a silica-gel column with elution by a mixture of cyclohexane and ethylacetate of increasing polarity (from 2:1 to 1:2). Yield of triol **13**, 0.025 g (46%), mp 221-223 C ($CHCl_3$). UV spectrum (λ_{max}, nm): 259 (ε 12,700). ^{1}H NMR spectrum ($CDCl_3$—CD_3OD, 2:1, δ, ppm): 0.72 (18-Me, s), 0.95 (21-Me, d, J = 6.0 Hz), 1.23 (19-Me, s), 2.91 (H-9α, m, W/2 = 21 Hz), 3.95 (H-2α, m, W/2 = 19 Hz), 4.22 (H-3α, t, J = 3.5 Hz), 6.00 (H-7, d, J = 2 Hz), 6.27 (H-4, d, J = 4.0 Hz).

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