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SYNTHESIS OF 6-CHLORONICOTINATES OF STEROIDAL 3β,5α,6β-TRIOLS AND 3β,5-DIHYDROXY-6-KETONES

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New esters of 3β,5α,6β-trihydroxysteroids and 3β,5-dihydroxy-6-ketosteroids containing 6-chloropyridine groups characteristic of the alkaloid epibatidine were synthesized by acylation with 6-chloronicotinoylchloride.

Key words: 3β,5α,6β-trihydroxysteroids, 3β,5-dihydroxy-6-ketosteroids, 6-chloronicotinates, 6-chloronicotinoylchloride, synthesis.

Steroids with C_{27}-C_{29}-sterol skeletons and 3β,5α,6β-triol or 3β,5-dihydroxy-6-ketone groups are interesting as biologically active compounds. These triols and dihydroxyketones have in several instances been identified in plants [1]. It was recently found that some of these compounds have pronounced insecticidal activity [2]. We hypothesized that the insecticidal activity of these steroids can be increased significantly by adding α-chloropyridine rings to their molecules. This group is a biologically important structural element of several effective modern insecticides such as imidacloprid, thiacloprid, nitenpyram, and acetamiprid, which are neonicotinoids [3]. It is also noteworthy that the 6-chloropyridine group occurs in the natural analgesic epibatidine, which was isolated from the Ecuadorian frog *Epipedobates tricolor* [4]. Furthermore, the literature suggests that compounds containing a pyridine ring occur among phytoecdysteroids, which are structurally related to the aforementioned compounds [5].

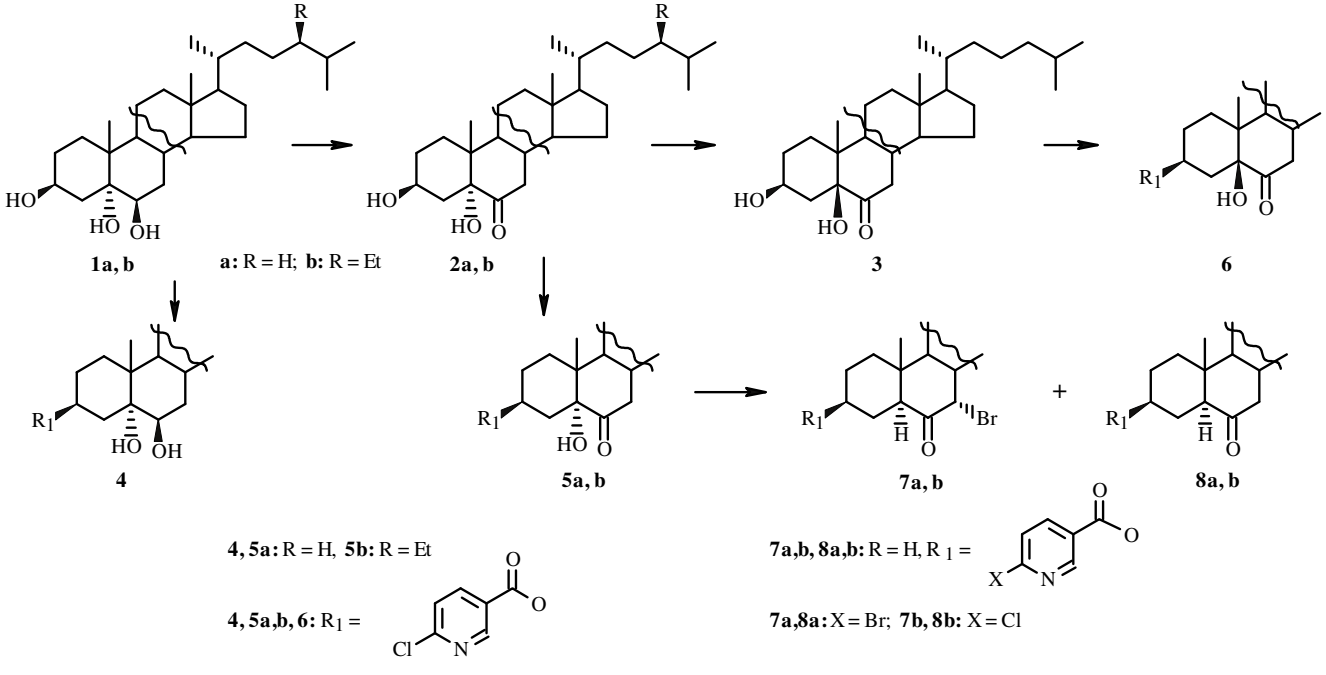

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TABLE 1. Chemical Shifts of C Atoms ($CDCl_3$, δ, ppm) in ^{13}C NMR Spectra of **5a–b**, **7a–b**, and **8a–b**

C atom	**5a**	**5b**	**7a–b***	**8a–b***
1	32.560	32.545	36.072	36.330
2	26.309	26.310	26.738	26.174
3	72.476	72.514	74.081 (74.046)	74.547 (74.509)
4	29.502	29.500	25.920	26.853
5	80.463	80.442	49.867	56.667
6	212.201	212.287	203.789	210.273
7	41.739	41.751	58.483	46.646
8	37.317	37.322	40.175	37.938
9	44.282	44.268	45.852	53.778
10	43.117	43.115	41.294	40.976
11	21.371	21.366	20.882	21.487
12	39.449	39.513	38.627	39.413
13	42.546	42.556	42.658	42.980
14	56.279	56.276	52.222	556.418
15	23.921	23.925	22.761	23.996
16	28.077	28.093	27.809	28.010
17	56.166	56.054	55.701	56.084
18	12.015	11.960	12.390	12.018
19	14.013	14.008	12.699	13.099
20	35.749	36.101	35.672	35.694
21	18.618	18.687	18.639	18.636
22	36.091	33.813	36.027	36.067
23	23.921	26.101	23.756	23.799
24	39.530	45.729	39.448	39.453
25	28.010	29.070	28.020	28.010
26	22.562	18.687	22.559	22.557
27	22.818	19.828	22.828	22.821
28		23.021		
29		12.013		
-O-C=O	164.170	164.190	163.938 (163.786)	164.003 (163.851)
Cl-Py	124.144 (CH), 125.237 (C), 139.595 (CH), 151.165 (CH), 155.677 (C)	124.154 (CH), 125.245 (C), 139.598 (CH), 151.168 (CH), 155.682 (C)	124.136 (CH), 125.635 (125.309) (C), 128.002 (CH), 139.181 (139.600) (CH), 146.768 (C), 151.413 (151.170) (CH), 157.961 (155.615) (C)	124.108 (CH), 125.709 (125.383) (C), 127.974 (CH), 139.151 (139.567) (CH), 146.716 (C), 151.428 (151.182) (CH), 155.569 (C)

*Data for 6-chloronicotinates **7b** and **8b** are given in parentheses.

We performed one of the possible chemical transformations of steroidal 3β,5α,6β-triols **1** and 3β-5-dihydroxy-6-ketones **2** and **3** with the goal of adding to them an α-chloropyridine ring. The transformation consisted of preparing the esters of these compounds with 6-chloronicotinic acid. 6-Chloronicotinoylchloride that was needed to add 6-chloronicotinic acid to **1**-**3** was prepared in high yield by reacting 6-methoxynicotinic acid and thionylchloride in refluxing DMF.

Subsequent acylation of 3β,5α,6β-triol **1a** by an equimolar amount of 6-chloronicotinoylchloride in refluxing toluene in the presence of 4-dimethylaminopyridine produced in >70% yield the mono-6-chloronicotinate. The structure of the product was established using PMR spectra. Thus, resonances of protons of the steroidal part and the 6-chloronicotinoic acid in a 1:1 ratio in the spectra established that the molecule contained both these groups. In this instance, two structural isomers of the ester as the 3- or 6-(6-chloronicotinate) were possible in principle. The structure of the product from monoacylation of triol **1a** was 3-(6-chloronicotinate) (**4**) according to the chemical shift of axial proton H-3α, which appeared in the PMR spectrum in deuteropyridine as a broad multiplet with δ 6.13 ppm. This unambiguously indicated that this proton was geminal to the ester group.

Monoacylation of 5-hydroxy-6-ketosteroids **2a**-**b** and **3** by 6-chloronicotinoylchloride in toluene in the presence of 4-dimethylaminopyridine produced in high yields the corresponding 3-(6-chloronicotinates) **5a**-**b** and **6**, respectively. The structures of these compounds were proved unambiguously by PMR spectra in which resonances of all characteristic protons occurred in the expected ranges. The structures of **5a**-**b** were also confirmed by ^{13}C NMR spectra (Table 1).

We attempted to add a 7(8)-double bond to the synthesized 6-chloronicotinate of 3β,5α-dihydroxy-6-ketone **5a**. We planned to add the group characteristic of ecdysteroids through bromination of the α-position to the 6-ketone with subsequent dehydrobromination. The reaction of **5a** with Br_2 and HBr in the presence of LiBr in CH_3CO_2H:$CHCl_3$ was rather complicated. Under these conditions, not only the steroid but also the pyridine group of the starting compound underwent reactions. We isolated 7α-bromo-6-ketones **7** and 6-ketosteroids **8** as corresponding mixtures of 6-bromo- and 6-chloronicotinates from the products. Despite several attempts, mixtures of **7a**-**b** and **8a**-**b** could not be separated into pure components.

The structures of these compounds were established using PMR and ^{13}C NMR spectra. In particular, the presence in the PMR spectra of **7a**-**b** of a characteristic doublet at δ 4.21 ppm, which corresponded to resonance of methine proton H-7β geminal to the Br atom, was interesting. It was also important for proving the structure that the resonance of methine proton H-3α (δ 5.33 ppm) in the PMR spectrum of starting steroid **5a** was shifted to weak field compared with the position of the resonance for the analogous proton in the spectra of **7a**-**b** (δ 5.01 ppm). This occurred because of the 5α-hydroxy group in the 1,3-diaxial orientation relative to H-3α in **5a**. These data led to the conclusion that **7a**-**b** lacked a 5α-hydroxy group. This was also confirmed by the fact that the resonances of C-5, C-6, and C-7 in ^{13}C NMR spectra had chemical shifts characteristic of 7α-bromo-6-ketosteroids without 5α-hydroxy groups [6].

The structures of **8a**-**b** were proved analogously using PMR and ^{13}C NMR spectra. The ^{13}C NMR spectra in which the chemical shifts of C-5, C-6, and C-7 suggest that these compounds contain a saturated 6-ketone and lack any functional groups on C-5 and C-7 are interesting.

The formation of **7a**-**b** and **8a**-**b** by the action on **5a** of the Br_2:HBr mixture in pyridine is not unexpected. First, it is noteworthy that the axial 5α-hydroxy group in **5a** hinders significantly bromination at the α-position to the 6-ketone on C-7 to form the 5α-hydroxy-7α-bromo-6-ketone. Therefore, the more active reagent in this instance was the HBr. We hypothesized that it caused both reduction of the 5α-hydroxy group to 6-ketosteroids **8a**-**b** and nucleophilic substitution by an S_N2 mechanism to form **7a**-**b**.

Thus, methods for synthesizing new derivatives of steroidal 3β,5α,6β-triols and 3β-5-dihydroxy-6-ketones that contained an added 6-chloronicotinic acid were developed. Biological activity of the synthesized compounds will be reported separately.

EXPERIMENTAL

Melting points were determined on a Kofler block. IR spectra in KBr disks were recorded on a UR-20 instrument at 700-3600 cm^{-1}. PMR and ^{13}C NMR spectra in deuterated solvents were obtained on a Bruker Avance 500 NMR spectrometer (operating frequency 500.13 MHz for ^1H and 125.75 MHz for ^{13}C). Chemical shifts are given relative to TMS (internal standard). The course of reactions and purity of products were monitored using Merck Kieselgel $60F_{254}$ plates.

6-Chloroniccotinoylchloride. A suspension of 6-methoxynicotinic acid (15.31 g, 0.1 mol) in thionylchloride (44 mL, 0.6 mol) was refluxed for 2 h, treated over 30 min with DMF (7.71 mL, 0.1 mol), and refluxed for another 3 h. When the reaction was finished, residual thionylchloride and DMF were distilled at reduced pressure (water aspirator) from the reaction flask with heating in an oil bath at from 20 to 80°C. The product was slowly distilled in vacuo (0.5-1.0 mm Hg) to afford 6-chloronicotinoylchloride (14.62 g, 0.083 mol, 83%), bp 72-78°C. The distilled product was recrystallized from petroleum ether to isolate analytically pure 6-chloronicotinoylchloride (12.11 g, 0.069 mol, 69%), mp 45-48°C (petroleum ehter) (lit. [7] mp 45-47°C). PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 7.52 (1H, d, J = 8.5, H-5), 8.32 (1H, dd, J_1 = 8.5, J_2 = 2.5, H-4), 9.09 (1H, d, J = 2.5, H-2).

5α-Cholestan-3β,5,6β-triol-3-(6-chloronicotinate) (4). A mixture of **1a** (0.44 g, 1.05 mmol) (synthesized by the literature method [8]) and 6-chloronicotinoylchloride (0.20 g, 1.14 mmol) in toluene (30 mL) was refluxed for 2 h 20 min. According to TLC, the reaction proceeded only slightly. Then, the mixture was treated with 4-dimethylaminopyridine (0.015 g), refluxed for another 6 h, and cooled to room temperature. The toluene was evaporated in vacuo in a rotary evaporator.

The solid was dissolved in CH_2Cl_2 (80 mL); washed successively with water (2 × 20 mL), aqueous $NaHCO_3$ solution (5%, 2 × 20 mL), and water (20 mL); and dried over $MgSO_4$. The solvent was evaporated. The solid (0.58 g) was rapidly chromatographed over a short column of silica gel with elution by CH_2Cl_2:CH_3OH (50:1) to afford crude product (0.50 g). Recrystallization from CH_3CN (70 mL) gave chromatographically pure homogeneous **4** (0.36 g), mp 220-223°C. A second crystallization of the mother liquor isolated additional **4** (0.060 g). Total yield 0.42 g (71.4%). IR spectrum (ν, cm^{-1}): 3440 (OH), 1700 (O–C=O), 1590 (C=C_{arom}), 780 (C–Cl). PMR spectrum (C_5D_5N, δ, ppm, J/Hz): 0.76 (3H, s, 18-Me), 0.90 (6H, d, J = 6.5, 26-Me, 27-Me), 1.04 (3H, d, J = 6.5, 21-Me), 1.65 (3H, s, 19-Me), 2.99 (1H, t, J = 12, H-7α), 4.22 (1H, br.s, H-6α), 6.13 (1H, m, W/2 = 23, H-3α), 7.53 (1H, d, J = 8.5, H-5′), 8.31 (1H, dd, J_1 = 8.5, J_2 = 2.5, H-4′), 9.20 (1H, d, J = 2.5, H-2′).

3β,5-Dihydroxy-5α-cholestan-6-one 3-(6-chloronicotinate) (5a). A mixture of **2a** (0.87 g, 2.08 mmol) (prepared by the literature method [8]), 6-chloronicotinoylchloride (0.39 g, 2.2 mmol), and 4-dimethylaminopyridine (0.03 g) in toluene (50 mL) was refluxed for 7.5 h and cooled. Toluene was removed in a rotary evaporator. The solid was dissolved in CH_2Cl_2 (150 mL); washed successively with water (2 × 50 mL), $NaHCO_3$ solution (5%, 2 × 50 mL), and water (50 mL); and dried over $MgSO_4$. Solvent was distilled. The solid (1.08 g) was rapidly chromatographed over a short column of silica gel with elution by CH_2Cl_2:CH_3OH (100:1) to isolate crude product (0.88 g). Crystallization from dichloroethane gave **5a** (0.72 g), mp 264-266°C. Crystallization of the mother liquors from dichloroethane (10 mL) isolated additional **5a** (0.08 g). Total yield 0.80 g (68.9%). IR spectrum (ν, cm^{-1}): 3440 (OH), 1715 (O–C=O), 1705 (C=O), 1590 (C=C_{arom}), 780 (C–Cl). PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.66 (3H, s, 18-Me), 0.86 (3H, d, J = 6.5, 26-Me), 0.87 (3H, d, J = 6.5, 27-Me), 0.88 (3H, s, 19-Me), 0.92 (3H, d, J = 6.5, 21-Me), 2.15 (1H, dd, J_1 = 13, J_2 = 4.5, H-4α), 2.77 (1H, t, J = 12, H-7α), 5.33 (1H, m, W/2 = 23, H-3α), 7.41 (1H, d, J = 8.5, H-5′), 8.21 (1H, dd, J_1 = 8.5, J_2 = 2.5, H-4′), 8.96 (1H, d, J = 2.5, H-2′); (C_5D_5N, δ, ppm, J/Hz): 0.67 (3H, s, 18-Me), 0.917 (3H, d, J = 6.5, 26-Me), 0.920 (3H, d, J = 6.5, 27-Me), 0.97 (3H, s, 19-Me), 0.98 (3H, d, J = 6.5, 21-Me), 2.61 (1H, dd, J_1 = 13, J_2 = 4.5, H-4α), 3.16 (1H, t, J = 12, H-7α), 5.92 (1H, m, W/2 = 23, H-3α), 7.53 (1H, d, J = 8.5, H-5′), 8.30 (1H, dd, J_1 = 8.5, J_2 = 2.5, H-4′), 9.19 (1H, d, J = 2.5, H-2′).

(24*R*)-3β,5-Dihydroxy-5α-stigmastan-6-one 3-(6-chloronicotinate) (5b). A mixture of **2b** (0.89 g, 2 mmol) prepared from **1b** by the literature method [1]), 6-chloronicotinoylchloride (0.37 g, 2.1 mmol), and 4-dimethylaminopyridine (0.05 g, 0.04 mmol) in toluene (40 mL) was refluxed for 5 h with passage of a weak stream of Ar through the mixture. Toluene was evaporated at reduced pressure. The solid was dissolved in CH_2Cl_2 (100 mL); washed successively with water (30 mL), aqueous $NaHCO_3$ solution (5%, 2 × 30 mL), and water (2 × 30 mL); and dried over $MgSO_4$. The desiccant was filtered off and washed with CH_2Cl_2 (2 × 50 mL). The CH_2Cl_2 was evaporated in vacuo. The solid was chromatographed over a column of silica gel with elution by CH_2Cl_2 (100 mL) and then CH_2Cl_2:CH_3OH (100:1, 800 mL) to afford crude product (0.94 g) that was recrystallized from dichloroethane to afford **5b** (0.79 g, 1.35 mmol, 68%), mp 233-237°C. PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.66 (3H, s, 18-Me), 0.88 (3H, s, 19-Me), 0.92 (3H, d, J = 6.5, 21-Me), 2.15 (1H, dd, J_1 = 13, J_2 = 4.5, H-4α), 2.73 (1H, s, 5α-OH), 2.77 (1H, t, J = 12.5, H-7α), 5.33 (1H, m, W/2 = 23, H-3α), 7.41 (1H, d, J = 8.5, H-5′), 8.21 (1H, dd, J_1 = 8.5, J_2 = 2.5, H-4′), 8.96 (1H, d, J = 2.5, H-2′).

3β,5-Dihydroxy-5β-chloestan-6-one (3). Compound **2a** (35.4 g) was dissolved with heating in CH_3OH (1.2 L), treated with water (100 mL) and KOH (240 g), refluxed for 4 h, left overnight at room temperature, evaporated in a rotary evaporator to half the volume, acidified to pH 3.4 by adding HCl (36%), diluted with water (1.5 L), left overnight in a refrigerator, and extracted with CH_2Cl_2 (1.0 L). The resulting crystals were filtered off. The organic layer of the filtrate was separated from the aqueous layer. The aqueous layer was extracted with additional portions of CH_2Cl_2 (400 and 200 mL). The combined organic extract was treated with water (750 mL). The resulting crystalline precipitate was filtered off. The organic layer of the filtrate was separated. The majority of the solvent was distilled at normal pressure; the residue, in vacuo in a rotary evaporator to afford an oily product (27.8 g). A portion of the product (5.0 g) was chromatographed over a column of silica gel with elution by CH_2Cl_2:CH_3OH (100:1, 80:1, 40:1) to afford **3** (4.7 g, 74%).

3β,5-Dihydroxy-5β-cholestan-6-one 3-(6-chloronicotinate) (6). A mixture of **3** (0.87 g, 2.08 mmol), 6-chloronicotinoylchloride (0.39 g, 2.2 mmol), and 4-dimethylaminopyridine (0.03 g) in toluene (50 mL) was refluxed for 12 h and cooled. Toluene was evaporated in a rotary evaporator. The solid was dissolved in CH_2Cl_2 (150 mL); washed successively with water (2 × 50 mL), aqueous $NaHCO_3$ solution (5%, 2 × 50 mL), and water (50 mL); and dried over $MgSO_4$. Solvent was distilled. The solid (1.20 g) was rapidly chromatographed over a short column of silica gel with elution by CH_2Cl_2 (300 mL) and then CH_2Cl_2:CH_3OH (100:1, total volume 808 mL) to afford crude product (0.85 g). Crystallization from petroleum ether (bp 85-92°C) gave **6** (0.66 g), mp 199-201.5°C. A second crystallization of the solid after evaporation of mother liquor from

petroleum ether (10 mL) produced additional **6** (0.06 g). Total yield 0.72 g (59%). IR spectrum (ν, cm^{-1}): 3450 (OH), 1700 (O–C=O, C=O), 1590 ($C=C_{arom}$), 780 (C–Cl). PMR spectrum (C_5D_5N, δ, ppm, J/Hz): 0.63 (3H, s, 18-Me), 0.92 (6H, d, J = 6.5, 26-Me, 27-Me), 0.95 (3H, s, 19-Me), 1.00 (3H, d, J = 6.5, 21-Me), 5.55 (1H, br.s, H-3α), 5.70 (1H, br.s, 5α-OH), 7.49 (1H, d, J = 8.5, H-5′), 8.48 (1H, dd, J_1 = 8.5, J_2 = 2.5, H-4′), 9.37 (1H, d, J = 2.5, H-2′).

Further elution by CH_2Cl_2:CH_3OH (100:1) isolated starting **3** (0.23 g, 12.3%).

Bromination of (24*R*)-3β,5-dihydroxy-5α-cholestan-6-one 3-(6-chloronicotinate) (5a). Steroid **5a** (0.56 g, 1 mmol) was dissolved with heating to 70°C in a mixture of acetic acid (20 mL) and $CHCl_3$ (10 mL); treated at this same temperature with a solution of Br_2 (2 M, 0.65 mL, 1.3 mmol of pure Br_2) in HOAc, LiBr (0.09 g, 1 mmol), and HBr (40%, 0.14 mL, 1 mmol HBr); refluxed for 6 h, and evaporated at reduced pressure. The solid was dissolved in CH_2Cl_2 (40 mL); washed successively with saturated aqueous $NaHCO_3$ (2 × 30 mL), aqueous Na_2SO_3 solution (10%, 30 mL), and water (2 × 30 mL), and dried over $MgSO_4$. The desiccant was filtered off and washed with CH_2Cl_2 (2 × 20 mL). The CH_2Cl_2 was evaporated in vacuo. The solid was chromatographed over a column of silica gel with elution by dichloroethane (1900 mL) and dichloroethane:CH_3OH (100:1, 400 mL) to afford the following fractions.

Fraction 1: A mixture of **7a** and **7b** (0.16 g). Recrystallization of the mixture of **7a** and **7b** from petroleum ether (bp 70-80°C) and EtOAc (8 mL:0.8 mL) gave a mixture of **7a**-**b** (0.12 g) in a 2:1 ratio, respectively (according to PMR spectra). PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): **7a**: 0.70 (3H, s, 18-Me), 0.83 (3H, s, 19-Me), 0.869 (3H, d, J = 6.5, 26-Me), 0.875 (3H, d, J = 6.5, 27-Me), 0.93 (3H, d, J = 6.5, 21-Me), 3.37 (1H, dd, J_1 = 12.5, J_2 = 3.0, H-5α), 4.21 (1H, d, J = 3.5, H-7β), 5.01 (1H, m, W/2 = 23, H-3α), 7.59 (1H, d, J = 8.0, H-5′), 8.12 (1H, dd, J_1 = 8.0, J_2 = 2.5, H-4′), 8.94 (1H, d, J = 2.5, H-2′); **7b**: 0.70 (3H, s, 18-Me), 0.83 (3H, s, 19-Me), 0.869 (3H, d, J = 6.5, 27-Me), 0.875 (3H, d, J = 6.5, 26-Me), 0.93 (3H, d, J = 6.5, 21-Me), 3.37 (1H, dd, J_1 = 12.5, J_2 = 3.0, H-5α), 4.21 (1H, d, J = 3.5, H-7β), 5.01 (1H, m, W/2 = 23, H-3α), 7.42 (1H, d, J = 8.0, H-5′), 8.24 (1H, dd, J_1 = 8.0, J_2 = 2.5, H-4′), 8.98 (1H, d, J = 2.5, H-2′).

Fraction 2: A mixture of **8a** and **8b** (0.27 g) in a 2:1 ratio, respectively (according to PMR spectra). PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): **8a**: 0.67 (3H, s, 18-Me), 0.83 (3H, s, 19-Me), 0.866 (3H, d, J = 6.5, 26-Me), 0.871 (3H, d, J = 6.5, 27-Me), 0.92 (3H, d, J = 6.5, 21-Me), 4.95 (1H, m, W/2 = 23, H-3α), 7.58 (1H, d, J = 8.0, H-5′), 8.11 (1H, dd, J_1 = 8.5, J_2 = 2.5, H-4′), 8.94 (1H, d, J = 2.0, H-2′); **8b**: 0.67 (3H, s, 18-Me), 0.83 (3H, s, 19-Me), 0.866 (3H, d, J = 6.5, 26-Me), 0.871 (3H, d, J = 6.5, 27-Me), 0.92 (3H, d, J = 6.5, 21-Me), 4.95 (1H, m, W/2 = 23, H-3α), 7.41 (1H, d, J = 8.0, H-5′), 8.23 (1H, dd, J_1 = 8.5, J_2 = 2.5, H-4′), 8.98 (1H, d, J = 2.0, H-2′).

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