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New pyrano[3,4-*b*]indoles from 2-hydroxymethylindole and L-dehydroascorbic acid

Sergey N. Lavrenov,[a] Konstantin F. Turchin,[b] Alexander M. Korolev,[a] Olga S. Anisimova[b] and Maria N. Preobrazhenskaya[a,*]

[a]*Gause Institute of New Antibiotics, Russian Academy of Medical Sciences, B. Pirogovskaya 11, 119021 Moscow, Russia*
[b]*Center for Drug Research, Russian Research Chimico-Pharmaceutical Institute, Zubovskaya 7, 119815 Moscow, Russia*

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Abstract—2-Hydroxymethylindole reacts with L-dehydroascorbic acid under mild conditions to give (3*R*,3a*R*,10c*S*)-3-[(1*S*)-1,2-dihydroxyethyl]-3a,10c-dihydroxy-3a,5,6,10c-tetrahydrofuro[3′,4′:5,6]pyrano[3,4-*b*]indol-1(3*H*)-one. Its tosyl derivative undergoes cyclization to form a pentacyclic ketal derivative.

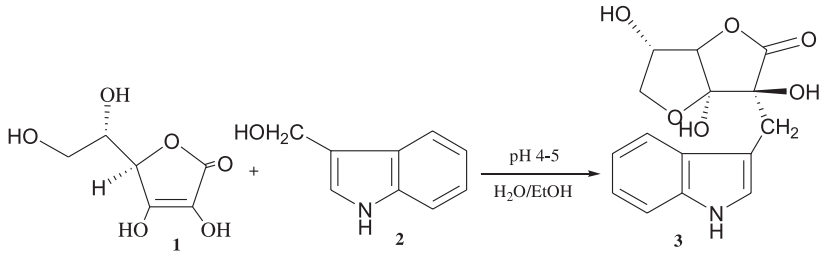
1. Introduction

L-Ascorbic acid easily undergoes 2-C-alkylation by 3-hydroxymethylindole, 4-hydroxybenzyl alcohol, and their analogues, which are able to produce quinone methide type structures under mild acidic conditions.[1,2] Ascorbigen, which is 2-C-[(indol-3-yl)methyl]-α-L-*xylo*-hex-3-ulofuranosono-4-lactone **3** is a product of the reaction of L-ascorbic acid **1** with the intermediate quinone methide formed from 3-hydroxymethylindole **2**.[2] Ascorbigen **3** is the main decomposition product of alkaloid glucobrassicin from cruciferous vegetables, and animals and humans receive it with meals. Recently, it was found that it is a strong non-specific immunomodulator with valuable properties (Scheme 1).[3]

Several ascorbigens have been synthesized in our laboratory and their unique chemical and biological properties have been investigated,[3] but the reaction of isomeric 2-hydroxymethylindole with L-ascorbic acid poses synthetic challenges and would help us to further elucidate the synthetic potential of this unique compound and its derivatives. The goal of our work was to study the preparation of a compound isomeric to ascorbigen by the reaction of 2-hydroxymethylindole **4** with L-ascorbic acid **1**.

2. Results and discussion

Unfortunately, 2-hydroxymethylindole **4a** does not react with **1** with the formation of an ascorbigen-like structure (**5**) at pH 1–6. It can be explained by the inability of **4a** to form a quinone methide structure under these conditions. However, on incubation of the reaction mixture (**1**+**4a** in



Scheme 1.

Keywords: L-Ascorbic acid; L-Dehydroascorbic acid; Ascorbigen; Indolopyrane; 2-Hydroxymethylindole.
* Corresponding author. Tel.: +7 095 245 37 53; fax: +7 095 245 02 95; e-mail: mnp@space.ru

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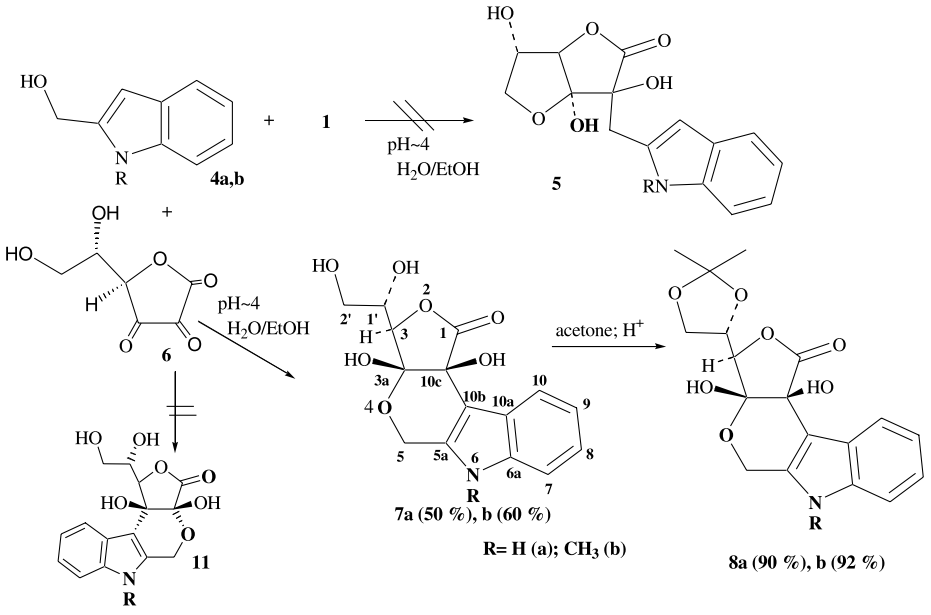
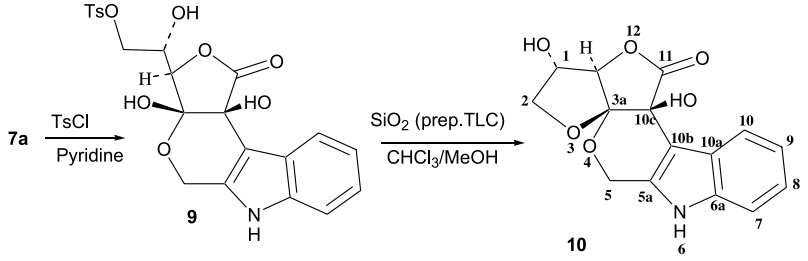


Scheme 2.



Scheme 3.

H_2O–MeOH mixture at pH ~ 4.7) for more than two weeks, we succeeded in the isolation of a new product in 20% yield. It was identified as (3*R*,3a*R*,10c*S*)-3-[(1*S*)-1,2-dihydroxyethyl]-3a,10c-dihydroxy-3a,5,6,10c-tetrahydrofuro[3′,4′:5,6]pyrano[3,4-*b*]indol-1(3*H*)-one **7a** (Scheme 2).

It is suggested that **7a** is a product of the reaction of L-dehydroascorbic acid **6** with **4a**. When L-ascorbic acid was oxidized to L-dehydroascorbic acid by the action of oxygen in the presence of activated charcoal in H_2O–MeOH[4] before addition of **4a**, the yield of compound **7a** increased to 50% and the reaction time was reduced to seven days. Similarly, compound **7b** was obtained in 60% yield from 1-methyl-2-hydroxymethyindole **4b** and L-dehydroascobic acid **6**. It suggests that the nucleophilic attack of 3-C indole atom on carbonyl group at 2-C of dehydroascorbic acid takes place followed by hemiacetal formation with the participation of 3-CO of dehydroascorbic acid and hydroxy group of **4**. The reaction of **7a** or **7b** with acetone in the presence of *p*-toluenesulfonic acid gave crystalline 1′,2′-*O*-isopropylidene derivatives **8a** or **8b**, respectively. By the reaction of **7a** with an excess of *p*-toluenesulfonyl chloride in pyridine 2′-*O*-monotosyl derivative **9** was obtained. On purification by preparative TLC, **9** partially underwent cyclization into acetal **10** (Scheme 3).

The stereochemistry of compounds **7a**,**b** was suggested by NOE experiments and appears to be in accord with the previously observed dominant mode of alkylation in such systems.[1,3,5] An isomeric structure with a different type of annelation of the pyranoindole and furanone rings than in compound **7** could be proposed for the product of reaction of **4** with **6**. A double resonance experiment allowed the identification in the ^{1}H NMR spectrum of **8a** of the signal of the OH-group (10c-OH), which is nearest to the carbonyl group. In the ^{1}H coupled ^{13}C NMR spectrum of compound **8a** a coupling constant $^3J_{1C,10c\text{-}OH} \approx 4$ Hz was observed. The NOE for this 10c-O*H* proton was determined ($\eta_{10c\text{-}OH}\{10\text{-}H\} \approx 3.5\%$) by saturation of 10-H. An analogous effect was observed in the reverse experiment ($\eta_{10\text{-}H}\{10c\text{-}OH\}$) in accordance with structure **7** and **8**.

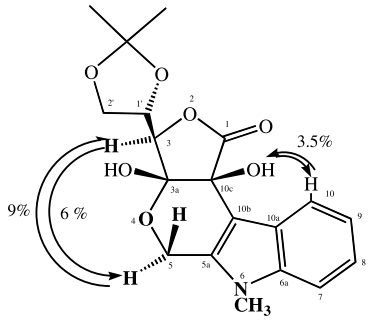


Figure 1. NOE experiments for **8b**.

The reciprocal orientation of two hydroxyl groups (10c-OH and 3a-OH) was elucidated based on rather high NOE values $\eta_{3\text{-H}}\{5\text{-Ha}\}\approx 9\%$ and $\eta_{5\text{-Ha}}\{3\text{-H}\}\approx 6\%$), in compound **8b** 5-Ha is the highfield doublet of AB system 5-H_2 (Fig. 1). Molecular modeling of compounds **7** and **8** led to a conclusion, that the distance between atoms 5-Ha and 3-H may be <2 Å only in the structure in, which the two hydroxyl groups in the tetrahydrofuranone cycle are *cis*-oriented.

The *S*-configuration at 10c atom follows from analysis of relevant literature, as there are no examples of attack on the 2C atom of L-ascorbic acid from the side *cis* to the bulky substituent at C-4 (CHOH–CH_2OH).[3]

The compounds obtained have a structural fragment of 1,3,4,9-tetrahydropyrano[3,4-*b*]indole, which represents a framework of some anti-inflammatory drugs such as etodolac.[6]

3. Experimental

3.1. General

NMR spectra were recorded on a Varian Unity +400 instrument (400 MHz for ^{1}H, 100.6 MHz for ^{13}C). NOE values ($\eta_{\text{Hi}}\{\text{H}_j, \%\}$) were measured as an increase of H_i signal intensity when H_j signal was saturated. Analytical TLC was performed on Kieselgel F_{254} plates (Merck), preparative TLC chromatography on plates (20×20 cm, 0.5 mm) with Kieselgel 60 F_{254} (Merck), and column chromatography on Kieselgel 60 (Merck), using the following systems of solvents: $CHCl_3$/MeOH 5:1 (A); 10:1 (B) and EtOAc/petroleum ester, 1:1 (C). Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Infrared spectra were recorded with a Nicolet Avatar 330 FT-IR spectrometer using KBr discs.

High resolution mass spectra were registered on a MAT 8430 Finnigan instrument (USA) with data operating system SS-300 (EI, 70 eV, direct introduction, temperature of ion source 250 °C). Electron impact (EI) mass-spectra were registered on a SSQ 710 Finnigan MAT instrument (USA), (EI: 70 eV, direct introduction). Melting points were determined on a Buchi SMP-20 apparatus and are uncorrected.

3.1.1. (3*R*,3a*R*,10c*S*)-3-[(1*S*)-1,2-Dihydroxyethyl]-3a,10c-dihydroxy-3a,5,6,10c-tetrahydrofuro[3′,4′:5,6]-pyrano[3,4-*b*]indol-1(3*H*)-one (7a). To a solution of **4a** (1.2 g, 7.36 mmol) in CH_3OH (10 mL) was added buffer solution prepared by dissolving of 2.7 g of citric acid and 6 g of Na_2HPO_4 in 300 mL of H_2O and solution of L-dehydroascorbic acid (**6**), obtained from **1** (6.5 g, 36.8 mmol) in 100 mL of CH_3OH. The reaction mixture was stirred for seven days at rt, saturated with NaCl, extracted with $CHCl_3$ (1×50 mL) and then with EtOAc (3×40 mL). EtOAc extract was dried (Na_2SO_4), evaporated and after column chromatography (A) gave **7a** (1.2 g, 50%) as a light-brown powder (as minimum 96% purity by NMR data); R_f 0.26 (A); $[\alpha]_D^{20}$ +4 (MeOH); ν_{max}: 3266, 1767, 1455, 1104, 741 cm^{-1}; HRMS Calcd for $C_{15}H_{15}NO_7$: 321.0849. Found: 321.0830; ^{1}H NMR: δ (DMSO-d_6) 3.54 (m, 2H, 2′-H_AH_B); 3.91 (m, 1H, 1′-H); 4.52 (d, J=3.8 Hz, 1H, 3-H); 4.82 (d, J=15.4 Hz, 1H, 5-H_B); 4.90 (br s, 1H, 2′-OH); 4.96 (d, J=15.4 Hz, 1H, 5-H_A); 5.97 (br s, 1H, 1′-OH); 6.50 (br s, 1H, 10-OH); 7.01 (ddd, J=7.8, 7.0, 1.0 Hz, 1H, 9-H); 7.08 (ddd, J=8.1, 7.0, 1.2 Hz, 1H, 8-H); 7.19 (br s, 1H, 3a-OH); 7.35 (ddd, J=8.1, 1.0, 0.7 Hz, 1H, 7-H); 7.73 (ddd, J=7.8, 1.2, 0.7 Hz, 1H, 10-H); 11.14 (s, 1H, 6-H); ^{13}C NMR: δ (DMSO-d_6) 58.0 (5-C); 61.5 (2′-C); 68.8 (1′-C); 70.9 (10c-C); 81.2 (3-C); 99.4 (3a-C); 104.1 (10b-C); 111.4 (7-C); 119.2 (9-C); 120.6 (10-C); 121.4 (8-C); 125.8 (10a-C); 134.3 (5a-C); 136.5 (6a-C); 174.3 (1-C).

3.1.2. (3*R*,3a*R*,10c*S*)-3-[(1*S*)-1,2-Dihydroxyethyl]-3a,10c-dihydroxy-6-methyl-3a,5,6,10c-tetrahydrofuro[3′,4′:5,6]pyrano[3,4-*b*]indol-1(3*H*)-one (7b). Compound **7b** was obtained from **4b** (1 g, 6.25 mmol) and purified by the same way as **7a**, as a light-brown powder (1.25 g, 60%); R_f 0.44 (A); $[\alpha]_D^{20}$ +6.5 (MeOH); ν_{max}: 3368, 1786, 1455, 1031, 759 cm^{-1}; HRMS Calcd for $C_{16}H_{17}NO_7$: 335.1005. Found: 335.0998; ^{1}H NMR: δ (CD_3OD) 3.64 (s, 3H, 6-CH_3); 3.81 (m, 2H, 2′-H_AH_B); 4.08 (m, 1H, 1′-H); 4.63 (d, J=5.3 Hz, 1H, 3-H); 5.04 (d, J=15.6 Hz, 1H, 5-H_B); 5.13 (d, J=15.6 Hz, 1H, 5-H_A); 7.10 (ddd, J=7.9, 7.1, 1.0 Hz, 1H, 9-H); 7.19 (ddd, J=8.3, 7.1, 1.2 Hz, 1H, 8-H); 7.37 (ddd, J=8.3, 1.0, 0.7 Hz, 1H, 7-H); 7.88 (ddd, J=7.9, 1.2, 0.7 Hz, 1H, 10-H); ^{13}C NMR: δ (CD_3OD) 29.9 (N–CH_3); 59.8 (5-CH_2); 63.3 (2′-C); 70.9 (1′-C); 72.5 (10c-C); 81.2 (3-C); 100.9 (3a-C); 104.3 (10b-C); 110.1 (7-C); 121.0 (9-C); 121.6 (10-C); 123.0 (8-C); 126.7 (10a-C); 136.3 (5a-C); 139.8 (6a-C); 175.9 (1-C).

3.1.3. (3*R*,3a*R*,10c*S*)-3-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3a,10c-dihydroxy-3a,5,6,10c-tetrahydrofuro[3′,4′:5,6]pyrano[3,4-*b*]indol-1(3*H*)-one (8a). To a solution of **7a** (500 mg, 1.56 mmol) in dry acetone (10 mL) was added *p*-toluenesulfonic acid (10 mg). The reaction mixture was stirred for 40 min at rt, diluted with 100 mL of 10% $NaHCO_3$ solution, extracted with EtOAc (2×30 mL). After drying (Na_2SO_4) of the extract, evaporating, and recrystallization from acetone **8a** (500 mg, 90%) was obtained as colorless crystals. Mp 190–196 °C (decomp.); R_f 0.16 (C); $[\alpha]_D^{20}$ +6.7 (MeOH); ν_{max}: 3329, 1785, 1085, 1059, 753 cm^{-1}; HRMS Calcd for $C_{18}H_{19}NO_7$: 361.1161. Found: 361.1143; ^{1}H NMR: δ (DMSO-d_6) 1.29 and 1.33 (2 s, 2×3H, 1′,2′-OC(CH_3)$_2$); 3.90 (dd, J=8.9, 6.5 Hz, 1H, 2′-H_B,); 4.14 (dd, J=8.9, 6.3 Hz, 1H, 2′-H_A); 4.34 (m, 1H, 1′-H); 4.39 (dd, J=8.0, 1.0 Hz, 1H, 3-H); 4.96 (d, J=15.8 Hz, 1H, 5-H_B); 5.02 (d, J=15.8 Hz, 1H, 5-H_A); 6.44 (s, 1H, 10c-OH); 6.96 (d, J=1.0 Hz, 1H, 3a-OH); 7.02 (ddd, J=7.9, 7.2, 1.1 Hz, 1H, 9-H); 7.10 (ddd, J=8.1, 7.2, 1.3 Hz, 1H, 8-H); 7.36 (ddd, J=8.1, 1.1, 0.8 Hz, 1H, 7-H); 7.72 (ddd, J=7.9, 1.3, 0.8 Hz, 1H, 10-H); 11.26 (s, 1H, 6-H); ^{13}C NMR: δ (DMSO-d_6) 25.5 and 26.6 (1′,2′-OC(CH_3)$_2$); 59.6 (5-C); 65.1 (2′-C); 70.7 (10c-C); 74.7 (1′-C); 79.3 (3-C); 99.7 (3a-C); 104.0 (10b-C); 108.8 (1′,2′-O*C*(CH_3)$_2$); 111.5 (7-C); 119.4 (9-C); 120.2 (10-C); 121.8 (8-C); 125.4 (10a-C); 134.0 (5a-C); 136.8 (6a-C); 173.3 (1-C).

3.1.4. (3*R*,3a*R*,10c*S*)-3-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3a,10c-dihydroxy-6-methyl-3a,5,6,10c-tetrahydro-

furo[3′,4′:5,6]pyrano[3,4-*b*]indol-1(3*H*)-one (8b). Compound **8b** was obtained and purified by the same way as **8a** from **7b** (500 mg, 1.5 mmol) as colorless crystals (517 mg, 92%). Mp 161–165 °C (decomp.); R_f 0.19 (C); $[\alpha]_D^{20}$ +5 (*c* 2.5, MeOH); HRMS Calcd for $C_{19}H_{21}NO_7$: 375.1318. Found: 375.1324; ^{1}H NMR: δ (DMSO-d_6) 1.29 and 1.33 (2 s, 2×3H, 1′,2′-OC(CH_3)$_2$); 3.62 (s, 3H, 6-CH_3); 3.88 (dd, J=8.8, 6.8 Hz, 1H, 2′-H_B,); 4.15 (dd, J=8.8, 6.5 Hz, 1H, 2′-H_A); 4.32 (m, 1H, 1′-H); 4.43 (dd, J=8.0, 1.2 Hz, 1H, 3-H); 5.04 (d, J=15.8 Hz, 1H, 5-H_B); 5.11 (d, J=15.8 Hz, 1H, 5-H_A); 6.47 (s, 1H, 10c-OH); 6.98 (d, J=1.2 Hz, 1H, 3a-OH); 7.06 (ddd, J=8.0, 7.1, 1.0 Hz, 1H, 9-H); 7.17 (ddd, J=8.2, 7.1, 1.2 Hz, 1H, 8-H); 7.48 (ddd, J=8.2, 1.0, 0.8 Hz, 1H, 7-H); 7.73 (ddd, J=8.0, 1.2, 0.8 Hz, 1H, 10-H); 11.26 (s, 1H, 6-H); ^{13}C NMR: δ (DMSO-d_6) 25.4 and 26.5 (1′,2′-OC(CH_3)$_2$); 29.7 (N–CH_3); 59.1 (5-C); 65.0 (2′-C); 70.5 (10c-C); 74.7 (1′-C); 79.0 (3-C); 99.8 (3a-C); 103.3 (10b-C); 108.8 (1′,2′-OC(CH_3)$_2$); 109.6 (7-C); 119.6 (9-C); 120.2 (10-C); 121.6 (8-C); 125.0 (10a-C); 135.2 (5a-C); 137.5 (6a-C); 173.1 (1-C).

3.1.5. (3*R*,3a*R*,10c*S*)-3a,10c-Dihydroxy-1-oxo-1,3,3a,5,6,10c-hexahydrofuro[3′,4′:5,6]pyrano[3,4-*b*]indol-3-yl]-2-hydroxyethyl tosylate (9), and (1*S*,3a*S*,10c*S*,12a*R*)-1,10c-dihydroxy-1,6,10c,12a-tetrahydro-2*H*-furo[2″,3″:4′,5′]furo[3′,4′:5,6]pyrano[3,4-*b*]indol-11(5*H*)-one (10). To a stirred solution of **7a** (500 mg, 1.56 mmol) in dry pyridine (10 mL) was added tosylchloride (305 mg, 1.6 mmol) and after 4 h incubation the reaction mixture was diluted by citric acid solution and extracted by EtOAc (2×30 mL). After evaporation 600 mg of brown oil was obtained. It consisted of 80% of **9** and not contained **10**. After preparative TLC chromatography (system B) 60 mg of **9** (8% yield,) and 300 mg of **10** (63% yield) were obtained. The latter was formed during chromatography.

Compound **9**. Colourless oil; R_f 0.52 (B); HRMS Calcd for $C_{22}H_{21}NO_9S$: 475.0937. Found: 475.0930; ^{1}H NMR: δ (DMSO-d_6) 2.48 (s, 3H, CH_3 of Ts); 4.04 (m, 1H, 1′-OH); 4.16 (dd, J=9.6, 6.4 Hz, 1H, 2′-H_A); 4.31 (dd, J=9.6, 3.2 Hz, 1H, 2′-H_B); 4.38 (d, J=8.1 Hz, 1H, 3-H); 4.97 (d, J=15.1 Hz, 5-H_A); 5.00 (d, J=15.1 Hz, 5-H_B); 5.98 (d, J=6.4 Hz, 1H, 1′-OH); 6.52 (s, 1H, 10c-OH); 7.02 (ddd, J=8.1, 7.0, 1.0 Hz, 1H, 9-H); 7.06 (s, 1H, 3a-OH); 7.12 (ddd, J=8.1, 7.0, 1.2 Hz, 1H, 8-H); 7.38 (ddd, J=8.1, 1.0, 0.8 Hz, 1H, 7-H); 7.52 (d, J=9.6 Hz, 2H, Ts) 7.70 (ddd, J=8.0, 1.2, 0.8 Hz, 1H, 10-H); 7.84 (d, J=9.6 Hz, 2H, Ts); 11.25 (s, 1H, 6-H).

Compound **10**. Colourless crystals. Mp 201–205 °C; R_f 0.61 (A); ν_{max}: 3416, 1778, 1477, 1087, 1038, 747 cm^{-1}; HRMS Calcd for $C_{15}H_{13}NO_6$: 303.0743. Found: 303.0738; ^{1}H NMR: δ (DMSO-d_6–benzene-d_6, 3:1) 4.26 (dd, J=9.3, 4.1 Hz, 1H, 2-H_A); 4.52 (dd, J=9.3, 6.1 Hz, 1H, 2-H_B); 4.60 (dd, J=6.1, 4.1 Hz, 1H, 1-H); 5.06 (s, 1H, 12a-H); 5.20 (d, J=15.6 Hz, 1H, 5-H_A); 5.31 (d, J=15.6 Hz, 1H, 5-H_B); 6.05 (br s, 1H, 1-OH); 6.25 (s, 1H, 10c-OH); 7.15 (t, J=7.5 Hz, 1H, 9-H); 7.22 (t, J=7.5 Hz, 1H, 8-H); 7.53 (d, J=7.9 Hz, 1H, 7-H); 8.05 (d, J=7.9 Hz, 1H, 10-H); 11.50 (s, 1H, 6-H); ^{13}C NMR: δ (DMSO-d_6–benzene-d_6, 3:1) 61.4 (2′-C); 70.5 (10c-C); 73.6 (1′-C); 75.9 (5-C); 82.1 (12a-C); 104.9 (10b-C); 110.2 (3a-C); 111.5 (7-C); 119.5 (9-C); 120.1 (10-C); 121.8 (8-C); 124.9 (10a-C); 134.1 (5a-C); 136.7 (6a-C); 172.9 (11-C).

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