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Bioorganic & Medicinal Chemistry 16 (2008) 1884–1889
Bioorganic & Medicinal Chemistry

Biomimetic synthesis of xuxuarines Eα and Eβ: Structure revision of *Rzedowskia* bistriterpenoids

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Received 14 August 2007; revised 25 October 2007; accepted 1 November 2007
Available online 6 November 2007

Abstract—Reaction of pristimerin with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) resulted in a biomimetic-type coupling leading to xuxuarines Eα and Eβ and not the previously reported *Rzedowskia* bistriterpenoids I and II suggesting that the structures proposed for these natural products need revision. A product obtained in this reaction by an unusual Diels-Alder addition followed by *retro*-Diels-Alder-type elimination was characterized as pristimerin dicyanophenalenedione. Complete ^{1}H, and ^{13}C NMR spectral assignments of xuxuarines Eα and Eβ have been made by the application of 1D and 2D NMR techniques.

1. Introduction

The triterpenoid quinonemethides (celastroloids) constitute a relatively small group of unsaturated and oxygenated D:A-*friedo*-*nor*-oleananes with interesting structures and a variety of biological activities.[1–3] A number of biscelastroloids have been recently encountered in plants of the family Celastraceae.[4] These are composed of quinonemethide and aromatic forms of *nor*-triterpenes derived from pristimerin (**4a**), tingenone (**4b**), and 22-hydroxytingenone (**4c**) and/or their congeners, joined by two ether linkages formed between the A rings of the two celastroloids, or between the A and the B rings; only exceptions being *Rzedowskia* bistriterpenoids I (**5a**) and II (**5b**)[5] which contain a single ether linkage between the two subunits.[4a] Surprisingly, to date, there are no reported syntheses of biscelastroloids in which the two celastroloid moieties are joined by two ether linkages. In continuing our studies on reactions of celastroloids,[6] we have explored the potential of DDQ-mediated oxidative coupling of triterpenoid quinonemethides for biomimetic-type syntheses of biscelastroloids, and herein we report that the reaction of pristimerin with DDQ yields xuxuarines Eα (**1**) and Eβ (**2**). An unusual product obtained from this reaction was identified as pristimerin dicyanophenalenedione (**3**), formed probably by Diels-Alder-type addition of DDQ to pristimerin followed by *retro*-Diels-Alder-type elimination. Close resemblance of the spectral data of **1** and **2** with those reported for *Rzedowskia* bistriterpenoids I (**5a**) and II (**5b**) together with some discrepancies in the assignment of their NMR data strongly suggest that the structures proposed by Gonzalez et al.[4a] for the *Rzedowskia* bistriterpenoids require revision.

2. Results and discussion

Treatment of pristimerin (**4a**) with DDQ in dioxane at room temperature and work-up after its disappearance (TLC control) followed by chromatographic separation of the resulting mixture afforded **1**–**3**. Compound **1** was obtained as a yellow solid that analyzed for $C_{60}H_{78}O_9$ by a combination of HRFABMS and ^{13}C NMR spectroscopy and indicated 22 degrees of unsaturation. Its IR spectrum showed absorption bands at 3448, 1728 and 1651 cm^{-1} suggesting the presence of OH, ester carbonyl, and α,β-unsaturated carbonyl groups. The ^{1}H NMR spectrum (Table 1) indicated the presence of 14

Keywords: Biscelastroloids; DDQ oxidation; *Rzedowskia* bistriterpenoids; Xuxuarine Eα; Xuxuarine Eβ; Biomimetic synthesis.
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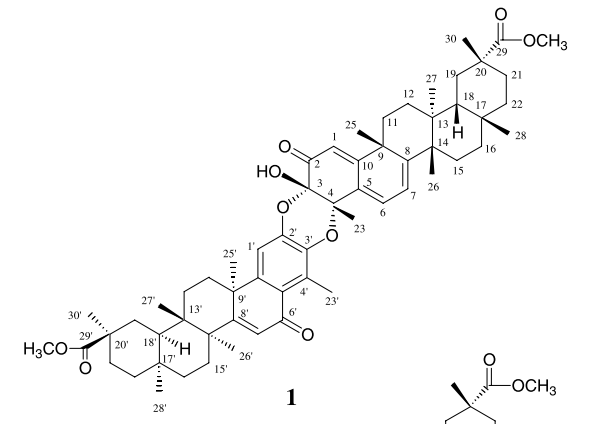
doi:10.1016/j.bmc.2007.11.008



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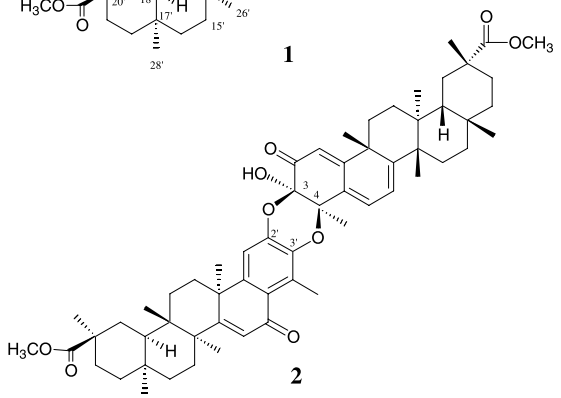

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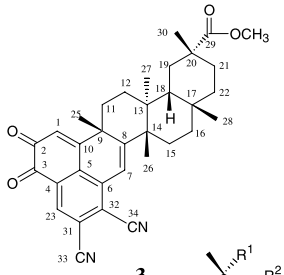

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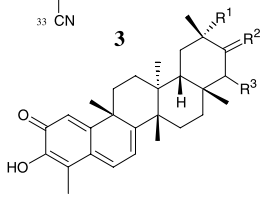
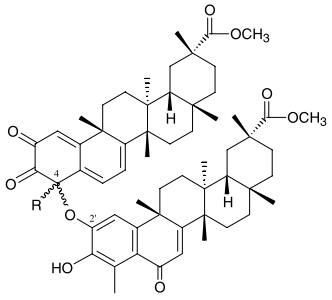


4a $R^1 = CO_2CH_3$; $R^2 = H_2$; $R^3 = H$
4b $R^1 = H$; $R^2 = O$; $R^3 = H$
4c $R^1 = H$; $R^2 = O$; $R^3 = OH$



5a R = α-CH_3
5b R = β-CH_3

methyl singlets, two of which were due to OCH_3 groups (δ 3.54 and 3.60) and one attached to an aromatic ring (δ 2.74). In the low-field region, it had signals due to an aromatic proton [δ 6.80 (s)] and an olefinic proton [δ 6.25 (s)] of a 6-oxo-phenolic type triterpenoid system,[7] and protons of a quinonemethide system [δ 6.09 (1H, d, J = 1.6 Hz), 6.24 (1H, dd, J = 6.6 and 1.6 Hz), 5.94 (1H, d, J = 6.6 Hz)].[3a] The ^{13}C NMR spectrum of **1** had signals due to two α,β-unsaturated carbonyls (δ 187.89 and 190.22), two ester carbonyls (δ 178.73 and 178.82), and fourteen aromatic/olefinic carbons. These data suggested that **1** is a dimeric celastroloid consisting of quinonemethide and 6-oxo-phenolic subunits. The presence of a D_2O exchangeable signal at δ_H 5.11 and a dioxygenated carbon signal at δ_c 91.98 was indicative of a dimer joined by two ether linkages formed between the A rings of the two monomeric units. Oxidative coupling of quinonemethide and 6-oxo-phenolic subunits would give rise to two regioisomers (having C2′–O–C3–C4–O–C3′ and C2′–O–C4–C3–O–C3′ ether linkages) each with two stereoisomers. Analysis of the HMBC spectrum (Table 1) indicated the presence of a weak long-range correlation between CH_3-23 and C-3′ suggesting C2′–O-C3–C4–O–C3′ regiochemistry for **1** which was confirmed by the proton chemical shift of CH_3-23′ (δ 2.74),[4e,h–j] and the NOE between H-6 and CH_3-23′ in its ROESY spectrum. The CH_3-23′ signals of its regioisomers (isoxuxuarines) have been reported to occur in the region δ 2.48–2.52.[4g–i] The foregoing suggested that **1** has the gross structure identical with xuxuarine E,[4h,j] and the positive specific rotation confirmed its identity as xuxuarine Eα.[4j]

The molecular formula of compound **2** was determined to be $C_{60}H_{78}O_9$. The ^{1}H, and ^{13}C NMR spectroscopic data of **2** were almost identical with those of **1** (Table 1). The $[\alpha]_D$ value of **2** (−349.4) was found to be the opposite of that of **1** (+361.7) suggesting that **2** is identical with xuxuarine Eβ and this was confirmed by comparison of ^{1}H and ^{13}C NMR data of **2** with those reported for xuxuarine Eβ.[4h] The regiochemical and stereochemical assignments of the dimer interface in compounds **1** and **2** were further confirmed on the basis of their 600 MHz ROESY spectra and from molecular modeling. Analyses of COSY, HSQC, HMBC, and ROESY spectra allowed the assignment of all the ^{1}H and ^{13}C signals of **1** and **2** (Table 1), some of which have not been assigned in previous studies.[4h,j]

Compound **3** was obtained as a red powder and its HRFABMS and ^{13}C NMR data suggested the molecular formula $C_{34}H_{36}O_4N_2$. Since DDQ is the only nitrogen containing compound that was present in the reaction mixture, it was suspected to have formed by the addition of DDQ ($C_8O_2Cl_2N_2$) to pristimerin (**4a**) ($C_{30}H_{40}O_4$) followed by the elimination of $C_4H_4O_2Cl_2$. The ^{1}H NMR spectrum of **3** in the low-field region showed the absence of quinonemethide protons with their typical splitting patterns.[3a] Instead, three 1H singlets were present at δ 8.19, 6.87, and 6.64. The ^{1}H NMR spectrum also indicated the absence of the signal due to quinonemethide CH_3-23 suggesting that it had participated in the reaction with DDQ. The ^{13}C NMR spectrum showed the presence of signals due to ten aromatic/olefinic carbons, two carbonyls, one ester carbonyl, and two nitrile carbons. In the HMBC spectrum, the low-field 1H singlet at δ_H 8.19 showed cross peaks with C-3, C-4, C-5, and one of the newly introduced quaternary carbons (C-32) placing this proton at C-23, which is indicative that oxidation of CH_3-23 had occurred to the level of a sp^2-hybridized methine. The additional four carbons and two nitrogens belong to a 1,2-dicyanoethylene moiety bridging C-23 and C-6 to make an aromatic ring, suggesting this product to be pristimerin dicyanophenalenedione (**3**). Detailed analysis of COSY, HMBC, and HSQC correlations (Fig. 1) allowed its structure elucidation and complete assignments of ^{1}H and ^{13}C NMR signals of **3**.

Formation of xuxuarines Eα (**1**) and Eβ (**2**) from pristimerin (**4a**) may require the initial conversion of **4a**

Table 1. ^{1}H, ^{13}C, and HMBC NMR Data for **1** and **2** in $CDCl_3$

Position	**1**						**2**					
	Quinonoid unit			Aromatic unit			Quinonoid unit			Aromatic unit		
	δ_H[a]	δ_C[b]	HMBC[c]	δ_H[a]	δ_C[b]	HMBC[c]	δ_H[a]	δ_C[b]	HMBC[c]	δ_H[a]	δ_C[b]	HMBC[c]
1	6.09d (1.6)	115.17d		6.80s	111.37d	23′	6.08d (1.6)	114.64d		6.74s	110.62d	
2		187.89s[d]			144.57s	1′,23′		187.35s	1		145.13s	1′
3	5.11s (OH)	91.98s	1,3-OH,23		137.55s	23,1′,23′	5.15s (OH)	91.01s	1,3-OH, 23		137.51s	1′,23
4		79.31s	3,6,23		127.59s	7′,23′		76.89s	3,6,23		128.30s	1′,23
5		129.87s	1,7,23		124.44s	1′,7′,23′		131.77s	1,7,23		123.79s	1′,7′,23′
6	6.24dd (6.6,1.6)	126.77d	7		190.22s[d]		6.51dd (6.9,1.6)	128.81d	7		189.42s	7′
7	5.94d (6.6)	116.12d		6.25s	126.11d		6.08d (6.9)	117.15d	6	6.21s	126.12d	
8		161.39s	6,25,26		171.67s	25′,26′		164.36s	6,25,26		171.12s	7′,25′,26′
9		41.93s	1,7,11α, 12α,25		39.94s	1′,7′,25′		43.87s	1,7,25		39.98s	1′,7′,25′
10		174.15s	6,25		150.45s	1′,23′,25′		173.23s	6,25		151.09s	1′,25′
11α	1.82dt (14,6)	32.82t	25	1.94dt (14,4)	34.10t	25′	1.71dt (14,6)	32.84t	25	1.80dt (14,6)	33.93t	25′
11β	1.95dd (14,5)			2.12dd (14,5)			2.03dd (14,5)			2.10brd (14)		
12α	1.77brd (14)	29.47t	27	1.73dd (14,4)	29.86t	27′	1.75dd (14,5)	29.51t	27	1.73dd (14,6)	29.82t	27′
12β	1.59brt (14)			1.64dt (14,5)			1.62dt (14,5)			1.64dt (14,4)		
13		38.12s	18,19β, 26,27		38.95s	18′,19′β, 26′,27′		38.60s	18,19β, 26,27		38.94s	18′,19β′ 26′,27′
14		44.63s	7,12α, 26,27		44.67s	7′,15′α, 15′β, 26′,27′		44.32s	7,26,27		44.63s	7′,26′,27′
15α	1.50dt (14,6)	28.34t	26	1.65dt (14,6)	28.49t	26′	1.56dt (14,6)	28.58t	26	1.61dt (14,6)	28.49t	26′
15β	1.43dd (14,6)			1.58dd (14,6)			1.43dd (14,6)			1.56dd (14,6)		
16α	1.42brd (14)	36.29t	28	1.50brd (14)	36.39t	28′	1.45dd (14,6)	36.34t	28	1.49dd (14,6)	36.37t	
16β	1.80dt (14,6)			1.87dt (14,6)			1.80dd (14,6)			1.87dt (14,6)		
17		30.51s	18,19α,28		30.50s	18′, 19′α,28′		30.51s	18,19α, 28		30.47s	18′,28′
18	1.52d (8)	44.12d	27,28	1.57d (8)	44.28d	19′α, 27′,28′	1.52brd (8.3)	44.22d	12α,19α 28	1.57d (8)	44.22d	27′,28′
19α	2.40d (16)	30.89t	30	2.40d (16)	30.81t	30′	2.39d (16)	30.76t	18	2.40d (16)	30.89d	18′,30′
19β	1.68dd (16,8)			1.64dd (16,8)			1.68dd (16,8)			1.65dd (16,8)		
20		40.40s	18,19α, 19β,30		40.40s	18′,19′α, 19′β,30′		40.41s	18,30		40.50s	18′,19′α, 30
21α	2.17brd (14)	29.83t	19α,30	2.18brd (14)	29.86t	19′α,30′	2.20brd (14)	29.80t	19α,30	2.17brd (14)	29.74t	30′
21β	1.36dt (14,5.5)			1.37dt (14,5)			1.36dt (14,5)			1.39dt (14,4)		
22α	2.00dt (14,4)	34.72t	28	2.05dt (14,5)	34.76t	28′	2.03dt (14,5)	34.70t	18,28	2.03dt (14,5)	34.94t	18′,28′
22β	0.93brd (14)			0.97dd (14,5)			0.95brd (14)			0.97brd (14)		
23	1.58s	22.19q		2.74s	12.95q		1.58s	24.55q		2.73s	13.18q	
25	1.42s	34.88q		1.50s	37.64q		1.38s	39.20q		1.48s	37.66q	

Table 1 (*continued*)

Position	1						2					
	Quinonoid unit			Aromatic unit			Quinonoid unit			Aromatic unit		
	δ_H[a]	δ_C[b]	HMBC[c]	δ_H[a]	δ_C[b]	HMBC[c]	δ_H[a]	δ_C[b]	HMBC[c]	δ_H[a]	δ_C[b]	HMBC[c]
26	1.17s	22.44q		1.28s	20.81q		1.17s	22.31q		1.26s	20.83q	
27	0.55s	18.63q	18	0.54s	18.27q	18′	0.53s	18.16q	18	0.55s	18.42q	18′
28	1.06s	31.54q	18	1.09s	31.58q	18′	1.06s	31.52q	18	1.09s	31.58q	18′
29		178.82s	19β,30, 29-OCH_3		178.73s	19′β,30′, 29′-OCH_3		178.82s	30		179.04s	19′β,30′, 29′-OCH_3
30	1.17s	32.72q	19β	1.16s	32.72q	19′β	1.17s	32.73q		1.15s	32.81q	19′β
OCH_3	3.60s	51.64q		3.54s	51.58q		3.59s	51.60q		3.48s	51.38q	

[a] At 600 MHz, *J* values in Hertz.
[b] At 125 MHz, assignments based on DEPT, HMQC and HMBC experiments.
[c] Protons showing long-range correlations with indicated carbon.
[d] Assignments may be interchanged.

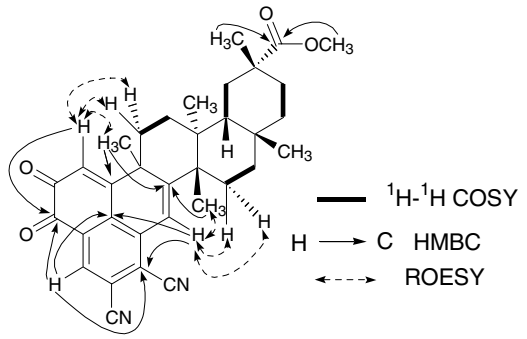


Figure 1. Significant ^{1}H-^{1}H COSY, HMBC, and ROESY correlations for **3**.

into 6-oxo-pristimerol (**6**) followed by (oxidative) coupling with pristimerin. We have previously demonstrated that the oxidation of pristimerol with *N*-bromosuccinimide produces 6-oxo-pristimerol (**6**).[7] As depicted in Figure 2, it is possible that **6** could be formed from pristimerin (**4a**) by the addition of water to its quinonemethide system followed by oxidation with DDQ. Coupling of **4a** and **6** to produce **1** and **2** with C4–O–C3′ linkage may then occur through oxidized pristimerin

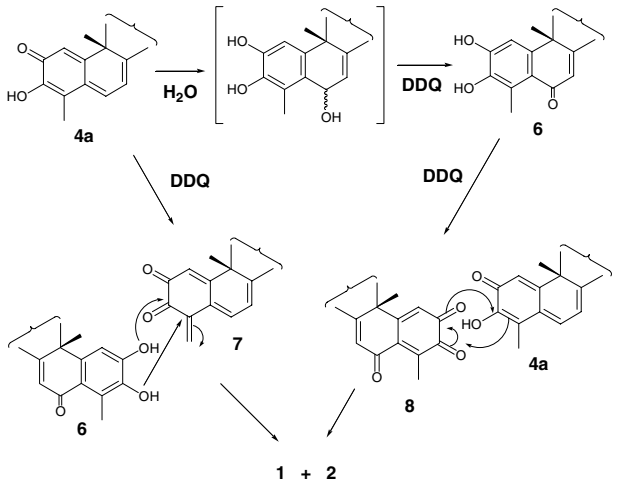


Figure 2. Possible reaction pathways for the formation of dimeric triterpenes **1** and **2** from oxidation of pristimerin (**4a**).

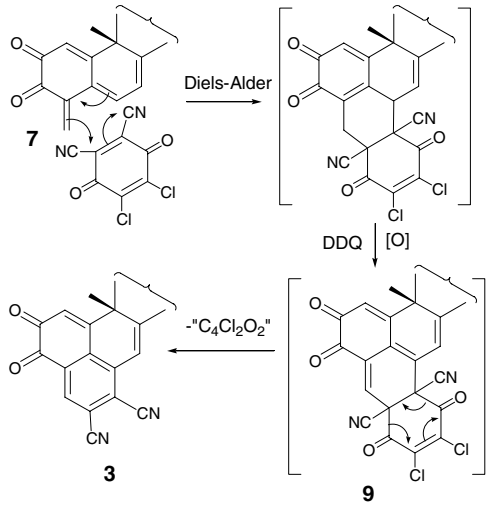


Figure 3. A possible pathway for the formation of **3** from pristimerin (**4a**) and DDQ.

(**7**) or oxidized 6-oxo-pristimerol (**8**). It is noteworthy that the intermediacy of *ortho*-quinones related to **8** has been implicated in the biosynthesis of xuxuarines,[4e] scutidins,[4f] and triscutins.[8] However, the formation of **3** during the DDQ oxidation of pristimerin (**4a**) suggests the possible intermediacy of **7** in the formation of **1** and **2** (Fig. 2). Although rare, Diels-Alder-type reactions between DDQ and dienes similar to that depicted in Figure 3 are known,[9] the hitherto unprecedented *retro*-Diels-Alder-type elimination of a molecule of O=C=(Cl)C–C(Cl)=C=O from the adduct **9** can be explained as due to the thermodynamic stability of the resulting aromatic product **3**. We are continuing our studies to elucidate the mechanism of DDQ-mediated biomimetic-type reaction of pristimerin (**4a**) leading to the formation of **1** and **2**.

3. Experimental

3.1. General experimental procedures

Pristimerin used was isolated from *Cassine balae*[10] and its purity was determined to be >98% by ^{1}H NMR. Re-

agents and solvents for chemical reactions were purchased from Aldrich Chemical Co. Melting points were determined on a Fisher-John's melting point apparatus and are uncorrected. Optical rotations were measured with a Jasco Dip–370 polarimeter. IR spectra were for KBr disks recorded on a Shimadzu FTIR-8300 spectrometer. NMR samples were prepared by dissolving each compound (3.7 mg of **1**, 4.8 mg of **2**, and 3.1 mg of **3**) in 0.5 mL of $CDCl_3$ (0.05% TMS) in a 5 mm NMR tube. ^1H and 2D NMR spectra were acquired at 25 °C on a Bruker DRX-600 spectrometer with a ^1H frequency of 600.13 MHz, using a Nalorac 5 mm inverse HCN Z-gradient probe. ^{13}C and DEPT spectra were acquired at 25 °C on a Bruker DRX-500 spectrometer using a Bruker 5 mm dual ($^{13}C/^1H$) probe. All NMR data were acquired with over-sampling and digital filtering (decimation factor 32 for 2D, 24 for ^1H and 6 for ^{13}C) and processed using the Felix software package (Accelerys, Inc., San Diego, CA).[11] All 1D spectra were referenced to TMS at 0 ppm for ^1H and $CDCl_3$ at 77.0 ppm for ^{13}C. HRMS were recorded on a JEOL HX110A spectrometer. TLC and prep. TLC were performed on silica gel 60 GF_{254} plates (Merck), whereas CC was carried out on silica gel type 60 (Baker).

3.2. Reaction of Pristimerin with DDQ

DDQ (30.1 mg, 131.3 μmol) was added to a stirred solution of pristimerin (51.2 mg, 109.5 μmol) in freshly distilled dry dioxane (5.0 mL) at 25 °C. Reaction was monitored by TLC. After 6 h, TLC indicated the disappearance of pristimerin and its transformation to at least three products. EtOAc (150 mL) was then added to the reaction mixture and the organic phase washed with distilled water (6×100 mL), dried (Na_2SO_4) and evaporated under reduced pressure yielding the crude product mixture (68.2 mg). This was adsorbed onto silica gel (200 mg) and chromatographed over a column of silica gel (3.5 g) made up in hexane and eluted with hexane followed by hexane containing increasing amounts of EtOAc. 10 mL fractions were collected. Fractions (13–15) eluted with 10% EtOAc in hexane were combined and purified on prep. TLC (eluant: 40% EtOAc) to give **1** (3.7 mg). Fractions (16 and 17) eluted with the same solvent were combined and purified on prep. TLC (eluant: 40% EtOAc in hexane) to give **2** (4.8 mg). Middle fractions (20–22) of the column eluted with 20% EtOAc in hexane were combined and purified on prep. TLC (eluant: 40% EtOAc in hexane) to give **3** (3.1 mg).

3.2.1. Xuxuarine Eα (1). Yellow powder; mp 219–221 °C; $[\alpha]_D^{27}$ +361.7 (*c* 1.0, $CHCl_3$) [lit. [4j] + 352.2]; UV (EtOH) λ_{max} (log ε) 207.0 (4.82), 252.5 (4.53), 296.5 (4.33), 379.5 (4.20) nm; IR ν_{max} (KBr) cm^{-1} 3448, 2947, 1728, 1651, 1465, 1303, 1203, 1149; ^1H and ^{13}C NMR see Table 1; HRFABMS *m/z* 943.5724 $[M+1]^+$(calcd for $C_{60}H_{79}O_9$, 943.5724).

3.2.2. Xuxuarine Eβ (2). Yellow powder; mp 198–201 °C; $[\alpha]_D^{27}$ −349.4 (*c* 1.0, $CHCl_3$) [lit. [4h] −352.9]; λ_{max} (log ε) 205.5 (4.60), 253.5 (4.25), 299.5 (4.09), 384.0 (4.03); IR ν_{max} (KBr) cm^{-1}3440, 2947, 1728, 1651, 1465, 1303, 1203, 1149, 1095, 1010; ^1H and ^{13}C NMR see Table 1; HRFABMS *m/z* 943.5724 $[M+1]^+$(calcd for $C_{60}H_{79}O_9$, 943.5724).

3.2.3. Pristimerin dicyanophenalenedione (3). Red powder; mp dec >254 °C; $[\alpha]_D^{27}$ −416.0 (*c* 1.0, $CHCl_3$); UV (EtOH) λmax (log ε) 226.5 (4.42), 305.5 (4.14), 388.5 (3.59) nm; IR ν_{max} (KBr) cm^{-1} 3433, 2947, 1728, 1666, 1589, 1458, 1380, 1203, 1149, 1103; ^1H NMR ($CDCl_3$) δ: 8.19 (1H, s, H-23), 6.87 (1H, s, H-7), 6.64 (1H, s, H-1), 3.57 (3H, s, OMe), 2.42 (1H, d, *J* = 15.7 Hz, H-19α), 2.23 (1H, br d, *J* = 14.2 Hz, H-21α), 2.14 (1H, m, H-11β), 2.04 (1H, dt, *J* = 14.4, 4.2 Hz, H-22α), 1.93 (1H, m, H-11α), 1.91 (1H, m, H-16β), 1.89 (1H, m, H-12α), 1.75 (2H, m, H-15α, H-15β), 1.72 (2H, m, H-12β, H-19β), 1.60 (1H, m, H-18), 1.59 (3H, s, CH_3-25), 1.57 (1H, m, H-16α), 1.41 (1H, dt, *J* = 14.2, 4.7 Hz, H-21β), 1.34 (3H, s, CH_3-26), 1.19 (3H, s, CH_3-30), 1.12 (3H, s, CH_3-28), 1.03 (1H, ddd, *J* = 14.4, 4.0, 3.0 Hz, H-22β), 0.64 (3H, s, CH_3-27); ^{13}C NMR ($CDCl_3$) δ: 178.8 (C, C-29), 178.5 (C, C-2), 177.1 (C, C-3), 165.9 (C, C-8), 164.3 (C, C-10), 137.3 (C, C-6), 131.8 (C, C-31), 130.7 (C, C-5), 130.4 (CH, C-23), 126.5 (CH, C-1), 118.1 (C, C-33/C-34), 116.9 (C, C-32), 115.2 (CH, C-7), 114.4 (C, C-4), 113.6 (C, C-33/C-34), 51.6 (CH_3, OCH_3), 45.5 (C, C-14), 44.2 (CH, C-18), 41.3 (C, C-9), 40.4 (C, C-20), 38.2 (C, C-13), 37.4 (CH_3, C-25), 36.1 (CH_2, C-16), 34.6 (CH_2, C-22), 33.2 (CH_2, C-11), 32.7 (CH_3, C-30), 31.5 (CH_3, C-28), 30.7 (CH_2, C-19), 30.5 (C, C-17), 29.7 (CH_2, C-21), 29.2 (CH_2, C-12), 28.7 (CH_2, C-15), 22.8 (CH_3, C-26), 18.5 (CH_3, C-27); HRFABMS *m/z* 537.6810 $[M+1]^+$ (calcd for $C_{34}H_{37}N_2O_4$, 537.6788).

Acknowledgments

We thank the University of Arizona College of Agriculture and Life Sciences for financial support, CAPES/PICDT (Brazil) for a graduate fellowship (to J.C.), Alex A. Jeller for the initial supply of pristimerin for optimization of reaction conditions, and Dr. Katalin Kövér, University of Debrecen, Hungary, for the gradient-selected phase-sensitive HMBC pulse sequence.

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