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Cyclooxygenase (COX)-1 and -2 Inhibitory Labdane Diterpenes from *Crassocephalum mannii*[#]

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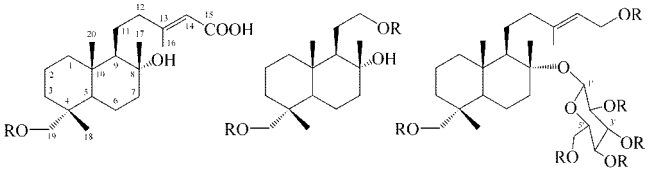
Two new labdane diterpenes, 8α,19-dihydroxylabd-13*E*-en-15-oic acid (**1**) and 13,14,15,16-tetranorlabdane-8α,12,14-triol (**2**), as well as an acetylated derivative, 8α-*O*-*β*-D-glucopyranosyllabd-13*E*-ene-15,19-diol-8α-2′,3′,4′,6′-hexaacetate (**3a**), were isolated from the aerial parts of *Crassocephalum mannii*. The structures of **1**, **2**, and **3a** were elucidated by spectroscopic data analysis. Selective inhibitory activity for **1** and **2** and their acetate derivatives, **1a** and **2a**, against cyclooxygenases (COX-1 and COX-2) was detected.

The genus *Crassocephalum* belongs to the very large and widely distributed Asteraceae family in the tribe Senicioneae.[1] *Crassocephalum* constitutes some 24 known species native to Africa.[1] Many of these species are used widely as food additives or in traditional medicine,[2] prompting phytochemical investigations that have in turn uncovered a variety of alkaloids and coumarins.[3,4] Extracts prepared from this genus exhibit diverse biological activity such as anti-inflammatory,[5] antioxidant, antimalarial, and antifungal effects.[6,7] *Crassocephalum mannii* Hook. f. is a high-elevation annual herb that grows commonly to a height of over 1.5 m. Although whole plant extracts of *C. mannii* are administered in Cameroon to treat stomach maladies, comprehensive chemical screening for bioactivity has yet to be reported. Essential oils have been obtained from leaves and analyzed by GC and GC/MS.[8] Herein we report our screening for terpenoids in *C. mannii*, resulting in the isolation and structure elucidation of two new compounds (**1** and **2**). To probe the stomachache-relieving properties of *C. mannii,* cyclooxygenase (COX) activities were assayed.



1 R = H
1a R = Ac

2 R = H
2a R = Ac

3a R = Ac

A variety of biological activities have been determined for labdane diterpenes including antibacterial, antifungal, antiprotozoal, and anti-inflammatory activities,[9–11] and additionally, recent studies reported the anti-inflammatory activity of labdane diterpenes through their inhibitory activity against cyclooxygenase.[12,13] For use in traditional medicine *Crassocephalum* tea is prepared from fresh plants (500 g plant material/L H_2O) and consumed three times daily until pain subsides.

Prostaglandin H_2 synthase has two isoforms, COX-1 and COX-2. COX-1 is constitutively expressed in mammalian tissues and supports prostaglandin synthesis necessary to maintain organ and tissue homeostasis.[14] In contrast, COX-2 is expressed in response to inflammatory stimuli.[15] Nonsteroidal anti-inflammatory drugs are relatively nonspecific, and since they target COX-1 as well as their intended COX-2 target, they can have adverse side effects such as gastrointestinal ulceration.[16,17] Several strategies have been followed to reduce these adverse effects, including enteric coating, parenteral administration, formulation of pro-drugs that require hepatic metabolism for the cyclooxygenase (COX) activity to be unmasked, and coadministration of either suppressors of acid secretion or exogenous prostaglandins (PGs), without the desired results.[18] A structure-based drug design program has been instituted to create inhibitors that could specifically target COX-2 without affecting COX-1. Since the three-dimensional structures of COX-1 and COX-2 are almost identical, only a few drugs with selective activity have been successfully developed.[19,20]

The air-dried parts of *C. mannii* were extracted sequentially with methylene chloride−methanol (1:1). Purification of this extract produced two new diterpenes, 8α,19-dihydroxylabd-13*E*-en-15-oic acid (**1**) and 13,14,15,16-tetranorlabdane-8α,12,14-triol (**2**), in addition to products **1a**−**3a** obtained after acetylation.

Compound **1** gave the molecular formula $C_{20}H_{34}O_4$, as determined by negative MALDI-TOFMS at *m/z* 337.2379 $[M - H]^-$, which was supported by its NMR data. The ^1H and ^{13}C NMR spectra (Table 1) together with DEPT and $^1H-^{13}C$ COSY experiments indicated the presence of a carboxyl group (δ_C 170.4), an oxygenated methylene (δ_H 3.12, 3.43; δ_C 71.9), and a trisubstituted olefin (δ_H 5.72; δ_C 114.5, 163.4). A one-proton multiplet at δ_H 1.12 was assigned to H-9; in addition, four methyl singlet signals at δ_H 0.74, 1.16, 0.84, and 2.18 were assigned to methyl groups at C-16, C-18, C-19, and C-20, respectively. The positions of the side chain and a hydroxyl group, at C-9 and C-19, respectively, were established by HMBC measurements. The main correlations were from H-9 to C-11 (δ_C 23.6), C-17 (δ_C 24.0), and C-8 (δ_C 74.2), for the side chain, and from H-19 to C-6 (δ_C 20.3), C-4 (δ_C 37.7), C-5 (δ_C 49.2), and C-3 (δ_C 35.2) for the hydroxyl group. The geometry of Δ^{13} was determined to be *E* on the basis of difference NOE experiments. Irradiation of H-14 enhanced H-12 by 1.6%. NOE correlations were observed between H-18/20, H-17/H-20, H-20/H-11, and H-9/H-5 (Figure 1), indicating a *β*-orientation for H-17, H-18, and H-20 and an α-orientation for H-5 and H-9.

Acetylation of **1** afforded the monoacetyl derivative (**1a**), which showed in the ^1H NMR spectrum an acetyl signal at δ_H 2.07 and was supported by negative MALDI-TOFMS, which gave an ion peak at *m/z* 379.2481 $[M - H]^-$. Also, the proton signals of H-19a/H-19b for **1a** were shifted downfield (δ_H 3.88/3.63), compared to those found in **1** (δ_H 3.43/3.12). The other proton and carbon signals

[#] Dedicated to the spirit of the late Prof. Ahmed A. Ahmed.

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Table 1. ^{1}H NMR and ^{13}C NMR Spectroscopic Data for Compounds **1a**, **2**, **2a**, and **3a**[a]

	1		**1a**		**2**		**2a**		**3a**	
no.	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C
1α	0.98 br t (12.4)	39.3 t	0.97 m	39.1 t	0.93 br t (11.0)	38.9 t	0.91 td (12.5, 3.3)	39.0 t	0.90 ddd (13.0, 13.0, 3.0)	38.9 t
1β	1.67 m		1.67 br d (11.0)		1.66 m		1.66 m		1.60 br d (13.0)	
2α	1.45 m	17.8 t	1.47 m	17.6 t	1.46 m	17.8 t	1.50 m	17.5 t	1.45 m	17.4 t
2β	1.57 m		1.51 m		1.51 m		1.63 m		1.50 m	
3α	1.42 m	35.2 t	1.35 m	35.6 t	1.21 m	35.2 t	1.34 m	35.6 t	1.31 m	35. Seven t
3β	1.25 m		1.35 m		1.43 m		1.34 m		1.31 m	
4		37.7 s		36.4 s		37.7 s		36.5 s		36.4 s
5α	1.28 m	49.2 d	1.22 m	49.9 d	1.29 m	49.0 d	1.23 br d (12.5)	49.8 d	1.09 br d (11.5)	50.0 d
5β										
6α	1.57 m	20.3 t	1.56 m	20.4 t	1.57 m	20.2 t	1.52 m	20.3 t	1.52 m	19.8 t
6β	1.26 m		1.24 m		1.29 m		1.29 qd (12.5, 2.9)		1.23 m	
7α	1.44 m	44.4 t	1.35 m	44.3 t	1.39 dd (12.5, 10.5)	44.0 t	1.39 br t (12.5)	43.9 t	1.14 m	40.0 t
7β	1.86 m		1.85 br d (11.0)		1.89 br d (10.5)		1.87 dt (12.5, 2.9)		1.90 m	
8		74.2 s		73.9 s		73.0 s		73.2 s		81.9 s
9	1.12 m	61.4 d	1.12 t (4.0)	61.2 d	1.33 m	59.0 d	1.15 t (4.0)	57.9 d	1.03 br t (3.8)	60.1 d
10		39.1 s		39.0 s		38.9 s		38.6 s		38.8 s
11α	1.67 m	23.6 t	1.35 m	23.5 t	1.64 m	27.9 t	1.62 m	24.5 t	1.55 m	24.3 t
11β	1.42 m		1.65 m		1.64 m		1.75 m		1.20 m	
12α	2.33 m	44.5 t	2.22 m	44.4 t	3.78 m	64.0 t	4.13 m	66.4 t	2.12 m	42.6 t
12β	2.22 m		2.38 m		3.46 m		4.13 m		1.95 m	
13		163.4 s		163.3 s						143.5 s
14	5.72 br s	114.5 d	5.72 br s	113.9 d					5.28 t (7.0)	117.4 d
15α		170.4 s							4.55 d (7.0)	61.5 t
15β			4.55 d (7.0)	169.3 s						
16	2.18 br s	19.4 q	2.18 br s	19.3 q					1.68 br s	16.4 q
17	1.16 s	24.0 q	1.17 s	24.1 q	1.19 s	24.6 q	1.17 s	24.0 q	1.18 s	20.6 q
18	0.74 s	17.4 q	0.81 s	17.3 q	0.73 s	17.4 q	0.81 s	17.4 q	0.76 s	17.2 q
19α	3.43 d (10.7)	71.9 t	3.88 d (11.0)	72.5 t	3.43 d (11.0)	71.8 t	3.87 d (11.0)	72.5 t	3.83 d (11.0)	72.7 t
19β	3.12 d (10.7)		3.63 d (11.0)		3.09 d (11.0)		3.64 (11.0)		3.58 d (11.0)	
20	0.84 s	15.9 q	0.84 s	15.7 q	0.83 s	15.7 q	0.83 s	15.6 q	0.80 s	16.1 q
1′									4.63 d (8.0)	93.9 d
2′									4.84 dd (9.5, 8.0)	71.6 d
3′									5.15 t (9.5)	73.1 d
4′									4.97 t (9.5)	68.9 d
5′									3.61 m	71.2 d
6′a									4.13 dd (12.0,5.5)	62.3 t
6′b									4.06 dd (12.0, 2.5)	
OAc			2.07 s	169.3 s, 21.0 q	2.07 s, 2.10 s	170.7 s, 170.7 s, 20.94 q, 21.06 q			1.95 − 2.02	(168.8−171.0), (20.6 − 21.1)

[a] Multiplicity was determined by DEPT experiments (s = quaternary, d = methine, t = methylene, q = methyl).

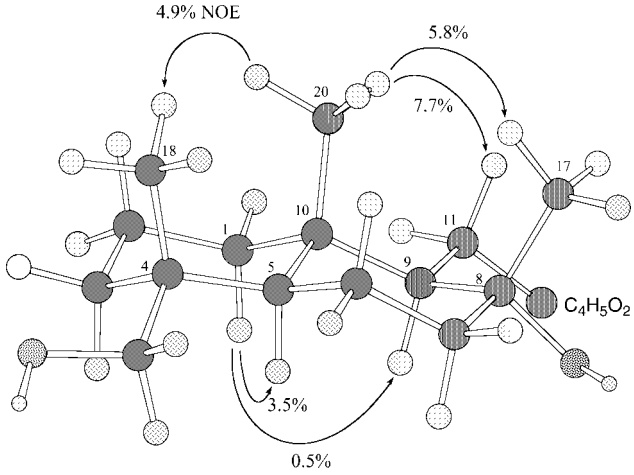

Figure 1. Key NOE correlations and relative stereochemistry for **1a**. Arrows indicate identified NOE correlations.

were close to those of **1** (Table 1). Therefore, compound **1** was identified as the new compound 8α,19-dihydroxylabd-13*E*-en-15-oic acid.

Compound **2** gave the molecular formula $C_{16}H_{30}O_3$ as determined by positive MALDI-TOFMS $[M + Na]^+$ at *m/z* 293.2087, which was supported by its NMR data. The NMR spectra of **2** are summarized in Table 1 and suggested the presence of several structural features in common with isolated compound **1**. The only differences were the disappearance of a carboxylic acid group, an olefinic methyl group (CH_3-16), and an olefinic proton (H-14) in compound **2** and the appearance of a new multiplet corresponding to oxygenated methylene protons at δ_H 3.78 and 3.46. Inspection of HMQC and DEPT spectra of **2** confirmed the presence of three methyls, eight methylenes, two methines, and three quaternary carbons (Table 1). Two of the methylene carbons were oxygenated at δ_C 64.0 (δ_H 3.46, m, H-12b/3.78, m, H-12a) and δ_C 71.8 (δ_H 3.09, d, J = 11.0 Hz, H-19b/3.43, d, J = 11.0 Hz, H-19a).

Acetylation of **2** afforded a diacetyl derivative (**2a**) in which two new acetyl signals at δ_H 2.07 and 2.10 appeared in the ^1H NMR spectrum, which was supported by the (+)-MALDI-TOFMS $[M + Na]^+$ at *m/z* 377.2305. These data were also supported by downfield shifts in the ^1H NMR spectrum of **2a**, H-19$_a$/H-19$_b$ to δ_H 3.87/3.64, compared to δ_H 3.43/3.09 in **2**, and H-12 to δ_H 4.13, compared to δ_H 3.78/3.46 in **2**. The other proton and carbon signals were close to those of **2**. The NOE correlations were observed between H-20/18, H-20/H-17, H-20/H-11, and H-9/H-5 (Figure S1, Supporting Information), indicating the β-orientation of H-16, H-18, and H-19 and the α-orientation of H-5 and H-9 of **2a**. On the basis of these data, the new compound **2** was identified as 13,14,15,16-tetranorlabdane-8α,12,14-triol.

Compound **3a** was isolated in the form of its acetylated derivative, as a yellowish oil with $[\alpha]^{25}_D$ −5.8 (*c* 0.38, $CHCl_3$). The positive MALDI-TOFMS of compound **3a** showed a pseudomolecular ion $[M + Na]^+$ at *m/z* 761.3747, and the molecular formula was established as $C_{38}H_{58}O_{14}$ and confirmed by ^{13}C NMR and DEPT analysis. The IR spectrum revealed absorption bands of carbonyl groups (1733 and 1647 cm^{-1}). The ^1H NMR spectrum of compound **3a** showed characteristic signals for six acetate groups, at δ_H 2.01, 2.02, 1.95, 1.98, and 1.99. In addition, a signal for an anomeric proton at δ_H 4.63 (1H, d, J = 8.0, H-1′) was coupled in the $^1H-^1H$ COSY spectrum with a signal at δ_H 4.84 (1H, dd, J = 8.0, 9.5 Hz, H-2′), and the signal at δ_H 4.97 (t, J = 9.5 Hz, H-4′) showed coupling with two signals at δ_H 5.15 (t, J = 9.5 Hz, H-3′) and δ_H 3.61 (m, H-5′). The two double-doublets at δ_H 4.13 (dd, J = 12.0, 5.5 Hz, H-6′a) and 4.06 (dd, J = 12.0, 2.5 Hz, H-6′$_b$) coupled with one other and with a complex signal at δ_H 3.61 (m, H-5′). The downfield shifts of these protons (H-1′−H-6′) and the HMBC correlations between H-1′−H-4′, H-6′ and the carboxyl carbons indicated complete glucose acetylation (**3a**). The glycosidic linkage was shown to be β on the basis of the magnitude of the coupling constant of the anomeric proton (J = 8.0 Hz).[21] The labdane diterpene skeleton showed an olefinic proton at δ_H 5.28 (1H, t, J = 7.0 Hz, H-14) and an olefinic methyl at δ_H 1.68 (3H, brs, H-16). In addition, two primary alcoholic protons at δ_H 4.55 (2H, d, J = 7.0 Hz, H-15) and 3.83 (1H, d, J = 11.0 Hz, H-19$_a$), which showed a coupling with the proton signal at δ_H 3.58 (1H, d, J = 11.0 Hz, H-19$_b$), indicating the presence of two CH_2−OH moieties, and three methyl groups at δ_H 1.18 (3H, s, H-17), 0.76 (3H, s, H-18), and 0.80 (3H, s, H-20) could be assigned. HMBC correlations between H-19a (δ_H 3.58) and a carboxyl carbon (δ_C 170.9) as well as H-15 (δ_H 4.55) and a carboxyl carbon (δ_C 171.0) indicated that two of the six acetate groups are situated on the aglycon.

Table 2. COX-1 and COX-2 Inhibitory Effects of Compounds **1**, **1a**, **2**, and **2a**

	% COX inhibition (100 μM)	
compound	COX-1	COX-2
1	29	64
1a	2	25
2	44	0
2a	18	0

^{13}C, HMQC, and DEPT NMR spectroscopic inspection of the aglycon moiety of **3a** confirmed the presence of four methyls, nine methylenes, three methines, and four quaternary carbons (Table 1). Two of the methylene carbons were oxygenated at δ_C 61.5 (δ_H 4.55) and 72.7 (δ_H 3.58/3.83), and on the basis of 2J and 3J correlations from the methyl protons at C-20 and C-16, respectively, observed in the HMBC spectrum, the methylene carbons at δ_C 61.5 and 72.7 could be assigned to C-15 and C-19, in turn. A further correlation was observed for methylene protons at C-19 with an olefinic carbon at δ_C 117.4. The HMBC spectrum also revealed the correlation between the anomeric proton and the carbon at δ_C 81.9, which established C-8 as the point of linkage to the aglycon. In addition, correlations between carbons at δ_C 24.3 (C-11), 42.6 (C-12), and 81.9 (C-8) and the methine proton at δ_H 3.8 allowed for the assignment of H-9. In the $^1H-^1H$ COSY spectrum, the above-mentioned methine at δ_H 3.8 (H-9) showed correlations with the methylene signal at δ_H 1.20 and 1.55 (H-11), which further correlated with another methylene at δ_H 1.95 and 2.12 (H-12). The $^1H-^1H$ COSY spectrum revealed the existence of fragment $-CH_2-CH_2-CH_2-$, from C-1 to C-3, and the fragment $-CH-CH_2-CH_2-C(CH_3)=CH-CH_2-$ from C-9 to C-15 for the side chain, which were confirmed by HMQC and HMBC spectroscopic analysis.

The geometry of Δ^{13} was determined to be *E* on the basis of difference NOE experiments. Irradiation of H-14 and H_3-16 enhanced H-12 and H-15, respectively. The relative configuration of **3a** was determined by the ^1H NMR coupling constants and the results of a series of difference NOE experiments (Figure S2, Supporting Information). Irradiation of H_3-20 enhanced CH_3-18 and CH_3-17. Irradiation of H-9 enhanced H-5 and suggested that CH_3-17, CH_3-18, and CH_3-20 are on the same side and H-9 and H-5 are on the opposite side. Compound **3a** was identified as 8α-*O*-β-D-glucopyranosyllabd-13*E*-ene-15,19-diol-8α-2′,3′,4′,6′-hexaacetate.

COX-1 and COX-2 inhibitory effects for compounds **1**, **1a**, **2**, and **2a** were assayed (Table 2). Compounds **1** and **1a** showed selective inhibitory activity against the inducible COX-2 isoform, while compounds **2** and **2a** exhibited inhibition with only the COX-1 isoform.

Experimental Section

General Experimental Procedures. Optical rotations were determined using a HORIBA SEPA-300 polarimeter. IR spectra were

recorded on a HORIBA FT -720 spectrometer. ^{1}H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$), and the 2D spectra were recorded on a JEOL AL400 spectrometer, with TMS as an internal standard. MALDI-TOFMS were recorded on an Applied Biosystems Voyager-DE PRO mass spectrometer.

Column chromatography was carried out on silica gel 60 (Merck; 230−400 mesh) and Sephadex LH-20 (Pharmacia Co., Tokyo, Japan). TLC: precoated silica gel type 60 (Merck). CC: silica gel type 60 (Merck) and Sephadex LH-20 (Pharmacia Co., Tokyo, Japan). HPLC was performed in the reversed phase with a Knauer pump 64 and using a preparative differential refractometer detector (column: Phenomenex RP-18, 250 × 25 mm, flow = 17 mL/min, elution with MeOH−H_2O mixtures).

Plant Material. The entire above-ground portion of *Crassocephalum mannii* was collected on Campus C, from the University of Dschang, Dschang, Cameroon, in July 2004. The plant material was identified by Dr. J. M. Onana of the National Herbarium in Yaoundé, Cameroon, where a voucher specimen (No. 23656 SFR/Cam) was deposited.

Extraction and Isolation. Air-dried plant material (800 g) was ground and extracted with CH_2Cl_2−MeOH (1:1) at room temperature. The extract was concentrated under reduced pressure to obtain a residue of 16 g. The residue was prefractionated by column chromatography (6 × 120 cm) on silica gel eluting with *n*-hexane (3 L) followed by a gradient of *n*-hexane−CH_2Cl_2 up to 100% CH_2Cl_2 and CH_2Cl_2−MeOH up to 50% MeOH (2 L each of the solvent mixture). The CH_2Cl_2 (100%) fraction was subjected to passage over a Sephadex LH-20 column (2 × 60 cm), eluted with *n*-hexane−CH_2Cl_2−MeOH, to give compounds **1** (8 mg) and **2** (10 mg). The CH_2Cl_2−MeOH (1:1) fraction was found to be a mixture of polar compounds and was acetylated as described under the acetylation section to facilitate purification. Compound **3a** was isolated from this acetylated fraction and ultimately purified by passage over a reversed-phase C_{18} column (250 × 4.6 mm i.d., 5 μm) eluted in a pure form with MeOH−H_2O (60:40) (5 mg).

Acetylation of Compounds 1 and 2. Compounds **1** and **2** were dried and stirred with Ac_2O and pyridine at room temperature for 24 h. Solvent was removed under reduced pressure, and individual products were subjected to Sephadex LH-20 column chromatography using *n*-hexane−CH_2Cl_2−MeOH (7:4:1) eluting solvent to yield compounds **1a** (4 mg), and **2a** (5 mg).

8α,19-Dihydroxylabd-13*E*-en-15-oic acid (1): yellowish-white powder; $[\alpha]^{25}_D$ +26 (*c* 0.27, $CHCl_3$); IR ν_{max} (film) 2500−3600, 1695, 1645 cm^{-1}; ^{1}H ($CDCl_3$, 400 MHz) and ^{13}C ($CDCl_3$, 100 MHz) NMR data, see Table 1; (−)-MALDI-TOFMS *m*/*z* $[M - H]^-$ 337.2379 (calcd for $C_{20}H_{33}O_4$ 337.2379).

8α,19-Diacetoxylabd-13*E*-en-15-oic acid (1a): yellowish oil; $[\alpha]^{25}_D$ +14 (*c* 0.18, $CHCl_3$); IR ν_{max} (film) 2500−3600, 1733, 1700, 1647 cm^{-1}; ^{1}H ($CDCl_3$, 400 MHz) and ^{13}C ($CDCl_3$, 100 MHz) NMR data, see Table 1; (−)-MALDI-TOFMS *m*/*z* $[M - H]^-$ 379.2481 (calcd for $C_{22}H_{35}O_5$, 379.2485).

13,14,15,16-Tetranorlabdane-8α,12,14-triol (2): yellowish-brown powder; $[\alpha]^{25}_D$ +11 (*c* 0.47, $CHCl_3$); IR ν_{max} (film) 3360 cm^{-1}; ^{1}H ($CDCl_3$, 400 MHz) and ^{13}C ($CDCl_3$, 100 MHz) NMR data, see Table 1; MALDI-TOFMS *m*/*z* $[M + Na]^+$ 293.2087 (calcd for $C_{16}H_{30}O_3Na$ 293.2092).

12,14-Diacetoxy-13,14,15,16-tetranorlabdan-8α-ol (2a): yellowish oil; $[\alpha]^{25}_D$ +25 (*c* 0.38, $CHCl_3$); IR ν_{max} (film) 3460, 1731 cm^{-1}; ^{1}H ($CDCl_3$, 400 MHz) and ^{13}C ($CDCl_3$, 100 MHz) NMR data, see Table 1; MALDI-TOFMS *m*/*z* $[M + Na]^+$ 377.2305 (calcd for $C_{20}H_{34}O_5Na$ 377.2303).

8α-*O*-*β*-D-Glucopyranosyllabd-13E-ene-15,19-diol-8α-2′,3′,4′,6′-hexaacetate (3a): yellowish oil; $[\alpha]^{25}_D$ −5.8 (*c* 0.38, $CHCl_3$); IR ν_{max} (film) 1733, 1647 cm^{-1}; ^{1}H ($CDCl_3$, 400 MHz) and ^{13}C ($CDCl_3$, 100 MHz) NMR data, see Table 1; (+)-MALDI-TOFMS *m*/*z* $[M + Na]^+$ 761.3747 (calcd for $C_{38}H_{58}O_{14}Na$ 761.3724).

In Vitro Cyclooxygenase (COX) Inhibitory Assay. The COX inhibitory activity of compounds **1** and **2** and their acetylated products **1a** and **2a** was measured using ovine COX-1 and human recombinant COX-2 enzymes by a COX inhibitor screening assay kit from Cayman Chemical Co. (Ann Arbor, MI). The data were normalized with a standard curve for COX inhibitors; inhibitors were provided by the manufacturer and run at the time of analysis as prescribed in the assay manual. The protocol allows for isozyme-specific inhibitor screening. Compounds were examined at a final concentration of 100 μM.[22,23] In the COX inhibitor screening assay, naproxen was used (100 μM) as a nonselective inhibitor and led to an inhibition of 72% and 86% for COX-1 and COX-2, respectively.

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Supporting Information Available: NOE correlations and relative stereochemistry for **2a** and **3a** are shown in Figures S1 and S2, respectively. This information is available free of charge via the Internet at http://pubs.acs.org.

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