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Uragogin and blepharodin, unprecedented hetero-Diels–Alder adducts from *Celastraceae* species

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ABSTRACT

Uragogin and blepharodin were isolated from *Crossopetalum uragoga* and *Maytenus magellanica*, respectively. They represent the first examples of a triterpene–neolignan ester and a heptacyclic arylpropanoid-nor-triterpenephenol, hetero-Diels–Alder adducts built with dioxane bridges. Their proposed biosynthetic route is discussed.

1. Introduction

There are a number of natural products whose structures involve biological Diels–Alder reactions in their biosynthesis.[1,2] It has been difficult to verify the existence of a biosynthetic Diels-Alderase, however, for the first time, cell-free extracts of the fungus *Alternaria solani* were shown to catalyze a Diels–Alder-type cycloaddition.[3] Furthermore, macrophomate synthase catalyzes an unusual multistep reaction cascade involving C–C bond formation, which has been proposed as proceeding through a concerted Diels–Alder mechanism.[4] The enzyme's crystal structure was reported as the first example of a biological Diels-Alderase.[5] Recently, the solanapyrone biosynthetic gene cluster was identified, and the functional analysis of solanapyrone synthase established that this protein catalyzes both the oxidation and the [4+2] cycloaddition, acting as a possible Diels-Alderase.[6] Furthermore, it appears that lovastatin and structurally related polyketides utilize a Diels-Alderase to cyclize their backbone.[7]

The species of the *Celastraceae* biosynthesize dimeric[8–10] and trimeric[11] triterpenes, and octacyclic sesquiterpene-triterpene adducts[12] possibly by hetero-Diels–Alder reactions through the formation of a 1-4 dioxane system. Moreover, the isolation of adducts Diels–Alder decacyclic C20–C30[13] and diterpene dimers[14,15] have been reported for *Celastraceae*.

In the present work, we report on the isolation, structure elucidation and possible biosynthetic route of the first examples of a triterpene–neolignan ester (**1**) and a heptacyclic arylpropanoid-nor-triterpenephenol (**2**), hetero-Diels–Alder adducts built with dioxane bridges. In addition, twelve known compounds were isolated and characterized by comparison of their spectra with data reported in the literature.

2. Results and discussion

The EtOH extract of the stems of *Crossopetalum uragoga* and the *n*-hexane:Et_2O (1:1) extract of the root bark of *Maytenus magellanica* were subjected to repeated chromatography on Sephadex LH-20 and silica gel, affording uragogin (**1**), and blepharodin (**2**), respectively. In addition, twelve known compounds were isolated and identified as 3β-caffeoyl-olean-12 ene,[16] β-amyrin,[17] β-amyrone,[18] oleanolic acid,[19] olean-12-ene-3,11-dione,[20] 3β-caffeoyl-olean-9:12-diene,[16] 9(11),12-oleanadien-3-one,[21] blepharodol,[22] tingenone,[23] celastrol,[24] dispermoquinone,[25] and pristimerin.[26]

Compound **1** was isolated as a colorless lacquer and its molecular formula, $C_{51}H_{68}O_8$, was established by HREIMS (M^+, *m*/*z* 808.4974), indicating 18 degrees of unsaturation. Its IR spectrum showed the presence of hydroxyl (3434 cm^{-1}), ester (1742 cm^{-1}), and α,β-unsaturated ester (1703 cm^{-1}) groups. The ^1H NMR spectrum of **1** (Table 1) indicated the presence of eight methyls (δ_H 0.84–1.15), a methine proton as a triplet at δ_H 4.63 (t, *J*=8.2 Hz, H-3) and a vinyl proton as a broad singlet at δ_H 5.19, characteristic of

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Table 1
^{1}H and ^{13}C NMR data for uragogin (**1**) and blepharodin (**2**) (δ in ppm, J in Hz)

Uragogin (**1**)								Blepharodin (**2**)							
Triterpenic unit				Neolignan unit				nor-Triterpenophenol unit				Aryl-propanoid unit			
	δ_H[a]	δ_C[b]	HMBC		δ_H[a]	δ_C[b]	HMBC		δ_H[a]	δ_C[b]	HMBC		δ_H[a]	δ_C[b]	HMBC
1	1.10, 1.65	38.3		1′		127.3		1	6.79 s	109.1	2,[c] 3, 5	1′		126.5	
2	1.69	22.7		2′	6.86 s	109.3	1′,[c] 4′, 6′, 7′	2		146.6		2′	6.58	104.2	1′,[c] 3′,[c] 4′, 6′,7′
3	4.63 t (8.2)	80.9	2,[c] 23, 24, 4,[c] 9″	3′		147.0		3		139.5		3′		147.4	
4		37.9		4′		146.6		4		130.0		4′		135.8	
5	0.90 m	55.3	7, 23, 24	5′	6.95 d (8.1)	114.8	1′, 3′	5		125.0		OH-4′	5.62 br s		3′, 4′,[c] 5′
6	1.55	18.3		6′	6.90 dd (1.5,8.1)	120.8	1′,[c] 2′, 4′, 7′	6		200.7		5′		147.4	
7	1.35, 1.53	32.5		7′	4.88 d (7.8)	76.4	1′,[c] 2′, 3″, 6′, 8′[c]	7	2.55 dd (5.1, 10.3)	37.7	6, 8, 9	6′	6.58	104.2	1′,[c] 2′, 4′, 5′,[c] 7′
8		39.8		8′	4.26 m	76.0	7′,[c] 1′, OAc s	8	2.25 d (5.7, 10.3)	42.6		7′	4.83 d (7.9)	77.2	1′, 2′, 6′, 8′[c]
9	1.95	47.5	7, 8, 26	9′	4.31 m 3.96 dd (4.5, 12.7)	62.9	OAc s	9		37.2		8′	4.25 m	75.5	
10		36.9		OMe	3.91 s	56.0		10		152.2		9′	4.04 dd (4.7, 12.0) 4.33 dd (4.3, 12.0)	62.8	8′,[c] OAc s
11	1.90	23.5	12,[c] 13	OAc	2.08 s	20.7 170.4	3′	11	1.88	33.2		OMe	3.90 s	56.4	3′, 5′
12	5.19 br s	121.6	11,[c] 13,[c] 14, 18	1″		128.5	9′	12	1.40	29.9		OAc	2.05 s	20.6170.3	OAc s
13		145.2		2″	7.16 d (1.6)	116.6		13		38.8					
14		41.7		3″		143.8	3″,[c] 4″, 6″, 7″	14		39.4					
15	0.97, 1.76	26.1		4″		144.8		15	1.22	28.5					
16	0.81, 2.00	26.9		5″	6.97 d (8.3)	117.5	4″,[c] 1″	16	1.40, 1.72	36.2					
17		32.6		6″	7.11 dd (1.6, 8.3)	122.2	2″, 4″, 5″,[c] 7″	17		30.3					
18	1.60	47.2	12	7″	7.57 d (15.9)	143.7	1″,[c] 2″, 6″, 9″	18	1.64	44.7					
19	1.20, 1.68	46.8		8″	6.30 d (15.9)	117.3	1″, 9″[c]	19	1.66, 2.40	30.5					
20		31.1		9″		167.0		20		40.1					
21	1.10, 1.33	34.7						21	1.38	29.8					
22	1.22, 1.43	37.1						22	0.99, 2.05	36.1					
23	0.92 s	28.1	3, 4,[c] 5					23	2.50 s	13.2	3, 4,[c] 5				
24	0.94 s	16.8	3, 4,[c] 5					25	1.16 s	25.6	8, 9,[c] 10, 11				
25	0.98 s	15.5	1, 5, 9, 10[c]					26	1.02 s	15.4	8, 13,[c] 14, 15				
26	0.99 s	16.8	8,[c] 14, 27					27	0.78 s	16.9	12, 13, 14,[c] 18				
27	1.15 s	25.9	13, 14,[c] 26					28	1.09 s	31.7	18, 22				
28	0.84 s	28.4	16, 17,[c] 22					29		179.1					
29	0.88 s	33.3	20, 30					30	1.18 s	32.2	20,[c] 19, 29				
30	0.88 s	23.7	19, 20, 29					OMe	3.59 s	51.4	29				

[a] Measured at 400 MHz in $CDCl_3$.
[b] Measured at 100 MHz in $CDCl_3$.
[c] Two-bond correlations.

a Δ^{12}-oleane skeleton.[27] This was confirmed by the ^{13}C NMR spectrum (Table 1) with signals at δ_C 15.5–33.3, δ_C 121.6, and δ_C 145.2, attributed to eight methyl groups and to carbons 12 and 13 of the Δ^{12}-oleane skeleton. In addition, the ^{1}H NMR spectrum revealed the presence of an *O*-caffeoyl moiety by the signals at δ_H 7.57 (H-7″) and δ_H 6.30 (H-8″), assigned to a trans double bond (J=15.9 Hz), and a typical ABX spin system in an aromatic ring with *meta*, *ortho*/*meta*, and *ortho* substitutions (H-2″, H-6″and H-5″). The *O*-caffeoyl moiety was located at C-3 by an HMBC experiment, showing long-range correlations between the proton signal at δ_H 4.63 (H-3) and the carbon signals at δ_C 22.7 (C-2), 28.1 (C-23), 16.8 (C-24), 37.9 (C-4), and 167.0 (C-9″). Due to the correlations of the H-3 with H-5 and Me-23 observed in a ROESY experiment (Fig. 1), the relative stereochemistry of the *O*-caffeoyl group was established to be β. These data indicated that compound **1** contains a unit corresponding to the 3β-caffeoyl-olean-12-ene, previously reported from *Celastrus hypoleucus*[16] and also isolated in this study.

Furthermore, proton signals assigned to an acetate methyl (δ_H 2.08), an oxymethylene (δ_H 3.96, dd, J=4.5, 12.7 Hz, H-9′ and δ_H 4.31, m, H-9′) and two oxymethines (δ_H 4.88, d, J=7.8 Hz, H-7′ and δ_H 4.26, m, H-8′), as well as signals corresponding to a methoxyl group (δ_H 3.91) and a benzyl aromatic ring [δ_H 6.86 (1H, s, H-2′), δ_H 6.90 (1H, dd, J=1.5, 8.1 Hz, H-6′), and δ_H 6.95 (1H, d, J=8.1 Hz, H-5′)] were observed. Careful analysis of the COSY and HMBC experiments indicated that compound **1** also presents an arylpropane unit related to the *trans*-coniferyl acetate.[28] The $^{1}H-^{1}H$ COSY revealed coupling patterns of the oxymethine protons H-7′ and H-8′ with the oxymethylene H_2-9′. Moreover, the deshielded doublet at δ_H 4.88 (H-7′), typical of a benzylic methine attached to an oxygen and the multiplet at δ_H 4.26 (H-8′), suggest the presence of a 1,4-dioxane ring[29] between the arylpropane and the 3β-caffeoyl-olean-12-ene units.

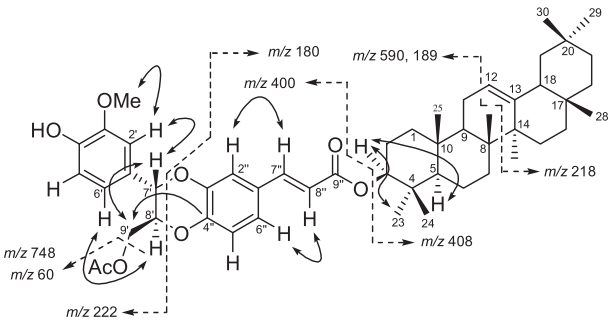

Fig. 1. Selected ROESY (double arrow) and selective 1D HMBC (single arrow) correlation, and mass fragmentation patterns (dashed line) for **1**.

These data indicated that compound **1** is a triterpene–neolignan ester built on a 1,4-dioxane bridge, which is also supported by the fragmentation peaks observed in the EIMS spectrum (Fig. 1). The regioisomeric orientation of the arylpropane unit was deduced by a selective 1D HMBC experiment (Fig. 1). Thus, selective irradiation at C-4′ (δ_C 144.8) collapsed the proton signal at δ_H 3.96 (H2-9′), indicating the linkages between the units as [7′-*O*-3″] and [8′-*O*-4″]. The relative trans stereochemistry of the dioxane moiety was determined by a $J_{H\text{-}7'/H\text{-}8'}$ value of 7.8 Hz. Furthermore, this was confirmed by a ROESY experiment, showing ROE effect of H-7′ with H_2-9′ and H-2′ and correlation of H-8′ with H-6′ (Fig. 1), clearly indicating a trans configuration of the chiral centers of the dioxane ring.[29] Accordingly, the structure of uragogin (**1**) was established as 3β-{(2*E*)-3-[2-(acetoxy)methyl-3-(4-hydroxy-3-methoxyphenyl)-2,3-dihydro-1,4-benzodioxin-6-yl]-2-(propenoyl)oxy}-olean-12-ene. To the best of our knowledge, it represents the first example of a triterpene–neolignan ester adduct.

Compound **2** was isolated as a colorless lacquer and showed a molecular formula of $C_{43}H_{56}O_{10}$ by HREIMS, ^{1}H and ^{13}C NMR data (Table 1), indicating 16° of unsaturation. The IR spectrum showed absorption bands for hydroxyl (3541 cm^{-1}), ester (1731 cm^{-1}), and ketone (1663 cm^{-1}) groups. The ^{13}C spectrum showed 30 resonances including, seven methyls, eight methylenes, three methines, and twelve quaternary carbons. The observed quaternary carbon resonances at δ_C 200.7 and 179.1 were consistent with the presence of a conjugate ketone and a carboxyl group, respectively. Moreover, the signals at δ_C 109.1, 125.0, 130.0, 139.5, 146.6, and 152.2 were assigned to an aromatic ring and the resonance at δ_C 51.4 was due to a methoxyl group. These assignments were in agreement with the ^{1}H NMR spectrum, showing signals corresponding to six methyls (δ_H 0.78, 1.02, 1.09, 1.16, 1.18, and 2.50), a singlet due to a methoxyl group at δ_H 3.59 and an aromatic methine proton at δ_H 6.79. Furthermore, the chemical shifts for the carbons attached to protons were corroborated by a 2D heteronuclear HSQC experiment. These data indicate that compound **2** contains a nor-triterpene phenolic unit based on a friedelan skeleton similar to blepharodol,[22] a nor-triterpenephenol also isolated in this study.

In addition, the HREIMS (Fig. 2), ^{1}H and ^{13}C NMR data of compound **2** showed signals revealing a C_6–C_3 unit related to sinapyl acetate.[30] Thus, the ^{1}H NMR spectrum showed a signal corresponding to two aromatic protons at δ_H 6.58 (H-2′ and H-6′), a resonance at δ_H 5.62, interchangeable with D_2O, indicating the presence of a phenolic group and two methoxyl groups (6H, δ_H 3.90). Moreover, resonances for two oxymethine and one oxymethylene protons [δ_H 4.83 (1H, d, J=7.9 Hz, H-7′), δ_H 4.25 (1H, m, H-8′), δ_H 4.04 and 4.33 (each 1H, dd, J=4.7, 12.0 Hz and 4.3, 12.0 Hz, H_2-9′)] were observed, as well as an acetyl group at δ_H 2.05. These data were confirmed by the ^{13}C NMR spectrum and a 2D heteronuclear HSQC experiment. The regiosubstitution of the C_6–C_3 unit was solved by an HMBC experiment, showing correlations of H-9′ with C-8′ and the acetoxy carbonyl, cross-peaks between H-7′ and C-1′, C-2′, C-6′, and C-8′, correlations of OH-4′ with C-3′, C-4′, and C-5′, and those of OCH_3 with C-3′ and C-5′. These observations confirmed the aryl-propanoid unit in **2**.

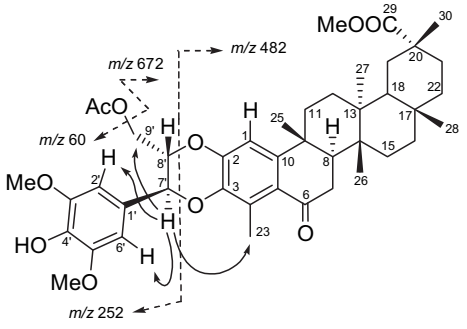

Fig. 2. NOE effects observed in a 1D GOESY experiment by irradiation of H-7′ (single arrow) and mass fragmentation patterns (dashed line) for **2**.

Both units are linked through a 1,4-dioxane bridge between the phenolic moiety in the triterpene and the C-7′, C-8′ carbons of the C_6–C_3 unit. This fact is consistent with the fragments at *m*/*z* 252 ($C_{13}H_{16}O_5$) and 482 ($C_{30}H_{42}O_5$) observed in the EIMS spectrum (Fig. 2). The relative trans stereochemistry of the dioxane moiety was assigned by the $J_{H\text{-}7'/H\text{-}8'}$ value of 7.9 Hz[29] and confirmed by a 1D GOESY experiment[31] (Fig. 2), as selective irradiation of H-7′ signal enhances H-9′. The regiosubstitution of the dioxane bridge was also determined by selective irradiation of H-9′ in the 1D GOESY experiment (Fig. 2), causing an enhancement of the Me-23, indicating the linkages between the units as [2-*O*-8′] and [3-*O*-7′]. Therefore, the structure of compound **2** was established as 2,3-{2-[(acetoxy) methyl]-3-(4-hydroxy-3,5-dimethoxyphenyl)ethane -1,2-dioxyl}-6-oxo-24-nor-friedelan-1:3:5(10)-trien-29-oic acid methyl ester. This compound, to which we have given the trivial name blepharodin, has an unprecedented heptacyclic aryl-propanoid-nor-triterpenephenol skeleton.

The biosynthesis of natural occurring compounds containing a 1,4-dioxane ring, as in neolignans, has been proposed through an oxidative coupling pathway.[32] Moreover, the biosynthesis of dimeric and trimeric triterpenes containing a 1,4-dioxane bridge, which are chemotaxanomic markers of the *Celastraceae* species, has been hypothesized via Diels-Alderase systems.[8–11] Based on this hypothesis, we propose the biosynthesis of the 1,4-dioxane ring in compounds **1** and **2** through hetero-Diels–Alder reactions, as shown in Fig. 3. Thus, **1** could be formed by the reaction of *trans*-coniferyl acetate[28] (**1a**) with 3β-caffeoyl-olean-12-ene[16] as *ortho*-quinone (**1b**). Furthermore, hetero-Diels–Alder reaction between blepharodol,[22] in its *ortho*-quinone form (**2b**), and sinapyl acetate[30] (**2a**) could afford compound **2**. This is also supported by the fact that their precursors, 3β-caffeoyl-olean-12-ene and blepharodol, have been isolated from *C. uragoga* and *M. magellanica*, respectively. Further investigation will be conducted to corroborate this hypothesis by synthesizing these particular metabolites from the isolated precursors via chemical and/or enzymatic procedures.

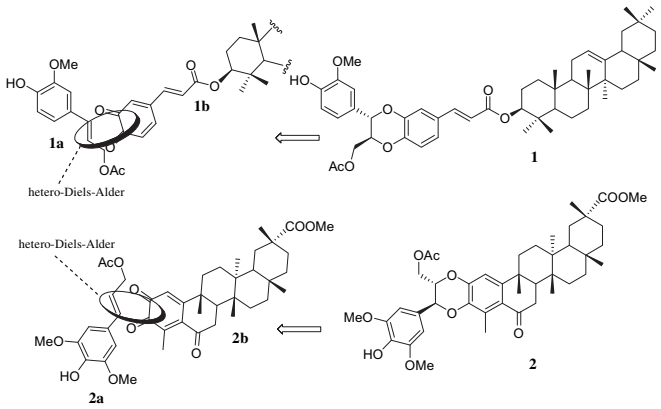

Fig. 3. Proposed biosynthesis of the 1,4-dioxane ring in uragogin (**1**) and blepharodin (**2**) via hetero-Diels–Alder reactions.

3. Experimental

3.1. General experimental procedures

Optical rotations were determined on a Perkin–Elmer 241 polarimeter equipped with a sodium lamp (589 nm) and 10 cm microcell. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker Avance 400 spectrometer; chemical shifts

were referred to the residual solvent signal ($CDCl_3$: δ_H 7.26, δ_C 77.0); DEPT, COSY, ROESY, HSQC and HMBC experiments were carried out with the pulse sequences given by Bruker. The selective 90° (^{13}C) pulse used in recording selective 1D HMBC was a 10 ms rectangular pulse, and the mixing time used in the selective 1D GOESY was 500 ms. UV and IR spectra were obtained employing Jasco V-560 and Bruker IFS 55 spectrophotometers, respectively. EIMS and HREIMS were measured on a Micromass Autospec spectrometer. Silica gel 60 (particle size 15–40 and 63–200 μm, Machery–Nagel) and Sephadex LH-20 (Pharmacia Biotech) were used for column chromatography, while silica gel 60 F_{254} (Machery–Nagel) was used for analytical and preparative TLC. The spots were visualized by UV light and heated silica gel plates sprayed with H_2O/H_2SO_4/HOAc (1:4:20).

3.2. Plant material

The stems of *C. uragoga* were collected in July 2008, in the Parque Nacional 'El Imposible', El Salvador. A voucher specimen (JMR-577) was deposited at the Herbario del Jardín Botánico La Laguna, Antiguo Cuscatlán, El Salvador. The root bark of *M. magellanica* was collected in the Novena Región in Temuca province on the slopes of the Osorno volcano, Chile, in December 2003 and a voucher specimen (93-5342-A) is on file with the Facultad de Ciencias Químicas, Universidad de Chile.

3.3. Extraction and isolation

The dried stems of *C. uragoga* (1.0 kg) were sliced into chips, extracted with EtOH in a Soxhlet apparatus, and concentrated under reduced pressure. The extract (50.6 g) was partitioned between CH_2Cl_2/H_2O (1:1) to provide CH_2Cl_2 (7.6 g) and H_2O fractions (25.3 g). The CH_2Cl_2 fraction was chromatographed on a silica gel column, using increasing polarity mixtures of *n*-hexane/EtOAc as eluant to afford four fractions. Fraction 2 was subjected to column chromatography over Sephadex LH-20 (*n*-hexane/$CHCl_3$/MeOH 2:1:1) and silica gel (CH_2Cl_2-acetone of increasing polarity). Preparative HPTLC was used to purify compound **1** (CH_2Cl_2/acetone 7:3, 4.3 mg).

The root bark of *M. magellanica* (570.0 g) was extracted with *n*-hexane/Et_2O in a Soxhlet apparatus. The extract (13.5 g) was chromatographed on Sephadex LH-20 (*n*-hexane/$CHCl_3$/MeOH 2:1:1) to afford 55 fractions, which were combined in eleven fractions (A–K) on the basis of their TLC profiles. Fraction C was repeatedly chromatographed on Sephadex LH-20, silica gel (CH_2Cl_2/Et_2O of increasing polarity), and preparative HPTLC developed with *n*-hexane/Et_2O (6:4) gave rise to compound **2** (9.3 mg).

*3.3.1. Uragogin (**1**).* Colorless lacquer; $[\alpha]_{D^{20}}$ +25.8 (*c* 0.12, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 217 (4.08), 235 (4.01), 288 (3.89), 297 (3.89), 320 (3.88) nm; IR (KBr) ν_{max} 3434, 2926, 2854, 1742, 1703, 1636, 1464, 1270, 760 cm^{-1}; ^1H NMR ($CDCl_3$), see Table 1; ^{13}C NMR ($CDCl_3$), see Table 1; EIMS *m*/*z* (rel int.) 808 (M^+, 4), 748 (21), 590 (21), 400 (37), 408 (9), 218 (100), 222 (28), 189 (23), 180 (7), 60 (5); HREIMS *m*/*z* 808.4974 (calcd for $C_{51}H_{68}O_8$, 808.4914).

*3.3.2. Blepharodin (**2**).* Colorless lacquer, $[\alpha]_{D^{20}}$ −8.5 (*c* 0.82, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 236 (4.02), 279 (3.77), 311 (3.34) nm; IR (KBr) ν_{max} 3541, 2927, 2870, 1731, 1663, 1464, 1313, 1216, 756 cm^{-1}; ^1H NMR ($CDCl_3$), see Table 1; ^{13}C NMR ($CDCl_3$), see Table 1; EIMS *m*/*z* (rel int.) 732 (M^+, 100), 672 (45), 565 (79), 507 (24), 252 (72), 209 (24), 192 (38), 105 (23), 60 (4); HREIMS *m*/*z* 732.3862 (calcd for $C_{43}H_{56}O_{10}$, 732.3874).

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Supplementary data

^1H, ^{13}C, and 2D NMR spectra for uragogin and blepharodin. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.03.019.

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