Piperidine and Tetrahydropyridine Alkaloids from *Lobelia siphilitica* and *Hippobroma longiflora*

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The hyphenated technique HPLC-PDA-MS-SPE-NMR was used to assist targeted preparative-scale isolation of constituents of *Lobelia siphilitica* and *Hippobroma longiflora* (both Campanulaceae). This resulted in the isolation of two new alkaloids, (*S*)-2-[(2*S*,6*R*)-1-methyl-6-(2-oxo-2-phenylethyl)piperidin-2-yl]-1-phenylethyl acetate (**3**) and 6-[(*E*)-2-(3-methoxyphenyl)ethenyl]-2,3,4,5-tetrahydropyridine (**4**), the latter possessing a skeleton hitherto unseen among alkaloids of *Lobelia* and related genera. Lobeline (**1**), (1*S*,1′*S*)-2,2′-[(2*R*,6*S*)-1-methylpiperidine-2,6-diyl]bis(1-phenylethanol) (**2**), and lobetyolin (**5**) were also isolated. The structures of **1**−**5** were established using spectroscopic methods including homo- and heteronuclear two-dimensional NMR experiments and optical rotation data.

Lobelia is a large genus belonging to the Campanulaceae family and distributed in all tropical and warm temperate regions of the world. *Lobelia inflata* (Indian tobacco, lobelia) is one of the most intensively investigated species, and more than 20 different alkaloids have been reported from this species.[1,2] *L. inflata* and other *Lobelia* species are rich sources of alkaloids containing a piperidine or *N*-methylpiperidine core and one or two substituents that are usually a 2-oxo-2-phenylethyl, a 2-hydroxy-2-phenylethyl, a 2-oxobutyl, or a 2-hydroxybutyl group. *Lobelia* species have also been reported to contain polyacetylenes,[3−6] anthocyanins,[7,8] and a triterpene palmitate,[9] as well as polyhydroxylated piperidine[10] and pyrrolidine alkaloids.[11] *Lobelia* alkaloids[1,12,13] have also been isolated from the monotypic genus *Hippobroma* (Campanulaceae),[14] formerly included in *Lobelia*.

Lobelia alkaloids possess a variety of biological activities, and lobeline (**1**) or extracts containing lobeline have been used as an emetic, a respiratory stimulant, and a tobacco smoking cessation agent.[1,15−17] Lobeline is a high-affinity ligand of the nicotinic acetylcholine receptor and acts as an agonist on some subtypes of the receptor and as an antagonist on others.[15] Results have indicated that **1** and its analogues possess different selectivity toward dopamine and vesicular monoamine transporters and may be potential leads for the development of drugs against psychostimulant abuse.[18] Lobeline has been reported to inhibit proliferation of vascular smooth muscle cells, which can potentially be an important therapeutic strategy for treatment of atherosclerosis and hypertension.[19] β-Amyrin palmitate isolated from leaves of *L. inflata* was claimed to possess antidepressant activity,[5] and polyhydroxylated piperidine[10] and pyrrolidine[11] alkaloids from *L. sessilifolia* and *L. chinensis*, respectively, have shown α-glucosidase inhibitory activity. The potential of using piperidine as a scaffold in lead discovery is evident from the large number of publications and patents related to clinical and preclinical research with chemical entities based on this simple ring system.[20−22] Piperidine forms a central part of many classical bioactive natural products (e.g., anabasine, tropane alkaloids, aporphines, morphinanes, and cinchona alkaloids). However, most of the phytochemical work with *Lobelia* was performed decades ago. Thus, structure elucidations were mostly based on chemical methods, IR spectroscopy, and optical rotation data, which means that availability of NMR data is scarce. In this work, the hyphenated HPLC-PDA-MS-SPE-NMR technique[23−28] was used for profiling extracts of *Lobelia siphilitica* L. and *Hippobroma longiflora* (L.) G. Don. Both plants have been investigated previously, but analysis of UV, MS, and NMR spectra obtained in the HPLC-PDA-MS-SPE-NMR mode suggested the presence of hitherto unknown compounds. Following this initial extract profiling, a novel piperidine alkaloid and a new tetrahydropyridine alkaloid were obtained in the targeted isolation procedure. High-field NMR reference data for two known *Lobelia* alkaloids are also given.

Crude extracts of aerial parts of *L. siphilitica* and *H. longiflora* were prepurified using C_{18} SPE cartridges to remove chlorophyll and hydrophobic constituents such as fatty acids and waxes. These two extracts, as well as a crude extract of roots of *H. longiflora* were investigated by HPLC-PDA-MS-SPE-NMR. Thus, three major peaks observed in the *H. longiflora* root extract were each cumulatively adsorbed four times on SPE cartridges after four repeated injections, whereas seven cumulative adsorptions were performed with eight major peaks observed in the chromatogram of a defatted extract of aerial parts of *H. longiflora*. For *L. siphilitica*, threshold-based trapping of five major peaks was peformed in combination with time-sliced mode of operation after six repetitive separations. The trappings were in all cases performed using GP-resin SPE cartridges. Although HPLC separations were hampered by the presence of broad peaks, tailing, and peak overlap, analysis of UV, MS, and ^{1}H NMR spectra obtained in the HPLC-PDA-MS-SPE-NMR mode indicated the presence of hitherto unknown piperidine alkaloids, in addition to known constituents. These results were used to assist targeted preparative-scale isolation of **1**, **2**, and **3** from the extract of aerial parts of *H. longiflora*, **1**, **2**, and **5** from the root extract of *H. longiflora*, and **4** and **5** from the extract of aerial parts of *L. siphilitica*.

Compound **1** was identified as (−)-lobeline, a major alkaloid of other *Lobelia* species and also found in *H. longiflora*.[12,13] Partial assignment of ^{1}H and ^{13}C resonances has previously been reported,[29−31] but fully assigned ^{1}H and ^{13}C NMR data obtained in CD_3OD are given in the Supporting Information.

Compound **2** was assigned the molecular formula $C_{22}H_{29}NO_2$, as determined by HRMS. The ^{13}C NMR spectrum resembled that of **1**, except for the absence of the downfield signal of C-2′ at δ 200.2 and the presence of a new signal at δ 70.6. This corresponded to a lobeline analogue with a hydroxy group at C-2′ instead of a carbonyl group, in agreement with the presence of an additional methine signal at δ 5.07 in the ^{1}H NMR spectrum. This structure was confirmed by analysis of COSY,

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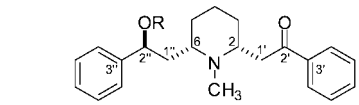

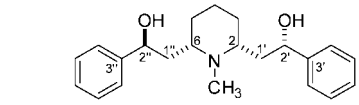

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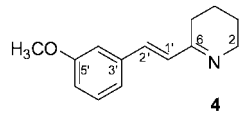

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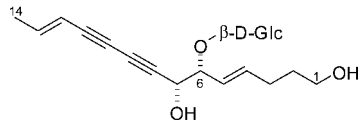

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NOESY, HSQC, and HMBC spectra, and the 1,3-diaxial orientation of H-2 and H-6 was confirmed by a strong NOESY correlation. The relative configuration of C-2″ was the same as in lobeline on the basis of similar coupling patterns (**1**: δ 5.05 [1H, dd, $J_{H\text{-}2'',H\text{-}1A''} = 11.1$ Hz, $J_{H\text{-}2'',H\text{-}1B''} = 2.8$ Hz, H-2″]; **2**: δ 4.96 [1H, dd, $J_{H\text{-}2'',H\text{-}1A''} = 11.0$ Hz, $J_{H\text{-}2'',H\text{-}1B''} = 2.8$ Hz, H-2″]), and from its negative optical rotation ($[\alpha]^{20}_D - 54.6$), compound **2** was assigned the 2*R*,6*S*,2″*S* configuration, as in **1**. The configuration at C-2′ was established by the observation of 18 different signals in the ^{13}C NMR spectrum, which excluded the possibility of a symmetric molecule (i.e., *R*-configuration at C-2′). This established the configuration at C-2′ as *S*. Thus, **2** was assigned the absolute configuration 2*R*,6*S*,2′*S*,2″*S* as opposed to the 2*R*,6*S*,2′*R*,2″*S* configuration of the symmetrical lobelanidine.[32,33] A stereoisomer of lobelanidine was reported from *H. longiflora*, and the compound was named (−)-*cis*-8,10-diphenyllobelidiol.[12,33] Although this compound was characterized only by its melting point and specific rotation ($[\alpha]^{20}_D - 70.7$), it is likely to be identical with **2**. ^{1}H and ^{13}C NMR spectroscopic data for **2** are presented for the first time.

Compared to **1**, the otherwise quite similar ^{13}C NMR spectrum of **3** showed additional signals corresponding to an acetyl group (δ 21.2 and 172.2), in agreement with the molecular formula $C_{24}H_{29}NO_3$ established by HRMS. The position of the acetyl group at C-2″ was confirmed by a downfield shift of H-2″ upon acetylation (**1**: $\delta_{H\text{-}2''}$ 5.05, **3**: $\delta_{H\text{-}2''}$ 5.85) as well as by HMBC connectivities from H-2″ to both ^{13}C resonances of the acetyl group. The relative configuration of **3** was the same as that of **1** on the basis of NOEs and coupling patterns, and the absolute configuration (2*R*,6*S*,2″*S*) was assigned from the negative optical rotation ($[\alpha]^{20}_D$ −54.3). Compound **3** is a new alkaloid, but a related compound, lobeline propionate, has previously been reported.[34]

Compound **4** was assigned the molecular formula $C_{14}H_{17}NO$ on the basis of HRMS, and its structure was confirmed by correlations found using COSY, NOESY, HSQC, and HMBC experiments. Fully assigned ^{1}H and ^{13}C NMR data are given in the Experimental Section. In the ^{1}H and ^{13}C NMR spectra of **4** acquired with a CD_3OD solution that was prepared several hours in advance, the resonances of H-5 and C-5 were not observed. However, when the compound was evaporated from CH_3OH and the spectra were acquired with a $CDCl_3$ solution, both resonances were present ($\delta_{H\text{-}5}$ 3.00 and $\delta_{C\text{-}5}$ 25.7). The same result was obtained with a freshly prepared solution in CD_3OD ($\delta_{H\text{-}5}$ 3.15 and $\delta_{C\text{-}5}$ 25.2). From these results, it can be concluded that the gradual disappearance of the signals of H-5 and C-5 in a CD_3OD solution is due to hydrogen-to-deuterium exchange caused by imine−enamine tautomerism (C-5 experiences large intensity loss due to coupling to deuterium, lack of NOE, and longer relaxation time). Direct evidence for this exchange was obtained by storing a solution of **4** in CD_3OD overnight and recording a ^{2}H NMR spectrum of the resulting material dissolved in $CHCl_3$; the spectrum displayed a signal of D-5 at δ 3.00. Compound **4** is a new compound, and it represents a new structural skeleton that has not been previously isolated from *Lobelia* species.

In addition to the above-described alkaloids, the polyacetylene lobetyolin (**5**) was isolated from the root extract of *H. longiflora* and from *L. siphilitica*. Lobetyolin has previously been found in hairy root cultures of *L. sessilifolia*[3] and *L. inflata*,[5] but this is the first report of lobetyolin in *L. siphilitica* and *H. longiflora*.

In conclusion, reinvestigation of *H. longiflora* and *L. siphilitica* resulted in isolation, in addition to the major alkaloid lobeline (**1**), of two new alkaloids **3** and **4** as well as in full characterization of the alkaloid **2**, previously isolated from *H. longiflora* but not characterized by ^{1}H and ^{13}C NMR spectroscopy. In addition, lobetyolin (**5**) was found in both plants for the first time, and **2** for the first time in *L. siphilitica*. This confirms that *Lobelia* species are a rich source of structurally diverse piperidine alkaloids and that the hyphenated technique HPLC-PDA-MS-SPE-NMR is useful for targeting the isolation efforts toward selected constituents.

Experimental Section

General Experimental Procedures. Optical rotations were recorded using a Perkin-Elmer 241 polarimeter. UV spectra were recorded using a Shimadzu UV-1601 spectrophotometer. ^{1}H and ^{13}C NMR spectra of isolated compounds were recorded at 25 °C using a Bruker Avance 600 MHz spectrometer equipped with a 5 mm ^{1}H{^{13}C} probe or a Bruker Avance 400 MHz spectrometer equipped with a 5 mm ^{13}C{^{1}H} probe (^{1}H resonance frequency 600.13 and 400.13 MHz, respectively). The spectra were calibrated using TMS as internal standard. The ^{2}H NMR spectrum was recorded at 61.42 MHz with a Bruker Avance 400 MHz spectrometer equipped with a 10 mm broadband probe; the spectrum was calibrated to the natural-abundance $CDCl_3$ signal (δ 7.27) of $CHCl_3$ used as solvent. High-resolution mass determinations were performed as previously described using a Bruker APEX Qe Fourier-transform mass spectrometer equipped with a 9.4 T superconducting magnet and an external electro-spray ion source.[35] Preparative-scale separations were performed using a HPLC system consisting of a Waters 590 pump, a Rheodyne 7125 injector, and a Lambda-Max model 481 LC UV detector, or an Agilent 1100 LC system, consisting of two preparative pumps, an autosampler, a sample collector, and a multiple-wavelength UV detector.

Plant Material. Aerial parts of *Lobelia siphilitica* L. (Campanulaceae) and aerial parts and roots of *Hippobroma longiflora* (L.) G. Don [syn. *Lobelia longiflora* L., *Laurentia longiflora* (L.) E. Wimm., *Isotoma longiflora* (L.) C. Presl, *Rapuntium longiflorum* (L.) Mill.] (Campanulaceae) were collected at the Botanical Garden of the Natural History Museum of Denmark, University of Copenhagen, Copenhagen, Denmark, in July 2007. Voucher specimens were deposited in Herbarium C (Botanical Museum, University of Copenhagen, Copenhagen, Denmark).

Extraction and Sample Prepurification. Ground plant material of *L. siphilitica* (aerial parts, 51 g) and *H. longiflora* (aerial parts, 89 g; roots, 40 g) were extracted with 1:1 dichloromethane/methanol (3 × 1 L, 3 × 1.5 L, and 3 × 1 L, respectively) by soaking overnight at room temperature. The extracts were filtered, pooled, concentrated in vacuo, and freeze-dried to give 6.0, 12.1, and 3.1 g, respectively, of raw extract. The extracts of the aerial parts were dissolved in 200 mL of acetonitrile/water (1:1 for *L. siphilitica* and 4:1 for *H. longiflora*) and applied to conditioned Supelco Superclean C_{18} SPE cartridges (5 g for *L. siphilitica* and 10 g for *H. longiflora*). The cartridges were subsequently eluted with mixtures of acetonitrile/water (160 mL of a 1:1 mixture, followed by 300 mL of a 3:1 mixture for *L. siphilitica* and 300 mL of a 4:1 mixture followed by 200 mL of neat acetonitrile for *H. longiflora*) to give 3.3 and 6.2 g of defatted extract of aerial parts of *L. siphilitica* and *H. longiflora*, respectively.

HPLC-PDA-MS-SPE-NMR Experiments. Conditions for HPLC-PDA-MS-SPE-NMR experiments were as previously described in detail[35] using 95:5 water/acetonitrile + 0.1% formic acid (eluent A) and 95:5 acetonitrile/water + 0.1% formic acid (eluent B). Six repeated

separations of defatted extract of *L. siphilitica* (50 μL injection volume, 60 mg/mL, gradient profile: 0 min, 0% B; 30 min, 100% B; 40 min, 100% B; 45 min, 0% B) were performed using a combination of UV threshold-based (254 and 315 nm) and time-slice trapping of analytes. Extracts of *H. longiflora* were chromatographed using the following gradient profile: 0 min, 0% B; 25 min, 15% B; 55 min, 50% B; 60 min, 100% B; 70 min, 100% B; 75 min, 0% B. Seven repeated chromatographic runs with the extract of aerial parts (40 μL injection volume, 55 mg/mL) and four runs with the root extract (30 μL injection volume, 33 mg/mL) were performed using UV threshold-based trapping (254 and 236 nm, respectively).

Preparative-Scale Isolation. All separations were performed on a 250 × 21.2 mm i.d. Phenomenex C_{18}(2) Luna column (5 μm, 100 Å) with elution solvents as described above except that formic acid was replaced with triflouroacetic acid. Defatted extract of aerial parts of *H. longiflora* (3.0 g of extract, 90 mg per injection) was separated into three fractions using the following gradient profile: 0 min, 0% B; 10 min, 15% B; 38 min, 50% B; 42 min, 100% B. Repeated chromatography of these fractions using isocratic elution (water/acetonitrile/formic acid, 33.8:66.2:0.1, 27.5:72.5:0.1, and 23:77:0.1, respectively) yielded 51.8 mg of **1**, 4.3 mg of **2**, and 9.4 mg of **3**. Root extract of *H. longiflora* was chromatographed (1.05 g of extract, 90 mg per injection) using the following solvent elution gradient profile: 0 min, 15% B; 20 min, 35% B; 35 min, 42% B; 40 min, 100% B. This yielded 9.2 mg of **1**, 8.2 mg of **2**, and 25 mg of **5**. Defatted extract of *L. siphilitica* was chromatographed (1.94 g of extract, 225 mg per injection) using the following solvent elution gradient profile: 0 min, 0% B; 16 min, 40% B; 18 min, 100% B. Two fractions were rechromatographed using isocratic solvent elution with 18% B. This yielded 9.6 mg of **4** and 6.4 mg of **5**.

(−)-*cis*-2′,2″-Diphenyllobelidiol [(1*S*,1′*S*)-2,2′-[(2*R*,6*S*)-1-Methyl-2,6-piperidinediyl]bis(1-phenylethanol)] (2): yellowish film; $[\alpha]^{20}_D$ −54.6 (*c* 0.22, $CHCl_3$), lit.[33] −70.7 ($CHCl_3$); ^{1}H NMR (CD_3OD, 400 MHz) δ 7.47 (2H, m, H-4′/H-8′), 7.43 (2H, m, H-4″/H-8″), 7.41 (2H, m, H-5′/H-7′), 7.36 (2H, m, H-5″/H-7″), 7.33 (1H, m, H-6″), 7.30 (1H, m, H-6′), 5.07 (1H, dd, $J_{H\text{-}2',H\text{-}1A'}$ = 4.7 Hz, $J_{H\text{-}2',H\text{-}1B'}$ = 4.6 Hz, H-2′), 4.96 (dd, $J_{H\text{-}2'',H\text{-}1A''}$ = 11.0 Hz, $J_{H\text{-}2'',H\text{-}1B''}$ = 2.77 Hz, H-2″), 3.71 (1H, m, H-2), 3.42 (1H, m, H-6), 2.90 (3H, s, N-CH_3), 2.44 (1H, ddd, $J_{H\text{-}1A',H\text{-}1B'}$ = 15.2 Hz, $J_{H\text{-}1A',H\text{-}2}$ = 9.4 Hz, $J_{H\text{-}1A',H\text{-}2'}$ = 4.7 Hz, H-1A′), 2.15 (1H, ddd, $J_{H\text{-}1A'',H\text{-}1B''}$ = 15.4 Hz, $J_{H\text{-}1A'',H\text{-}2''}$ = 11.3 Hz, $J_{H\text{-}1A'',H\text{-}6}$ = 11.0 Hz, H-1A″), 1.89 (1H, ddd, $J_{H\text{-}1B',H\text{-}1A'}$ = 15.4 Hz, $J_{H\text{-}1B',H\text{-}2}$ = 4.6 Hz, $J_{H\text{-}1B',H\text{-}2}$ = 4.1 Hz, H-1B′), 1.81 (2H, m, H-5), 1.78 (1H, m, H-1B″), 1.75 (2H, m, H-3), 1.61 (2H, m, H-4); ^{13}C NMR (CD_3OD, 100 MHz) δ 144.3 (CH, C-3′), 143.4 (CH, C-3″), 128.4 (2 × CH, C-5′/C-7′), 128.2 (2 × CH, C-5″/C-7″), 127.4 (CH, C-6″), 127.3 (CH, C-6′), 125.2 (2 × CH, C-4″/C-8″), 125.1 (2 × CH, C-4′/C-8′), 73.3 (CH, C-2″), 70.6 (CH, C-2′), 65.5 (CH, C-2), 62.0 (CH, C-6), 38.9 (CH_2, C-1″), 38.3 (CH_2, C-1′), 25.9 (CH_3, N-CH_3), 23.7 (CH_2, C-3), 23.3 (CH_2, C-4), 22.2 (CH_2, C-5); HREIMS *m*/*z* 340.22711 $[M + H]^+$, calcd for $[C_{22}H_{30}NO_2]^+$, 340.22711.

(2*R*,6*S*,2″*S*)-2″-*O*-Acetyllobeline [(*S*)-2-[(2*S*,6*R*)-1-Methyl-6-(2-oxo-2-phenylethyl)piperidin-2-yl]-1-phenylethyl acetate] (3): colorless film; $[\alpha]^{20}_D$ −54.3 (*c* 0.34, CH_3OH); UV (CH_3OH) λ_{max} (log ϵ) 244.0 (4.06), 279.5 (3.66) nm; IR (KBr) ν_{max} 3400, 2860, 1680, 1450, 1200, 1120, 780, 700 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 8.05 (2H, d, $J_{H\text{-}4'/H\text{-}8',H\text{-}5'/H\text{-}7'}$ = 7.4 Hz, H-4′/H-8′), 7.66 (2H, t, $J_{H\text{-}5'/H\text{-}7,H\text{-}4'/H\text{-}8'}$ = $J_{H\text{-}5'/H\text{-}7',H\text{-}6'}$ = 7.4 Hz, H-5′/H-7′), 7.4 (1H, tt, $J_{H\text{-}6',H\text{-}5'/H\text{-}7'}$ = 7.54 Hz, $J_{H\text{-}6',H\text{-}4'/H\text{-}8'}$ = 1.4 Hz, H-6′), 7.44−7.29 (5H, m, H-4″/H-5″/H-6″/H-7″/H-8″), 5.85 (1H, dd, $J_{H\text{-}2'',H\text{-}1A''}$ = 10.2 Hz, $J_{H\text{-}2'',H\text{-}1B''}$ = 3.6 Hz, H-2″), 4.04 (1H, m, H-2), 3.59 (1H, m, H-6), 3.51_{1A} (2H, m, H-1′), 2.80 (3H, s, N-CH_3), 2.48 (1H, m, H-1A″), 2.14 (3H, s, OC═OCH_3), 1.99 (1H, m, H-1B″), 1.85−1.66 (6H, m, H-3, H-4, H-5); ^{13}C NMR (CD_3OD, 100 MHz) δ 200.1 (C, C-2′), 172.2 (C, *COO*), 141.8 (C, C-3″), 137.6 (C, C-3′), 135.3 (CH, C-6′), 130.1−127.3 (5 × CH, C-4″/C-5″/C-6″/C-7″/C-8″), 74.9 (CH, C-2″), 63.9 (CH, C-6), 62.8 (CH, C-2), 40.3 (CH_2, C-1″), 29.8 (CH_3, N-CH_3), 25.3 + 23.7 + 18.6 (3 × CH_2, C-3/C-4/C-5), 21.2 (CH_3, OOC*CH_3*); HREIMS *m*/*z* 380.22207 $[M + H]^+$, calcd for $[C_{24}H_{30}NO_3]^+$, 380.22202.

6-[(*E*)-2-(3-Methoxyphenyl)ethenyl]-2,3,4,5-tetrahydropyridine (4): yellowish film; IR (KBr) ν_{max} 3400, 2860, 1680, 1120 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.89 (1H, d, $J_{H\text{-}2',H\text{-}1'}$ = 16.3 Hz, H-2′), 7.41 (1H, t, $J_{H\text{-}7',H\text{-}8'}$ = $J_{H\text{-}7',H\text{-}6'}$ = 8.0 Hz, H-7′), 7.30 (1H, dt, $J_{H\text{-}8',H\text{-}7'}$ = 8.0 Hz, $J_{H\text{-}8',H\text{-}6'}$ = $J_{H\text{-}8',H\text{-}4'}$ = 1.7 Hz, H-8′), 7.25 (1H, dd, $J_{H\text{-}4',H\text{-}6'}$ = 2.5 Hz, $J_{H\text{-}4',H\text{-}8'}$ = 1.7 Hz, H-4′), 7.11 (1H, ddd, $J_{H\text{-}6',H\text{-}7'}$ = 8.0 Hz, $J_{H\text{-}6',H\text{-}4'}$ = 2.5 Hz, $J_{H\text{-}6',H\text{-}8'}$ = 1.7 Hz, H-6′), 7.04 (1H, d, $J_{H\text{-}1',H\text{-}2'}$ = 16.3 Hz, H-1′), 3.85 (3H, s, O-CH_3), 3.76 (2H, m, H-2), 3.15 (2H, m, H-5), 1.99 (2H, m, H-3), 1.95 (2H, m, H-4); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.67 (1H, d, $J_{H\text{-}1',H\text{-}2'}$ = 16.1 Hz, H-1′), 7.55 (1H, d, $J_{H\text{-}2',H\text{-}1'}$ = 16.1 Hz, H-2′), 7.36 (1H, t, $J_{H\text{-}7',H\text{-}8'}$ = $J_{H\text{-}7',H\text{-}6'}$ = 8.0 Hz, H-7′), 7.22 (1H, dt, $J_{H\text{-}8',H\text{-}7'}$ = 8.0 Hz, $J_{H\text{-}8',H\text{-}6'}$ = $J_{H\text{-}8',H\text{-}4'}$ = 1.4 Hz, H-8′), 7.18 (1H, dd, $J_{H\text{-}4',H\text{-}6'}$ = 2.5 Hz, $J_{H\text{-}4',H\text{-}8'}$ = 1.4 Hz, H-4′), 7.05 (1H, ddd, $J_{H\text{-}6',H\text{-}7'}$ = 8.0 Hz, $J_{H\text{-}6',H\text{-}4'}$ = 2.5 Hz, $J_{H\text{-}6',H\text{-}8'}$ = 1.4 Hz, H-6′), 3.87 (3H, s, O-CH_3), 3.85 (2H, m, H-2), 3.00 (2H, m, H-5), 1.99 (4H, m, H-3, H-4); ^{13}C NMR (CD_3OD, 100 MHz) δ 181.3 (C, C-6), 161.9 (C, C-5′), 150.2 (CH, C-2′), 136.4 (C, C-3′), 131.5 (CH, C-7′), 122.7 (CH, C-8′), 121.4 (CH, C-1′), 119.2 (CH, C-6′), 115.2 (CH, C-4′), 56.0 (CH_3, O-CH_3), 45.8 (CH_2, C-2), 25.7 (CH_2, C-5), 20.9 (CH_2, C-3), 17.9 (CH_2, C-4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.0 (C, C-6), 160.4 (C, C-5′), 147.7 (CH, C-2′), 134.5 (C, C-3′), 130.4 (CH, C-7′), 122.4 (CH, C-8′), 120.9 (CH, C-1′), 119.2 (CH, C-6′), 112.9 (CH, C-4′), 55.5 (CH_3, O-CH_3), 44.4 (CH_2, C-2), 25.2 (CH_2, C-5), 20.1 (CH_2, C-3), 17.3 (CH_2, C-4); HREIMS *m*/*z* 216.13825 $[M + H]^+$, calcd for $[C_{14}H_{18}NO]^+$ 216.13829.

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Supporting Information Available: ^{1}H NMR, ^{13}C NMR, and optical rotation data of **1** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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