Dihydrofurochromones from *Prionosciadium thapsoides*

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Chemical investigations of *Prionosciadium thapsoides* roots led to the isolation of the new dihydrofurochromones (*S*)-(+)-4′-*O*-angeloyl-5-*O*-methylvisamminol (**1**) and (*S*)-(+)-4′-*O*-senecioyl-5-*O*-methylvisamminol (**2**), together with the known coumarins jatamansin, buchtormin, isopteryxin, isosamidin, psoralen, and bergapten. The structures of **1** and **2** were determined by 1D and 2D NMR experiments, and their absolute configuration was established by chemical correlation with (+)-5-*O*-methylvisamminol (**3**), whose structure was secured by single-crystal X-ray diffraction analysis and its absolute configuration was established as *S* by vibrational circular dichroism spectroscopy in comparison to DFT B3LYP/DGDZVP calculations.

Furochromones are the main constituents of Umbelliferae plants, such as *Ammi visnaga* L., which has a long history of use in the Middle East as an antispasmodic and for the treatment of angina pectoris.[1] Thus, khellin, visnagin, and (+)-visamminol (**4**) are found in the fruits of this species and are the active principles of a crude plant preparation often used as coronary vasodilator and antiasthmatic agent.[1,2] (+)-Visamminol (**4**), together with other related 2,3-dihydrofurochromones such as (+)-5-*O*-methylvisamminol (**3**) and (+)-cimifugin (**5**), have been isolated from *Angelica japonica* A. Gray. (Umbelliferae),[3] which is being investigated for its antitumor action.[4] The absolute configuration of (+)-5-*O*-methylvisamminol (**3**) and (+)-visamminol (**4**) has been proposed to be *S* from optical activity comparison with the structurally not very closely related (*S*)-(+)-marmesin,[2] a furocoumarin with the same chiral substitution, also isolated from *Angelica japonica*.[3] In addition, the absolute configuration of (+)-cimifugin (**5**) was assigned as *S* based on its conversion to (+)-5-acetyl-6-hydroxy-2-hydroxyisopropyl-4-methoxy-2,3-dihydrobenzo-furan (**7**) and comparison of the optical rotation of the latter compound with (*S*)-(+)-5-carboxy-4-hydroxy-2-hydroxyisopropyl-2,3-dihydrobenzofuran (**8**).[5,6] Therefore, the absolute configurations of (+)-visamminol (**4**) and their derivatives (+)-5-*O*-methylvisamminol (**3**) and (+)-cimifugin (**5**) have not yet been established convincingly.

Prionosciadium thapsoides (DC.) Mathias (Umbelliferae), locally known as "cominos rústicos", "jalocote", and "hierba del oso", is a medicinal plant found in humid habitats of the Mexican pine-oak forest from Sonora, Mexico, to Mexico City, whose fruits are employed to treat digestive disorders.[7,8] This paper reports an investigation of the chemical constituents of the roots of this species that has afforded the two new dihydrofurochromones (*S*)-(+)-4′-*O*-angeloyl-5-*O*-methylvisamminol (**1**) and (*S*)-(+)-4′-*O*-senecioyl-5-*O*-methylvisamminol (**2**), together with the known pyranocoumarins jatamansin,[9−11] buchtormin,[10] isopteryxin,[12,13] and isosamidin,[14] as well as the furocoumarins psoralen[15] and bergapten.[16] The absolute configuration of **1** and **2** was determined by chemical correlation with 5-*O*-methylvisamminol (**3**), for which the molecular structure was secured by single-crystal X-ray diffraction analysis and its absolute configuration was established by vibrational circular dichroism (VCD) spectroscopy in comparison to spectra generated by DFT calculations. VCD has been used in recent years as a powerful method for the determination of the absolute configuration of a number of natural chiral molecules,[17−20] including the structural elucidation of a dihydrofurocoumarin.[20]

1 R = Ang
2 R = Sen
3 R = H

4 $R^1 = R^2 = H$
5 R^1 = Me, R^2 = OH

6 R = Ang
7 R = H

8

Ang =

Sen =

Systematic column chromatography and HPLC fractionation of the hexane extracts from the roots of *P. thapsoides* led to the isolation of the 2,3-dihydrofurochromones **1** and **2**. Their structures were elucidated by spectroscopic analysis in comparison to published data. Detailed analysis of the NMR spectra indicated compounds **1** and **2** are 5-*O*-methylvisamminol esters. The angelate ester residue of **1** was evident by the signals at δ 5.98 (qq, J = 7.3, 1.5 Hz, H-3″), 1.89 (dq, J = 7.3, 1.5 Hz, Me-4″) and 1.68 (quintet, J = 1.5 Hz, Me-5″) in the ^{1}H NMR spectrum. Dihydrofurochromone **2** differed from **1** by the presence of a senecioate ester residue instead of an angelate moiety. This assignment was supported by the ^{1}H NMR signals at δ 5.56 (septet, J = 1.3 Hz, H-2″), 2.10 (d, J = 1.1 Hz, Me-4″), and 1.85 (d, J = 1.5 Hz, Me-5″). The remaining ^{1}H and ^{13}C NMR signals (Table 1) were assigned from 2D experiments including COSY, HMQC, and HMBC. Chemical shifts and multiplicities of these compounds are

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Table 1. NMR Spectroscopic Data (400 MHz, $CDCl_3$) for Dihydrofurochromones **1** and **2**

	1		**2**	
position	δ_C, mult.[a]	δ_H (J in Hz)	δ_C[a]	δ_H (J in Hz)
2	163.8, C		164.3	
3	111.2, CH	6.00, br s	112.1	6.00, q (0.7)
4	177.6, C		178.2	
4a	111.6, C		112.6	
5	155.7, C		156.7	
6	116.7, C		117.4	
7	164.6, C		165.3	
8	93.7, CH	6.53, s	94.4	6.53, s
8a	159.9, C		160.8	
9	19.8, CH_3	2.28, br s	20.0	2.28, d (0.7)
2′	89.4, CH	5.02, dd (9.5, 7.3)	89.5	5.12, dd (9.5, 7.3)
3′α	27.8, CH_2	3.33, dd (16.1, 9.5)	28.0	3.31, dd (16.1, 9.5)
3′β	-	3.27, dd (16.1, 7.3)	-	3.22, dd (16.1, 7.3)
4′	82.0, C		81.8	
5′	21.5, CH_3	1.62, s,	22.4	1.59, s
6′	20.5, CH_3	1.62, s	21.4	1.53, s
OMe	61.0, CH_3	3.93, s	61.5	3.94, s
1″	167.1, C		166.8	
2″	128.6, C		117.6, CH	5.56, septet (1.3)
3″	137.8, CH	5.98, qq (7.3, 1.5)	157.6, C	
4″	15.6, CH_3	1.89, dq (7.3, 1.5)	20.2	2.10, d (1.1)
5″	22.1, CH_3	1.68, quintet (1.5)	27.6	1.85, d (1.5)

[a] Assigned by HMQC and HMBC.

in agreement with NMR data found in related 2,3-dihydrofurochromone derivatives.[3,5]

Alkaline hydrolysis of a sample containing a mixture (ca. 2:1) of esters **1** and **2** was carried out using KOH in H_2O−MeOH to afford **3**, together with the new angelate ester derivative **6** and benzofuran **7**, which showed dextrorotatory optical activity. It is noteworthy that compound **6** arose from a retro-aldol reaction of the chromone moiety of **1**, while compound **7** was generated by hydrolysis of the ester residues and retro-aldol reaction of the chromone moiety.[2] Derivative **7** has previously been obtained from (+)-cimifugin (**5**) by a similar alkaline treatment.[5] The spectroscopic data of **3** and **7** were in good agreement with literature reports.[2,3,5,21]

Although ^{1}H NMR data of (+)-5-*O*-methylvisamminol (**3**) in $CDCl_3$ have been reported,[21] there are ambiguities about multiplicity and coupling constants for the signals belonging to the hydrogen atoms at C-2′ and C-3′. They have been described as a triplet (J = 9.0 Hz) and a doublet (J = 9.0 Hz) at δ 4.72 and 3.23, respectively. However the signal corresponding to H-2′ is in fact a triplet (J = 8.8 Hz) at δ 4.73, that of H-3′α is a double doublet (J = 16.0 and 9.1 Hz) at δ 3.28, and that of H-3′β is a double doublet (J = 16.0 and 8.6 Hz) at δ 3.24. Also, this is the first time that the ^{13}C NMR data of **3** in $CDCl_3$ have been reported, for which the assignments were confirmed through detailed analysis of the ^{1}H−^{1}H-COSY, HMQC, and HMBC spectra.

In order to secure the structure of (+)-5-*O*-methylvisamminol (**3**), a prism of this substance, obtained by crystallization from $CHCl_3$−hexane, was subjected to X-ray diffraction analysis. Figure 1 illustrates the molecular perspective of **3**, which reveals the conformation of the furan moiety. The asymmetric unit of the crystal cell contains two molecules that differ in the orientation of the methoxyl group, showing C_5−C_4−O_2−C_{15} dihedral angles of −75.65° for molecule 1 and of +75.69° for molecule 2. Also, there is a slight twisting of the chromone ring system in opposite directions as reflected by the C_6−C_5−C_9−C_{10} dihedral angle of −175.25° in molecule 1 versus +175.29° in molecule 2. Finally, the hydroxyl hydrogen occupies a different position in each molecule, as shown by the C_1−C_{12}−O_5−H dihedral angle of −58.26° in molecule 1 versus +83.40° in molecule 2. The furan moiety appears to be close to the planar conformation with C_1−C_2−C_3−C_{11} dihedral angles of −1.16° for molecule 1 and −5.90° for molecule 2. The hydrogen atoms of the vinylic methyl group, in each molecule, are disordered.[22]

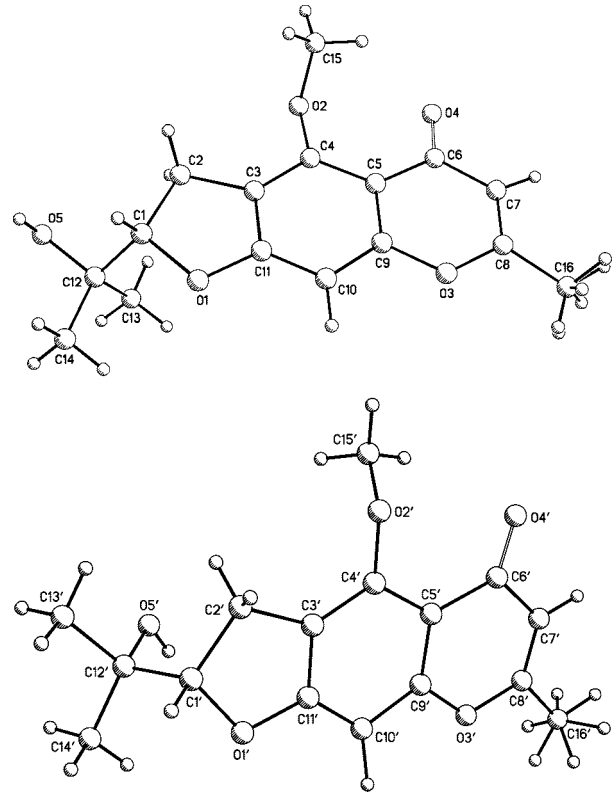

Figure 1. Perspective view of the X-ray crystal structure of **3**. Atom numbering differs from usual furobenzochromone numbering. Both molecules found in the asymmetric unit of the crystal cell are shown. The hydrogen atoms of the C-16 and C-16′ methyl groups are disordered.

The absolute configuration of 5-*O*-methylvisamminol (**3**) was determined from a vibrational circular dichroism (VCD) study in which the experimental spectrum measured in $CDCl_3$ (Figure 2a) was contrasted with the theoretical curve (Figure 2b) obtained by calculation of all possible conformations and their corresponding VCD frequencies using density functional theory at the B3LYP/DGDZVP level. The molecular modeling protocol initially involved the use of the Monte Carlo conformational searching method,[23]

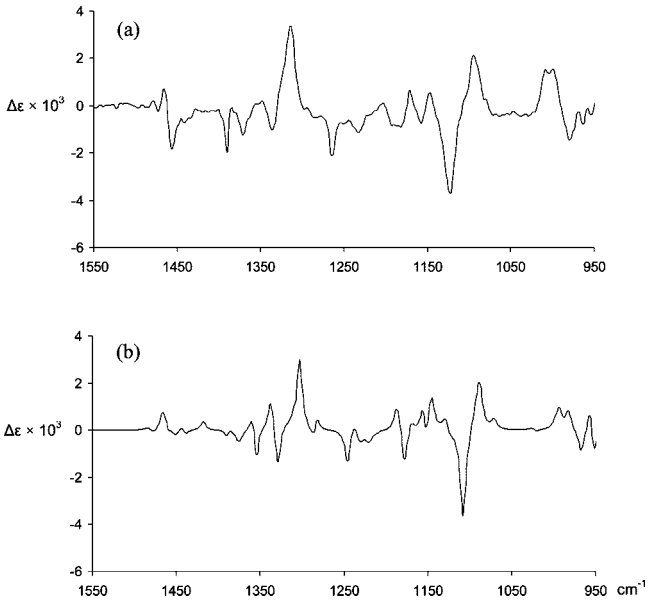

Figure 2. (a) Experimental and (b) B3LYP/DGDZVP DFT Boltzmann-weighted VCD spectra of (*S*)-5-*O*-methylvisamminol (**3**). The corresponding IR spectra are given in the Supporting Information.

which yielded a total of 14 conformers within a relative energy range of 5 kcal/mol. A systematic conformational exploration of 5-*O*-metilvisamminol (**3**) could in principle afford 18 conformers: three conformers arising from 120° rotation of the C2′−C4′ bond, times three conformers arising from 120° rotation of the C4′−O4′ bond, times two conformers generated by 180° rotation of the C5−O5 bond. The four conformers that were not found by the Monte Carlo searching procedure were constructed manually and subjected to minimization. In these four cases, no local minima for those geometries were found, thus confirming the accuracy of the Monte Carlo search.

The 14 minimum-energy structures of **3** were submitted to geometry optimization using DFT calculations[24,25] at the B3LYP/DGDZVP level of theory to obtain reliable molecular models. The molecular mechanics energy and the DFT thermochemical parameters for the estimation of the population of each species, which was calculated according to the $\Delta G = \Delta H - T\Delta S$ and $\Delta G = -RT \ln K$ equations, considering the B3LYP/DGDZVP calculated vibrational frequencies at 298 K and 1 atm are given in the Supporting Information. In all conformations, the hydroxyisopropyl group remains in a pseudo-equatorial orientation with notable variations in the H2′−C2′−C3′−H3′a and H2′−C2′−C3′−H3′b dihedral angles, while structures with the hydroxyisopropyl group in a pseudo-axial orientation were not located in minimum energy points.

After geometry optimization, VCD frequencies were obtained for the 14 conformations taken into account to generate the Boltzmann-averaged VCD theoretical spectrum. All individual VCD and IR spectra were scaled by a factor of 0.97, the bandshapes were calculated with Lorentzian functions, and bandwidths were set at 6 cm^{-1}. Comparison of the experimental VCD curve of (+)-5-*O*-methylvisamminol obtained by alkaline hydrolysis of the esters from *P. thapsoides* showed good agreement with the DFT B3LYP/DGDZVP VCD spectrum calculated for the *S*-enantiomer of 5-*O*-methylvisamminol (**3**), thus affording strong and direct evidence for the absolute configuration of this compound.

On the other hand, treatment of (*S*)-(+)-5-*O*-methylvisamminol (**3**) with angeloyl and senecioyl chlorides yielded (*S*)-(+)-4′-*O*-angeloyl-5-*O*-methylvisamminol (**1**) and (*S*)-(+)-4′-*O*-senecioyl-5-*O*-methylvisamminol (**2**), respectively, which showed identical physical and spectroscopic properties to the natural samples, confirming the structure and absolute configuration of both new natural products. Also, starting from the secured absolute configuration of (*S*)-(+)-5-*O*-methylvisamminol (**3**), and taking in to account the conversion of **3** into (*S*)-(+)-5-acetyl-6-hydroxy-2-hydroxyisopropyl-4-methoxy-2,3-dihydrobenzo-furan (**7**), it is possible to confirm the absolute configuration of (+)-cimifugin (**5**) as *S*, since this compound was also converted to **7**.[5] Finally, the reported preparation of (+)-5-*O*-methylvisamminol (**3**) from (+)-visamminol (**4**)[2] extends the *S* absolute configuration assignment to the C-2′ chiral center of the biologically relevant dihydrofurochromone **4**.

Experimental Section

General Experimental Procedures. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Optical rotations were determined in $CHCl_3$ on a Perkin-Elmer 341 polarimeter. UV spectra were determined on a Perkin-Elmer Lambda 12 UV/vis spectrophotometer. IR spectra were recorded on a Perkin-Elmer 16F PC IR-FT spectrophotometer using thin films of the compounds deposited on a CsI crystal. VCD measurements were performed on a dualPEM Chiral IR FT spectrophotometer at BioTools, Inc. (Jupiter, FL). A sample of **3** (5.3 mg) was dissolved in $CDCl_3$ (150 μL) and placed in a BaF_2 cell with a path length of 100 μm. Data were acquired at a resolution of 4 cm^{-1} for 6 h. NMR measurements, including COSY, HMQC, and HMBC experiments, were performed at 400 MHz for ^1H and 100 MHz for ^{13}C on a JEOL Eclipse 400 spectrometer from $CDCl_3$ solutions using TMS as internal standard. Low-resolution mass spectra were recorded at 70 eV on a Hewlett-Packard 5890 Series II spectrometer and at 20 eV on a Hewlett-Packard 5989A spectrometer, while high-resolution mass spectra were measured on an Agilent LCTOF instrument at the UCR Mass Spectrometry Facility, University of California, Riverside. Column chromatography was carried out on Merck silica gel 40 (Aldrich, 70−230 mesh ASTM) and 60 (Aldrich, 230−400 mesh ASTM). HPLC separations were carried out on a Perkin-Elmer series 200 chromatograph using a reversed-phase Microsorb 100 C_{18} column, i.d. 4.6 mm, length 150 mm, employing a UV−visible detector and a flow of 0.5 mL/min. Commercially available senecioyl chloride (3,3-dimethylacryloyl chloride) (Aldrich) was used as received, and angelic acid and angeloyl chloride were prepared following reported procedures.[26,27]

Molecular Modeling. Geometry optimizations for **3** were carried out using the MMFF94 force-field calculations as implemented in the Spartan'04 program. A Monte Carlo search protocol was carried out considering an energy cutoff of 10 kcal/mol, providing 14 conformers. A systematic search was also performed, but no additional minimum energy structures were found. The 14 conformers were optimized by DFT calculations at the B3LYP/DGDZVP level of theory[24,25] employing the Gaussian 03W program. The minimized structures were used to calculate the thermochemical parameters and the IR and VCD frequencies at 298 K and 1 atm. Molecular visualization was carried out with the GaussianView 3.0 program. Calculations required between 20 and 75 h of computational time per conformer when using a desktop personal computer (PC) with 2 Gb RAM operated at 3 GHz.

Plant Material. Specimens of *Prionosciadium thapsoides* were collected from Chiquihuite Hill in Mexico City during June 1998. A voucher specimen (M. González-Ledesma and M. Torres V. 1836) is deposited at the Herbarium of the Biological Research Centre, Universidad Autónoma del Estado de Hidalgo, Pachuca, Hidalgo, México, where it was identified by Professor Manuel González Ledesma.

Extraction and Isolation. Air-dried roots of *P. thapsoides* (1.5 kg) were extracted with hexane under reflux for 6 h. Filtration and evaporation of the extract afforded a yellow, viscous oil (35 g), which was dissolved in MeOH at 50 °C, then kept at 0 °C for 12 h and filtered to remove fatty materials. The filtrate was evaporated under vacuum, and a portion of the pale yellow, oily residue (1 g) was chromatographed over silica gel 40 (150 g) using a hexane−EtOAc gradient (4:1; 7:3, and 1:1, v/v) and EtOAc as eluents. Fractions of 500 mL of each polarity were collected and monitored by TLC. The resulting material from each fraction was marked as A (83 mg), B (140 mg), C (402 mg), and D (345 mg), respectively. This procedure was repeated five times. ^1H NMR analysis of these combined fractions showed the major constituents to be as follows: fatty materials in fraction A, jatamansin and buchtormin in fraction B, isopterysin and isosamidin in fraction C, and

dihydrochromones **1** and **2** (ca. 2:1) in fraction D. Column chromatography on silica gel 60 of fraction B (500 mg), using toluene−CH_2Cl_2−EtOAc (1:1:1.25, v/v) as the eluent and collecting fractions of 10 mL, resulted in the isolation of traces of psoralen (2 mg) and bergapten (3 mg) in the initial fractions, followed by a mixture of jatamansin and buchtormin (ca. 2:1, 24 mg) from fractions 8 and 9. Fraction C (500 mg) was chromatographed using the same conditions as fraction B, affording eluates 15−30 (245 mg) containing a mixture of isopteryxin and isosamidin, which was separated by HPLC using MeOH−H_2O (7:3, v/v) as the eluent and injecting samples of 3 μL of a solution containing 1 mg in 20 μL of eluent, to give pure isopteryxin (2 mg) and isosamidin (1.5 mg). Fraction D (500 mg) was separated in silica gel 60 using hexane−acetone (7:3, v/v) as the eluent and collecting 45 eluates of 10 mL, which were monitored by TLC and analyzed by ^{1}H NMR spectroscopy. A fraction containing eluates 10−23 (180 mg) showed the presence of chromones **1** and **2**. They were combined and subjected to HPLC with MeOH−H_2O (7:3, v/v), injecting samples of 3 μL of a solution containing 1 mg in 20 μL of eluent, affording **1** (1.5 mg) and **2** (1.2 mg).

Alkaline Hydrolysis of a Mixture of Dihydrochromones 1 and 2. A solution of a mixture of **1** and **2** (ca. 2:1, 200 mg) in 4 mL of MeOH was treated with KOH (300 mg) in H_2O (1 mL), stirred at room temperature for 42 h, and concentrated under vacuum to remove the MeOH. To the resulting viscous residue, H_2O (5 mL) was added, and the mixture was acidified with 20% aqueous H_2SO_4 until pH 5.0 and extracted with EtOAc (50 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4, filtered, and evaporated to provide 175 mg of residue. The crude product was subjected to flash chromatography on silica gel 40, using $CHCl_3$−acetone (10:1, 300 mL; and 1:1, 200 mL, v/v), and collecting fractions of 10 mL. Ester **6** (10 mg) was isolated from fractions 6−9, benzofuran **7** (28 mg) was obtained from fractions 19−26, and 5-*O*-methylvisamminol (**3**) (21 mg) was isolated from fractions 36−46.

Preparation of (*S*)-(+)-4′-*O*-Angeloyl-5-*O*-methylvisamminol (1) and (*S*)-(+)-4′-*O*-Senecioyl-5-*O*-methylvisamminol (2). Samples of esters **1** (3.5 mg) and **2** (15 mg) were prepared from **3** following reported procedures,[28] and chromatographic separation were performed on silica gel 60 and $CHCl_3$−acetone (10:1, v/v) as the eluent. Spectroscopic data were identical with those of natural samples of **1** and **2**.

(*S*)-(+)-4′-*O*-Angeloyl-5-O-methylvisamminol (1): colorless oil; $[\alpha]_D$ +59 (*c* 0.1, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 214 (4.33), 286 (3.93) nm; IR ($CHCl_3$) ν_{max} 2930, 1714, 1626, 1594, 1470, 1363, 1251, 1141, 772 cm^{-1}; ^{1}H and ^{13}C NMR (see Table 1); EIMS *m*/*z* 372 $[M]^+$ (36), 272 (24), 257 (100), 254 (67), 244 (52), 229 (56), 213 (24), 83 (42), 55 (24); HRESIMS *m*/*z* 373.1647 $[M + H]^+$ (calcd for $C_{21}H_{24}O_6H$, 373.1651).

(*S*)-(+)-4′-*O*-Senecioyl-5-*O*-methylvisamminol (2): colorless oil; $[\alpha]_D$ +42 (*c* 0.4, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 212 (4.49), 284 (3.92) nm; IR ($CHCl_3$) ν_{max} 2928, 1712, 1654, 1614, 1468, 1390, 1352, 1218, 1134, 756, 732, 674, 484 cm^{-1}; ^{1}H and ^{13}C NMR (see Table 1); EIMS *m*/*z* 373 $[M + 1]^+$ (41), 272 (18), 258 (22), 257 (100), 254 (48), 244 (27), 239 (17), 229 (37), 83 (42), 55 (30); HRESIMS *m*/*z* 373.1652 $[M + H]^+$ (calcd for $C_{21}H_{24}O_6H$, 373.1651).

(*S*)-(+)-5-*O*-Methylvisamminol (3): colorless prisms; mp 133−135 °C; $[\alpha]_D$ +66.5 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3398, 2975, 2929, 1654, 1610, 1469, 1432, 1389, 1354, 1171, 1148, 1096, 965, 847, 754, 572 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.50 (1H, s, H-8), 5.99 (1H, d, J = 0.7 Hz, H-3), 4.73 (1H, t, J = 8.8 Hz, H-2′), 3.93 (3H, s, OMe), 3.28 (1H, dd, J = 16.0, 9.1 Hz, H-3′), 3.24 (1H, dd, J = 16.0, 8.6 Hz, H-3′β), 2.27 (3H, d, J = 0.7 Hz, Me-9), 1.35 (3H, s, Me-5′), 1.25 (3H, s, Me-6′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.3 (C-4), 164.3 (C-7), 163.4 (C-2), 159.8 (C-8a), 160.0 (C-5), 117.1 (C-6), 111.9 (C-4a), 111.4 (C-3), 93.8 (C-8), 91.3 (C-2′), 71.7 (C-4′), 61.0 (OMe), 27.8 (C-3′), 25.8 (C-5′), 24.4 (C-6′), 19.8 (C-9).

(*S*)-(+)-1′-*O*-Angeloyl-5-acetyl-6-hydroxy-2-hydroxyisopropyl-4-methoxy-2,3-dihydrobenzofuran (6): colorless oil; $[\alpha]_D$ +61.5 (*c* 0.4, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 218 (4.35), 286 (4.16), 327 (3.61) nm; IR ($CHCl_3$) ν_{max} 2919, 2850, 1715, 1658, 1618, 1463, 1388, 1353, 1237, 1141, 1097, 967, 846 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 13.85 (1H, s, OH at C-6), 6.12 (1H, s, H-7), 6.00 (1H, dq, J = 7.3, 1.5 Hz, H-3″), 4.97 (1H, dd, J = 9.5, 7.3 Hz, H-2), 3.94 (3H, s, OMe), 3.31 (1H, dd, J = 15.0, 9.5 Hz, H-3α), 3.24 (1H, dd, J = 15.0, 7.3 Hz, H-3β), 2.61 (3H, s, Me-9), 1.90 (3H, dq, J = 7.3, 1.5 Hz, Me-4″), 1.72 (3H, quintet, J = 1.5 Hz, Me-5″), 1.61 (3H, s, Me-2′), 1.59 (3H, s, Me-3′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.9 (C-8), 167.4 (C-7a), 167.3 (C-6), 167.2 (C-1″), 158.7 (C-4), 137.8 (C-3″), 128.7 (C-2″), 108.2 (C-5), 107.0 (C-3a), 93.8 (C-7), 88.7 (C-2), 82.0 (C-1′), 59.1 (OMe), 32.3 (C-9), 29.0 (C-3), 22.4 (C-2′), 21.4 (C-3′), 20.7 (C-5″), 15.7 (C-4″); EIMS *m*/*z* 348 $[M]^+$ (5), 248 (33), 233 (100), 83 (14), 55 (7), 43 (4); HRESIMS *m*/*z* 349.1649 $[M + H]^+$ (calcd for $C_{19}H_{24}O_6H$, 349.1651).

(*S*)-(+)-5-Acetyl-6-hydroxy-2-hydroxyisopropyl-4-methoxy-2,3-dihydrobenzofuran (7): white powder; mp 85−87 °C; $[\alpha]_D$ +63 (*c* 2.7, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 218 (4.31), 288 (4.27), 325 (3.78) nm; IR ($CHCl_3$) ν_{max} 3453, 2978, 2934, 1714, 1625, 1471, 1367, 1252, 1144, 1100, 1059, 948, 824 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 13.87 (1H, s, OH at C-6), 6.11 (1H, s, H-7), 4.64 (1H, t, J = 8.6 Hz, H-2), 3.96 (3H, s, OMe), 3.24 (2H, d, J = 8.4 Hz, H-3), 2.61 (3H, s, Me-3), 1.35 (3H, s, Me-2′), 1.24 (3H, s, Me-3′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.1 (C-8), 167.2 (C-7a), 167.1 (C-6), 158.8 (C-4), 108.2 (C-5), 107.3 (C-3a), 93.7 (C-7), 90.6 (C-2), 71.7 (C-1′), 59.0 (OMe), 32.4 (C-9), 28.9 (C-3), 26.1 (C-2′), 24.4 (C-3′); EIMS *m*/*z* 266 $[M]^+$ (100), 251 (20), 233 (67), 207 (54), 193 (93), 190 (10), 165 (16), 151 (7), 109 (4), 59 (31), 43 (43).

Single-Crystal X-ray Analysis of 3. A crystal measuring 0.12 × 0.10 × 0.06 mm was mounted on a Bruker Smart 6000 diffractometer and cooled to 173 K in a cold nitrogen stream. The crystal was monoclinic, space group $P2_1$, with cell dimensions a = 6.999(4) Å, b = 17.028(8) Å, c = 12.545(8) Å, β = 105.18(2)°, V = 1442.9(1) Å^3, ρ_{calcd} = 1.281 g/cm^3 for Z = 2, Z' = 2, $C_{15}H_{18}O_5$, MW = 278.29, and $F(000)$ = 592 e. A total of 1321 frames were collected with a scan width of 0.3° and exposure time of 50 s/frame using Mo Kα radiation (λ = 0.71073 Å). The frames were processed with the SAINT software package provided by the diffractometer manufacturer. The data were corrected for background, Lorentz polarization, and absorption (μ = 0.096 mm^{-1}), while crystal decay was negligible. The structure was solved by direct methods using the Sir2004 program.[29] For the structural refinement, the non-hydrogen atoms were treated anisotropically, and the hydrogen atoms were refined isotropically. A total of 11 308 reflections were collected within a θ range of 3.57−27.48° for $-9 \le h \le 8$, $-22 \le k \le 20$, $0 \le l \le 16$. The unique reflections were 5870, the observed reflections were 3090, and final discrepancy indices, refining 407 parameters, were R_F = 5.9% and R_w = 12.6%. The final difference Fourier map was essentially featureless, the highest residual peaks having densities of 0.185 e/A^3. Crystallographic data are deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk. The CCDC deposition number is 704324.

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Supporting Information Available: X-ray atomic coordinates for 5-*O*-methylvisamminol (**3**). DFT calculated atomic Cartesian coordinates, DFT B3LYP/DGDZVP thermochemical parameters and population, and structures for the more relevant conformers of **3**. Experimental and B3LYP/DGDZVP DFT Boltzmann-weighted IR spectra of **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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