

Synthesis of Thalprzewalskiinone, a Revision of Structure

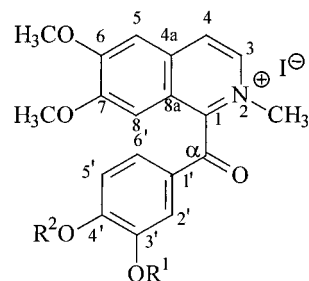
Tawfeq A. Al-Howiriny,[†] Michael A. Zemaitis,[†] Cong-yuan Gao,[‡] Chad E. Hadden,[§] Gary E. Martin,[§] Fu-tyan Lin,[‡] and Paul L. Schiff,^{*,†}

Department of Pharmaceutical Sciences, School of Pharmacy, University of Pittsburgh, Pittsburgh, Pennsylvania 15261, Department of Spectral Analysis, Beijing Medical University, Beijing, 100083, People's Republic of China, Pharmaceutical Development, Pharmacia Corporation, Kalamazoo, Michigan 49001, and Department of Chemistry, Faculty of Arts and Sciences, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Received March 2, 2001

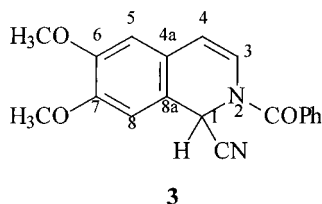
A direct comparison of the spectral data for synthetic 2-methyl-6,7-dimethoxy-3'-methoxy-4'-hydroxy-oxobenzylisoquinoline iodide (**1**) and its positional isomer 2-methyl-6,7-dimethoxy-3'-hydroxy-4'-methoxyoxobenzylisoquinoline iodide (**2**) with the data obtained for the oxobenzylisoquinoline alkaloid thalprzewalskiinone revealed that the original structural assignment of the alkaloid as **1** was in error. These results mandate the revision of structure of thalprzewalskiinone to 2-methyl-6,7-dimethoxy-3'-hydroxy-4'-methoxyoxobenzylisoquinoline iodide (**2**).

In 1999, a new oxobenzylisoquinoline alkaloid, thalprzewalskiinone, was isolated from the roots of the ancient Chinese medicinal herb *Thalictrum przewalskii* Maxim. (Ranunculaceae).¹ The structure of this quaternary alkaloid was assigned as 2-methyl-6,7-dimethoxy-3'-methoxy-4'-hydroxyoxobenzylisoquinoline iodide (**1**) on the basis of a consideration of the available spectral data.¹ However, since it was not possible to exclude that thalprzewalskiinone might correspond to the positional isomer of **1**, 2-methyl-6,7-dimethoxy-3'-hydroxy-4'-methoxyoxobenzylisoquinoline (**2**), it was decided to undertake a synthesis of both oxobenzylisoquinolines **1** and **2** in order to unambiguously assign the structure of the natural isolate.



1 R¹ = CH₃, R² = H

2 R¹ = H, R² = CH₃



The synthesis of these two compounds was accomplished in a conventional, two-part manner using well-established chemistry as described in the synthesis of the oxobenzyl-

isoquinoline alkaloids rugosinone (6,7-methylenedioxy-2'-hydroxy-3',4'-dimethoxyoxobenzylisoquinoline)² and thalmincrinone (5,6,7,4'-tetramethoxyoxobenzylisoquinoline).³ The first part involved the preparation of the Reissert compound 2-benzoyl-1-cyano-6,7-dimethoxy-1,2-dihydroisoquinoline (**3**) from 6,7-dimethoxyisoquinoline.^{2–5} This Reissert compound served as the common top-half for each of the two isomeric oxobenzylisoquinolines **1** and **2**. The second part involved coupling the Reissert anion (prepared via treatment of Reissert compound **3** with NaH in DMF) with the appropriate aldehyde (either *O*-benzylvanillin or *O*-benzylisovanillin)⁶ to afford the respective carbinols 3'-methoxy-4'-benzyloxyphenyl-1-(6,7-dimethoxyisoquinolyl) carbinol (**4**) and 3'-benzyloxy-4'-methoxyphenyl-1-(6,7-dimethoxyisoquinolyl) carbinol (**5**). These alcohols underwent facile oxidation with chromic acid^{2,3} to yield the respective ketones, 6,7-dimethoxy-3'-methoxy-4'-benzyloxyoxobenzylisoquinoline (**6**) and 6,7-dimethoxy-3'-benzyloxy-4'-methoxyoxobenzylisoquinoline (**7**), which were subsequently debenzylated to 6,7-dimethoxy-3'-methoxy-4'-hydroxyoxobenzylisoquinoline (**8**) and 6,7-dimethoxy-3'-hydroxy-4'-methoxyoxobenzylisoquinoline (**9**), respectively, on treatment with HCl/HOAc. Quaternization of tertiary amines **8** and **9** with MeI in MeCN afforded the desired compounds **1** and **2**, respectively.

A consideration of the UV spectral data (MeOH) for oxobenzylisoquinolines **1** and **2** with thalprzewalskiinone showed great similarity, as seen in Table 1. All three compounds had UV spectral maxima at 256, 302, and 326–327 nm. However, in the presence of strong alkali (0.1 N methanolic NaOH), compound **1** displayed an intense bathochromic shift (+52 nm) of the 327 nm band to 379 nm, consistent with the presence of the phenolic hydroxy group at C-4' (para to the carbonyl carbon).⁷ A review of the UV spectra of several known phenolic oxobenzylisoquinoline alkaloids is likewise consistent with these observations. The UV spectrum of gandharamine (6,7-dimethoxy-4'-hydroxyoxobenzylisoquinoline) showed absorption maxima at 255 nm (log ϵ 4.07) and 316 (3.65) nm, with the addition of strong alkali producing a pronounced bathochromic shift (+49 nm) of the latter band to 365 (3.89) nm.⁸ Furthermore, the UV spectrum of longifolonine (6-methoxy-7-hydroxy-4'-hydroxyoxobenzyl-3,4-dihydroisoquinoline) was characterized by absorption maxima at 231 and 295 nm, with the addition of strong base also resulting

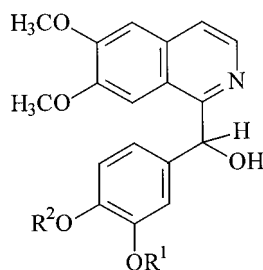
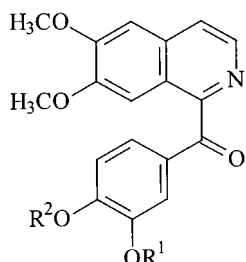
* To whom correspondence should be addressed. Tel: (412) 648-8462. Fax: (412) 383-7436. E-mail: pschiff+@pitt.edu.

[†] School of Pharmacy, University of Pittsburgh.

[‡] Beijing Medical University.

[§] Pharmacia Corporation.

[‡] Department of Chemistry, University of Pittsburgh.

4 $R^1 = \text{CH}_3$, $R^2 = \text{Bz}$ 5 $R^1 = \text{Bz}$, $R^2 = \text{CH}_3$ 6 $R^1 = \text{CH}_3$, $R^2 = \text{Bz}$ 7 $R^1 = \text{Bz}$, $R^2 = \text{CH}_3$ 8 $R^1 = \text{CH}_3$, $R^2 = \text{H}$ 9 $R^1 = \text{H}$, $R^2 = \text{CH}_3$

in a pronounced shift (+50 nm) of the latter band to 345 nm.⁷ By contrast, both compound **2** and natural thalprzewalskiinone underwent only a weak bathochromic shift (+15–16 nm) of the 302 nm band to 317–318 nm. This weak shift is characteristic of the presence of the phenolic hydroxy group in compound **1** at C-3' (meta to the carbonyl carbon).⁹

Therefore, a comparison of the UV absorption band shift behavior of isomers **1** and **2** in strongly alkaline medium with thalprzewalskiinone iodide prompts us to conclude that thalprzewalskiinone is identical to **2**.

With regard to the magnetic resonance spectral data, it may be reasonably anticipated that any significant differences in chemical shifts between positional isomers **1** and **2** would affect the following: first, the multiplicity and chemical shift of the H-2', H-5', and H-6' protons; second, the chemical shift of the protons found on the C-3' or C-4' aromatic methoxy group; and third, the carbon chemical shifts of the C-2', C-3', C-4', C-5', and C-6' atoms.

The ¹H NMR spectrum of phenol **1** revealed the presence of H-6' as a one-proton doublet at δ 6.85 ($J = 6.6$ Hz), while the same proton was observed as a one-proton doublet at δ 7.02 ($J = 8.4$ Hz) in phenol **2**. The H-6' proton was found at δ 7.06 in thalprzewalskiinone,¹ being much closer in chemical shift to that of phenol **2** (+0.04 Hz) than to that of phenol **1** (+0.21 Hz). This distinct difference in the chemical shift of H-6' is another compelling piece of evidence in support of the identity of thalprzewalskiinone as phenol **2**. The chemical shift of C-3' in phenol **1** was δ 155.9, and that of the same carbon in phenol **2** was δ 149.4. Although the C-4' in thalprzewalskiinone was originally assigned the chemical shift of δ 147.6,¹ reversing the C-3' and C-4' assignments is consistent with the results of the synthesis and the ultraviolet spectral data. Thus, the reassignment of the signal at δ 147.6 to C-3' allows a significantly closer agreement with phenol **2** (+1.8 Hz) than with phenol **1** (+8.3 Hz). Similarly, this reassignment

Table 1. MP and UV Spectral Data (nm/log ϵ) for Compounds **1** and **2** Iodides and Thalprzewalskiinone Iodide

	1	2	natural thalprzewalskiinone iodide ¹
mp	174–175 °C (Me ₂ CO)	196–197 °C (Me ₂ CO)	amorphous residue
UV (MeOH)	220 (4.43)		
	256 (4.57)	256 (4.54)	256 (4.38)
	302 (4.04)	302 (4.05)	302 (3.89)
	327 (4.17)	327 (4.11)	326 (3.94)
UV (MeOH + 0.1 N methanolic NaOH)	256 (4.59)	255 (4.57)	255 (4.55)
	323 (4.05) 379 (4.23)	318 (4.11)	317 (3.95)

allows a much closer agreement between the carbon chemical shift of the 4'-OCH₃ in phenol **2** (δ 57.7) and the methoxy in thalprzewalskiinone (δ 56.2) (+1.5 Hz) than between the 3'-OCH₃ in phenol **1** (δ 60.4) and the methoxy in thalprzewalskiinone (δ 56.2) (+4.2 Hz). The chemical shift of C-5' in phenol **1** was δ 133.2 and that of the same carbon in phenol **2** was δ 127.3. The chemical shift of C-5' in thalprzewalskiinone (δ 127.0) is characterized by significantly more agreement with that of phenol **2** (+0.3 Hz) than that of phenol **1** (+6.2 Hz). Similarly, the chemical shift of C-6' in phenol **1** was δ 120.6, and that of the same carbon in phenol **2** was δ 113.8. Thus, the chemical shift of C-6' in thalprzewalskiinone (δ 112.4) is found to be much more in agreement with that of phenol **2** (+1.4 Hz) than that of phenol **1** (+8.2 Hz). These magnetic resonance spectral considerations are complimentary to the previous ultraviolet data and mandate the revision of structure of thalprzewalskiinone to 2-methyl-6,7-dimethoxy-3'-hydroxy-4'-methoxyoxobenzylisoquinoline iodide (**2**).

Experimental Section

General Experimental Procedures. The UV spectra were obtained in MeOH on a Hewlett-Packard HP-845 UV-vis spectrophotometer. The IR spectra were measured on a Nicolet Impact 410 spectrophotometer as liquid films on KBr disks. Melting points were determined on a Fisher-Johns hot-stage apparatus and are uncorrected. ¹H and ¹³C NMR spectra were recorded in CDCl₃ or CD₃OD on a Bruker model WH-300 spectrometer operating at 300 and 75 MHz, respectively. The HSQC and HMBC experiments were performed in DMSO-*d*₆ on Varian INOVA spectrometers operating at a proton observation frequency of 399.803, 499.791, and 599.754 MHz. These instruments were equipped with a Nalorac MIDTG microdual obtained from Nalorac Cryogenics Corp, Martinez, CA. MS analysis was performed on an Extrel ELQ400 quadrupole mass spectrometer equipped with a DCI Probe HP direct probe from Vacumetrics Inc. or on a Hewlett-Packard 5971A mass spectrometer. High-resolution mass spectra were recorded on a Fisons VG Autospec spectrometer or a Fison VG Analytical 70-G spectrometer. FABMS was obtained using VG Analytical 70-G or Fisons VG Autospec spectrometer with *m*-nitrobenzyl alcohol (MNBA) as the matrix. Si gel was used for column chromatography, and TLC was performed using 5 × 20 cm precoated TLC sheets of silica gel 60 F₂₅₄, 0.2 mm layer thickness (E. Merck). Chemicals were purchased from Aldrich Chemical Co. Organic solvents such as Et₂O, CH₂Cl₂, and CHCl₃ that were used in partitioning procedures were dried over anhydrous Na₂SO₄ and filtered prior to evaporation.

Preparation of 1-Cyano-2-benzoyl-6,7-dimethoxyisoquinoline (3). To 6,7-dimethoxyisoquinoline^{2–4} (5.0 g, 0.026 mol) in CH₂Cl₂ (300 mL) was added a solution of KCN (13.6 g, 0.209 mol) in H₂O (60 mL). Benzoyl chloride (13.6 g, 11.25 mL, 0.097 mol) was added over 30 min under N₂ and the mixture allowed to stand at room temperature for 1 h. An additional

quantity of KCN (6.8 g, 0.105 mol) in H₂O (30 mL) was added and the mixture kept at room temperature for an additional 4 h. The CH₂Cl₂ layer was separated, partitioned consecutively with H₂O (2 × 100 mL), 2 M HCl (2 × 100 mL), 2 M NaOH (2 × 100 mL), and water (2 × 100 mL), and evaporated to dryness. The resulting residue was crystallized from MeOH as colorless needles (3.5 g, 42% yield) of 1-cyano-2-benzoyl-6,7-dimethoxyisoquinoline (**3**): mp 182–183 °C; UV (MeOH) λ_{\max} (log ϵ) 226 (4.51), 250 (sh) (4.30), 312 (4.01) nm; IR (KBr) ν_{\max} 2240, 1665, 1630, 1603, 1580, 1515, 1452, 1425, 1345, 1285, 1231, 1146, 1107 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 3.93 (3H, s, OCH₃), 3.95 (3H, s, OCH₃), 6.01 (1H, d, J = 7.5 Hz, H-4), 6.52 (1H, s, H-1), 6.73 (1H, s, H-8), 6.86 (1H, s, H-5), 7.54 (5H, m, 5ArH), 8.11 (1H, d, J = 7.15 Hz, H-3); ¹³C NMR (CDCl₃, 75 MHz) δ 168.8 (C=O), 150.3 and 149.2 (C-6 and C-7), 133.7 (C-1'), 132.3 and 132.0 (C-3 and C-4'), 130.2 (C-2'), 129.2 (C-3'), 128.7 and 128.4 (C-5' and C-6'), 124.5 (C-4a), 123.5 (C-8a), 116.6 (C≡N), 110.0 (C-4), 109.6 and 108.7 (C-5 and C-8), 56.3 (OCH₃), 56.1 (OCH₃), 44.8 (C-1); EIMS m/z 320 [M]⁺ (27), 215 (7), 189 (25), 146 (5), 105 (100), 77 (43).

Preparation of 3'-Methoxy-4'-benzyloxyphenyl-1-(6,7-dimethoxyisoquinolyl)carbinol (4). To NaH (100 mg, 4.2 mmol) suspended in DMF (10 mL) at -10 °C was added 1-cyano-2-benzoyl-6,7-dimethoxyisoquinoline (**3**) (1.0 g, 3.12 mmol) in DMF (15 mL) over a period of 5 min under N₂. After 5 min, *O*-benzylvanillin (822 mg, 3.4 mmol) in DMF (10 mL) was added over 10 min at -10 °C. The mixture was stirred for 2 h at 0 °C and then allowed to stand at room temperature for an additional 2 h. The mixture was treated with MeOH (50 mL) and then evaporated. The residue was dissolved in C₆H₆ (40 mL), partitioned with H₂O (2 × 30 mL), and evaporated. The resulting residue, consisting primarily of the benzoate ester of **4**, was dissolved in EtOH (25 mL) and hydrolyzed with KOH (0.2 g) in H₂O (10 mL) under reflux for 3 h. The solution was cooled and evaporated to dryness, and the resulting residue was partitioned with Et₂O (3 × 30 mL). The combined Et₂O extracts were evaporated to afford a white residue, which upon crystallization from MeOH afforded 3'-methoxy-4'-benzyloxyphenyl-1-(6,7-dimethoxyisoquinolyl)carbinol (**4**) (500 mg, 37% yield). The alcohol **4** had a mp of 142–143 °C; UV (MeOH) λ_{\max} (log ϵ) 238 (4.68), 278 (3.88), 313 (3.73), 326 (3.72) nm; IR (KBr) ν_{\max} 3500–3200, 1617, 1593, 1510, 1480, 1460, 1407, 1270, 1234, 1159, 1136, 1020 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 3.72 (6H, s, 2-OCH₃), 4.01 (3H, s, OCH₃), 5.10 (2H, s, OCH₂), 6.23 (1H, s, H- α), 6.67 (1H, d, J = 8 Hz, H-8'), 6.77 (1H, d, J = 8 Hz, H-6'), 6.92 (1H, s, H-8), 7.09 (1H, s, H-2'), 7.20 (1H, s, H-5), 7.33 (5H, m, ArH), 7.63 (1H, d, J = 5.8 Hz, H-4), 8.44 (1H, d, J = 5.8 Hz, H-3); ¹³C NMR (CDCl₃, 75 MHz) δ 156.5 (OCH₃, C-6), 152.9 (OCH₃, C-7), 150.0 (C-1 and C-4'), 147.8 (C-3'), 138.2 (C-3), 137.0 and 136.5 (C-1' and C-1''), 133.8 (C-4a), 128.5 (C-2'' and C-6''), 127.8 (C-4''), 127.2 (C-3'' and C-5''), 121.0 (C-6'), 120.2 and 120.0 (C-4 and C-8a), 113.8 (C-2'), 111.1 (C-5'), 105.3 (C-5), 103.4 (C-8), 72.5 (C- α), 70.9 (OCH₂), 56.1 (OCH₃), 56.0 (OCH₃), 55.9 (OCH₃); EIMS m/z 431 [M]⁺ (100), 416 (10), 340 (27), 324 (8), 188 (25), 91 (19).

Preparation of 6,7-Dimethoxy-3'-methoxy-4'-benzyloxyoxobenzylisoquinoline (6). To 3'-methoxy-4'-benzyloxyphenyl-1-(6,7-dimethoxyisoquinolyl)carbinol (**4**) (400 mg, 0.92 mmol) in HOAc (5 mL) was added a solution of Na₂CrO₄ (620 mg, 3.78 mmol) in HOAc (5 mL). The mixture was heated for 3 min on a steam bath, diluted with H₂O (50 mL), alkalized with NH₄OH to pH 8–9, and partitioned with Et₂O (3 × 50 mL). The Et₂O extracts were combined and evaporated, and the resulting residue was treated with MeOH to afford 6,7-dimethoxy-3'-methoxy-4'-benzyloxyoxobenzylisoquinoline (**6**) as yellow crystals (303 mg, 75% yield): mp 170 °C; UV (MeOH) λ_{\max} (log ϵ) 237 (4.49), 280 (3.99), 326 (3.97) nm; IR (KBr) ν_{\max} 1655, 1591, 1505, 1477, 1415, 1267, 1235, 1157, 1137, 1032, 861, 753 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 3.95 (3H, s, OCH₃), 3.98 (3H, s, OCH₃), 4.08 (3H, s, OCH₃), 5.24 (2H, s, OCH₂), 6.87 (1H, d, J = 8.4 Hz, H-5'), 7.17 (1H, s, H-8), 7.35 (6H, m, H-6' and 5ArH), 7.48 (1H, s, H-5), 7.73 (2H, d, J = 1.5 Hz, H-4 and H-2'), 8.45 (1H, d, J = 5.2 Hz, H-3); ¹³C NMR (CDCl₃, 75 MHz) δ 193.8 (C=O), 153.6 and 153.4 (C-6 and C-7), 153.1 (C-1), 151.2 (C-4'), 149.6 (C-3'), 139.8 (C-3), 136.3 (C-

1''), 134.2 (C-4a), 130.1 (C-1'), 128.8 (C-2'' and C-6''), 128.2 (C-4''), 127.2 (C-3'' and C-5''), 126.8 (C-6'), 122.9 (C-8a), 121.4 (C-4), 112.4 and 112.1 (C-2' and C-5'), 104.9 and 104.2 (C-5 and C-8), 70.9 (OCH₂), 56.2 (OCH₃), 56.2 (OCH₃), 56.2 (OCH₃); EIMS m/z 429 [M]⁺ (9), 338 (14), 188 (13), 91 (100).

Preparation of 6,7-Dimethoxy-3'-methoxy-4'-hydroxyoxobenzylisoquinoline (8). A solution of 6,7-dimethoxy-3'-methoxy-4'-benzyloxyoxobenzylisoquinoline (**6**) (280 mg, 0.652 mmol) in HCl–HOAc (1:1) (20 mL) was refluxed for 2 h. The solution was cooled, diluted with H₂O (40 mL), alkalized with NH₄OH to pH 8–9, and extracted with Et₂O (3 × 50 mL). The combined Et₂O extracts were evaporated to a white residue, which on crystallization from MeOH afforded 6,7-dimethoxy-3'-methoxy-4'-hydroxyoxobenzylisoquinoline (**8**) as white cubic crystals (140 mg, 64% yield): mp 179–180 °C; UV (MeOH) λ_{\max} (log ϵ) 240 (4.46), 315 (3.85) nm; UV (MeOH + 2 drops of 0.1 N NaOH) λ_{\max} (log ϵ) 369 (3.88); IR (KBr) ν_{\max} 3453, 1650, 1581, 1506, 1488, 1432, 1410, 1286, 1231, 1160, 1138, 1052, 1027, 865, 732 cm⁻¹; ¹H NMR (DMSO-*d*₆, 500 MHz) δ 3.78 (3H, s, OCH₃), 3.81 (3H, s, 3H, OCH₃), 3.94 (3H, s, OCH₃), 6.82 (1H, d, J = 8.5 Hz, H-5'), 7.15 (1H, dd, J = 8.5 Hz, J = 2.0 Hz, H-6'), 7.25 (1H, s, H-8), 7.46 (1H, s, H-5), 7.55 (1H, d, J = 2.0 Hz, H-2'), 7.82 (1H, d, J = 5.5 Hz, H-4) 8.38 (1H, d, J = 5.0 Hz, H-3); ¹³C NMR (CDCl₃, 75 MHz) δ 193.5 (C=O), 154 (C-1), 153.1 (C-7), 151.1 (C-6), 149.7 (C-3'), 148.2 (C-4'), 140.2 (C-3), 133.8 (C-4a), 128.4 (C-1'), 127.3 (C-6'), 122.1 (C-8a), 121.4 (C-4), 115.3 (C-5'), 112.9 (C-2'), 105.9 (C-5), 103.7 (C-8), 56.2 (OCH₃), 55.9 (OCH₃), 55.8 (OCH₃); HREIMS m/z 339.1091 [M]⁺ (calcd for C₁₉H₁₇O₅N, 339.1106), 151.0393 (calcd for C₈H₇O₃, 151.0395).

Preparation of 2-Methyl-6,7-dimethoxy-3'-methoxy-4'-hydroxyoxobenzylisoquinoline Iodide (1). To 6,7-dimethoxy-3'-methoxy-4'-hydroxyoxobenzylisoquinoline (**8**) (40 mg, 0.118 mmol) in CH₃CN (10 mL) was added CH₃I (1 mL). The solution was refluxed for 12 h, cooled, and evaporated to a yellow residue (49 mg). Treatment of the residue with Me₂CO afforded 2-methyl-6,7-dimethoxy-3'-methoxy-4'-hydroxyoxobenzylisoquinoline iodide (**1**) as yellow crystals (40 mg, 72% yield): mp 174–175 °C; UV (MeOH) λ_{\max} (log ϵ) 220 (4.43), 256 (4.57), 302 (4.04), 327 (4.17) nm; UV (MeOH + 2 drops of 0.1 N NaOH) λ_{\max} (log ϵ) 323 (4.05), 3.79 (4.23) nm; IR (KBr) ν_{\max} 3420, 1655, 1583, 1514, 1494, 1430, 1289, 1231, 1164, 1025, 994, 875, 755 cm⁻¹; ¹H NMR (DMSO-*d*₆, 600 MHz) δ 3.71 (3H, s, OCH₃, C-7), 3.85 (3H, s, OCH₃, C-3'), 4.06 (3H, s, OCH₃, C-6), 4.13 (3H, s, NCH₃), 6.85 (1H, d, J = 6.6 Hz, H-6'), 6.88 (1H, s, H-8), 7.15 (1H, br s, H-5'), 7.61 (1H, br s, H-2'), 7.85 (1H, s, H-5), 8.42 (1H, d, J = 6.6 Hz, H-4) 8.66 (1H, d, J = 7.2 Hz, H-3), 10.94 (1H, s, OH); ¹³C NMR δ 190.0 (C=O), 162.3 (C-6), 158.1 (C-7), 155.9 (C-3'), 154.7 (C-1), 153.9 (C-4'), 141.2 (C-4a), 141.1 (C-3), 133.2 (C-5'), 130.3 (C-1'), 128.4 (C-4), 126.1 (C-8a), 120.6 (C-6'), 115.9 (C-2'), 111.1 (C-5), 108.7 (C-8), 61.6 (C-6) (OCH₃), 60.8 (C-7) (OCH₃), 60.4 (C-3') (OCH₃), 50.1 (NCH₃); HREIMS m/z 353.1247 [M⁺ – HI] (calcd for C₂₀H₁₉O₅N, 353.1263), 339.1100 (calcd for C₁₉H₁₇O₅N, 339.1106).''

Preparation of 3'-Benzyloxy-4'-methoxyphenyl-1-(6,7-dimethoxyisoquinolyl)carbinol (5). To NaH (100 mg, 4.2 mmol) suspended in DMF (10 mL) at -10 °C was added 1-cyano-2-benzoyl-6,7-dimethoxyisoquinoline (**3**) (1.0 g, 3.12 mmol) in DMF (15 mL) over a period of 5 min under N₂. After 5 min, *O*-benzylisovanillin (822 mg, 3.4 mmol) in DMF (10 mL) was added over 10 min at -10 °C. The mixture was stirred for 2 h at 0 °C and then allowed to stand at room temperature for an additional 2 h. The mixture was treated with MeOH (50 mL) and then evaporated to a residue that was dissolved in C₆H₆ (40 mL), partitioned with H₂O (2 × 30 mL), and evaporated. The resulting residue, consisting primarily of the benzoate ester of **5**, was dissolved in EtOH (25 mL) and hydrolyzed by KOH (0.2 g) in H₂O (10 mL) under reflux for 3 h. The solution was cooled and evaporated to dryness, and the resulting residue was treated with Et₂O (3 × 30 mL). The combined Et₂O extracts were evaporated to a white residue, which upon crystallization from MeOH afforded 3'-benzyloxy-4'-methoxyphenyl-1-(6,7-dimethoxyisoquinolyl)carbinol (**5**) (430 mg, 32% yield): mp of 140–141 °C; UV (MeOH) λ_{\max} 239 (4.68), 278 (3.88), 313 (3.72), 326 (3.57) nm; IR (KBr) ν_{\max} 3437, 1622,

1570, 1510, 1481, 1434, 1406, 1272, 1235, 1158, 1138, 1022, 963, 754 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 3.72 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.02 (3H, s, OCH_3), 5.03 (2H, s, OCH_2), 6.22 (1H, s, 1H, H-'), 6.81 (1H, d, $J = 8.2$ Hz, H-5'), 6.86 (1H, s, H-8), 6.95 (1H, dd, $J = 8.2$ Hz and 1.9 Hz, H-6'), 7.08 (2H, s, H-2' and H-5), 7.29 (5H, m, ArH), 7.56 (1H, d, $J = 5.8$ Hz, H-4), 8.40 (1H, d, $J = 5.8$ Hz, H-3); ^{13}C NMR NMR (CDCl_3 , 75 MHz) δ 156.4 (C-6), 152.9 (C-7), 149.9 (C-1), 149.4 (C-4), 148.4 (C-3'), 138.2 (C-3), 136.9 (C-1'), 135.9 (C-1'), 133.7 (C-4a), 128.4 (C-2'' and C-6''), 127.7 (C-4''), 127.3 (C-3'' and C-5''), 120.9 (C-6'), 120.8 (C-8a), 119.9 (C-4), 113.4 (C-2'), 111.6 (C-5'), 105.2 (C-5), 103.3 (C-8), 72.4 (C- α), 70.9 (OCH_2), 56.1 (OCH_3), 56.0 (OCH_3), 55.8 (OCH_3); EIMS m/z 431 [M^+] (88), 416 (5), 340 (70), 324 (85), 310 (24), 280 (33), 218 (47), 188 (80), 91 (100).

Preparation of 6,7-Dimethoxy-3'-benzyloxy-4'-methoxyoxobenzylisoquinoline (7). To 3'-benzyloxy-4'-methoxyphenyl-1-(6,7-dimethoxyisoquinolyl) carbinol (5) (400 mg, 0.92 mmol) in HOAc (5 mL) was added a solution of Na_2CrO_4 (620 mg, 3.78 mmol) in HOAc (5 mL). The mixture was heated for 3 min on a steam bath, diluted with H_2O (50 mL), alkalized with NH_4OH to pH 8–9, and partitioned with Et_2O (3×50 mL). The Et_2O extracts were combined, partitioned with H_2O (3×100 mL), and evaporated. Treatment of the resulting residue with MeOH afforded 6,7-dimethoxy-3'-benzyloxy-4'-methoxyoxobenzylisoquinoline (7) as crystals (320 mg, 80% yield): mp 158–159 $^\circ\text{C}$; UV (MeOH) λ_{max} 238 (4.52), 282 (3.86), 326 (3.85) nm; IR (KBr) ν_{max} 1655, 1591, 1578, 1505, 1480, 1434, 1268, 1234, 1157, 1138, 1020, 861, 753 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 3.93 (6H, s, OCH_3), 4.05 (3H, s, OCH_3), 5.18 (2H, s, OCH_2), 6.90 (1H, d, $J = 8.4$ Hz, H-5'), 7.13 (1H, s, H-8), 7.35 (6H, m, H-6' and 5ArH), 7.48 (1H, s, H-5), 7.64 (1H, d, $J = 5.4$ Hz, H-4), 7.70 (1H, d, $J = 1.8$ Hz, H-2'), 8.42 (1H, d, $J = 5.4$ Hz, H-3); ^{13}C NMR NMR (CDCl_3 , 75 MHz) δ 193.8 (C=O), 154.4 (C-1), 153.7 (C-7), 153.3 (C-6), 151.0 (C-4), 148.1 (C-3'), 139.9 (C-3), 136.5 (C-1'), 134.0 (C-4a), 129.7 (C-1'), 128.6 (C-2'' and C-6''), 128.0 (C-4'), 127.5 (C-3'' and C-5''), 126.9 (C-6'), 122.8 (C-8a), 121.2 (C-4), 114.6 (C-2'), 110.4 (C-5'), 104.8 and 104.1 (C-5 and C-8), 70.9 (OCH_2), 56.2 (OCH_3), 56.2 (OCH_3), 56.1 (OCH_3); EIMS m/z 429 [M^+] (35), 400 (20), 338 (100), 324 (40), 308 (37), 296 (25), 188 (36), 152 (33), 91 (61).

Preparation of 6,7-Dimethoxy-3'-hydroxy-4'-methoxyoxobenzylisoquinoline (9). A solution of 6,7-dimethoxy-3'-benzyloxy-4'-methoxyoxobenzylisoquinoline (7) (300 mg, 0.70 mmol) in of HCl–HOAc (1:1) (20 mL) was refluxed for 2 h. The solution was cooled, diluted with H_2O (40 mL), alkalized with NH_4OH to pH 8–9, and extracted with Et_2O (3×50 mL). The combined Et_2O extracts were evaporated to a residue that upon crystallization from MeOH afforded 6,7-dimethoxy-3'-hydroxy-4'-methoxyoxobenzylisoquinoline (9) as pale yellow crystals (180 mg, 76% yield): mp 150–151 $^\circ\text{C}$; UV (MeOH) λ_{max} 238 (4.45), 280 (3.78), 329 (3.78) nm; UV (MeOH + 2 drops of 0.1 N NaOH) λ_{max} (log ϵ) 288 (3.79), 332 (3.80) nm; IR (KBr) ν_{max} 3500–3350, 1655, 1606, 1506, 1483, 1437, 1271, 1234, 1157, 1134, 859, 755 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 3.74 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 6.97 (1H, d, $J = 8.0$ Hz, H-5'), 7.18 (1H, s, H-8), 7.20 (1H, dd, $J = 8.8$ and 2.4 Hz, H-6'), 7.29 (1H, d, $J = 2.4$ Hz, H-2'), 7.44

(1H, s, H-5), 7.80 (1H, d, $J = 5.6$ Hz, H-4), 8.35 (1H, d, $J = 5.6$ Hz, H-3); ^{13}C NMR δ 195.1 (C=O), 155.5 (C-1), 154.4 (C-7), 154.3 (C-4), 152.2 (C-6), 147.8 (C-3'), 141.9 (C-3), 134.8 (C-4a), 130.5 (C-1'), 125.5 (C-6'), 123.2 (C-8a), 122.5 (C-4), 117.8 (C-2'), 112.8 (C-5'), 107.1 (C-5), 104.7 (C-8), 57.3 (OCH_3), 57.2 (OCH_3), 56.9 (OCH_3); HREIMS m/z 339.1091 [M^+] (calcd for $\text{C}_{19}\text{H}_{17}\text{O}_5\text{N}$, 339.1106), 188.0709 (calcd for $\text{C}_{11}\text{H}_{10}\text{O}_2\text{N}$, 188.0711), 151.0393 (calcd for $\text{C}_8\text{H}_7\text{O}_3$, 151.0395).

Preparation of 2-Methyl-6,7-dimethoxy-3'-hydroxy-4'-methoxyoxobenzylisoquinoline Iodide (2). To 6,7-dimethoxy-3'-hydroxy-4'-methoxyoxobenzylisoquinoline (9) (30 mg, 0.088 mmol) in CH_3CN (10 mL) was added CH_3I (1 mL). The solution was refluxed for 12 h, cooled, and evaporated to a yellow residue (42 mg). Treatment of the residue with Me_2CO afforded 2-methyl-6,7-dimethoxy-3'-hydroxy-4'-methoxyoxobenzylisoquinoline iodide (2) as yellow crystals (33 mg, 77% yield): mp 196–197 $^\circ\text{C}$; UV (MeOH) λ_{max} 256 (4.54), 302 (4.05), 327 (4.11) nm; UV (MeOH + 2 drops of 0.1 N NaOH) λ_{max} (log ϵ) 318 (4.11) nm; IR (KBr) ν_{max} 3500–3300, 1655, 1511, 1498, 1434, 1290, 1164, 1144, 1015, 995 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 3.70 (3H, s, OCH_3 , C-7), 3.86 (3H, s, OCH_3 , C-4'), 4.05 (3H, s, OCH_3 , C-6), 4.11 (3H, s, NCH_3), 6.85 (1H, s, H-8), 7.02 (1H, d, $J = 8.4$ Hz, H-6'), 7.21 (1H, br s, H-5'), 7.40 (1H, br s, H-2'), 7.85 (1H, s, H-5), 8.41 (1H, d, $J = 6.8$ Hz, H-4) 8.65 (1H, d, $J = 6.4$ Hz, H-3), 9.87 (1H, s, OH); ^{13}C NMR δ 188.1 (C=O), 159.2 (C-6), 157.0 (C-4'), 154.5 (C-7), 150.9 (C-1), 149.4 (C-3'), 137.9 (C-4a), 137.9 (C-3), 128.1 (C-1'), 127.3 (C-5'), 125.3 (C-4), 122.9 (C-8a), 116.2 (C-2'), 113.8 (C-6'), 108.0 (C-5), 105.5 (C-8), 58.6 (C-6) (OCH_3), 57.8 (C-7) (OCH_3), 57.7 (C-4') (OCH_3), 47.0 (NCH_3); HREIMS m/z 353.1271 [$\text{M}^+ - \text{HI}$] (calcd for $\text{C}_{20}\text{H}_{19}\text{O}_5\text{N}$, 353.1263), 339.1102 (calcd for $\text{C}_{19}\text{H}_{17}\text{O}_5\text{N}$, 339.1106), 150.9995 (calcd for $\text{C}_8\text{H}_7\text{O}_3$, 150.9991).

Acknowledgment. The authors gratefully acknowledge the partial financial support of King Saud University (TAA).

Supporting Information Available: Tables of the proton and carbon chemical shift assignments and long-range connectivities observed in the GHMBC spectra of compounds **1** and **2**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References and Notes

- Al-Rehailly, A. J.; Sharaf, M. H. M.; Zemaitis, M. J.; Gao, C.-Y.; Martin, G. E.; Chadden, C. E.; Thamann, T. J.; Lin, F.-T.; Schiff, P. L., Jr. *J. Nat. Prod.* **1999**, *62*, 146–148.
- Cheng, H. Y.; Doskotch, R. W. *J. Nat. Prod.* **1980**, *43*, 151–156.
- Al-Khalil, S.; Schiff, P. L., Jr. *J. Nat. Prod.* **1985**, *48*, 989–991.
- Birch, A. J.; Jackson, A. H.; Shannon, P. V. R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2190–2194.
- Birch, A. J.; Jackson, A. H.; Shannon, P. V. R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2185–2189.
- Schiff, P. L., Jr. The Isolation and Characterization of the Alkaloids of *Thalictrum minus* L. var. *adiantifolium* Hort. Ph.D. Dissertation, The Ohio State University, Columbus, OH, 1967; p 163.
- Bick, I. R. C.; Sevenet, T.; Sinchai, W.; Skelton, B.; White, A. H. *Aust. J. Chem.* **1981**, *34*, 195–207.
- Abu Zarga, M. H.; Miana, G. A.; Shamma, M. *Heterocycles* **1982**, *18*, 63–65.
- Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrophotometric Identification of Organic Compounds*, 5th ed.; John Wiley & Sons: New York, 1991; p 181.

NP0101200