Synthesis of Deserpidine from Reserpine

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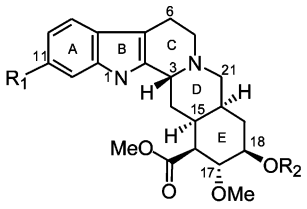
Received May 25, 2005

The Rauwolfia alkaloids reserpine (**1**) and deserpidine (**2**), two alkaloids from *Rauwolfia* species, have been widely used for their antihypertensive action. Deserpidine (**2**) is a compound with limited availability from natural sources, and its synthesis from **1** in six steps (41% overall yield) is reported here.

Reserpine (**1**) is a naturally occurring alkaloid that has been used for centuries in traditional Indian medicine. It was first isolated in 1952[1] from Indian snake root, *Rauwolfia serpentina*, and introduced for the treatment of hypertension and schizophrenia later in the 1950s.[2] Reserpine is known to act both centrally and peripherally by depletion of biogenic amines such as noradrenaline, dopamine, and serotonin. Its property of producing severe depression as a side effect also made it useful in psychiatry as a tranquilizer in the control of agitated psychotic patients, even though it was replaced by more effective drugs by the end of 1970s.[3−5] In addition to its biological properties, the complex molecular structure and the presence of numerous asymmetric centers stimulated the development of several approaches toward its synthesis.[6−9] The total synthesis of **1**, developed by Woodward and coworkers,[6] is considered one of the historical landmarks in natural product synthesis.

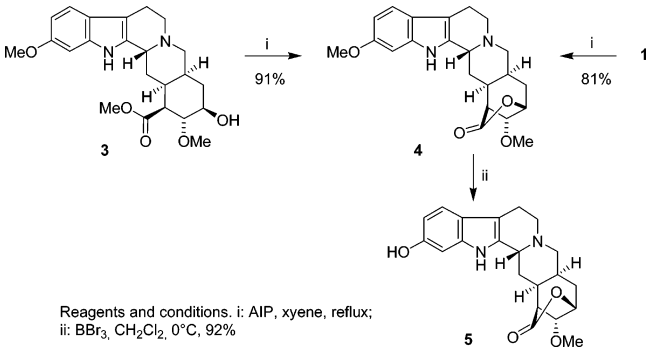
Deserpidine[10,11] (**2**), isolated from the root of *Rauwolfia canescens*, differs from reserpine (**1**) only by the absence of a methoxy group at C-11. Deserpidine (**2**) shows an interesting pharmacological profile and has been employed for the treatment of hypertension and as a tranquilizer. In addition, it appears to act as a controller of other cardiac disorders.[12]

Due to its poor availability from natural extracts, deserpidine (**2**) has not been widely employed in medicine. Reserpine usually occurs at about 0.10−0.16% of the extract and deserpidine (**2**) at about 0.04%. Moreover, few syntheses of deserpidine have been achieved so far;[13,14] thus we envisioned the possibility of developing a new and efficient procedure for the synthesis of deserpidine (**2**) from commercially available reserpine (**1**).



1 R_1 = OMe R_2 = 3,4,5-trimethoxybenzoyl (Reserpine)
2 R_1 = H R_2 = 3,4,5-trimethoxybenzoyl (Deserpidine)
3 R_1 = OMe R_2 = H (Methyl reserpate)

Scheme 1. Synthesis of 11-OH Reserpic Acid Lactone (**5**)



Results and Discussion

To the best of our knowledge, only one report has been published on the transformation of reserpine (**1**) into deserpidine (**2**) so far.[15] The key step of Sakai's procedure is the cleavage of the yohimbane skeleton, which provides a general method to give deserpidine derivatives having different substituent groups on the indole part. Attempts of direct removal of the methyl group at C-11 carried out on reserpine (**1**)[19] or on methyl reserpate (**3**)[10] have failed, affording only a complex mixture of byproducts or complete demethylation including the methoxy group at C-17. Thus, to favor demethylation at C-11 versus C-17, we first synthesized the reserpic acid lactone (**4**) by reaction of methyl reserpate (**3**)[10] with aluminum isopropoxide (AIP).[16]

We assumed that the formation of the lactone ring could have led to a skeletal rearrangement forcing the C-17 methoxy group to an axial position, thus no longer accessible to demethylating agents. The reaction proceeded smoothly, affording the desired product **4** in 91% isolated yield. The same result was achieved by direct reaction of reserpine (**1**) with AIP in refluxing xylene, affording reserpic acid lactone (**4**) in 81% overall yield (Scheme 1). As we expected, the following treatment with BBr_3 at 0 °C in CH_2Cl_2[9,17] afforded only the C-11 demethylated adduct **5** in 92% yield.

Lactone **5** was converted to the sulfonyl ester derivative **6a** (76% yield) by reaction with methanesulfonyl chloride and triethylamine (Scheme 2). Subsequent hydrogenation with molecular hydrogen performed in a Parr apparatus at 50 psi and in the presence of Ni-Raney[18] afforded derivative **7** in 60% isolated yield, along with the free alcohol **5** in 40% yield. To improve regioselectivity of the reductive cleavage, we attempted to favor C−O bond fission over S−O fission by replacement of the methanesulfonyl group with a better leaving group, such as *p*-toluene-

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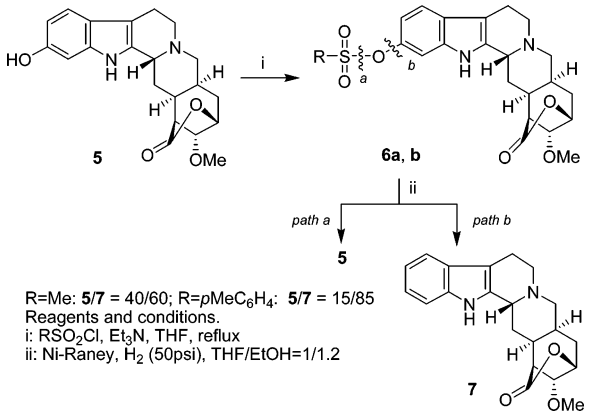
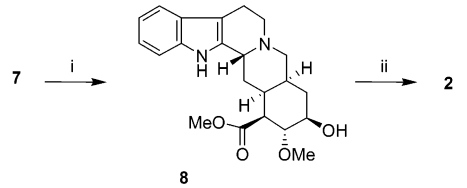
10.1021/np050179x CCC: $30.25
Published on Web 11/08/2005

Scheme 2. Synthesis of Reserpic Acid Lactones (**6a**,**b**) and Deserpidic Acid Lactone (**7**)



Scheme 3. Synthesis of Deserpidine (**2**)



Reagent and conditions. i) MeONa, MeOH, reflux, 90 min., 95 %
ii) 2, 4, 6-$(MeO)_3C_6H_2COCl$, pyridine, 5°C, 5 days, 91%

sulfonyl, thus favoring the formation of the desired product **7** instead of the free phenol **5** (Scheme 2). The reaction of **5** with *p*-toluenesulfonyl chloride and triethylamine afforded the desired sulfonyl ester **6b** in 76% yield. Subsequent reductive cleavage as described afforded **7** in 85% yield, thus confirming our initial hypothesis.

Deserpidic acid lactone (**7**) was then transformed into methyl deserpidate (**8**) by means of sodium methoxide in MeOH; the free alcohol **8** was than reacted at 5 °C with 3,4,5-trimethoxybenzoyl chloride in pyridine.[10] The target deserpidine (**2**) was isolated in 91% yield as a white solid (Scheme 3).

Thus, an efficient six-step protocol for the conversion of reserpine (**1**) to deserpidine (**2**) has been described. The key step of the synthesis is the lactone ring formation, which allows regioselective cleavage of the C-11 methoxyl group.

Experimental Section

General Experimental Procedures. Solvents were purified and dried prior to use. Reactions were monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60 F254) using UV light as a visualizing agent or a 7% ethanolic phosphomolybdic acid as developing agent. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer with Me_4Si or $CHCl_3$ (in $CDCl_3$) as internal reference. Infrared spectra were recorded on a Fourier transform IR spectrometer, and values are reported in cm^{-1} units. Positive ion mass spectra were obtained by direct infusion of 1.2 mM solutions in 0.02 M ammonium acetate/MeOH, 20/80, using a Thermoquest LCQ-duo ion trap mass spectrometer (Finnigan) equipped with an ESI ionization source. Methyl reserpate (**3**) and deserpidine (**2**) from methyl deserpidate (**8**) were prepared as reported elsewhere.[10]

Reserpic Acid Aactone (4). Procedure A: A mixture of aluminum isopropoxide (10.5 g, 51.4 mmol) and reserpine (**1**) (4.1 g, 6.74 mmol) in xylene (175 mL) was refluxed under vigorous stirring for 6 h. Reserpic acid lactone (**4**), precipitated from the solution, was filtered and washed with benzene (3 × 40 mL) and ethyl ether (3 × 40 mL). The residue was recrystallized from $CHCl_3$, affording 2.07 g (5.46 mmol, 81%) of **7** as a white solid. Procedure B: A mixture of aluminum isopropoxide (0.75 g, 3.65 mmol) and **3** (0.20 g, 0.48 mmol) in xylene (11 mL) was refluxed under vigorous stirring and under nitrogen for 2 h. The product was separated by filtration and washed with xylene (3 × 20 mL), then with ether (3 × 20 mL). The residue was recrystallized from $CHCl_3$, affording 0.17 g (0.44 mmol, 91%) of **4** as a white solid.

Compound 4: $[\alpha]^{20}_D$ 16.6° (*c* 0.3, $CHCl_3$); IR (KBr) ν_{max} 3328, 2925, 1770, 1464, 1198 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.5 (1H, bs, NH), 7.18 (1H, d, J = 8.4 Hz, H-9), 6.77 (1H, d, J = 2.3 Hz, H-12), 6.58 (1H, dd, J = 8.4, 2.3 Hz, H-10), 4.75 (1H, t, J = 4.0 Hz, H-18), 4.10 (1H, t, J = 5.2 Hz, H-17), 3.73 (3H, s, OMe), 3.45 (1H, d, J = 10.8 Hz, H-3), 3.35 (3H, s, OMe), 2.90 (1H, dd, J = 12.0, 4.8 Hz), 2.76−2.64 (1H, m), 2.62−2.48 (5H, m), 2.42−2.25 (3H, m), 2.00 (1H, dd, J = 14.4, 8.6 Hz, H-19), 1.77−1.68 (1 H, m, H-14), 1.56 (1 H, dd, J = 14.4, 4.0 Hz, H-19); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 178.3, 155.7, 137.5, 135.2, 121.9, 118.6, 108.5, 106.7, 95.5, 77.7, 77.1, 58.8, 57.1, 55.9, 54.9, 53.2, 45.5, 35.4, 31.3, 27.7, 26.4, 22.2; *anal*. C 67.7%, H 7.17%, calcd for $C_{22}H_{26}N_2O_4$, C 69.09%, H 7.32%.

11-Hydroxy Reserpic Acid Lactone (5). Reserpic acid lactone (**4**) (0.21 g, 0.55 mmol) was suspended in CH_2Cl_2 (8.0 mL) under argon, and the mixture was cooled to 0 °C. After 15 min, BBr_3 was added (1.4 mL, 1.37 mmol, 1.0 M solution in CH_2Cl_2) and the solution turned brick red. After 5 h the reaction was quenched with 10 mL of an aqueous saturated solution of $NaHCO_3$ and extracted with 10 mL of CH_2Cl_2. The aqueous phase was collected and extracted again with EtOAc (3 × 15 mL). The eventual precipitate was filtered, dissolved in a 1:1 THF/MeOH mixture, and added to the previously obtained organic solution. The organic phases were combined and dried. The solid residue was chromatographed (SiO_2, CH_2Cl_2/MeOH, 15:1, then 16:1) to give **5** as a white solid (0.19 g, 0. 51 mmol, 92%). Compound **5**: $[\alpha]^{20}_D$ 58.3° (*c* 0.3, THF); MS (*m/z*) ESI: 369 (M + H)$^+$; IR (KBr) ν_{max} 3415, 3312, 2923, 1779, 1629 cm^{-1}; ^{1}H NMR (THF-d_8, 400 MHz) δ 9.38 (1H, bs, NH), 7.54 (1H, bs, OH), 7.07 (1H, d, J = 8.4 Hz, H-9), 6.59 (1H, d, J = 2.0 Hz, H-12), 6.44 (1H, dd, J = 8.8, 2.0 Hz, H-10), 4.63 (1H, t, J = 4.3 Hz, H-18), 4.03 (1H, t, J = 5.2 Hz, H-17), 3.61 (1H, d, H-3, J = 14.6 Hz,), 3.40 (3H, s, OMe), 2.98−2.82 (1H, m, H-5), 2.84−2.45 (7H, m, H-5, H-6, H-6, H-21, H-21, H-15, H-16), 2.42−2.34 (1H, m, H-20), 2.22 (1H, dd, J = 13.5, 2.0 Hz, H-14), 2.14−2.08 (1H, m, H-19), 1.90−1.82 (1H, m, H-14), 1.61 (1H, dd, J = 14.8, 3.9 Hz, H-19); ^{13}C NMR (THF-d_8, 100 MHz) δ 176.6, 153.2, 138.0, 133.9, 121.3, 117.5, 108.4, 106.9, 96.6, 78.2, 76.7, 58.9, 56.2, 54.6, 53.1, 45.7, 35.8, 31.8, 27.9, 26.2, 22.1; *anal*. C 67.10%, H 7.46%, calcd for $C_{21}H_{24}N_2O_4$, C 68.46%, H 7.60%.

11-*O*-Methanesulfonyl Reserpic Acid Lactone (6a). Et_3N (0.01 mL, 0.11 mmol) was added to a solution of 11-hydroxy reserpic acid lactone (**5**) (0.03 g, 0.08 mmol) in 5.0 mL of dry THF, under N_2. After stirring 10 min, methanesulfonyl chloride (0.01 mL, 0.09 mmol) was added and the mixture was left at 20 °C for 60 h. Solvent was removed under reduce pressure, and purification of the residue by flash chromatography (SiO_2, CH_2Cl_2/MeOH, 17:1) afforded 0.03 g (0.06 mmol, 76%) of **6a** as a white solid. Compound **6a**: $[\alpha]^{20}_D$ 8.5° (*c* 0.3, $CHCl_3$); IR (KBr) ν_{max} 3295, 2923, 1758, 1179 cm^{-1}; ESIMS (*m/z*) 447 (M + H)$^+$; ^{1}H NMR (THF-d_8, 400 MHz) δ 10.1 (1H, bs, NH), 7.35 (1H, d, J = 8.8 Hz, H-9), 7.22 (1H, d, J = 2.0 Hz, H-12), 6.92 (1H, dd, J = 8.8, 2.0 Hz, H-10), 4.65 (1H, t, J = 4.4 Hz, H-18), 4.04 (1H, t, J = 5.2 Hz, H-17), 3.67 (1H, d, J = 11.6 Hz, H-3), 3.40 (3H, s, OMe), 3.06 (3H, s, OMe), 2.99−2.93 (1H, m, H-5), 2.89−2.81 (1H, m, H-6), 2.73 (1H, m, H-21), 2.67−2.48 (5H, m, H-5, H-6, H-21, H-15, H-16), 2.44−2.36 (1H, m, H-20), 2.27 (1H, dd, J = 13.6, 1.6 Hz, H-14), 2.17−2.09 (m, 1 H, H-19), 1.94−1.86 (1H, m, H-14), 1.62 (1H, dd, J = 15.0, 4.0 Hz, H-19); ^{13}C NMR (THF-d_8, 100 MHz) δ 176.7, 145.0, 136.4, 127.6, 126.5, 117.8, 112.8, 107.6, 104.8, 78.2, 76.8, 58.8, 56.3, 54.5, 52.9, 45.7, 35.6, 31.7, 29.9, 27.9, 26.2, 21.9; *anal*. C, 58.00%; H, 5.75%, calcd for $C_{22}H_{26}N_2O_6S$, C, 59.18%; H, 5.87%.

11-*O*-*p*-Toluenesulfonyl Reserpic Acid Lactone (6b). Et_3N (1.86 mL, 13.32 mmol) was added to a solution of 11-hydroxy reserpic acid lactone (**5**) (0.70 g, 1.90 mmol) in 65 mL of dry THF, under N_2. After stirring 10 min *p*-toluenesulfonyl

chloride (1.09 g, 5.71 mmol) was added, and the mixture was refluxed for 42 h. The crude mixture was than evaporated under reduced pressure. Chromatography (SiO_2, CH_2Cl_2/MeOH, 17:1) afforded 0.75 g (1.44 mmol, 76%) of **6b** as a white solid. Compound **6b**: $[\alpha]^{20}_D$ −9° (*c* 0.3, $CHCl_3$); IR (KBr) ν_{max} 3282, 2927, 1756, 1177 cm^{-1}; ESIMS (*m/z*) 523 $(M + H)^+$; ^1H NMR (THF-d_8, 400 MHz) δ 9.99 (1H, bs, NH), 7.64−7.62 (2H, m, Ar), 7.32−7.30 (2H, m, Ar), 7.15 (1H, d, J = 8.4 Hz, H-9), 6.90 (d, 1 H, J = 2.0 Hz, H-12), 6.47 (1H, dd, J = 8.4, 2.0 Hz, H-10), 4.64 (1H, t, J = 4.0 Hz, H-18), 4.03 (1H, t, J = 5.2 Hz, H-17), 3.62 (1H, d, J = 12.0 Hz, H-3), 3.39 (3H, s, OMe), 2.93−2.89 (1H, m, H-5), 2.84−2.43 (7H, m, H-5, H-6, H-6, H-21, H-21, H-15, H-16), 2.38−2.32 (4H, m, Me, H-20), 2.22 (1H, dd, J = 13.6, 1.6 Hz), 2.10 (1H, m, H-19), 1.90−1.81 (1H, m, H-14), 1.60 (1H, dd, J = 15.2, 4.0 Hz, H-19); ^{13}C NMR (THF-d_8, 100 MHz) δ 176.7, 144.9, 144.8, 136.2, 133.5, 129.6, 128.7, 126.3, 117.4, 113.2, 107.5, 105.0, 78.2, 76.7, 58.8, 56.3, 54.5, 52.9, 45.7, 35.7, 31.7, 29.9, 27.9, 26.2, 21.9, 20.8; *anal*. C 63.05%, H 5.70%, calcd for $C_{28}H_{30}N_2O_6S$, C 64.35%, H 5.79%.

Deserpidic Acid Lactone (7). Procedure A: Ni-Raney, previously washed with H_2O (twice), MeOH (twice), and EtOH (once), was introduced (0.13 g, wet) into a Parr apparatus under argon. Then 11-*O*-methanesulfonyl reserpic acid lactone (**6a**) (0.02 g, 0.04 mmol), dissolved in 4.0 mL of anhydrous THF and 6.0 mL of EtOH, was added. The hydrogenation was carried out under a pressure of 50 psi. After 8 h the solution was filtered through Celite and the Celite was carefully washed with $CHCl_3$ (6 × 10 mL) followed by MeOH (40 mL). Solvent was removed under vacuum, and the residue was purified by flash column chromatography (SiO_2, CH_2Cl_2/MeOH, 20:1), to afford 0.01 g of **7** as white solid (0.03 mmol, 60%), along with 0.005 g (0.01 mmol, 40%) of **5**. Procedure B: Ni-Raney, previously washed with H_2O (twice), MeOH (twice), and EtOH (once), was introduced (4.86 g, wet) into a Parr apparatus under argon, followed by 11-*O*-*p*-toluenesulfonyl reserpic acid lactone (**6b**) (0.30 g, 0.57 mmol) dissolved in 14 mL of anhydrous THF and 16.0 mL of EtOH. The hydrogenation was carried out under 50 psi hydrogen pressure, and after 8 h the solution was filtered through Celite and carefully washed with $CHCl_3$ (6 × 40 mL) and MeOH (100.0 mL). Solvent was removed under reduced pressure, and purification of the residue by flash chromatography (SiO_2, CH_2Cl_2/MeOH, 20:1) afforded 0.17 g of **7** as a white solid (0.49 mmol, 85%) along with 0.03 g (0.09 mmol, 15%) of **5**. Compound **7**: $[\alpha]^{20}_D$ 7.9° (*c* 0.3, $CHCl_3$); IR (KBr) ν_{max} 3316, 2922, 1764, 1454 cm^{-1}; ESIMS (*m/z*) 352 $(M + H)^+$; ^1H NMR (THF-d_8, 400 MHz) δ 9.80 (1H, bs, NH), 7.32 (1H, d, J = 7.6 Hz, H-9), 7.20 (1H, d, J = 7.6 Hz, H-12), 6.98−6.87 (2H, m, H-10, H-11), 4.65 (1H, t, J = 4.0 Hz, H-18), 4.04 (1H, t, J = 5.2 Hz, H-17), 3.66 (1H, d, J = 11.6 Hz, H-3), 3.40 (3H, s, OMe), 2.97−2.92 (1H, m, H-5), 2.89−2.79 (1H, m), 2.78−2.33 (7H, m), 2.28 (1H, dd, J_1 = 13.7 Hz, J_2 = 2.0 Hz, H-14), 2.15−2.10 (m, 1 H, H-19), 1.94−1.85 (1H, m, H-14), 1.62 (1H, dd, J = 14.8, 4.0 Hz, H-19); ^{13}C NMR (THF-d_8, 100 MHz) δ 176.7, 136.9, 136.1, 127.6, 120.2, 118.3, 117.4, 110.5, 107.2, 78.2, 76.7, 58.9, 56.2, 54.6, 53.1, 45.7, 35.8, 31.7, 27.9, 26.2, 22.1; *anal*. C 70.10%, H 6.74%, calcd for $C_{213}H_{24}N_2O_3$, C 71.57%, H 6.86%.

Methyl Deserpidate (8). Deserpidic acid lactone (**7**) (0.14 g, 0.40 mmol) was dissolved in 27 mL of anhydrous MeOH under N_2 atmosphere. NaOMe (0.03 g, 0.60 mmol) was added to the reaction mixture, which was then refluxed for 90 min. The reaction was quenched by addition of 0.2 mL of acetic acid, and the crude mixture was evaporated under reduced pressure, washed with a 0.2 M solution of NaOH, and extracted with $CHCl_3$ (4 × 25 mL). The organic phases were dried, filtered, and evaporated under reduced pressure. Flash chromatography purification of the crude compound (SiO_2, CH_2Cl_2/MeOH, 10:1) afforded 0.17 g (0.38 mmol, 95%) of **8** as a white solid. Compound **8**: $[\alpha]^{20}_D$ −80° (*c* 0.2, pyridine); IR (KBr) ν_{max} 3454, 3374, 2925, 1722, 1463 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.80 (1H, bs, NH), 7.46 (1H, d, J = 6.8 Hz), 7.31 (1H, d, J = 8.0 Hz), 7.14 (1H, td, J = 6.8, 1.2 Hz), 7.09 (1H, td, J = 7.6, 1.2 Hz), 4.46 (1H, bs, H-3), 3.79 (3H, s, OMe), 3.62−3.48 (5H, m, OMe and 2H), 3.26−3.15 (2H, m), 3.06−2.91 (2H, m), 2.59−2.45 (3H, m), 2.32−2.17 (2H, m), 2.03−1.91 (1H, m), 1.89−1.71 (3H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.7, 135.7, 132.1, 127.8, 121.7, 119.7, 118.3, 111.1, 108.3, 81.6, 75.3, 61.2, 53.9, 52.1, 51.5, 51.3, 49.5, 34.7, 33.0, 32.4, 24.5, 16.9; *anal*. C 67.41%, H 7.20%, calcd for $C_{22}H_{28}N_2O_4$, C 68.73%, H 7.34%.

Deserpidine (2). A solution of 3,4,5-trimethoxybenzoyl chloride (0.5 g, 2.17 mmol) in benzene (2.0 mL) was slowly added to a solution of methyl deserpidate (**8**) (0.5 g, 1.30 mmol) in dry pyridine (4.0 mL) at 5 °C. After disappearance of the starting material, followed by TLC analysis of the reaction mixture (5 days), the reaction was diluted with water (50.0 mL) and then treated with aqueous ammonia (10.0 mL). The aqueous phases were extracted with CH_2Cl_2 (3 × 25 mL), dried over sodium sulfate, filtered, and evaporated under reduced pressure. The crude material was recrystallized from acetone, yielding 0.17 g of **2** (0.44 mmol, 91%) as a white solid. Compound **2**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.83 (1 H, bs, NH), 7.48 (1 H, m), 7.33 (1 H, s), 7.33 (1 H, s), 7.32 (1 H, m), 7.17 (1 H, m), 7.12 (1 H, m), 5.07 (1 H, m), 4.52 (1 H, bs, H-3), 3.90 (1 H, dd, J_1 = 12.0 Hz, J_2 = 9.0 Hz), 3.89 (s, 3 H, OMe), 3.89 (3 H, s, OMe), 3.89 (3 H, s, OMe), 3.80 (3 H, s, OMe), 3.80 (3 H, s, OMe), 3.20 (1 H, m), 3.20 (1 H, m), 3.04 (dd, 1 H, J_1 = 12.0 Hz, J_2 = 4.0 Hz), 2.98 (1 H, m), 2.70 (1 H, dd, J_1 = 12.0 Hz, J_2 = 5.0 Hz), 2.54 (1 H, m), 2.47 (1 H, dd, J_1 = 12.0 Hz, J_2 = 2.0 Hz), 2.34 (1 H), 2.33 (1 H), 2.04 (1 H), 1.98 (1 H), 1.90 (1 H), 1.86 (1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.8, 169.4, 163.8, 161.0, 159.4, 144.0, 141.6, 141.6, 141.4, 140.1, 137.4, 133.1, 133.0, 115.5, 115.5, 86.2, 85.5, 82.3, 75.4, 74.0, 72.1, 67.8, 65.3, 61.8, 57.2, 50.7, 39.8, 27.3, 20.3.

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NP050179X