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Total Synthesis of (±)-Cytisine via the Intramolecular Heck Cyclization of Activated *N*-Alkyl Glutarimides

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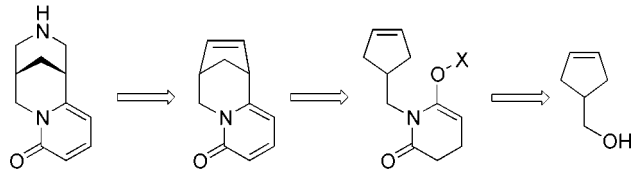
ABSTRACT



A synthesis of racemic cytisine 1 has been developed utilizing an intramolecular Heck cyclization to prepare the bridged tricyclic intermediate 2. The cyclization employs activated glutarimide-derived ketene aminals 3 (X = $P(O)OEt_2$ or SO_2CF_3) and represents the first use of such intermediates in metal-catalyzed processes.

The natural product (−)-cytisine, (**1**, as depicted), a member of the lupin alkaloid family,[1] is an important probe in nicotinic acetylcholine receptor research.[2] It displays high affinity at neuronal nicotinic receptors,[3] yet elicits weak agonist properties in cells expressing these receptors.[4] Though found ubiquitously in nature,[5] it is currently expensive and available only in small quantities commercially. Elegant syntheses of cytisine appeared in the 1950s by van Tamelen,[6] Bohlmann,[7] and Govindachari.[8] These efforts served to confirm its structure and establish efficient strategies for its construction; however, the syntheses are lengthy and suffer from low overall yields. To further probe the chemistry and biology of (−)-cytisine, we sought a synthetic source of the material. Herein we describe a concise 6-step synthesis of racemic cytisine from cyclopent-3-enylmethanol **4**.[9]

Our strategy features the intramolecular Heck cyclization[10] of glutarimide-derived ketene aminals, **3**, to construct the tricyclic carbon skeleton of cytisine, **2**. A variety of lactam-derived ketene aminal derivatives have recently appeared in methodological and total synthetic studies. Isobe,[11] Comins,[12]

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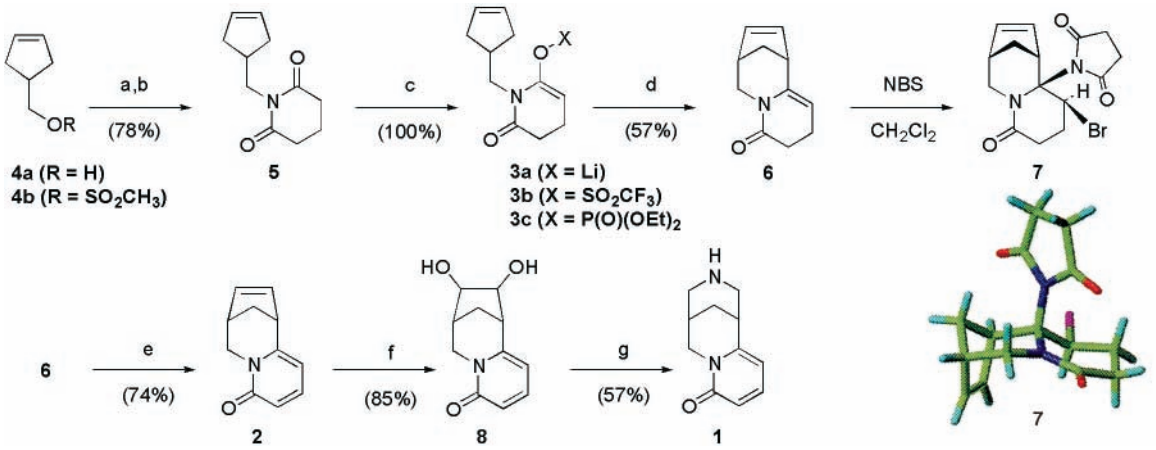
Scheme 1[a]



[a] (a) 1.0 equiv of glutarimide, 1.0 equiv of *t*-BuOK, 68 °C, THF 1 h, then 0.9 equiv of mesylate of **4**, cat. DMF, cat. n-Bu_4NI; (b) 1 equiv of LHMDS, THF, 0 to 23 °C; (c) see text, Supporting Information; (d) 2.5 mol % of $Pd(OAc)_2$, 5 mol % of P(*o*-tol)$_3$, 1.5 equiv of TEA, CH_3CN, 83 °C, 24 h; (e) 10−20 equiv of activated MnO_2, benzene, 80 °C, 3 h; (f) $(CH_3)_3NO{\cdot}2H_2O$, cat. OsO_4, CH_2Cl_2; (g) 1 equiv of $NaIO_4$, EtOH, H_2O, 30 min, then aqueous NH_4OH, H_2, $Pd(OH)_2$, 48−72 h.

Murai,[13] and Speckamp[14] introduced vinyl trifluoromethanesulfonates (vinyl triflates, X = SO_2CF_3) of *N*-acyllactams for transition metal catalyzed processes, and additional examples have appeared.[15] Nicolaou subsequently reported phosphate activation of both *N*-acyllactam[16] and lactone[17] derivatives (vinyl phosphates, X = $P(O)OR_2$). Phosphate-activated intermediates were found to be more robust than the corresponding triflates. Recently *N*-alkyl ketene aminal triflates and phosphates derived from *N*-alkyl lactam precursors were applied to asymmetric syntheses.[18] Herein we extend this approach to include examples of participation by cyclic imide derived ketene aminals in transition metal catalyzed processes.

The synthesis begins with the *N*-alkyl glutaramide **5**, prepared from cyclopent-3-enylmethanol **4a** by alkylation of the corresponding mesylate[19] **4b** with glutarimide (KO-*t*-Bu, THF, 68 °C, 24 h, 78−91%, Scheme 1).[20] Treatment of **5** with LHMDS in THF (0 °C to rt) provides a poorly soluble enolate (**3a**, X = Li). Our initial studies employed triflate activation ($PhN(SO_2CF_3)_2$, −78 to 0 °C, 1 h)[21] which provided dihydropyridone **3b** (X = SO_2CF_3) in low yield (<10%). The improved conditions reported by Comins provided little advantage (5-Cl-2-$N(SO_2CF_3)_2$-pyridine, −78 to 0 °C, THF, 1 h, 24%).[22] Under standard Heck conditions[23] (2.5 mol % of $Pd(OAc)_2$, 5 mol % of P(*o*-tol)$_3$, 1.5 equiv of TEA, CH_3CN, 83 °C, 24 h), **3b** was readily converted to the key tricyclic dihydropyridone **6** (52%).

Spectroscopic analysis (COSY and decoupling studies) supported the tricyclic skeletal structure of **6**. Confirmation was obtained by single-crystal X-ray diffraction analysis of the crystalline derivative **7**, a 1:1 adduct obtained by reaction of **6** with *N*-bromosuccinimide in CH_2Cl_2 or THF (Scheme 1). This result unambiguously defines the [3.2.1]-bridged tricyclic skeleton of **7**, derived from *cis*-addition of NBS to *N*-acyl enamine **6** from the least hindered face.

With an established route to the nucleus, we focused on alternative methods for ketene aminal activation. Treatment of lithium enolate **3a** (X = Li) with $ClP(O)(OEt)_2$ (1 equiv, THF, −78 to 20 °C) resulted in complete conversion to

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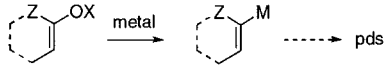

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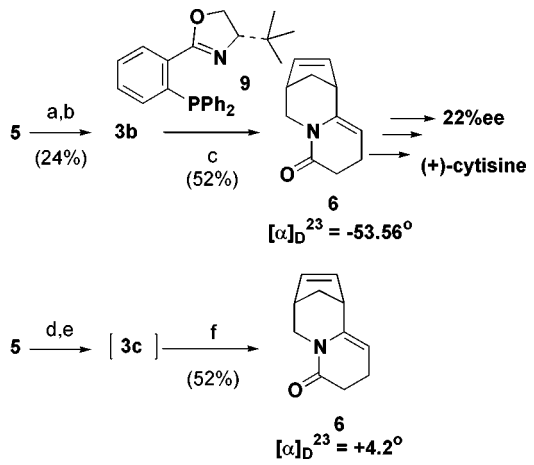
ketene aminal phosphate **3c** (X = P(O)(OEt)$_2$). This material was routinely used without further purification, requiring only simple evaporation of solvent from the crude reaction mixture.[24] Our initial attempts to cyclize **3c** were hampered by the presence of residual THF. Exchange of solvent to CH_3CN and introduction of base and catalyst (1.5 equiv of TEA, 2 mol % of Pd(OAc)$_2$, 4 mol % of P(*o*-tol)$_3$, 60 °C, 24 h) resulted in smooth conversion to bicyclic adduct **6** in 57% isolated yield.[25] Glutarimide **5** was recovered from the reaction (20−30%), presumably arising from hydrolysis of the phosphate ester. Other phosphate esters (Ph, *i*-Pr) and methods of preparation were explored but offered no measurable advantage. Ultimately, generation of the intermediate ketene aminal phophate **3c** (X = P(O)(OEt)$_2$) in toluene (KHMDS, 0 to 20 °C, 30 min, treatment with ClP(O)(OEt)$_2$ at −78 to 20 °C, 1 h) followed by in situ Heck cyclization provided a one-pot preparation of **6** from **5** (1.5 equiv of TEA, 2.5 mol % of Pd(OAc)$_2$ and 5 mol % of **9**, 110 °C, 5 d, 52%, see Scheme 2 below).

Scheme 2[a]



[a] (a) KHMDS, THF, 0 °C to rt, 1/2 h; (b) 5-Cl-2-*N*-(SO_2CF_3)-2-pyridine, −78 °C to rt, 1.5 h, 24%.; (c) 2.5 mol % of Pd(OAc)$_2$, 5 mol % of **9**, 1.5 equiv of *i*-Pr$_2$NEt, toluene, 110 °C, 18 h, 52%; (d) KHMDS, THF, 0 °C to rt, 1/2 h; (e) ClP(O)(OEt)$_2$, -78 °C to rt 1.5 h; (f) 2.5 mol % of Pd(OAc) $_2$, 5 mol % of **9**, 1.5 equiv of *i*-Pr$_2$NEt, toluene, 110 °C, 18 h, 52% from **5**.

Identifying an efficient dehydrogenation of **6** to pyridone **2** was initially an obstacle (Scheme 1). DDQ was capricious, as various conditions and reaction times produced product of poor quality in yields below 50%. Chloranil failed to react.[26] Efforts to effect allylic bromination led to products derived from *N*-acyl enamine addition, such as **7**, and attempts to efficiently convert these to pyridone **2** were unsuccessful. Difficulties have been observed in related oxidations of dihydropyrrones and NH-dihydropyridones.[27] Ultimately MnO_2 was found to be mild and effective, cleanly and reproducibly converting **6** to crystalline **2** (10−20 equiv, benzene, 80 °C, 3 h, 74%).[26b]

Finally, the piperidine ring was introduced in a two-pot operation using standard literature techniques. Dihydroxylation of olefin **2** was accomplished in 85% isolated yield ($(CH_3)_3NO{\cdot}2H_2O$, cat. OsO_4, CH_2Cl_2).[28] Filtration of the crude reaction mixture through a silica pad avoids extraction of the water-soluble diol **8** and produces crystalline material. Direct conversion of diol **8** to (±)-cytisine is accomplished by a one-pot procedure: oxidative cleavage ($NaIO_4$, EtOH, H_2O, 3 h), followed by treatment with 30% aqueous NH_4OH solution and catalytic hydrogenation (H_2, Pd(OH)$_2$) for 48 to 72 h provides racemic cytisine **1**, in 57% yield after chromatography.[29]

Preliminary studies on the influence of chiral ligands in the cyclization event have been promising (Scheme 2). Though Heck cyclization with BINAP as ligand did not progress under the conditions we studied, the Pfaltz ligand **9** successfully catalyzed the reaction of triflate **3b** to provide **6**.[30] This product was determined to be 22% ee after conversion to cytisine. Phosphate ester **3c** provided essentially racemic material under similar conditions (4% ee favoring the opposite antipode). Further work may uncover suitable ligands and conditions to induce useful enantioselection.[31]

We have established a protecting group free, 6-step, 16% overall yield synthesis of racemic cytisine from readily available starting materials. The key step features the novel

(24) The recovered yield of **5** was not enhanced when chromatographically pure **3c** was employed.

(25) Early experiments established the requirement that THF be exhaustively removed from the ketene aminal phosphate to allow a reasonable Heck cyclization rate. Azeotropic removal with CH_3CN (3×) under nitrogen gave reproducible results. Use of argon atmosphere, however, under the azoetropic conditions and during the subsequent Heck reaction prevented Heck cyclization. Introduction of a nitrogen atmosphere to the argon-purged reaction after 24 h initiated the Heck cyclization. Indeed, reaction in air ($CaCO_3$ tube) progressed rapidly, albeit causing decomposition of the air-sensitive cycloadduct and vinyl Heck intermediate. This observation suggests that catalytic oxygen is required to generate the active palladium catalyst.

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(31) An efficient resolution is known. See ref 6.

use of glutarimide derived ketene aminal phosphate as an activated substituent for an intramolecular Heck cyclization process.[32]

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(32) **Experimental Procedures:** Unless otherwise noted, all materials were purchased from commercial sources. Anhydrous solvents were used as provided (in Sure/Seal bottles) and reactions were performed under a dry nitrogen atmosphere. Thin-layer chromatography was performed with EM Separations Technology silica gel F_{254}. Silica gel chromatography was carried out with J. T. Baker 40 μm silica gel according to Still's procedure (Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923). All glassware was flame dried under dry nitrogen purge before use. ^{1}H NMR spectra were collected at 400 MHz with residual $CHCl_3$ as standard (7.26 ppm). Melting points are uncorrected. All spectroscopic data for known compounds was in complete accord with literature values.

Preparation of 4b: Cyclopent-3enylmethanol[9] (**4a**, 18.0 g, 184 mmol) and triethylamine (22.5 g, 222 mmol) were stirred in CH_2Cl_2 (300 mL) at 0 °C under nitrogen and treated with methanesulfonyl chloride (23.2 g, 202 mmol) over 15 min. After 15 min at 0 °C the reaction was poured into H_2O (150 mL), the layers were separated, and the organic layer was washed with H_2O (2 × 50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL), and the combined organic layer was washed with a saturated aqueous $NaHCO_3$ solution (2 × 50 mL) and a saturated aqueous NaCl solution (50 mL). The organic layer was dried through a cotton plug and a 1 in. silica gel pad to remove polar impurities. The filtrate was concentrated to afford mesylate **4b** (32.3 g, 100%) which was used without further purification (TLC 25% EtOAc/hexanes R_f 0.60): ^{1}H NMR ($CDCl_3$) δ 5.68 (br s, 2H), 4.14 (d, J = 8 Hz, 2H), 3.03 (s, 3H), 2.7 (m, 1H), 2.63−2.45 (m, 2H), 2.35−2.10 (m, 2H).

Preparation of 5: Glutarimide (15.4 g, 136 mmol) and KO-*t*-Bu (15.3 g, 136 mmol) were dispersed in THF (600 mL) under nitrogen and warmed under reflux for 1 h. To this mixture were added DMF (1 mL), *n*-Bu_4NI (1 g), and mesylate **4b** (21 g, 119 mmol) in THF (20 mL). The resulting mixture was stirred at this temperature for 24 h and then treated with additional DMF (25 mL). After 4 d the mixture was cooled, poured into H_2O (200 mL), and extracted with EtOAc (3 × 100 mL). The organic extracts were washed with H_2O (2 × 100 mL) and saturated aqueous NaCl solution (100 mL), dried over Na_2SO_4 and filtered through a 1 in. silica pad to remove baseline material. The concentrated product was filtered through a silica gel pad (3.5 × 5 in.) eluting with CH_2Cl_2 to generate **5** as an oil that crystallizes (18 g, 78%): mp 32−33 °C (TLC 25% EtOAc/hexanes R_f 0.37); ^{1}H NMR ($CDCl_3$) δ 5.64 (br s, 2H), 3.79 (d, J = 8 Hz, 2H), 2.65 (t, J = 6.6 Hz, 4H), 2.70 (m, 1H), 2.38−2.32 (m, 2H), 2.05−2.00 (m, 2H), 1.92 (m, 2H); GCMS *m*/*e* 193 (M^+). Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found C, 67.90; H, 7.58; N, 7.26.

Preparation of 3c: 1,1,1,3,3,3-Hexamethyldisilazane (7.15 mL, 33.9 mmol) was stirred in anhydrous THF (40 mL) under nitrogen at 0 °C and treated with 2.5 M *n*-BuLi in hexanes (13.2 mL, 32.9 mmol) over 2 min. After 20 min, glutarimide **5** (6.23 g, 32.3 mmol) in anhydrous THF (40 mL) was introduced over 5 min by cannula. The resulting thick slurry was stirred for 5 min at 0 °C and then allowed to warm with stirring to ambient temperature over a 30 min. It was then cooled to −78 °C and treated with chloro diethylphosphate (4.81 mL, 32.3 mmol) in anhydrous THF (15 mL) over 2 min. The mixture was stirred for 10 min at −78 °C and allowed to warm to ambient temperature over 1.5 h. This solution was concentrated on the rotary evaporator while a nitrogen atmosphere was maintained. The resulting oil was dried under reduced pressure for 2 h (0.01 mm). Data for enol phosphate (**3c**) (TLC 10% EtOAc/CH_2Cl_2 R_f 0.12): ^{1}H NMR ($CDCl_3$) δ 5.54 (br s, 2H), 5.13 (t, J = 5.0 Hz, 1H), 3.81 (m, 6H), 2.79 (m, 1H), 2.32−2.26 (m, 2H), 2.18 (t, J = 7.7 Hz, 2H), 2.12−2.07 (m, 2H), 1.65 (m, 2H), 0.90 (t, J = 7.0 Hz, 6H); APCI MS *m*/*e* 330 ($M^+ + 1$).

Preparation of 6: The above enol phosphate **3c** (32.3 mmol) was dissolved in anhydrous CH_3CN (100 mL, distilled from CaH) under nitrogen and treated with freshly distilled triethylamine (6.75 mL, 48.4 mL), tri-*o*-tolylphosphine (393 mg, 1.29 mmol), and palladium(II) acetate (145 mg, 0.65 mmol). The resulting mixture was stirred and warmed in an oil bath to 60 °C for 24 h. After cooling, the volatiles were removed in vacuo. H_2O was added (50 mL) and the product was extracted with Et_2O (5 × 40 mL). The organic layer was washed with H_2O (2 × 20 mL), a saturated aqueous $NaHCO_3$ solution (2 × 20 mL), and a saturated aqueous NaCl solution (50 mL) and then dried over Na_2SO_4. This mixture was filtered through a 1 in. silica pad eluting with Et_2O to remove baseline color. The filtrate was concentrated and purified by chromatography on silica gel eluting with 12% Et_2O/CH_2Cl_2 to provide **6** as an oil (3.25 g, 57% yield) (TLC 10% EtOAc/CH_2Cl_2 R_f 0.40): ^{1}H NMR ($CDCl_3$) δ 5.97 (m, 2H), 4.82 (dd, 5.8, 2.3 Hz, 1H), 3.68 (dd, 12.7, 1.5 Hz, 1H), 3.21 (dd, 12.7, 3.4 Hz, 1H), 3.05 (dd, 5.0, 2.5 Hz, 1H), 2.85 (dd, J = 5.0, 2.8, 1H), 2.43 (m, 2H), 2.24 (m, 1H), 2.08 (m, 2H), 1.73 (d, J = 10.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 135.23, 134.24, 100.47, 43.93, 43.52, 38.91, 37.58, 31.55, 19.26; GCMS *m*/*e* 175 (M^+).

Preparation of 7: Dihydropyridone **6** (175 mg, 1.0 mmol) was stirred in CH_2Cl_2 (10 mL) and treated dropwise with NBS (178 mg, 1.0 mmol) in CH_2Cl_2 (10 mL). A 10 min concentration affords an oily solid which crystallized. X-ray analysis confirmed the structure as the 1:1 adduct, **7** (TLC (EtOAc) R_f 0.36): ^{1}H NMR ($CDCl_3$) δ 6.16 (dd, J = 5.8, 3.0 Hz, 1H), 5.96 (dd, J = 5.8, 3.2 Hz, 1H), 4.38 (dd, J = 5.2, 3.2 Hz, 1H), 4.25 (m, 2H), 2.75−2.04 (aliphatic, 11 H), 1.48 (d, J = 11.2 Hz, 1H).

Preparation of 2: A dispersion of dihydropyridone **6** (1.58 g, 9.03 mmol) and activated MnO_2 (14.3 g, 165 mmol) were stirred in benzene (75 mL) and warmed under reflux for 3 h. The reaction mixture was filtered while hot through a Celite pad and eluted with EtOAc (400 mL). Concentration afforded pyridone **2** as an oil which crystallized on standing (1.16 g, 74%) (TLC 5% MeOH/CH_2Cl_2 R_f 0.50): mp 64−66.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.12 (dd, J = 9.0, 7.0 Hz, 1H), 6.36 (dd, J = 9.0, 1.0 Hz, 1H), 6.03 (dd, 5.5, 3.0 Hz, 1H), 5.95 (dd, 5.5, 3.0 Hz, 1H), 5.83 (dd, J = 7.0, 1.0 Hz, 1H), 3.67 (Abq, $\Delta\nu_{1-3}$ = 17.5 Hz, J = 15.5 Hz, 2H), 3.31 (dd, J = 4.0, 3.3 Hz, 1H), 3.06 (m, 1H), 2.16 (m, 1H), 1.87 (d, J = 10.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 138.40, 136.09, 133.28, 118.07, 103.34, 44.92, 43.85, 37.44, 36.09. GCMS *m*/*e* 173 (M^+). Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09; Found C, 76.21; H, 6.19; N, 7.95.

Preparation of 8: Pyridone **2** (228 mg, 1.32 mmol) and trimethylamine-*N*-oxide dihydrate (161 mg, 1.45 mmol) were stirred under nitrogen in CH_2Cl_2 (20 mL) with OsO_4 (0.32 mL of a 2.5 wt % solution in *t*-BuOH, 0.003 mmol, 0.24 mol %) for 36 h. The solution was filtered through a silica pad (1.5 × 2 in.) eluting with 19/1 CH_2Cl_2/CH_3OH and the filtrate was concentrated to provide **8** as white granular solid (232 mg, 85%) (TLC 5% MeOH/CH_2Cl_2 R_f 0.34): ^{1}H NMR ($CDCl_3$) δ 7.28 (dd, J = 9.0, 7.0 Hz, 1H), 6.41 (dd, J = 9.0, 1.0 Hz, 1H), 6.04 (d, J = 7.0 Hz, 1H), 4.13 (br s, 2H), 3.95 (d, J = 15.2 Hz, 1H), 3.77 (dd, J = 15.2, 4.8 Hz, 1H), 3.09 (br s, 1H), 2.62 (br s, 1H), 2.29 (m, 1H), 1.62 (d, J = 12.0 Hz, 1H).

Preparation of racemic 1: A solution of diol **8** (256 mg, 1.24 mmol) in EtOH/H_2O (3/1, 40 mL) was magnetically stirred in a Parr bottle and treated with a solution of $NaIO_4$ (265 mg, 1.24 mmol) in H_2O (2 mL). The resulting white dispersion was stirred 3 h, the stir bar was removed, and a 37% NH_4OH solution (30 mL) and $Pd(OH)_2$ (87 mg, 10% on C) were introduced. The mixture was shaken u der 50 psi of hydrogen for 72 h and then filtered through a Celite pad and eluted with ethanol. The filtrate was concentrated to an oily residue, dissolved in CH_3OH (30 mL), treated with silica gel (3 g), and concentrated to a powder. This powder was transferred onto a silica gel column and eluted with 92/7/1 CH_2Cl_2/CH_3OH/(37% NH_4OH) to provide **1** as a clear oil which crystallizes (135 mg, 57%) (TLC 92/7/1 CH_2Cl_2/CH_3OH/(37% NH_4OH) R_f 0.50): mp 139−142 °C (lit. 146−147 °C);[8c] ^{1}H NMR (CD_3OD) δ 7.46 (dd, J = 9.0, 7.0 Hz, 1H), 6.42 (d, J = 9.0 Hz, 1H), 6.27 (d, J = 7.0 Hz, 1H), 4.05 (d, J = 15.2 Hz, 1H), 3.90 (dd, J = 15.2, 6.3 Hz, 1H), 3.29 (br s, 2H), 2.98 (m, 4H), 2.34 (br s, 1H), 1.99 (m, 1H); GCMS *m*/*e* 190 (M^+); APCI MS *m*/*e* 191 ($M^+ + 1$). Anal. Calcd for 7 $C_{11}H_{14}N_2O \cdot H_2O$: C, 68.52; H, 7.47; N, 14.53. Found C, 68.64; H, 7.10; N, 14.22.