JOC The Journal of Organic Chemistry

Article

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A Raney-Cobalt-Mediated Tandem Reductive Cyclization Route to the 1,5-Methanoazocino[4,3-*b*]indole Framework of the Uleine and *Strychnos* Alkaloids

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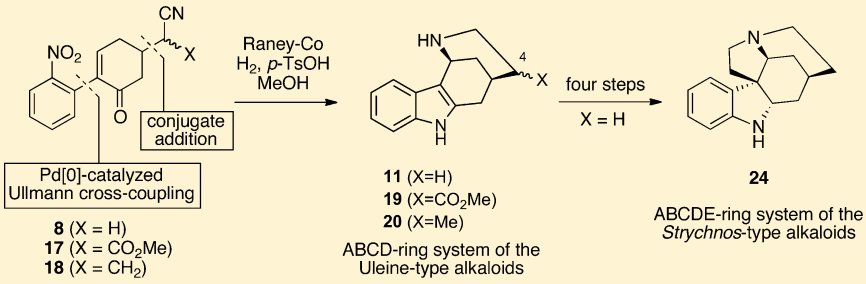
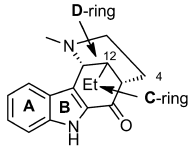
Supporting Information



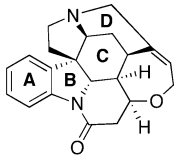
ABSTRACT: The readily accessible enones **8**, **17**, and **18** undergo 2-fold reductive cyclization reactions upon exposure to hydrogen in the presence of Raney-cobalt and thereby afford compounds **11** (72%), **19** (47%), and **20** (84%), respectively. These products embody the ABCD-ring system associated with the title alkaloids, and compound **11** can be converted, over four steps and in 33% yield, into congener **24** incorporating the ABCDE-ring system of the *Strychnos* alkaloids.

INTRODUCTION

The title framework is encountered, as a key structural element, in both the Uleine and *Strychnos* alkaloid families, members of which include dasycarpidone (**1**) and strychnine (**2**), respectively.[1] The biological properties and fascinating molecular architectures of such compounds have resulted in a sustained focus on the development of methods for the assembly of them. For example, recent work has culminated in extraordinarily concise syntheses of strychnine, arguably the structurally most demanding and certainly the most well-known member of the latter class of alkaloid.[2] Herein, we report an effective new protocol for the construction of the constituent tetracyclic 1,5-methanoazocino[4,3-*b*]indole or ABCD-ring system that involves, as the key step, a highly chemoselective Raney-cobalt-mediated tandem reductive cyclization of readily accessible, bicyclic substrates. This protocol should provide a useful means for the ready assembly of key substructures and analogues of these important alkaloidal systems.[3]



Dasycarpidone (**1**)

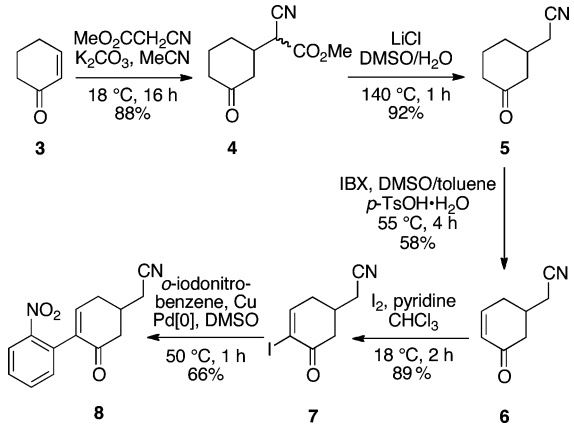


Strychnine (**2**)

RESULTS AND DISCUSSION

The reaction sequence used to prepare the substrate required for preliminary studies is shown in Scheme 1 and starts with the

Scheme 1



K_2CO_3-mediated Michael addition reaction of methyl α-cyanoacetate to cyclohexenone (**3**). The resulting adduct **4**,[4] which was obtained as a mixture of diastereoisomers in 88% combined yield, was subjected to a LiCl-induced demethylation/decarboxylation reaction sequence to give the previously reported cyclohexenone **5**[5] (81% yield). Dehydrogenation of compound **5** was effected with *o*-iodoxybenzoic acid (IBX) in the presence of *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O),[6] and the enone **6**[5] was thereby obtained in 58% yield. Subjection of the latter compound to the Johnson α-iodination

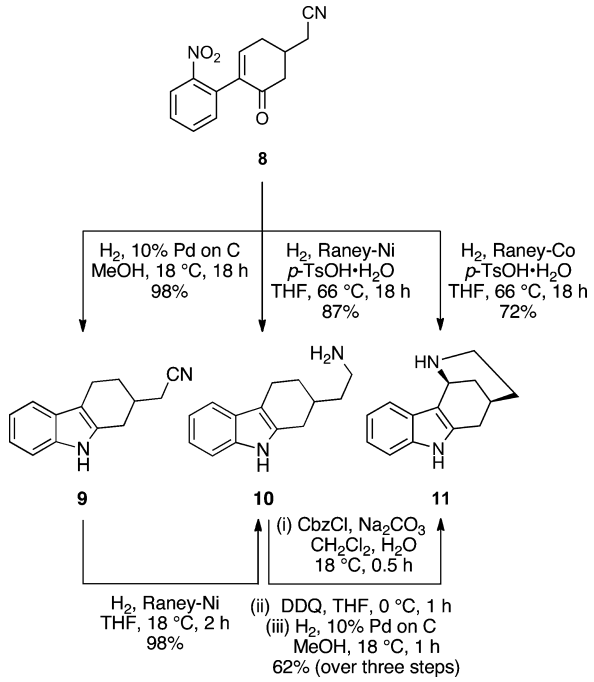
Received: September 28, 2012
Published: October 24, 2012

   dx.doi.org/10.1021/jo302132d | *J. Org. Chem.* 2012, 77, 10773−10781

protocol[7] using molecular iodine in chloroform/pyridine gave the iodoenone **7** (89%) that readily engaged in a Pd[0]-catalyzed Ullmann cross-coupling reaction[8] with *o*-iodonitrobenzene to afford α-arylcyclohexenone **8** (66%) that embodies all of the carbons and the two nitrogens required in the target 1,5-methanoazocino-[4,3-*b*]indole.

Exposure of a methanolic solution of compound **8** to dihydrogen in the presence of 10% Pd on C afforded (Scheme 2)

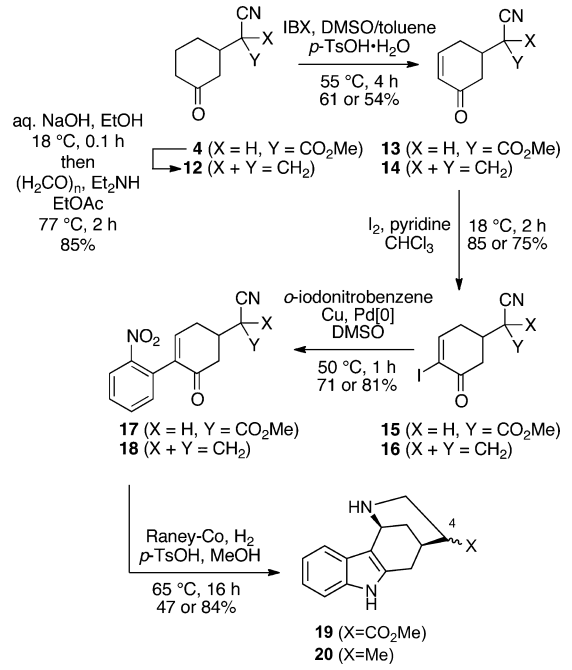
Scheme 2



the annulated indole **9**[9] in 98% yield. This product presumably arises from reduction of both the nitro group and the carbon−carbon double bond (no particular order implied) within substrate **8** as well as an intramolecular Schiff base condensation reaction between the resulting aniline and the pendant ketone. Exposure of a refluxing THF solution of the starting compound (**8**) to dihydrogen in the presence of Raney-nickel and *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O) afforded the amine analogue, **10**,[10] of compound **9** in 87% yield [compound **9** could be converted into amine **10** (98%) on exposure to hydrogen in the presence of Raney-nickel]. Product **10** presumably arises via the same processes as involved in the conversion **8** → **9**, but the rate of reduction of the carbon−carbon double bond must be faster than that of the nitrile moiety and is thereby preventing the hoped-for D-ring-forming intramolecular hetero-Michael addition reaction from taking place. In contrast, when substrate **8** was treated under the same conditions, but Raney-nickel was replaced with Raney-cobalt, the desired tetracyclic compound **11**[11] was obtained in 72% yield, and this could be separated from the small amounts of coproduced amine **10** (8%) using conventional chromatographic techniques. It was also possible to convert the latter product into the former one by initial protection of the amine (**10**) as its Cbz-protected derivative, cyclization of the latter with DDQ (to give the Cbz-protected form of compound **11**)[12] followed by protecting group removal (62% overall yield of **11**, see the Experimental Section for details).

The protocols defined above can be extended to the assembly of 1,5-methanoazocino[4,3-*b*]indoles incorporating functionality at C4, as would be required for their deployment in assembling members of the *Strychnos* alkaloid family.[13] Thus, for example, successive treatment of compound **4** with ethanolic sodium hydroxide then paraformaldehyde (Scheme 3) afforded acrylonitrile **12**

Scheme 3



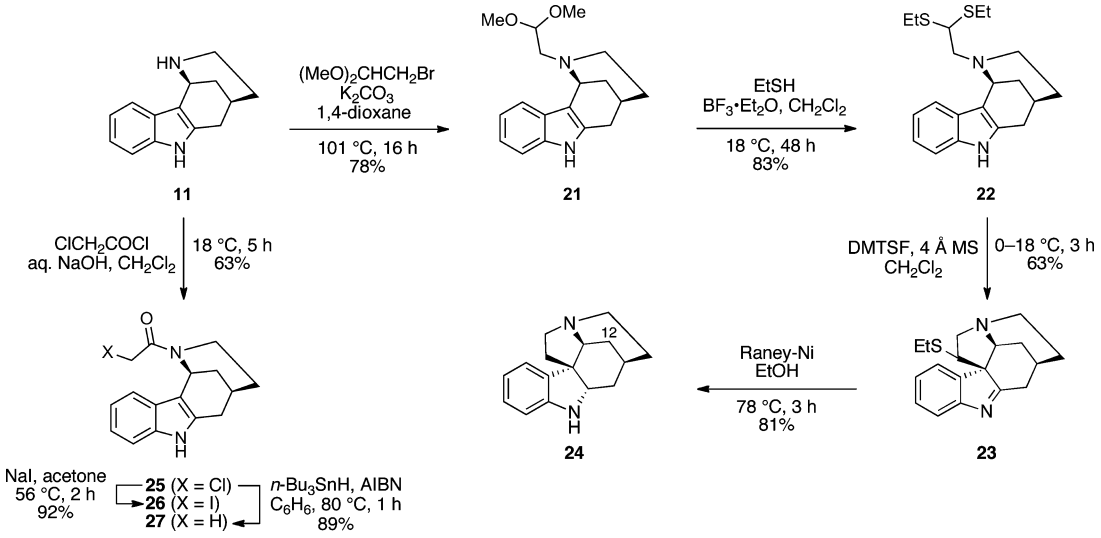
(85%) and exposure of either this compound or its precursor (**4**) to IBX in the presence of *p*-TsOH·H_2O afforded the corresponding enone **13** (61%) or **14** (54%), respectively. Subjection of each of these to the Johnson α-iodination protocol and engagement of the ensuing products **15** (85%) and **16** (75%) in the Pd[0]-catalyzed Ullmann cross-coupling reaction with *o*-iodonitrobenzene then gave the substrates **17** (71%) and **18** (81%) required for the pivotal tandem reductive cyclization reactions. The structure of the latter substrate was confirmed by single-crystal X-ray analysis.[14] Exposure of compound **17** to dihydrogen in the presence of Raney-cobalt and *p*-TsOH·H_2O gave the C4-carbomethoxy-substituted 1,5-methanoazocino[4,3-*b*]indole **19** which was obtained in 47% yield and as a ca. 1:1 mixture of diastereoisomers. Analogous treatment of compound **18** afforded the C4-methylated system **20** (84% combined yield of a ca. 1:1 and chromatographically separable mixture of diastereoisomers).

With 1,5-methanoazocino[4,3-*b*]indoles such as the parent compound **11** now readily to hand, various means for annulating the E-ring, as encountered in the *Strychnos* alkaloid family, were explored. To date, the only effective method we have found for doing so is that due to Bosch (Scheme 4).[15] Thus, treatment of amine **11** with the dimethylacetal of α-bromoacetaldehyde in the presence of K_2CO_3 afforded the anticipated tertiary amine **21** (88%)[12] that underwent a smooth *trans*-acetalization reaction on exposure to ethanethiol in the presence of boron trifluoride-diethyl etherate to give the bis-thioacetal **22** in 83% yield. Treatment of the last compound with dimethyl(methylthio)sulfonium tetrafluoroborate (DMSTF)[1c,16] in the presence of 4 Å molecular sieves resulted in a cationic cyclization reaction and the generation of the annulated isoindole **23** that was obtained in 63% yield.

Finally, exposure of compound **23** to Raney-nickel resulted in both reductive desulfurization and imine reduction, and thereby

dx.doi.org/10.1021/jo302132d | J. Org. Chem. 2012, 77, 10773−10781

Scheme 4



affording the pentacyclic indoline **24** (81%) embodying the ABCDE-ring system encountered in the *Strychnos* alkaloid family. The spectral data derived from this material were in good agreement with those reported previously by Shibasaki[12] and Bosch.[15b] A tabular comparison of the relevant ^{1}H and ^{13}C NMR data is provided in the Supporting Information.

Attempts to deploy a procedure used by Heathcock[17] for the installation of the E-ring of aspidospermidine proved ineffective in the present setting. So, while compound **11** was readily converted into the corresponding α-chloroacetamide **25**[10] (63%) under standard conditions and this, in turn, underwent a Finkelstein reaction with sodium iodide in acetone to give congener **26** (92%), this last compound proved to be unstable and failed to cyclize upon exposure to silver triflate under the prescribed[17] conditions. Only complex mixtures of products were observed. Attempts to engage compound **25** in a radical-mediated cyclization reaction by treating it with tri-*n*-butyltin hydride only afforded the direct reduction product **27**[10] (89%).

Efforts are now underway to adapt the protocols detailed above to the synthesis of various alkaloids. In particular, given the capacity to readily access optically active 4-substituted 2-cyclohex-2-en-1-ones,[18] the enantioselective synthesis of tubotaiwine-type alkaloids (which incorporate, inter alia, a two-carbon substituent at C12 on the ABCDE-framework of compound **24**)[1c,19] is now being pursued. Results will be reported in due course.

EXPERIMENTAL SECTION

General Experimental Procedures. Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 18 °C in base-filtered $CDCl_3$ on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. For ^{1}H NMR spectra, signals arising from the residual protio-forms of the solvent were used as the internal standards. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) J (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at δ_C 77.0 were used to reference ^{1}H and ^{13}C NMR spectra, respectively. Low-resolution ESI mass spectra were recorded on a single quadrupole liquid chromatograph–mass spectrometer, while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic-sector machine. Samples were analyzed by infrared spectrometry (ν_{max}) as thin films on KBr plates. Melting points are uncorrected. Analytical thin-layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid/ceric sulfate/sulfuric acid (conc)/water (37.5 g : 7.5 g : 37.5 g : 720 mL) or potassium permanganate/potassium carbonate/5% sodium hydroxide aqueous solution/water (3 g : 20 g : 5 mL : 300 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.[20] with silica gel 60 (40–63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials, reagents, drying agents and other inorganic salts were generally commercially available and were used as supplied. Tetrahydrofuran (THF), methanol, and dichloromethane (DCM) were dried using a solvent purification system that is based upon a technology originally described by Grubbs et al.[21] Where necessary, reactions were performed under an argon atmosphere.

Compound 4. A magnetically stirred solution of 2-cyclohexen-1-one (**3**) (2.93 g, 29.9 mmol) and methyl α-cyanoacetate (3.26 g, 32.9 mmol) in acetonitrile (74 mL) was treated with K_2CO_3 (2.48 g, 17.9 mmol) and the ensuing mixture stirred at 18 °C for 16 h. $NaHCO_3$ (50 mL of a saturated aqueous solution) was then added to the reaction mixture, which was extracted with dichloromethane (3 × 50 mL). The combined organic phases were dried ($MgSO_4$) before being filtered and then concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica, 1:9 → 1:1 v/v ethyl acetate/hexane gradient elution), and concentration of the relevant fractions (R_f = 0.4 in 1:1 v/v ethyl acetate/hexane) afforded the title compound **4**[4] (5.14 g, 88%) as a clear, colorless oil and as a 1:1 mixture of diastereoisomers: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.85 (s, 1.5H), 3.83 (s, 1.5H), 3.62 (d, J = 4.4 Hz, 0.5H), 3.48 (d, J = 5.2 Hz, 0.5H), 2.58–2.26 (complex m, 5H), 2.15 (m, 1H), 1.96 (m, 1H), 1.69 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 207.8 (C, two overlapping signals), 165.1 (C), 165.0 (C), 114.5 (C, two overlapping signals), 53.4 (CH_3, two overlapping signals), 45.2 (CH_2), 43.6 (CH_2), 43.2 (CH), 43.1 (CH), 40.4 (CH_2), 40.3 (CH_2), 38.4 (CH, two overlapping signals), 29.0 (CH_2), 27.3 (CH_2), 24.0 (CH_2), 23.9 (CH_2); IR ν_{max} 2956, 2249, 1746, 1713, 1437, 1317, 1263, 1227, 1104, 1009, 871 cm^{-1}; MS (EI, 70 eV) m/z 195 ($M^{+\bullet}$, 14), 164 (16), 152 (25), 124 (15), 108 (35), 100 (28), 97 (100), 96 (30), 69 (56), 68 (45); HRMS $M^{+\bullet}$ calcd for $C_{10}H_{13}NO_3$ 195.0895, found 195.0894.

Compound 5. A magnetically stirred solution of ester **4** (5.82 g, 29.8 mmol) in DMSO (152 mL) was treated with water (0.75 mL, 41.7 mmol) and LiCl (2.65 g, 62.6 mmol) and the resulting mixture heated to 140 °C for 2 h, cooled to 18 °C, and diluted with diethyl ether (200 mL) and water (300 mL). The separated aqueous phase was extracted with ethyl acetate (3 × 100 mL), and the combined organic phases were then washed with brine (1 × 100 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing

dx.doi.org/10.1021/jo302132d | J. Org. Chem. 2012, 77, 10773–10781

yellow oil was subjected to flash chromatography (silica, 3:7 v/v ethyl acetate/hexane elution), and concentration of the relevant fractions (R_f = 0.3 in 1:1 v/v ethyl acetate/hexane) afforded the title compound **5**[5] (3.76 g, 92%) as a clear, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.50 (m, 1H), 2.40 (m, 3H), 2.27 (m, 1H), 2.19 (m, 2H), 2.11 (m, 1H), 2.02 (m, 1H), 1.69 (m, 1H), 1.58 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 208.9 (C), 117.5 (C), 46.6 (CH_2), 40.6 (CH_2), 35.3 (CH), 30.2 (CH_2), 24.3 (CH_2), 24.0 (CH_2); IR ν_{max} 2930, 2245, 1711, 1629, 1449, 1423, 1368, 1347, 1226, 1057 cm^{-1}; MS (EI, 70 eV) *m*/*z* 137 ($M^{+\bullet}$, 58), 108 (21), 97 (56), 94 (50), 81 (22), 69 (33), 55 (100); HRMS $M^{+\bullet}$ calcd for $C_8H_{11}NO$ 137.0841, found 137.0841.

Compound 6. A magnetically stirred solution of ketone **5** (3.00 g, 21.9 mmol) in toluene/DMSO (225 mL of a 2:1 v/v mixture) was treated with *p*-TsOH·H_2O (1.25 g, 6.57 mmol) and IBX (8.59 g, 30.7 mmol) then heated at 55 °C for 16 h. The resulting solution was cooled to 18 °C and treated with diethyl ether (150 mL) followed by $NaHCO_3$ (250 mL of a 5% aqueous solution). The ensuing mixture was filtered through diatomaceous earth, and the solids thus retained were washed with diethyl ether (3 × 30 mL). The aqueous phase was separated from the combined filtrates and then extracted with ethyl acetate (3 × 100 mL). The combined organic phases were washed with brine (1 × 100 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing black oil was subjected to flash chromatography (silica, 3:7 v/v ethyl acetate/hexane elution), and concentration of the relevant fractions (R_f = 0.3 in 1:1 v/v ethyl acetate/hexane) afforded the title compound **6**[5] (1.72 g, 58%) as a clear, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.98 (m, 1H), 6.06 (dd, *J* = 13.2 and 4.0 Hz, 1H), 2.62−2.45 (complex m, 5H), 2.32 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.0 (C), 148.0 (CH), 129.8 (CH), 117.3 (C), 42.9 (CH_2), 31.8 (CH_2), 30.6 (CH), 23.1 (CH_2); IR ν_{max} 3016, 2933, 2247, 1679, 1426, 1408, 1389, 1334, 1313, 1299, 1251, 1140, 933, 885 cm^{-1}; MS (EI, 70 eV) *m*/*z* 135 ($M^{+\bullet}$, 100), 95 (17), 77 (10), 68 (83); HRMS $M^{+\bullet}$ calcd for C_8H_9NO 135.0684, found 135.0685.

Compound 7. A magnetically stirred solution of enone **6** (1.22 g, 9.03 mmol) in $CHCl_3$/pyridine (45 mL of a 1:1 v/v mixture) maintained at 18 °C was treated dropwise with a solution of molecular iodine (9.17 g, 36.1 mmol) in $CHCl_3$/pyridine (45 mL of a 1:1 v/v mixture). The ensuing mixture was stirred at 18 °C for 0.5 h and then diluted with diethyl ether (300 mL), and the resulting solution washed sequentially with water (1 × 100 mL), HCl (1 × 100 mL of a 1 M aqueous solution), and $Na_2S_2O_3$ (1 × 100 mL of a 5% w/v aqueous solution). The combined aqueous phases were extracted with ethyl acetate (3 × 100 mL), and the combined organic phases were washed with brine (1 × 200 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing black oil was subjected to flash chromatography (silica, 3:7 v/v ethyl acetate/hexane elution), and concentration of the relevant fractions (R_f = 0.4 in 1:1 v/v ethyl acetate/hexane) afforded the *title iodide* **7** (2.10 g, 89%), as a clear, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73 (dd, *J* = 5.6 and 3.2 Hz, 1H), 2.89 (dm, *J* = 15.2 Hz, 1H), 2.67−2.40 (complex m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.9 (C), 156.4 (CH), 116.9 (C), 103.5 (C), 41.8 (CH_2), 34.6 (CH_2), 31.9 (CH) 22.8 (CH_2); IR ν_{max} 2921, 2245, 1675, 1590, 1423, 1319, 1136, 940, 905 cm^{-1}; MS (EI, 70 eV) *m*/*z* 261 ($M^{+\bullet}$, 92), 221 (10), 194 (100), 166 (15), 94 (40), 66 (17); HRMS $M^{+\bullet}$ calcd for C_8H_8INO 260.9651, found 260.9651.

Compound 8. A magnetically stirred solution of iodide **7** (1.91 g, 7.32 mmol) and *o*-iodonitrobenzene (3.65 g, 14.6 mmol) in DMSO (15 mL) was treated with $Pd_2(dba)_3$ (536 mg, 0.59 mmol) and Cu powder (2.30 g, 36.6 g-atom). The resulting mixture was heated at 70 °C for 2 h and then cooled to 18 °C before being diluted with diethyl ether (100 mL). The ensuing mixture was filtered through diatomaceous earth, and the solids thus retained were washed with diethyl ether (3 × 30 mL). The combined filtrates were washed with water (2 × 100 mL) and the combined aqueous phases extracted with ethyl acetate (3 × 50 mL). The combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a light-yellow residue. Subjection of this material to flash chromatography (silica, 1:9 → 3:7 v/v ethyl acetate/hexane gradient elution) and concentration of the relevant fractions (R_f = 0.2 in 1:1 v/v ethyl acetate/hexane) afforded the *title compound* **8** (1.24 g, 66%) as a white, crystalline solid: mp 130−134 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05 (dd, *J* = 8.0 and 1.2 Hz, 1H), 7.63 (td, *J* = 7.6 and 1.2 Hz, 1H), 7.50 (td, *J* = 8.0 and 1.6 Hz, 1H), 7.25 (dd, *J* = 7.6 and 1.6 Hz, 1H), 6.98 (dd, *J* = 5.6 and 3.2 Hz, 1H), 2.85−2.66 (complex m, 3H), 2.60−2.48 (complex, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.9 (C), 148.4 (C), 143.5 (CH), 139.8 (C), 133.5 (CH), 131.5 (CH), 131.2 (C), 129.2 (CH), 124.0 (CH), 117.3 (C), 43.1 (CH_2), 31.7 (CH), 31.1 (CH_2), 23.0 (CH_2); IR ν_{max} 2924, 2245, 1676, 1572, 1521, 1428, 1349, 1181, 1139, 957, 913 cm^{-1}; MS (EI, 70 eV) *m*/*z* 256 ($M^{+\bullet}$, 2), 210 (92), 170 (75), 169 (100), 168 (91), 157 (82), 146 (62), 134 (66), 115 (63), 104 (58), 77 (55); HRMS $(M - NO_2^{\bullet})^+$ calcd for $C_{14}H_{12}N_2O_3$ 210.0919, found 210.0914.

Compound 9. A magnetically stirred solution of compound **8** (10 mg, 0.039 mmol) in methanol (1.95 mL) was treated with 10% palladium on carbon (2 mg), and the resulting suspension was stirred at 18 °C under an atmosphere of hydrogen (1 atm) for 18 h. The ensuing reaction mixture was filtered through diatomaceous earth, and the solids thus retained were washed with methanol (2 × 10 mL). The combined filtrates were concentrated under reduced pressure to give the title indole **9**[9] (8 mg, 98%) as a clear, colorless oil: R_f = 0.5 (in 1:1 v/v ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75 (broad s, 1H), 7.46 (d, *J* = 6.8 Hz, 1H), 7.30 (dd, *J* = 7.6 and 1.6 Hz, 1H), 7.15 (td, *J* = 7.6 and 1.6 Hz, 1H), 7.15 (td, *J* = 6.8 and 1.6 Hz, 1H), 2.99 (dd, *J* = 16.0 and 5.2 Hz, 1H), 2.88−2.71 (complex m, 2H), 2.62 (m, 1H), 2.50 (dd, *J* = 7.2 and 3.2 Hz, 2H), 2.40 (m, 1H), 2.11 (m, 1H), 1.76 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.0 (C), 131.4 (C), 127.2 (C), 121.5 (CH), 119.4 (CH), 118.6 (C), 117.9 (CH), 110.6 (CH), 109.4 (C), 31.8 (CH), 28.7 (CH_2, two signals overlapping), 23.3 (CH_2), 19.6 (CH_2); IR ν_{max} 3396, 2919, 2846, 2246, 1622, 1467, 1453, 1430, 1347, 1325, 1304, 1237, 1143, 1066, 1010 cm^{-1}; MS (EI, 70 eV) *m*/*z* 210 ($M^{+\bullet}$, 85), 168 (58), 143 (100), 130 (19), 115 (20), 77 (15); HRMS $M^{+\bullet}$ calcd for $C_{14}H_{14}N_2$ 210.1157, found 210.1156.

Compound 10. A magnetically stirred mixture of nitrile **8** (20 mg, 0.078 mmol), *p*-TsOH·H_2O (59 mg, 0.31 mmol), and Raney-nickel (40 mg, 200% w/w) in THF (3 mL) was heated at reflux under an atmosphere of hydrogen (1 atm) for 18 h. The cooled reaction mixture was filtered through diatomaceous earth, and the residual solids were washed with methanol (3 × 5 mL). The combined filtrates were concentrated under reduced pressure to afford a yellow oil that was subjected to column chromatography (silica, 1:19 → 1:4 v/v methanol/dichloromethane gradient elution). Concentration of the relevant fractions (R_f = 0.2 in 1:4 v/v methanol/dichloromethane) then afforded the title compound **10**[10] (15 mg, 87%) as a clear, colorless oil: ^{1}H NMR (CD_3OD, 400 MHz) δ 7.33 (d, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 1H), 6.95 (m, 2H), 2.86−2.73 (complex m, 4H), 2.64 (m, 1H), 2.39 (m, 1H), 1.98 (m, 2H), 1.66−1.47 (complex m, 3H), (signals due to NH protons not observed); ^{13}C NMR (CD_3OD, 100 MHz) δ 137.8 (C), 135.0 (C), 128.9 (C), 121.3 (CH), 119.2 (CH), 118.2 (CH), 111.4 (CH), 109.6 (C), 40.4 (CH_2), 40.2 (CH_2), 33.8 (CH), 31.1 (CH_2), 30.5 (CH_2), 21.4 (CH_2); IR ν_{max} 3398, 3051, 2912, 2842, 1567, 1466, 1302, 1235, 1142, 1009 cm^{-1}; MS (EI, 70 eV) *m*/*z* 214 ($M^{+\bullet}$, 85), 197 (27), 182 (16), 170 (68), 169 (83), 168 (100), 156 (17), 143 (89), 130 (33), 115 (19); HRMS $M^{+\bullet}$ calcd for $C_{14}H_{18}N_2$ 214.1470, found 214.1475.

Conversion of Compound 9 into 10. A magnetically stirred mixture of nitrile **9** (25 mg, 0.12 mmol) and Raney-nickel (40 mg, 200% w/w) in THF (3 mL) was maintained at 18 °C under an atmosphere of hydrogen (1 atm) for 2 h. The reaction mixture was then filtered through diatomaceous earth, and the solids thus retained washed with methanol (3 × 5 mL). The combined filtrates were concentrated under reduced pressure to afford a yellow oil that was subjected to column chromatography (silica, 1:19 → 1:4 v/v methanol/dichloromethane gradient elution). Concentration of the relevant fractions (R_f = 0.2 in 1:4 v/v methanol/dichloromethane) afforded compound **10** (24 mg, 96%) as a clear, colorless oil. This material was identical, in all respects, with that obtained as described immediately above.

Compound 11. A magnetically stirred mixture of nitrile **8** (362 mg, 1.41 mmol), *p*-TsOH·H_2O (1.07 g, 5.64 mmol), and Raney-cobalt (700 mg, 200% w/w) in THF (35 mL) was heated at reflux for 18 h while being maintained under an atmosphere of hydrogen (1 atm). The cooled reaction mixture was filtered through diatomaceous earth, and the solids thus retained were washed with methanol (3 × 30 mL).

The combined filtrates were then concentrated under reduced pressure to afford a yellow oil that was subjected to column chromatography (silica, 1:19 → 1:4 v/v methanol/dichloromethane gradient elution) and thereby afforded two fractions, A and B.

Concentration of fraction A (R_f = 0.3 in 1:4 v/v methanol/dichloromethane) afforded the title compound **11**[11] (215 mg, 72%) as a clear, colorless oil: ^{1}H NMR (CD_3OD, 400 MHz) δ 7.46 (d, J = 7.2 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 7.00 (m, 2H), 4.35 (m, 1H), 3.12 (dd, J = 17.6 and 6.8 Hz, 1H), 2.69 (d, J = 17.6 Hz, 1H), 2.59 (m, 2H), 2.40 (m, 1H), 2.15 (dt, J = 12.4 and 3.2 Hz, 1H), 1.91 (m, 2H), 1.62 (m, 1H) (signal due to NH proton not observed); ^{13}C NMR (CD_3OD, 100 MHz) δ 138.2 (C), 138.0 (C), 127.4 (C), 121.5 (CH), 119.7 (CH), 118.2 (CH), 111.6 (CH), 109.5 (C), 45.7 (CH), 38.0 (CH_2), 33.9 (CH_2), 33.7 (CH_2), 29.9 (CH_2), 27.4 (CH); IR ν_{max} 3394, 3221, 3052, 2922, 1618, 1527, 1453, 1426, 1362, 1303, 1273, 1236, 1197, 1070, 1029 cm^{-1}; MS (EI, 70 eV) m/z 212 ($M^{+\bullet}$, 23), 194 (6), 182 (17), 169 (100), 168 (75), 167 (55), 154 (6), 143 (11), 130 (6), 115 (6), 82 (11); HRMS $M^{+\bullet}$ calcd for $C_{14}H_{16}N_2$ 212.1313, found 212.1313.

Concentration of fraction B (R_f = 0.2 in 1:4 v/v methanol/dichloromethane) afforded the title compound **10** (24 mg, 8%) as a clear, colorless oil. This material was identical, in all respects, with that obtained via the method described immediately above.

Conversion of Compound 10 into 11. *Step i.* A solution of amine **10** (115 mg, 0.54 mmol) and Na_2CO_3 (114 mg, 1.07 mmol) in water (5.4 mL) was treated with benzyl chloroformate (84 μL, 0.59 mmol) and the ensuing mixture stirred magnetically at 18 °C for 0.5 h. Dichloromethane (10 mL) was then added and the separated aqueous phase extracted with additional dichloromethane (2 × 10 mL). The combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford the *Cbz-derivative of compound **10*** (133 mg, 81%) as a yellow foam: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 (s, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.34 (m, 5H), 7.21 (d, J = 8.0 Hz, 1H), 7.11 (m, 2H), 5.12 (s, 2H), 4.98 (s, 1H), 3.26 (m, 2H), 2.76 (m, 1H), 2.66 (m, 2H), 2.24 (m, 1H), 1.90 (m, 2H), 1.51 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.4 (C), 136.4 (C), 135.7 (C), 133.3 (C), 128.3 (CH), 127.9 (CH), 127.8 (CH), 127.2 (C), 120.7 (CH), 118.8 (CH), 117.5 (CH), 110.4 (CH), 109.3 (C), 66.4 (CH_2), 38.8 (CH_2), 35.8 (CH_2), 31.8 (CH), 29.4 (CH_2), 28.9 (CH_2), 20.1 (CH_2); IR ν_{max} 3400, 3334, 3055, 3032, 2916, 2844, 1697, 1520, 1467, 1453, 1327, 1302, 1239, 1138, 1063, 1010 cm^{-1}; MS (EI, 70 eV) m/z 348 ($M^{+\bullet}$, 16), 284 (13), 256 (15), 143 (15), 129 (16), 111 (18), 97 (33), 91 (22), 83 (41), 69 (100); HRMS $M^{+\bullet}$ calcd for $C_{22}H_{24}N_2O_2$ 348.1838, found 348.1830.

Step ii. A magnetically stirred solution of the Cbz-derivative of compound **10** (65 mg, 0.19 mmol) in THF (1.9 mL) maintained at 0 °C was treated, dropwise over 1 h via syringe pump, with a solution of DDQ (47 mg, 0.20 mmol) in THF (1.9 mL). The resulting solution was warmed to 18 °C and stirred at this temperature for a further 1 h and then diluted with NaOH (10 mL of a 2 M solution). The mixture thus obtained was extracted with ethyl acetate (3 × 10 mL), and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica, 1:9 → 1:1 v/v ethyl acetate/hexane gradient elution), and concentration of the relevant fractions (R_f = 0.4 in 1:1 v/v ethyl acetate/hexane) afforded the *Cbz-derivative of compound **11*** (46 mg, 80%) as a white foam and a 1:1 mixture of rotamers: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89 (s, 1H), 7.63 (d, J = 7.6 Hz, 0.5H), 7.44 (d, J = 7.6 Hz, 0.5H), 7.32 (m, 1H), 7.21 (m, 4H), 7.05 (m, 1.5H), 6.86 (t, J = 7.6 Hz, 0.5H), 5.66 (s, 0.5H), 5.53 (s, 0.5H), 5.25 (d, J = 12.0 Hz, 0.5H), 5.12 (m, 1H), 4.96 (d, J = 12.0 Hz, 0.5H), 3.80 (dd, J = 12.0 and 6.0 Hz, 0.5H), 3.70 (dd, J = 12.0 and 6.0 Hz, 0.5H), 3.02 (m, 1H), 2.65 (m, 2H), 2.38 (s, 1H), 2.01−1.80 (complex m, 4.5H), 1.51 (m, 0.5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.3 (C), 155.1 (C), 136.6 (C, two overlapping signals), 136.3(1) (C), 136.2(8) (C), 135.9 (C), 135.8 (C), 128.4 (CH), 128.2(1) (CH), 128.1(7) (CH), 128.0 (CH), 127.6 (CH), 127.4 (CH), 125.8 (C), 125.6 (C), 121.0 (CH), 120.9 (CH), 119.2 (CH), 119.1 (CH), 118.5 (CH), 117.9 (CH), 110.5 (CH), 110.4 (CH), 108.8 (C), 108.3 (C), 67.0 (CH_2), 66.7 (CH_2), 43.9 (CH), 43.6 (CH), 36.8 (CH_2), 36.6 (CH_2), 32.3 (CH_2), 32.0 (CH_2), 31.9 (CH_2), 31.7 (CH_2), 28.1 (CH_2), 28.0 (CH_2), 25.2 (CH), 25.1 (CH); IR ν_{max} 3398, 3309, 3034, 2928, 1669, 1464, 1455, 1426, 1365, 1351, 1318, 1300, 1270, 1231, 1194, 1099, 1067, 1027 cm^{-1}; MS (EI, 70 eV) m/z 346 ($M^{+\bullet}$, 90), 211 (13), 194 (73), 182 (17), 169 (77), 168 (100), 143 (12), 91 (85); HRMS $M^{+\bullet}$ calcd for $C_{22}H_{22}N_2O_2$ 346.1681, found 346.1682.

Step iii. A magnetically stirred solution of the Cbz-derivative of compound **11** (130 mg, 0.37 mmol) in methanol (3.7 mL) was treated with 10% palladium on carbon (5 mg), and the resulting suspension maintained under an atmosphere of hydrogen (1 atm) at 18 °C for 8 h. The reaction mixture was then filtered through diatomaceous earth and the solids thus retained were washed with methanol (2 × 10 mL). The combined filtrates were concentrated under reduced pressure to afford compound **11** (75 mg, 96%) as a clear, colorless oil. This material was identical, in all respects, with that obtained as described earlier.

Compound 12. *Step i.* A magnetically stirred solution of ester **4** (2.00 g, 10.2 mmol) in ethanol (23 mL) was treated with NaOH (23 mL of a 2 M aqueous solution, 46.1 mmol) and then stirred at 18 °C for 0.17 h before being concentrated under reduced pressure. The residue thus obtained was diluted with diethyl ether (75 mL) and the resulting solution treated with HCl (40 mL of a 2 M aqueous solution). The separated aqueous phase was extracted with diethyl ether (3 × 40 mL), and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the corresponding carboxylic acid as a light-yellow oil. This material was used, without purification, in step ii.

Step ii. The carboxylic acid obtained from ester **4** by the method detailed immediately above was dissolved in ethyl acetate (26 mL) and the resulting solution treated with $HNEt_2$ (1.21 mL, 11.73 mmol) and paraformaldehyde (429 mg, 14.3 mmol) and then heated at reflux for 2 h. The cooled reaction mixture was diluted with diethyl ether (75 mL) and then acidified with HCl (40 mL of a 2 M aqueous solution). The separated aqueous phase was extracted with diethyl ether (3 × 40 mL), and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash column chromatography (silica, 3:7 v/v ethyl acetate/hexane elution) and concentration of the relevant fractions (R_f = 0.3 in 3:7 v/v ethyl acetate/hexane) afforded the *title compound **12*** (1.29 g, 85% over two steps) as a clear, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.91 (s, 1H), 5.77 (s, 1H), 2.69 (m, 1H), 2.52 (m, 1H), 2.48−2.25 (complex m, 3H), 2.10 (m, 2H), 1.77 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 208.6 (C), 129.8 (CH_2), 126.0 (C), 117.2 (C), 45.4 (CH_2), 43.0 (CH), 40.8 (CH_2), 29.7 (CH_2), 24.3 (CH_2); IR ν_{max} 2943, 2868, 2221, 1713, 1619, 1449, 1408, 1346, 1318, 1224, 1098, 1036, 945, 874 cm^{-1}; MS (EI, 70 eV) m/z 149 ($M^{+\bullet}$, 23), 133 (19), 121 (35), 106 (100), 93 (24), 79 (30), 68 (30); HRMS $M^{+\bullet}$ calcd for $C_9H_{11}NO$ 149.0841, found 149.0842.

Compound 13. A magnetically stirred solution of ketone **4** (7.03 g, 36.0 mmol) in toluene/DMSO (120 mL of a 2:1 v/v mixture) was treated with p-TsOH·H_2O (2.05 g, 10.8 mmol) and IBX (14.1 g, 50.4 mmol) and the ensuing mixture heated at 55 °C for 18 h. The reaction mixture was then cooled to 18 °C, treated with diethyl ether (200 mL) and $NaHCO_3$ (250 mL of a 5% aqueous solution), and then filtered through diatomaceous earth. The solids thus retained were washed with diethyl ether (3 × 30 mL), and the separated aqueous phase was extracted with ethyl acetate (3 × 75 mL). The combined organic phases were washed with brine (1 × 100 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing black oil was subjected to flash column chromatography (silica, 3:7 → 1:1 v/v ethyl acetate/hexane gradient elution), and concentration of the relevant fractions (R_f = 0.2 in 1:1 v/v ethyl acetate/hexane) afforded the *title compound **13*** (4.24 g, 61%) as a pale-yellow oil and a 1:1 mixture of diastereoisomers: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.98 (m, 1H), 6.09 (dd, J = 10.4 and 2.0 Hz, 1H), 3.85 (s, 1.5H), 3.84 (s, 1.5H), 3.65 (d, J = 5.2 Hz, 0.5H), 3.59 (d, J = 5.6 Hz, 0.5H), 2.85 (m, 1H), 2.60−2.39 (complex m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.1(4) (C), 196.1(2) (C), 164.9 (C), 164.8 (C), 147.7 (CH), 147.5 (CH), 129.9 (CH), 129.8 (CH), 114.3 (C, two overlapping signals), 53.8 (CH_3), 53.7 (CH_3), 42.5 (CH, two overlapping signals), 41.7 (CH_2), 40.3 (CH_2), 35.3 (CH), 35.2 (CH), 29.5 (CH_2), 28.3 (CH_2); IR ν_{max} 2957, 2250, 1746, 1682, 1618, 1435, 1389, 1255, 1219, 1164, 1097, 1045, 1007, 965, 885 cm^{-1}; MS (EI, 70 eV) m/z 194 [$(M + H)^+$, <1%],

dx.doi.org/10.1021/jo302132d | J. Org. Chem. 2012, 77, 10773−10781

193 ($M^{+\bullet}$, <1), 178 (3), 162 (6), 95 (94), 77 (12), 68 (100); HRMS $(M + H)^+$ calcd for $C_{10}H_{11}NO_3$ 194.0817, found 194.0815.

Compound 14. A magnetically stirred solution of ketone **12** (4.00 g, 26.8 mmol) in toluene/DMSO (57 mL of a 2:1 v/v mixture) was treated with *p*-TsOH·H_2O (1.53 g, 8.04 mmol) and IBX (10.50 g, 37.5 mmol) and the ensuing mixture heated at 55 °C for 17 h before being cooled to 18 °C and diluted with diethyl ether (200 mL) followed by $NaHCO_3$ (250 mL of a 5% aqueous solution). The mixture thus obtained was filtered through diatomaceous earth, and the solids thus retained were washed with diethyl ether (3 × 30 mL). The separated aqueous phase was extracted with ethyl acetate (3 × 150 mL), and the combined organic phases themselves washed with brine (1 × 150 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing black oil was subjected to flash column chromatography (silica, 3:7 v/v ethyl acetate/hexane elution), and concentration of the relevant fractions (R_f = 0.3) afforded the *title compound* ***14*** (2.12 g, 54%) as a white, crystalline solid: mp 56−58 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.99 (m, 1H), 6.10 (dm, J = 10.0 Hz, 1H), 5.96 (d, J = 0.8 Hz, 1H), 5.82 (d, J = 0.8 Hz, 1H), 3.01 (m, 1H), 2.65−2.45 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.6 (C), 147.8 (CH), 130.5 (CH), 129.9 (CH_2), 125.0 (C), 117.0 (C), 41.7 (CH_2), 39.5 (CH), 30.2 (CH_2); IR ν_{max} 3041, 2929, 2221, 1681, 1619, 1430, 1407, 1388, 1247, 1167, 1140, 1086, 948, 915, 883 cm^{-1}; MS (EI, 70 eV) m/z 147 ($M^{+\bullet}$, 61), 119 (30), 105 (20), 104 (20), 69 (33), 68 (100); HRMS $M^{+\bullet}$ calcd for C_9H_9NO 147.0684, found 147.0685.

Compound 15. A magnetically stirred solution of enone **13** (3.64 g, 18.84 mmol) in $CHCl_3$/pyridine (50 mL of a 1:1 v/v mixture) maintained at 18 °C was treated dropwise with a solution of molecular iodine (19.1 g, 75.4 mmol) in $CHCl_3$/pyridine (50 mL of a 1:1 v/v mixture). The solution thus obtained was stirred for 4 h and then diluted with diethyl ether (500 mL) before being washed sequentially with water (1 × 300 mL), HCl (1 × 300 mL of a 1 M aqueous solution) and $Na_2S_2O_3$ (1 × 500 mL of a 5% w/v aqueous solution). The combined aqueous phases were extracted with ethyl acetate (3 × 200 mL) and the combined organic phases washed with brine (1 × 200 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing black oil was subjected to flash column chromatography (silica, 3:7 → 1:1 v/v ethyl acetate/hexane gradient elution) and concentration of the relevant fractions (R_f = 0.5 in 1:1 v/v ethyl acetate/hexane) afforded the *title compound* ***15*** (5.19 g, 85%) as a pale-yellow oil and as a 1:1 mixture of diastereoisomers: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72 (t, J = 4.4 Hz, 1H), 3.83 (s, 1.5H), 3.83 (s, 1.5H), 3.66 (d, J = 4.8 Hz, 0.5H), 3.62 (d, J = 5.2 Hz, 0.5H), 2.96−2.81 (complex m, 2H), 2.66 (d, J = 2.8 Hz, 0.5H), 2.62 (t, J = 2.8 Hz, 0.5H), 2.56 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.4 (C, two overlapping signals), 164.6 (C), 164.5 (C), 156.2 (CH), 156.0 (CH), 114.0 (C, two overlapping signals), 103.3 (CH), 103.1 (C), 53.9 (CH_3), 53.8 (CH_3), 41.9(4) (CH), 41.8(8) (CH), 40.5 (CH_2), 39.2 (CH_2), 35.1 (CH), 35.0 (CH), 33.3 (CH_2), 32.2 (CH_2); IR ν_{max} 2955, 2250, 1746, 1686, 1594, 1435, 1330, 1260, 1000, 940 cm^{-1}; MS (EI, 70 eV) m/z 319 ($M^{+\bullet}$, 5), 221 (61), 220 (94), 194 (30), 166 (13), 100 (27), 94 (100), 66 (34), 65 (40); HRMS $M^{+\bullet}$ calcd for $C_{10}H_{10}INO_3$ 318.9705, found 318.9671.

Compound 16. A magnetically stirred solution of enone **14** (1.50 g, 10.20 mmol) in $CHCl_3$/pyridine (50 mL of a 1:1 v/v mixture) maintained at 18 °C was treated dropwise with a solution of molecular iodine (10.3 g, 40.8 mmol) in $CHCl_3$/pyridine (50 mL of a 1:1 v/v mixture). The resulting solution was stirred at 18 °C for 2.5 h before being diluted with diethyl ether (400 mL) and then washed sequentially with water (1 × 150 mL), HCl (1 × 150 mL of a 1 M aqueous solution), and $Na_2S_2O_3$ (1 × 150 mL of a 5% w/v aqueous solution). The combined aqueous phases were extracted with ethyl acetate (3 × 100 mL), and the combined organic phases were then washed with brine (1 × 200 mL), before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing black oil was subjected to flash column chromatography (silica, 3:7 v/v ethyl acetate/hexane elution) and concentration of the relevant fractions (R_f = 0.4) afforded the *title iodide* ***16*** (2.09 g, 75%) as a white, crystalline solid: mp 108.5−110 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.74 (t, J = 4.4 Hz, 1H), 5.99 (s, 1H), 5.83 (s, 1H), 3.08 (m, 1H), 2.92 (dm, J = 16.8 Hz, 1H), 2.71 (m, 1H), 2.62 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.6 (C), 156.3 (CH), 131.1 (CH_2), 123.8 (C), 116.6 (C), 103.2 (C), 40.5 (CH_2), 39.2 (CH), 33.9 (CH_2); IR ν_{max} 3104, 3041, 2955, 2222, 1678, 1588, 1424, 1410, 1318, 1136, 999, 958, 932, 912 cm^{-1}; MS (EI, 70 eV) m/z 273 ($M^{+\bullet}$, 93), 230 (41), 193 (100), 165 (40), 104 (15), 91 (14), 65 (14); HRMS $M^{+\bullet}$ calcd for C_9H_8INO 272.9651, found 272.9651.

Compound 17. A magnetically stirred solution of iodide **15** (2.12 g, 6.64 mmol) and *o*-iodonitrobenzene (3.31 g, 13.29 mmol) in DMSO (14 mL) was treated with $Pd_2(dba)_3$ (304 mg, 0.332 mmol) and Cu powder (2.11 g, 32.2 g-atom). The resulting mixture was heated at 55 °C for 2 h, cooled to 18 °C, diluted with diethyl ether (100 mL), and filtered through diatomaceous earth. The solids thus retained were washed with diethyl ether (3 × 30 mL) and the combined filtrates washed with water (2 × 100 mL). The combined aqueous phases were, in turn, extracted with ethyl acetate (3 × 50 mL). The combined organic phases were dried ($MgSO_4$) before being filtered and concentrated under reduced pressure to afford a light-yellow residue. Subjection of this material to flash column chromatography (silica, 1:9 → 1:1 v/v ethyl acetate/hexane gradient elution) and concentration of the relevant fractions (R_f = 0.2 in 1:1 v/v ethyl acetate/hexane) afforded the *title compound* ***17*** (1.48 g, 71%) as a white foam and as a 1:1 mixture of diastereoisomers: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 (d, J = 8.4 Hz, 1H), 7.62 (t, J = 7.2 Hz, 1H), 7.50 (t, J = 7.2 Hz, 1H), 7.25 (m, 1H), 6.98 (m, 1H), 3.87 (s, 1.5H), 3.86 (s, 1.5H), 3.73 (d, J = 4.2 Hz, 0.5H), 3.62 (d, J = 4.6 Hz, 0.5H), 3.03 (m, 1H), 2.80−2.58 (complex m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.3 (C, two overlapping signals), 164.8(3) (C), 164.7(7) (C), 148.2 (C, two overlapping signals), 143.8 (CH), 143.7 (CH), 139.4 (C), 139.3 (C), 133.5(1) (CH), 133.4(8) (CH), 131.5 (CH, two overlapping signals), 130.9 (C), 130.8 (C), 129.1 (CH, two overlapping signals), 124.1 (CH, two overlapping signals), 114.4 (C, two overlapping signals), 53.6 (CH_3, two overlapping signals), 42.1 (CH, two overlapping signals), 41.6 (CH_2), 40.4 (CH_2), 34.9 (CH), 34.7 (CH), 29.8 (CH_2), 28.7 (CH_2); IR ν_{max} 3034, 2956, 2250, 1747, 1682, 1608, 1573, 1524, 1479, 1435, 1354, 1262, 1218, 1182, 1144, 1113, 1047, 1005, 956, 909, 855 cm^{-1}; MS (EI, 70 eV) m/z 314 ($M^{+\bullet}$, 4%), 284 (10), 268 (21), 216 (70), 199 (22), 198 (71), 185 (57), 170 (68), 169 (100), 162 (36), 145 (37), 134 (51), 115 (50), 104 (53), 77 (38); HRMS $M^{+\bullet}$ calcd for $C_{16}H_{14}N_2O_5$ 314.0903, found 314.0907.

Compound 18. A magnetically stirred solution of iodide **16** (1.23 g, 4.50 mmol) and *o*-iodonitrobenzene (2.24 g, 9.00 mmol) in DMSO (9 mL) was treated with $Pd_2(dba)_3$ (329 mg, 0.36 mmol) and Cu powder (1.43 g, 22.5 g-atom). The resulting mixture was heated at 50 °C for 1.5 h and then cooled to 18 °C before being diluted with diethyl ether (100 mL) and then filtered through a pad of diatomaceous earth. The solids thus retained were washed with diethyl ether (3 × 30 mL), and the combined filtrates were themselves washed with water (2 × 100 mL). The combined aqueous phases were, in turn, extracted with ethyl acetate (3 × 50 mL) and the combined organic phases then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil. Subjection of this oil to flash column chromatography (silica, 1:9 → 3:7 v/v ethyl acetate/hexane gradient elution) and concentration of the relevant fractions (R_f = 0.4 in 3:7 v/v ethyl acetate/hexane) afforded the *title compound* ***18*** (978 mg, 81%) as a white, crystalline solid: mp 87−89 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.03 (d, J = 8.4 Hz, 1H), 7.62 (m, 1H), 7.50 (m, 1H), 7.25 (m, 1H), 7.00 (m, 1H), 5.99 (s, 1H), 5.88 (s, 1H), 3.18 (m, 1H), 2.90−2.60 (complex m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.7 (C), 148.3 (C), 143.7 (CH), 139.6 (C), 133.5 (CH), 131.5 (C), 131.0 (C), 130.9 (CH_2), 129.2 (CH), 124.6 (C), 124.3 (C), 116.9 (C), 41.8 (CH_2), 39.1 (CH), 30.7 (CH_2); IR ν_{max} 2873, 2219, 1679, 1522, 1350, 1184, 945, 854 cm^{-1}; MS (EI, 70 eV) m/z 268 ($M^{+\bullet}$, 2), 238 (26), 222 (100), 169 (32), 162 (78), 145 (46), 134 (48), 115 (35), 106 (36), 104 (43), 77 (43); HRMS $M^{+\bullet}$ calcd for $C_{15}H_{12}N_2O_3$ 268.0848, found 268.0846.

Compound 19. A magnetically stirred mixture of compound **17** (230 mg, 0.73 mmol), *p*-TsOH·H_2O (557 mg, 2.93 mmol), and Raney-cobalt (460 mg, 200% w/w) in THF (15 mL) was heated at reflux under an atmosphere of hydrogen (1 atm) for 18 h. The cooled reaction mixture was filtered through diatomaceous earth, and the solids thus retained were washed with methanol (3 × 30 mL). The combined filtrates were concentrated under reduced pressure to afford a light-yellow oil that was dissolved in dichloromethane (25 mL). The solution

thus formed was washed with $NaHCO_3$ (40 mL, saturated aqueous solution) and the separated aqueous layer extracted with dichloromethane (3 × 25 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a light-yellow oil that was subjected to flash column chromatography (silica, 1:19 → 1:9 v/v methanol/dichloromethane gradient elution) to afford *compound* ***19*** (93 mg, 47%) as a white, crystalline solid and as a 1:1 mixture of diastereoisomers: mp 78−90 °C; R_f = 0.2 (in 1:4 v/v methanol/dichloromethane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05 (s, 0.5H), 7.93 (s, 0.5H), 7.51 (t, J = 6.8 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.11 (m, 2H), 4.43 (m, 1H), 3.77 (s, 1.5H), 3.70 (s, 1.5H), 3.23 (dd, J = 17.2 and 7.2 Hz, 0.5H), 3.11 (d, J = 13.2 Hz, 0.5H), 3.02−2.60 (complex m, 4H), 2.43 (m, 1H), 2.18 (tm, J = 3.2 Hz, 1H), 1.98 (tm, J = 2.8 Hz, 0.5H), 1.91 (s, 1H), 1.76 (m, 0.5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.9 (C), 173.9 (C), 136.0(8) (C), 136.0(5) (C), 135.2(5) (C), 135.2(2) (C), 126.1 (C), 125.8 (C), 121.3 (CH), 121.2 (CH), 119.6 (CH), 119.5 (CH), 117.6 (CH), 117.3 (CH), 110.6 (CH), 110.5 (CH), 110.0 (C), 109.9 (C), 52.0 (CH_3), 51.6 (CH_3), 46.4 (CH), 46.2 (CH), 44.1 (CH), 43.8 (CH), 38.5(0) (CH_2), 38.4(6) (CH_2), 33.1 (CH_2), 30.4 (CH_2), 29.6 (CH_2), 28.8 (CH), 28.0 (CH), 25.1 (CH_2); IR ν_{max} 3390, 3053, 2925, 2853, 1724, 1619, 1587, 1454, 1434, 1200, 1106, 1064, 1011, 924 cm^{-1}; MS (ESI, +ve ion) m/z 271 [(M + H)$^+$, 100)], 170 (80); HRMS (M + H)$^+$ calcd for $C_{16}H_{18}N_2O_2$ 271.1447, found 271.1448.

Epimeric Forms of Compound 20. A magnetically stirred mixture of nitrile **18** (24 mg, 0.09 mmol), *p*-TsOH·H_2O (51 mg, 0.27 mmol), and Raney-cobalt (50 mg, 200% w/w) in THF (3 mL) was heated at reflux under an atmosphere of hydrogen (1 atm) for 18 h. The cooled reaction mixture was then filtered through diatomaceous earth and the solids thus retained washed with methanol (3 × 10 mL). The combined filtrates were concentrated under reduced pressure to afford a light-yellow oil that was subjected to flash column chromatography (silica, 1:19 → 1:9 v/v methanol/dichloromethane gradient elution) and thereby afforded two fractions, A and B.

Concentration of fraction A [R_f = 0.5(1) in 1:4 v/v methanol/dichloromethane] afforded the *first epimeric form of compound* ***20*** (9 mg, 44%) as a clear, colorless oil: ^{1}H NMR (CD_3OD, 400 MHz) δ 7.48 (dd, J = 7.2 and 0.8 Hz, 1H), 7.28 (dd, J = 7.2 and 1.2 Hz, 1H), 7.01 (m, 2H), 4.46 (t, J = 2.4 Hz, 1H), 3.22 (dd, J = 17.6 and 2.8 Hz, 1H), 2.86 (dd, J = 12.8 and 4.0 Hz, 1H), 2.75 (d, J = 17.6 Hz, 1H), 2.45 (d, J = 13.2 Hz, 1H), 2.37 (dt, J = 13.2 and 3.6 Hz, 1H), 2.17 (m, 1H), 1.84 (m, 1H), 1.72 (dm, J = 13.2 Hz, 1H), 1.28 (d, J = 7.2 Hz, 3H) (signals due to NH protons not observed); ^{13}C NMR (CD_3OD, 100 MHz) δ 138.6 (C), 138.0 (C), 127.2 (C), 121.8 (CH), 120.0 (CH), 118.3 (CH), 111.7 (CH), 107.2 (C), 46.2 (CH), 43.2 (CH_2), 35.8 (CH), 33.1 (CH), 31.4 (CH_2), 27.9 (CH_2), 19.4 (CH_3); IR ν_{max} 3396, 3220, 2907, 1457, 1324, 1069, 920 cm^{-1}; MS (ESI, +ve ion) m/z 227 [(M + H)$^+$, 100]; HRMS (M + H)$^+$ calcd for $C_{15}H_{18}N_2$ 227.1548, found 227.1549.

Concentration of fraction B [R_f = 0.4(9) in 1:4 v/v methanol/dichloromethane] afforded the *second epimeric form of compound* ***20*** (8 mg, 40%) as a clear, colorless oil: ^{1}H NMR (CD_3OD, 400 MHz) δ 7.46 (dd, J = 7.2 and 1.6 Hz, 1H), 7.26 (dd, J = 7.2 and 1.2 Hz, 1H), 7.00 (m, 2H), 4.36 (t, J = 3.2 Hz, 1H), 2.86 (m, 2H), 2.52 (dd, J = 12.0 and 1.2 Hz, 1H), 2.19 (m, 2H), 2.12 (dt, J = 12.8 and 3.2 Hz, 1H), 1.98 (m, 2H), 0.94 (d, J = 7.2 Hz, 3H) (signals due to NH protons not observed); ^{13}C NMR (CD_3OD, 100 MHz) δ 138.0 (C), 137.9 (C), 127.3 (C), 121.6 (CH), 119.8 (CH), 118.2 (CH), 111.5 (CH), 109.3 (C), 45.2 (CH and CH_2, two overlapping signals), 36.2 (CH), 35.0 (CH_2), 33.3 (CH), 23.2 (CH_2), 17.8 (CH_3); IR ν_{max} 3397, 3215, 2921, 1617, 1453, 1320, 1291, 1238, 1073 cm^{-1}; MS (ESI, +ve ion) m/z 227 [(M + H)$^+$, 100]; HRMS (M + H)$^+$ calcd for $C_{15}H_{18}N_2$ 227.1548, found 227.1547.

Compound 21. A magnetically stirred solution of amine **11** (202 mg, 0.95 mmol) and bromoacetaldehyde dimethyl acetal (169 μL, 1.43 mmol) in 1,4-dioxane (12 mL) was treated with K_2CO_3 (197 mg, 1.43 mmol) and the resulting mixture heated at reflux for 16 h. The cooled reaction mixture was concentrated under reduced pressure and then diluted with dichloromethane (40 mL) and washed with $NaHCO_3$ (20 mL of a saturated aqueous solution) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil. Subjection of this material to column chromatography (silica, 1:19 → 1:1 v/v ethyl acetate/hexane gradient elution) afforded, after concentration of the relevant fractions (R_f = 0.2 in 1:19 v/v methanol/dichloromethane), the title compound **21**[12] (222 mg, 78%) as a light-brown oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.50 (broad s, 1H), 7.60 (dd, J = 6.2 and 2.0 Hz, 1H), 7.28 (dd, J = 6.4 and 1.2 Hz, 1H), 7.08 (m, 2H), 4.69 (t, J = 5.2 Hz, 1H), 4.31 (m, 1H), 3.43 (s, 3H), 3.32 (s, 3H), 3.03 (dd, J = 17.6 and 6.8 Hz, 1H), 2.98 (dd, J = 13.2 and 5.6 Hz, 1H), 2.68 (dd, J = 11.6 and 4.0 Hz, 1H), 2.58 (d, J = 17.2 Hz, 1H), 2.40−2.14 (complex m, 4H), 2.08 (m, 1H), 1.81 (dm, J = 12.4 Hz, 1H), 1.58 (dm, J = 12.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.0 (C), 135.7 (C), 128.0 (C), 120.6 (CH), 119.5 (CH), 118.3 (CH), 110.4 (CH), 106.3 (C), 103.1 (CH), 58.7 (CH_2), 53.5 (CH_3), 53.2 (CH_3), 51.6 (CH), 45.4 (CH_2), 32.9 (CH_2), 32.7 (CH_2), 29.1 (CH_2), 25.0 (CH); IR ν_{max} 3397, 3299, 3054, 2926, 2831, 1653, 1619, 1583, 1562, 1461, 1427, 1362, 1330, 1309, 1278, 1231, 1191, 1129, 1071, 1013, 1001, 964, 930, 900 cm^{-1}; MS (EI, 70 eV) m/z 300 (M$^{+\bullet}$, 12), 269 (7), 225 (100), 194 (49), 182 (8), 168 (28), 167 (22), 144 (10), 75 (13); HRMS M$^{+\bullet}$ calcd for $C_{18}H_{24}N_2O_2$ 300.1838, found 300.1838.

Compound 22. A magnetically stirred solution of acetal **21** (85 mg, 0.28 mmol), ethanethiol (6.3 mL, 84.9 mmol), and 3 Å molecular sieves (0.5 g) in dichloromethane (14 mL) maintained at 0 °C was treated with BF_3·OEt (354 μL, 2.8 mmol). The ensuing mixture was warmed to 18 °C, stirred at this temperature for 48 h, and then treated with $NaHCO_3$ (20 mL of a saturated aqueous solution). The ensuing mixture was filtered through diatomaceous earth, and the solids thus retained were washed with dichloromethane (3 × 20 mL). The combined organic phases were then dried ($MgSO_4$) before being filtered and concentrated under reduced pressure. Subjection of the ensuing light-yellow oil to column chromatography (silica, 1:19 → 1:0 v/v ethyl acetate/hexane gradient elution) and concentration of the relevant fractions (R_f = 0.5 in ethyl acetate) afforded the title compound **22**[12] (84 mg, 83%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93 (s, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.29 (d, J = 8.8 Hz, 1H), 7.10 (m, 2H), 4.21 (m, 1H), 4.06 (m, 1H), 3.10 (m, 1H), 3.05 (dd, J = 17.6 and 7.2 Hz, 1H), 2.81−2.55 (complex m, 5H), 2.49 (m, 1H), 2.37 (m, 1H), 2.30−1.96 (complex m, 2H), 1.86−1.50 (complex m, 4H), 1.30 (t, J = 7.2 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.7 (C), 135.7 (C), 128.0 (C), 120.9 (CH), 119.7 (CH), 118.4 (CH), 110.3 (CH), 107.4 (C), 62.9 (CH_2), 51.3 (CH), 49.8 (CH), 45.0 (CH_2), 33.2 (CH_2), 32.9 (CH_2), 29.2 (CH_2), 25.4 (CH), 24.6 (CH_2), 24.4 (CH_2) 14.6 (CH_3, two overlapping signals); IR ν_{max} 3399, 3054, 2923, 1618, 1583, 1562, 1458, 1474, 1328, 1308, 1264, 1230, 1157, 1142, 1099, 1084, 1055, 1012, 995, 970 cm^{-1}; MS (EI, 70 eV) m/z 360 (M$^{+\bullet}$, 1), 225 (100), 194 (38), 182 (9), 169 (19), 168 (30), 167 (22), 144 (9), 82 (10); HRMS M$^{+\bullet}$ calcd for $C_{20}H_{28}N_2S_2$ 360.1694, found 360.1695.

Compound 23. A magnetically stirred solution of DMSTF[1c,16] (45 mg, 0.23 mmol) in dichloromethane (3 mL) containing 4 Å molecular sieves (100 mg of anhydrous material) maintained at 0 °C under an atmosphere of nitrogen was treated with a solution of compound **22** (39 mg, 0.11 mmol) in dichloromethane (10 mL). The ensuing mixture was stirred magnetically at 0 °C for 3 h and then concentrated under reduced pressure to afford a light-yellow oil. Subjection of this material to column chromatography (silica, 1:19 v/v methanol/dichloromethane) and concentration of the relevant fractions (R_f = 0.2) afforded the title compound **23**[12] (21 mg, 63%) as a pale-yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.51 (d, J = 7.2 Hz, 1H), 7.35 (m, 2H), 7.19 (t, J = 7.2 Hz, 1H), 4.16 (dd, J = 11.2 and 5.6 Hz, 1H), 3.91 (m, 1H), 3.45 (dd, J = 11.6 and 5.6 Hz, 1H), 3.30 (m, 1H), 3.08 (m, 3H), 2.70 (m, 1H), 2.47 (m, 1H), 2.09 (m, 1H), 2.02−1.78 (complex m, 3H), 1.59 (m, 1H), 1.05 (dm, J = 12.4 Hz, 1H), 0.93 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.7 (C), 155.2 (C), 139.8 (C), 128.3 (CH), 124.8 (CH), 124.1 (CH), 119.9 (CH), 70.1 (CH), 69.1 (C), 64.9 (CH_2), 45.4 (CH and CH_2, two overlapping signals), 31.0 (CH_2), 30.5 (CH_2), 28.3 (CH), 27.3 (CH_2), 26.2 (CH_2), 14.5 (CH_3); IR ν_{max} 2926, 2864, 1659, 1566, 1455, 1329, 1288, 1194, 1116, 1096, 1071, 1016, 958, 927 cm^{-1}; MS (EI, 70 eV) m/z 298 (M$^{+\bullet}$, 72), 284 (18), 269 (23), 267 (20), 240 (50), 237 (100), 226 (23), 194 (54), 180 (29), 167 (25), 156 (33), 95 (66); HRMS M$^{+\bullet}$ calcd for $C_{18}H_{22}N_2S$ 298.1504, found 298.1505.

Compound 24. A magnetically stirred solution of imine **23** (15 mg, 0.05 mmol) in ethanol was treated with Raney Ni (excess) and the

ensuing mixture heated at reflux for 3 h. The cooled reaction mixture was filtered through diatomaceous earth and the solids retained were washed with ethanol (2 × 10 mL). The combined filtrates were concentrated under reduced pressure to give a yellow oil that was subjected to column chromatography (silica, 1:9 → 1:10 v/v diethylamine/diethyl ether gradient elution). Concentration of the relevant fractions (R_f = 0.1 in 1:49 v/v diethylamine/diethyl ether) then gave the title compound **24**[12,15b] (10 mg, 81%) as a pale-yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.04 (m, 2H), 6.75 (t, J = 7.5 Hz, 1H), 6.62 (d, J = 8.5 Hz, 1H), 3.77 (t, J = 8.0 Hz, 1H), 3.63 (broad s, 1H), 3.36 (broad s, 1H), 3.13 (m, 1H), 3.03 (m, 1H), 2.87 (m, 1H), 2.51 (m, 1H), 2.40 (dt, J = 15.5 and 8.0 Hz, 1H), 1.98−1.83 (complex m, 5H), 1.69−1.50 (complex m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.4 (C), 133.6 (C), 127.7 (CH), 122.2 (CH), 119.1 (CH), 109.6 (CH), 65.1 (CH), 62.3 (CH), 54.0 (CH_2), 52.7 (C), 47.7 (CH_2), 42.3 (CH_2), 37.4 (CH_2), 29.1 (CH_2), 26.6 (CH_2), 23.2 (CH); IR ν_{max} 3196, 2922, 1605, 1483, 1464, 1359, 1310, 1284, 1249, 1118, 1080, 1020, 963, 928 cm^{-1}; MS (EI, 70 eV) m/z 240 ($M^{+\bullet}$, 46), 212 (10), 143 (26), 130 (15), 110 (100), 96 (17), 82 (12), 55 (14); HRMS $M^{+\bullet}$ calcd for $C_{16}H_{20}N_2$ 240.1626, found 240.1625.

Compound 25. A magnetically stirred mixture of amine **11** (140 mg, 0.66 mmol), dichloromethane (6.6 mL), and NaOH (3.6 mL of a 1.0 M aqueous solution) was treated, dropwise, with a solution of α-chloroacetyl chloride (105 μL, 1.32 mmol) in dichloromethane (3.6 mL). The biphasic reaction mixture was stirred at 18 °C for 5 h after which time the organic phase was separated and the aqueous one extracted with dichloromethane (3 × 10 mL). The combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a light-yellow oil that was subjected to flash column chromatography (neutral alumina, 1:9 → 1:1 v/v ethyl acetate/hexane gradient elution). Concentration of the relevant fractions (R_f = 0.3 in 1:1 v/v ethyl acetate/hexane) afforded the title compound **25**[10] (120 mg, 63%) as a colorless, crystalline solid and as a 4:1 mixture of rotamers: mp 178−179 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14 (s, 0.2H), 8.02 (s, 0.8H), 7.60 (d, J = 7.2 Hz, 0.8H), 7.43 (d, J = 8.0 Hz, 0.2H), 7.33 (d, J = 7.6 Hz, 0.2H), 7.30 (d, J = 8.4 Hz, 0.8H), 7.11 (m, 2H), 6.11 (s, 0.8H), 5.26 (s, 0.2H), 4.40 (m, 0.4H), 3.99 (q, J = 12.0 Hz, 1.6H), 3.44−2.20 (complex m, 3H), 2.01 (m, 3H), 1.67 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.7 (C, two overlapping signals), 137.0 (C), 136.4 (C, two overlapping signals), 135.9 (C), 125.9 (C, two overlapping signals), 121.7 (CH, two overlapping signals), 120.0 (CH), 119.9 (CH), 118.9 (CH), 117.5 (CH), 110.9 (CH), 110.4 (CH), 109.1 (C, two overlapping signals), 47.2 (CH), 41.7 (CH_2), 41.6 (CH), 41.5 (CH_2), 39.5 (CH_2, two overlapping signals), 33.4 (CH_2), 32.6 (CH_2), 32.0 (CH_2), 31.9 (CH_2), 28.7 (CH_2), 28.6 (CH_2), 25.7 (CH), 25.7 (CH); IR ν_{max} 3401, 2924, 2853, 1630, 1455, 1378, 1071 cm^{-1}; MS (EI, 70 eV) m/z 290 and 288 ($M^{+\bullet}$, 52 and 17), 239 (22), 193 (53), 180 (27), 169 (40), 168 (100), 167 (50), 149 (27), 97 (33), 83 (35), 71 (48), 57 (65); HRMS $M^{+\bullet}$ calcd for $C_{16}H_{17}{}^{35}ClN_2O$ 288.1029, found 288.1030.

Compound 26. A magnetically stirred solution of acetamide **25** (80 mg, 0.28 mmol) in acetone (5 mL) was treated with NaI (410 mg, 2.8 mmol) and the resulting solution heated at reflux for 2 h, cooled to 18 °C, and concentrated under reduced pressure to give a white solid. This material was dissolved in ethyl acetate (10 mL) and the resulting solution washed with water (1 × 5 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give *compound* **26** (97 mg, 92%) as a yellow oil (R_f = 0.3 in 1:1 v/v ethyl acetate/hexane). This unstable material was immediately treated with silver triflate in an unsuccessful attempt to effect a Heathcock annulation reaction (see text for details).

Compound 27. A magnetically stirred solution of amide **25** (53 mg, 0.18 mmol) and AIBN (6 mg, 0.02 mmol) in benzene (12.3 mL) was treated, at 18 °C, with tri-*n*-butyltin hydride (148 μL, 0.54 mmol). The ensuing mixture was heated at reflux for 1 h, cooled to 18 °C, and concentrated under reduced pressure to give a light-yellow oil. This oil was subjected to flash column chromatography (silica, 0:1 → 1:4 v/v ethyl acetate/hexane gradient elution) and concentration of the relevant fractions (R_f = 0.1 in 1:1 v/v ethyl acetate/hexane) afforded the title compound **27**[10] (41 mg, 89%) as a white, crystalline solid and 5:2 mixture of rotamers: mp 192−198 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.38 (s, 0.3H), 8.21 (s, 0.7H), 7.64 (d, J = 7.2 Hz, 0.7H), 7.40 (d, J = 8.0 Hz, 0.3H), 7.30 (m, 1H), 7.10 (m, 2H), 6.20 (m, 0.7H), 5.23 (m, 0.3H), 4.38 (dd, J = 13.2 and 5.6 Hz, 0.3H), 3.42 (dd, J = 5.6 and 13.2 Hz, 0.7H), 3.16 (dd, J = 6.8 and 17.2 Hz, 1H), 3.03 (dt, J = 3.6 and 13.6 Hz, 1H), 2.73 (m, 1H), 2.53 (m, 1H), 2.43 (s, 0.9H), 2.01 (s, 2.1H), 2.10−1.88 (complex m, 3H), 1.66 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.7 (C), 167.9 (C), 136.8 (C), 136.3 (C, two overlapping signals), 136.0 (C), 126.0 (C), 125.8 (C), 121.5 (CH, two overlapping signals), 119.8 (CH), 119.7 (CH), 119.0 (CH), 117.5 (CH), 110.8 (CH), 110.3 (CH), 109.7 (C), 108.6 (C), 47.0 (CH), 40.6 (CH), 39.6 (CH_2, two overlapping signals), 34.4 (CH_2), 33.4 (CH_2), 32.7 (CH_2), 32.1 (CH_2), 32.0 (CH_2), 28.6 (CH_2), 25.7 (CH, two overlapping signals), 22.0 (CH_3), 21.8 (CH_3); IR ν_{max} 3227, 2924, 1609, 1425, 1360, 1330, 1270, 1247, 1216, 1194, 1121, 1072, 1023, 1000, 986 cm^{-1}; MS (EI, 70 eV) m/z 254 ($M^{+\bullet}$, 71), 239 (3), 211 (9), 195 (47), 182 (21), 169 (50), 168 (100), 167 (40), 143 (10), 87 (30), 72 (14); HRMS $M^{+\bullet}$ calcd for $C_{16}H_{18}N_2O$ 254.1419, found 254.1416.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Crystallographic data (CIF), anisotropic displacement ellipsoid plot, and unit cell packing diagram derived from the single-crystal analysis of compound **18**; ^{1}H and ^{13}C NMR spectra for compounds **4**−**25**, **27**, the Cbz-derivative of compound **10**, and the Cbz-derivative of compound **11**. This material is available free-of-charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Australian Research Council and the Institute of Advanced Studies for generous financial support.

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