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A Raney Cobalt Mediated Reductive Cyclization Route to the Uleine Alkaloid Gilbertine

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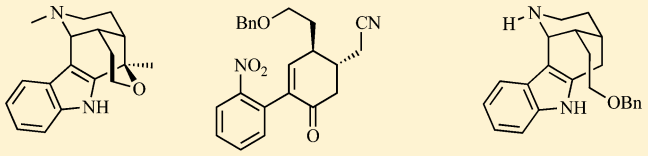
Supporting Information

ABSTRACT: Reductive cyclization of the 2,4,5-trisubstituted cyclohexenone **16** using dihydrogen in the presence of Raney cobalt afforded compound **17** (60%) that could be elaborated over a further five steps, including one involving a cationic cyclization process, into the racemic modification of the unusual uleine alkaloid gilbertine. Single-crystal X-ray analyses of compounds (±)-**1**, **16**, and a derivative of **17** are reported.



1 (gilbertine) **16** **17**

The uleine alkaloid (−)-gilbertine (**1**) was isolated in 1982 by Miranda and Blechert from the Brazilian tree *Aspidosperma gilbertii* (A. P. Duarte).[1] It differs from other, better known members of the class[2] such as the parent compound uleine (**2**), noruleine (**3**), dasycarpidone (**4**), and nordasycarpidone (**5**) by virtue of the presence of an additional, tetrahydropyran-based ring system and a fourth stereogenic center at C16.[3] The unusual pentacyclic framework associated with gilbertine has been the target of various synthetic studies,[4,5] but only one successful (and enantioselective) total synthesis has been reported to date. Thus, in 2004, Jiricek and Blechert reported[4] a cationic cascade cyclization of a tetrahydrocarbazole that successively established the piperidine and tetrahydropyran rings of (−)-gilbertine (Figure 1).

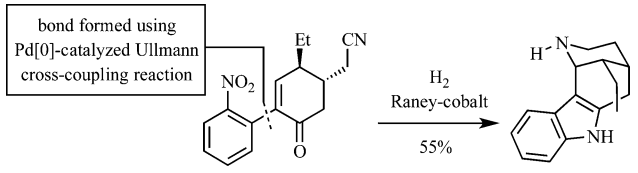
1 (gilbertine)

2 R=Me, X=CH_2 (uleine)
3 R=H, X=CH_2 (noruleine)
4 R=Me, X=O (dasycarpidone)
5 R=H, X=O (nordasycarpidone)

Figure 1. Structures of gilbertine (**1**) and certain simpler uleine alkaloids.

Recently, we reported[2] that when the α-arylated cyclohexeneone **6**, itself prepared through a palladium-catalyzed Ullmann cross-coupling reaction, was treated with dihydrogen in the presence of Raney cobalt[6] then a tandem reductive cyclization process took place (Scheme 1) to afford the tetracyclic indole **7** (55%) that embodies the uleine framework.[7] Through relatively straightforward manipulations, compound **7** was converted into the racemic modifications of alkaloids **2**−**5**. Herein, we describe the extension of these protocols to the synthesis of (±)-gilbertine and report the first single-crystal X-ray analysis of this molecular framework.

Scheme 1. Pivotal Tandem Reductive Cyclization Reaction Used To Prepare the Simpler Uleine Alkaloids 2−5



6 **7**

Inspired by the closing stages of the Jiricek−Blechert synthesis,[4] we envisaged that the tetrahydropyran ring of gilbertine could be formed through intramolecular nucleophilic attack of a C23 hydroxyl group onto a tertiary carbocation formed at C16 (see Figure 1 for the numbering scheme) within the uleine framework. Accordingly, the key subtarget associated with the present study was a protected form of the β-hydroxyethyl analogue of compound **6**. The synthesis of such a system is shown in Scheme 2 and involved initial alkylation of the ketone enolate derived from commercially available 3-ethyoxy-2-cyclohexen-1-one (**8**) with the benzyl ether of 2-iodoethanol.[8] Product **9** (50%) was reduced with lithium aluminum hydride, and the resulting allylic alcohol was subjected to acidic workup, thus providing the γ-substituted cyclohexenone **10** (75%). Nucleophilic cyclopropanation of this last compound using the Corey−Chaykovsky ylide[9] then afforded, in a highly diastereoselective manner,[10] the bicyclo[4.1.0]heptanone **11** (81%) that on treatment with sodium iodide in formic acid engaged in a homoconjugate addition reaction[2] to afford the *trans*-3,4-disubstituted cyclohexanone **12** in 82% yield. As with our earlier study,[2] a three-stage but operationally simple conversion of iodide **12** into nitrile **13** was required in order to prevent the former

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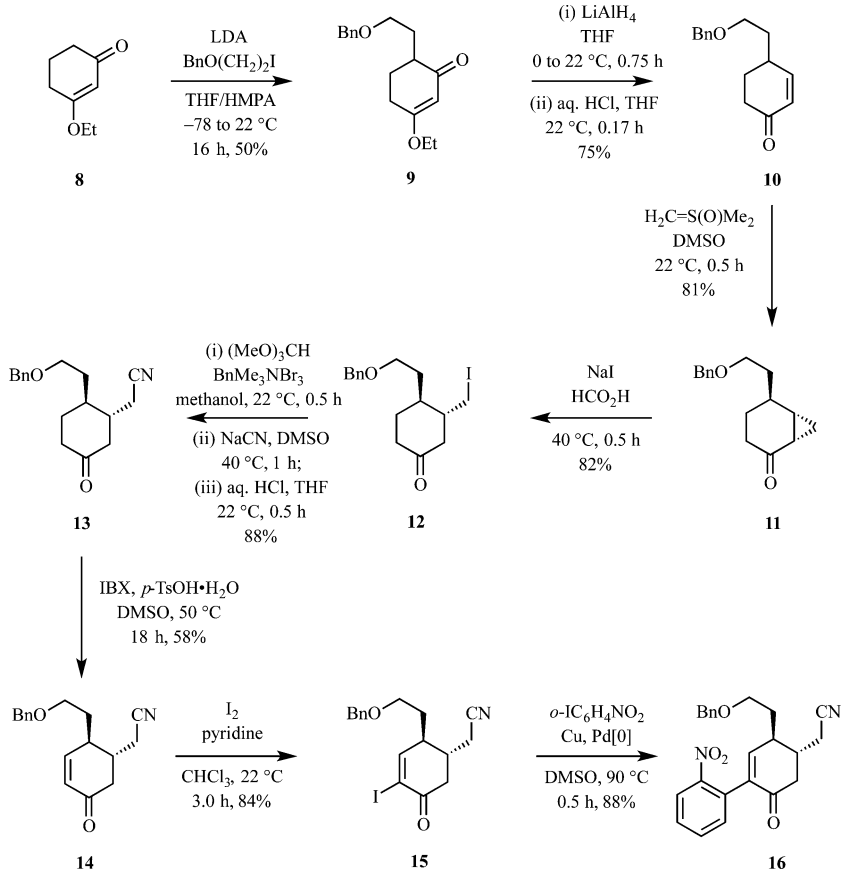
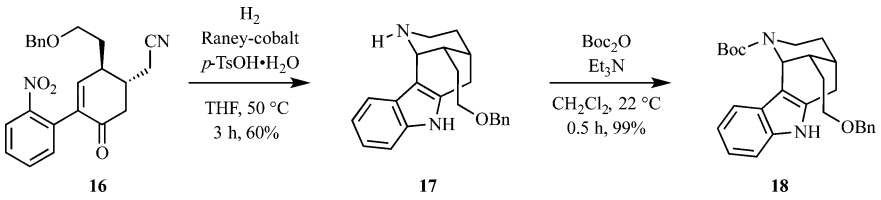
Scheme 2. Synthesis of the Substrate Required for the Tandem Reductive Cyclization Reaction



Scheme 3. Tandem Reductive Cyclization Reaction



compound from engaging in a 3-(enol-*exo*)-*exo-tet* cyclization reaction, thereby re-forming cyclopropane **11**. Specifically, then, cyclohexanone **12** was treated with trimethyl orthoformate and benzyltrimethylammonium tribromide, thus generating the dimethyl ketal that was immediately reacted with sodium cyanide in DMSO. The ketal residue associated with the product nitrile was cleaved using aqueous HCl in THF and the cyclohexanone **13** thereby obtained in 88% over the three steps involved. A modestly regioselective dehydrogenation of this last compound was achieved using 2-iodoxybenzoic acid (IBX) in the presence of *p*-TsOH·H_2O,[11] and the product cyclohexenone **14** (58%) was subjected to a Johnson-type α-iodination reaction[12] using molecular iodine in the presence of pyridine. Compound **15** (84%) thus formed was engaged in a palladium(0)-catalyzed Ullmann cross-coupling reaction[13] with *o*-iodonitrobenzene, and the targeted substrate, **16**, required for the pivotal reductive cyclization reaction, was obtained in 88% yield. All of the spectral data acquired on compound **16** were in complete accord with the assigned structure, but final confirmation of this followed from a single-crystal X-ray analysis, details of which are provided in the Experimental Section and the Supporting Information.

When compound **16** was exposed to dihydrogen in the presence of Raney cobalt[6] and *p*-TsOH·H_2O (Scheme 3), the anticipated reductive cyclization reaction took place, delivering tetracycle **17** in 60% yield. No hydrogenolytic cleavage of the associated benzyl ether moiety was observed, thus further emphasizing the chemoselectivity of reductions involving this catalyst system. Given the nature of the closing steps of the planned synthesis, the piperidine nitrogen within product **17** was protected, under standard conditions, as the corresponding *tert*-butyl carbamate **18** (99%). While the interpretation of the NMR spectral data recorded on compound **18** was complicated by the presence of carbamate rotamers,[14] its structure was confirmed through a single-crystal X-ray analysis.

The completion of the synthesis of (±)-gilbertine proved straightforward and involved (Scheme 4) the pyridinium chlorochromate (PCC) mediated oxidation of compound **18** to the corresponding ketone **19** (57%),[2] the benzyl ether moiety of which was cleaved using dihydrogen in the presence of 10% palladium on carbon and thus affording alcohol **20**

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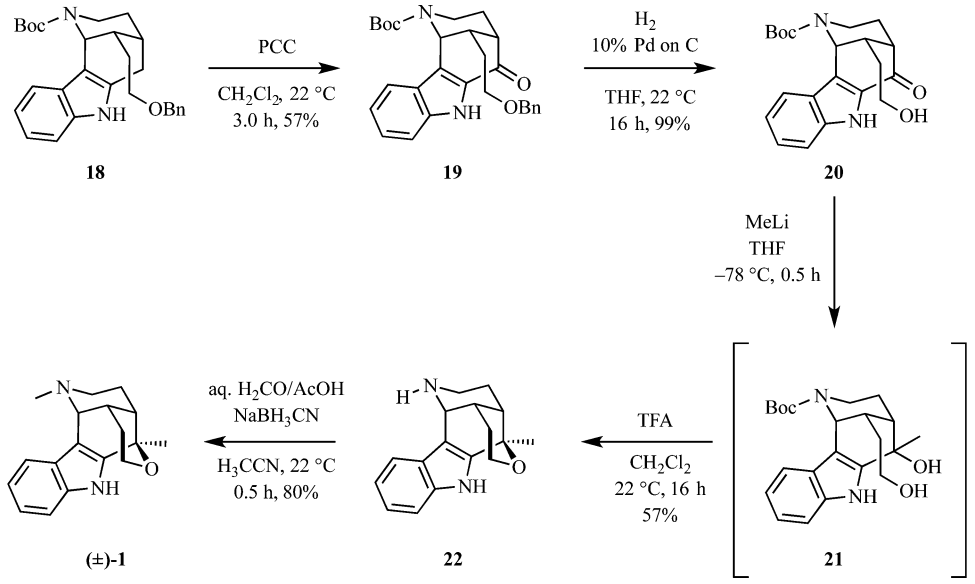
Scheme 4. Completion of the Synthesis of (±)-Gilbertine



(99%). Treatment of this last compound with an excess of methyllithium presumably resulted in the formation of the required C16-centered tertiary alcohol **21** (or an anionic form thereof), but this was not isolated. Rather, the reaction mixture was quenched with trifluoroacetic acid (TFA), and this resulted not only in the desired cationic cyclization process to form the required tetrahydropyran ring but also in cleavage of the Boc group, thereby producing (±)-norgilbertine (**22**) (57%). Reductive methylation of this last compound using formaldehyde in the presence of sodium cyanoborohydride then gave (±)-gilbertine [(±)-**1**] as a crystalline solid. All of the derived spectral data matched those reported[1,3] for both the natural product and previously synthesized material (see the Supporting Information for relevant comparisons of the ^{13}C NMR data sets). A single-crystal X-ray analysis of this last compound could also be obtained, details of which are provided in the Experimental Section and the SI.

The work detailed above serves to emphasize the utility of the Raney cobalt-mediated reductive cyclization protocol as a means for assembling the uleine framework. Given that an enantiomerically enriched form of enone **10** can be obtained through desymmetrization of the corresponding and prochiral cyclohexanone using Koga–Simpkins bases,[15] the present work is also likely to provide access to either enantiomeric form of gilbertine.

EXPERIMENTAL SECTION

General Protocols. Unless otherwise specified, proton (^1H) and carbon (^{13}C) NMR spectra were recorded at room temperature in base-filtered $CDCl_3$ on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. 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 ^1H and ^{13}C NMR spectra, respectively. ^1H NMR data are presented 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. Infrared spectra (ν_{max}) were recorded on an FTIR spectrometer. Samples were analyzed as thin films on KBr plates. 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. Melting points were measured on an automated melting point system and 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 (concd)/water (37.5 g:7.5 g:37.5 g:720 mL), potassium permanganate/potassium carbonate/5% sodium hydroxide aqueous solution/water (3 g:20 g:5 mL:300 mL)), *p*-anisaldehyde or vanillin/sulfuric acid (concd)/ethanol (15 g:2.5 mL:250 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.[16] 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 were dried using a solvent purification system that is based upon a technology originally described by Grubbs et al.[17] Where necessary, reactions were performed under a nitrogen atmosphere.

Specific Chemical Transformations: *(±)-6-(2-(Benzyloxy)-ethyl)-3-ethoxycyclohex-2-en-1-one (**9**).* A magnetically stirred solution of diisopropylamine (4.2 mL, 0.03 mol) in THF (15 mL) maintained under an atmosphere of nitrogen was cooled to −78 °C before being treated with *n*-BuLi (16.0 mL, 1.6 M in hexanes, 0.025 mol). The resulting solution was stirred at −78 °C for 0.17 h, warmed to 22 °C, and stirred at this temperature for 0.33 h. The ensuing mixture was treated with enone **8** (3.0 g, 0.02 mol), and stirring continued for 0.5 h before a solution of 1-(benzyloxy)-2-iodoethane[8] (6.8 g, 0.03 mol) in HMPA (6 mL) was added dropwise. The solution thus formed was stirred at room temperature for 16 h and then quenched with water (15 mL), and the resulting mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (1 × 50 mL) then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The yellow oil so formed was subjected to flash chromatography (silica, 1:15 → 1:5 v/v ethyl acetate/petroleum ether gradient elution), and concentration of relevant fractions (R_f = 0.4 in 1:3 v/v ethyl acetate/petroleum ether) afforded the title compound **9** (2.9 g, 50%) as a clear, light-yellow oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.38–7.21 (complex m, 5H), 5.33 (s, 1H), 4.53 (q, J = 7.1 Hz, 2H), 3.90 (m, 2H), 3.62 (t, J = 6.4 Hz, 2H), 2.51–2.34 (complex m, 3H), 2.32–2.24 (complex m, 1H), 2.14–2.06 (complex m, 1H), 1.79–1.69 (complex m, 1H), 1.65–1.57 (complex m, 1H), 1.37 (t, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.3, 176.8, 138.6, 128.3, 127.6, 127.5, 102.2, 72.8, 68.4, 64.2, 42.5, 29.7, 28.4, 26.9, 14.2; IR ν_{max} 2938, 2863, 1650, 1604, 1378,

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1358, 1187, 1097, 736, 697 cm^{-1}; MS (ESI, +ve) m/z 297 [$(M + Na)^+$, 100]; HRMS $(M + Na)^+$ calcd for $C_{17}H_{22}NaO_3$ 297.1467, found 297.1469.

*(±)-4-(2-(Benzyloxy)ethyl)cyclohex-2-en-1-one (**10**).* A magnetically stirred solution of compound **9** (360 mg, 1.31 mmol) in THF (10 mL) maintained under a nitrogen atmosphere was cooled to 0 °C and then treated with $LiAlH_4$ (1.30 mL of a 1.0 M solution in THF, 1.30 mmol). The resulting mixture was stirred at 0 °C for 0.17 h and then warmed to room temperature, and stirring was continued at this temperature for another 0.5 h. After this time, the reaction mixture was quenched with water (4 mL), and then sufficient HCl (1 M aqueous solution) was added to attain a pH of 1−2. The solution thus obtained was stirred vigorously at room temperature for 0.17 h and then extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (1 × 30 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash chromatography (silica, 1:15 → 1:5 v/v ethyl acetate/petroleum ether gradient elution), and concentration of relevant fractions (R_f = 0.5 in 1:3 v/v ethyl acetate/petroleum ether) afforded the title compound **10** (230 mg, 75%) as a clear, colorless oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.42−7.29 (complex m, 5H), 6.90 (dm, J = 10.2 Hz, 1H), 6.00 (dm, J = 10.2 Hz, 1H), 4.55 (s, 2H), 3.73−3.46 (complex m, 2H), 2.71−2.63 (complex m, 1H), 2.51 (dt, J = 16.8 and 4.9 Hz, 1H), 2.38 (m, 1H), 2.17−2.09 (complex m, 1H), 1.91−1.83 (complex m, 1H), 1.79−1.63 (complex m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.8, 154.9, 138.2, 129.0, 128.5, 127.7(3), 127.6(6), 73.1, 67.4, 36.9, 34.5, 33.3, 28.6; IR ν_{max} 3320, 3030, 2927, 2862, 1674, 1453, 1390, 1254, 1210, 1097, 739, 658 cm^{-1}; MS (ESI, +ve) m/z 253 [$(M + Na)^+$, 100]; HRMS $(M + Na)^+$ calcd for $C_{15}H_{18}NaO_2$ 253.1204, found 253.1208.

*rac-(1S,5S,6S)-5-(2-(Benzyloxy)ethyl)bicyclo[4.1.0]heptan-2-one (**11**).* A magnetically stirred suspension of NaH (41 mg, 1.7 mmol) in dry DMSO (10 mL) was treated with Me_3SOI (224 mg, 1.0 mmol) and after being maintained at room temperature for 0.17 h the reaction mixture was warmed to 50 °C and stirred at this temperature for a further 0.34 h. The cooled reaction mixture was treated with enone **10** (213 mg, 0.9 mmol) and then stirred at room temperature for 0.5 h before being quenched with water (15 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (1 × 50 mL) and then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica, 1:15 → 1:5 v/v ethyl acetate/petroleum ether gradient elution), and concentration of relevant fractions (R_f = 0.4 in 1:7 v/v ethyl acetate/petroleum ether) afforded the title compound **11** (183 mg, 81%) as a clear, colorless oil containing ca. 15% of an impurity assumed to be the diastereoisomeric cyclopropane: ^1H NMR ($CDCl_3$, 400 MHz) δ (major product) 7.33−7.17 (complex m, 5H), 4.45 (s, 2H), 3.52 (broadened t, J = 6.3 Hz, 2H), 2.22−2.13 (complex m, 1H), 2.09 (dd, J = 8.3 and 5.8 Hz, 2H), 1.81−1.41 (complex m, 6H), 1.19−1.05 (complex m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (major product) 209.5, 138.4, 128.4, 127.6(2), 127.6(0), 73.0, 68.1, 34.4, 33.1, 28.6, 25.5, 24.1, 24.0, 12.7; IR ν_{max} 3029, 2928, 2861, 1687, 1453, 1353, 1248, 1102, 738, 698 cm^{-1}; MS (ESI, +ve) m/z 267 [$(M + Na)^+$, 100]; HRMS $(M + Na)^+$ calcd for $C_{16}H_{20}NaO_2$ 267.1361, found 267.1359.

*rac-(3R,4S)-4-(2-(Benzyloxy)ethyl)-3-(iodomethyl)cyclohexan-1-one (**12**).* A magnetically stirred solution of ketone **11** (1.10 g, 4.5 mmol) and NaI (1.70 g, 11.3 mmol) in formic acid (10 mL) was heated at 40 °C for 0.5 h, cooled to room temperature, and quenched with water (15 mL). The resulting mixture was extracted with ethyl acetate (3 × 20 mL), and the combined organic phases were washed with $NaHCO_3$ (50 mL of a saturated aqueous solution) then brine (1 × 50 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica, 1:15 → 1:5 v/v ethyl acetate/petroleum ether gradient elution) and concentration of relevant fractions (R_f = 0.6 in 1:3 v/v ethyl acetate/petroleum ether) afforded the title compound **12** (1.40 g, 82%) as a clear, yellow oil containing ca. 15% of an impurity assumed to be the *cis*-isomer: ^1H NMR ($CDCl_3$, 400 MHz) δ (major product) 7.43−7.27 (complex m, 5H), 4.54 (ABq, J = 10.5 Hz, 2H), 3.60 (t, J = 6.5 Hz, 2H), 3.46 (dd, J = 10.4 and 5.0 Hz, 1H), 3.27 (dd, J = 10.4 and 2.9 Hz, 1H), 2.47−2.24 (complex m, 4H), 2.14−2.07 (complex m, 1H), 2.00−1.92 (complex m, 1H), 1.89−1.77 (complex m, 1H), 1.60−1.45 (complex m, 2H), 1.44−1.34 (complex m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (major product) 210.5, 138.3, 128.4, 127.7, 127.6, 73.1, 67.6, 47.2, 42.3, 40.6, 37.5, 31.6, 29.3, 15.0; IR ν_{max} 3029, 2935, 2862, 1713, 1453, 1425, 1359, 1317, 1265, 1218, 1177, 1099, 738, 698 cm^{-1}; MS (ESI, +ve) m/z 395 [$(M + Na)^+$, 100]; HRMS $(M + Na)^+$ calcd for $C_{16}H_{21}INaO_2$ 395.0484, found 395.0486.

*rac-2-((1R,2S)-2-(2-(Benzyloxy)ethyl)-5-oxocyclohexyl)acetonitrile (**13**).* *Step i.* A magnetically stirred solution of iodide **12** (1.40 g, 3.8 mmol) in anhydrous MeOH (10 mL) was treated with trimethyl orthoformate (1.80 mL, 5.7 mmol) and benzyltrimethylammonium tribromide (32 mg, 0.08 mmol). The resulting mixture was stirred at room temperature for 0.5 h, quenched with $NaHCO_3$ (10 mL of a saturated aqueous solution), and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (1 × 50 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting yellow oil, presumed to contain the dimethyl ketal of compound **12**, was immediately subjected to the reaction conditions defined in step ii.

Step ii. A magnetically stirred solution of crude material obtained from step i in DMSO (6 mL) was treated with KCN (366 mg, 5.6 mmol). The resulting solution was stirred at 40 °C for 1 h, quenched with water (15 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were concentrated under reduced pressure, and the yellow oil thus obtained, and presumed to contain the dimethyl ketal of compound **12**, was immediately subjected to the reaction conditions defined in step iii.

Step iii. A magnetically stirred solution of the oil obtained from step ii in THF (10 mL) was treated with HCl (5 mL of a 1 M aqueous solution) and the resulting mixture stirred at room temperature for 0.5 h before being quenched with $NaHCO_3$ (20 mL of a saturated aqueous solution) and then extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (1 × 50 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica, 1:10 → 1:5 v/v ethyl acetate/petroleum ether gradient elution), and concentration of relevant fractions (R_f = 0.3 in 1:2 v/v ethyl acetate/petroleum ether) afforded the title compound **13** (880 mg, 88%) as a white solid: mp = 60−63 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.41−7.29 (complex m, 5H), 4.53 (ABq, J = 10.0 Hz, 2H), 3.65−3.49 (complex m, 2H), 2.63 (dd, J = 17.1 and 6.2 Hz, 1H), 2.53 (m, 1H), 2.49−2.32 (complex m, 4H), 2.15−2.08 (complex m, 1H), 2.06−1.87 (complex m, 3H), 1.66−1.46 (complex m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 209.0, 138.1, 128.5, 127.8, 127.7, 117.4, 73.2, 67.3, 45.7, 40.3, 39.0, 36.7, 32.0, 29.8, 22.2; IR ν_{max} 2855, 2245, 1713, 1454, 1424, 1361, 1200, 1098, 739, 699 cm^{-1}; MS (ESI, +ve) m/z 294 [$(M + Na)^+$, 100]; HRMS $(M + Na)^+$ calcd for $C_{17}H_{21}NNaO_2$ 294.1470, found 294.1464

*rac-2-((1R,2S)-2-(2-(Benzyloxy)ethyl)-5-oxocyclohex-3-en-1-yl)-acetonitrile (**14**).* A magnetically stirred solution of ketone **13** (680 mg, 2.5 mmol) in DMSO (10 mL) was treated with *p*-TsOH·H_2O (143 mg, 0.8 mmol) and IBX (1.02 g, 3.6 mmol) and then heated at 55 °C for 18 h. The cooled reaction mixture was quenched with $NaHCO_3$ (15 mL of a saturated aqueous solution) and then filtered through a pad of diatomaceous earth. The solids thus retained were washed with ethyl acetate (3 × 20 mL), and the separated aqueous phase associated with the filtrate was extracted with ethyl acetate (3 × 40 mL). The combined organic phases were washed with brine (1 × 50 mL) and then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash chromatography (silica, 1:9 → 1:3 v/v ethyl acetate/petroleum ether gradient elution), and concentration of relevant fractions (R_f = 0.2 in 1:2 v/v ethyl acetate/petroleum ether) afforded the title compound **14** (389 mg, 58%) as a clear, colorless oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.32−7.20 (complex m, 5H), 6.78 (dd, J = 10.2 and 3.3 Hz, 1H), 5.97 (dd, J = 10.2 and 2.3 Hz, 1H), 4.43 (broadened s, 2H), 3.52 (m, 2H), 2.66−2.24 (complex m, 6H), 1.96−1.69 (complex m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.8, 152.2, 137.8, 129.1, 128.5, 127.9, 127.7,

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117.5, 73.3, 67.1, 41.4, 37.7, 35.8, 31.9, 21.7; IR ν_{max} 3032, 2863, 2246, 1676, 1454, 1421, 1391, 1355, 1251, 1095, 740, 699 cm^{-1}; MS (ESI, +ve) m/z 292 [$(M + Na)^+$, 100]; HRMS $(M + Na)^+$ calcd for $C_{17}H_{19}NNaO_2$ 292.1313, found 292.1310.

*rac-2-((1R,2S)-2-(2-(Benzyloxy)ethyl)-4-iodo-5-oxocyclohex-3-en-1-yl)acetonitrile (**15**).* A magnetically stirred solution of enone **14** (300 mg, 1.1 mmol) in $CHCl_3$/pyridine (4 mL of a 1:1 v/v mixture) maintained at room temperature was treated, dropwise, with a solution of molecular iodine (1.0 g, 3.6 mmol) in $CHCl_3$/pyridine (15 mL of a 1:1 v/v mixture). The solution thus obtained was stirred at room temperature for 3 h and then treated with water (10 mL). The separated aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic phases were washed, sequentially, with HCl (1 × 20 mL of a 1 M aqueous solution), $Na_2S_2O_3$ (1 × 20 mL of a 10% w/v aqueous solution), and brine (1 × 20 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash chromatography (silica, 1:6 → 1:3 v/v ethyl acetate/petroleum ether gradient elution), and concentration of relevant fractions (R_f = 0.3 in 1:2 v/v ethyl acetate/petroleum ether) afforded the title compound **15** (370 mg, 84%) as a clear, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65 (d, J = 3.3 Hz, 1H), 7.48−7.30 (complex m, 5H), 4.53 (ABq, J = 10.1 Hz, 2H), 3.62 (m, 2H), 2.90 (dd, J = 16.3 and 4.0 Hz, 1H), 2.80−2.74 (complex m, 1H), 2.68−2.40 (complex m, 4H), 2.06−1.81 (complex m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.0, 160.8, 137.7, 128.6, 128.0, 127.8, 117.1, 102.6, 73.4, 66.8, 42.2, 40.4, 35.9, 31.5, 21.5; IR ν_{max} 3030, 2922, 2861, 2245, 1682, 1588, 1453, 1418, 1362, 1329, 1098, 738, 698 cm^{-1}; MS (ESI, +ve) m/z 418 [$(M + Na)^+$, 100]; HRMS $(M + Na)^+$ calcd for $C_{17}H_{18}INNaO_2$ 418.0280, found 418.0279.

*rac-2-((4R,5S)-5-(2-(Benzyloxy)ethyl)-2′-nitro-2-oxo-2,3,4,5-tetrahydro[1,1′-biphenyl]-4-yl)acetonitrile (**16**).* A magnetically stirred solution of iodide **15** (300 mg, 0.76 mmol) and *o*-iodonitrobenzene (378 mg, 1.5 mmol) in DMSO (5 mL) was treated with $Pd_2(dba)_3$ (55 mg, 0.06 mmol) and Cu powder (195 mg, 3.1 g.atom). The resulting mixture was heated at 90 °C for 0.5 h before being cooled to room temperature and then diluted with ethyl acetate (10 mL). The ensuing mixture was filtered through diatomaceous earth and the solids thus retained washed with ethyl acetate (3 × 10 mL). The combined filtrates were washed with water (2 × 30 mL) and the combined aqueous phases extracted with ethyl acetate (3 × 30 mL). The combined organic phases were themselves washed with brine (1 × 30 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica, 1:10 → 1:4 v/v ethyl acetate/petroleum ether gradient elution), and concentration of relevant fractions (R_f = 0.2 in 1:2 v/v ethyl acetate/petroleum ether) gave the title compound **16** (261 mg, 88%) as a yellow, crystalline solid: mp = 74−78 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (dd, J = 7.9 and 1.5 Hz, 1H), 7.61−7.47 (complex m, 2H), 7.41−7.29 (complex m, 5H), 7.13 (dd, J = 7.3 and 1.7 Hz, 1H), 6.91 (d, J = 3.9 Hz, 1H), 4.55 (ABq, J = 10.5 Hz, 2H), 3.69 (t, J = 5.7 Hz, 2H), 2.92 (broad s, 1H), 2.87−2.77 (complex m, 1H), 2.72−2.54 (complex m, 4H), 2.15−1.94 (complex m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.7, 148.5, 148.1, 138.6, 137.8, 133.5, 131.6, 131.2, 129.1, 128.5, 127.9, 124.4, 117.7, 73.4, 67.4, 41.1, 38.3, 35.6, 32.4, 21.7 (one signal obscured or overlapping); IR ν_{max} 3031, 2923, 2862, 2245, 1679, 1523, 1351, 1100, 854, 739, 699 cm^{-1}; MS (ESI, +ve) m/z 413 [$(M + Na)^+$, 100]; HRMS $(M + Na)^+$ calcd for $C_{23}H_{22}N_2NaO_4$ 413.1477, found 413.1481.

*rac-(1R,5R,12S)-12-(2-(Benzyloxy)ethyl)-2,3,4,5,6,7-hexahydro-1H-1,5-methanoazocino[4,3-b]indole (**17**).* A magnetically stirred mixture of nitrile **16** (310 mg, 0.79 mmol), *p*-TsOH·H_2O (747 mg, 4.0 mmol), and Raney cobalt (620 mg, 200% w/w) in THF (15 mL) and maintained under dihydrogen was heated at 50 °C for 3 h. The resulting mixture was cooled to room temperature and filtered through diatomaceous earth, and the solids thus retained washed with methanol (3 × 20 mL). The combined filtrates were concentrated under reduced pressure to afford a pale-yellow oil that was subjected to flash chromatography (silica, 1:20 → 1:10 v/v methanol/dichloromethane gradient elution). Concentration of relevant fractions (R_f = 0.4 in 1:7 v/v methanol/dichloromethane) afforded the title compound **17** (165 mg, 60%) as a clear, yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05 (s, 1H), 7.40 (d, J = 7.5 Hz, 1H), 7.29−7.19 (complex m, 6H), 7.11−6.95 (complex m, 2H), 4.39 (s, 2H), 4.23 (s, 1H), 3.43 (m, 2H), 2.93 (dd, J = 17.5 and 6.6 Hz, 1H), 2.66−2.36 (complex m, 3H), 2.31−2.14 (complex m, 3H), 1.99−1.79 (complex m, 1H), 1.62−1.48 (complex m, 1H), 1.46−1.38 (complex m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.5, 136.3, 135.8, 128.3, 127.7, 127.5, 126.8, 121.1, 119.4, 117.4, 110.6, 107.4, 72.9, 68.6, 49.0, 39.0, 37.0, 34.1, 31.3, 30.4, 25.7; IR ν_{max} 3190, 3054, 2916, 2854, 1618, 1453, 1362, 1236, 1094, 1073, 735, 697 cm^{-1}; MS (ESI, +ve) m/z 347 [$(M + H)^+$, 100]; HRMS $(M + H)^+$ calcd for $C_{23}H_{27}N_2O$ 347.2123, found 347.2122.

*tert-Butyl rac-(1R,5R,12S)-12-(2-(Benzyloxy)ethyl)-1,3,4,5,6,7-hexahydro-2H-1,5-methanoazocino[4,3-b]indole-2-carboxylate (**18**).* A magnetically stirred solution of secondary amine **17** (100 mg, 0.29 mmol) in dichloromethane (5 mL) was treated with Boc_2O (76 mg, 0.35 mmol) and triethylamine (121 μL, 0.87 mmol). The ensuing mixture was stirred at room temperature for 0.5 h, quenched with water (20 mL), and extracted with dichloromethane (3 × 20 mL). The combined organic phases were washed with brine (1 × 30 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash chromatography (silica, 1:9 → 1:3 v/v ethyl acetate/petroleum ether gradient elution), and concentration of relevant fractions (R_f = 0.6 in 1:1 v/v ethyl acetate/petroleum ether) afforded the title compound **18** (129 mg, 99%) as a white, crystalline solid and a ca. 1:1 mixture of rotamers: mp = 148−152 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90 (broad s, 1H), 7.65 (d, J = 6.9 Hz, 1H), 7.41−7.27 (complex m, 6H), 7.13 (m, 2H), 5.50 (s, 1H), 4.51 (q, J = 11.9 Hz, 2H), 3.77 (m, 1H), 3.57 (t, J = 6.4 Hz, 2H), 3.06 (dd, J = 17.5 and 6.6 Hz, 1H), 2.62 (m, 2H), 2.32 (broad s, 1H), 2.24 (m, 1H), 1.94 (m, 1H), 1.74−1.58 (complex m, 3H), 1.53 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.1, 154.7, 138.5, 136.4, 136.2(4), 136.2(1), 135.4, 128.5, 128.4, 127.7, 127.6(3), 127.6(0), 127.5(5), 127.0, 126.2, 121.3, 119.5, 119.4, 118.1, 110.6, 110.4, 107.2, 79.4, 79.3, 73.1(0), 73.0(6), 68.5, 68.2, 46.3, 38.6, 36.6, 35.7, 33.3, 30.8, 30.7, 30.4, 29.8, 28.7, 28.6, 28.6, 28.5, 26.7, 25.2; IR ν_{max} 3300, 2975, 2928, 2868, 1659, 1454, 1415, 1355, 1168, 1115, 740, 698 cm^{-1}; MS (ESI, +ve) m/z 469 [$(M + Na)^+$, 100]; HRMS $(M + Na)^+$ calcd for $C_{28}H_{34}N_2NaO_3$ 469.2467, found 469.2470.

*tert-Butyl rac-(1R,5S,12S)-12-(2-(Benzyloxy)ethyl)-6-oxo-1,3,4,5,6,7-hexahydro-2H-1,5-methanoazocino[4,3-b]indole-2-carboxylate (**19**).* A magnetically stirred solution of compound **18** (80 mg, 0.18 mmol) in dichloromethane (5 mL) was treated with pyridinium chlorochromate (96 mg, 0.45 mmol) and the ensuing mixture stirred at room temperature for 3 h and then quenched with 2-propanol (3 mL). The resulting mixture was treated with water (15 mL) and then extracted with dichloromethane (3 × 20 mL). The combined organic phases were washed with brine (1 × 30 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash chromatography (silica, 1:9 → 1:4 v/v ethyl acetate/petroleum ether gradient elution), and concentration of relevant fractions (R_f = 0.5 in 1:2 v/v ethyl acetate/petroleum ether) afforded the title compound **19** (47 mg, 57%) as a clear, yellow oil and a ca. 1:1 mixture of rotamers: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.03 (m, 1H), 7.84 (d, J = 8.2 Hz, 0.5H), 7.69 (d, J = 8.1 Hz, 0.5H), 7.43−7.18 (complex m, 7H), 7.11 (m, 1H), 5.75 (s, 0.5H), 5.62 (s, 0.5H), 4.54−4.28 (complex m, 2H), 3.88 (m, 0.5H), 3.69 (m, 0.5H), 3.44 (t, J = 6.2 Hz, 2H), 2.70 (broad s, 1H), 2.63−2.53 (complex m, 1H), 2.44 (broad s, 1H), 2.06−1.75 (complex m, 2H), 1.60 (m, 2H), 1.51 (s, 4.5H), 1.35 (s, 4.5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.4, 154.9, 154.2, 138.3, 132.3, 128.4, 127.6, 127.4, 125.4, 125.3, 122.8, 121.8, 121.1, 112.7, 112.3, 80.4, 79.9, 73.1, 67.8, 48.3, 47.1, 46.6, 43.6, 43.1, 36.8, 35.6, 32.0, 30.1, 28.6, 28.4; IR ν_{max} 3257, 2975, 2930, 2862, 1655, 1470, 1407, 1356, 1276, 1253, 1152, 1117, 746, 734 cm^{-1}; MS (ESI, +ve) m/z 483 [$(M + Na)^+$, 100]; HRMS $(M + Na)^+$ calcd for $C_{28}H_{32}N_2NaO_4$ 483.2260, found 483.2257.

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*tert-Butyl (1R,5S,12S)-12-(2-Hydroxyethyl)-6-oxo-1,3,4,5,6,7-hexahydro-2H-1,5-methanoazocino[4,3-b]indole-2-carboxylate (**20**).* A magnetically stirred solution of compound **19** (35 mg, 0.08 mmol) in THF (8 mL) was treated with Pd/C (3.5 mg of 10% w/w material). The resulting mixture was stirred at room temperature for 16 h under an atmosphere of dihydrogen and then filtered through diatomaceous earth, and the solids thus retained were washed with ethyl acetate (3 × 15 mL). The combined filtrates were concentrated under reduced pressure to afford a light yellow oil that was subjected to flash chromatography (silica, 1:4 → 1:2 v/v ethyl acetate/petroleum ether gradient elution). Concentration of the relevant fractions (R_f = 0.1 in 1:1 v/v ethyl acetate/petroleum ether) afforded the title compound **20** (28 mg, 99%) as a clear, yellow oil and a ca. 1:1 mixture of rotamers: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.04 (broad s, 1H), 7.83 (broad s, 0.5H), 7.71 (broad s, 0.5H), 7.46−7.26 (complex m, 2H), 7.12 (m, 1H), 5.74 (broad s, 0.5H), 5.58 (broad s, 0.5H), 3.87 (broad s, 0.5H), 3.72−3.60 (complex m, 2.5H), 2.74 (broad s, 1H), 2.59 (broad s, 1H), 2.44 (m, 1H), 2.00 (m, 1H), 1.88 (m, 1H), 1.60 (m, 2H), 1.53 (m, 4.5H), 1.35 (s, 4.5H) (signal due to hydroxyl group proton not observed); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.7, 155.0, 154.2, 138.6, 132.3, 127.4, 125.3, 122.9, 122.6, 121.7, 121.2, 112.8, 112.5, 80.2, 60.3, 48.5, 46.8, 43.2, 42.7, 36.8, 35.5, 34.8, 30.1, 28.5, 28.4; IR ν_{max} 3274, 2923, 2853, 1653, 1409, 1366, 1277, 1252, 1150, 1013, 746 cm^{-1}; MS (ESI, +ve) m/z 393 [(M + Na)$^+$, 100]; HRMS (M + Na)$^+$ calcd for $C_{21}H_{26}N_2NaO_4$ 393.1790, found 393.1790.

*rac-(1R,5S,6R,15S)-1-Methyl-1,3,4,5,6,11-hexahydro-6,1,5-(epiminopropane[1,3,3]triyl)oxocino[3,4-b]indole (**22**).* *Step i.* A magnetically stirred solution of ketone **20** (25 mg, 0.07 mmol) in THF (4 mL) was cooled to −78 °C and then treated with methyllithium (135 μL of a 3.0 M solution in diethoxymethane). The resulting mixture was stirred at −78 °C for 0.5 h and then quenched with water (15 mL). After the resulting mixture was warmed to room temperature, the aqueous phase was extracted with dichloromethane (3 × 20 mL), and the combined organic phases were washed with brine (1 × 30 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing yellow oil, presumed to contain the anticipated *tert*-alcohol, was subjected to the step ii of the reaction sequence as described immediately below.

Step ii. A magnetically stirred solution of the yellow oil obtained from step i in dichloromethane (4 mL) was treated with trifluoroacetic acid (26 μL, 0.35 mmol). The resulting mixture was stirred at room temperature for 16 h and then concentrated under reduced pressure to afford a yellow oil that was subjected to flash chromatography (silica, 1:20 → 1:10 v/v methanol/dichloromethane gradient elution). Concentration of relevant fractions (R_f = 0.4 in 1:3 v/v methanol/dichloromethane) afforded the title compound **22** (10.3 mg, 57%) as a clear, yellow oil: ^{1}H NMR ($CDCl_3$, 800 MHz) δ 8.15 (s, 1H), 7.68 (d, J = 7.9 Hz, 1H), 7.41 (d, J = 8.1 Hz, 1H), 7.23 (m, 1H), 7.17 (m, 1H), 4.43 (broad s, 1H), 3.47 (m, 1H), 2.91 (m, 1H), 2.60 (broad s, 1H), 2.50 (broad s, 1H), 2.44 (broad s, 1H), 2.12 (broad s, 1H), 2.03 (m, 1H), 1.91−1.79 (complex m, 2H), 1.70−1.67 (complex m, 1H), 1.67 (s, 3H), 1.54 (dd, J = 13.9 and 4.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 136.6, 134.8, 124.8, 122.8, 120.2, 119.1, 111.4, 70.7, 60.3, 50.0, 41.5, 36.5, 36.4, 29.5, 26.4, 22.3 (signal due to one carbon obscured or overlapping); IR ν_{max} 3259, 2930, 1454, 1382, 1323, 1306, 1037, 1070, 912, 876, 830, 731 cm^{-1}; MS (ESI, +ve) m/z 269 [(M + H)$^+$, 65], 252 (100); HRMS (M + H)$^+$ calcd for $C_{17}H_{21}N_2O$ 269.1654, found 269.1656.

*rac-(1R,5S,6R,15S)-1,12-Dimethyl-1,3,4,5,6,11-hexahydro-6,1,5-(epiminopropane[1,3,3]triyl)oxocino[3,4-b]indole [(±)-**1**].* A magnetically stirred solution of the secondary amine **22** (10 mg, 0.04 mmol) in acetonitrile (4 mL) was treated, sequentially, with formaldehyde (67 μL of a 35% w/v aqueous solution, 0.8 mmol), acetic acid (40 μL of a 30% w/v aqueous solution, 0.2 mmol), and $NaCNBH_3$ (5 mg, 0.08 mmol). The resulting mixture was stirred at room temperature for 0.5 h and then quenched with $NaHCO_3$ (10 mL of a saturated aqueous solution). The separated aqueous phase was extracted with dichloromethane (3 × 20 mL), and the combined organic phases were washed with brine (1 × 30 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash chromatography (silica, 1:25 → 1:10 v/v methanol/dichloromethane gradient elution), and concentration of relevant fractions (R_f = 0.5 in 1:3 v/v methanol/dichloromethane) afforded the title compound **1** (8.4 mg, 80%) as a light-yellow, crystalline solid: mp = 122−125 °C. ^{1}H NMR ($CDCl_3$, 800 MHz) δ 8.31 (s, 1H), 7.60 (dd, J = 7.9 and 1.0 Hz, 1H), 7.40 (dt, J = 8.1 and 0.9 Hz, 1H), 7.21 (m, 1H), 7.15 (m, 1H), 4.08 (s, 1H), 3.43 (dd, J = 11.7 and 7.6 Hz, 1H), 2.62 (m, 1H), 2.51 (broad s, 1H), 2.40 (broad s, 1H), 2.38 (s, 3H), 2.09−1.88 (complex m, 4H), 1.85 (m, 1H), 1.65 (s, 3H), 1.50 (m, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 136.3, 135.2, 127.2, 122.4, 120.0, 119.9, 111.3, 108.4, 71.1, 60.6, 57.4, 45.6, 44.3, 40.5, 37.5, 29.5, 26.8, 22.2; IR ν_{max} 3230, 3054, 2930, 1457, 1380, 1324, 1305, 1194, 1083, 1029, 740, 625, 615 cm^{-1}; MS (ESI, +ve) m/z 283 [(M + H)$^+$, 100]; HRMS (M + H)$^+$ calcd for $C_{18}H_{23}N_2O$ 283.1810, found 283.1807.

Crystallographic Studies. *Crystallographic Data. Compound (±)-**1**:* $C_{18}H_{22}N_2O$, M = 282.39, T = 150 K, monoclinic, space group $P2_1$, Z = 4, a = 8.2370(2) Å, b = 21.2108(4) Å, c = 8.4707(2) Å; β = 98.7489(19)°; V = 1462.72(6) Å^3, D_x = 1.282 g cm^{-3}, 5741 unique data ($2\theta_{max}$ = 144.6°), R = 0.052 [for 5497 reflections with $I > 2.0\sigma(I)$]; wR = 0.137 (all data), S = 1.00.

*Compound **16**:* $C_{23}H_{22}N_2O_4$, M = 390.44, T = 150 K, triclinic, space group $P\bar{1}$, Z = 2, a = 5.8560(2) Å, b = 11.9176(4) Å, c = 15.3239(4) Å; α = 109.830(4)°, β = 97.254(3)°, γ = 99.900(3); V = 971.19(7) Å^3, D_x = 1.335 g cm^{-3}, 3819 unique data ($2\theta_{max}$ = 144.6°), R = 0.041 [for 3382 reflections with $I > 2.0\sigma(I)$]; wR = 0.105 (all data), S = 0.99.

*Compound **18**:* $C_{28}H_{34}N_2O_3$, M = 446.59, T = 150 K, monoclinic, space group $P2_1/n$, Z = 4, a = 10.2934(2) Å, b = 10.7138(2) Å, c = 22.2707(3) Å; β = 90.0949(14)°; V = 2456.04(7) Å^3, D_x = 1.208 g cm^{-3}, 4848 unique data ($2\theta_{max}$ = 144.6°), R = 0.038 [for 4609 reflections with $I > 2.0\sigma(I)$]; wR = 0.097 (all data), S = 1.00.

Structure Determination. Images were measured on a diffractometer (Cu Kα, mirror monochromator, λ = 1.54184 Å) fitted with an area detector and the data extracted using the CrysAlis package.[18] The structure solutions were solved by direct methods (SIR92).[19] The structures of compounds (±)-**1**, **16**, and **18** were refined using the CRYSTALS program package.[20] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 1482400, 1482401, and 1482402). These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk or by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01424.

Anisotropic displacement ellipsoid plots derived from the single-crystal X-ray analyses of compounds (±)-**1**, **16**, and **18** and ^{1}H and ^{13}C NMR spectra of compounds **9**−**20**, **22**, and (±)-**1** (PDF)

X-ray crystallographic data for (±)-**1** (CIF)

X-ray crystallographic data for **16** (CIF)

X-ray crystallographic data for **18** (CIF)

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Notes

The authors declare no competing financial interest.

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