Practical Total Synthesis of RS-15385[1]

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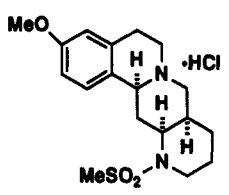
Introduction

The 6*H*-isoquino[2,1-*g*][1,6]naphthyridine RS-15385 (1) is a highly potent and selective antagonist of the α_2-adrenoreceptor which was reported by Clark and coworkers in 1989.[2] The compound displays an intriguing structural homology with α-yohimbine (2) and has proven to be a useful probe in neuropharmacology.[3] The potential of this agent for the treatment of male sexual dysfunction (impotence)[4] has prompted studies in this laboratory to develop a chemical synthesis amenable to kilogram-scale production.



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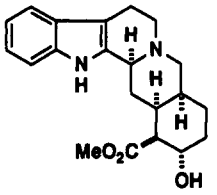

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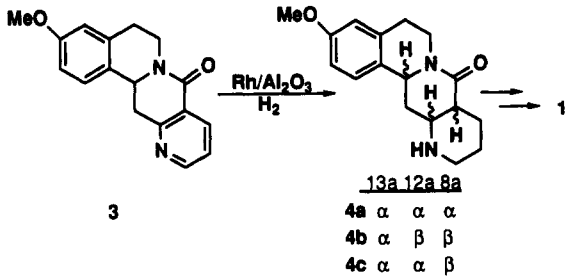
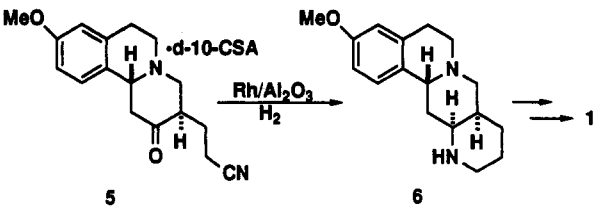
Clark first prepared 1 utilizing an elegant lithiated *o*-toluamide condensation which afforded pyridine 3 as a key intermediate (Scheme I).[2a] The pyridine 3 was saturated to yield a mixture of piperidines **4a–c**, from which the desired optical and geometric isomer was isolated by derivatization and chromatography. An asymmetric route was also reported[5] (Scheme II) which utilized an extension of the Openshaw–Whittaker synthesis of (–)-emetine. Optically pure nitrile 5 was prepared and reductively cyclized to tetracyclic piperidine 6. This approach efficiently introduced the absolute stereochemistry but required a costly C–H inversion as the final step to set the relative stereochemistry. This paper details a third route to 1 which employs novel annulation chemistry to construct the tetracyclic framework and which relies on a practical classical resolution procedure to isolate the desired stereoisomer.

Scheme I



Scheme II



Results and Discussion

N-Formylation of 3-methoxyphenethylamine (7),[6] followed by Bischler/Napieralski cyclization with phosphorus pentachloride afforded the starting material, 6-methoxy-3,4-dihydroisoquinoline (**9a**), in 83% yield (Scheme III). The high yield and mild reaction conditions make PCl_5 the reagent of choice for preparation of this compound.[2b,7] The crude product, containing ~5% of the 8-methoxy regioisomer **9b**, could be carried into the next step without purification.

On treatment of **9a** with dimethyl 1,3-acetonedicarboxylate (10, DAD) in water, the 1:1 adduct 11 formed spontaneously as a flocculent precipitate.[8] Impurity **9b** did not condense with DAD, presumably for steric reasons, and was readily separated. The adduct 11 was remarkably insoluble in both water and organic solvents and yet quite labile; addition of acids, organic bases, or heating caused rapid dissociation into the components **9a** and 10. On the other hand, direct treatment of the suspension of 11 in water with aqueous sodium or potassium hydroxide (4.5 equiv) induced lactam formation and concurrent ester hydrolysis, so that upon acidification (4.5 equiv of HCl) and decarboxylation keto amide 12 was isolated in 64% yield.

Annulation of the final ring was also accomplished in a one-pot reaction sequence. Heating 12 with 3-bromopropylamine hydrobromide and 2,6-lutidine in refluxing 1-butanol afforded tetracyclic enamide 14 in 81% yield after recrystallization from aqueous methanol. The intermediate bromo propyl enamide 13 could be isolated after briefly heating the mixture to 70 °C[9] but cyclized in situ upon heating above 100 °C. Less hindered bases like pyridine could not be used since they were N-alkylated by this intermediate primary bromide. This novel annulation of 1,3-diones to give 2-substituted-3-acyl-1,4,5,6-tetrahydropyridines[10] is a reaction of some generality. This is exemplified by the condensation of 3-bromopropylamine

(1) Contribution No. 866 from the Institute of Organic Chemistry, Syntex Discovery Research, Palo Alto, CA.

(2) (a) Clark, R. D.; Repke, D. B.; Kilpatrick, A. T.; Brown, C. M.; MacKinnon, A. C.; Clague, R. U.; Spedding, M. *J. Med. Chem.* **1989**, *32*, 2034. (b) Clark, R. D.; Repke, D. B.; Berger, J.; Nelson, J. T.; Kilpatrick, A. T.; Brown, C. M.; MacKinnon, A. C.; Clague, R. U.; Spedding, M. *Ibid.* **1991**, *34*, 705.

(3) (a) Clark, R. D.; Spedding, M.; MacFarlane, C. B. *Brit. J. Pharmacol.* **1990**, *99*, 123P. (b) Brown, C. M.; Clague, R. U.; Kilpatrick, A. T.; MacKinnon, A.; Martin, A. B.; Spedding, M. *Ibid.* **1990**, *99*, 272P. (c) MacKinnon, A. C.; Brown, C. M.; Kilpatrick, A. T.; Spedding, M. *Ibid.* **1991**, *100*, 377P.

(4) (a) *Pharmaprojects*; Hutton, I.; Ed.; PJB Publications: Richmond, Surrey, UK, 1992; Vol. 13 (G5), p 648a. (b) Clark, R. D.; Michel, A. D.; Whiting, R. L. *Progress in Medicinal Chemistry*; Ellis, G. P., West, G. B., Eds.; Elsevier: Amsterdam, 1986; Vol. 23, p 1.

(5) Clark, R. D.; Kern, J. R.; Kurz, L. J.; Nelson, J. T. *Heterocycles* **1990**, *31*, 353.

(6) Corrodi, H.; Jonsson, G. *Helv. Chim. Acta* **1966**, *49*, 798.

(7) (a) Guiland, J. M.; Virden, C. J. *J. Chem. Soc.* **1929**, 1791. (b) Euerby, M. R.; Waigh, R. D. *J. Chem. Res., Synop.* **1987**, 36. (c) Whaley, W. M.; Grovindachari, T. R. *Org. React.* **1951**, *6*, 74.

(8) Schneider, W.; Kammerer, E.; Schilken, K. *Pharm.* **1966**, *21*, 26.

(9) Akhrem, A. A.; Chernov, Y. G. *Synthesis* **1980**, 996.

(10) Quan, P. M.; Quin, L. D. *J. Org. Chem.* **1966**, *31*, 2487.

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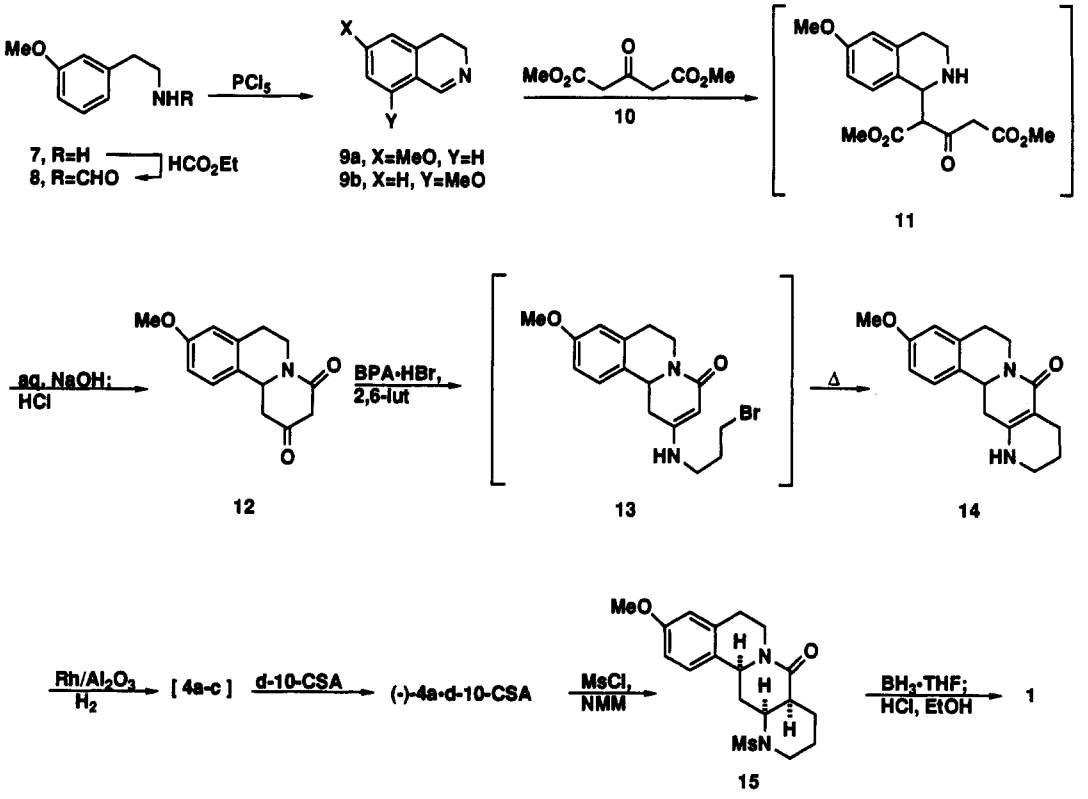
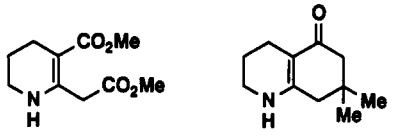
Scheme III



with DAD which gave adduct **16** in 73% yield and reaction with 5,5-dimethyl-1,3-cyclohexanedione (dimedone) which gave **17** in 61% yield.



16 17

Reduction of **14** with rhodium or platinum on alumina in acetic acid gave a quantitative yield of a mixture of piperidines, with **4a**:**4b**:**4c** as the major components in a 65:28:4 ratio. The hydrogenation products of enamide **14** closely paralleled those reported by Clark for pyridine **3**, implying that **14** is in fact an intermediate in the reduction of **3** to **4a–c**. Indeed, reduction of **3** with palladium on carbon in methanol[11] gave **14** in 95% yield, which on reduction with rhodium on alumina in acetic acid gave the usual mixture of **4a–c**. Chemical reduction of **14** with borane or borohydride reagents gave **4b** as the major product. Analysis of the mixtures was accomplished by derivatization of the secondary amines with (*R*)-(+)-α-methylbenzyl isocyanate ((*R*)-MBI).[12] Both enatiomers of the three major diastereomers could then be resolved in a single run (Figure 1a) on a standard RP-HPLC column.

Treatment of an acetone solution of the crude **4a–c** mixture with *d*-10-camphorsulfonic acid (0.4 equiv) reproducibly induced crystallization of the salt of the *single desired stereoisomer* **(−)-4a·*d*-10-CSA**, in 22–23.5% yield [based on (±)-**14**]. The first crop of crystals typically showed 0.5–1.3% of (±)-**4b** and 1.3–1.5% of (+)-**4a** as the only impurities (Figure 1b) and could be carried on without further manipulations.

Direct mesylation of the salt **(−)-4a·*d*-10-CSA** was accomplished in dichloromethane with 4-methylmorpholine as base. The mesyl lactam product **15** was isolated in 93% yield after crystallization from 2-propanol.

To complete the synthesis, lactam **15** was reduced with sodium borohydride and boron trifluoride etherate in THF.[13] After extractive workup, the crude product in ethanol was treated with concd aqueous HCl and upon crystallization, chemically and enatiomerically pure **1** was isolated in 92% yield.

In summary, a new total synthesis of RS-15385 (**1**) has been achieved utilizing the novel one-pot heterocyclic annulations **9a** → **12** and **12** → **14** and the remarkably efficient classical resolution of **(−)-4a·*d*-10-CSA**. This route has proven to be readily adaptable to kilogram-scale synthesis in that is uses relatively inexpensive commercial starting materials while avoiding chromatography, distillation, low temperature reactions, and organometallics reagents.

Experimental Section

General. All solvents and reagents were obtained commercially and were used without purification. All steps in the process have been repeated in 100-gal pilot plant equipment on at least ×25 the scale reported below without loss of yield.

***N*-Formyl-3-methoxyphenethylamine (8).** A solution of 3-methoxyphenethylamine (**7**) (1.00 kg, 6.61 mol), toluene (0.42 L), and ethyl formate (0.92 kg, 12.4 mol) was heated to reflux for 6 h. Volatile components were distilled in vacuo (80 °C, 20 Torr). The pale yellow oily residue of **8** (1.18 kg, 100%) assayed at >98.4% by HPLC (Zorbax Rx-C8, 40 °C, 70% 0.05 M KH_2PO_4 [pH = 6.2]/30% CH_3CN, 220 nm) and was used without purification: FT IR (film) 3885, 3054, 2939, 2868, 1665 cm^{-1}; ^1H

(11) Wenkert, E.; Dave, K. G.; Haglid, F. *J. Am. Chem. Soc.* **1965**, *87*, 5461.
(12) Demian, J.; Gripshover, D. F. *J. Chromatography* **1989**, *466*, 415.
(13) Brown, H. C.; Heim, P. *J. Org. Chem.* **1973**, *38*, 912.

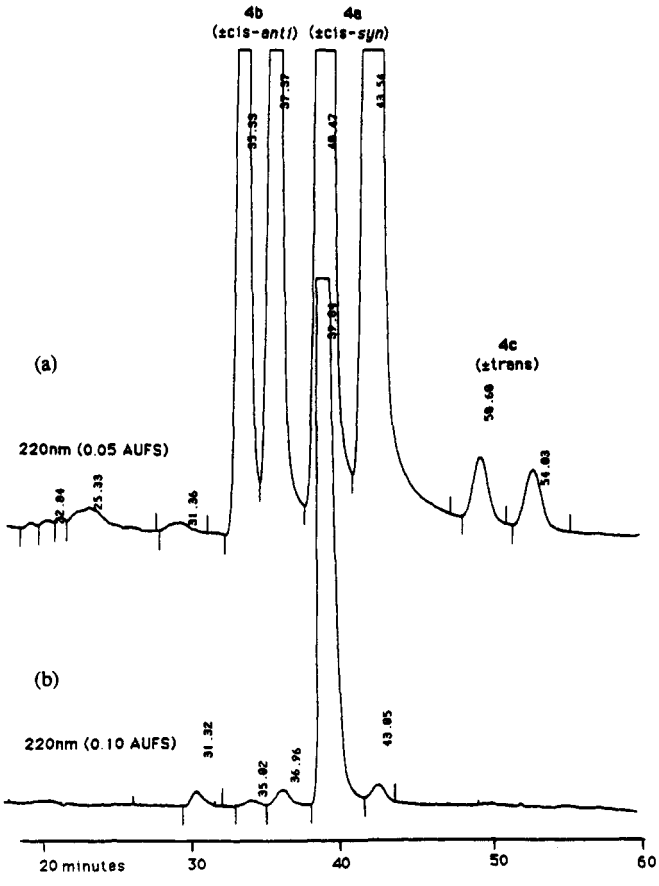


Figure 1. Reverse-phase HPLC separation of the enantiomers of piperidines **4a–c** as diastereomeric urea derivatives of (*R*)-MBI: (a) crude hydrogenation mixture; (b) first crop of resolved salt with *d*-10-CSA (23.5% yield). The major peak corresponds to (−)-**4a** (97% ee).

NMR ($CDCl_3$, 300 MHz) δ 8.00 (1 H, d, *J* = 1.5 Hz), 7.21 (1 H, m), 6.72 (3 H, m), 6.50 (1 H, bs), 3.73 (3 H, s), 3.47 (2 H, m), 2.75 (2 H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.6 (d), 159.7 (s), 140.3 (s), 129.6 (d), 121.0 (d), 114.4 (d), 111.8 (d), 55.1 (q), 39.2 (t), 35.5 (t); HRMS calcd for $C_{10}H_{13}NO_2$ 179.0946, found 179.0947. Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.95; H, 7.17; N, 8.01.

6-Methoxy-3,4-dihydroisoquinoline (9a). A solution of formamide **8** (1.18 kg, 6.61 mol) in CH_2Cl_2 (1.2 L) was added over 90 min to a well-stirred slurry of PCl_5 (1.54 kg, 7.40 mol) in CH_2Cl_2 (1.2 L). The temperature rose to 35–40 °C and the solvent refluxed as the exothermic reaction progressed. HCl gas was generated over the first half of the addition and was conveyed to a caustic scrubber. After being stirred for 30 min, the homogenous yellow reaction mixture was hydrolyzed by adding it in four portions to a well-stirred mixture of ice (3.6 kg) and hexane (1.1 L) (*Caution: delayed exotherm, recool fully between portions*). The aqueous acid (lower) layer containing **9**·HCl was separated. The organic residue was washed with water (0.8 L) and the combined aqueous layers were brought to pH > 12 by addition of 45% KOH (5.76 kg, 46.3 mol) (*Caution: strong immediate exotherm*). After cooling, the mixture was extracted with toluene (2 × 1.4 L) and the extracts were dried with Na_2SO_4. After filtration, the toluene was distilled in vacuo to leave an orange oil (1 kg) composed of a ~92:5:3 mixture of **9a**:**9b**:**7**. This material was typically used directly but could be purified by Kugelrohr distillation (110 °C, 1 mm) to afford a colorless oil, 0.88 kg (83%): FT IR (film) 2942, 2838, 1628, 1604, 1254 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.16 (1 H, bt, *J* = 2 Hz), 7.12 (1 H, d, *J* = 8.3 Hz), 6.71 (1 H, dd, *J* = 2.5, 8.4 Hz), 6.60 (1 H, d, *J* = 2.4 Hz), 3.74 (3 H, s), 3.66 (2 H, t, *J* = 8 Hz), 2.63 (2 H, t, *J* = 8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.6 (s), 159.7 (d), 138.4 (s), 129.0 (d), 128.2 (s), 113.0 (d), 112.0 (d), 55.3 (q), 46.9 (t), 25.5 (t); HRMS calcd for $C_{10}H_{11}NO$ 161.0841, found 161.0839. Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found (distilled): C, 74.28; H, 6.84; N, 8.74.

For **9b**, purified by column chromatography (Merck SG 60, 70–230 mesh, 5% MeOH/95% CH_2Cl_2): ^1H NMR ($CDCl_3$, 300 MHz) δ 8.72 (1 H, bt, *J* = 2 Hz), 7.28 (1 H, dd, *J* = 8.1, 7.8 Hz), 6.78 (1 H, d, *J* = 8.3 Hz), 6.72 (1 H, d, *J* = 7.5 Hz), 3.85 (3 H, s), 3.69 (2 H, dt, *J* = 2, 8 Hz), 2.67 (2 H, t, *J* = 8 Hz).

(±)-2,4-Dioxo-9-methoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (12). A well-stirred mixture of dihydroisoquinoline **9a** (0.98 kg, 92% purity, 6.08 mol) in water (7 L) was treated with dimethyl acetone-1,3-dicarboxylate (**10**) (1.0 kg, 5.74 mol) over 30 min. The adduct **11** separated as a thick precipitate. After the slurry was cooled to 15 °C, 50% NaOH (2.07 kg, 25.8 mol) was added in one portion. The resulting murky orange solution was stirred for 24 h and then was extracted with toluene (2 × 1.2 L) to remove unreacted **9b** and other impurities. The aqueous residue was brought to pH < 3 over 1 h with 37% HCl (2.6 kg, 26 mol) using ice–water cooling to maintain the temperature of <25 °C. CO_2 evolved and the dione **12** precipitated as an amorphous solid. After the slurry was aged for 12 h at 40 °C with vigorous stirring, the tan solid was filtered, washed with water (2 kg), and dried. After recrystallization from EtOH (12.5 L), **12** was obtained as off-white needles (0.92 kg, 64%): mp 153–4 °C; FT IR (KBr) 1726, 1657 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.05 (1 H, d, *J* = 8.6 Hz), 6.83 (1 H, dd, *J* = 2.6, 8.6 Hz), 6.73 (1 H, d, *J* = 2.6 Hz), 5.04 (1 H, dd, *J* = 3.2, 11.8 Hz), 4.70 (1 H, dt, *J* = 12.6, 3 Hz), 3.81 (3 H, s), 3.55 (1 H, d, *J* = 19 Hz), 3.41 (1 H, d, *J* = 19 Hz), 3.15–2.76 (4 H, m), 2.49 (1 H, dd, *J* = 11.8, 17 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.7 (s), 166.3 (s), 158.6 (s), 136.0 (s), 126.9 (d), 125.8 (s), 113.5 (d), 113.3 (d), 55.2 (q), 52.2 (d), 48.9 (t), 48.1 (t), 39.1 (t), 29.2 (t). Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.29; H, 6.28; N, 5.65.

For **11**, isolated by filtration and recrystallized from 2-propanol: mp 116–117 °C dec; FT IR (KBr) 1716, 1674 cm^{-1}. Anal. Calcd for $C_{17}H_{21}NO_6$: C, 60.89; H, 6.31; N, 4.18. Found: C, 60.97; H, 6.53; N, 4.04.

(±)-5,8,9,10,11,12,13,13a-Octahydro-3-methoxy-8-oxo-6*H*-isoquino[2,1-*g*][1,6]naphthyridine (14). A solution of ketone **12** (1.02 kg, 4.09 mol), 3-bromopropylamine·HBr (0.94 kg, 4.29 mol), 1-BuOH (4.2 L), and 2,6-lutidine (1.09 kg, 10.2 mol) was heated to reflux for 1 h. Complete conversion was verified on a dried (110 °C, 1 Torr, 5 min) aliquot by HPLC (Spherisorb ODS-2, 23 °C, 40% CH_3CN/60% H_2O, 220 nm). Volatiles were distilled in vacuo (100 °C, 20 Torr). The dry tan residue was crystallized from boiling MeOH (7.5 mL) on addition of water (6 L) preheated to 70 °C. The slurry was cooled to 10 °C with gentle stirring and the crude orange product was collected by filtration (protect **14** from light and air while impure). After recrystallization from aqueous MeOH, as above, and drying in vacuo (70 °C, 20 Torr) to constant weight, pure **14** was obtained as a flaky off-white solid (942 g, 81%): mp 202–4 °C; FT IR (KBr) 3422, 1605 cm^{-1}; UV (1:1 CH_3CN:H_2O) λ_{max} (log ε) 297 (4.13) 225 (4.21) nm; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.03 (1 H, d, *J* = 8.6 Hz), 6.75 (1 H, dd, *J* = 2.7, 8.6 Hz), 6.68 (1 H, d, *J* = 2.5 Hz), 4.81 (1 H, bs, NH), 4.76–4.61 (2 H, m), 3.78 (3 H, s), 3.25 (2 H, m), 2.91–2.26 (7 H, m), 1.94–1.82 (2 H, m); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 168.6 (s), 158.1 (s), 148.9 (s), 137.0 (s), 128.6 (s), 126.6 (d), 113.3 (d), 113.0 (d), 95.9 (s), 55.3 (q), 53.4 (d), 41.4 (t), 37.96 (t), 37.2 (t), 30.3 (t), 21.7 (t), 20.3 (t). Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.94; H, 7.14; N, 9.90.

For **13**, isolated by extractive workup and crystallized from 2-propanol: mp 160–1 °C; FT IR (KBr) 3430, 3283, 1617, 1593 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.05 (1 H, d, *J* = 8.6 Hz), 6.77 (1 H, dd, *J* = 2.6, 8.6 Hz), 6.69 (1 H, d, *J* = 2.6 Hz), 4.88 (1 H, s, NC=CH), 4.70 (2 H, m), 4.46 (1 H, bt, NH), 3.80 (3 H, s, OCH_3), 3.47 (2 H, t, *J* = 6.3 Hz, CH_2Br), 3.27 (2 H, q, *J* = 6 Hz), 2.87–2.49 (5 H, m), 2.18–2.13 (2 H, m). Anal. Calcd for $C_{17}H_{21}BrN_2O_2$: C, 55.90; H, 5.80; N, 7.67. Found: C, 55.96; H, 5.82; N, 7.67.

Methyl 3-carbomethoxy-1,4,5,6-tetrahydropyridine-2-acetate (16) was prepared from **10** in 73% yield, as described for compound **14**, except that Cl_3CCH_3 was used as solvent (reflux, 6 h). Pale yellow prisms were obtained on crystallization from EtOAc/hexane: mp 87–9 °C; FT IR (KBr) 3358, 1744, 1657, 1576,

1541 cm^{-1}; UV (1:1 CH_3CN:H_2O) λ_{max} (log ϵ) 291.5 (4.00) nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.62 (1 H, bs, NH), 4.05 (2 H, s), 3.73 (3 H, s), 3.64 (3 H, s), 3.22 (2 H, m), 2.40 (2 H, t, J = 6.2 Hz), 1.78 (2 H, m). Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57. Found: C, 55.80; H, 7.00; N, 6.47.

7,7-Dimethyl-1,2,3,4,5,6,7,8-octahydro-5-oxoquinoline (17) was prepared from dimedone in 61% yield, as described for compound 14. Fine colorless needles were obtained on crystallization from EtOAc/hexane: mp 176–182 °C; FT IR (KBr) 3426, 3238, 1572, 1524 cm^{-1}; UV (1:1 CH_3CN:H_2O) λ_{max} (log ϵ) 305 (4.39) nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.60 (1 H, bs, NH), 3.28 (2 H, m), 2.37 (2 H, t, J = 6.2 Hz), 2.22 (2 H, s), 2.14 (2 H, s), 1.81 (2 H, m), 1.06 (6 H, s). Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.36; H, 9.62; N, 7.74.

(−)-(8a*S*,12a*S*,13a*S*)-5,8,8a,9,10,11,12,12a,13,13a-Decahydro-3-methoxy-8-oxo-6*H*-isoquino[2,1-*g*][1,6]naphthyridine-*d*-10-Camphorsulfonic Acid Salt ((−)-4a-*d*-10-CSA). A well-stirred mixture of enamide 14 (942 g, 3.31 mol), 5% Rh/alumina (Degussa or Aldrich; 47.1 g, 0.023 mol), and HOAc (7.4 L) was maintained under H_2 (1.1 atm) for 6 days. After N_2 purging, the catalyst was removed by filtration on Celite. The filtrate was concentrated in vacuo (75 °C, 20 Torr) and residual HOAc was azeotropically distilled with toluene (2 × 5 L). The residual gummy piperidines 4a–c (1.4 kg) were dissolved in acetone (11 L) at 23 °C and treated with *d*-10-camphorsulfonic acid (307 g, 1.32 mol), giving a clear, brown solution. Crystallization commenced on stirring for ~15 min, or immediately on seeding. After 18 h of vigorous stirring at 20–23 °C, the solid was filtered and washed with acetone (2.5 L). Derivatization of a sample (3–5 mg), as its free base, dissolved in CH_2Cl_2 (1 mL) with (*R*)-MBI (120 mol %, 23 °C, 30 min) and analysis by HPLC (Spherisorb ODS-2, 40 °C, 68% 0.08 M $(NH_4)H_2PO_4$ [pH = 3]/32% CH_3CN, 220 nm) verified chemical and optical purity of >97%. Drying to constant weight at 45 °C left (−)-4a-*d*-10-CSA (403 g, 23.5%) as felty white tufts: mp 272 °C; $[\alpha]_D$ −44.4° (*c* 1, $CHCl_3$); FT IR (KBr) 3441, 2957, 1647, 1617 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.87 (2 H, vbs), 7.22 (1 H, d, J = 8.6 Hz), 6.90 (1 H, dd, J = 2.6, 8.6 Hz), 6.83 (1 H, d, J = 2.6 Hz), 4.81 (1 H, dd, J = 4.0, 11.4 Hz), 4.51 (1 H, m), 4.05 (1 H, m), 3.80 (3 H, s), 3.14–1.73 (19 H, m), 1.38 (2 H, m), 1.11 (3 H, s), 0.82 (3 H, s). Anal. Calcd for $C_{27}H_{38}N_2O_6S$: C, 62.52; H, 7.38; N, 5.40. Found: C, 62.52; H, 7.47; N, 5.56.

(−)-(8a*S*,12a*S*,13a*S*)-5,8,8a,9,10,11,12,12a,13,13a-Decahydro-3-methoxy-12-(methanesulfonyl)-8-oxo-6*H*-isoquino[2,1-*g*][1,6]naphthyridine (15). A suspension of (−)-4a-*d*-10-CSA (403 g, 0.777 mol) and 4-methylmorpholine (255 g, 2.53 mol) in CH_2Cl_2 (1.8 L) was cooled to 5–10 °C with an ice–water bath and treated dropwise with MsCl (150 g, 1.31 mol) over 1 h. Water (1.2 L) was added and the yellow organic layer was separated and combined with a CH_2Cl_2 washed (0.3 L). The combined organics were washed with 2 N HCl (1 L), dried over Na_2SO_4, and filtered. 2-Propanol (2.7 L) was added and CH_2Cl_2 was distilled out to a head temperature of 82 °C and a final volume of ~2 L. Crystallization commenced on cooling to 40 °C. After filtration, washing with 2-propanol (0.6 L), and drying to constant weight, mesyl lactam 15 was obtained as fine white needles (263 g, 93%): mp 134–6 °C; $[\alpha]_D$ −30° (*c* 1, CH_2Cl_2); FT IR (KBr) 1636, 1321, 1151 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.12 (1 H, d, J = 8.6 Hz), 6.78 (1 H, dd, J = 2.7, 8.6 Hz), 6.65 (1 H, d, J = 2.7 Hz), 4.73 (2 H, m), 4.44 (1 H, m), 3.78 (3 H, s), 3.69 (1 H, m), 2.95 (3 H, s), 2.97–2.65 (5 H, m), 2.50 (1 H, m), 2.19 (2 H, m), 1.78–1.45 (3 H, m); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.3 (s), 158.3 (s), 136.1 (s), 128.4 (s), 126.1 (d), 113.5 (d), 112.9 (d), 55.3 (q), 54.3 (d), 49.1 (q), 41.9 (d), 40.8 (d), 40.5 (t), 39.5 (t), 30.4 (t), 29.0 (t), 24.7 (t), 24.5 (t). Anal. Calcd for $C_{18}H_{24}N_2O_4S$: C, 59.32; H, 6.64; N, 7.69. Found: C, 59.39; H, 6.65; N, 7.74.

(+)-(8a*R*,12a*S*,13a*S*)-5,8,8a,9,10,11,12,12a,13,13a-Decahydro-3-methoxy-12-(methanesulfonyl)-6*H*-isoquino[2,1-*g*][1,6]naphthyridine Hydrochloride (1). A mixture of mesyl lactam 15 (253 g, 0.723 mol), $NaBH_4$ (54.5 g, 1.45 mol), and THF (3 L) was stirred under N_2 and chilled to 10 °C in an ice bath. Neat BF_3·OEt_2 (308 g, 2.17 mol) was added over 10 min. The slurry thickened and it was heated to reflux for 30 min. The mixture was cooled in ice and cautiously decomposed by dropwise addition of 1 N HCl (3 L). THF was distilled from the resulting clear solution until the head temperature reached 73 °C. On cooling, 6 N NaOH was added until pH > 12, and the mixture was extracted with CH_2Cl_2 (2 × 3 L). The combined extracts were diluted with EtOH (3 L) and the CH_2Cl_2 was distilled out until the head temperature reached 76 °C. Concd aqueous HCl (108 g, 1.08 mmol) was added to the hot solution and on cooling to 68 °C, 1 crystallized. After 12 h aging at 23 °C, the solid was filtered, washed with EtOH (0.8 L), and dried to constant weight affording 1 as fine white needles (253 g, 92%): mp 257–9 °C [lit.[2b] mp 265–6 °C]; $[\alpha]_D$ +14° (*c* 0.4, MeOH), [lit.[2b] $[\alpha]_D$ +13°]; FT IR (KBr) 3350, 1350, 1150 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 7.35 (1 H, d, J = 8.8 Hz), 7.02 (1 H, dd, J = 2.7, 8.8 Hz), 6.95 (1 H, d, J = 2.7 Hz), 4.82 (bs, HOD), 4.53 (2 H, m), 3.90 (3 H, s), 3.77 (2 H, m), 3.60 (2 H, m), 3.48 (2 H, m), 3.22 (3 H, s), 3.15 (2 H, m), 2.70 (1 H, m), 2.48 (2 H, m), 1.90 (3 H, m), 1.68 (1 H, m); ^{13}C NMR (75.4 MHz, D_2O) δ 159.7 (s), 133.9 (s), 127.2 (d), 124.0 (s), 114.4 (d), 114.4 (d), 63.3 (d), 59.6 (t), 56.4 (q), 53.2 (t), 51.8 (d), 41.1 (t), 40.8 (q), 34.1 (d), 27.9 (t), 26.4 (t), 25.4 (t), 23.3 (t). Anal. Calcd for $C_{18}H_{27}ClN_2O_3S$: C, 55.87; H, 7.03; N, 7.24. Found: C, 55.93; H, 7.03; N, 7.21. Chemical and optical purity of >99% was verified by the HPLC methods described previously.[2b]

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