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Karl G. Boldt [a], Michael S. Biggers [a], Sharnelle S. Phifer [a], George A. Brine [a] & Ken S. Rehder [a]
[a] Center for Organic and Medicinal Chemistry, RTI International, Research Triangle Park, North Carolina, USA
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Synthesis of (+)- and (−)-Tetrabenazine from the Resolution of α-Dihydrotetrabenazine

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Center for Organic and Medicinal Chemistry, RTI International, Research Triangle Park, North Carolina, USA

Abstract: Tetrabenazine (**1**) was reduced with $NaBH_4$ to α-dihydrotetrabenazine (**2**) and then resolved with di-*p*-toluoyl-L-tartrate and di-*p*-toluoyl-D-tartrate to subsequently give (+)- and (−)-α-dihydrotetrabenazine. The enantiomers were oxidized under Swern conditions to prepare samples of (+)-tetrabenazine and (−)-tetrabenazine. The samples were optically pure by chiral HPLC analysis.

Keywords: Dihydrotetrabenazine, resolution, tetrabenazine

Tetrabenazine (**1**) (Nitoman, Xenazine) is a drug used for treatment for hyperkinetic disorders and is a high-affinity inhibitor of the vesicular monoamine transporter in the mammalian brain.[1] In rodents and humans, tetrabenazine is rapidly metabolized by reduction of the 2-keto group to the α- and β-dihydrotetrabenazines (**2** and **3**).[2] As part of an ongoing research program, gram quantities of the optical isomers of **1** and **2** were required. The reported method involved preparative chiral high-performance liquid chromatographic (HPLC) separation of α-dihydrotetrabenazine or enzymatic resolution of the acetate ester, which provided small samples of the enantiomers of **2** but was difficult to scale up.[3] Reported herein is synthesis of the enantiomers of tetrabenazine and resolution of the enantiomers of α-dihydrotetrabenazine.

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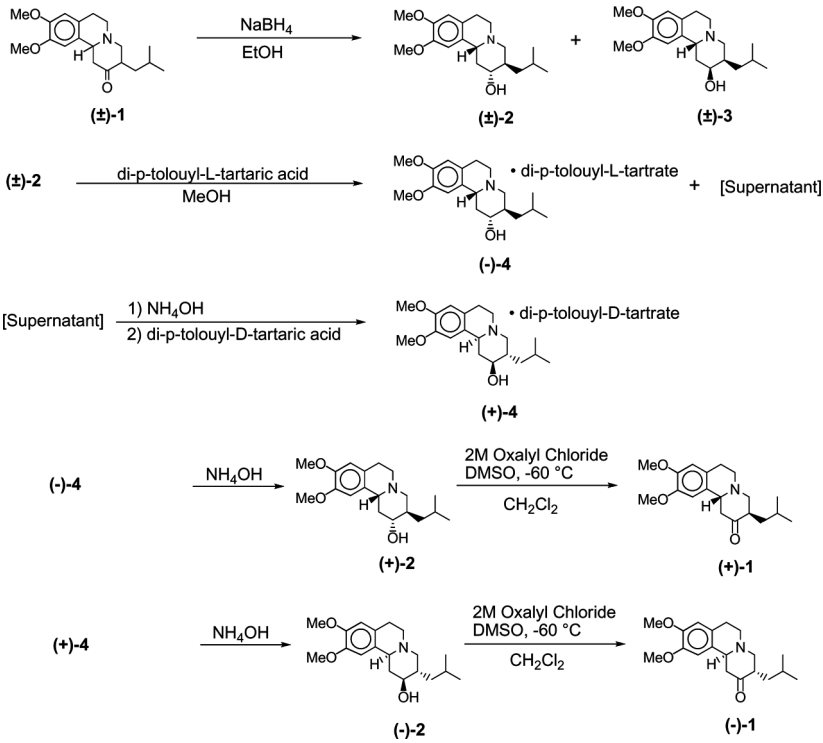
Address correspondence to Ken S. Rehder, Center for Organic and Medicinal Chemistry, RTI International, P. O. Box 12194, Research Triangle Park, NC 27709, USA. E-mail: krehder@rti.org



Scheme 1.

(±)-Tetrabenazine (**1**) was synthesized by the literature method.[4] Attempts to resolve **1** with chiral acids (di-*p*-toluoyl-D-tartaric acid, (+)-camphoric acid, or 1S-(+)-10-camphorsulfonic acid) were unsuccessful. Taking another approach, **1** was first reduced with $NaBH_4$ in ethanol (EtOH) to give a mixture of (±)-α-dihydrotetrabenazine (**2**) and (±)-β-dihydrotetrabenazine (**3**) in a 4:1 ratio as reported in the literature (Scheme 1).[5] The isomers were then separated by recrystallization from methanol (MeOH) to give pure (±)-**2**. Additional (±)-**2** was recovered from the filtrate by column chromatography for an overall yield of 64%.

Initially, a small sample (1 g) of (±)-**2** was treated with 1 equivalent of di-p-toluoyl-L-tartaric acid, and the salt was recrystallized (2×) from MeOH/acetone to give (+)-α-dihydrotetrabenazine di-p-toluoyl-L-tartrate [(−)-**4**]. [The (+)-α-dihydrotetrabenazine di-p-toluoyl-L-tartrate salt [(−)-**4**] has a (−) optical rotation and upon neutralization gives (+)-**2**. The (−)-α-dihydrotetrabenazine di-p-toluoyl-L-tartrate salt [(+)-**4**] has a (+) optical rotation and upon neutralization gives (−)-**2**]. Chiral HPLC analysis showed the salt was a single enantiomer and the (+)-isomer (as

the free base). The supernatant was evaporated under vacuum, and the residue was converted to the free base, which was treated with 1 equivalent of di-p-toluoyl-D-tartaric acid, and the salt was recrystallized (3×) from MeOH/acetone to give (−)-α-dihydrotetrabenazine di-p-toluoyl-D-tartrate [(+)-**4**]. Chiral HPLC analysis showed the salt was a single enantiomer and the (−)-isomer (as the free base). These resolved salt samples were used as seed crystals in larger scale resolutions. [The structural assignment of the absolute stereochemistry of (+)-**2** and (−)-**2**, and by analogy (+)-**1** and (−)-**1**, was made based on Ref. 3. However, this assignment has been questioned.[6] Because of this ambiguity, R/S designations were not used for the compounds herein.]

The resolution was repeated on a larger scale [22 g of (±)-**2**) to yield (−)-**4** and (+)-**4**. Each salt was ~95% enantiomerically pure by chiral HPLC analysis of the corresponding free base. The individual salts from two such large-scale-resolution batches were combined, recrystallized, and determined to be enantiomerically pure by chiral HPLC (as the free base). Overall, resolved (−)-**4** and (+)-**4** were obtained in 26% (52% theoretical) and 17% (34% theoretical) yield, respectively, from two batches of (±)-**2**.

Each salt was converted separately to the free base using concentrated aqueous NH_4OH followed by extraction. Compound (−)-**4** gave (+)-α-dihydrotetrabenazine [(+)-**2**] in 80% yield. Compound (+)-**4** gave (−)-α-dihydrotetrabenazine [(−)-**2**] in 74% yield. Chiral HPLC analysis showed each sample was 100% enantiomerically pure.

Samples of (+)-**2** and (−)-**2** were individually oxidized using Swern conditions[7] to give (+)-tetrabenazine [(+)-**1**] in 72% yield and (−)-tetrabenazine [(−)-**1**] in 74% yield. Chiral HPLC analysis showed each sample was 100% enantiomerically pure.

In summary, a resolution of (±)-α-dihydrotetrabenazine (**2**) using di-p-toluoyl-L-tartaric acid and di-p-toluoyl-D-tartaric acid followed by regeneration of optically pure samples of (+)-α-dihydrotetrabenazine [(+)-**2**] and (−)-α-dihydrotetrabenazine [(−)-**2**] is reported. The resolution is easily scaled up to produce gram quantities of the enantiomers. Subsequent Swern oxidation of the enantiomers of **2** to the enantiomers of **1** allows for the preparation of the optical isomers of tetrabenazine (**1**), which have not been previously reported in the literature.

EXPERIMENTAL

General

Melting points were obtained on a Thomas Hoover capillary apparatus and are corrected. Proton and carbon-13 nuclear magnetic resonance

(NMR) spectra were run on a Bruker Avance 300-MHz NMR spectrometer or a Varian AMX-500 NMR spectrometer. Mass spectra (MS) were run on a Perkin-Elmer Sciex API 150 EX mass spectrometer equipped with APCI (atmospheric pressure chemical ionization) or ESI (turbospray) sources. MS sample introduction was accomplished by means of an Agilent 1100 series liquid-chromatography system. Thin-layer chromatography (TLC) analyses were run on commercial precoated analytical silica-gel 60 F_{254} glass plates (E. Merck: 5×10 cm) using the solvent systems indicated. Spot visualization was achieved using a combination of 5% phosphomolybdic acid in EtOH and 10% ceric sulfate in 10% sulfuric acid followed by heating on a hot plate or with I_2. HPLC analysis were performed on a Rainin HPLC system utilizing two Rainin solvent pumps (25-mL pump heads), Rainin solvent mixer, Rheodyne injector, Varian dual-wavelength detector, and Power Macintosh 7200 running Rainin Dynamax software for gradient control and data handling. Chiral HPLC analysis was performed on a Varian system using a Varian Prostar 335 binary pump system, a Rheodyne injector, a Varian photodiode array (PDA) detector, and Varian Galaxie software (run on a Dell computer) for system operation and data handling. The column and solvents used for chiral purity analysis is defined hereinafter as system A: Phenomenex Chirex (S)-Valine (Val) and (R)-1-(α-naphthy)ethylamine (NEA) (250×4.6 mm) using isocratic 90% A/10% B at 1.0 mL/min with ultraviolet (UV) detection at 254 nm with solvent A being hexane/1,2-dichloroethane (5:1) and solvent B being 0.1% trifluoroacetic acid (TFA)/EtOH. Optical rotations were obtained using an Autopol IV automatic polarimeter (Rudolph Research Analytical Corporation) and a glass cell (1.5 mL volume, 100 mm pathlength). Column chromatography was performed on E. Merck silica gel 60, 230–400 mesh. In-house nitrogen gas (produced from liquid nitrogen) was utilized to supply an inert atmosphere. Elemental analyses were done by Atlantic Microlab Inc. (Norcross, GA).

(±)-α-Dihydrotetrabenazine (2)

Compound **1** (34.1 g, 0.107 mol) was dissolved in absolute EtOH (3.40 L) by warming. The resulting solution was stirred and cooled to 0 °C; then sodium borohydride was added (14.2 g, 0.376 mol). The reaction mixture was stirred at 0–3 °C for 3 h under N_2. The reaction mixture was checked by TLC (silica gel, EtOAc), which showed all the starting material had reacted. The reaction mixture was evaporated under vacuum to give a white solid. The solid was partitioned between CH_2Cl_2 (300 mL) and H_2O (300 mL), and the mixture was stirred overnight. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2

(2×150 mL). The CH_2Cl_2 layers were combined, dried (Na_2SO_4), filtered, and evaporated under vacuum to give a white solid (34.4 g). The solid was recrystallized from MeOH (50 mL) to give 17.9 g (52%) of (±)-**2** as white crystals: mp 164–168 °C (Lit.[8] 168 °C); TLC single spot, R_f 0.28, (silica gel, EtOAc); ^{1}H NMR ($CDCl_3$) δ 0.92 (3H, d, $J = 6.5$ Hz), 0.94 (3H, d, $J = 6.5$ Hz),1.05 (1H, m), 1.49 (1H, q, $J = 11.7$ Hz), 1.62 (1H, m), 1.75 (2H, m), 1.98 (1H, dd, $J = 11.4$, 11.3 Hz), 2.45 (1H, ddd, $J = 11.5$, 11.1, 4.6 Hz), 2.60 (1H, m), 2.63 (1H, m), 3.01 (1H, m), 3.06 (1H, m), 3.12 (1H, d, $J = 11.0$ Hz), 3.39 (1H, m), 3.84 (6H, s), 6.58 (1H, s), 6.68 (1H, s).

The filtrate was evaporated under vacuum to recover a yellow foamy solid (16.0 g). The solid was chromatographed on silica gel 60 (300 g) using 2% MeOH/CH_2Cl_2. Fractions were collected and checked by TLC (silica gel, EtOAc) before combination. Three samples resulted from the chromatography: 3.95 g (12%) of (±)-**2** as a white solid, 4.65 g (14%) of mixed α/β-dihydrotetrabenazine (**2**/**3**) as a white solid, and 2.74 g (8%) of β-dihydrotetrabenazine (**3**) as a white solid.

Resolution of (±)-α-Dihydrotetrabenazine (2)

Chiral HPLC Analysis Procedure

The resolution of (±)-**2** was monitored using system A. Samples of the di-p-toluoyltartrate salts were converted to the corresponding free bases for analysis. (+)-α-Dihydrotetrabenazine had a longer retention time than (−)-α-dihydrotetrabenazine under the analysis conditions. A standard of (±)-α-dihydrotetrabenazine was injected during each analysis to verify retention times and separation.

Small-Scale Resolution (Seed Crystals)

A solution of (±)-**2** (1.00 g, 3.13 mmol) in MeOH (40 mL) was obtained by warming on a steam bath. Di-p-toluoyl-L-tartaric acid (1.21 g, 3.13 mmol) was added to the solution. The resultant solution was evaporated to a white solid (2.30 g). This solid was recrystallized twice from acetone/MeOH to provide 0.551 g (25%) of (+)-α-dihydrotetrabenazine di-p-toluoyl-L-tartrate [(−)-**4**] as a white solid: mp 172–173 °C foaming, chiral HPLC single peak, t_R 10.2 min, (+)-isomer (99.6%). The filtrates from the recrystallizations were combined and evaporated to obtain a foamy pale yellow solid (1.33 g), which was suspended in H_2O (50 mL). Concentrated NH_4OH (20 drops) was added, and the mixture extracted with CH_2Cl_2 (2×50 mL). The combined CH_2Cl_2 layers were dried (Na_2SO_4) and evaporated to recover a yellow solid (0.70 g). The solid

(0.70 g, 2.19 mmol) was dissolved in MeOH (40 mL) by warming on a steam bath. Di-p-toluoyl-D-tartaric acid (0.847 g, 2.19 mmol) was added to the solution. The solution was evaporated to a yellow foamy solid (1.63 g). This solid was recrystallized three times from acetone/MeOH to give 0.313 g (14%) of (−)-α-dihydrotetrabenazine di-p-toluoyl-D-tartrate [(+)-**4**] as a white solid: mp 177–178 °C foaming, chiral HPLC major peak, t_R 9.4 min, (−)-isomer (100%). The analysis also showed a peak at t_R 10.52 min that was not from the (+)-isomer. The small samples of (−)-**4** and (+)-**4** were employed as seed crystals.

Large-Scale Resolution

The (±)-**2** (22.0 g, 0.069 mol) was dissolved in MeOH (300 mL) by warming, and di-p-toluoyl-L-tartaric acid (26.6 g, 0.069 mol) was added to the solution. The resulting solution was evaporated under vacuum to give an off-white foam (48.7 g). The foam was dissolved in MeOH (320 mL) and diluted with acetone (320 mL). The solution was concentrated to 320 mL, diluted to 640 mL with acetone, and concentrated to 320 mL. The resulting solution was seeded with (−)-**4** and allowed to stand at room temperature. After 7 days, the crystals were collected, washed with acetone, and dried under vacuum to give 14.9 g (31%) of (−)-**4**: mp 177–179 °C foaming; chiral HPLC major peak [95.4%, (+)-isomer free base], t_R 9.8 min, on system A.

The filtrate from the crystallization was evaporated under vacuum to give a yellow foamy solid (33.4 g). The solid was suspended in H_2O (100 mL), and concentrated NH_4OH (10 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 200 mL). The combined CH_2Cl_2 layers were dried (Na_2SO_4), filtered, and evaporated to recover a yellow solid (14.9 g). The solid (14.9 g, 0.047 mol) was dissolved in MeOH (200 mL) by warming, and di-p-toluoyl-D-tartaric acid (18.0 g, 0.047 mol) was added to the solution. The resulting solution was evaporated under vacuum to give a yellow foamy solid (32.7 g). The solid was dissolved in MeOH (400 mL), concentrated to 300 mL, and diluted with acetone (300 mL). The solution was concentrated to 300 mL, and diluted to 600 mL with acetone, and concentrated to 300 mL. The resulting solution was seeded with (+)-**4** and allowed to stand at room temperature. After 8 days, the crystals were collected, washed with acetone, and dried under vacuum to give 16.5 g (34%) of (+)-**4**: mp 179–180 °C foaming, chiral HPLC major peak [96%, (−)-isomer free base], t_R 9.2 min, on system A.

The filtrate was evaporated under vacuum to give a yellow foamy solid (16.0 g). The solid was suspended in H_2O (100 mL), and concentrated NH_4OH (5 mL) was added. The mixture was extracted with

CH_2Cl_2 (3 × 200 mL). The combined CH_2Cl_2 layers were dried (Na_2SO_4), filtered, and evaporated to recover 7.44 g (34% recovery) of a yellow solid of slightly enriched (+)-**2**.

(−)-α-Dihydrotetrabenazine Di-p-toluoyl-L-tartrate [(−)-4] (Salt of (+)-α-Dihydrotetrabenazine)

Two batches (14.9 g and 13.2 g) of (−)-**4** from the resolutions were combined, and 28.1 g were dissolved in boiling MeOH (500 mL), concentrated to 400 mL, diluted to 800 mL with acetone, concentrated to 400 mL, diluted with acetone to 800 mL, and concentrated to 300 mL. Crystallization started. After standing for 8 days, the crystals were collected, rinsed with acetone (100 mL), and vacuum dried at room temperature to give 19.9 g of (−)-**4** as white crystals: mp 182–183 °C foaming, chiral HPLC major peak [100%, (+)-isomer free base], t_R 10.2 min, on system A; $[\alpha]_D^{24^\circ}$ −49.4° (c 1.01, MeOH). Anal. calcd. for $C_{39}H_{47}NO_{11} \bullet 0.5\ H_2O$: C, 65.53; H, 6.77; N, 1.96. Found: C, 65.68; H, 6.58; N, 2.03.

The filtrate was concentrated to 80 mL and cooled to room temperature. After standing 2 days, the crystals were collected to give 4.25 g of (−)-**4** as white crystals: mp 178–179 °C foaming, chiral HPLC major peak [100%, (+)-isomer free base] t_R 9.8 min, on system A.

The filtrate was concentrated to 40 mL and cooled to room temperature. After standing 3 days, the crystals were collected to give 2.50 g of (−)-**4** as white crystals: chiral HPLC major peak [100%, (+)-isomer free base], t_R 10.0 min, on system A. The three recrystallized samples (26.6 g, 95% weight recovery) of (−)-**4** were used in the next reaction without further purification. A total of 26.6 g (26%) of (−)-**2** di-p-toluoyl-D-tartrate was prepared from 46.4 g of (±)-**2**.

(+)-α-Dihydrotetrabenazine Di-p-toluoyl-L-tartrate [(+)-4] (Salt of (−)-α-Dihydrotetrabenazine)

Two batches (16.5 g and 17.1 g) of (+)-**4** from the resolutions were combined, and 33.6 g were dissolved in boiling MeOH (550 mL), concentrated to 400 mL, diluted to 800 mL with acetone, concentrated to 400 mL, diluted with acetone to 800 mL, and concentrated to 300 mL. The solution was seeded with a crystal of (+)-**4**. After standing 2 days, the crystals were collected, rinsed with acetone (50 mL), and vacuum dried at room temperature to give 11.6 g of (+)-**4** as white crystals: mp

185–186 °C foaming, chiral HPLC major peak [100%, (−)-isomer free base], t_R 8.9 min, on system A; $[\alpha]_D^{24^\circ} + 46.4^\circ$ (c 1.03, MeOH). Anal. calcd. for $C_{39}H_{47}NO_{11}$: C, 66.37; H, 6.71; N, 1.98. Found: C, 66.35; H, 6.73; N, 2.05.

The filtrate was concentrated to 50 mL and cooled to room temperature. After standing 1 day, the crystals were collected to give 4.64 g of (+)-**4** as white crystals: mp 186–187 °C foaming, chiral HPLC major peak [100%, (−)-isomer free base], t_R 9.1 min, on system A.

The filtrate was concentrated to 40 mL and cooled to room temperature. After standing 1 day, the crystals were collected to give 1.25 g of (+)-**4** as white crystals: chiral HPLC major peak [100%, (−)-isomer free base], t_R 9.0 min, on system A. The three recrystallized samples (17.5 g, 52% weight recovery) of (+)-**4** were used in the next reaction without further purification. A total of 17.5 g (17%) of (+)-**2** di-p-toluoyl-D-tartrate was prepared from 46.4 g of (±)-**2**.

(+)-α-Dihydrotetrabenazine [(+)-2]

Compound (−)-**4** (26.6 g, 0.038 mol) was suspended in H_2O (350 mL), and concentrated NH_4OH (15 mL) was added, followed by CH_2Cl_2 (300 mL). The mixture was stirred for 15 min, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 300 mL). The CH_2Cl_2 layers were combined, dried (Na_2SO_4), filtered, and evaporated under vacuum to give a yellow foamy solid (12.0 g). The solid was chromatographed on silica gel 60 (400 g) using 2% MeOH/CH_2Cl_2. Fractions were collected and checked by TLC (silica gel, EtOAc), and similar fractions were combined and evaporated under vacuum to give a pale yellow solid (10.2 g). The solid was triturated with hexanes to give 9.68 g (80%) of (+)-**2** as a white solid: mp 106–108 °C, $[\alpha]_D^{24.7^\circ} + 62.4^\circ$ (c 1.066, MeOH), TLC single spot, R_f 0.74 [silica gel, $CHCl_3$/MeOH/concentrated NH_4OH (90:9:1)], chiral HPLC single peak (100%), t_R 9.4 min, on system A [The retention times during chiral HPLC analysis showed some variability, thus a co-injection strategy using racemic material was employed. Method A: chiral HPLC analysis in system A: (+)-**2** single peak, t_R 9.4 min; (±)-2 two peaks t_R 9.2 min and 10.0 min; and co-injection (+)-**2** and (±)-**2** two peaks, t_R 9.1 min (small peak) and 9.5 min (large peak)]; HPLC single peak (100%), t_R 7.7 min, on a Varian Dynamax C_{18} column (5 μ) (4.6 × 250 mm) using a gradient (25% B → 65% B over 30 min) at 1.0 mL/min with UV detection at 220 nm, with solvent A being 0.1% TFA/H_2O and solvent B being 0.1% TFA/CH_3CN; ^1H NMR ($CDCl_3$) (500 MHz) δ 0.92 (3H, d, $J = 6.5$ Hz), 0.94 (3H, d, $J = 6.5$ Hz), 1.06 (1H, ddd, $J = 13.7$, 9.7, 4.3 Hz), 1.49 (1H, q, $J = 11.4$ Hz), 1.58

(1H, ddd, $J = 13.5$, 10.2, 3.2 Hz), 1.63–1.79 (3H, m), 1.98 (1H, t, $J = 11.5$ Hz), 2.46 (1H, td, $J = 11.4$, 4.1 Hz), 2.58 (1H, ddd, $J = 12.4$, 4.6, 2.5 Hz), 2.64 (1H, dd, $J = 15.7$, 3.0 Hz), 3.00 (1H, ddd, $J = 11.3$, 5.9, 1.6 Hz), 3.04 (1H, dd, $J = 11.8$, 4.2 Hz), 3.06–3.10 (1H, m), 3.13 (1H, dd, $J = 11.8$, 3.2 Hz), 3.34–3.44 (1H, m), 3.84 (6H, s), 6.58 (1H, s), 6.68 (1H, s); ^{13}C NMR ($CDCl_3$) (125 MHz) δ 21.7, 24.1, 25.3, 29.1, 39.6, 40.5, 41.6, 51.9, 55.8, 55.9, 60.0, 60.9, 74.5, 107.8, 111.4, 126.3, 129.3, 147.1, 147.4; MS (ESI) (positive ion) m/z 320.2 (M + H). Anal. calcd. for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.15; N, 4.38. Found: C, 71.33; H, 9.10; N, 4.39.

(−)-α-Dihydrotetrabenazine [(−)-2]

Compound (+)-(**4**) (17.5 g, 0.025 mol) was suspended in H_2O (200 mL), and concentrated NH_4OH (10 mL) was added, followed by CH_2Cl_2 (200 mL). The mixture was stirred for 15 min, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (200 mL). The CH_2Cl_2 layers were combined, dried (Na_2SO_4), filtered, and evaporated under vacuum to give a yellow foamy solid (6.72 g). The solid (6.72 g) was chromatographed on silica gel 60 (275 g) using 2% MeOH/CH_2Cl_2. Fractions were collected and checked by TLC (silica gel, EtOAc), and similar fractions were combined and evaporated under vacuum to give a pale yellow solid (6.19 g). The solid was triturated with hexanes to give 5.85 g (74%) of (−)-(**2**) as an off-white solid: mp 107–108 °C; $[\alpha]_D^{24.6^\circ} - 59.1^\circ$ (c 1.248, MeOH); TLC single spot, R_f 0.74 [silica gel, $CHCl_3$/MeOH/concentrated NH_4OH (90:9:1)]; chiral HPLC single peak (100%), t_R 9.3 min, on system A [Co-injection strategy B: chiral HPLC analysis in system A: (−)-**2** single peak, t_R 9.3 min; (±)-**2** two peaks, t_R 9.6 min and 10.5 min; and co-injection (−)-**2** and (±)-**2** two peaks t_R 9.5 min (large peak) and 10.5 min (small peak)]; HPLC single peak (100%), t_R 7.5 min, on a Varian Dynamax C_{18} column (5 μ) (4.6 × 250 mm) using a gradient (25% B → 65% B over 30 min) at 1.0 mL/min with UV detection at 220 nm, with solvent A being 0.1% TFA/H_2O and solvent B being 0.1% TFA/CH_3CN; ^{1}H NMR ($CDCl_3$) (500 MHz) δ 0.92 (3H, d, $J = 6.5$ Hz), 0.94 (3H, d, $J = 6.5$ Hz), 1.06 (1H, ddd, $J = 13.6$, 9.7, 4.2 Hz), 1.49 (1H, q, $J = 11.5$ Hz), 1.58 (1H, ddd, $J = 13.4$, 10.2, 3.3 Hz), 1.64–1.78 (3H, m), 1.97 (1H, t, $J = 11.4$ Hz), 2.46 (1H, td, $J = 11.4$, 4.1 Hz), 2.58 (1H, ddd, $J = 12.3$, 4.5, 2.5 Hz), 2.64 (1H, dd, $J = 15.7$, 2.8 Hz), 3.00 (1H, ddd, $J = 11.3$, 5.9, 1.6 Hz), 3.04 (1H, dd, $J = 11.8$, 4.2 Hz), 3.06–3.10 (1H, m), 3.12 (1H, d, $J = 11.6$ Hz), 3.35–3.43 (1H, m), 3.84 (6H, s), 6.58 (1H, s), 6.68 (1H, s); ^{13}C NMR ($CDCl_3$) (125 MHz) δ 21.7, 24.1, 25.3, 29.1, 39.6, 40.5, 41.6, 51.9, 55.8, 55.9, 60.0, 60.9, 74.5,

107.8, 111.4, 126.3, 129.3 147.1, 147.4; MS (ESI) (positive ion) m/z 320.2 (M + H). Anal. calcd. for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.15; N, 4.38. Found: C, 71.51; H, 9.23; N, 4.40.

(+)-Tetrabenazine [(+)-1]

The chiral HPLC analyses of the tetrabenazine optical isomers were performed on a Regis (S, S) Whelk-01 10/100 column (4.6 × 250 mm) using 50:50 A/B (isocratic) at 2.0 mL/min with UV detection at 280 nm, and with solvent A being hexane/1,2-dichloroethane (5:1) and solvent B being 0.5% TFA/2-PrOH.

Under nitrogen in a three-neck, 1000-mL, round-bottom flask, CH_2Cl_2 (200 mL) was cooled in a dry ice/2-PrOH bath to −60 °C (internal reaction temperature), and 2.0 M oxalyl chloride in CH_2Cl_2 (8.9 mL, 17.8 mmol) was added by syringe. Afterward, dimethylsulfoxide (1.46 g, 18.7 mmol) was added by syringe, and the reaction mixture was stirred 5 min at −60 °C. A solution of (+)-α-dihydrotetrabenazine [(+)-**2**] (4.97 g, 15.5 mmol) in CH_2Cl_2 (50 mL) was added to the reaction mixture dropwise at −60 °C. Following the addition, the resultant reaction mixture was stirred at −60 °C for 2 h. Afterward, Et_3N (7.9 g, 0.078 mol) was added to the reaction mixture at −60 °C by syringe, and the mixture was allowed to warm to room temperature. It was then diluted with H_2O (200 mL), and the layers were separated. The CH_2Cl_2 layer was washed with additional H_2O (400 mL), dried (Na_2SO_4), and evaporated to obtain a yellow solid (5.12 g). This yellow solid was chromatographed on silica gel 60 (150 g), eluting with EtOAc and monitoring fractions by TLC (EtOAc). Appropriate fractions were combined and evaporated to recover a pale yellow solid (4.58 g). The 4.58 g sample was combined with a similar 1.12 g sample from a probe reaction. The resultant sample (5.70 g) was recrystallized from MeOH (20 mL) to give 4.46 g (72%) of (+)-**1** as white needles: mp 113–115 °C; $[\alpha]_D^{23^\circ}$ +71.6° (c 1.022, MeOH); TLC single spot, R_f 0.60, (EtOAc); chiral HPLC single peak (100%), t_R 5.89 min; analytical HPLC single peak (99.7%), t_R 6.19 min, on a Dynamax C_{18} column (4.6 × 250 mm) (5 μ) employing a gradient (40% B → 85% B over 15 min, then 85% B for 5 min) at 1.0 mL/min with UV detection at 220 nm, and with solvent A being 0.1% TFA/H_2O and solvent B being 0.1% TFA/CH_3CN; ^1H NMR ($CDCl_3$) δ 0.90 (3H, d, J = 6.0 Hz), 0.92 (3H, d, J = 6.0 Hz), 1.04 (1H, m), 1.65 (1H, m), 1.80 (1H, m), 2.35 (1H, dd, J = 12.0, 11.5 Hz), 2.54 (1H, m), 2.59 (1H, m), 2.71 (1H, m), 2.74 (1H, m), 2.89 (1H, dd, J = 14.0, 3.5 Hz), 3.09 (1H, m), 3.14 (1H, m), 3.28 (1H, dd, J = 11.0, 6.5 Hz), 3.50 (1H, d, J = 11.5 Hz), 3.80 (3H, s), 3.85 (3H, s), 6.54 (1H, s), 6.61 (1H, s);

^{13}C NMR ($CDCl_3$) δ 22.0, 23.2, 25.3, 29.3, 35.0, 47.4, 47.5, 50.5, 55.8, 55.9, 61.4, 62.4, 107.7, 111.3, 126.0, 128.4, 147.4, 147.7, 210.1; MS (ESI, positive ion) m/z 318.1 (M + H). Anal. calcd. for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.77; H, 8.64; N, 4.42.

(−)-Tetrabenazine [(−)-1]

Under nitrogen in a three-neck 1000-mL, round-bottom flask, CH_2Cl_2 (200 mL) was cooled in a dry ice/2-PrOH bath to −60 °C (internal reaction temperature) and 2.0 M oxalyl chloride in CH_2Cl_2 (11.6 mL, 2.3 mmol) was added by syringe. Afterward, dimethylsulfoxide (1.90 g, 2.4 mmol) was added by syringe, and the reaction mixture was stirred 5 min at −60 °C. A solution of (−)-α-dihydrotetrabenazine [(−)-**2**] (6.50 g, 20.3 mmol) in CH_2Cl_2 (50 mL) was added to the reaction mixture dropwise at −60 °C. Following the addition, the resultant reaction mixture was stirred at −60 °C for 2 h. Afterward, Et_3N (10.33 g, 0.102 mol) was added to the reaction mixture at −60 °C by syringe, and the mixture was allowed to warm to room temperature. It was then diluted with H_2O (250 mL), and the layers were separated. The CH_2Cl_2 layer was washed with additional H_2O (500 mL), dried (Na_2SO_4), and evaporated to obtain a yellow solid (6.51 g). This yellow solid was chromatographed on silica gel 60 (450 g), eluting with EtOAc and monitoring fractions by TLC (EtOAc). Appropriate fractions were combined and evaporated to recover a pale yellow solid (6.23 g). This solid was recrystallized from MeOH (20 mL) to provide 4.80 g (74%) of (−)-**1** as white needles: mp 113–115 °C; $[\alpha]_D^{23^\circ}$ − 69.7° (c 1.008, MeOH); TLC single spot, R_f 0.60, EtOAc; chiral HPLC single peak (100%), t_R 8.93 min; analytical HPLC single peak (99.7%), t_R 6.22 min, on a Dynamax C_{18} column (4.6 × 250 mm) (5 μ) using a gradient (40% B → 85% B over 15 min, then 85% B for 5 min) at 1.0 mL/min with UV detection at 220 nm, and with solvent A being 0.1% TFA/H_2O and solvent B being 0.1% TFA/CH_3CN. ^{1}H NMR ($CDCl_3$) δ 0.90 (3H, d, J = 6.0 Hz), 0.92 (3H, d, J = 6.0 Hz), 1.04 (1H, m), 1.65 (1H, m), 1.80 (1H, m), 2.35 (1H, dd, J = 11.5, 11.5 Hz), 2.54 (1H, m), 2.59 (1H, m), 2.71 (1H, m), 2.74 (1H, m), 2.89 (1H, dd, J = 13.5, 3.0 Hz), 3.09 (1H, m), 3.14 (1H, m), 3.28 (1H, dd, J = 11.0, 6.5 Hz), 3.50 (1H, d, J = 11.0 Hz), 3.82 (3H, s), 3.85 (3H, s), 6.54 (1H, s), 6.61 (1H, s); ^{13}C NMR ($CDCl_3$) δ 22.0, 23.2, 25.3, 29.3, 35.0, 47.4, 47.5, 50.5, 55.9, 55.9, 61.4, 62.4, 107.7, 111.4, 126.0, 128.4, 147.4, 147.7, 210.1; MS (ESI, positive ion) m/z 318.3 (M + H). Anal. calcd. for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.85; H, 8.61; N, 4.43.

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