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Synthesis of (±)-Tetrabenazine by Visible Light Photoredox Catalysis

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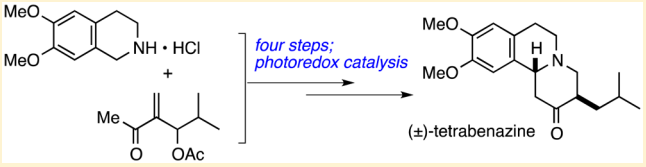
Supporting Information

ABSTRACT: (±)-Tetrabenazine was synthesized in six steps from commercially available compounds. The key cyclization substrate was assembled rapidly via Baylis–Hillman and aza-Michael reactions. Annulation of the final ring was achieved through visible light photocatalysis, wherein carbon–carbon bond formation was driven by the oxidation of a tertiary amine. Solvent played a critical role in the photoredox cyclization outcome, whereas methanol led to a mixed ketal, acetonitrile/water (10:1) gave direct cyclization to (±)-tetrabenazine and occurred more rapidly.



First prepared in the 1950s as an antipsychotic,[1,2] tetrabenazine (TBZ, (±)-**1**, Figure 1) has reemerged as a therapeutically useful compound for the treatment of hyperkinetic disorders. An important milestone for this benzo[*a*]-quinolizine came in 2008, when the FDA approved the racemic mixture of **1** for the treatment of Huntington's chorea in the United States.[3−5] Metabolically, TBZ is rapidly reduced to dihydrotetrabenazine (DTBZ, (±)-**2**), which is responsible for most of the pharmacological activity. Both TBZ and its metabolite, DTBZ, reversibly bind to vesicular monoamine transporter 2 (VMAT2) with nanomolar affinities.[6,7] VMAT2 is responsible for shuttling monoamines into the presynaptic vesicles from the neuronal cytoplasm.[8] Inhibition of VMAT2 directly decreases neurotransmitters available for release and further indirectly depletes monoamine levels, as those stranded in cytoplasm become degraded by monoamine oxidases. The value of these compounds extends beyond the treatment of hyperkinetic disorders. The high VMAT2 affinity of (+)-(2*R*,3*R*,11b*R*)-DTBZ (K_i 0.97 nM) has spurred the development of radiolabeled analogues that are valuable imaging agents for diagnosing neurological conditions.[9−15] Furthermore, Parkinsonian tremors can be modeled by dosing rodents with TBZ to induce tremulous jaw movements.[16]

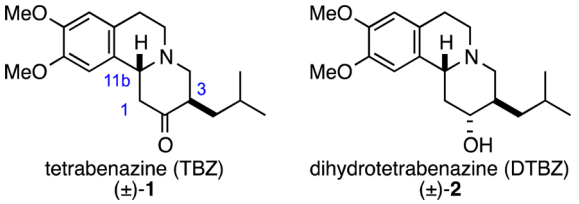
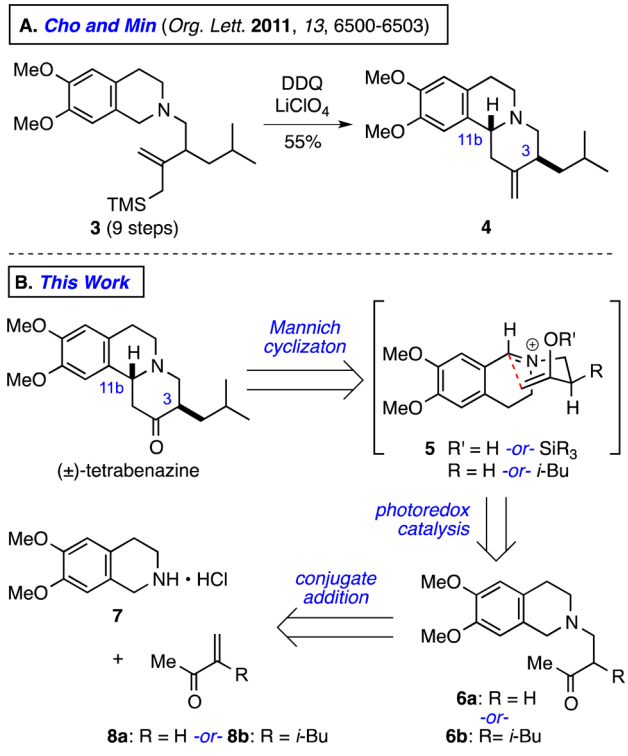


Figure 1. Tetrabenazine and dihydrotetrabenazine.

TBZ and DTBZ's compelling pharmacology has stimulated the development of several methods for the preparation of these alkaloids,[2,17−23] as well as the synthesis of numerous analogues.[11,24−27] Our synthetic approach was inspired by a late-stage oxidative aza-Prins cyclization strategy that was reported by Cho, Min, and co-workers (Scheme 1A).[21] In that work, stoichiometric DDQ oxidized tertiary amine **3** to an iminium ion, which cyclized with a tethered allylsilane to provide **4**. Tetrabenazine and dihydrotetrabenazine were subsequently obtained through additional oxidation state adjustments. A key finding of their work was that the iminium

Scheme 1. Prior Work and Retrosynthetic Analysis of Tetrabenazine



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ion cyclization occurred stereoselectively, establishing the correct relative stereochemistry between C-11b and C3. We envisioned that a related approach involving an oxidative Mannich cyclization would offer advantages with respect to step and redox economies (Scheme 1B).[28] In principle, the cyclization substrate would be available through the conjugate addition of tetrahydroisoquinoline **7** to an appropriately functionalized enone, exemplified by **8a**/**8b**.

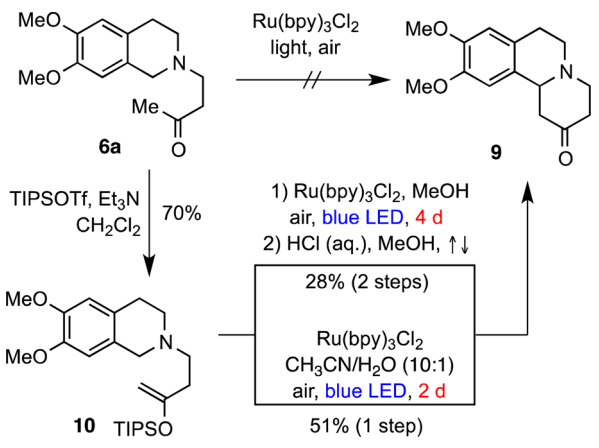
Furthermore, we recognized this as an opportunity to examine a more environmentally benign alternative to stoichiometric oxidants in the context of a target-directed synthesis. A number of aerobic methods have been developed for oxidative Mannich-type couplings of carbon nucleophiles with relevant tertiary amines,[29] including those mediated by transition metals, such as Cu[30−33] and Fe,[34,35] as well as other catalytic radical initiators, such as triarylaminium radical salts,[36] I_2,[37,38] and SO_2Cl_2.[39] Visible light photocatalysis has emerged as a capable and environmentally benign method for driving redox processes.[40−46] Specifically, Stephenson, and others, have shown that *N*-aryltetrahydroisoquinolines are excellent substrates for visible light photoredox catalysis.[47−53] We elected to pursue photoredox catalysis for the cyclization of **6** to TBZ based on our own work in this area that demonstrated that *N*-alkylated tetrahydroisoquinolines, as well as other tertiary amines, remain viable substrates for oxidation under these conditions.[54] *N*-Alkylated tetrahydroisoquinolines[55] have slightly more positive redox potentials compared to *N*-aryl analogues.[56,57] This could partially explain why oxidative coupling reactions of *N*-alkylated tetrahydroisoquinolines are not as developed as their *N*-aryl counterparts.[58] Diverse nucleophiles can be coupled with iminium ions generated under photoredox conditions, including enol ethers and ketones, although the later must be activated through enamine catalysis.[59−62] Although intermolecular couplings of *N*-arylte-trahydroisoquinolines generally require an excess of the nucleophilic partner, we reasoned that the proposed cyclization of **6a**/**6b** to TBZ would be facilitated by the high effective concentration inherent with an intramolecular process.

An important question was whether a ketone or an enol ether would be optimal for the cyclization (Scheme 2). This was addressed through the rapid preparation of **6a** in 93% yield through the reaction of tetrahydroisoquinoline **7** and methyl vinyl ketone in the presence of aqueous NaOH. Unfortunately, we were unable to identify conditions for the direct cyclization of **6a** to **9** under standard photoredox conditions with $Ru(bpy)_3Cl_2$. Cyclization of **6a** was also attempted in the presence of proline or pyrrolidine·TFA, conditions that have been effective for oxidative couplings of ketones with tetrahydroisoquinoline,[61,62] but annulation did not occur in this case. ^{1}H NMR analysis of the crude reaction mixture confirmed the presence of starting material **6a** and a component whereby the benzylic position of the tetrahydroisoquinoline ring had been oxidized to give an amide. Oxidation of some of this material to an amide was supported by the disappearance of its benzylic CH_2 singlet at 3.5 ppm and the downfield shift of an aromatic CH singlet from 6.51 to 7.55 ppm in the ^{1}H NMR spectrum. Our group, as well as others, has observed the oxidation of tetrahydroisoquinolines to amides under photoredox conditions.[54,63−65] We reasoned that the low levels of nucleophile, formed through keto/enol tautomerization or via catalytic formation of the enamines through 2° amine catalysis, were insufficient to compete with the undesired oxidation pathway. Thus, we converted **6a** to TIPS enol ether **10** and found that it cyclized slowly under photoredox conditions in MeOH to provide a mixed methyl triisopropylsilyl ketal that was immediately hydrolyzed to ketone **9** (28% yield for two steps). Two factors contributed to the poor yield of **9**. Conversion for the cyclization of **10** to the mixed ketal was incomplete, even after 4 d, and ketone **9** was difficult to purify by chromatography as it coeluted with TIPSOH. We attempted the photoredox cyclization of **10** in CH_3CN/H_2O (10:1) in hopes of avoiding the formation of the mixed ketal and the extra hydrolysis step. Fortunately, **10** cyclized directly to **9** in 51% yield after only 2 d of irradiation in this system. Gagné has noted that water as a cosolvent can improve the rates of photocatalytic reactions and posited that this rate enhancement stems from resolvation of the catalyst after reductive quenching, which decreases the rate of competing back-transfer reactions.[66]

Pleased that the photoredox cyclization would be a viable approach, we turned our attention to the preparation of branched substrate **6b** (Scheme 3). In addition to directly providing TBZ, the cyclization of **6b** should be more facile compared to **6a** due to gauche interactions present within the side chain, which should serve to preorganize the side chain and decrease the activation energy. The first step to prepare this substrate involved modified conditions for a known Baylis−Hillman reaction between methyl vinyl ketone (**8a**) and isobutyraldehyde,[67] followed by acetylation, to provide **12**. Treating **12** with commercially available tetrahydroisoquinoline salt **7** in the presence of aqueous hydroxide promoted rapid conjugate addition, which was accompanied by spontaneous *β*-elimination of acetate, forming enone **14** as a 6:1 mixture of *E*:*Z* isomers. Selective reduction of the alkene in **14** was not trivial—several conditions for 1,4-hydride delivery instead predominantly gave the undesired 1,2-reduction product.[68−71] Hydrogenation under acidic conditions ultimately proved to be a rapid and high yielding process, giving **6b** in 79% yield. Addition of TFA was essential in this reaction, as hydrogenolysis of the benzylic amine and other side products were formed in its absence. Standard conditions were then used to convert **6b** to TIPS enol ether **15**, which could be purified by chromatography.

Photoredox cyclization of **15** was accomplished using a blue LED light source with the standard $Ru(bpy)_3Cl_2$ catalyst. NMR analysis of the resulting mixed ketal **16** was complicated by the presence of multiple diastereomers, so it was immediately hydrolyzed by refluxing in aqueous HCl to provide

Scheme 2. Proof-of-Principle Photoredox Cyclization



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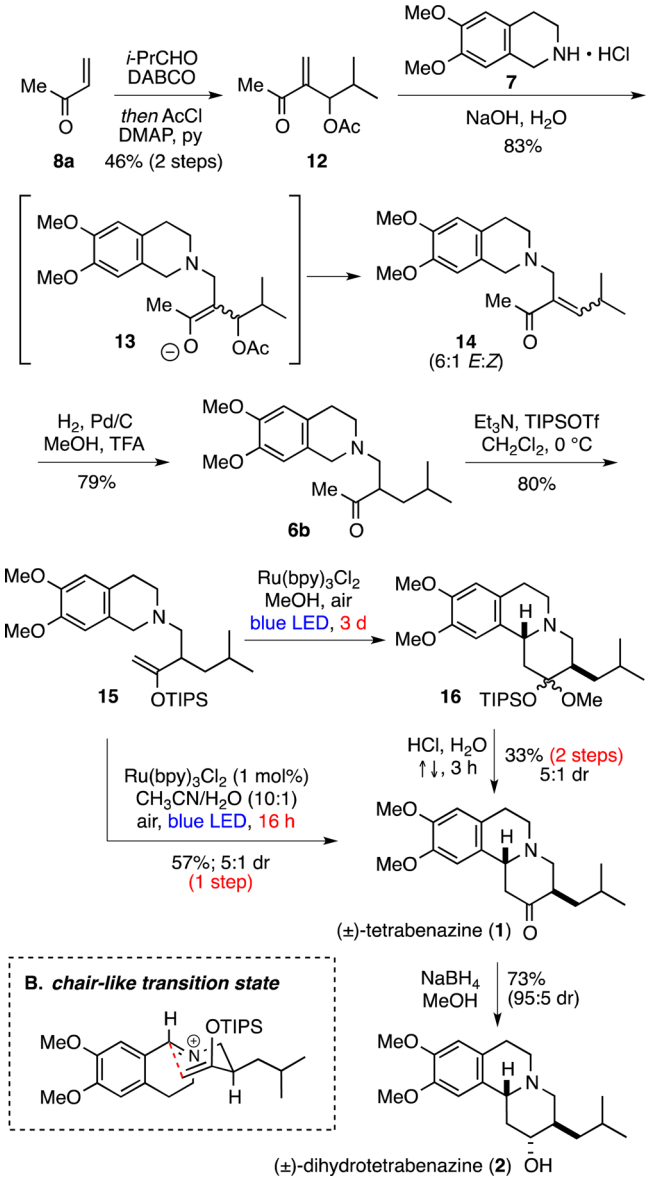
Scheme 3. Synthesis of (±)-Tetrabenazine



(±)-tetrabenazine (**1**) in 33% yield over two steps (5:1 dr). Although this represented a modest improvement in yield compared to the oxidative cyclization of **10** in MeOH, this sequence remained relatively inefficient due to incomplete conversion after 3 d and the need for an additional step to hydrolyze the ketal. Once again, CH_3CN/H_2O was a superior solvent system providing complete conversion of **15** to (±)-tetrabenazine after only 16 h.[66] It is interesting to note that both solvent systems ultimately provided **1** with identical diastereoselectivity. Unfortunately, we were unable to separate these diastereomers and thus could not investigate whether this is a kinetic or thermodynamic ratio. Finally, tetrabenazine (**1**) was reduced to dihydrotetrabenazine (**2**) by $NaBH_4$ reduction. The diastereoselectivity for this reduction was consistent with Rishel's results,[18] where **2** was formed in 73% yield as a 95:5 mixture, favoring the shown α-diastereomer.

In summary, (±)-tetrabenazine was prepared in six steps from commercially available materials. Application of the Baylis–Hillman and aza-Michael reactions enabled the rapid preparation of the tetrabenazine framework. Key observations from photoredox cyclization included the identification of silyl enol ether as the optimal nucleophile, and the critical role of solvent. Whereas cyclization of **15** in methanol led to the formation of mixed ketals, the desired ketone was obtained directly by changing the solvent to acetonitrile/water, which also improved the reaction rate. This work demonstrates the viability of photoredox catalysis as a key step for the synthesis of polycyclic alkaloids.

EXPERIMENTAL SECTION

4-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)butan-2-one (6a). Methyl vinyl ketone (1 mL, 11.0 mmol) was added to a solution of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (1.32 g, 5.74 mmol) in 2 M aqueous NaOH (3.5 mL). After stirring rapidly for 25 min, the reaction was diluted with water (20 mL), and extracted with ether (3 × 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to provide ketone **6a** (5.36 g, 93%) as a light tan syrup. This material was used immediately without further purification. **^{1}H NMR** ($CDCl_3$) δ 6.59 (1H, s), 6.52 (1H, s), 3.845 (3H, s), 3.838 (3H, s), 3.56 (2H, br s), 2.85–2.80 (4H, comp), 2.75–2.71 (4H, comp), 2.21 (3H, s); **^{13}C NMR** ($CDCl_3$) δ 207.9 (C), 147.5 (C), 147.2 (C), 126.1 (C), 125.9 (C), 111.2 (CH), 109.3 (CH), 55.9 (CH_3), 55.8 (CH_3), 55.6 (CH_2), 52.4 (CH_2), 51.0 (CH_2), 41.7 (CH_2), 30.2 (CH_3), 28.5 (CH_2); **IR** (film) 2912, 2833, 1709, 1516, 1226, 1129, 749 cm^{-1}; **HRMS** (CI) *m*/*z* 264.1604 [$C_{15}H_{22}NO_3$ (M + 1) requires 264.1600].

6,7-Dimethoxy-2-(3-((triisopropylsilyl)oxy)but-3-en-1-yl)-1,2,3,4-tetrahydroisoquinoline (10). Triethylamine (1 mL, 7.17 mmol) and TIPSOTf (1 mL, 3.72 mmol) were added sequentially to a room temperature solution of ketone **6a** (648.9 mg, 2.46 mmol) in CH_2Cl_2 (15 mL). After 1 h, the reaction mixture was treated with 2 M aqueous NaOH (50 mL). The resulting layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (alumina), eluting with EtOAc/hexanes (10:90, then 15:85) to provide TIPS enol ether **10** (723.6 mg, 70%) as a light yellow oil. **^{1}H NMR** ($CDCl_3$) δ 6.59 (1H, s), 6.52 (1H, s), 4.06 (2H, br s), 3.85 (3H, s), 3.84 (3H, s), 3.60 (2H, s), 2.83 (2H, t, *J* = 5.5 Hz), 2.77–2.73 (4H, comp), 2.38 (2H, AA'XX'), 1.22 (2H, m), 1.10 (18H, d, *J* = 7.0 Hz), 1.07 (1H, m); **^{13}C NMR** ($CDCl_3$) δ 158.0 (C), 147.4 (C), 147.1 (C), 126.6 (C), 126.1 (C), 111.3 (CH), 109.4 (CH), 89.6 (CH_2), 56.2 (CH_2), 55.9 (CH_3 × 2), 55.6 (CH_2), 51.1 (CH_2), 34.9 (CH_2), 28.7 (CH_2), 18.0 (CH_3 × 6), 12.6 (CH × 3); **IR** (film) 2944, 2866, 1517, 1216, 748 cm^{-1}; **HRMS** (CI) *m*/*z* 420.2927 [$C_{24}H_{42}NO_3Si$ (M + 1) requires 420.2934].

(±)-9,10-Dimethoxy-3,4,6,7-tetrahydro-1*H*-pyrido[2,1-*a*]isoquinolin-2(11b*H*)-one (9). A 20 mL vial was charged with a solution of TIPS enol ether **10** (270 mg, 0.643 mmol) and $Ru(bpy)_3Cl_2$ (5.6 mg, 0.0075 mmol) in MeOH (7.6 mL). The vial was sealed with a rubber septa, opened to the air with an 18 gauge needle, and was irradiated using a blue LED strip for 4 d at 45 °C. Although incomplete by TLC, solvent was removed under reduced pressure, and the residue was treated with 1 M aqueous HCl (4 mL) and MeOH (1 mL) and was refluxed for 1.5 h. The reaction mixture was cooled and treated with 2 M aqueous NaOH (10 mL). The resulting basic solution was extracted with CH_2Cl_2 (3 × 10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel), eluting with MeOH/CH_2Cl_2 (5:95) to provide **9** (47 mg, 28%) as a light yellow, waxy, solid. **mp** 153–154 °C; **^{1}H NMR** ($CDCl_3$) δ 6.63 (1H, s), 6.54 (1H, s), 3.86 (3H, s), 3.84 (3H, s), 3.52 (1H, dd, *J* = 12.4, 2.3 Hz), 3.29 (1H, m), 3.16–3.08 (2H, comp), 2.91 (1H, app dt, *J* = 14.7, 2.8 Hz), 2.75–2.69 (3H, comp), 2.61 (1H, app td, *J* = 12.8, 6.4 Hz), 2.49 (1H, dd, *J* = 14.2, 12.0 Hz), 2.44 (1H, app dt, *J* = 11.5, 2.3 Hz); **^{13}C NMR** ($CDCl_3$) δ 208.8 (C), 147.7 (C), 147.4 (C), 128.4 (C), 126.1 (C), 111.3 (CH), 107.6 (CH), 61.5 (CH_3), 55.9 (CH_3), 55.8 (CH), 54.7 (CH_2), 50.8 (CH_2), 47.6 (CH_2), 41.1 (CH_2), 29.3 (CH_2); **IR** (AT-IR) 1708, 1692 cm^{-1}; **HRMS** (CI) *m*/*z* 262.1437 [$C_{15}H_{20}NO_3$ (M + 1) requires 262.1443].

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One-Step Preparation of (±)-9,10-Dimethoxy-3,4,6,7-tetrahydro-1*H*-pyrido[2,1-*a*]isoquinolin-2(11b*H*)-one (9). A 20 mL vial was charged with a solution of TIPS enol ether **10** (205 mg, 0.49 mmol) and $Ru(bpy)_3Cl_2$ (7.8 mg, 0.0104 mmol) in CH_3CN (4 mL) and water (0.4 mL). The vial was sealed with a rubber septa, opened to the air with an 18 gauge needle, and was irradiated using a blue LED strip for 2 d. CH_2Cl_2 (10 mL) and 10% w/w aqueous NaOH (10 mL) were added to the reaction mixture. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Filtration through a plug of alumina, and trituration with hexanes, provided **9** as an off-white solid. Characterization data were identical for **9** as prepared above through the two-step procedure.

2-Methyl-4-methylene-5-oxohexan-3-yl Acetate (12).[72] A mixture of methyl vinyl ketone (6 mL, 74 mmol), isobutyraldehyde (8.5 mL, 93 mmol), 1,4-diazbicyclo[2.2.2]octane (1.64 g, 14.6 mmol), and 2,6-di-*tert*-butyl-4-methylphenol (122.4 mg, 0.55 mmol) was stirred overnight. The reaction mixture was diluted with ether (200 mL) and washed with 2 M aqueous HCl (2 × 50 mL), followed by brine (50 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to give the Baylis–Hillman adduct as an orange-colored oil (8.18 g). This oil was dissolved in CH_2Cl_2 (150 mL) and treated, in sequence, with pyridine (3 mL, 37.4 mmol) and acetyl chloride (2.4 mL). Once complete, as monitored by GC-MS, the reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with 2 M aqueous HCl (100 mL × 3), followed by 2 M aqueous NaOH (100 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (silica), eluting with EtOAc/hexanes (15:85 then 2:8) to give enone **12** (5 g, 46%) as a clear, colorless, oil. **^{1}H NMR** ($CDCl_3$) δ 6.15 (1H, s), 5.88 (1H, d, J = 0.9 Hz), 5.51 (1H, dd, J = 5.5, 0.9 Hz), 2.35 (3H, s), 2.08 (3H, s), 1.96 (1H, m), 0.9 (3H, d, J = 6.9 Hz), 0.86 (3H, d, J = 6.9 Hz); **^{13}C NMR** ($CDCl_3$) δ 197.9 (C), 170.0 (C), 147.5 (C), 125.4 (CH_2), 75.3 (CH), 31.3 (CH_3), 26.1 (CH_3), 21.0 (CH), 19.0 (CH_3), 16.9 (CH_3); **IR** (film) 2967, 2876, 1735, 1677, 1367, 1230, 1023 cm^{-1}; **HRMS** (CI) m/z 185.1179 [$C_{10}H_{17}O_3$ (M + 1) requires 185.1178].

3-((6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-5-methylhex-3-en-2-one (14). 6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (7) (2.03 g, 8.84 mmol) and enone **12** (1.93 g, 10.47 mmol) were suspended in 2 M aqueous NaOH (6.5 mL) and stirred at ambient temperature for 1 h. The reaction mixture was treated with aqueous 2 M HCl (125 mL) and then washed with ether (75 mL × 2). The pH of the aqueous layer was adjusted to 11 by addition of 2 M aqueous NaOH (150 mL), and was then extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were washed with brine (75 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (silica), eluting with MeOH/CH_2Cl_2 (1:9) to give enone **14** (2.336 g, 83%) as a clear, colorless, oil (6:1 mixture of *E*:*Z* isomers). *Characterization is provided for the major isomer.* **^{1}H NMR** ($CDCl_3$) δ 6.57 (1H, s), 6.55 (1H, d, J = 10.0 Hz), 6.49 (1H, s), 3.84 (3H, s), 3.83 (3H, s), 3.52 (2H, s), 3.40 (2H, s), 2.88 (1H, dsept, J = 10.0, 6.4 Hz), 2.75 (2H, t, J = 5.5 Hz), 2.66 (2H, t, J = 5.5 Hz), 2.37 (3H, s), 1.07 (6H, d, J = 6.4 Hz); **^{13}C NMR** ($CDCl_3$) δ 200.4 (C), 152.5 (CH), 147.3 (C), 147.0 (C), 135.6 (C), 126.7 (C), 126.2 (C), 111.2 (CH), 109.3 (CH), 55.8 (CH_3 × 2), 55.4 (CH_2), 51.9 (CH_2), 50.3 (CH_2), 28.7 (CH_2), 28.1 (CH), 26.4 (CH_3), 22.3 (CH_3 × 2); **IR** (film) 2958, 2868, 2835, 1665, 1517, 1254, 1226, 1126, 909, 727 cm^{-1}; **HRMS** (CI) m/z 318.2066 [$C_{19}H_{28}NO_3$ (M + 1) requires 318.2069].

(±)-3-((6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-methyl)-5-methylhexan-2-one (6b). A solution of enone **14** (2.47 g, 7.78 mmol) and trifluoroacetic acid (1.19 mL, 15.57 mmol) in MeOH (70 mL) was added to a flask containing 10% w/w Pd/C (0.33 g). Hydrogen was bubbled through the resulting suspension for 20 min. After completion by TLC, the reaction mixture was filtered through Celite, treated with 2 M aqueous NaOH (100 mL), and then extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extractions were dried (Na_2SO_4) and concentrated under reduced pressure. An analytically pure sample was obtained by flash chromatography (silica), eluting with MeOH/CH_2Cl_2 (1:9) to give ketone **6b** (1.96 g, 79%) as a light yellow solid. **mp** 62–65.5 °C; **^{1}H NMR** ($CDCl_3$) δ 6.56 (1H, s), 6.50 (1H, s), 3.82 (3H, s), 3.81 (3H, s), 3.60 (1H, d, J = 14.6 Hz), 3.46 (1H, d, J = 14.6 Hz), 2.93 (1H, m), 2.82–2.72 (4H, comp), 2.57 (1H, ddd, J = 10.5, 6.9, 5.3 Hz), 2.44 (1H, dd, J = 11.5, 5.7 Hz), 2.15 (3H, s), 1.57–1.47 (2H, comp), 1.23 (1H, m), 0.91 (3H, d, J = 6.0 Hz), 0.88 (3H, d, J = 6.0 Hz); **^{13}C NMR** ($CDCl_3$) δ 212.4 (C), 147.3 (C), 147.0 (C), 126.4 (C), 126.1 (C), 111.2 (CH), 109.2 (CH), 60.7 (CH_2), 55.9 (CH_2), 55.8 (CH_3 × 2), 50.9 (CH_2), 49.0 (CH), 39.3 (CH_2), 28.8 (CH_3), 28.6 (CH_2), 26.1 (CH), 23.0 (CH_3), 22.2 (CH_3); **IR** (film) 2954, 2869, 2836, 1709, 1517, 725 cm^{-1}; **HRMS** (CI) m/z 320.2226 [$C_{19}H_{30}NO_3$ (M + 1) requires 320.2226].

(±)-6,7-Dimethoxy-2-(4-methyl-2-(1-((triisopropylsilyl)oxy)-vinyl)pentyl)-1,2,3,4-tetrahydroisoquinoline (15). Ketone **6a** (510 mg, 1.60 mmol) was dissolved in CH_2Cl_2 (11 mL), followed by the sequential addition of Et_3N (0.7 mL, 5.02 mmol), and TIPSOTf (0.65 mL, 2.42 mmol). After 30 min, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and 2 M aqueous NaOH (50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). All organic extractions were combined, then dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (alumina), eluting with EtOAc/hexanes (1:9) to give TIPS enol ether **15** (610 mg, 80%) as a clear, colorless, oil. **^{1}H NMR** ($CDCl_3$) δ 6.58 (1H, s), 6.52 (1H, s), 4.00 (1H, br s), 3.98 (1H, br s), 3.84 (3H, s), 3.83 (3H, s), 3.54 (2H, ABq, J_{AB} = 14.6 Hz, $\Delta\delta$ = 0.06 ppm); 2.80–2.72 (3H, comp), 2.65–2.58 (2H, comp), 2.48–2.39 (2H, comp), 1.69 (1H, m), 1.49 (1H, ddd, J = 13.5, 10.5, 3.9 Hz), 1.27–1.18 (3H, comp), 1.09 (18H, d, J = 6.9 Hz), 1.06 (1H, m), 0.9 (6H, app d, J = 6.9 Hz); **^{13}C NMR** ($CDCl_3$) δ 160.0 (C), 147.2 (C), 147.0 (C), 127.2 (C), 126.5 (C), 111.2 (CH), 109.3 (CH), 88.9 (CH_2), 61.8 (CH_2), 56.0 (CH_2), 55.9 (CH_3 × 2), 51.2 (CH_2), 42.6 (CH), 39.8 (CH_2), 28.8 (CH_2), 25.4 (CH), 23.8 (CH_3), 21.6 (CH_3), 18.1 (CH_3 × 6), 12.8 (CH × 3); **IR** (film) 2944, 2865, 1612 (weak), 1517, 1256, 1228, 1016, 753, 680 cm^{-1}; **HRMS** (CI) m/z 474.3399 [$C_{28}H_{48}NO_3Si$ (M − 1) requires 474.3403].

(±)-3-Isobutyl-9,10-dimethoxy-3,4,6,7-tetrahydro-1*H*-pyrido[2,1-*a*]isoquinolin-2(11b*H*)-one [(±)-Tetrabenazine, TBZ, (±)-1]. A 25 mL round-bottom flask was charged with TIPS enol ether **15** (240.4 mg, 0.505 mmol), $Ru(bpy)_3Cl_2$ (7 mg, 0.0093 mmol), and CH_3CN/H_2O (10:1, 4.4 mL). The flask was equipped with a magnetic stir bar and septa, which was pierced with an 18 gauge needle, and irradiated with the light produced from a 8.5 W blue LED strip for 16 h at 45 °C. CH_2Cl_2 (10 mL) and 2 M aqueous NaOH (5 mL) were added to the reaction mixture. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (alumina), eluting with EtOAc/hexanes (15:85) to give (±)-tetrabenazine (**1**) (89.2 mg, 56%) as a white crystalline solid (5:1 dr). **mp** 108–110 °C; *Characterization is provided for the major diastereomer.* **^{1}H NMR** ($CDCl_3$) δ 6.62 (1H, s), 6.55 (1H, s), 3.86 (3H, s), 3.83 (3H, s), 3.51 (1H, br d, J = 10.5 Hz), 3.29 (1H, dd, J = 11.5, 6.4 Hz), 3.18–3.07 (2H, comp), 2.90 (1H, dd, J = 13.7, 3.0 Hz), 2.78–2.72 (2H, comp), 2.64–2.51 (2H, comp), 2.36 (1H, t, J = 11.5 Hz), 1.80 (1H, ddd, J = 14.0, 8.7, 5.5 Hz), 1.67 (1H, comp), 1.04 (1H, ddd, J = 13.7, 7.3, 5.9 Hz), 0.92 (3H, d, J = 5.0 Hz), 0.91 (3H, d, J = 5.0 Hz); **^{13}C NMR** ($CDCl_3$) δ 210.2 (C), 147.7 (C), 147.4 (C), 128.4 (C), 126.0 (C), 111.3 (CH), 107.7 (CH), 62.4 (CH), 61.4 (CH_2), 55.9 (CH_3), 55.8 (CH_3), 50.5 (CH_2), 47.6 (CH_2), 47.5 (CH), 35.0 (CH_2), 29.3 (CH_2), 25.3 (CH), 23.2 (CH_3), 22.0 (CH_3); **IR** (AT-IR) 2920, 2862, 1699, 1515, 1463, 1257, 882 cm^{-1}; **HRMS** (CI) m/z 318.2073 [$C_{19}H_{28}NO_3$ (M + 1) requires 318.2069].

(±)-3-Isobutyl-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-*a*]isoquinolin-2-ol [α-Dihydrotetrabenazine, DTBZ, (±)-2]. A solution of (±)-**1** (101.7 mg, 0.32 mmol) in EtOH (3 mL) was cooled to 0 °C and treated with $NaBH_4$ (42 mg, 1.11 mmol). After 1 h, 2 M aqueous NaOH (15 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (4 × 10 mL). The combined

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J. Org. Chem. 2015, 80, 12635–12640

organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel), eluting with MeOH/CH_2Cl_2 (10:250) to give α-dihydrotetrabenazine (±)-**2** (70.2 mg, 70%) as a white solid and 4.2 mg (4%) of the 2-epi-dihydrotetrabenazine. **α-dihydrotetrabenazine** (major diastereomer): **^{1}H NMR** ($CDCl_3$) δ 6.68 (1H, s), 6.58 (1H, s), 5.30 (1H, s), 3.85−3.84 (6H, comp), 3.40 (1H, app td, *J* = 10.5, 4.6 Hz), 3.13 (1H, br d, *J* = 11.9 Hz), 3.11−2.98 (3H, comp), 2.64 (1H, br dd, *J* = 16.9, 4.1 Hz), 2.59 (1H, ddd, *J* = 12.4, 4.6, 2.3 Hz), 2.46 (1H, app td, *J* = 11.5, 4.1 Hz), 1.98 (1H, app t, *J* = 11.5 Hz), 1.77−1.65 (2H, comp), 1.58 (1H, ddd, *J* = 13.3, 10.0, 3.2 Hz), 1.49 (1H, app q, *J* = 11.5 Hz), 1.07(1H, ddd, *J* = 13.7, 10.0, 4.1 Hz), 0.94 (3H, d, *J* = 6.7 Hz), 0.92 (3H, d, *J* = 6.7 Hz); **^{13}C NMR** ($CDCl_3$) δ 147.4 (C), 147.1 (C), 129.2 (C), 126.3 (C), 111.4 (CH), 107.8 (CH), 74.6 (CH), 60.9 (CH), 60.0 (CH_2), 55.9 (CH_3), 55.8 (CH_3), 51.9 (CH_2), 41.6 (CH), 40.5 (CH_2), 39.6 (CH_2), 29.1 (CH_2), 25.3 (CH), 24.2 (CH_3), 21.7 (CH_3); **IR** (AT-IR) 3381, 1513, 1261, 1212, 1008, 767 cm^{-}1; **HRMS** (CI) *m*/*z* 320.2219 [$C_{19}H_{30}NO_3$ (M + 1) requires 320.2226]. **2-epi-dihydrotetrabenazine** (minor diastereomer): **^{1}H NMR** ($CDCl_3$) δ 6.66 (1H, s), 6.58 (1H, s), 4.09 (1H, br d, *J* = 2.3 Hz), 3.844 (3H, s), 3.841 (3H, s), 3.54 (1H, br d, *J* = 9.2 Hz), 3.14 (1H, m), 3.00 (1H, m), 2.73−2.56 (3H, comp), 2.46 (1H, m), 2.44 (1H, app dt, *J* = 13.7, 2.8 Hz), 2.02 (1H, m), 1.76−1.64 (2H, comp), 1.31−1.24 (2H, comp), 1.20−1.13 (1H, m), 0.94 (3H, d, *J* = 7.0 Hz), 0.92 (3H, d, *J* = 7.0 Hz); **^{13}C NMR** ($CDCl_3$) δ 147.4 (C), 147.1 (C), 126.7 (C), 111.4 (CH), 107.9 (CH), 67.9 (CH), 56.4 (CH), 56.2 (CH_2), 55.9 (CH_3), 55.8 (CH_3), 52.4 (CH_2), 39.0 (CH_2), 38.8 (CH_2), 37.6 (CH), 29.0 (CH_2), 24.8 (CH), 22.9 (CH_3 × 2). These data were consistent with previously reported data.[18,26]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02199.

General experimental procedures, ^{1}H and ^{13}C NMR spectra, and comparisons of the NMR data for (±)-**1** and (±)-**2** with literature data (PDF)

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Notes

The authors declare no competing financial interest.

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