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A Concise Total Synthesis of (+)-Tetrabenazine and (+)-α-Dihydrotetrabenazine

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Abstract: Highly concise asymmetric total syntheses of (+)-tetrabenazine (**1**), a drug for the treatment of chorea associated with Huntington's disease, and of (+)-α-dihydrotetrabenazine (**2**), an active metabolite of **1**, have been accomplished. Our synthetic route features a *trans*-selective enol etherification, followed by an unprecedented cation-dependent aza-Claisen rearrangement to establish the carbon framework and two stereogenic centers of tetrabenazine. The syntheses consist of seven steps (34% overall yield) for (+)-**2** and eight steps (22% overall yield) for (+)-**1**.

Keywords: bentazines · Claisen rearrangement · rearrangement · total synthesis

Introduction

Chorea is one of the most common and debilitating motor symptoms associated with Huntington's disease (HD) and afflicts the lives of the HD patients and caregivers.[1] HD can affect people of all ethnic groups, but is more common in most western countries. In particular, about 30000 people in North America have HD and another 200000 are considered at risk of developing the condition.[2] Tetrabenazine (TBZ, Xenazine, (±)-**1**, Figure 1), the first and only drug approved by the US FDA as a racemate for the treatment of chorea (15th August 2008), represents a major advancement for HD patients.[3] In recent clinical tests in Europe and Australia, the majority (69–80%) of TBZ-treated patients showed dramatically decreased chorea, in contrast to patients treated with placebo.[4] With this pharmacological activity, TBZ (as the racemate) is now taken by HD patients.

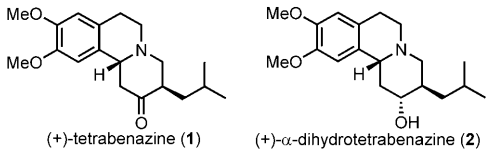

Figure 1. Structures of TBZ (**1**) and α-DHTBZ (**2**).

TBZ (**1**), in the form of the racemic, binds to vesicular monoamine transporter type 2 (VMAT2) and depletes cerebral monoamines in neuronal synapses with a K_i value of 3 nM.[5] In addition, α-dihydrotetrabenazine (α-DHTBZ, **2**), an active metabolite of TBZ, also showed high specific binding affinity to VMAT2.[6] More importantly, enzymatic resolution of racemic α-DHTBZ showed that its binding to VMAT2 is highly stereoselective [$K_i = 0.97$ nM for the (+) enantiomer of **2** but $K_i = 2.2$ μM for the (−) enantiomer].[7] In view of the high-affinity stereospecific binding of **2**, as well as the frequent occurrence of side effects caused by the undesired stereoisomers of racemic drugs, such as (*R*)-thalidomide,[8] intensive and prompt studies on optically pure **1** and **2** as chiral switches were necessary for the development of drugs with improved efficacy and fewer adverse drug reactions. In spite of the urgent demand for optically pure **1** or **2**, however, only one asymmetric synthetic route to these TBZ alkaloids—not including resolution of racemic **2** with the aid of HPLC, enzymes, or chemicals—has been developed.[7–9] With this in mind, we took on the challenge and

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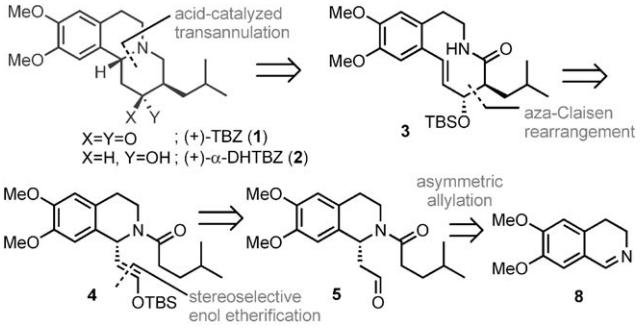
report here our success in the efficient asymmetric syntheses of (+)-**1** and (+)-**2**, based on a highly stereospecific ring-expansion through a cation-dependent amide-enolate-induced aza-Claisen rearrangement (ACR),[10–12] to create the two stereogenic centers of (+)-**1**, and a subsequent diastereoselective transannulation. Obviously, our strategies provide rapid access to a variety of medicinally important benzoquinolizidine alkaloids, including TBZ analogues.

Results and Discussion

Retrosynthetic analysis: Envisaging an efficient and unified synthetic procedure, we pursued a concise procedure for ready access to the key ten-membered lactam[13] intermediate **3** (Scheme 1), potentially effectively transformable into (+)-**1** and (+)-**2** by electrophile-catalyzed transannulation followed by amide reduction.[14]

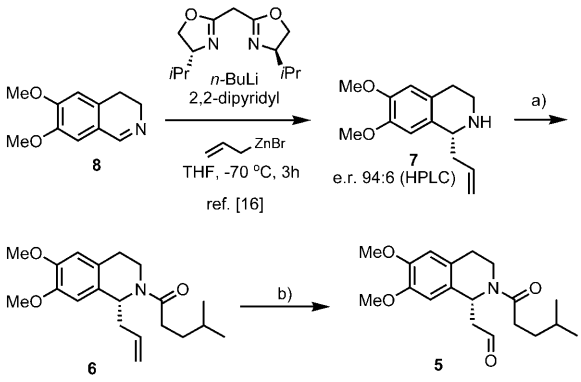


Scheme 1. Retrosynthetic analysis of (+)-TBZ (**1**) and (+)-α-DHTBZ (**2**).

The lactam **3** appeared obtainable by our lactam ring-expansion strategy,[12] with establishment of two of the requisite stereogenic centers of (+)-**2** through 1,4 and 1,5 chirality transfers. The *E* olefin geometry in the enol ether **4**, crucial for stereocontrol of the hydroxy group, was to be established from the corresponding aldehyde **5** through a selective enol etherification.[15] Finally, asymmetric allylation of the commercially available synthon **8** by Nakamura's method[16] and subsequent olefin cleavage appeared likely to afford the aldehyde **5**. It is noteworthy that the stereochemical outcome addressed by utilization of the conformational preference (substrate control) would render this approach to (+)-**1** and (+)-**2** practical.

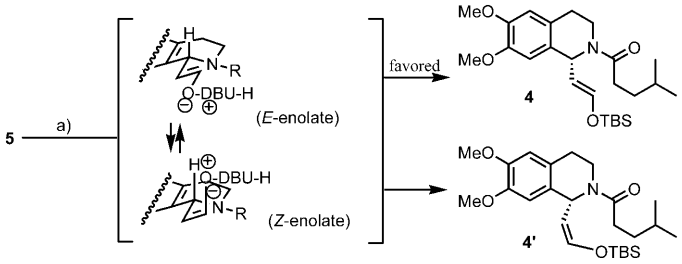
Synthesis: Our synthesis commenced with asymmetric allylation of the commercially available **8** to afford the enantiomerically enriched homoallylic amine **7** (Scheme 2).[16] The amine **7** was coupled with 4-methylvaleric acid, and subsequent olefin dihydroxylation followed by $NaIO_4$-mediated diol cleavage[17] gave the aldehyde **5**.

We next set out to address the formidable task of stereoselective enol ether formation. Our extensive studies revealed that treatment of the β-aminoaldehyde **5** with a non-



Scheme 2. a) 4-Methylvaleric acid, EDCI, HOBt, CH_2Cl_2, 0°C to RT, 86% for two steps; b) OsO_4, NMO then $NaIO_4$, acetone/H_2O, 88%.

chelating, bulky base such as DBU in the presence of TBSCl in CH_2Cl_2 at reflux could lead to the exclusive formation of the desired *E*-enol ether **4** (*E*/*Z* 34:1, isolated; Scheme 3) in 94% yield. The mechanism underlying the high selectivity is not entirely clear. One plausible explanation, however, could include initial generation of enolates from **5** followed by a preferred silylation of the sterically less encumbered *E*-enolate.[18,19]



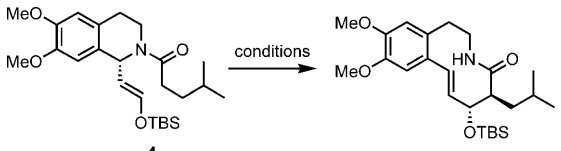
Scheme 3. a) TBSCl, DBU, CH_2Cl_2, 40°C, 5 h, 94%.

With enol ether **4** available in multigram quantities, we first tested the feasibility of the pivotal ACR with regard to the stereochemical course of the rearrangement under standard conditions (Table 1).

At first, enol ether **4** was treated with LHMDS (in hexane solution) in toluene at reflux. Unfortunately, these standard conditions afforded only a small amount of the desired ring-expanded product **3** (25%), along with a significant amount of unidentified side and degradation products. Because of the disappointing yield of **3**, we examined a variety of rearrangement conditions including solvent, base, temperature, and the enolate trapping reagent (entries 1–6). Reaction under most of the conditions resulted in substrate recovery or degradation. TMSOTf or TBSCl trapping of the amide enolate derived from **4** followed by ACR afforded the desired macrolactam **3** in 5~10% yield with the substrate intact.

However, after intensive examination of a variety of bases (entries 7–11), we finally observed that treatment of the *E*-enol ether **4** with *i*PrMgCl (2.0 M in THF solution) in ben-

Table 1. Aza-Claisen rearrangement under various reaction conditions.



Entry	Solvent	Base [equiv]	*T*	Product [%][a]
1	toluene	LHMDS [3]	120 °C	25 %
2	toluene	LHMDS [1.1]	RT	n.d.[b]
3	toluene	LHMDS [2]	RT	n.d.
4	THF	LHMDS [2]	−78 °C to 0 °C	n.d.
5	toluene	LHMDS [2], TMSOTf	−78 °C to 120 °C	5–10 %
6	toluene	LHMDS [2], TBSCl	RT to 120 °C	5–10 %
7	toluene	KHMDS [2]	120 °C	n.d.
8	toluene	*i*PrMgCl [2]	120 °C	52 %
9	benzene	*i*PrMgCl [5]	80 °C	76 %
10	benzene	*i*PrMgCl [2]	80 °C	75 %
11	benzene	*i*PrLi [2]	80 °C	n.d.
12	benzene	*t*BuMgCl [2]	80 °C	33 %

[a] Isolated yield. Other diastereomers were not detected. [b] Not detected.

zene at reflux exclusively provided the desired lactam **3** as a detectable single diastereomer (76 % yield). The superiority of *i*PrMgCl over LHMDS is likely due to the *gauche* interaction between the bulky MgCl complex and the OTBS group, which forces the highly ordered chair-like transition state (Figure 2). To the best of our knowledge, use of a Grignard reagent such as *i*PrMgCl is the first example for ACR.[20–23]

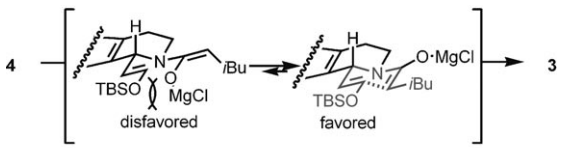
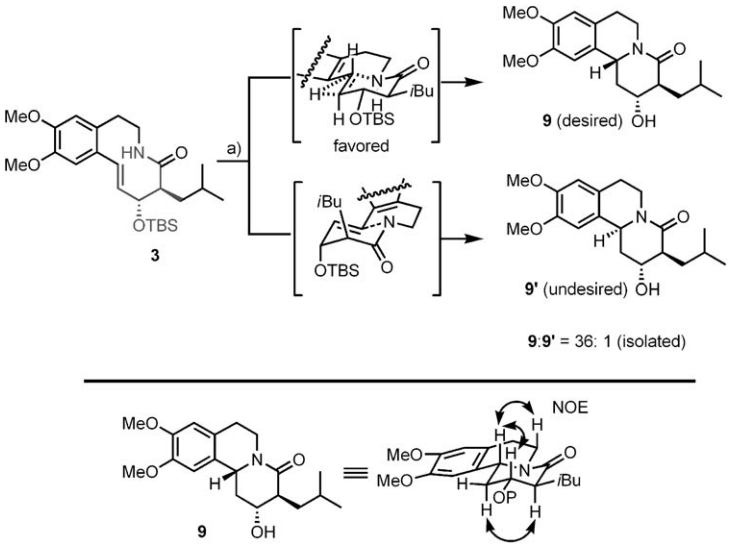


Figure 2. Proposed transition state for the aza-Claisen rearrangement.

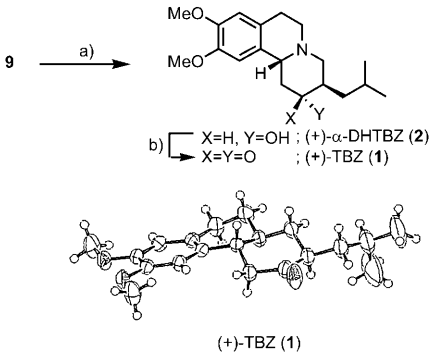
With the key ten-membered lactam **3** to hand, we explored an electrophile-assisted transannulation strategy[14,25] for the construction of the desired benzoisoquinolizidine scaffold of (+)-**2** (Scheme 4). Fortunately, the transannulation of lactam **3** to afford the benzoisoquinolizidine **9** could be accomplished with the assistance of TsOH (RT, benzene, 24 h) with the concomitant cleavage of the TBS ether in a highly diastereoselective fashion (36:1, 84 % yield, isolated).[24,25] It is noteworthy that the ACR/transannulation sequence allowed the stereoselective construction of benzoisoquinolizidine skeleton through remote chiral communication (Scheme 4).

Finally, LAH reduction of **9** afforded (+)-α-DHTBZ (**2**, Scheme 5) and subsequent TPAP/NMO oxidation gave (+)-TBZ (**1**); both compounds exhibited ^{1}H NMR, ^{13}C NMR, HRMS, IR spectral data,[26] and optical rotations[27] identical to those of the authentic products. The structure of (+)-**1**



Scheme 4. a) TsOH, benzene, 84 %.

was furthermore confirmed by X-ray crystallography (Scheme 5).[28]



Scheme 5. a) LAH, THF, 76 %; b) TPAP, NMO, CH_2Cl_2, 64 %.

Conclusion

In conclusion, we have achieved highly efficient and concise asymmetric total syntheses of (+)-TBZ (**1**) and (+)-α-DHTBZ (**2**) in seven and six steps from the known homoallyl amine **7** and in 22 % and 34 % overall yields, respectively. The key features of our synthetic route include stereoselective elaboration of the *E*-enol ether unit from the corresponding aldehyde, a subsequent amide-enolate-induced ACR, which afforded almost perfect 1,4 and 1,5 remote chiral transfer, and highly efficient construction of the benzoisoquinolizidine skeleton by acid-catalyzed transannulation. This highly stereoselective transformation allowed us to acquire the biologically important TBZ alkaloids without loss of enantiomeric purity; further studies of the clinical uses of the TBZ analogues and mechanistic investigation of the cation-dependent ACR are in progress.

Experimental Section

General procedure: Unless noted otherwise, all starting materials and reagents were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran and Et_2O were distilled from sodium benzophenone ketyl. Dichloromethane, triethylamine, acetonitrile, and pyridine were freshly distilled from calcium hydride. All solvents used for routine isolation of products and chromatography were reagent grade and glass-distilled. Reaction flasks were dried at 100 °C. Air- and moisture-sensitive reactions were performed under argon. Flash column chromatography was performed on silica gel 60 (230–400 mesh) with the solvents indicated. Thin-layer chromatography was performed on silica gel plates (0.25 mm). Optical rotations were measured with 100 mm cells of 1–2 mL capacity. Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane and are referenced to the deuterated solvent ($CDCl_3$). ^{1}H NMR data are reported in the order of chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and/or multiple resonance), coupling constant in hertz (Hz), and number of protons.

(*R*)-1-(1-Allyl-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-4-methylpentan-1-one (6): EDCI (1.7 g, 8.8 mmol) and HOBt (1.2 g, 8.8 mmol) were added at ambient temperature to a solution of amine **7** (1.0 g, 4.3 mmol) and 4-methylvaleric acid (0.89 mL, 7.0 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred for 12 h, quenched with aqueous NH_4Cl, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane/CH_2Cl_2 1:4:1 to 1:2:1) to afford the homoallylic amide **6** (1.2 g, 86%) as a colorless oil. The enantioselectivity was determined as 89% *ee* [chiral HPLC analysis (DAICEL chiralpak AD-H, hexane/propan-2-ol 75:25), flow rate = 1.0 mL min^{-1}, 23 °C, λ = 254 nm, retention time, major (9 min), minor (17 min), 89% *ee*]: $[\alpha]_D^{20} = -115.9$ (c = 1.9, MeOH); ^{1}H NMR (300 MHz, CD_3OD, mixture of rotamers): δ = 6.79 (s), 6.74 (s, 1H), 6.69 (s, 1H), 5.95–5.74 (m, 1H), 5.54 (dd, J = 5.3, 8.8 Hz, 1H), 5.14–4.95 (m, 2H), 4.54 (dd, J = 3.5, 13.0 Hz), 3.91 (ddd, J = 2.9, 5.3, 13.5 Hz, 1H), 3.80 (s), 3.78 (s, 6H), 3.53 (ddd, J = 4.95, 10.0, 13.7 Hz), 3.10 (ddd, J = 4.95, 11.3, 12.9 Hz, 1H), 2.91–2.24 (m, 6H), 1.67–1.39 (m, 3H), 0.94–0.87 ppm (m, 6H); ^{13}C NMR (100 MHz, CD_3OD, mixture of rotamers): δ = 175.6, 175.4, 150.3, 150.1, 149.8, 137.2, 136.6, 130.9, 130.7, 128.4, 127.9, 119.6, 118.2, 113.9, 113.7, 112.6, 112.3, 58.2, 57.3, 57.2, 53.7, 43.0, 42.9, 41.9, 37.2, 36.5, 36.3, 33.4, 30.4, 29.8, 29.7, 29.3, 23.5 ppm; IR (neat): $\tilde{\nu}$ = 2953, 1639, 1516, 1435, 1359, 1258, 1121, 1027 cm^{-1}; MS (EI$^+$): m/z: 331 $[M]^+$; HRMS (EI$^+$): m/z: calcd for $C_{20}H_{29}O_3N$: 331.2147 $[M]^+$; found: 331.2135.

(*R*)-2-[6,7-Dimethoxy-2-(4-methylpentanoyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]acetaldehyde (5): OsO_4 (0.05 M in toluene, 1.0 mL, 0.05 mmol) was added to a solution of *N*-methylmorpholine *N*-oxide (330 mg, 2.8 mmol) in acetone (2 mL) and H_2O (2 mL). After the system had been stirred for 10 min, the homoallylic amide **6** (310 mg, 0.93 mmol) in acetone (2 mL) was added and the reaction mixture was stirred for an additional 12 h. $NaIO_4$ (590 mg, 2.8 mmol) was added and the reaction mixture was stirred for 30 min. The reaction mixture was quenched with Na_2SO_3 at 0 °C and filtered, and the combined layers were extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane 2:1) to afford the aldehyde **5** (275 mg, 88%) as colorless crystals. $[\alpha]_D^{20} = -114.0$ (c = 0.86, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers): δ = 9.81–9.76 (m, 1H), 6.62 (s, 1H), 6.57 (s, 1H), 6.00 (q, J = 4.6 Hz, 1H), 3.91–3.76 (m, 1H), 3.81 (s, 6H), 3.47 (ddd, J = 4.5, 10.2, 13.3 Hz, 1H), 3.13–2.66 (m, 4H), 2.46–2.23 (m, 1H), 2.33 (q, J = 8.2 Hz, 1H), 1.61–1.44 (m, 2H), 0.88 (d, J = 2.4 Hz, 3H), 0.86 ppm (d, J = 2.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ = 200.0, 199.2, 172.5, 172.2, 148.2, 148.0, 147.9, 147.6, 127.8, 127.7, 126.4, 125.5, 111.6, 111.1, 109.6, 108.9, 55.9, 55.8, 51.8, 51.1, 49.9, 47.7, 40.1, 35.8, 34.0, 33.8, 33.5, 31.7, 31.6, 31.3, 28.6, 27.7, 27.5, 27.3, 22.4, 22.3, 22.2, 22.1 ppm; IR (neat): $\tilde{\nu}$ = 2954, 1720, 1637, 1516, 1460, 1360, 1258, 1122 cm^{-1}; MS (EI$^+$): m/z: 333 $[M]^+$; HRMS (EI$^+$): m/z: calcd for $C_{19}H_{27}O_4N$: 333.1940 $[M]^+$; found: 333.1976.

(*R*,*E*)-1-[1-(2-(*tert*-Butyldimethylsilyloxy)vinyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl]-4-methylpentan-1-one (4) and (*R*,*Z*)-1-[1-(2-(*tert*-butyldimethylsilyloxy)vinyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl]-4-methylpentan-1-one (4′): A mixture of the aldehyde **5** (82 mg, 0.25 mmol), TBSCl (70 mg, 0.46 mmol), and DBU (50 μL, 0.40 mmol) in CH_2Cl_2 (10 mL) was stirred at 40 °C for 5 h. The reaction mixture was quenched with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane/Et_3N 5:15:1) to afford the *E*-enol ether **4** (103 mg, 94%) as the major isomer and the undesired *Z*-enol ether **4′** (3 mg, 2.7%) as a colorless oil.

Compound 4: $[\alpha]_D^{20} = -114.1$ (c = 1.46, MeOH); ^{1}H NMR (300 MHz, CD_3OD, mixture of rotamers): δ = 6.58 (s, 1H), 6.51 (s, 1H), 6.42 (d, J = 11.5 Hz), 6.34 (d, J = 11.7 Hz, 1H), 5.72 (d, J = 8.2 Hz), 5.25 (d, J = 7.6 Hz, 1H), 5.09 (dd, J = 7.6, 11.9 Hz), 4.98 (dd, J = 8.0, 11.7 Hz, 1H), 4.40–4.36 (m), 3.85–3.81 (m, 1H), 3.66 (s, 3H), 3.65 (s, 3H), 3.39–3.29 (m), 2.97–2.87 (m, 1H), 2.79–2.52 (m, 2H), 2.38–2.24 (m, 2H), 1.50–1.34 (m, 3H), 0.79–0.77 (m, 15H), 0.00 ppm (m, 6H); ^{13}C NMR (75 MHz, CD_3OD, mixture of rotamers): δ = 183.6, 175.2, 174.8, 150.4, 150.2, 149.9, 146.9, 145.9, 129.8, 128.5, 128.9, 128.2, 127.0, 113.6, 113.5, 113.4, 113.2, 113.0, 60.8, 59.3, 59.2, 56.9, 52.9, 44.7, 41.9, 38.1, 36.4, 36.3, 33.5, 33.2, 30.6, 29.8, 29.6, 27.1, 26.9, 23.6, 23.5, 20.2, −4.3 ppm; IR (neat): $\tilde{\nu}$ = 2954, 1647, 1515, 1462, 1256, 1180, 1119 cm^{-1}; MS (EI$^+$): m/z: 447 $[M]^+$; HRMS (EI$^+$): m/z: calcd for $C_{25}H_{41}O_4NSi$: 447.2805 $[M]^+$; found: 447.2781.

Compound 4′: $[\alpha]_D^{20} = -218.4$ (c = 0.18, MeOH); ^{1}H NMR (300 MHz, CD_3OD, mixture of rotamers): δ = 6.45 (s, 1H), 6.43 (s, 1H), 6.20 (d, J = 9.3 Hz, 1H), 5.68 (d, J = 9.3 Hz, 1H), 4.59 (m, 1H), 4.47–4.27 (m, 1H), 3.53 (m, 1H), 3.53 (s, 3H), 3.49 (s, 3H), 2.80–2.70 (m, 1H), 2.67–2.14 (m, 5H), 1.37–1.03 (m, 4H), 0.77 (s, 9H), 0.66 (d, J = 2.1 Hz, 3H), 0.64 (d, J = 2.4 Hz, 3H), 0.02 (s, 3H), 0.00 ppm (s, 3H); ^{13}C NMR (75 MHz, CD_3OD, mixture of rotamers): δ = 174.3, 150.3, 150.1, 141.3, 140.8, 130.7, 128.7, 113.7, 113.5, 112.6, 112.2, 112.0, 111.8, 57.4, 57.2, 52.7, 38.5, 36.4, 36.3, 33.5, 33.0, 31.5, 30.7, 29.7, 27.0, 23.9, 23.6, 23.5, 19.9, −4.1, −4.3 ppm; IR (neat): $\tilde{\nu}$ = 2929, 1644, 1515, 1461, 1256, 1109 cm^{-1}; MS (FAB$^+$): m/z: 448 $[M+H]^+$; HRMS (FAB$^+$): m/z: calcd for $C_{25}H_{42}O_4NSi$: 448.2883 $[M+H]^+$; found: 448.2882.

(5*S*,6*R*,*E*)-6-(*tert*-Butyldimethylsilyloxy)-5-isobutyl-10,11-dimethoxy-2,3,5,6-tetrahydrobenzo[*d*]azecin-4(1*H*)-one (3): *i*PrMgCl (0.51 mL of a 2.0 M solution in THF, 1.0 mmol) was added dropwise at 80 °C to a solution of the enol ether **4** (230 mg, 0.51 mmol) in benzene (10 mL) and the resulting solution was heated at reflux for 5 h. The reaction mixture was quenched with H_2O and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane 1:3 with 5% MeOH) to afford the γ,δ-unsaturated lactam **3** (175 mg, 76%) as a white solid: m.p. 172 °C; $[\alpha]_D^{20} = -171.1$ (c = 0.22, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ = 7.68 (t, J = 6.2 Hz, 1H), 6.67 (s, 1H), 6.61 (s, 1H), 6.34 (d, J = 16.2 Hz, 1H), 5.31 (dd, J = 8.2, 16.4 Hz, 1H), 3.98 (t, J = 8.8 Hz, 1H), 3.72–3.60 (m, 1H), 3.67 (s, 3H), 3.65 (s, 3H), 3.20 (dt, J = 3.5, 12.8 Hz, 1H), 2.64 (ddt, J = 2.5, 4.7, 10.8 Hz, 1H), 2.13 (td, J = 2.6, 11.3 Hz, 1H), 2.00 (dt, J = 2.1, 9.5 Hz, 1H), 1.59 (dd, J = 8.9, 11.3 Hz, 1H), 1.39–1.30 (m, 2H), 0.80 (s, 9H), 0.75 (d, J = 6.2 Hz, 3H), 0.68 (d, J = 6.0 Hz, 3H), 0.00 ppm (s, 6H); ^{13}C NMR (75 MHz, CD_3OD): δ = 178.3, 150.4, 150.1, 139.7, 134.4, 133.0, 131.6, 116.0, 111.7, 79.0, 57.4, 56.6, 45.1, 45.0, 38.4, 32.2, 28.8, 27.1, 25.0, 22.9, 19.8, −3.0, −3.8 ppm; IR (neat): $\tilde{\nu}$ = 2924, 1631, 1458, 1257, 1099 cm^{-1}; MS (EI$^+$): m/z: 447 $[M]^+$; HRMS (EI$^+$): m/z: calcd for $C_{25}H_{41}O_4NSi$: 447.2805; found: 447.2825 $[M]^+$.

(2*R*,3*S*,11b*R*)-2-Hydroxy-3-isobutyl-9,10-dimethoxy-2,3,6,7-tetrahydro-1*H*-pyrido[2,1-*a*]isoquinolin-4(11b*H*)-one (9) and (2*R*,3*S*,11b*S*)-2-hydroxy-3-isobutyl-9,10-dimethoxy-2,3,6,7-tetrahydro-1*H*-pyrido[2,1-*a*]isoquinolin-4(11b*H*)-one (9′): *p*TSA·H_2O (23 mg, 0.12 mmol) was added to a solution of the lactam **3** (40 mg, 89 μmol) in benzene (5 mL). The mixture was stirred for 12 h at ambient temperature and additional *p*TSA·H_2O (23 mg, 0.12 mmol) was added. The reaction mixture was stirred for an additional 12 h, quenched with H_2O, and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and con-

centrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane 2:1 to EtOAc) to afford the desired product **9** (25 mg, 84%) as a colorless oil together with the undesired isomer **9′** (0.7 mg, 2.3%) as a colorless oil.

Compound 9: $[\alpha]_D^{20} = +101.8$ ($c = 0.56$, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.63$ (s, 1H), 6.59 (s, 1H), 4.79 (m, 1H), 4.60 (dd, $J = 3.9$, 11.1 Hz, 1H), 3.91 (dt, $J = 3.4$, 9.4 Hz, 1H), 3.84 (s, 6H), 2.86–2.82 (m, 1H), 2.78 (dd, $J = 2.6$, 12.0 Hz, 1H), 2.70 (td, $J = 3.9$, 12.6 Hz, 1H), 2.60 (d, $J = 15.3$ Hz, 1H), 2.30–2.25 (m, 1H), 2.01 (dt, $J = 6.6$, 14.1 Hz, 1H), 1.87 (td, $J = 6.5$, 13.4 Hz, 1H), 1.74 (q, $J = 11.4$ Hz, 1H), 1.58–1.53 (m, 1H), 0.96 (d, $J = 6.6$ Hz, 3H), 0.90 ppm (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.0$, 147.8, 147.7, 128.2, 127.2, 111.4, 107.9, 69.1, 56.0, 55.8, 53.3, 48.7, 39.9, 39.8, 38.8, 28.3, 26.6, 23.1, 22.4 ppm; IR (neat): $\tilde{\nu} = 3396$, 2923, 1617, 1515, 1458, 1257 cm^{-1}; MS (FAB$^+$): m/z: 334 $[M+H]^+$; HRMS (FAB$^+$): m/z: calcd for $C_{19}H_{28}O_4N$: 334.2018 $[M+H]^+$; found: 334.2022.

Compound 9′: $[\alpha]_D^{20} = -116.3$ ($c = 0.50$, MeOH); ^{1}H NMR (400 MHz, CD_3OD): $\delta = 6.79$ (s, 1H), 6.73 (s, 1H), 4.72–4.67 (m, 1H), 4.04 (t, $J = 2.2$ Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 2.90–2.67 (m, 3H), 2.61–2.55 (m, 1H), 2.49 (t, $J = 7.2$ Hz, 1H), 2.02–1.98 (m, 1H), 1.89–1.82 (m, 1H), 1.78–1.71 (m, 2H), 1.49–1.42 (m, 1H), 0.95 (d, $J = 6.8$ Hz, 3H), 0.91 ppm (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 174.8$, 150.2, 150.1, 131.4, 129.4, 114.0, 110.7, 67.7, 57.5, 57.2, 53.7, 49.1, 42.8, 41.8, 34.8, 30.1, 27.9, 24.2, 22.9 ppm; IR (neat): $\tilde{\nu} = 3388$, 2923, 2853, 1735, 1615, 1515, 1464 cm^{-1}; MS (FAB$^+$): m/z: 334 $[M+H]^+$; HRMS (FAB$^+$): m/z: calcd for $C_{19}H_{28}O_4N$: 334.2018 $[M+H]^+$; found: 334.2011.

(+)-α-Dihydrotetrabenazine (2): LAH (10 mg, 0.26 mmol) was added at ambient temperature to a solution of amide **9** (13 mg, 39 μmol) in THF (3 mL). The reaction mixture was warmed to 70°C, stirred for 2 h, and quenched with H_2O and NaOH (10%). The resulting mixture was dried over $MgSO_4$ at 0°C and filtered under reduced pressure. The organic layer was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel (EtOAc/MeOH 20:1) to afford (+)-α-dihydrotetrabenazine (**2**, 9.5 mg, 76%) as a white solid: $[\alpha]_D^{20} = +53.5$ ($c = 1.6$, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.65$ (s, 1H), 6.55 (s, 1H), 3.82 (s, 3H), 3.82 (s, 3H), 3.37 (dt, $J = 4.5$, 10.5 Hz, 1H), 3.11–3.03 (m, 2H), 2.62 (d, $J = 15.7$ Hz, 1H), 2.57 (ddd, $J = 2.4$, 4.4, 12.3 Hz, 1H), 2.43 (dt, $J = 3.9$, 11.4 Hz, 1H), 1.95 (t, $J = 11.3$ Hz, 1H), 1.73–1.64 (m, 2H), 1.55 (ddd, $J = 3.1$, 10.2, 13.4 Hz, 1H), 1.49 (q, $J = 11.4$ Hz, 1H), 1.04 (ddd, $J = 4.1$, 9.9, 13.5 Hz, 1H), 0.91 (d, $J = 6.5$ Hz, 3H), 0.89 ppm (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 147.4$, 147.2, 129.3, 126.3, 111.4, 107.8, 74.6, 60.8, 60.0, 55.9, 55.8, 51.9, 41.6, 40.5, 39.6, 29.1, 25.3, 24.1, 21.7 ppm; IR (neat): $\tilde{\nu} = 3397$, 2950, 1649, 1515, 1460, 1367, 1255 cm^{-1}; MS (FAB$^+$): m/z: 320 $[M+H]^+$; HRMS (FAB$^+$): m/z: calcd for $C_{19}H_{30}O_3N$: 320.2226 $[M+H]^+$; found: 320.2233.

(+)-Tetrabenazine (1): TPAP (2.4 mg, 6.9 μmol) was added at 0°C to a solution of (+)-α-dihydrotetrabenazine **2** (22 mg, 69 μmol), MS (4 Å, 20 mg), and NMO (12 mg, 103 μmol) in CH_2Cl_2 (4 mL). The reaction mixture was allowed to warm to ambient temperature, stirred for 2 h, and filtered through silica gel. The organic layer was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel (EtOAc/hexane 1:1) to afford (+)-tetrabenazine (**1**, 14 mg, 64%) as a white solid. The enantioselectivity was determined as 89% *ee* [chiral HPLC analysis (DAICEL chiralpak OD-H, hexane/propan-2-ol 95:5), flow rate = 1.0 mL min^{-1}, 23°C, $\lambda = 254$ nm, retention time, minor (14 min), major (17 min), 89% *ee*]: $[\alpha]_D^{20} = +62.5$ ($c = 0.180$, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.60$ (s, 1H), 6.53 (s, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.49 (d, $J = 9.3$ Hz, 1H), 3.27 (dd, $J = 6.0$, 11.6 Hz, 1H), 3.12–3.03 (m, 2H), 2.87 (dd, $J = 2.8$, 13.6 Hz, 1H), 2.76–2.68 (m, 2H), 2.58 (dd, $J = 10.0$, 11.6 Hz, 1H), 2.52 (t, $J = 12.8$ Hz, 1H), 2.36–2.31 (m, 1H), 1.82–1.76 (m, 1H), 1.72–1.58 (m, 1H), 1.04–0.95 (m, 1H), 0.89 (d, $J = 6.4$ Hz, 3H), 0.88 ppm (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD): $\delta = 211.8$, 150.3, 149.8, 130.6, 128.2, 113.9, 110.7, 64.4, 62.9, 57.4, 57.2, 51.9, 48.6, 48.3, 37.0, 30.7, 27.4, 24.2, 23.3 ppm; IR (neat): $\tilde{\nu} = 3397$, 2950, 1649, 1515, 1460, 1367, 1255 cm^{-1}; MS (FAB$^+$): m/z: 318 $[M+H]^+$; HRMS (FAB$^+$): m/z: calcd for $C_{19}H_{28}O_3N$: 318.2069; found 318.2061 $[M+H]^+$.

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[28] Two TBZ molecules were co-crystallized and one TBZ molecule is shown. For details see the Supporting Information.

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