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Asymmetric Synthesis of Tetrabenazine and Dihydrotetrabenazine

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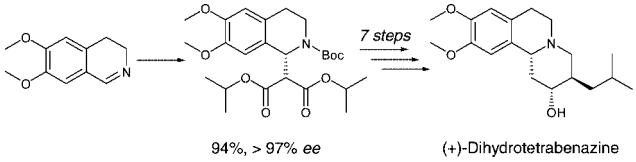
Received March 3, 2009



The enantioselective synthesis of (+)-tetrabenazine (TBZ) and (+)-dihydrotetrabenazine (DTBZ), agents of significant interest for therapeutic and molecular imaging applications, has been completed in 21% (TBZ) and 16% (DTBZ) overall yield and in >97% ee from the starting dihydroisoquinoline. The synthesis utilizes Sodeoka's palladium-catalyzed asymmetric malonate addition to set the initial stereocenter followed by a number of diastereoselective transformations to incorporate the remaining asymmetric centers.

Dihydrotetrabenazine (DTBZ) and tetrabenazine (TBZ), synthetic analogs of the ipecac alkaloid emetine, were first reported as racemic mixtures in the 1950s.[1] They are potent inhibitors of vesicular monoamine transporter-2 (VMAT-2), binding with affinities of 6 and 8 nM, respectively, for the racemic compounds in in vitro assays.[2] Inhibition of VMAT-2 by TBZ and DTBZ results in monoamine depletion via metabolism of cytoplasmic monoamines by the monoamine oxidase enzymes.[3]

In August 2008, racemic TBZ (Xenazine) was approved for use in the U.S. for the treatment of chorea associated with Huntington's disease.[4] DTBZ is the major metabolite of TBZ in vivo.[5] Enantiomerically pure (+)-DTBZ radiolabeled with ^{11}C has been widely used to image VMAT-2 in the brain[6] for the purpose of understanding neurological and psychiatric disorders such as schizophrenia,[7] Tourette's syndrome,[8] Parkinson's,[9] Huntington's,[10] and Alzheimer's diseases,[11] as well as the mechanism of narcotics and addiction.[12] Recently, (+)-[^{11}C]DTBZ has been used to detect the loss of pancreas β-cell mass/function in rodent models of diabetes.[13] VMAT-2 has been identified as a potential β-cell selective biomarker via gene expression profiling.[14] Type II diabetes represents a growing worldwide economic challenge.[15] Detection of β-cell dysfunction prior to hyperglycemia might enable interventions that delay or even prevent the onset of hyperglycemia and the debilitating health issues associated with it.[16]

The (+)-(2*R*,3*R*,11b*R*)-DTBZ enantiomer binds more tightly to rat VMAT-2 (K_i = 0.97 nM) than does the corresponding (−) enantiomer (K_i = 2.2 μM).[17] Consistent with this observation, biodistribution of (+)-[^{11}C]DTBZ correlated with VMAT-2 distribution in vivo, whereas the (−) isomer did not.[6b] The literature presents examples of enantiomerically pure ^{11}C[8–13,17,18] and ^{18}F[19] DTBZ analogs for imaging VMAT-2. In all cases, the synthesis of these agents required resolution of a racemic mixture. To our knowledge, no asymmetric synthesis of DTBZ

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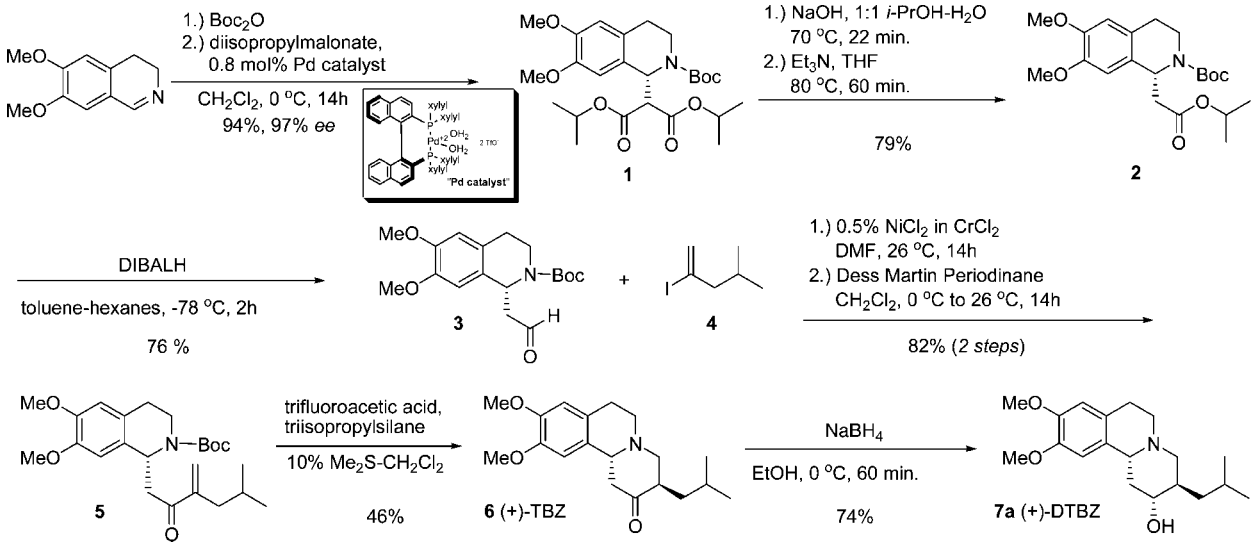
10.1021/jo900480n CCC: $40.75 © 2009 American Chemical Society
Published on Web 04/17/2009

SCHEME 1. Synthesis of (+)-DTBZ



has been reported to date.[20] A facile asymmetric synthesis would allow access to large quantities of enantiomerically pure material that may be useful for further studies involving this class of compounds.

Our retrosynthetic approach is outlined in Figure 1. We envisioned that (+)-DTBZ could be accessed from **A** via a selective *6-endo-trig* cyclization[21] followed by reduction of the resultant ketone with a sterically unencumbered hydride source. The compound **A** could be disconnected to the key chiral aldehyde **B** through removal of the vinylogous group that would ultimately become the aliphatic side chain of (+)-DTBZ. We initially considered two possible routes to the key intermediate **B**. The first route originated from manipulation of the chiral allyltetrahydroisoquinoline **C** to provide **B**. Access to the chiral intermediate **C** was enabled by a few recent reports on the asymmetric allylation of dihydroisoquinoline (**E**).[22] Alternatively, the catalytic asymmetric addition of malonates to dihydroisoquinolines (**E**) to provide intermediates resembling **D** has also been reported.[23] After careful consideration we eventually decided to pursue the asymmetric malonate addition approach (**E** to **D**) in favor of the asymmetric allylation route based on reported yields, ee's, and catalyst stoichiometry.

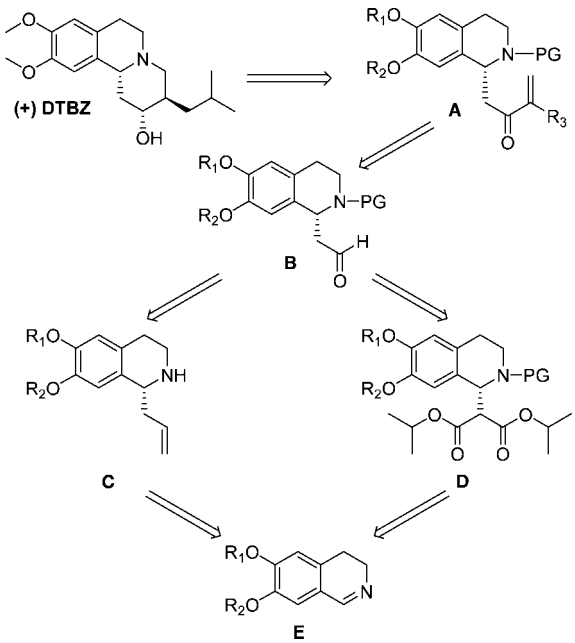


FIGURE 1. Retrosynthetic analysis of (+)-DTBZ.

The asymmetric synthesis of (+)-DTBZ is described in Scheme 1. Starting from the commercially available dihydroisoquinoline, we were able to incorporate the desired malonate according to the published procedure[23] to provide **1** in excellent yield and enantiomeric excess. We found that the palladium catalyst derived from (*S*)-DM-binap was quite suitable for mediating the asymmetric transformation. Our initial attempts to convert the malonate **1** directly to the monoester **2** using Krapcho's method[24] invariably left us with a complex mixture of products. We discovered that partial hydrolysis under carefully controlled conditions followed by thermally catalyzed decarboxylation in the presence of triethylamine[25] provided the desired monoester **2** in 79% yield. Reduction of the monoester to provide the key intermediate **3** was effected cleanly by treatment with DIBALH in a mixture of toluene and hexanes. With **3** in hand we were ready to install the desired aliphatic side chain through the application of a Nozaki−Hiyama−Kishi coupling reaction.[26] The requisite vinyl iodide for this transformation was prepared from the commercially available terminal alkyne with a modification to the standard procedure using *B*-iodo-9-BBN (see Supporting Information). With the necessary precursors **3** and **4** in hand we were able to mediate the desired coupling reaction in excellent yield to provide the desired allylic alcohol as a nearly 1:1 mixture of diastereomers. Direct oxidation of this mixture using Dess−Martin periodinane cleanly yielded the desired α,β-unsaturated ketone **5**. Conversion of **5** to (+)-TBZ was achieved under the mildly acidic conditions required for Boc deprotection. The cyclization routinely yielded a 5:1 mixture of diastereomers unsurprisingly favoring the isomer in which the aliphatic side chain resided in the equatorial position. Final reduction of **6** to (+)-DTBZ (**7a**) was accomplished according to conventional procedures using sodium borohydride in ethanol.[1b,5a,27] The reduction typically

(20) We have published patent applications around this process: (a) Rishel, M. J.; Amarasinghe, K. K. D.; Dinn, S. R.; Johnson, B. F. US 20080306267 A1. (b) Rishel, M. J.; Amarasinghe, K. K. D.; Dinn, S. R.; Johnson, B. F. US 20080306269 A1. (c) Rishel, M. J.; Amarasinghe, K. K. D.; Dinn, S. R.; Johnson, B. F. WO 2008154243.

yielded a 5:1 mixture of diastereomers favoring the product of axial hydride addition to the (+)-TBZ core. The product of equatorial hydride addition (**7b** not shown, see Experimental Section) was also characterized. The diastereomers were easily separated by flash chromatography on silica gel.

In conclusion, we have demonstrated a simple asymmetric synthesis of (+)-DTBZ, a compound currently of significant interest for use as an imaging agent for the prediction and therapeutic monitoring of type I and type II diabetes and for use as a neurological imaging agent. The product was prepared in 16% overall yield and in 9 steps from the starting dihydroisoquinoline.

Experimental Section

(*R*)-*tert*-Butyl-1-(2-isopropoxy-2-oxoethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (2). The starting material (9.8 g, 20.4 mmol) was taken up in 100 mL of isopropyl alcohol to provide a 0.2 M solution of **1**. To this solution was added 100 mL of a 1 M aqueous NaOH solution, bringing the final concentration of the reaction mixture to 0.1 M with respect to the malonate. The reaction mixture was heated to and maintained at 70 °C for 22 min (timing was started when the temperature of the reaction mixture exceeded 65 °C). Following the allotted time the reaction mixture was quickly cooled to 0 °C by immersion in an ice−water bath. The reaction mixture carefully acidified with 2 M aqueous HCl and extracted with three portions of dichloromethane. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The isolated material was taken up in 200 mL of THF to provide a 0.1 M solution (based on the original quantity of **1** used in the reaction mixture), and 2.8 mL (20.4 mmol) of triethylamine (1.0 equiv) was added to the reaction mixture at room temperature. The reaction mixture was heated to 80 °C and maintained at this temperature for 90 min. The reaction mixture was cooled, concentrated under reduced pressure, dissolved in a minimal quantity of CH_2Cl_2, and immediately purified by column chromatography on SiO_2 (15−40% EtOAc−hexanes; the eluant was monitored at 284 nm). The product existed as a mixture of rotamers at room temperature (variable temperature NMR analysis of this product provided in the Supporting Information (Figure S1) clearly indicated a rotameric mixture). The product was a colorless foam 79%: $[\alpha]^{26}_D$ −82 (*c* 0.24, CH_2Cl_2); IR (film) 2977, 2934, 1732, 1695, 1519, 1419, 1365, 1257, 1164, 1102 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19−1.25 (m, 6H), 1.43−1.49 (m, 9H), 2.58−2.69 (m, 2H), 2.70−2.77 (m, 1H), 2.78−2.92 (m, 1H), 3.13−3.43 (m, 1H), 3.81−3.85 (m, 6H), 3.86−4.01 (m, 1H), 4.91−5.05 (m, 1H), 5.38−5.61 (m, 1H), 6.56−6.61 (m, 1H), 6.64−6.70 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.8, 21.90, 27.93, 28.1, 28.4, 37.5, 38.8, 42.2, 42.8, 51.1, 51.9, 55.9, 56.0, 68.1, 79.7, 80.2, 109.6, 110.0, 111.4, 111.5, 126.3, 126.5, 128.5, 128.8, 147.5, 148.0, 154.4, 154.5, 170.4, 170.6; LRMS-(ESI+) calcd for ($C_{21}H_{31}NO_6$ + H) ($[M + H]^+$ 394.22, found 394.16; HRMS-(ESI+) calcd for ($C_{21}H_{31}NO6$) + H) $[M + H]^+$ 394.2224, found 394.2225.

(*R*)-*tert*-Butyl 6,7-Dimethoxy-1-(5-methyl-3-methylene-2-oxohexyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (5). To a neat mixture of 1.2 g (5.6 mmol) of the vinyl iodide **4** (1.7 equiv) and 3.2 g (9.5 mmol) of the aldehyde **3** (1.0 equiv) at room temperature was added 3.0 equiv of chromium chloride (2.1 g, 16.9 mmol) doped with 0.5% $NiCl_2$ (w/w). The mixture was vortexed for about 2 min to provide a homogeneous, green/gray paste and then stirred under nitrogen for an additional 10 min, after which time 20 mL of anhydrous DMF was added to bring the final reaction concentration to 0.34 M. The reaction mixture was deep green in color and was permitted to continue stirring at room temperature for 14 h. Following the allotted time, the reaction mixture was diluted with 1:1 EtOAc−hexanes, an aqueous 0.5 M EDTA solution (pH 9) was added, and the entire mixture was allowed to stir for 1.5 h. The aqueous layer was extracted with three portions of EtOAc, dried ($MgSO_4$), and filtered, and the filtrate was concentrated under reduced pressure to provide a green oil. The crude material was subjected to column chromatography on SiO_2 (35% EtOAc−hexanes; elution was observed at 285nm and 228 nm). The product was a pale yellow oil (2.3 g, 5.5 mmol) isolated in 98% yield. The diastereomeric mixture of products was taken up in 50 mL of dichloromethane to provide a 0.1 M solution and was then cooled to 0 °C. To the mixture was then added 1.1 equiv of the Dess−Martin reagent (2.6 g, 6.2 mmol). The reaction mixture was allowed to stir, slowly warming to room temperature over 2.5 h. The reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution and diluted with ethyl acetate. The organic and aqueous layers were partitioned and separated, and the aqueous layer was extracted with three additional portions of ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography on SiO_2 (10−30% EtOAc−hexanes, elution was observed at 285 and 228 nm). The product was a colorless, foul-smelling oil (2.0 g, 4.7 mmol) that existed at 26 °C as a 60:40 mixture of rotamers in solution (84%): ^1H NMR ($CDCl_3$) δ 0.82 (apparent t, $J = 7.6$ Hz, 6H), 1.42 (s, 9H), 1.70 (apparent sept, $J = 6.62$ Hz, 1H), 2.08−2.15 (m, 1H), 2.15−2.24 (m, 1H), 2.62−2.70 (m, 1H), 2.75−2.91 (m, 1H), 2.93−3.07 (m, 1H), 3.07−3.29 (m, 1.6H), 3.30−3.43 (m, 0.4H), 3.79 (s, 3H), 3.81 (s, 3.4H), 4.04−4.16 (m, 0.6H), 5.52−5.62 (m, 1H), 5.69 (s, 1H), 5.90 (s, 0.6H), 6.04 (s, 0.4H), 6.57 (s, 1H), 6.63 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.5, 27.0, 27.3, 28.1, 28.4, 38.0, 39.3, 40.4, 45.2, 45.9, 51.6, 55.9, 56.0, 79.8, 80.2, 109.9, 110.3, 110.3, 111.4, 125.7, 125.7, 126.3, 129.3, 147.6, 147.9, 148.2, 148.3, 148.4, 154.4, 154.5, 199.5; HRMS-(ESI+) calcd for ($C_{24}H_{35}NO_5$) + H) $[M + H]^+$ 418.2594, found 418.2590.

(3*R*,11b*R*)-3-Isobutyl-9,10-dimethoxy-3,4,6,7-tetrahydro-1*H*-pyrido[2,1-*a*]isoquinolin-2(11b*H*)-one (6). The starting material **5** (2.0 g, 4.7 mmol, 1.0 equiv) was dissolved in 60 mL of 20% Me_2S-dichloromethane to provide an 81 mM solution of the starting material. The solution was cooled to 0 °C, and 1.1 mL (5.2 mmol) of triisopropylsilane (1.1 equiv) followed by 58 mL (0.75 mol) of TFA (precooled to 0 °C) was added to the reaction mixture to provide a final concentration of 41 mM. The reaction mixture was permitted to stir at 0 °C for 1 h. Following the allotted time the reaction mixture was quenched at 0 °C by the addition of saturated aqueous potassium carbonate solution and then concentrated under reduced pressure to remove the majority of the dimethylsulfide. The mixture was extracted with five portions of dichloromethane, and the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide the crude product as a yellow solid. The crude product was recrystallized from 3.5% dimethoxyethane in hexanes. The resulting colorless crystals were washed with hexanes to provide pure (+)-tetrabenazine (**6**) 46%: mp 126.0 °C (3.5% DME−hexanes) (a crystal polymorph was observed at 116 °C); $[\alpha]^{26}_D$ +37.2 (*c* 0.41, CH_2Cl_2); IR (film) 2952, 2920, 1712, 1517, 1465, 1368, 1326, 1263, 1230, 1206, 1155, 1144, 1107, 1009 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 0.89 (apparent t, $J = 7.2$ Hz, 6H), 0.98 (ddd, $J = 12$, 6.0, 4.0

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Hz, 1H), 1.59−1.68 (m, 1H), 1.74 (ddd, J = 12, 5.9, 5.7 Hz, 1H), 2.32 (apparent t, J = 11.7 Hz, 1H), 2.46 (apparent t, J = 12.3 Hz, 1H), 2.55 (ddd, J = 12, 10.0, 3.8 Hz, 1H), 2.65−2.73 (m, 2H), 2.83 (dd, J = 5.5, 2.8 Hz, 1H), 2.97−3.07 (m, 1H), 3.07−3.14 (m, 1H), 3.25 (dd, J = 9.7, 6.3 Hz, 1H), 3.47 (apparent d, J = 12 Hz, 1H), 3.75 (s, 3H), 3.77 (s, 3H), 6.55 (s, 1H), 6.60 (s, 1H) ^{13}C NMR (CD_2Cl_2) δ 22.0, 23.0, 25.5, 29.5, 35.2, 47.5, 47.6, 50.5, 55.9, 56.0, 61.5, 62.5, 108.5, 111.7, 126.4, 129.0, 147.7, 148.0, 209.7; HRMS-(ESI+) calcd for ($C_{19}H_{27}NO_3$ + H) ([M + H]$^+$ 318.2069, found 318.2082.

(2*R*,3*R*,11b*R*)-3-Isobutyl-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-*a*]isoquinolin-2-ol (7a) and (2*S*,3*R*,11b*R*)-3-Isobutyl-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-*a*]isoquinolin-2-ol (7b). To a 0.11 M solution of 100 mg (0.32 mmol) of (+)-TBZ (**6**) in 3 mL of ethanol at 0 °C was added 34 mg (0.90 mmol) of $NaBH_4$ (2.85 equiv). The reaction mixture was allowed to stir for 60 min at room temperature. The excess solvent was carefully removed under reduced pressure, and the residue was taken up in dichloromethane and washed with three portions of saturated aqueous K_2CO_3. The aqueous washings were back extracted with two portions of dichloromethane. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide a colorless oil. Purification of the crude product was achieved by chromatography on SiO_2 (2.5−5% MeOH−CH_2Cl_2, elution was observed at 285nm) UV active fractions were reanalyzed by TLC. Two products, **7a** and **7b** (see Supporting Information), were isolated from this procedure. The major product **7a** was a colorless solid 74 mg (0.23 mmol) 74%: $[\alpha]^{26}_D$ +48 (*c* 0.30, CH_2Cl_2); IR (film) 3381, 2951, 2920, 2866, 1611, 1532, 1465, 1452, 1366, 1334, 1258, 1247, 1231, 1208, 1149, 1084, 1036, 1009 cm^{-1}; ^{1}H NMR (CD_2Cl_2) δ 0.93 (d, J = 6.6 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H), 1.04 (ddd, J = 14.6, 8.7, 4.3 Hz, 1H), 1.42 (dd, J = 20.2, 11.4 Hz, 1H), 1.59 (ddd, J = 13.7, 9.6, 3.3 Hz, 1H), 1.64−1.78 (m, 2H), 1.96 (apparent t, J = 11.4 Hz, 1H), 2.27 (br s, 1H), 2.40−2.48 (m, 1H), 2.54 (ddd, J = 12.3, 3.7, 2.3 Hz, 1H), 2.60−2.67 (m, 1H), 2.95−3.09 (m, 3H), 3.11 (apparent d, J = 11.1 Hz, 1H), 3.35 (ddd, J = 10.4, 10.4, 4.5 Hz, 1H), 3.80−3.81 (m, 6H), 6.60 (s, 1H), 6.69 (s, 1H); ^{13}C NMR (CD_2Cl_2) δ 21.6, 24.0, 25.3, 29.3, 39.7, 40.8, 41.6, 51.8, 55.7, 55.9, 60.0, 60.9, 74.3, 108.4, 111.7, 126.7, 129.8, 147.4, 147.6; HRMS-(ESI+) calcd for ($C_{19}H_{29}NO_3$ + H) ([M + H]$^+$ 320.2226, found 320.2242.

Acknowledgment. We would like to thank Hans Grade for aid in obtaining high resolution mass spectral data and Tracy Zhang, Tom Early, and Paul Donahue for aid in obtaining and interpreting NMR spectra. Additionally, the authors would like to thank our colleagues at GE Healthcare Medical Diagnostics for their generous support and counsel.

Supporting Information Available: General experimental procedures along with detailed procedures for the preparation of compounds **1**, **3**, and **4**, spectral data for compound **7b** and copies of ^{1}H and ^{13}C NMR spectra of all reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO900480N