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The stereoselective total synthesis of (−)-dihydrotetrabenazine

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ABSTRACT

A highly stereoselective synthesis of (−)-dihydrotetrabenazine has been accomplished using (*R*)-*tert*-butanesulfinamide as a chiral source. The synthesis involves the allylation of chiral *N*-sulfinyl imine followed by ring closure of the resulting secondary amide with a tethered halide and the Evans-Aldol reaction as key steps.

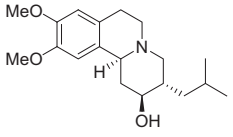
In 1950s, the ipecac alkaloids such as emetine, dihydrotetrabenazine (**1**, DTBZ), and tetrabenazine (**2**, TBZ) were first isolated as racemic mixtures (Fig. 1)[1] Of these, dihydrotetrabenazine is an active metabolite of tetrabenazine. The racemic tetrabenazine has recently been approved as a drug candidate by FDA for the treatment of Chorea, which represents a major advancement of Huntington's disease (HD).[2] The clinical research test reveals that TBZ dramatically decreases the Chorea when compared to the patients treated with placebo.[3] TBZ and DTBZ are useful as vesicular monoamine transporter 2 (VMAT2) inhibitors. The radio labeled TBZ and DTBZ are used as radiotracers in Positron Emission Tomography (PET) for imaging the dopamine neuron degeneration diseases and recently the beta-cell mass related to diabetes.[4]

Due to its promising biological activity, DTBZ has attracted many synthetic chemists to take up its total synthesis. As a result, various approaches have appeared in the literature.[5]

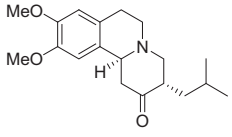
The chiral *N*-*tert*-butanesulfinamide is a versatile chiral auxiliary for the asymmetric induction in the preparation of synthetically useful chiral amines.[6] Addition of an organometallic reagent to C=N bond of an enantiopure sulfinimine is one of the most elegant methods for the synthesis of chiral amines. The electron-withdrawing sulfinyl group is highly stereodirecting and activates the C=N bond effectively in nucleophilic addition reactions, and can easily be removed to provide the enantiopure amine derivatives.[7] However, the use of this useful chiral auxiliary in the total synthesis of complex natural products is still unexplored to a great extent. Inspired by its potential application in natural products synthesis, we attempted the total synthesis of dihydrotetrabenazine using *N*-*tert*-butanesulfinamide as a source of chirality.

Herein, we report a highly efficient total synthesis of (−)-dihydrotetrabenazine (**1**) *via* the allylation of an enantiopure sulfinimine. Our retrosynthetic approach for the synthesis of (−)-dihydrotetrabenazine (**1**) is outlined in Scheme 1. Accordingly, we envisioned that (−)-dihydrotetrabenazine could be accessed from lactam **15** which in turn could be prepared by an intramolecular amidation of ester **14**. The compound **13** was proposed to be obtained from enantiopure *N*-sulfinyl imine **5** by two consecutive reactions *viz* allylation and Evans aldol reaction. The aldimine **5** could be prepared by the condensation of (*R*)-*tert*-butanesulfinamide with an aldehyde **4** which was prepared by a known procedure from 2-(3,4-dimethoxyphenyl)ethanol **3**.

The construction of fragment **9** of dihydrotetrabenazine is outlined in Scheme 2. Accordingly, we began the synthesis of **9** from a commercially available 2-(3,4-dimethoxyphenyl)ethanol **3**, which was converted into the corresponding aldehyde **4** in 70% yield using a known procedure.[8] The condensation of an aldehyde **4** with (*R*)-*tert*-butanesulfinamide in the presence of $CuSO_4$ afforded the respective *N*-sulfinyl imine **5** in 81% yield.[9] Addition of



(-)-Dihydrotetrabenazine **(1)**



(-)-Tetrabenazine **(2)**

Figure 1. Examples of tetrahydroisoquinoline alkaloids, (-)-dihydrotetrabenazine (**1**) and (-)-tetrabenazine (**2**).

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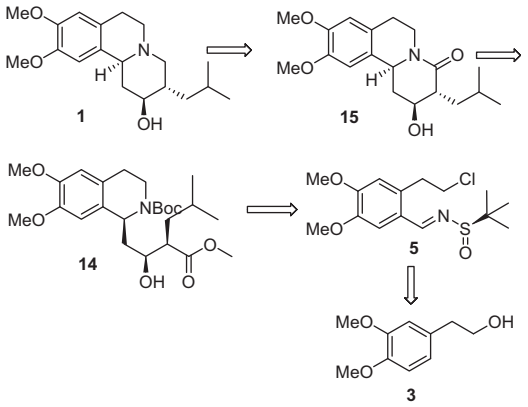
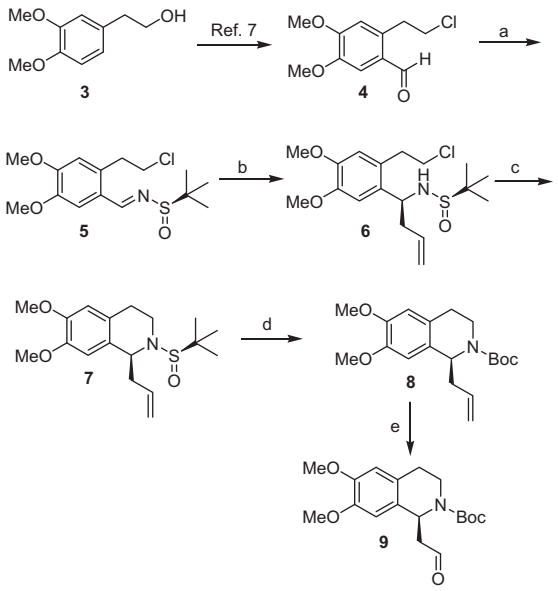


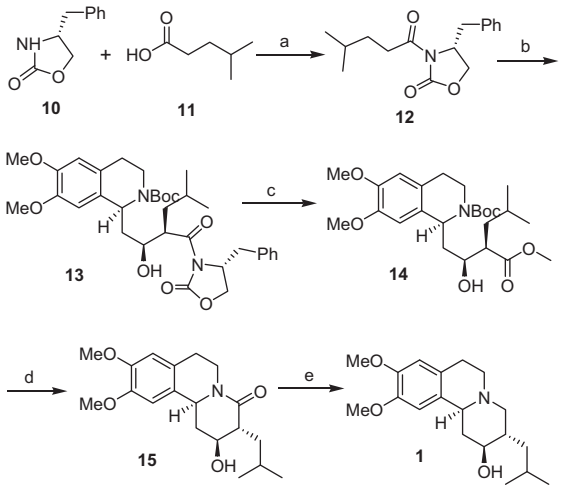
Scheme 1. Retrosynthetic approach of (−)-dihydrotetrabenazine.



Scheme 2. Synthesis of aldehyde **9**. Reagents and conditions: (a) (*R*)-*tert*-butanesulfinamide, $CuSO_4$, CH_2Cl_2, 25 °C, 24 h, 81%; (b) AllylMgBr, CH_2Cl_2, −78 °C, 1 h, 80%; (c) NaH, DMF, 0 °C to rt, 6 h, 76%; (d) (i) EtOH/HCl, 1,4-dioxane, 5 h, 0 °C; (ii) Boc_2O, Et_3N, CH_2Cl_2, rt, 1 h, 75% (over two steps); (e) OsO_4, 2,6-lutidine, $NaIO_4$, 1,4-dioxane, 2 h, 78%.

allylmagnesium bromide onto aldimine **5** at −78 °C in dichloromethane gave the homoallylic sulfinamide **6** in 80% yield with 9:1 ratio of diastereomers.[10] The diastereomeric mixtures could easily be separated by column chromatography. An intramolecular cyclization of a major isomer **6** in the presence of NaH in DMF at room temperature gave the cyclized product **7** in 76% yield.[11] Removal of the sulfinyl group with ethanolic HCl gave the tetrahydroisoquinoline in 85% yield.[12] The resulting free amine was then protected as a Boc derivative **8** in 80% yield by treatment with an excess of TEA in dichloromethane followed by the addition of Boc anhydride.[9] Oxidative cleavage of the terminal olefin of **8** using OsO_4, 2,6-lutidine, and $NaIO_4$ gave the aldehyde **9** in 78% yield in a single step (Scheme 2).[13]

Next we attempted the preparation of (*R*)-acyloxazolidinone **12** by acylation of the (*R*)-oxazolidinone **10** with 4-methyl-pentanoic acid **11** using a known experimental procedure.[14] Asymmetric aldol reaction of boron enolate, derived from acyloxazolidinone **12** with an aldehyde **9** gave the *syn* aldol adduct **13** in 80% yield.[15] The chiral auxiliary was then removed using sodium methoxide in



Scheme 3. Coupling of aldehyde **9** with **12**. Reagents and conditions: (a) Et_3N, pivalolyl chloride, LiCl, THF, 0 °C; 78% (b) (*R*)-4-benzyl-3-(4-methylpentanoyl) oxazolidin-2-one, Bu_2BOTf, Et_3N, CH_2Cl_2, −78 °C–0 °C; 80% (c) NaOMe, MeOH/CH_2Cl_2, −25 °C, 1 h, 63%; (d) (i) TMSOTf, CH_2Cl_2, rt, 5 h; (ii) K_2CO_3, 18-crown-6, MeOH, rt, 1d, 80%; (over two steps); (e) LAH, THF, 70 °C, 2 h, 76%.

methanol (63%) to afford the ester **14**.[16] Removal of the Boc group from compound **14** with TMSOTf in CH_2Cl_2 followed by cyclization of the resulting secondary amine with a tethered ester in the presence of K_2CO_3 and 18-crown-6 in methanol gave the lactam **15** in 80% yield (over two steps).[17] The reduction of lactam **15** with LAH in THF afforded the (−)-dihydrotetrabenazine (**1**) in 76% yield [$\alpha_D = -54.5$, $c = 0.6$, MeOH] (Scheme 3).[18] The optical rotation and spectral data of the (−)-dihydrotetrabenazine (**1**) are in good agreement with the data reported in the literature.[19,20]

In summary, we have demonstrated a highly efficient total synthesis of (−)-dihydrotetrabenazine using (*R*)-*tert*-butanesulfinamide as a chiral source. The use of asymmetric Evans-Aldol reaction establishes the stereochemistry of another two chiral centers which makes this synthesis more simple, quite efficient, and attractive.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.017.

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20. *Spectral data for selected compounds*
*(−)-Dihydrotetrabenazine (**1**)*: $[\alpha]_D^{28}$ −54 (*c* = 0.6, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.67 (1H, s), 6.58 (1H, s), 3.84 (6H, s), 3.45–3.32 (1H, m), 3.20–2.97 (4H, m), 2.69–2.53 (2H, m), 2.51–2.39 (1H, m), 2.04–1.95 (1H,m), 1.80–1.65 (2H, m), 1.63–1.47 (2H, m), 1.11–1.01 (1H, m), 0.96–0.70 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.6, 147.3, 129.1, 126.3, 111.6, 108.1, 74.5, 60.9, 59.9, 56.0, 55.9, 51.7, 41.4, 40.4, 39.7, 29.0, 25.4, 24.1, 21.7. IR (KBr): ν_{max} 3396, 2925, 1566, 1409, 1259, 760 cm^{-1}; ESIMS: *m*/*z* 320 $[M+H]^+$. *Compound (**15**)*: $[\alpha]_D^{28}$ −102 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.66 (1H, s), 6.61 (1H, s), 4.81–4.73 (1H, m), 4.60 (1H, dd, *J* = 4.0, 11.3 Hz), 3.87–3.85 (6H, m), 2.94–2.58 (4H, m), 2.36–2.26 (1H, m), 2.11–1.95 (2H, m), 1.93–1.69 (2H, m), 1.67–1.55 (1H, m), 0.98 (3H, d, *J* = 6.6 Hz), 0.92 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 147.7, 128.2, 127.1, 111.4, 107.9, 68.9, 55.9, 55.8, 53.2, 48.6, 39.9, 39.8, 38.8, 29.6, 28.3, 26.5, 23.1, 22.3; IR(KBr): υ_{max} 3410, 2924, 2854, 1616, 1515, 1460, 1256, 1222, 1078, 757, 701 cm^{-1}; ESIMS: *m*/*z* 334 $[M+H]^+$. *Compound (**13**)*: $[\alpha]_D^{28}$ +15 (*c* = 1.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.16 (5H, m), 6.65 (1H, s), 6.58 (1H, s), 5.28–5.18 (1H, m), 4.76–4.64 (1H, m), 4.26–3.99 (3H, m), 3.87 (3H, s), 3.85 (3H, s), 3.82–3.70 (1H, m), 3.33 (1H, dd, *J* = 3.2, 13.0 Hz), 3.18–3.05 (1H, m), 2.96–2.79 (1H, m), 2.75–2.52 (2H, m), 2.04–1.70 (4H, m), 1.60–1.52 (2H, m), 1.47 (9H, s), 0.95 (3H, d, *J* = 2.4 Hz), 0.92 (3H, d, *J* = 2.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.0, 156.3, 153.1, 147.5, 135.2, 129.2, 128.7, 127.1, 125.6, 111.1, 109.7, 80.5, 68.8, 65.7, 56.0, 55.8, 55.5, 50.5, 45.5, 40.3, 38.0, 37.8, 37.2, 28.2, 26.3, 23.5, 22.0; IR (KBr): υ_{max} 3421, 2958, 1780, 1692, 1659, 1517, 1254, 1006, 701 cm^{-1}; ESIMS: *m*/*z* 611 $[M+H]^+$. *Compound (**6**)*: $[\alpha]_D^{28}$ −29 (*c* = 0.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.8 (1H, s), 6.61 (1H, s), 5.73–5.60 (1H, m), 5.19–5.06 (2H, m), 4.60–4.51 (1H, m), 3.81 (3H, s), 3.76 (3H, s), 3.73–3.66 (1H, m), 3.64–3.55 (1H, m), 3.10–2.99 (2H, m), 2.53–2.44 (1H, m), 2.43–2.32 (1H, m), 1.13 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.2, 148.1 134.1, 131.2, 128.7, 119.2, 112.9, 110.3, 55.8, 55.4, 51.8, 44.6, 43.1, 35.7, 22.5; IR (KBr): υ_{max} 3425, 2927, 1518, 1213, 1030 cm^{-1}; ESIMS: *m*/*z* 374 $[M+H]^+$.