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A short enantioselective synthesis of ephedrine, amphetamine and their analogues via two stereocentered Co(III)-catalyzed hydrolytic kinetic resolution of racemic *syn*-benzyloxy epoxide

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ABSTRACT

An efficient route for the synthesis of 6 drugs belonging to phenethylamine and amphetamine classes in excellent overall yields and high optical purity has been described. The strategy involves introduction of stereogenic centers by means of two-stereocentered Co(III)-catalyzed hydrolytic kinetic resolution (HKR) of racemic *syn*-benzyloxy epoxide followed by Pd-catalyzed regioselective cationic hydrogenation of amino alcohols as the key reactions.

Introduction

Aryl derivatives of β-amino alcohols (e.g., **1**–**2**) with two consecutive stereocenteres are important structural motifs in natural products and pharmacologically active substances.[1–3] Some of their uses include nervous system stimulants, bronchodilators, appetite suppressants, and most significantly, as β-blockers.[4–7] Also, they serve the function of chiral ligands in various stereoselective reactions.[8] Furthermore, derivatives of 2-amino-1-phenylpropane (e.g., **3**–**5**; amphetamines) belong to the psychopharmacological active class of sympathomimetic drugs and are of pharmacological interest because they are used as stimulants, decongestants, and anorectics.[9] More importantly, (*R*)-selegiline **6**, a selective irreversible MAO-B inhibitor, is used in combination with L-DOPA or carbidopa for the treatment of early-stage Parkinson's disease, depression, and senile dementia[10] (Fig. 1).

Although many strategies for the synthesis of either enantiomers of ephedrine **1**–**2** and amphetamine analogues **3**–**6** have been reported, most of them have mainly relied on racemic approaches,[11] chiral pool starting materials,[12] asymmetric hydrogenation,[13] classical and kinetic resolutions,[14] regioselective ring opening of a stable aziridinium ion and *cis*-3-aminooxetanes,[15] double asymmetric induction approach,[16] addition of nitromethane to the chiral chromium tricarbonyl complex of *o*-tolualdehyde,[17] reduction of protected cyanohydrins,[18] and biotransformations.[19] However, most of the reported methods for the synthesis of these drugs suffer from certain limitations such as use of expensive reagents, long reaction sequences, low yields, and low diastereo- and enantioselectivities.

Recently, we have reported a novel method that involves the (salen)Co(III)OAc catalyzed hydrolytic kinetic resolution (HKR) of racemic alkoxy epoxides that provides a highly practical route to the enantiopure *syn*- and *anti*-alkoxy epoxides and the corresponding 1,2-diols in a single step.[20] The reaction is convenient to carry out under mild conditions displaying a wide range of substrate scope. As an application of this methodology, we envisaged that the chiral hydroxyl and amine functionalities in the target phenethylamines and amphetamines (**1**–**6**) could be introduced via HKR of racemic α-benzyloxy epoxide **9**. In this communication, we report a short, enantioselective synthesis of several drug molecules **1**–**6** based on HKR of racemic α-benzyloxy epoxide **9** (Scheme 1).

Results and discussion

Scheme 1 shows the reaction sequence for two key intermediates **10** and **11** that are prepared from commercially available cinnamyl alcohol **7**. Thus, the synthesis of racemic *syn*-benzyloxy

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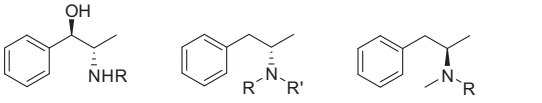


1, R = Me [(-)-ephedrine]
2, R = H [(-)-norephedrine]

3, R, R' = H [(+)-amphetamine]
4, R = Me, R' = H [(+)-metamphetamine]
5, R = Me, R' = Bn [(+)-benzphetamine]

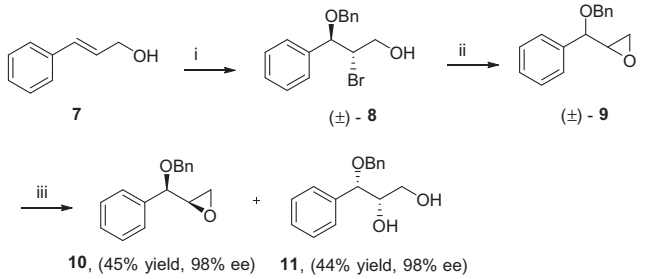
ent- **4**, R = H [(-)-metamphetamine]
6, R = propargyl [(-)-selegiline]

Figure 1. Sympathomimetic drugs of non-catecholamine class.

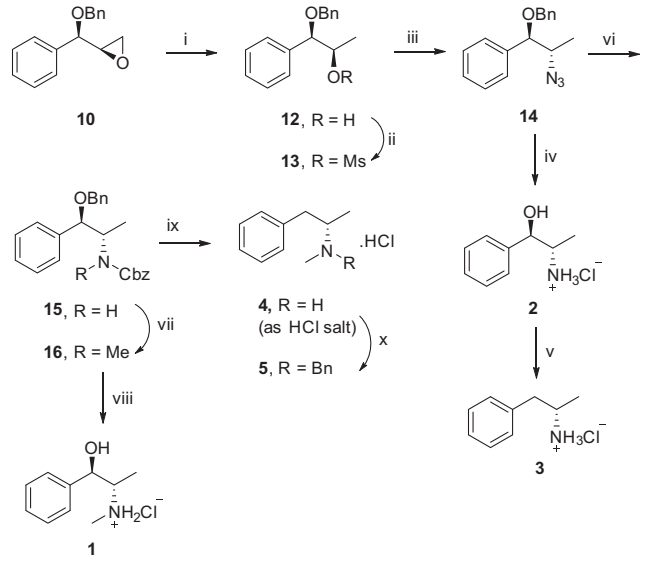
epoxide **9** was achieved from **7** by following a modified procedure involving essentially a two-step reaction sequence of NBS-bromination in the presence of benzyl alcohol to give bromo benzyloxy alcohol **8** regioselectively, followed by treatment with powdered NaOH in THF to form (±)-**9** in 84% yield. The HKR of racemic epoxide **9** was performed using (*S*,*S*)-salenCo(III)OAc as the catalyst and water as the nucleophile (0.5 equiv) that produced the corresponding (1*R*,2*R*)-benzyloxy epoxide **10** (45% yield; 98% ee) and (1*S*,2*S*)-benzyloxy diol **11** (44% yield; 98% ee) in high optical purity. Epoxide **10** was readily separated from diol **11** by a simple chromatographic purification.

Regiospecific reductive ring opening of epoxide **10** with $LiAlH_4$ was carried out to give benzyloxy alcohol **12** (92% yield). Alcohol **12** was mesylated quantitatively to give mesylate **13,** which was subjected to S_N2 displacement with NaN_3 to provide azide **14** with complete inversion (82% yield over two steps).[21] Catalytic hydrogenation of azide **14** [10% Pd/C, H_2 (1 atm), MeOH, 25 °C] followed by its treatment with methanolic HCl furnished (1*R*,2*S*)-norephedrine hydrochloride **2** in quantitative yield and high optical purity (98% ee).[22] Further, catalytic hydrogenolysis of hydrochloride **2** over 10% Pd/C in the presence of methanolic HCl gave (*S*)-amphetamine hydrochloride **3** in 70% yield and 98% ee.[23] Further, $LiAlH_4$ reduction of azide **14** gave the corresponding free amine in situ which was immediately protected as its benzyl carbamate **15** (90% over two steps). N-methylation of **15** (CH_3I, NaH, DMF) gave **16** (75% yield), which was again subjected to catalytic hydrogenation [10% Pd/C, H_2 (1 atm), MeOH, 25 °C] followed by its treatment with methanolic HCl produced (1*R*, 2*S*)-ephedrine hydrochloride **1** in quantitative yield over 2 steps.[24] Compound **16** on catalytic hydrogenation in the presence of methanolic HCl gave (*S*)-methamphetamine hydrochloride **4**[25] which was condensed with benzaldehyde to form the corresponding imine in situ, $NaCNBH_3$ reduction of which furnished (*S*)-benzphetamine **5** in free state (88% yield, 98% ee)[26] (Scheme 2).

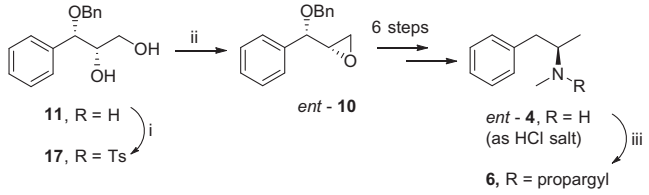
For the synthesis of (*R*)-metamphetamine *ent*-**4** and (*R*)-selegiline **6**, chiral diol **11** was chosen as the starting material, which was smoothly converted to benzyloxy epoxide *ent*-**10** in two steps: (i) selective protection of primary alcohol in the presence of Bu_2SnO to give **17** (98% yield); (ii) treatment of tosylate **17** with K_2CO_3 in MeOH to produce *ent*-**10** (94% yield). A similar sequence of reactions was carried out on *ent*-**10** as described in Scheme 1 ($LiAlH_4$ reduction, mesylation, azidation, reduction of azide group, methylation, catalytic hydrogenolysis) that produced (*R*)-metamphetamine hydrochloride *ent*-**4** in 45% yield over 6 steps.[24] Compound *ent*-**4** was finally propargylated to give (*R*)-selegiline **6** in 85% yield (98% ee)[27] (Scheme 3).



Scheme 1. Reagents and conditions: (i) NBS, BnOH, CH_3CN, 25 °C, 3 h, 85%; (ii) NaOH powder, THF, 0 °C, 2 h, 84%; (iii) (*S*,*S*)-(salen)Co(III)OAc complex (0.5 mol %), H_2O (0.5 equiv), THF, 23 °C, 14 h.



Scheme 2. Reagents and conditions: (i) $LiAlH_4$, THF, 0 °C, 3 h, 92%; (ii) MsCl, Et_3N, CH_2Cl_2, 1 h; (iii) NaN_3, DMF, 80 °C, 82%; (iv) (a) 10% Pd/C, H_2 (1 atm), MeOH, 25 °C, 4 h; (b) methanolic HCl, quantitative yield over 2 steps; (v) 10% Pd/C, H_2 (60 psi), methanolic HCl, 25 °C, 20 h, 70%; (vi) (a) $LiAlH_4$, THF, 0 °C, 3 h; (b) CbzCl, Et_3N, CH_2Cl_2, 2 h, 90% over two steps; (vii) MeI, NaH, 60 °C, DMF, 6 h, 75%; (viii) (a) 10% Pd/C, H_2 (1 atm), MeOH, 25 °C, 4 h; (b) methanolic HCl, quantitative yield over 2 steps; (ix) 10% Pd/C, H_2 (60 psi), methanolic HCl, 25 °C, 20 h, 77%; (x) (a) PhCHO, NaOAc, 1,2-dichloroethane, 4 Å molecular sieves, 25 °C, 4 h; (b) $NaCNBH_3$, MeOH, 0 °C, overnight, 88% over two steps.



Scheme 3. Reactions and conditions: (i) TsCl, Et_3N, Bu_2SnO, CH_2Cl_2, 0 °C, 2 h, 98%; (ii) K_2CO_3, MeOH, 0 °C, 1 h, 94%; (iii) propargyl bromide, anhydrous K_2CO_3, CH_3CN, 25 °C, 85%.

Conclusion

In conclusion, we have provided an effective procedure for the enantioselective synthesis of (1*R*,2*S*)-ephedrine **1**, (1*R*,2*S*)-norephedrine **2**, (*S*)-amphetamine **3**, (*S*)-metamphetamine **4**, (*S*)-benzphetamine **5**, (*R*)-metamphetamine *ent*-**4** and (*R*)-selegiline **6** from commercially available cinnamyl alcohol. In this approach, the key intermediates (**10** and **11**) were readily prepared in high diastereo- and enantioselectivity from the racemic *syn*-benzyloxy epoxide **9** by employing hydrolytic kinetic resolution reaction. The present catalytic synthesis is efficient and involves simple reagents with high yielding steps providing for large scale production of these biologically promising compounds. To the best of our knowledge, this is the first synthetic strategy for accessing

non-catecholamine class of compounds where one common intermediate (±)-**9** was used for synthesis of all the selected compounds.

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Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra for all compounds, detailed experimental procedures) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.10.010.

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21. *Compound* **14**: Yield: 82%; yellowish oil; $[\alpha]_D^{25}$ +11.377 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): ν_{max} 859, 868, 875, 1039, 1101, 1389, 1456, 1493, 1602, 2120; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.25 (d, *J* = 6.7 Hz, 3H), 3.50–3.63 (m, 1H), 4.28–4.66 (m, 3H), 7.24–7.37 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.6, 61.6, 70.8, 83.8, 127.50, 127.6, 127.7, 128.2, 128.4, 128.5, 137.9, 138.2; HRMS (ESI) Calcd for $C_{16}H_{17}N_3O$ $[M+Na]^+$ 290.1264; Found: 290.1263.
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26. *(+)-Benzphetamine* (**5**): Yield: 88%; colorless liquid; $[\alpha]_D^{25}$ +52.8 (*c* 1.0, $CHCl_3$)) {lit.[9h] $[\alpha]_D^{25}$ +53.9 (*c* 1.0, $CHCl_3$)}; ^{1}H NMR (400 MHz, CD_3OD): δ 0.98 (d, *J* = 6.9 Hz, 3H), 2.26 (s, 3H), 2.46–2.52 (dd, *J* = 9.6, 12.8 Hz, 1H), 2.93–3.04 (m, 2H), 3.63 (d, *J* = 2.3 Hz, 2H), 7.12–7.29 (m, 10H); ^{13}C NMR (100 MHz, CD_3OD): δ 14.4, 37.4, 39.8, 58.9, 60.9, 127.0, 128.3, 129.4, 130.4, 140.5, 141.9; HRMS (ESI) Calcd for $C_{17}H_{22}N$ $[M+H]^+$ 240.1747; Found: 240.1750.
27. *(−)-Selegiline* (**6**): Yield: 85%; *gum*; $[\alpha]_D^{25}$ −10.6 (*c* 1.2, EtOH) {lit.[24] $[\alpha]_D^{25}$ −10.8 (*c* 1.2, EtOH)}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.96 (d, *J* = 6.6 Hz, 3H), 2.21 (t, *J* = 2.4 Hz, 1H), 2.30–2.38 (dd, *J* = 3.2, 12.4 Hz, 1H), 2.42 (s, 3H), 2.98–3.08 (m, 2H), 3.42 (d, *J* = 2.4 Hz, 2H), 7.14–7.31 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.1, 37.4, 39.8, 43.1, 59.3, 72.6, 80.3, 125.9, 128.2, 129.2, 140.1; HRMS (ESI) Calcd for $C_{13}H_{18}N$ $[M+H]^+$ 188.1434; Found: 188.1435.