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Enantioselective synthesis of (1*S*,2*R*)-ephenamine

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ABSTRACT

A short and efficient enantioselective synthesis of (1*S*,2*R*)-ephenamine is described employing Sharpless asymmetric dihydroxylation and regioselective nucleophilic opening of a cyclic sulfite as the key steps.

1. Introduction

(1*S*,2*R*)-Ephenamine **1**, (1*S*,2*S*)-pseudoephenamine **2**, and their aminoalcohol analogues (1*S*,2*R*)-1,2-diphenyl-2-aminoethanol **3** and (1*S*,2*S*)-1,2-diphenyl-2-aminoethanol **4**, respectively, have been used as chiral auxiliaries in diastereoselective alkylation reactions, providing easy access to enantiomerically pure alcohols, carboxylic acids, α-methyl α-amino acids,[1] and Williams amino acid synthesis.[2] The biological activity of ephenamine and pseudoephenamine analogues significantly varies and depends on the substituents present at the amino functional group. Therefore, the introduction of *N*-substituents in ephenamine and pseudoephenamine analogues is of great importance for the syntheses of pharmaceuticals and chiral auxiliaries.[3] Ephenamine has been used to resolve penicillin and glycine derivatives,[4] and also in a salt form of penicillin G, an antibiotic additive used to stimulate growth in livestock and poultry.[5] Ephenamine-glutamine salts have been used to provide effective amounts of glutamine for human consumption[6] (Fig. 1).

Various methods for the syntheses of (1*S*,2*R*)-ephenamine **1** and (1*S*,2*R*)-**3** in their different stereoisomeric forms, mainly based on chiral pool or auxiliary supported approaches, have been documented in the literature.[7] In continuation of our research program toward the asymmetric syntheses of bioactive compounds,[8] the Sharpless asymmetric dihydroxylation and cyclic sulfite methodology were envisioned as powerful tools for synthetic functional group transformations. Herein we report a new and short synthesis of (1*S*,2*R*)-ephenamine by employing Sharpless asymmetric dihydroxylation as the source of chirality and cyclic sulfite methodology as the key steps.

2. Results and discussion

As outlined in Scheme 1, the synthesis of (1*S*,2*R*)-ephenamine **1** began with commercially available *trans*-stilbene **5**, which upon treatment with osmium tetraoxide and potassium ferricyanide as the co-oxidant, in the presence of $(DHQ)_2PHAL$ under Sharpless asymmetric dihydroxylation conditions[9] furnished diol **6** in 97% yield (99% ee) {$[\alpha]_D^{25}$ = +95.5 (*c* 1.28, C_2H_5OH) [Lit.[10] $[\alpha]_D^{25}$ = +95.2 (*c* 1.28, C_2H_5OH)]}.

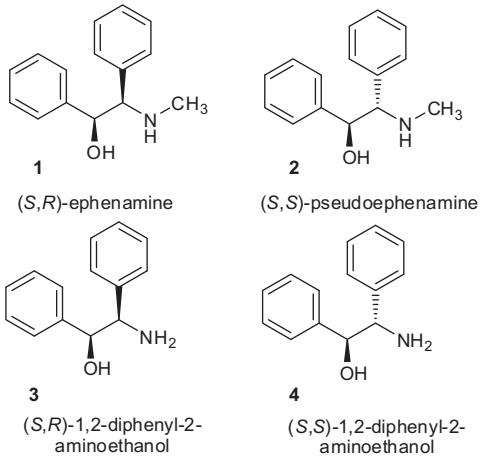

Figure 1. Structures of 1,2-diphenyl-2-aminoalcohols.

With enantiomerically pure (1*S*,2*S*)-1,2-diphenylethane-1,2-diol **6** in hand, we then subjected it to treatment with thionyl chloride in the presence of Et_3N as the base to afford **7**, which upon subsequent treatment with NaN_3 furnished azido alcohol derivative **8** in 89% yield. Concomitant one-pot reduction of the azide group and Boc protection of the resulting amino alcohol were carried out via hydrogenation in the presence of catalytic amounts of Pd–C (20%) and Boc_2O to afford Boc protected amino alcohol derivative **9** in excellent yield. The Boc protected derivative via LAH reduction furnished (1*S*,2*R*)-ephenamine **1** as a white crystalline solid in 83% yield, {$[\alpha]_D^{25}$ = +32.7 (*c* 0.5, C_2H_5OH)

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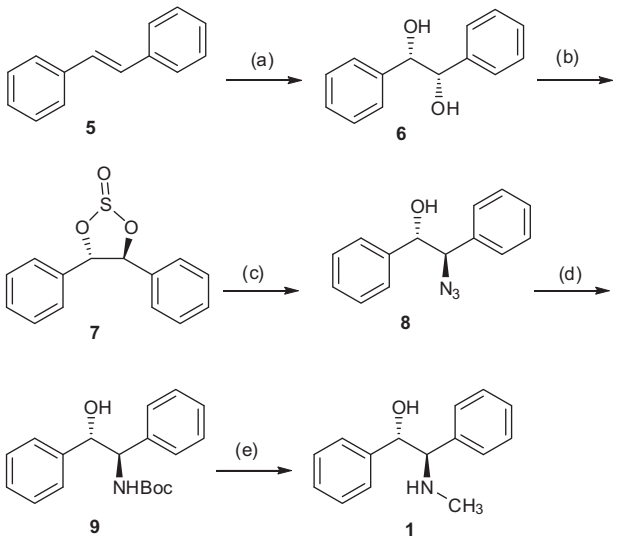
[Lit.[7b] $[\alpha]_D^{25}$ = +32.8 (*c* 0.5, C_2H_5OH)]}. The physical and spectroscopic data were in full agreement with those reported in the literature.



Scheme 1. Reagents and conditions: (a) $K_3Fe(CN)_6$, K_2CO_3, $(DHQ)_2PHAL$, *t*-BuOH/H_2O 1:1 v/v, OsO_4, $CH_3SO_2NH_2$, 0 °C, 24 h, 97%; (b) $SOCl_2$, Et_3N, DCM, 0 °C, 30 min, 85%; (c) NaN_3, DMF, 60 °C, 12 h, 89%; (d) H_2/Pd–C (20%), $(Boc)_2O$, EtOAc, rt, 12 h, 91%; (e) $LiAlH_4$, THF, reflux, 6 h, 83%.

3. Conclusion

In conclusion, a highly enantioselective and short synthesis of (1*S*,2*R*)-ephenamine has been achieved by employing the Sharpless asymmetric dihydroxylation and cyclic sulfite methodology as the key steps. The merits of this synthetic approach are high enantioselectivity with high yielding reaction steps. This synthetic strategy has significant potential for further extension to other stereoisomers via double inversion at the α-carbon. Work is currently in progress, and the results will be disclosed in due course.

4. Experimental

4.1. (1*S*,2*S*)-1,2-Diphenylethane-1,2-diol 6

Spectral data of compound **6**: White solid; {$[\alpha]_D^{25}$ = +95.5 (*c* 1.28, C_2H_5OH) [Lit.[9] $[\alpha]_D^{25}$ = +95.2 (*c* 1.28, C_2H_5OH)]}; IR (CH_2Cl_2) *ν*: 3380, 2935, 1510, 937 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 7.22–7.24 (m, 6H), 7.12–7.14 (m, 4H), 4.72 (s, 2H), 2.83 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 139.75, 128.08, 127.88, 126.89, 79.05.

4.2. (1*S*,2*S*)-1,2-Diphenylethane-1,2-diol cyclic sulfite 7

Spectral data of compound **7**: White solid, {$[\alpha]_D^{25}$ = +52.6 (*c* 1, C_2H_5OH)}; IR (CH_2Cl_2) *ν*: 2935, 1362, 723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 7.24–7.42 (m, 10H), 5.68 (d, *J* = 9.64 Hz, 1H), 5.22 (d, *J* = 10.08 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 133.15, 132.07, 129.63, 129.30, 128.93, 128.88, 127.51, 127.16, 91.19, 85.91; HRMS (ESI^+) *m*/*z* calcd for $C_{14}H_{12}O_3SNa^+$ ([M+Na]$^+$) 283.0400; Found 283.0403.

4.3. (1*S*,2*R*)-2-Azido-1,2-diphenylethanol 8

Spectral data of compound **8**: White solid, {$[\alpha]_D^{25}$ = +71.1 (*c* 0.5, C_2H_5OH)}; IR (CH_2Cl_2) *ν*: 2945, 2096, 1260, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 7.25–7.37 (m, 10H), 4.83 (d, *J* = 6.88 Hz, 1H), 4.69 (d, *J* = 6.88 Hz, 1H), 2.13 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 139.60, 135.90, 128.67, 128.62, 128.34, 128.25, 128.01, 127.00, 71.19; HRMS (ESI^+) *m*/*z* calcd for $C_{14}H_{13}N_3ONa^+$ ([M+Na]$^+$) 262.1000; Found 262.0951.

4.4. *tert*-Butyl (1*R*,2*S*)-2-hydroxy-1,2-diphenylethylcarbamate 9

Spectral data of compound **9**: White solid, {$[\alpha]_D^{25}$ = +114.1 (*c* 1, C_2H_5OH); IR (CH_2Cl_2) *ν*: 3250, 1685, 1172, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 7.24–7.23 (m, 6H), 7.02–7.05 (m, 4H), 5.29 (s, 1H), 5.04 (s, 1H), 4.98 (br s, 1H), 2.71 (br s, 1H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 155.65, 139.82, 128.09, 127.97, 127.73, 127.66, 127.59, 126.56, 79.94, 60.55, 29.67, 28.28; HRMS (ESI^+) *m*/*z* calcd for $C_{19}H_{23}NO_3Na^+$ ([M+Na]$^+$) 336.1600; Found 336.1575.

4.5. (1*S*,2*R*)-2-(Methylamino)-1,2-diphenylethanol 1

Spectral data of compound **1**: White crystalline solid, mp 134–136 °C, Lit.[7b] mp 135–136; {$[\alpha]_D^{25}$ = +32.7 (*c* 0.5, C_2H_5OH) [Lit.[7b] = +32.8 (*c* 0.5, C_2H_5OH)]; IR (CH_2Cl_2) *ν*: 3311, 3060, 3043, 2812, 1441 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) *δ*: 7.11–7.17 (m, 10H), 5.31(br s, 1H), 4.66 (d, *J* = 5.48 Hz, 1H), 3.62 (d, *J* = 5.48 Hz, 1H), 2.03 (s, 3H), 1.46 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) *δ*: 143.35, 140.79, 127.69, 127.04, 126.93, 76.07, 70.12, 34.08.

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