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Asymmetric synthesis of (−)-pseudoephedrine from (2*S*,3*S*)-3-phenyloxiran-2-ylmethanol. Stereospecific interchange of amino and alcohol functions

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Abstract—A ring-opening reaction of *N*-methylaziridines with Boc_2O/NaI has been applied to the asymmetric synthesis of pseudoephedrine. 3-Methylamino-3-phenyl-1,2-propanediol **1**, derived from (2*S*,3*S*)-3-phenyloxiran-2-ylmethanol, was converted into the oxazolidin-2-one **4**, a precursor of pseudoephedrine. The reaction occurs with a stereospecific interchange of amino and alcohol functions.

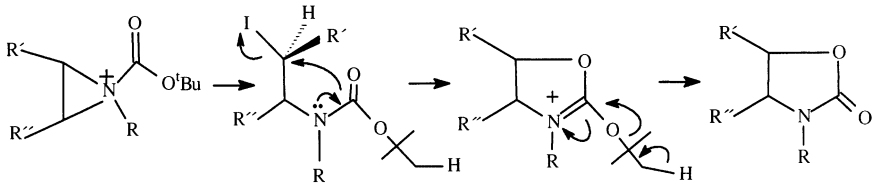
1. Introduction

In a previous paper[1] we reported the ring transformation of *N*-alkyl aziridines into oxazolidin-2-ones in one step by reaction with di-*tert*-butyl dicarbonate and sodium iodide in acetone. The proposed reaction mechanism supposed initial quaternization of the aziridine nitrogen, ring opening by iodide and backside nucleophilic attack by the carbonyl oxygen of the carbamate on the halogenated carbon, followed by carbonylation of the *tert*-butoxy group and elimination of 2-methylpropene (Scheme 1).

Herein, we show how this ring transformation can be used as the key reaction for the synthesis of (−)-pseudoephedrine or (+)-pseudoephedrine starting from (2*S*,3*S*)-3-phenyloxiran-2-ylmethanol.

2. Results and discussion

(*E*)-3-Phenyl-2-propen-1-ol ((*E*)-cinnamyl alcohol) was converted by asymmetric epoxidation into (2*S*,3*S*)-3-phenyloxiran-2-ylmethanol,[2] which reacted regioselectively with aqueous methylamine[3] to yield (2*R*,3*R*)-3-methylamino-3-phenyl-1,2-propanediol **1**. The primary alcohol group was selectively silylated with *tert*-butyldimethylsilyl chloride and the resulting 1-methylamino-3-(dimethyl-*tert*-butylsilyloxy)-1-phenyl-2-propanol **2** converted under Mitsunobu conditions[4] into the corresponding *N*-methylaziridine **3**, which was transformed without isolation into the oxazolidinone **4** by treatment with di-*tert*-butyl dicarbonate and sodium iodide in acetone. As discussed previously, this rearrangement occurs by quaternization of the aziridine nitrogen, ring opening by iodide in this case occurs at



Scheme 1.

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the most reactive benzylic position and nucleophilic attack by the carbamate then occurs. Removal of the silyl group of oxazolidinone **4** afforded the alcohol **5**, which was transformed into the tosyl derivative **6**, reduced with sodium borohydride-dimethylsulfoxide[5] to the oxazolidinone **7**[6] and then subjected to alkaline hydrolysis[5] to afford the requisite product, (–)-pseudoephedrine (Scheme 2). The same sequence starting with (*E*)-cinnamyl alcohol and Sharpless asymmetric epoxidation using diethyl-D-tartrate would give (+)-pseudoephedrine.

The transformation of the amino alcohol **2** to the oxazolidinone **4** supposes a simultaneous and stereospecific interchange of the amino and alcohol functions. There is double inversion at both carbons in the transformation of the epoxide into the aziridine,[7] but rearrangement to the oxazolidinone occurs with retention of configuration and transformation of **2** to **4** affords the *syn*-amino alcohol configuration contained in the pseudoephedrine.

Chemical shifts, coupling constants and the specific rotation for oxazolidine **7** prepared using the synthetic route we have presented are identical to those reported in the literature for *trans*-3,4-dimethyl-5-phenyl-2-oxazolidinone.[6]

3. Conclusion

In summary, we have presented an appropriate new synthetic method for the preparation of pseudoephedrine based on an aziridine ring expansion methodology.

4. Experimental

4.1. Materials and general methods

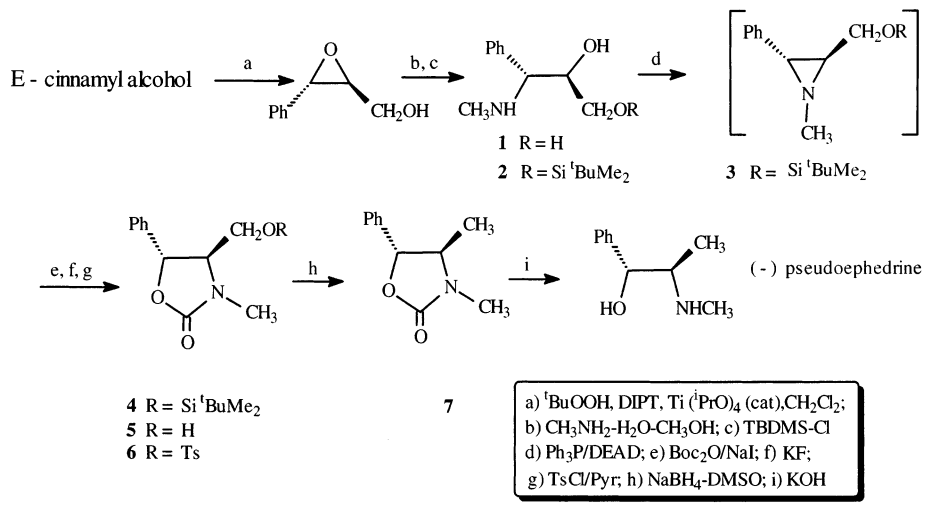
Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. Dichloromethane was distilled from calcium chloride under argon. Analytical thin layer chromatography was performed on Merck precoated silica gel (60 F_{254}) plates and flash column chromatography was accomplished on Merck Kieselgel 60 (230–240 mesh). Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured at room temperature in a Perkin–Elmer 241 polarimeter. IR spectra were recorded on a FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were measured for $CDCl_3$ solutions at 300 and 75.4 MHz, respectively, using a Bruker AC-300 spectrometer and chemical shifts were recorded relative to Me_4Si. High-resolution mass spectral data were obtained under EI conditions at 70 eV with a VG Autospec spectrometer.

4.2. (1*R*,2*R*)-3-(*tert*-Butyldimethylsilyloxy)-1-methylamino-1-phenylpropan-2-ol 2

A solution of (2*R*,3*R*)-3-methylamino-3-phenyl-1,2-propanediol **1**[3a] (2.5 g, 13.8 mmol), *tert*-butyldimethylsilyl chloride (2.21 g, 14.7 mmol), imidazole (2.4 g, 34.7 mmol) in dichloromethane (25 mL) was stirred at room temperature for 1.5 h. The reaction mixture was washed with water, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (1/1) to afford **2** (3.29 g, 81%) as an oil. $[\alpha]_D^{20} = -47.4$ (*c* 3.80, $CHCl_3$). IR (KBr): 3389 cm^{-1}. ^{1}H NMR: 0.12 (s, 3H), 0.19 (s, 3H), 1.00 (s, 9H), 2.37 (s, 3H), 2.91 (br, 1H), 3.31 (dd, 1H, $J=10.2$ and 4.7 Hz), 3.41 (dd, 1H, $J=10.2$ and 5.8 Hz), 3.69 (d, 1H, $J=4.4$ Hz), 3.80 (m, 1H), 7.23 (m, 5H). ^{13}C NMR: 5.6 (q), 17.9 (s), 25.7 (q), 33.6 (q), 63.8 (t), 66.2 (d), 72.8 (d), 127.3 (d), 127.9 (d), 128.3 (d), 138.0 (s). HRMS (MH^+) 296.2042. Calcd for $C_{16}H_{30}NO_2Si$ 296.2045.

4.3. (2*R*,3*S*)-3-(*tert*-Butyldimethylsilyloxymethyl)-1-methyl-2-phenylazirane 3

To a solution of (1*R*,3*R*)-3-(*tert*-butyldimethylsilyloxy)-1-methylamino-1-phenyl-propan-2-ol **2** (1.44 g, 6.5



Scheme 2.

mmol) and triphenylphosphine (2.5 g, 9.5 mmol) in dry ether (35 mL) stirred under nitrogen in an ice bath, was slowly added di-*iso*-propyl azodicarboxylate (1.7 mL, 9.5 mmol) via syringe. The ice bath was removed and the mixture was stirred at room temperature for 24 h. A crystalline precipitate (triphenylphosphine oxide/di-*iso*-propyl hydrazinedicarboxylate complex) was filtered off and washed with hexane/ether, 1:1 (30 mL). The filtrate was evaporated under reduced pressure and the crude product was used for the following reaction.

4.4. (4*R*,5*R*)-4-(*tert*-Butyldimethylsilyloxymethyl)-3-methyl-5-phenyl-1,3-oxazolan-2-one 4

Di-*tert*-butyl dicarbonate (1.4 g, 6.5 mmol) in acetone (5 mL) was added to a mixture of the crude aziridine derivative **3** (6.5 mmol) and sodium iodide (0.95 g, 6.5 mmol) and stirred under reflux for 4 h. After removing the solvent, the residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (1/1) to afford **4** (1.35 g, 65%) as a white solid. $[\alpha]_D^{20}=+10.1$ (*c* 0.91, $CHCl_3$). Mp 70–72°C. IR (KBr): 1759 cm^{-1}. ^1H NMR: 0.01 (s, 6H), 0.81 (s, 9H), 2.81 (s, 3H), 2.91 (br, 1H), 3.44–3.48 (m, 1H), 3.67 (dd, 1H, $J=10.9$ and 3.7 Hz), 3.76 (dd, 1H, $J=10.9$ and 4.5 Hz), 5.14 (d, 1H, $J=5.4$ Hz), 7.23–7.30 (m, 5H). ^{13}C NMR: 5.6 (q), 17.9 (s), 25.5 (q), 29.2 (q), 61.2 (t), 66.2 (d), 76.7 (d), 125.3 (d), 128.5 (d), 128.7 (d), 138.9 (s), 157.8 (s). HRMS (MH^+) 322.1843. Calcd for $C_{17}H_{28}NO_3Si$ 322.1838.

4.5. (4*R*,5*R*)-4-Hydroxymethyl-3-methyl-5-phenyl-1,3-oxazolan-2-one 5

A mixture of 4-(*tert*-butyldimethylsilyloxymethyl)-3-methyl-5-phenyl-1,3-oxazolan-2-one **4** (1.5 g, 4.7 mmol), potassium fluoride (0.8 g, 14.0 mmol) and methanol (10 mL) was heated to reflux for 3 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with hexane/ethyl acetate (2/3), affording **5** (0.8 g, 83%) as a white solid. $[\alpha]_D^{20}=+12.2$ (*c* 1.96, $CHCl_3$). Mp 88–90°C. IR (KBr): 3418, 1746 cm^{-1}. ^1H NMR: 2.88 (s, 3H), 3.40 (m, 1H), 3.71 (dd, 1H, $J=12.4$ and 3.5 Hz), 3.90 (dd, 1H, $J=12.4$ and 3.5 Hz), 5.37 (d, 1H, $J=6.2$ Hz), 7.34–7.39 (m, 5H). ^{13}C NMR: 29.2 (q), 59.7 (d), 66.7 (t), 76.7 (d), 125.6 (d), 128.8 (d), 128.9 (d), 138.7 (s), 158.5 (s). HRMS (M^+) 207.0890. Calcd for $C_{11}H_{13}NO_3$ 207.0895.

4.6. (4*R*,5*R*)-4-(4-Methylphenylsulfonyloxymethyl)-3-methyl-5-phenyl-1,3-oxazolan-2-one 6

To a solution of alcohol **5** (0.2 g, 0.96 mmol) in pyridine (3 mL) was added *p*-toluenesulfonyl chloride (0.7 g, 3.7 mmol) at 5°C. After 15 h of stirring, the reaction mixture was quenched with 2 M aqueous HCl (14 mL) and extracted with diethyl ether (3×15 mL), the organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with hexane/ethyl acetate (3/2) gave **6** (0.25 g, 72%) as an oil. $[\alpha]_D^{20}=+20.6$ (*c* 0.64, $CHCl_3$). IR (KBr): 1761 cm^{-1}. ^1H NMR: 2.38 (s, 3H), 2.71 (s, 3H), 3.61 (m, 1H, $J=6.1$, 3.7 and 3.9 Hz), 4.08 (dd, 1H, $J=11.1$ and 3.7 Hz), 4.16 (dd, 1H, $J=11.1$ and 3.9 Hz), 5.05 (d, 1H, $J=6.2$ Hz), 7.23–7.30 (m, 7H), 7.71 (d, 2H, $J=8.3$ Hz). ^{13}C NMR: 22.1 (q), 29.8 (q), 64.2 (d), 66.6 (t), 76.6 (d), 125.4 (d), 127.8 (d), 128.9 (d), 129.0 (d), 130.1 (d), 131.8 (s), 137.4 (s), 145.6 (s), 157.1 (s). HRMS (M^+) 361.0999. Calcd for $C_{18}H_{19}NO_5S$ 361.0984.

4.7. (4*R*,5*R*)-3,4-Dimethyl-5-phenyl-1,3-oxazolan 2-one 7

Sodium borohydride (0.112 g, 3.0 mmol) was added to a solution of the tosyl derivative **6** (0.5 g, 1.5 mmol) in dimethylsulfoxide (8 mL). The mixture was heated to 150°C and kept at this temperature for 2 h. After cooling at room temperature, the solution was diluted with water (40 mL) and extracted with dichloromethane (3×100 mL). The organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford a white solid that was identified as the oxazolidinone **7** (0.22 g, 76%). $[\alpha]_D^{20}=-29.4$ (*c* 3.46, $CHCl_3$). Mp 45–46°C. IR (KBr): 1757 cm^{-1}. ^1H NMR: 1.26 (d, 3H, $J=6.2$ Hz), 2.80 (s, 3H), 3.45 (m, 1H), 4.83 (d, 1H, $J=7.7$ Hz), 7.28 (m, 5H). ^{13}C NMR: 17.1 (q), 28.5 (q), 61.1 (d), 82.2 (d), 125.7 (d), 128.6 (d), 128.7 (d), 137.4 (s), 157.6 (s). HRMS (M^+) 191.0941. Calcd for $C_{11}H_{13}NO_2$ 191.0946.

4.8. (−)-Pseudoephedrine

A solution of oxazolidinone **6** (0.5 g, 2.6 mmol) in an aqueous solution of KOH (20% KOH in water:ethanol, 1:1, 2.5 mL) was stirred under reflux for 2 h. The mixture was cooled to room temperature, neutralized with a saturated aqueous NH_4Cl solution (25 mL) and extracted with CH_2Cl_2 (2×20 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure affording a white solid that was identified as (−)-pseudoephedrine (0.35 g, 88%). Mp 119–120°C. $[\alpha]_D^{20}=-47.2$ (*c* 1.0, $CHCl_3$); ^1H NMR: 0.79 (d, 3H, $J=6.0$ Hz), 2.29 (s, 3H), 2.52 (dq, 1H, $J=8.2$ and 6.0 Hz), 2.96 (b, 1H), 4.08 (d, 1H, $J=8.2$ Hz), 7.24 (m, 5H). ^{13}C NMR: 15.4 (q), 33.4 (q), 61.1 (d), 77.4 (d), 126.9 (d), 127.5 (d), 128.1 (d), 142.5 (s).

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