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TETRAHEDRON: *ASYMMETRY*

Asymmetric synthesis of enantiomerically pure spiro[((2*S*)-hydroxy)indane-1,4′-piperidine]

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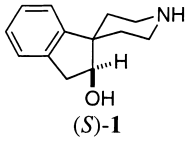
Abstract

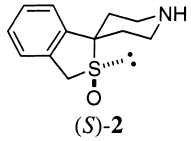
We report herein, efficient and practical synthetic methods for the preparation of enantiomerically pure spiro[((2*S*)-hydroxy)indane-1,4′-piperidine] (*S*)-**1**, a key intermediate for the synthesis of a tachykinin receptor antagonist, using catalytic asymmetric reduction or catalytic asymmetric epoxidation as a key step. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

Spiro-substituted piperidine analogues are important compounds as subunits in a number of biologically active compounds. Spiro[(2-hydroxy)indane-1,4′-piperidine] **1** has been known as a component of growth hormone secretagogues,[1] and also as one of the key constituents of a tachykinin receptor antagonist.[2] In the course of our studies on tachykinin receptor antagonists, we have synthesized a variety of spiro-substituted piperidine analogues. Among these analogues, the compounds which possess properties such as spiro[((2*S*)-hydroxy)indane-1,4′-piperidine] (*S*)-**1** or spiro[benzo[*c*]thiophene-1(3*H*),4′-piperidine]-(2*S*)-oxide (*S*)-**2**[3] moiety had strong binding affinities to the tachykinin receptor. Preliminary studies indicated that the stereochemistry of the hydroxy group of **1** and sulfoxide of **2** has great impact on the binding activity to tachykinin receptor, and the (*S*)-configuration has been shown to be an essential requirement for more potent binding affinities.



(*S*)-**1**



(*S*)-**2**

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The conformations of these spiro-piperidine analogues clearly play a key role in binding to the tachykinin receptor. The aromatic rings of (*S*)-**1** and (*S*)-**2** are required to exploit a hydrophobic or π–π interaction with the receptor, and the secondary hydroxy group of **1** and sulfoxide of **2** are needed for high affinity to the receptor, probably through their actions as hydrogen bond acceptors or donors, or due to the steric effect. In fact, geometry optimizations of **1** and **2** were carried out using the semiempirical molecular orbital method PM3 in the program SPARTAN. It was found that both compounds have very similar conformations, as shown in Fig. 1.

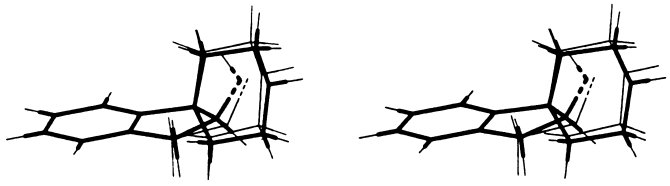
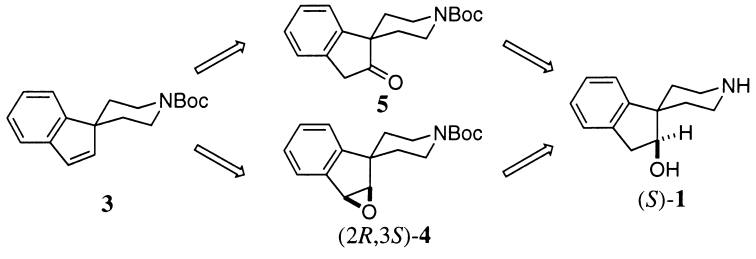


Figure 1. Stereoview of the superimposition of stable conformers of (*S*)-**1** (bold line) and (*S*)-**2** (solid line)

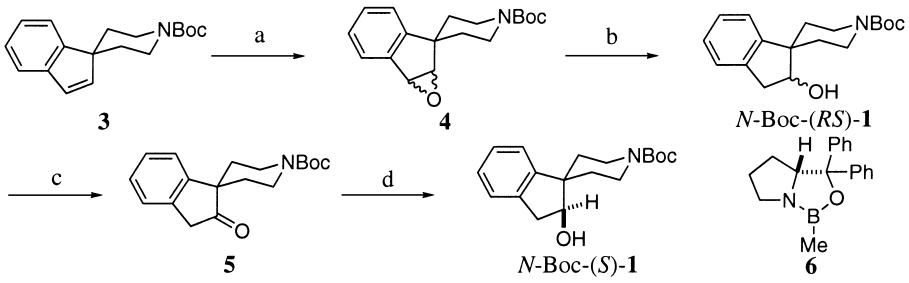
In a previous paper,[1] racemic *N*-Boc-(*RS*)-**1** was prepared by hydroboration of indene analogue **3** as a mixture with the 3-hydroxy derivative. Studies to date have yet to address successfully the enantioselective preparation of both enantiomers of **1**. We report herein, efficient and practical synthetic methods for the preparation of enantiomerically pure (*S*)-**1**. The key features of our approach are Corey's CBS-oxazaborolidine-catalyzed reduction of ketone **5**, and Jacobsen's asymmetric epoxidation of indene derivative **3** followed by reductive opening of the epoxide (Scheme 1).



Scheme 1.

2. Results and discussion

At first, we focused on the asymmetric reduction of ketone **5**. Ketone **5** was synthesized according to Scheme 2. Epoxide **4** was obtained in 95% yield by treating indene **3**[4] with aqueous H_2O_2 and pyridine in the presence of a catalytic amount of methyltrioxorhenium(VII) in CH_2Cl_2,[5] and subsequent regioselective reductive opening[6] of the epoxide produced racemic *N*-Boc-(*RS*)-**1** in 86% yield. Next, *N*-Boc-(*RS*)-**1** was oxidized to ketone **5** with pyridinium chlorochromate (PCC) in 86% yield. While there are a great number of chiral reducing agents described in the literature, we focused our attention on CBS (Corey–Bakshi–Shibata)-oxazaborolidine catalysts,[7] an extremely important class of asymmetric reducing catalysts. Actually, by treating ketone **5** with 5.0 mol% of (*R*)-2-methyl-CBS-oxazaborolidine **6** as catalyst and BH_3–THF (0.5 equiv.) as the reducing reagent in THF at room temperature for 30 min, we obtained *N*-Boc-(*S*)-**1** with 89% *ee* in quantitative yield (Scheme 2). This synthesis also led to the synthesis of *N*-Boc-(*R*)-**1** with the opposite configuration by using (*S*)-2-methyl-CBS-oxazaborolidine instead of (*R*)-2-methyl-CBS-oxazaborolidine.



Scheme 2. Reagents: (a) methyltrioxorhenium(VII) (2 mol%), H_2O_2, pyridine, CH_2Cl_2 (95%); (b) 5% Pd–C, HCO_2NH_4, dioxane, 80°C (86%); (c) PCC, MS 4A, CH_2Cl_2 (86%); (d) (*R*)-2-methyl-CBS-oxazaborolidine **6** (5 mol%), BH_3–THF, THF (100%, 89% *ee*)

The *ee* of *N*-Boc-(*S*)-**1** could be determined by HPLC analysis. The secondary alcohol was converted to the 4-nitrobenzoate with 4-nitrobenzoyl chloride and triethylamine in CH_2Cl_2, and the resulting 4-nitrobenzoate was analyzed by chiral HPLC (column, CHIRALPAK AD (4.6ϕ×250 mm); eluent, 50:50 *n*-hexane:2-propanol mixture; flow rate, 0.5 mL/min; t_R of (*S*)-isomer, 10.1 min; t_R of (*R*)-isomer, 17.1 min). The stereochemistry of (*S*)-**1** was confirmed by X-ray analysis of α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) amide of (*S*)-**1**. A single-crystal X-ray structure determination of (*R*)-MTPA amide of (*S*)-**1** unambiguously established the relative configuration, and hence, the absolute stereochemistry of the hydroxy group is *S*, as shown in Fig. 2.[8]

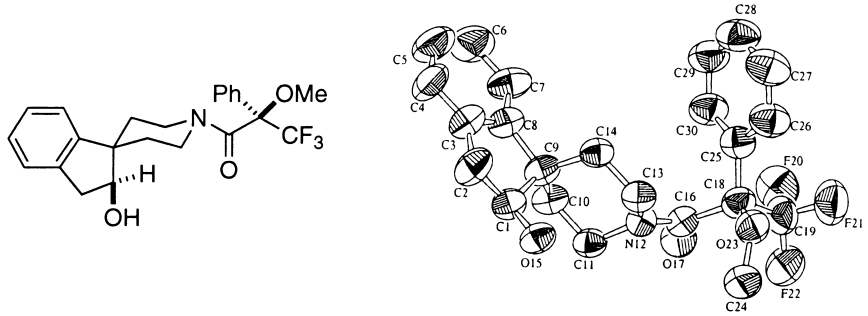
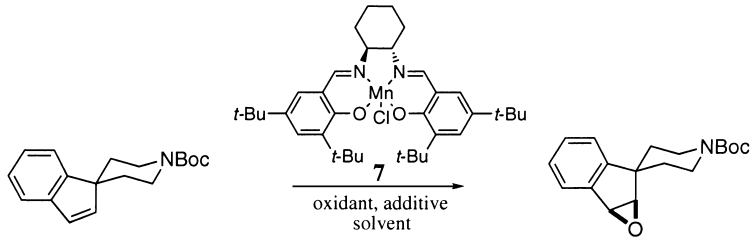


Figure 2. X-Ray ORTEP of (*R*)-MTPA amide of (*S*)-**1**

As an alternative method, asymmetric epoxidation of **3** followed by reductive epoxide opening is a straightforward route to *N*-Boc-(*S*)-**1**. In the past few years, a number of highly promising strategies for asymmetric epoxidation catalysis have been successfully developed. Among these strategies, the use of Jacobsen's (salen)Mn(III)Cl[9] complexes is effective for the catalysis of the asymmetric epoxidation. High enantioselectivities and yields are obtained for a variety of substrates, especially *cis*-alkenes. Asymmetric epoxidation of **3** using Jacobsen's (*S,S*)-*N,N′*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride **7** was investigated in various combinations of solvent, oxidant, and additive, and selected results are summarized in Table 1.

High enantioselectivities and moderate chemical yields were obtained under a variety of conditions. A screening of appropriate solvents for oxidation showed a dramatic solvent effect, and the best solvent was dichloromethane. On the other hand, the oxidants and additives had little effect on the enantioselectivities. The *ee* of (2*R*,3*S*)-**4** could be determined directly by chiral HPLC analysis (column, CHIRALCEL OD (4.6ϕ×250 mm); eluent, 80:20 *n*-hexane:2-propanol mixture; flow rate, 0.5 mL/min; t_R of (2*S*,3*R*)-isomer, 10.7 min; t_R of (2*R*,3*S*)-isomer, 13.2 min). This method also led to the synthesis of *N*-Boc-(*R*)-**1** with the opposite configuration by using (*R,R*)-(salen)Mn(III)Cl.

Table 1
Asymmetric epoxidation of **3**

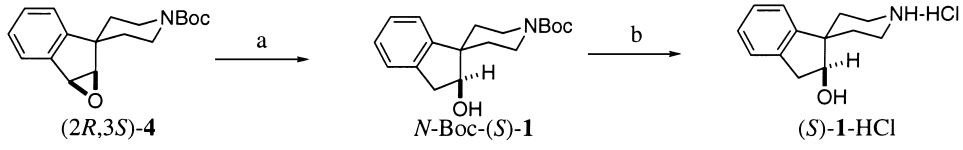


3 (2*R*,3*S*)-**4**

Run	**7** (mol %)	Solvent	Oxidant (eq)	Additive (eq)	Yield (%)	%*ee* of **4**
1	10	CH_2Cl_2	NaOCl (2.0)	4-PPNO[a] (0.3)	44	92
2	10	CH_2Cl_2	NaOCl (2.0)	NMO[b] (5.0)	51	87
3	10	CH_2Cl_2	mCPBA (2.0)	NMO (5.0)	44	93
4	5	CH_2Cl_2	NaOCl (2.0)	4-PPNO (0.3)	51	91
5	2	CH_2Cl_2	NaOCl (2.0)	4-PPNO (0.3)	55	88
6	5	*t*-BuOMe	NaOCl (2.0)	4-PPNO (0.3)	36	74
7	5	PhCl	NaOCl (2.0)	4-PPNO (0.3)	trace	-

[a] 4-PPNO = 4-phenylpyridine *N*-oxide; [b] NMO = 4-methylmorpholine *N*-oxide

The resulting epoxide (2*R*,3*S*)-**4** was then subjected to reductive opening with 5% Pd–C and HCO_2NH_4 in dioxane at 80°C to provide the desired *N*-Boc-(*S*)-**1** in 86% yield. Thus, two complementary approaches to the conversion of **3** to *N*-Boc-(*S*)-**1** were explored. Single recrystallization of the resulting *N*-Boc-(*S*)-**1** (87–93% *ee*) from *n*-hexane and ethyl acetate produced enantiomerically pure *N*-Boc-(*S*)-**1** (>99% *ee*) as white crystals (mp 105–107°C, $[\alpha]_D^{24}$ +50.0 (*c* 1.0, MeOH)) in 70–80% recovery. Subsequent deprotection of the Boc group with 4 N HCl/dioxane produced (*S*)-**1** HCl salt as white crystals (mp 246–248°C, $[\alpha]_D^{24}$ +46.2 (*c* 0.5, MeOH)) in 93% yield (Scheme 3).



(2*R*,3*S*)-**4** *N*-Boc-(*S*)-**1** (*S*)-**1**-HCl

Scheme 3. Reagents: (a) 5% Pd–C, HCO_2NH_4, dioxane, 80°C (86%); (b) 4 N HCl/dioxane, room temperature (93%)

In conclusion, potentially useful and effective methods for the preparation of (*S*)-**1** have been achieved. The enantiomerically pure (*S*)-**1** prepared by the above methods has been successfully incorporated into a number of tachykinin receptor antagonists. The results of this work will be published elsewhere.

3. Experimental

3.1. General

All melting points were measured on a Yanaco MP-500D micro melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO P-1030 digital polarimeter. The IR spectra

were measured on a JASCO FT/IR 8300 spectrophotometer as KBr plates, and peaks are reported in cm^{-1}. ^1H NMR spectra were recorded on a JEOL JNM-GSX 400 spectrometer in $CDCl_3$ or DMSO-d_6. ^1H NMR chemical shifts are reported in ppm downfield of internal tetramethylsilane. Mass spectra were recorded using a JEOL JMS-BU 20 or JMS-700 spectrometer. Thin layer chromatography (TLC) was used routinely to monitor the progress and purity of compounds and was performed on Merck Kieselgel 60 F_{254} plates. For flash column chromatography, silica gel (Kieselgel 60, 230–400 mesh) was employed.

3.2. N-tert-*Butoxycarbonyl-spiro[((2,3)-epoxy)indane-1,4′-piperidine]* **4**

N-tert-Butoxycarbonyl-spiro(1*H*-indene-1,4′-piperidine) **3** (10.0 g, 35.1 mmol) and 174 mg (0.70 mmol, 2.0 mol%) of methyltrioxorhenium(VII) were dissolved in 20 mL of CH_2Cl_2. To this solution, 0.67 mL (8.40 mmol, 24.0 mol%) of pyridine was added, and then 7.90 mL (70.0 mmol, 1.5 equiv.) of 30% aqueous H_2O_2 was added dropwise from a syringe at 0°C over a period of 10 min. The resulting mixture was stirred for 5 h at rt. After the addition of 70.0 mL (70.0 mmol) of a 1.0 M aqueous solution of sodium hypochlorite, the resulting mixture was stirred for 1 h. Water was added and the resulting mixture was extracted with AcOEt. The organic extract was washed with brine and then dried over anhydrous Na_2SO_4. The solvent was then removed in vacuo, and the residue was purified by silica gel flash column chromatography (eluent, *n*-hexane:AcOEt=2:1) to obtain **4** (10.0 g, 95% yield) as white crystals. Mp 148–150°C. IR (KBr) ν_{max}: 2949, 1679, 1424, 1365, 1244, 1168, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49 (1H, d, *J*=7.3 Hz), 7.32–7.15 (3H, m), 4.28 (1H, d, *J*=2.9 Hz), 4.11 (1H, d, *J*=2.9 Hz), 4.30–4.03 (2H, m), 3.15 (2H, broad t, *J*=12.0 Hz), 1.95–1.74 (3H, m), 1.51 (9H, s), 1.58–1.50 (1H, m); MS (EI) *m/z*: 301 (M^+). Anal. calcd for $C_{18}H_{23}NO_3$: C, 71.74; H, 7.69; N, 4.65. Found: C, 71.59; H, 7.54; N, 4.64.

3.3. N-tert-*Butoxycarbonyl-spiro[(2-hydroxy)indane-1,4′-piperidine]* N-*Boc-(*RS)-***1**

N-tert-Butoxycarbonyl-spiro[((2,3)-epoxy)indane-1,4′-piperidine] **4** (10.0 g, 33.2 mmol) was dissolved in 1,4-dioxane (200 mL). To the resulting solution, 12.0 g of ammonium formate and 300 mg of 5% palladium–carbon were added, followed by stirring at 80°C for 1 h. To the reaction mixture, 6.0 g of ammonium formate and 150 mg of 5% palladium–carbon were added and the resulting mixture was stirred for 1 h. After the reaction mixture was allowed to stand at rt, it was filtered. The solvent of the filtrate was removed in vacuo, and the residue was purified by silica gel flash column chromatography (eluent, *n*-hexane:AcOEt=3:1) to obtain *N*-Boc-(*RS*)-**1** (8.60 g, 86% yield) as white crystals. IR (KBr) ν_{max}: 3349, 2934, 1698, 1425, 1367, 1168, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.28–7.18 (4H, m), 4.50 (1H, dd, *J*=4.9, 1.9 Hz), 4.07–3.83 (2H, m), 3.32 (1H, dd, *J*=16.7, 4.9 Hz), 3.30–3.12 (2H, m), 2.86 (1H, dd, *J*=16.7, 1.9 Hz), 2.08–1.99 (1H, m), 1.89–1.78 (1H, m), 1.49 (9H, s), 1.64–1.42 (2H, m); MS (FAB) *m/z*: 304 $(M+H)^+$. Anal. calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 70.99; H, 8.24; N, 4.68.

3.4. N-tert-*Butoxycarbonyl-spiro[(2-indanone)-1,4′-piperidine]* **5**

N-tert-Butoxycarbonyl-spiro[(2-hydroxy)indane-1,4′-piperidine] *N*-Boc-(*RS*)-**1** (8.10 g, 26.7 mmol) was dissolved in 160 mL of CH_2Cl_2. To the resulting solution, 8.10 g of molecular sieves (4 Å, powder) and 11.5 g (53.4 mmol) of pyridinium chlorochromate were added under ice-cooling, followed by stirring for 30 min at rt. After the addition of 250 mL of Et_2O to the reaction mixture, the resulting mixture was filtered through Celite. The filtrate was concentrated under reduced pressure, and the residue was purified

by silica gel flash column chromatography (eluent, *n*-hexane:AcOEt=5:1) to afford **5** (6.91 g, 86% yield) as white crystals. IR (KBr) ν_{max}: 2931, 1749, 1686, 1417, 1366, 1178, 1150, 1031, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.46–7.22 (4H, m), 3.93 (2H, broad s), 3.60 (2H, s), 3.52 (2H, broad s), 1.79–1.76 (4H, m), 1.50 (9H, s); MS (EI) *m/z*: 301 (M^+). Anal. calcd for $C_{18}H_{23}NO_3$: C, 71.74; H, 7.69; N, 4.65. Found: C, 71.75; H, 7.79; N, 4.57.

3.5. N-tert-*Butoxycarbonyl-spiro[((2*S*)-hydroxy)indane-1,4′-piperidine]* N-*Boc-(*S*)-**1***

To 0.42 mL (0.42 mmol) of a 1.0 M toluene solution of (*R*)-2-methyl-CBS-oxazaborolidine, a THF (8.30 mL) solution of 2.50 g (8.30 mmol) of *N-tert*-butoxycarbonyl-spiro[(2-indanone)-1,4′-piperidine] **5** and 4.20 mL of a 1.0 M THF solution of BH_3–THF complex were added, each at a rate of 1.0 mL/min. The resulting mixture was stirred at rt for 1 h, followed by the addition of water under ice-cooling. After extraction of the reaction mixture with AcOEt, the organic extract was washed with brine and dried over anhydrous Na_2SO_4. The solvent was then removed in vacuo, and the residue was purified by silica gel flash column chromatography (eluent, *n*-hexane:AcOEt=1:1) to afford *N*-Boc-(*S*)-**1** (2.51 g, 100% yield) as white crystals of optical purity 89% *ee*. The resulting crystals were dissolved in 5.0 mL of AcOEt under heating in a water bath. After the addition of 150 mL of *n*-hexane, the resulting mixture was allowed to stand to yield 1.91 g of white crystals. The same procedure was repeated again to furnish 1.52 g (yield: 61%, >99% *ee*) of *N*-Boc-(*S*)-**1** as white crystals. The *ee* of *N*-Boc-(*S*)-**1** was determined by subjecting the 4-nitrobenzoate to chiral HPLC analysis [column, CHIRALPAK AD (4.6ϕ×250 mm); eluent, 50:50 *n*-hexane:2-propanol mixture; flow rate, 0.5 mL/min; t_R(*S*)=10.1 min, t_R(*R*)=17.1 min]. Mp 105–107°C. $[\alpha]_D^{24}$ +50.0 (*c* 1.0, MeOH); IR (KBr) ν_{max}: 3349, 2934, 1698, 1425, 1367, 1168, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.28–7.18 (4H, m), 4.50 (1H, dd, *J*=4.9, 1.9 Hz), 4.07–3.83 (2H, m), 3.32 (1H, dd, *J*=16.7, 4.9 Hz), 3.30–3.12 (2H, m), 2.86 (1H, dd, *J*=16.7, 1.9 Hz), 2.08–1.99 (1H, m), 1.89–1.78 (1H, m), 1.49 (9H, s), 1.64–1.42 (2H, m); MS (FAB) *m/z*: 304 $(M+H)^+$. Anal. calcd for $C_{l8}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 70.99; H, 8.24; N, 4.68.

3.6. N-tert-*Butoxycarbonyl-spiro[((2*R*,*3*S*)-epoxy)indane-1,4′-piperidine] (2*R*,*3*S*)-**4***

N-tert-Butoxycarbonyl-spiro(1*H*-indene-1,4′-piperidine) **3** (100 mg, 0.35 mmol) was dissolved in CH_2Cl_2 (2.0 mL). To the resulting solution, 11.4 mg (0.018 mmol) of (*S,S*)-(+)-*N,N′*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride was added, followed by the addition of 19.0 mg (0.11 mmol) of 4-phenylpyridine *N*-oxide. The resulting mixture was stirred for 10 min. After the addition of 0.7 mL (0.7 mmol) of a 1.0 M aqueous solution of sodium hypochlorite, the resulting mixture was stirred for 2 h. Water was added and the resulting mixture was extracted with AcOEt. The organic extract was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by silica gel flash column chromatography (eluent, *n*-hexane:AcOEt=2:1) to afford (2*R*,3*S*)-**4** (53.6 mg, 51% yield) as white crystals of 91% *ee*. The *ee* of (2*R*,3*S*)-**4** was determined by chiral HPLC analysis [column, CHIRALCEL OD (4.6ϕ×250 mm); eluent, 80:20 *n*-hexane:2-propanol mixture; flow rate, 0.5 mL/min; t_R(2*S*,3*R*)=10.7 min, t_R(2*R*,3*S*)=13.2 min]. Single recrystallization of the resulting (2*R*,3*S*)-**4** (87–93% *ee*) from *n*-hexane and AcOEt yielded enantiomerically pure (2*R*,3*S*)-**4** (>99% *ee*) as white crystals. Mp 148–150°C. $[\alpha]_D^{24}$ +62.2 (*c* 1.0, MeOH). IR (KBr) ν_{max}: 2949, 1679, 1424, 1365, 1244, 1168, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49 (1H, d, *J*=7.3 Hz), 7.32–7.15 (3H, m), 4.28 (1H, d, *J*=2.9 Hz), 4.11 (1H, d, *J*=2.9 Hz), 4.30–4.03 (2H, m), 3.15 (2H, broad t, *J*=12.0 Hz), 1.95–1.74 (3H, m), 1.51 (9H, s), 1.58–1.50 (1H, m); MS (EI) *m/z*: 301 (M^+). Anal. calcd for $C_{l8}H_{23}NO_3$: C, 71.74; H, 7.69; N, 4.65. Found: C, 71.62; H, 7.67; N, 4.59.

3.7. N-tert-*Butoxycarbonyl-spiro[((2S)-hydroxy)indane-1,4′-piperidine]* N-*Boc-(S)-**1***

According to a similar procedure for the preparation of *N*-Boc-(*RS*)-**1**, *N*-Boc-(*S*)-**1** (109 mg) was prepared in 86% yield from (*2R,3S*)-**4** (125 mg, 0.42 mmol) as white crystals. The physiochemical properties of this compound were the same as those of the product produced as described in Section 3.5.

3.8. *Spiro[((2S)-hydroxy)indane-1,4′-piperidine] hydrochloride (S)-**1**·HCl*

N-tert-Butoxycarbonyl-spiro[((2*S*)-hydroxy)indane-1,4′-piperidine] *N*-Boc-(*S*)-**1** (1.50 g, 4.95 mmol) was dissolved in EtOH (12.4 mL). To the resulting solution, 6.20 mL of 4 N solution of hydrogen chloride in 1,4-dioxane was added under ice-cooling, followed by stirring at rt for 5 h. The solvent was removed in vacuo, and the residue was washed with Et_2O to afford (*S*)-**1**·HCl (1.10 g, 93% yield) as white crystals. Mp 246–248°C. $[\alpha]_D^{24}$ +46.2 (*c* 0.50, MeOH); IR (KBr) ν_{max}: 3413, 3269, 2937, 1607, 1431, 1074, 765 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.98 (2H, m), 7.22–7.17 (4H, m), 5.20 (1H, d, *J*=5.0 Hz), 4.40–4.37 (1H, m), 3.26–3.13 (5H, m), 2.77 (1H, dd, *J*=16.5, 3.2 Hz), 2.07 (1H, d, *J*=14.0 Hz), 1.99–1.82 (2H, m), 1.60 (1H, d, *J*=14.0 Hz); MS (EI) *m/z*: 203 ((M^+); free form). Anal. calcd for $C_{13}H_{18}NOCl$: C, 65.13; H, 7.57; N, 5.84; Cl, 14.79. Found: C, 64.89; H, 7.48; N, 5.82; Cl, 15.01.

Acknowledgements

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