Notes

Synthesis of Optically Active 1,2-Indene Oxide and Vicinal *cis*-Aminoindanols *via* Asymmetric Reduction of 2-Tolylsulfonyloxy-1-indanone with (–)-*B*-Chlorodiisopinocampheylborane

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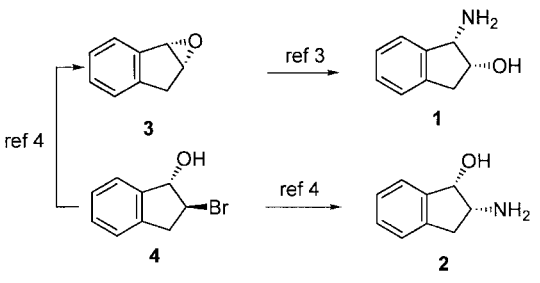
Received July 18, 2001

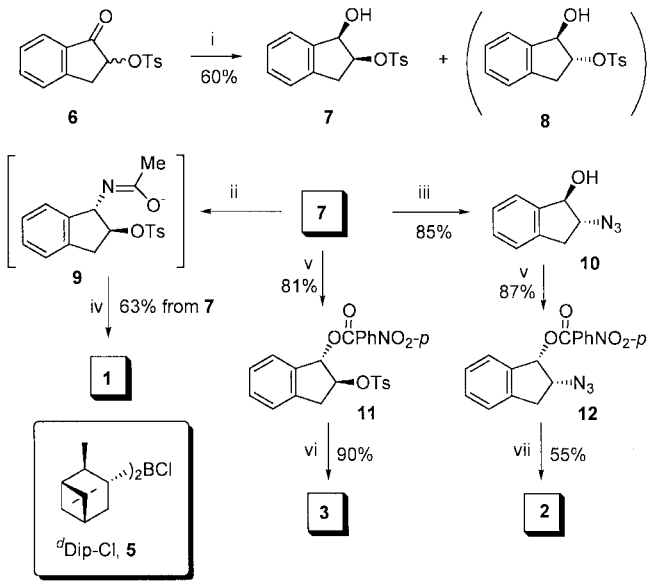
Keywords : (–)-*B*-Chlorodiisopinocampheylborane, (1*S*,2*R*)-1,2-Indene oxide, (1*S*,2*R*)-1-Amino-2-indanol, (1*S*,2*R*)-2-Amino-1-indanol, Asymmetric reduction.

Optically active vicinal *cis*-aminoindanols such as (1*S*,2*R*)-1-amino-2-indanol **1** and (1*S*,2*R*)-2-amino-1-indanol **2** are important substances which can be widely used as a vital source of an orally active HIV-1 protease inhibitor, Indinavir, and as chiral ligands or auxiliaries for chiral stationary phase and asymmetric transformations including carbonyl reductions, aldol reactions, diethylzinc addition to aldehydes and Diels-Alder reactions.[1,2] For the synthesis of these compounds, chemical transformations starting from (1*S*,2*R*)-indene oxide **3** and *trans*-(1*S*,2*S*)-2-bromo-1-indanol **4** have been reported (Scheme 1).[3,4] Very recently, we reported the synthesis of optically active **3** and **4** *via* (*S*)-CBS oxazaborolidine-catalyzed borane reduction of 2-tolylsulfonyloxy-1-indanone **6**.[5] However, the reduction provided an inseparable 59 : 41 mixture of *cis*- and *trans*-tosyloxy alcohols **7** and **8**. On the other hand, it has been known that (–)-*B*-chlorodiisopinocampheylborane ($^{d}Ipc_2BCl$, **5**) is a commercially available and highly effective asymmetric reducing agent for the asymmetric reduction of various prochiral ketones to provide high enantioselectivity with predictable stereochemistry.[6] During the study of asymmetric reduction of 2-sulfonyloxy ketones with this reagent,[7] we found that the reduction of **6** afforded only *cis* isomer **7**. Herein we wish to report a simple synthesis of optically active *cis*-aminoindanols (**1** and **2**) and indene oxide **3** from **7** by performing Ritter[3,8] and Mitsunobu reactions.[9,10]

Using the known procedure,[11] the reduction of **6** with **5** was carried out at -25 °C for 7 days. The reduction provided only (1*R*,2*S*)-2-*p*-tolylsulfonyloxy-1-indanol **7** with 80% ee in 60% yield without the formation of the corresponding *trans* isomer **8**. The stereochemistry and enantiomeric purity of **7** were determined by comparing vicinal coupling constants between α and β protons of C-1 and C-2 by ^{1}H NMR analysis and optical rotation value with the reported data.[5] To obtain **1**, the reaction of **7** with acetonitrile in the presence of fuming sulfuric acid under Ritter reaction[3c] was carried out. The reaction gave (1*S*,2*R*)-1-amino-2-indanol **1** with 65% ee in 63% yield, showing that partial racemization (*ca*. 7%) occurred in the course of production of an intermediate **9** of Ritter reaction. On the other hand, to obtain **2**, we first carried out the S_N2 type azidation of **7** with sodium azide in DMSO to give *trans*-2-azido-1-indanol (1*R*,2*R*)-**10** with 80% ee in 85% yield. Enantiomeric excess of **10** was



Scheme 1



Scheme 2. *Reagents and reaction conditions*: i. [a]**5** (1.1 eq), –25 °C, THF, 7 days; [b]MeCHO, 0 °C, 4 h; MeCN, fuming H_2SO_4 (2 eq), –40 °C. [b]water, rt; iii. NaN_3, DMSO, 80 °C; iv. H_2O, reflux; v. PPh_3 (5 eq), *p*-$NO_2C_6H_4CO_2H$ (4 eq), DEAD (5 eq), THF-tolune, –25 °C → rt; vi. 3 M-KOH-MeOH, rt; vii. $LiAlH_4$.

determined by a HPLC analysis using a Whelk-O1 chiral column. The azido alcohol **10** was directly converted to *cis* isomer **12** of the corresponding *p*-nitrobenzoate by reaction with *p*-nitrobenzoic acid under Mitsunobu conditions.[10b] The ester **12** obtained was reduced by lithium aluminum hydride to (1*S*,2*R*)-**2** with 80% ee in 55% yield. Applying the same Mitsunobu reaction to **7**, we obtained *trans* isomer **11** of the corresponding benzoate in 81% yield. Subsequent treatment of **11** with 3 M KOH in methanol at room temperature for 0.5 h gave (1*S*,2*R*)-**3** with 80% ee in 90% yield. Enantiomeric excess of the product **3** determined by HPLC analysis using a Chiralcel OB column showed it to be 80% ee. The chemical transformations were illustrated in Scheme 2.

In summary, we have developed a convenient synthesis of optically active 1,2-indene oxide **3**, *cis*-1-amino-2-indanol **1** and *cis*-2-amino-1-indanol **2** *via* asymmetric reduction of 2-tolylsulfonyloxy-2-indanone **6** with a commercially available (−)-*B*-chlorodiisopino-campheylborane **5**, followed by Ritter and/or Mitsunobu reaction. This procedure can be used as an alternative to synthesis of compounds **1**-**3**. Further applications using this methodology are currently under investigation.

Experimental Section

General. All operations with air-sensitive materials were carried out under a nitrogen atmosphere with oven-dried glassware. Liquid materials were transferred with a double-ended needle. The reactions were monitored by TLC using silica gel plates and the products were purified by flash column chromatography on silica gel (Merck; 230-400 mesh). NMR spectra were recorded at 400 MHz for ^{1}H and 100 or 125 MHz for ^{13}C using Me_4Si as the internal standard in $CDCl_3$. Optical rotations were measured with a high resolution digital polarimeter. Melting points were uncorrected. Enantiomeric excesses (% ee) of the product epoxides were determined with a HPLC apparatus fitted with Whelk-O1(Regis) and Chiralcel OB column (Daicel).

Materials. Most of organic compounds utilized in this study were commercial products of the highest purity. They were further purified by distillation when necessary. THF was distilled over sodium benzophenone ketyl and stored in ampules under nitrogen atmosphere. (−)-*B*-chlorodiisopino-campheylborane (^{d}Ipc$_2$BCl, **5**) was purchased from the Aldrich Chemical Company.

Preparation of (1*R*,2*S*)-2-*p*-tolylsulfonyloxy-1-indanol 7. An oven-dried, 10-mL round bottom flask equipped with a septum-capped side arm, magnetic stirring bar, and a connecting tube was cooled to room temperature in a stream of nitrogen. ^{d}Ipc$_2$BCl (**5**, 786 mg, 2.4 mmol) was transferred to the flask in a glove bag and dissolved in THF (0.5 mL). The solution was cooled to –25 °C and THF (2 mL) solution of **6**[5] (605 mg, 2.0 mmol) was added. The reaction mixture was maintained at –25 °C. After 7 days, the mixture was warmed up to 0 °C and acetaldehyde (200 μL, 3.6 mmol) was added dropwise. The mixture was warmed to room temperature and stirred for 4 h. After solvent was evaporated under reduced pressure, the residue was purified by a flash column chromatography on silica gel (230-400 mesh) using EtOAc/hexane (1/2). The product (1*R*,2*S*)-**7** was isolated in 60% yield; R_f 0.47; mp 70-71 °C [lit.[5] mp 70-71 °C]; $[\alpha]_D^{22}$ +16.34 (*c* 1.14, $CHCl_3$), 80% ee based on $[\alpha]_D^{22}$ −17.7 (*c* 1.0, $CHCl_3$) for (1*S*,2*R*)-**7**[5], 87% ee; IR, ^{1}H and ^{13}C NMR spectral data of this compound were identical with those of (1*S*,2*R*)-**7** reported.[5]

Preparation of (1*S*,2*R*)-1-amino-2-indanol 1. To a solution of (1*R*,2*S*)-**7** (433 mg, 1.5 mmol) in acetonitrile (2 mL) and 1,2-dichloroethane (2 mL) cooled at −40 °C, 65% fuming sulfuric acid (150 μL, 3 mmol) was added slowly over 5 min. The reaction mixture was warmed up to room temperature and stirred for 3 h. To this, water (5 mL) was added and the mixture was heated to reflux for 4 h. After cooling the mixture to room temperature, it was washed with 1,2-dichloromethane (2 × 10 mL). Aqueous layer was basified to pH 12 with a 25% solution of sodium hydroxide in water and extracted with dichloromethane (3 × 10 mL). Organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was purified by a flash column chromatography on silica gel (230-400 mesh) using MeOH/$CHCl_3$ (1/1). The product (1*S*,2*R*)-**1** was isolated in 63% yield; R_f 0.21; mp 114-115 °C [lit.[10b] mp 116-117 °C]; $[\alpha]_D^{22}$ −43.12 (*c* 1.02, $CHCl_3$), 65% ee based on $[\alpha]_D^{22}$ −61.03 (*c* 0.3, $CHCl_3$) for (1*S*,2*R*)-**1**[10b]; IR, ^{1}H and ^{13}C NMR spectral data of this compound were identical with the reference data.[10b]

Preparation of (1*R*,2*R*)-2-azido-1-indanol 10. A mixture of (1*R*,2*S*)-**7** (228 mg, 0.75 mmol) and sodium azide (68 mg, 1.05 mmol) in dimethyl sulfoxide (3 mL) was stirred at 80 °C for 2 h. After addition of water (10 mL) to the reaction mixture, the mixture was cooled to room temperature, and extracted with dichloromethane (3 × 15 mL). Organic layer was dried over anhydrous magnesium sulfate, concentrated and the residue was purified by a flash column chromatography on silica gel (230-400 mesh) using EtOAc/hexane (1/2) to give (1*R*,2*R*)-**10** in 85 % yield; R_f 0.53; mp 104-6 °C [lit.[10b] mp 116-117 °C]; $[\alpha]_D^{22}$ −27.12 (*c* 2.04, $CHCl_3$), 80% ee based on $[\alpha]_D^{22}$ −34 (*c* 11, $CHCl_3$) for (1*R*,2*R*)-**10**[10a]. A HPLC analysis using a Whelk-O1 chiral column (Regis) showed it to be 80% ee [eluent: hexane/*i*-PrOH = 99/1; flow rate: 1.0 mL/min; t_R(1*R*,2*R*) 13.30 min and t_R(1*S*,2*S*) 15.13 min]. ^{1}H and ^{13}C NMR spectra of (1*R*,2*R*)-**10** obtained were in good agreement with reported data.[10a]

Preparation of (1*S*,2*S*)-2-*p*-tolylsulfonyloxy-1-indanyl *p*-nitrobenzoate 11. The reaction was carried out by slightly modified literature procedure.[10b] The solution of (2*R*,2*S*)-**7** with 80% ee obtained from the above experiment (244 mg, 0.8 mmol), triphenylphosphine (1.05 g, 4 mmol) and *p*-nitrobenzoic acid (535 mg, 3.2 mmol) in a mixture of dry toluene (8 mL) and THF (8 mL) was cooled to –25 °C. To this, diethylazodicarboxylate (DEAD, 630 mL, 4 mmol) was added dropwise over 5 min at –25 °C. After the reaction mixture was stirred for 3 h at the same temperature, the mixture was warmed up to room temperature and stirred additionally for 2 h. Solvent was pumped off *in vacuo*. To this, dichloromethane (15 mL) was added, and the mixture was washed

with saturated sodium bicarbonate solution in water and in turn brine (15 mL). Organic layer was dried over anhydrous magnesium sulfate, concentrated and the residue was dissolved in ether (10 mL). When the solution was stand in a refrigerator, the product ester (1*S*,2*S*)-**11** was obtained as a white crystal in 81% yield; mp 136-138 °C; $[\alpha]_D^{22}$ +37.46 (*c* 1.02, $CHCl_3$); IR (KBr, cm^{-1}): 1757, 1526, 1367, 1269, 1179, 1117; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s 3H), 3.17 (dd, 1H, *J* = 6.22 and 16.47 Hz), 3.49 (dd, 1H, *J* = 7.64 and 16.48 Hz), 5.36 (m, 1H), 6.57 (d, 1 H, *J* = 4.86), 7.26 (m, 5H), 7.33 (m, 1H), 7.80 (d, 2H, *J* = 8.24 Hz), 6.11 (m, 2H), 8.28 (m, 2H); ^{13}C NMR (100 MHz) δ 21.61, 36.54, 81.76, 84.32, 123.49, 125.06, 125.25, 127.93, 127.97, 129.88, 129.99, 130.96, 133.46, 134.84, 136.65, 138.77, 145.02, 150.72, 163.72; Anal. Calcd. for $C_{23}H_{19}NO_7S$: C, 60.92; H, 4.22; N, 3.09; S, 7.07. Found: C, 60.81; H, 4.35; N, 3.16; S, 7.27.

Preparation of (1*S*,2*R*)-indene oxide 3. (1*S*,2*S*)-**11** (272 mg, 0.6 mmol) prepared from (2*R*,2*S*)-**7** with 80% ee as described above was dissolved in chloroform (2 mL) and was treated with 3 M KOH in methanol (1 mL, 3 mmol) at room temperature for 0.5 h. To this, water (5 mL) was added and aqueous layer was extracted with chloroform (3 × 10 mL). The combined organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by a flash column chromatography on silica gel (230-400 mesh) using EtOAc/hexane (1/2) to give (1*S*,2*R*)-**3** in 90% yield; R_f 0.70; oil; $[\alpha]_D^{22}$ +44.82 (*c* 1.04, $CHCl_3$), 80% ee based on $[\alpha]_D^{22}$ −55 ($CHCl_3$), >98% ee for (1*R*,2*S*)-**3**[12]; The % ee of (1*S*,2*R*)-**3** was confirmed by a HPLC analysis using a Chiralcel OB chiral column (Daicel) [eluent: hexane/*i*-PrOH = 99.5/0.5; flow rate: 1.0 mL/min; t_R(1*S*,2*R*) 23.24 min and t_R(1*S*,2*S*) 37.07 min]. IR, ^{1}H and ^{13}C NMR spectral data of this compound were identical with the reference data.[5]

Preparation of (1*S*,2*R*)-2-azido-1-indanyl *p*-nitrobenzoate 12. The Mitsunobu reaction for **10** was carried out under the same reaction conditions as described in the preparation of **11**. The reaction provided **12** in 87% yield: R_f 0.76 (EtOAc/hexane = 1/2); oil; IR (neat): 2102, 1725, 1608, 1529, 1346, 1281, 1258, 1113; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.31 (d, 2H, *J* = 6.70), 4.39 (q, 1H, *J* = 6.57 Hz), 6.42 (d, 1H, *J* = 5.34 Hz), 7.29 (m, 3H), 7.51 (d, 1H, *J* = 7.49), 8.20-8.30 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.45, 62.41, 78.41, 123.56, 123.61, 125.19, 126.14, 127.78, 130.17, 130.73, 131.07, 135.03, 137.63, 140.40, 150.72, 164.38.

Preparation of (1*S*,2*R*)-2-amino-1-indanol 2. To a suspension of lithium aluminum hydride (91 mg, 2.4 mmol) in ethyl ether (5 mL) was added a solution of (1*S*,2*R*)-**12** (259 mg, 0.8 mmol) in ethyl ether (1 mL) over 5 min. The reaction mixture was heated to reflux for 5 h. After excess of lithium aluminum hydride was destroyed with water, the residue obtained was extracted with ethyl ether (2 × 15 mL). The combined ether was concentrated to give white solid (1*S*,2*R*)-**2** in 55% yield. mp 130-132 °C; $[\alpha]_D^{22}$ −51.12 (*c* 0.4, $CHCl_3$), 80% ee based on $[\alpha]_D^{25}$ −63 (*c* 0.4, $CHCl_3$) for (1*S*,2*R*)-**2**.[13] IR, ^{1}H and ^{13}C NMR spectral data of this compound were identical with the reference data.[10a]

Acknowledgment. This study was financially supported by the Hallym Academy of Sciences at Hallym University, Korea, 2001.

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