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# Syntheses of (*S*)-(-)-Pindolol and [3'-$^{13}$C]-(*R*)-(-)-Pindolol Utilizing a Lanthanum-Lithium-(*R*)-BINOL ((*R*)-LLB) Catalyzed Nitroaldol Reaction

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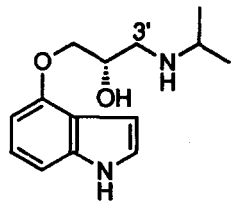
***Abstract:*** An efficient synthesis of (-)-pindolol, an effective β-blocker, has been achieved utilizing a lanthanum-lithium-(*R*)-BINOL ((*R*)-LLB) catalyzed nitroaldol reaction as a key step. This methodology was applicable to a synthesis of $^{13}$C-labeled (-)-pindolol, which would be useful as a biological tool for tracing the metabolism of β-blocker and 5-HT$_{1A}$ receptor antagonist. The mechanistic aspects of the LLB catalyzed nitroaldol reaction are also discussed.

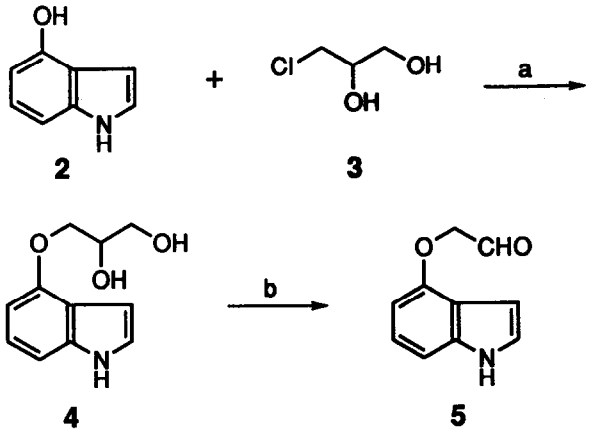
Conversion of racemic therapeutics into their optically active forms is one of the most important goals in catalytic asymmetric synthesis. In previous publications[1] we have demonstrated that the lanthanum-lithium-BINOL (LLB) complex **7** is an efficient asymmetric catalyst which can be utilized in the synthesis of β-blockers, such as (*S*)-propranolol[1c] and (*S*)-metoprolol.[1d] Pindolol (**1**, Figure 1) is also an effective β-adrenergic antagonist with prominent intrinsic sympathomimetic activity and has been practically utilized as a racemate, although, (*S*)-(-)-pindolol (**1**) is more effective than racemic pindolol.[2] In addition, (*S*)-(-)-**1** has shown a high affinity for the 5-hydroxytryptamine (5-HT$_1$) binding site and has proved to be useful as 5-HT$_{1A}$ receptor antagonist.[3] Although, several enantioselective syntheses of (*S*)-(-)-**1** have been reported,[2,4] the enantioselectivity and/or the total number of steps needed are unsatisfactory. Herein we would like to report a catalytic asymmetric synthesis of (*S*)-(-)-pindolol (**1**) of 92% ee utilizing (*R*)-LLB catalyst **7**, and its application to the synthesis of stable isotope labeled (-)-pindolol. In order to further elucidate the mechanism of action of pindolol and to fully characterize the physiological roles of the 5-HT$_{1A}$ receptor in human beings, it is essential to develop novel methodology to analyze the metabolism of pindolol without the assistance of radioisotopes. Stable isotope labeling combined with either NMR spectroscopy or GC analysis could serve as a versatile method for this purpose.[5]




**1** : (*S*)-(-)-pindolol

**Figure 1**

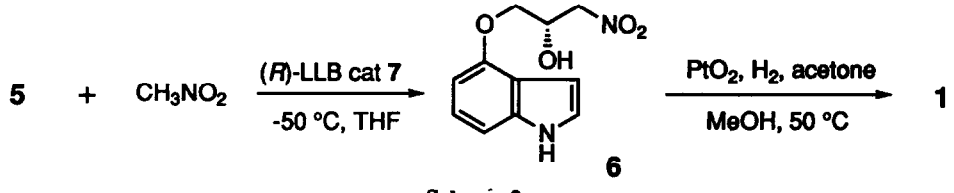
The precursor for the LLB catalyzed nitroaldol reaction was prepared from commercially available 4-hydroxyindole (**2**) as shown in Scheme 1. Condensation of the compound **2** with 3-chloro-1,2-propanediol (**3**), followed by oxidative cleavage[6] with periodate gave the desired aldehyde **5** in 80% yield from two steps. Although hydroxyindole derivatives have been known to be slightly air sensitive,[7] all the reactions in the syntheses of **5** and pindolol have been accomplished without any restricted conditions.




(a) $K_2CO_3$ (10 equiv), $CH_3CN$, reflux, 14 h, 87%; (b) $NaIO_4$ (1.3 equiv), silica gel, $CH_2Cl_2$-$H_2O$, room temperature, 2.5 h, 92%.

**Scheme 1**

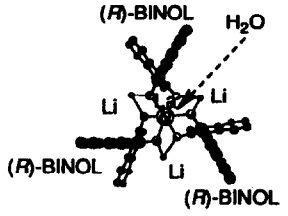
The catalytic asymmetric nitroaldol reaction of the aldehyde **5** with nitromethane was examined under the conditions as shown in Scheme 2 and Table 1. Using 10 mol equivalents of nitromethane at -50 °C in the presence of 10 mol % of (*R*)-LLB catalyst,[8] the reaction gave 76% yield of nitroaldol **6** in 92% ee (entry 1).[9] When only 3 mol % of **7** was used, the yield and the optical purity of the nitroaldol **6** remained almost




**Scheme 2**

**Table 1. Nitroaldol Reaction of Aldehyde 5 with Nitromethane Utilizing (*R*)-LLB Catalyst 7**

| entry | $CH_3NO_2$ (eq) | (*R*)-LLB 7 (mol %) | yield (%) | ee (%) |
|---|---|---|---|---|
| 1 | 10 | 10 | 76 | 92 |
| 2 | 10 | 3 | 74 | 90 |
| 3 | 50 | 10 | 77 | 89 |
| 4 | 50 | 3 | 70 | 71 |
| 5 | 100 | 10 | 74 | 54 |
| 6 | 100 | 3 | 78 | 67 |




7: Lanthanum-Lithium-(*R*)-BINOL ((*R*)-LLB) Catalyst

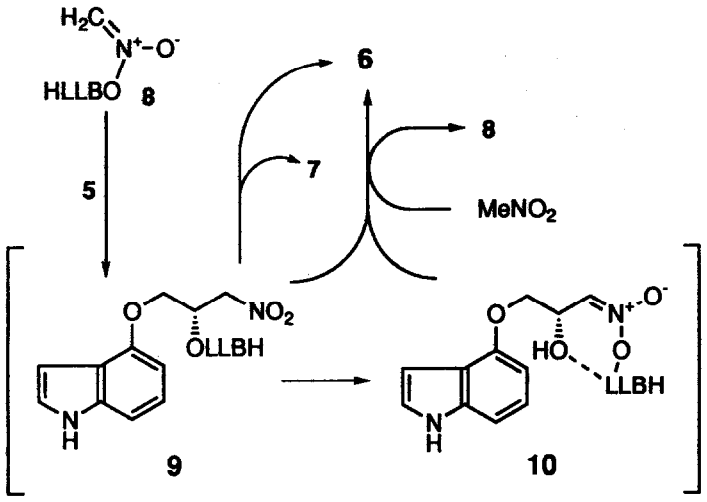
unchanged (entry 2). However, an increase in the amount of nitromethane resulted in a decrease in the optical purity of **6**. It seems likely that nitromethane produces an unfavorable solvent effect in the asymmetric synthesis which causes this drop in optical purity. Reductive alkylation of the nitroaldol **6** to **1** was accomplished in 88% yield by a $PtO_2$ catalyzed hydrogenation in the presence of 1 to 5 mol equivalents of acetone in methanol (Scheme 2).[1c,1d] Thus, (*S*)-(-)-pindolol (**1**) has been synthesized in only four steps from 4-hydroxyindole (**2**). In this sequence of reactions, no protective group was necessary even for the air sensitive secondary amino group on the indole ring.

This methodology for the short synthesis of (*S*)-(-)-pindolol (**1**) was expected to be applicable to an isotope labeled optically active β-blocker from commercially available $^{13}$C-labeled nitromethane. In order to decrease the molar ratio of relatively expensive $^{13}$C-labeled nitromethane to the aldehyde **5**, we first optimized the reaction conditions utilizing unlabeled nitromethane. As shown in Table 2, the reaction proceeded very slowly with 2 equiv of nitromethane to give **6** in only 45% yield along with a mixture of unseparable by-products (entry 1).[10] Although the exact mechanism of LLB catalyzed nitroaldol reaction has not been clarified yet, the reaction seems to proceed via either the intermediary LLBH-alkoxide **9** or LLBH-nitronate **10** (Scheme 3). Thus, the decrease in the yield was ascribed to the lower concentration of nitromethane. In order to prevent the formation of by-products even in the case of 2 equivalents of nitromethane, we next used a stoichiometric amount of LLB catalyst **7**, since the reaction of **10** with the aldehyde **5** was assumed to be slower than that of **8** with **5**. Indeed, as shown in Table 2 (entry 4 and 5), the use of a stoichiometric amount of **7** in the presence of 2 or 4 equivalents of nitromethane made it possible to obtain nitroaldol adducts **6** in acceptable yield and enantioselectivity.[11] On the basis of the conditions described above, [3'-$^{13}$C]-nitroaldol **6** was synthesized by the reaction of **5** with $^{13}$C-labeled nitromethane (4 equiv) in 80% yield. The [3'-$^{13}$C]-nitroaldol **6** was then converted into desired [3'-$^{13}$C]-(*R*)-(-)-pindolol in 75% yield (85% ee). $^{13}$C-NMR spectra of $^{13}$C-labeled **6** and [3'-$^{13}$C]-(*R*)-(-)-pindolol showed strong peaks at δ 78.1 and 50.9, respectively, which confirmed incorporation of the label.

In conclusion, an efficient short synthesis of (*S*)-(-)-pindolol (**1**), an effective β-blocker, has been achieved utilizing the lanthanum-lithium-(*R*)-BINOL ((*R*)-LLB, **7**) catalyzed nitroaldol reaction as a key step. This methodology was applicable to a synthesis of $^{13}$C-labeled (-)-pindolol as a biological tool for tracing metabolism of β-blocker and 5-$HT_{1A}$ receptor antagonist.

**Table 2. Optimization of Reaction Conditions in the Nitroaldol Reaction of Aldehyde 5 with Nitromethane towards the Synthesis of [3'-$^{13}$C]-(-)-Pindolol**

| entry | $CH_3NO_2$ (equiv) | (*R*)-LLB cat **7** (mol %) | yield (%) | ee (%) |
|---|---|---|---|---|
| 1 | 2 | 10 | 45 | 89 |
| 2 | 4 | 10 | 58 | 90 |
| 3 | 1.2 | 100 | 41 | 83 |
| 4 | 2 | 100 | 59 | 82 |
| 5 | 4 | 100 | 80 | 85 |




**Scheme 3**

## EXPERIMENTAL SECTION

**General.** Unless otherwise indicated, all materials were obtained from commercial sources and were used without further purification. $^1$H NMR and $^{13}$C NMR spectra were recorded on a JEOL EX-270 spectrometer. All solvents were dried prior to use.

**4-(2,3-Dihydroxypropoxy)indole (4).** 4-Hydroxyindole (2) (500 mg, 3.76 mmol) and $K_2CO_3$ (2.60 g, 18.8 mmol) were dissolved in acetonitrile (11 mL) and heated under reflux for 1 h. 3-Chloro-1,2-propanediol (3) (0.314 mL, 3.76 mmol) was added dropwise to the reaction mixture and stirred at the same temperature. After 14 h, the mixture was cooled to room temperature, filtered and concentrated to give an amorphous solid. Silica gel column chromatography (hexane-acetone, 3/1-3/2) and washing with petroleum ether gave a white solid of 4 (678 mg, 87%): mp 96-98 °C; IR (KBr) 3414, 3391, 3260, 2931 cm$^{-1}$; $^1$H-NMR ($Me_2SO$-$d_6$) δ 3.43-3.57 (m, 2H), 3.82-3.89 (m, 1H), 3.96 (dd, $J$ = 9.6, 4.3 Hz, 1H), 4.07 (dd, $J$ = 9.6, 4.3 Hz, 1H), 4.66 (t, $J$ = 5.6 Hz, 1H), 4.94 (d, $J$ = 4.6 Hz, 1H), 6.43-6.57 (m, 2H), 6.93-6.97 (m, 2H), 7.20 (t, $J$ = 2.0 Hz, 1H), 11.0 (bs, 1H); MS m/z 207 ($M^+$), 147, 133 (base peak). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.46; H, 6.36; N, 6.88.

**4-(Formylmethoxy)indole (5).** To a vigorously stirred mixture (1h) of aqueous $NaIO_4$ (0.65 *M*, 11.6 mL) and silica gel (Merck, 230-400 mesh, 11.6 g) in $CH_2Cl_2$ (93 mL) was added a suspension of 4 (1.20 g, 5.79 mmol) in $CH_2Cl_2$ (12 mL) at room temperature. After being stirred for 1.5 h, the mixture was filtered and the silica gel was thoroughly washed with $CH_2Cl_2$ (2 X 10 mL). Concentration of the filtrate gave an analytically pure 5 as a brown solid (934 mg, 92%), which was utilized in the nitroaldol reaction without further purification: mp 132-134.5 °C; IR (KBr) 3363, 2845, 1727 cm$^{-1}$; $^1$H-NMR ($Me_2SO$-$d_6$) δ 4.91 (s, 2H), 6.36-6.48 (m, 2H), 6.92-7.05 (m, 2H), 7.25 (t, $J$ = 2.6 Hz, 1H), 9.75 (s, 1H), 11.13 (bs, 1H); $^{13}$C-NMR (67.8 MHz, $Me_2SO$-$d_6$) δ 72.4, 98.3, 100.0, 105.5, 118.1, 121.5, 123.9, 137.5, 151.0, 199.9; MS m/z 175 ($M^+$, base peak). HRMS (EI) calcd for $C_{10}H_9NO_2$ 175.0634, found 175.0634.

**(*S*)-4-(2-Hydroxy-3-nitropropoxy)indole (6).** The aldehyde 5 (40.1 mg, 0.229 mmol) and nitromethane (124 μL, 2.29 mmol) were dissolved in THF (0.97 mL) and the mixture was cooled to -50 °C.

The (*R*)-LLB catalyst 7[8] in THF (16.7 m*M*, 1.37 mL) was added dropwise over a period of 20 min. After being stirred for 96 h at the same temperature, the reaction mixture was quenched with 1*N* HCl (1 mL) and extracted with AcOEt. The organic layer was washed with brine, dried then concentrated to give a colorless oil. The residue was purified by silica gel column chromatography (hexane-acetone, 4/1) to give **6** as a white solid (41 mg, 76%). The optical purity of **6** proved to be 92% ee after the conversion into (*S*)-(-)-pindolol. : The following spectral data were obtained using **6** with 86% ee. mp 67.5-69 °C; $[\alpha]_D^{22}$ -18.3 ° (*c* 1.02, chloroform); IR (KBr) 3517, 3309, 2932, 1553, 1359 cm$^{-1}$; $^1$H-NMR ($CDCl_3$) δ 2.86-2.91 (m, 1H), 4.19-4.31 (m, 2H), 4.65-4.87 (m, 3H), 6.49-6.63 (m, 2H), 7.08-7.27 (m, 3H), 8.21 (bs, 1H); MS m/z 236 ($M^+$), 175, 133 (base peak). Anal. Calcd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.86. Found: C, 55.85; H, 5.14; N, 11.63.

Under analogous conditions described above, reaction of the aldehyde **5** (42.3 mg, 0.241 mmol) with [$^{13}$C]-nitromethane (52 μl, 0.97 mmol) in THF (0.42 mL) catalyzed by 1 equiv of (*R*)-LLB **7** (66.7 m*M*, 3.62 mL) gave 45.3 mg (80%, 85% ee) of [3'-$^{13}$C]-(*R*)-4-(2-hydroxy-3-nitropropoxy)indole: mp 67-68 °C (85% ee); $[\alpha]_D^{22}$ -15.3 ° (*c* 0.61, chloroform, 85% ee); IR (KBr) 3517, 3310, 2929, 1554, 1359 cm$^{-1}$; $^1$H-NMR ($CDCl_3$) δ 2.87-2.90 (m, 1H), 4.20-4.53 (m, 3H), 4.82-5.07 (m, 2H), 6.51-6.63 (m, 2H), 7.07-7.13 (m, 3H), 8.22 (bs, 1H); MS m/z 237 ($M^+$), 175, 132 (base peak). HRMS (EI) calcd for $C_{10}{}^{13}CH_{12}N_2O_4$ 237.0831, found 237.0840; $^{13}$C-NMR (67.8 MHz, $CDCl_3$) δ 67.5 (d, *J* = 39.0 Hz), 68.5, 78.1, 99.05, 100.9, 105.6, 118.5, 122.7, 123.2, 137.4, 151.4.

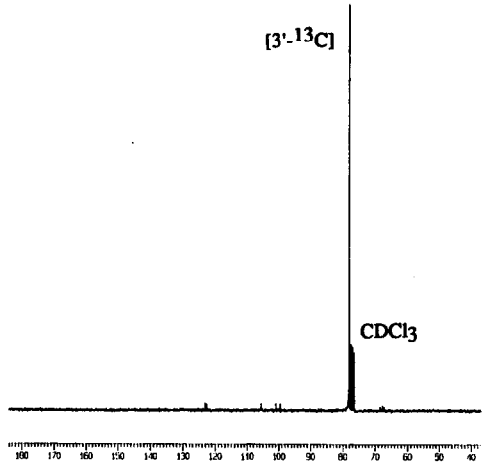



**Figure 2.** $^{13}$C NMR of [3'-$^{13}$C]-**6**

**(*S*)-(-)-Pindolol (1).** To a solution of the nitroaldol **6** (21.6 mg, 0.091 mmol, 92% ee) in methanol (1.83 mL) were added $PtO_2$ (1.04 mg) and acetone (26.6 μL, 0.457 mmol). The solution was then stirred under a hydrogen atmosphere for 16 h at 50 °C. The reaction mixture was filtered through a pad of Celite and washed thoroughly with methanol. The filtrate was concentrated and the residue thus obtained was purified by silica gel column chromatography (chloroform-methanol-28% $NH_{3\ aq}$, 30/1/0.05-10/1/0.05) to give (*S*)-(-)-pindolol (**1**) (19.9 mg, 88%) as white needles: mp 91-92 °C (92% ee); $[\alpha]_D^{22}$ -3.8° (*c* 0.62, methanol, 92% ee); IR (KBr) 3408, 3303, 2964, 2924 cm$^{-1}$; $^1$H-NMR ($CD_3OD$) δ 1.10

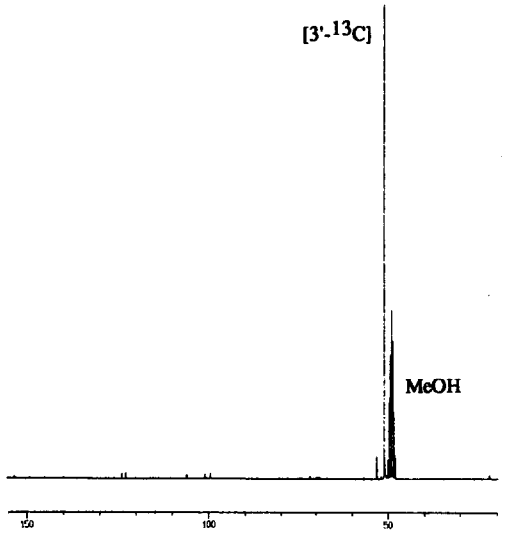



**Figure 3.** $^{13}$C NMR of [3'-$^{13}$C]-**1**

(d, $J$ = 3.0 Hz, 3H), 1.12 (d, $J$= 3.0 Hz, 3H), 2.70-2.99 (m, 3H), 4.03-4.19 (m, 3H), 6.45-6.53 (m, 2H), 6.95-7.10 (m, 3H); MS m/z 249 ($M^+$+1), 248 ($M^+$), 149, 134, 113, 72, 61 (base peak). HRMS (EI) calcd for $C_{14}H_{20}N_2O_2$ 248.1526, found 248.1526.

Analogous treatment of [3'-$^{13}$C]-nitroaldol **6** (30.1 mg, 0.127 mmol, 85% ee) afforded 23.9 mg of [3'-$^{13}$C]-(*R*)-(-)-pindolol in 75% yield: mp 96-99 °C; IR (KBr) 3410, 2964, 2922 cm$^{-1}$; $^1$H-NMR ($CD_3OD$) δ 1.12 (d, $J$ = 2.3 Hz, 3H), 1.14 (d, $J$= 2.6 Hz, 3H), 2.48-2.76 (m, 1H), 2.87-2.97 (m, 1H), 2.98-3.27 (m, 1H), 4.06-4.14 (m, 3H), 6.47-6.53 (m, 2H), 6.95-7.10 (m, 3H); MS m/z 249 ($M^+$), 133, 105 (base peak). HRMS (EI) calcd for $C_{13}{}^{13}CH_{20}N_2O_2$ 249.1560, found 249.1552; $^{13}$C-NMR (67.8 MHz, $CD_3OD$) δ 22.0, 50.9, 53.0, 69.3 (d, $J$ = 39 Hz), 71.7 (d, $J$ = 2.4 Hz), 99.5, 101.0, 106.0, 120.1, 122.8, 123.8, 139.1, 153.4.

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## References and Notes

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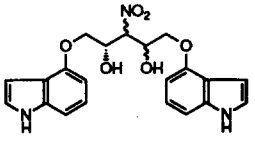
7. Beer, R. J. S.; Clarke, K.; Khorana, H. G.; Robertson, A. *J. Chem. Soc.*, **1948**, 1605-1609.
8. All the (*R*)-LLB catalyst **7** utilized in this article was prepared from $LaCl_3{\cdot}7H_2O$ and (*R*)-BINOL dilithium salt in the presence of NaOH. See reference 1b.
9. Optical purities of nitroaldol adduct **6** were not determined at this stage since base separation in HPLC analysis (DAICEL CHIRALCEL OD, hexane-isopropanol-$Et_2NH$, 80/20/0.1) was unsatisfactory. As a result, optical purities of **6** were unequivocally determined after conversion of **6** into (-)-pindolol by HPLC analysis using DAICEL CHIRALCEL OD (hexane-isopropanol-$Et_2NH$, 80/20/0.1).
10. By-products would be a mixture of diastereomers which have the following structure.




11. Slight changes in optical purities depending on the molar ratio of employed nitromethane may suggest that more than 2 mol equivalents of nitromethane couple or coordinate with (*R*)-LLB catalyst **7** to form a more effective asymmetric nitronate.

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