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Enantioselective synthesis of (*R*)-(−)-baclofen via Ru(II)–BINAP catalyzed asymmetric hydrogenation

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Abstract—A short and efficient enantioselective synthesis of (*R*)-(−)-baclofen, a selective $GABA_B$ agonist has been described with an overall yield of 26% and 90% ee. Ru(II)–(*S*)-BINAP catalyzed asymmetric hydrogenations of C=C and C=O groups constitute the key steps in introducing stereogenic centers into the molecule.

1. Introduction

Baclofen [γ-amino-β-(*p*-chlorophenyl)butyric acid], **1**, a derivative of γ-aminobutyric acid (GABA), plays an important role as an inhibitory neurotransmitter in central nervous system (CNS) of mammalians.[1,2] It helps to reduce the excitatory effect of active compounds such as benzodiazepine, barbiturates, etc.[3] The deficiency of GABA is associated with diseases that exhibit neuromuscular dysfuntions such as epilepsy, Huntington, Parkinsons' diseases, etc.[4] Baclofen is also one of the most promising drugs in the treatment of the paroxysmal pain of trigeminal neuralgia[5] as well as spasticity of spinal without influencing the sedation.[6] Although baclofen is commercialized in its racemic form, it has been reported that its biological activity resides exclusively in (*R*)-enantiomer.[7]

There are many methods available in the literature on the synthesis of (*R*)-(−)-baclofen **1**. They are concerned mostly with resolution,[8] chemoenzymatic[9] or enantioselective synthesis.[10] However, these methods suffer from disadvantages such as the low overall yields, the need for separation of diastereoisomers and the use of expensive chiral reagents in stochiometric amounts. In this context, a more practical approach for the synthesis of (*R*)-(−)-baclofen **1** is highly desirable. This article describes a new enantioselective synthesis of (*R*)-(−)-baclofen **1** by employing Ru-catalyzed asymmetric hydrogenation of ethyl 4-azido-3-(4-chlorophenyl)-2-butenoate **6** as well as ethyl 4-chlorophenylbenzoyl acetate **5**.

2. Results and discussion

Retrosynthetic analysis (Fig. 1) of (*R*)-(−)-baclofen **1** reveals that many precursors such as β-hydroxy ester **2**, azidoester **6**, β-cyano ester **3** or nitroketone **7** can be visualized as the key intermediates. In order to prepare enantiomerically pure β-hydroxy ester **2**, Pd-catalyzed oxidative kinetic resolution[11] of the corresponding racemic β-hydroxyester (±)-**4** was attempted. However, the desired chiral alcohol **2** was obtained in low enantiomeric excess (7% ee). Further, the Michael addition of nitromethane catalyzed by L-proline on 4-chlorobenzylideneacetophenone was also attempted to get the chiral nitroketone **7** (Corey's intermediate) but with poor enantioselectivity (15% ee). Ni-catalyzed asymmetric hydrocyanation of 4-chlorobenzylideneacetophenone was also attempted using trimethylsilyl cyanide and acetone cyanohydrin as the HCN source but the catalyst failed to induce any stereoselectivity although it gave the racemic product. We then turned our attention to asymmetric hydrogenation of azidoester **6**.

The key precursor, (*E*)-ethyl 3-(4-chlorophenyl)-2-butenoate **8**, was obtained in 78% overall yield (*E*:*Z*= 70:30) by the Reformatsky reaction of 4-chloroacetophenone with ethyl bromoacetate followed by *p*-TSA catalyzed dehydration of the intermediate alcohol. The allylic bromination of **8** with *N*-bromosuccinimide (NBS) in the presence of 2,2′-azobisisobutyronitrile (AIBN) resulted in the formation of ethyl 4-bromo-3-(4-chlorophenyl)-2-butenoate **9** in 92% yield. The bromoester **9** was then transformed to ethyl

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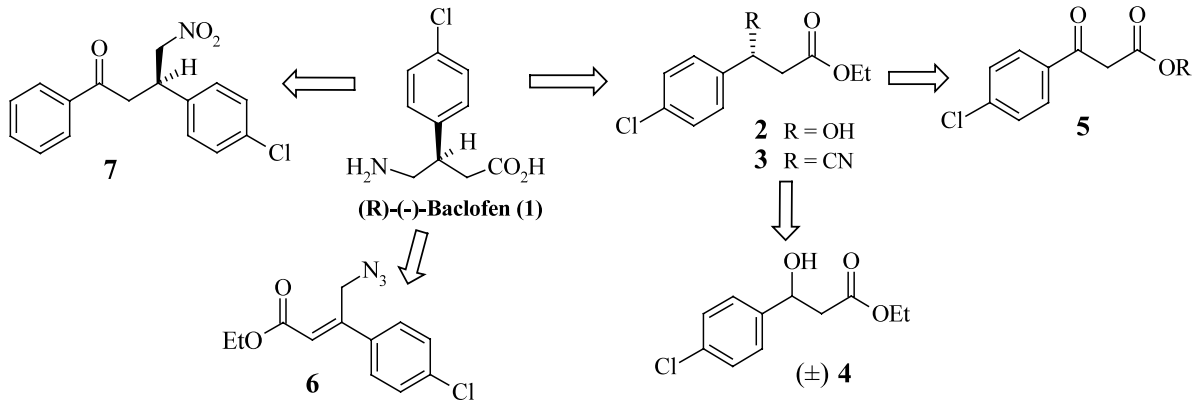
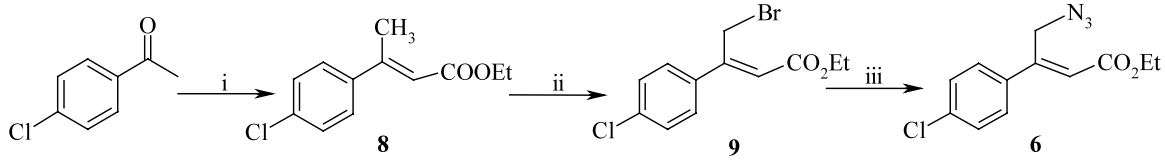


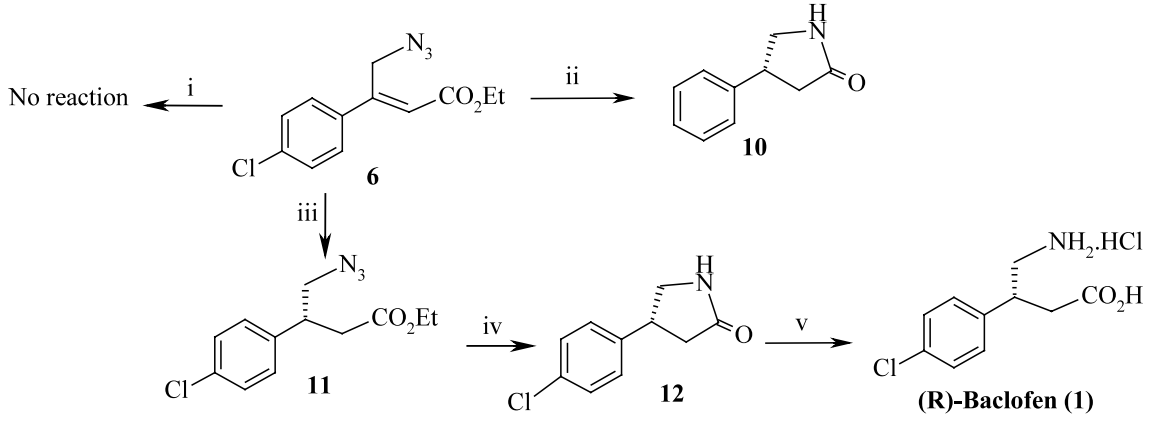
Figure 1. Retrosynthetic analysis of (*R*)-(−)-baclofen **1**.

4-azido-3-(4-chlorophenyl)-2-butenoate **6** by nucleophilic displacement of Br by N_3 using NaN_3. The IR spectrum of **6** showed an intense band at 2104 cm^{-1} indicative of N_3 group (Scheme 1).

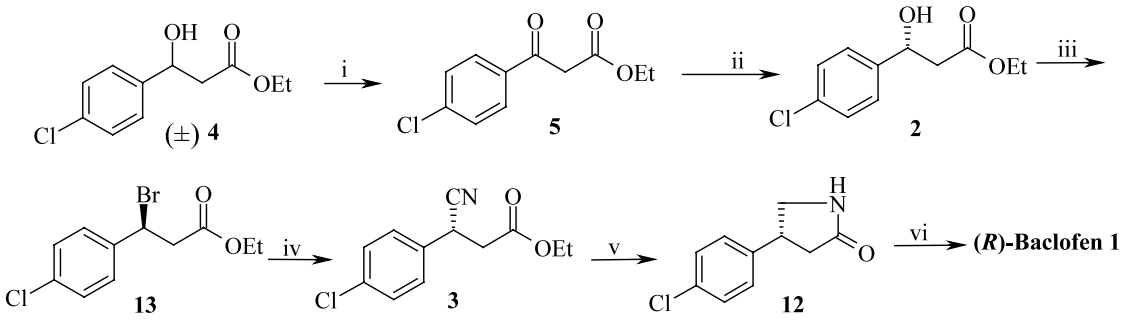
Diphosphine complexes of Rh and Ru have been used as catalysts for the asymmetric hydrogenation of C=C and ketoesters.[12] The key intermediate, azidoester **6** was subjected to Ru(II)–(*S*)-BINAP catalyzed asymmetric hydrogenation in MeOH in a Parr reactor (Scheme 2). When the experiment was performed at 200 psi of H_2 and 25°C for 24 h, there was no reaction and all the starting material was recovered. However, increase of temperature to 50°C and 200 psi of H_2 resulted in the formation of a mixture of products, the major product (68% yield and 68% ee determined by HPLC) being (*R*)-ethyl 4-azido-3-(4-chlorophenyl)-1-butanoate **11** formed via the reduction of the olefinic bond. In order to improve the yield and selectivity of the C=C reduction process and to ensure the simultaneous reduction of N_3 moiety, reaction was performed at higher H_2 pressure (500 psi) and at 70°C to afford a single product **10** (80% yield, 65% ee[14]), in which all the three functional groups of olefin, azido and C–Cl groups had undergone reduction. Such hydrogenolysis of aryl C–Cl bond is known in the literature.[13] The formation of (*R*)-(−)-3-phenylpyrrolidone **10** is rationalized as a result of reductive cyclization occurring during the asymmetric hydrogenation. Co-catalyzed[15] reduction of N_3 moiety in **11** with $NaBH_4$ gave the cyclized product 4-(4-chlorophenyl)-2-pyrrolidone **12** in 80% yield. The hydrolysis of 4-(4-chlorophenyl)pyrrolidine-2-one (**12**)



Scheme 1. *Reagents and conditions*: (i) $BrCH_2CO_2Et$, Zn, benzene, reflux, *p*-TSA, toluene, reflux, 78%; (ii) NBS, AIBN, CCl_4, reflux, 10 h, 92%; (iii) NaN_3, EtOH:H_2O (80:20), 80°C, 8 h, 78%.



Scheme 2. *Reagents and conditions*: (i) Ru(II)–BINAP, H_2 (200 psi), MeOH, 25°C, 24 h; (ii) Ru(II)–BINAP, MeOH, H_2 (500 psi), 70°C, 26 h; (iii) Ru(II)–(*S*)-BINAP, H_2 (200 psi), MeOH, 50°C, 20 h; 68%; (iv) $CoCl_2$, $NaBH_4$, H_2O, 25°C, 30 min; 80%; (v) 6N HCl, 100°C, 10 h, 76%.



Scheme 3. *Reagents and conditions*: (i) PCC, CH_2Cl_2, 25°C, 3 h or $H_2Cr_2O_7$, Et_2O, 0–25°C, 4 h, 75%; (ii) Ru(II)–(*S*)-BINAP, MeOH, H_2 (800 psi), 95% yield, 96% ee; (iii) PBr_3, pyridine, Et_2O, −20 to 0°C, 53 h, 79%; (iv) NaCN, DMF, 70°C, 18 h, 88%; (v) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, MeOH, 25°C, 1 h, 75%; (vi) 6N HCl, reflux, 16 h, 78%.

with 6N HCl at 100°C gave (*R*)-(−)-baclofen hydrochloride **1** as a white solid in 76% yield, enantiomeric excess of **1** was identical, as expected, to **11**.

As the enantiomeric excess of **1** obtained by the above method was low (67%), we decided to explore an alternative route involving β-ketoester **5** as a prochiral substrate (Scheme 3). (*R*)-β-Hydroxyester **2**, the key intermediate was synthesized by the enantioselective reduction of β-ketoester **5**, which was in turn prepared from 4-chlorobenzaldehyde in two steps with an overall yield of 72%. The asymmetric reduction of keto function was performed using (*S*)-BINAP–Ru(II) complex and H_2 at a pressure of 800 psi at 30°C to afford the corresponding (*R*)-β-hydroxy ester **2** in 95% yield and 96% ee [determined by Eu(hfc)$_3$ shift reagent]. Alcohol **2** was then converted to bromoderivative **13** using PBr_3 and pyridine in Et_2O at −20°C in 79% yield with complete inversion of configuration.[16] The β-bromo ester **13** was subjected to S_N2 nucleophilic displacement using NaCN in DMF at 70°C to afford the β-cyanoester **3** in 88% yield. Cyano ester **3** was chemoselectively reduced either with $NaBH_4$ and $NiCl_2$[17] or with catalytic amount of PtO_2 in presence of H_2 (40 psi)[18] to afford the lactam **12** in 75% yield. The enantiomeric purity of lactam **12** was determined to be 92% by comparison of its specific rotation $[\alpha]_D^{25} = -35.8$ (*c* 1, EtOH) with that reported {lit. $[\alpha]_D^{25} = -39.1$ (*c* 1, EtOH)}. The loss in ee can probably be attributed to the successive nucleophilic S_N2 displacements at the stereogenic center causing marginal racemization. Lactam **12** was finally hydrolyzed with 6N HCl to give (*R*)-(−)-baclofen **1** as its hydrochloride salt with 26% overall yield and 90% ee {$[\alpha]_D = -1.81$, (*c* 0.6, H_2O)}.

3. Conclusion

We have achieved an efficient, enantioselective synthesis of (*R*)-(−)-baclofen **1** using two different routes. In one route, Ru-catalyzed asymmetric hydrogenation of ethyl 4-azido-3-(4-chlorophenyl)-2-butenoate **6** was used as a key step to give (*R*)-(−)-baclofen **1** in 24% overall yield and 67% ee. Alternately, Ru-catalyzed asymmetric reduction of ethyl 4-chlorophenylbenzoyl acetate **5** was used as a key step to afford (*R*)-(−)-baclofen **1** in 26% overall yield and 90% ee.

4. Experimental

4.1. General information

Solvents were purified and dried by standard procedures before use; petroleum ether of boiling range 60–80°C was used. Melting points are uncorrected. Optical rotations were measured using sodium D line on a JASCO-181 digital polarimeter. Infrared spectra were recorded on an Shimadzu FTIR-8400 spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on Bruker AC-200 and MSL-300 NMR spectrometers, respectively. Mass spectra were obtained with a Finnigan MAT-1020 B-70 eV mass spectrometer. Elemental analysis was carried on a Carlo Erba CHNS-O analyzer. Enantiomeric excess was determined by chiral HPLC or by using chiral shift reagent Eu(hfc)$_3$.

4.2. Ethyl 3-(4-chlorophenyl)-2-butenoate 8

A 100 ml two-necked round-bottomed flask was charged with activated zinc (2.32 g, 35.7 mmol), and kept under N_2 atmosphere. Dry benzene (30 ml) was introduced and the reaction mixture was heated to 80°C (oil bath temp.). A solution of ethyl bromoacetate (5.88 g, 35.7 mmol) and *p*-chloroacetophenone (5.0 g, 32.46 mmol) in dry benzene (20 ml) was added dropwise to the reaction mixture. After completion of the addition, the resulting reaction mixture was refluxed for 6 h, cooled to rt and quenched by adding ice cold 4N H_2SO_4 (30 ml). The crude hydroxyester was extracted in diethyl ether and then was subjected to dehydration with *p*-toluenesulphonic acid (0.7 g, 3.68 mmol) in toluene at reflux. The water generated during the dehydration was azeotropically separated and then toluene was distilled off. The crude olefinic ester **8** was purified by column chromatography packed with silica gel, eluting with petroleum ether to give 5.67 g (78%, *trans*/*cis* = 70/30). Yield: 78%; bp: 154°C at 0.64 mm; IR ($CHCl_3$, cm^{-1}): 3060, 2982, 1712, 1625, 1577, 1448, 1367, 1344, 1286, 1176, 1047, 879, 769, 696; ^{1}H NMR ($CDCl_3$): δ 1.25 (t, J = 7.4 Hz, 3H), 2.48 (s, 3H), 4.12 (q, J = 7.4 Hz, 2H), 6.02 (s, 1H), 7.23–7.35 (dd, J = 8.0 Hz, 4H); ^{13}C NMR ($CDCl_3$): δ 14.14, 17.58, 59.78, 117.56, 127.55, 128.62, 134.93, 140.51, 153.68, 166.31; MS *m*/*z* (% rel. int.): 224 (M^+, 96), 209 (8), 195 (55),

179 (100), 152 (32), 115 (92). Anal. calcd for $C_{12}H_{13}ClO_2$ requires: C, 64.15; H, 5.83; Cl, 15.78. Found: C, 63.94; H, 5.81; Cl, 15.72%.

4.3. Ethyl 4-bromo-3-(4-chorophenyl)-2-butenoate 9

A solution of α,β-unsaturated ester 8 (3.5 g, 15.62 mmol), NBS (2.81 g, 17.2 mmol) and AIBN (0.102 g, 0.62 mmol) in dry CCl_4 (35 ml) was refluxed under nitrogen atmosphere for 10 h. The resulting reaction mixture was cooled to room temperature and then filtered through a sintered funnel to separate succinimide formed during the reaction. The filtrate was concentrated under reduced pressure to obtain bromoester **9**. It was then purified by column chromatography packed with silica gel to give pure 4.37 g of pale yellow colored gum, bromoester **9**. Yield: 92%; IR ($CHCl_3$, cm^{-1}): 3060, 2982, 1710, 1625, 1490, 1369, 1340, 1288, 1182, 1095, 1012, 908, 734, 649; ^1H NMR ($CDCl_3$): δ 1.34 (t, $J=8.0$ Hz, 3H), 4.26 (q, $J=8.0$ Hz, 2H), 4.94 (s, 2H), 6.19 (s, 1H), 7.36–7.51 (dd, $J=8.0$ Hz, 4H); ^{13}C NMR ($CDCl_3$): δ 14.10, 26.09, 60.52, 119.94, 127.85, 128.88, 135.66, 136.70, 151.74, 165.17; MS m/z (% rel. int.): 304 (M^+, 5), 289 (5), 224 (8), 179 (10), 152 (100), 137 (55), 115 (92), 101 (48), 91 (22), 75 (15). Anal. calcd for $C_{12}H_{12}BrClO_2$ requires: C, 47.48; H, 3.95; Br, 26.32; Cl, 11.71. Found: C, 47.75; H, 4.18; Br, 26.44; Cl, 11.34%.

4.4. Ethyl 4-azido-3-(4-chlorophenyl)-2-butenoate 6

A 50 ml round-bottomed flask containing a solution of bromoester **9** (1.85 g, 6.1 mmol) and sodium azide (0.594 g, 9.14 mmol) in ethanol: water (80:20, 15 ml) mixture was refluxed for 8 h. Resulting yellow color solution was concentrated under reduced pressure to yield crude azidoester **6**, which was purified by column chromatography packed with silica gel to give pure azidoester **6** (1.26 g) as a colorless viscous liquid. Yield: 78%; IR ($CHCl_3$, cm^{-1}): 2982, 2104, 1712, 1629, 1591, 1492, 1454, 1369, 1249, 1180, 1095, 1012, 910, 831, 732; ^1H NMR ($CDCl_3$): δ 1.34 (t, $J=6.0$ Hz, 3H), 4.23 (q, $J=6.0$ Hz, 2H), 4.71 (s, 2H), 6.29 (s, 1H), 7.32–7.47 (dd, $J=8.0$ Hz, 4H); ^{13}C NMR ($CDCl_3$): δ 13.96, 47.92, 60.53, 120.96, 127.84, 128.83, 135.63, 136.88, 149.12, 165.33. Anal. calcd for $C_{12}H_{12}ClN_3O_2$ requires: C, 54.26; H, 4.52; Cl, 13.34; N, 15.82. Found: C, 54.29; H, 4.24; Cl, 13.31, N, 15.99%.

4.5. Preparation of (*S*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl Ru(II) complex[19]

A dry, 25 ml two-necked, round bottomed flask was charged with $[RuCl_2(benzene)_2]$ (38.3 mg, 0.0765 mmol) and (*S*)-BINAP (100 mg, 0.16 mmol). The flask was then evacuated, filled with argon and then *N*,*N*′-dimethylformamide (2.6 ml) was introduced through syringe. The suspension was stirred under argon atmosphere at 100°C for 10 min the resulting clear reddish brown reaction mixture was cooled and concentrated at 60°C (3 mmHg) with vigorous stirring. Finally, it was dried at 3 mmHg for 3 h to yield reddish brown solid of Ru(II)–(*S*)-BINAP complex (135 mg). This solid was directly used as catalyst for the asymmetric hydrogenation.

4.6. Asymmetric reduction of azidoester 6 using Ru(II)–BINAP

A 100 ml autoclave charged with azidoester **6** (0.200 g, 1.88 mmol), Ru(II)–(*S*)-BINAP (10 mg), dry MeOH (40 ml) and the resulting yellowish-orange solution was degassed with N_2. It was then pressurized with H_2 to 200 psi and the reaction mixture was vigorously stirred at 50°C for 20 h. Resulting solution cooled to room temperature and the excess of H_2 was carefully blend off. The deep reddish-orange colored reaction mixture was transformed to 100 ml round bottomed flask and the solvent was removed under reduced pressure. The residue was purified by column chromatography packed with silica gel to give pure (0.137 g) light yellow colored viscous liquid of (*R*)-ethyl 4-azido-3-(4-chlorophenyl)-1-butanoate **11**. Yield: 68%; $[\alpha]_D^{25}=-18.7$ (*c* 0.3, MeOH), 68% ee, HPLC: LichroCART® 250-4 ChiraDex® GAMMA, 5 μm, 5% EtOH/hexane, 0.5 ml/min, retention time: 14.22 min; IR ($CHCl_3$, cm^{-1}): 3020, 2928, 2103, 1730, 1692, 1493, 1374, 1305, 1261, 2151, 1175, 1095, 827, 761, 668.; ^1H NMR ($CDCl_3$): δ 1.18 (t, $J=8.0$ Hz, 3H), 2.58–2.66 (dd, $J_{AB}=16.0$ Hz, $J_{BX}=8.0$ Hz, 1H); 2.72–2.83 (dd, $J_{BA}=16.0$ Hz, $J_{BX}=6.0$ Hz, 1H), 3.33–3.54 (m, 3H), 4.07 (q, $J=8.0$ Hz, 2H), 7.15–733 (dd, $J=8.0$ Hz, 4H); ^{13}C NMR ($CDCl_3$): δ 14.25, 37.74, 41.34, 56.05, 60.57, 129.01, 133.24, 139.16, 159.89, 171.21; MS m/z (% rel. int.): 239 (M^+-N_2, 5), 212 (15), 195 (5), 169 (65), 152 (30), 139 (100), 125 (50), 115 (30), 103 (70), 89 (20), 77 (40). Anal. calcd for $C_{12}H_{14}ClN_3O_2$ requires: C, 53.84; H, 5.27; Cl, 13.24; N, 15.70. Found: C, 53.74; H, 5.21; Cl, 13.19; N, 15.68%.

4.7. (*R*)-3-(4-Chloropheny)-2-pyrrolidone 12

To a 25 ml round-bottomed flask containing a mixture of azidoester **11** (0.100 g, 0.375 mmol) and $CoCl_2{\cdot}6H_2O$ (0.010 g, 0.042 mmol) in 0.5 ml water, at 25°C was added dropwise under stirring a solution of $NaBH_4$ (0.028, 0.75 mmol) in 0.5 ml H_2O. The resulting reaction mixture was stirred for 30 min in which the appearance of black precipitate indicated the formation of cobalt–boride species. After the reaction was complete, the mixture was extracted with chloroform (3×10 ml). The chloroform layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue obtained was then purified by column chromatography to give pure light yellow colored solid of (*R*)-3-(4-chloropheny)-2-pyrrolidone **12**, 0.058 g. Yield: 80%; mp: 115–117°C; $[\alpha]_D^{25}=-26.35$ (*c* 1.0, EtOH), 68% ee {lit.[13] $[\alpha]_D^{25}=-39.0$ (*c* 1, EtOH)}; IR ($CHCl_3$, cm^{-1}): 3420, 3200, 2103, 1698, 1492, 1374, 1216, 1090, 758, 700, 668; ^1H NMR ($CDCl_3$): δ 2.39–2.51 (dd, $J=16.90$ Hz and 8.41 Hz, 1H), 2.68–2.81 (dd, $J=16.90$ Hz and 8.72 Hz, 1H); 3.35–3.43 (m, 1H), 3.62–3.84 (m, 2H), 7.18 (d, $J=9.12$ Hz, 2H), 7.31 (d, $J=9.12$ Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 38.22, 39.51, 49.43, 128.02, 128.83, 132.72, 140.59, 178.01; MS m/z (% rel. int.): 195 (M^+, 15), 140 (24), 138 (100), 75 (5).

Anal. calcd for $C_{10}H_{10}ClNO$ requires: C, 61.39; H, 5.15; Cl, 18.12; N, 7.16. Found: C, 61.29; H, 4.98; Cl, 18.18; N, 7.09%.

4.8. (*R*)-(−)-Baclofen hydrochloride 1

A mixture of compound **12** (0.050 g, 0.256 mmol) in aqueous 6N HCl (0.5 ml) was heated at 100°C for 10 h. The excess of water in the reaction mixture was removed under reduced pressure to obtain solid residue, which was triturated in isopropanol affording (*R*)-(−)-baclofen hydrochloride as a colorless solid (0.045 mg). Yield: 76%; mp: 195–197°C; $[\alpha]_D^{25}=-1.34$ (*c* 0.6, H_2O), 67% ee {lit.[10c] $[\alpha]_D^{25}=-2.00$ (*c* 0.6, H_2O)}; IR ($CHCl_3$, cm^{-1}): 3200, 2092, 2955, 1620, 1550, 1490, 1090, 758, 704, 698; ^1H NMR (DMSO-d_6): δ 2.65–2.91 (AB part of ABX pattern, $J_{AB}=16.6$ Hz, $J_{AX}=6.9$ Hz, $J_{BX}=7.7$ Hz, 2H), 3.10–3.39 (AB part of ABX pattern, $J_{BA}=12.8$ Hz, $J_{AX}=6.0$, $J_{BX}=8.9$ Hz, 2H); 3.64–3.72 (m, 1H), 7.41–7.43 (m, 4H); ^{13}C NMR (DMSO-d_6): δ 37.70, 40.22, 48.50, 128.11, 128.93, 131.24, 141.81, 176.00; MS *m*/*z* (% rel. int.): 195 (10), 140 (61), 138 (100), 125 (6), 115 (10), 103 (45), 89 (9), 77 (29). Anal. calcd for $C_{10}H_{13}Cl_2NO_2$ requires: C, 48.02; H, 5.24; Cl, 28.35; N, 5.60. Found: C, 48.24; H, 5.15; Cl, 28.41; N, 5.49%.

4.9. Ethyl 4-chlorophenylbenzoyl acetate 5

A 100 ml two-necked round-bottomed flask was charged with activated zinc (2.32 g, 35.7 mmol), and kept under N_2 atmosphere. Dry benzene (30 ml) was introduced and the reaction mixture was heated to 80°C (oil bath temp.). A solution of ethyl bromoacetate (5.88 g, 35.7 mmol) and *p*-chlorobenzaldehyde (4.56 g, 32.46 mmol) in dry benzene (20 ml) was added dropwise to the reaction mixture. After completion of the addition, the resulting reaction mixture was refluxed for 6 h, cooled to rt and quenched by adding ice cold 4N H_2SO_4 (30 ml). The crude hydroxyester **4** was extracted with diethyl ether evaporated under reduced pressure.

To a mixture of β-hydroxy ester **4** (4.56 g, 20 mmol) in diethyl ether (40 ml) was added dropwise through addition funnel freshly prepared chromic acid solution (15 ml) under ice-cold conditions with vigorous stirring. The reaction mixture was allowed to come to room temperature and stirring continued for 3 h (monitored by TLC). The organic layer was separated and the aqueous layer was extracted with ether (2×15 ml). The combined ethereal extracts were washed with water (15 ml) followed by brine (15 ml) and concentrated under reduced pressure to give crude product, which was further purified by column chromatography on silica gel using petroleum ether:EtOAc (9:1) as eluent to afford β-ketoester **5** (3.39 g). Yield: 75%; IR ($CHCl_3$, cm^{-1}): 2981, 2927, 1739, 1689, 1623, 1589, 1490, 1423, 1325, 1265, 1201, 1091, 1012, 840, 819; ^1H NMR ($CDCl_3$): δ 1.21–1.36 (m, 3H), 3.96 (s, 2H), 4.19–4.30 (m, 2H), 5.62 (s, 1H), 7.34–7.45 (m, 2H), 7.69 (d, $J=8.21$ Hz, 1H), 7.88 (d, $J=8.24$ Hz, 1H), 12.60 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 13.48, 13.67, 45.17, 59.91, 60.83, 87.07, 126.81, 127.95, 128.20, 128.42, 128.68, 129.20, 129.38, 131.29, 133.90, 136.66, 139.45, 166.65, 169.41, 172.50, 190.77; MS *m*/*z* (% rel. int.): 226 (M^+, 16), 180 (8), 139 (100), 111 (19), 75 (10). Anal. calcd for $C_{11}H_{11}ClO_3$ requires: C, 58.29; H, 4.89; Cl, 15.64. Found: C, 58.31; H, 4.80; Cl, 15.55%.

4.10. Asymmetric reduction of ethyl 4-chlorophenylbenzoyl acetate 5

A dry two-necked round-bottomed flask was charged with β-ketoester **5** (2.27 g, 10 mmol) and dry ethanol (60 ml). To this mixture was added (*S*)-BINAP–Ru(II) complex (40 mg, 0.05 mmol) under a stream of argon. The resulting yellowish orange solution was degassed with argon and then transferred by cannula to dry and clean autoclave. Hydrogen was introduced into the autoclave until the pressure gauge indicates 5 atm. The pressure was then carefully released to 1 atm. This procedure was repeated twice, and finally hydrogen was pressurized to 800 psi. The reaction mixture was vigorously stirred at 30°C for 100 h. The stirring was stopped and excess hydrogen was carefully bled off. The deep reddish orange reaction mixture was transferred to 100 ml round bottom flask and the autoclave was rinsed with dichloromethane (3×15 ml). The solvent was removed in vacuo and the residue was subjected to column chromatography (10% ethyl acetate in petroleum ether as eluent) to get pure (*R*)-alcohol **2** (2.24 g). Yield: 95%; gum; $[\alpha]_D^{25}=+41.3$ (*c* 1.5, $CHCl_3$), 96% ee (determined by Eu(hfc)$_3$ shift reagent); IR (Neat, cm^{-1}): 3461, 2981, 1718, 1595, 1490, 1400, 1375, 1284, 1193, 1091, 1014, 831; ^1H NMR ($CDCl_3$): δ 1.25 (t, $J=7.10$ Hz, 3H), 2.65–2.70 (m, 2H), 4.17 (q, $J=7.10$ Hz, 2H), 5.07–5.14 (m, 1H), 7.31 (s, 4H); ^{13}C NMR ($CDCl_3$): δ 14.00, 43.22, 60.83, 69.54, 127.03, 128.53, 133.31, 141.11, 171.98; MS *m*/*z* (% rel. int.): 228 (M^+, 3), 182 (6), 156 (53), 139 (100), 111 (54), 75 (73). Anal. calcd for $C_{11}H_{13}ClO_3$ requires: C, 57.78; H, 5.73; Cl, 15.50. Found: C, 57.77; H, 5.69; Cl, 15.68%.

4.11. (*S*)-Ethyl 3-bromo-3-(4-chlorophenyl)propionate 13

To a mixture containing β-hydroxy ester **2** (0.500 g, 2.2 mmol) in dry ether (15 ml), pyridine (0.40 ml, 4.84 mmol) was added under argon atmosphere. The reaction mixture was cooled to −20°C. Then PBr_3 (0.650 g, 0.230 ml, 2.4 mmol) in ether (5 ml) was added dropwise at −20°C. The reaction mixture was then stirred for 3 h at −20°C and then for 50 h at 0°C (monitored by TLC). The reaction was quenched by the addition of crushed ice the ether layer was washed with ice water, 85% phosphoric acid, cold saturated sodium bicarbonate, twice with cold water and brine, and dried over anhydrous Na_2SO_4. The crude product was finally purified by column chromatography on silica using petroleum ether:EtOAc (9:1) as eluent to afford β-bromoester **13** (0.504 g). Yield: 79%; $[\alpha]_D^{25}=-104.2$ (*c* 2.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 2981, 2935, 1735, 1595, 1492, 1411, 1313, 1263, 1199, 1093, 1014, 829, 617; ^1H NMR ($CDCl_3$): δ 1.23 (t, $J=7$ Hz, 3H), 3.08–3.35 (m, 2H), 4.12 (q, $J=7$ Hz, 2H), 5.33 (t, $J=6$ Hz, 1H), 7.29–7.38 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 14.00, 44.73, 46.42, 60.79, 128.50, 128.79, 134.34, 139.38, 168.82; MS *m*/*z*

(% rel. int.): 292 (M^+, 6), 247 (10), 211 (69), 169 (98), 138 (88), 103 (100), 77 (88), 63 (36). Anal. calcd for $C_{11}H_{12}BrClO_2$ requires: C, 45.31; H, 4.15; Br, 27.41; Cl, 12.61. Found: C, 45.53; H, 4.13; Br, 27.44; Cl, 12.55%.

4.12. (*R*)-Ethyl 3-cyano-3-(4-chlorophenyl)propionate 3

In a 25 ml flask were added β-bromoester **13** (0.474 g, 1.6 mmol), NaCN (0.106 g, 4 mmol) and dry DMF (10 ml) under argon atmosphere. The reaction mixture was heated at 70°C for 14 h (monitored by TLC). After completion of the reaction it was diluted with water (5 ml) and extracted with EtOAc (4×15 ml) combined organic extracts were washed with brine (10 ml), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product. The crude product was further purified by column chromatography on silica gel using petroleum ether:EtOAc (8:2) as eluent to afford cyanoester **3** (0.340 g). Yield: 88%; mp: 62–63°C; $[\alpha]_D^{25}=+14.1$ (*c* 1.5, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 2983, 2917, 2294, 1737, 1492, 1375, 1251, 1190, 1093, 1016, 831; ^1H NMR ($CDCl_3$): δ 1.24 (t, $J=8.04$ Hz, 3H), 2.72–2.84 (dd, $J=16.08$ Hz and 8.12 Hz, 1H), 2.92–3.04 (dd, $J=16.08$ Hz and 8.12 Hz, 1H), 4.10–4.30 (m, 3H), 7.33 (s, 4H); ^{13}C NMR ($CDCl_3$): δ 13.78, 32.27, 39.40, 61.23, 119.35, 128.61, 129.12, 132.87, 134.27, 168.67; MS *m*/*z* (% rel. int.): 237 (M^+, 7), 163 (30), 150 (27), 137 (13), 101 (15), 88 (15), 75 (100), 63 (50). Anal. calcd for $C_{12}H_{12}ClNO_2$ requires: C, 60.64; H, 5.09; Cl, 14.92; N, 5.89. Found: C, 60.83; H, 5.12; Cl, 14.88; N, 5.98%.

4.13. (*R*)-3-(4-Chloropheny)-2-pyrrolidone 12

To a 25 ml round-bottomed flask containing a mixture of cyanoester **3** (0.300 g, 1.3 mmol) and $NiCl_2{\cdot}6H_2O$ (0.619 g, 2.6 mmol) in MeOH (8.0 ml), at 25°C was added in portions under stirring solid $NaBH_4$ (0.532 g, 14 mmol). Evolution of hydrogen was observed and the black precipitate appeared during the addition of $NaBH_4$. The resulting reaction mixture was stirred for 30 min. After the reaction was complete (monitored by TLC), the mixture was extracted with chloroform (10×3 ml). The chloroform layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue obtained was then purified by column chromatography using petroleum ether and EtOAc as eluents to give pure (*R*)-3-(4-chloropheny)-2-pyrrolidone **12**, 0.186 g as light yellow colored solid. Yield: 75%; mp: 115–117°C; $[\alpha]_D^{25}=-35.8$ (*c* 1.0, EtOH), 92% ee {lit.[13] $[\alpha]_D^{25}=-39$ (*c* 1.0, EtOH)}.

4.14. (*R*)-(−)-Baclofen hydrochloride 1

Lactam **12** (0.170 g, 0.9 mmol) in 6N HCl (4 ml) was heated at 100°C for 16 h. The excess of water in the reaction mixture was removed under reduced pressure to obtain solid residue, which was triturated in isopropanol affording (*R*)-(−)-baclofen hydrochloride **1** as a colorless solid (0.170 mg). Yield: 78%; mp: 195–197°C; $[\alpha]_D^{25}=-1.81$ (*c* 0.6, H_2O), 90% ee {lit.[10c] $[\alpha]_D^{25}=-2.00$ (*c* 0.6, H_2O)}.

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