Asymmetric synthesis of \((R)-(–)-\)baclofen via asymmetric dihydroxylation

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A short and efficient asymmetric synthesis of \((R)-(–)-\)baclofen, a selective GABAB agonist has been described with an overall yield of 14% and 85% ee. The Os-catalyzed Sharpless asymmetric dihydroxylation of \(\alpha,\beta\)-unsaturated olefin constitutes the key step in introducing stereogenic centers into the molecule.

Keywords: Asymmetric dihydroxylation, baclofen, \(\gamma\)-aminobutyric acid, Parkinsons’ disease, cyclic sulfate

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Baclofen \([\gamma\text{-amino-}\beta-(p\text{-chlorophenyl})\text{butyric acid, 1}],\) a derivative of \(\gamma\)-aminobutyric acid (GABA), plays an important role as an inhibitory neurotransmitter in the central nervous system (CNS) of mammalians. It helps to reduce the excitatory effect of active compounds such as benzodiazepine, barbiturate, etc. The deficiency of GABA is associated with diseases that exhibit neuromuscular dysfuntions such as epilepsy, Huntington, Parkinsons’ diseases etc. Baclofen is also one of the most promising drugs in the control and treatment of the paroxysmal pain of trigeminal neuralgia as well as spasticity of spine without influencing the sedation. Although baclofen is commercialized in its racemic form, it has been reported that its biological activity resides exclusively in \(R\)-enantiomer only.

There are many methods available in the literature for the synthesis of \((R)-(–)-\)baclofen 1. They are concerned mostly with resolution, chemo-enzymatic or enantioselective synthesis. 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 stoichiometric amounts. In this context, a more practical approach for the synthesis of \((R)-(–)-\)baclofen 1 is highly desirable. This article describes a new asymmetric synthesis of \((R)-(–)-\)baclofen 1 by employing Os-catalyzed Sharpless asymmetric dihydroxylation (AD) of \(\alpha,\beta\)-unsaturated olefin 2 (Scheme I).

The \(trans\)-olefinic ester 2 was prepared in 85% yield by the Reformatsky reaction of 4-chloro-benzaldehyde with ethyl bromoacetate followed by \(p\)-TSA catalyzed dehydration of the corresponding \(\beta\)-hydroxy alcohol. The olefinic ester 2 was then subjected to AD reaction using catalytic amount of (DHQ)\(_2\)PHAL [hydroquinine \(1,4\text{-phthalazinediyl diether}\)] as chiral ligand to give the chiral diol 3 in 94% yield and 95% ee [determined by using Eu(hfc)\(_3\) as a chiral shift reagent]. The diol 3 was then treated with SOCl\(_2\) in presence of Et\(_3\)N in CH\(_2\)Cl\(_2\) at 0°C for 30 min to yield the cyclic sulfite 4 in 86% yield. The cyclic sulfite 4 was then subjected to oxidation with catalytic amount of RuCl\(_3\).3H\(_2\)O in presence of NaIO\(_4\) as oxidant in CH\(_3\)CN:H\(_2\)O at 0°C, but all attempts to isolate the corresponding cyclic sulfate failed. To overcome this difficulty, the cyclic sulfate formed \(in situ\) was directly reacted with LiBr followed by acid hydrolysis to give the corresponding bromoalcohol 5 in 65% yield. The bromoalcohol 5 was then selectively reduced with Bu\(_3\)SnH in presence of 2,2'-azobisisobutyronitrile (2,2'-azobis(2-methylpropionitrile)) in benzene at 80°C to afford the corresponding \(\beta\)-bromoester 6 in 75% yield and 90% ee [determined by using shift reagent Eu(hfc)\(_3\)]. Alcohol 6 was then brominated using PBr\(_3\) and pyridine in Et\(_2\)O at –20°C to give the corresponding \(\beta\)-cyanoester 7 in 79% yield with complete inversion of configuration. The \(\beta\)-bromo ester 7 underwent S\(_N\)2 nucleophilic displacement using NaCN in DMF at 70°C to give the \(\beta\)-cyanoester 8 in 88% yield. Cyanoester 8 was chemoselectively reduced either with NaBH\(_4\) and NiCl\(_2\) or with catalytic amount of PtO\(_2\) in presence of H\(_2\) (40 psi).
to afford lactam 9 in 75% yield. The ee of lactam 9 was found to be 87% based on comparison of its data on optical rotation $\left[\alpha\right]_{25}^{D} = -35.8^\circ$ (c 1.0, EtOH), Lit. (ref. 14) $\left[\alpha\right]_{25}^{D} = -39.0^\circ$ (c 1.0, EtOH). Hydrolysis of lactam 9 with 6N HCl afforded (R)-baclofen 1 as its hydrochloride salt in 78% yield and 85% ee, $\left[\alpha\right]_{D} = -1.70^\circ$ (c 0.6, H2O), {Lit. (ref. 10c) $\left[\alpha\right]_{25}^{D} = -2.00^\circ$ (c 0.6, H2O)}. In conclusion, an efficient, asymmetric synthesis of (R)-(–)-baclofen using Os-catalyzed Sharpless asymmetric dihydroxylation of $\alpha,\beta$-unsaturated olefin 2 in 14% overall yield and 85% ee has been achieved.

Experimental Section

Melting points are uncorrected. Microanalysis was performed on a Carlo Erba EA 110B instrument. Infrared spectra were recorded on a Perkin-Elmer 683B instrument. The $^1$H and $^{13}$C NMR spectra were recorded on a 200 MHz instrument.

Preparation of (E)-ethyl 3-(4-chlorophenyl)-acrylate, 2. A 100 mL two-necked RB flask was charged with activated zinc (2.32 g, 35.7 mmole), and kept under N2 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 mmole) and $p$-chlorobenzaldehyde (4.56 g, 32.46 mmole) 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 hr, cooled to 25°C and quenched by adding ice cold 4N H2SO4 (30 mL). The crude hydroxyester was extracted with diethyl ether, evaporated under reduced pressure and then was subjected to dehydration with p-toluenesulfonic acid (0.7 g, 3.98 mmole) in toluene at reflux. Water generated during the dehydration was azeotropically separated and then toluene was distilled off. The crude olefinic ester 2 was purified by column chromatography packed with silica gel, eluting with pet. ether to give 5.81 g of 2.

Scheme I — (i) cat. OsO4, (DHQ)2-PHAL, K2Fe(CN)6, MeSO2NH2, K2CO3, $\textit{t}$BuOH:H2O (1:1), 0-25°C, 24 hr, 94% yield, 95% ee; (ii) SOCl2, Et3N, CH2Cl2, 0°C, 30 min. 86%; (iii) a) cat. RuCl3.3H2O, NaIO4, CH3CN: H2O, 0°C, 10 min. b) anhydrous LiBr, THF, 25°C, 45 min. c) 20% H2SO4, Et3O, 25°C, 4 hr, overall 65%; (iv) Bu3SnH, AIBN, benzene, 80°C, 79%; (v) NaCN, DMF, 70°C, 18 hr, 88%; (vi) NiCl2.6H2O, NaBH4, MeOH, 25°C, 1 hr, 75%; (vii) NiCl2.6H2O, NaBH4, MeOH, 25°C, 1 hr, 75%; (viii) 6N HCl, reflux, 16 hr, 78%, $\left[\alpha\right]_{D} = -1.70^\circ$ (c 0.6, H2O), 85% ee.

Yield: 85% overall in two steps; gum; IR (Neat): 685, 712, 998, 1064, 1172, 1202, 1312, 1450, 1578, 1640, 1720, 2874, 2933, 2960 cm$^{-1}$; $^1$H NMR (CDCl3): $\delta$ 1.33 (t, $J = 7.1$ Hz, 3H), 4.26 (q, $J = 7.1$ Hz, 2H), 6.40 (d, $J = 16.1$ Hz, 1H), 7.33 (d, $J = 9.1$ Hz, 2H), 7.45 (d, $J = 9.1$ Hz, 2H), 7.63 (d, $J = 16.1$ Hz, 2H); $^{13}$C NMR (CDCl3): $\delta$ 13.92, 60.13, 118.54, 128.83, 132.61, 135.63, 142.58, 166.10; MS: m/z (% rel. intensity) 210 (M+, 50), 182 (30), 165 (100), 155 (70), 139 (55), 101 (50), 75 (40). Anal. C11H11ClO2 requires C, 62.72; H, 5.25; Cl, 16.83%. Found C, 62.47; H, 5.12; Cl, 16.68%.

Preparation of ethyl (2R,3S)-2,3-dihydroxy-3-(4-chlorophenyl) propanoate, 3. A double-walled 250 mL RB flask was charged with K2FeCN6 (9.4 g, 28.5 mmole), K2CO3 (3.93 g, 28.5 mmole), (DHQ)2-PHAL (200 mg, 0.2 mmole), MeSO2NH2 (0.901 g, 9.5 mmole) and t-BuOH:H2O (1:1 v/v, 90 mL) and stirred for 5 min at 25°C. Then the reaction mass was cooled to 0°C and a solution of OsO4 (200 μL, 0.1 mmole, 0.5M solution in toluene) was added followed by 4-chloroethyl cinnamate 2 (2.0 g, 9.5 mmole). The reaction mixture was stirred for 24 hr at 25°C (progress of reaction was monitored by TLC). The reaction was quenched with sodium sulfite (10 g) and extracted with ethyl acetate (3×60 mL). The organic layer was washed
with brine (50 mL), dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography using EtOAc: pet. ether (1:1) as eluent to yield 3 as a white solid (2.18 g).

Yield: 94%; m.p. 112-13°C (recrystallized from EtOH); [α]22D + 15.6° (c 0.4, EtOH), 95% ee; IR (CHCl$_3$): 715, 1018, 1121, 1220, 1288, 1455, 1560, 1608, 1715, 2978, 2980, 3445 cm$^{-1}$; $^1$H NMR (CDCl$_3$): δ 1.28 (t, $J = 7.2$ Hz, 3H), 2.92 (bs, 1H), 3.26 (bs, 1H), 4.21-4.32 (m, 3H), 4.97 (bs, 1H), 7.34 (S, 4H); $^{13}$C NMR (CDCl$_3$): δ 13.96, 62.19, 73.91, 74.61, 127.73, 128.42, 133.72, 138.42, 172.53; MS: m/z (% rel. intensity) 244 (M+, 4), 227 (4), 153 (14), 74 (100), 58 (14). Anal. C$_{11}$H$_{13}$ClO$_4$ requires C, 54.00; H, 5.36; Cl, 14.49.

Preparation of ethyl (4S,5R)-4-carbethoxy-5-(4-chlorophenyl) 1,3,2-dioxathiolane-2-oxide, 4. The diol 3 (1.9 g, 7.8 mmole) was dissolved in triethylamine (23 mL) and cooled to 0°C in an ice-bath under argon atmosphere. Freshly distilled thionyl chloride (1.18 g, 0.72 mL, 9.88 mmole) was added and the reaction mixture was stirred at 0°C for 30 min (progress of reaction was monitored by TLC). After completion, ice-cold water (20 mL) was added and the reaction mixture extracted with ether (3×30 mL). The ether layer was washed with 10% HCl, saturated sodium bicarbonate solution and with brine successively. The ether extract was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography using pet. ether: EtOAc (9:1) as eluent to furnish 4 as light yellow oil (1.94 g).

Yield: 86%; yellow oil; [α]$_{25}^{22}$D − 120.43° (c 0.5, EtOH); IR (CHCl$_3$): 700, 1010, 1121, 1200, 1260, 1445, 1725, 2976, 2990, 3450 cm$^{-1}$; $^1$H NMR (CDCl$_3$): δ 1.25 (S, 4H), 2.67-2.71 (m, 2H), 3.19 (bs, 1H), 4.17 (q, $J = 7.2$ Hz, 2H), 4.68 (d, $J = 6.1$ Hz, 2H), 5.14 (d, $J = 6.1$ Hz), 5.56 (d, $J = 6.1$ Hz), 6.12 (d, $J = 6.1$ Hz) for 2H, 7.27-7.48 (m, 4H); $^{13}$C NMR (CDCl$_3$): δ 23.58, 62.74, 82.30, 82.44, 83.21, 86.81, 128.09, 128.90, 129.12, 132.43, 132.84, 135.52, 135.70, 165.77, 166.62; MS: m/z (% rel. intensity) 290 (M$^+$, 1), 226 (27), 188 (13), 180 (25), 154 (25), 139 (93), 125 (86), 104 (64), 89 (54), 77 (100), 63 (25). Anal. C$_{11}$H$_{11}$ClO$_5$S requires C, 45.45; H, 3.81; Cl, 12.20; S, 11.03. Found C, 45.43; H, 3.69; Cl, 12.31; S, 11.08%.

Preparation of ethyl (2S,3S)-2-bromo-3-hydroxy-3-(4-chlorophenyl) propanoate 5. To a solution of cyclic sulfite 4 (1.45 g, 5 mmole) in CH$_2$CN:H$_2$O mixture (9:1, 10 mL) at 0°C was added solid NaIO$_4$ (1.61 g, 7.5 mmole) and RuCl$_3$ (0.11 g, 0.5 mmole). The reaction mixture was stirred for 5 min at 0°C and immediately filtered through a pad of silica and celite directly into the solution of anhydrous LiBr (4.35 g, 50 mmole) in dry THF (30 mL). The resulting solution was stirred at 25°C for 1 hr and then concentrated under reduced pressure to dryness. To this was added 20% H$_2$SO$_4$ and diaetyl ether (1:1, 40 mL) and stirred at 25°C for 5 hr. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3×15 mL) the combined ether extracts were washed with saturated NaHCO$_3$ solution, brine and dried over anhydrous Na$_2$SO$_4$. The ether layer was evaporated under reduced pressure to give crude product which was further purified by column chromatography on silica gel to give pure bromaoolcohol 5 (1.00 g) as a colorless viscous liquid.

Yield: 65% overall; viscous liquid; [α]$_{25}^{22}$D − 120.43° (c 0.5, EtOH); IR (CHCl$_3$): 700, 1010, 1121, 1200, 1260, 1445, 1725, 2976, 2990, 3450 cm$^{-1}$; $^1$H NMR (CDCl$_3$): δ 1.25 (t, $J = 7.2$ Hz, 3H), 3.20 (bs, 1H), 4.19 (q, $J = 7.2$ Hz, 2H), 4.68 (d, $J = 4.1$ Hz, 1H), 5.25 (d, $J = 4.1$ Hz, 1H), 7.29 (d, $J = 8.2$ Hz, 2H), 7.42 (d, $J = 8.2$ Hz, 2H); $^{13}$C NMR (CDCl$_3$): δ 13.92, 51.57, 62.62, 75.09, 128.50, 134.71, 135.30, 170.36; MS: m/z (% rel. intensity) 308 (M$^+$, 7), 210 (20), 282 (10), 255 (15), 139 (20), 125 (100), 91 (60), 75 (40), 63 (23). Anal. C$_{11}$H$_{11}$BrClO$_5$S requires C, 42.96; H, 3.93; Br, 25.98; Cl, 11.53. Found C, 42.85; H, 3.82; Br, 25.84; Cl, 11.48%.

Preparation of ethyl (3R)-3-hydroxy-3-(4-chlorophenyl) propanoate 6. To a solution of bromoaoolcohol 5 (1.00 g, 3.3 mmole) in benzene (10 mL) in 50 mL RB flask, was added AIBN (2, 2'-azobisisobutyronitrile or 2,2'-azobis(2-methylpropionitrile, 2 mg, 0.012 mmole) and Bu$_3$SnH (1.16 g, 4.0 mmole) and the reaction mixture was heated at 80°C for 3 hr (progress of reaction was monitored by TLC). The reaction mixture was then cooled to RT and concentrated under reduced pressure to give crude product which was further purified by column chromatography on silica gel using pet. ether: EtOAc (8:2) as eluent to give 6 (0.555 g).

Yield: 75%; gum; [α]$_{25}^{22}$D + 38.7° (c 1.5, CHCl$_3$), 90% ee; IR (Neat): 831, 1014, 1091, 1193, 1284, 1375, 1400, 1490, 1595, 1718, 2981, 3461 cm$^{-1}$; $^1$H NMR (CDCl$_3$): δ 1.26 (t, $J = 7.1$ Hz, 3H), 2.67-2.71 (m, 2H), 3.19 (bs, 1H), 4.17 (q, $J = 7.1$ Hz, 2H), 5.06-
5.13 (m, 1H), 7.31 (s, 4H); 13C NMR (CDCl3): 1 δ 14.00, 43.22, 60.83, 69.54, 127.03, 128.53, 133.31, 141.11, 171.98; MS: m/z (% rel. intensity) 228 (M+1, 3), 182 (6), 156 (53), 139 (100), 111 (54), 75 (73).

Preparation of ethyl (3S)-3-bromo-3-(4-chlorophenyl) propanoate 7. To a mixture containing β-hydroxy ester 6 (0.500 g, 2.2 mmole) in dry ether (15 mL), pyridine (0.40 mL, 4.84 mmole) was added under argon atmosphere. The reaction mixture was cooled to –20°C. Then PBr3 (0.650 g, 0.230 mL, 2.4 mmole) in ether (5 mL) was added drop wise at –20°C. The reaction mixture was then stirred for 3 hr at –20°C and then for 48 hr at 0°C (progress of reaction was 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 Na2SO4. The crude product was finally purified by column chromatography on silica gel using pet. ether: EtOAc (9:1) as eluent to afford β-bromooester 7 (0.504 g).

Yield: 79%; gum; [α]D25° = 96.3° (c 2.0, CHCl3); IR (CHCl3): 617, 829, 1014, 1093, 1199, 1263, 1313, 1411, 1492, 1595, 1735, 2935, 2981 cm−1; 1H NMR (CDCl3): δ 1.23 (t, J = 7.0 Hz, 3H), 3.08-3.35 (m, 2H), 4.12 (q, J = 7.1 Hz, 2H), 5.33 (t, J = 6.2 Hz, 1H), 7.29-7.38 (m, 4H); 13C NMR (CDCl3): δ 14.00, 44.73, 46.42, 60.79, 128.50, 128.79, 134.34, 139.38, 168.82; MS: m/z (% rel. intensity) 237 (M+1, 7), 163 (30), 150 (27), 137 (13), 101 (15), 88 (15), 75 (100), 63 (50). Anal. C11H13ClO3 requires C, 57.78; H, 5.73; Cl, 12.55. Found C, 45.53; H, 4.13; Br, 27.44; Cl, 12.55%.

Preparation of ethyl (3R)-3-cyano-3-(4-chlorophenyl) propanoate 8. In a 25 mL flask were added β-hydroxy ester 6 (0.340 g). To a mixture containing a mixture of cyanoester 8 (0.300 g, 1.3 mmole) and NiCl2.6H2O (0.619 g, 2.6 mmole) in MeOH (8.0 mL), at 25°C was added in portions under stirring solid NaBH4 (0.532 g, 14 mmole). Evolution of hydrogen was observed and the black precipitate appeared during the addition of NaBH4. The resulting reaction mixture was stirred for 30 min. After the reaction was complete (progress of reaction was monitored by TLC), the mixture was extracted with chloroform (10×3 mL). The chloroform layer was washed with brine, dried over anhydrous Na2SO4 and evaporated under reduced pressure. The residue obtained was then purified by column chromatography using pet. ether and EtOAc as eluents to give pure 3-(4-chlorophenyl)-2-pyrrolidone 9, 0.186 g as light yellow colored solid.

Yield: 75%; m.p. 115-17°C; [α]D25° = –33.9° (c 1.0, EtOH), 87% ee, 92% ee (Lit.14 [α]D25° = –39° (c 1.0, EtOH)); IR (CHCl3): 3420, 3200, 2103, 1698, 1492, 1380, 1263, 1193, 1074, 758, 700, 668 cm−1; 1H NMR (CDCl3): δ 2.39-2.51 (dd, J = 16.9 Hz and 8.41 Hz, 1H), 2.68-2.81 (dd, J = 16.9 Hz and 8.72 Hz, 1H), 3.35-3.43 (m, 1H), 3.62-3.84 (m, 2H), 7.18 (d, J = 9.1 Hz, 2H), 7.31 (d, J = 9.1 Hz, 2H); 13C NMR (CDCl3): δ 138.22, 139.51, 49.43, 128.02, 128.83, 132.72, 140.59, 178.01; MS: m/z (% rel. intensity) 237 (M+1, 15), 178 (100), 75 (5). Anal. C13H12ClNO 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%.  

Preparation of (R)-(–)-Baclofen hydrochloride 1. Lactam 9 (0.170 g, 0.9 mmole) in 6N HCl (4 mL) was heated at 100°C for 16 hr. 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). 1H and 13C NMR spectral data observed for (R)-(–)-Baclofen obtained by the...
present method is identical with those reported in literature.\textsuperscript{10c}

Yield: 78\%; m.p. 195-197\(^{\circ}\)C; \([\alpha]_{D}^{25} = -1.70^\circ (c \ 0.6, \ H_2O)\), 85 \% ee, \{Lit. (ref. 10c) \([\alpha]_{D}^{25} = -2.00^\circ (c \ 0.6, \ H_2O)\); IR (CHCl\textsubscript{3}): 698, 704, 758, 1090, 1490, 1550, 1620, 2955, 2092, 3200 cm\textsuperscript{-1}; \(^1\)H NMR (DMSO-d\textsubscript{6} + CDCl\textsubscript{3}): 2.51-2.71 (m, 2H), 3.42-3.65 (m, 2H), 4.15-4.21 (m, 1H), 7.01-7.21 (m, 4H); 13C NMR (DMSO-d\textsubscript{6}): \(\delta\) 37.57, 38.88, 43.00, 129.27, 129.62, 131.57, 138.95, 171.95; MS: m/z (% rel. intensity) 195 (10), 140 (61), 138 (100), 125 (6), 115 (10), 103 (45), 89 (9), 77 (29).

Anal. C 10H13Cl2NO2 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%.

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