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# An efficient synthesis of (*R*)- and (*S*)-baclofen via desymmetrization

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ABSTRACT

A short and highly enantioselective synthesis of both enantiomers of GABA agonist baclofen in four steps with total yields of 32.8% [for (*S*)-isomer] and 35.1% [for (*R*)-isomer] is reported. The key step involved desymmetrization of cyclic anhydride with modified cinchona alkaloids.

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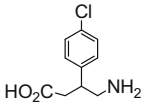
4-Aminobutanoic acid (GABA) is the major inhibitory neurotransmitter in the mammalian central nervous system (CNS), and it operates through ionotropic ($GABA_A$ and $GABA_C$) as well as G protein-coupled ($GABA_B$) receptors.[1–3] The dysfunction of the central GABA system is responsible for the development and outbreak of epilepsy, Huntington's and Parkinson's diseases, and other psychiatric disorders, such as anxiety and pain.[4] (±)-4-Amino-3-(4-chlorophenyl)butanoic acid (**1**, baclofen), which interacts stereospecifically with $GABA_B$ receptor, is a selective and therapeutically available $GABA_B$ agonist.[5–7] It is used in the treatment of paroxysmal pain of trigeminal neuralgia as well as spasticity of spinal, a serious disease characterized by an increase in muscle tone usually perceived as muscle tightness or achiness in limbs.[8,9] Although commercialized in its racemic form, the (*R*)-enantiomer has been found to be more active.[10] Many methods on the syntheses of (*R*)-baclofen have been reported, including resolution,[11–13] and chemoenzymatic[14–18] or enantioselective synthesis.[19–25] In general, the syntheses required more than six steps and proceed with a relatively low overall yield.




**1**

In this letter, we report a very short and efficient synthesis of both enantiomers of baclofen, obtained in highly enantiomeric excess (ee) and good yield by a four-step sequence involving desymmetrization of cyclic anhydride.

Enantioselective opening of readily accessible prochiral cyclic anhydrides was proven to be a valuable approach in the synthesis of chiral hemiesters by Oda and Aitken et al.[26–30] Deng recently discovered that modified cinchona alkaloids were able to function as effective chiral Lewis base catalysts for asymmetric methanolysis of various cyclic anhydrides.[31,32] In particular, a highly enantioselective (83–91%) desymmetrization of prochiral monocyclic anhydrides was obtained by using bis-cinchona alkaloids such as $(DHQD)_2AQN$ and $(DHQ)_2AQN$.[31]

With these encouraging results, we then attempted this application as a key step in the synthesis of (*R*)-baclofen. Two strategies for the synthesis of (*R*)-baclofen were put forward. The first strategy was based on a Curtius rearrangement of the key intermediate ester (*R*)-**4** and the second one involved a Hoffmann rearrangement of ester (*S*)-**4**.

In order to prepare chiral hemiester **4**, $(DHQD)_2AQN$- and $(DHQ)_2AQN$-catalyzed enantioselective alcoholysis of prochiral anhydride **3** was attempted. 3-(4-Chlorophenyl)glutaric acid anhydride **3** was prepared according to the procedure described[33] from the commercially available 3-(4-chlorophenyl)glutaric acid **2** and acetic anhydride under refluxing condition in 81% yield. Consequently, reaction of 1 equiv of anhydride **3** with 10 equiv of methanol in ethyl ether using 30 mol % of $(DHQD)_2AQN$ or $(DHQ)_2AQN$ as catalyst affected the desymmetrization of anhydride **3** to furnish chiral hemiester **4** (Scheme 1). The chiral catalyst was conveniently recovered quantitatively by basifying the aqueous phase followed by extraction with ethyl acetate and concentration under reduced pressure. It is worthy of note that the recovered catalyst could be used for another preparative scale reaction to afford the desired product without any loss of efficiency in terms of yield and enantioselectivity.

As a result, both $(DHQ)_2AQN$ and $(DHQD)_2AQN$ were found to be effective in desymmetrization of cyclic anhydride **3**. Particularly, a better enantioselectivity was obtained when using $(DHQD)_2AQN$ (95% ee) as a catalyst than when using $(DHQ)_2AQN$ (75% ee) as a catalyst, which is consistent with the original reports by Deng et al.[31]

The configuration of (*S*)-**4** was confirmed by comparing its specific rotation ($[\alpha]_D^{25}$ −8.0 (*c* 0.88, $CHCl_3$)) with literature reports[34] ($[\alpha]_D^{20}$ −9.6 (*c* 0.88, $CHCl_3$)).

Since the desymmetrization of cyclic anhydride **3** catalyzed by $(DHQD)_2AQN$ afforded higher ee, the final synthetic route

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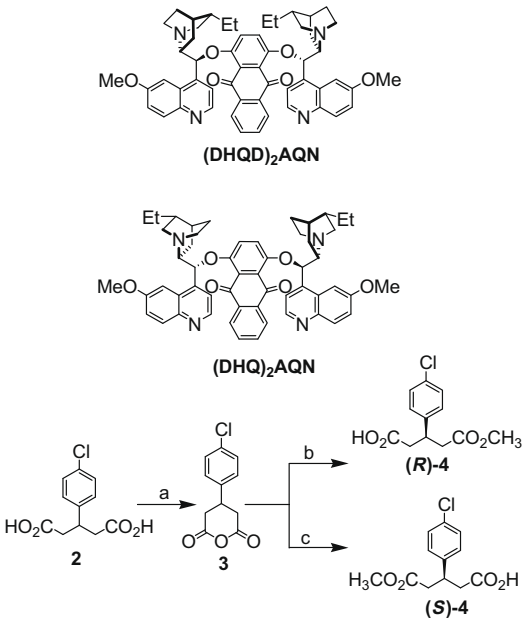



**Scheme 1.** Synthesis of (*R*)- and (*S*)-hemiester **4**. Reagents and conditions: (a) $Ac_2O$, reflux, 81%; (b) MeOH, $(DHQ)_2AQN$, −40 °C, 120 h, 80%, 75% ee; and (c) MeOH, $(DHQD)_2AQN$, −40 °C, 120 h, 76%, 95% ee.

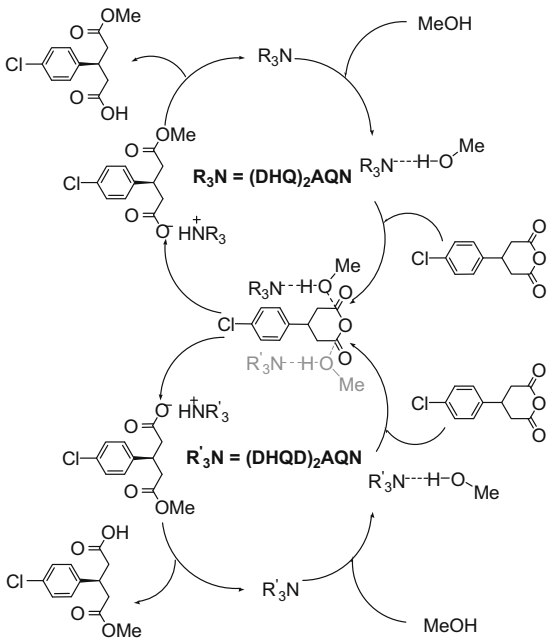



**Figure 1.** General base catalysis mechanism.

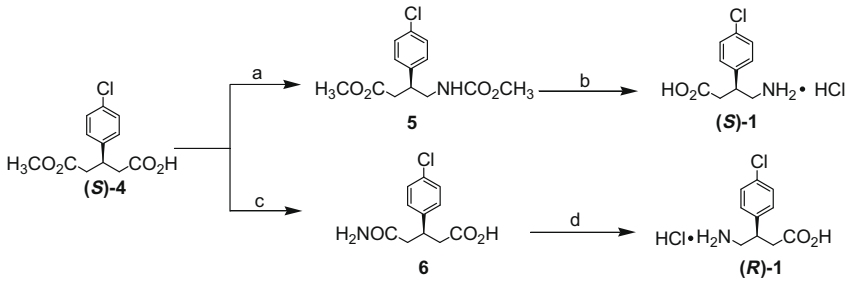
for the synthesis of (*R*)-baclofen was carried out as depicted in Scheme 2.

The hemiester (*S*)-**4** was converted to both (*R*)-baclofen and (*S*)-baclofen hydrochloride through the reaction sequences as shown in Scheme 2. Ammonolysis of hemiester (*S*)-**4** with ammonium hydroxide at room temperature furnished amide **6** in 95% yield. The amide **6** was then treated with [bis(trifluoroacetoxy)iodo]benzene (PIFA) at room temperature,[35] followed by stirring with HCl to provide (*R*)-**1** in 60% yield, which was identical to the authentic sample of (*R*)-baclofen hydrochloride in $^1H$ NMR, $^{13}C$ NMR, IR, MS (ESI), and HRMS spectra. Optical rotation: $[\alpha]_D^{23}$ −2.6 (*c* 1.00, $H_2O$) (lit.[23] $[\alpha]_D^{23}$ −1.5 (*c* 1.00, $H_2O$), for (*R*)-baclofen hydrochloride).

In addition, (*S*)-baclofen hydrochloride was also prepared using hemiester (*S*)-**4** by Curtius rearrangement. The reaction of (*S*)-**4** with diphenylphosphoryl azide (DPPA) and $Et_3N$ under reflux for 7 h was followed by addition of methanol to the reaction mixture. The resulting mixture was further refluxed for 10 h to furnish methyl ester **5** in 62% yield.[36–38] The methyl ester **5** was then hydrolyzed using HCl/AcOH to provide (*S*)-baclofen hydrochloride [(*S*)-**1**] in 86% yield, $[\alpha]_D^{25}$ +2.2 (*c* 1.00, $H_2O$).

It is known that nucleophilic catalysis and general base catalysis are two plausible mechanistic pathways for the cinchona alkaloid-catalyzed asymmetric ring opening of cyclic anhydrides.[39] The mechanistic role of the tertiary amine in the cinchona alkaloids is expected to be that of a general base rather than of a nucleophile,[26,39–41] as depicted in Figure 1. The first step is anticipated to form a chiral amine–methanol complex via hydrogen-bonding. Methanol is activated and attacks the anhydride for the ring opening. The resulting ion pair undergoes proton transfer, forming the hemiester product and regenerating the chiral amine catalyst.

Limited mechanistic studies have been reported to date on cinchona alkaloid-catalyzed desymmetrization of prochiral anhydrides via alcoholysis, especially on the stereoselectivity. We hypothesized that the anhydride **3** as a substrate fit into a U-shaped conformation enzyme-like binding pocket composed of the two parallel methoxyquinoline units of $(DHQD)_2AQN$ as depicted in Figure 2. This proposal builds on a transition-state model which has been developed by Corey for the bis-cinchona alkaloid-$OsO_4$ system.[42–44] The AQN moiety at the bottom of the U-shaped cavity trended to be oriented so as to allow the substrate **3** to fit into the packet with a favorable energy. Excellent binding between the substrate and the catalyst can be expected because of extensive π-stacking between the phenyl ring with the two methoxyquinoline units. The methanol activated by $(DHQD)_2AQN$ attacks the nearest carbonyl group of the substrate to give the (*S*)-hemiester **4**. In the same way, the product of opposite configuration was obtained using $(DHQ)_2AQN$ as a catalyst. The transition state model described above accommodates all of the experimental facts which we have observed.




**Scheme 2.** Synthesis of both (*R*)- and (*S*)-baclofen hydrochloride. Reagents and conditions: (a) DPPA, $Et_3N$, MeOH, 62%; (b) HCl, HOAc, reflux, 10 h, 86%; (c) $NH_3{\cdot}H_2O$, rt, 5 d, 95%; and (d) PIFA, $CH_3CN$, $H_2O$, rt, 24 h; concentrated HCl, rt, 1 h, 60%.

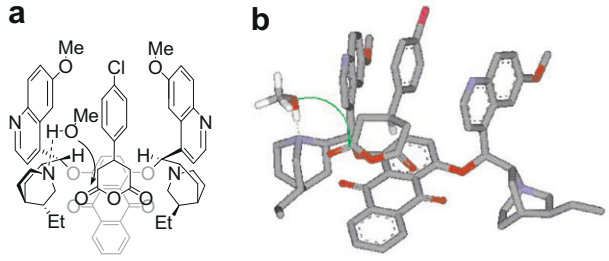



**Figure 2.** Two views of the proposed transition-state assembly for methanolytic desymmetrization of the anhydride substrate **3**. Putative intermolecular hydrogen bonds are highlighted by dashed lines. The AQN spacer unit located behind the anhydride substrate **3** is shown in gray for clarity.

Thus, we have developed a convenient and efficient route to synthesize both enantiomers of baclofen. The desymmetrization of cyclic anhydride reaction developed by Deng's group was used as the key step to give (*S*)-baclofen hydrochloride in 32.8% overall yield. Alternatively, the (*S*)-**4** was converted to (*R*)-baclofen hydrochloride in 35.1% overall yield.

## Acknowledgments

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38. Spectroscopic data of compounds **3**–**6** and (*R*)-**1**. *Compound* **3**: $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 2.81–2.87 (m, 2H), 3.07–3.11 (m, 2H), 3.40–3.45 (m, 1H), 7.16 (d, $J$ = 9.0 Hz, 2H), 7.37 (d, $J$ = 9.0 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 33.5, 36.9 (2C), 127.6 (2C), 129.5 (2C), 134.0, 137.5, 165.6 (2C); MS (*m/z*, % relative intensity): 226 ($M^+$, $^{37}$Cl, 6), 224 ($M^+$, $^{35}$Cl, 15), 140 (33), 138 (100), 115 (9), 103 (26), 77 (9); HRMS (ESI): calcd for $C_{11}H_{10}ClO_3$ $[M+H]^+$: 225.0318, found: 225.0316. *Compound* (*S*)-**4**: $[\alpha]_D^{25}$ −8.0 (*c* 0.88, $CHCl_3$); HPLC analysis with a Chiracel OD-H column [hexane/*i*-PrOH/$CH_3COOH$, 185:14:1; $\lambda$ = 226 nm; 1.0 mL/min; $t_R(S)$ = 16.5 min; $t_R(R)$ = 20.0 min] 95% ee; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 2.59–2.78 (m, 4H), 3.58 (s, 3H), 3.59–3.62 (m, 1H), 7.16 (d, $J$ = 8.5 Hz, 2H), 7.27 (d, $J$ = 8.5 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 37.3, 40.0, 40.3, 51.7, 128.6 (2C), 128.8 (2C), 132.8, 140.7, 171.7, 176.9; FT-IR (KBr, $cm^{-1}$): 3035, 1729, 1699, 1435, 1273, 1162, 1096, 825; MS (*m/z*, % relative intensity): 258 ($M^+$, $^{37}$Cl, 4), 256 ($M^+$, $^{35}$Cl, 14), 238 (11), 227 (6), 225 (18), 212 (33), 210 (100), 198 (18), 196 (52), 168 (27), 165 (22), 152 (55), 141 (45), 138 (21), 115 (27), 103 (32), 77 (29), 59 (20); HRMS (ESI): calcd for $C_{12}H_{13}ClNaO_4$ $[M+Na]^+$: 279.0400, found: 279.0395. *Compound* **5**: $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 2.46–2.63 (m, 2H), 3.20–3.22 (m, 2H), 3.38 (m, 1H), 3.49 (s, 3H), 3.51 (s, 3H), 4.70 (brs, 1H), 7.04 (d, $J$ = 8.5 Hz, 2H), 7.18 (d, $J$ = 8.5 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 38.0, 41.7, 45.9, 51.7, 52.1, 128.8 (2C), 128.9 (2C), 132.9, 139.5, 156.9, 172.1; FT-IR (KBr, $cm^{-1}$): 3345, 2953, 1732, 1534, 1256, 1167, 1092, 1014, 828; HRMS (ESI) calcd for $C_{13}H_{16}ClNNaO_4$ $[M+Na]^+$: 308.0666, found: 308.0664. *Compound* **6**: $[\alpha]_D^{25}$ +7.3 (*c* 1.20, MeOH); $^1$H NMR (500 MHz, MeOH-$d_4$): $\delta$ 2.46–2.75 (m, 4H), 3.54–3.59 (m, 1H), 7.26 (br s, 4H); $^{13}$C NMR (125 MHz, MeOH-$d_4$): $\delta$ 39.7, 41.3, 42.8, 129.5 (2C), 130.3 (2C), 133.5, 143.1, 175.2, 176.5; FT-IR (KBr, $cm^{-1}$): 3444, 3327, 2924, 1699, 1634, 1250, 1093, 1040, 1013, 823; MS (*m/z*, % relative intensity): 243 ($M^+$, $^{37}$Cl, 5), 241 ($M^+$, $^{35}$Cl, 21), 225 (7), 197 (31), 196 (37), 195 (100), 180 (54), 178 (35), 167 (83); HRMS (ESI) calcd for $C_{11}H_{12}ClNNaO_3$ $[M+Na]^+$: 264.0403, found: 264.0401. *Compound* (*R*)-**1**: $[\alpha]_D^{23}$ −2.6 (*c* 1.00, $H_2O$); $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 2.54–2.88 (m, 2H), 2.97–3.11 (m, 2H), 3.35–3.41 (m, 1H), 7.36 (d, $J$ = 8.5 Hz, 2H), 7.40 (d, $J$ = 8.5 Hz, 2H), 8.07 (s, 3H), 12.24 (s, 1H); $^1$H NMR (500 MHz, $D_2O$): $\delta$ 2.73–2.89 (m, 2H), 3.24–3.28 (m, 1H), 3.38–3.45 (m, 2H), 7.36 (d, $J$ = 8.5 Hz, 2H), 7.46 (d, $J$ = 8.5 Hz, 2H); $^{13}$C NMR (125 MHz, $D_2O$): $\delta$ 39.0, 40.2, 44.3, 130.0 (2C), 130.2 (2C), 134.1, 137.8, 176.1; FT-IR (KBr, $cm^{-1}$): 3030, 1725, 1494, 1411, 1205, 1182, 1127, 1089, 1015, 948, 828; MS (ESI) *m/z*: 214 $[M-Cl]^+$; HRMS (ESI) calcd for $C_{10}H_{13}ClNO_2$ $[M-Cl]^+$: 214.0635, found: 214.0631.
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