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A Chemoenzymatic Strategy for the Synthesis of Enantiopure (*R*)-(-)-Baclofen

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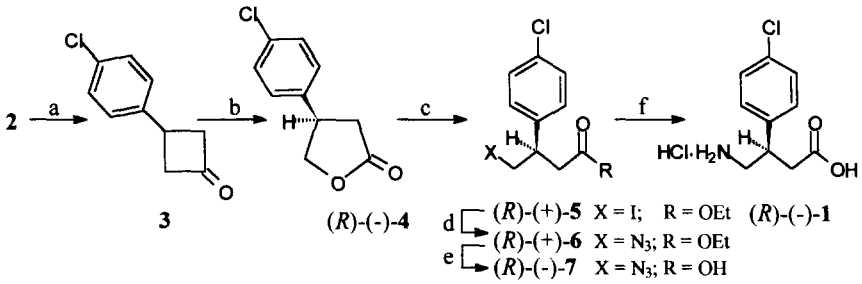
Abstract: *A seven-step enantioselective synthesis of (R)-(-)-baclofen 1 is described. The strategy developed involved, as a key step, a microbiologically mediated Baeyer Villiger oxidation of the prochiral 3-(4'-chlorobenzyl)-cyclobutanone 3 which led to the optically pure (R)-(-)-4 lactone. This was further transformed throughout chemospecific reactions into the target molecule (R)-(-)-1.*

GABA (γ-aminobutyric acid) is the major inhibitory neurotransmitter in the central nervous system[1] and it has been shown to interact with two types of receptors designated as $GABA_A$ and $GABA_B$ by Hill and Bowery.[2] Baclofen **1**, a lipophilic derivative of GABA, was synthesized for the first time in 1962. Some more recent studies have described the synthesis of the biologically active (*R*) enantiomer of **1**[3] which, until recently, has been the only selective and therapeutically useful agonist of the $GABA_B$ receptor. A large number of its analogues have also been prepared during the last years.[4] In the course of our work focused on developing efficient methodologies to prepare enantiopure biologically active molecules *via* integrated chemoenzymatic approaches,[5] we have been interested in devising a new way to synthesize this drug. We propose herein a short synthesis of (*R*)-(-)-**1**.

Our strategy was based on the use of an enantiopure lactone as a key building block. This was prepared using the whole-cell biotransformation methodology we have developed previously, which allows to prepare, *via* enzymatic Baeyer-Villiger oxidation, gram scale quantities of such lactones.[5]

Scheme: Synthesis of (*R*)-(-)-baclofen 1



Reaction Conditions: (a) (i) Cl_3CCOCl, Et_2O, $POCl_3$, reflux; (ii) Zn, AcOH, reflux, 65% overall; (b) Culture of *C. echimulata*, 31%; (c) Me_3SiI, EtOH, CH_2Cl_2, 0 °C to rt, 95%; (d) NaN_3, DMF, 75 °C, 95%; (e) (i) NaOH 2 M, rt; (ii) HCl_{conc}, rt, 95% overall; (f) (i) H_2 1 atm, Pd-C, Et_2O/EtOH, rt; (ii) HCl_{gas}, 80% overall.

Thus, starting from the commercially available 4-chlorostyrene **2**, we prepared the prochiral 3-(4'-chlorobenzyl)-cyclobutanone **3**[6] following a two step procedure.[7] This ketone was then submitted to oxidation

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using a culture of the fungus *Cunninghamella echinulata* NRLL 3655 which allowed to perform the stereoselective incorporation of an oxygen atom into one single enantiotopic C-C bond (adjacent to the carbonyl moiety), thus leading to the (*R*)-(-)-chlorobenzyl lactone **4**[3a] in very high enantiomeric purity (ee >99%, yld 30%).[8] Further chemical transformation of this key intermediate was as follows. Regioselective lactone ring opening using iodotrimethylsilane and ethanol in dichloromethane[9] gave the iodo ester (*R*)-(+)-**5**, which was easily transformed into the corresponding azido ester (*R*)-(+)-**6** by treatment with sodium azide. Next, base catalyzed hydrolysis of the ester moiety, followed by neutralization with hydrochloric acid, afforded the azido acid (*R*)-(-)-**7**. This was further reduced by catalytic hydrogenation over Pd/C (using a 1:1 mixture of diethyl ether and methanol as solvent), thus leading to the desired (*R*)-(-)-baclofen **1** target which was isolated as its hydrochloride salt after treatment with gaseous hydrochloric acid in dry diethyl ether. This was obtained in high optical purity (o.p. >96%).[10] It should be mentioned that, using a culture of the bacteria *Acinetobacter calcoaceticus* NCIMB 9871, the enantiomeric lactone (*S*)-(+)-**4**,[11] could similarly be obtained but in lower enantiomeric purity (85% ee). This thus allows to synthesize, in the same way, the (*S*)-(+) enantiomer of baclofen **1**.

In conclusion, we have set up an efficient strategy allowing for the synthesis of the biologically active (*R*)-(-)-baclofen **1** enantiomer in high optical purity and in reasonable yield (7 step synthesis, 13% overall from the commercial 4-chlorostyrene **2**). If required, this procedure could certainly be further optimized, in particular as far as the yield of the biooxidation is concerned.

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6. Experimental data: 3: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.96-3.09 (m, 2H), 3.25-3.40 (m, 2H), 3.40-3.55 (m, 1H), 7.05 and 7.14 (d's, *J* = 8.4, 2H each); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 28.09, 54.83, 128.04, 128.91, 132.52, 142.15, 206.23; $\nu_{C=O}$ 1778 cm^{-1}. (*R*)-(+)-5: $[\alpha]_D^{25}$ = +7.7 (c = 8.9, CHCl3); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.94 (t, *J* = 7.1, 3H), 2.35-2.5 (m, 1H), 2.64-2.74 (m, 1H), 3.12-3.2 (m, 3H), 3.83 (q, *J* = 7.1, 2H), 6.93 and 7.09 (d's, *J* = 8.5, 2H each); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 11.86, 14.27, 40.50, 43.50, 60.80, 129.10, 129.52, 133.23, 140.23, 171.14; $\nu_{C=O}$ 1732 cm^{-1}. (*R*)-(+)-6: $[\alpha]_D^{25}$ = +7.9 (c = 2.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.2 (t, *J* = 7.1, 3H), 2.40 (dd, *J* = 15.9, 7.9, 1H), 2.57 (dd, *J* = 15.9, 6.7, 1H), 3.12-3.25 (m, 1H), 3.25-3.39 (m, 2H), 3.87 (q, *J* = 7.1, 2H), 6.97 and 7.11 (d's, *J* = 8.4, 2H each); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 14.25, 37.94, 41.42, 56.12, 60.81, 129.01, 129.23, 133.23, 139.46, 171.40; ν_{azide} 2100 cm^{-1}, $\nu_{C=O}$ 1732 cm^{-1}. (*R*)-(-)-7: $[\alpha]_D^{25}$ = -0.7 (c = 2.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.81 (dd, *J* = 16.4, 8.0, 1H), 3.00 (dd, *J* = 16.4, 6.5, 1H), 3.44-3.56 (m, 1H), 3.56-3.75 (m, 2H), 7.32 and 7.47 (d's, *J* = 8.5, 2H each), 9.5 (s/b, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 37.56, 41.09, 56.07,129.13, 129.16, 133.37, 139.15, 177.09; ν_{azide} 2100 cm^{-1}, $\nu_{C=O}$ 1713 cm^{-1}.
7. Kaiwar V., Reese C. B., Gray E. J., Neidle S. *J. Chem. Soc., Perkin Trans. 1*, **1995**, 2281-2287. Some modifications in the procedure allowed us to synthesize a 10 g scale of cyclobutanone **3** in 65% yield from 4-chlorostyrene **2** as starting material.
8. (*R*)-(-)-4: $[\alpha]_D^{25}$ = -51 (c = 0.5, $CHCl_3$); lit.[3a] $[\alpha]_D^{25}$ = -44 (c = 0.5, $CHCl_3$). Enantiomeric excesses were determined by chiral GC analysis using a 25 m capillary column Lipodex E (Macherey-Nagel) at 160°C and a racemic sample as reference: (*R*)-(-)-4 t_R = 27.3 min and (S)-(+)-4 t_R = 26.8 min.
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10. (*R*)-(-)-1: $[\alpha]_D^{25}$ = -2 (c = 0.6, H_2O); lit.[3a], $[\alpha]_D^{25}$ = -1.7 (c = 0.2, H_2O). Owing to the very low value of the optical rotation of this product, its optical purity was assessed by transformation of a sample into the corresponding lactame: $[\alpha]_D^{25}$ = -40 (c = 0.5), EtOH; lit.[3a], $[\alpha]_D^{25}$ = -39 (c = 1.0, EtOH).
11. (*S*)-(+)-4: yield = 88% from **3**; $[\alpha]_D^{25}$ = +42 (c = 0.5, $CHCl_3$).

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