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CHEMOENZYMATIC SYNTHESIS OF BOTH ENANTIOMERS OF BACLOFEN

Robert Chênevert* and Michel Desjardins

Département de Chimie, Faculté des Sciences et de Génie
Université Laval, Québec , Canada, G1K 7P4

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Abstract: *Both enantiomers of baclofen have been synthesized in five steps from 4-chlorocinnamic acid. The key step is the highly stereoselective enzymatic hydrolysis of dimethyl 3-(4-chlorophenyl)glutarate by chymotrypsin.*

Baclofen [4-amino-3-(4-chlorophenyl)-butanoic acid] is an analog of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) but, unlike GABA, it can cross the blood/brain barrier. Racemic baclofen is widely used as an antispastic agent. The enantiomers of this compound differ in their pharmacodynamic and toxicological properties: the (-)-enantiomer is much more active but also more toxic than the (+)-enantiomer.[1] The R-configuration was assigned to the active enantiomer on the basis of X-ray crystallography.[2] We report here a chemoenzymatic synthesis of both enantiomers of baclofen.

Esterification of 4-chlorocinnamic acid (**1**) with methanol in the presence of an acidic resin as a catalyst gave ester **2** (scheme 1). The base-catalyzed (sodium methoxide) Michael type reaction of dimethyl malonate with **2** gave triester **3**. The demethoxycarbonylation[3] of **3** on heating in aqueous DMSO containing NaCl led to diester **4**. The symmetric diester **4** was treated with chymotrypsin[4] to afford the chiral half-ester **5a** in 85% chemical and ≥ 98% optical yields. Hydrolysis of **4** in the presence of PLE[4] in aqueous DMSO (40%) gave the other enantiomer in a lower optical yield (ee = 80%). The optical purities of compound **5** were determined by ^{1}H NMR (200 MHz) and confirmed by HPLC analysis (LC-(S)-naphthyl urea column). Both methods were based on the reaction of mono-ester **5** with the R enantiomer of 1-(phenyl) ethylamine in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) followed by analysis of the resulting diastereomeric amides.

The carboxyl group of **5** was converted to an amino group with retention of configuration through a Curtius rearrangement: thus, the half-ester was treated with ethyl chloroformate at 0 °C in acetone and then with sodium azide. Acetone was replaced by toluene and the solution was heated to 100 °C and the resulting isocyanate was hydrolysed with aqueous HCl to give R-(-)-baclofen hydrochloride (**6**): $[\alpha]^{25}_D$ - 1.5° (c 0.2, H_2O); lit.[1] $[\alpha]^{25}_D$ - 1.4° (c 1, H_2O). Ammonolysis of the mono-ester **5** in a pressure tube produced the corresponding amide which was submitted to an Hofmann rearrangement with bis(trifluoroacetoxy)iodobenzene[5] and acidification to give S-(+)-baclofen hydrochloride (**6**): $[\alpha]^{25}_D$ + 1.5° (c 0.2, H_2O); lit.[1] $[\alpha]^{25}_D$ +1.4° (c 1, H_2O). Both enantiomers were purified by ion exchange chromatography (Dowex® 50X2-200).

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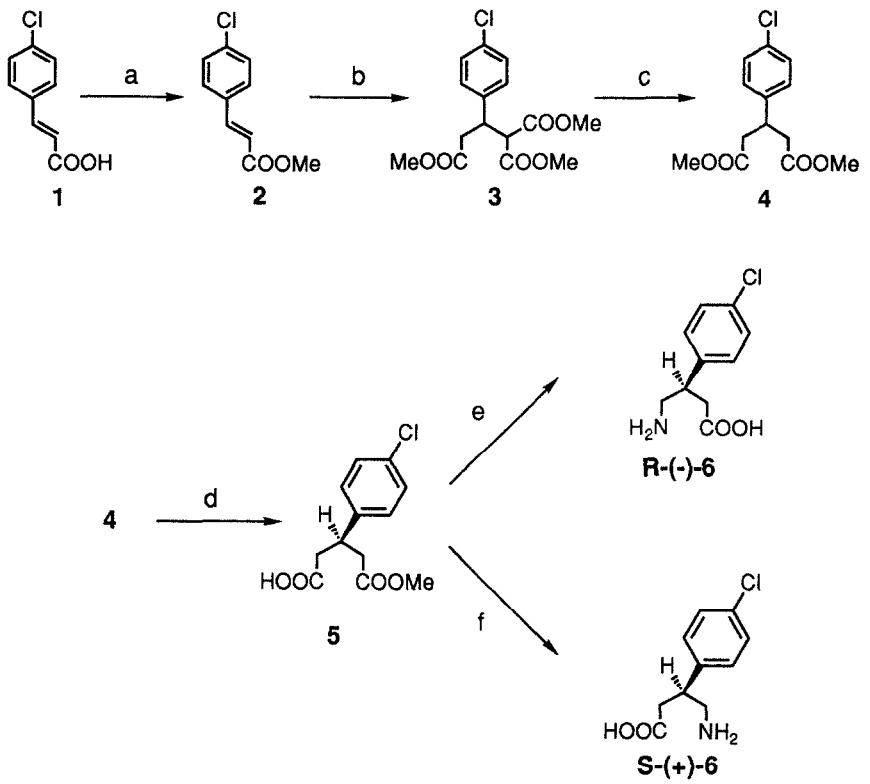
Scheme 1



Reagents and Conditions: (a) MeOH, Dowex® H^+ resin, reflux (95%); (b) Methyl malonate, CH_3ONa, THF, reflux, (85%); (c) NaCl, H_2O, DMSO, 160°C, (79%); (d) α-chymotrypsin, phosphate buffer pH 7.7, 25°C, (85%); (e) *i*) Ethyl chloroformate, Et_3N, acetone, 0°C, *ii*) NaN_3, H_2O, acetone, *iii*) toluene, reflux, *iv*) HCl, H_2O, (40%); (f) *i*) NH_3, MeOH, pressure, *ii*) Bis(trifluoroacetoxy)iodobenzene, DMF, H_2O, (60%)

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