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Enantioselective synthesis of β-substituted butyric acid derivatives via orthoester Claisen rearrangement of enzymatically resolved allylic alcohols: application to the synthesis of (*R*)-(−)-baclofen

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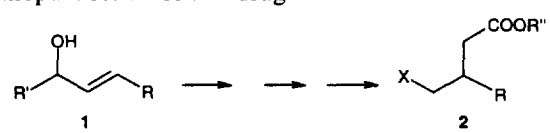
Abstract: A three step synthesis of (R)-(−)-baclofen is described. The key step is the orthoester Claisen rearrangement of enantiopure allylic alcohol (*S,E*)-(−)-**1a**, affording γ,δ-unsaturated ester (*S,E*)-(+)-**6** with high stereoselectivity. This latter derivative is converted into (*R*)-(−)-baclofen through a high yield one-pot reaction. © 1997 Elsevier Science Ltd

Introduction

In an effort to develop new strategies for the enantioselective synthesis of chiral biologically active molecules,[1] we have been interested in studying the acid catalysed orthoester Claisen rearrangement[2] of enantiomerically enriched allylic alcohols **1**. This well-known (3,3)-sigmatropic shift is highly stereoselective: depending on the configuration of the double bond, and of the stereocentre of the starting allylic alcohol, both the enantiomers of the corresponding chiral γ,δ-unsaturated ester can be obtained.[3] In our experience, enantiopure alcohols **1** could be prepared, for example, by biocatalysed kinetic resolution.[4]

We investigated this synthetic approach with the aim of synthesising chiral derivatives containing the structural fragment of type **2**: we first applied the procedure in order to obtain (*R*)-4-amino-3-(4-chlorophenyl)butyric acid **2a** (baclofen), as recent literature reports[5] showed a renewed interest in the preparation of the enantiopure forms of this drug.



1
1a: R = 4-ClC$_6$H$_5$, R' = Me

2
2a: R = 4-ClC$_6$H$_5$, R'' = H, X = NH$_2$

(±)-Baclofen is a lipophilic derivative of γ-amino butyric acid (GABA), and it has been usefully employed for the treatment of spasticity.[6] Pharmacological studies have shown that the (*R*)-enantiomer is the therapeutically useful agonist of the $GABA_B$ receptor.[7] We report herein a three-step route to prepare (*R*)-**2a**, starting from racemic alcohol **1a**.

Results and discussion

Aldol condensation between acetone and 4-chlorobenzaldehyde afforded (*E*)-4-(4-chlorophenyl)-3-buten-2-one, which was reduced to (*E*)-(±)-**1a** with sodium borohydride in methylene chloride:methanol (1:1) solution. Kinetic resolution of the racemic allylic alcohol by enzymatic acetylation was performed in *t*-butylmethyl ether solution, in the presence of porcine pancreas lipase, using vinyl acetate as the acylating agent (24 h, rt, c=48%, E=156).[8] Column chromatography on silica gel gave acetate (*E*)-(+)-**3** (ee >99%, HPLC) and alcohol (*E*)-(−)-**1a** (ee >99%, HPLC).

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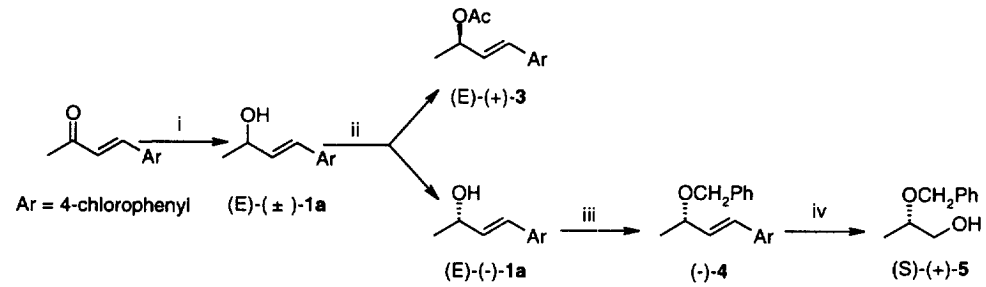
The absolute configuration of (−)-**1a** was determined by chemical correlation. Reaction of (−)-**1a** with NaH and benzyl chloride in tetrahydrofuran solution gave benzyl ether (−)-**4**, which was ozonized in methylene chloride:methanol (1:1) solution. *In situ* reduction with sodium borohydride allowed us to recover (+)-2-benzyloxypropan-1-ol **5**, which was known to have the *S*-configuration (Scheme 1).[9]



Scheme 1. (i) $NaBH_4$, CH_2Cl_2:MeOH (1:1); (ii) PPL, *t*-butylmethyl ether, vinyl acetate; (iii) NaH, THF, $PhCH_2Cl$; (iv) O_3, CH_2Cl_2:MeOH (1:1), then $NaBH_4$.

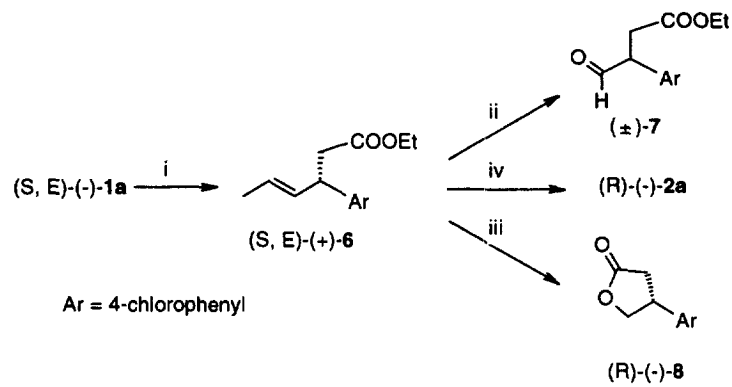
Thus, the alcohol (*E*)-(−)-**1a**, which was left unreacted in the biocatalysed acetylation, was found to be the *S* enantiomer. This isomer was submitted to an orthoester Claisen rearrangement: a solution of (*S*,*E*)-(−)-**1a** in triethyl orthoacetate, in the presence of propionic acid as a catalyst, was heated at 120°–130°C, removing ethanol by distillation. The residue obtained upon evaporation of the solvent was distilled bulb-to-bulb, to give γ,δ-unsaturated ester (*E*)-(+)-**6**, showing ee >99% (GC). This latter derivative was ozonized at −78°C for 45 min: after treatment with triphenylphosphine, aldehyde **7** could be isolated. Unfortunately, this substrate was found to be configurationally unstable at room temperature, probably because of a facile enolization equilibrium involving the hydrogen atom of the stereocentre.

However, when a sample of the ozonolysis mixture was decomposed with sodium borohydride, lactone (−)-**8** could be recovered directly. The isolation of this latter enantiomerically pure (ee >99%, GC) precursor of (*R*)-(−)-baclofen,[5b] with the *R* configuration at the stereocentre, suggested to us a valuable improvement of the synthetic route. We treated the reaction mixture of the ozone oxidative cleavage of (+)-**6** at −78°C with ammonium acetate and sodium cyanoborohydride. The temperature was allowed to rise with stirring over a 12 h period; and then a 2 M sodium hydroxide solution was added. The mixture was stirred at room temperature for 2 h, and, after the usual work-up, the desired (−)-baclofen was directly recovered as its hydrochloride salt. A high yield one-pot reaction allowed us to convert (+)-**6** into (*R*)-(−)-baclofen (Scheme 2), and to assign *S*-configuration to the right-handed enantiomer of ester **6** with a positive specific rotation.

Conclusions

Orthoester Claisen rearrangement of allylic alcohol (*S*,*E*)-**1a** provided unsaturated ester (*S*,*E*)-**6** with high stereoselectivity. Bond formation occurred in the most stable conformation of the cyclic six-membered transition state having the methyl group equatorial, as the literature data confirmed.[3] This new and highly enantioselective synthesis of (*R*)-baclofen has clearly shown the great potential of this simple sequence, combining two well known procedures of organic synthesis, such as lipase-mediated kinetic resolution and Claisen rearrangement.

Work is now in progress to apply this synthetic route widely for the preparation of other β-substituted butyric acid derivatives, by exploiting the great reactivity of the double bond of unsaturated esters of type **6**. For example, we are interested in obtaining enantiopure β-substituted-γ-lactones by sodium borohydride treatment of the ozonolysis mixture of the corresponding chiral ester, as a few enantioselective syntheses of this kind of substrates are known.[10]



Scheme 2. (i) $CH_3C(OEt)_3$, propionic acid, Δ; (ii) O_3, CH_2Cl_2:MeOH (1:1), then PPh_3; (iii) O_3, CH_2Cl_2:MeOH (1:1), then $NaBH_4$; (iv) O_3, CH_2Cl_2:MeOH (1:1), then NH_4OAc, $NaCNBH_3$; 2 M NaOH; HCl.

Experimental

HPLC analyses were performed on a chiral column (Chiracel OD, Daicel Japan): 254 nm, 0.6 mL/min, hexane:isopropanol (95:5), (*S*)-(−)-**1a** R_t=18.48 min, (*R*)-(+)-**1a** R_t=17.62 min, (*S*)-(−)-**3** R_t=7.90 min, (*R*)-(+)-**3** R_t=7.55 min. GC analyses were performed on a chiral column (DEtTBuβCDX, Mega, 25 m, id 0.25 mm, df 0.25 μm): 40°C (1 min); 20°C/min; 110°C (2 min); 1.5°C/min: (*R*)-(−)-**6** R_t=39.28 min, (*S*)-(+)-**6** R_t=39.51 min; 40°C (1 min); 20°C/min; 170°C (2 min); 1°C/min: (*R*)-(−)-**8** R_t=22.77 min, (*S*)-(+)-**8** R_t=23.34 min. ^{1}H NMR spectra were recorded in $CDCl_3$ solutions at room temperature unless otherwise stated, on a Bruker AC-250 spectrometer (250 MHz ^{1}H). The chemical shift scale was based on internal tetramethylsilane: J values are in Hz. Optical rotations were measured on a Jasco DIP 181 digital polarimeter. TLC analyses were performed on Merck Kieselgel 60 F_{254} plates. All the chromatographic separations were carried out on silica gel columns.

(E)-4-(4-Chlorophenyl)-3-buten-2-one

A mixture of 4-chlorobenzaldehyde (50.0 g, 0.357 mol), acetone (45 mL) and sodium hydroxide 30% (5 mL) in water (400 mL) was stirred at room temperature for 12 h. The precipitate was recovered by filtration, and crystallised from hexane to afford the title compound (45.0 g, 70%). Found: C, 66.41; H, 4.97; Cl, 19.58; $C_{10}H_9ClO$ requires C, 66.49; H, 5.02; Cl, 19.63%. ^{1}H NMR δ 2.41 (3H, s), 6.69 (1H, d, J=16.3), 7.33 (4H, m), 7.46 (1H, d, J=16.3).

(E)-(±)-4-(4-Chlorophenyl)-3-buten-2-ol ***1a***

Sodium borohydride (3.23 g, 0.085 mol) was added to a solution of (*E*)-4-(4-chlorophenyl)-3-buten-2-one (30 g, 0.17 mol) in methanol:methylene chloride (1:1, 400 mL) at 10°C. The reaction mixture was concentrated *in vacuo*, diluted with water and extracted with methylene chloride. The organic phase was dried on sodium sulphate, and the solvent was removed under reduced pressure.

The solid residue was crystallised from hexane, to afford (*E*)-(±)-**1a** (27.2 g, 88%) as a white crystalline solid: mp 62°C. Found: C, 65.67; H, 6.13; Cl, 19.35; $C_{10}H_{11}ClO$ requires C, 65.76; H, 6.07; Cl, 19.41%. ^{1}H NMR δ 1.37 (3H, d, J=6.3), 1.64 (1H, broad s), 4.52 (1H, m), 6.25 (1H, dd, J=6.2 and 15.8), 6.53 (1H, dd, J=15.8 and 1.2), 7.30 (4H, m).

(E)-(±)-3-(4-Chlorophenyl)-1-methyl-2-propenyl acetate ***3***

Acetylation of (*E*)-(±)-(**1a**) with acetic anhydride and pyridine in methylene chloride provided a sample of racemic acetate **3** to use as a reference. Found: C, 64.08; H, 5.79; Cl, 15.69; $C_{12}H_{13}ClO_2$ requires C, 64.15; H, 5.83; Cl, 15.78%. ^{1}H NMR δ 1.42 (3H, d, J=6.3), 2.08 (3H, s), 5.51 (1H, m), 6.16 (1H, dd, J=15.9 and 6.5), 6.55 (1H, dd, J=15.9 and 1.1), 7.31 (4H, m).

Kinetic resolution of (E)-(±)-1a by enzymatic acetylation

A mixture of (*E*)-(±)-**1a** (10 g, 0.055 mol), porcine pancreas lipase (Sigma Type II, 8 g), and vinyl acetate (80 mL) in *t*-butylmethyl ether (160 mL) was stirred at room temperature for 24 h (c=48%, E=156, HPLC).[8] The residue obtained upon evaporation of the filtered reaction mixture was chromatographed on a silica gel column, eluting with hexane:ethyl acetate. The first eluted fractions provided acetate (*R,E*)-(+)-**3** (5.12 g, 42%, ee >99%, HPLC) showing $[\alpha]_D^{20}$=+139.2 (c 1, $CHCl_3$). The last eluted fractions gave (*S,E*)-(−)-**1a**, which was crystallised from hexane (4.10 g, 41%, ee >99% HPLC) and showed $[\alpha]_D^{20}$=−25.4 (c 1, $CHCl_3$).

Determination of the absolute configuration of (−)-1a by chemical correlation

(−)-[(E)-3-(Benzyloxy)-1-butenyl]-4-chlorobenzene 4

A solution of (*E*)-(−)-**1a** (1.82 g, 0.01 mol) in dimethylformamide (5 mL) was dropped into a suspension of sodium hydride (60% dispersion in mineral oil, 0.600 g, 0.015 mol) in dimethylformamide (20 mL). After 30 min at 40°C, a solution of benzyl chloride (1.39 g, 0.011 mol) in dimethylformamide (20 mL) was added dropwise. After stirring at room temperature for 2 h, the reaction mixture was concentrated *in vacuo*, diluted with water, and extracted with diethyl ether. The organic phase was dried on sodium sulphate, and the solvent was removed under reduced pressure.

The residue was purified by column chromatography (hexane:ethyl acetate), to afford (−)-**4** (1.96 g, 72%) showing $[\alpha]_D^{20}$=−103.6 (c 1, $CHCl_3$). Found: C, 74.93; H, 6.33; Cl, 12.92; $C_{17}H_{17}ClO$ requires C, 74.86; H, 6.28; Cl, 13.00%. ^{1}H NMR δ 1.38 (3H, d, J=6.4), 4.11 (1H, m), 4.45 (1H, d, J=11.9), 4.62 (1H, d, J=11.9 Hz), 6.14 (1H, dd, J=16.1 and 7.5 Hz), 6.51 (1H, dd, J=16.1 Hz), 7.32 (9H, m).

(S)-(+)-2-Benzyloxypropan-1-ol 5

A solution of (−)-**4** (1.80 g, 6.62 10^{-3} mol) in methanol:methylene chloride (1:1, 1 mL) was ozonized for 30 min at −78°C. After the addition of sodium borohydride, the temperature was allowed to rise to room temperature. The reaction mixture was concentrated *in vacuo*, diluted with water and extracted with diethyl ether. The organic phase was dried on sodium sulphate, and the solvent was removed under reduced pressure.

The residue was purified by column chromatography (hexane:ethyl acetate) and distilled bulb-to-bulb, to afford (*S*)-(+)-**5**[9] (0.923 g, 84%), showing $[\alpha]_D^{20}$=+48 (c 1, $CHCl_3$): bp 95-107°C (3 mmHg). Found: C, 72.29; H, 8.54; Cl, 19.19; $C_{10}H_{14}O_2$ requires C, 72.26; H, 8.49; Cl, 19.25%.

(S,E)-(+)-Ethyl 3-(4-chlorophenyl)-4-hexenoate 6

A solution of (*S,E*)-(−)-**1a** (5.00 g, 0.027 mol) in triethyl orthoacetate (70 mL), in the presence of propionic acid (0.5 mL) as a catalyst, was heated at 120°–130°C, removing ethanol by distillation. The residue, obtained upon evaporation of the solvent, was distilled bulb-to-bulb under reduced pressure, to give ester (*S,E*)-(+)-**6** (5.11 g, 75%, ee >99% GC), showing $[\alpha]_D^{20}$=+10.1 (c 1, $CHCl_3$): bp=140°C (0.01 mmHg). Found: C, 66.49; H, 6.73; Cl, 14.08; $C_{14}H_{17}ClO_2$ requires C, 66.53; H, 6.78; Cl, 14.03%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.17 (3H, t, J=7.2 Hz), 1.65 (3H, dd, J=4.7 and 0.7 Hz), 2.65 (2H, m), 3.78 (1H, q, J=7.7 Hz), 4.06 (2H, q, J=7.2 Hz), 5.53 (2H, m), 7.21 (4H, m).

The same reaction was performed on (±)-**1a**, in order to have a sample of racemic **6** to use as a reference.

(±)-Ethyl 3-(4-chlorophenyl)-4-oxobutanoate 7

A solution of (*S,E*)-(+)-**6** (5.00 g, 0.020 mol) in methylene chloride:methanol (1:1, 100 mL) was treated with ozone at −78°C for 45 min. After decomposition with triphenylphosphine, the reaction mixture was concentrated under reduced pressure, diluted with water, and extracted with methylene chloride. The organic phase was dried on sodium sulphate, and the solvent was removed under reduced pressure.

The residue was purified by column chromatography, eluting with hexane:ethyl acetate, to afford aldehyde **7** which was found to be racemic by GC analysis (3.41 g, 71%). Found: C, 59.81; H, 5.49; Cl, 14.68; $C_{12}H_{13}ClO_3$ requires C, 59.88; H, 5.44; Cl, 14.73%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.24 (3H, t, J=7.1 Hz), 2.60 (1H, dd, J=16.6 and 6.6 Hz), 3.14 (1H, dd, J=16.6 and 8.0 Hz), 4.12 (3H, m), 7.27 (4H, m), 9.71 (1H, s).

(R)-(−)-4-(4-Chlorophenyl)tetrahydro-2-furanone ***8***

A solution of (*S,E*)-(+)-**6** (5.00 g, 0.020 mol) in methylene chloride:methanol (1:1, 100 mL) was treated with ozone at −78°C for 45 min. After decomposition with sodium borohydride, the reaction mixture was concentrated under reduced pressure, diluted with water, and extracted with methylene chloride. The organic phase was dried on sodium sulphate, and the solvent was removed under reduced pressure.

The residue was purified by column chromatography, eluting with hexane:ethyl acetate, to afford lactone (*R*)-(−)-**8** (2.98 g, 76%, ee >99% GC) showing $[\alpha]_D^{20}$=−48.5 (c 0.5, $CHCl_3$), lit.[5b]: $[\alpha]_D^{20}$=−51 (c 0.5, $CHCl_3$). Found: C, 61.13; H, 4.68; Cl, 18.09; $C_{10}H_{19}ClO_2$ requires C, 61.08; H, 4.61; Cl, 18.03%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.63 (1H, dd, J=17.5 and 8.6 Hz), 2.93 (1H, dd, J=17.5 and 8.9 Hz), 3.78 (1H, m), 4.24 (1H, dd, J=9.0 and 7.8 Hz), 4.65 (1H, dd, J=9.0 and 7.6 Hz), 7.32 (4H, m); FTIR (neat): ν (cm^{-1}) 1782 (C=O).

(R)-(−)-Baclofen ***2a***

A solution of (*S,E*)-(+)-**6** (5.00 g, 0.020 mol) in methylene chloride:methanol (1:1, 100 mL) was treated with ozone at −78°C for 45 min. After addition of ammonium acetate (1.54 g, 0.020 mol) and sodium cyanoborohydride (1.26 g, 0.020 mol), the temperature was allowed to rise under stirring in 12 h time. Then, a solution of 2 M sodium hydroxide was added. The reaction mixture was stirred at room temperature for 2 h, concentrated under reduced pressure, diluted with water, and extracted with methylene chloride. The organic phase was dried on sodium sulphate, and the solvent was removed under reduced pressure.

The residue was dissolved in isopropanol, and treated with gaseous hydrogen chloride. (*R*)-(−)-**2a** (3.65 g, 73%) was recovered as its hydrochloride salt by filtration, and showed $[\alpha]_D^{20}$=−1.8 (c 0.6, H_2O), lit.[5b]=−2 (c 0.6, H_2O).

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