Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 2113–2118

TETRAHEDRON: *ASYMMETRY*

An efficient synthesis of (*R*)-(−)-baclofen

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Received 6 April 1999; accepted 27 May 1999

Abstract

In this report we describe an efficient synthesis of (*R*)-(−)-baclofen, a selective $GABA_B$ agonist used as an antispastic agent. Our strategy is based on an enantioselective deprotonation of a cyclobutanone easily obtained by [2+2] cycloaddition of 4-chlorostyrene and dichloroketene.

1. Introduction

GABA or γ-aminobutyric acid is the major inhibitory neurotransmitter in the mammalian central nervous system (CNS).[1] This simple amino acid has two major receptor subtypes ($GABA_A$ and $GABA_B$).[2,3] These receptors apparently play an important role both in the central and peripheral nervous system through ion-channel regulation.[4]

The $GABA_B$ receptor in peripheral and central nervous systems is implicated in many biological processes including analgesia muscle relaxation, hypertension, increased gastric motility, and inhibition of the liberation of corticotropin releasing hormone.[5a,b] In contrast with the several reports concerning the development of specific agonists or antagonists acting at the $GABA_A$ receptor site,[2–6] there are only few examples of those acting at the $GABA_B$ receptor site.

Baclofen, or (3*R*)-4-amino-3-(4-chlorophenyl)butanoic acid (**1**, Fig. 1), is the only selective and therapeutically available $GABA_B$ agonist known (Lioresal® and Baclon®).[7a–c] It is used in the treatment of spasticity, a serious disease characterized by an increased muscle tone usually perceived as muscle tightness or achiness in the limbs. These symptons are normally associated with multiple sclerosis (MS).

Baclofen is commercialized in its racemic form, however literature observations suggested that the biological activity of **1** resides in the *R* enantiomer.[8] According to legislation already approved in many countries of the world concerning the commercialization of pharmaceutical products, drugs such as

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0957-4166/99/$ - see front matter
PII: S0957-4166(99)00235-9

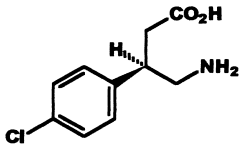


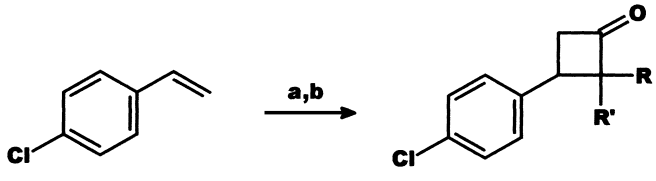
Figure 1.

1 will soon be sold only in their enantiomerically pure form. This requirement justifies the need for enantioselective strategies leading to the preparation of these compounds, if possible in a simple and efficient way.

In our studies on the structure–activity relationship of analogs of **1**, it has been necessary to prepare a series of derivatives with different substitution patterns. However none of the already described syntheses[9,10] permitted us to easily achieve our target. In view of these limitations, we have recently reported a four step synthesis of (±)-baclofen,[11a] based on a [2+2][11b] cycloaddition reaction between dichloroketene and a suitable substituted olefin. Now we report herein an asymmetric version of our original methodology, in which the asymmetry was introduced through an enantioselective deprotonation step.

2. Results and discussion

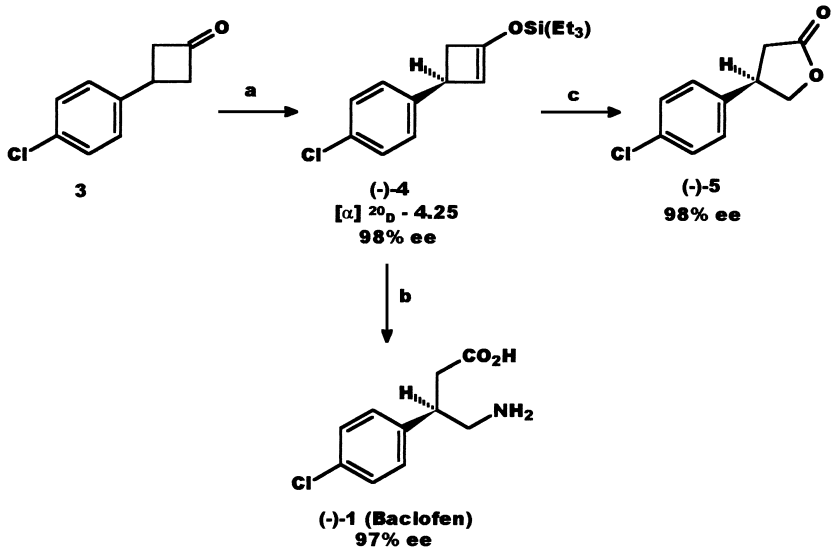
Cycloadduct **2** was obtained as the only detectable regioisomer by the reaction between in situ generated dichloroketene[11b] and commercial 4-chlorostyrene in 91% yield (Scheme 1). Reductive dechlorination of **2** in acetic acid/Zn dust furnished the cyclobutanone derivative **3** in 92% yield.



Scheme 1. Reagents and conditions: (a) Zn–Cu, $POCl_3$, CCl_3COCl, Et_2O, 12 h, rt, 91%; (b) Zn/AcOH, 14 h, rt, 93%

Enantioselective deprotonation of *meso* or prochiral compounds using lithium amide bases provides useful chiral intermediates for the synthesis of a wide variety of organic compounds including natural products.[12] The high enantioselectivity obtained by this methodology associated with its operational simplicity encouraged us to use it as a way to introduce asymmetry into our synthetic approach.

The enantioselective deprotonation of cyclobutanone **2** was carried out by using the chiral base, lithium (*S*,*S*′)-α,α′-dimethylbenzylamide[13,14] at −100°C in tetrahydrofuran (THF) and the resulting enolate was trapped by triethylsilyl chloride to provide the silylenol ether **4** (Scheme 2) in 70% yield. Although the enantiomeric excess of the silylenol ether **4** could not be determined at this stage, it was converted further into the γ-butyrolactone **5** by ozonolysis (Scheme 2), followed by sodium borohydride reduction of the ozonide.[15] The optical purity of lactone **5** was determined to be ≥97%, by comparison of its specific optical rotation $[\alpha]_D^{20}$ −43 (c=0.5, $CHCl_3$) with that reported (lit.[10c] $[\alpha]_D^{20}$ −44 (c=0.5, $CHCl_3$)). Since none of the transformations could have epimerized the stereogenic carbon of **4**, we can assume that its optical purity should be comparable to that found for lactone **5**, i.e. an enantiomeric excess of 98%.



Scheme 2. Reagents and conditions: (a) lithium (*S,S′*)-α,α′-dimethylbenzylamide, THF, TESCl, −100°C, 15 min, 70%; (b) (i) O_3, CH_2Cl_2, −78°C, 40 min; (ii) Me_2S, −78°C → rt, 12 h; (iii) $NaBH_3CN$, $AcONH_4$, 12 h; (iv) 6N HCl, 100°C, 70% overall yield (one-pot sequence); (c) O_3, MeOH, −78°C, 45 min, then $NaBH_4$, then dilute HCl (70%)

At this stage we had envisaged the use of the reductive amination conditions described by Brenna et al.[10i] to directly transform the ozonide into (−)-**1**. Unfortunately, we were unable to isolate any reductive amination product, even by changing the ratio of hydride:substrate, the solvent and the reaction time.

To overcome this problem, we decided to reduce the ozonide in the presence of dimethyl sulfide and then the crude material was treated with sodium cyanoborohydride and ammonium acetate. This simple modification had permitted us to prepare (−)-baclofen (**1**) in 70% yield with an enantiomeric excess of 97.5% ($[\alpha]_D^{20}$ −1.95 (c, 0.6, H_2O), lit.[5j–i] $[\alpha]_D^{20}$ −2.0 (c, 0.6, H_2O)).

3. Conclusion

In summary, the synthesis of (*R*)-(−)-baclofen was developed by a four-step sequence in 40% overall yield from 4-chlorostyrene. As several substituted styrenes are commercially available or could be easily prepared,[16] this approach should also provide convenient access to enantiomerically pure analogs.

4. Experimental

4.1. General procedures

^1H NMR and ^{13}C NMR spectra were recorded on a Varian GEMINI BB-300 at 300 MHz and 75.1 MHz, respectively. The mass spectra were recorded on an HP model 5988A GC–MS. The melting points were measured in open capillary tubes using an Electrothermal apparatus model 9100, and are uncorrected. The $[\alpha]_D$ values are corrected and were measured in Polamat A. Column chromatography was performed on silica gel (70–230 or 200–400 mesh). Ether and THF were distilled from benzophenone ketyl under nitrogen. Trichloroacetyl chloride and phosphorus oxychloride (both Aldrich) were distilled

before use. TLC visualization was achieved by spraying with 5% ethanolic phosphomolybdic acid and heating. 4-Chlorostyrene was purchased from Aldrich and used without purification.

4.2. Racemic 2,2-dichloro-3-(4′-chlorophenyl)cyclobutanone **2**

To a stirred suspension of Zn–Cu[17] (3.10 g, 45.48 mmol) and 4-chlorostyrene (3.00 g, 21.66 mmol) in dry ether (44 mL) was added dropwise, during 1 h at room temperature, a solution of phosphorus oxychloride (4.98 g, 3.03 mL, 32.49 mmol) and trichloroacetyl chloride (5.90 g, 3.63 mL, 32.49 mmol) in dry ether (22 mL). The suspension was stirred for 20 h at room temperature. The mixture was filtered through a pad of Celite and washings were performed with hexane (3×100 mL). The filtrate was concentrated in vacuo to one third of the original volume. The residue was diluted with hexane (100 mL) and again concentrated to one third. This operation was repeated twice more. The final concentrate (~150 mL) was washed with cold water (200 mL), saturated $NaHCO_3$ (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate and filtered. Concentration under reduced pressure followed by flash chromatography on silica gel with hexane:ethyl acetate (8:2) gave a solid residue. Recrystallization from dichloromethane gave dichlorocyclobutanone **2** as a white solid (4.90 g, 91%). M.p. 73–75°C; IR (KBr, λ_{max}): 2928, 1812, 1493, 1403, 1094, 1014, 827 cm^{-1}; MS (70 eV, m/e): 250 (M^++2), 248 (M^+), 208, 206, 138; ^1H NMR (300 MHz, $CDCl_3$) δ 3.51–3.73 (m, 2H), 4.21 (t, J=10.2 Hz, 1H), 7.17–7.43 (dd, J=8.4 and 8.8 Hz, 4H); ^{13}C NMR (75.1 MHz, $CDCl_3$) δ 29.8, 46.0, 50.2, 129.4, 129.9, 192.2. Anal. calcd for $C_{10}H_7Cl_3O$: C, 48.39; H, 2.84. Found: C, 48.37; H, 2.83.

4.3. 3-(4′-Chlorophenyl)cyclobutanone **3**

To a stirred solution of **2** (4.0 g, 16.09 mmol) in acetic acid (100 mL) was added Zn dust (6.43 g, 99.0 mmol). The suspension was stirred at room temperature for 14 h and then the mixture was diluted with ether (300 mL) and filtered. The solid was washed with ether (100 mL) and the combined organic extracts washed with a saturated solution of $NaHCO_3$ (3×150 mL), brine (200 mL) and dried over anhydrous sodium sulfate. Concentration under reduced pressure followed by flash chromatography on silica gel with hexane:ethyl acetate (9:1) gave compound **3** (2.70 g, 93%) as a yellow-tinged oil. IR (neat, λ_{max}): 2924, 1787, 1493, 1378, 1013, 821 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.16–3.26 (m, 2H), 3.44–3.55 (m, 2H), 3.60–3.69 (m, 1H), 7.21–7.34 (m, 4H); ^{13}C NMR (75.1 MHz, $CDCl_3$) δ 27.9, 54.6, 127.9, 128.7, 142.0, 206.0; MS (70 eV, m/e): 180 (M^+), 110, 138, 103, 89, 77. Anal. calcd for $C_{10}H_9ClO$: C, 66.65; H, 5.04. Found: C, 66.63; H, 5.03.

4.4. 1-[(3S)-3-(4-Chlorophenyl)cyclobut-1-enyloxyl]-1,1-diethyl-1-silapropane **4**

To a stirred solution of (*S*,*S*′)-α,α′-dimethylbenzylamine (1.28 g, 5.2 mmol) in dry THF (35 mL) was added *n*-butyllithium (3.72 mL, 1.4 M solution in hexanes, 5.2 mmol) at −78°C under nitrogen and the resulting solution was allowed to warm to room temperature over 10 min. The solution was cooled to −100°C and triethylsilyl chloride (0.8 mL, 0.762 g, 4.8 mmol) was added, followed by addition of a solution of cyclobutanone **3** (0.722 g, 4 mmol) in THF (10 mL) at the same temperature. After stirring for 10 min, triethylamine (5 mL) and saturated sodium carbonate were added and the mixture was concentrated in vacuo. The residue was extracted with hexane, washed with saturated sodium hydrogen carbonate and brine, and then dried over Na_2SO_4. Evaporation of the solvent gave a residue which was purified by column chromatography on silica gel. Elution with hexane:ethyl acetate (99:1, v/v) afforded the silyl enol ether **4** (1.178 g, 70%) as a colorless fluid oil. $[\alpha]_D^{20}$ −4.25 (c 2.0, $CHCl_3$); IR (neat, λ_{max}):

3070, 2966, 2914, 1641, 1626, 1574, 1300, 1284, 1215, 999, 844 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.7 (t, 6H), 0.9 (q, 9H), 2.3 (d, J=16 Hz, 1H), 3.02 (dd, J=4 Hz; J=16 Hz, 1H), 3.5 (d, J=4 Hz, 1H), 4.83 (d, J=0.7 Hz, 1H), 7.0 (s, 4H, aromatic); ^{13}C NMR (75.1 MHz, $CDCl_3$) δ 6.0, 7.0, 48.4, 54.2, 128.3, 128.6, 128.7, 129.9, 141.0, 151.0. Anal. calcd for $C_{16}H_{23}ClOSi$: C, 65.167; H, 7.861. Found: C, 65.150; H, 7.852.

*4.5. (R)-(−)-Baclofen, hydrochloride **1***

A solution of (−)-**4** (0.8 g, 2.71 mmol) in methylene chloride:methanol (1:1, 15 mL) was treated with ozone at −78°C for 40 min. After addition of dimethyl sulfide (5 mL) at −78°C, the temperature was allowed to rise over 12 h with stirring. Evaporation of the solvents was accompanied by the addition of methanol (10 mL), ammonium acetate (0.256 g, 4.065 mmol) and sodium cyanoborohydride (0.313 g, 4.065 mmol). The reaction mixture was stirred for 12 h at room temperature. Then a solution of 2 M sodium hydroxide was added and the reaction was stirred for an additional 2 h, concentrated under reduced pressure, diluted with water and extracted with ethyl acetate. The organic phase was dried over sodium sulfate, and the solvent was removed under reduced pressure. The residue was treated with aqueous 6N HCl (5 mL) and heated at 100°C for 12 h. The solvent was removed in vacuo and the residue was triturated in isopropanol yielding crystalline baclofen (0.37 g, 70%). M.p. 195°C (lit.[9a] 195°C); $[\alpha]_D^{20}$ −1.95 (c 0.6, H_2O), lit.[5] $[\alpha]_D^{20}$ −2.0 (c 0.6, H_2O); IR (KBr, λ_{max}): 3000–2500, 1620, 1550, 1490, 1090 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 2.65–2.91 (AB part from ABX, J_{AB}=16.6 Hz, J_{AX}=6.9 Hz, J_{BX}=7.7 Hz, 2H), 3.10–3.39 (AB part from ABX, J_{AB}=12.8 Hz, J_{AX}=6.0 Hz, J_{BX}=8.9 Hz, 2H), 3.64–3.72 (m, 1H), 7.41–7.43 (m, 4H); ^{13}C NMR (75.1 MHz, DMSO-d_6): δ 176.0, 141.8, 131.2, 128.9, 128.8, 48.5, 37.7.

Acknowledgements

We thank the Brazilian National Research Council (CNPq) for F.C.'s fellowship and FAPESP for financial support and P.R.'s fellowship (# 97/08571-2).

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