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Enantioselective synthesis of (*R*)-(−)-baclofen using Fischer-type carbene anions

Emanuela Licandro,* Stefano Maiorana, Clara Baldoli, Laura Capella and Dario Perdicchia

Dipartimento di Chimica Organica e Industriale, Università di Milano e CNR-Centro Studio Sintesi e Stereochimica Speciali Sistemi Organici, Via C. Golgi 19, I-20133 Milano, Italy

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Abstract

The antispastic drug (*R*)-(−)-baclofen has been synthesized enantioselectively using a diastereoselective Michael addition reaction of the conjugate base of an enantiopure Fischer-type amino carbene to *p*-chloro-nitrostyrene.

1. Introduction

β-Substituted GABA derivatives[1,2] play an important role in a number of central nervous system functions. The most lipophilic of these derivatives is 3-(*p*-chlorophenyl)-γ-aminobutyric acid (baclofen),[3,4] which has already been used as an antispastic agent; however, although the (*R*)-(−)-enantiomer[4] is acknowledged as being the biologically active element, baclofen has so far been used only as a racemic mixture. Some attempts at the resolution,[4] or the chemoenzymatic[5] or enantioselective synthesis,[6–10] of (*R*)-(−)- and (*S*)-(+)-baclofen have recently been reported.

2. Results and discussion

During the course of our work on new metallocarbenes and their application in the synthesis (including stereoselective synthesis) of organic molecules, we have devised a synthetic procedure for obtaining pure (*R*)-(−)-baclofen **1** or the (*S*)-(+)-enantiomer (Fig. 1).

We have recently reported[11,12] the diastereoselective Michael addition reaction of the anion of (±)-pentacarbonyl[(*trans*-2,6-dimethylmorpholino)(methyl)carbene]chromium complex **2** to a number of

* Corresponding author. Tel: +39-02-2663978; fax: +39-02-2364369; e-mail: emanuela.licandro@unimi.it

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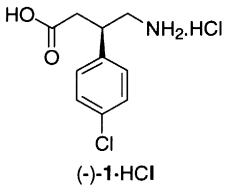
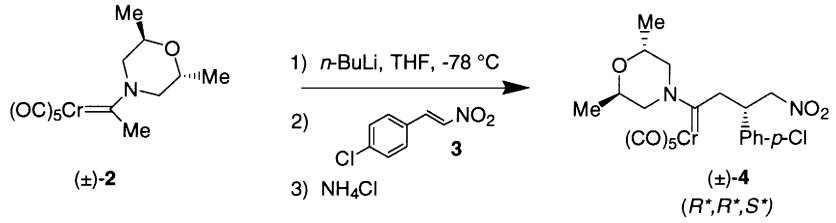


Fig. 1.

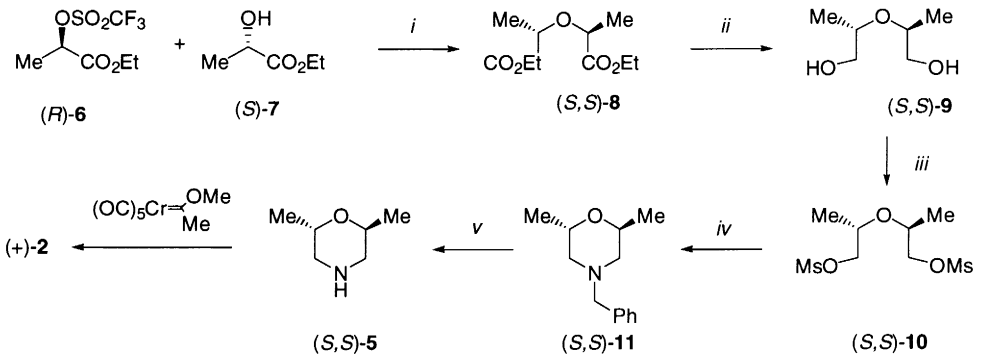
nitroalkenes, including *trans-p*-chloro-nitrostyrene **3**. From this reaction, run at −78 °C, the 1,4-adduct (±)-**4** was recovered in 50% d.e. (Scheme 1).



Scheme 1.

This reaction is now proposed as the key step in a new enantioselective synthesis of (*R*)-(−)-baclofen **1** (see Scheme 3). Our previous work[11] showed that the configuration of the newly formed stereocenter of the major diastereomer in the 1,4-adduct (±)-**4** (Scheme 1) was opposite to that of the two stereocenters of the chiral auxiliary 2,6-dimethylmorpholine and, because the new stereocenter formed in the Michael addition is the one present in baclofen, (2*S*,6*S*)-2,6-dimethylmorpholine **5** was needed to synthesize the (*R*)-enantiomer of **1**.

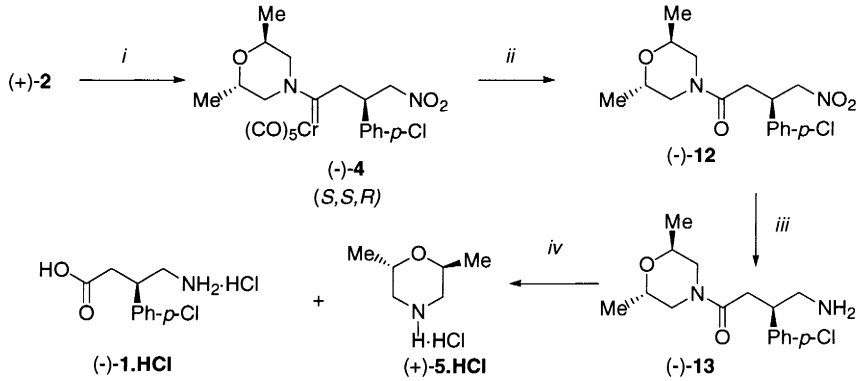
We have recently reported[13] an enantioselective total synthesis of the (2*R*,6*R*)-enantiomer of 2,6-dimethylmorpholine **5** and, in the present study, we have applied the same reaction sequence to the synthesis of the (2*S*,6*S*)-**5** enantiomer (Scheme 2).



Scheme 2. Reagents and conditions: (i) K_2CO_3, 1,2-dichloroethane:*n*-pentane, 1:4, 24 h, rt; (ii) $LiAlH_4$, Et_2O, 45 min, reflux; (iii) MsCl, Py, 0°C, 4 h; (iv) $BnNH_2$, dioxane, 40 h, reflux; (v) H_2, Pd/C, MeOH–AcOH

(*S*,*S*)-**5** was prepared starting from the (*R*)-*O*-trifluoromethyl sulphonyl lactate **6** and (*S*)-ethyl lactate **7**. The diester **8** was then reduced to diol **9** which, in turn, was mesylated to **10**. The morpholine ring formation was achieved by reacting (*S*,*S*)-**10** with benzylamine in order to give (*S*,*S*)-**11**. The subsequent debenzylation afforded (*S*,*S*)-**5.** The corresponding enantiomerically pure amino carbene complex (+)-**2** was then obtained in 86% yield by means of the aminolysis of pentacarbonyl(methoxymethylcarbene)chromium (Scheme 2).

For the synthesis of (−)-baclofen **1** (Scheme 3), we generated the anion of (+)-**2**[†] in THF by reaction with *n*-butyllithium at −78°C; the mixture was cooled to −97°C[‡] and then *trans*-*p*-chloro-nitrostyrene **3** was added over a period of 20 min and allowed to react for a further 30 min. We isolated the 1,4-adduct **4** as a mixture of two diastereoisomers in 90% yield and 76% d.e. The enantiopure (*S*,*S*,*R*)-**4** was then recovered in 77% yield by means of silica gel chromatographic separation of the diastereomeric mixture. The γ-nitrocarbene complex (−)-**4** was transformed into the corresponding amide (−)-**12** using CAN as the oxidizing agent.[§]



Scheme 3. Reagents and conditions: (i) *n*-BuLi, THF, −97°C, then **3**, chromatographic separation to give (−)-**4**; (ii) CAN, acetone, 4 h, rt; (iii) Ra–Ni, dry MeOH, 1 h, 5 atm; (iv) 6 M HCl, 8 h, reflux

The second task was to reduce the nitro function selectively without affecting the amido group or the chlorine atom. After several attempts, we found that hydrogenation[14] in methanol at 5 atm and rt, and in the presence of Raney-Ni, was the most reliable method. After about 1 h, the nitroamide (−)-**12** was completely transformed into the corresponding aminoamide (−)-**13**, which was isolated after filtration and evaporation of the solvent (yield >90%).

The last reaction of deprotecting the carboxylic function to give (−)-**1** did not present any particular problem. A special effort was made to recover the chiral auxiliary, dimethylmorpholine, and subsequently to recycle it. Complete deprotection was attained after reflux was carried out for 8 h in 6 M hydrochloric acid.[7] After removing the solvent, a mixture of baclofen (−)-**1** and morpholine (+)-**5** hydrochlorides was recovered as a white powder. The two hydrochlorides were separated by means of reverse phase column chromatography with nearly quantitative yields of both components.

3. Conclusions

This study shows that the Michael addition reaction of the anion of enantiopure carbene complex (+)-**2** to *trans*-nitrostyrenes can be efficiently applied to the synthesis of (*R*)-(−)-3-(*p*-chlorophenyl)-γ-aminobutyric acid, the active component of the potent antispastic baclofen, which is currently marketed in its racemic form. In principle, this procedure is also suitable for the synthesis of the (*S*)-enantiomer.

[†] The synthetic procedure described in Scheme 3 was first optimized with (±)-**2**, and then run with the enantiopure carbene complex (+)-**2**.

[‡] Our studies of the effect of the temperature of the Michael addition on d.e. values have shown that running the reaction at −97°C leads to the best balance between chemical yield (90%) and d.e. (76%); a lower reaction temperature (−108°C) led to a higher d.e. (80%) but poorer chemical yield (66%).

[§] We also tried oxygen and sunlight for this reaction, but the chemical yield was lower and the reaction time longer.

4. Experimental

4.1. General

All of the reactions were carried out in a nitrogen atmosphere; the solvents were dried by means of distillation over sodium wire. Flash and vacuum chromatography was performed using Silica Gel 60 Merck 230–400 mesh. Compound (*S*)-(−)-**7** is commercially available. We have previously reported the racemic forms of compounds **4** and **12**.[11] IR: Perkin–Elmer FT-IR 1725 X. ^{1}H NMR (300 MHz, $CDCl_3$), ^{13}C NMR (75 MHz, $CDCl_3$): Bruker AC 300. MS (EI, FAB): VG Analytical 7070 EQ. GC–MS: MS Varian Saturn 3, GC Varian Star 3400 CX.

4.2. (2S,6S)-Dimethylmorpholine 5

Compound **5** was prepared according to the procedure reported by us for the (2*R*,6*R*)-**5** enantiomer,[13] following the reaction sequence shown in Scheme 2. The spectroscopic and analytical data were in accordance with those reported previously: $[\alpha]_D$=+3.0 (*c* 0.33, $CHCl_3$), $[\alpha]_{546}$=+6.1 (*c* 0.33, $CHCl_3$). The recorded $[\alpha]_D$ values of each intermediate were: (*R*)-**6**: $[\alpha]_D$=+38.5 (*c* 2.4, $CHCl_3$); (*S*,*S*)-**8**: $[\alpha]_D$=−104.4 (*c* 2, $CHCl_3$), $[\alpha]_{546}$=−120.1 (*c* 2, $CHCl_3$); (*S*,*S*)-**9**: $[\alpha]_D$=+83.4 (*c* 0.76, $CHCl_3$); (*S*,*S*)-**10**: $[\alpha]_D$=+25.6 (*c* 0.736, $CHCl_3$), $[\alpha]_{546}$=+29.85 (*c* 0.736, $CHCl_3$); (*S*,*S*)-**11**: $[\alpha]_D$=−12.2 (*c* 1.04, $CHCl_3$).

4.3. Complex (S,S)-(+)-2

Compound **2** was synthesized using the same procedure as that reported in the literature for the racemic mixture.[15] $[\alpha]_D$=+6.6 (*c* 0.26, $CHCl_3$), $[\alpha]_{546}$=+12.5 (*c* 0.26, $CHCl_3$).

4.4. Michael addition of (S,S)-(+)-2 to 3

The reaction at −78°C has been reported previously.[11] The addition reaction at −97°C was performed using the following procedure. The morpholinyl chromium carbene (+)-**2** (10 mmol, 3.33 g) was dissolved in dry THF (487 ml, 2.05×10^{-2} M solution) in a three-necked flask equipped with an alcohol thermometer. The solution was cooled to −78°C under magnetic stirring. A hexane solution of *n*-butyllithium (10 mmol) was added dropwise and allowed to react for 30 min at −78°C. The solution was then cooled to −97°C (in an absolute methanol/liquid nitrogen bath) and a pre-cooled solution of *trans*-*p*-chloro-nitrostyrene **3** (10.8 mmol, 1.981 g) in THF (60 ml) was added over 30 min; the mixture was allowed to react for a further 2 h. A saturated ammonium chloride solution was then added and the reaction vessel was brought to room temperature. The THF was evaporated under vacuum, and the mixture was extracted with dichloromethane, dried over Na_2SO_4 and filtered over a Celite pad. After removal of the solvent under reduced pressure, column chromatography (with light petroleum/dichloromethane as eluents) gave the addition product (*S*,*S*,*R*)-(−)-**4** (3.970 g, 77% yield), its diastereoisomer (*S*,*S*,*S*)-**4** (0.620 g, 12% yield), and the recovered starting complex **2** (0.166 g, 5% yield). (*S*,*S*,*R*)-**4**: $[\alpha]_D$=−45 (*c* 0.4, $CHCl_3$), $[\alpha]_{546}$=−53.3 (*c* 0.4, $CHCl_3$); (*S*,*S*,*S*)-**4**: $[\alpha]_D$=+88 (*c* 0.4, $CHCl_3$).

4.5. Oxidation of compound (S,S,R)-(−)-4 to (S,S,R)-(−)-12

Compound (−)-**4** (2.580 g, 5 mmol) was dissolved in acetone ACS Fluka (200 mL) and cerium ammonium nitrate CAN (8.270 g, 15 mmol) dissolved in 50 mL of acetone was added dropwise at room

temperature over 4 h. The reaction mixture was then evaporated, extracted with methylene chloride (3×50 mL) and washed with brine. The organic layer was dried over dry sodium sulphate. Chromatography (eluent: petroleum:ethyl acetate, 2:1) gave 1.525 g (90% yield) of (−)-**12**. Racemic **12** was synthesized on the mixture of both diastereoisomers of compound **4**, leading to a mixture of the diastereoisomers of **12** [(*R*,*R*,*S*)-(*S*,*S*,*R*)+(*R*,*R*,*R*)-(*S*,*S*,*S*)], which were separated by chromatography (eluent: petroleum:diethyl ether:ethyl acetate, 1:1:1). (*S*,*S*,*R*)-**12**: $[\alpha]_D=-17$ (*c* 0.7, $CHCl_3$), $[\alpha]_{546}=-20$ (*c* 0.7, $CHCl_3$).

4.6. *Reduction of (*S,S,R*)-(−)-**12** to (*S,S,R*)-(−)-**13***

Compound (−)-**12** (1.023 g, 3 mmol) was dissolved in dry methanol (120 ml) in a glass bench autoclave and 50% weight Raney-Ni (Aldrich, freshly opened) washed with dry methanol was added; the reaction mixture was brought to about 5 atm of hydrogen and stirred until the theoretical volume was consumed (about 1 h). The solution was then filtered, washed with a saturated NaOH solution, extracted with diethyl ether, and dried over sodium sulphate. After the elimination of the solvent, product (−)-**13** was recovered as a colorless oil (0.885 g, 95% yield). Compound **13** was used without further purification, but could occasionally be purified by means of reverse phase column chromatography (stationary phase: RP-8; eluent: acetonitrile:HCl, 1% water solution, 9:1), leading to the corresponding hydrochloride. During the set-up of the synthesis, the minor diastereomer (*R*,*R*,*R*)-(*S*,*S*,*S*)-**12** was also reduced, leading to (*R*,*R*,*R*)-(*S*,*S*,*S*)-**13**.

4.6.1. *(*S,S,R*)-**13** (Major diastereoisomer)*

A colorless oil. IR (neat): ν=3410, 3368, 3310, 1636, 1493, 1455 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.08 (d, *J*=5.9 Hz, 3H, CH_3), 1.11 (d, *J*=5.9 Hz, 3H, CH_3), 1.40–1.60 (brs, 2H, NH_2), 2.52 (dd, part A of ABX, ^2J=15.4 Hz, ^3J=7.4 Hz, 1H, CH*H*–NH_2), 2.67 (dd, part B of ABX, ^2J=15.4 Hz, ^3J=6.6 Hz, 1H, C*H*H–NH_2), 2.85 (dd, part A of ABX, ^2J=14.0 Hz, ^3J=8.1 Hz, 1H, CH*H*–CO), 2.95 (dd, part B of ABX, ^2J=14.0 Hz, ^3J=5.5 Hz, 1H, C*H*H–CO), 3.07 (dd, ^2J=12.9 Hz, ^3J=5.9 Hz, 1H, N–CHH_{ax}), 3.15 (dd, ^2J=13.2 Hz, ^3J=6.6 Hz, 1H, N–CHH_{ax}) 3.23 (m, 1H, *p*ClPh–C*H*), 3.43 (dd, ^2J=12.9 Hz, ^3J=2.3 Hz, 1H, N–CH_{eq}H), 3.65 (dd, ^2J=13.0 Hz, ^3J=2.3 Hz, 1H, N–CH_{eq}H), 3.88 (m, 2H, CH_3C*H*–O), 7.10 (d, 2H, *J*=8.4 Hz, H arom.), 7.30 (d, 2H, *J*=8.4 Hz, H arom.). ^{13}C NMR ($CDCl_3$): δ=17.18 (CH_{3ax}), 17.49 (CH_{3eq}), 36.66 (*C*H_2–CO), 44.64 (*p*ClPh–*C*H), 46.44 (N–CH_2), 47.21 (CH_2–NH_2) 50.39 (N–CH_2), 65.86 (CH_3*C*H–O), 66.01 (CH_3*C*H–O), 128.73, 129.10 (CH arom.), 132.43 (Cq arom.), 141.24 (Cl–Cq arom.), 170.01 (CO). MS (70 eV): *m/z* 311 (65) [M^++1], 294 (8) [M^+-NH_2], 281(75), 260 (70), 247 (35), 236 (100), 168 (63), 138 (68), 116 (83). Hydrochloride: $C_{16}H_{23}ClN_2O_2\cdot HCl$: HRMS calcd: 281.11178; found: 281.1030. Signal assignments were confirmed by 2D NMR experiments. (*S*,*S*,*R*)-**13**: $[\alpha]_D=-24.3$ (*c* 2.4, $CHCl_3$), $[\alpha]_{546}=-28.8$ (*c* 2.4, $CHCl_3$).

4.6.2. *(*R,R,R*)-(*S,S,S*)-**13** (Minor diastereoisomer)*

A colorless oil. IR (neat): ν=3410, 3368, 3310, 1636, 1493, 1455 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.12 (d, *J*=6.5 Hz, 3H, CH_3), 1.21 (d, *J*=6.5 Hz, 3H, CH_3), 2.15 (brs, 2H, NH_2), 2.60–2.80 (part AB of ABX, CH_2–NH_2), 2.98 (dd, part A of ABX, ^2J=12.7 Hz, ^3J =8.1 Hz, 1H, CH*H*–CO), 3.10 (dd, part B of ABX, ^2J=12.7 Hz, ^3J=7.1 Hz, 1H, C*H*H–CO), 3.13 (dd, ^2J=13.1 Hz, ^3J=6.6 Hz, 1H, N–CHH_{ax}), 3.32 (m, 1H, *p*ClPh–C*H*), 3.33 (dd, ^2J=13.2 Hz, ^3J=6.0 Hz, 1H, N–CHH_{ax}) 3.42 (dd, ^2J=13.1 Hz, ^3J=3.2 Hz, 1H, N–CH_{eq}H), 3.65 (dd, ^2J=13.2 Hz, ^3J=3.5 Hz, 1H, N–CH_{eq}H), 3.77 (m, 2H, CH_3C*H*–O), 4.00 (m, 2H, CH_3C*H*–O), 7.25 (d, 2H, *J*=8.4 Hz, H arom.), 7.36 (d, 2H, *J*=8.4 Hz, H arom.). ^{13}C NMR ($CDCl_3$): δ=17.22 (CH_{3ax}), 17.39 (CH_{3eq}), 36.83 (*C*H_2–CO), 45.27 (*p*ClPh–*C*H), 46.28 (N–CH_2), 47.34 (CH_2–NH_2) 50.76 (N–CH_2), 65.60 (CH_3*C*H–O), 66.27 (CH_3*C*H–O), 128.77, 129.14 (CH arom.), 132.55

(Cq arom.), 141.16 (Cl–Cq arom.), 170.13 (CO). Signal assignments were confirmed by 2D NMR experiments.

*4.7. Synthesis of baclofen hydrochloride (*R*)-(−)-**1***

Compound (−)-**13** (0.310 g, 1 mmol) was quantitatively hydrolyzed in boiling 6 M hydrogen chloride (40 mL). After 8 h, the water was evaporated under vacuum, and a mixture of baclofen (−)-**1** hydrochloride and dimethylmorpholine (+)-**5** hydrochloride was recovered as a white solid. After reverse phase column chromatography (stationary phase: RP-8; eluent: acetonitrile and acetonitrile:conc. HCl, 100 mL:10 drops), the two hydrochlorides were separated and quantitatively recovered (**1**: 0.242 g, 97% yield; **5**: 0.144 g, 95% yield). The spectral data of compound (−)-**1** were in accordance with those reported in the literature.

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