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First asymmetric synthesis of an acyclic β,β-dialkylated-γ-aminobutyric acid

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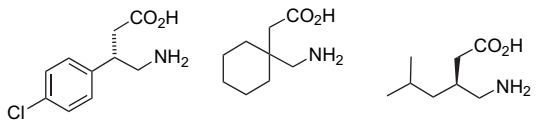
Abstract—Enantiomerically pure (*R*)-γ-amino-β-benzyl-β-methylbutyric acid, an acyclic β,β-dialkyl GABA derivative, is efficiently synthesised from (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisobornyl 2-cyanopropanoate by a sequence based on benzylation, Arndt–Eistert homologation and nitrile reduction. Benzylation of (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisobornyl 2-cyanopropanoate using potassium carbonate under not strictly anhydrous conditions occurs diastereoselectively to afford (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisobornyl (*S*)-2-cyano-2-methyl-3-phenylpropanoate, the key chiral intermediate from which the desired γ-amino acid is obtained in five steps in 65% overall yield.

1. Introduction

In recent years the need for enantiomerically pure γ-amino acids has grown markedly, not only due to their biological activity[1] and presence in the structures of natural products with antitumoral activity,[2] but also because peptides consisting of optically active γ-amino acids can form stable helical structures in solution and in the solid state, even for peptides consisting of as few as four residues.[3]

γ-Aminobutyric acid (GABA), the simplest γ-amino acid, is the major inhibitory neurotransmitter in the central nervous system (CNS) of mammalians.[4] Its derivatives, in particular those analogues bearing substituents at the β-position, have been the subject of extensive investigations because of their potential biological activity.[1b] A number of these compounds are important therapeutic agents for a range of CNS disorders (Fig. 1).



(*R*)-Baclofen, **1** Gabapentin, **2** (*S*)-Pregabalin, **3**

Figure 1. Structures of (*R*)-Baclofen, Gabapentin and (*S*)-Pregabalin.

For instance, γ-amino-β-(4-chlorophenyl)butyric acid, or Baclofen (**1**), was introduced in 1973 for the therapy of muscle spasticity and is still the prototype of a selective $GABA_BR$ agonist.[5] Although the desired biological activity is known to reside in the (*R*)-enantiomer,[6] Baclofen is therapeutically commercialised (Lioresal® and Baclon®) as a racemate for the treatment of multiple sclerosis and cerebral palsy.

Gabapentin (**2**), a β,β-disubstituted GABA analogue, has been commercialised by Pfizer under the name Neurontin®. Gabapentin is used for the treatment of cerebral diseases such us epilepsy, faintness, hypokinesis and cranial traumas.[7] Furthermore, to date it is the only drug specifically licenced for the treatment of neuropathic pain. This compound shows few, if any, toxic side effects at clinically relevant doses. Moreover, a Gabapentin-lactam is neuroprotective in retinal ischaemia.[8]

(*S*)-γ-Amino-β-isobutylbutyric acid, or Pregabalin (**3**), is another β-substituted GABA analogue. Like Gabapentin this compound has anticonvulsant, anxiolytic-like and analgesic properties but it displays more potent and robust activity than Gabapentin in preclinical models for epilepsy, neuropathic pain and anxiety.[9]

A careful search in Scifinder® database showed that among the several hundred scientific studies on β-substituted GABA analogues that have been published in the last 10 years, not one deals with the stereoselective preparation of acyclic β,β-dialkylated γ-aminobutyric acids. Thus, we wish to report here the development of a new, efficient and concise methodology for the asymmetric synthesis of this

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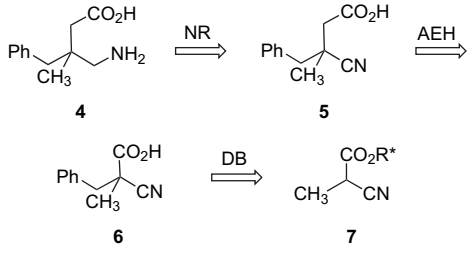
kind of γ-amino acid from chiral α-cyanoesters. As a model to establish the synthetic methodology, the preparation of enantiomerically pure (*R*)-γ-amino-β-benzyl-β-methylbutyric acid was selected. This route started from the 2-cyanopropanoate derived from the commercially available chiral alcohol (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisoborneol, known as (−)-Oppolzer's alcohol.[10]

2. Results and discussion

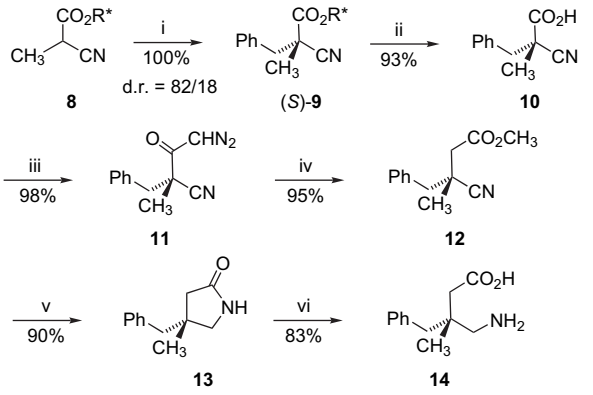
According to the retrosynthetic analysis shown in Scheme 1, we envisaged that the aminomethyl moiety in the target compound could be obtained by nitrile reduction (NR) of 3-cyano-3-methyl-4-phenylbutyrate and the carboxymethyl moiety could be obtained by Arndt–Eistert homologation[11] (AEH) of 2-cyano-2-methyl-3-phenylpropanoate. Enantiomerically pure 2-cyano-2-methyl-3-phenylpropanoate can be obtained by diastereoselective α-benzylation (DB) of a chiral 2-cyanopropanoate.



Scheme 1. Retrosynthetic steps to (*R*)-γ-amino-β-benzyl-β-methylbutyric acid from chiral cyanopropanoates.

In a previous paper,[12] we described how the diastereoselective α-benzylation of 2-cyanopropanoate **8**, yielded (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisobornyl 2-cyano-2-methyl-3-phenylpropanoate **9** in 96% yield as a mixture of diastereoisomers (*S*/*R*=91/9). This reaction was performed using LDA as the base in an anhydrous medium and in the presence of HMPA.[13] As the reported pK_a value of methyl α-cyanoacetate is about 13,[14] we reasoned that the α-benzylation reaction could be promoted by weaker bases than LDA. Such bases would not require the use of strictly anhydrous reaction conditions and harmful reagents. In this context the use of potassium carbonate as a base was tested. To our delight, treatment of a solution of 2-cyanopropanoate **8** and benzyl bromide in acetone with potassium carbonate at room temperature cleanly afforded compound **9** in quantitative yield as a mixture of diastereoisomers. A diastereomeric ratio of 82/18 was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. The major diastereoisomer (*S*)-**9** could be easily isolated in satisfactory yield by recrystallisation from methanol. Although the diastereoselectivity decreased slightly, these new reaction conditions are safer and more convenient for large-scale work.[15]

(*R*)-γ-Amino-β-benzyl-β-methylbutyric acid (**14**) was efficiently prepared from chiral 2-cyanopropanoate **8** by the six-step procedure outlined in Scheme 2. After benzylation the isolated cyanoacetate (*S*)-**9** was hydrolysed with 2 N potassium hydroxide in methanol to afford cyanoacid **10** in 93% yield. This compound was then subjected to the corresponding homologation process.



Scheme 2. Reagents and conditions: (i) K_2CO_3, BnBr, acetone; (ii) KOH, MeOH, Δ; (iii) $ClCO_2{}^tBu$, NMM, THF, −20 °C, then dry CH_2N_2 in ether; (iv) AgBzO, Et_3N, MeOH, THF; (v) H_2, Ni (Ra), NH_3/MeOH, 35 °C; (vi) HCl, Δ.

Arndt–Eistert reaction is the most important and most commonly used procedure for converting a carboxylic acid into its acid or ester homologue with one extra carbon in only two steps.[16] The synthesis of sterically hindered diazoketones is often inefficient or even impossible to achieve using standard procedures.[17] However, we tested the acylation of diazomethane using acyl chlorides or mixed anhydrides as activated carboxylic acid derivatives. Firstly, the α-cyanoacyl chloride obtained from **10** and thionyl chloride was treated with an excess of a dry ethereal solution of diazomethane.[18] This reaction yielded a mixture of the desired diazoketone **11**, with a quaternary α-carbon atom, and the methyl ester derived from **10** in a 3/1 ratio. Diazoketone **11** was a stable solid that could be isolated by column chromatography without noticeable degradation. The partial success of the aforementioned procedure is clearly due to the hydrolysis of the highly activated acid chloride under the reaction conditions and subsequent esterification with diazomethane. Alternatively, cyanoacid **10** was converted to a mixed anhydride using isobutyl chloroformate in the presence of *N*-methylmorpholine at low temperature. Subsequent addition of a dry ethereal solution of diazomethane gave rise to diazoketone **11** in 98% yield, which was sufficiently pure to be used in the next step without purification.

Wolff rearrangement[19] of diazoketone **11** to methyl ester **12** was achieved using the procedure described by Savithri et al.[20] This approach involved the addition of a catalytic amount of silver benzoate in triethylamine to a homogeneous solution of compound **11** and methanol in THF. Although it has recently been suggested[17] that the silver-catalysed Wolff rearrangement tends to fail with sterically hindered diazoketones, we cleanly obtained β-cyanoester **12** in 95% yield. Alternatively, we found that the triethylamine and silver benzoate-catalysed Wolff rearrangement of **11** also proceeded at 70 °C in a mixture of dioxane and water to give the corresponding β-cyanoacid in 90% yield. The configurational stability in the silver-catalysed Wolff rearrangement was assessed by ^{1}H NMR using Eu(hfc)$_3$. The addition of 0.2 equiv of the lanthanide shift reagent, sufficient to cause splitting in a racemic mixture, to methyl ester **12** gave rise to only one set of signals. Accordingly, this compound was obtained with an enantiomeric excess greater than 96%.

Hydrogenation of the cyano group in compound **12** was cleanly achieved at atmospheric pressure and 35 °C using Raney nickel as catalyst and a solution of 0.5% ammonia in methanol as the solvent. This procedure afforded γ-lactam **13** in 90% yield. This compound was hydrolysed by heating under reflux with 5 N aqueous HCl. Elution of the γ-amino acid hydrochloride through an ion-exchange column yielded (*R*)-γ-amino-β-benzyl-β-methylbutyric acid (**14**) in 83% yield. It is worth mentioning that although compounds **12** and **13** were isolated for characterisation purposes by filtration through a short silica gel pad, the crude products were sufficiently pure to carry out the next step without any purification.

(*R*)-2-Cyano-2-methyl-3-phenylpropanoic acid *ent*-**9** can clearly be obtained by α-benzylation of the 2-cyanopropanoate derived from the commercially available (+)-Oppolzer's alcohol or, alternatively as described previously by us,[21] by diastereoselective α-methylation of the 3-phenyl-2-cyanopropanoate derived from (−)-Oppolzer's alcohol. Therefore, the methodology described here also constitutes a formal synthesis of (*S*)-γ-amino-β-benzyl-β-methylbutyric acid *ent*-**14**.

3. Conclusion

We have developed a concise, practical and efficient procedure for the asymmetric synthesis of (*R*)-γ-amino-β-benzyl-β-methylbutyric acid in overall high yield from a chiral ester derived from 2-cyanopropanoic acid and (1*S*,2*R*,4*R*)-(−)-10-dicyclohexylsulfamoylisoborneol as the chiral auxiliary. Highly diastereoselective α-alkylations of chiral 2-cyano esters derived from this alcohol have been achieved previously in our laboratory with good yields to afford a wide variety of enantiopure dialkylated cyanoacetates.[21] For this reason, we believe that the present synthetic methodology should find broad application in the stereoselective synthesis of other enantiopure β,β-dialkylated γ-amino acids of interest.

4. Experimental

4.1. General

All reagents for reactions were of analytical grade and were used as obtained from commercial sources. Compound **8** was obtained according to Ref. 12. Whenever possible the reactions were monitored by TLC. TLC was performed on precoated silica gel polyester plates and products were visualised using UV light (254 nm) and phosphomolybdic acid. Column chromatography was performed using silica gel (Kieselgel 60, 230–400 mesh). Melting points were determined in open capillary tubes and are uncorrected. FTIR spectra of liquids were recorded as thin films on NaCl plates and FT-IR spectra of solids were recorded as Nujol dispersions on NaCl plates; ν_{max} values expressed in cm^{-1} are given for the main absorption bands. Optical rotations were measured in a cell with a 10 cm path length and concentrations are given in g/100 mL. ^1H and ^{13}C NMR spectra were acquired at room temperature in the corresponding deuterated solvent at 300 and 75 MHz, respectively. The chemical shifts (δ) are reported in parts per million and the coupling constants (*J*) in hertz. The following abbreviations are used: s, singlet; d, doublet; q, quartet; dd, doublet of doublets; m, multiplet; br s, broad singlet. Elemental analyses were performed using a C, H, N, S elemental analyser. High-resolution mass spectra were obtained using the FAB^+ ionisation mode with a 3-NBA matrix.

4.2. (1*S*,2*R*,4*R*)-10-Dicyclohexylsulfamoylisobornyl (*S*)-2-cyano-2-methyl-3-phenylpropanoate (*S*)-9

Potassium carbonate (3.45 g, 25 mmol) was added to a solution of (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisobornyl (*R*/*S*)-2-cyanopropanoate (**8**) (2.4 g, 5 mmol) and benzyl bromide (1.7 g, 10 mmol) in acetone (60 mL) and the resulting mixture was stirred at room temperature for 24 h. The reaction mixture was filtered and the solid residue was washed with diethyl ether. The combined filtrates were concentrated in vacuo and the residue was dissolved in diethyl ether, washed with water, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to afford 2.84 g (100% yield) of **9** as an 82/18 mixture of diastereoisomers. Silica gel column chromatography (first eluent: diethyl ether/hexanes 1/6, second eluent: diethyl ether/hexanes 1/2) and recrystallisation from methanol yielded 2.17 g (76% yield) of major diastereoisomer (*S*)-**9** as a white solid. The physical and spectroscopic data of the product are consistent with those reported previously.[12]

4.3. (*S*)-2-Cyano-2-methyl-3-phenylpropanoic acid 10

(*S*)-**9** (2.3 g, 4 mmol) was added to a solution of 2 N KOH in methanol (20 mL) and the reaction mixture was refluxed for 4 h. The resulting solution was cooled and the solvent was evaporated in vacuo. The residue was diluted in water (20 mL) and washed with diethyl ether (2×40 mL). The aqueous layer was then acidified and extracted with diethyl ether (2×40 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo to yield 703 mg (93% yield) of **10** as a white solid. The physical and spectroscopic data of the product are consistent with those reported previously.[12]

4.4. (*S*)-2-Benzyl-4-diazo-2-methyl-3-oxobutyronitrile 11

N-Methylmorpholine (0.45 mL, 4.08 mmol) and isobutyl chloroformate (0.54 mL, 4.08 mmol) were consecutively added dropwise to a stirred solution of **10** (700 mg, 3.70 mmol) in dry THF (65 mL) at −20 °C under argon and stirred at this temperature for 30 min. An excess of dry ethereal solution of diazomethane in diethyl ether (ca. 10 mmol) was added and the solution was allowed to warm to room temperature. [*Caution*: diazomethane is a very harmful reagent and must be handled with extreme care in an efficient fume cupboard.][22] After 2 h, several drops of acetic acid were added to destroy the excess diazomethane and the solvent was removed by distillation in vacuo. The residue was dissolved in diethyl ether (40 mL) and the resulting organic solution was washed successively with 10% aqueous citric acid (20 mL), saturated aqueous sodium hydrogen carbonate (20 mL), dried over anhydrous $MgSO_4$ and concentrated in vacuo to yield 772 mg (98% yield) of **11** as a white solid. Mp=72 °C; $[\alpha]_D^{26}$ 245.0 (*c* 2,

$CHCl_3$); IR (Nujol) 2236, 2118, 1639 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.54 (s, 3H), 2.91 (d, 1H, J= 13.5 Hz), 3.21 (d, 1H, J=13.5 Hz), 5.72 (s, 1H), 7.21–7.33 (m 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.3, 43.3, 48.1, 55.3, 121.3, 127.7, 128.5, 130.1, 134.4, 188.7. Elemental analysis calcd (%) for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.78; H, 5.11; N, 19.58.

4.5. (*R*)-Methyl 3-cyano-3-methyl-3-phenylbutyrate 12

A solution of silver benzoate (220 mg, 0.96 mmol) in triethylamine (3.09 mL, 22.1 mmol) was added dropwise to a stirred solution of **11** (717 mg, 3.36 mmol) and methanol (0.34 mL, 8.4 mmol) in dry THF (20 mL) at room temperature under argon. After 3 h, an additional solution of silver benzoate (110 mg, 0.48 mmol) in triethylamine (1.55 mL, 11.1 mmol) and methanol (0.17 mL, 4.2 mmol) was added. After 4 h, the solvent was evaporated under reduced pressure and the residue was dissolved in diethyl ether (40 mL). The organic layer was filtered, then washed successively with 1 N aqueous HCl, saturated aqueous sodium hydrogen carbonate and brine, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude methyl ester was purified by filtration through a short silica gel pad using a mixture of diethyl ether/hexane 1/1 as eluent to give 692 mg (95% yield) of **12** as an oil. $[\alpha]_D^{24}$ −5.2 (*c* 2, $CHCl_3$); IR (film) 2236, 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.43 (s, 3H), 2.49 (d, 1H, J=15.8 Hz), 2.60 (d, 1H, J=15.8 Hz), 2.92 (d, 1H, J=13.6 Hz), 3.03 (d, 1H, J=13.6 Hz), 3.72 (s, 3H), 7.23–7.36 (m 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.0, 35.1, 41.7, 44.3, 51.8, 122.7, 127.4, 128.3, 130.2, 134.5, 169.4. HRMS (FAB^+) calcd for $C_{13}H_{16}NO_2$ (MH^+): 218.1181. Found: 218.1175.

4.6. (*R*)-4-Benzyl-4-methyl-2-pyrrolidinone 13

A solution of **12** (698 mg, 3.22 mmol) in 0.5% ammonia/methanol (40 mL) was hydrogenated at 35 °C and atmospheric pressure using 50% slurry of Raney® nickel 2800 in water (1.36 mL) as the catalyst. The reaction was monitored by TLC and, on completion (20 h), the catalyst was filtered off and washed with several portions of ethanol and dichloromethane. The filtrate was evaporated to dryness in vacuo and the residue was purified by filtration through a short silica gel pad using ethyl acetate as eluent to give 547 mg (90% yield) of **13** as a white solid. Mp=110 °C; $[\alpha]_D^{26}$ −12.7 (*c* 2, $CHCl_3$); IR (Nujol) 1681, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.12 (s, 3H), 2.01 (d, 1H, J=16.6 Hz), 2.36 (d, 1H, J=16.6 Hz), 2.73 (s, 2H), 2.98 (d, 1H, J=9.6 Hz), 3.32 (d, 1H, J=9.6 Hz), 6.31 (br s, 1H), 7.10–7.31 (m 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.4, 40.1, 43.5, 45.9, 53.3, 126.6, 128.2, 130.1, 137.6, 177.7. Elemental analysis calcd (%) for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 75.97; H, 8.15; N, 7.53.

4.7. (*R*)-γ-Amino-β-benzyl-β-methylbutyric acid 14

A mixture of compound **13** (473 mg, 2.5 mmol) and 5 N aqueous HCl (10 mL) was heated under reflux for 20 h. The solvent was removed under reduced pressure to give a residue, which was dissolved in water. The resulting aqueous solution was washed with dichloromethane and evaporated in vacuo to give the crude γ-amino acid hydrochloride. This material was submitted to ion-exchange column chromatography on Dowex 50Wx8 to afford 430 mg (83% yield) of **14** as a white solid. Mp=159 °C; $[\alpha]_D^{25}$ 13.6 (*c* 1, H_2O); IR (Nujol) 1624 cm^{-1}; ^1H NMR (D_2O, 300 MHz) δ 0.96 (s, 3H), 2.29 (s, 2H), 2.61 (d, 1H, J=13.3 Hz), 2.75 (d, 1H, J=13.3 Hz), 2.90 (d, 1H, J=13.1 Hz), 3.00 (d, 1H, J=13.1 Hz), 7.15–7.40 (m 5H); ^{13}C NMR (D_2O, 75 MHz) δ 22.0, 35.4, 44.8, 47.2, 48.4, 126.9, 128.4, 131.0, 136.9, 180.5. Elemental analysis calcd (%) for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.87; H, 8.33; N, 6.64.

Acknowledgements

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