Tetrahedron: *Asymmetry* 19 (2008) 2864–2869

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Stereoselective synthesis of cyclobutyl γ-amino acids leading to branched peptides with a cyclobutane core

Jordi Aguilera [a], Raquel Gutiérrez-Abad [a], Àlex Mor [a], Albertina G. Moglioni [b], Graciela Y. Moltrasio [b], Rosa M. Ortuño [a,*]

[a] *Departament de Química, Universitat Autònoma de Barcelona, 08193 Bellaterra, Barcelona, Spain*
[b] *Departamento de Química Orgánica, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Argentina*

ARTICLE INFO

Article history:
Received 15 October 2008
Accepted 16 December 2008
Available online 20 January 2009

ABSTRACT

Alternative synthetic routes are provided to synthesize γ-amino acids in their free form or conveniently protected for their selective incorporation into ramified γ-peptides with a cyclobutane core. The key synthetic-step involves the stereoselective conjugate addition of nitromethane to chiral cyclobutyl alkenoates prepared from (−)-verbenone.

1. Introduction

The biological activity of some γ-amino acids is well known and, consequently, they play a prominent role in the clinical treatment of diseases related to the central nervous system (CNS) such as epilepsy, neuropathic pain, and anxiety. The most simple representative of this family of amino acids, the γ-amino butyric acid (GABA), is a neurotransmitter that is thought to play a major inhibitor role in the CNS.[1] However, GABA itself has not been shown to be useful for clinical uses;[2] much effort has been devoted to producing GABAergic drugs and prodrugs. Among the earlier employed prototype GABA agents, baclofen has shown a low absorption by CNS.[3] Gabapentin (GBP, Neurontin®) is a more recent GABAergic agonist, which displays important anticonvulsant[4] and analgesic[5] activity as well as other interesting properties (Chart 1). Moreover, several derivatives bearing substituents at the cyclohexane ring, including chiral compounds, have been shown to be useful for the treatment of diabetic retinopathy,[6] and gabapentin-lactam (GBP-L) is neuroprotective in retinal ischemia, whereas GBP is not neuroprotective in vivo.[7] As a follow-up compound to gabapentin for the treatment of epilepsy, neuropathic pain, anxiety, and social phobia, (*S*)-pregabalin (Lyrica®) has been developed. This drug displays a new mechanism of action, and acts as a voltage-dependent calcium channel α2-δ subunit ligand.[8]

γ-Peptides (γ-oligomers derived from γ-residues), although less studied than α- or β-oligomers, have shown an ability to fold to give secondary structures, some of which have displayed important biological activities, which are presumably related to their conformational bias.[9]

Due to these relevant biological and therapeutic properties, the search for efficient and versatile synthetic strategies to gain access to a variety of γ-amino acids, as well as their incorporation into γ-peptides, is a very active research field.[10]

In our laboratory, we have shown that the presence of a cyclobutane ring in the backbone or as a substituent moiety of the main skeleton of α-,[11] β-,[12] and γ-[13] peptides induces well determined conformations of these compounds in solution and in the solid state. In addition, we have developed efficient and stereoselective methodologies to synthesize different types of cyclobutane amino acids, starting from (−)-verbenone or (−)-α-pinene as commercially available and inexpensive chiral precursors.[14–17]

Recently, we described the stereoselective addition of nitromethane to cyclobutyl alkenoates derived from (−)-verbenone to afford nitrocompounds that could be transformed into cyclobutyl γ-amino acids.[18] On the basis of these preliminary results, we report on the development of alternative synthetic routes to prepare γ-amino acids containing an additional functional group linked to the cyclobutane ring, in a highly stereoselective and efficient manner. These compounds are orthogonally protected and, therefore, are convenient for selective coupling with other amino acids to afford branched peptides with a cyclobutane core. As a simple example, the synthesis of a γ-dipeptide derived from a cyclobutane γ-amino acid and a GABA residue is reported.

2. Results and discussion

We have recently described the use of (−)-verbenone as a chiral precursor in the synthesis of cyclobutyl aldehydes, **1a–c**,[19] bearing different substitutions on the ring. Wittig olefinization of these compounds by using suitable phosphoranes afforded alkenoate **2** (*route* 1) and alkenoates **10a–c**[14] (*route* 2) (Scheme 1) as mixtures of *Z*/*E* isomers, which could be chromatographically isolated. With

* Corresponding author. Tel.: +34 93 5811 602; fax: +34 93 5811 265.
E-mail address: rosa.ortuno@uab.es (R.M. Ortuño).

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doi:10.1016/j.tetasy.2008.12.019

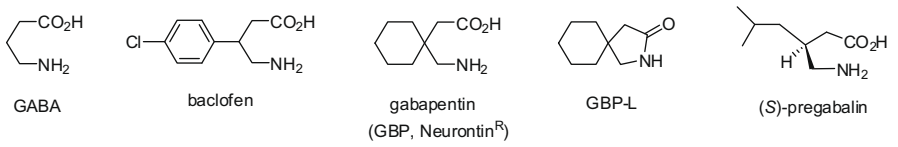
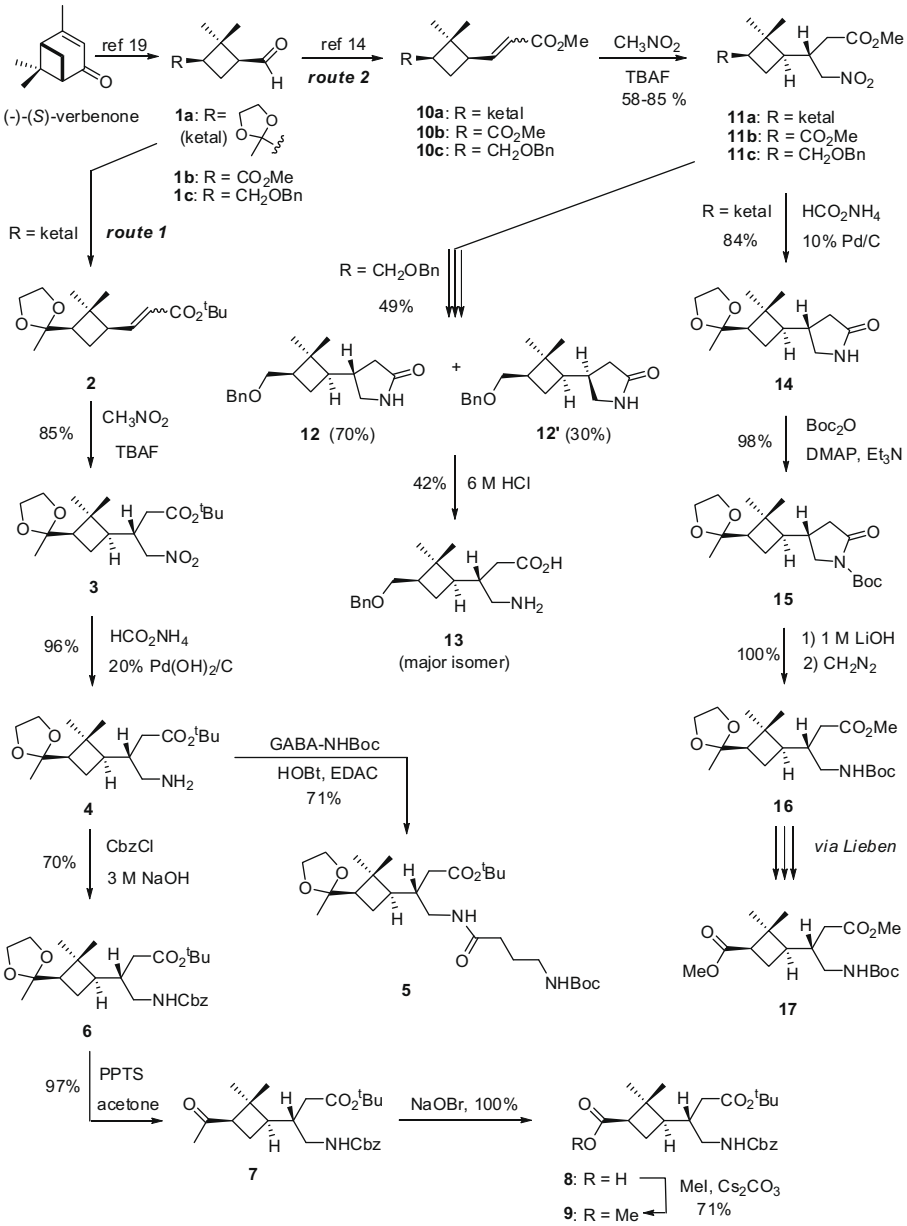


Chart 1.



Scheme 1.

respect to these substrates, the addition of nitromethane in the presence of tetrabutylammonium fluoride was carried out in order to introduce a synthon providing a functional group that could be easily transformed into the amino function and the additional carbon atom of the γ-amino acid skeleton. The conjugate addition of nitromethane to conveniently functionalized olefins has been successfully used in the stereoselective synthesis of pharmacologically relevant products.[20] We found that the addition of nitromethane to substrates **2** and **10a–b** was totally stereoselective, providing adducts as single diastereoisomers independent of the ester alkyl group (methyl or *tert*-butyl). Moreover, the reaction between nitromethane and both *Z*- and *E*-isomers converged in the same product. The configuration of the new stereogenic center was assigned to be (*S*) by X-ray structural analysis of lactam **14** (Scheme 1).[19] The configuration of compounds **3** and **11b** was assigned by comparison of the NMR data of these products or some derivatives with **11a** and **14**. When nitromethane addition was carried out on the benzyl ether **11c**, a 7:3 mixture of diastereoisomers **12**/**12′** was produced showing the influence on the stereoselectivity of the substituent at the C_3 position of the cyclobutane ring, probably due to

the steric effects. The stereochemical outcome of the process was rationalized by assuming that the preferential attack of nitromethane was to the less hindered C_2-*re* face of the double bond, which is opposite to the *gem*-dimethyl group in the most stable conformation (Fig. 1). Similar results have been found in the stereoselective addition of diazomethane[21] and alkyl hydroxylamines[14] to these substrates.

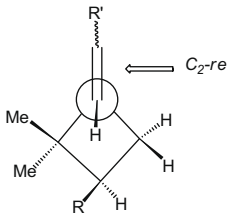


Figure 1. The attack of nitromethane to the double bond occurs on the C_2-*re* face, which is the less hindered side of the double bond.

Reduction of the nitro group was accomplished by treatment of the nitro esters with ammonium formate in the presence of 10% Pd/C in boiling methanol. In the case of methyl esters **10a, c**, lactams **12, 12′**, and **13** were, respectively, obtained without isolation of the intermediate amino esters, which underwent in situ cyclization to lactams. Conversely, in the case of the very poor nucleophilic *tert*-butyl nitroester **3**, amino ester **4** could be isolated. This compound was already suitable for incorporation into peptides as verified by the coupling of **4** with Boc-NH-GABA under the usual conditions (HOBt, EDAC) to provide γ-dipeptide **5** in 71% yield. Alternatively, the amino group in **4** was protected as a Cbz carbamate to afford **6** in 70% yield. Deprotection of the methyl ketone under mild conditions (PPTS, boiling acetone, 2 h) afforded compound **7** in almost quantitative yield without epimerization. Lieben degradation by using sodium hypobromite in dioxane at 0 °C quantitatively furnished acid **8**. Subsequent methylation under treatment with methyl iodide and cesium carbonate gave orthogonally protected compound **9** in 71% yield. This product is useful as it can be submitted to successive peptide couplings through selective deprotection of the three functional groups.

According to *route* 2, the diastereomeric mixture of lactams **12** and **12′** could not be resolved, while acid hydrolysis with 6 M HCl provided the free amino acid **13** which was enriched in the major diastereomer by crystallization.

In turn, lactam **14** provided, almost quantitatively, the *N*-Boc derivative **15** which, upon mild hydrolysis with 1 M LiOH followed by methylation, led to compound **16**. Ketal protection was removed under similar conditions to those described above in *route* 1 (transformation of **6** into **7**) to afford a methyl ketone which, under Lieben degradation and subsequent methylation, as described in *route* 1, provided the protected derivative **17**.

3. Conclusion

We have reported highly stereoselective and alternative synthetic-routes to prepare cyclobutyl γ-amino acids, in their free form or conveniently protected to be incorporated into branched γ-peptides with a cyclobutane core.

4. Experimental

4.1. *tert*-Butyl 3-[(1*R*,3*R*)-2,2-dimethyl-3-(2-methyl-1,3-dioxolan-2-yl)cyclobutyl]-acrylate, 2

To a solution of $Ph_3P{=}CHCO_2{}^tBu$ (8.3 g, 14.9 mmol) in 20 mL of anhydrous methanol under a nitrogen atmosphere was added a solution of aldehyde **1a**[19] (3.01 g) in 80 mL of anhydrous methanol, and the resulting mixture was stirred for 15 h. Afterwards, the solvent was evaporated under vacuo. The resulting crude was dissolved in hot diethyl ether, and the solution was filtered through a sintered glass funnel. Again, the solvent was evaporated under vacuo, and the resulting crude was purified by flash chromatography (1:1 hexane–ethyl acetate) to afford **2** (3.9 g, 86%) as a 53:47 mixture of *Z*/*E* olefins. IR: 2979, 2935, 2879, 1717, 1713, 1647, 1420, 1368 cm^{-1}. ^1H NMR ($CDCl_3$) for isomer *Z*: 1.08 (s, 3H), 1.17 (s, 3H), 1.26 (s, 3H), 1.50 (s, 9H), 1.93–1.98 (m, 1H), 2.05–2.10 (m, 1H), 2.20–2.30, (m, 1H), 3.82–4.05 (complex, 4H), 5.64–5.75 (m, 1H), 6.06 (dd, $^3J_{3,2}$ = 11.6 Hz, $^4J_{3,4}$ = 10.2 Hz, 1H). ^1H NMR ($CDCl_3$) for isomer *E*: δ 1.04 (s, 3H), 1.17 (s, 3H), 1.26 (s, 3H), 1.50 (s, 9H), 1.72–1.83 (m, 1H), 2.20–2.30 (m, 1H), 2.46–2.55 (m, 1H), 3.82–4.05 (m, 4H), 5.64–5.75 (m, 1H), 6.84 (dd, $^3J_{2,1}$ = 15.6 Hz, $^4J_{2,3}$ = 7.4 Hz). ^{13}C NMR ($CDCl_3$): 18.11, 23.18, 23.42, 23.68, 25.17, 28.08, 28.14, 30.91, 31.41, 39.83, 43.66, 44.16, 44.69, 49.73, 49.87, 63.62, 65.45, 65.51, 79.98, 109.55, 109.76, 121.94, 123.08, 147.68, 148.62, 165.77, 165.97. Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89 ; H, 9.52. Found C, 69.08; H, 9.55.

4.2. (*S*)-*tert*-Butyl 3-[(1*R*,3*R*)-2,2-dimethyl-3-(2-methyl-1,3-dioxolan-2-yl)cyclobutyl]-4-nitrobutanoate, 3

To a solution of alkenes **2** (4.1 g, 13.9 mmol) in 150 mL of anhydrous THF under nitrogen atmosphere were subsequently added nitromethane (0.9 mL, 15.8 mmol) and 1.0 M TBAF in THF (16.1 mL, 16.8 mmol). The resulting mixture was let to stir for 18 h. Next, the solvent was evaporated at reduced pressure, and the resulting crude was chromatographed on silica gel (4:1, hexane–ethyl acetate) to afford compound **3** as a colorless oil (4.2 g, 85%). $[\alpha]_D = -22.0$ (*c* 1.00, CH_2Cl_2). IR: 2980, 2950, 2876, 1724, 1549, 1463, 1428, 1369 cm^{-1}. ^1H NMR ($CDCl_3$): 1.09 (s, 3H), 1.16 (s, 3H), 1.20 (s, 3H), 1.23 (s, 9H), 1.60 (m, 1H), 1.73 (m, 1H), 1.90 (m, 1H), 2.03–2.09 (m, 1H), 2.23–2.29 (complex absorption, 2H), 2.38–2.53 (m, 1H), 3.78–3.96 (complex absorption, 4H), 4.36–4.51 (complex absorption, 2H). ^{13}C NMR ($CDCl_3$): 16.40, 23.16, 23.67, 27.97, 31.79, 35.53, 35.92, 41.22, 42.91, 48.97, 63.58, 65.40, 76.43, 81.11, 109.42, 170.50. HRMS: **c**alcd for $C_{18}H_{31}NO_6Na$ (M+Na): 380.2044. Found: 380.2040.

4.3. (*S*)-*tert*-Butyl 4-amino-3-[(1*R*,3*R*)-2,2-dimethyl-3-(2-methyl-1,3-dioxolan-2-yl)cyclobutyl]butanoate, 4

To a solution of **3** (5.0 g, 14.0 mmol) in 125 mL of anhydrous methanol were subsequently added ammonium formate (3.2 g, 49.4 mmol) and 20% $Pd(OH)_2/C$ (1.1 g). The resulting mixture was heated at reflux for 2 h. Afterwards, the reaction mixture was filtered through Celite®, and the solvent was eliminated under vacuo to obtain a yellow oil identified as amine **4** (4.6 g, 96%). $[\alpha]_D = -8.3$ (*c* 0.48, CH_2Cl_2). IR: 3384, 2978, 1725, 1461, 1392, 1368, 1256, 1224, 1156, 1102, 1038, 949, 863, 842, 734 cm^{-1}. ^1H NMR ($CDCl_3$): 1.10 (s, 3H), 1.18 (s, 3H), 1.23 (s, 3H), 1.45 (s, 9H), 1.55–1.72 (complex absorption, 2H), 1.81–1.97 (complex absorption, 2H), 2.02–2.16 (complex absorption, 4H), 2.26 (dd, *J* = 14.5 Hz, *J′* = 3.6 Hz), 2.57 (dd, *J* = 12.9 Hz, *J′* = 6.7 Hz, 1H), 2.75 (dd, *J* = 12.9 Hz, *J′* = 3.9 Hz, 1H), 3.78–3.97 (complex absorption, 4H). ^{13}C NMR ($CDCl_3$): 16.53, 23.44, 23.77, 28.00, 31.99, 36.67, 41.04, 41.99, 43.68, 49.19, 63.60, 65.42, 109.59, 172.50. HRMS: calcd for $C_{18}H_{33}NO_4Na$ (M+Na): 328.2482. Found: 328.2484.

4.4. (*S*)-*tert*-Butyl 4-(4-(*tert*-butoxycarbonylamino)butanamido)-3-[(1*R*,3*R*)-2,2-dimethyl-3-(2-methyl-1,3-dioxolan-2-yl)-cyclobutyl]butanoate, 5

A mixture containing GABA-NHBoc (372 mg, 1.8 mmol), EDAC (702 mg, 3.7 mmol), HOBt (248 mg, 1.8 mmol), and triethylamine

(0.56 mL, 4.1 mmol) in dry DMF (15 mL) was stirred for 30 min, and then amine **4** (400 mg, 1.7 mmol) in dry DMF (10 mL) was added. After stirring at room temperature for 40 h, most of the DMF was removed under vacuo. The residue was dissolved in ethyl acetate (50 mL), and the solution was washed with saturated aqueous sodium bicarbonate (4 × 20 mL). The organic phase was dried over magnesium sulfate, and the solvents were removed. The reaction crude was purified by column chromatography on neutral silica gel (1:5 ethyl acetate–hexane) to afford pure **5** (608 mg, 71% yield). $[\alpha]_D$ = +7.3 (*c* 3, CH_2Cl_2). IR: 3316, 2975, 2877, 1711, 1691, 1648, 1524, 1452 cm^{-1}. ^1H NMR ($CDCl_3$): 1.08 (s, 3H), 1.22 (s, 3H), 1.44–1.45 (ds, 18H), 1.55–1.65 (complex absorption, 2H), 1.80 (m, 2H), 1.87–1.92 (m, 1H), 1.95–2.10 (complex absorption, 3H), 2.19 (t, *J* = 7 Hz, 2H), 2.26 (dd, *J* = 14 Hz, *J*′ = 2.2 Hz, 1H), 2.94–3.02 (m, 1H), 3.13–3.18 (m, 2H), 3.35 (ddd, *J* = 13 Hz, *J*′ = 5 Hz, *J*″ = 4 Hz, 1H), 3.77–3.99 (complex absorption, 4H), 4.81 (br s, 1H), 4.81 (br s, 1H). ^{13}C NMR ($CDCl_3$): 16.65, 23.80, 23.86, 26.18, 28.06, 28.36, 32.11, 33.75, 36.28, 37.68, 39.83, 41.08, 41.31, 44.33, 49.33, 63.69, 64.48, 79.15, 80.94, 110.06, 156.25, 172.54, 172.84. HRMS: calcd for $C_{27}H_{48}N_2NaO_7$, (M+Na): 535.3354. Found: 335.3352.

4.5. (*S*)-*tert*-Butyl 4-(benzyloxycarbonylamino)-3-[(1*R*,3*R*)-2,2-dimethyl-3-(2-methyl-1,3-dioxolan-2-yl)cyclobutyl]butanoate, 6

To an ice cooled solution of 60% sodium hydride (189 mg, 4.9 mmol) in 20 mL of anhydrous THF was subsequently added a solution of amine **5** (1.0 g, 3.1 mmol) in 40 mL of anhydrous THF and benzyl chloroformate (0.7 mL, 4.4 mmol). The resulting mixture was let to react for 15 h, after which, 30 mL of water was added and THF was evaporated under vacuo. To the resulting crude was added 40 mL of dichloromethane, and the resulting solution was washed with saturated aqueous sodium bicarbonate (4 × 20 mL). The organic phase was dried over magnesium sulfate, and the solvent was removed at reduced pressure. The reaction crude was purified by column chromatography on neutral silica gel (1:4 ethyl acetate–hexane) to afford a colorless oil identified as compound **6** (1.0 g, 70%). $[\alpha]_D$ = +14.6 (*c* 0.55, CH_2Cl_2). IR: 3339, 2977, 2952, 2880, 1724, 1518, 1455, 1368, 1247 cm^{-1}. ^1H NMR ($CDCl_3$): 1.07 (s, 3H), 1.14 (s, 3H), 1.20 (s, 3H), 1.41 (s, 9H), 1.54–1.66 (complex absorption, 2H), 1.87–2.05 (complex absorption, 4H), 2.23 (dd, *J* = 18.5 Hz, *J*″ = 7.2 Hz, 1H), 2.98 (m, 1H), 3.32 (ddd, *J* = 12.7 Hz, *J*′ = 5.7 Hz, *J*″ = 3.2 Hz, 1H), 3.72–3.98 (complex absorption, 4H), 5.07 (s, 2H), 5.20 (dd, *J* = 5.7 Hz, *J*′ = 6.0 Hz, 1H), 7.24–7.38 (complex absorption, 5H). ^{13}C NMR ($CDCl_3$): 16.48, 23.63, 23.72, 27.92, 31.95, 36.80, 37.28, 40.97, 42.50, 44.03, 49.29, 63.54, 65.34, 66.35, 80.60, 109.56, 127.84, 127.91, 128.30, 136.59, 156.33. HRMS: calcd for $C_{26}H_{39}NO_6Na$ (M+Na): 484.2670. Found: 484.2671.

4.6. (*S*)-*tert*-Butyl 3-[(1*R*,3*R*)-3-acetyl-2,2-dimethylcyclobutyl)-4-(benzyloxy-carbonylamino]butanoate, 7

A mixture containing compound **6** (250 mg, 0.5 mmol), PPTS (41 mg, 0.2 mmol), and water (2 mL, 111 mmol) in acetone (40 mL) was heated at reflux for 2 h. Afterwards, acetone was evaporated under vacuo. The resulting crude was poured into 40 mL of ethyl acetate, and the solution was washed with saturated aqueous sodium bicarbonate (3 × 20 mL). The organic phase was dried over magnesium sulfate. The solvent was removed at reduced pressure, and the residue was chromatographed on silica gel (ethyl acetate) to afford pure methyl-ketone **7** (220 mg, 97%) as an oil. $[\alpha]_D$ = +37.4 (*c* 2.12, CH_2Cl_2). IR: 3365, 2954, 1724, 1705, 1523, 1455.84 cm^{-1}. ^1H NMR ($CDCl_3$): 0.92 (s, 3H), 1.35 (s, 3H), 1.44 (s, 9H), 1.73–2.26 (complex absorption, 9H), 2.65–2.82 (m, 1H), 2.98–3.14 (m, 1H), 3.19–3.34 (m, 1H), 5.00–5.28 (complex absorption, 3H), 7.29–7.41 (complex absorption, 5H). ^{13}C NMR ($CDCl_3$): 17.19, 22.85, 28.46, 30.66, 31.64, 37.66, 42.77, 43.71, 44.25, 54.06, 67.71, 81.52, 110.00, 124.44, 128.87, 137.09, 156.31, 172.13, 207.85. HRMS: calcd for $C_{24}H_{35}NO_5Na$ (M+Na): 440.2407. Found: 440.2398.

4.7. Benzyl (2*S*,1′*R*,3′*R*)-3-(*tert*-butoxycarbonyl)-2-(2′,2′-dimethyl-3′-carboxycyclobutyl)propylcarbamate, 8

To an ice cooled solution of ketone **8** (220 mg, 0.5 mmol) in 18 mL of dioxane–water (7:2) was added 40 mL of a sodium hypobromite solution, prepared from bromine (0.4 mL, 8.43 mmol) and sodium hydroxide (1.3 g, 31.6 mmol) in 3:1 water–dioxane; the resulting mixture was stirred for 5 h at 0 °C. Next, 10 mL of sodium bisulfate was added, and the mixture was brought to acidic pH by adding 5% hydrochloric acid. The acid solution was extracted with dichloromethane (4 × 30 mL), the organic extracts were dried over anhydrous magnesium sulfate, and the solvent was removed to afford carboxylic acid **8** (221 mg, quantitative). $[\alpha]_D$ = +93.3 (*c* 0.15, CH_2Cl_2). IR: 3341, 2957, 1709, 1707, 1524, 1455 cm^{-1}. ^1H NMR ($CDCl_3$): 1.12 (s, 3H), 1.29 (s, 3H), 1.45 (s, 9H), 1.75–1.89 (m, 1H), 1.90–2.14 (complex absorption, 4H), 2.17–2.32 (m, 1H), 2.59–2.75 (m, 1H), 3.00–3.15 (m, 1H), 3.20–3.38 (m, 1H), 5.03–5.23 (complex absorption, 3H), 7.30–7.43 (complex absorption, 5H). ^{13}C NMR ($CDCl_3$): 17.38, 23.97, 28.47, 30.09, 31.30, 37.56, 42.80, 43.38, 44.43, 45.92, 67.08, 81.45, 128.50, 128.89, 136.89, 156.97, 172.48, 178.21. HRMS: calcd for $C_{23}H_{33}NO_6Na$ (M+Na): 442.2200. Found: 442.2197.

4.8. (1*R*,3*R*)-Methyl 3-[(*S*)-1-(benzyloxycarbonylamino)-4-*tert*-butoxy-4-oxobutan-2-yl)-2,2-dimethylcyclobutanecarboxylate, 9

To a solution of carboxylic acid **8** (150 mg, 0.4 mmol) in 40 mL of dimethylformamide, cesium carbonate (140 mg, 0.4 mmol) and iodomethane (0.1 mL, 1.60 mmol) were subsequently added. The resulting mixture was left to stir for 16 h at room temperature. Afterwards, ethyl acetate (40 mL) was added, and the solution was washed with saturated aqueous sodium bicarbonate (4 × 20 mL). The organic phase was dried over magnesium sulfate, and the solvent was removed at reduced pressure. The residue was chromatographed on silica gel (1:1 hexane–diethyl ether) to afford pure ester **9** (110 mg, 71%). $[\alpha]_D$ = +64.4 (*c* 0.29, CH_2Cl_2). IR: 3366, 2951, 1721, 1720, 1518, 1455 cm^{-1}. ^1H NMR ($CDCl_3$): 0.98 (s, 3H), 1.26 (s, 3H), 1.45 (s, 9H), 1.71–1.85 (m, 1H), 1.90–2.11 (complex absorption, 4H), 2.16–2.34 (m, 1H), 2.54–2.71 (m, 1H), 2.98–3.12 (m, 1H), 3.20–3.35 (m, 1H), 3.67 (s, 3H), 5.00–5.21 (complex absorption, 3H), 7.29–7.44 (complex absorption, 5H). ^{13}C NMR ($CDCl_3$): 17.01, 23.67, 28.00, 30.85, 37.09, 42.34, 42.66, 43.92, 45.56, 51.12, 66.53, 80.90, 109.53, 127.97, 128.41, 136.33, 156.41, 171.84, 172.84. HRMS: calcd for $C_{24}H_{35}NO_6Na$ (M+Na): 456.2357. Found: 456.2349.

4.9. (*S*)-Methyl-3-[(1*R*,3*R*)-2,2-dimethyl-3-(2-methyl-1,3-dioxolan-2-yl)cyclobutyl]-4-nitrobutanoate, 11a

Nitromethane (2.3 mL, 42 mmol) was added to a mixture of 9.4 g of **10a**[15] (37 mmol) and 42 mL of TBAF (1 M in THF, 42 mmol) in 400 mL of THF at −5 °C. The mixture was stirred for 3 h, and the solvent was evaporated under vacuo. The crude was dissolved in EtOAc (350 mL) and washed with brine (3 × 15 mL). The organic phase was dried over magnesium sulfate, and the solvent was evaporated at reduced pressure. The residue was chromatographed on silica gel (1:4 ethyl acetate–hexane) to afford **11a** (11.1 g, 95% yield). ^1H NMR ($CDCl_3$): 1.09 (s, 3H), 1.15 (s, 3H), 1.21 (s, 3H), 1.60 (m, 1H), 1.72 (m, 1H), 1.87–1.96 (m, 1H), 2.03–2.11 (complex

absorption, 1H), 2.37–2.40 (complex absorption, 2H), 2.44–2.59 (m, 1H), 3.68 (s, 3H), 3.75–4.02 (complex absorption, 4H), 4.42–4.47 (complex absorption, 2H). ^{13}C NMR ($CDCl_3$): 16.46, 23.15, 23.67, 31.75, 34.19, 35.71, 41.22, 42.99, 48.93, 51.66, 63.59, 65.41, 76.35, 109.41, 171.71.

4.10. (*S*)-4-[(1*R*,3*R*)-3-Benzyloxymethyl-2,2-dimethylcyclobutyl]pyrrolidin-2-one, 12

A mixture containing 250 mg of nitroester **11c** (0.71 mmol), 346 mg of ammonium formate (5 mmol), and 125 mg of 20% $Pd(OH)_2$/C in 25 mL of dry methanol was heated at reflux overnight. Afterwards, reaction mixture was filtered through Celite, and solvent was removed under vacuo and chromatographed on silica gel (30:1 methylene chloride–methanol) to afford **12** as a mixture of diastereomers in a 7:3 ratio (103 mg, 49% yield). Spectroscopic data for major epimer are as follows. ^{1}H NMR ($CDCl_3$): 0.93 (s, 3H), 1.29 (s, 3H), 1.8–2.1 (m, 3H), 2.20 (m, 1H), 2.37 (m, 2H), 2.93 (m, 1H), 3.41–3.52 (m, 4H), 4.48 (s, 2H), 6.9 (br s, 1H), 7.36–7.41 (complex absorption, 5H). ^{13}C NMR ($CDCl_3$): 17.60, 25.33, 32.11, 36.05, 36.31, 41.16, 42.31, 47.55, 49,12, 71.50, 73.23, 127.11, 129.62, 138.34, 178.76.

4.11. (*S*)-4-Amino-3-[(1*R*,3*R*)-3-benzyloxymethyl-2,2-dimethylcyclobutyl] butanoic acid, 13

At first, 80 mg of the mixture **11** (0.28 mmol) was dissolved in 4 mL of 6 M HCl and heated at reflux for 3 h. After that time, solvent was removed under vacuo and chromatographed on silica gel (10:1 dichloromethane–methanol) to afford **13** as a diastereomeric mixture (35 mg, 42% yield). Spectroscopic data for the major epimer are as follows. ^{1}H NMR (D_2O): 0.93 (s, 3H), 1.08 (s, 3H), 1.71 (m, 1H), 1.87–1.92 (m, 2H), 1.95 (m, 1H), 2.17 (m, 1H), 2.37 (m, 1H), 2.57 (m, 1H), 2.71–2.87 (m, 2H), 3.28 (m, 1H), 3.40 (m, 1H), 3.55 (m, 1H), 4.57 (s, 2H), 7.32 (complex absorption, 5H). ^{13}C NMR (D_2O): 15.52, 25.15, 30.99, 35.69, 39.49, 41.45, 42.45, 42.76, 43.58, 44.59, 62.74, 128.50, 130.01, 139.92, 180.89. HRMS: calcd For $C_{11}H_{21}NO_3$ (M+H−Bn): 216,1594. Found: 216,1596.

4.12. (*S*)-4-[(1*R*,3*R*)-2,2-Dimethyl-3-(2-methyl-1,3-dioxolan-2-yl)cyclobutyl]-pyrrolidin-2-one, 14

A mixture containing nitroester **11a** (1.1 g 3.38 mmol), ammonium formate (0.78 g, 28 mmol), and 10% Pd/C (1.2 mg) in 100 mL dry methanol was heated at reflux overnight. The reaction mixture was filtered through Celite®, and the solvent was evaporated to obtain **14** as a white solid (722 mg, 84% yield). Crystals, mp 70–71 °C (acetone). $[\alpha]_D = -15$ (*c* 0.65, CH_2Cl_2). IR: 3176, 2954, 2885, 1707, 1459 cm^{-1}. ^{1}H NMR ($CDCl_3$): 1.07 (s, 3H), 1.16 (s, 3H), 1.23 (s, 3H), 1.52 (m, 1H), 1.70–2.00 (complex absorption, 3H), 2.12 (dd, J = 7.5 Hz, J' = 12 Hz, 1H), 2.30–2.55 (complex absorption, 2H), 2.95 (dd, J = 6 Hz, J' = 9 Hz, 1H), 3.41 (m, 1H), 3.78–4.04 (complex absorption, 4H), 5.84 (br s, 1H). ^{13}C NMR ($CDCl_3$): 17.67, 23.76, 29.94, 32.31, 36.44, 37.02, 41.45, 46.22, 47.83, 50.05, 63.93, 64.17, 110.22, 177.26. Anal. Calcd for: C, 61.97; H, 9.29; N, 5.16. Found: C, 62.27; H, 8.83; N, 4.74.

4.13. (*S*)-*tert*-Butyl-4-[(1*R*,3*R*)-2,2-dimethyl-3-(2-methyl-1,3-dioxolan-2-yl)cyclobutyl]-2-oxopyrrolidine-1-carboxylate, 15

To a solution of lactam **14** (200 mg, 0.8 mmol) in 5 mL of anhydrous dichloromethane, 99 mg of DMAP, 0.12 mL of triethylamine, and 0.36 mL of Boc_2O were subsequently added, and the resulting mixture was stirred overnight. Afterwards, the mixture was washed with sodium bicarbonate (3 × 2 mL), and the organic phase was dried over magnesium sulfate. Solvent was removed, and the residue was chromatographed on silica gel (1:1 ethyl acetate–hexane) to afford **15** as a white powder (277 mg, 98% yield). Crystals, mp 110–112 °C (pentane). $[\alpha]_D = -23.7$ (*c* 2.55, CH_2Cl_2). IR: 2978, 1793, 1692, 1458 cm^{-1}. ^{1}H NMR ($CDCl_3$): 1.06 (s, 3H), 1.14 (s, 3H), 1.23 (s, 3H), 1.53 (s, 9H), 1.71 (m, 1H), 1.92 (dd, J = 7.5 Hz, J' = 11.5 Hz, 1H), 2.15 (m, 1H), 2.27 (m, 1H), 2.56 (dd, J = 7.5 Hz, J' = 15 Hz, 1H), 3.25 (dd, J = 11 Hz, J' = = 15 Hz, 1H), 3.90 (complex absorption, 5H). ^{13}C NMR ($CDCl_3$): 17.72, 23.38, 24.40, 28.26, 33.40, 39.30, 41.84, 47.27, 49.32, 50.61, 64.22, 64.54, 83.42, 110.47, 150.80, 174.43. HRMS: calcd for $C_{19}H_{31}NO_5Na$ (M+Na): 376.2094. Found: 376.2088.

4.14. (*S*)-Methyl-4-(*tert*-butoxycarbonylamino)-3-[(1*R*,3*R*)-2,2-dimethyl-3-(2-methyl-1,3-dioxolan-2-yl)cyclobutyl]butanoate, 16

An aqueous solution of 1 M LiOH (0.61 mL) was added to a solution of lactam **15** (100 mg, 0.31 mmol) in 5 mL of THF. The mixture was stirred for 2 h, after which the solvents were evaporated under vacuo until dryness. The product was extracted with methanol (3 × 10 mL), and the organic solvent was evaporated. The resulting carboxylic acid was methylated without previous purification using a saturated solution of diazomethane in dichloromethane to afford **16** as a colorless oil (120 mg, quantitative). $[\alpha]_D = -34$ (*c* 1.20, CH_2Cl_2). IR: 3378, 2952, 1720, 1714, 1511 cm^{-1}. ^{1}H NMR ($CDCl_3$): 1.10 (s, 3H), 1.17 (s, 3H), 1.24 (s, 3H), 1.44 (s, 9H), 1.61 (m, 1H), 1.69 (m, 1H), 1.87 (m, 1H), 2.10 (complex absorption, 3H), 2.29 (m, 1H), 2.90 (m, 1H), 3.23 (m, 1H), 3.68 (s, 3H), 3.77–4.01 (complex absorption, 4H), 4.74 (br s, 1H). ^{13}C NMR ($CDCl_3$): 16.81, 23.67, 24.15, 28.31, 31.98, 35.99, 37.04, 41.28, 42.07, 44.41, 49.44, 51.72, 63.8, 65.59, 109.81, 156.15, 173.41. HRMS: Calc. for $C_{20}H_{35}NO_6Na$ (M+Na): 408.2357. Found: 408.2358.

4.15. (1*R*,3*R*)-Methyl-3-((*S*)-1-(*tert*-butoxycarbonylamino)-4-methoxy-4-oxobutan-2-yl)-2,2-dimethylcyclobutane-carboxylate, 17

Following a similar procedure to that described above for the synthesis of **9**, compound **17** was obtained (69% yield from **16**). $[\alpha]_D = -13$ (*c* 2.5, CH_2Cl_2). IR: 3388, 2952, 1720, 1712, 1510, 1164 cm^{-1}. ^{1}H NMR ($CDCl_3$): 0.97 (s, 3H), 1.31 (s, 3H), 1.42 (s, 9H), 1.73 (m, 1H), 1.83–2.34 (complex absorption, 5H), 2.56 (m, 1H), 2.94 (m, 1H), 3.21 (m, 1H), 3.67 (s, 3H), 3.70 (m, 3H), 4.75 (br s, 1H). ^{13}C NMR ($CDCl_3$): 16.95, 23.49, 28.35, 30.78, 35.40, 36.99, 41.69, 42.70, 44.13, 45.55, 51.00, 51.59, 79.11, 155.89, 172.72, 172.98. HRMS: calcd for $C_{19}H_{31}NO_5Na$ (M+Na): 380.2044. Found: 380.2046.

Acknowledgments

Financial support from Ministerio de Ciencia e Innovación (CTQ2007-61704/BQU) and Generalitat de Catalunya (2005SGR-103) is gratefully acknowledged. R.G. thanks the Ministerio de Educación for a predoctoral fellowship.

References

1. Roberts, E. *Biochem. Pharmacol.* **1974**, *23*, 2637.
2. (a) Velmupalli, S.; Barletta, M. *Arch. Int. Pharmacodyn.* **1984**, *267*, 46; (b) Nurnberger, J. I.; Berrettini, W. H.; Simmons-Alling, S.; Guroff, J. I.; Gershon, E. S. *Psychiat. Res.* **1986**, *19*, 113.
3. Wall, G. M.; Baker, J. K. *J. Med. Chem.* **1989**, *32*, 1340. and references cited therein.
4. Cczuczwar, S. J.; Patsalos, P. N. *CNS Drugs* **2001**, *15*, 339.
5. Gu, Y.; Huang, L.-Y. M. *Pain* **2001**, *93*, 85.
6. Bryans, J. S.; Hu, L.-Y.; Hutson, S. M.; Lanoue, K. F.; Lieth, E.; Rafferty, M. F.; Ryder, T. R.; Su, T.-Z.; Welty, D. F.; Wustrow, D. J. PCT Int. Appl. 2001 (*Chem. Abstr.*, **2001**, *135*, 46446j).

7. Jehle, T.; Feuerstein, T. J.; Lagreze, W. A. *Ophtalmologe* **2001**, *98*, 237.
8. (a) Bryans, J. S.; Wustrow, D. J. *Med. Res. Rev.* **1999**, *19*, 149; (b) Belliotti, T.; Capiris, T.; Ekhato, V.; Kinsora, J. J.; Field, M. J.; Heffner, T. G.; Meltzer, L. T.; Schwarz, J. B.; Taylor, C. P.; Thorpe, A. J.; Vartanian, M. G.; Wise, L. D.; Zhi-Su, T.; Weber, M.; Wustrow, D. J. *J. Med. Chem.* **2005**, *48*, 2294. and references cited therein.
9. (a) Hintermann, T.; Gadermann, K.; Jaun, B.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 983; (b) Seebach, D.; Hook, D. F.; Glatti, A. *Biopolymers* **2006**, *84*, 23.
10. Ordoñez, M.; Cativiela, C. *Tetrahedron: Asymmetry* **2007**, *18*, 3.
11. Aguado, G. P.; Moglioni, A. G.; Brousse, B. N.; Ortuño, R. M. *Tetrahedron: Asymmetry* **2003**, *14*, 2445.
12. (a) Izquierdo, S.; Kogan, M. J.; Parella, T.; Moglioni, A. G.; Branchadell, V.; Giralt, E.; Ortuño, R. M. *J. Org. Chem.* **2004**, *69*, 5093; (b) Izquierdo, S.; Rúa, F.; Sbai, A.; Parella, T.; Álvarez-Larena, Á.; Branchadell, V.; Ortuño, R. M. *J. Org. Chem.* **2005**, *70*, 7963; (c) Rúa, F.; Boussert, S.; Parella, T.; Diez-Pérez, I.; Branchadell, V.; Giralt, E.; Ortuño, R. M. *Org. Lett.* **2007**, *9*, 3643.
13. Aguilera, J.; Moglioni, A. G.; Moltrasio, G. Y.; Ortuño, R. M. *Tetrahedron: Asymmetry* **2008**, *19*, 302.
14. Moglioni, A. G.; Muray, E.; Castillo, J. A.; Álvarez-Larena, Á.; Moltrasio, G. Y.; Branchadell, V.; Ortuño, R. M. *J. Org. Chem.* **2002**, *67*, 2402.
15. Aguado, G. P.; Moglioni, A. G.; García-Expósito, E.; Branchadell, V.; Ortuño, R. M. *J. Org. Chem.* **2004**, *69*, 7971.
16. Ortuño, R. M.; Moglioni, A. G.; Moltrasio, G. *Curr. Org. Chem.* **2005**, *9*, 237.
17. Ortuño, R. M. In *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Soloshonok, V. A., Eds., 2nd ed.; John Wiley and Sons: New Jersey, 2005; pp 117–137.
18. Moglioni, A. G.; Brousse, B. N.; Álvarez-Larena, Á.; Moltrasio, G. Y.; Ortuño, R. M. *Tetrahedron: Asymmetry* **2002**, *13*, 451.
19. Moglioni, A. G.; García-Expósito, E.; Aguado, G. P.; Parella, T.; Moltrasio, G. Y.; Branchadell, V.; Ortuño, R. M. *J. Org. Chem.* **2000**, *65*, 3934.
20. (a) Domingos, J. L. O.; Lima, E. C.; Dias, A. G.; Costa, P. R. R. *Tetrahedron: Asymmetry* **2004**, *15*, 2313; (b) Izquierdo, S.; Aguilera, J.; Buschmann, H.; García, M.; Torrens, A.; Ortuño, R. M. *Tetrahedron: Asymmetry* **2008**, *19*, 651.
21. (a) Moglioni, A. G.; García-Expósito, E.; Álvarez-Larena, Á.; Branchadell, V.; Moltrasio, G. Y.; Ortuño, R. M. *Tetrahedron: Asymmetry* **2000**, *11*, 4903; (b) Muray, E.; Illa, O.; Amsallem, D.; Moglioni, A. G.; Gornitzka, H.; Branchadell, V.; Baceiredo, A.; Ortuño, R. M. *Tetrahedron: Asymmetry* **2002**, *13*, 2593.