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Stereodivergent synthesis of the first bis(cyclobutane) γ-dipeptides and mixed γ-oligomers

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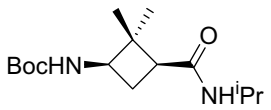
Abstract—Diastereomeric bis(cyclobutane) γ-dipeptides, a new class of γ-peptides, have been synthesized efficiently from both enantiomers of conveniently protected 3-amino-2,2-dimethyl-1-carboxylic acid. These amino acids have been prepared in very good overall yields through enantiodivergent synthetic routes starting from (−)-*cis*-pinononic acid. Mixed γ-oligomers have also been prepared from GABA and cyclobutane residues.

1. Introduction

γ-Amino acids play important roles in the mechanism of the neurotransmission in mammalian systems and, therefore, some natural or designed derivatives are being used in the clinical treatment of central nervous system (CNS) disorders.[1] Otherwise, γ-peptides, although less investigated than α- or β-oligomers, display an ability to fold giving defined secondary structures, some of which show important biological activities which are presumably related to their conformational bias.[2]

Some years ago, Burgess synthesized compounds **1** and **2** from (+)-α-pinene.[3] X-ray diffraction analyses showed that both the molecules have an extended conformation. Moreover, crystal packing of compound **1** displays a β-sheet orientation of intermolecularly hydrogen-bonded molecules. In contrast, product **2** did not stack in such a regular arrangement. This is the only precedent on the synthesis and the study of cyclobutane containing γ-peptides.



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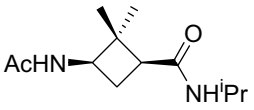

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According to our research program on the synthesis and structural study of conformationally restricted amino acids and peptides,[4] we decided to synthesize cyclobutane γ-amino acids to incorporate them in γ-oligomers and investigate their behaviour as foldamers.

Thus, we herein report on the stereodivergent synthesis of both the enantiomers of 3-amino-2,2-dimethylcyclobutane-1-carboxylic acid derivatives from (−)-*cis*-pinononic acid. These compounds are suitably protected for their incorporation into oligomers and herein we report for the first time the preparation of diastereomeric bis(cyclobutane)-γ-dipeptides as well as other γ-peptides.

2. Results and discussion

We recently described the preparation of compound **4** from (−)-*cis*-pinononic acid, **3**, obtained, in turn, from commercially available (−)-verbenone (Scheme 1).[5]

Methylation of the carboxylic acid with MeI in the presence of Cs_2CO_3 followed by a Schmidt rearrangement promoted by treatment with sodium azide and methanesulfonic acid led to protected amino acid **4** in 64% yield for the two steps. Saponification of the methyl ester under mild conditions (0.25 M NaOH) allowed the preparation of acid **5** in 91% yield without epimerization.[6] This product was coupled with MeO-GABA under the usual conditions (EDAC as a dehydrating agent and HOBt as a catalyst) to afford γ-dipeptide **6**, which contains a rigid cyclobutane

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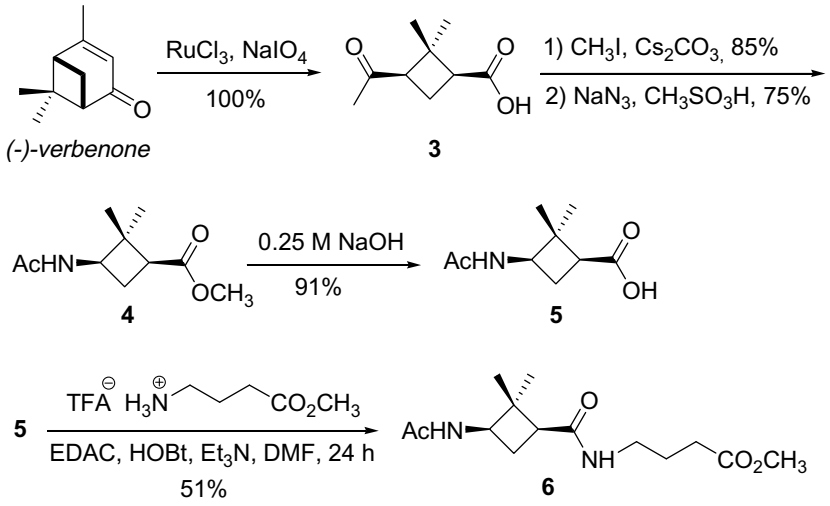


Scheme 1.

residue and a flexible segment proceeding from GABA. This product was studied by ^{1}H NMR to establish its ability to fold in solution by means of intramolecular hydrogen-bond formation.

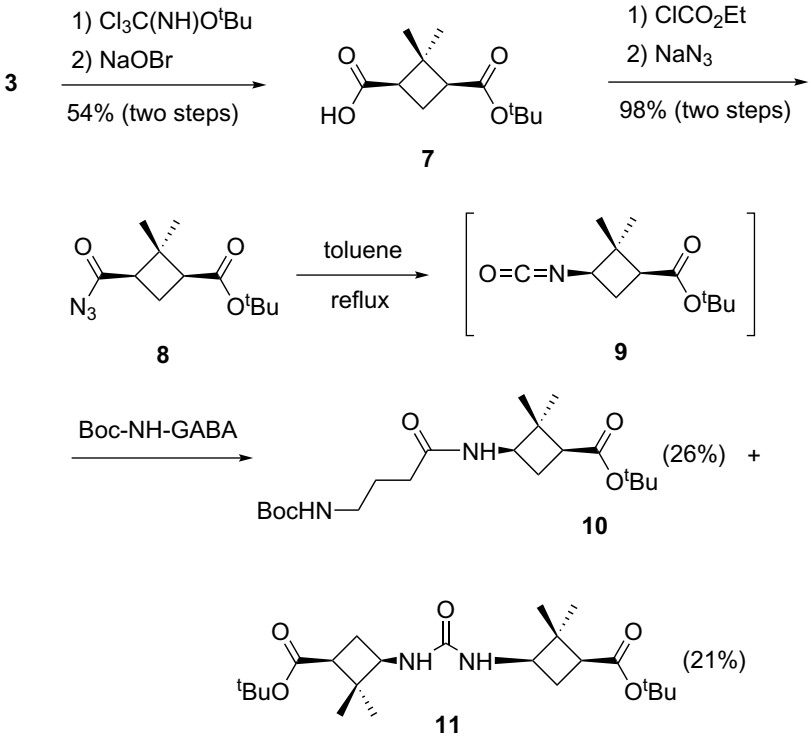
The temperature coefficients for both the N*H* protons were determined between 233 and 308 K and showed values of $\Delta\delta/\Delta T = -5.9$ (acetamide) and -4.5 (peptide amide) ppb/K,[7] which appear not to be compatible with the presence of intramolecular hydrogen bonds. We can assume, therefore, that dipeptide **6** adopts an extended conformation in solution, similar to the peptide surrogates **1** and **2** in the solid state, which were described by Burgess.

Next, we considered the incorporation of a second cyclobutane residue to introduce rigidity in the molecule but a difficulty arose from the fact that it was not possible to hydrolyze acetamide **4** without concomitant deprotection of the carboxylic acid. Thus, finding alternative synthetic methodologies emerged as a crucial goal. Previously, to prepare highly rigid bis(cyclobutane) γ-peptides derived from 2-aminocyclobutane-1-carboxylic acid in our laboratory, we performed the addition of a carboxylic acid to the isocyanate resulting from the Curtius rearrangement of an acyl azide.[8] This protocol afforded dimers in good yields and made the synthetic sequence shorter when compared to the classical coupling of an acid with an amine. We chose the reaction between easily available Boc-NH-GABA[9] and isocyanante **9** as a model to study the feasibility of the method when applied to 2,2-dimethylcyclobutane derivatives. For this purpose, half-ester **7**, previously prepared in our laboratory as depicted in Scheme 2,[10] was reacted with ethyl chloroformate followed by the treatment with sodium azide to produce acyl-azide **8** in 98% for two steps. The treatment of an equimolar mixture of **8** and Boc-NH-GABA in boiling anhydrous toluene gave dipeptide **10** in 26% yield. The reaction was monitored by IR following the disappearance of the signal corresponding to the acyl azide at 2136 cm^{-1} and the formation of the isocyanate by the new signal at 2260 cm^{-1} that, in turn, disappeared upon completion (ca. 5 h). From this reaction, urea **11** was also obtained as a by-product, in 21% yield. The formation of ureas had been observed in the reactions involving the β-series and can be attributable to the presence of traces of water.[7] The ratio of urea increases with the steric hindrance of the isocyanate structural surroundings that makes it difficult and, consequently, retards the carboxylate addition, which competes with rapid water addition.

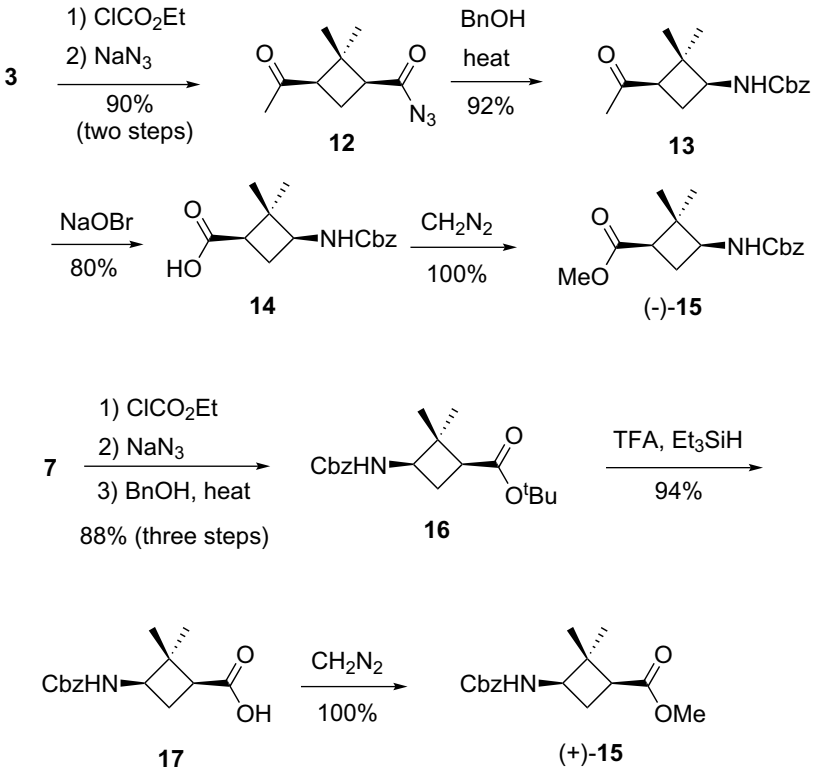
Owing to this result, we thought that the preparation of a bis(cyclobutane) dipeptide using this protocol would not be successful. Therefore, we decided to prepare the orthogonally protected amino acid monomers and to synthesize the target dipeptides through the classic peptide coupling methods. Thus, acid **3** was converted into acyl azide **12** (Scheme 3), which was submitted to a Curtius rearrangement in the presence of benzyl alcohol to produce carbamate **13**. Lieben degradation of the methyl ketone followed by the methylation of the resultant acid **14** led to completely protected γ-amino acid (−)-**15** in 66% overall yield from **3**, with mp 93–95 °C and $[\alpha]_D = -36$ (*c* 4.0, CH_2Cl_2).

Alternatively, half-ester **7** was converted into the amino-acid derivative **16** whose configuration is opposite to (−)-**15** (Scheme 3). Nevertheless, this compound was transformed into enantiomer (+)-**15** to verify that the stereochemical integrity of these molecules was preserved throughout the synthetic sequence. Thus, the *tert*-butyl ester was submitted to the action of trifluoroacetic acid in the presence of triethylsilane and the resulting carboxylic acid **17** was methylated with diazomethane to give (+)-**15** in 45% overall yield from **3**, with mp 94–95 °C and $[\alpha]_D = +34$ (*c* 3.1, CH_2Cl_2). The ^{1}H NMR spectra of both the enantiomers were superimposable proving that epimerization did not occur.

Once these compounds were synthesized, carboxylic acid **17** was coupled with amine **18** (Scheme 4) to provide, after seven days, bis(cyclobutane) γ-dipeptide **19** in 67% yield. The high rigidity and steric hindrance of the cyclobutane residues resulted in long reaction times to produce peptides

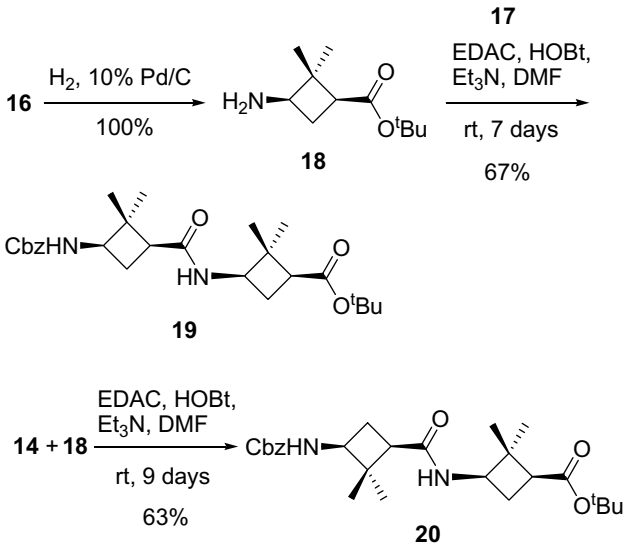


Scheme 2.



Scheme 3.

efficiently. Even longer reaction times (nine days) were needed for coupling amine **18** with carboxylic acid **14** affording γ-dipeptide **20**, which is the diastereomer of **19**, in 63% yield.



Scheme 4.

3. Conclusion

We have herein provided an efficient methodology for the preparation of enantiomeric cyclobutane γ-amino acids and their incorporation into different types of γ-peptides with modulated rigidity, from extended GABA derivatives to presumably more rigid bis(cyclobutane) γ-peptides. In particular, poly(cyclobutane) γ-peptides, a new class of γ-oligomers, appear as promising scaffolds to induce a variety of foldings and, perhaps, self-aggregation. Active investigations are being carried out in our laboratory to study the secondary and tertiary structures of these oligomers.

4. Experimental

4.1. (1*S*,3*R*)-3-Acetamido-2,2-dimethylcyclobutane-1-carboxylic acid methyl ester 4

A mixture containing (−)-*cis*-pinononic acid[11] (4.8 g, 28.2 mmol), cesium carbonate (11.0 g, 33.8 mmol) and 2.1 mL of methyl iodide in dry DMF (65 mL) was stirred at room temperature for 18 h. Ethyl acetate (50 mL) was then added and the resultant solution was washed with saturated aqueous sodium bicarbonate. The organic liquors were dried over magnesium sulfate and the solvent was evaporated under vacuo to provide (−)-*cis*-pinononic acid methyl ester[11] (4.5 g, 85% yield). To a solution of this ester (2.0 g, 11 mmol) in monoglyme (25 mL), cooled at −40 °C, methanesulfonic acid (14 mL) and sodium azide (2.1 g) were subsequently added. The mixture was stirred at −40 °C for 15 min and at room temperature for 3 days. Then, 40% aqueous ammonia was added to reach pH 8–9 and volatiles were removed at reduced pressure. The residue was poured into saturated aqueous sodium chloride and extracted with dichloromethane (4 × 20 mL). The organic extracts were dried over magnesium sulfate and the solvent was evaporated to afford an orange solid, which was crystallized to afford pure **4** (1.75 g, 80% yield). $[\alpha]_D = +111$ (*c* 2.9, CH_2Cl_2). Mp 127–129 °C (EtOAc–pentane). IR: 3283, 2957, 1697, 1636, 1558, 1458, 1294, 1191 cm^{-1}. ^1H NMR ($CDCl_3$): 0.90 (s, 3H), 1.29 (s, 3H), 1.9 (s, 3H), 2.07 (dt, $J = 12$, 10 Hz, 1H), 2.33 (dt, $^3J = 12$, 8 Hz, 1H), 2.60 (dd, $J = 10$, 8 Hz, 1H), 3.66 (s, 3H), 4.12 (m, 1H), 5.72 (br s, NH). ^{13}C NMR ($CDCl_3$): 17.57, 23.55, 26.52, 29.31, 43.56, 46.31, 50.30, 51.88, 170.28, 173.76. HRMS: calcd for $C_{10}H_{17}NO_3Na$, M+Na: 222.1101. Found: 222.1111.

4.2. (1*S*,3*R*)-3-Acetamido-2,2-dimethylcyclobutane-1-carboxylic acid 5

To an ice-cooled solution of ester **4** (1.0 g, 5 mmol) in 1:10 THF–water (88 mL), 0.25 M sodium hydroxide (10 mmol) was added and the resultant mixture was stirred for 2 h. (Reaction progress was monitored by TLC). The reaction mixture was washed with dichloromethane (20 mL), and 5% HCl was added to the aqueous phase to reach pH 2. The acid solution was extracted with ethyl acetate (4 × 50 mL) and dried over magnesium sulfate. Solvent was removed at reduced pressure to afford crude **5**, which was purified by crystallization (670 mg, 72% yield). $[\alpha]_D = +105$ (*c* 2.1, MeOH). Mp 223–225 °C (EtOAc–pentane). {Lit.[6]: $[\alpha]_D = +198.3$ (*c* 0.5, MeOH), mp 226–228 °C.} IR: 3331, 2952, 1697, 1653, 1554, 1425, 1373, 1190 cm^{-1}. ^1H NMR (methanol-d_4): 0.92 (s, 3H), 1.25 (s, 3H), 1.93 (s, 3H), 2.20 (m, 1H), 2.6 (m, 1H), 4.06 (m, 1H), 8.1 (br s, 1H). ^{13}C NMR (methanol-d_4): 17.43, 22.71, 25.09, 29.24, 42.56, 45.88, 49.38, 169.28, 173.85. HRMS: calcd for $C_9H_{15}NO_3Na$, M+Na: 208.0944. Found: 208.0946.

4.3. Methyl 4-[(1′*S*,3′*R*)-3′-acetamido-2′,2′-dimethylcyclobutane-1′-carboxamido]-butanoate 6

A mixture containing acid **5** (386 mg, 2.85), EDAC (1.8 g, 5.4 mmol), and triethylamine (0.9 mL, 5.4 mmol) in dry DMF (15 mL) was stirred for 40 min and then GABA-OMe triflate (950 mg, 4.0 mmol) in dry DMF (15 mL) was added. After stirring at room temperature for 24 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 (1:1 ethyl acetate–hexane) and subsequent crystallization to afford pure **6** (393 mg, 51% yield). $[\alpha]_D = +50$ (*c* 0.5, CH_2Cl_2). Mp 92–93 °C (EtOAc). IR: 3295, 2959, 1731, 1633, 1550 cm^{-1}. ^1H NMR ($CDCl_3$): 0.914 (s, 3H), 1.33 (s, 3H), 1.9 (m, 2H), 2.02 (s, 3H), 2.13 (m, 1H), 2.37 (complex absorption, 4H), 3.33 (m, 2H), 3.71 (s, 3H), 3.15 (m, 1H), 5.67 (t, 1H), 6.12 (d, $J = 6$ Hz, 1H). ^{13}C NMR ($CDCl_3$): 17.29, 23.23, 24.68, 25.9, 29.40, 31.52, 39.14, 44.76, 45.86, 50.41, 51.67, 169.94, 172.17, 173.89. HRMS: calcd for $C_{14}H_{24}N_2NaO_4$, M+Na: 307.1628. Found: 307.1616. Anal. Calcd for: C, 59.13; H, 8.51; N, 9.85. Found: C, 58.24; H, 9.05; N, 9.65.

4.4. *tert*-Butyl (1*S*,3*R*)-3-azidocarbonyl-2,2-dimethylcyclobutane-1-carboxylate 8

To an ice-cooled solution of half-ester **7**, prepared according to Ref. 3, (300 mg, 1.3 mmol) in dry acetone, triethylamine (0.29 mL, 2.0 mmol) and ethyl chloroformate (0.2 mL, 2.0 mmol) were subsequently added and the mixture was stirred at 0 °C for 3 h. Then sodium azide (145 mg, 2.2 mmol) in 5 mL of water was added and the resultant solution was stirred at room temperature for 1.5 h. The reaction mixture was extracted with dichloromethane (4 × 15 mL), and the organic extracts were dried over magnesium sulfate. Solvents were removed at reduced pressure to give acyl azide **8** as an oil (323 mg, 98% yield), which was characterized by their spectroscopic data and used in the next step without further purification. IR: 2962, 2136, 1722, 1459, 1333, 1139 cm^{-1}. ^1H NMR (acetone-d_6): 1.29 (s, 3H), 1.35 (s, 3H), 1.45 (s, 9H), 1.93 (m, 1H), 2.49 (m, 1H), 2.87 (complex absorption, 2H). ^{13}C NMR (acetone-d_6): 18.06, 20.11, 27.3, 30.03, 45.11, 46.25, 47.58, 80.20, 171.20, 179.53.

4.5. Dipeptide 10 and urea 11

Triethylamine (0.4 mL, 1.7 mmol) was added to a solution containing Boc-NH-GABA (350 mg, 1.7 mmol) in 3 mL of anhydrous toluene. After stirring at room temperature for 15 min, acyl azide **8** (290 mg, 1.1 mmol) in toluene (3 mL) was added and the mixture was heated at reflux for 5 h (the reaction progress was monitored by IR following the signals for the acyl azide at 2136 cm^{-1} and the isocyanate at 2260 cm^{-1}). After the elimination of toluene at reduced pressure, the residue was dissolved in ethyl acetate (15 mL) and the solution was washed with saturated aqueous sodium bicarbonate (4 × 5 mL) and dried over magnesium sulfate. Solvent was removed and the residue was chromatographed on silica gel (1:1 ethyl acetate–hexane) to afford dipeptide **10** (85 mg, 26% yield) and urea **11** (90 mg, 21% yield). Dipeptide **10**: $[\alpha]_D = +98$ (*c* 2.75, CH_2Cl_2). Mp 88–90 °C (hexane). IR: 3309, 2930, 1712, 1647, 1523 cm^{-1}. ^1H NMR ($CDCl_3$): 0.90 (s, 3H), 1.25 (s, 3H), 1.4 (s, 18H), 1.82 (m, 2H), 1.95 (m, 1H), 2.2 (m, 3H), 2.49 (t, $J = 7$, 9.5 Hz, 1H), 3.03 (m, 2H), 3.15 (m, 1H), 4.05 (dd, $J = 8.5$, 17 Hz, 1H), 4.97 (m, 1H), 6.56 (d, $J = 8.5$ Hz, 1H). ^{13}C NMR ($CDCl_3$): 17.40, 26.21, 25.9, 28.6, 28.8, 29.35, 33.9, 40.28, 46.44, 50.27, 79.64, 80.83, 158.01, 172.62, 173.15. Anal. Calcd for $C_{20}H_{36}N_2O_5$: C, 62.47; H, 9.44; N, 7.29. Found: C, 62.70; H, 9.66; N, 7.26. Urea **11**: $[\alpha]_D = +56$ (*c* 0.63, CH_2Cl_2). Mp 210–211 °C (ether–pentane). IR: 3320, 2959, 1723, 1647 cm^{-1}. ^1H NMR ($CDCl_3$): 0.92 (s, 6H), 1.30 (s, 6H), 1.46 (s, 18H), 1.95 (dd, $J = 9$, 22 Hz, 2H), 2.3 (m, 2H), 2.5 (m, 2H), 3.91 (t, $J = 9$, 18 Hz, 2H), 4.64 (br s, 1H). ^{13}C NMR ($CDCl_3$): 17.47, 27.11, 28.92, 29.72, 43.9, 46.59, 80.93. HRMS: calcd for $C_{23}H_{40}N_2O_5Na$, M+Na: 447.2829. Found: 447.2841.

4.6. (1*R*,3*S*)-3-Azidocarbonyl-2,2-dimethylcyclobutyl methyl ketone 12

This azide was prepared in 90% yield according to the procedure described above for **8**. IR: 2957, 2134, 1703, 1523, 1354, 1177 cm^{-1}. ^1H NMR (acetone-d_6): 0.92 (s, 3H), 1.47 (s, 3H), 2.05 (s, 3H), 2.57 (dd, $J = 8.75$ Hz, $J' = 20.5$ Hz, 1H), 2.89 (complex absorption, 2H), 3.1 (dd, $J = 8$ Hz, $J' = 11.25$ Hz, 1H). ^{13}C NMR (acetone-d_6): 16.25, 27.4, 27.9, 30.3, 45.46, 46.69, 53.82, 179.1.

4.7. Benzyl (1*S*,3*R*)-3-acetyl-2,2-dimethylcyclobutyl-1-carbamate 13

A solution of **12** (310 mg, 1.6 mmol) and benzyl alcohol (0.4 mL, 3.3 mmol) in toluene (9 mL) was heated to reflux for 3.5 h. Toluene was removed at a reduced pressure and then excess benzyl alcohol was eliminated by liophilization. The residue was chromatographed on silica gel (1:1 to 2:1 ethyl acetate–hexane) to afford carbamate **13** (402 mg, 92% yield). $[\alpha]_D = -82$ (*c* 0.51, CH_2Cl_2). Mp 78–81 °C (ether–pentane). IR: 3386, 2957, 1701, 1683 cm^{-1}. ^1H NMR ($CDCl_3$): 0.84 (s, 3H), 1.41 (s, 3H), 2.08 (s, 3H), 2.1 (m, 2H), 2.75 (dd, $J = 4.25$ Hz, $J' = 6.5$ Hz, 1H), 3.93 (m, 1H), 4.82 (complex absorption, 1H), 5.1 (dd, $J = 6.5$ Hz, $J' = 11$ Hz, 2H), 7.38 (complex absorption, 5H). ^{13}C NMR ($CDCl_3$): 16.42, 24.84, 28.98, 30.30, 46.49, 50.69, 51.30, 66.78, 128.13, 128.18, 128.55, 136.32, 155.96, 206.79. HRMS: calcd for ($C_{16}H_{21}NNaO_3$, M+Na): 298.1414. Experimental: 298.1417.

4.8. Benzyl (1*S*,3*R*)-3-methoxycarbonyl-2,2-dimethylcyclobutyl-1-carbamate (−)-15

An ice-cooled solution of sodium hypobromite [prepared from bromine (2 mL, 6.3 mmol) and sodium hydroxide (5.5 g, 137 mmol)] in 75 mL of water was added to a solution of ketone **13** (1.2 g, 4.5 mmol) in 3:1 dioxane–water, previously cooled at −5 °C. The mixture was diluted with further dioxane (12 mL) and stirred at −5 °C for 5 h. Then, the reaction mixture was washed with dichloromethane (2 × 50 mL), treated with sodium sulfite and, finally, 5% HCl was added to reach pH 2–3. The acid solution was extracted with ethyl acetate (4 × 50 mL) and the organic extracts were dried over magnesium sulfate. The solvent was removed to afford acid **14** (1 g, 80% yield), which was identified by its ^1H and ^{13}C NMR spectra and used in the next steps without further purification. ^1H NMR ($CDCl_3$): 0.99 (s, 3H), 1.35 (s, 3H), 2.06 (m, 1H), 2.33 (m, 1H), 2.58 (m, 1H), 3.94 (m, 1H), 5.11 (complex absorption, 3H), 7.37 (complex absorption, 5H), 10.15 (br s, 1H). ^{13}C NMR (methanol-d_4): 15.68, 25.75, 27.58, 42.13, 45.65, 49.75, 65.46, 127.09, 127.30, 127.81, 158.36, 174.35.

This acid was treated with an excess of diazomethane, as a dichloromethane solution, to quantitatively afford ester (−)-**15**. $[\alpha]_D = +36$ (*c* 4.05, CH_2Cl_2). Mp 93–95 °C (ether–pentane). IR: 3331, 2956, 1725, 1686 cm^{-1}. ^1H NMR ($CDCl_3$): 0.90 (s, 3H), 1.29 (s, 3H), 2.05 (m, 1H), 2.36 (m, 1H), 2.57 (dd, $J = 8$ Hz, $J' = 9.75$ Hz, 1H), 3.67 (s, 3H), 3.92 (dd, $J = 8$ Hz, $J' = 17.25$ Hz, 1H), 4.91 (d,$J = 11.75$ Hz, 1H), 5.05 (d, $J = 19$ Hz, 1H), 5.12 (d, $J = 20.25$ Hz, 1H), 7.36 (complex absorption, 5H). ^{13}C NMR ($CDCl_3$): 16.68, 26.41, 28.48, 42.62, 45.81, 51.31, 66.57, 76.96, 127.93, 128.57, 136.014, 155.66, 172.57. Anal. Calcd for $C_{13}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.72; H, 7.30; N, 5.16.

4.9. Benzyl (1*R*,3*S*)-3-*tert*-butoxycarbonyl-2,2-dimethyl-cyclobutyl-1-carbamate 16

Following similar procedures than those described above for the synthesis of acyl azide **8** and carbamate **13** through a Curtius rearrangement in the presence of benzyl alcohol, respectively, compound **6** was prepared in 88% overall yield for the three steps. $[\alpha]_D = +31$ (*c* 0.7, CH_2Cl_2). Mp 92–94 °C (ether–pentane). IR: 3351, 2925, 1710, 1697 cm^{-1}. ^1H NMR ($CDCl_3$): 0.95 (s, 3H), 1.30 (s, 3H), 1.46 (s, 9H), 2.02 (dd, $J = 9.5$ Hz, $J' = 18$ Hz), 2.31 (a.c, 1H), 2.51 (dd, $J = 6.75$ Hz, $J' = 9.5$ Hz), 3.9 (dd, $J = 9.5$ Hz, $J' = 18$ Hz, 1H), 4.9 (d, $J = 9.5$ Hz, 1H), 5.1 (d, $J = 21$ Hz, 1H), 5.13 (d, $J = 21$ Hz, 1H), 7.37 (complex absorption, 5H). ^{13}C NMR ($CDCl_3$): 16.92, 26.7, 28.32, 29.96, 43.86, 45.98, 51.49, 66.79, 80.55, 128.19, 128.57, 155.85, 171.50. Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.43; H, 8.19; N, 4.27.

4.10. Benzyl (1*R*,3*S*)-3-methoxycarbonyl-2,2-dimethyl-cyclobutyl-1-carbamate (+)-15

A mixture containing compound **16** (700 mg, 2.1 mmol), trifluoroacetic acid (2.1 mL, 27.3 mmol) and triethylsilane (0.84 mL, 5.2 mmol) in anhydrous dichloromethane (6 mL) was stirred at room temperature for 2 h. The solvent was evaporated and the excess of trifluoroacetic acid was removed by liophilization affording acid **17** as a solid, which was identified by its ^1H NMR spectrum and used in the next steps without purification. ^1H NMR ($CDCl_3$): 0.99 (s, 3H), 1.35 (s, 3H), 2.06 (m, 1H), 2.33 (m, 1H), 2.58 (m, 1H), 3.94 (m, 1H), 5.11 (complex absorption, 3H), 7.37 (complex absorption, 5H), 10.15 (br s, 1H). This acid was methylated by the action of an excess of diazomethane as a dichloromethane solution to provide quantitatively (+)-**15**. $[\alpha]_D = +34$ (*c* 3.11, CH_2Cl_2). Mp 94–95 °C (ether–pentane). IR: 3331, 2956, 1725, 1686 cm^{-1}. ^1H NMR ($CDCl_3$): 0.90 (s, 3H), 1.29 (s, 3H), 2.05 (m, 1H), 2.36 (m, 1H), 2.57 (dd, $J = 8$ Hz, $J' = 9.75$ Hz, 1H), 3.67 (s, 3H), 3.92 (dd, $J = 8$ Hz, $J' = 17.25$ Hz, 1H), 4.91 (d, $J = 11.75$ Hz, 1H), 5.05 (d, $J = 19$ Hz, 1H), 5.12 (d, $J = 20.25$ Hz, 1H), 7.36 (complex absorption, 5H). ^{13}C NMR ($CDCl_3$): 16.68, 26.41, 28.48, 42.62, 45.81, 51.31, 66.57, 76.96, 127.93, 128.57, 136.014, 155.66, 172.57. Anal. Calcd for $C_{13}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 66.12; H, 7.34; N, 5.04.

4.11. *tert*-Butyl (1*S*,3*R*)-3-amino-2,2-dimethylcyclobutane-1-carboxylate 18

Carbamate **16** (700 mg, 2.1 mmol) in methanol (30 mL) was hydrogenated under 2 atm pressure in the presence of 10% Pd/C (147 mg) overnight. The reaction mixture was filtered through Celite and the solvent was removed under vacuo to provide quantitatively amine **18**, which was identified by its ^1H NMR and used in the coupling step without further purification. ^1H NMR ($CDCl_3$): 0.93 (s, 3H), 1.14 (s, 3H), 1.40 (s, 9H), 1.88 (m, 1H), 2.19 (m, 1H), 2.38 (m, 1H), 2.99 (dd, $J = 5.25$ Hz, $J' = 8.75$ Hz, 1H), 3.2 (br s, 2H).

4.12. Dipeptide 19

By using a similar procedure than that described above for the synthesis of **6**, dipeptide **19** was obtained after 7 days of reaction time in 67% yield. $[\alpha]_D = +30$ (*c* 0.7, CH_2Cl_2). Mp 229–231 °C (hexane). IR: 3330, 3321, 2959, 1726, 1694, 1659 cm^{-1}. ^1H NMR ($CDCl_3$): 0.91 (s, 3H), 1.31 (s, 3H), 1.47 (s, 9H), 1.93 (complex absorption, 2H), 2.30 (complex absorption, 3H), 2.6 (m, 1H), 3.9 (m, 1H), 4.1 (m, 1H), 5.13 (complex absorption, 3H), 5.37 (d, 1H), 7.37 (complex absorption, 5H). ^{13}C NMR ($CDCl_3$): 16.92, 16.99, 26.23, 26.42, 28.96, 28.97, 29.17, 44.03, 44.8, 45.34, 45.61, 49.97, 51.49, 66.77, 80.49, 128.11, 128.51, 156.00, 171.50, 172.30. Anal. Calcd for $C_{16}H_{38}N_2O_5$: C, 68.10; H, 8.35; N, 6.11. Found: C, 68.21; H, 7.98; N, 6.34.

4.13. Dipeptide 20

By using a similar procedure to that described above for the synthesis of **6**, dipeptide **20** was obtained after 9 days reaction time in 63% yield. $[\alpha]_D = +43$ (*c* 0.71, CH_2Cl_2). Mp 165–167 °C (hexane). IR: 3355, 3306, 2953, 1720, 1699, 1660 cm^{-1}. ^1H NMR ($CDCl_3$): 0.922 (s, 3H), 0.934 (s, 3H), 1.29 (s, 3H), 1.31 (s, 3H), 1.47 (s, 9H), 2.01 (complex absorption, 2H), 2.26 (complex absorption, 3H), 2.52 (m, 1H), 3.91 (m, 1H), 4.1 (m, 1H), 5.1 (complex absorption, 3H), 5.37 (complex absorption, 1H), 7.38 (complex absorption, 5H). ^{13}C NMR ($CDCl_3$): 16.76, 16.98, 26.26, 28.86, 28.23, 28.97, 29.15, 43.97, 44.05, 44.81, 45.020, 51.56, 51.64, 66.75, 80.62, 128.12, 128.55, 136.49, 155.96, 170.33, 172.33. HRMS: calcd for $C_{26}H_{38}N_2NaO_5$, M+Na: 481.2673. Experimental: 481.2659.

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