Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 2403–2405

TETRAHEDRON: *ASYMMETRY*

Stereodivergent syntheses of the first bis(cyclobutane) β-dipeptides

Sandra Izquierdo, Marta Martín-Vilà, Albertina G. Moglioni,† Vicenç Branchadell and Rosa M. Ortuño*

Departament de Química, Universitat Autònoma de Barcelona, 08193 Bellaterra, Barcelona, Spain

Received 26 September 2002; accepted 10 October 2002

Abstract—The efficient synthesis of methyl 2-benzyloxycarbonylamino-(1*S*,2*R*)-cyclobutane-1-carboxylate starting from 2-methoxycarbonyl-(1*R*,2*S*)-cyclobutane-1-carboxylic acid is described. This β-amino acid derivative is antipodal with respect to the (1*R*,2*S*)-compound that was previously synthesized in our laboratory from the same chiral hemi ester. In turn, these enantiomeric β-amino acids have been self-condensed and coupled with one another to provide, respectively, enantiomeric and diastereomeric bis(cyclobutane) β-dipeptides. These products are the first reported β-amino acid oligomers containing two directly linked cyclobutane residues.

β-Peptides have attracted the particular attention of scientists in recent years since their ability to produce secondary structures, i.e. helixes, turns, and sheets, was established.[1,2] In general, the number of residues required to form these structures in a β-peptide is lower than in a peptide formed from α-amino acids.[3] Another advantage is that their resistance to enzymatic hydrolysis is also enhanced with respect to the α-peptides.[1a,4] Therefore, these properties are being considered in order to develop new therapeutic agents.[5] Very recently, amphiphilic β-amino acid oligomers that mimic the properties of defence peptides have been designed and synthesized by the group of Gellman.[6] Their antibiotic activity against several bacterial species, some of them being resistant to common antibiotics, has been shown.

Regarding the peptides bearing carbocyclic moieties, it is noteworthy that, to the best of our knowledge, although studies on some cyclobutane α-amino acid oligomers have been reported[7] there are no precedents on cyclobutane β-peptides prior to our work.

Recently, we described the synthesis of an orthogonally protected cyclobutane β-amino acid, (−)-**2** (Scheme 1),[8,9] that was converted into the free acid (−)-**4** and condensed with one β-alanine residue to afford a β-dipeptide whose structural study showed a hairpin-like conformation in the solid state.[9] The starting material in that synthesis was hemi ester **1**, prepared through chemoenzymatic hydrolysis of the corresponding *meso*-dimethyl ester. In this way, amino acid derivative (−)-**2** was prepared in 91% e.e. as determined by HPLC using chiral stationary phases.

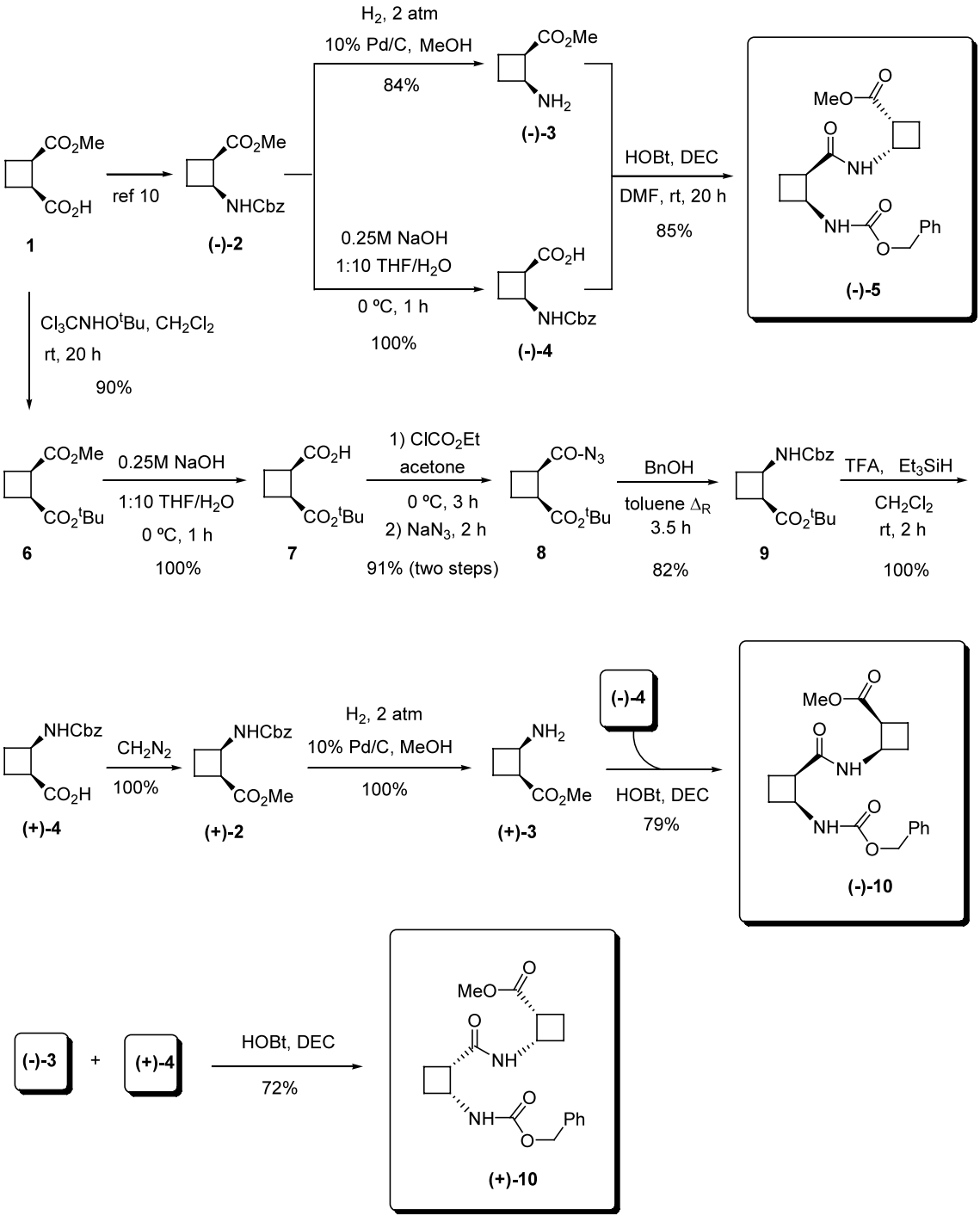
In this communication, we describe the synthesis of the enantiomeric cyclobutane β-amino acid derivative, (+)-**2**, from the same chiral precursor, **1** (Scheme 1). Self-coupling of the conveniently-protected enantiomeric amino acids, as well as one with another, provides a stereodivergent route to enantiomeric and diastereomeric bis(cyclobutane) β-dipeptides. We described herein dipeptides (−)-**5**, (+)- and (−)-**10**, which are representative examples of the firstly synthesized title compounds.

Acid (−)-**4** was prepared quantitatively by treatment of (−)-**2** with a 0.25 M aqueous NaOH solution in (1:10) THF/H_2O at 0°C for 1 h. Epimerisation of the stereogenic centres was avoided under such mild conditions.[10] This acid was condensed with amine (−)-**3**, resulting from hydrogenolysis of the benzyl carbamate (−)-**2**, in the presence of excess 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (DEC) as dehydrating agent and 1 equiv. of 1-hydroxybenzotriazole (HOBt) as a catalyst,

* Corresponding author. E-mail: rosa.ortuno@uab.es

† Present address: Departamento de Química Orgánica, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, 1113 Buenos Aires, Argentina.

0957-4166/02/$ - see front matter
PII: S0957-4166(02)00652-3



Scheme 1.

in anhydrous DMF at room temperature for 20 h. In this way, fully protected β-dipeptide (−)-**5** was obtained as a viscous oil, $[\alpha]_D$ −108.[11]

In order to synthesize the enantiomers (+)- and (−)-**10**, amino acid derivative (+)-**2** was prepared as follows. Hemi ester **1** was treated with *tert*-butyl trichloroacetimidine[12] in dichloromethane at room temperature for 20 h to afford diester **6** in 90% yield. The methyl ester was selectively hydrolysed as described above to produce the *tert*-butyl hemi ester **7** quantitatively. The acyl azide **8** was prepared in 91% yield by reaction of **7** with ethyl chloroformate in acetone at 0°C for 3 h, followed by treatment with sodium azide for 2 h. Subsequently, Curtius rearrangement was achieved by heating **8** for 3.5 h in the presence of excess benzyl alcohol in refluxing toluene solution to give the fully protected β-amino acid **9**. In order to verify the opposed chirality of this compound with respect to (−)-**2**, the *tert*-butyl ester was replaced by a methyl ester. For this purpose, **9** was made to react with trifluoroacetic acid and triethylsilane[13] in

dichloromethane at room temperature for 2 h to provide acid (+)-**4** quantitatively. Esterification with diazomethane gave the methyl ester (+)-**2**, $[\alpha]_D$ +83 (lit.[9] $[\alpha]_D$ −83 for the enantiomer) whose ^1H and ^{13}C NMR spectra were fairly superimposed on those of (−)-**2**. Hydrogenolysis of (+)-**2** gave the free amine (+)-**3** that was condensed with acid (−)-**4**, under the conditions described above, to produce β-dipeptide (−)-**10**, $[\alpha]_D$ −63, in 79% yield.

In the same way, amine (−)-**3** was coupled with acid (+)-**4** to furnish the enantiomeric β-dipeptide (+)-**10**, $[\alpha]_D$ +62, in 72% yield.

Thus, from a single chiral precursor, enantiomeric cyclobutane β-amino acids have been synthesized and, in turn, these compounds have been incorporated into enantiomeric or diastereomeric β-dipeptides containing two directly linked cyclobutane residues. These molecules are highly constrained and their structural and conformational study, by using experimental techniques and theoretical calculations, is under current investigation in our laboratory.

Acknowledgements

S.I. thanks the UAB for a predoctoral fellowship. Financial support from DGI (MCyT) through the project BQU2001-1907 is gratefully acknowledged.

References

1. For the pioneer works, see: (a) Seebach, D.; Overhand, M.; Kühnle, F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1996**, *79*, 913; (b) Appella, D.; Christianson, L. A.; Karle, I. L.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc*. **1996**, *118*, 13071.
2. DeGrado, W. F.; Schneider, J. P.; Hamuro, Y. *J. Pept. Res*. **1999**, *54*, 206.
3. Appella, D.; Christianson, L. A.; Klein, D. A.; Richards, M. R.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc*. **1996**, *121*, 7574.
4. (a) Hintermann, T.; Seebach, D. *Synlett* **1977**, 437; (b) Seebach, D.; Abele, S.; Schreiber, J. V.; Martinoni, B.; Nussbaum, A. K.; Schild, H.; Schulz, H.; Hennecke, H.; Woessner, R.; Bitsch, F. *Chimia* **1998**, *52*, 734.
5. For recent reviews, see: (a) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev*. **2001**, 3219; (b) Steer, D. L.; Lew, R. A.; Perlmutter, P.; Smith, A. I.; Aguilar, M.-I. *Curr. Med. Chem*. **2002**, *9*, 811.
6. Porter, E. A.; Weisblum, B.; Gellman, S. H. *J. Am. Chem. Soc*. **2002**, *124*, 7324.
7. Gatos, M.; Formaggio, F.; Crisma, M.; Toniolo, C.; Bonora, G. M.; Benedetti, Z.; Di Blasio, B.; Iacovino, R.; Santini, A.; Saviano, M.; Kamphuis, J. *J. Pept. Sci*. **1997**, *3*, 110.
8. Martín-Vilà, M.; Minguillón, C.; Ortuño, R. M. *Tetrahedron: Asymmetry* **1998**, *9*, 4291.
9. Martín-Vilà, M.; Muray, E.; Aguado, G. P.; Álvarez-Larena, A.; Branchadell, V.; Minguillón, C.; Giralt, E.; Ortuño, R. M. *Tetrahedron: Asymmetry* **2000**, *11*, 3569.
10. Niwayama, S. *J. Org. Chem*. **2000**, *65*, 5834.
11. All new products were identified and fully characterized by their spectroscopic data and physical constants. Selected data follow. Compound **5**: viscous oil, $[\alpha]_D$ −108 (*c* 1.79, MeOH); compound **6**: oil, $[\alpha]_D$ +4.0 (*c* 0.50, MeOH); compound **7**: oil, $[\alpha]_D$ +9.3 (*c* 1.08, MeOH); compound **9**: oil, $[\alpha]_D$ +41 (*c* 0.42, $CHCl_3$); compound (+)-**2**: oil, $[\alpha]_D$ +83 (*c* 0.70, $CHCl_3$) [lit.,[10] $[\alpha]_D$ −83 (*c* 2.05, $CHCl_3$)]; compound (+)-**10**: pasty solid, $[\alpha]_D$ +62 (*c* 0.44, MeOH); compound (−)-**10**: pasty solid, $[\alpha]_D$ −63 (*c* 1.59, MeOH).
12. Thierry, J.; Yue, C.; Potier, P. *Tetrahedron Lett*. **1998**, *39*, 1557.
13. Mehta, A.; Jaouhari, R.; Benson, T. J.; Douglas, K. T. *Tetrahedron Lett*. **1992**, *33*, 5441.