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Stereoselective synthesis of (−)-(1*R*,2*S*)-2-aminocyclobutane-1-carboxylic acid, a conformationally constrained β-amino acid

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Abstract

The title compound as well as some derivatives have been synthesized for the first time in optically active form by means of a chemoenzymatic transformation used to induce asymmetry in achiral precursors. The enantio- and diastereomeric purity has been determined by HPLC and NMR techniques.

β-Amino acids are a widespread class of non-proteinogenic amino acids found in nature in free form or as part of peptidic products with antibiotic, antifungal, cytotoxic and other pharmacological properties. Among the non-peptidic products the β-lactams are prominent, including antibiotics and other medicinal agents. β-Amino acids are also key structural components of important compounds such as the potent enzyme inhibitors statins and the anticancer agent taxol (Paclitaxel®).[1] These amino acids have recently been the subject of renewed interest since the pioneering works of Seebach[2] and Gellman[3] showing that polymers composed of β-amino acids (i.e. β-peptides), can fold into a stable helical secondary structure analogous to the α-helix in proteins.[4]

Conformationally constrained α- and β-amino acids have been incorporated into peptides to be used in structural and biomechanistic investigations as well as to obtain peptides with new or improved properties.[5] With this aim and as a part of our research program on the synthesis and structural study of carbocyclic amino acids and related peptide surrogates,[6] we envisaged the synthesis of cyclobutane β-amino acids as an example of rigid molecules.[7] Although several 2-aminocyclobutane-1-carboxylic acids are known to be of interest as biologically active compounds or antioxidants,[8] they have been synthesized only in racemic form. In this paper we report the first synthesis of the optically active parent compound **9**,[9] with *cis* stereochemistry, both in free form and conveniently protected for its latter incorporation into β-peptides. The enantio- and diastereomeric purity of the synthesized products has been determined by NMR and by HPLC using new non-commercial chiral phases.

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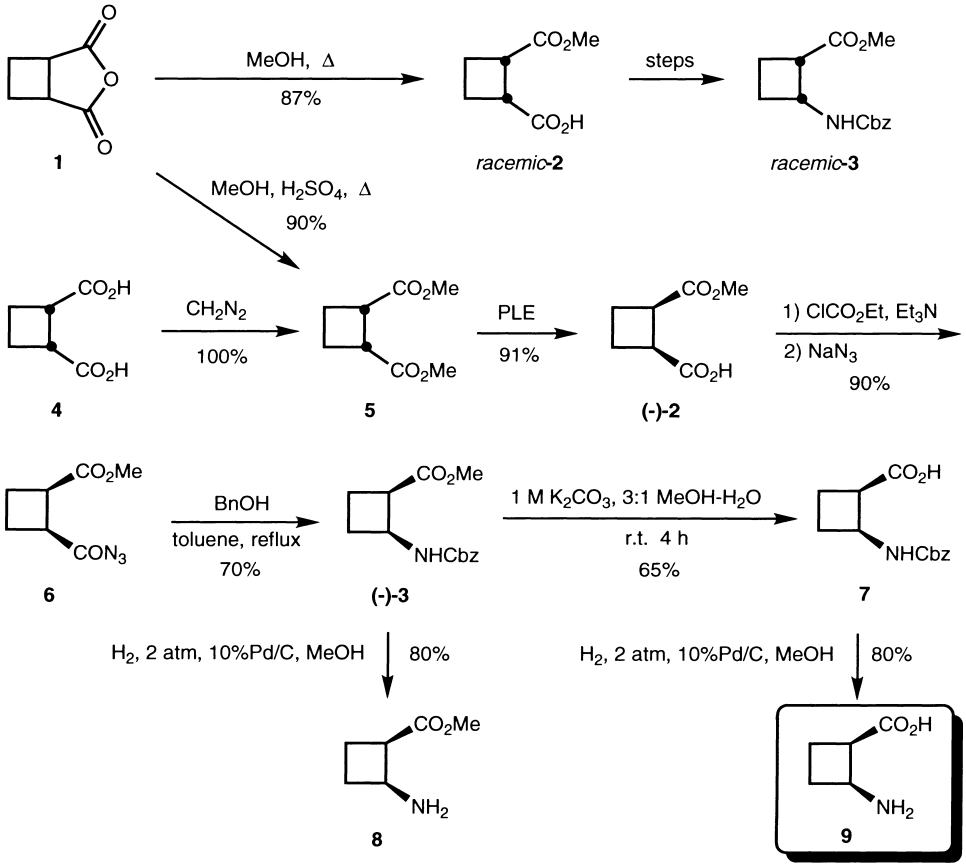
1. Synthesis of (−)-(1*R*,2*S*)-2-aminocyclobutane carboxylic acid 9 and related products

The synthesis of amino acid **9** and some derivatives was achieved by using a chemoenzymatic approach to induce asymmetry in achiral precursors. Selective manipulation of the functional groups allowed the free amino acid to be obtained, as well as the fully and the partially protected compounds **3**, **7** and **8**, respectively, shown in Scheme 1.



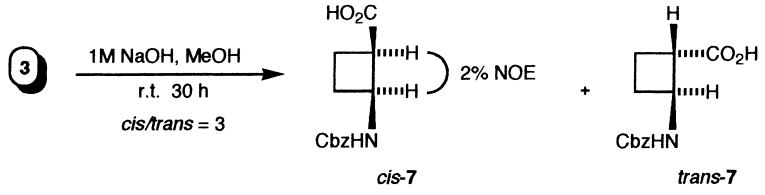
Scheme 1.

The *meso*-diester **5** was obtained from diazomethane-promoted methylation of the commercial diacid **4** or by Fisher esterification of the bicyclic anhydride **1**. Compound **1** is the [2+2] adduct of ethylene and maleic anhydride[10] and also provides the racemic hemiester **2** on heating in methanol without acid catalysis. In turn, optically active (−)-(1*R*,2*S*)-**2** was obtained through pig liver esterase-induced chemoselective hydrolysis of **5**, in >97% *ee* and 91% chemical yield following the procedure described by Jones et al.[11] In this work, the *ee* was determined by NMR.[11] The parallel syntheses of both racemic and (−)-(1*R*,2*S*)-**3** were accomplished from these two intermediates. Racemic **3** was used in this work as the reference standard in HPLC *ee* measurements, and (−)-**3** is the key intermediate to prepare compounds **7**, **8** and **9**.

The attempted one-pot Curtius rearrangement from the acid **2** using diphenylphosphoryl azide was unsuccessful. Therefore, the fully protected amino acid **3** was prepared stepwise by treatment of **2** with ethyl chloroformate and triethylamine, followed by reaction with sodium azide. The resultant acyl azide was decomposed by heating to reflux a toluene solution of **6** and benzylic alcohol, affording compound

3 in 63% yield from **2**. The product (−)-(1*R*,2*S*)-**3**[12] was determined to be 91% *ee*, by HPLC employing two different chiral phases (vide infra).[13]

Saponification of (−)-**3** to give the acid **7** was carried out by treatment with potassium carbonate in methanol:water at room temperature for 4 h. The reaction time was crucial to avoid epimerization and the use of stronger bases was precluded. Thus, a mixture of the acids **7** (*cis:trans* ratio of 3:1) resulted after stirring ester (−)-**3** in a methanolic 1 M NaOH solution at room temperature for 30 h (Scheme 2). The *cis* configuration of the major stereoisomer was confirmed by NOE experiments, allowing significant enhancements of the protons at the two stereogenic centers to be observed when, in separate experiments, each proton was selectively irradiated to presaturation.



Scheme 2.

The amine protection was removed by Pd/C catalyzed hydrogenation of **7** to furnish the free amino acid **9** as a hygroscopic solid, $[\alpha]_D$ −9.0, in 40% overall yield from **4**. The diastereomeric homogeneity of **9** was established by ^{13}C NMR.[12] Alternatively, catalytic hydrogenation of (−)-**3** yielded the amino ester **8**. Both compounds **7** and **8** are suitable for incorporation into peptides.

2. HPLC determinations

In order to develop an appropriate analytical method to assess the enantiomeric content of **3**, several chiral stationary phases based on immobilized polysaccharide derivatives[14] were tested. Heptane:2-propanol mixtures were used as the mobile phase. The low wavelength of maximal absorption (210 nm) and the low absorptivity of **3** prevented the use of other solvent systems. Refractive index detection was not possible because of the low response of the sample. Under these conditions,[15] a slight splitting of peaks was observed when using columns based on amylose 3,5-dimethylphenylcarbamate (α=1.08)[16] or chitosan 3,5-dichlorophenylcarbamate (α=1.17). Cellulose 3,5-dimethylphenylcarbamate and amylose 4-chlorophenylcarbamate were unable to distinguish between the two enantiomers of **3**. Resolved peaks were obtained with cellulose 3,5-dichlorophenylcarbamate (α=1.32), chitosan 3,5-dimethylphenylcarbamate (α=2.17) and amylose 3,5-dichlorophenylcarbamate (α=1.47). However, completely resolved peaks were only obtained with the latter two (R_s=3.07 and R_s=2.55, respectively) when using a heptane:2-propanol (95:5) mixture as the mobile phase (k_1'=1.90 and k_1'=5.33, respectively). When (−)-(1*R*,2*S*)-**3** was chromatographed on both columns, an enantiomeric excess of 91% was determined.

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12. All new products were fully characterized. Some selected data follow. Compound (−)-**2**, $[\alpha]_D$ −3.6 (*c* 2.36, $CHCl_3$) (Lit[11] $[\alpha]_D$ −3.0 (*c* 2.11, $CHCl_3$)). Compound (−)-**3**, $[\alpha]_D$ −83.2 (*c* 2.05, $CHCl_3$). Compound **7**, $[\alpha]_D$ −96.0 (*c* 1.06, methanol). Compound **8**, $[\alpha]_D$ −27.4 (*c* 3.57, methanol). Amino acid **9**, $[\alpha]_D$ −9.0 (*c* 1.55, H_2O); 62.5 MHz ^{13}C NMR (D_2O) δ 25.1, 28.0, 38.9, 41.8, 184.8 (only one set of signals was observed).
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15. Columns: 150×4.6 mm, flow rate: 1 ml/min, UV detection: 210 nm.
16. Selectivity factor, $\alpha = t_2 - t_0 / t_1 - t_0$; where t_i is the retention time for each enantiomer and t_0 the dead time of the column. Resolution factor, R_s, calculated as $R_s = 2\,(t_2 - t_1)/w_2 + w_1$; where w_i is the peak width at the baseline. An R_s value over 1.5 implies the complete resolution of peaks. Capacity factor for the first eluted enantiomer, $k_1' = t_1 - t_0 / t_0$