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Synthesis of (+)-(1*S*,2*R*) and (−)-(1*R*,2*S*)-2-aminocyclobutane-1-carboxylic acids

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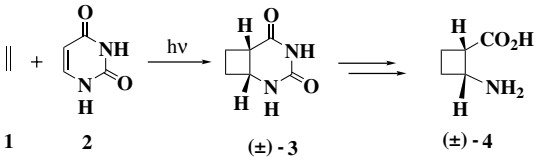
Abstract—(+)-(1*S*,2*R*) and (−)-(1*R*,2*S*)-2-aminocyclobutane-1-carboxylic acids have been prepared in >97% ee and in 33% and 20% overall yields starting from a single, chiral, bicyclic compound perceived as a chiral uracil equivalent. Construction of the cyclobutane ring is achieved via a [2+2] photocycloaddition reaction of this chiral precursor with ethylene.

The incorporation of conformationally constrained β-amino acids into peptides can dramatically influence their secondary and tertiary structures and biological activities.[1] In consequence, interest for the synthesis and study of alicyclic β-amino acids has rapidly increased.[2] Most efforts are devoted to cyclohexane,[3] cyclopentane[4] and cyclopropane[5] derivatives. Indeed, oligopeptide chains containing *trans*-2-aminocyclohexanecarboxylic acid have been shown to adopt 14-helical structures while those containing *trans*-2-aminocyclopentanecarboxylic acid prefer 12-helices.[3b] *cis*-Cyclopropane derivatives, too, give highly stable helical conformations in peptides.[5c] Moreover, some alicyclic β-amino acid derivatives display antifungal, antibiotic or analgesic activities.[2,6] Despite the clear potential of cyclobutane β-amino acid building blocks in this context, and some positive indications of their ability to impose secondary structure from preliminary studies,[7,8a] there are currently very few means of access to these compounds.

Only two enantioselective syntheses of *cis*-2-aminocyclobutane-1-carboxylic acid have been described so far: first by Martín-Vilà et al.[8] and then recently by Bolm et al.[9] Both procedures are based on an enantioselective *meso*-cyclobutane-1,2-dicarboxylic acid desymmetrization strategy, involving enzymatic hydrolysis of a diester in the first case and alkaloid-mediated opening of the anhydride in the second. Subsequent transformations led to the (−)-(1*R*,2*S*) antipode in each case. We present here an alternative strategy allowing rapid access to both enantiomers using simple and easily accessible materials.

We previously described the synthesis of racemic 2-aminocyclobutane-1-carboxylic acid **(±)-4**.[10] The strategy was based on a photochemical reaction of ethylene (**1**) with uracil (**2**) to give the cyclobutane adduct **(±)-3**, followed by controlled degradation of the heterocyclic ring. The target amino acid **(±)-4** was obtained with an overall yield of 52% (Scheme 1).

Our aim was to develop an enantioselective version of this synthesis. To this end, we decided to introduce a chiral auxiliary on the uracil ring in order to induce diastereochemical discrimination of cyclobutane adducts. There was also the possibility for diastereofacial selection during the photochemical [2+2] reaction,[11] although results with ethylene as one of the reaction components are highly variable.[12] We selected to use



1 2 (±)-3 (±)-4

Scheme 1.

Keywords: β-Amino acid; Cyclobutane; Stereoselective synthesis; [2+2] Photocycloaddition reaction.
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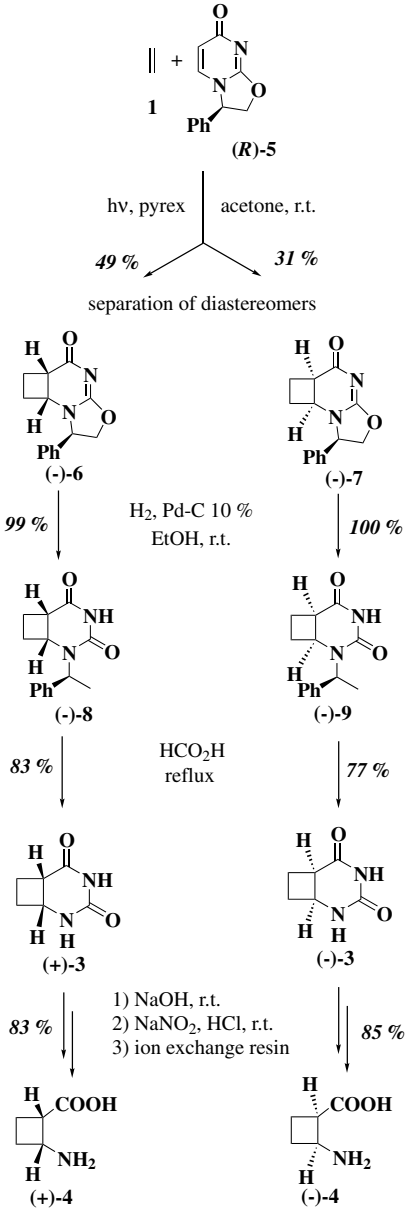
the *N*1-substituted uracil mimic **(*R*)-5**. This bicyclic compound was easily obtained in enantiomerically pure form in two steps from commercial (*R*)-phenylglycinol, essentially as described by Agami et al. for the *S*-enantiomer.[13]

Compound **(*R*)-5** was submitted to [2+2] photocycloaddition reaction conditions (Scheme 2). Ethylene (**1**) was bubbled through a solution of **(*R*)-5** in acetone at room temperature, which was irradiated with a 400 W medium-pressure mercury lamp fitted with a Pyrex filter during 2 h. In the event, the desired cyclobutane adduct was obtained as a mixture of two diastereoisomers. In conformity with our previous study involving uracil **2** (Scheme 1),[10] cyclobutane compounds **(−)-6** and **(−)-7** each had a *cis* configuration; a de of 14% was determined by integration of ^{1}H NMR data obtained on the crude material. Separation was easily achieved by column chromatography on silica gel, giving both **(−)-6** and **(−)-7** in stereochemically pure form in 49% and 31% yield, respectively. Subsequent transformations were carried out under identical conditions for each pure compound.



Scheme 2.

Selective opening of the five-membered rings of **(−)-6** and **(−)-7** was achieved by catalytic hydrogenation in the presence of palladium on charcoal, as described by Agami et al. for related heterocyclic structures.[13] Single diastereoisomers **(−)-8** and **(−)-9** were thus obtained in effectively quantitative yield.

Next, the α-methylbenzyl group was removed cleanly and efficiently with refluxing formic acid.[14] We thus obtained enantiomers **(+)-3** and **(−)-3** whose spectroscopic data were identical with those of our previous sample of **(±)-3**.[10] The two-step transformation of the heterocyclic ring—involving mild base hydrolysis followed by diazotization with 1 equiv of sodium nitrite in acidic medium—followed by purification on ion exchange resin proceeded in good yield without trace of epimerization and led to the target β-amino acids **(+)-4** and **(−)-4** in zwitterionic form (Scheme 2). NMR spectroscopic data[15] were comparable with those for racemic material[10] and with those reported by Bolm et al.[9] for **(−)-4**.

The overall yields following this short sequence were 33% and 20% for **(+)-4** and **(−)-4**, respectively, from **(*R*)-5**. Their respective optical rotations were +71 (*c* 0.88, H_2O) and −70 (*c* 1.03, H_2O). We determined an enantiomeric excess of >97% for each enantiomer **(+)-4** and **(−)-4** by HPLC on chiral column.[16] Since the ee of **(*R*)-5** was 98%, as determined by ^{1}H NMR with the chiral shift reagent Eu(hcf)$_3$, we can conclude that there was no loss of stereochemical fidelity during the synthesis.

The attribution of the 1*R*,2*S* absolute configuration of the β-amino acid **(−)-4** was made by correlation with the previous observations made by Martín-Vilà et al.[8] and Bolm et al.[9] The absolute configuration of **(+)-4** is therefore 1*S*,2*R*.

In summary, we have succeeded in synthesizing both (+)-(1*S*,2*R*) and (−)-(1*R*,2*S*)-2-aminocyclobutane-1-carboxylic acid **4** in five steps from **(*R*)-5**. Previous desymmetrization based stereoselective syntheses started with derivatives of *cis*-cyclobutane-1,2-dicarboxylic acid, which, although commercially available, is rather expensive. Our synthesis represents a useful complementary strategy and provides the first described access to the (+) antipode.[17] Millimolar-range quantities of the title β-amino acids are routinely accessible in this way and their incorporation into peptides is currently under study.

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15. Compounds **(+)-4** and **(−)-4**: ^{1}H NMR (400 MHz, D_2O, calibration on 1,4-dioxane at δ_H 3.75 ppm) δ 1.75 (m, 1H), 1.95 (m, 2H), 2.03 (m, 1H), 2.92 (m, 1H), 3.61 (q, 1H, $J = 6.8$ Hz); ^{13}C NMR (100 MHz, D_2O, calibration on 1,4-dioxane at δ_C 67.2 ppm) δ 21.2, 25.0, 41.3, 45.5, 181.0.
16. HPLC analysis was performed using a Waters 590 apparatus equipped with a Waters 484 UV detector and a Crownpak CR(+) column (0.4 × 15 cm) with the following conditions: perchloric acid solution (pH = 1) as mobile phase; $T = 4$ °C; $\lambda = 220$ nm; flow rate = 0.2 mL/min. Retention times: **(+)-4**: 12.20 min; **(−)-4**: 19.48 min.
17. It is also worth noting that this route incurs no difficulties related to the facile ring-opening propensity of the final products; see: Aitken, D. J.; Gauzy, C.; Pereira, E. *Tetrahedron Lett.* **2004**, *45*, 2359–2361.