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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.

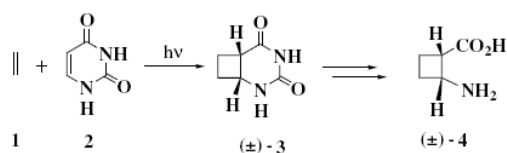
The incorporation of conformationally constrained  $\beta$ -amino acids into peptides can dramatically influence their secondary and tertiary structures and biological activities.<sup>1</sup> In consequence, interest for the synthesis and study of alicyclic  $\beta$ -amino acids has rapidly increased.<sup>2</sup> Most efforts are devoted to cyclohexane,<sup>3</sup> cyclopentane<sup>4</sup> and cyclopropane<sup>5</sup> 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.<sup>3b</sup> *cis*-Cyclopropane derivatives, too, give highly stable helical conformations in peptides.<sup>5c</sup> Moreover, some alicyclic  $\beta$ -amino acid derivatives display antifungal, antibiotic or analgesic activities.<sup>2,6</sup> Despite the clear potential of cyclobutane  $\beta$ -amino acid building blocks in this context, and some positive indications of their ability to impose secondary structure from preliminary studies,<sup>7,8a</sup> 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.<sup>8</sup> and then recently by Bolm et al.<sup>9</sup> 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 ( $\pm$ )-4.<sup>10</sup> The strategy was based on a photochemical reaction of ethylene (1) with uracil (2) to give the cyclobutane adduct ( $\pm$ )-3, followed by controlled degradation of the heterocyclic ring. The target amino acid ( $\pm$ )-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,<sup>11</sup> although results with ethylene as one of the reaction components are highly variable.<sup>12</sup> We selected to use



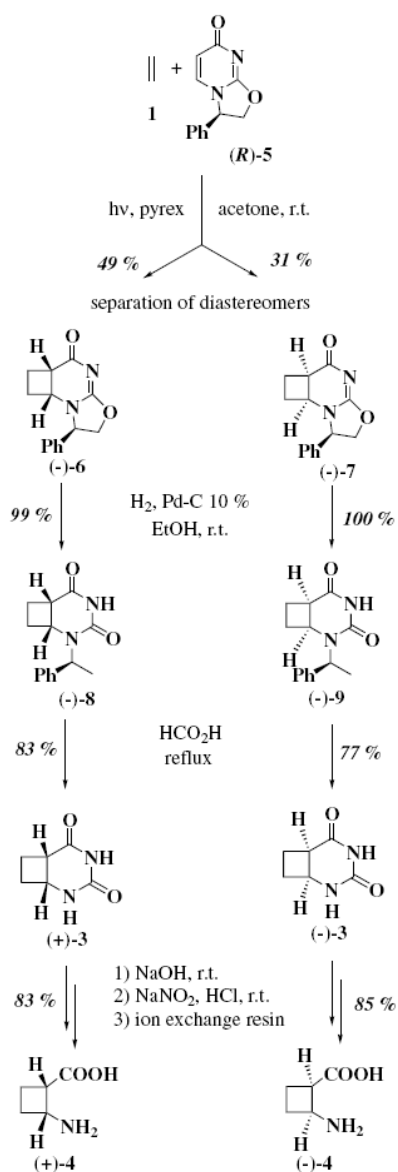
Scheme 1.

**Keywords:**  $\beta$ -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.<sup>13</sup>

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),<sup>10</sup> cyclobutane compounds (–)-**6** and (–)-**7** each had a *cis* configuration; a de of 14% was determined by integration of <sup>1</sup>H NMR data obtained on the crude material. Separation was easily achieved by



Scheme 2.

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.

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.<sup>13</sup> Single diastereoisomers (–)-**8** and (–)-**9** were thus obtained in effectively quantitative yield.

Next, the  $\alpha$ -methylbenzyl group was removed cleanly and efficiently with refluxing formic acid.<sup>14</sup> We thus obtained enantiomers (+)-**3** and (–)-**3** whose spectroscopic data were identical with those of our previous sample of ( $\pm$ )-**3**.<sup>10</sup> 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  $\beta$ -amino acids (+)-**4** and (–)-**4** in zwitterionic form (Scheme 2). NMR spectroscopic data<sup>15</sup> were comparable with those for racemic material<sup>10</sup> and with those reported by Bolm et al.<sup>9</sup> 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<sub>2</sub>O) and –70 (*c* 1.03, H<sub>2</sub>O). We determined an enantiomeric excess of >97% for each enantiomer (+)-**4** and (–)-**4** by HPLC on chiral column.<sup>16</sup> Since the ee of (*R*)-**5** was 98%, as determined by <sup>1</sup>H NMR with the chiral shift reagent Eu(hcf)<sub>3</sub>, 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  $\beta$ -amino acid (–)-**4** was made by correlation with the previous observations made by Martín-Vilà et al.<sup>8</sup> and Bolm et al.<sup>9</sup> 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.<sup>17</sup> Millimolar-range quantities of the title  $\beta$ -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**: <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O, calibration on 1,4-dioxane at δ<sub>H</sub> 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); <sup>13</sup>C NMR (100 MHz, D<sub>2</sub>O, calibration on 1,4-dioxane at δ<sub>C</sub> 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; λ = 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.