



**HAL**  
open science

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

Christine Gauzy, Elisabeth Pereira, Sophie Faure, David J Aitken

► **To cite this version:**

Christine Gauzy, Elisabeth Pereira, Sophie Faure, David J Aitken. Synthesis of (+)-(1S,2R) and (-)-(1R,2R)-2-aminocyclobutane-1-carboxylic acids. *Tetrahedron Letters*, 2004, 45, pp.7095-7097. 10.1016/j.tetlet.2004.07.110 . hal-00135859

**HAL Id: hal-00135859**

**<https://hal.science/hal-00135859v1>**

Submitted on 9 Mar 2007

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

Christine Gauzy, Elisabeth Pereira, Sophie Faure and David J. Aitken\*

Laboratoire SEESIB-CNRS, Département de Chimie, Université Blaise Pascal, Clermont-Ferrand II, 24 Avenue des Landais, 63177 Aubière cedex, France

**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.

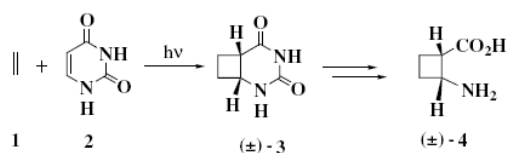
The incorporation of conformationally constrained  $\beta$ -amino acids into peptides can dramatically influence their secondary and tertiary structures and biological activities.<sup>1</sup> In consequence, interest for the synthesis and study of alicyclic  $\beta$ -amino acids has rapidly increased.<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



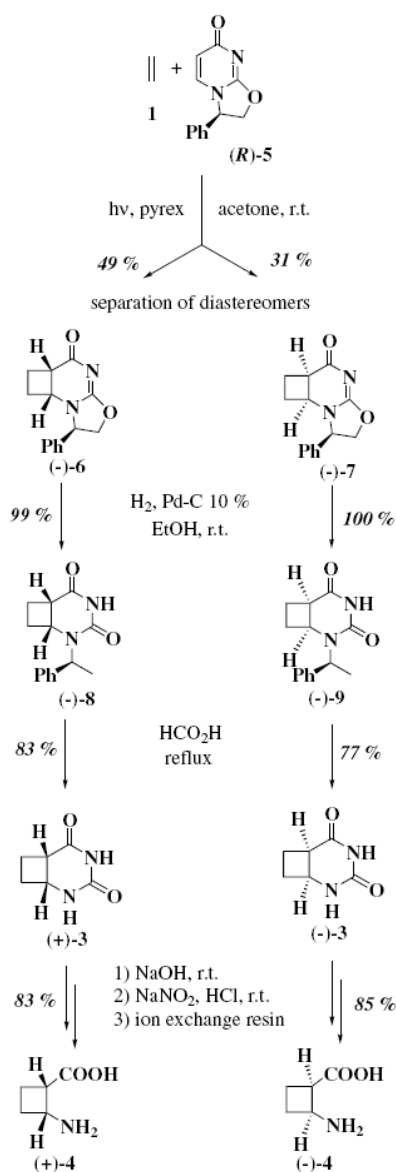
Scheme 1.

**Keywords:**  $\beta$ -Amino acid; Cyclobutane; Stereoselective synthesis; [2+2] Photocycloaddition reaction.

\* Corresponding author. Tel.: +33 4 73 40 71 84; fax: +33 4 73 40 77 17; e-mail: aitken@chimie.univ-bpclermont.fr

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.

#### Acknowledgements

We are grateful to the MENRT for a grant (to C.G.) and the CNRS for 'Jeune Equipe' (AIP) funding. We also thank undergraduate students E. Rossignol (Cler-

mont-Ferrand) and P. Ferchaud (Poitiers) for carrying out some initial experiments competently.

### References and notes

1. (a) North, M. *J. Pept. Sci.* **2000**, *6*, 301–313; (b) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219–3232.
2. Fülöp, F. *Chem. Rev.* **2001**, *101*, 2181–2204.
3. (a) Appella, D. H.; Christianson, L. A.; Karle, I. L.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1999**, *121*, 6206–6212; (b) Barechi, J. J., Jr.; Huang, X.; Appella, D. H.; Christianson, L.; Durell, S. R.; Gellman, S. H. *J. Am. Chem. Soc.* **2000**, *122*, 2711–2718; (c) Raguse, T. L.; Porter, E. A.; Weisblum, B.; Gellman, S. H. *J. Am. Chem. Soc.* **2002**, *124*, 12774–12785.
4. (a) Appella, D. H.; Christianson, L. A.; Klein, D. A.; Huang, X.; Barchi, J. J.; Powell, D. R.; Gellman, S. H. *Nature (London)* **1997**, *387*, 381–384; (b) Appella, D. H.; Christianson, L. A.; Klein, D. A.; Richards, M. R.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1999**, *121*, 7574–7581; (c) Fülöp, F. *Stud. Nat. Prod. Chem.* **2000**, *22*, 273–306.
5. (a) Hibbs, D. E.; Hursthouse, M. B.; Jones, I. G.; Jones, W.; Abdul Malik, K. M.; North, M. *Tetrahedron* **1997**, *53*, 17417–17424; (b) Gnad, F.; Reiser, O. *Chem. Rev.* **2003**, *103*, 1603–1623; (c) De Pol, S.; Zorn, C.; Klein, C. D.; Zerbe, O.; Reiser, O. *Angew. Chem., Int. Ed.* **2004**, *43*, 511–514.
6. Mittendorf, J.; Kunisch, F.; Matzke, M.; Militzer, H.-C.; Schmidt, A.; Schönfeld, W. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 433–436.
7. Izquierdo, S.; Martín-Vilà, M.; Moglioni, A. G.; Branchadell, V.; Ortuño, R. M. *Tetrahedron: Asymmetry* **2002**, *13*, 2403–2405.
8. (a) Martín-Vilà, M.; Muray, E.; Aguado, G. P.; Alvarez-Larena, A.; Branchadell, V.; Minguillón, C.; Giralt, E.; Ortuño, R. M. *Tetrahedron: Asymmetry* **2000**, *11*, 3569–3584; (b) Martín-Vilà, M.; Minguillón, C.; Ortuño, R. M. *Tetrahedron: Asymmetry* **1998**, *9*, 4291–4294.
9. Bolm, C.; Schiffrers, I.; Atodiresei, I.; Hackenberger, C. P. R. *Tetrahedron: Asymmetry* **2003**, *14*, 3455–3467.
10. Aitken, D. J.; Gauzy, C.; Pereira, E. *Tetrahedron Lett.* **2002**, *43*, 6177–6179.
11. Bach, T. *Synthesis* **1998**, 683–703.
12. (a) Meyers, A. I.; Fleming, S. A. *J. Am. Chem. Soc.* **1986**, *108*, 306–307; (b) Alibés, R.; Bourdelande, J. L.; Font, J.; Gregori, A.; Parella, T. *Tetrahedron* **1996**, *52*, 1267–1278; (c) Tsujishima, H.; Nakatani, K.; Shimamoto, K.; Shigeri, Y.; Yumoto, N.; Ohfune, Y. *Tetrahedron Lett.* **1998**, *39*, 1193–1196; (d) de March, P.; Figuerdo, M.; Font, J.; Raya, J. *Tetrahedron Lett.* **1999**, *40*, 2205–2208.
13. (a) Agami, C.; Dechoux, L.; Melaimi, M. *Org. Lett.* **2000**, *2*, 633–634; (b) Agami, C.; Cheramy, S.; Dechoux, L.; Melaimi, M. *Tetrahedron* **2001**, *57*, 195–200.
14. (a) Semple, J. E.; Wang, P. C.; Lysenko, Z.; Joullié, M. *J. Am. Chem. Soc.* **1980**, *102*, 7505–7510; (b) Davies, S. G.; Fenwick, D. R.; Ichihara, O. *Tetrahedron: Asymmetry* **1997**, *8*, 3387–3391; (c) Magnus, N. A.; Confalone, P. N.; Storace, L. *Tetrahedron Lett.* **2000**, *41*, 3015–3019.
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.