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A short synthesis of the *cis*-cyclobutane β-aminoacid skeleton using a [2+2] cycloaddition strategy

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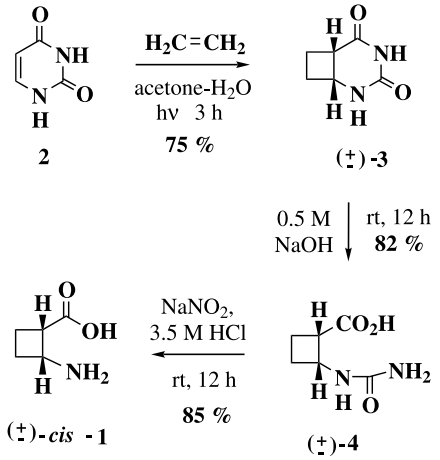
Abstract—A short synthesis of (±)-*cis*-2-amino-1-cyclobutanecarboxylic acid is described with an overall yield of 52%. The key step is the photochemical [2+2] cycloaddition reaction between ethylene and uracil.

β-Aminoacids and peptide structures which incorporate them are of considerable interest due to their unusual structures[1,2] and biological activities,[2] and there has been a corresponding interest in methods of synthesis of such compounds.[3] Conformationally constrained alicyclic β-aminoacids and β-peptides are of particular interest, and intensive studies have been carried out on cyclohexane,[4] cyclopentane,[2c,4a,5] cyclopropane[6] and other alicyclic derivatives.[7] In contrast, almost no work has been done on cyclobutane compounds.

Only two strategies have been reported for entry to the cyclobutane β-aminoacid skeleton. Kennewell et al. described the synthesis of racemic *cis*- and *trans*-2-amino-1-cyclobutanecarboxylic acid **1** from the corresponding cyclobutane-1,2-dicarboxylic acids by a series of selective transformations after chemical desymmetrization.[8] Recently, Ortuño's group adapted this strategy for the first enantioselective synthesis of the *cis*-(1*R*,2*S*) antipode of **1** using an esterase to carry out the enantioselective partial hydrolysis of the *meso*-diester.[9] In earlier work, Brannock et al.[10] synthesized a series of *N*,*N*-disubstituted cyclobutane β-aminoesters or nitriles by thermal cycloaddition between *N*,*N*-disubstituted enamines and acrylic esters or nitriles. These reactions worked well with highly substituted reagents, but had no apparent control of stereoselectivity.

We were interested in the [2+2] strategy, but prefered a disconnection in the alternative sense, so that one of the two olefins should supply both the amine and the acid functions. A cheap and readily available equivalent of such an olefin is uracil **2**; indeed, photochemical [2+2] cycloaddition reactions are known to provoke dimerization of pyrimidinedione-type DNA bases,[11] and several examples of cycloaddition reactions between uracil derivatives and alkenes have been described.[12] In this communication, we report the first application of this new approach for the preparation of the cyclobutane β-aminoacid system, in the short, efficient synthesis of *cis*-**1** (Scheme 1).

Ethylene was bubbled through a solution of uracil **2** in acetone–water (1:1) at room temperature which was irradiated with a 400 W medium-pressure mercury lamp fitted with a Pyrex filter. The expected cyclobutane



Scheme 1.

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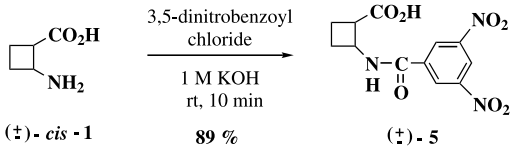
compound **3** was formed, accompanied by ethylene oligomers and small amounts of uracil photodimers,[13] and was isolated in 75% yield after washing with cyclohexane, then acetone, then rapid filtration through silica gel.[14] The second step consisted of the hydrolysis of the heterocyclic moiety of **3** by treatment with 0.5 M aqueous NaOH at room temperature.[15] After neutralization with H^+ cation exchange resin, the corresponding *N*-carbamoyl-β-aminoacid **4** was isolated directly as a single stereoisomer in 82% yield.[16]

Hydrolysis of a urea function generally calls for the use of strongly basic conditions, which was of some concern here, since Ortuño observed that derivatives of *cis*-**1** are prone to epimerization. In the event, the action of nitrous acid[17]—recently used by Azerad[18] in similar circumstances for decarbamoylation of epimerization-sensitive arylglycines—permitted the smooth transformation of **4** into the required target molecule *cis*-**1** which was isolated in zwitterionic form in 85% yield after passage through cation exchange resin.[19]

The *cis* relative configuration of the cyclobutane substituents was suggested at each step in the sequence by the observation of nuclear Overhouser effects between the H1 and H2 methine protons in NMR experiments (**3**, 9%; **4**, 10%; **1**, 8%). Since our ^1H and ^{13}C NMR data for *cis*-**1** were different from those presented in both previous publications,[9] we confirmed the structure by preparation of the 3,5-dinitrobenzamide **5** (89% yield; 6% NOE between H1 and H2; Scheme 2)[20] which gave the X-ray crystallographic structure shown in Fig. 1.[21]

This short and efficient synthesis (52% overall yield from readily available starting materials; no requirement for chromatographic separations at any stage) illustrates a useful strategy which should be of a general character. Development of the method for access to ring-substituted cyclobutane β-aminoacids (through use of other uracils and/or olefins) and its adaptation for enantioselective synthesis are currently in progress.



Scheme 2.

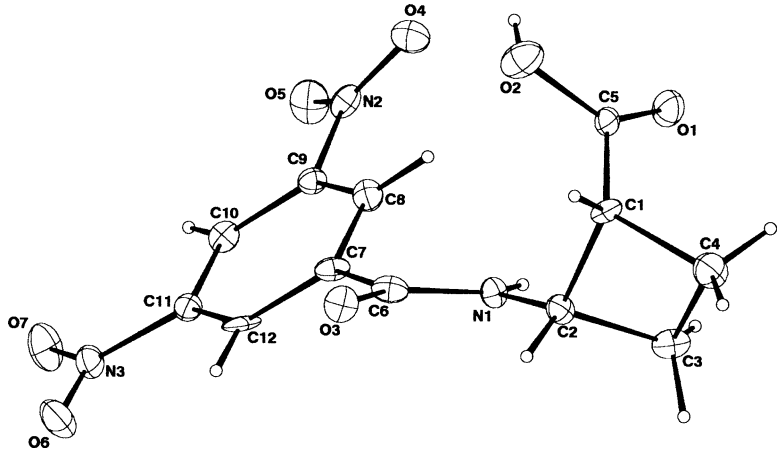


Figure 1. X-Ray crystallographic structure of derivative **5**.

Acknowledgements

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14. Compound **3**: mp 258–259°C (sublimes) (H_2O); CIMS m/z 141 $[MH]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 1.92 (m, 2H), 2.18 (m, 2H), 3.11 (m, 1H), 3.90 (m, 1H), 7.68 (s, 1H), 10.02 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.4, 30.6, 37.2, 44.8, 152.7, 173.3.
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16. Compound **4**: mp 187–189°C (H_2O); CIMS m/z 159 $[MH]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 1.79 (m, 2H), 2.06 (quint, $J=10.0$ Hz, 1H), 2.16 (m, 1H), 3.14 (m, 1H), 4.40 (quint, $J=8.8$ Hz, 1H), 5.55 (s, 2H), 6.19 (d, $J=9.2$ Hz, 1H), 12.1 (bs, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 17.4, 29.2, 44.9, 45.8, 157.4, 174.7.
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19. Compound *cis*-**1**: white solids, mp 128–130°C, decomposed on attempted recrystallization (lit.[8] mp 129–132°C); CIMS m/z 116 $[MH]^+$; ^1H NMR (400 MHz, D_2O) δ 2.05 (m, 1H), 2.24 (m, 2H), 2.36 (m, 1H), 3.24 (m, 1H), 3.92 (m, 1H); ^{13}C NMR (100 MHz, D_2O) δ 23.8, 27.7, 44.0, 48.2, 183.7.
20. Compound **5**: mp 220–222°C (H_2O); CIMS m/z $[310]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 1.98 (quint, $J=8.8$ Hz, 1H), 2.14 (m, 1H), 2.31 (m, 1H), 2.52 (m, 1H), 3.40 (m, 1H), 4.81 (quint, $J=8.3$ Hz, 1H), 9.00 (d, $J=1.8$ Hz, 1H), 9.10 (d, $J=1.8$ Hz, 2H), 9.42 (d, $J=7.3$ Hz, 1H), 12.15 (bs, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 18.0, 25.7, 44.8, 45.8, 120.9, 127.5, 136.7, 148.1, 161.6, 173.5.
21. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 183875.