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Rapid access to *cis*-cyclobutane γ-amino acids in enantiomerically pure form

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ABSTRACT

The (+)-(1*R*,2*S*) and (−)-(1*S*,2*R*) stereoisomers of 2-(aminomethyl)cyclobutane-1-carboxylic acid have been prepared using a short and efficient strategy, which employs the photochemical [2+2] cycloaddition reaction between ethylene and an unsaturated γ-lactam as the key step.

γ-Aminobutyric acid (GABA) plays a key role as a neurotransmitter in the mammalian central nervous system. A wide variety of derivatives of GABA have therefore been of interest to chemists and pharmacologists and some structural analogues are of significant therapeutic value.[1] Independently, in the rapidly developing area of foldamer science,[2] oligopeptides containing γ-amino acids have been shown to adopt well-defined conformations.[3–5] Following the lead from the related area of oligomers of cyclic β-amino acids,[6] peptides which incorporate cyclic γ-amino acids are now becoming a focus of attention due to the additional conformational restrictions which are imposed by the rigidified backbone. Recently, Gellman observed helical conformations in α/γ- and β/γ-peptides containing *cis*-cyclohexyl γ-amino acids,[4] while Smith reported a parallel sheet structure for trimers of a *trans*-cyclopropyl γ-amino acid.[5] Despite recent advances in general synthetic methods,[7] access to cyclic γ-amino acids in enantiomerically pure form remains something of a challenge.[8]

In order to expand the inventory of readily available backbone-restricted γ-amino acid building blocks, we sought an efficient route to the *cis*-cyclobutane γ-amino acid **1**. Only two previous syntheses of this compound in enantiomerically pure form have been described; they are lengthy (>8 steps)[9] or employ polymer supported enzymes and reagents leading to only one enantiomer.[10]

Inspired by recent successes in the synthesis of *cis*-cyclobutane β-amino acids,[11] we felt that a photochemical approach, schematised in Figure 1, represented an attractive alternative. There is some precedent for [2+2] photocycloaddition reactions of alkenes with unsaturated γ-lactams bearing substituents at ring carbons.[12] While diastereoselectivity in intermolecular [2+2] enone/alkene photocycloadditions is something of a hit-or-miss affair, notably with small unhindered alkenes such as ethylene, we reasoned that the presence of a chiral, non racemic, removable substituent on the ring nitrogen should in any case facilitate separation of diastereomers and thus provide a very rapid entry to the target structure.

Initial investigations were carried out to identify a convenient stereogenic nitrogen substituent for the 2-pyrrolinone core. A representative structure of each of three substituent types—acyl, oxyacyl and alkyl—was selected on the basis of its ready (commercial) availability (Scheme 1). The *N*-acyl and *N*-oxyacyl compounds, **3** and **4**, were each derived from 4-trimethylsilyloxy-2-pyrrolidinone **2**, which was prepared efficiently from β-hydroxy-GABA according to a literature procedure.[13] Reaction of **2** with the appropriate chiral acid chloride in basic conditions introduced the N-substituent, and acidic work-up hydrolysed the silyl ether. Straightforward dehydration using mesyl chloride and triethylamine provided **3** and **4** in 58 and 52% yields, respectively, for the three steps from **2**. The *N*-alkyl 2-pyrrolinone **5** was prepared in a single step (70% yield) from 2,5-dimethoxy-2,5-dihydrofuran and (*S*)-α-methylbenzylamine, using a minor adaptation of the literature procedure.[14]

Each of the 2-pyrrolinones **3**–**5** was irradiated for 90 min (400 W lamp, Pyrex filter) in acetone solution while ethylene was bubbled through the mixture (Scheme 2). In these conditions, the solvent is probably acting as a photosensitiser; reactions carried out using non-sensitising solvents (acetonitrile; CH_2Cl_2) gave much lower conversions. Results obtained in acetone are summarised in Table 1. In each case, the desired cyclobutane adducts **6**–**8** were formed in good yield, exclusively with a *cis*-configuration at the

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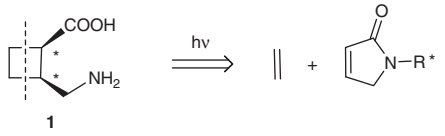
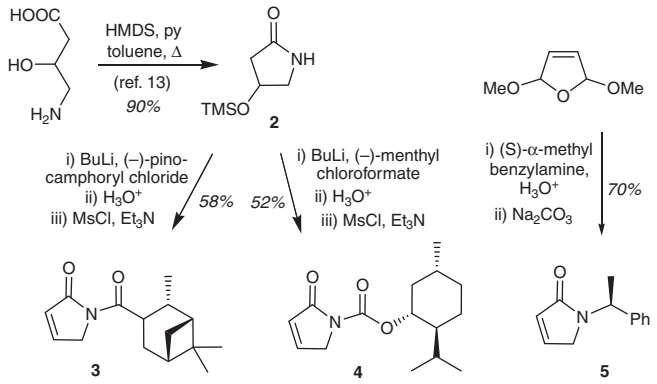
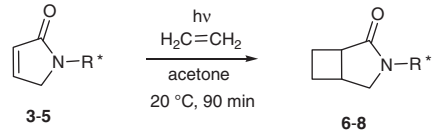


Figure 1. The photochemical strategy for access to the title compounds.



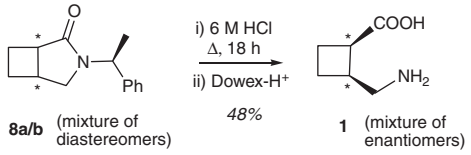
Scheme 1.



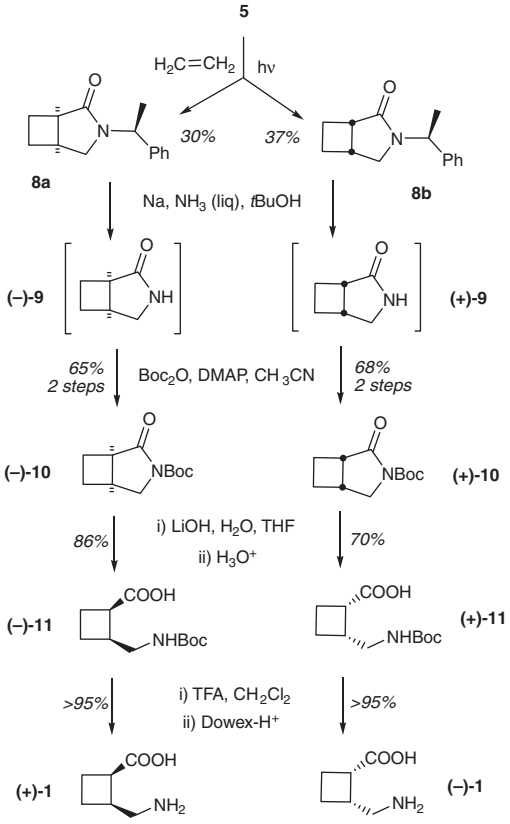
Scheme 2.

Table 1
Photochemical [2+2] cycloaddition reactions of chiral 2-pyrrolinones **3–5** as shown in Scheme 2

Entry	Substrate	Product	Yield (%)	Diastereomer ratio	Diastereomer separation
1	**3**	**6**	76	~50:50	No
2	**4**	**7**	71	~50:50	No
3	**5**	**8**	67	55:45	Yes



Scheme 3.



Scheme 4.

ring junction. The diastereoselectivity was negligible, as might be expected with substrates having stereogenic centres which are not in the immediate vicinity of the reacting enone moiety. A key observation, though, was that the chromatographic separation of diastereomers of product **8** was very simple (15–40 μm silica gel; petroleum ether/EtOAc gradient 4:1 to 1:1): preparatively, **8a** and **8b** were obtained in 30% and 37% yields, respectively. Given the rapidity of the new access to these enantiomerically pure intermediates, obtained easily on gramme scale (around 10 mmol), we pursued the synthesis of the target γ-amino acid using this route.

The two-step transformation of **8a** or **8b** into the title compounds has been reported,[9] and we initially considered a one-step operation. Indeed, in a test experiment, when a solution of the diastereomeric mixture **8a**/**8b** in 6 M HCl was heated under reflux for 18 h, the target γ-amino acid was isolated in 48% yield after elution through cation-exchange resin (Scheme 3). However samples obtained in this way were not of satisfactory purity, and a less drastic sequence was sought.

The synthesis of each enantiomer of the title compound, and—importantly—their N-protected derivatives, was best achieved as shown in Scheme 4. The *N*-alkyl substituent of each stereoisomer of **8** was replaced by a Boc group in a two-step operation, via **9**, to introduce the protecting group and to facilitate the ring opening. Each new derivative **10** was hydrolysed smoothly with lithium hydroxide to provide the *N*-Boc γ-amino acids **11**. These N-protected derivatives are a convenient form for amino acid storage and also a starting point for peptide synthesis. To complete the synthesis of the free γ-amino acids, each derivative **11** was treated at rt with TFA then eluted through a cation exchange resin (H^+ form), using ammonium hydroxide to give the zwitterionic forms of **1** in near-quantitative yields. All compounds shown in Scheme 4 had spectral and analytical data in complete agreement with their assigned structure.[15–17]

In summary, we have established a very rapid photochemical approach for the synthesis of *cis*-cyclobutane γ-amino acids and N-protected derivatives in enantiomerically pure form, validated at present on a several-millimolar scale. Starting from readily available (commercial) starting materials, this procedure requires only four synthetic operations and one chromatographic separation to obtain both enantiomers of the building blocks **11**, and constitutes a concise and attractive alternative to the other existing routes to the title compounds and their derivatives.

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15. **8a**, **8b**, (−)-**9** and (+)-**9** are known (Ref.[9]). Our spectral and optical rotation data for these compounds were consistent with the literature, and were used to assign the absolute configurations of our compounds.
16. Compound (−)-**10**: IR (film) ν (cm^{-1}) 2979, 1782, 1744, 1713, 1314; ^1H NMR ($CDCl_3$; 360 MHz) δ (ppm) 1.55 (s, 9H), 1.93–2.08 (m, 1H), 2.08–2.21 (m, 1H), 2.28–2.41 (m, 1H), 2.41–2.58 (m, 1H), 2.91 (q, J = 7 Hz, 1H), 3.05–3.15 (m, 1H), 3.62 (d, J = 11 Hz, 1H), 3.79 (dd, J = 11 Hz and 7 Hz, 1H); ^{13}C NMR ($CDCl_3$; 90 MHz) δ (ppm) 23.6, 25.7, 27.7, 28.5, 42.3, 52.6, 82.4, 150.3, 177.3; MS (CI-NH_3) m/z 229 $[MH+NH_3]^+$, 212 $[MH]^+$; $[\alpha]_D$ −58 (c 1, $CHCl_3$). Compound (+)-**10** had comparable spectral data and $[\alpha]_D$ +60 (c 1, $CHCl_3$). Compound (−)-**11**: IR (film) ν (cm^{-1}) 3353, 2977, 1704, 1517, 1367, 1170; ^1H NMR ($CDCl_3$; 360 MHz) δ (ppm) 1.47 (s, 9H), 1.73–1.90 (m, 1H), 2.00–2.12 (m, 2H), 2.28–2.39 (m, 1H), 2.80–2.98 (m, 1H), 3.20–3.45 (m, 3H), 4.91 (br s, 1H), 9.70 (br s, 1H); ^{13}C NMR ($CDCl_3$; 90 MHz) δ (ppm) 20.6, 22.3, 27.9, 37.3, 39.7, 42.0, 79.3, 160.2, 178.8; MS (CI-NH_3) m/z 247 $[MH+NH_3]^+$, 230 $[MH]^+$; HRMS (ESI): $C_{11}H_{19}NNaO_4$ requires m/z 252.1206 $[M+Na]^+$; found 252.1194; $[\alpha]_D$ −15 (c 1, $CHCl_3$). Compound (+)-**11**: had comparable spectral data and $[\alpha]_D$ +15 (c 1, $CHCl_3$). Compound (+)-**1**: IR (KBr) ν (cm^{-1}) 3345, 2999, 2931, 2148, 1648, 1578, 1529, 1416; RMN ^1H (D_2O; 360 MHz) δ (ppm) 1.50–1.70 (m, 1H), 2.00–2.10 (m, 3H), 1.70–1.90 (m, 1H), 3.15 (dd, J = 12 Hz and 6 Hz, 1H), 3.29 (dd, J = 12 Hz and 9 Hz, 1H), 3.17–3.30 (m, 1H); ^{13}C NMR (D_2O; 90 MHz) δ (ppm) 20.9, 22.2, 34.5, 41.5, 42.2, 182.3; HRMS (ESI): $C_6H_{12}NO_2$ requires m/z 130.0863 $[M+H]^+$; found 130.0866; $[\alpha]_D$ +23 (c 1, H_2O). Compound (−)-**1** had comparable spectral data and $[\alpha]_D$ −24 (c 1, H_2O).
17. In our hands, (−)-**9** furnished (+)-**1** as shown in Scheme 4. The literature (Ref.[9]) gives $[\alpha]_D$ −24.5 (c 0.5, MeOH) for **1**·**HCl** prepared from (−)-**9**. Samples of **1**·**HCl** prepared from our (+)-**1** had $[\alpha]_D$ +5.5 (c 0.5, MeOH). This is inconsistent with the literature (Refs.[9] and[10]) both in sign and magnitude. We therefore dehydrated a sample of our (+)-**1** (1.5 equiv DCC, CH_2Cl_2, rt, 90 min) to obtain (−)-**9** once again and found it to have an ee of >95% by chiral hplc analysis. We conclude that out collected data are internally coherent and consistent with complete stereochemical integrity of our samples.