[2+2] Photocycloadditions with Chiral Uracil Derivatives: Access to All Four Stereoisomers of 2-Aminocyclobutanecarboxylic Acid

Carlos Fernandes,[a] Christine Gauzy,[a] Yi Yang,[a] Olivier Roy,[a] Elisabeth Pereira,[a] Sophie Faure,[a] David J. Aitken*[a,b]

[a] Laboratoire de Synthèse et Etude de Systèmes d'Intérêt Biologique, SEESIB (UMR 6504–CNRS), Département de Chimie, Université Blaise Pascal – Clermont-Ferrand II, 24 Avenue des Landais, 63177 Aubière cedex, France

[b] Laboratoire de Synthèse Organique et Méthodologie, ICMMO (UMR 8182–CNRS), Université Paris-Sud XI, Bât. 420, 15 rue Georges Clemenceau, 91405 Orsay cedex, France
Fax +33(1)69156278; E-mail: David.Aitken@icmo.u-psud.fr

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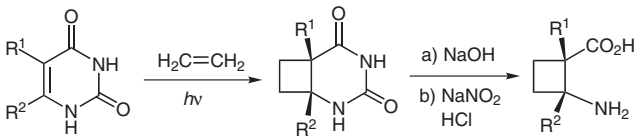
Abstract: Starting from a single, chiral, bicyclic derivative of uracil, all four stereoisomers of 2-aminocyclobutanecarboxylic acid have been prepared in enantiomerically pure form, using a synthetic sequence which begins with a key photochemical [2+2] cycloaddition reaction and includes a practical *cis* to *trans* β-amino acid isomerisation procedure.

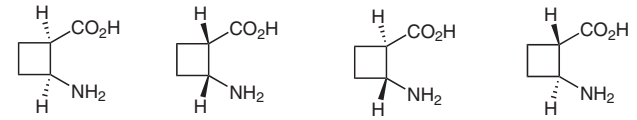
Key words: photochemistry, heterocycles, β-amino acids, cyclobutanes, stereoselective synthesis

The impact of β-amino acids and β-peptides in nature,[1] in medicinal chemistry,[2] and in the controlled design of peptide folding structures[3] is evident from the exponential increase in the volume of published research on these substances.[4] Commensurately, an increasing variety of methods have been described for the synthesis of β-amino acids in both racemic and enantiomerically enriched form.[5] A particular interest has developed for alicyclic β-amino acids;[6] these compounds are of biological interest in their own right,[6,7] while hybrid or homo-oligomers which contain these rigid cyclic motifs pre-organize in a well-defined manner leading to unique 'foldamer' structures. Thus, stable helical motifs have been prepared using oligomers of *trans*-2-aminocyclohexanecarboxylic acid[8] and *trans*-2-aminocyclopentanecarboxylic acid,[8b,9] and some of these oligopeptides are bestowed with biological activities[10] or liquid crystal properties.[11] In marked contrast, oligomers of *cis*-2-aminocyclopentanecarboxylic acid adopt a sheet-like structure.[12] Much less work has been done using small-ring β-amino acids, although initial results have been promising: for example, *cis*-2-aminocyclopropanecarboxylic acid derived oligopeptides adopt stable helical conformations.[13] In the only studies involving cyclobutane β-amino acid building blocks described to date, β-dipeptide derivatives of *cis*-2-aminocyclobutanecarboxylic acid (*cis*-**1**) displayed strong hydrogen-bond-forming propensities,[14] while β-tetrapeptides containing two *cis*-**1** units and two β-alanine residues formed 14-helices in solution.[15] There is an obvious interest in pursuing studies on cyclobutane β-amino acids, but progress has been hampered because of the limited access to these compounds.[16,17] Indeed, only two enantioselective syntheses of *cis*-**1** have been described so far, by the groups of Ortuño[14,18] and Bolm.[19] Both procedures are based on the enantioselective desymmetrisation of *meso*-1,2-cyclobutanedicarboxylic acid, via enzymatic hydrolysis of a diester in the first case and alkaloid-mediated opening of the anhydride in the second. The only syntheses of *trans*-**1** (and a few of its derivatives) have provided racemic materials via desymmetrisation of the racemic *trans*-diacid.[20]

We recently established a simple strategy for the preparation of (±)-*cis*-**1** as well as a variety of C1- or C2-substituted derivatives, in which the key step was the photochemical [2+2] cycloaddition reaction of ethylene with a uracil (Scheme 1).[21,22,23] In this paper, we describe a practical 'chiral adaptation' of this photochemical approach in order to prepare enantiomerically pure samples of all four stereoisomers of the parent cyclobutane β-amino acid **1** (Figure 1).[24]



Scheme 1 Photochemical approach for the general synthesis of racemic *cis*-2-aminocyclobutanecarboxylic acids.



(1*R*,2*S*)-*cis*-**1** (1*S*,2*R*)-*cis*-**1** (1*R*,2*R*)-*trans*-**1** (1*S*,2*S*)-*trans*-**1**

Figure 1 The four stereoisomers of 2-aminocyclobutanecarboxylic acid **1**, target molecules in this work.

We decided to study the photochemical [2+2] cycloaddition reactions of ethylene with uracils bearing a chiral auxiliary.[25] N1-Substituted uracils with the stereogenic centre close to the reactive C5–C6 double bond seemed appropriate, and two different chiral moieties were selected on the basis of their simplicity and ready availability: an α-methylbenzyl group and a ribose moiety. The five compounds **2**–**6** were, therefore, selected for reactivity and stereoselectivity evaluation (Figure 2).

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Biographical Sketches

Carlos Fernandes was born in Clermont-Ferrand (France) in 1978. He studied chemistry and biology at the University Blaise Pascal in Clermont-Ferrand. He has worked on the reactivity of chiral organomagnesium amides, and on the synthesis of iodobenzamide derivatives for melanoma research, and he is currently preparing his Ph.D. under the supervision of Prof. D. J. Aitken, working on synthetic access to cyclobutane amino acids and their use in β-peptide synthesis.

Christine Gauzy was born the French Mediterranean city of Sète, in 1975. She first studied organic chemistry at the University of Montpellier II then moved in 1999 to Clermont-Ferrand to join Prof. D. J. Aitken's group, where she obtained her Ph.D. in 2003. She did post-doctoral work with Dr. S. Bull at the University of Bath, then with Prof. G. Guillaumet at the University of Orléans, the latter in collaboration with the CEA-Le Ripault until 2005. She then worked as an R&D medicinal chemist with Sanofi-Aventis in Vitry-sur-Seine, on CNS and oncology programmes. She is currently looking to pursue work in these fields.

Yi Yang studied chemistry at the Lanzhou University (China), where he enrolled in a joint education program with The Shanghai Institute of Organic Chemistry (Chinese Academy of Sciences). Working in the field of total synthesis, he obtaining his Ph.D. in 2003, then joined Prof. D. J. Aitken's group in Clermont-Ferrand as a postdoctoral fellow (2004). He then went to Guangzhou Institute of Chemistry (Chinese Academy of Sciences). Currently, he works as a post-doctoral fellow in Nanyang Technological University (Singapore) focusing on chemical biology.

Olivier Roy was born in Reims (France) in 1974. He studied chemistry in the University of Reims-Champagne-Ardennes where he obtained his Ph.D. in 2001 under the supervision of Dr. J. Muzart, working on catalysed asymmetric protonation of enolic species. He did a first post-doc with Prof. G. Pattenden in Nottingham working on taxanes, then a second post-doc in Lyon with Dr. B. Langlois. In 2004, he moved to the University Blaise Pascal in Clermont-Ferrand as temporary Lecturer and in 2006 he was given tenure. He currently works on the synthesis of glycosylated β-peptides.

Elisabeth Pereira was born in Melun (France) in 1969. She received her Ph.D. in 1996 from the University Blaise Pascal in Clermont-Ferrand under the supervision of Prof. M. Prudhomme, working on the synthesis of protein kinase C inhibitors. After a post-doctoral stay at the University of Kyoto with Prof. Y. Ito, she became Lecturer in 1998 at University Blaise Pascal and joined the group of Prof. D. J. Aitken where she currently works on the synthesis of conformationally constrained β-amino acids especially cyclobutane derivatives and α-aminonitriles.

Sophie Faure, born in 1973, studied chemistry at the University of Reims-Champagne-Ardennes where she received her Ph.D. in 1999 under the supervision of Prof. O. Piva, working on photocycloadditions and photoisomerisations. She worked in the group of Prof. D. Enders in Aachen as a postdoctoral fellow in 2000. Following postdoctoral work in medicinal chemistry with Prof. H.-P. Husson at University of Paris V, she joined the CNRS in 2002 as Chargé de Recherche in the group of Prof. D. J. Aitken in Clermont-Ferrand. Her research interests include synthesis of macrocyclic peptides and conformationally constrained amino acids, especially cyclobutane derivatives.

David Aitken was born in 1963 and studied chemistry at the University of Strathclyde, Scotland, obtaining his Ph.D. in 1986. Thanks to a two-year NATO–Royal Society post-doctoral Fellowship at the ICSN in Gif-sur-Yvette, he acquired a taste for research in France and was appointed CNRS Researcher in 1990, in Prof. H.-P. Husson's group at the University of Paris V. In 1998, he became Professor at Blaise Pascal University in Clermont-Ferrand. In 2006, he transferred to his present position as Professor of Organic Chemistry at Orsay. His research interests include all aspects of synthetic methodology, including photochemistry, and the preparation of molecules and molecular scaffolds of biological and therapeutic interest.

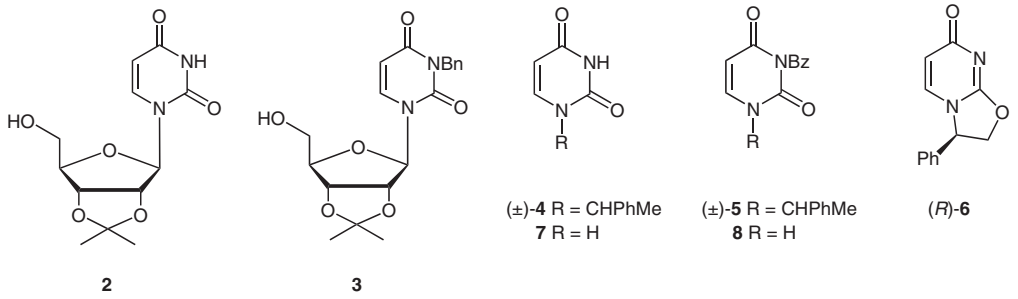
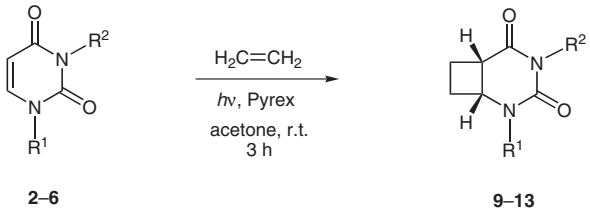


Figure 2 Chirally adapted uracils used in photochemical reactions.

Uridine **3** was prepared by reaction of the commercial product **2** with benzyl bromide in the presence of sodium carbonate and tetrabutylammonium bromide.[26] Compound (±)-**4** was prepared by direct reaction of uracil (**7**) with racemic (1-bromoethyl)benzene in the presence of sodium hydride in *N*,*N*-dimethylformamide; these conditions are known to give high N1-alkylation selectivity.[27] This method was superior to the alternative Mitsunobu procedure,[28] which gave mixtures of O- and N-alkylated uracils as well as dialkylated material. Similarly, compound (±)-**5** was obtained by N1-alkylation of 3-benzoyluracil (**8**).[29] Due to their ready availability, the racemic forms of **4** and **5** were used in this initial study, which was designed to examine the diastereoselectivity of the photochemical reactions. Compound (*R*)-**6** was prepared in two steps from commercial (*R*)-phenylglycinol, again following the literature.[30]

Each of the five uracil derivatives **2**–**6** was engaged in a [2+2] photocycloaddition reaction with ethylene. Thus, ethylene was bubbled through a solution (c = 5–10 mM) of the substrate in acetone at room temperature, which was irradiated over a three-hour period with a 400 W medium-pressure mercury lamp fitted with a Pyrex filter (Scheme 2). Results are presented in Table 1. In each case, the desired cyclobutane adduct was obtained in good to excellent yield (53–89%). As with previous [2+2] photocycloadditions involving olefins and uracil derivatives,[21,31] all cyclobutane compounds had *cis* configuration at the ring junction. The diastereomeric excesses, however, determined from signal integration in ^{1}H NMR spectra of the initial isolates, were invariably weak (4–26%). In particular, the bicyclic constraints present in (*R*)-**6** (conceived as an analogue of **4** that had been rigidified by a bond between O2 and the α-methyl carbon atom of the N1 substituent) imparted no beneficial effects to the selectivity (18% de; entry 5).

Reports of intermolecular [2+2] photocycloaddition reactions between simple alkenes and uracil derivatives are relatively rare.[21,31] Uridines similar to **2** and **3** undergo stereoselective photochemical [2+2] cycloadditions with the sterically demanding tetramethylethylene,[31a–d] but reactions with ethylene have not been described. Compound (*R*)-**6** undergoes highly stereoselective Michael addition of nucleophiles at the β-carbon,[30] but its photochemical reactivity has not been examined previously. Likewise,



Scheme 2 Photochemical reactions of chiral uracils **2**–**6** with ethy-

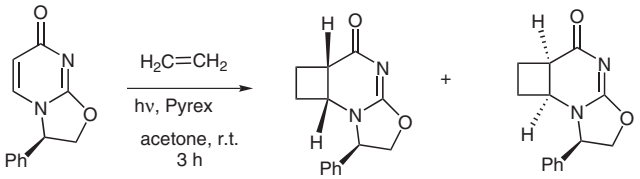
the photochemistry of compounds of type **4** and **5** has not been disclosed. In a general context, ethylene is a cooperative partner for [2+2] photocycloaddition reactions with enones;[32] however with chiral versions of the latter reagents the diastereomeric excess values vary considerably and can be difficult to control.[33]

Rather than continue the uncertain search for an alternative chiral auxiliary in the hope of improving stereoselectivity, we sought to exploit the chiral adducts in hand. Uridine-derived cyclobutane diastereomer mixtures **9a/9b** and **10a/10b** (Table 1, entries 1 and 2) could not be separated by column chromatography nor by crystallisation. Similarly, the cyclobutane diastereomer mixtures **11a/11b** and **12a/12b** obtained from the *N*1-α-methylbenzyl uracils (Table 1, entries 3 and 4) were barely separable by chromatography; furthermore, useful exploitation of either of these adducts would require their preparation in enantiomerically pure form from single antipodes of **4** or **5**, for which a synthesis had not yet been devised. The most useful result was obtained using (*R*)-**6**, since separation of the diastereomers (–)-**13a** and (–)-**13b** was possi-

Table 1 Results of Photochemical Reactions of Chirally Adapted Uracils with Ethylene (Scheme 2)

Entry	Starting material	Products	Yield (%)	de (%)
1	**2**	**9a** + **9b**	67	4
2	**3**	**10a** + **10b**	53	26
3	(±)-**4**	(±)-**11a** + (±)-**11b**	89	4
4	(±)-**5**	(±)-**12a** + (±)-**12b**	57	5
5	(*R*)-**6**	(–)-**13a** + (–)-**13b**	80	18

ble by straightforward column chromatography of the crude reaction product (Table 1, entry 5). These compounds were thus obtained in 49% and 31% yield, respectively, each in enantiomerically pure form. We expected that the major diastereomer (–)-**13a** would be derived from the approach of ethylene from the least hindered face of the enone reaction centre, and would thus have a *syn* relationship between both bridgehead hydrogens and the phenyl group; this hypothesis was confirmed by an X-ray diffraction study of a single crystal of (–)-**13a** (Figure 3).[34] The future configuration of the 2-aminocyclobutanecarboxylic acid to be derived from this compound was therefore 1*S*,2*R*. Given the rapid access to enantiomerically pure (*R*)-**6** and the ease of product separation, we retained the reaction in Scheme 3 for the next part of our synthesis.



Scheme 3 Photochemical preparation of the key intermediates.

Selective opening of the five-membered rings of (–)-**13a** and (–)-**13b** was achieved by hydrogenolysis in the presence of palladium on charcoal, as described by Agami et al. for related heterocyclic structures.[30] Single stereoisomers (–)-**11b** and (–)-**11a**, respectively, were thus obtained in quantitative yield and were correlated with racemic materials available from the appropriate reaction on Scheme 2 (see Table 1, entry 3). The α-methylbenzyl group was removed cleanly and efficiently from each of these compounds by refluxing in formic acid for 15 hours.[35] Enantiomers (+)-**14** and (–)-**14** were each obtained in 78% yield; spectroscopic data were identical with those obtained previously for the racemic material

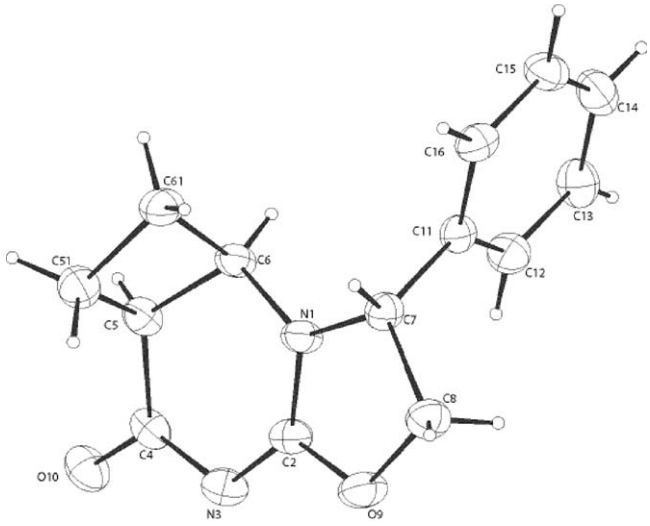
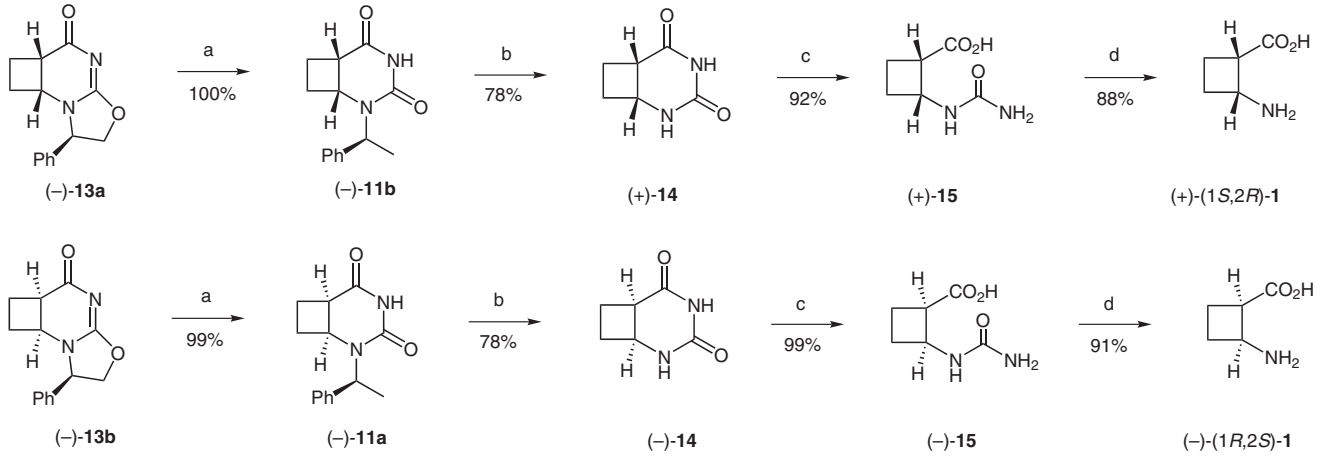


Figure 3 X-ray diffraction structure of major diastereomer (–)-**13a**.

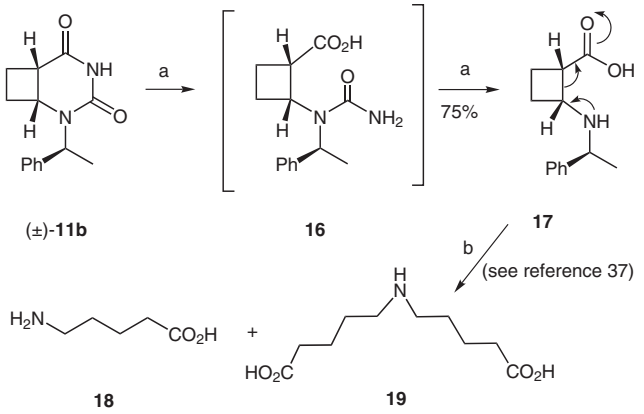
(±)-**14**.[21a] The controlled two-step degradation of the heterocyclic rings of (+)-**14** and (–)-**14** was performed by treatment with mild base, providing the *N*-carbamoyl-β-amino acids (+)-**15** and (–)-**15** then diazotization with one equivalent of sodium nitrite in acidic medium[36] followed by purification on cation-exchange resin, to provide the target *cis*-β-amino acids (+)-(1*S*,2*R*)-**1** and (–)-(1*R*,2*S*)-**1** in good yields (Scheme 4). The enantiomeric excess of each sample was established as >97% by chiral HPLC analysis. The attribution of a 1*R*,2*S* absolute configuration for the (–)-*cis*-**1** enantiomer correlates with the previous assertions made by Ortuño[14,18] and Bolm.[19]

An attempt to carry out heterocyclic ring opening prior to removal of the α-methylbenzyl group produced unexpected results (Scheme 5). A long reaction time (4 days) was required for the sodium hydroxide mediated transformation of a sample of (±)-**11b** (available from Table 1, entry 3); the intermediate urea-acid **16** was not isolated, evidently having been further transformed during this time into the N-α-methylbenzylated cyclobutane β-amino acid



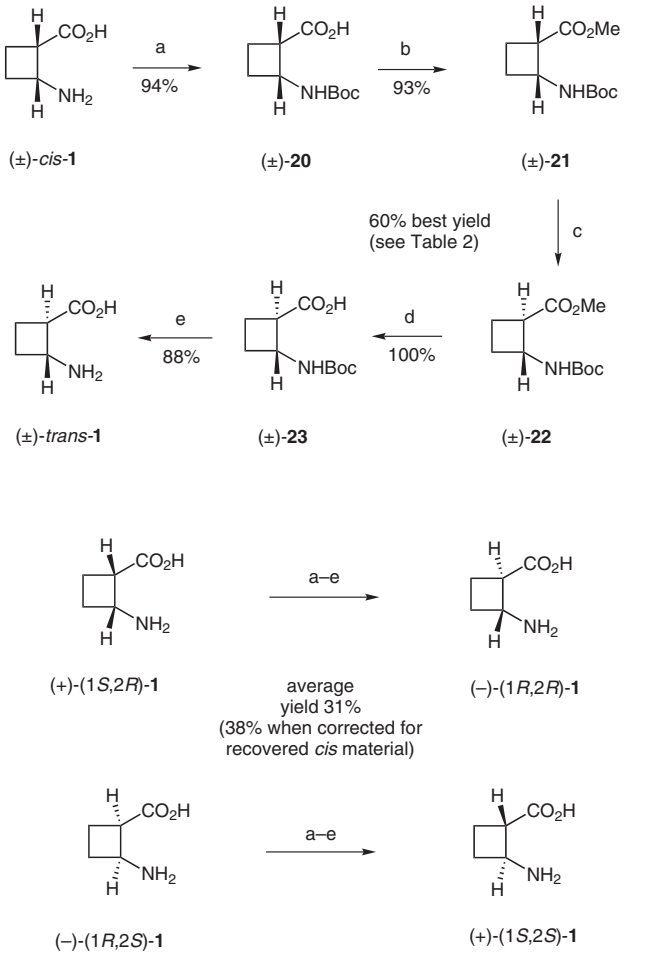
Scheme 4 *Reagents and conditions*: (a) H_2 (4 bar), Pd/C, EtOH, r.t., 3 h; (b) HCO_2H, reflux, 15 h; (c) 0.5 M NaOH, r.t., 18 h; (d) $NaNO_2$, 3.5 M HCl, r.t., 18 h.

17. This material proved to have limited stability in protic solution, and attempts to obtain *cis*-**1** through catalytic hydrogenation failed. Instead, a mixture of acyclic products was obtained, amongst which 5-aminopentanoic acid **18** and the amino diacid **19** were identified. These products arise from the facile push–pull ring opening of the cyclobutane system, as we described in a recent communication (Scheme 5).[37]



Scheme 5 *Reagents and conditions*: (a) 0.5 M NaOH, r.t., 4 d; (b) H_2 (3 bar), $Pd(OH)_2$/C, MeOH–H_2O, r.t., 3 d.

Our next objective was to develop an entry to *trans*-2-aminocyclobutanecarboxylic acid (*trans*-**1**). For this purpose, regiospecific base-mediated C1-epimerisation of a *cis*-**1** derivative was envisaged. To facilitate handling and to avoid stability problems arising from the push–pull ring-opening process, both amine and acid functions were protected. We carried out initial optimisation studies on racemic samples. Thus, fully protected derivative (±)-**21** was obtained uneventfully from (±)-*cis*-**1** in two steps and in good yield (Scheme 6).



Scheme 6 Preparation of (±)-*trans*-**1**, (1*R*,2*R*)-*trans*-**1** and (1*S*,2*S*)-*trans*-**1** from the appropriate *cis*-**1** precursors. *Reagents and conditions*: (a) Boc_2O, NaOH, H_2O–dioxane, 0 °C to r.t., 4 h; (b) DCC, DMAP, MeOH, 0 °C to r.t., 20 h; (c) see Table 2; (d) LiOH, THF–H_2O, r.t., 1 h; (e) TFA, CH_2Cl_2, r.t., 30 min.

Results of epimerisation studies are presented in Table 2. Davies et al. described the epimerisation of related five- and six-membered alicyclic β-amino acid derivatives using lithium hexamethyldisilazane in the presence of *tert*-butyl alcohol;[38] however, these conditions provoked total degradation of (±)-**21** (entry 1). The same result was obtained using potassium *tert*-butoxide[39] as base (entry 2). An excess of 1,8-diazabicyclo[5.4.0]undec-7-ene in *N*,*N*-dimethylformamide induced no change whatsoever in (±)-**21** over a 24 hour period at ambient temperature (entry 3), but after 18 hours at 100 °C, all starting material had been consumed. The desired *trans*-isomer (±)-**22** was indeed formed, but was isolated in poor yield (24%; entry 4); evidently, degradation was still a significant problem. A similar result was obtained when sodium hydride was used as the base (entry 5). We finally succeeded in improving the conversion/degradation profile by employing sodium methoxide in methanol[17e] (entry 6). The epimerisation was sensitive to the precise experimental conditions; a slightly better result was obtained using five equivalents of sodium methoxide under reflux for one hour (entry 7). Longer reaction times resulted in lower material recovery. In the best run, the required *trans*-isomer (±)-**22** was obtained in a satisfactory 60% isolated yield and the recovered *cis* starting material (±)-**21** (12% isolated) could be reused later in a repeat isomerisation procedure. In practice, repeat runs using the conditions of entry 7 provided (±)-**22** in yields that varied from 45–60%, while (±)-**21** was recovered in 10–25% yield. These two isomers were easily separated by column chromatography.

For the deprotection of compound (±)-**22**, methyl ester hydrolysis was performed by employing exactly one equivalent (or even a slight deficit) of lithium hydroxide over one hour, to give (±)-**23** quantitatively. If the base was present in slight excess, or if the reaction was left too long, the *cis*-isomer (±)-**20** was formed instead. Trifluoroacetic acid mediated cleavage of the *tert*-butyl carbamate group of (±)-**23** in standard conditions provided the target *trans*-2-aminocyclobutanecarboxylic acid, (±)-*trans*-**1**, in 88% yield. Spectroscopic data were identical with those described by Kennewell.[20a]

Table 2 Epimerisation Conditions for Conversion of (±)-**21** into (±)-**22**

Entry	Base	Solvent	Temp	Time	Recovered (±)-**21** (%)	Yield (%) of (±)-**22**
1	LiHMDS (4 equiv)/*t*-BuOH (8 equiv)	THF	r.t.	24 h	0	–[a]
2	*t*-BuOK (2 equiv)	THF	r.t.	24 h	0	–[a]
3	DBU (5 equiv)	DMF	r.t.	24 h	100	–
4	DBU (5 equiv)	DMF	100 °C	18 h	0	24
5	NaH (1.1 equiv)	THF	reflux	0.5 h	0	20
6	NaOMe (5 equiv)	MeOH	r.t.	36 h	13	40
7	NaOMe (5 equiv)	MeOH	reflux	1 h	12	60

[a] Degradation of materials.

The five-step sequence was then applied, essentially without modification, to samples of each of the two enantiomerically pure samples of *cis*-**1**. As anticipated, this operation furnished successfully the corresponding *trans*-**1** compounds, each as a single enantiomer (Scheme 6). In four five-step runs, the average overall yield was 31% (corrected to 38% if recovered *cis* material is taken into account at the isomerisation step). The enantiomeric excess of each sample of *trans*-**1** obtained in this way was established as >97% by chiral HPLC analysis.

In conclusion, we have prepared all four possible stereoisomers of the prototype cyclobutane β-amino acid **1** via the [2+2] photocycloaddition reaction of a single, readily prepared chiral uracil derivative. Although the diastereomeric excess was modest in the cyclobutane-forming step, the easy separation of the resulting diastereomers guarantees the enantiomeric purity of all subsequently derived materials. Each of the final products was obtained in enantiomerically pure form, and this work provides the first access to either enantiomer of *trans*-**1**.

Melting points were determined with a Reichert microscope apparatus. Elemental analyses were carried out on a Thermofinnigan Flash EA 1112 apparatus. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were obtained on a Bruker AC 400 spectrometer. IR spectra were recorded on a Perkin Elmer Paragon 500 FTIR spectrometer; only structurally important peaks are presented. MS spectra were recorded on an HP 5989 B instrument in chemical ionisation mode (150 eV) using isobutane as the vector gas. HRMS were recorded in ESI (3000 V) on a Micromass micro q-tof with an internal lock mass (H_3PO_4) and an external lock mass (Leu-enkephalin). Specific optical rotations were measured with a Jasco DIP-370 polarimeter. Reactions were analysed by TLC on silica gel 60 F_{254} (Merck). Preparative chromatography was performed on silica gel 60 (40–60 μm) (Merck) using 15-cm length columns. HPLC analysis was performed on a Waters 590 instrument equipped with a Crownpak CR(+) column (i.d. 0.4 cm × 15 cm) and a Waters 484 UV detector, using the following conditions: 0.17 M $HClO_4$ (pH = 1) as mobile phase; T = 4 °C; λ = 220 nm; flow rate = 0.3 mL·min^{-1}.

All organic solvents were dried and purified by standard procedures prior to use. Compounds **2** and **7** and all other standard reagents were obtained commercially and used as supplied. Compounds (±)-**1**,[21] **3**,[26] and **8**[29] were synthesised following published procedures or minor modifications thereof. Compound (*R*)-**6** was synthesised from (*R*)-phenylglycinol according to the literature;[30] its enantiomeric excess was determined as >97% by ^{1}H NMR experiments in the presence of Eu(hfc)$_3$.

1-(1-Phenylethyl)uracil [(±)-4]

To a suspension of NaH (60% in oil, 0.393 g, 9.82 mmol) in anhyd DMF (15 mL) was added a suspension of uracil **7** (1.00 g, 8.92 mmol) in DMF (15 mL) in small aliquots. The mixture was stirred under argon at r.t. for 2 h then (±)-(1-bromoethyl)benzene (1.60 mL, 11.7 mmol) was added dropwise. The mixture was refluxed for 2 h then cooled. H_2O (15 mL) and CH_2Cl_2 (15 mL) were added successively. The organic phase was isolated and the aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL). The organic extracts were combined, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude mixture was purified by chromatography (cyclohexane–EtOAc, gradient from 75:25 to 50:50) to give (±)-**4** as a white solid (1.16 g, 60%); mp 115–118 °C; R_f = 0.3 (cyclohexane–EtOAc, 50:50). Spectroscopic data were identical with those in the literature.[40]

3-Benzoyl-1-(1-phenylethyl)uracil [(±)-5]

To a suspension of NaH (60% in oil, 0.142 g, 3.55 mmol) in anhyd DMF (8 mL) was added 3-benzoyluracil (**8**) in portions (0.640 g, 2.96 mmol). The mixture was stirred under argon at r.t. for 2 h then (±)-(1-bromoethyl)benzene (0.527 mL, 3.86 mmol) was added dropwise and the mixture was stirred for a further 2 h. H_2O (15 mL) and CH_2Cl_2 (15 mL) were added successively. The organic phase was isolated and the aqueous phase was extracted with CH_2Cl_2 (4 × 15 mL). The organic extracts were combined, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude mixture was purified by chromatography (cyclohexane–EtOAc, 70:30) to give (±)-**5** as a white foam (0.726 g, 77%); mp 46–48 °C; R_f = 0.5 (cyclohexane–EtOAc, 50:50).

IR (KBr): 1745, 1702, 1664, 1438, 1362, 1255 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.75 (d, J = 7.0 Hz, 3 H, CH_3), 5.76 (d, J = 8.1 Hz, 1 H, H5), 5.98 (q, J = 7.0 Hz, 1 H, CH–CH_3), 7.13 (d, J = 8.2 Hz, 1 H, H6), 7.36–7.46 (m, 5 H, Ph), 7.52 (t, J = 7.5 Hz, 2 H, Ph); 7.67 (t, J = 7.4 Hz, 1 H, Ph), 7.95 (d, J = 7.7 Hz, 2 H, Ph).

^{13}C NMR ($CDCl_3$): δ = 18.5, 53.9, 102.7, 127.4 (2 C), 128.8, 129.3 (4 C), 130.5 (2 C), 131.6, 135.1, 138.3, 140.8, 150.1, 162.0, 168.9.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{19}H_{16}N_2NaO_3$: 343.1059; found: 343.1067.

[2+2] Photocycloaddition of Uracils with Ethylene; General Procedure

Photochemical reactions were carried out at r.t. in an annular reactor equipped with a water-cooling circuit using a 400 W medium-pressure Hg lamp fitted with a Pyrex filter. A soln of the uracil derivative in acetone was deoxygenated with an argon stream for 15 min, then irradiated for 3 h while ethylene was bubbled through. The solvent was then removed under reduced pressure and the crude product was purified by chromatography.

2-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-*cis*-2,4-diazabicyclo[4.2.0]octane-3,5-dione (9a/9b)

A soln of compound **2** (0.250 g, 0.88 mmol) in acetone (170 mL) was irradiated following the general photocycloaddition procedure. After chromatography (CH_2Cl_2–MeOH, 97:3) a mixture of two diastereomers **9a** and **9b** was isolated as a white solid (0.185 g, 67%); R_f = 0.2 (CH_2Cl_2–MeOH, 97:3).

IR (KBr): 3447, 3244, 1698 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.31 (s, 3 H, CH_3), 1.32 (s, 3 H, CH_3), 1.51 (s, 3 H, CH_3), 1.52 (s, 3 H, CH_3), 2.14–2.39 (m, 8 H, CH_2), 3.28–3.37 (m, 2 H), 3.68–3.73 (m, 2 H), 3.79–3.86 (td, *J* = 12, 2.8 Hz, 2 H), 4.09–4.19 (m, 4 H), 4.86 (m, 2 H), 4.92 (dd, *J* = 6.4, 3.6 Hz, 1 H), 5.03 (dd, *J* = 6.4, 3.2 Hz, 1 H), 5.11 (d, *J* = 3.2 Hz, 1 H), 5.24 (d, *J* = 3.2 Hz, 1 H), 8.61 (br s, 2 H, NH).

^{13}C NMR ($CDCl_3$): δ = 21.7, 22.0, 25.4 (2 C), 27.4 (2 C), 30.6, 30.7, 38.7, 39.4, 50.8, 51.7, 62.8, 62.9, 80.3, 80.6, 82.4 (2 C), 85.3, 85.5, 94.2, 94.7, 114.1, 114.2, 151.9, 152.0, 172.0, 172.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{20}N_2NaO_6$: 335.1219; found: 335.1230.

4-Benzyl-2-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-*cis*-2,4-diazabicyclo[4.2.0]octane-3,5-dione (10a/10b)

A soln of compound **3** (0.154 g, 0.41 mmol) in acetone (170 mL) was irradiated following the general photocycloaddition procedure. After chromatography (CH_2Cl_2–MeOH, 97:3) a mixture of two diastereomers **10a** and **10b** was isolated as a white solid (0.088 g, 53%); R_f = 0.5 (CH_2Cl_2–MeOH, 98:2).

IR (KBr): 3457, 1710, 1666 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.26 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 1.47 (s, 3 H, CH_3), 2.05–2.30 (m, 8 H, CH_2), 3.33 (m, 2 H), 3.36 (s, 2 H, OH), 3.64 (dd, *J* = 12.2, 3.0 Hz, 2 H), 3.73–3.77 (m, 2 H), 3.99–4.07 (m, 4 H), 4.82–4.98 (2 m, 8 H), 5.03 (d, *J* = 3.6 Hz, 1 H), 5.15 (d, *J* = 3.6 Hz, 1 H), 7.17 (d, *J* = 7.2 Hz, 2 H), 7.22 (t, *J* = 6.8 Hz, 4 H), 7.29 (d, *J* = 7.6 Hz, 4 H).

^{13}C NMR ($CDCl_3$): δ = 22.3, 22.7, 25.3, 27.3 (2 C), 29.2, 30.6, 30.6, 38.5, 39.2, 43.8, 43.9, 49.3, 50.1, 62.8, 62.9, 80.1, 80.5, 82.2, 82.3, 85.1, 85.3, 95.3, 95.7, 113.9, 114.1, 127.4 (2 C), 128.4 (4 C), 128.6 (4 C), 137.3, 137.4, 152.3, 152.4, 170.9, 171.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{26}N_2NaO_2$: 425.1689; found: 425.1675.

2-(1-Phenylethyl)-*cis*-2,4-diazabicyclo[4.2.0]octane-3,5-dione [(±)-11a/(±)-11b]

A soln of compound (±)-**4** (2.50 g, 11.6 mmol) in acetone (1 L) was irradiated following the general photocycloaddition procedure. After chromatography (cyclohexane–EtOAc, 60:40), two diastereomers (±)-**11a** (1.24 g, 44%) and (±)-**11b** (1.27 g, 45%) were isolated as white solids in 89% overall yield.

Diastereomer (±)-11a

Mp 151–154 °C; R_f = 0.5 (cyclohexane–EtOAc, 50:50).

IR (KBr): 3240, 1700 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.53 (d, *J* = 7.2 Hz, 3 H, CH_3), 2.09–2.21 (m, 2 H), 2.30–2.42 (m, 2 H), 3.11 (m, 1 H, H6), 3.75 (q, *J* = 8.2 Hz, 1 H, H1), 5.80 (q, *J* = 7.2 Hz, 1 H, CH–CH_3), 7.30–7.40 (m, 5 H, Ph), 8.18 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 18.4, 21.9, 32.7, 40.2, 46.3, 51.6, 127.2, 127.9, 128.8, 139.9, 151.9, 172.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{16}N_2NaO_2$: 267.1109; found: 267.1113.

Diastereomer (±)-11b

Mp: 122–124 °C; R_f = 0.4 (cyclohexane–EtOAc, 50:50).

IR (KBr): 3240, 1700 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.23–1.28 (m, 1 H), 1.57 (d, *J* = 7.0 Hz, 3 H, CH_3), 1.76–1.82 (m, 1 H), 1.93–2.07 (m, 2 H), 3.22 (m, 1 H, H6), 3.93 (q, *J* = 8.0 Hz, 1 H, H1), 5.83 (q, *J* = 7.0 Hz, 1 H, CH–CH_3), 7.26–7.38 (m, 5 H, Ph), 8.15 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 15.9, 21.6, 31.7, 40.3, 46.5, 51.3, 127.9, 128.0, 128.6, 139.4, 151.7, 172.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{16}N_2NaO_2$: 267.1109; found: 267.1115.

4-Benzoyl-2-(1-phenylethyl)-*cis*-2,4-diazabicyclo[4.2.0]octane-3,5-dione [(±)-12a and (±)-12b]

A soln of compound (±)-**5** (0.200 g, 0.62 mmol) in acetone (150 mL) was irradiated following the general photocycloaddition procedure. After chromatography (cyclohexane–EtOAc, 60:40) two diastereomers (±)-**12a** (0.057 g, 26%) and (±)-**12b** (0.067 g, 31%) were isolated as viscous liquids in 57% overall yield. Overlapping elution profiles of the two components made the chromatographic separation difficult.

Diastereomer (±)-12a

R_f = 0.6 (cyclohexane–EtOAc, 50:50).

IR (CCl_4): 3020, 1743, 1701, 1669, 1442, 1215 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.57 (d, *J* = 7.1 Hz, 3 H, CH_3), 2.27 (m, 1 H), 2.42 (m, 2 H), 2.54 (m, 1 H), 3.28 (m, 1 H, H6), 3.83 (q, *J* = 7.9 Hz, 1 H, H1), 5.77 (q, *J* = 7.1 Hz, 1 H, CH–CH_3), 7.40 (m, 5 H, Ph), 7.53 (m, 2 H, Ph), 7.67 (m, 1 H, Ph), 7.96 (d, *J* = 7.5 Hz, 2 H, Ph).

^{13}C NMR ($CDCl_3$): δ = 17.0, 22.1, 33.3, 40.4, 45.7, 52.0, 127.4, 128.0, 128.9, 129.0, 130.1, 132.6, 134.4, 139.5, 151.1, 170.0, 171.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{20}N_2NaO_3$: 371.1372; found: 371.1388.

Diastereomer (±)-12b

R_f = 0.5 (cyclohexane–EtOAc, 50:50).

IR (CCl_4): 3025, 1749, 1704, 1672, 1440, 1253 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.36 (m, 1 H), 1.62 (d, *J* = 7.0 Hz, 3 H, CH_3), 1.92 (m, 1 H), 2.09 (m, 2 H), 3.41 (m, 1 H, H6), 4.02 (q, *J* = 8.0 Hz, 1 H, H1), 5.79 (q, *J* = 7.0 Hz, 1 H, CH–CH_3), 7.37 (m, 5 H, Ph), 7.52 (m, 2 H, Ph), 7.65 (m, 1 H, Ph), 7.94 (d, *J* = 7.5 Hz, 2 H, Ph).

^{13}C NMR ($CDCl_3$): δ = 15.8, 21.9, 32.2, 40.6, 43.4, 51.7, 127.2, 127.9, 128.2, 128.9, 130.1, 132.6, 134.6, 139.0, 150.9, 170.0, 171.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{20}N_2NaO_3$: 371.1372; found: 371.1387.

1-Phenyl-1,2,5a,6,7,7a-hexahydro-5*H*-cyclobuta[*e*][1,3]oxazolo[3,2-*a*]pyrimidin-5-one (13a/13b)

A soln of compound (*R*)-**6** (1.10 g, 5.13 mmol) in acetone (1 L) was irradiated following the general photocycloaddition procedure. After chromatography (gradient of EtOAc–MeOH from 100:0 to 95:5), two diastereomers (–)-**13a** (0.609 g, 49%) and (–)-**13b** (0.390 g, 31%) were isolated as white solids.

(–)-(1*R*,5a*S*,7a*R*)-13a
Mp >300 °C; $[\alpha]_D^{25}$ –187 (*c* 1.00, $CHCl_3$); R_f = 0.2 (EtOAc–MeOH, 95:5).

IR (KBr): 2950, 1660 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.23–2.29 (m, 2 H, H9), 2.38–2.44 (m, 2 H, H8), 3.26 (q, *J* = 8.2 Hz, 1 H, H6), 3.83 (dt, *J* = 8.6, 6.4 Hz, 1 H, H7), 4.36 (dt, *J* = 12.9, 7.0 Hz, 1 H, H11), 4.87–4.95 (m, 2 H, H1, H11), 7.30 (m, 2 H, Ph), 7.46 (m, 3 H, Ph).

^{13}C NMR ($CDCl_3$): δ = 24.2, 26.8, 35.9, 47.3, 59.9, 72.6, 127.0, 129.5, 129.6, 134.9, 167.0, 181.0.

MS (CI): *m*/*z* = 243 $[M + H]^+$.

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83; N, 11.56. Found: C, 68.91; H, 5.89; N, 11.38.

(–)-(1*R*,5a*R*,7a*S*)-13b
Mp 179–182 °C; $[\alpha]_D^{25}$ –8 (*c* 1.00, $CHCl_3$); R_f = 0.1 (EtOAc–MeOH, 95:5).

IR (KBr): 2950, 1670 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.75–1.80 (m, 1 H, H9), 1.89–1.94 (m, 1 H, H9), 2.18–2.32 (m, 2 H, H8), 3.17–3.23 (m, 1 H, H6), 4.03 (q, *J* = 8.5 Hz, 1 H, H7), 4.40 (m, 1 H, H11), 4.82–4.88 (m, 2 H, H1, H11), 7.35–7.39 (m, 2 H, Ph), 7.42–7.47 (m, 3 H, Ph).

^{13}C NMR ($CDCl_3$): δ = 23.9, 29.6, 36.7, 49.8, 63.1, 72.7, 127.4, 129.2, 129.5, 136.2, 167.0, 181.6.

MS (CI): *m*/*z* = 243 $[M + H]^+$.

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83; N, 11.56. Found: C, 68.96; H, 6.11; N, 11.17.

(–)-(1*R*,6*S*)-2-[(1*S*)-1-Phenylethyl]-2,4-diazabicyclo[4.2.0]octane-3,5-dione [(–)-11b]
A soln of compound (–)-**13a** (2.00 g, 8.18 mmol) in EtOH (200 mL) was stirred under H_2 (4 bar) in presence of 10% Pd/C (0.890 g, 0.84 mmol) for 4 h. After filtration through a pad of Celite, the filtrate was concentrated to give compound (–)-**11b** as colourless crystals (1.99 g, 100%); mp 130–131 °C. Other data: as for (±)-**11b**.

$[\alpha]_D^{25}$ –139 (*c* 1.00, $CHCl_3$).

Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.41; H, 6.70; N, 11.25.

(–)-(1*S*,6*R*)-2-[(1*S*)-1-Phenylethyl]-2,4-diazabicyclo[4.2.0]octane-3,5-dione [(–)-11a]
A soln of compound (–)-**13b** (0.920 g, 3.77 mmol) in EtOH (200 mL) was stirred under H_2 (4 bar) in presence of 10% Pd/C (0.413 g, 0.39 mmol) for 3 h. After filtration through a pad of Celite, the filtrate was concentrated to give compound (–)-**11a** as colourless crystals (0.910 g, 99%); mp 171–173 °C. Other data: as for (±)-**11a**.

$[\alpha]_D^{25}$ –33 (*c* 1.00, $CHCl_3$).

Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.68; H, 6.64; N, 11.46.

(+)-(1*R*,6*S*)-2,4-Diazabicyclo[4.2.0]octane-3,5-dione [(+)-14]
A soln of compound (–)-**11b** (3.67 g, 15.0 mmol) in 97% HCO_2H (147 mL) was stirred under reflux for 15 h. Elimination of HCO_2H under reduced pressure left a brown solid which was washed with Et_2O and then recovered by filtration. Compound (+)-**14** was obtained as an off-white solid after drying under vacuum (1.64 g, 78%); mp 247–249 °C; R_f = 0.3 (EtOAc).

$[\alpha]_D^{25}$ +24 (*c* 1.00, HCO_2H).

IR (KBr): 3230, 3080, 1720 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.92 (m, 2 H, H7), 2.18 (m, 2 H, H8), 3.11 (m, 1 H, H6), 3.90 (m, 1 H, H1), 7.68 (s, 1 H, NH), 10.02 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 21.4, 30.6, 37.2, 44.8, 152.7, 173.3.

MS (CI): *m*/*z* = 141 $[M + H]^+$.

Anal. Calcd for $C_6H_8N_2O_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.35; H, 5.77; N, 19.83.

(–)-(1*S*,6*R*)-2,4-Diazabicyclo[4.2.0]octane-3,5-dione [(–)-14]
A soln of compound (–)-**11a** (2.43 g, 9.94 mmol) in 97% HCO_2H (100 mL) was stirred under reflux for 15 h. Elimination of HCO_2H under reduce pressure left a brown solid which was washed with Et_2O and then recovered by filtration. Compound (–)-**14** was obtained as an off-white solid after drying under vacuum (1.08 g, 78%); mp 249–251 °C. Other data: as for (+)-**14**.

$[\alpha]_D^{25}$ –24 (*c* 1.00, HCO_2H).

(+)-(1*S*,2*R*)-2-[(Aminocarbonyl)amino]cyclobutanecarboxylic Acid [(+)-15]
Compound **(+)-14** (1.64 g, 11.7 mmol) was dissolved in 0.5 M NaOH (140 mL) and stirred overnight at r.t. Cation exchange resin (Bio-Rad AG 50W-X8, H^+, 20–50 mesh) was then added until pH was about 4. Filtration and then evaporation of H_2O from the filtrate left (+)-**15** as a white solid (1.70 g, 92%); mp 149–154 °C; R_f = 0.2 (EtOAc–MeOH, 90:10).

$[\alpha]_D^{25}$ +143 (*c* 1.02, HCO_2H).

IR (KBr): 3400, 3320, 3220, 1700, 1650 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.79 (m, 2 H, H4), 2.08 (quint, *J* = 9.9 Hz, 1 H, H3), 2.17 (m, 1 H, H3), 3.14 (m, 1 H, H1), 4.40 (m, 1 H, H2), 5.56 (s, 2 H, NH_2), 6.23 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 17.4, 29.2, 44.9, 45.8, 157.4, 174.7.

MS (CI): *m*/*z* = 159 $[M + H]^+$.

Anal. Calcd for $C_6H_{10}N_2O_3$: C, 45.57; H, 6.37; N, 17.71. Found: C, 45.68; H, 6.48; N, 17.64.

(–)-(1*R*,2*S*)-2-[(Aminocarbonyl)amino]cyclobutanecarboxylic Acid [(–)-15]
Compound (–)-**14** (1.00 g, 7.14 mmol) was dissolved in 0.5 M NaOH (50 mL) and stirred overnight at r.t. Cation exchange resin (Bio-Rad AG 50W-X8, H^+, 20–50 mesh) was then added until pH was about 4. Filtration and then evaporation of H_2O from the filtrate left (–)-**15** as a white solid (1.12 g, 99%); mp 149–151 °C. Other data: as for (+)-**15**.

$[\alpha]_D^{25}$ –143 (*c* 1.02, HCO_2H).

(+)-(1*S*,2*R*)-2-Aminocyclobutanecarboxylic Acid [(+)-(1*S*,2*R*)-1]
Compound (+)-**15** (1.70 g, 10.7 mmol) was dissolved in 3.5 M HCl (250 mL). $NaNO_2$ (0.75 g, 10.7 mmol) was added and the mixture was stirred overnight at r.t. The soln was deposited on a cation-exchange column (Dowex 50WX8-100, H^+, 50–100 mesh). The column was washed with H_2O until the eluent was neutral, then the product was eluted with 1 M NH_4OH soln. After pooling and evaporation of appropriate fractions, pure (+)-(1*S*,2*R*)-**1** was obtained as a white solid (1.08 g, 88%); mp 128–130 °C; R_f = 0.4 (PrOH–H_2O, 70:30); HPLC: t_R = 7.2 min, >97% ee.

$[\alpha]_D^{25}$ +71 (*c* 1.02, H_2O).

IR (KBr): 3422, 2957, 1542, 1406, 1293 cm^{-1}.

^1H NMR (D_2O): δ = 2.05 (m, 1 H, H4), 2.25 (m, 2 H, H4, H3), 2.35 (m, 1 H, H3), 3.22 (m, 1 H, H1), 3.92 (q, *J* = 7.2 Hz, 1 H, H2).

^{13}C NMR (D_2O): δ = 21.1, 24.9, 41.3, 45.4, 180.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_5H_{10}NO_2$: 116.0712; found: 116.0706.

(–)-(1*R*,2*S*)-2-Aminocyclobutanecarboxylic Acid [(–)-(1*R*,2*S*)-1]

Compound (–)-**15** (0.660 g, 4.20 mmol) was dissolved in 3.5 M HCl (92 mL). $NaNO_2$ (0.29 g, 4.20 mmol) was added and the mixture was stirred overnight at r.t. The soln was deposited on a cation-exchange column (Dowex 50WX8-100, H^+, 50–100 mesh). The column was washed with H_2O until the eluent was neutral, then the product was eluted with 1 M NH_4OH soln. After pooling and evaporation of appropriate fractions, pure (–)-(1*R*,2*S*)-**1** was obtained as a white solid (0.440 g, 91%); mp 126–128 °C; HPLC: t_R = 10.9 min, >97% ee. Other data: as for (+)-(1*R*,2*S*)-**1**.

$[\alpha]_D^{25}$ –70 (*c* 1.03, H_2O).

2-[(1-Phenylethyl)amino]cyclobutanecarboxylic Acid (17)

Compound (±)-**11b** (0.100 g, 0.41 mmol) was dissolved in 0.5 M NaOH (5 mL) and stirred at r.t. for 4 d. Then the soln was deposited on a cation-exchange column (Dowex 50WX8-100, H^+, 50–100 mesh). The column was washed with H_2O until the eluent was neutral, then the product was eluted with 1 M NH_4OH. After pooling and evaporation of appropriate fractions, **17** was obtained as a white solid (0.067 g, 75%), which had limited stability in protic soln.[37]

^{1}H NMR (D_2O): δ = 1.49 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.69 (m, 1 H), 1.97 (quint, *J* = 9.3 Hz, 1 H), 2.07–2.21 (m, 2 H), 2.42 (m, 1 H, H1), 3.58 (q, *J* = 8.2 Hz, 1 H, H2), 4.11 (q, *J* = 6.9 Hz, 1 H, CH–CH_3), 7.32 (br s, 5 H, Ph).

^{13}C NMR (D_2O): δ = 18.6, 20.8, 25.9, 42.0, 50.4, 56.5, 127.7, 129.1, 129.2, 136.9, 181.8.

MS (CI): *m/z* = 220 $[M + H]^+$.

Catalytic Hydrogenation of Compound 17

A soln of compound **17** (0.030 g, 0.14 mmol) in a mixture of MeOH–H_2O (20 mL:2.5 mL) was stirred under H_2 (3 bar) in presence of 20% $Pd(OH)_2$/C (0.030 g) for 3 d. After filtration through a pad of Celite, the filtrate was concentrated to dryness to leave a white solid (0.030 g).The analysis of this crude material by ^{1}H and ^{13}C NMR spectroscopy revealed a mixture of several products, amongst which 2 major compounds were identified: 5-aminopentanoic acid (**18**) (by comparison with a commercial sample), and 5-(4-carboxybutylamino)pentanoic acid (**19**) (described previously[37]).

(±)-*cis*-2-[(*tert*-Butyloxycarbonyl)amino]cyclobutanecarboxylic Acid [(±)-20]

To a soln of (±)-*cis*-**1** (1.66 g, 14.6 mmol) in a mixture of dioxane–1 M NaOH (34 mL, 2:1, v/v) at 0 °C was added Boc_2O (3.32 g, 15.9 mmol). The soln was stirred at 0 °C for 5 min then at r.t. for 4 h. Solvents were evaporated and H_2O (15 mL) was added, followed by acidification to pH 1 by addition of 1 M HCl . The aqueous mixture was extracted with EtOAc (3 × 90 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and evaporated to give (±)-**20** as a white powder (2.95 g, 94%); mp 169–172 °C; R_f = 0.6 (EtOAc).

(+)-(1*S*,2*R*)-20

Mp 116–119 °C; $[\alpha]_D^{27}$ +48 (*c* 0.85, $CHCl_3$).

(–)-(1*R*,2*S*)-20

Mp 116–119 °C; $[\alpha]_D^{27}$ –47 (*c* 0.90, $CHCl_3$) [Lit.[14a] $[\alpha]_D$ –48.6 (*c* 0.74, CH_2Cl_2)].

IR (KBr): 3347, 2985, 1696, 1516 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.45 (s, 9 H, *t*-Bu), 1.82 (m, 1 H, H4), 2.09 (m, 1 H, H4), 2.33 (m, 2 H, H3), 3.37 (m, 1 H, H1), 4.35 (quint, *J* = 8.6 Hz, 1 H, H2), 7.22 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 16.7, 27.7, 28.1, 45.9, 47.3, 81.3, 157.6, 177.0.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{10}H_{17}NNaO_4$: 238.1065; found: 238.1055.

Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.31; H, 7.86; N, 6.57.

Methyl (±)-*cis*-2-[(*tert*-Butyloxycarbonyl)amino]cyclobutanecarboxylate [(±)-21]

To a soln of (±)-**20** (2.95 g, 13.7 mmol) in anhyd CH_2Cl_2 (150 mL) under argon, were added DMAP (0.180 g, 1.5 mmol) then MeOH (1.79 mL, 44.2 mmol). After cooling at 0 °C in an ice bath, DCC (2.95 g, 14.9 mmol) was introduced and the stirring was maintained at 0 °C for 5 min then at r.t. for 20 h. Evaporation of solvent under reduced pressure left a slightly brown solid that was purified by chromatography (EtOAc–cyclohexane, 90:10) to afford (±)-**21** as a white powder (2.91 g, 93%); mp 46–48 °C; R_f = 0.7 (EtOAc–cyclohexane, 60:40).

(+)-(1*S*,2*R*)-21

Mp 47–49 °C; $[\alpha]_D^{27}$ +122 (*c* 1.17, $CHCl_3$).

(–)-(1*R*,2*S*)-21

Mp 47–49 °C; $[\alpha]_D^{27}$ –122 (*c* 1.09, $CHCl_3$) [Lit.[14a] $[\alpha]_D$ –131.0 (*c* 0.62, CH_2Cl_2)].

IR (KBr): 3337, 1685, 1527 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.44 (s, 9 H, *t*-Bu), 1.95 (m, 2 H, H4), 2.19 (quint, *J* = 10 Hz, 1 H, H3), 2.33 (m, 1 H, H3), 3.37 (m, 1 H, H1), 3.69 (s, 3 H, CH_3), 4.45 (t, *J* = 7 Hz, 1 H, H2), 5.33 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 18.5, 28.3, 29.5, 45.2, 45.8, 51.7, 79.3, 154.7, 174.7.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{11}H_{19}NNaO_4$: 252.1205; found: 252.1212.

Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35; N, 6.11. Found C, 57.96; H, 8.20; N, 6.13.

Methyl (±)-*trans*-2-[(*tert*-Butyloxycarbonyl)amino]cyclobutanecarboxylate [(±)-22]

Na (0.190 g, 8.26 mmol) was dissolved in anhyd MeOH (85 mL) at r.t. under argon. Compound (±)-**21** (0.420 g, 1.83 mmol) was added to the resulting soln and the mixture was stirred at reflux for 1 h. After cooling in an ice bath, the reaction was quenched by addition of 1 M HCl (17 mL). Excess MeOH was evaporated under reduced pressure and the aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to give a white solid that was purified by chromatography (cyclohexane–EtOAc, 90:10) to afford starting material (±)-**21** recovered as a white powder (0.050 g, 12%) and (±)-**22** as a white powder (0.250 g, 60%); mp 73–75 °C; R_f = 0.5 (EtOAc–cyclohexane, 70:30).

(+)-(1*S*,2*S*)-22

Mp 73–75 °C; $[\alpha]_D^{27}$ +54 (*c* 1.07, $CHCl_3$).

(–)-(1*R*,2*R*)-22

Mp 74–76 °C; $[\alpha]_D^{27}$ –55 (*c* 0.97, $CHCl_3$).

IR (KBr): 3422, 1636, 1525 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.43 (s, 9 H, *t*-Bu), 1.93 (m, 3 H, H4, H3), 2.25 (qd, *J* = 8, 2 Hz, 1 H, H3), 2.98 (m, 1 H, H1), 3.67 (s, 3 H, CH_3), 4.21 (m, 1 H, H2), 4.77 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 18.2, 27.3, 28.3, 46.8, 48.9, 51.7, 79.3, 154.6, 173.4.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{11}H_{19}NNaO_4$: 252.1205; found: 252.1215.

Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.78; H, 8.42; N, 6.11.

(±)-*trans*-2-[(*tert*-Butyloxycarbonyl)amino]cyclobutanecarboxylic Acid [(±)-23]

At r.t., LiOH·H_2O (0.050 g, 1.00 mmol) was added to a soln of (±)-**22** (0.250 g, 1.00 mmol) in THF–H_2O (1:1, 30 mL). The mixture was stirred 1 h and the solvent was evaporated. Successively, H_2O (10 mL) and 1 M HCl (2.5 mL) were added and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated giving compound (±)-**23** as a white powder (0.220 g, 100%); mp 155–157 °C; R_f = 0.6 (EtOAc).

(+)-(1*R*,2*R*)-23

Mp 103–105 °C; $[\alpha]_D^{27}$ +45 (*c* 1.00, $CHCl_3$).

(–)-(1*S*,2*S*)-23

Mp 103–105 °C; $[\alpha]_D^{27}$ –44 (*c* 0.52, $CHCl_3$).

IR (KBr): 3372, 2989, 1702, 1527 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.45 (s, 9 H, *t*-Bu), 1.79 (quint, *J* = 10 Hz, 1 H, H4), 2.20 (m, 3 H, H3, H4), 3.13 (q, *J* = 8.0 Hz, 1 H, H1), 4.10 (m, 1 H, H2), 5.05 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 18.6, 23.7, 28.2, 47.8, 48.7, 82.0, 157.3, 174.3.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{10}H_{17}NNaO_4$: 238.1065; found: 238.1069.

(±)-*trans*-2-Aminocyclobutanecarboxylic Acid [(±)-*trans*-1]

To a soln of compound (±)-**23** (0.220 g, 1.02 mmol) in anhyd CH_2Cl_2 (2.5 mL) was added dropwise TFA (2.6 mL, 34.8 mmol). The soln was stirred 30 min, then evaporated under reduced pressure to afford a brown solid, which was dissolved in H_2O. The soln was deposited on a cation-exchange column (Dowex 50WX8-100, H^+, 50–100 mesh). The column was washed with H_2O until the eluent was neutral, then the product was eluted with 1 M NH_4OH . After pooling and evaporation of appropriate fractions, pure (+)-*trans*-**1** was obtained as a white solid (0.100 g, 88%); mp 151–154 °C; R_f = 0.3 (PrOH–H_2O, 9:1).

(+)-(1*S*,2*S*)-1

Mp 152–154 °C; HPLC: t_R = 12.5 min, >97% ee; $[\alpha]_D^{27}$ +99 (*c* 0.39, H_2O).

(–)-(1*R*,2*R*)-1

Mp 152–154 °C; HPLC: t_R = 19.3 min, >97% ee; $[\alpha]_D^{27}$ –99 (*c* 0.52, H_2O).

IR (KBr): 3449, 2989, 1560, 1415 cm^{-1}.

^1H NMR (D_2O): δ = 1.90 (quint, *J* = 9.8, 1 Hz, 1 H, H4), 2.02 (quint, *J* = 9.2 Hz, 1 H, H4), 2.22 (q, *J* = 9.1 Hz, 2 H, H3), 3.13 (q, *J* = 9.3 Hz, 1 H, H1), 3.88 (q, *J* = 8 Hz, 1 H, H2).

^{13}C NMR (D_2O): δ = 19.8, 22.6, 45.7, 47.6, 180.4.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_5H_{10}NO_2$: 116.0712; found: 116.0719.

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