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Practical Syntheses of Both Enantiomers of the Conformationally Restricted GABA Analogue *cis*-(2-Aminocyclobutyl)acetic Acid

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Two efficient routes have been established for the preparation of both enantiomers of *cis*-(2-aminocyclobutyl)acetic acid, a conformationally restricted analogue of GABA. Both procedures converged on the racemic *N*-*tert*-butoxycarbonyl derivative of the target compound, which was resolved through chiral derivatization with an oxazolidinone auxiliary, which also allowed determination of the absolute configuration of the new compounds. The first route involved the homologation of *cis*-2-aminocyclobutanecarboxylic acid, whereas the second route employed an intramolecular photocyclization protocol, which provided an expedient, *cis*-selective access to the lactam form of the target structure.

Introduction

γ-Amino acids are of considerable interest to organic and medicinal chemists alike, and a considerable number of strategies have been developed for their stereoselective synthesis.[1] The parent compound in the family, γ-aminobutyric acid (GABA), plays an important role in the mammalian central nervous system and behaves as a major inhibitory neurotransmitter (Figure 1).[2] GABA deficiency may be related to significant neurological disorders and derivatives and structural analogues of GABA are of considerable potential for the treatment of neurodegenerative pathologies, such as Parkinson's and Alzheimer's diseases.[3] GABA derivatives that have been commercialized as therapeutics include vigabatrin,[4] baclofen,[5] pregabalin,[6] and gabapentin[7] (Figure 1). γ-Amino acids are becoming increasingly popular as building blocks for peptidomimetics that display well-defined conformational preferences.[8,9] Other synthetic applications of γ-amino acid derivatives have been identified, *e.g.* in the preparation of nucleoside analogues[10] or in organocatalysis,[11] and they are of general interest as functional building blocks for drug discovery.

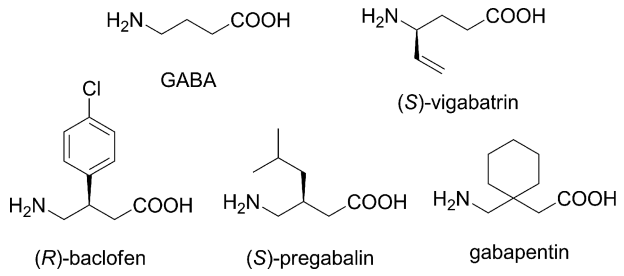

Figure 1. GABA and some commercialized derivatives that have therapeutic applications.

GABA is a highly flexible molecule and to discover and develop selective ligands for GABA receptors, conformationally restricted cyclic analogues of GABA have been of particular interest[12] (Figure 2). In studies of the 2,3-methano-GABA core, (+)-*cis*-2-aminomethylcyclopropanecarboxylic acid [(+)-CAMP] is a potent agonist of ρ1 and ρ2 $GABA_C$ receptors, whereas (–)-CAMP exerts weak antagonist activity.[13] Racemic (±)-*trans*-2-aminomethylcyclopropanecarboxylic acid (TAMP) is a substrate for GABA and pyruvate transaminases,[14] and differentiates ρ3 from other $GABA_C$ receptors in vitro.[15] Both enantiomers of TAMP show partial agonist activity at both $GABA_C$ and $GABA_A$ receptors.[13b] Recently, (1*S*,2*R*)-*trans*-3,4-methano-GABA showed inhibitory effects on the Type-3 GABA transporter and on the Type-1 betaine-GABA transporter.[16] Commensurate synthetic efforts have been made to meet the demands for access to these compounds in non-racemic form.[17–19]

In contrast, much less is known about cyclobutane restricted GABA analogues (Figure 2). Both *cis* and *trans* isomers of 3-aminocyclobutanecarboxylic acid (2,4-methano-GABA) were prepared and were found to exhibit moderate

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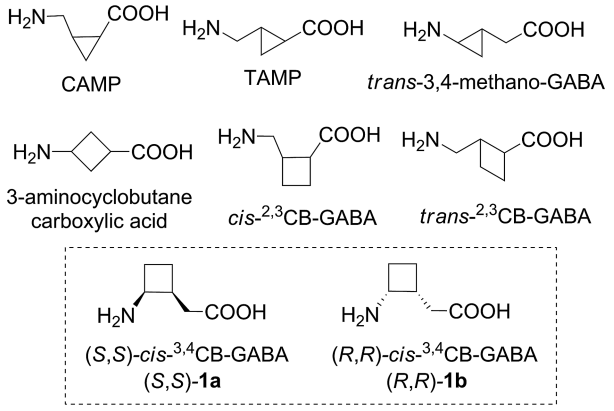


Figure 2. Previously studied small-ring restricted analogues of GABA and the targets in this work.

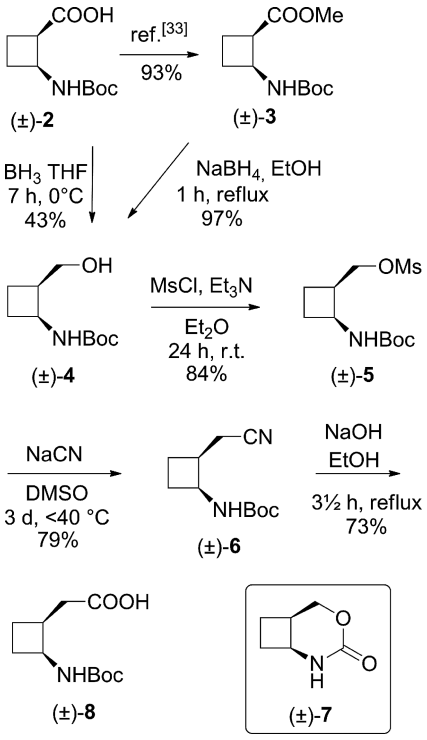
affinity for GABA receptors.[20] The corresponding 2,2-dimethyl derivative has been prepared in enantiomerically pure form, although no biological data have been reported.[21] *cis*-2-(Aminomethyl)cyclobutane-1-carboxylic (*cis*-^{2,3}CB-GABA) has been prepared in enantiomerically pure form,[17c,22] and the first preparation of *trans*-^{2,3}CB-GABA in non-racemic form was described very recently.[23] An interesting bicyclic GABA analogue incorporating a *trans*-^{2,3}CB-GABA feature was prepared recently in racemic form.[24] The third cyclobutane-restricted GABA manifold, (2-aminocyclobutyl)acetic acid (^{3,4}CB-GABA), is even less well explored: only one lengthy synthesis of racemic *cis*- and *trans*-^{3,4}CB-GABAs has been described in the literature, which starts from *cis* and *trans* cyclobutane-1,2-dicarboxylic acids, respectively.[25,26] To expand the availability of conformationally restricted cyclobutane analogues of GABA, we describe here a practical synthetic route to both enantiomers of *cis*-^{3,4}CB-GABA, **1a** and **1b** (Figure 2).

Results and Discussion

Homologation of (±) *cis*-ACBC

A plausible entry to the *cis*-^{3,4}CB-GABA target structure was the homologation of the corresponding β-amino acid, *cis*-2-amino-cyclobutanecarboxylic acid (*cis*-ACBC). Homologation has been a cornerstone strategy for the preparation of enantiomerically enriched β^3-amino acids from their readily available α-amino acid counterparts.[27] The technique has also been applied to the synthesis of certain γ-amino acids from their appropriate β-amino acid precursors, if the latter are available.[28,29]The best-known homologation methodology is the two-step Arndt–Eistert protocol. However, this transformation employs the hazardous reagent diazomethane, which is toxic, carcinogenic and explosive. Furthermore, when the protocol has been applied for the homologation of β-amino acid derivatives,[28] yields of γ-amino acids have been variable, and in some cases large amounts of diazomethane have been required. Although laudable efforts are being made to reduce the risks associated with the use of diazomethane,[30] we preferred to develop a practical synthesis of *cis*-^{3,4}CB-GABA that did not rely on the use of this reagent and would be more amenable to scale-up.[31] On this premise, we set out to establish a *cis*-ACBC homologation sequence loosely inspired by Kennewell's approach for the synthesis of (2-aminocycloalkyl)acetic acids[25] and also by the protocol later employed by Krogsgaard-Larsen for the preparation of homo-β-proline.[29]

Our starting material was racemic *tert*-butoxycarbonyl (Boc)-*cis*-ACBC, **2**, conveniently prepared on gram scale by following a simple three-step procedure (65% yield) that starts from uracil and ethylene.[32] Smooth transformation into methyl ester derivative **3** was accomplished by using MeOH and *N*,*N*′-dicyclohexylcarbodiimide (DCC)/4-dimethylaminopyridine (DMAP), as described previously[33] (Scheme 1). Selective reduction of **3** was achieved with $NaBH_4$ in EtOH at reflux temperatures without any detectable epimerization, which led to alcohol **4** in 97% yield. Direct reduction of **2** to **4** by using BH_3/tetrahydrofuran (THF) could also be achieved, although the two-step procedure was actually easier and gave a better yield.



Scheme 1. Synthesis of (±)-**8** from Boc-*cis*-ACBC, (±)-**2**.

Several approaches were examined for the transformation of the alcohol group of **4** into a nucleofugal leaving group, with the intention to introduce the homologating one-carbon unit as a cyanide ion (Scheme 1). After some inconclusive attempts to convert **4** into the corresponding iodo derivative (PPh_3/I_2/imidazole, CH_2Cl_2) or bromo derivative [PPh_3/CBr_4, dimethylformamide (DMF)], we focused our attention on mesylate derivative **5**. This compound was prepared easily (MsCl, Et_3N, Et_2O) and isolated

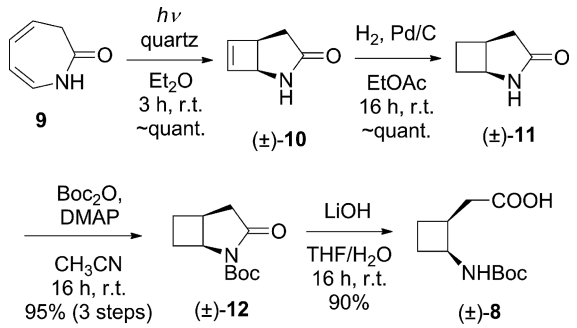
as a stable material in 84% yield after chromatography. Treatment of mesylate **5** with NaCN (5 equiv.) in hot dimethyl sulfoxide (DMSO; 90 °C, 3 h) gave a crude product mixture that contained several components, as indicated by TLC analysis. Desired nitrile **6** was indeed present, but was isolated in a disappointing 10% yield after chromatography. One of the reaction by-products, isolated in up to 27% yield, was bicyclic oxazinone **7**.[26] The cyclization of *N*-Boc *O*-sulfonyl derivatives of 1,3-amino alcohol fragments to give oxazinones has been observed previously, and appears to be induced by base and/or heating.[34] To suppress the formation of **7** (and other by-products) during the nucleophilic substitution reaction, a lower reaction temperature seemed warranted. In the event, nitrile **6** was obtained in a gratifying 79% yield after exposure of mesylate **5** to NaCN (10 equiv.) in DMSO at 35–40 °C for 3 days. *N*-Boc-*cis*-^{3,4}CB-GABA derivative **8** was obtained uneventfully by basic hydrolysis of nitrile **6** by using NaOH in EtOH at reflux temperatures and was isolated in 73% yield after chromatography (Scheme 1).

This homologation sequence provided *N*-protected derivative **8** of the target *cis*-^{3,4}CB-GABA core in racemic form in a reasonable about 44% overall yield from β-amino acid starting material **2**. Because the latter compound is also available in single enantiomer form,[32a,32b,33] the sequence should, in principle, be amenable to the preparation of each enantiomer of **8**. However, the total number of steps from commercial precursors (including racemic preparation of **2**) is eight, with an overall yield of about 28%. Even though this is more efficient than Kennewell's synthesis[25] we felt that the establishment of a more expedient access to derivative **8** would be a worthwhile achievement.

Intramolecular Photocycloaddition of an Azepin-2-one

The axiom for the second approach to the preparation of **8** arose from a perusal of earlier literature reports that described rapid photochemical access to 2-azabicyclo-[3.2.0]hept-6-en-3-one (**10**).[35] Irradiation of a solution of 1,3-dihydro-2*H*-azepin-2-one (**9**; prepared in two steps and 60% yield from caprolactam,[36,37]) in Et_2O for 3 h with a 400 W Hg vapor lamp and a quartz filter provided cycloaddition adduct **10** cleanly in near quantitative yield (Scheme 2).[35a,36,38] Without purification, this material was promptly suspended in EtOAc and reduced overnight under H_2 (1 atm) in the presence of 10% Pd/C. Bicyclic lactam **11** was obtained easily, again in near quantitative yield. Without purification this compound was treated with Boc_2O/DMAP in acetonitrile to install the *N*-Boc protecting group; this operation was equally efficient and provided derivative **12** after chromatography in a highly satisfactory 95% overall yield for three steps.

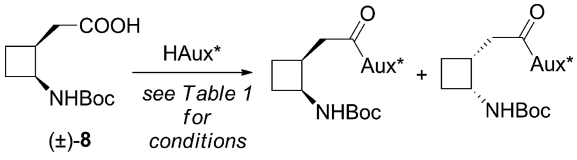
Compound **12** underwent smooth lactam ring opening upon treatment with LiOH in a THF/H_2O mixture in mild conditions, to provide racemic *N*-Boc-*cis*-^{3,4}CB-GABA **8** in 90% yield after chromatography (Scheme 2). Spectroscopic and physicochemical characterization confirmed that material obtained through this route was identical with samples of **8** obtained through the first route (Scheme 1). With fewer steps, less purification of intermediates, and a higher overall yield (ca. 51% for six steps), the second route presents some advantages over the first.



Scheme 2. Synthesis of (±)-**8** from caprolactam **9**.

Chiral Resolution of *N*-Boc-Protected Derivative 8

As indicated above, the first route to **8** should accommodate enantiomerically pure starting material **2**. However, a convenient resolution procedure for (±)-**8** is still warranted. We considered several chiral resolving agents, and took into account the yield of the derivatization step, the ease of separation of diastereoisomers thus obtained, and the efficiency of the chiral auxiliary cleavage and its recycling potential (Scheme 3, Table 1).

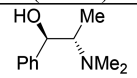
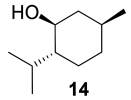
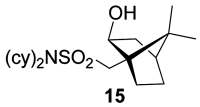
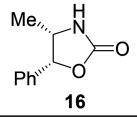


Scheme 3. Chiral derivatization of (±)-**8** for resolution studies.

Three chiral enantiopure alcohols were tested for the formation of diastereoisomeric esters from (±)-**8** under standard coupling conditions (DCC, DMAP, CH_2Cl_2). Despite the relative lack of steric hindrance in the vicinity of the carboxylic acid function of (±)-**8** the yields of esters were rather disappointing. The ester obtained with (–)-*N*-methylephedrine (**13**) was isolated in 51% yield as diastereoisomeric mixture, inseparable by chromatography or crystallization. The diastereoisomeric ester mixture obtained in 73% yield with (+)-menthol (**14**) could only be partly separated by chromatography or by crystallization from hot cyclohexane. The attempted esterification with (–)-*N*,*N*-dicyclohexyl-(1*S*)-isoborneol-10-sulfonamide (**15**) failed to progress even after 4 days.

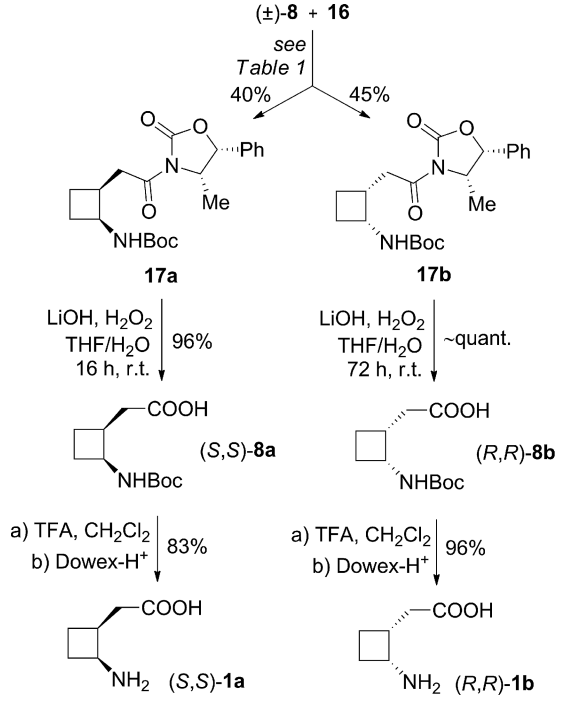
We turned our attention to the use of an oxazolidinone, a chiral auxiliary that has proven useful in the resolution of four-membered ring β-amino acids.[32a,39] The coupling reaction of (±)-**8** with (4*S*,5*R*)-4-methyl-5-phenyloxazolidin-2-one (**16**; prepared in accordance with the literature[40]) gave a diastereoisomeric mixture in 85% yield and

Table 1. Studies on the resolution of (±)-**8**.

Chiral auxiliary (HAux*)	Coupling conditions	Overall yield	Separation of diastereomers
 **13**	DCC, DMAP CH_2Cl_2, 4 d, r.t.	51%	not separable by chromatography[a] or crystallisation[b]
 **14**	DCC, DMAP CH_2Cl_2, 16 h, r.t.	73%	not separable by chromatography,[c] partially separable by crystallisation[d]
 **15**	DCC, DMAP CH_2Cl_2, 4 d, r.t.	no reaction	
 **16**	a) PivCl, Et_3N, THF, 1 h, 0 °C b) *n*BuLi, **16**, THF, 1 h, –75 °C	85%	separable by chromatography[e]

[a] EtOAc/petroleum ether (50:50) as eluent: single spot, R_f 0.28. [b] Solvent was cyclohexane. [c] EtOAc/petroleum ether (50:50) as eluent: single spot, R_f 0.67. [d] Solvent was cyclohexane. [e] See Experimental Section for details.

allowed straightforward chromatographic separation of diastereoisomers **17a** and **17b**, obtained as single isomers in 40 and 45% yields, respectively (Scheme 4).



Scheme 4. Preparation of enantiomerically pure *cis*-^{3,4}CB-GABA, **1a** and **1b**.

To determine the absolute configuration of these non-racemic derivatives, a single crystal of diastereoisomer **17b** was analyzed by X-ray diffraction; the molecular structure is shown in Figure 3. Because the configuration of the oxazolidinone fragment is known to be 4*S*,5*R*, the configuration of the cyclobutane γ-amino acid moiety of this compound could be identified unambiguously as *R*,*R*.

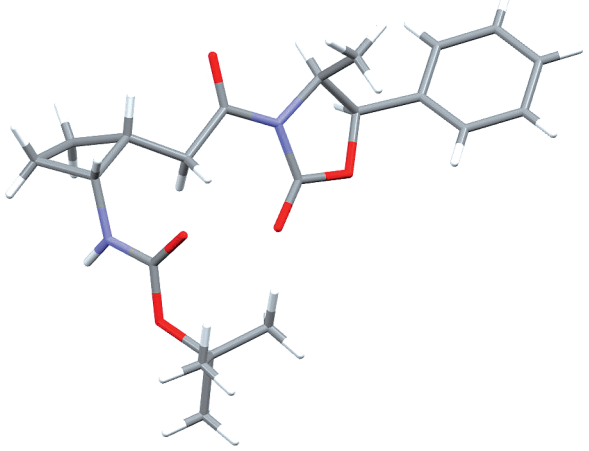


Figure 3. Single-crystal X-ray diffraction structure of compound **17b**.

Each derivative **17a** and **17b** was treated with LiOH/H_2O_2 in THF/H_2O to remove chiral auxiliary **16**, which was easily recovered during reaction work up and recycled (Scheme 4). The resolved *N*-Boc-*cis*-^{3,4}CB-GABA enantiomers **8a** and **8b** were therefore obtained in quantitative or near quantitative yields. The enantiomeric excesses of these materials were checked at this stage by GC analysis with a chiral column, and it was found that **8a** had an *ee* of 98.5%, whereas **8b** had an *ee* of 97.2%. Finally, the *N*-Boc group cleavage from each derivative **8a** and **8b** was achieved by using trifluoroacetic acid (TFA)/CH_2Cl_2 to provide single enantiomers of *cis*-2-aminocyclobutylacetic acid, **1a** and **1b**, in 83 and 96% yield, respectively (Scheme 4).

Conclusions

Two practical routes have been established for the synthesis of both enantiomers of the conformationally restricted γ-amino acid, *cis*-^{3,4}CB-GABA, for the first time. The complementary routes converge on a common *N*-Boc derivative of the racemate, which is resolved through conversion into diastereoisomeric derivatives with a chiral non-racemic oxazolidinone. The first route, although slightly longer, could be applied to the starting material of the sequence in single enantiomer form.

Experimental Section

General Procedures: THF and Et_2O were distilled on sodium/benzophenone under a nitrogen atmosphere. DMSO, DMF and Et_3N were distilled under reduced pressure from CaH_2. NaCN was finely ground and dried in vacuo at 120 °C for 20 h. Chiral compounds **13**, **14** and **15** were obtained from commercial sources and had *ee* > 96%. Oxazolidinone **16** was prepared from commercial (1*R*,2*S*)-norephedrine in accordance with the literature procedure[40] and had $[a]_D^{24}$ = –161 (*c* = 1.00; $CHCl_3$) {ref.[40] $[a]_D^{23}$ = –163.8 (*c* = 1.02; $CHCl_3$). $[a]_D^{20}$ = –170 (*c* = 1.20; $CHCl_3$)}. Literature procedures were used to prepare compounds **2**,[32] **3**[33] and **9**.[36,37] All other solvents and reagents were used as received from commercial sources without further purification. Preparative

chromatography was performed on columns of silica either manually (flash) or automatically piloted by an ISCO Combiflash system (combiflash). In all cases, the stationary phase was SDS silica gel 60A, 35–70 μm mesh, with the exception of the chromatographic separation of compounds **17a** and **17b**, which was carried out with Macherey–Nagel silica gel 60, 15–40 μm mesh. Analytical TLC plates (silica gel 60 F_{254}, Merck) were viewed by using UV fluorescence at 254 nm then stained with basic aqueous $KMnO_4$ solution or ninhydrin solution. Optical rotations were measured in solution in a 10 cm quartz cell with a Jasco P-1010 polarimeter. UV spectra were recorded for solutions in 1 cm quartz cells with an Analytik-Jena Specord 205 instrument. IR spectra were recorded with a Bruker Vertex 70 FTIR spectrophotometer equipped with an ATR accessory. NMR spectroscopic data were acquired at 20 °C with Bruker AC250, AM300 or AM360 spectrometers. Standard Bruker software was used for all experiments. Chemical shifts are reported with respect to the residual proton signal in deuterated chloroform (δ = 7.27 ppm) or deuterated water (δ = 4.70 ppm) for ^{1}H, and with respect to $CDCl_3$ (δ = 77.00 ppm) for ^{13}C. Splitting patterns for ^{1}H signals are designated as: s (singlet), d (doublet), br. s (broad singlet) q (quartet) and m (multiplet). High-resolution mass spectra were recorded on a Bruker MicroTOFq instrument in electrospray ionization mode. Melting points were recorded on a Reichert heating deck microscope. Elemental analyses were carried out by the CNRS Microanalysis Service, Gif-sur-Yvette, France. Enantiomeric excesses (*ee*) were determined by gas chromatography with a Shimadzu GC-2010 Plus instrument equipped with a Supelco B-Dex225 chiral column (30 m × 0.25 mm; 0.25 μm) under the following conditions: helium vector gas; isotherm 170 °C; injection split/splitless (split 1/50) and detection (FID) at 200 °C; constant linear speed 50 cm/sec; pressure equivalence 215 kPa. Under these conditions, t_R = 17.5 min for **8a** and t_R = 16.4 min for **8b**.

***cis*-(2-*tert*-Butoxycarbonylaminocyclobutyl)methanol (±)-4. Method A:** Small portions of $NaBH_4$ (1.64 g, 43.3 mmol, 10 equiv.) were added at 0 °C, to a stirred solution of ester **3** (992 mg, 4.33 mmol) in absolute EtOH (20 mL). The reaction mixture was slowly heated to reflux for 1 h. After cooling to room temperature, lumps that formed were broken up to give a slurry that was poured into brine (20 mL). The mixture was filtered. The filtrate was concentrated under reduced pressure and extracted with Et_2O (6 × 15 mL). The residual solid was extracted by stirring in Et_2O (4 × 20 mL) for 2 h. The combined ether extracts were dried with $MgSO_4$, filtered, and concentrated to give a white solid that was purified by chromatography (combiflash) with EtOAc/petroleum ether as eluent (gradient 30:70 to 100:0). Compound **4** was obtained as a white solid (840 mg, 4.18 mmol, 97%).

Method B: To a solution of **2** (250 mg, 1.16 mmol) in dry THF (20 mL), cooled to 0 °C under an atmosphere of argon, was added BH_3·THF (5.7 mL, 5.7 mmol, 4.9 equiv.). The reaction mixture was stirred at 0 °C for 7 h. Excess borane was quenched by dropwise addition of water. The resulting solution was warmed to room temperature, diluted with brine (20 mL) and extracted with EtOAc (2 × 40 mL). Combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by chromatography as described above. Compound **4** was obtained as a white solid (100 mg, 0.50 mmol, 43%).

M.p. 75 °C. R_f 0.51 (EtOAc/petroleum ether, 50:50). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.44 (s, 9 H), 1.57–1.70 (m, 1 H), 1.72–1.97 (m, 2 H) 2.31–2.61 (m, 2 H), 2.64–2.78 (m, 1 H), 3.60 (dd, *J* = 11.3, *J* = 4.1 Hz, 1 H), 3.76 (dd, *J* = 11.3, *J* = 8.5 Hz, 1 H), 4.20 (q, *J* = 7.5 Hz, 1 H), 5.11 (br. s, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 18.8, 27.7, 28.4, 41.5, 47.7, 62.4, 79.7, 156.4 ppm. IR: $\tilde{\nu}$ = 1168, 1286, 1533, 1683, 2980, 3310 cm^{-1}. HRMS: calcd. for $C_{10}H_{19}NO_3Na$ 224.1257; found 224.1260. $C_{10}H_{19}NO_3$ (201.26): calcd. C 59.68, H 9.52, N 6.96; found C 59.84, H 9.45, N 6.69.

***cis*-(2-*tert*-Butoxycarbonylaminocyclobutyl)methyl Methanesulfonate (±)-5:** At 0 °C under an argon atmosphere, Et_3N (467 μL, 3.36 mmol) and MsCl (222 μL, 2.86 mmol) were added to a solution of alcohol **4** (439 mg, 2.18 mmol) in dry Et_2O (40 mL). The reaction was stirred for 5 h at room temperature. Additional portions of Et_3N (304 μL, 2.18 mmol) and MsCl (169 μL, 2.18 mmol) were added and stirring was continued for 19 h. The solution was filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by chromatography (combiflash) with EtOAc/petroleum ether (30:70) as eluent, to give compound **5** as a white solid (511 mg, 1.83 mmol, 84%), m.p. 97 °C. R_f 0.69 (EtOAc/petroleum ether, 60:40). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.42 (s, 9 H), 1.61–1.73 (m, 1 H), 1.88–2.05 (m, 2 H); 2.29–2.40 (m, 1 H), 2.82–2.89 (m, 1 H), 3.03 (s, 3 H), 4.32–4.43 (m, 3 H), 4.90 (d, *J* = 7.7 Hz, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 17.9, 28.0, 28.3, 37.3, 39.0, 46.0, 69.4, 79.5, 155.1 ppm. IR: $\tilde{\nu}$ = 1163, 1178, 1339, 1512, 1683, 2991, 3372 cm^{-1}. HRMS: calcd. for $C_{11}H_{21}NO_5SNa$ 302.1046; found 302.1033.

***cis*-(2-*tert*-Butoxycarbonylaminocyclobutyl)acetonitrile (±)-6:** To a stirred solution of **5** (500 mg, 1.79 mmol) in dry DMSO (10 mL) at 0 °C, under an argon atmosphere, was added powdered NaCN (877 mg, 17.89 mmol) in small portions. The reaction mixture was stirred at 35–40 °C for 3 d. The solvent was evaporated under reduced pressure with the help of a water bath kept below 40 °C. Brine (25 mL) was added to the residue and the aqueous layer was extracted with CH_2Cl_2 (4 × 15 mL). Combined CH_2Cl_2 extracts were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by chromatography (combiflash) with EtOAc/petroleum ether as eluent (20:80) to afford compound **6** as a white solid (297 mg, 1.42 mmol, 79%), m.p. 151 °C. R_f 0.82 (EtOAc/petroleum ether, 50:50). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.44 (s, 9 H), 1.69–1.75 (m, 1 H), 1.99–2.16 (m, 2 H), 2.37–2.41 (m, 1 H), 2.44–2.63 (m, *2* H), 2.78–2.90 (m, 1 H), 4.27–4.33 (m, 1 H), 4.77 (br. s, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 17.6, 20.7, 26.5, 28.3, 36.5, 46.6, 79.7, 119.2, 155.1 ppm. IR: $\tilde{\nu}$ = 1161, 1275, 1525, 1680, 2248, 2984, 3342 cm^{-1}. HRMS: calcd. for $C_{11}H_{18}N_2O_2Na$ 233.1260; found 233.1260. $C_{11}H_{18}N_2O_2$ (210.27): calcd. C 62.83, H 8.63, N 13.32; found C 62.91, H 8.74, N 13.19.

Compound (±)-7: To a solution of compound **5** (117 mg, 0.42 mmol) in dry DMSO (700 μL) was added powdered NaCN (105 mg, 2.15 mmol) in small portions. The reaction was heated at 90 °C and stirred for 3 h. After cooling, water (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (4 × 5 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography (flash) with EtOAc/petroleum ether as eluent (gradient 20:80 to 100:0) to afford compound **6** as a white solid (10 mg, 0.04 mmol, 10%) and compound **7**, not analytically pure, as a yellow solid (15 mg, 0.12 mmol, 27%), m.p. 75 °C (ref.[26] m.p. 89.5–90.5 °C). R_f 0.20 (EtOAc). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.93–2.19 (m, 3 H), 2.30–2.47 (m, 1 H), 2.79–2.98 (m, 1 H), 4.01 (m, 1 H), 4.25 (dd, *J* = 5.6, *J* = 11.2 Hz, 1 H), 4.34 (dd, *J* = 4.8, *J* = 11.2 Hz, 1 H), 5.85 (br. s, 1 H) ppm. ^{13}C NMR (90 MHz, $CDCl_3$): δ = 19.0, 29.8, 31.3, 48.3, 68.4, 155.6 ppm. IR: $\tilde{\nu}$ = 1053, 1288, 1707, 2920, 3226 cm^{-1}. HRMS: calcd. for $C_6H_9NO_2Na$ 150.0525; found 150.0521.

***cis*-2-Azabicyclo[3.2.0]hept-6-en-3-one (±)-10:** A solution of azepinone **9** (450 mg, 4.13 mmol) in dry Et_2O (300 mL), in a water-co-

oled photochemical quartz reactor fitted with a reflux condenser, was degassed with an argon stream for 15 min. The stirred solution was irradiation with a 400 W medium-pressure mercury vapor lamp for 3 h and the solvent evaporated under reduced pressure. Compound **10** was obtained as a yellow solid (450 mg), which was used without purification in the next experiment. R_f 0.11 (Et_2O). ^1H NMR (250 MHz, $CDCl_3$): δ = 2.27 (dd, J = 17.9, J = 3.4 Hz, 1 H), 2.46 (dd, J = 17.9, J = 10.2 Hz, 1 H), 3.53 (dt, J = 10.2, J = 3.4 Hz, 1 H), 4.43–4.44 (m, 1 H), 6.30–6.33 (m, 2 H), 7.05 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 33.7, 41.4, 57.9, 142.3, 142.5, 178.7 ppm. IR: $\tilde{\nu}$ = 1250, 1302, 1645, 1676, 2961, 3266 cm^{-1}. HRMS: calcd. for C_6H_8NO 110.600; found 110.0599.

***cis*-2-Azabicyclo[3.2.0]heptan-3-one (±)-11:** To a suspension of crude compound **10** (450 mg) in EtOAc (30 mL), was added Pd/C catalyst (10%, 130 mg). The mixture was purged with a hydrogen stream and stirred for 16 h under a hydrogen atmosphere. The reaction mixture was then filtered through Celite and the filtrate evaporated. Crude lactam **11** was obtained as a colorless liquid (439 mg), which was used without purification in the next experiment. R_f 0.11 (Et_2O). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.87 (m, 2 H), 2.17 (d, J = 18.0 Hz, 1 H), 2.23–2.33 (m, 2 H), 2.47 (dd, J = 9.1, J = 18.0 Hz, 1 H), 3.05–3.09 (m, 1 H), 4.04–4.07 (m, 1 H), 7.20 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.5, 26.3, 33.1, 37.1, 54.2, 179.3 ppm. IR: $\tilde{\nu}$ = 1287, 1310, 1677, 2939, 3237 cm^{-1}. HRMS: calcd. for C_6H_9NONa 112.0757; found 112.0761.

***cis*-2-*tert*-Butoxycarbonyl-3-oxo-2-azabicyclo[3.2.0]heptane (±)-12:** To a solution of crude lactam **11** (439 mg) in acetonitrile (40 mL) under argon atmosphere, was added DMAP (48 mg, 0.39 mmol). The mixture was cooled to 0 °C then Boc_2O (1.73 g, 7.93 mmol) was added. The mixture was stirred at 0 °C for 5 min and then at room temperature for 16 h. The solvent was evaporated and the crude product was purified by chromatography (combiflash) with Et_2O/petroleum ether as eluent (gradient 5:95 to 100:0) to afford compound **12** as a white solid (834 mg, 3.95 mmol, 95% overall yield for 3 steps), m.p. 51 °C. R_f 0.75 (EtOAc). ^1H NMR (360 MHz, $CDCl_3$): δ = 1.50 (s, 9 H), 1.80–1.92 (m, 1 H), 1.96–2.06 (m, 1 H), 2.23–2.35 (m, 1 H), 2.39–2.53 (m, 2 H), 2.42 (dd, J = 13.2, J = 5.4 Hz, 1 H), 2.91–3.00 (m, 1 H), 4.40–4.43 (m, 1 H) ppm. ^{13}C NMR (90 MHz, $CDCl_3$): δ = 25.1, 27.8, 28.0, 28.4, 39.5, 58.0, 82.5, 149.7, 175.1 ppm. IR: $\tilde{\nu}$ = 1140, 1164, 1295, 1760, 2982 cm^{-1}. HRMS: calcd. for $C_{11}H_{17}NO_3Na$ 234.1101; found 234.1096. $C_{11}H_{17}NO_3$ (211.26): calcd. C 62.54, H 8.11, N 6.63; found C 62.51, H 8.23, N 6.65.

***cis*-(2-*tert*-Butoxycarbonylaminocyclobutyl)acetic Acid (±)-8. Method A:** To a stirred solution of nitrile **6** (277 mg, 1.32 mmol) in EtOH (7 mL) was added NaOH (6 M, 7 mL). The reaction mixture was heated to reflux for 3.5 h before the solvent was evaporated under reduced pressure. The residual mixture was cooled in an ice bath and acidified with HCl (2 M, 30 mL) and extracted with EtOAc (4× 20 mL). The combined organic extracts were dried with $MgSO_4$, filtered, concentrated and purified by chromatography (combiflash) with EtOAc/petroleum ether as eluent (gradient 30:70 to 100:0). Compound **8** was obtained as a white solid (220 mg, 0.96 mmol, 73%).

Method B: A solution of compound **12** (200 mg, 0.95 mmol) in THF (15 mL) and water (15 mL) was treated with LiOH (228 mg, 9.52 mmol) then stirred at room temperature for 16 h. THF was evaporated under reduced pressure and the residual aqueous phase was acidified with HCl (0.5 M, to pH 1). The mixture was saturated with solid NaCl and extracted with EtOAc (5× 30 mL). The combined organic extracts were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography (combiflash) with EtOAc/petroleum ether as eluent (gradient 50:50 to 100:0). Compound **8** was obtained as a white solid (195 mg, 0.72 mmol, 90%), m.p. 118 °C. R_f 0.28 (EtOAc/petroleum ether, 50:50). ^1H NMR (360 MHz, $CDCl_3$): δ = 1.43 (s, 9 H), 1.53–1.61 (m, 1 H), 1.87–1.94 (m, 1 H), 1.96–2.05 (m, 1 H), 2.32 (m, 1 H), 2.43 (dd, J = 15.8, J = 9.0 Hz, 1 H), 2.55 (dd, J = 15.8, J = 6.8 Hz, 1 H), 2.91 (m, 1 H), 4.04–4.30 (m, 1 H), 4.85 (br. s, 0.7 H), 6.07 (br. s, 0.3 H), 11.00 (br. s, 1 H) ppm. ^{13}C NMR (90 MHz, $CDCl_3$): δ = 21.3, 27.2, 28.3, 34.2, 36.8, 47.0, 79.4, 155.2, 177.8 ppm. IR: $\tilde{\nu}$ = 1155, 1168, 1275, 1684, 2986, 3361 cm^{-1}. HRMS: calcd. for $C_{11}H_{19}NO_4Na$ 252.1206; found 252.1212. $C_{11}H_{19}NO_4$ (229.27): calcd. C 57.62, H 8.35, N 6.11; found C 57.74, H 8.46, N 6.31.

Compounds 17a and 17b: To a solution of compound **8** (1.00 g, 4.37 mmol) in dry THF (40 mL) under an argon atmosphere, was added Et_3N (1.22 mL, 8.74 mmol). The mixture was cooled to –78 °C, and pivaloyl chloride (565 µL, 4.59 mmol) was added slowly. The mixture was warmed to 0 °C and stirred for 1 h, then cooled again to –78 °C. In a separate flask, *n*BuLi (2.7 mL, 4.37 mmol) was added to a solution of oxazolidinone **16** (774 mg, 4.37 mmol) in dry THF (20 mL) at –40 °C under an argon atmosphere. This mixture was stirred for 5 min then transferred by cannula to the cold solution that contained compound **8**. The combined mixture was stirred for 1 h at –78 °C then warmed to 0 °C. A saturated solution of $NaHCO_3$ (20 mL) was added. THF was evaporated under reduced pressure and the residual aqueous layer was extracted with CH_2Cl_2 (4× 20 mL). Combined organic extracts were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (combiflash) with Et_2O/petroleum ether as eluent (gradient 15:55 to 60:40) to afford compound **17a** (679 mg, 1.75 mmol, 40% yield) and compound **17b** (757 mg, 1.95 mmol, 45% yield) as white solids.

***tert*-Butyl *N*-[(1*S*,2*S*)-2-{2-[(4*S*,5*R*)-4-Methyl-2-oxo-5-phenyl-1,3-oxazolidin-3-yl]-2-oxoethyl}cyclobutyl]carbamate (17a):** M.p. 121 °C. R_f 0.44 (Et_2O/petroleum ether, 50:50). $[\alpha]_D^{25}$ = –69 (c = 1.02; $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 0.90 (d, J = 6.5 Hz, 3 H), 1.45 (s, 9 H), 1.51–1.59 (m, 1 H), 1.84–2.10 (m, 2 H), 2.29–2.34 (m, 1 H), 2.96–3.14 (m, 2 H), 3.18–3.26 (m, 1 H), 4.21–4.31 (m, 1 H), 4.76 (q, J = 6.6 Hz, 1 H), 4.83 (br. s, 1 H), 5.68 (d, J = 7.6 Hz, 1 H), 7.29–7.43 (m, 5 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 14.6, 21.4, 27.4, 28.4, 35.1, 36.4, 47.2, 54.8, 79.0, 79.3, 125.6, 128.7, 129.1, 133.4, 153.3, 155.2, 171.9 ppm. IR: $\tilde{\nu}$ = 1352, 1511, 1688, 1711, 1771, 2982, 3377 cm^{-1}. HRMS: calcd. for $C_{21}H_{28}N_2O_5Na$ 411.1890; found 411.1881.

***tert*-Butyl *N*-[(1*R*,2*R*)-2-{2-[(4*S*,5*R*)-4-Methyl-2-oxo-5-phenyl-1,3-oxazolidin-3-yl]-2-oxoethyl}cyclobutyl]carbamate (17b):** M.p. 100 °C. R_f 0.35 (Et_2O/petroleum ether, 50:50). $[\alpha]_D^{25}$ = +22 (c = 1.02; $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 0.88 (d, J = 6.0 Hz, 3 H), 1.41 (s, 9 H), 1.47–1.54 (m, 1 H), 1.85–2.08 (m, 2 H), 2.27–2.38 (m, 1 H), 2.91 (dd, J = 16.4, J = 8.2 Hz, 1 H), 3.00–3.12 (m, 1 H), 3.30 (dd, J = 16.1, J = 6.6 Hz, 1 H), 4.31–4.36 (m, 1 H), 4.75 (q, J = 7.6 Hz, 1 H), 4.93 (d, J = 7.3 Hz, 1 H), 5.67 (d, J = 7.0 Hz, 1 H), 7.28–7.44 (m, 5 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 14.4, 21.2, 27.6, 28.3, 35.2, 36.5, 46.8, 54.8, 79.0, 79.2, 125.6, 128.6, 133.2, 153.2, 155.1, 171.8 ppm. IR: $\tilde{\nu}$ = 1350, 1525, 1688, 1707, 1777, 2979, 3361 cm^{-1}. HRMS: calcd. for $C_{21}H_{28}N_2O_5Na$ 411.1890; found 411.1871.

***cis*-[(1*S*,2*S*)-2-*tert*-Butoxycarbonylaminocyclobutyl]acetic Acid (8a):** To a solution of **17a** (266 mg, 0.69 mmol) in THF/H_2O (17 mL, 1:1) were added H_2O_2 (35 wt.-% solution in water; 400 µL, 4.12 mmol) and LiOH (82 mg, 3.42 mmol). The mixture was stirred

at room temperature for 16 h. A solution of Na_2SO_3 (1 M, 5 mL) and a saturated solution of $NaHCO_3$ (5 mL) were added successively. THF was removed under reduced pressure and the residual aqueous layer was extracted with CH_2Cl_2 (4 × 4 mL). The organic extracts were dried with $MgSO_4$, filtered and concentrated to afford oxazolidinone **16** (120 mg, 0.68 mmol) for recycling. The aqueous phase was cooled to 0 °C, acidified with concentrated HCl (to pH 1) and extracted with CH_2Cl_2 (4 × 4 mL). The organic extracts were dried with $MgSO_4$, filtered and concentrated to afford compound **8a** as white solid (151 mg, 0.66 mmol, 96%), m.p. 127 °C. $[\alpha]_D^{27}$ = –69 (*c* = 0.99; $CHCl_3$). *ee* = 98.5%. ^{1}H NMR, ^{13}C NMR, and IR spectroscopic data were identical to those observed for **(±)-8**.

***cis*-[(1*R*,2*R*)-2-*tert*-Butoxycarbonylaminocyclobutyl]acetic Acid (8b):** Compound **17b** (253 mg, 0.65 mmol) was treated in the same manner as above, for a reaction time of 72 h. In addition to oxazolidinone **16** (113 mg, 0.64 mmol) for recycling, compound **8b** was obtained as a white solid (149 mg, 0.65 mmol, 100%), m.p. 127 °C. $[\alpha]_D^{27}$ = +68 (*c* = 0.96; $CHCl_3$). *ee* 97.2%. ^{1}H NMR, ^{13}C NMR, and IR spectroscopic data were identical to those observed for **(±)-8**.

***cis*-[(1*S*,2*S*)-2-Aminocyclobutyl]acetic Acid (1a):** A solution of **8a** (100 mg, 0.44 mmol) in CH_2Cl_2 (12 mL) was cooled to 0 °C and TFA (670 μL, 8.74 mmol) was added. The solution was stirred for 2 h at room temperature. The mixture was evaporated under reduced pressure and the residue was taken up in water (3 mL) and this solution applied to a column of cation-exchange resin (Dowex 50Wx8, H^+, 50–100 mesh). Elution with aqueous NH_3 (3 M) provided free amino acid **1a** as a white solid (47 mg, 0.36 mmol, 83%), m.p. 195 °C. $[\alpha]_D^{25}$ = +8 (*c* = 0.98; H_2O). ^{1}H NMR (250 MHz, D_2O): δ = 1.59–1.70 (m, 1 H), 1.95–2.10 (m, 2 H), 2.20–2.29 (m, 1 H), 2.31 (dd, *J* = 8.1, *J* = 14.8 Hz, 1 H), 2.40 (dd, *J* = 8.1, *J* = 14.8 Hz, 1 H), 2.75–2.89 (m, 1 H), 3.83 (q, *J* = 7.7 Hz, 1 H) ppm. ^{13}C NMR (90 MHz, D_2O): δ = 21.6, 23.8, 34.4, 37.2, 47.5, 180.8 ppm. IR: $\tilde{\nu}$ = 1425, 1530, 1563, 1677, 2943, 3419 cm^{-1}. HRMS: calcd. for $C_6H_{11}NO_2Na$ 130.0863; found 130.0863.

***cis*-[(1*R*,2*R*)-2-Aminocyclobutyl]acetic Acid (1b):** Compound **8b** (150 mg, 0.65 mmol) was treated in the same manner as above. Free amino acid **1b** was obtained as a white solid (81 mg, 0.62 mmol, 96%), m.p. 195 °C. $[\alpha]_D^{27}$ = –8 (*c* = 0.98; H_2O). HRMS: calcd. for $C_6H_{11}NO_2Na$ 130.0863; found 130.0864. ^{1}H NMR and ^{13}C NMR spectroscopic data were identical to those observed for **1a**.

X-ray Diffraction Study of Compound 17b: Diffraction data were collected with a Kappa X8 APPEX II Bruker diffractometer with graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å). The crystal was mounted on a CryoLoop (Hampton Research) with Paratone-N (Hampton Research) as cryoprotectant and then flash-frozen in a nitrogen gas stream at 100 K. The temperature of the crystal was maintained at the selected value (100 K) by means of a 700 series Cryostream cooling device to within an accuracy of ±1 K. Data were corrected for Lorentz polarization, and absorption effects. The structure was solved by direct methods by using SHELXS-97[41] and refined against F^2 by full-matrix least-squares techniques by using SHELXL-97[42] with anisotropic displacement parameters for all non-hydrogen atoms. Hydrogen atoms were located on a difference Fourier map and introduced into the calculations as a riding model with isotropic thermal parameters. All calculations were performed by using the Crystal Structure crystallographic software package WINGX.[43]

CCDC-1000621 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Copies of ^{1}H and ^{13}C NMR spectra of all significant compounds, copies of chiral GC chromatograms for compounds **(±)-8**, **8a** and **8b**.

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