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Versatile Access to 2-Aminocyclobutene-1-carboxylic Acid Derivatives and Their Incorporation into Small Peptides[‡]

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Under a newly developed set of mild conditions [EtN(*i*Pr)$_2$, LiI, DMF, 20 °C, 3 d], methyl 2-chloro-2-cyclopropylideneacetate (**1**) smoothly undergoes Michael addition of various benzylamines (4 examples) with ensuing ring enlargement and elimination to give in very good yields (81–99 %) the correspondingly substituted methyl 2-(benzylamino)cyclobutenecarboxylates **3a**–**d**, which were subsequently converted into the *N*-Boc-protected derivatives **4a**–**d**. After hydrolysis of the esters, the free β-amino acids **5a**,**b** were cleanly condensed with the methyl esters of glycine, (*S*)-proline, (*S*)-phenylglycine and (*S*)-tryptophan to give the dipeptides **6a**–**8a**, **9b** in 58–89 % yield. The cyclic dipeptides **15e**,**f**, consisting of a 2-aminocyclobutenecarboxylic acid and a glycine fragment, were obtained in 38 and 45 % yield, respectively, upon treatment of the spirocyclopropanated chlorohexahydrodiazepinediones **10e**,**f** with sodium cyanide in DMSO at elevated temperatures. Palladium-catalyzed hydrogenation of **4a** afforded methyl *N*-Boc-2-aminocyclobutanecarboxylate **19** as a mixture of *cis* and *trans* isomers.

Introduction

Methylenecyclopropane and its derivatives[1] are endowed with enhanced reactivities across their double bonds[2] as well as their three-membered rings,[3] and this has been utilized in a multitude of synthetically useful transformations. With an electron-withdrawing group attached to the double bond such as in an alkyl 2-cyclopropylideneacetate,[4] a dialkyl cyclopropylidenemalonate,[5] methyl 2-(benzyloxycarbonylamino)-2-cyclopropylideneacetate,[6] an alkyl 2-bromo-2-cyclopropylideneacetate[7] or an alkyl 2-chloro-2-cyclopropylideneacetate such as **1**,[8] methylenecyclopropanes are particularly good dienophiles as well as Michael acceptors.

Michael adducts of benzophenoneimine and secondary amines with **1** have been found to undergo facile transformations to protected 2-aminocyclobutene-1-carboxylates under appropriate conditions.[9,10] So far, the only two examples of sensitive adducts of primary amines to **1** have been prepared in moderate yields and employed in the synthesis of the first 2-azaspiropentanecarboxylic acid derivatives.[10] Notably, only a few examples of 2-aminocyclobutenecarboxylic acid derivatives, all of them with a dialkylamino group on the double bond, have previously been synthesized.[11,12] Here we report on a convenient synthesis of some new 2-aminocyclobut-1-ene-1-carboxylates, and their incorporation into conformationally restricted dipeptide mimics as well as their possible catalytic hydrogenation to provide 2-aminocyclobutanecarboxylates.

Results and Discussion

Upon treatment of the meanwhile conveniently accessible methyl 2-chloro-2-cyclopropylideneacetate (**1**)[13] with benzylamine (**2a**) in *N*,*N*-dimethylformamide in the presence of 1 equiv. of lithium iodide and ethyldiisopropylamine (Hünig's base) at 0–20 °C for 3 d, methyl 2-(benzylamino)-cyclobut-1-ene-1-carboxylate (**3a**) was isolated in 85 % yield. Apparently, the initially formed Michael adduct of **2a** onto **1**, just like those of benzophenoneimine and secondary amines under certain conditions,[9,10] immediately underwent rearrangement with ring enlargement and ensuing elimination of hydrogen chloride. As the multifunctional structural unit of **3a** appeared to be interesting for incorporation into small peptides to be subjected to biological screening, *p*-chloro- (**2b**), *m*-methoxy- (**2c**) and *o*-methoxybenzylamine (**2d**) were employed under the same conditions to furnish the correspondingly substituted products **3b**–**d** in very good yields (Scheme 1 and Table 1).

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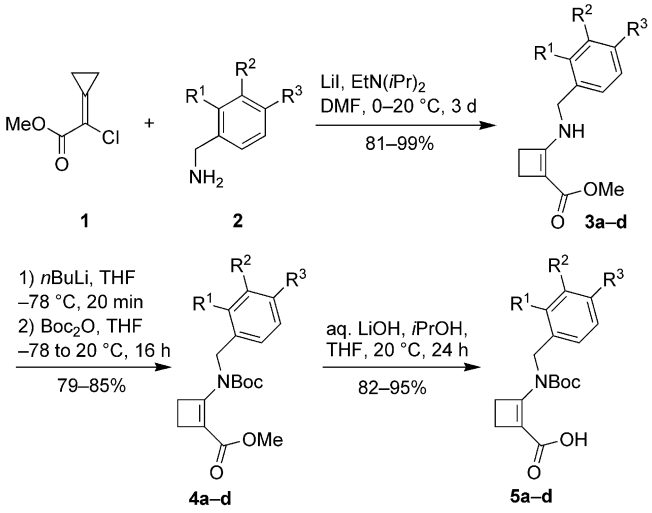


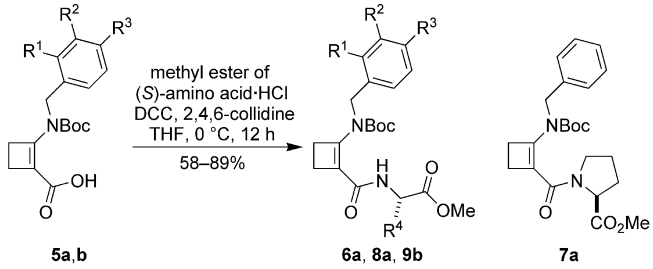
Scheme 1. Optimized conditions for the conversion of methyl 2-chloro-2-cyclopropylideneacetate (**1**) with benzylamines **2** to 2-[(benzyl)(*tert*-butoxycarbonyl)amino]cyclobut-1-ene-1-carboxylic acids **5** (for details see Table 1).

Table 1. 2-[(Benzyl)(*tert*-butoxycarbonyl)amino]cyclobut-1-ene-1-carboxylic acids **5** from of methyl 2-chloro-2-cyclopropylideneacetate (**1**) and benzylamines **2** (see Scheme 1).

Entry	R^1	R^2	R^3	Yield of **3** [%]	Yield of **4** [%]	Yield of **5** [%]
a	H	H	H	85	85	89
b	H	H	Cl	99	82	95
c	H	OMe	H	87	75	91
d	OMe	H	H	81	79	82

The enamine moieties in **3a**–**d** are sensitive towards hydrolysis; thus, upon an attempted acylation of **3a** with bromoacetyl chloride under Schotten–Baumann conditions, only benzylamine (**2a**) and *N*-benzyl-2-bromoacetamide were isolated. However, the amino function in the vinylogous carbamates **3a**–**d** could be deprotonated by treatment with *n*-butyllithium at –78 °C, and the thus formed anions were readily trapped with di-*tert*-butyl pyrocarbonate (Boc_2O) to yield **4a**–**d** in 75–85% yield as colorless and stable solids, which could be purified by column chromatography. Mild hydrolysis of the ester functions in **4a**–**d** with aqueous lithium hydroxide and 2-propanol as cosolvent furnished the *N*-protected α,β-unsaturated β-amino acids **5a**–**d** as colorless solids (Scheme 1, Table 1).

Condensation of **5a** with glycine (Gly) and with (*S*)-proline (Pro) by employing dicyclohexylcarbodiimide (DCC) in the presence of 2,4,6-collidine yielded the dipeptides **6a** and **7a**, respectively, in very good yields of 89 and 87% (Scheme 2, Table 2). The coupling of **5a** with (*S*)-phenylglycine (Phg) and of **5b** with (*S*)-tryptophan (Trp) furnished the dipeptides **8a** (84%) and **9b** (58% yield). An attempted removal of the *N*-(*tert*-butoxycarbonyl) (Boc) group from **9b** by treatment with 50% trifluoroacetic acid in dichloromethane led to a complex mixture of unidentified products.



Scheme 2. Preparation of some dipeptides from the *N*-protected 2-(benzylamino)cyclobut-1-ene-1-carboxylic acids **5a**,**b** (for details see Table 2).

Table 2. Preparation of some dipeptides from the *N*-protected 2-(benzylamino)cyclobut-1-ene-1-carboxylic acids **5a**,**b** (see Scheme 2).

Starting material	R^1	R^2	R^3	R^4	Product	Yield [%]
5a	H	H	H	H	**6a**	89
5a	H	H	H		**7a**[a]	87
5a	H	H	H	CH_2(indol-3-yl)	**8a**	58
5b	H	H	Cl	C_6H_5	**9b**	84

[a] For the structure of **7a**, see Scheme 2.

Due to the coplanar arrangement of the amino and the carboxy group in the 2-aminocyclobutenecarboxylic acid, dipeptides like **6a**–**8a** and **9b** incorporating this conformationally rigid moiety, have an extended conformation. This apparently leads to an enhanced driving force for self-organization as evidenced by the fact that **7a**, **8a** and **9b** readily crystallize. If such dipeptides were endowed with appropriate pharmacophoric groups, this special arrangement might be favorable for their biological activity. However, the current compounds **6a**–**8a** and **9b** turned out to be inactive in general cell tests.

A 2-aminocyclobutenecarboxylic acid fragment would also be incorporated in a cyclobutene-annelated tetrahydrodiazepinedione of type **15**, which would constitute a simple cyclic dipeptide of the former with glycine. In principle, such compounds should be accessible by Lewis acid induced ring-enlarging rearrangement of the cyclopropylmethyl chloride subunit in the spirocyclopropanated hexahydrodiazepinediones of type **10**, which are also easily obtained from methyl 2-chloro-2-cyclopropylideneacetate (**1**) by Michael addition of a primary amine, condensation of the adduct with *N*-Boc-glycine and cyclization of the resulting open-chain dipeptide ester by treatment with sodium carbonate in dichloromethane[14a] or better with ammonia in methanol.[13b] Yet, treatment of the *N*-*n*-pentyl derivative **10f**[15] with LiI and Hünig's base in DMF neither at room temperature nor at 80 °C yielded the cyclobutene-annelated tetrahydrodiazepinedione. Even the attempt to enforce the cationic rearrangement in **10f** by treatment with the much stronger Lewis acid aluminum trichloride in dichloromethane (20 °C, 18 h) led to the recovery of 95% of the starting material. Since cyclopropylcarbenes are known to spontaneously rearrange to cyclobutenes,[16] α-

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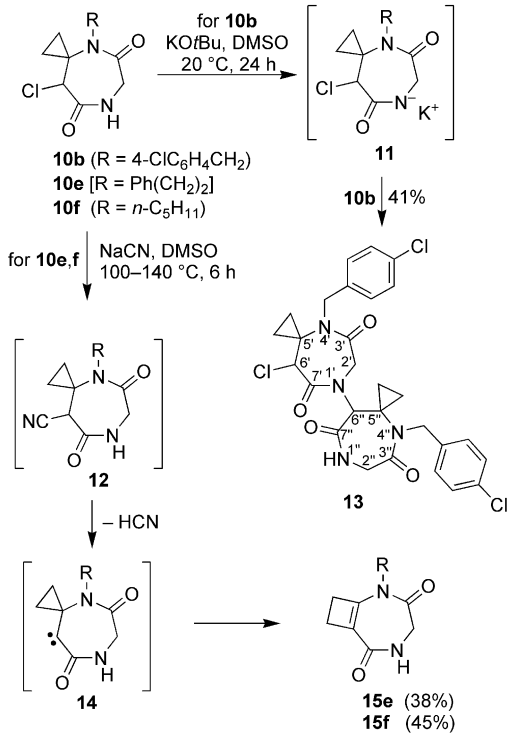
elimination of hydrogen chloride from **10b** to generate the carbene **14** was attempted. Yet, treatment of **10b** with the strong and sterically demanding base potassium *tert*-butoxide in dimethyl sulfoxide did not yield the expected rearrangement product **15b**, but the bis(lactam) **13**, which was obviously formed by nucleophilic substitution of chlorine in **10b** by the amide anion **11** arising by deprotonation of a second molecule of **10b**. According to the ^{1}H NMR spectrum of the crude product, **13** was formed as a single diastereomer (Scheme 3). The 1′-6′′ rather than 6′-6′′ connection of the two seven-membered rings in **13** was assigned on the basis of two resonances in the ^{13}C NMR spectrum at δ = 64.6 and 66.7 ppm with positive DEPT signals and of the HMQC spectrum. Whereas the C-6′ signal is correlated to the resonance at δ = 3.92 ppm (s), the cross peak for the C-6′′ signal is in the range of the aromatic proton resonances at δ = 7.20 ppm, probably due to an anisotropy effect of one of the phenyl groups, which may come close to the proton on C-6′′.



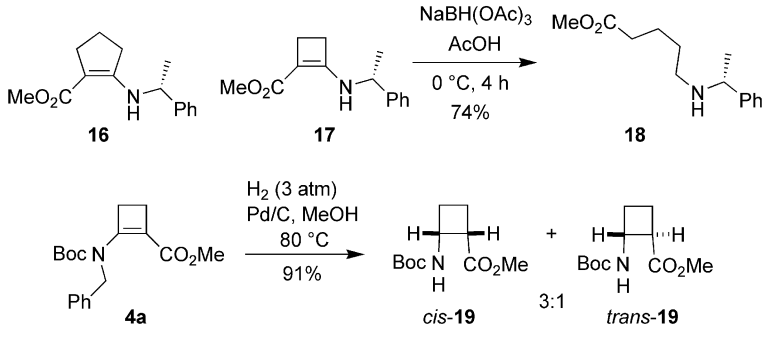
Scheme 3. Two unexpected reactions of spirocyclopropanated chlorohexahydrodiazepinediones **10**.

Unexpectedly, an attempted transformation of the chlorohexahydrodiazepinedione **10e** with sodium cyanide in dimethyl sulfoxide at 100–140 °C to the corresponding cyano-substituted heterocycle furnished the cyclobutene-annelated tetrahydrodiazepinedione **15e** in 38% yield (Scheme 3). Under the same conditions, **10f** gave the analogous **15f** in 45% yield. This interesting transformation can be rationalized as occurring via the initially formed substitution product **12**, which, due to its enhanced C–H acidity at the cyano-substituted position, may undergo α-elimination of hydrogen cyanide. The resulting carbene **14** would then rearrange to the cyclobutene derivative **15**.

In view of the growing interest in peptides derived from *cis*- and *trans*-2-aminocyclobutanecarboxylic acids,[17] it appeared worthwhile to test the hydride-induced reduction and/or catalytic hydrogenation of the double bond in methyl 2-aminocyclobutenecarboxylates of type **3** and/or **4**. The shortest and possibly even enantioselective route to these β-amino acids would be by reduction of the chirally modified 2-aminocyclobutenecarboxylate **17**, prepared from **1** and (*R*)-1-phenylethylamine, with sodium borohydride in acetic acid in complete analogy to a previously published protocol for the conversion of the homologue **16** to 2-aminocyclopentanecarboxylate, which proceeded with high diastereo- and enantioselectivity (Scheme 4).[18]

Under the same conditions as employed for **16**, however, the reaction of the cyclobutene analogue **17** provided the open-chain (*S*)-aminovalerate derivative **18** in 74% yield as the sole product. This again is a consequence of the vicinal donor/acceptor substitution pattern – previously termed captodative substituent effect by Viehe et al.[19] – in the initially formed saturated analogue of **17**.

An attempted hydrogenation of **4a** in the presence of a palladium on carbon catalyst under different conditions always led to mixtures of products. Apparently, hydrogenation of the double bond was accompanied by removal of the benzyl group and partial ring opening of the initially formed cyclobutene derivative. Under the best conditions found (10% Pd/C, 3 atm H_2, 80 °C, 12 h), a 3:1 mixture of methyl *cis*- and *trans*-2-(*tert*-butoxycarbonylamino)cyclobutanecarboxylate (**19**) was isolated in a total yield of 91% (Scheme 4). The isomers could be separated by column



Scheme 4. Hydride-induced reduction and catalytic hydrogenation of the double bond in two methyl 2-aminocyclobutenecarboxylates.

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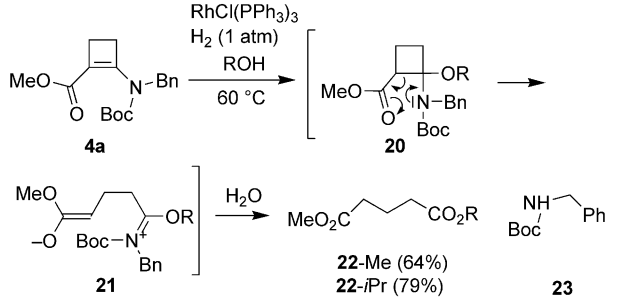
chromatography on silica gel. In a control experiment it was shown that under the employed conditions for hydrogenation, *cis*-**19** is not converted to *trans*-**19** to any extent.

Hydrogenation of **4a** under homogeneous-catalysis conditions, if successful, would be more attractive, as it could also be carried out in an enantioselective fashion by employing appropriate chirally modified catalysts.[20,21] As a test, **4a** in methanol under hydrogen was treated with Wilkinson's catalyst [$RhCl(PPh_3)_3$]. Surprisingly, no cyclobutane amino acid derivative was detected in the reaction mixture, but only dimethyl glutarate (**22**-Me) and *N*-(*tert*-butoxycarbonyl)benzylamine (**23**). In 2-propanol, the mixed isopropyl methyl ester of glutaric acid **22**-*i*Pr along with the carbamate **23** was observed. Interestingly, without the (phosphane)rhodium complex present, with the complex present and under nitrogen instead of hydrogen, or in the presence of triphenylphosphane and otherwise the same conditions, the cyclobutenecarboxylate **4a** remained intact. The mechanism of this transformation is unclear; most probably it involves a somehow catalyzed Michael addition of an alcohol to **4a**. The adduct **20** then undergoes a retro-Claisen ring opening, once again a consequence of the captodative substituent effect,[18] to provide the iminium salt **21**, which is easily hydrolyzed by traces of water in the solvent or upon workup. However, carrying out the reaction in anhydrous alcohols did not change the final result (Scheme 5).



Scheme 5. Attempted Rh^I-catalyzed hydrogenation of **4a** in methanol and 2-propanol.

It remains a challenge to find a homogeneous catalyst and conditions, under which the enantioselective hydrogenation of the dehydro-β-amino acids of type **4** would proceed without ring opening.

Conclusions

The β-amino acid derivatives **4a**–**d** with a cyclobutene backbone, which are efficiently obtained by Michael addition of primary amines to **1** with ensuing cyclopropylcarbinyl-to-cyclobutyl cation ring enlargement and elimination as well as subsequent *N*-Boc protection, constitute new conformationally rigid building blocks for oligopeptides. Condensation of **5a**,**b** with the methyl esters of glycine, tryptophan, phenylglycine and proline leads to the dipeptides **6a**–**8a**, **9b**, three of which are crystalline materials, apparently as a consequence of their conformationally rigidifyed cyclobutene subunits. The successful catalytic hydrogenation of methyl 2-[(benzyl)(*tert*-butoxycarbonyl)-amino]cyclobutenecarboxylate (**4a**) opens up a new access to *cis*- and *trans*-2-aminocyclobutanecarboxylic acids **19**. Whether this carries any advantage over previously developed routes[16] is debatable. One advantage might be, that the new route is extendable to 3- and 4-substituted analogues of **4a**, which would be accessible from the correspondingly substituted 2-chloro-2-cyclopropylideneacetates according to previously published procedures.[9]

Experimental Section

General Remarks: All reagents were used as purchased from commercial suppliers without further purification. All reactions in non-aqueous solvents were carried out by using standard Schlenk techniques under dry nitrogen. Solvents were purified and dried according to conventional methods prior to use. ^1H and ^{13}C NMR spectra were recorded with a Bruker AM 250 (250 MHz for ^1H and 62.9 MHz for ^{13}C) or Varian UNITY-300 (300 MHz for ^1H and 75.5 MHz for ^{13}C) instrument. Chemical shifts δ are given in ppm relative to residual resonances of solvents (^1H: δ = 7.26 ppm for $CHCl_3$, δ = 2.50 ppm for [D_5]DMSO; ^{13}C: δ = 77.0 ppm for $CDCl_3$, δ = 39.52 ppm for [D_6]DMSO) or tetramethylsilane (^1H: δ = 0.00 ppm; ^{13}C: δ = 0.0 ppm); coupling constants J are given as absolute values in Hz. The multiplicities of ^{13}C signals were determined by the DEPT or the APT technique. IR: Bruker IFS 66 (FT-IR) spectrometer, measured as KBr pellets or oils between KBr plates. EI-MS: Finnigan MAT 95, 70 eV. ESI-MS: Finnigan LCQ. High resolution mass spectrometry (HRMS): APEX IV 7T FTICR, Bruker Daltonic. Chromatography: Separations were carried out on Merck Silica 60 (0.063–0.200 mm, 70–230 mesh ASTM). TLC: Macherey–Nagel, TLC plates Alugram® Sil G/UV254. Detection under UV light at 254 nm, development with MOPS reagent (10% molybdophosphoric acid solution in ethanol). Melting points: Büchi 540 capillary melting point apparatus; values are uncorrected. Elemental analyses: Mikroanalytisches Laboratorium des Instituts für Organische und Biomolekulare Chemie der Universität Göttingen.

Methyl 2-(Benzylamino)cyclobut-1-enecarboxylate (3a): To a solution of benzylamine (**2a**) (1.63 g, 15.2 mmol) in DMF (10 mL) was added a solution of methyl 2-chloro-2-cyclopropylideneacetate (**1**) (2.23 g, 15.2 mmol) in DMF (10 mL), $EtN(iPr)_2$ (2.18 g, 16.9 mmol) and LiI (2.26 g, 16.9 mmol). The solution was stirred at 20 °C for 3 d, then aq. satd. $NaHCO_3$ solution (400 mL) was added, and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic phases were washed with aq. satd. $NaHCO_3$ solution (2 × 200 mL) and dried (Na_2SO_4). Chromatographic purification of the residue on 50 g of silica [3 × 20 cm, pentane/Et_2O = 1:1, R_f = 0.64 (Et_2O), ninhydrine] yielded the crude product, which was crystallized from Et_2O/pentane to yield 2.81 g (85%) of **3a** as colorless needles, m.p. 66 °C. IR (KBr): $\tilde{\nu}$ = 3327 (N–H) , 2928 (C–H), 2863 (C–H), 1620 (C=C), 1456 (CH_2), 1354 (OCH_3), 1293, 1242, 1220, 1187, 1133, 1100, 1077, 1032, 967, 936, 763, 738, 697, 601, 522, 457 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 2.42–2.46 (m, 2 H, cbt-H), 2.48–2.59 (m, 2 H, cbt-H), 3.66 (s, 3 H, OCH_3), 4.32 (d, ^3J = 6.6 Hz, 2 H, CH_2Ph), 5.77–5.87 (br. s, 1 H, NH), 7.26–7.39 (m, 5 H, aryl-H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 21.6 (–, CH_2), 26.7 (–, CH_2), 47.5 (–, CH_2), 50.1 (+, OCH_3), 92.3 (C_{quat}, cbt-C), 127.0 (+, 2 C, aryl-C), 127.5 (+, aryl-C), 128.7 (+, 2 C, aryl-C), 138.6 (C_{quat}, C_{ipso}), 158.7 (C_{quat},

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cbt-C), 164.6 (C_{quat}, C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 217 (36) [M^+], 186 (16) [M^+ – OMe], 158 (17) [M^+ – CO_2Me], 91 (100) [$PhCH_2^+$], 65 (10). $C_{13}H_{14}NO_2$ (217.3): calcd. C 71.87, H 6.96, N 6.45; found C 71.74, H 6.89, N 6.41.

Methyl 2-{(Benzyl)(*tert*-butoxycarbonyl)amino]cyclobut-1-enecarboxylate (4a): A solution of **3a** (2.98 g, 13.7 mmol) in THF (100 mL) was cooled to –78 °C, *n*BuLi (7.46 mL, 16.4 mmol, 2.2 M in hexane) was added over 10 min, and the deeply colored solution was stirred at the same temperature for 30 min. A solution of Boc_2O (3.59 g, 16.5 mmol) in THF (20 mL) was added, and the mixture was stirred under rewarming to 20 °C for 16 h. The reaction was quenched with satd. aq. NH_4Cl solution (10 mL), and the mixture extracted with CH_2Cl_2 (100 mL). Drying (Na_2SO_4) and chromatographic purification of the residue by column chromatography on 50 g of silica (3 × 20 cm, pentane/Et_2O = 10:1, R_f = 0.40, ninhydrine) yielded 3.68 g (85%) of **4a** as a colorless solid, m.p. 63 °C. IR (KBr): $\tilde{\nu}$ = 2980 , 2942, 1726, 1700, 1603, 1453, 1385, 1368, 1234, 1219, 1139, 1111, 1008, 755, 699 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.41 (s, 9 H, *t*Bu-H), 2.41 (t, ^3J = 4.4 Hz, 2 H, cbt-H), 2.97 (t, ^3J = 4.4 Hz, 2 H, cbt-H), 3.61 (s, 3 H, OCH_3), 5.35 (s, 2 H, CH_2), 7.18–7.37 (m, 5 H, aryl-H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 24.0 (–, cbt-C), 28.0 (+, *t*Bu-C), 32.3 (–, cbt-C), 50.5 (–, CH_2), 50.9 (+, OCH_3), 82.5 (C_{quat}, *t*Bu-C), 106.7 (C_{quat}, cbt-C), 126.7 (+, 2 C, aryl-C), 128.2 (+, 2 C, aryl-C), 131.6 (+, aryl-C), 138.6 (C_{quat}, C_{ipso}), 150.1 (C_{quat}, cbt-C), 152.7 (C_{quat}, NC=O), 162.5 (C_{quat}, C=O) ppm. MS (ESI, 70 eV): *m*/*z* (%) = 656 (14) [2 M + Na]$^+$, 340 (100) [M + Na]$^+$. $C_{18}H_{23}NO_4$ (317.4): calcd. C 68.12, H 7.30, N 4.41; found C 68.33, H 7.04, N 4.36.

2-[(Benzyl)(*tert*-butoxycarbonyl)amino]cyclobut-1-enecarboxylic Acid (5a): To a solution of **4a** (2.56 g, 8.07 mmol) in water/THF/*i*PrOH (1:1:1, 90 mL) was added $LiOH·2H_2O$ (1.45 g, 24.2 mmol) at 20 °C, and the mixture was stirred for 24 h. The solvents were evaporated under reduced pressure, the residue was taken up with EtOAc (100 mL), the mixture was acidified with aq. 1 N HCl solution (30 mL), the phases were separated, the aqueous layer was extracted with EtOAc (2 × 50 mL), and the organic phases were dried (Na_2SO_4) to yield 2.18 g (89%) of **5a** as a colorless solid, m.p. 109 °C. R_f = 0.53 (pentane/Et_2O = 1:1, ninhydrine). IR (KBr): $\tilde{\nu}$ = 2936, 1731, 1663, 1570, 1457, 1369, 1345, 1233, 1217, 1143 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 9 H, *t*Bu-H), 2.40 (t, ^3J = 3.6 Hz, 2 H, cbt-H), 2.84 (t, ^3J = 3.6 Hz, 2 H, cbt-H), 5.17 (s, 2 H, CH_2Ph), 7.15–7.36 (m, 5 H, aryl-H), 11.95 (br. s, 1 H, CO_2H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, APT): δ = 23.6 (–, cbt-C), 27.9 (+, *t*Bu-C), 31.3 (-, cbt-C), 50.6 (–, CH_2), 83.4 (–, *t*Bu-C), 107.4 (–, cbt-C), 126.7 (+, 2 C, aryl-C), 127.0 (+, aryl-C), 128.3 (+, 2 C, aryl-C), 138.4 (C_{quat}, C_{ipso}), 150.2 (–, cbt-C), 153.1 (–, NC=O), 165.9 (–, C=O) ppm. MS (ESI, 70 eV): *m*/*z* (%) = 629 (26) [2 M + Na]$^+$, 627 (76) [2 M – 2 H + Na]$^-$, 326 (100) [M + Na]$^+$, 304 (8) [M + H]$^+$, 302 (30) [M – H]$^-$. $C_{17}H_{21}NO_4$ (303.4): calcd. C 67.31, H 6.98, N 4.62; found C 67.16, H 6.75, N 4.73.

Methyl ({2-[(Benzyl)(*tert*-butoxycarbonyl)amino]cyclobut-1-ylcarbonyl}amino)acetate (6a): To a solution of **5a** (1.44 g, 4.75 mmol) in THF (50 mL) at 0 °C were added glycine methyl ester hydrochloride (656 mg, 5.23 mmol), 2,4,6-collidine (1.38 g, 11.4 mmol) and DCC (1.18 g, 5.70 mmol), and the suspension was stirred under rewarming to 20 °C for 12 h. The precipitate was filtered off, all volatile components were removed under reduced pressure, the residue was dissolved in EtOAc (150 mL), the solution washed with aq. 1 N HCl solution (50 mL), satd. aq. $NaHCO_3$ solution (2 × 50 mL) and brine (50 mL). Drying (Na_2SO_4) and chromatographic purification of the residue by column chromatography on 50 g of silica [3 × 20 cm, pentane/Et_2O = 1:1 → 1:2, ninhydrine, R_f = 0.32 (pentane/Et_2O = 1:2)] provided 1.58 g (89%) of **6a** as a colorless oil. IR (film): $\tilde{\nu}$ = 3386, 2991, 2935, 1717, 1653, 1635, 1540, 1457, 1368, 1265, 1239, 1208, 1153, 741, 703 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.42 (s, 9 H, *t*Bu-H), 2.27–2.52 (m, 2 H, cbt-H), 2.81–3.07 (m, 2 H, cbt-H), 3.71 (s, 3 H, OCH_3), 5.24 (d, ^2J = 7.76 Hz, 1 H, A-part of an AB system), 5.33 (d, ^2J = 7.76 Hz, 1 H, B-part of an AB system), 5.57 (dd, ^2J = 3.57 Hz, 1 H, CH), 6.48 (dd, ^2J = 3.57 Hz, 1 H, CH), 7.28–7.49 (m, 5 H, aryl-H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 23.3 (–, CH_2), 28.0 (+, *t*Bu-C), 32.8 (–, CH_2), 49.8 (–, CH_2), 52.8 (–, CH_2), 56.1 (+, OCH_3), 82.5 (C_{quat}, *t*Bu-C), 109.5 (C_{quat}, cbt-C), 127.2 (+, 2 C, aryl-C), 128.3 (+, 2 C, aryl-C), 128.4 (+, aryl-C), 132.4 (C_{quat}, C_{ipso}), 146.3 (C_{quat}, cbt-C), 152.8 (C_{quat}, NC=O), 161.6 (C_{quat}, NC=O), 171.4 (C_{quat}, C=O) ppm. MS (ESI, 70 eV): *m*/*z* (%) = 771 (96) [2 M + Na]$^+$, 397 (100) [M + Na]$^+$, 375 (70) [M + H]$^+$. $C_{20}H_{26}N_2O_5$ (374.4): calcd. C 64.15, H 7.00, N 7.48; found C 64.19, H 6.98, N 7.43.

6′-Chloro-4′-(4-chlorobenzyl)-2′,3′,4′,5′,6′,7′-hexahydrospiro[cyclopropane-1,5′-[1*H*][1,4]diazepine]-3′,7′-dione (10b): To a solution of 4-chlorobenzylamine (4.83 g, 34.1 mmol) in THF (50 mL) at 0 °C was added dropwise a solution of methyl 2-chloro-2-cyclopropylideneacetate (**1**) (5.00 g, 34.1 mmol) in THF (50 mL), and stirring was continued at the same temperature for 5 h. The mixture was treated at 0 °C with a solution of Boc-Gly-OH (11.9 g, 67.9 mmol) and pyridine (5.39 g, 68.1 mmol) in THF (50 mL) and DCC (14.1 g, 68.3 mmol) in THF (50 mL). After stirring under rewarming to room temp. overnight, the precipitated DCU was removed by filtration, and the solution was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (100 mL), and the solution was washed with cold 15% $KHSO_4$ solution (20 mL), water (20 mL), satd. aq. $NaHCO_3$ solution (3 × 20 mL) and dried (Na_2SO_4). After concentration in vacuo, the adduct of 4-chlorobenzylamine to **1** was obtained as a yellow solid (14.0 g, 92%) by column chromatography on 500 g of silica gel (petroleum ether/EtOAc = 6:3, R_f = 0.4). This adduct was dissolved in CH_2Cl_2 (50 mL), and trifluoroacetic acid (20.0 g, 175 mmol) was added dropwise at 0 °C to the resulting stirred solution. The reaction mixture was warmed to room temp. with stirring overnight and was poured into a well-stirred mixture of satd. aq. Na_2CO_3 solution (50 mL) and CH_2Cl_2 (50 mL). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were washed with brine (100 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was treated with diethyl ether, the precipitate was filtered off and recrystallized from EtOAc to give **10b** (6.51 g, 66% over two steps) as a colorless solid, m.p. 203–204 °C (dec., EtOAc). IR (KBr): $\tilde{\nu}$ = 3319 (NH), 3213 (NH), 3090, 3068, 2961, 2928, 1682 (C=O), 1495, 1462, 1443, 1325, 1229, 1092, 1016, 819, 813, 804, 735, 604, 553, 433 cm^{-1}. ^1H NMR (250 MHz, [D_6]DMSO): δ = 0.96–1.09 (m, 2 H, cPr-H), 1.47–1.52 (m, 2 H, cPr-H), 3.45 (dd, *J* = 14.5, 7.8 Hz, 1 H), 4.31 (s, 1 H), 4.33 (d, ^2J = 16.2 Hz, 1 H), 4.57 (d, ^2J = 14.5 Hz, 1 H), 5.01 (d, ^2J = 16.2 Hz, 1 H), 7.13 (d, ^3J = 8.4 Hz, 2 H, aryl-H), 7.32 (d, ^3J = 8.4 Hz, 2 H, aryl-H), 8.43 (d, ^3J = 7.8 Hz, 1 H, NH) ppm. ^{13}C NMR (62.9 MHz, [D_6]DMSO, DEPT): δ = 14.1 (–, cPr-C), 19.6 (–, cPr-C), 42.1 (C_{quat}, cPr-C), 46.7 (–, CH_2), 51.5 (–, CH_2), 65.9 (+, CH), 127.9 (+, 2 aryl-C), 128.5 (+, 2 aryl-C), 131.5 (C_{quat}, aryl-C), 137.8 (C_{quat}, aryl-C), 167.1 (C_{quat}, C=O), 171.1 (C_{quat}, C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 312 (1) [M^+], 279/277 (23/69) [M^+ – Cl], 251/249 (2/5) [M^+ – Cl – C_2H_4], 222/220 (23/71), 127/125 (33/100) [$C_7H_6Cl^+$]. $C_{14}H_{14}Cl_2N_2O_2$ (313.2): calcd. C 53.69, H 4.51, Cl 22.64, N 8.94; found C 53.85, H 4.70, Cl 22.36, N 8.80.

6′-Chloro-4′-(4-chlorobenzyl)-1′-{4′′-(4-chlorobenzyl)-2′′,3′′,4′′,5′′,6′′,7′′-hexahydro-3′′,7′′-dioxospiro[cyclopropane-1′′′,5′′-[1*H*]-

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[1,4]diazepin]-6′′-yl}-2′,3′,4′,5′,6′,7′-hexahydrospiro[cyclopropane-1,5′-[1*H*][1,4]-diazepine]-3′,7′-dione (13): To a solution of **10b** (1.10 g, 3.51 mmol) in DMSO (10 mL) was added freshly sublimed KO*t*Bu (394 mg, 3.51 mmol), and the solution was stirred at 20 °C for 24 h. The reaction mixture was poured into an ice-cold aq. 2 M HCl solution (150 mL), and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with brine (100 mL) and dried ($MgSO_4$). Purification of the residue by column chromatography on 50 g of silica (2.5 × 14 cm, CH_2Cl_2/MeOH = 100:5, R_f = 0.33, ninhydrine) yielded 421 mg (41%) of 13 as a colorless solid, m.p. 175–177 °C (CH_2Cl_2/Et_2O). IR (KBr): $\tilde{\nu}$ = 3539 (NH), 3098, 3052, 3050, 2950, 1660 (C=O), 1492, 1398, 1345, 1299, 1189, 1092, 1015, 964, 794 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.80–0.87 (m, 1 H, cpr-H), 1.00–1.06 (m, 1 H, cpr-H), 1.13–1.28 (m, 5 H, cpr-H), 1.34–1.42 (m, 1 H, cpr-H), 1.46–1.55 (m, 1 H, CH), 1.82 (d, ^3J = 18.4 Hz, 1 H), 2.74 (d, ^3J = 18.4 Hz, 1 H), 3.92 (s, 1 H, 6′-H), 4.27 (d, ^2J = 15.0 Hz, 1 H), 4.32 (d, ^2J = 15.0 Hz, 1 H), 4.50 (d, ^2J = 15.1 Hz, 1 H), 4.82 (d, ^2J = 15.0 Hz, 1 H), 5.14 (d, ^2J = 15.1 Hz, 1 H), 5.44 (d, ^2J = 15.0 Hz, 1 H), 6.96 (s, 1 H, NH), 7.10 (d, ^3J = 8.4 Hz, 2 H, aryl-H), 7.15–7.29 (m, 6 H, aryl-H, 6′′-H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 13.3 (–, cpr-C), 14.9 (–, cpr-C), 17.8 (–, cpr-C), 20.7 (–, cpr-C), 34.6 (C_{quat}, cpr-C), 42.3 (C_{quat}, cpr-C), 44.1 (–, CH_2), 48.1 (–, CH_2), 48.9 (–, CH_2), 51.9 (–, CH_2), 64.6 (+, C-6′), 66.7 (+, C-6′′), 127.7 (+, 2 aryl-C), 128.97 (+, 2 aryl-C), 128.99 (+, 2 aryl-C), 129.1 (+, 2 aryl-C), 133.1 (C_{quat}, aryl-C), 133.6 (C_{quat}, aryl-C), 135.4 (C_{quat}, aryl-C), 136.5 (C_{quat}, aryl-C), 167.3 (C_{quat}, C=O), 168.7 (C_{quat}, C=O), 171.1 (C_{quat}, C=O), 171.2 (C_{quat}, C=O) ppm. MS (ESI, 70 eV): *m*/*z* (%) = 588 (<1) [M^+], 554/552 (1/1) [M^+ – Cl], 277 (22), 222/220 (6/12), 127/125 (32/100) [$C_7H_6Cl^+$]. $C_{28}H_{27}Cl_3N_4O_4$ (589.9): calcd. C 57.01, H 4.61, Cl 18.03, N 9.50; found C 57.07, H 4.72, Cl 17.88, N 9.71.

2,3,4,5,6,7-Hexahydro-1-pentyl-1*H*-cyclobuta[*e*][1,4]diazepine-2,5-dione (15f): To a solution of **10f**[13a] (345 mg, 1.33 mmol) in DMSO (15 mL) was added sodium cyanide (74 mg, 1.50 mmol), and the reaction mixture was stirred at 100 °C for 3 h, then at 140 °C for an additional 3 h. After cooling to 20 °C, the brown oil was treated with water (100 mL) and the mixture extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with brine (2 × 50 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure and purification of the residue by column chromatography on 25 g of silica (2 × 10 cm, CH_2Cl_2/MeOH = 100:3 → 100:4, R_f = 0.37) yielded 133 mg (45%) of **15f** as a colorless oil. IR (film): $\tilde{\nu}$ = 3390 (NH), 3243 (NH), 3175 (NH) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.78 (t, ^3J = 6.7 Hz, 3 H, CH_3), 1.14–1.38 (m, 4 H, 2 CH_2), 1.70–1.81 (m, 2 H, CH_2), 2.33 (t, ^3J = 3.7 Hz, 2 H, cbt-H), 2.48 (t, ^3J = 3.7 Hz, 2 H, cbt-H), 3.68–3.81 (m, 2 H, CH_2), 3.86 (d, ^3J = 5.2 Hz, 2 H, CH_2), 6.65 (br. s, 1 H, NH) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 13.7 (+, CH_3), 21.4 (–, cbt-C), 22.0 (–, CH_2), 27.2 (–, cbt-C), 27.7 (–, CH_2), 28.5 (–, CH_2), 45.8 (–, CH_2), 47.2 (–, CH_2), 114.3 (C_{quat}, cbt-C), 148.5 (C_{quat}, cbt-C), 166.8 (C_{quat}, C=O), 167.4 (C_{quat}, C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 222 (100) [M^+], 165 (18), 152 (43), 108 (52). $C_{12}H_{18}N_2O_2$ (222.28): calcd. C 64.84, H 8.16, N 12.60; found C 64.67, H 8.25, N 12.55.

Methyl 2-[(*R*)-(1-Phenylethyl)amino]cyclobut-1-enecarboxylate (17): To a solution of **1** (2.0 g, 13.7 mmol) in DMF (10 mL) was added (*R*)-(1-phenylethyl)amine (1.66 g, 13.7 mmol), LiI (2.05 g, 15.3 mmol) and EtN(*i*Pr)$_2$ (1.97 g, 15.3 mmol) at 0 °C, and the mixture was stirred under rewarming to 20 °C for 3 d. Satd. aq. $NaHCO_3$ solution (150 mL) was added, and the mixture was extracted with Et_2O (3 × 70 mL). The combined organic phases were washed with satd. $NaHCO_3$ (2 × 50 mL) and dried (Na_2SO_4). The oily residue (2.91 g, 92%) was used in the next step without further purification. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.48 (d, J = 6.9 Hz, 3 H, CH_3), 2.19–2.25 (m, 1 H, cbt-H), 2.30–2.50 (m, 3 H, cbt-H), 3.65 (s, 3 H, OCH_3), 4.49 (m, 1 H, CH), 5.83 (br. s, 1 H, NH), 7.20–7.34 (m, 5 H, Ph) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.9 (CH_2), 23.7 (CH_2), 21.1 (CH_3), 50.0 (OCH_3), 53.2 (CH), 77.2 (C_{quat}, cbt-C), 92.4 (C_{quat}, cbt-C), 125.7 (2 CH, aryl-C), 127.2 (CH, aryl-C), 128.6 (2 CH, aryl-C), 144.0 (C_{quat}, C_{ipso}), 158.5 (C_{quat}, cbt-C), 164.6 (C_{quat}, C=O) ppm. MS (ESI = 70 eV): *m*/*z* (%) = 231.4 (30) [M^+], 105.2 (100). HRMS: calcd. for $C_{14}H_{17}NO_2$ 231.12593; found 231.12597.

Methyl 5-[(*R*)-(1-Phenylethyl)amino]pentanoate (18): A solution of $NaBH(OAc)_3$ was prepared by adding $NaBH_4$ (0.34 g, 9.0 mmol) to glacial acetic acid (5 mL), while keeping the temperature between 10 and 20 °C. After 1 h, acetonitrile (5 mL) was added, and the solution was cooled to 0 °C. The β-enamino ester **17** (693 mg, 3 mmol) was added and the mixture stirred at 0 °C for 4 h. The acetic acid and acetonitrile were evaporated at room temp. in vacuo, the residue dissolved in CH_2Cl_2 (100 mL) and the solution washed with a satd. aq. Na_2CO_3 solution (2 × 50 mL). Drying of the solution (Na_2SO_4) and evaporation of the solvent gave a crude product, which was purified by column chromatography on 100 g of silica gel (Et_2O, R_f = 0.23) to give 522 mg (74%) of **18** as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.34 (d, J = 6.6 Hz, 3 H, CH_3), 1.43–1.52 (m, 2 H, CH_2), 1.57–1.67 (m, 2 H, CH_2), 2.28 (t, J = 7.4 Hz, 2 H, CH_2), 2.37–2.55 (m, 2 H, CH_2), 3.64 (s, 3 H, OCH_3), 3.74 (q, J = 3.3 Hz, 1 H, CH), 7.30 (m, 5 H, Ph) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 22.7 (CH_2), 24.3 (CH_2), 29.7 (CH_2), 33.9 (CH_3), 47.3 (CH_2), 51.4 (CH), 58.3 (OCH_3), 126.5 (2 CH, aryl-C), 128.8 (CH, aryl-C), 128.4 (2 CH, aryl-C), 145.8 (C_{quat}, aryl-C), 174.0 (C_{quat}, C=O) ppm. MS (ESI 70 eV): *m*/*z* (%) = 235.2 (4) [M^+], 220.2 (32), 105.1 (100). HRMS: calcd. for $C_{14}H_{22}NO_2$ [M + H]$^+$ 236.16451; found 236.16444.

***tert*-Butyl *cis*- and *trans*-2-(Methoxycarbonyl)cyclobutylcarbamate (*cis*-/*trans*-19):** A mixture of **4a** (100 mg, 0.32 mmol), MeOH (5 mL) and 10% Pd/C (34 mg, 10 mol-%) was shaken under hydrogen (3 atm H_2) at 80 °C for 12 h. After cooling, the mixture was filtered through a short pad of Celite, which was subsequently washed with MeOH (50 mL). The solvent was removed under reduced pressure to provide the crude product (a 3:1 mixture of isomers according to ^1H NMR), which was purified by column chromatography on 50 g of silica gel (pentane/Et_2O = 4:1).

***cis*-19:**[22] 50 mg (69%), R_f = 0.18 (pentane/Et_2O, 4:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.36 (s, 9 H, *t*Bu), 1.85–1.94 (m, 2 H, cbt-H), 2.15 (quint, J = 10.3 Hz, 1 H, cbt-H), 2.26 (m, 1 H, cbt-H), 3.31 (m, 1 H, CH), 3.64 (s, 3 H, OCH_3), 4.39 (m, 1 H, CH), 5.30 (br. s, 1 H, NH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 18.4 (CH_2), 28.3 (CH_3, *t*Bu), 29.5 (CH_2), 45.2 (CH), 45.7 (CH), 51.6 (OCH_3), 79.4 (C_{quat}, *t*Bu), 154.7 (C_{quat}, NC=O), 174.7 (C_{quat}, C=O) ppm. MS (ESI, 70 eV): *m*/*z* (%) = 481.3 (100) [2 M + Na^+], 252.3 (64) [M + Na^+]. HRMS: calcd. for $C_{11}H_{19}NNaO_4$ [M + Na]$^+$ 252.1206; found 252.1211.

***trans*-19:**[22] 16 mg (22%) R_f = 0.29 (pentane/Et_2O, 4:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 9 H, *t*Bu), 1.84 (m, 1 H, cbt-H), 2.08–2.19 (m, 2 H, cbt-H), 2.64 (quint, J = 10.5 Hz, 1 H, cbt-H), 3.22 (m, 1 H, CH), 3.37 (m, 1 H, CH), 3.65 (s, 3 H, OCH_3), 4.44 (br. s, 1 H, NH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 17.6 (CH_2), 26.0 (CH_2), 28.3 (CH_3, *t*Bu), 45.8 (CH), 50.0 (CH), 51.6 (CH_3), 79.4 (C_{quat}, *t*Bu), 155.4 (C_{quat},NC=O), 174.0 (C_{quat}, C=O) ppm. MS (ESI = 70 eV): *m*/*z* (%) = 481.3 (100) [2 M + Na^+], 252.3 (68) [M + Na^+]. HRMS: calcd. for $C_{11}H_{19}NNaO_4$ [M + Na]$^+$ 252.1206; found 252.1214.

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Supporting Information (see footnote on the first page of this article): Experimental details for compounds **3b**–**d**, **4b**–**d**, **5b**–**d**, **7a**, **8a**, **9b**, **15e**, **22**-Me, **22**-*i*Pr, **23**, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds without elemental analysis data.

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