Synthesis of New Cyclopropylisonitriles and their Applications in Ugi Four-Component Reactions

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Abstract: Several new cyclopropylisonitriles were synthesized from the corresponding cyclopropylamines (41–69% yield) and utilized in Ugi four-component reactions to furnish 12 new dipeptides in 38–86% yield. The structures of four of these dipeptides were determined by X-ray crystallography.

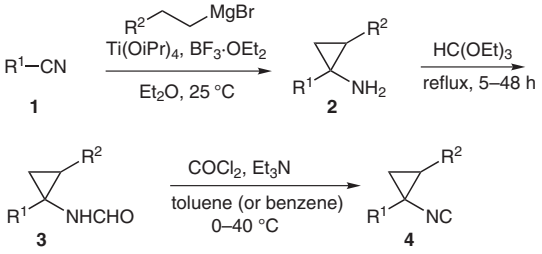
Key words: ring constructions, titanium chemistry, multicomponent reactions, dipeptides, isonitriles

Many natural isonitriles show strong antibiotic, fungicidal, or antineoplastic effects.[2] Compounds containing a cyclopropane moiety also often exhibit interesting biological activities. Multicomponent reactions attract more and more attention because of their applicability in the combinatorial construction of small molecule libraries as well as in the synthesis of natural products and their analogues. In particular, the Ugi four-component condensation has been widely employed because it provides various dipeptide-type products according to a very simple experimental procedure under mild conditions.[2] Many of these products have drug-like structures and might therefore exhibit a variety of interesting biological activities. Since cyclopropylamines are now easily available,[3–5] we transformed several into a number of new cyclopropylisonitriles, and applied them in Ugi multicomponent reactions.

Synthesis of New Cyclopropylisonitriles

Cyclopropylisonitriles **4a–c** were synthesized from the corresponding cyclopropylamines **2** via the *N*-formyl derivatives **3** according to an established protocol (Scheme 1 and Table 1).[2]

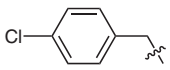
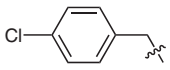
Primary cyclopropylamines can conveniently be prepared by reductive cyclopropanation of *N,N*-dibenzylcarboxamides with ethyl- or substituted ethylmagnesium bromide in the presence of titanium tetraisopropoxide with subsequent hydrogenative debenzylation,[4] or directly from certain nitriles.[5] Thus, the commercially available nitriles **1a–c** were treated with ethyl-, butyl- and phenylethylmagnesium bromide, respectively, in the presence of



Scheme 1 Synthesis of some substituted cyclopropylisonitriles (Table 1).

$Ti(O\textit{i}\text{-}Pr)_4$ according to an established protocol,[5] to give the correspondingly substituted cyclopropylamines **2a–c** in 47%, 57% and 30% yield, respectively (Table 1). The latter were heated under reflux with triethyl orthoformate to give the *N*-formyl derivatives **3a–c** (97, 64 and 61% yield), and these were dehydrated by treatment with a solution of phosgene in toluene in the presence of triethylamine to yield **4a–c** (71, 88 and 68% yield, Table 1).

Table 1 Synthesis of Some Substituted Cyclopropylisonitriles **4** from Nitriles **1** (Scheme 1)

			Yield (%)		
	R^1	R^2	**2**	**3**	**4**
a		H	47	97	71
b		Et	57	64	88
c	$BnOCH_2$	Ph	30	61	68

The bicyclic isonitrile **7** was synthesized analogously from the mono-*N*-Boc-protected bicyclic diamine **5** which was obtained from the corresponding *N,N*-dibenzyl derivative according to an established protocol.[6] The formylation of **5** with ethyl formate proceeded virtually quantitatively, and the dehydration of the *N*-formyl derivative **6** with phosgene furnished **7** in 65% yield (Scheme 2).

Ethyl 1-isocyanocyclopropanecarboxylate (**11**) was prepared by cyclizing bisalkylation of ethyl isocyanoacetate (**10**).[7,8]

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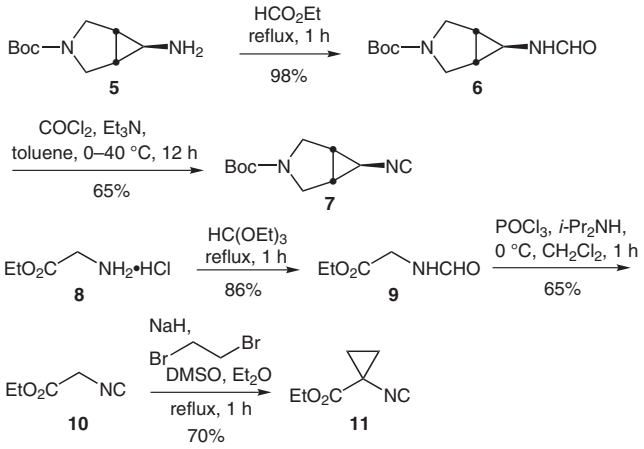
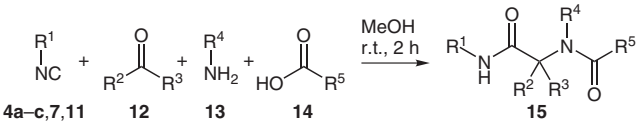


Scheme 2 Synthesis of 3-*tert*-butoxycarbonyl-3-azabicyclo[3.1.0]-hex-2-ylisonitrile (**7**) and ethyl 1-isocyanocyclopropanecarboxylate (**11**).

Ugi Four-Component Reactions

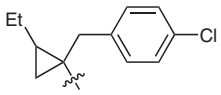
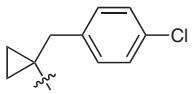
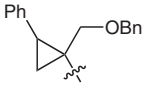
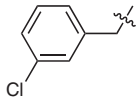
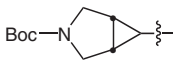
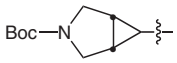
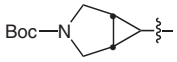
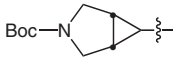
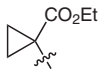
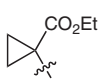
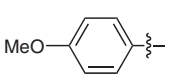
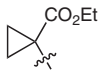
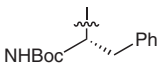
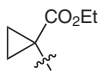
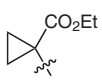
The reactivities of the new cyclopropylisonitriles were tested in the classic version of the 4CC Ugi reaction. In this, an isonitrile **4a–c**, **7**, **11**, an aldehyde or a ketone **12**, a primary amine **13** and a carboxylic acid **14** in MeOH react at ambient temperature to give a dipeptide **15**[2] (Scheme 3, Table 2).



Scheme 3 The 4CC Ugi reaction applied to the new cyclopropylisonitriles **4a–c**, **7**, **11** (Table 2).

A total of 12 new cyclopropyl-group containing dipeptides were synthesized from the cyclopropylisonitriles **4a–c**, **7**, **11** and a variety of ketones, amines and carboxylic acids (see Table 2).

Table 2 New Cyclopropyl-Group-Containing Dipeptides **15** Prepared (Scheme 3)

15	R^1	R^2	R^3	R^4	R^5	Yield (%)
a			H	Bn		69
b			H	Bn		55
c		–$(CH_2)_5$–			CH_2NHBoc	86
d			H	Bn		81
e			H	Ph		76
f			H	H	Me	52
g		–$(CH_2)_5$–		H	Me	68
h			H	Bn		81
i			H			86
j		–$(CH_2)_5$–		H		75
k		–$(CH_2)_5$–		H	Ph	66
l			H	H	Ph	38

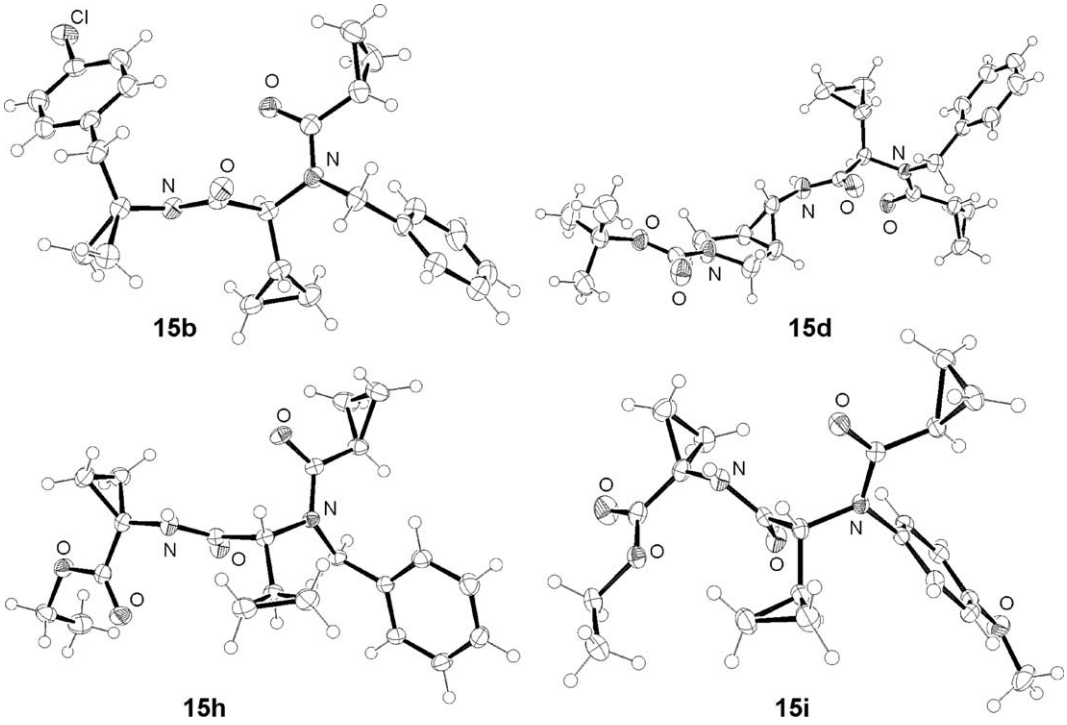


Figure 1 Structures of the cyclopropyl-group-containing dipeptides **15b**,**d**,**h**,**i** in the crystals.[9]

The geometries and conformations of dipeptides **15b**,**d**,**h** und **i** in the solid state were established by X-ray crystal structure analyses.[9] The conformations of the dipeptide fragments in all four compounds studied by X-ray crystallography, are close to each other. The orientations of the substituents R^2, R^4 and R^5 are also similar. However, the orientation of the cyclopropyl ring corresponding to R^1 in compound **15b** is different from that in molecules **15d**,**h**,**i**; the corresponding torsional φ-angles are –78.5°, –70.1°, and –84.1°, respectively.

The structure of **15b** also differs from others by the arrangement of the molecules in the crystal. Whereas the molecules **15b** in the crystal are linked together in chains by N–H…O=C (carbonyl group adjacent to NH) hydrogen bonds, the molecules of **15d**,**h**,**i** form centrosymmetrical dimers by pairs of N–H…O=C (carbonyl of the other peptide group) hydrogen bonds (Figure 1).

A simple and convenient access to new dipeptides, each containing at least one cyclopropyl moiety, based on the 4CC Ugi reaction applying cyclopropylisonitriles has been developed.

NMR spectra were recorded in $CDCl_3$ on a Varian UNITY-200 (200 MHz for ^1H and 50.3 MHz for ^{13}C NMR), a Bruker AM 250 (250 MHz for ^1H and 62.9 MHz for ^{13}C NMR), a Varian UNITY-300 (300 MHz for ^1H and 75.5 MHz for ^{13}C NMR) or a Varian Inova 500 (500 MHz for ^1H and 125.7 MHz for ^{13}C NMR) instrument. Chemical shifts are reported in ppm relative to residual peaks of the deuterated solvent. Multiplicities were determined by APT (Attached Proton Test) measurements. For compound **15c** an HSQC (Heteronuclear Single Quantum Coherence) spectrum was also measured. IR: Bruker IFS 66 (FT-IR) spectrometer, measured as KBr or oil between KBr plates. MS (EI at 70 eV or DCI with NH_3 or HCO_2H): Finnigan MAT 95 spectrometer. Melting points: Büchi 510 capillary melting point apparatus, values uncorrected. TLC: Macherey-Nagel precoated sheets, 0.25 mm Sil G/UV_{254}. Column chromatography: Merck silica gel, grade 60, 230–400 mesh. Elemental analyses: Mikroanalytisches Laboratorium des Instituts für Organische und Biomolekulare Chemie, Universität Göttingen. Starting materials: all chemicals were used as commercially available materials. Ethyl 1-isocyanocyclopropanecarboxylate (**11**) was prepared according to a reported method.[7,8]

Amines 2a–c; General Procedure 1 (GP1)

A solution of the respective Grignard reagent in Et_2O was added to a solution of the respective nitrile and Ti(O*i*-Pr)$_4$ in anhyd Et_2O at 25 °C. Within 30 min, a solution of $BF_3{\cdot}OEt_2$ (48% in Et_2O) was added dropwise. After stirring for an additional 15 min, the mixture was cooled to 0 °C, and a 10% aq solution of NaOH was added dropwise. The obtained suspension was extracted with Et_2O, the combined organic layers were dried (Na_2SO_4), and the solution concentrated under reduced pressure. The crude product was purified by distillation or crystallization or via the hydrochloride.

1-(4-Chlorobenzyl)cyclopropylamine (2a)

According to the GP1, a solution of ethylmagnesium bromide (27.0 mL, 40.0 mmol, 1.5 M in Et_2O) was added to a solution of 4-chlorobenzyl cyanide (2.57 mL, 20.0 mmol) and Ti(O*i*-Pr)$_4$ (6.58 mL, 22.0 mmol) in Et_2O (20 mL). $BF_3{\cdot}OEt_2$ (5.10 mL, 40.0 mmol, 48% in Et_2O) and 10% aq NaOH (50 mL) were added. The crude product obtained by extraction with Et_2O (3 × 40 mL) was distilled using a Kugelrohr apparatus (100–120 °C/0.005 Torr) to give the amine **2a** (1.72 g, 47%) as a pale yellow oil.

IR (film): 3366, 3281, 3083, 3003, 2965, 2916, 2853, 1595, 1491, 1091, 1016 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 0.50–0.70 (m, 2 H, Cpr-H), 0.80–0.90 (m, 1 H, Cpr-H), 1.20–1.40 (m, 3 H, Cpr-H, NH_2), 2.65 (s, 2 H, ArCH_2), 7.10–7.30 (m, 4 H, Ar-H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.1 (Cpr-CH_2), 34.7 (Cpr-C), 45.7 (CH_2), 128.1, 128.5, 131.8, 137.9 (6 C, Ar-CH + Ar-C_{quat}).

MS (DCI): *m/z* (%) = 201/199 (9/44, [M + NH_4^+]), 184/182 (17/55, [M + H^+]).

HRMS-DCI: *m/z* calcd for $C_{10}H_{13}ClN$ [M + H^+]: 182.0737; found: 182.0731.

Anal. Calcd for $C_{10}H_{12}ClN$: C, 66.12; H, 6.66; N, 7.71. Found: C, 66.16; H, 6.93; N, 7.48.

1-(4-Chlorobenzyl)-2-ethylcyclopropylamine (2b)

According to the GP1, a solution of butylmagnesium bromide (70 mL, 109 mmol, 1.55 M in Et_2O) was added to a solution of 4-chlorobenzyl cyanide (7.0 mL, 54.5 mmol) and Ti(O*i*-Pr)$_4$ (18.0 mL, 60.0 mmol) in Et_2O (30 mL). $BF_3{\cdot}OEt_2$ (13.8 mL, 109 mmol, 48% in Et_2O) and 10% aq NaOH (27 mL) were added. Aq HCl (20 mL, 5 N) was added to the crude product obtained by extraction of the reaction mixture with Et_2O (3 × 70 mL), the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), then the aqueous layer was basified with aq NaOH (30 mL, 5 N) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers from the last extraction were dried (Na_2SO_4) and the solution concentrated under reduced pressure to give the amine **2b** (6.47 g, 57%) as a pale yellow oil.

IR (film): 3369, 3067, 2990, 2959, 2929, 2871, 1898, 1596, 1491, 1092, 1016 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ (2 diastereomers) = 0.00–0.10 (m, 2 H, Cpr-H), 0.40–1.50 (m, 18 H, Et, Cpr-H, NH_2), 2.30–2.70 (m, 4 H, CH_2), 6.90–7.20 (m, 8 H, Ar-H).

^{13}C NMR (75.5 MHz, APT, $CDCl_3$): δ (2 diastereomers) = 14.2, 14.4 (+, Cpr-CH), 19.2, 20.4 (–, Cpr-CH_2), 21.7, 23.4 (–, *C*H_2CH$_3$), 26.8, 28.3 (+, CH$_2$*C*H$_3$), 38.2, 38.5 (–, Cpr-C$_{quat}$), 40.9, 47.3 (–, *C*H_2Ar), 128.4, 128.5 (+, Ar-CH), 130.5, 130.6 (+, Ar-CH), 2 × 132.1 (–, Ar-C$_{quat}$), 2 × 138.1 (–, Ar-C$_{quat}$).

MS (EI): *m/z* (%) = 211/209 (<1/2, [M^+]), 182/180 (32/100), 127/125 (10/31).

1-Benzyloxymethyl-2-phenylcyclopropylamine (2c)

According to the GP1, a solution of 2-phenylethylmagnesium bromide (51 mL, 51 mmol, 1.00 M in Et_2O) was added to a solution of benzyloxyacetonitrile (3.70 g, 25.2 mmol) and Ti(O*i*-Pr)$_4$ (8.3 mL, 28 mmol) in Et_2O (25 mL). $BF_3{\cdot}OEt_2$ (6.40 mL, 50.4 mmol, 48% in Et_2O) and 10% aq NaOH (70 mL) were added. The crude product obtained by extraction with Et_2O (3 × 50 mL) was crystallized, the solid was collected by filtration, washed with Et_2O–hexane (1:1, 20 mL) to yield **2c** as a yellow solid (1.94 g, 30%); mp 95–97 °C.

IR (KBr): 3431, 3023, 2853, 2683, 2589, 1495, 1453, 1095, 733, 689 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.3 Hz, 1 H, Cpr-H), 1.94 (dd, *J* = 7.0, 10.0 Hz, 1 H, Cpr-H), 3.14 (dd, *J* = 7.5, 10.0 Hz, 1 H, Cpr-H), 3.33 (d, *J* = 11.0 Hz, 1 H, CH_2), 3.40 (d, *J* = 11.0 Hz, 1 H, CH_2), 4.37 (d, *J* = 12.0 Hz, 1 H, CH_2), 4.45 (d, *J* = 12.0 Hz, 1 H, CH_2), 7.10–7.30 (m, 10 H, Ph-H), 8.69 (br s, 2 H, NH_2).

^{13}C NMR (50.3 MHz, APT, $CDCl_3$): δ = 13.1 (–, Cpr-CH_2), 26.1 (+, Cpr-CH), 39.4 (–, Cpr-C$_{quat}$), 68.9, 73.1 (–, CH_2), 127.1, 127.5, 128.3, 128.4, 128.5, 129.2 (+, 10 C, Ph-CH), 134.6, 137.3 (–, Ph-C$_{quat}$).

MS (EI): *m/z* (%) = 253 (5, [M^+]), 162 (12), 144 (9), 132 (27), 105 (16), 91 (100), 77 (12).

HRMS-EI: *m/z* calcd for $C_{17}H_{20}NO$ [M + H^+]: 254.1545; found: 254.1539.

***N*-Formamides 3a–c; General Procedure 2 (GP2)**

A mixture of the respective amine and ethyl orthoformate was heated under reflux for the indicated time. The excess of ethyl orthoformate was removed in vacuo, the residue was collected on a filter and washed with Et_2O or purified by column chromatography on silica gel.

***N*-[1-(4-Chlorobenzyl)cyclopropyl]formamide (3a)**

Formamide **3a** (611 mg, 97%) was obtained according to the GP2 from the amine **2a** (545 mg, 3.00 mmol) and ethyl orthoformate (2.1 mL, 12.6 mmol) as a colorless solid; mp 70–71 °C.

IR (film): 3435, 3314, 2873, 1662, 1522, 1490, 1014, 533 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ (2 tautomers) = 0.75–0.95 (m, 8 H, Cpr-CH_2), 2.75 (s, 2 H, C*H*$_2$Ar), 2.88 (s, 2 H, CH_2Ar) 5.80 (br s, 1 H, N*H*CHO), 6.10 (d, *J* = 12.5 Hz, 1 H, N*H*CHO), 7.10–7.35 (m, 8 H, Ar-H), 7.85 (d, *J* = 12.7 Hz, 1 H, NHC*H*O), 7.98 (d, *J* = 2.0 Hz, 1 H, NHC*H*O).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ (2 tautomers) = 12.8, 13.2 (Cpr-CH_2), 33.3, 34.8 (Cpr-C$_{quat}$), 40.5, 44.3 (CH_2), 128.5, 128.8, 130.6, 130.8 (Ar-CH), 132.4, 132.9, 135.8, 137.2 (Ar-C$_{quat}$), 161.5, 165.9 (NHCHO).

MS (EI): *m/z* (%) = 211/209 (10/28, [M^+]), 166/164 (14/23), 129 (88), 127/125 (21/45), 56 (100).

Anal. Calcd for $C_{11}H_{12}ClNO$: C, 63.01; H, 5.77; N, 6.68. Found: C, 62.95; H, 5.51; N, 6.79.

***N*-[1-(4-Chlorobenzyl)-2-ethylcyclopropyl]formamide (3b)**

Formamide **3b** (4.68 g, 64%) was obtained according to the GP2 from amine **2b** (6.47 g, 30.9 mmol) and ethyl orthoformate (15.0 mL, 90 mmol) as a colorless solid; mp 61–62 °C.

IR (KBr): 3293, 3072, 3006, 2961, 2873, 2760, 1662, 1529, 1492, 1390, 1091 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ (2 diastereomers, 2 tautomers) = 0.04–0.06 (m, 4 H, Cpr-CH), 0.80–1.90 (m, 28 H, CH_2CH_3, Cpr-CH_2), 2.60–3.25 (m, 8 H, C*H*$_2$Ar), 5.35–5.95 (m, 4 H, N*H*CHO), 7.00–7.20 (m, 16 H, Ar-H), 7.80–8.10 (m, 4 H, NHC*H*O).

^{13}C NMR (75.5 MHz, APT, $CDCl_3$): δ (2 diastereomers, 2 tautomers) = 13.69, 13.73, 13.83, 13.91 (+, CH$_2$*C*H$_3$), 18.53, 18.56, 18.76, 19.08, 21.93, 21.98, 22.83, 23.03 (–, Cpr-CH_2, *C*H_2CH$_3$), 25.42, 26.07, 27.72, 28.30 (+, Cpr-CH), 35.97, 37.03, 37.77, 38.30, 38.83, 39.82, 41.52, 45.75 (–, Cpr-C$_{quat}$, *C*H_2Ar), 128.46, 128.49, 128.80, 128.84, 130.58, 130.62, 130.71, 130.85 (+, 16 C, Ar-CH), 132.19, 132.32,132.75, 132.86, 135.93, 136.01, 137.37, 137.63 (–, 8 C, Ar-C$_{quat}$), 161.10, 161.84, 165.93, 166.52 (+, 4 C, NCHO).

MS (EI): *m/z* (%) = 239/237 (14/52, [M^+]), 210/208 (26/65), 165/163 (16/39), 127/125 (33/100), 116 (82), 91/98 (19/62), 84 (42).

Anal. Calcd for $C_{13}H_{16}ClNO$: C, 65.68; H, 6.78; N, 5.89. Found: C, 65.42; H, 6.55; N, 5.96.

***N*-(1-Benzyloxymethyl-2-phenylcyclopropyl)formamide (3c)**

Formamide **3c** (1.26 g, 61%) was obtained according to the GP2 from the amine **2c** (1.86 g, 7.34 mmol) and ethyl orthoformate (3.6 mL, 22.0 mmol) as a yellow oil after purification by column chromatography on silica gel; R_f = 0.17 (EtOAc–hexane, 1:2).

IR (film): 3276, 3061, 3027, 2860, 1659, 1495, 1295, 1098, 738, 698 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ (2 tautomers) = 1.35 (dd, *J* = 6.3, 14.6 Hz, 4 H, Cpr-CH_2), 2.54 (dd, *J* = 7.3, 15.8 Hz, 2 H, Cpr-CH), 3.07 (d, *J* = 10.3 Hz, 1 H, CH_2), 3.14 (d, *J* = 10.3 Hz, 1 H, CH_2), 3.26 (d, *J* = 10.3 Hz, 1 H, CH_2), 3.46 (d, *J* = 10.3 Hz, 1 H, CH_2), 4.21 (d, *J* = 12.0 Hz, 1 H, CH_2), 4.23 (d, *J* = 12.0 Hz, 1 H, CH_2), 4.32 (d, *J* = 12.0 Hz, 1 H, CH_2), 4.34 (d, *J* = 12.0 Hz, 1 H, CH_2), 6.27 (br s, 2 H, NH), 7.00–7.20 (m, 20 H, Ph-H), 8.14 (d, *J* = 1.3 Hz, 1 H, CHO), 8.46 (d, *J* = 11.8 Hz, 1 H, CHO).

^{13}C NMR (75.5 MHz, APT, $CDCl_3$): δ (2 tautomers) = 15.4, 16.5 (–, Cpr-CH_2), 29.8, 30.0 (+, Cpr-CH), 37.3, 39.1 (–, Cpr-C$_{quat}$), 71.5,

72.4, 73.0, 73.1 (–, CH_2), 126.7, 127.0, 127.3, 127.5, 127.7, 127.8, 128.2, 128.3, 128.4, 128.6, 129.0, 129.1 (+, 20 C, Ph-CH), 135.7, 136.6, 137.7, 137.9 (–, Ph-C_{quat}), 161.6, 166.7 (+, CHO).

MS (EI): *m*/*z* (%) = 281 (<1, [M^+]), 197 (15), 173 (34), 172 (33), 128 (29), 105 (26), 91 (100), 77 (22).

HRMS-EI: *m*/*z* calcd for $C_{18}H_{20}NO_2$ [M + H^+]: 282.1494; found: 282.1489.

Isonitriles 4a,b and 7; General Procedure 3 (GP3)

To a stirred solution of the respective *N*-formamide and Et_3N in anhyd toluene, was added at 0 °C a solution of $COCl_2$ (20% in toluene). The mixture was heated at 40 °C for 30 min, and stirred at 25 °C for some additional time as indicated. The residue was collected by filtration and washed with toluene. The filtrate was concentrated under reduced pressure, and the residue was purified by distillation, filtration through a pad of silica gel or column chromatography on silica gel.

1-(4-Chlorobenzyl)cyclopropylisonitrile (4a)

The crude **4a** was obtained according to the GP3 from the formamide **3a** (1.00 g, 4.77 mmol), Et_3N (1.3 mL, 9.33 mmol) and $COCl_2$ (2.3 mL, 4.79 mmol, 20% in toluene) in anhyd toluene (10 mL) with additional stirring for 8 h. The residue was distilled using a Kugelrohr apparatus (80–100 °C, 0.005 Torr) to give **4a** (651 mg, 71%) as a colorless oil, which turned brown immediately.

IR (film): 3358, 2972, 2928, 2861, 2133, 1653, 1491, 1256, 1093, 1016, 738 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.84–0.95 (m, 2 H, Cpr-H), 1.10–1.20 (m, 2 H, Cpr-H), 2.88 (s, 2 H, CH_2), 7.20–7.40 (m, 4 H, Ar-H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.4 (Cpr-CH_2), 34.5 (Cpr-C_{quat}), 41.2 (CH_2), 128.7, 130.5, 133.2, 134.7 (6 C, Ar-CH + Ar-C_{quat}), 153.3 (NC).

MS (EI): *m*/*z* (%) = 193/191 (<1/2, [M^+]), 153/151 (9/29), 116 (100).

HRMS-EI: *m*/*z* [M^+] calcd for $C_{11}H_{10}ClN$: 191.0502; found: 191.0502.

Anal. Calcd for $C_{11}H_{10}ClN$: C, 68.94; H, 5.26; N, 7.31. Found: C, 68.84; H, 5.25; N, 7.14.

1-(4-Chlorobenzyl)-2-ethylcyclopropylisonitrile (4b)

The crude **4b** was obtained according to the GP3 from formamide **3b** (2.17 g, 9.13 mmol), Et_3N (3.2 mL, 22.8 mmol) and $COCl_2$ (4.8 mL, 9.1 mmol, 20% in toluene) in anhyd toluene (20 mL) with additional stirring for 12 h. The residue was filtered through a pad of silica gel (10 g), and the filtrate was concentrated under reduced pressure to give **4b** (1.75 g, 88%) as a yellow oil, which turned brown immediately.

IR (film): 2964, 2932, 2874, 2129, 1684, 1492, 1456, 1092, 1016 cm^{-1}.

^{1}H NMR (250 MHz, , $CDCl_3$): δ (2 diastereomers) = 0.58–0.64 (m, 1 H, Cpr-H), 0.80–0.90 (m, 1 H, Cpr-H), 0.95–1.15 (m, 7 H, CH_2CH_3, Cpr-H), 1.10–1.70 (m, 7 H, CH_2CH_3, Cpr-H), 2.68–3.06 (m, 4 H, CH_2Ar), 7.10–7.38 (m, 8 H, Ar-H).

^{13}C NMR (62.9 MHz, , $CDCl_3$): δ (2 diastereomers) = 12.9, 13.4 (Cpr-CH_2), 20.1, 20.4, 22.4, 22.7, 26.0, 28.9 (CH_2CH_3, Cpr-CH), 38.5 (CH_2), 38.4, 38.6 (Cpr-C_{quat}), 42.1 (CH_2), 128.5, 128.6, 130.2, 130.4 (8 C, Ar-CH), 132.8, 132.9, 135.0, 135.2 (Ar-C_{quat}), 157.2, 157.3 (NC).

MS (EI): *m*/*z* (%) = 221/219 (9/27, [M^+]), 179/177 (9/35), 155/153 (12/42), 142 (82), 127/125 (30/100), 115 (64).

Anal. Calcd for $C_{13}H_{14}ClN$: C, 71.07; H, 6.42; N, 6.37. Found: C, 70.81; H, 6.29; N, 6.18.

1-Benzyloxymethyl-2-phenylcyclopropylisonitrile (4c)

To a stirred solution of formamide **3c** (1.16 g, 4.12 mmol) in benzene (10 mL) and Et_3N (1.43 mL, 10.3 mmol), was added at 0 °C a solution of phosgene (2.2 mL, 4.1 mmol, 20% in toluene). After stirring for 4 h at 0 °C, H_2O (30 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried (Na_2SO_4) and concentrated under reduced pressure to leave a black oil which was purified by column chromatography on silica gel to give compound **4c** (738 mg, 68%) as a colorless oil; R_f = 0.69 (EtOAc–hexane, 1:2).

IR (film): 3029, 2864, 2134, 1735, 1497, 1453, 1102, 740, 698 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.54 (dd, *J* = 6.3, 7.8 Hz, 1 H, Cpr-CH_2), 1.69 (dd, *J* = 6.3, 9.8 Hz, 1 H, Cpr-CH_2), 2.89 (t, *J* = 8.8 Hz, 1 H, Cpr-CH), 3.27 (s, 2 H, CH_2O), 4.33 (d, *J* = 12.3 Hz, 1 H, CH_2Ph), 4.39 (d, *J* = 12.3 Hz, 1 H, CH_2Ph), 7.10–7.30 (m, 10 H, Ph-H).

^{13}C NMR (75.5 MHz, APT, $CDCl_3$): δ = 17.2 (–, Cpr-CH_2), 31.0 (+, Cpr-CH), 39.5 (–, Cpr-C_{quat}), 69.7, 72.9 (–, CH_2), 127.4, 127.5, 127.7, 128.4, 128.5, 128.0 (+, 8 C, Ph-CH), 134.1, 137.4 (–, Ph-C_{quat}), 153.8 (–, NC).

MS (DCI): *m*/*z* (%) = 263 (3, [M^+]), 157 (25), 118 (18), 115 (14), 91 (100).

***N*-(3-*tert*-Butoxycarbonyl-3-azabicyclo[3.1.0]hex-6-yl)formamide (6)**

A mixture of the amine **5** (396 mg, 2.00 mmol) and ethyl formate (5 mL, 62 mmol) was heated under reflux for 1 h. The excess of the ethyl formate was removed in vacuo to leave compound **6** (442 mg, 98%) as a solid; mp 168–170 °C.

IR (film): 3291, 3056, 2977, 2935, 2877, 1695, 1426, 1394, 1174, 1122, 735 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ (2 tautomers) = 1.40 [s, 18 H, $C(CH_3)_3$], 1.65–1.82 [m, 4 H, CH (bicycle)], 2.45 (s, 2 H, CHN), 3.30–3.44 [m, 4 H, CH_2 (bicycle)], 3.60–3.80 [d, *J* = 11.1 Hz, 4 H, CH_2 (bicycle)], 6.16 (s, 1 H, NH), 6.35 (d, *J* = 11.0 Hz, 1 H, NH), 8.00–8.30 (m, 2 H, CHO).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ (2 tautomers) = 23.3, 24.8 [CH (bicycle)], 28.3, 28.4 [$C(CH_3)_3$], 31.2, 32.8 [CH (bicycle)], 47.3, 47.6 [CH_2 (bicycle)], 79.7, 79.9 [$C(CH_3)_3$], 154.3, 154.4 (NCOO), 162.2, 166.4 (CHO).

MS (DCI): *m*/*z* (%) = 470 (5, [2 M + NH_4^+]), 453 (5, [2 M + H^+]), 244 (100, [M + NH_4^+]), 227 (59, [M + H^+]), 188 (75).

3-*tert*-Butoxycarbonyl-3-azabicyclo[3.1.0]hex-6-ylisonitrile (7)

The crude **7** was obtained according to the GP3 from formamide **6** (226 mg, 1.00 mmol), Et_3N (0.35 mL, 2.50 mmol) and $COCl_2$ (0.53 mL, 1.00 mmol, 20% in toluene) in anhyd toluene (10 mL) with additional stirring for 12 h. The residue was purified by column chromatography on silica gel to give compound **7** (135 mg, 65%) as a colorless solid; mp 51–52 °C; R_f = 0.43 (Et_2O–hexane, 1:1).

IR (KBr): 3447, 2982, 2941, 2878, 2145, 1697, 1415, 1394, 1113 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.39 [s, 9 H, $C(CH_3)_3$], 2.06 (s, 2 H, CH), 2.52 (t, *J* = 2.4 Hz, 1 H, CHNC), 3.33 (d, *J* = 11.5 Hz, 2 H, CH_2), 3.5–3.7 (m, 2 H, CH_2).

^{13}C NMR (50.3 MHz, APT, $CDCl_3$): δ = 25.6 (+, CH), 26.3 (+, CH), 28.3 [+, $C(CH_3)_3$], 30.5 (+, CHNC), 46.8 (–, CH_2), 46.9 (–, CH_2), 80.1 [–, $C(CH_3)_3$], 154.2 (–, COO), 155.0 (–, NC).

MS (EI): *m*/*z* (%) = 208 (3, [M^+]), 153 (14), 135 (7), 57 (100).

HRMS-EI: *m*/*z* calcd for $C_{11}H_{16}N_2O_2$ [M^+]: 208.1212; found: 208.1212.

Dipeptides 15; General Procedure 4 (GP4)
A solution of the respective aldehyde (or ketone) **12**, the amine **13**, the isonitrile **4a–c**, **7**, **11** and the acid **14** in MeOH was stirred for 2 h at 25 °C. The solvent was removed in vacuo, and the crude product was purified by recrystallization or column chromatography on silica gel.

Cyclopropanecarboxylic Acid Benzyl{[1-(4-chlorobenzyl)-2-ethylcyclopropylcarbamoyl]cyclopropylmethyl}amide (15a)
Crude **15a** was prepared according to GP4 from cyclopropanecarbaldehyde (210 mg, 3.00 mmol), benzylamine (107 mg, 1.00 mmol), isonitrile **4b** (220 mg, 1.00 mmol) and cyclopropanecarboxylic acid (129 mg, 1.50 mmol) in MeOH (5 mL) and was purified by column chromatography on silica gel to give **15a** (322 mg, 69%) as a pale yellow oil; R_f = 0.45 (Et_2O–hexane, 1:1).

IR (film): 3313, 3067, 3006, 2961, 2930, 2873, 1739, 1684, 1617, 1492, 1430, 1241 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ (mixture of the 8 diastereomers) = 0.05–0.20 (m, 4 H, Cpr-CH), 0.30–1.80 (m, 32 H, Cpr-CH, CH_2CH_3), 2.55–3.25 (m, 4 H, CH_2Ar), 3.82 (t, *J* = 12.0 Hz, 2 H, CH), 4.65–4.75 (m, 4 H, NC*H*$_2$Ph), 6.40–6.75 (m, 2 H, NH), 7.05–7.35 (m, 18 H, Ph-H + Ar-H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ (mixture of the 8 diastereomers) = 4.78, 4.83, 4.91, 5.04, 5.14, 5.29, 8.09, 8.29, 8.36, 8.53, 8.78, 8.89, 8.94, 9.03, 10.06, 10.14, 10.18, 10.30, 11.90, 11.97, 12.01, 12.54, 12.94, 13.70, 13.80, 13.82, 18.72, 18.79, 19.21, 19.32, 21.85, 21.94, 23.06, 23.15, 25.92, 26.06, 28.03, 28.19, 35.84, 35.94, 37.07, 37.30, 38.01, 38.06, 41.27, 41.37, 48.63, 48.74, 48.85 (Cpr-C, CH_2CH_3, *C*H_2Ph, *C*H_2Ar), 63.40, 63.56, 63.90, 64.04 (CH), 126.14, 126.20, 126.97, 127.03, 128.22, 128.25, 128.30, 128.33, 128.40, 128.43, 128.73, 130.46, 130.50, 130.55, 130.63, 130.73, 131.91, 132.01, 137.80, 137.92, 137.97, 138.01, 138.04 (Ph-CH/C_{quat} + Ar-CH/C_{quat}), 170.70, 170.82, 171.13, 171.63, 175.72, 175.80 (CNO); it was not possible to single out all carbon signals.

MS (EI): *m*/*z* (%) = 466/464 (<1/<1, [M^+]), 291/289 (6/21), 256 (98), 228 (42), 160 (100), 91 (89).

Anal. Calcd for $C_{28}H_{33}ClN_2O_2$: C, 72.32; H, 7.15; N, 6.02. Found: C, 72.10; H, 6.99; N, 5.88.

Cyclopropanecarboxylic Acid Benzyl-{[1-(4-chlorobenzyl)cyclopropylcarbamoyl]cyclopropylmethyl}amide (15b)
Crude **15b** was prepared according to GP4 from cyclopropanecarbaldehyde (350 mg, 5.00 mmol), benzylamine (107 mg, 1.00 mmol), isonitrile **4a** (287 mg, 1.50 mmol) and cyclopropanecarboxylic acid (129 mg, 1.50 mmol) in MeOH (5 mL) and was purified by column chromatography on silica gel to give dipeptide **15b** (242 mg, 55%) as a colorless solid; mp 112–114 °C; R_f = 0.23 (Et_2O–hexane, 1:1).

IR (KBr): 3429, 3307, 3083, 3022, 2953, 2929, 2853, 1640, 1533, 1431 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.10–0.20 (m, 2 H, Cpr-H), 0.50–1.10 (m, 11 H, Cpr-H), 1.50–1.60 (m, 1 H, Cpr-H), 2.78 (d, *J* = 13.2 Hz, 1 H, C*H*$_2$Ar), 2.98 (d, *J* = 13.2 Hz, 1 H, C*H*$_2$Ar), 3.82 (d, *J* = 10.8 Hz, 1 H, CH), 4.74 (s, 2 H, C*H*$_2$Ph), 6.52 (s, 1 H, NH), 7.10–7.40 (m, 9 H, Ph-H + Ar-H).

^{13}C NMR (50.3 MHz, APT, $CDCl_3$): δ = 4.8, 5.3, 8.3, 8.9 (–, Cpr-CH_2), 10.1, 11.9 (+, Cpr-CH), 13.3, 13.4 (–, Cpr-CH_2), 33.7 (–, Cpr-C_{quat}), 40.4 (–, *C*H_2Ph), 48.8 (–, *C*H_2Ar), 63.7 (+, CH), 126.2, 127.0, 128.6, 128.4, 130.6 (+, 9 C, Ph-CH + Ar-CH), 132.2, 137.6, 137.9 (–, Ph-C + Ar-C), 171.2, 175.8 (–, CON).

MS (EI): *m*/*z* (%) = 438/436 (<1/<1, [M^+]), 256 (54), 228 (43), 160 (100), 91 (60).

Anal. Calcd for $C_{26}H_{29}ClN_2O_2$: C, 71.46; H, 6.69; N, 6.41. Found: C, 71.65; H, 6.60; N, 6.53.

***N*-*tert*-Butoxycarbonylglycinyl[(1-benzyloxymethyl-2-phenylcyclopropylcarbamoyl)cycloxehyl](3-chlorobenzyl)amide (15c)**
Crude **15c** was prepared according to GP4 from cyclohexanone (49 mg, 0.5 mmol), 3-chlorobenzylamine (71 mg, 0.5 mmol), isonitrile **4c** (132 mg, 0.50 mmol) and *N*-Boc-Gly-OH (88 mg, 0.5 mmol) in MeOH (5 mL) and was purified by column chromatography on silica gel to give dipeptide **15c** (285 mg, 86%) as a colorless solid; mp 57–59 °C; R_f = 0.13 (Et_2O–hexane, 1:1).

IR (KBr): 3428, 3358, 3067, 3028, 2979, 2933, 2865, 1684, 1497, 1165 cm^{-1}.

^1H NMR (300 MHz): δ = 1.05–1.44 (m, 11 H, *t*-C_4H_9, Cpr-H), 1.48–1.64 (m, 8 H, cHex-H), 2.42 (m, 2 H, cHex-H), 2.48 (t, *J* = 7.2 Hz, 1 H, Cpr-H), 3.08 (d, *J* = 10.8 Hz, 1 H, CH_2O), 3.51 (d, *J* = 10.8 Hz, 1 H, CH_2O), 3.84 (br s, 2 H, NCOC*H*$_2$NHCOO), 4.25 (d, *J* = 12.0 Hz, 1 H, C*H*$_2$Ph), 4.33 (d, *J* = 12.0 Hz, 1 H, C*H*$_2$Ph), 4.55 (s, 2 H, C*H*$_2$Ar), 5.38 (br s, 1 H, NH), 6.70 (s, 1 H, NH), 7.08–7.42 (m, 14 H, Ph-H + Ar-H).

^{13}C NMR (75.5 MHz, APT, add. HSQC, $CDCl_3$): δ = 16.4 (–, Cpr-CH_2), 22.8 (–, cHex-CH_2), 25.3 (–, cHex-CH_2), 28.3 [+, C(*C*H_3)$_3$], 29.7 (+, Cpr-CH), 32.8 (–, cHex-CH_2), 38.2 (–, Cpr-C_{quat}), 43.7 (–, NCO*C*H_2NHCOO), 46.5 (–, *C*H_2Ar), 66.5 (–, cHex-C_{quat}), 71.6 (–, Cpr-CH_2O), 72.9 (–, Ph*C*H_2O), 79.6 [–, *C*(CH$_3$)$_3$], 124.0, 126.0, 126.4, 127.4, 127.5, 127.8, 128.0, 128.2, 129.3, 130.4 (+, 14 C, Ph-CH + Ar-CH), 135.0, 137.2, 138.3, 139.9 (–, Ph-C_{quat} + Ar-C_{quat}), 155.6, 170.1, 173.2 (–, CON).

MS (ESI): *m*/*z* (%) = 1345/1343/1341 (8/39/71, [2 M + Na^+]), 684/682 (5/19, [M + Na^+]).

Anal. Calcd for $C_{38}H_{46}ClN_3O_5$: C, 69.13; H, 7.02; N, 6.36. Found: C, 68.94; H, 6.89; N, 6.08.

Cyclopropanecarboxylic Acid (Benzyl)[(3-*tert*-butoxy-*N*-carbonyl-3-azabicclo[3.1.0]hexylcarbamoyl)cyclopropylmethyl]-amide (15d)
Crude **15d** was prepared according to GP4 from cyclopropanecarbaldehyde (107 mg, 1.53 mmol), benzylamine (54.6 mg, 0.51 mmol), isonitrile **7** (161 mg, 0.77 mmol) and cyclopropanecarboxylic acid (66.2 mg, 0.77 mmol) in MeOH (5 mL) and was purified by column chromatography on silica gel (Et_2O–Hexane, 1:1) to give dipeptide **15d** (186 mg, 81%) as a colorless solid; mp 122–124 °C; R_f = 0.08 (Et_2O–hexane, 1:1).

IR (KBr): 3440, 3281, 3067, 2973, 2932, 2859, 1705, 1612, 1420, 1394, 1114 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 0.10–0.30 (m, 3 H, Cpr-H), 0.40–1.30 (m, 5 H, Cpr-H), 1.39 (s, 9 H, tBu), 1.50–1.70 [m, 4 H, Cpr-H, CH (bicycle)], 2.37 [m, 1 H, C*H*NH (bicycle)], 3.30–3.40 [m, 2 H, CH_2 (bicycle)], 3.55–3.70 [m, 2 H, CH_2 (bicycle)], 3.93 (d, *J* = 10.3 Hz, 1 H, CH), 4.92 (s, 2 H, C*H*$_2$Ph), 6.77 (s, 1 H, NH), 7.10–7.35 (m, 5 H, Ph-H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 5.1, 8.3, 8.7, 9.0, 10.4, 12.2 (Cpr-CH), 23.7, 24.2 [CH (bicycle)], 28.4 [C(*C*H$_3$)$_3$], 32.3 [CHNH (bicycle)], 47.4, 47.6 [CH_2 (bicycle)], 48.9 (*C*H_2Ph), 63.5 (CH), 79.4 [*C*(CH$_3$)$_3$], 126.1, 127.0, 128.4, 137.9 (6 C, Ph-CH + Ph-C_{quat}), 154.4 (NCOO), 171.8, 175.9 (CON).

MS (ESI): *m*/*z* (%) = 498 (57, [M + $HCOO^-$]), 452 (100, [M – H^+]).

Anal. Calcd for $C_{26}H_{35}N_3O_4$: C, 68.85; H, 7.78; N, 9.26. Found: C, 68.64; H, 7.51; N, 9.04.

Cyclopropanecarboxylic Acid [(3-*tert*-Butoxycarbonyl-3-azabicyclo[3.1.0]hexylcarbamoyl)cyclopropylmethyl](phenyl)amide (15e)
Crude **15e** was prepared according to GP4 from cyclopropanecarbaldehyde (105 mg, 1.50 mmol), aniline (47 mg, 0.5 mmol), isonitrile **7** (156 mg, 0.75 mmol) and cyclopropanecarboxylic acid (64.5

mg, 0.75 mmol) in MeOH (5 mL) and was purified by column chromatography on silica gel to give dipeptide **15e** (168 mg, 76%) as a colorless solid; mp 184–185 °C; R_f = 0.05 (Et_2O–hexane, 1:1).

IR (KBr): 3434, 3369, 3317, 3059, 3012, 2979, 2927, 2882, 1694, 1627, 1541, 1424, 1388, 1114 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.20–0.35 (m, 2 H, Cpr-CH), 0.35–0.50 (m, 1 H, Cpr-CH), 0.55–0.70 (m, 3 H, Cpr-CH), 0.80–1.00 (m, 3 H, Cpr-CH), 1.15–1.30 (m, 1 H, Cpr-CH), 1.38 (s, 9 H, *t*-C_4H_9), 1.60–1.70 [m, 2 H, 2 CH (bicycle)], 2.42–2.48 (m, 1 H, C*H*NH), 3.35 [d, *J* = 12.0 Hz, 2 H, CH_2 (bicycle)], 3.68 [dd, *J* = 3.0, 4.5 Hz, 2 H, CH_2 (bicycle)], 3.95 (d, *J* = 6.0 Hz, 1 H, CH), 6.78 (s, 1 H, NH), 7.30–7.45 (m, 5 H, Ph-H).

^{13}C NMR (50.3 MHz, APT, $CDCl_3$): δ = 4.3, 5.5, 8.6, 9.0 (–, Cpr-CH_2), 10.6, 12.9 (+, Cpr-CH), 23.8, 24.1 [+, CH (bicycle)], 28.4 [+, C(CH_3)$_3$], 32.5 [+, CHNH (bicycle)], 47.5 [–, CH_2N (bicycle)], 65.3 (+, CH), 79.4 [*C*(CH_3)$_3$], 128.3, 129.2, 129.9 (+, 5 C, Ph-CH), 139.8 (–, Ph-C_{quat}), 154.4 (–, NCOO), 171.9, 174.7 (–, CON).

MS (ESI): *m*/*z* (%) = 901 (100, [2 M + Na^+]), 462 (6, [M + Na^+]).

Anal. Calcd for $C_{25}H_{33}N_3O_4$: C, 68.31; H, 7.57; N, 9.56. Found: C, 68.00; H, 7.51; N, 9.29.

Acetic Acid [(3-*tert*-Butoxycarbonyl-3-azabicyclo[3.1.0]hexylcarbamoyl)cyclopropylmethyl]amide (15f)

Crude **15f** was prepared according to GP4 from cyclopropanecarbaldehyde (35 mg, 0.5 mmol), NH_4OH (0.1 mL, 0.7 mmol, 28–30 wt% of NH_3 in H_2O), isonitrile **7** (104 mg, 0.50 mmol) and AcOH (36 mg, 0.6 mmol) in MeOH (5 mL) and was purified by recrystallization (Et_2O–hexane, 1:1) to give dipeptide **15f** (86 mg, 52%) as a colorless solid; mp 202–204 °C.

IR (KBr): 3440, 3245, 3069, 2978, 2933, 2886, 1700, 1634, 1559, 1395, 1120 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.25–0.40 (m, 2 H, Cpr-CH), 0.44–0.56 (m, 2 H, Cpr-CH), 1.00–1.10 (m, 1 H, Cpr-CH), 1.39 (s, 9 H, *t*-C_4H_9), 1.62 [s, 2 H, CH (bicycle)], 1.98 (s, 3 H, CH_3), 2.42 [s, 1 H, CH (bicycle)], 3.30–3.40 [m, 2 H, CH_2 (bicycle)], 3.56–3.70 [m, 2 H, CH_2 (bicycle)], 3.82 (t, *J* = 9.0 Hz, 1 H, CH), 6.96 (d, *J* = 7.0 Hz, 1 H, NH), 7.42 (d, *J* = 21 Hz, 1 H, NH).

^{13}C NMR (50.3 MHz, APT, $CDCl_3$): δ = 3.1, 3.2 (–, Cpr-CH_2), 14.1 (+, Cpr-CH), 23.1 (+, CH_3), 23.3, 24.3 [+, CH (bicycle)], 28.4 [+, C(*C*H_3)$_3$], 32.5 [+, CH (bicycle)], 47.4, 47.6 [–, CH_2 (bicycle)], 56.5 (+, CH), 79.5 [–, *C*(CH_3)$_3$], 154.4 (–, COO), 170.3, 172.5 (–, CONH).

MS (ESI): *m*/*z* (%) = 697 (100, [2 M + Na^+]), 360 (63, [M + Na^+]).

HRMS-ESI: *m*/*z* calcd for $C_{17}H_{27}N_3O_4$ + Na [M + Na^+]: 360.1899; found: 360.1894.

Acetic Acid [(3-*tert*-Butoxycarbonyl-3-azobicyclo[3.1.0]hexylcarbamoyl)cyclohexyl]amide (15g)

Crude **15g** was prepared according to GP4 from cyclohexanone (49 mg, 0.5 mmol), NH_4OH (0.1 mL, 0.7 mmol, 28–30 wt% of NH_3 in H_2O), isonitrile **7** (104 mg, 0.5 mmol) and AcOH (36 mg, 0.6 mmol) in MeOH (5 mL) and was purified by recrystallization (Et_2O–hexane, 1:1) to give dipeptide **15g** (124 mg, 68%) as a colorless solid; mp 104–105 °C.

IR (KBr): 3440, 3304, 3056, 2974, 2932, 2869, 1710, 1653, 1540, 1394, 1172, 1117 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.20–1.40 (m, 12 H, *t*-C_4H_9, cHex-CH_2), 1.40–1.70 (m, 5 H, cHex-CH_2), 1.70–1.90 (m, 2 H, cHex-CH_2), 1.90–2.10 [m, 5 H, CH_3, CH (bicycle)], 2.35–2.40 [m, 1 H, CH (bicycle)], 3.25–3.40 [m, 2 H, CH_2 (bicycle)], 3.56–3.70 [m, 2 H, CH_2 (bicycle)], 5.65 (br s, 1 H, NH), 7.35 (br s, 1 H, NH).

^{13}C NMR (75.5 MHz, APT, $CDCl_3$): δ = 21.5 (–, 2 C, cHex-CH_2), 23.6 [+, CH (bicycle)], 24.0 (+, CH_3), 24.7 [+, CH (bicycle)], 25.1 (–, cHex-CH_2), 28.4 [+, C(*C*H_3)$_3$], 32.1, 32.3 (–, cHex-CH_2), 32.6 (+, CHNH), 47.4, 47.7 [–, CH_2 (bicycle)], 60.2 (–, C_{quat}), 79.4 [–, *C*(CH_3)$_3$], 154.4 (COO), 171.1, 175.3 (CONH).

MS (EI): *m*/*z* (%) = 365 (<1, [M^+]), 265 (9), 168 (43), 140 (82), 98 (100), 69 (76).

Ethyl 1-[2-(Benzylcyclopropanecarbonylamino)-2-cyclopropylacetylamino]cyclopropanecarboxylate (15h)

Crude **15h** was prepared according to GP4 from cyclopropanecarbaldehyde (210 mg, 3.00 mmol), benzylamine (107 mg, 1.00 mmol), isonitrile **11**[7,8] (209 mg, 1.50 mmol) and cyclopropanecarboxylic acid (129 mg, 1.50 mmol) in MeOH (5 mL) and was purified by column chromatography on silica gel to give dipeptide **15h** (312 mg, 81%) as a colorless solid; mp 92–93 °C; R_f = 0.17 (Et_2O–hexane, 1:1).

IR (KBr): 3429, 3267, 3089, 3039, 3006, 2985, 1738, 1690, 1605, 1539, 1179 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 0.10–0.30 (m, 3 H, Cpr-H), 0.60–1.00 (m, 5 H, Cpr-H), 1.05–1.35 (m, 5 H, CH_2CH_3, Cpr-H), 1.40–1.50 (m, 1 H, Cpr-H), 1.55–1.70 (m, 3 H, Cpr-H), 4.08–4.18 (m, 3 H, CH, CH_2CH_3), 4.80 (d, *J* = 18.0 Hz, 1 H, CH_2Ph), 4.96 (d, *J* = 18.0 Hz, 1 H, CH_2Ph), 7.02 (s, 1 H, NH), 7.20–7.40 (m, 5 H, Ph-H).

^{13}C NMR (50.3 MHz, APT, $CDCl_3$): δ = 4.7, 5.4, 8.0, 8.9 (–, Cpr-CH_2), 9.9, 12.2, 14.2 (+, Cpr-CH, CH_2CH_3), 17.2, 17.5, 33.4 (–, Cpr-C), 48.8 (–, CH_2Ph), 61.2 (–, CH_2CH_3), 63.3 (+, CH), 126.2, 126.9, 128.4 (+, 5 C, Ph-CH), 138.1 (–, Ph-C), 171.6, 172.1, 176.3 (–, CON, COO).

MS (EI): *m*/*z* (%) = 384 (2, [M^+]), 256 (18), 228 (78), 160 (100), 91 (40), 69 (37).

Anal. Calcd for $C_{22}H_{28}N_2O_4$: C, 68.73; H, 7.34; N, 7.29. Found: C, 68.41; H, 7.08; N, 7.48.

Ethyl 1-{2-[Cyclopropanecarbonyl-(4-methoxyphenyl)amino]-2-cyclopropylacetylamino}cyclopropanecarboxylate (15i)

Crude **15i** was prepared according to GP4 from cyclopropanecarbaldehyde (105 mg, 1.50 mmol), 4-methoxyaniline (62 mg, 0.5 mmol), isonitrile **11**[7,8] (104 mg, 0.75 mmol) and cyclopropanecarboxylic acid (105 mg, 1.22 mmol) in MeOH (5 mL) and was purified by column chromatography on silica gel to give dipeptide **15i** (171 mg, 86%) as a colorless solid; mp 132–134 °C; R_f = 0.22 (Et_2O–hexane, 1:1).

IR (KBr): 3324, 3299, 3083, 3034, 3000, 2957, 2908, 2835, 1722, 1694, 1620, 1510, 1420, 1250, 1179 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.30–0.50 (m, 3 H, Cpr-CH), 0.60–0.75 (m, 3 H, Cpr-CH), 0.90–1.10 (m, 4 H, Cpr-CH), 1.10–1.40 (m, 5 H, CH_2CH_3, Cpr-CH), 1.42–1.50 (m, 1 H, Cpr-CH), 1.60–1.70 (m, 1 H, Cpr-CH), 3.79 (s, 3 H, OCH_3), 4.05–4.20 (m, 3 H, CH, CH_2CH_3), 6.90 (dd, *J* = 1.4, 7.6 Hz, 2 H, Ar-H), 7.20–7.45 (m, 3 H, Ar-H, NH).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 5.8, 8.4, 9.0, 10.1, 12.9, 14.3, 17.6, 17.8, 33.4 (Cpr-C, CH_2CH_3), 55.5 (OCH_3), 61.3 (CH_2CH_3), 64.5 (CH), 114.3, 131.1, 132.2, 159.3 (5 C, Ar-CH), 171.7, 172.4, 175.3 (CON, COO).

MS (EI): *m*/*z* (%) = 400 (3, [M^+]), 272 (7), 244 (45), 176 (100), 69 (34).

Anal. Calcd for $C_{22}H_{28}N_2O_5$: C, 65.98; H, 7.07; N, 6.99. Found: C, 65.77; H, 6.74; N, 6.64.

Ethyl 1-{[1-(2-*tert*-Butoxycarbonylamino-3-phenylpropionylamino)cyclohexanecarbonyl]amino}cyclopropanecarboxylate (15j)

Crude **15j** was prepared according to GP4 from cyclohexanone (49 mg, 0.5 mmol), NH_4OH (0.1 mL, 0.7 mmol, 28–30 wt% of NH_3 in H_2O), isonitrile **11**[7,8] (70 mg, 0.5 mmol) and N-Boc-Pha-OH (135 mg, 0.51 mmol) in MeOH (5 mL) and was purified by column chromatography on silica gel to give dipeptide **15j** (187 mg, 75%) as a colorless solid; mp 93–94 °C; R_f = 0.13 (Et_2O–hexane, 1:1).

IR (KBr): 3437, 3287, 3034, 3006, 2981, 2930, 2866, 1714, 1672, 1509, 1163 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.00–1.30 (m, 7 H, CH_2CH_3, Cpr-CH), 1.30–1.60 (m, 15 H, t-C_4H_9, cHex-CH_2), 1.78–2.05 (m, 4 H, cHex-CH_2), 2.96 (dd, *J* = 7.2, 14.0 Hz, 1 H, CH_2Ph), 3.09 (dd, *J* = 7.2, 14.0 Hz, 1 H, CH_2Ph), 4.06 (q, *J* = 14.3 Hz, 2 H, CH_2CH_3), 4.18 (dd, *J* = 7.1, 13.5 Hz, 1 H, CH), 5.05 (d, *J* = 6.1 Hz, 1 H, N*H*-Boc), 6.01 (s, 1 H, NH), 7.15–7.35 (m, 5 H, Ph-H), 7.42 (s, 1 H, NH).

^{13}C NMR (50.3 MHz, APT, $CDCl_3$): δ = 14.1 (+, CH_3), 17.3, 17.5 (–, Cpr-CH_2), 21.0, 24.9, (–, cHex-CH_2), 28.2 [+, C(CH_3)$_3$], 31.8, 33.4, 37.3 (–, cHex-CH_2, CH_2Ph, CH_2CH_3), 56.9 (+, CH), 60.4, 61.1 (–, cHex-CH_2, Cpr-C), 80.9 [–, $C(CH_3)_3$], 127.2, 128.9, 129.1 (+, 5 C, Ph-CH) 136.3 (–, Ph-C), 155.9 (–, HNCOO), 171.1, 172.5, 174.9 (–, COO, CONH).

MS (EI): *m*/*z* (%) 501 (4, [M^+]), 289 (10), 237 (9), 120 (10), 98 (100).

Anal. Calcd for $C_{27}H_{39}N_3O_6$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.85; H, 7.78; N, 9.15.

Ethyl 1-[(1-Benzoylaminocyclohexanecarbonyl)amino]cyclopropanecarboxylate (15k)

Crude **15k** was prepared according to GP4 from cyclohexanone (98 mg, 1.0 mmol), ammonium benzoate (70 mg, 0.5 mmol) and isonitrile **11** (70 mg, 0.5 mmol) in MeOH (5 mL) and was purified by column chromatography on silica gel to give dipeptide **15k** (118 mg, 66%) as a colorless solid; mp 207–209 °C; R_f = 0.07 (Et_2O–hexane, 1:1).

IR (KBr): 3347, 3266, 3028, 2979, 2935, 2858, 1725, 1663, 1637, 1521, 1339, 1185 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.10–1.20 (m, 5 H, Cpr-H, cHex-H), 1.30–1.75 (m, 8 H, CH_2CH_3, cHex-H), 2.00 (t, *J* = 11.0 Hz, 2 H, cHex-H), 2.26 (d, *J* = 14.0 Hz, 2 H, cHex-H), 4.06 (q, *J* = 14.3 Hz, 2 H, CH_2CH_3), 6.11 (s, 1 H, NH), 7.40–7.60 (m, 3 H, Ph-H), 7.70–7.80 (m, 2 H, Ph-H), 7.95 (s, 1 H, NH).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.0, 17.5, 21.6, 25.2, 32.1, 33.5 (Cpr-CH, cHex-CH_2, CH_2CH_3), 60.6, 61.2 (Cpr-C_{quat}, cHex-C_{quat}), 126.8, 128.7, 131.9, 134.4 (6 C, Ph-CH + Ph-C), 168.1, 172.4, 174.9 (COO, CONH).

MS (EI): *m*/*z* (%) = 358 (6, [M^+]), 237 (20), 230 (17), 202 (70), 105 (100), 77 (20).

Anal. Calcd for $C_{20}H_{26}N_2O_4$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.71; H, 7.23; N, 7.70.

Ethyl 1-(2-Benzoylamino-2-cyclopropylacetylamino)cyclopropanecarboxylate (15l)

Crude **15l** was prepared according to GP4 from cyclopropanecarbaldehyde (105 mg, 1.50 mmol), ammonium benzoate (70 mg, 0.5 mmol) and isonitrile **11** (70 mg, 0.5 mmol) in MeOH (5 mL) and was recrystallized from EtOAc–hexane (1:1) to give dipeptide **15l** (62 mg, 38%) as a colorless solid; mp 158–160 °C.

IR (KBr): 3429, 3282, 3177, 3057, 2930, 2858, 1733, 1684, 1634, 1534, 1449 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.45–0.60 (m, 4 H, Cpr-H), 1.05–1.35 (m, 6 H, Cpr-H, CH_2CH_3), 1.40–1.60 (m, 2 H, Cpr-H), 4.08 (q, *J* = 13.8 Hz, 2 H, CH_2CH_3), 4.25 (t, *J* = 7.8 Hz, 1 H, CH), 7.42–7.58 (m, 4 H, Ph-H, NH), 7.75–7.86 (m, 3 H, Ph-H).

^{13}C NMR (125.7 MHz, APT, $CDCl_3$): δ = 3.1, 3.3 (–, Cpr-CH_2), 13.9, 14.1 (+, CH_2CH_3, Cpr-CH), 17.2, 17.5 (–, Cpr-CH_2), 33.5 (–, Cpr-C_{quat}), 56.7 (+, CH), 61.3 (–, CH_2CH_3), 127.2, 128.4, 131.8 (+, 5 C, Ph-CH), 133.6 (–, Ph-C), 167.3, 172.1, 172.7 (–, CON, COO).

MS (EI): *m*/*z* (%) = 330 (4, [M^+]), 174 (29), 122 (14), 105 (100).

Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.17; H, 6.43; N, 8.39.

Crystallographic Data

Suitable crystals of the compounds **15b**,**d**,**h**,**i** for X-ray crystal structure determinations were obtained by slow evaporation of solvents from their solutions in Et_2O–hexane mixtures. X-ray crystallographic data for compounds **15h**,**d** and **i** were collected on a Bruker Proteum-M CCD diffractometer (for **15b** – on a Bruker SMART 6000 CCD diffractometer) (Mo-Kα, λ = 0.71073 Å, ω-scan, 0.3°/frame) at 120 K (**15b**,**h**,**i**) and 200 K (**15d**). All structures were solved by direct methods and refined by full-matrix least squares on F^2 for all data using SHELXTL software. All non-hydrogen atoms were refined with anisotropic displacement parameters, H-atoms were located on the difference map and refined isotropically.

Crystal Data for 15b

$C_{26}H_{29}ClN_2O_2$, *M* = 436.96, monoclinic, space group $P2_1/c$, *a* = 11.7811(2), *b* = 19.5913(3), *c* = 10.0373(2) Å, β = 95.03(1)°, *V* = 2307.8(1) Å^3, F(000) = 928, *Z* = 4, D_c = 1.258 Mg m^{-3}, μ = 0.191 mm^{-1}. 21118 reflections (1.74 ≤ θ ≤ 29.00°) were collected yielding 6123 unique data (R_{merg} = 0.0458). Final wR_2(F^2) = 0.1121 for all data (396 refined parameters), conventional *R*(F) = 0.0400 for 4490 reflections with I ≥ 2σ, GOF = 1.053.

Crystal Data for 15d

$C_{26}H_{35}N_3O_4$, *M* = 453.57, triclinic, space group P–1, *a* = 8.0801(9), *b* = 9.947(1), *c* = 15.668(2) Å, α = 94.697(3), β = 91.886(4), γ = 92.197(4)°, *V* = 1253.3(3) Å^3, F(000) = 488, *Z* = 2, D_c = 1.202 Mg m^{-3}, μ = 0.081 mm^{-1}. 11581 reflections (2.52 ≤ θ ≤ 28.00°) were collected yielding 5833 unique data (R_{merg} = 0.0685). Final wR_2(F^2) = 0.1446 for all data (427 refined parameters), conventional *R*(F) = 0.0398 for 2017 reflections with I ≥ 2σ, GOF = 0.964.

Crystal Data for 15h

$C_{22}H_{28}N_2O_4$, *M* = 384.46, triclinic, space group P–1, *a* = 9.7358(5), *b* = 9.8306(5), *c* = 12.2647(6) Å, α = 70.078(2), β = 71.432(5), γ = 82.394(2)°, *V* = 1045.77(9) Å^3, F(000) = 412, *Z* = 2, D_c = 1.221 Mg m^{-3}, μ = 0.084 mm^{-1}. 8373 reflections (2.81 ≤ θ ≤ 29.00°) were collected yielding 5153 unique data (R_{merg} = 0.0322). Final wR_2(F^2) = 0.1041 for all data (365 refined parameters), conventional *R*(F) = 0.0407 for 3966 reflections with I ≥ 2σ, GOF = 0.945.

Crystal Data for 15i

$C_{22}H_{28}N_2O_5$, *M* = 400.46, triclinic, space group P–1, *a* = 11.3239(5), *b* = 13.8172(6), *c* = 14.2573(6) Å, α = 90.008(2), β = 93.736(2), γ = 111.296(2)°, *V* = 2073.3(2) Å^3, F(000) = 856, *Z* = 4, D_c = 1.283 Mg m^{-3}, μ = 0.091 mm^{-1}. 18232 reflections (2.86 ≤ θ ≤ 29.50°) were collected yielding 10701 unique data (R_{merg} = 0.0375). Final wR_2(F^2) = 0.0818 for all data (747 refined parameters), conventional *R*(F) = 0.0410 for 7283 reflections with I ≥ 2σ, GOF = 0.954.

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(9) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited as supplementary publication no. CCDC 604790 (**15b**), CCDC 604791 (**15d**), CCDC 604792 (**15h**), CCDC 604703 (**15i**) with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk.