Productive Syntheses of 1-Ethynylcyclopropylamine and 1-Ethynylcyclobutylamine[1]

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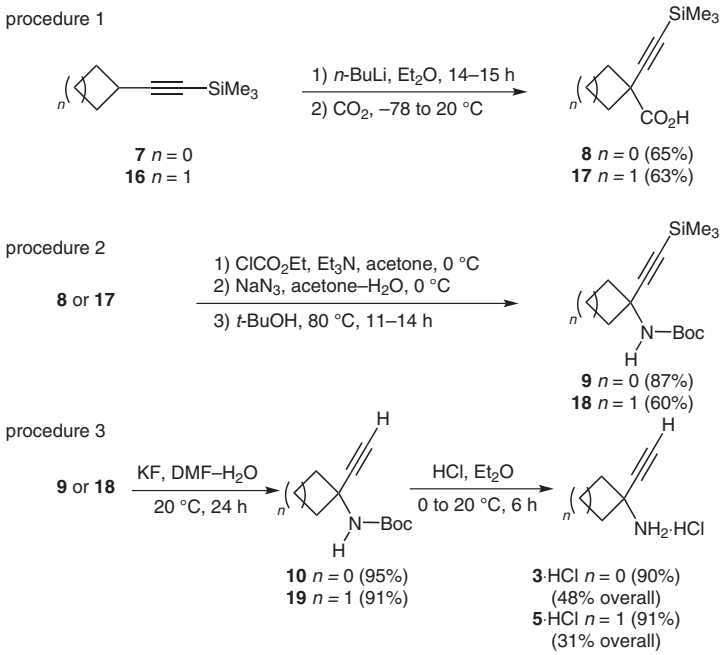
Dedicated to Professor Günter Helmchen on the occasion of his 70th birthday

Abstract: The new 1,1-dimethylpropargylamine surrogates, 1-ethynylcyclopropylamine (**3**) and 1-ethynylcyclobutylamine (**5**), were prepared as hydrochlorides from cyclopropylacetylene and 6-chlorohex-1-yne in overall yields of 39 and 25%, respectively, on a scale of up to 300 mmol. The amine **3** was converted into the new ethynyl-extended 1-aminocyclopropanecarboxylic acid **4**, and both the amine **3** as well as the amino acid **4** were made available as their *N*-Fmoc-protected derivatives.

Key words: alkynes, amines, amino acids, Curtius degradation, small rings



Scheme 1 General procedure for the preparation of 1-ethynylcyclopropylamine (**3**) and 1-ethynylcyclobutylamine (**5**)

Introduction

The 3,3-disubstituted oxetane moiety is currently being promoted as a mimic for *gem*-dimethyl substitution in biologically active and pharmacologically relevant compounds.[2] Due to its polarity, it reduces the increase in lipophilicity that *gem*-dimethyl substitution causes, and thereby supposedly improves metabolic robustness. In terms of enhanced metabolic inertness, the 1,1-disubstituted cyclopropane moiety has previously been employed as a mimic for *gem*-dimethyl groups.[3] Such a cyclopropane group is smaller than an isopropyl moiety[4] and, due to the enhanced electronegativity of its carbon atoms, also more polar.[5] Recently, 3-ethynyloxetan-3-amine (**2**) has been reported[6] as a surrogate for 1,1-dimethylpropargylamine (**1**) (Figure 1), which is a useful building block for certain pharmacophores.[7]

With the aim of accessing the ethynyl-extended analogue **4** of 1-aminocyclopropanecarboxylic acid (ACC) for incorporation in various peptidomimetics,[8] we developed a

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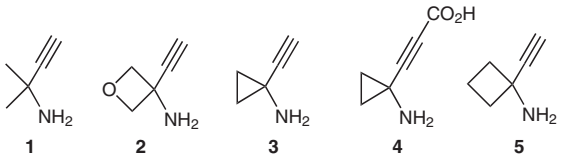


Figure 1 Amines **1**–**5**

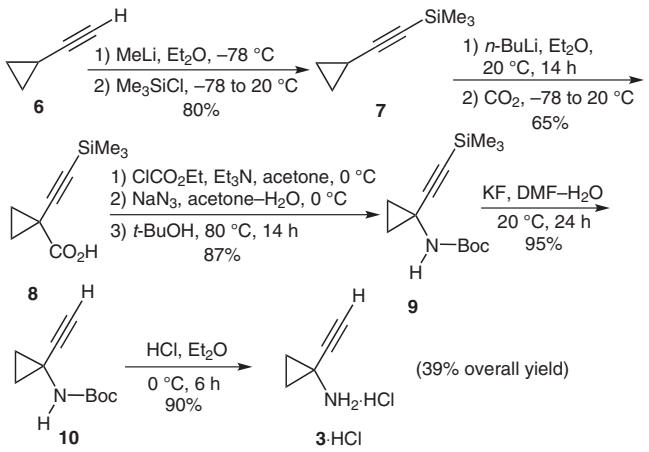
productive synthesis of 1-ethynylcyclopropylamine (**3**), another interesting surrogate for **1** and for **2**. Various oligosubstituted analogues of **3** with complex substituents at the acetylene terminus have been prepared either from cyclopropanone equivalents under different conditions, by selective dihalocyclopropanation of appropriately functionalized enamines or via cyclopropene intermediates.[9] While the structural and conformational properties of the parent **3** had been published without preparative details by us before,[10] the (1-ethynylcyclobutyl)amine (**5**) (Figure 1) has been unknown so far. A number of compounds with a (1-ethynylcyclobutyl)amine moiety have demonstrated an enhanced anticancer activity.[11] However, the preparation of the parent (1-ethynylcyclobutyl)amine (**5**) had not been disclosed. This holds true also for the amino acid **4**, the ethyl ester of which – an important synthetic intermediate towards antimicrobial drugs – has previously been synthesized[12] applying a Wittig alkenation/Fritsch–Buttenberg–Wiechell (FBW-type) rearrangement sequence[13] to 1-*tert*-butoxyxcarbonylaminocyclopropane carbaldehyde. The latter can be prepared from dimethyl malonate or from ACC and its derivatives in four to five steps.[14] The productive syntheses of 1-ethynylcyclopropylamine (**3**), of its cyclobutane analogue **5** (Scheme 1), and of the amino acid **4** are reported here.

Results and Discussion

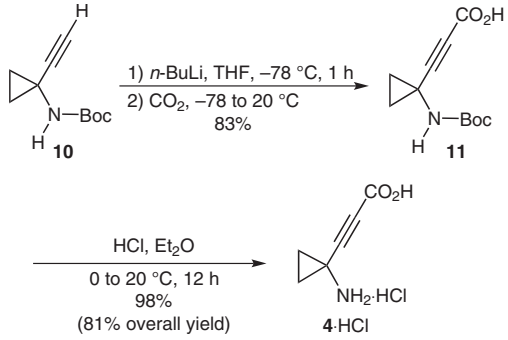
Cyclopropylacetylene (6),[15] which is now commercially available, was deprotonated with methyllithium in diethyl ether, and the resulting anion silylated with trimethylsilyl chloride adopting a published procedure[16] to give (trimethylsilylethynyl)cyclopropane (7) in 80% yield.[17] The latter was then deprotonated with *n*-butyllithium in diethyl ether,[18] and the resulting propargyl anion treated with dry ice to yield the acid 8 (65%) (Scheme 2).

Curtius degradation of the acid **8** according to the Weinstock protocol[19] as previously employed in a different example,[20] furnished the *N*-Boc-protected 1-(trimethylsilylethynyl)cyclopropylamine **9** (95% yield), which was fully deprotected by treatment with potassium fluoride in dimethylformamide–water and subsequently with hydrogen chloride in diethyl ether. The amine hydrochloride **3**·HCl was thus obtained from cyclopropylacetylene (**6**) in 39% overall yield (Scheme 2).

The *N*-Boc-protected amine **10** was also used to prepare the new acetylene-extended 1-aminocyclopropanecarboxylic acid (**4**). Towards that end, **10** was deprotonated with *n*-butyllithium in tetrahydrofuran,[21] the acetylide then carboxylated, and finally the *N*-Boc group in **11** removed by treatment with hydrogen chloride in diethyl ether. The amine hydrochloride **4**·HCl was thus obtained from **10** in 81% overall yield (Scheme 3).

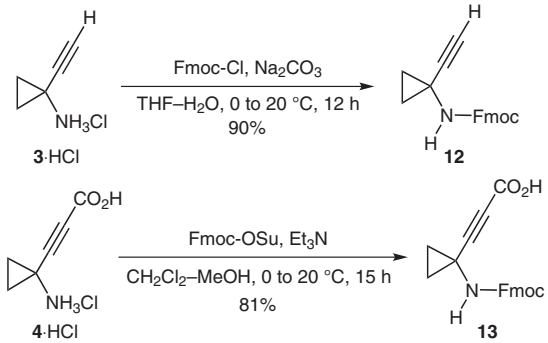


Scheme 2 Preparation of 1-ethynylcyclopropylamine hydrochloride (**3**·HCl)



Scheme 3 Synthesis of 3-(1-aminocyclopropyl)propiolic acid hydrochloride (**4**·HCl)

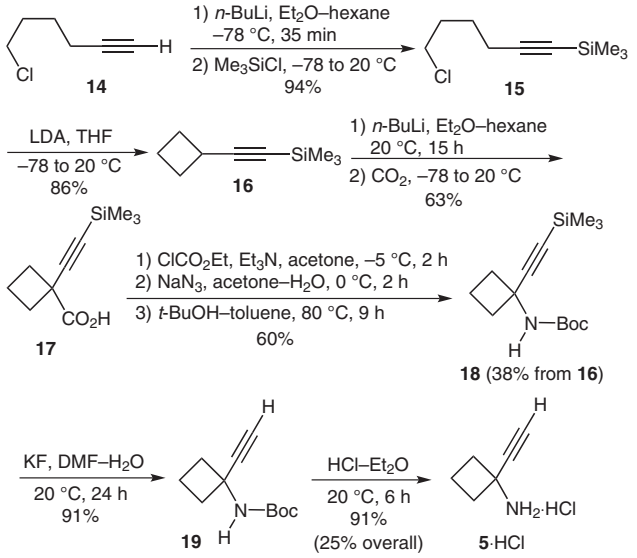
For further elaboration, the amine hydrochloride **3**·HCl and the amino acid hydrochloride **4**·HCl can be reprotected applying routine procedures.[22,23] For example, the Fmoc derivatives **12** and **13**, the latter to be employed in automated oligopeptide synthesis,[24] were thus prepared in 90 and 81% yield, respectively (Scheme 4).



Scheme 4 *N*-Fmoc protection of the amine **3** and the amino acid **4**

The starting material in the current synthesis of (1-ethynylcyclobutyl)amine (**5**), cyclobutylacetylene, has previously been prepared as a solution in tetrahydrofuran by treatment of commercially available 6-chlorohex-1-yne

(**14**) with *n*-butyllithium[25a] or bis(dialkylamino)magnesiums.[25b] For the synthesis of the fully protected 1-ethynylcyclobutylamine **18** it turned out to be better to first protect the terminal acetylene **14** with a trimethylsilyl group and then treat the resulting 6-chloro-1-trimethylsilylhex-1-yne (**15**) with lithium diisopropylamide in tetrahydrofuran to furnish 2-cyclobutyl-1-trimethylsilylacetylene (**16**) in an overall yield of 81%. Deprotonation of **16** at the propargylic position had to be carried out with *n*-butyllithium at ambient temperature without cooling, in fact the temperature rose to 31 °C for six hours, and subsequent treatment with powdered dry ice gave the crude carboxylic acid **17** in 63% yield. Curtius degradation of **17** again employing the Weinstock protocol[19,20] furnished the *N*-Boc-protected 1-(trimethylsilylethynyl)cyclobutylamine **18** in 38% overall yield from the silylated acetylene **16**. Complete deprotection of **18** was achieved as above for **9** to give the amine hydrochloride **5**·HCl in an overall yield of 25% from 6-chlorohex-1-yne (**14**) (Scheme 5).



Scheme 5 Preparation of 1-ethynylcyclobutylamine hydrochloride (**5**·HCl)

^{1}H and ^{13}C NMR spectra were recorded at 250 (^{1}H), 300 (^{1}H), 62.9 [^{13}C, additional DEPT (Distortionless Enhancement by Polarization Transfer)] and 125.7 MHz (^{13}C) on Bruker AM 250, Varian Mercury Vx300 and Inova-500 instruments in $CDCl_3$, D_2O, THF-d_8, and DMSO-d_6 solutions, $CHCl_3/CDCl_3$, DHO, C_4HD_7O and CD_3SOCD_2H as internal references. EI-MS, ESI-MS, and HRMS spectra were measured with Finnigan MAT 95 (at 70 eV), Finnigan LCQ and Bruker Daltonic APEX IV 7T FTICR instruments, respectively. Melting points were determined on a Büchi 510 capillary melting point apparatus and are uncorrected. TLC analyses were performed on precoated sheets (0.25 mm Sil G/UV254) from Macherey-Nagel). All chemicals were used as commercially available. Ethynylcyclopropane (**6**) was obtained by distillation from its commercially available 50% solution in toluene (bp 52–53 °C). Anhyd Et_2O, THF, and toluene were obtained by distillation from sodium benzophenone ketyl; acetone by distillation from anhyd K_2CO_3. Organic extracts were dried over $MgSO_4$, if not otherwise specified. All reactions in anhydrous solvents were carried out under an argon atmosphere in flame-dried glassware.

Starting Materials

(Cyclopropylethynyl)trimethylsilane (7)

Compound **7** was prepared adopting a published protocol,[16] which had not been applied to ethynylcyclopropane (**6**).[15] A magnetically stirred solution of the alkyne **6** (66.0 g, 84.6 mL, 1.064 mol) in anhyd Et_2O (300 mL), cooled to –78 °C, was treated with MeLi (1.18 mol, 550 mL of a 2.15 M solution in Et_2O) at such a rate that the temperature was maintained below –60 °C. After stirring the solution at –78 °C for an additional 2 h, Me_3SiCl (119.5 g, 139.6 mL, 1.1 mol) was added, again taking care to maintain the temperature below –60 °C. The resulting mixture was stirred at –40 °C for an additional 2 h, then allowed to warm up to r.t. After an additional stirring at r.t. for 1 h, the reaction mixture was poured into ice-cold H_2O (1 L). The layers were separated, and the aqueous layer was extracted with Et_2O (300 mL). The combined organic layers were washed with brine (300 mL) and dried. The solvent was removed by distillation at atmospheric pressure through a 25 cm column packed with Aldrich® glass helices, coil I.D. ~ 3 mm. Vacuum distillation of the residue yielded 119.9 g (80%) of **7** as a colorless liquid; bp 87 °C/137 mbar (Lit.[15b] bp 49–52 °C/20 mbar). The ^{1}H and ^{13}C NMR spectra were identical to the published ones.[15b] This compound is commercially available as well; the lowest price is US $ 1755.00/kg from Shanghai FWD Chemicals.

6-Chloro-1-trimethylsilylhex-1-yne (15)

A solution of 6-chlorohex-1-yne (**14**; 47.2 g, 49.8 mL, 0.412 mol) in anhyd Et_2O (0.8 L) was treated at –78 °C with *n*-BuLi (0.450 mol, 180 mL of a 2.5 M solution in hexane). After stirring for 35 min, Me_3SiCl (53.6 g, 62 mL, 0.492 mol) was added. The mixture was warmed up to r.t. and then hydrolyzed with a sat. aq NH_4C1 solution (400 mL). The aqueous phase was extracted with Et_2O (3 × 200 mL), the combined organic layers were washed with brine (200 mL), and dried (Na_2SO_4). The solvent was removed on a rotary evaporator, and the residue purified by distillation under reduced pressure to give 72.9 g (94%) of **15** as a colorless liquid; bp 90–92 °C/37 mbar (Lit.[26a] bp 104 °C/760 Torr). The ^{1}H and ^{13}C NMR spectra were identical to the published ones.[26]

(Cyclobutylethynyl)trimethylsilane (16)

A solution of $(i\text{-Pr})_2NH$ (78.12 g, 109 mL, 0.772 mol) in anhyd THF (1.5 L) was treated at 0 °C with *n*-BuLi (0.772 mol, 309 mL of a 2.5 M solution in hexane), and the mixture stirred for 20 min. After cooling down to –78 °C, a solution of **15** (72.9 g, 0.386 mol) in anhyd THF (200 mL) was added slowly. The mixture was warmed up to r.t. and hydrolyzed with a sat. aq NH_4C1 solution (800 mL). The aqueous phase was extracted with pentane (5 × 200 mL), the combined organic layers were washed with brine (200 mL), and dried (Na_2SO_4). The solvent was removed on a rotary evaporator, and the residual yellow liquid was purified by vacuum distillation under reduced pressure to yield 50.53 g (86%) of **16** as a colorless liquid; bp 70–72 °C/54 mbar.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.08–2.97 (m, 1 H), 2.30–2.23 (m, 2 H), 2.23–2.05 (m, 2 H), 1.94–1.79 (m, 2 H), 0.15 [s, 9 H, $Si(CH_3)_3$].

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 111.2 (C≡), 84.6 (C≡), 30.0 (2 CH_2), 25.9 (CH), 19.1 (CH_2), 0.20 (3 CH_3).

MS (EI, 70 eV): *m*/*z* = 152 (M^+), 137, 124, 109, 83.

HRMS (EI): *m*/*z* calcd for $C_9H_{16}Si$: 152.0121; found: 152.0120.

Anal. Calcd for $C_9H_{16}Si$ (152.31): C, 70.97; H, 10.59. Found: C, 71.14; H, 10.38.

Carboxylation of Me_3Si-Protected Cycloalkylacetylenes 7 and 16; Preparation of the Acids 8 and 17; General Procedure 1 (GP 1)

The acids **8** and **17** were prepared according to a modified published procedure.[13] To a solution of **7** or **16** (0.250 mol) in anhyd Et_2O (500 mL) was added a solution of *n*-BuLi in hexane. The reaction mixture was stirred at r.t. for 9–14 h, then the dark-yellow solution was cooled to –78 °C, and a large excess of powdered dry ice was added in several portions. The reaction mixture was allowed to warm up to 20 °C and poured into ice-cold H_2O (400 mL). The layers were separated; the aqueous layer was washed with Et_2O (2 × 100 mL), acidified by adding 12 N aq HCl solution (21 mL) and extracted with Et_2O (4 × 100 mL). The combined organic layers were dried and concentrated under reduced pressure to give **8** or **17** as colorless solids, which were used without further purification; analytical samples were obtained by recrystallization from hexane.

1-[(Trimethysilyl)ethynyl]cyclopropanecarboxylic Acid (8)

According to GP 1, from **7** (34.6 g, 42.2 mL, 0.250 mol) and *n*-BuLi (0.250 mol, 98.8 mL of a 2.53 M solution in hexane; 14 h stirring at r.t.) was obtained the acid **8** (29.5 g, 65%) as a colorless solid, which was used without further purification; mp 69–71 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.64–1.53 and 1.49–1.39 (m AA′BB′, 4 H), 0.16 [s, 9 H, $Si(CH_3)_3$].

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 178.4 (C), 103.8 (C), 84.5 (C), 21.9 (2 CH_2), 16.4 (C), –0.1 (3 CH_3).

HRMS (EI): *m*/*z* calcd for $C_9H_{14}O_2Si$: 182.0763; found: 182.0760.

1-[(Trimethylsilyl)ethynyl]cyclobutanecarboxylic Acid (17)

According to GP 1, a solution of **16** (39.89 g. 0.263 mol) was rapidly treated with *n*-BuLi (0.290 mol, 116 mL of a 2.50 M solution in hexane) without external cooling. The temperature of the mixture reached 31 °C and remained for 6 h, then slowly it began to fall down to r.t. The reaction mixture was stirred for an additional 9 h and then treated with powdered dry ice according to GP 1 to give 32.27 g (63%) of **17** as a colorless solid, which was used without further purification; mp 69–71 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.73–2.63 (m, 2 H), 2.47–2.38 (m, 2 H), 2.22–1.95 (m, 2 H), 0.18 [s, 9 H, $Si(CH_3)_3$].

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 178.7 (C), 106.1 (C), 88.2 (C), 41.7 (C), 33.6 (2 CH_2), 16.7 (CH_2), –0.0 (3 CH_3).

MS (EI, 70 eV): *m*/*z* = 196 (M^+), 181, 153, 135, 125, 109, 99, 75.

HRMS (EI): *m*/*z* calcd for $C_{10}H_{16}O_2Si$: 196.0921; found: 196.0920.

Anal. Calcd for $C_{10}H_{16}O_2Si$ (196.32): C, 61.18; H, 8.21. Found: C, 61.34; H, 8.04.

Curtius Degradation of the Acids 8 and 17; Preparation of the Protected Ethynylamines 9 and 18; General Procedure 2 (GP 2)

The carbamates **9** and **18** were prepared and deprotected in two consecutive steps applying a modified protocol of our previously published procedure.[20] To a stirred solution of the crude acid **8** or **17** in anhyd acetone was added Et_3N dropwise at –5 °C. After additional stirring at this temperature for 15 min, a solution of ethyl chloroformate in acetone was added at the same temperature over a period of 1 h, and the resulting mixture was stirred at this temperature for an additional 1.5 h. Then a solution of NaN_3 in H_2O was added over a period of 1 h, and the reaction mixture was stirred at 0 °C for 1.5 h, then poured into ice-cold water and extracted with Et_2O and pentane. The combined organic solutions were washed with ice-cold H_2O, dried with stirring for 2 h, and concentrated on a rotary evaporator under reduced pressure at 0 °C. To the concentrate was added anhyd toluene, and ca. 50% of the toluene was removed on a rotary evaporator under reduced pressure. The remainder was added dropwise to boiling anhyd *t*-BuOH within 1.5 h, and the resulting solution was then heated under reflux for 9–11 h. After cooling, the reaction mixture was concentrated under reduced pressure, the residue was taken up with Et_2O, washed with H_2O, dried, and concentrated again. The residue was purified as indicated below.

***tert*-Butyl 1-[(Trimethylsilyl)ethynyl]cyclopropylcarbamate (9)**

The acid **8** (93.94 g, 515.3 mmol) in acetone (1900 mL) was treated with Et_3N (66.6 g, 91.7 mL, 658.2 mmol), $ClCO_2Et$ (90.7 g, 79.9 mL, 836.0 mmol) in acetone (400 mL), and NaN_3 (56.94 g, 875.9 mmol) in H_2O (230 mL) according to GP 2. The reaction mixture was poured into ice-cold water (3 L), the mixture extracted with Et_2O (5 × 400 mL) and pentane (3 × 200 ml). The combined organic solutions were worked up as described in GP 2 using ice-cold H_2O (500 mL) and anhyd toluene (250 mL), and the crude azide was heated in anhyd *t*-BuOH (1600 mL, 11 h heating under reflux). The residue after concentration of the reaction mixture was taken up with Et_2O (1200 mL), the solution washed with H_2O (2 × 300 mL), dried and concentrated again to give 113.7 g (87%) of the carbamate **9** as a colorless solid, which was used without further purification; an analytical sample was obtained by recrystallization from hexane; mp 86 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.99 (br s, 1 H), 1.46 (s, 9 H), 1.22–1.01 (m AA′BB′, 4 H), 0.12 [s, 9 H, $Si(CH_3)_3$].

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 156.0 (C), 107.6 (C), 82.4 (C), 79.9 (C), 28.3 (3 CH_3), 24.2 (C), 18.3 (2 CH_2), –0.05 (3 CH_3),

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{23}NO_2Si$ + Na: 276.1396; found: 276.1390.

***tert*-Butyl 1-[(Trimethylsilyl)ethynyl]cyclobutylcarbamate (18)**

The acid **17** (37.44 g, ca.190 mmol) in acetone (740 mL) was treated with Et_3N (25.9 g, 35.6 mL, 255.5 mmol), $ClCO_2Et$ (35.2 g, 31 mL, 324.5 mmol) in acetone (150 mL), and NaN_3 (22.1 g, 340 mmol) in H_2O (90 mL) according to GP 2. The reaction mixture was poured into ice-cold H_2O (1.1 L) and the mixture extracted with Et_2O (4 × 100 mL) and pentane (3 × 100 ml). The combined organic solutions were worked up as described in GP 2 using ice-cold H_2O (200 mL) and anhyd toluene (100 mL), and the crude azide was heated in anhyd *t*-BuOH (620 mL, 9 h heating under reflux). The residue after concentration of the reaction mixture was taken up with Et_2O (400 mL), the solution washed with H_2O (2 × 100 mL), dried, and concentrated again. Column chromatography of the residue (silica gel, Et_2O–pentane, 1:20) afforded 27.08 g (60%) of the carbamate **18** as a colorless solid; mp 91–92 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.84 (br s, 1 H), 2.40–2.37 (m, 4 H), 2.05–1.83 (m, 2 H), 1.44 (s, 9 H), 0.14 [s, 9 H, $Si(CH_3)_3$].

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 154.8 (C), 109.4 (C), 79.8 (C), 50.0 (C), 35.6 (2 CH_2), 28.3 (3 CH_3), 15.2 (CH_2), –0.04 (3 CH_3).

MS (EI, 70 eV): *m*/*z* = 210 ($M^+ - C_4H_9$), 196, 183, 166, 139, 124, 97, 73, 57.

Anal. Calcd for $C_{14}H_{25}NO_2Si$ (267.44): C, 62.87; H, 9.42; N, 5.24. Found: C, 63.08; H, 9.64; N, 5.06.

Deprotection of the Carbamates 9 and 18; Preparation of the Amine Hydrochlorides 3·HCl and 5·HCl; General Procedure 3 (GP 3)

To a solution of KF in a 10:1 mixture of DMF and H_2O was added the respective carbamate **9** or **18**, and the reaction mixture was stirred at r.t. for 24 h. The resulting mixture was poured into H_2O, and extracted with Et_2O (3 × 80 mL). The combined organic layers were washed with H_2O and brine, then dried and ***very carefully*** concentrated under reduced pressure at 0 °C. The residue was sublimed at 0.05 Torr to give the desilylated carbamate **10** or **19**, respectively, which was taken up in ca. 5.0 N HCl solution in Et_2O (500 mL) and intensively stirred at 0–20 °C in the dark for 6 h. The formed pre-

cipitate was collected on a filter, washed with Et_2O (200 mL), and dried in a vacuum desiccator over P_4O_{10} overnight.

1-Ethynylcyclopropylamine Hydrochloride (3·HCl)

The residue, obtained from the carbamate **9** (105.1 g, 415 mmol) and KF (72.4 g, 1.244 mol) in a DMF–H_2O mixture (660 mL) according to GP 3 (2 L H_2O and 3 × 800 mL Et_2O for the workup), was sublimed at 85 °C to give 71.5 g (95%) of *tert*-butyl 1-(ethynyl)cyclopropylcarbamate (**10**) as a highly volatile colorless solid; mp 68–70 °C.

10

^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.03 (br s, 1 H), 2.13 (s, 1 H), 1.45 (s, 9 H), 1.29–1.03 (m AA′BB′, 4 H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 155.3 (C), 65.6 (C), 78.0 (C), 61.6 (CH), 28.2 (3 CH_3), 23.3 (C), 17.8 (2 CH_2).

Anal. Calcd for $C_{10}H_{15}NO_2$ (181.23): C, 66.27; H, 8.34; N, 7.73. Found: C, 66.55; H, 8.03; N, 7.45.

3·HCl

Carbamate **10** (63.444 g, 350.0 mmol) was treated with a ca. 5.0 N HCl solution in Et_2O (500 mL) according to GP 3 to give 37.0 g (90%) of **3**·HCl as a slightly yellowish solid; mp 185–186 °C (dec.).

^{1}H NMR (250 MHz, D_2O): δ = 2.66 (s, 1 H, C≡H), 1.14–1.11 (m, 4 H).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 8.91 (br s, 3 H, $^+NH_3$), 2.28 (s, 1 H, C≡H), 1.40–1.34 and 0.96–0.90 (m AA′BB′, 4 H).

^{13}C NMR (62.9 MHz, D_2O): δ = 82.2 (C≡H), 75.4 (C), 26.7 (C), 15.9 (2 CH_2).

Anal. Calcd for C_5H_8ClN (117.58): C 51.08; H, 6.86; N, 11.91. Found: C, 50.03; H, 7.11; N, 11.67.

1-Ethynylcyclobutylamine Hydrochloride (5·HCl)

The residue, obtained from the carbamate **18** (27.08 g, 101 mmol) and KF (17.6 g, 303 mmol) in a DMF–H_2O mixture (165 mL) according to GP 3 (400 mL H_2O and 3 × 100 mL Et_2O for the workup), was sublimed at 90 °C to give 17.94 g (91%) of *tert*-butyl 1-(ethynyl)cyclobutylcarbamate (**19**) as a colorless solid; mp 70–72 °C.

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^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.84 (br s, 1 H), 2.38 (s, 1 H), 2.49–2.35 (m, 4 H), 2.11–1.87 (m, 2 H), 1.45 (s, 9 H).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 87.2 (C), 79.9 (C), 69.3 (C), 49.1 (C), 35.6 (2 CH_2), 28.3 (3 CH_3), 15.4 (CH_2).

MS (EI, 70 eV): *m*/*z* = 138 ($M^+ - C_4H_9$), 111, 95, 77, 67, 57.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{17}NO_2$ + Na: 218.1151; found: 218.1157.

Anal. Calcd for $C_{11}H_{17}NO_2$ (195.26): C, 67.66; H, 8.78; N, 7.17. Found: C, 67.48; H, 8.57; N, 7.06.

5·HCl

Carbamate **19** (20.109 g, 103 mmol) was treated with a ca. 5.0 N HCl solution in Et_2O (200 mL) according to GP 3 to give 12.34 g (91%) of **5**·HCl as a colorless solid; mp 220 °C (dec.).

^{1}H NMR (300 MHz, D_2O): δ = 3.23 (s, 1 H), 2.67–2.51 (m, 4 H), 2.30–2.04 (m, 2 H).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.05 (br s, 3 H, $^+NH_3$), 2.57–2.47 (m, 2 H), 2.49 (s, 1 H), 2.34–2.25 (m, 2 H, CH_2), 2.05–1.89 (m, 2 H).

^{13}C NMR (125.7 MHz, D_2O): δ = 81.7 (C), 76.1 (C), 48.9 (C), 33.5 (2 CH_2), 14.1 (CH_2).

MS (EI): *m*/*z* = 95 (M^+ – HCl), 94, 80, 67, 52, 40.

Anal. Calcd for $C_6H_{10}ClN$ (131.60): C, 54.76; H, 7.66; N, 10.64. Found: C, 54.58; H, 7.79; N, 10.38.

3-[1-(*tert*-Butoxycarbonylamino)cyclopropyl]propiolic Acid (11)

The amino acid **11** was prepared applying a modified previously published procedure.[21] To a cooled (–78 °C) mechanically stirred solution of the carbamate **10** (5.78 g, 31.87 mmol) in anhyd THF (200 mL) was added dropwise *n*-BuLi (71.7 mmol; 20.7 mL of a 3.47 M solution in hexane). After stirring at this temperature for an additional 1 h, a large excess of powdered dry ice was added in one portion. The reaction mixture was allowed to warm up to 20 °C overnight and then poured into ice-cold water (400 mL). The layers were separated; the aqueous layer was washed with Et_2O (2 × 100 mL), acidified by adding a 2 N aq HCl solution (36 mL) and immediately extracted with Et_2O (2 × 100 + 2 × 50 mL). The combined organic layers from these last four extractions were dried and concentrated under reduced pressure to give 5.95 g (83%) of **11** as a colorless oil, which solidified upon standing at +4 °C overnight. This colorless solid was used without further purification; an analytical sample was obtained by recrystallization from hexane–THF (–20 °C, overnight); mp 136 °C (dec. with vigorous gas evolution).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.15 (br s, 1 H, NH), 1.47 (s, 9 H), 1.42–1.24 (m AA′BB′, 4 H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 156.8 (C), 155.3 (C), 92.0 (C), 81.9 (C), 71.1 (C), 28.2 (3 CH_3), 23.1 (C), 19.2 (2 CH_2).

Anal. Calcd for $C_{11}H_{15}NO_4$ (225.24): C, 58.66; H, 6.71. Found: C, 59.05; H, 7.07.

3-(1-Aminocyclopropyl)propiolic Acid Hydrochloride (4·HCl)

Carbamate **11** (3.29 g, 14.6 mmol) was treated with a ca. 5.0 N HCl solution in Et_2O (50 mL) according to GP 3 (0–20 °C, 12 h stirring) to give 2.12 g (96%) of **4**·HCl as a colorless solid; mp 134–135 °C (dec. with vigorous gas evolution).

^{1}H NMR (250 MHz, D_2O): δ = 1.29–1.27 (m, 4 H).

^{13}C NMR (62.9 MHz, D_2O): δ = 158.8 (C), 85.9 (C), 78.0 (C), 26.3 (C), 17.2 (2 CH_2).

Anal. Calcd for $C_6H_8ClNO_2$ (161.57): C, 44.60; H, 4.99; N, 8.67. Found: C, 44.35; H, 5.11; N, 8.54.

(9*H*-Fluoren-9-yl)methyl 1-(Ethynyl)cyclopropylcarbamate (12)

To a stirred suspension of the amine hydrochloride **3**·HCl (2.41 g, 20.5 mmol) in THF (50 mL) was added a 10% aq solution of Na_2CO_3 (200 mL). The reaction mixture was cooled to 0 °C, and a solution of Fmoc-Cl (6.89 g, 26.6 mmol) in THF (50 mL) was added at this temperature over a period of 0.5 h. The reaction mixture was allowed to warm up to 20 °C overnight, then poured into sat. aq NH_4Cl solution (150 mL), and the mixture was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with brine (100 mL), dried, and concentrated under reduced pressure. The solid residue was recrystallized from hexane–EtOAc (1:1; ca. 200 mL, –20 °C overnight) to give 5.62 g (90%) of **12** as a colorless solid; mp 163 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.51–7.79 (m, 8 H), 5.30 (br s, 1 H), 4.46–4.39 (m, 2 H), 4.23 (br s, 1 H), 2.16 (s, 1 H), 1.30–1.05 (m AA′BB′, 4 H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 163.7 (C), 143.8 (2 C), 141.3 (2 C), 127.7 (2 CH), 127.0 (2 CH), 125.0 (2 CH), 120.0 (2 CH), 85.1 (CH), 67.1 (C), 66.8 (CH_2), 47.1 (CH), 23.7 (C), 17.8 (2 CH_2).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{17}NO_2$ + Na: 326.1157; found: 326.1155.

3-{1-(9*H*-Fluoren-9-yl)methoxycarbonylamino]cyclopropyl}propiolic Acid (13)

Et_3N (3.05 g, 4.2 mL, 30.2 mmol) was added dropwise to an ice-cooled solution of *N*-(9-fluorenylmethoxycarbonyloxy)succinimide (Fmoc-OSu) (6.06 g, 18.0 mmol), and the amino acid hydrochloride **4**·HCl (2.12 g, 14.4 mmol) in a mixture of MeOH (100 mL) and CH_2Cl_2 (100 mL) was then added at 0 °C over a period of 0.5 h. The reaction mixture was allowed to warm up to 20 °C overnight, and the solvents were evaporated. The residue was taken up with a H_2O–Et_2O mixture (100 + 100 mL), acidified by adding 1 N aq HCl solution (35 mL) and the mixture immediately extracted with Et_2O (3 × 100 mL). The combined organic layers were dried and concentrated under reduced pressure. The residue was stirred with a hot hexane–THF mixture (80 + 5 mol) for 5 min and then kept at –20 °C overnight to yield 4.11 g (81%) of the pure compound **13** as a colorless solid, which is poorly soluble in $CDCl_3$; mp 181–183 °C (dec.).

^{1}H NMR (250 MHz, THF-d_8): δ = 7.79–7.62 (m, 4 H), 7.37–7.25 (m, 5 H), 4.43–4.30 (m, 2 H), 4.19 (m s, 1 H), 1.30–1.13 (m AA′BB′, 4 H, cyclopropane CH_2).

^{13}C NMR (62.9 MHz, THF-d_8): δ = 156.5 (C), 154.3 (C), 145.2 (2 C), 142.3 (2 C), 128.3 (2 CH), 127.8 (2 CH), 125.9 (2 CH), 120.6 (2 CH), 90.3 (C), 72.5 (C), 66.8 (CH_2), 48.2 (CH), 24.1 (C), 19.0 (2 CH_2).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{17}NO_4$ + Na: 370.1055; found: 370.1050.

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