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A Concise Stereoselective Synthesis of 2-Substituted 1-Aminocyclopropanecarboxylic Acids

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A simple and stereoselective method for the preparation of (Z)-2-substituted 1-aminocyclopropanecarboxylic acids is described. The common key step for these reaction sequences involves the stereoselective Ti-mediated coupling of benzyloxy nitrile and homoallylic alcohol. The resulting 2-hydroxyethyl-substituted cyclopropylamine can be transformed shortly into various cyclopropane amino acid analogues on the gram scale, in good overall yields. Several syntheses of 2,3-methanoamino acids, that is, ACCs derived from proteinogenic α-amino acids or analogues, such as glutamic acid, arginine, homoarginine, and lysine derivatives are presented to exemplify the usefulness of the method. Additionally, starting from cyanoesters, spirocyclopropane γ-amino acid analogues are available in this way.
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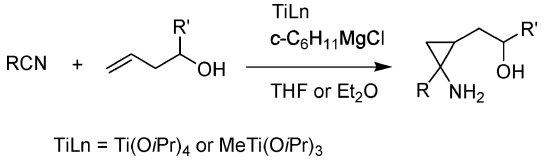
Introduction

1-Aminocyclopropanecarboxylic acids (ACCs or 2,3-methanoamino acids) are currently attracting great attention because of their various and significant biological activities. Both naturally occurring and nonnatural compounds are widely represented in the literature.[1] Importantly, ACCs have been incorporated into peptides in order to constrain the backbone into well-defined secondary structures such as turns, frequently found in the biologically active conformations. The major difficulty here remains in inducing the correct folding of the peptide while retaining the critical recognition elements (i.e., amino acids side chain functionalities) involved in the interaction.[2] Cyclopropane-derived peptidomimetics have already been found to exhibit interesting enzyme inhibitor activities and to reveal receptor antagonist or agonist activity.[3]

Several syntheses of ACCs have been reported.[4] The typical synthetic approaches include (i) dialkylation of glycine or malonate derivatives, (ii) 1,3-dipolar cycloaddition involving diazomethane and β-substituted acrylic acid derivatives, and (iii) intramolecular cyclization of γ-substituted α-amino butyric acid derivatives. More recently, the de Meijere variant of the Kulinkovich cyclopropanation reaction made it possible to prepare some α-ACCs of biological interest.[5,4d] A number of rather specific approaches to optically active ACCs involved asymmetric additions of ylides,[6] rhodium-catalyzed cyclopropanations,[7] and the use of amino acid equivalents[8] or cyclopropyl lactone chirons as building blocks.[9] Also, syntheses of 2,3-methanoamino acids, that is, ACCs derived from proteinogenic α-amino acids, were carried out; some glutamic acid, arginine, and lysine ACC analogues were prepared.[4b,10] Although different synthetic approaches to ACCs have been reported, many of them require elaborated starting materials and/or complex multistep reactions. The development of simple and general synthetic methods to prepare stereodefined substituted 2,3-methanoamino acids is still precious.

In 2001, we discovered that primary cyclopropylamines can be obtained easily from nitriles and Grignard reagents.[11] Since then, the reaction has been developed and offers wide access not only to simple cyclopropylamines but also to various derivatives.[12] Very recently, we and others applied the reaction to the preparation of cyclopropylamines bearing hydroxy side chains,[13] by ligand exchange-assisted coupling of a nitrile and a homoallylic alcohol (Scheme 1).[14]



Scheme 1.

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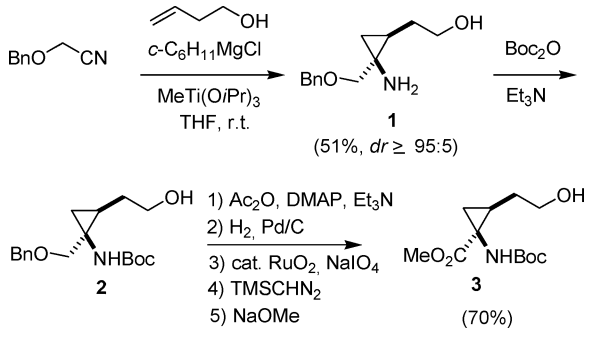
On the basis of this approach, we present herein a straightforward and general method for the synthesis of 2-substituted 1-aminocyclopropanecarboxylic acids. The described method is particularly applied here to the preparation of 2,3-methanoamino acid derivatives bearing the side chains of natural amino acids but can also be extended to the synthesis of other ACC analogues. Moreover, these compounds are obtained suitably protected for further peptide synthesis.

Results and Discussion

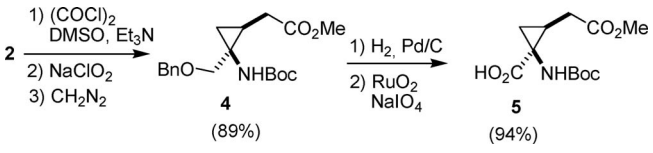
The title synthesis started with the cyclopropanation of benzyloxy acetonitrile. This reaction was carried out at room temperature as described previously[13b] and afforded 2-hydroxyethyl-substituted cyclopropylamine **1** in moderate yield and with high diastereoselectivity ($dr \geq 95:5$) as *Z* stereoisomer (Scheme 2).[15] The Boc protection of **1** provided compound **2**. Subsequent acetylation of the OH group, followed by debenzylation, ruthenium-based oxidation, esterification, and saponification of the acetate provided **3** in an overall 70% yield.[16]



Scheme 2.

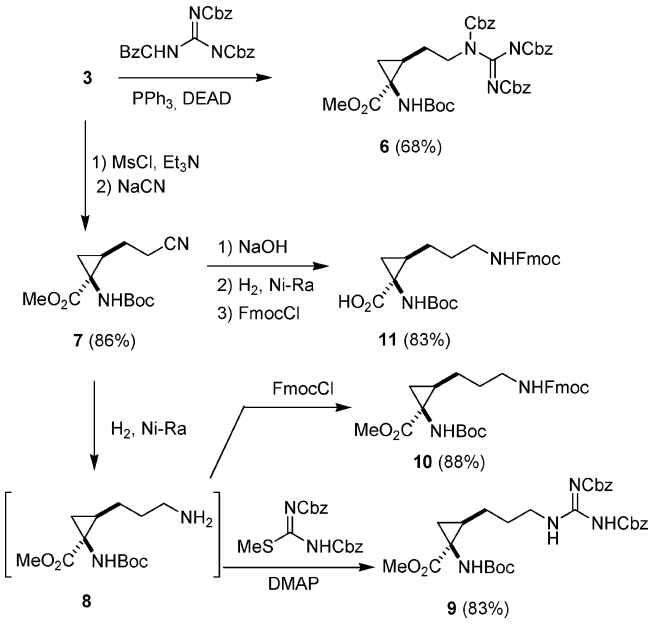
Compounds **2** and **3**, which can be readily obtained on the gram scale, appear as key synthetic intermediates for the synthesis of various ACC analogues. Examples given below show the preparation of 2,3-methanoamino acids related to glutamic acid, arginine, homoarginine, and lysine.

(*Z*)-2,3-Methanoglutamic acid derivative **5** was obtained starting from compound **2** (Scheme 3). Swern and sodium chlorite oxidation,[17] followed by diazomethane esterification afforded compound **4** in 89% yield. Subsequent deprotection of the OBn group and oxidation with in situ generated ruthenium tetroxide provided compound **5** in 94% yield. The orthogonal protection makes **5** ready to be incorporated into peptides.



Scheme 3.

Not only **2**, but also **3**, appear to be useful precursors for the synthesis of 2-substituted 1-aminocyclopropanecarboxylic acids. From this synthetic intermediate, several 2,3-methanoamino acid derivatives were prepared following the sequences shown in Scheme 4. Starting from **3**, methanoarginine derivative **6** was directly obtained by guanidinylation under Mitsunobu conditions.[18] Furthermore, the easy one carbon-lengthening of the side chain by cyanation and Ni-Ra reduction afforded intermediate lysine analogue **8**, which was further used as a common intermediate for the syntheses of methanoarginine homoanalogue **9** and orthogonally protected methanolysine ester **10**. Alternatively, free-carboxylic acid **11** was obtained from common nitrile intermediate **7**.



Scheme 4.

The Ti-mediated cyclopropanation of nitriles not only allows the synthesis of 2,3-methanoamino acids (α-amino acids) but also might be applied to the preparation of other cyclopropanated amino acids. The example given below represents the synthesis of spirocyclopropane GABA analogue **15** (Scheme 5). The reaction sequence is based on our previous findings indicating that β-cyanoesters can be converted into spirocyclopropane lactams through Ti^{II} chemistry.[19,12b] When the reaction was carried out starting from ethyl cyanopropionate and homoallylic alcohol under the ligand exchange conditions, spirocyclopropane lactam-bearing hydroxyethyl chain **13** was obtained in moderate yield as a 9:1 mixture of diastereoisomers.[13b] The successive TBDPS and Boc protections afforded **14** as a unique *Z* diastereoisomer (after purification). Subsequent lactam reduction with $BH_3 \cdot SMe_2$, TBDPS deprotection, and oxidation provided (*Z*)-spirocyclopropane amino acid **15** in 72% yield starting from **13**. The constrained structure of **15** anticipates useful bioorganic applications, especially in the field of the peptide research.

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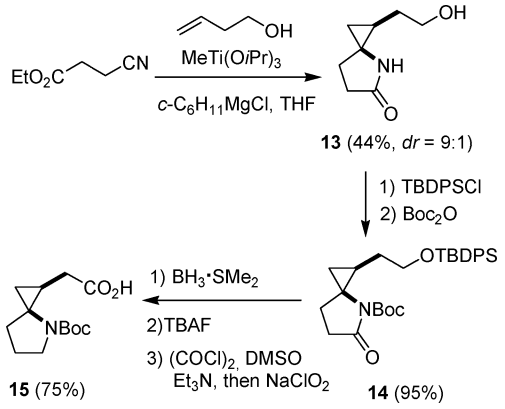

Scheme 5.

Conclusions

In conclusion, we have presented a new method for the stereoselective synthesis of 1-aminocyclopropanecarboxylic acids (2,3-methanoamino acids). Simplicity and the high diastereoselectivity of the cyclopropanation key step, cheap and readily available starting materials are the major advantages of this method. The reactions can be carried out on the gram scale, and the products are prepared in the orthogonally protected form. By employing this method, various ACCs for biological studies, particularly those involving cyclopropane-derived peptidomimetics, will be readily available.

Experimental Section

General: All reactions were conducted under an atmosphere of argon by using standard Schlenk techniques. Prior to use, THF and Et_2O were distilled under an atmosphere of argon from sodium benzophenone ketyl. $MeTi(OiPr)_3$ was prepared according to a known procedure,[20] and cyclohexylmagnesium chloride was purchased from Aldrich. ^1H and ^{13}C NMR spectra were recorded with a Bruker AC-250. Chemical shifts are reported in delta (δ) units, expressed in parts per million (ppm). Electrospray ionization (ESI) mass spectrometry was performed by using a hybrid tandem quadruple/time-of-flight (Q-TOF) instrument, equipped with a pneumatically assisted electrospray (Z-spray) ion source (Micromass, Manchester, UK) operated in the positive mode (EV = 30 V, 80 °C, flow of injection 5 μL min^{-1}).

(*Z*)-2-[2-Amino-2-(benzyloxymethyl)cyclopropyl]ethanol (1): To a solution of benzyloxyacetonitrile (1 mmol) and but-3-en-1-ol (1.2 mmol) in THF (10 mL) was added $MeTi(OiPr)_3$ (1.2 mmol, 288 μL) dropwise, and the mixture was stirred for 30 min at room temperature. Then, a solution of cyclohexylmagnesium chloride (2 M in Et_2O, 1.2 mL) was added dropwise, and the reaction mixture was stirred for 1.5 h. The reaction was quenched with water (5 mL). The aqueous layer was extracted with AcOEt (3 × 10 mL). The combined organic phase was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (MeOH/AcOEt, 10:90) to give **1** as an orange oil (113 mg, 51%). ^1H NMR (250 MHz, $CDCl_3$): δ = 0.44 (t, J = 5.5 Hz, 1 H), 0.67 (dd, J = 9.3, 5.5 Hz, 1 H), 0.75–0.86 (m, 1 H), 1.68–1.96 (m, 2 H), 2.69 (br. s, 3 H), 3.24 (d, J = 9.8 Hz, 1 H), 3.45 (d, J = 9.8 Hz, 1 H), 3.65 (dd, J = 6.7, 5.3 Hz, 2 H), 4.55 (s, 2 H), 7.25–7.38 (m, 5 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 16.3, 21.5, 30.0, 36.6, 62.0, 72.9, 79.0, 127.7, 127.8, 128.5, 138.3 ppm. HRMS (ESI+): calcd. for $C_{13}H_{20}NO_2$ [M + H]$^+$ 222.1494; found 222.1490.

(*Z*)-*tert*-Butyl 1-(Benzyloxymethyl)-2-(2-hydroxyethyl)cyclopropylcarbamate (2): To a solution of amino alcohol **1** (1.879 g, 8.51 mmol) and Et_3N (1.420 mL, 10.21 mmol) in THF (50 mL) was added a solution of Boc_2O (2.043 g, 9.36 mmol) in THF (20 mL) at 0 °C, and the resulting mixture was stirred for 12 h at room temperature. Water (10 mL) was added and the layers were separated. The aqueous phase was extracted with AcOEt (3 × 10 mL). The combined organic extract was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (AcOEt) to give **2** (2.68 g, 98%) as a white solid. M.p. 88 °C. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.59–0.63 (m, 1 H), 0.77–0.92 (m, 1 H), 0.93–1.04 (m, 1 H), 1.35–1.48 (m, 10 H), 1.72–1.88 (m, 1 H), 3.13 (d, J = 9.7 Hz, 1 H), 3.27 (br. s, 1 H), 3.53 (dd, J = 15.9, 12.3 Hz, 2 H), 3.72–3.84 (m, 3 H), 5.64 (s, 1 H), 7.25–7.37 (m, 5 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 17.2, 20.6, 28.3, 30.5, 36.4, 62.4, 72.9, 75.7, 79.2, 127.5, 127.6, 128.4, 138.0, 156.1 ppm. HRMS (ESI+): calcd. for $C_{18}H_{27}NNaO_4$ [M + Na]$^+$ 344.1838; found 344.1842.

(*Z*)-Methyl 1-(*tert*-Butoxycarbonylamino)-2-(2-hydroxyethyl)cyclopropanecarboxylate (3): To a solution of **2** (321 mg, 1 mmol), pyridine (0.3 mL), and DMAP (few crystals) in CH_2Cl_2 (10 mL) was added acetic anhydride (1.2 mL, 1.25 mmol) at room temperature. After 2 h of stirring, the mixture was acidified with HCl (1 M, 5 mL) and a saturated aqueous solution of $NaHCO_3$ (5 mL) was added. The organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure to give (*Z*)-2-[-2-(benzyloxymethyl)-2-(*tert*-butoxycarbonylamino)cyclopropyl]ethyl acetate (355 mg, 98%), which was used in the next step without purification. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.56 (s, 1 H), 0.94–0.97 (m, 2 H), 1.43 (s, 9 H), 1.59–1.68 (m, 1 H), 1.80–1.89 (m, 1 H), 2.01 (s, 3 H), 3.53–3.35 (m, 2 H), 4.18 (t, J = 4.0 Hz, 2 H), 4.51 (s, 2 H), 5.15 (s, 1 H), 7.24–7.36 (m, 5 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 15.5, 18.8, 19.6, 26.1, 27.0, 35.5, 63.0, 73.5, 73.4, 79.5, 126.1, 126.2, 127.0, 137.0, 154.6, 169.6 ppm. HRMS (ESI+): calcd. for $C_{20}H_{29}NNaO_5$ [M + Na]$^+$ 386.1843; found 386.1937.

A mixture of the resulting acetate (355 mg, 0.98 mmol) and Pd/C (10%, 110 mg) in MeOH (10 mL) was stirred under a hydrogen atmosphere for 12 h at 25 °C. The reaction mixture was filtered through a pad of Celite. The filtrate was evaporated, and the residue was purified by flash chromatography on silica gel (AcOEt) to afford (*Z*)-2-[-2-(*tert*-butoxycarbonylamino)-2-(hydroxymethyl)cyclopropyl]ethyl acetate (243 mg, 89%) as a colorless oil. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.51–0.53 (m, 1 H), 0.98–1.11 (m, 2 H), 1.44 (s, 9 H), 1.63–1.87 (m, 2 H), 2.08 (s, 3 H), 3.44–3.67 (m, 3 H), 4.13–4.23 (m, 2 H), 5.20 (br. s, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 17.8, 20.6, 21.0, 27.6, 28.3, 38.9, 64.3, 70.5, 80.3, 155.1, 171.1 ppm. HRMS (ESI+): calcd. for $C_{13}H_{23}NNaO_5$ [M + Na]$^+$ 296.1474; found 296.1472.

To a solution of the resulting alcohol (243 mg, 0.87 mmol) in CCl_4/CH_3CN/H_2O (2:2:3, 12 mL) was added $NaIO_4$ (1.09 g, 5.2 mmol), followed by $RuO_2{\cdot}H_2O$ (11 mg, 0.09 mmol). The reaction mixture was stirred at 25 °C for 1.5 h and then diluted with water (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extract was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in Et_2O (10 mL), then MeOH (2 mL) and $TMSCHN_2$ (1 M in Et_2O, 1.1 mL) were added at room temperature. After 1 h of stirring, the

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solvent was removed and the residue was purified by flash chromatography on silica gel [petroleum ether (PE)/AcOEt, 75:25] to give (*Z*)-methyl 2-(2-acetoxyethyl)-1-(*tert*-butoxycarbonylamino)-cyclopropylcarboxylate (227 mg, 84%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.83 (br. s, 1 H), 1.36 (s, 9 H), 1.63–1.84 (br. m, 4 H), 1.99 (s, 3 H), 3.64 (s, 3 H), 4.01–4.11 (m, 2 H), 5.25 (br. s, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 20.9, 22.3, 25.4, 27.4, 28.2, 37.8, 52.4, 63.8, 79.9, 156.4, 170.8, 173.4 ppm. HRMS (ESI+): calcd. for $C_{14}H_{23}NNaO_6$ 324.1423; found 324.1429.

A mixture of the resulting methyl ester (255 mg, 0.73 mmol) and NaOMe (181 mg, 3.35 mmol) in MeOH (10 mL) was stirred for 1 h at room temperature. Most of the solvent was removed under reduced pressure (ca 3 mL), then an aqueous solution of HCl (1 M) was added to pH 3. The aqueous phase was extracted with AcOEt (3 × 5 mL). The combined organic extract was washed with water (10 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (AcOEt) to afford compound **3** (206 mg, 95%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.89 (br. s, 1 H), 1.43 (s, 9 H), 1.81–1.85 (m, 4 H), 2.30 (br. s, 1 H), 3.67–3.83 (m, 5 H), 5.67 (br. s, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 22.7, 26.6, 28.4, 30.9, 38.1, 52.5, 62.1, 80.0, 156.7, 174.1 ppm. HRMS (ESI+): calcd. for $C_{12}H_{21}NNaO_5$ 282.1317; found 282.1311.

(*Z*)-Methyl 2-[-2-(Benzyloxymethyl)-2-(*tert*-butoxycarbonylamino)-cyclopropyl]acetate (4): A solution of DMSO (1.23 mL, 17.2 mmol) in CH_2Cl_2 (32 mL) was added dropwise to a solution of oxalyl chloride (0.73 mL, 8.61 mmol) in CH_2Cl_2 (32 mL) at –78 °C, and the mixture was stirred for 20 min. A solution of alcohol **2** (1.84 g, 5.74 mmol) in CH_2Cl_2 (16 mL) was then added at –78 °C, and the resulting mixture was stirred for 2 h. Et_3N (4 mL, 28.7 mmol) was then added. After 1 h of stirring, the mixture was slowly warmed to room temperature. Water (10 mL) and brine (10 mL) were subsequently added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting aldehyde was used in the next step without purification. To a solution of aldehyde in *t*BuOH (46 mL) and THF (46 mL) at 0 °C was added 2-methylbutene (11.5 mL) and a solution of $NaClO_2$ (1.309 g, 11.48 mmol) and $NaH_2PO_4{\cdot}2H_2O$ (1.79 g, 11.48 mmol) in H_2O (46 mL). The reaction mixture was stirred 12 h at room temperature. The mixture was concentrated under reduced pressure and an aqueous HCl solution (1 M, 100 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extract was dried with $MgSO_4$, filtered, and concentrated under reduce pressure to give the crude acid as a clear oil, which was used in the next step without purification. A slow stream of CH_2N_2 was passed through a solution of the crude acid in Et_2O until a yellow color appeared. The solution was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (PE/AcOEt, 90:10) to give **4** (1.77 g, 89%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.72 (m, 1 H), 1.10 (dd, *J* = 8.7, 6.0 Hz, 1 H), 1.33 (m, 1 H), 1.48 (s, 9 H), 2.47 (dd, *J* = 16.3, 6.9 Hz, 1 H), 2.53 (dd, *J* = 16.3, 7.6 Hz, 1 H), 3.45–3.57 (m, 2 H), 3.74 (s, 3 H), 4.59 (s, 2 H), 5.32 (br. s, 1 H), 7.30–7.39 (m, 5 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 17.0, 18.6, 28.3 33.5, 36.6, 51.8, 72.8, 74.2, 79.4, 127.50, 127.55, 128.3, 138.4, 156.0, 174.5 ppm. HRMS (ESI+): calcd. for $C_{19}H_{27}NNaO_5$ [M + Na]$^+$ 372.1787; found 372.1790.

(*Z*)-1-(*tert*-Butoxycarbonylamino)-2-(2-methoxy-2-oxoethyl)cyclopropyl Acid (5): A mixture of **4** (1.77 g, 5.05 mmol) and Pd/C (10%, 540 mg) in MeOH (50 mL) was stirred under a hydrogen atmosphere at room temperature overnight. The mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure to give (*Z*)-methyl 2-[-2-(*tert*-butoxycarbonylamino)-2-(hydroxyethyl)cyclopropyl]acetate (1.309 g, 100%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.67 (br. s, 1 H), 1.10 (br. s, 1 H), 1.27–1.32 (m, 1 H), 1.42 (s, 9 H), 2.33 (dd, *J* = 16.5, 8.9 Hz, 1 H), 2.55 (dd, *J* = 16.5, 5.6 Hz, 1 H), 3.28 (br. s, 1 H), 3.45 (d, *J* = 11.4 Hz, 1 H), 3.64 (d, *J* = 11.4 Hz, 1 H), 3.72 (s, 3 H), 5.26 (br. s, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 18.0, 19.2, 28.4, 33.5, 38.5, 52.1, 70.1, 80.3, 157.7, 173.9 ppm. HRMS (ESI+): calcd. for $C_{12}H_{21}NNaO_5$ [M + Na]$^+$ 282.1317; found 282.1317.

To a solution of the resulting alcohol (1.38 g, 5.05 mmol) in CCl_4/CH_3CN/H_2O (2:2:3, 70 mL) was added $NaIO_4$ (7.57 g, 35.4 mmol), followed by $RuO_2{\cdot}H_2O$ (68 mg, 0.5 mmol). The reaction mixture was stirred at 25 °C for 1.5 h and then diluted with water (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure, and the residue was purified by flash chromatography (PE/AcOEt, 50:50) to give **5** (1.27 g, 92%) as a white solid. M.p. 152–153 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.03 (br. s, 1 H), 1.38 (s, 9 H), 1.77 (br. s, 1 H), 1.98 (br. s, 1 H), 2.32–2.67 (m, *2* H), 3.65 (s, 3 H), 5.34 (br. s, 1 H), 9.79 (br. s, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 23.2, 24.5, 28.3, 33.6, 37.6, 52.2, 77.2, 80.4, 156.7, 172.8, 178.6 ppm. HRMS (ESI+): calcd. for $C_{12}H_{19}NNaO_6$ [M + Na]$^+$ 296.1110; found 296.1118.

(*Z*)-Methyl 1-(*tert*-Butoxycarbonylamino)-2-[2-(*N*,*N*,*N*-tribenzyloxycarbonyl)guanidinoethyl]cyclopropanecarboxylate (6): Triphenylphosphane (196 mg, 0.75 mmol) and tris(benzyloxycarbonyl)guanidine (692 mg, 1.5 mmol) were added to a solution of **3** (130 mg, 1 mmol) in THF (30 mL) at 0 °C. Diethyl azodicarboxylate (0.118 mL, 0.75 mmol) was added over a 30 min period, and the reaction mixture was stirred for 20 h at room temperature. The reaction was concentrated under reduced pressure, and the residue was extracted with EtOAc (3 × 25 mL). The combined organic extract was washed with water (20 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography over silica (PE/AcOEt/CH_2Cl_2, 7:2:1) to afford **9** (240 mg, 68%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.91 (br. s, 1 H), 1.42–1.81 (m, 13 H), 3.61 (s, 3 H), 3.93–4.01 (m, 2 H), 5.06–5.11 (m, 6 H), 5.34 (br. s, 1 H), 7.30–7.34 (m, 15 H), 11.02 (br. s, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 22.9, 25.2, 27.9, 28.3, 29.5, 38.4, 40.7, 47.3, 52.4, 66.6, 80.1, 120.0, 125.1, 127.1, 127.7, 141.3, 144.0, 156.4, 173.6 ppm. HRMS (ESI+): calcd. for $C_{37}H_{42}N_4NaO_{10}$ [M + Na]$^+$ 725.2799; found 725.2806.

(*Z*)-Methyl 1-(*tert*-Butoxycarbonylamino)-3-(2-cyanoethyl)cyclopropanecarboxylate (7): To a solution of **3** (259 mg, 1 mmol) and Et_3N (0.2 mL, 1.5 mmol) in CH_2Cl_2 (5 mL) was added methanesulfonyl chloride (0.1 mL, 1.2 mmol) at 0 °C, and the mixture was stirred for 5 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with water (5 mL). The organic extract was dried with $MgSO_4$, filtered and concentrated under reduced pressure to give the corresponding mesylate (330 mg, 98%), which was used directly in the next step without purification. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.91 (br. s, 1 H), 1.45 (s, 9 H), 1.63–2.04 (m, 4 H), 3.04 (s, 3 H), 3.70 (s, 3 H), 4.31–4.40 (m, 2 H), 5.11 (br. s, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 21.9, 24.6, 28.0, 28.3, 37.4, 38.2, 52.6, 69.5, 80.3, 156.4, 173.1 ppm.

A solution of the mesylate and NaCN (147 mg, 3 mmol) in DMF (3 mL) was stirred for 15 h at 50 °C. The reaction mixture was concentrated under reduced pressure, the residue was diluted with Ac-

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OEt (50 mL), and the organic layer was washed with water (10 mL), dried with $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (PE/AcOEt, 50:50) to give **7** (230 mg, 86%) as a pale-yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.88 (br. s, 1 H), 1.37 (s, 9 H), 1.52–1.82 (m, 4 H), 2.89 (br. s, 2 H), 3.62 (s, 3 H), 5.42 (br. s, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 16.5, 21.6, 24.0, 26.4, 27.9, 38.1, 52.2, 79.8, 119.4, 156.2, 172.7 ppm. HRMS (ESI+): calcd. for $C_{13}H_{20}N_2NaO_4$ $[M + Na]^+$ 291.1321; found 291.1327.

Methyl (*Z*)-2-{3-[3-(*9H*-Fluoren-9-yl)propanamido]propyl}-1-(*tert*-butoxycarbonylamino)cyclopropanecarboxylate (10): A mixture of cyano ester **7** (1.2 g, 4.5 mmol), NH_4OH (28% solution, 20 mL), and a catalytic amount of Raney-Ni (100 mg) in MeOH (20 mL) was stirred under a hydrogen atmosphere for 6 h at room temperature. The reaction mixture was filtered through a plug of Celite and washed with MeOH/H_2O (1:1, 100 mL) to give the crude (*Z*)-methyl 2-(3-aminopropyl)-1-[(*tert*-butoxycarbonyl)amino]cyclopropanecarboxylate (**8**) after evaporation of the solvent. FmocCl (1.75 g, 6.75 mmol) was added to a solution of **8** and Na_2CO_3 (750 mg, 9 mmol) in a mixture of dioxane/water (1:1, 60 mL) at 0 °C, and stirring was continued for 5 h at 0 °C. The volume of the reaction mixture was reduced, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic extract was washed with brine (30 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (PE/AcOEt, 70:30) to afford **10** (1.95 g, 88%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.79 (br. s, 1 H), 1.17–1.78 (m, 15 H), 3.15 (br. s, 2 H), 3.60 (s, 3 H), 4.15 (d, *J* = 6.75 Hz, 1 H), 4.32 (d, *J* = 6.75 Hz, 2 H), 4.86 (br. s, 1 H), 4.98 (br. s, 1 H), 7.26–7.41 (m, 4 H), 7.52 (d, *J* = 7.5 Hz, 2 H), 7.69 (d, *J* = 7.5 Hz, 2 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 22.9, 25.3, 27.9, 28.3, 29.6, 38.4, 40.7, 47.4, 52.5, 66.6, 80.2, 120.0, 125.1, 127.1, 127.7, 141.4, 144.0, 156.5, 173.6 ppm. HRMS (ESI+): calcd. for $C_{28}H_{34}N_2NaO_6$ $[M + Na]^+$ 517.2315; found 517.2319.

(*Z*)-Methyl 2-{3-[2,3-Bis(benzyloxycarbonyl)guanidine]propyl}-1-(*tert*-butyloxycarbinylamino)cyclopropanecarboxylate (9): A mixture of **8** (272 mg, 1 mmol), DMAP (12 mg, 0.1 mmol), and SMe(C=NCbz)NHCbz (395 mg, 1.1 mmol) in CH_2Cl_2 (10 mL) was stirred for 20 h at room temperature. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography over silica (PE/AcOEt, 60:40) to afford **9** (485 mg, 83%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.92 (br. s, 1 H), 1.29–1.32 (m, 2 H), 1.48 (s, 9 H), 1.74 (br. s, 4 H), 3.49–3.51 (m, 2 H), 3.71 (s, 3 H), 5.11 (br. s, 1 H), 5.16 (s, 2 H), 5.20 (s, 2 H), 7.34–7.44 (m, 10 H), 8.37 (br. s, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 22.7, 25.3, 27.7, 28.2, 28.5, 38.2, 40.7, 52.3, 67.1, 68.1, 79.9, 104.5, 127.8, 128.1, 128.3, 128.4, 128.6, 128.7, 134.6, 136.7, 153.8, 155.9, 156.3, 163.7, 173.5 ppm. HRMS (ESI+): calcd. for $C_{30}H_{39}N_4O_8$ $[M + H]^+$ 582.2768; found 583.2778.

(*Z*)-2-{3-[3-(*9H*-Fluoren-9-yl)propanamido]propyl}-1-(*tert*-butoxycarbonylamino)cyclopropanecarboxylic Acid (11): To a solution of **7** (1.05 mmol) in MeOH (3 mL) was added NaOH (50 mg, 1.25 mmol) and the stirring was continued for 2 h at room temperature. HCl (1 M) was added to pH 4, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give the corresponding cyano acid (95%), for which spectroscopic data are in accordance with the literature.[10b] The cyano acid (254 mg, 1 mmol), NH_4OH (28% solution, 7 mL), and a catalytic amount of Raney-Ni (20 mg) in MeOH (7 mL) was stirred under a hydrogen atmosphere for 6 h at room temperature. The reaction mixture was filtered through a plug of Celite and washed with MeOH/H_2O (1:1, 20 mL). After evaporation of the solvent, the residue was dissolved in a mixture of dioxane/water (1:1, 15 mL). Na_2CO_3 (170 mg, 2 mmol) was added, and the mixture was cooled to 0 °C. FmocCl (258 mg, 1 mmol) was added and stirring was continued for 5 h at 0 °C. The volume of the reaction mixture was reduced to 5 mL, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The organic extracts were combined, washed with brine (10 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (AcOEt) to afford **11** (398 mg, 83%) as a colorless solid. M.p. 97–98 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.79 (br. s, 1 H), 1.13–1.60 (m, 15 H), 3.11 (br. s, 2 H), 4.01–4.12 (m, 1 H), 4.26–4.33 (m, 2 H), 5.1 (br. s, 1 H), 7.31 (m, 4 H), 7.50 (d, *J* = 7.5 Hz, 2 H), 7.66 (d, *J* = 7.5 Hz, 2 H), 10.11 (br. s, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 23.3, 25.3, 28.3, 28.4, 38.0, 40.7, 47.3, 66.6, 80.1, 120.0, 125.1, 127.1, 127.7, 144.0, 156.6, 178.3 ppm. HRMS (ESI+): calcd. for $C_{27}H_{32}N_2NaO_6$ $[M + Na]^+$ 503.2315; found 503.2159.

(*Z*)-1-(2-Hydroxyethyl)[2.4]4-azaspiroheptan-5-one (13): Compound **13** was prepared according to the procedure described for the preparation of **1** by using ethyl 3-cyanopropanoate instead of nitrile. ^{1}H NMR (250 MHz, CD_3OD): δ = 0.55 (t, *J* = 5.9 Hz, 1 H), 0.85 (dd, *J* = 9.3, 5.9 Hz, 1 H), 0.96 (m, 1 H), 1.61 (q, *J* = 6.8 Hz, 2 H), 2.04 (m, 1 H), 2.36–2.61 (m, 3 H), 3.36 (t, *J* = 6.6 Hz, 2 H) ppm. ^{13}C NMR (62.5 MHz, CD_3OD): δ = 15.8, 21.1, 31.6, 31.9, 32.8, 44.5, 62.6, 180.8 ppm. HRMS (ESI+): calcd. for $C_8H_{13}NNaO_2$ $[M + Na]^+$ 178.1102; found 178.1103.

***tert*-Butyl (*Z*)-1-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-5-oxo-4-azaspiro[2.4]heptane-4-carbamate (14):** To a solution of **13** (1.44 g, 9.31 mmol) in dry DMF (25 mL) was sequentially added imidazole (768 mg, 11.27 mmol) and *tert*-butyldiphenylsilyl chloride (2.92 mL, 11.27 mmol) at room temperature. After 18 h of stirring, a saturated aqueous solution of NH_4Cl (50 mL) was added. The aqueous layer was extracted with AcOEt (3 × 25 mL). The combined organic layer was washed with water (2 × 30 mL), dried with $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (AcOEt) to give (*Z*)-1-[2-(*tert*-butyldiphenylsilyloxy)ethyl][2.4]4-azaspiroheptan-5-one (3.55 g, 97%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.44 (m, 1 H), 0.74 (dd, *J* = 9.3, 5.9 Hz, 1 H), 0.93–1.12 (m, 10 H), 1.46–1.75 (m, 2 H), 1.91–2.18 (m, 2 H), 2.40 (t, *J* = 7.7 Hz, 2 H), 3.66–3.80 (m, 2 H), 7.35–7.45 (m, 6 H), 7.65–7.68 (m, 4 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 16.3, 19.3, 20.0, 26.9, 30.4, 31.2, 32.1, 43.3, 63.7, 127.7, 129.6, 133.9, 135.6, 179.0 ppm. HRMS (ESI+): calcd. for $C_{25}H_{31}NNaO_2Si$ $[M + Na]^+$ 416.2022; found 416.2024.

To a stirred solution of this protected alcohol (2.55 g, 9.03 mmol) in dry CH_3CN (30 mL) was sequentially added Boc_2O (2.93 g, 13.45 mmol) and DMAP (111 mg, 0.9 mmol) at room temperature. After 4 h of stirring, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (PE/AcOEt, 85:15) to afford **14** (4.35 g, 98%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.80–1.29 (m, 11 H), 1.40–1.73 (m, 12 H), 1.99 (t, *J* = 6.0 Hz, 1 H), 2.29–2.61 (m, 3 H), 2.63–3.79 (m, *2* H), 7.32–7.46 (m, 6 H), 7.64–7.68 (m, 4 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 14.0, 19.2, 21.0, 26.9, 28.0, 30.8, 32.2, 32.3, 48.2, 63.7, 83.0, 127.7, 129.6, 133.8, 135.5, 150.7, 175.5 ppm. HRMS (ESI+): calcd. for $C_{29}H_{39}NNaO_4Si$ $[M + Na]^+$ 516.2546; found 516.2557.

(*Z*)-2-[4-(*tert*-Butyloxycarbonyl)-4-azaspiro[2.4]heptan-1-yl]acetic Acid (15): To a solution of **14** (2.92 g, 5.91 mmol) in THF (30 mL)

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was added $BH_3{\cdot}SMe_2$ (5 M, 3 mL) at room temperature, and the mixture was heated at reflux for 4 h. The reaction mixture was cooled to room temperature and diluted with Et_2O (200 mL), then a saturated aqueous solution of NH_4Cl (25 mL) was added. The organic phase was separated, washed with HCl (0.1 M, 10 mL), saturated aqueous solution of $NaHCO_3$ (10 mL), and brine (10 mL), dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography on silica gel (PE/AcOEt, 95:5) to give *tert*-butyl 1-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-4-azaspiro[2.4] heptane-4-carbamate as a colorless oil (2.32 g, 82%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.61–0.73 (m, 1 H), 0.84 (dd, J = 9.5, 5.9 Hz, 1 H), 1.04 (m, 9 H), 1.20–1.29 (m, 1 H), 1.42 (s, 9 H), 1.54–1.84 (m, 4 H), 1.93–2.21 (m, 2 H), 3.26 (ddd, J = 11.2, 8.8, 2.6 Hz, 1 H), 3.48–3.74 (m, 3 H), 7.34–7.45 (m, 6 H), 7.65–7.70 (m, 4 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 12.5, 19.2, 20.7, 22.0, 26.8, 28.5, 31.1, 36.4, 47.0, 47.9, 64.0, 79.1, 127.5, 129.4, 134.0, 134.1, 135.5, 154.6 ppm. HRMS (ESI+): calcd. for $C_{29}H_{41}NNaO_3Si$ 502.2753; found 502.2756.

To a solution of the resulting amine (2.24 g, 4.68 mmol) in THF (60 mL) was added a solution of TBAF in THF (1 M, 11.7 mL). The reaction mixture was stirred at room temperature until complete consumption of the substrate, as monitored by TLC (2 h). The reaction mixture was diluted with ethyl acetate (100 mL), washed with water (20 mL) and brine (20 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (PE/AcOEt, 70:30) to afford *tert*-butyl 1-[2-Hydroxyethyl]-4-azaspiro[2.4]heptane-4-carbamate (1.04 g, 92%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.52–0.63 (m, 1 H), 0.74 (dd, J = 9.4, 5.9 Hz, 1 H), 1.18 (m, 1 H), 1.33 (s, 9 H), 1.48 (dd, J = 13.2, 6.6 Hz, 2 H), 1.69–1.77 (m, 2 H), 1.83–2.11 (m, 2 H), 3.17–3.37 (m, 1 H), 3.39–3.63 (m, 4 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 12.0, 20.5, 21.7, 28.2, 30.7, 36.2, 46.7, 47.7, 62.1, 78.9, 154.4 ppm. HRMS (ESI+): calcd. for $C_{13}H_{23}NNaO_3$ $[M + Na]^+$ 264.1576; found 264.1582.

To a solution of DMSO (920 µL, 12.85 mmol) in CH_2Cl_2 (24 mL) was added oxalyl chloride (555 µL, 6.45 mmol) at –78 °C, and the mixture was stirred for 20 min. A solution of the above alcohol (1.03 g, 4.3 mmol) in CH_2Cl_2 (12 mL) was next added at –78 °C, and the resulting mixture was stirred for 2 h at –78 °C. Et_3N (3 mL, 21.6 mmol) was added. After 1 h of stirring, the mixture was warmed to room temperature. Water (10 mL) and brine (10 mL) were added, and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting aldehyde was used in the next step without purification. To a solution of the crude aldehyde and *t*BuOH (34.5 mL) in THF (35 mL) was added 2-methylbutene (9 mL), an aqueous solution of $NaClO_2$ (980 mg, 8.58 mmol), and $NaH_2PO_4{\cdot}2H_2O$ (1.34 g, 8.58 mmol) in H_2O (25 mL) at 0 °C. The reaction was stirred for 12 h at room temperature. The volatiles were removed under reduced pressure, and an aqueous solution of HCl (1 M, 150 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic extract was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (PE/AcOEt, 70:30) to provide **15** as a white paste (1.01 g, 92%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.81–1.03 (m, 2 H), 1.29–1.53 (m, 10 H), 1.71–2.28 (m, 4 H), 2.34–2.46 (m, 1 H), 2.63 (dd, J = 17.4, 4.3 Hz, 1 H), 3.36 (t, J = 9.2 Hz, 1 H), 3.54 (dd, J = 18.4, 9.9 Hz, 1 H), 10.91 (br. s, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 12.3, 19.4, 22.0, 28.6, 33.2, 36.6, 46.8, 48.5, 79.6, 154.8, 179.8 ppm. HRMS (ESI+): calcd. for $C_{13}H_{21}NNaO_4$ $[M + Na]^+$ 278.1368; found 278.1369.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of new compounds.

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