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# β-Aminocyclopropanecarboxylic acids with α-amino acid side chain functionality

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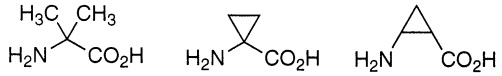
**Abstract**—The synthesis of conformationally restricted *trans*-β-aminocyclopropanecarboxylic acids (β-ACCs) having α-amino acid side chain functionality of asparagine, arginine, cysteine, or serine is described. 

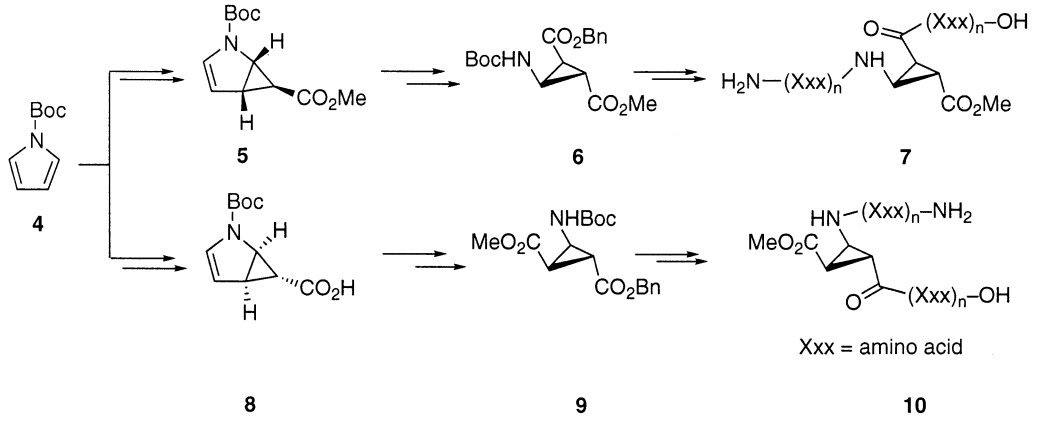
## 1. Introduction

The use of rigid amino acids has been a most successful approach to investigate the bioactive structure of peptides.[1] Among the most widely used non-protein α-amino acids are α-aminoisobutyric acid[2] (Aib, **1**) and α-aminocyclopropanecarboxylic acid[3] (α-ACC, **2**), which are capable of stabilizing helices or inducing turns into peptides. More recently, β-amino acids have been recognized as novel building blocks for the assembly of peptides, either in combination with α-amino acids[4] or, most spectacularly, as the new emerging class of β-peptides.[5] Consequently, conformational rigidity should also be a valuable tool for probing structural implications caused by the introduction of β-amino acids into a peptide.



**1** (Aib) **2** (*α*-ACC) **3** (*β*-ACC)

The bridging of the carbons bearing the amino and the carboxylic acid functionality by a methylene group creates one of the most severely restricted β-alanine derivatives that can be envisioned. The resulting class of β-aminocyclopropanecarboxylic acids (β-ACCs) **3** appears therefore attractive as constituents of peptides, however, their synthesis and utilization as building blocks in peptide synthesis




**Scheme 1.** Synthesis of trifunctional β-ACCs and their incorporation into peptides.

*Keywords*: α-amino acids; β-amino acids; β-alanine; aminocyclopropanecarboxylic acid.
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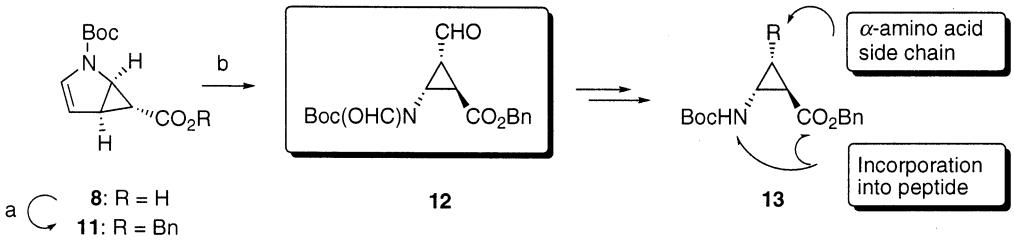



**Scheme 2.** Synthesis of amino aldehyde **12**. *Reagents and conditions*: (a) $NaHCO_3$, BnBr, DMF, 90%; (b) i: $O_3$, $CH_2Cl_2$; ii: DMS, 95%.

poses a number of challenges. With the introduction of the methano bridge two new stereocenters are created, requiring the control of diastereoselectivity (*cis*- vs. *trans*-β-ACCs) as well as of enantioselectivity. Moreover, β-ACCs belong to the class of vicinally donor–acceptor substituted cyclopropanes, which are extremely prone toward ring opening.[6] Therefore, β-ACCs are only stable if the amino group is protected by at least one electron withdrawing group.[7]

## 2. Results and discussion

There have been a number of different approaches towards the synthesis[8,9] of β-ACCs and their incorporation[10,11] into peptides. Based on the cyclopropanation of *N*-Boc-pyrrole[12] (**4**) with diazoesters we have developed the diastereo- and enantioselective synthesis of **6** and **9**.[9] Furthermore, we demonstrated the coupling of these derivatives with α-amino acids via the *cis*- and *trans*-β-aminocyclopropanecarboxylic acid array to arrive at peptides with the general structure **7** and **10**, respectively (Scheme 1).[11] Following this strategy, the introduction of the β-ACC core into Neuropeptide Y has led to highly active and selective ligands for various Neuropeptide Y receptors.[13]

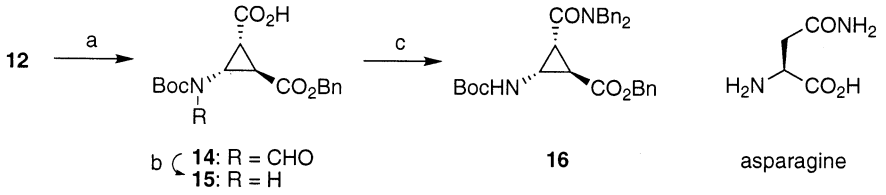
However, besides a defined conformation of the backbone the presence of the correct amino acid side chains is equally important for the proper function of a peptide. Consequently, an ideal building block for peptide mimics is restricted in its conformation but also displays side chain functionality of natural α-amino acids. Our trifunctional β-ACCs **6** and **9** offer the possibility to introduce α-amino acid side chains via the remaining carboxylic ester group not being used for the incorporation into the peptide. We report here the synthesis of novel *trans*-β-ACC derivatives **13** having α-amino acid side chain functionality of asparagine, arginine, cysteine, or serine.

Pursuing the strategy developed by us,[9a] the amino aldehyde **12** is readily prepared by conversion of **8** to its benzyl ester **11**, followed by ozonolysis and reductive work up with dimethyl sulfide (Scheme 2). The aldehyde group in **12** seems to be an ideal functionality for the introduction of various α-amino acid side chains. Consequently, **12** served as the key compound for all further transformations reported here, however, since no stereochemical consequences arise during these transformations, **12** was employed diastereomerically pure but in racemic form. Possible epimerization leads to diastereomers, which is readily detected by NMR and HPLC (vide infra).

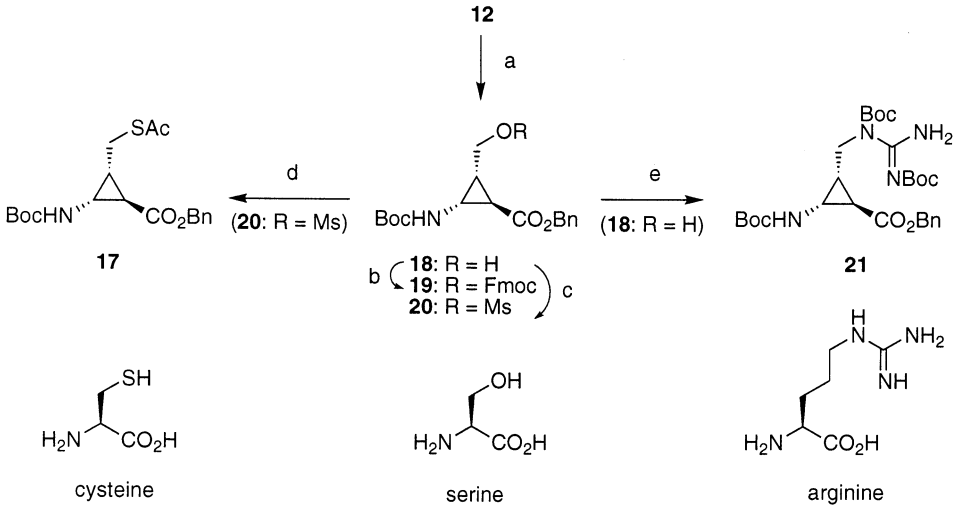
The following generalizations can be made for the use of amino aldehyde **12** and subsequent β-ACC derivatives as synthetic building blocks. The protecting groups on nitrogen can be individually and selectively removed by amine bases (*N*-CHO: 2-diethylaminoethylamine (DEAEA)) or acid (*N*-Boc: TFA or HCl/EtOAc) to yield stable products. However, double protection of nitrogen is necessary as long as an aldehyde function is present as in **12**. Lewis acid catalysis to activate **12** for the addition of nucleophiles can be successfully applied,[14] while aldehyde functionalization with strongly basic reagents such as unstabilized ylides is not possible. Moreover, aqueous basic conditions must be avoided with all β-ACC derivatives reported here, because deprotonation on the amine function can lead to epimerization of the adjacent carbon center or to ring opening of the cyclopropane moiety.

Accordingly, a β-ACC asparagine side chain mimic can be obtained in three steps starting with the oxidation of **12** to the corresponding carboxylic acid **14**. Removal of the *N*-formyl group by DEAEA proceeded smoothly to yield **15**, which was converted to the amide **16** by activation of the carboxylic acid with EDC/HOBt and treatment with dibenzylamine (Scheme 3).

The synthesis of the β-ACC serine mimic **18** was accomplished by reduction of **12** with sodium borohydride, which took place with concurrent deformylation on the amino group. For further elaboration, the hydroxyl group in **18** can be either orthogonally protected as Fmoc ester **19**, or, more important, can be displaced by nucleophiles. Thus, a β-ACC cysteine mimic can be obtained by converting **18** into the mesylate **20**, followed by treatment with thioacetic




**Scheme 3.** Synthesis of a β-ACC asparagine mimic. *Reagents and conditions*: (a) $NaClO_2$, $H_2O_2$, $KH_2PO_4$, $H_2O$, 100%; (b) DEAEA, $CH_3CN$, 86%; (c) $HNBn_2$, EDC, HOBt, $CH_2Cl_2$, 76%.




**Scheme 4.** Synthesis of a β-ACC serine, cysteine and arginine mimic. *Reagents and conditions*: (a) $NaBH_4$, EtOH / $H_2O$ (9:1), 81%; (b) Fmoc-Cl, pyridine, 79%; (c) MsCl. $NEt_3$, $CH_2Cl_2$, 100%; (d) i: $K_2CO_3$, AcSH, $CH_3CN$; ii: recrystallization $CH_2Cl_2$/hexanes 1:4, 83% (94% *de*); (e) DEAD, $PPh_3$, BocHNC-(NBoc)$NH_2$, THF, 63%.

acid/$K_2CO_3$. **17** was isolated in high yields, however, some epimerization at the amino substituted carbon center (93:7 mixture of 2 epimers) had occurred during this transformation. Nevertheless, the minor epimer could be almost completely removed by a single recrystallization to give rise to **17** in 83% yield (97:3 epimeric mixture). The choice of the base turned out to be crucial for suppressing the erosion of stereochemistry to a minimum: if $Cs_2CO_3$[15] is used instead of $K_2CO_3$ **17** was obtained as a 1:1 mixture of epimers. Similar results were obtained when thiomethanolate instead of thioacetate was employed.

Finally, in situ activation of the hydroxyl group in **18** under Mitsunobu conditions is also possible, which allowed the synthesis of the β-ACC arginine mimic **21** in a straightforward manner. Nevertheless, 5 equiv. of the guanidinium nucleophile[16] had to be employed to ensure complete conversion of **18** (Scheme 4).

In conclusion, we have developed the synthesis of novel β-ACC derivatives with arginine, asparagine, cysteine and serine side chain mimics. The evaluation of these amino acids, compared to the previously used **6** and **9**, as constituents in Neuropeptide Y analogs with the aim to determine if increased affinity and selectivity for the corresponding receptors can be achieved through the side chain mimics, is currently under investigation.

## 3. Experimental

### 3.1. General

All reactions were carried out in flame-dried glassware under nitrogen. All commercially available reagents (Aldrich, Fluka) were used as received. The solvents were dried by distillation over the following drying agents and were transferred under nitrogen: DMF, $CH_3CN$, $CH_2Cl_2$ ($CaH_2$), THF (K) and pyridine (KOH). Analytical thin-layer chromatography (TLC) was performed using Merck-Schuchardt silica gel 60 F254 precoated plates (0.2 mm thickness). TLC $R_f$ values are reported. Visualization was accomplished by irradiation with a UV lamp and/or staining with phosphomolybdic acid in EtOH. Flash column chromatography was performed using Merck silica gel 60 (230–400 mesh). Melting points were determinated in a Büchi SMP 20 apparatus and are uncorrected. $^1H$ and $^{13}C$ NMR spectra were measured on a Bruker AC 250 spectrometer operating at 250 and 62.9 MHz, respectively. Chemical shifts (δ) are given in ppm relative to internal tetramethylsilane (δ 0.0), coupling constants (*J*) in Hz. Infrared spectra were recorded on a ATI Mattson Genesis Series FTIR spectrometer. Mass spectra and high resolution mass spectra (HRMS) were measured at the Mass Spectrometry Laboratory of the University of Regensburg. The method of ionisation is given in parentheses. Elemental analyses were obtained at the Microanalytical Laboratory of the University of Regensburg.

**3.1.1. 2-Azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylic acid 2-*tert*-butyl ester ((*rac*)-8) and (8).** *Run a)* To a solution of (*rac*)-**5** (9.00 g, 37.61 mmol) in MeOH (77 mL) was added a solution of NaOH (2.26 g, 56.42 mmol) in water (30 mL) and the reaction mixture was stirred for 8 h at room temperature. *Caution: It is important that the reaction is monitored continuously by TLC and worked up immediately after disappearing of* (*rac*)-**5**, *otherwise the yield decreases due to the instability of* (*rac*)-**8** *under these conditions.* The mixture was concentrated in vacuo (ca. 30 mL) and the remaining solution was extracted with $Et_2O$ (2×20 mL). The aqueous layer was acidified to pH 2 with 1 M $KHSO_4$ and extracted with EtOAc (3×50 mL). The combined organic layers were dried over $Na_2SO_4$ and concentrated in vacuo to yield 8.47 g (100%) of (*rac*)-**8** as a colorless solid.

*Run b)* In the same way as described in *Run a)*, (*ent*)-**5** (600 mg, 2.51 mmol) in MeOH (9 mL), NaOH (150 mg, 3.75 mmol) in water (3 mL) were reacted for 15 h to yield 562 mg (100%) **8**.

Mp 126°C; $^1H$ NMR ($CDCl_3$, signal doubling because of

rotamers) δ 11.87 (br s, 1H), 6.61–6.45 (m, 1H), 5.40–5.31 (m, 1H), 4.50–4.31 (m, 1H), 2.87 (br s, 1H), 1.51 and 1.48 (s, 9H), 0.92 (br s, 1H); $^{13}$C NMR ($CDCl_3$, signal doubling because of rotamers) δ 179.75 and 179.15, 151.15 and 150.96, 129.98 and 129.73, 109.83, 82.02, 45.00 and 44.77, 33.10 and 31.87, 28.15, 22.95; IR (KBr) $\nu$ cm$^{-1}$ 2982, 1686, 1585, 1409, 1367, 1302, 1253, 1210, 1168, 1143, 1099, 1022, 934, 842, 817, 760; HRMS (DCI($NH_3$)) $[M+H]^+$ calcd for $C_{21}H_{15}NO_4$ 225.1006, found: 225.1001. $[\alpha]_D^{21}$=+274.8 (c=1.006. $CH_2Cl_2$).

**3.1.2. 2-Azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylic acid 2-*tert*-butyl ester 6-benzyl ester ((*rac*)-11).** To a solution of (*rac*)-**8** (3.94 g, 17.50 mmol) in DMF (50 mL) were added $NaHCO_3$ (7.35 g, 87.48 mmol) and benzyl bromide (14.96 g, 87.48 mmol). After being stirred for 48 h at 40°C, the solution was diluted with EtOAc (100 mL) and water (100 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3×50 mL). The combined organic layers were washed with water (2×50 mL) and dried over $Na_2SO_4$. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (first pure hexanes to separate excess benzyl bromide, then 20:1 hexanes/EtOAc) to afford 4.95 g (90%) (*rac*)-**11** as a yellow oil. TLC $R_f$ 0.16 (20:1 hexanes/EtOAc); $^1$H NMR ($CDCl_3$) δ 7.34 (s, 5H), 6.64–6.60 (m, 1H), 5.39–5.29 (m, 1H), 5.14–5.08 (m, 2H), 4.50–4.30 (m, 1H), 2.84 (br s, 1H), 1.50 (s, 9H), 1.01 (br s, 1H); $^{13}$C NMR ($CDCl_3$, signal doubling because of rotamers) δ 172.91 and 172.71, 150.87, 135.72, 129.82, 129.60, 128.48, 128.17, 127.65, 109.82, 81.68, 66.45, 44.42 and 44.22, 32.32 and 31.19, 28.15, 22.97; IR (neat) $\nu$ cm$^{-1}$ 2977, 1709, 1586, 1401, 1368, 1343, 1286, 1163, 1028, 947, 736, 698; MS (EI(70eV)) 315 (1) $[M]^+$, 57 (100) $[C_4H_9]^+$.

**3.1.3. (1*R**,2*R**,3*R**)-*N*-*tert*-Butoxycarbonyl-*N*-formyl-2-formyl-3-aminocyclopropanecarboxylic acid benzyl ester (12).** A solution of (*rac*)-**11** (4.95 g, 15.70 mmol) in $CH_2Cl_2$ (50 mL) was treated with ozone at −78°C until the solution maintained a blue color. After removal of the excess ozone by passing oxygen through the solution, dimethyl sulfide (4.88 g, 78.50 mmol) was added and the solution was stirred for 12 h at room temperature. *Caution: It is important that the time of reduction is sufficiently long, otherwise the reduction is incomplete*. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (5:1 hexanes/EtOAc) to yield 5.16 g (95%) of a colorless oil, which was crystallized from $Et_2O$ (3 mL)/cyclohexane (10 mL) to afford **12** as a white solid. Mp 59°C; TLC $R_f$ 0.29 (5:1 hexanes/EtOAc); $^1$H NMR ($CDCl_3$) δ 9.52 (d, *J*=2.4 Hz, 1H), 9.08 (s, 1H), 7.39–7.33 (m, 5H), 5.22 (d, *J*=12.2 Hz, 1H), 5.14 (d, *J*=12.2 Hz, 1H), 3.25 (dd, *J*=8.0, 4.7 Hz, 1H), 3.01–2.95 (m, 1H), 2.79 (dd, *J*=5.8, 4.7 Hz, 1H), 1.50 (s, 9H); $^{13}$C NMR ($CDCl_3$) δ 192.85, 169.29, 163.32, 151.95, 135.21, 128.63, 128.51, 128.37, 85.34, 67.36, 36.69, 35.06, 27.97, 27.88; IR (KBr) $\nu$ cm$^{-1}$ 3429, 2972, 2847, 1752, 1732, 1703, 1458, 1371, 1318, 1288, 1185, 1174, 1157, 1060, 964, 847, 740; MS (DCI($NH_3$)) 712 (45) $[2M+NH_3+H]^+$, 365 (100) $[M+NH_3+H]^+$; Anal. Calcd for $C_{18}H_{21}NO_6$: C, 62.23; H, 6.13; N, 4.03. Found: C, 62.24; H, 6.09; N, 4.03.

**3.1.4. (1*R**,2*R**,3*R**)-*N*-*tert*-Butoxycarbonyl-*N*-formyl-3-aminocyclopropane-1,2-dicarboxylic acid 2-monobenzyl ester (14).** A solution of **12** (1.93 g, 5.54 mmol) in $CH_3CN$ (14 mL) was cooled to 0°C. Under rigorous stirring a solution of $KH_2PO_4$ (444 mg) in water (4.5 mL), followed by $H_2O_2$ (30%, 0.56 mL) and a solution of $NaClO_2$ (1.11 g, technical, 80%) in water (11.0 mL) were added. The reaction solution was stirred at 0°C until gas evolution had stopped (ca. 2 h). $Na_2SO_3$ (554 mg) was added to destroy excess $NaClO_2$ and the solution was stirred for 1 h at 0°C. After acidification to pH 2 with 1 M $KHSO_4$, the solution was extracted with EtOAc (5×30 mL). The combined organic layers were dried over $Na_2SO_4$. Evaporation of the solvent under reduced pressure yielded 2.02 g (100%) of **14** as a colorless oil. $^1$H NMR ($CDCl_3$) δ 9.13 (s, 1H), 7.39–7.31 (m, 5H), 5.23 (d, *J*=12.2 Hz, 1H), 5.14 (d, *J*=12.2 Hz, 1H), 3.25 (dd, *J*=7.7, 5.0 Hz, 1H), 2.72–2.64 (m, 1H), 2.61 (dd, *J*=7.7, 5.9 Hz, 1H), 1.48 (s, 9H); $^{13}$C NMR ($CDCl_3$) δ 173.68, 169.29, 163.37, 151.92, 135.13, 128.67, 128.55, 128.40, 85.21, 67.50, 35.93, 29.77, 27.99, 27.77; IR (neat) $\nu$ cm$^{-1}$ 3276, 3001, 2617, 1718, 1457, 1372, 1285, 1144, 1058, 847, 749, 698; MS (DCI($NH_3$)) 381 (100) $[M+NH_3+H]^+$.

**3.1.5. (1*R**,2*R**,3*R**)-*N*-*tert*-Butoxycarbonyl-3-aminocyclopropane-1,2-dicarboxylic acid 2-monobenzyl ester (15).** To a solution of **14** (1.93 g, 5.32 mmol) in $CH_3CN$ (15 mL) was added DEAEA (1.24 g, 10.63 mmol). The reaction mixture was stirred for 24 h at room temperature. The solution was acidified to pH 2 with 1 M $KHSO_4$ and extracted with EtOAc (3×40 mL). The combined organic layers were dried over $Na_2SO_4$ and concentrated in vacuo to yield 1.53 g (86%) of **15** as a colorless solid. Mp 131°C; $^1$H NMR ($CDCl_3$, signal doubling because of rotamers) δ 11.63 (br s, 1H), 7.38–7.28 (m, 5H), 6.79 and 5.45 (br s, 1H), 5.14 (s, 2H), 3.95 and 3.46 (br s, 1H), 2.49–2.43 (m, 1H), 2.37–2.33 (m, 1H), 1.42 (s, 9H); $^{13}$C NMR ($CDCl_3$) δ 172.03, 169.81, 158.28, 135.32, 128.66, 128.52, 128.43, 82.41, 67.13, 37.61, 29.63, 28.21, 26.84; IR (KBr) $\nu$ cm$^{-1}$ 3317, 2984, 1725, 1701, 1647, 1451, 1430, 1370, 1306, 1230, 1171, 1146, 1066, 930, 891, 696; MS (DCI($NH_3$)) 353 (36) $[M+NH_3+H]^+$, 192 (100); Anal. Calcd for $C_{17}H_{21}NO_6$: C, 60.89; H, 6.31; N, 4.18. Found: C, 60.71; H, 6.34; N, 4.06.

**3.1.6. (1*R**,2*R**,3*R**)-*N*-*tert*-Butoxycarbonyl-3-amino-2-dibenzylcarbamoylcyclopropanecarboxylic acid benzyl ester (16).** To a solution of **15** (150 mg, 0.45 mmol) in $CH_2Cl_2$ (5 mL) were added HOBt (103 mg, 0.67 mmol), EDC (129 mg, 0.67 mmol) and dibenzylamine (442 mg, 2.24 mmol). The mixture was stirred for 20 h at room temperature. The reaction mixture was concentrated in vacuo and the residue was diluted with EtOAc (20 mL), then washed with saturated $NaHCO_3$ (5 mL), 1 M $KHSO_4$ (2×5 mL) and saturated $NaHCO_3$ (5 mL) and dried over $Na_2SO_4$. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (4:1 hexanes/EtOAc) to yield 175 mg (76%) **16** as a colorless oil. TLC $R_f$ 0.30 (4:1 hexanes/EtOAc); $^1$H NMR ($CDCl_3$) δ 7.58–7.12 (m, 15H), 6.07 (br s, 1H), 5.05 (s, 2H), 4.77–4.44 (m, 4H), 3.87 (br s, 1H), 2.63 (dd, *J*=8.3, 5.2 Hz, 1H), 2.52–2.47 (m, 1H), 1.44 (s, 9H); $^{13}$C NMR ($CDCl_3$) δ 170.30, 168.97, 155.60, 136.57, 135.83, 135.34, 129.57, 128.96, 128.67, 128.51, 128.29, 128.20, 128.11,

127.75, 127.57, 126.43, 79.95, 66.93, 50.37, 48.89, 38.29, 28.29, 28.09, 25.30; IR (KBr) $\nu$ $cm^{-1}$ 3433, 3308, 2924, 2304, 1730, 1684, 1644, 1520, 1452, 1369, 1275, 1252, 1215, 1166, 1059, 730, 701; MS (FAB(NBA)) 1029 (74) $[2M+H]^+$, 515 (100) $[M+H]^+$; Anal. Calcd for $C_{31}H_{34}N_2O_5$: C, 72.35; H, 6.66; N, 5.44. Found: C, 72.37; H, 6.68; N, 5.37.

**3.1.7. (1*R**,2*S**,3*R**)-*N-tert*-Butoxycarbonyl-3-acetylthiomethyl-2-aminocyclopropanecarboxylic acid benzyl ester (17).** To a solution of **20** (965 mg, 2.42 mmol) in $CH_3CN$ (25 mL) was added $K_2CO_3$ (367 mg, 2.66 mmol) followed by thioacetic acid (202 mg, 2.66 mmol). The mixture was stirred for 20 h at room temperature. Water (20 mL) was added and the resulting solution was extracted with EtOAc (3×20 mL). The combined organic layers were dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (3:1 hexanes/EtOAc) yielding 812 mg (89%, de 86%) **17** as a yellow oil. Recrystallization from $CH_2Cl_2$ (1 mL)/hexanes (4 mL) afforded 759 mg (83%, de 94%) of **17** as a yellow solid. Mp 95°C; TLC $R_f$ 0.34 (3:1 hexanes/EtOAc); $^1$NMR ($CDCl_3$) δ 7.38–7.28 (m, 5H), 5.39 (br s, 1H), 5.15 (d, $J$=12.3 Hz, 1H), 5.07 (d, $J$=12.3 Hz, 1H), 3.16 (br s, 1H), 3.10 (dd, $J$=14.3, 8.7 Hz, 1H), 2.94 (dd, $J$=14.3, 8.7 Hz, 1H), 2.36 (s, 3H), 1.90–1.79 (m, 1H), 1.67 (dd, $J$=5.6, 3.2 Hz, 1H), 1.44 (s, 9H); $^{13}$C NMR ($CDCl_3$) δ 196.16, 171.19, 156.15, 135.72, 128.58, 128.31, 80.19, 66.74, 36.76, 30.53, 28.31, 27.51, 26.31; IR (KBr) $\nu$ $cm^{-1}$ 3401, 2981, 2358, 2330, 1719, 1697, 1509, 1454, 1327, 1258, 1229, 1193, 1175, 1154, 951, 751, 697; MS (DCI($NH_3$)) 397 (12) $[M+NH_3+H]^+$, 380 (2) $[M+H]^+$, 204 (100); Anal. Calcd for $C_{19}H_{25}NO_5S$: C, 60.14; H, 6.64; N, 3.69. Found: C, 60.18; H, 6.61; N, 3.68.

**3.1.8. (1*R**,2*R**,3*R**)-*N-tert*-Butoxycarbonyl-3-hydroxymethyl-2-aminocyclopropanecarboxylic acid benzyl ester (18).** A solution of **12** (2.21 g, 6.35 mmol) in EtOH/water (9:1, 28 mL) was cooled to 0°C. $NaBH_4$ (150 mg, 3.97 mmol) was added and the solution was stirred for 50 min at 0°C. The organic layer was separated after acidification to pH 2 with saturated $KHSO_4$ and addition of brine (10 mL). The aqueous layer was extracted with EtOAc (3×20 mL) and the combined organic layers were dried over $Na_2SO_4$. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (1:1 hexanes/EtOAc) to provide 1.66 g (81%) of **18** as a colorless oil which crystallized after prolonged storage at 2°C. Mp 82°C; TLC $R_f$ 0.43 (1:1 hexanes/EtOAc); $^1$H NMR ($CDCl_3$) δ 7.40–7.29 (m, 5H), 5.11 (s, 2H), 5.06 (br s, 1H), 3.96 (dd, $J$=11.8, 3.9 Hz, 1H), 3.33–3.25 (m, 2H), 3.15 (dd, $J$=7.3, 3.1 Hz, 1H), 2.07–2.04 (m, 1H), 1.55 (dd, $J$=5.3, 3.1 Hz, 1H), 1.44 (s, 9H); $^{13}$C NMR ($CDCl_3$) δ 171.08, 157.38, 135.64, 128.61, 128.38, 128.31, 81.04, 66.78, 59.51, 35.15, 29.91, 28.24, 25.11; IR (KBr) $\nu$ $cm^{-1}$ 3421, 3337, 2989, 1705, 1692, 1519, 1450, 1436, 1369, 1344, 1308, 1283, 1239, 1189, 1151, 1027, 964, 755; MS (DCI($NH_3$)) 339 (63) $[M+NH_3+H]^+$, 322 (9) $[M+H]^+$, 283 (100); Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.37; H, 6.95; N, 4.09.

**3.1.9. (1*R**,2*S**,3*R**)-*N-tert*-Butoxycarbonyl-3-(9*H*-fluoren-9-ylmethoxycarbonyl)oxymethyl-2-aminocyclopropanecarboxylic acid benzyl ester (19).** To a solution of **18** (150 mg, 0.47 mmol) in pyridine (5 mL) was added Fmoc-Cl (133 mg, 0.51 mmol) at 0°C. The reaction mixture was stirred for 20 h at room temperature. The solution was diluted with EtOAc (20 mL), washed with saturated $KHSO_4$ (3×10 mL) and dried over $Na_2SO_4$. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (5:1 hexanes/EtOAc) to yield 201 mg (79%) of 19 as a colorless solid. Mp 114°C; TLC $R_f$ 0.20 (5:1 hexanes/EtOAc); $^1$H NMR ($CDCl_3$) δ 7.78–7.75 (m, 2H), 7.62–7.59 (m, 2H), 7.44–7.28 (m, 9H), 5.34 (br s, 1H), 5.17 (d, $J$=12.2 Hz, 1H), 5.09 (d, $J$=12.2 Hz, 1H), 4.45–4.38 (m, 3H), 4.28–4.10 (m, 2H), 3.17 (br s, 1H), 2.09–1.89 (m, 1H), 1.76–1.74 (m, 1H), 1.43 (s, 9H); $^{13}$C NMR ($CDCl_3$) δ 170.87, 156.14, 155.35, 143.25, 143.21, 141.34, 135.59, 128.62, 128.61, 128.40, 127.98, 127.23, 125.14, 120.13, 80.30, 70.17, 66.93, 64.76, 46.75, 35.65, 28.29, 26.65, 25.52; IR (KBr) $\nu$ $cm^{-1}$ 3396, 2977, 1740, 1722, 1694, 1508, 1499, 1451, 1376, 1320, 1272, 1259, 1231, 1165, 953, 742; MS (FAB(NBA)) 1087 (91) $[2M+H]^+$, 544 (29) $[M+H]^+$, 204 (100); Anal. Calcd for $C_{32}H_{33}NO_7$: C, 70.70; H, 6.12; N, 2.58. Found: C, 70.38; H, 6.10; N, 2.40.

**3.1.10. (1*R**,2*S**,3*R**)-*N-tert*-Butoxycarbonyl-3-methanosulfonyloxymethyl-2-aminocyclopropanecarboxylic acid benzyl ester (20).** Methanesulfonyl chloride (430 mg, 3.75 mmol) was added dropwise to a solution of **18** (1.01 g, 3.13 mmol) and $NEt_3$ (380 mg, 3.75 mmol) in $CH_2Cl_2$ (10 mL) at 0°C. The mixture was stirred for 2 h at 0°C and for 1 h at room temperature. The solvent was evaporated under reduced pressure and the residue was taken up in water (5 mL) and EtOAc (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were dried over $Na_2SO_4$ and concentrated in vacuo to yield 1.24 g (100%) of **20** as a colorless solid. Mp 103°C; $^1$H NMR ($CDCl_3$) δ 7.39–7.30 (m, 5H), 5.17 (d, $J$=12.2 Hz, 1H), 5.09 (d, $J$=12.2 Hz, 1H), 5.08 (s, 1H), 4.43–4.27 (m, 2H), 3.26–3.22 (m, 1H), 3.03 (s, 3H), 2.08 (ddd, $J$=13.1, 7.5, 5.2 Hz, 1H), 1.83 (dd, $J$=5.2, 3.4 Hz, 1H), 1.43 (s, 9H); $^{13}$C NMR ($CDCl_3$) δ 170.36, 156.10, 135.50, 128.61, 128.42, 128.37, 80.76, 67.04, 66.72, 38.00, 35.72, 28.24, 26.75, 25.59; IR (KBr) $\nu$ $cm^{-1}$ 3395, 2976, 2934, 1719, 1696, 1505, 1456, 1349, 1266, 1231, 1172, 943, 816, 749, 697; MS (DCI($NH_3$)) 417 (10) $[M+NH_3+H]^+$, 204 (100); Anal. Calcd for $C_{18}H_{25}NO_7S$: C, 54.12; H, 6.31; N, 3.51. Found: C, 53.94; H, 6.30; N, 3.52.

**3.1.11. (1*R**,2*R**,3*R**)-*N-tert*-Butoxycarbonyl-3-(*N*′,*N*′-di-*tert*-butoxycarbonylguanidinyl)methyl-2-aminocyclopropanecarboxylic acid benzyl ester (21).** $PPh_3$ (49 mg, 0.19 mmol) and bis(*tert*-butoxycarbonyl)-guanidine (121 mg, 0.47 mmol) were added to a solution of **18** (30 mg, 0.09 mmol) in THF (2 mL). This solution was cooled to 0°C, diethyl azodicar-boxylate (32 mg, 0.19 mmol) was slowly added over 5 min, and the reaction mixture was stirred for 20 h at room temperature. The solution was concentrated in vacuo and the residue extracted with EtOAc (10 mL). The organic layer was washed with water (5 mL) and brine (5 mL) and dried over $Na_2SO_4$. The solvent was evaporated under reduced pressure and the residue was

purified by flash chromatography (5:1 hexanes/EtOAc) to yield 33 g (63%) of 21 as a colorless solid. Mp 151°C; TLC $R_f$ 0.31 (5:1 hexanes/EtOAc); $^1$H NMR ($CDCl_3$, signal doubling because of rotamers) δ 9.36 (br s, 1H), 9.10 (br s, 1H), 7.36–7.31 (m, 5H), 7.04 and 6.66 (br s, 1H), 5.17 (d, $J$=12.3 Hz, 1H), 5.07 (d, $J$=12.3 Hz, 1H), 3.92 (br d, $J$=3.0 Hz, 2H), 3.15 (br s, 1H), 1.80–1.72 (m, 1H), 1.68 (s, 1H), 1.50 (s, 9H), 1.46 (s, 9H), 1.44 (s, 9H); $^{13}$C NMR ($CDCl_3$) δ 171.84, 163.21, 160.36, 156.61, 154.55, 136.03, 128.54, 128.32, 128.22, 84.66, 79.41, 77.24, 66.41, 41.55, 37.15, 28.46, 28.32, 28.16, 27.95, 26.78; IR (KBr) $\nu$ cm$^{-1}$ 3383, 3279, 2973, 1727, 1709, 1649, 1609, 1509, 1393, 1369, 1333, 1285, 1241, 1175, 1142, 1096, 1050, 987, 779; MS (FAB(NBA)) 1125 (100) $[2M+H]^+$, 563 (98) $[M+H]^+$; Anal. Calcd for $C_{28}H_{42}N_4O_8$: C, 59.77; H, 7.52; N, 9.96. Found: C, 59.69; H, 7.45; N, 9.90.

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