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Synthesis of a Bicyclic Proline Analogue from L-Ascorbic Acid

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Abstract: The efficient synthesis of a bicyclic α-amino acid from L-ascorbic acid is presented. The synthetic procedure is a three-step process involving an S_N2 reaction of an amino acetal with an L-ascorbic acid derivative, followed by protection of the amine as a Fmoc urethane, and acid-promoted *trans*-acetalization to give the title compound. Inversion of the configuration at the stereocenter of the precursor derived from L-ascorbic acid allowed the formation of the corresponding bicyclic α-amino acid bearing the carboxylic group in the 2-*exo* configuration. Such Fmoc-protected α-amino acids can be considered as bicyclic mimetics of proline, and are particularly suited for solid-phase peptidomimetic chemistry.

Key words: scaffold, peptidomimetic, amino acids, peptides, proline

During the last years, much interest has been paid to peptidomimetics, both in organic and medicinal chemistry, as they are much more selective and efficient than native peptides. Furthermore, they can have fewer side effects and greater oral bioavailability, as the lowered enzymatic degradation allows for longer biological activity.[1] Therefore, there is an ever-increasing need for versatile scaffolds, including new amino acid templates, to be applied in peptidomimetic design.[2] Among the various approaches for mimicking peptide structures,[3] numerous mimetics and analogues of proline have been developed and applied in the synthesis of biologically active compounds,[4] especially with the aim of modulating the *cis*/*trans* isomerism of acyl–proline bonds, and producing proline-like reverse turn inducers.[5]

Since the development of the first examples of 6,8-dioxa-3-azabicyclo[3.2.1]octane-based scaffolds (BTAa, see Figure 1), functionalities have been introduced at positions 3, 4, 5, and 7,[6] whereas position 2 has remained largely unexplored, occupied only by C=O, C=S, or CH_2 groups. In particular, the possibility of generating scaffolds with differently positioned carboxy groups (Figure 1, **A**–**C**) has been pursued recently, to expand the scope of peptidomimetic chemistry within this class of bicyclic scaffolds. For this approach, new synthetic strategies have been necessary, using different building blocks from the chiral pool.[7]

Recently, we moved from tartaric acid to sugars as building blocks for new versatile scaffolds in enantiopure form with complete control of the stereochemistry.[7] In particular, it was possible to generate new enantiopure bicyclic amino acids, such as γ- or δ-amino acids as reverse turn inducers, by use of erythrose derivatives[7b] and bicyclic proline mimetics starting from serine and glyceraldehyde derivatives.[7a] We reasoned that starting from L-ascorbic acid derivative **1** (Scheme 1), we could produce a new set of scaffolds bearing a substituent at position 2 (Figure 1, **D**). L-Ascorbic acid has appeared in literature as a valuable source of chiral building blocks for the preparation of enantiopure β-lactams[8] and L-hexoses.[9] Moreover, the use of such an inexpensive starting material is an advantage in multigram-scale organic synthesis.

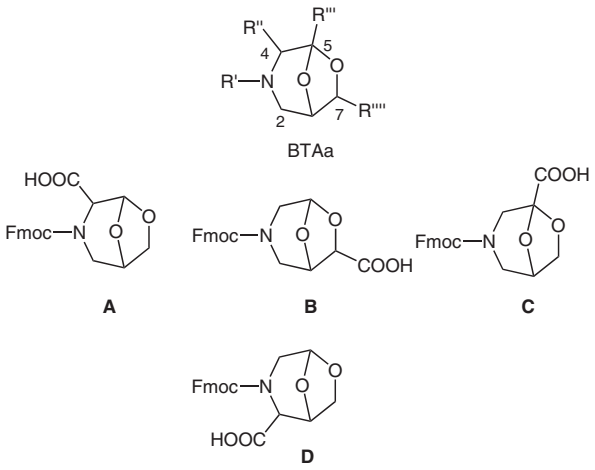

Figure 1 General formula of BTAa scaffolds (*top*) and isomeric bicyclic amino acids **A**–**D**, with **A** and **D** as proline mimetics

Thus, starting from triflate **2**, obtained from the protected L-ascorbic acid derivative **1**,[8,10] compound **4** was obtained in 99% yield by nucleophilic substitution with aminoacetaldehyde dimethyl acetal (**3**) at room temperature and after overnight stirring (Scheme 1). Further protection gave Fmoc urethane **5**, which was obtained with 9-fluorenylmethyl chloroformate in 1,4-dioxane as solvent, whereas *N*-(9-fluorenylmethoxycarbonyloxy)succinimide did not yield any product. Then, Fmoc derivative **5** was subjected to acid cyclization at 0 °C, according to reported procedures,[7] to afford the the methyl ester of scaffold **6**. Surprisingly, the corresponding carboxylic acid **6** was obtained as the major product by concomitant deprotection of the carbomethoxy group, and the conversion to acid **6** went to completion when the reaction was conducted at 25 °C. Since the preparation of 4-*endo*-carboxy scaf-

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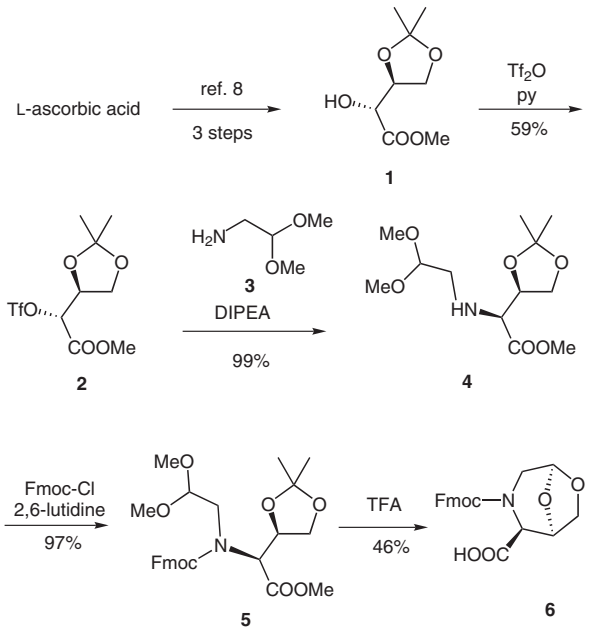
folds proved to be problematic and low yielding, as previously reported (see Figure 1, structure **A**),[7a] the facile synthesis of **6**, with the carboxy group in the *endo* position, provides a more complete collection of bicyclic amino acids for application in peptidomimetic chemistry.

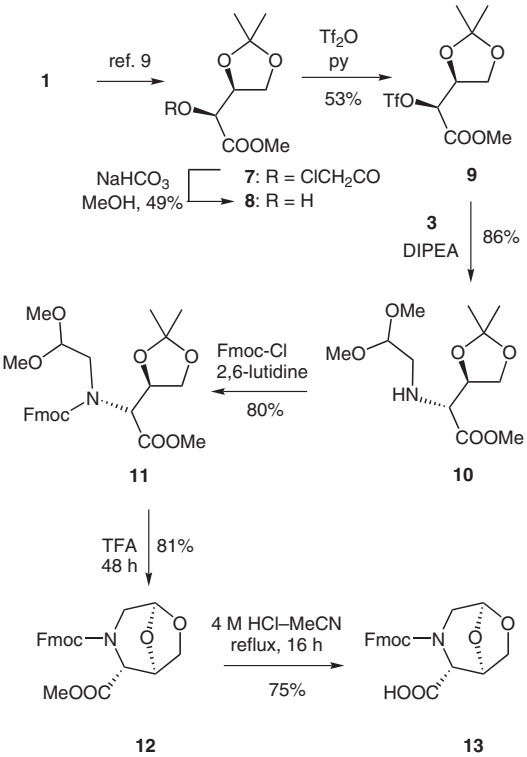


Scheme 1 Synthesis of a bicyclic α-amino acid with an *endo*-carboxy group from L-ascorbic acid

Formal inversion of the configuration at the C-2 stereocenter of compound **1** gives **13**, the corresponding diastereomer of **6**, carrying the carboxy group in the 2-*exo* position (Scheme 2). Thus, treatment of L-ascorbic acid derivative **1** with chloroacetic acid and triphenylphosphine, as previously reported,[9] produced the corresponding ester derivative **7** with inversion of configuration at C-2 (Scheme 2). Subsequent hydrolysis with sodium hydrogen carbonate in place of triethylamine gave **8**, the stereoisomer of **1**, which was converted into the corresponding triflate derivative **9** in 53% yield. The reaction of triflate **9** with acetal **3** gave adduct **10**, a diastereomer of **4**, with inversion of configuration at C-2. Successively, Fmoc protection by the same procedure used to prepare **5** yielded **11**, which was subsequently cyclized by treatment with trifluoroacetic acid. Interestingly, in this case, the reaction provided the bicyclic scaffold as methyl ester derivative **12** (Scheme 2), since the concomitant hydrolysis failed to occur, probably because of the axial orientation of the methoxycarbonyl group. This led to the hypothesis that the facile hydrolysis to give compound **6** might occur through the urethane carbonyl group providing anchimeric assistance to the equatorial methoxycarbonyl group. Compound **12** could be obtained in excellent yield when the cyclization time was prolonged from 16 hours (35% yield) to 48 hours (81% yield).

Hydrolysis of **12** (Scheme 2) proved to be problematic, and different methods were tried. Specifically, basic hydrolysis with lithium hydroxide did not yield α-amino acid **13** in significant amounts, and partial Fmoc-deprotection of **12** was observed. Hydrolysis with a dioxane–water system at room temperature for 48 hours gave **13** in 19% conversion, and a similar result (17%) was achieved when ester **12** was treated with 4 M aqueous hydrogen chloride in acetonitrile. However, when ester **12** was refluxed in the same aqueous hydrogen chloride–acetonitrile system for 16 hours, acid **13** was obtained in satisfactory yield (75%) (Scheme 2).

In conclusion, a new bicyclic α-amino acid was synthesized in a three-step procedure starting from an L-ascorbic acid derivative, producing amino acid derivative **6** directly after acid cyclization. In addition, inversion of configuration at the carbon atom bearing the triflate group of the L-ascorbic acid derivative allowed the synthesis of the corresponding diastereomeric bicyclic amino acid **13**, which has the carboxy group in the 2-*exo* configuration. These two new bicyclic proline analogues may thus find application in peptidomimetic research, and, in particular, are suited for solid-phase organic and peptide synthesis by the Fmoc protocol.



Scheme 2 Synthesis of a bicyclic α-amino acid with an *exo*-carboxy group from L-ascorbic acid

Melting points are uncorrected. Chromatographic separations were performed on silica gel by flash-column techniques. R_f values were obtained by TLC carried out on 25-mm silica gel plates (Merck F254), with the same eluent used for the column chromatography. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Gemini 200 or a Varian MercuryPlus 400 instrument. IR spectra of CH_2Cl_2 or $CDCl_3$ solns were recorded on a Perkin-Elmer 881 spectrophotometer. Mass spectra were carried out with a Shimadzu spectrometer

operating with EI at 70 eV. Microanalyses were carried out with a Perkin-Elmer 2400/2 elemental analyzer. Optical rotations were determined on a JASCO DIP-370 instrument.

Methyl (*R*)-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl](trifluoromethylsulfonyloxy)acetate (2)

A soln of **1** (5.00 g, 26.3 mmol) in dry CH_2Cl_2 (45.5 mL) was cooled to –10 °C, and precooled dry pyridine (4.50 mL) was added. Then a soln of Tf_2O (7.30 mL, 34.2 mmol) in dry CH_2Cl_2 (13.6 mL) was added over 30 min, and the mixture was stirred at r.t. for 30 min. After the organic phase had been washed with a sat. $NaHCO_3$ soln (3 × 50 mL), the organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to give a dark oil. Flash chromatography (silica gel, PE–EtOAc, 2:1) afforded **2** as a white solid; yield: 4.98 g (59%).

Mp 51–54 °C; $[\alpha]_D^{25}$ +38.8 (*c* 0.8, CH_2Cl_2); R_f = 0.6 (PE–EtOAc, 2:1).

IR ($CDCl_3$): 3052, 2986, 1733, 1265 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.04 (d, *J* = 5.5 Hz, 1 H, TfOCH), 4.56–4.52 (m, 1 H, ring H-4), 4.18 (dd, *J* = 9.4, 6.7 Hz, 1 H, C*H*H), 4.06 (dd, *J* = 9.4, 4.7 Hz, 1 H, CH*H*), 3.88 (s, 3 H, OCH_3), 1.45 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1 (s, C=O), 121.5 (s, CF_3), 111.1 [s, $C(CH_3)_2$], 82.6 (d, TfOCH), 74.1 (d, ring C-4), 65.4 (t, CH_2), 53.5 (q, OCH_3), 25.9 (q, CH_3), 25.0 (q, CH_3).

MS (EI, 70 eV): *m*/*z* (%) = 322 (8) [M^+], 69 (100), 55 (77).

Anal. Calcd for $C_9H_{13}F_3O_7S$: C, 33.54; H, 4.07. Found: C, 33.46; H, 3.99.

Methyl (*S*)-[(2,2-Dimethoxyethyl)amino][(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]acetate (4)

A soln of **2** (1.30 g, 4.01 mmol) in dry CH_2Cl_2 (20 mL) was cooled to 0 °C under N_2, and then a soln of **3** (0.50 mL, 4.81 mmol) and DIPEA (1.40 mL, 8.02 mmol) in dry CH_2Cl_2 (20 mL) was added. The mixture was stirred at r.t. for 15 h, and then it was extracted with a sat. $NaHCO_3$ soln (3 × 40 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to give a dark oil. Flash chromatography (silica gel, PE–EtOAc, 3:1) afforded pure **4** as a yellow oil; yield: 1.11 g (99%).

$[\alpha]_D^{25}$ +15.6 (*c* 0.9, CH_2Cl_2); R_f = 0.47 (PE–EtOAc, 3:1).

IR ($CDCl_3$): 2991, 2955, 2836, 1733, 1250, 1219 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.41 [t, *J* = 4.8 Hz, 1 H, $(OCH_3)_2CHCH_2NH$)], 4.18–4.13 (m, 1 H, ring H-4), 4.07–4.00 (m, 2 H, ring CH_2), 3.76 (s, 3 H, CO_2CH_3), 3.35 (s, 3 H, OCH_3), 3.34 (s, 3 H, OCH_3), 3.27 (d, *J* = 7.3 Hz, 1 H, C*H*NH), 2.76 (dd, *J* = 12.1, 6.3 Hz, 1 H, CH_2NH), 2.63 (dd, *J* = 12.1, 4.6 Hz, 1 H, CH_2NH), 1.72 (br, 1 H, NH), 1.41 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3 (s, C=O), 109.7 (s), 103.5 [d, *C*H$(OMe)_2$], 76.8 [d, *C*HOC$(CH_3)_2$], 67.1 (t, CH_2NH), 64.4 (d, *C*HCO_2Me), 53.9 (q, OCH_3), 53.2 (q, OCH_3), 51.9 (q, OCH_3), 49.5 (t, ring CH_2), 26.7 (q, CH_3), 25.3 (q, CH_3).

MS (EI, 70 eV): *m*/*z* (%) = 277 (4) [M^+], 177 (79), 144 (100), 75 (96).

Anal. Calcd for $C_{12}H_{23}NO_6$: C, 51.97; H, 8.36; N, 5.05. Found: C, 51.84; H, 8.40; N, 5.12.

Methyl (*S*)-[(2,2-Dimethoxyethyl)(9*H*-fluoren-9-ylmethoxycarbonyl)amino][(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]acetate (5)

To a soln of **4** (616 mg, 2.22 mmol) in dioxane (44 mL), at 0 °C and under N_2 were added FmocCl (863 mg, 3.33 mmol) and 2,6-lutidine (388 μL, 3.33 mmol). The mixture was stirred at r.t. for 15 h. The soln was then concentrated in vacuo, the crude was dissolved in CH_2Cl_2 (20 mL), and the soln was washed with 5% citric acid soln (3 × 20 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to give **5** as a clear oil. Flash chromatography (silica gel, PE–EtOAc, 5:1) afforded **5** as a colorless oil; yield: 1.07 g (97%).

$[\alpha]_D^{25}$ –48.1 (*c* 1.45, CH_2Cl_2); R_f = 0.1 (PE–EtOAc, 5:1).

IR ($CDCl_3$): 2958, 1794, 1709 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 5.4 Hz, 2 H, Ar), 7.51 (d, *J* = 3.9 Hz, 2 H, Ar), 7.33–7.22 (m, 4 H, Ar), 4.61 (m, 2 H), 3.62 (s, 3 H, OCH_3), 4.56–3.02 (m, 14 H), 1.28 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers): δ = 169.7 (s), 156.1 and 155.9 (s), 143.5 (s, 2 C), 141.4 and 141.3 (s, 2 C), 127.7 (d, 2 C), 127.1 (d, 2 C), 124.8 and 124.5 (d, 2 C), 120.1 and 119.9 (d, 2 C), 110.1 and 109.9 (s), 103.4 and 102.9 (d), 74.9 and 74.6 (d), 67.2 and 66.6 (d), 66.1 (q), 62.2 and 61.9 (d), 55.3 and 55.1 (t), 54.4 and 54.1 (t), 52.2 (q, 2 C), 49.6 (d), 47.4 and 47.1 (t), 26.8 and 25.4 (q), 26.6 and 25.4 (q).

MS (EI, 70 eV): *m*/*z* (%) = 499 (0.3) [M^+], 178 (99), 75 (100).

Anal. Calcd for $C_{27}H_{33}NO_8$: C, 64.92; H, 6.66; N, 2.80. Found: C, 64.91; H, 6.62; N, 2.75.

(1*R*,2*S*,5*S*)-3-(9-Fluorenylmethoxycarbonyl)-6,8-dioxa-3-azabicyclo[3.2.1]octane-2-*endo*-carboxylic Acid (6)

Compound **5** (1.02 g, 2.00 mmol) was dissolved in TFA (4.20 mL), and the soln was stirred at 25 °C overnight. The soln was then concentrated in vacuo to give a dark oil. Flash chromatography (silica gel, CH_2Cl_2–MeOH, 20:1, buffered with 0.1% TFA) afforded **6** as a white solid; yield: 0.351 g (46%).

Mp = 198–201 °C; $[\alpha]_D^{25}$ –78.1 (*c* 1.0, CH_2Cl_2–1% TFA); R_f = 0.3 (CH_2Cl_2–MeOH, 20:1, buffered with 0.1% TFA).

IR ($CDCl_3$): 3691, 2958, 1794, 1602 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) (2:1 mixture of rotamers): δ = 7.69 (d, *J* = 7.1 Hz, 2 H, Ar), 7.50 (d, *J* = 7.8 Hz, 2 H, Ar), 7.33–7.22 (m, 4 H, Ar), 5.16 (s, 2/3 H, H-5, rot. A), 5.11 (d, *J* = 2.7 Hz, 1/3 H, H-5, rot. B), 4.68–4.21 (m, 7 H), 3.95 (d, *J* = 13.4 Hz, 1/3 H, H-4, rot. B), 3.85 (d, *J* = 13.6 Hz, 2/3 H, H-4, rot. A), 3.06 (d, *J* = 13.6 Hz, 2/3 H, H-4, rot. A), 2.99 (d, *J* = 13.4 Hz, 1/3 H, H-4, rot. B).

^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers): δ = 173.0 (s, O–C=O), 158.6 (s, N–C=O), 143.2 (s, 2 C, Ar), 141.0 (s, 2 C, Ar), 127.9 (d, 2 C, Ar), 127.4 and 127.3 (d, 2 C, Ar), 124.9 (d, 2 C, Ar), 120.1 and 119.8 (d, 2 C, Ar), 88.7 and 88.6 (d, C-5), 72.2 and 71.2 (t, C-7), 70.9 and 69.8 (t), 65.4 and 65.0 (d, C-1), 53.9 and 53.8 (d, C-2), 47.0 and 46.7 (d), 44.4 and 43.7 (t, C-4).

MS (EI, 70 eV): *m*/*z* (%) = 381 (1.3) [M^+], 178 (100).

Anal. Calcd for $C_{21}H_{19}NO_6$: C, 66.13; H, 5.02; N, 3.67. Found: C, 65.94; H, 4.94; N, 3.55.

Methyl (*S*)-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl](trifluoromethylsulfonyloxy)acetate (9)

A soln of **8** (150 mg, 0.79 mmol) in dry CH_2Cl_2 (1.4 mL) was cooled to –10 °C, precooled dry pyridine (135 μL) was added, followed by the addition of a soln of Tf_2O (219 μL, 1.02 mmol) in dry CH_2Cl_2 (0.40 mL) over 30 min. The mixture was stirred at r.t. for 30 min and then neutralized with a sat. $NaHCO_3$ soln. The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated in vacuo to give a dark oil. Flash chromatography (silica gel, PE–EtOAc, 2:1) afforded **9** as a yellow oil; yield: 136 mg (53%).

R_f = 0.6 (PE–EtOAc, 2:1).

^1H NMR (200 MHz, $CDCl_3$): δ = 5.24 (d, *J* = 3.6 Hz, 1 H, TfOCH), 4.58–4.50 (m, 1 H, ring H-4), 4.10–3.94 (m, 2 H, ring CH_2), 3.84 (s, 3 H, OCH_3), 1.43 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.0 (s, C=O), 121.5 (s, CF_3), 110.9 [s, $C(CH_3)_2$], 81.0 (d, TfOCH), 74.0 (d, ring H-4), 65.4 (t, CH_2), 53.5 (q, O CH_3), 25.8 (q, OCH_3), 24.9 (q, CH_3).

MS (EI, 70 eV): *m*/*z* (%) = 322 (3) [M$^+$], 75 (100), 55 (62).

Methyl (*R*)-[(2,2-Dimethoxyethyl)amino][(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]acetate (10)

A soln of **9** (136 mg, 0.42 mmol) in dry CH_2Cl_2 (2.1 mL) was cooled to 0 °C under N_2, and then a soln of **3** (56 μL, 0.51 mmol) and DIPEA (144 μL, 0.84 mmol) in dry CH_2Cl_2 (2.1 mL) was added. The mixture was stirred under N_2 at r.t. overnight, and then neutralized with a soln of $NaHCO_3$. The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated in vacuo to give a dark oil. Flash chromatography (silica gel, PE–EtOAc, 3:1) afforded pure **10** as a colorless oil; yield: 101 mg (86%).

$[\alpha]_D^{25}$ +19.3 (*c* 0.7, CH_2Cl_2); R_f = 0.47 (PE–EtOAc, 3:1).

IR (CH_2Cl_2): 2990, 2954, 2834, 1739, 1271, 1261 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.41 [t, *J* = 5.4 Hz, 1 H, $(CH_3O)_2CHCH_2NH$], 4.26 (q, *J* = 6.5 Hz, 1 H, ring H-4), 4.01–3.86 (m, 2 H, ring CH_2), 3.71 (s, 3 H, OCH_3 ester), 3.31 (s, 7 H, OCH_3, $CHNH$), 2.80 (dd, *J* = 12.1, 5.9 Hz, 1 H, CH_2NH), 2.57 (dd, *J* = 12.4, 5.1 Hz, 1 H, CH_2NH), 1.36 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.7 (s, C=O), 109.6 (s, C_{quat}), 103.9 [d, $CH(OCH_3)_2$], 76.2 [d, $CHOC(CH_3)_2$], 66.4 (t, CH_2NH), 62.9 (d, $CHCO_2Me$), 54.0 (q, OCH_3), 53.2 (q, OCH_3), 52.1 (q, OCH_3), 49.5 (t, ring CH_2), 26.5 (q, CH_3), 25.4 (q, CH_3).

MS (EI, 70 eV): *m*/*z* (%) = 277 (6) [M$^+$], 177 (75), 144 (89), 75 (100).

Anal. Calcd for $C_{12}H_{23}NO_6$: C, 51.97; H, 8.36; N, 5.05. Found: C, 52.10; H, 8.55; N, 5.14.

Methyl (*R*)-[(2,2-Dimethoxyethyl)(9H-fluoren-9-ylmethoxycarbonyl)amino][(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]acetate (11)

To soln of **10** (80 mg, 0.29 mmol) in dioxane (5.8 mL), at 0 °C and under N_2, was added FmocCl (112 mg, 0.43 mmol) and 2,6-lutidine (50 μL, 0.43 mmol). The mixture was stirred at r.t. under N_2 for 15 h. The solvent was concentrated in vacuo, then the crude was dissolved in CH_2Cl_2, and the soln was washed with 5% citric acid soln (3 × 10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to give a clear oil. Flash chromatography (silica gel, PE–EtOAc, 5:1) afforded **11** as a colorless oil; yield: 115 g (80%).

$[\alpha]_D^{25}$ +48.4 (*c* 0.95, CH_2Cl_2); R_f = 0.1 (PE–EtOAc, 5:1).

IR (CH_2Cl_2): 2988, 1739, 1701, 1261, 1066 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) (mixture of rotamers): δ = 7.81–7.74 (m, 2 H, Ar), 7.63–7.53 (m, 2 H, Ar), 7.44–7.31 (m, 4 H, Ar), 4.77–3.55 (m, 10 H), 3.68 (s, 3 H, OCH_3), 3.37 and 3.32 (s, 6 H, OCH_3), 1.41 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$) (mixture of rotamers): δ = 169.4 and 168.7 (s), 155.5 and 155.3 (s), 143.7 and 143.6 (s, 2 C), 141.6 and 141.3 (s, 2 C), 127.6 and 127.0 (d, 2 C), 124.8 (d, 2 C), 124.3 and 124.1 (d, 2 C), 120.1 and 119.9 (d, 2 C), 108.9 and 108.6 (s), 104.4 and 104.3 (d), 73.6 and 73.5 (d), 68.6 and 68.5 (d), 67.1 (q), 65.0 and 64.5 (d), 55.8 and 55.6 (t), 55.5 and 55.4 (t), 52.3 and 51.9 (q), 51.8 and 51.3 (q), 47.4 and 47.1 (t), 26.8 and 26.7 (q), 25.2 and 25.1 (q).

MS (EI, 70 eV): *m*/*z* (%) = 499 (0.3) [M$^+$], 178 (100), 75 (60).

Anal. Calcd for $C_{27}H_{33}NO_8$: C, 64.92; H, 6.66; N, 2.80. Found: C, 64.90; H, 6.51; N, 2.70.

Methyl (1*R*,2*R*,5*S*)-3-(9-Fluorenylmethoxycarbonyl)-6,8-dioxa-3-azabicyclo[3.2.1]octane-2-*exo*-carboxylate (12)

Compound **11** (226 mg, 0.45 mmol) was dissolved in TFA (950 μL), and the soln was stirred at 25 °C for 48 h. Then the soln was concentrated in vacuo; this gave a dark oil, which was purified by flash chromatography (silica gel, CH_2Cl_2–MeOH, 20:1, buffered with 0.1% TFA) to give pure **12** as a white solid; yield: 145 mg (81%).

Mp 56–59 °C; $[\alpha]_D^{25}$ +48.5 (*c* 0.35, CH_2Cl_2); R_f = 0.8 (CH_2Cl_2–MeOH, 20:1, buffered with 0.1% TFA).

IR (CH_2Cl_2): 2927, 1752, 1708, 1269 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) (3:2 mixture of rotamers): δ = 7.69 (m, 2 H, Ar), 7.51 and 7.41 (m, 2 H, Ar), 7.36–7.21 (m, 4 H, Ar), 5.45 (s, 1 H, H-5), 4.92 (d, *J* = 3.9 Hz, 3/5 H, H-1, rot. A), 4.78 (d, *J* = 3.9 Hz, 2/5 H, H-1, rot. B), 4.52–3.64 (m, 7 H), 3.74 and 3.64 (s, 3 H, OCH_3), 3.30 (d, *J* = 12.5 Hz, 3/5 H, H-4, rot. A), 3.14 (d, *J* = 13.0 Hz, 2/5 H, H-4, rot. B).

^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers): δ = 168.9 (s, O–C=O), 156.6 (s, N–C=O), 143.5 (s, 2 C, Ar), 141.2 (s, 2 C, Ar), 127.7 and 127.0 (d, 2 C, Ar), 124.9 (d, 2 C, Ar), 124.6 and 124.5 (d, 2 C, Ar), 120.0 (d, 2 C, Ar), 98.9 and 98.4 (d, C-5), 72.7 and 72.3 (d, C-1), 68.2 and 67.7 (t), 67.3 (t, C-7), 59.5 and 58.9 (d, C-2), 52.8 (q), 47.5 and 47.2 (t, C-4), 47.3 (d).

MS (EI, 70 eV): *m*/*z* (%) = 395 (0.7) [M$^+$], 336 (2), 178 (100), 165 (14), 89 (7), 55(8).

Anal. Calcd for $C_{22}H_{21}NO_6$: C, 66.83; H, 5.35; N, 3.54. Found: C, 66.34; H, 5.30; N, 3.46.

(1*R*,2*R*,5*S*)-3-(9-Fluorenylmethoxycarbonyl)-6,8-dioxa-3-azabicyclo[3.2.1]octane-2-*exo*-carboxylic Acid (13)

A soln of **12** (55 mg, 0.14 mmol) in MeCN (2 mL) and 4 M HCl (3 mL) was refluxed for 16 h, and then the solvent was evaporated in vacuo. The white solid was treated with Et_2O (10 mL), and the soln was filtered and evaporated. This gave a yellow solid, which was purified by flash chromatography (silica gel, CH_2Cl_2–MeOH, 20:1, buffered with 0.1% TFA), to give **13** as a white solid; yield: 40 mg (75%).

Mp 86–88 °C; $[\alpha]_D^{25}$ +62.9 (c 0.5, CH_2Cl_2); R_f = 0.2 (CH_2Cl_2–MeOH, 20:1, buffered with 0.1% TFA).

IR ($CDCl_3$): 3066, 2960, 2900, 1709, 1451, 1413 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) (3:2 mixture of rotamers): δ = 10.34 (br, 1 H, COOH), 7.75 (m, 2 H, Ar), 7.60–7.27 (m, 6 H, Ar), 5.55 and 5.53 (s, 1 H, H-5), 5.04 (d, *J* = 4.6 Hz, 3/5 H, H-1, rot. A), 4.86 (m, 2/5 H, H-1, rot. B), 4.66–3.67 (m, 7 H), 3.36 (d, *J* = 12.8 Hz, 3/5 H, H-4, rot. A), 3.19 (d, *J* = 13.0 Hz, 2/5 H, H-4, rot. B).

^{13}C NMR (50 MHz, $CDCl_3$) (mixture of rotamers): δ = 173.5 and 173.3 (s, O–C=O), 156.5 and 155.4 (s, N–C=O), 143.2 (s, 2 C, Ar), 140.9 (s, 2 C, Ar), 128.4 (d, 2 C, Ar), 127.5 (d, 2 C, Ar), 124.7 and 124.3 (d, 2 C, Ar), 119.7 (d, 2 C, Ar), 98.6 and 98.0 (d, C-5), 72.3 and 71.8 (d, C-1), 67.9 (t), 67.3 and 66.9 (t, C-7), 58.7 and 58.4 (d, C-2), 47.1 and 46.7 (t, C-4), 46.8 (d).

MS (EI, 70 eV): *m*/*z* (%) = 381 (0.3) [M$^+$], 178 (100).

Anal. Calcd for $C_{21}H_{19}NO_6$: C, 66.13; H, 5.02; N, 3.67. Found: C, 66.05; H, 4.92; N, 3.65.

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