With compliments of the Author
Synthesis of a Bicyclic Proline Analogue from L-Ascorbic Acid

Claudia Lalli, Andrea Trabocchi,* Francesco Guarna, Claudia Mannino, Antonio Guarna

Dipartimento di Chimica Organica “Ugo Schiff” and Laboratorio di Progettazione, Sintesi e Studio di Eterocicli Biologicamente Attivi (HeteroBioLab), Università degli Studi di Firenze, Via della Lastruccia 13, 50019 Sesto Fiorentino (FI), Italy
Fax +39(055)4573531; E-mail: andrea.trabocchi@unifi.it
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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. Therefore, there is an ever-increasing need for versatile scaffolds, including new amino acid templates, to be applied in peptidomimetic design. Among the various approaches for mimicking peptide structures, numerous mimetics and analogues of proline have been developed and applied in the synthesis of biologically active compounds, especially with the aim of modulating the cis/trans isomerism of acyl–proline bonds, and producing proline-like reverse turn inducers.

Since the development of the first examples of 6,8-dioxo-3-azabicyclo[3.2.1]octan-based scaffolds (BTAs, see Figure 1), functionalities have been introduced at positions 3, 4, 5, and 7, 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.

Recently, we moved from tartaric acid to sugars as building blocks for new versatile scaffolds in enantiopure form with complete control of the stereochemistry. 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 and bicyclic proline mimetics starting from serine and glyceraldehyde derivatives. We reasoned that starting from L-ascorbic acid derivative (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 and L-hexoses. Moreover, the use of such an inexpensive starting material is an advantage in multigram-scale organic synthesis.

Thus, starting from triflate 2, obtained from the protected L-ascorbic acid derivative 1, compound 4 was obtained in 99% yield by nucleophilic substitution with aminoacetaldehyde dimethyl acetal at room temperature and after overnight stirring (Scheme 1). Further protection gave Fmoc urethane 5, which was obtained with 9-fluorenylethyl chloroformate in 1,4-dioxane as solvent, whereas N-(9-fluorenylethoxycarbonyloxy)succinimide did not yield any product. Then, Fmoc derivative 5 was subjected to acid cyclization at 0 °C, according to reported procedures, to afford 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-
folds proved to be problematic and low yielding, as previously reported (see Figure 1, structure A). 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 \( \alpha \)-amino acid with an endo-carboxy group from L-ascorbic acid](image)

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, 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 anhimeric 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 \( \alpha \)-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 \( \alpha \)-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 \( \alpha \)-amino acid with an exo-carboxy group from L-ascorbic acid](image)

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\(_2\)Cl\(_2\) or CDCl\(_3\) solns were recorded on a Perkin-Elmer 881 spectrophotometer. Mass spectra were carried out with a Shimadzu spectrometer.
operating with El 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)-(1-S)-2,2-Dimethyl-1,3-dioxolan-4-yl[(trifluoromethyl) sulfonyloxy]acetate (2)**

A soln of 1 (5.00 g, 26.3 mmol) in dry CH2Cl2 (45.5 mL) was cooled to −10 °C, and precooled dry pyridine (4.50 mL) was added. Then a soln of Tf2O (7.30 mL, 34.2 mmol) in dry CH2Cl2 (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. NaHCO3 soln (3 × 50 mL), the organic layer was dried (Na2SO4), 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: 9.48 g (99%).

**IR (CDCl3):** 3052, 2986, 1733, 1265 cm−1.

**1H NMR (400 MHz, CDCl3):** 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, 4.7 Hz, 1 H, CH2), 3.88 (s, 3 H, OCH3), 1.45 (s, 3 H, CH3), 1.36 (s, 3 H, CH3).

**13C NMR (100 MHz, CDCl3):** δ = 121.5 (s, CF3), 111.1 (s, C(CH3)2), 74.1 (d, TfOCH), 65.4 (t, CH3), 53.9 (q, OCH3), 25.9 (q, CH3), 25.0 (q, CH3).

**MS (EI, 70 eV):** m/z (% = 344 (17) [M+], 100 (100), 77 (77).

Anal. Calcd for C12H23NO6: C, 51.97; H, 8.40; N, 5.05. Found: C, 51.84; H, 8.40; N, 5.12.

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**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 CH2Cl2 (20 mL) was cooled to 0 °C under N2, and then a soln of 3 (0.50 mL, 4.81 mmol) and DIPEA (1.40 mL, 8.02 mmol) in dry CH2Cl2 (20 mL) was added. The mixture was stirred at r.t. for 15 h, and then it was extracted with 3 × 40 mL. The organic layer was dried (Na2SO4), 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%).

**IR (CDCl3):** 2991, 2955, 2836, 1733, 1250, 1219 cm−1.

**1H NMR (400 MHz, CDCl3):** δ = 4.41 (t, J = 4.8 Hz, 1 H, OCH2(CMe)2), 4.18–4.14 (m, 1 H, ring H-4), 4.07–4.00 (m, 2 H, ring CH2), 3.76 (3 H, CO2CH3), 3.35 (3 H, OCH3), 3.23 (s, 3 H, OCH3), 2.76 (d, J = 7.3 Hz, 1 H, CH2NH), 2.67 (dd, J = 12.1, 6.5 Hz, 1 H, CH2NH), 2.63 (dd, J = 12.1, 4.6 Hz, 1 H, CH2NH), 1.72 (br, 1 H, NH), 1.41 (s, 3 H, CH3), 1.31 (s, 3 H, CH3).

**13C NMR (100 MHz, CDCl3):** δ = 173.3 (s, C=O), 109.7 (s, 103.5 [d, CH(OMe)], 76.8 [d, CHOC(CH3)2], 67.1 [t, CH2NH], 64.4 [d, CHCO(Me)], 53.9 [q, OCH3], 53.2 [q, OCH3], 51.9 [q, OCH3], 49.5 [t, ring CH2], 26.7 [q, CH3], 25.3 [q, CH3].

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

Anal. Calcd for C8H15NO3C: C, 51.97; H, 8.36; N, 5.05. Found: C, 51.84; H, 8.40; N, 5.12.

**Methyl (S)-(2,2-Dimethoxyethyl)[2H-fluoren-9-ylethynylcarbonyl]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 N2, 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 CH2Cl2 (20 mL), and the soln was washed with 5% citric acid soln (3 × 20 mL). The organic layer was dried (Na2SO4), 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: 107 g (97%).
1^1C NMR (50 MHz, CDCl₃): δ = 165.0 (s, C=O), 121.5 (s, C₆H₅), 110.9 (s, C(CH₃)), 81.0 (d, TiOCH), 74.0 (d, ring H-4), 65.4 (t, CH₃), 53.5 (q, O CH₃), 25.8 (d, OCH₃), 24.9 (q, CH₃).

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 solution of 9 (136 mg, 0.42 mmol) in dry CH₂Cl₂ (2.1 mL) was cooled to 0 °C under N₂, and then a solution of 3 (56 µL, 0.51 mmol) and DIPEA (144 µL, 0.84 mmol) in dry CH₂Cl₂ (2.1 mL) was added. The mixture was stirred under N₂ at r.t. overnight, and then neutralized with NaHCO₃. The organic layer was separated, dried (Na₂SO₄), 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%).

IR (CHCl₃): 2954, 2927, 1752, 1708, 1269 cm⁻¹.

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References


