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A concise, asymmetric synthesis of (2*R*,3*R*)-3-hydroxyaspartic acid

Short Communication

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Summary. 3-Hydroxyaspartic acid and its derivatives are found both in the free form and as peptide constituents in various microorganisms and fungi. Considering the biological importance of this amino acid and its potential utility as a multifunctional building block in organic syntheses, we have developed a short-step, asymmetric synthetic route to a strategically protected 3-hydroxyaspartic acid derivative in enantiopure form. The key steps in the synthesis involve, Sharpless asymmetric aminohydroxylation of commercially available *trans*-ethyl cinnamate, and, utilization of the phenyl group as a masked carboxylic acid synthon towards construction of the complete structural framework of the title compound.

Keywords: Non-proteinogenic amino acid – Sharpless asymmetric aminohydroxylation – Exhaustive oxidation – Orthogonally protected functional groups

Introduction

Different stereoisomers of β-hydroxyaspartic acid and derivatives thereof are found as the free amino acid and as peptide constituents in various microorganisms and fungi (Wieland, 1961; Bulen and Lecomte, 1962; Kornberg and Morris, 1965; Ishiyama et al., 1975; Sugawara et al., 1984; Reshef and Carmeli, 2006). A number of macrocyclic peptide antibiotics, such as plusbacins (Shoji et al., 1992), katanosins (Kato et al., 1988; Shoji et al., 1988), cepacidine A_1 (Lim et al., 1994), and Ramoplanin (Cavalleri et al., 1984; Pallanza et al., 1984; Ciabatti et al., 1989) contain the 3-hydroxyaspartic acid (or, 3-hydroxyasparagine) structural motif in their peptidic framework. Due to their strong antibacterial activity against vancomycin-resaistant entercocci (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) (Maki et al., 2001), several members of the plusbacin and katanosin family of compounds are of current interest as new generations of antibacterial agents (Guzman et al., 2007; von Nussbaum et al., 2007; Wohlrab et al., 2007). Interestingly, L-*threo*-β-hydroxyaspartic acid itself display significant inhibitory activity against various strains of human pathogenic fungi (Zygmunt et al., 1963; Ishiyama et al., 1975). Free 3-hydroxyaspartic acid has also been detected in human urine (Ikegami, 1975). Several vitamin K dependent plasma proteins involved in the blood clotting cascade were found to contain the (*2S*,3*R*)-3-hydroxyaspartic acid diastereoisomer, although its biological role and function in these proteins have not yet been elucidated (Fernlund and Stenflo, 1983; Sugo et al., 1984). Additionally, in studies involving excitatory amino acid transporters, 3-*O*-benzyl-aspartic acid derivatives were found to be efficient blockers of glutamate transporters in the central nervous system (Lebrun et al., 1997; Shimamoto et al., 2000; Shigeri et al., 2001). In a more recent study, L-*erythro*-β-hydroxyaspartic acid was among the most potent inhibitors of mouse serine racemase (mSR), an enzyme which catalyzes the biosynthesis of D-serine, an *N*-methyl-D-aspartate (NMDA) receptor coagonist in the brain (Strisovsky et al., 2005).

From an organic synthesis perspective, enantiopure 3-hydroxyaspartic acids also represent multifunctional building blocks of potential utility in various synthetic endeavors (Kollonitsch et al., 1979; Mattingly et al., 1983; Palomo et al., 1992). Consequently, development of methods for the stereoselective synthesis of the various 3-hydroxyaspartic acids is an active area of research (Mattingly et al., 1983; Hansson and Kihlberg, 1986; Wagner and Tilley, 1990; Palomo et al., 1992; Hanessian and Vanasse, 1993; Fernandez-Megia et al., 1994; Charvillon and Amouroux,

1997; Merino et al., 1998; Cardillo et al., 1999; Boger et al., 2000; Shimamoto et al., 2000; Zhang et al., 2000; Dudding et al., 2002; De Angelis and Campiani, 2004).

In continuation of our studies on the synthesis of bioactive amino acids (Khalaf and Datta, 2004; Liang and Datta, 2005), we report herein the results of our efforts culminating in an efficient asymmetric synthetic route to a strategically protected (*2R*,3*R*)-3-hydroxyaspartic acid intermediate, as well as the subsequent fully deprotected parent amino acid, in enantiopure form.

Materials and methods

General remarks

All of the solvents and reagents used were obtained commercially and used as such, unless noted otherwise. Moisture-sensitive reactions were performed under a positive pressure of argon, using oven-dried glassware (120 °C), unless otherwise noted. The silica gel (230–400 mesh) used for flash column chromatography was purchased from Sorbent Technologies, while thin layer chromatography was performed using Silica Gel HLF Uniplates™, purchased from Analtech Inc. All the reaction products were concentrated and dried using standard rotavap and high-vacuum techniques. Proton and carbon nuclear magnetic resonance spectra were recorded using Bruker DRX 400 MHz, or Bruker DRX 500 MHz, or Bruker DRX 800 MHz spectrometers. All chemical shifts (δ) were recorded as parts per million (ppm), and all samples were dissolved in $CDCl_3$ using residual solvent peak as internal standard unless otherwise noted. Mass spectra were obtained from a ZAB HS mass spectrometer equipped with a 11/250 data system. Fast-atom bombardment mass spectrometry (FAB-MS) experiments were performed with a Xenon gun operated at 8 Kev energy and 0.8 mA emission at the MS laboratory at the University of Kansas. Fast-atom bombardment high resolution mass spectra (FAB-HRMS) were recorded at 1:10,000 resolution using linear voltage scans under data system control and collected in a multi-channel analyzer mode (MCA). HPLC analyses were carried out using a Shimadzu LC-6AL liquid chromatograph coupled to a SPD-20A prominence UV/VIS detector. All columns were purchased from Agilent. A Shimadzu FTIR-8400S spectrophotometer was used to record infrared spectra. Optical rotations were obtained using an Autopol IV Automatic Polarimeter at room temperature. Melting points were obtained using a Thomas Hoover Uni-melt capillary melting point apparatus and are uncorrected.

*Preparation of (2R,3S)-ethyl 3-(tert-butoxycarbonylamino)-2-hydroxy-3-phenylpropanoate (**2**)*

To a magnetically stirred solution of *tert*-butyl carbamate (3.63 g, 31.0 mmol) in *n*-propyl alcohol (40 ml) was added an aqueous solution of NaOH (1.22 g, 30.5 mmol in 75 ml of H_2O), followed by a freshly prepared solution of *tert*-butyl hypochlorite (3.31 g, 30.5 mmol, ca. 3.5 ml). Subsequently, a solution of the ligand $(DHQ)_2PHAL$ (400 mg, 0.5 mmol, 5 mol%) dissolved in *n*-propyl alcohol (35 ml) was added to the reaction mixture and stirred until homogenous (approx. 10 min). Ethyl cinnamate (**1**) (1.76 g, 10 mmol) and the osmium catalyst $K_2O_sO_4 \cdot 2H_2O$ (147 mg, 0.4 mmol, 4 mol%) was then added sequentially to the mixture and stirring continued for 1 h. The reaction mixture was diluted with EtOAc (70 ml), the organic layer separated, and the aqueous layer was extracted with EtOAc (3 × 50 ml). The combined organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. Purification of the crude product by flash column chromatography (hexane/EtOAc = 4:1 to 7:3) afforded the amino alcohol derivative **2** as a white solid (2.4 g, 78%): mp = 124–126 °C {Ref. (Commerçon et al., 1992) mp = 124 °C)}; $[\alpha]_D$ + 6.2 (c 1.02, $CHCl_3$) {Ref. (Commerçon et al., 1992) $[\alpha]_D$ +6.3 (c = 1, $CHCl_3$)}; IR (NaCl): 3506, 3389, 1728, 1686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.35 (t, *J* = 7.81 Hz, 3H), 1.43 (s, 9H), 3.18 (s, 1H, exchangeable with D_2O), 4.29–4.37 (m, 2H), 4.45 (br s, 1H), 5.27 (d, *J* = 9.4 Hz, 1H), 5.45 (d, *J* = 8.72 Hz, 1H), 7.31–7.41 (m, 5H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.1, 28.3, 55.9, 62.5, 73.6, 79.8, 126.7, 127.7, 128.6, 139.3, 155.1, 173.0 ppm; HRMS (ES+) calcd for $C_{16}H_{23}NO_5$ *m*/*z* $(M + Na)^+$ 332.1474, found 332.1474. HPLC: Zorbax SB-C18 column, 3.5 μm, 3.0 × 150 mm, MeCN/H_2O, 1 ml/min, 254 nm, t_R = 16.9 min (97% ee).

*Preparation of (4S,5R)-3-tert-butyl-5-ethyl-2,2-dimethyl-4-phenyloxazolidine-3,5-dicarboxylate (**3**)*

The amino alcohol **2** (1.3 g, 4.2 mmol) was dissolved in a mixture of acetone (15 ml) and 2,2-dimethoxypropane (10 ml) and a catalytic amount of $BF_3 \cdot Et_2O$ (0.1 ml) was added to it. The resulting solution was stirred at room temperature for 4 h. The reaction was quenched with NEt_3 (0.2 ml), and the solvent was removed under vacuum. Purification of the residue by flash column chromatography (hexane/EtOAc = 95:5) yielded the acetonide **3** as a colorless oil (1.2 g, 82%): $[\alpha]_D$ −8.0 (c 1.02, $CHCl_3$) {lit. (Commerçon et al., 1992) $[\alpha]_D$ −7.3 (c = 1.0, $CHCl_3$)}; IR (NaCl): 1759, 1701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotameric mixtures): δ = 1.09, 1.34 (2 br s, 9H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.72, 1.80 (s, 6H), 4.27–4.31 (q, *J* = 6.1 Hz, 2H), 4.48 (d, *J* = 5.2 Hz, 1H), 5.04, 5.31 (2br s, 1H), 7.31–7.39 (m, 5H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$, rotameric mixtures): δ = 14.1, 28.0, 61.7, 63.9, 76.7, 80.2, 81.0, 96.9, 126.3, 127.6, 128.5, 151.6, 170.2 ppm; HRMS (ES+) calcd for $C_{19}H_{27}NO_5$ *m*/*z* $(M + Na)^+$ 372.1787, found 372.1795.

*Preparation of (4R,5R)-3-(tert-butoxycarbonyl)-5-(ethoxycarbonyl)-2,2-dimethyloxazolidine-4-carboxylic acid (**4**)*

To a well-stirred, room temperaure solution of $NaIO_4$ (8.0 g, 37.4 mmol) dissolved in H_2O (20 ml) was added a solution of the acetonide **3** (0.86 g, 2.46 mmol) in CH_3CN–CCl_4 (20 ml; 1:1). The resulting mixture was stirred for 15 min, followed by addition of $RuCl_3 \cdot H_2O$ (0.06 g, 29 mmol) in one portion. After stirring for 24 h at room temperature, the reaction mixture was diluted with EtOAc (20 ml) and filtered. After washing the residue with EtOAc, the organic layer was separated from the filtrate and the aqueous layer was extracted with EtOAc (3 × 10 ml). The combined organic layer was extracted with a saturated solution of $NaHCO_3$ (5 × 50 ml) and the combined $NaCHO_3$ extracts was washed once with CH_2Cl_2. After cooling to 0 °C (ice-bath), the above aqueous solution was acidified carefully to pH 2-3 by addition of a saturated solution of $KHSO_4$. The resulting solution was saturated with NaCl and extracted thoroughly with EtOAc (7 × 100 ml). The combined organic extracts were concentrated and the residual oil was purified by flash chromatography (hexane/EtOAc = 2:3 to 1:3) to afford the 3-hydroxyaspartic acid derivative **4** as a colorless oil (0.554 g, 71%): $[\alpha]_D$ −5.6 (c 1.01, $CHCl_3$); IR (NaCl) 2982, 1755, 1739, 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotameric mixtures): δ = 1.32 (t, *J* = 6.4 Hz, 3H), 1.40, 1.49 (2s, 9H), 1.60, 1.63 (2s, 6H), 4.28–4.39 (m, 2H), 4.70 (d, *J* = 4.9 Hz, 1H), 4.86 (s, 1H), 7.10 (br s, 1H, exchangeable with D_2O) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$, rotameric mixtures): δ = 14.1, 24.7, 25.2, 26.2, 26.4, 27.1, 28.2, 28.3, 45.4, 49.6, 61.4, 61.6, 62.2, 62.3, 74.4, 75.8, 76.3, 81.4, 82.2, 96.9, 97.5, 150.8, 152.3, 169.3, 169.5, 174.3, 175.7 ppm; HRMS (ES+) calcd for $C_{14}H_{23}NO_7$ *m*/*z* $(M + Na)^+$ 340.1372, found 340.1368.

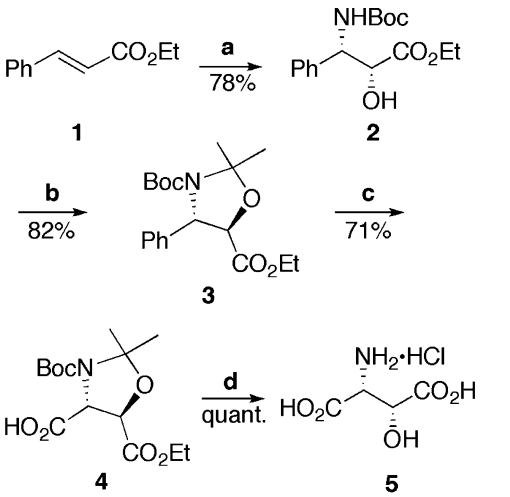
*Preparation of (2R,3R)-3-hydroxyaspartic acid hydrochloride (**5**)*

The protected hydroxyaspartic acid derivative **4** (78 mg, 0.25 mmol) was taken in 6 N HCl (5 ml) and refluxed for 2 h. The reaction mixture was cooled to room temperature and extracted once with CH_2Cl_2 (10 ml) to

remove any organic soluble impurities. Concentration of the aqueous layer under vacuum followed by overnight drying of the residue under high vacuum afforded the desired 3-hydroxyaspartic acid hydrochloride **5** as a light yellow solid (45 mg, quantitative): $[\alpha]_D$ +7.2 (c 0.8, 5N HCl) {Ref. (Dudding et al., 2002; Cardillo et al., 1999) $[\alpha]_D$ +7.5 (c = 1, 5N HCl)}; ^{1}H NMR (400 MHz, D_2O): $\delta = 4.45$ (d, $J = 2.6$ Hz, 1H), 4.87 (d, $J = 2.6$ Hz, 1H) ppm; ^{13}C NMR (100.6 MHz, D_2O): $\delta = 55.2$, 68.4, 169.5, 173.1 ppm; HRMS (ES+) calcd for $C_4H_7NO_5$ (free amine) m/z $(M+H)^+$ 150.0402, found 150.0402.

Results and discussion

Readily available *trans*-ethyl cinnamate, containing an optimum carbon framework and appropriate functionalities as necessary for the desired transformations, was envisioned to be an ideal starting point for our proposed synthesis. The key steps in the synthetic strategy involved an initial regio- and stereoselective incorporation of the *syn*-1,2-aminoalcohol motif utilizing the enone moiety of the starting cinnamate, followed by utilization of its phenyl group as a masked carboxylic acid precursor towards installation of the second carboxylic acid functionality as present in the target product. Accordingly, employing the standard Sharpless asymmetric aminohydroxylation (SAA) protocol (Reddy and Sharpless, 1998; Bodkin and McLeod, 2002; Montiel-Smith et al., 2002), *trans*-ethyl cinnamate (**1**) was efficiently converted to the corresponding *syn*-1,2-aminoalcohol derivative **2** (Scheme 1) in a highly regio- and stereoselective manner. High resolution NMR, mass spectral study and HPLC analysis of the *N*-Boc-aminoalcohol **2** confirmed its assigned structure and stereochemical integrity. Subsequent acetonide protection of the hydroxyl and the amine functionality resulted in the uneventful formation of the fully protected oxazolidine derivative **3** in good yield. The spectral and analytical data of intermediates **2** and **3** were in good agreement with the literature reported values (Commerçon et al., 1992). Exhaustive oxidative degradation of the strategic phenyl group of **3** installed the second carboxylic acid functionality of the aspartic acid framework, providing the orthogonally protected (2*R*,3*R*)-3-hydroxyaspartic acid derivative **4** in good overall yield. A noteworthy feature of compound **4** is its differentially protected functionalities, offering a convenient handle towards easy and selective manipulation of these groups for further synthetic transformations. Finally, a one-pot global removal of all the protecting groups culminated in a concise synthetic route to enantiopure (2*R*,3*R*)-3-hydroxyaspartic acid (**5**) as its hydrochloride salt. The structural and analytical data of **5** were in good agreement with the literature reported values (Cardillo et al., 1999; Dudding et al., 2002), thereby reconfirming the structural assignment and stereochemical integrity of the product.



a. $BocNH_2$, t-BuOCl, $K_2OsO_4 \cdot 2H_2O$, $(DHQ)_2PHAL$, aq. NaOH, n-PrOH. **b.** $Me_2C(OMe)_2$, $BF_3 \cdot Et_2O$. **c.** $NaIO_4$, $RuCl_3 \cdot xH_2O$, MeCN-CCl_4-H_2O. **d.** 6 N HCl, Δ

Scheme 1

In conclusion, although several methods have been reported for the stereoselective synthesis of various 3-hydroxyaspartic acid derivatives, many of these routes entail often-lengthy reaction sequence to accomplish the desired synthesis. In contrast, the present catalytic asymmetric synthetic approach involves a relatively short synthetic sequence (4 steps), leading to the title compound in good overall yield (45%). Additionally, the penultimate intermediate **4** provides a strategically protected aspartic acid derivative for further synthetic transformation (e.g. peptidic coupling, etc.). In summary, the efficiency, brevity, and easy scalability of the present synthesis compares favourably with the literature reported methods, and is expected to provide an attractive alternative pathway to access the above class of structurally and biologically important amino acid.

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