Synthesis of 2-aminosuberic acid derivatives as components of some histone deacetylase inhibiting cyclic tetrapeptides

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Full Research Paper

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Keywords:
α-amino acid; catalysis; chiral pool; cross metathesis; cyclic peptides

Received: 03 August 2017
Accepted: 25 September 2017
Published: 17 October 2017

Abstract
A new synthesis of the important amino acid 2-aminosuberic acid from aspartic acid is reported. The methodology involves the alternate preparation of (S)-2-aminohept-6-enoate ester as a building block and its diversification through a cross-metathesis reaction to prepare the title compounds. The utility of the protocol is demonstrated through the preparation of three suberic acid derivatives of relevance to the design and the synthesis of peptides of biological relevance.

Results and Discussion
Our synthesis started with the preparation of bishomoallylglycine derivative 11 (Scheme 1) from the known aspartic acid derived aldehyde 4 [13]. The latter was converted to its doubly homologated derivative 8 through four conventional steps viz. HWE-type olefination leading to the unsaturated ester 5, satura-
Figure 1: Biologically active naturally occurring cyclic tetrapeptide HDAC inhibitors.

Scheme 1: Reagents and conditions: (i) Triethyl phosphonoacetate, n-Bu4N+I−, aq K2CO3, rt, 18 h, 86%; (ii) H2, Pd/C, EtOAc, rt, 6 h, 83%; (iii) LAH, THF, 0 °C to rt, 2 h, 81%; (iv) (COCl)2, DMSO, N-methylmorpholine, CH2Cl2, −78 °C to 0 °C; (v) MePh3PBr, n-BuLi, THF, 0 °C, 3 h, 72% over two steps; (vi) chromic acid, acetone, 2 h, 73%; (vii) Cs2CO3, CH3I, DMF, 2 h, 88%.

Having access to the building block 11, we focused on its conversion to the targeted Asu derivatives through cross metathesis (CM) [20] with conjugated olefins 13a–d (Scheme 2).

In recent years, the cross-metathesis reaction has emerged as a valuable tool in the preparation of α-amino acids [21-27] and few useful general guidelines have emerged from these studies. Pleasingly, cross metathesis of our building block 11 with tert-butyl acrylate (13a) proceeded quickly in the presence of Grubbs’ 2nd generation catalyst [(1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)(trichlorohexylphosphine)ruthenium, 12] in refluxing dichloromethane and the product 14a was obtained in good yield. The corresponding reaction of 11 with benzyl acrylate (13b) proceeded with similar facility, yield and isomeric composition. Although the cross-metathesis reaction with α,β-unsaturated esters and ketones have been extensively studied, the corresponding reactions with amides and anilides are less documented [28]. An elegant solution to one of this problems is the use of acryloyl chloride as CM partner followed by functionali-
Scheme 2: Reagents and conditions: (i) Grubbs’ catalyst 12 (2.5 mol %), DCM, reflux, 2 h, 14a, 83%; 14b, 90%; 14c, 88%; (ii) H₂, Pd/C, MeOH, rt, 2 h, 15a, 79%; 15b, 82%; 15c, 90%.

zation of the cross product [29]. To our delight, the reaction of 11 with anilide 13c proceeded well under our developed conditions and the CM product was obtained as a single isomer (E-). Only a few successful reports on cross metathesis with Weinreb’s amide of acrylic acid, and N-alkylated acrylamides are known [30-33]. However, all attempts of CM reaction of 11 with the olefin 13d proved to be futile, a major problem being the inadequate solubility of the olefin in the reaction solvents tried, e.g., dichloromethane, dichloroethane, benzene, toluene etc. The solubility problem may be avoided by dilution and increasing the temperature but the reaction is too slow to be useful. The CM product 14a was then hydrogenated to obtain the known Asu derivative 15a [34] under conventional conditions. Similarly, the known N-Boc-L-Asu-OH (15b) [35] was obtained by hydrogenation of the benzyl ester 14b with concomitant saturation of the double bond. The conversion of 14c into 15c proceeded without events.

Conclusion
In conclusion, we have developed a modestly diversified synthesis of important Asu derivatives through an alternate preparation of the building block 11 of proven utility in the design and synthesis of peptidomimetics. A cross-metathesis reaction has been utilized to create the diversification on the template 11 in order to obtain orthogonally protected Asu derivatives. Moreover, the Asu derivative 15a has been demonstrated to be useful in the preparation of a plethora of HDAC inhibitors [34]. The methodology may therefore find application in the synthesis of related targets and may complement to the existing literature. The work will be continued to explore syntheses of other Asu derivatives using the developed methodology.

Experimental
General procedure for cross metathesis
This was carried out in a manner as described in [36]. Grubb’s second generation catalyst 12 (10 mg, 0.012 mmol, 2.5 mol %) was added to a stirring solution of olefin 11 (130 mg, 0.50 mmol) in dry DCM (1 mL) and then a solution of the appropriate electron-deficient olefin 13 (1.5 mmol) in dry DCM (1 mL) was added dropwise under an argon atmosphere. The resulting reaction mixture was then heated to reflux for 2 h. The reaction mixture was allowed to cool to room temperature and then concentrated in vacuo. The residue was subjected to column chromatographic purification over silica gel using an appropriate mixture of ethyl acetate in hexane to provide the coupled product as colorless viscous liquid.

(S,E)-1-tert-Butyl 8-methyl 7-(tert-butoxycarbonylamino)oct-2-enedioate (14a)
Colourless liquid. Yield: 148 mg, 83%; [α]D25 +12.60 (c 1.00, CHCl₃); IR (neat): 3363, 2978, 2933, 1715, 1652, 1505, 1367, 1164 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.81 (td, J = 6.8, 15.6 Hz, 1H), 5.74 (d, J = 15.6 Hz, 1H), 5.10 (d, J = 7.6 Hz, 1H), 4.31 (m, 1H), 3.74 (s, 3H), 2.23–2.17 (m, 2H), 1.81 (m, 1H), 1.65 (m, 1H), 1.58–1.48 (m, 11H), 1.44 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 173.2, 165.9, 155.3, 146.7, 123.6, 80.1, 79.9, 53.1, 52.3, 32.2, 31.4, 28.3, 28.1, 23.8 ppm; HRMS (TOF–MS ES⁺) m/z: [M + Na]⁺ calcd for C₁₈H₃₁NNaO₆, 380.2049; found, 380.2056.

Supporting Information
Supporting Information File 1
Experimental details and analytical data of all new compounds as well as copies of their ¹H and ¹³C NMR spectra. [http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-13-214-S1.pdf]

Acknowledgements
We are thankful to CSIR, New Delhi, for funds (02/0164/13/EMR-II), and fellowship to two of us (JPM, SS).

References