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USE OF L-ASPARTIC ACID β-SEMIALDEHYDE IN THE SYNTHESIS OF MORE COMPLEX NON PROTEIN AMINO ACIDS

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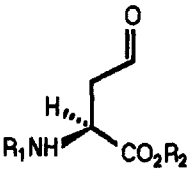
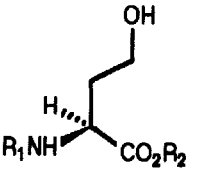
Summary: The potential of aspartic acid β-semialdehyde as a starting material for the synthesis of more complex amino acids is illustrated by its conversion to L-2-amino hept 4,6-dienoic acid and 2S,4R,5S-2-amino-4,5,6 trihydroxy hexanoic acid.

Aspartic acid β-semialdehyde (1) is an increasingly important synthetic intermediate.[1] The aldehyde function of (1) provides a useful handle for manipulation to more complex structures. We describe here some uses of (1).

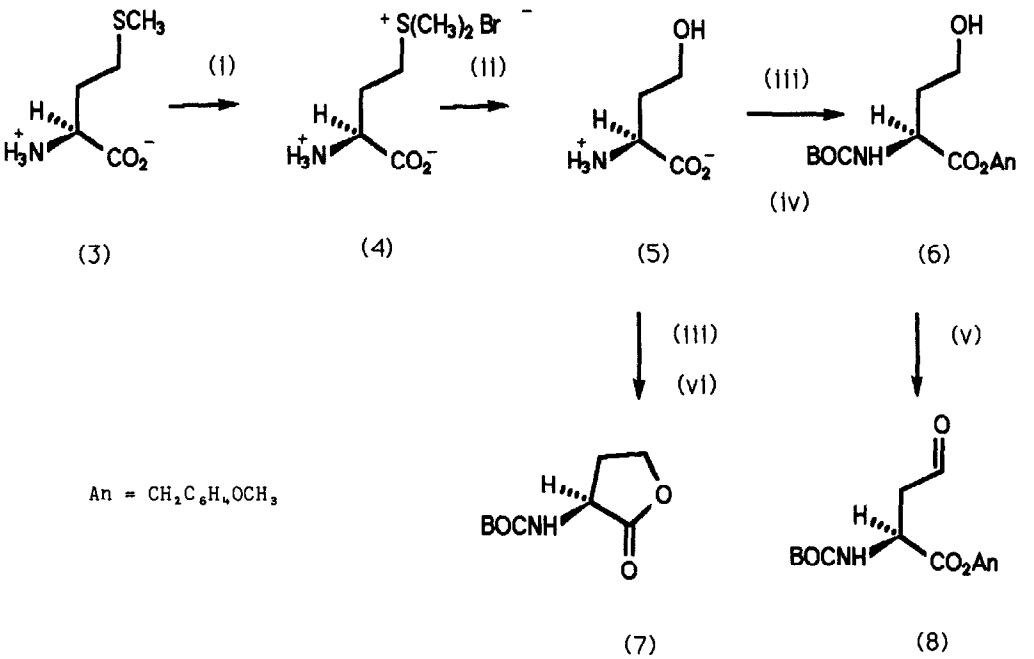


(1)



(2)

We required a convenient synthesis of (1) or alcohol (2) from inexpensive precursors. The route from BOC-L-Methionine[2] appeared attractive; however in our hands proved difficult.[3] The following procedure was found to work very well. The sulphonium salt of L-Methionine (4) prepared by reaction with CH_3Br, after removal of excess CH_3Br, was treated with $NaHCO_3$ to give an aqueous solution of L-homoserine (5), which was used directly. Protection on nitrogen then evaporation provided the sodium salt which was esterified to give the L-homoserine derivative (6). This alcohol (6) proved unstable to chromatography, cyclising to the lactone (7), therefore was oxidised directly with PCC to the aldehyde (8), $[\alpha]_D$ +14.0° ($CHCl_3$), in 40% yield from (3). Commercially available[4] L-homoserine (5) after protection and oxidation gives the aldehyde (8) $[\alpha]_D$ +12.3° ($CHCl_3$), in 44% yield. This implies that the conversion (3) to (5) must proceed in at least 90% yield. The transformation (3) to (8) is carried out in 'one pot' and represents a convenient and inexpensive preparation of this aldehyde (8).[5] A variation of this sequence involves acidification after the N-protection. This leads to the lactone (7), m.p. 125-126.5° (lit.,[2] 125-127°), $[\alpha]_D$ -29.5° (CH_3OH) (lit.,[2] D-enantiomer, +29°, CH_3OH), in 75% yield from (3).

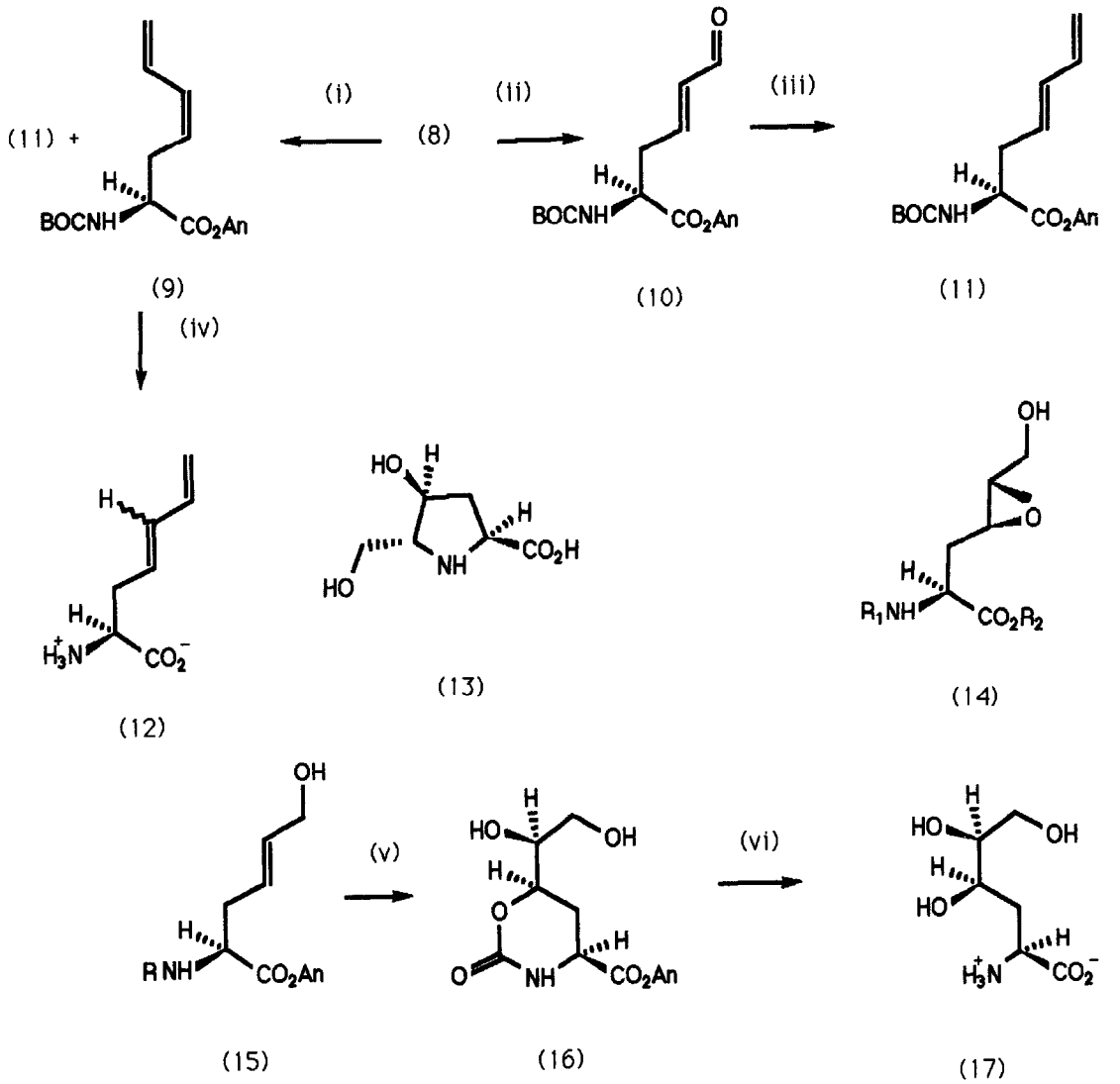


(i) excess CH_3Br, CH_3OH, H_2O, 18 hr; (ii) 1.0 $NaHCO_3$, reflux, 20 hr; (iii) 1.1 $(BOC)_2O$, 1.0 $NaHCO_3$, dioxane, 18 hr; (iv) $CH_3OC_6H_4CH_2Cl$, HMPA or DMF, 70 hr; (v) PCC, 4 Å molecular sieves, NaOAc, CH_2Cl_2, 90 min; (vi) 10% Citric acid, continuous extraction into EtOAc.

Aldehyde (8) reacts with allylidenetriphenylphosphorane to provide the dieneamincacid (9) as a 1:1 E:Z mixture, $[\alpha]_D$ -2.8° ($CHCl_3$), in 36% yield, and with the stabilised Wittig reagent, formylmethylenetriphenylphosphorane, to give the unsaturated aldehyde (10), $[\alpha]_D$ +1.3° ($CHCl_3$), in 75% yield. The E diene (11) is available from (10) as a crystalline solid, mp 54-55°, in 25% (unoptimised) yield by reaction with methylene triphenyl phosphorane. Deprotection of (9) with trifluoroacetic acid provided L-2-amino hept 4,6-dienoic acid (12),[6] in 81% yield.

The amino acid Bulgecinine (13), a natural amino acid[7] represents an attractive synthetic target.[8] We envisaged that N-cyclisation to an epoxide intermediate of structure (14) would furnish the Bulgecinine stereochemistry directly. Thus, the allyl alcohol (15 a) was prepared by treatment of (10) with ethanolic sodium borohydride, $[\alpha]_D$ -10.7° ($CHCl_3$), in 70% yield. Subjection of (15a) to the conditions of Sharpless[9] resulted in formation of the cyclic urethane derivative (16),[10] in 55-60% yield. The stereochemistry of (16) is assumed on the basis of the well established enantioface selectivity of the Sharpless epoxidation reaction.[9] The epoxide cleavage itself has several precedents.[11] Varying the N-protecting group to prevent its participation or encourage N-cyclisation VIZ with N-Tosyl (15 b), N-Trityl (15 c) and unprotected (15 d)[12] derivatives, led to complex mixtures of products.

Alkaline hydrolysis of (16) followed by purification by ion exchange chromatography provided the trihydroxy amino acid (17),[13] in 93% yield.



a R = BOC (i) $2Ph_3PCHCHCH_2$, -10°, THF, 5 min; (ii) $3Ph_3PCHCHO$, CH_2Cl_2, 20 hr;
b R = Ts (iii) $2Ph_3PCH_2$, THF, -10°, 5 min; (iv) 90% CF_3COOH, 2 hr, Ion
c R = Tr exchange chromatography; (v) 1.1 $Ti(o^iPr)_4$, 1.1 (+) DET, 2.1 ^tBuOOH,
d R = H CH_2Cl_2, -23°, 18 hr, then 10% tartaric acid, 1 hr, RT; (vi) 3NaOH,
CH_3OH, H_2O, 18 hr, 65° then ion exchange resin, dil. NH_3 elution.

This procedure allows potential access into a range of polyfunctional non protein and unnatural amino acids. The amino acid (16) itself and isomers available by varying the Sharpless reaction and olefin geometry have potential in the stereospecific synthesis of compounds such as the 4,5 dihydroxypipecolic acids.[14]

New compounds gave satisfactory spectroscopic and analytical data.

References and Notes

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2. R.D.G. Cooper, F. Jose, L. McShane and G.A. Koppel, Tet Lett., 1978, 2243. G.A. Koppel and R.D.G. Cooper, U.S. Patent, N^{O} 4,355,172 (1982).

3. The specific rotation of the lactone (7) obtained from the procedure of ref. 2 was -20.1° (CH_3OH) (lit.,[2] D-isomer +29°, CH_3OH). Modifying the procedure by substituting Bu_4NF treatment for the BuOK step gave lactone (7) with rotation -26.7° and improved yield.

4. Purchased from Aldrich Chemical Company.

5. Related reactions have been reported. See reference 2 above, K. Barlos, D. Theodoro poulos, Z. Naturforsch Teil., B, 1982, 37, 886. P. Friis, P. Helboe and P.O. Larsen Acta.Chem.Scandinavica, 1974, B28, 317 and references therein.

6. $[\alpha]_D$ -25.6 (H_2O), m.s m/z 142, MH^+ (DCI, NH_3), NMR (300 MHz, D_2O), δ_H 2.48 and 2.62 (m, 2H); 3.58 (dd, 1H, J = 5.36 and 6.7 Hz); 5.1-5.3 (m, 1.5H); 5.49 (m, 0.5H); 6.0-6.3 (m, 2.5H); 6.53 (m, 0.5H). (500 MHz) δ_C 29.95, 34.79, 55.49, 55.63, 118.82, 121.05, 125.36, 128.09, 132.57, 135.04, 137.09, 137.69, 175.22.

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10. Physical and analytical data for (16) mp 93.5-95°, $[\alpha]_D$ -37.6° ($CHCl_3$), IR, 1705 and 1740 cm^{-1}, m.s. m/z 325, M^+ (FD), NMR (300 MHz, $CDCl_3$), δ 1.82 (m, 1H); 2.50 (dm, 1H, J = 11.9 Hz); 3.68 (m, 3H); 3.78 (s, 3H); 4.15 (dd, 1H, J = 4.88 and 11.58 Hz); 4.30 (dd, 1H, J = 4.90 and 10.40 Hz); 5.11 (s, 2H); 6.87 (d, 2H, J = 8.4 Hz); 7.28 (d, 2H, J = 8.4 Hz). $C_{15}H_{19}NO_7$ requires C 55.38; H 5.89; N 4.30%, Found C 55.12; H 6.12; N 4.17%. ^1H NMR decoupling and ^{13}C NMR further confirm the structure of (16).

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12. Compound (14 d) was obtained by treating (14a) with 1.5 p Toluene sulphonic acid in vacuo and basifying. Reprotection with ditert butyldicarbonate/triethylamine regenerated (14) in 74% overall yield.

13. $[\alpha]_D$ +12° (H_2O), m.s m/z 162, $[(M-H_2O) + H]^+$ 179, $[(M-H_2O) + NH_4]^+$ (DCI, NH_3), NMR (300 MHz, D_2O) δ_H 1.67 (m, 1H); 2.10 (ddd, 1H, J = 2.57, 5.0 and 14.91 Hz); 3.4-3.8 (m, 5H), (500 MHz) δ_C 34.13 (CH_2), 54.98 (CH), 63.39 (CH_2), 71.67 (CH), 75.70 (CH), 175.79 (C).

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