## Synthesis of *N*-*t*-Boc-L-α-aminoadipic Acid 1-*t*-Butyl 6-Ethyl Ester from L-Aspartic Acid: A New Route to L-α-Aminoadipic Acid

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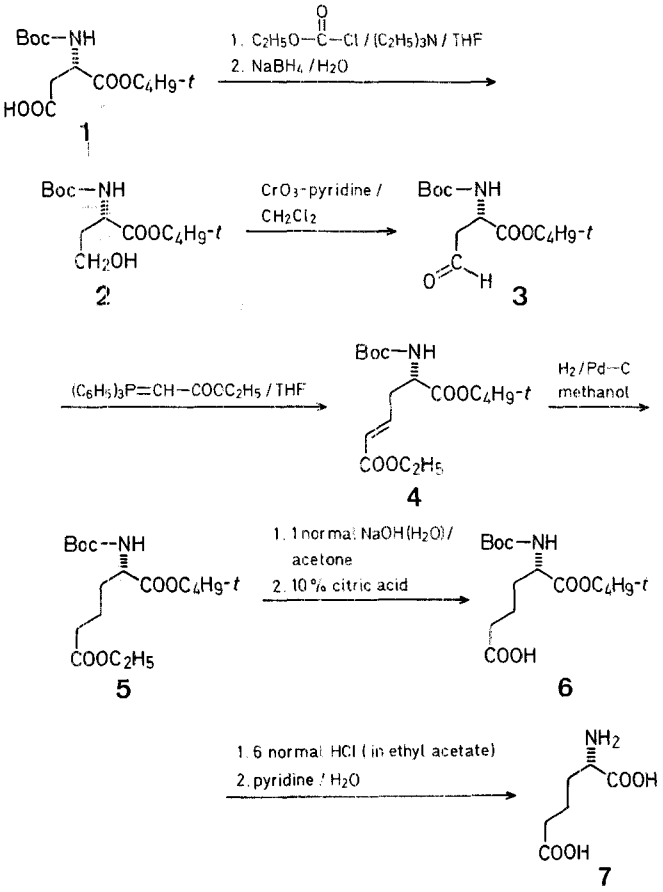
In conncetion with our interest and need for derivatives of L-α-aminoadipic acid suitably protected for use in peptide synthesis, we have developed a convenient method for the synthesis of the title compound from L-aspartic acid.

Interest in the synthesis of L-α-aminoadipic acid stems from the fact that it is one of the constituents of the Arnstein tripeptide[1], δ-(L-α-aminoadipyl)-L-cysteinyl-D-valine, a precursor[2] of the penicillins and cephalosporins. Various syntheses of L-α-aminoadipic acid have been reported[3-6]; all procedures have involved a resolution step except one method[6] which proceeded from L-lysine.

This paper presents the successful synthesis of *N*-*t*-Boc-L-α-aminoadipic acid 1-*t*-butyl 6-ethyl ester **(5)** and its conversion to L-α-aminoadipic acid **(7)** in which a key transformation involves a Wittig reaction with the γ-aldehyde derived from L-aspartic acid. This method provides directly L-α-aminoadipic acid having differentiated protecting groups already incorporated in the molecule. Previous syntheses furnished L-α-aminoadipic acid that would require additional protection for use in subsequent peptide syntheses.

Reduction of *N*-*t*-Boc-L-aspartic acid 1-*t*-butyl ester[7] **(1)** via the mixed carbonic anhydride with sodium borohydride[8] gives the corresponding *N*-*t*-Boc-L-homoserine *t*-butyl ester **(2)**. Oxidation of the alcohol **2** with chromium(VI) oxide-pyridine in dichloromethane[9] provides *t*-butyl L-2-(*t*-Boc-amino)-4-oxobutanoate **(3)** in 74% yield after column chromatography. Condensation of aldehyde **3** with ethoxycarbonylmethylenetriphenylphosphorane in dry tetrahydrofuran at 50°C for 24 h readily furnishes 1-*t*-butyl 6-ethyl L-(*E*)-2-(*t*-Boc-amino)-4-hexenedioate **(4)** in 72% yield. Hydrogenation of **4** over palladium/carbon in methanol provides 1-*t*-butyl 6-ethyl *N*-*t*-Boc-L-α-aminoadipate **(5)** in 93% yield. The two carboxy groups in **5** are protected with ester functions that can be selectively removed and, thereby, allow differentiation between the two carboxy groups in any subsequent transformations. Removal of the ethyl group from **5** is accomplished by the action of 1 normal sodum hydroxide in acetone at room temperature for 1 h, followed by acidification with 10% citric acid to give *N*-*t*-Boc-L-α-aminoadipic acid 1-*t*-butyl ester **(6)**. Simultaneous cleavage of the *N*-*t*-Boc and *t*-butyl ester groups from the amino acid **6** with 6 normal hydrogen chloride in ethyl acetate yields L-α-aminoadipic acid hydrochloride, from which L-α-aminoadipic acid **(7)** is obtained in good yields and in optically pure form.




Melting points were determined with a Thomas Hoover capillary melting point apparatus and are uncorrected. $^1$H-N.M.R. spectra were obtained for all compounds using a Varian EM360 and JEOL FX90Q spectrometers. Optical rotations were recorded on a Perkin-Elmer Model 241 polarimeter. Microanalyses were performed by M-H-W Laboratories, Pheonix, AZ. Tetrahydrofuran was distilled prior to use from sodium benzophenone ketyl or from lithium aluminum hydride. Dichloromethane was distilled from phosphorus pentoxide and stored over Linde 3A molecular sieves. Purified products were shown to be homogeneous by T.L.C. on silica gel plates (1″ × 3″) with visualization by iodine vapor. Column chromatography was performed using medium pressure liquid chromatography (M.P.L.C.) with glass columns packed with silica gel 60 (0.040–0.63 mm).

***N*-*t*-Boc-L-homoserine *t*-Butyl Ester (2):**

A solution of ethyl carbonochloridate (5.4 g, 50 mmol) in dry tetrahydrofuran (50 ml) is added to a solution of *N*-*t*-Boc-L-aspartic acid 1-*t*-butyl ester[7] (**1**; 14.45 g, 50 mmol) and triethylamine (5.05 g, 50 mmol)

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in tetrahydrofuran (50 ml) at −5 °C and the mixture is stirred for 30 min. Triethylammonium chloride is removed by filtration and the filtrate is added over a period of 15 min to a solution of sodium borohydride (3.7 g, 100 mmol) in water (25 ml) at 10–15 °C[8]. The mixture is stirrred at room temperature for 4 h, acidified with 3 normal hydrochloric acid, and extracted with ethyl acetate (2 × 100 ml). The organic extract is washed with aqueous 10% sodium hydroxide (100 ml), water (100 ml), and saturated sodium chloride solution (100 ml), and is dried with sodium sulfate. The filtrate is evaporated in vacuo and the resulting oil is chromatographed on silica gel using hexane/acetone (7/3) as eluent to give **2**; yield: 8.5 g (73%); $[\alpha]_D^{25}$: −37.5° (*c* 1, ethanol).

| | | | | |
|---|---|---|---|---|
| $C_{13}H_{25}NO_5$ | calc. | C 56.71 | H 9.15 | N 5.08 |
| (275.3) | found | 56.67 | 9.02 | 5.12 |

$^1$H-N.M.R. ($CDCl_3$/TMS): $\delta$ = 1.45 (s, 18 H, Boc and *t*-$C_4H_9$); 1.66–2.0 (m, 2 H, —$CH_2CH_2$—); 3.33–3.9 (m, 2 H, —$C\underline{H}_2OH$); 4.16–4.63 (m, 1 H, α-CH); 5.40 ppm (d, 1 H, NH).

**t-Butyl L-2-(t-Boc-amino)-4-oxobutanoate (3):**

Chromium(VI) oxide (20 g, 200 mmol) is added to a stirred solution of pyridine (35 g) in dry dichloromethane[9] (250 ml). The deep red solution is stirred for 15 min at room temperature. Then, a solution of compound **2** (13.5 g, 50 mmol) in dichloromethane (50 ml) is added in one portion and stirring is continued for 15 min at room temperature. The solution is decanted from the residue and the residue is washed with dichloromethane (100 ml). The combined organic phase is washed with aqueous 5% sodium hydroxide (3 × 200 ml), 5% hydrochloric acid (250 ml), aqueous 5% sodium hydrogen carbonate (250 ml), and saturated sodium chloride solution (200 ml), and is dried with sodium sulfate. The solvent is evaporated at reduced pressure and the residual crude **3** purified by column chromatography on silica gel using hexane/acetone (7/3) as eluent: yield of **3** as an oil: 10 g (74%); $[\alpha]_D^{25}$: −21.6° (*c* 1.5, ethanol).

| | | | | |
|---|---|---|---|---|
| $C_{13}N_{23}NO_5$ | calc. | C 57.13 | H 8.48 | N 5.12 |
| (273.3) | found | 56.93 | 8.30 | 4.82 |

$^1$H-N.M.R. ($CDCl_3$/TMS): $\delta$ = 1.45 (s, 18 H, Boc and *t*-$C_4H_9$); 3.00 (d, 2 H, $C\underline{H}_2$—CHO); 4.36–4.76 (m, 1 H, 2-H); 5.70 (d, 1 H, NH); 9.86 ppm (s, 1 H, CHO).

**1-t-Butyl 6-Ethyl L-(*E*)-2-(t-Boc-amino)-4-hexenedioate (4):**

A solution of aldehyde-ester **3** (9.0 g, 33 mmol) and ethoxycarbonylmethylenetriphenylphosphorane (17 g, 40 mmol) in dry tetrahydrofuran (100 ml) is stirred at 50 °C for 24 h. The mixture is then concentrated in vacuo and the crude product **4** chromatographed on silica gel using hexane/acetone (7/3) as eleuent; yield: 8.0 g (72%); m.p. 75–77 °C; $[\alpha]_D^{25}$: +4.2 (*c* 1, ethanol).

| | | | | |
|---|---|---|---|---|
| $C_{17}H_{29}O_6$ | calc. | C 59.45 | H 8.51 | H 4.07 |
| (343.4) | found | 59.66 | 8.34 | 4.15 |

$^1$H-N.M.R. ($CDCl_3$/TMS): $\delta$ = 1.26 (t, 3 H, $CH_2$—$C\underline{H}_3$); 1.44 (2 s, 18 H, Boc and *t*-$C_4H_9$); 2.62 (t, 2 H, 3,3-$H_2$); 4.17 (q, 2 H, $C\underline{H}_2$—$CH_3$); 5.1 (m, 1 H, 2-H); 5.86 (d, 1 H, C=CH, *J* = 16 Hz); 6.8 (m, 1 H, C=CH); 7.28 ppm (d, 1 H, NH).

**1-t-Butyl 6-Ethyl *N*-t-Boc-L-α-aminoadipate [5; 1-t-Butyl 6-Ethyl L-2-(t-Boc-amino)-hexanedioate]:**

The unsaturated diester **4** (8.0 g, 23 mmol) and 5% palladium on carbon (0.8 g) in methanol (100 ml) is shaken in a Parr apparatus under a hydrogen atmosphere for 12 h. The catalyst is filtered off and the filtrate concentrated to give **5** as an oil; yield: 7.5 g (93%); $[\alpha]_D^{25}$: +7.3° (*c* 1.5, chloroform).

| | | | | |
|---|---|---|---|---|
| $C_{17}H_{31}NO_6$ | calc. | C 59.11 | H 9.04 | N 4.05 |
| (345.4) | found | 59.13 | 8.86 | 4.21 |

$^1$H-N.M.R. ($CDCl_3$/TMS): $\delta$ = 1.16 (t, 3 H, $CH_2$—$C\underline{H}_3$); 1.46 (s, 18 H, Boc and *t*-$C_4H_9$); 1.6–2.6 (m, 6 H, $C\underline{H}_2$—$C\underline{H}_2$—$C\underline{H}_2$); 4.23 (m, 3 H, 2-H and $C\underline{H}_2$—$CH_3$); 5.45 ppm (d, 1 H, NH).

***N*-t-Boc-L-α-aminoadipic Acid 1-t-Butyl Ester [6, 1-t-Butyl L-2-(t-Boc-amino)-hexanedioate]:**

A solution of diester **5** (5.8 g, 17 mmol) and aqueous 1 normal sodium hydroxide (34 ml, 34 mmol) in acetone (35 ml) is stirred at room temperature for 1 h. The solution is then adjusted to pH 2–3 with 10% citric acid and the acetone is evaporated in vacuo. The aqueous phase is extracted with ethyl acetate (2 × 100 ml), the extract is washed with saturated sodium chloride solution (100 ml), dried with sodium sulfate, and evaporated in vacuo to give **6** as an oil; yield: 5.2 g (97%); $[\alpha]_D^{25}$: +5.8° (*c* 2, chloroform).

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|---|---|---|---|---|
| $C_{15}H_{27}NO_6$ | calc. | C 57.76 | H 8.57 | N 4.41 |
| (317.4) | found | 57.62 | 8.59 | 4.50 |

$^1$H-N.M.R. ($CDCl_3$/TMS): $\delta$ = 1.48 (s, 18 H, Boc and *t*-$C_4H_9$); 1.6–2.6 (m, 6 H, $C\underline{H}_2$—$C\underline{H}_2$—$C\underline{H}_2$); 4.26 (m, 1 H, 2-H); 5.33 ppm (d, 1 H, NH).

**L-α-Aminoadipic Acid (7, L-2-Aminohexanedioic Acid):**

A 6 normal solution of hydrogen chloride in ethyl acetate (20 ml) is added to a stirred ice-cold solution of aminoester **6** (2.2 g, 6.9 mmol) in ethyl acetate (20 ml) and stirring is continued for 2 h at room temperature. The solvent is evaporated in vacuo and the oily residue suspended in 0.1 normal hydrochloric acid (5 ml). This suspension is adjusted to pH 5 with pyridine and diluted with absolute ethanol (25 ml). The solution is cooled overnight, the crystalline product **7** isolated by suction, and dried; yield: 0.8 g (72%); m.p. 200–202 °C (Ref.[4], m.p. 205 °C); $[\alpha]_D^{25}$: +23.2° (c = 2, 5 normal hydrochloric acid [Ref.[5], $[\alpha]_D^{25}$: +23.5° (*c* 2, 5 normal hydrochloric acid)].

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