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SYNTHESIS OF N-BENZYLOXYCARBONYL-L-α-AMINOADIPIC ACID, α-BENZYL ESTER

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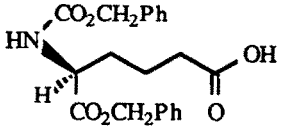
Abstract: A new synthesis of N-benzyloxycarbonyl-L-α-aminoadipic acid, α-benzyl ester (1) from L-lysine monohydrochloride (2) is reported.

Diprotected L-α-aminoadipic acid (1) is an important synthetic intermediate in the preparation of δ-(L-α-aminoadipoyl)-L-cysteinyl-D-valine (3),[1] and related peptides,[2] essential to studies on penicillin biosynthesis.[3] Conventional routes to (1) involve protection of the amino and α-carboxylate functionalities of L-α-aminoadipic acid, derived from natural sources or prepared synthetically. Since these steps proceed in only 40% yield overall, such routes are inefficient with respect to the value of the starting material. This synthesis shares its strategy with an earlier approach in preparing (1) from readily available L-lysine, without the intermediacy of L-α-aminoadipic acid.[4] The use of an alternative procedure to convert a primary amino group to a primary alcohol results in a facile and economical pathway to (1).



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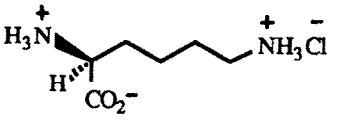

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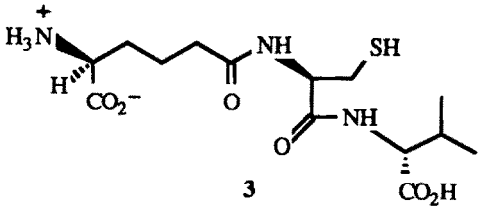

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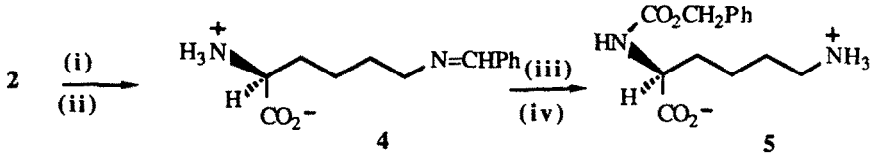
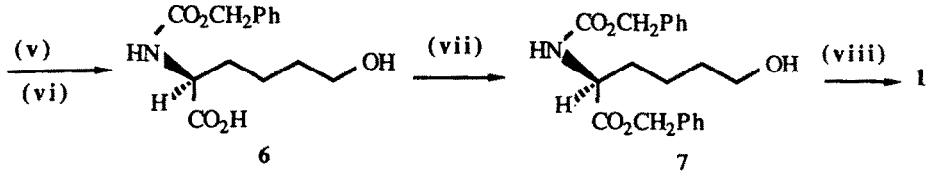
Selective N-α-protection of L-lysine was achieved by standard procedures.[5,6] The ε-amino group of (2) was masked by formation of the benzylidene imine (4), followed by urethane protection of the α-amino group and hydrolytic cleavage of the imine *in situ* to give N-α-benzyloxycarbonyl-L-lysine (5). Initially low yields in the urethane reaction were subsequently avoided using the low temperature modification described by Scott to reduce temperature dependent hydrolysis of the imine.[7]

A recent literature report described the use of sodium nitroprusside to convert L-lysine to piperidine -2-carboxylic acid.[8] This reaction is effectively a diazotization followed by intramolecular substitution. When the urethane (5) was treated with sodium nitroprusside at pH 9.5, the alcohol (6) was extracted as a yellow oil after removal of complex breakdown products. Reaction of (6) with benzyl bromide under anhydrous conditions gave the diprotected alcohol (7), further purified by silica gel chromatography. Conversion of (7) to the desired diprotected acid (1) required a simple oxidation, under relatively mild conditions. Oxidation of (7) with ruthenium tetroxide, generated in situ from sodium periodate and ruthenium (IV) oxide in a biphasic reaction mixture, gave (1) in 50% yield.





Reagents: (i) LiOH; (ii) PhCHO; (iii) $PhCH_2OCOCl$, NaOH; (iv) $H_3O^+ Cl^-$, 50°, 5 min. ; (v) $Na_2[Fe^{II}(CN)_5NO].2H_2O$, pH 9.5, 60°, 6.5 h. ; (vi) $H_3O^+ Cl^-$; (vii) $PhCH_2Br$, NEt_3; (viii) $RuO_2.H_2O$, $NaIO_4$, CCl_4, H_2O, CH_3CN.

In conclusion, this synthesis offers a facile and economical route to N-benzyloxycarbonyl-L-α-aminoadipic acid, α-benzyl ester in yields of approximately 20% from the readily prepared intermediate, N-α-benzyloxycarbonyl-L-lysine.

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EXPERIMENTAL

Reactions were monitored by TLC using Merck Kieselgel 60 F_{254} aluminium backed plates (0.2 mm layer thickness). TLC plates were visulized using a UV lamp or charring with 10% ammonium molybdate in 1.0 M H_2SO_4. Reaction mixtures were evaporated at 25°C on a Büchi rotovapor R110 followed by further evaporation under high vacuum. Melting points (m.p.) were determined on a Gallenkamp hot stage apparatus and are uncorrected. Flash chromatography was carried as described by Still.[9]

Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. IR spectra were recorded on a Perkin-Elmer 681 spectrophotometer and bands are designated broad (br), strong (s), medium (m), or weak (w). ^{1}H NMR spectra were recorded at 300 MHz on a Bruker WH 300 spectrometer, and internally referenced to residual protiated solvent species in deuterated organic solvents. ^{13}C NMR spectra were recorded at 62.8 MHz on a Bruker AM250 spectrometer and internally referenced to dioxan (aqueous), or $CDCl_3$ (organic). Multiplicities are designated singlet (s), doublet (d), triplet (t), quartet (q), or multiplet (m). Mass spectra were recorded on a V.G. Micromass 30F spectrometer in DCI (NH_3) mode. Microanalyses were performed by the Microanalytical Laboratory, Dyson Perrins Laboratory, University of Oxford. All reagents and solvents were either of superior quality or further purified[10] before use.

Preparation of N-ε-benzylidene -L-lysine (4).

L-lysine monohydrochloride (27.3 g, 0.15 mmol) was dissolved in 2M lithium hydroxide (75 ml, 0.15 mol), and the solution cooled to 4°C. Freshly distilled benzaldehyde (15.9 ml, 0.16 mol) was added, and the solution shaken vigorously. A white precipitate formed, the mixture set solid. After cooling at 4°C for 2 hours, cold ethanol (100 ml) was added, and the slurry filtered through sintered glass. The precipitate was resuspended in cold ethanol (2 x 30 ml) and refiltered. The product was dried in vacuo over phosphoric oxide to yield N-ε-benzylidene-L-lysine (4) as a fine white powder (28.9 g, 0.12 mol, 80%); m.p. 187-189°C; ν_{max} (Nujol) 1635 (C=N), 1595 (Ph), 1565 and 1395 (CO_2^-), 1500 (NH_2) cm^{-1}; m/z (DCI, NH_3) 235 (M^++1).

Preparation of N-α-benzyloxycarbonyl-L-lysine (5).

1M sodium hydroxide (100 ml) and ethanol (100 ml) were mixed, and the resultant mixture cooled to an internal temperature of -20°C. N-ε-benzylidene-L-lysine (23.4 g, 0.10 mol) was finely ground in a pestle, and added in a single portion to the reaction vessel. Almost immediately, precooled solutions of benzyloxycarbonyl chloride (95%, 31 ml, 0.2 mol), and 1M sodium hydroxide (250 ml, 0.25 mol) in ethanol (200 ml) were added alternately in portions, in equivalent amounts over ca. 30 minutes. The temperature of the reaction mixture was maintained between -15°C and -20°C throughout the additions. The mixture was stirred, with cooling, until the temperature began to rise again. After allowing the temperature to rise to -5°C, precooled hydrochloric acid (25 ml) was added, and the solution stirred for 5 minutes. The solution was warmed to 50°C for 5 minutes, and then concentrated on a rotary evaporator until all the ethanol had been removed. The soltuion was adjusted to pH 6.2, and left overnight at 4°C. Any brown precipitate was removed by filtration. The filtrate was concentrated on a rotary evaporator at 40°C/1 mm Hg to a volume of 100 ml, and left at 4°C for 24 hours. The precipitate was collected by filtration, recrystallized from water, and dried in vacuo over phosphoric oxide to yield N-α-benzyloxycarbonyl-L-lysine (10.0 g, 0.036 mol, 36%); m.p. 280°C (dec.); $[\alpha_D]^{20}$ -12.4° (c 5.5, 2M HCl); (Found: C, 59.67; H, 7.21; N, 9.79. Calc. for $C_{14}H_{20}N_2O_4$: C, 60.00; H, 7.14; N, 10.00%); ν_{max} (Nujol): 3320 (N-H), 3100-2300 br and 2220 w (NH_3^+), 1725 (C = O), 1660 (C = O, Amide I and N-H overlap), 1580 and 1405 (CO_2^-) cm^{-1}; δ_H (300 MHz; D_2O) 1.17-1.65 (6H, m, 3 x CH_2), 2.78 (2H, t, J 7.5 Hz, $CH_2NH_3^+$), 3.75-3.80 (1H, m, α-CH), 4.89-5.00 (2H, m, CH_2Ar), 7.20-7.31 (5H, m, ArH); δ_C (62.8 MHz, D_2O) 21.86, 26.10, 31.01, 38.97 (4 x t, CH_2), 55.91 (d, α-CH), 66.60 (t, $ArCH_2$), 127.46, 128.07, 128.51, 136.25 (3 x d, 1 x s, Ar), 157.51, 179.30 (2 x s, C=O); m/z (DCI, NH_3) 281 (M^++1), 237 (M^++1-44).

Preparation of 2(S)-2-(benzyloxycarbonylamino)-6-hydroxyhexanoic acid (6).

N-α-Benzyloxycarbonyl-L-lysine (5) (3.50 g, 12.5 mmol) was dissolved in water (50 ml), the solution was warmed to 60°C, and adjusted to pH 9.5 with 4M sodium hydroxide. Sodium nitroprusside dihydrate (4.47 g, 15 mmol, 1.2 equivalents) was added slowly, with vigorous stirring, over 20 minutes. The temperature of the reaction mixture was kept at 60°C, and the pH maintained at 9.5 by addition of 4M sodium hydroxide as the reaction proceeded. The red-brown slurry was stirred at 60°C, pH 9.5 for a further 6 hours. The mixture was filtered through a bed of celite, cautiously acidified with hydrochloric acid to pH 1, and extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were washed with water brine, dried over magnesium sulphate, and evaporated to yield 2(S)-2-(benzyloxycarbonylamino)-6-hydroxyhexanoic acid as a pale yellow oil (2.70 g, 77% crude yield), used without purification in the next step. For the purpose of characterization, crude alcohol (450 mg) was purified on flash silica "H" [25 g, eluant ethyl acetate] to give the title compound (6) as an oil (166 mg, 28% overall); TLC (ethyl acetate (R_f 0.2; $[\alpha_D]^{20}$ +15.0° [c 1.07 in $CHCl_3$]; (Found: C, 59.40; H, 6.87; N, 4.81. $C_{14}H_{19}NO_5$ requires C, 59.79; H, 6.76; N, 4.98%); ν_{max} ($CHCl_3$) 3700-2400 br and 3610 w (O-H), 3430 m (C=O), 3320 w (N-H), 3010 m (Ar-H), 2940 m (C-H), 1710 s (C=O), 1600 w (N-H Amide II), 1510 s, 1455 m, 1440 m, 1405 m, 1220 s, 1065 s, 915 w, 698 s (Ar-H) cm^{-1}; δ_H (300 MHz; $CDCl_3$) 1.37-1.88 (6H, m, 3 x CH_2), 3.58 (2H, t, J 6 Hz, CH_2OH), 4.30-4.37 (1H, m, αCH), 5.07 (2H, s, $ArCH_2$), 5.84 (1H, d, J 8 Hz, NH), 6.90 (2H, bs, CO_2H and CH_2OH), 7.27-7.37 (5H, m, ArH); δ_C (62.8 MHz; $CDCl_3$) 21.36, 31.62, 31.95 (3 x t, 3 x CH_2), 53.82 (d, αCH), 62.06 (t, CH_2OH), 67.01 (t, $ArCH_2$), 127.97, 128.11, 128.46, 136.18 (3 x d, 1 x s, Ar), 156.35, 175.37 (2 x s, C=O); m/z [DCI, NH_3] 299 (M^++18), 282 (M^++1), 281 (M^+), 264, 238 (M^++1-44).

Preparation of 2(S)-2-(benzyloxycarbonylamino)-6-hydroxyhexanoic acid, benzyl ester (7).

Crude 2(S)-2-(benzyloxycarbonylamino)-6-hydroxyhexanoic acid (6) (10.68 g, from (5) 51 mmol), dried under high vacuum, was dissolved in AR acetone (250 ml), freshly distilled from phosphoric oxide under nitrogen. Benzyl bromide (5 ml, 42 mmol, 1.1 equivalents), triethylamine (5.8 ml, 42 mmol), and anhydrous sodium sulphate (2 g) were added to this solution, and the mixture stirred under argon for 18 hours. The mixture was filtered, and the solvent removed from the filtrate on a rotary evaporator. The product was purified by chromatography on flash silica [500 g, eluant dichloromethane: ethyl acetate (1:0-4:1)] to give 2(S)-2-(benzyloxycarbonylamino)-6-hydroxyhexanoic acid, benzyl ester as a pale oil [7.26 g, 19.6 mmol, 38% from (5)]; TLC [dichloromethane: ethyl acetate (4:1)] R_f 0.30; $[\alpha_D]^{20}$ -5.1° (c 1.17 in $CHCl_3$); (Found: C, 67.91; H, 7.12; N, 3.65. Calc. for $C_{21}H_{25}NO_5$; C, 67.92; H, 6.74; N, 3.77%); ν_{max} ($CHCl_3$) 3700-3100 br and 3620 w (O-H), 3440 m (C=O overtone), 3340 w (N-H), 3035 m, 3010 m (Ar-H), 2945 m (C-H), 1720 s (C = O), 1590 w (N-H Amide band II), 1510 s, 1455 m, 1390 m, 1345 m, 1220 s, 1065 s, 915 w, 700 m, and 670 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 1.30-1.94 (7H, m, OH and 3 x CH_2), 3.58 (2H, t, J 6 Hz, CH_2OH), 4.41-4.48 (1H, m, αCH), 5.11 (2H, s, $ArCH_2$), 5.16, 5.21 (2H, AB d, J 12 Hz, $ArCH_2$), 5.37 (1H, d, J 8 Hz, NH), 7.29-7.41 (10 H, m, ArH); δ_C (62.8 MHz; $CDCl_3$) 21.37, 32.01, 32.42 (3 x t, 3 x CH_2), 53.85 (d, αCH), 62.32 (t, CH_2OH), 67.00, 67.09 (2 x t, 2 x $ArCH_2$), 128.05, 128.14, 128.29, 128.48, 128.58, (5 x d, ArH), 135.31, 136.23 (2 x s, Ar), 155.88, 172.24 (2 x s, 2 x C=O); m/z [DCI NH_3] 389 (M^++18), 372 (M^++1), 328 (M^++1-44).

Preparation of N-benzyloxycarbonyl-L-α-aminoadipic acid, α-benzyl ester (1).

2(S)-2-(Benzyloxycarbonylamino)-6-hydroxyhexanoic acid, benzyl ester (7) (4.19 g, 11.3 mmol), was dissolved in acetonitrile (40 ml), carbon tetrachloride (40 ml), and water (50 ml). Sodium periodate (5.44 g, 25.4 mmol, 2.25 equivalents), and ruthenium dioxide monohydrate (180 mg, 1.19 mmol, 9.5% mol equivalents), were added and the mixture stirred vigorously at 20°C for 2 hours. Dichloromethane (100 ml) was added to the biphasic reaction mixture, and the layers separated. The aqueous phase was acidified with 2M hydrochloric acid, and extracted with ethyl acetate (2 x 100 ml). The organic extracts were pooled, dried over sodium sulphate, filtered, and the solvent evaporated to give a grey oil. The oil was purified by chromatography on flash silica (200 g, eluant diethyl ether) to give the crude acid (3.03 g, 70%), which was crystallized from dichloromethane-light petrol to give N-benzyloxycarbonyl-L-α-aminoadipic acid, α-benzyl ester (1) (2.17 g, 50%); TLC (diethyl ether) R_f 0.3, (ethyl acetate) R_f 0.8; m.p. 88°C; $[\alpha_D]^{20}$ -13.9° (c 1.02 in acetone); ν_{max} ($CHCl_3$) 3670 w, 3500-2500 br w (O-H), 3435 m (C=O overtone), 3100 m (Ar-H), 2950 m (C-H), 1716 s (C=O), 1600 w (N-H Amide band II), 1510 s, 1455 w, 1345 m, 1220 s, 1060 m, 930 w, 700 s, 670 s cm^{-1}; δ_H (300 MHz; $CDCl_3$) 1.53-2.02 (4H, m, 2 x CH_2), 2.36 (2H, bt, J 6.5 Hz, CH_2CO_2H), 4.43-4.51 (1H, m, αCH), 5.10, 5.17 (4H, 2 x s, 2 x $ArCH_2$), 5.41 (1H, d, J 8.0 Hz, NH), 7.33 (10 H, bs, 2 x ArH); m/z [DCI NH_3] 403 (M^++18), 383 (M^++1); (Lit.,[4] m.p. 87-9°C; $[\alpha_D]^{20}$ -13.3° (C 2, acetone).

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