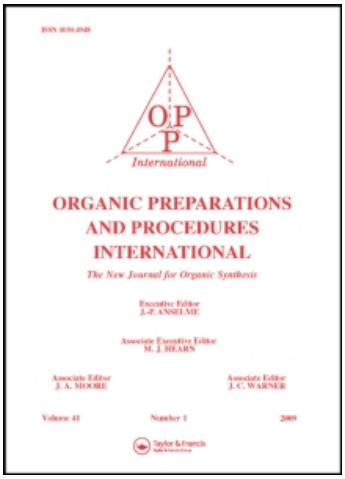

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DI-*tert*-BUTYL4-[(2-*tert*-BUTOXYCARBONYL)ETHYL]-4-AMINOHEPTANEDICARBOXYLATE

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DI-*tert*-BUTYL 4-[(2-*tert*-BUTOXYCARBONYL)ETHYL]-4-AMINOHEPTANEDICARBOXYLATE

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(2/21/96)

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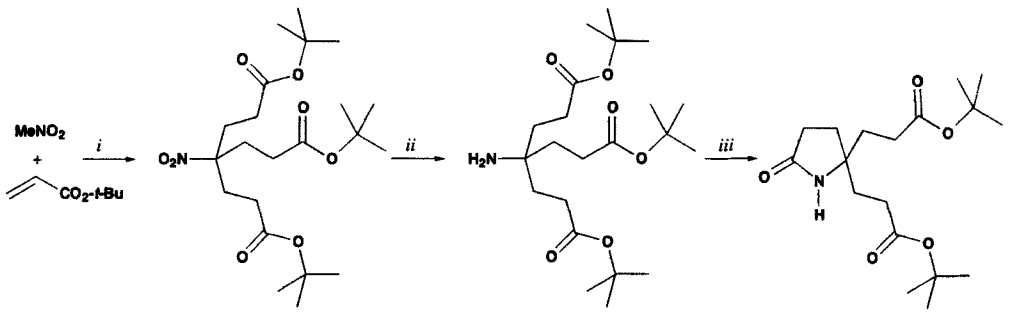
Many highly branched aliphatic dendritic or cascade macromolecules have been prepared[1] using different molecular building blocks[2] (or bricks). In particular, crystalline[3] di-*tert*-butyl 4-[(2-*tert*-butoxycarbonyl)ethyl]-4-aminoheptanedicarboxylate **2** ("Behera's amine") has found diverse applications owing to its unique versatility.[4] Attractive features of this dendritic brick include (a) an sp^3 carbon branching center, (b) preformed branches, (c) facile acylation of the amino moiety, and (d) quantitative removal of the carboxylic acid protecting groups. However, the original synthesis[4] of amine **2** was not readily amenable to large scale preparations; specifically, chromatographic purification of **2** was expensive in terms of both time and materials. We herein report improved procedures for the synthesis of nitrotriester **1** and its subsequent reduction to Behera's amine **2**.

Nitrotriester **1** was prepared via treatment of nitromethane with slightly more than three equivalents of *tert*-butyl acrylate in dimethoxyethane (DME). Trace yellow impurities produced in the reaction were easily removed by recrystallization; removal of these colored contaminants circumvents chromatographic purification of the desired monomer **2**.



1 (75-81%) **2** (89-93%) **3** (100%)

i) TritonB, DME *ii*) T-1 Raney Ni, H_2, 50-55°, *iii*) Δ

Hydrogenation of the nitrotriester **1** to the aminotriester **2** at slightly elevated temperature presented a serendipitous exception to the reduction products of known tertiary, γ-nitroesters.[5] All previously known examples of such reductions readily cyclize to afford the corresponding 2,2'-disubstituted pyrrolidones. Therefore, catalytic hydrogenation conducted under carefully controlled temperature conditions using freshly prepared T-1 Raney Nickel at 45-55° provided (ca. 90%) the pure monomer **2**.

The crystalline amine **2** is stable for prolonged periods when stored at ≤15°, however the presence of solvent or extended storage at 25° may result in the formation (about 5-7% over several months) of di-*tert*-butyl 5-oxo-2,2-pyrrolidinedipropionate (**3**).[6] Attempts to recrystallize **2** were initially frustrated by the thermal cyclization at elevated temperatures, which further dictated that *in vacuo* solvent removal should be performed below 50°. Subsequently, it has been determined that aminoester **2** can be cyclized quantitatively in the solid state at 105-110°; while, in solution, cyclization occurs at 65-80°.

EXPERIMENTAL SECTION

All starting materials were purchased from Aldrich Chemical Co. Melting points were uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AC 250 MHz spectrometer.

Large Scale Preparation of Di-*tert*-butyl 4-[2-(*tert*-Butoxycarbonyl)ethyl]-4-nitroheptanedicarboxylate (1).- A 5-liter 3-necked flask, equipped with a 500 mL addition funnel, a thermometer, a reflux condenser and a 2-inch magnetic stirring bar was charged with 1,2-dimethoxyethane (DME, 500 mL) and $MeNO_2$ (122 g, 108.3 mL, 2 mol). The solution was heated to 65-70°, and Triton-B (20 mL, 40% in MeOH) was added. *tert*-Butyl acrylate (794 g, 908 mL, 6.20 mol) was added at such a rate to maintain a temperature of 75-85°; the addition was completed within 2-2.5 hrs. When the temperature began to drop, Triton B (4 x 10 mL) was added. Stirring was continued while the temperature was maintained at 70-80° for 2 hrs. The solution was decanted from insoluble polymeric material (which adheres to the wall of the flask) and concentrated *in vacuo*. The resulting light yellow, residue was dissolved in ether (2.5 L), washed with ice cold 10% aq. HCl (2 x 200 mL), an aqueous saturated $NaHCO_3$ (2 x 200 mL), and water (2 x 200 mL), then dried and clarified [Na_2SO_4 (100 g) with Celite (10 g)]. The ether was removed *in vacuo* to give a solid mass, which was dissolved in warm EtOH (ca. 1.3 L). The solution was allowed to cool and maintained at 0° for 24 hrs. The resultant colorless crystals were collected, washed with precooled MeOH (500-600 mL) to remove any residual colored impurities, and dried *in vacuo* to afford 668-721 g (75-81%) of the white crystalline **1**; mp. 99-100°, lit.[4] mp. 98-100°. ^1H NMR: δ 1.45 (s, C*H*$_3$, 27*H*), 2.21 (m, C*H*$_2$, 12*H*); ^{13}C NMR: δ 27.9 (*C*H$_3$), 29.7 (*C*H$_2$CO), 30.2 (CCH$_2$), 80.9 (*C*CH$_3$), 92.1 (*C*NO$_2$), 170.9 (*C*O$_2$).

Di-*tert*-butyl 4-[2-(*tert*-Butoxycarbonyl)ethyl]-4-aminoheptanedicarboxylate (2). A. Preparation of T-1 Raney Nickel Catalyst.[7]- [*Caution: This catalyst is easily handled when wet; however, it is extremely pyrophoric when dried and exposed to air.*] To 750 mL of water in a 2 L beaker rapidly stirred using a 2-inch magnetic stirring bar was added NaOH pellets (75 g). After dissolution, aluminum nickel alloy [30 g, Aldrich Chemical Co. (22,165-1), Raney R-type alloy] was added in one portion to the hot solution. There was a vigorous evolution of hydrogen and the temperature rose to ca. 85-90°; stirring was continued for 1 hr. The beaker was covered with a watch glass, and the supernatant alkaline solution was carefully decanted from the black catalyst. Distilled water (300-400 mL) was added, stirred for 1-2 min., and then decanted; this procedure was repeated 4 times. The catalyst

was transferred into a 250 mL beaker and washed with absolute EtOH (5 x 150-200 mL); each time the catalyst was allowed to settle before the supernatant EtOH was decanted. The moist catalyst was used immediately.

B. Reduction Procedure.- To a Parr hydrogenation bottle was added EtOH (25 mL), followed by the above freshly prepared catalyst [which should be covered (50-100 mL) with EtOH during the entire procedure]. The nitrotriester **1** (50 g, 112 mmol) was added, followed by EtOH to ca. 75% of the total flask volume. The hydrogenation was performed at an initial pressure of 60 psi at 50-55°, and generally required 45-75 min. Nitrotriester **1** is quite insoluble in EtOH, while amine **2** is soluble. External cooling may be necessary so that *the temperature does not exceed 55°*. The catalyst was removed by filtration through a sintered glass funnel, then washed with EtOH (50-80 mL).[8] If there are traces of catalyst in the filtrate, filtration must be repeated. The solvent was removed *in vacuo* at *a temperature not to exceed 55°*. Traces of EtOH were removed *in vacuo* (0.1 mm) to yield an oil, which was transferred to a crystallizing dish and allowed to solidify *in vacuo* to give 41.5-44.1 g (89-93%) of **2** as a white crystalline mass, mp. 51°, lit.[4] mp. 51-52°. ^{1}H NMR: δ 1.44 (s, C*H*$_3$, 27*H*), 1.78 (m, C*H*$_2$, 12*H*); ^{13}C NMR: δ 27.8 (*C*H$_3$), 29.8 (*C*H$_2$CO), 34.2 (CCH$_2$), 52.2 (*C*NH$_2$), 80.0 (*C*CH$_3$), 172.8 (*C*O$_2$); MS m/e 415.4 (M$^+$+1, 20).

Amine **2** may be cyclized upon heating to 110° for 48 hrs to yield (100%) lactam **3**, mp. 132-133°, lit.[6] mp. 131-132°. ^{1}H NMR: δ 1.44 (s, C*H*$_3$,18 *H*), 1.83 (t, *J* = 7.2 Hz, C*H*$_2$CO, 4*H*), 1.92 (t, *J* = 8.0 Hz, C*H*$_2$CONH, 2*H*), 2.26 (t, *J* = 7.2 Hz, CC*H*$_2$, 4*H*), 2.38 (t, *J* = 8.0 Hz, CC*H*$_2$CH$_2$CONH, 2*H*), 6.92 (s, N*H*, 1H); ^{13}C NMR: δ 27.9 (*C*H$_3$), 30.1 (*C* H$_2$O), 30.2, 30.25 [*C*H$_2$*C*H$_2$ (ring)], 34.6 (*C*H$_2$CH$_2$CO$_2$), 60.6 (HN*C*), 80.6 (CO$_2$*C*), 172.3 (*C*O$_2$), 177.2 (*C*ONH); IR 1723, 1707 (C=O) cm^{-1}. *Anal.* Calcd for C$_{18}$H$_{31}$NO$_5$: C, 63.32; H, 9.15; N, 4.10. Found: C, 63.52; H, 9.25; N, 4.28

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8. Catalyst destruction following the hydrogenation can be effected by direct addition of the moist material to a 5% aqueous HCl solution.