JOC*Note*

Direct Synthesis of 1,1′-[1,4-Phenylenebis(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane Octahydrochloride (AMD 3100) without the Use of Protecting Groups

Michal Achmatowicz and Louis S. Hegedus*

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

hegedus@lamar.colostate.edu

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Abstract: A four-step synthesis of the title compound starting from methyl acrylate, ethylenediamine, and dimethyl malonate is reported. The synthesis can be run on a multigram scale and is operationally simple. The use of protecting groups is avoided by utilizing the trioxocyclam as the key coupling intermediate.

Bis-cyclams (14-membered tetrazamacrocycles) connected by hydrocarbon linkers at one of the secondary amine nitrogens are of current interest because of their potential anti-HIV activity.[1,2] The *p*-xylyl-linked bis-cyclam AMD 3100 (**1**) is currently in clinical trials against AIDS. Because of this biological activity, several syntheses of **1** have appeared. Most of these involve starting with the preformed cyclam, 1,4,8,11-tetraazacyclotetradecane, selectively protecting three of the four secondary amino groups, coupling by bis amination of α,α′-dibromo-*p*-xylene, and deprotecting. Protected intermediates used include the tris-tosylamide,[3] the bis-tosylamide-Boc,[4] the bis-aminal,[5] and metal carbonyl,[6] phosphoryl,[6] thiophosphoryl,[6] boron,[6] and trimethylsilyl derivatives.[6] These approaches afford varying degrees of efficiency and scalability but suffer from the high cost of the starting cyclam.

A related approach started with the 5,12-dioxocyclam (1,4,8,11-tetraazacyclotetradecane-5,12-dione) in which two of the cyclam ring nitrogens were masked as amides.[7] Protection of one of the two amines as the tosyl or Boc derivative, followed by alkylation, deprotection, and finally reduction of the amides to amines, produced the desired compound in reasonable overall yield. The requisite dioxocyclam starting material was prepared in very low (10%) yield, but from very inexpensive starting materials (ethylenediamine and dimethyl malonate).

A final approach started with the inexpensive acyclic tetraamine *N*,*N*′-bis(3-aminopropyl)ethylenediamine and involved selective triprotection, coupling to α,α′-dibromo-*p*-xylene, ring closure, and finally removal of the six tosyl protecting groups.[8] This could be run on a reasonable scale, but, as was the case with the tritosylated cyclam route above, over 60% of the mass is removed in the deprotection step.

Desiring a more direct route that did not start from the expensive cyclam and avoided protection/deprotection sequences, the route shown in Scheme 1 was developed in these laboratories. Trioxocyclam **3** was synthesized by a minor variation of a literature procedure,[9] from ethylenediamine, methyl acrylate, and dimethyl malonate. With only one free secondary amine, protection of **3** was not required for the coupling step with α,α′-dibromo-*p*-xylene, which proceeded in good yield on a 30 g scale. Reduction of the six amides to amines followed by precipitation with HCl in methanol produced AMD 3100 (**1**) in overall 16% yield from methyl acrylate and 47% yield from trioxocyclam **3**.

This synthesis is reasonably efficient and direct, and is operationally simple. The first purification required was for trioxocyclam **3**. A first crop of crude product precipitated from the reaction mixture, but the mother liquors required filtration through silica gel to remove oligomeric material before a second crop of product could be isolated. Compounds **4** and **1** were purified by simple recrystallization. The route presented in Scheme 1 offers an attractive alternative to other routes extant.

Experimental Section

Condensation/Michael Addition of Ethylenediamine with Methyl Acrylate to Produce Triamine Amide 2. Methyl acrylate (71 mL, 0.79 mol) was slowly added to neat ethylenediamine (0.85 L, 13 mol) with stirring. A slightly exothermic reaction took place. The clear reaction mixture was allowed to stand at room-temperature overnight and then was stirred at 60 °C for 4 h. Excess ethylenediamine was removed under reduced pressure and then under high vacuum overnight (at room temperature) and for 1 h at 70 °C, affording pure product **2** as clear, colorless oil (133 g, 97%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.80 (bs, 1H), 3.24 (q, J = 5.7 Hz, 2H), 2.85 (t, J = 6.0 Hz, 2H), 2.76 (t, J = 5.4 Hz, 4H), 2.65 (t, J = 5.7 Hz, 2H), 2.33 (t, J = 5.7 Hz, 2H), 1.30 (s, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.6, 52.0, 45.5, 41.9, 41.6, 41.5, 35.9; IR (film) 3275, 3068, 2934, 2866, 1646, 1558, 1476, 1318 cm^{-1}.

Condensation of 2 with Dimethyl Malonate to Produce Trioxocyclam 3. To the triamine (66.5 g, 0.38 mol) solution in methanol (3.8 L) was added a solution of dimethyl malonate (58 mL, 0.38 mol) in methanol (0.2 L) in one portion. A slightly exothermic reaction took place. The resulting pinkish reaction

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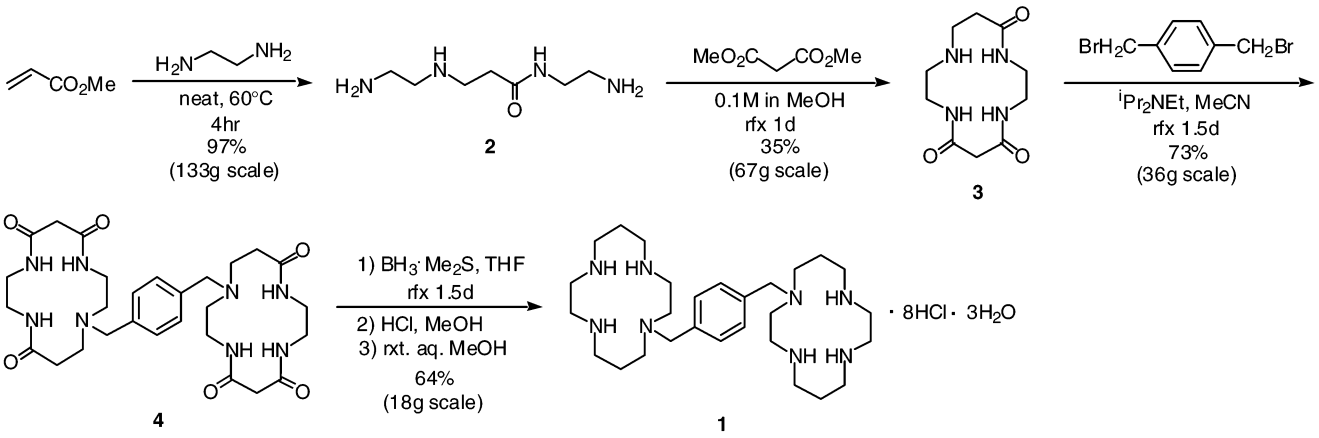
SCHEME 1



mixture was allowed to stand at room temperature for 2 days and was then stirred at reflux for 1 day. The reaction mixture was concentrated under vacuum to a volume of 0.5 L, and the resulting dark red viscous solution was allowed to stand at room temperature for 2 days. The crude product that separated as thick pink needles was collected by filtration (16 g). Concentrated mother liquors were chromatographed on silica (0.40 kg; CH_2Cl_2/MeOH = 8:2) to give additional crop of crude trioxocyclam as a pink powder (24 g). The combined crops of crude material were recrystallized from methanol/diethyl ether to give trioxocyclam **3** as colorless crystals (32 g, 35%): mp 206−207 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.06 (bs, 1H), 7.77 (bs, 1H), 7.65 (bs, 1H), 3.22−3.08 (m, 6H), 2.95 (s, 2H), 2.66 (t, J = 5 Hz, 2H), 2.55 (t, J = 4 Hz, 2H), 2.13 (t, J = 5 Hz, 2H), 1.64 (bs, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 171.9, 166.7 (2C), 47.7, 45.4, 44.9, 38.3, 38.2, 37.3, 35.4; IR (KBr) 3314, 3078, 2940, 1677, 1633, 1436, 1358 cm^{-1}. Anal. Calcd for $C_{10}H_{18}N_4O_3$: C, 49.59; H, 7.44; N, 23.14. Found: C, 49.82; H, 7.60; N, 23.33.

Synthesis of *p*-Xylene-Linked Bis-Trioxocyclam 4. To a suspension of trioxocyclam **3** (35.5 g, 147 mmol) in MeCN (0.50 L) was added α,α′-dibromo-*p*-xylene (18.2 g, 68.9 mmol) followed by diisopropylethylamine (0.13 L). The resulting suspension was stirred at reflux (bath temperature = 90 °C) for 42 h and then was cooled to room temperature. The off-white precipitate was collected on a paper filter, washed thoroughly with MeCN, and dried in air (36.7 g). The solid was then treated with hot DMSO (0.25 L) at which time most of the material went into solution. After the mixture was cooled to room temperature, an orange resinous precipitate was removed by filtration through a Celite pad leaving a clear yellow-orange solution. This was concentrated to ca. 0.18 L, diluted with CH_2Cl_2 (0.8 L), and left at −20 °C overnight to produce colorless sand-like crystals of bis-trioxocyclam solvate (29.6 g, 65%): mp 285 °C (dec). Anal. Calcd for $C_{28}H_{42}N_8O_6\cdot H_2O\cdot 0.7CH_2Cl_2$: C, 52.02; H, 6.64; N, 16.92; Cl, 7.51. Found: C, 52.16; H, 6.70; N, 16.91; Cl, 7.75. Further crops of pure bis-trioxocyclam **4** were obtained by recrystallization from DMSO/MeOH (3.2 g, 8%): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.96 (bs, 2H), 7.83 (bs, 2H), 7.26 (bs, 2H), 7.18 (s, 4H), 3.48 (s, 4H), 3.33 (s, 4H), 3.30−3.07 (br m, 12H), 2.99 (s, 4H), 2.37 (br m, 4H), 2.15 (br m, 4H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 171.9, 167.0, 165.6, 136.5, 128.9, 57.0, 51.6, 48.8, 45.6, 37.7, 35.6, 33.3; IR (KBr) 3296, 3084, 2937, 2820, 1666, 1550, 1435, 1360, 1319, 1258, 1152 cm^{-1}.

Synthesis of AMD 3100. To a suspension of bis-trioxocyclam solvate (18.0 g, 27.2 mmol) in dry THF (0.63 L) was slowly added borane dimethyl sulfide complex (ca. 10 M, 0.16 L, 1.6 mol) under argon. Once the vigorous bubbling ceased, the suspension was stirred at reflux (bath temperature = 80 °C) for 43 h. The yellowish slurry was cooled to room temperature and placed in an ice-bath, and the excess borane was destroyed by careful addition of MeOH (0.20 L). Volatiles were removed under vacuum. The light-yellow powdery residue (21 g) was treated with 0.6 M HCl in MeOH (0.50 L) and stirred at reflux until all the material dissolved, giving a clear, colorless solution. Volatiles were removed under vacuum, and the residue was redissolved in MeOH (0.10 L) and stripped again in vacuo leaving a colorless foam (19.3 g). This was taken up in distilled water (0.30 L), gently warmed with stirring, and then passed through a Celite pad to remove insoluble yellow material. The slightly cloudy aqueous solution (0.5 L, pH 1) was washed with CH_2Cl_2 (2 × 0.25 L) to remove sulfur byproducts, carefully basified using NaOH pellets (pH > 11), and extracted once with CH_2Cl_2 (0.5 L). The aqueous layer was set aside. The organic solution was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to afford pure bis-cyclam as a colorless foam (6.4 g, 47%). The aqueous layer was stripped under vacuum, and the resulting colorless material was extracted once with CH_2Cl_2 (0.5 L). Subsequent drying (Na_2SO_4) and solvent removal afforded an additional crop of bis-cyclam as an off-white foam (5.4 g, 40%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30 (s, 4H), 4.23 (bs, 6H), 3.53 (s, 4H), 2.95−2.50 (m, 32H), 1.87 (bs, 4H), 1.75 (bs, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.4, 129.3, 57.8, 53.4 (2C), 50.7, 49.4, 48.9, 48.4, 47.1, 47.0, 27.0, 25.3; IR (film) 3280, 2927, 2883, 2807, 1458, 1265, 1117 cm^{-1}. A methanolic solution (1 L) of the free bis-cyclam (11.8 g, 23.5 mmol) was treated with 1.3 M HCl in MeOH (0.28 L, 0.37 mol). Recrystallization from hot MeOH afforded the bis-cyclam hydrochloride salt H_2O/MeOH solvate as a fine colorless powder (15.3 g, 64%): mp 232 °C (dec); ^{1}H NMR (D_2O, 300 MHz) δ 7.55 (s, 4H), 4.66 (bs, 16H), 4.40 (s, 4H), 3.65−3.40 (br m, 16H), 3.40−3.20 (br m, 16H), 2.06 (br m, 8H); ^{13}C NMR (D_2O, 75 MHz) δ 132.0, 130.9, 58.6, 47.7, 44.6, 41.7, 41.1 (2C), 37.6, 37.2 (2C), 18.8, 18.3. Anal. Calcd for $C_{28}H_{54}N_8\cdot 9HCl\cdot H_2O\cdot CH_3OH$: C, 39.52; H, 7.84; N, 12.72; Cl, 36.29. Found: C, 39.49; H, 7.62; N, 12.85; Cl, 36.64. A sample of this material was dissolved in a minimal amount of water and treated with excess methanol followed by cooling in a freezer. This resulted in the precipitation of fine colorless crystals of the bis-cyclam octahydrochloride trihydrate (**1**). Anal. Calcd for $C_{28}H_{54}N_8\cdot 8HCl\cdot 3H_2O$: C, 39.62; H, 8.02; N, 13.21; Cl, 33.49. Found: C, 39.56; H, 7.89; N, 12.94; Cl, 33.61.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for **1**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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