Micelles series. 31. Building blocks for cascade polymers. 11. Synthesis of functionalized cascade cores: tetrakis(.omega.-bromoalkyl)methanes

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Synthesis of Functionalized Cascade Cores:[1a] Tetrakis(ω-bromoalkyl)methanes

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A series of tetrakis(bromoalkyl)methanes was synthesized and characterized. The tetrakis(3-bromopropyl)methane was chosen as ideal core to cascade polymers, since it undergoes facile substitution with bulky nucleophiles, denoting the need for at least three carbon atoms between the quaternary center and the leaving group to circumvent major steric problems caused by the core carbon. The readily available 4-nitro-4-(3-hydroxypropyl)-1,7-heptanediol was used to afford a novel entry to tetrakis(3-bromopropyl)methane as well as other building blocks to cascade polymers.

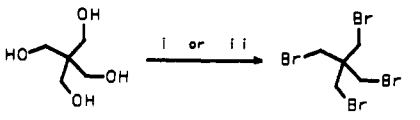
Introduction

Our initial approaches to the preparation of spherical, alkyl unimolecular micelles [Micellanes][2] were based on the utilization of a simple quaternary carbon building block, such as pentaerythritol (1), which is commercially available and very inexpensive. With the expectation of employing S_N2 transformations to form the new carbon–carbon bonds, a study of methane cores with saturated hydrocarbon alkyl moieties was undertaken.

Pentaerythritol can be easily converted to the desired tetrakis(bromomethyl)methane (2) utilizing the two-step procedure of Herzog or by direct reaction of the substrate with PBr_3[4] (Scheme I). In our hands tetrabromide 2, however, failed to react with triethyl sodiomethanetricarboxylate[5] or potassium cyanide.[6] Perusal of the literature revealed that 2 under classical Finkelstein conditions afforded the more hindered tetrakis(iodomethyl)methane;[4] with dimethyl malonate, tetramethyl spiro[3.3]heptane-2,2,6,6-tetracarboxylate was generated;[7,8] with diphenyl phosphide, only trisphosphine substitution was realized;[9] with diamines[10] (140 °C/50 h), the corresponding tetraamine was afforded (20%); with sodio *p*-toluenesulfonamide (210 °C/8 h), the tetraamide was produced, along with a cyclized product,[11] and with the potassium alkoxide of the bicyclic pentaerythrityl orthoester (>150 °C) the desired tetraether[12] was prepared.

Since the previously reported[13] X-ray crystal structure of 2 exhibited disorder and decay, a low-temperature (150 K) reexamination of 2 was conducted.[14] Figure 1 shows a highly ordered orientation and the openness necessary for nucleophilic attack. If the reaction conditions are sufficiently rigorous and/or anchimeric assistance[15] is operative, substitution can be realized. However, taking into account the necessity to circumvent the substitutive retardation caused by the juxtaposed quaternary center[16] and the desire to conduct the subsequent tetra-C-substitution reactions under mild conditions (<100 °C) and in acceptable yield, nucleofuge homologation was deemed necessary.

Scheme I[a]



1 2

[a] Key: (i) PBr_3/180 °C/24 h; (ii) (a) $ClSO_2C_6H_5$/Pyr/40 °C/1 h, (b) diethylene glycol/NaBr/150 °C/12 h.

Results and Discussion

Although the homolog of 2, tetrakis(2-bromoethyl)methane (3), had been prepared[17] from citric acid in 12 steps (2% overall yield), our approach[18] from tetrahydro-4*H*-pyran-4-one[19] used only six steps with 20% overall yield (Scheme II). Counter to expectations, there was still an inability to realize *facile C–C* bond formation when reaction 3 with triethyl sodiomethanetricarboxylate was attempted under typical reaction conditions[20] or diverse

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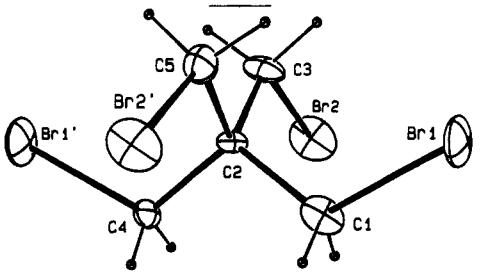


Figure 1. ORTEP drawing of tetrakis(bromomethyl)methane (**2**).

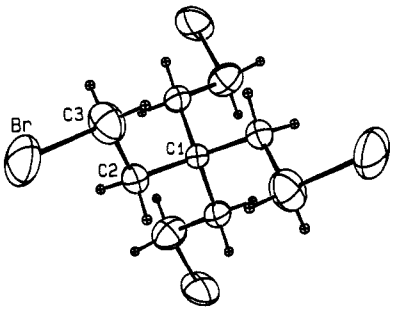
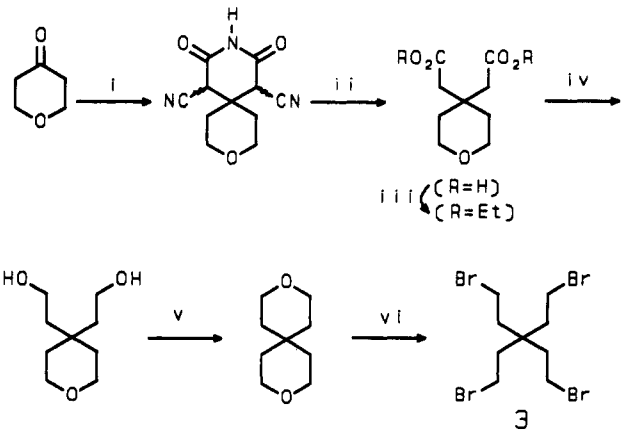


Figure 2. ORTEP drawing of tetrakis(2-bromoethyl)methane (**3**).

Scheme II[a]

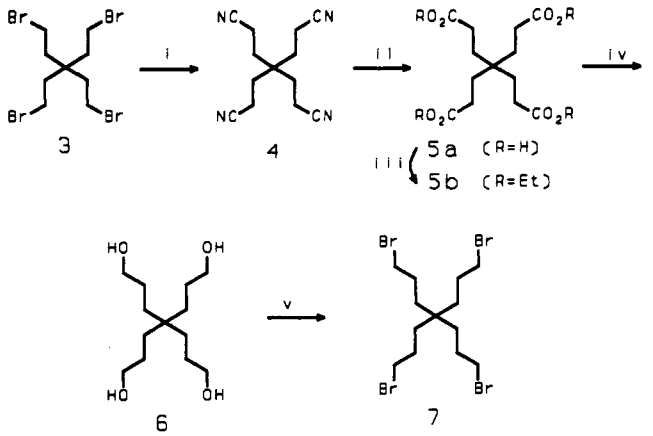


[a] Key: (i) (a) anhyd NH_3/EtOH/$NCCH_2CO_2Et$/−5 °C, (b) concd HCl/H_2O/25 °C; (ii) concd HCl/reflux/24 h; (iii) EtOH/C_6H_6/H_2SO_4/reflux; (iv) $LAlH_4/Et_2O$; (v) concd HCl/95 °C/3 h; (vi) 48% HBr/H_2SO_4/100 °C/20 h.

modification as noted in the Experimental Section. Furthermore, bromide **3**, when treated with dimethyl malonate in the presence of anhydrous K_2CO_3 in DMF, gave (59%) the tetramethyl spiro[5.5]undecane tetraester.[21] The vicissitude associated with attempting four substitutions in a highly constrained and covalently bound domain, with four discrete nucleophiles, was further exemplified when bromide **3** was treated with NaI in acetone; only three bromides were displaced[6] suggesting a diminished anchimeric assistance contribution.

The X-ray crystal structure of **3** (Figure 2) was undertaken[14] to ascertain if there were any interactions that attribute to this retardation. The structure of **3** confirms the compact, ordered array, which apparently retards the

Scheme III[a]



[a] Key: (i) KCN/CH_3CN/reflux/12 h; (ii) HCl/reflux/12 h; (iii) cat. H_2SO_4/EtOH/reflux/18 h; (iv) $LiAlH_4/Et_2O$/30 °C/6 h; (v) HBr/H_2SO_4/100 °C/18 h.

backside approach to the terminal carbons. Although small nucleophiles, such as cyanide, can approach under mild conditions, the use of bulky nucleophilic building blocks was not favored. This selectivity is almost certainly caused by steric congestion. Since, in cascade construction, high-yield conversions under mild conditions ensuring the minimization of side reactions and decomposition[22] are essential; further homologation to afford a distance of three methylene groups between the nucleofuge and the quaternary carbon was thus deemed product.

This homologation was accomplished in five steps by traditional, high-yield procedures[21] (Scheme III). Contrary to **2**, bromo*ethyl* homolog **3** readily reacted with cyanide[23] to give (79%) the desired tetranitrile **4**. The appearance of the typical nitrile absorption (2250 cm^{-1}) in the IR spectrum and the four-carbon pattern in the ^{13}C NMR spectrum (120.8, *C*≡N; 37.4, C_{quat}; 29.1, CH_2CH_2CN; 10.7, CH_2CN) confirm the conversion. Nitrile **4** was hydrolyzed (>95%) to the tetraacid **5a**, and subsequently esterified (>95%) under normal Fischer conditions. The loss of the nitrile carbon absorption at δ 120.8 in the ^{13}C NMR spectrum and the appearance of the peaks at 173.7 (*C*=O), 60.6 (CH_2O), and 14.2 (CH_3) ppm support the conversion.

Ester **5b** was reduced with $LiAlH_4$ in diethyl ether to give (>95%) tetrol **6**, which upon treatment with 48% HBr in concentrated H_2SO_4 afforded (84%) the crystalline tetrakis(3-bromopropyl)methane (**7**). The appearance of the four-peak pattern (^{13}C NMR) with an upfield shift of the terminal methylene moieties from 62.1 (CH_2OH) ppm to 34.4 (CH_2Br) ppm was indicative of the transformation.

Treatment of tetrabromide **7** with dimethyl methanedicarboxylate in DMF with anhydrous K_2CO_3 gave (79%) the desired octaester **8** with no evidence of spirane formation. Tetraalkylation was confirmed by the appearance in the ^1H NMR spectrum of a triplet at 3.36 ppm (C*H*) as well as signals (^{13}C NMR) at 51.3 ppm (*C*H) and 52.5 ppm (CH_3). Similarly, the use of the bulky triethyl methanetricarboxylate[5] afforded (42%) the corresponding dodecaester **9** (Scheme IV). Structural assignments supporting tetrasubstitution included ^{13}C NMR absorptions at 167.0, 65.7, 62.0, and 14.0 ppm corresponding to *C*=O, $C(CO_2Et)_3$, OCH_2, OCH_2CH_3, respectively.

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Scheme IV[a]

[a] Key: (i) K_2CO_3/DMF/90 °C/$H_2C(CO_2Et)_2$/12 h; (ii) K_2CO_3/DMF/90 °C/$HC(CO_2Et)_3$/12 h.

The X-ray crystal structure of **7** was carried out[14] to visualize the spacial factors. As shown in Figure 3, approach to the backside of the bromomethyl moiety appears to be sterically free. Thus, since it has been suggested[24] that "neopentyl systems react so slowly as to make such reactions, in general, synthetically useless", and based on the chemical selectivity exhibited by the tetrakis(bromoalkyl)methanes **2**, **3**, and **7** (Table I), the general observation is as follows: *one must insert at least three carbon atoms between the quaternary center and the leaving group to circumvent major steric problems caused by the said center.*

Even though this is a straightforward route to **7**, it is a cumbersome, time-consuming procedure. It was, therefore, necessary to prepare a series of reagents which could be readily converted to the appropriate building blocks with the minimal number of steps—alternative procedures were devised.

A more expedient entry into easily transformable quaternary carbon synthons was provided by the synthesis of 4-amino-4-(3-hydroxypropyl)-1,7-heptanediol (bishomotris).[25] The key intermediate, 4-nitro-4-(3-hydroxypropyl)-1,7-heptanediol (**10**), is readily available and possesses three terminally functionalized three-carbon appendages, thereby making it necessary only to introduce the fourth substituent with the desired length.

Pioneering work by Kornblum, et al.[26] afforded an avenue to these quaternary centers. On the basis of their work, it was found that these materials underwent denitrohydrogenation in the presence of n-Bu_3SnH and a radical initiator, such as :*hν* or AIBN.[27] Ono et al.[28] and Giese et al.[29] added to the versatility of these nitroalkane fragmentations by trapping the intermediate tertiary alkyl radicals with electron-deficient alkenes, such as acrylonitrile, thus, forming a new C–C bond. Application of this procedure to nitrotriol **10**, or a derivative, would give direct entry into a useful series of termini-differentiated monomer building blocks possessing tetraalkyl-substituted, quaternary carbon branching centers. Furthermore, each alkyl moiety would contain an easily transformable functionality three methylenes removed from the core carbon.

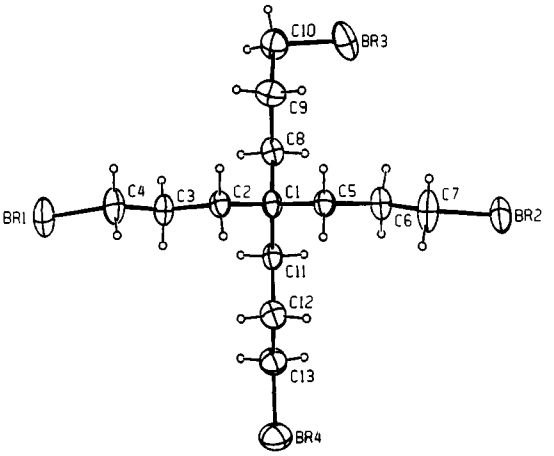

Figure 3. ORTEP drawing of tetrakis(3-bromopropyl)methane (**7**).

Conditions for the cyanoethylation of tertiary nitro compounds, as described by Ono et al.,[28] employed toluene or benzene, as solvent. Therefore, in order to enhance the solubility of the nitrotriol **10** in the hydrocarbon solvent, the hydroxy groups were protected as benzyl ethers, which also had the advantage of being stable to these reaction conditions and are readily removed by hydrogenolysis[30] or cleaved with HBr[18] (Scheme V).

Treatment[31] of triol **10** with benzyl chloride and either NaH or KOH in DMSO afforded the nitro triether **11**. Conversion was confirmed (^{13}C NMR) by the loss of the signal at 60.9 ppm (CH_2OH) and the appearance of peaks at 69.6 and 72.8 ppm ($CH_2OCH_2C_6H_5$), respectively. Denitration–cyanoethylation of triether **11** with acrylonitrile, AIBN, n-Bu_3SnH, and toluene at 100 °C for 60 min gave the desired nitrile triether **12** in approximately 50% yield. The upfield shift (^{13}C NMR) of the quaternary carbon absorption from 94.2 ppm (CNO_2) to 36.5 ppm [$C(CH_2-)_4$] as well as signals at 120.1, 31.6, and 11.2 ppm ($C{\equiv}N$, CH_2CH_2CN, and CH_2CN, respectively) and the appearance of a new spike (IR) at 2250 cm^{-1} for the nitrile support the assignment. The major byproduct was the formation (ca 12%) of $HC(CH_2CH_2CH_2OBz)_3$ via H-atom abstraction; varying percentages of the denitration–hydrogenation product were isolated depending on the nature of the electron-deficient alkene and terminal functional groups present in the tertiary nitro substrate.[32]

Hydrolysis[33] of the nitrile moiety of cyano triether **12** with H_2O_2/KOH in EtOH/H_2O afforded the corresponding

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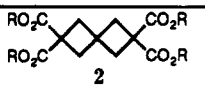
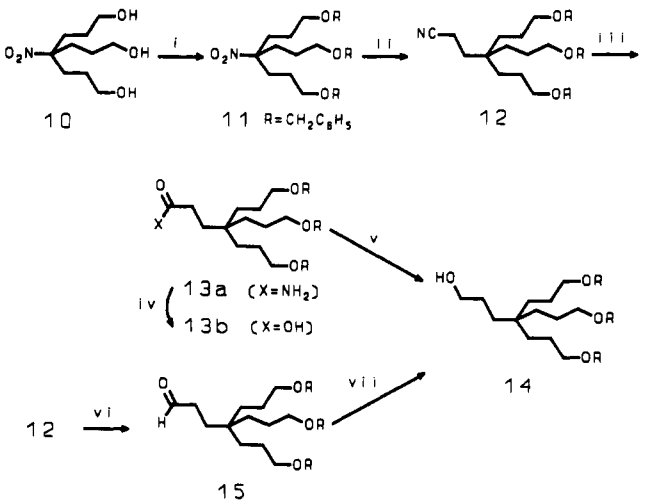
Table I. Tetrakis(bromoalkyl)methanes with Various Nucleophiles

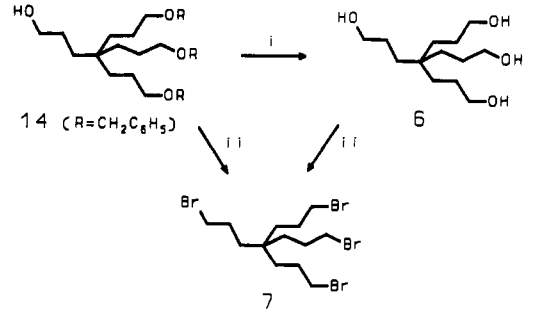
	nucleophile				
tetrabromide	KCN	NaI	$^{-}PPh_2$	$H_2C(CO_2R)_2$	$HC(CO_2R)_3$
$C(CH_2Br)_4$	no reaction	$C(CH_2I)_4$	$BrCH_2C(CH_2PPh_2)_3$	 2	no reaction
$C(CH_2CH_2Br)_4$	$C(CH_2CH_2CN)_4$	$BrCH_2CH_2C(CH_2CH_2I)_3$			no reaction
$C(CH_2CH_2CH_2Br)_4$	$C(CH_2CH_2CH_2CN)_4$			$C[CH_2CH_2CH_2CH(CO_2R)_2]_4$	$C[CH_2CH_2CH_2C(CO_2R)_3]_4$

Scheme V[a]



[a] Key: (i) KOH/DMSO/$ClCH_2C_6H_5$/3 h; (ii) n-Bu_3SnH/acrylonitrile/CH_3Ph/AIBN/100 °C/1 h; (iii) H_2O_2/KOH/EtOH/H_2O/60 °C/3 h; (iv) KOH/EtOH/reflux/12 h; (v) BH_3·THF/THF/reflux/3 h; (vi) DIBAL-H/THF/25 °C/12 h; (vii) $NaBH_4$/95% EtOH/CH_2Cl_2/25 °C/3 h.

Scheme VI[a]



[a] Key: (i) 10% Pd–C/EtOH/25 °C/18 h; (ii) 48% HBr/concd H_2SO_4/2:1$_{(v/v)}$/100 °C/12 h.

amide **13a**, which can be isolated or transformed with refluxing KOH in EtOH/H_2O to acid **13b**. Hydrolysis was confirmed (^{13}C NMR) by the disappearance of peaks attributed to the cyanoethyl moiety and the appearance of new signals at 179.7 (*C*=O), 30.8 (CH_2CO_2), and 28.2 ppm ($CH_2CH_2CO_2$) as well as the retention of 72.7 and 36.2 ppm for the benzylic methylene and quaternary carbons, respectively. Reduction[34] of acid **13b** with BH_3·THF afforded the desired alcohol **14**, as evidenced (^{13}C NMR) by loss of the carbonyl absorption and the formation of new peaks at 63.3, 32.0, and 26.3 ppm corresponding to CH_2OH, $CH_2(CH_2)_2OH$, and CH_2CH_2OH ppm, respectively. Alternatively, nitrile **12** was reduced[35] with DIBAL-H to give low yields (20%) of aldehyde **15** (^{13}C NMR δ 202.7, *C*=O; 36.8, CH_2CHO: ^1H NMR δ 11.21, *CH*O: IR 1735 cm^{-1}), which upon further reduction[36] with $NaBH_4$ also afforded alcohol **14** possessing the same spectral characteristics as that obtained by BH_3·THF reduction of acid **13b**.

Debenzylation[37] of **14** via catalytic reduction with Pd/C (10%) at 55 psi in EtOH gave (>95%) tetrol **6**, identical to a known sample.[6] Bromination[6] of both polyol **6** as well as hydroxy triether **14**, with 48% HBr in concentrated H_2SO_4 afforded (ca. 70–80%) equivalent samples of tetrabromide **7** (Scheme VI).

Conclusions. This study suggests that a distance of at least three carbon atoms (or 3.90 Å) should be incorporated between a quaternary center and a nucleofuge to facilitate requirements for mild reaction conditions (<100 °C) and that little or no steric effects are present at a reactive center undergoing a S_N2 transformation. Also, by starting with appropriately substituted nitroalkanes useful building blocks possessing termini-equivalent and termini-differentiated functional groups are readily available for the construction of cascade polymers.

Experimental Section

General Comments. All melting points were taken in capillary tubes and are uncorrected. ^1H and ^{13}C NMR spectra were determined at MHz using $CDCl_3$ as solvent, except where noted, with Me_4Si as internal standard (δ = 0 ppm). All new materials, unless otherwise indicated, were purified via dry column flash chromatography[38] employing a quartz glass column and preparative silica gel ($HF_{254+366}$ or PF_{254}; available from EM Science). R_f values wer ascertained by standardized TLC procedure: Baker-Flex silica gel IB2-F plates. Elemental analyses were performed by MicAnal Laboratories in Tucson, AZ.

Solvents. Anhydrous *N,N*-dimethylformamide (DMF) was purified in order to remove cyanide impurities via refluxing for 4–6 h in the dark over CaH_2 at 29 mmHg, followed by fractional distillation from which the middle fraction was stored in a dark bottle under argon.[39] Anhydrous tetrahydrofuran (THF) was distilled from benzophenone ketyl under argon, immediately prior to use. All other solvents were distilled before use.

Tetrakis(bromomethyl)methane (2) was prepared (51%) via treatment of the white crystalline pentaerythrityl benzenesulfonate in diethylene glycol with NaBr at 140–150 °C for 10 h: colorless crystals (acetone); mp 155–157 °C (lit.[3] mp 156.5–158 °C).

Tetrakis(2-bromoethyl)methane (3) was prepared (overall 20% from γ-pyrone[19]) according to a published procedure[18] in six steps: mp 181–182 °C.

Attempted Preparation of Tetrakis(3,3,3-tricarbethoxypropyl)methane. A stirred mixture of tetrabromide **3** (1 equiv), triethyl sodiomethanetricarboxylate (4.5 equiv), and anhydrous K_2CO_3 in anhydrous solvents was warmed at up to 110 °C for up to 2 days. After workup, greater than 95% unchanged starting

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material was recovered. Diverse solvents (DMSO, DMF, DMF/benzene, benzene, THF, acetone, DMA, HMPA, MeCN, and sulfolane) were used as well as with added reagents (e.g., NaI, 18-crown-6, $AgNO_3$, or R_4NOH); no evidence for cascade formation was noted.

Tetramethyl Spiro[5.5]undecane-3,3,9,9-tetracarboxylate. A mixture of tetrabromide **3** (888 mg, 2 mmol), dimethyl malonate (2.64 g, 20 mmol) and anhydrous K_2CO_3 (1.33 g, 9.6 mmol) in anhydrous DMF (25 mL) was stirred for 24 h at 25 °C and then warmed for 2 h at 100 °C. After concentration in vacuo and the addition of benzene (100 mL), the solution was washed sequentially water (50 mL), 15% aqueous NaOH (20 mL), and water (50 mL), dried ($MgSO_4$), and concentrated in vacuo to afford a residue, which was chromatographed (SiO_2) eluting with C_6H_{12}/EtOAc (5:1) to give (59%) the desired spirane, as a colorless oil, which solidified on standing: 450 mg; mp 57.4–59.2 °C; ^{1}H NMR δ 1.36 (m, CH_2CH_2C, 8 H), 2.01 (m, CH_2C, 8 H), 3.72 (s, CH_3, 12 H); ^{13}C NMR δ 26.6 [$CH_2CH_2C(CO_2Me)_2$], 30.7 (quaternary *C*), 32.6 [$CH_2C(CO_2Me)_2$], 52.6 (OCH_3), 55.2 (CCO_2), 172.5 (*C*=O). Anal. Calcd for $C_{19}H_{28}O_8$: C, 59.36; H, 7.34. Found: C, 59.34; H, 7.47.

Tetrakis(2-cyanoethyl)methane (4) was prepared (79%) by treatment of **3** with KCN in MeCN: tan needles (MeCN/EtOH); mp 179.5–180.5 °C (lit.[6] mp 179–180 °C); ^{1}H NMR δ (DMSO-d_6) 1.56 (m, $CH_2CH_2C{\equiv}N$, 8 H), 2.45 (m, $CH_2C{\equiv}N$, 8 H); ^{13}C NMR δ 10.7 ($CH_2C{\equiv}N$), 29.1 (CH_2CH_2CN), 37.4 (C_4), 120.8 (*C*≡N); IR 2250 (C≡N) cm^{-1}.

Tetrakis(2-carbethoxyethyl)methane (5b) was prepared by hydrolysis of **4** with concentrated HCl to give (100%) the desired tetraacid **5a**, as white microcrystals: mp 262–263 °C (lit.[6] mp 262–263 °C); ^{1}H NMR (DMSO-*d*) δ 1.47 (m, $CH_2CH_2CO_2H$, 8 H), 2.08 (m, CH_2CO_2H, 8 H); ^{13}C NMR δ 27.8 (CH_2CO_2H), 30.0 ($CH_2CH_2CO_2H$), 35.7 (C_4), 174.6 (*C*=O). Without further purification, this acid was esterified to afford (99%) the corresponding ethyl ester **5b**, as a pale yellow oil: bp 180–190 °C (0.1 mm) [lit.[6] bp 187–192 °C (0.1 mm)]; ^{1}H NMR δ 1.25 (t, CH_3, J = 7.1 Hz, 12 H), 1.5 (m, CH_2CH_2CO, 8 H), 2.2 (m, CH_2CO, 8 H), 4.12 (q, CH_2CH_3, J = 7.1 Hz, 8 H); ^{13}C NMR δ 14.2 (CH_3), 28.5 (CH_2CO), 30.5 (CH_2CH_2CO), 36.4 (C_4), 60.6 (OCH_2), 173.7 (C=O).

Tetrakis(3-hydroxypropyl)methane (6). Method A. To a stirred suspension of $LiAlH_4$ (3.6 g, 95 mmol) in anhydrous ether (360 mL) was slowly added a solution of ester **5b** (3.60 g, 8.6 mmol) in anhydrous ether (35 mL). The mixture was refluxed for 6 h and then cooled and decomposed by adding water (15 mL). The solvents were removed in vacuo to give a solid, which was continuously extracted with hot absolute EtOH. The combined extract was evaporated to dryness to afford (80%) the tetrol **6**, as a white powder: 1.72 g; mp 163–164.5 °C; ^{1}H NMR (DMSO-d_6) δ 1.20 (m, $CH_2CH_2CH_2O$, 16 H), 3.39 (t, CH_2O, J = 5 Hz, 8 H); ^{13}C NMR δ 26.4 (CH_2CH_2O), 32.7 ($C(CH_2)_4$), 36.1 (C_4), 62.1 (CH_2OH); IR 3650–3140, 2955, 2866, 1050 cm^{-1}; MS *m/e* 249.5 (M^+ + 1, 100). Anal. Calcd for $C_{13}H_{28}O_4$: C, 62.90; H, 11.29. Found: C, 62.88; H, 11.15.

Method B. The alcohol **14** (1.0 g; 1.87 mmol), absolute EtOH (100 mL), and a catalytic amount of 20% Pd–C (100 mg) were placed in a glass bomb. The vessel was placed on a Parr hydrogenator and charged to 55 psi with H_2 at 25 °C. After 15 h, the catalyst was removed via filtration through Celite and the filtrate concentrated to give (91%) the tetrol **6**; 422 mg.

Tetrakis(3-bromopropyl)methane (7). Method A. To a stirred, cooled solution of tetraol **6** (1 g, 4 mmol) in 48% HBr (25 mL) was added concentrated H_2SO_4 (12.5 mL), and then the mixture was heated at 100 °C for 20 h. After cooling, the mixture was poured into water (200 mL) and extracted with CH_2Cl_2. The extract was washed with saturated aqueous $NaHCO_3$ and then water, dried (Na_2SO_4), and concentrated in vacuo to give the crude product, which was recrystallized from Et_2O to afford (84%) **7**, as colorless crystals: 1.68 g; mp 73–73.5 °C (lit.[6] mp 73–74 °C); ^{1}H NMR δ 1.2–2.0 (m, $CH_2CH_2CH_2Br$, 16 H), 3.39 (t, CH_2Br, J = 6.2 Hz, 8 H); ^{13}C NMR δ 26.5 (CH_2CH_2Br), 36.0 ($C(CH_2)_4$), 36.2 (CH_2Br), 38.0 (C_4); IR 2975, 2860 cm^{-1}.

Method B. A mixture of hydroxy triether **14** (1.08 g, 2.0 mmol), concentrated H_2SO_4 (5.0 mL), and 48% HBr (10.0 mL) was heated at 90 °C for 12 h. After the mixture was cooled to 25 °C, CH_2Cl_2 (50 mL) was added and subsequently washed with H_2O (2 × 40 mL) and saturated $NaHCO_3$ (50 mL), dried ($MgSO_4$), filtered, concentrated to give a brown residue. After passing through a short path silica column, the material was recrystallized from Et_2O to afford (72%) the pure tetrabromide **7** (725 mg; mp 70–72 °C), identical to the above sample.

4-(Cyanoethyl)-4-[3-(benzyloxy)propyl]-1,7-bis(benzyloxy)heptane (12). A solution of nitrotribenzyl ether[31] **11** [prepared (65%) from nitromethanetris(propanol)[25] (**10**); 2.02 g, 4 mmol)], tri-*n*-butyltin hydride (3.5 g, 12 mmol), acrylonitrile (2.3 g, 44 mmol), and 2,2′-azobis(4-methylpropionitrile) (660 mg, 4 mmol) in toluene (10 mL) was heated at 100 °C for 1 h. Upon cooling, EtOAc (100 mL) was added and the residue was filtered. After concentration in vacuo, MeCN (100 mL) was added and subsequently washed with hexane[40] (2 × 100 mL). The MeCN layer was concentrated in vacuo and dry-flash chromatographed (SiO_2) eluting with C_6H_{12}/CH_2Cl_2 to give (52%) pure **12**, as an oil: 1.07 g; ^{1}H NMR δ 0.70–1.70 (m, quaternary CCH_2CH_2O, 14 H), 2.10–2.40 (m, CH_2CN, 2 H), 3.40 (t, CH_2O, J = 5.6 Hz, 6 H), 4.42 (s, $CH_2C_6H_5$, 6 H), 7.25 (bs, C_5H_5, 15 H); ^{13}C NMR δ 11.2 (CH_2CN), 23.1 ($CH_2CH_2CH_2$), 31.6 ($NCCH_2CH_2$), 31.8 ($CH_2CH_2CH_2O$), 36.5 (C_4), 70.5 (CH_2O), 72.0 ($CH_2C_6H_5$), 120.1 (*C*N), 128.4, 128.8, 133.2, 137.0 (C_6H_5); IR (neat) 2247 (C≡N) cm^{-1}; MS *m/e* 514 (M^+ + 1, 100). Anal. Calcd for $C_{34}H_{43}NO_3$: C, 79.53; H, 8.38. Found: C, 79.61; H, 8.40.

4-(Carboxyethyl)-4-[3-(benzyloxy)propyl]-1,7-bis(benzyloxy)heptane (13b). A 1:1 solution of 30% H_2O_2 and H_2O (80 mL) was added in portions (2 × 40 mL; 10-min intervals) to a stirred mixture of nitrile **12** (10 g, 19.5 mmol), 95% EtOH (520 mL), KOH (24 g, 428 mmol), and H_2O (50 mL) at 25 °C. After addition, the temperature was increased to 60 °C for 3 h and then refluxed for 18 h. After the solution was cooled to 25 °C, the solvent was removed in vacuo, and cold water was added. The solution was acidified with concentrated HCl, and then CH_2Cl_2 (200 mL) was added. The organic layer was separated, washed sequentially with H_2O (2 × 100 mL) and brine (2 × 100 mL), dried ($MgSO_4$), filtered, concentrated in vacuo, and column chromatographed eluting with CH_2Cl_2/EtOAc to afford (73%) pure monoacid **13b**, as an oil: 7.6 g; ^{1}H NMR δ 1.10–1.65 [m, $CH_2C(CH_2CH_2-)_3$, 14 H], 2.15–2.40 (m, CH_2CO_2, 2 H), 3.41 (t, CH_2O, J = 7.3 Hz, 6 H), 4.47 (s, $OCH_2C_6H_5$, 6 H), 7.29 (s, C_6H_5, 15 H), 9.30 (bs, O*H*, 1 H); ^{13}C NMR δ 23.2 ($CH_2CH_2CH_2$), 28.2 ($CH_2CH_2CO_2$), 30.8 (CH_2CO_2), 32.3 ($CH_2CH_2CH_2O$), 36.2 (C_4), 70.8 (CH_2O), 72.7 ($OCH_2C_6H_5$), 127.5, 127.6, 128.3, 138.6 (C_6H_5); IR 3500–2489, 3070, 3024, 2930, 2851 cm^{-1}; MS *m/e* 533 (M^+ + 1, 100). Anal. Calcd for $C_{34}H_{44}O_5$: C, 76.69; H, 8.27. Found: C, 76.66; H, 8.52.

4-(3-Carbamoylpropyl)-4-[3-(benzyloxy)propyl]-1,7-bis[(benzyloxy)propyl]heptane (13a). Hydrolysis of the nitrile **12** to obtain the amide **13a** was performed the same as the hydrolysis to yield the acid except that after stirring at 60 °C for 3 h, the reaction was cooled to 25 °C and then subjected to isolation and purification: ^{1}H NMR δ 1.00–1.65 [m, $C(CH_2CH_2)_4$, 16 H], 1.75–2.00 (m, CH_2CONH_2, 2 H), 3.40 (t, CH_2CH_2O, J = 7.2 Hz, 6 H), 4.43 (s, $OCH_2C_6H_5$, 6 H), 5.90 (br s, NH_2, 2 H), 7.27 (s, C_6H_5, 15 H); ^{13}C NMR δ 22.9 ($CH_2CH_2CH_2$), 29.5 (CH_2CH_2CON), 31.4 (CH_2CON), 32.0 ($CH_2CH_2CH_2O$), 36.1 (C_4), 70.6 (CH_2CH_2O), 72.4 ($OCH_2C_6H_5$), 127.3, 127.3, 128.1, 138.3 (C_6H_5), 176.4 (*C*=O); IR 3347, 3185, 3068, 3021, 2936, 2854, 1674, 1100, 740, 700 cm^{-1}. Anal. Calcd for $C_{34}H_{45}NO_4$: C, 76.83; H, 8.47. Found: C, 77.01; H, 8.50.

4-(Formylethyl)-4-[3-(benzyloxy)propyl]-1,7-bis(benzyloxy)heptane (15). To a stirred solution of nitrile **12** (600 mg, 970 μmol) in THF (50 mL) under N_2 at 0 °C was added a solution of DIBAL-H (1.95 mmol, 1.29 mL; 1.5 M in toluene) via a syringe. After the solution was stirred for 12 h at 25 °C, dilute (10%) HCl (10 mL) was added. The solvent was removed in vacuo, and ether (50 mL) was added. The ethereal solution was washed with saturated aqueous $NaHCO_3$ and brine (2 × 50 mL), dried ($MgSO_4$), filtered, concentrated in vacuo, and column chromatographed eluting with CH_2Cl_2/C_6H_{12} to give (20%) aldehyde **13**: 100 mg; ^{1}H NMR δ 11.21 (s, *CH*O, 1 H); ^{13}C NMR δ 23.4 (CH_2CH_2O), 27.8 ($CH_2CH_2CH_2O$), 32.4 (CH_2CH_2CHO), 36.8 (CH_2CHO), 38.3 (C_4), 71.0 (CH_2CH_2O), 72.9 ($OCH_2C_6H_5$),

(40) Giese, B.; Gröninger, K. S. *Org. Synth.* **1990**, *69*, 66.

127.7, 128.4, 138.7 (C_6H_5), 202.7 (C=O); IR 1735 cm^{-1}; MS *m/e* 409 (M^+ + OBzl, 20). Anal. Calcd for $C_{34}H_{44}O_4$: C, 79.07; H, 8.53. Found: C, 79.13; H, 8.53.

4-(3-Hydroxypropyl)-4-[3-(benzyloxy)propyl]-1,7-bis(benzyloxy)heptane (14). Method A. To a stirred solution of acid **13b** (3.1 g, 5.8 mmol) in dry THF (150 mL) at 10 °C under N_2, was added borane (11.7 mmol, 11.7 mL; 1.0 M BH_3·THF) via a syringe. After addition, the mixture was refluxed for 3 h and then cooled to 10 °C and quenched carefully with aqueous HCl (10%; 20 mL). The solvent was removed in vacuo affording a residue, which was dissolved in CH_2Cl_2 (100 mL) and washes sequentially with H_2O (2 × 75 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was column chromatographed (SiO_2) eluting with CH_2Cl_2/C_6H_{12} to afford (89%) pure alcohol **12**, as an oil: 2.7 g; ^1H NMR δ 1.00–1.80 [m, $C(CH_2CH_2-)_4$, 16 H], 3.25–3.60 (m, CH_2O 8 H), 4.42 (s, $CH_2C_6H_5$, 6 H), 7.25 (s, C_6H_5, 15 H); ^{13}C NMR δ 23.3 ($CH_2CH_2OCH_2$), 26.3 (CH_2CH_2O), 32.0 [$CH_2(CH_2)_2OH$], 32.4 [$CH_2(CH_2)_2OCH_2$], 36.2 (C_4·), 63.3 (CH_2OH), 71.1 ($CH_2OCH_2C_6H_5$), 72.7 ($OCH_2C_6H_5$), 127.4, 127.5, 128.3, 138.6 (C_6H_5); IR 3676–3149, 3070, 3025, 2949, 2859, 1450 cm^{-1}; MS *m/e* 519 (M^+ + 1, 100). Anal. Calcd for $C_{34}H_{46}O_4$: C, 78.76; H, 8.88. Found: C, 78.48; H, 9.04.

Method B. To a stirred solution of EtOH (95%, 7.5 mL), CH_2Cl_2 (2.5 mL), and aldehyde **15** (100 mg, 190 μmol) at 25 °C was added $NaBH_4$ (130 mg, 3.4 mmol). After 3 h, the mixture was cooled, quenched slowly with HCl (10%), and concentrated in vacuo to give a residue which was washed with H_2O (50 mL) and then brine, dried ($MgSO_4$), filtered, concentrated, and column chromatographed (SiO_2) eluting with CH_2Cl_2/C_6H_{12} to afford alcohol **12**, identical in all respects to the above sample.

Tetrakis(4,4-dicarbomethoxybutyl)methane (8). A mixture of tetrabromide **7** (100 mg, 200 μmol), dimethyl malonate (211 mg, 1.6 mmol), and anhydrous K_2CO_3 (133 mg, 960 μmol) in anhydrous DMF (5 mL) was stirred at 25 °C for 24 h. The solvent was removed in vacuo, and then benzene (100 mL) was added. The organic layer was washed sequentially with water (50 mL), 15% aqueous $NaHCO_3$ (20 mL), and water (3 × 30 mL) and then dried ($MgSO_4$) and concentrated in vacuo to afford a residue, which was chromatographed (SiO_2) eluting with C_6H_{12}/EtOAc (4:1) to give (79%) the octaester **8**, as a colorless oil: ^1H NMR δ 1.13 (m, CCH_2CH_2, 16 H), 1.80 (m, CH_2CH, 8 H), 3.36 (t, CH, J = 7.4 Hz, 4 H), 3.94 (s, CH_3, 24 H); ^{13}C NMR δ 20.6 (CCH_2CH_2), 29.4 (CH_2CH), 35.8 ($C(CH_2)_4$), 37.0 (C_4·), 51.3 (CH), 52.5 (CH_3). Anal. Calcd for $C_{33}H_{52}O_{18}$: C, 56.24; H, 7.44. Found: C, 56.07; H, 7.33.

Tetrakis(4,4,4-tricarbethoxybutyl)methane (9). A mixture of **7** (100 mg, 200 μmol), triethyl methanetricarboxylate[5] (372 mg, 1.6 mmol), and anhydrous K_2CO_3 (133 mg, 960 μmol) in anhydrous DMF (5 mL) was stirred at 60 °C for 19 h. Workup was similar to that of **8** to afford (42%) the pure dodecaester **9**, as a colorless oil: 94 mg; R_f 0.11; ^1H NMR δ 1.2–2.2 (m, $CH_2CH_2CH_2$, CH_3, 60 H), 4.25 (q, CH_2CH_3, J = 7.1 Hz, 24 H); ^{13}C NMR δ 14.0 (CH_3), 18.6 ($CH_2CH_2CH_2$), 34.2 [$CH_2C(CO_2Et)_3$], 37.0 (quaternary CCH_2O), 62.0 (OCH_2O, 65.7 [$C(CO_2Et)_3$], 167.0 (C=O). Anal. Calcd for $C_{53}H_{87}O_{24}$: C, 57.60; H, 7.66. Found: C, 57.74; H, 7.57.

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Registry No. **2**, 3229-00-3; **3**, 5794-98-9; **4**, 10428-68-9; **5a**, 10428-69-0; **5b**, 10428-70-3; **6**, 35060-82-3; **7**, 35060-83-4; **8**, 144492-83-1; **9**, 144492-84-2; **10**, 116747-80-9; **11**, 135646-71-8; **12**, 135646-72-9; **13a**, 144492-85-3; **13b**, 135646-73-0; **14**, 135646-74-1; **15**, 144492-86-4; $C(CH_2CH_2CH_2CN)_4$, 35060-84-5; pentaerythriyl benzenesulfonate, 2514-70-7; triethyl sodiomethanetricarboxylate, 68922-87-2; dimethyl malonate, 108-59-8; tetramethyl spiro[5.5]undecane-3,3,9,9-tetracarboxylate, 144492-87-5; acrylonitrile, 107-13-1; triethyl methanetricarboxylate, 6279-86-3.