Table III. Isomer Ratio of the Products of Friedel-Crafts Monoethylation and Mononitration

	ethylation				nitration			
substrate	ortho	meta	para	m/p	ortho	meta	para	m/p
PhCHO	19.0	60.9	20.1	3.0	19	68	9	7.6
$PhCO_2Et$	4.6	78.3	17.2	4.6	28.3	68.4	3.3	20.7
PhCOMe	1.9	81.0	16.9	4.8	30	68		>30
$PhNO_2$	22.5	66.6	10.9	6.1	6.4	93.3	0.3	311

abundant but more reactive unprotonated state. Because Friedel-Crafts alkylation is the least selective of the electrophilic aromatic substitutions,[3] the meta to para ratio, m/p, of the products should be relatively small if the reaction proceeds via the unprotonated state. If, however, the reaction proceeds via the protonated state, the products should consist almost solely of the meta isomer, as is found in Friedel-Crafts alkylation in the presence of large excesses of $AlCl_3$[4] or in super acids.[2] From a comparison of the m/p ratios of the products of the monoethylation and mononitration[5] (Table III), it is evident that alkylation by alcohols in protonic acids proceeds mainly via the unprotonated state.

During the ethylation of acetophenone a small amount of crystalline substance formed on the wall of the condenser. It was collected and was identified as acetophenone. This observation suggested that some unprotonated acetophenone exists in equilibrium with the more abundant protonated acetophenone.

Acknowledgment. We wish to thank Mr. Walter Kossa for editorial assistance.

Registry No. CH_3OH, 67-56-1; *tert*-BuOH, 75-65-0; H_2SO_4, 7664-93-9; H_3PO_4, 7664-38-2; PhCHO, 100-52-7; $PhCO_2Et$, 93-89-0; PhCOMe, 98-86-2; $PhNO_2$, 98-95-3; *o*-EtC_6H_4CHO, 22927-13-5; *m*-EtC_6H_4CHO, 34246-54-3; *p*-EtC_6H_4CHO, 4748-78-1; *o*-$EtC_6H_4CO_2Et$, 56427-44-2; *m*-$EtC_6H_4CO_2Et$, 136569-05-6; *p*-$EtC_6H_4CO_2Et$, 36207-13-3; *m*-EtC_6H_4COMe, 22699-70-3; *p*-EtC_6H_4COMe, 937-30-4; *o*-$EtC_6H_4NO_2$, 612-22-6; *m*-$EtC_6H_4NO_2$, 7369-50-8; *p*-$EtC_6H_4NO_2$, 100-12-9; EtOH, 64-17-5; *n*-PrOH, 71-23-8; *i*-PrOH, 67-63-0; *n*-BuOH, 71-36-3; *m*-EtC_6H_4COPh, 66067-43-4; *m*-*i*-PrC_6H_4COPh, 32388-73-1; Ph_2CO, 119-61-9; benzonitrile, 100-47-0; *N*-ethylbenzamide, 614-17-5.

(3) Stock, L. M.; Brown, H.C. *Advances in Physical Organic Chemistry* Academic: London, 1963; Vol. 1, p 50.
(4) Campbell, B. N., Jr.; Spaeth, E. C. *J. Am. Chem. Soc.* **1959**, *81*, 5933.
(5) Ingold, C.K. *Structure and Mechanism in Organic Chemistry*; Ithaca, NY, 1953; p 262.

Cascade Polymers:[1] Syntheses and Characterization of One-Directional Arborols Based on Adamantane

George R. Newkome,* Rajani K. Behera,[2] Charles N. Moorefield, and Gregory R. Baker

Center for Molecular Design and Recognition, Department of Chemistry, University of South Florida, Tampa, Florida 33620-5250

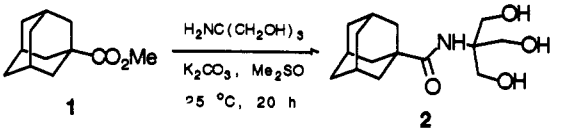
Received June 4, 1991

Several methods for the synthesis of cascade polymers (dendritic macromolecules) on adamantane have been investigated. The synthesis of two novel, branched monomers, 4-amino-4-(3-acetoxypropyl)-1,7-diacetoxyheptane and di-*tert*-butyl 4-amino-4-[2-(*tert*-butoxycarbonyl)ethyl]heptanedioate, possessing 3-fold symmetry and branches emanating from a tetrahedral carbon branch point, is described. These monomers were reacted with a monofunctional adamantane core to evaluate the reaction efficiency, ease of purification of products, and spectral characteristics.

Introduction

The syntheses and spectral features of cascade polymers (arborols)[3] possessing two-,[4,5] three-,[6] and four-directional[7-10] microenvironments with functionalized polar outer surfaces have been recently reported from our laboratories; related work on these dendritic macromolecules has been reviewed.[11] Depending on their molecular shape, many of these macromolecules aggregate to form aqueous gels[5] or show novel micellar characteristics in aqueous solution.[9,10] In view of our continued interest in generating a spherical hydrophilic surface with a compact lipophilic core,[12] we herein probe the development of a cascade system emanating from a central adamantane core. The

Scheme I

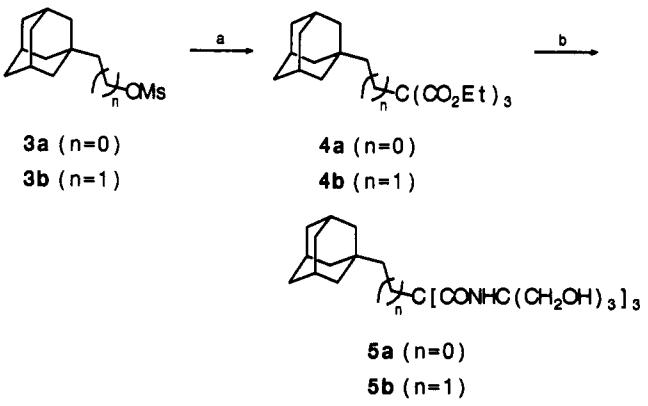


1 2

(1) (a) Chemistry of Micelles Series. Part 18. (b) Proceeding paper (Part 17) see: Weis, C. D.; Newkome, G. R. *J. Org. Chem.* **1991**, *56*, 4798.
(2) Visiting Scholar, Sambalpur University, India, 1989-1991.
(3) Newkome, G. R.; Yao, Z.-q.; Baker, G. R.; Gupta, V. K. *J. Org. Chem.* **1985**, *50*, 2003.
(4) Newkome, G. R.; Baker, G. R.; Saunders, M. J.; Russo, P. S.; Gupta, V. K.; Yao, Z.-q. Y.; Miller, J. E.; Bouillion, K. *J. Chem. Soc., Chem. Commun.* **1986**, 752.
(5) Newkome, G. R.; Baker, G. R.; Aria, S.; Saunders, M. J.; Russo, P. S.; Theriot, K. J.; Moorefield, C. N.; Rogers, L. E.; Miller, J. E.; Lieux, T. R.; Murray, M. E.; Phillips, B.; Pascal, L. *J. Am. Chem. Soc.* **1990**, *112*, 8458.
(6) Newkome, G. R.; Yao, Z. q.; Baker, G. R.; Gupta, V. K.; Russo, P. S.; Saunders, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 849.
(7) Newkome, G. R.; Hu, Y.; Saunders, M. J.; Fronczek, F. R. *Tetrahedron Lett.* **1991**, *32*, 1133.
(8) Newkome, G. R.; Moorefield, C. N.; Baker, G. R.; Johnson, A. J.; Behera, R. K. *Angew. Chem.* **1991**, *103*, 1205; *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1176.
(9) Newkome, G. R.; Moorefield, C. N.; Baker, G. R.; Saunders, M. J.; Grossman, S. H. *Angew. Chem.* **1991**, *103*, 1207; *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1178.
(10) Newkome, G. R.; Lin, X. *Macromolecules* **1991**, *24*, 1443.
(11) Reviews: Seiji, S. *Kagaku* **1987**, *42*, 74. Chen, Y. *Youji Huaxue* **1990**, *10*, 289; *Chem. Abstr.* **1990**, *113*, 190809t. Amato, I. *Science News* **1990**, *138*, 298. Tomalia, D. A.; Naylor, A. M.; Goddard, W. A. III *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 138. Also see: Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638. Wooley, K. L.; Hawker, C. J.; Fréchet, J. M. J. *J. Chem. Soc., Perkin Trans 1* **1991**, 1059.
(12) Newkome, G. R.; Arai, S.; Gupta, V. K.; Griffin, R. W. *J. Org. Chem.* **1987**, *52*, 5480.

0022-3263/91/1956-7162$02.50/0

Scheme II[a]



3a (n=0)
3b (n=1)

4a (n=0)
4b (n=1)

5a (n=0)
5b (n=1)

[a] Reagents: (a) $HC(CO_2Et)_3$, K_2CO_3, dry DMF, 100–110 °C, 4 h; (b) $H_2NC(CH_2OH)_3$, K_2CO_3, Me_2SO, 25 °C, 12 h.

bridgehead positions of adamantane provide the suitable geometry to mimic a tetrahedral nucleus and, thus, can be envisioned as an extended methane core and an ideal starting point toward four-directional cascade arborols. We herein report the preliminary synthetic methodology toward the construction of a one-directional arborol moiety on an adamantane nucleus.

Results and Discussion

The simplest arborol in this series **2** was prepared (90%), as colorless crystals, by reacting methyl 1-adamantanecarboxylate (**1**)[13] with tris(hydroxymethyl)aminomethane (Tris) under the standard (K_2CO_3/Me_2SO) conditions (Scheme I). The ^{13}C NMR spectrum of triol **2** confirmed the amidation by the upfield shift (Δ 2 ppm) of the carbonyl carbon (δ 180.3) and new signals at δ 41.0 and 62.8 for the α-bridgehead and side-chain quaternary carbons, respectively. This facile, high-yield conversion has been shown[5] to occur via initial transesterification followed by an intramolecular amidation.

In order to probe the effects of the tied-back quaternary center and to investigate the application of our reported routes[4–8] to the adamantane series, the synthesis of the simple arborol **5a** with a one-carbon side chain on the adamantane skeleton was attempted (Scheme II). Treatment of 1-[(mesyloxy)methyl]adamantane[14] (**3a**) with triethyl methanetricarboxylate[15,16] in DMF and anhydrous K_2CO_3 under diverse reaction conditions afforded the unchanged mesylate rather than the desired triester **4a**. On the other hand, its homologue, 1-[2-(mesyloxy)-ethyl]adamantane (**3b**), was smoothly converted (70%) to triester **4b**, which upon treatment with Tris and anhydrous K_2CO_3 in Me_2SO afforded (90%) arborol **5b** as a colorless solid. The ^{13}C NMR spectrum of **5b** supported the desired conversion: ester (167.3 ppm) vs amide (170.2 ppm) C=O as well as the loss of ethyl signal and the appearance of the new peak at 59.5 ppm for the hydroxymethyl moieties.

After establishing the limitations caused by the neighboring bridgehead position, the inherent reduced reactivity of the neopentyl moiety of the Tris terminal groups had to be circumvented. Homologation by introduction of a separate spacer moiety is possible[3] but adds further steps to the iterative synthetic process. Key reagents, which incorporate the necessary two-atom spacer, are easily obtained derivatives of "bis-homotris".[1b,17] Commercially available[18] 4-nitro-4-(3-hydroxypropyl)-1,7-dihydroxyheptane was treated with Ac_2O in pyridine to give the corresponding triacetate,[19] which was catalytically reduced with T-1 Raney nickel,[20] affording the desired 4-amino-4-(3-acetoxypropyl)-1,7-diacetoxyheptane (**6**) in nearly quantitative overall yield.

Treatment of 1-adamantanecarbonyl chloride with amine **6** afforded (78%) the triacetate **7** (Scheme III) as white microcrystals. The ^{13}C NMR for **7** confirmed the transformation by the presence of peaks at 170.6 ppm (*C*OMe) and 176.7 ppm (CONH) in a nearly 3:1 intensity ratio. A quantitative transesterification of **7** was accomplished by the use of anhydrous K_2CO_3 in ethanol giving the bis-homologated derivative **8**. Although the spectral data support the structure by the retention of the 179.9 ppm signal for the amide carbonyl and shift (64.1–63.3 ppm) for the CH_2O moieties, the analytical data were outside acceptable standards due to its hygroscopic characteristics. Subjecting **8** to Ac_2O in pyridine under mild conditions regenerated (ca. 100%) the initial triacetate **7**, which was identical in all respects to the starting material.

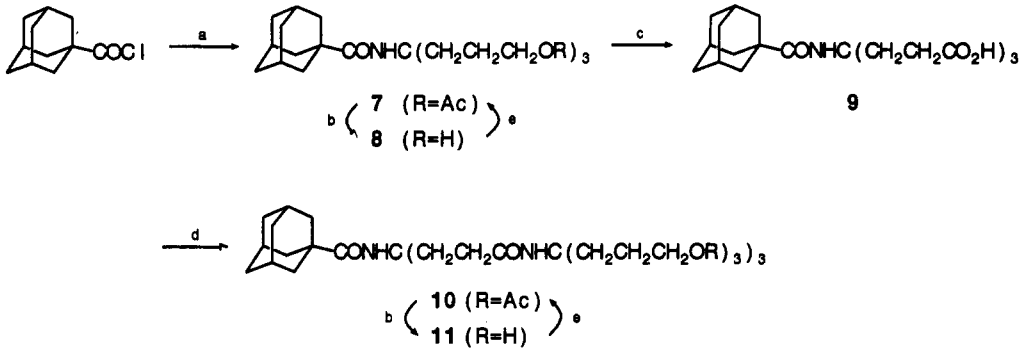
Generation of the next tier was possible via several options. Oxidation of triol **8** to the corresponding triacid **9** would permit application of peptide coupling procedures.[21] Therefore, triol **8** was treated with RuO_2[22] in the presence of $NaIO_4$ to afford (86%) the desired triacid **9** (Scheme III), which was supported (^{13}C NMR) by loss of the peak at 63.3 ppm (CH_2OH) and appearance of a peak at 177.5 ppm (CO_2H). It should be noted that peak assignments in the ^{13}C NMR were based on the data obtained from DEPT experiments[23] as well as the intensities of related peaks; such calculations and intensity relationships were also used for the larger structures in this series.

Treatment of triacid **9** with amine **6**, dicyclohexylcarbodiimide (DCC), and 1-hydroxybenzotriazole in anhydrous DMF at 25 °C for 24 h afforded (72%) the nonaacetate **10**. The ^{13}C NMR spectrum for **10** showed two carbonyl peaks at 171.0 ppm ($COCH_3$) and 172.7 ppm (CONH) in an approximate 3:1 intensity ratio and the two peaks at 58.5 and 59.4 ppm for the two side-chain quaternary carbons; all other absorptions are easily assignable. This nonaacetate **10** was quantitatively converted to the corresponding arborol **11** via transesterification in ethanol. The ^{13}C NMR data for **11** support its assignment by the retention of the peak at 175.3 ppm (CONH) and loss of the acetate signals (171.0 and 20.5 ppm); the shifted triplet to 3.36 ppm for the CH_2OH (4.05 ppm for CH_2OAc) in the ^1H NMR spectrum lend further support.

Attempted oxidation of **11** via a RuO_2 procedure met with limited success in that complete oxidation was not reproducible. To circumvent this problem as well as to shorten the overall iterative procedure, a new building block di-*tert*-butyl 4-amino-[2-(*tert*-butoxycarbonyl)-ethyl]heptanedioate (**12**) was prepared (Scheme IV). An attempt to synthesize the desired nitro precursor **13** by modification of the procedure reported by Bruson and

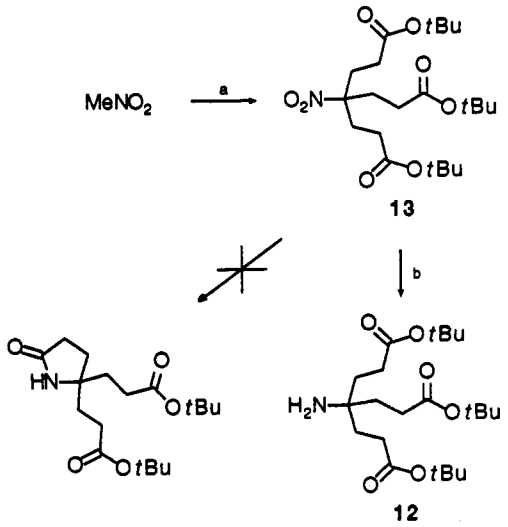
(13) Halls, G. *J. Chem. Soc. B* **1967**, 91.
(14) Pfeiffer, F. R.; Weisbach, J. A. U.S. Pat. 3,705,213, Dec. 5, 1972; U.S. Pat. 3,678,137, July 18, 1972.
(15) Newkome, G. R.; Baker, G. R. *Org. Prep. Proc. Int.* **1986**, *18*, 119.
(16) Skarżewski, J. *Tetrahedron* **1989**, *45*, 4593; *Synthesis* **1990**, 1125.
(17) Broussard, M.; Juma, B.; Fronczek, F. R.; Watkins, S. F.; Newkome, G. R.; Moorefield, C. N. *Acta Crystallogr. C*, in press.
(18) Aldrich Chemical Co. No. 36, 153-4.
(19) Weis, C. D.; Newkome, G. R. *J. Org. Chem.* **1990**, *55*, 5801.
(20) Domingues, X. A.; Lopez, I. C.; Franco, R. *J. Org. Chem.* **1961**, *26*, 1625.
(21) Bodanszky, M.; Bodanszky, A. The Practice of Peptide Synthesis. In *Reactivity and Structure: Concepts in Organic Chemistry*; Springer-Verlag: New York, 1984; Vol. 21, p 145.
(22) Irngartinger, H.; Reimann, W. *J. Org. Chem.* **1988**, *53*, 3046.
(23) Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy*; VCH: New York, 1987; pp 80–84.

Scheme III[a]



[a] Reagents: (a) amine **6**, NEt_3, C_6H_6, 25 °C, 20 h; (b) anhyd K_2CO_3, absolute EtOH, 25 °C, 15 h; (c) with **8**: $NaIO_4$, RuO_2, acetone, H_2O, 25 °C, 5 h; (d) amine **6**, DCC, 1-hydroxybenzotriazole, DMF, 25 °C, 24 h; (e) Ac_2O, py.

Scheme IV[a]

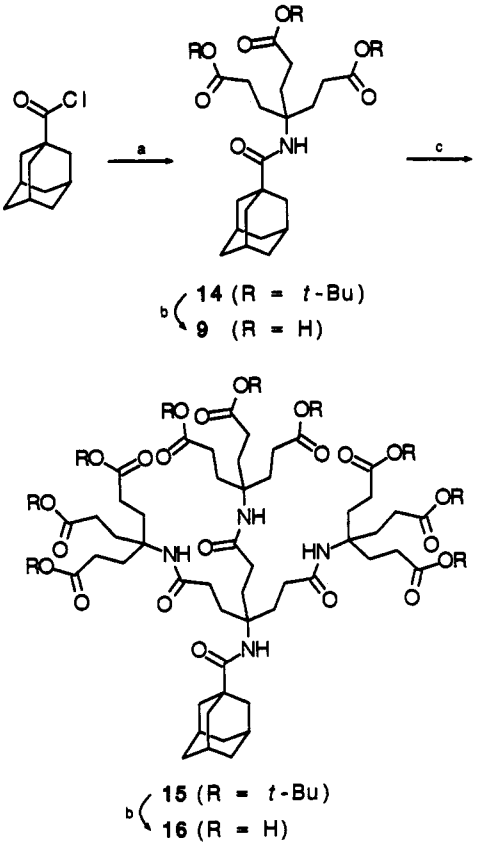


[a] Reagents: (a) DME, Triton-B, $CH_2{=}CHCO_2$-*t*-Bu, 70–80 °C; (b) T-1 Raney nickel, EtOH, 60 °C.

Riener[24] using *tert*-butyl acrylate in place of acrylonitrile gave a poor yield (5%). To circumvent this sluggish nucleophilic addition, the reaction temperature was elevated during the initial addition phase and then maintained at 70–75 °C for 1 h. This modified procedure gave (72%) the desired triester **13**, which was confirmed (^{13}C NMR) by the peaks for the quaternary and carbonyl carbons (92.1 and 170.9 ppm, respectively). The ^1H NMR spectrum showed a singlet at 1.45 ppm assigned to $(CH_3)_3CO$ and a multiplet at 2.21 ppm for the methylene protons. Ultimate confirmation was subsequently obtained by crystal structure analysis.[25]

Diverse reductive conditions have been reported[26] for the conversion of nitroalkanols to aminoalkanols; in this case, the use of platinum, palladium, and Raney nickel catalysts all resulted in very poor yields and gave mostly recovered **13**. However, reduction with specially generated T-1 Raney nickel[20] at elevated temperature (60 °C) gave (88%) the amino ester **12** after purification. Successful

Scheme V[a]



[a] Reagents: (a) $H_2NC(CH_2CH_2CO_2$-*t*-$Bu)_3$ (**12**), NEt_3, C_6H_6, 25 °C, 20 h; (b) 96% HCO_2H, 25 °C, 20 h; (c) **12**, DCC, 1-hydroxybenzotriazole, DMF, 25 °C, 24 h.

reduction was confirmed (^{13}C NMR) by an upfield shift for the quaternary carbon (52.2 ppm). The ^1H NMR spectrum of **12** showed a singlet at 1.44 ppm for the *tert*-butyl group, multiplets at 1.68 and 2.26 ppm for the methylene protons, and a broad singlet at 5.49 ppm for the amino moiety.

Since related alkyl esters of amine **12** could not be prepared because of facile intramolecular lactam formation[27] during the hydrogenation of the nitro moiety, the *tert*-butyl ester seems to be ideal in that no cyclization was observed (Scheme IV). The advantages of *tert*-butyl ester **12** are (a) reduced number of overall steps for cascade

(24) Bruson, H. A.; Riener, T. W. *J. Am. Chem. Soc.* **1943**, *65*, 23.
(25) Newkome, G. R.; Behera, R. K.; Fronczek, F. R.; Baker, G. R. *Acta Crystallogr., Sect. C*, submitted for publication.
(26) Gakenheimer, W. C.; Hartung, W. H. *J. Org. Chem.* **1944**, *9*, 85. Noland, W. E.; Kneller, J. F.; Rice, D. E. *Ibid.* **1957**, *22*, 695. Fanta, P. E.; Smat, R. J.; Piecz, L. F.; Clemens, L. *Ibid.* **1966**, *31*, 3113. Controulis, J.; Rebstock, M. C.; Crooks, H. M., Jr. *J. Am. Chem. Soc.* **1949**, *71*, 2463. Wheatly, W. B. *Ibid.* **1954**, *76*, 2832. Newman, M. S.; Edwards, W. M. *Ibid.* **1954**, *76*, 1840. Herz, W.; Tocker, S. *Ibid.* **1955**, *77*, 3554. Baer, H. H.; Fischer, H. O. L. *Ibid.* **1960**, *82*, 3709.

(27) Allen, S. J.; Napler, J. G. U.S. Patent 2,502,548, Apr. 4, 1950. Butler, D. E. U.S. Patent 4,454,327, June 12, 1984.

synthesis; (b) easy preparation on a large scale; (c) facile hydrolysis to the desired acids in nearly quantitative yields; and (d) the poly *tert*-butyl esters were easily purifiable solids.

Treatment of adamantanecarbonyl chloride with amine **12** furnished (71%) the desired triester **14** (Scheme V), whose structure was confirmed (^{13}C NMR) by the peaks at 172.8 (ester C=O), 177.4 (CONH), and 56.7 ppm (side-chain quaternary carbon). Hydrolysis of ester **14** to the triacid **9** was accomplished (ca. 100%) by treatment with formic acid and was identical in all respects to a sample prepared by the above procedure. Application of peptide coupling procedures of acid **9** with amine **12** in the presence of DCC and 1-hydroxybenzotriazole in dry DMF afforded (61%) nonaester **15**. The presence (^{13}C NMR) of two carbonyl peaks at 172.6 (ester C=O) and 177.0 ppm (CONH) as well as the peaks for the side-chain quaternary carbons at 57.6 and 57.0 ppm confirmed the transformation. The specific assignment of internal and external methylene signals was based on the intensity ratios as well as shape (the internal methylenes were broader). Acid **16** was obtained (95%) by the treatment of ester **15** with formic acid. The obvious absence of the *tert*-butyl groups in the NMR spectra and the shift for the carbonyl, 172.6 ppm (ester) to 177.6 ppm (acid), support the hydrolysis.

Conclusion

Cascade polymers can be easily prepared using either 4-amino-4-(3-acetoxypropyl)-1,7-diacetoxyheptane (**6**) or di-*tert*-butyl 4-amino-[2-(*tert*-butoxycarbonyl)ethyl]heptanedioate (**12**) as the building-block reagent. Both reagents are readily available in high yield and on large scale, react with multiacid cascades via traditional peptide synthetic methods, and are readily deprotected. The *tert*-butyl ester affords the additional benefit of not requiring an oxidation step to generate the next tier. Work is currently in progress utilizing this technology for the preparation of four-directional cascade polymers.

Experimental Section

General Comments. Melting point data were obtained in capillary tubes with a Gallenkamp melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were obtained in $CHCl_3$, except where noted, with Me_4Si as the internal standard (δ = 0 ppm), and recorded at either 80 or 360 MHz. IR spectral data were obtained on an IBM IR-38 spectrometer. Elemental analyses were performed by MicAnal Laboratories in Tucson, AZ.

1-(Methoxycarbonyl)adamantane (1). A solution of 1-adamantanecarbonyl chloride (Aldrich No. 11,772-2; mp 52–54 °C, 2 g) in dry MeOH (25 mL) was refluxed under an inert atmosphere for 4 h. After concentration in vacuo to ca. 10 mL and cooling (0 °C), ester **1** separated (83%) as colorless needles: mp 39 °C (lit.[13] mp 38–39 °C); ^{13}C NMR δ 27.3 (γ-CH_2), 36.4 (δ-CH), 38.7 (β-CH_2), 40.6 (α-C), 51.3 (CH_3O), 178.3 (C=O).

1-[[*N*-[2-Hydroxy-1,1-bis(hydroxymethyl)ethyl]amino]carbonyl]adamantane (2). A stirred mixture of **1** (450 mg, 2.3 mmol), tris(hydroxymethyl)aminomethane (Tris; 280 mg, 2.3 mmol), and anhydrous K_2CO_3 (350 mg) in redistilled Me_2SO (20 mL) was maintained at 25 °C for 20 h. After filtration, the solvent was removed in vacuo to give a solid, which was dissolved in a minimum volume of water and precipitated with added acetone. The solid was washed with absolute ethanol and then dried in vacuo to give (90%) the hygroscopic triol **2** as a white solid: mp 160 °C; ^1H NMR (Me_2SO-d_6) δ 1.7 (m, β-CH_2, 6 H), 1.9 (m, δ-CH_2, 6 H), 2.1 (m, γ-CH, 3 H), 3.5 (bs, CH_2O, 6 H), 4.75 (bs, OH, 3 H), 6.8 (bs, NH, 1 H); ^{13}C NMR δ 28.0 (γ-CH), 36.3 (δ-CH_2), 39.2 (β-CH_2), 41.0 (α-C), 61.2 (CH_2O), 62.8 (CCH_2), 180.3 (C=O); IR (KBr) 3468–3280, 2929, 2838, 1658, 1506, 1236, 1062 cm^{-1}.

1-[2-(Mesyloxy)ethyl]adamantane (3b). To a stirred solution of 1-(2-hydroxyethyl)adamantane (Aldrich No. 18,811-5; 1.8 g, 10 mmol) and redistilled Et_3N (1.5 g, 15 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added methanesulfonyl chloride (1.3 g, 11 mmol) at such a rate that the temperature does not exceed 5 °C. After an additional 10 min, the contents were washed successively with ice water, 10% HCl, saturated aqueous $NaHCO_3$, and finally with brine. The organic layer was dried ($MgSO_4$), and the solvent was removed in vacuo to give a thick viscous residue, which solidified after ca. 12 h, and then was recrystallized from $CHCl_3$/ether (1:3) to give (76%) mesylate **3b** as a colorless solid: mp 47 °C; 1.98 g; ^1H NMR δ 1.5 (m, β-CH_2, CH_2C, 8 H), 1.7 (m, δ-CH_2, 6 H), 1.9 (m, γ-CH, 3 H), 3.0 (s, CH_3, 3 H), 4.30 (t, CH_2O, J = 4 Hz, 2 H); ^{13}C NMR δ 28.2 (γ-CH), 31.6 (α-C), 36.7 (δ-CH_2), 37.2 (CH_3S), 42.2 (β-CH_2C), 42.6 (CH_2CH_2O), 66.6 (CH_2O); IR (KBr) 2897, 1500, 1452, 1360, 1140, 978 cm^{-1}. Anal. Calcd for $C_{13}H_{22}O_3S$: C, 60.46; H, 8.52. Found: C, 60.31; H, 8.40.

Ethyl 2,2-Bis(ethoxycarbonyl)-4-(1-adamantyl)butanoate (4b). A stirred mixture of mesylate **3b** (2.6 g, 10 mmol), ethyl methanetricarboxylate[15] (2.6 g, 11.2 mmol), and anhydrous K_2CO_3 (1.5 g, 11 mmol) in dry DMF[28] (50 mL) was heated at 100–110 °C for 48 h. After concentration in vacuo, the residue was treated with water and extracted with benzene. The organic extract was washed sequentially with aqueous NaOH (10%), water, and brine, dried ($MgSO_4$), filtered, and concentrated to give a residue, which was distilled to afford (70%) the desired ester **4b** as colorless viscous liquid: 2.8 g; bp 210 °C (0.5 mm); ^1H NMR δ 1.28 (t, J = 7.2 Hz, CH_3, 9 H), 1.5 [m, β-CH_2, $(CH_2)_2$, 10 H], 1.75 (m, δ-CH_2, 6 H), 2.1 (m, γ-CH, 3 H), 4.25 (q, CH_2O, J = 7.2 Hz, 6 H); ^{13}C NMR δ 13.7 (CH_3), 26.7 (α-CCH_2), 28.5 (γ-CH), 31.9 (α-C), 37.0 (δ-CH_2), 38.4 (CH_2C), 41.9 (β-CH_2), 61.7 (CH_2O), 62.2 (CC=O), 167.3 (C=O); IR (neat) 2983, 2903, 2846, 1738, 1448, 1072 cm^{-1}. Anal. Calcd for $C_{22}H_{34}O_6$: C, 67.00; H, 8.62. Found: C, 66.89; H, 8.60.

***N*-[2-Hydroxy-1,1-bis(hydroxymethyl)ethyl]-2,2-bis[[[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]amino]carbonyl]-4-(1-adamantyl)butanamide (5b).** A mixture of triester **4b** (700 mg, 1.8 mmol), Tris (690 mg, 5.6 mmol), and anhydrous K_2CO_3 (800 mg, 5.8 mmol) in dry Me_2SO (20 mL) was stirred for 12 h at 25 °C. After filtration, the solvent was removed in vacuo to give a residue, which was worked up as described above to give (90%) the triamide **5b** as a light hygroscopic yellow solid: 700 mg; mp 140 °C dec; ^1H NMR (Me_2SO-d_6) δ 1.5 (m, β-CH_2, CH_2-α-C, 10 H), 1.92 (m, δ-CH_2, 6 H), 2.1 (m, γ-CH, 3 H), 3.5 (bs, CH_2O, 18 H), 4.6 (bs, OH, 9 H), 7.5 (bs, NH, 3 H); ^{13}C NMR (Me_2SO-d_6) δ 26.1 (α-CCH_2), 27.0 (γ-CH_2), 30.6 (α-C), 35.6 (δ-CH_2), 40.8 (α-CCH_2CH_2), 41.2 (β-CH_2), 55.2 (CCO), 59.5 (CH_2O), 61.1 (HNC), 170.2 (C=O); IR (KBr) 3472–3300, 2928, 2841, 1660, 1246, 1060 cm^{-1}.

4-Amino-4-(3-acetoxypropyl)-1,7-diacetoxyheptane (6). Freshly prepared T-1 Raney nickel[20] was added to a solution of tris(γ-acetoxypropyl)nitromethane (6.7 g, 20 mmol), prepared[19] from the available tris(γ-hydroxypropyl)nitromethane,[18] in EtOH (80 mL) and hydrogenated at 50 psi on a Paar hydrogenator. After hydrogen uptake ceased (ca. 24 h), the solution was carefully filtered and the solvent was removed in vacuo to give (92%) amine **6** as colorless oil, which was flashed chromatographed (SiO_2), eluting with EtOAc: 6.3 g; ^1H NMR δ 1.32–1.59 (m, CH_2CH_2, 12 H), 2.06 (s, CH_3, 9 H), 4.10 (t, CH_2O, J = 6.0 Hz, 6 H); ^{13}C NMR δ 20.83 (CH_3), 22.40 (CH_2CH_2O), 35.41 ($CH_2CH_2CH_2O$), 51.93 (quat C), 64.40 (CH_2O), 170.39 (C=O); IR (neat) 3371 (NH), 1735 (C=O) cm^{-1}. Anal. Calcd for $C_{16}H_{29}NO_6$: C, 57.98; H, 8.82; N, 4.23. Found: C, 58.14; H, 8.74; N, 4.26.

1-[[*N*-[4-Acetoxy-1,1-bis(3-acetoxypropyl)butyl]amino]carbonyl]adamantane (7). A solution of 1-adamantanecarbonyl chloride (1 g, 5 mmol), amine **6** (1.98 g, 5 mmol), and Et_3N (600 mg, 6 mmol) in dry benzene (25 mL) was stirred at 25 °C for 20 h. The mixture was washed sequentially with aqueous $NaHCO_3$ (10%), water, cold aqueous HCl (10%), and brine. The organic layer was dried (Na_2SO_4), and the solvent was removed in vacuo to afford a viscous residue, which was flash chromatographed (SiO_2), eluting with EtOAc to give an oil, which on standing gave (78%) **7**, as a white solid: 1.9 g; mp 48–50 °C; ^1H NMR δ 1.57–1.69 (m, CH_2, CH, 27 H), 1.90 (s, CH_3CO, 9 H), 3.90 (t, J = 6.1 Hz, CH_2O, 6 H), 4.85 (bs, NH, 1 H); ^{13}C NMR δ 20.7 (CH_3), 22.4 (CH_2CH_2O), 27.9 (γ-CH), 30.7 (CCH_2), 36.2 (δ-CH_2), 39.2 (β-CH_2), 40.9 (α-C), 56.8 (NHC), 64.1 (CH_2O), 170.6 ($COCH_3$), 176.7

(28) Trisler, J. C.; Feasier, B. F.; Wu, S.-M. *Tetrahedron Lett.* **1974**, 687. Newkome, G. R.; Robinson, J. M. *Ibid.* **1974**, 691.

(CONH); IR (KBr) 3348, 2939, 2844, 1736, 1635, 1255, 1038 cm^{-1}. Anal. Calcd for $C_{27}H_{43}NO_7$: C, 65.69; H, 8.78; N, 2.80. Found: C, 65.72; H, 8.76; N, 2.78.

1-[[*N*-[4-Hydroxy-1,1-bis(3-hydroxypropyl)butyl]amino]carbonyl]adamantane (8). A mixture of triacetate **7** (1.5 g, 3 mmol) and anhydrous K_2CO_3 (125 mg, 0.9 mmol) in absolute EtOH (25 mL) was stirred at 25 °C for 15 h. After filtration through Celite, the solvent was removed in vacuo to give (100%) triol **8**[29] as a white solid: 1.1 g; mp 98–100 °C; ^1H NMR (CD_3OD) δ 1.75, 1.86 (m, CH_2, CH, 27 H), 3.53 (t, J = 6.5 Hz, CH_2OH, 6 H); ^{13}C NMR δ 27.5 (CH_2CH_2O), 29.8 (γ-CH), 32.4 (CCH_2), 37.6 (δ-CH_2), 40.3 (β-CH_2), 42.4 (α-C), 59.2 (NHC), 63.3 (CH_2OH), 179.9 (CONH); IR (KBr) 3500–3000, 3328, 2930, 1650, 1304, 1055 cm^{-1}. Anal. Calcd for $C_{21}H_{37}NO_4$: C, 68.63; H, 10.15; N, 3.80. Found: C, 66.05; H, 9.82; N, 3.22.

1-[[*N*-[3-Carboxy-1,1-bis(2-carboxyethyl)propyl]amino]carbonyl]adamantane (9). Method A. Sodium periodate (4.5 g, 21 mmol) and RuO_2 (65 mg, 486 μmol) were added to a cold solution of triol **8** (1 g, 2.7 mmol) in acetone–water (1:1, 40 mL). The resultant suspension was stirred vigorously for 5 h at 25 °C, filtered through Celite, and washed with acetone (50 mL). The solvent was removed in vacuo to give a white solid, which was extracted with warm acetone (5 × 50 mL). The combined extract was filtered (SiO_2), eluting with acetone. The residue obtained after concentration was dissolved in aqueous NaOH (10%) and acidified with concentrated HCl to give (86%) triacid **9** as a white solid: 950 mg; mp 204–208 °C; ^1H NMR (Me_2SO-d_6) δ 1.64–1.92 (m, CH_2, CH, 27 H), 3.33 (bs, OH, 3 H), 6.29 (bs, NH, 1 H); ^{13}C NMR δ 29.3 (CH_2CO_2H), 29.6 (γ-CH), 30.7 (CCH_2), 37.4 (δ-CH_2), 40.1 (β-CH_2), 42.4 (α-C), 58.4 (HNC), 177.5 (CO_2H), 179.8 (CONH); IR (KBr) 3360, 3330–2600, 2903, 1741, 1700, 1245, 1095 cm^{-1}. Anal. Calcd for $C_{21}H_{31}NO_7$: C, 61.59; H, 7.63; N, 3.42. Found: C, 61.60; H, 7.61; N, 3.39.

Method B. A solution of the *tert*-butyl ester **13** (1.7 g, 3 mmol) in formic acid (96%, 10 mL) was stirred at 25 °C for 12 h. After concentration, toluene (5 mL) was added and the solution was again evaporated in vacuo to remove azeotropically any residual formic acid. Purification, as described in method A, gave (94%) triacid **9**: 1.1 g.

1-[[*N*-[3-[[*N*-[4-Acetoxy-1,1-bis(3-acetoxypropyl)butyl]amino]carbonyl]-1,1-bis[2-[[*N*-[4-acetoxy-1,1-bis(acetoxypropyl)butyl]amino]carbonyl]ethyl]propyl]amino]carbonyl]adamantane (10). A mixture of triacid **9** (400 mg, 1 mmol), amine **6** (1.16 g, 3.5 mmol), dicyclohexylcarbodiimide (DCC; 620 mg, 3 mmol), and 1-hydroxybenzotrizole (400 mg, 3 mmol) in dry DMF[28] (15 mL) was stirred at 25 °C for 24 h. After filtration of the dicyclohexylurea, the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 (50 mL) and sequentially washed with cold aqueous HCl (10%), water, aqueous $NaHCO_3$ (10%), and brine. The organic phase was dried (Na_2SO_4). Removal of solvent in vacuo gave a thick viscous residue, which was subjected to flash chromatography (SiO_2), eluting with EtOAc and then 10% MeOH in EtOAc to furnish (72%) **10** as a light yellow oil: 970 mg; bp >300 °C (2 mm); ^1H NMR δ 1.69–1.85 (m, CH_2, CH, 63 H), 2.04 (s, CH_3, 27 H), 4.05 (t, CH_2O, J = 6.1 Hz, 18 H), 5.87 (bs, HN, 4 H); ^{13}C NMR δ 20.5 (CH_3), 22.3 (CH_2CH_2O), 27.9 (γ-CH), 30.7 ($CH_2CH_2CH_2O$), 31.5, 32.1 (CH_2CH_2CO), 36.2 (δ-CH_2), 39.1 (β-CH_2), 41.1 (α-C), 57.0 (HNCCH_2CH_2CO), 57.6 (HN$CCH_2CH_2CH_2O$), 64.2 (CH_2O), 171.0 ($COCH_3$), 172.7 (CONH); IR (neat) 3352, 2936, 2848, 1740, 1638, 1250, 1036 cm^{-1}. Anal. Calcd for $C_{68}H_{112}N_4O_{22}$: C, 61.40; H, 8.40; N, 4.15. Found: C, 61.39; H, 8.42; N, 4.11.

1-[[*N*-[3-[[*N*-[4-Hydroxy-1,1-bis(3-hydroxypropyl)butyl]amino]carbonyl]-1,1-bis[2-[[*N*-[4-hydroxy-1,1-bis(3-hydroxypropyl)butyl]amino]carbonyl]ethyl]propyl]amino]carbonyl]adamantane (11). A mixture of the nonaacetate **10** (900 mg, 667 mmol) and K_2CO_3 (200 mg) in absolute EtOH (200 mL) was stirred at 25 °C for 15 h. The mixture was filtered through Celite, and the solvent was removed in vacuo to give (97%) the very hygroscopic alcohol **11**[29] as a white solid: 630 mg; ^1H NMR (CD_3OD) δ 1.09–1.84 (m, CH_2, CH, 63 H), 3.36 (t, CH_2OH, J = 6.4 Hz, 18 H); ^{13}C NMR δ 27.4 (CH_2CH_2O), 29.6 (γ-CH), 32.2 (CH_2CH_2CO, $CH_2CH_2CH_2O$), 37.5 (δ-CH_2), 40.2 (β-CH_2), 42.4 (α-C), 58.5 (CCH_2CH_2CO), 59.4 ($CCH_2CH_2CH_2O$), 63.3 (CH_2OH), 175.3 (CONH); IR (KBr) 3304–3409, 2936, 1648, 1550, 1455, 1059 cm^{-1}.

Di-*tert*-butyl 4-Nitro-4-[2-(*tert*-butoxycarbonyl)ethyl]heptanedioate (13). A stirred solution of $MeNO_2$ (6.1 g, 100 mmol), Triton B (benzyltrimethylammonium hydroxide, 40% in MeOH; 1.0 mL) in dimethoxyethane (DME; 20 mL) was heated to 65–70 °C. *tert*-Butyl acrylate (39.7 g, 310 mmol) was added portionwise to maintain the temperature at 70–80 °C. Additional Triton B (2 × 1 mL) was added when the temperature started to decrease; when the addition was completed, the mixture was maintained at 70–75 °C for 1 h. After concentration in vacuo, the residue was dissolved in $CHCl_3$ (200 mL), washed with 10% aqueous HCl (50 mL) and brine (3 × 50 mL), and dried ($MgSO_4$). Removal of solvent in vacuo gave a pale yellow solid, which was crystallized (95% EtOH) to afford (72%) triester **13** as white microcrystals: 33 g; mp 98–100 °C; ^1H NMR δ 1.45 (s, CH_3, 27 H), 2.21 (m, CH_2, 12 H); ^{13}C NMR δ 27.9 (CH_3), 29.7 (CH_2CO), 30.2 (CCH_2), 80.9 (CCH_3), 92.1 (O_2NC), 170.9 (CO); IR (KBr) 1542 (NO_2), 1740 (CO) cm^{-1}. Anal. Calcd for $C_{22}H_{39}O_9N$: C, 59.30; H, 8.82; N, 3.14. Found: C, 59.27; H, 9.00; N, 3.14.

Di-*tert*-butyl 4-Amino-4-[2-(*tert*-butoxycarbonyl)ethyl]heptanedioate (12). A solution of nitro triester **13** (4.46 g, 10 mmol) in absolute EtOH (100 mL) with T-1 Raney Ni[20] (4.0 g) was hydrogenated at 50 psi and 60 °C for 24 h. The catalyst was cautiously filtered through Celite. The solvent was removed in vacuo, affording a viscous liquid, which was column chromatographed (SiO_2), eluting with EtOAc to give (88%) the amino triester **12** as a white crystalline solid: 3.7 g; mp 51–52 °C; ^1H NMR δ 1.44 (s, CH_3, 27 H), 1.78 (m, CH_2, 12 H); ^{13}C NMR δ 27.8 (CH_3), 29.8 (CH_2CO), 34.2 (CCH_2), 52.2 (H_2NC), 80.0 (CCH_3), 172.8 (CO); IR (KBr) 1745 (CO) cm^{-1}. Anal. Calcd for $C_{22}H_{41}O_6N$: C, 63.58; H, 9.95; N, 3.37. Found: C, 63.72; H, 10.05; N, 3.38.

1-[[*N*-[3-(*tert*-Butoxycarbonyl)-1,1-bis[2-(*tert*-butoxycarbonyl)ethyl]propyl]amino]carbonyl]adamantane (14). A solution of 1-adamantanecarbonyl chloride (1 g, 5 mmol), amine **12** (2.1 g, 5 mmol), and Et_3N (600 mg, 6 mmol) in dry benzene (25 mL) was stirred at 25 °C for 20 h. The mixture was washed sequentially with aqueous $NaHCO_3$ (10%), water, cold aqueous HCl (10%), and brine. The organic layer was dried (Na_2SO_4) and then concentrated in vacuo to give a residue which was chromatographed (SiO_2), eluting first with CH_2Cl_2 to remove some byproducts and then with EtOAc to give (71%) ester **14** as a white solid: 2 g; mp 84–86 °C; ^1H NMR δ 1.46 (s, CH_3, 27 H), 1.68–2.1 (m, CH, CH_2, 27 H), 4.98 (bs, NH, 1 H); ^{13}C NMR δ 28.0 (CH_3), 28.2 (γ-CH), 29.8, 30.1 ($NHCCH_2CH_2CO$), 36.4 (δ-CH_2), 39.2 (β-CH_2), 41.2 (α-C), 56.7 (NHC), 80.5 (CCH_3), 172.8 (COO), 177.4 (CONH); IR (KBr) 3350, 2934, 2846, 1740, 1638, 1255, 1038 cm^{-1}. Anal. Calcd for $C_{33}H_{55}O_7N$: C, 68.58; H, 9.60; N, 2.43. Found: C, 68.36; H, 9.66; N, 2.36.

1-[[*N*-[3-[[*N*-[3-(*tert*-Butoxycarbonyl)-1,1-bis[2-(*tert*-butoxycarbonyl)ethyl]propyl]amino]carbonyl]-1,1-bis[2-[[*N*-[3-(*tert*-butoxycarbonyl)-1,1-bis[2-(*tert*-butoxycarbonyl)ethyl]propyl]amino]carbonyl]ethyl]propyl]amino]carbonyl]adamantane (15). A mixture of triacid **9** (400 mg, 1 mmol), amine **12** (1.45 g, 3.5 mmol), DCC (620 mg, 3 mmol), and 1-hydroxybenzotriazole (400 mg, 3 mmol) in dry DMF[28] (15 mL) was stirred at 25 °C for 48 h. Using the procedure described above for **10**, but in the purification stage eluting first with EtOAc/CH_2Cl_2 (1:1) then with 5% MeOH in EtOAc, furnished (61%) ester **15** as a white solid: 970 mg; mp 115–118 °C; ^1H NMR δ 1.42 (s, CH_3, 81 H), 1.64–2.20 (m, CH, CH_2, 63 H), 5.88 (bs, NH, 4 H); ^{13}C NMR δ 27.9 (CH_3), 28.4 (γ-CH), 29.6, 30.0 ($NHCCH_2CH_2COO$), 31.6, 32.2 ($NHCCH_2CH_2CONH$), 36.6 (δ-CH_2), 39.2 (β-CH_2), 41.1 (α-C), 57.0 ($NHCCH_2CH_2COO$), 57.6 ($NHCCH_2CH_2CONH$), 80.3 (CCH_3), 172.6 (COO), 177.0 (CONH); IR (KBr) 3348, 2936, 2850, 1740, 1665, 1260, 1040 cm^{-1}. Anal. Calcd for $C_{87}H_{148}O_{22}N_4$: C, 65.22; H, 9.31; N, 3.50. Found: C, 65.41; H, 9.30; N, 3.39.

1-[[*N*-[3-[[*N*-[3-Carboxy-1,1-bis(2-carboxyethyl)propyl]amino]carbonyl]-1,1-bis[2-[[*N*-[3-carboxy-1,1-bis(2-carboxyethyl)propyl]amino]carbonyl]ethyl]propyl]amino]carbonyl]adamantane (16). A solution of the *tert*-butyl ester **15** (800 mg, 500 μmol) in formic acid (96%, 5 mL) was stirred

(29) Due to the hygroscopic nature of the arborols, this polyol was treated with freshly distilled Ac_2O in the presence of pyridine at 100 °C for 18 h to regenerate the starting acetate, whose spectra were superimpossible with a known sample.

at 25 °C for 12 h. The workup and purification as described above in method A gave (95%) acid **16** as a white solid: 520 mg, mp 346 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.82–2.40 (m, C*H*, CH_2, 63 H), 4.45 (bs, OH, 9 H, exchanged with D_2O), 6.28 (bs, NH, 4 H); ^{13}C NMR (Me_2SO-d_6) δ 29.6 (γ-CH), 30.2 ($NHCCH_2CH_2COOH$), 31.0, 32.4 ($NHCCH_2CH_2CONH$), 37.8 (δ-CH_2), 40.1 (β-CH_2), 42.5 (α-C), 58.0 ($NHCCH_2CH_2CONH$), 58.4 ($NHCCH_2CH_2COOH$), 177.6 (COOH), 179.8 (CONH); IR (KBr) 3360, 3340–2600, 2900, 1744, 1690, 1245, 1090 cm^{-1}. Anal. Calcd for $C_{51}H_{76}O_{22}N_4$: C, 55.83; H, 6.98; N, 5.11. Found: C, 55.71; H, 7.04; N, 4.98.

Acknowledgment. We thank the National Science Foundation (DMR 86-00929; 89-06792) and the donors of the Petroleum Research Foundation, administered by the American Chemical Society, for partial support of this research.

Registry No. 1, 711-01-3; 2, 136586-90-8; 3b, 36949-72-1; 4b, 136586-91-9; 5b, 136586-92-0; 6, 136586-93-1; 7, 136586-94-2; 8, 136586-95-3; 9, 136586-96-4; 10, 136586-97-5; 11, 136586-98-6; 12, 136586-99-7; 13, 136587-00-3; 14, 136587-01-4; 15, 136587-02-5; 16, 136587-03-6; $H_2NC(CH_2OH)_3$, 77-86-1; $MeSO_2Cl$, 124-63-0; $HC(CO_2Et)_3$, 6279-86-3; $O_2NC(CH_2CH_2CH_2OAc)_3$, 129918-72-5; $MeNO_2$, 75-52-5; *t*-BuOC(O)CH=CH_2, 1663-39-4; 1-adamantanecarbonyl chloride, 2094-72-6; 1-(2-hydroxymethyl)-adamantane, 6240-11-5; triton B, 100-85-6.

Notes

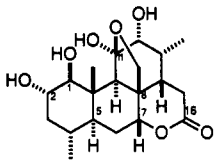
Synthesis of the Highly Oxygenated Quassinoid Shinjulactone D

Raymond S. Gross, Paul A. Grieco,* and Jon L. Collins

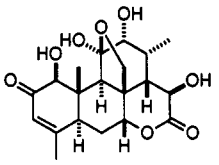
Department of Chemistry, Indiana University, Bloomington, Indiana 47405

Received July 9, 1991

Shinjulactone D (1) belongs to a group of highly oxygenated quassinoids isolated from *Ailanthus altissima* Swingle.[1] The C(8), C(11) bridged hemiketal structural unit present in shinjulactone D is common to a large number of quassinoids (cf. glaucarubolone, 2). The role, if any, that this functional arrangement plays in the observed pharmacological properties[2] (e.g. antitumor activity) of quassinoids remains unclear. We detail below the first synthesis of shinjulactone D which confirms the structural assignment for 1 which was based on ^{1}H NMR and ^{13}C NMR measurements recorded by Takahashi and coworkers in 1983.[1]

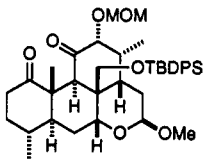


1

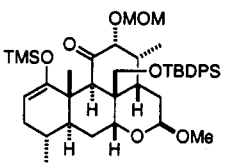


2

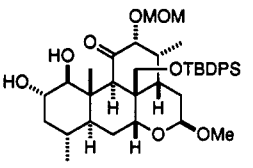
The synthesis of shinjulactone D commences with the known tetracyclic compound 3 which served as a key intermediate in a recently completed total synthesis of chaparrinone.[3] With the necessary functionality already present in ring C of 3 for construction of the C(8), C(11) bridged hemiketal unit, the primary task was elaboration of the vicinal trans-diol arrangement in ring A. Toward this end tetracyclic dione 3 was selectively converted (88%) into silyl enol ether 4 by employing lithium hexamethyldisilazide. The selective formation of 4 was anticipated due to the fact that the C(9) proton is extremely hindered. The trans-diequatorial arrangement of the vicinal C(1), C(2) diol was realized via hydroboration of the less hindered α face of the silyl enol ether.[4] Thus addition of diborane in tetrahydrofuran to 4 provided in 72% yield tetracyclic diol 5. Protection of the C(1), C(2) diol as its cyclic carbonate followed by selective hydrolysis of the protected lactone and subsequent oxidation at C(16) provided crystalline tetracyclic lactone 6, mp 188–189 °C.



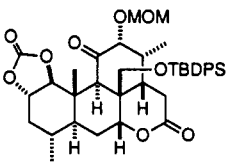
3



4

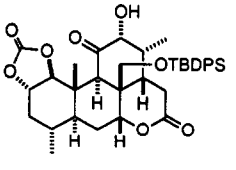


5

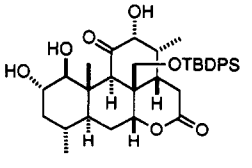


6

Completion of the synthesis of shinjulactone D was realized by a three-step process. Trimethylsilyl iodide induced cleavage of the C(12) methoxymethyl ether afforded (90%) ketol 7, mp 208–210 °C, which upon treatment with potassium carbonate in methanol–tetrahydrofuran (1:1) generated crystalline tetracyclic triol 8 in 87% yield.



7



8

Exposure of 8 to tetra-*n*-butylammonium fluoride in tetrahydrofuran provided crystalline racemic shinjulactone D whose spectral properties (IR, ^{1}H NMR, ^{13}C NMR) were identical with spectra kindly provided by Professor Tak-

(1) Ishibashi, M.; Furuno, T.; Tsuyuki, T.; Takahashi, T.; Matsushita, K. *Chem. Pharm. Bull.* **1983**, *31*, 2179–2181. Furuno, T.; Ishibashi, M.; Noara, H.; Murae, T.; Hirota, H.; Tsuyuki, T.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2484–2489.

(2) (a) Cassady, J. M.; Suffness, M. In *Anticancer Agents Based on Natural Product Models*; Academic Press: New York 1980; pp 254–267. (b) Polonsky, J. Chemistry and Biological Activity of the Quassinoids. In *The Chemistry and Chemical Taxonomy of the Rutales*; Waterman, P. G., Grundon, M. F., Eds.; Academic Press: New York, 1983; p 247.

(3) Gross, R. S.; Grieco, P. A.; Collins, J. L. *J. Am. Chem. Soc.* **1990**, *112*, 9436–9437.

(4) Klein, J.; Levene, R.; Dunkelblum, E. *Tetrahedron Lett.* **1972**, 2845–2848.

0022-3263/91/1956-7167$02.50/0