Cascade Molecules: 15.[1] Synthesis of Tris(3-substituted) Tripropylnitromethanes

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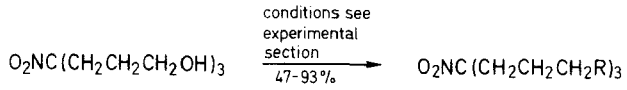
Starting from 4-(3-hydroxypropyl)-4-nitro-1,7-heptanediol, a series of polyfunctional nitromethane derivatives, 1,3',7-trisubstituted 4-nitro-4-propylheptanes, has been prepared and spectroscopically correlated; these derivatives validate methodologies for surface derivativization of specifically sized cascade polymers.

We have reported[2,3,4] the use of tris(2-cyanoethyl)nitromethane as a convenient and inexpensive starting material for the construction of cascade polymers ("arborols"); conversion of this trinitrile to nitrotris(3-hydroxypropyl)methane **1** and aminotris(3-hydroxypropyl)methane has been described.[5] We herein report derivativization of **1** with a broad range of reagents; these reactions were performed for several reasons. Nitrotriol **1** possesses solubility properties similar to those of resulting cascade molecules (soluble in water and polar solvents, but essentially insoluble in less polar organic solvents); thus, **1** serves as a model system for determining appropriate conditions for modification of the hydroxylic moieties of these spherical polymers. Subsequent elaboration of the nitro moiety, via the methods of Ono,[6] Kornblum,[7] and others,[8] requires protection of the hydroxy groups; thus, several derivatives were prepared not only to find the most convenient protecting group, but also in hopes of obtaining either solid or volatile[9] products, which would simplify purification of large scale preparations. Functionalization of the NO_2 moiety (e.g., to give $-NH_2$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2CH_2NH_2$, or $-CH_2NH_2$) would allow direct attachment of prefunctionalized synthons to topologically discrete cascade polymers. Finally, analysis of the ^{13}C-NMR data for this series will assist in the characterization of the functionalized cascade polymers.



1 **2**

Nr	R	Nr	R
2	OTs	**9**	$OCH_2C_6H_4Cl$-4
3	F	**10**	$OSiMe_2Bu$-*t*
4	Cl	**11**	$OSiMe_3$
5	Br	**12**	OCHO
6	I	**13**	OAc
7	OMe	**14**	OCOPh
8	OBn	**15**	$OCOC_6H_4Cl$-4

Tritosylate **2** was prepared (47%)[10] and its ^{13}C-NMR spectrum was indicative of successful conversion (Table): the CH_2O signal shifts downfield to $\delta = 69.4$ (cf. **1**: $\delta = 60.6$. Synthesis of the trifluoro derivative **3** was accomplished by three methods: treatment of tritosylate **2** with tetrabutylammonium fluoride (75%);[11] fluorination of **1** by diethylaminosulfur trifluoride (DAST, yield 65%);[12] and reaction of **1** with tetrabutylammonium fluoride and *p*-toluenesulfonyl fluoride (86%).[13] Formation of the trifluoride was substantiated by the ^{1}H- and ^{13}C-NMR spectra, which exhibited multiplets arising from fluorine coupling (Table).

Direct conversion of nitrotriol **1** with thionyl chloride, thionyl bromide, or phosphorus tribromide, following modified literature methods[14,15] gave the respective trichloro, **4**, and tribromo, **5**, derivatives. Synthesis of **5** and triiodo **6** were also prepared from tritosylate **2** with alkali halides.[16] The chemical shifts of the α-methylene (^{1}H-NMR) of the trihalo derivatives were almost identical to that of triol **1** and tritosylate **2**; whereas shifts (^{13}C-NMR) of the α-carbons (cf. **1**: $\delta = 60.6$; **2**: $\delta = 69.4$) to $\delta = 44.1$ (Cl), 33.9 (Br), and 4.8 (I) were instructive.

The ether derivatives **7–9** were prepared in good to excellent yield via treatment of **1** with either sodium hydroxide or sodium hydride in dimethyl sulfoxide,[17] and addition of the appropriate alkyl (benzyl) halide. Purifications were generally straightforward; however, prolonged reaction times gave considerable formation of sideproducts. The NMR spectra of **7–9** are indicative of ether formation: a ca. 10 ppm downfield shift of the α-carbons (^{13}C-NMR; $\underline{C}H_2OR$); a ca. 2.9 ppm upfield shift of the β-carbons (^{13}C-NMR; $\underline{C}H_2CH_2OR$); and the appearance of signals attributable to $-OCH_3$ (**7**: ^{1}H-NMR: $\delta = 3.23$; ^{13}C-NMR: $\delta = 58.3$), or $-OCH_2Ar$ (**8**: ^{1}H-NMR: $\delta = 4.47$, 7.31; ^{13}C-NMR: $\delta = 72.8$, 127.6, 128.4, 138.4. **9**: ^{1}H-NMR: $\delta = 4.46$, 7.30; ^{13}C-NMR: $\delta = 72.0$, 128.5, 128.9, 133.4, 136.9) moieties. The silyl derivatives **10** and **11** were prepared in good yields[18] and characterized by not only the appearance of signals arising from $-SiMe_3$ or $-SiMe_2Bu$-*t*, but also a 1.3–1.8 ppm downfield shift (^{13}C-NMR) of the α-carbon.

Ester derivatives **12–15** were prepared[1,19] and characterized by NMR spectroscopy. The α-methylene protons shift downfield (^{1}H-NMR) to ca. 4.2 ppm upon ester formation; the α-carbon shifts (^{13}C-NMR) from $\delta = 60.6$ to ca. $\delta = 63.5$, while the β-carbons shift upfield from $\delta = 26.8$ to ca. $\delta = 23.0$.

In conclusion, various derivatives of **1** were prepared via careful selection of an appropriate standard procedure. Comparison of the relative ^{13}C-NMR chemical shift increments will allow prediction of expected chemical shift changes observed upon functionalization of spherical cascade polymers possessing the tripropylmethyl moiety.

All melting points were taken in capillary tubes and are uncorrected. DMSO was dried and stored over 3 Å molecular sieves and dry DMF was specifically purified[20] to ensure the absence of decomposition products. Pyridine was dried over solid KOH then distilled and stored over KOH. Unless specified, solvents were purified by simple distillation. Column chromatography procedures utilized silica gel (Brinkmann) eluting with (CH_2Cl_2/cyclohexane, 7:3), unless otherwise stipulated. Tris(3-hydroxypropyl)nitromethane was obtained from Aldrich (No. 36, 153-4) or prepared as previously described.[5]

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Table. 1,3',7-Trisubstituted 4-Nitro-4-propylheptanes Prepared

Product[a]	Yield (%) (Method)	mp (°C) or bp (°C)/Torr	^{13}C-NMR[b] δ					^{1}H-NMR[b] δ				IR (neat)[c] ν (cm^{-1})	
			XC	(CH_2	CH_2	CH_2	$R)_3$	XC(CH_2	CH_2	CH_2	$R)_3$	NO_2	R
1[21]	–	–	94.7	31.2	26.8	60.6		1.92	1.30	3.39	4.12	1533	
2	47	oil	92.6	31.4	23.2	69.4	21.3	1.90	1.56	3.99	2.45	1542	
3	75(A), 65(B), 86(C)	198–199/3	93.2	31.2 (4.6)	24.5 (20.4)	82.9 (166.3)	–	1.4–2.2		4.42 (46.9)	–	1540	1044, 1008
4	80		92.9	32.8	26.5	44.1	–	2.12	1.72	3.56	–	1535	
5	69(A), 55(B), 64(C)	50–51	92.7	32.4	26.4	33.9	–	1.6–2.2		3.35	–	1532[d]	
6	89	65.5–66.5	92.6	36.5	27.3	4.80	–	1.6–2.2		3.16	–	1530	
7	89	oil	94.0	32.2	23.8	71.8	58.3	1.84	2.53	3.28	3.23	1538	1113 (COC)
8	78(A), (B)	oil	94.2	32.3	24.0	69.6	72.8	1.45	1.93	3.45	4.47, 7.31	1535	1103 (COC)
9	63	oil	94.1	32.2	23.9	69.9	72.0	1.20–2.25		3.44	4.46, 7.30	1579	1089
10	73	oil	94.3	32.1	26.9	62.4	−5.59, 18.1, 25.8	1.87	1.58	3.58	0.19, 0.67	1545	
11	90	oil	94.2	32.0	26.7	61.9	−0.79	1.91	1.49	3.54	0.076	1538	
12	89	oil	92.9	31.5	22.6	62.7	160.8	1.5–2.2		4.10	8.06	1537	1727 (C=O)
13[1]	–	–	93.1	31.8	22.9	63.3	20.6, 170.6	1.86		4.00	1.99	1542	1743 (C=O)
14	51	62–62.5	93.3	32.0	23.2	63.9	166.3	1.6–2.3		4.33	7.3–7.6, 7.9–8.1	1532[d]	1712 (C=O)
15	93	117	93.9	31.3	22.9	64.4	164.9	1.7–2.0		4.25	7.5–7.9	1535[d]	1730 (C=O)

[a] Satisfactory combustion analyses were obtained for all new compounds: C ±0.27, H ±0.30, N ±0.14.
[b] NMR spectra were recorded on an IBM/Bruker NR-80, or Jeol FX-90, using $CDCl_3$ as solvent unless otherwise noted. For **3** numbers in parentheses are the $J_{C\text{-}F}$ or $J_{H\text{-}F}$ values (Hz); X = NO_2.
[c] IR spectra were recorded as thin films (neat), except where noted.
[d] KBr pellet.

4-Nitro-1,7-ditosyloxy-4-(3-tosyloxypropyl)heptane (2):
Recrystallized TsCl (3.25 g, 17.0 mmol) is added to a solution of triol **1** (1.00 g, 4.26 mmol) in dry pyridine (20 mL) at 0 °C. After dissolution, the reaction is refrigerated for 12 h, or until formation of pyridinium hydrochloride has ceased. The dark purple solution is poured into ice water (100 g) and the oily tritosylate is extracted with Et_2O (3 × 50 mL). The combined ethereal extract is washed with 10% HCl (50 mL), then H_2O (50 mL), dried (K_2CO_3/Na_2SO_4), and concentrated in vacuo to give an oil, which is purified by radial chromatography [silica gel (2 mm); cyclohexane/EtOAc, 70:30] to afford pure tritosylate **2**; yield: 1.41 g (47%).

1,7-Difluoro-4-(3-fluoropropyl)-4-nitroheptane (3):
Method A: A stirred mixture of tosylate **2** (670 mg, 880 μmol) and $Bu_4NF \cdot THF$ (15 mL, 15 mmol) in dry MeCN (10 mL) is refluxed (90 °C) for 12 h. After cooling to 25 °C, the solution is poured into ice water, acidified with 20% aq HCl, and extracted with CH_2Cl_2. The combined extract is washed with H_2O, dried (Na_2SO_4), concentrated in vacuo, and chromatographed to give trifluoride **3**.

Method B: A solution of diethylaminosulfur trifluoride[21] (DAST; 2.7 g, 16.7 mmol) in CH_2Cl_2 (10 mL) is added dropwise at 25 °C over 5 min to a stirred suspension of triol **1** (1.25 g, 5.3 mmol) in CH_2Cl_2 (10 mL). Although dissolution occurs within 3 min, stirring is continued for 24 h. MeOH (2 mL) is added and the volatiles are removed in vacuo to give a yellow oil, which is chromatographed, then distilled in vacuo to afford **3**.

Method C: A mixture of triol **1** (350 mg, 1.48 mmol), $Bu_4NF \cdot THF$ (13 mL, 13.3 mmol), and TsF (1.54 g, 8.88 mmol) in anhydr. THF (10 mL) is stirred over molecular sieves (4 Å) at 25 °C for 24 h. H_2O is added, then the mixture is filtered and extracted with CH_2Cl_2 (3 × 50 mL). The combined extract is washed with H_2O, dried (Na_2SO_4), and concentrated in vacuo to give a residue, which is chromatographed to afford **3**.

1,7-Dichloro-4-(3-chloropropyl)-4-nitroheptane (4):
To a stirred mixture of the triol **1** (900 mg, 3.85 mmol), $CHCl_3$ (10 mL), and dry pyridine (1 mL), is added dropwise a solution of $SOCl_2$ (10 mL, 134 mmol) in dry $CHCl_3$ (5 mL) over 10 min. The mixture is maintained at 50 °C for 2 h, then cooled to 25 °C and poured into cold aq 2N HCl (10 mL). The organic layer is separated, washed with H_2O (10 mL), dried (Na_2SO_4), and concentrated in vacuo to give a residue, which is chromatographed to afford **4**.

1,7-Dibromo-4-(3-bromopropyl)-4-nitroheptane (5):
Method A: A solution of PBr_3 (5 mL) in dry pyridine (2 mL) is added dropwise to a stirred slurry of triol **1** (900 mg, 3.85 mmol) in $CHCl_3$/benzene (1:1, 20 mL), then stirred for 2 h at 50–70 °C. After cooling, the mixture is poured into ice water, and extracted with $CHCl_3$ (50 mL). The extract is washed with sat. aq $NaHCO_3$ (50 mL), H_2O (50 mL), and sat. brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo to give a residue, which is chromatographed to give tribromide **5**.

Method B: A stirred mixture of tosylate **2** (300 mg, 429 μmol) and excess NaBr (300 mg, 2.9 mmol) in diethylene glycol (1 mL) is heated at 150–170 °C for 3 h. After cooling to 25 °C, H_2O is added and the solution is extracted with $CHCl_3$ (3 × 15 mL). The combined extract is washed with H_2O, dried (Na_2SO_4), and chromatographed to give **5**.

Method C: A mixture of triol **1** (500 mg, 2.1 mmol), $SOBr_2$ (5 mL), dry pyridine (5 drops) and CH_2Cl_2 (10 mL) is refluxed for 2 h, then cooled to 25 °C. The mixture is transferred with additional CH_2Cl_2 (10 mL), washed with sat. aq $NaHCO_3$ (25 mL), 2N HCl (25 mL), and brine (25 mL), then dried (Na_2SO_4) and concentrated *in vacuo* to give a residue, which is chromatographed (CH_2Cl_2) to afford **5**.

1,7-Diiodo-4-(3-iodopropyl)-4-nitroheptane (6):
To a stirred solution of the tosylate **2** (500 mg, 720 μmol) in dry acetone (6 mL), is added a solution of NaI (1.5 g, 10 mmol) in acetone (12 mL). The mixture is maintained at 25 °C for 12 h, then filtered, evaporated in vacuo, and the residue extracted with $CHCl_3$ (3 × 15 mL). The combined extract is washed with H_2O (3 × 10 mL), dried (Na_2SO_4), and concentrated in vacuo to give a crude solid, which is recrystallized (cyclohexane) to afford pure triiodide **6**.

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1,7-Dimethoxy-4-(3-methoxypropyl)-4-nitroheptane (7):
A slurry of powdered KOH (26.88 g, 480 mmol) in anhydr. DMSO (150 mL) is stirred for 5 min at 25°C, then the triol **1** (9.4 g, 40 mmol) and MeI (34.08 g, 240 mmol) are added. After 2 h, brine (1 L) is added and the solution is extracted with benzene (4 × 250 mL). The combined extract is washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to give ether **7**; an analytical sample is flash-chromatographed (benzene).

1,7-Dibenzyloxy-4-(3-benzyloxypropyl)-4-nitroheptane (8):
Method A: To a stirred suspension of powdered KOH (2.86 g, 510 mmol) and triol **1** (1 g, 4.26 mmol) dissolved in dry DMSO (15 mL), BnBr (4.38 g, 256 mmol) is slowly added. The mixture is stirred for 30 min, then H_2O (50 mL) is added and the organic material is extracted with benzene (2 × 50 mL). The combined extract is washed with brine (2 × 40 mL) and H_2O (2 × 40 mL), then concentrated in vacuo to give a residue, which is chromatographed (silica gel; 30 g, 60–200 μm) eluting with EtOAc/hexane (1:9) or benzene to give benzyl alcohol and other side products, followed by EtOAc/hexane (3:7) or EtOAc/cyclohexane (2:8) to afford **8**.

Method B: To a stirred solution of triol **1** (8.1 g, 35 mmol) and DMSO (250 mL) is added NaH (2.8 g, 115 mmol). After stirring 30 min at 25°C, BnCl (14.6 g, 115 mmol) is added as a 50% solution in DMSO over 30 min. The resulting mixture is stirred for 15 h at 25°C. The solvent is removed in vacuo and benzene (250 mL) is added. The resultant solution is washed with H_2O (2 × 150 mL) and sat. brine (2 × 150 mL), then dried ($MgSO_4$) and concentrated in vacuo to give (83%) the crude product, which is purified (silica gel) to afford triether **8**, as a colorless oil.

1,7-Bis(4-chlorobenzyloxy)4-[3-(4-chlorobenzyloxy)propyl]-4-nitroheptane (9):
Compound **9** is prepared by the procedure described for benzyl ether **8** (Method B), using 4-chlorobenzyl chloride (18.6 g, 115 mmol).

1,7-Bis(*tert*-butyldimethylsiloxy)-4-[3-(*tert*-butyldimethylsiloxy)-propyl]-4-nitroheptane (10):
A solution of triol **1**(1.0 g, 4.26 mmol) and Et_3N (1.72 g, 17 mmol) in dry DMF (10 mL) is stirred at 25°C for 10 min, then DMAP (620 mg, 5.1 mmol) and *t*-$BuMe_2SiCl$ (2.56 g, 17 mmol) are added. After 24 h, H_2O (10 mL) is added and the mixture is extracted with benzene (25 mL). The combined extract is washed with H_2O (4 × 40 mL) and brine (4 × 40 mL), dried ($MgSO_4$), and concentrated in vacuo to give silyl ether **10**.

1,7-Bis(trimethylsiloxy)-4-nitro-4-[(3-(trimethylsiloxy)propyl]-heptane (11):
Compound **11** is prepared by the above method, and substituting Me_3SiCl (1.85 g, 17 mmol) for *t*-$BuMe_2SiCl$.

1,7-Diformyloxy-4-(3-formyloxypropyl)-4-nitroheptane (12):
Conc. H_2SO_4 (1 drop) is added to a stirred solution of triol **1** (4.7 g, 20 mmol) in formic acid (95%). After 6 h at 70°C, the excess formic acid is removed in vacuo to give a residue, which is poured into H_2O (100 mL) and neutralized with aq $NaHCO_3$. The oily product is extracted with Et_2O (3 × 50 mL), and the combined extract is washed with H_2O (15 mL), dried ($MgSO_4$), and concentrated in vacuo to give triformate **12**.

1,7-Diacetoxy-4-(3-acetoxypropyl)-4-nitroheptane (13):
Compound **13** is prepared by acetylation of **1** via reported[1] methods.

1,7-Dibenzoyloxy-4-(3-benzoyloxypropyl)-4-nitroheptane (14):
Benzoyl chloride (4.92 g, 35 mmol) is added dropwise to a stirred mixture of triol **1** (2.35 g, 10 mmol) and dry pyridine (15 mL) at 0°C under N_2. The mixture is warmed to 70°C for 15 h, cooled to 25°C, poured into H_2O (30 mL), then extracted with CH_2Cl_2 (3 × 50 mL). The combined extract is washed with aq $CuSO_4$ (2 × 50 mL), 1 N HCl (2 × 50 mL), and H_2O (2 × 50 mL), then dried (Na_2SO_4) and concentrated in vacuo to give a residue, which is chromatographed (EtOAc/cyclohexane, 1:9) to afford the colorless crystalline tribenzoate **14**.

1,7-Bis(4-chlorobenzoyloxy)-4-[3-(4-chlorobenzoyloxy)propyl]-4-nitroheptane (15):
A solution of 4-chlorobenzoyl chloride (5.25 g, 30 mmol) and triol **1** (2.35 g, 10 mmol) in dry pyridine (20 mL) is allowed to stand for 30 h. The resultant slurry is added to H_2O (100 mL), acidified with conc. HCl (23 mL), then extracted with Et_2O (2 × 40 mL). The combined Et_2O extract is washed with dil. aq $NaHCO_3$ (2 × 40 mL) and H_2O (40 mL), dried ($MgSO_4$), then concentrated in vacuo to give **15**.

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