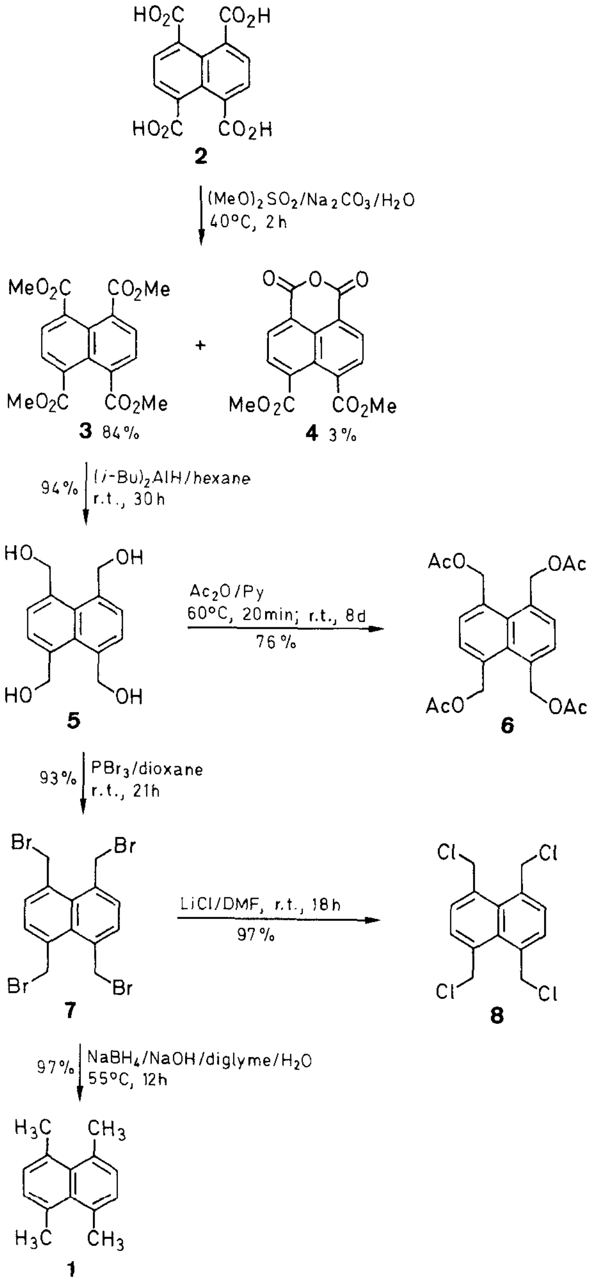
A New Synthesis of 1,4,5,8-Tetramethylnaphthalene

Toshihiro Kamada,* Nobuhide Wasada

National Chemical Laboratory for Industry, Higashi-1, Tsukuba, Ibaraki 305, Japan

A convenient four-step preparation of 1,4,5,8-tetramethylnaphthalene from commercially available 1,4,5,8-naphthalenetetracarboxylic acid is presented.

1,4,5,8-Tetramethylnaphthalene[1] (**1**) is employed in the preparation of polymethylarenes[2] as well as in the study of the chemistry of bis-perisubstituted naphthalenes,[3,4] which are of current interest. Several syntheses of **1** have been reported, utilizing either a Friedel-Crafts type route starting from *p*-xylene (five-step process)[5] or a Diels-Alder type route starting from 2,5-dimethylaniline (seven-step process);[2,6] however, all these syntheses proceed in very low overall yields (< 10 %). A modification[4] of the Friedel-Crafts procedure proceeds with an overall yield of less than 20%. We now report a novel and simple four-step process which proceeds with an overall yield of 71 %.



Our approach to the synthesis of **1** uses the commercially available 1,4,5,8-naphthalenetetracarboxylic acid (**2**) as starting material. Treatment of **2** with dimethyl sulfate in aqueous sodium carbonate solution produced an 84% yield (after crystallization) of tetramethyl 1,4,5,8-naphthalenetetracarboxylate[7] (**3**) along with a small amount (3% yield) of 4,5-dimethoxycarbonyl-1,8-naphthalenedicarboxylic anhydride[8] (**4**). The earlier paper[8] reported that the esterification of the silver salt of **2** with methyl iodide provided **3** only in small amounts in addition to the major product **4**. The tetramethyl ester **3**, which was unreactive against lithium aluminum hydride, smoothly underwent reduction with diisobutylaluminum hydride in hexane to afford 1,4,5,8-tetrakis(hydroxymethyl)naphthalene (**5**) in 94% yield. Attempts to prepare **5** from **4** by hydride reductions were not successful, however.

The tetraol **5** was readily converted to the tetraacetyl derivative **6**, by treatment with acetic anhydride/pyridine, whereas treatment of **5** with phosphorus(III) bromide in dioxane led to the corresponding tetrabromide **7** (93% yield). Compound **7** smoothly reacted with lithium chloride in dimethylformamide to yield the tetrachloro compound **8**. Finally, reduction of **7** with sodium borohydride[9] in the presence of aqueous alkali afforded the desired hydrocarbon **1**[1] in 97% yield. All products obtained including the new compounds **5–8** gave microanalyses and spectra in accord with their structures.

All reagents employed were of commercial quality. 1,4,5,8-Naphthalenetetracarboxylic acid was purchased from Aldrich. Melting points were taken on a microscopic hot-stage melting-point apparatus and are uncorrected. Analytical TLC was performed with Merck 0.2 mm thick precoated silica gel 60F-254 plates. Mass spectra (MS) were recorded with a JEOL-01SG-2 instrument operating at an ionizing energy of 75 eV. High resolution molecular weight determinations (Exact Mass) were carried out on a CEC 21-110B high-resolution mass spectrometer with an ionization potential of 70 eV. IR absorption spectra were recorded with a JASCO Model IR-G spectrometer using Nujol mulls calibrated with polystyrene. The ^{1}H-NMR spectra were recorded with a Bruker AC-200 FT NMR spectrometer at 200 MHz.

Tetramethyl 1,4,5,8-Naphthalenetetracarboxylate (3):

To a stirred solution of Na_2CO_3 (16.0 g, 150 mmol) in H_2O (200 mL) at 40 °C is added, portionwise, 1,4,5,8-naphthalenetetracarboxylic acid (**2**) (15.2 g, 50 mmol) followed by Me_2SO_4 (19 mL, 200 mmol), and stirring is continued for 1 h at 40 °C. Then, Na_2CO_3 (16.0 g, 150 mmol) and Me_2SO_4 (29 mL, 300 mmol) are successively added, and stirring is continued for 1 h. The precipitated solid is isolated by suction, washed with H_2O, dried, and crystallized from dioxane to give product **3** as colorless crystals. Concentration of the mother liquor then precipitates 4,5-dimethoxycarbonyl-1,8-naphthalenedicarboxylic anhydride (**4**), which is collected and crystallized from benzene/EtOH as slightly colored needles.

Compound **3**; yield: 15.0 g (84%); mp 198–199 °C (Lit.[7] mp 196–198 °C); R_f 0.63 (silica gel/MeOH/CH_2Cl_2, 1 : 13).

		C	H
$C_{18}H_{16}O_8$	calc.	60.00	4.48
(360.3)	found	60.21	4.50

MS (75 eV): m/z (%) = 360 M^+, 40), 329 ($M^+ - OCH_3$, 56), 301 ($M^+ - CO_2CH_3$, 100), 255 (28).

Exact Mass: mz calc. 360.085, found 360.080.

IR (Nujol): ν = 1713, 1726 cm^{-1} (CO_2CH_3).

^{1}H-NMR ($CDCl_3$/TMS): δ = 3.93 (s, 12H, 4CH_3), 8.05 (s, 4H_{arom}).

Compound **4**; yield: 0.42 g (3.0%); mp 266–267 °C (Lit.[8] mp 278–278.5 °C); R_f 0.72 (silica gel/CH_2Cl_2/MeOH, 13:1).

$C_{16}H_{10}O_7$	calc.	C 61.15	H 3.21
(314.2)	found	61.30	3.05

MS (75 eV): m/z (%) = 314 (M^+, 40), 283 ($M^+ - OCH_3$, 100), 255 ($M^+ - CO_2CH_3$, 20).

Exact Mass: m/z calc. 314.043, found 314.045.

IR (Nujol): ν = 1780, 1740 (carboxylic anhydride), 1720 cm^{-1} (ester).

^{1}H-NMR ($CDCl_3$/TMS): δ = 4.00 (s, 6H, 2CH_3), 8.25 (ABd, 2H, J = 8.0 Hz, H-3, H-6), 8.71 (ABd, 2H, J = 8.0 Hz, H-2, H-7).

1,4,5,8-Tetrakis(hydroxymethyl)naphthalene (5):

To a stirred solution of (i-Bu)$_2$AlH (1000 mmol) in hexane (1000 mL) under N_2, the tetramethyl ester **3** (25.0 g, 69 mmol) is added in portions keeping the temperature below 30 °C. The resultant clear solution is stirred at r.t. for 30 h. Then, aq MeOH (300 mL) is slowly added, followed by 6 N aq. HCl (700 mL). The precipitated solid is isolated by suction and crystallized from DMSO/$CHCl_3$ to give the tetraol **5** as colorless microcrystals; yield: 16.2 g (94%); mp 231–233 °C.

$C_{14}H_{16}O_4$	calc.	C 67.73	H 6.50
(248.3)	found	67.85	6.38

MS (75 eV): m/z (%) = 230 ($M^+ - H_2O$, 3), 212 ($M^+ - 2H_2O$, 100), 154 (47).

Exact Mass: m/z calc. 248.105, found 248.099.

IR (Nujol): ν = 3321, 3224 cm^{-1} (OH).

^{1}H-NMR (DMSO-d_6/TMS): δ = 5.05 (d, 8H, J = 5.5 Hz, 4ArCH_2), 5.19 (t, 4H, J = 5.5 Hz, 4OH), 7.56 (s, 4H_{arom}).

1,4,5,8-Tetrakis(acetoxymethyl)naphthalene (6):

A mixture of the tetraol **5** (100 mg, 0.4 mmol), Ac_2O (4 mL, 42.3 mmol), and pyridine (4 mL) is stirred at 60 °C for 20 min. The clear solution is then allowed to stand at r.t. for 8 days to complete the reaction. The mixture is poured into ice/H_2O (100 mL), and the resultant mixture is stirred at r.t. for 1 h. The precipitated solid is isolated by suction and crystallized from EtOH to give the tetraacetate **6** as colorless microcrystals; yield: 127 mg (76%); mp 172–173 °C; R_f 0.50 (silica gel/CH_2Cl_2/AcOEt, 5:1).

$C_{22}H_{24}O_8$	calc.	C 63.45	H 5.81
(416.4)	found	63.61	5.95

MS (75 eV): m/z (%) = 416 (M^+, 7), 254 (11), 236 (8), 194 (100), 176 (80), 165 (17), 43 (54).

IR (Nujol): ν = 1740, 1250 cm^{-1} (acetate).

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.10 (s, 12H, 4$COCH_3$), 5.61 (s, 8H, 4ArCH_2), 7.67 (s, 4H_{arom}).

1,4,5,8-Tetrakis(bromomethyl)naphthalene (7):

To a stirred suspension of the tetraol **5** (42.5 g, 171 mmol) in anhydrous dioxane (1400 mL) under N_2, PBr_3 (180 mL, 1900 mmol) is dropwise added during 10 min. After 1 h, more PBr_3 (180 mL, 1900 mmol) is added and the mixture is stirred at room temperature for 20 h. Then H_2O (300 mL) is added with ice cooling, to the resultant mixture is added more H_2O (1200 mL), and stirring is continued at r.t. for 30 min. The precipitated solid is isolated by suction and crystallized from dioxane to give the tetrabromide **7** as colorless crystals; yield: 79.1 g (93%); dec > 220 °C.

$C_{14}H_{12}Br_4$	calc.	C 33.63	H 2.42
(499.9)	found	33.80	2.51

MS (75 eV): m/z (%) = 500 [M^+ ($C_{14}H_{12}{}^{79}Br_2{}^{81}Br_2$), 8], 419 ($M^+ - Br$, 80); 340 ($M^+ - 2Br$, 44), 259 ($M^+ - 3Br$, 88), 180 ($M^+ - 4Br$, 100), 165 (64).

Exact Mass: m/z calc. 499.764 ($C_{14}H_{12}{}^{79}Br_2{}^{81}Br_2$), found 499.769.

IR (Nujol): ν = 545 cm^{-1} (C-Br).

^{1}H-NMR spectrum of **7** not obtained because of poor solubility in NMR solvents.

1,4,5,8-Tetrakis(chloromethyl)naphthalene (8):

The tetrabromide **7** (300 mg, 0.6 mmol) is added to a solution of LiCl (300 mg, 7 mmol) in DMF (15 mL), and stirring is continued at r.t. for 18 h. The resultant clear solution is poured into H_2O (100 mL), and the mixture is stirred at room temperature for 1 h. The precipitated solid is isolated by filtration and crystallized from DMSO/MeOH/H_2O to give product **8** as colorless crystals; yield: 187 mg (97%); mp 207–209 °C; R_f 0.59 (silica gel/benzene).

$C_{14}H_{12}Cl_4$	calc.	C 52.20	H 3.76
(322.1)	found	52.35	3.51

MS (75 eV): m/z (%) = 322 [M^+ ($C_{14}H_{12}{}^{35}Cl_3{}^{37}Cl_1$), 54]; 285 ($M^+ - Cl$, 100), 250 ($M^+ - 2Cl$, 48), 215 ($M^+ - 3Cl$, 50), 179 ($M^+ - 4Cl{-}H$, 46).

IR (Nujol): ν = 620 cm^{-1} (C–Cl).

^{1}H-NMR (DMSO-d_6/TMS): δ = 5.39 (s, 8H, 4ArCH_2), 7.82 (s, 4H_{arom}).

1,4,5,8-Tetramethylnaphthalene (1):

To a stirred mixture[9] of $NaBH_4$ (46.0 g, 1216 mmol), NaOH (12.0 g, 300 mmol), diglyme (260 mL), and H_2O (130 mL) at 55 °C is slowly added the tetrabromide **7** (13.35 g, 26.7 mmol), and stirring is continued for 12 h at 55 °C. The mixture is then carefully poured into ice and 6 N aq HCl (300 mL) with vigorous stirring. The resultant mixture is diluted with H_2O (2000 mL) and stirred at r.t. for 1 h. The precipitated solid is isolated by suction and crystallized from EtOH to afford product **1** as colorless long needles; yield: 4.76 g (97%); mp 130.5–131.5 °C (Lit.[1] mp 131 °C); R_f 0.19 (silica gel/hexane).

$C_{14}H_{16}$	calc.	C 91.25	H 8.75
(184.3)	found	91.10	8.51

MS (75 eV): m/z (%) = 184 (M^+, 100); 169 ($M^+ - CH_3$, 68).

IR (Nujol): ν = 3020, 1597, 817 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.82 (s, 12H, 4CH_3), 7.10 (s, 4H_{arom}).

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