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Synthesis of Hydrolytically Stable TBDMS Derivatives of Hydroxynaphthoquinones

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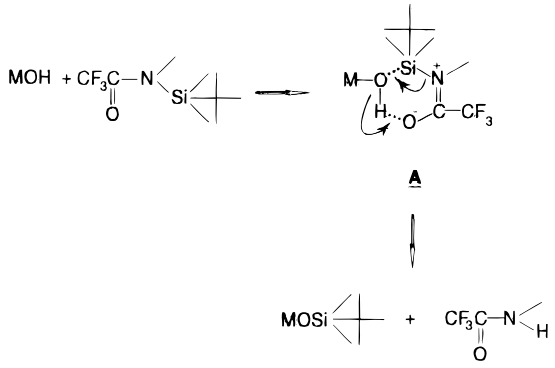
Numerous organosilicon compounds have been shown to possess potent biological activity.[1] Silyl derivatives of the well-known bioactive hydroxyquinones[2] are expected to be also highly bioactive.[3] Within our continuing interest in the silylation reaction of quinones,[4] we recently reported on the trimethylsilylation of hydroxyquinones.[5] Since, sterically crowed TBDMS ethers were found to be much more stable than the hydrolytically unstable TMS ethers,[6] we were prompted to study *tert*-butyldimethylsilylation of hydroxynaphthoquinones on which we hereby report. The silylation is achieved by a general, clear, and one-step process.

Treatment of hydroxyquinones **1a**−**d** (Table 1) with *N*-methyl-*N*-(*tert*-butyldimethylsilyl)-1,1,1-trifluoroacetamide (MTBSTFA) afforded two types of TBDMS ethers in nearly quantitative yields. The first one (**2a**−**d**) was the result of partial silylation, i.e., only of the hydroxyl groups, of **1a**−**d**. The TBDMS ethers of the corresponding hydroquinones (**3a**−**d**), constitute the second type of compounds prepared by reductive silylation of **1a**−**d** in the presence of NH$_4$I. The optimum reaction conditions are presented in Table 1. Due to the limited solubility of **1a**−**d** in MTBSTFA, acetonitrile (CH$_3$CN) was used as the reaction solvent. Heating was also necessary in order to dissolve the NH$_4$I added. All silylation reactions were handled under a blanket of dry nitrogen since MTBSTFA is a moisture-sensitive reagent.[7] In contrast, no precaution was taken against moisture in the following workup. Use of 1% *tert*-butyldimethylsilyl chloride (TBDMSCl) as a catalyst was found to increase the efficiency of the silylation reaction.[7]

MTBSTFA is a widely used silylating agent for the silylation of hydroxyl groups.[8] The partial silylation of **1a**−**d** probably proceeds *via* an intermediate pentacoordinated silicon species, **A** (Scheme 1). Consequent cleavage of the Si−N bond is due to the reduced chemical affinity of silicon for nitrogen, which is about two-thirds of the corresponding one for oxygen.[9]

Scheme 1. Proposed Reaction Mechanism for the Partial Silylation of 1a−d



The enhanced reactivity of MTBSTFA in the presence of NH$_4$I, resulting in the reductive silylation of **1a**−**d** to **3a**−**d**, is attributed to the *in situ* generation of *tert*-butyldimethylsilyl iodide (TBDMSI)[10] (eq 2). Formation of TBDMSI[11] is verified by the evolution of NH$_3$ and the precipitation of *N*-methyl-1,1,1-trifluoroacetamide (MTFA). Controlled *in situ* generation of TBDMSI was applied in order to avoid its decomposition on standing[12] and formation of iodides instead of pure silyl ethers.[13] *In situ* generation of TBDMSI has also been achieved by treating (phenylseleno)silanes with iodine;[14] however, the hereby applied method has the advantage of regenerating NH$_4$I from the reaction byproducts, NH$_3$ and I$_2$[15] (eq 3).

TBDMSI is so far known to readily silylate tertiary alcohols to their TBDMS ethers and cleave oxiranes to the TBDMS ethers of the corresponding iodohydrins.[14] Besides, its catalytic effect on the silylation of enolizable carbonyl groups with MTBSTFA, is also known.[8] Even though enolization is impossible for **1a**−**d**, no evidence was found for the formation of iodides or other side products as did with its analogue trimethylsilyl iodide (TMSI).[10] Incomplete reactions were realized when amounts of MTBSTFA or NH$_4$I smaller than the optimum ones (Table 1) were used.

A facile reaction pathway for the reductive silylation is shown in Scheme 2. The initial step is an electrophilic attack of silicon to a quinonoid oxygen (1, 2 addition[9]) to form silyl iodide **B**, which in turn may be attacked by iodine. Aromatization of the quinonoid ring is achieved with a concomitant iodine molecule elimination.[16]

The TBDMSI consumed for the silylation of hydroxyl groups of **1a**−**d** in reductive silylation is quantitatively regenerated by interaction of HI with MTBSTFA. The 75% recovery of NH$_4$I (eqs 1 and 3) is not sufficient for

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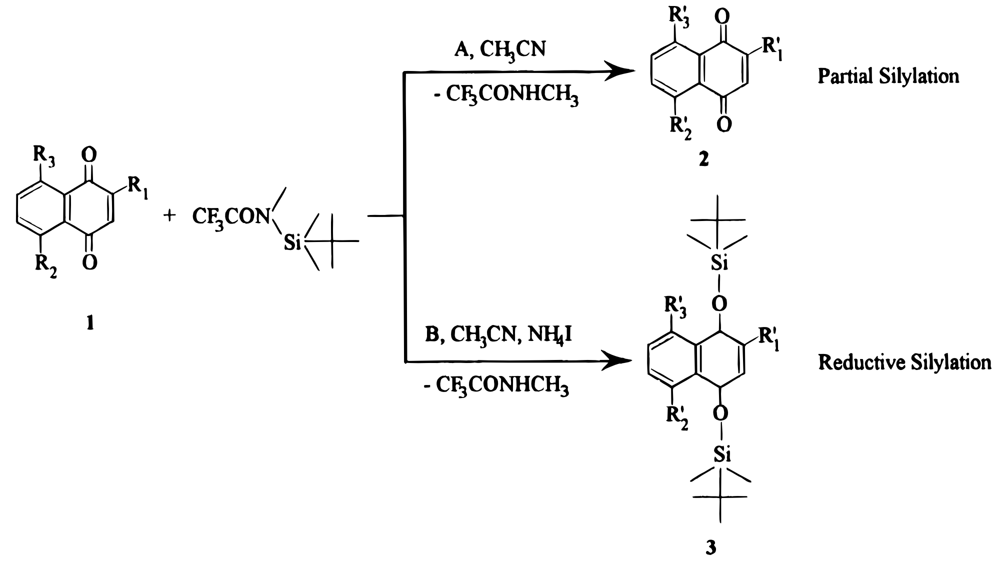
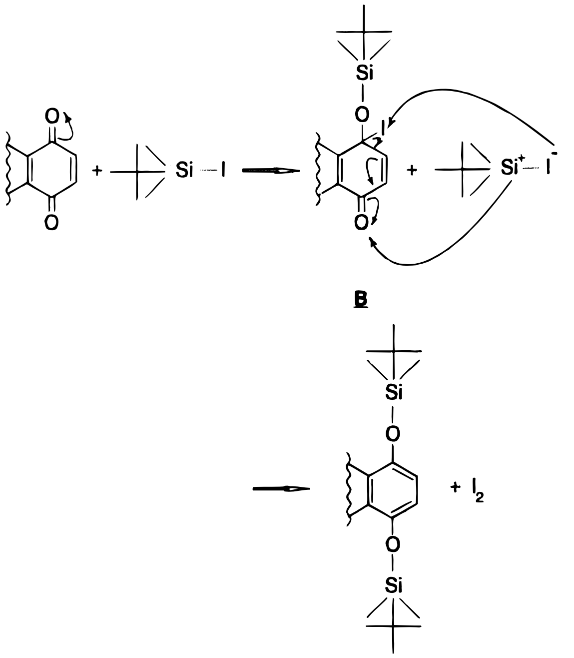
Table 1. Reaction Conditions for the *tert*-Butyldimethylsilylation of Hydroxynaphthoquinones 1a−d



substrate					reaction conditions				product			
no.	R_1	R_2	R_3	method	temp (°C)	time (min)	MTBSTFA/ quin (mmol)	NH_4I/ quin (mmol)	no.	R'_1	R'_2	R'_3
1a	OH	OH	H	A	60	30	10		**2a**	H	$OSi(CH_3)_2C(CH_3)_3$	H
				B	reflux (81.6)	15	30	0.6	**3a**	H	$OSi(CH_3)_2C(CH_3)_3$	H
1b	OH	H	H	A	60	30	11		**2b**	$OSi(CH_3)_2C(CH_3)_3$	H	H
				B	reflux (81.6)	15	42	0.8	**3b**	$OSi(CH_3)_2C(CH_3)_3$	H	H
1c	OH	OH	OH	A	60	30	12		**2c**	H	$OSi(CH_3)_2C(CH_3)_3$	$OSi(CH_3)_2C(CH_3)_3$
				B	reflux (81.6)	15	40	0.8	**3c**	H	$OSi(CH_3)_2C(CH_3)_3$	$OSi(CH_3)_2C(CH_3)_3$
1d	$CH(OH)CH_2CH{=}C(CH_3)_2$	OH	OH	A	60	30	9		**2d**	$CH(OSi(CH_3)_2C(CH_3)_3)CH_2CH{=}C(CH_3)_2$	$OSi(CH_3)_2C(CH_3)_3$	$OSi(CH_3)_2C(CH_3)_3$
				B	reflux (81.6)	15	60	1.2	**3d**	$CH(OSi(CH_3)_2C(CH_3)_3)CH_2CH{=}C(CH_3)_2$	$OSi(CH_3)_2C(CH_3)_3$	$OSi(CH_3)_2C(CH_3)_3$

Scheme 2. Proposed Reaction Mechanism for the Reductive Silylation of the Quinone System of 1a−d



the reductive silylation of the quinone system, therefore NH_4I/**1** ratios larger than the predicted 0.5 (eq 4) has to be used (Table 1). Twenty-five percent of the iodine produced does not regenerate NH_4I and may have a catalytic effect on silylation reaction.[9,17]

All TBDMS ethers displayed a single, well-shaped chromatographic peak without any significant peak tailing. Their elution order was the same for reductively and partially silylated hydroxynaphthoquinones. In general, the mass spectral characteristics of the studied TBDMS ethers are similar to those of the corresponding TMS ethers studied previously.[5]

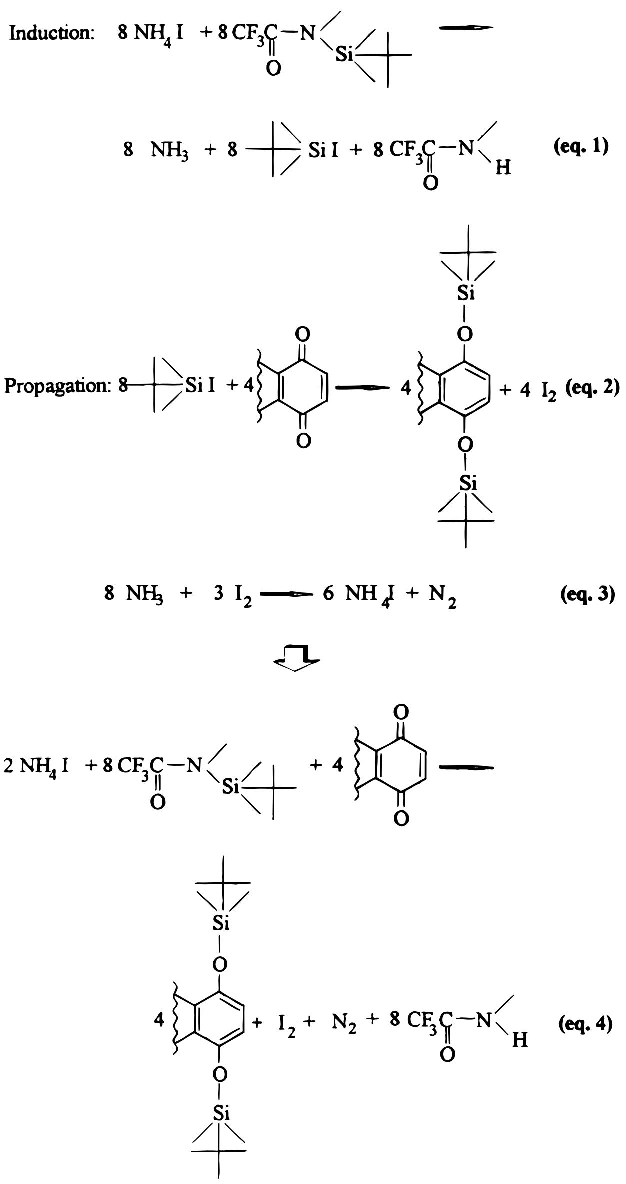
Stability experiments involved storage of the produced TBDMS ethers at −4 °C, in the dark, without addition of drying agent, either in hexane or in the reacting solution, without cleanup and reagent removal. TLC analyses verifying this stability were carried out over a period of six months. The behavior observed indicates that long term stability of **2** and **3** can be expected even in contact with the solvent or the derivatization reagents.

The foregoing results demonstrate the feasibility of this simple, new approach to the synthesis of hydrolytically stable TBDMS ethers from **1a**−**d** in nearly quantitative yields which, if normal precautions are taken, are stable for a long period of time. In conclusion, MTBSTFA was found to readily silylate the hydroxyl groups of hydroxynaphthoquinones while *in situ* generation of TBDMSI, facilitated by NH_4I addition, resulted in the reductive silylation of the quinone system.

Experimental Section

General. All melting points were determined in a heated oil bath and are uncorrected. ^1H NMR spectra were measured with a 80 MHz spectrometer, in $CDCl_3$ using TMS as internal reference, and chemical shifts are reported in δ values. Combined GC/MS analysis was performed as described.[5]

Scheme 3 Reaction Series for the Reductive Silylation of the Quinone System of 1a−d



The hydroxynaphthoquinones employed were purchased from Fluka Chemical Co. and were of analytical reagent grade. The silylating agent, MTBSTFA, containing 1% TBDMSCl and NH_4I, were also obtained from Fluka Chemical Co. and were normally stored in the cold and dark under nitrogen. All solvents were freshly dried by distillation over anhydrous sodium sulfate.

Method A. General Procedure for the Partial Silylation of Hydroxynaphthoquinones 1a−d. Preparation of 5-(*tert*-Butyldimethylsiloxy)-1,4-naphthoquinone (2a). In an oven-dried, nitrogen-filled flask, fitted with a water condenser and a dry nitrogen inlet and equipped with a magnetic stir ring bar, **1a** (87 mg, 0.5 mmol) in 5 mL of dry acetonitrile was treated with (1.16 mL, 5 mmol) of the silylating mixture MTBSTFA + 1% TBDMSCl. The mixture was heated at 60 °C and stirred for 30 min, during which time dry nitrogen was bubbled through the solution. The progress of the reaction was monitored by removing aliquots periodically and analyzing them by TLC by following the disappearance of **1a.** Soon after the completion of the reaction, the mixture was evaporated to dryness under vacuum to remove acetonitrile and excess MTBSTFA, and the residue was taken up in hexane. After the hexanic solution had cooled enough (−4 °C, 2−3 h) it was filtered to remove the white crystalline precipitate which refers to the insoluble MTFA in hexane. Evaporation to dryness under vacuum of the filtrate afforded the pure silyl ether of **1a** (**2a**), which was further purified by sublimation (except for **2d** and **3a**−**d**) to obtain 136.8 mg (95%) of a yellow solid: mp 112−113 °C; TLC (silica gel,

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$CHCl_3$−MeOH, 70:30), R_f 0.74; GC t_R 8.14 min; UV-vis ($CHCl_3$) λ_{max} 251, 328, 388 nm; IR (KBr) 2950, 2930, 2850, 1665, 1270, 1040, 830, 780, 710 cm^{-1}; ^{1}H NMR δ 0.88 (s, 6H), 1.04 (s, 9H), 6.81 (s, 2H), 7.84−7.05 (m, 3H); MS m/z (rel inten) 273 [(M − Me)$^+$, 5], 233(11), 232 (33), 231 (100), 203 (17), 185 (5), 173 (11), 149 (8), 73 (16), 57 (20), 41 (8), 29 (6). Anal. Calcd for $C_{16}H_{20}O_3Si$: C, 66.63; H, 6.99. Found: C, 66.58; H, 6.78.

Preparation of 2-(*tert*-Butyldimethylsiloxy)-1,4-naphthoquinone (2b). **1b** (87 mg, 0.5 mmol) was treated with MTBSTFA + 1% TBDMSCl (1.28 mL, 5.5 mmol) in dry acetonitrile (5 mL) as described above to give 133.9 mg (93%) of **2b** as a pale yellow solid: mp 113−114 °C; TLC (silica gel, $CHCl_3$−ethyl ether, 90:10), R_f 0.76; GC t_R 8.55 min; UV-vis ($CHCl_3$) λ_{max} 248, 311, 332 nm; IR (KBr) 2950, 2900, 2850, 1680, 1260, 1040, 830, 780, 720 cm^{-1}; ^{1}H NMR δ 0.82 (s, 6H), 0.88 (s, 9H), 6.34 (s, 1H), 8.28−7.62 (m, 4H); MS m/z (rel inten) 233(8), 232 (32), 231 [(M − *t*-Bu)$^+$, 100], 129 (8), 101 (7). Anal. Calcd for $C_{16}H_{20}O_3Si$: C, 66.63; H, 6.99. Found: C, 66.46; H, 6.80.

Preparation of 5,8-Bis(*tert*-butyldimethylsiloxy)-1,4-naphthoquinone (2c). **1c** (95 mg, 0.5 mmol) was treated with MTBSTFA + 1% TBDMSCl (1.39 mL, 6 mmol) in dry acetonitrile (5 mL) as described above to give 196.46 mg (94%) of **2c** as a pale yellow solid: mp 115−116 °C; TLC (silica gel, $CHCl_3$−ethyl ether, 90:10), R_f 0.87; GC t_R 7.53 min; UV-vis ($CHCl_3$) λ_{max} 247, 321, 347, 364 nm; IR (KBr) 2960, 2930, 2860, 1620, 1240, 970, 830, 780, 710 cm^{-1}; ^{1}H NMR δ 0.98 (s, 12H), 1.01 (s, 18H), 6.82 (s, 2H), 7.17 (s, 2H); MS m/z (rel inten) 306 (8), 305 (25), 304 [(M − 2 × *t*-Bu)$^{\bullet+}$, 100], 275 (6), 274 (21), 244 (8), 152 (5), 137 (16), 122 (9). Anal. Calcd for $C_{22}H_{34}O_4Si_2$: C, 63.11; H, 8.19. Found: C, 62.95; H, 8.20.

Preparation of 5,8-Bis(*tert*-butyldimethylsiloxy)-2-[1-(*tert*-butyldimethylsiloxy)-4-methyl-3-pentenyl]-1,4-naphthoquinone (2d). **1d** (144 mg, 0.5 mmol) was treated with MTBSTFA + 1% TBDMSCl (1.05 mL, 4.5 mmol) in dry acetonitrile (5 mL) as described above to give 296.1 mg (94%) of **2d** as a yellow chromatographically homogeneous viscous oil: TLC (silica gel, $CHCl_3$−ethyl ether, 90:10), R_f 0.80; GC t_R 11.05 min; UV-vis ($CHCl_3$) λ_{max} 258, 364, 427 nm; IR (film) 2950, 2930, 2890, 2850, 1655, 1250, 1090, 830, 780, 680 cm^{-1}; ^{1}H NMR δ 0.86 (s, 18H), 1.01 (s, 27H), 1.23 (m, 2H), 1.43 (s, 6H), 1.72 (s, 2H), 5.3−4.74 (m, 2H), 6.76 (s, 1H), 7.03 (d, 2H); MS m/z (rel inten) 507 (5), 506 (10), 505 [(M − C_5H_8 − *t*-Bu)$^+$, 32], 449 (8), 448 (20), 447 (48), 391 (8), 317 (12), 304 (10), 274 (6), 73 (91), 69 (15), 68 (9), 57 (91), 41 (100), 29 (33). Anal. Calcd for $C_{34}H_{58}O_5Si_3$: C, 64.71; H, 8.26. Found: C, 64.59; H, 9.12.

Method B. General Procedure for the Reductive Silylation of Hydroxynaphthoquinones 1a−d. Preparation of 1,4,5-Tris(*tert*-butyldimethylsiloxy)naphthalene (3a). In the previously mentioned apparatus and to a well-stirred suspension of NH_4I (41.8 mg, 0.29 mmol) in freshly dried acetonitrile (5 mL), heated to 40−45 °C were added portionwise MTBSTFA + 1% TBDMSCl (3.48 mL, 15 mmol) and **1a** (87 mg, 0.5 mmol) in succession. The apparatus was flushed with nitrogen, and the stirred mixture was heated at reflux for 15 min. The progress of the reaction was monitored by TLC at regular intervals by following disappearance of the hydroxynaphthoquinone. Soon after the completion of the reaction, the crude product was worked up in the same manner as described in method A, to yield 232 mg (89%) of **3a**, as a yellow chromatographically homogeneous, viscous oil: TLC (silica gel, $CHCl_3$−ethyl ether, 90:10) R_f 0.79; GC t_R 9.57 min; UV-vis ($CHCl_3$) λ_{max} 246, 315, 330, 345 nm; IR (film) 2950, 2880, 2855, 1260, 1050, 980, 780, 680 cm^{-1}; ^{1}H NMR δ 0.57 (s, 18H), 0.9 (s, 27H), 6.61−6.15 (m, 3H), 7.61−7.91 (m, 2H); MS m/z (rel inten) 348 (9), 347 (25), 346 [(M − *t*-Bu_2SiMe_2)$^{\bullet+}$, 100], 291 (14), 290 (36), 289 (94), 274 (8), 273 (33), 258 (5), 73 (59). Anal. Calcd for $C_{28}H_{50}O_3Si_3$: C, 64.80; H, 9.71. Found: C, 64.56; H, 9.82.

Preparation of 1,2,4-Tris(*tert*-butyldimethylsiloxy)naphthalene (3b). Following the general silylation procedure described above, **1b** (87 mg, 0.5 mmol) was treated with MTBSTFA + 1% TBDMSCl (4.88 mL, 21 mmol) and NH_4I (58.5 mg, 0.40 mmol) in dry acetonitrile (5 mL) to give 242 mg (93%) of **3b** as a yellow, chromatographically homogeneous, viscous oil: TLC (silica gel, $CHCl_3$−ethyl ether, 90:10), R_f 0.75; GC t_R 11.04 min; UV-vis ($CHCl_3$) λ_{max} 247, 277 nm; IR (film) 2950, 2930, 2880, 2855, 1615, 1250, 990, 830, 780, 705 cm^{-1}; ^{1}H NMR δ 0.79 (s, 18H), 1.03 (s, 27H), 6.52 (s, 1H), 7.27−7.5 (m, 2H), 7.9−8.18 (m, 9H); MS m/z (rel inten) 520 (13), 519 (29), 518 (M$^{\bullet+}$, 65), 331 (7), 75 (5), 74 (7), 73 (100). Anal. Calcd for $C_{28}H_{50}O_3Si_3$: C, 64.80; H, 9.71. Found: C, 64.68; H, 9.56.

Preparation of 1,4,5,8-Tetrakis(*tert*-butyldimethylsiloxy)naphthalene (3c). Following the general silylation procedure described above, **1c (**95 mg, 0.5 mmol) was treated with MTBSTFA + 1% TBDMSCl (4.65 mL, 20 mmol) and NH_4I (55.7 mg, 0.38 mmol) in acetonitrile (5 mL) to give 288 mg (89%) of **3c** as a brown, chromatographically homogeneous, viscous oil: TLC (silica gel, $CHCl_3$−ethyl ether, 90:10), R_f 0.78; GC t_R 9.49 min; UV-vis ($CHCl_3$) λ_{max} 251, 327, 345, 363, 474 nm; IR (film) 2950, 2930, 2855, 1260, 970, 830, 780, 680 cm^{-1}; ^{1}H NMR δ 0.66−1.11 (m, 60H), 6.5−6.75 (m, 4H); MS m/z (rel inten) 478 (5), 477 (21), 476 [(M − *t*-Bu_2SiMe_2)$^{\bullet+}$, 39], 305 (6), 304 (10), 74 (8), 73 (100). Anal. Calcd for $C_{34}H_{64}O_4Si_4$: C, 62.9; H, 9.94. Found: C, 62.75; H, 10.02.

Preparation of 1,4,5,8-Tetrakis(*tert*-butyldimethylsiloxy)-2-[1-(*tert*-butyldimethylsiloxy)-4-methyl-3-pentenyl]naphthalene (3d). Following the general silylation procedure described above, **1d** (144 mg, 0.5 mmol) was treated with MTBSTFA + 1% TBDMSCl (6.97 mL, 30 mmol) and NH_4I (83.5 mg, 0.58 mmol) in acetonitrile (5 mL) to give 384 mg (89%) of **3d** as a brown, chromatographically homogeneous, viscous oil: TLC (silica gel, $CHCl_3$−ethyl ether, 90:10), R_f 0.89; GC t_R 12.95 min; UV-vis ($CHCl_3$) λ_{max} 252, 346, 362, 430 nm; IR (film) 2950, 2930, 2880, 2855, 1250, 980, 830, 780, 670 cm^{-1}; ^{1}H NMR δ 1−0.65 (m, 75H), 1.25 (s, 2H), 1.4−1.7 (d, 6H), 5−5.35 (m, 2H), 6.65−7 (m, 3H); MS m/z (rel inten) 619 [(M − C_5H_9 − *t*-Bu_2SiMe_2)$^+$, 7], 506 (9), 505 (37), 448 (16), 447 (51), 391 (6), 304 (10), 75 (36), 74 (6), 73 (100), 69 (14), 59 (7), 57 (62), 42 (16), 29 (11). Anal. Calcd for $C_{46}H_{88}O_5Si_5$: C, 64.12; H, 10.29. Found: C, 63.89; H, 10.18.

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