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Orthogonally protected Dialkynes

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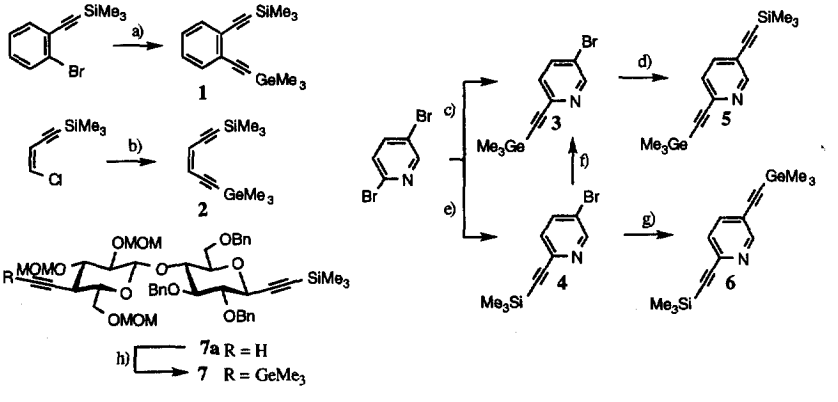
Abstract: Several *C*–$SiMe_3$ and *C*–$GeMe_3$ protected dialkynes have been synthesized and regioselectively deprotected by protodesilylation or protodegermylation. Catalytic amounts of CuBr in THF/MeOH or in aqueous acetone lead exclusively to protodegermylation. The Me_3Si group was removed with KF/[18]-crown-6 in aqueous THF without affecting the $GeMe_3$ group. *C*–$SiMe_3$ protected propargyl ethers are also selectively cleaved with K_2CO_3 in THF/ MeOH.

Nanoscale molecules ('nanostructures') with potentially new electronical, optical, or chemical properties are most efficiently prepared in a binomial way[2,3]. Ideally, this strategy uses orthogonally protected[4] building blocks, as demonstrated in the synthesis of oligoethylenes[3a], oligo(arylalkyne)s [3b,c], oligophenyls[3d], oligoesters[3e], oligonucleotides [3f], and oligosaccharides[3g]. Orthogonally protected (α,ω)-dialkynes will allow the preparation of unsymmetrical oligo(butadiynediyl)s. They should considerably broaden the scope of the synthesis of nanostructures and also prove useful, *e.g.*, in the synthesis of enediyne antibiotics[5a], enzyme mimics[5b], and carbon rich networks[5c].

In connection with our binomial synthesis of oligosaccharide analogues[6] we have introduced the first orthogonal protecting groups for dialkynes, *viz.* the Me_3Si and the dimethyl-[1,1-dimethyl-3-(tetrahydro-2*H*-pyran-2-yloxy)propyl]silyl (DOPS[7]) groups. They can independently be proto- or bromodesilylated. As the synthesis of the DOPS protected ethynyl building block requires six steps, we have prepared *C*–$SiMe_3$ and *C*–$GeMe_3$ protected carbohydrate-derived dialkynes and demonstrated[6,8] that they are selectively protodesilylated and bromo- or iododegermylated.

We now describe convenient procedures for the preparation of *C*–$SiMe_3$ and *C*–$GeMe_3$ protected dialkynes and for their orthogonal deprotection by protodesilylation and protodegermylation.

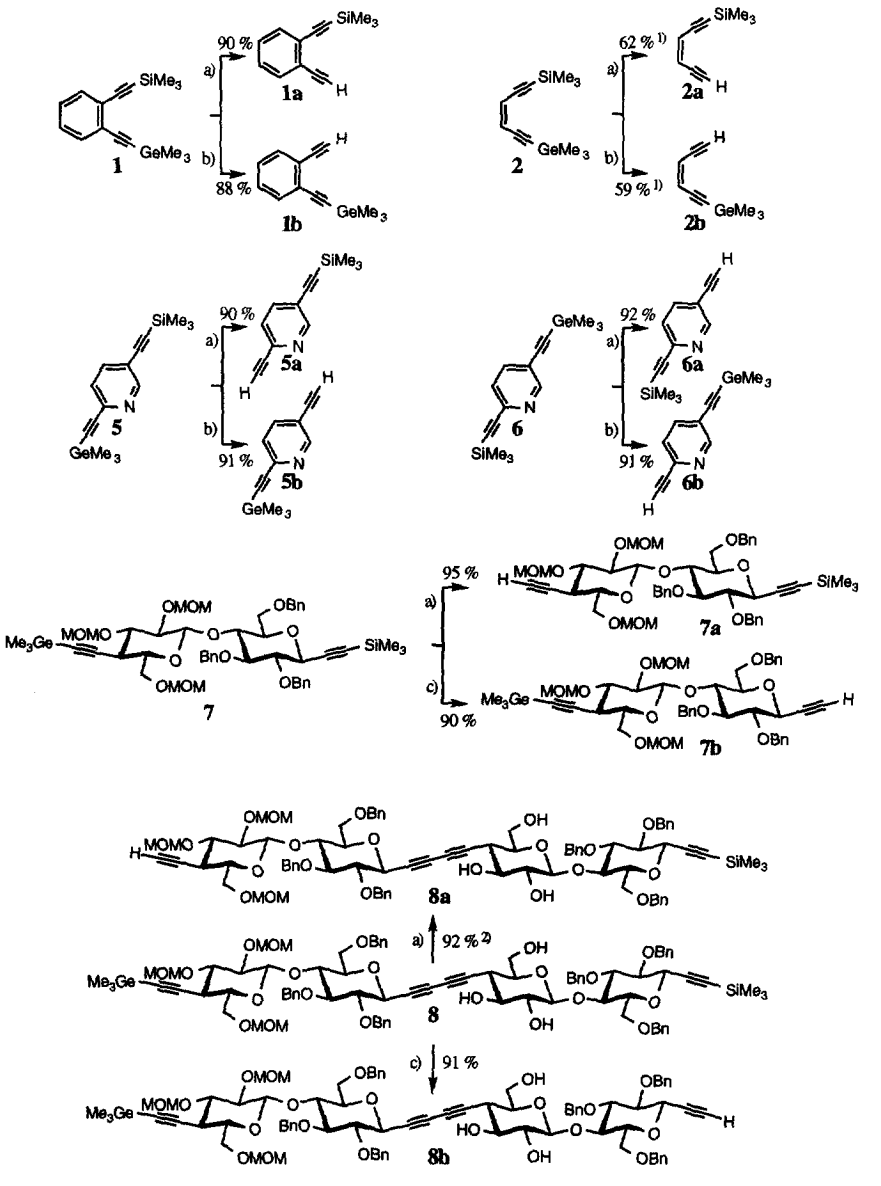
Scheme 1



Conditions: a) $HC{\equiv}CGeMe_3$, $Pd(PPh_3)_4$, CuI, NEt_3; 62%. b) $HC{\equiv}CGeMe_3$, $Pd(PPh_3)_4$, CuI, n-$BuNH_2$, PhH, 65%. c) $HC{\equiv}CGeMe_3$, $PdCl_2(PPh_3)_2$, CuI, NEt_3; 85%. d) $HC{\equiv}CSiMe_3$, $PdCl_2(PPh_3)_2$, CuI, NEt_3; 88%. e) $HC{\equiv}CSiMe_3$, $PdCl_2(PPh_3)_2$, CuI, NEt_3; 74%, see ref. 13. f) i: $NaOH_{aq}$ in MeOH, see ref. 13. ii: EtMgBr, THF, $ClGeMe_3$; 81%. g) $HC{\equiv}CGeMe_3$, $PdCl_2(PPh_3)_4$, CuI, NEt_3; 82%. h) n-BuLi, THF, $ClGeMe_3$; 93%, see ref. 6.

The *C*–$SiMe_3$ and *C*–$GeMe_3$ protected dialkynes[9] **1** and **2** (*Scheme 1*) were made by a *Castro-Stephens-Sonogashira*-type cross-coupling of ethynyltrimethylgermane[10a] with 1-bromo-2-(tri-

Scheme 2



Conditions: a) CuBr (10 mol-%), THF/MeOH. b) KF, [18]-crown-6, THF aq. c) K_2CO_3 in MeOH/THF.

1) Lower yields reflect the high volatility of **2a** and **2b**. 2) acetone/H_2O (5:1, v/v) was used as solvent.

methylsilyl)ethynylbenzene[11] and (Z)-1-chloro-4-(trimethylsilyl)but-1-en-3-yne[12], respectively. Cross-coupling 2,5-dibromopyridine with ethynyltrimethylsilane[10b] and ethynyltrimethylger-

mane[10a] gave the alkynyl bromides **3**[14] and **4**[13], which were coupled under the same conditions to the dialkynes **5** and **6**. Alternatively, **3**[14] was prepared from **4**[13] by desilylation with aqueous NaOH in MeOH and treatment with EtMgBr in THF for 45 min at 0°C, followed by the addition of $ClGeMe_3$. The synthesis of the cellobiose-derived dialkyne **7** has been described[6].

The Me_3Ge group was best removed (*Scheme 2*) with catalytic amounts of CuBr[15] in the presence of MeOH or H_2O. We suppose that an intermediate copper acetylide is formed *via* an initial π-complex between CuBr and the more nucleophilic germanium substituted alkynyl moiety. The ethynyl-silicon bond was regioselectively cleaved with KF in the presence of [18]-crown-6 in aqueous THF. These conditions[16] led to a completely selective deprotection; they are compatible with double bonds, acetal functions, butadiynediyl, hydroxyl and alkoxy groups. The *C*–$SiMe_3$ protected propargyl ethers **7** and **8** are expected to be more highly electrophilic; indeed K_2CO_3 in MeOH/ THF sufficed to selectively desilylate these compounds.

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References and Notes:

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9. Satisfactory analytical data (^1H, ^{13}C, IR, $[\alpha]_D$, MS and/or elemental analysis) were obtained for the new compounds. Selected physical data: **1**: R_f (hexane) 0.24. ^1H-NMR (300 MHz, $CDCl_3$): 7.50–7.42 (*m*, 2 H arom.); 7.29–7.17 (*m*, 2 H arom.); 0.46 (*s*, $GeMe_3$); 0.28 (*s*, $SiMe_3$). **2**: R_f (hexane) 0.26. ^1H-NMR (200 MHz, $CDCl_3$): 5.87 (*d*, J = 11.0, *H*C=); 5.81 (*d*, J = 11.0, *H*C=); 0.40 (*s*, $GeMe_3$); 0.22 (*s*, $SiMe_3$). **5**: R_f (toluene/AcOEt 50:1) 0.58. ^1H-NMR (200 MHz, $CDCl_3$): 8.61 (br.*d*, J= 2.0, H–C(6)); 7.66 (*dd*, J= 7.9, J = 2.1, H–C(4)); 7.36 (br.*d*, J= 8.1, H–C(3)); 0.44 (*s*, $GeMe_3$); 0.25 (*s*, $SiMe_3$). **6**: R_f (toluene/AcOEt 50:1) 0.59. ^1H-NMR (200 MHz, $CDCl_3$): 8.61 (br.*d*, J= 2.1, H–C(6)); 7.66 (*dd*, J= 8.0, 2.2, H–C(4)); 7.37 (br.*d*, J= 8.0, H–C(3)); 0.43 (*s*, $GeMe_3$); 0.26 (*s*, $SiMe_3$). **7**[6]: R_f (hexane/AcOEt 3:1) 0.35. ^1H-NMR (300 MHz, $CDCl_3$): selected signals: 4.02 (*d*, J = 9.6, H–C(3)); 2.65 (*t*, $J \approx$ 10.5, H–C(4')); 0.35 (*s*, $GeMe_3$); 0.18 (*s*, $SiMe_3$). **8**: R_f (toluene/AcOEt 1:1) 0.46. ^1H-NMR (500 MHz, $CDCl_3/D_2O$ 98:2): selected signals: 2.63 (*t*, $J \approx$ 10.5, H–C(4'")); 2.52 (*t*, $J \approx$ 10.4, H–C(4')); 0.34 (*s*, $GeMe_3$); 0.19 (*s*, $SiMe_3$).
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14. *Typical procedure: Preparation of the alkynyl bromide 3:*
A. From 2,5-dibromobenzene: A degassed soln. of 2,5-dibromobenzene (150 mg, 0.63 mmol) in triethylamine (3 ml) was treated with $PdCl_2(PPh_3)_2$ (10 mg, 2 mol-%), CuI (2.4 mg, 2 mol-%) and cooled to 0°C. Ethynyltrimethylgermane (100 mg, 0.7 mmol) was added slowly. The mixture was stirred at r.t. for 2.5 h, poured into sat. aq. NH_4Cl-soln., extracted with Et_2O (3x), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The black residue was chromatographed on a silica gel column (AcOEt/hexane 1:50) to give **3** (152 mg, 81%) as light orange solid. A small sample was recrystallized in hexane at –40°C.
B. From 4: The desilylation has been described[13]. A soln. of 5-bromo-2-ethynyl-pyridine (98 mg, 0.54 mmol) in THF (5.5 ml) was cooled to 0°C, treated dropwise with 1.84M EtMgBr (0.3 ml, 0.56 mmol) in THF, stirred at 0° for 45 min., treated dropwise with $ClGeMe_3$ (0.07 ml, 0.56 mmol), and stirred at r.t. for 15 min. Usual workup and chromotography gave **3** (118 mg, 85%). R_f (hexane/AcOEt 50:3) 0.32. M.p. 53–55°C. IR (CCl_4): 3040*m*, 3020*w*, 2982*m*, 2913*m*, 2130*w*, 1910*w*, 1660*w*, 1564*m*, 1544*m*, 1460*s*, 1448*s*, 1415*m*, 1364*m*, 1351*m*, 1244*s*, 1221*w*, 1123*w*, 1091*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 8.64 (br.*d*, *J* = 2.5, H–C(6)); 7.79 (*dd*, *J* = 8.3, 2.5, H–C(4)); 7.35 (*dd*, *J* = 8.3, 0.8, H–C(3)); 0.47 (*s*, $GeMe_3$). ^{13}C-NMR (75 MHz, $CDCl_3$): 150.80 (*d*, C(6)); 141.20 (*s*, C(2)); 138.59 (*d*, C(4)); 127.93 (*d*, C((3)); 119.79 (*s*, C(5)); 101.88 (*s*, *C*≡CGe); 97.38 (*s*, C≡*C*Ge); –0.49 (*q*, CH_3). MS–EI: 300.9 (10), 298.9 (14, M^+), 296.9 (11), 285.9 (22), 283.9 (100, $[M - Me]^+$), 282.9 (20), 281.9 (74). Anal. calc for $C_{10}H_{12}NBrGe$ (298.73): C 40.21, H 4.05; found C 40.06, H 4.09.
15. Purchased from Aldrich and used without further purification.
16. *General procedure for the protodegermylation*: A 0.05–0.1M soln. of the *C*–$SiMe_3$/*C*–$GeMe_3$ protected dialkyne in MeOH/THF (1:1, v/v) or acetone/H_2O (5:1, v/v) was treated with CuBr (10 mol-%) at r.t. The orange mixture was stirred for 1-4 h[17], diluted with sat. NH_4Cl soln. and extracted with Et_2O (3x). The combined org. layers were washed with water (2x) and brine (1x), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was chromatographed on a silica gel column to give the degermylated dialkyne[18].
General procedure for the protodesilylation: A 0.3M soln. of KF in [18]-crown-6 (1.1 eq.) was added dropwise to a 0.05–0.1M soln. of the *C*–$SiMe_3$/*C*–$GeMe_3$ protected dialkyne in THF/H_2O (98:2, v/v) at 0°C. The mixture was stirred for 0.5-3 h, diluted with water and extracted with Et_2O (3x). The combined org. layers were washed with water (2x) and brine (1x), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was chromatographed on a silica gel column to give the desilylated dialkyne[19].
17. The reaction should be monitored carefully by tlc and worked up as soon as the starting material has been consumed.
18. Selected physical data: **1a**[11]: R_f (hexane) 0.29. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.52–7.46 (*m*, 2 H arom.); 7.29–7.16 (*m*, 2 H arom.); 3.30 (*s*, H–C≡); 0.28 (*s*, $SiMe_3$). **2a**[20]: R_f (hexane) 0.28. ^{1}H-NMR (200 MHz, $CDCl_3$): 5.90 (*d*, *J* = 11.1, H–C(3)); 5.82 (*dd*, *J* = 11.1, 2.2, H–C(4)); 3.37 (*d*, *J* = 2.3, H–C≡); 0.23 (*s*, $SiMe_3$). **5a**: R_f (hexane/AcOEt 7:1) 0.32. ^{1}H-NMR (200 MHz, $CDCl_3$): 8.64 (*d*, *J* = 2.0, H–C(6)); 7.69 (*dd*, *J* = 7.8, 2.0, H–C(4)); 7.41 (br.*d*, *J* = 8.3, H–C(3)); 3.24 (*s*, H–C≡); 0.26 (*s*, $SiMe_3$). **6a**[7]: R_f (toluene/AcOEt 50:1) 0.42. ^{1}H-NMR (200 MHz, $CDCl_3$): 8.65 (*d*, *J* = 2.1, H–C(6)); 7.71 (*dd*, *J* = 7.7, 1.9, H–C(4)); 7.40 (br.*d*, *J* = 8.0, H–C(3)); 3.29 (*s*, H–C≡); 0.26 (*s*, $SiMe_3$). **7a**[6]: R_f (hexane/AcOEt 2:1) 0.76. ^{1}H-NMR (300 MHz, $CDCl_3$): selected signals: 2.66 (*td*, *J* ≈ 10.4, 2.3, H–C(4')); 2.20 (*d*, *J* ≈ 2.3, HC≡C–C(4'); 0.20 (*s*, $SiMe_3$). **8a**: R_f (toluene/AcOEt 1:1) 0.55. ^{1}H-NMR (400 MHz, $CDCl_3$): selected signals: 2.64 (*td*, *J* ≈ 10.4, 2.3, H–C(4'''); 2.18 (*d*, *J* = 2.3, HC≡C–C(4'''); 0.19 (*s*, $SiMe_3$).
19. Selected physical data: **1b**: R_f (hexane/AcOEt 50:1) 0.49. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.50–7.42 (*m*, 2 H arom.); 7.32–7.18 (*m*, 2 H arom.); 3.29 (*s*, H–C≡); 0.44 (*s*, $GeMe_3$). **2b**: R_f (pentane) 0.36. ^{1}H-NMR (200 MHz, $CDCl_3$): 5.93 (*d*, *J* = 11.2, H–C(3)); 5.79 (*dd*, *J* = 11.0, *J* = 2.2, H–C(4)); 3.35 (*d*, *J* = 2.2, H–C≡); 0.40 (*s*, $GeMe_3$). **5b**: R_f (toluene/AcOEt 50:1) 0.43. ^{1}H-NMR (200 MHz, $CDCl_3$): 8.64 (*d*, *J* = 2.0, H–C(6)); 7.70 (*dd*, *J* = 8.2, 2.1, H–C(4)); 7.38 (br.*d*, *J* = 8.2, H–C(3)); 3.28 (*s*, H–C≡); 0.45 (*s*, $GeMe_3$). **6b**: R_f (toluene/AcOEt 50:1) 0.38. ^{1}H-NMR (200 MHz, $CDCl_3$): 8.62 (*d*, *J* = 2.1, H–C(6)); 7.68 (*dd*, *J* = 7.7, 1.9, H–C(4)); 7.39 (br.*d*, *J* = 8.0, H–C(3)); 3.23 (*s*, H–C≡); 0.44 (*s*, $GeMe_3$). **7b**[6]: R_f (hexane/AcOEt 2:1) 0.46. ^{1}H-NMR (300 MHz, $CDCl_3$): selected signals: 4.02 (*dd*, *J* = 9.6, 2.1, H–C(3)); 2.66 (*t*, *J* ≈ 10.5, H–C(4')); 2.52 (*d*, *J* = 2.1, HC≡C–C(3); 0.35 (*s*, $GeMe_3$). **8b**: R_f (toluene/AcOEt 1:1) 0.56. ^{1}H-NMR (300 MHz, $CDCl_3$): selected signals: 2.56 (*d*, *J* = 2.1, HC≡C–C(3); 0.36 (*s*, $GeMe_3$).
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