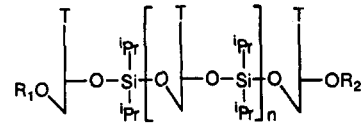
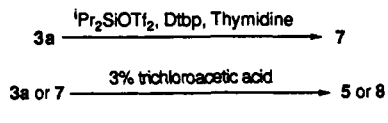
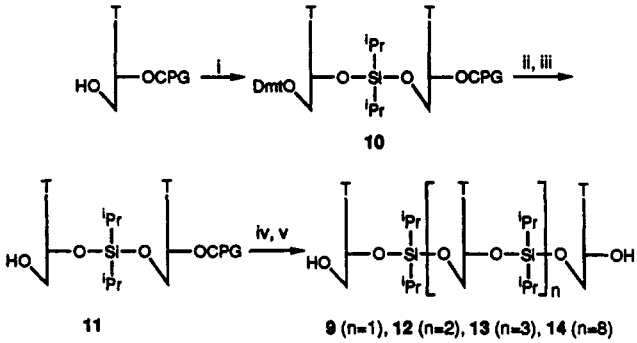
**Scheme III**






| Product | $R_1$ | n | $R_2$ |
|---|---|---|---|
| 3a | Dmt | 0 | H |
| 7 | Dmt | 1 | H |
| 5 | H | 0 | H |
| 8 | H | 1 | H |
| 6 | Dmt | 0 | $P(OCH_2CH_2CN)N^iPr_2$ |
| 9 | Dmt | 1 | $P(OCH_2CH_2CN)N^iPr_2$ |

**Scheme IV**




[a]CPG = controlled pore glass, Dmt = dimethoxytrityl. [b](i) 1a, Dtbp, imidazole; (ii) $Ac_2O$, *N*-methylimidazole; (iii) 3% trichloroacetic acid; (iv) cycle repeat (i) to (iii); (v) aqueous $NH_3$, $^iPrOH$–$CH_3CN$.

linkage as a phosphodiester mimic, we synthesized phosphodiester-linked DNA oligomers containing single or multiple units of the silyl-linked di- and trithymidylates. The building blocks **6** and **9** for automated synthesis were prepared from **3a** and **7** respectively, by reaction with 2-cyanoethyl *N,N* diisopropylphosphoramidochloridite (Scheme III). The yields of isolated products ranged from 60 to 80%. The following 11-mer oligonucleotides were prepared[5] incorporating the T-Si-T dimer and the T-Si-T-Si-T trimer at the indicated positions within the strands:

1. 5′ TTT TTT TTTSiT T-3′
2. 5′ TTT TTT TTSiT TT-3′
3. 5′ TTT TTTSiT TTT T-3′
4. 5′ TTT TTT TTSiTSiT T-3′
5. 5′ TTT TTSiTSiT TTT T-3′

The mean coupling yield for these incorporations was >97%. The synthesized products were cleaved from the CPG support with $NH_4OH$ (30% aqueous)/2-propanol/$CH_3CN$ (6:3:1) and the crude overall product yield was determined on the basis of the OD 260 nm measurement. A preparative reverse-phase HPLC procedure allowed isolation of the major peak from the failure sequences and molecular weight was verified by FAB/MS. The purified compounds were also analyzed by ion exchange HPLC and a repeat reverse-phase HPLC. A single major peak was seen by both methods indicating good purity. Chemical stability in buffered media [(0.01 M TEAA (pH 7.5)/acetonitrile (4–20%)] was monitored by reverse-phase HPLC and no significant degradation was detected for the 6 weeks tested.

A nuclease stability assay, analyzed by anion exchange HPLC for the above five chimeric oligothymidylate compounds, was run in the presence of 10% FBS (fetal bovine serum which contains 3′-exonucleases) media, with control standards run in parallel. Retention times of the standards were used to identify fragment lengths. The control $T_{11}$ strand was completely digested in 3 min. For each of the five oligomers, the exonuclease cleaved the phosphodiester bonds in the 3′-5′ direction but stopped at the siloxane link.

Thermodynamic melting[6] data ($T_m$) were acquired by mixing the above oligomers with complementary $dA_{11}$ strands in equimolar amounts and annealing at 4° in a phosphate buffer (0.1 M NaCl) for 24 h. The UV absorbance at 260 nm was measured every 0.25° while the temperature was ramped from 20 to 70°. The $T_m$ value for dissociation of the duplex was obtained from the first derivative of the absorbance vs temperature plot. In all cases, the $T_m$ values were less than the control $T_{11}/dA_{11}$ duplex by 2–5°, depending on extent of the modification.[7] The melting curve shapes were however normal, indicating good duplex formation. Full details of these studies will be reported elsewhere.

In conclusion, a versatile and efficient synthetic method has been developed for solution- and automated solid-phase synthesis of dialkylsilyl-linked oligonucleotide analogs. This method employs minimal protection and avoids problems of self-coupling. Our solid-phase automated synthesis allows preparation of uniformly dialkylsilyl-linked DNA analogs of any sequence. This method also allows high yield solution synthesis of dialkylsilyl-linked dimers and trimers of any sequence. We have also accomplished the synthesis of mixed phosphodiester-silyl-linked oligonucleotide analogs containing 1–2 incorporations of diisopropylsilyl-linked thymidylate dimers or trimers. These mixed backbone oligomers were soluble and chemically stable in buffered aqueous systems. Evidence for the potential utility of the siloxane modification in antisense and related research was also obtained.

## Experimental Section

**General.** All chemicals used in this study were reagent grade unless otherwise stated. Nucleosides were purchased from Raylo Chemical Company, Edmonton, Canada, or Pharma-Waldorf,

(5) Gait, M. J., Ed. *Oligonucleotide Synthesis: A Practical Approach*; IRL Press: Washington, DC, 1984.

(6) (a) Cantor, C. R.; Schimmel, P. R., Eds. *Biophysical Chemistry*, III; W. H. Freeman and Company: New York, 1980; pp 1134–1160. (b) Tinoco, I.; Puglisi, J. D. in *Methods in Enzymology*; Dahlberg, J. E., Abelson, J. N., Eds.; Academic Press: San Diego, 1989, Vol. 180 (A), 304.

(7) Replacement of the natural phosphodiester linkage with modified counterparts leads to a minimum of 1–3 °C drop in $T_m$ value. See, for example: (a) Gao, X.; Brown, F. K.; Jeffs, P.; Bischofpberger, N.; Lin, K.-Y.; Pipe, A. J.; Noble, S. A. *Biochemistry* **1992**, *31*, 6228. (b) Kibler-Herzog, L.; Zon, G.; Uznanski, B.; Whittier, G.; Wilson, W. D. *Nucleic Acids Res.* **1991**, *19*, 2979.

Dusseldorf, Germany. Bis(trifluoromethanesulfonyl)diisopropylsilane was purchased from Petrarch Systems Inc., Bertram, PA, or Fluka Chemical Corporation, Ronkonkoma, NY, and distilled from $K_2CO_3$ prior to use. Phosphoramidites were purchased from Applied Biosystems, Foster City, CA. All other reagents were purchased from Aldrich and dried as appropriate, by standard procedures prior to use. All solvents were purchased from Aldrich (<0.0005% $H_2O$) and used as received. All nucleosides were dried by coevaporation from a mixture of pyridine and acetonitrile *in vacuo* and furthur dried over $P_2O_5$ in high vacuum prior to use.

Nuclear magnetic resonance (NMR) spectra were recorded on a Varian XL-300, Varian FX-270, or Bruker AMX 360 spectrometer and data are presented as ppm downfield from either tetramethylsilane or 85% $H_3PO_4$. The FAB–mass spectra were recorded on a Finnigan MAT TSQ70 triple quadrupole instrument or on a VG Analytical ZAB 2-SE instrument. UV absorbance and $T_m$ studies were carried out in a Perkin-Elmer spectrophotometer equipped with a temperature controller. HPLC was carried out on a Waters HPLC apparatus Model 3000 with a Waters 481 UV detector set at 254 nm. Reverse-phase chromatography was done on Beckman Ultrasphere ODS (10 mm × 25 cm) and Vydac (51 mm × 250 mm) columns. Normal-phase HPLC was performed on a Zorbax Sil (21 mm × 25 cm) column, purchased from Dupont. Silica gel used for flash chromatography was Merck Silica Gel 60 (70–230 mesh). Elemental analysis was obtained from Microanalysis Inc., Wilmington, DE.

**General Procedure for Preparation of 3′-*O*-(Diisopropylsilyl)-2′-deoxynucleoside Triflate Intermediates 1.** Bis(trifluoromethanesulfonyl)diisopropylsilane (2 mmol, 0.60 mL) was added via syringe to a solution of 2,6-di-*tert*-butyl-4-methylpyridine (2 mmol, 0.41 g) in $CH_3CN$ (5 mL) in a 100-mL round-bottom flask under $N_2$. The clear solution was cooled to −40 °C (dry ice–$CH_3CN$) and to it a solution of 5′-*O*-(dimethoxytrityl)-2′-deoxynucleoside (1.84 mmol, 1.0 g) and 2,6-di-*tert*-butyl-4-methylpyridine (0.46 mmol, 94 mg) in DMF (5 mL) was added dropwise via syringe over 10 min. The reaction was stirred at −40 °C for 1 h. For characterization, a small amount was isolated by precipitation from water followed by chromatography on a small silica column eluting with 60% to 100% EtOAc/hexanes. Yield of 3′-*O*-diisopropylsilanols: 95–100%. $R_f$s: 0.56–0.90 (0.5% MeOH/EtOAc). Data for 1c: $R_f$ 0.71 (0.5% MeOH/EtOAc); $^1$H NMR (300 MHz, $CDCl_3$) δ 8.43 (d, $J$ = 7.6 Hz, 1 H), 7.88 (d, $J$ = 8.2 Hz, 2 H), 7.60–7.26 (m, 13 H), 6.87 (d, $J$ = 8.4 Hz, 4 H), 6.25 (t, $J$ = 6.5 Hz, 1 H), 4.71 (m, 1 H), 4.10 (m, 1 H), 3.80 (s, 6 H), 3.48 (ABq, $J$ = 3 Hz, 11 Hz, Δν = 30 Hz, 2 H), 2.67 (m, 1 H), 2.35 (m, 1 H), 0.97 (m, 14 H); MS (FAB) $m/z$ 764.7 (M + H)$^+$.

**5′-*O*-(Dimethoxytrityl)-3′-*O*-(5′-*O*-thymidyldiisopropylsilyl)thymidine (3a).** Thymidine (0.8 mmol, 193 mg) was added to a solution of intermediate 1a (0.92 mmol) prepared as above. The reaction was stirred for 1 h and then added dropwise into a vigorously-stirred ice–water mixture (500 mL). The mixture was filtered to give a white solid which was air dried and subjected to column chromatography ($SiO_2$, gradient of 60% to 100% EtOAc/hexanes). Yield: 0.581 g, 70%; $R_f$ 0.45 (5% MeOH/EtOAc); $^1$H NMR (300 MHz, $CDCl_3$) δ 9.85 (s, 1 H, NH), 9.44 (s, 1 H, NH), 7.64 (s, 1 H), 7.41–7.24 (m, 10 H), 6.84 (d, $J$ = 7.8 Hz, 4 H), 6.33 (m, 2 H), 4.65 (s, 1 H), 4.43 (d, $J$ = 2.2 Hz, 1 H), 4.11 (d, $J$ = 2.56, 1 H), 4.00 (d, $J$ = 3.36, 1 H), 3.93 (ABq, $J$ = 3.7 Hz, 11.0 Hz, Δν = 24.6 Hz, 2 H), 3.79 (s, 6 H), 3.39 (ABq, $J$ = 3.0 Hz, 10.8 Hz, Δν = 49.5 Hz, 2 H), 2.50–2.38 (m, 2 H), 2.30–2.07 (m, 2 H), 1.88 (s, 3 H), 1.56 (s, 3 H), 1.05–0.98 (m, 14 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 164.84, 164.80, 159.40, 151.72, 151.25, 144.89, 136.16, 136.01, 135.86, 130.60, 128.58, 127.75, 113.80, 112.10, 111.42, 87.48, 87.38, 85.76, 85.48, 73.90, 71.70, 63.82, 63.48, 60.75, 55.57, 41.71, 40.85, 21.24, 17.52, 17.47, 17.39, 14.35, 12.69, 12.18, 12.10, 11.85; $^{29}$Si NMR (53.5 MHz) δ −8.09; MS (FAB): $m/z$ 899 (M + H)$^+$; HR-MS (FAB) calcd for $C_{47}H_{58}N_4O_{12}Si$ 898.3821, obsd 898.3748.

**3′-*O*-(5′-*O*-Thymidyldiisopropylsilyl)thymidine (5).** A solution of dimer 3a (0.22 mmol, 200 mg) in $CH_2Cl_2$ (4 mL) was added to 3% trichloroacetic acid in $CH_2Cl_2$ (6 mL). The bright orange solution was stirred at room temperature for 10 min. The reaction mixture was poured into 5% aqueous $NaHCO_3$ (5 mL) and extracted into 5% MeOH/EtOAc. The organic layer was washed with brine (10 mL) and dried over $Na_2SO_4$. The crude product was purified by column chromatography ($SiO_2$, gradient of 60:40 EtOAc/hexanes to 10% MeOH/EtOAc): yield 90 mg, 70%; $R_f$ 0.40 (10% MeOH/EtOAc); $^1$H NMR (300 MHz, $CD_3OD$) δ 7.54 (s, 1 H), 7.28 (s, 1 H), 6.03 (m, 2 H), 4.46 (m, 1H), 4.18 (m, 1 H), 3.82–3.69 (m, 3 H), 3.50 (m, 4 H), 2.06–1.97 (m, 4 H), 1.62 (s, 6 H), 0.85 (m, 14 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 167.0, 152.6, 138.6, 138.2, 112.1, 89.8, 88.7, 86.8, 86.5, 74.6, 72.3, 64.6, 63.1, 42.0, 41.2, 18.0, 17.9, 13.4, 13.3, 12.8, 12.7; $^{29}$Si NMR (53.5 MHz) δ −8.2; MS (FAB): $m/z$ 597.3 (M + H)$^+$; HR-MS (FAB) calcd for $C_{26}H_{41}N_4O_{10}Si$ 597.2592, obsd 597.2612.

**5′-*O*-(Dimethoxytrityl)-3′-*O*-[(3′-*O*-5′-*O*-thymidyldiisopropylsilyl)-3′-*O*-[(3′-*O*-(5′-*O*-5′-*O*-thymidyl)diisopropylsilyl]thymidine (7).** A solution of dimer 3a (1.11 mmol, 1.0 g) and 2,6-di-*tert*-butyl-4-methylpyridine (0.28 mmol, 60 mg) in DMF (3 mL) was added via syringe to a solution of bis(trifluoromethanesulfonyl)diisopropylsilane (1.22 mmol, 0.504 g, 0.360 mL) and 2,6-di-*tert*-butyl-4-methylpyridine (1.22 mmol, 0.25 g) in $CH_3CN$ (3 mL) at −40 °C (dry ice–$CH_3CN$). The reaction was stirred for 1 h at −40 °C. A solution of imidazole (1.22 mmol, 0.16 g) in $CH_3CN$ (2.5 mL) was added and the reaction was warmed to room temperature. A solution of thymidine (1.11 mmol, 0.269 g) in DMF (2 mL) was added. The reaction was stirred for 1 h and added dropwise to a vigorously-stirred ice/water mixture (1 L) and stirred for 30 min. The precipitate was filtered and air dried to give a white solid (1.5 g). This crude product was triturated with hexanes (20 mL) to give pure product: isolated yield 1.05 g, 76%; $R_f$ 0.38 (5% MeOH/EtOAc); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.62 (s, 1 H), 7.36–7.22 (m, 11 H), 6.80 (d, $J$ = 7.7, 4 H), 6.36–6.22 (m, 3 H), 4.62–4.54 (m, 2 H), 4.45 (m, 1 H), 4.06–3.83 (m, 7 H), 3.75 (s, 6 H), 3.36 (ABq, $J$ = 10 Hz, Δν = 47.6 Hz, 2 H), 2.45–2.30 (m, 3 H), 2.28–2.14 (m, 1 H), 2.13–2.00 (m, 2 H), 1.85 (s, 3 H), 1.81 (s, 3 H), 1.48 (s, 3 H), 0.98 (m, 28 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 164.54, 164.45, 164.33, 159.00, 151.12, 150.99, 144.40, 135.73, 135.51, 135.40, 130.15, 128.16, 127.35, 113.37, 111.54, 111.32, 111.07, 87.50, 87.02, 85.23, 85.02, 73.35, 72.98, 71.24, 63.28, 63.02, 55.15, 41.33, 40.64, 40.25, 17.04, 17.00, 16.92, 12.26, 11.70, 11.59, 11.53, 11.47; $^{29}$Si NMR (53.5 MHz) δ −7.9, −8.2; MS (FAB): $m/z$ 1252.5 (M + H)$^+$. Anal. Calcd for $C_{63}H_{84}N_6O_{17}Si_2$: C, 60.38; H, 6.71; N, 6.71. Found: C, 60.44; H, 6.84; N, 6.56.

**3′-*O*-[(3′-*O*-(5′-*O*-Thymidyldiisopropylsilyl)-(5′-*O*-thymidyl)diisopropylsilyl]thymidine (8).** A solution of 5′-*O*-(dimethoxytrityl trimer 7 (0.638 mmol, 0.80 g) in $CH_2Cl_2$ (12 mL) was added to 3% trichloroacetic acid/$CH_2Cl_2$ (14 mL). The bright orange solution was stirred at room temperature for 1 h. The reaction mixture was poured into 5% aqueous $NaHCO_3$ (15 mL) and extracted into 5% MeOH/EtOAc. The organic layer was washed with brine (20 mL) and dried over $Na_2SO_4$. The crude product was purified by column chromatography ($SiO_2$, gradient of EtOAc/MeOH 100% to 95%): isolated yield 420 mg, 70%; $R_f$ 0.50 (10% MeOH/EtOAc); $^1$H NMR (360 MHz, DMSO-$d_6$) δ 11.3 (s, br, 2 H), 7.66 (s, 1 H), 7.37 (s, 2 H), 6.19 (m, 3 H), 5.29 (s, br, 1 H), 5.09 (s, br, 1 H), 4.56 (m, 2 H), 4.20 (m, 1 H), 3.9–3.8 (m, 7 H), 3.55 (m, 2 H), 2.26–2.1 (m, 6 H), 1.75 (s, 9 H), 1.04 (m, 28 H); MS (FAB) $m/z$ 949.5 (M − H)$^-$; HR-MS (FAB) calcd for $C_{42}H_{66}N_6O_{18}Si_2Na$ 973.4022, obsd 973.3979.

**5′-*O*-(Dimethoxytrityl)-3′-*O*-[(3-*O*′-[(3-*O*′-(5′-*O*-thymidyldiisopropylsilyl)-5-*O*-thymidyl)diisopropylsilyl)-5′-*O*-(thymidyldiisopropyl)silyl]thymidine (12).** 5′-*O*-Dimethoxytrityl trimer 7 (20 μmol, 25 mg) and 2,6-di-*tert*-butyl-4-methylpyridine (40 μmol, 8.25 mg) were dissolved in DMF (200 μL) and added slowly via syringe to a solution of bis(trifluoromethanesulfonyl)diisopropylsilane (20 μmol, 6 μL) and 2,6-di-*tert*-butyl-4-methylpyridine (20 μmol, 4.1 mg) in DMF (100 μL) in a 5-mL round-bottom flask cooled to −40 °C (dry ice–$CH_3CN$). The reaction was stirred for 1 h and to it a solution of thymidine (20 μmol, 4.84 mg) and imidazole (40 μmol, 2.7 mg) in DMF (200 μL) was added. Stirring was continued at −40 °C for 30 min. The reaction was warmed to room temperature; 5% aqueous $NaHCO_3$ (1 mL) was added and the reaction mixture extracted into $CHCl_3$ (2 × 5 mL), washed with brine (1 mL), and dried over $Na_2SO_4$. The crude product was purified by preparative reverse-phase HPLC on Ultrasphere ODS (20% 0.01 M triethylammonium acetate pH 7.5/80% $CH_3CN$; $t_R$ = 35.4 min): yield 10 mg, 31%; $R_f$ 0.16 (5% MeOH/EtOAc); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.65 (s, 1 H), 7.39–7.26 (m, 12 H), 6.85 (d, $J$ =

**Chart I**

A. Programming Cycles
1. All oxidation and subsequent iodine wash step/purges were disabled.
2. Tetrazole step was disabled by programming/hardwiring off.
3. Increased coupling times, increased monomer molarity, and double couple cycles were used to enhance coupling efficiency.

B. Reagents
1. Iodine solution was not used and removed from valveblock.
2. $NH_4OH$ bottle position was used for 6:3:1 solution of $NH_4OH$:$^i$PrOH:$CH_3CN$.
3. Spare position 5 and X were used for synthon 1a on Models 380B and 381A, respectively, after accurate flowcheck.

7.7 Hz, 4 H), 6.38–6.27 (m, 4 H), 4.66–4.45 (m, 4 H), 4.10–3.85 (m, 10 H), 3.80 (s, 6 H), 3.39 (ABq, $J$ = 11 Hz, $\Delta\nu$ = 45 Hz, 2 H), 2.45–2.08 (m, 8 H), 1.92 (s, 3 H), 1.90 (s, 3 H), 1.87 (s, 3 H), 1.56 (s, 3 H), 1.03 (m, 42 H); MS (FAB) calcd for $C_{79}H_{110}N_8O_{22}Si_3$ 1607.6770, obsd 1607.6765.

**Solid-Phase Synthesis of Thymidine Decanucleoside 14.** The monomeric synthetic unit **1a** was prepared from 5′-(dimethoxytrityl)thymidine according to the procedure described earlier with the exception that 2 equiv of imidazole was added prior to warming the reaction to room temperature and that acetonitrile was added to a final synthon concentration of 0.1 M. $R_f$ of **1a**: 0.56, 60% EtOAc/hexanes. This intermediate was employed in solid-phase automated synthesis as described below (see text also).

All reagents used for synthesis were purchased from Applied Biosystems Inc. (Foster City, CA). Oligomer synthesis using 0.2 and 1 μmol of derivatized thymidine controlled pore glass support was used employing both ABI 380B and ABI 381A programmable DNA synthesizers. Synthesis cycles closely followed the high efficiency DNA cycles ABI001 and CE103A with modifications as indicated in Chart I. Step yields averaged 96.3% for 3 identical 10 base syntheses. Data for **14**: $^1$H NMR (300 MHz, $CD_3OD$) δ 7.55–7.47 (m, 10 H), 6.23–6.33 (m, 10 H), 4.69 (s, br, 9 H), 4.40 (s, br, 1 H), 4.10–3.40 (m, 19 H), 3.25–3.08 (m, 1 H), 2.55–2.20 (m, 20 H), 1.87 (s, br, 27 H), 1.30 (s, br, 3 H), 1.08 (m, 126 H); MS (FAB) calcd for $C_{154}H_{249}N_{20}O_{50}Si_9$ 3430.55, obsd 3430.6.[8]

**3′-*O*-(2′-Deoxy-*N*$^2$-isobutyryl-5′-*O*-guanosyl)diisopropylsilyl)-5′-*O*-(dimethoxytrityl)thymidine (3d).** This compound was prepared according to the procedure described for **3a**, with purification by column chromatography ($SiO_2$, 3–4% MeOH/EtOAc): yield 40%; $R_f$ 0.30 (5% MeOH/EtOAc); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.98 (s, 1 H), 7.67 (s, 1 H), 7.5–7.25 (m, 9 H), 6.84 (d, $J$ = 8.5 Hz, 4 H), 6.3 (t, $J$ = 6 Hz, 1 H), 6.21 (t, $J$ = 6 Hz, 1 H), 4.83 (m, 1 H), 4.72 (m, 1 H), 4.61 (m, 1 H), 4.07 (m, 2 H), 3.90 (m, 2 H), 3.77 (s, 6 H), 3.47–3.29 (m, 2 H), 2.85 (m, 1 H), 2.55–2.20 (m, 4 H), 1.48 (s, 3 H), 1.2 (d, $J$ = 6.0 Hz, 6 H), 1.0–0.9 (m, 14 H); MS (FAB) $m/z$ 992.4 (M − H)$^-$; HR-MS (FAB) calcd for $C_{51}H_{63}N_7O_{12}SiNa$ 1016.4202, obsd 1016.4238.

**N$^6$-Benzoyl-2′-deoxy-5′-*O*-(dimethoxytrityl)-3′-*O*-(5′-*O*-thymidyldiisopropylsilyl)adenosine (3e).** This compound was prepared according to the procedure described for **3a**, with purification by preparative TLC ($SiO_2$, 3% MeOH/EtOAc): yield 78%; $R_f$ 0.32 (2% MeOH/EtOAc); $^1$H NMR (300 MHz, $CDCl_3$) δ 9.99 (s, 1 H, NH), 8.76 (s, 1 H), 8.22 (s, 1 H), 8.09 (d, $J$ = 7.8 Hz, 2 H), 7.55–7.13 (m, 13 H), 6.74 (m, 4 H), 6.42 (t, $J$ = 5.8 Hz, 1 H), 6.25 (t, $J$ = 6.0 Hz, 1 H), 4.96 (d, $J$ = 5.4 Hz, 1 H), 4.48 (s, 1 H), 4.19 (d, $J$ = 3.8 Hz, 1 H), 3.94 (s, 1 H), 3.83–3.72 (m, 2 H), 3.72 (s, 6 H), 3.38 (d, $J$ = 3.4 Hz, 2 H), 2.83–2.76 (m, 1 H), 2.60–2.52 (m, 1 H), 2.45–2.38 (m, 1 H), 2.05–1.95 (m, 1 H), 1.79 (s, 3 H), 0.95 (m, 14 H); MS (FAB): $m/z$ 1011.1 (M − H)$^-$.

**N$^4$-Benzoyl-2′-deoxy-5′-*O*-(dimethoxytrityl)-3′-*O*-(5′-*O*-thymidyldiisopropylsilyl)cytidine (3f).** This compound was prepared according to the procedure described for **3a**, with purification by preparative TLC ($SiO_2$, 3% MeOH/EtOAc): yield 70%; $R_f$ 0.40 (2% MeOH/EtOAc); $^1$H NMR ($CDCl_3$) δ 9.54 (s, 1 H, NH), 8.21 (d, $J$ = 7.6 Hz, 1 H), 7.94 (d, $J$ = 8.2 Hz, 2 H), 7.59–7.24 (m, 14 H), 6.83 (d, $J$ = 8.4 Hz, 4 H), 6.25 (m, 2 H), 4.58 (s, 1 H), 4.46 (s, 1 H), 4.17 (s, 1 H), 4.07–3.80 (m, 3 H), 3.77 (s, 6 H), 3.39 (ABq, $J$ = 3.0 Hz, 10.9 Hz, $\Delta\nu$ = 29.1, 2 H), 2.84–2.78 (m, 1 H), 2.46–2.41 (m, 1 H), 2.14–1.79 (m, 2 H), 1.84 (s, 3H), 0.98 (m, 14 H); MS (FAB) $m/z$ 987.2 (M − H)$^-$.

**5′-*O*-(Dimethoxytrityl)-3′-*O*-(5′-*O*-thymidyldiisopropylsilylthymidine-3′-(2-Cyanoethyl *N,N*-diisopropylphosphoramidite (6).** 5′-*O*-Dimethoxytrityl dimer **3a** (coevaporated from THF (4 mL)/pyridine (2 mL) twice, 0.1 mmol, 90 mg) was dissolved in THF (500 μL) and added dropwise via syringe to a stirred solution of 4-(dimethylamino)pyridine (cat., 4 mg), diisopropylethylamine (distilled from $CaH_2$, 0.4 mmol, 87 μL), and 2-cyanoethyl *N,N*-diisopropylphosphoramidochloridite (0.15 mmol, 28.77 μL) in THF (500 μL) under $N_2$ flow at room temperature. The reaction was allowed to stir for 2 h. To remove trace amount of **5**, additional 2-cyanoethyl *N,N*-diisopropylphosphoramidochloridite (0.025 mmol, 5 μL) was added. The reaction was stirred 1 h and added to EtOAc (10 mL, prewashed with 5 mL of brine), washed with brine (2 × 2 mL), and dried over $Na_2SO_4$. This crude product was purified by column chromatography ($SiO_2$, 1:1 EtOAc/hexanes): isolated yield 82 mg, 74.5%; $R_f$ 0.70 (1% MeOH/EtOAc); RP-HPLC $t_R$ = 38.6 and 39.7 min (mixture of diastereomers); $^1$H NMR (300 MHz, $CDCl_3$) δ 8.20 (s, br, 1 H, NH), 7.64 (s, 1 H), 7.40–7.22 (m, 10 H), 6.84 (d, $J$ = 8.8, 4 H), 6.40 (t, $J$ = 6.5 Hz, 1 H), 6.27 (t, $J$ = 6.5 Hz, 1 H), 4.67 (m, 1 H), 4.53 (m, 1 H), 4.10 (m, 2 H), 3.93 (m, 1 H), 3.87 (m, 1 H), 3.80 (s, 6 H), 3.72 (m, 1 H), 3.61 (m, 1 H), 3.39 (ABq, $J$ = 4 Hz, 10 Hz, $\Delta\nu$ = 42 Hz, 2 H), 2.64 (m, 2 H), 2.53–2.05 (m, 4 H), 1.86 (s, 3 H), 1.51 (s, 3 H), 1.26 (m, 2 H), 1.17 (m, 12 H), 1.01 (m, 14 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 163.6, 163.4, 158.7, 150.1, 144.2, 135.5, 135.2, 130.0, 128.0, 127.2, 117.6, 113.3, 111.2, 111.0, 110.9, 87.0, 86.2, 85.8, 85.7, 84.9, 84.7, 84.6, 73.4, 73.2, 63.4, 62.9, 62.7, 58.2, 58.2, 58.0, 57.9, 55.29, 43.4, 43.2, 41.5, 39.7, 39.5, 24.5, 24.4, 23.0, 20.4, 20.3, 17.2, 17.0, 12.4, 11.9, 11.7, 11.6. $^{31}$P NMR ($CDCl_3$) δ 149.16; MS (FAB): $m/z$ 1098.8 (M + H)$^+$.

**5′-*O*-(Dimethoxytrityl)-3′-*O*-[(3′-*O*-(5′-*O*-thymidyldiisopropylsilyl)(5′-*O*-thymidyl)diisopropylsilyl]thymidine 3′-(2-Cyanoethyl *N,N*-diisopropylphosphoramidite (9).** Trimer **7** (0.44 mmol, 550 mg) was dissolved in $CH_2Cl_2$ (2 mL) and added dropwise via syringe to a stirred solution of 4-(dimethylamino)-pyridine (cat., 20 mg), diisopropylethylamine (distilled from $CaH_2$; 1.69 mmol, 370 μL), and 2-cyanoethyl *N,N*-diisopropylphosphoramidochloridite (0.64 mmol, 120 μL) in $CH_2Cl_2$ (2.0 mL) under $N_2$ flow at 0 °C. The reaction mixture was brought to room temperature, stirred for 1 h, poured into EtOAc (prewashed with 25 mL brine; 50 mL), washed with brine (2 × 20 mL), and dried over $Na_2SO_4$. The crude product was purified by column chromatography (10 g of $SiO_2$, EtOAc): isolated yield 320 mg, 64%; $R_f$ 0.76 (EtOAc); RP-HPLC $t_R$ = 47.7 and 48.7 min (mixture of diastereomers); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.63 (s, 1 H), 7.41–7.22 (m, 11 H), 6.83 (d, $J$ = 7.8 Hz, 4 H), 6.40–6.24 (m, 3 H), 4.67–4.54 (m, 3 H), 4.13–3.85 (m, 7 H), 3.75 (s, 6 H), 3.55 (m, 2 H), 3.48–3.28 (m, 2 H), 2.74 (t, $J$ = 6 Hz, 2H) 2.45–2.03 (m, 6H), 1.88 (s, 3 H), 1.83 (s, 3 H), 1.50 (s, 3 H), 1.28–1.13 (m, 14 H), 1.00 (m, 28 H); MS (FAB): $m/z$ 1453 (M − H)$^-$.

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**Supplementary Material Available:** NMR and mass spectral data for all compounds, HPLC data for selected compounds including silyl-linked decathymidylate **14**, and mass spectrum of mixed backbone oligomer **5** (48 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(8) The sample was analyzed by negative ion FAB mass spectrometry with an instrument resolution of 1500. An exact mass analysis was not conducted due to poor sensitivity observed at higher resolution.

# First Metalation of Aryl Iodides: Directed Ortho-Lithiation of Iodopyridines, Halogen-Dance, and Application to Synthesis

P. Rocca, C. Cochennec, F. Marsais, L. Thomas-dit-Dumont, M. Mallet, A. Godard, and G. Quéguiner*

*Laboratoire de Chimie Organique Hétérocyclique de l'Institut de Recherche en Chimie Organique Fine, URA CNRS 1429, Institut National des Sciences Appliquées de Rouen, BP 08, 76131 Mont-Saint-Aignan Cédex, France*

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Metalation of iodopyridines was successfully achieved by LDA at low temperature. In many cases, lithiation is ortho directed by the iodo group which subsequently ortho-migrates very fast to give stabilized iodolithiopyridines. This procedure was applied to 2-fluoro- and 2-chloro-3-iodopyridines, 3-fluoro-4-iodopyridine, and 2-chloro-3-fluoro-4-iodopyridine. The resulting lithio intermediates were obtained in high yields before being reacted with electrophiles leading to various polysubstituted pyridines. Some of these iodopyridines were used as key molecules for the synthesis of fused polyaromatic alkaloids. Thus, perlolidine, δ-carbolines, and 2,10-diazaphenanthrenes were readily prepared in few steps taking advantage of the iodo reactivity for heteroring cross-coupling.

## Introduction

Metalation of aryl fluorides and chlorides has been previously reported in both aromatic as well as heteroaromatic systems. The scope of applications of this methodology is currently well defined.[1,2] Compared to chloro and fluoro aromatics, few metalations have been done with the other halogens, but some interesting results have been obtained in the field of the lithiation of aryl bromides. Thus, metalation of bromoaromatic compounds (benzene) has been carried out, and the "halogen-dance" phenomenon has been discovered.[3] Similarly, the inductive effect of bromine provides an excellent regioselectivity in the metalation of hetaryl bromides[1,2] like bromothiophene or bromoisothiazole derivatives.

In the early 1980s, 2-bromopyridine[4] and 3-bromopyridine[5,6] were regio- and chemoselectively ortho-lithiated with LDA at low temperature. Thus, various 3- and 4-substituted derivatives were respectively prepared. As early as 1972, we established that a 2-fold excess of 3-bromopyridines treated with *n*-butyllithium at low temperature resulted in the metalation of the pyridine ring together with halogen migration to the 4-position.[7] Further studies showed that treatment of 2-halo-3-bromopyridines with *n*-butyllithium or LDA followed by reaction of electrophiles yielded mixtures of 4-substituted 3-bromo-2-halopyridines and 3-substituted 4-bromo-2-halopyridines.[8] A mechanism was proposed to explain the bromo migration, and this reaction was operated for synthetic purposes.[5,8-11]

To our knowledge, no iodo-directed metalation of aromatics has been described whatever the series except for the α-lithiation of iodothiophenes[12] or iodoisothiazoles.[13] This subject remains, however, a promising challenge for two main reasons. First, aryl iodides are easily synthesized either by classical routes (halogenation, diazotization, or halogen-exchange) or by a more selective pathway such as organometallic chemistry. Secondly, iodine displays a high reactivity in such useful reactions as halogen–lithium exchange, $S_{RN1}$, Heck reaction, cross-coupling, or carbonylation. Looking for a simple access to polysubstituted iodopyridines for the synthesis of complex polyaromatics, we were thus interested in the metalation of iodopyridines. We wish to report in the present paper on the directed ortho-lithiation of iodopyridines, and some applications of this reaction will be given.

## Results

**(I) Metalation of 2-Halo-3-iodopyridines (Chloro and Fluoro).** 2-Fluoro- and 2-chloro-3-iodopyridines (**1** and **2**) were readily prepared from the corresponding 2-halopyridines by a metalation–iodination sequence.[14] Treatment of these iodopyridines **1** and **2** with LDA at −75 °C followed by quenching with electrophiles led to the 3-substituted 2-halo-4-iodopyridines **7a-g** and **8a-g** in good to high yields (Scheme I, Table I). Identification of these derivatives and their 4-iodo structure were inferred from the $^1H$ and $^{13}C$ NMR spectra: a strong shielding[15] of the carbon bearing the iodo atom could be observed (Table II).

This overall strategy could be easily extended to 2-fluoro-5-methylpyridine (**5**). Thus, 3-substituted 2-fluoro-4-iodo-5-methylpyridines **9b-d** were prepared in two steps in very good overall yields (Scheme II and Table III).

**(II) Metalation of 3-Fluoro-4-iodopyridines. (a) 2-Chloro-3-fluoro-4-iodopyridine.** 2-Chloro-3-fluoro-

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**Scheme I**

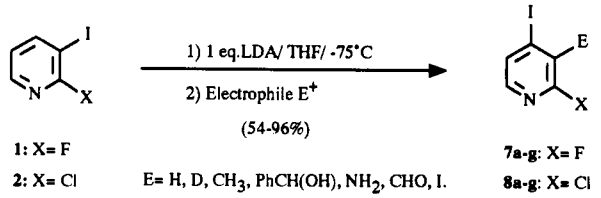
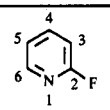
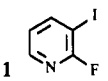
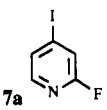
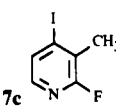



**Table I**

| electrophile | E | yield (%) X = F | yield (%) X = Cl |
|---|---|---|---|
| $H_2O$ | H | 96 (**7a**) | 73 (**8a**) |
| $D_2O$ | D | 96 (**7b**) | 75 (**8b**) |
| $CH_3I$ | $CH_3$ | 93 (**7c**) | 69 (**8c**) |
| PhCHO | PhCH(OH) | 61 (**7d**) | 64 (**8d**) |
| $TsN_3$[a] | $NH_2$ | 81 (**7e**) | 57 (**8e**) |
| HCOOEt | CHO | 75 (**7f**) | 64 (**8f**) |
| $I_2$ | I | 54 (**7g**) | 71 (**8g**) |

[a] The intermediary crude azide was reduced by treatment with $H_2S$ in MeOH.[16]

**Table II**

| | $^{13}C$ NMR ($\delta$ ppm) | $C_3$ | $C_4$ |
|---|---|---|---|
|  | expl | 109.4 | 140.8 |
|  1 | calcd[a] | 81.0 | 149.9 |
| | expl | 75.4 | 150.0 |
|  7a | calcd[a] | 117.5 | 112.4 |
| | expl | 119.1 | 107.8 |
|  7c | calcd[a] | 126.5 | 112.6 |
| | expl | 124 | 114 |

[a] Calculated values were obtained from 2-fluoropyridine by using the method described by Pretsch et al.[15]

**Scheme II**

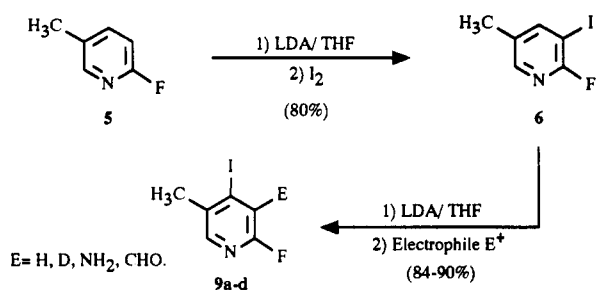



**Table III**

| electrophile | E | yield (%) |
|---|---|---|
| $H_2O$ | H (**9a**) | 88 |
| $D_2O$ | D (**9b**) | 90 |
| $TsN_3$[a] | $NH_2$ (**9c**) | 85 |
| HCOOEt | CHO (**9d**) | 84 |

[a] Intermediary crude azide was reduced by treatment with $H_2S$ in MeOH.[16]

4-iodopyridine[25] (**3**) was subjected to lithiation by LDA (THF/−75 °C) before reaction with various electrophiles. 4-Substituted 2-chloro-3-fluoro-5-iodopyridines **10a-e** were isolated and characterized (Scheme III, Table IV). The 2,3,4,5-tetrasubstitution and the 5-iodo structure of compounds **10a-e** were deduced from $^1H$ and $^{13}C$ NMR analyses as previously shown.

**Scheme III**

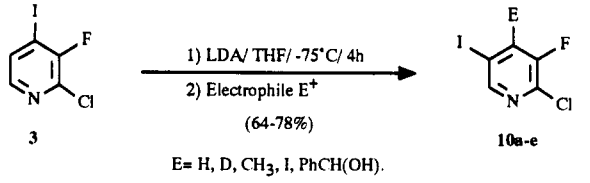
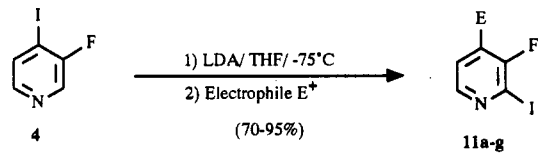



**Table IV**

| electrophile | E | yield (%) |
|---|---|---|
| $H_2O$ | H (**10a**) | 78 |
| $D_2O$ | D (**10b**) | 78 |
| $CH_3I$ | $CH_3$ (**10c**) | 70 |
| $I_2$ | I (**10d**) | 64 |
| PhCHO | PhCH(OH) (**10e**) | 77 |

**Scheme IV**




E= H, D, $CH_3$, I, PhCH(OH), 3,4-$(OMe)_2$PhCH(OH), COOH.

**Table V**

| electrophile | E (product) | yield (%) |
|---|---|---|
| $H_2O$ | H (**11a**) | 95 |
| $D_2O$ | D (**11b**) | >99 |
| $CH_3I$ | $CH_3$ (**11c**) | 70 |
| $I_2$ | I (**11d**) | 73 |
| PhCHO | PhCH(OH) (**11e**) | 75 |
| 3,4-$(OMe)_2$PhCHO | 3,4-$(OMe)_2$PhCH(OH) (**11f**) | 80 |
| $CO_2$ | COOH (**11g**) | 72 |

**(b) 3-Fluoro-4-iodopyridine.** As expected,[2] metalation of 3-fluoro-4-iodopyridine[14] (**4**) with LDA (THF/−75 °C) is not directed by the iodo substituent but by the fluoro one. Nevertheless, a very fast iodo migration from the 4-position to the 2-position is also observed: this confirms the high migration ability of the iodo moiety as previously described. Thus, quenching of the resulting lithio intermediary with electrophiles afforded 4-substituted 3-fluoro-2-iodopyridines **11a-g** in good yields (Scheme IV, Table V). The 2,3,4-substitution and the 2-iodo structure of compounds **11a-g** were deduced from $^1H$ and $^{13}C$ NMR analyses as previously shown.

**(III) Application to Synthesis.** Some of the previously prepared iodopyridines were used as key intermediates in the synthesis of polyaromatic alkaloids.

**(a) Synthesis of Perlolidine.** Reaction between 2-fluoro-4-iodo-3-pyridinecarboxaldehyde (**7f**) and (2-(pivaloylamino)phenyl)boronic acid[14] (**12**) using $Pd(PPh_3)_4$ as catalyst under the Suzuki conditions[18] resulted in heteroring cross-coupling and subsequent cyclization to the diazaphenanthrene **13**. Hot acid treatment of the fluoro compound **13** induces hydrolysis to perlolidine[17]

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