Supporting Information for

Synthesis of dinucleoside acylphosphonites by phosphonodiamidite chemistry and investigation of phosphorus epimerization

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Experimental

General methods. All reactions and sample analysis preparations were carried out in an inert-atmosphere glovebox with recirculating nitrogen, using oven-dried glassware. NMR spectra were recorded on 400 and 500 MHz Bruker spectrometers referenced to CDCl$_3$ solvent peaks [1,2] and for $^{31}$P NMR to external PPh$_3$ at -5.25 ppm. Peak assignments were made where possible using 2D COSY and HETCOR or HSQC spectra, with $^{13}$C-$^1$H correlations shown in the spectral data where needed, as well as by comparison to the thymidine starting materials. Reaction solvents were distilled under nitrogen and then dried over activated 3 Å molecular sieves [3]. Column chromatography was carried out in the glovebox on 230-400 mesh silica gel that had been dried several hours at 250 °C under vacuum. For the peak assignments in the $^1$H NMR spectra of 12 and 13, the 3'-phosphorylated thymidine and the 5'-phosphorylated thymidine are labeled T1 and T2, respectively.

$(iPr_2N)_2PC(O)CH_3$ (7). The starting material $(iPr_2N)_2PH$ (4) was prepared via a modification of the literature procedure [4]. In the glovebox, powdered LiAlH$_4$ (0.242 g, 6.37 mmol, 1.17 equiv) was added in one portion to 1.451 g (5.44 mmol) of $(iPr_2N)_2PCl$ [5] in 10 mL of THF, and the suspension was stirred vigorously for two hours; while it was stoppered, the stopper was removed periodically to release pressure. The grey suspension was filtered through a layer of dry Celite (*CAUTION: the grey solid smokes and occasionally briefly ignites when removed from the glovebox*), and the solvent was then removed from the yellow solution using a vacuum pump. The resultant white solid suspended in a yellow oil was extracted with $7 \times \sim 8$ mL of hexanes, filtering each 8 mL extract through dried Celite. Solvent removal using a vacuum pump gave 1.16 g (5.00
mmol, 92% yield) of 4 as a white solid suspended in a clear oil, which on the basis of $^1$H and $^{31}$P NMR was ~93% pure. This material could be stored cold in the glovebox at −35 °C but was typically used immediately.

A sample of 4 (0.311 g, 1.34 mmol) was suspended in 7 mL CH$_2$Cl$_2$, the flask was fitted with a dropping funnel containing a solution of 0.119 g of CH$_3$C(O)Cl (1.52 mmol, 1.13 equiv) in 3 mL of CH$_2$Cl$_2$, and the dropping funnel was then attached to a solenoid-controlled vacuum valve. The acetyl chloride solution was added dropwise over ~1 min, while periodically opening the reaction to vacuum in order to keep the reaction under partial vacuum. Gentle bubbling of the solution occurred, presumably due to release of HCl gas, giving a yellow solution. Solvent removal gave a yellow solid that was then extracted with 3 × 5 mL of hexanes (the last extract was clear), filtering each extract through Celite. Final solvent removal gave 0.234 g (0.852 mmol, 64% yield) of 7 as a yellow oil at room temperature; storage at −35 °C gave a crystalline mass but it quickly melted at room temperature. The material so produced was used as is with no further purification; on the basis of $^{31}$P NMR it was > 95% pure. $^1$H NMR (400 MHz, CDCl$_3$) δ 3.29 (m, (CH$_3$)$_2$CH, 4H), 2.27 (d, $^3$J$_{PH}$ = 8.8 Hz, CH$_3$C(O) 3H), 1.23 (d, J = 6.8 Hz, 12H), 1.18 (d, J = 6.4 Hz, 12H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 227.9 (d, $^1$J$_{PC}$ = 22.4 Hz), 49.8 (br d, (CH$_3$)$_2$CH, $^2$J$_{PC}$ = 9.1 Hz), 30.7 (d, CH$_3$C(O), $^2$J$_{PC}$ = 49.7 Hz), 24.4 (d, J = 6.2 Hz), 24.3 (d, J = 6.4 Hz); $^{31}$P NMR (162 MHz, CDCl$_3$) δ 63.5; IR (CDCl$_3$) 2969, 1654 cm$^{-1}$. HRMS (ESI): Calcd for C$_{14}$H$_{32}$N$_2$OP [M+H]$^+$ 275.2247, found 275.2247.

(iPr$_2$N)$_2$PC(=CH$_2$)OC(O)CH$_3$ (8). Reaction of 4 (0.876 g, 3.77 mmol), CH$_3$C(O)Cl (0.319 g, 4.06 mmol, 1.08 equiv), and Et$_3$N (0.392 g, 3.87 mmol, 1.03 equiv) in 13 mL of CH$_2$Cl$_2$ gave a mixture of 43% 8, 32% 7, and 25% unreacted 4, on the basis of
integration of the $^1$H and $^{31}$P NMR spectra. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.48 (t, $J_{HH} = J_{PH} = 1.1$ Hz, 1H), 5.29 (dd, $J_{HH} = 1.1$ Hz, $J_{PH} = 7.3$ Hz, 1H), 2.09 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 168.8 (s), 161.5 (d, $J_{PC} = 8.8$ Hz), 111.4 (d, $J_{PC} = 16.8$ Hz), 48.0 (d, $J_{PC} = 12.0$ Hz, CH(CH$_3$)$_2$); $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ 49.7. The iPr peaks could not be identified except as noted, and it appeared that the presumed OC(O)CH$_3$ carbon also overlapped the iPr region on the basis of the DEPT NMR.

(iPr$_2$N)$_2$PC(O)C$_6$H$_5$ (9). A sample of 4 (0.852 g, 3.67 mmol) prepared as described for the synthesis of 7 was suspended in 10 mL CH$_2$Cl$_2$ and Et$_3$N (0.402 g, 3.97 mmol, 1.08 equiv). The flask was fitted with a dropping funnel containing a solution of 0.563 g of C$_6$H$_5$C(O)Cl (4.01 mmol, 1.09 equiv) in 4 mL of CH$_2$Cl$_2$, which was then attached to a solenoid-controlled vacuum valve. The benzoyl chloride solution was added dropwise over ~1 min, while periodically opening the reaction to vacuum in order to keep the reaction under partial vacuum. Gentle bubbling of the solution occurred, presumably due to release of some HCl gas, giving an orange solution. Solvent removal gave an orange solid that was then extracted with $4 \times 5$ mL of hexanes (the last extract was clear), filtering each extract through Celite. Final solvent removal gave 1.10 g (3.27 mmol, 89% yield) of 9 as a yellow-orange solid. The material so produced was used as is with no further purification; on the basis of $^{31}$P NMR it was > 99.6% pure. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.00 (m, $H_{ortho}$, 2H), 7.46 (m, $H_{para}$, 1H), 7.38 (t, $J = 7.8$ Hz, $H_{meta}$, 2H), 3.32 (m, 4H), 1.21 (d, $J = 6.8$ Hz, 12H), 1.08 (d, $J = 6.8$ Hz, 12H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 220.9 (d, $^1J_{PC} = 23.7$ Hz), 140.8 (d, $^2J_{PC} = 39.7$ Hz, C$_{ipso}$), 132.3 (d, $^5J_{PC} = 1.5$ Hz, C$_{para}$), 128.2 (C$_{meta}$), 127.9 (d, $^3J_{PC} = 11.8$ Hz, C$_{ortho}$), 49.5 (br d, $^2J_{PC} = 8.1$ Hz), 24.3 (d, $^3J_{PC} = 5.7$ Hz), 23.9 (d, $^3J_{PC} = 6.1$ Hz); $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$
59.3; IR (CDCl$_3$) 2969, 1631 cm$^{-1}$HRMS (ESI): Calcd for C$_{19}$H$_{34}$N$_2$OP [M+H]$^+$ 337.2403, found 337.2402.

**3′-(5′-DMTr-OT)P(N(iPr)$_2$)C(O)CH$_3$ (10).** Solid N-methylimidazolium triflate (NMI·Tf, 0.399 g, 1.72 mmol, 0.74 equiv) [6] was added to a suspension of 7 (0.639 g, 2.33 mmol, ) and 5′-O-(4,4′-dimethoxytrityl)thymidine (5′-DMTr-OT) [7] (1.20 g, 2.21 mmol, 0.95 equiv) in 10 mL acetonitrile. After stirring for 1.25 h, only a small amount of solid remained and the solution was filtered through Celite. Solvent removal using a vacuum pump gave a foamy yellow solid that was taken up in 10 mL benzene, 20 mL ether was added to precipitate salts, the mixture was filtered, and the solvent was again removed using a vacuum pump to give a yellow solid. This was stirred with 10 mL hexane to remove some of the starting acyl, giving 1.56 g of product as a yellow powder (99% crude yield) that was 12% starting acyl and 85% product by $^{31}$P NMR but also contained impurities of DMTr-OT and iPr$_2$NH$_2^+$ Tf$^-$. Significant purification was achieved by taking up 1.32 g of this material in 8 mL benzene, filtering, and then precipitating out the product by addition of 24 mL of hexane. After cooling for 1 hr at −35 °C, the solvent was poured off and the residue pumped under vacuum to give a sticky orange solid; final solvent removal was achieved by addition of a small amount of ether and pulling a vacuum again to give a yellow foam (1.26 g, 95% recovery) that was 89% pure by $^{31}$P NMR.

Chromatography of 0.65 g of this material on 40 mL of silica gel on a 60 mL fritted funnel, eluting with 9:1 CH$_2$Cl$_2$:THF, gave a yellow band collected in three fractions (60 mL 9:1 CH$_2$Cl$_2$:THF, 20 mL 1:1 CH$_2$Cl$_2$:THF and 40 mL THF); all three fractions exhibited a spot with $R_f = 0.5$-0.55 on TLC (9:1 CH$_2$Cl$_2$:THF), with material at
the origin eluting at the end of the last fraction. Analysis by $^{31}$P NMR showed that the first two fractions (97.8 mg) were ~95% pure and ~86% the “fast” isomer at 117.6 ppm, while the third fraction (429 mg; 81% total recovery) was ~81% pure and ~33:67 “fast” : “slow” isomers at 117.6 and 116.8 ppm. The two samples were separately re-chromatographed.

The “fast” isomer was chromatographed on 10 mL of silica eluting only with 9:1 CH$_2$Cl$_2$ : THF, and gave in the first two UV-active fractions 57.1 mg of material that was ~95% pure as a 93:7 mixture of “fast”: “slow” isomers. $^1$H NMR (500 MHz, CDCl$_3$) δ 8.51 (br s, NH, 1H), 7.66 (~q, $^4$J ≈ 1.2 Hz, H$_6$, 1H), 7.40 (m, Ph, 2H), 7.31 – 7.22 (m, Ph and 4H of MeOC$_6$H$_4$ AA'BB', 3H), 6.83 (m, 4H of MeOC$_6$H$_4$ AA'BB'), 6.40 (dd, $^3$J = 7.7, 5.9 Hz, H$_1$'), 4.65 (ddd, $^3$J ≈ 3.2 Hz, H$_3'$, 1H), 4.32 (~ddd, $^3$J ≈ 1.3 Hz, H$_4'$, 1H), 3.79 (s, MeOC$_6$H$_4$, 6H), 3.52 (dd, $^2$J = 10.7 Hz, $^3$J = 2.8 Hz, H$_5'$, 1H), 3.37 (dd, $^2$J = 10.7 Hz, $^3$J = 2.6 Hz, H$_5'$, 1H), 3.28 (m, CH(CH$_3$)$_2$, 2H), 2.51 (m, H$_2'$, 1H), 2.33 (m, H$_2'$, 1H), 2.24 (d, $^3$J$_{PH}$ = 5.4 Hz, CH$_3$C(O)P, 3H), 1.44 (d, $^4$J = 1.0 Hz, CH$_3$C$_1$, 3H), 1.19 (br d, $^3$J = 7.8 Hz, CH(CH$_3$)$_2$, 3H), 1.18 (br d, $^3$J = 7.3 Hz, CH(CH$_3$)$_2$, 3H); $^{13}$C NMR (125.8 MHz, CDCl$_3$) δ 226.9 (d, $^1$J$_{PC}$ = 25.3 Hz), 163.8, 158.9, 150.3, 144.4, 135.7 (CH$_1$), 135.5 (4°), 135.4 (4°), 130.27, 130.26 (Ar CH ~7.3; MeOC$_6$H$_4$ CH ~6.8), 128.3 (Ph CH ~7.4), 128.1, (Ar CH, ~7.3), 127.3 (Ar CH, ~7.25), 113.40, 113.38 (Ar CH, ~7.3; MeOC$_6$H$_4$ CH, ~6.8), 111.3 (4°), 87.1 (4°), 85.7 (d, $^3$J$_{PC4'}$ = 5.4 Hz, C$_4'$), 84.9 (CH$_1''$, 6.40), 77.6 (d, $^2$J$_{PC3''}$ = 19.9 Hz, CH$_3''$), 63.3 (CH$_5''$), 55.4 (MeO, 3.79), 46 (iPr CH, from HSQC cross peak with $^1$H at δ 3.28), 40.5 (d, $^3$J$_{PC2''}$ = 3.9 Hz, CH$_2''$), 30.8 (d, $^2$J$_{PC}$ = 36.4 Hz, CH$_3$C(O)P), ~25 (broad, iPr Me at 1.19 and 1.18), 15.4 (iPr Me at 1.19 and 1.18), 11.9 (CH$_3$C$_1$) ; $^{31}$P NMR (162
MHz, CDCl$_3$ $\delta$ 117.6, 116.8 (93.2:6.8); IR (CDCl$_3$) 3396, 2969, 1688 cm$^{-1}$. HRMS (ESI): Calcd for C$_{39}$H$_{49}$N$_3$O$_8$P [M+H]$^+$ 718.3252, found 718.3252.

The 32:68 "fast" :"slow" mixture was chromatographed on 30 mL of silica eluting only with 9:1 CH$_2$Cl$_2$ :THF, giving three fractions as white foams consisting of isomeric mixtures of the "fast" :"slow" isomers as follows: 46:54 (~96% pure, 81.5 mg), 25:75 (~91% pure, 40.0 mg), and 18:82 (~92% pure, 55.7 mg). Detailed spectra were obtained for the 46:54 mixture (only peaks for the "slow" isomer are given except as noted): $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.82, 8.77 (fast, slow, br s, NH), 7.60 (~q, $^4$J $\approx$ 1.3 Hz, H$_1$), 7.39 (m, 2H, Ph), 7.30 – 7.26 (m, 3H, Ph and 4H of MeOC$_6$H$_4$ AA‘BB’), 6.83 (m, 4H of MeOC$_6$H$_4$ AA‘BB’), 6.48 (dd, $^3$J $= 8.2$, 5.7 Hz, H$_{1'}$), 4.64 (m, H$_3$), 4.19 (~q, $^3$J $\approx$ 2.6 Hz, H$_4$), 3.78 (s, 6H, MeOC$_6$H$_4$), 3.47 (dd, $^2$J $= 10.6$ Hz, $^3$J $= 2.7$ Hz, H$_{5'}$), 3.32 (dd, $^2$J $= 10.6$ Hz, $^3$J $= 2.7$ Hz, H$_{5'}$), 2.65 (m, H$_2'$, 1H), 2.33 (m, H$_2'$, 1H), 2.34 (d, $^3$J$_{PH}$ = 5.4 Hz, CH$_3$C(O)P), 1.44 (br s (overlaps fast isomer), CH$_3$C$_1$), 1.40 (d, $^3$J $= 6.7$ Hz, part of CH(CH$_3$)$_2$), 1.17 (br m, CH(CH$_3$)$_2$), 1.04 (br d, $^3$J $= 5.3$ Hz, part of CH(CH$_3$)$_2$); $^{13}$C NMR (125.8 MHz, CDCl$_3$) $\delta$ 226.8 (d, $^1$J$_{PC}$ = 25.3 Hz), 163.9, 158.9, 150.4, 144.3, 135.7 (CH$_1$), 135.5 (4°), 135.4 (4°), 130.25, 130.21 (Ar CH, ~7.3; MeOC$_6$H$_4$ CH ~6.8), 128.3 (Ph CH ~7.4), 128.1, (Ar CH, ~7.3), 127.3 (Ar CH, ~7.25), 113.39, 113.37 (Ar CH, ~7.3; MeOC$_6$H$_4$ CH, ~6.8), 111.4 (4°), 87.1 (4°), 85.8 (d, $^3$J$_{PC4'}$ = 4.7 Hz), 84.9 (CH$_1'$, 6.48), 78.0 (d, $^2$J$_{PC3'}$ = 19.0 Hz), 63.5 (C$_5'$), 55.3 (MeO, 3.79), 46.7 (iPr CH, from HSQC cross peak with $^1$H at $\delta$ 3.3), 40.1 (d, $^3$J$_{PC2'}$ = 4.7 Hz), 30.83 (d, $^2$J$_{PC} = 36.8$ Hz, CH$_3$C(O)P), ~25 (broad, iPr Me at 1.17, 1.04), 19.3 (iPr Me at 1.40), 11.9 (CH$_3$C$_1$); $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ 117.6, 116.8 (46:54); IR (CDCl$_3$) 3396,
2969, 1688 cm\(^{-1}\). HRMS (ESI): Calcd for C\(_{39}\)H\(_{49}\)N\(_3\)O\(_8\)P [M+H]\(^+\) 718.3252, found 718.3254.

\(3'-(5'\text{-DMTr-OT})\)P(N(iPr)\(_2\))C(O)C\(_6\)H\(_5\) (11). An orange suspension of 9 (0.502 g, 1.49 mmol, 1.07 equiv), DMT-OT (0.758 g, 1.39 mmol), and NMI-Tf (0.326 g, 1.40 mmol, 1.01 equiv) in 10 mL acetonitrile was stirred for 2 h to give a clear orange solution. Solvent removal using a vacuum pump gave an orange-yellow foam. Chromatography on 30 mL of silica gel on a 60 mL fritted funnel, eluting with 9:1 CH\(_2\)Cl\(_2\):THF gave a yellow band in 60 mL of solvent, discarding a pale yellow tail; solvent removal gave 0.757 g (70% crude yield) of yellow foam consisting of product and starting material. Final purification was achieved by taking up the material in 4 mL ether, and precipitating out product by addition of 10 mL of hexane with swirling, cooling briefly to −35 °C, and filtration to give the product as a yellow solid. Addition of CH\(_2\)Cl\(_2\) followed by solvent removal was required to remove the hexane, giving 0.632 g of yellow foam (58% yield). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.70, 8.62 (minor, major, br s, NH, 1H), 7.91 (m, 2H of Ph), 7.69, 7.62 (minor, major, \(~q\), \(^4\)J \(\approx\) 1.6, 1.3 Hz, H\(_1\), 1H), 7.62 – 7.2 (m, 8H of Ph and 4H of MeOC\(_6\)H\(_4\) AA′BB′), 6.80 (m, 4H of MeOC\(_6\)H\(_4\) AA′BB′), 6.51, 6.40 (major, minor, dd, \(^3\)J \(\approx\) 7.8, 6.2, and 7.2, 6.2 Hz, H\(_4\)' 1H), 4.70 (m, H\(_3\)', 1H), 4.43, 4.26 (minor, major, \(~q\), \(^3\)J \(\approx\) 3.0, 2.7 Hz, H\(_4\)', 1H), 3.781, 3.779 and 3.73, 3.71 (major, minor, each two diastereotopic s, MeOC\(_6\)H\(_4\), 6H), 3.52, 3.43 (m, (H\(_5\)′)\(_2\), 2H), 3.27 (m, CH(CH\(_3\))\(_2\), 2H), 2.73 (major, ddd, \(^2\)J = 13.8 Hz, \(^3\)J = 6.1, 2.7 Hz, H\(_2\)', \(~0.5\) H), 2.58 (minor, ddd, \(^2\)J = 13.6 Hz, \(^3\)J = 5.9, 3.2 Hz, H\(_2\)', \(~0.5\) H), 2.34 (m, H\(_2\)', 1H), 1.45 (br s, CH\(_3\)C\(_1\), 3H), 1.22, 1.09, 0.7 (br, CH(CH\(_3\))\(_2\), 6H); \(^{13}\)C NMR (125.8 MHz, CDCl\(_3\)) \(\delta\) 217.2, 217.1 (major, minor, d, \(^1\)J\(_{PC}\) = 30.6, 29.9 Hz), 163.94, 163.90, 163.86, 163.84, 163.82,
158.83, 158.81, 158.77, 158.73, 150.34, 150.30, 144.58, 144.46, 139.08, 139.02, 138.83, 158.81, 158.77, 158.73, 150.34, 150.30, 144.58, 144.46, 139.08, 139.02, 138.83, 138.75 (all 4°), 135.92 (CH\textsubscript{1} (major) 7.62), 135.82 (CH\textsubscript{1} (minor) 7.69), 135.55, 135.52, 135.51 (4°), 133.16, 133.08 (Ar CH ~7.5), 128.5, 128.4, 128.3, 128.09, 128.06, 127.89, 127.83, 127.24, 127.17 (Ar CH 7.9-7.2), 113.36, 113.34, 113.32 (MeOC\textsubscript{6}H\textsubscript{4}CH ~6.8), 111.22, 111.14 (4°), 86.99, 86.98 (4°), 85.8, 85.6 (d, \textit{J}_{PC4} = 5.5, 4.3 Hz), 85.0, 84.8 (CH\textsubscript{1}', major, minor), 77.32, 77.16, 76.96 (visible in DEPT\textsubscript{145}, C\textsubscript{3}H 4.70), 63.5, 63.1, 55.4, 55.30, 55.28 (MeO, 3.78-3.71), 46.6, 40.2, ~24.5 (broad, iPr Me), 11.9 (CH\textsubscript{3}C\textsubscript{1}); \textsuperscript{31}P NMR (162 MHz, CDCl\textsubscript{3} \ \delta 119.8, 116.7 (42.5:57.5); IR (CDCl\textsubscript{3}) 3396, 2970, 1688 cm\textsuperscript{-1}. HRMS (ESI): Calcd for C\textsubscript{44}H\textsubscript{51}N\textsubscript{3}O\textsubscript{8}P [M+H]\textsuperscript{+} 780.34083, found 780.33935.

\textbf{3'-\textit{(5'-DMTr-OT)-5'-\textit{(3'-\textit{t-BuMe\textsubscript{2}Si-OT})PC(O)CH\textsubscript{3}} (12)}. To a stirred solution of 69.4 mg of 10 (0.097 mmol, 1.46 equiv) and 23.6 mg of 3'-\textit{O-\textit{(\textit{t}-butyldimethylsilyl)thymidine [8,9] (3'-TBS-OT, 0.066 mmol, 1 equiv) in 1 mL of acetonitrile was added 0.95 g (1.2 mL) of 0.20 M/0.10 M pyridinium trifluoroacetate/N-methylimidazole (PTFA/NMI) in acetonitrile (0.24/0.12 mmol, 2.5/1.2 equiv relative to 10), in one portion. The clear solution was stirred for 25 min, the solution was concentrated to about half its volume using a vacuum pump, and the solution was applied to a column of 6 mL of silica gel packed in THF. A UV-active band was eluted in about 10 mL of THF, the solvent was removed using a vacuum pump, and triturated with ether to give 105.4 mg of pale yellow foam. \textsuperscript{31}P NMR indicated complete reaction of 10 and the presence of ~12% of unidentified material in the dinucleoside acyl region, and \textsuperscript{1}H NMR indicated ~14% of unreacted 3'-TBS-OT. The mixture was applied in 2 mL of CH\textsubscript{2}Cl\textsubscript{2} to a 15 mL column of silica packed in 5% THF in CH\textsubscript{2}Cl\textsubscript{2}. After elution with 20
mL of 5% THF in CH₂Cl₂ followed by 10 mL of 10% THF in CH₂Cl₂, unidentified weakly UV-active material (6.6 mg total) eluted in 5 mL of 10% THF in CH₂Cl₂ followed by 20 mL of 20% THF in CH₂Cl₂. The remaining UV-active material eluted in 30 mL of 20-30% THF in CH₂Cl₂ followed by 20 mL of THF, giving 54.5 mg of 12 (~85% yield) that was ~84% pure by ³¹P NMR and contained ~14 mol% unreacted 3'-TBS-OT.

Rechromatography of this material combined with similar fractions from prior syntheses (99 mg total) on a 15 mL column of silica packed in 10% THF in ethyl acetate gave after a 17 mL forerun an 8 mL UV-active fraction with virtually all the 12 recovered (55 mg), containing 6% of an unidentified impurity (³¹P NMR: 142.9 ppm) and ~36 mol% of 3'-TBS-OT. ¹H NMR (500 MHz, CDCl₃)  ⁹ 9.57-9.35 (5 s, NH, 2H), 7.59, 7.55 (q, ⁴J ≈ 1.2, 1.1 Hz, H₆, 1H), 7.37 (m, 3H), 7.26 (m, 7H), 6.83 (d, J = 7.5 Hz, 4H of MeOC₆H₄AA’BB’), 6.42, 6.39 (dd, ³J ≈ 8.5, 6.0 Hz and 7.5, 6.0 Hz, T¹H₁’, 1H), 6.29, 6.24 (t, ³J ≈ 6.5, 6.8 Hz, T²H₁’, 1H), 4.80 (~q, ³J ≈ 6.8 Hz, T¹H₃’, 0.5 H), 4.38, 4.21, 4.06 (m, ~2H), 3.93, 3.89 (m, 2H, overlapping with 3'-TBS-OT), 3.781, 3.778 (s, MeO, 6H), 3.52, 3.36 (m, T¹H₅’, 1.5H), 2.91 (m, T¹H₅’, 0.5 H), 2.6-2.2 (m, H₂’, 4H), 2.36, 2.28 (d, J = 4.0 and 4.0 Hz, CH₃C(O), 3H, with overlapping 3'-TBS-OT), 1.87, 1.83 (s, T²CH₃C-5, 3H), 1.46, 1.45 (d, ⁴J ≈ 0.5 Hz, T¹CH₃C-5, 3H), 0.88 (s, t-Bu, 9H), 0.078, 0.054, 0.040 (s, Me₂Si, 6H); ¹³C NMR (125.8 MHz, CDCl₃)  ⁹ 223.28, 223.25 (d, JPC = 38.6, 41.4 Hz), 164.11, 164.04, 158.9, 150.68, 150.63, 150.51, 144.20, 144.16 (all 4°), 137.15, 136.0, 135.24 (CH₆ 7.59, 7.55), 135.17 (CH₆ 7.59, 7.55), 130.2, 128.2, 127.4, 113.4, (MeOC₆H₄ 6.83), 111.7 (4°), 111.27 (4°), 111.20 (4°), 111.11 (4°), 87.7 (3'-TBS-OT, CH₁’), 87.33, 87.28, 87.0, 86.0, 85.7, 85.4, 85.1, 84.75, 84.69, 71.7, 71.36, 71.32, 68.4, 66.7, 63.2, 63.1, 62.1, 55.4 (MeO), 40.75, 40.59, 39.9, 30.2 (CH₃C(O)), 29.9 (CH₃C(O)), 25.83 (t-Bu),
25.79 (t-Bu), 18.06, 18.04, 18.00 (t-Bu 4° C), 12.63, 12.54 (\(T^2\)CH₃C-5), 11.99, 11.92
\((T^1\)CH₃C-5), -4.52, -4.58, -4.72, -4.74 (CH₃Si); \(^{31}\)P NMR (202 MHz, CDCl₃) \(\delta\) 148.2,
145.2 (49:51); IR (CDCl₃) 3395, 2957, 2932, 1690 cm\(^{-1}\). HRMS (ESI): Calcd for
C\(_{49}\)H\(_{62}\)N\(_4\)O\(_{13}\)PSi\(^+\) [M+H\(^+\)] 973.38148, found 973.38100.

3’-(5’-DMTr-OT)-5’-(3’-t-BuMe\(_2\)Si-OT)PC(O)C\(_6\)H\(_5\) (13). To a stirred solution of
118.0 mg of 11 (0.151 mmol, 1.34 equiv) and 40.0 mg of 3’-TBS-OT (0.112 mmol, 1
equiv) in 2 mL of acetonitrile was added 1.51 g (1.93 mL) of 0.20 M/0.10 M PTFA/NMI
in acetonitrile (0.385/0.193 mmol, 2.6/1.3 equiv relative to 11), in one portion. The
yellow solution was stirred for 30 min, the solution was concentrated to about half its
volume using a vacuum pump, and the solution was applied to a column of 7 mL of
silica gel packed in THF. The yellow band was eluted in about 10 mL of THF, the
solvent was removed using a vacuum pump, and triturated with ether to give 156.8 mg
of yellow foam. \(^{31}\)P NMR indicated the mixture contained 34 mol% of 11. The mixture
was applied in 3 mL of CH\(_2\)Cl\(_2\) to a 15 mL column of silica packed in 5% THF in CH\(_2\)Cl\(_2\).
After elution with 32 mL of 5% THF in CH\(_2\)Cl\(_2\) followed by 10 mL of 10% THF in CH\(_2\)Cl\(_2\),
unreacted 11 eluted in 45 mL of 10% THF in CH\(_2\)Cl\(_2\), towards the end of which ~6 mg of
13 was eluted. The main yellow band eluted in 30 mL of 1:1 THF:CH\(_2\)Cl\(_2\), giving 88 mg
of 13 as a yellow solid, containing 7.5% of unidentified impurities \((\(^{31}\)P NMR: 150.1,
148.0 ppm, 5.5% and 2% respectively), a trace of 11, and ~12% of 3’-TBS-OT. \(^1\)H NMR
(500 MHz, CDCl₃) \(\delta\) 9.19-9.05 (4 s, NH, 2H), 7.96-7.93 (m, Ar, 2H), 7.60-7.19 (m, Ar,
\(T^1\)H\(_6\), \(T^2\)H\(_6\), 14H), 6.84-6.81 (m, 4H of MeOC\(_6\)H\(_4\) AA’BB’), 6.44, 6.40 (dd, \(3\)\(J\) = 7.8, 6.3 Hz
and 8.5, 5.5 Hz, \(T^1\)H\(_1\), 1H), 6.30 (m, \(T^2\)H\(_1\), 1H), 4.86, 4.79 (~br dd, \(3\)\(J\) ≈ 6.9, 6.9 Hz, \(T^1\)H\(_3\),
1 H), 4.43, 4.34 (~dd and m, \(3\)\(J\) ≈ 9.0, 5.0 Hz, \(T^2\)H\(_3\), 1 H), 4.2-4.00 (m, 1H, \(T^1\)H\(_4\), 2H,
T²H₅′), 3.93 (m, 1H overlapping with 3′-TBS-OT, T²H₄′), 3.786, 3.785, 3.77 (s, MeO, 6H),
3.44-3.34 (m, T¹H₅′, 1.5 H), 3.11 (dd, ³J = 2.3 Hz, ²J = 10.8 Hz, T¹H₅′, 0.5 H), 2.50, 2.42
(br dd, ³J = 12.3, 5.3 Hz and 13.1, 5.8 Hz, T¹H₂′, 1H), 2.38-2.23 (m, T¹H₂′, 1H), 2.22-2.11
(m, T²H₂′, 2H), 1.85, 1.79 (d, ⁴J = 0.7 Hz, T²CH₃C-5, 3H), 1.45, 1.38 (d, ⁴J = 0.7 Hz,
T¹CH₃C-5, 3H), 0.86 (s, t-Bu, 9H), 0.032, 0.028, 0.014, 0.003 (s, Me₂Si, 6H); ¹³C NMR
(125.8 MHz, CDCl₃) δ 211.6, 211.1 (minor, major, d, ¹JPC = 44.3, 42.4 Hz), 163.9, 158.9,
150.6, 150.4, 144.28, 144.22, 137.4 (all 4°), 137.17, 136.9 (4°), 136.3, 135.9, 135.4,
135.3, 135.22 (4°), 135.19 (4°), 135.18 (4°), 134.49, 134.41, 130.20, 130.13, 129.19,
129.16, 128.44, 128.37, 128.31, 128.19, 128.13, 127.38, 113.47 (MeOC₆H₄ 6.84-6.81),
113.42 (MeOC₆H₄ 6.84-6.81), 113.41 (MeOC₆H₄ 6.84-6.81), 111.67 (4°), 111.62 (4°),
111.4 (4°), 111.20 (4°), 111.16 (4°), 87.7, 87.3, 86.1, 85.8, 85.5, 85.4, 84.9 (C₄H₁’), 84.7
(C₄H₁’), 84.6 (C₄H₁’), 71.8, 71.6, 68.6, 68.5, 66.95, 66.91, 63.29 (T¹CH₅’), 63.17 (T¹CH₅’),
62.2 (CH₅’ of 3′-TBS-OT), 55.39 (MeO), 55.37 (MeO), 40.67 (CH₂’), 40.58 (CH₂’), 39.94,
25.8 (t-Bu), 18.0 (t-Bu 4° C), 12.59, 12.56 (T²CH₃C-5), 11.9, 11.8 (T¹CH₃C-5), -4.52,
-4.59, -4.71, -4.76 (CH₃Si); ³¹P NMR (202 MHz, CDCl₃) δ 151.5, 150.2 (46:54); IR
(CDCI₃) 3395, 2955, 2932, 1690 cm⁻¹. HRMS (ESI): Calcd for C₅₄H₆₅N₄NaO₁₃PSi⁺
[M+Na]^+ 1057.37907, found 1057.37949.

Conversion of 12 and 13 to 17. Sulfurization of 13 occurred by reaction in
CD3CN with excess phenylacetyl disulfide (PADS) [10] or DDTT [11] and gave new
peaks at 66.4 and 66.0 ppm in the ³¹P NMR spectrum consistent with formation of the
tetraental sulfides. Reaction with 2 M triethylammonium bicarbonate (TEAB) or with
bis(trimethylsilyl)acetamide (BSA) [12] followed by TEAB gave material with only one
major peak in the ³¹P NMR spectrum at 113.3 ppm, and it could not be identified.
Oxidation of 13 in acetonitrile with anhydrous 3.3 M tert-butyl hydroperoxide [13] gave two peaks in the $^{31}$P NMR spectrum for the diastereomeric oxides at -0.9 and -1.1 ppm. Treatment with TEAB gave the H-phosphonate ($^{31}$P NMR (CDCl$_3$): 8.8, 7.5 ppm [12]), and treatment with PADS gave the diastereomeric phosphorothioates ($^{31}$P NMR (CDCl$_3$): 58.0, 57.9 ppm [12]).

Oxidation of 12 in the same manner gave the diastereomeric oxides ($^{31}$P NMR (CDCl$_3$): -2.5, -2.7 ppm), and TEAB and PADS gave the same H-phosphonate and phosphorothioate spectra as for 13.

**Thermal decomposition of 12 and 13.** Samples of 12 or 13 were dissolved in acetonitrile and added to a one-piece teflon vacuum stopcock-sealed heavy-walled glass vessel. The vessel was evacuated using a vacuum pump and then heated in a thermostatted oil bath. Periodically the solvent was removed under vacuum and the contents analyzed by NMR after extraction into CDCl$_3$ solution; after adding the NMR sample back to the vessel, the solvent was once again removed under vacuum and replaced with acetonitrile. Two samples of 12 were examined. A 1:1 mixture of diastereomers was heated for 12 h at 50 °C followed by 4 h at 75 °C, with no change in diastereomer ratio but extensive decomposition to unidentified materials that exhibited very broad bands in the $^1$H and particularly the $^{31}$P NMR spectra. A 42:58 sample of diastereomers was heated sequentially for 1.5 h at 100 °C, 1.5 h at 130°C, and 1.5 h at 150 °C. No change in diastereomer ratio occurred, but decomposition was nearly complete at the end. One sample of 13 was heated, for 2.5 h at 75 °C and 6 h at 100 °C, with no change in the 1:1 diastereomer ratio, and again with nearly complete decomposition.
**X-ray structure of 9.** A yellow fragment of 9 with approximate dimensions 0.31 mm x 0.37 mm x 0.41 mm, cleaved from a large crystal obtained by slow cooling of a saturated hexanes solution at –35 °C, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured on a Bruker Smart Breeze CCD system equipped with a graphite monochromator at 100(2) K, cooled by an Oxford Cryosystems 700 Series Cryostream. A total of 1464 frames were collected. The total exposure time was 12.20 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 21786 reflections to a maximum θ angle of 27.10° (0.78 Å resolution), of which 4311 were independent (average redundancy 5.054, completeness = 100.0%, \( R_{\text{int}} = 2.00\%, \ R_{\text{sig}} = 1.47\% \)) and 3921 (90.95%) were greater than 2\( \sigma(F^2) \). The final cell constants of \( a = 15.8768(8) \) Å, \( b = 9.2589(5) \) Å, \( c = 14.0614(7) \) Å, \( \beta = 108.8770(10)\° \), volume = 1955.87(17) Å\(^3\), were based upon the refinement of the XYZ-centroids of 9998 reflections above 20 \( \sigma(I) \) with 5.168° < 2\( \theta \) < 54.18°. Data were corrected for absorption effects using the numerical method (SADABS). The ratio of minimum to maximum apparent transmission was 0.927. The calculated minimum and maximum transmission coefficients (based on crystal size) were 0.9430 and 0.9550.

The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P2\(_1\)/c, with Z = 4 for the formula unit, \( \text{C}_{19}\text{H}_{33}\text{N}_2\text{OP} \). The final anisotropic full-matrix least-squares refinement on \( F^2 \) with 249 variables converged at \( R_1 = 3.11\% \), for the observed data and \( wR_2 = 8.21\% \) for all data. The goodness-of-fit was 1.048. The largest peak in the final difference electron density synthesis was 0.412
e⁻/Å³ and the largest hole was -0.202 e⁻/Å³ with an RMS deviation of 0.041 e⁻/Å³. On the basis of the final model, the calculated density was 1.143 g/cm³ and F(000), 736 e⁻.

Cambridge Crystallographic Data Centre deposition number for 9: CCDC 1030743. The data can be obtained free from Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

Calculations. All geometry and NMR calculations were carried out using Gaussian 09 Revision A.02 and D.01 [14] by first carrying out a geometry optimization (DFT, 6-31G(d), B3LYP) with modeling of solvation in chloroform using the polarization continuum model (IEFPCM), with calculation of vibrational frequencies to insure the finding of an energy minimum; NMR calculations (GIAO) were then carried out on the optimized structures using the 6-311+G(2d,p) basis set and the same IEFPCM solvation method.

Each of the inversion barrier calculations was carried out by optimizing using the 6-31+G(d) basis set, but without solvation modeling, with the exception of the phosphite triester where acetonitrile modeling was used. Following optimization, one of the groups was rotated to give the inverted structure, which was then reoptimized; 18 and 19 gave back the same structures but in the opposite configuration at phosphorus. For the transition state calculations, one enantiomer of each optimized structure was converted to a trigonal planar structure, and then used as the starting point for the transition state search. Both the QST3 option in Gaussian as well as the simpler Berny TS option ts=(opt,estmfc,noeigentest) described by the Collum group [15] were successfully used. The reported barriers are the smaller barrier from each ground state, as the sum of the electronic and thermal free energies at 298.15 K.
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| Name     | whil0273e4 |
|----------|------------|
| RXN no.  | 10         |
| Date     | 2014/10/25 |
| Time     | 10:45      |
| Instrument | spect      |
| Probe     | 5 mm QXI 1H 2- |
| Pulsprog  | zgbl        |
| Solvent   | CHDCl3     |
| NMR       | 16         |
| SS        | 2          |
| SMe        | 64         |
| SMe2       | 10320.376 Hz |
| PDMES     | 0.107652 Hz |
| AQ        | 3.171992 sec |
| DW        | 48.400 usec |
| TE        | 7.500 usec  |
| T1        | 1.0000000000 sec |
| T2g       | 1          |

| CHANNEL 1 |
|-----------|
| No.       | 16        |
| PI1       | 0.18 usec |
| PLC1      | 3.00 dB   |
| PLC1.W    | 15.18715526 W |
| SPM1      | 250.53305255 MHz |
| SI        | 32768     |
| SF        | 500.53055255 MHz |
| WCM       | 500.53052552 MHz |
| SFO       | 0.00 Hz   |
| LB        | 0.30 Hz   |
| GR        | 0.90 Hz   |
| FC        | 1.00 Hz   |
| SR        | 12.60 Hz  |
XYZ Coordinates for 7 from DFT optimization;
E(6-311G+(2d,p)) = -1078.49563987 au

| Atom Number | Atomic Number | Coordinates (Angstroms) |
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| 2           | 8             | -0.734670 2.771713 -0.257079 |
| 3           | 7             | 1.421462 -0.241278 0.007741 |
| 4           | 7             | -1.433560 -0.180628 0.076356 |
| 5           | 6             | 0.110745 2.055204 -0.770891 |
| 6           | 6             | 1.954595 0.457598 1.206204 |
| 7           | 1             | 1.265477 1.285959 1.401025 |
| 8           | 6             | 1.230538 2.668374 -1.604044 |
| 9           | 6             | -2.595677 -0.749460 -0.660859 |
| 10          | 1             | -3.379189 -0.882476 0.091785 |
| 11          | 6             | -1.855706 -1.127351 2.350269 |
| 12          | 1             | -2.792431 -1.634746 2.091102 |
| 13          | 1             | -1.905181 -0.875026 3.416413 |
| 14          | 1             | -1.036204 -1.837205 2.199139 |
| 15          | 6             | 1.979011 -0.427224 2.465267 |
| 16          | 1             | 0.992353 -0.847254 2.677949 |
| 17          | 1             | 2.295303 0.163317 3.333244 |
| 18          | 1             | 2.686572 -1.257599 2.360206 |
| 19          | 6             | -2.779004 1.157441 1.746813 |
| 20          | 1             | -2.595511 2.066033 1.170573 |
| 21          | 1             | -2.825313 1.416214 2.811931 |
| 22          | 1             | -3.758830 0.751448 1.469363 |
| 23          | 6             | 2.194976 -1.423811 -0.461701 |
| 24          | 1             | 3.064451 -1.485386 0.199956 |
| 25          | 6             | -2.317140 -2.137115 -1.256476 |
| 26          | 1             | -1.558304 -2.085880 -2.044680 |
| 27          | 1             | -3.231916 -2.549515 -1.699533 |
| 28          | 1             | -1.966114 -2.830066 -0.485131 |
| 29          | 6             | -1.647562 0.143043 1.506400 |
| 30          | 1             | -0.723446 0.615459 1.849028 |
| 31          | 6             | 3.342222 1.078660 0.960888 |
| 32          | 1             | 4.107956 0.313744 0.789077 |
| 33          | 1             | 3.652009 1.658062 1.838532 |
| 34          | 1             | 3.331079 1.748489 0.096710 |
| 35          | 6             | -3.151826 0.212103 -1.724480 |
| 36          | 1             | -3.361303 1.194693 -1.291130 |
| 37          | 1             | -4.079940 -0.183996 -2.155062 |
| 38          | 1             | -2.434737 0.346880 -2.542690 |
| 39          | 6             | 1.428934 -2.746677 -0.313775 |
| 40          | 1             | 1.066611 -2.878333 0.711023 |
| 41          | 1             | 2.081359 -3.593516 -0.559514 |
| Atom Number | Atomic Number | X         | Y         | Z         |
|-------------|---------------|-----------|-----------|-----------|
| 1           | 15            | -0.029622 | -0.290573 | 0.388031  |
| 2           | 7             | 0.331583  | 1.370506  | 0.127581  |
| 3           | 7             | -1.665212 | -0.645341 | -0.027312 |
| 4           | 6             | 0.948391  | -1.059218 | -0.988680 |
| 5           | 6             | 0.515259  | 2.018791  | -1.196116 |
| 6           | 1             | 0.261494  | 1.256220  | -1.938670 |
| 7           | 6             | -2.398183 | -1.560601 | 0.891703  |
| 8           | 1             | -3.421917 | -1.602572 | 0.507199  |
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| 10          | 1             | -4.234176 | 0.527592  | 0.137127  |
| 11          | 1             | -3.986613 | 1.599798  | -1.246116 |
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| 15          | 1             | -0.315832 | 3.602647  | -2.431171 |
| 16          | 1             | -0.209777 | 4.036209  | -0.722980 |
| 17          | 6             | -3.187529 | -0.907068 | -2.031617 |
| 18          | 1             | -2.496339 | -1.610535 | -2.504175 |
| 19          | 1             | -3.673304 | -0.327311 | -2.825358 |
| 20          | 1             | -3.969733 | -1.488157 | -1.530399 |
| 21          | 6             | 0.680811  | 2.191272  | 1.319254  |
| 22          | 1             | 0.898673  | 3.191351  | 0.931461  |
| 23          | 6             | -2.492367 | -1.055986 | 2.341422  |
| 24          | 1             | -1.508460 | -1.038454 | 2.821093  |
| 25          | 1             | -3.139745 | -1.718740 | 2.928592  |
| 26          | 1             | -2.912087 | -0.045719 | 2.380395  |
| 27          | 6             | -2.463810 | 0.047196  | -1.062340 |
| 28          | 1             | -1.749262 | 0.620925  | -1.657532 |
| 29          | 6             | 1.974576  | 2.429447  | -1.467459 |
| 30          | 1             | 2.313301  | 3.208932  | -0.775176 |
### XYZ Coordinates for 18 from DFT optimization;

Sum of electronic and thermal Free Energies(6-31G+(d))= -691.998977 au

| Atom Number | Atomic Number | Coordinates (Angstroms) | X    | Y    | Z     |
|-------------|---------------|-------------------------|------|------|-------|
| 1           | 6             | -2.395875               | 1.348909 | -0.250561 |
| 2           | 6             | -3.305990               | 0.289175 | -0.329180 |
| 3           | 6             | -2.852673               | -1.023242 | -0.180918 |
| 4           | 6             | -1.494845               | -1.272653 | 0.045765 |
| 5           | 6             | -0.567901               | -0.220820 | 0.125882 |
| 6           | 6             | -1.041285               | 1.094246 | -0.025389 |
| 7           | 15            | 1.215158                | -0.658838 | 0.419399 |
| 8           | 6             | 3.553367                | 0.041777 | -1.053137 |
| 9           | 6             | 2.026509                | 0.204764 | -1.039799 |
| 10          | 6             | 1.656013                | 0.528174 | 1.795329 |
| 11          | 1             | -2.742049               | 2.373614 | -0.364742 |
| 12          | 1             | -4.360560               | 0.487733 | -0.503957 |
| 13          | 1             | -3.552962               | -1.853029 | -0.239194 |
| 14          | 1             | -1.147473               | -2.296842 | 0.162938 |
XYZ Coordinates for 18 transition state from DFT optimization;
Sum of electronic and thermal Free Energies(6-31G+(d))= -691.947172 au

| Atom Number | Atomic Number | X     | Y     | Z     |
|-------------|---------------|-------|-------|-------|
| 1           | 6             | 2.834870 | 0.855352 | 0.234687 |
| 2           | 6             | 3.291750 | -0.457361 | 0.077929 |
| 3           | 6             | 2.356301 | -1.472865 | -0.150160 |
| 4           | 6             | 0.993569 | -1.189413 | -0.220144 |
| 5           | 6             | 0.521841 | 0.135172 | -0.067570 |
| 6           | 6             | 1.474714 | 1.154192 | 0.164504 |
| 7           | 15            | -1.211261 | 0.519598 | -0.172081 |
| 8           | 6             | -2.907505 | -1.648502 | 0.691271 |
| 9           | 6             | -2.448595 | -0.806549 | -0.510153 |
| 10          | 6             | -1.747138 | 2.266628 | 0.029452 |
| 11          | 1             | 3.543851 | 1.660685 | 0.413915 |
| 12          | 1             | 4.352566 | -0.684755 | 0.134037 |
| 13          | 1             | 2.688778 | -2.501371 | -0.272497 |
| 14          | 1             | 0.293032 | -2.002527 | -0.392960 |
| 15          | 1             | 1.151979 | 2.184737 | 0.289689 |
| 16          | 1             | -3.630047 | -2.411115 | 0.367984 |
| 17          | 1             | -2.062127 | -2.159287 | 1.164162 |
| 18          | 1             | -3.384740 | -1.022485 | 1.452597 |
| 19          | 1             | -3.304314 | -0.295947 | -0.969505 |
| 20          | 1             | -2.033203 | -1.451322 | -1.294621 |
| 21          | 1             | -2.831058 | 2.284109 | -0.127840 |
| 22          | 1             | -1.545628 | 2.658341 | 1.032032 |
| 23          | 1             | -1.289018 | 2.927039 | -0.714681 |
XYZ Coordinates for 19 from DFT optimization;  
Sum of electronic and thermal Free Energies \((6-31G+(d)) = -766.036587\) au

| Atom Number | Atomic Number | Coordinates (Angstroms) |
|-------------|---------------|-------------------------|
| X           | Y             | Z                       |
| 1           | 6             | -2.332829 0.055021 1.437940 |
| 2           | 6             | -3.290100 0.279684 0.442357 |
| 3           | 6             | -2.916996 0.225074 -0.902225 |
| 4           | 6             | -1.591192 -0.054336 -1.249886 |
| 5           | 6             | -0.619296 -0.279242 -0.261478 |
| 6           | 6             | -1.009530 -0.221243 1.088513 |
| 7           | 15            | 1.115680 -0.640195 -0.806029 |
| 8           | 6             | 2.067601 0.734962 0.082548 |
| 9           | 6             | 1.611924 -2.080081 0.258289 |
| 10          | 8             | 3.045519 0.467672 0.759838 |
| 11          | 6             | 1.636892 2.166326 -0.180619 |
| 12          | 1             | -2.616854 0.097075 2.486675 |
| 13          | 1             | -4.320150 0.494524 0.715388 |
| 14          | 1             | -3.655643 0.394879 -1.681664 |
| 15          | 1             | -1.307673 -0.102437 -2.298680 |
| 16          | 1             | -0.278035 -0.389503 1.875496 |
| 17          | 1             | 2.673771 -2.281415 0.089696 |
| 18          | 1             | 1.036429 -2.959498 -0.048406 |
| 19          | 1             | 1.463815 -1.902480 1.327786 |
| 20          | 1             | 2.364152 2.854252 0.259292 |
| 21          | 1             | 0.646606 2.350259 0.252646 |
| 22          | 1             | 1.555374 2.348894 -1.259133 |

XYZ Coordinates for 19 transition state from DFT optimization;  
Sum of electronic and thermal Free Energies \((6-31G+(d)) = -766.002998\) au

| Atom Number | Atomic Number | Coordinates (Angstroms) |
|-------------|---------------|-------------------------|
| X           | Y             | Z                       |
| 1           | 6             | -2.989774 0.765051 -0.679087 |
| 2           | 6             | -3.506502 -0.367112 -0.041367 |
| 3           | 6             | -2.644195 -1.224481 0.647920 |
| 4           | 6             | -1.277615 -0.945800 0.715989 |
| 5           | 6             | -0.742794 0.176661 0.054693 |
| 6           | 6             | -1.619274 1.026889 -0.648425 |
| 7           | 15            | 1.026577 0.550220 0.110624 |
| 8           | 6             | 2.354735 -0.621259 -0.172889 |
| 9           | 6             | 1.551401 2.259579 0.518064 |
| 10          | 8             | 3.522774 -0.254005 -0.063112 |
| 11          | 6             | 1.989009 -2.043502 -0.557687 |
| 12          | 1             | -3.651756 1.436440 -1.220293 |
XYZ Coordinates for 20 from DFT optimization;
Sum of electronic and thermal Free Energies (6-31G+(d)) = -936.138233 au

| Atom Number | Atomic Number | Coordinates (Angstroms) | X     | Y     | Z     |
|-------------|---------------|-------------------------|-------|-------|-------|
| 1           | 6             | -2.054739               | 0.044486 | -0.300289 |
| 2           | 6             | -2.940209               | -0.973618 | 0.436752 |
| 3           | 6             | -4.354482               | -0.822392 | 0.088488 |
| 4           | 7             | -5.473514               | -0.692587 | -0.196166 |
| 5           | 8             | -0.715862               | -0.157069 | 0.161113 |
| 6           | 15            | 0.549743                | 0.223342 | -0.890229 |
| 7           | 6             | 2.194851                | -1.760140 | -0.121028 |
| 8           | 8             | 1.762588                | -0.374544 | 0.055362 |
| 9           | 8             | 0.768444                | 1.827666 | -0.628002 |
| 10          | 6             | 0.941617                | 2.429625 | 0.686626 |
| 11          | 1             | -2.376141               | 1.066377 | -0.070372 |
| 12          | 6             | 3.679172                | -1.744192 | -0.465997 |
| 13          | 1             | 1.632212                | -2.195611 | -0.958582 |
| 14          | 6             | 1.879371                | -2.532016 | 1.155251 |
| 15          | 1             | -2.124125               | -0.106865 | -1.384949 |
| 16          | 1             | -2.830468               | -0.843861 | 1.519349 |
| 17          | 1             | -2.623123               | -1.992938 | 0.190102 |
| 18          | 6             | 0.911972                | 3.938642 | 0.525724 |
| 19          | 1             | 1.897357                | 2.090180 | 1.097187 |
| 20          | 1             | 0.135627                | 2.082099 | 1.340833 |
| 21          | 1             | 2.189290                | -3.578210 | 1.047850 |
| 22          | 1             | 4.046169                | -2.767518 | -0.606859 |
| 23          | 1             | 0.806554                | -2.509073 | 1.370993 |
| 24          | 1             | 4.255394                | -1.279126 | 0.342726 |
| 25          | 1             | 3.858506                | -1.182683 | -1.389140 |
| 26          | 1             | 2.416489                | -2.099480 | 2.007732 |
| 27          | 1             | 1.048171                | 4.414954 | 1.503946 |
| 28          | 1             | -0.046243               | 4.270960 | 0.111374 |
| 29          | 1             | 1.716107                | 4.277961 | -0.136549 |
XYZ Coordinates for 20 after rotation to opposite configuration, from DFT optimization;  
Sum of electronic and thermal Free Energies (6-31G+(d)) = -936.137960 au

| Atom Number | Atomic Number | Coordinates (Angstroms) |
|-------------|---------------|-------------------------|
|             |               | X  | Y   | Z    |
| 1           | 6             | 2.038365 | -0.332346 | -0.240296 |
| 2           | 6             | 3.087921 | 0.468896  | 0.548525  |
| 3           | 6             | 4.451315 | 0.020820  | 0.257507  |
| 4           | 7             | 5.528094 | -0.343814 | 0.017209  |
| 5           | 8             | 0.752412 | 0.148930  | 0.158980  |
| 6           | 15            | -0.469082 | 0.263299 | -0.999639 |
| 7           | 6             | -1.769137 | -1.737475 | 0.390085  |
| 8           | 8             | -1.269116 | -1.154859 | -0.863489 |
| 9           | 8             | -1.476091 | 1.214423  | -0.089394 |
| 10          | 6             | -1.168394 | 2.624497  | 0.038825  |
| 11          | 1             | 2.118076  | -1.399170 | -0.005565 |
| 12          | 6             | -3.291884 | -1.751465 | 0.329960  |
| 13          | 1             | -1.435138 | -1.103132 | 1.216732  |
| 14          | 6             | -1.160049 | -3.127471 | 0.525561  |
| 15          | 1             | 2.191481  | -0.200461 | -1.318705 |
| 16          | 1             | 2.905330  | 0.360018  | 1.623658  |
| 17          | 1             | 3.006766  | 1.533670  | 0.303516  |
| 18          | 6             | -2.384660 | 3.333245  | 0.607938  |
| 19          | 1             | -0.904939 | 3.031720  | -0.946485 |
| 20          | 1             | -0.302105 | 2.736384  | 0.700578  |
| 21          | 1             | -1.508658 | -3.600495 | 1.451239  |
| 22          | 1             | -3.699301 | -2.185614 | 1.250883  |
| 23          | 1             | -0.066781 | -3.075602 | 0.557092  |
| 24          | 1             | -3.638513 | -2.355275 | -0.517218 |
| 25          | 1             | -3.686643 | -0.736653 | 0.221907  |
| 26          | 1             | -1.455285 | -3.762723 | -0.317953 |
| 27          | 1             | -2.166838 | -4.401092 | 0.726783  |
| 28          | 1             | -2.649296 | 2.924937  | 1.589570  |
| 29          | 1             | -3.247082 | -2.283555 | -0.059309 |

XYZ Coordinates for 20 transition state from DFT optimization;  
Sum of electronic and thermal Free Energies (6-31G+(d)) = -936.072122 au

| Atom Number | Atomic Number | Coordinates (Angstroms) |
|-------------|---------------|-------------------------|
|             |               | X  | Y   | Z    |
| 1           | 6             | 2.370958 | -0.332605 | 0.000023 |
| 2           | 6             | 3.536484 | -1.341651 | 0.000325 |
| 3           | 6             | 4.840569 | -0.675170 | 0.000196 |
| 4           | 7             | 5.865295 | -0.126270 | 0.000115 |
| 5           | 8             | 1.155797 | -1.069680 | 0.000426 |
| Number | Atomic Number | X    | Y    | Z    |
|--------|---------------|------|------|------|
| 1      | 6             | 0.417580 | 2.965013 | 0.584131 |
| 2      | 8             | -1.854501 | 2.326648 | 0.122276 |
| 3      | 1             | -0.021325 | 3.905237 | 0.930003 |
| 4      | 6             | -0.671930 | 2.036281 | 0.104336 |
| 5      | 15            | -0.234200 | 0.359015 | -0.690536 |
| 6      | 6             | 2.076795 | -0.948312 | -0.244079 |
| 7      | 8             | 1.188423 | 0.141491 | 0.130612 |
| 8      | 8             | -1.273562 | -0.595438 | 0.194031 |
| 9      | 6             | -2.430370 | -1.164635 | -0.454690 |
| 10     | 1             | 0.984150 | 2.484599 | 1.390053 |
| 11     | 6             | 3.467341 | -0.359128 | -0.453263 |
| 12     | 1             | 1.717047 | -1.377673 | -1.191180 |
| 13     | 6             | 2.031773 | -2.012664 | 0.848426 |
| 14     | 1             | 1.132742 | 3.159813 | -0.225472 |

XYZ Coordinates for 21 from DFT optimization;
Sum of electronic and thermal Free Energies(6-31G+(d))= -842.668118 au
| Atom Number | Atomic Number | X     | Y     | Z     |
|-------------|---------------|-------|-------|-------|
| 1           | 6             | -0.203875 | -2.883460 | 0.605711 |
| 2           | 8             | -2.288031 | -1.829577 | 0.045501 |
| 3           | 1             | -0.833309 | -3.694144 | 0.983372 |
| 4           | 6             | -1.071232 | -1.791765 | 0.019087 |
| 5           | 15            | -0.207857 | -0.382810 | -0.949807 |
| 6           | 6             | 2.258944  | 0.466609  | -0.258749 |
| 7           | 8             | 1.035201  | -0.200323 | 0.157097 |
| 8           | 8             | -1.226791 | 0.881889  | -0.693503 |
| 9           | 6             | -1.755834 | 1.274144  | 0.598913 |
| 10          | 1             | 0.489900  | -3.270217 | -0.151996 |
| 11          | 6             | 2.209174  | 1.936934  | 0.149920 |
| 12          | 2             | 2.330849  | 0.394450  | -1.354175 |
| 13          | 6             | 3.421097  | -0.287633 | 0.377602 |
| 14          | 1             | 0.412596  | -2.469757 | 1.412216 |
| 15          | 6             | -2.491640 | 2.591130  | 0.423588 |
| 16          | 1             | -0.923033 | 1.374861  | 1.304831 |
| 17          | 1             | -2.430248 | 0.488949  | 0.952252 |
| 18          | 1             | 4.375615  | 0.169691  | 0.091203 |
| 19          | 1             | 3.130944  | 2.448328  | -0.153256 |
| 20          | 1             | 3.430087  | -1.334494 | 0.056135 |
| 21          | 1             | 2.106926  | 2.028068  | 1.237886 |
| 22          | 1             | 1.363926  | 2.447995  | -0.322829 |
| 23          | 1             | 3.341383  | -0.262169 | 1.470843 |
| 24          | 1             | -2.915317 | 2.911199  | 1.383559 |
| 25          | 1             | -3.309599 | 2.482887  | -0.296466 |
| 26          | 1             | -1.815692 | 3.374834  | 0.064331 |

**XYZ Coordinates for 21 after rotation to opposite configuration, from DFT optimization; Sum of electronic and thermal Free Energies (6-31G(d)) = -842.668984 au**
XYZ Coordinates for 21 transition state from DFT optimization;
Sum of electronic and thermal Free Energies (6-31G+(d)) = -842.601643 au

| Atom Number | Atomic Number | Coordinates (Angstroms) | X    | Y    | Z    |
|-------------|---------------|-------------------------|------|------|------|
| 1           | 6             | -0.495296               | 3.064340 | 0.146405 |
| 2           | 8             | 1.842796                | 2.421002 | 0.257126  |
| 3           | 1             | -0.537962               | 3.485847 | 1.157291  |
| 4           | 6             | 0.675162                | 2.104010 | 0.067021  |
| 5           | 15            | 0.248203                | 0.420344 | -0.364057 |
| 6           | 6             | -2.065146               | -0.832641 | 0.334162  |
| 7           | 8             | -1.265434               | -0.115225 | -0.672690 |
| 8           | 8             | 1.433060                | -0.680735 | -0.578212 |
| 9           | 6             | 2.034054                | -1.350955 | 0.570492  |
| 10          | 1             | -0.312104               | 3.884990 | -0.556750 |
| 11          | 6             | -3.476388               | -0.266813 | 0.253700  |
| 12          | 1             | -1.625936               | -0.618516 | 1.317330  |
| 13          | 6             | -1.997499               | -2.325226 | 0.036178  |
| 14          | 1             | -1.450141               | 2.590396 | -0.095224 |
| 15          | 6             | 3.222689                | -2.146085 | 0.065840  |
| 16          | 1             | 1.280585                | -2.002751 | 1.030266  |
| 17          | 1             | 2.337103                | -0.590808 | 1.297488  |
| 18          | 1             | -0.966589               | -2.692094 | 0.080269  |
| 19          | 1             | -4.130162               | -0.777711 | 0.970548  |
| 20          | 1             | -2.392330               | -2.533157 | -0.964714 |
| 21          | 1             | -3.888864               | -0.407929 | -0.751758 |
| 22          | 1             | -3.484175               | 0.803656 | 0.484008  |
| 23          | 1             | -2.592642               | -2.885608 | 0.767380  |
| 24          | 1             | 3.700070                | -2.669410 | 0.903321  |
| 25          | 1             | 3.961262                | -1.482838 | -0.395788 |
| 26          | 1             | 2.910014                | -2.889352 | -0.675379 |