Supporting Information

"An Olefin Cross-Metathesis Approach to Vinylphosphonate-Linked Nucleic Acids"

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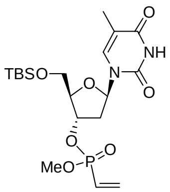
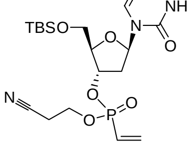
General Details.- IR spectra were obtained using a Perkin-Elmer 1600 series FT-IR instrument as dilute sample solutions in spectroscopic grade $CHCl_3$. Sample solutions in $CDCl_3$ were used for the determination of NMR spectra. Shifts are expressed in ppm downfield from Me_4Si, as internal standard. The ^1H , ^{13}C and ^{31}P nmr spectra were obtained using either a Bruker AM400, AV400 or DRX500 spectrometer. Multiplicities of signals are assigned using the following abbreviations: s = singlet, d = doublet, t = triplet, q=quartet, m = multiplet, br = broad, app= apparent. Coupling constants (*J*) are given in Hertz. Assignments in the ^1H spectra were consistent with signal intensities, and in the ^{13}C spectra with the results of the DEPT pulse sequence. Mass spectra were recorded on a MM-701CF instrument using fast atom bombardment (FAB) or electrospray (ES) techniques. Flash chromatography was performed using Merck silica gel 60. All reactions were monitored by TLC using Merck silica gel 60 F254 pre-coated aluminium plates which were visualised with ultraviolet light and then with basic potassium permanganate solution. CH_2Cl_2 was distilled from calcium hydride before use in reactions. All reactions were performed in oven dried apparatus.

Vinylphosphonate 9.



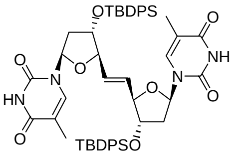
A 4.5ml screw cap reaction vial was charged with Pd(OAc)$_2$ (0.019g, 0.085mmol, 0.1eq), Ph$_3$P (0.044g, 0.17mmol, 0.2eq), *H*-phosphonate **8** (0.367g, 0.846mmol), vinylbromide (3.5ml, 1.0M soln in THF, 4.1eq) and propylene oxide (1.0ml, 14.3mmol, 17eq). The mixture was heated at 70^{o}C (oil bath temperature) for 15h. After cooling to RT, the volatiles were removed *in vacuo* and the residue was purified by column chromatography (AcOEt:MeOH 3:1) to give **9** (0.248g, 64%) as a 1:1 mixture of diastereoisomers. (Data given for the mixture of diastereomers): (Found (HRMS ES) M^{+}+Na, 483.1669, $C_{19}H_{33}O_7N_2PSiNa$ requires 483.1692); ν_{max}/cm^{-1} 3393, 3186, 2954, 2930, 2858, 1694, 1463, 1400, 1385, 1363, 1322, 1292, 1277, 1128, 1065, 1050, 1005, 977, 892, 838; δ_H(400 MHz) 9.96 (1H, br s), 7.42 (1H, s), 6.38-6.20 (2.5H, m), 6.13-5.95 (1.5H, m), 5.02 (0.5H, app t, *J* 6.5), 4.96 (0.5H, app t, *J* 6.5), 4.22 (0.5H, m), 4.17 (0.5H, m), 3.84 (0.5H, m), 3.82 (0.5H, m), 3.70 (1.5H, d, *J* 11.2), 3.69 (1.5H, d, *J* 11.3), 2.50 (0.5H, dd, *J* 13.8, 6.3), 2.43 (0.5H, dd, *J* 13.8, 6.3), 2.12-2.01 (1H, m), 1.86 (3H, s), 0.87 (9H, s), 0.07 (6H, s); δ_C(100 MHz) 164.1 (C), 150.6 (C), 137.0/136.8 (CH$_2$), 134.9 (CH), 124.9 (d, $^1J_{CP}$ 185.2)/124.8 (d, $^1J_{CP}$ 184.2)(CH), 111.1 (C), 86.0 (d, $^2J_{CP}$ 3.2)/85.9 (d, $^2J_{CP}$ 4.8)(CH), 84.4 (CH), 76.6/76.5 (CH), 52.6 (d, $^2J_{CP}$ 5.5)/52.4 (d, $^2J_{CP}$ 5.5)(CH$_3$), 39.5 (d, $^3J_{CP}$ 3.3)/39.4 (d, $^3J_{CP}$ 4.6)(CH$_2$), 25.8 (CH$_3$), 18.2 (C), 12.4 (CH$_3$), -5.5/-5.6 (CH$_3$); δ_P(161.98 MHz) 20.4/20.1.

Vinylphosphonate 15.

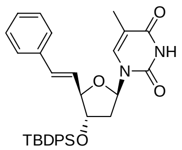


A 4.5ml screw cap reaction vial was charged with Pd(OAc)$_2$ (0.025g, 0.111mmol, 0.1eq), Ph$_3$P (0.098g, 0.374mmol, 0.4eq), 5'-O-(*tert*butyldimethylsilyl)-α-thymidine-3'-O-(2-cyanoethyl)-*H*-phosphonate (0.440g, 0.930mmol), vinylbromide (3.5ml, 1.0M soln in THF, 4.1eq) and propylene oxide (1.0ml, 14.3mmol, 15eq) and the mixture was heated at 70^{o}C (oil bath temperature) for 15h. After cooling to RT, the volatiles were removed *in vacuo* and the residue was purified by column chromatography (AcOEt) to give **15** (0.115g, 25%) as a 1:1 mixture of diastereomers. (Data for the mixture of diastereomers): (Found (HRMS ES) M^++Na, 522.1829, $C_{21}H_{34}O_7N_3PSiNa$ requires 522.1801); ν_{max}/cm^{-1} 3393, 3187, 2954, 2931, 2859, 2257, 1694, 1462, 1400, 1385, 1363, 1322, 1292, 1126, 1075, 978, 905, 838; δ_H(400 MHz) 9.25 (0.5H, br s), 9.19 (0.5H, br s), 7.47 (0.5H, q, *J* 1.3), 7.46 (0.5H, q, *J* 1.2), 6.49-6.30 (2.5H, m), 6.26-6.04 (1.5H, m), 5.08 (0.5H, app t, *J* 5.9), 5.05 (0.5H, app t, *J* 7.6), 4.30-4.17 (3H, m), 3.90 (1H, m), 3.89 (0.5H, dd, *J* 11.5, 2.3), 3.84 (0.5H, dd, *J* 11.5, 2.3), 2.81-2.74 (2H, m), 2.58 (0.5H, dd, *J* 13.9, 5.2), 2.50 (0.5H, dd, *J* 13.8, 6.4), 2.20-2.06 (1H, m), 1.91 (3H, d, *J* 1.2), 0.92 (9H, s), 0.12 (3H, s), 0.12 (3H, s); δ_C(100 MHz) 163.8 (C), 150.5/150.5 (C), 138.1/137.7 (CH_2), 134.9 (CH), 124.7 (d, $^1J_{CP}$ 185.5)/124.6 (d, $^1J_{CP}$ 184.5)(CH), 116.5/116.5 (C), 111.3 (C), 86.0 (d, $^2J_{CP}$ 3.5)/85.9 (d, $^2J_{CP}$ 5.2)(CH), 84.6 (CH), 77.3/77.2 (CH), 63.3/63.2 (CH_2), 60.5 (d, $^2J_{CP}$ 4.7)/60.3 (d, $^2J_{CP}$ 4.2)(CH_2), 39.6 (d, $^3J_{CP}$ 3.8)/39.5 (d, $^3J_{CP}$ 4.6)(CH_2), 26.0 (CH_3), 20.0 (2 x CH_2), 18.4 (C), 12.6 (CH_3), -5.4/-5.4 (CH_3); δ_P(161.98 MHz) 19.8/19.6.

Alkenes 13 and 12.



12



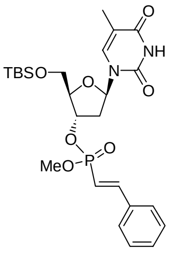
13

A flask charged with 1-alkene **7** (0.046g, 0.097mmol), catalyst **5** (0.017g, 0.020mmol) and dichloromethane (2.0ml) under an argon atmosphere was heated at reflux for 14h. The solvent was removed under reduced pressure and the residue purified by column chromatography (hexane:AcOEt 1:1) to give **13** (0.010g, 20%, *E:Z* 5:1) and **12** (0.032g, 72%). Data for **13**: (Found (HRMS ES) M^++Na, 575.2323, $C_{21}H_{34}O_7N_3PSiNa$ requires 575.2342); ν_{max}/cm^{-1} 3391, 2932, 2859, 1690, 1464, 1364, 1273, 1112, 1052, 965, 908; δ_H(400 MHz) 8.29 (1H, br s), 7.66-7.63 (4H, m), 7.48-7.22 (11H, m), 7.07 (1H, s), 6.45 (1H, d, *J* 15.8), 6.38 (1H, app t, *J* 6.6), 5.84 (1H, dd, *J* 15.8, 7.0), 4.51 (1H, ddd, *J* 6.6, 4.0, 1.0), 4.27 (1H, m), 2.44 (1H, ddd, *J* 13.6, 6.6, 4.0), 1.93 (1H, app dt, *J* 13.6, 6.7), 1.87 (3H, s), 1.10 (9H, s); δ_C(100 MHz) 163.4 (C), 150.1 (C), 136.0 (CH), 135.8 (CH), 135.3 (CH), 133.5 (CH), 133.1 (C), 133.1

(C), 130.2 (CH), 130,2 (CH), 128.7 (CH), 128.3 (CH), 128.0 (CH), 128.0 (CH), 126.6 (CH), 125.8 (CH), 111.1 (C), 87.4 (CH), 85.0 (CH), 76.4 (CH), 40.2 (CH_2), 26.9 (CH_3), 19.1 (C), 12.7 (CH_3).

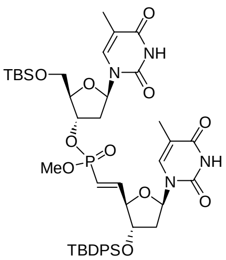
Data for **12**: (Found (HRMS FAB positive ion) M^++Na, 947.3930, $C_{21}H_{34}O_7N_3PSiNa$ requires 947.3847); ν_{max}/cm^{-1} 3392, 2932, 2895, 2859, 1694, 1463, 1364, 1276, 1112, 1051, 990, 908; *Trans*-isomer: δ_H(400 MHz) 8.42 (2H, br s), 7.65-7.57 (8H, m), 7.45-7.30 (12H, m), 6.92 (2H, br s), 6.32 (2H, app t, *J* 6.8), 5.19 (2H, dd, *J* 3.6, 1.6), 4.18 (2H, m), 4.06 (2H, m), 2.32 (2H, ddd, *J* 13.3, 5.8, 2.6), 1.85 (2H, m), 1.81 (6H, s), 1.08 (18H, s); δ_C(100 MHz) 163.3 (C), 150.1 (C), 135.9 (CH), 135.8 (CH), 135.2 (CH), 133.1 (C), 133.0 (C), 130.3 (CH), 130.2 (CH), 128.0 (CH), 127.9 (CH), 111.3 (C), 86.4 (CH), 85.3 (CH), 76.4 (CH), 39.6 (CH_2), 26.9 (CH_3), 19.1 (C), 12.6 (CH_3); *Cis*-isomer (where signals not occluded by the *trans*-isomer): δ_H(400 MHz) 6.13 (2H, app t, *J* 6.5), 5.44 (2H, m), 4.69 (2H, m).

Vinylphosphonate 14.



A flask charged with the vinylphosphonate **9** (0.046g, 0.100mmol), catalyst **5** (0.016g, 0.019mmol) and dichloromethane (2.0ml) under an argon atmosphere was heated at reflux for 14h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (AcOEt) to give **14** (0.011g, 20%) as a 1:1 mixture of separable diastereomers. Least polar diastereomer: (Found (HRMS FAB positive ion) M+H^+, 537.2159, $C_{25}H_{38}O_7N_2PSi$ requires 537.2186); ν_{max}/cm^{-1} 3392, 2954, 2930, 2858, 1689, 1615, 1463, 1353, 1322, 1275, 1128, 1049, 1007, 976, 908, 863, 836; δ_H(400 MHz) 8.16 (1H, br s), 7.61-7.41 (7H, m), 6.41 (1H, dd, *J* 9.1, 5.3), 6.25 (1H, dd, *J* 17.7, 17.7), 5.06 (1H, app t, *J* 6.3), 4.33 (1H, m), 3.93 (2H, m), 3.78 (3H, d, *J* 11.3), 2.51 (1H, ddd, *J* 14.0, 5.7, 0.9), 2.12 (1H, m), 1.92 (3H, s), 0.92 (9H, s), 0.13 (3H, s), 0.13 (3H, s); δ_C(100 MHz) 163.4 (C), 150.4 (CH, d, $^2J_{CP}$ 7.0), 150.1 (C), 135.1 (CH), 134.5 (C, d, $^3J_{CP}$ 23.8), 130.8 (CH), 129.1 (CH), 128.0 (CH), 112.6 (CH, d, $^1J_{CP}$ 192.2), 111.2 (C), 86.3 (CH, d, $^2J_{CP}$ 3.6), 84.7 (CH), 76.6 (CH), 63.3 (CH_2), 52.6 (CH_3, d, $^2J_{CP}$ 5.6), 39.7 (CH_2, d, $^3J_{CP}$ 4.8), 26.0 (CH_3), 18.4 (CH_3), 12.6 (CH_3), -5.3 (CH_3), -5.4 (CH_3); δ_P(161.98 MHz) 22.9; most polar diastereomer: (Found (HRMS ES) M^++Na, 559.2022, $C_{25}H_{37}O_7N_2PSiNa$ requires 559.2005); ν_{max}/cm^{-1} 3392, 2954, 2930, 2858, 1689, 1616, 1463, 1362, 1322, 1276, 1128, 1064, 1048, 1006, 976, 908, 864, 838; δ_H(400 MHz) 8.28 (1H, br s), 7.71-7.40 (7H, m), 6.41 (1H, dd, *J* 8.9, 5.3), 6.25 (1H, dd, *J* 18.0, 18.0), 5.11 (1H, m), 4.26 (1H, m), 3.89 (1H, dd, *J* 11.4, 2.1), 3.85 (1H, dd, *J* 11.4, 2.1), 3.79 (3H, d, *J* 11.2), 2.60 (1H, ddd, *J* 14.3, 5.3, 1.0), 2.16 (1H, m), 1.93 (3H, s), 0.91 (9H, s), 0.11 (3H, s), 0.11 (3H, s); δ_C(100 MHz) 163.4 (C), 150.2 (C), 150.1 (CH, d, $^2J_{CP}$ 7.7), 135.1 (CH), 134.5 (C, d, $^3J_{CP}$ 23.3), 130.8 (CH), 129.1 (CH), 127.9 (CH), 112.7 (CH, d, $^1J_{CP}$ 193.4), 111.2 (C), 86.2 (CH), 84.7 (CH), 76.7 (CH), 63.3 (CH_2), 52.7 (CH_3, d, $^2J_{CP}$ 5.2), 39.8 (CH_2, d, $^3J_{CP}$ 3.8), 26.0 (CH_3), 18.4 (CH_3), 12.6 (CH_3), -5.3 (CH_3), -5.4 (CH_3); δ_P(161.98 MHz) 22.7.

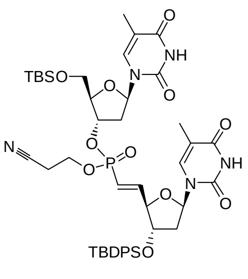
Methyl phosphonate T*T Dimer 11



A flask was charged with 1-alkene **7** (0.107g, 0.225mmol, 1.00eq), vinylphosphonate **9** (0.130g, 0.282mmol, 1.25eq), catalyst **5** (0.038g, 0.045mmol, 0.20eq) and dichloromethane (4.0ml) under an argon atmosphere. The mixture was heated at reflux for 16h and then, the solvent was removed under reduced pressure. The residue was purified by column chromatography (AcOEt) to give **11** (0.118g, 58%) as a 1:1 mixture of separable diastereoisomers. (Found (HRMS FAB positive ion) M+H^+ 909.3657, $C_{44}H_{62}N_4O_{11}PSi_2$ requires 909.3691); ν_{max}/cm^{-1} 3392, 2956, 2991, 2859, 1694, 1591, 1464, 1438, 1364, 1322, 1276, 1120, 1049, 1000, 976, 939, 908 and 648; least polar isomer: δ_H (500 MHz) 8.84 (1H, br s, NH), 8.74 (1H, br s, NH), 7.64 (4H, m, ArH), 7.46 (7H, m, ArH, H-6), 6.99 (1H, s, H-6), 6.55 (1H, ddd, *J* 22.5, 17.1, 4.6, T_2-H-5’), 6.33 (1H, dd, *J* 9.2, 5.1, H-1’), 6.22 (1H, dd, *J* 7.6, 6.3, H-1’), 5.73 (1H, ddd, *J* 20.2, 17.1, 1.7, T_2-H-6’), 5.01 (1H, app t, *J* 6.2, T_1-H-3’), 4.35 (1H, m, H-4’), 4.48 (1H, m, H-3’), 4.20 (1H, m, H-4’), 3.90 (1H, dd, *J* 11.2, 2.9, T_1-H-5’), 3.84 (1H, dd, *J* 11.2, 2.5, T_1-H-5’), 3.65

(3H, d, *J* 11.3, OMe), 2.48 (1H, dd, *J* 13.7, 5.1, H-2’), 2.24 (1H, ddd, *J* 13.7, 6.3, 3.3, H-2’), 2.20 (1H, m, H-2’), 2.01 (1H, ddd, *J* 14.0, 9.0, 5.1, H-2’), 1.92 (3H, s, Me), 1.89 (3H, s, Me), 1.10 (9H, s, 3 x Me), 0.93 (9H, s, 3x Me), 0.12 (6H, s, 2 x Me); δ_C (125 MHz) 163.8 (C), 150.5 (C), 150.4 (C), 149.3 (CH), 135.8 (CH), 134.9 (CH), 132.8 (C), 132.7 (C), 130.3 (CH), 128.1 (CH), 117.7 (CH, d, $^1J_{CP}$ 189.2), 111.5 (C), 111.4 (C), 86.4 (CH), 86.2 (CH), 84.6 (CH), 76.1 (CH), 63.3 (CH_2), 52.5 (CH_3, d, $^2J_{CP}$ 5.7), 39.4 (CH_2), 39.0 (CH_2), 26.9 (CH_3), 26.0 (CH_3), 19.1 (C), 18.4 (C), 12.6 (CH_3), -5.4 (CH_3); δ_P (161.98 MHz) 20.2; most polar isomer: δ_H (400 MHz) 8.33 (1H, s, NH), 8.28 (1H, s, NH), 7.67 (4H, m ArH), 7.49 (7H, m, ArH, H-6), 6.93 (1H, s, H-6), 6.52 (1H, ddd, *J* 22.6, 17.1, 4.7, H-5’), 6.41 (1H, dd, *J* 7.8, 6.1, H-1’), 6.37 (1H, dd, *J* 9.2, 5.3, H-1’), 5.70 (1H, ddd, *J* 19.6, 17.1, 1.7, H-6’), 5.01 (1H, app t, *J* 5.9, T_1-H-3’), 4.48 (1H, m, H-3’/H-4’), 4.28 (1H, m, H-3’/H-4’), 4.16 (1H, m, H-3’/H-4’), 3.87 (1H, dd, *J* 11.6, 2.0, H-5’), 3.81 (1H, dd, *J* 11.6, 2.0, H-5’), 3.68 (3H, d, *J* 11.2, OMe), 2.50 (1H, dd, *J* 13.7, 5.3, H-2’), 2.30 (1H, ddd, *J* 13.7, 6.1, 3.2, H-2’), 2.11 (1H, m, H-2’), 1.98 – 1.90 (1H, obscured m, H-2’), 1.93 (3H, s, Me), 1.88 (3H, s, Me), 1.10 (9H, s, 3 x Me), 0.93 (9H, s, 3 x Me), 0.12 (6H, 2 x s, 2 x Me); δ_C (125 MHz) 163.8 (C), 163.6 (C), 150.4 (C), 150.3 (C), 149.1 (CH), 135.8 (CH), 135.3 (CH), 135.0 (CH), 132.7 (C), 130.4 (CH), 128.1 (CH), 117.6 (CH, d, $^1J_{CP}$ 190.5), 111.7 (C), 111.3 (C), 86.3 (CH), 86.1 (CH), 85.7 (CH), 84.7 (CH), 76.1 (CH), 63.3 (CH_2), 52.8 (CH_3, d, $^2J_{CP}$ 5.8), 39.7 (CH_2), 39.1 (CH_2), 26.9 (CH_3), 26.0 (CH_3), 19.1 (C), 18.4 (C), 12.6 (CH_3), -5.3 (CH_3), -5.4 (CH_3); δ_P (161.98 MHz) 20.0.

Cyanoethylphosphonate T*T Dimer 16



A flask was charged with 1-alkene **7** (0.017g, 0.036mmol, 1.00eq), vinylphosphonate **15** (0.022g, 0.044mmol, 1.22eq), catalyst **5** (0.012g, 0.014mmol, 0.38eq) and dichloromethane (1.0ml) under an argon atmosphere. The mixture was heated at reflux for 16h and then, the solvent was removed under reduced pressure. The residue was purified by column chromatography (AcOEt) to give **16** (0.011g, 32%) as an inseparable 1:1 mixture of diastereoisomers. (Found (HRMS FAB positive ion) M+H$^+$ 948.3779, $C_{46}H_{63}N_5O_{11}PSi_2$ requires 948.3800); ν_{max}/cm^{-1} 3392, 3194, 2931, 2897, 2859, 2258, 1715, 1590, 1462, 1385, 1363, 1322, 1294, 1104, 1074, 998, 977, 892, 839, 644 and 607; δ_H (400 MHz) 9.23 (0.5H, s, NH), 9.19 (0.5H, s, NH), 9.10 (0.5H, s, NH), 9.07 (0.5H, s, NH), 7.65 (4H, m, ArH), 7.45 (7H, m, ArH, T_1-H-6), 7.01 (1H, s, T_2-H-6), 6.59 (1H, ddd, *J* 23.2, 17.2, 4.5, T_2-H-5'), 6.39 – 6.30 (1.5H, m, H-1'), 6.26 (0.5H, dd, *J* 7.7, 6.5, H-1'), 5.75 (1H, ddd, *J* 20.2, 17.2, 1.7, T_2-H-6'), 5.04 (1H, m, T_1-H-3'), 4.48 (1H, m, H-3'/H-4'), 4.36 (0.5H, m, H-3'/H-4'), 4.31 (0.5H, m, H-3'/H-4'), 4.23 (0.5H, m, H-3'/H-4'), 4.13 (2.5H, m, H-3'/H-4', CH_2CH$_2$CN), 3.87 (1H, m, T_1-H-5'), 3.81 (1H, dd, *J* 11.5, 1.9, T_1-H-5'), 2.70 (2H, m, CH$_2$CN), 2.55 (0.5H, dd, *J* 13.1, 5.1, H-2'), 2.48 (0.5H, dd, *J* 13.1, 5.1, H-2'), 2.31 – 1.99 (3H, m, H-2'), 1.92 (3H, s, Me), 1.89 (1.5H, s, Me), 1.88 (1.5H, s, Me), 1.10 (4.5H, s, 1.5 x Me), 1.09 (4.5H, s, 1.5 x Me), 0.92 (9H, 2 × s, 3 x Me), 0.11 (6H, s, 2 x Me); δ_C (125 MHz) 164.0 (C), 163.9 (C), 150.7 (C), 150.6 (C), 150.5 (C), 150.4 (C), 150.3 (CH), 149.8 (CH), 135.7 (CH), 134.9 (CH), 132.7 (C), 132.6 (CH), 130.3 (CH), 128.1 (CH), 128.0 (CH), 117.6 (C), 116.8 (CH, d, $^1J_{CP}$ 190.8), 116.5 (C), 86.7 (CH), 86.3 (CH), 86.0 (CH), 85.9 (CH), 85.7 (CH), 84.6 (CH), 77.7 (CH), 76.0 (CH), 75.9 (CH), 63.3 (CH$_2$), 63.2 (CH$_2$), 60.7 (CH$_2$), 60.3 (CH$_2$), 39.6 (CH$_2$), 39.3 (CH$_2$), 38.9 (CH$_2$), 38.8 (CH$_2$), 26.9 (CH$_3$), 25.9 (CH$_3$), 19.9 (CH$_2$), 19.0 (C), 18.3 0 (C), 12.5 (CH$_3$), -5.4 (CH$_3$); δ_P (161.98 MHz) 19.8/19.7.