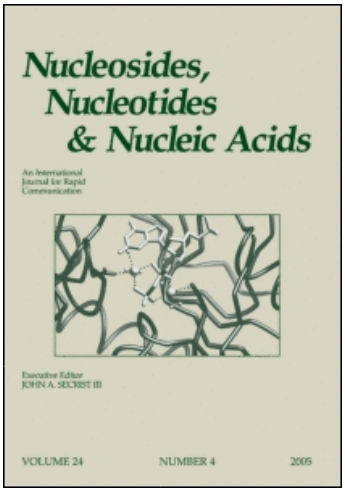

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THE SYNTHESIS OF CARBOCYCLIC 5'-NOR THYMIDINE AND AN ISOMER AS OLIGONUCLEOTIDE MONOMERS

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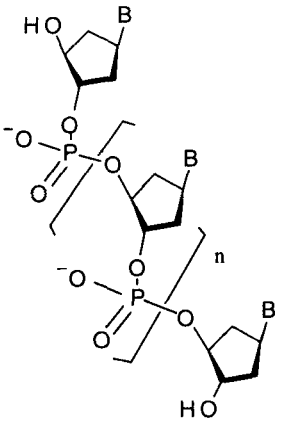
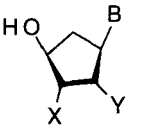
ABSTRACT

The chiral synthesis of (1*S*,3*S*,4*S*)-1-(3,4-dihydroxycyclopent-1-yl)-*1H*-thymine (carbocyclic 5'-nor thymidine, **4**) has been achieved in 5 steps from (+)-(1*R*,4*S*)-4-hydroxy-2-cyclopenten-1-yl acetate (**5**) and N^3-benzoylthymine. Compound **4** is viewed as a monomeric building block for poly-T-like oligomers.

We recently reported[1] the synthesis and properties of oligonucleotides (**1**) possessing carbocyclic 5'-nor-2'-deoxyadenosine (**2**).[2] As a logical outgrowth of this study, the complementary thymidine oligomer (**3**) has been targeted for investigation. To commence that effort, this paper presents the preparation of the necessary pyrimidine monomer **4** in chiral form.



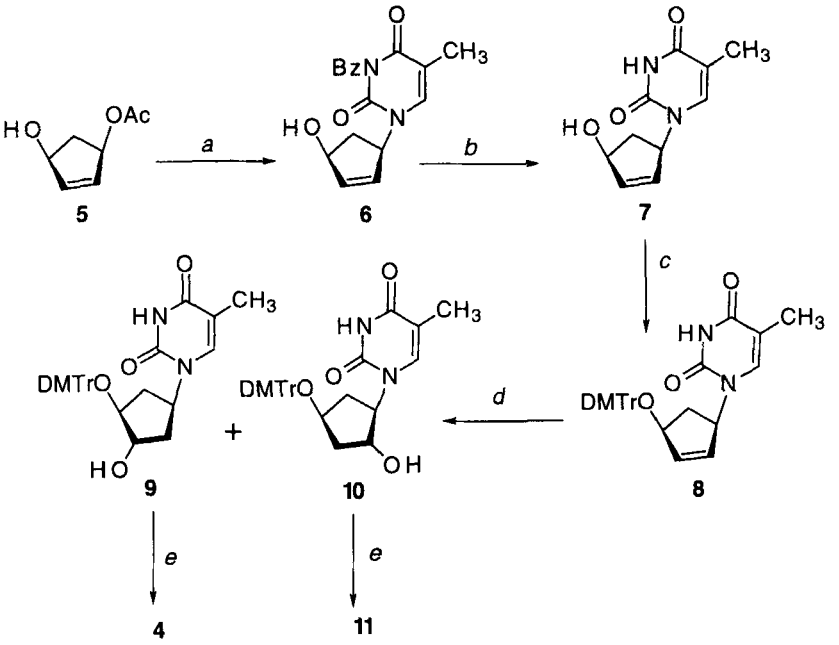
1, B=adenine (A)
3, B=thymine (T)



2, B=A; X=OH; Y=H
4, B=T; X=OH; Y=H
11, B=T; X=H; Y=OH

FIG. 1

*Author to whom correspondence should be addressed



Reaction conditions: *a*, N^3-benzoylthymine, NaH, $Pd(PPh_3)_4$, PPh_3, 55°C; *b*, NH_4OH, MeOH, 120 °C; *c*, DMTrCl, pyridine; *d*, (i) borane-THF; (ii) NaOH, H_2O_2; *e*, *p*-TSA, MeOH/$CHCl_3$.

SCHEME 1

In planning the synthesis of **4** a review of the literature revealed that the racemic dehydro derivative of **4** had been prepared[3] as a precursor to its phosphonate derivative[3a,c] for use as a potential reverse transcriptase inhibitor and chain terminator. These syntheses involved reaction of 6-oxabicyclo[3.1.0]hex-2-ene (cyclopentadiene monoepoxide) with thymine in the presence of a palladium catalyst. However, for our purposes, a chiral synthetic approach was necessary and this began with a palladium promoted reaction between (+)-(1*R*,4*S*)-4-hydroxy-2-cyclopenten-1-yl acetate (**5**)[4] and N^3-benzoylthymine,[5] used to assure coupling only at N-1. The resulting product **6** (Scheme 1) was then deblocked with ammonium hydroxide to **7**.

To direct the planned hydroboration of the 2',3'-double bond to the bottom face of the cyclopentenyl ring of **7**, it was converted into **8** with dimethoxytrityl chloride (DMTrCl). Treatment of **8** with borane yielded a mixture of the monohydroxy derivatives **9** and **10**. Detritylation of **9** provided the desired **4**.[6] Similarly, **10** was converted into **11**, which could serve as another potential monomer for oligonucleotide analogue construction.

The structures for **4** and **11** were assigned using advanced 2-D NMR techniques as described[2] for **2** and its 2'-hydroxy isomer.

While not relevant to the long range oligomeric goals, **4** and **11** were evaluated for their effects on a number of DNA and RNA viruses and found to be inactive.

Experimental. Melting points were recorded on a Meltemp *II* melting point apparatus and are uncorrected. Combustion analyses were performed by M-H-W Laboratories, Phoenix AZ. ^1H and ^{13}C spectra were recorded on a Bruker AC 250 spectrometer (operated at 250 and 62.5 MHz, respectively) all referenced to internal tetramethylsilane (TMS) at 0.0 ppm. The spin multiplicities are indicated by the symbols s (singlet), d (doublet), t (triplet), m (multiplet) and br (broad). Coupling constants (*J*) are expressed in Hz. Optical rotations were measured on a JASCO DIP-360 polarimeter. Reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm Whatman Diamond silica gel 60-F_{254} precoated plates with visualization by irradiation with a Mineralight UVGL-25 lamp. Column chromatography was performed on Whatman silica, 230-400 mesh, 60 Å and elution with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials.

(1*R*,4*S*)-N^3-Benzoyl-1-(4-hydroxy-2-cyclopenten-1-yl)-*1H*-thymine (6). To a solution of N^3-benzoylthymine[5] (4.6 g, 20 mmol) in dry DMSO (50 mL) was added NaH (0.51 g, 95% dry, 20 mmol) and the reaction mixture stirred at rt for 20 min. To this suspension was added tetrakis(triphenylphosphine)palladium (1.13 g, 16 mmol), PPh_3 (0.57 g, 2.16 mmol) and a solution of (+)-(1*R*,4*S*)-4-hydroxy-2-cyclopenten-1-yl acetate (**5**)[4] (3.4 g, 24 mmol) in dry THF (50 mL). This new mixture was stirred at 55 °C for 48 h. The volatiles were removed by rotary evaporation, and the residue removed by filtration, the filtrate diluted with H_2O (250 mL) and extracted into CH_2Cl_2 (5 x 100 mL). The organic layers were combined, washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was then purified via column chromatography eluting with EtOAc/MeOH (9:1). The fractions containing product were combined, and the solvent removed under reduced pressure to give 5.0 g of **6** (82%) as a white solid, mp 179 °C; ^1H NMR ($CDCl_3$) δ 1.55 (dt, *J*=10, 10, and 15, 1H), 1.88 (s, 3H), 2.75 (dt, 1H), 4.82 (m, 1H), 5.48 (m, 1H), 5.62 (br, 1H), 5.85 (dd, *J*=2.5 and 5, 1H), 6.20 (dd, *J*=2.5 and 5, 1H), 7.25 (s, 1H), 7.45-8.00 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 12.6, 38.7, 57.7, 73.8, 110.5, 128.1, 128.9, 132.8, 132.9, 135.1, 135.8, 137.1, 138.2, 152.3, 156.8, 164.3, 165.1. Calcd. for $C_{17}H_{16}N_2O_4$: C, 65.37; H, 5.16; N, 8.97. Found: C, 65.55; H, 5.21; N, 8.76.

(1*R*,4*S*)-1-(4-Hydroxy-2-cyclopenten-1-yl)-*1H*-thymine (7). A solution of **6** (5.0 g, 16 mmol) in NH_4OH/MeOH (1:1, 100 mL) was sealed in a steel

vessel and heated at 120 °C overnight. The reaction vessel was cooled and the solvents removed under reduced pressure. The residue was then purified via column chromatograhpy eluting with EtOAc/MeOH (19:1), and the fractions containing product were combined and then evaporated under reduced pressure to afford 3.4 g of **7** (100%) as a white solid, mp 189-190°C; ^{1}H NMR ($CDCl_3$) δ 1.39 (dt, *J*=10, 10, and 15, 1H), 1.75 (s, 3H), 2.73 (dt, 1H), 4.43 (br, 1H), 4.62 (m, 1H), 5.73 (dd, *J*=2.5 and 5, 1H), 6.09 (dd, *J*=2.5 and 5, 1H), 7.27 (s, 2H), 12.01 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 12.5, 38.6, 58.2, 73.7, 109.4, 127.2, 127.7, 138.5, 152.1, 163.4. Calcd. for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.46. Found: C, 57.60; H, 5.88; N, 13.54.

(1*R*,4*S*)-1-[4-[(4',4''-Dimethoxytrityl)oxy]-2-cyclopenten-1-yl]-*1H*-thymine (8). To a solution of **7** (2.0 g, 9.6 mmol) in anhydrous pyridine (20 mL) was added 4,4'-dimethoxytrityl chloride (3.9 g, 11.52 mmol) and the solution stirred overnight under argon. The reaction was then quenched with MeOH, and the solvents removed under reduced pressure. The residue was co-evaporated with toluene (2 x 20 mL), and purified via column chromatography, eluting with EtOAc/CH_2Cl_2 (1:1). Fractions containing product were combined and then evaporated to give 4.4 g (90 %) of **8** as a white powder, mp 128-129°C; ^{1}H NMR ($CDCl_3$) δ 1.49 (dt, *J*=10, 10, and 15, 1H), 1.77 (s, 3H), 1.99 (dt, 1H), 3.79 (s, 6H), 4.75 (m, 1H), 5.52 (m, 1H), 5.63 (dd, *J*=2.5 and 5, 1H), 5.87 (dd, *J*=2.5 and 5, 1H), 6.84 (m, 4H), 7.15-7.48 (m, 10H), 12.85 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 12.5, 38.6, 55.2, 57.9, 65.8, 76.7, 87.2, 109.4, 113.0, 127.0, 127.7, 128.0, 128.6, 136.2, 136.6, 137.3, 145.4, 151.9, 158.7, 164.3. Calcd. for $C_{31}H_{30}N_2O_5$: C, 72.92; H, 5.92; N, 5.49. Found: C, 72.89; H, 6.18; N, 5.29.

(1*R*,2*R*,4*S*)-1-[2-Hydroxy-4-[(4',4''-dimethoxytrityl)oxy]cyclopent-1-yl]-*1H*-thymine (10) and (1*S*,3*S*,4*S*)-1-[3-Hydroxy-4-[(4',4''-dimethoxytrityl)oxy]cyclopent-1-yl]-*1H*-thymine (9). To a chilled (0 °C), stirring solution of **8** (1.5 g, 2.94 mmol) in dry THF (20 mL) was added borane-THF complex (1.0 M solution in THF, 15.6 mL, 15.6 mmol) by means of a dropping funnel over a period of 15 min under an argon atmosphere. The reaction mixture was stirred for an additional 6 h at 0 °C, at which point H_2O was added dropwise (15 mL), followed by the dropwise addition of 3 M NaOH (23 mL, 69 mmol), and, finally, the addition of H_2O_2 (30%, 42 mL, 379 mmol) over a period of 20 min, while maintaining the temperature at 0 °C. To the crude reaction mixture was then added EtOH (15 mL) and the mixture stirred under argon at rt for 20 h. The mixture was then cooled to 0 °C, sat. Na_2SO_4 solution was added, and the resulting mixture stirred at rt for 1 h. The aqueous layer was extracted with CH_2Cl_2 (5 x 25 mL), washed with brine (2 x 20 mL), dried (Na_2SO_4), and evaporated. The resultant residue was purified via column chromatography on silica gel eluting with CH_2Cl_2/MeOH (98:2). The fractions containing the desired products were combined and

evaporated to afford 0.48 g of **10** (31%) as a white solid, mp 158.5 °C, and 0.26 g of **9** (17%) as a white solid, mp 158.8 °C; ^{1}H NMR for **10**, ($CDCl_3$) δ 1.50 (dt, *J*=10, 10, and 15, 1H), 1.84 (s, 3H), 2.20 (m, 1H), 2.36 (m, 1H), 2.50 (dt, *J*=10, 10, and 12.5, 1H), 3.77 (s, 6H), 3.82 (m, 1H), 4.12 (m, 1H), 4.83 (s, 1H), 5.00 (m, 1H), 6.84 (d, 4H), 7.21-7.57 (m, 10H), 11.19 (br, 1H); ^{13}C NMR ($CDCl_3$) for **10** δ 12.5, 36.9, 39.6, 53.3, 55.5, 77.2, 79.5, 87.8, 111.5, 113.6, 127.4, 128.2, 128.3, 130.2, 136.4, 138.2, 145.4, 151.3, 159.0, 164.0. Calcd. for $C_{31}H_{32}N_2O_6$: C, 70.44; H, 6.16; N, 5.30. Found: C, 70.56; H, 6.26; N, 5.23. ^{1}H NMR for **9**, ($CDCl_3$) δ 1.76 (dt, *J*=10, 10, and 12.5, 2H), 1.85 (s, 3H), 2.00 (m, 1H), 2.20 (dt, *J*=10, 10, and 15, 1H), 3.80 (s, 6H), 4.22 (m, 1H), 4.40 (m, 1H), 4.52 (m, 1H), 4.76 (br, 1H), 6.82 (d, 4H), 7.20-7.49 (m, 10H), 11.32 (br, 1H); ^{13}C NMR ($CDCl_3$) for **9** δ 12.5, 36.5, 42.0, 55.5, 62.9, 72.8, 75.5, 87.5, 111.1, 113.6, 127.3, 128.2, 128.3, 130.2, 136.7, 145.6, 152.3, 158.7, 159.0, 164.0. Calcd. for $C_{31}H_{32}N_2O_6$: C, 68.12; H, 6.27; N, 5.12. Found: C, 68.18; H, 6.10; N, 4.82.

(1*S*,3*S*,4*S*)-1-(3,4-Dihydroxycyclopent-1-yl)-*1H*-thymine (4).[7] To a solution of **9** (0.46 g, 0.85 mmol) in MeOH/$CHCl_3$ (1:1, 10 mL) was added *p*-toluenesulfonic acid (0.10 g) and the mixture stirred at rt for 30 min.[8] To this was then added aqueous NaOH (5 mL, 0.2 M) and the mixture stirred for 15 min and evaporated to dryness under reduced pressure. The residue was then purified via column chromatography eluting with CH_2Cl_2/MeOH (9:1). Fractions containing product were combined and evaporated to afford 0.15 g (79 %) of **4** as a white crystalline solid following recrystallization in MeOH/CH_2Cl_2, mp 179-180 °C; $[\alpha]^{23}_D$ +3.41° (*c* 0.70, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.49 (dt, *J*=10, 10, and 15, 1H), 1.77 (s, 3H), 1.86 (m, 1H), 2.36 (m, 2H), 3.86 (dt, *J*=10, 10, and 12.5, 1H), 3.94 (m, 1H), 4.92 (br, 1H), 5.10 (m, 1H), 5.24 (br, 1H), 7.64 (m, 1H), 11.21 (br, 1H); ^{13}C NMR (DMSO-d_6) δ 12.4, 37.7, 38.0, 52.5, 76.0, 76.6, 109.6, 138.3, 151.2, 163.9. Calcd. for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.00; H, 6.45; N, 12.28.

(1*R*,2*R*,4*S*)-1-(2,4-Dihydroxycyclopent-1-yl)-*1H*-thymine (11). In an analogous manner as was used to obtain **4**, compound **10** (0.23 g, 0.43 mmol) gave 0.07 g (70 %) of **11** as a white crystalline solid following recrystallization in MeOH/CH_2Cl_2, mp 180-180.5 °C; $[\alpha]^{23}_D$ -26.47° (*c* 0.61, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.78 (s, 3H), 1.82 (dt, *J*=10, 10, and 15, 1H), 2.12 (m, 2H), 2.50 (m, 1H), 4.18 (dt, *J*=10, 10, and 15, 1H), 4.43 (m, 1H), 4.52 (m, 1H), 5.20 (br, 1H), 5.25 (br, 1H), 7.65 (m, 1H), 11.19 (br, 1H); ^{13}C NMR (DMSO-d_6) δ 12.3, 39.5, 42.2, 61.6, 67.3, 73.6, 109.4, 138.4, 152.0, 164.0. Calcd. for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.17; H, 6.45; N, 12.24.

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