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A Convenient Synthesis of Racemic 2'-Deoxy Carbocyclic Thymidines Lacking the 5'-Methylene Group

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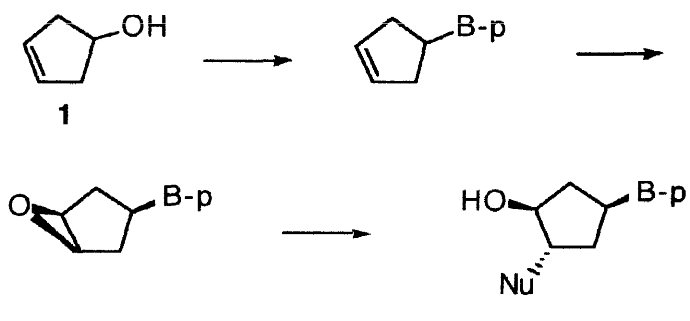
Abstract. A convenient synthesis of racemic 2'-deoxy carbocyclic thymidines lacking the 5'-methylene group is reported. Thus, appropriately protected nucleic acid bases are coupled to 3-cyclopentenol, **1**, via the Mitsunobu reaction. Epoxidation of the protected thymine substituted cyclopentene gives the corresponding syn and anti-epoxides in a 4:1 ratio. Ring opening of the syn-epoxide by a variety of nucleophiles leads to the racemic 2'-deoxy carbocyclic thymidines lacking the 5'-methylene group.

We wish to report a convenient and potentially general method for synthesis of 2'-deoxy carbocyclic nucleoside analogs lacking the 5'-methylene group.[1] As outlined in eq 1, our synthetic strategy involves an early stage attachment of an appropriately protected nucleic acid base to 3-cyclopentenol, **1**, followed by epoxidation. Ring opening of the epoxides by various types of nucleophiles leads to the desired 2'-deoxy carbocyclic nucleosides lacking the 5'methylene with a variety of functional groups at the 3'- position. Direct coupling



(1)

B-p = Protected nucleic acid base

of the nucleic acid bases with cyclopentenol under Mitsunobu conditions and minimum use of protecting groups make the synthetic route very short, simple and economical. Reversing the order of Mitsunobu coupling and epoxidation allows the synthesis of the anti base substituted epoxide.

An ideal starting material, 3-cyclopentenol, **1**, can be prepared from cyclopentadiene in large scale by a two-step epoxidation-reduction sequence in an overall yield of 35%.[2] The Mitsunobu reaction of **1** with protected nucleic acid bases was carried out in dioxane in the presence of triphenylphosphine and diethyl azodicarboxylate (DEAD) at room temperature to give **2a-d**. Thymine or uracil were protected

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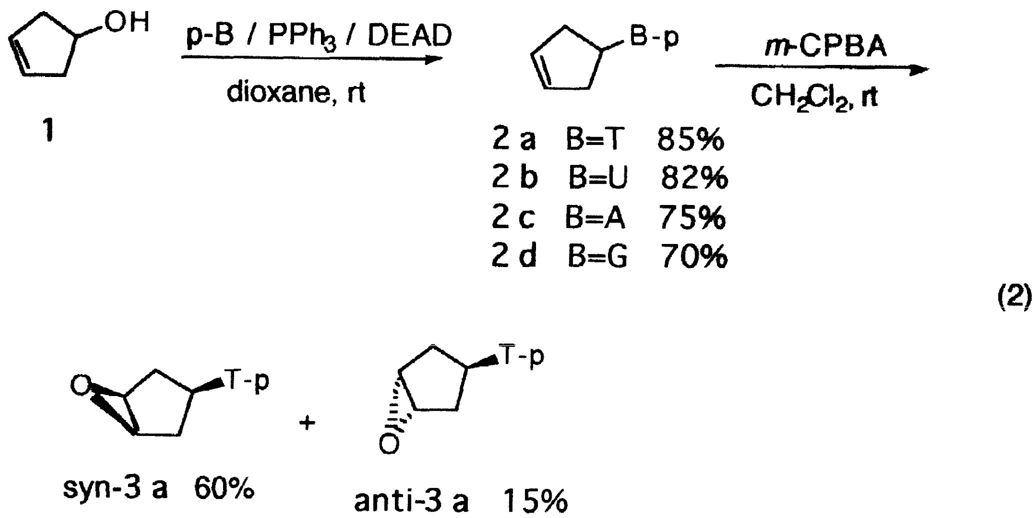
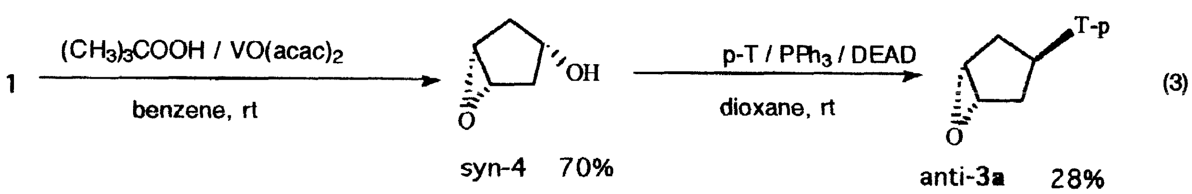
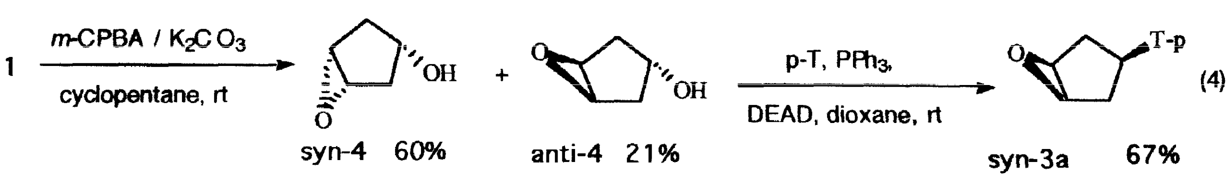
as 3-benzoylthymine (p-T) or 3-benzoyluracil (p-U) which were prepared from thymine or uracil by a two step benzoylation-hydrolysis.[3] Adenine and guanine were protected as 6-Isobutyrylaminopurine (p-A)[4] and N_2-acetyl-O_6-(2-(p-nitrophenyl)-ethyl)guanine (p-G)[5] respectively.

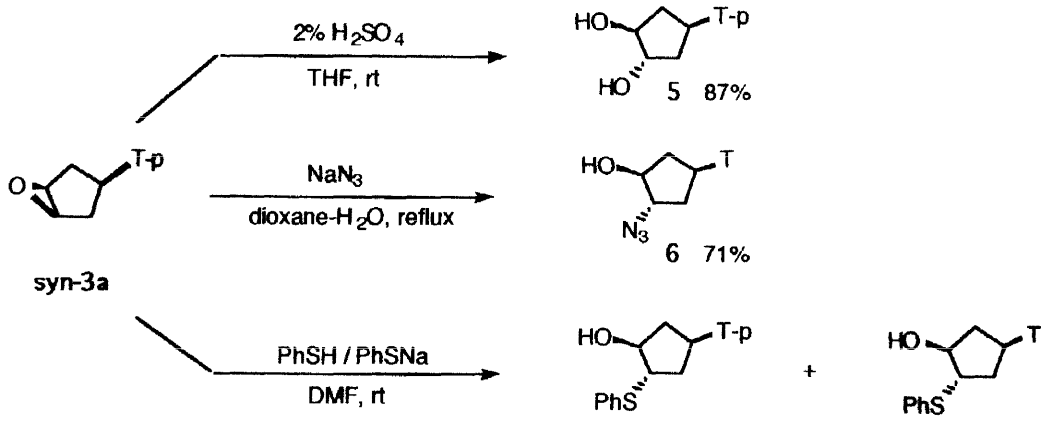


Oxidation of **2a** using *m*-CPBA in methylene chloride gave a 75% yield of syn and anti-**3a**, in a 4 to 1 ratio (eq 2), which were easily separable by column chromatography.[6] The assignment of stereochemistry to syn and anti-**3a** relies on their independent synthesis. Thus the known syn-**4** was prepared in 70% yield by hydroxy directed epoxidation of **1** with *t*-butyl hydroperoxide in benzene in the presence of a catalytic amount of $VO(acac)_2$.[7] Reaction of syn-**4** with **p-T** under Mitsunobu conditions (eq 3) gave a compound in 28% isolated yield which was identical to anti-**3a**. In order to further confirm the configuration of syn and anti-**3a**, **1** was oxidized with m-CPBA in cyclopentane to give the known[8] syn and anti-**4** in a 3:1 ratio. Anti-**4** was separated by chromatography and allowed to undergo Mitsunobu coupling with **p-T** to generate a compound identical to syn-**3a** in 67% yield (eq 4).





In order to test the synthetic utility of **3a** in generating 3,4-disubstituted carbocyclic nucleoside analogs, several ring opening reactions were carried out. Thus, synthesis of (±)-3-benzoyl-((3'α,4'β)-bishydroxycyclopentyl)-1H-thymine, **5**, was accomplished by treating syn or anti-**3a** with dilute sulfuric acid in THF.[1b] Ring opening of syn-**3a** with sodium azide in dioxane-H_2O under reflux was accompanied by simultaneous removal of 3-benzoyl group to give (±)-(3'-α-azido-4'β-hydroxy cyclopentyl)-1H-thymine **6** in an isolated yield of 71%.[9] Treatment of syn-**3a** with PhSH/PhSNa in DMF at room temperature[10] gave the protected thymine, (±)-3-benzoyl-3'-α-phenylthio-4'β-hydroxycyclopentyl)-1H-thymine, **7**, and the deprotected (±)-3'α-phenylthio-4'β- hydroxycyclopentyl)-1H-thymine, **8** in a 1:2.8 ratio.



5 87%

syn-3a

6 71%

7 24%

8 67%

As illustrated in eqs 3 and 4, these procedures permit the preparation of either syn or anti-**3a** as the major product depending upon the order of Mitsunobu coupling and epoxidation. The fact that syn-**4** is the only product of stereospecific epoxidation[7] allows the synthesis of anti-**3a**. The preparation of anti-**3b-d** via this route should also be straightforward. Although amine oxide formation may complicate the preparation of syn-**3c,d**, syn-**3b** should be available via the process in eq 2. These synthetic transformations illustrate the potential versatility of these compounds in leading to carbocyclic nucleoside analogs.

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6. Selected spectroscopic data for **2a-d**, syn and anti-**3a**:

2a: ^{1}H NMR ($CDCl_3$, 250 Mhz) δ 1.94 (s, 3H), 2.41 (dd, J = 3.0, 16.4 Hz, 2H), 2.92 (dd, J = 8.9, 16.7 Hz, 2H), 5.32-5.42 (m, 1H), 5.87 (s, 2H), 7.05 (s, 1H), 7.49 (t, J = 7.8 Hz, 2H), 7.62-7.67 (m, 1H), 7.91-7.95 (m, 2H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 12.5, 39.7, 52.4, 111.6, 129.1, 129.5, 130.5, 131.7, 135.0. 136.4, 149.8, 162.9, 169.4; HRMS calcd for $C_{17}H_{17}N_2O_3$ 297.1239, found 297.1242.

2b: ^{1}H NMR ($CDCl_3$, 300 Mhz) δ 2.42 (dd, J = 3.0, 16.8 Hz, 2H), 2.95 (dd, J = 8.7, 16.8 Hz, 2H), 5.32-5.38 (m, 1H), 5.81 (d, J = 7.9 Hz, 1H), 5.87 (s, 2H), 7.25 (d, J = 7.9 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 7.63-7.68 (m, 1H), 7.93-7.96 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 39.4, 52.9, 102.5, 129.0, 129.2, 130.3, 131.3, 135.0, 140.9, 149.6, 162.0, 169.1; MS *m/z* 283 (M+1, 100); HRMS calcd for $C_{16}H_{15}N_2O_3$ 283.1083, found 283.1078.

2c: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.32 (d, J = 9.0 Hz, 6H), 2.65 (dd, J = 3.3, 15.7 Hz, 2H), 3.04 (dd, J = 8.0, 16.0 Hz, 2H), 3.19-3.30 (m, 1H), 5.37-5.46 (m, 1H), 5.95 (s, 2H), 8.05 (s, 1H), 8.74 (s, 1H), 9.13 (br s, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 19.4, 36.1, 40.5, 53.1, 122.3, 129.2, 141.0, 149.5, 151.5, 152.4, 176.6; HRMS calcd for $C_{14}H_{18}N_5O$ 272.1511, found 272.1520.

2d: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.58 (s, 3H), 2.65 (dd, J = 3.6, 15.6 Hz, 2H), 3.00 (dd, J = 8.1,15.9 Hz, 2H), 3.31 (t, J = 6.9 Hz, 2H), 4.78 (t, J = 6.9 Hz, 2H), 5.19-5.28 (m, 1H), 5.92 (s, 2H), 7.49 (d, J = 8.7 Hz, 2H), 7.83 (br s, 2H), 8.16 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 25.0, 34.8, 39.9, 52.9, 66.5, 117.7, 123.6, 128.9, 129.9, 139.9, 145.7, 146.8, 151.8, 152.7, 160.5, 171.2; HRMS calcd for $C_{20}H_{21}N_6O_4$ 409.1624, found 409.1643.

Syn-3a: Yield 60%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.98 (d, J = 1.2 Hz, 3H), 2.12 (dd, J = 1.8, 16.2 Hz, 2H), 2.49 (dd, J = 10.2, 16.2 Hz, 2H), 3.64 (s, 2H), 5.36-5.43 (m, 1H), 7.48 (t, J = 7.5 Hz, 2H), 7.60-7.65 (m, 1H), 7.76 (d, J = 1.2 Hz, 1H), 7.89-7.92 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 12.5, 35.0, 52.8, 58.3, 110.9, 129.1, 130.4, 131.7, 134.9, 138.3, 150.5, 162.8, 169.4; HRMS calcd for $C_{17}H_{17}N_2O_4$ 313.1188, found 313.1186.

Anti-3a: Yield 15%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.96 (d, J = 1.2 Hz, 3H), 2.11 (dd, J = 9.3, 14.1 Hz, 2H), 2.43 (dd, J = 7.8, 13.8 Hz, 2H), 3.60 (s, 2H), 4.42-4.53 (m, 1H), 7.04 (d, J = 1.2 Hz, 1H), 7.50 (t, J = 7.5 Hz, 2H), 7.63-7.66 (m, 1H), 7.90-7.93 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 12.3, 31.3, 54.4, 55.4, 111.1, 129.2, 130.4, 131.5, 135.2, 138.6, 149.7, 162.8, 169.3; HRMS calcd for $C_{17}H_{17}N_2O_4$ 313.1188, found 313.1185.

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