Diastereomeric 5,6-Dihydrothymidines. Preparation, Stereochemical Assignments, and MnO_2 Oxidation Studies to Thymidines

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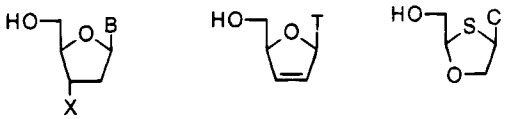
A useful method for the stereospecific synthesis of β-thymidine and β-5,6-dihydrothymidine nucleosides is described. Condensation of methyl 2-formylpropionate and methyl methacrylate with oxazolines **8** furnished the corresponding 2,2′-anhydrothymidine **11** and a 2:1 diastereomeric mixture of 2,2′-anhydro-5,6-dihydrothymidine **10**, respectively. While DDQ oxidation of **10** furnished **11**, active MnO_2 resulted in a selective dehydrogenation hitherto unreported in nucleoside chemistry. The minor diasteromer **10b** was quantitatively converted to **11**, leaving **10a** unchanged. A plausible explanation for this selectivity was based on the stereochemistry at C5 which was determined by one-dimensional NOE studies.

Sugar-modified nucleosides have assumed a major role in antiviral chemotherapy. Among these, AZT (**1**), ddC (**2**), ddI (**3**), and D_4T[1] (**4**) are in clinical use, and 3TC[2] (**5**) is expected to reach the clinical stage in the future. Although the structures of these nucleosides are varied, they all fall in the 2′-deoxy nucleoside category.



1. X = N_3, B = Thymine
2. X = H, B = Cytosine
3. X = H, B = Hypoxanthine

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Unlike their ribo counterparts, the synthesis of 2′-deoxy nucleosides from 2-deoxyribofuranose leads to the formation of α,β mixtures[3] needing chromatographic separation prior to biological evaluation. There have been attempts to overcome this problem to produce, in most cases, the desirable β-isomer. Such efforts include the use of naturally occurring 2′-deoxy nucleosides such as thymidine as the starting material,[4] 2′,3′-deoxygenation of β-D-ribofuranonucleosides,[5] proper choice of a metal catalyst to favor the β/α ratio,[6] and the use of 2′-α-phenylseleno[7] and 2′-α-phenylthio[8] functionalities to direct the formation of β-isomers.

Sugar chirality has been used to influence the stereochemistry of the nucleoside bond. 3-α-Substituted 2-deoxyribofuranoses have been used to direct the approach of the base in the glycosidation step.[9] The chirality at C4 in the sugar has also been successfully employed for the exclusive formation of β-nucleosides.[10]

In earlier work, the 2*S*-chirality of D-arabinose was used to prepare a 1,2-*cis*-fused tetrahydrofuranooxazoline **6** for the construction of the heterocyclic base. This took place by reacting **6** with a number of propargylate esters and nitriles to make the corresponding uridine and cystosine derivatives.[11] The use of propargylates in this reaction precludes the synthesis of thymidine derivatives since the placement of an α-methyl group would violate the valence of the α-carbon. On the other hand, the use of methacrylates would provide thymidine derivatives, provided the oxidation state of the system is maintained. This has been accomplished by oxidizing either the β- or the methyl carbons. When β-bromo- or β-methoxy methacrylate as well as methyl 3,3-dimethoxy-2-methyl- and 2-formylpropionates were condensed with oxazoline **8**, the corresponding 5-methylpyrimidines **11** were formed (Scheme 1).[12] Similarly, α-bromomethyl acrylate derivatives gave pyrimidine nucleosides.[13] In a recent publication, we reported on an attractive method for the preparation of methyl 2-formylpropionate and its condensation with the 3-deoxy derivative of **8** to give D_4T.[14] Repetition of this chemistry using aminooxazoline **8** resulted in an

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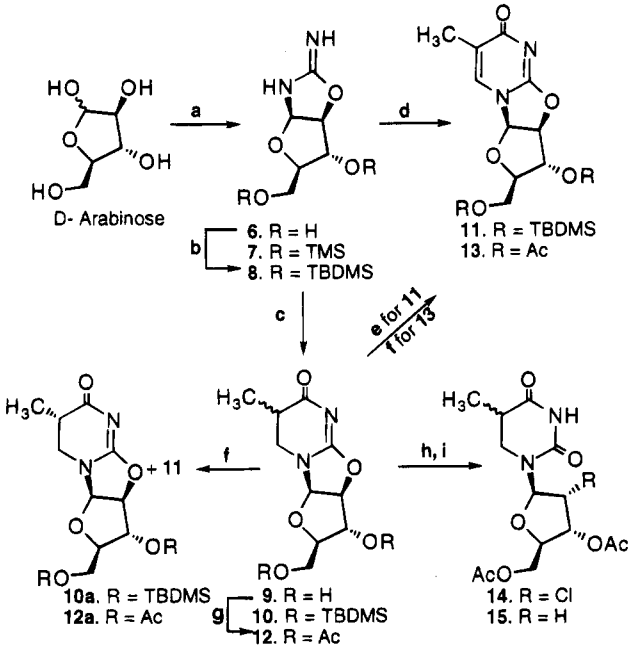
Scheme 1



[a] (a) Reference 11a; (b) TBDMSCl, imidazole, DMF, 87%; (c) 2-methyl methacrylate, 100 °C, 16 h, 80%; (d) methyl 2-formylpropionate, benzene, reflux, 66%; (e) DDQ, benzene, reflux, 9 h, 70%; (f) MnO_2, toluene, reflux, 24 h, 33% conversion; (g) Ac_2O, pyridine, 12 h, 100%; (h) AcCl, acetonitrile, reflux, 4 h, 80%; (i) *n*-Bu_3SnH, AIBN, toluene, 2 h, 83%.

improvement in the yield of **11** from 26 to 66%. Although the oxidized methacrylate approaches are synthetically attractive, they still suffer from a poor yielding step. In this paper, we report on a further improvement of this approach along with an unusually selective MnO_2 oxidation reaction of dihydrothymidines to the corresponding thymidines.

5,6-Dihydrothymidines can serve as intermediates for the preparation of 5-oxygenated derivatives.[15] This has been recently demonstrated in the synthesis of 5-peroxy-5,6-dihydrothymidine for incorporation into oligonucleotides to explore DNA strand scission chemistry.[15a] This synthetic utility and the ready availability of methyl methacrylate prompted us to investigate its condensation with oxazolines **7** and **8** as a convenient route to prepare 5,6-dihydrothymidines. In an earlier report, Hall and coworkers carried out a similar condensation of **6** with methyl methacrylate where the desired product **9** was obtained as a 2:1 diastereomeric mixture in 36% yield.[16] However, when the bis-silyl derivatives **7** and **8** were used, anhydro nucleosides **9** and **10** were obtained in 79 and 80% yield, respectively. During the condensation reaction of **7** with methyl methacrylate, the TMS groups were cleaved by methanol which is formed as a byproduct in the reaction.

Having obtained **10**, we looked for suitable methods to introduce the 5,6-double bond. Oxidation of **10** with DDQ in refluxing benzene led to the formation of the desired product **11** in 70% yield. ^1H NMR analysis of **11** showed signals supporting the structure. A methyl doublet at δ 1.96 ppm coupled to a proton at 7.18 ppm (J = 1.26 Hz) are two characteristic absorptions of thymines.

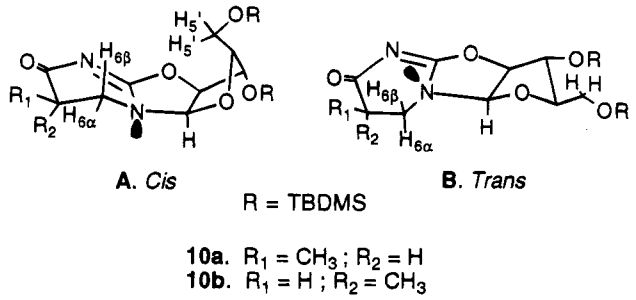


Figure 1. *Cis* and *trans* forms of diastereomeric mixture **10**.

Due to the high cost of DDQ, several other oxidizing agents such as NBS, *o*- and *p*-chloranil, copper bromide, and Br_2/HOAc and catalytic dehydrogenations were tried. All these reactions either resulted in decomposition of the starting material or gave very poor yields of the product. However, when **10** was treated with activated MnO_2 in refluxing xylene, toluene, benzene, or $CHCl_3$, only the minor diastereomer was oxidized to **11** while the major diastereomer remained unchanged. This unusual finding prompted us to examine the reaction further, necessitating structural determination of the diastereomeric pair.

The pure diastereomers **10a** and **10b** were obtained by careful preparative thin layer chromatography. Homo COSY studies led to the identification, but not the stereochemical orientation, of the protons at C6 in both isomers appearing as doublets of AB quartets, δ 3.74 and 3.23 ppm in the major isomer and δ 3.63 and 3.24 ppm in the minor isomer. These differences, however, could not be used to assign the stereochemistry at C5. Construction of molecular models led to two different frameworks where the lone pair of electrons at N1 can be either *cis* (**A**) or *trans* (**B**) to the anomeric proton at C1′. While the *cis* form is L-shaped, the *trans* is rather planar, resulting in varied distances between identical protons in both forms (Figure 1).

Differentiation between these two forms as well as between diastereomers **10a** and **10b** was accomplished by one-dimensional NOE experiments. The lack of observed dipolar relaxations between protons 6 and 5′ led us to assign the structure of diastereomer **10** as the *trans* form **B**. Similarly, the known α-orientation of the anomeric proton was used to identify the 6α- and 6β-protons. These, in turn, were used to assign the stereochemistry of the 5-proton as α and β in **10a** (major) and **10b** (minor), respectively.

The failure of the major isomer **10a** to be oxidized could not be easily explained. However, examination of molecular models led us to speculate that steric effects of the bulky TBDMS group prevented the approach of the oxidant from the β-face of the molecule where the 5-proton is oriented. On the basis of this rationale, other derivatives were prepared for oxidation. Diacetate **12**, prepared from **9**, gave the same results, forming a mixture of **12a** and **13** as evidenced by ^1H NMR analysis, suggesting that the 5′-acetate group still hinders the β-side of the molecule.

Since the 2,2′-anhydro bond is responsible for the rigid structure of **10**, we decided to open this bond with the hope of relieving the steric effects exerted by the substituents at C5′. Cleavage of the anhydro bond in **12** with

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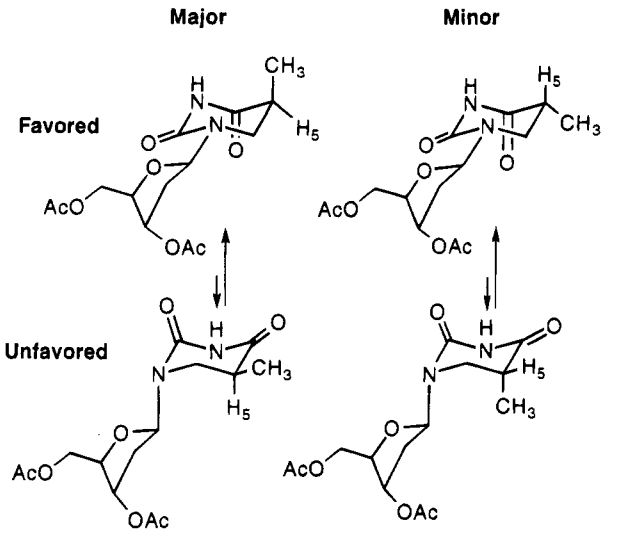

Figure 2. Conformations of **15**.

acetyl chloride furnished the 2′-chloroderivative **14** which was reductively dehalogenated with *n*-Bu_3SnH to give the corresponding 2′-deoxy derivative **15** as a diastereomeric mixture. When this was subjected to MnO_2 oxidation, again, only the minor isomer was converted to thymidine 3,5-diacetate. This result can no longer be rationalized on steric grounds. A more plausible explanation was arrived at on the basis of the stereochemical orientation of the 5-proton.

It is well-known that MnO_2 oxidations proceed preferentially for axial protons compared to equatorial protons.[17,18] Figure 2 depicts the preferred conformations of the major and minor isomers of **15**, where the 5-proton is equatorial in the former and axial in the latter. However, it can be argued that the other chair conformations would reverse these orientations, predicting results opposite to those found experimentally. As can be seen in Figure 2, such conformations are energetically unfavorable since they create severe 1,3-diaxial interactions in the minor isomer and place the bulky sugar in an axial position in the major isomer.

In summary, an interesting MnO_2 dehydrogenation reaction has been described. Although MnO_2 oxidations have been extensively reviewed,[17,18] apparently no mention of a similar reaction has been made in the nucleoside literature. Attempts to capitalize on the synthetic utility of this reaction by preparing 5-hydroxy-5,6-dihydrothymidine[15] as DNA oxidative degradation metabolites are being pursued.

Experimental Section[19]

2,2′-Anhydro-1-[3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-arabinofuranosyl]-5,6-dihydrothymine (10). A mixture of aminooxazoline **8** (1.01 g, 2.51 mmol) and methyl methacrylate (1.34 mL, 12.55 mmol) stabilized with hydroquinone (0.01%) was heated at 90 °C for 16 h. Excess methyl methacrylate was removed under reduced pressure, and the residue obtained was purified by silica gel column chromatography using $CHCl_3$–hexanes (3:1) to afford **10** (0.98 g, 79%) as a diastereomeric mixture: mp 116–117 °C.

Careful separation of the two isomers by preparative TLC (EtOAc–hexanes–MeOH, 40:60:1) gave pure **10a** and **10b** in the order of increasing polarity.

10a: $[\alpha]^{25}_D$ −114.47 (*c* 0.76, $CHCl_3$); ^1H NMR δ 0.05 (s, 6H), 0.13 (s, 3H), 0.15 (s, 3H), 0.88 (s, 9H), 0.91 (s, 9H), 1.25 (d, *J* = 7.0 Hz, 3H), 2.56 (ddq, *J* = 10.0, 7.6, 5.0, 7.0 Hz, 1H), 3.22 (dd, *J* = 11.9, 10.0 Hz, 1H), 3.48 (dd, *J* = 10.0, 7.6 Hz, 1H), 3.63 (dd, *J* = 10.7, 5.0 Hz, 1H), 3.73 (dd, *J* = 11.9, 7.3 Hz, 1H), 4.05 (ddd, *J* = 7.60, 5.0, 2.80 Hz, 1H), 4.54 (ddt, *J* = 2.8, 1.4, 1.0 Hz, 1H), 4.97 (ddd, *J* = 5.7, 1.0, 0.35 Hz, 1H), 5.74 (d, *J* = 5.7 Hz, 1H).

10b: $[\alpha]^{25}_D$ −33.72 (*c* 0.605, $CHCl_3$); ^1H NMR δ 0.04 (s, 6H), 0.12 (s, 3H), 0.14 (s, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 1.25 (d, *J* = 6.9 Hz, 3H), 2.62 (ddq, *J* = 11.8, 7.4, 6.9 Hz, 1H, 5H), 3.24 (dd, *J* = 11.8, 11.8 Hz, 1H), 3.41 (dd, *J* = 10.6, 7.4 Hz, 1H), 3.57 (dd, *J* = 10.6, 5.2 Hz, 1H), 3.63 (dd, *J* = 11.8, 7.4 Hz, 1H), 4.03 (ddd, *J* = 7.4, 2.5, 5.23 Hz, 1H), 4.51 (ddd, *J* = 2.5, 1.1, 0.6 Hz, 1H), 4.92 (ddd, *J* = 5.4, 1.1, 0.5 Hz, 1H), 5.74 (d, *J* = 5.4, 1H); ^{13}C NMR δ −5.42, −5.38, −4.91, 13.75, 17.88, 18.254, 25.60, 25.81, 33.55, 45.27, 62.26, 75.95, 87.76, 88.59, 90.84, 165.65, 180.53. Anal. Calcd for $C_{22}H_{42}O_5N_2Si_2$: C, 56.13; H, 8.99; N, 5.95. Found: C, 56.29; H, 8.85; N, 5.85.

2,2′-Anhydro-1-β-D-arabinofuranosyl-5,6-dihydrothymine (9). A mixture of aminooxazoline derivative **7** (3.18 g, 10 mmol), hydroquinone (0.01%), and methyl methacrylate (15 mL) was heated at 90 °C for 16 h. After this period, MeOH (5 mL) was added and the reaction mixture was heated for 1 h. Excess solvents were removed, and the residue obtained was recrystallized from MeOH to afford **9** (1.94 g, 80%): mp 196–197 °C (lit.[16] mp 196.5–198 °C).

2,2′-Anhydro-1-[3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-arabinofuranosyl]thymine (11). Method A. A benzene (5 mL) solution of compound **10** (0.1 g, 0.213 mmol) and dichlorodicyanoquinone (DDQ, 0.05 g, 0.22 mmol) was refluxed for 9 h. Completion of the reaction was determined by TLC. The reaction mixture was cooled and then filtered through a neutral alumina column. Eluting with $CHCl_3$ afforded compound **11** (0.07 g, 70%) as a white solid: mp 140–141 °C; ^1H NMR δ 0.03 (s, 12H), 0.81 (s, 9H), 0.88 (s, 9H), 1.96 (d, *J* = 1.26 Hz, 3H), 3.33 and 3.53 (q_{AB}, *J* = 11.05, 7.36, 4.78 Hz, 2H), 4.12 (ddd, *J* = 2.50, 4.78, 7.36 Hz, 1H), 4.59 (dd, *J* = 0.73, 2.5 Hz, 1H), 5.05 (dd, *J* = 5.51, 0.73 Hz, 1H), 6.10 (d, *J* = 5.51 Hz, 1H), 7.18 (d, *J* = 1.26 Hz, 1H). Anal. Calcd for $C_{22}H_{40}O_5N_2Si_2$: C, 56.37; H, 8.60; N, 5.98. Found: C, 56.21; H, 8.49; N, 5.79.

Method B. A benzene solution (15 mL) of compound **8** (1.12 g, 3 mmol) and methyl 2-formylpropionate (3.48 g, 30 mmol) was refluxed for 20 h. Residual benzene was removed under reduced pressure, and the crude product was chromatographed over silca gel (5% MeOH–$CHCl_3$) to obtain a white solid (920 mg, 66%) with spectral data identical to those of the product obtained in method A.

2,2′-Anhydro-1-(3′,5′-di-*O*-acetyl-β-D-arabinofuranosyl)-5,6-dihydrothymine (12). To a stirred solution of **9** (0.242 g, 1 mmol) in pyridine (5 mL) was added acetic anhydride (0.5 mL, 5.3 mmol), and stirring was continued for 12 h at rt. The mixture was poured into water (10 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic solutions were washed with cold 1 N HCl (2 × 5 mL) and water (2 × 5 mL) and dried ($MgSO_4$). Evaporation of the solvent gave the diacetate **12** quantitatively: ^1H NMR ($CDCl_3$) δ 1.21 (d, *J* = 6 Hz, 3H), 2.03 (s, 3H), 2.11 (s, 3H), 2.28–2.86 (m, 1H), 2.99–3.38 (m, 1H), 3.46–4.49 (m, 4H), 5.03–5.33 (m, 2H), 5.79 (d, *J* = 6 Hz, 1H). Anal. Calcd for $C_{14}H_{18}O_7N_2$: C, 51.53; H, 5.56; N, 8.59. Found: C, 51.41; H, 5.68; N, 8.48.

1-(3′,5′-Di-*O*-acetyl-2′-chloro-2′-deoxy-β-D-ribofuranosyl)-5,6-dihydrothymine (14). Compound **12** (0.97 g, 2.97 mmol) was dissolved in dry CH_3CN (50 mL) and the solution heated to reflux. Acetyl chloride (8 mL) was then added, and refluxing was continued for 4–5 h. The residue obtained after concentration of the reaction mixture was dissolved in CH_2Cl_2 (20 mL), washed with water, dried ($MgSO_4$), and concentrated to give **14** as 2:1 diastereomeric mixture in 90% yield along with

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traces of N3 acetylated product, which could be removed by crystallization from methanol: ^{1}H NMR δ 1.28 (d, J = 6.9 Hz, minor) and 1.29 (d, J = 6.9 Hz, major, 1H), 2.11 (s, 3H), 2.17 (s, 3H), 2.70–2.78 (m, 1H), 3.31 (doublet of AB quartet center, $\Delta\nu$ = 123 Hz, J = 12.0, 10.5, 6.0 Hz, major) and 3.33 (doublet of AB quartet center, $\Delta\nu$ = 54 Hz, J = 12.0, 9.0, 5.4 Hz, minor, 2H), 4.20–4.41 (m, 4H), 5.23 (dd, J = 5.7, 3.2 Hz, minor) and 5.26 (dd, J = 5.8, 3.1 Hz, major, 1H), 6.06 (d, J = 7.7 Hz) and 6.08 (d, J = 7.6 Hz, 1H), 8.51 (bs, 1H, D_2O exchangeable). Anal. Calcd for $C_{14}H_{19}ClN_2O_7$: C, 46.35; H, 5.28; N, 7.72. Found: C, 46.16; H, 5.04; N, 7.56.

1-(3′,5′-Di-*O*-acetyl-2′-deoxy-β-D-ribofuranosyl)-5,6-dihydrothymine (15). Tributyltin hydride (0.82 mL, 2.9 mmol) and azabisisobutyronitrile (0.003 g) were added to compound **14** (0.362 g, 1 mmol) dissolved in dry toluene (5 mL), and the mixture was refluxed for 2 h. The residue obtained after concentrating the reaction mixture was purified by column chromatography over silica gel using EtOAc–MeOH (95:5) as eluent to provide **15** (0.275 g, 83%) as a 2:1 diastereomeric mixture: ^{1}H NMR δ 1.2 (d, J = 6.0 Hz, 3H), 1.8–2.3 (m, 8H), 2.4–3.66 (m, 1H), 3.9–4.3 (m, 3H), 4.9–5.1 (m, 1H), 6.1–6.33 (two sets of triplets, 1H), 8.3 (bs, 1H, D_2O exchangeable). Anal. Calcd for $C_{14}H_{20}N_2O_7$: C, 51.22; H, 6.14; N, 8.53. Found: C, 51.02; H, 5.98; N, 8.41.

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