Efficient and Stereoselective Synthesis of 3′-Deoxy 3′-*C*-Branched-Chain Substituted Thymidine

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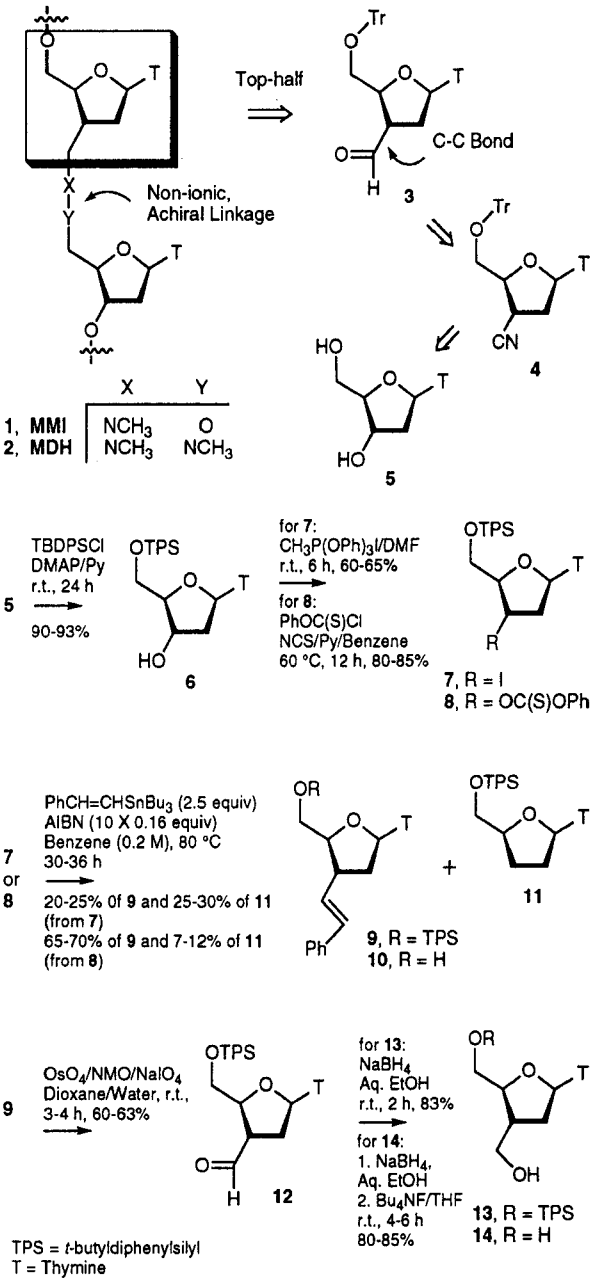
In this report, we provide for the first time a facile, efficient, and stereoselective synthesis of 1-[5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-3-*C*-formyl-β-D-*erythro*-pentofuranosyl]thymine (**12**), using an intermolecular radical C–C bond formation reaction. The utility of this compound for antisense application is discussed and, as an extension, **12** was converted into 1-[2,3-dideoxy-3-*C*-(hydroxymethyl)-β-D-*erythro*-pentofuranosyl]thymine (**14**), a potent antiviral and antitumor agent.

In antisense oligonucleotide (AO) research, the interest for design of novel, neutral and achiral linkages that replace the native phosphodiester bond has recently gained much attention.[1] We have identified methylene(methylimino) (**1**, MMI) and methylene(dimethylhydrazo) (**2**, MDH) linkages (Scheme) as potentially useful backbone modifications for the rational design of a second generation AO.[2] The MMI (**1**) and MDH (**2**) linkages were synthesized by a convergent approach in which 2′-deoxynucleosides were functionalized at the 3′- or 5′-positions and coupled with another nucleoside to establish the novel linkage between the sugar moieties of the two nucleosides. The commercial availability of 2′-deoxynucleosides makes this approach very attractive for the scale-up of 3′- or 5′-modified nucleoside analogs. The 3′-deoxy-3′-*C*-formyl nucleoside analogs **3** or **12** constitute the top half of the MMI and MDH linkages (Scheme). Moreover, compound **3** is also a key intermediate for the synthesis of our new backbone modifications containing an amide function as replacement for the natural phosphodiester linkage.[16,19] Thus, it became important for us to develop an efficient and large-scale synthesis of such compounds for the success of our AO program.



Scheme

Additionally, we realized that a series of 3′-*C*-branched-chain sugar nucleosides have been synthesized via multistep procedures and the compounds were evaluated as antiviral and anticancer agents.[3] The interesting biological activity of these sugars and nucleosides have also triggered studies of their conformational analysis using NMR spectroscopy and molecular modelling.[4] More recently, certain 3′-deoxy-3′-*C*-hydroxymethyl nucleosides were shown to be effective antiviral (HIV-1)[5] and anticancer (L1210, P388)[6] agents. Such reports prompted us to explore further the possiblity of developing a methodology which is general for the *C*-branched nucleosides.[7]

A straightforward synthesis of 3′-*C*-formylthymidine **3** via DIBAL-H reduction of 3′-deoxy-3′-*C*-cyanothymidine **4** has been reported by us.[2] The synthesis of **4** via the radical reaction of Parkes et al.[8] proved to be nonstereoselective in our hands[9] and by others.[10] Even accepting the nonstereoselectivity of this process, the expense, toxicity and large molar excess of *tert*-butyl isocyanide made this method unattractive for scale-up.

A C–C bond forming radical addition–elimination reaction has been reported to be preparatively useful and performed under mild, neutral and safe conditions.[11] Therefore, we decided to investigate this method as an alternative radical reaction which provided for complete stereocontrol on C–C bond formation and was amenable to cost-effective and non-hazardous scale-up to **12**. The reaction involved regioselective addition of a *C*-centered

radical to β-tributylstannylstyrene (TBSS) followed by β-elimination of a $Bu_3Sn\cdot$ species. We reported[12] an intermolecular C–C bond formation reaction utilizing 3′-deoxy-3′-iodo-5′-*O*-tritylthymidine as a radical precursor. Thus, for the present study iodo nucleoside **7** became an attractive starting material. Using a modified literature procedure, the 5′-*O*-TBDPS protected thymidine **6** was prepared on a large-scale (> 1 mol) from commercially available thymidine **(5)** in 90–93% yield. Crystalline **6** was then iodinated utilizing Moffatt's procedure in 60–65% yield.[13]

In a test reaction, a degassed solution of **7** in benzene containing TBSS and 2,2′-azobisisobutyronitrile (AIBN) was heated to reflux for 3 hours under an argon atmosphere. TLC analysis of the reaction mixture indicated formation of two major and two minor products. Silica gel chromatography of the mixture provided the expected 3′-*C*-styryl-**9** (20–25%) and 2′,3′-dideoxynucleoside **11** (25–30%). Even though the yield of desired product **9** was low, a high selectivity for the *erythro* configuration was achieved. Among the minor unidentified products, the *threo* isomer was not detected. The high stereoselectivity observed in the reaction is due to the presence of bulky substituents. A 5′-*O*-TBDPS group on one side and a thymine base on the other side of the molecule completely blocks the top face of the nucleoside. This forces the incoming styryl species to approach from the least hindered α-face of the 3′-*C*-center radical. Similar observations of selectivity have been reported by others.[14]

In order to reduce the amount of side product **11** formed during the reaction described above, we turned our attention to another radical precursor. Xanthate esters have been shown[15] to be an effective source of alkyl radicals. This, coupled with our success[16] with xanthates in C–C bond formation on nucleosides, prompted us to prepare 3′-*O*-phenylthiocarbonate ester **8** as a radical precursor. We have developed a practical and convenient method for the acylation of **6** using a modified Barton protocol.[17]

A solution of phenoxythiocarbonyl chloride in benzene was added dropwise to a stirred mixture of **6**, *N*-hydroxysuccinimide and pyridine in benzene at ca. 50 °C under an argon atmosphere. The acylation was quantitative and completed in 3–4 hours. The reaction mixture was cooled (10 °C) and the precipitated pyridine hydrochloride was separated by filtration. The filtrate was pure enough for the subsequent radical reaction. A sample of xanthate **8** was fully characterized by NMR and FAB mass spectroscopy, and elemental analysis.

The radical addition reaction was performed by portionwise addition of AIBN (10 × 0.16 mol equiv) over 35 hours at 80 °C under an atmosphere of argon to a degassed solution containing crude xanthate **8** (1 mol equiv) and TBSS (2.5 mol equiv) in benzene (0.2 M solution). Standard work up followed by flash chromatography on silica gel furnished ca. 70% the desired 3′-*C*-styryl nucleoside **9** and ca. 10% of the undesired dideoxynucleoside **11**. The yields of **9** and **11** varied between ± 5% of the reported values depending on the quality of TBSS and AIBN used for the reaction, the reaction time, and the control of the internal temperature of the reaction mixture. The structures of **9** and **11** were established by COSY and NOESY NMR techniques, FAB mass spectroscopy and elemental analysis. It is noteworthy that this reaction was stereoselective, high yielding, and utilized only a moderate excess of the styrene reagent (TBSS). The presence of the styryl group was further confirmed by removal of the TBDPS group from **9** with Bu_4NF to afford **10** (80–85%). Subsequently, the desired builing block **12** for the construction of MMI and MDH linkages was obtained by a two-step one-pot reaction. First, *cis*-hydroxylation of **9** with catalytic OsO_4 in the presence of *N*-methylmorpholine oxide, and, second, cleavage of the intemediate *cis*-diol with $NaIO_4$ to furnish **12** in ca. 60% yield.

Furthermore, 3′-*C*-formyl nucleoside **12** was reduced with $NaBH_4$/aq. EtOH to furnish 3′-*C*-hydroxymethyl nucleoside **13** in 83% yield. Deblocking of **13** with Bu_4NF afforded the antiviral/antitumor agent **14** in 85% yield. The UV and ^1H NMR spectral data of our sample of **14** were identical with the data reported in the literature for the same compound prepared via a completely different and multistep synthesis.[18]

In conclusion, the chemistry described herein represents a stereoselective free-radical reaction that introduces formyl or hydroxymethyl equivalents into carbohydrates and nucleosides. The methodology developed for the synthesis of *C*-branched nucleosides is versatile and should be applicable to other molecules of biological interest. Its attractiveness stems from its use of readily available reagents. In particular, the *C*-styryl group may serve as a protected or masked form of a formyl group during multistep synthetic transformations and could be unmasked to the formyl group under mild oxidative-cleavage conditions. We are currently investigating the extension of this methodology to the synthesis of various carbohydrates and nucleosides.[19]

Melting points (uncorrected) were determined in a Thomas-Hoover capillary melting-point apparatus. Elemental analyses were performed by Quantitative Technologies, Bound Brook, New Jersey, USA. TLC was performed on plates of silica gel 60F-254 (EM Reagents). Silica gel (ICN32/63; 60Å) was used for flash column chromatography. All solvents used were reagent grade. The detection of nucleoside components on TLC was by UV light, and with 10% sulfuric acid in methanol spray followed by heating. Evaporations were conducted under reduced pressure, with the water-bath temperature below 30 °C. The chemical-shift values are expressed in parts per million (ppm) δ values, relative to tetramethylsilane as the internal standard. Preparative HPLC was performed utilizing the Waters 600E system. FD = Field Desorption.

1-[5-*O*-(*tert*-Butyldiphenylsilyl)-2-deoxy-β-D-*erythro*-pentofuranosyl]thymine (6):[20]

To a mixture of thymidine (**5**, Chem-Impex International, Wood Dale, Illinois, USA) (400 g, 1.65 mol), 4-dimethylaminopyridine (2 g, 1.63 mmol) in pyridine (2.2 L) was added dropwise *tert*-butyldiphenylsilyl chloride (TBDPSCl)(FMC Corporation, Lithium Division, Gastonia, North Carolina, USA) (347 g, 1.26 mol) over 1 h at r.t. under an Ar atmosphere. The reactants were allowed to stir at r.t. for 24 h. An additional amount of TBDPSCl (150 g, 0.5 mol) was added in an identical manner and stirring was continued for 24 h. TLC (CH_2Cl_2/MeOH; 93:7) of the reaction mixture showed

a single major spot for the desired product (R_f 0.32) along with traces of unreacted **5** (R_f 0.05). The solution was concentrated (> 45 °C; 2 mmHg) to obtain a mobile syrupy residue. The residue was diluted with MeOH (1.5 L) and the clear solution was slowly poured into vigorously stirred Et_2O/hexanes/water (1:4:11.5; 16.5 L) over 15–20 min. A few crystals of pure **6** as a seeding agent were added and the biphasic mixture was stored at r.t. for 1 h. Colorless crystalline material was separated from the suspension by filtration and the powder washed with distilled water (3 × 3 L). The product **6** was dried in vacuo (> 50 °C; 2 mmHg) over P_2O_5 to a constant weight (743 g, 93%), mp 162 °C (Lit.,[20] 170–171 °C).

MS (FD): m/z = 481 $(M)^+$, 423 $(M-H-C_4H_9)^+$.

1-{5-*O*-(*tert*-Butyldiphenylsilyl)-3-*O*-[(phenoxy)thiocarbonyl]-2-deoxy-β-D-*erythro*-pentofuranosyl}thymine (8):

A suspension of **6** (209 g, 0.44 mol), *N*-hydroxysuccinimide (20.0 g, 0.17 mol) and pyridine (120 g, 1.51 mol) in anhydr. benzene (1.4 L) was degassed with Ar while stirring vigorously at ca. 50–55 °C. A solution of phenylchlorothionoformate (Lancaster Synthesis, Windham, New Hampshire, USA) (125 g, 0.72 mol) in benzene (0.4 L) was added over 1 h to the stirred reaction mixture such that internal temperature was maintained below 60 °C (caution! exothermic reaction). The stirring was continued at 68–70 °C for 3–4 h under an Ar atmosphere. TLC (CH_2Cl_2/MeOH, 93:7) of the reaction mixture indicated that all of the starting material was consumed, and only one major spot for the product (R_f 0.79) was observed. The reaction mixture was then cooled (ca. 15 °C), whereupon pyridine hydrochloride crystallized out of the solution. Filtration of the mixture under an Ar atmosphere provided a clear solution free of salts. The solids (pyridine hydrochloride) were further washed with anhydr. benzene (2 × 100 mL) to recover the product. The combined filtrates were found to be pure enough for the next step and the benzene solution was carried over to the next reaction as such. However, a small sample of xanthate **8** was purified by silica gel column chromatography for complete characterization. Our attempts to crystallize a sample of **8** failed, therefore, following data were gathered from a sample which remained as a colorless glass.[16]

MS (FD): m/z = 617 $(M)^+$, 560 $(M-C_4H_9)^+$.

^{1}H NMR ($CDCl_3$): δ = 1.11 (s, 9H, CMe_3), 1.65 (s, 3H, 5-CH_3), 2.37 (m, 1H, 2′-H_β), 2.75 (m, 1H, 2-H_α), 4.07 (br d, 2H, 5′-CH_2), 4.4 (br s, 1H, 4′-H), 5.95 (d, 1H, J = 6.0 Hz, 3′-H), 6.55 (dd, 1H, J = 9.3, 5.6 Hz, 1′-H), 7.10–7.70 (m, 16H, 6-H and ArH), 8.7 (br s, 1H, NH).

1-[5-*O*-(*tert*-Butyldiphenylsilyl)-2,3-dideoxy-3-iodo-β-D-*erythro*-pentofuranosyl]thymine (7):

To a stirred solution of **6** (24.0 g, 50 mmol) in DMF (200 mL) was added freshly prepared methyltriphenoxyphosphonium iodide[13] (33.9 g, 75 mmol) in one portion under an Ar atmosphere at r.t. After 3 h, TLC (CH_2Cl_2/MeOH, 95:5) indicated complete consumption of the starting material and the formation of a less polar spot (R_f 0.75) as the sole product. The stirring was continued for 1 h, and to the reaction mixture MeOH (20 mL) was added dropwise to quench the excess reagent. After 30 min, the red colored solution was poured into ice-water (500 mL) containing $Na_2S_2O_3$ (50 g). The suspension was stirred for 1 h and extracted with CH_2Cl_2 (2 × 250 mL). The combined extracts were washed with water (2 × 250 mL) and dried ($MgSO_4$). The solvent was evaporated in vacuo and the residue purified by column chromatography (silica gel; CH_2Cl_2/MeOH, 99:1). Pooling of the appropriate fractions and evaporation furnished **7** as a colorless foam (19.2 g, 65%).

MS (FD): m/z = 590 $(M)^+$, 533 $(M-C_4H_9)^+$, 406 $(M-C_4H_9-I)^+$.

^{1}H NMR ($CDCl_3$): δ = 1.09 (s, 9H, CMe_3), 1.56 (s, 3H, 5-CH_3), 2.60–2.93 (m, 2H, 2′-CH_2), 3.90–4.11 (m, 2H, 5′-CH_2), 4.29 (m, 1H, 4′-H), 4.43 (dd, 1H, J = 7.9, 8.1 Hz, 3′-H), 6.23 (dd, 1H, J = 4.3, 6.8 Hz, 1′-H), 7.35–7.55, 7.63–7.70 (2 m, 11H, ArH, 6-H), 8.30 (br s, 1H, NH).

1-[5-(*tert*-Butyldiphenylsilyl)-2,3-dideoxy-3-*C*-styryl-β-D-*erythro*-pentofuranosyl]thymine (9):

A stirred mixture of β-tributylstannylstyrene[21] (192 g, 0.48 mol) and one half the volume of crude xanthate **8** (ca. 117 g in ca. 1.0 L of benzene, ca. 0.19 mol) from the earlier reaction was thoroughly degassed (× 3) with Ar at 40 °C. To the stirred reaction mixture, AIBN (10 × 5.25 g, 0.32 mol) (the temperature of the reaction mixture was lowered to ca. 50 °C for a short time during the additions of AIBN and argon flow was increased to maintain an oxygen-free atmosphere) was added in small portions over 30–36 h, while the internal temperature was maintained around 80–82 °C. The progress of the reaction was monitored by TLC (EtOAc/hexanes, 9:11; double developments) which indicated complete consumption of the starting material **8**, and appearance of the desired product **9** (R_f 0.31) and the side product **11** (R_f 0.26) in ca. 30 h. A third spot (> 5%, R_f 0.21) was not fully characterized. The entire reaction mixture was cooled to r.t. and transferred to the top of a prepacked (hexanes) medium pressure silica gel column (ca. 7 psi, 15 × 60 cm, 2.8 kg). Elution with hexanes (100%) removed almost all of the tin byproducts (R_f 0.77, 0.85, 0.88). A gradual increase in polarity of the elution solvent with a mixture of hexanes/EtOAc (8:2→ 7:3) furnished the desired product **9**. Appropriate fractions were pooled and concentrated to furnish 75.4 g (70%) of **9** as a colorless foam. The continued elution of the column with hexanes/EtOAc (6:4) furnished more polar products (R_f 0.26 and 0.21) as a mixture. The major product from this mixture was characterized as **11** (5.8 g, ca. 7%).

Compound **9**:

MS (CI, NH_3): m/z (+) = 584 $(M+NH_4)^+$, 567 $(M+H)^+$.

m/z (−): 601 $(M+Cl)^-$, 565 $(M-H)^-$.

HRMS (FAB) ($C_{34}H_{39}SiN_2O_4$, $M+H)^+$: m/z calc. 567.2679; found 567.2682.

^{1}H NMR ($CDCl_3$): δ = 1.15 (s, 9H, CMe_3), 2.02 (s, 3H, 5-CH_3), 2.35 (ddd, 1H, J = 14.0, 3.0, 8.0 Hz, 2′-H_β), 2.46 (ddd, 1H, J = 10.2, 7.1, 2′-H_α), 3.28 (m, 1H, 3′-H), 3.88 (m, 1H, 4′-H), 6.0 (dd, 1H, ArCH=C*H*), 6.21 (dd, 1H, 1′-H), 6.50 (d, 1H, ArC*H*=CH), 7.23–7.75 (m, 16H, ArH, 6-H), 8.80 (br s, 1H, NH).

Compound **11**:

HRMS (FAB) ($C_{26}H_{33}N_2O_4Si$, $M+H)^+$: m/z calc. 465.2209; found 465.2214.

^{1}H NMR ($CDCl_3$): δ = 1.09 (s, 9H, CMe_3), 1.64 (s, 3H, 5-CH_3), 2.03 (m, 3H, 2′-CH_2, 3′-H), 2.38 (m, 1H, 3′-H), 3.74 (dd, 1H, 5′-CH_2), 4.02 (dd, 1H, 5′-CH_2), 4.16 (m, 1H, 4′-H), 6.12 (m, 1H, 1′-H), 7.36–7.68 (m, 10H, ArH), 7.49 (s, 1H, 6-H), 8.83 (br s, 1H, NH).

1-(2,3-Dideoxy-3-*C*-styryl-β-D-*erythro*-pentofuranosyl)thymine (10):

To a stirred solution of **9** (5.40 g, 10 mmol) in THF (50 mL) was added TBAF (1 M in THF; 2 mL) under an Ar atmosphere at r.t. After 24 h, TLC (CH_2Cl_2/MeOH, 9:1) indicated complete consumption of the starting material, and formation of a less polar spot (R_f 0.45) as the sole product. The solvent was evaporated in vacuo and the residue purified by silica gel column chromatography, (silica gel; hexanes/EtOAc, 1:1 → 2:8). Pooling of the appropriate fractions and evaporation furnished **10** as a colorless solid (2.69 g, 82%, mp 70 °C decomp.).

^{1}H NMR ($CDCl_3$): δ = 1.91 (s, 3H, 5-CH_3), 2.32 (m, 1H, 2′-H_β), 2.43 (m, 1H, 2′-H_α), 2.91 (br s, 1H, 5′-OH), 3.21 (m, 1H, 3′-H), 3.85 (m, 1H, 4′-H), 3.75, 4.07 (2 m, 2H, 5′-CH_2), 6.02 (dd, 1H, ArCH=C*H*), 6.22 (dd, 1H, 1′-H), 6.56 (d, 1H, ArC*H*=CH), 7.24–7.36 (m, 15H, ArH), 7.69 (s, 1H, 6-H), 9.31 (br s, 1H, N*H*).

1-[5-(*tert*-Butyldiphenylsilyl)-2,3-dideoxy-3-*C*-formyl-β-D-*erythro*-pentofuranosyl]thymine (12):

To a mixture of styryl nucleoside **9** (40.0 g, 70.5 mmol) and 4-methylmorpholine *N*-oxide (9.0 g, 76.8 mmol) in 1,4-dioxane (360 mL) was added an aqueous solution of OsO_4 (E.M. Corp. Chestnut Hill, Massachusetts, USA) (0.7 g in 70 mL water, 2.75 mmol) at r.t. The reaction mixture was protected from light (covered with black paper) and stirred for 1–2 h. TLC (CH_2Cl_2/MeOH, 93:7) indicated that the starting material (R_f 0.66) had been consumed, and the formation of a product spot (R_f 0.25) was observed. At this point, $NaIO_4$ (26.4 g, 123.4 mmol) was added in small portions over ca. 30 min (exothermic reaction). After 3 h, TLC showed that there

was a new spot (R_f 0.39) for the desired product **12** and disappearance of the intermediate diol spot (R_f 0.25). The reaction mixture was diluted with EtOAc (800 mL) and filtered through a pad of Celite. The solids were thoroughly washed with EtOAc (2 × 200 mL) and the combined filtrates were washed with sat. aq NaCl (2 × 250 mL) and dried ($MgSO_4$). The solvent was evaporated to furnish a yellowish gummy residue, which turned darker on exposure to the air and light. However, the integrity of the desired *C*-formyl nucleoside **12** was unaffected during darkening of the residue. The crude product **12** was purified by silica gel column chromatography (16 × 30 cm, 400 g). The appropriate fractions were eluted with CH_2Cl_2/MeOH (97:3), pooled and concentrated to furnish the product **12** (22.04 g, 63.4%) as a colorless foam.

MS (FD): $m/z = 493\ (M + H)^+$, $435\ (M - C_4H_9)^+$.

^1H NMR ($CDCl_3$): $\delta = 1.09$ (s, 9H, CMe_3), 1.59 (s, 3H, 5-CH_3), 2.25 (ddd, 1H, $J = 15.3, 6.1, 9.4$ Hz, 2′-H_β), 2.78 (ddd, 1H, $J = 6.2$, 2′-H_α), 3.38 (m, 1H, 3′-H), 3.82, 4.08 (2 m, 2H, 5′-CH_2), 4.33 (m, 1H, 4′-H), 6.09 (pseudo t, 1H, $J = 5.3, 6.6$ Hz, 1′-H), 7.18–7.75 (m, 11H, ArH, 6-H), 8.20 (br s, 1H, NH), 9.70 (s, 1H, C*H*O).

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(1) Recent reviews on backbone-modified antisense oligonucleotides:
Sanghvi, Y.S.; Cook, P.D. In *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*; Chu, C.K.; Baker, D.C.; Eds; Plenum: New York, 1993; p 311.
Beaucage, S.L.; Iyer, R.P. *Tetrahedron* **1993**, *49*, 6123.
Milligan, J.F.; Matteucci, M.D.; Martin, J.C. *J. Med. Chem.* **1993**, *36*, 1923.
Uhlmann, E.;Peyman, A. In *Protocols for Oligonucleotides and Analogs*; Agrawal, S., Ed.; Humana: Totowa, New Jersey, 1993; p 355.
Varma, R.S. *Synlett* **1993**, 621.

(2) We refer to phosphate modified (phosphorothioate, methylphosphonate etc.) as the first generation antisense oligonucleotides.
Vasseur, J.-J.; Debart, F.; Sanghvi, Y.S.; Cook, P.D. *J. Am. Chem. Soc.* **1992**, *114*, 4006.
Debart, F.; Vasseur, J.-J.; Sanghvi, Y.S.; Cook, P.D. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1479.
Sanghvi, Y.S.; Vasseur, J.-J.; Debart, F.; Cook, P.D. *Nucleic Acids Res. Symp. Ser. 27* **1992**, 133.
Sanghvi, Y.S.; Vasseur, J.-J.; Debart, F.; Cook, P.D. *Collect. Czech. Chem. Commun.* Special Issue **1993**, *58*, 158.

(3) Bamford, M.J.; Coe, P.L.; Walker, R.T. *J. Med. Chem.* **1990**, *33*, 2488.
Bamford, M.J.; Coe, P.L.; Walker, R.T. *J. Med. Chem.* **1990**, *33*, 2494.
Tseng, C.K.-H.; Marquez, V.E.; Milne, G.W.A.; Wysocki, R.J.; Mitsuya, H.; Shirasaki, T.; Driscoll, J.S. *J. Med. Chem.* **1991**, *34*, 343.
Sterzycki, R.Z.; Martin, J.C.; Wittman, M.; Brankovan, V.; Yang, H.; Hitchcock, M.J.; Mansuri, M.M. *Nucleosides Nucleotides* **1991**, *10*, 291.
Ioannidis, P.; Classon, B.; Samuelsson, B.; Kvarnström, I. *Nucleosides Nucleotides* **1992**, *11*, 1205.
Ioannidis, P.; Classon, B.; Samuelson, B.; Kvarnström, I. *Nucleosides Nucleotides* **1993**, *12*, 865.
Svansson, L.; Kvarnström, I.; Classon, B.; Samuelsson, B. *Nucleosides Nucleotides* **1992**, *11*, 1353.
Tino, J.A.; Clark, J.M.; Field, A.K.; Jacobs, G.A.; Lis, K.A.; Michalik, T.L.; McGeever-Rubin, B.; Slusarchyk, W.A.; Spergel, S.H.; Sundeen, J.E.; Tuomari, A.V.; Weaver, E.R.; Young, M.G.; Zahler, R. *J. Med. Chem.* **1993**, *36*, 1221.
Czernecki, S.; Ezzitouni, A. *J. Org. Chem.* **1992**, *57*, 7325.
Xi, Z.; Agback, P.; Plavec, J.; Sandström, A.; Chattopadhyaya, J. *Tetrahedron* **1992**, *48*, 349.
Fiandor, J.; Tam, S.Y. *Tetrahedron Lett.* **1990**, *31*, 597.

(4) Plavec, J.; Garg, N.; Chattopadhyaya, J. *J. Chem. Soc. Chem. Commun.* **1993**, 1011.
Lankin, D.C.; Nugent, S.T.; Rao, S.N. *Carbohydr. Res.* **1993**, *244*, 49.

(5) Svansson, L.; Kvarnström, I.; Classon, B.; Samuelsson, B. *J. Org. Chem.* **1991**, *56*, 2993.

(6) Lin, T.-S.; Zhu, J.-L.; Dutschman, G.E.; Cheng, Y.-C.; Prusoff, W.H. *J. Med. Chem.* **1993**, *36*, 353.

(7) De Mesmaeker, A.; Lebreton, J.; Hoffmann, P.; Freier, S.M. *Synlett* **1993**, 677.
Marco-Contelles, J. *J. Chem. Res.* **1993**, 330.
Lee-Ruff, E.; Jiang, J.-L.; Wan, W.-Q. *Tetrahedron Lett.* **1993**, *34*, 261.
Lau, J.; Walczak, K.; Pupek, K.; Buch, C.; Nielsen, C.M.; Pedersen, E.B. *Arch. Pharm.* **1991**, *324*, 953.
Chu, C.K.; Doboszewski, B.; Schmidt, W.; Ullas, G.V.; Van Roey, P. *J. Org. Chem.* **1989**, *54*, 2767.
Yu, D.; D'Alarcao, M. *J. Org. Chem.* **1989**, *54*, 3240.
Santiago de Alvarenga, E.; Mann, J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2141, and references cited therein.
Jenny, T.F.; Benner, S.A. *Tetrahedron Lett.* **1992**, *33*, 6619.

(8) Parkes, K.E.B.; Taylor, K. *Tetrahedron Lett.* **1988**, *29*, 2995.

(9) See supplementary material in Vasseur, J.-J.; Debart, F.; Shanghvi, Y.S.; Cook, P.D. *J. Am. Chem. Soc.* **1992**, *114*, 4006.

(10) Bankston, D.D.; Almond, M.R. *J. Heterocycl. Chem.* **1992**, *29*, 1405.

(11) Baldwin, J.E.; Kelly, D.R. *J. Chem. Soc., Chem. Commun.* **1985**, 682.
Russell, G.A.; Tashtoush, H.; Ngoviwatchai, P. *J. Am. Chem. Soc.* **1984**, *106*, 4622.

(12) Debart, F.; Vasseur, J.-J.; Sanghvi, Y.S.; Cook, P.D. *Tetrahedron Lett.* **1992**, *33*, 2645.

(13) Verheyden, J.P.H.; Moffatt, J.G. *J. Org. Chem.* **1970**, *35*, 2868.

(14) Walczak, K.; Pupek, K.; Pedersen, E.B. *Liebigs Ann. Chem.* **1991**, 1041.
Giese, B. *Angew. Chem.* **1989**, *101*, 993; *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 969.

(15) Robins, M.J.; Wilson, J.S.; Hansske, F. *J. Am. Chem. Soc.* **1983**, *105*, 4059.

(16) Lebreton, J.; De Mesmaeker, A.; Waldner, A.; Fritsch, V.; Wolf, R.M.; Freier, S.M. *Tetrahedron Lett.* **1993**, *34*, 6383.
De Mesmaeker, A.; Lebreton, J.; Waldner, A.; Fritsch, V.; Wolf, R.M.; Freier, S.M. *Synlett* **1993**, 733.
De Mesmaeker, A.; Waldner, A.; Lebreton, J.; Hoffmann, P.; Fritsch, V.; Wolf, R.M.; Freier, S.M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 226.

(17) Barton, D.H.R.; Jaszberenyi, J.C. *Tetrahedron Lett.* **1989**, 2619.

(18) Pudlo, J.S.; Townsend, L.B. *Nucleosides Nucleotides* **1992**, *11*, 279.

(19) See for similar applications: De Mesmaeker, A.; Lebreton, J.; Waldner, A.; Cook, P.D. International Patent WO 92/20823, 1992.
Cook, P.D.; Sanghvi, Y.S.; Vasseur, J.-J.; Debart, F. International Patent WO 92/20822, 1992.

(20) Matulic-Adamic, J.; Watanabe, K.A. *J. Chem. Soc., Chem. Commun.* **1985**, 1535.
Teng, K.; Cook, P.D. *J. Org. Chem.* **1994**, *59*, 278.

(21) Saihi, M.L.; Pereyre, M. *Bull. Soc. Chim. Fr.* **1977**, 1251.
Matsubara, S.; Hibino, J.-L.; Morizawa, Y.; Oshima, K. *J. Organomet. Chem.* **1985**, *285*, 163.
Ager, D.J.; Cooke, G.E.; East, M.B.; Mole, S.J.; Rampersaud, A.; Webb, V.J. *Organometallics* **1986**, *5*, 1906.