



S0040-4039(96)00090-1

Four Step Synthesis of a 5'-Deoxy-5'-iodomethylthymidine

Daniel K. Baeschlin, Michael Daube, Monika O. Blättler, Steven A. Benner,
Clemens Richert^{*a}

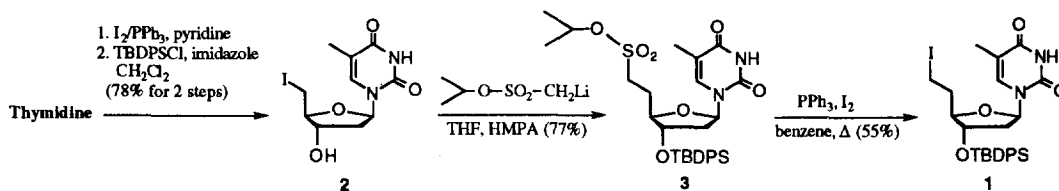
Department of Chemistry, Swiss Federal Institute of Technology, Universitätstr. 16, CH-8092 Zürich, Switzerland.

^a Permanent Address: Department of Chemistry, Tufts University, 62 Talbot Avenue, Medford, MA 02155 USA.

Abstract: The conversion of an alkylsulfonate to an iodide with triphenylphosphine/iodine in benzene has been performed for a nucleoside. Starting from thymidine, 3'-protected 5'-deoxy-5'-iodomethylthymidine was synthesized in 4 steps.

Modified nucleic acids are important biochemical and biomedical tools.¹ In oligonucleotides, the replacement of atoms of the phosphodiester linkage is one way of conferring hydrolytic stability and/or electrostatic neutrality, two properties believed to be advantageous for bioavailability.² While building blocks bearing heteroatoms at the 3'- and 5'-position are mostly accessible from natural nucleosides by functional group interconversions, the extension of the carbon backbone to homonucleosidic structures can be more challenging³ and often necessitates target molecule assembly from modified sugars and nucleobases.⁴

In the course of our work on sulfone-linked oligonucleotides, a 3'-protected 5'-homonucleoside with a 6'-leaving group was needed as one of the two nucleoside precursors for incorporation of dimethylenesulfone linkages in natural DNA. 6'-Halonucleosides such as **1** (Scheme 1) were the preferred target molecules.⁵



Scheme 1

At the outset of our study, the nine-step synthesis of the base-protected bromo-derivative of **16** had not yet been published. Other methods for the preparation of 5'-homonucleosides appeared either too laborious (>10 steps),⁷ lead to nucleosides with 6'-functional groups with no obvious interconversion to leaving groups,⁸ or to ribonucleosides⁹ necessitating 2'-deoxygenations that were low yielding in our hands. Hydrogenation of a 6'-bromo-5',6'-dihydro-derivative of **110** failed. We attempted homologization of 3'-silylated 5'-iodothymidine **211** via its 5'-isopropoxydimethylsilylmethyl derivative, oxidative hydrolysis, and iodination under conditions described for terpenoids.¹² The low reactivity of the 5'-iodothymidine made this route unsuccessful. Analogous 5'-bromo- and 5'-chloro-thymidines suffered from the same drawback.

Sulfonate ester **3**¹¹ proved to be a useful intermediate in the synthesis of target molecule **1**. Under the conditions described for hydrocarbon substrates by Oae and Togo¹³ **1** was obtained from **3** in acceptable yield. Interestingly, the sulfonate to iodide conversion, for which a mechanism has been proposed,¹⁴ was unsuccessful in pyridine and acetonitrile and low yielding in toluene and THF. Further, the desired conversion occurred only in the presence of a precipitate (most probably [PPh₃I]⁺ I⁻) and the yield increased when as the solvent volume decreased. If full dissolution of the reagent was observed, the conversion stopped, indicating that the reaction may require the surface of the precipitate. Under the chosen conditions,¹⁵ iodide **1** was isolated in 55% isolated yield on a 0.5 g scale. Higher yields based on recovered starting material were obtained when the reaction was stopped prior to full conversion of the educt. Building block **1** thus obtained was successfully incorporated in sulfone bridged oligonucleotides¹⁶ and may in the future be used for other modified nucleic acids.^{6,3}

References and Notes

- Selected reviews: (a) Huryñ, D.M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745-1768. (b) Eckstein, F. *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 160-166; *Angew. Chem.* **1975**, *87*, 179-185. (c) Milligan J. F.; Matteucci M. D.; Martin J. C. *J. Med. Chem.* **1993**, *36*, 1923-1937.
- Uhlmann E., Peyman A. *Chem. Rev.* **1990**, *90*, 544-584.
- Hunziker, J.; Leumann, C. Nucleic Acid Analogues: Synthesis and Properties. In *Modern Synthetic Methods 1995*: Ernst, B.; Leumann, C. Eds.; Verlag Helvetica Chimica Acta: Basel, 1995; pp. 333-417.
- (a) Rosenthal, A.; Sprinzl, M. *Can. J. Chem.* **1969**, *47*, 4477-4481. (b) Acton, E. M.; Goerner, R. N.; Uh, H. S.; Ryan, K. J.; Henry, D. W.; Cass, C. E.; LePage, G. A. *J. Med. Chem.* **1979**, *22*, 518-525. (c) Huang, Z.; Schneider, K. C.; Benner S. A. *J. Org. Chem.* **1991**, *56*, 3869-3882.
- These have proven advantageous over e.g. mesylates in the assembly of all-dimethylenesulfone linked oligomers, Richert, C.; Roughton, A. L.; Benner S. A., manuscript submitted.
- Wendeborn, S.; Wolf, R. M.; De Mesmaeker, A. *Tetrahedron Lett.* **1995**, *36*, 6879-6882 and references cited therein and preceding papers. Presuming a one step conversion of the thymine-protected carboxylic acid described in reference 3 of this paper to the starting molecule of the route and a three-step synthesis of 5'-DMT-3'-TBDPS-protected thymidine (Wendeborn, S.; personal communication, 1995), a nine-step synthesis is reported for the 5'-deoxy-5'-bromomethylthymidine-derivative.
- Padyukova N. S.; Fomicheva, M. V.; Mikhailov, S. N.; Janta-Lipinski, M. *Bioorg. Khim.* **1990**, *16*, 370-375.
- (a) Barton, D. H. R.; Gero, S. D.; Quiclet-Sire, B.; Samadi, M. *Tetrahedron Lett.* **1989**, *37*, 4969-4972. (b) Boehringer, M. P.; Graff, D.; Caruthers, M. H. *Tetrahedron Lett.* **1993**, *34*, 2723-2726.
- (a) Kappler F., Hampton, A. Homoadenosine [9-(5-Deoxy-β-D-ribo-hexofuranosyl)adenine] hydroboration of 5',6'-anhydro-2',3'-O-isopropylidene-homoadenosine formed from 2',3'-O-isopropylideneadenosine-5'-aldehyde by a Wittig reaction. In *Nucleic Acid Chemistry, Part 4*; Townsend, L.B.; Tipson, R.S. Eds; Wiley Interscience, New York 1991; pp. 240-244. (b) Lassota, P.; Kusmierek, J. T.; Stolarski, R.; Shugar, D. *Z. Naturforsch.* **1987**, *42c*, 589-598.
- Lebreton, J.; De Mesmaeker, A.; Waldner, A. *Synlett* **1994**, 54-56.
- Huang, J.; McElroy, E. B.; Widlanski, T. S. *J. Org. Chem.* **1994**, *59*, 3520-3521. The thymidine sulfonate ester described in this reference differs from the compound described here in the use of a TBDMS group rather than a TBDPS moiety for protecting the 3'-hydroxyl group.
- McMurry, J. E.; Bosch, G. K. *J. Org. Chem.* **1987**, *52*, 4885-4893.
- Oae, S.; Togo, H. *Synthesis* **1981**, 371-373.
- Oae, S.; Togo, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3802-3812.
- A mixture of sulfonate ester **3** (0.90 g, 1.50 mmol) and triphenylphosphine (2.35 g, 9 mmol) was coevaporated with toluene, dried under HV and dissolved in benzene (6 mL). Iodine (1.52 g, 6 mmol) was added, leading to a brown precipitate. The thick slurry was stirred for 2.5 h at 90-100 °C (bath temp.). Prolonged reaction times led to formation of a side product and eventually to decomposition. Ethyl acetate (50 mL) was added after brief cooling followed by conventional workup involving aqueous Na₂S₂O₃, brine and drying over MgSO₄. Flash-chromatography (silica; ethyl acetate:petroleum ether 1:2) yielded iodide **1** (0.50 g, 0.83 mmol, 55%) as a colorless solid. Selected analytic data: FAB-MS *m/z* 605 (M+H⁺); ¹³C-NMR (CDCl₃, 125 MHz) δ 0.5, 12.6, 19.0, 26.8, 37.3, 39.8, 75.3, 85.0, 86.1, 111.3, 127.9, 128.0, 130.1, 130.2, 132.95, 132.96, 135.1, 135.7, 135.8, 150.1, 163.4; Anal. calcd for C₂₇H₃₃N₂O₄Si: C, 53.64; H, 5.50; N, 4.63. Found: C, 53.55; H, 5.29; N, 4.50.
- Baeschlin, D. K.; Hyrup, B.; Daube, M.; Benner, S. A.; Richert, C., manuscript in preparation.