Carbohydrate Research, 203 (1990) 324–329
Elsevier Science Publishers B.V., Amsterdam

Note

Transient protection in nucleoside synthesis using trityl groups: is it necessary to block hydroxyl groups?

Leon N. Beigelman and Sergey N. Mikhailov*
Engelhardt Institute of Molecular Biology, Academy of Sciences of the U.S.S.R., Vavilov str. 32, Moscow 117984 (U.S.S.R.)

(Received August 31st, 1989; accepted for publication, December 28th, 1989)

The method of Vorbrüggen[1] is now being used extensively in the synthesis of ribonucleosides and their analogs. The method involves glycosylation of trimethylsilyl derivatives of nucleic bases with completely acylated sugars in the presence of Lewis acids, preferentially tin(IV) chloride or trimethylsilyl trifluoromethanesulfonate (triflate). The presence of a 2-*O*-acyl group in a carbohydrate residue is believed to be crucial for the stereospecificity of this reaction, since it stabilizes the C-1 carbonium ion generated *via* an intermediate 1,2-acyloxonium ion[2,3] and yields 1,2-*trans*-derivatives. As a rule, an $\alpha\beta$-mixture of anomeric nucleoside derivatives is produced in the absence of a 2-*O*-acyl group[4]. However, α- and β-nucleosides can be synthesized stereoselectively starting from monosaccharide derivatives with such non-participating groups at C-2 as chlorine[5], *O*-tert-butyldimethylsilyl[6], 2,3-*O*-isopropylidene[7,8], and *O*-tosyl[9]. Steric factors seem to be responsible for the stereospecificity of these glycosylation reactions.

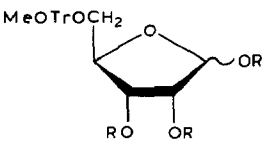
Therefore, a knowledge of how the protecting groups of a ribofuranose residue influence the regio-[10] and stereo-selectivity of condensation reactions will help to develop suitable methods for the synthesis of selectively protected nucleoside analogs.

We now illustrate the use of the monomethoxytrityl group to protect the primary hydroxyl group of a ribofuranose residue in nucleoside synthesis and its elimination during the reaction. It is known that trityl groups can be removed by the action of Lewis acids[11,12]. The D-ribofuranose derivatives **1** and **2** were synthesized in high yields by monomethoxytritylation of D-ribose followed by acylation. A similar tritylation and acetylation sequence has been reported[13,14]. Glycosylation of bis(trimethylsilyl)uracil with **1** in the presence of triflate (2.3 equiv.) in 1,2-dichloroethane for 16 h at 20° gave 70% of the β-nucleoside derivative **3**. Likewise, glycosylation of the trimethylsilyl derivatives of N^4-benzoylcytosine (16 h, 20°) and N^6-benzoyladenine (boiling for 2 h, 1,2-dichloroethane) with **2** yielded the β-nucleoside derivatives **4** (70%) and **5** (66%), respectively. The structures of **3**–**5** were confirmed by ^{1}H-n.m.r. data and independent

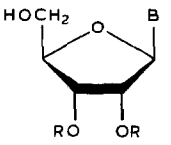
* Author for correspondence.

0008-6215/90/$ 03.50

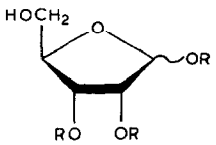
synthesis. Condensation of uridine, N^4-benzoylcytidine[15], and N^6-benzoyladenosine[15] with monomethoxytrityl chloride in pyridine, followed by acylation and acid hydrolysis, generated **3–5**, respectively, in high yields.



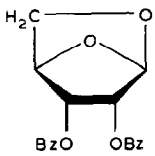
1 R = Bz
2 R = Ac



3 R = Bz, B = uracilyl
4 R = Ac, B = N^4-benzoylcytosinyl
5 R = Ac, B = N^6-benzoyladeninyl



6 R = Bz
7 R = Ac



8

Therefore, triflate-catalysed glycosylation of heterocyclic bases with **1** and **2** yields β-nucleoside derivatives with the simultaneous elimination of the monomethoxytrityl group which can be regarded as a transient protective group. The question arises as to whether hydroxyl groups must be blocked in nucleoside synthesis.

In seeking to answer this question, the partly protected D-ribofuranose derivatives **6** and **7** were obtained by hydrolysis of **1** and **2**, respectively. Further glycosylation generated **3–5** in yields of 55–60%. By-products were formed in these reactions which affected the yields of the nucleoside derivatives. The formation of 1,5-anhydro derivatives may be a possible side reaction[16]. Thus, treatment of **6** with a small excess of triflate in 1,2-dichloroethane gave a high yield of **8** and reaction was complete within 30 min at 20°. Similar treatment of **1** gave a complex mixture from which 12% of **8** was isolated. This anhydro derivative was not an intermediate in the nucleoside synthesis because its condensation with bis(trimethylsilyl)uracil for 16 h at 20° in the presence of 1.2 equiv. of triflate or upon boiling for 2 h did not yield any **3**.

The use of (at least partially) protected sugar derivatives in nucleoside synthesis enhances the solubility in organic solvents and simplifies isolation and purification. For example, 2′,3′-di-*O*-acetyluridine, synthesized from **2** or **7**, dissolves readily in water and is poorly extractable with chloroform. Hence, the benzoates **1** and **6** should be used for the synthesis of uridine derivatives.

The use of monosaccharide derivatives with HO-5 unsubstituted or the corresponding 5-*O*-monomethoxytrityl derivatives in nucleoside synthesis allows access to selectively protected derivatives in a high yield.

EXPERIMENTAL

General methods. — Melting points (uncorrected) were determined with a TP (U.S.S.R.) instrument. Optical rotations were measured with a Perkin–Elmer Model 141 automatic polarimeter. Silica Gel L (40–100 μm) (Czechoslovakia) was used for column chromatography. T.l.c. was conducted on Silufol UV_{254} (Czechoslovakia), using *A*, $CHCl_3$; *B*, 49:1 $CHCl_3$–EtOH; and *C*, 1:1 $CHCl_3$–hexane; and detection by u.v. light or by heating to 150–200°. ^{1}H-N.m.r. spectra (internal hexamethyldisiloxane) were recorded using a Varian XL-100 spectrometer. The signals were assigned by using double resonance techniques.

1,2,3-Tri-O-benzoyl-5-O-monomethoxytrityl-α,β-D-ribofuranose (**1**). — A solution of D-ribose (3.0 g, 20 mmol) and monomethoxytrityl chloride (7.0 g, 22.8 mmol) in pyridine (40 mL) was kept for 24 h at 20°. A solution of benzoyl chloride (10.5 mL, 90 mmol) in 1,2-dichloroethane (30 mL) was added with stirring and cooling (0°). The mixture was kept for 16 h at 20°, then diluted with ethanol (10 mL) with cooling, and, after storage for 30 min at 20°, concentrated to dryness. The residue was partitioned between chloroform (100 mL) and water (30 mL). Conventional work-up of the organic layer and column chromatography (solvent *C*) of the product on silica gel (500 g) gave **1** (14.0 g, 95%), R_F 0.40. ^{1}H-N.m.r. data ($CDCl_3$): δ 8.10–7.08 (m, 27 H, aromatic protons), 6.84 (d, 1 H, *J* 9.0 Hz, *Ph*OMe), 6.82 (d, 0.5 H, $J_{1,2}$ 4.0 Hz, H-1α), 6.68 (d, 1 H, *J* 9.0 Hz, *Ph*OMe), 6.64 (d, 0.5 H, $J_{1,2}$ 1.0 Hz, H-1β), 6.02–5.81 (m, 2 H, H-2,3), 4.76–4.55 (m, 1 H, H-4), 3.82 (s, 1.5 H, OMe), 3.72 (s, 1.5 H, OMe), 3.60–3.32 (m, 2 H, H-5a,5b).

Anal. Calc. for $C_{46}H_{38}O_9$: C, 75.19; H, 5.21. Found: C, 74.96; H, 4.99.

1,2,3-Tri-O-acetyl-5-O-monomethoxytrityl-α,β-D-ribofuranose (**2**). — Monomethoxytrityl chloride (17.0 g, 55 mmol) was added in two portions to a solution of D-ribose (7.5 g, 50 mmol) in dry pyridine (100 mL). The solution was stored for 24 h at 20°, dry 1,2-dichloroethane (100 mL), pyridine (50 mL), and then acetic anhydride (20 mL) were added with stirring and cooling (5°), and the mixture was stored for 16 h at 20°. Conventional work-up and column chromatography (solvent *A*) of the product on silica gel (300 g) gave **2**, isolated as an oil (23.3 g, 85%), R_F 0.55. ^{1}H-N.m.r. data ($CDCl_3$): δ 7.46–7.04 (m, 12 H, aromatic protons), 6.75 (d, 1 H, *J* 9.0 Hz, *Ph*OMe), 6.74 (d, 1 H, *J* 9.0 Hz, *Ph*OMe), 6.46 (d, 0.5 H, $J_{1,2}$ 4.0 Hz, H-1α), 6.13 (bs, 0.5 H, H-1β), 5.51–5.26 (m, 2 H, H-2,3), 4.34–4.16 (m, 1 H, H-4), 3.75 (s, 3 H, OMe), 3.45–3.00 (m, 2 H, H-5a,5b), 2.08, 2.07, 2.06, 2.04, 1.98, 1.96 (6 s, each 1.5 H, 3 Ac).

Anal. Calc. for $C_{31}H_{32}O_9$: C, 67.87; H, 5.88. Found: C, 67.51; H, 5.42.

1,2,3-Tri-O-benzoyl-α,β-D-ribofuranose (**6**). — A solution of **1** (3.7 g, 5 mmol) in aqueous 80% acetic acid (50 mL) was kept for 6 h at 20°, then concentrated to dryness, and toluene (2 × 20 mL) was evaporated from the residue. Column chromatography (solvent *A*) of the residue on silica gel (100 g) gave **6** (2.0 g, 88%), isolated as an oil, R_F 0.48. ^{1}H-N.m.r. data ($CDCl_3$): δ 8.08–7.72 and 7.58–7.08 (2 m, 6 and 9 H, 3 Bz), 6.88 (d, 0.5 H, $J_{1,2}$ 4.2 Hz, H-1α), 6.62 (bs, 0.5 H, H-1β), 5.88 (m, 1 H, H-2β,3β), 5.78 (dd, 0.5 H, $J_{3,2}$ 6.5, $J_{3,4}$ 2.5 Hz, H-3α), 5.60 (dd, 0.5 H, H-2α), 4.68–4.48 (m, 1 H, H-4), 4.02–3.70 (m, 2 H, H-5a,5b), 2.32 (bs, 1 H, OH).

Anal. Calc. for $C_{26}H_{22}O_8$: C, 67.53; H, 4.80. Found: C, 67.28; H, 4.61.

1,2,3-Tri-O-acetyl-α,β-D-ribofuranose (**7**). — Treatment of **2** (5.5 g, 10 mmol), as described for **1**, gave **7** (2.4 g, 87%), isolated as an oil, R_F 0.19 (solvent *B*). ^{1}H-N.m.r. data ($CDCl_3$): δ 6.35 (d, 0.5 H, $J_{1,2}$ 4.0 Hz, H-1α), 6.08 (bs, 0.5 H, H-1β), 5.39–5.10 (m, 2 H, H-2,3), 4.30–4.13 (m, 1 H, H-4), 4.00–3.53 (m, 2 H, H-5a,5b), 2.09, 2.08, 2.04 (3 s, each 3 H, 3 Ac).

Anal. Calc. for $C_{11}H_{16}O_8$: C, 47.83; H, 5.84. Found: C, 47.62; H, 5.61.

1-(2',3'-Di-O-benzoyl-β-D-ribofuranosyl)uracil (**3**). — (*a*) A suspension of uracil (235 mg, 2.2 mmol) in hexamethyldisilazane (15 mL) and dry pyridine (5 mL) was boiled under reflux in the absence of moisture until dissolution was complete (5 h). The mixture was concentrated *in vacuo* to dryness and dry toluene (2 × 5 mL) was evaporated from the residue. A solution of **1** (1.5 g, 2.04 mmol) in dry 1,2-dichloroethane (50 mL) and a 2M solution of $CF_3SO_2OSiMe_3$ in 1,2-dichloroethane (2.3 mL) were added to the residue. The mixture was stored for 16 h at 20°, then diluted with chloroform (20 mL), washed successively with aqueous 10% $NaHCO_3$ (10 mL) and water (10 mL), dried (Na_2SO_4), filtered, and concentrated to dryness. Column chromatography (solvent *B*) of the residue on silica gel (30 g) afforded **3** (600 mg, 70%), R_F 0.17, m.p. 193–195° (from EtOH), $[\alpha]_D^{25}$ −139° (*c* 1.1, methyl sulfoxide); lit.[17] m.p. 195–197°.

(*b*) The procedure in (*a*) was followed, using uracil (235 mg, 2.2 mmol) and **6** (930 mg, 2.0 mmol) in dry 1,2-dichloroethane (50 mL) in the presence of 2M $CF_3SO_2OSiMe_3$ in 1,2-dichloroethane (2.3 mL), to give **3** (550 mg, 60%).

N⁴-Benzoyl-1-(2',3'-di-O-acetyl-β-D-ribofuranosyl)cytosine (**4**). — (*a*) *N*⁴-Benzoyl-bis(trimethylsilyl)cytosine (2.2 mmol) and **2** (1.1 g, 2.0 mmol) in 1,2-dichloroethane (50 mL) were treated in the presence of 2M $CF_3SO_2OSiMe_3$ in 1,2-dichloroethane (2.3 mL) as described in (*a*), to give **4** as a foam (600 mg, 70%), R_F 0.15 (solvent *B*), $[\alpha]_D^{25}$ +26° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 9.05 (bs, 1 H, NH), 8.12 (d, 1 H, $J_{6,5}$ 8.0 Hz, H-6), 7.98–7.74 (m, 2 H, Bz), 7.58–7.31 (m, 4 H, Bz, H-5), 6.05 (d, 1 H, $J_{1',2'}$ 4.5 Hz, H-1'), 5.58 (dd, 1 H, $J_{2',3'}$ 5.5 Hz, H-2'), 5.46 (dd, 1 H, $J_{3',4'}$ 4.0 Hz, H-3'), 4.20 (ddd, 1 H, $J_{4',5'a}$ 2.0, $J_{4',5'b}$ 2.5 Hz, H-4'), 3.98 (dd, 1 H, $J_{5'a,5'b}$ −12.0 Hz, H-5'a), 3.85 (dd, 1 H, H-5'b), 2.08 (s, 3 H, Ac), 2.05 (s, 3 H, Ac).

Anal. Calc. for $C_{20}H_{21}N_3O_8$: C, 55.68; H, 4.91; N, 9.74. Found: C, 55.51; H, 4.85; N, 9.53.

(*b*) Reaction of *N*⁴-benzoyl-bis(trimethylsilyl)cytosine (2.1 mmol) and **7** (550 mg, 2.0 mmol) in dry 1,2-dichloroethane (50 mL), in the presence of 2M $CF_3SO_2OSiMe_3$ (2.3 mL) as described above, gave **4** (200 mg, 58%).

N⁶-Benzoyl-9-(2',3'-di-O-acetyl-β-D-ribofuranosyl)adenine (**5**). — (*a*) Reaction (boiling, 2 h) of *N*⁶-benzoyl-bis(trimethylsilyl)adenine (2.1 mmol) and **2** (1.0 g, 1.83 mmol) in dry 1,2-dichloroethane (50 mL), in the presence of 2M $CF_3SO_2OSiMe_3$ in 1,2-dichloroethane (2.2 mL) as described above, gave **5** as a foam (550 mg, 66%), R_F 0.17 (solvent *B*), $[\alpha]_D^{25}$ −77° (*c* 1.2, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 9.00 (bs, 1 H, NH), 8.68 (s, 1 H, H-8), 8.05 (s, 1 H, H-2), 7.98–7.88 (m, 2 H, Bz), 7.55–7.35 (m, 3 H, Bz), 6.08 (d, 1 H, $J_{1',2'}$ 7.0 Hz, H-1'), 5.98 (dd, 1 H, $J_{2',3'}$ 5.0 Hz, H-2'), 5.64 (dd, 1 H, $J_{3',4'}$ 1.5 Hz, H-3'), 4.32 (dt, 1 H, $J_{4',5'a} = J_{4',5'b}$ = 1.8 Hz H-4'), 3.96 (dd, 1 H, $J_{5'a,5'b}$ −12.5 Hz, H-5'a), 3.88 (dd, 1 H, $J_{5'b,4'}$ 1.8 Hz, H-5'b), 2.15 (s, 3 H, Ac), 2.00 (s, 3 H, Ac).

Anal. Calc. for $C_{21}H_{21}N_5O_7$: C, 55.38; H, 4.65; N, 15.38. Found: C, 55.21; H, 4.53; N, 15.16.

(*b*) Reaction of N^6-benzoyl-bis(trimethylsilyl)adenine (2.1 mmol) and **7** (550 mg, 2.0 mmol) in 1,2-dichloroethane (50 mL), in the presence of 2M $CF_3SO_2OSiMe_3$ (2.3 mL) as described above, gave **5** (500 mg, 55%).

Preparation of **3–5** *from ribonucleosides.* — A mixture of uridine, N^4-benzoylcytidine[15], or N^6-benzoyladenine[15] (2 mmol) and monomethoxytrityl chloride (700 mg, 2.3 mmol) in pyridine was kept in the dark for 24 h at 20°. Acetic anhydride (0.8 mL, 8 mmol) or benzoyl chloride (5 mmol) was added and the mixture was kept for 16 h at 20°. Ethanol (5 mL) was added and, after 30 min, each mixture was concentrated *in vacuo* to dryness. A solution of the residue in chloroform (50 mL) was washed successively with water (20 mL), aqueous 10% $NaHCO_3$ (2 × 10 mL), and water, dried (Na_2SO_4), filtered, and concentrated to dryness, and toluene (2 × 10 mL) was evaporated from the residue. A solution of the residue in 2% CF_3COOH in chloroform (50 mL) was kept for 15 min at 20°, then neutralized with aqueous 10% $NaHCO_3$ (10 mL); from the organic layer, after chromatography on silica gel, nucleosides **3–5** were isolated in overall yields of 80–85%.

*1,5-Anhydro-2,3-*O*-di-*O*-benzoyl-β-*D*-ribofuranose* (**8**). — 2M $CF_3SO_2OSiMe_3$ in 1,2-dichloroethane (1.9 mL) was added to a solution of **7** (1.6 g, 3.46 mmol) in dry 1,2-dichloroethane (30 mL). The mixture was stored for 30 min at 20°, then diluted with chloroform (15 mL), and stirred with saturated aqueous $NaHCO_3$ for 5 min, and the organic layer was separated, washed with water (2 × 10 mL), dried (Na_2SO_4), and concentrated to dryness. Column chromatography (solvent *A*) of the residue on silica gel (70 g) gave **8** (1.0 g, 81%), R_F 0.84, m.p. 204–205° (from EtOH), $[\alpha]_D^{25}$ +110° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 8.06–7.76 (m, 4 H, Bz), 7.50–7.14 (m, 6 H, Bz), 6.00 (dd, 1 H, $J_{3,2}$ 5.0, $J_{3,4}$ 7.0 Hz, H-3), 5.61 (d, 1 H, H-2), 5.20 (s, 1 H, H-1), 4.40 (bd, 1 H, H-4), 4.16 (dd, 1 H, $J_{5a,4}$ 1.0, $J_{5a,5b}$ −12.5 Hz, H-5a), 3.85 (dd, 1 H, $J_{5b,4}$ 1.5 Hz, H-5b).

Anal. Calc. for $C_{19}H_{16}O_6$: C, 67.05; H, 4.74. Found: C, 67.16; H, 4.89.

REFERENCES

1 H. Vorbrüggen, in R. T. Walker, E. DeClercq, and F. Eckstein (Eds.), *Nucleoside Analogues. Chemistry, Biology and Medical Applications*, Vol. 26, Ser. A, NATO Advanced Study Institute, Plenum Press, New York, 1979, pp. 35–69.
2 K. A. Watanabe, D. H. Hollenberg, and J. J. Fox, *J. Carbohydr. Nucleosides, Nucleotides*, 1 (1974) 1–37.
3 R. L. Shone, *Tetrahedron Lett.*, (1977) 993–996.
4 W. Wierenga and H. I. Skulnick, *Carbohydr. Res.*, 90 (1981) 41–52.
5 G. Ritzman, R. S. Klein, D. H. Hollenberg, and J. J. Fox, *Carbohydr. Res.*, 39 (1975) 227–241.
6 C. Chavis, F. Dumont, R. H. Wightman, J. C. Ziegler, and J.-L. Imbach, *J. Org. Chem.*, 47 (1982) 202–206.
7 J. Kiss and R. D'Souza, *J. Carbohydr. Nucleosides Nucleotides*, 7 (1980) 141–157.
8 S. N. Mikhailov and W. Pfleiderer, *Synthesis*, (1985) 397–399.
9 C. Papageorgiou and C. Tamm, *Tetrahedron Lett.*, 27 (1986) 555–558.
10 P. Garner and S. Ramakanth, *J. Org. Chem.*, 53 (1988) 1294–1298.
11 K. Dax, W. Wolflehner, and H. Weidman, *Carbohydr. Res.*, 65 (1978) 132–138.
12 L. N. Beigelman, B. S. Ermolinsky, G. V. Gurskaya, E. N. Tsapkina, M. Ya. Karpeisky, and S. N. Mikhailov, *Carbohydr. Res.*, 166 (1987) 219–232.
13 H. Bredereck, M. Köthnig, and E. Berger, *Ber.*, (1940) 956–962.

14 B. L. Kam and N. J. Oppenheimer, *Carbohydr. Res.*, 69 (1979) 308–310.
15 D. Flockerzi, G. Silber, R. Charubala, W. Schlosser, R. S. Varma, F. Creegan, and W. Pfleiderer, *Justus Liebigs Ann. Chem.*, (1981) 1568–1585.
16 E. Zara-Kaczian, G. Deak, and S. Holly, *Acta Chim. Hung.*, 113 (1983) 379–391.
17 R. Lohrman and H. G. Khorana, *J. Am. Chem. Soc.*, 86 (1964) 4188–4194.