4,4',4''-Tris(benzoyloxy)trityl as a New Type of Base-Labile Group for Protection of Primary Hydroxyl Groups

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4,4',4''-Tris(benzoyloxy)trityl bromide (TBTrBr) available from rosolic acid has proved to have several advantages as a primary-selective blocking agent for nucleoside hydroxyl groups over previously known hindered acylating agents. N-Protected deoxynucleosides underwent selective 5'-tritylation with TBTrBr in pyridine at 65 °C or in pyridine–methylene chloride–triethylamine at room temperature, giving rise to 5'-O-protected deoxyribonucleoside derivatives in high yields. The high selectivity of TBTrBr toward primary hydroxyl groups has also been shown in its reactions with N-protected ribonucleosides and methyl α-D-glucopyranoside. The 4,4',4''-tris(benzoyloxy)trityl (TBTr) group was found to be more stable than the trityl group under acidic conditions, whereas it could be readily removed by treatment with 0.5 M sodium hydroxide for 10 min. Several thymidine derivatives protected at the 3'-position with acid-labile protecting groups have been synthesized by use of the TBTr group.

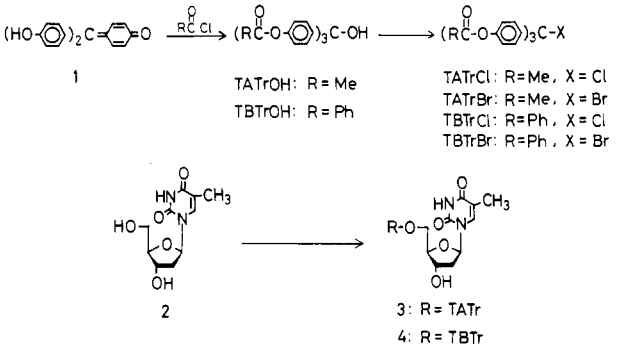
Selective protection of a multifunctional compound is of great importance.[1] In nucleoside chemistry, a primary hydroxyl group has generally been protected with a trityl or modified trityl group that can be removed under acidic conditions.[2] On the other hand, hindered base-labile protecting groups such as the adamantoyl,[3] pivaloyl,[4] (isobutyloxy)carbonyl,[5] (triphenylmethoxy)acetyl,[6] and [(fluoren-9-yl)methoxy]carbonyl[7] groups have also been used. These are generally designed by modifying acyl groups. On the whole, among these acid- and base-labile masking groups, the trityl group and its analogues seem to be most selective in blocking a primary hydroxyl group.

In this paper, we report that the 4,4',4''-tris(acyloxy)trityl group is a base-labile group useful for protection of primary hydroxyl groups.

Results and Discussion

In the parasubstituted benzoic acid series, the hydroxyl and acetoxyl substituents with Hammett σ_p values of −0.37 and 0.31,[8] respectively, have completely opposite effects on the dissociation constants of the acids. This fact suggests that an acyloxyl → hydroxyl conversion may be available for controlling the stability of protecting groups with *p*-(acyloxy)phenyl substituents. Originally, this idea was realized by Taunton-Rigby,[9a] who reported that in acidic media the 4-hydroxytrityl group is removed more easily than the *p*-(acyloxy)trityl group. Wakselman[9b] reported that the [[3-chloro-4-(acyloxy)benzyl]oxy]carbonyl group was useful for protecting an amino group. These facts led us to consider that introduction of three acyloxy groups into the para positions of the trityl group might not only increase its stability but also facilitate its removal via the acyloxyl → hydroxyl conversion.

For the purpose of this study we prepared the modified trityl halides 4,4',4''-tris(acyloxy)trityl chloride and bromide (TATrCl and TATrBr)[10] and 4,4',4''-tris(benzoyloxy)trityl chloride and bromide (TBTrCl and TBTrBr), which were readily prepared from a commercially available cheap dye, rosolic acid (1). Reactions of thymidine (2)



with TATrCl and TBTrCl in pyridine required high temperatures and prolonged periods of time. The rates of the reactions were not markedly increased by adding 4-(dimethylamino)pyridine known as a powerful catalyst for the tritylation.[11] On the contrary, TATrBr readily reacted with **2** at room temperature to give **3** quantitatively on TLC. However, the TATr group was unstable during silica gel column chromatography, and **3** was obtained in a poor yield. On the other hand, tritylation of **2** with TBTrBr resulted in a heterogeneous mixture due to the insolubility of a 1:1 adduct of TBTrBr with pyridine, and hence a prolonged reaction time was required. Upon being warmed to 65 °C, however, the reaction proceeded homogeneously and rapidly to give **4** in high yield. The TBTr group proved to be stable on silica gel. To ascertain the generality of the high selectivity of TBTrBr toward primary hydroxyl functions, we applied it to other deoxyribo- and ribonucleosides (**5**–**11**) and methyl α-D-glucopyranoside (**12**). These results are summarized in Table I.

The reactions of N^6-benzoyldeoxyadenosine (**6**) and N^2-isobutyryldeoxyguanosine (**7**) with TBTrBr at 65 °C led to their complete depurination. In the case of **6**, the depurination was depressed by addition of triethylamine. The reaction was also carried out homogeneously at room temperature by adding methylene chloride as a cosolvent. In the case of **7**, the depurination occurred to a considerable extent even in the presence of triethylamine, and

(1) (a) Reese, C. B. "Protective Groups in Organic Synthesis"; Mcomie, J. F. W.; Ed.; Plenum: New York, 1973; pp 95–143. (b) Greene, T. W. "Protective Groups in Organic Synthesis"; Wiley: New York, 1981.

(2) See ref 1a. pp 100–103. See also the following papers: Chattopadhyaya, J. B.; Reese, C. B. *J. Chem. Soc., Chem. Commun.* **1978**, 639. Barnett, W. E.; Needham, L. L.; Powell, R. W. *Tetrahedron* **1972**, *28*, 419.

(3) Gerzon, K.; Kau, D. *J. Med. Chem.* **1967**, *10*, 189.

(4) Griffin, B. E.; Jarman, M.; Reese, C. B. *Tetrahedron* **1968**, *24*, 639. Ogilvie, K. K.; Iwacha, D. J. *Tetrahedron Lett.* **1973**, 317. Robins, M. J.; Hawrelak, S. D.; Kanai, T.; Siefert, J. -M.; Mengel, R. *J. Org. Chem.* **1979**, *44*, 1317. van Boeckel, C. A. A.; van Boom, J. H. *Tetrahedron Lett.* **1979**, 3561.

(5) Letsinger, R. L.; Miller, P. S. *J. Am. Soc. Chem.* **1969**, *91*, 3356.

(6) Werstiuk, E. S.; Neilson, T. *Can. J. Chem.* **1972**, *50*, 1283.

(7) Gioeli, C.; Chattopadhyaya, J. B. *J. Chem. Soc., Chem. Commun.* **1982**, 672.

(8) Gordon, A. G.; Ford, R. A. "The Chemist's Companion"; Wiely: New York, 1972; p 146.

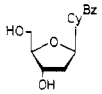
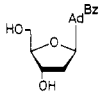
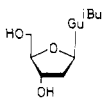
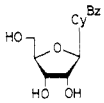
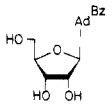
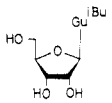
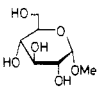
(9) (a) Taunton-Rigby, A.; Kim, Y-H.; Crosscup, C. J.; Starkovsky, N. A. *J. Org. Chem.* **1972**, *37*, 956. (b) Wakselman, M.; -Jampel, E. G. *J. Chem. Soc., Chem. Commun.* **1973**, 593. Corre, G. L.; Jampel, E. G.; Wakselman, M. *Tetrahedron* **1978**, 34 3105.

(10) Gomberg, M.; Snow, H. R. *J. Am. Chem. Soc.* **1925**, *47*, 198.

(11) Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, 95.

0022-3263/83/1948-3011$01.50/0

Table I. Conditions and Results of Reactions of Nucleoside Derivatives 2 and 5-11 and Methyl α-D-Glucopyranoside (12)[a]

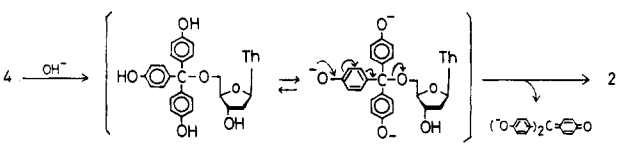
substrate	compd no.	equiv of TBTrBr	solv	temp, °C	time	product	% yield
	2	1.2	Py	65	2 h	4	91
	5	1.2	Py	65	30 min	13	81
		1.25	Py-CH_2Cl_2-Et_3N	*b*	3 h	13	90
	6	1.2	Py-CH_2Cl_2-Et_3N	*b*	5 h	14	85
	7	2.2	Py-CH_2Cl_2-Et_3N	*b*	7 h	15	45
						16	42
	8	1.2	Py	65	40 min	17	86
	9	1.2	Py	65	40 min	18	83
	10	1.2	Py	65	20 min	19	82
	11	2.3	Py-CH_2Cl_2-Et_3N	*b*		20	82
	12	1.2	Py-Et_3N	65	20 min	21	81

[a] The amounts of the solvents and triethylamine used were as follows: Py, 3 mL; Py-CH_2Cl_2-Et_3N, 2 mL-2 mL-196 μL (1.4 mmol); Py-Et_3N: 2 mL-196 μL (1.4 mmol). [b] Room temperature.

a TBTr-containing guanine derivative (16) of unknown structure was isolated.[12] All the reactions except for that of 7 gave the desired products in high yields.

Next, the stability of the TBTr group under acidic conditions was examined. In 80% acetic acid, the TBTr group proved to be removed 6 times more slowly than the trityl group as shown in Table II.

In order to obtain the trihydroxytrityl ether 23 and examine its stability in acidic media, we treated 4 with ammonia in MeOH or in MeOH–dioxane for 7 h. However, the reaction caused quantitative conversion to 2 and rosolic acid. At the early stage, the intermediate 23 could be detected on TLC but was gradually converted to 2. When treated with 0.5 M sodium hydroxide, 23 could not be detected, and its conversion to 2 was complete in 10 min. From these results, it is concluded that the direct trasformation to 2 proceeds via a trioxidotrityl ether (24) through the following electron flow.



23 24

It seems that the cleavage of the $O^{5'}$–C bond becomes feasible since the oxido group has a lower Hammett σ_p value of −0.52 than the hydroxyl group. It was also con-

Table II. Stabilities of Tr, TATr, and TBTr Groups in 80% Acetic Acid[a,b]

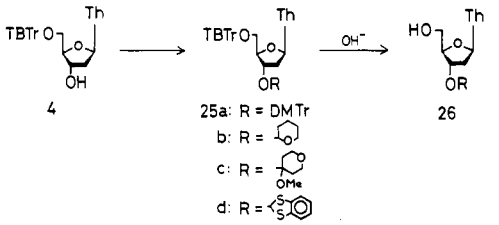
	TrT	TATrT	TBTrT
$t_{1/2}$	5 h	23 h	25 h
t_{com}	17 h	5 days	5 days

[a] These experiments were carried out at 20 °C, and the concentration of the substrate was 10 μmol/mL. [b] TrT, TATrT, and TBTrT refer to 5′-*O*-tritylthymidine, 3, and 4, respectively.

(12) The position of the TBTr group attached to the guanine residue could not be determined. The C–N bond cleavage might occur either via the O^6-alkylation or via the N^7-alkylation. In the latter case, the C–N bond was split by an attack of bromide ion on the 1′-carbon after the N^7-alkylation. The former can be equally considered as follows: The O^6-modification of the guanine residue is known to cause dramatic changes in the stability of the glycoside bond and in the reactivity of the N^2-amino group. Therefore, the glycoside bond of 7 became more labile than that of 6. The characteristic changes in the properties of the guanine ring have been reported by the following papers: Daskalov, H. P.; Sekine, M.; Hata, T. *Tetrahedron Lett.* **1980**, *21*, 3899; *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3076. Ti, G. S.; Gaffney, B. L.; Jones, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 1316. Caffney, B. L.; Marky, L. A.; Jones, R. A. *Nucleic Acids Res.* **1982**, *10*, 4351. We feel now that, in connection with recent developments of oligodeoxyribonucleotide synthesis, the protection of the guanine moiety should be desighed by not changing its original skeleton to avoid the deprination. In this sense, we have very recently reported 1,2-bis(isobutyryloxy)ethylene group as a new type of protecting group for the guanine moiety, which fulfills the above requisite (Sekine, M.; Matsuzaki, J.; Hata, T. *Tetrahedron Lett.* **1982**, *23*, 5287).

firmed that the TBTr group could quantitatively be removed from **13–20** by a one-step alkaline treatment.

To see if acid-labile protecting groups can servive under conditions where the TBTr group is removed, we synthesized compounds **25a–d** (see the Experimetal Section). In the synthesis of **25b** and **25c**, pyridinium 3-nitrobenzenesulfonate[13] was chosen as a nonhygroscopic new catalyst for the pyranylations. The new reagent proved to be very useful since it provided the smooth and clean reactions.



Alkaline hydrolysis of **25a–d** yielded the 5'-free thymidine derivatives **26a–d** in more than 95% yields. The isolation of **26a–d** was simply done since the byproducts, benzoic acid and rosolic acid, could be removed into the aqueous layer. Evaporation of the organic extract usually gave the deblocked material with a satisfactory purity. Selective deprotection of the DMTr group from **25a** was also achieved by treatment with 80% acetic acid to give **4** in 95% yield.

Generally, compounds containing the TBTr group can be easily detected as distinct spots on TLC since it has a very strong UV absorbance around 254 nm. For example, the ϵ values (dioxane) of **21** are 1.84×10^4 at 254 nm and 3.91×10^4 at 240 nm (λ_{max}). TBTr-containing compounds can also be detected on TLC by heating, which gives an orange color like that of 4,4',4''-trimethoxytritylcarbonium ion. The orange spot turns gradually reddish orange upon prolonged heating. More interestingly, the presence of the TBTr group can be confirmed by exposure to a vapor of concentrated ammonia. This treatment gives a reddish orange product. The isolation of products with the TBTr group is generally very easy because it is readily eluted in eary fractions from a column.

In these points, the TBTr group is superior to the previously known hindered base-labile protecting groups of primary hydroxyl groups.

Experimental Section

^{1}H NMR spectra were recorded at 60 MHz on a Hitachi R24-B spectrometer and at 100 MHz-PS-100 spectrometer. UV spectra were measured on a Hitachi 124 spectrophotometer. Melting points were taken on a Fisher-Johns melting point block and are uncorrected. Reagent grade pyridine was distilled after being refluxed over *p*-toluenesulfonyl chloride for several hours, redistilled over calcium hydride after being refluxed for several hours, and stored over 3A molecular sieves. Methylene chloride was dried over P_4O_{10} overnight, decanted, distilled from potassium carbonate, and stored over 3A molecular sieves. Benzene was distilled and stored over sodium wire. Dioxane (1 L) was purified by passing nitrogen gas into the refluxing mixture which contained concentrated hydrochloric acid (13 mL) and water (10 mL) followed by neutralization with potassium hydroxide, extraction, and distillation over sodium wire. TATrCl and TBTrCl were prepared according to the literature methods.[10] Column chromatography was performed by using silica gel C-200 purchased from Wako Co. Ltd., and a mini air pump for a goldfish basin was conveniently used to gain a medium pressure for rapid chromatographic separation. Thin-layer chromatography was performed on precoated TLC plates (silica gel 60 F-254, Merck, Art. No. 5715). The R_f values of the protected nucleoside derivatives were measured after development with CH_2Cl_2–MeOH (9:1 v/v) unless otherwise noted. Elemental analyses were performed by the Microanalytical Laboratory, Tokyo Institute of Technology, at Nagatsuta. Analytically pure samples of nucleoside derivatives were obtained by reprecipitation from chloroform with hexane. Their melting points were not given here because they did not have clear melting points except for **4** which was obtained as crystals. No attempts to crystallize the powdery materials from appropriate solvents have been made.

4,4',4''-Triacetoxytrityl Bromide (TATrBr). A mixture of TATrOH (1.74 g, 4 mmol) and thionyl bromide (372 μL, 4.8 mmol) in dry benzene (20 mL) was heated until sulfur dioxide and hydrogen bromide gases began to be generated. The mixture was then refluxed for 15 min. The solution was evaporated to remove the solvent, and the gases were removed by an aspirator at room temperature. The residue was dissolved in hot benzene (30 mL). The insoluble materials were filtered, and the filtrate was cooled. The crystals were collected and washed with benzene (3 mL) to give TATrBr: 1.1 g (54%); mp 164–166 °C (161 °C soften); ^{1}H NMR ($CDCl_3$) δ 2.27 (s, 1, $C(O)CH_3$), 6.93 (d, J = 8 Hz, 6, Ar H), 7.25 (d, J = 8 Hz, 6, Ar H). Anal. Calcd for $C_{25}H_{21}O_6Br$: C, 60.38; H, 4.26. Found: C, 60.22; H, 4.51.

4,4',4''-Tris(benzoyloxy)trityl Bromide (TBTrBr). A mixture of TBTrOH (4.4 g, 6 mmol) and acetyl bromide (2 mL) in dry benzene (15 mL) was refluxed for 1 h. After being cooled, the solution was diluted with dry benzene (20 mL) and filtered to remove a small amount of insoluble material. To the benzene solution was added dry hexane (40 mL). The resulting precipitate was collected and washed with dry hexane–benzene (2:1 v/v, 50 mL) and then with dry hexane (10 mL) to afford the white crystals of TBTrBr: 4.1 g (95%); mp 189–191 °C (185 °C soften); ^{1}H NMR ($CDCl_3$) δ 6.98 (m, 24, benzene and Ar H), 8.02–8.30 (m, 6, Ar H). Anal. Calcd for $C_{40}H_{27}O_6Br$: C, 70.29; H, 3.98. Found: C, 70.66; H, 4.08.

5'-*O*-(4,4',4''-Triacetoxytrityl)thymidine (3). Thymidine (242 mg, 1 mmol) was coevaporated twice with dry pyridine and dissolved in dry pyridine (3 mL). The solution was allowed to react with TATrBr (663 mg, 1.3 mmol) and stirred for 24 h. After being quenched by water, the mixture was extracted with CH_2Cl_2 (3 × 20 mL) and dried over Na_2SO_4. After filtration the solvent was removed in vacuo, and the residue was coevaporated with toluene to remove the last traces of pyridine. Column chromatography on silica gel (25 g) with CH_2Cl_2–hexane to give **3** (439 mg, 67%) as crude material. Further chromatographic purification with silica gel (20 g) gave 202 mg of **3**, which appeared as almost one spot on TLC. The repeated purification in this manner caused loss of half the material: R_f 0.49; ^{1}H NMR ($CDCl_3$) δ 1.57 (s, 3, CH_3), 2.29 (s, 9, $CH_3(O)$), 3.39 (m, 2, 5'-H), 3.54 (m, 1, OH), 4.01 (m, 1, 4'-H), 4.38 (m, 1, 3'-H), 6.30 (t, J = 6 Hz, 1, 1'-H), 7.01 (d, J = 8 Hz, 6, Ar H), 7.24 (s, 1, C=CH), 9.61 (br s, 1, NH). Anal. Calcd for $C_{35}H_{34}N_2O_{11}$: C, 63.82; H, 5.20; N 4.25. Found: C, 63.93; H, 5.67; N, 4.04.

5'-*O*-[4,4',4''-Tris(benzoyloxy)trityl]thymidine (4). Thymidine (242 mg, 1 mmol) was coevaporated twice with dry pyridine and dissolved in dry pyridine (3 mL). To the solution was added TBTrBr (828 mg, 1.15 mmol), and the mixture was stirred vigorously at 65 °C for 2 h. After being cooled to room temperature, the mixture was quenched with water and extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was coevaporated with toluene (2 × 10 mL). To the resulting syrup was added benzene (20 mL) with vigorous shaking. The resulting precipitate was collected and washed with benzene (20 mL) to give **4**: 771 mg (91%); mp 150–152 °C (145 °C soften). The other physical properties are listed in Table III (supplementary material).

General Procedure for Reactions of Nucleoside Derivatives 5–11 and Methyl α-D-Glucopyranoside (12). An appropriate substrate (1 mmol) was coevaporated several times with dry pyridine and dissolved or suspended in the solvent listed in Table I. If necessary, triethylamine was added. Then TBTrBr

(13) Sekine, M.; Hata, T. *J. Am. Chem. Soc.*, in press.
(14) Matteucci, M. D.; Caruthers, M. H. *Tetrahedron Lett.* **1980**, *21*, 3243.
(15) Sierakowska, H.; Shugar, D. *Acta Biochim. Pol.* **1971**, *18*, 143.
(16) Reese, C. B.; Saffhill, R.; Sulton, J. E. *J. Am. Chem. Soc.* **1967**, *89*, 3366. Arentzen, R.; Reese, C. B. *J. Chem. Soc., Perkin Trans. 1* **1977**, 445.

was added, and the mixture was stirred. After the reaction was carried out at room temperature or at 65 °C, the mixture was quenched with ice–water and then extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. After removal of the solvent in vacuo, the residue was coevaporated twice with toluene (2 × 10 mL) and chromatographed on a column of silica gel (30 g) with hexane–CH_2Cl_2, CH_2Cl_2, and then CH_2Cl_2–MeOH to give the product as listed in Table I.

The physical properties and elemental analyses of the products are summarized in Table III (supplementary material).

General Procedure for Removal of TBTr Group from 13–19. An appropriate sample (0.1 mmol) was dissolved in dioxane (1.25 mL) and then a mixture of 2 M sodium hydroxide (1.25 mL) and ethanol (2.5 mL) was added. The solution was kept at room temperature for 10 min and neutralized with Dowex 50W-X2 (pyridinium form). The resin was filtered, and the filtrate was evaporated and coevaporated with toluene (2 × 2 mL). The residue was analyzed by thin-layer chromatography. Generally, only three spots of the unprotected product, rosolic acid, and benzoic acid were observed on TLC. The R_f values of the unprotected material obtained in several solvent systems were identical with those of an authentic sample. In the case of **14**, N^6-benzoyladenine was formed in ca. 5–10% yield by this treatment.

3′-*O*-(4,4′-Dimethoxytrityl)-5′-*O*-[4,4′,4″-tris(benzoyloxy)trityl]thymidine (25a). Compound **4** (253 mg, 0.3 mmol) was coevaporated with dry pyridine and dissolved in dry pyridine (1.5 mL). To the mixture was added DMTrCl (203 mg, 0.6 mmol), and the solution was heated at 70 °C for 4 h. After being cooled to room temperature, the mixture was quenched with water and extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were combined, evaporated in vacuo, and coevaporated with toluene (2 × 5 mL). The residue was chromatographed on a column of silica gel (20 g) with hexane–CH_2Cl_2 to give **25a**: 330 mg (96%); R_f 0.77; ^{1}H NMR ($CDCl_3$) δ 1.56 (s, 3, CH_3), 1.88 (m, 1, 2′-H_a), 2.34 (m, 1, 2′-H_b), 3.18 (m, 2, 5′-H), 3.76 (s, 6, OCH_3), 4.04 (m, 1, 4′-H), 4.42 (m, 1, 3′-H), 6.40 (t, J = 7 Hz, 1, 1′-H), 6.68–7.75 (m, 35, Ar H and C=CH), 8.19 (m, 6, Ar H), 8.33 (s, 1, NH). Anal. Calcd for $C_{71}H_{58}N_2O_{13}$: C, 74.33; H, 5.10; N, 2.44. Found: C, 73.89; H, 5.19; N, 2.36.

3′-*O*-(Tetrahydropyran-2-yl)-5′-*O*-[4,4′,4″-tris(benzoyloxy)trityl]thymidine (25b). A mixture of **4** (85 mg, 0.1 mmol) and pyridinium *m*-nitrobenzenesulfonate[13] (28 mg, 0.1 mmol) was dissolved in dry CH_2Cl_2 (1 mL), and 2,3-dihydropyran (91 μL, 1 mmol) was added. After the mixture was stirred for 15 h, the mixture was extracted with CH_2Cl_2 (3 × 20 mL) and H_2O (20 mL). The organic extracts were combined, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by chromatography on a column of silica gel (5 g) with hexane–CH_2Cl_2 to afford **25b**: 88 mg (95%); R_f 0.71; ^{1}H NMR ($CDCl_3$) δ 1.40–1.96 (m, 6, THP), 2.33 (m, 2, 2′-H), 3.49 (m, 2, 5′-H), 3.69 (m, 2, THP), 4.10 (m, 1, 4′-H), 4.56 (m, 1, 3′-H), 4.65 (m, 1, OCHO), 6.34 (t, J = 6.8 Hz, 1, 1′-H), 7.10–7.76 (m, 22, 6-H and Ar H), 8.19 (m, 6, Ar H), 8.53 (s, 1, NH). Anal. Calcd for $C_{55}H_{48}N_2O_{12}·0.5H_2O$: C, 70.42; H, 5.27; N, 2.99. Found: C, 70.69; H, 5.12; N, 2.99.

3′-*O*-(4-Methoxytetrahydropyran-2-yl)-5′-*O*-[4,4′,4″-tris(benzoyloxy)trityl]thymidine (25c). A mixture of **4** (85 mg, 0.1 mmol) and pyridinium *m*-nitrobenzenesulfonate[13] (28 mg, 0.1 mmol) was dissolved in dry CH_2Cl_2 (1 mL), and 4-methoxy-5,6-dihydro-2*H*-pyran[17] (1 mmol) was added. The mixture was stirred for 20 min and then extracted with CH_2Cl_2 (3 × 20 mL) and H_2O (20 mL). The usual workup gave **26c**: 92 mg (96%); R_f 0.68; ^{1}H NMR ($CDCl_3$) δ 1.68 (s, 3, CH_3), 1.72 (m, 4, CH_2), 2.32 (m, 2, 2′-H), 3.12 (s, 3, OCH_3), 3.20–3.88 (m, 6, CH_2–O and 5′-H), 4.16 (m, 1, 4′-H), 4.60 (m, 1, 3′-H), 6.35 (t, J = 7 Hz, 1, 1′-H), 7.10–7.75 (m, 22, Ar H and C=CH), 8.19 (m, 6, Ar H), 8.85 (s, 1, NH). Anal. Calcd for $C_{56}H_{50}N_2O_{13}·H_2O$: C, 68.84; H, 5.36; N, 2.87. Found: C, 69.04; H, 5.05; N, 2.84.

3′-*O*-(1,3-Benzodithiol-2-yl)-5′-*O*-(4,4′-dimethoxytrityl)thymidine (25d). Compound **4** (253 mg, 0.3 mmol) was dissolved in a mixture of dry CH_2Cl_2 (1.2 mL) and dry pyridine (58 μL, 0.72 mmol), and 1,3-benzodithiolium tetrafluoroborate[18,19] (108 mg, 0.45 mmol) was added. After the mixture was stirred for 18 h, the salt (36 mg, 0.15 mmol) was added. After being stirred for an additional 7 h, the mixture was extracted with CH_2Cl_2 (3 × 20 mL) and H_2O (20 mL). The usual workup gave **25d**: 203 mg (68%); R_f 0.74; ^{1}H NMR ($CDCl_3$) δ (s, 1, CH_3), 2.12 (m, 1, 1′-H_a), 2.56 (m, 1, 1′-H_b), 3.38 (m, 2, 5′-H), 4.11 (m, 1, 4′-H), 4.38 (m, 1, 3′-H), 6.23 (t, J = 6 Hz, 1, 1′-H), 6.71 (s, 1, SCHS), 7.00, 7.75 (m, 26, 6-H and Ar H), 8.10–8.34 (m, 7, Ar H and NH). Anal. Calcd for $C_{57}H_{44}N_2O_{11}S_2·H_2O$: C, 67.44; H, 4.57; N, 2.80. Found: C, 67.64; H, 4.34; N, 2.66.

General Procedure for Removal of TBTr Group from 25a–d. An appropriate sample (0.1 mmol) was dissolved in dioxane (1.25 mL) and a mixture of 2 H sodium hydroxide (1.25 mL) and ethanol (2.5 mL) was added. After 10 min the mixture was diluted with water (5 mL) and extracted with CH_2Cl_2 (2–6 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, and evaporated in vacuo. The residue was almost one spot of the unprotected product. Purification was performed by short column chromatography on a column of silica gel (2 g). The isolated unprotected product was identified with an authentic sample by comparison of its NMR spectrum.

Selective Deprotection of the DMTr Group from 25a. Compound **25a** (229 mg, 0.2 mmol) was suspended in 80% acetic acid (20 mL). The suspension was vigorously stirred. After 25 min, the homogeneous solution was obtained. Vigorous stirring was continued for an additional 25 min, and then the mixture was evaporated in vacuo. The residue was chromatographed on a column of silica gel (5 g) with CH_2Cl_2 to give **4** (101 mg, 95%).[17]

Registry No. **2**, 50-89-5; **3**, 86610-68-6; **4**, 86610-69-7; **5**, 4836-13-9; **6**, 4546-72-9; **7**, 68892-42-2; **8**, 58-96-8; **9**, 13089-48-0; **10**, 4546-55-8; **11**, 64350-24-9; **12**, 97-30-3; **13**, 86610-70-0; **14**, 86610-71-1; **15**, 86610-72-2; **17**, 86610-73-3; **18**, 86610-74-4; **19**, 86610-75-5; **20**, 86610-80-2; **21**, 86610-81-3; **25a**, 86610-76-6; **25b**, 86610-77-7; **25c**, 86610-78-8; **25d**, 86610-79-9; **26a**, 76054-81-4; **26b**, 76541-04-3; **26c**, 86610-82-4; **26d**, 84752-64-7; TATrBr, 86610-65-3; TATrOH, 86632-04-4; TBTrBr, 86610-66-4; TBTrOH, 86610-67-5.

Supplementary Material Available: Table III containing elemental analysis and physical properties of compounds containing the TBTr group (3 pages). Ordering information is given on any current masthead page.

(17) Reese, C. B.; Saffihill, R.; Sulston, J. E. *Tetrahedron* **1970**, *26*, 1023.
(18) Nakayama, J.; Fujiwara, K.; Hoshino, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3567.
(19) Degani, I.; Fochi, R. *Synthesis* **1976**, 489.