Synthesis of 3'-O-(ω-Aminoalkoxymethyl)thymidine 5'-Triphosphates, Terminators of DNA Synthesis that Enable 3'-Labelling

Jari Hovinen,*a,b Elena Azhayeva,a,c Alex Azhayev,a*c Andrei Guzaeva and Harri Lönnberg

*University of Turku, Department of Chemistry, FIN-20 500 Turku, Finland
b Turku Centre for Biotechnology, BioCity, FIN-20 520 Turku, Finland
c Joint Biotechnology Laboratory, BioCity, FIN-20 520 Turku, Finland

Treatment of 5'-O-benzoylthymidine 1 with a mixture of acetic anhydride, acetic acid and dimethyl sulfoxide yielded 5'-O-benzoyl-3'-O-methylthiomethylthymidine 2, which was converted via the 3'-O-bromomethyl derivative into 3'-O-(ω-aminoalkoxymethyl)thymidines 7 bearing a 6, 8 or 10 methylene groups long hydrocarbon chain, and finally to their 5'-triphosphates 10. The latter compounds were shown to be terminators of DNA synthesis catalysed by thermostable Tet/λ DNA-polymerase, and may be labelled at the aliphatic amino group with fluorescent probes.

Quite recently a rapid solid-phase method, called mini-sequencing, has been introduced for the detection of point mutation of DNA.1,2 The method involves hybridization of immobilized single-stranded DNA with a primer that ends immediately before the site of mutation, and elongation of the chain with a single labelled deoxyribonucleoside 5'-triphosphate. Parallel runs with each of the four possible nucleotides enable identification of the mutated base. Thus far only radiochemically labelled nucleotides have been used. Application of nonradioactive techniques, such as fluorescence detection, is hampered by the fact that the nucleoside triphosphates bearing the fluorescent probe should be reasonably good substrates of DNA polymerase. As a first step in our efforts to find a common labelling strategy for all the nucleotides occurring in DNA, we now report on the preparation of some thymidine 5'-triphosphates bearing a long chain aminoalkoxymethyl side arm at 3'-O. Their ability to serve as specific terminators of DNA synthesis catalysed by DNA polymerases was studied before and after attachment of fluorescent probes to their amino function.

Results and Discussion
The reaction sequence utilized in the preparation of 3'-O-(ω-aminoalkoxymethyl)thymidine 5'-triphosphates is depicted in Scheme 1. The key steps are discussed below.

Formation of the Methylthiomethyl Ether 2.—Methylthiomethyl ethers are well-known by-products of the oxidation of alcohols with a mixture of acetic anhydride and dimethyl sulfoxide (DMSO).3,4 The amount of these by-products has been shown to vary from traces to more than 70% depending on the nature of the alcohol. Addition of acetic acid to the reaction mixture markedly increases the yield of the methylthiomethyl ether.5 This observation was exploited in the preparation of 3'-O-methylthiomethylthymidine. Treatment of 5'-O-benzoylthymidine10 1 with a mixture of DMSO, acetic acid and acetic anhydride (54:11:35, v/v) for 2 days at ambient temperature gave, after purification, an almost 70% yield of the desired 3'-O-methylthiomethyl derivative 2.

Attachment of the Aliphatic Arm to O3'.—The methylthiomethyl ether, 2, was first converted into the more reactive bromomethyl ether,6,7,11-14 by treating 2 with N-bromosuccinimide (NBS) or molecular bromine in dry dichloroethane. When the 5'-O-benzoyl-3'-O-bromomethylthymidine obtained was allowed to react in situ with a long-chain ω-bromo alcohol (6 to 10 carbons), in the presence of 2,6-lutidine (2,6-dimethylpyridine), the corresponding 3'-O-(ω-aminoalkoxymethyl)thymidines 3a-c were formed. The same methodology has successfully been used also with appropriately protected guanosine, cytidine and adenosine analogues without severe side reactions.6 It has been shown that when N-iodosuccinimide (NIS) is used as the halogen source in a large excess (sixfold), the main product is the corresponding succinimide derivative, 3d.12,13 In the present synthesis only traces of this kind of side product were formed, and the formation of the side product was completely prevented by using molecular bromine as a thiophilic promoter instead of N-halogenosuccinimide. However, a small amount (~ 10%) of another, slow-migrating side product was formed (Rf 0.29 compared to 0.37 of 3a; MeOH–CHCl3, 3:97, v/v). The product had an identical UV spectrum with the main product, and its 1H NMR spectrum exhibited double signals for H6 and sugar protons, but only single peaks for the aliphatic arm and a singlet (2H) at δ 5.47 probably referring to NCH2O. After deprotection with methanolic ammonia, the 13C NMR showed four signals in the carbonyl carbon region of the thymidine residue. Accordingly, the side product may tentatively be assigned as a dimer 3e containing a methylene bridge between O3' of one thymidine and N3' of the other.

The ω-bromo substituent was displaced by azide ion by heating 3a-c in a mixture of sodium azide and lithium chloride in dimethylformamide (DMF). The reaction mixture was ‘buffered’ with ammonium chloride to prevent the cleavage of the base labile 5'-O-benzoyl group. The displacement was almost quantitative. After conventional work up, the product, 4a-c, was purified by silica gel column chromatography. The overall yield starting from 2 was normally about 50%.

The original idea was to debenzyloate 4a-c, phosphorylate the deblocked 5'-OH (5a-c) and then reduce the azido group to an amino function. Unfortunately, the reduction of azido to amino with triphenylphosphine in a mixture of aqueous ammonia and dioxane failed, when applied to triphosphates, although the corresponding azido nucleosides 5a-c were rapidly reduced with an excess of triphenylphosphine in pyridine. It has also been reported that 3'-azido-3'-deoxythymidine 5'-triphosphate can easily be reduced to the 3'-amino analogue by the method described above.15

Since the azido group was reduced at nucleoside level, the resulting amino function has to be protected before phosphorylation of 5'-OH. This was done by treating the aminoalkoxy-
methyl nucleosides 7a-c with an excess of methyl trifluoroacetate in dry DMF. When the ester was dry and freshly distilled, the reaction was quantitative and the product 8a-c was easily isolated on a short silica gel column.

Synthesis of 5′-Triphosphates.—A modification of the method of Ötvös et al.16 was applied to the preparation of the nucleoside 5′-triphosphates, 9a-c. According to the original method, the nucleoside is allowed to react with phosphorus oxychloride in dry trimethyl phosphate, and the intermediate formed is treated in situ with bis(tributylammonium) pyrophosphate. Unfortunately, phosphorylation of the nucleoside with POCl₃ requires a prolonged treatment, and hence the hydrogen chloride liberated may cleave the acetal linkage in 8a-c. To avoid this, a slightly different approach was applied. The nucleoside was first treated with phosphoryltris(triazole) in dry acetonitrile17 and the intermediate obtained was allowed to react overnight with bis(tributylammonium) pyrophosphate. The remaining triazole ligand was hydrolysed by addition of water to give 9a-c. Treatment of 9a-c with aqueous ammonia gave 10a-c as the final products.

In order to demonstrate the usefulness of 3′-O-(o-aminoalkoxymethyl)thymidine 5′-triphosphates prepared as substrates of DNA polymerases even when attached to bulky fluorescent groups, 10a was labelled with fluorescein isothiocyanate. The reaction was quantitative and the product, 11, was purified by HPLC.

Termination of DNA Synthesis Catalysed by Thermotable Tetz-DNA Polymerase.—Compounds 10a-c differ significantly from the well-known terminators of DNA synthesis, such as 2′,3′-dideoxyribonucleoside 5′-triphosphates and 3′-amino-2′,3′-dideoxyribonucleoside 5′-triphosphates. Their o-aminoalkoxymethyl side arms enable attachment of reporter groups, either before or after enzymatic incorporation into DNA, and hence labelling of the 3′-terminus of DNA. The potential advantages of the usage of a long flexible acetal arm were...
expected to be (i) the reporter groups may be kept distant from the catalytic centre of the polymerase enzymes, and (ii) the flexible arm would not severely restrict the conformational motion that the sugar ring undergoes on binding to enzyme. Indeed, compounds 10a-c, as well as their analogues bearing a trifluoroacetyl 9a-c or fluorescein group 11, at the amino function were observed to be specific terminators of DNA synthesis catalysed by thermostable polymerases.* Fig. 1 shows the results obtained with Tet/ D, using 2',3'-dideoxyribonucleoside 5'-triphosphates and compounds 9a, 10a-c and 11 as terminators. It is clearly seen that 3'-O-(o-aminoalkoxymethyl)thymidine 5'-triphosphates 10a-c as well as their analogues, 9a and 11, terminate DNA synthesis, giving patterns very similar to that of 2',3'-dideoxythymidine 5'-triphosphate.

**Experimental**

All solvents used were of analytical grade and were distilled and dried before use. Thymidine was purchased from Sigma and o-bromo alcohols and fluorescein isothiocyanate from Aldrich. Adsorption column chromatography was performed on columns of silica gel 60 (Merck), and triphosphates were purified on Fractogel TSK DEAE-640(M) (Merck). TLC was conducted on silica-60 F254 plates (Merck). The melting points reported are uncorrected. NMR spectra were recorded on a JEOL JNM GX-400 spectrometer operating at 399.8, 100.5 and 161.9 MHz for 1H, 13C and 31P, respectively. Coupling constants are given in Hz. Tetramethylylsilane was used as internal (1H, 13C) and H3PO4 as external reference (31P). 13C NMR data of the compounds prepared are listed in Table 1. IR spectra were recorded on Perkin-Elmer 1600 FT-IR spectrophotometer and UV spectra on Perkin-Elmer lambda-2 spectrophotometer. Elemental analyses were performed by Analytische Laboratorien, Germany, or at Department of Chemistry, University of Oulu, Finland. Tet/ D DNA-polymerase from *Thermus* thermophilus was generously supplied by Dr. V. Kiselev (Research Center of Molecular Diagnostics and Therapy, Moscow, Russia). 2'-Deoxyadenosine 5'-[32P]triphosphate (initial specific activity 1300 Ci mmol−1) was obtained from NEN. 2'-Deoxy-and 2',3'-dideoxy-ribonucleoside 5'-triphosphates were from Pharmacia, and control single stranded M 13 mp 18 DNA from USB.

5'-O-Benzoyl-3'-O-methylthiomethylthymidine 2.—Compound 110 (15.0 g, 43.3 mmol) was dissolved in DMSO (145 cm3) and acetic acid (29 cm3) and acetic anhydride (93 cm3) were added. The mixture was stirred at room temperature for 2 days, i.e. until no starting material was detected by TLC, and then was evaporated to give an oily residue. The oil was dissolved in methylene chloride (150 cm3) and washed with sat. aq. NaHCO3 (33 cm3). The organic layer was dried (Na2SO4), filtered and evaporated to dryness. The resulting solid was purified on a silica gel column, using CH2Cl2 containing from 0 to 2% MeOH as eluent. Pure fractions were combined and concentrated, and the residue was crystallized from toluene to give the title compound 2 (12.0 g, 68%) as a white powder; m.p. 135 °C; Rf 0.66 (silica gel, CH2Cl2–MeOH, 9:1, v/v); λmax (MeOH)/nm 266; δ(CDCl3) 8.68 (1H, br s, H3), 8.04–7.48 (5H, m, arom), 7.24 (1H, s, H6), 6.30 (1H, dd, J1=1.7, J2=3.4, H1), 4.69 (2H, J4=13.6, OCH2S), 4.65 (1H, dd, J4=3.4, J5=12.2, H5), 4.58 (1H, s, H3'), 4.55 (1H, dd, J5=4.0, H5'), 4.37 (1H, m, H4'), 2.16 (1H, dd, J2=13.8, J3=3.4, H2'), 2.16 (3H, s, SCH3), 2.13 (1H, m, J2=3.9, J3=3.4).

* These results will be published elsewhere.

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*Fig. 1 Gel pattern of the DNA synthesis catalysed by a thermostable DNA-polymerase, Tet/ D, and terminated with 2',3'-dideoxyribonucleoside 5'-triphosphates (ddNTP) and various 3'-O-(o-aminoalkoxymethyl)thymidine 5'-triphosphates 10a-c as well as their analogues, 9a and 11. Tracks 1–4 show termination with ddGTP (7 pmol dm−3), ddATP (147 pmol dm−3), ddCTP (56 pmol dm−3) and ddTTP (86 pmol dm−3), respectively. Tracks 5–9 show termination with 10a (455 pmol dm−3), 10b (350 pmol dm−3) and 10c (210 pmol dm−3), 9a (455 pmol dm−3) and 11 (260 pmol dm−3), respectively.*
The reaction was quenched by addition of aq. NaHSO₃ (20 cm³). The organic layer was separated, dried over Na₂SO₄, and added. The mixture was stirred overnight at room temperature. When the reaction was complete, solvent was evaporated under reduced pressure and the residue was purified on a silica gel column eluting with CH₂Cl₂-MeOH, 97:3 (v/v). λmax(MeOH)/nm 266; δH(CDCl₃) 9.73 (1 H, s, H₃), 8.03-7.47 (5 H, arom.). 7.24 (1 H, s, H₆), 6.32 (1 H, dd, J₄,₅, 2.9, J₅,₆, 11.9, H₅'), 4.55 (1 H, m, J₆,₇, 4.8, H₅'), 4.44 (1 H, m, H₃), 4.35 (1 H, m, H₄'), 3.56 (2 H, m, OCH₂), 3.39 (2 H, t, J 6.8, CH₂Br), 2.52 (1 H, m, J₆,₇, 14.2, H₂'), 2.17 (1 H, m, J₅,₆, 2.8, J₅',₆', 5.1, H₂'), 1.83 (2 H, m, OCH₂CH₂), 1.66 (3 H, s, CH₃), 1.59 (2 H, m, CH₂CH₂CH₂Br), 1.44 (2 H, m, OCH₂CH₂CH₂CH₂Br) and 1.38 (2 H, m, CH₂CH₂CH₂CH₃).

3'-O-(Azidoalkoxymethyl)-5'-O-benzoylthymidines 5a-c.—Compound 5a-c were obtained as colourless oils (95% yield). 5a: Rf 0.52 (silica gel, CH₂Cl₂-MeOH, 9:1, v/v); λmax(MeOH)/nm 267; δH(CDCl₃) 9.30 (1 H, br s, H₃), 7.43 (1 H, s, H₆), 6.18 (1 H, dd, J₆,₇, 7.0, J₅,₆, 6.7, H₁'), 4.73 (2 H, s, OCH₂), 4.43 (1 H, m, H₃), 4.07 (1 H, m, H₄'), 3.94 (1 H, dd, J₅,₆, 2.7, J₅',₆', 11.9, H₅'), 3.81 (1 H, dd, J₄,₅, 3.1, H₅'), 3.55 (2 H, t, J 6.7, CH₂), 3.27 (2 H, t, J 6.7, CH₂), 2.96 (1 H, br 5'-OH), 2.36 (2 H, m, H',₇', H₂'), 2.19 (1 H, m, 5'-CH₃), 1.60 (4H, m, 2 x CH₂) and 1.40 (4 H, m, 2 x CH₂); νmax/cm⁻¹ 2096 (νC=O). 5b: Rf 0.54 (silica gel, CH₂Cl₂-MeOH, 9:1, v/v); λmax(MeOH)/nm 267; δH(CDCl₃) 8.30 (1 H, br s, H₃), 7.38 (1 H, s, H₆), 6.15 (1 H, dd, J₆,₇, 6.8, H₁'), 4.73 (2 H, s, OCH₂), 4.43 (1 H, m, H₃), 4.08 (1 H, m, H₄'), 3.95 (1 H, dd, J₆,₇, 11.8, H₅'), 3.80 (1 H, dd, H₅', 3.54 (2 H, t, J 6.8, OCH₂), 3.28 (2 H, t, J 6.8, CH₂), 2.96 (1 H, br 5'-OH), 2.36 (2 H, m, H',₇', H₂'), 2.19 (1 H, m, 5'-CH₃), 1.60 (4H, m, 2 x CH₂) and 1.40 (4 H, m, 2 x CH₂); νmax/cm⁻¹ 2096 (νC=O). 5c: Rf 0.56 (silica gel, CH₂Cl₂-MeOH, 9:1, v/v); λmax(MeOH)/nm 267; δH(CDCl₃) 8.40 (1 H, br s, H₃), 7.38 (1 H, s, H₆), 6.16 (1 H, dd, J₆,₇, 7.0, J₅,₆, 6.8, H₁'), 4.73 (2 H, s, OCH₂), 4.41 (1 H, m, H₃), 4.07 (1 H, m, H₄'), 3.95 (1 H, dd, J₆,₇, 11.8, H₅'), 3.80 (1 H, dd, H₅', 3.54 (2 H, t, J 6.8, OCH₂), 3.28 (2 H, t, J 6.8, CH₂), 2.96 (1 H, br 5'-OH), 2.36 (2 H, m, H',₇', H₂'), 2.19 (1 H, m, 5'-CH₃), 1.60 (4H, m, 2 x CH₂) and 1.40 (4 H, m, 2 x CH₂); νmax/cm⁻¹ 2096 (νC=O).
H4'), 3.94 (1 H, dd, J6.8, H5'), 3.81 (1 H, dd, J11.9, H5') and 3.54 (2 H, t, J6.8, OCH2), 3.36 (2 H, q, J6.8, CH2NHCOCF3), 3.28 (1 H, m, 5'-OH); 2.32 (2 H, m, H2', H2''), 1.92 (3 H, s, 5-CH3) and 1.64-1.29 (16 H, m, 8 × CH2). 

The mixture was stirred at room temperature until no starting material could be detected by TLC. The resulting ylide was hydrolysed with 3% ammonia, evaporated to dryness under reduced pressure, suspended in water (30 cm3) and then extracted with diethyl ether (3 × 25 cm3). The aqueous layer was evaporated to dryness to give compound 7a as a white solid (0.93 g, 93.7%).

9a: d,(D,O) 7.60 (1 H, s, H6), 6.15 (1 H, dd, J6.8, H5'), 4.70 (2 H, s, OCH2), 4.42 (1 H, br, 5'-OH), 4.35 (1 H, t, J6.8, H1'), 1.78 (3 H, s, 5-CH3) and 1.50-1.29 (16 H, m, 8 × CH2). The title compound was obtained as a white solid (0.94 g, 94%); d,(MeOH)/nm 266; d,(CDCl3) 8.63 (1 H, br, H3'), 6.17 (1 H, dd, J6.8, H5'), 4.69 (2 H, s, OCH2), 4.31 (1 H, m, H4', J6.8, H5'), 3.93 (1 H, m, H4'), 3.67 (1 H, m, H5'), 3.45 (2 H, t, J6.8, OCH2), 2.50 (2 H, m, CH2NH2, partially overlapping with the signal of solvent), 2.22 (2 H, m, H2', H2''), 1.77 (3 H, s, 5-CH3) and 1.50-1.29 (16 H, m, 8 × CH2).

3'-O-(N-Trifluorocetacetyl-o-aminoalkoxymethyl)thymidines 8a-c—Compound 8a (1.12 g, 2.4 mmol) was dissolved in pyridine (30 cm3) and Ph3P (2 equiv., 4.0 mmol, 1.05 g) was added. The mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated on a rotary evaporator to give 8a (1.10 g, 96%).

9a-c—Compound 9a (0.44 g, 95.1%), 3'-O-(N-trifluoroacetyl-o-aminoalkoxymethyl)thymidine 9a-c was collected and concentrated. The oily residue was further purified on a preparative RP-18 column (Reliasil 300 A, 9 mm) and eluted with water containing 40% (v/v) acetonitrile. The crude material was applied onto an ion exchange column and eluted with a linear gradient [0.0–0.3 mol dm–3 TEAB (triethylammonium hydrogen carbonate) in 50% (v/v, MeCN). The fraction eluted at 0.2 mol dm–3 TEAB was collected and concentrated. The oily residue was further purified on a preparative RP-18 column (Reliasil 300 A, 5 pm, 250 mm × 9 mm) and eluted with water containing 40% (v/v) acetonitrile. 9a: d,(D,O) 7.59 (1 H, s, H6), 6.15 (1 H, dd, J6.8, H5'), 4.72 (2 H, s, OCH2), 4.32 (1 H, m, H4', J6.8, H5'), 3.92 (1 H, m, H4'), 3.66 (1 H, m, H5'), 3.40 (2 H, t, J6.8, OCH2), 2.50 (2 H, m, CH2NH2, partially overlapping with the signal of solvent), 2.22 (2 H, m, H2', H2''), 1.77 (3 H, s, 5-CH3) and 1.50-1.29 (16 H, m, 8 × CH2).

9b: d,(D,O) 7.61 (1 H, s, H6), 6.15 (1 H, d, J6.8, H5'), 4.70 (2 H, s, OCH2), 4.32 (1 H, m, H4', J6.8, H5'), 3.50 (2 H, m, CH2NH2, partially overlapping with the signal of solvent), 4.42 (1 H, m, H3'), 4.15 (1 H, m, H4'), 4.07 (2 H, m, H5', H5''), 4.35 (2 H, m, OCH2), 3.37 (1 H, m, H4', J6.8, H1'), 2.21 (1 H, m, H2', H2''), 1.77 (3 H, s, 5-CH3) and 1.41–1.30 (12 H, m, 6 × CH2).
Purification was performed on reversed-phase HPLC as described above for 9a–c, 10a: δD(D2O) 7.61 (1 H, s, H6), 6.17 (1 H, dd, J1/2, 6.8, J1/2, 5.4, H1'), 4.70 (2 H, s, OCH2O, partial overlapping with the solvent signal), 4.40 (1 H, m, H3'), 2.23 (1 H, m, H2'), 1.79 (3 H, s, 5-CH3) and 1.45–1.15 (12 H, m, 4-CH2); Table 2 records the HPLC retention times, UV absorption maxima and 31P NMR shifts of 9a–c and 10a–c.

**Labelling of Compound 10a with Fluorescein Isothiocyanate.**—Compound 10a (10 OD) (OD = optical density unit) was dissolved in carbonate buffer (0.1 mol dm⁻³, 2.5 cm³, pH = 10.3). Fluorescein isothiocyanate (50 mg) in DMF (2.5 cm³) was added and the pH was readjusted to 10 with NaOH (0.1 mol dm⁻³). The mixture was kept overnight in the dark at room temperature. The pH was adjusted to 3 with HCl (1.0 mol dm⁻³), after which the mixture was extracted with ethyl acetate (4 × 10 cm³). The organic layer was discarded and the aqueous layer was neutralized with sat. NaHCO3, NaHCO3. The crude product was purified by ion exchange column (Synchropak AX-300, 6.5 µm, 6 × 250 mm), wash flow rate 1.0 cm³ min⁻¹, A = 0.03 mol dm⁻³ KH2PO4, 50% formamide (pH = 5.2), B = 0.03 mol dm⁻³ KH2PO4, 1.0 mol dm⁻³ (NH4)2SO4, 50% formamide (pH = 5.6), from A to B in 30 min. * Reversed-phase column (Nucleosil 300-5 C4, 5 µm, 250 mm × 9 mm; Macherey-Nagel, A = 0.05 mol dm⁻³ TEAA, pH 5.5; B = A + 50% MeCN, from 40 to 70% B in 45 min, flow rate 0.8 cm³ min⁻¹). In D2O, external reference H3PO4 (0.00 ppm). Assignments of (P(α) and P(β)) are tentative.

### Table 2 Properties of 3'-O-modified thymidine 5'-triphosphates prepared

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* Abbreviations: dG, 2'-deoxyguanosine; dA, 2'-deoxyadenosine; dC, 2'-deoxycytidine; dT, thymidine; dGTP, dGTP; dATP, dATP; dGMP, 2'-deoxyguanosine 5'-triphosphate; dCTP, 2'-deoxythymidine 5'-triphosphate; dTTP, 2'-deoxyadenosine 5'-triphosphate; dAMP, 2'-deoxyadenosine 5'-triphosphate; dGMP, 2'-deoxyguanosine 5'-triphosphate; dCTP, 2'-deoxythymidine 5'-triphosphate; dTTP, 2'-deoxyadenosine 5'-triphosphate; dAMP, 2'-deoxyadenosine 5'-triphosphate.

### References