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Phenyl phosphotriester derivatives of AZT: Variations upon the SATE moiety

Anne-Laure Villard [a], Gaëlle Coussot [a], Isabelle Lefebvre [a], Patrick Augustijns [b], Anne-Marie Aubertin [c], Gilles Gosselin [a,d], Suzanne Peyrottes [a], Christian Périgaud [a,*]

[a] Institut des Biomolécules Max Mousseron (IBMM), UMR 5247 CNRS - UM 1 & 2, Université Montpellier 2, Case courrier 1705, place E. Bataillon, 34095 Montpellier Cedex 5, France
[b] Laboratory for Pharmaceutical Technology and Biopharmacy, 3000 Leuven, Belgium
[c] Université Louis Pasteur, INSERM 544, 67000 Strasbourg, France
[d] Laboratories Idenix Sarl, Cap Gamma, 1682 rue de la Valsière, 34819 Montpellier Cedex 04, France

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ABSTRACT

Synthesis, in vitro anti-HIV activity, stability studies as well as potential for oral absorption of some novel phenyl *S*-acyl-2-thioethyl (SATE) phosphotriester derivatives of AZT (zidovudine; 3′-azido-2′,3′-dideoxythymidine) are described herein. These pronucleotides are characterized by the presence of polar functions on the SATE biolabile phosphate protections. Whereas derivatives incorporating an amino residue in the vicinity of the thioester functionality display low chemical stability, the introduction of one or two hydroxyl groups on the SATE moieties confers high resistance of the resulting prodrugs towards esterase hydrolysis. Thus, one of these pronucleotides, the monohydroxylated SATE derivative of AZT **2**, is able to cross a Caco-2 cell monolayer mainly in intact form, probing that further development is warranted as a possible HIV-pronucleotide candidate.

1. Introduction

Over the last decade, we have demonstrated the potency of mononucleotide prodrugs (pronucleotides) bearing the *S*-acyl-2-thioethyl (SATE) biolabile phosphate protection. Initially developed with bis(SATE) phosphotriesters,[1–3] this approach was pursued with mixed phosphoester derivatives,[4,5], that is, SATE aryl phosphotriesters[6,7] and SATE phosphoramidate diesters.[8] Such pronucleotides were shown to exhibit enhanced activity in cell culture experiments compared to the corresponding parent nucleoside especially in the case when the first phosphorylation step is hampered.

As part of the development of the SATE aryl phosphotriesters' family, we were interested in studying the influence of polar functions introduced on the acyl portion of the SATE group. Indeed, such a modification would increase the enzymatic stability of the corresponding pronucleotide because of a higher resistance of the polar SATE moiety against esterase hydrolysis, as previously shown in other series of pronucleotides.[9] In this study, we successively introduced one or two hydroxyl functions, as well as amino groups on the *S*-pivaloyl-2-thioethyl (*t*BuSATE) skeleton and evaluated the effect of such variations upon the in vitro anti-HIV activity and enzymatic stability of the resulting phenyl phosphotriester derivatives of AZT (compounds **2**–**4**, Fig. 1) in comparison with the corresponding *t*BuSATE phenyl phosphotriester **1**. Furthermore, we were also interested in studying a SATE moiety built up with an amino acid such as L-valine (compound **5**) in order to favour an active transport of the pronucleotide through cell membranes. Indeed, it is well documented in the literature[10–12] that esterification of the hydroxyl group at the 5′- or 3′-position of nucleoside analogues with L-valine significantly increases their oral bioavailability.

2. Results and discussion

2.1. Chemistry

The preparation of the (*t*BuSATE) phenyl phosphotriester derivative of AZT **1** has previously been described,[13] and the synthesis of the modified SATE derivatives **2**–**5** requires the corresponding thioesters **6**–**9** (Scheme 1). The procedure initially developed[1] for the preparation of the thioester precursors involves thioacids as starting materials. As only few of them are commercially available or as they need to use gaseous and bad-smelling reagent (i.e., dihydrogen sulfide) for their synthesis, we decided to propose an alternative pathway using a one-pot reaction from carboxylic acids. Our new procedure to prepare thioesters **6**–**9** (Scheme 1) involves first an activation of the corresponding acids **10**–**13** using a small excess of 1,1′-carbonyl-diimidazole (CDI) in non polar solvents to avoid the formation of symmetrical anhydrides.[14] Then, the addition of 2-mercaptoethanol was performed at low temperature after dilution of the reaction mixture to limit transposition of the *S*-acyl-2-thioethanol (kinetic isomer) into the corresponding ester

* Corresponding author. Tel.: +33 467 14 38 55; fax: +33 4 67 54 96 10.
E-mail address: perigaud@univ-montp2.fr (C. Périgaud).

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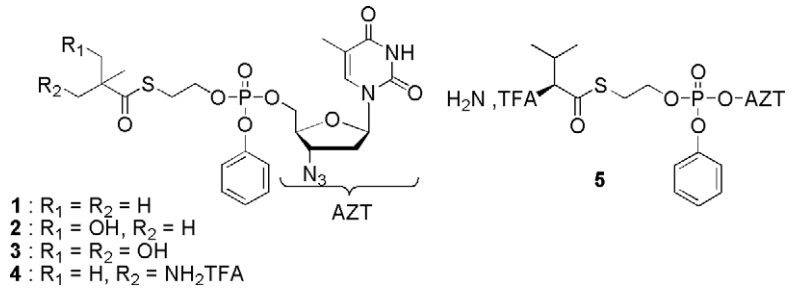
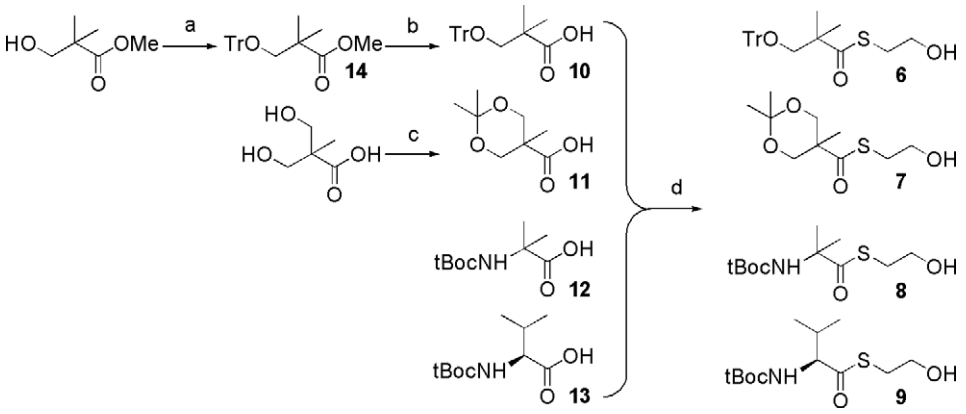


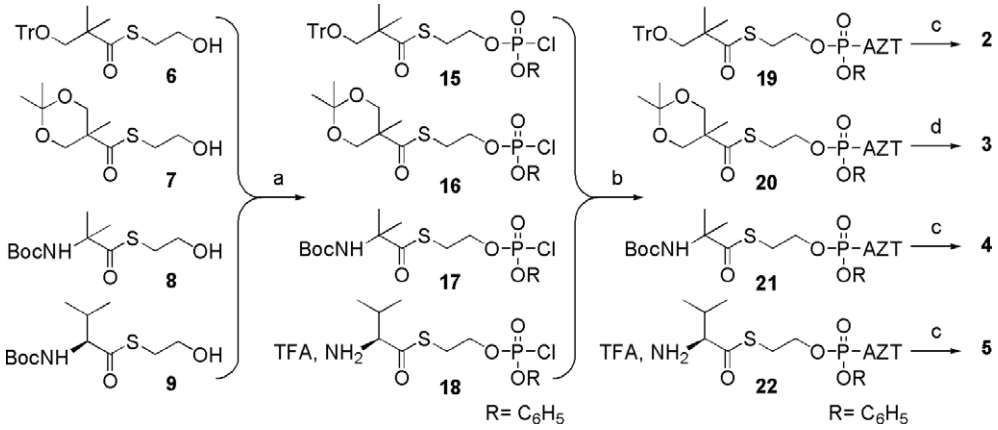
Figure 1. Structures of target compounds.



Scheme 1. Synthesis of thioester precursors. Reagents and condition: (a) TrCl, NEt_3, CH_2Cl_2; (b) NaOH aq 30%, dioxan; (c) $MeC(OMe)_2$, $APTS_{cat}$, CH_2Cl_2, 2 h; (d) CDI, DMF/toluene or CH_2Cl_2, 30 min; then $HO(CH_2)_2SH$, −10 °C, 2 h.

(*O*-acyl-2-thioethanol, thermodynamic isomer).[15] The required acid partners were obtained as follows:

The choice of the protecting groups born by the modified SATE moieties should be done thoughtfully and we decided to use acid-labile protecting groups (trityl, isopropylidene acetal and *tert*-butyloxycarbonyl, *t*Boc) in order to keep the integrity of the target compounds. Indeed, they possess base and nucleophile sensitive functions (thioester, phosphotriester). Consequently, the hydroxyl function of the 2,2-dimethyl-3-hydroxypropanoic methyl ester was protected with a trityl group and led to derivative **14**, which was saponified to obtain the desired acid **10** in 81% overall yield after crystallization. The two hydroxyl functions of the 2,2-bis(hydroxymethyl) propanoic acid were simultaneously protected with an isopropylidene group following a previously published procedure in order to obtain compound **11**.[16] Compounds **12** and **13** were commercially available. Finally, commercial phenyl dichlorophosphate was coupled with the various thioesters **6**–**9** to give the corresponding SATE phenyl phosphorochloridates (compounds **15**–**18**, Scheme 2), which were pure enough (on the basis of their ^1H and ^{31}P NMR spectra) and directly engaged in the next step without further purification. Coupling with AZT was performed in presence of *N*-methylimidazole and led to protected SATE phenyl phosphotriesters **19**–**22** in 63 to 76% yields over the two steps. Removal of the various protecting groups was carried out using diluted trifluoroacetic acid (TFA) or aqueous acetic acid solutions and the target compounds **2**–**5** were isolated,



Scheme 2. Synthetic pathway to the SATE aryl phosphotriester derivatives of AZT. Reagents and conditions: (a) $PhOP(O)Cl_2$, NEt_3, THF, −78 °C to rt, 4 h; (b) AZT, *N*-methylimidazole, THF, 4 h; (c) 20% TFA in CH_2Cl_2, −10 °C to rt, 15 min to 2 h; d) 50% aq AcOH, 4 h.

as mixtures of two diastereoisomers, in high yields after silica gel column chromatography.

2.2. Antiviral activity

All the four SATE phenyl phosphotriesters **2**–**5** were evaluated for their anti-HIV activity in three cell lines, in comparison to the parent nucleoside (AZT) and to the *t*BuSATE phenyl phosphotriester derivative **1** as reference pronucleotide (Table 1). Whereas all compounds showed similar submicromolar activity against HIV-1 replication in CEM-SS and MT-4 cell lines, striking differences were observed in CEM/TK$^-$, thus reflecting their ability to bypass the TK mediated phosphorylation step and/or to deliver AZTMP within the cells.[17,2] Indeed, derivative **2** bearing only one hydroxyl function on the SATE residue exhibited EC_{50} in the micromolar range, demonstrating its potency to act as a pronucleotide of 5′-monophosphate, whereas the introduction of a second hydroxyl group (compound **3**) led to a drastic loss of antiviral activity in the CEM/TK$^-$ cell line. A similar observation could be made for derivatives **4** and **5** incorporating a free amino residue. Determination of the log P values of compounds **1**–**5**, ranging from 2 to 3, showed that any of these derivatives may be able to enter cells through a passive diffusion process. Consequently, a lack of permeation of the cell membrane should not be responsible for the loss of antiviral activity observed for derivatives **3**–**5**. This prompted us to study the behaviour of such new series of SATE phenyl phosphotriesters in various biological media in order to understand the different parameters involved in the variations of antiviral activities observed for the three cell lines used.

2.3. Enzymatic and chemical stability

Stability studies of SATE phenyl phosphotriesters **1**–**5**, as well as *N*-Boc protected derivatives **21** and **22** (vide infra), were carried out in CEM-SS cell extracts and culture medium using our previously described 'HPLC-*on line cleaning*' method.[1] Metabolites were identified using both HPLC/MS coupling and/or standard co-injections.

In the cell culture medium, the derivatives **1**–**3** are slowly hydrolyzed into the corresponding phenyl phosphodiester derivative of AZT through an esterase mediated activation (Scheme 3).[13] A similar decomposition process was observed in cell extracts, but the rate of hydrolysis of the SATE group was quicker in the latter medium. Furthermore, the successive introduction of hydroxyl groups on the acyl residue led to a progressive increase of the stability of the corresponding SATE moiety against esterase hydrolysis (Table 2). This variation of half-life in cell extracts from a few hours for compounds **1** and **2** to several days for derivative **3** may be correlated with the drop of the antiviral effect observed for **3** in the CEM/TK$^-$ cell line. As we previously observed,[6,9] a relative stability in extra cellular medium associated with a rapid intracellular decomposition are key factors for compounds designed to release, within the cells, the parent 5′-mononucleotide through enzymatic activation. It is reasonable to assume that the enzymatic stability of compound **3** may not be appropriate in the context of a cell culture evaluation.

SATE phenyl phosphotriesters **4** and **5** appeared highly unstable in both media and led to the formation of the same metabolite, that is, the phenyl phosphodiester derivative of AZT. As the estimated half-life was less than few minutes, a chemical mechanism of hydrolysis rather than an enzymatic one was suspected. Furthermore, such chemical instability has been previously reported for aminoacyloxymethyl ester prodrugs.[18,19] Thus, stabilities of both derivatives **4** and **5** were evaluated in water and in RPMI 1640. Results are given in Table 3 and compared to the *N*-Boc protected

Table 1
Anti-HIV-1 activity[a] (μM) in three cell culture systems of target compounds **2**–**5** in comparison to the parent nucleoside AZT and the *t*BuSATE phenyl phosphotriester derivative **1**, as a reference pronucleotide

Compound	CEM-SS		MT-4		CEM/TK$^-$	
	EC_{50}[b]	CC_{50}[c]	EC_{50}[b]	CC_{50}[c]	EC_{50}[b]	CC_{50}[c]
AZT	0.003	>100	0.015	>100	> 100	>100
1	0.015	>10	0.81	>10	0.45	>10
2	0.006	>130	0.03	>130	3.9	>130
3	0.012	>150	0.074	>150	>100	>150
4	0.009	>120	0.054	>120	90	>120
5	0.001	>120	0.004	>120	81	>120

[a] All data represent average values for at least three separate experiments. The variation of these results under standard operating procedures is below ±10%.
[b] EC_{50}: effective concentration or concentration required to inhibit the replication of HIV-1 by 50%.
[c] CC_{50}: cytotoxic concentration or concentration required to reduce the viability of uninfected cells by 50%.

Table 2
Calculated half-lives of the phosphotriester derivatives **1**–**5** in CEM-SS cell extracts and culture medium[a]

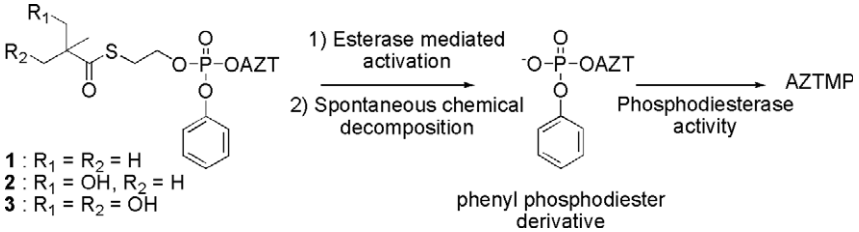
	Compound						
	1	**2**	**3**	**4**	**21**	**5**	**22**
$t_{1/2}$ in culture medium	25.3 d	13.8 d	8.8 d	<1 min	14.1 d	<1 min	8.2 d
$t_{1/2}$ in cell extracts	1.5 h	14.8 h	7.4 d	8 min	1.7 d	<1 min	4.4 d

[a] All data represent average values for three separate experiments and variability was lower than 10%.

Table 3
Chemical stability of the phosphotriester derivatives **4**, **5**, **21** and **22** in various media[a]

	Compound			
	4	**21**	**5**	**22**
$t_{1/2}$ in water (pH 6.8)	>6 d	> 20 d	>6 d	> 40 d
$t_{1/2}$ in RPMI 1640 (pH 7.5)	6 min	>12 d	<1 min	> 9 d

[a] All data represent average values for two separate experiments and variability was lower than 10%.



Scheme 3. Proposed decomposition pathway for the phosphotriester derivatives of AZT **1**–**3**.[13,6]

derivatives **21** and **22**. All four compounds were stable in water, while half-lives observed in RPMI 1640 were similar to the ones obtained in culture medium.

With regard to the nature of the metabolite observed in all experiments, that is, the phenyl phosphodiester derivative of AZT, we dismissed the hypothesis of a nucleophilic attack on the phosphorus atom. Two mechanisms of decomposition could then be proposed, involving a nucleophilic attack either (i) on the carbon atom in the α position to the phosphorus atom or (ii) on the thiocarbonyl function of the SATE chain. This last process may be favoured by the electron-withdrawing effect of the ammonium group of the valine and of the α-amino butyric acid in the vicinity of the thiocarbonyl.[18,19] In this respect, the stability of derivatives **21** and **22** may be due to the presence of a bulky and electron donor protecting group, such as the *t*Boc group. This induced a less susceptibility of the corresponding SATE moieties towards a nucleophilic attack on the vicinal thiocarbonyl.

The implication of the free amino function (within the SATE moiety) which could be involved in the decomposition mechanism through a SN_i or an intermolecular nucleophilic attack was also denied considering the p*K*a of valine being 9.7. Indeed the corresponding amino function mainly exists in its protonated form at the pH of the RPMI 1640 (7.5).

Finally, we highly suspected the participation of nucleophiles present in this medium in the hydrolysis process leading to the loss of the SATE moiety in compounds **4** and **5**.

2.4. Uptake and metabolism in Caco-2 cells

The potential for intestinal absorption was evaluated by assessing the transport properties of the studied pronucleotides in the Caco-2 system. Considering the behaviour of derivatives incorporating the amino acid residues, compounds **4** and **5**, we did not examine their transport properties. In addition, due to the relatively low aqueous solubility (57 μg/mL) of *t*BuSATE phenyl phosphotriester **1**, a reliable quantitative description of its transport was not possible. Thus, transport of phosphotriesters **2** and **3** was evaluated at a target concentration of 100 μM and was initiated by adding the test solution to the apical side (absorptive transport) or basolateral side (exsorptive transport) of the monolayer. Transport was assessed by measuring concentrations of the pronucleotide and its metabolites in the receiver compartment after an incubation period of 2 h. During transport, pronucleotides **2** and **3** were partially metabolized into the corresponding phenyl phosphodiester derivative (Scheme 3), AZTMP, and AZT. These metabolites were identified by co-injection with authentic samples. Absorptive and exsorptive transport of the pronucleotides **2** and **3** in which one or two hydroxyl functions are present on the acyl residue are outlined in Figure 2.

Pronucleotide **2** was able to cross the Caco-2 monolayer mainly in intact form in the absorptive as well as in the exsorptive directions. When assessing its absorptive transport, the analogue **3** could not be detected in the basolateral compartment and the parent nucleoside was essentially observed. In contrast, the pronucleotide **3** appeared in the apical compartment when exsorptive transport was studied and transport in this direction was threefold higher than the absorptive one (on the basis of AZT-equivalents).

These data suggest that the dihydroxylated prodrug **3** may be a substrate for an apically localized efflux carrier modulating its absorptive transport. Compared to pronucleotide **2**, the substrate properties of **3** for a P-gp-like efflux mechanism, associated with a lower diffusion across the cell membrane due to a decreased lipophilicity (Table 4) may be responsible for the observed result and might prevent its intestinal transport. Consequently, lipophilic metabolites (i.e., AZT), resulting from its partial hydrolysis inside mucosal cells, were only observed in the basolateral compartment.

3. Conclusion

Novel SATE phenyl phosphotriesters bearing polar functions (hydroxyl or amine) on the acyl moiety have been synthesized and studied. These mononucleotide prodrugs were shown to exhibit greatly to moderately enhanced activity against HIV compared to the parent nucleoside in vitro. Furthermore, antiviral activity

Table 4
Physicochemical properties of pronucleotides **1**, **2** and **3** in comparison with their parent nucleoside

Compound	M_W	$c\log P_{o/w}$[a]	Aqueous solubility (**g**/**l**)
1	567.56	3.34	0.057
2	583.55	2.30	6.64
3	599.55	1.76	60.6
AZT	267.24	0.06	29.3

[a] Calculated values; log*P* determination was performed using Advanced Chemistry Development (Toronto, Canada) log*P* dB 4.5 calculations.

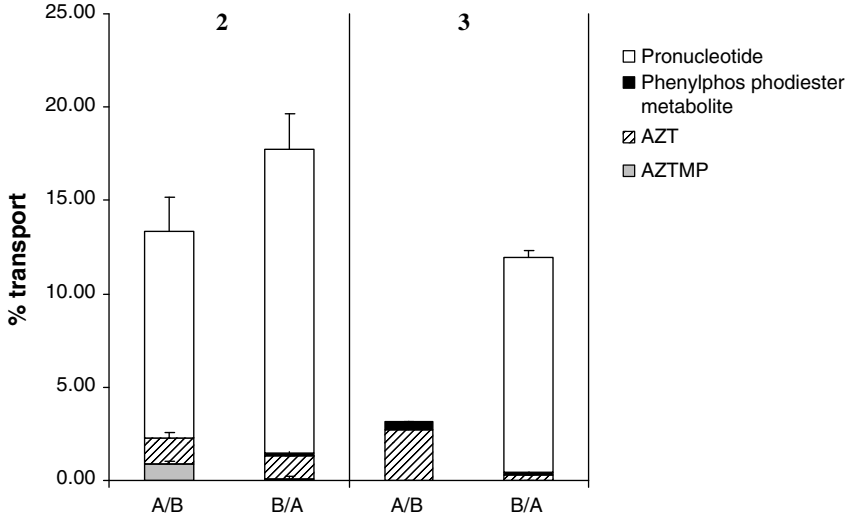


Figure 2. Total cumulative absorptive (A/B) and exsorptive (B/A) transport (±SD) of 100 μM of derivatives **2** and **3** across Caco-2 monolayer (2 h incubation). All data are expressed as percentage of the amount initially added to the apical side (donor compartment).

was mainly retained in kinase-deficient cell lines, which was consistent with the efficient bypass of the first phosphorylation step. Derivatives **2** and **3** proved to be more resistant to esterase mediated hydrolysis than the parent *t*BuSATE phenyl phosphotriester **1** and appeared to deserve further investigations from their biological properties. Thus, intestinal absorption study was carried out and revealed that the monohydroxylated prodrug **2**, being able to cross a Caco-2 cell monolayer in intact form, as the most promising compound prepared in this series. So, combinations of adequate aqueous solubility and enzymatic stability of SATE phenyl phosphotriester derivatives may result in prodrugs with improved pharmacokinetic properties and contribute to the development of orally administered pronucleotides.

4. Experimental

Unless otherwise stated, ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at 75 MHz with proton decoupling at 25 °C on a Bruker 300 Avance or DRX 400. Chemical shifts are given in δ values referenced to the residual solvent peak ($CDCl_3$ at 7.26 ppm and 77 ppm, DMSO-d_6 at 2.49 ppm and 39.5 ppm) relative to TMS. Deuterium exchange, decoupling and COSY experiments were performed in order to confirm proton assignments. Coupling constants, *J*, are reported in Hertz. Two-dimensional ^{1}H–^{13}C heteronuclear COSY were recorded for the attribution of ^{13}C signals. Unless otherwise stated, ^{31}P NMR spectra were recorded at ambient temperature at 121 MHz with proton decoupling. Chemical shifts are reported relative to external H_3PO_4. FAB mass spectra were recorded in the positive-ion or negative-ion mode on a JEOL JMS DX 300 using thioglycerol/glycerol (1:1, v/v, GT) as matrix. Melting points were determined in open capillary tubes on a Büchi-545 and are uncorrected. UV spectra were recorded on an Uvikon 931 (Kontron). Elemental analyses were carried out by the Service de Microanalyses du CNRS, Division de Vernaison (France). TLC was performed on precoated aluminium sheets of silica gel 60 F_{254} (Merck, Art. 9385), visualization of products being accomplished by UV absorbance followed by charring with 5% ethanolic sulfuric acid with heating for nucleotides. Flash chromatography was carried out using 63–100 μm silica gel (Merck Art. No. 115101) otherwise 40–63 μm silica gel (Merck Art. No. 109385) was used. Thin layer chromatography was carried out using aluminium supported silica gel 60 plates (Merck Art. No. 105554). Solvents were reagent grade or purified by distillation prior to use, and solids were dried over P_2O_5 under reduced pressure at rt. Moisture sensitive reactions were performed under argon atmosphere using oven-dried glassware. All aqueous (aq) solutions were saturated with the specified salt unless otherwise indicated. Organic solutions were dried over Na_2SO_4 after workup and solvents were removed by evaporation at reduced pressure.

Analytical HPLC studies were carried out on an Alliance 2690 system (Waters, Milford, Massachusetts, USA) equipped with 996 photodiode detector and a Millennium data workstation. A reverse-phase analytical column (Nucleosil, C_{18}, 150 × 4.6 mm, 5 μm) equipped with a prefilter, and a precolumn (Nucleosil, C_{18}, 5 μm) were used. Detection was monitored at 267 nm. Nucleotidic derivatives were eluted using a linear gradient of 0–80% acetonitrile in 20 mm triethylammonium acetate buffer (pH 6.9) over 30 min at 1 mL/min flow rate. Electrospray ionization–mass spectrometry (ESI-MS) was performed using an SSQ 7000 single quadrupole mass spectrometer (Finnigan, San Jose, CA, USA) in the negative-ion mode with a spray voltage at −4.5 kV. The capillary temperature was maintained at 250 °C. Nitrogen served both as sheath gas (operating pressure of 80 psi) and as auxiliary gas with a flow rate of 15 U. Under these conditions, full scan data acquisition was performed from *m/z* 200 to 800 in centröid mode and using a cycle time of 1.0 s. AZT was from Brantford Chemicals Inc.; phenyl phosphorodichloridate was purchased from Aldrich; N^{α}-*tert*-butoxycarbonyl-L-valine (*t*Boc-Val) and N^{α}-*tert*-butoxycarbonyl-amino isobutyric acid (*t*Boc-Aib) were from Novabiochem. *t*BuSATE phenyl phosphotriester derivative of AZT **1**[13] and 5′-monophosphate of AZT (AZTMP)[20] were synthesized following previously published procedures.

4.1. Biological methods

The origin of the viruses and the techniques used for measuring inhibition of virus multiplication have been previously described.[1]

4.2. Transport studies

Material and methods used were as previously described.[9]

4.3. Stability studies

HPLC analyses were carried out using an improved 'On-line ISRP cleaning method'.[1] Briefly, the crude sample (80 μL, initial concentration 50 μM) was injected onto the precolumn and eluted firstly with 20 mM triethylammonium acetate buffer (pH 6.9) for 5 min at a flow rate of 2 mL/min. Then by activating a six port Rheodine valve and back-flushing the analytes from the precolumn to the column, the analytes were eluted with a linear gradient of 0–80% acetonitrile over 30 min at 1 mL/min flow rate. The decomposition products were identified by HPLC/MS coupling after calibration and/or by co-injection with authentic samples (AZTMP, AZT, etc.). For each incubation time, the calculation of the relative concentration of each species was related to the peak areas, these data were considered as the experimental data. The rate constants of disappearance and the half-lives (kinetic data) of the phosphotriester and phosphodiester derivatives were calculated according to pseudo-first order kinetic models and optimized using mono- or poly-exponential regressions.

For chemical stability studies; buffers and various media were 20 mM TPK (at pH 5.2, 7.2, and 8.2), RPMI 1640 (Gibco BRL) and culture medium (90% RPMI 1640 and 10% Foetal calf serum from Gibco BRL inactivated 30 min at 56 °C).

For biological stability studies; CEM-SS cell extracts were prepared and studies were performed according to published procedure.[1]

4.4. Chemistry

4.4.1. Standard procedure 1: preparation of thioester precursors 6–9

To a stirred solution of the required acid (**10**–**13**, 30 mmol) in a mixture of toluene and anhydrous *N*,*N*-dimethylformamide (20 mL, 2:1, v/v) for **10** and **11**, or anhydrous dichloromethane (for **12** and **13**) was added 1,1′-carbonyldiimidazole (1.3 equiv, 39 mmol) under argon. After 30 min at room temperature, the mixture was cooled to −10 °C, and then diluted with dry toluene (120 mL) and dry *N*,*N*-dimethylformamide (8 mL). 2-Mercaptoethanol (1.3 equiv, 39 mmol) was added under argon and the mixture was allowed to stir at −10 °C. After 2 h, all the volatiles were removed under reduced pressure; the obtained residue was dissolved in chloroform (200 mL), and then extracted twice with water (150 mL). The organic phase was separated, dried over Na_2SO_4, filtered and evaporated under reduced pressure to give the expected *S*-acyl-2-thioethanol derivatives **6**–**9**.

4.4.2. 2,2-Dimethyl-*O*-3-(triphenylmethyl)-propionyl-thioethan-2-ol, 6

Standard procedure 1 from 10.8 g of **10** yielded 12.3 g (98%) of **6** obtained as a colourless oil.

R_f 0.50 (AcOEt/toluene, 2:8, v/v). ^{1}H NMR ($CDCl_3$) δ 7.48 (m, 6H, Ph), 7.33 (m, 9H, Ph), 3.79 (pq, 2H, CH_2CH_2O), 3.25 (s, 2H, $TrOCH_2$), 3.14 (t, 2H, J = 6.0 Hz, SCH_2CH_2), 2.08 (t, 1H, J = 5.7 Hz, OH), 1.30 (s, 6H, $C(CH_3)_2$). ^{13}C NMR ($CDCl_3$) δ 205.4 (CO), 143.7 (Ph ipso), 128.7, 127.7, 127.0 (3s, Ph), 86.3 ($(Ph)_3C$), 70.1 ($TrOCH_2$), 61.8 (CH_2CH_2O), 50.9 ($C(CH_3)_2$), 31.6 (SCH_2CH_2), 22.8 ($C(CH_3)_2$). IR (CCl_4) ν_{max} 1682 cm^{-1}(C=O). MS (FAB > 0, GT) m/z 663 [M+Tr]$^+$, 421 [M+H]$^+$, (FAB < 0, GT) m/z 375 [M−CH_2CH_2OH]$^-$. Anal. for ($C_{26}H_{28}O_3S$): calcd: C, 74.25; H, 6.71; S, 7.62; found: C, 74.05; H, 6.44; S, 7.53.

4.4.3. 2-[(2,2-Dimethyl-1,3-dioxolan)-2-hydroxyethyl]-2-methylpropionyl-thioethan-2-ol, 7

Standard procedure 1 from 5.22 g of **11** yielded 6.89 g (98%) of **7** obtained as a colourless oil.

R_f 0.41 (CH_2Cl_2/CH_3OH, 95:5, v/v). ^{1}H NMR (DMSO-d_6) δ 4.96 (t, 1H, J = 5.5, OH), 4.06 (d, 2H, J = 12.1 Hz, CH_2), 3.68 (d, 2H, J = 12.1 Hz, CH_2), 3.45 (pq, 2H, CH_2CH_2O), 2.94 (t, 2H, J = 6.6 Hz, SCH_2CH_2), 1.35, 1.24 (2s, 6H, $C(CH_3)_2$), 1.06 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 202.2 (CO), 97.5 ($C(CH_3)_2$), 65.2 (CH_2), 59.7 (CH_2CH_2O), 48.4 ($C(CH_3)$), 30.7 (SCH_2CH_2), 25.3, 21.9 (2s, $C(CH_3)_2$), 18.9 (CH_3). IR (CCl_4) ν_{max} 1676 cm^{-1} (C=O). Anal. for ($C_{10}H_{18}O_4S$): calcd: C, 51.26; H, 7.74; S, 13.69; found: C, 51.04; H, 7.88; S, 13.33.

4.4.4. 2-[(*tert*-Butoxycarbonyl)amino]-2-methylpropionyl-thioethan-2-ol, 8

Standard procedure 1 from 6.10 g of **12** yielded 7.68 g (97%) of **8** obtained as a colourless oil.

R_f 0.24 (AcOEt/hexane, 4:6, v/v). ^{1}H NMR (DMSO-d_6) δ 7.55 (bs, 1H, NH), 4.87 (pt, 1H, J = 4.9 Hz, OH), 3.39–3.37 (m, 2H, CH_2CH_2O), 2.82 (t, 2H, J = 6.7 Hz, SCH_2CH_2), 1.37 (s, 9H, *t*Bu), 1.30 (1s, 6H, $C(CH_3)_2$). ^{13}C NMR (DMSO-d_6) δ 204.3 (COS), 154.3 (COO), 78.3 ($C(CH_3)_3$), 61.4 ($C(CH_3)_2$), 60.1 (CH_2CH_2O), 30.6 (SCH_2CH_2), 28.3 ($C(CH_3)_3$), 25.1 ($C(CH_3)_2$). IR (CCl_4) ν_{max} 1700 cm^{-1}(C=O thioester), 1727 cm^{-1}(C=O carbamate). Anal. for ($C_{11}H_{21}NO_4S$): calcd: C, 50.17; H, 8.04; S, 12.18; found: C, 50.54; H, 7.94; S, 12.43.

4.4.5. 2-[(*tert*-Butoxycarbonyl)amino]-3-methylbutionyl-thioethan- 2-ol, 9

Standard procedure 1 from 6.52 g of **13** yielded 8.16 g (98%) of **9** obtained as a colourless oil.

R_f 0.36 (AcOEt/hexane, 4:6, v/v). ^{1}H NMR (DMSO-d_6) δ 7.49 (d, 1H, J = 8.3 Hz, CHN*H*), 4.91 (t, 1H, J = 5.4 Hz, OH), 3.90 (m, 1H, *CH*NH), 3.42 (m, 2H, CH_2CH_2O), 2.87 (m, 2H, SCH_2CH_2), 2.41–1.98 (m, 1H, $CH(CH_3)_2$), 1.40 (s, 9H, *t*Bu), 0.86, 0.84 (2s, 6H, $CH(CH_3)_2$). ^{13}C NMR (DMSO-d_6) δ 201.6 (COS), 155.8 (COO), 78.5 ($C(CH_3)_3$), 66.1 (*C*HNH), 59.9 (CH_2CH_2O), 30.7 (SCH_2CH_2), 29.7 ($CH(CH_3)_2$), 28.2 ($C(CH_3)_3$), 19.1, 17.8 (2s, $CH(CH_3)_2$). IR (CCl_4) ν_{max} 1691 cm^{-1}(C=O thioester), 1726 cm^{-1}(C=O carbamate). Anal. for ($C_{12}H_{22}NO_4S$): calcd: C, 52.15; H, 8.02; S, 11.60; found: C, 52.45; H, 8.34; S, 11.53.

4.4.6. Standard procedure 2: preparation of SATE phenyl phosphorochloridates 15–18

To a stirred solution of the required thioesters (**6**–**9**, 10 mmol) and freshly distilled triethylamine (2 equiv, 20 mmol, 2.79 mL) in anhydrous THF (100 mL) at −78 °C was added phenyl phosphoro dichloridate (1.02 equiv, 10.2 mmol, 1.49 mL). The mixture was stirred at room temperature for 4 h, filtered and the filtrate concentrated on vacuum. The residue was diluted in anhydrous carbon tetrachloride and filtered again, to yield after concentration to the desired SATE phenyl phosphorochloridate as oils.

4.4.7. *S*-(2,2-Dimethyl-3-triphenylmethoxypropionyl)-2-thioethyl phenyl phosphorochloridate, 15

Standard procedure 2 from 4.21 g of **6**.

^{1}H NMR ($CDCl_3$) δ 7.33 (m, 20H, Ph, $C(Ph)_3$), 4.37 (m, 2H, CH_2CH_2O), 3.30 (m, 2H, SCH_2CH_2), 3.20 (s, 2H, $TrOCH_2$), 1.25 (s, 6H, $C(CH_3)_2$). ^{31}P NMR ($CDCl_3$) δ 0.51. MS (FAB > 0, GT) m/z 559 [M−Cl]$^+$, (FAB < 0, GT) m/z 731 [M + ($HNEt_3^+Cl^-$) − H]$^-$, 575 [M−Cl+O]$^-$, 489 [M + ($HNEt_3^+Cl^-$) − Tr]$^-$.

4.4.8. *S*-[2-(2,2-Dimethyl-1,3-dioxan-5-yl)propionyl]-2-thioethyl phenyl phosphorochloridate, 16

Standard procedure 2 from 2.34 g of **7**.

^{1}H NMR ($CDCl_3$) δ 7.19 (m, 5H, Ph), 4.41 (m, 2H, CH_2CH_2O), 4.24, 3.72 (2d, 4H, J = 12.2 Hz, CH_2), 3.33 (m, 2H, SCH_2CH_2), 1.45, 1.44 (2s, 6H, $C(CH_3)_2$), 1.23 (s, 3H, CH_3). ^{31}P NMR ($CDCl_3$) δ 0.65. MS (FAB > 0, GT) m/z 409 [M+H]$^+$, (FAB < 0, GT) m/z 545 [M + ($HNEt_3^+Cl^-$) − H]$^-$, 505 [M + ($HNEt_3^+Cl^-$) − $C(CH_3)_2$ + H]$^-$, 389 [M−Cl+O]$^-$, 331 [M−Ph]$^-$, 191 [M−SATE]$^-$.

4.4.9. *S*-[(2,2-Dimethyl-N^{α}-*tert*-butyloxycarbonyl) glycinyl]-2-thioethylphenyl phosphoro chloridate, 17

Standard procedure 2 from 2.03 g of **8**.

^{1}H NMR ($CDCl_3$) δ 7.28 (m, 5H, Ph), 5.0 (sl, 1H, NH), 4.35 (m, 2H, CH_2CH_2O), 3.23, 3.22 (2t, 2H, J = 6.6 Hz, SCH_2CH_2), 1.47 (s, 9H, *t*Bu), 1.43, 1.42 (2s, 6H, $C(CH_3)_2$). ^{31}P NMR ($CDCl_3$) δ 0.57. MS (FAB > 0, GT) m/z 839 [2M−Cl]$^+$, 438 [M+H]$^+$, 382 [M−*t*Bu+2H]$^+$, 420 [M−Cl+H_2O]$^+$, 364 [M−*t*BuO]$^+$, 338 [M−*t*Boc+2H]$^+$, (FAB < 0, GT) m/z 837 [2M−2Cl+2O+H]$^-$, 574 [M + ($HNEt_3^+Cl^-$) − H]$^-$, 498 [M + ($HNEt_3^+Cl^-$) − Ph]$^-$, 418 [M−Cl+O]$^-$, 360 [M−Ph]$^-$.

4.4.10. *S*-(N^{α}-*tert*-butyloxycarbonyl-(L)-valinyl)-2-thioethyl phenyl phosphorochloridate, 18

Standard procedure 2 from 2.17 g of **9**.

^{1}H NMR ($CDCl_3$) δ 7.29 (m, 5H, Ph), 4.96 (d, 1H, J = 9.3 Hz, CHN*H*), 4.34 (m, 3H, *CH*NH, CH_2CH_2O), 3.26 (t, 2H, J = 6.5 Hz, SCH_2CH_2), 2.27 (m, 1H, $CH(CH_3)_2$), 1.46 (s, 9H, *t*Bu), 1.00, 0.97, 0.91, 0.86 (4s, 6H, $CH(CH_3)_2$). ^{31}P NMR ($CDCl_3$) δ 0.60. MS (FAB > 0, GT) m/z 452 [M+H]$^+$, 396 [M−*t*Bu+2H]$^+$, 352 [M−*t*Boc+2H]$^+$, 434 [M−Cl+H_2O]$^+$, (FAB < 0, GT) m/z 588 [M + ($HNEt_3^+Cl^-$) − H]$^-$, 512 [M + ($HNEt_3^+Cl^-$) − Ph]$^-$, 432 [M−Cl+O]$^-$, 374 [M−Ph]$^-$.

4.4.11. Standard pocedure 3: preparation of SATE phenyl phosphotriester derivatives 19–22 of AZT

To a stirred solution of the required SATE phenyl phosphorochloridates (**15**–**18**, 6 mmol, 3 equiv) in anhydrous THF (20 mL) were successively added AZT (0.53 mg, 2.0 mmol) and *N*-methyl imidazole (0.95 mL, 12 mmol, 6 eq.). After four hours stirring at room temperature, the reaction mixture was diluted with dichloromethane (80 mL) and quenched with diluted 0.1 N HCl solution. The organic layer was decanted and washed with an aqueous saturated solution of $NaHCO_3$ and then water. The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum; finally the residue was purified on silica gel column chromatography.

4.4.12. *O* -(3′-Azido-2′,3′-dideoxythymidin-5′-yl)-*O*′-[*S*-(2,2-dimethyl-3-triphenylmethoxy propionyl)-2-thioethyl]-*O*″-phenyl phosphate, 19

Standard procedure 3 from 3.58 g of **15** yielded 1.19 g (72%) of **19** obtained as white foam after silica gel column chromatography (dichloromethane/methanol, gradient 0 to 1.5%).

R_f 0.45 (CH_2Cl_2/CH_3OH, 95:5, v/v). ^{1}H NMR (DMSO-d_6) δ 11.4 (bs, 1H, Thy-NH), 7.46, 7.44 (2d, 1H, J = 0.9 Hz, H-6), 7.37–7.16 (m, 20H, Ph, $(Ph)_3C$), 6.13, 6.12 (2t, 1H, J = 6.6 Hz, H-1′), 4.44 (m, 1H, H-3′), 4.33 (m, 2H, H-5′, H-5″), 4.16 (m, 2H, CH_2CH_2O) 4.00 (m, 1H, H-4′), 3.17, 3.16 (2t, 3H, J = 6.5 Hz, SCH_2CH_2), 3.04 (s, 2H, $TrOCH_2$), 2.35 (m, 2H, H-2′, H-2″), 1.71 (s, 3H, Thy-CH_3), 1.12 (s, 6H, $C(CH_3)_2$). ^{13}C NMR (DMSO-d_6) δ 203.4 (CO), 163.6 (C-4), 150.3 (C-2), 149.9 (d, J_{P-C} = 6.7 Hz, Ph ipso), 143.4 ($C(Ph)_3$ ipso), 135.8 (C-6), 129.9, 129.8 (2s, Ph), 128.2, 127.8, 127.0 (3s, $C(Ph)_3$), 125.4 (Ph), 119.9 (d, J = 4.2 Hz, Ph ortho), 109.9 (C-5), 85.8

((Ph)$_3$C), 83.7 (C-1′), 81.1 (d, J_{P-C} = 7.9 Hz, C-4′), 69.5 (TrOCH_2), 67.3 (d, J_{P-C} = 5.6 Hz, C-5′), 66.4 (d, J_{P-C} = 5.7 Hz, CH_2CH_2O,), 59.8, 59.7 (2s, C-3′), 50.4 ($C(CH_3)_2$), 35.5 (C-2′), 28.1 (d, J_{P-C} = 7.1 Hz, SCH_2CH_2), 22.3 (C(CH_3)$_2$), 12.0 (Thy-CH_3). ^{31}P NMR (DMSO-d_6) δ −5.24, −5.46. MS (FAB > 0, GT) *m/z* 826 $[M+H]^+$, 800 $[M-N_2+3H]^+$, 127 $[BH_2]^+$, (FAB < 0, GT) *m/z* 1400 $[2M-AZT]^-$, 824 $[M-H]^-$, 748 $[M-Ph]^-$, 575 $[M-AZT]^-$, 422 $[M-SATE]^-$, 125 $[B]^-$. UV (Ethanol 95) λ_{max} (ε) = 263 nm (10800), λ_{min} (ε) = 240 nm (7400). Anal. for ($C_{42}H_{44}N_5O_9PS$): calcd: C, 61.08; H, 5.37; N, 8.48; found: C, 61.19; H, 5.46; N, 8.32.

4.4.13. *O* -(3′-Azido-2′,3′-dideoxythymidin-5′-yl)-*O*′-[*S*-(2-(2,2-dimethyl-1,3-dioxan-5-yl)propionyl)-2-thioethyl]-*O*″-phenyl phosphate, 20

Standard procedure 3 from 2.45 g of **16** yielded 0.81 g (63%) of **20** obtained as colourless oil after silica gel column chromatography (dichloromethane/methanol, gradient 0–2%).

R_f 0.34 (CH_2Cl_2/CH_3OH, 95:5, v/v). ^{1}H NMR (DMSO-d_6) δ 11.4 (bs, 1H, Thy-NH), 7.46, 7.44 (2d, 1H, *J* = 0.7 Hz, H-6), 7.38 (m, 2H, Ph), 7.22 (m, 3H, Ph), 6.13 (m, 1H, H-1′), 4.46 (m, 1H, H-3′), 4.34 (m, 2H, H-5′, H-5″), 4.19 (m, 2H, CH_2CH_2O), 4.04 (m, 3H, CH_2, H-4′), 3.69 (d, 2H, *J* = 12.1 Hz, CH_2), 3.19, 3.18 (2pt, 2H, *J* = 6.2 Hz, SCH_2CH_2), 2.37 (m, 2H, H-2′, H-2″), 1.72 (s, 3H, Thy-CH_3), 1.35, 1.23 (2s, 6H, C(CH_3)$_2$), 1.03 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 201.7 (CO), 163.6 (C-4), 150.3 (C-2), 150.0 (d, J_{P-C} = 6.8 Hz, Ph ipso), 135.8 (C-6), 129.9, 129.8, 125.4 (3s, Ph), 119.9 (d, J_{P-C} = 4.7 Hz, Ph ortho), 109.9 (C-5), 97.6 ($C(CH_3)_2$), 83.7 (C-1′), 81.1 (d, J_{P-C} = 7.8 Hz, C-4′), 67.3 (d, J_{P-C} = 5.6 Hz, C-5′), 66.4 (d, J_{P-C} = 5.5 Hz, CH_2CH_2O,), 59.8, 59.7 (2s, C-3′), 48.5 ($C(CH_3)$), 35.5 (C-2′), 28.1 (d, J_{P-C} = 7.2 Hz, SCH_2CH_2), 25.6, 21.5 (2s, C(CH_3)$_2$), 18.6 (CH_3), 12.1, 12.0 (2s, Thy-CH_3). ^{31}P NMR (DMSO-d_6) δ −5.41, −5.53. MS (FAB > 0, GT) *m/z* 640 $[M+H]^+$, 614 $[M-N_2+3H]^+$, 424 $[M-SATE+2H]^+$, 127 $[BH_2]^+$, (FAB < 0, GT) *m/z* 1277 $[2M-H]^-$, 1028 $[2M-AZT]^-$, 638 $[M-H]^-$, 562 $[M-Ph]^-$, 422 $[M-SATE]^-$, 389 $[M-AZT]^-$, 125 $[B]^-$. UV (Ethanol 95) λ_{max} (ε) = 263 nm (9700), λ_{min} (ε) = 240 nm (6300). Anal. for ($C_{26}H_{34}N_5O_{10}PS$): calcd: C, 48.32; H, 5.36; N, 10.95; found: C, 48.77; H, 5.47; N, 10.78.

4.4.14. *O* -(3′-Azido-2′,3′-dideoxythymidin-5′-yl)-*O*′-[*S*-((2,2-dimethyl-N^{α}-*tert*-butyloxycarbonyl) glycinyl)-2-thioethyl]-*O*″-phenyl phosphate, 21

Standard procedure 3 from 2.62 g of **17** yielded 0.923 g (69%) of **21** obtained as white foam after silica gel column chromatography (dichloromethane/methanol, gradient 0–1.5%).

R_f 0.39 (CH_2Cl_2/CH_3OH, 95:5, v/v). ^{1}H NMR (DMSO-d_6) δ 11.4 (bs, 1H, Thy-NH), 7.6 (bs, 1H, NH), 7.46, 7.44 (s and d, 1H, *J* = 0.8 Hz, H-6), 7.38 (m, 2H, Ph), 7.22 (m, 3H, Ph), 6.12 (t, 1H, *J* = 6.6 Hz, H-1′), 4.45 (m, 1H, H-3′), 4.34 (m, 2H, H-5′, H-5′), 4.11 (m, 2H, CH_2CH_2O), 4.00 (m, 1H, H-4′), 3.08 (m, 2H, SCH_2CH_2), 2.36 (m, 2H, H-2′, H-2″), 1.71 (s, 3H, Thy-CH_3), 1.36 (s, 9H, *t*Bu), 1.29 (2s, 6H, C(CH_3)$_2$). ^{13}C NMR (DMSO-d_6) δ 203.7 (COS), 163.6 (C-4), 154.3 (COO), 150.3 (C-2), 150.0 (d, J_{P-C} = 6.7 Hz, Ph ipso), 135.8 (C-6), 130.0, 129.9, 125.4 (3s, Ph), 119.9 (d, J_{P-C} = 4.6 Hz, Ph ortho), 109.9 (C-5), 83.7 (C-1′), 81.1 (d, J_{P-C} = 7.8 Hz, C-4′), 78.5 ($C(CH_3)_3$), 67.3 (d, J_{P-C} = 5.5 Hz, C-5′), 66.5 (d, J_{P-C} = 5.8 Hz, CH_2CH_2O,), 61.4 ($C(CH_3)_2$), 59.9, 59.8 (2s, C-3′), 35.6 (C-2′), 28.2 ($C(CH_3)_3$), 27.9 (d, J_{P-C} = 6.5 Hz, SCH_2CH_2), 24.9 (C(CH_3)$_2$), 12.1, 12.0 (2s, Thy-CH_3). ^{31}P NMR (DMSO-d_6) δ −5.38, −5.56. MS (FAB > 0, GT) *m/z* 669 $[M+H]^+$, 643 $[M-N_2+3H]^+$, 569 $[M-$*t*Boc+2H$]^+$, 543 $[M-$*t*Boc-N_2+4H$]^+$, 424 $[M-$*t*BocAibSATE+2H$]^+$, 398 $[M-$*t*BocValSATE-N_2+4H$]^+$, 127 $[BH_2]^+$, (FAB < 0, GT) *m/z* 1335 $[2M-H]^-$, 1259 $[2M-Ph]^-$, 1086 $[2M-AZT]^-$, 667 $[M-H]^-$, 591 $[M-Ph]^-$, 422 $[M-$*t*BocAibSATE$]^-$, 418 $[M-AZT]^-$, 218 [*t*BocAib-SATE-CH_2CH_2]$^-$, 125 $[B]^-$. HR-MS (FAB > 0, GT) *m/z* calcd. 669.2108 $[M+H]^+$, found 669.2130 $[M+H]^+$. UV (Ethanol 95) λ_{max} (ε)= 263 nm (9900), λ_{min} (ε)=233 nm (5300). Anal. for ($C_{27}H_{37}N_6O_{10}PS$): calcd: C, 48.50; H, 5.58; N, 12.57; found: C, 48.20; H, 5.25; N, 12.36.

4.4.15. *O*-(3′-Azido-2′,3′- dideoxythymidin-5′-yl)-*O*′-[*S*-(N^{α}-*tert*-butyloxycarbonyl-(L)-valinyl)-2-thioethyl]-*O*″-phenyl phosphate, 22

Standard procedure 3 from 2.71 g of **18** yielded 1.04 g (76%) of **22** obtained as white foam after silica gel column chromatography (dichloromethane/methanol, gradient 0 to 1.5%).

R_f 0.41 (CH_2Cl_2/CH_3OH, 95:5, v/v). ^{1}H NMR (DMSO-d_6) δ 11.4 (br s, 1H, Thy-NH), 7.57 (d, 1H, *J* = 8.1 Hz, CHN*H*), 7.46, 7.44 (2s, 1H, H-6), 7.38 (m, 2H, Ph), 7.22 (m, 3H, Ph), 6.13 (t, 1H, *J* = 6.6 Hz, H-1′), 4.45 (m, 1H, H-3′), 4.33 (m, 2H, H-5′, H-5″), 4.15 (m, 2H, CH_2CH_2O), 4.01 (m, 1H, H-4′), 3.93 (m, 1H, C*H*NH), 3.11 (pt, 2H, *J* = 6.3 Hz, SCH_2CH_2), 2.36 (m, 2H, H-2′, H-2″), 2.06 (m, 1H, C*H*(CH_3)$_2$), 1.71 (s, 3H, Thy-CH_3), 1.32 (s, 9H, *t*Bu), 0.85, 0.83 (2s, 6H, CH(CH_3)$_2$). ^{13}C NMR (DMSO-d_6) δ 201.3 (COS), 163.6 (C-4), 155.8 (COO), 150.3 (C-2), 150.0 (d, J_{P-C} = 6.7 Hz, Ph ipso), 135.8 (C-6), 129.7, 129.6, 125.4 (3s, Ph), 119.9 (d, J_{P-C} = 3.9 Hz, Ph ortho), 109.9 (C-5), 83.7 (C-1′), 81.1 (d, J_{P-C} = 7.5 Hz, C-4′), 78.7 ($C(CH_3)_3$), 67.3 (d, J_{P-C} = 5.6 Hz, C-5′), 66.4 (d, J_{P-C} = 5.4 Hz, CH_2CH_2O,), 66.2 (*C*HNH), 59.8, 59.7 (2s, C-3′), 35.5 (C-2′), 29.6 (*C*H(CH_3)$_2$), 28.0 (d, J_{P-C} = 7.6 Hz, SCH_2CH_2), 19.0, 17.8 (2s, CH(*C*H_3)$_2$), 12.0 (Thy-CH_3). ^{31}P NMR (DMSO-d_6) δ −5.45, −5.53. MS (FAB > 0, GT) *m/z* 683 $[M+H]^+$, 657 $[M-N_2+3H]^+$, 583 $[M-$*t*Boc+2H$]^+$, 557 $[M-$*t*Boc-N_2+4H$]^+$, 424 $[M-SATE+2H]^+$, 398 $[M-SATE-N_2+4H]^+$, 127 $[BH_2]^+$, (FAB < 0, GT) *m/z* 1363 $[2M-H]^-$, 1287 $[2M-Ph]^-$, 1114 $[2M-AZT]^-$, 681 $[M-H]^-$, 605 $[M-Ph]^-$, 432 $[M-AZT]^-$, 422 $[M-SATE]^-$, 125 $[B]^-$. HR-MS (FAB > 0, GT) *m/z* calcd. 683.2264 $[M+H]^+$, found 683.2254 $[M+H]^+$. UV (Ethanol 95): λ_{max} (ε)=266 nm (10900), λ_{min} (ε)=235 nm (6900). Anal for ($C_{28}H_{39}N_6O_{10}PS$): calcd: C, 49.26; H, 5.76; N, 12.31; found: C, 49.55; H, 5.76; N, 12.13.

4.4.16. *O* -(3′-Azido-2′,3′-dideoxythymidin-5′-yl)-*O*′-[*S*-(2,2-dimethyl-3- hydroxypropionyl)-2-thioethyl]-*O*″-phenyl phosphate, 2

To a stirred solution of protected derivative **19** (0.61 g, 0.74 mmol) in dry dichloromethane (4 mL) was added a solution of TFA (4 mL, 50% in dichloromethane) drop wise at 0 °C. The reaction reached completion in 15 min and the reaction mixture was quenched by adding a saturated aqueous solution of $NaHCO_3$ (~5 mL), then diluted with dichloromethane (50 mL). After separation of the phases, the organic layer was washed with a saturated aqueous solution of $NaHCO_3$ and then brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. Purification of the residue by silica gel chromatography (dichloromethane/methanol, gradient 2 to 5%) afforded the desired compound **2**(0.367 g, 85%) as a colourless oil.

R_f 0.41 (CH_2Cl_2/CH_3OH, 9:1, v/v). ^{1}H NMR (DMSO-d_6) δ 11.3 (bs, 1H, Thy-NH), 7.46, 7.44 (2d, 1H, *J* = 0.9 Hz, H-6), 7.38 (m, 2H, Ph), 7.22 (m, 3H, Ph), 6.13, 6.12 (2t, 1H, *J* = 6.7 Hz, H-1′), 4.91 (t, 1H, *J* = 5.2 Hz, OH), 4.46 (m, 1H, H-3′), 4.34 (m, 2H, H-5′, H-5″), 4.16 (m, 2H, CH_2CH_2O) 4.02 (m, 1H, H-4′), 3.42 (m, 2H, CH_2OH), 3.12, 3.11 (2t, 2H, *J* = 6.4 Hz, SCH_2CH_2), 2.37 (m, 2H, H-2′, H-2″), 1.72 (1s, 3H, Thy-CH_3), 1.10, 1.09 (2s, 6H, C(*C*H_3)$_2$). ^{13}C NMR (DMSO-d_6) δ 203.8 (CO), 163.6 (C-4), 150.3 (C-2), 150.0 (d, J_{P-C} = 6.7 Hz, Ph ipso), 135.8 (C-6), 129.9, 129.8, 125.4 (3s, Ph), 119.9 (d, *J* = 4.6 Hz, Ph ortho), 109.9 (C-5), 83.7 (C-1′), 81.1 (d, J_{P-C}=7.7 Hz, C-4′), 68.3 (*C*H_2OH), 67.3 (d, J_{P-C} = 5.7 Hz, C-5′), 66.5 (d, J_{P-C} = 5.7 Hz, CH_2CH_2O,), 59.8, 59.7 (2s, C-3′), 51.7 ($C(CH_3)_2$), 35.5 (C-2′), 28.0 (d, J_{P-C} = 7.6 Hz, SCH_2CH_2), 21.8 (C(CH_3)$_2$), 12.1, 12.0 (2s, Thy-CH_3). ^{31}P NMR (DMSO-d_6) δ −5.41, −5.53. MS (FAB > 0, GT) *m/z* 584 $[M+H]^+$, 558 $[M-N_2+3H]^+$, 424 $[M-SATE+2H]^+$, 127 $[BH_2]^+$, (FAB < 0, GT) *m/z* 1748 $[3M-H]^-$, 1165 $[2M-H]^-$, 1005 $[2M-SATE]^-$, 916 $[2M-AZT]^-$, 582 $[M-H]^-$, 506 $[M-Ph]^-$, 422 $[M-SATE]^-$, 333 $[M-AZT]^-$, 125 $[B]^-$. UV (Ethanol 95) λ_{max} (ε) = 263 nm (10200), λ_{min} (ε) = 240 nm (6500). Anal for ($C_{23}H_{30}N_5O_9PS$): calcd: C, 47.34; H, 5.18; N, 12.00; found: C, 47.63; H, 5.34; N, 11.81.

4.4.17. *O* -(3′-Azido-2′,3′-dideoxythymidin-5′-yl)-*O*′-[*S*-(2,2-hydroxymethyl)propionyl)-2-thioethyl]-*O*″-phenyl phosphate, 3

A stirred solution of derivative **20** (0.911 g, 1.42 mmol) in 50% aqueous acetic acid (16 mL) was maintained at room temperature for 4 h, then the reaction mixture was concentrated under vacuum and co-evaporated with toluene. Purification of the residue by silica gel chromatography (dichloromethane/methanol, gradient 2–4%) afforded the desired compound **3** (0.652 g, 76%) as a colourless oil.

R_f 0.29 (CH_2Cl_2/CH_3OH, 93:7, v/v). ^{1}H NMR (DMSO-d_6) δ 11.3 (bs, 1H, Thy-NH), 7.46, 7.44 (2s, 1H, H-6), 7.38 (m, 2H, Ph), 7.22 (m, 3H, Ph), 6.13 (m, 1H, H-1′), 4.76 (t, 2H, $J_{OH,\ H}$ = 5.4 Hz, OH), 4.46 (m, 1H, H-3′), 4.34 (m, 2H, H-5′, H-5″), 4.16 (m, 2H, CH_2CH_2O), 4.02 (m, 1H, H-4′), 3.54 (m, 2H, CH_2OH), 3.43 (pdd, 2H, $J_{vicinal}$ = 10.7 Hz, $J_{H,OH}$ = 5.4 Hz, CH_2OH), 3.12 (m, 2H, SCH_2CH_2), 2.37 (m, 2H, H-2′, H-2″), 1.72 (1s, 3H, Thy-CH_3), 1.12, 1.11 (2s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 202.5 (CO), 163.6 (C-4), 150.3 (C-2), 150.0 (d, J_{P-C} = 6.8 Hz, Ph ipso), 135.8 (C-6), 129.9, 129.8, 125.4 (3s, Ph), 120.0 (d, J_{P-C} = 4.6 Hz, Ph ortho), 109.9 (C-5), 83.7 (C-1′), 81.1 (d, J_{P-C} = 7.8 Hz, C-4′), 67.2 (d, $J_{P-\ C}$ = 4.6 Hz, C-5′), 66.5 (d, J_{P-C} = 5.8 Hz, CH_2CH_2O,), 64.3 (CH_2OH), 59.8, 59.7 (2s, C-3′), 57.5 ($C(CH_3)$), 35.5 (C-2′), 27.8 (d, J_{P-C} = 7.4 Hz, SCH_2CH_2), 16.8 (CH_3), 12.0 (Thy-CH_3). ^{31}P NMR (DMSO-d_6) δ −5.40, −5.51. MS (FAB > 0, GT) m/z 600 $[M+H]^+$, 574 $[M-N_2+3H]^+$, 424 $[M-SATE+2H]^+$, 127 $[BH_2]^+$, (FAB < 0, GT) m/z 1796 $[3M-H]^-$, 1197 $[2M-H]^-$, 948 $[2M-AZT]^-$, 598 $[M-H]^-$, 522 $[M-Ph]^-$, 422 $[M-SATE]^-$, 349 $[M-AZT]^-$, 125 $[B]^-$. UV (Ethanol 95) λ_{max} (ε) = 263 nm (8600), λ_{min} (ε) = 240 nm (5600). Anal for ($C_{23}H_{30}N_5O_{10}PS$): calcd: C, 46.08; H, 5.04; N, 11.68; found: C, 46.11; H, 5.20; N, 11.36.

4.4.18. *O* -(3′-Azido-2′,3′-dideoxythymidin-5′-yl)-*O*′-[*S*-(2,2-dimethylglycinyl)-2-thioethyl]-*O*″-phenyl phosphate (trifluoroacetate salt), 4

To a stirred solution of protected derivative **21** (0.20 g, 0.30 mmol) in dry dichloromethane (2 mL) was added a solution of TFA (2 mL, 50% in dichloromethane) drop wise at 0 °C. The reaction reached completion in 2 h and the reaction mixture was concentrated and co-evaporated with toluene. The residue was dried under high vacuum and afforded the expected compound **4** (0.20 g, 98%) as a white foam.

R_f 0.42 (CH_2Cl_2/CH_3OH, 9:1, v/v). ^{1}H NMR (DMSO-d_6) δ 11.4 (br s, 1H, Thy-NH), 8.5 (bs, 3H, NH_3^+), 7.48, 7.45 (2d, 1H, J = 0.7 Hz, H-6), 7.40 (m, 2H, Ph), 7.23 (m, 3H, Ph), 6.14, 6.13 (2t, 1H, J = 6.7 Hz, H-1′), 4.46 (m, 1H, H-3′), 4.34 (m, 2H, H-5′, H-5″), 4.24 (m, 2H, CH_2CH_2O), 4.00 (m, 1H, H-4′), 3.29 (m, 2H, SCH_2CH_2), 2.38 (m, 2H, H-2′, H-2″), 1.73 (s, 3H, Thy-CH_3), 1.49, 1.48 (2s, 6H, $C(CH_3)_2$). ^{13}C NMR (DMSO-d_6) δ 199.1 (COS), 163.6 (C-4), 150.4 (C-2), 149.9 (d, J_{P-C} = 6.6 Hz, Ph ipso), 136.0 (C-6), 130.0, 129.9, 125.5 (3s, Ph), 120.0 (m, Ph ortho), 110.0, 109.9 (2s, C-5), 83.7 (C-1′), 81.1 (d, J_{P-C} = 7.7 Hz, C-4′), 67.4 (d, $J_{P-\ C}$ = 4.8 Hz, C-5′), 65.9 (d, J_{P-C} = 5.7 Hz, CH_2CH_2O), 61.7 ($C(CH_3)_2$), 59.7 (C-3′), 35.5 (C-2′), 28.8 (d, $J_{P-\ C}$ = 7.4 Hz, SCH_2CH_2), 24.0 ($C(CH_3)_2$), 12.1, 12.0 (2s, Thy-CH_3). ^{31}P NMR (DMSO-d_6) δ −5.39, −5.45. MS (FAB > 0, GT) m/z 1137 $[2M-2CF_3COO-H]^+$, 1111 $[(2M-2CF_3COO-N_2+H)^+$, 888 $[2M-2CF_3COO-AZT]^+$, 569 $[M-CF_3COO]^+$, 543 $[M-CF_3COO-N_2+2H]^+$, 424 $[M-CF_3COO-SATE+2H]^+$, 320 $[M-CF_3COO-AZT+H]^+$, 127 $[BH_2]^+$, (FAB < 0, GT) m/z 1135 $[2M-2CF_3COO-3H]^-$, 681 $[M-H]^-$, 567 $[M-CF_3COO-2H]^-$, 491 $[M-CF_3COO-Ph-H]^-$, 422 $[M-CF_3COO-SATE]^-$, 318 $[M-CF_3COO-AZT-H]^-$, 125 $[B]^-$. HR-MS (FAB > 0, GT) m/z calcd. 569.1583 $[M-CF_3COO]^+$, found 569.1588 $[M-CF_3COO]^+$. UV (Ethanol 95) λ_{max} (ε)=263 nm (9600), λ_{min} (ε) = 232 nm (3600).

4.4.19. *O* -(3′-Azido-2′,3′-dideoxythymidin-5′-yl)-*O*′-[*S*-(L)-valinyl-2- thioethyl]-*O*″-phenyl phosphate (trifluoroacetate salt), 5

To a stirred solution of protected derivative **22** (0.205 g, 0.30 mmol) in dry dichloromethane (2 mL) was added a solution of TFA (2 mL, 50% in dichloromethane) drop wise at 0 °C. The reaction reached completion in 2 h and the reaction mixture was concentrated and co-evaporated with toluene. The residue was dried under high vacuum and afforded the expected compound **5**(0.207 g, 99%) as a white foam.

R_f 0.39 (CH_2Cl_2/CH_3OH, 9:1, v/v). ^{1}H NMR (DMSO-d_6) δ 11.4 (bs, 1H, Thy-NH), 8.3 (bs, 3H, NH_3^+), 7.48, 7.45 (2s, 1H, H-6), 7.39 (m, 2H, Ph), 7.23 (m, 3H, Ph), 6.13 (1t, 1H, J = 6.6 Hz, H-1′), 4.46 (m, 1H, H-3′), 4.36 (m, 2H, H-5′, H-5″), 4.24 (m, 3H, CH_2CH_2O, $CHNH_3^+$), 4.00 (m, 1H, H-4′), 3.34 (m, 2H, SCH_2CH_2), 2.37 (m, 2H, H-2′, H-2″), 2.16 (m, 1H, $CH(CH_3)_2$), 1.72 (s, 3H, Thy-CH_3), 0.97, 0.96, 0.93, 0.91 (4s, 6H, $CH(CH_3)_2$). ^{13}C NMR (DMSO-d_6) δ 195.9 (COS), 163.6 (C-4), 150.3 (C-2), 149.9 (d, J_{P-C} = 6.8 Hz, Ph ipso), 135.9 (C-6), 130.0, 129.9, 125.5 (3s, Ph), 120.0 (m, Ph ortho), 109.9 (C-5), 83.8 (C-1′), 81.1 (d, J_{P-C} = 7.7 Hz, C-4′), 67.4 (C-5′), 66.0 (d, $J_{P-\ C}$ = 5.5 Hz, CH_2CH_2O), 63.4 ($CHNH_3^+$), 59.8 (C-3′), 35.5 (C-2′), 30.1 ($CH(CH_3)_2$), 28.8 (d, J_{P-C} = 7.5 Hz, SCH_2CH_2), 18.0, 17.2 ($CH(CH_3)_2$), 12.1 (Thy-CH_3).^{31}P NMR (DMSO-d_6) δ −5.41, −5.46. MS (FAB > 0, GT)m/z 1165 $[2M-2CF_3COO-H]^+$, 583 $[M-CF_3COO]^+$, 557 $[M-CF_3COO-N_2+2H]^+$, 424 $[M-CF_3COO-SATE+2H]^+$, 334 $[M-CF_3COO-AZT+H]^+$, (FAB < 0, GT) m/z 1163 $[2M-2CF_3COO-3H]^-$, 695 $[M-H]^-$, 581 $[M-CF_3COO-2H]^-$, 505 $[M-CF_3COO-Ph-H]^-$, 422 $[M-CF_3COO-SATE]^-$, 332 $[M-CF_3COO-AZT-H]^-$, 125 $[B]^-$. HR-MS (FAB > 0, GT) m/z calcd. 583.1740 $[M-CF_3COO]^+$, found 583.1729 $[M-CF_3COO]^+$. UV (Ethanol 95) λ_{max} (ε) = 263 nm (8600), λ_{min} (ε)=232 nm (4600).

4.4.20. 2,2-Dimethyl-*O*-3-(triphenylmethyl)-propanoic acid, 10

A suspension of 2,2-dimethyl-3-*O*-(triphenylmethyl)-propanoic acid methyl ester **14** (7.0 g, 16.6 mmol) in an aqueous solution of NaOH (147 mL, 30%) and dioxan (147 mL) was heated under reflux for 14 h. The reaction mixture was then cooled to room temperature. The dioxan and the aqueous layers were separated. The dioxan phase was acidified using an aqueous solution of HCl 1N until pH 3. The organic phase was extracted with dichloromethane (20 mL), dried over sodium sulfate, and filtered. Evaporation under reduced pressure of all the volatiles gave yellow oil which solidified upon standing. The crude solid was purified by crystallization (dichloromethane/petroleum ether, 95:5) to give 2,2-dimethyl-3-*O*-(triphenylmethyl)-propanoic acid **10** (5.20 g, 87%) as colourless crystal.

R_f 0.5 (cyclohexane/AcOEt, 8:2, v/v). m.p.: 167 °C. ^{1}H NMR ($CDCl_3$) δ 7.41(m, 6H, Ph), 7.27 (m, 9H, Ph), 3.19 (s, 2H, OCH_2), 1.24 (s, 6H, CH_3). ^{13}C NMR ($CDCl_3$) δ 181.9 (CO), 143.3 (Ph ipso), 128.7, 127.0, 127.8 (Ph), 86.5 ($(Ph)_3C$), 69.4 (OCH_2), 43.4 ($C(CH_3)_2$), 22.5 ($C(CH_3)_2$). IR (CCl_4) ν_{max} 1706 cm^{-1} (C=O). MS (FAB > 0, GT) m/z361 $[M+H]^+$, (FAB < 0, GT) m/z710 $[2M-H]^-$, 359 $[M-H]^-$, 117 $[M-Tr]^-$. Anal. for ($C_{24}H_{24}O_3$): calcd: C, 79.97; H, 6.71; found: C, 79.66; H, 6.80.

4.4.21. 5-Carboxy-2,2,5-trimethyl-1,3-dioxane, 11

To a solution of 2,2-bis(hydroxymethyl) propionic acid (20 g, 149.1 mmol) in anhydrous dichloromethane (150 mL) were added 2,2-dimethoxypropane (55.5 mL, 447.3 mmol) and APTS monohydrate (*p*-toluene sulfonic acid, 0.284 g, 1.49 mmol). The reaction mixture was allowed to stir at room temperature under argon for 4:30 min then neutralized with triethylamine (10 mL). After 10 min, dichloromethane was added (500 mL) and the mixture was washed once with water (100 mL). The aqueous phase was extracted three times with dichloromethane (300 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. 5-Carboxy-2,2,5-trimethyl-1,3-dioxane **11** was isolated as colourless crystals (16.1 g, 62%) after crystallization in hexane/diethyl ether (9:1, v/v).

R_f 0.52 (dichloromethane/methanol, 9:1, v/v). m.p.: 120 °C. ^{1}H NMR (DMSO-d_6) δ 3.99 (d, 2H, J = 11.5 Hz, CH_2), 3.54 (d, 2H, J = 11.5 Hz, CH_2), 1.33, 1.25 (2s, 6H, $C(CH_3)_2$), 1.06 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 175.5 (CO), 97.2 ($C(CH_3)_2$), 65.2 (CH_2), 40.7

($C(CH_3)_2$), 24.6, 22.7 (2s, $C(CH_3)_2$), 18.2 (CH_3). IR (CCl_4) ν_{max} 1707 cm^{-1} (C=O). MS (FAB > 0, GT) *m/z* 175 $[M+H]^+$, (FAB < 0, GT) *m/z* 173 $[M-H]^-$. Anal. for ($C_8H_{10}O_4$), calcd: C, 55.16; H, 8.10; found: C, 54.97; H, 8.13.

4.4.22. 2,2-Dimethyl-*O*-3-(triphenylmethyl)-propionic acid methyl ester, 14

To a solution of methyl-2,2-dimethyl-3-hydroxypropionate (1 mL, 7.84 mmol) in dry dichloromethane (63 mL) were added triethylamine (1.54 mL, 10.97 mmol), triphenylmethane chloride (2.62 g, 9.4 mmol) and DMAP (0.096 g, 0.74 mmol). The reaction mixture was heated under reflux overnight then cooled to room temperature and diluted with dichloromethane (150 mL). The organic phase was washed twice with an aqueous solution of $NaHCO_3$ (10%, 100 mL) and once with water (100 mL). The organic phase was dried over sodium sulfate, filtered and evaporated under reduced pressure. A yellow-orange oil was obtained which was purified by column chromatography on silica gel (*n*-hexane/dichloromethane, 6:4, v/v) to give 2,2-dimethyl-3-trityloxy-propionic acid methyl ester **14** (2.75 g, 94%) as a colourless oil.

R_f 0.25 (*n*-hexane/dichloromethane, 6:4, v/v). ^1H NMR (DMSO-d_6) δ 7.3 (m, 15H, Ph), 3.61 (s, 3H, OCH_3), 3.02 (s, 2H, OCH_2), 1.10 (s, 6H, CH_3). ^{13}C NMR (DMSO-d_6) δ 175.9 (CO), 143.3 (Ph ipso), 127.9, 127.2 (2s, Ph ortho and meta), 126.3 (Ph para), 85.5 ($(Ph)_3C$), 69.4 (OCH_2), 54.8 (OCH_3), 42.8 ($C(CH_3)_2$), 18.7 ($C(CH_3)_2$). MS (FAB > 0, GT) *m/z* 277 $[M-Tr-OMe]^+$, 243 $[Tr]^+$, (FAB < 0, GT) *m/z* 275 $[M-Tr-OMe]^-$.

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