ELSEVIER

Chemistry and Physics of Lipids
89 (1997) 75–81

CPL
CHEMISTRY AND
PHYSICS OF LIPIDS

Short communication

Synthesis of 1-β-D-arabinofuranosyl-cytosine 5′-phosphate-L-1,2-diacylglycerols

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Received 28 April 1997; received in revised form 7 July 1997; accepted 10 July 1997

Abstract

5′-*O*-MMTr-cytosine arabinoside was prepared on a large scale from 5′-*O*-MMTr-cytidine with diphenyl carbonate via 5′-protected cytidine-2′,3′-carbonate-ara-cytidine-2′,2-anhydro derivative at a 67% yield. 1,2-Dipalmitoyl-*sn*-glycerol, 1,2-distearoyl-*sn*-glycerol and 1,2-dioleoyl-*sn*-glycerol were phosphorylated first with 2-chlorphenyl-phosphoro-bis-triazolide quantitatively (Welch and Chattopadhyaya, 1985. Acta Chem. Scand. B39, 47–57). This method was used in order to avoid acyl migration, then the glycerophosphate intermediates were condensed with 2′,3′,N^4-trileulinyl-1-β-D-arabinofuranosylcytosine in the presence of 2-mesytilensulphonyl chloride (MSCl) and 1-methylimidazole (MeIm)—which was used in the coupling of nucleotides (Nyilas et al., 1986. Acta Chem. Scand. B40, 678–684)—in an 85–88% yield compared with the low yielding diester method of Ryu et al., 1982. J. Med. Chem. 25, 1322–1329. Deblocking was carried out in two steps with tetrabutylammonium fluoride (TBAF) and hydrazine hydrate, producing target compounds (**9a, 9b, 9c**) at a 50% yield. © 1997 Elsevier Science Ireland Ltd.

Keywords: Leukemia; Ara-CMP-dipalmitin; Ara-CMP-distearin; Ara-CMP-diolein; MMTr-ara-C; Diphenyl carbonate

1. Intoduction

Cytosine arabinoside (ara-C) is an important drug used against leukemia (Alberto, 1978). A survey of the literature shows, that ara-C has been prepared from 2′-*O*-methanesulphonyl derivative of cytidine (Fromageot and Reese, 1966). Condensation of the appropriate sugar and base produced ara-C also (Shimidzu and Shimidzu, 1970). Cytidine 2′,3′-cyclic phosphate was converted to aracytidine 3′-phosphate (Nagyváry and Tapiero, 1969; Nagyváry, 1969). These procedures need several steps with a relatively low yield. Ogilvie

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PII S0009-3084(97)00056-X

(1972) introduced a one step process from cytidine using diphenyl carbonate. Beranek et al. (1974) improved the reproducibility with several additions of diphenyl carbonate and purification of the reaction mixture with Zerolite FF and Dowex 50WX2 (H^+). However the purification was tedious and time consuming and gave ara-C in only a 32% yield overall. These two papers did not give NMR data of the product.

The clinical effectiveness of ara-C may be improved with granulocite colony-stimulating factor (G-CSF) (Waga et al., 1992) and interleukin-3 (IL-3) (Brach et al., 1991). Furthermore the use of hydrocortisone will protect cells from the toxic effect of ara-C (Yang et al., 1991). Another way to improve the effectiveness of ara-C and overcome the problems associated with its use as a chemotherapeutic agent is to synthesize ara-C-phospholipid. Ryu et al. (1982) and Hong et al. (1995) have prepared several conjugates. Their in vivo and in vitro studies concentrated mostly on the ara-C diphosphate analogue. Ryu et al. (1982) have synthesized one ara-C monophosphate analogue by the diester method, thus the yield of condensation of protected ara-C and L-α-diacylglycero-phosphoric acid did not exceed 22%. It should be worth preparing monophosphate analogue with different lengths of fatty acids also, because the 1-β-D-arabinofuranosyl-cytosine 5′-phosphate-1,2-dipalmitoyl-*sn*-glycerol showed antiproliferative activity (Ryu et al., 1982).

The synthesis of ara-C-phospholipid needs a careful choice of protecting groups for the different functionalities and a mild deprotection condition in order to avoid acyl migration. Since the activation method of coupling could cause isomerisation, the glycerol part should be phosphorylated first (Welch and Chattopadhyaya, 1985).

2. Experimental procedures

Diphenyl carbonate and TBAF were purchased from Sigma.

A Jeol FX90 spectrometer was used at 89.5 MHz to measure ^{1}H NMR; tetramethylsilane was used as an internal standard in $CDCl_3$–CD_3OD = 9:1 solutions (δ scale). ^{31}P NMR spectra were recorded at 36 MHz in the same solvent mixture as in ^{1}H NMR using 85% phosphoric acid as an external standard on the δ scale.

UV absorption spectra were recorded with a Varian-Cary 2200 spectrometer in ethanol.

Short column chromatographic separations were carried out using Merck G60 silica gel eluted with a linear gradient of mixtures of *n*-hexane–CH_2Cl_2 and MeOH–CH_2Cl_2.

Elemental analyses were performed in Uppsala. Results were within $\pm$0.4% of the theoretical values.

2.1. 5′-*O*-MMTr-cytidine (**2**)

The 5′-OH function of cytidine (2.43 g, 10 mmol) was protected with monomethoxyrtityl chloride (MMTrCl) (3.71 g, 12 mmol) in dry pyridine overnight in the dark. The reaction mixture was partitioned between chloroform (500 ml) and saturated sodium bicarbonate (500 ml), followed by evaporation of the organic phase and coevaporation with toluene in vacuo. One aliquot (about 20 mg) was purified on a silica gel column with dichloromethane followed by 10% methanol–dichloromethane in order to record the ^{1}H NMR spectrum of 5′-*O*-MMTr-cytidine (**2**). ^{1}H NMR ($CDCl_3$, CD_3OD) δ: 8.1 (d, 1H, $J_{\text{H-5, H-6}} = 9.0$ Hz) H-6, 7.3 (m, 12H) aromatic, 6.9 (d, 2H) aromatic, 5.8 (d, 1H, $J_{\text{H-1′,H-2′}} = 2.0$ Hz) H-1′, 5.4 (d, 1H) H-5, 4.2 (m, 3H) H-2′, H-3′ and H-4′, 3.8 (s, 3H) OCH_3, 3.5 (m, 2H) H-5′ and H-5″. UV (pH 2): λ_{max} 285 nm; (pH 7) 276 nm; (pH 12) 274 nm.

2.2. 5′-*O*-MMTr-ara-cytidine (**3**)

The major part of the reaction mixture was treated with diphenyl carbonate (9.0 g, 42 mmol) and sodium bicarbonate (6.7 g, 80 mmol) in dimethylformamide (24 ml) for 3 h at 80°C. After evaporation in vacuo the residue was dissolved in chloroform (about 20 ml) and purified by silica gel chromatography with chloroform then 10% methanol–dichloromethane as eluents.

Evaporation of the appropriate fractions gave compound **3** (3.3 g, 67% for two reaction steps) ^{1}H NMR ($CDCl_3$, CD_3OD) δ: 7.9 (d, 1H, $J_{5,6}$ = 9.0 Hz) H-6, 7.3 (m, 12H) aromatic, 6.8 (d, 2H) aromatic, 6.2 (d, 1H, $J_{1',2'}$ = 5.1 Hz) H-1′, 5.5(d, 1H) H-5, 4.1 (m, 3H) H-2′, H-3′ and H-4′, 3.8 (s, 3H) OCH_3, 3.4 (m, 2H) H-5′, H-5″. UV (pH 2): λ_{max} 285 nm; (pH 7) 276 nm; (pH 12) 274 nm.

*2.3. 5′-O-MMTr-2′,3′,N^4-trilevulinyl-1-β-D-arabinofuranosylcytosine (**4**)*

5′-*O*-MMTr-ara-C was levulinated as in the literature (Ryu et al., 1982) with a 96% yield. ^{1}H NMR ($CDCl_3$) δ: 7.0 (d, 1H, $J_{5,6}$ = 7.6 Hz) h-6, 7.3 (m, 14H) aromatic of MMTr, 6.8 (d, 1H, $J_{5,6}$ = 7.6 Hz) H-5, 6.2 (d, 1H, $J_{1',2'}$ = 4.2 Hz) H-1′, 5.2 (m, 1H) H-2′, 5.1 (m, 1H) H-3′, 4.2 (m, 1H) H-4′, 3.7 (s, 3H) OCH_3, 3.4 (m, 2H) H-5′, H-5″, 2.7–2.4 (m, 12H) CH_2 of Lev, 2.1–2.0 (m, 9H) CH_3 of Lev.

*2.4. 2′,3′,N^4-trilevulinyl-1-β-D-arabinofuranosylcytosine (**5**)*

Compound **4** (0.802, 1.07 mmol) was dissolved in 10 ml 80% aqueous acetic acid. The reaction mixture was stirred at room temperature for 3 h then evaporated and coevaporated with water several times. The resulting foam was dissolved in CH_2Cl_2 and loaded onto silica gel. The target compound was eluted with CH_2Cl_2. The yield was 0.34 g, 67%. ^{1}H NMR ($CDCl_3$) δ: 8.2 (d, 1H, $J_{5,6}$ = 7.8 Hz) H-6, 7.4 (d, 1H, $J_{5,6}$ = 7.8 Hz) H-5, 6.2 (d, 1H, $J_{1,2}$ = 4.2 Hz) H-1′. 5.5 (m, 1H) H-2′, 5.2 (m, 1H) H-3′, 4.1 (m, 1H) H-4′, 3.9 (m, 2H) H-5′, H-5″, 2.7–2.4 (m, 12H) CH_2 of Lev, 2.1–2.0 (m, 9H) CH_3 of Lev.

*2.5. 1,2-Dipalmitoyl-sn-glycero-3-(2-chlorophenyl)-phosphate triethylammonium salt (**6a**)*

1,2-Dipalmitoyl-*sn*-glycerol (0.219, 0.384 mmol) was dissolved in 2 ml dry CH_2Cl_2 and 2 ml dry pyridine. 3 ml 2-Chlorophenyl-phosphoro-bis-triazolide solution (0.768 mmol, in acetonitrile) was added. The reaction mixture was stirred at room temperature for 20 min, then quenched with 0.5 M triethylammonium bicarbonate solution (10 ml) and partitioned between 50 ml CH_2Cl_2 and 50 ml saturated sodium bicarbonate. The organic layer was extracted with water (2 × 100 ml) then evaporated and coevaporated several times to remove any traces of pyridine. The resulting gum was 0.324 g, 100%. ^{31}P NMR ($CDCl_3$, CD_3OD) δ: − 7.4.

*2.6. 1,2-Distearoyl-sn-glycero-3-(2-chlorophenyl)-phosphate triethylammonium salt (**6b**)*

Distearoyl-*sn*-glycerol was phosphorylated analogously to the preparation of **6a** to give **6b** (0.32 g, 100%). ^{31}P NMR ($CDCl_3$, CD_3OD) δ: − 7.1

*2.7. 1,2-Dioleoyl-sn-glycero-3-(2-chlorophenyl)-phosphate triethylammonium salt (**6c**)*

Dioleoyl-*sn*-glycerol was phosphorylated analogously to the preparation of **6a**. The yield was 0.41 g, 93.5%. ^{31}P NMR ($CDCl_3$, CD_3OD) δ: − 6.5.

2.8. 2′,3′,N^4-trilevulinyl-1-β-arabinofuranosylcytosine-5′-(2-chlorophenyl)-phosphate-1,2-dipalmitoyl-sn-glycerol (7a)

Compound **6a** (0.1 g, 0.12 mmol) and compound **5** (0.047 g, 0.098 mmol) were dissolved in 1 ml dry pyridine. MsCl (0.077 g, 0.35 mmol) and MeIm (0.058g, 0.71 mmol) were added to the reaction mixture. After 20 min stirring the reaction mixture was partitioned between 10 ml CH_2Cl_2 and 10 ml citric acid solution. The organic phase was evaporated and dissolved in 2 ml CH_2Cl_2 and loaded onto silica gel. 50% CH_2Cl_2–*n*-hexane and CH_2Cl_2 eluted the target compound. The proper fractions were evaporated and gave a foam, 0.123 g, 86%. ^{31}P NMR ($CDCl_3$, CD_3OD) δ: − 6.6, − 6.8.

*2.9. 2′,3′,N^4-trilevulinyl-1-β-arabinofurano-sylcytosine-5′-(2-chlorophenyl)-phosphate-1,2-distearoyl-sn-glycerol (**7b**)*

Compound **6b** and **5** were condensed analogously to **6a**. The yield was 0.335 g, 95%. ^{31}P NMR ($CDCl_3$, CD_3OD) δ: −6.6, −6.8.

*2.10. 2′,3′,N^4-trilevulinyl-1-β-arabinofurano-sylcytosine-5′-(2-chlorophenyl)-phosphate-1,2-dioleoyl-sn-glycerol (**7c**)*

Compound **6c** and **5** were condensated analogously to **6a**. The yield was 0.38 g, 85%. ^{31}P NMR ($CDCl_3$, CD_3OD) δ: −6.7, −6.9.

*2.11. 2′,3′,N^4-trilevulinyl-1-β-arabinofurano-sylcytosine-5′-monophosphate-1,2-dipalmitoyl-sn-glycerol tributylammonium salt (**8a**)*

Compound **7a** (0.129 g, 0.115 mmol) was dissolved in 31 ml pyridine–H_2O–THF(tetrahydrofuran) = 1:1:8 and 1 M TBAF solution in THF (1.55 ml) was added. After 4.5 h stirring at room temperature the reaction mixture was evaporated and the residue was dissolved in 2 ml CH_2Cl_2 and loaded onto silica gel. Compound **8a** was eluted with 10% MeOH–CH_2Cl_2. The proper fractions were combined and evaporated. The yield was 0.185 g, 88%. ^{31}P NMR ($CDCl_3$, CD_3OD) δ: −2.3.

*2.12. 2′,3′,N^4-trilevulinyl-1-β-arabinofurano-sylcytosine-5′-monophosphate-1,2-distearoyl-sn-glycerol tributylammonium salt (**8b**)*

Compound **7b** was treated with TBAF and worked up analogously to compound **7a**. The yield was 0.188 g, 80%.^{31}P NMR ($CDCl_3$, CD_3OD) δ: −1.9.

*2.13. 2′,3′,N^4-trilevulinyl-1-β-arabinofurano-sylcytosine-5′-monophosphate-1,2-dioleoyl-sn-glycerol tributylammonium salt (**8c**)*

Compound **7c** was partially deblocked analogously to compound **7a**. The yield was 0.352 g, 100%. ^{31}P NMR ($CDCl_3$, CD_3OD) δ: −1.0.

*2.14. 1-β-arabinofuranosylcytosine-5′-monophosphate-1,2-dipalmitoyl-sn-glycerol tributylammonium salt (ara-CMP-dipalmitin) (**9a**)*

Compound **8a** was delevulinated with hydrazine hydrate as described in the literature (Ryu et al., 1982). The yield was 0.076 g, 50%. ^{1}H NMR ($CDCl_3$-CD_3OD-D_2O, 2:3:1) δ: 7.8 (d, 1H, $J_{5,6}$ = 7.8 Hz) H-6, 6.1 (d, $J_{1',2'}$ = 4.4 Hz) H-1′, 6.0 (d, 1H, $J_{5,6}$ = 7.8 Hz) H-5, 5.2 (m, 1H) 2-CH of glycerol, 4.3–3.9 (m, 15H) H-2′, H-3′, H-4′, H-5′, H-5″ + glycerol CH_2's + tributylamine CH_2's, 2.3 (m, 2H) CH_2CO, 1.6–1.3 (m, 26H) CH_2 of palmitoyl, 0.9 (t, 9H) palmitoyl + tributylamine CH_3. ^{31}P NMR ($CDCl_3$, CD_3OD) δ: −2.3. UV (pH 2) λ_{max} 285 nm; (pH 7) 276 nm; (pH 12) 274 nm.

*2.15. 1-β-arabinofuranosylcytosine-5′-monophosphate-1,2-distearoyl-sn-glycerol tributylammonium salt (ara-CMP-dipalmitin) (**9b**)*

Compound **8b** was treated with hydrazine hydrate analogously to compound **8a**. The yield was 0.073 g, 52%. ^{1}H NMR ($CDCl_3$–CD_3OD–D_2O, 2:3:1) δ: 7.8 (d, 1H, $J_{5,6}$ = 7.6 Hz) H-6, 6.1 (d, 1H, $J_{1',2'}$ = 4.4 Hz) H-1′, 5.9 (d, 1H, $J_{5,6}$ = 7.6 Hz) H-5, 5.2 (m, 1H) CH of glycerol. 4.7–3.8 (m, 15H) H-2′, H-3′, H-4′, H-5′, H-5″ + glycerol CH_2's + tributylamine CH_2's, 2.3 (m, 4H) CH_2CO, 1.6–1.0 (m, 30H) CH_2 of stearoyl, 0.9 (t, 9H) CH_3 of stearoyl and tributylamine. ^{31}P NMR ($CDCl_3$, CD_3OD) δ: −0.9. UV (pH 2) λ_{max} 285 nm; (pH 7) 276 nm; (pH 12) 274 nm.

2.16. 1-β-arabinofuranosylcytosine-5′-monophosphate-1,2-dioleoyl-sn-glycerol tributylammonium salt (ara-CMP-dipalmitin) (9c)

Compound **8c** was deblocked analogously to compound **8a**. The yield was 0.067 g, 53%. ^{1}H NMR ($CDCl_3$–CD_3OD–D_2O, 2:3:1) δ: 7.9 (d, 1H, $J_{5,6}$ = 7.6 Hz) H-6, 6.1 (d, 1H, $J_{1',2'}$ = 4.4 Hz) H-1′, 5.9 (d, 1H, $J_{5,6}$ = 7.6 Hz) H-5, 5.3 (m, 5H) CH of glycerol + $(CH=CH)_2$, 4.7–3.7 (m, 15H)

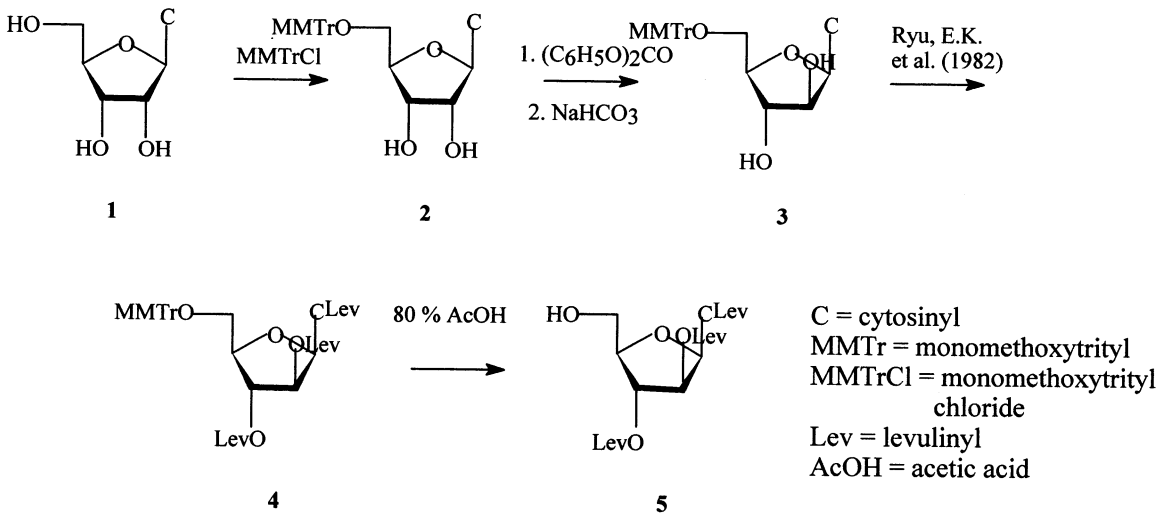

Fig. 1. Synthesis of the protected ara-C.

H-2′, H-3′, H-4′, H-5′, H-5″ + glycerol CH_2's + tributylamine CH_2's, 2.3 (m, 4H) CH_2CO, 1.6–1.3 (m, 26H) CH_2 of oleoyl, 0.9 (m, 9H) CH_3 of oleoyl and tributylamine. ^{31}P NMR ($CDCl_3$, CD_3OD) δ: − 0.6. UV (pH 2) λ_{max} 285 nm; (pH 7) 276 nm; (pH 12) 274 nm.

3. Results and discussions

In the synthesis of 5′-*O*-MMTr-ara-C (Fig. 1) we showed that increasing the liphophility of the starting material (cytidine) by protecting the 5′-OH of cytidin with monomethoxytrityl chloride we could prepare 5′-*O*-MMTr-ara-C 3 with the Ogilvie, 1972 procedure then purify from the remaining few percent of starting material with fast short silica gel chromatography instead of with Zerolite FF and Dowex 50WX2 (H^+) by Beranek et al. (1974). Compound **3** could be used directly with the temporary 5′-*O*-MMTr protection of ara-C for the synthesis of ara-C phospholipid. The UV spectra of 5′-*O*-MMTr-cytidine **2** and 5′-*O*-MMTr-ara-cytidine **3** are the same and the ^1H NMR spectra corroborate the structure of compound **3**. In the 5′-*O*-MMTr-ara-C **3** the anomeric proton becomes more shielded (Bazin et al., 1986) compared to compound **2**. This relative shielding of H-1′ may be due to a lone pair effect of the C-2′ substituent. The H-1′ chemical shift of compound **3** (6.2 ppm) is 0.4 ppm more shielded than that of compound **2** (5.8 ppm). $J_{H,H}$ of 2′ or 3′ increases as the configuration of the substituent—which is directly attached to it—changes (Bazin et al., 1986). We have noticed the same tendency because in the 5′-*O*-MMTr-cytidin **2** $J_{H\text{-}1',H\text{-}2'} = 2.0$ Hz and in the 5′-*O*-MMTr-ara-cytidine **3** it has a higher value (5.1 Hz).

The synthesis of phospholipid was carried out as previously described (Nyilas, 1997) employing the Eibl, 1981 method for the preparation of isopropilidene glycerol. The 3 position of glycerol was protected by FMOC in an 80% yield and the isopropilidene group was removed with formic acid treatment. The fatty acids were introduced quantitative, then the FMOC group was removed by dry triethylamine (Nyilas, 1997).

The levulination of 5′-*O*-MMTr-ara-C was carried out as in the literature (Ryu et al., 1982) and the MMTr group was removed with aqueous acetic acid treatment at room temperature for 3 h, giving compound **5** (67%) (Fig. 1). The phospho-

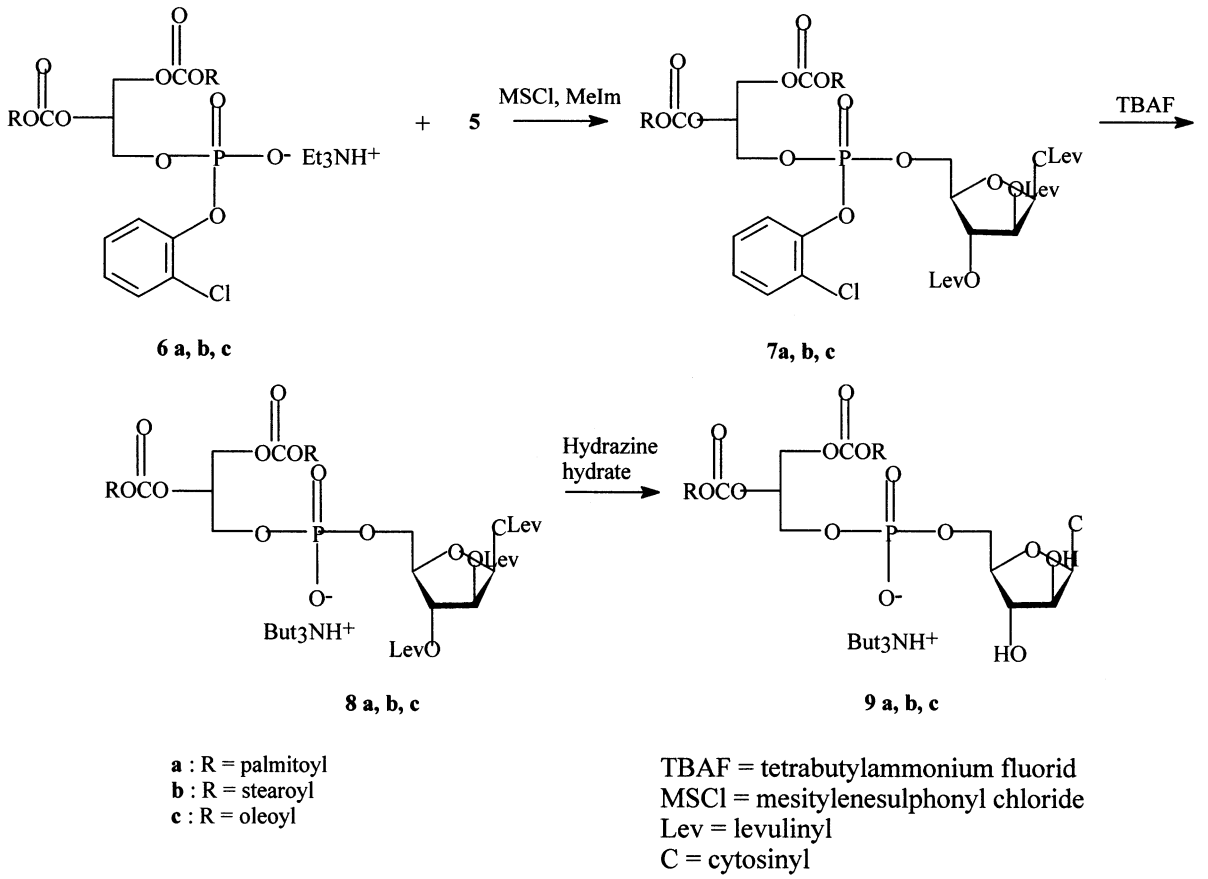

Fig. 2. Synthesis of ara-C-phospholipid conjugates.

rylation of diacyl-*sn*-glycerols was performed with 2-chlorophenyl-phosphoro-bis-triazolide (Welch and Chattopadhyaya, 1985) giving the phosphoglycerols (**6a**, **6b**, **6c**) quantitative. Condensation of phosphoglycerols with 2′,3′,N^4-trilevulinyl-ara-C **5** (Fig. 2) was performed also with a high yield in the presence of MsCl and MeIm (Nyilas et al., 1986). The TBAF treatment and delevulination with hydrazine hydrate gave the target compounds (**9a**, **9b**, **9c**) at a 50% yield, which were characterized by UV, ^{1}H NMR and ^{31}P NMR spectroscopy. The λ_{max} at different pH was the same as that of cytidine. ^{1}H NMR spectrum of compound **9a** is similar to the literature (Ryu et al., 1982). Chemical shifts of ^{31}P NMR spectra of the triesters (**6a**, **6b**, **6c**) and diesters (**9a**, **9b**, **9c**) were similar to the dinucleotides (Nyilas et al., 1986).

4. Summary

We have improved the yield of the synthesis of ara-C from 32 to 67% with MMTr protection of 5′-OH of cytidine and shortened the time of purification with silica gel of the reaction mixture.

We have characterized the 5′-*O*-MMTr-ara-C by ^{1}H NMR spectroscopy compared with the spectrum of 5′-*O*-MMTr-C.

We showed here that the 1,2-diacylglycerols synthesized by FMOC protection on the *sn*-3 position could be phosphorylated with 2-

chlorophenyl-phosphoro-bis-triazolide and could be used for the preparation of ara-C-phospholipid conjugates without acyl migration, within the limit of the sensitivity of ^{1}H NMR.

Employing the phosphotriester methodology of Welch and Chattopadhyaya (1985) instead of the diester method of Ryu et al. (1982) the yield of condensation of phosphoglycerols and 2′,3′N^4-trilevulinyl-ara-C could be improved from 22 to 85–95%.

Acknowledgements

The autor gratefully acknowledge financial support from the Swedish Board of Technical Development and the Swedish Natural Science Research Council. I thank Professor Dr Jyoti Chattopadyaya for valuable discussions.

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