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SYNTHESIS OF NOVEL OPTICALLY ACTIVE CYCLIC PHOSPHOLIPID CONJUGATES OF TEGAFUR AND URIDINE STARTING FROM L-SERINE

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Abstract: Starting from L-serine, cyclic phospholids **2,3** and **4** were synthesized and successfully separated in the form of pure diastereomer. Their configurations were discussed and assigned according to their NMR spectra data. The asymmetric induction effects were also observed in two phosphorylation cyclizations.

Previously we have reported the syntheses and preliminary antitumor activities of some new types of cyclic glycerophosphatide conjugates[1-5]. Those reported compounds were all prepared and evaluated as antitumor agents in racemic forms. In this paper, it is reported the synthesis of a novel type of optically active cyclic phospholipid derivatives of Tegafur and uridine starting from L-serine. All of these derivatives have a heteroatom nitrogen at C_2 position and one alkoxy carboxy group as the replacement of hydroxy-derived group at C_1

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position. Although there is a remarkable structural difference between this type of conjugates and traditional phospholipid, they still remain the main carbon backbone of phospholipid. Moreover, these conjugates possess another feature that phosphorus atom is chiral. All of their diastereomers were successfully isolated, thus, this provides a possibility for studying on the stereoselectivty of a pair distereomers to the antitumor activity.

Chlorination of L-serine, followed by esterification with alcohols afforded L-serinoate **1**. Direct cyclization of **1** with iodine-activated hexaethyl phosphorous triamide, followed by condensation with uridine or Tegafur derivatives provided three-coordinated cyclic phosphorus compounds, which were sulfurized with elemental sulfur to give four-coordinated cyclic thiophosphates **2** and **3**. Another cyclic phosphate **4** was synthesized from L-serinoate **1**. **1** was N-benzylated into N-benzyl L-serinoate **5**, which was cyclized with phosphorus oxychloride giving cyclic chloridate **6**. **6** reacted with Tegafur derivative yielding **4**.

In above synthetic reactions, the asymmetric cyclizations of L-serinoate **1** with $(Et_2N)_3P$ / I_2 and N-benzyl L-serinoate **5** with $POCl_3$ were investigated. The asymmetric induction effect of chiral carbon centre to phosphorus atom was evaluated in terms of diastereomeric excess percentage (de%), which can be calculated from ^{31}P NMR intensities of a pair of diastereomers mixture. In the above-mentioned cyclizations, the induction effect is poor, and crude products **2**, **3**, and **4** as diastereomeric mixture were obtained with 8.2%, 30.0% and 17.6% de values, respectively. Fortunately, **2**, **3** and **4** were all separated in individual diastereomer form by column chromatography on silica gel. Their related data of physical properties are listed in Table 1 and their antitumor activity is under investigation in our laboratory.

According to the literature method based on the data of ^{31}P- and ^{13}C-NMR[6-7], compounds **2a**, **3a**, **4a**(**a** series) and **2b**, **3b**, **4b**(**b** series) should be trans-(**7a**) and cis-(**7b**) form respectively. Thus, the phosphorus configuration in these compounds can be preliminarily assigned(Table 1).

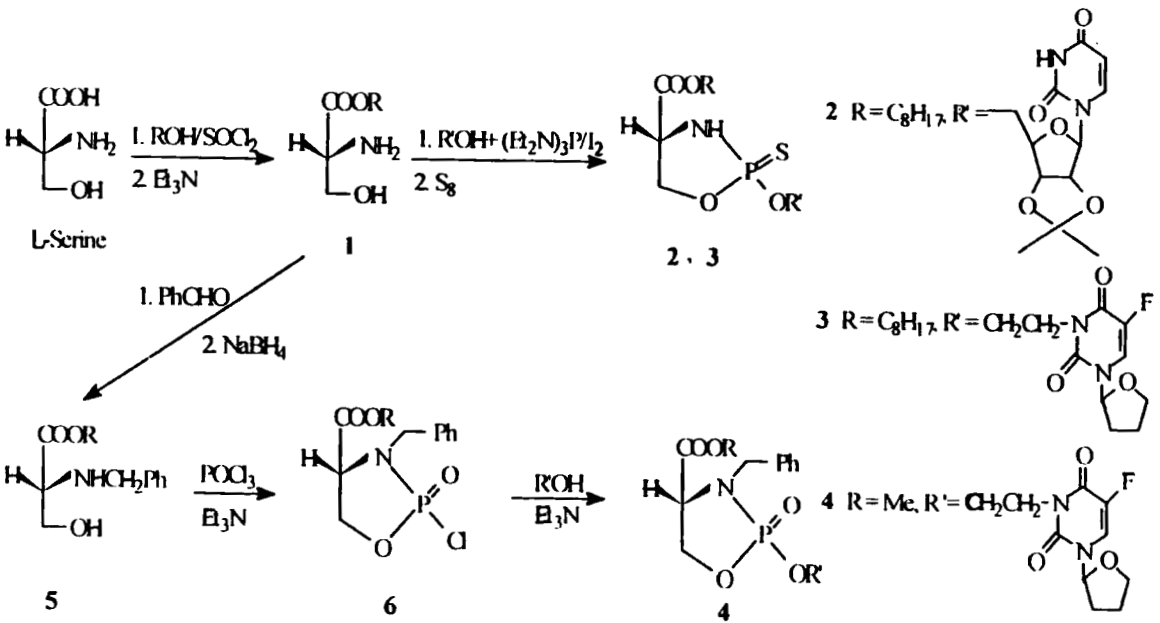
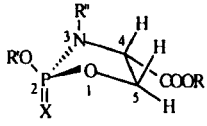


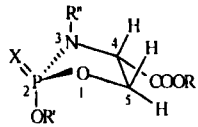
Table 1. The data of Compds. **2**, **3** and **4**

Compd.	m.p. (°C)	$[\alpha]_D$	%de	Yield (%)*	^{31}PNMR δ(ppm)	^{13}CNMR δ (ppm) of C_4	Config. (cis/trans)	Config. at P
2a	32~33	-10.8	8.2	34.9	85.86	55.50	trans	R
2b	43~45	-11.2	8.2	41.9	86.85	56.21	cis	S
3a	thick liq.	-10.3	30.0	32.5	85.95	55.81	trans	S
3b	thick liq.	-20.1	30.0	38.5	87.32	56.29	cis	R
4a	thick liq.	-26.0	17.6	26.2	20.20	55.88	trans	S
4b	thick liq.	+16.7	17.6	31.9	20.87	55.00	cis	R

*Isolated yield



7a trans



7b cis

Experimental

1. Preparation of Compound **2**

To a solution of n-octyl L-serinoate hydrochloride (0.53 g, 2.1 mmol) in 15 mL of methylene chloride, triethylamine (0.22 g, 2.2 mmol) was added at room temperature. The reaction mixture was then stirred at 20-30 °C for 4 h. After evaporation of methylene chloride under reduced pressure, 15 mL of anhydrous benzene was incorporated with the residue, and triethylamine hydrochloride precipitate was filtered off and washed with a small amount of anhydrous benzene. The filtrate was collected as a benzene solution of n-octyl L-serinoate for the next step.

A mixture of hexaethyl phosphorous triamide (0.52 g, 2.1 mmol) and 50 mL of anhydrous benzene was heated to 70 °C with stirring. Iodine (0.025 g) was added and reacted for 15 min

at 70 °C, and then 2',3'-isopropylidene uridine (0.568 g, 2.0 mmol) was added and reacted for additional 2 h at the same temperature. The benzene solution of n-octyl L-serinoate prepared above was dropwise added and the resulting reaction mixture was stirred at 70-80 °C for 2 h. Elemental sulfur powder (0.067 g, 2.1 mmol) was added and reacted for 0.5 h. After cooling to room temperature, a sample was taken from the reaction mixture for ^{31}P NMR test, which disclosed that the diastereomeric excess percentage of the desired product **2** was 8.2%. After removal of solvent under reduced pressure, the crude resultant was purified and isolated by column chromatography on silica gel (petroleum ether – ethyl acetate, gradient elution) to afford two fractions. **2a**, 0.22 g, isolated yield 34.9%, white solid, m.p.32-33 °C, $[\alpha]_D$ −10.8° (c = 0.60, $CHCl_3$), TLC R_f = 0.43 (petroleum ether (60 - 90°) / ethyl acetate 1:1 (v/v)), ^{31}P NMR: δ 85.86 ppm. **2b**, 0.26 g, isolated yield 41.9%, white solid, m.p. 43-45 °C, $[\alpha]_D$ - 11.2° (c = 0.67, $CHCl_3$), TLC R_f = 0.34 (petroleum ether (60 - 90°) / ethyl acetate 1:1 (v/v)), ^{31}P NMR: δ 86.85 ppm.

2. Preparation of Compound **3**

Crude compound **3** was obtained from the same procedure as that for compound **2** except that N^3-(2-hydroxyethyl) Tegafur (0.488 g, 2.0 mmol) was used as substrate instead of 2',3'-isopropylidene uridine. Its ^{31}P NMR showed that the diastereomeric excess percentage was 30.0%. Chromatographic isolation gave two fractions. **3a**, 0.18 g, isolated yield 32.5%, pale yellow viscous oil, $[\alpha]_D$ −10.3° (c = 1.80, $CHCl_3$), TLC R_f = 0.64 (petroleum ether (60 - 90°) / ethyl acetate 1:1 (v/v)), ^{31}P NMR: δ 85.95 ppm. **3b**, 0.22 g, isolated yield 38.5%, pale yellow viscous oil, $[\alpha]_D$ −20.1° (c = 6.80, $CHCl_3$), TLC R_f = 0.56 (petroleum ether (60 - 90°) / ethyl acetate 1:1 (v/v)), ^{31}P NMR: δ 87.32 ppm.

3. Preparation of Compound **4**

Methyl N-benzyl L-serinoate (2.10 g, 10 mmol) was dissolved in 40 mL of anhydrous toluene and cooled to 0 °C with stirring, and triethylamine (3 mL) was added. Then a solution

of phosphorus oxychloride in 10 mL of anhydrous toluene was dropwise added and the reaction was stirred at room temperature for 2 h. After evaporation of solvent under reduced pressure (vapor temperature above 40 °C), crude product cyclic phosphorochloridate **6** as a diastereomeric mixture was obtained with 17.6% de value based on ^{31}P NMR spectrum. The diastereomers were separated by column chromatography on silica gel (200 – 300 mesh, petroleum ether / ethyl acetate, gradient elution). **6a**, 1.3 g, ^{31}P NMR. δ 23.42 ppm; **6b**, 1.4 g, ^{31}P NMR: δ 23.78 ppm, total yield 94.7% (lit.[9]: ^{31}P NMR: δ 23.68 and 23.92 ppm, respectively, yield 92%).

To a solution of N^3-(2-hydroxyethyl) Tegafur (0.50 g, 2.0 mmol) dissolved in 20 mL of chloroform, a solution of **6a** (0.58 g, 2.0 mmol) in 5 mL of chloroform was dropwise added, followed by triethylamine (0.3 mL). The reaction mixture was stirred at room temperature overnight, and then washed with water (2 × 15 mL), dried over Na_2SO_4, and evaporated in vacuo to yield crude product, which was purified by column chromatographic method (200 – 300 mesh silica gel, petroleum ether / ethyl acetate, gradient elution) to afford 0.26 g of **4a** as a pale yellow viscous oil, yield 26.2%, $[\alpha]_D$ -26.0° (c = 0.60, $CHCl_3$), ^{31}P NMR: δ 20.20 ppm.

Similarly, **4b** (0.32 g) was prepared as a pale yellow viscous oil from **6b** (0.58 g, 2.0 mmol) in 31.9% isolated yield, $[\alpha]_D$ +16.7° (c = 0.60, $CHCl_3$), ^{31}P NMR: δ 20.87 ppm.

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