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SYNTHESIS OF THE OPTICALLY ACTIVE α-NUCLEIC ACID BASE SUBSTITUTED PROPANOIC ACIDS

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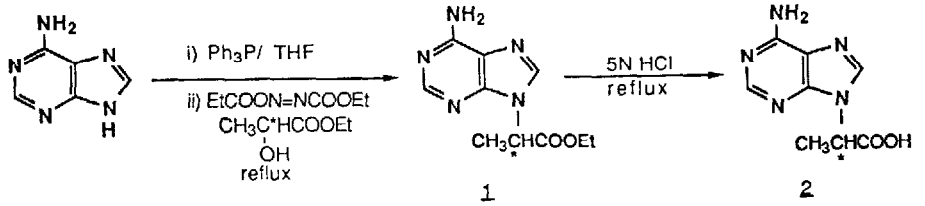
Summary: The (R)-2-(adenin-9-yl)propanoic acid 2 was prepared from adenine and (S)-ethyl lactate by using the triphenyl phosphine-diethyl azodicarboxylate system. The (R)-2-(thymin-1-yl)-propanoic acid, (R)-2-(cytosin-1-yl)propanoic acid, and (R)-2-(hypoxanthin-9-yl)propanoic acid were also prepared.

The optically active polynucleotide analogs with synthetic polymer backbones have been obtained by reaction of optically active nucleic acid base derivatives with functional polymers such as polyethylenimine,[1] polyvinylamine,[2] poly(vinyl alcohol),[3] and polytrimethylenimine.[4] Some of these polymers have attracted great attention due to their antiviral activity.[5,6]

An α-nucleic acid base substituted propanoic acid has been used most widely as a pendant group because it is one of the simplest derivatives of a nucleic acid base that has an asymmetric center and an acidic functional group. The acidic functional group is essential for optical resolution and the grafting reaction. The 2-(thymin-1-yl)propanoic acid was resolved by using quinine and grafted onto several polymer backbones by an amidation or an esterification reaction.[1-4] However, the conventional resolution methods are very tedious and give a poor result in many cases. For example, all attempts at the resolution of 2-(adenin-9-yl)propanoic acid were unsuccessful.[5] We now wish to report a novel procedure to prepare the optically active α-nucleic acid base substituted propanoic acids by utilizing the diethyl azodicarboxylate-triphenyl phosphine system developed by Mitsunobu and coworkers.[7]

The synthesis of (R)-ethyl 2-(adenin-9-yl)propanoate is outlined in Scheme 1. The mixture of 0.54 g (4 mmole) of adenine and 1.57 g (6 mmole) of triphenyl phosphine in 100 mL of tetra-

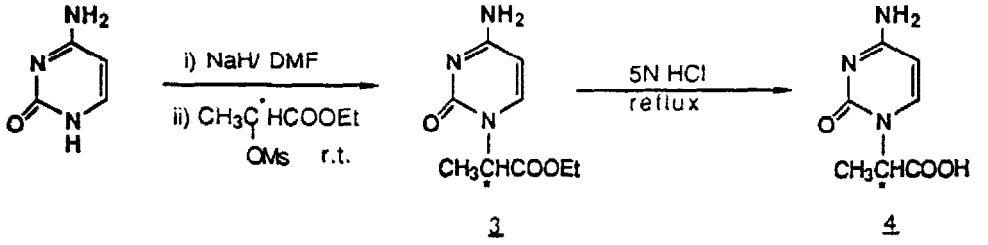


1 2

Scheme 1

hydrofuran was refluxed for 2 hrs. The reaction mixture was cooled to room temperature and 0.95 mL (6 mmole) of diethyl azodicarboxylate and 0.97 mL (8 mmole) of (S)-ethyl lactate were added dropwise. The reaction mixture was refluxed for 15 hrs. The unreacted adenine (0.19 g) was removed by filtration and tetrahydrofuran was evaporated under reduced pressure. The desired product, 0.20 g (33% yield), was isolated by flash column chromatography on silica gel, R_f 0.38 (ethyl acetate-ethyl alcohol 4:1), $[\alpha]_D$ = +2.0° [C = 0.25, trifluoroethanol (TFE)]. The optical purity of the ester 1 was greater than 97% as determined by proton NMR with tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium(III) [Eu(tfc)$_3$]. The ester 1, 0.94 g (4 mmole), was dissolved in 25 mL of 5N HCl and the resulting solution refluxed for 3 hrs. After evaporation of the solvent, the residue was dissolved in the minimum amount of water. The solution was adjusted to pH 4.5 with 3N NaOH. The precipitated acid, 0.58 g (70% yield), was collected by filtration, $[\alpha]_D$ = -46.1° (C = 0.2, TFE-H_2O 1:1). The acyl urea 6 was prepared by reaction of the acid 2 with dicyclohexylcarbodiimide (DCC) in dimethylformamide at room temperature to examine possible racemization during hydrolysis. The optical purity determined by proton NMR was greater than 97%, which indicates no significant racemization during hydrolysis. In a similar manner, (R)-(thymin-1-yl)propanoic acid was obtained in 15% overall yield, $[\alpha]_D$ = +49.0° (C = 0.2, TFE) [lit.[1] $[\alpha]_D$ = +47.8° (C = 0.8, TFE)].

The (R)-2-(Cytosin-1-yl)propanoic acid was prepared according to Scheme 2. The S_N2 reaction between sodium cytosine and (S)-ethyl [(methylsulfonyl)oxy]propanoate was carried out to give the ester 3 with 20% racemization. The ester was recrystallized from ethyl alcohol and the compound of higher optical rotation was found in the filtrate. The optically pure ester was recovered from the final filtrate in 15% yield, $[\alpha]_D$ = +70.2° (C = 0.25, TFE). The attempted synthesis by the Mitsunobu reagent was unsuccessful due to the extremely low solubility of cytosine in THF.



3 4

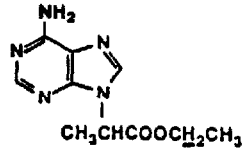
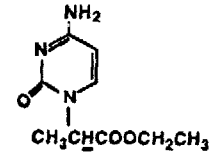
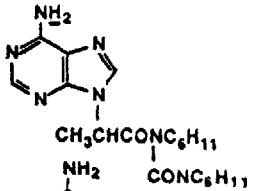
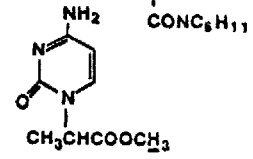
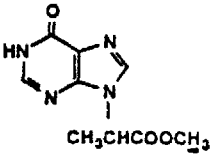
Scheme 2

The ester 3 was hydrolyzed under acidic conditions. The precipitated acid was collected at pH 4.5 in 58% yield. The methyl ester 7 was prepared by an esterification reaction with DCC in DMF at room temperature to determine optical purity of the acid. The ester 7 was only slightly soluble in chloroform-d_1 but dissolved with addition of Eu(tfc)$_3$. The ester 7 showed 78% optical purity, which indicates 9% racemization during these reactions.

The (R)-2-(hypoxanthin-9-yl)propanoic acid 5, $[\alpha]_D$ = -18.7° (C = 0.25, TFE:H_2O 1:1), was converted from (R)-2-(adenin-9-yl)propanoic acid by reaction with nitrous acid in 55% yield. The methyl ester 8 was prepared for determination of the optical purity of the acid 5. The active ester obtained by reaction of the acid 5 with N-hydroxysuccinimide in the presence of DCC in DMF at 4°C was methanolyzed at room temperature to give the ester 8. The attempted esterification reaction of the acid 5 with methanol in the presence of DCC gave only the acyl urea.

The proton NMR analyses results with a chiral chemical shift reagent in chloroform-d_1 are summarized in Table 1.

Table 1. Chemical Shifts of the Specific Protons with a Chiral Shift Reagent [Eu(tfc)$_3$] in chloroform-d_1.

Compound	Eu(tfc)$_3$ (equiv.)	Chemical Shift (ppm)	Optical Purity [(R)-enantiomer]
1 	1.0	5.19 (R) 5.32 (S)	97%
3 	0.5	6.68 (R) 6.54 (S)	97%
6 	0.2	7.08 (R) 7.55 (S)	97%
7 	0.8	4.38 (R) 4.52 (S)	78%
8 	0.7	3.87 (R) 3.83 (S)	95%

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