SYNTHESIS OF CHIRAL 3-SUBSTITUTED γ-LACTONES AND 9-FURANOSYL-ADENINE FROM (*R*)-2-(2,2-DIETHOXYETHYL)-1,3-PROPANEDIOL MONOACETATE PREPARED BY LIPASE-CATALYZED REACTION

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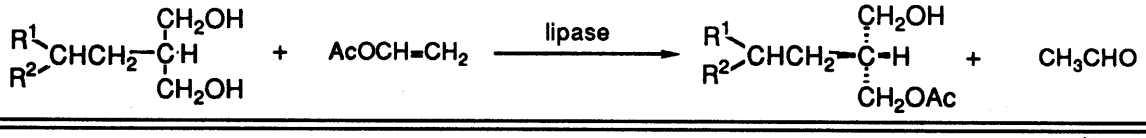
A chiral building block, (*R*)-2-(2,2-diethoxyethyl)-1,3-propanediol monoacetate was synthesized in high optical and chemical yields by lipase-catalyzed transesterification. From this compound, we synthesized chiral 3-substituted γ-lactones and a new nucleoside with antiviral activity.

KEYWORDS lipase; asymmetric synthesis; γ-lactone; nucleoside; A-factor

Enzyme-catalyzed asymmetric synthesis has become one of the practical methods for production of useful chiral molecules because of the development of enzyme preparation and the advantages of enzymatic reactions such as the high stereospecificity of enzyme and mild reaction conditions.[1] In particular, the reaction in organic media is an extremely convenient procedure.[2] In this paper we describe the efficient synthesis of optically pure (*R*)-2-(2,2-diethoxyethyl)-1,3-propanediol monoacetate (**1b**) by lipase-catalyzed transesterification in a noneaqueous system and its utility for the syntheses of optically active 3-substituted γ-lactones and a unique nucleoside with antiviral activity.

We have reported that lipase-catalyzed transesterification of 2-substituted 1,3-propanediols in vinyl acetate gave optically active monoesters in high optical and chemical yields,[3] where lipase P (*pseudomonas fluorescens)* and lipase B (*Pseudomonas fragi*) were well adapted to the substrates.[4] When 2-(2-benzyloxyethyl)-1,3-propanediol was allowed to react in vinyl acetate, the corresponding (*R*)-monoacetate (**1a**) was obtained in moderate optical yield. However, lipase P in the 2-(2,2-diethoxyethyl)-1,3-propandiol showed extremely high enantioselectivity (entry 3 in Table I). The absolute configuration of both products were determined as the *R* form by conversion into the (*S*)-(-)-2-methyl-1,4-butanediol reported previously.[5] (*R*)-2-(2,2-Diethoxyethyl)-1,3-propanediol monoacetate (**1b**)[6] is a useful chiral building block with three easily convertible functional groups at an asymmetric carbon even though it is a simple molecule.

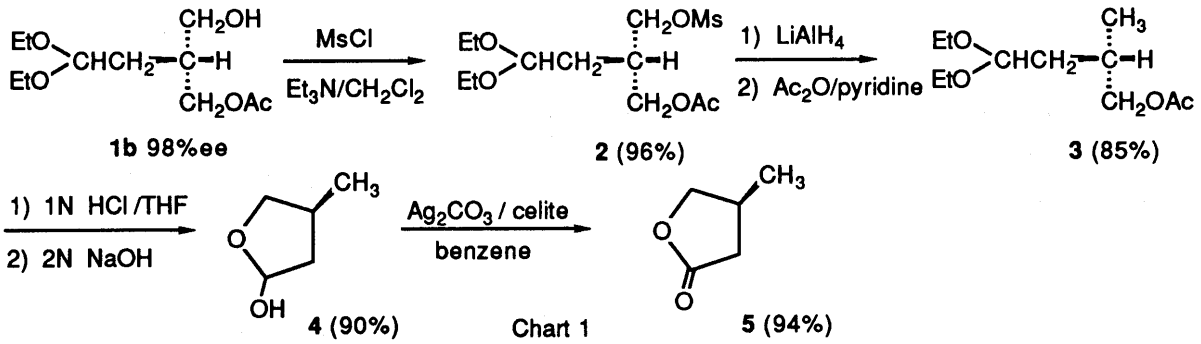
Table I. Lipase-Catalyzed Transesterification[a]



Entry	Substrate R^1	Substrate R^2	Lipase	Reaction time(h)	Product No.	Yield (%)	Optical yield[b] (%ee)
1	$PhCH_2O$	H	lipase P	1.0	**1a**	90	81
2	$PhCH_2O$	H	lipase B	0.5	**1a**	82	55
3	C_2H_5O	C_2H_5O	lipase P	1.0	**1b**	95	98
4	C_2H_5O	C_2H_5O	lipase B	1.0	**1b**	89	82

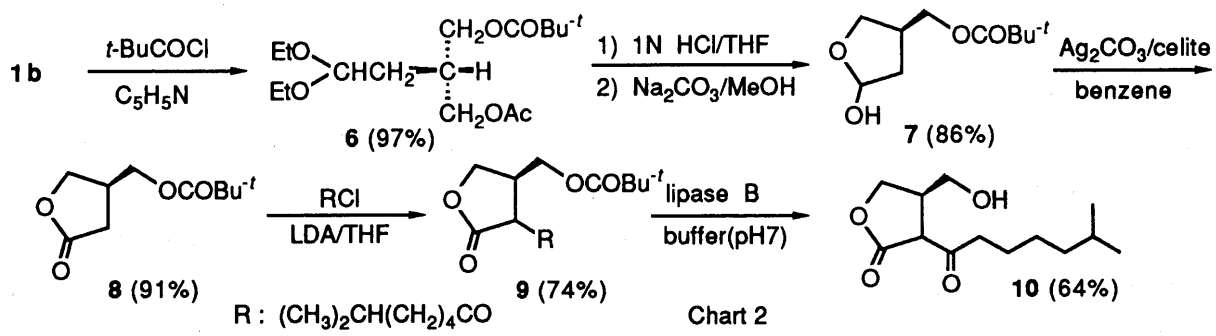
a) All reactions were carried out with substrate (5 mmol), vinyl acetate (7.5mmol), and lipase P (100mg) or lipase B (50mg) at 20°C. *b)* Optical yields were determined by HPLC analyses (after benzoylation in entries 3 and 4) using a column packed with Chiralcel OD (2-propanol / n-hexane system).

(*S*)-3-Methyl-γ-lactone, from which the side chain of α-tocopherol was prepared[7], was synthesized as shown in Chart 1. The reaction and isolation procedures in each step were carried out in the usual manner. The structure of the final product (**5**) was determined by its spectral data and the specific rotation was in agreement with the reported value.[8]



1b 98%ee **2** (96%) **3** (85%) **4** (90%) Chart 1 **5** (94%)

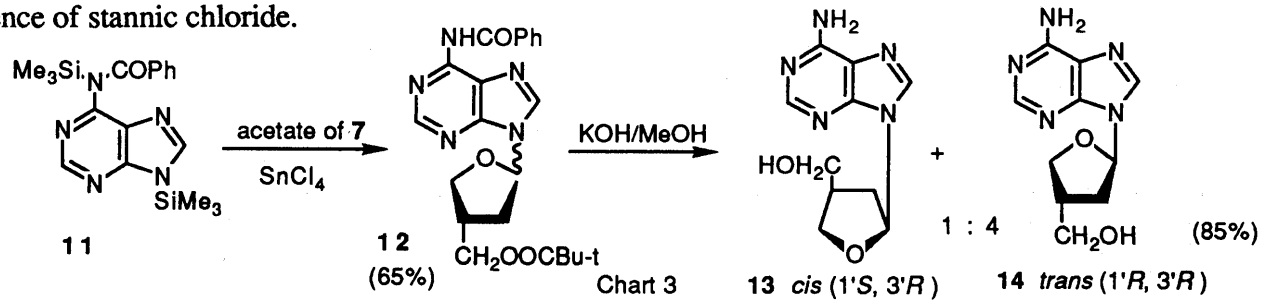
Our next synthesis target was A-Factor which had been isolated from *Streptmyces griseus* as the inducer for the production of streptomycin by Khokhlov.[9] By using **1b**, A-factor was successfully synthesized according to the route described in Chart 2.



6 (97%) **7** (86%) **8** (91%) **9** (74%) **10** (64%) Chart 2

After hydrolysis of the acetal moiety of **6**, treatment with 10% aqueous Na_2CO_3 in methanol gave the required (2-hydroxy-4-(*S*)-tetrahydrofuranyl)methyl pivalate (**7**). The lactone **8** obtained by Fetizon's oxydation of **7** was acylated with 7-methylheptanoyl chloride in the presence of LDA at -70°C. Because of the lability of the final product (**10**) the hydrolysis of the pivalic acid ester group of **9** was carried out with lipase B catalyst in a neutral buffer solution. The spectral data[10] and specific rotation of product **10** were quit like those reported.[11]

In the course of this work, we focused on hemiacetal (**7**) because the nucleosides with various sugar moeties showed antiviral activities [12] and **7** seems to be a unique sugar moiety which does not exist in nature. The protected 6-[2,3,4-trideoxy-3-hydroxymethyl)furanosyl]adenine (**12**) was synthesized according to the reported method[13] from the fully silylated N^6-benzoyladenine prepared *in situ* and the acetate of **7** in the presence of stannic chloride.



11 **12** (65%) Chart 3 **13** *cis* (1'*S*, 3'*R*) **14** *trans* (1'*R*, 3'*R*)

After deprotection with alkaline methanol, the adenosine obtained was a 1:4 mixture of 1,3-*cis* (**13**) and 1,3-*trans* isomer (**14**).[14] The preliminary examination of their biological activities indicated that the 1,3-*cis* isomer (**13**) had anti-HIV activity in MT-4 cells, and no cytotoxicity.

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4) Lipase P and lipase B were kindly supplied by Amano Pharmaceutical Co. and Sapporo Breweries Ltd., respectively.

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6) **1b**: IR(neat)cm^{-1}: 3410, 1730, ^{1}H-NMR($CDCl_3$) δ: 1.12(6H, t, J=7.0Hz, 2xCH_3), 1.55-1.85 (3H, m, -CH_2CH<), 2.02(3H, s, $COCH_3$), 2.30(1H, br.s, OH), 3.30-3.60(6H, m, -C$\underline{H_2}$OH, 2xC$\underline{H_2}$O-), 4.05(2H, d, J=6Hz, CH_2OAc), 4.65(1H, t, J=5.5Hz, -$CH(OEt)_2$).

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8) **6**: $[a]_D^{20}$ -25.4°(*c*=1.0, MeOH), [*lit.*[7], $[a]_D^{20}$ -24.7°(*c*=4.0, MeOH)], IR(neat)cm^{-1}: 1765, ^{1}H-NMR ($CDCl_3$) δ: 1.16(3H, d, J=6.4Hz, CH_3), 2.13(1H, dd, J_1,J_2=10.2Hz, -C$\underline{H_A}H_B$CO), 2.61-2.68(2H, m, . >CH-, -CH_AC$\underline{H_B}$CO), 3.87(1H, dd, J=6.2, 9.2Hz, -C$\underline{H_A}H_B$-), 4.41(1H, dd, J=6.9, 9.2Hz, -O$CH_A\underline{H_B}$-), ^{13}C-NMR($CDCl_3$) δ: 17.9, 30.4, 36.1, 74.7, 177.3, Ms(*m/z*): 100(M^+).

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10) **10:** $[a]_D^{20}$ -12.7°(c=1.0, $CHCl_3$), [lit.[11], $[a]_D^{20}$ -13.1°(c=1.18, $CHCl_3$) or -12.5°(c=1.10, $CHCl_3$)], IR(neat)cm^{-1}: 3640, 1765, 1720, ^{1}H-NMR($CDCl_3$) δ: 0.86(6H, d, J=6.9Hz), 1.1-1.8(9H, m), 2.5-3.3(3H, m), 3.5-3.85(2H, m), 4.0-4.3(2H, m), ^{13}C-NMR($CDCl_3$) δ: 22.5, 23.5, 26.5, 27.8, 38.6, 39.1, 42.5, 54.9, 61.8, 69.0, 172.4, 202.9, MS(*m/z*): 242 (M^+).

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14) The ^{1}H- as well as the ^{13}C-NMR spectra of **13** and **14** were similar to each other and their elemenents were satisfactorily analysed. The isomeric structures were also supported by the results of the nuclear Overhauser effect (NOE).

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