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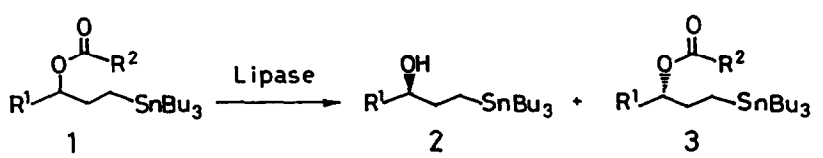
AN EFFICIENT PREPARATION OF THE OPTICALLY ACTIVE γ -HYDROXY STANNANES USING LIPASE-CATALYZED HYDROLYSIS

Toshiyuki ITOH*, Tadataka OHTA and Mitsue SANO
Department of Chemistry, Faculty of Education
Okayama University, Okayama 700, Japan

Summary: A perfect optical resolution of γ -hydroxystannanes was demonstrated by the method of lipase-catalyzed enantioselective hydrolysis of the corresponding racemic acetates using lipase P(Pseudomonas sp.).

The utilization of organotin compounds in modern synthesis continues to grow at an impressive rate.[1] Although some excellent studies on the application of γ -hydroxystannanes have been reported,[2] they have concentrated on the use of the achiral ones. For optically active γ -hydroxystannanes, there has been no contribution not only for their use but also for the method of their preparation. However, considering their potential as synthetic precursors, a simple method for the preparation of enantiomerically pure compounds would be desirable. After searching such method, we decided to use an enzymatic method of kinetic resolution using lipases. Recently, lipases are widely used to effect the kinetic resolution of chiral alcohols via enantioselective hydrolysis of their esters.[3] The availability and low cost of lipases render them a very attractive class of catalysts for effective use in applications even at the industrial level. This report describes the use of a lipase to effect perfect kinetic resolution of γ -hydroxystannanes.[4] The first application of them to the synthesis of an optically active tetrahydrofuran derivative is also described.

The bacterial lipase P(from Pseudomonas sp.) catalyzed enantioselectively the hydrolysis of γ -hydroxystannanes. 1-Tributylstannyl-3-hydroxybutane (1a), 1-tributylstannyl-3-hydroxyoctane (1c), and 1-tributylstannylundecane (1d) were resolved kinetically in high enantiomeric excess. The results are summarized in Table I. The enantioselective hydrolysis of substrates 1 with lipase P[5] was accomplished in a buffered aqueous medium at pH 7.2 with acetone as a cosolvent. When the hydrolysis of the above substrates



1 2 3

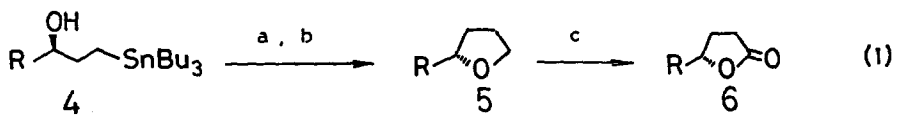
Table I. Kinetic resolution of ester 1 by the lipase hydrolysis

Entry	R^1	R^2	Time(h)	%ee of 2 (Conv.%)[b]	E[c]	$[\alpha]_D$[a] of 2 (config.)[d]	^{19}F NMR:CF_3[a] L : H
1	CH_3	CH_3	22	>98(50)	>460	-2.5° (R)	<1.0 :>99.0
2	C_2H_5	CH_3	16	21(49)	2	-2.7° (R)	39.5 : 60.5
3	n-C_5H_{11}	CH_3	16	63(48)	8	-1.0° (S)	81.4 : 18.6
4	n-C_5H_{11}	CH_2SMe	120	>98(36)	>170	-2.0° (R)	<1.0 :>99.0
5	n-C_5H_{11}	CH_2SPh	65	>98(41)	>200	-2.0° (R)	<1.0 :>99.0
6	n-C_5H_{11}	CH_2OPh	51	>98(31)	>150	-2.5° (R)	<1.0 :>99.0
7	n-C_8H_{17}	CH_3	114	51(49)	5	+1.4° (S)	75.7 : 18.6
8	n-C_8H_{17}	CH_2SMe	73	>98(23)	>130	+1.0° (R)	<1.0 :>99.0
9	n-C_8H_{17}	CH_2OPh	73	>98(50)	>460	+1.6° (R)[e]	<1.0 :>99.0

a)in $CHCl_3$. b)(+)-MTPA ester of 2. c)Determined by ^1H NMR analysis. d)Assignment is tentative. The results were based on the ^{19}F-NMR analysis by the comparison with the diastereomeric differences of the CF_3 group of (+)-MTPA esters with reference to (R)-2d(R=n-C_8H_{17}). e)see text.

was allowed to proceed to about 50% conversion, the hydrolyzed alcohol 2 and unreacted ester 3 were isolated after extraction with ethyl acetate followed by purification using silica gel flash column chromatography. The enantiomeric excess (% ee) of hydroxystannanes was determined by 470 MHz ^{19}F NMR analysis of the corresponding (S)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetate (MTPA ester).[7] The ee of the remaining ester, 3, was also determined by hydrolysis to the corresponding alcohols with a 2M-KOH (in methanol) solution and esterification with 100% excess of (S)-(+)-MTPA chloride. It should be recommended that perfect resolution was achieved when 1-tributylstannyl-3-acetoxybutane (1a) was subjected to the hydrolysis. After a 22 h reaction at 35°C, the crude extract was analyzed by 200 MHz ^1H NMR. The hydrolysis ratio was found to be about 50% conversion. Both of the (+)-MTPA esters derived from 2a and 3a appeared as single peaks at 90.46 ppm and 90.51 ppm in the ^{19}F NMR spectra, respectively. Therefore, it was found that both 2a and 3a were optically pure and the E[6] value of the resolution was calculated as >460. On the other hand, results of other acetates, 1c(R=n-C_5H_{11}) and 1d(R=n-C_8H_{17}), were far from satisfactory. However, it was discovered that the enantioselectivity of lipase P towards these substrates was drastically improved[8] when they were subjected to the hydrolysis with methylthioacetate (Entries 4 and 8). It should also be recommended that both phenoxyacetate (Entries 6 and 9) and phenylthioacetate (Entry 5) are suitable for the resolution. Only 1b (R=ethyl) was not a good substrate for this lipase even when it was subjected to the reaction with methylthio ester.

The absolute stereochemistry of the resulting carbinols was established



(1)

a)MOMCl, iPr_2NEt, CH_2Cl_2, rt, 12 h. b)$TiCl_4$(0.5eq.),-78°C→ 0°C, 23 h, CH_2Cl_2. c)$RuO_2 \cdot H_2O$(5.6eq), $NaIO_4$(6.3eq.), CH_3CN, CCl_4, 0.05M phosphate buffer(pH 7.0).

by a tetrahydrofuran ring forming sequence, which had been shown to proceed as follows (Eq 1). The alcohol 4(R=n-C_8H_{17}) was converted into the corresponding methoxymethyl ether, then treated with 0.5 equivalent of $TiCl_4$ in THF at -78°C.[9] The reaction mixture was allowed to react at 0°C with stirring for 23 h, extracted with ether and distillated in vacuo giving the tetrahydrofuran derivative, 5:$[\alpha]^{22}_D$ -10.2°(c0.45, $CHCl_3$);bp 150°C/90 mmHg, in 77% yield. To the best of our knowledge, this is the first example of optically active γ -hydroxystannanes being applied towards the synthesis of optically active tetrahydrofurannyl compound. (S)-4-Undecanolide, 6: $[\alpha]^{22}_D$ +30.7°(c0.43, $CHCl_3$), lit.[10] -34.0°(S), was derived from 5 by RuO_4 catalyzed -oxidation.[11] Therefore, the absolute configuration of 2d was found as R. The configuration assignment of other hydroxystannanes was performed by ^{19}F NMR analysis of the corresponding (+)-MTPA esters with reference to (R)-2d. From the diastereomeric differences in chemical shifts made by the trifluoromethyl group in the (+)-MTPA esters, the configuration was presumed.

A typical procedure of the present reaction for the preparation of optically active hydroxystannyl compound is described as follows. A solution of racemic stannane, 1i:R^1=n-C_8H_{17}, R^2=CH_2OPh;28 mg; 0.047 mmol, in 0.1M phosphate buffer (pH 7.2, 1.0 mL) and acetone (0.1 mL) was incubated with lipase P(28 mg) at 35°C for 73 h. The mixture, which was analyzed using 200 MHz ^1H NMR for determining the hydrolysis ratio as 50% conversion, was extracted with ethyl acetate and separated by SiO_2 thin layer chromatography to provide 2d(10 mg, 0.022 mmol;$[\alpha]_D$+1.6°,c0.85 in $CHCl_3$) and 3i(14 mg, 0.024 mmol;$[\alpha]_D$-7.5°,c0.80 in $CHCl_3$) in yield of 47% and 50%, respectively.

Considering the broad substrate specificity of the lipases, the present method should be recommended for use as a versatile and efficient method that provides optically pure γ -hydroxystannanes. Since both tetrahydrofurannyl compounds and γ -lactones are frequently found in biologically active natural products, the present method should become an important method for preparing them. Further experiments for the determination of the scope and limitation of this reaction and application of these optically active γ -hydroxystannanes are now in progress.

Acknowledgment. We are indepted to Amano Pharmaceutical Co., Ltd. and Meito

Sangyo Co., Ltd. for kind supply of lipases.

Reference and Notes

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4) Tipical procedure for the synthesis of γ -hydfroxystannane is described as follows: 3-oxo-1-undecene(2.90g, 17.2 mmol) was treated with n-Bu_3SnLi (17.2 mmol), which was prepared from the corrresponding tributyltinhydride by treatment of 1 eq. of LDA at 0°C, in THF(15 mL) at -70°C for 5 h to afford 3-oxo-1-tributylstannylundecane(8.25g). The stannane was then treated with $NaBH_4$(0.673g, 17.8 mmol), in EtOH(60 mL) at 0°C. The reaction mixture was allowed to gradually warm to RT with stirring for 5.5 h. After quench reaction using aqueous NH_4Cl, the resulting mixture was extracted with ethyl acetate, and the combined organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to give an oily residue(7.12g). Purification by silica gel flash chromatogaphy (Hexane/AcOEt=20/1) afforded (±)-2d(1.86g, 4.03 mmol, 23% yield from 3-oxo-1-undecene) as a coloress oil:^{1}H NMR(200 MHz,δ ,$CDCl_3$)0.5-1.1(20H,m)1.2-1.7(28H,m)3.3-3.5(1H+OH,m);^{13}C NMR(50MHz, $CDCl_3$) 3.80, 8.77, 13.63, 13.72, 14.11, 22.68, 25.73, 26.88, 27.29, 27.40, 27.91, 27.94, 29.04, 29.24, 29.24, 29.61, 29.71, 29.76, 31.89, 34.34, 36.60, and 74.94 ppm; IR(neat) 3400, 2950, 2880, 1500, 1200, and 800 cm^{-1}.

5) Tested lipases were described as follows: Lipase A, A-6, F-AP15, P, M-10, Newlase F, Pancreatin F (Amano), Lipase-MY (Meito), and PPL (Sigma). Among these lipases, lipase P gave the best result.

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9) The reaction conditions have not been optimized yet. However, it was discovered that, among 4 Lewis acids tested ($TiCl_4$, $Ti(OiPr)_4$, BF_3OEt_2, and $ZnCl_2$), only $TiCl_4$ was effective towards this reaction.

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