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Preparation of Enantiomerically Enriched α-Hydroxystannanes via Enzymatic Resolution

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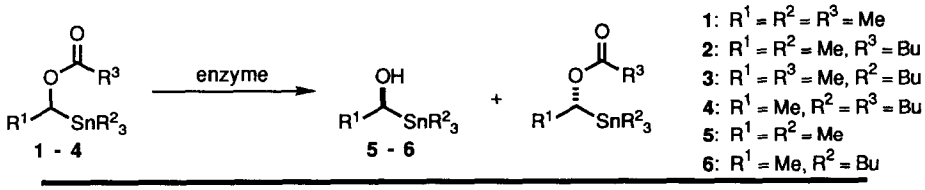
Key Words: α-alkoxystannanes; enantiomerically enriched; enzymatic esterification; porcine pancreatic lipase.

Abstract: *The porcine pancreatic lipase (PPL) catalyzed esterifications of α-hydroxystannanes RCH(OH)SnMe3 (R = Me, Et) and MeCH(OH)SnEt3 with 2,2,2-trifluoroethyl valerate afford good yields and excellent enantiomeric (>95% ee) purities of the (S)-valerate and the (R)-α-hydroxystannane.*

Chiral, non-racemic α-alkoxystannanes are useful precursors of α-alkoxyorganolithium reagents.[1] For example, they may be used for the synthesis of enantiomerically enriched 1,2-diols,[2] γ-substituted-γ-butyrolactones,[3] and α-alkoxy acids.[4] Enantioselective syntheses of α-alkoxystannanes by asymmetric reduction of acylstannanes[5] and via chiral boronates[6] have been described. Another possible approach to these compounds is via an enzyme catalyzed esterification of α-hydroxystannanes.[7] Very recently, the first report of the use of an enzyme (Amano lipase P) to prepare optically active α-acyloxystannanes (by enantioselective hydrolysis) appeared.[8] We now report our findings in this area.

Table 1. Hydrolysis of Esters **1-4** with CCL and PPL.



Entry	Enzyme	Ester	R^3	Time (d)	Conversion[b] (%)	**5** or **6**, ee[c] (%)	Ester, ee[c] (%)
1	CCL	(±)-**1**	Me	1	<10	89	<10
2	CCL	(±)-**2**	Bu	1	<10	90	<10
3	PPL	(±)-**1**	Me	1	<5	–	–
4	PPL	(±)-**2**	Bu	2	<10	93	5
5[d]	PPL	(±)-**2**	Bu	15	40	83	59
6	CCL	(±)-**3**	Me	1	<5	–	–
7	CCL	(±)-**4**	Bu	15	20	74	23

a All reactions, unless otherwise noted, were conducted with 0.1-0.2 mmol of ester and 50-60 mg of enzyme in 3 mL of 0.1 N pH 7 phosphate buffer.
b Estimated by TLC.
c Determined by ^{1}H NMR analysis of the derived (+)-MTPA ester.[9]
d Conducted with 0.7 mmol of ester and 1 g of PPL in 50 mL of 0.1 N pH 7 buffer.

Initial studies were focussed on hydrolysis of esters of 1-trialkylstannylethanols (Table 1).[10] We examined three lipases that have been shown to be very effective with esters of secondary alcohols: porcine pancreatic lipase (PPL), *Candida cylindracea* lipase (CCL), and *Pseudomonas fluorenscens* lipase (PFL). Under the conditions used (see Table 1), PFL was completely ineffective (no detectable hydrolysis after 72 h). Esters of 1-tributylstannylethanol (**6**) were not hydrolyzed by PPL but were hydrolyzed by CCL, albeit very slowly (entries 6 and 7). Both CCL and PPL hydrolyzed esters of trimethylstannylethanol (**5**). With CCL, hydrolysis provided alcohol **5** with respectable (90% ee) enantiomeric purity (entries 1,2); however, isolated yields were dismal (usually <10% based on the extent of conversion), conversions were low, and the reactions were very slow. Similar results were observed with PPL (entries 3-5). Our results with these hydrolyses are comparable to the results recently reported by Itoh[8] in which the alcohols could not be isolated and the enantiomeric purities of the recovered esters ranged from 40 to 86% ee.

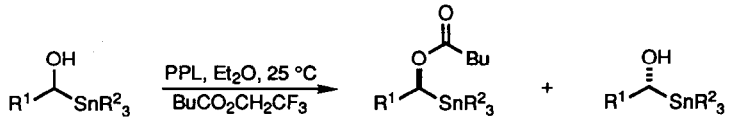
Our initial results suggested that although highly enantioselective hydrolyses of esters **1-4** might be possible, the instability of the resulting alcohol under the reaction conditions[11] would make it impossible to recover both the alcohol and the ester in high chemical yields. Thus we examined the esterification of trimethylstannyl carbinols using PPL in an organic solvent, in which the alcohol would be much more stable. Klibanov has shown that esterification of secondary alcohols using PPL and 2,2,2-trichloroethyl butyrate in organic solvents can be very selective.[12] We chose to use the lower boiling 2,2,2-trifluoroethyl valerate[13] to facilitate product isolation. The PPL was dried under vacuum for two days before use since it had been shown previously that such prior treatment could give better rates and selectivities.[14] Results are shown in Table 2.

The isolated yields of the α-hydroxystannanes were significantly improved compared to that obtained from the enzymatic hydrolysis process. As well, excellent enantioselectivities of the product ester were obtained in almost all cases. The substrate most quickly esterified was trimethylstannylethanol **5** (entries 1-3) which showed conversions of 42-49% after 48 h; the product ester **2** was of 94-98% ee. The acyl donor used seemed to play an important role: when vinyl valerate[15] was used in place of $BuCO_2CH_2CF_3$, ester of slightly lower ee was isolated (entry 2); no esterification occurred with isopropenyl acetate.[16] Entry 3 is noteworthy as it represents the preparation of 10 g of ester **2** (98% ee) and 8 g of **5** (97% ee) from 19 g of racemic alcohol **5**.

The size of the substrate has a major effect on the rate of this enantioselective esterification. With trimethylstannylpropanol **7** (entry 4), the reaction was slower but a respectable yield (36%) of enantiomerically enriched (99% ee) ester **11** could be isolated after 64 h. Trimethylstannylbutanol **8** could be esterified with good selectivity (entry 5) but the reaction became prohibitively slow. Finally, triethylstannylethanol **9** was esterified sluggishly (but very stereoselectively, entry 6) while tributylstannylethanol **6** was completely unreactive. Thus it appears that only alcohols **5**, **7**, and **9** are small enough to be effective substrates in this system. However, since methyl carbinols are very prevalent in natural products,[17] these alcohols and their esters may be useful enantiomerically enriched building blocks.

The absolute configuration of alcohol **5** was shown by a transmetalation-trapping sequence (Scheme). Thus recovered alcohol **5** (98% ee) was converted to BOM ether **15** which was then treated sequentially with *n*-BuLi and CO_2. The resulting α-alkoxy acid **16** exhibited a specific rotation of -50° (*c* 0.465, $CHCl_3$); (*S*)-**16** is known to show $[\alpha]_D^{25}$ -37° (*c* 1.39, $CHCl_3$).[4] Since transmetalation-carboxylation proceeds with retention of configuration, stannanes **5** and **15** must have the (*R*)-configuration.[18] It follows that ester **2** produced from the enzymatic esterification must have the (*S*)-configuration.

Table 2. PPL-Catalyzed Esterifications of α-Hydroxystannanes.[a]

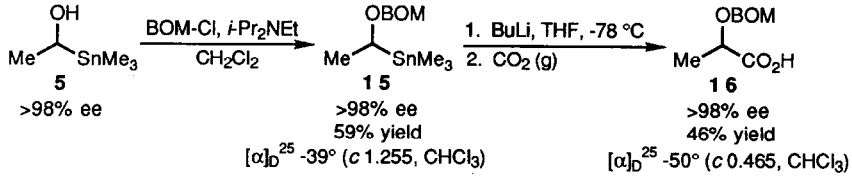


	α-Hydroxy Stannane				Product Ester			Recovered Alcohol			
Entry		R^1	R^2	Time (h)		Yield[b] (%)	ee[c] (%)	Yield[b] (%)	ee[c] (%)	c[d] (%)	E[e]
1	(±)-**5**	Me	Me	48	**2**	31	97	27	71	42.3	130
2[f]	(±)-**5**	Me	Me	41		37	94	22	90	48.9	100
3[g]	(±)-**5**	Me	Me	48		38	98	41	97	49.7	460
4	(±)-**7**	Et	Me	64	**11**	36	99	36	56	36.1	270
5	(±)-**8**	Pr	Me	129	**12**	7	97	68	7	6.7	70
6	(±)-**9**	Me	Et	84	**13**	35	99	47	51	34.0	330
7	(±)-**10**	Et	Et	85	**14**	14	97	57	14	12.6	70
8[h]	(±)-**6**	Me	Bu	111	**4**	0	–	–	–	–	–

a All reactions, unless otherwise noted, were conducted with 1.0 mmol of alcohol, 1.5 mmol of $BuCO_2CH_2CF_3$, and 250-260 mg of PPL (vacuum dried at room temperature for two days) in 5 mL of ether.
b Isolated yields after distillation or chromatography.
c Enantiomeric excesses (ee) were determined by ^{19}F NMR analysis of the derived (+)-MTPA ester.[9]
d The extent of conversion (c) was determined by the equation[19]: c = ee(alcohol) / [ee(alcohol) + ee(ester)].
e The enantioselectivity factor (E) was determined by the equation[19]: E = {ln[(1 - c)(1 - ee(alcohol))]} / {ln[(1 - c)(1 + ee(alcohol))]}.
f Vinyl valerate was used as the acyl donor.
g Conducted with 90 mmol of alcohol, 144 mmol of $BuCO_2CH_2CF_3$, and 24 g of PPL in 120 mL of ether.
h No reaction was also observed using CCL instead of PPL.

While the absolute configurations of esters **11-14** were not rigorously established it is highly probable that they are all of the (*S*)-configuration since (a) their rotations are all of the same sign[20] and (b) the major diastereomers of the derived (+)-MTPA esters all show a OMe signal in their ^1H NMR spectra which is consistently 0.04 ppm upfield of the corresponding signal for the minor isomer.[21]

Scheme



A preparative procedure follows: A mixture of 19 g (90 mmol) of (±)-**5**, 26 g of 2,2,2-trifluoroethyl valerate, and 24 g of PPL (Sigma L 3126) in 120 mL of anhydrous ether was stirred at room temperature for 48 h. The reaction mixture was filtered through Celite, concentrated, and chromatographed on silica gel to provide two fractions: one containing unreacted alcohol [(R)-**5**, 8 g, 37 mmol, 97% ee) and the other containing a mixture of $BuCO_2CH_2CF_3$ and ester **2**. Kugelrohr distillation of this less polar fraction removed $BuCO_2CH_2CF_3$, leaving behind ester (*S*)-**2** (10 g, 34 mmol, 98% ee).

A distinct advantage of the enzyme catalyzed esterification of α-hydroxystannanes over the corresponding hydrolysis is that both the ester and alcohol may be recovered. The alcohol may be recycled to increase its enantiomeric purity and thus both ester and alcohol of high ee (and opposite absolute stereochemistry) may be isolated.[22]

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References and Notes

1. (a) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201.
   (b) For a recent review, see: Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: London, 1987, chapter 9.
2. Chong, J. M.; Mar, E. K. *Tetrahedron* **1989**, *45*, 7709.
3. Chong, J. M.; Mar, E. K. *Tetrahedron Lett.* **1990**, *31*, 1981.
4. Chan, P. C.-M.; Chong, J. M. *Tetrahedron Lett.* **1990**, *31*, 1985.
5. (a) Chan, P. C.-M.; Chong, J. M. *J. Org. Chem.* **1988**, *53*, 5584.
   (b) Marshall, J. A.; Gung, W. Y. *Tetrahedron Lett.* **1988**, *29*, 1657; **1989**, *30*, 2183.
6. Matteson, D. S.; Tripathy, P. B.; Sarkar, A.; Sadhu, K. M. *J. Am. Chem. Soc.* **1989**, *111*, 4399.
7. For a review, see: Sih, C. J.; Wu, S.-H. *Top. Stereochem.* **1989**, *19*, 63.
8. Itoh, T.; Ohta, T. *Tetrahedron Lett.* **1990**, *31*, 6407.
9. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
10. α-Hydroxytributylstannanes were prepared by the reaction of aldehydes with Bu_3SnLi[1a] while Me_3SnLi was used to prepare the trimethylstannyl derivatives: Tamborski, C.; Ford, F. E.; Soloski, E. J. *J. Org. Chem.* **1963**, *28*, 237.
11. α-Hydroxytributylstannanes decompose to aldehydes and Bu_3SnH in basic aqueous solution at room temperature: Lindermann, R. J.; Godfrey, A.; Horne, K. *Tetrahedron*, **1989**, *45*, 495.
12. For a review, see: Klibanov, A. M. *Acc. Chem. Res.* **1990**, *23*, 114.
13. Prepared [74% yield, bp (air bath) 60-80°C/30 torr] by reaction of 2,2,2-trifluoroethanol with valeric anhydride (1 eq) in pyridine (cat. DMAP, RT, 18 h).
14. Stokes, T. M.; Oehschlager, A. C. *Tetrahedron Lett.* **1987**, *28*, 2091.
15. Wang, Y.-F.; Lalonde, J. J.; Momongan, M.; Bergbreiter, D. E.; Wong, C.-H. *J. Am. Chem. Soc.* **1988**, *110*, 7200.
16. Wang, Y.-F.; Wong, C.-H. *J. Org. Chem.* **1988**, *53*, 3127.
17. See, for example: Hanessian, S. *Total Synthesis of Natural Products: The 'Chiron' Approach*; Pergamon Press: New York, 1983.
18. The notation changes from (*S*) to (*R*) due to the higher atomic number of Sn.
19. (a) Chen, C.-S.; Wu, S.-H.; Girdaukas, G.; Sih, C. J. J. *Am. Chem. Soc.* **1987**, *109*, 2812.
    (b) Chen, C. S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.
20. **2** (97% ee): $[\alpha]_D^{25}$ +100° (*c* 1.212, $CHCl_3$); **11** (99% ee): $[\alpha]_D^{25}$ +92° (*c* 1.117, $CHCl_3$); **13** (99% ee): $[\alpha]_D^{25}$ +82° (*c* 1.168, $CHCl_3$).
21. It has been observed that the methoxy group of esters derived from (*R*)-(+)- MTPA acid and (*S*)-α-hydroxytributylstannanes are consistently ca. 0.04 ppm upfield (^1H NMR, $CDCl_3$) of the (*R,R*) diasteromer: Chan, P. C.-M. Ph.D. Dissertation, University of Waterloo, 1990.
22. For example, recovered alcohol **5** (69% ee) was recycled (footnote a of Table 2) to provide ester **2** (8% yield, 97% ee) and alcohol **5** (72% yield, >98% ee).

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