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Efficient preparation of enantiomerically pure (*E*)-4-(tributylstannanyl)but-3-en-2-ol via lipase-mediated resolution

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Abstract—The practical preparation of enantiomerically pure (*E*)-4-(tributylstannanyl)but-3-en-2-ol **1** from 3-butyn-2-ol **2** is reported. A modified Guibé's Pd-catalyzed hydrostannation of **2** provided the racemic γ-hydroxy vinylstannane **1** in a good yield. The enzymatic esterification of **1**, with an inexpensive lipozyme, afforded (*R*)-**3** and (*S*)-**1** with very high enantiomeric excesses and chemical yields. This procedure is suitable for the multigram scale preparation of the potential chiral building blocks, (*R*)-**1** and (*S*)-**1**. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

Chiral building blocks have ever-increasing importance in the pharmaceutical and agrochemical industries as well as in the development of rapid and efficient syntheses of bioactive compounds and natural products.[1] As part of a program directed towards the total asymmetric synthesis of various natural products, we needed to obtain optically active (*E*)-4-(tributylstannanyl)but-3-en-2-ol **1** in large quantities. This optically active γ-hydroxy vinylstannane **1** could be a potential chiral building block, as exemplified in Figure 1.

Vinylstannane **1** contains two synthetically useful functional groups, the vinylstannane and the allylic alcohol,

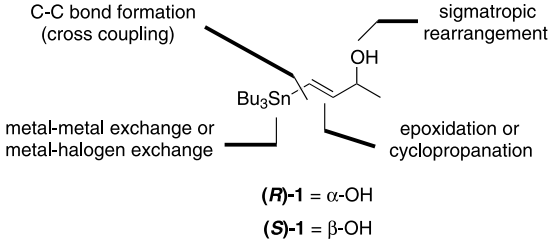

Figure 1. Utilities of (*R*)-**1** or (*S*)-**1**.

with which it is possible to design a wide range of synthetic strategies.[2] The vinylstannane functional group of **1** can be used in carbon–carbon bond formation with a large array of electrophiles under a variety of conditions, with retention of the double bond geometry.[3,4] The chiral secondary allylic alcohol of **1** is a versatile functional group for asymmetric synthesis, as it has a useful stereodirecting influence for a number of chemical transformations, such as hydroxyl-directed epoxidations, cyclopropanations, and sigmatropic rearrangements.

There could be a number of possible synthetic pathways for accessing the optically active γ-hydroxy vinylstannane **1**,[2,5,6] of which the direct preparation of **1**, from the commercially available enantiomerically pure 3-butyn-2-ol **2**,[7] by hydrostannation (Fig. 2, path A) is attractive. However, the high cost of enantiomerically pure **2** limits the utilization of this pathway. Another attractive route could be a utilization of the enzymatic resolution[8] of appropriate racemic substrates **1** and **3** (Fig. 2, path B and C). In fact, Itoh et al.[2,9] achieved the efficient resolution of γ-hydroxy vinylstannanes with a long alkyl chain, by the lipase-catalyzed enantioselective hydrolysis of the corresponding racemic acetates. Alternatively, Lee et al.[10] presented a patented process for the enzymatic resolution of various γ-hydroxy vinylstannanes, including **1**. Their method employed an enantioselective acetylation of hydroxyl

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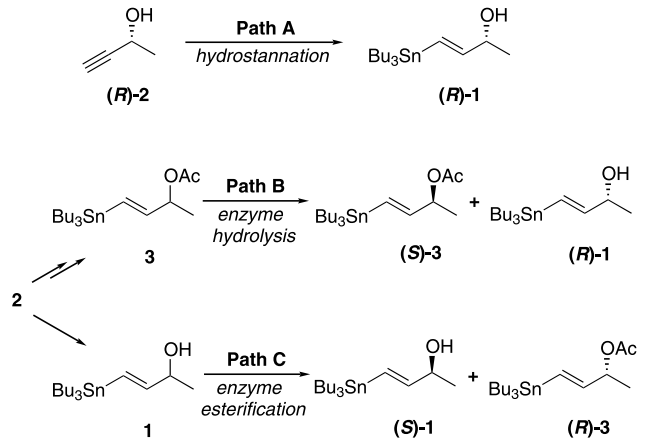
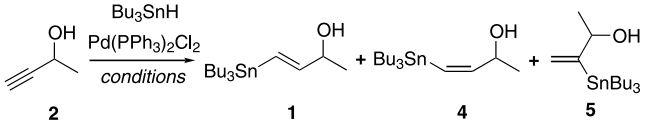


Figure 2.

group, with acetate or anhydride, catalyzed by *Pseudomonase* AK, PS or K-10 lipases, which were relatively expensive. Although the application of previous methods for the preparation of **1** seemed suitable for our goal, we felt that an efficient, inexpensive and scalable route to the enantiomerically pure **1** was still required. Herein, we report our studies for the practical preparation of optically active (*E*)-4-(tributylstannanyl)but-3-en-2-ol **1**, from 3-butyn-2-ol **2**, using lipozyme-catalyzed kinetic resolution.

2. Results and discussion

At the start of this investigation, it was important to establish an efficient method for the preparation of racemic (*E*)-4-(tributylstannanyl)but-3-en-2-ol **1**. It has been reported that the hydrostannation of commercially available 3-butyn-2-ol **2** led predominantly to the formation of **1**. Johnson[6] reported that the radical hydrostannation of **2**, with tributyltin hydride, afforded the desired *trans*-isomer of **1** (>60%) as the major isomer, together with the *cis*-isomer **4** and α-regioisomer **5** (>15%). A wide-ranging study by Guibé,[4] on the hydrostannation of variously substituted alkynes using either Pd or Mo catalysis, showed that the metal-catalyzed hydrostannation of **2**, in the presence of $Pd(PPh_3)_2Cl_2$ at room temperature, gave a mixture of **1** and **5** in a ratio of 4:1 (Scheme 1).



conditions	
THF, rt [4]	ratio **1** / **4** / **5** = 4 / 0 / 1
CH_2Cl_2, rt	ratio **1** / **4** / **5** = 3.5 / 0 / 1
THF, 0 °C	ratio **1** / **4** / **5** = 5.5 / 0 / 1
THF, -78 °C	ratio **1** / **4** / **5** = 8 / 0 / 1

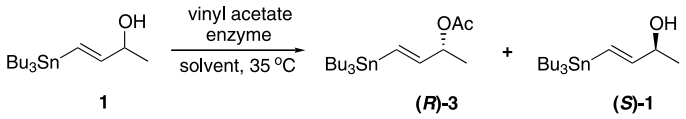
Scheme 1.

When employing the above mentioned reaction conditions for the preparation of **1**, it was found that the isolation of the desired vinylstannane **1**, from the unwanted isomers, by chromatography was not an easy task due, in part, to silica gel-mediated protonolysis. The use of alumina or triethylamine-treated silica gel, to alleviate the destannylation, was not satisfactory. We felt that it was important to minimize the residency time of this compound on the chromatography column in order to obtain the product in high yield. Therefore, efforts were made to improve the isolated yield of the desired **1** by increasing the selectivity in the hydrostannation of **2**. Among the modifications of Guibé's Pd-catalyzed hydrostannation conditions,[4] changing the solvent and temperature (Scheme 1), lowing the temperature down to −78°C significantly affected the regiochemical outcome of the reaction to give an 8:1 mixture of **1** and **5** (97% combined yield). A rapid triethylamine-treated silica gel chromatographic separation of the above crude mixture provided the pure vinylstannane **1**, generally at a >80% isolation yield, along with α-regioisomer **5**, and a mixture of **1** and **5**.

With multigram quantities of **1** in hand, we set out to explore its enzymatic resolution. In the first set of experiments, three inexpensive lipases were tested for the esterification reaction of γ-hydroxy vinylstannane **1** with vinyl acetate in diisopropyl ether (DIPE, 0.02 M) at 35°C. As shown in Table 1, with lipase Amano AY or PPL (entry 1 and 2) the conversion was very low after 10 days of reaction, with the majority of the unaltered starting material being recovered. However, the immobilized lipase, lipozyme,[11] proved to be suitable for the enzymatic resolution of **1** (entry 3). Lipozyme showed a 49% conversion after 7 days, and purification by silica gel flash column chromatography provided the product ester (*R*)-**3** almost enantiomerically pure (>99% ee), and the unreacted alcohol (*S*)-**1** (93% ee), in yields of 48 and 50%, respectively.[12] In this case, the enantioselectivity[13] of the acetylation was very high ($E=684$), but the reaction rate was somewhat low.

In an attempt to optimize this reaction, the effects of other reaction parameters were studied. First, the influence of the organic solvent was examined. The reaction in cyclohexane (entry 4) was slower and less enantioselective ($E=377$) than that in diisopropyl ether. When vinyl acetate was used as an acyl donor and solvent (entry 5), the reaction rate and enantioselectivity ($E=474$) both decreased. As a result, we studied the effects of varying the amount of vinyl acetate and enzyme on the selectivity and reaction rate. As expected, the reaction rate decreased with lesser amounts of vinyl acetate (entry 6). In this case, the enantioselectivity remained high ($E=659$), while the chemical yields of the (*R*)-**3** and (*S*)-**1** were significantly decreased. However, the amount of lipase only slightly influenced the enantioselectivity, without causing significant influence on the reaction rate (entry 7).

Table 1. Enzymatic resolution of γ-hydroxy vinylstannane **1**[a]



1 (*R*)-**3** (*S*)-**1**

Entry	Enzyme	Solvent	Concentration (M)	Reaction time (days)	Conversion (%)[b]	(*R*)-**3**		(*S*)-**1**		*E*[f]
						Yield (%)[c]	% ee[d]	Yield (%)[c]	% ee[e]	
1	PPL	DIPE	0.02	10	3	3	–	90	–	–
2	Amano AY	DIPE	0.02	10	2	2	–	88	–	–
3	Lipozyme	DIPE	0.02	7	49	48	>99	50	93	684
4	Lipozyme	Cyclohexane	0.02	7	39	34	>99	53	62	377
5	Lipozyme	Vinyl acetate	0.02	7	45	38	>99	49	78	474
6[g]	Lipozyme	DIPE	0.02	10	48	36	>99	37	92	659
7[h]	Lipozyme	DIPE	0.02	7	49	39	>99	41	95	747
8	Lipozyme	DIPE	0.2	0.5	51	37	>99	36	>99	>1000
9	Lipozyme	DIPE	0.1	0.5	50	49	>99	48	>99	>1000

[a] All reactions, unless otherwise noted, were performed on 36 mg (0.1 mmol) scale with 36 mg (100 wt%) of enzyme and DIPE/vinyl acetate (10/1 (v/v)).
[b] Determined by GC analysis.
[c] Isolated yield.
[d] Determined by chiral stationary phase HPLC analysis after hydrolysis to the corresponding alcohol.
[e] Determined by chiral stationary phase HPLC analysis.
[f] The enantiomeric ratio,[13] $E=\ln[(1-c)(1+ee_p)]/\ln[(1-c)(1-ee_p)]$, $c=ee_s/(ee_s+ee_p)$.
[g] DIPE/vinyl acetate (20/1, (v/v)).
[h] 72 mg (200 wt%) of lipozyme.

Finally, it was found that by altering the concentration provided satisfactory results. Changing the reaction concentration from 0.02 to 0.2 M (entry 8) resulted in a higher enantioselectivity (E >1000) and reaction rate. However, the isolation yields of the (*R*)-**3** and (*S*)-**1** were significantly decreased. When the procedure was carried out at a concentration of 0.1 M (entry 9), the enantioselectivity and reaction rate remained excellent (E >1000), and the chemical yields of (*R*)-**3** (>99% ee) and (*S*)-**1** (>99% ee) were considerably improved, to 49% and 48%, respectively. For preparative purpose, multigram quantities of racemic **1** (3.78 g) were reacted under the optimized reaction conditions (entry 9) to again give (*R*)-**3** (>99% ee) and (*S*)-**1** (>99% ee), with identical enantiomeric purities and excellent chemical yields (48 and 47%, respectively). Lastly, the antipode alcohol, (*R*)-**1**, could be prepared by the alkaline methanolysis of the acetate (*R*)-**3** in 98% yield.

3. Conclusion

In conclusion, we have been able to obtain enantiomerically pure (*E*)-4-(tributylstannanyl)but-3-en-2-ol **1** using a cheap and commercially available lipozyme. Good overall yields, and excellent enantioselectivity, were achieved by exploring the appropriate experimental conditions. In addition, this procedure would be suitable for the multigram scale preparation of the potential chiral building block **1**.

4. Experimetal

4.1. General methods

All chemicals were reagent grade and used as purchased. Reactions were monitored by GC or TLC. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ as internal reference by Varian 300 MHz NMR instrument. In NMR spectra of stannane compounds, ^{117}Sn and ^{119}Sn satellite peaks were not indicated. High resolution mass spectra (HRMS) were recoded using chemical ionization (CI).

4.2. Catalytic hydrostannation of (±)-3-butyn-2-ol 2

To a solution of (±)-3-butyn-2-ol **2** (1.00 mL, 12.8 mmol) and $Pd(PPh_3)_2Cl_2$ (91 mg, 0.13 mmol) in THF (30 mL) was slowly added Bu_3SnH (4.40 mL, 16.4 mmol) over 5 min at −78°C. The reaction mixture was stirred for 2 h at −78°C. After the solvent was evaporated to dryness, the resulting dark brown oil residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 30:1 to 10:1, gradient, 1% NEt_3) to give 3.74 g of **1** (81%) as a colorless oil, 412 mg of α-regioisomer **5** (9%) as a colorless oil, and a mixture of **1** and **5** (329 mg, 7%). The regioselectivity was determined by GC analysis. GC (HP-1, 30 m×0.320 mm× 0.25 μm column, detector temperature 190°C, injector temperature 275°C, column temperature 160°C (5 min) to 290°C (5 min) through 5°C/min); retention time (min) **5** (9.38), **1** (10.12) (ratio **5**/**1**, 1:8).

4.3. (*E*)-4-(Tributylstannanyl)but-3-en-2-ol 1

^{1}H NMR ($CDCl_3$) δ 0.78–1.01 (m, 15), 1.24–1.36 (m, 6H), 1.27 (d, $J=6.3$ Hz, 3H), 1.42–1.61 (m, 6H), 4.26 (dq, $J=4.2$, 6.3 Hz, 1H), 6.04 (dd, $J=4.2$, 19.2 Hz, 1H), 6.14 (d, $J=19.2$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 9.37, 13.62, 23.02, 27.19, 29.01, 71.20, 126.37, 152.12; HRMS (CI) calcd $C_{16}H_{35}SnO$ $[M+H]^+$ 363.1710, found 363.1714.

4.4. 3-(Tributylstannanyl)but-3-en-2-ol 5

^{1}H NMR ($CDCl_3$) δ 0.86–0.96 (m, 15), 1.23 (d, $J=6.6$ Hz, 3H), 1.25–1.37 (m, 6H), 1.44–1.55 (m, 6H), 1.68 (br s, 1H), 4.40 (q, $J=6.6$ Hz, 1H), 5.16 (dd, $J=1.5$, 2.1 Hz, 1H), 5.78 (dd, $J=1.5$, 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 10.09, 13.63, 24.08, 27.36, 29.09, 74.70, 122.73, 160.40; HRMS (CI) calcd $C_{16}H_{35}SnO$ $[M+H]^+$ 363.1710, found 363.1704.

4.5. Enzymatic resolution of (*E*)-4-(tributylstannanyl)-but-3-en-2-ol 1

To a solution of hydroxyl stannnane **1** (3.78 g, 10.5 mmol) in diisopropyl ether (105 mL, 0.1 M) was added lipozyme (3.78 g, 100 wt%) and vinyl acetate (10.5 mL). The reaction mixture was stirred for 12 h at 35°C (50% conversion by GC analysis, GC (HP-1, 30 m×0.320 mm×0.25 μm column, detector temperature 190°C, injector temperature 275°C, column temperature 160°C (5 min) to 290°C (5 min) through 5°C/min) retention time (min) (*S*)-**1** (10.15), (*R*)-**3** (11.99)). The suspension was then filtered, and the filtrate was concentration in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 20:1, 1% NEt_3) afforded (*R*)-**3** (less polar, 2.03 g, 48%) and (*S*)-**1** (more polar, 1.81 g, 47%) as a colorless oil.

4.6. (*R*)-(*E*)-4-(Tributylstannanyl)but-3-en-2-yl acetate (*R*)-3

$[\alpha]_D^{20}=+51.65$ (c 0.95, CH_2Cl_2) (lit.:[10] $[\alpha]_D=+56.8$ (c 0.33, CH_2Cl_2)); ^{1}H NMR ($CDCl_3$) δ 0.77–0.96 (m, 15), 1.23–1.35 (m, 6H), 1.29 (d, $J=6.6$ Hz, 3H), 1.42–1.53 (m, 6H), 2.04 (s, 3H), 5.29 (ddq, $J=1.2$, 5.1, 6.6 Hz, 1H), 5.94 (dd, $J=5.1$, 19.2 Hz, 1H), 6.15 (dd, $J=1.2$, 19.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 9.39, 13.65, 19.92, 21.34, 27.18, 28.99, 73.05, 129.43, 146.91, 170.22; HRMS (CI) calcd $C_{18}H_{37}SnO_2$ $[M+H]^+$ 405.1815, found 405.1821.

4.7. (*S*)-(*E*)-4-(Tributylstannanyl)but-3-en-2-ol (*S*)-1

The enantiopurity was determined by chiral HPLC analysis (CHIRALCEL OD-H, hexane, flow rate: 0.2 mL/min, retention time: 76.54 min (*S*)-isomer, 82.36 min (*R*)-isomer, >99% ee, detected at 205 nm); $[\alpha]_D^{20}=-3.65$ (c 1.23, CH_3OH) (lit.:[10] $[\alpha]_D=-1.45$ (c 0.27, CH_3OH)). The spectroscopic data (^{1}H and ^{13}C NMR) were identical with those of racemic **1**.

4.8. Hydrolysis of (*R*)-(*E*)-4-(tributylstannanyl)but-3-en-2-yl acetate (*R*)-3

To a solution of (*R*)-**3** (1.90 g, 4.71 mmol) in MeOH/H_2O (15 mL, 4/1 (v/v)) was added K_2CO_3 (699 mg, 5.06 mmol). The reaction mixture was stirred for 40 h at 40°C and then partitioned between hexanes (100 mL) and brine (80 mL). The aqueous phase was extracted with hexanes (100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to dryness. The resulting oil residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 15:1, 1% NEt_3) to give (*R*)-**1** (1.67 g, 98%) as a colorless oil. The enantiopurity was determined by chiral HPLC analysis (CHIRALCEL OD-H, hexane, flow rate: 0.2 mL/min, retention time: 76.54 min (*S*)-isomer, 82.36 min (*R*)-isomer, >99% ee, detected at 205 nm); $[\alpha]_D^{20}=+3.5$ (c 0.91, CH_3OH); The spectroscopic data (^{1}H and ^{13}C NMR) were identical with those of racemic **1**.

Acknowledgements

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