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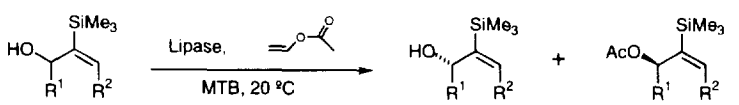
Kinetic resolution of hydroxy vinylsilanes by lipase–catalyzed enantioselective acetylation

Waldemar Adam, Cordula Mock-Knoblauch and Chantu R. Saha-Möller *
Institute of Organic Chemistry, University of Würzburg, Am Hubland, D-97074 Würzburg, Germany

Abstract: The lipase-catalyzed enantioselective acetylation of racemic hydroxy vinylsilanes **1** with vinyl acetate in methyl *tert*-butyl ether afforded the optically active hydroxy vinylsilanes **1** and the corresponding acetoxy vinylsilanes **2** in excellent enantiomeric excess (ee 93–99%). © 1997 Elsevier Science Ltd

In recent years the use of enzymes has often simplified the synthesis of optically active materials. In particular the lipase-catalyzed enantioselective acetylation of secondary alcohols has abundantly been demonstrated to be of great value for the synthesis of enantiomerically pure compounds.[1] These hydrolases distinguish between the two enantiomers based on the steric demand of the substituents at the stereocenter. However, for substrates with substituents of similar size rather poor resolution is usually observed. This problem can be circumvented by enlarging one of the substituents and thereby achieve better steric differentiation.[2] For example, the direct resolution of cyclopent-2-enol and cyclohex-2-enol by lipase-catalyzed hydrolysis of the corresponding acetates showed only low enantioselectivity (ee 15%),[3] whereas the 2-bromo- or 2-iodocycloalk-2-enols could be resolved by acetylation in very good enantioselectivties (ee >95%).[4] We now demonstrate that the addition of a trimethylsilyl group also serves this purpose well. 2-Trimethylsilylcyclopent-2-enol **1b** and -cyclohex-2-enol **1c**, as well as the acyclic derivative **1a**, may be resolved in excellent enantiomeric excess (ee 93–99%) (Scheme 1).



rac-**1a-c** *S*-(-)-**1a-c** *R*-(+)-**2a-c**

1a, 2a: R^1 = Me, R^2 = H
1b, 2b: $R^1 + R^2 = (CH_2)_2$
1c, 2c: $R^1 + R^2 = (CH_2)_3$

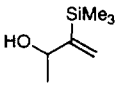
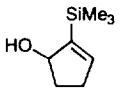
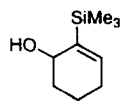
Scheme 1. Lipase-catalyzed kinetic resolution of hydroxy vinylsilanes **1**.

The racemic hydroxy vinylsilanes were prepared from commercially available material according to the synthesis formerly developed in our group.[5] For the kinetic resolution ten lipases were tested, of which the four in Table 1 showed good to excellent enantiomeric excesses.[6]

The enzyme screening revealed that the lipase BSL [from *Burkholderia species* (CHIRAZYME® L-1, Boehringer Mannheim)] is the most efficient biocatalyst for the resolution of the hydroxy vinylsilanes **1a–c** (entries 4 and 8–10). Thus, with this enzyme the acyclic hydroxy vinysilane **1a** was enantioselectively acetylated by vinyl acetate in methyl *tert*-butyl ether and at about 50% conversion the hydroxy vinylsilane **1a** and the corresponding acetate **2a** were obtained in high (ee values 93 and 98%) enantiomeric purity (entry 4). For the cyclic hydroxy vinylsilanes **1b** and **1c** an almost perfect kinetic resolution (ee values 97 up to >99%) was achieved with BSL. Application of the lipases PSL1

* Corresponding author. Email: Adam@chemie.uni-wuerzburg.de

Table 1. Enantiomeric excess in the lipase-catalyzed kinetic resolution of hydroxy vinylsilanes **1**

Entry	Substrate	Lipase	Substrate : Lipase	Time	Conv.[a]	Enantiomeric Excess (%)[b]		E[c]
			mmol : mg	(d)	(%)	Alcohol **1**[d]	Acetate **2**[e]	
1		PCL[f]	0.231 : 15.1[g]	13	0	-	-	-
2		PSL1[h]	0.135 : 20.1[i]	7	23	27	93	26
3	**1a**	PSL2[k]	0.148 : 21.2[i]	7	47	82	93	65
4		BSL[l]	3.47 : 200[i]	6	49	93	98	>200
5		PCL[f]	0.219 : 18.2[g]	21	50	95	93	146
6		PSL1[h]	0.129 : 22.3[i]	4	54	99	83	61
7	**1b**	PSL2[k]	0.131 : 21.0[i]	3	54	95	80	35
8		BSL[l]	3.20 : 200[i]	3	50	>99	97	>200
9		BSL[l]	0.132 : 21.6	8	50	98	99	>200
10	**1c**	BSL[l]	2.94 : 250[i]	6	44	77	99	>200

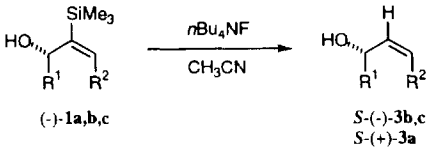
[a]Calculated from c=ee(alcohol)/[ee(alcohol)+ee(acetate)] (see Ref.[7]). [b]Determined by GC analysis. [c]Enantiomeric ratio measures the preference of the enzyme for one enantiomer over the other (see Ref.[7]). [d]Absolute configuration *S*-(−). [e]Absolute configuration *R*-(+). [f]Lipase from *Pseudomonas cepacia* (Fluka). [g]Per mol hydroxy vinylsilane 5 mol isopropenyl acetate were added. [h]Lipase from *Pseudomonas* species (CHIRAZYME® L-4, Boehringer Mannheim). [i]Per mol hydroxy vinylsilane 3 mol vinyl acetate were added. [k]Lipase from *Pseudomonas* species (CHIRAZYME® L-6, Boehringer Mannheim). [l]Lipase from *Burkholderia* species (CHIRAZYME® L-1, Boehringer Mannheim).

and PSL2 [lipases from *Pseudomonas species* (CHIRAZYME® L-4 and L-6, Boehringer Mannheim)] also yielded good enantioselectivities (ee values from 82 up to 93% at about 50% conversion) for the substrates **1a** and **1b**. For the cyclic substrate **1b**, the lipase PCL [from *Pseudomonas cepacia* (Fluka)] also produced enantiomeric excesses of 95 and 93%, although a very long reaction time of 21 days was needed for 50% conversion. In contrast, the acyclic substrate **1a** did not react at all with the PCL lipase. Consequently, of the ten enzymes that were screened for the kinetic resolution of hydroxy vinylsilanes, only those four isolated from the various *Pseudomonas species* gave good to excellent enantioselectivities on 50% conversion within a tolerable time (3 to 8 days).

Also, for all enzymes the five-membered ring cyclic hydroxy vinylsilane **1b** reacted significantly faster than the acyclic **1a** and the six-membered ring cyclic **1c** substrates. Apparently the fixed conformation of the five-membered ring fits best into the active centre of the enzyme.

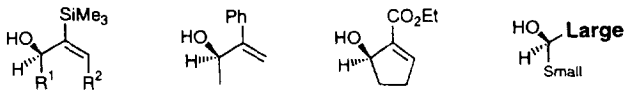
The optically active hydroxy vinylsilanes **1a–c** and acetoxy vinylsilanes **2a–c** are all hitherto unknown. The absolute configurations of the hydroxy vinylsilanes were determined by chemical correlation. For this purpose the hydroxy vinylsilanes **1a–c** were desilylated to the known allylic alcohols **3a–c**[8] with fluoride ions[9] (Scheme 2).

The lipases accept selectively the (*R*)-(+)-hydroxy vinylsilanes **1a–c** to convert them to the (*R*)-(+)-acetates **2a–c**, the (*S*)-(−)-hydroxy enantiomers **1a–c** are left behind. This stereoselectivity is in agreement with the established empirical rule for the kinetic resolution of secondary alcohols by



(-)-**1a,b,c** *S*-(-)-**3b,c** *S*-(+)-**3a**

Scheme 2. Configurational assignment of the hydroxy vinylsilanes (−)-**1a,b,c** by chemical correlation.



R-(+)-**1**

Figure 1. Preferred enantiomer in the lipase-catalyzed acetylations.

lipases, which states that the preferrably consumed alcohol enantiomer is the one with the configuration shown in Figure 1 [mostly the (*R*)-configuration].[10]

In summary, the BSL lipase is a very efficient biocatalyst for the kinetic resolution of hydroxy vinylsilanes **1** by acetylation, which provides a convenient enzymatic route for the preparation of enantiomerically pure hydroxy vinylsilanes **1** and acetoxy vinylsilanes **2** on the preparative scale. Moreover, desilylation of the optically active hydroxy vinyl silanes **1** provides a convenient access to the enantiomerically pure allylic alcohols **3**, which constitute valuable building blocks in the asymmetric synthesis of natural products.

Experimental

Materials and methods

The lipase sources are reported in the footnotes to Table 1. The hydroxy vinyl silanes were prepared according to literature procedures. Enantiomeric excesses were determined by GC on a permethylated β-cyclodextrin column (30% on OV 1701, 30 m, 0.25 mm ID; H_2 gas) for the vinylsilanes **1a** [temperature program: 40°C (1 min)→ 5°C/min→ 60°C], **1b** (60°C isotherm) and **1c** (90°C isotherm), for the acetates **2a** [temperature program: 40°C (1 min)→ 5°C/min→ 60°C] and **2b** (70°C isotherm), and on a 2,6-dimethyl-3-pentyl β-cyclodextrin column (on OV 1701, 25 m, 0.25 mm ID, 0.25 μm film; H_2 gas) for the acetate **2c** (90°C isotherm).

*General procedure for the preparative-scale, lipase-catalyzed acetylation of hydroxy vinylsilanes **1a–c***

To a solution of ca. 500 mg (3.20 mmol) hydroxy vinylsilane **1** in 40 mL methyl *tert*-butyl ether were added three equivalents (9.60 mmol or 0.89 mL) of vinyl acetate and 200 mg BSL lipase powder. The heterogeneous mixture was vigorously stirred at room temperature (ca. 20°C) for 3 to 8 d, the enzyme was removed by centrifugation and the solvent was evaporated (20°C/12 Torr). The two products were separated by flash chromatography [50 g silica gel, 4:1 petroleum ether (30–50°C): ethyl ether] to afford the enantiomerically enriched hydroxy vinylsilanes **1** and the corresponding acetates **2**.

*Kinetic resolution of 3-(trimethylsilyl)-3-buten-2-ol (**1a**)*

According to the above general procedure, the kinetic resolution of 500 mg (3.47 mmol) of **1a** gave 146 mg (29%) of (*S*)-**1a** [e.e. 93%; $[\alpha]_D^{20}$ =−7.5 (c 1.4, $CHCl_3$, for 100% e.e.)] and 295 mg (46%) of (*R*)-**2a**[11] [e.e. 98%; $[\alpha]_D^{20}$ =+18.4 (c 0.9, $CHCl_3$, for 100% e.e.)].

*Kinetic resolution of 2-(trimethylsilyl)-2-cyclopentenol (**1b**)*

According to the above general procedure, the kinetic resolution of 500 mg (3.20 mmol) of **1b** gave 214 mg (43%) of (*S*)-**1b** [e.e. >99%; $[\alpha]_D^{20}$ =−14.4 (c 1.2, $CHCl_3$, for 100% e.e.)] and 144 mg (23%) of (*R*)-**2b** [e.e. 97%; $[\alpha]_D^{20}$ =+18.2 (c 1.4, $CHCl_3$, for 100% e.e.)].

1b. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.14 (s, 9 H), 1.14–2.28 (m, 2 H), 1.68 (s, 1 H, OH), 2.37–2.44 (m, 1 H), 2.44–2.7 (m, 1 H), 4.92 (m, 1 H), 6.16 (m, 1 H); ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 0.0 (3×q), 34.0 (t), 35.8 (t), 82.5 (d), 138.2 (s), 145.6 (d); IR (neat): 3650–3030 (OH), 1592 (C=C), 1247 (SiMe), 836 (SiMe) cm^{-1}. Anal. calcd. for $C_8H_{16}OSi$ (156.3): C, 61.48; H 10.32. Found: C, 61.19; H, 10.28.

2b. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.08 (s, 9 H), 1.66–1.80 (m, 1 H), 2.01 (s, 3 H), 2.23–2.40 (m, 2 H), 2.45–2.60 (m, 1 H), 5.84–5.90 (m, 1 H), 6.26–6.29 (m, 1 H); ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 0.0 (3×q), 22.7 (q), 33.1 (t), 34.6 (t), 84.9 (d), 144.3 (s), 148.2 (d), 172.3 (s); IR (neat): 1736 (C=O), 1593 (C=C), 1252 (SiMe), 838 (SiMe) cm^{-1}. Anal. calcd. for $C_{10}H_{18}O_2Si$ (198.3): C, 60.56; H, 9.15. Found: C, 60.27; H, 9.24.

*Kinetic resolution of 2-(trimethylsilyl)-2-cyclohexenol (**1c**)*

According to the above general procedure, the kinetic resolution of 500 mg (2.94 mmol) of **1c** gave 162 mg (32%) of (*S*)-**1c** [e.e. 77%; $[\alpha]_D^{20}$ =−53.2 (c 0.8, $CHCl_3$, for 100% e.e.)] and 175 mg (28%) of (*R*)-**2c** [e.e. 99%; $[\alpha]_D^{20}$ =+56.4 (c 1.1, $CHCl_3$, for 100% e.e.)].

2c. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.03 (s, 9 H), 1.58–1.85 (m, 4 H), 2.02 (s, 3 H), 2.00–2.14 (m, 2 H), 5.40 (m, 1 H), 6.21 (m, 1 H); ^{13}C NMR (62.8 MHz, $CDCl_3$): δ −1.4 (3×q), 16.4 (q), 21.5 (t), 26.5 (t), 28.7 (t), 70.1 (d), 137.3 (s), 141.4 (d), 170.5 (s); IR (neat): 1736 (C=O), 1615 (C=C), 1236 (SiMe), 752 (SiMe) cm^{-1}. Anal. calcd. for $C_{11}H_{20}O_2Si$ (212.4): C, 62.21; H, 9.49. Found: C, 61.99; H 9.63.

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6. The other lipases tested were PPL from *Porcine pancreas* (Sigma), CCL from *Candida cylindracea* (Sigma), CRL from *Candida rugosa* (Boehringer Mannheim), CAL-A from *Candida antarctica*, Fraktion A, (Boehringer Mannheim), CAL-B from *Candida antarctica*, Fraktion B, (Boehringer Mannheim) and HSL from *Humicola species* (Boehringer Mannheim).
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