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Enzymatic resolution of diethyl (3-hydroxy-1-butenyl) phosphonate

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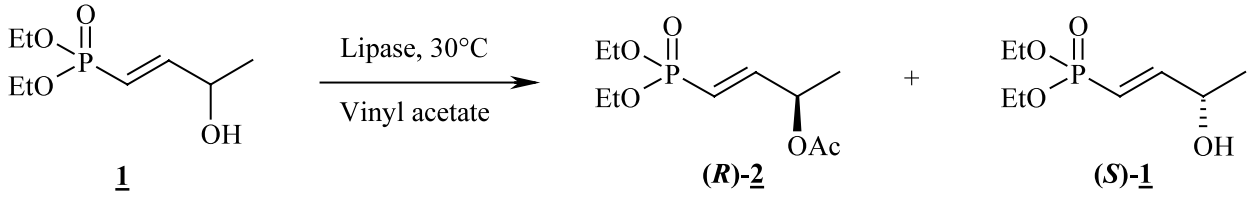
Abstract—The enzymatic esterification of diethyl (3-hydroxy-1-butenyl) phosphonate **1** with different enzymes has been carried out, and allows the preparation of (*S*)-**1** and (*R*)-diethyl (3-acetoxy-1-butenyl) phosphonate **2** with very high enantiomeric excess. The absolute conguration of **1** was determined by independent synthesis from (*S*)-ethyl lactate.

Functionalised vinyl phosphonates are useful building blocks,[1] particularly for the synthesis of biologically active compounds. We have shown[2] that dialkyl 3-acetoxy-1-alkenyl phosphonates can be used to prepare phosphono amino acids which are known to be active against epilepsy and Parkinson's disease.[3] They can also be used to prepare the corresponding allyl alcohols which have in turn been used as starting materials for the synthesis of antiviral nucleosides.[4,5] Moreover, the related chiral 3-hydroxy-1-alkenyl phosphine oxides are used for the synthesis of optically active cyclopropyl ketones.[6] Since chirality is determinant for the biological activity of these above cited compounds, an enantioselective synthesis of dialkyl 3-acetoxy (or 3-hydroxy)-1-alkenyl phosphonates is of interest.

Recently, the enzymatic resolution of several hydroxy phosphonates has been described.[7] Prompted by these reports, we wish to disclose our results on the enzymatic resolution[8] of diethyl (3-hydroxy-1-butenyl) phosphonate **1**[9] (Scheme 1).

For this purpose, several enzymes were assayed as summarised in Table 1.

It appears that lipozyme (entry 1) gave the best results, since diethyl (3-acetoxy-1-butenyl) phosphonate **2** was obtained with an enantiomeric excess (ee) of 96% and unreacted **1** was recovered almost enantiomerically pure (ee = 99%) when the reaction was stopped after 51% conversion. Lipases Amano AK (entry 2) and Amano PS (entry 3) also gave rather good results, with lower ee for unreacted **1**, but Amano PS led to the highest ee for compound **2** (ee = 98%). In these cases, the reaction occurred after rather short periods, and the enantioselectivity factors[10] *E* where superior to 200. *Asp. melleus* acylase (entry 4) also gave very good enantioselectivity for **2** (ee = 98% after 33% conversion), but unreacted **1**



1 (*R*)-**2** (*S*)-**1**

Scheme 1.

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Table 1. Enzymatic esterification of **1**

Entry	Enzyme	Time	Conv. (%)[a]	**1**		**2**		*E*
				ee (%)[b,c]	Abs. conf.	ee (%)[b,c]	Abs. conf.	
1	Lipozyme (Fluka)	21 h	51	99	(*S*)	96	(*R*)	>200
2	Amano AK	21 h	50	97	(*S*)	96	(*R*)	>200
3	Amano PS	17 h	45	81	(*S*)	98	(*R*)	>200
4	*Asp. melleus* Acyl. (Amano)	72 h	33	49	(*S*)	98	(*R*)	160
5	Amano AP6	10 d	9	7	(*S*)	74	(*R*)	7
6	Amano AY	10 d	15	12	(*S*)	67	(*R*)	6
7	CAL-B (Novo)	17 h	87	91	(*S*)	14	(*R*)	3
8	PPL (Sigma)	49 h	19	22	(*S*)	99	(*R*)	130
9	CRL (Meito Sangyo)	10 d	13	8	(*S*)	54	(*R*)	4
10	Amano R-10	10 d	8	6	(*S*)	69	(*R*)	6
11	Lipozyme (Fluka)	17 h	49	95	(*S*)	>99	(*R*)	>200

[a] Conversion, determined by GC.
[b] Determined by chiral GC.
[c] Determined after acetylation.

was recovered with only 49% ee. The use of other enzymes (entries 5–10) proceeded with lower kinetics and enantioselectivities.

Finally, the reaction carried out with lipozyme on a preparative scale (1 g of **1**) proceeded with identical results (entry 11), and the chemical yields were 46% for **1** and 48% for **2**, respectively.

The enzymatic solvolysis of **2** was also studied, the reaction being performed in diisopropyl ether with isopropanol as an acyl acceptor. Although the enantioselectivities were high, reaction times were much more important and the enzymes tested were found to be less efficient (Table 2). As expected, **1** was produced as the (*R*) enantiomer, whereas (*S*)-**2** was recovered.

The absolute configuration of (+)-**1** was shown to be *S*, by an independent synthesis from (*S*)-ethyl lactate **3**, as depicted in Scheme 2.

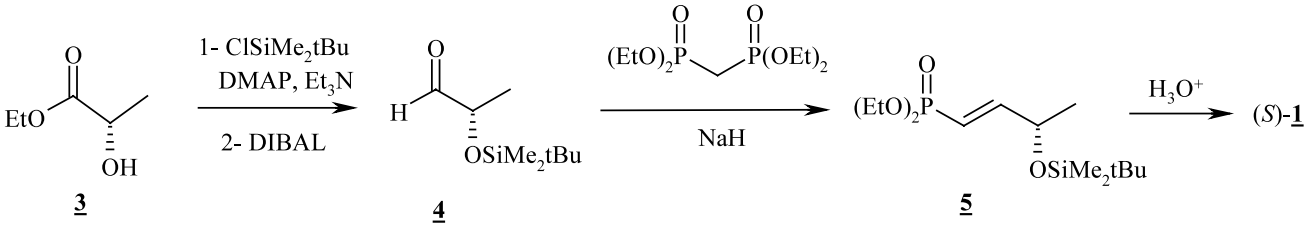
O-Silylation followed by reduction with Dibal-H yielded the protected aldehyde **4**[11] which was subjected to a Wadsworth–Emmons reaction with tetraethyl methylene bis phosphonate, thus providing phosphonate **5**,[12] which led, after acidic deprotection to enantiomerically pure (*S*)-**1** whose optical rotation was $[\alpha]_D^{20} = +19$ (*c* 0.315, CH_2Cl_2).

In summary, we have shown that enzymatic resolution of diethyl (3-hydroxy-1-butenyl) phosphonate **1** can be efficiently carried out through esterification with lipozyme, leading to diethyl (3-acetoxy-1-butenyl)

Table 2. Enzymatic solvolysis of **2**

Entry	Enzyme[a]	Time (days)	Conv. (%)[b]	**1**		**2**		*E*
				ee (%)[c,d]	Abs. conf.	ee (%)[c]	Abs. conf.	
1	Lipozyme (Fluka)	7	45	98	(*R*)	80	(*S*)	>200
2	Amano AK	7	38	82	(*R*)	51	(*S*)	18
3	Amano PS	6	25	89	(*R*)	30	(*S*)	24

[a] **2** (40 mg) and the enzyme (50 mg) in diisopropyl ether (10 ml) and isopropanol (100 μl) were stirred at 30°C.
[b] Conversion, determined by GC.
[c] Determined by chiral GC.
[d] Determined after acetylation.



Scheme 2.

phosphonate **2** and unreacted **1** with very high ee. Upscaling to up to one gram of substrate led essentially to the same results (95 and 99%, respectively for **1** and **2**).

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8. **General procedure**: The enzyme (50 mg) was added to a solution of **1** (48 mg; 0.23 mmol) and vinyl acetate (1 ml) in diisopropyl ether (10 ml), and the suspension was stirred at 30°C. The reaction was monitored by GC. After ca. 50% conversion (see Table 1), the mixture was filtered to remove the enzyme, the solvents were removed in vacuo, and the crude was subjected to flash chromatography (silica, ethyl acetate/methanol, 95:5) to yield **2** followed by **1**. Ee's were measured by GC on a chiral column (CP-chirasil-DEX CB, 25 m, 32 mm I.D.), isothermal 160°C. Retention times: *rac*. **1**: 12.9 min, (*S*)-**2**: 10.93 min, (*R*)-**2**: 11.38 min. Ee's for **1** were measured after acetylation.
9. Compound **1** was prepared by rearrangement of diethyl (2,3-epoxy-1-butyl) phosphonate according to: Just, J.; Potvin, P.; Hakimelahi, G. H. *Can. J. Chem*. **1980**, *58*, 2780. It can alternatively be obtained by palladium-catalysed acetoxylation of diethyl (1-butenyl) phosphonate to provide **2**, followed by saponification, see: Principato, B.; Maffei, M.; Siv, C.; Buono, G.; Peiffer, G. *Tetrahedron* **1996**, *52*, 2087.
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12. **(*S*)-Diethyl-(*E*)-(3-tertbutyldimethylsilyloxy-1-butenyl) phosphonate 5**: A solution of tetraethyl methylene bis phosphonate (576 mg; 2 mmol) in anhydrous dimethoxyethane (10 ml) was added to a suspension of sodium hydride (48 mg; 2 mmol) in dimethoxyethane (10 ml) at 0°C. The mixture was stirred at room temperature until hydrogen evolution ceased (ca. 1 h). It was then cooled to 0°C and a solution of **4** (376 mg; 2 mmol) in dimethoxyethane (5 ml) was added dropwise. Stirring was continued for 2 h at room temperature after which the mixture was quenched with a sat. NH_4Cl solution. Ether extraction, standard workup and flash chromatography (silica, ethyl acetate) afforded 330 mg (51%) of **5**. ^1H NMR (300 MHz, $CDCl_3$): 0.04 (s, 6H); 0.89 (s, 9H); 1.22 (d, 3H, $^3J_{HH}=6.7$ Hz); 1.30 (td, 6H, $^3J_{HH}=6.9$ Hz, $^4J_{HP}=2.0$ Hz); 4.05 (m, 4H); 4.40 (m, 1H); 5.80–5.93 (ddd, 1H, $^2J_{HP}=21.1$ Hz, $^3J_{HH}=16.9$ Hz, $^4J_{HH}=1.5$ Hz); 6.69–6.83 (ddd, 1H, $^3J_{HP}=22.1$ Hz, $^3J_{HH}=16.9$ Hz, $^3J_{HH}=3.5$ Hz). ^{13}C NMR: –4.95 (s); 16.30 (d, $^3J_{PC}=6.2$ Hz); 18.17 (s); 23.27 (d, $^4J_{PC}=2.2$ Hz); 25.74 (s); 61.61 (d, $^2J_{PC}=5.7$ Hz); 68.40 (d, $^3J_{PC}=21.9$ Hz); 114.12 (d, $^1J_{PC}=188.0$ Hz); 156.30 (d, $^2J_{PC}=5.0$ Hz). ^{31}P NMR: 19.9. $[\alpha]_D^{20}=+7.76$ (*c* 1.16, CH_2Cl_2).
Deprotection was carried out by stirring a solution of **5** in THF with 1 M H_2SO_4. Standard workup and flash chromatography (ethyl acetate/methanol, 95:5) afforded enantiomerically pure (*S*)-**1** as checked by chiral GC analysis after acetylation.
^1H NMR (300 MHz, $CDCl_3$): 1.28 (d, 3H, $^3J_{HH}=6.8$ Hz); 1.30 (t, 6H, $^3J_{HH}=7.1$ Hz); 3.95 (br. s, 1H); 4.05 (q, 4H, $^3J_{HH}=7.2$ Hz); 4.42 (m, 1H); 5.90 (ddd, 1H, $^2J_{HP}=20.8$ Hz, $^3J_{HH}=17.0$ Hz, $^4J_{HH}=1.7$ Hz); 6.79 (ddd, 1H, $^3J_{HP}=22.5$ Hz, $^3J_{HH}=17.0$ Hz, $^3J_{HH}=4.0$ Hz). ^{13}C NMR: 16.26 (d, $^3J_{PC}=7.0$ Hz); 22.39 (s); 61.90 (d, $^2J_{PC}=5.9$ Hz); 67.62 (d, $^3J_{PC}=21.8$ Hz); 114.3 (d, $^1J_{PC}=189.3$ Hz); 156.2 (d, $^2J_{PC}=4.6$ Hz). ^{31}P NMR: 19.4. $[\alpha]_D^{20}=+19$ (*c* 0.315, CH_2Cl_2).