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Enzymatic resolution of diethyl 3-hydroxycycloalkenyl phosphonates

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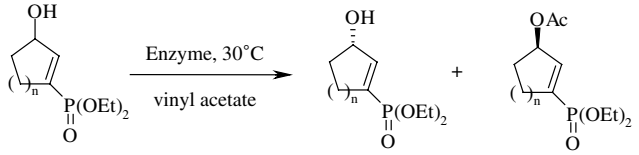
Abstract—Enantiomerically pure cyclic (*S*)-diethyl 3-hydroxy-1-alkenyl phosphonates **1**–**3** were obtained by enzymatic resolutions. The corresponding (*R*)-acetates were also obtained with high enantiomeric excess, except in the case of the five-membered ring compound. The most efficient enzyme (lipase Amano AK or Amano PS) in each case depends on the structure of the substrate (five to seven-membered ring compounds).

1. Introduction

Functionalized 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] Since the configuration is determinant for the biological activity of these chiral compounds, an enantioselective synthesis of dialkyl 3-acetoxy (or 3-hydroxy)-1-alkenyl phosphonates is of interest.

In this area, we have already reported an enantioselective synthesis of cyclic dialkyl 3-hydroxy-1-alkenyl phosphonates via baker's yeast asymmetric reduction of the corresponding cyclic 3-phosphono-1-enones.[6] This methodology was found to be effective only for the six-membered ring compounds, whereas the seven-membered ring homologue (i.e., diethyl 3-hydroxy-1-cycloheptenyl phosphonate) was obtained only with up to 34% enantiomeric excess (ee). Furthermore, the five-membered ring homologue did not lead to the expected diethyl 3-hydroxy-1-cyclopentenyl phosphonate.



1 n = 2
2 n = 1
3 n = 3

4 n = 2
5 n = 1
6 n = 3

Scheme 1.

For these reasons, we turned our attention towards the enzymatic resolution of these hydroxy phosphonates in order to obtain enantiomerically pure compounds. This methodology has been exploited for the enantioselective esterification of hydroxy phosphonates[7–10] and we recently described the enzymatic resolution of diethyl 3-hydroxy butenyl phosphonate.[11] Herein, we report the enzymatic resolution of diethyl 3-hydroxy cycloalkenyl phosphonates **1**–**3** (Scheme 1).

2. Results and discussion

First, different enzymes for the resolution of **1** were assayed, and the results are summarized in Table 1.

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Table 1. Enzymatic resolution of **1**

Entry	Enzyme	Time	Conversion[a] (%)	Recovered **1**			**4**			E[d]
				Yield (%)	Ee[b] (%)	Absolute configuration	Yield (%)	Ee[b] (%)	Absolute configuration	
1	Amano AY	10 d	15	73	11	(*S*)	12	60	(*R*)	5
2	PPL[c]	9 d	11	79	11	(*S*)	9	93	(*R*)	33
3	Amano PS	22 h	49	43	92	(*S*)	49	96	(*R*)	155
4	Amano AK	6 h	50	48	98	(*S*)	50	>99	(*R*)	>200
5	Amano AK	9 h	50	47	>99	(*S*)	50	>99	(*R*)	>200

[a] Conversion, determined by chiral HPLC.
[b] Determined by chiral HPLC after column chromatography.
[c] Porcine Pancreatic Lipase.
[d] Calculated following Ref. 12.

It appears that with lipase Amano AY (entry 1) or Porcine Pancreatic Lipase (entry 2), the reaction was slow and occurred with low enantioselectivity. Lipase Amano PS (entry 3) gave good results, but the most satisfactory enantioselectivities were obtained with lipase Amano AK (entry 4), where enantiomerically pure **4** and unreacted **1** were obtained, both with almost quantitative yields. On a preparative scale (1 g of **1**), we obtained essentially the same results (entry 5). Those two reactions occurred with an enantioselectivity factor[12] E superior to 200.

The above results prompted us to look at five- and seven-membered ring hydroxy phosphonates **2** and **3** using lipases Amano AK and Amano PS (Table 2). Esterification of **2** was moderately enantioselective with $E = 24$ and 43, respectively (entries 1 and 2). The most efficient lipase was Amano PS and a 500 mg scale resolution with this lipase gave enantiomerically pure unreacted substrate (*S*)-**2** and the acetate (*R*)-**5** with 84% ee (entry 3). With the substrate **3**, the reaction kinetics were slower but higher enantioselectivities were encountered. Thus, lipase Amano AK was used on a preparative scale (500 mg of **3**) and led to enantiomerically pure (*S*)-(+)-**3** and (*R*)-(+)-**6** after 3 days (entry 6).

3. Determination of absolute configurations

The absolute configurations for compounds **1**[6] and **3**[13] have already been determined by chemical correlation. We used the same methodology for the determination of the absolute configuration of hydroxy phosphonate **2** (Scheme 2). Thus, 3-bromo-2-cyclopentenone (easily obtained from 1,3-cyclopentanedione[14]) was reduced to the bromoalcohol **7** as already described,[15] which was submitted to enzymatic resolution by lipase Amano AK. This led to a mixture of (*S*)-(−)-**7** (20% yield) and (*R*)-**8** (78% yield) whose enantiomeric purities could not be determined at this stage. However, the absolute configuration of (−)-**7** was ascribed as (*S*) by comparison of its specific rotation with the value given by Silverton co-workers.[15]

Enantiomerically enriched (*S*)-(−)-**7** was then used in a palladium-catalyzed reaction[16,17] with diethylphosphite and led to (*S*)-(−)-**2** (35% yield) whose enantiomeric purity was found to be 61% ee by chiral HPLC after acetylation[†] (see Experimental). Its specific rotation was $[\alpha]_D^{20} = -24.0$ (c 0.49, CH_2Cl_2).

4. Conclusion

Enantiomerically pure cyclic diethyl (*S*)-3-hydroxy-1-alkenyl phosphonates **1**–**3** were obtained via enzymatic resolution with lipases Amano AK or Amano PS. The corresponding (*R*) acetates were also obtained with up to 99% ee, except in the case of the five-membered ring substrate. Thus, this method is far superior than the baker's yeast reduction of 3-phosphono-1-enones described previously,[6] whose chemical outcome is highly dependent of the structure of the starting material.

5. Experimental

5.1. General

All solvents were purified according to reported procedures, and reagents were used as received. ^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectra were recorded in $CDCl_3$, on a Bruker Avance 300 spectrometer working at 300.00, 75.47 and 121.49 MHz, respectively (the usual abbreviations are used: s: singulet, d: doublet, t: triplet, q: quadruplet, qt: quintuplet, m: multiplet). The references were $\delta = 7.26$ ppm for residual chloroform (^{1}H), $\delta = 77$ ppm (^{13}C) and 85% H_3PO_4 as external standard (^{31}P). All chemical shifts are given in ppm. Optical rotations were measured on a Perkin Elmer 341 polarimeter. Compounds **1**–**3** have been obtained by saponification of the corresponding acetates.[18,19]

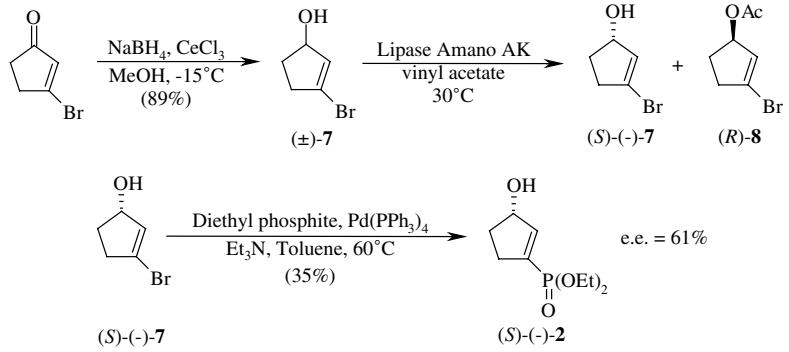
Enantiomeric purities for **1**, **2**, **3**, **4**, **5** and **6** were measured by HPLC analysis on a Chiralcel OD-H column with a UV detection (214 nm), eluent: hexane/isopropanol (90:10), flow rate: 0.5 mL/min. For compound **2**,

[†] This indicates that the enantiomeric purity of (*S*)-(−)-**7** is at least 61% ee.

Table 2. Enzymatic resolution of **2** and **3**

Entry	Hydroxy phosphonate	Enzyme	Time	Conversion[a] (%)	Recovered hydroxy phosphonate			Acetate			*E*
					Yield (%)	Ee[b] (%)	Absolute configuration	Yield (%)	Ee[b] (%)	Absolute configuration	
1	**2**	Amano AK	24 h	54	28	91[c]	(*S*)	63	76	(*R*)	24
2	**2**	Amano PS	24 h	56	47	>99[c]	(*S*)	52	78	(*R*)	43
3	**2**	Amano PS	24 h	54	41	>99[c]	(*S*)	48	84	(*R*)	57
4	**3**	Amano AK	3 d	49	52	96	(*S*)	45	98[d]	(*R*)	>200
5	**3**	Amano PS	7 d	42	56	70	(*S*)	42	97[d]	(*R*)	130
6	**3**	Amano AK	3 d	50	48	>99	(*S*)	50	>99[d]	(*R*)	>200

[a] Conversion, determined by chiral HPLC.
[b] Determined by chiral HPLC.
[c] Determined after acetylation.
[d] Determined after hydrolysis.



Scheme 2.

ee were determined after acetylation since these hydroxy phoshonates were not separated under these conditions. For compound **6**, ee were determined after saponification since these acetoxyphosphonates were not separated under these conditions. Retention times: (*R*)-**1**: 18.3 min; (*S*)-**1**: 16.8 min, (*R*)-**3**: 16.6 min; (*S*)-**3**: 22.2 min, (*R*)-**4**: 13.6 min; (*S*)-**4**: 11.3 min, (*R*)-**5**: 15.3 min; (*S*)-**5**: 18.4 min.

5.2. Syntheses

5.2.1. General procedure for the enzyme assay in the resolution of hydroxy phosphonates 1–3.

5.2.1.1. Enzymatic resolution of diethyl phosphonates. The enzyme (100 mg) was mixed to a solution of hydroxy phosphonate (100 mg) and vinyl acetate (15 mL), the suspension was shaken at 30 °C and the reaction was monitored by chiral HPLC. After removal of the enzyme by filtration and solvent in vacuo, the crude was subjected to flash chromatography (silica, ethyl acetate/methanol, 90/10) to yield the (*R*)-acetate followed by unreacted (*S*)-hydroxy phosphonate.

Spectral data for compounds **1** and **3**,[6] and **4**, **5** and **6**[18] were identical to those already reported. Additional data: (*S*)-**1**: $[\alpha]_D^{20} = -34.6$ (*c* 0.5, CH_2Cl_2), (*S*)-**3**: $[\alpha]_D^{20} = +9.9$ (*c* 0.49, CH_2Cl_2), (*R*)-**4**: $[\alpha]_D^{20} = +91.3$ (*c* 0.51, CH_2Cl_2), (*R*)-**5**: $[\alpha]_D^{20} = +94.1$ (*c* 0.49, CH_2Cl_2), (*R*)-**6**: $[\alpha]_D^{20} = +15.5$ (*c* 0.5, CH_2Cl_2).

5.2.1.2. Diethyl 3-hydroxy-1-cyclopentenyl phosphonate 2. Colourless oil (R_f: 0.19, ethyl acetate/methanol 90:10). IR (thin film, cm^{-1}): 3373, 2981, 2936, 1614, 1235, 1025. ^1H NMR: 1.2 (t, 6H, $2CH_3$, $^3J_{HH} = 7.0$ Hz); 1.8 (m, 1H); 2.4 (m, 2H, CH_2); 2.6 (m, 1H); 3.4 (s, 1H, OH); 4.0 (qt, 4H, $2CH_2$, $^3J_{HH} = 7.0$ Hz, $^3J_{PH} = 7.0$ Hz); 5.1 (s, 1H); 6.5 (dd, 1H, $^3J_{PH} = 11.1$ Hz; $^3J_{HH} = 1.9$ Hz). ^{13}C NMR: 16.4 (d, $^3J_{PC} = 6.4$ Hz); 31.7 (d, $^2J_{PC} = 12.9$ Hz); 33.9 (d, $^3J_{PC} = 10.6$ Hz); 62.0 (d, $^2J_{PC} = 5.7$ Hz); 77.3; 135.0 (d, $^1J_{PC} = 185.7$ Hz); 148.5 (d, $^2J_{PC} = 12.4$ Hz). ^{31}P NMR: 15.0. $[\alpha]_D^{20} = -49.8$ (c 0.47, CH_2Cl_2), ee > 99%.

5.2.2. Determination of absolute configuration of (*S*)-(−)-2.

5.2.2.1. 3-Bromo-1-cyclopentenol 7. A solution of cerium trichloride heptahydrate (9.2 g, 24.6 mmol) in methanol (60 mL) was cooled to −15 °C with stirring under a nitrogen atmosphere. A solution of bromocyclopentenone (3.3 g, 20.5 mmol) in methanol (10 mL)

was added, followed by addition of sodium borohydride (935 mg, 24.6 mmol) in portions, and the reaction was monitored by TLC. The mixture was quenched by slow addition of water (10 mL), and most of the methanol was removed in vacuo. Diethyl ether (50 mL) and water (30 mL) were added, the aqueous layer was extracted with diethyl ether (4×20 mL), the combined organic layers were washed with saturated NaCl, and dried with $MgSO_4$. Filtration, removal of solvent, and flash chromatography (silica, diethyl ether/pentane 2:1) yielded 2.97 g (89%) of **7** as a colourless oil. (R_f: 0.49). ^{1}H NMR: 1.8 (m, 1H); 2.5 (m, 4H); 4.7 (m, 1H); 5.9 (m, 1H). ^{13}C NMR: 34.0; 38.4; 76.4; 127.4; 133.6.

5.2.2.2. Enzymatic resolution of 7. Lipase Amano AK (250 mg) was added to a solution of **7** (500 mg, 3.07 mmol) in vinyl acetate (20 mL) and the suspension was stirred at 30 °C. After 3 h, the mixture was filtered, the solvent removed in vacuo and the residue was subjected to flash chromatography on silica gel with pentane/diethyl ether (75/25). (*R*)-**8** (491 mg) was isolated (78% yield) followed by 102 mg of (*S*)-**7** (20% yield), which displayed $[\alpha]_D^{20} = -38.4$ (*c* 0.59, CH_2Cl_2).

5.2.2.3. (*S*)-(−)-Diethyl (3-hydroxy-1-cyclopentenyl) phosphonate 2. A solution of (*S*)-(−)-**7** (117 mg, 0.7 mmol), triethylamine (200 μL, 1.45 mmol) and diethyl phosphite (100 μL, 0.7 mmol) in anhydrous toluene (2 mL) was degassed by bubbling with nitrogen, and added to tetrakis triphenylphosphine palladium (42 mg, 0.036 mmol) in a round bottomed flask under nitrogen. The mixture was gradually heated to 70 °C and maintained at this temperature for 1 h, after which a white precipitate appeared. After cooling to room temperature, ethyl acetate was added (20 mL), the mixture was filtered and the solvents were removed in vacuo. Flash chromatography with ethyl acetate/methanol (90:10) afforded 53 mg (35%) of (*S*)-(−)-**2** as a colourless oil. Its spectral data were identical to those described above {with $[\alpha]_D^{20} = -24$ (*c* 0.49, CH_2Cl_2)}, and its enantiomeric purity was 61% ee (after acetylation).

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