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Enantioselective synthesis of cyclic dialkyl (3-hydroxy-1-alkenyl) phosphonates by baker's yeast-mediated reduction of the corresponding enones

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Abstract—Cyclic dialkyl (3-oxo-1-cycloalkenyl) phosphonates were subjected to baker's yeast-mediated enantioselective reductions to afford the corresponding dialkyl (3-hydroxy-1-alkenyl) phosphonates. The six- and seven-membered ring enones were reduced with moderate to good enantiomeric excesses, whereas the five-membered ring substrate always yielded the double bond reduced compound. The use of different reduction conditions did not improve the ee's markedly, but it was found, for the six-membered analogues, that the alkyl groups held by phosphorus influence dramatically the enantioselectivity of the reduction, leading to up to 95% enantiomeric excess.

1. Introduction

Dialkyl 3-acetoxy-1-alkenyl phosphonates are useful starting materials for the synthesis of precursors of biologically active phosphono amino acids,[1] which are known to be active against epilepsy and Parkinson's disease.[2] 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.[3,4] Moreover, the related chiral 3-hydroxy-1-alkenyl phosphine oxides are used for the synthesis of optically active cyclopropyl ketones.[5] Since chirality is determinant for the biological activity of the above cited compounds, an enantioselective synthesis of dialkyl 3-acetoxy (or 3-hydroxy)-1-alkenyl phosphonates is of interest. We already reported our attempts in setting up a diastereoselective synthesis of dialkyl 3-acetoxy-1-alkenyl phosphonates through the palladium-catalysed acetoxylation of chiral dialkyl allyl phosphonates which gave only moderate diastereomeric excess.[6]

We felt that the use of the well known baker's yeast-mediated reduction[7,8] applied to dialkyl (3-oxo-1-alkenyl) phosphonates would offer a valuable synthesis of chiral dialkyl (3-hydroxy-1-alkenyl) phosphonates. Since 3-phosphonocycloalkyl amino acids have also been shown to exhibit biological activities,[9] we focussed on the synthesis of chiral cyclic dialkyl (3-hydroxy-1-alkenyl) phosphonates and therefore we selected for this study the cyclic enones **1**–**3** as model substrates (Scheme 1).

Compounds **1**–**3** were obtained by oxidation[10] of the dialkyl (1-hydroxy-2-cycloalkenyl) phosphonates **7**–**9** which in turn were prepared by the base-catalyzed 1,2 addition of dialkyl phosphites to the corresponding enones[11] (Scheme 2).

2. Results and discussion

2.1. Use of fermenting and dry yeast

Compounds **1**–**3** were subjected first to baker's yeast-mediated reduction under two different conditions, e.g. fermenting yeast, or dry yeast, and the results are summarised in Table 1.

Thus, diethyl (3-hydroxy-1-cyclohexenyl) phosphonate **4** was obtained with ca. 75% enantiomeric excess (ee) whatever the conditions employed, whereas the seven-membered analogue **6** had only moderate enantioselectivity. In the case of the cyclopentenone **2**, no trace amounts of the corresponding 3-hydroxy-1-alkenyl phosphonate were detected. Instead, diethyl (3-oxocylopentyl) phosphonate **5**[†] was

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[†] The structure of **5** was unambiguously attributed by comparison with an authentic sample.[12]

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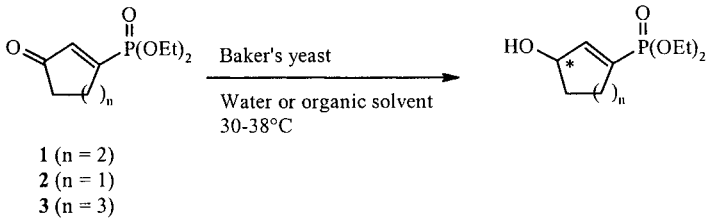
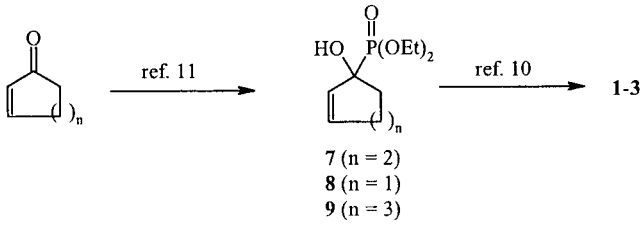


Scheme 1.



Scheme 2.

isolated in 45% yield in almost racemic form (1–2% ee, HPLC analysis on chiralcel ODH column). The selective baker's yeast-mediated reduction of the double bond of an enone has already been reported[13] and can also be related to the similar microbial reduction of deuterated cyclopentenones.[14,15] We also found that pure **5** subjected to the same reduction conditions remains unchanged and is not further reduced to diethyl (3-hydroxy cyclopentyl) phosphonate.

2.2. Use of yeast acetone powder

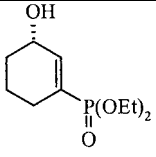
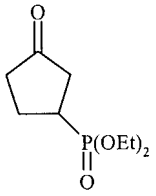
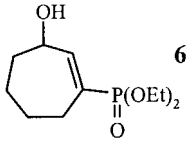
Nakamura et al. [16,17] have shown that the use of an acetone powder improves the enantioselectivity of the reduction of various ketones by the yeast *Geotrichum candidum*, in the presence of NAD(H) as coenzyme and isopropanol as reducing agent. Therefore, we decided to assess the efficiency of the acetone powder of baker's yeast with our substrates (Table 2).

These results show that for the six-membered substrate **1**, the chemical yields are slightly increased, whereas the ee's are similar to those obtained previously. On the other hand, the chemical yields are markedly decreased for the seven-membered compound **3** for which analysis of the crude product shows an incomplete reaction. Again, the cyclopentenone substrate **2** leads only to racemic **5**.

2.3. Use of organic solvents

Since only the six-membered enone **1** gave satisfactory

Table 1. Baker's yeast reduction of **1–3** under different conditions

Entry	Substrate	Conditions[a]	Compound obtained	Yield (%)[b]	Ee (%)[c]	Configuration[d]
1	**1**	A	 **4**	44	76	*S*
2	**1**	B	**4**	54	75	*S*
3	**2**	A	 **5**	45	–[e]	–
4	**2**	B	**5**	47	–[e]	–
5	**3**	A	 **6**	65	29	nd[f]
6	**3**	B	**6**	51	34	nd[f]

[a] (A): Fermenting yeast (38°C, five days, added glucose), (B): Dry yeast (30°C, 24 h).
[b] Of pure product.
[c] Measured by HPLC on a Chiralcel ODH column.
[d] Absolute configurations were determined by chemical correlation, see Determination of absolute configurations for compounds **4**, **14** and **15**.
[e] Almost racemic product.
[f] Not determined.

Table 2. Enantioselective reduction of **1**–**3** by the acetone powder of baker's yeast (30°C, 24 h), according to conditions (B)

Entry	Substrate	Coenzyme	Reducing agent	Compound obtained	Yield (%)	Ee (%)
1	**1**	None	None	**4**	55	76[a]
2	**1**	NADH	None	**4**	70	65[a]
3	**1**	None	*i*-PrOH	**4**	54	74[a]
4	**1**	NADH	*i*-PrOH	**4**	59	70[a]
5	**2**	None	None	**5**	40	–
6	**3**	None	None	**6**	28[b]	21
7	**3**	None	*i*-PrOH	**6**	21[c]	18

[a] The major enantiomer is (*S*).
[b] 39% conversion.
[c] 25% conversion.

Table 3. Baker's yeast reduction of **1** in organic solvents (conditions C, see Experimental)

Solvent	Yield (%)	Ee (%)[a]
n-Hexane	84	65
Methyl *t*-Butyl Ether (MTBE)	15	82
Benzene	7	69

[a] The major enantiomer is (*S*).

results, we decided to use it for the assessment of the influence of other factors on the performance of the reaction. The rather low chemical yields are probably due to the high solubility of the hydroxyphosphonates in the aqueous phase, which necessitates a tedious extraction step. We therefore carried out the baker's yeast-mediated reductions in an organic solvent[18–23] (Table 3).

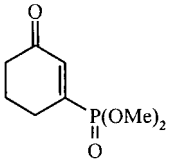
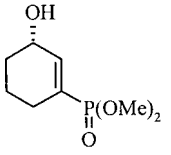
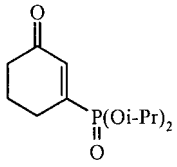
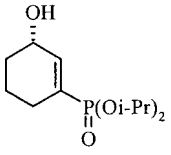
Chemical yields are increased only for the use of *n*-hexane, for which the ee's are decreased (compare to Table 1, entries 1 or 2). MTBE and benzene gives very low yields due to poor conversions in both cases. Thus, the use of organic solvents seems to be disfavourable in our case.

2.4. Influence of phosphorus substituents

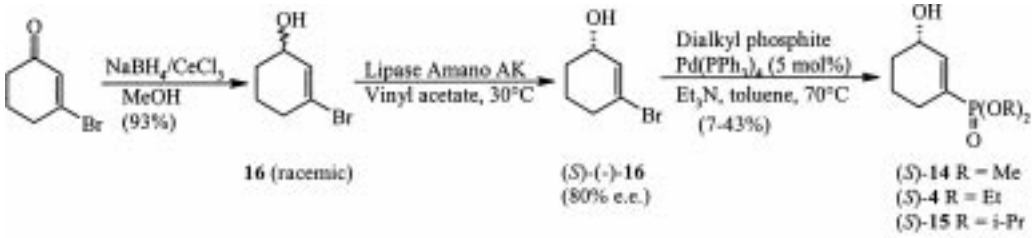
Since all the reactions conditions used above did not result in a significant increase of ee, we wondered if the steric bulk of the substituents held by phosphorus could have an influence on the stereochemical outcome of the reaction. For this purpose, the six-membered enones **10**[10] and **11** were prepared[‡], and submitted to the baker's yeast-mediated reduction under different selected conditions. The results, together with those already obtained for **1** (Table 1, entries 1 and 2) are collected in Table 4 for comparison.

We were pleased to note that an increase in the size of these alkyl groups (from methyl to isopropyl) resulted in a dramatical increase of the ee's (from 45% to 95%), whatever the conditions employed. Although this feature remains unclear, it clearly shows that the reduction can be influenced by steric factors, owing to a possible interaction of the phosphonato group with the enzyme.

Table 4. Influence of the phosphorus substituent on the enantioselectivity of the baker's yeast reduction

Substrate	Conditions	Product	Yield (%)	Ee (%)
 **10**	Fermenting yeast (conditions A)	 **14**	45	48
	Dry yeast (conditions B)		55	62
	Acetone powder (conditions B)		52	68
	Acetone powder+isopropanol (conditions B)		62	45
1	Fermenting yeast (conditions A)	**4**	44	76
	Dry yeast (conditions B)		54	75
	Acetone powder (conditions B)		55	76
	Acetone powder+isopropanol (conditions B)		54	74
 **11**	Fermenting yeast (conditions A)	 **15**	46	93
	Dry yeast (conditions B)		57	95
	Acetone powder (conditions B)		60	94
	Acetone powder + isopropanol (conditions B)		40	94

‡ Compounds **10** and **11** were prepared from dialkyl (1-hydroxy-2-cyclohexenyl) phosphonates **12** and **13**, respectively, see Experimental.



Scheme 3.

2.5. Determination of absolute configurations for compounds 4, 14 and 15

The absolute configurations for the six-membered compounds were determined by chemical correlations, as outlined in Scheme 3. Thus, the bromoalcohol **16** was prepared by reduction of 3-bromocyclohexenone[24] with sodium borohydride/$CeCl_3$ in methanol, and further submitted to enzymatic resolution by lipase Amano AK to afford (*S*)-(−)-**16** with 80% enantiomeric purity.[§] Its palladium-catalysed coupling[26,27] with diethyl-, dimethyl-, or diisopropyl phosphite led respectively to compounds (*S*)-**4**, (*S*)-**14** and (*S*)-**15** with the same enantiomeric purities (as shown by HPLC on Chiralcel ODH). This reaction sequence thus allowed the knowledge of the specific optical rotations for these (3-hydroxy-1-alkenyl) phosphonates.

3. Conclusion

We have shown that the baker's yeast-mediated reduction of six- and seven-membered cyclic dialkyl (3-oxo-1-alkenyl) phosphonates provides the corresponding dialkyl (3-hydroxy-1-alkenyl) phosphonates with moderate to good ee's, whereas the five-membered analogue leads only to racemic diethyl (3-oxocylopentyl) phosphonate resulting from double bond reduction. Varying the reaction conditions (such as the nature of the yeast, the addition of cosubstrates, or the use of organic solvents instead of water) did not result in a significant increase of the enantiomeric excess. However, for the six-membered compounds, we found that the alkyl groups located on phosphorus influence dramatically the enantioselectivity of the reduction, and an increase of their steric bulk results in an higher enantiomeric excess, culminating up to 95% ee.

4. Experimental

4.1. General

All solvents were purified according to reported procedures, and reagents were used as received. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$, on a Bruker AC 200 spectrometer working at 200.00 and 50.16 MHz, respectively (the usual abbreviations are used: s: singlet, d: doublet, t: triplet, q: quartet, qt: quintet, o: octet, m: multiplet). Tetramethylsilane was used as internal standard. ^{31}P NMR spectra were recorded on a Bruker AC 100 spectrometer working at 40.54 MHz, using 85% H_3PO_4 as external standard. All chemical shifts are given in ppm. Elemental analyses were carried out at the microanalytical centre, Faculté de Saint Jérôme, Marseille. Optical rotations were measured on a Perkin–Elmer 341 polarimeter. Enantiomeric excesses were measured by HPLC on a Chiralcel ODH column with a UV detection (214 nm), eluent: hexane/isopropanol (90:10), flow rate: 0.5 ml/min, retention times: (*S*)-**4**: 11.8 min; (*R*)-**4**: 15.9 min; (*S*)-**14**: 24.0 min; (*R*)-**14**: 25.8 min; (*S*)-**15**: 10.25 min; (*R*)-**15**: 11.5 min. For compound **6**, whose absolute configuration was not determined, the retention times for the minor enantiomer and the major enantiomer were respectively 15.9 and 19.2 min.

4.2. Synthesis of dialkyl (1-hydroxy-2-alkenyl) phosphonates

These compounds were prepared using the reported procedure.[11]

4.2.1. Diethyl (1-hydroxy-2-cyclohexenyl) phosphonate 7. 90% yield. (R_f: 0.3, ethyl acetate). [Found: C, 51.32; H, 8.08; P, 13.28. $C_{10}H_{19}O_4P$ requires: C, 51.28; H, 8.12; P, 13.25%]. ^{1}H NMR: 1.2 (t, CH_3, $^3J_{HH}$=7.1 Hz); 1.6–2.0 (m, 6H, CH_2); 4.0 (s, OH); 4.1 (qt, OCH_2, $^3J_{HH}$=$^3J_{PH}$=7.1 Hz); 5.7 (dd, PCC*H*=, $^3J_{HH}$=9.9 Hz, $^3J_{HP}$=6.9 Hz); 6.0 (dt, CH=C*H*–CH_2, $^3J_{HH}$=10.0 Hz, $^3J_{HH}$=3.7 Hz). ^{13}C NMR: 16.3 (d, CH_3, $^3J_{PC}$=5.6 Hz); 17.2 (d, CH_2, $^3J_{PC}$=7.7 Hz); 24.8 (d, CH_2, $^4J_{PC}$=2 Hz); 30.6 (d, CH_2, $^2J_{PC}$=2.8 Hz); 63.8 (d, OCH_2, $^2J_{PC}$=7.6 Hz); 69.2 (d, P–C, $^1J_{PC}$=166.1 Hz); 124.8 (s, PC*C*=); 134.4 (d, C=C, $^3J_{PC}$=11.5 Hz). ^{31}P NMR: 24.3.

4.2.2. Diethyl (1-hydroxy-2-cyclopentenyl) phosphonate 8. 91% yield. (R_f: 0.48, ethyl acetate/methanol 90/10). [Found: C, 49.10; H, 7.70; P, 14.13. $C_9H_{17}O_4P$ requires: C, 49.09; H, 7.73; P, 14.09%]. ^{1}H NMR: 1.7 (t, CH_3, $^3J_{HH}$=7.1 Hz); 2.4 (m, 2H, CH_2); 3.0 (m, 2H, CH_2); 3.8 (m, OH); 4.6 (qt, OCH_2, $^3J_{HH}$=$^3J_{PH}$=7.1 Hz); 6.2 (dd, PCC*H*=, $^3J_{HH}$=5.5 Hz, $^3J_{HP}$=2 Hz); 6.5 (m, =C*H*–CH_2). ^{13}C NMR: 16.5 (d, CH_3, $^3J_{PC}$=5.7 Hz); 32.0 (d, CH_2, $^3J_{PC}$= 4.9 Hz); 34.7 (d, CH_2, $^2J_{PC}$=7.9 Hz); 63.0 (2d, OCH_2, $^2J_{PC}$=7.4 Hz); 83.3 (d, C–P, $^1J_{PC}$=169.5 Hz); 130.8 (d, PCC=, $^2J_{PC}$=1.7 Hz); 137.7 (d, =*C*H–CH_2, $^3J_{PC}$= 13.4 Hz). ^{31}P NMR: 23.9.

4.2.3. Diethyl (1-hydroxy-2-cycloheptenyl) phosphonate 9. 86% yield. (R_f: 0.58, ethyl acetate/methanol 95/5). [Found: C, 53.25; H, 8.51; P, 12.47. $C_{11}H_{21}O_4P$ requires:

[§] (*R*)-(+)-16 of enantiomeric purity of 80% has already been obtained by enzymatic resolution of its corresponding chloroacetate.[25] We found that the enzymatic esterification of racemic **16** with vinyl acetate in the presence of lipase Amano AK gave unreacted (*S*)-(−)-**16** with similar enantiomeric purity.

C, 53.23; H, 8.47; P, 12.50%]. ^{1}H NMR: 1.3 (t, CH_3, $^3J_{HH}$=7.1 Hz); 1.5–2.3 (m, 8H, CH_2); 3.8 (m, O*H*); 4.1 (qt, OCH_2, $^3J_{HH}$=$^3J_{PH}$=7.1 Hz); 5.6 (dd, PCC*H*=, $^3J_{HH}$= 11.9 Hz, $^3J_{HP}$=5.6 Hz); 5.9 (m, PCCH=C*H*). ^{13}C NMR: 16.5 (d, CH_3, $^3J_{PC}$=5 Hz); 22.9 and 23.0 (2s, CH_2); 27.5 (s, CH_2); 34.9 (s, CH_2); 63.1 (2d, OCH_2, $^2J_{PC}$=7.6 Hz); 76.3 (d, C–P, $^1J_{PC}$=158.2 Hz); 131.2 (s, PC*C*H=); 134.1 (d, C=CH_2, $^3J_{PC}$=12.7 Hz). ^{31}P NMR: 24.3.

4.2.4. Dimethyl (1-hydroxy-2-cyclohexenyl) phosphonate 12. NMR data were identical to those already reported.[11] Additional data: R_f: 0.2, ethyl acetate, ^{31}P NMR: 26.5.

4.2.5. Diisopropyl (1-hydroxy-2-cyclohexenyl) phosphonate 13. (R_f: 0.6, ethyl acetate/methanol 90/10). [Found: C, 55.00; H, 8.76; P, 11.85. $C_{12}H_{23}O_4P$ requires: C, 54.96; H, 8.78; P, 11.83%]. ^{1}H NMR: 1.3 (d, CH_3, $^3J_{HH}$=6.3 Hz); 1.6–2.1 (m, 6H, CH_2); 4.7 (o, OCH, $^3J_{HH}$=$^3J_{PH}$=6.2 Hz); 5.3 (s, OH); 5.8 (dd, PCCH=, $^3J_{HH}$=9.9 Hz, $^3J_{HP}$=7.0 Hz); 6.0 (dt, =C*H*–CH_2, $^3J_{HH}$=10.0 Hz, $^3J_{HH}$=3.2 Hz). ^{13}C NMR: 17.4 (d, CH_2, $^3J_{PC}$=7.3 Hz); 23.8 (d, CH_3, $^3J_{PC}$=5.0 Hz); 24.9 (s, CH_2); 30.7 (d, CH_2, $^2J_{PC}$=2.8 Hz); 69.0 (d, P–C, $^1J_{PC}$= 167.5 Hz); 71.8 (d, OCH, $^2J_{PC}$=3.6 Hz); 125.4 (s, PCH*C*=); 133.9 (d, =CH–*C*H_2, $^3J_{PC}$=11.3 Hz). ^{31}P NMR: 22.9.

4.3. Synthesis of dialkyl (3-oxo-1-cycloalkenyl) phosphonates

These compounds were prepared by oxidation[10] of the corresponding dialkyl (1-hydroxy-2-alkenyl) phosphonates **7**–**9** and **12**–**13** described above.

4.3.1. Diethyl (3-oxo-1-cyclohexenyl) phosphonate 1. 65% yield. (R_f: 0.3, ethyl acetate/ether: 70/30). [Found: C, 51.74; H, 7.35; P, 13.33. $C_{10}H_{17}O_4P$ requires: C, 51.72; H, 7.33; P, 13.36%]. ^{1}H NMR: 1.2 (2t, CH_3, $^3J_{HH}$=7.1 Hz); 1.9 (m, 2H, CH_2); 2.4 (m, 4H, CH_2); 4.0 (qt, CH_2O, $^3J_{HH}$= $^3J_{PH}$=7.1 Hz); 6.4 (d, =CH, $^3J_{PH}$=21.1 Hz). ^{13}C NMR: 16.3 (2d, CH_3, $^3J_{PC}$=5.8 Hz); 22.7 (d, CH_2, $^3J_{PC}$= 11.6 Hz); 25.2 (d, CH_2, $^2J_{PC}$=7.9 Hz); 37.7 (s, CH_2); 62.6 (d, CH_2O, $^2J_{PC}$=6.8 Hz); 136.1 (d, =CH, $^2J_{PC}$=7.3 Hz); 149.5 (d, =C–P, $^1J_{PC}$=171.9 Hz); 198.2 (d, C=O, $^3J_{PC}$=20.2 Hz). ^{31}P NMR: 14.5.

4.3.2. Diethyl (3-oxo-1-cyclopentenyl) phosphonate 2. 45% yield. (R_f: 0.35, ethyl acetate/ether: 70/30). [Found: C, 49.51; H, 6.90; P, 14.20. $C_9H_{15}O_4P$ requires: C, 49.54; H, 6.88; P, 14.22%]. ^{1}H NMR: 1.3 (t, CH_3, $^3J_{HH}$=7.1 Hz); 2.4 (m, CH_2); 2.7 (m, CH_2); 4.1 (qt, CH_2O, $^3J_{HH}$=$^3J_{PH}$=7.1 Hz); 6.5 (d, =CH, $^3J_{PH}$=10.7 Hz). ^{13}C NMR: 16.1 (d, CH_3, $^3J_{PC}$=6.0 Hz); 28.6 (d, CH_2, $^2J_{PC}$=9.9 Hz); 34.7 (d, CH_2 $^3J_{PC}$=5.6 Hz); 62.5 (d, CH_2O, $^2J_{PC}$=6.0 Hz); 141.5 (d, =CH, $^2J_{PC}$=11.7 Hz); 164.2 (d, =C–P, $^1J_{PC}$=183.9 Hz); 208.2 (d, C=O, $^3J_{PC}$=26.4 Hz). ^{31}P NMR: 11.1.

4.3.3. Diethyl (3-oxo-1-cycloheptenyl) phosphonate 3. 41% yield. (R_f: 0.28, ethyl acetate/ether: 70/30). [Found: C, 53.68; H, 7.75; P, 12.61. $C_{11}H_{19}O_4P$ requires: C, 53.66; H, 7.72; P, 12.60%]. ^{1}H NMR: 1.3 (t, CH_3, $^3J_{HH}$=7.1 Hz); 1.8 (m, 4H, CH_2); 2.5 (m, 4H, CH_2); 4.1 (qt, CH_2O, $^3J_{HH}$= $^3J_{PH}$=7.2 Hz); 6.6 (d, =CH, $^3J_{PH}$=24.8 Hz). ^{13}C NMR: 16.3 (d, CH_3, $^3J_{PC}$=5.9 Hz); 21.0 (s, CH_2); 25.2 (d, CH_2, $^3J_{PC}$=8.7 Hz); 27.8 (d, CH_2, $^2J_{PC}$=8.6 Hz); 42.3 (s, CH_2); 62.5 (d, CH_2O, $^2J_{PC}$=5.8 Hz); 140.7 (d, =CH, $^2J_{PC}$= 8.2 Hz); 144.4 (d, =C–P, $^1J_{PC}$=168.9 Hz); 203.3 (d, C=O, $^3J_{PC}$=25.4 Hz). ^{31}P NMR: 17.7.

4.3.4. Dimethyl (3-oxo-1-cyclohexenyl) phosphonate 10. NMR data were identical to those already reported.[9] Additional data: R_f: 0.2, ethyl acetate/ether: 70/30, ^{31}P NMR: 17.4.

4.3.5. Diisopropyl (3-oxo-1-cyclohexenyl) phosphonate 11. 61% yield. (R_f: 0.65, ethyl acetate/methanol: 90/10). [Found: C, 55.41; H, 8.12; P, 11.94. $C_{12}H_{21}O_4P$ requires: C, 55.39; H, 8.08; P, 11.92%]. ^{1}H NMR: 1.2 (d, CH_3, $^3J_{HH}$=6.2 Hz); 1.9 (m, 2H, CH_2); 2.4 (m, 4H, CH_2); 4.6 (o, CH–O, $^3J_{HH}$= $^3J_{PH}$=6.1 Hz); 6.5 (d, =CH, $^3J_{PH}$= 21.0 Hz). ^{13}C NMR: 22.7 (d, CH_2, $^3J_{PC}$=10.6 Hz); 23.9 (2d, CH_3, $^3J_{PC}$= 3.9 Hz); 25.3 (d, CH_2, $^2J_{PC}$=7.9 Hz); 37.7 (s, CH_2); 71.5 (d, CH–O, $^2J_{PC}$=6.3 Hz); 135.7 (d, =CH, $^2J_{PC}$=6.8 Hz); 150.9 (d, =C–P, $^1J_{PC}$=172.3 Hz); 198.4 (d, C=O, $^3J_{PC}$= 20.4 Hz). ^{31}P NMR: 12.4.

4.4. Baker's yeast-mediated reductions

All experiments were run in triplicate, and the given results correspond to the average value (less than 5% standard deviation). Dry yeast was obtained from local market.

4.4.1. Fermenting conditions (conditions A). A solution of ammonium phosphate (200 mg), potassium phosphate (200 mg) and glucose (4 g) in distilled water (50 ml) was boiled for 5 min, and cooled to 38°C. Dry yeast (2 g) was added, and the mixture was stirred at 38°C for 30 min. A solution of (3-oxo-1-cycloalkenyl) phosphonate (1 mmol) in ethanol (1 ml) was added, and stirring at the same temperature was continued. Glucose (2 g) and yeast (2 g) were added every 24 h, and the reaction was monitored by TLC. After five days, the mixture was filtered over a short pad of celite and the filter cake was rinsed with ethanol (20 ml). The solvent was removed in vacuo, and the aqueous layer was extracted continuously with diethyl ether overnight. The ether layer was then washed with saturated NaCl, and dried over $MgSO_4$. After filtration and removal of solvent, the residue was subjected to flash chromatography on silica gel.

4.4.2. Aqueous phase (conditions B). To a solution of (3-oxo-1-cycloalkenyl) phosphonate (0.5 mmol) in ethanol (1 ml) were added 15 ml of a phosphate buffer solution followed by dry yeast or acetone powder (2.5 g). If necessary, NAD(H) and/or isopropanol were added at this stage. The mixture was stirred at 30°C for 24 h, and worked up as above.

4.4.3. Preparation of acetone powder. The moist yeast (obtained from a local bakery) was mixed with cold acetone (−18°C), and the resulting suspension was filtered. The procedure was repeated three times, and the powder was finally dried under vacuum. It was used as such for the reductions, according to conditions B.

4.4.4. Reductions in organic phase (conditions C). To a solution of (3-oxo-1-cycloalkenyl) phosphonate (100 mg) in

organic solvent (hexane, MTBE or benzene) (15 ml) were added 2.5 ml of a phosphate buffer solution (prepared from Na_2HPO_4 0.1 M and NaH_2PO_4 0.1 M) followed by moist yeast (2.5 g). The mixture was stirred at 30°C for 24 h, and worked up as above.

4.5. Spectroscopic data for (3-hydroxy-1-alkenyl) phosphonates

4.5.1. Diethyl (3-hydroxy-1-cyclohexenyl) phosphonate 4. (R_f: 0.46, ethyl acetate/methanol: 90/10). [Found: C, 51.31; H, 8.15; P, 13.20. $C_{10}H_{19}O_4P$ requires: C, 51.28; H, 8.12; P, 13.25%]. ^{1}H NMR: 1.2 (t, CH_3, $^3J_{HH}$=7.1 Hz); 1.6 (m, 2H, CH_2); 1.75–1.9 (m, 2H, CH_2); 2.1 (m, 2H, CH_2); 4.0 (qt, 5H, CH_2O and OH, $^3J_{HH}$=$^3J_{PH}$=7.1 Hz); 4.2 (m, C*H*–OH); 6.7 (d, =CH, $^3J_{PH}$=22.5 Hz).^{13}C NMR: 16.3 (d, CH_3, $^3J_{PC}$= 6.6 Hz); 19.6 (d, CH_2, $^3J_{PC}$=10.6 Hz); 24.3 (d, CH_2, $^2J_{PC}$=8.8 Hz); 30.8 (s, CH_2); 61.9 (d, CH_2O, $^2J_{PC}$= 5.6 Hz); 65.4 (d, *C*H–OH, $^3J_{PC}$=19.9 Hz); 129.0 (d, =C–P, $^1J_{PC}$= 177.7 Hz); 145.2 (d, =C–H, $^2J_{PC}$=7.4 Hz). ^{31}P NMR: 18.4.

4.5.2. Diethyl (3-hydroxy-1-cycloheptenyl) phosphonate 6. (R_f: 0.4, ethyl acetate/methanol: 90/10). [Found: C, 53.25; H, 8.47; P, 12.52. $C_{11}H_{21}O_4P$ requires: C, 53.23; H, 8.47; P, 12.50%]. ^{1}H NMR: 1.2 (t, CH_3, $^3J_{HH}$=7.1 Hz); 1.4–2.4 (m, 8H, CH_2); 4.0 (qt, CH_2O, $^3J_{HH}$=$^3J_{PH}$=7.1 Hz); 4.4 (m, C*H*–OH and OH); 6.8 (d, =CH, $^3J_{PH}$=24.8 Hz).^{13}C NMR: 16.3 (d, CH_3, $^3J_{PC}$=7.5 Hz); 25.9 (d, CH_2, $^3J_{PC}$= 6.5 Hz); 27.9 (s, CH_2); 28.2 (d, CH_2, $^2J_{PC}$=9.8 Hz); 35.3 (d, CH_2, $^4J_{PC}$=2.5 Hz); 61.8 (2d, CH_2O, $^2J_{PC}$=5.3 Hz); 72.3 (d, *C*H–OH, $^3J_{PC}$=25.4 Hz); 129.1 (d, =C–P, $^1J_{PC}$=177.7 Hz); 155.3 (d, =CH, $^2J_{PC}$=9.2 Hz). ^{31}P NMR: 20.3.

4.5.3. Dimethyl (3-hydroxy-1-cyclohexenyl) phosphonate 14. NMR data were identical to those already reported.[11] Additional data: R_f: 0.51, ethyl acetate/methanol: 80/20, ^{31}P NMR: 21.0.

4.5.4. Diisopropyl (3-hydroxy-1-cyclohexenyl) phosphonate 15. (R_f: 0.41, ethyl acetate/methanol: 90/10). [Found: C, 54.99; H, 8.81; P, 11.79. $C_{12}H_{23}O_4P$ requires: C, 54.96; H, 8.78; P, 11.83%]. ^{1}H NMR: 1.2 (d, CH_3, $^3J_{HH}$=6.3 Hz); 1.5 (m, 2H, CH_2); 1.8 (m, 2H, CH_2); 2.0 (m, 2H, CH_2); 4.0 (s, OH); 4.1 (m, C*H*–OH); 4.5 (o, CH–OP, $^3J_{HH}$= $^3J_{PH}$=6.2 Hz); 6.6 (d, =CH, $^3J_{PH}$=22.4 Hz).^{13}C NMR: 19.6 (d, CH_2, $^3J_{PC}$=11.4 Hz); 23.9 (d, CH_3, $^3J_{PC}$= 3.3 Hz); 24.4 (d, CH_2, $^2J_{PC}$=8.7 Hz); 30.8 (s, CH_2); 65.4 (d, *C*H–OH, $^3J_{PC}$=20.1 Hz); 70.4 (d, CH–OP, $^2J_{PC}$=5.8 Hz); 130.3 (d, =C–P, $^1J_{PC}$=179.0 Hz); 144.4 (d, =CH, $^2J_{PC}$= 8.2 Hz). ^{31}P NMR: 16.1.

4.5.5. Diethyl (3-oxocyclopentyl) phosphonate 5. Isolated by flash chromatography from the reduction of **2**, the spectroscopic data were identical to those of a sample prepared as described in Ref. 12. (R_f: 0.5, ethyl acetate/methanol: 90/10). [Found: C, 49.05; H, 7.69; P, 14.05. $C_9H_{17}O_4P$ requires: C, 49.09; H, 7.73; P, 14.09%]. ^{1}H NMR: 1.24 (t, CH_3, $^3J_{HH}$=7.0 Hz); 2.04–2.37 (m, 7H); 4.1 (qt, CH_2O, $^3J_{HH}$= 7.2 Hz, $^3J_{PH}$=7.2 Hz). ^{13}C NMR: 16.4 (d, CH_3, $^3J_{PC}$=5.7 Hz); 23.4 (d, CH_2, $^2J_{PC}$=3.6 Hz); 32.5 (d, CH, $^1J_{PC}$=152.4 Hz); 37.5 (d, CH_2, $^3J_{PC}$=7.9 Hz); 38.6 (d, CH_2, $^2J_{PC}$=3.1 Hz); 62.1 (2d, OCH_2, $^2J_{PC}$=4.1 Hz). ^{31}P NMR: 29.8.

4.6. Determination of absolute configuration of compounds 4, 14 and 15

4.6.1. 3-Bromo-cyclohexen-2-ol 16. 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 3-bromocyclohexen-2-one[24] (3.6 g, 20.6 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 50:50) yielded 3.39 g (93%) of **16** as a colourless oil. (R_f: 0.49, diethyl ether/pentane 50:50). ^{1}H NMR: 1.5–1.9 (m, 6H, CH_2); 2.4 (m, OH); 4.2 (m, C*H*–OH); 6.1 (m, =CH). ^{13}C NMR: 20.4 (CH_2); 30.5 (CH_2); 35.1 (CH_2); 67.0 (CH–OH); 127.0 (H*C*=C); 131.4 (=C–Br).

4.6.2. Enzymatic resolution of 16. Lipase Amano AK (104 mg) was mixed with a solution of 813 mg (4.6 mmol) of **16** in vinyl acetate (40 ml), the suspension was shaken at 30°C and the reaction was monitored by HPLC on Chiralcel ODH column. After 21 h, the mixture was filtered over a short pad of celite, and the residue was subjected to flash chromatography on silicagel with diethyl ether/pentane (50:50). This led to the isolation of 497 mg of (*R*)-3-bromocyclohexen-2-ol acetate (46% yield, 71% ee), followed by (*S*)-**16** (338 mg, 41% yield) with 80% ee.

4.6.3. Synthesis of dialkyl (3-hydroxy-1-cyclohexenyl) phosphonates by the coupling reaction. General procedure. A solution of (*S*)-(−)-**16** (158 mg, 0.89 mmol), triethylamine (430 μl, 3 mmol), and the dialkyl phosphite (1 mmol) in anhydrous toluene (1.5 ml) was degassed by bubbling with nitrogen, and added to tetrakis triphenylphosphine palladium (115.6 mg, 0.1 mmol) in a round bottomed flask under nitrogen. The mixture was gradually heated to 70°C and maintained at this temperature for one hour, after which a white precipitate appeared. After cooling to room temperature, ethyl acetate was added (20 ml) and the mixture was filtered. Removal of solvents, and purification by flash chromatography with ethyl acetate/methanol (90:10) afforded the dialkyl (3-hydroxy-1-cyclohexenyl) phosphonate as a slightly yellow oil. Its spectral data were identical to those indicated above, and its optical purity (ca. 80%) was checked by HPLC on a Chiralcel ODH column.

Additional data: (*S*)-**4**: Chemical yield: 43%, α_D=−29.4 (c=0.85, CH_2Cl_2). (*S*)-**14**: Chemical yield: 7%, α_D=−11 (c=0.25, CH_2Cl_2). (*S*)-**15**: Chemical yield: 43%, α_D=−9 (c=0.567, CH_2Cl_2).

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