Stereoselective Aldol Reactions *via* Enolates of α-Acylphosphonate Diesters[1]

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In the reaction between the lithium enolate (**2**) of diethyl propionylphosphonate (**1**) and benzaldehyde, the *syn*-product (**3s**) is formed with high diastereoselectivity, as a result of structural rigidity caused by Li^+ interactions with the phosphoryl oxygen.

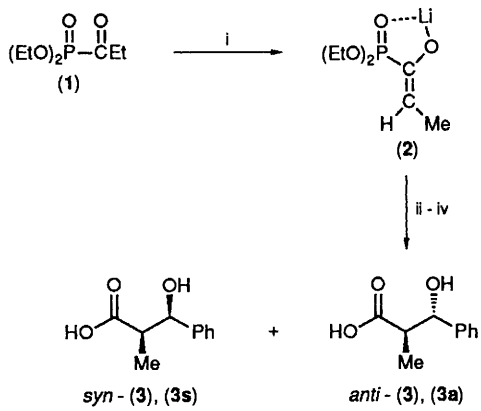
The phosphoryl bond (–P=O) is highly polar and exhibits a high propensity for co-ordination to metal ions. We speculated that in an appropriate organophosphorus substrate (*i.e.*, α-acyl phosphonate diester)[2] intramolecular ligation between a lithium enolate and a proximal phosphoryl group would encourage both enolate as well as 'transition-state' structural rigidity, perhaps leading to significant diastereofacial selectivity in an aldol reaction. The synthetic scope, stereochemistry, and mechanism of such a reaction have not been previously described, although the use of an α-acylphosphonate in an 'aldol-type reaction' appeared as a footnote in a report by Sekine *et al.*[3]

Deprotonation of diethyl propionylphosphonate (**1**)† with lithium bis(trimethylsilyl)amide (LHMS) [−78 °C, tetrahydrofuran solvent (THF)] affords exclusively the *Z*-enolate (**2**) (^{31}P NMR δ 21.8 ppm, THF, −78 °C) which is expected to be strongly chelated[4] as a structurally rigid enolate. Reaction with excess of benzaldehyde, base-promoted hydrolysis (5 equiv. NaOH/H_2O, −78 °C), and acidification (HCl/H_2O, pH <2.5, ~25 °C) gave a 97% yield of the diastereoisomeric 3-hydroxy-2-methylbenzenepropanoic acids, *syn*- (**3**) and *anti*- (**3**),[5,6] with a >97% *syn* diastereoisomeric excess (Scheme 1, X = 2.2 mol equiv.). Diethyl α-hydroxybenzylphosphonate (**4**)[7]† was also isolated from the reaction mixture, in a yield similar to that of (**3**). With one equivalent of benzaldehyde, the *syn* diastereoselectivity was unchanged, but only a 47% yield of the α-hydroxy acids (**3**) was obtained (Scheme 1, X = 1.0 mol equiv.), together with a similar yield of (**4**).

A tentative, but reasonable, mechanistic proposal which accounts for (i) the need for 2 equivalents of benzaldehyde to ensure that the yield of (**3**) is high, and (ii) the formation of the phosphonate (**4**) in comparable quantities to hydroxy acids (**3**) is illustrated in Scheme 2.

Rapid lactonization of aldol phosphonate intermediate (**5**) liberates diethylphosphonate anion (**6**) which condenses with benzaldehyde to afford oxyanion (**7**).[8] When two equivalents of benzaldehyde are present, one is incorporated into the aldol product and one is 'sacrificed' by condensation with phosphonate anion (**6**). Basic hydrolysis (−78 °C) leads to ring opening of the lactone (**8**)[9] at the carbonyl centre.[10] Finally, acidification and ether extraction lead to isolation of aldols (**3**) and α-hydroxy phosphonate (**4**) (Scheme 1).

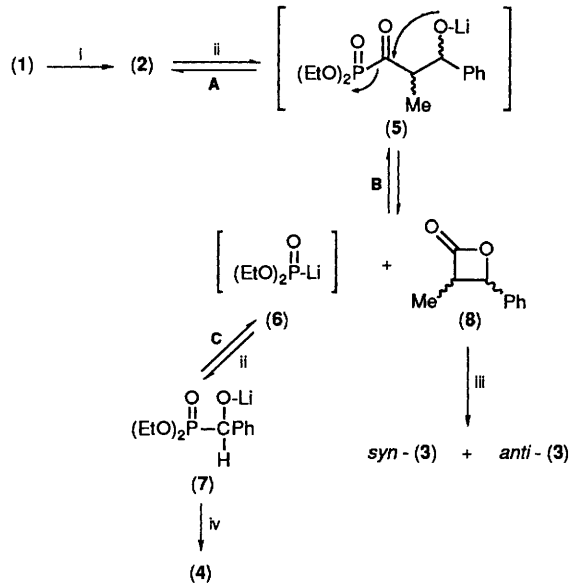
Indirect evidence supporting the proposed intramolecular collapse of (**5**) was obtained by ^{13}C NMR spectral observation of lactone (**8**) in the reaction mixture (−40 °C). α-Acylphos-



	% Yield	
X	(**3s**) + (**3a**)[a]	(**4**)[b]
1.0	47	48
2.2	97	95

[a] Isolated yield; (**3s**):(**3a**) 98.8:1.2. [b] By ^1H NMR spectroscopy before isolation.

Scheme 1. *Reagents and conditions*: i, LHMS, −78 °C; ii, X equiv. PhCHO, −78 °C; iii, OH/H_2O; iv, H^+, ether extraction.



Scheme 2. *Reagents and conditions*: i, LHMS, −78 °C; ii, PhCHO; iii, H^+; iv, NaOH, then H^+.

† (**1**): ^{13}C NMR (C_6D_6) δ 16.36 [d, ($CH_3CH_2O)_2$, $^3J_{CP}$ 5.6 Hz], 63.33 [d, ($CH_3CH_2O)_2$, $^2J_{CP}$ 7.1 Hz], 211.9 [d, C(O), $^1J_{PC}$ 166.1 Hz], 36.87 [d, C(O)CH_2CH_3, $^2J_{PC}$ 56.0 Hz], and 6.41 [d, C(O)CH_2CH_3, $^3J_{PC}$ 4.2 Hz]; ^{31}P NMR (THF) δ −1.4 (relative to 85% aqueous H_3PO_4). (**4**): ^{31}P NMR (THF) δ 22.0; ^{13}C NMR (C_6D_6) δ 16.42 [d, ($CH_3CH_2O)_2$, $^3J_{PC}$ 5.5 Hz], 63.43 (d, CH_3CH_2O, $^2J_{PC}$ 159.4 Hz), 62.75 (d, CH_3CH_2O, $^2J_{PC}$ 7.5 Hz), 71.31 [d, CH(OH), $^1J_{PC}$ 159.4 Hz], 136.62 (s, *ipso*-C_6H_5), 127.96 (d, *o,m*-C_6H_5, J_{PC} 2.5 Hz), 127.02 (d,*o,m*-C_6H_5, J_{PC} 5.5 Hz), and 127.74 (d, *p*-C_6H_5, $^5J_{PC}$ 3.0 Hz).

phonate intermediate (**5**) and phosphonate anion (**6**) are not observable by ^{31}P NMR even at −78 °C implying that equilibria A, B, and C (Scheme 2) apparently lie far to the side of oxyanion (**7**) and lactone (**8**). Since the stereocentres are established in reaction sequence A, it is a reasonable assumption that they are secure during the intramolecular collapse of *syn*-(**5**) *en route* to *cis*-β-lactone (**8**) and ultimately to hydroxy acid, *syn*-(**3**), after hydrolysis.

The most interesting feature of this aldol reaction is that if the reaction mixture is warmed from −78 to 25 °C and stirred for 1.5 h, a 1.0 : 1.2 ratio of *syn*-(**3**) : *anti*-(**3**) is obtained after basic hydrolysis at −78 °C and acidification. It seems apparent that at ambient temperature, the activation energy is low enough to encourage recombination of (**6**) with lactones (**8**) for rapid reversion to intermediate (**5**) which suffers a retroaldol reaction to enolate (**2**) and benzaldehyde. This suggestion provides a reasonable mechanism for equilibration of *cis*-(**8**) to the thermodynamically more stable *trans*-lactone (**8**).

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