Asymmetric Synthesis of α-Aminophosphonates via Diastereoselective Addition of Lithium Diethyl Phosphite to Chelating Imines

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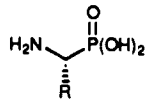
α-Aminophosphonic acids (**1**) serve as important surrogates for carboxylic amino acids. Synthetic examples inhibit proteolytic enzyme activity[1] and bacterial growth;[2] other representative structures occur in nature as components of hypertensive tripeptide analogs.[3] It is not surprising that the absolute configuration of the α carbon strongly influences the biological properties of **1**; for example, the *S,R* diastereomer of the antibiotic alafosfalin (**2**) offers considerably greater potency than the other three isomers against both Gram-positive and -negative bacteria.[2]



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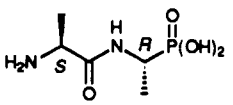
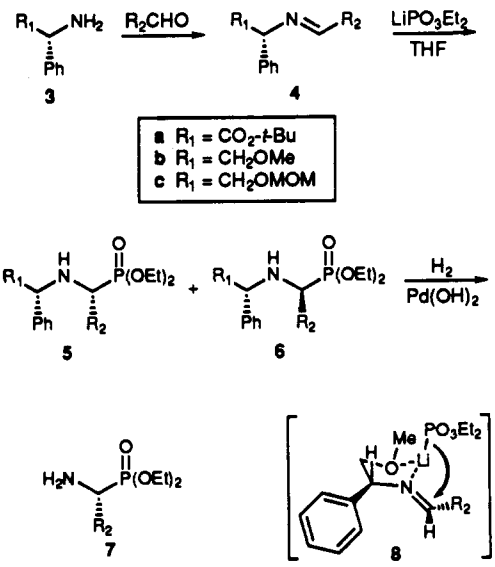


Alafosfalin (**2**)

In connection with our efforts to develop catalytic antibodies for peptide coupling,[4] we required an efficient synthetic route to a series of homochiral α-aminophosphonate esters, versatile precursors of the acids **1** and derivatives thereof. Several published strategies,[5,6] although not without merit, are limited by lengthy sequences, low to moderate enantiomeric purities, and inflexible absolute stereochemistries. Our search for a more general method led to earlier work by Zon,[7] who demonstrated that addition of dialkyl phosphites to imines is strongly promoted by Lewis acids. We reasoned that high diastereofacial selectivity could be achieved if a suitable imine could coordinate with a Lewis acid to form a rigid, cyclic structure. This design principle has been exploited previously in the asymmetric hydrocyanation of imines[8] and in conjugate additions of Grignard reagents to α,β-unsaturated imines.[9]

Promising initial experiments involved the reaction of scalemic imino ester **4a** (R_2 = cyclohexyl, Scheme 1) with diethyl phosphite

Scheme 1



and $MgBr_2$ or $ZnCl_2$. Although the diasteromer ratios were unsatisfactory (ca. 48% de), it occurred to us that the selectivity might be greatly enhanced if the phosphite reactant were also bound to the chelating metal ion. Indeed, substitution of lithium diethyl phosphite ($LiPO_3Et_2$) for its protio counterpart led to much faster addition, affording predominantly the *R,R* diastereomer **5a** (≥98:2, HPLC and 500-MHz ^{1}H NMR) in 75–80% yield. Numerous attempts to cleave the benzylic C–N bond in **5a**, involving catalytic or transfer hydrogenolyses, dissolving metal reductions, and oxidative decarboxylation followed by imine hydrolysis, all resulted in epimerization[10] at the α carbon. Because the products of phosphite addition to α-phenethylamine-derived imines reportedly undergo facile hydrogenolysis without loss of stereochemical integrity,[5,11] we turned next to the methyl and methoxymethyl (MOM) ethers[12] of (*R*)-2-phenylglycinol[13] (**3b** and **3c**). We anticipated that the ether functionality would participate in bidentate coordination of the cation, as required for high diastereoselectivity, without interfering with subsequent hydrogenolysis of the chiral auxiliary.

Both (*R*)- and (*S*)-2-phenylglycinol and their ether derivatives can be obtained in quantity (ca. 25 g) via the procedures of Meyers.[12,13] The *R* enantiomers (illustrated herein) were selected in an effort to generate (*R*)-α-aminophosphonate mimics of the coded L-α-amino acids. According to a published protocol,[12] the hydrolytically unstable imines **4b** and **4c** (R_2 = cyclohexyl; Scheme 1) were prepared from cyclohexanecarboxaldehyde and used immediately, without purification. Addition of $LiPO_3Et_2$ (0.95 equiv) to **4b** (R_2 = cyclohexyl) (THF, ambient temperature, 18–20 h) furnished a 49:1 mixture (500-MHz ^{1}H NMR) of adducts **5b** and **6b** (R_2 = cyclohexyl) in 68% yield after flash chromatography. MOM ether **4c** (R_2 = cyclohexyl) afforded **5c** and **6c** with identical diastereoselectivity; however, the reaction proved to be exceedinglysluggish, and amine **3b** was therefore employed

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(14) Published optical rotation data: (+)-(*S*)-phosphovaline diethyl ester (**7**, entry 3) $[\alpha]^{25}_D$ +0.4° (*c* 1.7, $CHCl_3$); (+)-(*S*)-phosphoalanine diethyl ester (**7**, entry 5) $[\alpha]^{25}_D$ +7.3° (*c* 1.3, $CHCl_3$); (+)-(*S*)-phosphoserine diethyl ester (**7**, entry 8) $[\alpha]^{25}_D$ +9.0° (*c* 1, $CHCl_3$). See: Huber, R.; Knierzinger, A.; Obrecht, J.-P.; Vasella, A. *Helv. Chim. Acta* **1985**, *68*, 1730.

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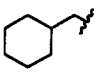
Table 1

Entry	R^1	Yield 4b (%)[a]	5b:6b Ratio	de (%)	Yield 5b,6b (%)[c]	Yield 7 (%)[c]	7 $[\alpha]_D^{25}$	Mosher ee 7 (%)
1		90	49:1[b]	96.0	68	94	-52.2° (c 1.2, Me_2CO)	96
2		89	114:1[d]	98.3	70	87	-20.9° (c 0.6, $CHCl_3$)	≥99
3		82	55:1	96.5	82	86	-0.8°[14] (c 1.3, $CHCl_3$)	97
4		84	>114:1[d]	>98.3	81	89	-20.8° (c 1.6, $CHCl_3$)	≥99
5	Me	90	41:1	95.2	77	99	-5.4°[14] (c 1.8, $CHCl_3$)	≥99
6		95	49:1[b]	96	78	98	-12.2° (c 1.1, $CHCl_3$)	≥98
7	MeS	84	55:1	96.5	69	89[f,g]	-21.6° (c 0.6, $CHCl_3$)	75
8[15a]	BnO	92	49:1[b]	96.0	36	100[e]	-10.6°[14] (c 1.5, $CHCl_3$)	≥98
9[15b]	t-BuO_2C	95	49:1[b]	96.0	37	83	-14.3° (c 0.7, $CHCl_3$)	96
10		82	7.3:1[b]	76	90[h]	88	-13.3° (c 1.9, $CHCl_3$)	71

[a] Crude product. [b] Determined by 500-MHz ^1H NMR. [c] After chromatography. [d] Trace **6b** detectable. [e] $R_2 = CH_2OH$. [f] Based on recovered starting material. [g] Pd black (5 equiv), H_2, AcOH, 48 h. [h] Reaction time, 48 h.

exclusively in subsequent studies. The effects of the phosphite counterion on the rate and diastereoselectivity were investigated with **4b** (R_2 = cyclohexyl) and the sodium and potassium salts of diethyl phosphite. Remarkably, neither the sodium nor the potassium reagent gave any detectable product, even after several days at room temperature.

To explore the generality of the phosphite addition, a variety of aldehydes were studied (Table 1). Authentic samples of **5b** and **6b**, typically ca. 2:1 mixtures favoring the *R,R* diastereomers, were prepared by treatment of each imine with diethyl phosphite and catalytic anhydrous $ZnCl_2$ (benzene, room temperature). Diastereomer ratios were generally determined via capillary gas–liquid chromatography; when low volatility precluded GC analysis, 500-MHz ^1H NMR spectroscopy was employed. In most examples, the de values were 95–96.5%; for entries 2 and 4, the de values exceeded 98%. Although the reaction appears to be relatively insensitive to the structure of the aldehyde, we were unable to apply the new protocol to the preparation of phospho-(phenylalanine), as the requisite phenylacetaldehyde-derived imine appeared to isomerize to the enamine before or during reaction with $LiPO_3Et_2$. We also observed that steric congestion completely inhibited addition to the imine prepared from pivalaldehyde; no reaction occurred after 72 h at ambient temperature or 24 h at 67 °C. Similarly, the ketimine derived from **3b** and 4,4-dimethyl-2-pentanone provided only minor amounts (ca. 4%) of the α,α-disubstituted aminophosphonates.

To account for the high diastereofacial selectivity of the phosphite addition, we propose the transition state model **8** (Scheme 1). Chelation of the lithium cation by the ether oxygen and imine nitrogen creates a rigid, five-membered ring with a trans disposition of the phenyl and phosphite groups. The phosphite anion thus is suitably disposed for addition to the *re* (i.e., top) face of the imine double bond, leading to the observed *R,R* diastereomers **5b**.

Removal of the chiral directing group via palladium-catalyzed hydrogenolysis afforded the corresponding amino esters **7** in 83–100% yields after flash chromatography. As anticipated, the latter cleavage could be effected without loss of enantiomeric purity, as ascertained by 500-MHz ^1H NMR analyses of the (*S*)-Mosher amides.[16,17] The Mosher derivative of the minor diastereomer could not be detected by NMR for entries 2, 4, and 5. With the exception of entries **7** and **10**, the ee values were at least as high as the de values determined for **5b**.[18]

In summary, we have developed a versatile and efficient protocol for the synthesis of α-aminophosphonate esters of high enantiomeric purity. This method proved central to the synthesis of a novel phosphonate hapten[19] which on immunization resulted in catalytic antibodies capable for the first time of peptide bond formation;[4] ongoing studies are expected to further demonstrate the importance of this new methodology.

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Supplementary Material Available: Representative experimental procedures; spectroscopic and analytical data for **5b** and **7** (entries 1–10); tables of X-ray positional and thermal parameters for **7** (entry 1) and the (*S*)-Mosher amides of **7** (entries 2, 4, and 5) (66 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(17) The absolute configurations of **7** (entries 1–10) were generally established via optical rotations (Table 1), X-ray analyses, and circular dichroism (CD) spectra (supplementary material). *R,R* and *R* configurations were assigned to **5b** and **7** for entry 6 (R_2 = *n*-hexyl) on the basis of the stereochemical congruity observed within the series and the strongly negative CD curves (λ_{max} ca. 200 nm) for **5b** (entries 1–10).

(18) Principally, in order to secure polarimetric corroboration of the absolute stereochemistries, four of the diethyl phosphonates **7** (entries 4, 7, 9, and 10) were hydrolyzed (concentrated HCl, 100 °C, 14–16 h), furnishing the known α-aminophosphonic acids **1**. In these preliminary experiments, the product optical rotations (see supplementary material) suggested that hydrolysis was accompanied by partial racemization, as observed previously.[14] The ee values of the acids **1** were not determined, and the hydrolysis conditions remain to be optimized.

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