A highly efficient asymmetric synthesis of β-aminophosphonic acids *via* addition of α-phosphonate carbanions to chiral, enantiopure sulfinimines

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Addition of α-phosphonate carbanions to (*S*)-sulfinimines 1 affords *N*-sulfinyl β-aminophosphonates 2 in a diastereoisomeric ratio from 5:1 to 10:1; the major diastereoisomers of 2, after separation, are converted to the corresponding β-aminophosphonates 3 or to (+)-β-amino-β-phenylethane phosphonic acid 4, whose absolute configuration was established as (*R*) by X-ray crystallography.

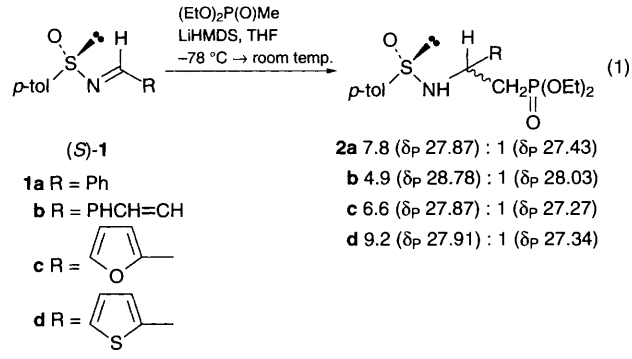
Aminophosphonic acids are an important class of compounds that exhibit interesting biological properties.[1–4] Many aminophosphonic acids have been reported to show antibacterial, antibiotic and antiviral properties as well as pesticidal, insecticidal and herbicidal activity and have therefore found diverse industrial applications, *e.g.* in pharmaceuticals and agrochemicals.[5–8]

As expected, the biological activity of aminophosphonic acids strongly depends on their structure and especially on the carbon chirality. Thus, for example, the (*S*)-enantiomer of 2-amino-4-phosphonobutanoic acid is 20–40 times more active than the (*R*)-form in the suppression of glutamate mediated neurotransmission[9] and the activity of 2-amino-5-phosphonopentanoic acid as the *N*-methyl-D-aspartate antagonist has been attributed mainly to its (*R*)-enantiomer.[10] For this reason, the synthesis of chiral, non-racemic aminophosphonic acids has recently attracted considerable attention. However, in contrast to the widely investigated α-aminophosphonic acids,[2,4] the synthetic approaches to achiral, racemic and enantiomeric β-aminophosphonic acids are few in number and of limited applicability.[11–20]

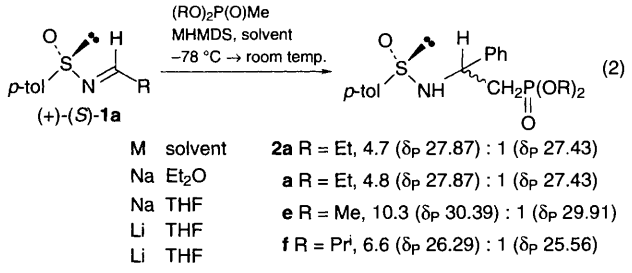
Here, we disclose a novel asymmetric synthesis of β-aminophosphonic acids which is based on a highly diastereoselective addition of α-phosphonate carbanions to the enantiopure sulfinimines **1**. The starting (+)-(*S*)-sulfinimines **1a** {R = Ph, $[\alpha]_D^{22}$ +117.0 (*c* 2.1, $CHCl_3$)} and **1b** {R = PhCH = CH, ($\alpha[_D^{22}$ +337.0 (*c* 1.54, $CHCl_3$)} were prepared from (−)-(*S*)-menthyl toluene-*p*-sulfinate according to the procedure described by Davis.[17] By this method we also obtained two new (*S*)-sulfinimines **1c** {R = 2-furyl, $[\alpha]_D^{22}$ +82.5 (*c* 1.34, $CHCl_3$), yield 75%} and **1d** {R = 2-thienyl, $[\alpha]_D^{22}$ −107.6 (*c* 1.09, $CHCl_3$, yield 71%} containing heteroaromatic substituents.

The reaction of **1a–d** with 1.5 equiv. of the lithium salt of diethyl methanephosphonate was found to afford a mixture of the diastereoisomeric adducts **2a–d** in 75–80% yield. The diastereoisomeric ratio of **2** was determined by ^{31}P NMR spectroscopy, [eqn. (1)].

In another set of experiments [eqn. (2)] the effect of the phosphonate structure and reaction conditions on the addition diastereoselectivity was briefly investigated. The results obtained reveal that the use of the least hindered dimethyl methanephosphonate and lithium hexamethyldisilazane (LiHMDS) as a base leads to the highest diastereoisomeric ratio (10.3:1 for **2e**).



(1)



(2)

The major diastereoisomer of *N*-sulfinylaminophosphonate (+)-**2e** was isolated by flash chromatography on silica gel ($CHCl_3$:acetone, 3:1) in 52% yield.† It was subsequently converted to β-aminophosphonate (−)-**3a** by trifluoroacetic acid catalysed methanolysis[22] in 66% yield resulting in a selective deprotection of the amino group.‡ The phosphonate (+)-**2e** was converted to (+)-β-amino-β-phenylethanephosphonic acid **4** by heating under reflux for 7 h in a mixture of glacial acetic acid and hydrochloric acid (36% aq.).[23] After usual work-up (evaporation, addition of ethanol and methyloxirane, and filtration) the crude phosphonic acid (+)-**4** was crystallized from ethanol–water; mp 308–310° (decomp.), yield 78%. The chirality at the β-carbon atom in (+)-**4** was established as (*R*) by single crystal X-ray analysis.§ Fig. 1 shows the corresponding ORTEP drawing with the appropriate atom numbering. Since in the conversion of (+)-**2e** to (−)-**3e** and (+)-(*R*)-**4** the bonds around the chiral β-carbon atom are not broken, it is possible to assign the (S_S,R_C)-configuration to the major diastereoisomer (+)-**2e** and the (*R*)-configuration to the β-aminophosphonate (−)-**3e** as depicted in Scheme 1.

Finally, the preferential formation of the diastereoisomeric adduct (+)-**2e** with the S_RR_C-configuration may be rationalized by assuming that the nucleophilic attack of α-phosphonate carbanion on the *s-cis* conformation (S = O and C = N *syn* coplanar) of the sulfinimine **1a** as a reactive conformation¶

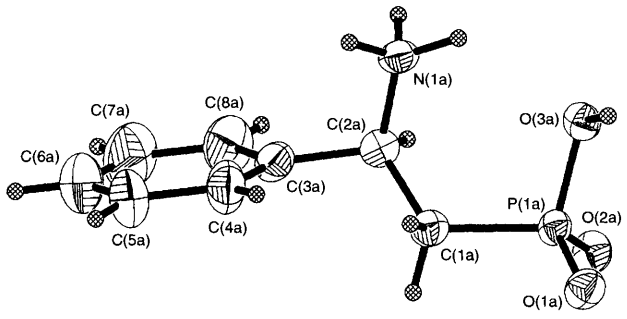
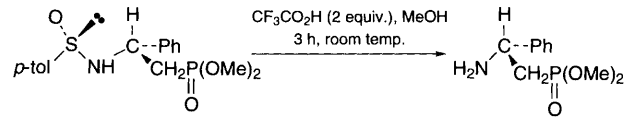
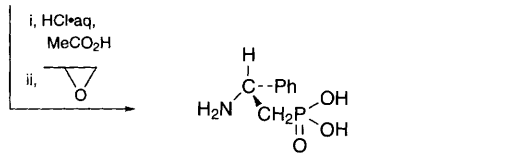


Fig. 1 ORTEP view of the β-aminophosphonic acid (+)-**4**



(+)-(S_S,R_C)-**2e**, δ_P 30.39 ($CDCl_3$) (−)-(*R*)-**3e**, δ_P 32.50 ($CDCl_3$)

$[\alpha]_D^{22}$ + 17.65 (*c* 2.0, $CHCl_3$) $[\alpha]_D^{22}$ − 18.18 (*c* 1.2, $CHCl_3$)



(+)-(*R*)-**4**, δ_P 22.10 (D_2O)

$[\alpha]_D^{22}$ + 15.64 (*c* 1.24, 1 mol dm^{-3} NaOH))

Scheme 1

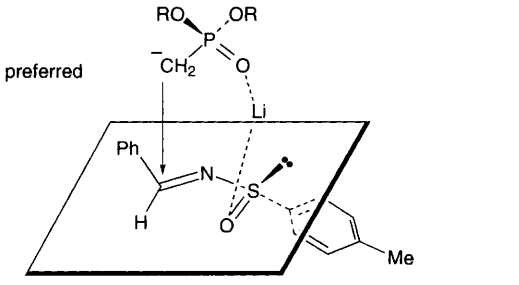


Fig. 2 The proposed transition state for the preferred α-phosphonate carbanion addition to (+)-(*S*)-sulfinimine **1a**

takes place from the least hindered π-face (*i.e. anti* to the *p*-tolyl group at sulfur) (see Fig. 2).

Footnotes

† Starting from the sulfinimine (−)-(*R*)-**1a** the diastereoisomer (−)-**2e**, $[\alpha]_D^{22}$ −17.08 (*c* 1.2, $CHCl_3$), was obtained in a similar way and converted to the aminophosphonic acid (−)-**4**, $[\alpha]_D^{22}$ −16.05 (*c* 1.04, 1 mol dm^{-3} NaOH).

‡ The isolated, major diastereoisomers **2a** {$[\alpha]_D^{22}$ +17.43 (*c* 3.0, $CHCl_3$)} and **2f** {$[\alpha]_D^{22}$ +18.82 (*c* 0.66, $CHCl_3$)} were also converted into β-aminophosphonates **3a** {$[\alpha]_D^{22}$ −18.80 (*c* 1.25, $CHCl_3$), δ_P 29.82, yield 58%} and **3f** {$[\alpha]_D^{22}$ −15.30 (*c* 1.13, $CHCl_3$), δ_P 27.91, yield 64%}, respectively.

§ *Crystal data* for (+)-**4**; $C_8H_{12}NO_3P$, M_r = 201.16, *a* = 6.256(2), *b* = 10.379(1), *c* = 28.786(5) Å, *V* = 1869.0(7) $Å^3$, orthorombic, space group $P2_12_12_1$, *Z* = 8, D_c = 1.430(2) gcm^{-3}, (Cu-Kα) = 24.4 cm^{-1}. Data collection: scan mode ω/2θ; scan width (°) 0.74 ± 0.14 tanθ; intensity correction min, max, av: 1.00 003, 1.02 655, 1.01 284; absorption correction min, max, av: 0.8750, 0.9984, 0.9599; transmission min, max, av: 76.56, 99.88, 92.13; measured reflections (2θ max 150°) 4371, independent reflections 3852, observed reflections ($I \geqslant 3\sigma(I)$] 3799. Crystal and molecular structure of (+)-**4** was determined using data collected at room temperature on a CAD4 diffractometer. Lattice constants were refined by least-squares fit of 25 reflections in θ range 23.7–32.8°. The decline in intensities of three standard reflections (2,2-11; 1,5,-7; 3,-2,-4) was 5.1% during 41.2 h. Intensity data were corrected by DECAY program. An empirical absorption was applied using the Ψ-scan method. A total of 3799 observed reflections were used to solve the structure by direct methods and to refine it by full matrix least-squares using *F*'s. Hydrogen atoms were found in a difference Fourier map (except phenyl hydrogens which were placed geometrically at idealized positions) and refined isotropically. Anisotropic thermal parameters were refined for all nonhydrogen atoms. The final refinement converged to R = 0.0512. The absolute structure of (+)-**4** was determined by three methods: the Rogers η-test, the Hamilton test and calculation of the Flack parameter *x*. Results: Rogers' method: η = 0.98(5), η_{inv} = −0.98(5); Hamilton test: R_{ratio} = 1.0773, *N* = 3538, then probability of opposite (inv) configuration $\alpha \leqslant 10^{-6}$; Flack parameter *x* = 0.02(3). Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/81.

¶ A similar *s-cis* conformation of vinyl sulfoxides has been assumed by Koizumi[24] in the addition reactions of nuclophilic reagents to the carbon–carbon double bond.

References

1 P. Kafarski and P. Mastalerz, in *Beiträge zur Wirkstofforschung*, ed. P. Oehme, H. Löwe and E. Gores, J. Axt, Inst. f. Wirkstofforschung, Berlin, vol. 21.
2 B. Dhawan and D. Redmore, *Phosphorus and Sulfur*, 1987, **32**, 119.
3 P. Kafarski and B. Lejczak, *Phosphorus, Sulfur and Silicon*, 1991, **63**, 193.
4 V. P. Kukhar, V. A. Soloshonok and V. A. Solodenko, *Phosphorus, Sulfur and Silicon*, 1994, **92**, 239.
5 J. A. Colanduomi and J. J. Villafranca, *Biorg. Chem.*, 1986, **14**, 163.
6 F. Schwerdtle, H. Bieringer and M. Finke, *Z. Pflanzenkr., Pflanzenschutz*, 1981, **9**, 431.
7 D. T. Monaghan, R. J. Bridges and C. W. Cotman, *Ann. Rev. Pharmacol. Toxicol.*, 1989, **29**, 365.
8 L. Maier, *Phosphorus, Sulfur and Silicon*, 1983, **14**, 295.
9 J. F. Koerner and C. W. Cotman, *Brain Res.*, 1981, **216**, 192.
10 R. H. Evans, A. A. Francis, A. W. Jones, D. A. S. Smith and J. W. Wathius, *Br. J. Pharmacol.*, 1982, **75**, 65.
11 G. Richtarski, M. Soroka, P. Mastalerz and H. Starzewski, *Rocz. Chem.*, 1975, **49**, 2001; *Chem. Abstr.*, 1976, **85**, 5776
12 J. M. Varlet, N. Collignon and P. Savignac, *Tetrahedron*, 1981, **37**, 3713.
13 L. Maier, *Phosphorus, Sulfur and Silicon*, 1990, **53**, 43; 1991, **62**, 15.
14 L. Maier and P. J. Diel, *Phosphorus, Sulfur and Silicon*, 1995, **107**, 295.
15 J. Nieschalk, A. S. Batsanov, D. O'Hagan and J. A. K. Howard, *Tetrahedron*, 1996, **52**, 165.
16 T. Oshikawa and M. Yamashita, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 2728.
17 F. Sauveur, N. Collignon, A. Guy and P. Savignac, *Phosphorus and Sulfur*, 1983, **14**, 341.
18 J. M. Villaneuva, N. Collignon, A. Guy and P. Savignac, *Tetrahedron*, 1983, **39**, 1299.
19 V. A. Soloshonok, Y. N. Belokon, N. A. Kuzmina, V. I. Maleev, N. Y. Svistunova, V. A. Solodenko and V. P. Kukhar, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1525.
20 S. Hanessian, Y. L. Bennani and Y. Herve, *Synlett*, 1993, 35.
21 F. A. Davis, R. E. Reddy, J. M. Szewczyk and P. S. Portonowo, *Tetrahedron Lett.*, 1993, **34**, 6229.
22 M. Mikołajczyk, J. Drabowicz and B. Bujnicki, *J. Chem. Soc., Chem. Commun.*, 1976, 568.
23 J. R. Chambers and A. I. Isbell, *J. Org. Chem.*, 1964, **29**, 832.
24 T. Koizumi, Y. Arai and H. Takayama, *Tetrahedron Lett.*, 1987, **28**, 3689.

Received, 12th March 1996; Com. 6/01734G