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TETRAHEDRON: *ASYMMETRY*

A straightforward entry into enantiomerically enriched β-amino-α-hydroxyphosphonic acid derivatives

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Abstract

The asymmetric aminohydroxylation (AA) reaction of β-substituted vinylphosphonates under Sharpless protocol followed by hydrolysis afforded β-amino-α-hydroxyphosphonic acids in moderate to good ee.

Recent trends in the development of chemotherapeutic agents utilize pseudopeptide transition state analogues of the substrate cleavage sites as effective inhibitors. The phosphonic isosteres (e.g, β-amino-α-hydroxyphosphonic acids) have been shown to be an effective insert for the preparation of potent inhibitors of renin[1] and HIV-protease.[2] For the evaluation of the biological activity as well as for structure–activity relationship (SAR) studies there is a need to develop new synthetic protocols for chiral non-racemic β-amino-α-hydroxyphosphonic acids. To date, the preparation methods for these enantiomerically enriched compounds have been limited to the addition of phosphites to N-protected aminoaldehydes under different reaction conditions (base, solvent, Lewis acid catalysis).[1–3]

As part of a program directed to the synthesis of aminophosphonic acids, we envisioned a Sharpless asymmetric aminohydroxylation (AA)[4] of dialkyl α,β-unsaturated phosphonates to provide straightforward access to optically active β-amino-α-hydroxyphosphonic acid derivatives. Although both AA and asymmetric dihydroxylation (AD)[5] of α,β-unsaturated carbonyls have been thoroughly investigated with a great deal of success, the study of their phosphonated analogues still remains undeveloped. Only recently, was the AD reaction applied to dialkyl vinylphosphonates to give the corresponding α,β-dihydroxy derivatives in modest to good ee. These intermediates were further elaborated to either α-heteroatom-substituted phosphonates[6] or *erythro*-hydroxyaminophosphonates *via* ring opening of the corresponding cyclic sulfites.[7]

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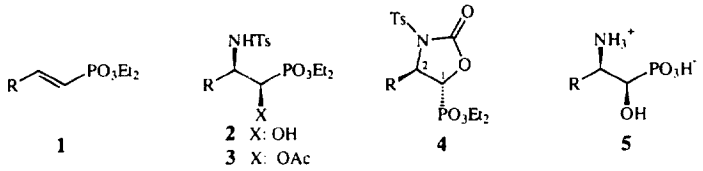

1 2 X: OH 3 X: OAc 4 5

a R = Ph; **b** R = 4-Br-Ph; **c** R = 4-(NO_2)Ph; **d** R = 4-(MeO)Ph; **e** R = H

For the initial investigations into the AA reaction we employed dihydroquinidine 1,4-phthalazinediyl diether $(DHQD)_2$-PHAL as the asymmetric inductor and reaction accelerator, however, as already highlighted by Sharpless,[4] the use of the *pseudo*-enantiomeric ligand $(DHQ)_2$-PHAL would direct the addition of the reagent to the opposite α-face of the double bond, giving rise to *ent*-**2**, through complementary discrimination of the C=C enantiotopic face.

Following the procedure of Mikolajczyk et al.[8] the required diethyl (*E*)-styryl-phosphonates **1a–d** were prepared in good yields (80–90%) by the Wadsworth–Emmons–Horner olefination protocol on aromatic aldehydes with tetraethyl methylene diphosphonate. Thus, **1a–d** and commercially available **1e** were submitted to the AA reaction with potassium osmate(VI) dihydrate $K_2OsO_2(OH)_4$ (4% mol) as the catalyst, chloramine-T hydrate (3 equiv.), $(DHQD)_2$-PHAL (5% mol) in *t*-BuOH:H_2O (1:1, v/v) at room temperature. The reactions required about 2–24 h to reach >95% conversion and gave the β-amino-α-hydroxy derivatives **2a–e** with no detectable amounts of the regioisomer (^1H and ^{13}C NMR). The *threo* assignment to **2** stemmed from a combination of coupling constants and NOE experiments on the oxazolidin-2-one derivatives **4** easily obtained by exposure of **2** to *N*,*N*′-carbonyldiimidazole (CDI) in the presence of catalyst DABCO. Relevantly, for **4d** (R: *p*-anisyl), the NOE experiment showed that a selective irradiation of H-1 (4.49 ppm; d, $^3J_{H-H}$=3.7 Hz) produced a 5% enhancement of the two-proton doublet ($^3J_{H-H}$=8.6 Hz) at 7.18 ppm arising from *ortho*-hydrogens H-2′/H-6′ in the *p*-methoxyphenyl moiety. The dihedral angle between H-1 and the vicinal methine H-2 must approach 130° to accomodate both coupling constants (3.7 Hz) and the lack of a measurable NOE between them. H-2, in turn, displayed a large vicinal C–P coupling constant (16.7 Hz) strongly suggesting a *trans*-relative stereochemistry.[9,10] Molecular modeling studies generating minimum energy structures with the NOE constraints described above, gave rise to the predicted J-values that agree with the actual experimental values.

Although the absolute stereochemistry was not assessed, it seems reasonable to speculate that $(DHQD)_2$-PHAL should direct, as in the case of α,β-unsaturated esters, the addition to the β-face of **1a–d** (*re*, *si* approach) giving rise to a (1*R*,2*S*)-*threo*-configuration.[11] Thus, the AA reaction on styrylphosphonate **1a** afforded **2a**[12] in 65% isolated yield with an ee of 60%, from which material of high enantiomeric excess (>95%) could be obtained after two recrystallizations from *i*-Pr_2O–CH_2Cl_2. Finally, these compounds could be hydrolysed in excellent yields to the corresponding β-amino-α-hydroxyphosphonic acids **5** [HBr (5.7 M solution in AcOH) at 75°C in the presence of phenol as a scavenger of bromine,[4b] followed by neutralisation with propylene oxide]. Interestingly, **5a** (available in 61% overall yield) represents the *ent*-isostere[13] of (2*R*,3*S*)-3-phenylisoserine, a precursor of the side chains of the promising anticancer agents paclitaxel (Taxol®) and docetaxel (Taxotere®). The side chain has been determined to be crucial for biological activity, and our isostere **5a** could further contribute to SAR studies directed to the elucidation of the paclitaxel pharmacophore.[14]

The results are summarized in Table 1 and indicate that a double bond having an electron-withdrawing group on the aromatic system gave the highest ee. As previously recorded by Yokomatsu et al.,[6] the lack of the aromatic moiety in the α,β-unsaturated phosphonate seems to have a detrimental effect on the ee making this procedure unappealing for the synthesis of some optically active β-amino-α-hydroxyphosphonates. Access to the β-aminophosphonic acid analogues by standard deoxygena-

Table 1
AA reaction of the phosphonates **2a–e**

Compound	Yield (%)[a]	ee (%)[b]
2a	65	60
2b	71	75
2c	75	92
2d	72	45
2e	55	15

a) Isolated yield, after chromatographic purification.
b) Determined by ^{1}H-NMR analysis of the corresponding acetoxy derivatives **3** in the presence of Eu(hfc)$_3$

tion protocols could also be envisaged,[15] thereby expanding the entries to enantiomerically enriched aminophosphonic acids.

Further work is in progress to elucidate the role played by the phosphonic moiety on the enantioselectivity of the AA reaction with the aim of improving the enantiomeric excess in the case of β-alkyl substituted vinylphosphonates.[16]

1. General procedure of the AA reaction

To a solution of $(DHQD)_2$-PHAL (0.05 mmol, 3.5 mol%) and chloramine-T hydrate (3.15 mmol) in *t*-BuOH:H_2O 1:1 (20 ml) the appropriate vinylphosphonate **1a–e** (0.72 mmol) and potassium osmate dihydrate (0.035 mmol, 2.4 mol%), were added in that order at room temperature under stirring. The colour of the mixture changed from yellow to green in 10 min, and then turned back to yellow in a time varying from 90 min to 2 h. The remainder of chloramine-T hydrate (1.25 mmol) and vinyl phosphonate (0.72 mmol) **1a–e** was added and stirring was continued at room temperature until TLC ($CHCl_3$:MeOH=49:1) indicated consumption of starting material (2–24 h). *t*-BuOH was then evaporated under vacuum and the mixture was quenched with sodium sulfite (0.45 g). After stirring for 10 min, dichloromethane (10 ml) was added, the organic layers were separated and the aqueous layer was exhaustively extracted with dichloromethane (2×10 ml). The combined organic extracts were dried over sodium sulphate and concentrated to yield the crude product. Purification by flash silica gel chromatography (chloroform:methanol=99:1 or ethyl acetate) afforded the tosylamido-derivatives **2a–e** as colorless solids. The yields reported in Table 1 refer to pure compounds after silica gel chromatography.

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12. Selected data: **2a**: m.p. 119°C (*i*Pr_2O–CH_2Cl_2); ^{1}H-NMR (DMSO-d_6/D_2O, 200 MHz) δ 7.37 d [2H] (^{3}J=8.2 Hz), 7.09–7.04 m [7H], 4.55 dd [1H] ($^3J_1$=$^3J_2$=5.8 Hz), 4.05–3.62 m [5H], 2.24 s [3H], 1.13 t [3H] (^{3}J=7.0 Hz), 1.01 t [3H] (^{3}J=7.0 Hz); ^{13}C-NMR (DMSO–d_6/D_2O, 50.3 MHz) δ 142.0 (C), 138.5 (C), 128.9 (CH), 127.6 (CH), 126.9 (C), 126.6 (CH), 70.5 (CH, $^1J_{C-P}$=163.7 Hz), 62.3 (CH_2, $^2J_{C-P}$=6.6 Hz), 61.4 (CH_2, $^2J_{C-P}$=6.5 Hz), 58.9 (CH, $^2J_{C-P}$=5.3 Hz), 20.9 (CH_3), 16.3 (CH_3, $^3J_{C-P}$=4.9 Hz), 16.1 (CH_3, $^3J_{C-P}$=4.9 Hz); elem. anal.: C 53.11%, H 6.29%, N 3.19%; calc. for $C_{19}H_{26}NO_6PS$: C 53.39%, H 6.13%, N 3.28%. **5a**: M.p. 261°C (dec.) (EtOH–H_2O); ^{1}H-NMR (D_2O, 200 MHz) δ 7.31 m [5H], 4.50 dd [1H] (J_1=4.4 Hz, J_2=1.7 Hz), 3.73 dd [1H] (J_1=9.4 Hz, J_2=1.7 Hz); ^{13}C-NMR (D_2O, 50.3 MHz) δ 138.2 (C, $^3J_{C-P}$=12.0 Hz), 131.4 (CH), 131.1 (CH), 129.0 (CH), 72.3 (CH, $^2J_{C-P}$=140.6 Hz), 58.2 (CH); elem. anal.: C 44.38%, H 5.71%, N 6.27%; calc. for $C_8H_{12}NO_4P$: C 44.25%, H 5.57%, N 6.45%.
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