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Enantioselective Synthesis of *threo*-α,β-Dihydroxyphosphonates by Asymmetric Dihydroxylation of Vinylphosphonates. An Application to the Stereocontrolled Synthesis of (4*S*,5*S*)-4-Diethylphosphono-5-hydroxymethyl-2,2-dimethyl-1,3-dioxolane

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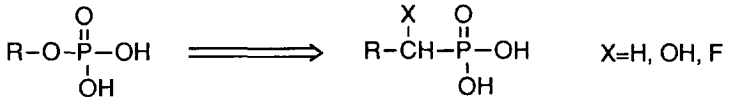
Abstract: The asymmetric dihydroxylation (AD) reaction of vinylphosphonates with AD-mix-α and -β reagents was successfully applied to the enantioselective synthesis of *threo*-α, β-dihydroxyphosphonates. β-Aryl substituents on the vinyl phosphonates were found to be good directors for the reaction with respect to the yield and enantioselectivity. The utility of chiral α, β-dihydroxyphosphonate **2c** was illustrated by the stereocontrolled synthesis of (4*S*,5*S*)-4-diethylphosphono-2,2-dimethyl-5-hydroxymethyl-1,3-dioxolane **6**, a potentially useful chiron for asymmetric synthesis of α-heteroatom-substituted phosphonates.

The transformations of phosphate biomolecules to the phosphonate isosteres by replacement of the labile ester oxygen with a methylene group is one of the most interesting subjects in medicinal chemistry to elucidate their antimetabolite activities (Fig. 1).[1] A number of phosphonate analogues of phosphate biomolecules are known to show the expected activities.[1] Introductions of an additional functional group such as hydroxy- and fluoro substituents at the α-position of the phosphonates are sometimes required to achieve sufficient biological activities[2] (Fig. 1). While the stereochemistry at α-position in these substituted phosphonates should be important for the biological activities, little information on the biological effect of the three-dimensional structures is available due to a lack of efficient stereocontrolled methods for the synthesis of α-heteroatom-substituted phosphonates.

Fig. 1



Our interest in this area centers on the development of versatile phosphonic containing chirons for the synthesis of various α-heteroatom-substituted phosphonic acid derivatives which would be of biological interest. The chiral glycol phosphonates **2** would constitute one of the most useful phosphonic chirons for this purpose, if efficient stereoselective syntheses of **2** were available and subsequently transformed to the suitably functionalized and protected forms such as **5** and **6**. Of various strategies for the stereoselective synthesis of **2**,

the catalytic asymmetic dihydroxylation (AD) strategy[3] of vinylphosphonates **1** would be the most desirable and efficient. In this paper we disclose the results on the osmium-catalyzed AD reaction of vinylphosphonates to yield chiral glycol phosphonates of high enantiomeric purity and an application to the synthesis of (4*S*,5*S*)-4-diethylphosphono-2,2-dimethyl-5-hydroxymethyl-1,3-dioxolane **6**, a useful phosphonic chiron for the stereocontrolled synthesis of α-heteroatom-substituted phosphonic acid derivatives.

AD reactions of vinylphosphonates **1a-e**[5] were carried out at 25 °C for 48 h with AD-mix-α or -β reagents[9] under the standard conditions[3] in the presence of additional potassium osmate (0.8 mol %) (Scheme 1). The results are summarized in Table 1. All reactions gave the desired *threo*-α, β-dihydroxyphosphonates **2a-e**[10,11] in modest to good yields.

Scheme 1

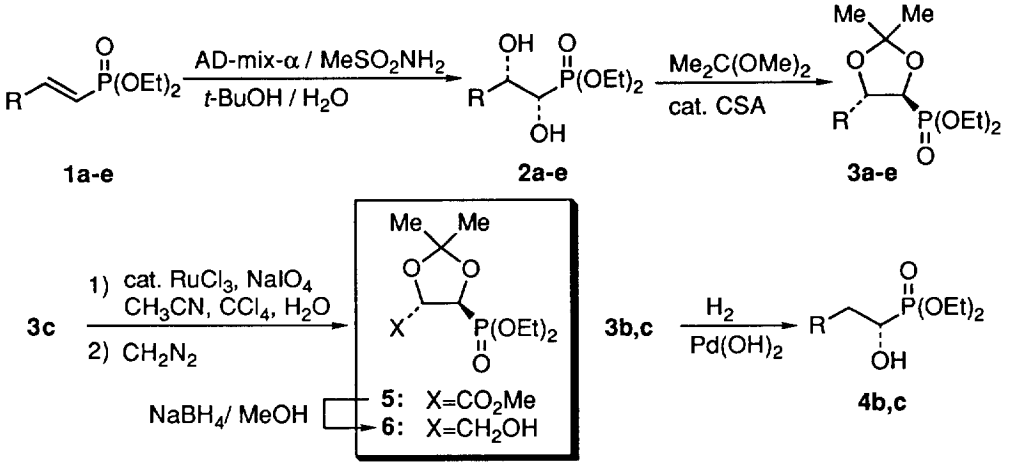


Table 1. AD reaction of vinylphosphonates **1a-e** with AD-mix-α and -β reagents.

Entry	Reagent	R (**2**)[a]	Yield (%)	Ee (%)[b]	$[\alpha]_D$[c]
1	AD-mix-α	Me (**2a**)	48	33	+3.73
2	AD-mix-α	C_6H_5 (**2b**)	42	91	+33.7
3	AD-mix-α	4-$MeOC_6H_4$ (**2c**)	71	>95	+28.8
4	AD-mix-β	4-$MeOC_6H_4$ (*ent*-**2c**)	69	>98	−31.6
5	AD-mix-α	$PhCH_2O(CH_2)_2$ (**2d**)[d]	30	44	−6.55
6	AD-mix-β	*t*-$BuMe_2SiOCH_2$ (*ent*-**2e**)[e]	65	38	−8.25

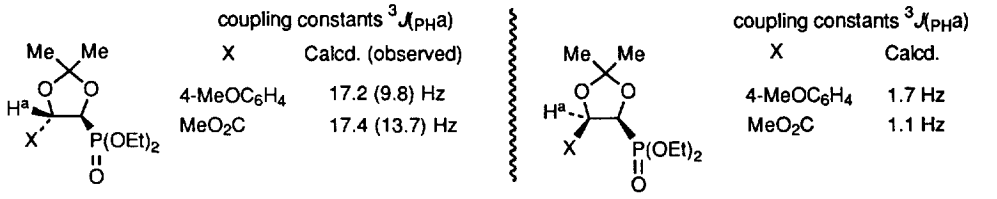
[a] Obtained as oils. [b] Determined by NMR (^1H and/or ^{31}P) analysis of the corresponding bis-MTPA esters derived from (+)- and (-)-MTPA. [c] Measured in MeOH (c 1.0) at 20 °C. [d] Absolute stereochemistry was not determined. [e] Stereochemistry was determined by chemical correlation to **6**.[12]

While the AD reaction of vinylphosphonates **1a**, **1d**, and **1e** possessing alkyl substituens at the β-position proceeded with poor enantioselectivities in modest yields (entries 1, 5, and 6), remarkably high

enantioselectivities (>95% *ee*) were attained from the reactions with β-arylvinylphosphonates **1b, c** (entries 2-4); the *p*-methoxyphenyl group was found to be superior to a phenyl group as a director in terms of enantioselection and chemical yield (entries 2 *vs* 3).

The relative stereochemistry of **2c** was confirmed to be threo after conversion to the acetonides **3a** [2,2-dimethoxypropane, camphorsulfonic acid, benzene]. The dihedral angles between HCCP were measured with the lowest energy conformations of *trans*-**3c** and *cis*-**3c** produced by MOPAC calculations.[13] On the basis of these considerations and the phosphorus version of the Karplus equations,[14] a large vicinal proton-phosphorus coupling constant ($^3J_{PH}$=17.2 Hz) is expected for *trans*-**3c**, while the small coupling constant ($^3J_{PH}$=1.7 Hz) is assumed for *cis*-**3c** (Fig. 2). The close analysis of the ^{1}H-NMR spectrum (300 MHz, $CDCl_3$) of **3c** established the vicinal coupling constants to be 9.8 Hz, strongly suggesting its *trans* relative stereochemistry. Hydrogenolysis of **3b, c** over $Pd(OH)_2$ in MeOH gave α-hydroxyphosphonates **4b**, $[\alpha]_D^{20}$ +21.2 (*c* 0.9, $CHCl_3$), and **4c**, $[\alpha]_D^{20}$ +17.4 (*c* 0.6, $CHCl_3$), respectively. Observed optical rotation of **4b** revealed that it was antipodal to that reported previously.[15] Thus, the absolute stereochemistry of **2c** was unambiguously established as 1*S*, 2*S*.

Fig. 2



Having established an efficient method for the stereoselective synthesis of **2c**, our attention was focussed on its transformations to **5** and **6**, useful phosphonic containing chirons possessing suitable functionalities. Oxidative degradation of the *p*-methoxyphenyl group in **3c** with $RuCl_3$-$NaIO_4$ under the conditions of Martín,[16] followed by esterification with CH_2N_2 gave the methyl ester **5**,[10] $[\alpha]_D^{20}$ –26.2 (*c* 1.0, $CHCl_3$), as an oil in 95% yield. The observed vicinal proton-phosphorus coupling constant ($^3J_{PH}$=13.7 Hz) is consistent with the caluculated one ($^3J_{PH}$=17.4 Hz) for *trans*-**5** (Fig. 2). Treatment of **5** with $NaBH_4$ in MeOH selectively reduced the methyl ester to give alcohol **6**,[10] $[\alpha]_D^{20}$ –15.5 (*c* 1.0, MeOH), in 80% yield.

In conclusion we have developed an efficient method for stereoselective synthesis of phosphonic containing chirons **5** and **6** with practically useful levels of enantiomeric purity by an application of AD-reaction of vinylphosphonates. Further work on utility of **6** in the field of asymmetric synthesis of α-heteroatom-substituted phosphonic bioisosteres of phosphate antimetabolites is in progress in our laboratory.

References and Notes

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5. Vinylphosphonate **1a** was prepared by litrature method.[6] Vinylphosphonates **1b-d** were prepared from the corresponding aldehydes by Horner-Emmons-Wadsworth (HEW) reaction [$(EtO)_2P(O)CH_2P(O)(OEt)_2$ / *n*-BuLi].[7] The silyloxyvinylphosphonates **1e** was synthesized by silylation of corresponding (*E*)-1-(diethylphosphono)-3-hydroxypropene.[8]
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9. Purchased from Aldrich.
10. All new compounds gave satisfactory spectroscopic and analytical data.
2c: an oil; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.34 (2H, d, *J*=6.8 Hz), 6.88 (2H, d, *J*=6.8 Hz), 5.08-5.02 (1H, m), 4.20-4.09 (4H, m), 3.99 (1H, ddd, *J*=3.5, 8.2, 8.2 Hz), 3.94-3.88 (1H, m), 3.79 (3H, s), 3.75-3.67 (1H, m), 1.32 (3H, t, *J*=6.8 Hz), 1.27 (3H, t, *J*=6.8 Hz); ^{31}P-NMR ($CDCl_3$, 160 MHz) δ 22.56; MS *m/z* 340 (M^+); IR (neat) 3344, 1246, 1029 cm^{-1}. **3c**: an oil; $[\alpha]_D^{20}$ +6.87 (*c* 1.0, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.37 (2H, d, *J*=8.8 Hz), 6.89 (2H, d, *J*=8.8 Hz), 5.20 (1H, dd, *J*=9.8, 9.8 Hz), 4.2-4.0 (4H, m), 3.99 (1H, dd, *J*=9.1, 2.4 Hz), 3.80 (3H, s), 1.56 (3H, s), 1.55 (3H, s), 1.24 (3H, t, *J*=7.1 Hz), 1.21 (3H, dd, *J*=7.1 Hz); ^{31}P-NMR ($CDCl_3$, 160 MHz) δ 19.0; MS m/z 329 (M^+-15); IR (neat) 3484, 1250, 1024 cm^{-1}. **5**: an oil; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 4.74 (1H, dd, *J*=13.7, 7.6 Hz), 4.48 (1H, dd, *J*=7.6, 1.2 Hz), 4.3-4.1 (4H, m), 3.81 (3H, s), 1.52 (3H, s), 1.44 (3H, s), 1.35 (3H, t, *J*=7.0 Hz), 1.34 (3H, *J*=7.0 Hz); ^{31}P-NMR ($CDCl_3$, 160 MHz) δ 18.0; MS m/z 297 (M^++1), 281 (M^+-15); IR(neat) 1757, 1256, 1050 cm^{-1}. **6**: an oil; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 4.4-4.3 (1H, m), 4.3-4.15 (4H, m), 4.09 (1H, dd, *J*=9.4, 2.5 Hz), 3.90 (1H, ddd, *J*=12.1, 3.9, 3.7 Hz), 3.74 (1H, ddd, *J*=12.1, 9.0, 3.3 Hz), 2.37 (1H, dd, *J*=9.0, 3.7 Hz), 1.46 (3H, s), 1.44 (3H, s), 1.37 (3H, t, *J*=7.1 Hz), 1.36 (3H, t, *J*=7.1 Hz); ^{31}P-NMR ($CDCl_3$, 160 MHz) δ 19.7; IR (neat) 3407, 1647, 1240, 1024 cm^{-1}.
11. Stereochemistry of **2a** was determined by its comparison with the authentic sample prepared through titanium-mediated threo-selective hydrophosphonylation of (*S*)-α-benzyloxypropionaldehyde, followed by debenzylation: Yokomatsu, T.; Yoshida, Y.; Shibuya, S. *J. Org. Chem.* **1994**, in press.
12. Desilylation of *ent*-**3e** [*n*-Bu_4NF / THF], derived from *ent*-**2e**, gave *ent*-**6**, $[\alpha]_D^{20}$+6.14 (c 1.0, MeOH), in quantitative yield.
13. Calculations were performed by MOPAC v 6.10 (PM 3) implemented in CAChe Worksystem (SONY/Tektronix Corporation) after MM 2 optimization of *trans*-**3c** and *cis*-**3c**.
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