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Enantiospecific Synthesis of 2-Amino-3-methyl-4-phosphonobutanoic Acids *via* 1,4-Addition of Lithiated Schöllkopf Anion to Prop-2-enylphosphonates

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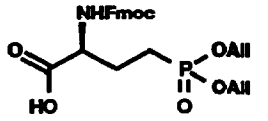
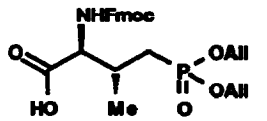
Abstract: High diastereoselectivity in the conjugate addition of lithiated Schöllkopf's bislactim ethers to *E*- and *Z*-prop-2-enylphosphonates was utilized to achieve a direct asymmetric synthesis of all four diastereoisomers of 2-amino-3-methyl-4-phosphonobutanoic acid, *i.e.* (+)-(2*S*, 3*R*)-*4a*, (+)-(2*S*, 3*S*)-*4b* and their corresponding enantiomers. Their relative configuration was definitively assigned from an NMR study of oxaphosphinane derivatives of both diastereoisomers.

Conjugate additions of organometallic reagents to α,β-unsaturated carbonyl compounds constitute a powerful method which has found extensive use in stereospecific synthesis.[1] In contrast, analogous 1,4-addition reactions to α,β-unsatured phosphoryl compounds have received little attention.[2] We have recently reported the synthesis of *N*-Fmoc-*O,O*-diallyl protected phosphonic acid analogues of phosphoserine (*1a*, *Fmoc-Abu[PO(OAll)$_2$]-OH*), *via* the coupling of the Schöllkopf anion *(-)-2* with a bromoethylphosphonate. The unusually high diasterofacial selectivity in the coupling was attributed to a reaction mechanism involving conjugate addition to a vinylphosphonate generated *in situ*.[3]



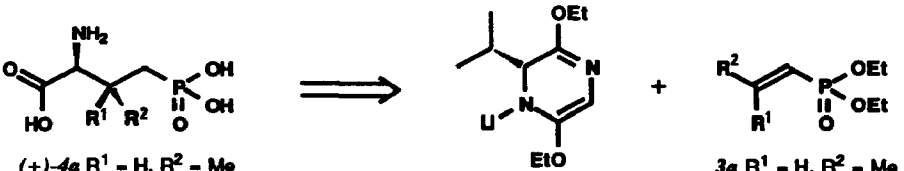
1a L-Fmoc-Abu[PO(OAll)$_2$]-OH



1b L-Fmoc-Ambu[PO(OAll)$_2$]-OH

Figure 1

As part of a study directed toward the synthesis of the *N*-Fmoc-*O,O*-diallyl protected phosphonic acid analogues of phosphothreonine (*1b*, *Fmoc-Ambu[PO(OAll)$_2$]-OH*) we decided to investigate the conjugate addition of *2* to prop-2-enylphosphonates *3*. This communication presents the first enantiospecific synthesis of all four diastereoisomers of 2-amino-3-methyl-4-phosphonobutanoic acid,[4] (+)-(2*S*, 3*R*)-*4a*, (+)-(2*S*, 3*S*)-*4b* and their enantiomers, by using a highly face-selective addition of the lithium salt of Schöllkopf's bislactim ether *(+)-2* or *(-)-2* to *E*- and *Z*-prop-2-enylphosphonates (*3a* and *3b*, respectively).

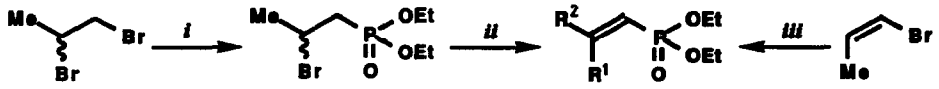


(+)-*4a* R^1 = H, R^2 = Me
(+)-*4b* R^1 = Me, R^2 = H

(-)-2

3a R^1 = H, R^2 = Me
3b R^1 = Me, R^2 = H

Scheme 1



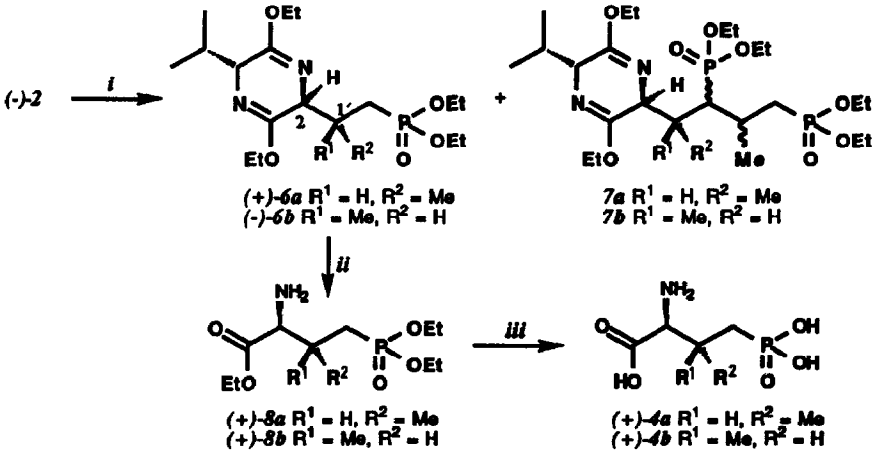
5

3a R^1 = H, R^2 = Me
3b R^1 = Me, R^2 = H

Scheme 2 *i* = $P(OEt)_3$, reflux, 14 h, 70%; *ii* = 1.5 eq DBU, CH_2Cl_2, 0 °C, 1 h, 85%; *iii* = $HPO(OEt)_2$, $[Pd(Ph)_3]_4$, toluene, 90 °C, 3h, 90%.

In spite of reports in the literature,[5] Arbuzov reaction of excess 1,2-dibromopropane with triethylphosphite gave *5* [6] which was readily dehydrobrominated to *3a* (Scheme 2). The *Z-O,O*-diethyl-prop-2-enylphosphonate *3b* was prepared by Pd(0)-catalyzed coupling of *cis*-1-bromo-1-propene and diethylphosphite, as described in the literature.[7]

Schöllkopf described conjugate additions of lithiated bislactim ethers to α,β-unsaturated carboxylic acid esters,[8a] and of the corresponding cuprates to α,β-unsaturated ketones.[8b] These reactions were characterized by exceptionally high (*d.e.*>99%) diastereoselectivity at C-2 of the bislactim ether;[9] however, variable diasteroselectivities at C-1′, the β-carbon of the Michael acceptor, were observed. In the present study we found that the lithium salts of Schöllkopf's bislactim ether *(+)-2* or *(-)-2* rapidly add to both *E* and *Z* vinyl phosphonates (*3a* and *3b* , respectively) with very high asymmetric induction for *both* chiral centers. As in the above Schöllkopf conjugate additions, the diastereoselectivity at C-2 was excellent (*d.e.*> 95) in both cases, and in addition the diastereoselectivity at C-1′ was also good (*d.e.*> 88%).[10] Thus, the slow addition of *3a* to *(-)-2* at -78° C in THF followed by immediate quenching with acetic acid (-78 °C) and aqueous work-up gave a mixture of the Michael adducts *6a:6b* in 94:6 ratio but in a combined yield of only 33% after chromatography. The low chemical yield is due to further capture of the initially formed Michael adduct anion by a second molecule of propenylphosphonate *3a* to give *7a*, a mixture of diastereoisomeric 1:2 addition products. The isolated yield of the 1:1 adducts was improved to 86% simply by using excess (3 equivalents) *(-)-2* thereby suppressing formation of higher adducts. Addition of 3 equivalents of *(-)-2* to *Z*-prop-2-enyl-phosphonate *3b* proceeded with opposite stereoselectivity at C-1′ to give *6a* and *6b* in 5:95 ratio and 84% isolated yield.



(+)-6a R^1 = H, R^2 = Me
(-)-6b R^1 = Me, R^2 = H

7a R^1 = H, R^2 = Me
7b R^1 = Me, R^2 = H

(+)-8a R^1 = H, R^2 = Me
(+)-8b R^1 = Me, R^2 = H

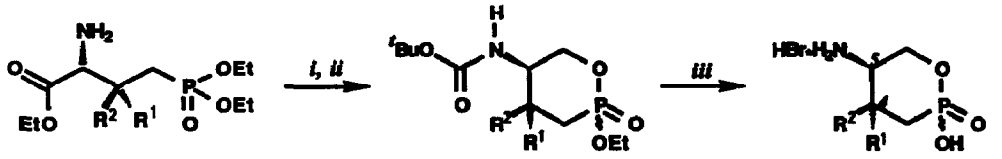
(+)-4a R^1 = H, R^2 = Me
(+)-4b R^1 = Me, R^2 = H

Scheme 3 *i* : *a.* *n*-BuLi, -78°C, THF, 30 min; *b.* *3a* or *3b*, THF, dropwise (*ca* 20 min); *c.* 3 AcOH; 84-86% . *ii* : 2.5 eq HCl 0.25 N, THF/H_2O 1:1, RT 24 h. 95% *iii* : *a.* HCl 12N, reflux, 3 h; *b.* propylene oxide, EtOH, RT 1h. 80-85%

The separation of (+)-*6a* {$[\alpha]_D^{20}$= + 24.2 (CH_2Cl_2, c = 1)} from (-)-*6b* {$[\alpha]_D^{20}$= - 14.6 (CH_2Cl_2, c = 1.1)}could be achieved by medium pressure liquid chromatography (AcOEt-hexane, 1:1, SiO_2 230-400 mesh) to provide products of high purity (d.e. > 98%) on a multigram scale. Mild acid hydrolysis of the bislactim ether provided the aminoesters (+)-*8a* and (+)-*8b* in excellent yield after chromatography (MeOH/AcOEt 10:1 after

removing valine ester with AcOEt). Vigorous acid hydrolysis of these aminoesters followed by treatment of the crude hydrochlorides with propylene oxide and purification by reverse phase flash chromatography [11] afforded the corresponding 2-amino-3-methyl-4-phosphonobutanoic acids (+)-(2*S*, 3*R*)-***4a*** and (+)-(2*S*, 3*S*)-***4b***. Starting from *(+)-2*, the corresponding enantiomers (-)-***4a*** and *(-)-**4b*** were prepared in analogous fashion.[12]

Since none of the compounds ***4-8*** provided crystals suitable for an X-ray crystal structure determination, a cyclic derivative was sought which would enable assignment of the relative configurations of ***4a*** and ***4b*** by ^{1}H NMR spectroscopy. The six-membered amino-oxaphosphinane derivatives ***10a,b*** were attractive in this regard because of the the strong preference for chair conformation reported for similarly 4-methyl-substituted systems.[13] Chemoselective reduction of the carboxylic ester in the presence of the phosphonic ester was eventually achieved on the *N*-Boc derivatives of (-)-***8a*** and (-)-***8b*** with $LiBH_4$ in anhydrous THF at RT.[14] Under these conditions, cyclization of the reduction intermediates to afford the corresponding *N*-Boc-amino-oxaphosphinane derivatives (+)-***9a*** (70%) and ***9b*** (69%) was observed.



(-)-***8a*** R^1 = H, R^2 = Me
(-)-***8b*** R^1 = Me, R^2 = H

(+)-***9a*** R^1 = H, R^2 = Me
9b R^1 = Me, R^2 = H

(+)-***10a*** R^1 = H, R^2 = Me
(+)-***10b*** R^1 = Me, R^2 = H

Scheme 4

i : 1.2 eq $(BOC)_2O$, 0.8 eq Na_2CO_3, 0.9 eq $NaHCO_3$, dioxane:H_2O 1:1, RT, 3 h, 90-95%;
ii : 1.5 eq $LiBH_4$, THF, RT, 16 h, 70-75%; *iii* : 2.3 eq TMSBr, CH_2Cl_2, RT, 14 h, 80-84%

Compound (+)-***9a*** was obtained as one single diastereoisomer {mp (AcOEt) = 121-124 °C, $[\alpha]_D^{20}$ = + 74.8 (CH_2Cl_2, c = 1)}, while ***9b*** was isolated as a mixture of isomers at the phosphorus center in 2.7:1 ratio which could not be separated by simple chromatography.[15] The Boc and ethyl ester groups of (+)-***9a*** and ***9b*** were cleaved with TMSBr in CH_2Cl_2 to give (+)-***10a*** {$[\alpha]_D^{20}$ = + 35.6 (H_2O, c = 1)} and (+)-***10b*** {mp (H_2O) = > 200 °C (dec.); $[\alpha]_D^{20}$ = + 7.6 (H_2O, c = 0.95)} as pure diastereoisomers. A single chair conformation was observed for each compound ***10*** in the ^{1}H NMR spectra (D_2O, 400 MHz, 25 °C). For compound (+)-***10b*** a triple doublet was observed for H-5 at δ = 3.24 with coupling constants J = 9.1, 3.1 Hz. The coupling constant of 9.1 Hz indicated a diaxial relationship between H-5 and H-4 with degenerate coupling of H-5 to H-6ax. Futhermore, the complete set of NOE cross peaks that were observed by ^{1}H-^{1}H ROESY [16] was consistent with this *trans*-stereochemical assignment (see Fig. 2). The assignment of the *cis*-configuration for diastereoisomer (+)-***10a*** follows by default and is also consistent with the NOEs observed (see Fig. 2). The absolute configuration was then assigned under the assumption that the configuration at C-5 is determined by the configuration of the valine residue in the bislactim ether, as there is ample precedent.

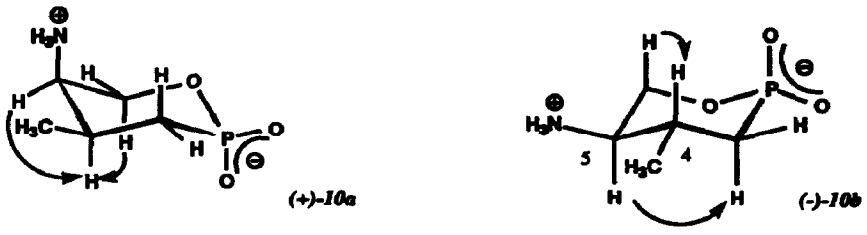


Figure 2. Selected observed NOE's.

The stereochemical course of these conjugate additions to vinyl phosphonates is similar to that previously encountered in the case of α,β–unsaturated carboxylic esters;[8a] thus the selective formation of the Michael adducts (2*S*, 1′*R*)-***6a*** in the reaction of *(-)-2* with the *E*-prop-2-enylphosphonate and (2*S*, 1′*S*)-***6b*** when *(-)-2* reacted with *Z*-prop-2-enylphosphonate can be understood as a consequence of almost exclusive interaction of

the Si-face of *(-)-2* with the *Si*-face of *3a* and the *Re*-face of *3b*. Presumably, lithium chelation and interactions between π-systems, as was suggested by Schöllkopf,[8a] are operating similarly in this case. However, the higher stereoselectivity observed in the present work may be accounted for by the different steric and electronic interactions of the tetrahedral phosphoryl group.

ACKNOWLEDGEMENTS

M.R. and V.O. gratefully acknowledge FEUGA and the EEC for COMMET grants.

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2. Few precedents have been found. See for example: *a.* Minami, T.; Motoyoshiya, J. *Synthesis* **1992**, 333. *b.* Hong, S.; Chang, K.; Ku, B.; Oh, D.Y. *Tetrahedron Lett.* **1989**, *30*, 3307. *c.* Chang, K.; Ku, B.; Oh, D.Y. *Synthetic Communications* **1989**, *19*, 1891. *d.* Minowa, N.; Hirayama, M.; Fukatsu, S. *Tetrahedron Lett.* **1984**, *25*, 1147. *e.* Schanmann, E.; Fittkau, S. *Synthesis* **1983**, 449. *f.* Bodalski, R.; Michalski, T.; Monkiewicz, J.; Pietruskewicz, K.M. *Phosphorus Chemistry* **1981**, 243 and references cited therein.
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5. Arbuzov reaction of triethylphosphite with one equivalent of 1,2-dibromopropane was reported to be completely unsuccessful: Ford-Moore, A.H.; Howarth Williams, J. *J. Chem. Soc.* **1947**, 1465.
6. Using excess of 1,2-dibromopropane (6 equivalents) after 14 h reflux *5* was obtained (70% yield) together with *O,O*-diethyl-ethylphosphonate as a side product (25%). Both products and unreacted 1,2-dibromopropane could be readily separated by distillation at reduced pressure. This provides a more direct synthesis of β-bromophosphonic esters, than that recently reported: Retherford, C.; Chou, T.-S.; Schelkun, R.M.; Knochel, P. *Tetrahedron Lett.* **1990**, *31*, 1833.
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9. See for example: Schöllkopf, U.; Groth, U.; Deng, C. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 798.
10. The *d.e.* in all cases was determined by the relative integrals of appropiate absorptions in the decoupled ^{31}P NMR spectra of the crude reaction mixtures, and confirmed by ^{1}H NMR spectra after removal of excess of *2* and side products by flash chromatography.
11. Chromatography through a short column (Merck LiChroprep RP-18, 40-63 μ) using H_2O as eluent afforded amino acids *4a,b* almost with the solvent front, other impurities being retained.
12. *(+)-(2S, 3R)-4a*: mp (EtOH) = >80 °C (dec.); $[\alpha]_D^{20}$ = + 31.8 (H_2O, c = 1); ^{1}H NMR (D_2O, 360 MHz): 1.17 (1H, d, *J* = 7.2 Hz, CH_3), 1.77 (1H, ddd, *J* = 9.1, 15.0, 18.1 Hz, H-4), 1.82 (1H, ddd, *J* = 6.1, 15.0, 19.2 Hz, H-4), 2.52 (1H, m, H-3), 4.09 (1H, d, *J* = 3.6 Hz, H-2); ^{13}C NMR (D_2O, 90 MHz); 18.7 (d, *J* = 6.4 Hz, CH3), 33.1 (C-3), 33.8 (d, *J* = 128 Hz, C-4), 61.1 (d, *J* = 12.7 Hz, C-2), 174.3 (C-1). *(+)-(2S, 3S)-4b*: mp (EtOH) = >80 °C (dec.); $[\alpha]_D^{20}$ = + 14.2 (H_2O, c = 1); ^{1}H NMR (D_2O, 360 MHz): 1.15 (1H, d, *J* = 7.1 Hz, CH_3), 1.73 (1H, ddd, *J* = 23.1, 15.3, 7.8 Hz, H-4), 1.87 (1H, ddd, *J* = 18.7, 15.3, 6.1 Hz, H-4), 2.60 (1H, m, H-3), 4.08 (1H, d, *J* = 3.4 Hz, H-2); ^{13}C NMR (D_2O, 90 MHz); 18.6 (d, *J* = 7.6 Hz, CH3), 32.9 (C-3), 33.7 (d, *J* = 132 Hz, C-4), 61.2 (d, C-2), 174.7 (C-1).
13. Bergesen, K.; Vikane, T. *Acta Chem. Scand.* **1972**, *26*, 1794.
14. Other attempts to achieve this reduction were unsuccessful. With $LiAlH_4$ in THF complex mixtures of products resulted by simultaneous reduction of the phosphonic ester and epimerization at the α-center. $NaBH_4$ in refluxing MeOH caused transesterification of the carboxylic ester and epimerization at the α-center, while with $CaBH_4$ or DIBAL in THF there was no reaction.
15. Conformational preferences of the substituents in a six-membered cyclic transition state with a trigonal bipyramidal phosphorus atom may account for these results, as it was reported for the related specific ring opening of cyclic phosphonates by alkoxides. See, for example: Thatcher, G.R.J.; Kluger, R. *Adv. Phys. Org. Chem.* **1989**, *25*, 99 and Hall, C.R.; Inch, T.D. *Tetrahedron* **1980**, *36*, 2059.
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