JOC Article

Diastereoselective Synthesis of 2-Amino-4-phosphonobutanoic Acids by Conjugate Addition of Lithiated Schöllkopf's Bislactim Ethers to Vinylphosphonates

María Ruiz,* M. Carmen Fernández,† Aniana Díaz, José M. Quintela, and Vicente Ojea*

Departamento de Química Fundamental, Facultade de Ciencias, Universidade da Coruña, Campus da Zapateira s/n, 15071 A Coruña, Spain

ruizpr@udc.es; ojea@udc.es

Received May 24, 2003

Conjugate additions of lithiated bislactim ethers derived from cyclo-[Gly-Val] and cyclo-[Ala-Val] to α-, *β*-, or α,*β*-substituted vinylphosphonates allow direct and stereoselective access to a variety of 3- or 4-monosubstituted and 2,3-, 2,4-, or 3,4-disubstituted 2-amino-4-phosphonobutanoic acids (AP4 derivatives) in enantiomerically pure form. The relative stereochemistry was assigned by X-ray diffraction analysis or NMR study of 1,2-oxaphosphorinane derivatives. Competitive eight-membered "compact" and "relaxed" transition-state structures are invoked to rationalize the stereochemical outcome of the conjugate additions.

Introduction

As the principal excitatory neurotransmitter in the mammalian central nervous system, (*S*)-glutamic acid plays a pivotal role in the regulation and maintenance of fast synaptic transmission and long-term potentiation/depression. Besides its physiological functions, glutamic acid is involved in a variety of neuropathologies including epilepsy, stroke, nociception, cognitive disorders, and Alzheimer's disease.[1] For many years, glutamate was assumed to operate through specific ion-gated-channel receptors, called ionotropic glutamate receptors.[2] More recently, the G-protein-coupled receptors for glutamate (mGluRs) have been discovered and perceived as valuable therapeutic targets.[3] According to sequence similarity, pharmacological profile, and effector system differences, mGluRs have been classified into three groups. Among the receptors of group III, mGluR4, mGluR7, and mGluR8 are presynaptically localized and inhibit the release of glutamate and *γ*-aminobutyric acid, whereas mGluR6 receptors are exclusively expressed by ON bipolar cells in the retina and play an important role in the amplification of visual imputs. Due to the diversity of receptor subtypes within this class and the paucity in the development of tools for their study, the molecular pharmacology of group III mGluRs is not yet well established. In particular, group III mGluRs are characterized by their selective response to several phosphonic acid isosters of glutamic acid. They are selectively activated by L-2-amino-4-phosphonobutanoic acid (L-AP4, **1**; see Chart 1) and competitively antagonized by α-methylated derivatives of L-AP4 (MAP4, **2**) and 4-phosphonophenylglycine (MPPG, **3**). Therefore, there is considerable interest in the development of practical and versatile asymmetric methodologies for the preparation of AP4 derivatives that may result in useful tools for delineating the requirements for receptor binding[3e] and physiological responses at group III of the mGluRs.

Three major strategies have been devised for the preparation of AP4 derivatives. Phosphites have been utilized for the conjugate addition to carbonyl compounds which were subsequently converted to amino acids via Strecker reaction,[4] or have been reacted with halides,[5] triflates,[6] or carbonyl functionalities[7] located at the side chain of α-amino acid derivatives. Alternative syntheses have relied on glycine enolate equivalents for the alkylation of,[8] 1,3-dipolar cycloaddition to,[9] or conjugate

† Present address: Lilly S.A., Alcobendas, Madrid, Spain.

(1) (a) *CNS Neurotransmitters and Neuromodulators: Glutamate*; Stone, T. W., Ed.; CRC: Boca Raton, FL, 1995. (b) Parthasarathy, H. S., Ed. *Nature* **1999**, *399* (Suppl.), A1−A47.

(2) *The Ionotropic Glutamate Receptors*; Monahan, D. T., Wenthold, R. J., Eds.; Humana: Totowa, NJ, 1997.

(3) (a) De Blasi, A.; Conn, P. J.; Pin, J.-P.; Nicoletti, F. *Trends Pharmacol. Sci.* **2001**, *22*, 114−120. (b) Bräuner-Osborne, H.; Egebjerg, J.; Nielsen, E. O.; Madsen, U.; Krogsgaard-Larsen, P. *J. Med. Chem.* **2000**, *43*, 2609−2645. (c) Schoepp, D. D.; Jane, D. E.; Monn, J. A. *Neuropharmacology* **1999**, *38*, 1431−1476. (d) Pellicciari, R.; Costantino, G. *Curr. Opin. Chem. Biol.* **1999**, *3*, 433−440. (e) Bertrand, H.-O.; Bessis, A.-S.; Pin, J.-P.; Acher, F. C. *J. Med. Chem.* **2002**, *45*, 3171−3183.

(4) Crooks, S. L.; Robinson, M. B.; Koerner, J. F.; Johnson, R. L. *J. Med. Chem.* **1986**, *29*, 1988−1995.

(5) (a) Nair, S. A.; Lee, B.; Hangauer, D. G. *Synthesis* **1995**, 810−814. (b) Ma, D.; Ma, Z.; Jiang, J.; Yang, Z.; Zheng, C. *Tetrahedron: Asymmetry* **1997**, *8*, 889−893.

(6) (a) Berkowitz, D. B.; Eggen, MJ.; Shen, Q.; Shoemaker, R. K. *J. Org. Chem.* **1996**, *61*, 4666−4675. (b) Amori, L.; Costantino, G.; Marinozzi, M.; Pellicciari, R.; Gasparini, F.; Flor, P. J.; Kuhn, R.; Vranesic, I. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1447−1450.

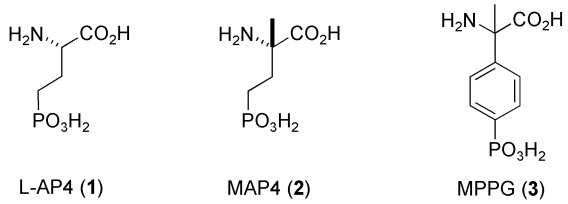
(7) (a) Wiemann, A.; Frank, R.; Tegge, W. *Tetrahedron* **2000**, *56*, 1331−1337. (b) Perich, J. W. *Int. J. Pept. Protein Res.* **1994**, *44*, 288−294.

(8) (a) Soloshonok, V. A.; Belokon, Y. N.; Kuzmina, N. A.; Maleev, V. I.; Svistunova, N. Y.; Solodenko, V. A.; Kukhar, V. P. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1525−1529. (b) Schöllkopf, U.; Busse, U.; Lonsky, R.; Hinrichs, R. *Liebigs Ann. Chem.* **1986**, 2150−2163.

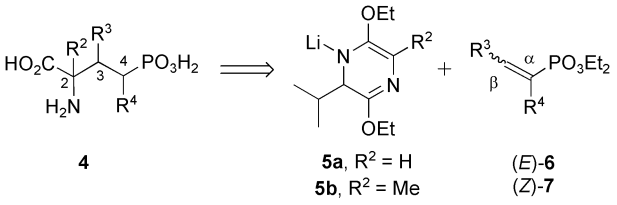
(9) (a) Casas, J.; Grigg, R.; Nájera, C.; Sansano, J. M. *Eur. J. Org. Chem.* **2001**, 1971−1982. (b) Matoba, K.; Yonemoto, H.; Fukui, M.; Yamazaki, T. *Chem. Pharm. Bull.* **1984**, *32*, 3918−3925.

10.1021/jo034707q CCC: $25.00
Published on Web 09/09/2003

CHART 1. Selective Ligands for the mGluRs of Group III



SCHEME 1

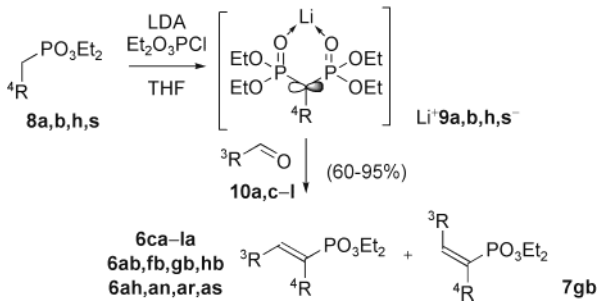


addition to[10] suitable functionalized phosphonates. In this area, we have reported a direct approach to 2-amino-3-methyl-4-phosphonobutanoic acids, in enantiomerically pure form, by using a highly regio- and stereoselective conjugate addition of metalated Schöllkopf's bislactim ethers to 1-propenylphosphonate esters.[11] The high level of π-facial discrimination found in these processes prompted us to explore the scope and limitations of the reactions between lithium azaenolates **5a** and **5b**, derived from cyclo-[Gly-Val] and cyclo-[Ala-Val] (see Scheme 1) and a series of vinylphosphonates **6** and **7**, carrying different functional groups at the α- and/or β-position. Thus, in this paper we report in full detail the application of such a methodology to the synthesis of a variety of enantiomerically pure 3-, 4-, 2,3-, 2,4-, and 3,4-substituted AP4 derivatives **4**, which may be useful for characterizing the molecular pharmacology of the mGluRs of group III.[12]

Results[13]

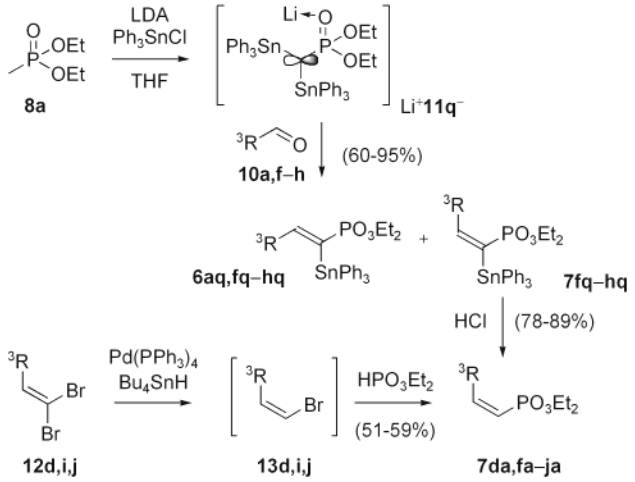
Synthesis of Vinylphosphonates. Representative series of mono- and disubstituted vinylphosphonates were prepared by known procedures, as depicted in Schemes 2−4. Monosubstituted vinylphosphonates **6ca**−**la**, with alkyl, aryl, or heteroaryl groups at the β-position and (*E*)-configuration, were stereoselectively obtained by Wadsworth−Emmons olefination of aldehydes **10c**−**l** with the lithium salt of tetraethyl methylenebisphosphonate, Li$^+$**9a**$^-$,[14] which was generated in situ by treatment of

SCHEME 2[a]



[a] Legend: **a**, R^3, R^4 = H; **b**, R^3, R^4 = Me; **c**, R^3 = Bn; **d**, R^3 = CH_2OBn; **e**, R^3 = CH_2NHCbz; **f**, R^3 = *i*-Bu; **g**, R^3 = *i*-Pr; **h**, R^3, R^4 = Ph; **i**, R^3 = 3-C_5H_4N; **j**, R^3 = 2-C_4H_3S; **k**, R^3 = 2-C_4H_3O; **l**, R^3 = *t*-Bu; **n**, R^4 = PO_3Et_2; **r**, R^4 = NMe_2; **s**, R^4 = OBn.

SCHEME 3[a]



[a] Legend: **a**, R^3 = H; **d**, R^3 = CH_2OBn; **f**, R^3 = *i*-Bu; **g**, R^3 = *i*-Pr; **h**, R^3 = Ph; **i**, R^3 = 3-C_5H_4N; **j**, R^3 = 2-C_4H_3S; **q**, R^3 = $SnPh_3$.

methyl phosphonate **8a** with 2 equiv of LDA and diethyl chlorophosphate (see Scheme 2).[15] β-Substituted 1-vinylphosphonates with (*Z*)-configuration, **7da**,**fa**−**ja**, were stereospecifically synthesized by either the acidic cleavage of (*E*)-α-triphenylstannylvinylphosphonates **7fq**−**hq**[16] or the Pd(0)-catalyzed coupling of diethyl phosphite and (*Z*)-1-bromo-1-alkenes[17] **13d**,**i**,**j** (see Scheme 3). The required α-stannylvinylphosphonates were obtained by condensation of isovaleraldehyde (**10f**), isobutyraldehyde (**10g**), and benzaldehyde (**10h**) with α-bis(triphenylstan-

(10) (a) Shapiro, G.; Buechler, D.; Ojea, V.; Pombo-Villar, E.; Ruiz, M.; Weber, H.-P. *Tetrahedron Lett.* **1993**, *34*, 6255−6258. (b) Minowa, N.; Hirayama, M.; Fukatsu, S. *Tetrahedron Lett.* **1984**, 25, 1147−1150.

(11) Ojea, V.; Ruiz, M.; Shapiro, G.; Pombo-Villar, E. *J. Org. Chem.* **2000**, *65*, 1984−1995.

(12) Part of this work was already presented as preliminary communications: (a) Fernández, M. C.; Quintela, J. M.; Ruiz, M.; Ojea, V. *Tetrahedron: Asymmetry* **2002**, *13*, 233−237. (b) Ruiz, M.; Ojea, V.; Fernández, M. C.; Conde, S.; Díaz, A.; Quintela, J. M. *Synlett* **1999**, 1903−1906. (c) Ojea, V.; Fernández, M. C.; Ruiz, M.; Quintela, J. M. *Tetrahedron Lett.* **1996**, *37*, 5801−5804.

(13) Throughout this paper, vinylphosphonates will be referred to with numerals followed by two letters, to distinguish the identity of their substituents R^3 and R^4, at the β- and α-positions, respectively, while the addition products and their derivatives will be referred to with numerals followed by three letters, to distinguish the identity of the substituents at positions 2−4 of the targeted AP4 derivatives (R^2, R^3, and R^4, respectively).

(14) (a) Aboujaoude, E. E.; Lietjé, S.; Collignon, N.; Teulade, M. P.; Savignac, P. *Tetrahedron Lett.* **1985**, *26*, 4435−4438. (b) Teulade, M. P.; Savignac, P.; Aboujaoude, E. E.; Liétge, S.; Collignon, N. *J. Organomet. Chem.* **1986**, *304*, 283−300. (c) Kiddle, J. J.; Babler, J. H. *J. Org. Chem.* **1993**, *58*, 3572−3574.

(15) For previous syntheses of 2-(3-pyridyl)-, 2-(2-thiophenyl)-, 2-(2-furyl)-, and 2-*tert*-butylvinylphosphonates **6ia**, **6ja**, **6ka**, and **6la** see, respectively: (a) L'vova, S. D.; Kozlov, Yu. P.; Gunar, V. I. *Zh. Obshch. Khim.* **1977**, *47*, 1251−1256. (b) Zyablikova, T. A.; Il'yasov, A. V.; Mukhametzyanova, E. Kh.; Shermergorn, I. M. *Zh. Obshch. Khim.* **1982**, *52*, 287−291. (c) Andreae, S.; Seeboth, H. *J. Prakt. Chem.* **1979**, *321*, 353−360. (d) Palomo, C.; Aizpurua, J. M.; García, J. M.; Ganboa, I.; Cossío, F. P.; Lecea, B.; López, C. *J. Org. Chem.* **1990**, *55*, 2498−503.

(16) (a) Mimouni, N.; Al Badri, H.; About-Jaudet, E.; Collignon, N. *Synth. Commun.* **1995**, *25*, 1921−1932. (b) Mimouni, N.; About-Jaudet, E.; Collignon, N.; Savignac, P. *Synth. Commun.* **1991**, *21*, 2341−2348.

(17) Hirao, T.; Masunaga, T.; Yamada, N.; Ohshiro, Y.; Agawa, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 909−913.

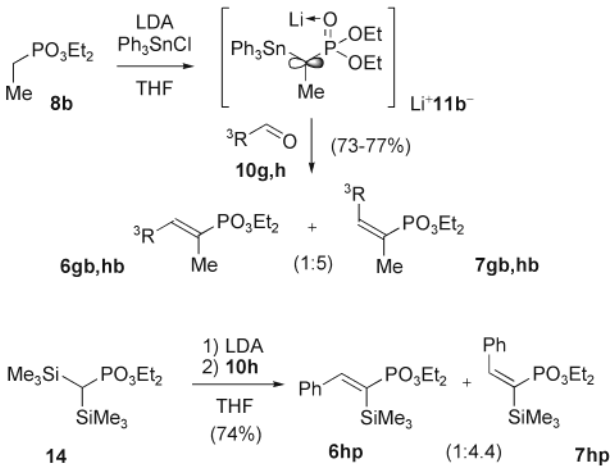
nyl)methylphosphonate carbanion Li$^+$**11q**$^-$, while the (*Z*)-1-bromo-1-alkenes **13d**,**i**,**j** were generated in situ by the Pd(0)-catalyzed hydrogenolysis[18] of 3-benzyloxymethyl, 3-(3-pyridyl)- and 3-(2-thiophenyl)-substituted 1,1-dibromopropenes **12d**,**i**,**j** with tributyltin hydride.

Vinylphosphonates with methyl, phenyl, trimethylsilyl, triphenylstannyl, or benzyloxy groups at the α-position (**6ab**, **6ah**, **6ap**, **6aq**, and **6as**, respectively) were synthesized by an extension of the procedures described above for the *β*-substituted series (see Scheme 2). Thus, treatment of ethyl-, benzyl-, and benzyloxymethylphosphonates **8b**, **8h**, and **8s**, respectively, with 2 equiv of LDA and diethyl chlorophosphate led to the corresponding substituted methylenebisphosphonate lithium salts Li$^+$**9b**$^-$, Li$^+$**9h**$^-$, and Li$^+$**9s**$^-$, which reacted with formaldehyde (**10a**) to afford the α-methyl-,[19a] α-phenyl-,[19b] and α-benzyloxyvinylphosphonates **6ab**, **6ah**, and **6as** in good yields. Sequential treatment of methyl phosphonate **8a** with 3 equiv of LDA, diethyl chlorophosphate, trimethylsilyl chloride, and formaldehyde led to the α-trimethylsilylvinylphosphonate[19c,d] **6ap** (not shown in the schemes). Reaction of α-bis(triphenylstannyl)methylphosphonate carbanion Li$^+$**11q**$^-$ with formaldehyde gave the α-triphenylstannylvinylphosphonate **6aq** (see Scheme 3).

α,*β*-Disubstituted vinylphosphonates were also prepared by Wadsworth−Emmons or Peterson olefinations. Thus, addition of **10g** to the phosphonate carbanion Li$^+$**9b**$^-$, generated in situ from ethylphosphonate **8b**, LDA, and diethyl chlorophosphate, led to a mixture of the (*E*)- and (*Z*)-vinylphosphonates **6gb** and **7gb** in a 5:1 ratio (see Scheme 2). Olefination of **10h** in the same conditions was completely stereoselective, and afforded (*E*)-vinylphosphonate **6hb** in 77% yield. Conversely, sequential treatment of ethylphosphonate **8b** with LDA and triphenylstannyl chloride, followed by the addition of **10g** or **10h**, led to the corresponding *β*-substituted α-methylvinylphosphonates as mixtures of (*E*)-isomers (**6gb** or **6hb**) and (*Z*)-isomers (**7gb** or **7hb**) in a 1:5 ratio (see Scheme 4). Starting with the α,α-bis(trimethylsilyl)-methylphosphonate **14**, reaction with LDA and **10h** afforded a 1:4.4 mixture of the (*E*)- and (*Z*)-α-trimethylsilylvinylphosphonates[19d] **6hp** and **7hp**.

According to ^{31}P NMR analyses, all the *β*-substituted vinylphosphonates were obtained after chromatography with diastereomeric excesses higher than 98%. The configurations of the new *β*-substituted vinylphosphonates **6da**, **6ea**, **7da**, and **7ja** were assigned on the basis of the $^3J_{H-P}$ and the $^3J_{C-P}$ observed in the ^{1}H and ^{13}C NMR spectra. Thus, for **7da**,**fa**−**ja**, $^3J_{H-P}$ (trans) values range from 49.3 to 53.2 Hz and $^3J_{C-P}$ (cis) values range from 7.8 to 10.6 Hz, which are characteristic for the vinylphosphonates with (*Z*)-configuration. Conversely, for

SCHEME 4[a]



[a] Legend: **g**, R^3 = *i*-Pr; **h**, R^3 = Ph.

6ca−**la**, with (*E*)-configuration, $^3J_{H-P}$ (cis) values range from 21.6 to 22.9 and $^3J_{C-P}$ (trans) values range from 19.6 to 25.0.[20]

Additions to the *β*-Substituted Vinylphosphonates. We first examined the additions of Schöllkopf's bislactims derived from cyclo-[L-Val-Gly] and cyclo-[D-Val-d,l-Ala] ((*S*)-**15a** and (*R*)-**15b**, respectively) to the *β*-substituted acceptors. Vinylphosphonates **6ca**−**ka** and **7da**,**fa**−**ja** underwent a stereoselective conjugate addition of lithium azaenolates **5a**,**b**, in a fashion similar to that previously reported for 1-propenylphosphonates,[11] acrylate and cinnamate esters,[21] nitroolefines,[22] and vinyl sulfones.[23] In this manner, slow addition of *n*-BuLi to a solution of bislactim ether (*S*)-**15a** in THF at −78 °C was followed 15 min later by the dropwise addition of the acceptors **6ca**−**ka** or **7da**,**fa**−**ja**. Reactions took place rapidly, and after quenching with acetic acid and aqueous workup, ^{1}H-decoupled ^{31}P NMR analyses of the crude mixtures revealed the formation of mixtures of 1:1 and 1:2 addition products **16**−**18aca**−**aka** and **20aca**−**aka**, respectively (see Scheme 5). In an analogous fashion, slow addition of *β*-phenylvinylphosphonate **6ha** or **7ha** over a solution of 1.2 equiv of the lithium azaenolate (*R*)-**5b** at low temperature led, after quenching and aqueous workup, to mixtures of 1:1 adducts **16bha** and **17bha**, virtually free of 1:2 addition byproducts (according to ^{31}P NMR analysis). Conversely, no reaction was observed under these conditions or with longer reaction times and warming (up to 10 h and 0 °C) when *β*-*tert*-butylvinylphosphonate **6la** was used as the acceptor partner.

The ratio between 1:1 and 1:2 adducts was found to be dependent on the nature of the *β*-substituent of the acceptor. Thus, *β*-alkylvinylphosphonates **6ca**−**ga** and

(18) Uenishi, J.; Kawahama, R.; Yonemitsu, O. *J. Org. Chem.* **1998**, *63*, 8965−8975 and references therein.

(19) For previous syntheses of **6ab**, **6ah**, **6ap**, **22**, and **23** see: (a) Skowronska, A.; Dybowski, P. *Heteroat. Chem.* **1991**, *2*, 55−61. (b) Han, L.-B.; Tanaka, M. *J. Am. Chem. Soc.* **1996**, *118*, 1571−1572. (c) Kouno, R.; Okauchi, T.; Nakamura, M.; Ichikawa, J.; Minami, T. *J. Org. Chem.* **1998**, *63*, 6239−6246. (d) Chang, K.; Ku, B.; Oh, D. Y. *Bull. Korean Chem. Soc.* **1989**, *10*, 320−321. (e) Gerber, J. P.; Modro, T. A.; Wagener, C. C. P.; Zwierzak. *Heteroat. Chem.* **1991**, *2*, 643−649. (f) Yamashita, M.; Morizane, T.; Fujita, K.; Nakatani, K.; Inokawa, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 812−814. (g) **23** was prepared by bromination of 2-hydroxycyclopentylphosphonic acid diethyl ester, which was obtained from 2-diethoxyphosphorylcyclopentanone. See: Koo, L.; Wiemer, D. F. *J. Org. Chem.* **1991**, *56*, 5556−5560.

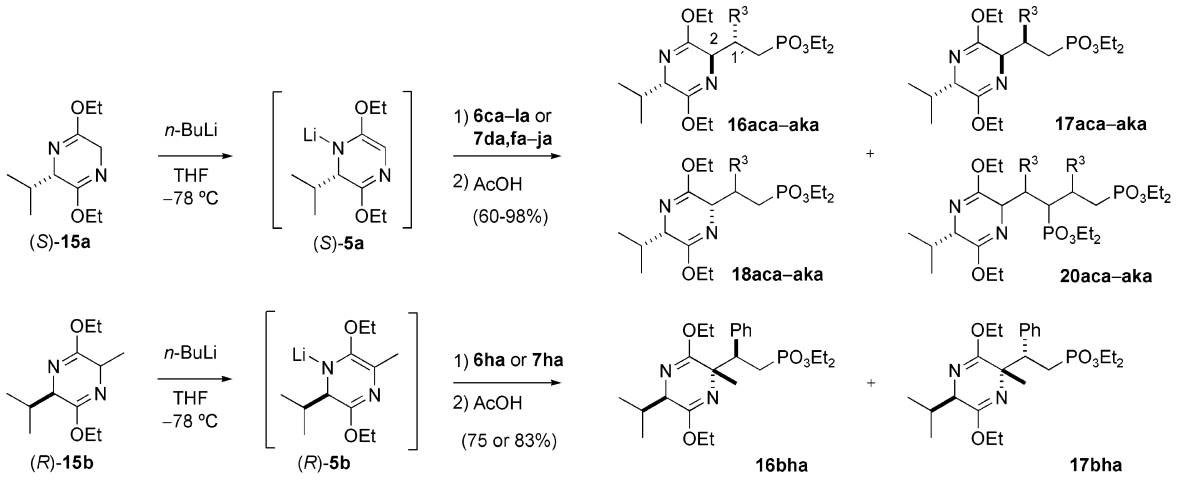
(20) (a) Gorenstein, D. G. *Prog. Nucl. Magn. Reson. Spectrosc.* **1983**, *16*, 1−98. (b) *Phosphorus-31 NMR Spectral Properties in Compound Characterization and Structural Analysis;* Quin, L. D., Verkade, J. G., Eds.; Wiley: New York, 1994.

(21) (a) Jane, D. E.; Chalmers, D. J.; Howard, J. A. K.; Kilpatrick, I. C.; Sunter, D. C.; Thompson, G. A.; Udvarhelyi, P. M.; Wilson, C.; Watkins, J. C. *J. Med. Chem.* **1996**, *39*, 4738−4743. (b) Hartwig, W.; Born, L. *J. Org. Chem.* **1987**, *52*, 4352−4358. (c) Schöllkopf, U.; Pettig, D.; Busse, U.; Egert, E.; Dyrbusch, M. *Synthesis* **1986**, 737−740.

(22) Schöllkopf, U.; Kühnle, W.; Egert, E.; Dyrbusch, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 480−482.

(23) Shapiro, G.; Buechler, D.; Marzi, M.; Schmidt, K.; Gomez-Lor, B. *J. Org. Chem.* **1995**, *60*, 4978−4979.

SCHEME 5[a]



[a] Legend: **c**, R^3 = Bn; **d**, R^3 = CH_2OBn; **e**, R^3 = CH_2NCbz; **f**, R^3 = *i*-Bu; **g**, R^3 = *i*-Pr; **h**, R^3 = Ph; **i**, R^3 = 3-C_5H_4N; **j**, R^3 = 2-C_4H_3S; **k**, R^3 = 2-C_4H_3O.

TABLE 1. Addition of Lithium Azaenolates 5a,b to *β*-Substituted Vinylphosphonates 6aa−la and 7da,fa−ja

				1:1 adducts		
entry	azaenolate (equiv)	acceptor (confign)	R^3	yield[a] (%)	**16**:**17**:**18** ratio[b]	yield[a] of **20** (%)
1	**5a** (1.1)	**6ca** (*E*)	Bn	39	97:2.5:0.5	26
2	**5a** (1.1)	**6da** (*E*)	CH_2OBn	65	99:0.5:0.5	17
3	**5a** (1.1)	**7da** (*Z*)	CH_2OBn	50	8.0:92:0.0	15
4	**5a** (1.1)	**6ea** (*E*)	CH_2NHCbz	63	94:5.2:0.8	21
5	**5a** (1.1)	**6ga** (*E*)	*i*-Pr	43	95:3.5:1.5	41
6	**5a** (1.1)	**6ha** (*E*)	Ph	88	98:0.7:1.3	5
7	**5a** (1.1)	**6ha** (*E*)	Ph	88	72:19:9.0[c]	5
8	**5a** (1.1)	**7ha** (*Z*)	Ph	87	5.0:93:2.0	5
9	**5a** (1.1)	**6ia** (*E*)	3-C_5H_4N	81	97:1.0:2.0	5
10	**5a** (1.1)	**7ia** (*Z*)	3-C_5H_4N	84	3.5:96:0.5	5
11	**5a** (1.1)	**6ja** (*E*)	2-C_4H_3S	92	97:2.0:1.0	4
12	**5a** (1.1)	**6ja** (*E*)	2-C_4H_3S	92	63:20:17[c]	4
13	**5a** (1.1)	**7ja** (*Z*)	2-C_4H_3S	84	2.5:97:0.5	4
14	**5a** (1.1)	**6ka** (*E*)	2-C_4H_3O	85	97:1.0:2.0	4
15	**5a** (1.1)	**6la** (*E*)	*t*-Bu	NR		
16	**5a** (2.2)	**6ca** (*E*)	Bn	55	97:2.5:0.5	16
17	**5a** (2.2)	**6da** (*E*)	CH_2OBn	82	99:0.5:0.5	13
18	**5a** (2.2)	**7da** (*Z*)	CH_2OBn	89	8.0:92:0.0	5
19	**5a** (2.2)	**6ea** (*E*)	CH_2NHCbz	77	94:5.2:0.8	9
20	**5a** (2.2)	**6fa** (*E*)	*i*-Bu	89	97:3.0:0.0	3
21	**5a** (2.2)	**7fa** (*Z*)	*i*-Bu	85	13:86:1.0	4
22	**5a** (2.2)	**6ga** (*E*)	*i*-Pr	61	95:3.5:1.5	23
23	**5a** (2.2)	**7ga** (*Z*)	*i*-Pr	80	18:81:1.0	5
24	**5b** (1.2)	**6ha** (*E*)	Ph	75	97:3.0:0.0	*d*
25	**5b** (1.2)	**6ha** (*E*)	Ph	75	50:50:0.0[c]	*d*
26	**5b** (1.2)	**7ha** (*Z*)	Ph	83	4.0:96:0.0	*d*

[a] Isolated yield of mixtures of adducts, after column chromatography. NR = no reaction was observed. [b] Determined by integration of the ^{31}P NMR spectra of the crude mixtures. [c] Reaction performed at 0 °C instead of −78 °C. [d] No 1:2 addition products were observed in the ^{31}P NMR spectra of the crude mixtures.

7da,**ga**,**ha** (with benzyl, benzyloxymethyl, benzyloxycarbonylaminomethyl, isobutyl, or isopropyl groups) gave rise to mixtures of 1:1 adducts in 39−63% yield, while *β*-arylvinylphosphonates **6ha**−**ka** and **7ha**−**ka** (with phenyl, 3-pyridyl, 2-furyl, or 2-thiophenyl groups) gave the corresponding 1:1 addition products with 80−92% yield (compare entries 1−5 and 6−14 in Table 1). We reasoned that conversion to 1:1 adducts was lowered by further addition of the initially formed adduct anion to the *β*-alkyl-substituted vinylphosphonates. To reduce the dimerization of these acceptors, we carried out the addition process using an excess of azaenolate. By using 2 equiv of the lithium azaenolate (*S*)-**5a**, the yields of the mixtures of 1:1 adducts resulting from the addition to vinylphosphonates **6ca**−**ga** or **7da**,**ga**,**ha** were increased to 61−89%, without modification of the stereoselectivity of the process (see entries 16−23 of Table 1). The excess of Schöllkopf's reagent could be almost completely recovered and showed no racemization.

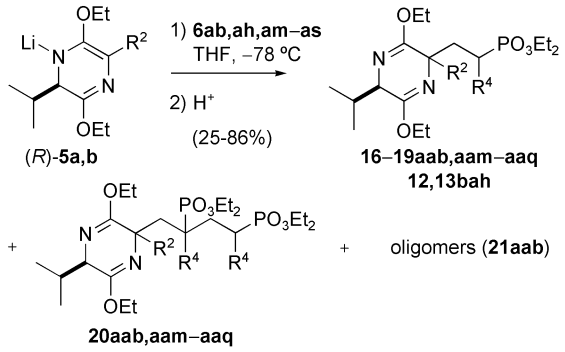
After isolation of the fractions containing the 1:1 adducts by flash chromatography, integration of the ^1H-decoupled ^{31}P NMR spectra (or the pairs of doublets corresponding to the isopropyl groups in the ^1H NMR spectra) revealed a high level of asymmetric induction in the formation of the new chiral centers, as well as complementary stereochemical outcomes in the additions

to vinylphosphonates with (*E*)- and (*Z*)-configuration. Additions of azaenolate (*S*)-**5a** to vinylphosphonates **6ca**−**ka** and **7da**,**fa**−**ja** led to mixtures of isomers **16**/**17**/**18aca**−**aka** with ratios ranging from 99:0.5:0.5 to 2.5:97:0.5, while additions of (*R*)-**5b** to **6ha** and **7ha** resulted in mixtures of adducts **16bha** and **17bha** with 97:3 and 4:96 ratios, respectively. Thus, azaenolates (*S*)-**5a** and (*R*)-**5b** underwent highly 2,5-trans-selective conjugate additions to the *β*-substituted vinylphosphonates, in which the (*E*)- or (*Z*)-configuration of the acceptor was predominantly translated into adducts with 2,1′-anti or 2,1′-syn configuration. In this manner, the observed diastereomeric ratios of the major adducts, the 2,5-trans-2,1′-anti isomers **16aca**−**aka**,**bha** in the additions to **6ca**−**ka** and the 2,5-trans-2,1′-syn isomers **17ada**,**afa**−**aha**,**bha** in the additions to **7da**,**fa**−**ha**, ranged from 93% to 99% and from 81% to 97%, respectively. The correlation between azaenolate and acceptor geometries was found to be weaker with the (*Z*) acceptors, particularly with the *β*-alkyl-substituted ones (compare entries 17 and 18, 20 and 21, and 22 and 23 of Table 1). Product distribution of the conjugate addition was found to be markedly dependent on the reaction temperature. When the addition of azaenolate (*S*)-**5a** to vinylphosphonate **6ha** or **6ja** was performed at 0 °C, the mixtures of 1:1 adducts were obtained in similar yields but containing the isomers **16**/**17**/**18aha**,**aja** in 72:19:9.0 and 63:20:17 ratios, respectively (see entries 7 and 12). Also, addition of azaenolate (*R*)-**5b** to vinylphosphonate **6ha** at 0 °C gave a mixture of adducts **16**/**17bha** with a 1:1 ratio in 75% yield (see entry 25).

Additions to the α-Substituted Vinylphosphonates. Having shown the feasibility of performing stereoselective additions of lithiated bislactims to *β*-substituted vinylphosphonates, we explored the extension of this reactivity to a series of α-substituted vinylphosphonates. Upon addition of vinylphosphonates **6ab**,**ah**,**am**−**aq** to 1 equiv of azaenolate (*R*)-**5a** at −78 °C in THF, reactions took place within 5 min. Conversely, no reaction was observed after 10 h and warming to 0 °C in the case of the vinylphosphonates **6ar** and **6as**, with α-dimethylamino and α-benzyloxy substituents, respectively. After quenching with acetic acid and workup, ^{31}P NMR analysis of the crude mixtures revealed the formation of mixtures of 1:1 and 1:2 adducts in the reactions of **6ah**,**am**−**aq**, and of 1:2 adducts along with oligomerization products in the reaction of **6ab** (see Scheme 6).

Both the ratio between 1:1 and 1:2 adducts and the stereoselectivity of the addition were found markedly dependent on the nature of the α-substituent of the acceptor (see Table 2). Vinylphosphonates **6am** and **6an** with an electron-withdrawing substituent, as the ethoxycarbonyl or the diethoxyphosphoryl group, gave rise to the 1:1 adducts in lower proportion than vinylphosphonates **6ah**,**ao**−**aq** (with phenyl, phosphoryloxy, silyl, or stannyl groups) probably due to the increased electron deficiency and higher acceptor character of the former acceptors. Conversion of the vinylphosphonates **6am** and **6aq** to the desired 1:1 adducts could be increased as above for the *β*-series, simply by using an excess of the lithium azaenolate. Thus, after chromatographic separation the fractions containing the 1:1 adducts **16**−**19aah**,**aam**−**aaq** were isolated in moderate to good yields.

SCHEME 6[a]



[a] Legend: **a**, R^2, R^4 = H; **b**, R^2, R^4 = Me; **h**, R^4 = Ph; **m**, R^4 = CO_2Et; **n**, R^4 = PO_3Et_2; **o**, R^4 = OPO_3Et_2; **p**, R^4 = $SiMe_3$; **q**, R^4 = $SnPh_3$; **r**, R^4 = NMe_2; **s**, R^4 = OBn.

TABLE 2. Additions of Lithium Azaenolates 5a,b to α-Substituted Vinylphosphonates 6ab,ah,am−as

			1:1 adducts			
acceptor	R^4	azaenolate (equiv)	yield[a] (%)	**16**:**17**:**18**:**19** ratio[b]	yield[a] of **20** (%)	yield[a] of **21** (%)[a]
6ab	Me	**5a** (1.1)			42	27
6ah	Ph	**5a** (1.1)	85	1:1:−:−	5	
6ah	Ph	**5a** (1.1)	74	1:1:−:−[c]	5	
6ah	Ph	**5a** (1.1)	89	3:2:−:−[d]	3	
6am	CO_2Et	**5a** (1.2)	25	4:4:3:3	65	
6am	CO_2Et	**5a** (2.2)	56	4:4:3:3	42	
6an	PO_3Et_2	**5a** (1.2)	35	3:2[e]	25	
6ao	OPO_3Et_2	**5a** (1.2)	83	1:1:−:−	8	
6ap	TMS	**5a** (1.2)	72	1:1:−:−	11	
6ap	TMS	**5a** (1.2)	62	3:2:−:−[c]	4	
6aq	$SnPh_3$	**5a** (1.1)	42	1:1:−:−	42	
6aq	$SnPh_3$	**5a** (2.2)	78	1:1:−:−	15	
6ar	NMe_2	**5a** (1.2)	NR			
6as	OBn	**5a** (1.2)	NR			
6ah	Ph	**5b** (1.2)	86	3:1:−:−	*f*	
6ah	Ph	**5b** (1.2)	86	6:1:−:−[c]	*f*	
6ah	Ph	**5b** (1.2)	86	10:7:−:−[g]	*f*	

[a] Isolated yield of mixtures of adducts, after column chromatography. NR = no reaction was observed upon warming to 0 °C. [b] Determined by integration of the ^{31}P NMR spectra of the crude mixtures. [c] 2,4,6-Tri-*tert*-butylphenol as proton source. [d] Cinchone or cinchonidine as proton source. [e] There is no anti/syn isomerism in this case. [f] No 1:2 addition products were observed in the ^{31}P NMR spectra of the crude mixtures. [g] Quenching with acetic acid at rt.

The addition to vinylphosphonates **6ah**,**ao**−**aq** took place in a highly diastereoselective fashion and led, exclusively, to the formation of 2,5-trans adducts **16aah**,**aao**−**aaq** and **17aah**,**aao**−**aaq** (see Figure 1), while acceptors **6am** and **6an** gave rise to mixtures of all the possible 2,5-trans and 2,5-cis adducts **16**−**19aam**,**aap**. The poor trans selectivity observed in the conjugate additions to **6am** and **6an** may derive from the higher reactivity of vinylphosphonates **6am** and **6an**.[24] We reasoned that the formation of 1:1 mixtures of adducts **16**/**17aah**,**aao**−**aaq** should take place with quenching by a nonselective protonation of the phosphonate carbanions arising from the 2,5-trans-selective addition to vinylphosphonates **6ah**,**ao**−**aq**. Such phos-

(24) Low diastereoselectivities have been reported in certain alkylations of Shöllkopf's bislactim ethers. See: (a) Ma, C.; Liu, X.; Li, X.; Flippen-Anderson, J.; Yu, S.; Cook, J. M. *J. Org. Chem.* **2001**, *66*, 4525−4542. (b) Shinohara, H.; Fukuda, T.; Iwao, M. *Tetrahedron* **1999**, *55*, 10989−11000. (c) Adamczyk, M.; Akireddy, S. R.; Reddy, R. E. *Tetrahedron: Asymmetry* **1999**, *10*, 3107−3110.

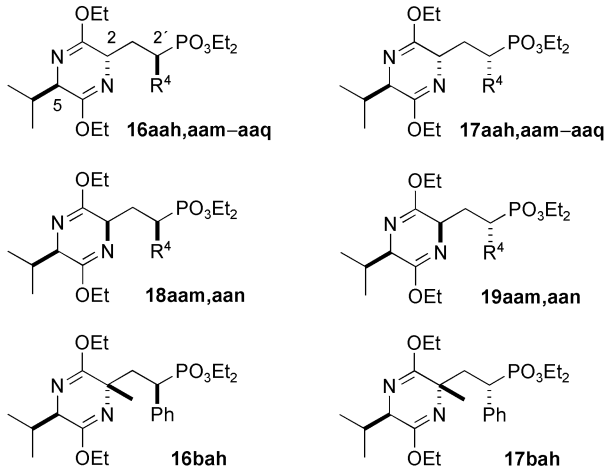


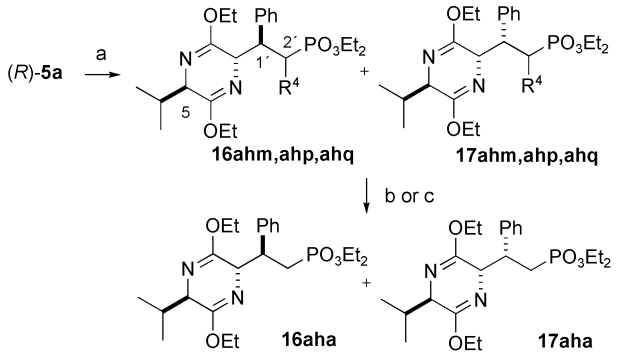
FIGURE 1. Adducts obtained from α-substituted vinylphosphonates. Legend: **h**, R^4 = Ph; **m**, R^4 = CO_2Et; **n**, R^4 = PO_3Et_2; **o**, R^4 = OPO_3Et_2; **p**, R^4 = $SiMe_3$; **q**, R^4 = $SnPh_3$.

phonate carbanions should be sufficiently stabilized, probably by chelation of the lithium with the phosphoryl oxygen and a nitrogen atom of the bislactim ring (as depicted in Scheme 13), thus suppressing transmetalation processes that could compromise the integrity of the newly formed chiral center at position 2. With these ideas in mind and pursuing a more stereoselective synthesis of the 4-substituted AP4 derivatives, we decided to study the effect of different proton sources in the additions to α-substituted vinylphosphonates. We examined first the addition of azaenolate (*R*)-**5a** to the α-phenylvinylphosphonate **6ah** using a bulky proton source. When the intermediate adduct anion was allowed to react with 2,4,6-tri-*tert*-butylphenol in THF at −78 °C for 1 h prior to the addition of HOAc, no asymmetric induction occurred in the protonation. Nevertheless, when the same treatment was performed with the intermediate anion generated in the addition of (*R*)-**5a** to the α-trimethylsilylvinylphosphonate **6ap**, the 2,5-trans adducts **16aap** and **17aap** were obtained in 62% yield with a 3:2 ratio. Attempting to increase the diastereoselectivity, chiral proton sources were examined next. When cinchonine or cinchonidine was used as the proton source as above, the addition of azaenolate (*R*)-**5a** to vinylphosphonate **6ah** furnished a mixture of the 2,5-trans-2,2′-anti and 2,5-trans-2,2′-syn products **16aah** and **17aah** in a 3:2 ratio and 89% combined yield.

Addition of azaenolate (*R*)-**5b** to α-phenylvinylphosphonate **6ah** also took place regio- and stereoselectively, to afford a mixture of 2,5-trans adducts **16bah**/**17bah** in a 3:1 ratio and 86% yield. When the intermediate adduct was allowed to react with 2,4,6-tri-*tert*-butylphenol in THF at −78 °C for 1 h prior to the addition of HOAc, a **16bah**/**17bah** mixture was obtained in a 6:1 ratio. Thus, the 2,2′-anti stereoselectivity was remarkable in these cases, and could not be completely suppressed by increasing the temperature of the quenching. When the addition of acetic acid was carried out at rt, the mixture **16bah**/**17bah** was obtained in similar yield, and **16bah** was formed with a diastereomeric excess of 17% over its epimer **17bah**.

Although low diastereoselectivities were achieved at this stage, the protonation experiments revealed that the

SCHEME 7[a]



[a] Reagents and conditions: (a) (i) **6**,**7hb**,**hm**,**hp**,**hq**, THF, −78 °C, 5 min; (ii) HOAc; (b) (i) BuLi, THF, −78 °C, 30 min; (ii) HOAc; (c) Bu_4NF, THF, rt, 10 min. Legend: **m**, R^4 = CO_2Et; **p**, R^4 = $SiMe_3$; **q**, R^4 = $SnPh_3$.

phosphonate carbanions, originating as intermediates in the conjugate additions of azaenolates **5a**,**b** to α-substituted vinylphosphonates, might react with electrophilic reagents with synthetically useful levels of stereoselection.[25]

Additions to the α,*β*-Disubstituted Vinylphosphonates. To explore further the scope of the conjugate additions of lithiated bislactim ethers to vinylphosphonates, we examined the additions to a series of α,*β*-disubstituted vinylphosphonates with either (*E*)- or (*Z*)-configuration. Reaction of lithium azaenolate (*R*)-**5a** and the *β*-phenylvinylphosphonates **6hm**,**hp**,**hq** and **7hp**,**hq**, with ethoxycarbonyl, trimethylsilyl, or triphenylstannyl groups at the α-position, took place rapidly in THF at −78 °C. Conversely, no reaction was observed in the same conditions for the vinylphosphonates **6hb** and **7hb**, with a methyl group at the α-position, nor in the case of a *β*,*β*-dimethyl-substituted vinylphosphonate.

According to the ^{31}P NMR spectra of the crude mixtures, additions to the α-substituted *β*-phenylvinylphosphonates were highly stereoselective, and led to the exclusive formation of the 2,5-trans adducts, as pairs of epimers at the 2′-position with either 2,1′-anti or 2,1′-syn configuration (**16** and **17**, respectively, in Scheme 7). Demetalation of the 2′-trimethylsilyl-substituted adducts with tetrabutylammonium fluoride at rt, and of the 2′-triphenylstannyl-substituted adducts by treatment with *n*-BuLi at −78 °C followed by quenching with HOAc, gave mixtures of the 2,5-trans-2,1′-anti and 2,5-trans-2,1′-syn adducts **16aha** and **17aha**, respectively. In this manner, additions to **6hp** and **6hq** were found 2,1′-anti-selective (as was previously observed for other vinylphosphonates with a trans relationship between the phosphorus and the *β*-substituent) and furnished mixtures of the adducts **16**/**17ahp** and **16**/**17ahq** with 8:1 and 3:1 ratios, respectively, in excellent yields. Thus, increasing the bulk of the α-substituent R^4 from trimethylsilyl (in **6ahp**) to triphenylstannyl (in **6ahq**) resulted in lower anti selectivity in the conjugate addition (see Table 3). Conversely,

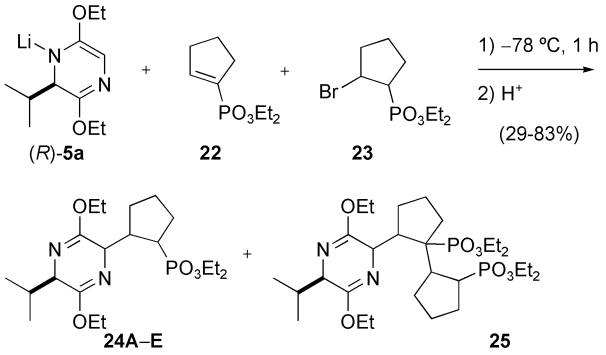
(25) Prompted by these results, we have studied the electrophilic substitutions and the olefination processes of lithiated bislactim ethers derived from cyclo-[L-AP4-D-Val]; see: (a) Fernández, M. C.; Quintela, J. M.; Ruiz, M.; Ojea, V. *Tetrahedron: Asymmetry* **2002**, *13*, 233−237. (b) Ruiz, M.; Ojea, V.; Quintela, J. M.; Guillín, J. J. *Chem. Commun.* **2002**, 1600−1601. (c) Fernández, M. C.; Ruiz, M.; Ojea, V.; Quintela, J. M. *Tetrahedron Lett.* **2002**, *43*, 5909−5912.

TABLE 3. Additions of Lithium Azaenolate (*R*)-5a to α,β-Disubstituted Vinylphosphonates 6,7hb,hm,hp,hq

azaenolate (equiv)	acceptor (confign)	R^3	R^4	yield[a] (%)	16:17 ratio[b,c]	16 ratio[b,d]	17 ratio[b,d]
5a (1.1)	**6hb** (*E*)	Ph	Me	NR			
5a (1.1)	**7hb** (*Z*)	Ph	Me	NR			
5a (1.1)	**6hm** (*E*)	Ph	CO_2Et	87	1:3	1:1	2:3
5a (1.1)	**6hp** (*E*)	Ph	$SiMe_3$	90	8:1	4:1	1:1
5a (1.1)	**7hp** (*Z*)	Ph	$SiMe_3$	80	3:4	8:1	2:1
5a (1.1)	**6hq** (*Z*)	Ph	$SnPh_3$	93	3:1	4:1	2:1
5a (1.1)	**7hq** (*E*)	Ph	$SnPh_3$	87	15:1	4:1	1:1

[a] Isolated yield of mixtures of adducts, after column chromatography. NR = no reaction was observed upon warming to 0 °C. [b] Determined by integration of the ^{31}P NMR spectra of the crude mixtures. [c] 2,1′-anti:2,1′-syn ratio. [d] Epimeric ratio at position 2′.

SCHEME 8



additions to **7hp** and **7hq**, with a cis relationship between the phosphonate group and the β-phenyl group, were nonregular and produced mixtures of adducts **16**/**17ahp** and **16**/**17ahq** with 3:4 and 15:1 ratios, respectively. On the basis of the stereochemical course described above for the additions to **6ap** and **6ah**, a 2,2′-anti stereoselectivity can also be assumed for the protonation of the intermediate α-trimethylsilyl- and α-triphenylstannyl-stabilized phosphonate carbanions arising from the additions to **6hp**,**hq** and **7hp**,**hq**. Addition to the α-(diethoxyphosphoryl)-substituted cinnamate ester **6hm**, with a cis relationship between the phenyl and carboxylate groups, resulted in a 1:3 mixture of the corresponding 2,1′-anti and 2,1′-syn adducts. This moderate syn selectivity is in accordance with previous results reported for the additions of Schöllkopf's bislactims to other α,β-unsaturated carboxylates of (*Z*)-configuration.[21]

Addition of 2 equiv of lithium azaenolate (*R*)-**5a** to cyclopentenylphosphonate **22**[19e,f] at −78 °C in THF required 1 h to be complete. After quenching with acetic acid, aqueous workup, and removal of the excess of Schöllkopf's reagent by chromatography, mixtures of the corresponding 1:1 adducts **24A**−**E** and 1:2 adducts **25** were obtained in 50% and 20% yields, respectively (see Scheme 8). According to the ^{31}P NMR spectra of the crude reactions, the mixtures of 1:1 adducts contained five different isomers. Using acetic acid, cinchonine, cinchonidine, or 2,4,6-tri-*tert*-butylphenol as the proton source in the additions to **22**, the ratios of the isomers **24A**/**24B**/**24C**/**24D**/**24E** were 34:−:7:32:27, 48:2:1:17:33, 47:5:7:12:29, and 51:7:6:10:26, respectively (see Table 4). Conversion to the desired 1:1 adducts could not be significantly increased by using higher excesses of Schöllkopf's reagent. Nevertheless, on the basis of previous studies on the conjugate addition to vinylphosphonates,[10a,11] it was expected that the initial anionic adduct would be effective in producing cyclopentenylphosphonate **22** in situ, via dehydrohalogenation of the 2-bromocyclopentylphosphonate **23**,[19g] thus suppressing dimerization. When mixtures of **22**/**23** were added to the lithium azaenolate (*R*)-**5a**, the 1:1 adducts **24** were obtained with improved yields and higher diastereoselectivities. In this manner, using a mixture of **22** and **23** in a 1:2 ratio and 2 equiv of (*R*)-**5a**, the fraction of 1:1 adducts was isolated in 75% yield, containing a mixture of **24A**/**24B**/**24C**/**24D**/**24E** in a 64:11:5:10:10 ratio. Apparently, the initially formed cyclopentylphosphonate carbanion is more basic and less nucleophilic than the lithium azaenolate.

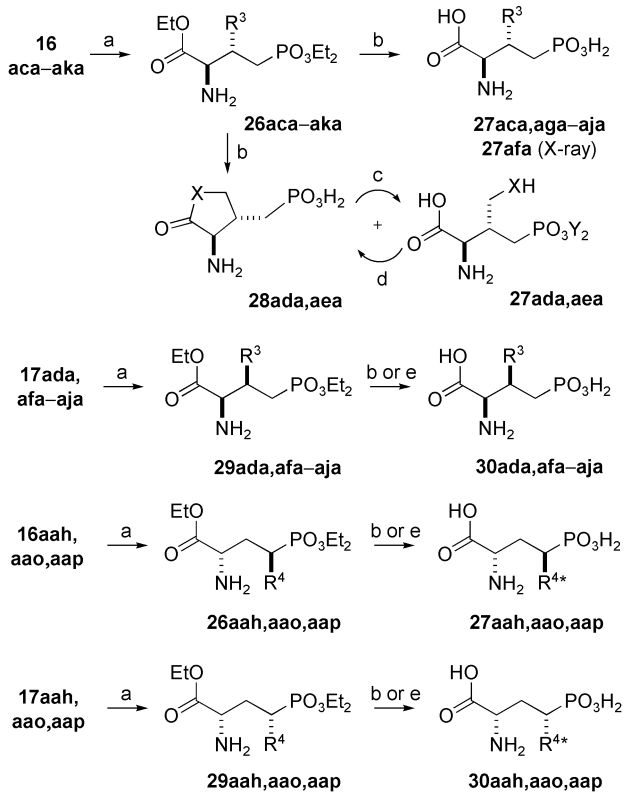
TABLE 4. Addition of Lithiated Bis-lactim Ether (*R*)-5a to Cyclopentenylphosphonate

	acceptor		24		25
azaenolate (equiv)	equiv of **22**	equiv of **23**	yield[a] (%)	**A**:**B**:**C**:**D**:**E** isomeric ratio[b]	yield[a] (%)
5a (2.0)	1.00		50	34:−:7:32:27[c]	20
5a (2.0)	1.00		50	48:2:1:17:33[d]	20
5a (2.0)	1.00		50	47:5:7:12:29[e]	20
5a (2.0)	1.00		50	51:7:6:10:26[f]	20
5a (1.0)	0.50	0.50	35		15
5a (1.0)	0.33	0.66	27		2
5a (1.0)	0.50	0.50	35		15
5a (1.0)	0.33	0.66	27		2
5a (2.0)	0.50	0.50	59	58:11:6:12:13	12
5a (2.0)	0.33	0.66	75	64:11:5:10:10	8
5a (2.0)	0.20	0.80	56	64:12:4:10:10	4
5a (2.0)	0.10	0.80	10	77:9:−:14:−	

[a] Isolated yield of mixtures of adducts, after column chromatography. [b] Determined by integration of the absorptions with δ 32.57, 34.00, 36.03, 36.20, and 36.34 ppm in the ^{31}P NMR spectra of the crude mixtures. [c] HOAc as proton source. [d] 2,4,6-Tri-*tert*-butylphenol as proton source. [e] Cinchone as proton source. [f] Cinchonidine as proton source.

Transformation of the Addition Products into Mono- and Disubstituted AP4 Derivatives. After separation of the mixtures of addition products by flash chromatography, all the 1′-substituted adducts, the adducts with phenyl, trimethylsilyl, or triphenylstannyl groups at position 2′, and four of the five cyclopentylated adducts could be isolated with diastereomeric excesses higher than 98%. Conversion of the addition products into the desired 2-amino-4-phosphonobutanoic acid derivatives was straightforward. Mild acid hydrolysis of the 1′-substituted bislactims **16aca**−**aka** and **17ada**,**afa**−**aja** provided the corresponding 2,3-anti or 2,3-syn amino esters **26aca**−**aka** and **29ada**,**afa**−**aja** in high yields after removal of the valine ester by chromatography (see Scheme 9). Subjecting the 2′-substituted bislactims **16aah**,**aao**,**aap** and **17aah**,**aao**,**aap** to the same reaction conditions furnished the 2,4-anti or 2,4-syn amino esters **26aah**,**aan**−**aap** and **29aah**,**aan**−**aap**. Hydrolysis of the amino esters was accomplished by either heating in concentrated hydrochloric acid (in the cases of **aca**−**aja**, and **aah**) or sequential treatment with lithium hydroxide and trimethylsilyl bromide (in the cases of **ada**, **aao**, and **aap**, with benzyloxymethyl, diethoxyphosphoryloxy, or trimethylsilyl groups). After purification by reversed-phase chromatography, the monosubstituted AP4 derivatives in the 2,3-anti, 2,4-anti, 2,3-syn, and 2,4-syn series (**27aca**,**afa**−**aja**, **27aah**,**aao**,**aap**, **30ada**,**afa**−**aja**, and **30aah**,**aao**,**aap**) were isolated in high yields. Upon

SCHEME 9[a]



[a] Reagents and conditions: (a) 0.25 N HCl, THF, rt, 8−15 h (72−93%); (b) 12 N HCl, reflux, 6 h (85−98%); (c) KOH, H_2O, rt, 1 h (88%); (d) (i) 25 M NH_4OH, reflux, 48 h; (ii) Dowex-H^+, 1% NH_4OH (94%); (e) (i) LiOH, H_2O, rt, 1 h; (ii) (TMS)Br, CH_2Cl_2, rt, 48 h; (iii) MeOH (63−95%). Legend: **c**, R^3 = Bn; **d**, R^3 = CH_2OBn, X = O, Y = K; **e**, R^3 = CH_2NHCbz, X = NH, Y = H; **f**, R^3 = *i*-Bu; **g**, R^3 = *i*-Pr; **h**, R^3, R^4 = Ph; **i**, R^3 = 3-C_5H_4N; **j**, R^3 = 2-C_4H_3S; **k**, R^3 = 2-C_4H_3O; **o**, R^4 = OPO_3Et_2, R^{4*} = OPO_3H_2; **p**, R^4 = $SiMe_3$.

crystallization from water, amino acid **27afa** yielded crystals amenable to X-ray structure determination, allowing the confirmation of its 2,3-anti stereochemistry (see the Supporting Information). Hydrolysis of amino ester **26ada** in hydrochloric acid took place with simultaneous cyclization to lactone **28ada**, while amino ester **26aea** afforded in the same conditions a 2:1 mixture of the corresponding amino acid **27aea** and lactam **28aea**. By heating this mixture in boiling NH_4OH, the amino acid:lactam ratio decreased to 1:7. Amino acid **27ada** was obtained as its potassium salt by basic hydrolysis of the lactone **28ada**.

Mild acid hydrolysis (0.25 N HCl, THF, rt) of the 1′,2′-disubstituted bislactim ether **24A**, obtained as the major isomer in the addition of **5a** to **22** + **23**, provided the corresponding amino ester **31** (Figure 2) in 83% yield after chromatography. On the other hand, hydrolysis of the 2,1′- and 2,2′-disubstituted bislactims required some experimentation: treatment of **16bha**,**bah** and **17bha**,**bah** with 0.25 N HCl in THF, 3 equiv of *p*-toluenesulfonic acid in EtOH/H_2O (7:3), or an excess of TFA in THF/H_2O (1:2), at rt for 3 days, only gave mixtures of the intermediate dipeptides. Hydrolysis was eventually accomplished by heating of the 2-methylated bislactims in 12 N HCl for 30−40 h. Thus, after separation of the auxiliary D-valine by reversed-phase chromatography, amino acids **27bah**,**bha** and **30bah**,**bha** (Figure 2) were isolated as their hydrochloride salts in 78−95% yield. Heating of amino ester **31** in 12 N HCl for 5 h afforded the corresponding amino acid **32** (Figure 2) in 82% yield.

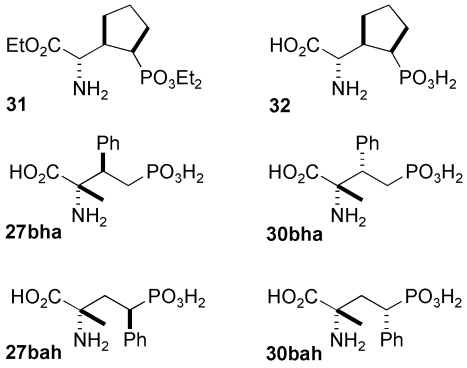


FIGURE 2. Disubstituted AP4 analogues.

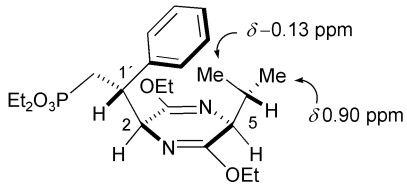


FIGURE 3. Aryl-inside or folded conformation of bislactim ethers.

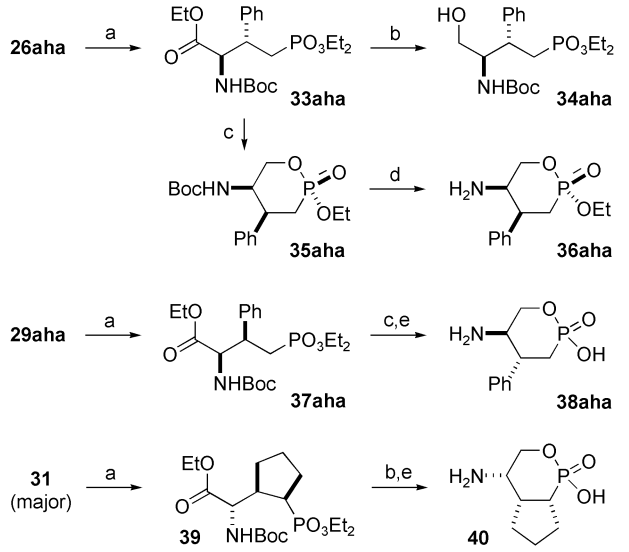
Determination of the Relative Configurations. Evidence supporting the relative configurations of the addition products was obtained by NMR analyses. For compounds **16** and **17** in the cases of **aca**−**aka**, **aah**, **aap**−**aao**, and for three of the cyclopentylated adducts **24**, the H5 resonance appears between 3.25 and 4.25 ppm, as a triplet with $^5J_{H2-H5}$ close to 3.5 Hz, which is general for the trans relationship of substituents at the pyrazine ring. Conversely, the NMR spectra of adducts **18aca**−**aka** and one of the cyclopentylated isomers show the absorption corresponding to H5 at similar δ, as a doublet of doublets with a $^5J_{H2-H5}$ close to 6.5 Hz, which is typical of a cis relationship at the bislactim ring.[26] Also characteristic of the ^{1}H NMR spectra of 2,5-cis adducts **18aha**−**aka**, with an aromatic substituent at position 1′, is the unusually low-frequency chemical shifts observed for the protons of one of the methyl groups of the isopropyl substituent, which appear between −0.19 and 0.31 ppm at 20 °C in $CDCl_3$. This shielding ($\Delta\delta$ between −0.30 and −0.80 with respect to the same absorptions in 2,5-trans adducts **16**,**17aha**−**aka**) may be caused by the preference for an "aryl-inside" or "folded" conformation in solution (see Figure 3),[27] in which the protons of one of the methyl groups lie within the region of the aromatic ring current of the substituent at position 1′. The relative configurations at position 1′ were assigned on the basis of the sets of NOEs observed for cyclic

(26) See, for instance: Busch, K.; Groth, U. M.; Kühnle, W.; Schöllkopf, U. *Tetrahedron* **1992**, *48*, 5607−5618.

(27) Aryl-inside or folded conformations have been determined in the solid state (according to X-ray analysis) for bislactim ethers with trans configuration (see ref 22) and also for *cis*-diketopiperazines[28] in solution.

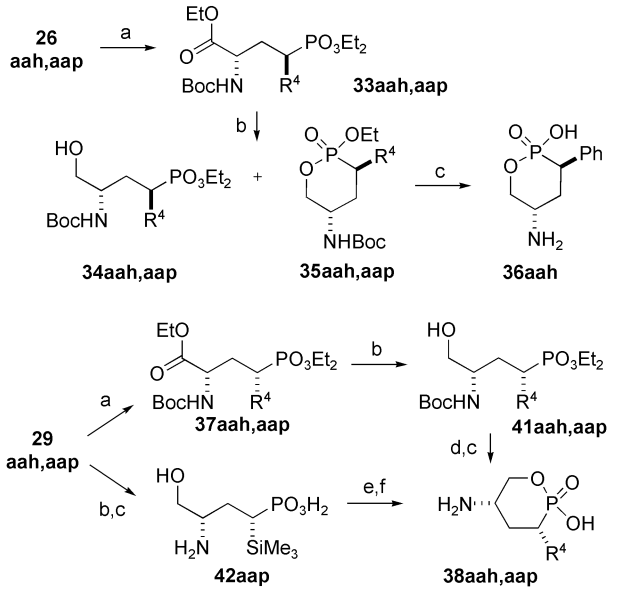
(28) Apperley, D.; North, M.; Stokoe, R. B *Tetrahedron: Asymmetry* **1995**, *6*, 1869−1872 and references therein.

SCHEME 10[a]



[a] Reagents and conditions: (a) $(Boc)_2O$, $NaHCO_3$, Na_2CO_3, dioxane/H_2O (1:1), rt, 3 h (89−98%); (b) (i) 1.5 M $LiBH_4$, THF, rt, 3 h; (ii) MeOH (87% or 98%) (c) (i) 1.5 M $LiBH_4$, THF, rt, 16 or 48 h; (ii) MeOH (78%); (d) TFA/H_2O (1:1), rt, 5 h (92%); (e) (i) (TMS)Br, CH_2Cl_2, rt, 13−23 h; (ii) MeOH (70−77%).

SCHEME 11[a]



[a] Reagents and conditions: (a) $(Boc)_2O$, $NaHCO_3$, Na_2CO_3, dioxane/H_2O (1:1), rt, 2−7 h (89−96%); (b) (i) 1.5 M $LiBH_4$, THF, rt, 1−4 d; (ii) MeOH (58−96%); (c) (i) (TMS)Br, CH_2Cl_2, rt, 13−23 h; (ii) MeOH (75−83%); (d) *n*-BuLi, THF, rt, 24 h (45%); (e) BnOCOCl, $NaHCO_3$, Na_2CO_3, dioxane/H_2O (1:1), rt, 24 h (63%); (f) H_2, Pd/C, MeOH/H_2O (2:1), rt, 5 h (92%). Legend: **h**, R^4 = Ph; **p**, R^4 = $SiMe_3$.

derivatives, as will be described below. Absolute configurations follow from the use of bislactim ethers derived from L- and D-Val, as there is ample precedent.[22]

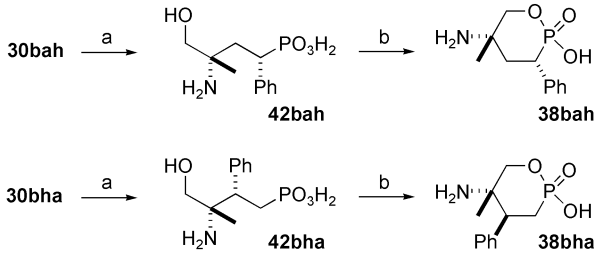
Since none of the synthesized adducts, esters, or amino acids (other than **27afa**) provided crystals suitable for X-ray crystal structure determination, cyclic derivatives were sought that could enable the assignment of the relative configurations by NOESY. Six-membered aminooxaphosphorinane derivatives were attractive in this regard, because of the strong preference for the chair conformation reported for several substituted systems.[29] Conversion of amino esters **26aah**,**aap**,**aha** and **29aah**,**aap**,**aha** and amino acids **30bah**,**bha** into such cyclic derivatives was achieved according to Schemes 10−12, by extending the applicability of previously developed methodology.[11,25]

Chemoselective reduction of the carboxylic ester in the presence of the phosphonate was accomplished on the *N*-Boc derivatives of amino esters **33aah**,**aap**,**aha**, **37aah**,**aap**,**aha**, and **39**, employing lithium borohydride in THF at rt (see Scheme 10). Reduction of **33aha** under these conditions was complete in 3 h, and after quenching with methanol, workup, and chromatography, alcohol **34aha** could be isolated in 87% yield. Moreover, when the reduction mixture was stirred for 13 h further at rt, cyclization of the intermediates was observed, to afford the *N*-Boc-aminooxaphosphorinane **35aha** as a single diastereoisomer of (*R*)-configuration at the phosphorus center. Cyclization of the intermediates in the reduction of *N*-Boc-amino ester **37aha** required 48 h, and gave the corresponding *N*-Boc-aminooxaphosphorinane as a 3:1 mixture of epimers at the phosphorus center. In the same conditions, reduction and cyclization of the *N*-Boc-amino ester **39** was complete in 3 h, and furnished the corresponding bicyclic derivative (2:1 mixture of epimers at the phosphorus) in excellent yield. Carbamate **35aha** was selectively cleaved by treatment with TFA in water (1:1 mixture) at rt for 5 h, to furnish **36aha** in 92% yield. The *N*-Boc and *O*-ethyl ester groups were cleaved with trimethylsilyl bromide in CH_2Cl_2 at rt to give **38aha** and **40** as pure diastereoisomers.

Reduction of the 4-phenyl- and 4-trimethylsilyl-substituted carbamates **33aah**,**aap** and **37aah**,**aap** with lithium borohydride in THF at rt took place within hours, but cyclization of the intermediates was unsatisfactory or did not occur at all after 4 days (see Scheme 11). Thus, carbamates **33aah**,**aap**, with anti configuration, gave mixtures of the alcohols **34aah**,**aap** and oxaphosphorinanes **35aah**,**aap** (as 4:1 mixtures of epimers at the phosphorus center) in 66−67% and 26−27% yields, respectively. Treatment of **35aah** with trimethylsilyl bromide in CH_2Cl_2 at rt gave **36aah** as one diastereoisomer. On the other hand, reduction of carbamates **37aah**,**aap**, with syn configuration, afforded exclusively the alcohols **41aah**,**aap** in 58−98% yield. Cyclization of the *syn*-alcohol **41aah** could be partially achieved in the conditions of Berkowitz[29b] (*n*-Buli, THF, rt, 24 h, 45% yield), but unfortunately, it was accompanied with 28% racemization α to the phosphorus atom. Cyclization of the trimethylsilyl-substituted alcohol to the oxaphosphorinane **38aap** was eventually achieved after cleavage of the protecting groups, by treatment of the δ-hydroxyphosphonic acid **42aap** with benzyl chloroformate in basic media followed by the catalytic hydrogenolysis of the benzyl carbamate.

(29) (a) Harvey, T. C.; Simiand, C.; Weiler, L.; Withers, S. G. *J. Org. Chem.* **1997**, *62*, 6722−6725. (b) Berkowitz, D. B.; Eggen, M.-J.; Shen, Q.; Shoemaker, R. K. *J. Org. Chem.* **1996**, *61*, 4666−4675. (c) Tasz, M. K.; Rodriguez, O. P.; Cremer, S. E.; Hussain, M. S.; Mazhar-ul-Haque *J. Chem. Soc., Perkin Trans. 2* **1996**, 2221−2226. (d) Lane, T. M.; Rodriguez, O. P.; Cremer, S. E.; Bennett, D. W. *Phosphorus, Sulfur Silicon Relat. Elem.* **1995**, *103*, 63−75. (e) Bergesen, K.; Vikane, T. *Acta Chem. Scand.* **1972**, *26*, 1794−1798. See also refs 11 and 25.

SCHEME 12[a]



[a] Reagents and conditions: (a) (i) HMDS, H_2SO_4, reflux, 12 h; (ii) 1.5 M $LiBH_4$, 2 M in THF, rt, 24 h; (ii) MeOH (73% or 78%); (b) $SOCl_2$, reflux, 14 h (62% or 83%).

After temporary protection of the acidic functionalities at amino acids **30bah** and **30bha** (hexamethyldisilazane, reflux, 12 h), reduction with lithium borohydride gave rise to amino alcohols **42bah** and **42bha** in good yields (see Scheme 12). Cyclization to the corresponding oxaphosphorinanes **38bah** and **38bha** took place by heating the amino alcohols in thionyl chloride.

A single chair conformation was observed for each compound **35aha**, **36aah**, **38aah**, **38aap**, **38aha**, **38bah**, **38bha**, and **40** in the ^{1}H NMR spectra (D_2O, 500 or 200 MHz, 25 °C). The lactone **28ada**, the lactam **28aea**, and all the oxaphosphorinanes, with the exception of **36aah**, showed patterns of signals suitable for the study of their relative stereochemistry by NOESY. After the ^{1}H NMR assignments were corroborated by COSY experiments, the analysis of the sets of observed NOEs allowed the assignment of the relative configuration of the stereogenic centers formed in the conjugate addition. The observed NOEs were supported by PM3/COSMO semiempirical calculations:[30] the refined geometries for the cyclic derivatives in a polarizable dielectric continuum (simulating water) were in agreement with the conformations in aqueous solution deduced from NMR spectroscopy, as depicted in Figure 4. Thus the stereochemistry of lactone **28ada** and lactam **28aea** was determined as 3,4-trans, while oxaphosphorinanes **35aha** and **40** showed a 4,5-cis configuration. These results and the X-ray crystal structure analysis for **27afa** allow us to assume a 2,1′-anti configuration for the major isomers **16aca**−**aka**,**bha** resulting from the additions of lithium azaenolates to the *β*-substituted vinylphosphonates with (*E*)-configuration. The assignment of 2,1′-syn configuration for the major isomers **17ada**,**afa**−**aha**,**bha** in the additions to the *β*-substituted acceptors with (*Z*)-configuration follows by elimination and is also consistent with the NOEs observed for the oxaphosphorinanes **38aha** and **38bha**, which showed a 4,5-trans configuration. The 3,5-cis configuration determined for the oxaphosphorinanes **38aah**, **38aap**, **38bah**, and **40** enables the assignment of a 2,2′-syn configuration for the minor isomers **17aah**,**aap**,**bah**, obtained from the additions to α-substituted acceptors, and a 1′,2′-cis configuration for the major adduct **24A**, arising from the addition to cyclopentenylphosphonate.

Discussion of Stereochemical Models for the Conjugate Addition. Translation of (*Z*)- or (*E*)-geometry of the acceptor into syn or anti configuration at the 1,4-addition products was previously encountered in other conjugate additions of lithiated bislactim ethers (derived from cyclo-[Val-Gly]) to 1-propenylphosphonates,[10b,11] acrylate and cinnamate esters,[21] nitroolefines,[22] and vinyl sulfones.[23,31] The stereochemical course of the additions of lithium azaenolates **5a**,**b** to α-substituted, *β*-substituted, or α,*β*-disubstituted vinylphosphonates can be rationalized by extending the transition-state model that was semiempirically optimized for the additions of **5a** to 1-propenylphosphonates.[11] In this way, an initial lithium−phosphoryl coordination to form a chelate complex, **43**, followed by a rate-determining reorganization through competitive eight-membered transition-state structures

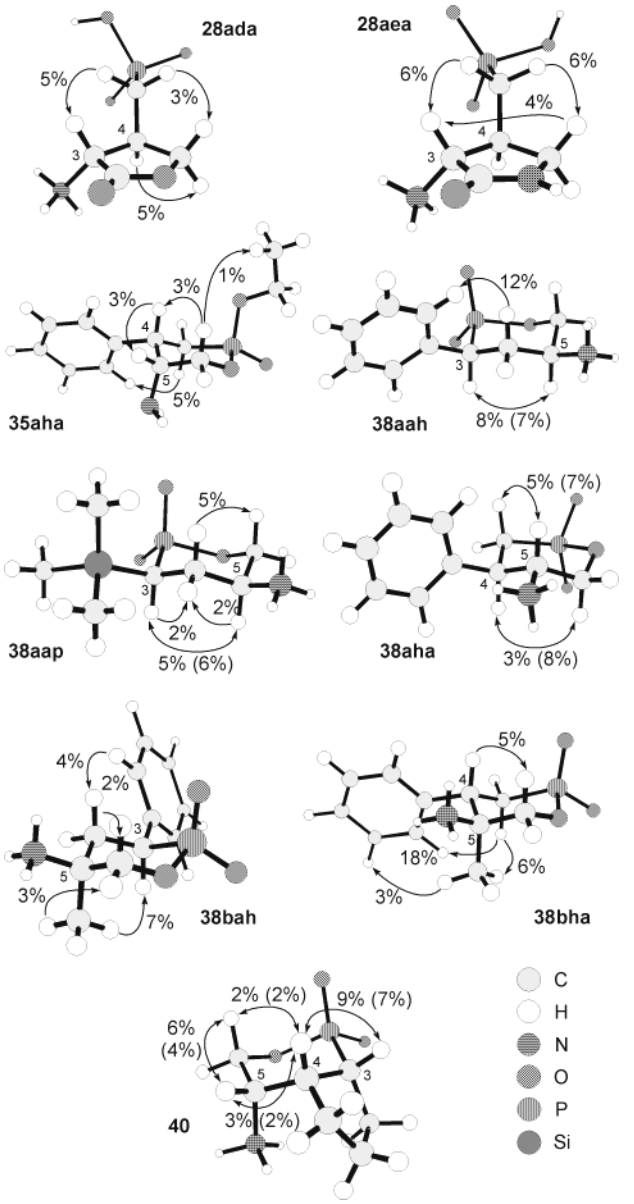
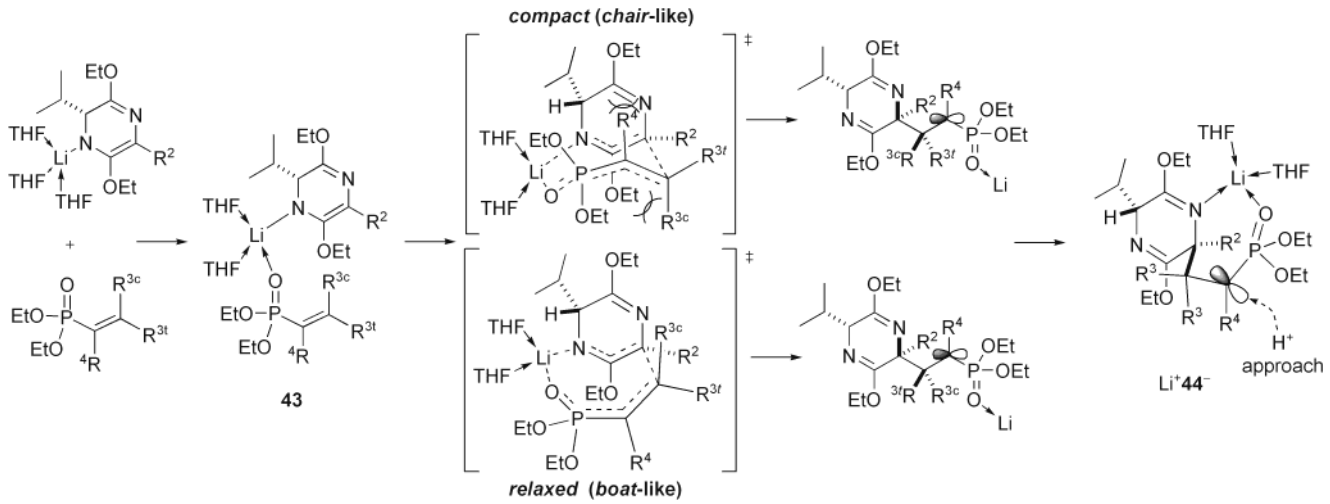


FIGURE 4. PM3/COSMO-optimized geometries for the cyclic derivatives, showing characteristic NOEs.

(30) (a) PM3: Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209−220, 221−264. (b) COSMO: Klamt, A.; Schüürmann, G. *J. Chem. Soc., Perkin Trans. 2* **1993**, 799−805.

(31) For reviews of the stereochemistry of the Michael addition reaction, see: (a) Leonard, J. *Contemp. Org. Synth.* **1994**, *1*, 387−415. (b) Oare, D. A.; Heathcock, C. H. *Top. Stereochem.* **1989**, *19*, 227−406.

SCHEME 13. Proposed Transition-State Structures and Intermediate Phosphonate Carbanions



(TSs), can account for the stereochemical features of the present conjugate additions (see Scheme 13). According to such a model, 2,1′-anti/syn stereoselection relies on the energy difference between the "compact" (*chair*-like) and "relaxed" (*boat*-like) TSs resulting from the approach of the reactive face of the azaenolate (trans to the isopropyl group) to the prochiral faces of the β-carbon atom of the acceptor. Thus, the preferential translation of the (*Z*)- or (*E*)-geometry of the β-substituted vinylphosphonate into a 2,1′-syn or 2,1′-anti configuration at the 1,4-addition products must originate from a clear kinetic preference for the compact TSs over the relaxed counterparts. We speculate that secondary order hyperconjugative interactions between the π systems of the acceptor and donor partners in the compact TSs may contribute to this preference. Conversely, nonbonding interactions between the ethoxy groups of the bislactim ring and bulky R^{3c} substituents can reduce the energy gap between the competitive TSs, thus accounting for the lower 2,1′-syn selectivity in the additions to the β-alkyl vinylphosphonates with (*Z*)-configuration.

The stereochemical outcome observed in the addition to the α,β-substituted acceptors can be understood in similar terms. Nonbonding interactions between the bislactim and the α-substituent of the acceptor (R^4) raise the energy of the compact TSs, and the relaxed TSs also become important in these cases. Thus, for the acceptors with a trans relationship between the phosphorus atom and the β-substituent (R^{3t}), increasing the bulk of the α-substituent (from H to $SiMe_3$ and to $SnPh_3$) results in a closer energy for the competing TSs and a reduced anti selectivity (the anti/syn dr being diminished from >18:1 to 8:1 and 3:1). Moreover, the preference for the compact TSs is not maintained in the additions to the α,β-substituted acceptors with a cis relationship between the phosphorus atom and the β-substituent, probably due to simultaneous interactions between both R^4 and R^{3c} substituents and the bislactim moiety in such TSs. Thus, translation of the (*E*)-geometry of the α-triphenylstannyl-substituted vinylphosphonate **7hq** into a 2,1′-anti configuration of the major addition products **17ahq** can be rationalized by invoking the preference for the relaxed TS.

The stereoselective protonation of the intermediate phosphonate carbanions arising from the additions to the α-substituted acceptors can be rationalized by considering the involvement of cyclic chelate complexes such as Li^+**44**$^-$. Thus, approach of the proton with an axial trajectory to the less hindered face of the cyclic phosphonate carbanion may account for the 2,2′-anti stereoselection observed in the additions.

Conclusions

In summary, the scope and limitations of the conjugate additions of Schöllkopf's reagents to substituted vinylphosphonates have been studied. It has been shown that the reactions of lithiated bislactim ethers derived from cyclo-[Gly-Val] and cyclo-[Ala-Val] with α-, β-, or α,β-substituted vinylphosphonates take place regio- and stereoselectively at low temperature. For the vinylphosphonates with alkyl, aryl, or functionalized substituents at the β-position, the conjugate addition results in a preferential translation of the (*E*)- or (*Z*)-geometry into 2,1′-anti or 2,1′-syn configuration at the addition products. The level of stereoselection attained in the additions to α-substituted and α,β-disubstituted vinylphosphonates was found markedly dependent on the nature of the α-substituent of the acceptor, but these reactions allowed the preparation of enantiomerically pure compounds with phenyl, silyl, stannyl, or phosphoryloxy groups α to the phosphorus atom. Although low diastereoselectivities were achieved at this stage, protonation experiments revealed that the intermediate phosphonate carbanions might react with electrophilic reagents with synthetically useful levels of stereoselection. The stereochemical outcomes of the conjugate additions have been rationalized by invoking competitive eight-membered TSs. According to this model, the stereochemical response of the addition to the acceptor geometry originates from an orientational preference in the TSs for a compact (*chair*-like) disposition of the reaction partners, which may reduce nonbonding interactions and increase secondary order hyperconjugative interactions between the π systems of the acceptor and donor moieties. Finally, the addition products have been efficiently transformed into a variety of 3- or 4-monosubstituted and 2,3-, 2,4-, or 3,4-disubstituted AP4 derivatives in enantiomerically pure form, which may result in useful tools for the study of group III of mGluRs.

Acknowledgment. We gratefully acknowledge the Ministerio de Ciencia y Tecnología (Grant BQU2000-0236) for financial support, and Novartis Pharma for the generous gift of bislactim ethers derived from cyclo-[Val-Gly]. We also thank Dr. Miguel A. Maestro for resolving the X-ray structure.

Supporting Information Available: Experimental procedures and spectral data for all new compounds and crystallographic data for **27afa**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034707Q