Pure Appl. Chem., Vol. 82, No. 3, pp. 577–582, 2010.
doi:10.1351/PAC-CON-09-11-06

Asymmetric synthesis of aminophosphonic acids mediated by chiral sulfinyl auxiliary: Recent advances*,**

Piotr Łyżwa and Marian Mikołajczyk‡

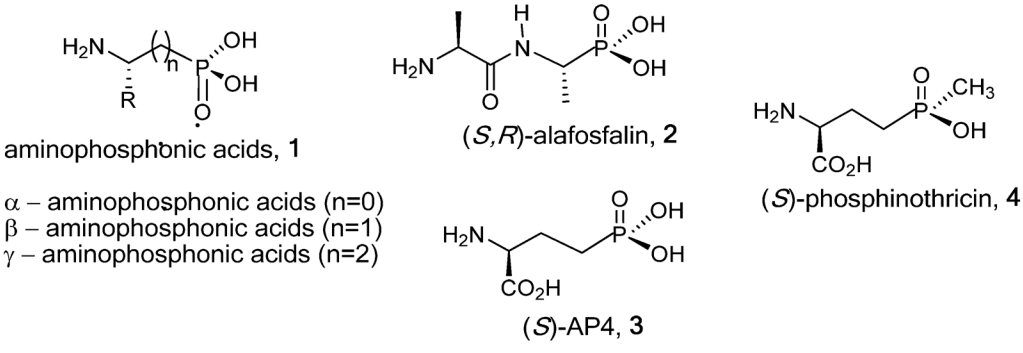
Department of Heteroorganic Chemistry, Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, 90-363 Łódź, Sienkiewicza 112, Poland

Abstract: New approaches to asymmetric synthesis of α-, β- and γ-aminophosphonic acids using enantiopure *p*-toluenesulfinimines as key reagents are reported. The utility of the devised methods is illustrated by the syntheses of enantiomeric aminophosphonic acids such as AP4, AP3, and its 3-amino isomer.

Keywords: aminophosphonic acids; asymmetric syntheses; bioactivity; chiral sulfinimines; diastereoselectivity.

INTRODUCTION

Aminophosphonic acids **1** are phosphorus analogs of amino acids in which the planar carboxylic group is replaced by a tetrahedral phosphonic acid moiety. Because of the tetrahedral configuration at phosphorus, aminophosphonic acids mimic the unstable tetrahedral carbon intermediates formed in enzyme-mediated peptide bond cleavage and act as enzyme inhibitors. They selectively inhibit peptidases and proteinases (e.g., HIV protease, serine protease). Many natural and synthetic aminophosphonic acids and their conjugates with peptides exhibit antibacterial, anticancer, and antiviral properties. Some of them show pesticidal, insecticidal, and herbicidal activity. As such, a few of them have found commercial applications in medicine and agriculture [1,2].



Scheme 1 General structure and significant examples of aminophosphonic acids.

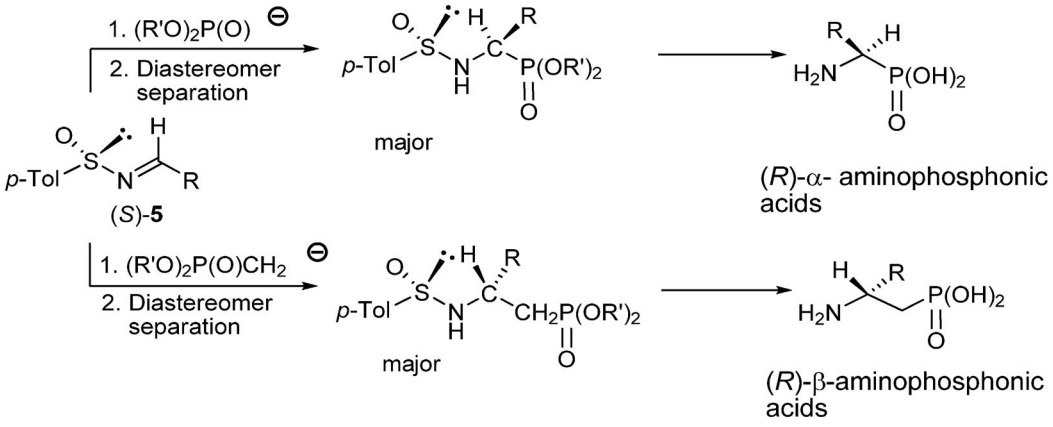
*Paper based on a presentation at the 9th International Conference on Heteroatom Chemistry (ICHAC-9), 30 June–4 July 2009, Oviedo, Spain. Other presentations are published in this issue, pp. 505–677.

**Dedicated to Prof. Franklin A. Davis on the occasion of his 70th birthday.

‡Corresponding author: E-mail: marmikol@bilbo.cbmm.lodz.pl

The biological activity of aminophosphonic acids **1** depends on the absolute configuration of the stereogenic carbon atom bearing the amino group. For example, (*S*,*R*)-alafosfalin **2** shows higher antibacterial activity than the other three diastereomers. Similarly, the (*S*)-enantiomer of 2-amino-4-phosphonobutanoic acid (AP4) **3** is 40 times more active than the (*R*)-form in suppression of glutamate-mediated neurotransmission. In view of these distinct differences in bioactivity, the development of suitable methodologies for the preparation of enantiomerically pure forms of aminophosphonic acids **1** has been a challenging task.

As part of our program on the synthesis of enantiomeric aminophosphonic acids, we devised a new and general asymmetric approach to α- and β-aminophosphonic acids using the enantiopure *p*-toluenesulfinimines **5** as chiral reagents [3]. A key reaction in this synthesis was a highly diastereoselective addition of phosphite anions or α-phosphonate carbanions to sulfinimines **5** (Scheme 2).

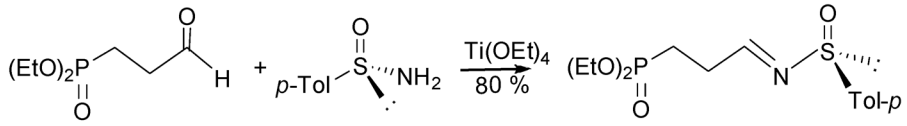


Scheme 2 Synthesis of enantiomerically pure α- and β-aminophosphonic acids **1**.

Our methodology has been applied by other research groups for the synthesis of diverse structures of enantiomeric α- and β-aminophosphonic acids [4]. However, it is well known that there is a long list of γ-aminophosphonic acids which exhibit very interesting biological properties. The most important among them are AP4 mentioned above and phosphinothricin **4**. The latter is a potent inhibitor of glutamine synthetase and shows antibacterial and herbicidal activity. Although syntheses of individual structures of enantiomeric γ-aminophosphonic acids are reported, they are not general in scope and of limited applicability. This prompted us to extend the scope of our sulfinimine methodology for asymmetric synthesis of γ-aminophosphonic acids with a focus on AP4 as well as to elaborate new approach to bioactive AP3 and its 3-amino isomer. The results obtained are reported herein.

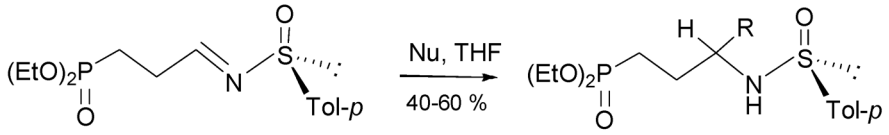
ASYMMETRIC SYNTHESIS OF γ-AMINOPHOSPHONIC ACIDS

A key chiral reagent in our synthesis is (+)-(*S*)-sulfinimine **6**. It was readily prepared by condensation of 3-(diethoxyphosphoryl)propanal with (+)-(*S*)-*p*-toluenesulfinamide in the presence of $Ti(OEt)_4$ (eq. 1). The three reaction components were used in a 1:1:0.5 molar ratio. The product isolated in 80 % yield was contaminated with ca. 5 % of double-bond isomers and unreacted aldehyde, which are difficult to remove by column chromatography. Therefore, as such, it was used for addition reactions.



(+)-(*S*) (+)-(*S*)-**6**, δ_p = 30.3. ppm (1)

Having in mind the synthesis of AP4 as a representative example of γ-aminophosphonic acids, we investigated at first addition of the cyano group to the sulfinimine (+)-(*S*)-**6** (Scheme 3). Thus, the addition of Et_2AlCN to (+)-**6** in the presence of $BF_3{\cdot}Et_2O$ afforded the corresponding addition product **7** as a mixture of two diastereomers in a 3:1 ratio (^{31}P NMR assay). When Me_3SiCN/CsF reagent system was used, the diastereoselectivity of addition was higher (6:1). A most effective diastereoselectivity (9:1) was obtained with Et_2AlCN in the presence of isopropanol.



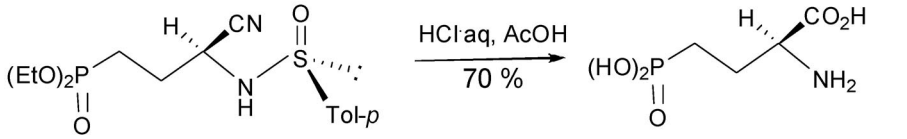
(+)-(*S*)-**6**

Nu	Adduct	dr
$Et_2AlCN/BF_3{\cdot}Et_2O$	**7,** R=CN	3 : 1
Me_3SiCN/CsF	**7,** R=CN	6 : 1
Et_2AlCN/i-PrOH	**7,** R=CN	9 : 1
$(MeO)_2C(Li)CN$	**7,** R=CN	9 : 1
$(EtO)_2P(O)Li$	**8**, R=$(EtO)_2P(O)$	9 : 1
$(Et_2N)_2P(O)Li$	**9**, R= $(Et_2N)_2P(O)$	6 : 1
$(EtO)_2P(O)CH_2Li$	**10,** R= $(EtO)_2P(O)CH_2$	3 : 1
EtO_2CCH_2Li	**11**, R=EtO_2CCH_2	3 : 1

Scheme 3 Addition of nucleophiles to sulfinimine (+)-(*S*)-**6**.

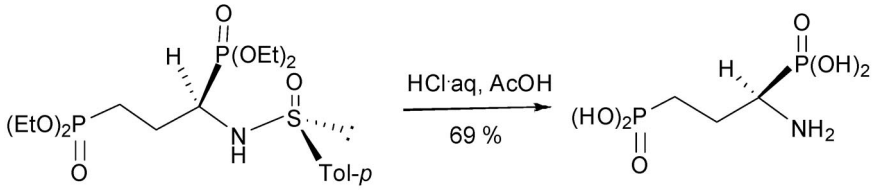
Addition of diethyl phosphite to (+)-**6** under standard conditions (LiHMDS, –78 °C, 5 h, THF) gave the adduct **8** with high diastereoselectivity (9:1). With bis-diethylamido phosphite, the ratio of diastereomeric adducts **9** was 6:1. A low diastereoselectivity of addition (3:1) was observed with the α-carbanion derived from diethyl methylphosphonate and with ethyl acetate anion.

As the diastereomers of **7** could not be separated by column chromatography, the adduct **7** with dr 9:1 was subjected to hydrolysis under acidic conditions to afford (+)-2-amino-4-phosphonobutanoic acid (AP4), **3** (eq. 2). The absolute configuration of (+)-AP4 obtained is (*S*). Therefore, the major diastereomer of the adduct **7** should have the (*S*)-chirality at the stereogenic carbon atom formed in the addition reaction. This two-step synthetic sequence allowed us to synthesize our target in 43 % yield starting from the sulfinimine (+)-**6** [5].



(S_c,S_s)-**7** + (R_c,S_s)-**7** (9 : 1) (+)-(*S*)-AP4, **3**, δ_P = 24.1 ppm
$[\alpha]_D$ = + 12.6 (c 1.19, H_2O) (2)

Similarly, acidic hydrolysis of the adduct **8** (dr 9:1) resulted in the formation of (–)-1-amino-3-phosphono-propylphosphonic acid **12** (eq. 3). Assuming the same steric course of the addition of phosphite and cyano anions to (+)-(*S*)-**6**, it is reasonable to ascribe the (*R*)-configuration to the levorotatory amino-bis-phosphonic acid **12**.



(3)

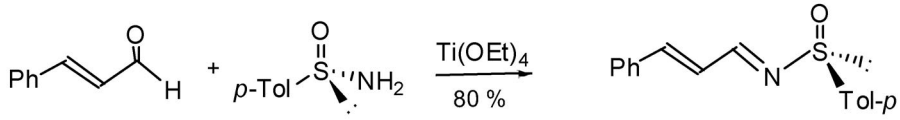
(R_c,S_s)-**8** + (S_c,S_s)-**8** (9 : 1)

(-)-(*R*)-**12**, δ_P = 12.8, 27.2 ppm
$[\alpha]_D$ = - 2.3 (c 1.29, H_2O)

It is interesting to point out that the amino-bis-phosphonic acid **12** has been obtained earlier only in racemic form [6].

ASYMMETRIC SYNTHESIS OF 2-AMINO-3-PHOSPHONOPROPANOIC ACID (AP3) AND ITS 3-AMINO REGIOISOMER

A successful synthesis of (+)-(*S*)-AP4 presented above encouraged us to elaborate a new approach to AP3 which is also modulator for the *N*-methyl-D-aspartate (NMDA) receptor site. According to simple retrosynthetic analysis, the sulfinimine (+)-(*S*)-**13** was selected as a chiral reagent. The chiral sulfinyl group should control diastereoselectivity of the addition reaction to the C=N bond while the C=C moiety should be easily transformed into the carboxylic goup. The required enantiopure (+)-**13** was prepared by a standard procedure [7] from cinnamic aldehyde, (+)-(*S*)-*p*-toluenesulfinamide and $Ti(OEt)_4$ used in a 1.5:1:5 molar ratio (eq. 4).

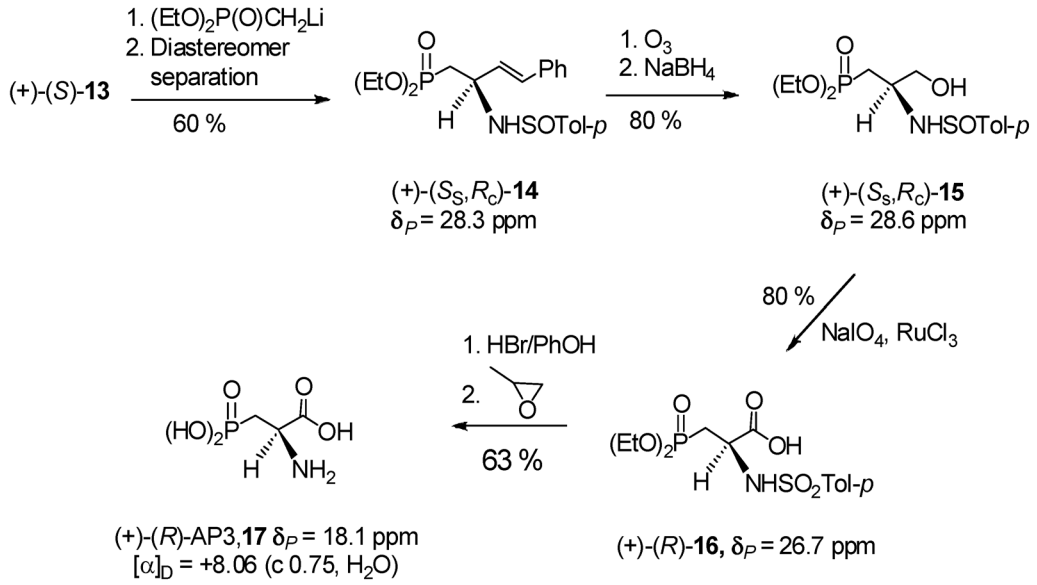


(4)

(+)-(*S*) (+)-(*S*)-**13**

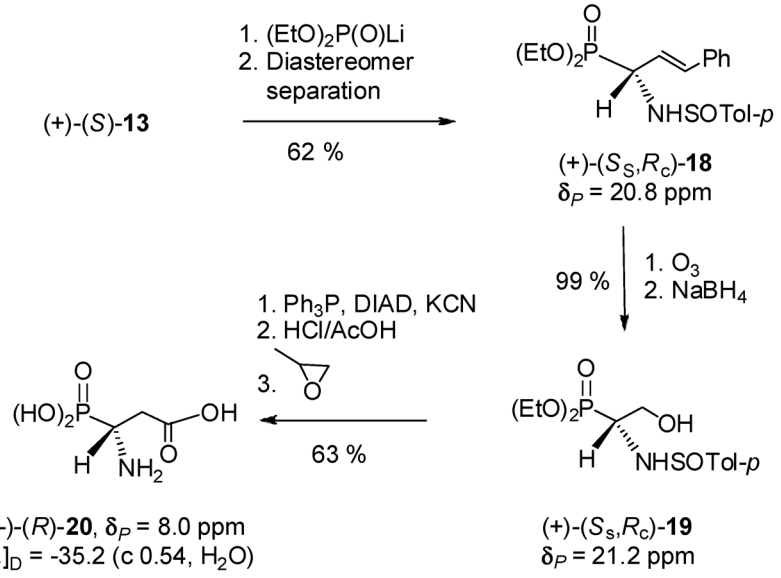
The synthesis of (+)-(*R*)-AP3 is shown in Scheme 4 and briefly discussed below. The addition of the lithium salt of diethyl methylphosphonate to (+)-(*S*)-**13** was found to afford a mixture of the diastereomeric adducts **14** in a 9:1 ratio from which the major diastereomer was isolated by column chromatography and crystallization. The absolute (*R*)-configuration was ascribed to the newly formed stereogenic β-carbon atom based on the transition-state model for addition of α-phosphonate carbanions to chiral sulfinimines [3a].

Ozonolysis of (+)-**14** and subsequent reduction with $NaBH_4$ gave the corresponding alcohol (+)-**15**. This, in turn, was subjected to oxidation with sodium metaperiodate in the presence of ruthenium chloride to afford the carboxylic acid (+)-**16**. As the chiral *N*-sulfinyl group was oxidized to the *N*-sulfonyl moiety in this reaction, the final conversion of (+)-**16** to the desired (+)-AP3 **17** was carried out under strongly acidic conditions to achieve complete deprotection of the phosphonate and amino functions. It was gratifying to find that no racemization occurred under these conditions and the enantiopure (+)-(*R*)-AP3 was obtained in 24 % overall yield.



Scheme 4 Synthesis of enantiopure (+)-(*R*)-AP3.

The sulfinimine (+)-(*S*)-**13** was also found to be a key chiral reagent in the synthesis of 3-amino-3-phosphonopropanoic acid **20** which is isomer of AP3 with regard to a position of the amino group. The synthesis of **20** shown in Scheme 5 started with the addition of diethyl phosphite anion to (+)-(*S*)-**13**. It occurred in a highly diastereoselective manner and gave the corresponding adduct **18** as a mixture of the (S_S,R_C)- and (S_S,S_C)-diastereomers in a 16:1 ratio. The major diastereomer (+)-**18** isolated in a pure state was then subjected to ozonolysis followed by $NaBH_4$ reduction to afford the alcohol (+)-**19**. The latter was converted under the Mitsunobu reaction conditions into the corresponding



Scheme 5 Synthesis of enantiopure (–)-(*R*)-3-amino-3-phosphonopropanoic acid

cyanide which, without isolation, was hydrolyzed to the desired acid (–)-(*R*)-**20** [8]. This synthesis as well as those of AP3 and AP4 presented above compare favorably in terms of use of simple reagents and transformations with the previously reported syntheses.

ACKNOWLEDGMENT

Financial support of this work by the Ministry of Science and Higher Education (Grant No. PBZ-KBN-126/T09/2004) is gratefully acknowledged.

REFERENCES

1. For an excellent monograph, see: V. P. Kukhar, H. R. Hudson (Eds.). *Aminophosphonic and Aminophosphinic Acids: Acids: Chemistry and Biological Activity*, John Wiley, New York (2000).
2. P. Kafarski, B. Lejczak. *Phosphorus, Sulfur, Silicon Relat. Elem.* **63**, 193 (1991).
3. (a) M. Mikołajczyk, P. Łyżwa, J. Drabowicz, M. W. Wieczorek, J. Błaszczyk. *Chem. Commun*. 568 (1996); (b) M. Mikołajczyk, P. Łyżwa, J. Drabowicz. *Tetrahedron: Asymmetry* **8**, 3991 (1997); (c) M. Mikołajczyk, P. Łyżwa, J. Drabowicz. *Tetrahedron: Asymmetry* **13**, 2571 (2002); (d) for a summary of our work, see: M. Mikołajczyk. *J. Organomet. Chem.* **690**, 2488 (2005).
4. For recent reviews on the synthesis of α- and β-aminophosphonic acids, see: (a) M. Ordóñez, H. Rojas-Cabrera, C. Cativiela. *Tetrahedron* **65**, 17 (2009); (b) F. Palacios, C. Alonso, J. M. de los Santos. *Chem. Rev*. **105**, 899 (2005).
5. For recent syntheses of enantiomeric AP4, see: (a) G. Reyes-Rangel, V. Maranon, C. G. Avila-Ortiz, C. Anaya de Parrodi, L. Quintero, E. Juaristi. *Tetrahedron* **62**, 8404 (2006); (c) M. C. Fernandez, A. Diaz, J. J. Guillin, O. Blanco, M. Ruiz, V. Ojea. *J. Org. Chem*. **71**, 6958 (2006); (b) Ch. Selvam, C. Goudet, N. Queslati, J.-P. Pin, F. C. Acher. *J. Med. Chem*. **50**, 4656 (2007).
6. Z. H. Kudzin, A. Kotyński, G. Andrijewski. *J. Organomet. Chem.* **479**, 199 (1994).
7. F. A. Davis, Y. Zhang, Y. Andemichael, T. Fang, D. L. Fanelli, H. Zhang. *J. Org. Chem.* **64**, 1403 (1999).
8. For absolute configuration of (–)-**20**, see: A. Vaseila, R. Voeffray. *Helv. Chim. Acta* **65**, 1953 (1982).

