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Double Asymmetric Induction in the Synthesis of Enantiomeric α-Aminophosphonic Acids Mediated by Sulfinimines

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ABSTRACT: *A double asymmetric induction in the synthesis of α-aminophosphonic acids is described. It involves the nucleophilic addition of anions of enantiomeric dimenthyl phosphites to both (+)-(S)- and (–)-(R)-enantiomers of N-(p-tolylsulfinyl)benzaldimine and subsequent acidic hydrolysis of the adducts formed. The match and mismatch effects were observed.* © 2013 Wiley Periodicals, Inc. Heteroatom Chem. 25:15–19, 2014; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.21130

INTRODUCTION

Aminophosphonic acids (APs) are phosphorus analogues of amino acids in which the planar carboxylic group is replaced by a tetrahedral phosphonic acid moiety. Because of the tetrahedral configuration at phosphorus, APs mimic the unstable tetrahedral carbon intermediate formed in the enzyme-mediated peptide bond cleavage and, therefore, act as enzyme inhibitors. Many phosphonic analogues of protein and nonprotein amino acids exhibit antibacterial, anticancer, and antiviral properties as well as pesticidal, insecticidal, and herbicidal activities. Therefore, selected APs have found commercial application in medicine and agriculture [1–3].

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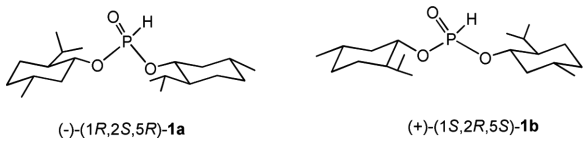
As the biological activity of APs strongly depends on the absolute configuration of the stereogenic carbon atom bearing the amino group, the development of general methods for the preparation of enantiomeric APs has been a challenging task. One of the simplest and effective methods of asymmetric synthesis of optically active APs developed in our laboratory is based on the nucleophilic addition of phosphite anions or α-phosphonate carbanions to enantiomeric *N*-sulfinylaldimines, and subsequent hydrolysis of the adducts [4, 5].

This procedure proved to be versatile, and has been later on used in the synthesis of a broad variety of APs [6–8]. In addition to their ready availability, enantiomerically pure sulfinimines [9, 10] contain chiral, sulfinyl moiety as a powerful stereodirecting group inducing high diastereoselectivity and an activated carbon–nitrogen double bond prone to the attack of nucleophilic reagents. Some of such additions lead to the formation of the single diastereomers of the adducts formed [11], others give mixtures of diastereomeric adducts, which have to be separated and effectively hydrolized to the free, enantiomerically pure APs.

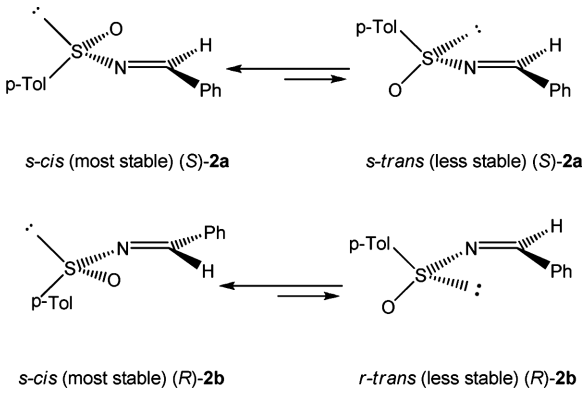
As a part of our efforts to improve the synthesis of enantiopure APs by using the sulfinimine methodology, and especially the diastereoselectivity of the addition reaction, we turned our attention to the possibility of a double asymmetric induction in the addition reaction, that is, the use not only of enantiopure aldimines but also of enantiomeric phosphites.

The first example of such an asymmetric induction in the addition reaction of (–)-O,



(-)-(1*R*,2*S*,5*R*)-**1a** (+)-(1*S*,2*R*,5*S*)-**1b**

FIGURE 1 Structures of (–)-dimenthyl phosphite **1a** and (+)-dimenthyl phosphite **1b**.



s-cis (most stable) (*S*)-**2a** *s-trans* (less stable) (*S*)-**2a**

s-cis (most stable) (*R*)-**2b** *r-trans* (less stable) (*R*)-**2b**

FIGURE 2 The most stable conformations of (+)-(S)- and (–)-(R)-sulfinimine **2a** and **2b**.

O-di-(1*R*,2*S*,5*R*)-menthyl phosphite to aldimine derived from (*R*)-2-methylbenzylamine was described by Kolodiazhnyi [12].

In this paper, we disclose our results on the double asymmetric induction observed in the addition reaction of lithium salts of enantiomeric dimenthyl phosphites **1a** and **1b** to both enantiomers of *N*-(p-tolylsulfinyl)benzaldimine **2**.

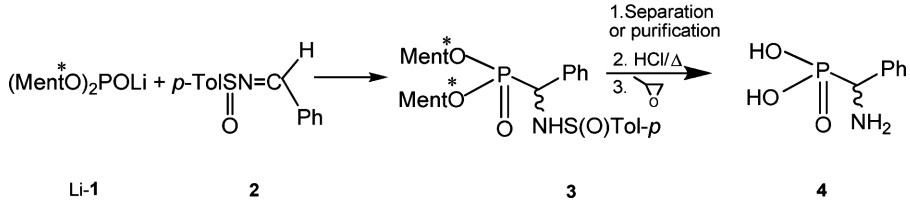
RESULTS AND DISCUSSION

The starting (–)-dimenthyl phosphite **1a** was obtained for the first time by Miłobędzki [13] in 1931 in the reaction of (–)-menthol and phosphorus trichloride and subsequent hydrolysis of dimenthyl chlorophosphite formed. Later on, this procedure was successfully repeated by Kafarski [14] and Bałczewski [15], who reported its spectral data as well as elemental analysis and optical rotation value. According to the method mentioned above, we have obtained both enantiomeric (–)- and (+)-dimenthyl phosphites **1a** and **1b** (Fig. 1) for which the spectral data and the value of $[\alpha]_D$ were consistent with the literature [15]. The enantiomeric sulfinimines (Fig. 2) were prepared according to the Davis procedure from enantiomeric p-tolylsulfinamide and benzaldehyde [9].

The addition reactions of **1** to **2** were carried out according to the standard procedure. Thus, a solution of chiral sulfinimine (–)-**2**, (+)-**2** in tetrahydrofuran (THF) was dropwise added to the lithium salt of (–)-**1** or (+)-**1** (generated from the corresponding phosphite and LiHMDS in THF at –78°C under nitrogen) and stirred for 4 h. After quenching the reaction mixture with ammonium chloride at this temperature, the adducts formed were isolated and analyzed (Scheme 1). The results of the experiments performed are presented in Table 1.

For the characterization of the products and determination of the diastereoselectivity of the addition reactions, the ^{1}H and ^{31}P nuclear magnetic resonance (NMR) spectra of the crude reaction mixtures were recorded. In all cases, in the addition reaction of the anions of chiral dimenthyl phosphites to the (–)-(*S*)- and (+)-(*R*)-enantiomers of the *N*-(*p*-tolylsulfinyl)benzaldimine, the ^{1}H NMR spectra showed only a singlet coming from methyl protons of *p*-tolylsulfinyl group at 2.42 ppm and multiplet due to the CH and NH protons at 4.66–4.77 ppm.

The ^{31}P NMR spectrum showed only one single resonance signal for phosphorus coming from the adduct **3a** formed in the reaction of (+)-(*S*)-sulfinimine **2a** with (–)-phosphite **1a** at $\delta = 18.7$ ppm (entry 1). Similarly, for the adduct **3d** obtained in the addition reaction of (–)-(*R*)-sulfinimine **2b** to (+)-phosphite **1b**, the phosphorus singlet at $\delta =$ 18.5 ppm was observed (entry 4). On the other hand, in the ^{31}P NMR spectrum of the reaction mixture of (–)-(*R*)-sulfinimine **2b** and (–)-phosphite **1a**, two signals of phosphorus at $\delta = 18.5$ ppm (major) and $\delta =$ 19.0 ppm (minor) in a ratio 92:8 were observed (entry 2). Two phosphorus signals in a ratio 91:9 (entry 3) at 19.1 ppm (major) and 19.3 ppm (minor) were also visible in the ^{31}P NMR spectrum of the reaction

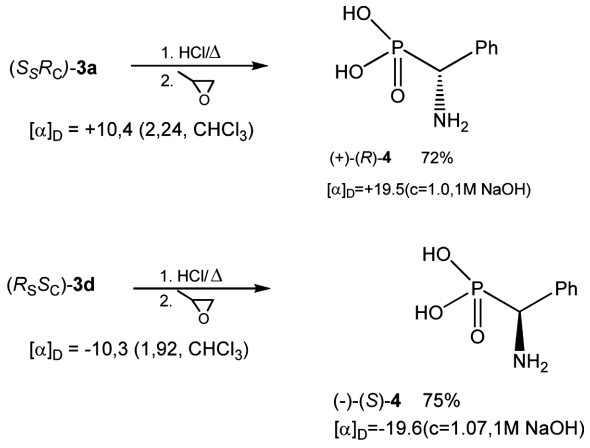


Li-**1** **2** **3** **4**

SCHEME 1 Asymmetric addition of dimenthyl phosphites **1** to sulfinimines **2**.

TABLE 1 Addition of Chiral Dimenthyl Phosphites **1** to Chiral Sulfinimines **2**

Entry	*Phosphite*	*Sulfinimine*	*Adduct **3** dr*	*Yield of major **3** (%)*	*α-Aps **4***
1	(–) **1a**	(+) **2a**	(S_SR_C)-**3a**:(S_SS_C)-**3a**′ 100:0	88	(+)-(*R*)
2	(–) **1a**	(–) **2b**	(R_SS_C)-**3b**:(R_SR_C)-**3b**′ 92:8	77	(–)-(*S*)
3	(+) **1b**	(+) **2a**	(S_SR_C)-**3c**:(S_SS_C)-**3c**′ 91:9	75	(+)-(*R*)
4	(+) **1b**	(–) **2b**	(R_SS_C)-**3d**:(R_SR_C)-**3d**′ 100:0	86	(–)-(*S*)



SCHEME 2 Hydrolysis of aminophosphonates 3.

mixture of (+)-(*S*)-sulfinimine **2a** and (+)-phosphite **1b**.

As it was discussed in our earlier papers [5, 8], in the addition reactions of achiral phosphite anions to (+)-(*S*)-sulfinimine, the signals of major diastereomeric adducts occurred in ^{31}P NMR spectra at the lower fields, whereas the signals of the minor adducts lie at the higher one. The latter information strongly suggested that the stereochemical outcome of the addition of (–)- and (+)-enantiomers of phosphite **1** to the (+)-(*S*)-**2** is the same and should lead to the formation of the adducts **3** with (S_SR_C) configuration (entries 1 and 3), and addition of (+)- and (–)-phosphites **1** to the (–)-(*R*)- sulfinimine **2** should give the (R_SS_C) adducts as the major products (entries 2 and 4). Finally, the stereochemistry of the addition reaction of dimenthyl phosphites **1** to enantiomeric sulfinimines **2** was confirmed by purification of the adducts **3** (entries 1 and 4) and separation of the major diastereomers of **3** (entries 2 and 3) using flash chromatography and their acidic hydrolysis to the free α-APs **4** for which the absolute configurations are known [16] (Scheme 2).

Because, during the deprotection of the amino function and phosphonate ester moiety the bonds around the stereogenic α-carbon atom are not broken, and the fact that (+)-(*R*)- and (–)-(*S*)- α-APs **4** were obtained from adducts **3a** or **3c** and **3b** or **3d**, respectively, it was possible to assign the (S_SR_C)- and (R_SS_C)-configuration to the major diastereomers of adducts **3** (entries 1, 3 and 2, 4).

CONCLUSIONS

In summary, we have demonstrated that in the nucleophilic addition of chiral phosphite anions **1** to chiral *N*-(p-toluenesulfinyl)benzaldimine **2**, the enantiomers of (–)-**1a** and (+)-(*S*)-**2a** as well as of (+)-**1b** and (–)-(*R*)-**2b** are the matched pairs of isomers. The single diastereomers of the adducts **3** formed have opposite absolute configurations at the newly formed stereogenic center of the α-carbon atom. On the other hand, the enantiomers (–)-**1a** and (–)-(*R*)-**2b** or (+)-**1b** and (+)-(*S*)-**2a** are the mismatch pairs, and the diastereomeric ratio (dr) of the major adducts are above 10:1. Also, in these cases, the new stereogenic center at the α-carbon atom of major diastereomers formed possesses the opposite absolute configurations.

In this paper, we have demonstrated that the method of double asymmetric induction using matched pairs of chiral phosphites **1** and enantiomers of *N*-(p-tolylsulfinyl)benzaldimine **2** (**1a** and **2a** or **1b** and **2b**) allows to obtain both enantiomerically pure (+)-(*R*)- and (–)-(*S*)-α-aminobenzyl phosphonic acids **4** in good yields.

EXPERIMENTAL

Nuclear magnetic resonance spectra were recorded on a Bruker 1C200 (Poznań, Poland) spectrometer 200 MHz. All optical rotation measurements were carried out on a Perkin–Elmer MC 241 (Warsaw, Poland) photopolarimeter at room temperature. Progress of reactions was monitored by thin layer chromatography (Merck Kisselgel 60_{254}). Column chromatography was conducted on a Merck (Warsaw, Poland) silica gel (70–230 mesh).

General Procedure for the Addition of Lithium Salt of Dimenthyl Phosphite **1** *to Sulfinimines* **2**

Dimenthyl phosphite **1** (1.5 mmol) in THF (10 mL) was cooled to –78°C and LiHMDS (1.5 mmol) in THF (5 mL) was added. The reaction mixture was

stirred for 1 h at this temperature and sulfinimine **2** (1.0 mmol) in THF (5 mL) was dropped. After stirring for 4 h at –78°C, the reaction mixture was quenched with a water solution of ammonium chloride and the organic layer was separated. The aqueous layer was extracted with ethyl ether and combined organic layers were dried over $MgSO_4$ and evaporated. The product of reaction (the single diastereomer or major diastereomer) was isolated using flash chromatography (silica gel, petroleum ether/ethyl ether 1:1, then ethyl ether).

(+)-Di-(1R,2S,5R)-menthyl(S_SR_C)-1-phenyl-1-(p-tolylsulfinylamino)-methanephosphonate **3a**

$[\alpha]_D$ = +10,4 (2,24; $CHCl_3$), melting point (mp) = 145–146°C. ^{31}P NMR ($CDCl_3$): δ 18.7; ^1H NMR ($CDCl_3$): δ 0.62–0.96 (m, 22H), 1.00–2.06 (m, 14H), 1.9–2.06 (m, 4H), 2.42 (s, 3H), 4.09–4.20 (m, 2H), 4.66–4.77 (m, 2H), 7.26–7.37 (m, 5H) 7.52–7.63 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 15.19, 15.46, 20.80, 21.20, 21.71, 22.39, 22.45, 24.95, 25.04, 31.18, 31.40, 33.61, 33.71, 42.06, 43.21, and 48.26 (d, J_{CP} = 6,99Hz), 55.75 (d, J P_{CP} = 156.61Hz), 79.00 (d, J_{CP} = 8,06Hz), 125.20, 128.07, 129.36, 133.64, 133.77, 141.35, and 141.59; HRMS calcd for $C_{34}H_{52}O_4PSN$ (M+H) 602,8208; found 602,34257.

(–)-Di-(1R,2S,5R)-menthyl (R_SS_C)-1-phenyl-1-(p-tolylsulfinylamino)-methanephosphonate **3b**

$[\alpha]_D$ = –107,8 (1,29; $CHCl_3$), oil. ^{31}P NMR ($CDCl_3$): δ 18.5; ^1H NMR ($CDCl_3$): δ 0.57 (d, J = 6,89Hz, 3H), 0.62 (d, J = 6,93Hz, 3H), 0.75–0.95 (m, 14H), 0.97–1.07 (m, 4H), 1.10–1.49 (m, 4H), 1.58–1.63 (m, 4H), 1.73–2.27 (m, 4H), 2.42 (s, 3H), 4.09–4.20 (m, 2H), 4.66–4.71 (m, 1H), 4.76 (d, J = 2.93 Hz, 1H), 7.26–7.42 (m, 5H), 7.50–7.62 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 15.31, 15.73, 20.97, 21.35, 21.86, 22.60, 25.08, 31.49, 33.85, 43.05, 43.46, 48.41 (d, J_{CP} = 6,89Hz), 56.26 (d, J_{CP} = 156,77 Hz), 78.59 (d, J_{CP} = 8,38Hz), 125.20, 128.27, 129.54, 129.69, 133.80, 133.93, 141.59, 141.88; HRMS calcd. for: $C_{34}H_{52}O_4PSN$ (M+H) 602,8208, found 602,34268.

(+)-Di-(1S,2R,5S)-menthyl (S_SR_C)-1-phenyl-1-(p-tolylsulfinylamino)-methanephosphonate **3c**

$[\alpha]_D$ = +108,9 (0,71; $CHCl_3$), mp = 44–46°C. ^{31}P NMR ($CDCl_3$): δ 19.1; ^1H NMR ($CDCl_3$): δ 0.57 (d, J = 6,90Hz, 3H), 0.69 (d, J = 6,9Hz, 3H), 0.78–0.86 (m, 14H), 0.91–1.17 (m, 4H), 1.18–1.35 (m, 4H), 1.58–1.63 (m, 4H), 1.83–2.17 (m, 4H), 2.42 (s, 3H), 4.09–4.21 (m, 2H), 4.67–4.71 (m, 1H), 4.76 (d, J = 2.91Hz, 1H), 7.29–7.42 (m, 5H), 7.51–7.63 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 15.35, 15.77, 21.06, 21.39, 21.90, 22.65, 25.12, 31.53, 33.89, 43.10, 43.51, 48.45 (d, J_{CP} = 6,12Hz), 56.31 (d, J_{CP} = 156,91Hz), 78.64 (d, J_{CP} = 8,09Hz), 125.24, 128.30, 129.58, 133.98, 141.62; HRMS calcd for $C_{34}H_{52}O_4PSN$ (M+H) 602,8208; found 602,3422

(–)-Di-(1S,2R,5S)-menthyl (R_SS_C)-1-phenyl-1-(p-tolylsulfinylamino)-methanephosphonate **3d**

$[\alpha]_D$ = –10,3 (1,92; $CHCl_3$), mp = 143–144°C. ^{31}P NMR ($CDCl_3$): 18.8; ^1H NMR ($CDCl_3$): δ 0.62–0.97 (m, 22H), 1.00–2.06 (m, 14H), 1.91–2.27 (m, 4H), 2.42 (s, 3H), 4.04–4.22 (m, 2H), 4.66–4.7 (m, 2H), 7.29–7.48 (m, 5H), 7.52–7.63 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 15.31, 15.59, 20.92, 21.31, 21.82, 22.57, 25.06, 25.17, 31.30, 31.53, 33.73, 33.85, 42.19, 43.34, 48.40 (d, J_{CP} = 6,09 Hz), 55.89 (d, J_{CP} = 156,7 Hz), 79.14 (d, J_{CP} = 7,96 Hz), 125.31, 128.21, 129.50, 129.56, 129.71, 133.73, 133.86, 141.49, 141.7; HRMS: calcd for $C_{34}H_{52}O_4PSN$ (M+H) 602.8208; found 602,34200.

*Hydrolysis of adducts **3** to α-APs* **4**

Adducts **3a** or **3d** (0.87mmol) were refluxed with HCl (36%, 10 mL) for 6 h. After cooling to room temperature, H_2O (10 mL) was added and extracted with $CHCl_3$ (3 × 5 mL). The water fraction was evaporated, and EtOH (5 mL) was added and neutralized with propylene oxide. The precipitate formed was filtered off and washed with EtOH and diethyl ether and dried over P_2O_5. The pure APs **4** was obtained as a white crystaline solid: (+)-(R)-**4** (0,115g, 72%), $[\alpha]_D$ = +19.5 (c = 1.0, 1 M NaOH), mp 286–288°C. (–)-(S)-**4** (0.124g, 75%), $[\alpha]_D$ = –19.6(c = 1.07, 1M NaOH), mp 285–288°C.

REFERENCES

[1] Mucha, A.; Kafarski, P.; Berlicki, L. J Med Chem 2001, 54, 5955–5980.
[2] Kukhar, V. P.; Hudson, H. R. (Eds.). Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity, Willey: New York, 2000.
[3] Kudzin, Z. H.; Kudzin, M. H.; Drabowicz, J.; Stevens, C. V. Curr Org Chem 2011, 15, 2015–2071.
[4] Mikołajczyk, M.; Łyżwa, P.; Drabowicz, J.; Wieczorek, M. W. Chem Commun 1997, 1503–1504.
[5] Mikołajczyk, M.; Łyżwa, P.; Drabowicz, J. Tetrahedron: Asymmetry 1997, 8, 3991–3994.
[6] Davis, F. A.; Lee, S.; Yan, H.; Titus, D. D. Org Lett 2001, 3, 1757–1760.
[7] Łyżwa, P.; Błaszczyk, J.; Sieroń, L.; Mikołajczyk, M. Eur J Org Chem 2013, 11, 2106–2115.

[8] Mikołajczyk, M. J Organomet Chem 2005, 690, 2571.
[9] Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Reddy, G. V.; Portonovo, P. S.; Fanelli, D.; Reddy, T. E.; Zhou, R.; Caroll, P. J. J Org Chem 1997, 62, 2555–2563.
[10] Davis, F. A. J Org Chem 2006, 71, 8993–9003.
[11] Mikołajczyk, M.; Łyżwa, P.; Drabowicz, J. Tetrahedron: Asymmetry 2002, 13, 2571-2576.
[12] Kolodiazhnyi, O. I.; Sheiko, S. Yu Russ J Gen Chem (Zh Obsch Khim) 2001, 71, 1039–1040
[13] Miłobędzki, T.; Janczak, W. Roczniki Chemii 1931, 11, 840.
[14] Dżygiel, P.; Wieczorek, P.; Jonsson, J. A.; Milewska, M.; Kafaski, P. Tetrahedron 1999, 55, 9923–9932.
[15] Bałczewski, P.; Szadowiak, A.; Bodzioch, A.; Białas, T.; Wieczorek, W. M.; Szyrej, M. J Organomet Chem 2007, 692, 997–1009.
[16] Głowiak, T.; Sawka-Dobrowolska, W.; Kowalik, J.; Mastalerz, P.; Soroka, M.; Zoń, J. Tetrahedron Lett 1997, 3965.