Tetrahedron 66 (2010) 9840-9848

Contents lists available at ScienceDirect

Tetrahedron



N-Carbamate α -aminoalkyl-*p*-tolylsulfones—convenient substrates in the nitro-Mannich synthesis of secondary *N*-carbamate protected *syn*-2-amino-1-nitroalkanephosphonates

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ARTICLE INFO

Article history: Received 7 July 2010 Received in revised form 5 October 2010 Accepted 25 October 2010 Available online 29 October 2010

Keywords: Aza-Henry reaction Diethyl nitromethanephosphonate α-Amido sulfones PTC reaction Aminonitrophosphonates 1,2-Diaminoalkanephosphonates

ABSTRACT

An efficient one-pot synthesis of secondary *N*-carbamate protected syn- β -amino- α -nitroalkanephosphonates using diethyl nitromethanephosphonate and *N*-Boc or *N*-Cbz imines, generated in situ from stable *N*-Boc or *N*-Cbz α -aminoalkyl-*p*-tolylsulfones has been developed under PTC conditions. A model enantioselective version of this reaction is also described. Enantioselectivity up to 67% ee is achieved using a chiral thiourea catalyst derived from a cinchona alkaloid. Completely stereoselective conversion of the title compounds into partially *N*-carbamate protected *syn*-1,2-diaminoalkanephosphonates has also been elaborated.

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1. Introduction

The aza-Henry reaction,^{1–7} known also as the nitro-Mannich reaction, is usually base promoted addition of nitro compounds to Nprotected imines, often being employed in the asymmetric synthesis of vicinal diamines and α,β-diamino acids.^{1b,e,g,2,3a-c,h-j,l,4b,c,5d,6,8,9} There are however, only isolated examples of the nitro-Mannich approach to the preparation of β -amino- α -nitro- and α , β -diaminophosphonates^{10–12} utilizing 1-nitroalkanephosphonates and N-protected imines as starting materials. In the late 1970s Petrov et al.¹² described the addition of nitromethane- and 1-nitroethanephosphonates to N-benzylidenebenzeneamine leading to *N*-phenyl analogues of aminonitrophosphonates. Recently, during our investigations, Johnston et al.¹⁰ published a highly diastereoand enantioselective addition of dialkyl 1-nitroethanephosphonates to N-Boc imines, catalyzed by chiral Brønsted acids, which allows obtaining anti-2-amino-1-nitroethanephosphonates with a quaternary center next to a phosphorus atom. Until now however, the reaction of diethyl nitromethanephosphonate with N-carbamate α aminoalkyl-p-tolylsulfones, as convenient precursors of unstable Ncarbamate imines, leading to the title compounds has not been described. This prompted us to present here our contribution as a new, practical synthesis of secondary 1-amino-2-nitroalkaneand 1,2-diaminoalkanephosphonates utilizing diethyl nitromethanephosphonate¹³ (1) and *N*-carbamate α -aminoalkyl-*p*tolylsulfones **2** as starting materials.

2. Results and discussion

It is well documented that *N*-Boc and *N*-Cbz protected α -aminoalkyl-*p*-tolylsulfones^{1d,14–16} **2** can be considered as stable, crystalline, and easy to handle equivalents of *N*-Boc and *N*-Cbz imines. Not surprisingly, nucleophilic additions of deprotonated nitroalkanes to *N*-carbamate imines generated in situ from the α -amido sulfones, mentioned above by base-induced elimination, have recently been the subject of extensive studies.^{4i,5a,b,d,7} In this context, easy to perform and low demanding as far as reactions conditions are concerned, phase transfer catalysis (PTC)^{1f,17} approaches to the aza-Henry reaction seemed to be especially beneficial. After preliminary experimentations, standard liquid–solid PTC conditions using potassium carbonate as a base for simultaneous deprotonation and elimination, tetrabutylammonium bromide (TBAB) as catalyst and toluene as solvent were selected for the reaction of diethyl nitromethanephosphonate (**1**) with *N*-carbamate protected α -aminoalkyl-*p*-tolylsulfones **2** (Scheme 1).





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 $\label{eq:scheme1} \begin{array}{l} \mbox{Scheme 1. Reagents and conditions: (i) K_2CO_3 solid (5 equiv), TBAB (10 mol \%), toluene, rt, 26 h; (ii) aq $KHSO_4$.} \end{array}$

As shown in Scheme 1, a vigorously stirred mixture of 1, *N*-Boc protected α -aminoalkyl-*p*-tolylsulfones **2a**–**f** (1.03 equiv), potassium carbonate (5 equiv) and TBAB (10 mol %) in toluene afforded, after 26 h at room temperature, the mixture of *syn*- and *anti*-adducts **3a**–**f** in good yields (79–88%) after flash chromatography. The results are summarized in Table 1.

The results given in Table 1 indicate that adducts **3** are formed with low and comparable *syn*-diastereoselectivity (*syn*-**3a**–**f**/*anti*-**3a**–**f**=56/44–64/36). The reaction also works for *N*-Cbz protected α -aminoalkyl-*p*-tolylsulfones **2g**–**h** as imine surrogates, for which,

Table 1

Diethyl β -amino- α -nitrophosphonates **3a**-**h** prepared

Entry	3	R	PG	Yield ^{a,b} (%)	syn/anti ^c	syn- 3 Yield ^d (%)	31 P NMR, δ	
							syn	anti
1	3a	Ph	Boc	87	59/41	40 ^e	10.36	11.02
2	3b	p-MeOC ₆ H ₄		83	63/37	39	10.08	10.79
3	3c	p-ClC ₆ H ₄		88	64/36	41	10.10	10.76
4	3d	2-Furyl		87	63/37	41	9.88	10.55
5	3e	Me		88	61/39	_	11.09	11.27
6	3f	Et		79	56/44	_	11.00	11.29
7	3g	Ph	Cbz	71	53/47	28 ^f	10.17	10.93
8	3h	Me		84	57/43	_	10.67	10.81

^a All reactions were carried out on a 2 mmol scale.

^b Overall yield of pure *syn-* and *anti-*adducts **3a-h** isolated after flash chromatography.

^c Diastereomeric ratio measured by ³¹P NMR of the crude products.

^d Yields of pure *syn-***3**, after crystallization from CCl₄.

^e Second crop of crystals was isolated in 19% yield and consisted of *anti-***3a** mainly (*syn/anti=*25/75).

^f The mixture of *syn*- and *anti*-**3g** (*syn/anti*=10/90) was isolated in 27% yield from the mother liquor.

the mixtures of *N*-Cbz protected *syn*- and *anti*-adducts **3g** and **3h** are isolated in much the same yields and with similar *syn*-diastereoselectivity (Table 1, entries 7–8). Facile epimerization on the carbon atom C-1, next to the nitro group, in adducts **3** and/or retro addition/re-addition occurring under the reaction conditions, seem to be responsible for the low diastereoselectivity of the above mentioned reactions.[†] We found, additionally, that stirring the mixture of **1** and **2a** or **1**, and **2g** for 10 days under the same PTC conditions, resulted, within the experimental error, in the same diastereomeric ratios of the final adducts **3a** or **3g**, respectively.

The evaluation of the scope of the reaction shows that the method is applicable to aromatic, heteroaromatic and aliphatic *N*-Boc, and *N*-Cbz protected α -aminoalkyl-*p*-tolylsulfones **2**. Pure

syn-**3a**–**d** and *syn*-**3g** could easily be isolated in 28–41% yields from the mixture of **3a**–**d** and **3g** via simple crystallization from carbon tetrachloride (Table 1, entries 1–5 and 7, respectively). Pure aliphatic derived *syn*-adducts **3e**–**f** and **3h**, which are formed as viscous oils, could not be separated from the mixture either by crystallization or chromatography.

The mother liquors of adducts **3**, obtained after crystallizations, consisted mainly of *anti*-diastereomers **3**, and these mixtures slowly enriched themselves in *syn*-**3** after prolonged standing at room temperature.

Attempted widening of the scope of the above nitro-Mannich reaction on diethyl 1-nitroethanephosphonate,¹⁸ a homologue of **1**, was unsuccessful. Starting 1-nitroethanephosphonate was always recovered from the reaction mixture.

Determination of the relative *syn/anti* configuration of adducts **3** based on NMR analysis of diagnostic vicinal coupling constants $({}^{3}J_{HH}, {}^{3}J_{HP}, {}^{3}J_{CP})$ failed. In almost all of the adducts diagnostic protons (H₁ and H₂) appeared as complex multiplets or the differences in the values of their vicinal coupling constants ${}^{3}J_{HH}$ were too small to be diagnostic. Therefore, the relative *syn/anti* configurations of **3** were established by conversion of selected compounds **3** into the appropriate imidazolidine-2-thiones **5** (vide infra). However, the phosphorus chemical shifts of **3** were consistent with the given diastereomer. In the 31 P NMR spectra of all of nitrophosphonates **3** the signals of the *syn*-isomers appeared 0.14–0.74 ppm upfield relative to those of the *anti*-isomers (Table 1).

Having established the synthesis of *N*-carbamate protected 2-amino-1-nitroalkanephosphonates **3**, we focused our attention on their conversion into partially protected 1,2-diaminoalkanephosphonates **4**. Several 1,2-diaminoalkanephosphonic acids act as leucine aminopeptidase inhibitors.¹⁹ However, the number of known α , β -diaminoalkanephosphonates is limited and only a few routes to both racemic or enantioenriched compounds have been reported till now.^{10,20,21}

Sodium borohydride/nickel(II) chloride²² system in methanol was used as the reductant of choice for the nitro group. Such reductions occurred under very mild conditions, and they were shown to proceed with retention of configuration at the stereogenic center on the carbon atom next to the nitro group.^{31,4c,h,6b,d,e,23}

As shown in Scheme 2, solid NaBH₄ was added at -30 °C to the solution of nitrophosphonates **3** and nickel(II) chloride hexahydrate in methanol. The mixture was allowed to warm to 0 °C, and desired 1,2-diaminophosphonates **4** were isolated in moderate yields (43–75%), after quenching with aq ammonium chloride followed by flash chromatography. The approach mentioned above enables a two-step synthesis of secondary 1,2-diaminophosphonate esters (Table 2).

As shown in Table 2, *syn*-1,2-diaminophosphonates **4a**–**d** and **4g** were only obtained from the reduction of pure *syn*-adducts



p-ClC₆H₅ (c), 2-furyl (d), Me (e), Et (f) 3,4 PG = Cbz; R = Ph (g), Me (h)

Scheme 2. Reagents and conditions: (i) NaBH₄ (10 equiv), NiCl₂×6H₂O (1.05 equiv), MeOH, -30 °C, 5 min, 0 °C; (ii) aq NH₄Cl, 0 °C.

3a–d and **3g** (Table 2, entries 1, 3–5, and 8, respectively). In turn, the mixture of *syn-* and *anti-*adducts **3a** and **3e–h** afforded, after reduction, the diastereomeric mixture of *syn-* and *anti-*diaminophosphonates **4a** and **4e–h** in approximately the same ratio as starting nitro adducts **3** (Table 2, entries 2, 6–7, and 9–10, respectively). These results confirm that reduction of the nitro group

[†] When the solution of pure *syn*-**3a** in CDCl₃ was kept in the presence of pyridine for 4 h at room temperature, or when pure *syn*-**3a** was stirred in toluene in the presence of K₂CO₃/TBAB system for 48 h at room temperature, followed by standard work-up, epimerized mixture of *syn*- and *anti*-**3a** (*syn*/*anti*=58/42) was always formed. No formation of starting diethyl nitromethanephosphonate (**1**) was observed in the ³¹P NMR spectrum of the reaction mixture, however.

Table 2	
1.2-Diaminophosphonates 4a-h	prepare

Entry	3/4	R	PG	3 syn/anti	4		^{31}P NMR, δ	
					Yield ^a (%)	syn/anti ^b	syn- 4	anti- 4
1	a	Ph	Boc	100/0	63	100/0	25.69	25.56
2	а	Ph		25/75 ^c	54	25/75		
3	b	p-MeOC ₆ H ₄		100/0	53	100/0	26.17	_
4	с	p-ClC ₆ H ₄		100/0	66	100/0	25.77	_
5	d	2-Furyl		100/0	55	100/0	25.27	_
6	e	Me		61/39	43	58/42	27.16	27.08
7	f	Et		60/40	60	64/36 ^d	27.5 ^d	27.5 ^d
8	g	Ph	Cbz	100/0	75	100/0	25.48	25.28
9	g	Ph		$\sim 10/90^{e}$	43	16/84 ^d		
10	h	Me		57/43	58	59/41	26.97	26.78

^a Overall yield of pure syn- and anti-adducts **3a-h** after flash chromatography.
 ^b Diastereomeric ratio measured by ³¹P NMR of the crude products.

^c The mixture of adducts **3a** (*syn/anti*=25/75), isolated from the mother liquor was used as substrate.

^d As a result of overlapping of ³¹P NMR signals, *syn/anti* ratio of diastereomeric diaminophosphonates **4** was determined by their cyclization into *trans*- and *cis*-imidazolidine-2-thiones **5** (³¹P NMR).

^e The mixture of nitro adducts **3g** (*syn/anti=* \sim 10/90), isolated from the mother liquor, was used as substrate. As a result of relatively quick epimerization of **3g** approximate ratio of diasteromer is only given.

takes place with retention of configuration on the carbon atom next to this group and simultaneously, correlate the configuration of 1,2-diaminophosphonates **4** with parent *N*-carbamate protected nitrophosphonates **3**.

Relative configuration of 1,2-diaminophosphonates **4**, in turn, was assigned by conversion of the selected adducts **4** into the appropriate imidazolidine-2-thiones **5** for which, relative configuration could easily be determined by ³¹P NMR analysis of their chemical shifts and the ring protons vicinal coupling constant (${}^{3}J_{\text{HH}}$) in ¹H NMR (Scheme 3).

As shown in Scheme 3, imidazolidine-2-thiones **5a** and **5b** were prepared in 51% and 41% overall yield via standard deprotection (TFA/CH₂Cl₂) of *N*-Boc protected *syn*-1,2-diamino-2-phenyl-ethylphosphonate **4a** and *syn/anti*-1,2-diaminobutylphosphonates **4f**, followed by the conversion of free 1,2-diaminophosphonates thus obtained into *trans*-imidazolidine-2-thione **5a** and the mixture of *trans*- and *cis*-imidazolidine-2-thiones **5b** (trans/cis=64/36), using 1,1'-thiocarbonyldiimidazole as condensing agent in the presence of



Scheme 3. Reagents and conditions: (i) TFA, CH₂Cl₂, rt, 2 h; (ii) Et₃N, 1,1'-thiocarbonyldiimidazole, CH₂Cl₂, rt, 24 h; (iii) aq HCl; (iv) ammonium formate (10 equiv), 10% Pd/C (cat), MeOH, rt, 2 h, Ar.

triethylamine.²⁴ Similarly, the mixture of *trans*- and *cis*-**4g** (cleavage of *N*-Cbz group was accomplished using ammonium formate/Pd–C system²⁵) afforded the mixture of the appropriate *trans*- and *cis*-imidazolidine-2-thiones **5a** (trans/cis=16/84) in 23% yield.

The stereochemistry of the imidazolidine-2-thiones **5** was assigned by ¹H and ³¹P NMR analysis. The values of the vicinal coupling constants for **5a** (³*J*_{HH(trans)}=6.25 Hz, ³*J*_{HH(cis)}=10.0 Hz) and **5b** (³*J*_{HH(trans)}=6.36 Hz) are consistent with the observation that *trans*-imidazolidine-2-thiones have smaller coupling constants than the corresponding *cis*-diastereomer.²⁶ In the ³¹P NMR spectra of **5a** (δ_P (trans/cis)=18.46/16.42) and **5b** (δ_P (trans/cis)=19.24/18.21) the signals of the trans-isomers appeared 1.03–2.04 ppm downfield relative to those of the cis-isomers.^{21k} As all steps of the above mentioned transformations occur with the retention of configurations, these results confirm the assignment of relative configuration in the parent nitro adducts **3**.

Having established the conditions of the reaction of diethyl nitromethanephosphonate (1) with *N*-carbamate protected α -aminoalkyl-*p*-tolylsulfones **2** we next attempted the asymmetric PTC reaction,^{1f,17} using cinchona alkaloid derived quaternary ammonium salts as catalysts. Such chiral PTC catalysts were successfully employed in the highly stereoselective aza-Henry reactions of simple nitroalkanes and *N*-protected imines generated in situ from *N*-formyl or *N*-carbamate α -aminoalkyl-arylsulfones.^{5a,b,d}

N-tert-Butoxycarbonylamino(phenyl)methyl-*p*-tolylsulfone (**2a**) was chosen as a model compound, and its reaction with **1** in the presence of solid K_2CO_3 or Cs_2CO_3 was investigated using quinine-derived catalyst **6** (Scheme 4).

However, irrespective of the base applied, model studies did not give significant asymmetric induction under these conditions. The major *syn*-**3a**' was formed with low diastereoselectivity and poor enantioselectivity (Table 3, entries 1 and 2). The enantiomeric excesses were assessed from ³¹P NMR spectra of the crude reaction mixture, taking into account diagnostic chemical shifts (δ_P) of diethyl *syn*- and *anti*-{(2-*tert*-butoxycarbonylamino)-1-[(*S*)-2-(6-methoxynaphthalen-2-yl)propionylamino]-2-phenyl-ethyl}phos-



Scheme 4. Asymmetric aza-Henry reaction of 1 with 2a.

phonates prepared by reduction of the crude nitro adducts **3a**' (NaBH₄/NiCl₂), followed by derivatization²⁷ of thus formed *syn/anti*-**4a**' amines with (*S*)-Naproxen chloride [(S)-2-(6-methoxynaphthalen-2-yl)propionyl chloride].²⁸

(*S*)-Naproxen chloride was proved to be a convenient chiral derivatizing agent (CDA) for the determination of enantiomeric purity as well as the absolute configuration assignments of diethyl 1-amino- and 2-aminoalkanephosphonates by NMR.^{27,29} Amidation under these conditions proceeds quantitatively, and is not accompanied by racemization.^{27 ‡} The diastereomeric anisochronicity in naproxen amide of **4a**' was sufficiently large to estimate the ee of the *syn*-isomer (δ_P =21.63/22.06, $\Delta\delta$ =0.43). However, for the *anti*-isomer only a broad singlet (δ_P =22.38) was observed in ³¹P NMR spectrum.

[‡] Entire derivatization (scale: 0.05 mmol) using (*S*)-Naproxen chloride as CDA, followed by determination of the ee as well as the absolute configurations assignments were performed in an NMR tube using anhydrous CDCl₃ as solvent and pyridine as a base.

Table 3	
The asymmetric aza-Henry reaction of 1 with <i>N</i> -Boc-amino(phenyl)methyl- <i>p</i> -tolylsulfone (2a)	

Entry	Base/solvent/time ^a	Temperature °C	cat*	Conv. (%)	3a ' syn/anti ^b	<i>syn—3a'/syn—4a' ee^c (%)</i>
1	K ₂ CO _{3(s)} /toluene/26 h	rt	6	99	58/42	12
2	Cs ₂ CO _{3(s)} /toluene/26 h	rt	6	93	59/41	10
3	K ₂ CO _{3(s)} /MeCN/3d	rt	7	100	55/45	10
4	$K_2CO_{3(s)}/CH_2Cl_2/3d$	rt	7	100	56/44	21
5	K ₂ CO _{3(s)} /THF/26h	rt	7	100	59/41	20
6	K ₂ CO _{3(s)} /toluene/3d ^{d,e,f}	rt	7	99	57/43	47
7	K ₂ CO _{3(s)} /toluene/3d	0	7	96	58/42	60
8	K ₂ CO _{3(s)} /toluene/8d	-20	7	94 ^g	58/42	67

^a Reaction conditions: scale 0.1 mmol, (c 0.1 mol/L); cat 6 (10 mol %) or cat 7 (20 mol %), base (5 equiv). Isomers 3a', 4a', and 3g' have the same structure as their racemic counterparts.

^b Diastereomeric ratio measured by ³¹P NMR of the crude products.

^c Calculated from the ³¹P NMR spectra of (S)-Naproxen amides of *syn/anti*-**4a**' amines (δ_{syn} =21.63/22.06; δ_{anti} =22.38) obtained via reduction of **3a**' using NaBH₄/NiCl₂ system, followed by derivatization of thus formed amines **4a**' with (S)-Nap-Cl. Absolute configurations of the major *syn*-isomers **3a**' and **4a**', respectively, were determined to be (*1S,2S*). ^d For the reaction of **1** with N-Cbz sulfone **2g** the mixture of *syn/anti*-**3g**' (*syn/anti*=58/42) was obtained with 34% ee for *syn*-**3g**' under the same reaction conditions. In turn, only 68% conversion was obtained for the reaction conducted at 0 °C for 3 days.

^e When the reaction of **1** with *N*-Boc sulfone **2a** was repeated at rt on 1 mmol scale, pure *syn*-nitro adduct **3a**' and *syn*-diamino adduct **4a**' (47% ee) were isolated in 27% and 61% yields, respectively.

^f When the reaction of **1** with *N*-Boc imine, preformed independently from **2a**, was repeated at room temperature without the addition of K_2CO_3 , only in the presence of catalyst **7**, 68% conversion was obtained after 24 h (*syn/anti*-**3a**'=56/44) and no *syn*-enantioselectivity was observed.

^g After 24 h only 10% conversion was observed.

Much better enantioselectivities were obtained when PTC catalyst 6 was substituted for the bifunctional thiourea derived from 9-amino(9-deoxy)epiquinine³⁰ **7** in the model reaction. (Scheme 4, Table 3, entries 3-8). Recently, thiourea-based bifunctional organocatalysts were successfully employed in nitro-Mannich reactions of nitroalkanes with activated imines ^{4a,b,h,k} Thus, in the reaction of 1a with 2a, in the presence of 7(20 mol %), the mixture of syn-3a' and anti-3a' was formed with low syn-diastereoselectivity and with moderate to good syn-enantioselectivity, the latter being highly solvent and temperature dependent. The use of toluene gave the highest enantioselectivity at room temperature (47% ee. Table 3. entry 6). Lower enantioselectivities were observed for other solvents (Table 3, entries 3–5). By lowering the reaction temperature to -20 °C, the ee was improved up to 67% for the major syn-**3a**', however at the expense of the reaction time (Table 3, entry 8). We also found that substitution of α -amido sulfone **2a** for *N*-benzyloxycarbonylamino(phenyl)methyl-p-tolylsulfone (2g) resulted in the formation of a mixture of syn/anti-3g' (syn/anti=58/42) with lower syn-enantioselectivity (34% ee) compared with the analogous reaction in which sulfone 2a was used as imine precursor (Table 3, footnote d). However, when the addition of diethyl nitromethanephosphonate (1) to N-Boc imine,^{16c} preformed independently from N-Boc-amino(phenyl)methyl-p-tolylsulfone (2a), was repeated at room temperature in toluene without the addition of K₂CO₃, only in the presence of chiral catalyst 7, the reaction was sluggish and gave a mixture of syn/anti-3a' (syn/anti=56/44) with no syn-enantioselectivity (Table 3, footnote f). This result shows that the catalyst 7 could only act as the chiral Brønsted acid in the reactions accomplished in the presence of K₂CO₃.

The results obtained for the model reaction are encouraging, however, to achieve better enantioselectivity further tuning of the catalyst structure is necessary.

Finally, the absolute configuration of two consecutive stereogenic centers in the enantioenriched *syn*-**4a**' was determined by ³¹P NMR analysis using (*S*)-Naproxen chloride as chiral derivatizing agent[§] for amidation^{29,31} of each stereogenic center separately (Scheme 5). As shown in Scheme 5, nitro adducts *syn*-**3a**' were reduced to partially protected *syn*-**4a**' amines, followed by derivatization with (*S*)-Naproxen chloride²⁷ to give the mixture of diasterometic (*S*)-Naproxen amides *syn*-**8a**' (δ_P =22.06 (major) and 21.63 (minor); ratio: 74/26).

According to the model proposed by us^{29} for the Naproxen amides of 1-amino- and 2-aminoalkanephosphonates (Scheme 6), the upfield ³¹P NMR chemical shift, attributed to the shielding effect of the naproxen naphthyl ring on the phosphorus atom, should be assigned to aminophosphonate with configuration (1*S*) at C-1 stereogenic center, whereas a minor, downfield chemical shift corresponds to configuration (1*R*) at the same center.

In turn, bisamides syn-**9a**' (δ_P =21.61 (minor), 21.40 (major); ratio: 26/74) were prepared via consecutive acylation of syn-**4a**' using acetic anhydride as acetylating agent, chemoselective deprotection of Boc group in thus obtained *N*-acetyl derivatives followed by derivatization



Scheme 5. The absolute configuration determination of the enantioenriched syn-4a' amines by ³¹P NMR spectroscopy. Reagents and conditions: (i) NaBH₄ (10 equiv), NiCl₂×6H₂O (1.05 equiv), MeOH, -30 °C, 5 min, 0 °C; (ii) aq NH₄Cl, 0 °C; (iii) (S)-Nap-Cl (2.5 equiv), Pyridine/CDCl₃, rt, 1 h; (iv) Ac₂O (3 equiv), Et₃N (3 equiv), 4 h, rt; (v) TFA/ CH₂Cl₂ (1:1 v/v), rt, 2 h.

of free amino group using (*S*)-Naproxen chloride. Employing the model mentioned above,²⁹ (Scheme 6) the major, upfield ³¹P NMR chemical shift should be assigned to aminophosphonate with configuration (2*S*) at carbon C-2, whereas downfield one corresponds to configuration (2*R*) at the same center.[¶] Thus, the absolute configurations of major stereoisomers of *syn*-**8a**' and *syn*-**9a**' were determined to be (1*S*) and (2*S*), respectively. This allows assigning the same configuration for parent *syn*-**4a**' and *syn*-**3a**'.

[§] Since the diaminoderivative syn-4a' is a mixture of enantiomers it is enough to use one enantiomer of Naproxen chloride for the absolute configuration assignment.

[¶] As a matter of fact, the configuration at C-2 carbon atom could also be assigned based on the absolute configuration at C-1 stereogenic center in *syn*-**8**a' and relative configuration of compounds **3** and **4**.



Scheme 6. Model for the assignment of the configuration of diethyl 1-amino- and 2aminoalkylphosphonates from the ³¹P NMR spectra of their (*S*)-Naproxen amides, based on the shielding effect exerted by the anisotropy cone of the naproxen naphthyl ring on the substituents in aminophosphonates ²⁹.

3. Conclusions

In conclusion, we have shown that the reaction of diethyl nitromethanephosphonate (1) with N-Boc and N-Cbz protected α -aminoalkyl-*p*-tolylsulfones **2a**-**h**, as stable equivalents of *N*-carbamate imines, is a convenient and efficient method for the preparation of *N*-protected β -amino- α -nitrophosphonates **3g**-**h** and in consequence also α,β -diaminophosphonates **3a**-**h**. Additions are accomplished under PTC conditions and give the mixture of synand anti- nitro adducts **3g**-**h** in high yields and low syn-diastereoselectivity. Homologue of the nitrophosphonate **1** is unreactive under these conditions. Crystallization of the reaction mixture allows obtaining pure syn-3a-d and syn-3g derived from the corresponding aromatic aldehydes, which, after the reduction by NaBH₄/NiCl₂ system afford partially protected syn-1,2-diaminoalkanephosphonates 4a-d and 4g in moderate yields. A model catalytic, enantioselective version of this aza-Henry reaction was only partially successful. The moderate enantioselectivity (67%) achieved for syn-diastereomer 3a', when bifunctional thiourea derived from 9-amino(9-deoxy)epiquinine 7 is used as a catalyst in the presence of K₂CO₃. Using ³¹P NMR spectroscopy and (S)-Naproxen chloride as chiral derivatizing agent the absolute configuration of the consecutive stereogenic centers in syn-4a' amine was determined.

4. Experimental

4.1. General

NMR spectra were recorded on a Bruker Avance DPX 250 instrument at 250.13 MHz for ¹H NMR, 62.90 MHz for ¹³C NMR, and 101.3 MHz for ³¹P NMR in CDCl₃ solution, using either tetramethylsilane as an internal and 85% H₃PO₄ as an external standard. Positive chemical shifts are downfield from external 85% H₃PO₄ for $^{31}\mathrm{P}$ NMR spectra. Chemical shifts (δ) are indicated in parts per million and coupling constants (J) in hertz. For ¹³C NMR spectra, the peak assignments were made with the assistance of CH-COSY and DEPT experiments. Partially overlapped signals are assigned by asterisks (*). The enantiomeric excesses (ee) were determined by ³¹P NMR spectroscopy using (S)-Naproxen chloride as chiral derivatizing agent (CDA). Optical rotations were measured on a PolAAr 3001 (Optical Activity Ltd.) polarimeter. Elemental analyses were performed on a Perkin-Elmer PE 2400 Analyzer. IR spectra were measured on an IR Alpha Bruker (ATR) instrument and are reported in cm⁻¹. Melting points were determined in open capillaries and are uncorrected. All reagents were purchased from Fluka and were used without further purification. Diethyl nitromethanephosphonate,¹³ diethyl 1-nitroethanephosphonate,¹⁸ and *N*-Boc α -amidoalkyl-*p*-tolylsulfones¹⁵ were prepared as described previously.

4.2. Preparation of substituted diethyl *N*-carbamate 2-amino-1-nitroalkanephosphonates 3a—h; general procedure

Solid, anhydrous K₂CO₃ (1.40 g, 10.0 mmol) was added to a solution of diethyl nitromethanephosphonate (**1**, 394 mg, 2.0 mmol), α -amido sulfone (**2**, 2.05 mmol) and tetrabutylammonium bromide (TBAB, 70 mg, 0.20 mmol) in anhydrous toluene (20 mL). The suspension was vigorously stirred for 26 h at room temperature. The mixture was carefully quenched with 10% aq KHSO₄ (10 mL), the organic layer separated and the aqueous phase extracted with CH₂Cl₂ (3×20 mL). The combined organic phases were washed with brine (2×10 mL), dried over MgSO₄, evaporated, and subjected to flash chromatography on silica gel (AcOEt/hexanes 5:2 or 5:3 v/v) to give pure mixtures of *syn*- and *anti*-adducts **3a**–**h**. Pure *syn*-**3a**–**d** and *syn*-**3g** were obtained after crystallization from CCl₄ (Table 1).

4.2.1. Diethyl syn-(2-tert-butoxycarbonylamino-1-nitro-2-phenylethyl) phosphonate 3a. Crude product was purified by flash chromatography (AcOEt/hexanes 5:2 v/v), followed by crystallization from CCl₄ to give the title compound **3a** (322 mg, 40%) as a colorless solid, mp 136-139 °C; [found: C, 50.73; H, 6.82; N, 6.98. C₁₇H₂₇N₂O₇P requires C, 50.74; H, 6.76; N, 6.96%]; Rf (AcOEt/hexanes 5:2 v/v) 0.44; v_{max} (ATR) 3315, 2974, 1711, 1560, 1520, 1256, 1161, 982, 699; δ_P (101 MHz, CDCl₃) 10.36; $\delta_{\rm H}$ (250 MHz, CDCl₃) 7.38–7.29 (m, 5H_{Ar}), 6.09–5.95 (m, 1H, NHBoc), 5.77-5.50 (m, 1H, CHNHBoc), 5.34, 5.28 (dd and br dd, respectively, 1H, ³/_{HH} 7.4, 5.8 Hz, ²/_{HP} 13.0, 16.0 Hz, CHNO₂, rotamers), 4.35-3.80 (m, 4H, 2CH₃CH₂O), 1.42, 1.41 (2s, 9H, (CH₃)₃C, rotamers), 1.36–1.10 (m, 6H, 2CH₃CH₂O); δ_{C} (63 MHz, CDCl₃) 154.4 (s, C=O), 136.8 (d, ³*J*_{CP} 6.4 Hz, CHC_{Ar}), 128.6, 128.3, 126.8 (s, 5CH_{Ar}), 88.4 (d, ¹*J*_{CP} 141.1 Hz, CHNO₂), 80.1 (s, (CH₃)₃C), 64.2 (d, ²J_{CP} 6.1 Hz, 2CH₃CH₂O), 53.9 (s, CHNHBoc), 28.1 (s, (CH₃)₃C), 16.0, 15.9 (2d, ³J_{CP} 6.0, 5.8 Hz, $2CH_3CH_2O$).

4.2.2. Diethyl syn-[2-tert-butoxycarbonylamino-2-(4-methoxyphenyl)-1-nitroethyl]phosphonate 3b. Crude product was purified by flash chromatography (AcOEt/hexanes 5:2 v/v), followed by crystallization from CCl₄ to give the *title compound* **3b** (337 mg, 39%) as a colorless solid, mp 145–148 °C; [found: C, 49.98; H, 6.63; N, 6.33. C₁₈H₂₉N₂O₈P requires C, 50.00; H, 6.76; N, 6.48%]; *R*_f(AcOEt/hexanes 5:2 v/v) 0.39; $v_{\rm max}$ (ATR) 3334, 2939, 1704, 1559, 1517, 1247, 1160, 1012, 841, 714; $\delta_{\rm P}$ (101 MHz, CDCl₃) 10.08; $\delta_{\rm H}$ (250 MHz, CDCl₃) 7.31–6.85 (m, 4H_{Ar}), 6.17 (d, 1H, ³J_{HH} 9.2 Hz, NHBoc), 5.55-5.42 (m, 1H, CHNHBoc), 5.48-5.29 (m, 1H, CHNO₂), 4.33-3.96 (m, 4H, 2CH₃CH₂O), 3.78 (s, 3H, OCH₃), 1.41 (s, 9H, (CH₃)₃C), 1.39–1.16 (m, 6H, 2CH₃CH₂O); δ_C (63 MHz, CDCl₃) 157.8 (s, C=O), 152.8 (s, CH₃OC_{Ar}), 127.1 (d, ${}^{3}J_{CP}$ 6.2 Hz, CHC_{Ar}), 112.4, 126.5, (2s, 4CH_{Ar}), 86.8 (d, ¹J_{CP} 141.1 Hz, CHNO₂), 78.4 (s, (CH₃)₃C), 62.5 (d, ²J_{CP} 6.4 Hz, 2CH₃CH₂O), 53.4 (s, OCH₃), 52.1 (br s, CHNHBoc), 26.4 (s, (CH₃)₃C), 14.4, 14.3 (2d, ³J_{CP} 5.6 Hz, 2CH3CH2O).

4.2.3. Diethyl syn-[2-tert-butoxycarbonylamino-2-(4-chlorophenyl)-1-nitroethyl]phosphonate **3c**. Crude product was purified by flash chromatography (AcOEt/hexanes 5:3 v/v), followed by crystallization from CCl₄ to give the *title compound* **3c** (358 mg, 41%) as a colorless solid, mp 157–160 °C; [found: C, 46.52; H, 5.85; N, 6.65. C₁₇H₂₆ClN₂O₇P requires C, 46.74; H, 6.00; N, 6.41%]; *R*_f(AcOEt/hexanes 5:2 v/v) 0.39; ν_{max} (ATR) 3332, 2974, 1709, 1560, 1514, 1246, 1159, 1011, 867; δ_P (101 MHz, CDCl₃) 10.10; δ_H (250 MHz, CDCl₃) 7.35–6.85 (m, 4H_{Ar}), 6.09 (br d, ³*J*_{HH} 8.1 Hz, 1H, NHBoc), 5.60–5.48 (m, 1H, CHNHBoc), 5.31 (br dd, ³*J*_{HH} 7.8 Hz, ²*J*_{HP} 13.0 Hz, 1H, CHNO₂), 4.37–3.92 (m, 4H, 2CH₃CH₂O), 1.41 (s, 9H, (CH₃)₃C), 1.38–1.19 (m, 6H, 2CH₃CH₂O); δ_{C} (63 MHz, CDCl₃) 152.8 (s, C=O), 133.8 (d, ³*J*_{CP} 6.5 Hz, CHC_{Ar}), 132.2 (*C*_{Ar}), 126.7, 126.3 (*C*H_{Ar}), 86.4 (d, ¹*J*_{CP} 141.0 Hz, CHNO₂), 78.7 (s, (CH₃)₃C), 62.9, 63.8 (2d, ²*J*_{CP} 6.3, 7.5 Hz, 2CH₃CH₂O), 51.7 (br s, CHNHBoc), 26.4 (s, (CH₃)₃C), 14.4, 14.3 (2d, ³*J*_{CP} 6.0 Hz, 2CH₃CH₂O).

4.2.4. Diethyl syn-(2-tert-butoxycarbonylamino-2-furan-2-yl-1-nitroethyl)phosphonate **3d**. Crude product was purified by flash chromatography (AcOEt/hexanes 5:2 v/v), followed by crystallization from CCl₄ to give the *title compound* **3d** (322 mg, 41%) as a colorless solid, mp 92–95 °C; [found: C, 45.86; H, 6.42; N, 7.03. C₁₅H₂₅N₂O₈P requires C, 45.92; H, 6.42; N, 7.14%]; *R*_f(AcOEt/hexanes 5:2 v/v) 0.44; ν_{max} (ATR) 3294, 2976, 1714, 1555, 1390, 1270, 1245, 1022, 752; δ_P (101 MHz, CDCl₃) 9.88; δ_H (250 MHz, CDCl₃) 7.38–7.36 (m, 1H, H_{Ar}), 6.37–6.32 (m, 2H_{Ar}), 5.83–5.62 (m, 2H, CHNHBoc, NHBoc), 5.50–5.39 (m, 1H, CHNO₂), 4.33–3.95 (m, 4H, 2CH₃CH₂O), 1.45, 1.44 (2s, 9H, (CH₃)₃C; rotamers), 1.38–1.18 (m, 6H, 2CH₃CH₂O); δ_C (63 MHz, CDCl₃) 152.7 (s, *C*=O), 147.5 (d, ³J_{CP} 7.3 Hz, CHC_{Ar}), 141.0, 108.9, 106.7 (CH_{Ar}), 84.2 (d, ¹J_{CP} 142.0 Hz, CHNO₂), 78.7 (s, (CH₃)₃C), 63.1, 62.6 (2d, ²J_{CP} 6.5, 7.0 Hz, 2CH₃CH₂O), 46.8 (s, CHNHBoc), 26.4 (s, (CH₃)₃C), 14.5, 14.2 (2d, ³J_{CP} 5.7 Hz, 2CH₃CH₂O).

4.2.5. Diethyl syn/anti-(2-tert-butoxycarbonylamino-1-nitropropyl) phosphonates 3e. Crude product was purified by flash chromatography (AcOEt/hexanes 5:3 v/v) to give the title compound 3e (599 mg, 88%) as a colorless viscous oil; [found: C, 42.55; H, 7.60; N, 8.08. C₁₂H₂₅N₂O₇P requires C, 42.35; H, 7.40; N, 8.23]; R_f (AcOEt/hexanes 5:3 v/v) 0.37; v_{max} (neat) 3305, 2980, 1701, 1556, 1249, 1160, 1013, 730; δ_P (101 MHz, CDCl₃) 11.27 (anti-**3e** 39%), 11.09 (syn-**3e** 61%); δ_H (250 MHz, CDCl₃) 5.34–5.00 (m, 2H, CHNO₂, NHBoc, syn and anti), 4.54-4.36 (m, 1H, CHNHBoc, syn and anti), 4.33-4.08 (m, 4H, 2CH₃CH₂O, syn and anti), 1.45-1.33 (m, 18H, 2CH₃CH₂O, CH₃CH, $(CH_3)_3C$, syn and anti); δ_C (63 MHz, CDCl₃) 152.9 (br s, C=O, syn and anti), 86.1, 84.8 (2d, ¹J_{CP} 143.3, 141.3 Hz, CHNO₂, syn and anti), 78.3 (br s, $(CH_3)_3C$, syn and anti), 62.9, 62.7, 62.5, 62.2 (4d, ${}^2J_{CP}$ 6.7, 7.0, 7.9, 6.8 Hz, 2CH₃CH₂O, syn and anti), 45.4 (s, CHNHBoc, syn), 45.2 (s, CHNHBoc, anti), 26.4 (s, (CH₃)₃C, syn and anti), 16.5 (s, CH₃CH, syn), 15.5 (s, CH₃CH, anti), 14.4 (d, ³*J*_{CP} 5.8 Hz, 2CH₃CH₂O, syn and anti).

4.2.6. Diethyl syn/anti-(2-tert-butoxycarbonylamino-1-nitrobutyl) phosphonates 3f. Crude product was purified by flash chromatography (AcOEt/hexanes 5:3 v/v) to give the *title compound* 3f (560 mg, 79%) as a colorless viscous oil; [found: C, 44.27; H, 7.72; N, 7.71. C₁₃H₂₇N₂O₇P requires C, 44.07; H, 7.68; N, 7.91%]; R_f (AcOEt/hexanes 5:3 v/v) 0.39; *v*_{max} (neat) 2975, 1716, 1557, 1315, 1244, 1162, 1010, 730, 567, 464; δ_P (101 MHz, CDCl₃) 11.29 (*anti*-**3f** 44%), 11.0 (*syn*-**3f** 56%); δ_H (250 MHz, CDCl₃) 5.25-5.09 (m, 2H, CHNO₂, NHBoc, syn and anti), 4.36-4.16 (m, 5H, 2CH₃CH₂O, CHNHBoc, syn and anti), 1.80-1.60 (m, 2H, CH₃CH₂CH, syn and anti), 1.44 (s, 9H, (CH₃)₃C, syn and anti), 1.41–1.31 (m, 6H, 2CH₃CH₂O, syn and anti), 1.00 (br t, ³J_{HH} 7.4 Hz, 3H, CH₃CH₂CH, syn and anti); δ_{C} (63 MHz, CDCl₃) 155.1, 154.9 (2s, C=O, syn and anti), 86.8 (d, ¹J_{CP} 142.4 Hz, CHNO₂, syn), 86.3 (d, ¹J_{CP} 145.6 Hz, CHNO₂, anti), 79.8 (br s, (CH₃)₃C, syn and anti), 64.9, 64.4, 64.3, 63.8 (4d, ²*J*_{CP} 6.8, 5.0, 4.0, 6.9, 2CH₃CH₂O, *syn* and *anti*), 52.9 (s, CHNHBoc, anti), 52.1 (s, CHNHBoc, syn), 28.1 (s, (CH₃)₃C, syn and anti), 25.3 (d, ³J_{CP} 5.2 Hz, CH₃CH₂, syn), 24.7 (d, ³J_{CP} 4.3 Hz, CH₃CH₂, anti), 16.1 (d, ³J_{CP} 6.0 Hz, 2CH₃CH₂O, syn and anti), 10.3 (d, ⁴J_{CP} 2.9 Hz, CH₃CH₂).

4.2.7. Diethyl syn-(2-benzyloxycarbonylamino-1-nitro-2-phenylethyl) phosphonate **3g**. Crude product was purified by flash chromatography (AcOEt/hexanes 5:2 v/v), followed by crystallization from CCl₄. to give the *title compound* **3g** (244 mg, 28%) as a colorless solid, mp 100–103 °C; [found: C, 55.16; H, 5.60; N, 6.38. C₂₀H₂₅N₂O₇P requires C, 55.05; H, 5.77; N, 6.42%]; *R*_f (AcOEt/hexanes 5:2 v/v) 0.39; *v*_{max} (ATR) 3306, 2957, 1742, 1555, 1528, 1246, 1006, 813, 694; δ_P (101 MHz, CDCl₃) 10.93 (*anti*-**3g** 47%), 10.17 (*syn*-**3g** 53%); δ_H (250 MHz, CDCl₃)

7.39–7.29 (m, 10H_{Ar}), 6.40 (br d, ${}^{3}J_{HH}$ 9.3 Hz, 1H, NH), 5.70–5.62 (m, 1H, CHPh), 5.40 (dd, ${}^{3}J_{HH}$ 6.1 Hz, ${}^{2}J_{HP}$ 16.5 Hz, 1H, CHNO₂), 5.17–5.03 (m, 2H, CH₂Ph), 4.15–4.01 (m, 4H, 2CH₃CH₂O), 1.33–1.08 (m, 6H, 2CH₃CH₂O); δ_{C} (63 MHz, CDCl₃) 155.3 (s, C=O), 136.3 (d, ${}^{3}J_{CP}$ 5.8 Hz, CHC_{Ar}), 136.0 (s, C_{Ar}), 128.7, 128.5, 128.3, 128.0, 127.2 (s, CH_{Ar}), 88.1 (d, ${}^{1}J_{CP}$ 141.0 Hz, CHNO₂), 67.0 (s, CH₂Ph), 64.3 (d, ${}^{2}J_{CP}$ 6.0 Hz, 2CH₃CH₂O), 54.6 (s, CHNH), 16.0, 15.9 (2d, ${}^{3}J_{CP}$ 6.3 Hz, 2CH₃CH₂O).

4.2.8. Diethyl syn/anti-(2-benzyloxycarbonylamino-1-nitropropyl) phosphonates 3h. Crude product was purified by flash chromatography (AcOEt/hexanes 5:3 v/v) to give the title compound **3h** (623 mg, 84%) as a colorless viscous oil; [found: C, 48.33; H, 6.37; N, 7.21. C₁₅H₂₃N₂O₇P requires C, 48.13; H, 6.19; N, 7.48%]; R_f (AcOEt/hexanes 5:2 v/v) 0.43; v_{max} (neat) 3285, 2983, 1718, 1555, 1245, 1012, 697, 671; δ_P (101 MHz, CDCl₃) 10.81 (anti-**3h** 43%), 10.67 (*syn*-**3h** 57%); δ_H (250 MHz, CDCl₃) 7.36–7.29 (m, 5H_{Ar}), 5.93 (d, 1H, ³J_{HH} 8.9 Hz, NHCbz, syn), 5.84 (d, ³J_{HH} 8.3 Hz, NHCbz, 1H, anti), 5.26 (dd, ³*J*_{HH} 5.2 Hz, ²*J*_{HP} 14.5 Hz, 1H, CHNO₂, anti), 5.16 (dd, ³*J*_{HH} 7.2 Hz, $^{2}J_{\rm HP}$ 15.2 Hz, 1H, CHNO₂, syn), 5.10, 5.05 (2s, 2H, CH₂Ph, syn and anti), 4.67-4.39 (m, 1H, CHNHCbz, syn and anti), 4.25-4.06 (m, 4H, 2CH₃CH₂O, syn and anti), 1.42, 1.39 (2d, ³J_{HH} 3.0 Hz, 3H, CH₃CH, syn and anti), 1.36–1.26 (m, 6H, 2CH₃CH₂O, syn and anti); δ_{C} (63 MHz, CDCl₃) 153.5 (s, C=O, syn and anti), 134.4, 134.3, (2s, CH₂C_{Ap}, syn and anti), 126.7, 126.4, 126.3 (3s, CH_{AP}, syn and anti), 86.0, 84.8 (2d, ¹J_{CP}) 145.0, 141.9 Hz, CHNO₂, syn and anti), 65.1 (s, CH₂Ph, syn and anti), 63.0, 62.7, 62.6, 62.2 (4d, ²J_{CP} 6.7, 6.8, 7.5, 6.8 Hz, 2CH₃CH₂O, syn and anti), 45.9, 45.7 (2s, CHNH, syn and anti), 16.5 (s, CH3CH, syn), 15.4 (s, CH₃CH, anti), 14.4 (d, ³*J*_{CP} 5.7 Hz, 2*C*H₃CH₂O, syn and anti).

4.3. Preparation of diethyl 2-(*N*-carbamate) protected 1,2diaminoalkanephosphonates 4a-h; general procedure

Sodium borohydride (113 mg, 3.0 mmol) was added in two portions to a cooled to -30 °C solution of diethyl *N*-carbamate protected 2-amino-1-nitroalkanephosphonate **3** (0.3 mmol) and NiCl₂×6H₂O (71 mg, 0.3 mmol) in methanol (3 mL). The mixture was allowed to warm up to 0 °C for 10 min, quenched with saturated aq NH₄Cl (9 mL), and extracted with CH₂Cl₂ (3×15 mL). The combined organic phases were washed with brine (5 mL), dried over MgSO₄, evaporated, and subjected to flash chromatography on silica gel (AcOEt) to give pure adducts **4**.

4.3.1. Diethyl syn-(1-amino-2-tert-butoxycarbonylamino-2-phenylethyl)phosphonate **4a**. Crude product was purified by flash chromatography (AcOEt) to give the *title compound* **4a** (70 mg, 63%) as a colorless solid, mp 108–111 °C; [found: C, 54.63; H, 7.60; N, 7.30. C₁₇H₂₉N₂O₅P requires C, 54.83; H, 7.85; N, 7.52%]; *R*_f (AcOEt) 0.26; ν_{max} (ATR) 3391, 3032, 1703, 1530, 1362, 1265, 1246, 1212, 1017, 966, 933, 860, 703; δ_P (101 MHz, CDCl₃) 25.69; δ_H (250 MHz, CDCl₃) 7.42–7.22 (m, 5H_{Ar}), 6.06 (brs, 1H, NHBoc), 5.06 (ddd, ³*J*_{HH} 3.3, 8.0 Hz, ³*J*_{HP} 11.6 Hz, 1H, CHNHBoc), 4.22–3.99 (m, 4H, 2CH₃CH₂O), 3.40 (dd, ³*J*_{HH} 3.3 Hz, ²*J*_{HP} 15.6 Hz, 1H, CHNH₂), 1.66 (br s, 2H, CHNH₂), 1.40 (s, 9H, (CH₃)₃C), 1.35, 1.25 (2 t, ³*J*_{HH} 7.1 Hz, 6H, 2CH₃CH₂O); δ_C (63 MHz, CDCl₃) 155.2 (s, *C*=O), 140.3 (d, ³*J*_{CP} 4.7 Hz, CHC_{Ar}), 128.5, 127.4, 126.6 (*C*_{ar}), 79.4 (s, (CH₃)₃C), 62.6, 62.4 (2d, ²*J*_{CP} 6.9 Hz, 2CH₃CH₂O), 54.9 (br s, CHNHBoc), 53.5 (d, ¹*J*_{CP} 152.0 Hz, CHNH₂), 28.3 (s, (CH₃)₃C), 16.5, 16.3 (2d, ³*J*_{CP} 6.7, 7.0 Hz, 2CH₃CH₂O).

4.3.2. Diethyl syn-[1-amino-2-tert-butoxycarbonylamino-2-(4-methoxyphenyl)-ethyl]phosphonate **4b**. Crude product was purified by flash chromatography (AcOEt) to give the *title compound* **4b** (64 mg, 53%) as a colorless solid, mp 96–99 °C; [found: C, 53.51; H, 7.82; N, 6.92. C₁₈H₃₁N₂O₆P requires C, 53.72; H, 7.76; N, 6.96%]; *R*_f (AcOEt) 0.20; ν_{max} (ATR) 3276, 2977, 1704, 1511, 1244, 1158, 1026, 961, 767; δ_P (101 MHz, CDCl₃) 25.17; δ_H (250 MHz, CDCl₃) 7.29–7.22 (m, 2H_{Ar}), 6.90–6.84 (m, 2H_{Ar}), 5.95 (br s, 1H, NHBoc), 4.95 (ddd, ³J_{HH} 3.4, 8.0 Hz, ³J_{HP} 13.4 Hz, 1H, CHNHBoc), 4.21–3.98 (m, 4H, 2CH₃CH₂O), 3.79 (s, 3H, CH₃O), 3.36 (dd, ${}^{3}J_{HH}$ 3.4 Hz, ${}^{2}J_{HP}$ 15.0 Hz, 1H, CHNH₂), 1.45 (br s, 2H, NH₂), 1.39 (s, 9H, (CH₃)₃C), 1.34, 1.27 (2 t, ${}^{3}J_{HH}$ 7.1 Hz, 6H, 2CH₃CH₂O), δ_{C} (63 MHz, CDCl₃) 158.8 (s, CH₃OC_{Ar}), 155.1 (s, C=O), 132.2 (br s, CHC_{Ar}), 127.6, 113.7 (CH_{Ar}), 79.2 (s, (CH₃)₃C), 62.4, 62.2 (2d, ${}^{2}J_{CP}$ 6.9 Hz, 2CH₃CH₂O), 55.1 (s, CH₃O), 54.3 (br s, CHNHBoc), 53.5 (d, ${}^{1}J_{CP}$ 151.0 Hz, CHNH₂), 28.2 (s, (CH₃)₃C), 16.3, 16.2 (2d, ${}^{3}J_{CP}$ 6.6 Hz, 2CH₃CH₂O).

4.3.3. Diethyl syn-[1-amino-2-tert-butoxycarbonylamino-2-(4-chlorophenyl)-ethyl]phosphonate **4c**. Crude product was purified by flash chromatography (AcOEt) to give the title compound 4c (81 mg, 66%) as a colorless solid, mp 111–114 °C; [found: C, 50.38; H, 7.04; N, 6.97. C₁₇H₂₈ClN₂O₅P requires C, 50.19; H, 6.94; N, 6.89%]; R_f (AcOEt) 0.26; v_{max} (ATR) 3273, 2931, 1703, 1532, 1247, 1212, 1161, 1012, 966, 738; $\delta_{\rm P}$ (101 MHz, CDCl₃) 25.77; $\delta_{\rm H}$ (250 MHz, CDCl₃) 7.32-7.12 (m, 4H_{Ar}), 6.20 (br s, 1H, NHBoc), 4.94 (ddd, ³J_{HH} 3.4, 7.7 Hz, ³J_{HP} 11.6 Hz, 1H, CHNHBoc), 4.13–3.93 (m, 4H, 2CH₃CH₂O), 3.26 (dd, ³J_{HH} 3.4 Hz, ²J_{HP} 16.1 Hz, 1H, CHNH₂), 1.50 (br s, 2H, NH₂), 1.32 (s, 9H, (CH₃)₃C), 1.34, 1.26 (2t, ³J_{HH} 7.1 Hz, 6H, CH₃CH₂O); δ_C (63 MHz, CDCl₃) 153.4 (s, C=O), 137.2 (br d, ³J_{CP} 7.0 Hz, CHCAr), 131.3 (s, ClCAr), 126.7, 126.3 (2s, 2CHAr), 77.7 (s, (CH₃)₃C), 60.8, 60.6 (2d, ²J_{CP} 7.0 Hz, 2CH₃CH₂O), 52.7 (br s, CHNHBoc), 51.5 (d, ¹J_{CP} 152.1 Hz, CHNH₂), 26.5 (s, (CH₃)₃C), 14.6, 14.5 (2d, ³*J*_{CP} 6.4 Hz, 2*C*H₃CH₂O).

4.3.4. Diethyl syn-[(1-amino-2-tert-butoxycarbonylamino-2-furan-2-yl)ethyl]phosphonate 4d. Crude product was purified by flash chromatography (AcOEt) to give the *title compound* **4d** (60 mg, 55%) as a colorless solid, mp 49–52 °C; [found: C, 49.53; H, 7.59; N, 7.80. C₁₅H₂₇N₂O₆P requires C, 49.72; H, 7.51; N, 7.73%]; R_f (AcOEt) 0.26; $\nu_{\rm max}$ (ATR) 3311, 2980, 1703, 1526, 1215, 1161, 1018, 953, 759; $\delta_{\rm P}$ (101 MHz, CDCl₃) 25.27; δ_H (250 MHz, CDCl₃) 7.36–7.35 (m, 1H_{Ar}), 6.33–6.31 (m, 1H_{Ar}), 6.27–6.25 (m, 1H_{Ar}), 5.95 (d, ³J_{HH} 8.8 Hz, 1H, NHBoc), 5.12 (ddd, ³J_{HH} 3.7, 8.8 Hz, ³J_{HP} 12.9 Hz, 1H, CHNHBoc), 4.23-3.93 (m, 4H, 2CH₃CH₂O), 3.53 (dd, ³J_{HH} 3.7 Hz, ²J_{HP} 15.6 Hz, 1H, CHNH₂), 1.69 (br s, 2H, NH₂), 1.44 (s, 9H, (CH₃)₃C), 1.33, 1.27 (2d, ${}^{3}J_{\text{HH}}$ 7.1 Hz, 6H, 2CH₃CH₂O); δ_{C} (63 MHz, CDCl₃) 154.9 (s, C=O), 153.0 (d, ³J_{CP} 11.1 Hz, CHC_{Ar}), 141.2, 110.1, 106.9 (CH_{Ar}), 79.4 (s, (CH₃)₃C), 62.3, 62.1 (2d, ²*J*_{CP} 7.0, 6.9 Hz, 2CH₃CH₂O), 51.5 (d, ¹*J*_{CP} 153.1 Hz, CHNH₂), 50.1 (br s, CHNHBoc), 28.1 (s, (CH₃)₃C), 16.2, 16.1 (2d, ³*J*_{CP} 4.7 Hz, 2*C*H₃CH₂O).

4.3.5. Diethyl syn/anti-(1-amino-2-tert-butoxycarbonylamino-propyl)phosphonates 4e. Crude product was purified by flash chromatography (AcOEt) to give the title compound 4e (40 mg, 43%) as a colorless oil; [found: C, 46.54; H, 8.54; N, 8.80. C₁₂H₂₇N₂O₅P requires C, 46.44; H, 8.77; N, 9.03%]; R_f(AcOEt) 0.29; v_{max} (neat) 3305, 2977, 1698, 1365, 1230, 1164, 1021, 959, 730; δ_P (101 MHz, CDCl₃) 27.16 (syn-4e 58%), 27.08 (anti-4e 43%); δ_H (250 MHz, CDCl₃) 5.24 (br s, 1H, NHBoc, syn and anti), 4.24-4.09 (m, 4H, 2CH₃CH₂O, syn and *anti*), 4.08–3.83 (m, 1H, CHNHBoc, syn and *anti*), 3.17 (dd, ³J_{HH} 3.4 Hz, ${}^{2}J_{HP}$ 15.5 Hz, 1H, CHNH₂, anti), 3.09 (dd, ${}^{3}J_{HH}$ 4.4 Hz, ${}^{2}J_{HP}$ 14.9 Hz, 1H, CHNH₂, syn), 1.77 (br s, 2H, CHNH₂, syn and anti), 1.44 (s, 9H, (CH₃)₃C, syn and anti), 1.35 (t, ${}^{3}J_{HH}$ 7.1 Hz, 6H, 2CH₃CH₂O, syn and anti), 1.26 (d, ³J_{HH} 6.8 Hz, 3H, CH₃CH, syn), 1.22 (d, ³J_{HH} 7.0 Hz, 3H, CH₃CH, anti); δ_C (63 MHz, CDCl₃) 153.4 (s, C=O, syn and anti), 77.1(s, (CH₃)₃C, syn and anti), 60.5 (br s, CHNHBoc, syn and anti), 60.4, 60.2 (2d, ²J_{CP} 7.1, 7.0 Hz, 2CH₃CH₂O, syn and anti), 50.9 (d, ¹J_{CP} 148.3 Hz, CHNH₂, syn), 50.2 (d, ¹J_{CP} 144.1 Hz, CHNH₂, anti), 26.4 (s, (CH₃)₃C, syn and anti), 14.5 (d, ³J_{CP} 5.6 Hz, 2CH₃CH₂O, syn and anti), 14.1 (br s, CH₃CH, syn and anti).

4.3.6. Diethyl syn/anti-(1-amino-2-tert-butoxycarbonylamino-butyl) phosphonates **4f**. Crude product was purified by flash chromatography (AcOEt) to give the *title compound* **4f** (58 mg, 60%) as a colorless oil; [found: C, 48.39; H, 9.26; N, 8.45. $C_{13}H_{29}N_2O_5P$ requires C, 48.14; H,

9.01; N, 8.64 %]; R_f (AcOEt) 0.30; ν_{max} (neat) 3300, 2975, 1706, 1507, 1238, 1164, 1021, 958, 783, 558; δ_P (101 MHz, CDCl₃) 27.5 (*syn*- and *anti*-**4f**); δ_H (250 MHz, CDCl₃) 5.23, 5.12 (2br d, ³*J*_{HH} 8.4, 9.4 Hz, 1H, CHNHBoc, *syn* and *anti*), 4.23–4.08 (m, 4H, 2CH₃CH₂O, *syn* and *anti*), 3.93–3.69 (m, 1H, CH₃CH₂CH, *syn* and *anti*), 3.17, 3.14 (2dd, ³*J*_{HH} 3.6, 3.7 Hz ²*J*_{HP} 15.6, 14.5 Hz, 1H, CHNH₂, *syn* and *anti*), 1.80–1.49 (m, 4H, NH₂, CH₃CH₂CH, *syn* and *anti*), 1.44 (*s*, 9H, (CH₃)₃C, *syn* and *anti*), 1.35, 1.34 (2t, ³*J*_{HH} 7.1 Hz, 6H, 2CH₃CH₂O, *syn* and *anti*), 1.00–0.90 (m, 3H, CH₃CH₂CH, *syn* and *anti*); δ_C (63 MHz, CDCl₃) 153.9 (*s*, *C*=O, *syn* and *anti*), 60.7, 60.1 (2br d, ²*J*_{CP} 7.9 Hz, 2CH₃CH₂O, *syn* and *anti*), 51.0, 50.6 (2d, ¹*J*_{CP} 144.9, 148.8 Hz, CHNH₂, *syn* and *anti*), 27.4 (*s*, (CH₃)₃C, *syn* and *anti*), 27.4 (*s*, (CH₃)₄C, *syn* and *anti*), 27.4 (*s*, (CH₃)₄C, *syn* and *anti*), 27.4 (*s*, (CH₃)₄C, *syn* and *anti*), 27.4 (*s*, (CH₃)₃C, *s*

4.3.7. Diethyl syn-(1-amino-2-benzyloxycarbonylamino-2-phenylethyl)phosphonate 4g. Crude product was purified by flash chromatography (AcOEt) to give the *title compound* 4g (91 mg, 75%) as a colorless solid, mp 64-66 °C; [found: C, 58.99; H, 6.66; N, 6.86. C₂₀H₂₇N₂O₅P requires C, 59.11; H, 6.70; N, 6.89%]; *R*_f (AcOEt) 0.20; *v*_{max} (ATR) 3267, 2980, 1716, 1534, 1249, 1017, 965, 790, 697, 527, 509; δ_P (101 MHz, CDCl₃) 25.48; δ_H (250 MHz, CDCl₃) 7.33–7.25 (m, 10H_{Ar}), 6.65 (br d, ${}^{3}J_{HH}$ 8.3 Hz, 1H, NHCbz), 5.15 (ddd, ${}^{3}J_{HH}$ 3.0, 8.3 Hz, ³J_{HP} 11.5 Hz, 1H, CHNHCbz), 5.09–5.00 (m, 2H, CH₂Ph), 4.17–3.90 (m, 4H, 2CH₃CH₂O), 3.39 (dd, ³J_{HH} 3.0 Hz, ²J_{HP} 16.0 Hz, 1H, CHNH₂), 1.65 (br s, 2H, NH₂), 1.26, 1.20 (2t, ³J_{HH} 7.1 Hz, 6H, 2CH₃CH₂O); δ_{C} (63 MHz, CDCl₃) 155.6 (s, C=O), 139.8 (d, ${}^{3}J_{CP}$ 5.0 Hz, CHCAr), 136.4 (CAr), 128.3, 128.2, 127.9, 127.8, 127.3, 126.4, (CHAr), 66.4 (s, CH₂Ph), 62.4, 62.2 (2d, ²J_{CP} 9.4 Hz, 2CH₃CH₂O), 55.1 (s, CHNHCbz), 53.3 (d, ¹/_{CP} 152.3 Hz, CHNH₂), 16.2, 16.1 (2d, ³/_{CP} 5.3 Hz, 2CH3CH2O).

4.3.8. Diethyl syn/anti-(1-amino-2-benzyloxycarbonylamino-propyl) phosphonates 4h. Crude product was purified by flash chromatography (AcOEt) to give the *title compound* **4h** (60 mg, 58%) as a colorless oil; [found: C, 52.53; H, 7.35; N, 8.16. C₁₅H₂₅N₂O₅P requires C, 52.32; H, 7.32; N, 8.14%]; R_f (AcOEt) 0.14; ν_{max} (neat) 3296, 2979, 1710, 1530, 1224, 1018, 957, 696; $\delta_{\rm P}$ (101 MHz, CDCl₃) 26.97 (syn-**4h** 59%), 26.78 (anti-**4h** 41%); $\delta_{\rm H}$ (250 MHz, CDCl₃) 7.36-7.24 (m, 5HAr, syn and anti), 6.00-5.87 (m, 1H, NHCbz, syn and anti), 5.08 (s, 2H, CH2Ph, syn and anti), 4.15-3.97 (m, 5H, 2CH₃CH₂O, CHNHCbz, syn and anti), 3.18 (dd, ³J_{HH} 3.7 Hz, ²J_{HP} 16.1 Hz, 1H, CHNH₂, anti), 3.05 (dd, ³J_{HH} 3.7 Hz, ²J_{HP} 15.2 Hz, 1H, CHNH₂, syn), 1.89 (br s, 2H, NH₂, syn and anti), 1.41-1.15 (m, 9H, 2CH₃CH₂O, CH₃CH, syn and anti); δ_C (63 MHz, CDCl₃) 154.0, 153.9 (2s, C=O, syn and anti), 134.9, 134.8 (2s, C_{Ar}, syn and anti), 126.6, 126.5, 126.1 (3s, CH_{Ar}, syn and anti), 64.6 (s, CH₂Ph, syn and anti), 60.6, 60.3 (2d, ²J_{CP} 6.5, 6.1 Hz, CH₃CH₂O, syn and anti), 51.0 (d, ${}^{1}J_{CP}$ 148.5 Hz, CHNH₂, syn), 50.2 (d, ${}^{1}J_{CP}$ 144.5 Hz, CHNH₂, anti), 46.6 (s, CHNHCbz, syn), 46.0 (d, ²J_{CP} 9.1 Hz, CHNHCbz, anti), 14.6 (d, ³*J*_{CP} 5.7 Hz, 2*C*H₃CH₂O, *syn* and *anti*), 14.2 (s, *C*H₃CH, *syn* and anti).

4.4. Diethyl *trans*-(5-phenyl-2-thioxoimidazolidin-4-yl) phosphonate^{21k} 5a

Trifluoroacetic acid (0.9 mL, 12 mmol) was added dropwise to the solution of *syn*-**4a**, (100 mg, 0.27 mmol) in CH_2Cl_2 (1.5 mL). The mixture was stirred for 1.5 h at room temperature, and the volatile materials evaporated under reduced pressure. The oily residue was dissolved in CH_2Cl_2 (1.0 mL), triethylamine (0.19 mL, 1.35 mmol) was added to the solution and the mixture was stirred for 30 min at room temperature. Then, the solution of 1,1'thiocarbonyldiimidazole (56 mg, 1.35 mmol) in CH_2Cl_2 (1.5 mL) was added and the mixture was stirred for 24 h at room temperature. Reaction mixture was diluted with CH_2Cl_2 (30 mL), and washed successively with 1 M aq HCl (2×3 mL), saturated NaHCO₃ (2×3 mL), and brine (3 mL). Organic phase was dried over MgSO₄, evaporated, and subjected to flash chromatography on silica gel (eluent: CH₂Cl₂/acetone 3:1 v/v) to give pure *trans*-**5a** (43 mg, 51%) as a colorless solid, mp 151–153 °C; [found: C, 49.41; H, 5.80; N, 8.69. C₁₃H₁₉N₂O₃PS requires C, 49.67; H, 6.09; N, 8.91%]; *R_f* (CH₂Cl₂–acetone 3:1) 0.36; *v*_{max} (ATR) 3144, 2904, 1532, 1472, 1232, 1024, 780; δ_P (101 MHz, CDCl₃) 18.46; δ_H (250 MHz, CDCl₃) 7.42–7.30 (m, 5H, H_{Ar}), 7.03 (br s, 2H, 2 NH), 5.21 (dd, ³*J*_{IH} 6.3 Hz, ³*J*_{IP} 20.5 Hz, 1H, CHC_{Ar}), 4.32–4.05 (m, 4H, CH₃CH₂O), 4.00 (d, ³*J*_{IH} 6.3 Hz, 1H, CHP), 1.35, 1.31 (2t, ³*J*_{IH} 7.1 Hz, 6H, CH₃CH₂O); δ_C (63 MHz, CDCl₃) 183.2 (d, ³*J*_{CP} 4.8 Hz, *C*=S), 139.9 (d, ³*J*_{CP} 10.1 Hz, CHC_{Ar}), 129.0, 128.8, 126.1 (s, CH_{Ar}), 63.8 (d, ²*J*_{CP} 6.8 Hz, CH₃CH₂O), 63.3 (d, ²*J*_{CP} 7.2 Hz, CH₃CH₂O), 61.8 (s, CHC_{Ar}), 61.6 (d, ¹*J*_{CP} 161.7 Hz, CHP), 16.5 (d, ³*J*_{CP} 5.3 Hz, CH₃CH₂O), 16.4 (d, ³*J*_{CP} 5.7 Hz, CH₃CH₂O).

4.5. Diethyl *trans/cis*-(5-ethyl-2-thioxoimidazolidin-4-yl) phosphonates^{21k} 5b

A crude mixture of trans- and cis-5b was obtained in the same way as 5a. Crude product was purified by flash chromatography (CH₂Cl₂/acetone 1:1) to give the *title trans-* and *cis-***5b** (29 mg, 41%) as yellow solid, mp 120-123 °C; [found: C, 40.74; H, 7.38; N, 10.18. C₉H₁₉N₂O₃PS requires C, 40.59; H, 7.19; N, 10.52%]; R_f (CH₂Cl₂/acetone 1:1) 0.45; v_{max} (ATR) 3163, 2967, 1523, 1225, 1011, 965, 719, 624; δ_P (101 MHz, CDCl₃) 19.24 (trans-**5b** 64%), 18.21 (*cis*-**5b** 36%); δ_H (250 MHz, CDCl₃) 7.27, 7.21 (2br s, 1H, NH, cis), 6.83, 6.57 (2br s, 1H, NH, trans), 4.31-4.04 (m, 6H, 2CH₃CH₂O, CH₃CH₂CH, trans and cis, CHP, cis), 3.83 (br d, ³/_{HH} 6.4 Hz, 1H, CHP, trans), 2.03-1.77 (m, 2H, CH₃CH₂CH, cis), 1.75–1.61 (m, 2H, CH₃CH₂CH, trans), 1.36, 1.35 (2t, 6H*, ³J_{HH} 7.1 Hz, 2CH₃CH₂O, trans and cis), 1.01 (t, 3H*, ³J_{HH} 7.5 Hz, CH₃CH₂, cis), 0.97 (t, 3H*, ³J_{HH} 7.4 Hz, CH₃CH₂, trans); δ_C (63 MHz, CDCl₃) 183.3 (d, ³J_{CP} 3.7 Hz, C=S, cis), 182.2 (d, ³J_{CP} 4.3 Hz, C=S, trans), 63.6 (d, ²J_{CP} 6.8 Hz, CH₃CH₂O, trans), 63.2 (d, ²J_{CP} 6.1 Hz, CH₃CH₂O, trans), 63.1 (d, ²J_{CP} 7.3, CH₃CH₂O, trans), 63.0 (d, ²J_{CP} 7.4, CH₃CH₂O, cis), 61.1 (s, CH₃CH₂CH, cis), 60.0 (s, CH₃CH₂CH trans), 57.8 (d, ¹J_{CP} 163.2 Hz, CHP, trans), 56.7 (d, ¹J_{CP} 157.3 Hz, CHP, cis), 28.7 (d, ³J_{CP} 10.7 Hz, CH₃CH₂CH, trans), 23.9 (d, ³J_{CP} 7.0 Hz, CH₃CH₂CH, cis), 16.4, 16.3 (2br d, ³J_{CP} 5.9 Hz, CH₃CH₂O, trans and cis), 11.4 (s, CH₃CH₂CH, cis), 9.0 (s, CH₃CH₂CH, trans).

4.6. Enantioselective synthesis of diethyl *syn*-(1-amino-2*tert*-butoxycarbonylamino-2-phenylethyl)phosphonates 4a'

Solid, anhydrous K₂CO₃ (700 mg, 5.0 mmol) was added to the solution of diethyl nitromethanephosphonate (1, 197 mg, 1.0 mmol), α-amido sulfone 2a (379 mg, 1.05 mmol), and chiral thiourea 7 (120 mg, 0.20 mmol) in anhydrous toluene (10 mL). The suspension was vigorously stirred for 3 d at room temperature. Then, the mixture was carefully quenched with 10% aq KHSO₄ (10 mL). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic phases were washed with brine $(2 \times 10 \text{ mL})$, dried over MgSO₄, evaporated, and subjected to flash chromatography on silica gel (AcOEt/hexanes 5:2 v/v) to give 310 mg (71%) of pure syn- and antiadducts 3a' (syn/anti=57/43). Pure enantioenriched syn-3a' (109 mg) was obtained in 27% yield after crystallization from CCl₄ (Table 3). Compound syn-3a' (100 mg, 0.247 mmol) was subjected to NaBH₄/NiCl₂ system in methanol according to the general procedure described in Section 4.3 to give, after reduction and flash chromatography, 56 mg (61%) of *syn*-**4a**', $[\alpha]_D^{20}$ –9.2 (*c* 0.15, CHCl₃, for a sample with 47% ee). The spectroscopic data of syn-**3a**' and syn-**4a**' were identical to racemic syn-**3a** and syn-**4a**.

Acknowledgements

Financial support by a grant 1T 09A 054 30 (2006–2009) from the Ministry of Education and Science is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.10.072.

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