Tetrahedron 65 (2009) 8587–8595

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Highly stereoselective synthesis of new α-amino-β-hydroxy six-membered heterocyclic phosphonic acids, serine analogues

Nicolas Louaisil, Nicolas Rabasso, Antoine Fadel *

Laboratoire de Synthèse Organique et Méthodologie, CNRS, UMR 8182, Institut de Chimie Moléculaire et des Matériaux d'Orsay, Bât. 420, Université Paris-Sud 11, 91405 Orsay, France

ARTICLE INFO

Article history:
Received 26 May 2009
Received in revised form 9 July 2009
Accepted 17 July 2009
Available online 23 July 2009

Keywords:
Aminophosphonic acids
Heterocycles
Serine analogues
Nucleophilic addition
Piperidines

ABSTRACT

The synthesis of 2-hydroxy-4-heterocyclic phosphonic acids was achieved in a six-step sequence from the appropriate ketones. Thus, 2-hydroxyheterocyclic ketone acetals were prepared and then esterified by *N*-Boc-L-phenylalanine, used as a chiral auxiliary. The resulting heterocyclic acetal esters gave by a one-pot reaction bicyclic ketimines. These imines underwent nucleophilic addition with phosphite to provide efficiently and stereoselectively, under kinetic control, bicyclic aminophosphonates. Cleavage of the phenylalanine moiety by oxidation followed by acidic hydrolysis of the resulting heterocyclohexylphosphonates provided the new (4-amino-3-hydroxypiperidin-4-yl)-, (4-amino-3-hydroxytetrahydro-2*H*-pyran-4-yl)- and (1-amino-2-hydroxycyclohexyl)phosphonic acids.

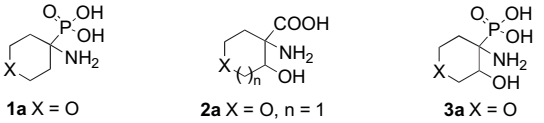
© 2009 Elsevier Ltd. All rights reserved.

1. Introduction

Several α-aminophosphonic acids show activity, as enzyme inhibitors, antibacterials, herbicides, or plant growth regulators.[1] These acid derivatives, in which the tetrahedral phosphorus moiety acts as a transition-state analogue of peptide bond cleavage, selectively inhibit peptidases and proteinases (e.g., HIV protease,[2] serine protease[3]). In recent years, many cyclic α-aminophosphonic acids have been prepared from ketones,[4–11] mainly by Mannich-type reactions using cyclohexanones.[12] Very few examples of heterocyclic α-aminophosphonic acids **1a–c** or the corresponding phosphonates have been reported by others[13–16] and by us.[17] In all theses synthetic approaches the Kabachnick–Fields reaction[15a,b] was used to provide α-aminophosphonates in moderate to good yields.

L-Serine plays a crucial role in peptides and proteines, not only as a hydrophilic residue but also, with the hydroxy moiety, as a catalytic site of serine proteases.[18] In this context, 1-amino-2-hydroxycyclohexanecarboxylic acid (c_6Ser) **2d** (n=1) has received considerable attention since high rigidity is achieved in this molecule by having the α-carbon on the amino acid incorporated into a six-membered-ring. Only few syntheses of c_6Ser **2d** have been reported in the literature. These syntheses involved Bucherer–Berg and Strecker reactions[19] in a racemic version, and intramolecular Strecker reaction,[20,21] or Diels–Alder cycloaddition[22] in asymmetric version. The synthesis of the heterocyclic derivatives **2a**, **2b** and **2c** have been little studied,[23] especially since the amide derivatives of **2c** are useful antiarrhythmic agents.[23a] In contrast, 3-hydroxy-, 4-piperidine-aminophosphonic acid **3c** (antiarrhythmic analogue), tetrahydropyran acid **3a**, and tetrahydrothiopyran acid **3b** phosphonic analogues are still unknown (Fig. 1).

In continuation of our ongoing program on the synthesis of cyclic aminophosphonic acids,[8] we recently described a short and efficient synthesis of new heterocyclic α-aminophosphonic acids **1a–d** in good yields from ketone imines **4** via aminophosphonates **5** (Scheme 1).[17a] We also applied the same sequence to obtain (3-amino-piperidin-3-yl)-phosphonic acids from the corresponding cyclic ketones.[17b] However, the synthesis of cucurbitine phosphonic analogues **8a–d** required the use of hydrazone intermediates **6** instead of imine to provide hydrazinophosphonates **7**. Subsequent cleavage of N–N bonds gives aminophosphonic acid **8a–d** (cucurbitine analogue) (Scheme 1).[24]



1a X = O
1b X = S
1c X = NH
1d X = CH_2

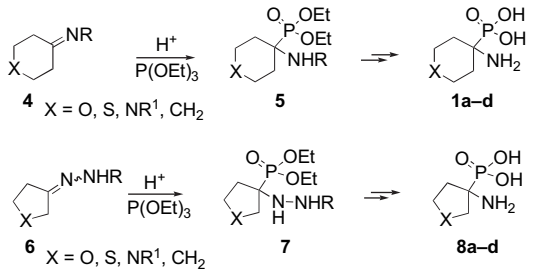
2a X = O, n = 1
2b X = S, n = 1
2c X = NR, n = 1
2d X = CH_2, n = 0, 1

3a X = O
3b X = S
3c X = NH
3d X = CH_2

Figure 1. Heterocyclic α-aminocarboxylic and phosphonic acids.

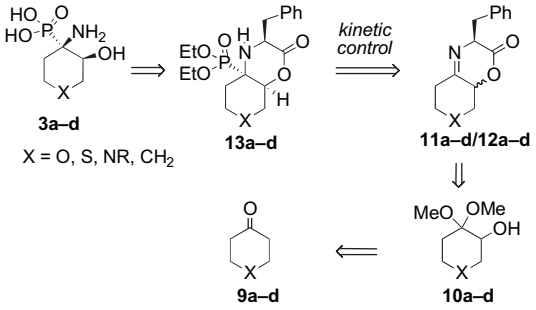
* Corresponding author. Tel.: +33 1 6915 3239; fax: +33 1 6915 6278.
E-mail address: antfadel@icmo.u-psud.fr (A. Fadel).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.07.040



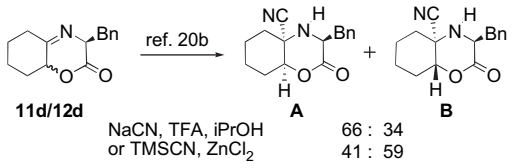
Scheme 1.

In order to expand the scope of our method,[17] we decided to prepare c_6Ser phosphonic analogues **3a–d** (Fig. 1) involving the addition of phosphite to bicyclic imine intermediates **11a–d**/**12a–d**, as key-step. Such imines are prepared from heterocyclic ketones **9a–d** via acetals **10a–d**. Thus the nucleophilic addition should occur stereoselectively, under kinetic control, to provide aminophosphonates **13a–d**, precursors of aminophosphonic acids **3a–d** (Scheme 2).



Scheme 2. Retrosynthetic sequence for the peparation of β-hydroxy aminophosphonic acids.

Studies on the reactivity of imine **11d** under Strecker reaction conditions were reported by Ohfune et al.[20b] In the presence of a Brønsted acid the aminonitriles **A** and **B** were formed in moderates selectivities, whereas with a Lewis acid a reverse selectivity was observed (Scheme 3).

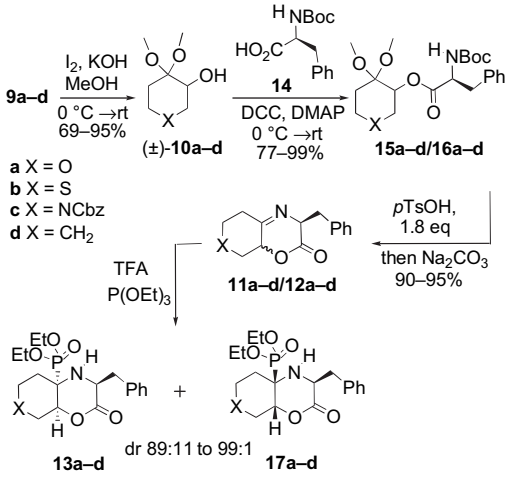


Scheme 3.

2. Results and discussion

In this paper we present an efficient strategy for the synthesis of enantiopure 2-hydroxyheterocyclic aminophosphonic acids. For this purpose, imine formation was carried out under mild conditions. The commercially available ketones **9a–d** reacted, following known reaction,[25] with iodine/potassium hydroxide in methanol at 0 °C to furnish hydroxy acetals **10a–d** in good yields. However, use of potassium hydroxide/PhI(OAc)$_2$[26] as the reagent gave hydroxy acetals **10a–d** in moderate yields. Subsequent esterification with L-*N*-Boc-phenylalanine **14** in the presence of 1,3-dicyclohexylcarbodiimide (DCC) and a catalytic amount of dimethylaminopyridine (DMAP, 10 mol %)[27] led to diastereomeric mixtures (50:50) of esters **15a–d**/**16a–d** in excellent yields (Scheme 4).

In order to examine the possibility to achieve in a one-pot reaction: deacetalization, deprotection and condensation of the resulting keto amines **15**/**16** into imines **11**/**12**, we changed several reaction conditions depending on the nature of the heteroatom (X) (Table 1).



Scheme 4.

Table 1
Preparation in a one-pot reaction of imines **11a–d**/**12a–d** from acetals **15a–d**/**16a–d** produced via Scheme 4[a]

Entry	Acetal **15**/**16** (X)	*p*-TsOH (equiv)	*T* (°C)/*t* (h)	Imine **11**/**12**
1	**15a**/**16a** (O)	1.8	20/24	**11a**/**12a**
2	**15b**/**16b** (S)	1.8	20/24	**11b**/**12b**
3	**15c**/**16c** (NCbz)	2.8	20/24	**11c**/**12c**
4	**15d**/**16d** (CH_2)	1.8	20/24	**11d**/**12d**

[a] Reactions conditions: Acetals **15a–d**/**16a–d**, *p*-TsOH (*n* equiv), acetone, 25 or 55 °C, 24 h, then Na_2CO_3 (5 equiv).

We found that no imines **11**/**12** were formed directly from acetals **15**/**16** using 0.15 or 1.2 equiv *para*-toluenesulfonic acid (*p*-TsOH). However, complete conversion of **15a**/**16a**, **15b**/**16b** and **15d**/**16d** into corresponding imines **11**/**12** was achieved by increasing *p*-TsOH to 1.8 equiv and for compounds **15c**/**16c** (X=NCbz) (Table 1, entries 1, 2, 4 and 3) to 2.8 equiv. The resulting crude imines **11a–d**/**12a–d**, obtained as a 50:50 to 35:65 mixture, were used in the next step without further purification.

Reaction of crude imines **11a–d**/**12a–d** (Scheme 4) with 2 equiv of triethyl phosphite in the presence of 1 equiv of TFA in ethanol at 30 °C for 17 h (method A) gave the corresponding aminophosphonates **13a–d** in acceptable yields (46–70%) and high diasteroselectivity (Table 2, entries 1, 3, 5, and 6). On the other hand,

Table 2
Preparation of aminophosphonates **13a–d** from imines **11a–d**/**12a–d** produced via Scheme 4[a]

Entry	Imine (X)	Condition[a]	Phosphonate **13**/**17**	Yield[b] (%)	dr[c]
1	**11a**/**12a** (O)	A	**13a**	60	96:4
2	**11a**/**12a** (O)	B	**13a**	72	99:1
3	**11b**/**12b** (S)	A	**13b**	46	96:4
4	**11b**/**12b** (S)	B	**13b**/**17b**	77	89:11
5	**11c**/**12c** (NCbz)	A	**13c**	49	95:5
6	**11c**/**12c** (NCbz)	A[d]	**13c**	70	96:4
7	**11c**/**12c** (NCbz)	B	**13c**	71	99:1
8	**11c**/**12c** (NCbz)	A[e]	**13ca**	54	97:3
9	**11d**/**12d** (CH_2)	A	**13d**	62	95:5

[a] Reactions conditions: method A: imine (prepared from acetals **15**/**16** with *p*-TsOH, then aq $NaHCO_3$) reacted with P(OEt)$_3$ (1.2 equiv), TFA (1.0 equiv) in EtOH, 30 °C, 17 h; method B: imine (prepared from acetal with *p*-TsOH, then aq Na_2CO_3) reacted with P(OEt)$_3$ (2.0 equiv), TFA (1.0 equiv) in CH_2Cl_2, −78 °C to rt, 6 h.
[b] Overall yield calculated from acetals **15**/**16**.
[c] Ratio was determined from ^{31}P NMR spectra of the crude mixture.
[d] With P(OEt)$_3$ (2 equiv).
[e] P(OMe)$_3$ in MeOH was used instead of P(OEt)$_3$ in EtOH.

reaction with triethyl phosphite (2 equiv) in the presence of TFA (1 equiv) in dichloromethane at −78 °C for 6 h (method B), provided the aminophosphonates **13a**–**c** in good yields (71–77%) and excellent diastereoselectivities (Table 2, entries 2 and 7). Replacing triethyl phosphite with trimethyl phosphite and ethanol with methanol in method A gave the corresponding aminophosphonate **13ca** in 54% yield and with the same selectivity (entry 8).

Likewise, the carbocyclic imines **11d**/**12d** by method A furnished the expected aminophosphonate **13d** in good yield and high selectivity (95:5) (entry 9). By comparison, reaction of imines **11d**/**12d** with cyanide anion (instead of triethyl phosphite) is reported to give the corresponding aminonitrile analogues **A**/**B** with a lower selectivity (66:34) (Scheme 3).[20b]

The diastereoselectivity ratios were determined from their ^{31}P NMR spectra of crude aminophosphonate products. Attempts to isolate the minor isomers by purification on silica gel column flash chromatography for entries 1, 5, 6 and 8 failed. Although, the aminophosphonates **13a**–**d** are solids, only **13b** afforded crystals suitable for X-ray crystallographic analysis (Fig. 2).[28]

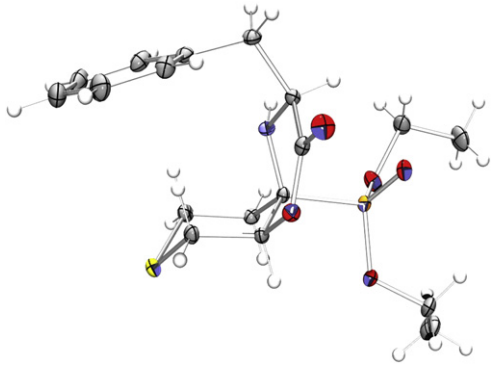
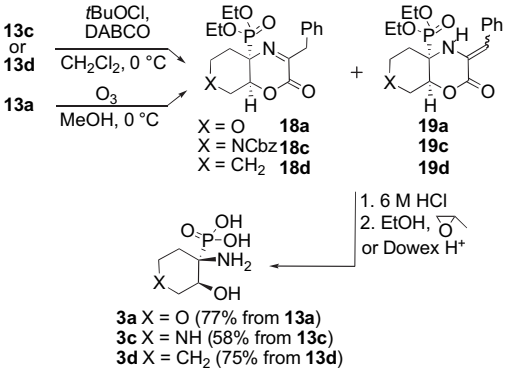


Figure 2. X-ray diffraction analysis of compound **13b**.

We next examined the conversion of **13a**–**d** into the expected aminophosphonic acid by removal of the phenylalanine moiety. Treatment of phosphonates **13c** and **13d**, with *tert*-butyl hypochlorite at 0 °C and 1,4-diazabicyclooctane (DABCO) at room temperature gave the imine/enamine mixture **18c**/**19c** and **18d**/**19d** in good yields, respectively. However, it gave **20a**/**21a** only in 30% yield with a degradation product for **13a** and a sulfoxide byproduct from **13b**. To overcome this problem **13a** was oxidized with ozone[29] to give a mixture of **18a** and **19a** in excellent yield. Acidic hydrolysis of this mixture provided the new optically pure (3*S*,4*S*)-**3a** in 77% yield from **13a**.

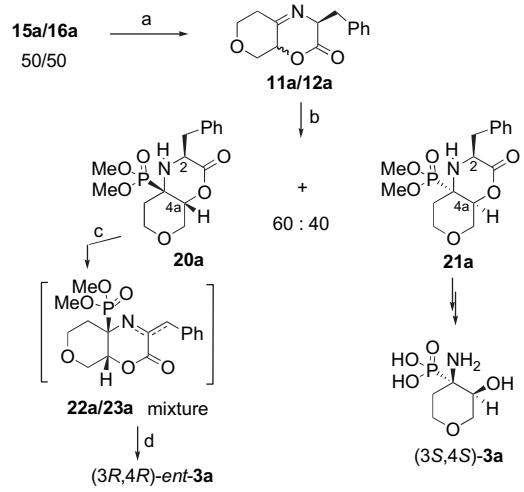
The crude imine/enamine mixtures **18c**/**19c** and **18d**/**19d** were then treated with 6 M HCl at reflux for 15 h and the resulting crude



Scheme 5.

3c·HCl and **3d**·HCl were purified by propylene oxide in ethanol, or by Dowex·H^+ to give new (3*S*,4*S*)-**3c** and (3*S*,4*S*)-**3d** in good yields (Scheme 5).

In order to examine the selectivity of phosphite addition to imines **11a**/**12a**, the reaction was performed using boron trifluoridediethyletherate ($BF_3{\cdot}OEt_2$) and trimethylsilyl-dimethylphosphite [$TMSP(O)(OMe)_2$] in methylene chloride at −78 °C and then quenched by adding an aq $NaHCO_3$ solution. The resulting aminophosphonates were composed of a mixture of diastereomers (**20a**/**21a**, 60:40) in 51% overall yield from esters **15a**/**16a**. The minor dimethyl phosphonate **21a**, with similar NMR data than **13a**, gave the acid (3*S*,4*S*)-**3a** as shown above. While the major dimethyl phosphonate **20a** was separately treated by ozone in ethyl acetate at −78 °C followed by addition of dimethylsulfide to give a non-isolated mixture of an imine/enamine **22a**/**23a**. Subsequent acidic hydrolysis of the crude mixture of **22a**/**23a** provided (3*R*,4*R*)-*ent*-**3a**, which showed the same analytical data but the opposite sign of specific rotation of (3*S*,4*S*)-**3a** (Scheme 6).



Scheme 6. Reactions conditions: (a)1.8 equiv of *p*-TsOH in acetone at 25 °C, 15 h, then solid Na_2CO_3 in CH_3CN; (b) $TMSP(O)(OMe)_2$ (2 equiv), $BF_3{\cdot}OEt_2$ (1.1 equiv) in CH_2Cl_2, −78 to rt, 17 h, 51% overall yield from **15a**/**16a**; (c) O_3 in EtOAc, −78 °C, 10 min, then Me_2S; (d) 6 M HCl at reflux, 17 h, then propylene oxide, 58% two steps from **20a**.

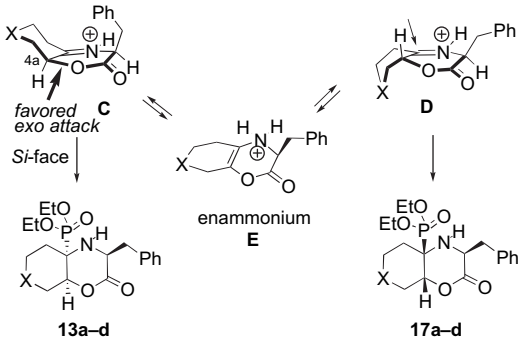
2.1. Absolute configuration and mechanistic discussion

The absolute configuration of the major aminophosphonate **13b** was assigned by X-ray analysis as (2*S*,4a*R*,8a*S*) (Fig. 2). Therefore, aminophosphonates **13a** and **13c** are also assigned as (2*S*,4a*S*,8a*S*) and **13d** as (3*S*,4a*S*,8a*S*), respectively (Scheme 4, Table 2). However, the absolute configuration of the minor isomer **17b** (X=S) is assigned by comparison with NMR data. Examination of the ^1H NMR data of **20a** and **17b** showed a high field shift of 2-H compared, respectively, to compounds **21a** and **13b** in which the proton 2-H and the phosphonate function are *syn*. However, the 4a-H proton, *syn* to the phosphonate function, showed roughly the same chemical shifts in **21a**/**20a** and **13b**/**17b**, respectively (Table 3). Consequently, the same absolute configuration was attained for compounds **17b** and **20a**, but (due to sulfur atom in **17b**)[30] the configuration is described as (2*S*,4a*S*,8a*R*) for **17b** and as (2*S*,4a*R*,8a*R*) for **20a**.

Table 3
Comparison of chemical shifts for **21a**/**20a** and **13b**/**17b**

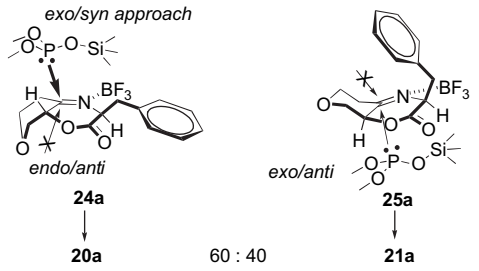
Proton	**21a**	**20a**	**13b**	**17b**
2-H	4.29	4.05	4.33	4.04
4a-H	4.56	4.66	4.73	4.83

The high stereoselectivity observed in the phosphite addition to the iminium ion could be explained as described in Scheme 7. It is understood that the iminium intermediates **C** and **D** are equilibrated via an enammonium-type intermediate **E** (equilibrium supported by deuterium exchange) similar to the pathway reported for the five- and six-membered-ring system (X=CH_2).[20b] Furthermore, it seems that the selectivity of aminophosphonate formation is under kinetic and not thermodynamic control. Since the aminophosphonates **13b** and **17b** separately treated under reaction conditions (TFA/$P(OEt)_3$) gave the recovered starting material without any epimerization. We estimate that chair–boat conformation (iminium ion **C**) is favoured by about 2.14–5.56 kcal mol^{-1} (X=O, S, NCbz and CH_2) relative to the epimeric-**4a** twist boat–boat conformation (iminium ion **D**), based on DFT calculations at the B3LYP/6-31G* level. Optimized conformers of intermediates **C** and **D** were obtained by molecular mechanics calculations.[31] Based on this analysis, the highly diastereoselective formation of **13** results from a kinetic addition of phosphite (rate determining-step) to the less hindred *Si*-face of the iminium **C** (*exo* bicyclic attack and *anti* attack versus benzyl group) conformer, yielding **13a–d** as the major products and the sole products under method B (X=O, NCbz) (Scheme 7).



Scheme 7. Plausible approach of phosphite to the iminium intermediates.

From the results shown in Scheme 6, the kinetic addition of phosphite in the presence of Lewis acid to both iminium intermediates is also *exo*-attack favoured. The major isomer **20a** should be (2*S*,4a*R*,8a*R*) and formed from imine **24a**, while the minor **21a** should come from **25a** (Scheme 8).



Scheme 8. Plausible approach of nucleophile in the presence of $BF_3{\cdot}OEt_2$.

In contrast, the reported Strecker addition of cyanide anion on carbocyclic imines **11d**/**12d** (X=CH_2) in the presence of Lewis acid provided the major product **B** by an *endo*/*anti* attack of cyanide (Scheme 3).[20b,32]

3. Conclusion

In summary, we have developed an easy and efficient synthesis of new α-amino-β-hydroxyheterocyclohexylphosphonic acids **3a**, **3c** and α-amino-β-hydroxycyclohexylphosphonic acid **3d** from the appropriate ketones. The chiral transfer process from the phenylalanyl group, with construction of two consecutive chiral centres, appeared very highly stereoselective. This efficient transfer of chirality with the phosphite addition was better than those previously reported for the analogue Strecker addition of cyanide anion in carbocyclic systems.[20b,32] The heterocyclic aminophosphonates **13a–d**, were obtained in good yields and excellent stereoselectivity. Finally, oxidation with *tert*-butyl hypochlorite or ozone followed by subsequent hydrolysis provided aminophosphonic acids **3** in good yields.

4. Experimental section

4.1. General

All reactions were carried out under argon with magnetic stirring. Di- and triethyl phosphite were distilled at reduced pressure and stored under argon. All other solvents and chemical compounds were purified based on standard procedures. Reagent-grade solvents were used without purification for all extractions and work-up procedures. R_f values refer to values obtained by TLC on 0.25 mm silica gel plates (60-F_{254}). Flash chromatography (FC) was performed on silica gel 60 (0.040–0.063 mm). Yields refer to chromatographically and spectroscopically pure compounds, except where noted. IR spectra were acquired on a FTIR and are reported in wavenumbers (cm^{-1}) with polystyrene as a standard. Melting points were determined on a Büchi B-545 capillary melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a Bruker AM250 (250 MHz) or Bruker AC360 (360 MHz) spectrometer. Chemical shifts were recorded in parts per million from the solvent resonance ($CDCl_3$ at 7.27 and D_2O at 4.8 ppm). ^{13}C NMR spectra were recorded on a Bruker AM250 (62.9 MHz) or Bruker AC360 (90.56 MHz) spectrometer. Chemical shifts are reported in parts per million from the solvent resonance ($CDCl_3$ at 77.16 ppm). ^{31}P NMR spectra were recorded on a Bruker AC250 (101.25 MHz), and chemical shifts are quoted relative to internal 85% H_3PO_4 (δ=0 ppm). High-resolution mass spectra were recorded on a Finnigan MAT 95S using the following ionization techniques: chemical ionization (CI), electron impact (EI) and electrospray (ES). All new compounds were determined to be >95% pure by ^1H NMR spectroscopy. Elemental analyses were performed by The Microanalytical Service Laboratory of CNRS at Gif/Yvette (France).

4.2. Synthesis of 2-hydroxy dimethyl acetals

*4.2.1. Benzyl 3-hydroxy-4,4-dimethoxypiperidine-1-carboxylate (**10c**).* Unknown compound was prepared by using literature procedure.[25] Yield 88%; colourless oil; R_f=0.46 (EtOAc/petroleum ether: 50:50). IR (film): ν_{max}=3446, 2946, 1695, 1435, 1243, 1116, 1075 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 330 K) δ=1.68 (ddd, *J*=13.8, 2.7, 2.7 Hz, 1H, H-5), 1.85 (ddd, *J*=13.8, 12.0, 4.8 Hz, 1H, H-5), 2.54 (br s, OH), 2.92 (ddd, *J*=12.0, 13.2, 2.7 Hz, 1H, H-6), 3.00–3.20 (m, 1H, H-2), 3.19 (s, 3H, CH_3), 3.21 (s, 3H, CH_3), 3.72 (br s, 1H, H-3), 3.94 (br d, *J*=13.2 Hz, 1H, H-6), 4.05 (dd, *J*=13.2, 1.2 Hz, 1H, H-2), 5.10 (s, 2H, H-2, $CH_{2benzyl}$), 7.14–7.38 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ=27.5 (C-5), 40.7 (C-6), 47.8 (C-2), 47.5 (CH_3), 47.9 (CH_3), 67.0 ($CH_{2benzyl}$), 67.05 (C-3), 99.1 (C-4) [6 arom C: 127.5 (2CH), 127.6 (CH), 128.2 (2CH), 137.0 (Cq)], 156.0 (COO). ES^+MS *m*/*z*: 318.1 $[M+Na]^+$. HRMS (ES) *m*/*z* $[M+Na]^+$ calcd for $C_{15}H_{21}NO_5$+Na: 318.1312; found: 318.1321.

*4.2.2. (2S)-4,4-Dimethoxytetrahydro-2H-pyran-3-yl N-(tert-butoxycarbonyl)-L-phenylalaninate (**15a**/**16a**).* General procedure A: A solution of (*S*)-*N*-*tert*-butyloxycarbonylphenylalanine **14** (4.00 g, 15 mmol), and dicyclohexylcarbodiimide (DCC), (3.10 g, 15 mmol) in dry CH_2Cl_2 (33 mL) was stirred at 0 °C for 10 min. Then, a solution of crude hydroxy acetal **10a** (1.62 g, 10 mmol) in CH_2Cl_2 (26 mL) and

dimethylaminopyridine (DMAP)[27] (122 mg, 1.0 mmol) were added, successively. The reaction mixture was allowed to warm to room temperature with stirring for 17 h. The urea formed was filtered off, and washed with CH_2Cl_2. The organic layer was diluted with water (10 mL) and extracted with CH_2Cl_2 (2×200 mL) then dried, filtered and concentrated under vacuum. The residue was purified by flash chromatography (silica gel, eluent, EtOAc/petroleum ether, 20:80 to 40:60) to give the corresponding esters **15a**/**16a** (3.815 g, 93% from ketone **9a**).

Yield 93% (two steps); colourless oil; R_f=0.47 (EtOAc/petroleum ether: 30:70). IR (film): ν_{max}=3442, 3360, 2974, 1742 (COO), 1716 (NCO), 1497, 1367, 1173, 1072 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$) two isomers (**15a**/**16a**, 50:50) δ=1.36/1.39 (s, 9H, C(CH_3)$_3$, **15a**/**16a**), 1.70–2.00 (m, 2H, H-5), 2.90–3.26 (m, 2H, H_{benzyl}), 3.07/3.10 (s, 3H, OCH_3), 3.16/3.18 (s, 3H, OCH_3), 3.40–3.54 (m, 1H, H-6), 3.60–3.74 (m, 1H, H-2), 3.74–3.90 (m, 2H, H-2 and H-6), 4.52–4.70 (m, 1H, CH–N), 4.82/4.92 (br s, 1H, H-3), 5.01–5.18 (m, 1H, HN), 7.10–7.32 (m, 5H). ^{13}C NMR (90.56 MHz, $CDCl_3$) (two diastereomers **15a**/**16a**, 50:50) δ=28.3 (C(CH_3)$_3$), 29.3/29.5 (C-5, **15a**/**16a**), 37.8 ($CH_{2benzyl}$), 47.6 ($2CH_3O$), 54.4/54.5 (CH–N, **15a**/**16a**), 64.2 (C-6), 67.1/67.4 (C-2, **15a**/**16a**), 69.2/69.6 (C-3, **15a**/**16a**), 79.6 (*C*(CH_3)$_3$), 96.9/97.0 (C-4, **15a**/**16a**) [6 arom C: 126.9 (CH), 129.4 (2CH), 129.4/129.5 (2CH, **15a**/**16a**), 136.0/136.2 (Cq, **15a**/**16a**)], 155.0 (NCO), 171.0/171.1 (COO, **15a**/**16a**). ES^+MS *m*/*z*: 432.2 $[M+Na]^+$. HRMS (ES) *m*/*z* $[M+Na]^+$ calcd for $C_{21}H_{31}NO_7$+Na: 432.1993; found: 432.1996. $C_{21}H_{31}NO_7$ (409.47): calcd C 61.60, H 7.63, N 3.42; found C 61.21, H 7.54, N 3.87.

*4.2.3. (2S)-4,4-Dimethoxy-tetrahydro-2H-thiopyran-3-yl N-(tert-butoxycarbonyl)-L-phenylalaninate (**15b**/**16b**).* Prepared following procedure A: yield 69% (two steps); colourless oil; R_f=0.26 (ether/petroleum ether: 30:70). IR (film): ν_{max}=3369, 2931, 1745 (COO), 1716 (NCO), 1497, 1369, 1243, 1172, 1060 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) (diastereomers **15b**/**16b**) δ=1.42 (s, 9H, C(CH_3)$_3$), 1.99–2.17 (m, 2H, H-5), 2.40–2.54 (m, 1H, H-6), 2.60–2.72 (m, 1H, H-2), 2.72–2.85 (m, 1H, H-6), 3.00–3.33 (m, 3H, H-2 and $2H_{benzyl}$), 3.13/3.16 (s, 3H, OCH_3, **15b**/**16b**), 3.19/3.20 (s, 3H, OCH_3, **15b**/**16b**), 4.61–4.73 (m, 1H, CHN), 4.94–5.09 (m, 1H, HN), 5.09/5.14 (d, *J*=3.2 Hz, 1H, H-3, **15b**/**16b**), 7.10–7.35 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$) (diastereomers **15b**/**16b**) δ=24.7 (C-6), 28.3 (C(CH_3)$_3$), 29.8/30.0 (C-2, **15b**/**16b**), 30.3/30.5 (C-5, **15b**/**16b**), 37.9/38.0 ($CH_{2benzyl}$, **15b**/**16b**), 47.5 (OCH_3), 47.6/47.7 (OCH_3, **15b**/**16b**), 54.4 (CHN), 68.3 (C-3), 79.8 (*C*(CH_3)$_3$), 97.8/97.9 (C-4, **15b**/**16b**) [6 arom C: 127.0 (CH), 128.5 (2CH), 129.5 (2CH), 136.0 (Cq)], 155.0 (NCO), 170.9 (COO). HRMS (ES) *m*/*z* $[M+Na]^+$ calcd for $C_{21}H_{31}NO_6S$+Na: 448.1764; found: 448.1767. $C_{21}H_{31}NO_6S$ (425.54): calcd C 59.27, H 7.34, N 3.29; found C 59.64, H 7.41, N 3.54.

*4.2.4. (2S)-1-[(Benzyloxy)carbonyl]-4,4-dimethoxypiperidin-3]-yl N-(tert-butoxycarbonyl)-L-phenylalaninate (**15c**/**16c**).* Prepared following procedure A: yield 77% (two steps); colourless oil; R_f=0.72 (EtOAc/petroleum ether: 50:50). IR (film): ν_{max}=3438, 3348, 2976, 1747 (COO), 1714 (N-Boc), 1699 (NCO), 1497, 1435, 1367, 1163, 1115, 1064 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 330 K) (two diastereomers **15c**/**16c**, 50:50) δ=1.40 (s, 9H, C(CH_3)$_3$), 1.70–1.96 (m, 2H, H-5), 2.77–3.00 (m, 2H, 2H, H-6 and H_{benzyl}), 3.00–3.39 (m, 2H, H-2 and H_{benzyl}), 2.93/3.23 (s, 3H, OCH_3, **15c**/**16c**), 3.15/3.24 (s, 3H, OCH_3, **15c**/**16c**), 4.00–4.20 (m, 1H, H-6), 4.20–4.40 (m, 1H, H2), 4.40–4.62 (m, 1H, CH–N), 4.80–5.14 (m, 2H, CH_2Cbz), 5.17/5.22 (s, 1H, H-3, **15c**/**16c**), 5.25 (s, 1H, NH), 7.06–7.44 (m, 10H). ^{13}C NMR (75.5 MHz, $CDCl_3$, 330 K) (diastereomers **15c**/**16c**) δ=28.3 (C(CH_3)$_3$), 28.3 (C-5), 37.9 ($CH_{2benzyl}$), 40.6/40.7 (C-6, **15c**/**16c**), 45.1/45.2 (C-2, **15c**/**16c**), 47.65/47.7 (OCH_3, **15c**/**16c**), 47.9 (OCH_3), 54.5 (CH–N), 67.3 (CH_2, Cbz), 68.5 (C-3), 79.7 (*C*(CH_3)$_3$), 97.88/97.95 (C-4, **15c**/**16c**) [12 arom C: 126.7 (CH), 127.8 (2CH), 128.0 (CH), 128.4 (2CH), 129.4 (2CH), 136.3 (Cq), 136.7 (Cq)], 154.9 (NCO), 155.7 (NCOO), 170.7 (COO). ES^+MS *m*/*z*: 565.3 $[M+Na]^+$. HRMS (ES) *m*/*z* $[M+Na]^+$ calcd for $C_{29}H_{38}N_2O_8$+Na: 565.2520; found: 565.2524. $C_{29}H_{38}N_2O_8$ (542.62): calcd C 64.19, H 7.06, N 5.16; found C 63.75, H 7.03, N 5.18.

4.3. Formation of imines 11a–d/12a–d from esters 15a–d/16a–d, procedure B

To a solution of esters **15a**/**16a** (410 mg, 1 mmol) in acetone (5 mL) was added *para*-toluenesulfonic acid (*p*-TsOH·H_2O) (350 mg, 1.8 mmol). After stirring at 25–30 °C for 17 h, complete conversion was observed. The solvent was removed and the residue was taken with CH_3CN (4 mL) then solid Na_2CO_3 (530 g, 5 mmol) and $MgSO_4$ (1.20 g, 10 mmol) were added. After stirring for 2 h at room temperature, the mixture was filtered over Celite® and the cake washed with CH_3CN (50 mL). The organic layer concentrated gave the crude imines **11a**/**12a** (245 mg, quant. yield), which was used in the next step without further purification. Purification of a sample on silica gel for spectral characterization.

*4.3.1. (2S,4aR/S)-2-Benzyl-4a,5,7,8-tetrahydropyrano[3,4-b][1,4]oxazin-3(2H)-one (**11a**/**12a**).* Pale yellow oil; R_f=0.20/0.34 (ether). IR (film): ν_{max}=3342, 2929, 1760/1739 (COO), 1695/1683, 1496, 1075 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$) (two diastereomers, **11a**/**12a**, 50:50) δ=1.87 (dd, *J*=10.4, 10.4 Hz, 1H, H-5, **12a**), 2.30–2.70 (m, 2H, H-8, **11a**/**12a**), 3.10 (dd, *J*=10.8, 10.8 Hz, 1H, H-5, **11a**), 3.10–3.30 (m, 3H, H-7, H_{benzyl}, **12a** and H-4a, **11a**), 3.30 (dd, J_{AB}=13.3 Hz, *J*=4.7 Hz, 1H, H_{benzyl}, **11a**), 3.38–3.50 (m, 3H, H_{benzyl}, **12a** and H-7, H_{benzyl}, **11a**), 3.88 (dd, *J*=10.4, 6.5, 1.1 Hz, 1H, H-5, **12a**), 3.97–4.15 (m, 3H, H-5, H-7, **11a**; and H-7, **12a**), 4.55–4.65 (m, 1H, H-2, **11a**), 4.70 (ddd, *J*=3.6, 6.5, 10.4 Hz, 1H, H-4a, **12a**), 4.83 (ddd, *J*=4.7, 4.7, 3.6 Hz, 1H, H-2, **12a**), 7.00–7.40 (m, 5H **11a**/**12a**). ^{13}C NMR (90.56 MHz, $CDCl_3$) (diastereomers **11a**/**12a**) δ=36.1/37.4 (C-8, **11a**/**12a**), 39.6/39.8 ($CH_{2benzyl}$, **12a**/**11a**), 59.0/60.3 (C-2, **12a**/**11a**), 67.6/68.0 (C-7, **11a**/**12a**), 70.0/70.5 (C-5, **11a**/**12a**), 73.6/75.8 (C-4a, **11a**/**12a**) [arom C: 127.4/127.7 (CH, **12a**/**11a**), 128.4/128.6 (2CH, **12a**/**11a**), 130.4/130.6 (2CH, **11a**/**12a**), 135.1/136.0 (Cq, **12a**/**11a**)], 163.9/165.3 (C-8a, **12a**/**11a**), 166.9/168.0 (C-3, **11a**/**12a**). ES^+MS *m*/*z* 268.0 $[M+Na]^+$. HRMS (ES) *m*/*z* $[M+Na]^+$ calcd for $C_{14}H_{15}NO_3$+Na: 268.0944; found: 268.0944.

*4.3.2. (2S,4aR/S)-2-Benzyl-4a,5,7,8-tetrahydro-thiopyrano[3,4-b][1,4]oxazin-3(2H)-one (**11b**/**12b**).* Prepared following procedure B: yellow oil; R_f=0.20/0.27 (EtOAc/petroleum ether: 70:30). IR (film): ν_{max}=3031, 2921, 1747, 1694, 1496, 1455, 1064 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) (two diastereomers **11b**/**12b**, 35:65) δ=0.89 (dd, *J*=11.5, 12.5 Hz, 1H, H-5, **12b**), 2.40–2.80 (m, 7H, 2H-7, H-8, **12b**, and 2H-5, 2H-7, **11b**), 2.47 (ddd, *J*=2.0, 5.0, 12.5 Hz, 1H, H-5, **12b**), 2.80–3.10 (m, 3H, H-8, **12b**, and 2H-8, **11b**), 3.20 (dd, J_{AB}=13.5 Hz, *J*=4.5 Hz, 1H, H_{benzyl}, **11b**), 3.27 (dd, J_{AB}=13.2 Hz, *J*=4.5 Hz, 1H, H_{benzyl}, **12b**), 3.41 (dd, J_{AB}=13.5 Hz, *J*=4.5 Hz, 1H, H_{benzyl}, **11b**), 3.52 (dd, J_{AB}=13.2 Hz, *J*=4.3 Hz, 1H, H_{benzyl}, **12b**), 3.45–3.62 (m, 1H, H-4a, **11b**), 4.63–4.73 (m, 1H, H-2, **12b**), 4.73–4.90 (m, 1H, H-2, **11b**), 4.82 (ddd, *J*=3.2, 5.0, 11.5 Hz, 1H, H-4a, **12b**), 7.04–7.42 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$) (diastereomers **11b**/**12b**, 35:65) δ=28.3/29.0 (C-7, **11b**/**12b**), 33.9/34.1 (C-8, **11b**/**12b**), 39.0/39.2 ($CH_{2benzyl}$, **12b**/**11b**), 39.6/40.5 (C-5, **11b**/**12b**), 58.5/59.4 (C-2, **12b**/**11b**), 77.2/78.9 (C-4a, **11b**/**12b**) [6 arom C: 125.7/128.5 (CH, **11b**/**12b**), 127.1/128.0 (2CH, **11b**/**12b**), 129.9/130.4 (2CH, **11b**/**12b**), 134.9/135.2 (Cq, **11b**/**12b**)], 164.8/165.1 (C-8a, **12b**/**11b**), 166.3/167.1 (C-3, **12b**/**11b**). ES^+MS *m*/*z*: 284.1 $[M+Na]^+$.

*4.3.3. Benzyl (2S,4aR/S)-2-Benzyl-3-oxo-2,3,4a,5,7,8-hexahydro-6H-pyrido[3,4-b][1,4]oxazine-6-carboxylate (**11c**/**12c**).* Prepared following procedure B: pale yellow foam; R_f=0.29/0.23 (EtOAc/petroleum

ether, 60:40). ^{1}H NMR (360 MHz, $CDCl_3$) (two diastereomers **11c**/**12c**, 55:45) δ=1.26 (dd, J=10.3, 11.2 Hz, 1H, H-5, **12c**), 2.18–2.75 (m, 4H, 2H-8, **11c**, and 2H-8, **12c**), 2.75–2.96 (m, 1H, H-5, **11c**), 3.00–3.30 (m, 2H, H-7, **12c** and H-4a, **11c**), 3.14 (dd, J_{AB}=13.3 Hz, J=4.7 Hz, 1H, H_{benzyl}, **12c**), 3.29 (dd, J_{AB}=13.0 Hz, J=4.3 Hz, 1H, H_{benzyl}, **11c**), 3.80 (dd, J_{AB}=13.3 Hz, J=4.3 Hz, 1H, H_{benzyl}, **12c**), 3.46 (dd, J_{AB}=13.0 Hz, J=4.3 Hz, 1H, H_{benzyl}, **11c**), 4.00–4.50 (m, 4H, H-5, H-7, **11c**, and H-5, H-7, **12c**), 4.48–4.66 (m, 1H, H-4a, **12c**), 4.58 (sharp m, 1H, H-2, **11c**), 4.81(dd, J=4.7, 4.3 Hz, 1H, H-2, **12c**), 5.00–5.15 (m, 4H, CH_2O, **11c**, and CH_2O, **12c**), 6.96–7.64 (m, 20H, 10H **11c**, and 10H **12c**). ^{13}C NMR (90.56 MHz, $CDCl_3$) (two diastereomers **11c**/**12c**, 55:45) δ=35.1/36.0 (C-8, **11c**/**12c**), 39.5/39.6 ($CH_{2benzyl}$, **11c**/**12c**), 43.8/44.2 (C-7, **11c**/**12c**), 47.9/48.4 (C-5, **11c**/**12c**), 58.9/60.1 (C-2, **12c**/**11c**), 67.1/67.8 (OCH_2, **12c**/**11c**), 73.4/75.4 (C-4a, **11c**/**12c**) [12 arom C: 128.0, 128.4, 128.5, 128.6, 130.2, 130.6, 135.0 (Cq, **11c**), 135.7 (Cq, **12c**), 136.0 (Cq, **11c**), 136.6 (Cq, **12c**)], 154.6 (NCOO, **11c** and **12c**), 164.1/165.2 (C-8a, **12c**/**11c**), 166.6/167.6 (C-3, **12c**/**11c**). HRMS (ES) m/z $[M+Na]^+$ calcd for $C_{22}H_{22}N_2O_4$+Na: 401.1477; found: 401.1482.

*4.3.4. (3S,8aR/S)-3-Benzyl-3,5,6,7,8,8a-hexahydro-2H-1,4-benzoxazin-2-one (**11d**/**12d**).* Prepared following procedure B: colourless oil; R_f=0.29/0.14 (EtOAc/petroleum ether, 50:50). ^{1}H NMR (360 MHz, $CDCl_3$) (two diastereomers **11d**/**12d**, 50:50) δ=0.02 (dddd, J=12.6, 12.3, 12.3, 3.6 Hz, 1H, H-8, **12d**), 1.10–1.70 (m, 6H, 2H-6, H-8, **11d** and 2H-6, H-8, **12d**), 1.70–2.25 (m, 7H, 2H-7, H-5, **11d** and 2H-7, H-5, H-8, **12d**), 2.48–2.70 (m, 2H, H-5, **11d** and H-5, **12d**), 3.17 (dd, J_{AB}=13.3 Hz, J=4.3 Hz, 1H, H_{benzyl}, **12d**), 3.29 (dd, J_{AB}=13.0 Hz, J=4.7 Hz, 1H, H_{benzyl}, **11d**), 3.20–3.38 (m, 1H, H-8a, **11d**), 3.39 (dd, J_{AB}=13.3 Hz, J=4.3 Hz, 1H, H_{benzyl}, **12d**), 3.48 (dd, J_{AB}=13.0 Hz, J=3.6 Hz, 1H, H_{benzyl}, **11d**), 4.53–4.65 (m, 1H, H-3, **11d**), 4.57 (ddd, J=12.3, 5.9, 3.2 Hz, 2H, H-3, **11d**, and H-8a, **12d**), 4.76 (ddd, J=4.5, 4.5, 3.2 Hz, 1H, H-3, **12d**), 7.05–7.45 (m, 5H, **11d** and **12d**). ^{13}C NMR (62.9 MHz, $CDCl_3$) (diastereomers **11d**/**12d**, 55:45) δ=22.5/23.1 (C-6, **12d**/**11d**), 25.0/25.8 (C-7, **12d**/**11d**), 33.5/33.9 (C-8, **12d**/**11d**), 35.5/36.0 (C-5, **12d**/**11d**), 39.2 ($CH_{2benzyl}$, **11d** and **12d**), 58.3/59.3 (C-3, **11d**/**12d**), 77.2/79.0 (C-8a, **12d**/**11d**) [6 arom C: 126.6/126.8 (CH, **11d**/**12d**), 127.7/127.8 (2CH, **11d**/**12d**), 129.8/130.2 (2CH, **12d**/**11d**), 135.1/135.6 (Cq, **12d**/**11d**)], 167.0 (C-4a, **11d** and **12d**), 167.6/167.7 (C-2, **11d**/**12d**). The ^{1}H NMR spectral data are in accord with the literature values.[32]

4.4. Formation of aminophosphonates 13a–d from imines 15a–d/16a–d

4.4.1. General procedure C, method A. To a solution of crude imines **15a–d**/**16a–d** (1.6 mmol) in absolute EtOH (4 mL/mmol of imine) was added TFA (1.6 mmol, 123 μL). After stirring at room temperature for 10 min, $P(OEt)_3$ (1.75 mmol, 300 μL) was added. The reaction mixture was stirred at room temperature for 17 h, then the volatile solvent was evaporated under vacuum. The resulting residue was mixed with a satd aq $NaHCO_3$ (3 mL) and then extracted with EtOAc (3×20 mL). The combined organic layers were dried over ($MgSO_4$), filtered and then concentrated under vacuum. The pure bicyclic aminophosphonates **13a–d** were purified on silica gel column chromatography.

4.4.2. General procedure C, method B. A solution of crude imines **15a–d**/**16a–d** (1.0 mmol) in CH_2Cl_2 (5 mL/mmol of imine) was added TFA (1.0 mmol, 77 μL). After stirring for 10 min, $P(OEt)_3$ (2.0 mmol, 345 μL) was added. The reaction mixture was stirred at −78 °C and slowly warmed to room temperature over 6 h. After removal of the volatile solvent under vacuum, the residue was mixed with a satd aq $NaHCO_3$ (2 mL) and then extracted with EtOAc (3×20 mL). The organic layers were dried ($MgSO_4$), filtered and then concentrated under vacuum. Purification of aminophosphonates **13a–d** was accomplished as noted in method A.

*4.4.3. Diethyl [(2S,4aS,8aS)-2-benzyl-3-oxo-hexahydropyrano[3,4-b][1,4]oxazin-8a(1H)-yl]phosphonate (**13a**).* Prepared by procedure C, method B: yield 72% from esters **15a**/**16a**; yellow foam; R_f=0.59 (EtOAc); $[\alpha]_D$ −24 (c 1.00, $CHCl_3$). IR (film): ν_{max}=3460, 2980, 1747 (COO), 1455, 1231, 1019, 967 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$, 330 K) δ=1.24 (t, J=7.0 Hz, 3H, CH_3), 1.26 (t, J=7.2 Hz, 3H, CH_3), 1.59 (dddd, J=3.6, 4.3, 14.0, 14.0 Hz, 1H, H-8), 2.00–2.19 (m, 2H, H-8 and NH), 2.96 (dd, J=13.7, 7.9 Hz, 1H, H_{benzyl}), 3.23 (dd, J=13.7, 4.0 Hz, 1H, H_{benzyl}), 3.20–3.34 (m, 1H, H-5), 3.54–3.78 (m, 3H, H-5 and 2H-7), 3.96–4.15 (m, 4H, CH_2OP), 4.27 (ddd, $^4J_{PH}$=3.6 Hz, J=4.0, 7.9 Hz, 1H, H-2), 4.53 (ddd, $^4J_{PH}$=7.4 Hz, J=7.9, 4.7 Hz, 1H, H-4a), 7.10–7.30 (m, 5H). ^{13}C NMR (90.56 MHz, $CDCl_3$) δ=16.4 (d, $^3J_{PC}$=6.1 Hz, CH_3), 16.5 (d, $^3J_{PC}$=5.5 Hz, CH_3), 31.6 (C-8), 38.9 ($CH_{2benzyl}$), 52.1 (d, $^1J_{PC}$=151.7 Hz, C-8a), 55.3 (C-2), 61.7 (d, $^3J_{PC}$=6.8 Hz, C-7), 62.5 (d, $^2J_{PC}$=7.9 Hz, CH_2OP), 63.6 (d, $^2J_{PC}$=7.4 Hz, CH_2OP), 65.2 (d, $^3J_{PC}$=6.1 Hz, C-5), 72.2 (C-4a) [6 arom C: 126.9 (CH), 128.5 (2CH), 129.8 (2CH), 137.0 (Cq)], 169.8 (C-3). ^{31}P NMR (101.25 MHz, $CDCl_3$) δ=24.11, (δ=23.92 ppm for minor isomer obtained by method A). ES$^+$MS m/z: 406.1 $[M+Na]^+$. HRMS (ES) m/z $[M+Na]^+$ calcd for $C_{18}H_{26}NO_6P$+Na: 406.1390; found: 406.1398.

*4.4.4. Diethyl [(2S,4aR,8aS)-2-benzyl-3-oxo-hexahydro-thiopyrano-[3,4-b][1,4]oxazin-8a(1H)-yl]phosphonate (**13b**).* Prepared by procedure C, method B: yield 68% from **15b**/**16b**; white solid, mp 132 °C; R_f=0.24 (EtOAc/petroleum ether: 60:40); $[\alpha]_D$ +1.5 (c 1.00, $CHCl_3$). IR (film): ν_{max}=3454, 3317, 2981, 1740 (COO), 1455, 1372, 1237, 1171, 1020, 963 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ=1.27 (t, J=7.0 Hz, 3H, CH_3), 1.275 (t, J=7.0 Hz, 3H, CH_3), 1.40 (br s, 1H, NH), 1.98–2.17 (m, 1H, H-8), 2.17–2.40 (m, 2H, H-5 and H-8), 2.40–2.65 (m, 2H, H-7), 2.65–2.93 (m, 1H, H-5), 3.00 (dd, J=13.5, 8.0 Hz, 1H, H_{benzyl}), 3.21 (dd, J=13.5, 4.0 Hz, 1H, H_{benzyl}), 3.95–4.25 (m, 4H, CH_2OP), 4.23–4.38 (m, 1H, H-2), 4.73 (ddd, J=4.0, 4.3, 8.3 Hz, 1H, H-4a), 7.20–7.40 (m, 5H). ^{13}C NMR (62.90 MHz, $CDCl_3$) δ=16.4 (d, $^3J_{PC}$=6.0 Hz, CH_3), 16.5 (d, $^3J_{PC}$=5.4 Hz, CH_3), 21.2 (d, $^2J_{PC}$=9.5 Hz, C-8), 28.0 (d, $^3J_{PC}$=8.1 Hz, C-7), 34.5 (C-5), 39.7 (CH_2 benzyl), 54.1 (d, $^1J_{PC}$=145.2 Hz, C-8a), 56.0 (C-2), 62.4 (d, $^2J_{PC}$=7.9 Hz, CH_2OP), 63.5 (d, $^2J_{PC}$=7.5 Hz, CH_2OP), 75.1 (C-4a) [6 arom C: 127.0 (CH), 128.5 (2CH), 129.9 (2CH), 137.0 (Cq)], 169.3 (C-3). ^{31}P NMR (101.25 MHz, $CDCl_3$) δ=25.23. ES$^+$MS m/z: 422.0 $[M+Na]^+$. HRMS (ES) m/z $[M+Na]^+$ calcd for $C_{18}H_{26}NO_5PS$+Na: 422.1162; found: 422.1178. $C_{18}H_{26}NO_5PS$ (399.44): calcd C 54.12, H 6.56, N 3.51; found C 54.02, H 6.55, N 3.43.

*4.4.5. Data for the minor isomer (2S,4aS,8aR)-**17b**.* R_f=0.31 (EtOAc/petroleum ether: 60:40). ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.36 (t, J=7.0 Hz, 3H, CH_3), 1.38 (t, J=7.0 Hz, 3H, CH_3), 1.86–2.20 (br s, 1H, NH), 2.10–2.30 (m, 1H, H-5), 2.40–2.60 (m, 1H, H-8), 2.60–2.80 (m, 1H, H-8), 2.80–3.20 (m, 3H, 2H-7 and H-5), 3.08 (dd, J_{AB}=14.0 Hz, J=9.6 Hz, 1H, H_{benzyl}), 3.52 (dd, J=14.0, 3.6 Hz, 1H, H_{benzyl}), 4.04 (dd, J=3.6, 9.6 Hz, 1H, H-2), 4.08–4.38 (m, 4H, CH_2OP), 4.83 (ddd, J=5.1, 5.4, 7.6 Hz, 1H, H-4a), 7.10–7.50 (m, 5H). ^{13}C NMR (75.50 MHz, $CDCl_3$) δ=16.5 (d, $^3J_{PC}$=3.4 Hz, $2CH_3$), 21.9 (d, $^2J_{PC}$=7.2 Hz, C-8), 29.1 (d, $^3J_{PC}$=7.5 Hz, C-7), 31.9 (C-5), 39.4 ($CH_{2benzyl}$), 53.5 (d, $^1J_{PC}$=152.1 Hz, C-8a), 53.9 (d, $^3J_{PC}$=3.1 Hz, C-2), 63.1 (d, $^2J_{PC}$=7.7 Hz, CH_2OP), 63.4 (d, $^2J_{PC}$=7.2 Hz, CH_2OP), 76.1 (C-4a) [6 arom C: 127.1 (CH), 128.9 (2CH), 129.4 (2CH), 137.0 (Cq)], 169.6 (C-3). ^{31}P NMR (121.50 MHz, $CDCl_3$) δ=24.90. ES$^+$MS m/z: 422.0 $[M+Na]^+$.

*4.4.6. Benzyl [(2S,4aS,8aS)-2-Benzyl-8a-(diethoxyphosphoryl)-3-oxo-octahydro-6H-pyrido[3,4-b][1,4]oxazine-6-carboxylate (**13c**).* Prepared by procedure C, method B: yield 71% from **15c**/**16c**; white solid; R_f=0.14 (ether); mp 125.9 °C; $[\alpha]_D$ −78.2 (c 1.00, $CHCl_3$). IR (film): ν_{max}=3472, 3280, 2981, 1748 (COO), 1704 (NCO), 1435, 1229,

1174, 1041, 1022, 967 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$, 330 K) δ=1.28 (t, J=7.0 Hz, 3H, CH_3), 1.30 (t, J=7.0 Hz, 3H, CH_3), 1.34–1.50 (br s, 1H, NH), 1.50–1.72 (m, 1H, H-8), 1.95–2.17 (m, 1H, H-8), 2.98 (dd, J_{AB}=14.0 Hz, J=8.3 Hz, 1H, H_{benzyl}), 3.12 (dd, J=13.3, 8.4 Hz, 1H, H_{benzyl}), 3.29 (dd, J_{AB}=14.0 Hz, J=4.0 Hz, 1H, H_{benzyl}), 3.30–3.43 (m, 1H, H-7), 3.71 (ddd, J=4.7, 4.7, 13.3 Hz, 1H, H-7), 3.92 (ddd, J=4.0, 1.5, 13.3 Hz, 1H, H-5), 3.98–4.17 (m, 4H, CH_2OP), 4.24–4.37 (m, 1H, H-2), 4.53–4.64 (m, 1H, H-4a), 5.15 (s, 2H, CH_2, Cbz), 7.10–7.47 (m, 10H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ=16.5 ($2CH_3$), 30.9 (C-8), 37.9 (d, $^3J_{PC}$=7.2 Hz, C-7), 38.9 ($CH_{2benzyl}$), 43.6 (C-5), 52.9 (d, $^1J_{PC}$=150.7 Hz, C-8a), 55.4 (C-2), 62.6 (d, $^2J_{PC}$=7.8 Hz, CH_2OP), 63.8 (d, $^2J_{PC}$=7.4 Hz, CH_2OP), 67.4 (CH_2, Cbz), 72.5 (d, $^2J_{PC}$=5.2 Hz, C-4a) [12 arom C: 127.0 (CH), 128.0 (CH), 128.1 (2CH), 128.6 (4CH), 129.8 (2CH), 136.4 (Cq), 136.9 (Cq)], 154.9 (NCO), 169.7 (C-3). ^{31}P NMR (145.78 MHz, $CDCl_3$, 330 K) δ=24.13; at 293 K two rotamers: δ=24.20 and 23.96 ppm (minor isomer at δ=23.91 ppm). ES^+MS m/z: 539.2 $[M+Na]^+$. HRMS (ES) m/z $[M+Na]^+$ calcd for $C_{26}H_{33}N_2O_7P+Na$: 539.1918; found: 539.1927.

*4.4.7. Benzyl (2S,4aS,8aS)-2-Benzyl-8a-(dimethoxyphosphoryl)-3-oxo-octahydro-6H-pyrido[3,4-b][1,4]oxazine-6-carboxylate (**13ca**).* Prepared by procedure C, method A with $P(OMe)_3$ in MeOH instead of $P(OEt)_3$ in EtOH: yield 54% from esters **15c**/**16c**; white solid; R_f=0.20 (EtOAc/petroleum ether, 80:20); mp 138.7 °C; $[\alpha]_D$ −44.3 (c 1.00, $CHCl_3$). ^1H NMR (360 MHz, $CDCl_3$, 330 K) δ=1.43 (br s, 1H, NH), 1.52–1.75 (m, 1H, H-8), 1.98–2.13 (m, 1H, H-8), 3.00 (dd, J_{AB}=14.0 Hz, J=7.9 Hz, 1H, H_{benzyl}), 3.09 (dd, J=13.3, 8.3 Hz, 1H, H-5), 3.27 (dd, J_{AB}=14.0 Hz, J=4.0 Hz, 1H, H_{benzyl}), 3.35 (dddd, J=1.1, 3.2, 10.5, 13.3 Hz, 1H, H-7), 3.60–3.78 (m, 1H, H-7), 3.71 (s, 3H, CH_3), 3.74 (s, 3H, CH_3), 3.90 (dd, J=4.0, 13.3 Hz, 1H, H-5), 4.28 (ddd, J=3.2, 4.0, 7.9 Hz, 1H, H-2), 4.56 (ddd, J=4.0, 8.3 Hz, $J_{P,H}$=6.8 Hz, 1H, H-4a), 5.14 (sharp m, 2H, CH_2, Cbz), 7.20–7.45 (m, 10H). ^{13}C NMR (90.56, MHz, $CDCl_3$) δ=30.8 (C-8), 37.7 (d, $^3J_{PC}$=7.3 Hz, C-7), 38.9 ($CH_{2benzyl}$), 43.4 (C-5), 62.9 (d, $^2J_{PC}$=7.9 Hz, CH_3OP), 53.1 (d, $^1J_{PC}$=151.0 Hz, C-8a), 54.1 (d, $^2J_{PC}$=6.9 Hz, CH_3OP), 55.3 (C-2), 67.4 (CH_2, Cbz), 72.4 (d, $^2J_{PC}$=5.2 Hz, C-4a) [12 arom C: 127.0 (CH), 128.1 (CH), 128.5 (4CH), 129.7 (4CH), 136.2 (Cq), 136.6 (Cq)], 154.7 (NCO), 169.3 (C-3). ^{31}P NMR (145.78 MHz, $CDCl_3$, 330 K) δ=26.53; at 293 K two rotamers: δ=26.49 and 26.71 ppm (minor isomer at δ=26.23 ppm). HRMS (ES) m/z $[M+Na]^+$ calcd for $C_{24}H_{29}N_2O_7P+Na$: 511.1610; found: 511.1616.

*4.4.8. Diethyl [(3S,4aS,8aS)-3-benzyl-2-oxo-hexahydro-2H-1,4-benzoxazin-4a(5H)-yl]phosphonate (**13d**).* Prepared by procedure C, method A: yield 62% from **15d**/**16d**; white solid; R_f=0.26 (EtOAc/petroleum ether: 50:50); mp 98.9 °C, $[\alpha]_D$ −35 (c 1.00, $CHCl_3$). IR (film): ν_{max}=3460, 3281, 2935, 1747 (COO), 1455, 1235, 1021, 963 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$, 330 K) δ=1.19 (t, J=7.2 Hz, 3H, CH_3), 1.21 (t, J=7.2 Hz, 3H, CH_3), 1.23–1.34 (m, 1H, H-7), 1.34–1.68 (m, 5H, H-5, H-7, 2H-6 and H-8), 1.70–1.95 (m, 2H, H-8 and H-5), 2.89 (dd, J=13.7, 8.6 Hz, 1H, H_{benzyl}), 3.22 (dd, J=13.7, 3.6 Hz, 1H, H_{benzyl}), 3.90–4.10 (m, 4H, CH_2O), 4.15 (dd, J=3.6, 8.6 Hz, 1H, H-3), 4.56 (m, 1H, H-8a), 7.10–7.32 (m, 5H). ^{13}C NMR (90.56 MHz, $CDCl_3$) δ=16.4 ($2CH_3$), 19.4 (d, $^3J_{PC}$=6.1 Hz, C-6), 22.2 (C-7), 28.3 (d, $^2J_{PC}$=5.5 Hz, C-5), 31.6 (C-8), 38.7 ($CH_{2\ benzyl}$), 54.5 (d, $^1J_{PC}$=150.2 Hz, C-4a), 55.3 (C-3), 62.3 (d, $^2J_{PC}$=7.9 Hz, CH_2O), 63.3 (d, $^2J_{PC}$=7.5 Hz, CH_2O), 75.7 (d, $^2J_{PC}$=6.3 Hz, C-8a), [6 arom C: 126.7 (CH), 128.4 (2CH), 129.7 (2CH), 137.3 (Cq)], 171.1 (C-2). ^{31}P NMR (145.78 MHz, $CDCl_3$) δ=25.93 ppm (minor isomer at δ=25.73 ppm). ES^+MS m/z: 404.1 $[M+Na]^+$. HRMS (ES) m/z $[M+Na]^+$ calcd for $C_{19}H_{28}NO_5P+Na$: 404.1597; found: 404.1600. $C_{19}H_{28}NO_5P$ (381.40): calcd C 59.83, H 7.40, N 3.67; found C 59.94, H 7.56, N 3.66.

*4.4.9. Dimethyl [(2S,4aR,8aR)-2-benzyl-3-oxo-hexahydropyrano[3,4-b][1,4]oxazin-8a(1H)-yl]phosphonate (**20a**).* $BF_3{\cdot}OEt_2$ (110 μl, 0.873 mmol) was added to a solution of imines **11a**/**12a** (214 mg, 0.873 mmol) in CH_2Cl_2 (5 mL) at −78 °C. After stirring for 10 min, $TMSP(O)(OMe)_2$ (333 μL, 1.747 mmol) was added. The mixture was then warmed to room temperature over 17 h, and then concentrated to dryness in vacuo. The residue was mixed with satd aq $NaHCO_3$ and extracted with EtOAc (3×30 mL). The organic layers were dried ($MgSO_4$), filtered, and then concentrated to give the crude phosphonates as a mixture. Purification by flash chromatography (silica gel, Et_2O/CH_2Cl_2, 60:40) gave pure **20a** (95 mg, 31% from **15a**/**16a**) and **21a** (65 mg, 21% from **15a**/**16a**).

Data for aminophosphonate **20a**: pale yellow oil; R_f=0.29 (EtOAc); $[\alpha]_D$ −61.6 (c 1.00, $CHCl_3$). IR (film): ν_{max}=3467, 3358, 2957, 1747 (COO), 1242, 1167, 1051, 1030 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ=1.77 (br t, J=5.0 Hz, 1H, NH), 1.75–2.14 (m, 2H, H-8), 3.08 (dd, J_{AB}=13.7 Hz, J=9.2 Hz, 1H, H_{benzyl}), 3.47 (dd, J_{AB}=13.7 Hz, J=3.7 Hz, 1H, H_{benzyl}), 3.66–3.90 (m, 3H, 2H-7 and H-5), 3.81 (d, $^3J_{PH}$=2.0 Hz, 3H, CH_3O), 3.85 (d, $^3J_{PH}$=2.0 Hz, 3H, CH_3O), 3.94 (ddd, J_{AB}=11.7 Hz, J=3.7 Hz, 1.7 Hz, 1H, H-5), 4.05 (dddd, J=1.2, 3.7, 3.8, 7.7 Hz, 1H, H-2), 4.66 (ddd, J=3.7, 4.0, 7.0 Hz, 1H, H-4a), 7.23–7.45 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ=29.4 (C-8), 39.4 ($CH_{2benzyl}$), 51.7 (d, $^1J_{PC}$=156.1 Hz, C-8a), 53.8 (C-2), 54.0 (d, $^2J_{PC}$=7.0 Hz, $2CH_3OP$), 62.1 (d, $^3J_{PC}$=4.9 Hz, C-7), 66.1 (d, $^3J_{PC}$=5.5 Hz, C-5), 74.4 (C-4a) [6 arom C: 127.2 (CH), 129.0 (2CH), 129.5 (2CH), 137.0 (Cq)], 169.2 (C-3). ^{31}P NMR (121.25 MHz, $CDCl_3$) δ=26.49. ES^+MS m/z: 378.1 $[M+Na]^+$. HRMS (ES) m/z $[M+Na]^+$ calcd for $C_{16}H_{22}NO_6P+Na$: 378.1077; found: 378.1089.

*4.4.10. Dimethyl [(2S,4aS,8aS)-2-benzyl-3-oxo-hexahydropyrano[3,4-b][1,4]oxazin-8a(1H)-yl]phosphonate (**21a**).* Yield 21% from **15a**/**16a**; white solid; R_f=0.24 (EtOAc); mp 143.5 °C; $[\alpha]_D$=−26.4 (c 1.00, $CHCl_3$). IR (film): ν_{max}=3462, 3287, 2956, 1747 (COO), 1455, 1234, 1178, 1114, 1051 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ=1.46 (br t, J=7.2 Hz, 1H, NH), 1.65 (dddd, J=3.3, 3.7, 13.2, 13.2 Hz, 1H, H-8), 2.04–2.30 (m, 1H, H-8), 3.03 (dd, J_{AB}=13.8 Hz, J=7.7 Hz, 1H, H_{benzyl}), 3.24 (dd, J_{AB}=13.8 Hz, J=4.2 Hz, 1H, H_{benzyl}), 3.16–3.35 (m, 1H, H-7), 3.55–3.95 (m, 3H, H-7 and 2H-5), 3.73 (d, $^3J_{PH}$=0.9 Hz, 3H, CH_3O), 3.76 (d, $^3J_{PH}$=0.9 Hz, 3H, CH_3O), 4.29 (ddd, J=3.5, J=4.1, J=7.7 Hz, 1H, H-2), 4.50–4.70 (m, 1H, H-4a), 7.14–7.48 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ=31.8 (C-8), 39.3 ($CH_{2benzyl}$), 52.4 (d, $^1J_{PC}$=151.4 Hz, C-8a), 53.0 (d, $^2J_{PC}$=7.8 Hz, CH_3OP), 54.25 (d, $^2J_{PC}$=7.6 Hz, CH_3OP), 55.4 (C-2), 61.7 (d, $^3J_{PC}$=6.9 Hz, C-7), 65.2 (d, $^3J_{PC}$=6.3 Hz, C-5), 72.3 (d, $^2J_{PC}$=3.2 Hz, C-4a), [6 arom C: 127.2 (CH), 128.7 (2CH), 130.0 (2CH), 136.9 (Cq)], 169.6 (C-3). ^{31}P NMR (121.49 MHz, $CDCl_3$) δ=26.60. ES^+MS m/z: 378.2 $[M+Na]^+$. HRMS (ES) m/z $[M+Na]^+$ calcd for $C_{16}H_{22}NO_6P+Na$: 378.1077; found: 378.1090.

4.5. Oxidation of α-aminophosphonates 13c or 13d: procedure D, method A

To a solution of **13c** or **13d** (1,07 mmol) in CH_2Cl_2 (2 mL) was added *t*-BuOCl (145 μL, 1.28 mmol) at 0 °C. After stirring the reaction mixture at 0 °C for 30 min, DABCO (290 mg, 2.56 mmol) was added. The reaction mixture was stirred at the same temperature for 30 min, quenched by the addition of water and extracted with AcOEt, dried over $MgSO_4$ and then concentrated in vacuo. The crude mixture without separation was converted to acids **3c** and **3d** by heating in 6 M aq HCl (5 mL) at reflux for 15 h. The solvent was evaporated under reduced pressure. The residue was dissolved in 2 mL of MeOH, and then the solution was concentrated again, to afford the crude aminophosphonic acid·*x*HCl, hydrochloride salt, quantitatively. The crude hydrochloride aminophosphonic acid·*x*HCl was dissolved in minimum amount of EtOH (2 mL), then to which was added dropwise an excess of propylene oxide (3 mL) and stirring at room temperature for 6 h. The volatile compounds were removed by evaporation under vacuum, to give 122 mg of aminophosphonic acid **3c** and 157 mg of **3d** in 58% and 75% yields, respectively.

4.6. Oxidation of α-aminophosphonates 13a: procedure D, method B

Ozone was bubbled through a solution of **13a** (210 mg, 0.550 mmol) in EtOH (30 mL) at −78 °C for 15–30 min (persistent blue colour solution). The excess of ozone was removed by argon flow and then dimethylsulfide (2 mL) was added. The mixture **18a**/**19a** was warmed to room temperature, and concentrated in vacuo. The residue without separation was hydrolyzed to acid **3a** according to method A, in 77% yield from **13a**.

*4.6.1. Diethyl [(4aS,8aS)-2-Benzyl-3-oxo-4a,5,7,8-tetrahydropyrano-[3,4-b][1,4]oxazin-8a(3H)-yl]phosphonate (**18a**).* Oxydation of **13a** using procedure D, method A, without acidic hydrolysis, gave a mixture of three compounds. Purification of the crude mixture (silica gel, ether/petrol ether/CH_2Cl_2, 65:25:10) allowed to only isolate **18a** enough pure for spectral characterization: pale yellow oil; R_f=0.42 (EtOAc/CH_2Cl_2, 50:50). ^{1}H NMR (360 MHz, $CDCl_3$) δ=1.27 (t, J=7.2 Hz, 3H, CH_3), 1.34 (t, J=7.2 Hz, 3H, CH_3), 2.25–2.41 (m, 2H, H-8), 3.07 (ddd, J=10.3, J=10.3, 1.1 Hz, 1H, H-7), 3.47 (dddd, J=1.8, 4.3, 10.1, 11.5 Hz, 1H, H-5), 3.82 (ddd, J=2.5, J=5.4, 11.5 Hz, 1H, H-5), 3.84–3.91 (m, 1H, H-7), 3.93 (dd, J_{AB}=13.3 Hz, J=2.0 Hz, 1H, H_{benzyl}), 4.04–4.28 (m, 5H, 1H_{benzyl} and 4H, CH_2OP), 4.95 (ddd, J=5.4, 9.0, 10.1 Hz, 1H, H-4a), 7.20–7.40 (m, 5H). ^{13}C NMR (90.56 MHz, $CDCl_3$) δ=16.4 (CH_3), 16.6 (CH_3), 31.7 (C-8), 41.5 ($CH_{2benzyl}$), 59.4 (d, $^1J_{PC}$=152.4 Hz, C-8a), 63.3 (d, $^3J_{PC}$=10.7 Hz, C-5), 63.9 (d, $^2J_{PC}$=7.2 Hz, $2CH_2OP$), 64.4 (d, $^3J_{PC}$=8.7 Hz, C-7), 72.9 (C-4a) [6 arom C: 127.3 (CH), 128.9 (2CH), 129.7 (2CH), 135.0 (Cq)], 154.2 (C-3), 165.7 (CO); ^{31}P NMR (145.78 MHz, $CDCl_3$) δ=19.14. HRMS (ES) m/z $[M+Na]^+$ calcd for $C_{18}H_{24}NO_7P$+Na: 404.1239; found 404.1233.

4.6.2. Diethyl [(2S,4aR,8aS)-2-Benzyl-6-oxido-3-oxo-hexahydro-thiopyrano[3,4-b][1,4]oxazin-8a(1H)-yl]phosphonate. Byproduct obtained from **13b** by oxidation using method A without acidic hydrolysis, and purified on silica gel for spectral characterization: yield 71%; pale yellow oil; R_f=0.20 (MeOH/CH_2Cl_2: 5:95); $[\alpha]_D$ −14.4 (c 1.00, $CHCl_3$). IR (film): ν_{max}=3463, 3289, 2983, 1744 (COO), 1375, 1239, 1168, 1046, 966 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ=1.34 (t, J=7.0 Hz, 3H, CH_3), 1.35 (t, J=7.0 Hz, 3H, CH_3), 1.50 (dd, J=12.3, 12.3 Hz, 1H, H-5), 1.90 (br s, 1H, NH), 1.94–2.09 (m, 1H, H-8), 2.63–2.82 (m, 3H, 2H-7 and H-5), 2.82–2.95 (m, 1H, H-8), 3.23 (dd, J_{AB}=13.3 Hz, J=4.3 Hz, 1H, H_{benzyl}), 3.49 (dd, J_{AB}=13.3 Hz, J=5.8 Hz, 1H, H_{benzyl}), 4.04–4.25 (m, 4H, CH_2OP), 4.44–4.54 (m, 1H, H-2), 4.99–5.09 (m, 1H, H-4a), 7.09–7.29 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ=16.4 (d, $^3J_{PC}$=8.5 Hz, CH_3), 16.5 (d, $^3J_{PC}$=5.3 Hz, CH_3), 22.2 (C-8), 38.3 (d, $^3J_{PC}$=9.5 Hz, C-7), 39.7 ($CH_{2benzyl}$), 44.4 (d, $^2J_{PC}$=7.5 Hz, C-5), 53.0 (d, $^1J_{PC}$=145.3 Hz, C-8a), 56.7 (C-2), 62.9 (d, $^2J_{PC}$=8.0 Hz, CH_2OP), 63.7 (d, $^2J_{PC}$=7.5 Hz, CH_2OP), 70.5 (C-4a) [6 arom C: 127.3 (CH), 128.4 (2CH), 130.4 (2CH), 136.8 (Cq)], 168.8 (C-3). ^{31}P NMR (101.25 MHz, $CDCl_3$) δ=24.28. HRMS (ES) m/z $[M+Na]^+$ calcd for $C_{18}H_{26}NO_6PS$+Na: 438.1111; found: 438.1113.

*4.6.3. [(3S,4S)-4-Amino-3-hydroxy-tetrahydro-2H-pyran-4-yl]phosphonic acid (**3a**).* Prepared by procedure D, method B: yield 77% from **13a**; white solid; mp 230 °C; R_f=0.29 (NH_3 aq/H_2O/EtOH, 10:30:90); $[\alpha]_D$ +21.5 (c 0.50, H_2O). IR (KBr): ν_{max}=3420, 3369, 3120, 2932, 1614, 1494, 1207, 1160, 1109, 1065, 916 cm^{-1}. ^{1}H NMR (360 MHz, D_2O) δ=2.00–2.26 (m, 2H, H-5), 3.80 (dd, J=4.0, 12.2 Hz, 1H, H-2), 3.84–3.93 (m, 1H, H-6), 4.00 (ddd, J=3.6, 8.6, 12.2 Hz, 1H, H-6), 4.13 (d, J=12.2 Hz, 1H, H-2), 4.15 (br s, 1H, H-3). ^{1}H NMR (250 MHz, D_2O+NaOD) δ=1.53 (br dd, J=5.0, 14.5 Hz, 1H, H-5), 1.86–2.10 (m, 1H, H-5), 3.52–3.84 (m, 4H), 3.99 (ddd, J=5.2, 5.2, 10.5 Hz, 1H, H-3). ^{13}C NMR (90.56 MHz, D_2O) δ=27.4 (C-5), 55.6 (d, $^1J_{PC}$=140.5 Hz, C-4), 63.0 (C-6), 64.4 (d, $^2J_{PC}$=4.2 Hz, C-3), 67.9 (C-2). ^{31}P NMR (101.25 MHz, D_2O) δ=12.05, in (D_2O+NaOD, 101.25 MHz) δ=21.47 ppm. ES$^+$MS m/z: 198.0 $[M+H]^+$. HRMS (ES) m/z $[M+H]^+$ calcd for $C_5H_{13}NO_5P$: 198.0526; found: 198.0531.

*4.6.4. [(3R,4R)-4-Amino-3-hydroxy-tetrahydro-2H-pyran-4-yl]phosphonic acid (ent-**3a**).* Prepared by procedure D, method B: yield 58% from **20a**; white solid; mp 232 °C decomp.; R_f=0.30 (NH_3 aq/H_2O/EtOH, 10:30:90); $[\alpha]_D$ −18.6 (c 0.5, H_2O). ^{1}H NMR (360 MHz, D_2O) δ=2.00–2.26 (m, 2H, H-5), 3.80 (dd, J=4.0, 12.2 Hz, 1H, H-2), 3.84–3.93 (m, 1H, H-6), 4.00 (ddd, J=3.6, 8.6, 12.2 Hz, 1H, H-6), 4.13 (d, J=12.2 Hz, 1H, H-2), 4.15 (br s, 1H, H-3). All spectral data are identical with those noted above for (3*S*,4*S*)-**3a**.

*4.6.5. [(3S,4S)-4-Amino-3-hydroxypiperidin-4-yl]phosphonic acid, hydrochloride (**3c**·2HCl).* Prepared by procedure D, method A: yield 58% from **13c**; white solid; mp 240 °C decomp.; $[\alpha]_D$ +9.5 (c 1.00, H_2O). IR (KBr): ν_{max}=3494, 2927, 1612, 1530, 1299, 1188, 1160, 925 cm^{-1}. ^{1}H NMR (360 MHz, D_2O) δ=2.05–2.34 (m, 2H, H-5), 3.33 (d, J=13.3 Hz, 1H, H-2), 3.35 (d, J=12.0 Hz, 1H, H-6), 3.48 (ddd, J=4.0, 12.6, 12.0 Hz, 1H, H-6), 3.67 (d, J=13.3 Hz, 1H), 4.34 (br s, 1H, H-3). ^{13}C NMR (90.56 MHz, D_2O) δ=23.6 (C-5), 40.4 (C-6), 46.9 (C-2), 54.7 (d, $^1J_{PC}$=138.0 Hz, C-4), 62.2 (d, $^2J_{PC}$=6.2 Hz, C-3). ^{31}P NMR (101.25 MHz, D_2O) δ=10.32. HRMS (ES) m/z $[M+H]^+$ calcd for $C_5H_{14}N_2O_4P$: 197.0686; found: 197.0692.

*4.6.6. [(1S,2S)-1-Amino-2-hydroxycyclohexyl]phosphonic acid (**3d**).* Prepared by procedure D, method A: yield 75% from **13d**; white solid; mp 208 °C decomp.; R_f=0.11 (EtOAc); $[\alpha]_D$ −9.4 (c 1.00, H_2O). IR (KBr): ν_{max}=3390, 3255, 2939, 1624, 1538, 1163, 1079, 916 cm^{-1}. ^{1}H NMR (250 MHz, D_2O) δ=1.20–1.60 (m, 3H), 1.60–2.50 (m, 5H), 4.00–4.16 (m, 1H, H-2). ^{1}H NMR (360 MHz, CD_3OD) δ=1.30–1.62 (m, 3H), 1.62–1.87 (m, 2H), 1.87–2.16 (m, 3H), 4.01 (ddd, J=4.2, 5.0, 10.1 Hz, 1H, H-2). ^{13}C NMR (90.56 MHz, CD_3OD) δ=19.3 (d, $^3J_{PC}$=6.8 Hz, C-4), 22.4 (C-5), 27.9 (C-6), 28.5 (C-3), 58.0 (d, $^1J_{PC}$=141.5 Hz, C-1), 68.3 (C-2). ^{31}P NMR (101.25 MHz, D_2O) δ=14.93; in (CD_3OD, 145.78 MHz) δ=14.76 ppm. HRMS (ES) m/z $[M+Na]^+$ calcd for $C_6H_{14}NO_4P$+Na: 218.0553; found: 218.0553.

Acknowledgements

We thank Mr. Regis Guillot for performing X-ray crystal analysis.

Supplementary data

Experimental procedures, characterization data for new compounds not reported in the experimental section, copies of ^{1}H and ^{13}C NMR spectra for some new compounds, X-ray data for compound **13b**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.07.040.

References and notes

1. (a) Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *63*, 193–215; (b) Maier, L. *Phosphorus Sulfur* **1983**, *14*, 295–322; (c) Baylis, E. K.; Campbell, C. D.; Dingwall, J.-G. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2845–2853; (d) Maier, L. *Phosphorus, Sulfur Silicon Relat. Elem.* **1990**, *53*, 43–67; (e) Hudson, H. R.; Pianka, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **1996**, *109–110*, 345–348.
2. Peyman, A.; Budt, K. H.; Spanig, J.; Ruppert, D. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1720–1722.
3. Cheng, L.; Goodwin, C. A.; Scully, M. F.; Kakkar, V. V.; Claeson, G. *Tetrahedron Lett.* **1991**, *32*, 7333–7336.
4. (a) Kukhar, V. P.; Hudson, H. R. *Aminophosphonic and Aminophosphinic Acids*; Wiley: New York, NY, 2000; (b) For a review on stereoselective synthesis of α-aminophosphonic acids, see: Ordonez, M.; Rojas-Cabrera, H.; Cativiela, C. *Tetrahedron* **2009**, *65*, 17–49.
5. For enantioselective synthesis of α-aminophosphonic acids, see: (a) Kukhar, V. P.; Soloshonok, V. A. *Phosphorus, Sulfur Silicon Relat. Elem.* **1994**, *92*, 239–264; (b) Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161–3195; (c) Kolodiazhnyi, O. I. *Tetrahedron: Asymmetry* **1998**, *9*, 1279–1332 and references cited therein.

6. (a) Lefebvre, I. M.; Evans, S. A., Jr. *J. Org. Chem.* **1997**, *62*, 7532–7533; (b) Vercruysse, K.; Dejugnat, C.; Munoz, A.; Etemad-Moghadam, G. *Eur. J. Org. Chem.* **2000**, 281–299 and references cited therein; (c) Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102–4103 and references cited therein; (d) Maury, C.; Gharbaoui, J.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1996**, *61*, 3687–3693.
7. For synthesis of cyclopropyl aminophosphonic acids, see: (a) Groth, U.; Lehmann, L.; Richter, L.; Schöllkopf, U. *Liebigs Ann. Chem.* **1993**, 427–431; (b) Yamazaki, S.; Takada, T.; Imanishi, T.; Moriguchi, Y.; Yamabe, S. *J. Org. Chem.* **1998**, *63*, 5919–5928.
8. For synthesis of chiral nonracemic cyclopropyl aminophosphonic acids, see: (a) Fadel, A. *J. Org. Chem.* **1999**, *64*, 4953–4955; (b) Fadel, A.; Tesson, N. *Eur. J. Org. Chem.* **2000**, 2153–2159; (c) Fadel, A.; Tesson, N. *Tetrahedron: Asymmetry* **2000**, *11*, 2023–2031; (d) Tesson, N.; Dorigneux, B.; Fadel, A. *Tetrahedron: Asymmetry* **2002**, *13*, 2267–2276.
9. (a) Hercouet, A.; Le Corre, M.; Carboni, B. *Tetrahedron Lett.* **2000**, *41*, 197–199; (b) For cyclobutyl and cyclopentyl derivative, see: Guéguen, C.; About-Jaudet, E.; Collignon, N.; Savignac, P. *Synth. Commun.* **1996**, *26*, 4131–4143.
10. For cyclopentyl derivatives, see: (a) Ranu, B. C.; Hajra, A. *Green Chem.* **2002**, *4*, 551–554; (b) Wieczorek, J. C.; Gancarz, R.; Bielecki, K.; Grzys, E.; Sarapuk, J. *Phosphorus, Sulfur Silicon Relat. Elem.* **2001**, *174*, 119–128; (c) Stoikov, I. I.; Repejkov, S. A.; Antipin, I. S.; Konovalov, A. I. *Heteroat. Chem.* **2000**, *11*, 518–527.
11. For recent synthesis of cyclohexyl aminophosphonic acids, see: (a) Wieczorek, J. S.; Gancarz, R.; Bielecki, L.; Grzys, E.; Sarapuk, J. *Phosphorus, Sulfur Silicon Relat. Elem.* **2000**, *166*, 111–123; (b) Yadav, J. S.; Subba Reddy, B. V.; Madan, C. *Synlett* **2001**, 1131–1133; (c) Matveera, E. D.; Podrugina, T. A.; Tishkovskaya, E. V.; Tomilova, L. G.; Zefirov, N. S. *Synlett* **2003**, 2321–2324; (d) Ravinder, K.; Reddy, A. V.; Krishnaiah, P.; Venkataramana, G.; Reddy, V. L. N.; Venkateswarlu, Y. *Synth. Commun.* **2004**, *34*, 1677–1683; (e) Firouzabadi, H.; Iranpoor, N.; Sobhani, S. *Synthesis* **2004**, 2692–2696; (f) Ghosh, R.; Maiti, S.; Chakraborty, A.; Maiti, D. K. *J. Mol. Catal. A: Chem.* **2004**, *210*, 53–57.
12. For microwave irradiation, see: Kabachnick, M. M.; Zobnina, E. V.; Belatskaya, I. P. *Synlett* **2005**, 1393–1396 and references cited therein.
13. GABA-related drugs have shown promising properties as antilepileptic, antispastic and antidepressive agents Fonnum, F. In *Psychopharmacology*; Meltzer, H., Ed.; Raven: New York, NY, 1987; Vol. 18, pp 173–182.
14. (a) Tukanova, S. K.; Dzhiembaev, B. Z.; Butin, B. M. *Zh. Obshch. Khim.* **1991**, *61*, 1118–1120; *Chem. Abstr.* **1992**, *116*, 6637; (b) Gancarz, R.; Latajka, R.; Halama, A.; Kafarski, P. *Magn. Reson. Chem.* **2000**, *38*, 867–871; (c) For substituted piperidine and tetrathiophen aminophosphonic acid derivatives, see: Bosyakov, Y. G.; Maishinova, G. T.; Logunov, A. P.; Revenko, G. P. *Izv. Nats. Akad. Nauk. Resp. Kaz., Ser. Khim.* **1993**, *6*, 72–76; *Chem. Abstr.* **1995**, *123*, 112161.
15. For aminophosphonates of substituted tetrahydropyrans, see: (a) Kabatschnick, M. I. *Izr. Akad. Nauk SSSR, Ser. Khim.* **1967**, 1362; *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1967**, 1379; (b) Fields, E. K. *J. Am. Chem. Soc.* **1952**, *74*, 1528–1531; (c) For unsubstituted tetrahydropyran derivatives, see Ref. 16a.
16. (a) Tukanova, S. K.; Dzhiembaev, B. Z.; Khalilova, S. F.; Butin, B. M. *Zh. Obshch. Khim.* **1993**, *63*, 938–939; *Chem. Abstr.* **1993**, *119*, 250038; (b) Kiyashev, D. K.; Turisbekova, L. K.; Sadykov, T. S.; Erzhanov, K. B.; Nurakhov, D. B. *Izv. Akad. Nauk. Kaz., Ser. Khim.* **1990**, *6*, 82–84; *Chem. Abstr.* **1991**, *114*, 122537; (c) See Ref. 14c.
17. (a) Rabasso, N.; Louaisil, N.; Fadel, A. *Tetrahedron* **2006**, *62*, 7445–7454; (b) Louaisil, N.; Rabasso, N.; Fadel, A. *Synthesis* **2007**, 289–293.
18. (a) Walsh, C. *Enzyme Reaction Mechanisms*; W. H. Freeman: San Francisco, CA, 2000; pp 94–97; (b) Cleland, W. W.; Kreevoy, M. M. *Science* **1994**, *264*, 1887–1890 and references cited therein.
19. Christensen, H. N.; Handlogten, M. E. *Biochim. Biophys. Acta* **1977**, *469*, 216–220.
20. (a) Ohfune, Y.; Horikawa, M. *J. Synth. Org. Chem. Jpn.* **1997**, *55*, 982–993; (b) Ohfune, Y.; Nanba, K.; Takada, I.; Kan, T.; Horikawa, M.; Nakajima, T. *Chirality* **1997**, *9*, 459–462; (c) Namba, K.; Kawasaki, M.; Takada, I.; Iwama, S.; Izumida, M.; Shinada, T.; Ohfune, Y. *Tetrahedron Lett.* **2001**, *42*, 3733–3736; (d) Ohfune, Y.; Demura, T.; Iwama, S.; Matsuda, H.; Namba, K.; Shimemoto, K.; Shinada, T. *Tetrahedron Lett.* **2003**, *44*, 5431–5434.
21. (a) Pai Fondekar, K. P.; Volk, F.-J.; Frahm, A. W. *Tetrahedron: Asymmetry* **1999**, *10*, 727–735; (b) Pai Fondekar, K. P.; Volk, F.-J.; Khaliq-uz-Zaman, S. M.; Bisel, P.; Frahm, A. W. *Tetrahedron: Asymmetry* **2002**, *13*, 2241–2249.
22. (a) Burkett, B. A.; Chai, C. L. L. *Tetrahedron Lett.* **2000**, *41*, 6661–6664; (b) Avenoza, A.; Barriobero, J. I.; Cativiela, C.; Fernandez-Recio, M. A.; Peregrine, J. M.; Rodriguez, F. *Tetrahedron* **2001**, *57*, 2745–2755; (c) Jayakanthan, K.; Vankar, Y. D. *Org. Lett.* **2005**, *7*, 5441–5444.
23. (a) Van Daele, G. H. P.; De Bruyn, M. F. L.; Verdonck, M. G. C. Eur. Patent EP0121972, 1984, 1017; *Chem. Abstr.* **1984**, *102*, 149116; (b) Prepared from glyco-α-aminonitriles, see: Postel, D.; Nguyen Van Nhien, A.; Villa, P.; Ronco, G. *Tetrahedron Lett.* **2001**, *42*, 1499–1502; (c) Santo Gonzalez, F.; Robles Diaz, R.; Calvo-Flores, F. A. G.; Vargas Berenguel, A.; Gimenez Martinez, J. J. *Synthesis* **1992**, 631–632.
24. Rabasso, N.; Fadel, A. *Synthesis* **2008**, 2353–2362.
25. Zacuto, M. J.; Cai, D. *Tetrahedron Lett.* **2005**, *46*, 447–450.
26. Moriarty, R. M.; Hu, H.; Gupta, S. C. *Tetrahedron Lett.* **1981**, *22*, 1283–1286.
27. Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522–524.
28. Colourless crystal of $0.220\times0.180\times0.035\ mm^3$. $C_{18}H_{26}NO_5PS$, M=399.44: monoclinic system, space group $P2_1$ (No. 4), Z=2, with a=6.0889(3), b=15.8496 (8), c=10.0715 (6) Å, α=90, β=95.5040 (10), γ=90.00°, V=967.49 (9) Å^3, d=1.371 g cm^{-3}, $F(000)$=424, λ=0.71073 Å (Mo Kα), μ=0.279 mm^{-1}, 6423 reflections measured ($-8\leq h\leq 9$, $-21\leq k\leq 24$, $-15\leq l\leq 15$) on a Bruker X8 diffractometer. The structure was solved and refined with SHELXL-97.[33] Hydrogen atom riding, refinement converged to $R(gt)$=0.0335 for the 5860 reflections having $I>2\sigma(I)$, and $wR(gt)$=0.0775, Goodness-of-fit S=1.026, residual electron density: −0.353 and 0.481 e Å^{-3}; for more details, see Supplementary data included.[34]
29. Namba, K.; Shinada, T.; Teramoto, T.; Ohfune, Y. *J. Am. Chem. Soc.* **2000**, *122*, 10708–10709.
30. The numbering of the fused system and the absolute configuration are noted following IUPAC rules, and taking into account the sulfur atom priority.
31. All calculations were performed using Spartan' 06.
32. Shinada, T.; Kawakami, T.; Sakai, H.; Matsuda, H.; Umezawa, T.; Kawasaki, M.; Namba, K.; Ohfune, Y. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 768–774.
33. Scheldrick, G. M. *SHELXL-97, Programme for Crystal Structure Refinement*; Universität Göttingen: Göttingen, 1997.
34. Crystallographic data for compound (+)-**13b** have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Number CCDC 725296. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, fax: +44 1233 336033, E-mail: deposit-@ccdc.cam.ac.uk.