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Synthesis and conformational analysis of 1,3,2-diazaphosphorino[6,1-*a*]isoquinolines, a new ring system

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Abstract—Through ring-closure reactions of *N*- or 1′-substituted 1-(2′-aminoethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (**5a**-**e**) with phenylphosphonyl dichloride, 1- or 3-substituted 4-phenyl-1,3,4,6,7,11b-tetrahydro-2*H*-1,3,2-diazaphosphorino[6,1-*a*]isoquinolin-4-one diastereomers (**7a**–**e** and **8a**–**c**,**e**), the first representatives of a new ring system, were prepared. The diastereomeric ratios in the cyclizations and the conformer (**A**–**E**) populations of the nitrogen-bridged tricyclic systems (**7** and **8**) were strongly influenced by the *N*- and 1′-substituents of the starting diamines. The conformational analysis of compounds **7** and **8** was performed by ^{1}H, ^{13}C and ^{31}P NMR methods.

1. Introduction

In contrast with the 1,3,2-oxazaphosphorinane-2-oxides, which have been thoroughly investigated from both pharmacological and stereochemical points of view,[1,2] less attention has been paid to the synthesis and stereochemistry of the aza-analogue 1,3,2-diazaphosphorinane-2-oxides. The first publications on the conformations of saturated 1,3,2-diazaphosphorinane-2-oxides contained a much uncertainty concerning the axial/equatorial orientation of the *P*-substituents.[3–6] The stereochemical investigation of this type of heterocyclic compounds became of considerable interest when chiral cyclic phosphoramides proved to be effective auxiliaries with which to induce stereoselective carbon–carbon or carbon–hydrogen bond-forming reactions, e.g. asymmetric aldol reactions,[7] allylations of aldehydes,[8] α-alkylations of *P*-alkyl derivatives[9] and reductions of ketones.[10] Stereochemical studies on some 1,3,2-dizaphosphorinane-2-oxide model compounds, including their lithiated anion derivatives, led to the conclusion that, in contrast with the conformationally diverse 1,3,2-oxazaphosphorinane analogues, these compounds could be characterized by chair or flattened chair conformations.[11,12] Despite their wide synthetic applicability, no systematic investigations have been performed to unravel the substituent effects on the conformational equilibria of 1,3,2-diazaphosphorine-2-oxides.

Our present aim was to prepare some *P*-, *N*- and *C*-substituted 1,3,2-diazaphosphorinane-2-oxides, angularly condensed with 1,2,3,4-tetrahydroisoquinoline, in order to investigate the effects of the substituents and the configurations of the substituted atoms on the predominant conformations of the 1,3,2-diazaphosphorinane ring and the nitrogen-bridged tricyclic system.

2. Results and discussion

2.1. Syntheses

1-(2′-Aminoethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines **5a**–**e**, the starting materials for the preparation of the target diazaphosphorinanes, were prepared in five steps, similarly to the 1-(aminomethyl)-substituted homologues,[13] starting from the corresponding *N*-protected β-alanines (**1a**–**c**) and homoveratrylamine (Schemes 1 and 2). β-Alanine derivatives **1b** and **1c** were obtained by transformations of ethyl 3-anilinopropanoate[14] and ethyl 3-amino-2-methylpropanoate,[15] respectively. Reduction of urethane **4a** with $LiAlH_4$ produced the *N*-methyl-substituted diamine (**5c**).

In the transformations of dihydroisoquinoline **3c**, the reducing agent applied and the sequence of the reduction and deprotection steps proved to have marked effects on the formation of the possible diamine diastereomers. Reduction of **3c** with $NaBH_4$ gave a 7:1 mixture of tetrahydroisoquinoline diastereomers **4c** and **4d**, from which **4c** could be obtained by crystallization and converted to the $1R^*,1'R^*$ diamine diastereomer **5d**. Catalytic hydrogenation of the deprotected dihydroisoquinoline **6** in the presence of palladium on charcoal catalyst resulted in a 1:10 mixture of the $1R^*,1'R^*$ (base of **5d**) and $1R^*,1'S^*$ (base of **5e**) diamine diastereomers, from which **5e** could be isolated by

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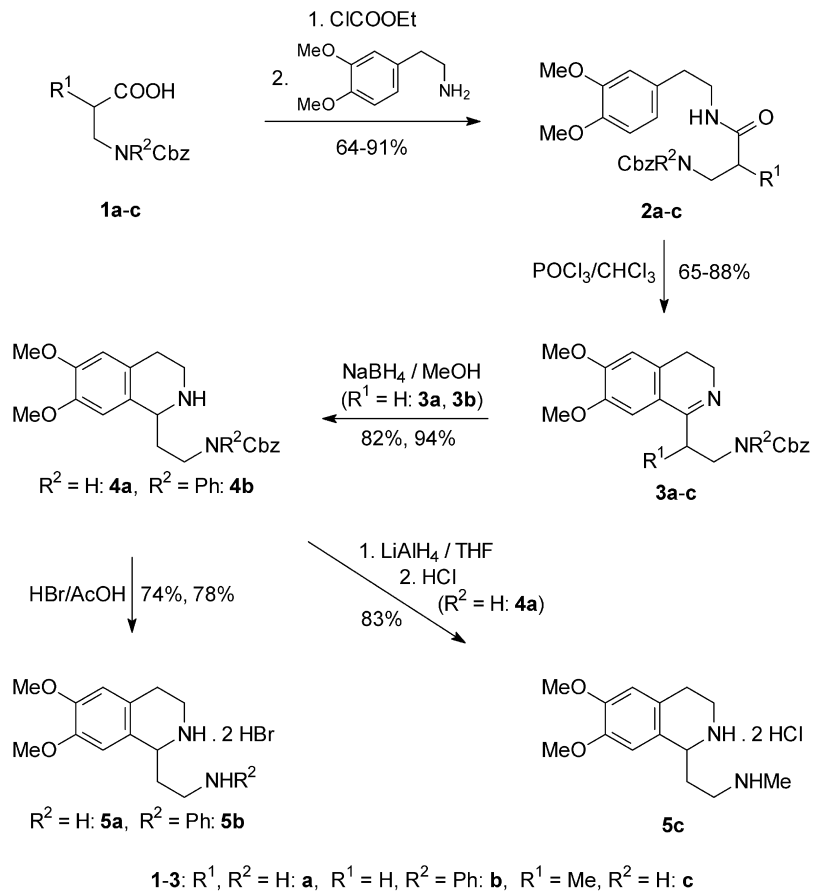


Scheme 1.

fractional crystallization of the dihydrochloride salt (Scheme 2). Reduction of **6** with $NaBH_4$ led to a 3:2 mixture of the $1R^*,1'R^*$ (**5d**) and $1R^*,1'S^*$ (**5e**) diamine diastereomers, while these isomers were formed in 1:1 ratio when compound **3c** was hydrogenated under the same conditions as applied in the catalytic reduction of **6**. The diastereomeric ratios for **4c/4d** and **5d/5e** were determined from the ^1H NMR spectra by integration of the well-separated 1′-Me doublets. The relative configurations of **5d** and **5e** were deduced from their ring-closed diazaphosphorinane derivatives (**7** and **8**) (see below).

The considerable diastereoselectivity observed in the reductions of **3c** and **6** can be rationalized by the steric effects of the methyl or Cbz groups in the dihydroisoquinolines **3c** and **6** being somewhat restricted conformationally by intramolecular hydrogen bonds. The attack by hydride ions or hydrogen occurred from the sterically less hindered side of the molecule. However, the opposite diastereoselectivity observed in the reduction of **6**, depending on the reducing agent, demands further explanation.

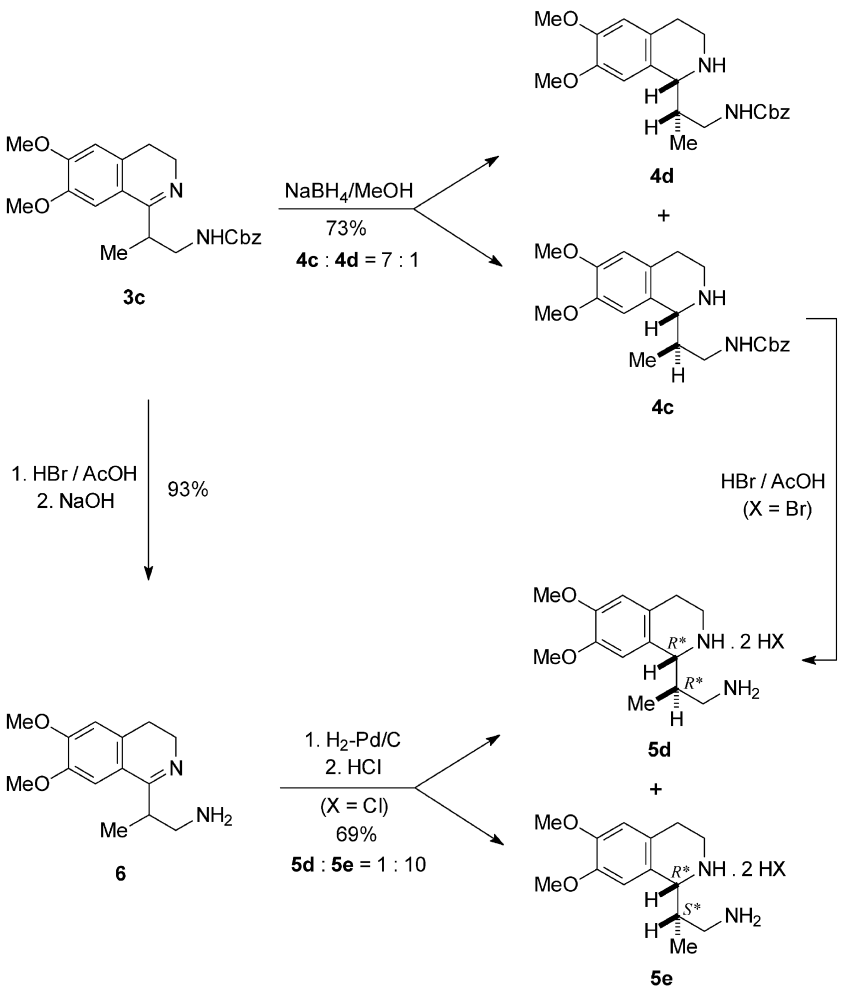
The ring-closure reactions of diamines **5a**–**e** with phenylphosphonyl dichloride were accomplished by the usual literature methods,[16] to yield 1,3,2-diazaphosphorino[6,1-*a*]isoquinolines (**7** and **8**), which are the first representatives of this ring system (Scheme 3). Bis(2-chloroethyl)amino-substituted (nitrogen mustard) derivatives with isoquino[2,1-*c*][1,3,2]benzodiazaphosphorines skeleton, which is the benzologue of the ring system of **7/8**, have recently been prepared and found to possess anticancer activity, but no data have been given on the stereochemistry of these tetracyclic compounds.[17]

The *N*-substituents proved to have significant effects on the ratios of the diastereomers formed: in the case of the *N*-unsubstituted diamines (**5a**,**d**,**e**), the diastereomers of type **7**, containing a 4-phenyl group and H-11b in the *cis* position, were the major isomers, while the *N*-phenyl- and *N*-methyl-substituted diamines (**5b**,**c**) gave isomers of type **8** as the main products. In the ring-closure of the $1R^*,1'R^*$ 1′-methyl-substituted diamine diastereomer (**5d**), the minor diazaphosphorinane isomer of type **8** could not be detected, even in the crude product.

2.2. Structure

2.2.1. Determination of the configurations. With respect to the relative configuration on the phosphorus, there is a series of diastereomer pairs **7** and **8**. The spatiality of the substituents on the phosphorus has a substantial effect on the spectral parameters of the model compounds. The most useful observables are the ^{31}P chemical shifts, the proton chemical shift changes due to the 1,3-diaxial interactions, and the NOE effects between the substituent on the phosphorus and other ring protons or substituents.

For compounds **8**, a systematic increase in the chemical shifts of H-2ax is detected as compared with compounds **7** (Table 1), which is due to the shielding effect of the oxygen



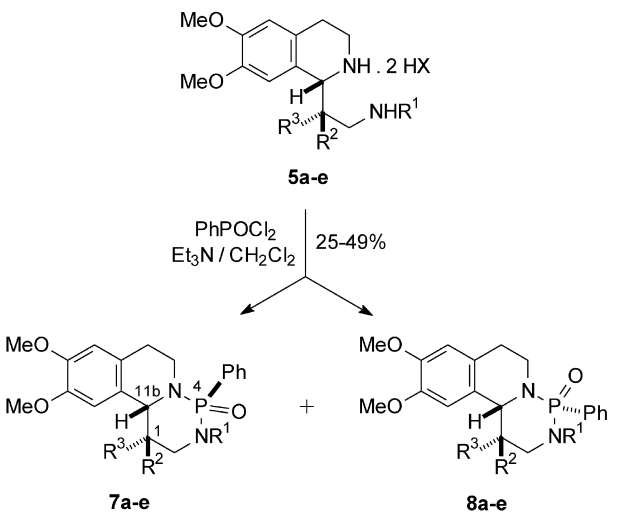
Scheme 2.

in the 1,3-diaxial position relative to H-2ax. (H-2ax is assigned because of the NOE interaction with H-11b.) The NOE interactions between the *ortho*-hydrogens of the phenyl group on the phosphorus and H-11b can be detected in each case in the series **7**. These findings unequivocally show that H-11b and the phenyl substituent on the phosphorus are located on the same side of the best plane of the diazaphosphorinane ring in **7**. The assignment of the relative configuration is supported by the ^{31}P chemical shifts; an upfield shift is measured for the ^{31}P chemical shifts on going from **7** to **8**, with the exception of the diastereomeric pair **7a** and **8a** (Table 1). It must be noted that the ^{31}P chemical shifts do not always display a systematic change together with the phosphorus relative configuration.[1,18] As a consequence of the diastereomeric counterpart not being available, the spatiality of **7d** was assigned purely on the basis of the observed NOE interactions.

As regards the relative configurations in **7d**, **7e** and **8e**, the ^{3}J(H-1,H-11b) couplings are informative. For **7d** the coupling constant of 9.2 Hz between H-1 and H-11b proves their *trans*-diaxial arrangement. The low ^{3}J(H-1,H-11b) values of 2.8 and 2.9 Hz observed in **7e** and **8e**, respectively, indicate almost orthogonal geometry for the vicinal protons in question, proving their *cis*-axial-equatorial relative

Table 1. Selected chemical shifts and vicinal coupling constants

	δ ^{31}P (ppm)	δ H2ax (ppm)	δ H2eq (ppm)	^{3}J(H-11b,P) (Hz)	^{3}J(H-2ax,P) (Hz)	^{3}J(H-2eq,P) (Hz)	^{3}J(H-11b,H-1eq) (Hz)	^{3}J(H-11b,H-1ax) (Hz)
7a	26.0	3.35	3.44	2.8	5.0	22.1	6.8	9.0
8a	24.9	3.54	3.33	2.9	6.0	21.8	3.3	11.9
7b	22.5	3.89	3.73	3.3	11.3	16.6	5.5	8.8
8b	23.1	4.00	3.63	4.4	6.6	16.2	4.2	10.8
7c	25.2	3.46	3.25	2.6	4.0	17.0	4.4	9.9
8c	29.1	3.54	3.08	2.2	4.7	20.9	2.0	11.6
7d	28.6	2.91	3.47	4.8	10.8	18.6	–	9.2
7e	24.7	3.56	3.23	1.8	3.5	24.3	2.8	–
8e	29.4	3.87	3.11	3.5	5.6	23.5	2.9	–



	R^1	R^2	R^3	diastereomeric ratio (**7** : **8**) in the crude product
a	H	H	H	56 : 44
b	Ph	H	H	29 : 71
c	Me	H	H	27 : 73
d	H	Me	H	~100 : ~0
e	H	H	Me	57 : 43

Scheme 3.

configuration. In consequence of the synthetic pathway, these are also the relative configurations of the starting diamines **5d** and **5e**.

2.2.2. Conformational analysis. The phosphorus-containing heterocycles are prone to participate in a conformational equilibrium involving chair, twisted chair and other distorted conformations[1] (**A**–**E**) (Fig. 1). This conformational flexibility stems from the greater bond lengths associated with the phosphorus. The straightforward way to obtain information on the conformational equilibria of the

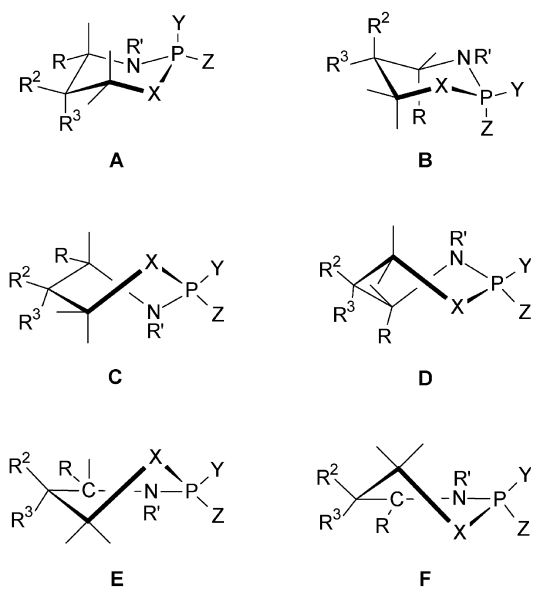


Figure 1. Possible conformations of 1,3,2-diazaphosphorinanes (X=NR[1]) and the related 1,3,2-oxazaphosphorinanes[1] (X=O).

model compounds is analysis of the ^3J(P,H) coupling constants, which allows estimation of the dihedral angle distribution by using formula (1):

$$P_B = ({}^3J_{obs} - {}^3J_A)/({}^3J_B - {}^3J_A), \qquad P_A = 1 - P_B \qquad (1)$$

where P_A and P_B are the populations, $^3J_{obs}$ is the experimentally observed coupling constant, and ^3J_A and ^3J_B are the reference coupling constants in states A and B, respectively. On the basis of the literature data[19] and our earlier observations,[1,18] the estimated reference values of 25 and 3 Hz are chosen for ^3J(P,Heq) and ^3J(P,Hax), respectively. The low values observed for ^3J(P,H-11b) clearly show its predominantly axial orientation in the diazaphosphorinane ring (Table 1), which rules out conformers **B** and **D** containing an equatorial H-11b, and points to conformers **A** and **C**. For **7d** and **8b**, a slightly increased ^3J(P,H-11b) value is observed, suggesting that the conformation reflects a degree of similarity to the flattened ring geometry of **E** and **F**;[1] however, we describe the present diazaphosphorinane ring conformations as involving an equilibrium between the idealized conformers **A** and **C**. The estimated ratios are given in Table 2. The sum of the conformer populations calculated independently from ^3J(P,H-2eq) and ^3J(P,H-2ax) exceeds 100% significantly for **8b** and **7c**, where N-3 possesses Me or Ph substituents. Such anomalous behavior of the coupling constants can be explained by the assumption of distorted conformational states differing from **A** and **C**, which might be caused by unfavorable 1,2 interactions between the substituents on N-3 and P. In order to clarify the nature of these distorted structures, quantum chemical calculations are in progress.

As concerns the conformation of the annelated isoquinoline moiety, the vicinal coupling constants between H-6ax and H-7ax are within the range 7.9–11.8 Hz, indicating their diaxial orientation. A NOESY cross-peak between H-11b and H-6ax can be observed for each compound. These spectral parameters render the twist conformation likely for the tetrahydroisoquinoline moiety, which is a general feature of tetrahydroisoquinoline derivatives condensed angularly to a saturated 1,3- or 1,2,3-heterocycle.[1,18,20]

3. Conclusions

The first representatives of a new ring system, 1,3,2-diazaphosphorino[6,1-*a*]isoquinolin-4-one derivatives, were successfully synthesized by ring-closure reactions of

Table 2. Conformer populations (%)

	[**A**]	[**C**]	[**A**]+[**C**][a]
7a	91	13	104
8a	87	15	101
7b	62	38	100
8b	84	40	124
7c	95	36	132
8c	92	19	111
7d	65	29	94
7e	98	3	101
8e	88	7	95

[a] For explanation, see the text.

N- or 1′-substituted 1-(2′-aminoethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines with phenylphosphonyl dichloride. The ratios of the P-4 epimeric 4-phenyl-1,3,4,6,7,11b-tetrahydro-2*H*-1,3,2-diazaphosphorino[6,1-*a*] isoquinolin-4-one diastereomers formed (**7a**–**e** and **8a**–**c**,**e**) were strongly influenced by the substituents (H, Me or Ph) at position 3 and, to a less extent, by the substituents (H or Me) at position 1. Conformational analysis on **7** and **8** led to the conclusion that the proton at the annelation (H-11b) takes up an axial position (relative to the 1,3,2-diazaphosphorinane ring) in each case and the conformational behavior of these compounds can be characterized by the equilibria of conformers having a chair (**A**) and a twisted chair (**C**) 1,3,2-diazaphosphorinane ring. The conformer populations were also influenced by the substituents at positions 1 and 3, and by the relative configurations of C-11b and C-1 or P-4.

4. Experimental

4.1. General

The NMR spectra were recorded in $CDCl_3$ or in D_2O solutions at 300 K on a Bruker AVANCE DRX 400 spectrometer. Chemical shifts are given in δ (ppm) relative to TMS ($CDCl_3$) or to TSP (D_2O) as internal standards; multiplicites were recorded as s (singlet), br s (broad singlet), d (doublet), dd (double doublet), ddd (double double doublet), dt (double triplet), t (triplet), q (quartet), m (multiplet) and om (overlapping multiplet). IR spectra were run in KBr discs on a Perkin–Elmer Paragon 1000 PC FT-IR spectrometer controlled by GRAMS Analyst for PE 1000 3.01A software. Mass spectra were recorded on a Finnigan MAT TSQ 7000 (San Jose, USA) instrument using electrospray ionization. Melting points were recorded on a Kofler hot-plate microscope apparatus and are uncorrected. For column chromatography, silica gel 60 (0.063–0.200 mm) was used.

4.1.1. *N*-Phenyl- (1b) and 2-methyl-substituted (1c) 3-(benzyloxycarbonylamino)propanoic acid. A mixture of ethyl 3-anilinopropanoate[14] or ethyl 3-amino-2-methylpropanoate[15] (0.1 mol) and 10% HCl solution (250 mL) was refluxed for 10 h. The solution was evaporated and the evaporation was repeated twice after the addition of toluene (2×50 mL). 3-Amino-2-methylpropanoic acid hydrochloride was crystallized by treatment of the oily residue with acetone. The crystals were filtered off and washed with acetone. All attempts to crystallize 3-anilinopropanoic acid hydrochloride failed. The oily product was used in the next step without further purification.

3-Anilinopropanoic acid hydrochloride. Yield: 17.70 g (~100%), a light-brown oil. ν_{max} 1730, 1495, 1406, 1194, 693 cm^{-1}; δ_H (400 MHz, D_2O) 7.46–7.63 (5H, m, C_6H_5), 3.74 (2H, t, J=6.5 Hz, NCH_2), 2.85 (2H, t, J=6.5 Hz, $COCH_2$); MS m/z 166 $[M+1]^+$.

3-Amino-2-methylpropanoic acid hydrochloride. Yield: 11.48 g (82%), mp 129–132°C (lit.[21] mp 128–129°C). The ^1H NMR data on the product correspond to the literature[21] data.

The above amino acid hydrochlorides were converted to the corresponding *N*-Cbz derivatives by using a standard procedure (ClCbz, NaOH).[22] The oily products crystallized on treatment with *n*-hexane.

Compound **1b**. Beige solid; yield: 19.36 g (74%), mp 83–90°C. [Found: C, 68.37; H, 5.64; N, 4.71. $C_{17}H_{17}NO_4$ requires C, 68.22; H, 5.72; N, 4.68%]; ν_{max} 1694, 1408, 1297, 1196, 693 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.15–7.40 (10H, om, 2×Ph), 5.14 (2H, s, CH_2), 3.99 (2H, t, J=7.3 Hz, NCH_2), 2.63 (2H, t, J=7.3 Hz, CH_2CO); MS m/z 300 $[M+1]^+$.

Compound **1c**. White solid; yield: 12.90 g (66%), mp 86–87°C (lit.[21] mp 51–52°C). The ^1H NMR data on the product correspond to the literature[21] data. ν_{max} 1721, 1663, 1535, 1279, 1191 cm^{-1}; MS m/z 238 $[M+1]^+$.

4.1.2. 3-Benzyloxycarbonylamino-*N*-[2-(3,4-dimethoxyphenyl)ethyl]propanamides (2a–c). To a stirred and ice-salt bath-cooled solution of the corresponding *N*-benzyloxycarbonyl-β-alanine (**1a**–**c**) (0.08 mol) and triethylamine (8.10 g, 0.08 mol) in anhydrous toluene (300 mL), ethyl chloroformate (8.68 g, 0.08 mol) was added dropwise at a rate low enough to keep the internal temperature below −10°C. After 5 min, a solution of 2-(3,4-dimethoxyphenyl) ethylamine (14.50 g, 0.08 mol) in CH_2Cl_2 (50 mL) was added dropwise, the internal temperature being kept below 0°C. When the addition was complete, the reaction mixture was heated under reflux for 5 min. The mixture was allowed to cool down to room temperature and $CHCl_3$ (300 mL) was added. The mixture was washed with a saturated $NaHCO_3$ solution (3×75 mL) and water (2×75 mL), and then dried (Na_2SO_4), and the solvent was removed in vacuo to give crude crystalline (**2a**,**c**) or oily (**2b**) products. The crystals were filtered off, washed with Et_2O and recrystallized from EtOAc. Crude oily **2b** was used in the next step without purification. An analytical sample of **2b** was purified by column chromatography (silica gel, EtOAc–*n*-hexane=10:1).

Compound **2a**. White solid; yield: 22.93 g (74%), mp 121–122°C. [Found: C, 64.98; H, 6.57; N, 7.19. $C_{21}H_{26}N_2O_5$ requires C, 65.27; H, 6.78; N, 7.25%]; ν_{max} 3330, 1693, 1637, 1518, 1273 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.27–7.38 (5H, m, Ph), 6.79 (1H, d, J=8.5 Hz, C_6H_3), 6.69–6.73 (2H, m, C_6H_3), 5.63 (1H, br s, N*H*), 5.42 (1H, br s, N*H*), 5.08 (2H, s, OCH_2), 3.86 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.42–3.52 (4H, om, 2×NCH_2), 2.74 (2H, t, J=7.1 Hz, CH_2CO), 2.36 (2H, t, J=5.5 Hz, $ArCH_2$); MS m/z 387 $[M+1]^+$.

Compound **2b**. Yield: 33.76 g (91%). [Found: C, 70.34; H, 6.63; N, 5.95. $C_{27}H_{30}N_2O_5$ requires C, 70.11; H, 6.54; N, 6.06%]; ν_{max} 2935, 1701, 1515, 1266, 1027 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.12–7.37 (10H, om, 2×Ph), 6.77 (1H, d, J=8.6 Hz, C_6H_3), 6.66–6.71 (2H, m, C_6H_3), 5.98 (1H, br s, N*H*), 5.11 (2H, s, OCH_2), 3.96 (2H, t, J=7.3 Hz, $PhNCH_2$), 3.83 (6H, 2×s, 2×OCH_3), 3.41 (2H, q, J=6.6 Hz, $NHCH_2$), 2.68 (2H, t, J=7.3 Hz, CH_2CO), 2.43 (2H, t, J=7.3 Hz, $ArCH_2$); MS m/z 463 $[M+1]^+$.

Compound **2c**. White solid; yield: 20.48 g (64%), mp

123–125°C. [Found: C, 65.76; H, 6.93; N, 6.96. $C_{22}H_{28}N_2O_5$ requires C, 65.98; H, 7.05, N, 7.00%]; ν_{max} 3296, 1688, 1637, 1518, 1274 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.26–7.35 (5H, m, Ph), 6.76–6.81 (1H, m, C_6H_3), 6.62–6.73 (2H, m, C_6H_3), 5.55 (1H, br s, N*H*), 5.26 (1H, br s, N*H*), 5.08 (2H, s, OCH_2), 3.86 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.35–3.54 (2H, m, NCH_2), 3.20–3.34 (2H, m, NCH_2), 2.73 (2H, t, J=7.2 Hz, $ArCH_2$), 2.35–2.50 (1H, m, MeC*H*), 1.10 (3H, d, J=7.0 Hz, $CHCH_3$); MS m/z 401 $[M+1]^+$.

4.1.3. 1-[2′-(Benzyloxycarbonylamino)ethyl]-6,7-dimethoxy-3,4-dihydroisoquinolines (3a–c). To a stirred solution of the corresponding propanamide (**2a–c**, 0.05 mol) in dry $CHCl_3$ (300 mL), $POCl_3$ (23.00 g, 0.15 mol) was added. The mixture was heated under reflux for 3 h, and then evaporated in vacuo. The oily residue was dissolved in water (250 mL) under gentle warming, and the solution was cooled and extracted with EtOAc (2×75 mL). The aqueous phase was made alkaline with 25% NaOH solution with cooling, and extracted with $CHCl_3$ (4×150 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to give crystalline (**3a**) or oily (**3b**,**c**) products. The crystals of **3a** were filtered off and washed with Et_2O. Crude oily **3b** and **3c** were converted to the crystalline hydrochloride by treatment of a solution in MeOH with an excess of 22% ethanolic HCl and Et_2O. The crude products (**3a**, **3b**·HCl and **3c**·HCl) were used in the next step without further purification.

Compound **3a**. Yield: 16.21 g (88%). An analytical sample of **3a** was recrystallized from iPr_2O–EtOAc to give pale butter-colour needles, mp 111–112°C. [Found: C, 68.71; H, 6.87; N, 7.48. $C_{21}H_{24}N_2O_4$ requires C, 68.46; H, 6.57; N, 7.60%]; ν_{max} 2926, 1708, 1516, 1282, 1217 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.27–7.38 (5H, m, Ph), 7.00 (1H, s, C_6H_2), 6.67 (1H, s, C_6H_2), 5.73 (1H, s, N*H*), 5.09 (2H, s, OCH_2), 3.91 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.57–3.66 (4H, m, 2 x NCH_2), 2.85–2.92 (2H, m, $CH_2C{=}N$), 2.58–2.63 (2H, m, CH_2Ar); MS m/z 369 $[M+1]^+$.

Compound **3b**·HCl. Yield: 19.85 g (83%). An analytical sample of **3b**·HCl was recrystallized from MeOH–Et_2O to give pale yellow needles, mp 150–153°C. [Found: C, 67.06; H, 5.92; N, 5.69. $C_{27}H_{29}ClN_2O_4$ requires C, 67.42; H, 6.08; N, 5.82%]; ν_{max} 2826, 1690, 1560, 1405, 1281 cm^{-1}; δ_H (400 MHz, D_2O) 7.12–7.48 (11H, om, 2×Ph, C_6H_2), 6.89 (1H, br s, C_6H_2), 4.94 (2H, s, OCH_2), 4.25 (2H, br s, CH_2N), 3.94 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.58–3.69 (2H, m, NCH_2), 3.21–3.31 (2H, m, $CH_2C{=}N$), 2.77 (2H, br s, $ArCH_2$); MS m/z 445 $[M+1]^+$.

Compound **3c**·HCl. Yield: 13.65 g (65%). An analytical sample of **3c**·HCl was recrystallized from MeOH–Et_2O to give white needles, mp 177–179°C. [Found: C, 62.95; H, 6.31; N, 6.38. $C_{22}H_{27}ClN_2O_4$ requires C, 63.08; H, 6.50; N, 6.69%]; ν_{max} 2767, 1703, 1556, 1521, 1275 cm^{-1}; δ_H (400 MHz, D_2O) 7.20–7.35 (5H, om, Ph), 7.12–7.18 (1H, m, C_6H_2), 6.98–7.02 (1H, m, C_6H_2), 4.80–4.89 (2H, m, OCH_2), 3.42–4.05 (11H, om, 2×NCH_2, 2×OCH_3, MeC*H*), 2.75–2.99 (2H, om, $ArCH_2$), 1.38 (3H, d, J=6.8 Hz, CH_3); MS m/z 383 $[M+1]^+$.

4.1.4. 1-[2′-(Benzyloxycarbonylamino)ethyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (4a–c). To a stirred and ice-cooled solution of the corresponding dihydroisoquinolines (**3a**, **3b**·HCl or **3c**·HCl, 35 mmol) in MeOH (200 mL), $NaBH_4$ (5.30 g, 0.14 mol) was added in small portions. The resulting mixture was stirred for 3 h with an ice-water bath cooling and for 3 h without, and then evaporated in vacuo. The residue was dissolved in 5% HCl (250 mL), and the solution was made alkaline with 20% NaOH while cooled, then extracted with $CHCl_3$ (4×150 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated in vacuo to give **4a–c** as oily products (in the crude oily product: **4c**–**4d**=7:1). **4a** and **4c** crystallized on treatment with *n*-hexane–Et_2O. The crystals were filtered off and washed with Et_2O. The crude crystalline **4c** proved to be the diastereomerically pure $1R^*,1'R^*$ isomer. The crude crystalline (**4a**,**c**) or oily (**4b**) products were used in the next step without further purification.

Compound **4a**. Yield: 10.63 g (82%). An analytical sample of **4a** was recrystallized from Et_2O to give white solid, mp 83–86°C. [Found: C, 67.80; H, 6.97; N, 7.59. $C_{21}H_{26}N_2O_4$ requires C, 68.09; H, 7.07; N, 7.56%]; ν_{max} 3318, 1689, 1545, 1284, 1220 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.27–7.40 (5H, om, Ph), 6.55 (2H, s, C_6H_2), 6.13 (1H, br s, N*H*), 5.03–5.10 (2H, m, OCH_2), 4.00 (1H, dd, J=9.0, 3.5 Hz, NC*H*), 3.84 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.30–3.51 (2H, om, NCH_2), 3.10–3.19 (1H, m, NCH_2), 2.92–3.01 (1H, m, NCH_2), 2.57–2.77 (2H, m, $ArCH_2$), 1.85–2.03 (2H, m, $CHCH_2$); MS m/z 371 $[M+1]^+$.

Compound **4b**. Yield: 14.65 g (94%). An analytical sample of **4b** was converted to the crystalline hydrochloride by treatment of its solution in MeOH with an excess of 22% ethanolic HCl and Et_2O to give **4b**·HCl as a white solid, mp 159–163°C. [Found: C, 67.33; H, 6.48; N, 5.69. $C_{27}H_{31}ClN_2O_4$ requires C, 67.14; H, 6.47; N, 5.80%]; ν_{max} 1686, 1521, 1301, 1263, 695 cm^{-1}; δ_H (400 MHz, D_2O) 7.20–7.49 (10H, om, 2×Ph), 6.86 (1H, s, C_6H_2), 6.57 (1H, s, C_6H_2), 5.09 (2H, s, OCH_2), 4.49 (1H, br s, NC*H*), 4.02–4.09 (1H, m, NCH_2), 3.71–3.85 (4H, om, OCH_3, NCH_2), 3.66 (3H, s, OCH_3), 3.29–3.54 (2H, om, NCH_2), 2.92–3.04 (2H, m, $ArCH_2$), 2.20–2.33 (2H, m, $CHCH_2$); MS m/z 447 $[M+1]^+$.

Compound **4c**. Yield: 9.80 g (73%). An analytical sample of **4c** was recrystallized from Et_2O to give white solid, mp 93–95°C. [Found: C, 68.56; H, 7.28; N, 7.34. $C_{22}H_{28}N_2O_4$ requires C, 68.73; H, 7.34; N, 7.29%]; ν_{max} 3327, 1682, 1513, 1250, 815 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.29–7.34 (5H, m, Ph), 6.62 (1H, s, C_6H_2), 6.56 (1H, s, C_6H_2), 6.15 (1H, br s, N*H*), 5.01–5.05 (2H, m, CH_2), 3.97–4.06 (1H, m, C*H*NH), 3.84 (6H, m, 2×OCH_3), 3.16–3.28 (2H, m, CH_2), 2.97–3.05 (1H, m, CH_2), 2.78–2.91 (2H, m, CH_2), 2.47–2.58 (1H, m, CH_2), 2.30–2.41 (1H, m, $CHCH_3$), 1.14 (3H, d, J=6.8 Hz, CH_3); MS m/z 385 $[M+1]^+$.

4.1.5. 1-(2′-Aminoethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline dihydrobromides (5a,b,d). A mixture of the corresponding *N*-Cbz diamine derivative (**4a–c**, 10 mmol) and 33% HBr in AcOH (15 mL) was heated gently in a flask equipped with a $CaCl_2$-tube, with occasional shaking, until all of the substance had dissolved.

The bubbling solution was left to stand at ambient temperature for 30 min, and Et_2O (25 mL) was then added. The yellow crystals of the dihydrobromides (**5a**,**b**,**d**) which formed were filtered off, washed with a mixture of MeOH and Et_2O, dried and recrystallized from MeOH–H_2O–Et_2O.

Compound **5a**. White solid; yield: 2.96 g (74%), mp 273–274°C. [Found: C, 38.97; H, 5.46, N, 6.89. $C_{13}H_{22}Br_2N_2O_2$ requires C, 39.22, H, 5.57; N, 7.04%]; ν_{max} 1519, 1455, 1257, 1113, 1011 cm^{-1}; δ_H (400 MHz, D_2O) 6.98 (1H, s, C_6H_2), 6.91 (1H, s, C_6H_2), 4.74 (1H, t, J=6.6 Hz, 1-C*H*), 3.91 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.60–3.69 (1H, m, NCH_2), 3.48–3.57 (1H, m, NCH_2), 3.04–3.35 (4H, om, ArCH_2, NCH_2), 2.40–2.56 (2H, m, CHCH_2). MS *m*/*z* 237 $[M+1]^+$.

Compound **5b**. Dirty white needles; yield: 3.69 g (78%), mp 243–245°C. [Found: C, 48.32; H, 5.41; N, 5.89. $C_{19}H_{26}Br_2N_2O_2$: requires C, 48.12; H, 5.53; N, 5.91%]; ν_{max} 2932, 1517, 1263, 1225, 1125 cm^{-1}; δ_H (400 MHz, D_2O) 7.53–7.64 (3H, m, Ph), 7.43–7.49 (2H, m, Ph), 6.94 (1H, s, C_6H_2), 6.73 (1H, s, C_6H_2), 4.75 (1H, t, J=6.1 Hz, NC*H*), 3.87 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.46–3.76 (4H, om, 2×NCH_2), 3.01–3.17 (2H, m, ArCH_2), 2.47–2.59 (2H, m, CHCH_2); MS *m*/*z* 313 $[M+1]^+$.

Compound **5d**. White solid; yield: 2.86 g, (69%), mp 267–271°C. [Found: C, 40.51; H, 5.69; N, 6.76. $C_{14}H_{24}Br_2N_2O_2$ requires C, 40.80; H, 5.87; N, 6.80%]; ν_{max} 2866, 1519, 1259, 1114, 1007 cm^{-1}; δ_H (400 MHz, D_2O) 6.97 (1H, s, C_6H_2), 6.91 (1H, s, C_6H_2), 4.75 (1H, d, J=4.0 Hz, NC*H*), 3.89 (6H, s, 2 x OCH_3), 3.59–3.67 (1H, m, NCH_2), 3.31–3.38 (1H, m, NCH_2), 2.78–3.17 (5H, om, NCH_2, ArCH_2, MeC*H*), 1.28 (3H, d, J=6.7 Hz, CH_3); MS *m*/*z* 251 $[M+1]^+$.

4.1.6. l-[2′-(Methylamino)ethyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline dihydrochloride (5c). To a stirred and cooled suspension of $LiAlH_4$ (1.14 g, 30 mmol) in dry THF (40 mL), compound **4a** (3.70 g, 10 mmol) was added in small portions. The mixture was stirred and refluxed for 3 h and then cooled, and the excess of $LiAlH_4$ was decomposed by the addition of a mixture of water (2.3 mL) and THF (20 mL). The inorganic salts were filtered off and washed with EtOAc (3×40 mL). The combined organic filtrate and washings were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude diamine as an oil, which was converted to the crystalline dihydrochloride by treatment of its solution in MeOH with an excess of 22% ethanolic HCl and Et_2O. The crystalline dihydrochloride was filtered off, dried and recrystallized from MeOH–H_2O–Et_2O to give the *title compound* **5c** as a pale white needle.

Yield: 2.68 g (83%), mp 229–233°C. [Found: C, 51.84; H, 7.25; N, 8.73. $C_{14}H_{24}Cl_2N_2O_2$ requires C, 52.02; H, 7.48; N, 8.67%]; ν_{max} 2962, 2718, 1524, 1260, 1123 cm^{-1}; δ_H (400 MHz, D_2O) 6.96 (1H, s, C_6H_2), 6.91 (1H, s, C_6H_2), 4.75 (1H, t, J=6.4 Hz, NC*H*), 3.90 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.62–3.67 (1H, m, NCH_2), 3.49–3.56 (1H, m, NCH_2), 3.27–3.35 (2H, m, NCH_2), 3.09–3.16 (2H, m, ArCH_2), 2.82 (3H, s, CH_3), 2.46–2.58 (2H, m, CHCH_2); MS *m*/*z* 251 $[M+1]^+$.

4.1.7. (1*R,1′*S**)-1-(2′-Amino-1′-methylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline dihydrochloride (5e).** Compound **3c**·HCl (4.19 g, 10 mmol) was suspended in 33% HBr in AcOH (15 mL) and the mixture was heated gently with occasional shaking until all of the substance had dissolved. The mixture was left to stand at ambient temperature for 30 min, and Et_2O (100 mL) was then added. The solvents were decanted from the precipitated oil and the residue was dissolved in water (20 mL). The solution was made alkaline with 20% NaOH under cooling and extracted with $CHCl_3$ (4×30 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give crude **6** (2.32 g, 9.3 mmol) as an oil, which was used in the next step without further purification.

To a solution of compound **6** (2.32 g, 9.3 mmol) in MeOH (50 mL), 10% palladium on charcoal catalyst (0.50 g) was added and the mixture was stirred under hydrogen at atmospheric pressure and at ambient temperature. When the hydrogen uptake had ceased, the catalyst was filtered off and the filtrate was evaporated in vacuo to give an oil, which was a 1:10 mixture of the 1*R**,1′*R** and 1*R**,1′*S** diamine diastereomers. The oily product was converted to the crystalline dihydrochloride with an excess of 22% ethanolic HCl and Et_2O. The crystals were filtered off, dried and recrystallized from MeOH–H_2O–Et_2O. The recrystallized product was the diastereomerically pure 1*R**,1′*S** isomer as white needles.

Yield: 2.22 g (69%), mp 255–260°C. [Found: C, 52.24; H, 7.36; N, 8.59. $C_{14}H_{24}Cl_2N_2O_2$ requires C, 52.02; H, 7.48; N, 8.67%]; ν_{max} 3411, 2983, 1523, 1261, 1123 cm^{-1}; δ_H (400 MHz, D_2O) 6.98 (1H, s, C_6H_2), 6.88 (1H, s, C_6H_2), 4.65 (1H, d, J=4.8 Hz, NC*H*), 3.89 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.61–3.70 (1H, m, NCH_2), 3.39–3.47 (1H, m, NCH_2), 3.98–3.31 (4H, om, NCH_2, ArCH_2,), 2.70–2.81 (1H, m, MeC*H*), 1.12 (3H, d, J=7.2 Hz, CH_3); MS *m*/*z* 251 $[M+1]^+$.

4.2. General procedure for the preparation of 1,3,2-diazaphosphorino[6,1-*a*]isoquinolines (7a–e and 8a–c,e)

To a solution of the diamine dihydrohalide (**5a**–**e**, 10 mmol) and Et_3N (5.06 g, 50 mmol) in anhydrous CH_2Cl_2 (100 mL) at 6–10°C, a solution of phenylphosphonyl dichloride (2.07 g, 10.6 mmol) in anhydrous CH_2Cl_2 (20 mL) was added dropwise over a period of 30 min. The mixture was stirred at 6–10°C for 24 h and was then washed consecutively with 5% HCl solution (2×100 mL) and water (2×100 mL). The organic phase was dried (Na_2SO_4) and evaporated in vacuo to afford a pale-yellow oil containing a mixture of the corresponding oxazaphosphorinane diastereomers (**7** and **8**). The diastereomeric ratios were determined from the ^1H NMR spectra of the crude products. Purification of the crude products by column chromatography gave **7**, as the more mobile, and **8**, as the less mobile diastereomer.

Compounds **7a**–**8a**=56:44. Eluent: EtOAc–MeOH=9:1.

Compound **7a**. White solid; yield: 1.12 g (31%), mp 189–193°C (*i*Pr_2O–EtOAc). [Found: C, 63.49; H, 6.33; N, 7.60.

$C_{19}H_{23}N_2O_3P$ requires C, 63.68; H, 6.47; N, 7.82%]; ν_{max} 3161, 1513, 1211, 1120, 989 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.89 (2H, d, J=7.7 Hz, Ph), 7.49 (1H, t, J=7.3 Hz, Ph), 7.44 (2H, t, J=7.5 Hz, Ph), 6.61 (1H, s, H8), 6.50 (1H, s, H-11), 4.39 (1H, dd, J=7.9, 6.6 Hz, H-11b), 3.86 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.62 (1H, dt, J=12.1, 4.8 Hz, H-6eq), 3.29–3.49 (2H, m, H-2ax, H-2eq), 3.18 (1H, ddd, J=12.1, 8.3, 3.9 Hz, H-6ax), 2.94 (1H, ddd, J=15.6, 8.3, 4.4 Hz, H-7ax), 2.73 (1H, dt, J=15.6, 4.6 Hz, H-7eq), 2.00–2.11 (2H, m, H-1ax, H-1eq); δ_C (100.03 MHz, $CDCl_3$) 148.1, 147.9, 133.8, 131.7, 131.6, 128.9 (2C), 127.8, 112.1, 109.5, 56.6, 56.4, 56.3, 41.9, 39.0, 34.1, 29.9; MS m/z 359 $[M+1]^+$.

Compound **8a**. Pale yellow solid; yield: 0.64 g (18%), mp 193–196.5°C ($i$$Pr_2O$–EtOAc). [Found: C, 63.90, H, 6.53; N, 7.78. $C_{19}H_{23}N_2O_3P$ requires C, 63.68; H, 6.47; N, 7.82%]; ν_{max} 1509, 1255, 1185, 1121, 991 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.90 (2H, d, J=7.5 Hz, Ph), 7.48 (1H, t, J=7.3 Hz, Ph), 7.41 (2H, t, J=7.5 Hz, Ph), 6.67 (1H, s, H-11), 6.53 (1H, s, H-8), 6.49 (1H, dd, J=11.4, 3.3 Hz, H-11b), 3.87 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.54 (1H, t, J=11.2 Hz, H-2ax), 3.29–3.41 (2H, m, H-2eq, H-6eq), 2.98 (1H, dt, J=12.3, 3.1 Hz, H-6ax), 2.57 (1H, ddd, J=15.6, 11.9, 5.1 Hz, H-7ax), 2.42–2.50 (1H, m, H-1eq), 2.38 (1H, d, J=15.6 Hz, H-7eq), 1.91–2.04 (1H, m, H-1ax); δ_C (100.03 MHz, $CDCl_3$) 148.0 (2C), 133.5, 133.1, 131.9, 129.5, 128.6, 127.4, 112.2, 109.1, 56.5, 56.3, 55.3, 41.1, 40.2, 35.4, 29.1; MS m/z 359 $[M+1]^+$.

Compounds **7b**–**8b**=29:71. Eluent: EtOAc–MeOH=9:1.

Compound **7b**. Pale yellow solid; yield: 0.62 g (14%), mp 155–162°C ($i$$Pr_2O$–EtOAc). [Found: C, 68.92; H, 6.04; N, 6.37. $C_{25}H_{27}N_2O_3P$ requires C 69.11, H 6.26, N 6.45%]; ν_{max} 1519, 1235, 1133, 696, 509 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.64 (2H, d, J=7.7 Hz, Ph), 7.37–7.44 (3H, m, Ph), 7.34 (2H, t, J=7.5 Hz, Ph), 7.25 (2H, t, J=7.7 Hz, Ph), 7.03 (1H, t, J=7.3 Hz, Ph), 6.63 (1H, s, H-11), 6.57 (1H, s, H-8), 4.56 (1H, dd, J=9.2, 6.2 Hz, H-11b), 3.79–3.92 (7H, m, H2ax, OCH_3), 3.73 (1H, dt, J=12.3, 4.0 Hz, H-2eq), 3.63 (1H, dt, J=12.5, 5.0 Hz, H-6eq), 3.26 (1H, ddd, J=12.3, 7.9, 4.0 Hz, H-6ax), 3.00 (1H, ddd, J=15.0, 7.9, 4.2 Hz, H-7ax), 2.76 (1H, dt, J=15.6, 4.8 Hz, H-7eq), 2.28–2.40 (2H, m, H-1ax, H-1eq); δ_C (100.03 MHz, $CDCl_3$) 148.3, 148.0, 145.4, 132.9, 131.9, 131.7, 129.3, 128.9, 128.7, 127.8, 124.1, 123.3, 112.2, 109.2, 56.5 (2C), 56.3, 49.9, 39.4, 34.1, 29.9; MS m/z 435 $[M+1]^+$.

Compound **8b**. White solid; yield: 1.14 g (26%), mp 194–196°C ($i$$Pr_2O$–EtOAc). [Found C, 69.01; H, 5.96; N, 6.42. $C_{25}H_{27}N_2O_3P$ requires C 69.11, H 6.26, N 6.45%]; ν_{max} 2920, 1514, 1375, 1207, 1122 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, J=7.7 Hz, Ph), 7.39 (1H, t, J=7.3 Hz, Ph), 7.31 (2H, t, J=7.7 Hz, Ph), 7.09–7.18 (4H, m, Ph), 6.96–7.04 (1H, m, Ph), 6.71 (1H, s, H-11), 6.54 (1H, s, H-8), 4.84 (1H, dd, J=4.6, 10.5 Hz, H-11b), 4.00 (1H, dt, J=3.3, 12.1 Hz, H-2ax), 3.89 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.63 (1H, dt, J=4.4, 12.1 Hz, H-2eq), 3.53 (1H, ddd, J=2.0, 5.3, 12.5 Hz, H-6eq), 3.06 (1H, dt, J=3.3, 12.5 Hz, H-6ax), 2.64–2.72 (1H, m, H-1eq), 2.57 (1H, ddd, J=5.3, 12.1, 15.6 Hz, H-7ax), 2.40 (1H, d, J=15.6 Hz, H-7eq), 2.17–2.29 (1H, m, H-1ax); δ_C (100.03 MHz, $CDCl_3$) 148.1, 148.0, 144.7, 133.3, 132.8, 131.7, 129.5, 129.3, 128.4, 127.4, 125.7, 125.0, 112.2, 108.9, 56.5, 56.3, 55.0, 49.6, 41.7, 35.3, 29.0; MS m/z 435 $[M+1]^+$.

Compounds **7c**–**8c**=27:73. Eluent: EtOAc–MeOH=9:1.

Compound **7c**. Beige solid; yield: 0.45 g (12%), mp 130–131.5°C (EtOAc). [Found: C, 64.28; H, 6.51; N, 7.45. $C_{20}H_{25}N_2O_3P$ requires C, 64.51; H, 6.77; N, 7.52%]; ν_{max} 1517, 1231, 1123, 992, 719 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.72 (2H, d, J=7.34 Hz, Ph), 7.40–7.51 (3H, m, Ph), 6.58 (1H, s, H-8), 6.55 (1H, s, H-11), 4.46 (1H, dd, J=4.0, 10.1 Hz, H-11b), 3.84 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.62 (1H, dt, J=3.9, 11.6 Hz, H-6eq), 3.46 (1H, dt, J=5.3, 11.6 Hz, H-2ax), 3.25 (1H, dt, J=4.2, 11.6 Hz, H-2eq), 2.82–3.0 (2H, m, H-6ax, H-7ax), 2.69 (3H, s, NCH_3), 2.63 (1H, dt, J=3.7, 15.2 Hz, H-7eq), 2.14–2.3 (2H, m, H-1ax, H-1eq); δ_C (100.03 MHz, $CDCl_3$) 148.1, 147.9, 133.4, 131.6 (2C), 128.9, 128.7, 127.8, 112.1, 109.2, 56.4, 56.2 (2C), 50.8, 39.4, 35.9, 34.1, 29.9; MS m/z 373 $[M+1]^+$.

Compound **8c**. Beige needles; yield: 1.05 g (28%), mp 176–177°C ($i$$Pr_2O$–EtOAc). [Found: C, 64.47; H, 6.48; N, 7.59. $C_{20}H_{25}N_2O_3P$ requires C, 64.51; H, 6.77; N, 7.52%]; ν_{max} 2829, 1513, 1254, 1129, 1063 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.89 (2H, d, J=7.5 Hz, Ph), 7.49 (1H, t, J=7.2 Hz, Ph), 7.43 (2H, t, J=7.5 Hz, Ph), 6.68 (1H, s, H-11), 6.53 (1H, s, H-8), 4.69 (1H, d, J=11.3 Hz, H-11b), 3.88 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.54 (1H, dt, J=3.5, 11.2 Hz, H-2ax), 3.34 (1H, dd, J=2.0, 5.1, 12.5 Hz, H-6eq), 3.08 (1H, dt, J=4.4, 11.2 Hz, H-2eq), 2.97 (1H, dt, J=3.1, 12.5 Hz, H-6ax), 2.50–2.61 (4H, m, NCH_3, H-7ax), 2.42–2.49 (1H, m, H-1eq), 2.35 (1H, d, J=15.6 Hz, H-7eq), 1.97–2.11 (1H, m, H-1ax); δ_C (100.03 MHz, $CDCl_3$) 148.0 (2C), 133.5, 132.3, 131.7, 129.3, 128.5, 127.3, 112.1, 109.1, 56.5, 56.2, 54.6, 49.1, 41.4, 35.7, 35.3, 29.1; MS m/z 373 $[M+1]^+$.

Compounds **7d**–**8d**=~100:~ 0. Eluent: EtOAc–MeOH=9:1.

Compound **7d**. White solid; yield: 1.64 g (44%), mp 188–192°C ($i$$Pr_2O$–EtOAc). [Found: C, 64.42; H, 6.73; N, 7.38. $C_{20}H_{25}N_2O_3P$ requires C, 64.51; H, 6.77; N, 7.52%]; ν_{max} 1513, 1193, 1123, 995, 699 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.90 (2H, d, J=8.0 Hz, Ph), 7.50 (1H, t, J=7.2 Hz, Ph), 7.44 (2H, t, J=7.5 Hz, Ph), 6.65 (1H, s, H-11), 6.51 (1H, s, H-8), 3.92 (1H, d, J=9.2 Hz, H-11b), 3.86 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.76 (1H, ddd, J=4.6, 5.9, 12.3 Hz, H-6eq), 3.47 (1H, dd, J=4.6, 12.5 Hz, H-2eq), 3.26 (1H, ddd, J=4.4, 7.9, 12.3 Hz, H-6ax), 2.86–2.99 (2H, m, H-2ax, H-7ax), 2.78 (1H, dt, J=5.1, 15.4 Hz, H-7eq), 2.10–2.18 (1H, m, H-1ax), 0.96 (3H, d, J=6.8 Hz, Me-1); δ_C (100.03 MHz, $CDCl_3$) 148.6, 147.1, 133.3, 132.2, 132.1, 129.3 (2C), 127.8, 112.4, 112.2, 61.6, 56.7, 56.5, 48.8, 39.6, 37.6, 30.4, 18.3; MS m/z 373 $[M+1]^+$.

Compounds **7e**–**8e**=57:43. Eluent: EtOAc–MeOH=9:1.

Compound **7e**. White needles; yield: 0.52 g (14%), mp 180–184°C ($i$$Pr_2O$–EtOAc). [Found: C, 64.71; H, 6.56; N, 7.42. $C_{20}H_{25}N_2O_3P$ requires C, 64.51; H, 6.77; N, 7.52%]; ν_{max} 3146, 1513, 1211, 1133, 988 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.8 (2H, d, J=7.7 Hz, Ph), 7.40–7.51 (3H, m, Ph), 6.59 (1H,

s, H-11), 6.50 (1H, s, H-8), 4.61 (1H, d, J=2.9 Hz, H-11b), 3.97 (1H, ddd, J=2.8, 4.4, 11.2 Hz, H-6eq), 3.86 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.56 (1H, dt, J=4.6, 13.4 Hz, H-2ax), 3.23 (1H, ddd, J=2.6, 5.8, 13.0 Hz, H-2eq), 2.95 (1H, ddd, J=4.4, 11.2, 15.4 Hz, H-7ax), 2.81 (1H, dt, J=2.4, 11.2 Hz, H-6ax), 2.58 (1H, dt, J=2.9, 15.4 Hz, H-7eq), 2.11–2.21 (1H, m, H-1ax), 0.90 (3H, d, J=6.8 Hz, Me-1); δ_C (100.03 MHz, $CDCl_3$) 148.2, 147.8, 134.1, 131.6, 131.3, 129.2, 128.9, 127.7, 111.9, 109.0, 60.0, 56.4, 56.3, 48.2, 40.3, 37.3, 30.2, 11.4; MS m/z 373 $[M+1]^+$.

Compound **8e**. White needles; yield: 0.41 g (11%), mp 178–182°C (iPr$_2$O–EtOAc). [Found: C, 64.40; H, 6.53; N, 7.47. $C_{20}H_{25}N_2O_3P$ requires C, 64.51; H, 6.77; N, 7.52%]; ν_{max} 1509, 1262, 1174, 1129, 1027 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.00 (2H, d, J=7.3 Hz, Ph), 7.54 (1H, t, J=7.3 Hz, Ph), 7.46 (2H, t, J=7.3 Hz, Ph), 6.63 (1H, s, H-11), 6.54 (1H, s, H-8), 4.97 (1H, d, J=3.1 Hz, H-11b), 3.80–3.90 (7H, m, H2ax, OCH_3, OCH_3), 3.04–3.21 (2H, m, H-2eq, H-6ax), 2.91 (1H, dt, J=2.8, 12.1 Hz, H-6ax), 2.69 (1H, ddd, J=5.3, 11.7, 15.9 Hz, H-7ax), 2.35–2.46 (2H, m, H-1eq, H-7eq), 0.92 (3H, d, J=6.8 Hz, Me-1); δ_C (100.03 MHz, $CDCl_3$) 148.3, 147.8, 133.3, 132.4, 131.7, 128.8, 128.5, 128.0, 111.9, 109.0, 58.0, 56.5, 56.2, 46.7, 41.2, 35.8, 29.4, 12.1; MS m/z 373 $[M+1]^+$.

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References

1. Martinek, T.; Forró, E.; Günther, G.; Sillanpää, R.; Fülöp, F. *J. Org. Chem.* **2000**, *65*, 316–321, and references cited therein.
2. Ludeman, S. M. From Nerve Agent to Anticancer Drug: The Chemistry of Phosphoramide Mustard. In *Biomedical Chemistry*; Torrence, P. F., Ed.; Wiley-Interscience: New York, 2000; pp 163–187.
3. Mosbo, J. A. *Tetrahedron Lett.* **1976**, *17*, 4789–4792.
4. Nifantev, E. E.; Zavalishina, A. I.; Sorokina, S. F.; Borisenko, A. A.; Smirnova, E. I.; Gustova, I. V. *Zh. Obshch. Khim.* **1977**, *47*, 1960–1970.
5. Nifantev, E. E.; Zavalishina, A. I.; Sorokina, S. F.; Borisenko, A. A.; Smirnova, E. I.; Kurochkin, V. V.; Moiseeva, L. I. *Zh. Obshch. Khim.* **1979**, *49*, 64–74.
6. Smirnova, E. I.; Zavalishina, A. I.; Borisenko, A. A.; Rybina, M. N.; Nifantev, E. E. *Zh. Obshch. Khim.* **1981**, *51*, 1956–1962.
7. (a) Denmark, S. E.; Winter, S. B. D.; Su, X.; Wong, K.-T. *J. Am. Chem. Soc.* **1996**, *118*, 7404–7405. (b) Denmark, S. E.; Fujimori, S. *Org. Lett.* **2002**, *4*, 3473–3476. (c) Denmark, S. E.; Fujimori, S. *Org. Lett.* **2002**, *4*, 3477–3480.
8. Denmark, S. E.; Coe, D. M.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6161–6163.
9. Denmark, S. E.; Kim, J.-H. *Can. J. Chem.* **2000**, *78*, 673–688.
10. Burns, B.; King, N. P.; Tye, H.; Studley, J. R.; Gamble, M.; Wills, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1027–1038.
11. (a) Denmark, S. E.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 864–866. (b) Denmark, S. E.; Miller, P. C.; Wilson, S. R. *J. Am. Chem. Soc.* **1991**, *113*, 1468–1470.
12. Denmark, S. E.; Miller, P. C.; Wilson, S. R. *J. Am. Chem. Soc.* **1991**, *113*, 1468–1470.
13. Hetényi, A.; Martinek, T. A.; Lázár, L.; Zalán, Z.; Fülöp, F. *J. Org. Chem.* **2003**, *68*, 5705–5712.
14. Kano, S.; Ebata, T.; Shibuya, S. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2105–2111.
15. Solymár, M.; Liljeblad, A.; Lázár, L.; Fülöp, F.; Kanerva, L. T. *Tetrahedron: Asymmetry* **2002**, *13*, 1923–1928.
16. Denmark, S. E.; Su, X.; Nishigaichi, Y.; Coe, D. M.; Wong, K.-T.; Winter, S. B. D.; Choi, J. Y. *J. Org. Chem.* **1999**, *64*, 1958–1967.
17. Bull, J. E. O.; Naidu, M. S. R. *Phosphorus, Sulfur, Silicon* **2000**, *162*, 231–243.
18. Fülöp, F.; Forró, E.; Martinek, T.; Günther, G.; Sillanpaa, R. *J. Mol. Struct.* **2000**, *554*, 119–125.
19. (a) Bentrude, W. G.; Day, R. O.; Holmes, J. N.; Quin, G. S.; Setzer, W. N.; Sopchik, A. E.; Holmes, R. R. *J. Am. Chem. Soc.* **1984**, *106*, 106–111. (b) Holmes, R. R.; Day, R. O.; Setzer, W. N.; Sopchik, A. E.; Bentrude, W. G. *J. Am. Chem. Soc.* **1984**, *106*, 2353–2358.
20. (a) Sohár, P.; Forró, E.; Lázár, L.; Bernáth, G.; Sillanpää, R.; Fülöp, F. *J. Chem. Soc., Perkin Trans. 2* **2000**, 287–293. (b) Fülöp, F.; Martinek, T.; Bernáth, G. *Arkivoc* **2001**, *3*, 33–39. (c) Heydenreich, M.; Koch, A.; Lázár, L.; Szatmári, I.; Sillanpää, R.; Kleinpeter, E.; Fülöp, F. *Tetrahedron* **2003**, *59*, 1951–1959.
21. Jackson, W. R.; Perlmutter, P.; Smallridge, A. J. *Aust. J. Chem.* **1988**, *41*, 1201–1208.
22. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, 1991; pp 335–338.