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Synthesis and conformational analysis of tetrahydroisoquinoline- and piperidine-fused 1,3,4,2-oxadiazaphosphinanes, new ring systems

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Dedicated to Professor Géza Stájer on his 70th birthday

Abstract—Through cyclization of tetrahydroisoquinoline and piperidine 1,2-hydrazino alcohols with phenylphosphonic dichloride and phenyl dichlorophosphate, *P*-epimeric diastereomers of 1,6,7,11b-tetrahydro-4*H*-1,3,4,2-oxadiazaphosphino[5,4-*a*]isoquinoline-3-oxides (**13** and **14**), 1,6,11,11a-tetrahydro-4*H*-1,3,4,2-oxadiazaphosphino[4,5-*b*]isoquinoline-3-oxides (**15** and **16**) and 1,6,7,8,9,9a-hexahydro-4*H*-pyrido[1,2-*d*][1,3,4,2]oxadiazaphosphinane-3-oxides (**17** and **18**), the first representatives of these ring systems, were prepared. NMR and X-ray diffraction studies revealed that, independently of the *P*-substituent and the relative configuration of the phosphorus atom, **13**, **14**, **17** and **18** could be characterized by trans-connected hetero rings and the chair conformation of the 1,3,4,2-oxadiazaphosphinane moiety, while the stereochemistry of the connection of the hetero rings in the 1,3,4,2-oxadiazaphosphinanes linearly fused to tetrahydroisoquinoline (**15** and **16**) was found to be dependent on the *P*-configuration relative to that of the carbon at the annelation.

1. Introduction

In consequence of their valuable pharmacological effects and wide-ranging potential for synthetic applications, considerable interest has been focused towards 1,3,2-O,N,P heterocycles.[1] The 1,3,2-oxazaphosphinane ring system is found in alkylating anticancer drugs (cyclophosphamide and ifosfamide), numerous derivatives of which have been prepared to determine their structure–activity relationships.[2] Compounds containing a 1,3,2-oxazaphosphinane moiety were recently reported to possess matrix metalloproteinase-inhibitory,[3] pesticidal[4] and antimicrobial[5] activities. Phosphorus-stabilized carbanions derived from chiral 1,3,2-oxazaphosphinane 2-oxides have been widely used in the diastereoselective formation of carbon–carbon bonds.[6]

In contrast with the thoroughly investigated 1,3,2-oxazaphosphinane-2-oxide derivatives, less attention has been paid to the preparation and transformations of the corresponding 1,3,4,2-oxadiazaphosphinane-2-oxides containing an additional nitrogen atom in the heterocyclic ring.[7–10] The first representatives of this ring system were prepared with the aim of identifying potential antitumour agents. However, despite the close structural analogy, cyclophosphamide-analogue 1,3,4,2-oxadiazaphosphinane-2-oxides, and the homologous 1,3,4,2-oxadiazaphosphepin-2-oxides, proved to exhibit negligible antileukaemic activity.[9,10] Furthermore, there has been only one stereochemical investigation of this ring system: 4-methyl-2-phenoxy-1,3,4,2-oxadiazaphosphinane-2-oxide proved to exist predominantly in the chair conformation, with the P═O group occupying an axial position.[8]

As a continuation of our previous stereochemical studies on 1,2,3,4-tetrahydroisoquinoline-condensed 1,3- and 1,2,3-heterocycles,[11] our present aim was to prepare 1,3,4,2-oxadiazaphosphinane-2-oxides attached angularly or linearly to the tetrahydroisoquinoline ring in order to investigate the effects of the substituents and the configurations of the substituted atoms on the predominant conformations of the nitrogen-bridged tricyclic system. To determine the effects of the attached aromatic ring on the stereochemistry of the ring junction, a further aim was to synthesise the parent piperidine-condensed derivatives. To the best of our knowledge, nitrogen-bridged 1,3,4,2-oxadiazaphosphinane-

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2-oxides with a condensed skeleton have not been reported previously in the literature.

2. Results and discussion

2.1. Syntheses

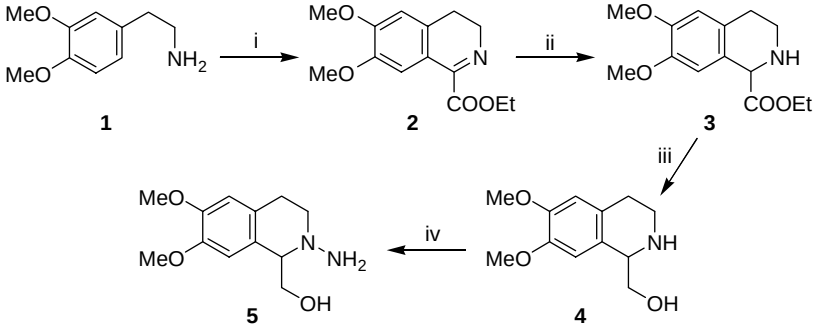
Most of the methods applied earlier to the synthesis of 1,3,4,2-oxadiazaphosphinanes were based on the ring closures of the corresponding hydrazino alcohols with the appropriate phosphorus-containing fragments.[7–9] This methodology was also applied for the preparation of our target compounds.

Regioisomeric tetrahydroisoquinoline hydrazino alcohols **5** and **8a**,**b**, starting materials for the phosphorus-containing model compounds, were prepared from the corresponding amino alcohol derivatives **4** and **7a**,**b** by using a two-step procedure (*N*-nitrosation and a subsequent $LiAlH_4$ reduction) usually applied for the preparation of *N*-substituted hydrazines or hydrazino alcohols from secondary amines or amino alcohols, respectively (Schemes 1 and 2).[12]

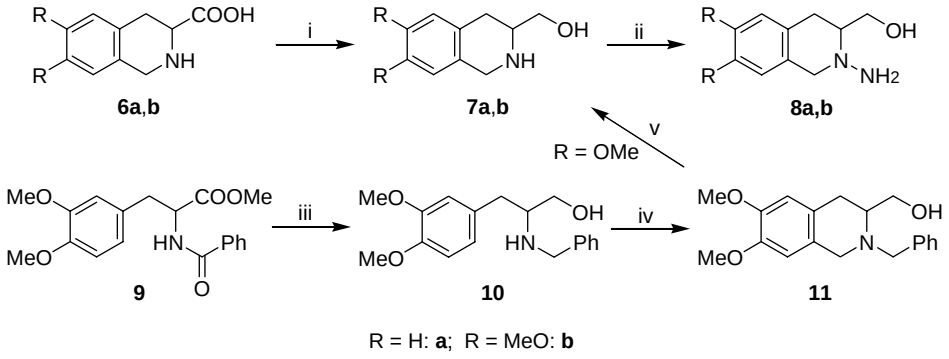
Due to its natural occurrence, many procedures have been developed for the preparation of the tetrahydroisoquinoline amino alcohol derivative calycotomine (**4**),[13] which was obtained by $LiAlH_4$ reduction of the corresponding amino ester **3**. Compound **3** was prepared using a three-step process starting from homoveratrylamine (**1**) (Scheme 1).[14]

The amino alcohols **7a**,**b** necessary for the linearly fused model compounds were prepared by $LiAlH_4$ reduction of the corresponding 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids (TIC: **6a** and 6,7-diMeO-TIC: **6b**) (Scheme 2).[15,16] The lengthy hydrolysis step of **9** towards 2-amino-3-(3,4-dimethoxyphenyl)propanoic acid,[15] an intermediate of **6b**, proved to be a tedious reaction on a 0.1 mol scale. Accordingly, an alternative procedure,[17] based on a change in the sequence of the transformation of the functional groups of **9**, was applied for the synthesis of larger quantities of **7b**. $LiAlH_4$ reduction of **9** resulted in *N*-benzyl amino alcohol **10**, which was converted to the corresponding tetrahydroisoquinoline derivative **11** by Pictet-Spengler cyclization with formaldehyde. Removal of the benzyl group of **11** by catalytic hydrogenation in the presence of Pd/C led to 6,7-dimethoxy-1,2,3,4-tetrahydro-3-isoquinolinylmethanol (**7b**) (Scheme 2).

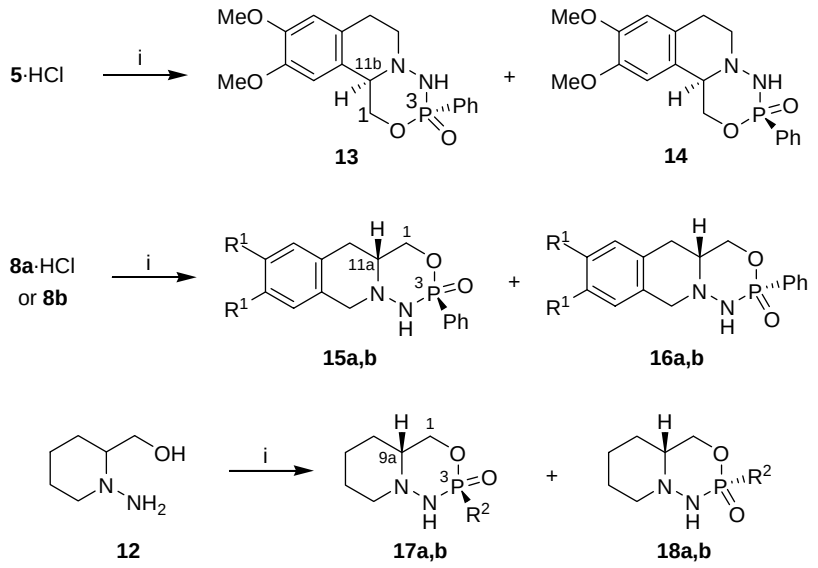
Hydrazino alcohols **5**, **8a**,**b** and **12**[18] were cyclized with phenylphosphonic dichloride, and phenyl dichlorophosphate at room temperature in THF in the presence of Et_3N, resulting in 1,6,7,11b-tetrahydro-4*H*-1,3,4,2-oxadiazaphosphino-[5,4-*a*]isoquinoline-3-oxides (**13** and **14**), 1,6,11,11a-tetrahydro-4*H*-1,3,4,2-oxadiazaphosphino[4,5-*b*]isoquinoline-3-oxides (**15** and **16**) and 1,6,7,8,9,9a-hexahydro-4*H*-pyrido[1, 2-*d*][1,3,4,2]oxadiazaphosphinane-3-oxides (**17** and **18**), which are the first representatives of these ring systems (Scheme 3). In most cases, two *P*-2 epimeric diastereomers, differing in the cis or trans position of the *P*-substituent and the hydrogen at the annelation (H-an), were formed and separated by column chromatography. A significant



Scheme 1. Reagents and conditions: (i) 1. $(COOOEt)_2$, 140 °C, 6 h, 2. $POCl_3$, PhMe, EtOH, Δ, 3.5 h, 49% (1+2); (ii) H_2, 5% Pt/C, EtOH, rt, 1 atm, 6 h, 82%; (iii) $LiAlH_4$, THF, Δ, 3 h, 66%; (iv) 1. $NaNO_2$, AcOH, H_2O, rt, 8 h, 2. $LiAlH_4$, THF, rt, 2 h, 52%.



Scheme 2. Reagents and conditions: (i) $LiAlH_4$, THF, Δ, 8 h, 51% (for R=MeO); (ii) 1. $NaNO_2$, AcOH, H_2O, rt, 8 h, 2. $LiAlH_4$, THF, rt, 2 h, 45% (**8a**), 67% (**8b**); (iii) $LiAlH_4$, THF, Δ, 5 h, 78%; (iv) CH_2O, HCl, H_2O, Δ, 6 h, 92%; (v) H_2, 10% Pd/C, MeOH, 30 bar, 40 °C, 30 h, ~100%.



Compound	R^1	R^2	Diastereomeric ratio in the crude product
13:**14**	–	–	48:52
15a:**16a**	H	–	50:50
15b:**16b**	OMe	–	~0:~100
17a:**18a**	–	Ph	21:79
17b:**18b**	–	OPh	50:50

Scheme 3. Reagents and conditions: (i) Cl_2POPh or $Cl_2PO(OPh)$, Et_3N, THF, rt, 48 h, 34–51%.

difference in the ratios of the *P*-2 epimers, was found for **17a** and **18a**, the trans isomer (**18a**) being the main product, while in the ring closure of **8b**, the minor oxadiazaphosphinane diastereomer (**15b**) could not be detected, even in the crude product (by ^{1}H NMR spectroscopy).

2.2. Structure

In keeping with the nitrogen-bridged saturated bi- or polycyclic heterocycles, the stereo-structures of the prepared 1,3,4,2-oxadiazaphosphinanes (**13**–**18**) can be described by a conformational equilibrium of cis[1]–trans–cis[2] type.[19] In the trans structure, the B/C hetero rings are trans-connected, with a trans-diaxial arrangement of H-an and the nitrogen lone pair. In the two other configurations, the hetero rings are cis-connected: for the cis-1 conformation, C-1 is in the inside, while for the cis-2 conformation, C-1 is in the outside position (Fig. 1). The phosphorus-containing 1,2,3-heterocycles are prone to participate in a conformational equilibrium involving chair, twisted chair and other distorted conformations.[1,20]

The stereochemistry of the model compounds was determined in two steps. First, the predominant conformation was assigned on the basis of the characteristic ^3J couplings and NOE interactions. Second, the relative configuration of the *P*-phenyl substituent was observed by using the NOEs from the *P*-phenyl group to the annelation protons (where applicable) and/or the significant differences in the chemical shifts for certain indicator nuclei.

The orientation of H-an (i.e., H-11b for **13** and **14**; H-11a for **15** and **16**; and H-9a for **17** and **18**) and the protons connected to the carbons adjacent to the annelation (H-1 and H-X; H-X: H-11 for **15** and **16**, and H-9 for **17** and **18**) or the protons connected to the carbons adjacent to the

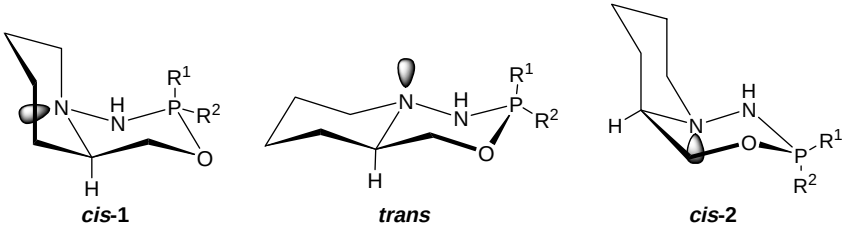


Figure 1. Possible ring connections of 1,6,7,8,9,9a-hexahydro-4*H*-pyrido[1,2-*d*]-[1,3,4,2]oxadiazaphosphinanes.

Table 1. Characteristic vicinal coupling constants in Hz[a]

Compound	H-1_{ax}-H-an	H-1_{eq}-H-an	H-X_{ax}-H-an	H-X_{eq}-H-an	H-1_{ax}-P	H-1_{eq}-P
13	9.3	4.3	—	—	5.3	17.1
14	10.6	2.8	—	—	1.3	18.6
15a	4.0	2.5	11.8	5.5	3.8	20.0
16a	9.8	4.0	10.6	4.8	7.3	18.4
16b	8.2	3.8	10.3	4.8	8.1	18.1
17a	9.8	3.3	10.1	2.8	3.5	18.9
18a	10.3	3.0	10.0	3.1	2.0	20.4
17b	10.6	3.5	10.1	3.0	1.6	19.9
18b	9.0	3.5	Overlap	Overlap	2.3	26.4

[a] For the meanings of H-an and H-X, see the text.

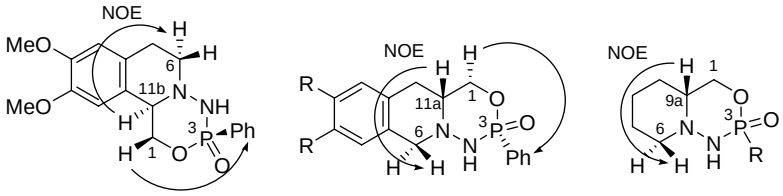


Figure 2. Detected NOEs.

nitrogen-bridge (H-6) were assigned by using the vicinal coupling constants (Table 1) and the detected NOESY cross-peaks (Fig. 2).

The data in Table 1 show that H-an for **16a**,**b**, **17a**,**b** and **18a** has two high vicinal couplings to the axial protons connected to the carbons adjacent to the annelation (H-X, i.e., H-11 for **15a**,**b** and **16a**,**b**; and H-9 for **17a**,**b** and **18a**,**b**), indicating that H-an is in an axial position and the hetero rings are trans-connected. The vicinal couplings of H-11b for **13** and **14** correspond to a trans diaxial position for H-11b and H-1_{ax}, which excludes the hetero ring connection of cis-2 type. The NOESY cross-peaks detected for H-11b and H-6_{ax} indicate the trans connection of the hetero rings for both compounds.

For **15a**, the ^3J (H-1_{ax}-H-11a) and ^3J (H-1_{eq}-H-11a) values were 4.0 and 2.5 Hz, respectively, which suggest that H-an is equatorial to the oxadiazaphosphinane ring. This is supported by a strong NOE from H-11a to both H-1 protons. The vicinal couplings between H-11a and H-11 show an axial orientation of H-11a with respect to the isoquinoline ring. These findings are in accord with two possible conformations: a cis-2-connected chair–chair and a trans-connected chair-boat. In order to establish the most stable conformer, ab initio calculations were performed at the HF/6-31* level. The calculations revealed that conformation cis-2 is 5.3 kcal/mol more stable, and we therefore believe that the hetero rings are predominantly cis-connected (cis-2 conformation; Fig. 3).

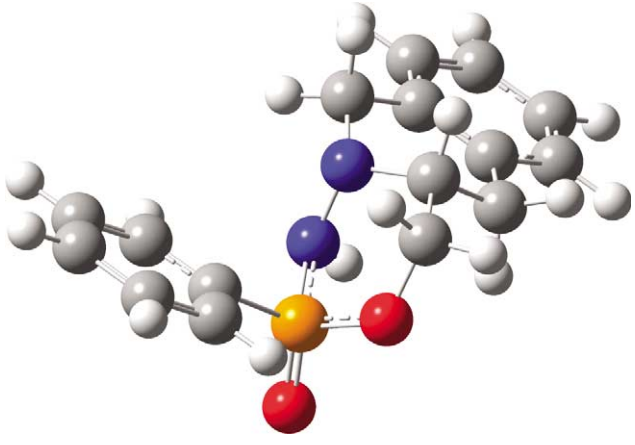


Figure 3. Ab initio geometry obtained for **15a**.

Concerning the orientation of the *P*-substituent, P-Ph-H-1_{ax} NOE interactions could readily be detected in **14** and **16a**,**b** (Fig. 2), which indicates the axial arrangement of the *P*-phenyl group and its position trans to H-an (H-11b or H-11a, respectively).

P-Ph-H-1_{ax} or P-OPh-H-1_{ax} NOE interactions could not be determined unambiguously for compounds **17a** and **18a**, and the *P*-configuration was therefore deduced from the chemical shifts calculated by using the GIAO method at the HF/6-31G* level and the geometrical constraints obtained by means of NMR. It is a trend that H-1_{ax} exhibits an upfield shift in compounds containing an axial *P*-phenyl group (i.e., trans to H-an), due to the ring current shielding. The comparison of the experimental and theoretical chemical shifts (Table 2) unambiguously corroborated the assignment. Unfortunately, the phenoxy derivatives

Table 2. Experimental and calculated characteristic chemical shifts in ppm ($\delta_{TMS}=0$)

Compound	H-1_{ax}		H-1_{eq}	
	Exp.	Calcd	Exp.	Calcd
13	4.72	4.09	4.58	3.91
14	4.05	3.29	4.72	3.87
15a	4.44	3.27	4.32	3.48
16a	3.99	3.04	4.51	3.53
16b	3.97	3.01	4.46	3.49
17a	4.42	3.97	4.13	3.45
18a	3.78	3.02	4.16	3.39
17b	4.23	3.69	4.17	3.18
18b	4.26	3.73	4.31	3.50

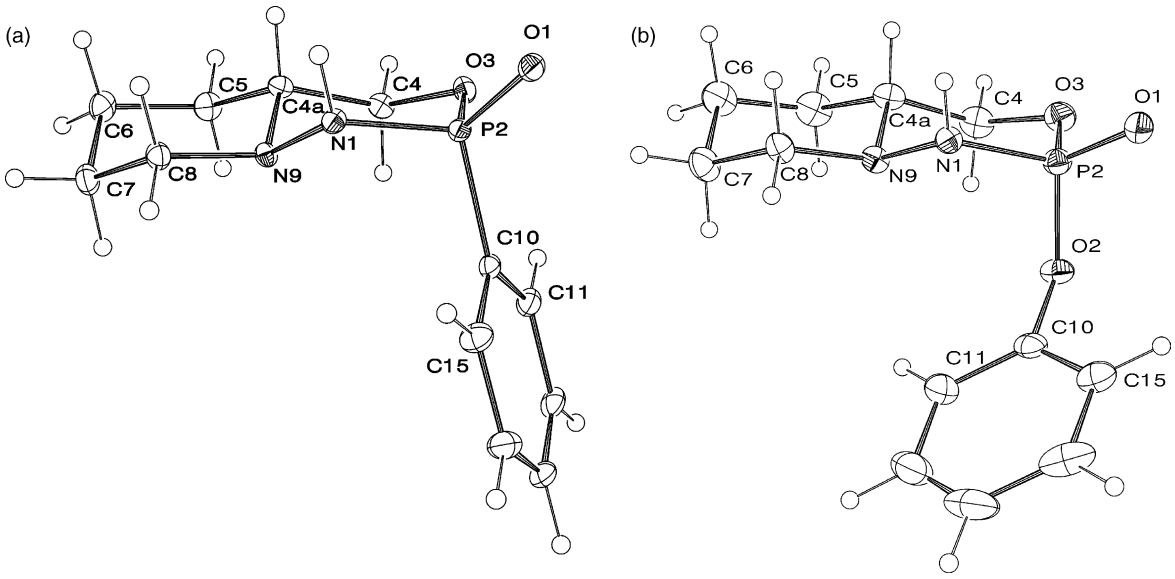


Figure 4. X-ray crystal structures of **18a** and **18b**. The thermal displacement ellipsoids are drawn at a probability level of 30%.

(**17b** and **18b**) did not allow utilization of the shielding effect because of the flexible aromatic substituent; the stereochemical assignment is therefore based purely on the X-ray data. The steric assignment of the *P*-2 epimers of **17** and **18**, based on the results of NMR experiments and theoretical calculations, was in accordance with the X-ray crystal structures of **18a** and **18b** (Fig. 4).

The stereochemical assignments for **13–18** are presented in Table 3.

Table 3. Stereochemical assignments for **13–18**

Compound	Steric position of H-an and the *P*-substituent	Stereochemistry of the junction of the hetero rings	Oxadiazaphosphinane ring conformation
13	cis	trans	chair
14	trans	trans	chair
15a	cis	cis	chair
16a	trans	trans	chair
16b	trans	trans	chair
17a	cis	trans	chair
18a	trans	trans	chair
17b	cis	trans	chair
18b	trans	trans	chair

The chair conformation found for 1,3,4,2-diazaphosphinanes angularly fused to tetrahydroisoquinoline (**13**, **14**) is substantially different from the steric structures of the analogous 1,3,2-oxazaphosphino[4,3-*a*]isoquinolines, which could be characterized by distorted conformations of the 1,3,2-oxazaphosphinane ring.[20]

3. Conclusions

The first representatives of the new ring systems, which are *P*-epimeric diastereomers of 1,6,7,11b-tetrahydro-4*H*-1,3,4,2-oxadiazaphosphino[5,4-*a*]isoquinoline-3-oxides (**13** and **14**), 1,6,11,11a-tetrahydro-4*H*-1,3,4,2-oxadiazaphosphino[4,5-*b*]isoquinoline-3-oxides (**15** and **16**) and 1,6,7,8,9,9a-hexahydro-4*H*-pyrido[1,2-*d*][1,3,4,2]oxadiazaphosphinane-3-oxides (**17** and **18**), have been prepared via cyclization of the corresponding tetrahydroisoquinoline or piperidine hydrazino alcohols. The NMR spectroscopic and X-ray diffraction data allowed the preferred conformation of **13–18** to be identified. This revealed that, independent of the *P*-substituent and the relative configuration of the phosphorus atom, **13**, **14**, **17** and **18** could be characterized by trans-connected hetero rings and the chair conformation of the 1,3,4,2-oxadiazaphosphinane moiety, while the stereochemistry of the connection of the hetero rings (trans or cis-2) was found to be dependent on the *P*-configuration relative to that of the carbon at the annelation site for 1,3,4,2-oxadiazaphosphinanes linearly fused to tetrahydroisoquinoline (**15** and **16**).

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; multiplicities were recorded as s (singlet), br s (broad singlet), d (doublet), dd (double doublet), ddd (double double doublet), td (triple doublet), dtd (double triple doublet), dddd (double double double doublet), t (triplet), dt (double triplet), tt (triple triplet), q (quartet), dq (double quartet), tq (triple quartet) and m (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. 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.

X-ray crystallographic study. Crystallographic data were collected at 173 K with a Nonius Kappa CCD area-detector diffractometer, with the use of graphite-monochromatized

Mo-K_α radiation (λ=0.71073 Å). The data collection was performed with ϕ and ω scans. The data were processed with DENZO-SMN ν 0.93.0.[21]

The structures were solved by direct methods with use of the SIR92 program,[22] and full-matrix, least-squares refinements on F^2 were performed with the SHELXL-97 program.[23] In both cases, all heavy atoms were refined anisotropically. The CH hydrogen atoms were included at fixed distances from their host atoms, with fixed displacement parameters. The NH hydrogen atoms were refined with isotropic displacement parameters. Figures were drawn with ORTEP-3 for Windows.[24] CCDC-284666 (**18a**) and CCDC-284667 (**18b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (Internet) +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk].

Compounds **6b**,[16] **7a**,[15] **9**[16] and **12**[18] were prepared according to known procedures.

4.1.1. Ethyl 6,7-dimethoxy-3,4-dihydroisoquinoline-1-carboxylate (2). A mixture of 2-(3,4-dimethoxyphenyl)-ethylamine (**1**) (54.4 g, 0.3 mol) and diethyl oxalate (131.5 g, 0.9 mol) was stirred at 140 °C for 6 h. The ethanol formed and the excess of diethyl oxalate were distilled off in vacuo, and the oily residue was treated with Et_2O, resulting in ethyl *N*-[2-(3,4-dimethoxyphenyl)ethyl]oxamate as a crystalline product. The crystals were filtered off, washed with Et_2O and used in the next step without further purification. Yield: 68.7 g (81%).

An analytical sample of the product was recrystallized from iPr$_2$O to give shining white plates. Mp: 68–70 °C (lit.[25] mp: 73–74 °C). [Found: C, 59.89; H, 6.75; N, 5.03. $C_{14}H_{19}NO_5$ requires C, 59.78; H, 6.81; N, 4.98%]; ν_{max} 1746, 1683, 1516, 1238, 1023 cm^{-1}; δ_H ($CDCl_3$) 1.38 (t, 3H, J=7.2 Hz, CH_2CH_3), 2.82 (t, 2H, J=6.8 Hz, ArCH_2), 3.58 (q, 2H, J=6.8 Hz, NCH_2), 3.87 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.33 (q, 2H, J=7.2 Hz, OCH_2), 6.70–6.76 (m, 2H, C_6H_3), 6.82 (d, 1H, J=8.1 Hz, C_6H_3), 7.14 (br s, 1H, N*H*).

To a stirred solution of ethyl *N*-[2-(3,4-dimethoxyphenyl) ethyl]oxamate (40.0 g, 0.142 mol) in abs toluene (350 mL) and abs EtOH (30 mL), $POCl_3$ (120.0 g, 0.783 mol) was added. The resulting mixture was stirred and refluxed for 3.5 h, and then evaporated under reduced pressure. The oily residue was carefully dissolved in warm 96% ethanol (100 mL) and the solution was added to a mixture of ice-cold water (500 mL) and EtOAc (250 mL). The resulting mixture was made alkaline with concd NH_4OH under vigorous stirring and external cooling on an ice-water bath. The organic layer was separated and the aqueous layer was extracted with EtOAc (2×250 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. The oily residue was treated with Et_2O to give **2** as a beige crystalline product, which was filtered off, washed with Et_2O and used in the next step without any further purification. Yield: 22.4 g (60%).

An analytical sample of **2** was recrystallized from iPr$_2$O to give pale-beige crystals. Mp: 76–78 °C (lit.[14b] mp: 81.5–83 °C). [Found: C, 63.95; H, 6.60; N, 5.30. $C_{14}H_{17}NO_4$ requires C, 63.87; H, 6.51; N, 5.32%]; ν_{max} 1719, 1518, 1277, 1198, 1135 cm^{-1}; δ_H ($CDCl_3$) 1.44 (t, 3H, J=7.1 Hz, CH_2CH_3), 2.67–2.74 (m, 2H, ArCH_2), 3.83–3.89 (m, 2H, NCH_2), 3.90 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.43 (q, 2H, J=7.1 Hz, OCH_2), 6.70 (s, 1H, C_6H_2), 7.39 (s, 1H, C_6H_2).

4.1.2. Ethyl 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (3). To a solution of dihydroisoquinoline **2** (22.0 g, 83.6 mmol) in EtOH (200 mL), 5% platinum on activated charcoal catalyst (1.00 g) was added and the mixture was stirred under hydrogen at atmospheric pressure and ambient temperature. When the hydrogen uptake had ceased (approx 6 h), the catalyst was filtered off and the filtrate was evaporated. The oily product was dissolved in EtOH (30 mL) and treated with 22% ethanolic HCl (20 mL) and Et_2O (100 mL) to yield crystalline **3**·HCl. The crystals were filtered off and washed with a 1:4 mixture of EtOH and Et_2O (100 mL). Yield: 20.7 g (82%). For the further transformations, the free base **3** was liberated from the above hydrochloride salt in the usual manner (Na_2CO_3 and EtOAc).

An analytical sample of **3**·HCl was recrystallized from EtOH–Et_2O to give yellowish-white crystals. Mp: 202–204 °C. [Found: C, 55.48; H, 6.37; N, 4.60. $C_{14}H_{20}ClNO_4$ requires C, 55.72; H, 6.68; N, 4.64%]; ν_{max} 1740, 1522, 1264, 1238, 1027 cm^{-1}; δ_H (D_2O) 1.34 (t, 3H, J=7.1 Hz, CH_2CH_3), 3.02–3.18 (m, 2H, ArCH_2), 3.59–3.72 (m, 2H, NCH_2), 3.88 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.38 (q, 2H, J=7.1 Hz, OCH_2), 5.40 (s, 1H, NC*H*), 6.95 (s, 1H, C_6H_2), 7.17 (s, 1H, C_6H_2).

4.1.3. (6,7-Dimethoxy-1,2,3,4-tetrahydro-1-isoquinolyl)-methanol (4). To a stirred and ice-cooled suspension of $LiAlH_4$ (3.10 g, 81.7 mmol) in dry THF (100 mL), a solution of compound **3** (12.0 g, 39.8 mmol) in dry THF (35 mL) was added dropwise. 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 (6.2 mL) and THF (50 mL). After stirring at room temperature for 1 h, the inorganic salts were filtered off and washed with hot EtOAc (3×120 mL). The combined organic filtrate and washings were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude amino alcohol **4** as a crystalline product, which was filtered off, washed with Et_2O and recrystallized from EtOAc. Yield: 5.87 g (66%). Mp: 138–139 °C (lit.[26] mp: 134–135 °C). ν_{max} 3316, 1517, 1259, 1225, 1060 cm^{-1}. The ^{1}H NMR spectrum of **4** was in accordance with the literature[27] data on the (*S*) enantiomer of **4**.

4.1.4. (6,7-Dimethoxy-1,2,3,4-tetrahydro-3-isoquinolyl)-methanol (7b). *Method A*. To a stirred and ice-cooled suspension of $LiAlH_4$ (5.85 g, 154 mmol) in dry THF (300 mL), compound **6b** (10.50 g, 38.4 mmol) was added in small portions. The mixture was stirred and refluxed for 8 h, which was followed by the usual work-up (see the previous procedure), resulting in the crude amino alcohol **7b** as a crystalline product. Recrystallization from EtOAc gave analytically pure **7b** as white needles. Yield: 4.4 g (51%). Mp: 146–147 °C. [Found: C, 64.73; H, 7.52; N, 6.33.

$C_{12}H_{17}NO_3$ requires C, 64.55; H, 7.67; N, 6.27%]; ν_{max} 3286, 1522, 1239, 1227, 1079 cm^{-1}; δ_H ($CDCl_3$) 2.50 (dd, 1H, J=10.5, 16.0 Hz, 4-CH_2), 2.61 (dd, 1H, J=4.4, 16.0 Hz, 4-CH_2), 3.00–3.08 (m, 1H, NCH), 3.52 (dd, 1H, J=8.0, 10.8 Hz, OCH_2), 3.77 (dd, 1H, J=3.7, 10.8 Hz, OCH_2), 3.83 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.98 (s, 2H, 1-CH_2), 6.53 (s, 1H, C_6H_2), 6.57 (s, 1H, C_6H_2).

Method B. A mixture of compound **11**·HCl (35.0 g, 0.1 mol), 10% Pd/C catalyst (2.0 g) and MeOH (500 mL) was hydrogenated in an autoclave at 40 °C and 30 bar for 30 h. The catalyst was removed by filtration, and the filtrate was evaporated to dryness to give **7b**·HCl as a crystalline product. The crystals were filtered off and washed with Et_2O. Yield: 25.8 g (~100%). For the further transformations, free base **7b** was liberated from the above hydrochloride salt in the usual manner (Na_2CO_3 and EtOAc).

An analytical sample of **7b**·HCl was recrystallized from 95% MeOH–Et_2O to give a white powder. Mp: 280–282 °C. [Found: C, 55.24; H, 6.81; N, 5.37. $C_{12}H_{18}ClNO_3$ requires C, 55.49; H, 6.99; N, 5.39%]; ν_{max} 3374, 2911, 2765, 1522, 1230, 1130 cm^{-1}; δ_H (D_2O) 2.92–3.07 (m, 2H, 4-CH_2), 3.60–3.68 (m, 1H, NCH), 3.78–3.90 (m, 7H, 2×OCH_3, OCH_2), 4.03 (dd, 1H, J=3.5, 12.5 Hz, OCH_2), 4.32–4.43 (m, 2H, 1-CH_2), 6.86 (s, 1H, C_6H_2), 6.89 (s, 1H, C_6H_2).

4.1.5. 2-Benzylamino-3-(3,4-dimethoxyphenyl)-1-propanol (10). To a stirred and ice-cooled suspension of $LiAlH_4$ (12.0 g, 316 mmol) in dry THF (400 mL), compound **9** (23.0 g, 67 mmol) was added in small portions. The mixture was stirred and refluxed for 5 h. The usual work-up (see above) resulted in crude amino alcohol **10** as a crystalline product. The crystals were filtered off, washed with Et_2O and used in the next step without further purification. Yield: 15.8 g (78%).

An analytical sample of the product was recrystallized from iPr$_2$O–EtOAc to give white needles. Mp: 115–115.5 °C (lit.[17] mp: 114–116 °C). [Found: C, 71.44; H, 7.49; N, 4.50. $C_{18}H_{23}NO_3$ requires C, 71.73; H, 7.69; N, 4.65%]; ν_{max} 3286, 2837, 1517, 1264, 1238, 1136 cm^{-1}; δ_H ($CDCl_3$) 2.70–2.77 (m, 2H, ArCH_2C), 2.88–2.96 (m, 1H, NCH), 3.36 (dd, 1H, J=4.9, 10.7 Hz, OCH_2), 3.66 (dd, 1H, J=3.9, 10.7 Hz, OCH_2), 3.72–3.82 (m, 2H, NCH_2), 3.83 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.63–6.67 (m, 1H, C_6H_3), 6.70 (dd, 2H, J=1.6, 8.0 Hz, C_6H_3), 6.77–6.82 (m, 5H, C_6H_5).

4.1.6. (2-Benzyl-6,7-dimethoxy-1,2,3,4-tetrahydro-3-isoquinolyl)methanol (11). A mixture of compound **10** (13.8 g, 45.8 mmol), water (500 mL), 36% formalin (55 mL) and concd HCl (28 mL) was stirred and refluxed for 6 h. The solution was left to cool to ambient temperature, then made alkaline (under ice-bath cooling) with 10% NaOH solution and extracted with $CHCl_3$ (4×150 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give crude **11** as a yellow oil. The oily product was dissolved in MeOH (50 mL) and converted to the crystalline hydrochloride of **11** by adding an excess of 22% ethanolic HCl (20 mL) and Et_2O (300 mL). The crystals were filtered off, washed with a 1:10 mixture of MeOH and Et_2O and used in the next step without further purification. Yield: 14.8 g (92%).

An analytical sample of **11**·HCl was recrystallized from MeOH–Et_2O to give white needles. Mp: 209–211 °C. [Found: C, 65.48; H, 7.03; N, 3.91. $C_{19}H_{24}ClNO_3$ requires C, 65.23; H, 6.91; N, 4.00%]; ν_{max} 3220, 1525, 1225, 1193, 1092 cm^{-1}; δ_H (D_2O) 3.04 (dd, 1H, J=6.9, 17.6 Hz, 4-CH_2), 3.21 (dd, 1H, J=2.8, 17.6 Hz, 4-CH_2), 3.84 (s, 3H, OCH_3) 3.85–3.99 (m, 5H, OCH_2, OCH_3, NCH), 4.02–4.11 (m, 1H, OCH_2), 4.16–4.49 (m, 4H, 2×NCH_2) 6.80 (s, 1H, C_6H_2), 6.98 (s, 1H, C_6H_2), 7.42–7.62 (m, 5H, C_6H_5).

4.2. General procedure for the preparation of the hydrazino alcohols 5, 8a and 8b

A solution of $NaNO_2$ (1.38 g, 20 mmol) in H_2O (10 mL) was added dropwise to a suspension of the corresponding amino alcohol (**4** or **7a** or **7b**, 10 mmol) in H_2O (50 mL) with vigorous stirring on an ice-cold bath, and AcOH (0.90 g, 15 mmol) was then added dropwise. The mixture was stirred at room temperature for 8 h and then extracted with EtOAc (4× 50 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the *N*-nitroso derivatives of **4**, **7a** and **7b** in nearly quantitative yields. According to TLC, the products were pure enough to be used in the next step without further purification.

The solution of the corresponding crude *N*-nitroso derivative of **4** or **7a** or **7b** in THF (15 mL) was added dropwise to a stirred and ice-cooled suspension of $LiAlH_4$ (0.76 g, 20 mmol) in THF (30 mL). The mixture was stirred at room temperature for 2 h, after which the usual work-up (see above) resulted in the crude hydrazino alcohols as oily (**5**, **8a**) or crystalline (**8b**) products. The crystalline **8b** was filtered off, washed with *n*-hexane and recrystallized from iPr$_2$O–EtOAc. The oily products (**5** and **8a**) were converted to the crystalline hydrochlorides by treatment of their solution in MeOH with an excess of 22% ethanolic HCl and Et_2O.

4.2.1. Compound 5·HCl. Yield: 1.95 g (71%). Mp: 210–215 °C (95% MeOH–Et_2O). [Found: C, 52.13; H, 6.85; N, 10.01. $C_{12}H_{19}ClN_2O_3$ requires C, 52.46; H, 6.97; N, 10.20%]; ν_{max} 3335, 3289, 1524, 1269, 1230 cm^{-1}; δ_H (D_2O) 3.13–3.19 (m, 2H, 4-CH_2), 3.56–3.62 (m, 1H, 3-CH_2), 3.82–3.89 (m, 1H, 3-CH_2), 3.90 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.99 (dd, 1H, J=8.0, 12.8 Hz, 1′-CH_2), 4.26 (dd, 1H, J=3.2, 12.8 Hz, 1′-CH_2), 4.57 (m, 1H, 1-CH), 6.94 (s, 1H, C_6H_2), 6.98 (s, 1H, C_6H_2).

4.2.2. Compound 8a·HCl. Yield: 1.42 g (66%). Mp: 195–197 °C. [Found: C, 55.63; H, 6.79; N, 12.98. $C_{10}H_{15}ClN_2O$ requires C, 55.94; H, 7.04; N, 13.05%]; ν_{max} 3341, 2980, 2752, 1449, 1086, 766 cm^{-1}; δ_H (D_2O) 3.04 (dd, 1H, J=10.5, 17.5 Hz, 4-CH_2), 3.13 (dd, 1H, J=5.2, 17.5 Hz, 4-CH_2), 3.68–3.76 (m, 1H, 3-CH), 3.79 (dd, 1H, J=6.8, 12.4 Hz, 1′-CH_2), 4.01 (dd, 1H, J=3.6, 12.4 Hz, 1′-CH_2), 4.46 (s, 2H, 1-CH_2), 7.24–7.37 (m, 4H, C_6H_4).

4.2.3. Compound 8b. Yield: 1.60 g (67%). Mp: 91–93 °C. [Found: C, 59.62; H, 7.70; N, 11.51. $C_{12}H_{18}N_2O_3$ requires C, 60.49; H, 7.61; N, 11.76%]; ν_{max} 1520, 1255, 1228, 1120, 1049 cm^{-1}; δ_H ($CDCl_3$) 2.59 (dd, 1H, J=4.2, 16.1 Hz, 4-CH_2), 2.67–2.88 (m, 2H, 4-CH_2, 3-CH), 3.73–3.88 (m, 9H, OCH_2, 2×OCH_3, 1-CH_2), 3.98 (d, 1H, J=14.5 Hz, 1-CH_2), 6.51 (1H, s, C_6H_2), 6.59 (1H, s, C_6H_2).

4.3. General procedure for the preparation of the 1,3,4,2-oxadiazaphosphino[5,4-*a*]isoquinolines (13, 14), 1,3,4,2-oxadiazaphosphino[4,5-*b*]isoquinolines (15a,b; 16b) and pyrido[1,2-*d*]1,3,4,2-oxadiazaphosphinanes (17a,b; 18a,b)

To a solution of the corresponding hydrazino alcohol (**8b** or **12**, 10 mmol) or hydrazino alcohol hydrochloride (**5**·HCl or **8a**·HCl, 10 mmol) and Et_3N (2.02 g, 20 mmol; in the case of **5**·HCl and **8a**·HCl: 3.04 g, 30 mmol) in anhydrous THF (100 mL) at room temperature, a solution of phenylphosphonic dichloride or phenyl dichlorophosphate (10 mmol) in anhydrous THF (20 mL) was added dropwise over a period of 30 min. The mixture was stirred at room temperature for 48 h and then filtered, and the filtrate was evaporated in vacuo to afford a yellow oil containing a mixture of the corresponding oxadiazaphosphinane diastereomers. The diastereomeric ratios were determined from the ^{1}H NMR spectra of the crude products. Purification of the crude products by column chromatography gave **14**, **15a**, **17b** and **18a** as the more mobile, and **13**, **16a**, **17a** and **18b** as the less mobile diastereomers. Compound **16b** was the only product in the ring closure.

Compounds **13**:**14**=48:52. Eluent: EtOAc.

Compound **13**. A white solid; yield: 0.44 g (12%). Mp: 173–176.5 °C (*i*Pr_2O–EtOAc). [Found: C, 59.95; H, 5.91; N, 7.82. $C_{18}H_{21}N_2O_4P$ requires C, 60.00; H, 5.87; N, 7.77%]; ν_{max} 3122, 1513, 1228, 1128, 797 cm^{-1}; δ_H ($CDCl_3$) 2.79 (dt, 1H, *J*=4.0, 15.4 Hz, H-9eq), 3.10 (dd, 1H, *J*=4.5, 8.8 Hz, H-9ax), 3.15 (td, 1H, *J*=4.0, 8.8 Hz, H-10ax), 3.6 (dd, 1H, *J*=4.5, 10.3 Hz, H-10eq), 3.88 (s, 3H, OC*H*$_3$), 3.89 (s, 3H, OC*H*$_3$), 4.25 (dd, 1H, *J*=4.3, 9.3 Hz, H-4a), 4.58 (ddd, 1H, *J*=4.3, 11.6, 17.1 Hz, H-4eq), 4.72 (ddd, 1H, *J*=5.3, 9.3, 11.6 Hz, H-4ax), 6.55 (s, 1H, H-5), 6.64 (s, 1H, H-8), 7.52 (dt, 2H, *J*=4.0, 7.5 Hz, *m*-Ar), 7.63 (dt, 1H, *J*=1.5, 7.3 Hz, *p*-Ar), 8.0 (ddd, 2H, *J*=1.5, 8.3, 13.0 Hz, *o*-Ar); δ_C ($CDCl_3$) 26.7 (C-9), 51.9 (C-10), 56.0 (C-6, C-7), 60.5 (C-4a), 67.6 (C-4), 108.5 (C-5), 112.1 (C-8), 123.2 (C-4b), 125.6 (C-8a), 128.1 (CP), 128.6 (*m*-Ar), 132.1 (*o*-Ar), 133.0 (*p*-Ar).

Compound **14**. A white foam; yield: 0.80 g (22%). [Found: C, 59.92; H, 5.89; N, 7.80. $C_{18}H_{21}N_2O_4P$ requires C, 60.00; H, 5.87; N, 7.77%]; ν_{max} 2933, 1522, 1235, 1129, 799 cm^{-1}; δ_H ($CDCl_3$) 2.67 (dt, 1H, *J*=3.0, 15.4 Hz, H-9eq), 2.93 (td, 1H, *J*=2.8, 10.3 Hz, H-10ax), 3.01 (ddd, 1H, *J*=5.0, 10.8, 15.9 Hz, H-9ax), 3.26–3.31 (m, 1H, H-10eq), 3.84 (s, 3H, OC*H*$_3$), 3.85 (s, 3H, OC*H*$_3$), 4.01 (d, 1H, *J*=11.0 Hz, H-4a), 4.05 (td, 1H, *J*=1.3, 10.6 Hz, H-4ax), 4.72 (ddd, 1H, *J*=2.8, 10.3, 18.6 Hz, H-4eq), 6.48 (s, 1H, H-5), 6.58 (s, 1H, H-8), 7.48 (dt, 2H, *J*=4.0, 7.5 Hz, *m*-Ar), 7.55 (dt, 1H, *J*=1.5, 7.3 Hz, *p*-Ar), 7.93 (ddd, 2H, *J*=1.5, 8.3, 13.6 Hz, *o*-Ar); δ_C ($CDCl_3$) 29.6 (C-9), 52.8 (C-10), 56.2 (C-6,C-7), 63.1 (C-4a), 73.4 (C-4), 108.0 (C-5), 111.7 (C-8), 122.8 (C-4b), 126.6 (C-8a), 130.1 (CP), 128.5 (*m*-Ar), 131.1 (*o*-Ar), 132.0 (*p*-Ar).

Compounds **15a**:**16a**=50:50. Eluent: EtOAc.

Compound **15a**. A white solid; yield: 0.81 g (27%). Mp: 145–148 °C [Found: C, 63.82; H, 5.55; N, 9.46. $C_{16}H_{17}N_2O_2P$ requires C, 64.00; H, 5.71; N, 9.33%]; ν_{max} 3118, 1390, 1241, 1130, 950 cm^{-1}; δ_H ($CDCl_3$) 2.73 (dd, 1H, *J*=5.5, 17.6 Hz, H-5eq), 3.19 (m, 1H, H-4a), 3.48 (dd, 1H, *J*=11.8, 17.6 Hz, H-5ax), 4.09 (d, 1H, *J*=16.1 Hz, H-10eq), 4.28 (dd, 1H, *J*=2.5, 6.5 Hz, H-10ax), 4.32 (ddd, 1H, *J*=2.5, 11.3, 17.9 Hz, H-4eq), 4.44 (ddd, 1H, *J*=3.3, 4.0, 11.3 Hz, H-4ax), 7.09 (dd, 1H, *J*=2.8, 6.3 Hz, H-9), 7.16–7.26 (m, 3H, H-6, H-7, H-8), 7.52 (dt, 2H, *J*=4.0, 7.3 Hz, *m*-Ar), 7.59 (dt, 1H, *J*=1.3, 7.5 Hz, *p*-Ar), 7.96 (ddd, 2H, *J*=1.3, 8.3, 13.6 Hz, *o*-Ar); δ_C ($CDCl_3$) 23.4 (C-5), 53.9 (C-4a), 58.2 (C-10), 70.8 (C-4), 127.2 (C-7, C-8), 127.4 (C-6), 129.0 (C-9), 130.5 (C-5a), 131.2 (C-9a), 127.3 (CP), 129.0 (*m*-Ar), 131.3 (*o*-Ar), 132.3 (*p*-Ar).

Compound **16a**. A white solid; yield: 0.42 g (14%). Mp: 209–211 °C. [Found: C, 64.15; H, 5.68; N, 9.21. $C_{16}H_{17}N_2O_2P$ requires C, 64.00; H, 5.71; N, 9.33%]; ν_{max} 3108, 1450, 1238, 1004, 817 cm^{-1}; δ_H ($CDCl_3$) 2.71 (dd, 1H, *J*=10.3, 16.1 Hz, H-5ax), 2.84 (dd, 1H, *J*=4.8, 16.2 Hz, H-5eq), 3.07 (tt, 1H, *J*=4.0, 10.8 Hz, H-4a), 3.78 (d, 1H, *J*=14.9 Hz, H-10ax), 3.99 (ddd, 1H, *J*=7.3, 9.8, 11.6 Hz, H-4ax), 4.36 (d, 1H, *J*=14.6 Hz, H-10eq), 4.51 (ddd, 1H, *J*=4.0, 11.6, 18.38 Hz, H-4eq), 7.09 (dd, 2H, *J*=3.3, 5.3 Hz, H-6, H-9), 7.19 (dd, 2H, *J*=3.5, 5.3 Hz, H-7, H-8), 7.48 (dt, 2H, *J*=4.0, 7.5 Hz, *m*-Ar), 7.55 (dt, 1H, *J*=1.3, 7.3 Hz, *p*-Ar), 7.98 (ddd, 2H, *J*=1.5, 8.3, 13.6 Hz, *o*-Ar); δ_C ($CDCl_3$) 31.1 (C-5), 58.6 (C-4a), 58.9 (C-10), 70.7 (C-4), 126.2 (C-6), 126.7 (C-7, C-8), 128.1 (C-9), 128.5 (*m*-Ar), 131.1 (C-9a), 131.4 (C-5a), 126.5 (CP), 131.5 (*o*-Ar), 132.4 (*p*-Ar).

Compound **16b**. Eluent: EtOAc/MeOH=9:1.

Compound **16b**. Transparent crystals; yield: 1.43 g (40%). Mp: 201–205 °C (*i*Pr_2O–EtOAc). [Found: C, 60.10; H, 5.74; N, 7.86. $C_{18}H_{21}N_2O_4P$ requires C, 60.00; H, 5.87; N, 7.77%]; ν_{max} 3092, 1519, 1236, 1028, 804 cm^{-1}; δ_H ($CDCl_3$) 2.61 (dd, 1H, *J*=10.3, 16.3 Hz, H-5ax), 2.74 (dd, 1H, *J*=4.8, 16.4 Hz, H-5eq), 3.06 (tt, 1H, *J*=4.0, 10.8 Hz, H-4a), 3.75 (d, 1H, *J*=14.1 Hz, H-10ax), 3.82 (s, 3H, OC*H*$_3$), 3.84 (s, 3H, OC*H*$_3$), 3.97 (td, 1H, *J*=8.1, 11.6 Hz, H-4ax), 4.23 (d, 1H, *J*=14.4 Hz, H-10eq), 4.46 (ddd, 1H, *J*=3.8, 11.6, 18.1 Hz, H-4eq), 6.53 (s, 2H, H-6, H-9), 7.47 (dt, 2H, *J*=4.0, 7.5 Hz, *m*-Ar), 7.55 (dt, 1H, *J*=1.3, 7.5 Hz, *p*-Ar), 7.96 (ddd, 2H, *J*=1.3, 8.3, 13.6 Hz, *o*-Ar); δ_C ($CDCl_3$) 30.6 (C-5), 55.9 (C-7, C-8), 58.4 (C-4a), 58.5 (C-10), 70.7 (C-4), 110.2 (C-6, C-9), 123.0 (C-5a), 124.2 (C-9a), 127.7 (CP), 128.6 (*m*-Ar), 132.0 (*p*-Ar), 132.1 (*o*-Ar).

Compounds **17a**:**18a**=21:79. Eluent: EtOAc/MeOH=9:1.

Compound **17a**. Transparent needles; yield: 0.50 g (20%). Mp: 178–181 °C (EtOAc). [Found: C, 57.11; H, 6.81; N, 11.13. $C_{12}H_{17}N_2O_2P$ requires C, 57.14; H, 6.79; N, 11.11%]; ν_{max} 3109, 2933, 1439, 1224, 801 cm^{-1}; δ_H ($CDCl_3$) 1.31 (tq, 1H, *J*=3.5, 12.3 Hz, H-6ax), 1.42 (dq, 1H, *J*=3.5, 12.8 Hz, H-5ax), 1.54–1.75 (m, 4H, H-5eq), 1.75–1.83 (m, 2H, H-6eq, H-7), 2.33 (dt, 1H, *J*=3.0, 11.3 Hz, H-8ax), 2.58 (tt, 1H, *J*=3.0, 13.4 Hz, H-4a), 3.29 (td, 1H, *J*=3.5, 10.8 Hz, H-8eq), 4.17 (ddd, 1H, *J*=3.3, 11.3, 18.9 Hz, H-4eq), 4.49 (ddd, 1H, *J*=3.5, 9.8, 11.3 Hz, H-4ax), 7.5 (dt, 2H, *J*=4.0, 7.8 Hz, *m*-Ar), 7.6 (dt, 1H, *J*=1.3, 7.5 Hz, *p*-Ar), 7.9 (ddd, 2H, *J*=1.3, 8.3, 12.8 Hz, *o*-Ar); δ_C ($CDCl_3$) 22.9 (C-6), 24.1 (C-7), 26.2 (C-5), 58.2 (C-8), 63.5 (C-4a), 70.2 (C-4), 126.7 (CP), 128.5 (*m*-Ar), 132.0 (*o*-Ar), 133.0 (*p*-Ar).

Compound **18a**. White crystals; yield: 0.54 g (21%). Mp: 146–148 °C (EtOAc). [Found: C, 57.20; H, 6.84; N, 11.09. $C_{12}H_{17}N_2O_2P$ requires C, 57.14; H, 6.79; N, 11.11%]; ν_{max} 3112, 2944, 1456, 1225, 810 cm^{-1}; δ_H ($CDCl_3$) 1.06 (dtd, 1H, J=3.8, 11.3, 13.4 Hz, H-5ax), 1.19–1.32 (m, 1H, H-6), 1.48–1.8 (m, 4H, H-5eq, H-6eq, H-7), 2.29 (ddd, 1H, J=2.3, 10.3, 12.6 Hz, H-8ax), 2.46 (tt, 1H, J=3.0, 10.8 Hz, H-4a), 3.26 (td, 1H, J=2.3, 11.0 Hz, H-8eq), 3.53 (d, 1H J=10.6 Hz, N*H*), 3.81 (ddd, 1H, J=2.0, 10.3, 11.3 Hz, H-4ax), 4.18 (ddd, 1H, J=3.0, 11.3, 20.4 Hz, H-4eq), 7.46 (dt, 2H, J=4.0, 7.3 Hz, *m*-Ar), 7.53 (dd, 1H, J=1.3, 7.3 Hz, *p*-Ar), 7.9 (ddd, 2H, J=1.3, 7.8, 12.8 Hz, *o*-Ar); δ_C ($CDCl_3$) 22.7 (C-6), 26.1 (C-7), 26.6 (C-5), 58.1 (C-8), 62.5 (C-4a), 73.13 (C-4), 128.3 (CP), 128.6 (*m*-Ar), 131.3 (*o*-Ar), 132.0 (*p*-Ar).

Compounds **17b**:**18b**=50:50. Eluent: EtOAc.

Compound **17b**. Transparent needles; yield: 0.54 g (20%). Mp: 153–154.5 °C (*i*Pr_2O–EtOAc). [Found: C, 53.80; H, 6.36; N, 10.41. $C_{12}H_{17}N_2O_3P$ requires C, 53.73; H, 6.39; N, 10.44%]; ν_{max} 3129, 2943, 1263, 1010, 942 cm^{-1}; δ_H ($CDCl_3$) 1.2 (dddd, 1H, J=3.8, 11.1, 13.6, 16.9 Hz, H-5ax), 1.31 (tq, 1H, J=4.0, 13.1 Hz, H-6ax), 1.56–1.81 (m, 4H, H-5eq, H-6eq, H-7), 2.26 (dt, 1H, J=2.8, 11.8 Hz, H-8ax), 2.45 (tt, 1H, J=3.0, 10.6 Hz, H-4a), 3.20 (dt, 1H, J=3.5, 10.8 Hz, H-8eq), 3.75 (d, 1H, J=9.8 Hz, N*H*), 4.17 (ddd, 1H, J=3.5, 11.0, 19.9 Hz, H-4eq), 4.21–4.27 (m, 1H, H-4ax) 7.19 (t, 1H, J=7.05 Hz, *p*-Ar), 7.29–7.38 (m, 4H, Ar); δ_C ($CDCl_3$) 22.6 (C-6), 25.0 (C-7), 25.8 (C-5), 57.6 (C-8), 62.1 (C-4a), 74.1 (C-4), 150.5 (CP), 120.8 (*m*-Ar), 124.9 (*p*-Ar), 129.7 (*o*-Ar).

Compound **18b**. A pale yellow solid; yield: 0.37 g (14%). Mp: 123–125 °C (*i*Pr_2O–EtOAc). [Found: C, 53.69; H, 6.41; N, 10.39. $C_{12}H_{17}N_2O_3P$ requires C, 53.73; H, 6.39; N, 10.44%]; ν_{max} 3129, 2940, 1251, 1209, 957 cm^{-1}; δ_H ($CDCl_3$) 1.26–1.44 (m, 2H, H-5ax, H-6ax), 1.44–1.84 (m, 4H, H-5eq, H-6eq, H-7), 2.64 (td, 1H, J=2.8, 12.3 Hz, H-8ax), 2.75 (m, 1H, H-4a), 3.23 (td, 1H, J=3.1, 11.8 Hz, H-8eq), 4.26 (dd, 1H, J=8.6, 11.6 Hz, H-4ax), 4.31 (ddd, 1H, J=3.5, 11.6, 26.4 Hz, H-4eq), 7.19 (t, 1H, J=7.3 Hz, *p*-Ar), 7.23–7.38 (*m*, 4H, Ar); δ_C ($CDCl_3$) 22.7 (C-7), 23.1 (C-6), 24.4 (C-5), 57.8 (C-8), 60.5 (C-4a), 72.9 (C-4), 150.5 (CP), 120.5 (*m*-Ar), 124.9 (*p*-Ar), 129.8 (*o*-Ar).

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