DOI: 10.1002/ejoc.200701026

Synthesis and Conformational Analysis of Tetrahydroisoquinoline-Fused 1,3,2-Oxazaphospholidines and 1,2,3-Oxathiazolidines

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Keywords: Phosphorus heterocycles / Sulfur heterocycles / Fused-ring systems / Conformational analysis / Molecular modelling

The cyclizations of tetrahydroisoquinoline 1,2-amino alcohols with phenylphosphonic dichloride, bis(2-chloroethyl)phosphoramidic dichloride, thionyl chloride and sulfuryl chloride were utilized to synthesize 1,5,6,10b-tetrahydro-1,3,2-oxazaphospholo[4,3-*a*]isoquinolines (**2**, **3**), 1,5,10,10a-tetrahydro-1,3,2-oxazaphospholo[3,4-*b*]isoquinolines (**8**, **9**), 1,5,6,10b-tetrahydro-1,2,3-oxathiazolo[4,3-*a*]isoquinolines (**4**–**6**) and a 1,5,10,10a-tetrahydro-1,2,3-oxathiazolo[3,4-*b*]isoquinoline (**11**), which are the first representatives of these ring systems. NMR spectroscopic analysis revealed the existence of conformational equilibria that are fast on the NMR timescale. Theoretical DFT calculations pointed to the participation of generally two preferred conformers in the conformational equilibria; the positions of the equilibria were indicated by the experimental NMR spectroscopic parameters, and they are in good agreement with the theoretically calculated energy differences of the participating conformers. For two compounds, which could be not isolated (**10**, **12**), both the preferred conformers and the stereochemistry could be concluded from the DFT calculation results.

Introduction

Thanks to their valuable pharmacological effects and potential for synthetic applications, 1,3,2-O,N,P and 1,2,3-O,S,N heterocycles have attracted great interest. The 1,3,2-oxazaphosphinane 2-oxide moiety is found in alkylating anticancer drugs (e.g., cyclophosphamide and ifosfamide), numerous derivatives of which have been prepared to determine their structure–activity relationships.[1] Asymmetric alkylations or aminations of phosphoryl-stabilized carbanions derived from 1,3,2-oxazaphospholidine or 1,3,2-oxazaphosphinane 2-oxides have been widely used in the preparation of synthetically and/or biologically interesting enantiomerically pure compounds.[2] The heterocyclic moiety of ephedrine-derived 2-ferrocenyl-1,3,2-oxazaphospholidine 2-oxide proved to be an efficient *ortho*-directing group for the stereoselective deprotonation of ferrocene, and it was utilized in the synthesis of 1,2-disubstituted ferrocene derivatives possessing planar chirality.[3]

1,2,3-Oxathiazolidine 2-oxides and 2,2-dioxides (five-membered cyclic sulfamidites and sulfamidates) have been applied in the synthesis of various products possessing heteroatomic functional groups, for example, enantiomerically enriched sulfinamides, sulfoxides or amino acid analogues.[4] Chiral nonracemic *N*-tosyl-1,2,3-oxathiazolidine 2-oxides were applied as recyclable chiral auxiliaries in the asymmetric synthesis of (*R*)-sibutramine.[5] The reactions of chiral nonracemic cyclic sulfimidates with enolates were utilized in the preparation of enantiomerically pure functionalized lactams.[6] Cyclic sulfamidates with 2-bromophenols were used to prepare 1,4-benzoxazines.[7] The nucleophilic ring opening of the corresponding sulfamidates allowed the facile preparation of stereochemically pure and orthogonally protected derivatives of the unusual amino acids *meso*-lanthionine and β-methyllanthionine.[8]

Of the nitrogen-bridged bi- or tricyclic analogues of 1,3,2-oxazaphosphinane 2-oxides and 1,2,3-oxathiazolidine 2-oxides, chemical studies have focused mainly on the pyrrolidine-condensed analogues prepared by ring-closures of chiral nonracemic prolinol derivatives.[9] Enantiopure pyrrolidine-condensed 1,3,2-oxazaphosphinane 2-oxide proved to be a highly efficient catalyst in the enantioselective reduction of ketones,[10] whereas the analogous pyrrolidine-fused 1,2,3-oxathiazolidine 2-oxide was utilized in the preparation of various chiral 2-substituted pyrrolidine difunctional compounds by its oxidized sulfamidate derivative.[11]

As a continuation of our systematic studies on the preparation and conformational analysis of tetrahydroisoquinoline-fused 1,3-, 1,2,3- and 1,2,3,4-heterocycles,[12] our present aim was to synthesize 1,3,2-oxazaphosphinane 2-oxides

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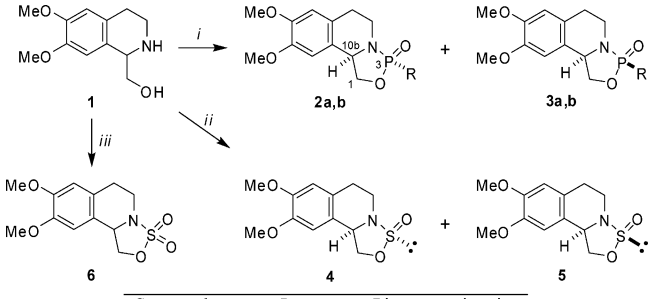
and 1,2,3-oxathiazolidine 2-oxides and 2,2-dioxides, condensed angularly or linearly to 1,2,3,4-tetrahydroisoquinoline, and to investigate the influence of the relative configurations of the substituted atoms on the conformational equilibria of these compounds.

Results and Discussion

Synthesis

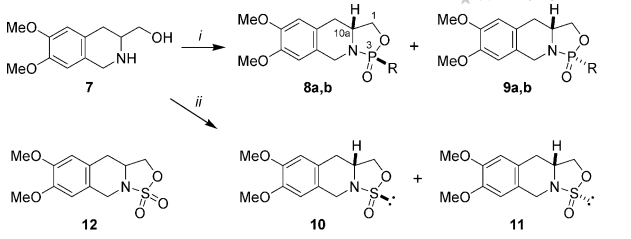
6,7-Dimethoxy-1,2,3,4-tetrahydro-1-isoquinolinemethanol (**1**) and 6,7-dimethoxy-1,2,3,4-tetrahydro-3-isoquinolinemethanol (**7**), required for the synthesis of the target compounds, were prepared by $LiAlH_4$ reduction of the corresponding tetrahydroisoquinoline α-amino esters.[12g] The ring-closures of **1** and **7** with phenylphosphonic dichloride and bis(2-chloroethyl)phosphoramidic dichloride were carried out in anhydrous CH_2Cl_2 in the presence of triethylamine to afford the first representatives of new ring systems: 1,3,2-oxazaphospholo[4,3-*a*]- (**2**, **3**) and 1,3,2-oxazaphospholo[3,4-*b*]isoquinolines (**8**, **9**). The NMR spectra of the crude products indicated that the ratio of the diastereomers, differing in the *cis* or *trans* position of the P substituent and the hydrogen atom at the annelation point, was only slightly influenced by the substituents on P, whereas for the bis(2-chloroethyl)amino derivatives **2b/3b** and **8b/9b**, the *major* product for the linearly condensed regioisomer proved to be the opposite diastereomer to that for the angularly condensed counterpart (Schemes 1 and 2). The P-epimeric diastereomers were separated by column chromatography.



Compound	R	Diastereomeric ratio in the crude product
2a/3a	Ph	50:50
2b/3b	$N(CH_2CH_2Cl)_2$	55:45
4/5	–	20:80

Scheme 1. Reagents and conditions: (i) $PhPOCl_2$, CH_2Cl_2, Et_3N, 6 °C→r.t., then r.t., 24 h, or $(ClCH_2CH_2)_2NPOCl_2$, CH_2Cl_2, Et_3N, r.t., 48 h, 6–26%; (ii) $SOCl_2$, Et_3N, CH_2Cl_2, –15 °C→r.t., then r.t., 50 h, 7–17%; (iii) SO_2Cl_2, Et_3N, CH_2Cl_2, –15 °C→r.t., then r.t., 50 h, 11%.

When amino alcohols **1** and **7** were treated with thionyl chloride or sulfuryl chloride, 1,2,3-oxathiazolo[4,3-*a*]- (**4**–**6**) and 1,2,3-oxathiazolo[3,4-*b*]isoquinoline derivatives (**10**, **11**) were obtained, the heterocyclic skeletons of which are also new ring systems (Schemes 1 and 2). The ^1H NMR spectra of the crude products indicated that the diastereomer of the 1,2,3-oxathiazolo 2-oxides containing the S=O bond and the hydrogen atom at the annelation point in the *cis* position predominates both in the angularly fused (**5**) and in



Compound	R	Diastereomeric ratio in the crude product
8a/9a	Ph	42:58
8b/9b	$N(CH_2CH_2Cl)_2$	43:57
10/11	–	~0:100

Scheme 2. Reagents and conditions: (i) $PhPOCl_2$, CH_2Cl_2, Et_3N, 6 °C→r.t., then r.t., 24 h, or $(ClCH_2CH_2)_2NPOCl_2$, CH_2Cl_2, Et_3N, r.t., 48 h, 6–24%; (ii) $SOCl_2$, Et_3N, CH_2Cl_2, –15 °C→r.t., then r.t., 50 h, 42%.

the linearly fused regioisomer (**11**). In contrast with the homologous 9,10-dimethoxy-1,6,7,11b-tetrahydro-2*H*-1,2,3-oxathiazino[4,3-*a*]isoquinoline 4-oxide, for which the *minor* diastereomer decomposed during the chromatographic purification,[12c] both *S*-epimeric diastereomers (**4**, **5**) of the five-membered analogue could be isolated by column chromatography. In the attempted cyclization of **7** with sulfuryl chloride, cyclic sulfamidate product **12** decomposed during the purification process.

Structure

Similar to those of nitrogen-bridged saturated bi- or polycycles, the stereostructures of the prepared 1,5,6,10b-tetrahydro-1,3,2-oxazaphospholo[4,3-*a*]isoquinolines (**2**, **3**), 1,5,10,10a-tetrahydro-1,3,2-oxazaphospholo[3,4-*b*]isoquinolines (**8**, **9**), 1,5,6,10b-tetrahydro-1,2,3-oxathiazolo[4,3-*a*]-isoquinolines (**4**–**6**) and 1,5,10,10a-tetrahydro-1,2,3-oxathiazolo[3,4-*b*]isoquinoline (**11**) can be described by conformational equilibria of *cis*^{1}–*trans*–*cis*^{2} type.[12–14] In the *trans* conformation, the heterorings are *trans* connected with dipseudoaxial arrangements of the N lone pair of electrons and the hydrogen atom at the annelation point (because of the different numbering of the angularly and linearly fused systems, the hydrogen atom at the annelation point, which is abbreviated as an-H, is 10b-H in **2**–**6** and 10a-H in **8**–**12**). In the two other conformations, the heterorings are *cis* connected: for the *cis*^{1} conformation, C-1 is in a pseudoaxial position, whereas for the *cis*^{2} conformation, C-1 is in a pseudoequatorial position relative to the tetrahydropyridine ring (Figure 1).

The configuration of the heteroatom (P or S) must first be determined by the significant differences in the chemical shifts of the indicator nuclei (an-H, 1-H_{ax} and P). Then, the conformation of the molecules (the annelation of the heterorings) is determined from the characteristic vicinal H,H coupling constants and a critical comparison of the measured and theoretically calculated NMR parameters: (i) The configuration of the P-containing compounds (**2**, **3**, **8** and **9**) can be determined from the chemical shifts of the P atom and an-H. The chemical shift of the P nucleus was

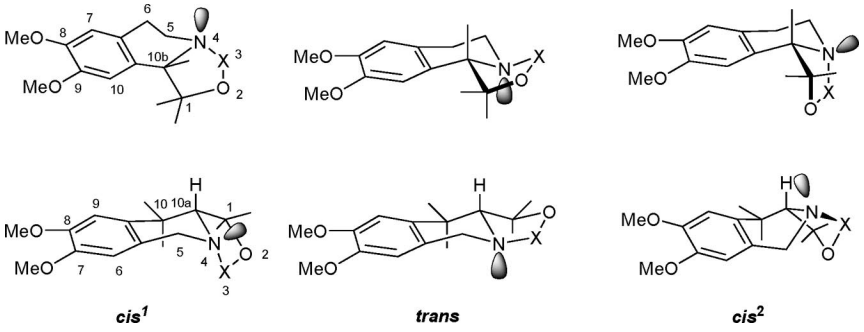


Figure 1. Possible connections of the B/C rings in saturated five-membered O,X,N heterocycles condensed angularly or linearly to 1,2,3,4-tetrahydroisoquinoline.

previously observed to be at low field if the P=O bond is in the axial position;[12a,12b] this criterion was employed in the present assignments. Additionally, if the X=O (X = P or S) bond is in the axial position and on the same side as an-H, the latter proton is at low field as well (due to the 1,3-diaxial effect; cf. Table 1).[15] This effect is not so pronounced in five-membered rings, because the substituents only adopt pseudoaxial or pseudoequatorial conformations (vide infra). (ii) The orientation of an-H was assigned by using the vicinal coupling constants between an-H and 1-H (Tables 2 and 3). One large and one small value of $^3J_{\text{an-H,1-H}}$ indicates the pseudoaxial conformation, and two moderate values of $^3J_{\text{an-H,1-H}}$ indicate the pseudoequatorial position of an-H in the five-membered ring.

Table 1. Selected chemical shifts (δ_{TMS} = 0 ppm, $\delta_{H_3PO_4}$ = 0 ppm).

Compound	^{31}P, δ [ppm]	1-H$_{ax}$, δ [ppm]	an-H[a], δ [ppm]
2a	15.8	4.06	4.89
2b	24.2	3.89	4.80
3a	15.9	4.09	5.01
3b	25.6	3.81	4.77
4	–	4.34	4.75
5	–	4.12	5.04
6	–	4.20	5.07
8a	35.1	4.62	3.82
8b	26.6	4.14	3.74
9a	32.8	4.82	3.95
9b	25.1	4.62	3.78
11	–	4.07	3.83

[a] an-H is the hydrogen atom at the annelation point, that is, 10b-H for **2**–**6** and 10a-H for **8**–**12**.

1,5,6,10b-Tetrahydro-1,3,2-oxazaphospholo[4,3-*a*]isoquinolines (2 and 3)

These compounds contain five-membered ring moieties, which readily interconvert by pseudorotation. Pseudorotation is a dynamic process that is too fast on the NMR timescale to detect. For this reason, the compounds were studied by theoretical calculations at the DFT level of theory, and preferred conformations were obtained. Both the global minimum and the energetically next higher conformer for **2a** are visualized in Figure 2; other local minima are less stable than 7–8 kcal mol^{-1} and were not considered further. Because of the flexibility of the pyridine ring, there could be an equilibrium between these two preferred *cis* conformers that is fast on the NMR timescale. From the NMR spectra and especially the H,H and H,P coupling

Table 2. Selected vicinal coupling constants [Hz].

Compound	1-H$_{ax}$,10b-H	1$_{eq}$-H,10b-H	5$_{ax}$-H,6$_{ax}$-H	5$_{ax}$-H,6$_{eq}$-H	5$_{eq}$-H,6$_{ax}$-H	5$_{eq}$-H,6$_{eq}$-H	10b-H,P	1$_{ax}$-H,P	1$_{eq}$-H,P	5$_{ax}$-H,P	5$_{eq}$-H,P
2a	6.4	5.7	11.4	6.3	4.2	1.2	<1	15.2	12.4	9.0	7.4
3a	9.9	6.6	14.4	4.0	< 1	<1	<1	0.9	20.7	[b]	23.7
2b	9.5	6.8	14.0	4.6	2.2	<1	2.5	<1	22.5	2.2	[b]
3b	[a]	[a]	12.3	6.5	3.5	<1	<1	[a]	21.7	2.3	[b]
4	8.8	6.8	11.2	3.3	5.0	2.6	–	–	–	–	–
5	11.5	6.5	8.0	5.0	5.0	5.0	–	–	–	–	–
6	9.6	6.7	6.8	4.9	6.2	4.8	–	–	–	–	–

[a] Overlapping signals. [b] Multiplets.

Table 3. Selected vicinal coupling constants [Hz].

Compound	1$_{ax}$-H,10a-H	1$_{eq}$-H,10a-H	10$_{ax}$-H,10a-H	10$_{eq}$-H,10a-H	10a-H,P	1$_{ax}$-H,P	1$_{eq}$-H,P	5$_{ax}$-H,P	5$_{eq}$-H,P
8a	8.0	6.3	10.5	2.4	4.2	5.5	11.7	2.7	2.8
9a	7.0	6.5	10.3	4.2	16.7	13.8	5.0	6.1	4.7
8b	7.2	6.5	10.9	3.7	3.0	5.2	11.6	6.7	8.3
9b	11.4	2.3	10.8	3.3	[a]	6.9	17.0	< 1	2.2
11	9.2	6.6	10.8	3.8	–	–	–	–	–

[a] Multiplets.

constants (cf. Table 2), the occurrence of this equilibrium can be proved for **2a**. For the other three compounds, only one conformer (*cis*[1] for **2b**, *trans* for **3a** and *trans* for **3b**) is preferred. As the calculated energy difference is >2 kcal mol^{-1}, the preferred conformers of **2b**, **3a** and **3b** were concluded to be the global minima structures as calculated at the DFT level of theory (cf. Figure 2).

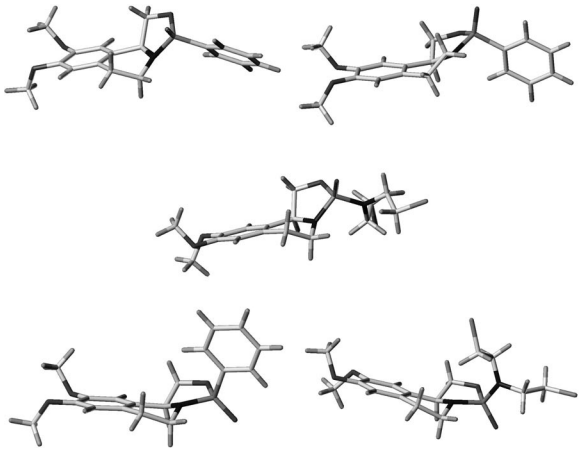


Figure 2. Calculated global (left) and local (right) energy minimum conformations for **2a** (top, ΔE = 2.63 kcal mol^{-1}), and the calculated global energy minimum conformations for **2b** (middle), **3a** (bottom left) and **3b** (bottom right).

1,5,6,10b-Tetrahydro-1,2,3-oxathiazolo[4,3-*a*]isoquinolines (4–6)

The configuration of the sulfur atom can be determined readily from the chemical shift of 10b-H. If 10b-H and the S=O are on the same side of the molecule (*cis* position) (**5**), the chemical shift for 10b-H is larger (δ = 5.03 ppm) than in the corresponding *trans* isomer, **4** (δ = 4.35 ppm), due to the 1,3-diaxial effect.[15] This effect is perceptible in the sulfone (**6**), which has S=O bonds in both the *cis* and *trans* positions, and the chemical shift of 10b-H is 5.07 ppm.

For these compounds, two energy minima were calculated as the most stable conformers; the energy differences are rather small (cf. Figure 3). Thus, conformational equilibria can be expected in all three cases. In view of the experimental ^{1}H NMR spectra and especially of the vicinal H,H coupling constants, the six-membered ring inversion in **4** should be shifted more towards the preferred conformer than in **5** or **6**, for both of which only moderate differences were obtained. The reverse situation may be concluded for the interconversion of the five-membered heterocyclic ring moieties in **4**–**6**; in **5**, the conformational equilibrium must be more one-sided than for the other two molecules, as indicated by the merely moderate $^3J_{10b\text{-}H,1ax\text{-}H}$, $^3J_{10b\text{-}H,1eq\text{-}H}$ coupling behaviour. The *cis*[1] conformer involved in the fast conformational equilibrium of **5** (Table 4) has been revealed in the solid state by X-ray analysis (cf. Figure 4), whereas the DFT calculations relating to energy and NMR parameters (cf. Table 4) suggest that the *trans* conformer is the more stable in solution.

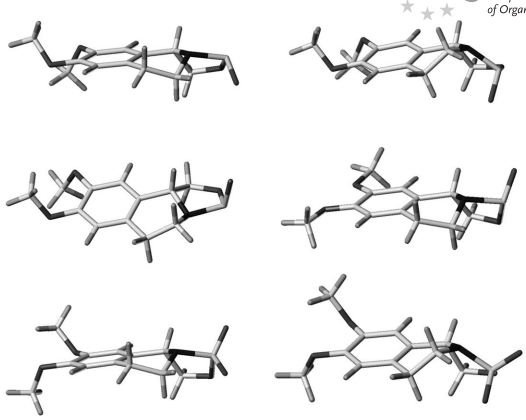


Figure 3. Calculated global (left) and local (right) energy minimum conformations for **4** (top, ΔE = 0.88 kcal mol^{-1}), **5** (middle, ΔE = 0.57 kcal mol^{-1}) and **6** (bottom, ΔE = 0.40 kcal mol^{-1}).

Table 4. Calculated and experimental characteristic vicinal coupling constants [Hz] and chemical shifts [ppm] for **5**.

	Calcd. 1. *trans*	Calcd. 2. *cis*[1]	Measured
10b-H,1-H$_{eq}$	5.9	7.9	6.5
10b-H,1$_{ax}$-H	9.5	8.2	11.5
5$_{ax}$-H,6$_{eq}$-H	6.3	3.1	5.0
5$_{ax}$-H,6$_{ax}$-H	10.3	10.6	8.0
5$_{eq}$-H,6$_{eq}$-H	1.1	1.8	5.0
5$_{eq}$-H,6$_{ax}$-H	3.6	5.0	5.0
10b-H	5.03	5.27	5.03
5$_{ax}$-H	3.00	2.65	3.43
5$_{eq}$-H	3.12	2.75	3.27
6$_{eq}$-H	2.55	2.31	2.95
6$_{ax}$-H	3.06	3.09	2.95
1$_{ax}$-H	4.64	4.31	5.07
1$_{eq}$-H	3.83	3.69	4.12
C-10b	57.7	60.2	57.1
C-5	40.9	40.4	40.1
C-6	31.5	31.0	28.7
C-1	74.4	71.1	76.0

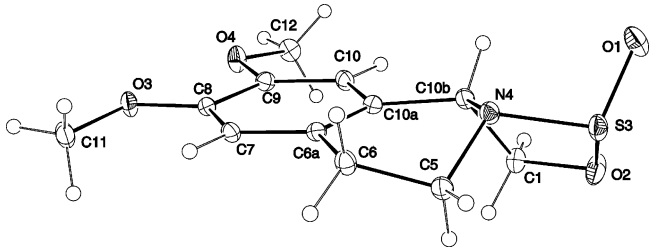


Figure 4. ORTEP plot (30% ellipsoids) of **5**, showing the numbering system and the stereochemistry of the compound.

1,5,10,10a-Tetrahydro-1,3,2-oxazaphospholo[3,4-*b*]isoquinolines (8 and 9)

The configuration of the P atom can be determined from the chemical shift of 10a-H. If 10a-H and the P=O moiety are on the same side of the molecule (i.e., *cis*; **9**), its ^{1}H NMR signal is low-field shifted relative to that for the *trans* isomer (**8**) (δ = 3.95 ppm for **9a** and 3.82 ppm for **8a**; 3.78 ppm for **9b** and 3.74 ppm for **8b**) again due to the 1,3-diaxial effect.[15]

As usual, two conformers were theoretically calculated as the two minimum structures; in **8a**,**b** and **9a**, the energy difference proved to be very small, but the situation was completely different in **9b** (cf. Figure 5). From the ^{1}H NMR spectra of **8** and **9**, the interconversion of the six-membered ring moiety was frozen ($^3J_{10a\text{-}H,10ax\text{-}H}$ = 10.3–10.9 Hz, $^3J_{10a\text{-}H,10eq\text{-}H}$ = 2.2–4.2 Hz), which is in complete agreement with the calculated result. However, the five-membered heteroring is still flexible in **8a**,**b** and **9a** ($^3J_{10a\text{-}H,1ax\text{-}H}$ = 7.0–8.0 Hz, $^3J_{10a\text{-}H,1eq\text{-}H}$ = 6.3–6.5 Hz), but frozen in **9b** ($^3J_{10a\text{-}H,1ax\text{-}H}$ = 11.4 Hz, $^3J_{10a\text{-}H,1eq\text{-}H}$ = 2.3 Hz). This compound exhibits the highest energy difference between the two energy-minimum conformers (7.99 kcal mol^{-1}), which is in complete accordance with the NMR spectra. From the calculated energy minima of the conformers and the couplings of an-H, *trans* connection of the B/C rings for **8a** and **9b** and *cis*[1] for **8b** and **9a** could be concluded, which indicates that not only the relative configuration but also the type of the substituent of the phosphorus exert strong influence on the conformational equilibria of these compounds.

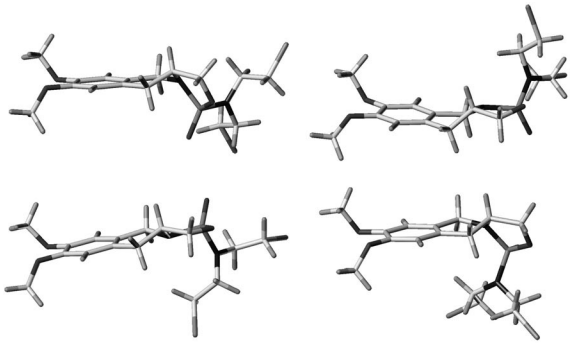


Figure 5. Calculated global (left) and local (right) energy minima for **8b** (top, ΔE = 0.02 kcal mol^{-1}) and **9b** (bottom, ΔE = 7.99 kcal mol^{-1}).

1,5,10,10a-Tetrahydro-1,2,3-oxathiazolo[3,4-*b*]isoquinolines (10–12)

As usual, the configuration of the S atom was determined from the chemical shift of 10a-H. If 10a-H and the S=O group are on the same side of the molecule (i.e., *cis*; **11**), the chemical shift of 10a-H is larger than that in the *trans* isomer (**10**) due to the 1,3-diaxial effect.[15] Comparison of the experimental chemical shift for 10a-H (δ = 3.83 ppm) with the calculated values of 3.52 ppm for **10** and 3.86 ppm for **11**, configuration **11** is suggested for our compound.

For these compounds, two conformers were calculated to be the most stable; the energy difference was rather small. Although only one isomer of each of **10** and **11** could be isolated, calculations were performed for both isomers. The DFT calculations showed that the six-membered rings in both **10** and **11** are frozen ($^3J_{10a\text{-}H,10ax\text{-}H}$ = 9.3 Hz for **11** and 10.1 Hz for **10**; $^3J_{10a\text{-}H,10eq\text{-}H}$ = 3.4 Hz for **11** and 4.1 Hz for **10**) but the corresponding five-membered ring is still flexible ($^3J_{10a\text{-}H,1ax\text{-}H}$ = 9.0 Hz for **11** and 5.8 Hz for **10**; $^3J_{10a\text{-}H,1eq\text{-}H}$ = 6.6 Hz for **11** and 0.7 Hz for **10**) (cf. Figure 6). The calculated ^{1}H chemical shifts for an-H and the theoretical $^3J_{an\text{-}H,10ax,eq\text{-}H}$ were compared with the measured values: in all cases, the calculated data were in better agreement with the stereochemistry in **11**, which indicates that the latter was the isomer actually isolated. Both of the H,H coupling constants of an-H are diaxial in type (cf. Table 5), which indicates the *trans* connection of the B/C heterorings.

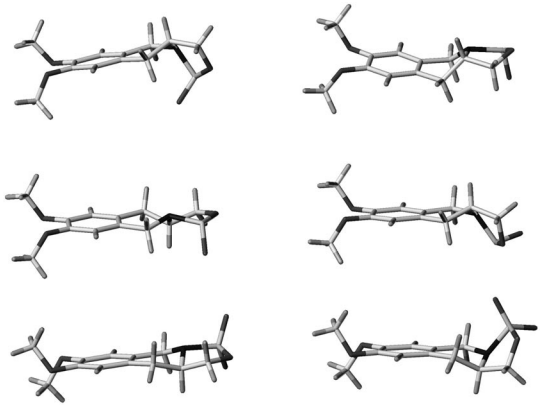


Figure 6. Calculated global (left) and local (right) energy minima for **10** (top, ΔE = 0.10 kcal mol^{-1}), **11** (middle, ΔE = 2.92 kcal mol^{-1}) and **12** (bottom, ΔE = 1.88 kcal mol^{-1}).

Table 5. Calculated and experimental characteristic vicinal coupling constants for **11** [Hz].

	Calcd. for *trans*	Calcd. for *cis*[2]	Experimental value
10_{ax}-H,10a-H	9.32	9.48	10.8
10_{eq}-H,10a-H	3.45	3.73	2.8
1_{ax}-H,10a-H	9.00	4.05	9.2
1_{eq}-H,10a-H	6.16	0.10	6.6

Quantum chemical calculations on **12** (although we were not able to isolate this compound) suggested the *trans* conformation as the most stable: 1.88 kcal mol^{-1} more stable than the energetically nearest conformer, with the *cis*[2] B/C annelation.

In comparison to similar structures, we observed the following: (i) The insertion of the sulfur or phosphorus heteroatoms caused significant changes in the preferred conformation relative to the parent 1,5,6,10b-tetrahydro-3*H*-1,3-oxazolo[4,3-*a*]isoquinoline with *cis*[1]- and 1,3,10,10a-tetrahydro-5*H*-oxazolo[3,4-*b*]isoquinoline with *trans*-connected heterorings.[14] (ii) For each diastereomeric pair of the prepared 1,3,2-oxazaphospholidine 2-oxides (**2**, **3** and **8**, **9**), the stereochemistry of the B/C ring connection was found to be dependent on the configuration of P relative to that of the carbon atom at the annelation point, which is similar to that found in the analogous 1,3,4,2-oxadiazaphosphinanes linearly fused to tetrahydroisoquinoline.[12g] (iii) The presence and the position of the annelated benzene ring did not exert any influence on the conformation of the 1,2,3-oxathiazolidine 2-oxides, as, similarly to 1,5,6,7,8,8a-hexahydro-1,2,3-oxathiazolo[4,3-*a*]pyridine 2-oxide,[9a] both iso-

lated diastereomers of regioisomeric tetrahydroisoquinoline-fused 1,2,3-oxathiazolidine 2-oxides (**5** and **11**) could be characterized by the *trans* connection of the B/C rings.

Conclusions

The first representatives of new ring systems, 1,5,6,10b-tetrahydro-1,3,2-oxazaphospholo[4,3-*a*]isoquinolines (**2**, **3**), 1,5,10,10a-tetrahydro-1,3,2-oxazaphospholo[3,4-*b*]isoquinolines (**8**, **9**), 1,5,6,10b-tetrahydro-1,2,3-oxathiazolo[4,3-*a*]-isoquinolines (**4**–**6**) and a 1,5,10,10a-tetrahydro-1,2,3-oxathiazolo[3,4-*b*]isoquinoline (**11**), were prepared by cyclization of the corresponding tetrahydroisoquinoline amino alcohols. The P- or S-epimeric diastereomers (**2** and **3**, **4** and **5**, **8** and **9**) were separated by column chromatography. The NMR spectroscopic conformational analyses on **2**–**6** and **8**–**11** revealed that they exist as conformational equilibria that are fast on the NMR timescale; both the piperidine ring and the five-membered ring moieties can interconvert. Accordingly, DFT calculations of the structures were processed. The major result of the calculations is that generally two conformers participate in the conformational equilibria. The experimental NMR spectra provided relevant information on the positions of these equilibria; in some cases, one conformer is strongly favoured, whereas in other cases the preferred conformers are present in similar amounts. In general, the theoretically calculated energy differences between the two preferred conformers proved to be in qualitative agreement with the experimental NMR results.

For compounds **10** and **12**, which were not isolated and experimentally studied, the theoretical calculations indicate the existence of conformational equilibria as well.

Experimental Section

General Procedures: Melting points were determined with a Kofler micromelting point apparatus and are not corrected. Silica gel 60 (0.063–0.200 mm) was used for column chromatography and Merck Kieselgel 60F_{254} plates for thin-layer chromatography.

NMR Measurements: The NMR spectra were recorded in $CDCl_3$ solution with Bruker Avance 500 or Avance 300 spectrometers. For the ^{1}H, ^{13}C, COSY, HMBC, HSQC and NOESY NMR spectra, TMS was applied as an internal standard; during the ^{31}P NMR measurements, 85% H_3PO_4 was used as an external standard.

Computations: Quantum chemical calculations were carried out with the ab initio program package GAUSSIAN 03 version C.02.[16] Different conformations and configurations of all studied compounds were preoptimized by using the PM3 Hamiltonian.[17] The B3LYP density functional method was selected for all calculations. The method is based on Beckes three-parameter hybrid functionals[18] and the correlation functional of Lee, Yang and Parr.[19] This method includes electron correlation effects. A moderate split valence basis set 6-31G*[20] was used because of the size of the studied compounds. Polarization functions on hydrogen atoms were not used because non-hydrogen bonds exist in this series. All optimizations were carried out without any restriction at this B3LYP/6-31G* level of theory. The selected minimum energy conformations were analyzed and the results were visualized with the modelling program Sybyl 7.0.[21] NMR chemical shifts were calculated by using the gauge-independent atomic orbital method (GIAO).[22] This method determined the magnetic shielding of the ^{1}H and ^{13}C nuclei. The differences in this magnetic shielding and the reference tetramethylsilane (TMS) are the chemical shifts. TMS GIAO calculation was performed at the same level of theory. The $^3J_{H,H}$ spin coupling constants[23] of different conformations were determined at the B3LYP/6-31G* level of theory for comparison with experimental values. These calculated spin–spin coupling constants consist of paramagnetic spin–orbit contributions, diamagnetic spin–orbit contributions, Fermi contact contributions and spin–dipolar contributions. Calculations were carried out on the SGI cluster and the Linux cluster.

X-ray Crystallographic Study: Crystallographic data were collected at 173 K with a Nonius-Kappa CCD area detector diffractometer by using graphite-monochromatized Mo-K_α radiation (λ = 0.71073 Å) as reported earlier.[24] The structure was solved by direct methods by using the SHELXS-97 program,[25] and full-matrix, least-squares refinements on F^2 were performed with the SHELXL-97 program.[25] The CH hydrogen atoms were included at fixed distances with fixed displacement parameters from their host atoms. CCDC-642279 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General Procedure for the Preparation of 3-Phenyl-Substituted 1,3,2-Oxazaphospholo[4,3-*a*]isoquinolines (2a, 3a) and 1,3,2-Oxazaphospholo[3,4-*b*]isoquinolines (8a, 9a): To an ice-water-cooled solution of amino alcohol **1** or **7** (0.67 g, 3 mmol) and triethylamine (0.61 g, 6 mmol) in anhydrous dichloromethane (50 mL) was added a solution of phenylphosphonic dichloride (0.62 g, 3.2 mmol) in anhydrous dichloromethane (10 mL) dropwise over a period of 5 min. The mixture was allowed to reach room temperature whilst stirring, and stirring was continued at room temperature for a further 24 h. The mixture was then transferred to a separatory funnel and was washed subsequently with 5% hydrochloric acid (2 × 25 mL) and with water (2 × 25 mL). The organic phase was dried (Na_2SO_4) and evaporated, and the crude product was purified by column chromatography (ethyl acetate).

2a: White solid; yield 0.16 g (16%); m.p. 178–181 °C (diisopropyl ether). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58–7.44 (m, 5 H, Ph), 6.68 (s, 1 H, 7-H), 6.47 (s, 1 H, 10-H), 4.89 (t, J = 8.1 Hz, 1 H, 10b-H), 4.70 (ddd, J = 6.6, 8.4, 20.7 Hz, 1 H, 1-H_{eq}), 4.06 (ddd, J = 0.9, 8.4, 9.9 Hz, 1 H, 1-H_{ax}), 3.87 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.70 (m, 1 H, 5-H_{ax}), 3.09 (dt, J = 5.0, 14.4 Hz, 1 H, 6-H_{ax}), 2.95 (ddd, J = 3.0, 11.7, 23.7 Hz, 1 H, 5-H_{eq}), 2.65 (d, J = 14.4 Hz, 1 H, 6-H_{eq}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.5 (C-9), 148.2 (C-8), 132.4, 132.1, 131.9, 129.3, 128.7, 127.0 (C-10a), 124.5 (C-6a), 112.5 (C-7), 108.1 (C-10), 71.5 (C-1), 56.6 (C-10b), 56.2, 56.0 (2 × OCH_3), 38.4 (C-5), 29.8 (C-6) ppm. $C_{18}H_{20}NO_4P$ (345.33): calcd. C 62.60, H 5.84, N 4.06, O 18.53, P 8.97; found C 62.73, H 5.79, N 4.13.

3a: White solid; yield 0.13 g (13%); m.p. 138–140 °C (diisopropyl ether). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82–7.40 (m, 5 H, Ph), 6.64 (s, 1 H, 7-H), 6.45 (s, 1 H, 10-H), 5.01 (t, J = 5.0 Hz, 1 H, 10b-H), 4.99 (dt, J = 6.4, 12.4 Hz, 1 H, 1-H_{ax}), 4.09 (dddd, J = 1.8, 5.7, 6.3, 15.2 Hz, 1 H, 1-H_{eq}), 3.85 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.47 (dddd, J = 1.2, 6.3, 7.4, 13.4 Hz, 1 H, 5-H_{eq}), 3.23 (ddt, J = 4.2, 9.0, 12.0 Hz, 1 H, 5-H_{ax}), 2.73 (ddd, J = 6.3, 11.4, 16.2 Hz, 1 H, 6-H_{ax}), 2.55 (dt, J = 2.7, 15.9 Hz, 1 H, 6-H_{eq}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.6, 148.3, 133.0, 132.9, 132.8,

128.8, 128.6, 128.3, 126.0, 125.9, 112.5 (C-7), 107.4 (C-10), 73.4 (C-1), 56.3, 56.1 (2×OCH_3), 54.4 (C-10b), 37.8 (C-5), 28.1 (C-6) ppm. $C_{18}H_{20}NO_4P$ (345.33): calcd. C 62.60, H 5.84, N 4.06, O 18.53, P 8.97; found C 62.63, H 5.91, N 4.02.

8a: White solid; yield 0.06 g (6%); m.p. 179–183 °C (diisopropyl ether). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86–7.39 (m, 5 H, Ph), 6.63 (s, 1 H, 9-H), 6.51 (s, 1 H, 6-H), 4.82 (ddd, J = 6.3, 8.7, 11.7 Hz, 1 H, 1-H_{eq}), 4.38 (dd, J = 2.7, 15.6 Hz, 1 H, 5-H), 4.11 (dd, J = 3.0, 15.3 Hz, 1 H, 5-H), 4.08 (ddd, J = 5.4, 8.0, 8.7 Hz, 1 H, 1-H_{ax}), 3.95 (ddddd, J = 2.4, 4.2, 6.3, 8.0, 10.4 Hz, 1 H, 10a-H), 3.86 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 2.90 (td, J = 2.4, 15.0 Hz, 1 H, 10-H_{eq}), 2.79 (dd, J = 10.5, 15.0 Hz, 1 H, 10-H_{ax}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.2 (C-8), 148.1 (C-7), 132.8, 132.7, 132.6, 128.8, 128.6, 127.8, 124.6 (C-9a), 123.7 (C-5a), 112.1 (C-9), 109.3 (C-6), 72.5 (C-1), 56.2, 56.1 (2×OCH_3), 52.9 (C-10a), 42.8 (C-5), 33.8 (C-10) ppm. $C_{18}H_{20}NO_4P$ (345.33): calcd. C 62.60, H 5.84, N 4.06, O 18.53, P 8.97; found C 62.68, H 5.80, N 4.11.

9a: White solid; yield 0.24 g (24%); m.p. 141–143 °C (diisopropyl ether). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82–7.46 (m, 5 H, Ph), 6.61 (s, 1 H, 9-H), 6.49 (s, 1 H, 6-H), 4.62 (ddd, J = 6.4, 8.9, 13.8 Hz, 1 H, 1-H_{eq}), 4.35 (dd, J = 4.7, 15.3 Hz, 1 H, 5-H_{eq}), 4.30 (ddd, J = 5.0, 7.0, 8.9 Hz, 1 H, 1-H_{ax}), 3.89 (dd, J = 6.1, 14.9 Hz, 1 H, 5-H_{ax}), 3.85 (s, 3 H, OCH_3), 3.82 (m, 1 H, 10a-H), 3.79 (s, 3 H, OCH_3), 2.94 (dd, J = 10.3, 15.0 Hz, 1 H, 10-H_{ax}), 2.84 (dd, J = 4.2, 15.0 Hz, 1 H, 10-H_{eq}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.2, 148.0, 132.6, 132.4, 132.2, 128.9, 128.7, 128.2, 124.3, 124.1, 112.1 (C-6), 109.1 (C-9), 71.5 (C-1), 56.2, 56.1 (2×OCH_3), 54.0 (C-10a), 42.6 (C-5), 33.2 (C-10) ppm. $C_{18}H_{20}NO_4P$ (345.33): calcd. C 62.60, H 5.84, N 4.06, O 18.53, P 8.97; found C 62.76, H 5.71, N 3.99.

General Procedure for the Preparation of 3-[Bis(2-chloroethyl)-amino]-Substituted 1,3,2-Oxazaphospholo[4,3-*a*]isoquinolines (2b, 3b) and 1,3,2-Oxazaphospholo[3,4-*b*]isoquinolines (8b, 9b): To a stirred solution of bis(2-chloroethyl)phosphoramidic dichloride (0.83 g, 3.2 mmol) in anhydrous dichloromethane (20 mL) was added a solution of amino alcohol **1** or **7** (0.67 g, 3 mmol) and triethylamine (0.61 g, 6 mmol) in anhydrous dichloromethane (20 mL) dropwise at room temperature over a period of 10 min. The mixture was stirred at room temperature for 48 h, and the crystalline salts were then filtered off. The filtrate was evaporated, and the crude product was purified by column chromatography (ethyl acetate).

2b: White solid; yield 0.32 g (26%); m.p. 114–116 °C (diisopropyl ether) ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.66 (s, 1 H, 9-H), 6.40 (s, 1 H, 6-H), 4.80 (ddd, J = 2.5, 6.9, 9.4 Hz, 1 H, 10b-H), 4.60 (ddd, J = 6.8, 8.6, 22.5 Hz, 1 H, 1-H_{eq}), 3.89 (dd, J = 8.9, 9.5 Hz, 1 H, 1-H_{ax}), 3.86 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 3.65 (t, J = 6.8 Hz, 4 H, 2×CH_2Cl), 3.61 (m, 1 H, 5-H_{eq}), 3.48 (m, 2 H, CH_2N), 3.40 (m, 2 H, CH_2N), 3.02 (ddd, J = 4.6, 12.6, 14.0 Hz, 1 H, 6-H_{ax}), 2.96 (ddt, J = 2.2, 11.5, 13.3 Hz, 1 H, 5-H_{ax}), 2.62 (d, J = 13.2 Hz, 1 H, 6-H_{eq}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.3 (C-9), 148.2 (C-8), 126.8 (C-10a), 125.0 (C-6a), 112.4 (C-7), 107.6 (C-10), 70.9 (C-1), 56.2, 56.0 (2×OCH_3), 55.9 (C-10b), 49.6, 49.6 (2×CH_2N), 42.5, 42.5 (2×CH_2Cl), 38.4 (C-5), 29.4 (C-6) ppm. $C_{16}H_{23}Cl_2N_2O_4P$ (409.24): calcd. C 49.96, H 5.66, Cl 17.33, N 6.85, O 15.64, P 7.57; found C 9.89, H 5.70, N 6.88.

3b: White solid; yield 0.13 g (11%); m.p. 112–115 °C (diisopropyl ether). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.67 (s, 1 H, 7-H), 6.36 (s, 1 H, 10-H), 4.79 (m, 1 H, 1-H_{eq}), 4.77 (m, 1 H, 10b-H), 3.87 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.81 (m, 1 H, 1-H_{ax}), 3.67 (td, J = 7.0, 11.0 Hz, 2 H, CH_2Cl), 3.62 (ddd, J = 5.4, 7.0 Hz, 11.0, 2 H, CH_2Cl), 3.65 (m, 1 H, 5-H_{eq}), 3.53 (dddd, J = 5.5, 7.1, 10.0, 15.0 Hz, 2 H, CH_2N), 3.37 (ddd, J = 7.0, 14.8, 21.9 Hz, 2 H, CH_2N), 3.13 (ddt, J = 2.3, 3.9, 12.3 Hz, 1 H, 5-H_{ax}), 2.93 (ddd, J = 6.5, 11.9, 15.9 Hz, 1 H, 6-H_{ax}), 2.70 (td, J = 3.5, 15.9 Hz, 1 H, 6-H_{eq}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.5 (C-9), 148.2 (C-8), 125.7 (C-10a), 125.5 (C-6a), 112.4 (C-7), 106.9 (C-10), 71.6 (C-1), 56.2, 56.0 (2×OCH_3), 54.1 (C-10b), 49.2, 49.2 (2×CH_2N), 42.7, 42.7 (2×CH_2Cl), 38.0 (C-5), 28.5 (C-6) ppm. $C_{16}H_{23}Cl_2N_2O_4P$ (409.24): calcd. C 49.96, H 5.66, Cl 17.33, N 6.85, O 15.64, P 7.57; found C 50.03, H 5.71, N 6.79.

8b: White solid; yield 0.19 g (15%); m.p. 159–162 °C (diisopropyl ether). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.58 (s, 1 H, 9-H), 6.57 (s, 1 H, 6-H), 4.62 (ddd, J = 6.9, 8.5, 11.4 Hz, 1 H, 1-H_{ax}), 4.24 (d, J = 15.3 Hz, 1 H, 5-H), 4.18 (dd, J = 2.2, 15.3 Hz, 1 H, 5-H), 3.90 (ddd, J = 2.4, 8.6, 17.0 Hz, 1 H, 1-H_{eq}), 3.83 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.78 (m, 1 H, 10a-H), 3.59 (m, 4 H, 2×CH_2Cl), 3.48 (m, 2 H, CH_2N), 3.34 (m, 2 H, CH_2N), 2.84 (td, J = 3.3, 15.3 Hz, 1 H, 10-H_{eq}), 2.68 (dd, J = 10.8, 15.1 Hz, 1 H, 10-H_{ax}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.2, 148.1, 124.2, 123.4, 112.0 (C-9), 109.2 (C-6), 71.0 (C-1), 56.1, 56.1 (2×OCH_3), 52.2 (C-10a), 49.6, 49.4 (2×CH_2N), 42.8 (C-5), 42.6, 41.9 (2×CH_2Cl), 33.9 (C-10) ppm. $C_{16}H_{23}Cl_2N_2O_4P$ (409.24): calcd. C 49.96, H 5.66, Cl 17.33, N 6.85, O 15.64, P 7.57; found C 50.05, H 5.58, N 6.92.

9b: White solid; yield 0.27 g (22%); m.p. 74–78 °C (diisopropyl ether). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.59 (s, 2 H, 6-H and 9-H), 4.46 (ddd, J = 6.5, 9.0, 11.6 Hz, 1 H, 1-H_{eq}), 4.37 (dd, J = 6.7, 15.6 Hz, 1 H, 5-H_{eq}), 4.16 (dd, J = 8.3, 15.5 Hz, 1 H, 5-H_{ax}), 4.14 (ddd, J = 5.2, 7.2, 9.0 Hz, 1 H, 1-H_{ax}), 3.85 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.74 (m, 1 H, 10a-H), 3.65 (ddd, J = 7.2, 10.8, 18.9 Hz, 4 H, 2×CH_2Cl), 3.48 (dddd, J = 5.5, 7.3, 10.7, 15.0 Hz, 2 H, CH_2N), 3.38 (m, 2 H, CH_2N), 2.87 (dd, J = 10.9, 15.0 Hz, 1 H, 10-H_{ax}), 2.75 (dd, J = 3.7, 15.2 Hz, 1 H, 10-H_{eq}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.1 (C-7), 147.9 (C-8), 124.3 (C-5a), 124.2 (C-9a), 112.0 (C-9), 109.0 (C-6), 70.2 (C-1), 56.1, 56.1 (2×OCH_3), 53.2 (C-10a), 49.4, 49.4, (2×CH_2N), 42.6 (C-5), 42.3, 42.2 (2×CH_2Cl), 33.5 (C-10) ppm. $C_{16}H_{23}Cl_2N_2O_4P$ (409.24): calcd. C 49.96, H 5.66, Cl 17.33, N 6.85, O 15.64, P 7.57; found C 49.83, H 5.78, N 6.91.

General Procedure for the Preparation of 1,2,3-Oxathiazolo[4,3-*a*]-isoquinolines (4–6) and 1,2,3-Oxathiazolo[3,4-*b*]isoquinoline (11): To an ice–salt-bath-cooled solution of amino alcohol **1** or **7** (0.67 g, 3 mmol) and triethylamine (0.61 g, 6 mmol) in anhydrous dichloromethane (20 mL) was added a solution of thionyl chloride (0.40 g, 3.4 mmol) or sulfuryl chloride (0.45 g, 3.3 mmol) in anhydrous dichloromethane (20 mL) dropwise over a period of 10 min. The mixture was stirred under ice–salt-bath cooling for 3 h and then warmed to room temperature whilst stirring. Stirring was continued at room temperature for a further 48 h. The mixture was then transferred to a separatory funnel and was washed subsequently with a saturated aqueous solution of $NaHCO_3$ (2×10 mL) and then with water (2×10 mL). The organic phase was dried (Na_2SO_4) and evaporated, and the crude product was purified by column chromatography (ethyl acetate). Compound **12** decomposed during the chromatographic purification.

4: Rose crystals; yield 0.06 g (7%); m.p. 187–191 °C (diisopropyl ether). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.65 (s, 1 H, 7-H), 6.48 (s, 1 H, 10-H), 4.79 (t, J = 7.0 Hz, 1 H, 1-H_{eq}), 4.75 (t, J = 8.2 Hz, 1 H, 10b-H), 4.34 (dd, J = 7.0, 8.5 Hz, 1 H, 1-H_{ax}), 3.86 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.78 (ddd, J = 2.5, 5.5, 14.1 Hz, 1 H, 5-H_{eq}), 3.23 (ddd, J = 3.5, 11.0, 14.1 Hz, 1 H, 5-H_{ax}), 3.00 (ddd, J = 5.0, 11.6, 15.6 Hz, 1 H, 6-H_{ax}), 2.66 (td, J = 2.5, 15.6 Hz, 1 H, 6-H_{eq}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.9, 148.4 (C-8

and C-9), 124.8 (C-10a), 120.8 (C-6a), 111.6 (C-7), 109.4 (C-10), 62.3 (C-1), 56.5 (C-10b), 56.3, 56.0 (2×OCH_3), 38.7 (C-5), 25.3 (C-6) ppm. $C_{12}H_{15}NO_4S$ (269.32): calcd. C 53.52, H 5.61, N 5.20, O 23.76, S 11.91; found C 53.39, H 5.52, N 5.27, S 12.02.

5: White solid; yield 0.13 g (17%); m.p. 120–123 °C (diisopropyl ether).^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.65 (s, 1 H, 7-H), 6.50 (s, 1 H, 10-H), 5.04 (dd, J = 6.5, 10.0 Hz, 2 H, 10b-H and 1-H_{eq}), 4.12 (dd, J = 10.1, 11.1 Hz, 1 H, 1-H_{ax}), 3.86 (s, 6 H, 2×OCH_3), 3.43 (td, J = 5.3, 12.0 Hz, 1 H, 5-H_{eq}), 3.27 (ddd, J = 5.4, 8.0, 12.0 Hz, 1 H, 5-H_{ax}), 2.95 (ddd, J = 5.0, 8.0, 16.0 Hz, 1 H, 6-H_{ax}), 2.90 (dd, J = 5.0, 16.0 Hz, 1 H, 6-H_{eq}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.7 (C-9), 148.3 (C-8), 126.0 (C-10a), 123.5 (C-6a), 111.9 (C-7), 109.2 (C-10), 76.0 (C-1), 57.1 (C-10b), 56.3, 56.1 (2×OCH_3), 40.1 (C-5), 28.7 (C-6) ppm. $C_{12}H_{15}NO_4S$ (269.32): calcd. C 53.52, H 5.61, N 5.20, O 23.76, S 11.91; found C 53.61, H 5.69, N 5.13, S 11.83.

6: White solid; yield 0.09 g (11%); m.p. 124–127 °C (diisopropyl ether).^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.69 (s, 1 H, 7-H), 6.48 (s, 1 H, 10-H), 5.07 (dd, J = 6.7, 9.6 Hz, 1 H, 10b-H), 4.84 (dd, J = 6.7, 8.0 Hz, 1 H, 1-H_{eq}), 4.20 (dd, J = 8.0, 9.6 Hz, 1 H, 1-H_{ax}), 3.87 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.49 (ddd, J = 4.9, 6.8, 12.1 Hz, 1 H, 5-H_{ax}), 3.43 (ddd, J = 4.8, 6.2, 12.3 Hz, 1 H, 5-H_{eq}), 2.96 (td, J = 5.6, 16.5 Hz, 1 H, 6-H_{eq}), 2.89 (td, J = 5.8, 16.9 Hz, 1 H, 6-H_{ax}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.1 (C-9), 148.6 (C-8), 125.8 (C-6a), 122.0 (C-10a), 112.1 (C-7), 108.2 (C-10), 73.8 (C-1), 56.5 (C-10b), 56.3, 56.1 (2×OCH_3), 42.2 (C-5), 27.8 (C-6) ppm. $C_{12}H_{15}NO_5S$ (285.32): calcd. C 50.52, H 5.30, N 4.91, O 28.04, S 11.24; found C 50.46, H 5.39, N 4.88, S 11.29.

11: White crystalline substance; yield 0.34 g (42%); m.p. 133–136 °C (diisopropyl ether).^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.61 (s, 2 H, 9-H and 6-H), 4.99 (dd, J = 6.6, 7.7 Hz, 1 H, 1-H_{eq}), 4.28 (d, J = 14.2 Hz, 1 H, 5-H_{ax}), 4.17 (d, J = 14.2 Hz, 1 H, 5-H_{eq}), 4.07 (dd, J = 7.8, 9.2 Hz, 1 H, 1-H_{ax}), 3.85 (s, 6 H, 2×OCH_3), 3.83 (overlapping m, 1 H, 10a-H), 3.03 (dd, J = 3.8, 15.4 Hz, 1 H, 10-H_{eq}), 2.75 (dd, J = 10.8, 15.2 Hz, 1 H, 10-H_{ax}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.3, 148.2 (C-7 and C-8), 124.0, 123.6, 111.8 (C-9), 109.6 (C-6), 77.4 (C-1), 56.2, 56.1 (2×OCH_3), 53.6 (C-10a), 44.6 (C-5), 32.1 (C-10) ppm. $C_{12}H_{15}NO_4S$ (269.32): calcd. C 53.52, H 5.61, N 5.20, O 23.76, S 11.91; found C 53.60, H 5.43, N 5.15, S 11.84.

Acknowledgments

I. Sch. is grateful for a grant from the German Academic Exchange Service (DAAD). The authors thank the Hungarian Scientific Research Foundation (grant no. OTKA T 049407) for financial support.

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Received: October 30, 2007
Published Online: January 17, 2008

