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Diastereoselective synthesis of 1,2,3,6-tetrahydrophosphinine 1-oxides with an exocyclic P-function by a Michael type addition

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Abstract—The anions generated from diphenylphosphine oxide or dialkyl phosphites add easily at the α,β-double-bond of 1,2-dihydrophosphinine oxides **1** to afford a single diastereomer of 3-substituted tetrahydrophosphinine oxides **2**–**4** existing in a twist-boat conformation.

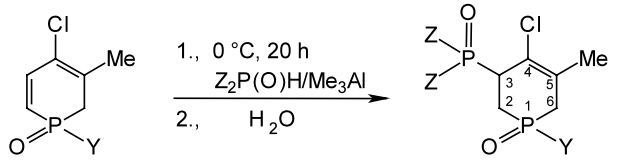
1,2-Dihydrophosphinine oxides are versatile intermediates in the synthesis of other *P*-heterocycles[1,2] and they can be obtained most simply by the ring enlargement of 2,5-dihydro-1*H*-phosphole oxides.[3]

To prepare tetrahydrophosphinine oxides with an exocyclic P=O moiety, we wished to add a variety of >P(O)H compounds to the electron-poor, 5,6-double-bond of 1,2-dihydrophosphinine oxides via a Michael type addition. To activate the diphenylphosphine oxide and the dialkyl phosphites selected as the reagents, they were first reacted with trimethylaluminium at 0°C in chloroform.

Then, the >P(O)$^-$ anion so formed reacted easily with the α,β-double-bond of the dihydrophosphinine oxide **1**[4,5] added to the reaction mixture at 0°C to furnish the corresponding product. The use of $Ph_2P(O)H$ led to 3-diphenylphosphinoxido-1,2,3,6-tetrahydrophosphinine oxide **2**, while that of dimethyl- and diethyl phosphite gave 3-phosphonato derivatives **3** and **4**, respectively (Scheme 1).[6]

One advantage of the above procedure is that only one of the possible diastereomers of products **2**–**4** was formed.

Column chromatography afforded products **2a**, **3a**,**b** and **4a**,**b** in 40–72% yields, whose structures were identified and characterised by ^{31}P, ^{13}C and ^1H NMR, as well as HR-FAB mass spectroscopy. The ^{31}P NMR spectra of the 3-P(O)Z_2-tetrahydrophosphinine oxides **2**–**4** revealed a doublet of doublets with a $^3J_{PP}$ of 13.8–20.1 Hz due to the presence of the two phosphorus atoms. In the ^{13}C NMR spectra, the C-3 and C-5 skeletal carbon atoms were, in each case, split by both



	Y
1a	Ph
1b	EtO

Z = Ph, MeO, EtO

	Y	Z
2a	Ph	Ph
3a	Ph	MeO
4a	Ph	EtO
3b	EtO	MeO
4b	EtO	EtO

Scheme 1.

Keywords: phosphorus heterocycles; Michael reactions; stereoselection; conformation.

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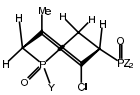
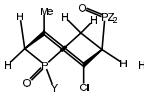
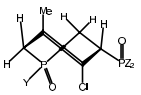
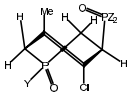
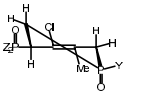
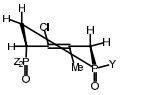
Table 1. Relative energies for the conformers of *cis* and *trans* diastereomers of tetrahydrophosphinine oxides **3b** and **2a** calculated by the B3LYP/6-31+G*//B3LYP/3-21G* method

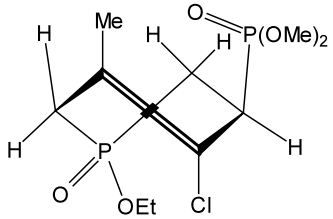
			 twist-boat$_1$	 twist-boat$_2$	 twist-boat$_3$	 twist-boat$_4$	 half-chair$_1$	 half-chair$_2$	 half-chair$_3$	 half-chair$_4$
Compound	Y	Z	Energy [kcal/mol]							
3b	EtO	MeO	3.7	0	8.6	2.7	3.8	4.7	3.7	3.1
2a	Ph	Ph	8.9	3.3	9.0	0	7.6	10.8	9.1	#

[#]was not found to be a minimum on the potential energy surface

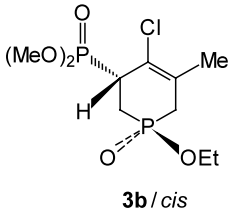
phosphorus atoms. The end of the conjugated double-bonds was unreactive due to steric hindrance caused by the skeletal methyl group.

Inspection of Dreiding models suggests that the products **2–4** can exist both in a *half-chair* and in a *twist-boat* conformation. Quantum chemical calculations have been carried out to evaluate which of the conformers of the *cis* and *trans* diastereoisomers is preferred.[7,8] The relative energies obtained for eight possible conformers of *cis* and *trans* diastereoisomers of the tetrahydrophosphinine oxides **3b** and **2a** at the B3LYP/6-31+G*//B3LYP/3-21G* level of theory are listed in Table 1.

It can be seen that in the case of **3b**, the *twist-boat* containing the double-bonded oxygen atom of the P_1=O group in the equatorial position and the $P(O)(OMe)_2$ moiety in the axial position is the preferred structure, that is, a *cis* diastereomer (**3b**/*twist-boat*$_2$, Table 1, Fig. 1). Hence, the equilibrium must be shifted toward this conformer (**3b**/*twist-boat*$_2$). Intramolecular interaction between the double-bonded oxygen atom of the $(MeO)_2P$=O moiety and the corresponding hydrogen atom of the PCH_2 unit may stabilise the boat conformer (**3b**/*twist-boat*$_2$) under discussion. The *half-chair* conformers (**3b**/*half-chair*$_1$, *half-chair*$_2$, *half-chair*$_3$ and *half-chair*$_4$) together with the three remaining *twist-boat* conformers (**3b**/*twist-boat*$_1$, *twist-boat*$_3$ *and twist-boat*$_4$) are unfavourable. Tetrahydrophosphinine oxide **4b** was assigned the *cis* structure by analogy.



3b / *twist-boat*$_2$



3b / *cis*

A similar conformational situation was found for tetrahydrophosphinine oxide **2a**. In this case, not the *twist-boat*$_2$, but the *twist-boat*$_4$ conformer containing the sterically demanding P_1-phenyl substituent in the equatorial position and the double-bonded oxygen atom of the P_1=O group in the axial position was found to be the most stable form (**2a**/*twist-boat*$_4$, Table 1, Fig. 2)

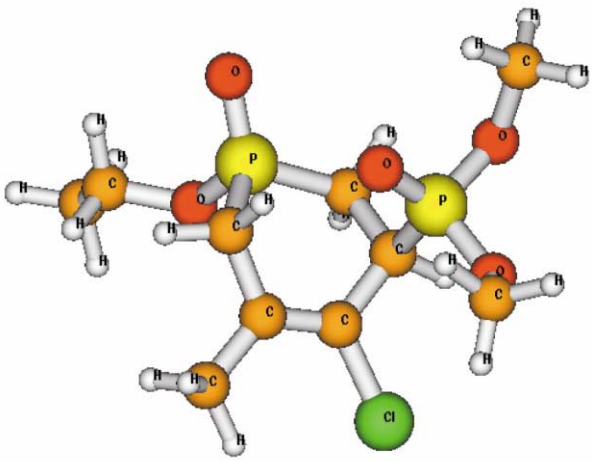
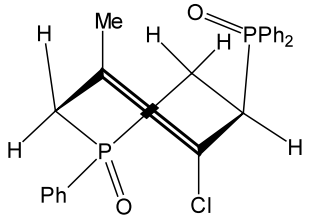
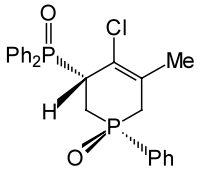


Figure 1. Stereostructure of the stable *twist-boat*$_2$ conformer of tetrahydrophosphinine oxide **3b** obtained at the B3LYP/6-31+G*//3-21G* level of theory P_1–C_2: 1.825 Å, C_2–C_3: 1.561 Å, C_3–C_4: 1.523 Å, C_4–C_5: 1.340 Å, C_5–C_6: 1.527 Å, C_6–P_1: 1.822 Å, O–P_1–C_2: 118.3°, O–P_1–C_6: 115.4°, O–P–O: 114.7°, C_2–P_1–C_6: 103.6°, P_1–C_2–C_3–P: −78.2°, P_1–C_2–C_3–C_4: 46.7°, P_1–C_6–C_5–CH_3: −131.7°, P_1–C_6–C_5–C_4: 49.8°, C_6–C_5–C_4–C_3: −5.1°, C_6–P_1–C_2–C_3: −6.5°.

that is, in this instance, the *trans* diastereomer. The bulky $Ph_2P(O)$ moiety is in the axial position. The stabilising interaction between the oxygen atom of the $Ph_2P(O)$ moiety and a hydrogen atom of the PCH_2 unit seems to be again the decisive factor. Tetrahydrophosphinine oxides **3a** and **4a** were assigned the *trans* structure again by analogy.



2a / *twist-boat*$_4$



2a / *trans*

The diastereoselectivity of the Michael type addition is connected with the preference for the *twist-boat* conformer with the axial $P(O)Y_2$ substituent providing the possibility of intramolecular stabilisation. For com-

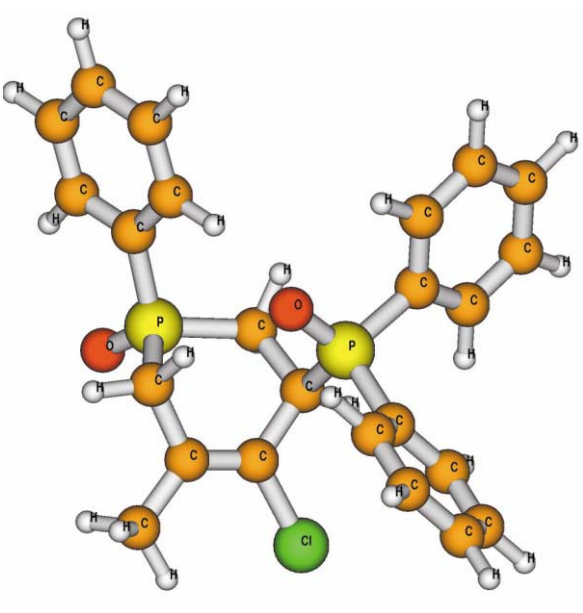


Figure 2. Stereostructure of the stable *twist-boat*$_4$ conformer of tetrahydrophosphinine oxide **2a** obtained at the B3LYP/6-31+G*//3-21G* level of theory P_1–C_2: 1.849 Å, C_2–C_3: 1.575 Å, C_3–C_4: 1.523 Å, C_4–C_5: 1.340 Å, C_5–C_6: 1.527 Å, C_6–P_1: 1.829 Å, O–P_1–C_2: 114.2°, O–P_1–C_6: 116.2°, O–P–C_1: 111.7°, C_2–P_1–C_6: 100.8°, P_1–C_2–C_3–P: −93.9°, P_1–C_2–C_3–C_4: 32.1°, P_1–C_6–C_5–CH_3: −121.23°, P_1–C_6–C_5–C_4: 55.5°, C_6–C_5–C_4–C_3: −1.7°, C_6–P_1–C_2–C_3: 13.6°.

pounds **3b** and **2a**, the distances between the oxygen atom of the $P(O)Y_2$ moiety and the hydrogen atom of the PCH unit are 2.098 and 2.149 Å, respectively, justifying a hydrogen-bonding interaction between the oxygen atom and the proton involved. Although H-bonding between a double-bonded oxygen atom and a saturated C-H hydrogen atom is not unknown, examples are rather rare.

It is noted that the Michael additions studied are not reversible under the conditions applied. Hence, we had to assume that the stability of the tetrahydrophosphinine oxides (**2–4**) controls the stereoselectivity according to the Hammond's principle.[9] This means that the rate of the addition is related to the stability of the products (**2–4**).

For other 1,2,3,6-tetrahydrophosphinine oxides lacking a bulky substituent in position 3, an equilibrium involving *half-chair* conformers was found.[10] It is clear that the conformational equilibrium of the tetrahydrophosphinine oxides is highly sensitive to substituent effects.

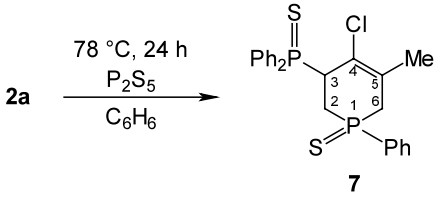
The new heterocycles with the exocyclic P-function are of interest as, from another point of view, they are bisphosphine oxides **2a**, phosphinoxido-phosphonates **3a** and **4a** and phosphinato-phosphonates **3b** and **4b** and as such, are of potential biological activity.

On the other hand, bisphosphinoxide **2a** is a precursor of the corresponding bisphosphine. The double deoxygenation was carried out by a standard procedure,[11] using 2 equiv. of trichlorosilane in the presence of a sixfold quantity of pyridine, in boiling benzene to afford bisphosphine **5** (Scheme 2) the structure of which was supported by ^{31}P NMR chemical shifts and FAB-MS. To protect the highly sensitive bisphosphine **5**, it was converted by reaction with 2 equiv. of borane to bisphosphine-borane **6** (Scheme 2).

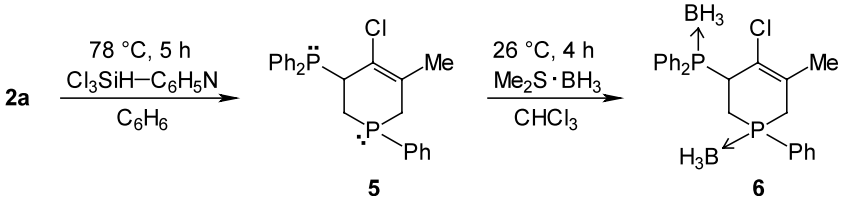
Borane complex **6** was characterised by ^{31}P and ^{11}B NMR, as well as FAB-MS. The phosphine-boranes can be regarded as precursors of the corresponding phosphines, as these latter species are regenerated by reaction of the complexes with secondary amines.[12] Bis(borane-complex) **6** did indeed give bisphosphine **5** by reaction with diethylamine.

Finally, phosphinoxido-tetrahydrophosphinine oxide **2a** was reacted with phosphorus pentasulfide to prepare disulfide **7** identified by ^{31}P and ^{13}C NMR, as well as HRFAB-MS (Scheme 3).

In summary, a useful method for forming a series of 1,2,3,6-tetrahydrophosphinine oxides with an exocyclic P-function **2–4** was developed. In addition, the simple procedure together with the diastereoselectivity makes the above synthesis a practical method.



Scheme 3.



Scheme 2.

Acknowledgements

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6. *General procedure*: To 2.47 mmol of the dialkyl phosphite or diphenylphosphine oxide in 15 ml of dry chloroform was added 1.24 ml (2.47 mmol) of 2 M trimethylaluminium in hexane at 0°C. After a period of 20 min stirring, 2.47 mmol of the corresponding dihydrophosphinine oxide (**1a** or **1b**) in 5 ml of chloroform was added dropwise. After complete addition, the cooling bath was removed and the contents of the flask were stirred for 20 h. Then, the mixture was hydrolysed by the addition of 2.4 ml of conc. hydrochloric acid in 22 ml of water. After filtration, the organic phase was separated and dried (Na_2SO_4). The crude product obtained after filtration and evaporation was purified by column chromatography (silica gel, 3% methanol in chloroform) to afford compound **2a** (from **1a** and $Ph_2P(O)H$), products **3a**,**b** and **4a**,**b** (from **1a**,**b** and $(MeO)_2P(O)H$ or $(EtO)_2P(O)H$, respectively). The following products were thus synthesized:
   Compound **2a**: Yield: 72%; δ_{P_1} 34.0, δ_{P_2} 34.8 ($^3J_{PP}$= 13.8); δ_C 23.6 (^1J=6.0, ^2J=1.71, C_5-CH_3), 25.3 (^1J= 71.8, C_2), 34.8 (^1J=61.0, C_6), 45.0 (^1J=5.2, ^2J=65.5, C_3), 122.7 (^1J=8.0, ^2J=16.7, C_5), 128.2 (^2J=12.0, $C_{3''}$),[a] 128.5 (^2J=11.8, $C_{3''}$),[a] 128.9 (^1J=11.3, $C_{3'}$),[a] 129.7 (^1J=8.9, $C_{2'}$),[a] 130.1 (^1J=3.6, C_4), 131.1 (^2J=63.2, $C_{1''}$), 131.1 (^2J=8.8, $C_{2''}$),[a] 131.4 (^2J=9.4, $C_{2''}$),[a] 131.7 (^1J=2.0, $C_{4'}$),[b] 132.0 ($C_{4''}$),[b] 132.1 (^2J=2.0, $C_{4''}$),[b] 133.7 (^1J=99.2, $C_{1'}$),[a,b] tentative assignment; δ_H 1.77 (J=4.4, 3H, C_5-CH_3), 7.42–7.94 (m, 15H, Ar); $(M+H)^+_{found}$=441.0873, $C_{24}H_{24}ClO_2P_2$ requires 441.0940 for the ^{35}Cl isotope.
   Compound **3a**: Yield: 40%; δ_{P_1} 32.2, δ_{P_2} 27.9 ($^3J_{PP}$= 18.4); $(M+H)^+_{found}$=349.0582, $C_{14}H_{20}ClO_4P_2$ requires 349.0525 for the ^{35}Cl isotope.
   Compound **4a**: Yield: 46%; δ_{P_1} 32.7, δ_{P_2} 25.5 ($^3J_{PP}$= 17.9); $(M+H)^+_{found}$=377.0781, $C_{16}H_{24}ClO_4P_2$ requires 377.0838 for the ^{35}Cl isotope.
   Compound **3b**: Yield: 54%; δ_{P_1} 50.1, δ_{P_2} 28.0 ($^3J_{PP}$= 20.1); δ_C 16.3 (^1J=5.9, CH_2CH_3), 23.5 (^1J=9.5, C_5-CH_3), 24.0 (^1J=97.5, ^2J=4.5, C_2), 31.6 (^1J=85.6, C_6), 41.1 (^1J=4.8, ^2J=144.3, C_3), 53.0 (^2J=6.8, MeO), 53.4 (^2J=6.9, MeO), 60.3 (^1J=6.1, CH_2O), 120.9 (^1J=10.3, ^2J=16.5, C_5), 130.0 (^1J=10.5, ^2J=7.5, C_4); δ_H 1.26 (t, J=7.0, 3H, CH_2CH_3), 1.91 (d, J=5.5, 3H, C_5-CH_3), 3.75 (J=7.7, 3H, CH_3O), 3.78 (J=8.0, 3H, CH_3O); $(M+H)^+_{found}$=317.0429, $C_{10}H_{20}ClO_5P_2$ requires 317.0475 for the ^{35}Cl isotope.
   Compound **4b**: Yield: 48%; δ_{P_1} 50.8, δ_{P_2} 25.4 ($^3J_{PP}$= 19.2); $(M+H)^+_{found}$=345.0730, $C_{12}H_{24}ClO_5P_2$ requires 345.0788 for the ^{35}Cl isotope.
   Compound **2a** served as starting material for other derivatives:
   Compound **5**: Yield: 96%; δ_{P_1} 34.8, δ_{P_2} −35.6; $(M+H)^+$= 409.
   Compound **6**: Yield: ~100%; δ_{P_1} 34.9, δ_{P_2} 11.2; δ_B 1.6 and −35.1; $(M+H)^+$=437.
   Compound **7**: Yield: 84%; δ_{P_1} 31.6, δ_{P_2} 55.7 ($^3J_{PP}$=27.1); δ_H 2.04 (J=4.6, 3H, C_5-CH_3), 7.42–8.08 (m, 15H, Ar); M^+_{found}=472.0286, $C_{24}H_{23}ClP_2S_2$ requires: 472.0405.
   All NMR spectra were obtained in $CDCl_3$ solution.
7. Quantum chemical calculations were carried out using the Gaussian98 program package. Geometries of the different conformers of **2a** and **3b** were optimised at the B3LYP/3-21G* level of theory. Relative energies were calculated with B3LYP/6-31+G* single point calculations. In the case of **3b**, further refinement of the geometries at this level of theory did not change the relative energies of the different conformers significantly.
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