# Synthesis and structure of stereoisomers of 3,4-benzo-5,10-diphenyl-1,3-diaza-7-oxa-6-phosphabicyclo[4.3.1]decane-2,6-dione

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**A mild approach to the synthesis of the title cage aminophosphonate has been developed based on the intramolecular cyclization of 2-(2-benzylideneaminoethoxy)-1-phenylbenzo-[e]-1,3,2-azaoxaphosphorin-4-one obtained from 1-phenyl-2-chlorobenzo[e]-1,3,2-azaoxaphosphorin-4-one and (2-benzylideneaminoethoxy)trimethylsilane. The structure of isolated diastereomers of the product was determined by NMR spectroscopy and single crystal X-ray diffraction analysis.**

two diastereomers (1 : 1)
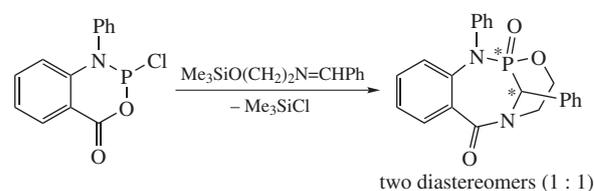
α-Aminophosphonic acids have useful properties such as biological activity[1] and capability to form complexes with several metals.[2] The Kabachnik–Fields and Pudovik reactions[3] provide versatile and popular approach to the synthesis of these compounds. Previously, we suggested to obtain 1-aminophosphonic acid esters by ring expansion reaction of 2-substituted benzo[e]-1,2,3-dioxaphosphorin-4-ones, containing the P–O–C(O) high-energy moiety, with imines. This approach resulted in only one of the two possible diastereomers of 3,4-dihydrobenzo[f]-1,4,2-oxazaphosphepine-2,5-diones with high selectivity.[4] The intramolecular version of this reaction carried out with 2-(2-aryl-methylideneaminophenoxy)benzo[e]-1,3,2-dioxaphosphorin-4-ones, containing a C=N exocyclic bond, allowed us to obtain cage α-aminophosphonates with high stereoselectivity.[5]

In this study, we successfully implemented a new modification of this intramolecular approach to the synthesis of cage aminophosphonates using the reaction of 2-chloro-1-phenylbenzo[e]-1,3,2-azaoxaphosphorin-4-one **1** with (2-benzylideneaminoethoxy)trimethylsilane **2** (Scheme 1).[†] The formation of P^III derivative, 2-(2-benzylideneaminoethoxy)-1-phenylbenzo[e]-1,3,2-azaoxaphosphorin-4-one **3**, was detected by ³¹P NMR (δ 120.3 ppm). Compound **3** was unstable under the reaction conditions and was immediately converted into the bicyclic cage aminophosphonate **4** as 1:1 diastereomeric mixture.[‡] Lack in stability for compound **3** as compared to 2-(2-benzylidene-
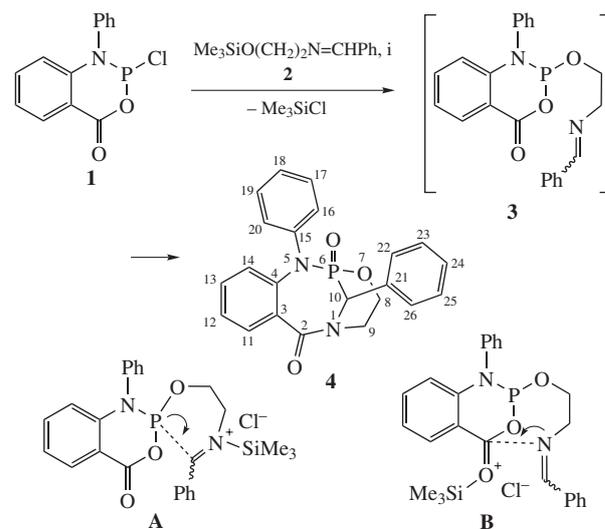
**Scheme 1** *Reagents and conditions*: i, CH₂Cl₂, 25 °C, 4 h.

[‡] *3,4-Benzo-5,10-diphenyl-1,5-diaza-7-oxa-6-phosphabicyclo[4.3.1]-decane-2,6-dione* **4**. A solution of 2-chloro-1-phenylbenzo[e]-1,3,2-aza-oxaphosphorin-4-one **1** (1.53 g, 5.5 mmol) in dichloromethane (10 ml) was added dropwise to the solution of the trimethylsilane **2** in dichloromethane (20 ml) at 20 °C under stirring for 5 min. The reaction mixture that immediately acquired a bright crimson colour was left overnight. Then volatile components were removed *in vacuo* (12 Torr). The residue was treated with diethyl ether and dried *in vacuo* to give a light red powder of product **4** as 1:1 mixture of diastereomers $d_1$ and $d_2$. Yield 1.82 g (85%). MS (EI), *m/z* (%): 390 [M]⁺ (83.9), 362 [M−C₂H₄]⁺ (19.4), 313 [M−C₆H₅]⁺ (66.8), 299 [M−P(O)OC₂H₄]⁺ (18.6), 285 [C₂₀H₁₇N₂]⁺ (2.9), 195 [C₈H₈N₂O₂P]⁺ (100.0), 167 [C₇H₈N₂OP]⁺ (58.9), 91 [C₆H₅CH₂]⁺ (23.5), 77 [C₆H₅]⁺ (28.4). Found (%): C, 67.28; H, 5.21; N, 7.09; P, 7.88. Calc. for C₂₂H₁₉N₂O₃P (%): C, 67.69; H, 4.87; N, 7.18; P, 7.95. Air-stable individual diastereomers **4**($d_1$) [0.85 g, mp 263–264 °C (decomp.), $δ_P$: 15.3 ppm] and **4**($d_2$) [0.74 g, mp 259–260 °C (decomp.), $δ_P$: 18.5 ppm] were sequentially isolated by chromatography on silica gel with chloroform and then chloroform–acetonitrile (5 : 1).

[†] *(2-Benzylideneaminoethoxy)trimethylsilane* **2**. A solution of chloro-trimethylsilane (8.1 g, 74.7 mmol) in diethyl ether (20 ml) was added dropwise to a mixture of 2-(benzylideneamino)ethanol (11.1 g, 74.5 mmol) and triethylamine (7.6 g, 75.3 mmol) in dry diethyl ether (100 ml) at 20 °C under an argon atmosphere, and the mixture was left overnight. The formed precipitate was filtered off, the volatiles from the filtrate were removed *in vacuo* and the residue was distilled. Yield 12.4 g (75%), light-yellow liquid, bp 171–173 °C (15 Torr), $n_D^{20}$ = 1.5097. ¹H NMR (600 MHz, CDCl₃) δ: 0.11 (s, 9H, Me₃Si), 3.75 (t, 2H, NCH₂, ³J 5.8 Hz), 3.91 (t, 2H, OCH₂, ³J 5.8 Hz), 7.41 (m, 3H, *m*-H, *p*-H), 7.74 (m, 2H, *o*-H), 8.28 (s, 1H, =CH). Compound **2** was previously obtained as a crude material by different procedure.[8]

aminophenoxy)benzo[*e*]-1,3,2-dioxaphosphorin-4-one with a similar structure[5] may be explained by the effect of chloro-trimethylsilane formed in the reaction, namely the activation of both the imine moiety (see Scheme 1, structure **A**) and the carbonyl group of **3** (see Scheme 1, structure **B**). Similar activation in polar acetonitrile by an equimolar amount or excess of chloro-trimethylsilane was demonstrated earlier for diethyl phosphite[6] or triethyl phosphite[7] addition to carbonyl compounds and imines.

The structure of the isolated diastereomers of product **4** was determined by NMR spectroscopy.[§] The bicyclodecane moiety was deduced from the spin–spin coupling constants in the $^{13}$C and $^{13}$C-{$^1$H} NMR spectra for the carbon atoms located at a distance of 1–4 bonds from the phosphorus atom. There is a noticeable difference for the chemical shifts of the H-8AB and H-9AB protons, as well as for the C[3], C[4], C[9], C[10], C[14], C[21] and
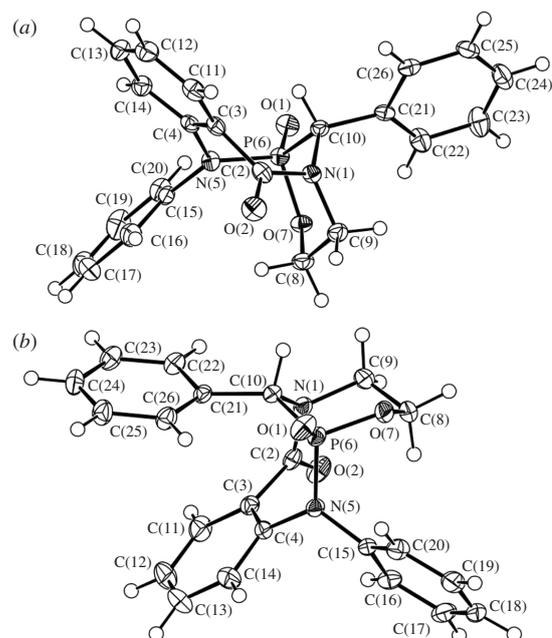
**Figure 1** Molecular structures of (*a*) compound **4**($d_1$) in the crystal, only the ($R_P$,$R_{C(10)}$)-enantiomer of the racemic mixture is shown; (*b*) compound **4**($d_2$) in the crystal, only the ($S_P$,$R_{C(10)}$)-enantiomer of the racemic mixture is shown. Non-hydrogen atoms are presented as thermal ellipsoids with 50% probability.

C[22,26] carbons in diastereomers $d_1$ and $d_2$, resulting from the different arrangement of the phenyl substituent at C[10] with respect to the plane of the phenylene and oxazaphosphorinane moieties. In fact, for $d_1$ the difference in the chemical shifts between the H-9A and H-9B protons reaches 1.05 ppm, while it is 1.33 ppm for the $d_2$ counterpart. The C[4], C[22,26] and C[24] carbons are considerably shielded in $d_2$ in comparison with $d_1$, whereas the C[3], C[9], C[10] and C[21] carbons are noticeably deshielded in $d_2$. These differences can be interpreted based on the assumption that the C[10] carbon atom in diastereomer $d_2$ has a configuration where the six-membered oxazaphosphorine ring bears an equatorial phenyl moiety that overhangs the phenylene substituent, whereas diastereomer $d_1$ has a configuration with an axial phenyl in this six-membered ring. The NMR-based assignment of the diastereomers structure was further confirmed by single crystal X-ray diffraction data for both isolated compounds (Figure 1).[¶]

The seven-membered heterocycles of the bicyclodecane cage in both diastereomers have a boat conformation [the N(1)–C(2)–N(5)–P(6) moiety is planar within 0.053(1) Å for $d_1$ and 0.047(2) Å

for $d_2$; the C(3), C(4) and C(10) atoms deviate to one side from this plane by 1.044(2), 0.942(1) and 0.808(1) Å for $d_1$ and by 1.014(3), 0.906(3) and 0.850(3) Å for $d_2$, respectively]. The six-membered heterocycles have a chair conformation; the N(1)–P(6)–O(7)–C(9) moiety is planar within 0.047(2) Å for $d_1$ and 0.045(2) Å for $d_2$; the corresponding deviations of the C(8) and C(10) atoms from this plane are 0.621(3) and –0.743(2) Å for $d_1$ as well as 0.619(2) and –0.814(1) Å for $d_2$. The difference in configuration of the diastereomeric molecules is in the position of the phenyl substituent at C(10) atom towards the seven-membered heterocycle, *viz.*, an equarorial position for $d_1$ and an axial position for $d_2$. The position of this substituent is opposite towards the six-membered heterocycle: it is axial for $d_1$ and equatorial for $d_2$. The carbonyl group [C(2)=O(2)] in both diastereomers is out of plane of the phenylene moiety: the dihedral angles between the N(1)–C(2)–O(2)–C(3) and C(2)–C(3)–C(4)–N(5) planar moieties are 55.0(2)° for $d_1$ and 57.5(1)° for $d_2$.

Thus, we have suggested an efficient approach to the synthesis of cage derivatives of aminophosphonic acids that involves the intramolecular reaction of the C=N exocyclic bond with the highly reactive P–O–C(O) moiety in 1,3,2-azaoxaphosphorin-4-ones. This approach can be extended to related cyclic systems where a phosphorus atom is bound to an exocyclic C=N bond through different possible spacers.

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*Crystal data for* **4**($d_2$). The structure was refined as a two-component twin. The twin law was found using the TwinRotMat routine of PLATON-200618[11] and the final model was refined against a combined set of diffraction indices. The minor domain with fractional contribution of 0.271(2) was rotated from the main one by reciprocal lattice two-fold twinning axis (1 0 0) and direct axis [5 0 1], the twin law was 1.000 0.000 0.335, 0.000 –1.000 0.000, 0.000 0.000 –1.000. $C_{22}H_{19}N_2O_3P$, $M = 390.36$, monoclinic, $P2_1/c$ (no. 14), $a = 9.2098(15)$, $b = 19.385(3)$ and $c = 10.5483(17)$ Å, $\beta = 101.048(8)°$, $V = 1848.3(5)$ Å$^3$, $Z = 4$, $Z' = 1$, $d_{calc} = 1.403$ g cm$^{-3}$, $\mu = 0.176$ mm$^{-1}$, $F(000) = 816$, $T_{max/min} = 0.5455/0.5115$; 54215 reflections were collected ($2.101° \leqslant \theta \leqslant 28.620°$), 4704 of which were unique, $R_\sigma = 0.0325$; completeness to $\theta$ of 25.242° was 99.7%. The refinement of 254 parameters with no restraints converged to $R_1 = 0.0392$, $wR_2 = 0.0996$ for 3958 reflections with $I > 2\sigma(I)$ and $R_1 = 0.0505$, $wR_2 = 0.1063$ for all data with $S = 1.040$ and residual electron density, peak/hole 0.302/–0.375 eÅ$^{-3}$.

CCDC 1863935 and 1863936 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

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