Transformation of myrtenoic acid nitrile to aminophospholene oxide by the reaction with dibenzylphosphine oxide: the X-ray structure of (1*S**,2*R**,6*R**,8*R**)-5-benzyl-9,9-dimethyl-5-oxo-4-phenyl-5-phosphatricyclo[6.1.1.0^{2,6}]dec-3-en-3-ylamine

Vasilii D. Kolesnik,[a] Tatyana V. Rybalova,[b] Yury V. Gatilov[b] and Alexey V. Tkachev*[b]

[a] *Department of Natural Sciences, Novosibirsk State University, 630090 Novosibirsk, Russian Federation*
[b] *N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, 630090 Novosibirsk, Russian Federation. Fax: +7 3832 34 4752; e-mail: atkachev@nioch.nsc.ru*

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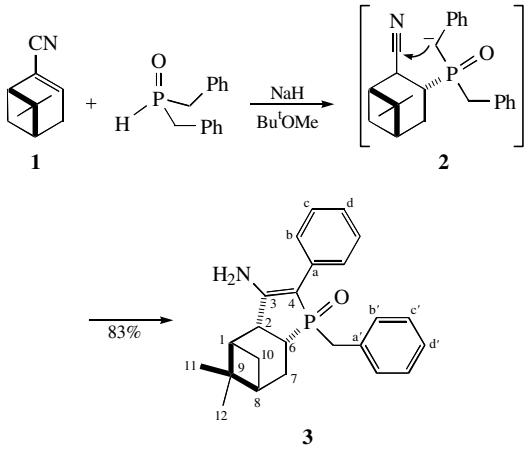
The reaction of dibenzylphosphine oxide with myrtenoic acid nitrile in *tert*-butyl methyl ether in the presence of sodium hydride results in the formation of substituted aminophospholene oxide in good yield (83%).

For a long time the addition of phosphorus(III) halides to dienes has been the basic way for the synthesis of five-membered phosphorus-containing heterocycles.[1–3] It was found that the reaction of α,β-unsaturated esters[4] and ketones[5] with secondary phosphine oxides containing a benzyl group results in the formation of corresponding phosphorus-containing heterocycles.

We found that treatment of myrtenoic acid nitrile **1** (prepared from racemic myrtenal oxime according to the known method[6]) with dibenzylphosphinous acid[7] in the presence of sodium hydride results in the formation of aminophospholene oxide **3** (Scheme 1). In contrast to the previously reported procedures for α,β-unsaturated esters and ketones with the use of THF,[4,5] we carried out the reaction in *tert*-butyl methyl ether as a solvent. The new solvent for this condensation possesses a good dissolving ability towards the sodium salt of dibenzylphosphinous acid. Additionally, *tert*-butyl methyl ether is immiscible with water and improves the isolation procedure as compared to the traditional procedures.†



Scheme 1 The numbering is given only for NMR interpretation.

The mechanism of addition of disubstituted phosphinous acids to unsaturated esters[8] includes the primary addition of phosphinites to the carbon–carbon double bond followed by the addition of a C-anion of the benzylic type to the carbonyl group. The mechanism of the reaction of α,β-unsaturated nitriles seems to be similar, and the addition of the sodium salt of dibenzylphosphine oxide to the carbon–carbon double bond results in primary adduct **2** (Scheme 1), which then undergoes intramolecular cyclisation to form aminophospholene oxide **3**. It was shown[8] that in case of the reaction of bulky substrates the use of the second equivalent of a base (to generate a dianion) increased the yields of phospholene oxides. We also used two equivalents of the base because the substrate is sterically hindered.

† Powdered NaH (0.27 g, 6.80 mmol, Fluka, assay 55–65%) was added portionwise to a solution of dibenzylphosphine oxide (1.56 g, 6.80 mmol) in *tert*-butyl methyl ether (25 ml). The suspension was refluxed with stirring for 20 min. A solution of myrtenoic acid nitrile **1** (6.80 mmol) in *tert*-butyl methyl ether (10 ml) was then added dropwise, and the resulting mixture was stirred at reflux for 1 h. A new portion of NaH (0.27 g, 6.80 mmol) was added, and the mixture was additionally refluxed for 1 h. The reaction mixture was cooled to room temperature, diluted with *tert*-butyl methyl ether (10 ml), washed with brine (30 ml) and dried over Na_2SO_4. Removal of the solvent left crude aminophospholene oxide as a crystalline solid in 83% yield.

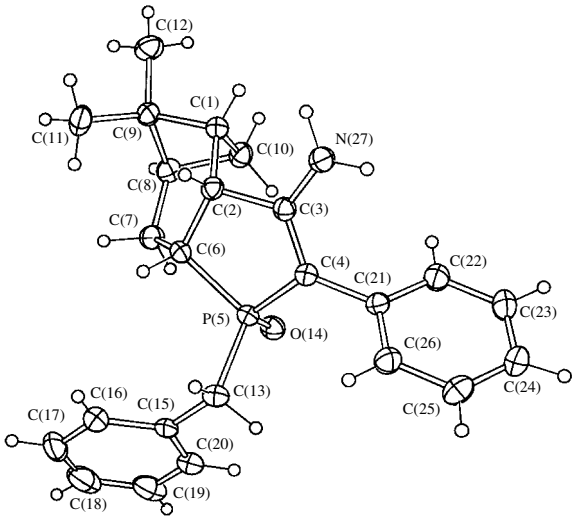


Figure 1 Molecular structure of compound **3**. The rings C(1)–C(2)–C(6)–C(7)–C(8)–C(9) and C(1)–C(2)–C(6)–C(7)–C(8)–C(10) adopt the sofa shape, for which the atoms C(9) and C(10) deviate from the plane C(1)–C(2)–C(6)–C(7)–C(8) [planar within 0.056(1) Å] by 1.043(3) and –1.104(3) Å, respectively. The four-membered ring is bent by 37.4(1)° along the C(1)···C(8) line. The phosphorus-containing ring takes the shape of an envelope, the C(6) atom being out of plane by 0.202(2) Å. The amino group is planar and conjugated with the double bond whereas the C(21)–C(26) phenyl ring is removed from conjugation: the dihedral angle between the double bond and ring planes is 71.04(7)°. Molecular chains along the *a* axis are formed by hydrogen bonds N(27)–H···O(14) (0.5 – *x*, y – 0.5, *z*) [H···O 1.95(3) Å, N–H···O 164(2)°].

^{1}H, ^{13}C and ^{31}P NMR data show the reaction product to be a single stereoisomer.‡ The addition of dibenzylphosphine oxide to nitrile **1** is possible only at the least hindered α-side of the molecule. According to PM3 calculations, the *cis*-fusion of a phospholene ring and a pinane moiety is preferable to the *trans*-fusion ($\Delta\Delta H_f^0$ = 12–15 kcal mol^{-1}). In case of the *trans*-fusion, the vicinal spin–spin coupling constants of P–C(6)–C(2)–C(1) and P–C(6)–C(7)–C(8) in the NMR spectra should be high. However, the experimental values $^3J_{C-P}$ 0–3 Hz lend support to the *cis*-fusion. The structure of compound **3** with a chiral phosphorus atom (phosphoryl oxygen *trans*- to the H^6 atom) was confirmed by X-ray analysis§ (Figure 1). Bond lengths in compound **3** were found to be usual.[9]

Thus, the reaction of dibenzylphosphine oxide with an unsaturated nitrile led to aminophospholene oxide. Previously, aminophospholene oxides were prepared by multi-step syntheses.[10,11]

‡ *(1S*,2R*,6R*,8R*)-5-Benzyl-9,9-dimethyl-5-oxo-4-phenyl-5-phosphatricyclo[6.1.1.0^{2,6}]dec-3-en-3-ylamine* **3**: white crystals, mp 218–220 °C (CCl_4–MeCN, 5:1 v/v), $[\alpha]^{25}$ 0.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.84 (s, H^{11}), 1.17 (s, H^{12}), 1.43 (d, $H^{10\beta}$, *J* 9.7 Hz), 1.76 (ddddd, $H^{7\beta}$, *J* 13.7, 13.2, 11.7, 1.4 and 1.4 Hz), 1.88 (dddd, H^8, *J* 5.7, 5.7, 3.9 and 2.1 Hz), 2.00 (m, H^1), 2.02 (m, $H^{10\alpha}$), 2.19 (dddd, H^6, *J* 10.5, 9.7, 9.4 and 2.8 Hz), 2.41 (dddd, $H^{7\alpha}$, *J* 20.6, 13.7, 3.8 and 2.8 Hz), 2.88 (dddd, H^2, *J* 16.3, 9.0, 1.0 and 1.0 Hz), 3.12 (d, CH_2Ph, *J* 16.4 Hz), 4.46 (s, NH_2), 7.00 (m, $H^{b'}$), 7.09–7.22 (m, $H^{c'}$, $H^{d'}$ and H^d), 7.35 (t, H^c, *J* 7.5 Hz), 7.52 (d, H^b, *J* 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.13 (C^{11}), 22.52 (C^7, $J_{C–P}$ 3.5 Hz), 22.91 (C^6, $J_{C–P}$ 65.4 Hz), 25.08 (C^{10}), 26.24 (C^{12}), 38.05 (C^9), 38.73 (*C*H_2Ph, $J_{C–P}$ 64.4 Hz), 40.12 (C^8), 42.39 (C^1, $J_{C–P}$ 3.2 Hz), 46.14 (C^2, $J_{C–P}$ 3.7 Hz), 100.04 (C^4, $J_{C–P}$ 116.3 Hz), 126.01 ($C^{b'}$, $J_{C–P}$ 2.8 Hz), 126.09 ($C^{d'}$), 128.10 (C^d), 128.12 (C^c, $J_{C–P}$ 3.8 Hz), 128.91 (C^b), 129.39 ($C^{c'}$, $J_{C–P}$ 5.1 Hz), 133.83 ($C^{a'}$, $J_{C–P}$ 6.2 Hz), 134.50 (C^a, $J_{C–P}$ 8.8 Hz), 157.77 (C^3, $J_{C–P}$ 44.3 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ: 64.49. IR ($CHCl_3$, ν/cm^{-1}): 3500, 3400, 3100–2900, 1630, 1490, 1150. MS, *m*/*z* (%): 377.19167 (M^+, 13%), 362 (10), 350 (22), 320 (17), 309 (10), 286 (49), 230 (13), 139 (21), 91 (100).

§ 3624 independent reflections were measured on a Bruker P4 diffractometer with graphite monochromated MoKα radiation using $\theta/2\theta$ scans with $\theta < 25°$. Compound **3** is orthorhombic, space group *Pbca*, a = 15.359(2), b = 11.693(1), c = 22.960(3) Å, V = 4123.5(8) Å^3, $C_{24}H_{28}NOP$, M = 377.44, Z = 8, d_{calc} = 1.216 g cm^{-3}, μ = 0.147 mm^{-1}, $F(000)$ = 1616, crystal size 0.15×0.43×1.08 mm. The structure was solved by the direct methods (SHELXS-86) and refined in the anisotropic-isotropic approximation using SHELXL-97 to wR_2 = 0.1190, S = 1.032 for all reflections (R = 0.0441 for 2890 $F > 4\sigma$). The positions of hydrogen atoms were located from a D-map. Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2001. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/86.

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