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(1*R*,3*S*,6*S*)-6-*tert*-Butyl-1-hydroxymethyl-5-methoxy-6-methyl-7-oxa-4-azaspiro[2.5]oct-4-en-8-one and dimethyl [(1*S*,1′*R*,3′*S*,6′*S*)-(6′-*tert*-butyl-5′-methoxy-6′-methyl-8′-oxo-7′-oxa-4′-azaspiro[2.5]oct-4′-en-1′-yl)hydroxymethyl]phosphonate

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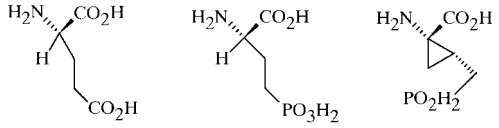
The molecules of the title compounds, $C_{13}H_{21}NO_4$, (I), and $C_{15}H_{26}NO_7P$, (II), are linked into chains along the *c* direction in (I) and along the *b* axis in (II) through O—H···O hydrogen bonds. The heteroatomic ring in (I) adopts a twist-boat conformation, while that in (II) has a conformation intermediate between boat and twist-boat. The P atom has a distorted tetrahedral geometry.

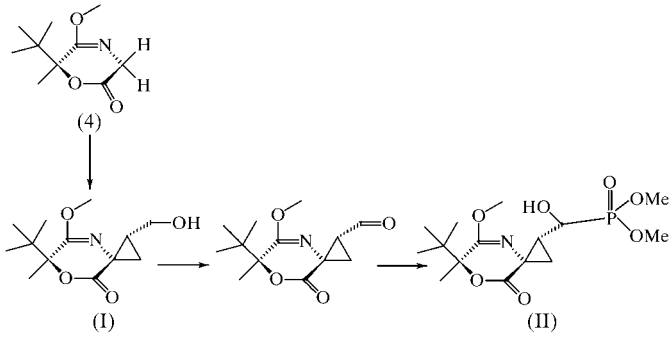
Comment

Aminophosphonic acids are the analogues of natural amino acids in which the carboxylic acid group is replaced by the phosphonic acid group. Aminophosphonic acids and their esters and salts have attracted attention because of their wide range of applications, *viz*. in analytical chemistry (ligands for transition metal cations), in agriculture (herbicides, pesticides and growth regulator in plants) and in medicine (antibiotics, antiviral treatments and enzyme inhibitors) (Kalir & Kalir, 1996; Hudson & Pianka, 1996; Kukhar & Hudson, 1999). In recent years, unnatural (synthetic) α-amino acids have played an important role in the field of peptide chemistry. In this context, excitatory amino acids (EAAs) are of special interest because of their neurotransmission propetries in the central nervous system. The discovery that phosphono-substituted analogues of α-amino acids possess an increased potency and selectivity led to a major advance in the design of *N*-methyl-D-aspartate (NMDA) receptor antagonists (Davies *et al.*, 1981; Evans *et al.*, 1982).

The importance of EAAs, and in particular of L-glutamic acid, (1), is becoming increasingly apparent. Specific and selective EAA agonists and antagonists have been developed (Hansen & Krogsgaard-Larsen, 1990; Johnson & Korner, 1988), and five EAA receptor subtypes have been defined (Monaghan *et al.*, 1989). One of these, the L-amino-4-phosphonobutanoic acid [L-AP4, (2)] EAA receptor subtype, is delineated by a unique responsiveness to L-AP4. Compounds with the structure of (3) mimic L-AP4 more closely than do the cyclopentyl analogues (Kroona *et al.*, 1991).



In this paper, we present the crystal structure of the title compounds, (I) and (II), as precursors to the synthesis of the cyclic analogue of L-AP4, employing a chiral 6-*tert*-butyl-5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one, (4).



A single-crystal X-ray diffraction study of these compounds was undertaken for a final examination of the absolute structure, establishing the configuration of the chiral atoms. The determination of the crystal structure revealed the reaction sequence shown above, in which attack of the deprotonated form of the oxazinone ring commenced with the terminal C atom in epichlorohydrin (Koch *et al.*, 2003). The structure of (II) was solved in order to elucidate the geometry around the P atom.

The substituents at C6 and C3 are in a *cis* conformation with respect to the heterocyclic ring (Figs. 1 and 2), which confirms the proposed mechanism of the chemical process (Koch *et al.*, 2003).

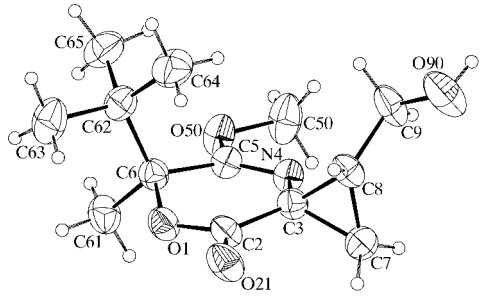


Figure 1
A view of (I), with the atom-labelling scheme. Displacement ellipsoids are shown at the 50% probability level.

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The heteroatomic ring in (I) has a twist-boat conformation, while in (II) the ring adopts a conformation intermediate between boat and twist-boat. The puckering parameters (Cremer & Pople, 1975) are as follows: $Q_T = 0.232\ (3)$ Å, $\varphi_2 = -144.6\ (8)^\circ$ and $\theta_2 = 104.5\ (8)^\circ$ in (I), and $Q_T = 0.194\ (3)$ Å, $\varphi_2 = -133.3\ (8)^\circ$ and $\theta_2 = 101.5\ (8)^\circ$ in (II), corresponding to the O1—C6—C5—N4—C3—C2 atom sequence, with a pseudo-twofold axis passing through the mid-point of the O1—C6 bond and atom C2 [asymmetry parameters are $\Delta_2 = 0.01\ (1)$ and $\Delta_2 = 0.03\ (1)$ for (I)]. Four low values of the asymmetry parameters for (II) confirm that the conformation of the ring is intermediate between boat and twist-boat. A pseudo-twofold axis passes through the mid-point of the O1—C6 bond and atom C2 [$\Delta_2 = 0.03\ (1)$ and $\Delta_2 = 0.03\ (1)$] and a mirror plane through the mid-point of the N4—C5 bond and atom C3 [$\Delta_s = 0.03\ (1)$ and $\Delta_s = 0.03\ (1)$; the atom sequence is as mentioned above].

Intermolecular O—H···O hydrogen bonds exist in both structures. In (I), an O90—H90···O21^{i} hydrogen bond is formed (Table 2), but in (II), atom O21 does not act as an acceptor for hydrogen bonds. Here, the presence of the phosphonate group has the effect of changing the acceptor atom (O30 instead of O21), and thus an O90—H91···O30^{ii} hydrogen bond is observed (Table 4). These interactions create $C(7)$ and $C(5)$ chain graph-set motifs in (I) and (II) (Bernstein *et al.*, 1995), running along the *c* and *b* axis, respectively (Figs. 3 and 4).

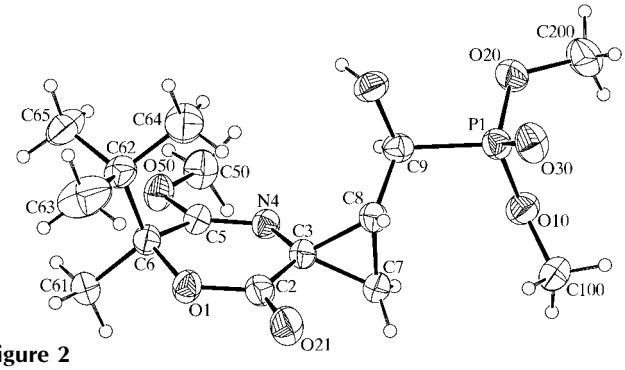

Figure 2
A view of (II), with the atom-labelling scheme. Displacement ellipsoids are shown at the 50% probability level.

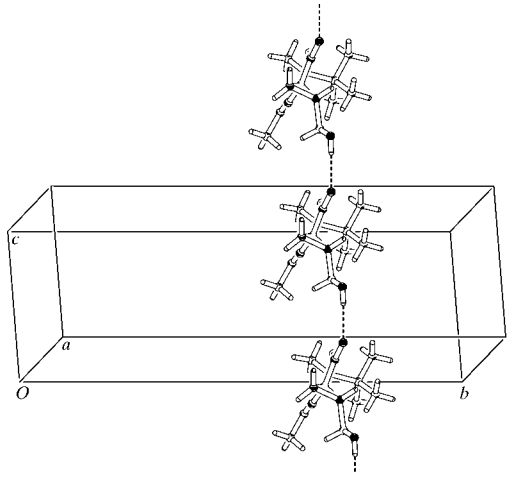

Figure 3
A view of the chain formed along the *c* axis by molecules of (I) linked by hydrogen bonds in the unit cell.

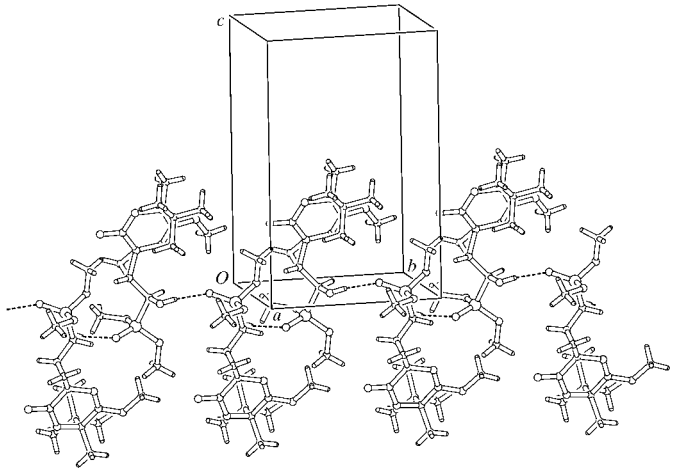

Figure 4
A view of the chain formed along the *b* axis by molecules of (II) linked by hydrogen bonds in the unit cell.

The P atom displays a distorted tetrahedral coordination geometry, with the largest deviations from the ideal values being for the O20—P1—C9 and O30—P1—C9 angles (the smallest and largest angles; Table 3).

Bond distances and angles (Tables 1 and 3) are in a good agreement with expected values (Allen *et al.*, 1987).

Experimental

Compound (I) was prepared from (*S*)-6-*tert*-5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (65 mg, 0.33 mmol) in tetrahydrofuran (THF, 3.5 ml), $NaN(SiCH_3)_2$ (685 µl, 0.685 mmol, 2.1 equivalents) and (*R*)-(−)-epichlorohydrin (92 mg, 78 µl, 0.99 mmol, 3.0 equivalents), with a reaction time of 24 h. Liquid chromatography (petroleum ether/acetate, 70:30) yielded (I) as colourless crystals (40 mg, 47%, from diisopropyl ether by slow evaporation; m.p. 434.5–436 K). $[\alpha]_D^{20} = -4.0$ ($c = 0.55$, $CHCl_3$). For the preparation of (II), to (1*R*,3*S*,6*S*)-6-*tert*-butyl-5-methoxy-6-methyl-8-oxo-7-oxa-4-azaspiro-[2.5]oct-4-ene-1-carbaldehyde) (64.0 mg, 0.253 mmol) in THF (3.0 ml) were added $HP(O)(OMe)_2$ (20.88 µl, 0.228 mmol, 0.9 equivalents) and triethylamine (2.55 mg, 0.0253 mmol, 3.5 µl). The reaction mixture was stirred for 1 h at room temperature. The crude product was filtered off, dried and crystallized from diisopropyl ether by slow evaporation (yield 86.6 mg, 97%; m.p. 434–436 K). $[\alpha]_D^{20} = +19.2$ ($c = 0.25$, $CHCl_3$).

Compound (I)

Crystal data

$C_{13}H_{21}NO_4$
$M_r = 255.31$
Orthorhombic, $P2_12_12_1$
$a = 8.134\ (3)$ Å
$b = 22.802\ (2)$ Å
$c = 7.744\ (2)$ Å
$V = 1436.3\ (7)$ Å^3
$Z = 4$
$D_x = 1.181$ Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 25 reflections
$\theta = 23.5$–29.4°
$\mu = 0.72$ mm^{-1}
$T = 293\ (2)$ K
Plate, colourless
0.5 × 0.2 × 0.1 mm

Data collection

Rigaku AFC-5*S* diffractometer
ω scans
Absorption correction: analytical (de Meulenaer & Tompa, 1965)
T_{min} = 0.82, T_{max} = 0.92
1480 measured reflections
1480 independent reflections
1195 reflections with $I > 2\sigma(I)$
θ_{max} = 67.5°
$h = -9 \rightarrow 9$
$k = -21 \rightarrow 27$
$l = -4 \rightarrow 9$
3 standard reflections
every 150 reflections
intensity decay: <2%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.052
$wR(F^2)$ = 0.163
S = 1.02
1480 reflections
170 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.1207P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.40 e Å^{-3}
$\Delta\rho_{min}$ = −0.16 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.017 (2)

Table 1
Selected geometric parameters (Å, °) for (I).

O1—C2	1.338 (4)	C3—N4	1.422 (4)
O1—C6	1.470 (4)	N4—C5	1.264 (4)
C2—O21	1.218 (4)	C5—O50	1.352 (4)
C2—C3	1.477 (5)	C5—C6	1.510 (5)
O1—C2—C3—C8	144.1 (3)	C2—O1—C6—C61	142.9 (3)
C8—C3—N4—C5	−134.6 (3)	N4—C5—C6—C62	101.4 (4)

Table 2
Hydrogen-bonding geometry (Å, °) for (I).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O90—H90···O21^{i}	0.82	1.94	2.757 (4)	174

Symmetry code: (i) $x, y, z-1$.

Compound (II)

Crystal data

$C_{15}H_{26}NO_7P$
M_r = 363.34
Monoclinic, $P2_1$
a = 6.894 (1) Å
b = 9.423 (1) Å
c = 14.428 (2) Å
β = 93.266 (10)°
V = 935.8 (2) Å^3
Z = 2
D_x = 1.290 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 22.9–27.1°
μ = 1.61 mm^{-1}
T = 293 (2) K
Block, white
0.4 × 0.3 × 0.3 mm

Data collection

Rigaku AFC-5*S* diffractometer
ω scans
Absorption correction: analytical (de Meulenaer & Tompa, 1965)
T_{min} = 0.555, T_{max} = 0.650
1887 measured reflections
1741 independent reflections
1578 reflections with $I > 2\sigma(I)$
R_{int} = 0.018
θ_{max} = 67.5°
$h = -6 \rightarrow 8$
$k = -11 \rightarrow 10$
$l = -17 \rightarrow 17$
3 standard reflections
every 150 reflections
intensity decay: <2%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.035
$wR(F^2)$ = 0.102
S = 1.08
1741 reflections
226 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0698P)^2 + 0.0119P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.22 e Å^{-3}
$\Delta\rho_{min}$ = −0.26 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0119 (14)
Absolute structure: Flack (1983), 76 Friedel reflections
Flack parameter = 0.03 (3)

Table 3
Selected geometric parameters (Å, °) for (II).

P1—O30	1.458 (3)	C2—O21	1.211 (4)
P1—O20	1.568 (3)	C2—O1	1.341 (4)
P1—O10	1.570 (2)	O1—C6	1.460 (4)
P1—C9	1.808 (3)	C6—C5	1.502 (5)
C3—N4	1.436 (5)	C5—N4	1.264 (4)
C3—C2	1.472 (5)	C5—O50	1.361 (4)
O30—P1—O20	115.31 (16)	O30—P1—C9	115.68 (17)
O30—P1—O10	113.75 (18)	O20—P1—C9	102.13 (15)
O20—P1—O10	102.41 (16)	O10—P1—C9	105.99 (14)
C8—C3—C2—O1	142.4 (3)	C62—C6—C5—N4	102.4 (4)
C2—O1—C6—C62	−101.8 (3)	C8—C3—N4—C5	−137.6 (3)

Table 4
Hydrogen-bonding geometry (Å, °) for (II).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O90—H91···O30^{ii}	0.82	1.95	2.735 (4)	161

Symmetry code: (ii) $2-x, \frac{1}{2}+y, -z$.

All H atoms were positioned geometrically and refined as riding, with O—H distances of 0.82 Å and C—H distances in the range 0.96–0.98 Å. U_{iso} values were constrained to be $1.5U_{eq}$ of the parent atom for H atoms of methyl groups and $1.2U_{eq}$ for other H atoms. For both compounds, the absolute configuration has been assigned on the basis of the known configuration of the reagents. The Flack (1983) parameter for (I) could not be defined because the number of Friedel pairs was insufficient. In the case of (II), the Flack parameter is in agreement with the expected configuration.

For both compounds, data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1989); cell refinement: *MSC/AFC Diffractometer Control Software*; data reduction: *TEXSAN* (Molecular Structure Corporation, 1989); program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2003); software used to prepare material for publication: *PARST*97 (Nardelli, 1996).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: NA1611). Services for accessing these data are described at the back of the journal.

References

Allen, F. H., Kennard, O., Watson, D. G., Brammer, L., Orpen, A. G. & Taylor, R. (1987). *J. Chem. Soc. Perkin Trans.* 2, pp. S1–19.
Bernstein, J., Davis, R. E., Shimoni, L. & Chang, N.-L. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 1555–1573.
Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.
Davies, J., Francis, A. A., Jones, A. W. & Watkins, J. C. (1981). *Neurosci. Lett.* **21**, 77–81.
Evans, R. H., Francis, A. A., Jones, A. W., Smith, D. A. S. & Watkins, J. C. (1982). *Br. J. Pharmacol.* **75**, 65–75.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Hansen, J. J. & Krogsgaard-Larsen, P. (1990). *Med. Res. Rev.* **10**, 55–94.
Hudson, H. R. & Pianka, M. (1996). *Phosphorus Sulfur Silicon Relat. Elem.* pp. 109–110.
Johnson, R. L. & Korner, J. F. (1988). *J. Med. Chem.* **31**, 2057–2066.
Kalir, A. & Kalir, H. H. (1996). *The Chemistry of Organophosphorus Compounds*, edited by F. R. Hartkey, Vol. 4, pp. 767–780. New York: Wiley and Sons.
Koch, C.-J., Šimonyiová, S., Pabel, J., Kärtner, A., Polborn, K. & Wanner, K. T. (2003). *Eur. J. Org. Chem.* pp. 1244–1263.
Kroona, H. B., Peterson, N. L., Koerner, J. F. & Johnson, R. L. (1991). *J. Med. Chem.* **34**, 1692–1699.
Kukhar, V. P. & Hudson, H. R. (1999). Editors. *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity*, ch. 1, pp. 483–535. London: John Wiley and Sons.
Meulenaer, J. de & Tompa, H. (1965). *Acta Cryst.* **19**, 1014–1018.
Molecular Structure Corporation (1989). *MSC/AFC Diffractometer Control Software* and *TEXSAN* (Version 5.0). MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.
Monaghan, D. T., Bridges, R. J. & Cotman, C. W. (1989). *Annu. Rev. Pharmacol. Toxicol.* **29**, 365–402.
Nardelli, M. (1996). *J. Appl. Cryst.* **29**, 296–300.
Sheldrick, G. M. (1990). *Acta Cryst.* A**46**, 467–473.
Sheldrick, G. M. (1997). *SHELXL*97. University of Göttingen, Germany.
Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.