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LACK OF MANIFESTATION OF AN ANOMERIC EFFECT IN 2-DIPHENYLPHOSPHINOYL-1, 3-DIOXANE AND 2-DIPHENYLPHOSPHINOYL-1, 3-OXATHIANE[1*]

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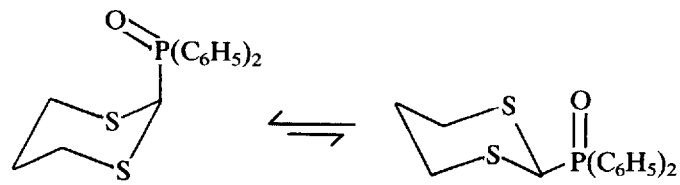
ABSTRACT

The spectroscopic evidence for the predominance of the equatorial conformers in the title compounds was confirmed by the study of derivatives containing counterpoise substituents, and by chemical equilibration of anancomeric models. $\Delta G^{\circ}_{27\,^{\circ}C}$ [$P(O)Ph_2$] $\gtrsim$ 3·2 kcal/mol was determined in the dioxane, and $\Delta G^{\circ}_{55\,^{\circ}C}$ [$P(O)Ph_2$] = 1·42 ± 0·12 kcal/mol in the oxathiane. It follows then that the strong anomeric interaction observed previously in S—C—P segments does not show up in the six-membered heterocycles **2** and **7**, which contain O—C—P moieties. This may be due to an inherent inability of oxygen to act as an electron donor to the axial $P(O)Ph_2$ substituent, or to a dominant repulsive steric interaction in the axial conformers.

INTRODUCTION

Several years ago the discovery of an important anomeric interaction in 2-diphenylphosphinoyl-1,3-dithiane (**1**, equation (1)) was reported.[2] Further confirmation of the existence of an anomeric effect between the second-row elements sulfur and phosphorus has recently been presented by us[1,3] and by Mikolajczyk *et al.*[4,5]



(1)

1-axial **1**-equatorial

In this communication we describe the conformational analysis of the title dioxane (**2**) and oxathiane (**7**), which incorporate the O—C—P segment. Interest in this study is significant from several points of view: (1) the evaluation of the relative ability of first- and second-row

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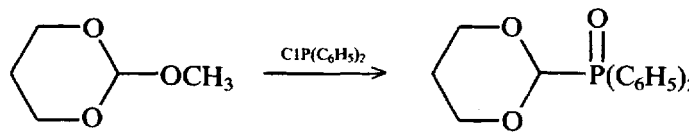
elements on anomeric interactions is just beginning to be explored,[6] (2) oxygen and phosphorus are ubiquitous in biomolecules,[7] and have been shown to give rise to remarkable stereoelectronic effects,[8] and (3) the attained information is relevant to the comprehension of the S—C—P anomeric effect.[3,5]

RESULTS

A. 2-Diphenylphosphinoyl-1,3-dioxane (**2**) was prepared in quantitative yield according to the procedure of Dietsche,[9] equation (2).



(2)

2, ~100%

The assignment of the ^{1}H-NMR spectrum of **2** was essential since the very large difference between axial and equatorial protons at C(4,6) = 1·2 ppm in **1** led to the discovery of the strong S—C—P anomeric interaction;[2,3] by contrast $\Delta\delta_{ax/eq}$ (H(4,6)) in **2** is only 0·44 ppm (see Table 1). Most significant, the predominantly axial phosphoryl group in **1** has a large deshielding effect on the *syn*-axial H(4,6);[2,3] however, the axial hydrogens at C(4,6) in **2** appear at *higher field* relative to H(4,6) equatorial.*

These spectroscopic observations are evidence of a *predominantly equatorial* conformation in **2**. Support for this reasoning comes from the comparison of the ^{13}C-NMR chemical shifts of **2** (Table 2) with those in unsubstituted 1,3-dioxane. In particular, the similar values for C(4,6) in **2** (δ = 67·85 ppm) and in the parent 1,3-dioxane (δ = 67·6 ppm)[10] show the absence of a γ-*gauche* shielding effect,[11] which would be expected for an equilibrium with significant participation of axial **2**.

In order to obtain quantitative data on the **2**-ax ⇌ **2**-eq equilibrium, the synthesis of the anancomeric analogues **3** and **4** was undertaken (Scheme 1a). Unfortunately, the obviously unstable axial epimer (**4**) was not formed in appreciable quantity, and attempts to generate it from **3** were not successful. Better results were achieved in the 5-methyl seies, where the methyl group acts as a counterpoise: since the conformational equilibrium of 5-Me is not very one-sided,[12] a *ca.* 3:1 *trans–cis* mixture of dioxanes **5** and **6** could be obtained (Scheme 1b). The most useful information was derived from their ^{13}C-NMR spectra: the observed chemical shifts for the methyl carbons indicate that this group is completely (≳95%) equatorial in dioxane **5**, but completely axial in the *cis* isomer (see Table 2).[13] Because the conformational energy of the 5-Me in 1,3-dioxane is 0·9 kcal/mol, [12] a minimum $\Delta G°[P(O)Ph_2] \gtrsim 2·7$ kcal/mol, favoring **2**-eq, is determined.

B. 2-Diphenylphosphinoyl-1,3-oxathiane (**7**) was prepared from 1,3-oxathiane, *tert*-butyllithium,[14] and chlorodiphenylphosphine; the phosphine intermediate oxidized spontaneously to **7** during workup, equation (3).

*That the signals at 3·76 and 4·20 ppm correspond to the axial and equatorial protons, respectively, was confirmed by double irradiation experiments

Table 1. Room temperature ^{1}H-NMR signal assignments in compounds **1–3** and **5–9** (ppm from Me_4Si, $CDCl_3$)

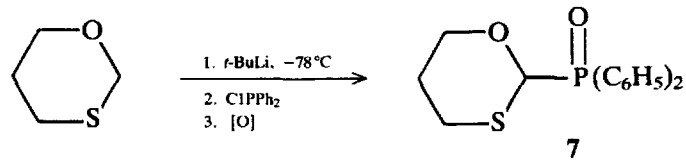
Compd	H(2)[a]	H(4ax)	H(4eq)	H(5ax)	H(5eq)	H(6ax)	H(6eq)	H_{ortho}	$H_{meta,para}$	other
1[b]	4·0 (6)	3·70	2·50	2·05	2·05	3·70	2·50	7·84	7·48	—
2	5·35(6)	3·76	4·20	2·15	1·35	3·76	4·20	7·97	7·53	—
3	5·37(6)	3·80	—	~1·50	~1·50	3·80	—	7·98	7·50	[c]
5	5·30(6)	3·33	4·17	2·17	—	3·33	4·17	7·98	7·53	[d]
6	5·40(6)	3·95	3·95	—	1·62	3·95	3·95	8·00	7·57	[e]
7	5·62(5.9)	2·98	2·98	2·10	1·82	3·64	4·27	7·86	7·53	—
8	5·65(9)	3·20	—	1·36	1·85	3·55	—	8·03	7·60	[f]
9	5·51(5)	4·45	—	1·27	1·85	4·26	—	7·93	7·57	[g]

[a] H/P coupling constants in parentheses.
[b] Taken from reference 2.
[c] CH_3—C(4,6): 1·23.
[d] CH_3—C(5): 0·68.
[e] CH_3—C(5): 1·14.
[f] CH_3—C(6): 1·20; CH_3—C(4): 1·20.
[g] CH_3—C(6): 1·27; CH_3—C(4): 0·94.

Table 2. Room temperature ^{13}C-NMR signal assignments in compounds **1–3** and **5–9** (ppm from Me_4Si, $CDCl_3$)[a,b]

Compd	C(2)	C(4)	C(5)	C(6)	C_{ipso}	C_{ortho}	C_{meta}	C_{para}	other
1[c]	37·15(70)	26·97	24·91	26·97	132·17(100)	131·07(9)	128·30(12)	131·69(2·5)	—
2	101·35(118)	67·85(9)	25·64	67·85(9)	129·47(101)	131·80(8·5)	127·82(12)	131·72	—
3	100·95(118)	74·36(11)	40·74	74·36(11)	130·21(99)	132·21(9)	127·99(11)	131·75	[d]
5	101·18(118)	74·43(11)	29·86	74·43(11)	129·71(101)	132·29(9)	128·24(12)	132·19	[e]
6	101·72(117)	73·16(10)	29·60	73·16(10)	129·48(101)	132·29(9)	128·26(13)	132·23	[f]
7	81·39(90)	27·95(6)	25·87	70·67(9)	129·87(101) 130·85(101)	131·80(10) 132·29(9)	128·26(13) 128·42(12)	132·27	—
8	82·01(91)	37·97(7)	41·46	77·46(11)	129·42(101) 130·52(101)	131·35(9) 132·93(10)	127·69(12) 127·88(12)	131·65	[g]
9	76·32(80)	33·28	41·52(2)	71·62(3)	131·49(92) 131·75(98)	131·38(9) 131·60(9)	128·46(12)	131·84(2)	[h]

[a] C/P coupling constants in parentheses.
[b] Note diastereotopic phenyl rings in oxathianes.
[c] Taken from reference 2.
[d] CH_3—C(4,6): 21·40.
[e] CH_3—C(5): 12·36(2).
[f] CH_3—C(5): 15·86.
[g] CH_3—C(4): 21·14; CH_3—C(6): 21·57.
[h] CH_3—C(4): 22·02; CH_3—C(6): 21·89.

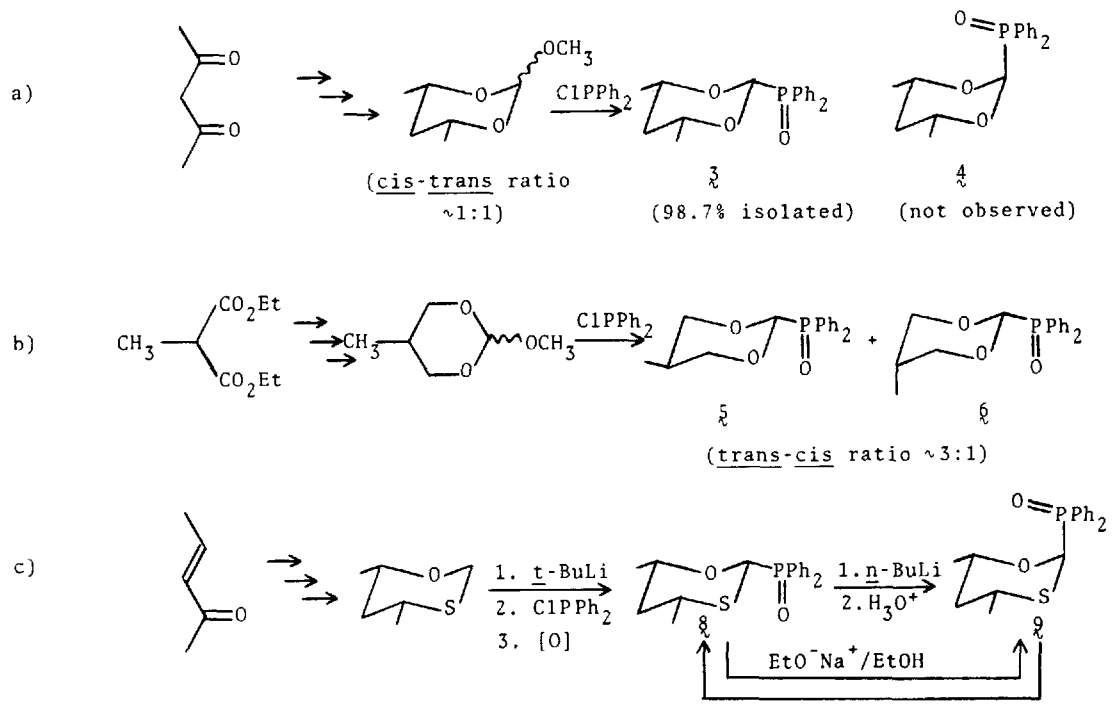


(3)

Distinct features of the proton NMR spectrum of **7** are a doublet of triplets at 4·27 ppm, and a doublet of doublets of doublets at 3·64 ppm; both signals correspond to one proton each (Table 1).

These chemical shifts and coupling patterns indicate that the higher-field signal must be assigned to H(4) axial in a *predominantly equatorial conformer of* **7**; i.e. the deshielding effect expected from an axial diphenylphosphinoyl group on *syn*-diaxial protons [2,3] is absent (*vide supra*).* Also missing is evidence of a γ-*gauche* upshielding effect at C(4,6): δ(C(6)) and δ(C(4)) in 1,3-oxathiane[15] are 69·68 and 27·45, respectively, while the corresponding carbon chemical shifts in **7** are 70·67 and 27·95 ppm. (Table 2).

Support for the conclusion that **7** exists predominantly as the equatorial conformer originates from the observation that the downfield shifting produced by the addition of $Eu(fod)_3$ is in the order H(2) > H(6-eq) > H(6-ax) > H(5-ax). Examination of Dreiding models indicates that this result is only possible it one assumes the equatorial orientation of the phosphoryl group;[16] by contrast, similar shift reagent experiment on mostly axial **1** afforded the LIS order H(4,6-ax) > H(2) > H(4,6-eq) > H(5).[2,3]



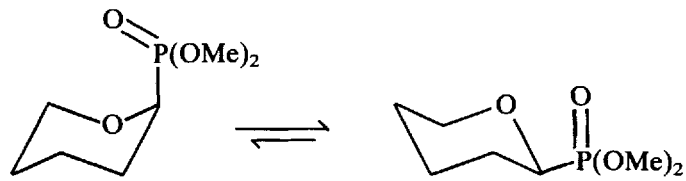
Scheme 1

*That the signals at 3·64 and 4·27 ppm correspond to the axial and equatorial protons at C(4), respectively, was confirmed by double irradiation experiments.

Quantitative determination of the conformational energy of the 2-diphenylphosphinoyl group was accomplished by chemical equilibration of the anancomeric models **8** and **9**, prepared as outlined in Scheme 1c. Ethanolic sodium ethoxide **8** = **9** equilibration, and integration of the H(4) and H(6) signals in the proton NMR spectra afforded an **8**:**9** ratio, K = 8·85 ± 1·75, and therefore a $\Delta G^{\circ}_{55\,^{\circ}C}$ [$P(O)Ph_2$] = 1·42 ± 0·12 kcal/mol.

DISCUSSION

The observed large predominance of **2**-eq over **2**-ax ($K \geq 100$), and **7**-eq over **7**-ax (K = 8·85) confirm the qualitative results of Mikolajczyk *et al.* on 5,5-dimethyl-2-diphenylphosphinoyl-1,3-dioxane,[5,17] and the results of Thiem and Meyer, which show that equatorial 2-dimethylphosphonatetetrahydropyran (**10**) predominates in solution (equation 4).[18]



10-ax **10**-eq (4)

It is obvious then that the strong anomeric interaction observed in S—C—P segments [2–5] does not manifest in the six-membered heterocycles **2**–**10**. This may be due to an inherent inability of oxygen to act as lone pair donor[19] to the antiperiplanar C—P acceptor bond in axial **2**–**10**, or to an inefficient $2p \rightarrow 3d$ stabilizing interaction in the O—C—P relative to S—C—P ($3p \rightarrow 3d$) segments.[1,3] In this respect, it is remarkable that the significant upfield shifts observed for the *ortho* and *para* carbons in the axial 2-diphenylphosphinoyl-, and 2-diphenylthiophosphinoyl-1,3-dithianes, relative to the equatorial isomers,[1,3] are not found in **9** *vis-a-vis* **8**. (Table 2).

There is at least one other obvious explanation: because of the shorter C—O bonds (*ca.* 1·43 Å) relative to the C—S bonds (*ca.* 1·82 Å) the steric repulsion of the diphenylphosphinoyl group (A-value = 2·74 kcal/mol)[20] with *syn*-diaxial hydrogens at C(4,6) is offset by the anomeric effect in **1** but not so in **2**–**10**.[21] Preliminary estimation of this steric term by means of the Hill equation [22] does indicate that the steric repulsion in axial **2**–**10** is quite substantial and could dominate over the electrostatic and/or stereoelectronic terms. In addition, polar factors (i.e. dipole/dipole interactions) may contribute to the result found, although it could be expected that these favor the axial isomers.[23]

EXPERIMENTAL SECTION

General information

Proton NMR spectra were recorded on Varian EM-360 (60 MHz) or Varian EM-390 (90 MHz) spectrometers. ^{13}C-NMR spectra were recorded on a Jeol FX-90Q (22·49 MHz) instrument operated in pulsed Fourier transform mode and locked on solvent deuterium. Samples were prepared as 5–10% solutions in $CDCl_3$ with 2–5% Me_4Si as internal reference in 5 mm o.d. tubes.

Flasks, stirring bars, and hypodermic needles used for the generation and reactions of alkyllithiums were dried for *ca.* 12 h at 120 °C and allowed to cool in a desiccator over anhydrous calcium sulfate. Anhydrous ether solvents were obtained by distillation from benzophenone ketyl.[24] The *t*-butyllithium employed was titrated according to the method of Juaristi *et al.*[25] Melting and boiling points are uncorrected.

Microanalyses were performed by Galbraith Laboratories, Inc.,Knoxville, TN.

2-Diphenylphosphinoyl-1,3-dioxane (2)

Following the procedure of Dietsche,[9] 0·118 g (1 mmol) of 2-methoxy-1,3-dioxane[26] and 0·22 g (1 mmol) of chlorodiphenylphosphine were warmed up to *ca.* 40 °C, and stirred under nitrogen for 30 minutes. The reaction mixture was then allowed to cool to room temperature, at which the desired product solidified. Recrystallization from ethanol afforded 288 mg (quantitative yield) of **2**; mp 213–215 °C (lit.[9] mp 206–211 °C). ^{1}H-NMR in Table 1. ^{13}C-NMR in Table 2. ^{31}P-NMR (36·23 MHz, $CDCl_3$) δ 23·45. MS, *m/e* 288 (M^+), 201 ($M^+ - 87$).

Anal. calcd for $C_{16}H_{17}O_3P$: C, 66·66; H, 5·94. Found: C, 66·53; H, 5·96.

r-2-Diphenylphosphinoyl-*c*-4,*c*-6-dimethyl-1,3-dioxane (3)

A *ca.*1:1 mixture of *r*-2-methoxy-*c*-4,*c*-6- and -*t*-4, *t*-6-dimethyl-1,3-dioxanes[26,27] (1·46 g, 0·01 mol) was treated with 2·2 g (0·01 mol) of chlorodiphenylphosphine, and the reaction mixture was heated to *ca.* 40 °C with stirring under nitrogen for 30 minutes. The crude product was recrystallized from ethanol to afford 3·16 g (98·7% yield) of **3** as white crystals; mp 150–153 °C. ^{1}H-NMR in Table 1. ^{13}C-NMR in Table 2. ^{31}P-NMR (36·23 MHz, $CDCl_3$) δ 22·74.

Anal. calcd for $C_{18}H_{21}O_3P$: C, 68·35; H, 6·69. Found: C, 68·12; H, 6·74.

cis- and *trans*-2-Diphenylphosphinoyl-5-methyl-1,3-dioxanes (5 and 6)

A *ca.* 1:1 mixture of *cis*- and *trans*-2-methoxy-5-methyl-1,3-dioxanes (prepared according to the general method of Eliel and Giza;[26] 3·96 g, 0·03 mol) was treated with 6·62 g (0·03 mol) of chlorodiphenylphosphine, and the reaction mixture was heated to *ca.* 40 °C with stirring under nitrogen during 20 minutes. The crude product (8·56 g, 94·5% yield), which solidified upon standing at room temperature, consisted of a *ca.* 3:1 ratio of the desired products **5** and **6**. The *cis* isomer (**5**) was purified by fractional crystallization from ethyl acetate: mp 159–161 °C. ^{1}H-NMR in Table 1. ^{13}C-NMR in Table 2. ^{31}P-NMR (36·23 MHz, $CDCl_3$) δ 24·08.

Anal. calcd for $C_{17}H_{19}O_3P$: C, 67·54; H, 6·32. Found: C, 67·38; H, 6·49.

The *trans* isomer (**6**) was purified by flash chromatography: mp 191–192 °C. ^{1}H-NMR in Table 1. ^{13}C-NMR in Table 2. ^{31}P-NMR (36·23 MHz, $CDCl_3$) δ 24·08.

1,3-Oxathiane

Following the procedure of Koskimies,[28] 3-mercaptopropanol (16·1 g, 0·175 mol), 6·55 g (0·22 mol) of paraformaldehyde, 2·37 ml of concentrated sulfuric acid and 20 ml of water were mixed in a 50-ml round-bottom flask. The flask was heated to reflux so that water and oxathiane distilled slowly. When about half of the water had been distilled, 10 ml of water was

added to the flask and the distillation was continued. This procedure was repeated until no more organic material was collected. The distillate was exracted twice with 20-ml portions of ether, the combined ether layers were washed once with dilute aqueous potassium carbonate, dried over anydrous potassium carbonate, filtered and concentrated to give 17·8 g (98% yield) of the crude product which was distilled in a Kugelrohr apparatus to afford 14·5 g (79·6% yield) of pure 1,3-oxathiane; bp 105 °C/100 mm (lit.[29] bp 96–100 °C/100 mm).

2-Diphenylphosphinoyl-1,3-oxathiane (7)

1,3-Oxathiane (2·3 g, 22 mmol) was placed in a 50-ml round-bottom flask provided with a rubber septum before the addition of 20 ml of THF under nitrogen. The flask was immersed in an acetone-dry ice bath (*ca.* −78 °C) and then 18·1 ml of 1·22 M *t*-BuLi in hexane (one equivalent) was added. The reaction mixture was stirred at −78 °C for 1 h and then transferred via cannula to another flask containing 4·86 g (22 mmol) of chlorodiphenylphosphine in 15 ml of THF, at −78 °C and under nitrogen. The reaction mixture was stirred at this temperature for 1 h, and then quenched with saturated ammonium chloride. Extraction with CH_2Cl_2 and the usual workup procedure afforded a yellowish solid which was recrystallized from ethyl acetate to give 2·43 g (36·2% yield) of **7** as white crystals, mp 165–167 °C. ^{1}H-NMR in Table 1. ^{13}C-NMR in Table 2. ^{31}P-NMR (36·23 MHz, $CDCl_3$) δ 27·19.

Anal. calcd for $C_{16}H_{17}O_2PS$: C, 63·14; H, 5·63. Found: C, 63·04; H, 5·46.

4-Thioacetyl-2-pentanone

Following the procdure of Koskimies,[28] thioacetic acid (58·0 g, 0·76 mol) in 50 ml of ether was added to a stirred solution of 50·5 g (0·60 mol) of 3-penten-2-one (prepared from acetone and acetaldehyde by aldol condensation; the resulting alcohol was dehydrated by distillation in the presence of a trace of iodine) during 45 minutes. The mixture was stirred for 2 h and then the solvent was removed in a rotary evaporator. The residue was distilled twice to give 84 g (87·6% yield) of the desired product, bp 50 °C/0·12 mm (lit.[30] 121–125 °C/25 mm).

4-Mercapto-2-pentanol

Following the procedure of Koskimies,[28] 4-thioacetyl-2-pentanone (39·5 g, 0·247 mol) was added to a suspension of 9·5 g (0·25 mol) of lithium aluminium hydride in 100 ml of ether. The mixture was refluxed for 1 h. Excess reagent was destroyed with ethyl acetate and the product was hydrolyzed with 10 ml of water and 300 ml of 15% aqueous sulfuric acid. The ether layer was separated and the aqueous layer extracted with chloroform. The combined organic solutions were dried over magnesium sulfate, filtered and concentrated on a rotary evaporator. Distillation at 90–92 °C/28 mm (lit.[31] bp 73–81 °C/8 mm) gave *ca.* 30 g (100% yield) of a mixture of stereoisomers.

***cis*- and *trans*-4,6-Dimethyl-1,3-oxathiane[28]**

A mixture of 12·0 g (0·10 mol) of stereoisomeric 4-mercapto-2-pentanols, 3·75 g (0·125 mol) of paraformaldehyde, 2·5 g of concentrated sulfuric acid, and 8 ml of water was distilled in the manner described for the synthesis of 1,3-oxathiane (see above). The crude product, 11·9 g

(90% yield) consisted of a mixture of *cis*- and *trans*-4,6-dimethyl-1,3-oxathiane. The *cis* isomer was separated by fractional distillation, bp 50 °C/6 mm (lit.[28] bp 80 °C/50 mm). ^{1}H-NMR (90 MHz, CCl_4) δ 1·14 (d, J = 7 Hz, 3 H), 1·29 (d, J = 7·2 Hz, 3 H), 1·60 (m, 2 H), 3·0 (m, 1 H), 3·41 (m, 1 H), 4·7 (s, 2 H). ^{13}C-NMR (22·49 MHz, $CDCl_3$) δ 21·76, 22·06, 36·97, 42·78, 70·99, 75·45.

r-2-Diphenylphosphinoyl-c-4,c-6-dimethyl-1,3-oxathiane (8)

cis-4,6-Dimethyl-1,3-oxathiane (see above; 1·0 g, 7·6 mmol) was placed in a dry round-bottomed flask provided with a magnetic stirring bar and capped with a rubber septum. The flask was flushed with nitrogen prior to the addition of 20 ml of dry THF via a cannula, after which the solution was cooled to −78 °C and *t*-butyllithium (4·73 ml of a 1·60 M hexane solution, 7·6 mmol) was syringed into it dropwise. The resulting solution was stirred for 1 h at −78 °C following which it was added to a THF solution (*ca.* 20 ml) of chlorodiphenylphosphine (1·36 ml, 1·68 g, 7·6 mmol) also at −78 °C. The reaction mixture was stirred at this temperature for 1 h and subsequently at room temperature for a further 1 h before being quenched with saturated aqueous ammonium chloride. Extraction with $CHCl_3$ followed by the usual workup procedure afforded 1·76 g (69·9% yield) of **8** as white crystals, pf 159–160 °C. ^{1}HNMR in Table 1. ^{13}C-NMR in Table 2. ^{31}P-NMR (36·23 MHz, $CDCl_3$) δ 25·34. Amal. calcd for $C_{18}H_{21}O_2PS$: C, 65·04; H, 6·37. Found: C, 64·81; H, 6·34.

r-2-Diphenylphosphinoyl-t-4-t-6-dimethyl-1,3-oxathiane (9)

8 (331 mg, 0·99 mmol) was placed in a 25 ml round-bottom flask provided with a rubber septum, and 15 ml of THF was added under nitrogen. The flask was immersed in an acetone-dry ice bath (*ca.* −78 °C) and then 0·533 ml of 2·5 M *n*-BuLi in hexane (one equivalent) was added. The reaction mixture was stirred at −78 °C for 1h and then quenched with saturated ammonium chloride. Extraction with chloroform and the usual workup procedure yielded 122 mg (37%) of **9** as white crystals: mp 198·5–199·5 °C. ^{1}H-NMR in Table 1. ^{13}C-NMR in Table 2. ^{31}P-NMR (36·23 MHz, $CDCl_3$) δ 32·01.

Anal. calcd for $C_{18}H_{21}O_2PS$: C, 65·04; H, 6·37. Found: C, 65·02; H, 6·40.

Note added in proof We have recently found that the *tert*-butyl group in *cis*-5-*tert*-butyl-2-diphenylphosphinoyl-1,3-dioxane adopts an axial orientation. Because $\Delta G°$ (5-*tert*-butyl) = 1·4 kcal/mol,[12] a minimum $\Delta G°$ (2-P(0)Ph_2) $\gtrsim$ 3·2 kcal/mol is determined.

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