

# Diastereoselective Lewis acid mediated hydrophosphonylation of heterocyclic imines: a stereoselective approach towards $\alpha$ -amino phosphonates

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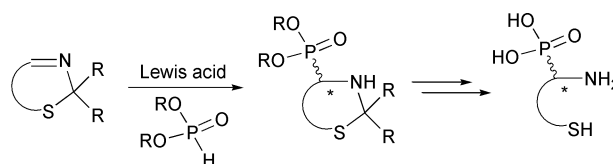
The synthesis of new chiral  $\alpha$ -amino phosphonates by the Lewis acid mediated addition of bisesters of phosphonic acid to 3-thiazolines (2,5-dihydro-1,3-thiazoles), is described. The diastereoselectivity of the reaction using chiral reactants was systematically investigated. The chiral BINOL-phosphonate **1** was found to be a highly stereoselective phosphonylating agent towards 3-thiazolines. Structural aspects of the resulting thiazolidinylphosphonates were studied by NMR and X-ray analyses. The role of the Lewis acid as a spatial mediator is discussed and a quantum chemical description of the Lewis acid mediated hydrophosphonylation presented.

## Introduction

Organophosphorus compounds are renowned for their diverse physiological activities. Among these, the phosphonate moiety is an important pharmacophore in agricultural as well as in pharmaceutical chemistry.<sup>1</sup>  $\alpha$ -Amino phosphonic acids and related derivatives represent a significant class of compounds with strong biological activities, e.g. as antibiotics,<sup>2</sup> herbicides,<sup>3</sup> insecticides,<sup>4</sup> fungicides<sup>5</sup> and anti-viral agents.<sup>6</sup> In one sense, phosphonic acids may be viewed as 'long life transition state analogues' for tetrahedral intermediates in amide/ester hydrolysis.<sup>7</sup> This relationship has led to a wide range of applications with respect to enzyme inhibition<sup>8</sup> (including e.g. HIV-protease<sup>9</sup>).

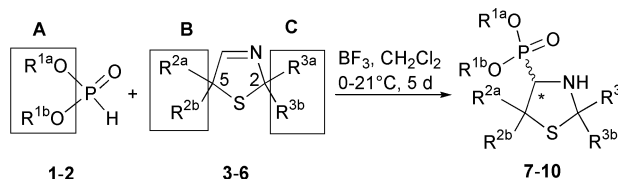
Accordingly, the preparation of these compounds, especially the stereoselective preparation of optically active  $\alpha$ -amino phosphonic acid derivatives, has been a field of great interest over the last years.<sup>10</sup> Among other synthetic methodologies, the addition of P-nucleophiles to a C=N double bond represents a general and versatile route to  $\alpha$ -amino functionalized organophosphorus compounds.<sup>11</sup> This route has been used for the synthesis of chiral  $\alpha$ -amino phosphonic acid derivatives with and without control of stereochemistry. Addition of an appropriate achiral P-nucleophile (e.g. dimethyl phosphonate) to a prochiral imine leads to the formation of the corresponding  $\alpha$ -amino phosphonate with a stereogenic centre in the  $\alpha$ -position. Mostly, such work has generated racemic products.<sup>12</sup> However, a few examples of synthesis by enantiomeric catalysis have also been published.<sup>13</sup> Application of chiral reactants (chiral phosphorus nucleophiles<sup>14</sup> or chiral imines<sup>15</sup> and derivatives<sup>16</sup>) in the hydrophosphonylation of (non-symmetrical) imines leads to varying degrees of diastereoselection. In general, simple aryl imines have been used in these reactions resulting in the synthesis of aromatic  $\alpha$ -amino phosphonic acids like phosphonophenylalanine. However, a stereoselective approach to  $\beta$ - or  $\gamma$ -functionalized species (e.g. phosphonocysteine and related compounds) has been largely neglected, although these compounds are of pharmaceutical importance and are able to undergo further derivatisation. Thus, we started our investigation on the synthesis of phosphonocysteine related compounds by the addition of phosphorus nucleophiles to heterocyclic imines bearing an *N,S*-acetal. It was anticipated

that subsequent cleavage of such an acetal could release  $\beta$ - or  $\gamma$ -functionalized  $\alpha$ -amino phosphonic acids (Scheme 1).



Scheme 1 Hydrophosphonylation of heterocyclic imines.

Recently, we introduced the enantioselectively catalyzed hydrophosphonylation of 3-thiazolines (2,5-dihydro-1,3-thiazoles) with lanthanoid BINOL (binaphthol) complexes.<sup>13</sup> Herein, we report our experiences regarding the diastereoselective hydrophosphonylation of these sulfur containing heterocycles. Inspired by the work of Schöllkopf *et al.*,<sup>17</sup> we decided to investigate the  $\text{BF}_3$ -mediated diastereoselective hydrophosphonylation of 3-thiazolines more systematically. They reported moderate diastereoselectivity ( $dr = 2 : 1$ ) in the addition of a tartaric acid derived cyclic phosphonate to 2,2,5,5-tetramethylthiazoline **3a**. We have communicated preliminary results of the utilisation of BINOL as a source of chirality in this diastereoselective addition reaction.<sup>18</sup> In the present report we summarize our experiences in the field of stereoselective C-P bond formation through Lewis acid mediated hydrophosphonylation of 3-thiazolines **3-6**, resulting in the pharmaceutically important<sup>19</sup> thiazolidin-4-ylphosphonates **7-10** (Scheme 2). In addition, we present structural



Scheme 2 Diastereoselective hydrophosphonylation of 3-thiazolines.

investigations of the products by NMR and X-ray analyses as well as a quantum chemical description of the reactions based on *ab initio* calculations.

**Table 1** Hydrophosphonylation of achiral 3-thiazolines **3a–3e** with BINOL-phosphonate **1** (case 1, Scheme 2)

Entry	Imine	Product	R <sup>2</sup> /R <sup>2</sup>	R <sup>3a</sup> /R <sup>3b</sup>	dr <sup>a</sup>	Yield (%)
1	<b>3a</b>	<b>7a</b>	Me/Me	Me/Me	83 : 17	47
2	<b>3b</b>	<b>7b</b>	Me/Me	–(CH <sub>2</sub> ) <sub>5</sub> –	>95 : 5	47
3	<b>3c</b>	<b>7c</b>	–(CH <sub>2</sub> ) <sub>5</sub> –	Me/Me	80 : 20	37
4	<b>3d</b>	<b>7d</b>	–(CH <sub>2</sub> ) <sub>5</sub> –	–(CH <sub>2</sub> ) <sub>5</sub> –	>95 : 5	68
5	<b>3e</b>	<b>7e</b>	H/H	–(CH <sub>2</sub> ) <sub>5</sub> –	>95 : 5	30

<sup>a</sup> The dr value was determined for the crude product by <sup>1</sup>H NMR spectroscopy.

## Results and discussion

As for any diastereoselective reaction, for diastereoselective control in the hydrophosphonylation of 3-thiazolines, a chiral auxiliary needs to be attached to one of the reactants to introduce ‘chiral information’ into the newly formed stereogenic centre of the product. In the case of the hydrophosphonylation reaction of 3-thiazolines, several possible pathways for ‘chiral information flow’ exist as shown in Scheme 2. Three major cases (A, B and C) of diastereoselective control can be distinguished with regard to the position of the donating chiral auxiliary. First, we focussed on the diastereoselecting ability of chiral phosphonates (case A). In a second step, we investigated diastereoselective control by chiral 3-thiazolines (cases B and C).

Hydrophosphonylation of the 3-thiazolines was carried out under mild conditions in a Lewis acid mediated process. An appropriate 3-thiazoline **3–6** was dissolved in dry dichloromethane at 0 °C and treated with one equivalent of BF<sub>3</sub>·Et<sub>2</sub>O. After an hour one equivalent of the desired phosphonate **1** or **2** was added. After five days of stirring at room temperature the mixture was hydrolyzed. Extractive work up yielded the corresponding crude thiazolidinylphosphonates **7–10** which were free of by-products in many cases. If needed, the product was purified by column chromatography on silica gel.

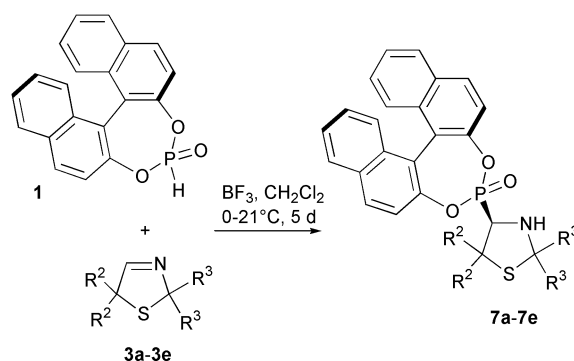
The typical pattern of coupling constants caused by the presence of phosphorus, especially the typically large coupling constants (<sup>1</sup>J<sub>PH</sub> = 16–18 Hz and <sup>1</sup>J<sub>PC</sub> = 135–148 Hz) as well as the characteristic deviation of the vicinal <sup>3</sup>J<sub>PC</sub> couplings,† supported identification of the diastereomeric products and allowed determination of all dr values by NMR analysis of the crude products.

### Diastereoselective hydrophosphonylation employing chiral phosphonate **1**

Since the chiral auxiliary might easily be removed by hydrolysis of the phosphonic ester after the addition reaction, employing chiral phosphonates in diastereoselective hydrophosphonylation (case A, Scheme 2) seemed to be a promising and versatile strategy. Some chiral phosphorus nucleophiles derived from ephedrine,<sup>20</sup> glucose<sup>14a</sup> and *trans*-cyclohexane-1,2-diamine<sup>21</sup> have been reported to be efficient diastereoselective phosphonylating reagents towards aromatic aldehydes such as benzaldehyde. The selectivity achievable in the phosphonylation of imines, however, was generally much lower (limited to 60 : 40 in case of 3-thiazolines<sup>17</sup>). Therefore, we investigated use of the chiral BINOL auxiliary. The chiral P-nucleophile **1** is available in both enantiomerically pure forms,<sup>22</sup> but has been used as a racemate by us. BINOL has already shown excellent chiral recognition properties in other systems.<sup>23</sup> However, silyl phosphite esters of BINOL have been reported to have a rather poor ability to act as phosphonylating agents towards benzaldehyde,

yielding just 11–16% of corresponding adducts after refluxing in toluene for three days.<sup>24</sup>

We found that BF<sub>3</sub>-mediated reaction of the BINOL ester of phosphonic acid **1** with cyclic imines **3a–3e** resulted in hydrophosphonylation in high yields with excellent diastereoselectivity (Table 1, Scheme 3).



**Scheme 3** Diastereoselective hydrophosphonylation using BINOL-phosphonate **1**. (One enantiomer of each of the racemic compounds **1** and **7a–7e** is shown. Major isomers of **7a** and **7c** are shown.)

Diastereomeric mixtures **7a** and **7c** could be separated easily by column chromatography. The almost exclusively formed major diastereomer was found to have relative (*R*<sub>a</sub><sup>\*</sup>,4*R*<sup>\*</sup>)-configuration by X-ray analysis<sup>18</sup> of the major diastereomer of thiazolidinylphosphonate **7a** (Fig. 1). It is noteworthy that stereoselection of the BINOL-phosphonate **1** seems to be independent of the steric demands of the nearby substituents R<sup>2</sup>. In contrast, the nature of the more distant substituent (R<sup>3</sup>) of the *N,S*-acetalic carbon atom influences the diastereoselectivity to a larger extent.

BINOL-phosphonate provides good selectivity in the hydrophosphonylation of 3-thiazolines **3a** and **3c** (R<sup>3</sup> = Me; entries 1 and 3 in Table 1), but the higher steric demands of R<sup>3</sup> (R<sup>3a</sup>/R<sup>3b</sup> = –(CH<sub>2</sub>)<sub>5</sub>–; entries 2, 4 and 5 in Table 1) lead to the formation of only one diastereomer of the corresponding thiazolidinylphosphonates **7b**, **7d** and **7e**. The larger influence of the *N,S*-acetalic substituents R<sup>3</sup> on diastereoselection might be reinforced by BF<sub>3</sub> coordination to the nitrogen atom of the 3-thiazoline. The Lewis acid might relay the spatial demand of residue R<sup>3</sup> and function as both an activator of the imine bond as well as a steric mediator for the incoming nucleophile. BINOL-phosphonate **1** proved to be a highly stereoselective phosphonylating agent towards heterocyclic imines, namely 3-thiazolines **3a–3e** leading to diastereomerically pure  $\alpha$ -amino phosphonic acid esters **7a–7e**. Removal of the chiral auxiliary<sup>25</sup> and cleavage of the *N,S*-acetal<sup>26</sup> might be performed by acidic hydrolysis as described in the literature, thus maintaining the chiral information of the released  $\alpha$ -amino phosphonic acid.

### Diastereoselective hydrophosphonylation employing chiral 3-thiazolines

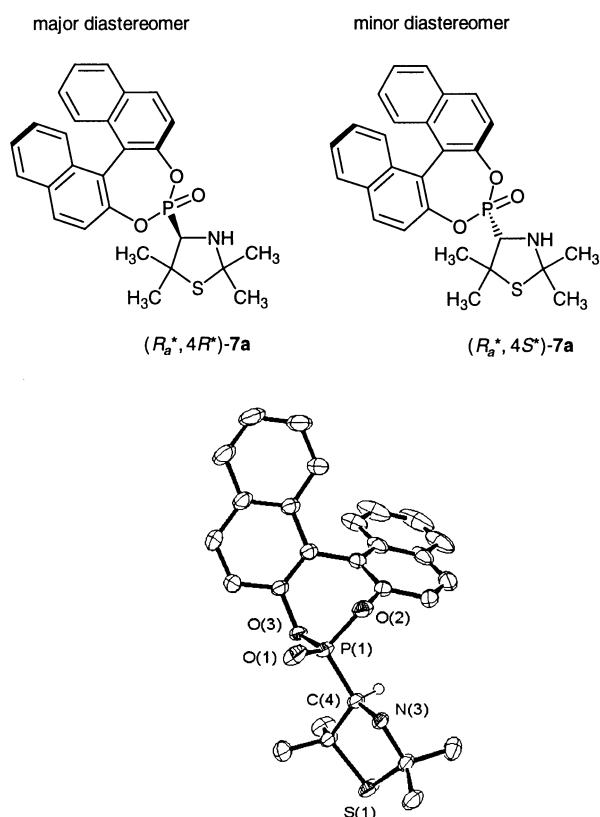
Depending on the position of the stereogenic centre at the 3-thiazoline (at C-5 or C-2), two major cases can be distinguished with respect to the hydrophosphonylation of chiral

† Independently of the substitution pattern, thiazolidinylphosphonates exhibit a remarkably large <sup>3</sup>J<sub>PC</sub> coupling (21–25 Hz) at the acetalic carbon of the heterocycle and an unusually small (often invisible) vicinal <sup>3</sup>J<sub>PC</sub> coupling (2–3 Hz) at the  $\alpha$ -position of the R<sup>2</sup> residue. See also ref. 13b.

**Table 2** Hydrophosphonylation of chiral 3-thiazolines **4** and **5a–5f** (case B/C, Scheme 2)

Entry	Reactants	Product	R <sup>1a</sup> /R <sup>1b</sup>	R <sup>2a</sup> /R <sup>2b</sup>	R <sup>3a</sup> /R <sup>3b</sup>	dr <sup>a</sup>	Yield (%)	
1	<sup>b</sup> <b>4</b>	<b>8a</b>	Me/Me	<i>i</i> -Pr/H	Me/Me	10 : 90	39	
2	<sup>b</sup> <b>2a</b>	<b>4</b>	<b>8b</b>	–CH <sub>2</sub> C(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub> –	<i>i</i> -Pr/H	Me/Me	<5 : 95	34
3	<sup>b</sup> <b>5a</b>	<b>9a</b>	<b>9a</b>	Me/Me	Me/Me	H/Ph	77 : 23	80
4	<sup>c</sup> <b>5a</b>	<b>9b</b>	<b>9b</b>	Et/Et	Me/Me	H/Ph	75 : 25	83
5	<b>2b</b>	<b>5a</b>	<b>9c</b>	<i>i</i> -Pr/ <i>i</i> -Pr	Me/Me	H/Ph	69 : 31	71
6	<b>2a</b>	<b>5a</b>	<b>9d</b>	–CH <sub>2</sub> C(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub> –	Me/Me	H/Ph	80 : 20	71
7	<b>2a</b>	<b>5b</b>	<b>9e</b>	–CH <sub>2</sub> C(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub> –	Me/Me	H/Bn	77 : 23	49
8	<b>2a</b>	<b>5c</b>	<b>9f</b>	–CH <sub>2</sub> C(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub> –	Me/Me	H/CH <sub>2</sub> Bn	73 : 27	73
9	<b>2a</b>	<b>5d</b>	<b>9g</b>	–CH <sub>2</sub> C(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub> –	Me/Me	H/ <i>t</i> -Bu	86 : 14	75
10	<b>2a</b>	<b>5e</b>	<b>9h</b>	–CH <sub>2</sub> C(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub> –	–(CH <sub>2</sub> ) <sub>5</sub> –	H/ <i>t</i> -Bu	87 : 13	45
11	<sup>b</sup> <b>5f</b>	<b>9i</b>	<b>9i</b>	Me/Me	–(CH <sub>2</sub> ) <sub>5</sub> –	H/ <i>i</i> -Pr	78 : 22	64
12	<b>2a</b>	<b>5f</b>	<b>9j</b>	–CH <sub>2</sub> C(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub> –	–(CH <sub>2</sub> ) <sub>5</sub> –	H/ <i>i</i> -Pr	82 : 18	66

<sup>a</sup> *cis* : *trans*; relative configuration according to NMR spectra. <sup>b</sup> Dimethyl phosphonate. <sup>c</sup> Diethyl phosphonate.



**Fig. 1** Relative configuration of the two diastereomers of **7a** and crystal structure of major isomer of **7a**. (One enantiomer of each of the racemic compounds is shown.)

3-thiazolines. Initially the simpler case, *i.e.* the hydrophosphonylation of the racemic 3-thiazoline **4** with a stereogenic centre in the C-5 position (R<sup>2a</sup> ≠ R<sup>2b</sup>, case B, Scheme 2) is discussed. As shown in Table 2 (entries 1 and 2), formation of the corresponding products **8a** and **8b** takes place in a highly diastereoselective manner. Use of the cyclic phosphonate **2a** provides a higher degree of stereoselection than dimethyl phosphonate. The almost exclusively formed diastereomer has the *trans*-configuration with respect to the two neighboured stereogenic centres of the sulfur heterocycle, as indicated by a large vicinal coupling constant (<sup>3</sup>J<sub>HH</sub> = 10.4 Hz) for the adjacent hydrogen atoms (4-H, 5-H). In summary, BF<sub>3</sub>-mediated hydrophosphonylation of 3-thiazolines like **4** with a stereogenic centre in the C-5 position gives a highly diastereoselective access to new chiral α-amino phosphonates.

The stereochemistry of hydrophosphonylation involving 3-thiazolines like **5a–5f** bearing a stereogenic centre at C-2 (in the position of the *N,S*-acetal) proved to be much more complex. At first glance it might appear advantageous to connect the chiral auxiliary through the *N,S*-acetal function of the hetero-

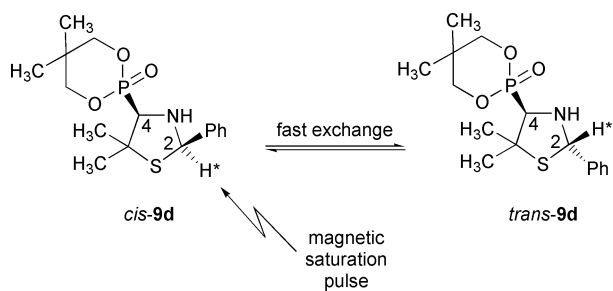
cycle since this directing chiral group can be readily removed following the hydrophosphonylation by acidic hydrolysis to give α-amino phosphonocysteine or analogues. However, the configuration of the *N,S*-acetalic carbon centre is known to be sensitive towards epimerisation under acidic conditions,<sup>27</sup> resulting in a severe problem for stereoselective reactions.

Chiral 3-thiazolines like **5a–5f** with a single stereo centre in the C-2 position are easily accessible *via* Asinger reaction of aldehydes,<sup>26</sup> leading to the heterocyclic imines as racemates. The results of BF<sub>3</sub>-mediated hydrophosphonylation of these thiazolines are given in Table 2 (entries 3–12). The observed dr values range from 69 : 31 to 87 : 13 favouring the 2,4-*cis*-configuration ‡ and depend on the substitution patterns of the reactants. As before, use of the cyclic phosphonate **2a** generally leads to the formation of the corresponding thiazolidinylphosphonates at higher dr values than the use of dimethyl phosphonate. Further, the dr values slightly increase with the steric demand of the *N,S*-acetalic substituent (R<sup>3b</sup>; *e.g.* Table 2, entries 6 and 9) and to a smaller extent with the higher steric demand of the R<sup>2</sup> residues (Table 2, *e.g.* entries 9 and 10). These observations are consistent with the proposal that the growing steric demand of the reactants increases the selectivity. Consequently, hydrophosphonylation would thus be categorized as a kinetically controlled reaction with moderate stereoselectivity. On the other hand, hydrophosphonylation with more bulky phosphonates leads to a decrease in dr values (Table 2, entries 3 to 5), which contradicts this proposal. Therefore, the observed dr values might not represent the selectivity of the actual P–C bond forming reaction but might be superimposed by epimerisation of the *N,S*-acetalic stereogenic centre leading to thermodynamic control of the diastereomeric ratio. The stereochemistry of the newly formed stereogenic centre in the α-position would thus depend on both the selectivity of the addition reaction and the occurrence of the epimerisation process. But even if epimerisation occurs at the *N,S*-acetal (C-2), the stereogenic centre in the α-position may be obtained in a single configuration under certain circumstances. In order for this to happen, the actual addition reaction has to be highly selective and irreversible.

We investigated the epimerisation of the *N,S*-acetal by NMR spectroscopy in CDBr<sub>3</sub> (in the absence of BF<sub>3</sub>) with thiazolidinylphosphonate **9d**. A series of magnetisation transfer experiments at the diastereotopic *N,S*-acetalic hydrogen atoms at different temperatures were performed. The 2-H proton of the *cis*-isomer was labelled by a presaturation pulse (Scheme 4). On fast chemical exchange this magnetic label should be transferred to the 2-H proton of the *trans*-isomer and *vice versa*.

We found that the chemical exchange of the two diastereotopic 2-H atoms was faster at higher temperatures indicating

‡ The relative configuration of the favoured diastereomer was identified by NMR spectroscopy. See the section “Relative configuration and ‘upfield rule’” for details.

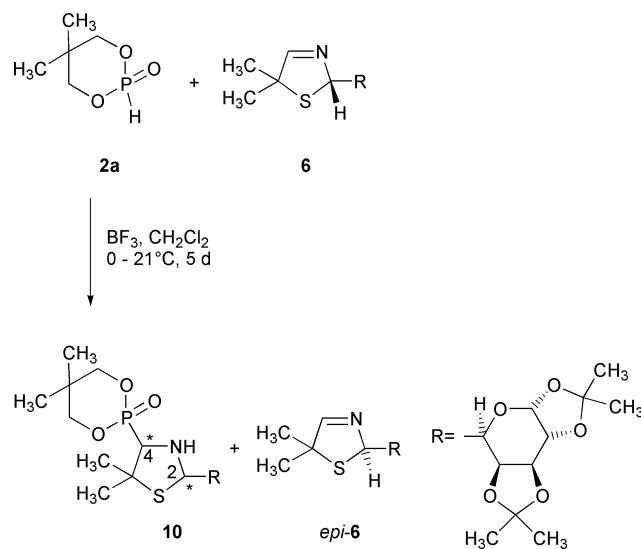


**Scheme 4** Magnetisation transfer NMR experiments on **9d**. (One enantiomer of each of the racemic compounds is shown.)

accelerated epimerisation of the *N,S*-acetal. The diastereomeric ratio of *dr* = 76 : 24 observed in  $\text{CDBr}_3$  can therefore be assigned to equilibrium conditions. Heating the thiazolidinylphosphonate **9d** in the Lewis basic solvent  $\text{DMSO-}d_6$  (100 °C for one hour) followed by sudden cooling changed the diastereomeric ratio from an initial value of *dr* = 81 : 19 towards an equalized metastable mixture of *dr* = 50 : 50, indicating acid catalysis of epimerisation of the *N,S*-acetal. §

The contributions of selectivity during C–P bond formation and epimerisation of the *N,S*-acetal to the final observed *dr* value of the product are indistinguishable if the 3-thiazolines (like **5a–5f**) have a single *N,S*-acetalic stereocentre. Application of the galactose derived, isomerically pure chiral 3-thiazoline **6**<sup>28</sup> provides internal control of epimerisation at the *N,S*-acetal due to the presence of additional stereogenic centres within the sugar residue.

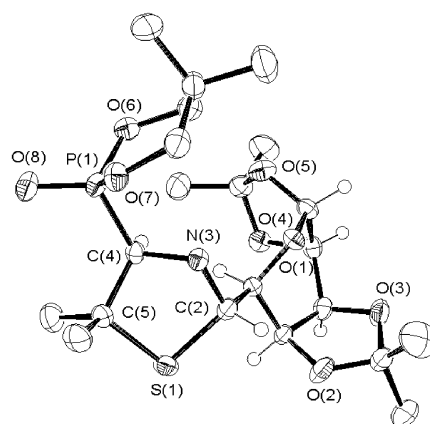
The  $\text{BF}_3$ -mediated hydrophosphonylation reaction of the 3-thiazoline **6** resulted in a crude mixture of three or four diastereomeric products **10** clearly demonstrating epimerisation during the reaction (Scheme 5).



**Scheme 5** Hydrophosphonylation of **6**.

Digestion of the crude product with diethyl ether led to the separation of 11% isomerically pure (2*S*,4*R*)-**10** (one of the minor isomers) as a colourless precipitate. We obtained suitable crystals for X-ray analysis, which revealed a 2,4-*trans*-configuration for this isomer (Fig. 2). Column chromatography of the residual crude product led to additional 57% **10** as a mixture of diastereomers and 5% of a 3-thiazoline *epi-6*, which was identified by NMR spectroscopy as the C-2-epimer of the initial 3-thiazoline **6**. The diastereomers of **10** could not be separated completely by chromatography.

§ In humid conditions, bromoform contains traces of HBr providing the opportunity for acid catalysis.



**Fig. 2** X-Ray analysis of *trans*-configured (2*S*,4*R*)-**10**.

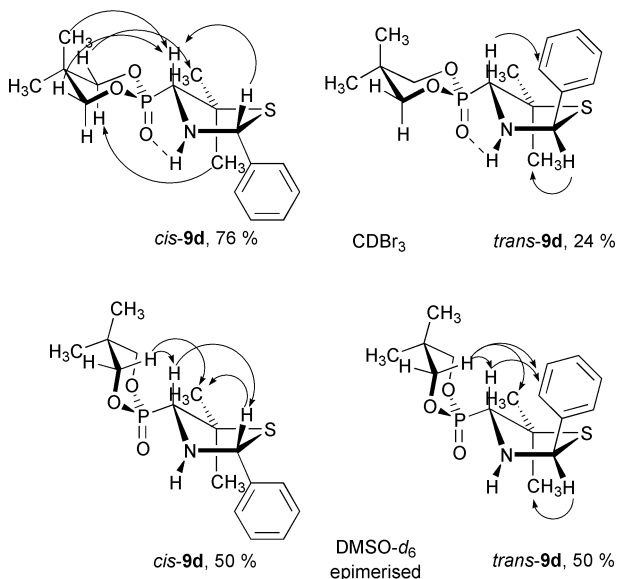
In order to determine the origin of 3-thiazoline *epi-6*, the C-2 epimer of **6**, we used TLC to monitor mixtures of  $\text{BF}_3$ -activated thiazoline **6** in the presence and absence of phosphonate **2a**. We found that  $\text{BF}_3$ -activated 3-thiazoline **6** undergoes little epimerisation in the absence of a phosphonate. Initial traces of thiazoline *epi-6* were detected after five days at room temperature, when the brown colour of the reaction mixture indicated partial decomposition. In presence of the phosphonate **2a** epimerisation of **6** occurs within a few hours. The occurrence of *epi-6* indicates that hydrophosphonylation has to be reversible under the reaction conditions, since epimerisation of the *N,S*-acetal takes place at the corresponding thiazolidinylphosphonate but not at the 3-thiazoline itself. As a consequence, the configuration at C-2 will be influenced by epimerisation as well as by the configuration at C-4 during the hydrophosphonylation reaction.

Use of chiral 3-thiazolines **5** and **6** bearing a stereogenic centre at the *N,S*-acetal in the  $\text{BF}_3$ -mediated hydrophosphonylation leads to the corresponding thiazolidinylphosphonates **9** and **10**. The observed *dr* values result from epimerisation of the diastereomeric products and do not represent selectivity of the actual hydrophosphonylation. So far, experimental results do not permit a reliable statement on the diastereoselectivity of the actual C–P bond formation and thus on the possibility of achieving configurational conformity at the newly formed stereogenic centre at C-4 if the reaction could be kept irreversible. Considerations on the diastereoselectivity of the actual addition step and a description of the reaction by *ab initio* calculations are discussed below.

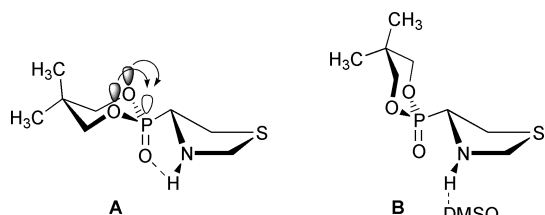
#### Relative configuration and ‘upfield rule’

The relative configuration of thiazolidinylphosphonates **8a** and **8b** bearing two neighbouring stereogenic centres can readily be assigned assessing suitable vicinal H–H spin coupling constants. However, in most cases the relative configuration of thiazolidinylphosphonates **9a–9j** with stereocentres at C-2 and C-4 cannot be assigned in this way because couplings with amino protons are usually not resolved. Despite this, we have been able to obtain suitable NMR spectra of a diastereomeric mixture of thiazolidinylphosphonate **9d** (*dr* = 80 : 20 in  $\text{CDCl}_3$ ) where the 4-H–NH–2-H coupling system was resolved for the major isomer ( $^3J_{4\text{-H,NH}} = 13.8 \text{ Hz}$ ,  $^3J_{\text{NH},2\text{-H}} = 12.1 \text{ Hz}$ ) suggesting alternating pseudo axial orientation of the hydrogen atoms and a 2,4-*cis*-configuration for the major diastereomer of **9d**. Unfortunately, the corresponding couplings were not resolved for the minor isomer.

To support this preliminary assignment of relative configuration, we decided to record NOESY spectra of the diastereomeric mixtures of **9d** (Fig. 3) and **9g** in different solvents. The spectra of **9d** were recorded after thermal epimerisation in  $\text{DMSO-}d_6$  for a metastable diastereomeric mixture (*dr* = 50 : 50) as well as for diastereomeric mixture of *dr* = 76 : 24 in  $\text{CDBr}_3$  at



**Fig. 3** NOESY geometries (qualitative) of **9d** in different solvents including selected NOEs.



**Fig. 4** Synergism of the H-bond and  $n_{\text{O}}-\sigma_{\text{P}=\text{O}}^*$  anomeric effect.

equilibrium conditions.<sup>¶</sup> For both thiazolidinylphosphonates **9d** and **9g** the major diastereomers were identified as having a 2,4-*cis*-configuration.

The phosphorus containing heterocycle was found to have a chair like conformation in both solvents, DMSO- $d_6$  and CDBr<sub>3</sub>. However, NOESY spectra conveyed a notable dependence of its orientation on the solvent. Especially strong crosspeaks of 4-H and the axial protons of the cyclic bisester, which are present in DMSO- $d_6$  but not in CDBr<sub>3</sub> for both diastereomers of **9d**, indicate an equatorial position of the P=O group in DMSO- $d_6$  and an axial position in CDBr<sub>3</sub>. The sterically demanding thiazolidinyl residue has to fit in an axial orientation in DMSO- $d_6$  as solvent. This conformational inversion of the phosphonic bisester seems to have its origin in different interactions of the thiazolidinylphosphonate with solvents of different Lewis acidity.

A common stereoelectronic motif in heterocyclic compounds is that anomeric effects influence the orientation of anomeric substituents, *i.e.*, the oxo group connected to phosphorus in this case. Axial orientation of the phosphoroxo residue agrees with an anomeric interaction of the heterocycle oxygen lone pairs and  $\sigma_{\text{P}=\text{O}}$  antibonding orbital ( $n_{\text{O}}-\sigma_{\text{P}=\text{O}}^*$ ). This anomeric effect increases the partial negative charge at the oxygen ligand, which is stabilized by a synergistic intramolecular H-bond ( $\text{P}=\text{O}\cdots\text{H}-\text{N}$ , Fig. 4).

The strongly Lewis basic DMSO might disturb this H-bond as a result of effective coordination of the amino proton and

<sup>¶</sup> NMR samples of thiazolidinylphosphonate **9d** in CDBr<sub>3</sub> and DMSO- $d_6$ , respectively, were degassed by an argon stream, heated to 100 °C for one hour and suddenly cooled with ice-water. The diastereomeric ratio of **9d** in DMSO- $d_6$  changed from an initial value of *dr* = 81 : 19 towards an equalised mixture of *dr* = 50 : 50. By contrast, in CDBr<sub>3</sub>, the diastereomeric mixture was found to have an unchanged *dr* value (*dr* = 74 : 26) after heating, possibly due to acid catalysis of the epimerisation of the *N,S*-acetal. Equalized amounts of the *cis/trans* diastereomers provided a more reliable comparison of the NOE contacts.

**Table 3** Differences in chemical shift ( $\Delta\delta$  in ppm) between *cis*- and *trans*-isomers (CDCl<sub>3</sub>, 300 K)<sup>a</sup>

	4-H	2-H	C-5	C-4	C-2
<b>9a</b>	0.09	-0.18	-0.6	2.8	3.1
<b>9b</b>	0.05	-0.19	-0.3	3.0	3.2
<b>9c</b>	0.10	-0.18	—	3.3	3.2
<b>9d</b>	0.07	-0.14	—	2.5	3.2
<b>9e</b>	-0.07	0.06	-0.5	1.7	2.1
<b>9f</b>	-0.18	— <sup>b</sup>	-0.7	2.5	2.7
<b>9g</b>	-0.10	0.13	—	—	—
<b>9i</b>	-0.09	0.15	0.9	—	2.0

<sup>a</sup> Negative  $\Delta\delta$  values represent an upfield shift for the *cis*-isomer. <sup>b</sup> Not detected because the peaks were convoluted or invisible.

thus counteract such stabilisation. Such coordination can be monitored by the NH-shift in DMSO- $d_6$  compared to CDBr<sub>3</sub> of  $\Delta\delta(\text{cis-9d}) = 0.36$  ppm and  $\Delta\delta(\text{trans-9d}) = 1.62$  ppm. The conformation of the P-heterocycle in DMSO corresponds to that found in the crystal structure of *trans*-**10** (see Fig. 2).<sup>29</sup> By contrast, *ab initio* calculations under vacuum conditions at the HF/6-31G(d,p) level reveal the equatorial orientation of the thiazolidinyl residue of **9d** (see Fig. 7) to be more stable.

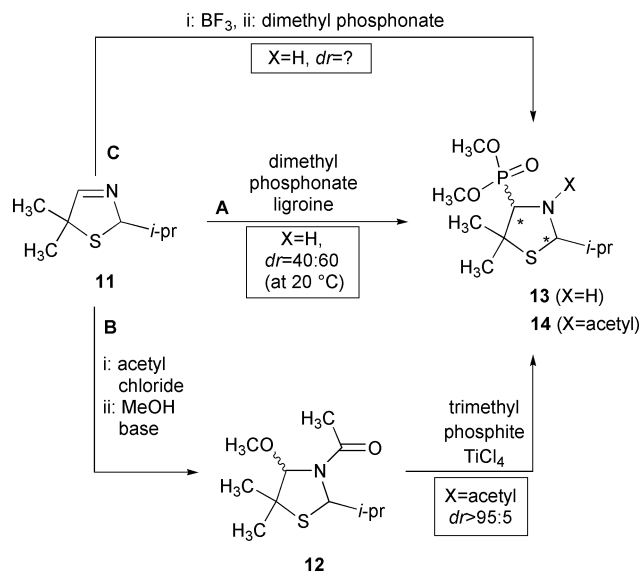
A simple indicator for relative configurational analysis of 2,4-disubstituted 1,3-heteropentanes<sup>30</sup> has been reported with NMR spectroscopic upfield (or shift) rules. Regarding <sup>13</sup>C NMR spectroscopy, the C-2 and C-4 signals appear downfield and the C-5 signal appears upfield for the 2,4-*cis*-isomer compared to the corresponding *trans*-isomer in several 2-substituted 1,3-thiazolidine-4-carboxylic acids.<sup>31</sup> In contrast, *N*-acylated 1,3-thiazolidine-4-carboxylic acids<sup>32</sup> show inverse behaviour. The upfield rule strongly depends on different conformational behaviour. While the nitrogen atom is surrounded by trigonal planar coordination in the *N*-acylated compounds, the free thiazolidinecarboxylic acid contains a pyramidal coordinated nitrogen atom with the amino proton predominantly in pseudo axial position due to an  $n_{\text{N}}-\sigma_{\text{C-S}}^*$  anomeric effect.<sup>33</sup> Each of the coordination types leads to conformational ensembles with different ring puckering.

The relative carbon shifts of the *cis/trans*-isomers of the thiazolidinylphosphonates with stereocentres in positions 2 and 4 of the thiazolidine heterocycle as in **9a–9j** follow the same upfield rule as the analogous carboxylic acids (Table 3). However, the bridging carbon atoms of spiro compounds (*e.g.* C-5 of **9i**) may cause exceptions to the rule.

Regarding <sup>1</sup>H NMR spectroscopy, different shift behaviour has been reported for the *cis/trans*-diastereomers of 2-substituted 1,3-thiazolidine-4-carboxylic acids.<sup>31–34</sup> The *cis/trans*-difference in chemical shift of 2-H and 4-H of diastereomeric thiazolidinylphosphonates investigated by us depends on the substituents of the *N,S*-heterocycle and the solvent. The derivatives might be divided into two groups. The *cis*-isomer of 2-phenyl derivatives **9a–9d** displays an upfield shift for 2-H and a downfield shift for 4-H compared to the *trans* analogues. The other thiazolidinylphosphonates **9e–9j** display an inverse behaviour. Proton chemical shifts strongly depend on several anisotropic effects of the neighbouring residues as well as on the solvent and may not be translated into puckering information without certain concerns.

### Stereochemical considerations on the BF<sub>3</sub>-mediated hydrophosphonylation

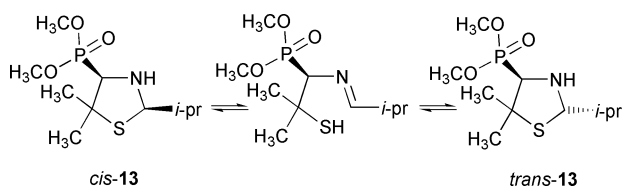
Recently, we reported on methods for the phosphonylation of 3-thiazolines by thermal activation in ligroine (path A, Scheme 6) and *via* formation of an *N*-acetylated intermediate (path B, Scheme 6).<sup>34b,35</sup> Comparison of the diastereoselectivity employing chiral 3-thiazolines bearing a chiral *N,S*-acetal in the different reactions made us believe that Lewis acid mediated hydrophosphonylation might actually be a highly stereo-



**Scheme 6** Dependence of diastereoselectivity of phosphonylation on *N*-acylation.

selective event (path C, Scheme 6). If this were the case, it should be possible to find optimized reaction conditions (variation of solvent, Lewis acid *etc.*) to obtain adducts of conformational conformity at the newly formed stereogenic centre at C-4.

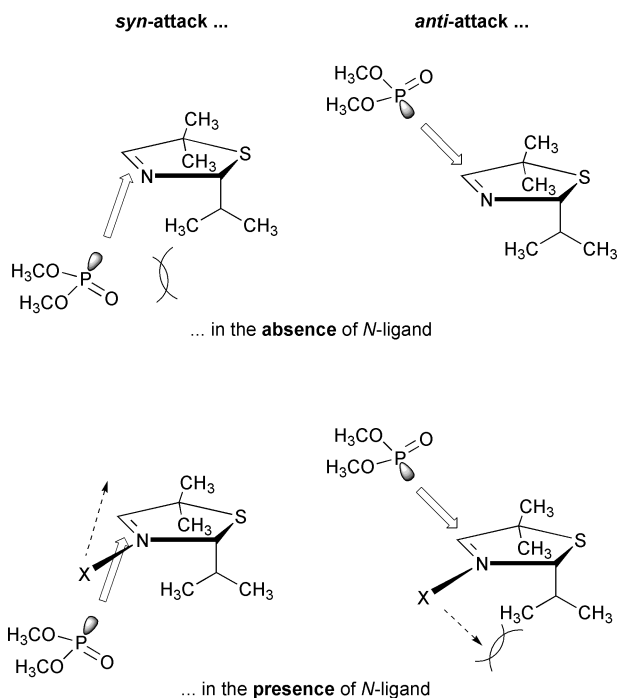
As depicted in Scheme 6, diastereoselectivity strongly depends on the method of phosphonylation. If hydrophosphonylation of 3-thiazoline **11** is carried out in ligroine without activation by a Lewis acid (path A, Scheme 6), the achieved diastereomeric ratio of the corresponding product **13** strongly depends on the reaction temperature ( $dr_{cis:trans} = 40 : 60$  at  $20\text{ }^\circ\text{C}$ ,  $75 : 25$  at  $100\text{ }^\circ\text{C}$ ).<sup>34b,35</sup> The temperature dependence of the *dr* values may be rationalized in terms of kinetic reaction control at lower temperatures and thermodynamic control at higher temperatures. The actual addition reaction slightly favouring 2,4-*trans*-configured thiazolidinylphosphonates is obviously followed by a ring-chain epimerisation (as depicted in Scheme 7), favouring the thermodynamically more stable 2,4-*cis*-configured thiazolidinylphosphonates.



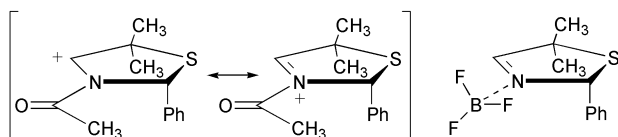
**Scheme 7** Ring-chain epimerisation at the *N,S*-acetalic stereocentre.

In contrast, phosphonylation of 3-thiazoline **11** *via* the *N*-acetylated intermediate **12** (path B, Scheme 6) conveyed the strong diastereoselecting potential of the *N,S*-acetalic substituent if an *N*-acyl ligand is present. Epimerisation of *N,S*-acetalic centre is suppressed by *N*-acylation in this synthesis. Treatment of 3-thiazoline **11** with acetyl chloride followed by methanol gives access to the *N*-acetylated intermediate **12** which can be converted into the 2,4-*cis*-configured *N*-acetylated  $\alpha$ -amino phosphonate **14** in a highly diastereoselective manner (path A, Scheme 6).<sup>34b,35</sup> We believe that the substantial difference in strength and even in the direction of diastereoselectivity between the two reaction pathways A and B (Scheme 6) results from mediation (or transport) of chiral information by the *N*-acetyl ligand. As depicted in Fig. 5, the P-nucleophile approaching the imine moiety of the heterocycle will possibly face different steric interaction in the presence or in the absence of a ligand at the nitrogen atom.

In the absence of an *N*-ligand (as in path A, Scheme 6) steric



**Fig. 5** Postulated mediation of 'steric information' by an *N*-ligand.

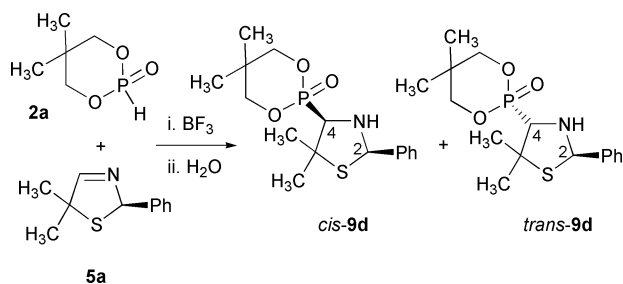


**Fig. 6** The structural analogy of the *N*-acyliminium ion and the  $\text{BF}_3$ -activated 3-thiazoline.

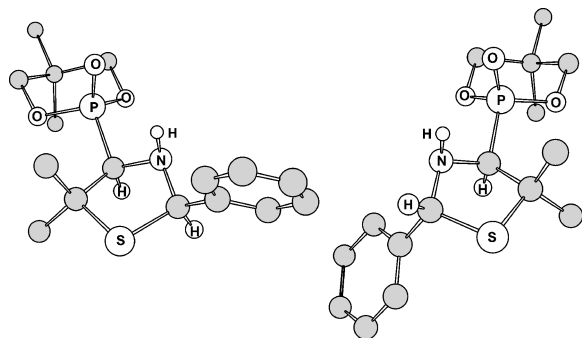
hindrance might be more effective if the nucleophile approaches from the same face as that on which the *N,S*-acetalic substituent resides (*syn*-attack, Fig. 5) and thus formation of 2,4-*trans*-configured products by an *anti*-attack is more favoured. In contrast, if an *N*-ligand is present, it may avoid steric hindrance with the incoming nucleophile by bending slightly towards the opposite face of the heterocycle (Fig. 5, dashed arrows). This time interaction of the *N*-ligand with the *N,S*-acetalic substituent should interfere with *anti*-attack of the nucleophile, leading to predominant formation of 2,4-*cis*-configured products. Phosphonylation of 3-thiazolines *via* *N*-acetylation involves an *N*-acyliminium ion as a reactive intermediate, which strongly favours 2,4-*cis*-products on nucleophilic attack by trimethyl phosphite (path B, Scheme 6).<sup>34b,35</sup> Since the *N*-acyliminium intermediate and the  $\text{BF}_3$ -activated 3-thiazoline used in the Lewis acid mediated hydrophosphonylation reaction (Fig. 6) are structural analogues, the actual addition step of the Lewis acid mediated hydrophosphonylation of 3-thiazolines with a stereogenic centre in the C-2 position might also be a highly selective event. In a similar fashion to the *N*-acyl group, the Lewis acid might serve as a steric mediator. We decided to evaluate this theory by theoretical examination of the Lewis acid mediated hydrophosphonylation reaction.

#### Modelling of the $\text{BF}_3$ -mediated hydrophosphonylation

Our focus of the quantum chemical modelling was on diastereoselective hydrophosphonylation of 2-substituted 3-thiazoline **5a** leading to the diastereomeric thiazolidinylphosphonates *cis*-**9d** and *trans*-**9d** (Scheme 8). We aimed to compare the experimental *dr* value with those predicted by our quantum chemical studies in case of thermodynamic as well as kinetic reaction control. It was our intention to isolate the individual contribution of the actual addition step to the *dr* value and to determine whether



**Scheme 8** Diastereoselective hydrophosphonylation. (One enantiomer of each of the racemic compounds is shown.)



**Fig. 7** Optimized geometries of the diastereomers of **9d**. (One enantiomer of the racemic compound is shown.)

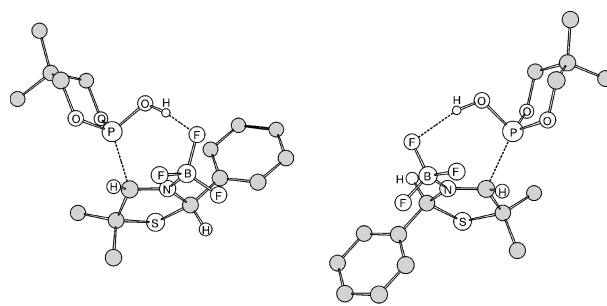
the reaction could be stereoselective if solely under kinetic control.

In the case of rapid epimerisation at the *N,S*-acetal the *dr* value of the product **9d** should be under thermodynamic control and thus be determined by the relative stability of the two diastereomers *cis*-**9d** and *trans*-**9d**. The two diastereomers were calculated with the phosphorus heterocycle in a chair conformation with an equatorial orientation for the thiazolidine residue as indicated by NOESY experiments in  $\text{CDBr}_3$  (Fig. 3).

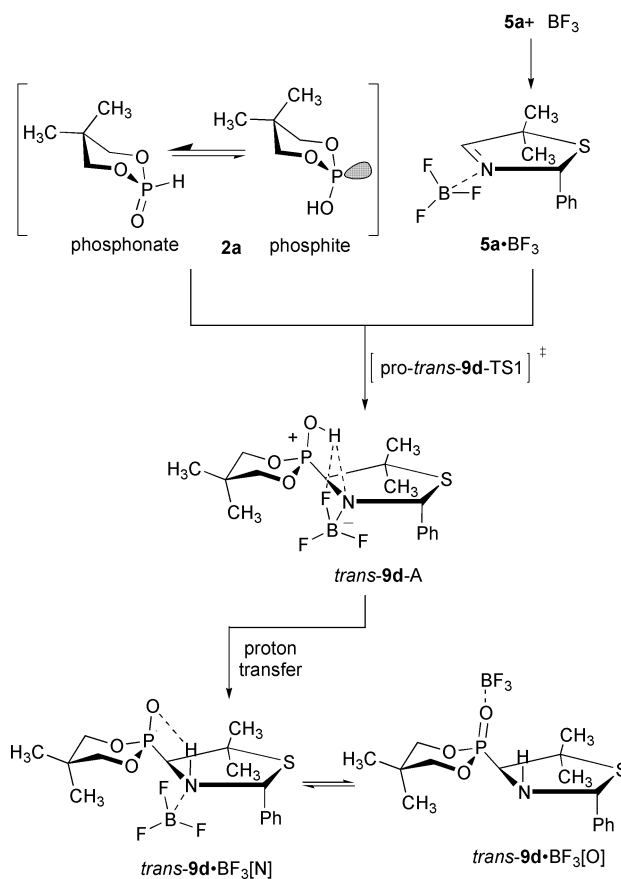
The geometries of *cis*-**9d** and *trans*-**9d** as presented in Fig. 7 were optimized at the HF/6-31G(d,p) level of theory. The two diastereomers show a slight difference in enthalpy of  $\Delta\Delta H = 0.27 \text{ kcal mol}^{-1}$  and in Gibbs free energy of  $\Delta\Delta G = 0.35 \text{ kcal mol}^{-1}$ . According to the experimental results, the *cis*-**9d** diastereomer was calculated to be more stable than the corresponding *trans*-isomer. Following the equation  $\Delta\Delta G_{\text{cis-trans}} = -RT \ln(\text{dr}_{\text{cis:trans}})$  the diastereomers of **9d** should appear in a mixture of *dr* 64 : 36 under equilibrium conditions. Thus, the modelling slightly underestimates the experimental *dr* value of **9d** in  $\text{CDBr}_3$  (*dr* = 76 : 24). Modelling at higher levels may give a more accurate representation, but also would acquire extensively computational efforts.

Modelling of the expected *dr* value in the case of kinetic control of the hydrophosphonylation reaction is more complex and involves examination of the whole reaction profile. The hydrophosphonylation reaction consists of several elementary reaction steps and the rate-controlling transition state for each of the two diastereotopic reaction sequences has to be determined for the theoretical description of the diastereoselectivity. We rationalized the mechanism of the  $\text{BF}_3$ -mediated hydrophosphonylation as follows (Scheme 9).

In accordance with the NMR spectra, the nitrogen lone pair of 3-thiazoline **5a** is coordinated and activated by the Lewis acid  $\text{BF}_3$ . The cyclic ester of phosphonic acid **2a**, which has been used as P-nucleophile, is known to undergo a phosphite-phosphonate tautomerism with the phosphite tautomer as the nucleophilic (active) form and the phosphonate tautomer as the almost exclusively favoured but non-nucleophilic (resting) form (Scheme 9).<sup>36</sup> Therefore, the phosphite tautomer of **2a** and the  $\text{BF}_3$ -activated 3-thiazoline **5a**· $\text{BF}_3$  are most likely the actual reactants of the addition reaction. *Ab initio* modelling of the following reaction path led to the prediction of a two-step



**Fig. 8** Optimized (HF/6-31G\*\*) transition states **9d-TS1**. (One enantiomer of racemic compound is shown.)



**Scheme 9** Postulated reaction mechanism. (Only formation of the *trans*-isomer of **9d** and one enantiomer of each of the racemates is shown.)

mechanism. In a first step the nucleophilic attack of the phosphorus lone pair on to the imine carbon leads to the formation of a new carbon–phosphorus bond and determines the configuration of the newly generated stereogenic centre of the two diastereomeric intermediates *cis*-**9d-A** and *trans*-**9d-A**. In the case of kinetic control, the difference in energy between the affiliated diastereotopic transition states **9d-TS1** (if they are rate-controlling) should thus determine the diastereoselectivity of the actual addition step. We have been able to optimize and verify these transition states as depicted in Fig. 8. || In the second part of the reaction, the intermediates **9d-A** undergo proton transfer leading to the more stable thiazolidinylphosphonates *cis*-**9d**· $\text{BF}_3$  and *trans*-**9d**· $\text{BF}_3$  with the Lewis acid  $\text{BF}_3$  coordinated at the nitrogen atom or the oxygen atom. \*\* The final

|| See also the description of computational details below in the Experimental section.

\*\* Magnetisation transfer NMR experiments conveyed the fast exchange of the Lewis acid between the two coordination sites of the adduct at room temperature [**9d**· $\text{BF}_3$ (N) and **9d**· $\text{BF}_3$ (O)]. It might be noteworthy that within these experiments chemical exchange of the *cis/trans* diastereomeric forms has not been detected, indicating a substantially smaller rate of exchange.

product is released by hydrolysis of this complex. Examination of the proton migration process indicated a possible pathway of lower energy than transition states **9d**-TS1. The latter thus has to be considered the configuration-controlling as well as the rate-controlling state for hydrophosphonylation.

Molecular geometries of both transition states *pro-cis*-**9d**-TS1 and *pro-trans*-**9d**-TS1 indicate that the BF<sub>3</sub> ligand moves slightly towards the opposite face of the thiazoline heterocycle to the incoming P-nucleophile, which is in accordance with our previous proposal. Comparing the energies of the two transition states the *pro-cis* transition state was calculated to be more stable than its corresponding *pro-trans* analogue. In detail, the *pro-cis*-**9d**-TS1 was favoured over the *pro-trans*-**9d**-TS1 by  $\Delta\Delta H_{cis-trans}^\ddagger = 1.05 \text{ kcal mol}^{-1}$  in enthalpy and  $\Delta\Delta G_{cis-trans}^\ddagger = 1.35 \text{ kcal mol}^{-1}$  in Gibbs free energy (Fig. 8). The difference in Gibbs free energies of the transition states turned out to be substantially higher than the corresponding difference of the final products *cis*- and *trans*-**9d**. Thus, the modelling studies predict high diastereoselectivity in the range of dr = 91 : 9 [on the basis of  $\Delta\Delta G_{cis-trans}^\ddagger = -RT\ln(\text{dr}_{cis:trans})$ ] of the BF<sub>3</sub>-mediated hydrophosphonylation in the case of kinetic control.

## Conclusion

We have described the synthesis of a number of previously unknown thiazolidinylphosphonates by the diastereoselective Lewis acid mediated hydrophosphonylation of 3-thiazolines and systematically investigated the stereoselecting potential of different chiral reactants. Application of the chiral BINOL-phosphonate **1**, available in both enantiomerically pure forms, provided highly stereoselective formation of the corresponding thiazolidinylphosphonates. The relative configuration of the products was elucidated by X-ray analysis. (*R*<sub>a</sub><sup>\*</sup>)-BINOL was shown to induce an *R*<sup>\*</sup>-configuration at the newly formed stereogenic centre in the  $\alpha$ -position of the amino phosphonates **7**.

Lewis acid mediated hydrophosphonylation of chiral 3-thiazoline **4** with the stereogenic centre in the C-5 position yielded 4,5-*trans*-configured products in a highly diastereoselective manner. Chiral 3-thiazolines **5**, which contain a stereogenic centre in the C-2 position of the cyclic *N,S*-acetal, undergo epimerisation at the *N,S*-acetal under the reaction conditions. In this case the observed dr values result rather from epimerisation than from stereoselection of the hydrophosphonylation reaction. The structural properties of the resulting thiazolidinylphosphonates **9** and **10** have been examined by X-ray and NMR techniques. Furthermore, the thiazolidinylphosphonates **9** have been shown to follow NMR shift rules in a similar fashion to the corresponding thiazolidinylcarboxylic acids.

Additionally, we have investigated theoretical considerations of the stereochemical course of BF<sub>3</sub>-mediated hydrophosphonylation involving chiral 3-thiazolines **5**, since the actual stereoselection during C–P bond formation could not be derived from experimental results. These considerations have been supported by *ab initio* modelling of the reaction, which revealed the *cis*-diastereomer to be the kinetically favoured product.

## Experimental

### General

If indicated with 'abs.' solvents were purified prior to use as follows: dichloromethane was distilled from CaCl<sub>2</sub>, THF and Et<sub>2</sub>O were distilled from sodium and benzophenone. Thin layer chromatography (TLC) analyses were performed on silica gel Polygram<sup>®</sup> plates with fluorescence indicator from Macherey Nagel & Co., Düren. For preparative chromatography Merck silica gel 60, 230–400 mesh was used. Melting points were determined in open capillaries in a Dr Lindström instrument

and are uncorrected. Optical rotations [ $\alpha$ ]<sub>D</sub> were determined on a Perkin Elmer polarimeter (241 MC), at 21 °C, *c* = 1 in chloroform. IR spectra were recorded on a Beckmann-Spectrophotometer (IR 4220). <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on a Bruker-Karlsruhe AM 300 spectrometer (300 MHz; 75 MHz) and on a Bruker-Karlsruhe ARX 500 spectrometer (500 MHz; 125 MHz). Chemical shifts,  $\delta$ , are presented in part per million (ppm) and coupling constants, *J*, in hertz (Hz) from tetramethylsilane (TMS) as the internal standard in deuterated solvents such as D<sub>2</sub>O, CDCl<sub>3</sub> and DMSO-*d*<sub>6</sub>. Mass spectra were obtained on a Finnigan-MAT 212 instrument in CI mode with isobutane as a reactant gas. Elemental analyses were performed on a C, H, N-Analyser EA 1108 from Fisons Instruments. All diastereomeric ratios were determined from NMR spectra of the crude products. Analytical details referring to the major diastereomer of the corresponding title compound are indicated by 'ma'. Accordingly, the minor diastereomer is indicated by 'mi'. The following compounds were synthesized according to known procedures: *rac*-7 $\lambda^5$ -dinaphtho[2,3-*d*:2,3-*f*][1,3,2]dioxaphosphepin-7-one (= BINOL-phosphonate, **1**),<sup>37</sup> 5,5-dimethyl-1,3,2 $\lambda^5$ -dioxaphosphinan-2-one (**2a**),<sup>38</sup> diisopropyl phosphonate (**2b**),<sup>39</sup> 2,2,5,5-tetramethyl-2,5-dihydro-1,3-thiazole (**3a**),<sup>26</sup> 2,2-dimethyl-1-thia-4-azaspiro[4.5]dec-3-ene (**3b**),<sup>26</sup> 2,2-dimethyl-1-thia-3-azaspiro[4.5]dec-3-ene (**3c**),<sup>40</sup> 7-thia-14-azadispiro[5.1.5.2]pentadec-14-ene (**3d**),<sup>40</sup> 1-thia-4-azaspiro[4.5]dec-3-ene (**3e**),<sup>41</sup> *rac*-2,2-dimethyl-5-isopropyl-2,5-dihydro-1,3-thiazole (**4**),<sup>42</sup> *rac*-2-phenyl-5,5-dimethyl-2,5-dihydro-1,3-thiazole (**5a**),<sup>41</sup> *rac*-2-*tert*-butyl-5,5-dimethyl-2,5-dihydro-1,3-thiazole (**5d**),<sup>43</sup> *rac*-2-*tert*-butyl-1-thia-3-azaspiro[4.5]dec-3-ene (**5e**),<sup>44</sup> *rac*-2-isopropyl-1-thia-3-azaspiro[4.5]dec-3-ene (**5f**).<sup>45</sup>

### General procedure for the BF<sub>3</sub>-catalyzed hydrophosphonylation of 2,5-dihydro-1,3-thiazoles **3–5** (GP1)

The appropriate 2,5-dihydro-1,3-thiazole **3–5** (5 mmol) was dissolved in dichloromethane (20 ml) and treated with one equivalent BF<sub>3</sub>·Et<sub>2</sub>O at 0 °C for one hour. The corresponding phosphonate **1** or **2** (5 mmol) was added at 0 °C and the resulting mixture was stirred for five days without further cooling. After hydrolysis with water (10 ml) the phases were separated and the aqueous layer was extracted twice with dichloromethane (20 ml). The combined organic layers were washed with water and dried with MgSO<sub>4</sub>. After evaporating the solvent *in vacuo* the crude products were colourless or light yellow oils, which crystallized at room temperature in some cases. Purification *via* flash column chromatography on silica gel (*n*-hexane–propan-2-ol, 95 : 5 eluent) gave the desired racemic compounds **7–9**.

***rac*-2-Benzyl-5,5-dimethyl-2,5-dihydro-1,3-thiazole (5b)**. The title compound was prepared using the modified Asinger reaction<sup>26</sup> employing phenylacetaldehyde in 18% yield, bp 85–90 °C (2.0 × 10<sup>-2</sup> mbar);  $\delta_{\text{H}}$ (300 MHz; CDCl<sub>3</sub>) 1.35, 1.49 [6 H, 2 s, C-5(CH<sub>3</sub>)<sub>2</sub>], 3.06 (1 H, dd, <sup>2</sup>*J* 13.7, <sup>3</sup>*J* 7.1, C-2-CH<sub>2</sub>), 3.33 (1 H, dd, <sup>2</sup>*J* 13.7, <sup>3</sup>*J* 5.5, C-2-CH<sub>2</sub>), 5.94 (1 H, ddd, <sup>3</sup>*J* 7.1, <sup>3</sup>*J* 5.5, <sup>4</sup>*J* 2.2, 2-H), 7.03 (1 H, d, <sup>4</sup>*J* 2.2, 4-H), 7.20–7.33 (5 H, m, phenyl);  $\delta_{\text{C}}$ (75 MHz; CDCl<sub>3</sub>) 29.1, 29.3, 44.8, 64.2, 84.5, 126.5, 128.0, 129.7, 137.5, 168.7. ††

***rac*-2-(2-Phenylethyl)-5,5-dimethyl-2,5-dihydro-1,3-thiazole (5c)**. The title compound was prepared using the modified Asinger reaction<sup>26</sup> employing 3-phenylpropionaldehyde in 44% yield, bp 110 °C (3.0 × 10<sup>-2</sup> mbar);  $\delta_{\text{H}}$ (300 MHz; CDCl<sub>3</sub>) 1.55, 1.59 [6 H, 2 s, C-5(CH<sub>3</sub>)<sub>2</sub>], 2.09 (1 H, m, C-2-CH<sub>2</sub>CH<sub>2</sub>), 2.35 (1 H, m, C-2-CH<sub>2</sub>CH<sub>2</sub>), 2.75–2.90 (2 H, m, C-2-CH<sub>2</sub>CH<sub>2</sub>), 5.67

†† Elemental analysis of 2,5-dihydro-1,3-thiazoles **5b** and **5c** was not carried out due to the intensive odour of these compounds. However, **5b** and **5c** were characterized by further derivatization to compounds **9e** and **9f**, which were fully characterized.

(1 H, ddd,  $J$  7.1,  $J$  5.5,  $^4J$  2.2, 2-H), 7.06 (1 H, d,  $^4J$  2.2, 4-H), 7.18–7.33 (5 H, m, phenyl);  $\delta_{\text{C}}$  (75 MHz;  $\text{CDCl}_3$ ) 29.1, 29.7, 32.7, 40.5, 64.0, 82.9, 125.8, 128.2, 128.4, 141.1, 168.2.  $\ddagger\ddagger$

**(2*S*,5*S*)-5,5-Dimethyl-2-(1,2,3,4-di-*O*-isopropylidene- $\beta$ -L-xyllo-1,5-pyranos-5-yl)-2,5-dihydro-1,3-thiazole (6).** The title compound was prepared using the modified Asinger reaction<sup>26</sup> employing 1,2:3,4-di-*O*-isopropylidene- $\alpha$ -D-galacto-hexodialdo-1,5-pyranose.<sup>46</sup> Crystallisation of the crude product (*n*-hexane, –28 °C) yielded 71% of the pure title compound, mp 164 °C;  $[a]_{\text{D}}^{20}$  –31.9 (*c* 1 in  $\text{CHCl}_3$ );  $R_{\text{f}}$  0.65 (*n*-hexane–propan-2-ol, 9 : 1) (Found: C, 55.91; H, 7.30; N, 4.00; S, 9.26.  $\text{C}_{16}\text{H}_{25}\text{NO}_5\text{S}$  requires C, 55.96; H, 7.34; N, 4.08; S, 9.34%).  $\delta_{\text{H}}$  (500 MHz;  $\text{CDCl}_3$ ) 1.28, 1.31, 1.43, 1.44, 1.51, 1.52 [18 H, 6 s,  $\text{C}(\text{CH}_3)_2$ ], 3.57 (1 H, dd,  $^3J$  9.4,  $^3J$  1.7, C-2-CHCHCHCHO), 4.30 (1 H, dd,  $^3J$  5.0,  $^3J$  2.8, C-2-CHCHCHCHO), 4.32 (1 H, dd,  $^3J$  7.7,  $^3J$  1.7, C-2-CHCHCHCHO), 4.59 (1 H, dd,  $^3J$  7.7,  $^3J$  2.8, C-2-CHCHCHCHO), 5.59 (1 H, d,  $^3J$  5.0, C-2-CHCHCHCHO), 5.78 (1 H, dd,  $^3J$  9.4,  $^4J$  2.2, 2-H), 7.11 (1 H, d,  $^4J$  2.2, 4-H) (assignment supported by HHCOSY);  $\delta_{\text{C}}$  (125 MHz;  $\text{CDCl}_3$ ) 25.1, 25.4, 26.4, 29.3, 30.4, 64.6, 70.7, 71.5, 72.4, 74.0, 82.6, 97.1, 109.0, 110.1, 170.0; *m/z* 344 ( $\text{MH}^+$ , 100%). For analytical data of *epi*-6, see compound 10 in the Experimental section.

**4-(7-Oxo-7 $\lambda^5$ -dinaphtho[2,3-*d*:2,3-*f*][1,3,2]dioxaphosphepin-7-yl)-2,2,5,5-tetramethyl-2,5-dihydro-1,3-thiazole (7a).** The title compound was prepared according to GPI using 1.43 g (10.0 mmol) of 2,2,5,5-tetramethyl-2,5-dihydro-1,3-thiazole 3a and 3.32 g (10.0 mmol) of racemic BINOL-phosphonate 1 as starting material to yield 1.67 g of the pure major diastereomer ( $R_{\text{a}}^*$ ,4*R*<sup>\*</sup>)-7a and 0.57 g of a diastereomeric mixture of 7a as colourless solids (47% overall yield), mp 207 °C (ma);  $R_{\text{f}}$  0.16 (ma), 0.08 (mi) (*n*-hexane–ethyl acetate, 9 : 1) (Found: C, 68.37; H, 5.52; N, 2.62; S, 6.62.  $\text{C}_{27}\text{H}_{26}\text{NO}_3\text{PS}$  requires C, 68.19; H, 5.51; N, 2.95; S, 6.74%).  $\nu_{\text{max}}$  ( $\text{CHCl}_3$ )/ $\text{cm}^{-1}$  3280 (NH), 1250 (P=O);  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ , ( $R_{\text{a}}^*$ ,4*R*<sup>\*</sup>)-7a) 1.44, 1.59, 1.75, 1.77 [12 H, 4 s,  $\text{C}(\text{CH}_3)_2$ ], 3.01 (1 H, s, NH), 3.36 (1 H, d,  $^2J_{\text{PH}}$  16.5, 4-H), 7.32–7.64, 8.00–8.09 (12 H, 2 m, Ar);  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ , ( $R_{\text{a}}^*$ ,4*S*<sup>\*</sup>)-7a) 1.32, 1.47, 1.68, 1.87 [12 H, 4 s,  $\text{C}(\text{CH}_3)_2$ ], 2.37 (1 H, s, NH), 3.80 (1 H, d,  $^2J_{\text{PH}}$  20.4, 4-H), 7.27–7.57, 7.88–8.05 (12 H, 2 m, Ar);  $\delta_{\text{C}}$  (75 MHz;  $\text{CDCl}_3$ , ( $R_{\text{a}}^*$ ,4*R*<sup>\*</sup>)-7a) 28.3, 29.4, 31.9, 32.8, 61.6 (d,  $^2J_{\text{CP}}$  4.4, C-5), 64.0 (d,  $^1J_{\text{CP}}$  140.4, C-4), 75.1 (d,  $^3J_{\text{CP}}$  24.8, C-2), 119.8, 120.9, 121.5, 121.7, 125.8, 125.9, 126.8, 127.0, 127.2, 128.5, 131.3, 131.7, 131.9, 132.3, 145.4 and 147.2 (2 d,  $^2J_{\text{CP}}$  10.6,  $^2J_{\text{CP}}$  10.4);  $\delta_{\text{C}}$  (75 MHz;  $\text{CDCl}_3$ , ( $R_{\text{a}}^*$ ,4*S*<sup>\*</sup>)-7a) 28.5, 28.7, 31.7, 32.3, 62.1 (C-5), 67.2 (d,  $^1J_{\text{CP}}$  135.7, C-4), 75.4 (d,  $^3J_{\text{CP}}$  23.5, C-2), 121.2, 121.6, 125.4, 125.8, 126.4, 126.7, 127.1, 127.1, 128.5, 129.3, 131.2, 133.5, 145.1 and 149.2 (2 d,  $^2J_{\text{CP}}$  8.7,  $^2J_{\text{CP}}$  10.9); *m/z* 476 ( $\text{MH}^+$ , 100%).

**( $R_{\text{a}}^*$ ,3*R*<sup>\*</sup>)-3-(7-Oxo-7 $\lambda^5$ -dinaphtho[2,3-*d*:2,3-*f*][1,3,2]dioxaphosphepin-7-yl)-2,2-dimethyl-1-thia-4-azaspiro[4.5]decane (7b).** The title compound was prepared according to GPI using 0.92 g (5.00 mmol) of 2,2-dimethyl-1-thia-4-azaspiro[4.5]dec-3-ene 3b and 1.66 g (5.00 mmol) of racemic BINOL-phosphonate 1 as starting material to yield 1.20 g (47%) of diastereomerically pure 7b as a colourless solid, mp 209 °C;  $R_{\text{f}}$  0.09 (*n*-hexane–ethyl acetate, 9 : 1) (Found: C, 69.71; H, 5.94; N, 2.55; S, 6.29.  $\text{C}_{30}\text{H}_{30}\text{NO}_3\text{PS}$  requires C, 69.88; H, 5.86; N, 2.72; S, 6.22%).  $\nu_{\text{max}}$  ( $\text{CHCl}_3$ )/ $\text{cm}^{-1}$  3320 (NH), 1260 (P=O);  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 1.29–2.00 (10 H, m, 6-H, 7-H, 8-H, 9-H, 10-H), 1.41, 1.73 [6 H, 2 s,  $\text{C}-2(\text{CH}_3)_2$ ], 3.36 (1 H, d,  $^2J_{\text{PH}}$  16.5, 3-H), 7.31–7.64, 7.95–8.08 (12 H, 2 m, Ar);  $\delta_{\text{C}}$  (75 MHz;  $\text{CDCl}_3$ ) 23.6, 25.2, 25.5, 28.1, 29.5, 41.1, 41.3, 59.0 (C-2), 63.1 (d,  $^1J_{\text{CP}}$  139.7, C-3), 80.7 (d,  $^3J_{\text{CP}}$  24.0, C-5), 119.8, 120.9, 121.5, 121.7, 125.8, 125.9, 126.8, 126.9, 126.9, 127.2, 128.5, 131.3, 131.7, 131.8, 132.3, 145.5 and 147.5 (2 d,  $^2J_{\text{CP}}$  10.3,  $^2J_{\text{CP}}$  10.3); *m/z* 516 ( $\text{MH}^+$ , 100%), 184 [ $\text{MH}^+$  – BINOL-P(O)H, 96].

**4-(7-Oxo-7 $\lambda^5$ -dinaphtho[2,3-*d*:2,3-*f*][1,3,2]dioxaphosphepin-7-yl)-2,2-dimethyl-1-thia-3-azaspiro[4.5]decane (7c).** The title compound was prepared according to GPI using 0.92 g (5.00 mmol) of 2,2-dimethyl-1-thia-3-azaspiro[4.5]dec-3-ene 3c and 1.66 g (5.00 mmol) of racemic BINOL-phosphonate 1 as starting material to yield 0.84 g of the pure major diastereomer ( $R_{\text{a}}^*$ ,4*R*<sup>\*</sup>)-7c and 0.10 g of a diastereomeric mixture of 7c as colourless solids (37% overall yield), mp 193 °C (ma);  $R_{\text{f}}$  0.32 (ma), 0.28 (mi) (*n*-hexane–acetone, 8 : 2) (Found: C, 69.73; H, 5.94; N, 2.58; S, 6.20.  $\text{C}_{30}\text{H}_{30}\text{NO}_3\text{PS}$  requires C, 69.88; H, 5.86; N, 2.72; S, 6.22%).  $\nu_{\text{max}}$  ( $\text{CHCl}_3$ )/ $\text{cm}^{-1}$  3280 (NH), 1255 (P=O);  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ , ( $R_{\text{a}}^*$ ,4*R*<sup>\*</sup>)-7c) 1.19–2.18 (10 H, m, 6-H, 7-H, 8-H, 9-H, 10-H), 1.58, 1.75 [6 H, 2 s,  $\text{C}-2(\text{CH}_3)_2$ ], 3.06 (1 H, s, NH), 3.32 (1 H, d,  $^2J_{\text{PH}}$  17.0, 4-H), 7.32–7.66, 7.93–8.08 (12 H, 2 m, Ar);  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ , ( $R_{\text{a}}^*$ ,4*S*<sup>\*</sup>)-7c) 1.19–2.26 (10 H, m, 6-H, 7-H, 8-H, 9-H, 10-H), 1.26, 1.46 [6 H, 2 s,  $\text{C}-2(\text{CH}_3)_2$ ], 2.51 (1 H, s, NH), 3.75 (1 H, d,  $^2J_{\text{PH}}$  20.9, 4-H), 7.24–7.66, 7.91–8.07 (12 H, 2 m, ar);  $\delta_{\text{C}}$  (300 MHz;  $\text{CDCl}_3$ , ( $R_{\text{a}}^*$ ,4*R*<sup>\*</sup>)-7c) 23.7, 25.5, 27.3, 37.2, 38.4, 31.9, 32.7, 64.3 (d,  $^1J_{\text{CP}}$  140.4, C-4), 69.6 (C-5), 74.1 (d,  $^3J_{\text{CP}}$  25.7, C-2), 119.9, 121.1, 121.5, 121.8, 125.9, 126.8, 126.9, 127.2, 128.5, 131.3, 131.7, 131.9, 132.3, 145.5 and 147.4 (2 d,  $^2J_{\text{CP}}$  10.9,  $^2J_{\text{CP}}$  10.9);  $\delta_{\text{C}}$  (300 MHz;  $\text{CDCl}_3$ , ( $R_{\text{a}}^*$ ,4*S*<sup>\*</sup>)-7c) 23.6, 25.2, 27.4, 36.2, 38.5, 31.7, 32.2, 67.5 (d,  $^1J_{\text{CP}}$  135.7, C-4), 70.1 (d,  $^2J_{\text{CP}}$  5.1, C-5), 73.3 (d,  $^3J_{\text{CP}}$  24.5, C-2), 120.9, 121.2, 121.3, 121.8, 121.8, 125.3, 125.7, 126.3, 126.6, 127.0, 127.1, 128.2, 128.4, 129.9, 131.0, 131.2, 131.2, 131.4, 145.2 and 149.3 (2 d,  $^2J_{\text{CP}}$  9.6,  $^2J_{\text{CP}}$  10.9); *m/z* 516 ( $\text{MH}^+$ , 35%), 184 [ $\text{MH}^+$  – BINOL-P(O)H, 100].

**( $R_{\text{a}}^*$ ,15*R*<sup>\*</sup>)-15-(7-Oxo-7 $\lambda^5$ -dinaphtho[2,3-*d*:2,3-*f*][1,3,2]dioxaphosphepin-7-yl)-7-thia-14-azadispiro[5.1.5.2]pentadecane (7d).** The title compound was prepared according to GPI using 1.12 g (5.00 mmol) of 7-thia-14-azadispiro[5.1.5.2]pentadec-14-ene 3d and 1.66 g (5.00 mmol) of racemic BINOL-phosphonate 1 as starting material to yield 1.86 g (68%) of diastereomerically pure 7d as a colourless solid. The product was not purified by chromatography but washed with diethyl ether (20 ml), mp 236 °C;  $R_{\text{f}}$  0.36 (*n*-hexane–acetone, 8 : 2) (Found: C, 71.06; H, 6.25; N, 2.23; S, 5.81.  $\text{C}_{33}\text{H}_{34}\text{NO}_3\text{PS}$  requires C, 71.33; H, 6.17; N, 2.52; S, 5.77%).  $\nu_{\text{max}}$  ( $\text{CHCl}_3$ )/ $\text{cm}^{-1}$  3300 (NH), 1255 (P=O);  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 1.06–2.12 (20 H, m, 1-H, 2-H, 3-H, 4-H, 5-H, 9-H, 10-H, 11-H, 12-H, 13-H), 3.30 (1 H, d,  $^2J_{\text{PH}}$  17.1, 15-H), 7.27–7.65, 7.96–8.07 (12 H, 2 m, Ar);  $\delta_{\text{C}}$  (75 MHz;  $\text{CDCl}_3$ ) 23.5, 25.3, 27.0, 37.0, 38.1, 23.5, 25.2, 25.4, 40.8, 41.3, 63.2 (d,  $^1J_{\text{CP}}$  139.9, C-15), 66.7 (d,  $^2J_{\text{CP}}$  4.4, C-6), 79.4 (d,  $^3J_{\text{CP}}$  23.8, C-8), 119.7, 120.9, 121.4, 121.7, 125.7, 126.6, 126.7, 126.8, 127.1, 128.4, 131.1, 131.6, 131.7, 132.2, 132.2, 145.4 and 147.2 (2 d,  $^2J_{\text{CP}}$  9.7,  $^2J_{\text{CP}}$  9.9); *m/z* 556 ( $\text{MH}^+$ , 0.3%), 224 [ $\text{MH}^+$  – BINOL-P(O)H, 100].

**( $R_{\text{a}}^*$ ,3*R*<sup>\*</sup>)-3-(7-Oxo-7 $\lambda^5$ -dinaphtho[2,3-*d*:2,3-*f*][1,3,2]dioxaphosphepin-7-yl)-1-thia-4-azaspiro[4.5]decane (7e).** The title compound was prepared according to GPI using 0.78 g (5.00 mmol) of 1-thia-4-azaspiro[4.5]dec-3-ene 3e and 1.66 g (5.00 mmol) of racemic BINOL-phosphonate 1 as starting material to yield 0.73 g (30%) of diastereomerically pure 7e as a colourless solid, mp 178 °C;  $R_{\text{f}}$  0.28 (*n*-hexane–acetone, 8 : 2) (Found: C, 68.70; H, 5.41; N, 2.79; S, 6.42.  $\text{C}_{28}\text{H}_{26}\text{NO}_3\text{PS}$  requires C, 68.98; H, 5.38; N, 2.87; S, 6.58%).  $\nu_{\text{max}}$  ( $\text{CHCl}_3$ )/ $\text{cm}^{-1}$  3290 (NH), 1245 (P=O);  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 1.27–2.02 (10 H, m, 6-H, 7-H, 8-H, 9-H, 10-H), 2.33 (1 H, s, NH), 3.13 (1 H, ddd,  $^2J_{\text{HH}}$  10.4,  $^3J_{\text{HH}}$  6.1,  $^3J_{\text{PH}}$  1.5, 2-H), 3.27 (1 H, ddd,  $^3J_{\text{PH}}$  11.0,  $^3J_{\text{HH}}$  11.0,  $^2J_{\text{HH}}$  10.4, 2-H), 3.49 (1 H, ddd,  $^2J_{\text{PH}}$  13.8,  $^3J_{\text{HH}}$  11.0,  $^3J_{\text{HH}}$  6.1, 3-H), 7.32–7.66, 7.96–8.07 (12 H, 2 m, Ar);  $\delta_{\text{C}}$  (75 MHz;  $\text{CDCl}_3$ ) 23.7, 25.2, 25.7, 40.0, 40.6, 35.7 (C-2), 54.6 (d,  $^1J_{\text{CP}}$  147.8, C-3), 83.2 (d,  $^3J_{\text{CP}}$  22.0, C-5), 120.0, 120.9, 125.9, 126.0, 126.9, 127.0, 127.2, 128.5, 131.4, 131.9, 132.4, 145.2 and 147.0 (2 d,  $^2J_{\text{CP}}$  10.9,  $^2J_{\text{CP}}$  10.9); *m/z* 488 ( $\text{MH}^+$ , 65%), 156 [ $\text{MH}^+$  – BINOL-P(O)H, 100].

**rac-Dimethyl (2,2-dimethyl-5-isopropyl-1,3-thiazolidin-4-yl)phosphonate (8a).** The title compound was prepared according to **GP1** using 0.31 g (2.00 mmol) of *rac*-2,2-dimethyl-5-isopropyl-2,5-dihydro-1,3-thiazole **4** and 0.22 g (2.00 mmol) of dimethyl phosphonate as starting material to yield 0.21 g (39%) of **8a** in a diastereomeric mixture of 10 : 90 ratio as a colourless oil,  $R_f$  0.40 (*n*-hexane–propan-2-ol, 8 : 2) (Found: C, 44.75; H, 8.11; N, 5.12; S, 11.68.  $C_{10}H_{22}NO_3PS$  requires C, 44.93; H, 8.30; N, 5.24; S, 11.99%);  $\nu_{max}$  (CHCl<sub>3</sub>)/cm<sup>-1</sup> 3290 (NH), 1265 (P=O);  $\delta_H$ (300 MHz; CDCl<sub>3</sub>) 0.76 [0.10 × 6 H, d,  $J$  6.6, CH(CH<sub>3</sub>)<sub>2</sub>], 0.90, 0.93 [0.90 × 6 H, 2 d,  $J$  6.6,  $J$  6.6, CH(CH<sub>3</sub>)<sub>2</sub>], 1.44 [3 H, s, C-2(CH<sub>3</sub>)<sub>2</sub>], 1.60 [0.90 × 3 H, s, C-2(CH<sub>3</sub>)<sub>2</sub>], 1.63 [0.10 × 3 H, s, C-2(CH<sub>3</sub>)<sub>2</sub>], 2.16–2.30 [1 H, m,  $J$  13.2,  $J$  6.6,  $J$  2.7, CH(CH<sub>3</sub>)<sub>2</sub>], 2.37 (1 H, s, NH), 3.29 (0.90 × 1 H, dd,  $^2J_{PH}$  15.9,  $^3J_{HH}$  10.4, 4-H), 3.52 (0.10 × 1 H, dd,  $^2J_{PH}$  21.43,  $J$  6.0, 4-H), 3.75–3.80 [6 H and 0.10 × 1 H, m, P(OCH<sub>3</sub>)<sub>2</sub> and 5-H], 3.91 (0.90 × 1 H, ddd,  $^3J_{PH}$  13.2,  $^3J_{HH}$  10.4,  $J$  2.7, 5-H);  $\delta_C$ (75 MHz; CDCl<sub>3</sub>) 15.2, 25.0 (ma), 17.3, 25.0 (mi), 28.6 (ma), 29.8 (mi), 30.0, 32.6 (mi), 30.8, 32.1 (ma), 51.9, 52.5 [2 d,  $^2J_{CP}$  6.5,  $^2J_{CP}$  8.7, P(OCH<sub>3</sub>)<sub>2</sub>, mi], 52.8, 53.2 [2 d,  $^2J_{CP}$  6.5,  $^2J_{CP}$  8.7, P(OCH<sub>3</sub>)<sub>2</sub>, ma], 59.7 (d,  $^1J_{CP}$  150.4, C-4), 62.4 (d,  $^2J_{CP}$  6.5, C-5, mi), 64.0 (d,  $^2J_{CP}$  4.4, C-5, ma), 74.2 (d,  $^3J_{CP}$  21.3, C-2);  $m/z$  268 (MH<sup>+</sup>, 100%).

**rac-4-(5,5-Dimethyl-2-oxo-1,3,2λ<sup>5</sup>-dioxaphosphinan-2-yl)-2,2-dimethyl-5-isopropyl-1,3-thiazolidine (8b).** The title compound was prepared according to **GP1** using 0.31 g (2.00 mmol) of *rac*-2,2-dimethyl-5-isopropyl-2,5-dihydro-1,3-thiazole **4** and 0.30 g (2.00 mmol) of the cyclic phosphonate **2a** as starting material to yield 0.21 g (34%) of diastereomerically pure **8b** as a colourless solid, mp 161 °C;  $R_f$  0.41 (*n*-hexane–propan-2-ol, 8 : 2) (Found: C, 50.67; H, 8.76; N, 4.52; S, 10.27.  $C_{13}H_{26}NO_3PS$  requires C, 50.80; H, 8.53; N, 4.56; S, 10.43%);  $\nu_{max}$  (CHCl<sub>3</sub>)/cm<sup>-1</sup> 3300 (NH), 1260 (P=O);  $\delta_H$ (300 MHz; CDCl<sub>3</sub>) 0.97, 1.00 [6 H, 2 d,  $J$  7.1,  $J$  5.5, CH(CH<sub>3</sub>)<sub>2</sub>], 1.00, 1.18 [6 H, 2 s, P(OCH<sub>2</sub>)<sub>2</sub>-C(CH<sub>3</sub>)<sub>2</sub>], 1.52, 1.67 [6 H, 2 s, C-2(CH<sub>3</sub>)<sub>2</sub>], 2.26–2.50 [2 H, m, NH, CH(CH<sub>3</sub>)<sub>2</sub>], 3.44 (1 H, dd,  $^2J_{PH}$  15.4,  $^3J_{HH}$  10.4, 4-H), 3.86–3.95 [2 H, m, P(OCH<sub>2</sub>)<sub>2</sub>], 4.08 (1 H, ddd,  $^3J_{PH}$  13.2,  $^3J_{HH}$  10.4,  $J$  3.3, 5-H), 4.26–4.32 [2 H, m, P(OCH<sub>2</sub>)<sub>2</sub>];  $\delta_C$ (75 MHz; CDCl<sub>3</sub>) 15.2, 25.0, 21.3, 21.9, 28.7, 30.9, 32.2, 32.7 [d,  $^3J_{CP}$  6.5, P(OCH<sub>2</sub>)<sub>2</sub>C], 59.2 (d,  $^1J_{CP}$  150.0, C-4), 63.8 (d,  $^2J_{CP}$  4.4, C-5), 74.5 (d,  $^3J_{CP}$  20.7, C-2), 75.2 and 75.3 [2 d convoluted, P(OCH<sub>2</sub>)<sub>2</sub>C];  $m/z$  308 (MH<sup>+</sup>, 100%).

**rac-Dimethyl (2-phenyl-5,5-dimethyl-1,3-thiazolidin-4-yl)phosphonate (9a).** The title compound was prepared according to **GP1** using 0.96 g (5.00 mmol) of *rac*-2-phenyl-5,5-dimethyl-2,5-dihydro-1,3-thiazole **5a** and 0.55 g (5.00 mmol) of dimethyl phosphonate as starting material to yield 1.20 g (80%) of **9a** in a diastereomeric mixture of 77 : 23 ratio without chromatography as a colourless solid, mp 74–76 °C;  $R_f$  0.44 and 0.50 (*n*-hexane–propan-2-ol, 8 : 2) (Found: C, 51.60; H, 6.60; N, 4.33; S, 10.82.  $C_{13}H_{20}NO_3PS$  requires C, 51.82; H, 6.69; N, 4.65; S, 10.64%);  $\nu_{max}$  (CHCl<sub>3</sub>)/cm<sup>-1</sup> 3260 (NH), 1250 (P=O);  $\delta_H$ (300 MHz; CDCl<sub>3</sub>) 1.57, 1.64 [0.23 × 6 H, 2 s, C-5(CH<sub>3</sub>)<sub>2</sub>], 1.64, 1.74 [0.77 × 6 H, 2 s, C-5(CH<sub>3</sub>)<sub>2</sub>], 2.71 (1 H, s, NH), 3.12 (0.23 × 1 H, d,  $^2J_{PH}$  17.1, 4-H), 3.21 (0.77 × 1 H, d,  $^2J_{PH}$  17.6, 4-H), 3.78–3.86 [6 H, m, P(OCH<sub>3</sub>)<sub>2</sub>], 5.67 (0.77 × 1 H, s, 2-H), 5.85 (0.23 × 1 H, s, 2-H), 7.26–7.52 (5 H, m, phenyl);  $\delta_C$ (75 MHz; CDCl<sub>3</sub>) 27.8, 28.1 (mi), 28.7, 29.4 (ma), 52.8 and 53.3 [2 d,  $^2J_{CP}$  6.3,  $^2J_{CP}$  6.6, P(OCH<sub>3</sub>)<sub>2</sub>], 60.2 (d,  $^2J_{CP}$  4.4, C-5, ma), 60.8 (d,  $^2J_{CP}$  4.4, C-5, mi), 66.2 (d,  $^1J_{CP}$  150.4, C-4, mi), 69.0 (d,  $^1J_{CP}$  150.4, C-4, ma), 69.6 (d,  $^3J_{CP}$  24.0, C-2, mi), 72.7 (d,  $^3J_{CP}$  26.2, C-2, ma), 126.5, 126.8, 127.3, 127.6, 128.3, 128.6, 138.8;  $m/z$  302 (MH<sup>+</sup>, 100%).

**rac-Diethyl (2-phenyl-5,5-dimethyl-1,3-thiazolidin-4-yl)phosphonate (9b).** The title compound was prepared according to **GP1** using 0.57 g (3.00 mmol) of *rac*-2-phenyl-5,5-dimethyl-2,5-dihydro-1,3-thiazole **5a** and 0.41 g (3.00 mmol) of diethyl phosphonate as starting material to yield 0.82 g (83%) of **9b** in a diastereomeric mixture of 75 : 25 ratio without chrom-

atography as a colourless oil,  $R_f$  0.57 (*n*-hexane–propan-2-ol, 9 : 1) (Found: C, 54.63; H, 7.32; N, 4.23; S, 9.65.  $C_{15}H_{24}NO_3PS$  requires C, 54.70; H, 7.34; N, 4.25; S, 9.73%);  $\nu_{max}$  (CHCl<sub>3</sub>)/cm<sup>-1</sup> 3280 (NH), 1270 (P=O);  $\delta_H$ (300 MHz; CDCl<sub>3</sub>) 1.31–1.39 [6 H, m, P(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>], 1.58, 1.65 [0.25 × 3 H, s, C-5(CH<sub>3</sub>)<sub>2</sub>], 1.64, 1.74 [0.75 × 3 H, s, C-5(CH<sub>3</sub>)<sub>2</sub>], 3.16 (1 H, br s, NH), 3.12 (0.25 × 1 H, d,  $^2J_{PH}$  16.5, 4-H), 3.17 (0.75 × 1 H, d,  $^2J_{PH}$  17.6, 4-H), 4.08–4.30 [4 H, m, P(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>], 5.67 (0.75 × 1 H, s, 2-H), 5.86 (0.25 × 1 H, s, 2-H), 7.24–7.52 (5 H, m, phenyl);  $\delta_C$ (75 MHz; CDCl<sub>3</sub>) 16.3, 27.7, 28.1 (mi), 28.7, 29.3 (ma), 60.4 (C-5, ma), 60.7 (C-5, mi), 62.2 [d,  $^2J_{CP}$  6.3, P(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>], 62.8 [d,  $^2J_{CP}$  6.3, P(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>], 66.4 (d,  $^1J_{CP}$  148.4, C-4, mi), 69.4 (d,  $^1J_{CP}$  148.9, C-4, ma), 69.4 (d,  $^3J_{CP}$  23.1, C-2, mi), 72.6 (d,  $^3J_{CP}$  26.0, C-2, ma), 126.7, 127.4, 127.6, 128.2, 128.5, 138.8;  $m/z$  330 (MH<sup>+</sup>, 100%).

**rac-Diisopropyl (2-phenyl-5,5-dimethyl-1,3-thiazolidin-4-yl)phosphonate (9c).** The title compound was prepared according to **GP1** using 0.57 g (3.00 mmol) of *rac*-2-phenyl-5,5-dimethyl-2,5-dihydro-1,3-thiazole **5a** and 0.50 g (3.00 mmol) of diisopropyl phosphonate **2b** as starting material to yield 0.76 g (71%) of **9c** in a diastereomeric mixture of 69 : 31 ratio without chromatography as a colourless oil,  $R_f$  0.61 (*n*-hexane–propan-2-ol, 9 : 1) (Found: C, 57.08; H, 7.86; N, 4.03; S, 8.84.  $C_{17}H_{28}NO_3PS$  requires C, 57.12; H, 7.90; N, 3.92; S, 8.97%);  $\nu_{max}$  (CHCl<sub>3</sub>)/cm<sup>-1</sup> 3270 (NH), 1250 (P=O);  $\delta_H$ (300 MHz; CDCl<sub>3</sub>) 1.31–1.37 [12 H, m, OCH(CH<sub>3</sub>)<sub>2</sub>], 1.56, 1.65 [0.31 × 6 H, 2 s, C-5(CH<sub>3</sub>)<sub>2</sub>], 1.63, 1.74 [0.69 × 6 H, 2 s, C-5(CH<sub>3</sub>)<sub>2</sub>], 2.98 (0.31 × 1 H, d,  $^2J_{PH}$  17.6, 4-H), 3.08 (0.69 × 1 H, d,  $^2J_{PH}$  18.2, 4-H), 4.66–4.88 [2 H, m, OCH(CH<sub>3</sub>)<sub>2</sub>], 5.64 (0.69 × 1 H, s, 2-H), 5.82 (0.31 × 1 H, s, 2-H), 7.21–7.50 (5 H, m, phenyl);  $\delta_C$ (75 MHz; CDCl<sub>3</sub>) 23.8, 24.0, 24.2, 27.8, 28.2 (mi), 28.8, 29.3 (ma), 60.5 (C-5), 66.7 (d,  $^1J_{CP}$  149.6, C-4, mi), 70.0 (d,  $^1J_{CP}$  150.5, C-4, ma), 70.8, 71.5, 69.4 (d,  $^3J_{CP}$  23.8, C-2, mi), 72.6 (d,  $^3J_{CP}$  26.0, C-2, ma), 126.7, 127.2, 127.5, 128.1, 128.4, 128.5, 139.1;  $m/z$  358 (MH<sup>+</sup>, 100%).

**rac-4-(5,5-Dimethyl-2-oxo-1,3,2λ<sup>5</sup>-dioxaphosphinan-2-yl)-2-phenyl-5,5-dimethyl-1,3-thiazolidine (9d).** The title compound was prepared according to **GP1** using 0.96 g (5.00 mmol) of *rac*-2-phenyl-5,5-dimethyl-2,5-dihydro-1,3-thiazole **5a** and 0.75 g (5.00 mmol) of the cyclic phosphonate **2a** as starting material to yield 1.13 g (71%) of **9d** in a diastereomeric mixture of 80 : 20 ratio as a colourless solid, mp 145 °C;  $R_f$  0.48 (*n*-hexane–propan-2-ol, 8 : 2) (Found: C, 56.32; H, 7.26; N, 3.96; S, 9.19.  $C_{16}H_{24}NO_3PS$  requires C, 56.29; H, 7.09; N, 4.10; S, 9.39%);  $\nu_{max}$  (CHCl<sub>3</sub>)/cm<sup>-1</sup> 3260 (NH), 1260 (P=O);  $\delta_H$ (300 MHz; CDCl<sub>3</sub>) 1.03 [0.80 × 3 H, s, P(OCH<sub>2</sub>)<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>], 1.08 [0.20 × 3 H, s, P(OCH<sub>2</sub>)<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>], 1.16 [3 H, s, P(OCH<sub>2</sub>)<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>], 1.63, 1.69 [0.20 × 6 H, 2 s, C-5(CH<sub>3</sub>)<sub>2</sub>], 1.69, 1.79 [0.80 × 3 H, 2 s, C-5(CH<sub>3</sub>)<sub>2</sub>], 2.90 (0.80 × 1 H and 0.20 × 1 H, ddd,  $^3J_{HH}$  13.8,  $^3J_{HH}$  12.1,  $^3J_{PH}$  6.1, NH), 3.27 (0.20 × 1 H, m, 4-H), 3.34 (0.80 × 1 H, dd,  $^2J_{PH}$  17.1,  $^3J_{HH}$  13.8, 4-H), 3.87–4.04 [2 H, m, P(OCH<sub>2</sub>)<sub>2</sub>], 4.23–4.29 [2 H, m, P(OCH<sub>2</sub>)<sub>2</sub>], 5.72 (0.80 × 1 H, d,  $^3J_{HH}$  12.1, 2-H), 5.86 (0.20 × 1 H, s, 2-H), 7.26–7.54 (5 H, m, phenyl);  $\delta_C$ (75 MHz; CDCl<sub>3</sub>) 21.4, 21.7 (ma), 21.6, 21.7 (mi), 27.6, 28.2 (mi), 28.6, 29.5 (ma), 32.7 [d,  $^3J_{CP}$  5.9, P(OCH<sub>2</sub>)<sub>2</sub>C], 60.1 (C-5), 66.4 (d,  $^1J_{CP}$  146.6, C-4, mi), 68.9 (d,  $^1J_{CP}$  146.3, C-4, ma), 69.3 (d,  $^3J_{CP}$  23.6, C-2, mi), 72.5 (d,  $^3J_{CP}$  26.2, C-2, ma), 75.4 and 75.8 [2 d,  $^2J_{CP}$  6.1,  $^2J_{CP}$  6.5, P(OCH<sub>2</sub>)<sub>2</sub>C], 126.5, 126.8, 127.6, 127.9, 128.4, 128.6, 138.7;  $m/z$  342 (MH<sup>+</sup>, 100%).

**rac-4-(5,5-Dimethyl-2-oxo-1,3,2λ<sup>5</sup>-dioxaphosphinan-2-yl)-2-benzyl-5,5-dimethyl-1,3-thiazolidine (9e).** The title compound was prepared according to **GP1** using 1.03 g (5.00 mmol) of *rac*-2-benzyl-5,5-dimethyl-2,5-dihydro-1,3-thiazole **5b** and 0.75 g (5.00 mmol) of the cyclic phosphonate **2a** as starting material to yield 0.87 g (49%) of **9e** in a diastereomeric mixture of 77 : 23 ratio as a colourless solid, mp 120 °C;  $R_f$  0.40 (*n*-hexane–propan-2-ol, 9 : 1) (Found: C, 57.40; H, 7.29; N, 3.98; S, 9.16.  $C_{17}H_{26}NO_3PS$  requires C, 57.45; H, 7.37; N, 3.94; S, 9.02%);  $\nu_{max}$

(CHCl<sub>3</sub>)/cm<sup>-1</sup> 3255 (NH), 1260 (P=O); δ<sub>H</sub>(300 MHz; CDCl<sub>3</sub>) 1.02, 1.16 [0.77 × 6 H, 2 s, P(OCH<sub>2</sub>)<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>], 1.06, 1.07 [0.23 × 6 H, 2 s, P(OCH<sub>2</sub>)<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>], 1.42, 1.65 [0.77 × 3 H, 2 s, C-5(CH<sub>3</sub>)<sub>2</sub>], 1.51, 1.68 [0.23 × 6 H, 2 s, C-5(CH<sub>3</sub>)<sub>2</sub>], 2.64 (1 H, s, NH), 2.86, 3.03 (0.23 × 2 H, 2 dd, <sup>2</sup>J<sub>HH</sub> 13.7, <sup>3</sup>J<sub>HH</sub> 6.6, C-2-CH<sub>2</sub>), 2.97 (0.77 × 1 H, dd, <sup>2</sup>J<sub>HH</sub> 13.7, <sup>3</sup>J<sub>HH</sub> 7.7, C-2-CH<sub>2</sub>), 3.16 (0.77 × 1 H, d, <sup>2</sup>J<sub>PH</sub> 17.0, 4-H), 3.23 (0.23 × 1 H, d, <sup>2</sup>J<sub>PH</sub> 17.0, 4-H), 3.31 (0.77 × 1 H, dd, <sup>2</sup>J<sub>HH</sub> 13.7, <sup>3</sup>J<sub>HH</sub> 4.4, C-2-CH<sub>2</sub>), 3.83–4.04 [2 H, m, P(OCH<sub>2</sub>)<sub>2</sub>], 4.12–4.26 [2 H, m, P(OCH<sub>2</sub>)<sub>2</sub>], 4.83 (0.23 × 1 H, t, <sup>3</sup>J<sub>HH</sub> 6.6, 2-H), 4.89 (0.77 × 1 H, dd, <sup>3</sup>J<sub>HH</sub> 7.7, <sup>3</sup>J<sub>HH</sub> 4.4, 2-H), 7.21–7.32 (5 H, m, phenyl); δ<sub>C</sub>(75 MHz; CDCl<sub>3</sub>) 21.3, 21.7 (ma), 21.4, 21.6 (mi), 27.4, 28.0 (mi), 28.7, 29.5 (ma), 32.6 [d, <sup>3</sup>J<sub>CP</sub> 6.0, P(OCH<sub>2</sub>)<sub>2</sub>C], 41.8 (ma), 44.3 (mi), 59.0 (d, <sup>2</sup>J<sub>CP</sub> 4.8, C-5, ma), 59.5 (C-5, mi), 66.5 (d, <sup>1</sup>J<sub>CP</sub> 145.8, C-4, mi), 68.2 (d, <sup>1</sup>J<sub>CP</sub> 146.2, C-4, ma), 69.0 (d, <sup>3</sup>J<sub>CP</sub> 22.3, C-2, mi), 71.1 (d, <sup>3</sup>J<sub>CP</sub> 24.8, C-2, ma), 75.4 and 75.8 [2 d, <sup>2</sup>J<sub>CP</sub> 5.9, <sup>2</sup>J<sub>CP</sub> 6.3, P(OCH<sub>2</sub>)<sub>2</sub>C], 126.6, 128.1, 129.7, 138.1 (mi), 126.9, 128.4, 129.3, 137.0 (ma); *m/z* 356 (MH<sup>+</sup>, 100%).

**rac-4-(5,5-Dimethyl-2-oxo-1,3,2λ<sup>5</sup>-dioxaphosphinan-2-yl)-2-(2-phenylethyl)-5,5-dimethyl-1,3-thiazolidine (9f).** The title compound was prepared according to **GPI** using 1.10 g (5.00 mmol) of *rac*-2-(2-phenylethyl)-5,5-dimethyl-2,5-dihydro-1,3-thiazole **5c** and 0.75 g (5.00 mmol) of the cyclic phosphonate **2a** as starting material to yield 1.00 g (73%) of **9f** in a diastereomeric mixture of 73 : 27 ratio as a colourless solid, mp 155 °C; *R<sub>f</sub>* 0.44 (*n*-hexane–propan-2-ol, 9 : 1) (Found: C, 58.49; H, 7.60; N, 3.71; S, 8.62. C<sub>18</sub>H<sub>28</sub>NO<sub>3</sub>PS requires C, 58.52; H, 7.64; N, 3.79; S, 8.68%); *v*<sub>max</sub> (CHCl<sub>3</sub>)/cm<sup>-1</sup> 3260 (NH), 1265 (P=O); δ<sub>H</sub>(300 MHz; CDCl<sub>3</sub>) 1.02, 1.16 [0.78 × 6 H, s, P(OCH<sub>2</sub>)<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>], 1.07, 1.15 [0.22 × 6 H, s, P(OCH<sub>2</sub>)<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>], 1.52 [0.22 × 3 H, s, C-5(CH<sub>3</sub>)<sub>2</sub>], 1.55 [0.78 × 3 H, s, C-5(CH<sub>3</sub>)<sub>2</sub>], 1.70 [3 H, s, C-5(CH<sub>3</sub>)<sub>2</sub>], 1.90–2.06 (1 H, m, C-2-CH<sub>2</sub>CH<sub>2</sub>), 2.13–2.39 (1 H, m, C-2-CH<sub>2</sub>CH<sub>2</sub>), 2.65–2.84 (3 H, m, C-2-CH<sub>2</sub>CH<sub>2</sub>, NH), 3.15 (0.78 × 1 H, d, <sup>2</sup>J<sub>PH</sub> 17.0, 4-H), 3.33 (0.22 × 1 H, d, <sup>2</sup>J<sub>PH</sub> 16.5, 4-H), 3.85–4.05 [2 H, m, P(OCH<sub>2</sub>)<sub>2</sub>], 4.17–4.27 [2 H, m, P(OCH<sub>2</sub>)<sub>2</sub>], 4.58–4.65 (1 H, m, 2-H), 7.17–7.31 (5 H, m, phenyl); δ<sub>C</sub>(75 MHz; CDCl<sub>3</sub>) 21.3, 21.7 (ma), 21.5 (mi), 27.8, 28.2 (mi), 28.8, 29.7 (ma), 32.7 [d, <sup>3</sup>J<sub>CP</sub> 6.0, P(OCH<sub>2</sub>)<sub>2</sub>C], 33.1 (mi), 33.8 (ma), 38.2 (ma), 40.5 (mi), 58.9 (d, <sup>2</sup>J<sub>CP</sub> 5.9, C-5, ma), 59.6 (d, <sup>2</sup>J<sub>CP</sub> 6.4, C-5, mi), 65.7 (d, <sup>1</sup>J<sub>CP</sub> 146.1, C-4, mi), 68.2 (d, <sup>1</sup>J<sub>CP</sub> 146.2, C-4, ma), 67.5 (d, <sup>3</sup>J<sub>CP</sub> 23.7, C-2, mi), 70.2 (d, <sup>3</sup>J<sub>CP</sub> 24.8, C-2, ma), 75.3 [d, <sup>2</sup>J<sub>CP</sub> 6.3, P(OCH<sub>2</sub>)<sub>2</sub>C, ma], 75.5 [d, <sup>2</sup>J<sub>CP</sub> 6.6, P(OCH<sub>2</sub>)<sub>2</sub>C, mi], 75.7 [d, <sup>2</sup>J<sub>CP</sub> 6.6, P(OCH<sub>2</sub>)<sub>2</sub>C], 125.9, 126.1, 128.4, 128.4, 128.5, 140.8, 141.2; *m/z* 370 (MH<sup>+</sup>, 100%).

**rac-4-(5,5-Dimethyl-2-oxo-1,3,2λ<sup>5</sup>-dioxaphosphinan-2-yl)-2-tert-butyl-5,5-dimethyl-1,3-thiazolidine (9g).** The title compound was prepared according to **GPI** using 0.86 g (5.00 mmol) of *rac*-2-tert-butyl-5,5-dimethyl-2,5-dihydro-1,3-thiazole **5d** and 0.75 g (5.00 mmol) of the cyclic phosphonate **2a** as starting material to yield 1.20 g (75%) of **9g** in a diastereomeric mixture of 86 : 14 ratio without chromatography as a colourless solid, mp 144 °C; *R<sub>f</sub>* 0.56 (*n*-hexane–propan-2-ol, 8 : 2) (Found: C, 52.28; H, 8.74; N, 4.12; S, 9.72. C<sub>14</sub>H<sub>28</sub>NO<sub>3</sub>PS requires C, 52.32; H, 8.78; N, 4.36; S, 9.97%); *v*<sub>max</sub> (CHCl<sub>3</sub>)/cm<sup>-1</sup> 3300 (NH), 1240 (P=O); δ<sub>H</sub>(300 MHz; CDCl<sub>3</sub>) 0.93 [0.14 × 9 H, s, C(CH<sub>3</sub>)<sub>3</sub>, UD], 1.02–1.04 [0.86 × 9 H and 3 H, m, C(CH<sub>3</sub>)<sub>3</sub> and P(OCH<sub>2</sub>)<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>], 1.14 [0.14 × 3 H, s, P(OCH<sub>2</sub>)<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>], 1.17 [0.86 × 3 H, s, P(OCH<sub>2</sub>)<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>], 1.47, 1.69 [0.86 × 6 H, 2 s, C-5(CH<sub>3</sub>)<sub>2</sub>], 1.51, 1.64 [0.14 × 6 H, 2 s, C-5(CH<sub>3</sub>)<sub>2</sub>], 2.62 (1 H, s, NH), 3.14 (0.86 × 1 H, d, <sup>2</sup>J<sub>PH</sub> 17.1, 4-H), 3.24 (0.14 × 1 H, d, <sup>2</sup>J<sub>PH</sub> 16.2, 4-H), 3.86–4.05 [2 H, m, P(OCH<sub>2</sub>)<sub>2</sub>], 4.15–4.27 [2 H, m, P(OCH<sub>2</sub>)<sub>2</sub>], 4.45 (0.14 × 1 H, s, 2-H), 4.58 (0.86 × 1 H, s, 2-H); δ<sub>C</sub>(75 MHz; CDCl<sub>3</sub>) 21.4, 21.6, 26.2 (mi), 26.8 (ma), 28.5, 29.1, 32.7 [d, <sup>3</sup>J<sub>CP</sub> 6.5, P(OCH<sub>2</sub>)<sub>2</sub>C], 33.9, 57.8 (d, <sup>2</sup>J<sub>CP</sub> 6.5, C-5), 68.6 (d, <sup>1</sup>J<sub>CP</sub> 146.3, C-4), 75.3 and 75.8 [2 d, <sup>2</sup>J<sub>CP</sub> 6.5, <sup>2</sup>J<sub>CP</sub> 8.7, P(OCH<sub>2</sub>)<sub>2</sub>C], 81.6 (d, <sup>3</sup>J<sub>CP</sub> 23.7, C-2); *m/z* 322 (MH<sup>+</sup>, 100%).

**rac-4-(5,5-Dimethyl-2-oxo-1,3,2λ<sup>5</sup>-dioxaphosphinan-2-yl)-2-tert-butyl-1-thia-3-azaspiro[4.5]decane (9h).** The title com-

pound was prepared according to **GPI** using 1.05 g (5.00 mmol) of *rac*-2-tert-butyl-1-thia-3-azaspiro[4.5]dec-3-ene **5e** and 0.75 g (5.00 mmol) of the cyclic phosphonate **2a** as starting material to yield 0.81 g (45%) of **9h** in a diastereomeric mixture of 87 : 13 ratio as a colourless solid, mp 189 °C; *R<sub>f</sub>* 0.62 (*n*-hexane–propan-2-ol, 8 : 2) (Found: C, 56.32; H, 8.98; N, 3.64; S, 8.58. C<sub>17</sub>H<sub>32</sub>NO<sub>3</sub>PS requires C, 56.49; H, 8.92; N, 3.87; S, 8.87%); *v*<sub>max</sub> (CHCl<sub>3</sub>)/cm<sup>-1</sup> 3300 (NH), 1250 (P=O); δ<sub>H</sub>(300 MHz; CDCl<sub>3</sub>) 0.99 [0.13 × 9 H, s, C(CH<sub>3</sub>)<sub>3</sub>], 1.04 [3 H, s, P(OCH<sub>2</sub>)<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>], 1.05 [0.87 × 9 H, s, C(CH<sub>3</sub>)<sub>3</sub>], 1.15 [0.13 × 3 H, s, P(OCH<sub>2</sub>)<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>], 1.18 [0.87 × 3 H, s, P(OCH<sub>2</sub>)<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>], 1.21–2.24 (10 H, m, 6-H, 7-H, 8-H, 9-H, 10-H), 3.16 (0.87 × 1 H, d, <sup>2</sup>J<sub>PH</sub> 17.1, 4-H), 3.31 (0.13 × 1 H, d, <sup>2</sup>J<sub>PH</sub> 16.5, 4-H), 3.91–4.06 [2 H, m, P(OCH<sub>2</sub>)<sub>2</sub>], 4.19–4.29 [2 H, m, P(OCH<sub>2</sub>)<sub>2</sub>], 4.43 (0.13 × 1 H, s, 2-H), 4.54 (0.87 × 1 H, s, 2-H); δ<sub>C</sub>(75 MHz; CDCl<sub>3</sub>) 21.4, 21.6, 23.4, 23.9, 25.3, 25.6, 36.3, 36.9, 38.1, 26.3 (mi), 26.8 (ma), 32.7 [d, <sup>3</sup>J<sub>CP</sub> 6.2, P(OCH<sub>2</sub>)<sub>2</sub>C], 33.9, 65.8 (d, <sup>2</sup>J<sub>CP</sub> 6.3, C-5), 69.0 (d, <sup>1</sup>J<sub>CP</sub> 146.0, C-4), 75.3 and 75.8 [2 d, <sup>2</sup>J<sub>CP</sub> 6.3, <sup>2</sup>J<sub>CP</sub> 6.5, P(OCH<sub>2</sub>)<sub>2</sub>C], 80.7 (d, <sup>3</sup>J<sub>CP</sub> 24.0, C-2); *m/z* 362 (MH<sup>+</sup>, 100%).

**rac-Dimethyl (2-isopropyl-1-thia-3-azaspiro[4.5]decan-4-yl)-phosphonate (9i).** The title compound was prepared according to **GPI** using 0.95 g (5.00 mmol) of *rac*-2-isopropyl-1-thia-3-azaspiro[4.5]dec-3-ene **5f** and 0.55 g (5.00 mmol) of dimethyl phosphonate as starting material to yield 0.99 g (64%) of **9i** in a diastereomeric mixture of 78 : 22 ratio as a colourless solid, mp 65 °C; *R<sub>f</sub>* 0.54 and 0.62 (*n*-hexane–propan-2-ol, 8 : 2) (Found: C, 50.74; H, 8.72; N, 4.68; S, 10.60. C<sub>13</sub>H<sub>26</sub>NO<sub>3</sub>PS requires C, 50.80; H, 8.53; N, 4.56; S, 10.43%); *v*<sub>max</sub> (CHCl<sub>3</sub>)/cm<sup>-1</sup> 3270 (NH), 1250 (P=O); δ<sub>H</sub>(300 MHz; CDCl<sub>3</sub>) 0.95 [0.22 × 3 H, d, *J* 6.6, CH(CH<sub>3</sub>)<sub>2</sub>], 1.01–1.04 [3 H, m, CH(CH<sub>3</sub>)<sub>2</sub>], 1.07 [0.78 × 3 H, d, *J* 6.6, CH(CH<sub>3</sub>)<sub>2</sub>], 1.13–2.14 [11 H, m, 6-H, 7-H, 8-H, 9-H, 10-H, CH(CH<sub>3</sub>)<sub>2</sub>], 2.99 (0.78 × 1 H, d, <sup>2</sup>J<sub>PH</sub> 18.2, 4-H), 3.08 (0.22 × 1 H, d, <sup>2</sup>J<sub>PH</sub> 17.6, 4-H), 3.83–3.88 [6 H, m, P(OCH<sub>3</sub>)<sub>2</sub>], 4.26 (0.22 × 1 H, d, *J* 8.8, 2-H), 4.41 (0.78 × 1 H, d, *J* 6.6, 2-H); δ<sub>C</sub>(75 MHz; CDCl<sub>3</sub>) 19.5, 20.2 (mi), 19.5, 20.4 (ma), 23.5, 25.4, 27.3, 36.8, 38.4 (ma), 23.8, 25.5, 27.2, 35.0, 37.8 (mi), 33.5 (ma), 35.6 (mi), 52.6 and 53.3 [2 d, <sup>2</sup>J<sub>CP</sub> 6.6, <sup>2</sup>J<sub>CP</sub> 11.0, P(OCH<sub>3</sub>)<sub>2</sub>], 65.4 (C-5, mi), 66.3 (d, <sup>2</sup>J<sub>CP</sub> 6.5, C-5, ma), 69.0 (d, <sup>1</sup>J<sub>CP</sub> 148.5, C-4), 74.9 (d, <sup>3</sup>J<sub>CP</sub> 21.1, C-2, mi), 76.9 (d, <sup>3</sup>J<sub>CP</sub> 23.8, C-2, ma); *m/z* 308 (MH<sup>+</sup>, 100%).

**rac-4-(5,5-Dimethyl-2-oxo-1,3,2λ<sup>5</sup>-dioxaphosphinan-2-yl)-2-isopropyl-1-thia-3-azaspiro[4.5]decan-4-yl (9j).** The title compound was prepared according to **GPI** using 0.95 g (5.00 mmol) of *rac*-2-isopropyl-1-thia-3-azaspiro[4.5]dec-3-ene **5f** and 0.75 g (5.00 mmol) of the cyclic phosphonate **2a** as starting material to yield 1.14 g (66%) of **9j** in a diastereomeric mixture of 82 : 18 ratio as a colourless solid, mp 138 °C; *R<sub>f</sub>* 0.56 and 0.62 (*n*-hexane–propan-2-ol, 8 : 2) (Found: C, 55.18; H, 8.80; N, 3.88; S, 9.45. C<sub>16</sub>H<sub>30</sub>NO<sub>3</sub>PS requires C, 55.31; H, 8.70; N, 4.03; S, 9.23%); *v*<sub>max</sub> (CHCl<sub>3</sub>)/cm<sup>-1</sup> 3300 (NH), 1270 (P=O); δ<sub>H</sub>(300 MHz; CDCl<sub>3</sub>) 0.92–1.17 [12 H, m, CH(CH<sub>3</sub>)<sub>2</sub>], P(OCH<sub>2</sub>)<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>], 1.19–2.19 [11 H, m, 6-H, 7-H, 8-H, 9-H, 10-H, CH(CH<sub>3</sub>)<sub>2</sub>], 2.48 (1 H, s, NH), 3.09 (0.82 × 1 H, d, <sup>2</sup>J<sub>PH</sub> 17.6, 4-H), 3.19 (0.18 × 1 H, d, <sup>2</sup>J<sub>PH</sub> 17.1, 4-H), 3.85–3.97 [2 H, m, P(OCH<sub>2</sub>)<sub>2</sub>], 4.21–4.28 [2 H and 0.18 × 1 H, m, P(OCH<sub>2</sub>)<sub>2</sub> and 2-H], 4.40 (0.82 × 1 H, d, *J* 7.2, 2-H); δ<sub>C</sub>(75 MHz; CDCl<sub>3</sub>) 19.7, 20.5 (ma), 19.8, 20.3 (mi), 21.2, 21.7 (mi), 21.4, 21.7 (ma), 23.5, 25.3, 27.4, 36.9, 38.2 (ma), 24.0, 25.1, 27.4, 35.5, 37.6 (mi), 32.6 [d, <sup>3</sup>J<sub>CP</sub> 6.5, P(OCH<sub>2</sub>)<sub>2</sub>C], 33.8 (ma), 34.6 (mi), 66.1 (d, <sup>2</sup>J<sub>CP</sub> 6.5, C-5), 69.0 (d, <sup>1</sup>J<sub>CP</sub> 147.5, C-4), 75.3 and 75.7 [2 d, <sup>2</sup>J<sub>CP</sub> 6.3, <sup>2</sup>J<sub>CP</sub> 6.3, P(OCH<sub>2</sub>)<sub>2</sub>C], 76.8 (C-2); *m/z* 348 (MH<sup>+</sup>, 100%).

**4-(5,5-Dimethyl-2-oxo-1,3,2λ<sup>5</sup>-dioxaphosphinan-2-yl)-5,5-dimethyl-2-(1,2:3,4-di-*O*-isopropylidene-β-*L*-xylo-1,5-pyranos-5-yl)-1,3-thiazolidine (10).** The title compound was prepared according to **GPI** using 1.72 g (5.00 mmol) of (2*S*,5*S*)-5,5-dimethyl-2-(1,2:3,4-di-*O*-isopropylidene-β-*L*-xylo-1,5-pyranos-5-yl)-2,5-dihydro-1,3-thiazole **6** and 0.75 g (5.00 mmol) of the

cyclic phosphonate **2a** as starting material. As an exception to **GP1**, a saturated aqueous solution of potassium hydrogen carbonate was used for hydrolysis of the reaction mixture. Extractive work-up following **GP1** yielded 2.31 g of compound **10** in a mixture of three or four diastereomers according to NMR spectra. Digestion of the crude product with diethyl ether led to the separation of 0.22 g isomeric pure (2*S*,4*R*,5*S*)-**10** (one of the minor isomers) as a colourless precipitate. Column chromatography on silica gel (*n*-hexane–propan-2-ol, 9 : 1 eluent) of the residual crude product led to an additional 1.12 g **10** as a mixture of diastereomers and 0.08 g of the C-2-epimeric 2,5-dihydro-1,3-thiazole *epi*-**6** (5% of the initial thiazoline **6**) as a by-product. The overall yield for compound **10** was 68%, mp 188 °C (decomp., mixture of isomers); mp 212 °C [decomp., (2*S*,4*R*,5*S*)-**10**];  $R_f$  0.35 (ma), 0.29 (mi) (*n*-hexane–propan-2-ol, 9 : 1);  $[\alpha]_D^{20}$  –49.8 (*c* 1 in CHCl<sub>3</sub>, mixture of isomers);  $[\alpha]_D^{20}$  –104.9 [*c* 1 in CHCl<sub>3</sub>, (2*S*,4*R*,5*S*)-**10**] (Found: C, 51.07; H, 7.31; N, 2.71; S, 6.39. C<sub>21</sub>H<sub>36</sub>NO<sub>8</sub>PS requires C, 51.10; H, 7.35; N, 2.84; S, 6.50%);  $\nu_{\max}$  (CHCl<sub>3</sub>)/cm<sup>–1</sup> 3295 (NH), 1240 (P=O);  $\delta_{\text{H}}$ [300 MHz; CDCl<sub>3</sub>, (2*S*,4*R*,5*S*)-**10**] 1.04, 1.16 [6 H, 2 s, P(OCH<sub>2</sub>)<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>], 1.31, 1.33, 1.43, 1.51, 1.54, 1.69 [18 H, 6 s, C(CH<sub>3</sub>)<sub>2</sub>], 2.99 (1 H, br s, NH), 3.16 (1 H, d, <sup>2</sup> $J_{\text{PH}}$  16.2, 4-H), 3.64 (1 H, d, <sup>3</sup> $J_{\text{HH}}$  9.0, C-2-CHCHCHCHO), 4.02–4.33 [5 H, m, C-2-CHCHCHCHO, P(OCH<sub>2</sub>)<sub>2</sub>], 4.36 (1 H, d, <sup>3</sup> $J_{\text{HH}}$  7.5, C-2-CHCHCHCHO), 4.60 (1 H, d, <sup>3</sup> $J_{\text{HH}}$  7.5, C-2-CHCHCHCHO), 4.77 (1 H, d, <sup>3</sup> $J_{\text{HH}}$  9.0, 2-H), 5.55 (1 H, d, <sup>3</sup> $J$  4.5, C-2-CHCHCHCHO) (assignment supported by HHCOSY);  $\delta_{\text{C}}$ [75 MHz; CDCl<sub>3</sub>, (2*S*,4*R*,5*S*)-**10**] 21.7, 22.3, 24.7, 25.4, 26.3, 26.7, 28.2, 28.4, 33.1 [d, <sup>3</sup> $J_{\text{CP}}$  7.0, P(OCH<sub>2</sub>)<sub>2</sub>C], 59.2 (d, <sup>2</sup> $J_{\text{CP}}$  4.8, C-5), 66.7 (d, <sup>1</sup> $J_{\text{CP}}$  146.4, C-4), 67.2 (d, <sup>3</sup> $J_{\text{CP}}$  23.8, C-2), 69.7, 71.1, 71.4, 71.6, 76.7 [d, <sup>2</sup> $J_{\text{CP}}$  6.6, P(OCH<sub>2</sub>)<sub>2</sub>C], 97.1, 109.0, 110.0; *m/z* 394 (MH<sup>+</sup>, 100%), 344 (20).

Analytical data of the by-product (2*R*,5*S*)-5,5-dimethyl-2-(1,2,3,4-di-*O*-isopropylidene-β-*L*-xylo-1,5-pyranos-5-yl)-2,5-dihydro-1,3-thiazole *epi*-**6**, mp 110 °C;  $R_f$  0.76 (*n*-hexane–propan-2-ol, 9 : 1);  $[\alpha]_D^{20}$  –84.3 (*c* 1 in CHCl<sub>3</sub>) (Found: C, 55.91; H, 7.30; N, 4.00; S, 9.26. C<sub>16</sub>H<sub>25</sub>NO<sub>5</sub>S requires C, 55.96; H, 7.34; N, 4.08; S, 9.34%);  $\delta_{\text{H}}$ (500 MHz; CDCl<sub>3</sub>) 1.29, 1.36, 1.45, 1.48, 1.49, 1.52 [18 H, 6 s, C(CH<sub>3</sub>)<sub>2</sub>], 3.61 (1 H, d, <sup>3</sup> $J$  9.5, C-2-CHCHCHCHO), 4.30 (1 H, dd, <sup>3</sup> $J$  5.1, <sup>3</sup> $J$  2.6, C-2-CHCHCHCHO), 4.49 (1 H, dd, <sup>3</sup> $J$  7.7, <sup>3</sup> $J$  1.9, C-2-CHCHCHCHO), 4.59 (1 H, dd, <sup>3</sup> $J$  7.7, <sup>3</sup> $J$  2.6, C-2-CHCHCHCHO), 5.51 (1 H, d, <sup>3</sup> $J$  5.1, C-2-CHCHCHCHO), 5.80 (1 H, dd, <sup>3</sup> $J$  9.5, <sup>4</sup> $J$  2.6, 2-H), 7.12 (1 H, d, <sup>4</sup> $J$  2.6, 4-H) (assignment supported by HHCOSY);  $\delta_{\text{C}}$ (75 MHz; CDCl<sub>3</sub>) 24.4, 24.9, 25.9, 29.0, 29.6, 63.2, 70.6, 70.7, 71.5, 73.6, 82.3, 96.3, 108.7, 109.5, 171.1; *m/z* 344 (MH<sup>+</sup>, 100%).

#### Crystal structure determination of a minor isomer of **10**

Single crystals of one of the minor isomers of **10** were crystallized from diethyl ether, mounted in inert oil and transferred to the cold gas stream of the diffractometer.

**Crystal data.** C<sub>21</sub>H<sub>36</sub>NO<sub>8</sub>PS,  $M = 493.54$ , orthorhombic,  $a = 9.8581(6)$ ,  $b = 10.6386(4)$ ,  $c = 24.4742(10)$  Å,  $U = 2566.8(2)$  Å<sup>3</sup>,  $T = 193(2)$  K, space group  $P2_12_12_1$ ,  $Z = 4$ ,  $\mu = 0.232$  mm<sup>–1</sup>,  $x = -0.01(6)$ , 18617 reflections measured, 4699 unique ( $R_{\text{int}} = 0.0441$ ) which were used in all calculations. The final  $\omega R(F^2)$  was 0.0672 (all data). CCDC reference number 146351. See <http://www.rsc.org/suppdata/p1/b1/b101501j/> for crystallographic files in .cif or other electronic format.

#### Computational details

All geometries have been optimized under vacuum conditions using restricted Hartree–Fock (HF) method and the 6-31G(d,p) basis set employing Gaussian98.<sup>47</sup> All points of stationary energy have been characterized by frequency calculations. Additionally, the transition states have been used as starting

points for the search of the two minima linked by each of these first order saddle points. Thermochemical properties have been calculated using the default conditions (25 °C, 1 atm) of Gaussian98.

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