A Hetero-Diels−Alder Approach to Phosphonothiashikimic Acid and New Thiaglycosides

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Phosphonodithioformates undergo hetero-Diels–Alder cycloadditions with a variety of dienes. In some cases, Lewis acid catalysts were used to control the rate and selectivity of the reactions. Selective radical desulfanylation and subsequent dihydroxylation of the cycloadducts allowed the syntheses of new thiapyran derivatives and, in particular, a phosphono and thio analogue of shikimic acid.

Introduction

Thiasugars in which a sulfur atom replaces an oxygen atom in the heterocycle are a class of compounds that exhibit various biological activities.[1] Their biological and physicochemical specificities are due in part to the electronic properties induced by the sulfur atom. Some six-membered-ring thiaglycosides (Figure 1) act as fucosidase[2] and glucosidase inhibitors,[3,4] and others are known as potential anti-thrombotic agents.[5,6] Because very few naturally occurring thiasugars are presently known (e.g., 5-thio-D-mannose), developing convenient methods for their synthesis and expanding the array of such compounds remains a challenge for organic chemists.

General methods to prepare thiaglycosides use chemical modification of available carbohydrate precursors.[7] Although carbonyl and imino groups have been used widely in hetero-Diels−Alder cycloaddition for the synthesis of sugars and aza-sugars, the thiocarbonyl group has found limited applications in this area.[8] Nevertheless, its dienophilic properties have been reviewed recently[9] and a few thiocarbonyl compounds have already been used as dienophiles in the synthesis of natural or bioactive products or their analogues.[10] It is well established now that dithioesters are less reactive, relative to thioaldehydes and thioketones, but their stability make them much easier to handle as synthetic intermediates. Moreover, when they are α-substituted by an electron-withdrawing group (CN, CO_2R, CF_3, SO_2R),[11] which decreases the LUMO energy of the thiocarbonyl group, dithioesters become efficient heterodienophiles. We previously reported some of our studies concerning the reactivity of phosphonodithioesters in [4+2] cycloadditions.[12] Phosphonodithioformates[12a,12b] and phosphonodifluorodithioacetates[12c] can act as efficient heterodienophiles, and α,β-unsaturated phosphonodithioacetates[12d,12e] as heterodienes. The resulting cycloadducts are interesting precursors of thiapyrans and related structures. For example, starting from phosphonodithioformates, the cycloaddition−desulfanylation−dihydroxylation sequence represents a versatile route toward the synthesis of new phosphorylated thiaglycosides and, therefore, we focused on its application directly for this purpose (Scheme 1).

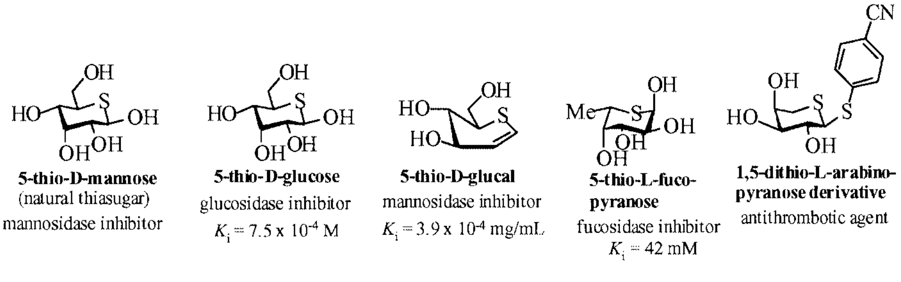

Figure 1. Biological activity of thiapyranosic sugars

We studied the scope and limitations of this strategy by varying the dienic partner and applied this strategy toward the synthesis of the first phosphono and thio analogue **II**

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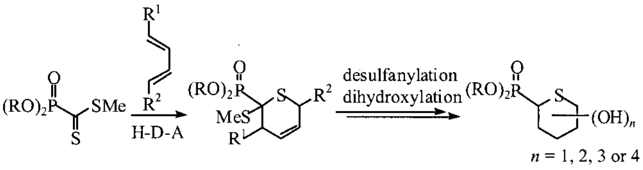


Scheme 1. Hetero-Diels−Alder approach to thiasugars

of shikimic acid **I**, which is an intermediate in the biosynthesis of aromatic amino acids from carbohydrates in plants[13] (Figure 2). In each case, we examined the influence of the experimental conditions (e.g., Lewis acids, temperature) on the rate and the regio- and stereoselectivity of the cycloaddition, together with the selectivity of the radical cleavage of the methylthio group and the cis-dihydroxylation, and characterized the newly synthesized, variously functionalized, phosphorylated thiapyrans. This paper reports the full details of this study.

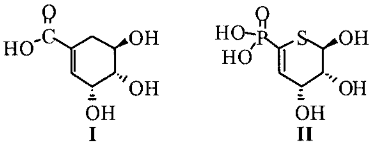


Figure 2. Shikimic acid and its phosphono and thio analogue

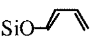
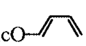
Results and Discussion

Cycloaddition with Butadiene

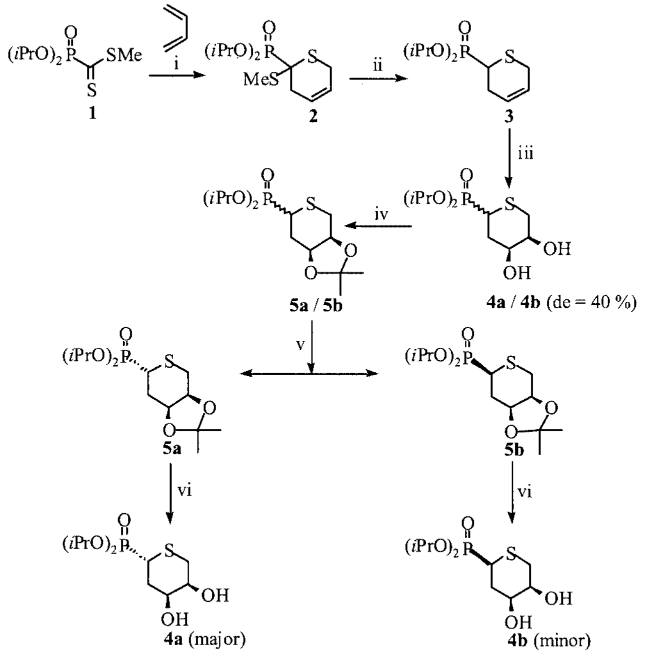
We have shown in a preliminary note[12a] that the reaction of the phosphonodithioformate **1** with butadiene led to the (3,6-dihydro-2-methylsulfanyl) thiapyranylphosphonate **2** in 95% yield when using the gaseous diene instead of its sulfolene precursor (only a 63% yield was obtained when using the latter compound). No example of catalysis by Lewis acids of a hetero-Diels−Alder reaction involving a thiocarbonyl group as the dienophile preceded this recent publication, in which we demonstrated the dramatic acceleration of the cycloaddition with 2,3-dimethylbutadiene by adding $ZnCl_2$ or $BF_3{\cdot}Et_2O$.[12a] We attribute this catalytic effect to chelation of the Lewis acid by the oxygen atom of the phosphonyl group, which is a process that increases its electron-withdrawing effect on the thiocarbonyl group. As shown in Table 1, the same effect was observed with butadiene (Scheme 2, entries 1 and 2) and the cycloadduct **2** was obtained in nearly quantitative yield. Subsequently, we carried out the two reactions needed for access to thiaglycosidic structures from **2**: desulfanylation followed by cis-dihydroxylation of the double bond. As has been shown already,[12a] the cleavage of one methylsulfanyl group from the dithioacetal units, using Bu_3SnH/AIBN[14] in refluxing benzene, is completely selective (no trace of the opened ring was detected) and leads to dihydrothiopyranyl phosphonate **3** (Scheme 2, Table 2, entry 1). The latter compound was submitted to dihydroxylation conditions[15] to afford the expected diol as two diastereoisomers, **4a** and **4b**, in a 70:30 ratio (Scheme 2, Table 3, entry 1) without any oxidation of the sulfur atom. Only the mixture of their acetonides **5a** and **5b** could be separated by chromatography, and each isomer was then deprotected to give the pure diols **4a** and **4b**.

The relative *syn* configuration between the phosphoryl unit and the two hydroxy groups, together with the realiz-

Table 1. Cycloadditions with phosphonodithioformate **1**

Entry	Diene	Solvent Lewis acid	T°, P	Time (h)	Cycloadduct	^{31}P NMR δ ppm (*ratio* %)[a]	Isolated Yield %
1		THF	RT	48	**2**	20.2	95
2		CH_2Cl_2 $ZnCl_2$	pressure tube idem	2	**2**	20.2	99
3	Me$_3$SiO	THF	Reflux	12	**10a**+**10b**+ **11a**+**11b**	19.9 (*16*); 18.9 (*41*); 18.8 (*18*) 18.3 (*25*)	30[b]
4		THF $BF_3.Et_2O$	RT	18	**12a**+**12b**	20.9 (*25*); 20.4 (*75*)	90[c]
5	AcO	CH_2Cl_2	Reflux	360	**13a**+**13b**	18.5 (*83*); 17.2 (*17*)	85[d]
6	PhS	THF -	Reflux	12	**17a**+**17b**	19.0 (*50*); 17.2 (*50*)	95[d]
7		THF $ZnCl_2$	RT	72	**17a**+**17b**	19.0 (*75*); 17.2 (*25*)	65[d]
8	MeOSPh	THF	RT, 12kbar	72	**20**+**21a**+**21b**	19.9 (*17*); 18.7 (*50*); 18.4 (*33*)	89[e]
9	AcOOAc	THF	50°C	168	**26a**+**26b**	15.8 (*67*); 14.7 (*33*)	87[f]
10		THF	MW	0.3	**26a**+**26b**	15.8 (*50*); 14.7 (*50*)	70

[a] Measured from the crude mixture; δ values given in decreasing peak order. [b] Only a mixture of **10a** and **10b** was isolated. [c] 67% of **12a** and 23% of **12b**. [d] Mixture of two isomers. [e] Mixture of the three isomers. [f] 58% of **26a** and 29% of **26b**.



Scheme 2. Synthesis of thiapyran derivatives starting from dithioester **1** and butadiene; *reagents and conditions*: i: see Table 1; ii: 2 equiv. Bu_3SnH, cat. AIBN, refluxing benzene, 2 h, 88%; iii: $K_3Fe(CN)_6$, K_2CO_3, cat. $OsCl_3$, cat. quinuclidine, $H_2O/tBuOH$, 88%; iv: acetone, cat. PTSA, 24 h, room temp., 90%; v: separation by chromatography; vi: $AcOH/H_2O$, 60 °C, 2 h, quantitative

Table 2. Radical desulfanylation

Entry	Substrate	Bu_3SnH (equiv.)	Product	^{31}P NMR δ ppm (*ratio* %)[a]	Isolated Yield %
1	**2**	2	**3**	22.9	88
2	**13a**	2	**14**	19.1	80
3	**13b**	2	**14**	19.1	82
4	**17a**+**17b**	4	**19**	11.6	60
5	**22**	4	**23**	10.3	75
6	**24a**+**24b**	2	**25**	20.4	39
7	**26a**	2	**27a**+**27b**	18.4 (*33*); 17.9 (*67*)	85[b]
8	**26b**	2	**27a**+**27b**	18.4 (*38*); 17.9 (*62*)	75[c]

[a] Measured from the crude mixture; δ values given in decreasing peak order. [b] 57% of **27a** and 28% of **27b**. [c] 46% of **27a** and 27% of **27b**.

Table 3. Dihydroxylation of dihydrothiapyranyl phosphonates

Entry	Substrate	OsO_4	Product	^{31}P NMR δ ppm (*ratio* %)[a]	Isolated Yield %
1	**3**	cat.	**4a** + **4b**	26.2 (*30*); 23.9 (*70*)	88[b]
2	**15**	cat.	**16**	23.7	70
3	**20**	cat.	**22**	18.3	70
4	**21a**	cat.	**24a**	16.1	83
5	**21b**	cat.	**24b**	20.9	70
6	**27a**	equimol.	**28a**	19.0	83
7	**27b**	equimol.	**28b**	18.9	78

[a] Measured from the crude mixture; δ values given in decreasing peak order. [b] Inseparable mixture.

ation that the more stable conformation has P-equatorial, C-4-(OH)-equatorial, and C-5-(OH)-axial, was demonstrated by analyzing the minor isomer **4b** by X-ray diffraction (Figure 3).

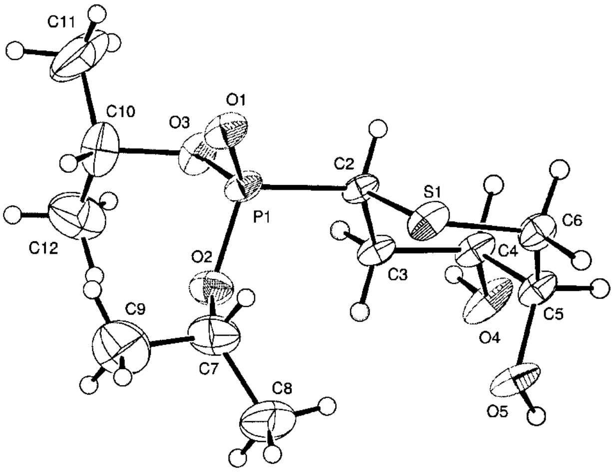


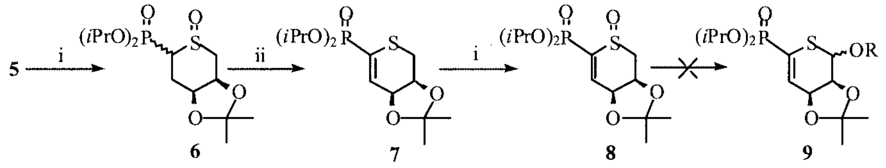
Figure 3. Crystal structure of diisopropyl 2-(4,5-dihydroxy-tetrahydro-thiapyranyl)phosphonate **4b**

Encouraged by the high yields and the easy preparation of the intermediates on a large scale, we attempted to access a thiashikimic derivative **9** starting from the mixture of acetonides **5** using two subsequently oxidation/Pummerer reaction steps (Scheme 3). The oxidation of **5** with $NaIO_4$ gave sulfoxide **6**, which was characterized only by its ^{31}P NMR spectrum; four diastereoisomeric sulfoxides are expected, but only three signals were observed (see Exp. Sect.). Crude **6** reacted with trifluoroacetic anhydride and led to the desired α,β-unsaturated phosphonate **7**, resulting from a Pummerer rearrangement accompanied by β-elimination, in 96% yield. The oxidation of **7** with $NaIO_4$ gave the vinylic sulfoxide **8** in 90% yield, as a single diastereoisomer, the relative configuration of which could not be determined by NMR spectroscopy experiments. A second Pummerer reaction from **8** was expected to allow an OR substituent to be introduced at the anomeric C-6 position and, thus, to create the target molecule **9**. All attempts to carry out this reaction failed when using a number of known reagents (such as acetic and trifluoroacetic anhydrides or silylated ketene acetals).[16] Therefore, we decided to introduce one or two OR groups by using functionalized dienes in the cycloaddition step.

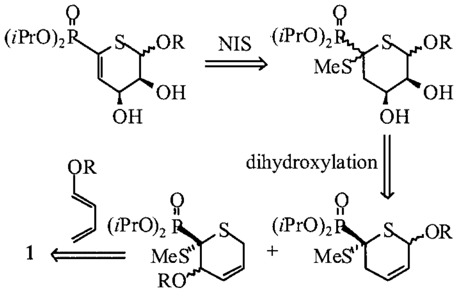
Cycloaddition with 1-Trimethylsilyloxybutadiene and 1-Acetoxybutadiene

In the reaction of **1** with these 1-substituted butadienes, two regioisomers could be formed (each one having two diastereoisomers). We expected that one of them (with an OR unit on C-6) could be converted into a phosphono thiashikimic derivative by dihydroxylation and desulfanylation using *N*-iodosuccinimide[12c] (NIS), as in the retrosynthesis depicted in Scheme 4.

The reaction of **1** with 1-trimethylsilyloxybutadiene in refluxing THF led to a mixture of four products (as observed

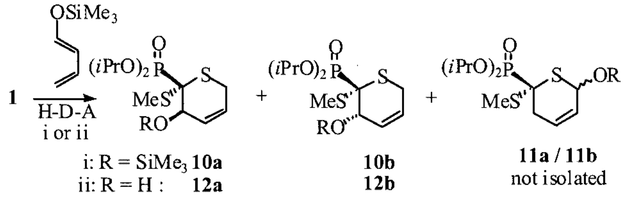


Scheme 3. Pummerer reactions of sulfoxides **6** and **8**; *reagents and conditions*: i: $NaIO_4$, $EtOH/H_2O$, 12 h, room temp., quant.; ii: $(CF_3CO)_2O$, THF, 2 h, room temp., 96%



Scheme 4

by ^{31}P NMR spectroscopy), which probably correspond to the expected cycloadducts **10a,b** and **11a,b**, with low regio- and diastereoselectivity (Scheme 5, Table 1, entry 3). After chromatography, only the two diastereoisomers **10a** and **10b** were isolated. We believe that regioisomer **11** was desilylated on the column and the resulting product, which bears a free anomeric OH group, degraded. Fortunately, when the reaction was carried out at room temperature and in presence of $BF_3{\cdot}Et_2O$, only one regioisomer (as two diastereoisomers in a 3:1 ratio) was obtained in excellent yield (Table 1, entry 4).



Scheme 5. Cycloaddition with dithioester **1** and 1-trimethylsilyloxybutadiene; *reagents and conditions*: i and ii: see Table 1

The resulting products were found to be cycloadducts **12a** and **12b**, which we obtained directly as deprotected alcohols. The crystallised minor isomer **12b** was analyzed by X-ray diffraction (Figure 4). In this way, the vicinal arrangement of the phosphoryl and hydroxy groups and their relative *anti* configuration were determined unambiguously. In this cycloadduct, in which the phosphorus and sulfur atoms are both borne by the anomeric carbon atom, the phosphoryl group is located again in the equatorial position. We deduce that the major isomer **12a** was formed according to a preferential phosphonyl-*endo* cycloaddition.

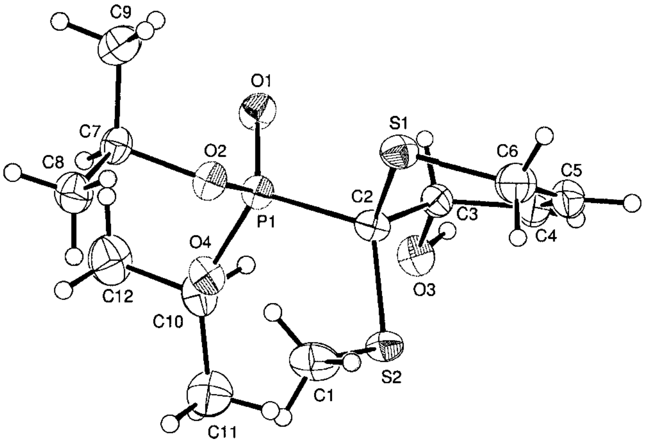
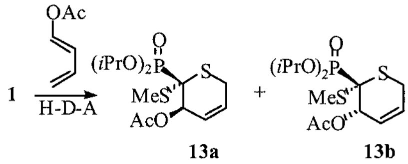


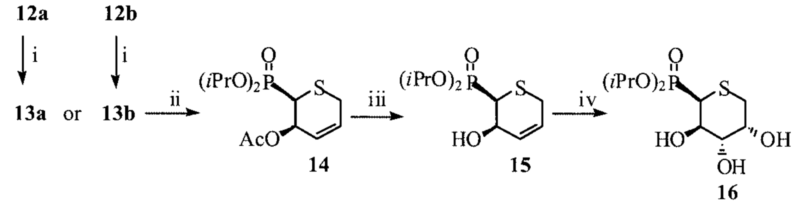
Figure 4. Crystal structure of diisopropyl 2-(3-hydroxy-2-methylsulfanyl-3,6-dihydro-2*H*-thiapyranyl)phosphonate **12b**

The reaction of **1** with the less reactive 1-acetoxybutadiene in refluxing THF led to only two cycloadducts, **13a** and **13b**, in an 83:17 ratio (Scheme 6, Table 1, entry 5). The regio- and diastereoselectivity were similar to those in the case described above, although no Lewis acid was added.



Scheme 6. Cycloaddition with dithioester **1** and 1-acetoxybutadiene; *conditions*: see Table 1

By acetylating alcohols **12a** and **12b**, the corresponding acetates, identical to **13a** and **13b** (by comparison of their ^{31}P NMR spectra) were obtained (Scheme 7). Although these compounds do not have the proper regiochemistry to be converted into a shikimic analogue, each one was then desulfanylated using the Bu_3SnH/AIBN system, from which the same single isomer **14** was obtained in each case (Table 2, entries 2 and 3). Compound **14** has a *syn* configuration (deduced from the $^3J_{H2-H3}$ coupling constants), which can be explained by a preferential hydrogen transfer to the anomeric radical through an axial attack *anti* to the vicinal acetoxy group. Acetate **14** was deprotected and the resulting alcohol **15** was dihydroxylated to give the trihydroxythiapyran **16** in 70% yield (Table 3, entry 2). The stereo-

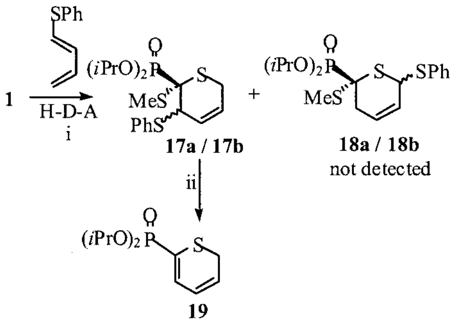


Scheme 7. Synthesis of thiapyran **16** by a desulfanylation/dihydroxylation sequence; *reagents and conditions*: i: Ac_2O/Py, 90%; ii: 2 equiv. Bu_3SnH, cat. AIBN, refluxing benzene, 2 h, 80%; iii: K_2CO_3, MeOH/H_2O, 90%; iv: $K_3Fe(CN)_6$, K_2CO_3, cat. $OsCl_3$, cat. quinuclidine, H_2O/*t*BuOH, 70%.

chemistry of this new P-thiaglycoside is very likely to be that illustrated in Scheme 7, as a result of preferential dihydroxylation *anti* to the preexisting allylic hydroxy or alkoxy group.[8c,17] It was difficult to confirm this stereochemistry, however, by NMR spectroscopy experiments.

Cycloaddition with 1-Phenylsulfanylbutadiene

A diene functionalized by an SR group is also an interesting candidate for the hetero-Diels−Alder cycloaddition, because it allows additional sulfur atoms to be introduced into the structure of new thiasugars. Moreover, when this group is placed in the anomeric position of a glycoside, it could be replaced by an OR group,[18] or by nucleic bases, to produce new nucleosidic structures.[19] Therefore, we decided to examine the reaction of 1-phenylsulfanylbutadiene[20] with the phosphonodithioformate **1**. Four cycloadducts (including two diastereoisomers for each of the regioisomers **17** and **18**) are expected (Scheme 8). Using thermal conditions, only two cycloadducts, in a 1:1 ratio, were observed by ^{31}P NMR spectroscopy (Table 1, entry 6). Using $ZnCl_2$ catalysis, the same cycloadducts were formed in a 3:1 ratio (Table 1, entry 7). Because of the electron-rich character of the diene, by analogy with the previous case of an OR substituent, the resulting regioisomer is expected to be the cycloadduct **17**, but the NMR spectroscopic data are inconclusive. The desulfanylation, however, of the inseparable mixture of **17a** and **17b**, using 4 equivalents of Bu_3SnH, afforded a single product, the new functionalized diene **19**, in 60% yield (Scheme 8, Table 2, entry 4). Its phosphonate vinylic double bond was formed by the radical cleavage of both the phenyl- and methylsulfanyl groups that are positioned vicinally. This chemical evidence confirms the structure of **17** and the regioselectivity of the cycloaddition.



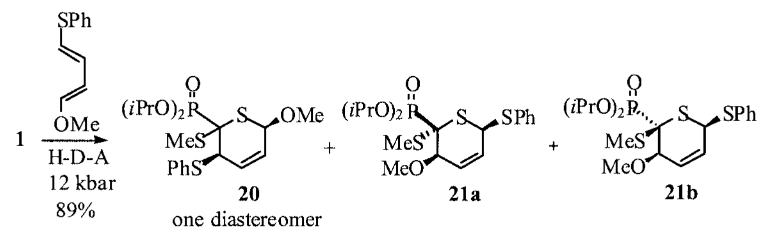
Scheme 8. Cycloaddition of dithioester **1** and 1-phenylsulfanylbutadiene and desulfanylation; *reagents and conditions*: i: see Table 1; ii: 4 equiv. Bu_3SnH, cat. AIBN, refluxing benzene, 5 h, 60%

Cycloaddition with 1-Methoxy-4-phenylsulfanylbutadiene

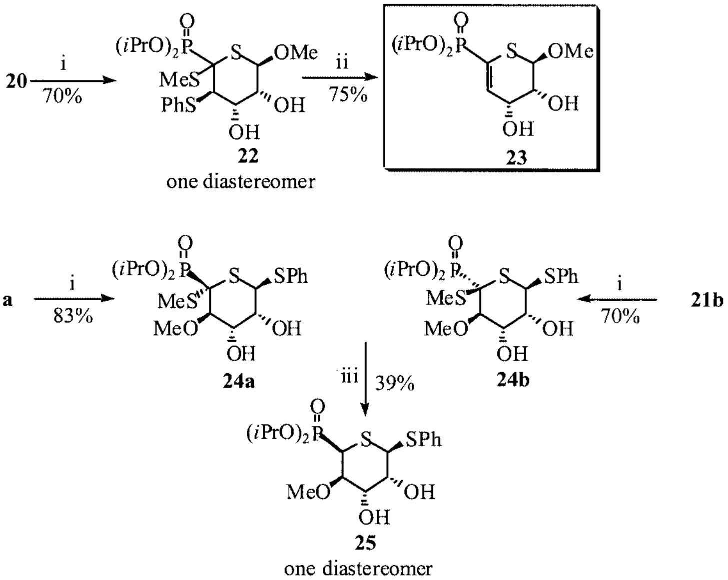
The efficiency of the radical double desulfanylation described above involving two vicinal SR groups, incited us to employ it to generate the desired double bond in the structure of the shikimic acid analogue. We selected 1-methoxy-4-phenylsulfanylbutadiene,[21] which features SR and OR substituents, to be the diene partner of **1**. In the first series of experiments, carried out under thermal conditions, or catalysed by Lewis acids ($ZnCl_2$ or $BF_3{\cdot}Et_2O$), the conversion did not exceed 15%. High pressure was used successfully in this case, and three products were obtained in a 1:3:2 ratio (measured as a crude mixture by ^{31}P NMR spectroscopy) (Scheme 9, Table 1, entry 8). The chromatographic separation was very difficult and we isolated only small amounts of enriched fractions of each component. Therefore, the dihydroxylation and desulfanylation experiments were carried out most often using a mixture of isomers. Nevertheless, all compounds could be characterized finally from their resulting products, the structures of which are shown in Scheme 9 and Scheme 10. The structures **20** and **21** indicate that the cycloaddition occurred without any regioselectivity, with a low diastereoselectivity for regioisomer **21**, and with a total diastereoselectivity for **20**. The relative configuration of the major cycloadduct **20** could not be confirmed by NMR spectroscopy, but a *syn* relationship between the phosphoryl and phenylsulfanyl groups, which agrees with a P-*endo* cycloaddition, is the most probable.

Cycloadduct **20** was dihydroxylated to give a single product **22** (Scheme 10, Table 3, entry 3). The double desulfanylation of the latter using 4 equivalents of Bu_3SnH led, in 75% yield, to **23**, which possesses the desired structure of the target molecule, a phosphonothiashikimic ester derivative (Table 2, entry 5). The structure of **23** and its relative configuration was confirmed by X-ray diffraction analysis (Figure 5).

Stereoselective *cis*-dihydroxylation of **21a** and **21b** (*anti* to the SPh and OMe groups) led to compounds **24a** and **24b**, respectively (Table 3, entries 4 and 5). The subsequent cleavage of the methylsulfanyl group in the mixture **24a/24b** afforded only one diastereoisomer (**25**) in 39% yield. Its structure was assigned again according to the most probable stereoselectivity of the reduction of the anomeric rad-



Scheme 9. Cycloaddition with dithioester **1** and 1-methoxy-4-phenylsulfanylbutadiene



Scheme 10. Synthesis of phosphonothiashikimic derivative **23** and thiopyran **25**; *reagents and conditions*: i: $K_3Fe(CN)_6$, K_2CO_3, $OsCl_3$, cat. quinuclidine., $H_2O/tBuOH$; ii: 4 equiv. Bu_3SnH, cat. AIBN, refluxing benzene, 5 h, 75%; iii: 2 equiv. Bu_3SnH, cat. AIBN, refluxing benzene, 2 h, 39%

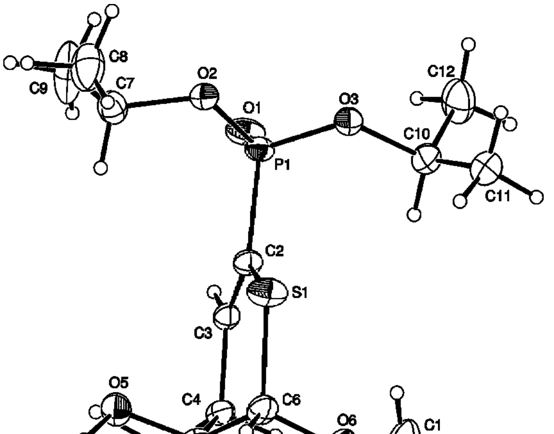
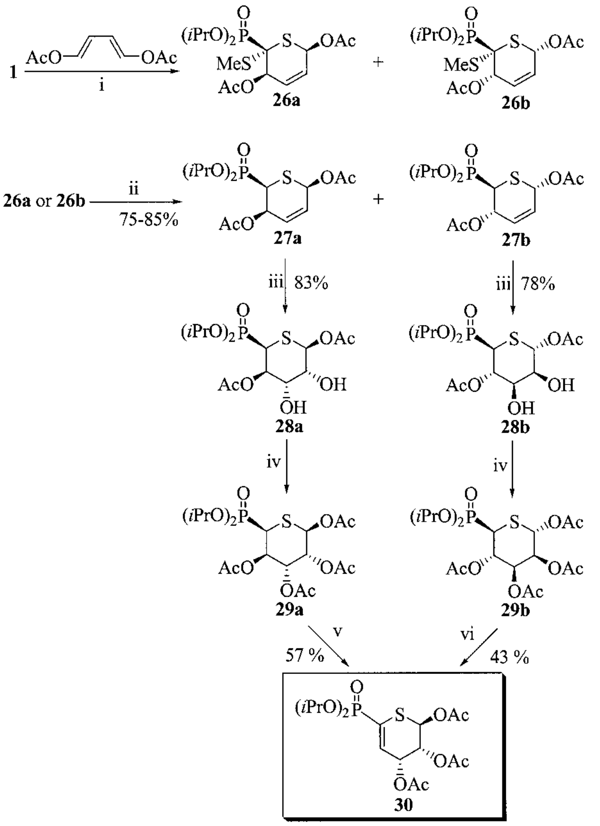


Figure 5. Crystal structure of diisopropyl 2-(4,5-dihydroxy-6-methoxy-5,6-dihydro-4*H*-thiapyranyl)phosphonate **23**

ical *trans* to the OMe substituent, as in the previous cases (Table 2, entry 6).

Cycloaddition with 1,4-Diacetoxybutadiene

The first synthesis of a phosphonothiashikimic derivative, from phosphonodithioester **1** and *(E,E)*-1,4-diacetoxybutadiene, was described in our previous communication.[12b] This diene is the most common one used in the preparation of the shikimic acid or its analogues by [4+2] cycloaddition.[10b,13] Although relatively slow (7 d), the reaction of this diene with **1** in refluxing THF led to the functionalized dihydrothiopyranic derivative as a mixture of diastereoisomers **26a** and **26b** in a 2:1 ratio and 87% yield (Scheme 11, Table 1, entry 9). The isomers were separated readily by chromatography on silica gel and the relative *syn* configuration between the two acetoxy and phosphono groups, resulting from a preferential phosphonyl-*endo* cycloaddition, expected for the major cycloadduct **26a**, was confirmed by ^1H NMR spectroscopy (coupling constants J_{H3-P} and J_{H6-P}). Although Lewis acids, which afford undesirable products of degradation, could not be used to accelerate the reaction, we found that activation by microwaves is very efficient: the reaction time decreased to 20 min. Under these conditions, no *endo*/*exo* selectivitiy was observed for the cycloaddition (Table 1, entry 10). Each



Scheme 11. Synthesis of phosphonothiashikimic derivative **30** starting from dithioester **1** and 1,4-diacetoxybutadiene; *reagents and conditions*: i: see Table 1; ii: 2 equiv. Bu_3SnH, cat. AIBN, refluxing benzene, 2 h; iii: OsO_4/Py, room temp., 2 h; iv: $(AcO)_2O$/Py, 80 °C, 12 h, 91%.; v: Py, reflux, 36 h; vi: 3 equiv. NaH, THF, room temp., 36 h

cycloadduct was then desulfanylated with Bu_3SnH and a mixture of isomers **27a** and **27b**, respectively, was obtained in nearly the same 2:1 ratio from **26a** or **26b** (Table 2, entries 7 and 8). Thus, relative to the desulfanylation of the monoacetylated substrate **13**, the reduction of the anomeric radical was not completely stereoselective, probably because of the presence of the second acetoxy group in the 6-position. Nevertheless, the favored isomer was **27a**, which resulted from attack of the hydride *anti* to the acetoxy substituent at C-3. To avoid deprotection of the two acetyl groups under basic aqueous conditions, the dihydroxylation was performed under classical conditions with an equimolecular amount of osmium tetraoxide in pyridine. Thus, isomer **27a** gave the dihydroxylated diacetoxythiapyran **28a**, and the other isomer **27b** gave **28b** (Table 3, entries 6 and 7). These products were transformed into tetraacetylated derivatives **29a** and **29b**. From **29a**, *trans* elimination of acetic acid occurred in hot pyridine to give the phosphono thiashikimic derivative **30** in 57% yield after purification. As expected, the elimination failed under similar conditions when using the epimer **29b**, in which the relevant proton and acetoxy group are not in a suitable configuration. By using a stronger base, however, such as NaH, elimination gave the expected compound **30** in 43% yield. In this manner, both isomeric cycloadducts **26a** and **26b** could lead to the desired product. The observed values of the coupling constants $^3J_{H5-H6}$ and $^3J_{H5-H4}$ for the 4,5,6-triacetoxy phosphono thiashikimate **30** are consistent with the attributed structure and are in good agreement with those values of its 4,5-dihydroxy-6-methoxy derivative **23**.

Conclusion

In conclusion, we have shown that the phosphonodithioformate **1** is a powerful hetero-dienophile, which reacts with different functionalised dienes. The rate and the selectivity of the cycloaddition can be influenced by the use of Lewis acids, which increase the reactivity of the thiocarbonyl group by their chelation with the phosphoryl group. The hetero-Diels−Alder reaction and the subsequent desulfanylation by the Bu_3SnH/AIBN system allows the stable and readily accessible phosphonodithioesters to be used (instead of the unknown and, presumably, very unstable thioaldehyde-phosphonates) for the efficient preparation of dihydrothiapyrans. These heterocycles are precursors of new thiaglycosides upon dihydroxylation of their double bonds. We have demonstrated the synthetic potential of this method in the synthesis of two derivatives (**23** and **30**) of a phosphono and thio analogue of shikimic acid. Some other new polyfunctionalized thiapyrans, bearing sulfanyl and hydroxy groups, have been also synthesized. The design of new thiaglycosidic and thianucleotidic structures as potential enzyme inhibitors, based on the hetero-Diels−Alder reaction involving dithioesters, is now under investigation.

Experimental Section

General: Most of reactions were monitored by TLC using silica-coated plates. Synthesized products were purified by flash column chromatography on silica gel and crystallized if necessary. Solvents were dried by distillation prior use. NMR spectra were recorded using a Bruker DPX 250 MHz (250 MHz/^{1}H, 62.9 MHz/^{13}C, 101.2 MHz/^{31}P) or a Bruker DRX 400 MHz (400 MHz/^{1}H, 100.62 MHz/^{13}C, 161.9 MHz/^{31}P) spectrometer, with TMS as the internal standard. Chemical shifts (δ) are given in ppm and coupling constants (*J*) in Hz, conventional abbreviations are used, and the atoms of the six-membered ring are numbered "1" on the sulfur atom and "2" on the carbon atom bearing the phosphorus atom. Some signals were attributed using COSY ^{13}C-^{1}H, ^{1}H{^{31}P} NMR spectroscopy experiments or from spectra recorded in the presence of D_2O (for some hydroxy group-containing compounds). Melting points are uncorrected. The infrared spectra were recorded using a Perkin−Elmer 16 PC spectrometer from liquid films, and are given as $\tilde{\nu}$ values (cm^{-1}). Mass spectra were recorded using a Nermag R 10 10H spectrometer in the electron-impact mode at 70 eV, and are given as *m*/*z* values and relative abundances. HRMS were obtained using a JEOL JMS-AX 500 mass spectrometer. Elemental microanalyses were performed on an automatic CHNS-O ThermoQuest apparatus. The high-pressure cycloaddition reaction was performed in a Unipress piston-cylinder apparatus for pressures up to 14 kbar.

Preparation of Diisopropyl (3,6-Dihydro-2-methylsulfanyl-2*H*-thiapyran-2-yl)phosphonate (2): A solution of diisopropyl phosphonodithioformate **1** (3 g, 11.7 mmol) and zinc chloride (1.6 g, 11.7 mmol) in CH_2Cl_2 (15 mL) was introduced into a pressure tube and cooled to −78 °C. At this temperature, butadiene (5 mL) was added as a liquefied gas and then the tube was closed and the mixture was stirred for 2 h at room temperature. The solution was then hydrolyzed with water (10 mL) and extracted with diethyl ether. The organic phase was dried ($MgSO_4$), and the solvents were evaporated under reduced pressure. Product **2** was obtained in quasi-quantitative yield (98%) and did not need any purification before use. For spectroscopic data see ref.[12a]

Typical Procedure for the Desulfanylation used to Prepare Diisopropyl (3,6-Dihydro-2*H*-thiapyran-2-yl)phosphonate (3): A solution of Bu_3SnH (3.50 mL, 12.9 mmol) and AIBN (240 mg, 1.45 mmol) in benzene (20 mL) was added over a few minutes to a refluxing solution of (thiapyran-2-yl)phosphonate **2** (2.00 g, 6.45 mmol) and azobis(isobutyronitrile) (AIBN; 80 mg, 0.48 mmol) in benzene (30 mL) under N_2. Heating under reflux was maintained for an additional 2 h. After evaporation of the solvent, flash chromatography on silica gel (petroleum ether/EtOAc, 80:20) gave pure **3** in 88% yield. For spectroscopic data see ref.[12a]

Typical Procedure for the Dihydroxylation Used to Prepare Diisopropyl 2-(4,5-Dihydroxy-tetrahydrothiapyranyl)phosphonate (4): Potassium ferricyanide (8.60 g, 26.1 mmol), potassium carbonate (3.60 g, 26.1 mmol), osmium(III) chloride hydrate (18 mg, 0.06 mmol), quinuclidine (35 mg, 0.31 mmol) and methanesulfonamide (831 mg, 8.7 mmol) were dissolved by stirring in a mixture of water (48 mL) and *tert*-butyl alcohol (48 mL). The dihydrothiapyran **3** (2.3 g, 8.8 mmol) was added to the mixture, which was stirred vigorously for 96 h at room temperature. Anhydrous sodium sulfite (14 g, 0.11 mol) was added and the stirring was continued for 1 h. The product was extracted with dichloromethane (3 × 50 mL) and then the organic phase was dried ($MgSO_4$) and the solvents were evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 100:0 to 95:5) to give the diols **4** (inseparable mixture of **4a** and **4b**) as a colorless paste (90%). Pure diols **4a** and **4b** were then obtained from the separation and deprotection of their respective acetonides **5a** and **5b** (see below).

Procedure for the Deprotection of 5a to Give Pure 4a: A solution of **5a** (338 mg, 1 mmol) in acetic acid (8 mL) and water (2 mL) was stirred at 60 °C for 2 h. The reaction mixture was then diluted with water (10 mL) and extracted with dichloromethane (3 × 10 mL). The organic phase was dried ($MgSO_4$) and the solvents were evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 90:10) to give the pure diol **4a.**

4a (major product): ^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 23.9 ppm. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (d, *J* = 5.6 Hz, 6 H, 2 × CH_3), 1.35 (d, *J* = 5.6 Hz, 6 H, 2 × CH_3), 2.09 (m, 1 H, H^3), 2.41 (m, 1 H, $H^{3'}$), 2.76 (dt, *J* = 13.0, 4.1 Hz, 1 H, H^6), 2.94 (dd, *J* = 13.0, 9.4 Hz, 1 H, $H^{6'}$), 3.15 (br. s, 3.26, 2 H, 2 × OH), 3.26 (dddd, *J* = 18.8, 9.9, 2.9, 12.9 Hz, 1 H, H^2), 3.85 (br. s, 1 H, H^5), 4.07 (br. s, 1 H, H^4), 4.63−4.79 (m, 2 H, 2 × CH−O) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 24.27 (d, *J* = 5.1 Hz, CH_3), 24.41 (d, *J* = 4.1 Hz, CH_3), 24.47 (d, *J* = 4.1 Hz, CH_3), 24.52 (d, *J* = 3.5 Hz, CH_3), 30.90 (d, *J* = 8.1 Hz, C^6), 32.18 (d, *J* = 150.3 Hz, C^2), 34.23 (s, C^3), 67.88 (d, *J* = 11.1; C^4), 69.70 (s, C^5), 71.89 (d, *J* = 6.9 Hz, CHOP), 72.27 (d, *J* = 7.0 Hz, CHOP) ppm.

4b (minor product): This compound was obtained from compound **5b** by the procedure mentioned above. Crystallisation of this compound in dichloromethane/petroleum ether provided a single crystal (m.p. 101 °C) that was analyzed by X-ray diffraction. ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 26.2. ^{1}H (400 MHz, $CDCl_3$): 1.35 (d, *J* = 6.1 Hz, 3 H, CH_3), 1.39 (d, *J* = 6.1 Hz, 3 H, CH_3), 1.4 (d, *J* = 6.1 Hz, 6 H, 2 × CH_3), 2.39 (dddd, *J* = 28.8, 14.8, 6.1, 3.5 Hz, 1 H, H^3), 2.52 (dd, *J* = 13.4, 3.9 Hz, 1 H, H^6), 2.58 (m, 1 H, $H^{3'}$), 2.66 (ddd, *J* = 20.8, 6.1, 3.61 Hz, 1 H; H^2), 2.94 (br. d, *J* = 7.21 Hz, 1 H, OH), 3.2 (ddd, *J* = 10.4, 13.4, 10.4 Hz, 1 H, $H^{6'}$), 3.75 (m, 1 H, H^5), 3.85 (m, 1 H, H^4), 4.75−4.90 (m, 2 H, 2 × CH−O), 5.09 (br. d, *J* = 4.31 Hz, 1 H, OH) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 23.97 (d, *J* = 6.8 Hz, CH_3), 24.38 (d, *J* = 3.5 Hz, CH_3), 24.4 (d, *J* = 4.72 Hz, CH_3), 24.94 (d, *J* = 2.1 Hz, CH_3), 28.08 (s, C^6), 31.24 (d, *J* = 148.7 Hz, C^2), 33.82 (s, C^3), 68.38 (d, *J* = 4.6 Hz, C^4), 69.53 (s, C^5), 71.87 (d, *J* = 7.8 Hz, CHOP), 74.28 (d, *J* = 7.6 Hz, CHOP) ppm. MS: *m/z* (%) = 298 $[M]^+$, 214 (15), 128 (24), 115 (22), 114 (18), 113 (19), 109 (36), 59 (20), 57 (16), 47 (21), 45 (46), 43 (100). IR (NaCl): ṽ = 766, 812, 856, 894, 990, 1058, 1104, 1142, 1178, 1228, 1376, 1386, 1428, 2928, 2980, 3380 cm^{-1}.

Preparation of Diisopropyl (2,2-Dimethyl-tetrahydrothiapyrano[3,4-*d*][1,3]dioxol-6-yl)phosphonate (5): *p*-Toluenesulfonic acid (PTSA) (0.1 mmol) was added to diol **4** (2.98 g, 10 mmol) dissolved in acetone (50 mL) and the solution was then stirred for 24 h at room temperature. The solvent was then evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 1:1 to 1:2) to give separated products **5a** (63%) and **5b** (27%) as colorless oils.

5a (major product): ^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 24.2 ppm. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (d, *J* = 6.0 Hz, 12 H, 4 × CH_3), 1.52 [s, 6 H, $C(CH_3)_2$], 2.13 (m, 1 H, H^3), 2.45 (m, 1 H, $H^{3'}$), 2.65 (dd, *J* = 14.0, 6.0 Hz, 1 H, H^6), 2.81 (ddd, *J* = 13.0, 3.6, 3.1 Hz, 1 H, $H^{6'}$), 3.17 (ddd, *J* = 15.1, 11.1, 3.8 Hz, 1 H, H^2), 4.30 (m, 1 H, H^5), 4.38 (m, 1 H, H^4), 4.71−4.79 (m, 2 H, 2 × CH−O) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = (62.9 MHz, $CDCl_3$): 24.27 (d, *J* = 5.3 Hz, CH_3), 24.35 (d, *J* = 4.6 Hz, CH_3), 24.47 (d, *J* = 3.6 Hz, CH_3), 24.56 (d, *J* = 3.4 Hz, CH_3), 25.84 (s, C*C*H_3), 27.8 (s, C*C*H_3), 28.37 (d, *J* = 3.0 Hz, C^3), 28.98 (d, *J* = 6.1 Hz, C^6), 31.39 (d, *J* = 153.2 Hz, C^2), 71.52 (d, *J* = 3.7 Hz, CHOP), 71.57 (d, *J* = 3.2 Hz, CHOP), 71.80 (d, *J* = 6.7 Hz, C^4), 71.94 (s, C^5), 108.50 (s, *C*CH_3) ppm.

5b (minor product): ^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 23.9 ppm. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (d, *J* = 6.0 Hz, 12 H, 4 × CH_3), 1.34 (s, 3 H, CCH_3), 1.46 (s, 3 H, CCH_3), 1.80 (m, 1 H, H^3), 2.37 (m, 1 H, $H^{3'}$), 2.65 (dd, *J* = 13.4, 5.3 Hz, 1 H, H^6), 2.80 (m, 1 H, $H^{6'}$), 2.90 (ddd, *J* = 17.3, 4.5, 13.3 Hz, 1 H, H^2), 4.15 (m, 1 H, H^5), 4.40 (m, 1 H, H^4), 4.70−4.80 (m, 2 H, 2 × CH−O) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 24.33 (d, *J* = 5.5 Hz, CH_3), 24.34 (d, *J* = 5.4 Hz, CH_3), 24.57 (d, *J* = 3.4 Hz, 2 × CH_3), 25.00 (s, C*C*H_3), 26.67 (d, *J* = 1.8 Hz, C^3), 26.97 (d, *J* = 3.2 Hz, C^6), 27.55 (s, C*C*H_3), 31.88 (d, *J* = 156.6 Hz, C^2), 71.91 (d, *J* = 7.2 Hz, 2 × CH−O), 74.07 (d, *J* = 20.2 Hz, C^4), 74.44 (s, C^5), 108.38 (s, *C*CH_3). MS: *m/z* (%) = 338 $[M]^+$, 209 (21), 167 (59), 149 (44), 115 (25), 97 (47), 82 (20), 59 (31), 58 (19), 45 (20), 43 (100). IR (NaCl): ṽ = 616, 654, 676, 740, 768, 786, 814, 834, 872, 894, 986, 1052, 1106, 1142, 1178, 1218, 1246, 1382, 1456, 1652, 2934, 2980 cm^{-1}.

Preparation of Diisopropyl 6-(2,2-Dimethyl-3a,7a-dihydro-4*H*-thiapyrano[3,4-*d*][1,3]dioxolyl)phosphonate (7). First Step: Oxidation of 5 to 6: A solution of **5** (mixture of the two diastereoisomers) (876 mg, 2.6 mmol) in ethanol (5 mL) was added slowly at 0 °C to a solution of $NaIO_4$ (612 mg, 2.8 mmol) in ethanol/water (5/5 mL) and the mixture was kept for 12 h at this temperature. The solution was then extracted with dichloromethane (2 × 10 mL). The organic phase was dried ($MgSO_4$) and the solvents were evaporated under reduced pressure. Sulfoxide **6** was characterized by ^{31}P NMR spectroscopy (101.25 MHz, $CDCl_3$): δ = 18.8, 19.6, 20.1 ppm (these three peaks were present in a 2:1:3 ratio). Crude **6** was used for the next step.

Second Step: Pummerer/β-Elimination Reaction: Trifluoroacetic anhydride (0.42 mL, 3 mmol) was added dropwise to a solution of **6** (891 mg, 2.6 mmol) in THF (20 mL) and then the mixture was stirred for 2 h at room temperature. The solution was then hydrolyzed with water and extracted with diethyl ether. The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure and then the residue was purified by flash chromatography on silica gel (eluent: diethyl ether/pentane, 6:4) to give pure **7** (96%) as a colorless oil. ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 9.8 ppm. ^{1}H (400 MHz, $CDCl_3$): δ = 1.32−1.38 (m, 12 H, 4 × CH_3), 1.40 (s, 3 H, CCH_3), 1.46 (s, 3 H, CCH_3), 2.46 (t, *J* = 11.3 Hz, 1 H, H^6), 2.90 (dt, *J* = 11.3, 4.2 Hz, 1 H, $H^{6'}$), 4.25 (m, 1 H, H^5), 4.45 (m, 1 H, H^4), 4.65−4.80 (m, 2 H, 2 × CH−O), 6.97 (dd, *J* = 8.2, 3.7 Hz, 1 H, H^3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 22.60 (d, *J* = 5.2 Hz, CH_3), 22.70 (d, *J* = 5.2 Hz, CH_3), 22.82 (d, *J* = 4.0 Hz, 2 × CH_3), 24.40 (s, CCH_3), 27.00 (s, CCH_3), 28.81 (d, *J* = 5.0 Hz, C^6), 68.85 (d, *J* = 18.9 Hz, C^4), 71.90 (s, C^5), 71.95 (d, *J* = 3.7 Hz, CHOP), 72.05 (d, *J* = 4.0 Hz, CHOP), 106.83 (s, CCH_3), 129.33 (d, *J* = 193.0 Hz, C^2), 133.70 (d, *J* = 9.6 Hz, C^3) ppm. $C_{14}H_{25}O_5PS$ (336.4): calcd. C 49.99, H 7.49, S 9.53; found C 49.72, H 7.28, S 9.68.

Synthesis of Sulfoxide (8): Compound **7** was oxidized with $NaIO_4$ following the procedure mentioned above (**5** to give **6**). The product was purified by flash chromatography on silica gel (EtOAc/MeOH, 95:5) to give sulfoxide **8** as a colorless, viscous oil (90% yield). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 7.8 ppm. ^{1}H (400 MHz, $CDCl_3$): δ = 1.32−1.38 (m, 18 H, 6 × CH_3), 2.53 (m, 1 H, H^6), 3.55 (d, *J* = 12.8 Hz, 1 H, $H^{6'}$), 4.65−4.80 (m, 2 H, 2 × CH−O), 4.85−4.90 (m, 2 H, H^4 and H^5), 7.25 (dd, *J* = 20.1, 2.6 Hz, 1 H, H^3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 22.75 (d, *J* = 5.2 Hz, CH_3), 22.83 (d, *J* = 5.2 Hz, CH_3), 22.92 (d, *J* = 4.0 Hz, 2 × CH_3), 24.01 (s, CCH_3), 26.17 (s, CCH_3), 46.72 (d, *J* = 5.2 Hz, C^6), 66.19 (d, *J* = 1.9, C^5), 69.26 (d, *J* = 16.3 Hz, C^4), 71.35 (d, *J* = 6.1 Hz, CHOP), 71.66 (d, *J* = 5.8 Hz, CHOP), 108.75 (s, CCH_3), 137.13 (d, *J* = 186.1 Hz, C^2), 144.97 (d, *J* = 7.5 Hz, C^3) ppm.

Preparation of Diisopropyl 2-(2-Methylsulfanyl-3-trimethylsilanyloxy-3,6-dihydro-2*H*-thiapyranyl) Phosphonate (10): A mixture of phosphonodithioformate **1** (384 mg, 1.5 mmol) and 1-(trimethylsilyloxy)-1,3-butadiene (0.8 mL, 3 mmol) in THF (7 mL) was stirred under nitrogen, at reflux, for 12 h. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on basic alumina gel (EtOAc/petroleum ether, 10:90) to give pure **10a** (18%) and **10b** (12%).

10a (major product): ^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 18.8 ppm. ^{1}H NMR (400 MHz, $CDCl_3$): δ = −0.01 [s, 9 H, $Si(CH_3)_3$], 1.15 (d, *J* = 4.5 Hz, 3 H, CH_3), 1.17 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.19 (d, *J* = 5.9 Hz, 3 H, CH_3), 1.22 (d, *J* = 6.3 Hz, 3 H, CH_3), 2.19 (s, 3 H, SCH_3), 2.75 (m, 1 H, H^6), 2.97 (m, 1 H, $H^{6'}$), 3.88 (m, 1 H, H^3), 4.56−4.71 (m, 2 H, 2 × CH−O), 5.33 (m; 1 H, H^4), 5.73 (m, 1 H, H^5) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = −0.25 [s, $Si(CH_3)_3$], 13.65 (s, SCH_3), 22.84 (d, *J* = 6.9 Hz, 2 × CH_3), 23.02 (d, *J* = 5.1 Hz, C^6), 23.06 (d, *J* = 6.1 Hz, 2 × CH_3), 56.30 (d, *J* = 159.2 Hz, C^2), 65.86 (d, *J* = 4.1 Hz, C^3), 70.79 (d, *J* = 7.7 Hz, CHOP), 71.49 (d, *J* = 7.8 Hz, CHOP), 124.16 (d, *J* = 1.2, C^5), 127.96 (d, *J* = 6.9, C^4) ppm.

10b (minor product): ^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 19.9 ppm. ^{1}H NMR (250 MHz, $CDCl_3$): δ = −0.10 [s, 9 H, $Si(CH_3)_3$], 1.15 (d, *J* = 4.5 Hz, 3 H, CH_3), 1.17 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.19 (d, *J* = 5.9 Hz, 3 H, CH_3), 1.22 (d, *J* = 6.3 Hz, 3 H, CH_3), 2.19 (s, 3 H, SCH_3), 2.62 (m, 1 H, H^6), 3.11 (m, 1 H, $H^{6'}$), 4.56−4.71 (m, 2 H, 2 × CH−O), 4.95 (m, 1 H, H^3), 5.33 (m, 1 H, H^4), 5.66 (m, 1 H, H^5) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = −0.01 [s, $Si(CH_3)_3$], 13.37 (s, SCH_3), 22.82 (d, *J* = 4.1 Hz, C^6), 23.33 (d, *J* = 3.2 Hz, CH_3), 23.56 (d, *J* = 3.0 Hz, CH_3), 23.72 (d, *J* = 2.7 Hz, CH_3), 23.96 (d, *J* = 2.2 Hz, CH_3), 55.23 (d, *J* = 155.1 Hz, C^2), 69.59 (d, *J* = 4.0 Hz, C^3), 70.86 (d, *J* = 7.6 Hz, CHOP), 72.28 (d, *J* = 7.8 Hz, CHOP), 123.30 (d, *J* = 1.8 Hz, C^5), 130.58 (d, *J* = 9.4 Hz, C^4) ppm. MS: *m*/*z* (%) = 399 $[MH]^+$, 233 (20), 229 (53), 113 (15), 97 (15), 91 (14), 53 (13), 45 (39), 44 (11), 43 (100). IR (NaCl): $\tilde{\nu}$ = 694, 754, 842, 894, 986, 1012, 1102, 1140, 1176, 1200, 1246, 1308, 1384, 1452, 1540, 1558, 1664, 2924, 2978, 3028 cm^{-1}.

Preparation of Diisopropyl 2-(3-Hydroxy-2-methylsulfanyl-3,6-dihydro-2*H*-thiapyranyl)phosphonate (12): 1-(Trimethylsilyloxy)-1,3-butadiene (0.8 mL, 3 mmol) was added to a stirred solution of phosphonodithioformate **1** (384 mg, 1.5 mmol) and $BF_3{\cdot}Et_2O$ (48%, 0.1 mL, 1.5 mmol) in THF (10 mL) and then the mixture was stirred under nitrogen at room temperature for 24 h. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel (EtOAc/petroleum ether, 20:80) to give pure **12a** (67%) and **12b** (23%).

12a (major product): White solid (m.p. 105 °C). ^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 20.4 ppm. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.39 (d, *J* = 5.4 Hz, 6 H, 2 × CH_3), 1.41 (d, *J* = 5.8 Hz, 6 H, 2 × CH_3), 2.39 (s, 3 H, SCH_3), 2.95 (dd, *J* = 17.5, *J* = 4.9, 1 H, H^6), 3.18 (d, *J* = 9.1 Hz, 1 H, OH), 3.24 (dd, *J* = 17.5, 1.6 Hz, 1 H, $H^{6'}$), 4.05 (m, 1 H, H^3), 4.84−4.94 (m, 2 H, 2 × CH−O), 5.92 (m, 1 H, H^4), 5.99 (m, 1 H, H^5) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): 13.87 (s, SCH_3), 24.06 (d, *J* = 4.1 Hz, CH_3), 24.14 (d, *J* = 3.9 Hz, CH_3), 24.32 (d, *J* = 4.5 Hz, C^6), 24.70 (d, *J* = 2.9 Hz, CH_3) 24.85 (d, *J* = 2.6 Hz, CH_3), 55.88 (d, *J* = 157.0 Hz, C^2), 64.54 (d, *J* = 2.8 Hz, C^3), 72.20 (d, *J* = 7.7 Hz, CHOP), 72.55 (d, *J* = 7.3 Hz, CHOP), 125.23 (d, *J* = 1.8 Hz, C^5), 127.90 (d, *J* = 7.5 Hz, C^4) ppm. MS: *m*/*z* (%) = 326 $[M]^+$, 257 (34), 215 (27), 173 (100), 113 (50), 97 (12), 91 (30), 85 (18), 70 (11), 69 (10), 65 (8), 45 (15), 43 (46). IR (KBr): $\tilde{\nu}$ = 650, 714, 760, 854, 896, 994, 1022, 1062, 1108, 1142, 1178, 1232, 1288, 1380, 1420, 2872, 2920, 2976, 3022, 3286 cm^{-1}. $C_{12}H_{23}O_4PS_2$ (326.4): calcd. C 44.16, H 7.10, S 19.64; found C 44.16, H 7.11, S 19.10.

12b (minor product): White solid (m.p. 96 °C). ^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 20.9 ppm. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.39 (d, *J* = 6.1 Hz, 3 H, CH_3), 1.42 (d, *J* = 3.1 Hz, 3 H, CH_3), 1.44 (d, *J* = 3.5 Hz, 3 H, CH_3), 1.45 (d, *J* = 6.7 Hz, 3 H, CH_3), 2.37 (s, 3 H, SCH_3), 2.83 (dd, *J* = 17.4, 4.2 Hz, 1 H, H^6), 3.33 (dd, *J* = 17.4, 2.5 Hz, 1 H, $H^{6'}$), 4.04 (d, *J* = 2.0 Hz, 1 H, OH), 4.82−4.93 (m, 2 H, 2 × CH−O), 5.05 (m, 1 H, H^3), 5.64 (m, 1 H, H^4), 5.92 (m, 1 H, H^5) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.16 (s, SCH_3), 23.64 (d, *J* = 5.4 Hz, C^6), 23.96 (d, *J* = 5.9 Hz, CH_3), 24.19 (d, *J* = 5.2 Hz, CH_3), 24.54 (d, *J* = 3.5 Hz, CH_3), 24.87 (d, *J* = 2.5 Hz, CH_3), 55.85 (d, *J* = 154.0 Hz, C^2), 68.98 (d, *J* = 2.6 Hz, C^3), 73.38 (d, *J* = 7.9 Hz, CHOP), 74.36 (d, *J* = 7.6 Hz, CHOP), 125.01 (d, *J* = 1.9 Hz, C^5), 129.26 (d, *J* = 11.3 Hz, C^4) ppm. MS: *m*/*z* (%) = 326 $[M]^+$, 257 (52), 215 (50), 173 (100), 113 (81), 97 (20), 91 (64), 85 (52), 70 (28), 69 (26), 65 (21), 45 (39), 43 (91). IR (KBr): $\tilde{\nu}$ = 696, 764, 826, 868, 990, 1018, 1106, 1068, 1106, 1142, 1216, 1280, 1312, 1350, 1374, 1432, 1456, 2890, 2920, 2980, 2920, 3024, 3290 cm^{-1}. $C_{12}H_{23}O_4PS_2$ (326.4): calcd. C 44.16, H 7.10, S 19.64; found C 44.55, H 7.19, S 19.39.

Preparation of Diisopropyl 2-(3-Acetoxy-2-methylsulfanyl-3,6-dihydro-2*H*-thiapyranyl)phosphonate (13)

a) From Dithioester 1 by Cycloaddition: A mixture of diisopropyl phosphonodithioformate **1** (384 mg, 1.5 mmol) and 1-acetoxy-1,3-butadiene (3 mmol) in CH_2Cl_2 (5 mL) was stirred under nitrogen, at room temperature, for 30 d. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel (EtOAc/petroleum ether, 20:80) to give pure **13a** (74%) and **13b** (11%).

b) From Alcohol 12 by Acetylation: A mixture of alcohol **12a** (326 mg, 1 mmol), pyridine (0.5 mL, 6 mmol), and acetic anhydride (2 mL) was stirred at 80 °C for 12 h. The solvents were evaporated under reduced pressure and the residue was purified by chromatography to give pure **13a** (90%). Acetate **13b** was obtained by the same procedure from alcohol **12b**.

13a (major product): White solid (m.p. 80 °C). ^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 18.5 ppm. ^1H NMR (400 MHz, $CDCl_3$): 1.32 (d, J = 6.3 Hz, 3 H, CH_3), 1.34 (d, J = 2.1 Hz, 6 H, 2 × CH_3), 1.37 (d, J = 6.7 Hz, 3 H, CH_3), 2.08 (s, 3 H, $COCH_3$), 2.39 (s, 3 H, SCH_3), 2.96 (dd, J = 17.4, 5.2 Hz, 1 H, H^6), 3.24 (dd, J = 17.4, 1.2 Hz, 1 H, $H^{6'}$), 4.76−4.90 (m, 2 H, 2 × CH−O), 5.12 (m, 1 H, H^3), 5.82 (m, 1 H, H^4), 6.10 (m, 1 H, H^5) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.91 (s, SCH_3), 21.46 (s, CO*C*H_3), 23.95 (d, J = 6.2 Hz, C^6), 24.26 (d, J = 6.3 Hz, CH_3), 24.32 (d, J = 6.1 Hz, CH_3), 24.73 (d, J = 3.1 Hz, CH_3) 24.82 (d, J = 4.1 Hz, CH_3), 55.58 (d, J = 159.1 Hz, C^2), 65.77 (d, J = 5.0 Hz, C^3), 72.32 (d, J = 8.1 Hz, CHOP), 73.45 (d, J = 7.5 Hz, CHOP), 124.76 (d, J = 6.2 Hz, C^4), 128.09 (d, J = 1.2 Hz, C^5), 169.93 (s, CO) ppm. MS: *m*/*z* (%) = 368 $[M]^+$, 257 (20), 237 (20), 195 (78), 177 (25), 173 (28), 161 (24), 113 (24), 97 (32), 85 (33), 43 (100). IR (KBr): $\tilde{\nu}$ = 542, 594, 638, 686, 722, 796, 862, 886, 990, 1028, 1104, 1144, 1162, 1178, 1240, 1374, 1452, 1660, 1734, 2884, 2928, 2982 cm^{-1}. $C_{14}H_{25}O_5PS_2$ (368.4): calcd. C 45.64, H 6.84, S 17.40; found C 45.89, H 7.12, S 17.53.

13b (minor product): White solid (m.p. 62 °C). ^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 17.2 ppm. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.35 (d, J = 6.5 Hz, 3 H, CH_3), 1.37 (d, J = 2.1 Hz, 3 H, CH_3), 1.40 (d, J = 6.5 Hz, 3 H, CH_3), 1.43 (d, J = 7.0 Hz, 3 H, CH_3), 2.09 (s, 3 H, $COCH_3$), 2.44 (s, 3 H, SCH_3), 2.89 (dd, J = 17.4, J = 3.2, 1 H, H^6), 3.35 (dd, J = 17.4, J = 1.1, 1 H, $H^{6'}$), 4.70−4.87 (m, 2 H, 2 × CH−O), 5.46 (m, 1 H, H^3), 5.95 (m, 1 H, H^4), 6.30 (m, 1 H, H^5) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.92 (s, SCH_3), 21.58 (s, CO*C*H_3), 23.84 (d, J = 5.2 Hz, C^6), 23.97 (d, J = 7.6 Hz, CH_3), 24.16 (d, J = 5.2 Hz, CH_3), 24.42 (d, J = 3.5 Hz, CH_3) 24.95 (d, J = 2.2 Hz, CH_3), 53.10 (d, J = 156.6 Hz, C^2), 70.73 (d, J = 2.6 Hz, C^3), 72.75 (d, J = 7.8 Hz, CHOP), 73.52 (d, J = 7.5 Hz, CHOP), 126.43 (d, J = 1.2 Hz, C^5), 127.35 (d, J = 8.8 Hz, C^4), 169.87 (s, CO) ppm. MS: *m*/*z* (%) = 368 $[M]^+$, 261 (30), 195 (36), 177 (20), 173 (20), 161 (33), 97 (29), 85 (28), 43 (100). IR (KBr): $\tilde{\nu}$ = 530, 560, 578, 628, 692, 738, 808, 884, 984, 1022, 1102, 1142, 1176, 1230, 1248, 1372, 1384, 1450, 1466, 1668, 1746, 2926, 2978 cm^{-1}.

Synthesis of Diisopropyl 2-(3-Acetoxy-3,6-dihydro-2*H*-thiapyranyl)phosphonate (14): Compound **14** was prepared following the procedure mentioned above for desulfanylation (**2** to give **3**) from **13a** or **13b** and purified by chromatography on silica gel, eluting with EtOAc/petroleum ether (40:60) to give pure compound as a colorless oil (80−82%). ^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 19.1 ppm. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.31 (d, J = 6.9 Hz, 3 H, CH_3), 1.33 (d, J = 4.3 Hz, 6 H, 2 × CH_3), 1.35 (d, J = 6.2 Hz, 3 H, CH_3), 2.09 (s, 3 H, $COCH_3$), 3.19−3.25 (m, 2 H, H^6, $H^{6'}$), 3.30 (dd, J = 3.8, J = 21.3, 1 H, H^2), 4.69−4.79 (m, 2 H, 2 × CH−O), 5.53 (m, 1 H, H^3), 5.91 (m, 1 H, H^5), 6.10 (m, 1 H, H^4) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.50 (s, CO*C*H_3), 24.18 (d, J = 5.8 Hz, CH_3), 24.36 (d, J = 4.6 Hz, CH_3), 24.42 (d, J = 3.5 Hz, CH_3), 24.66 (d, J = 3.0 Hz, CH_3) 26.39 (d, J = 6.2 Hz, C^6), 38.68 (d, J = 150.1 Hz, C^2), 64.33 (d, J = 4.9 Hz, C^3), 71.49 (d, J = 7.1 Hz, CHOP), 72.17 (d, J = 6.9 Hz, CHOP), 126.53 (d, J = 8.2 Hz, C^4), 129.03 (s, C^5), 170.64 (s, CO) ppm. MS: *m*/*z* (%) = 323 $[MH]^+$, 262 (5), 127 (12), 124 (10), 113 (25), 99 (10), 98 (14), 97 (100), 45 (19), 43 (97). IR (NaCl): $\tilde{\nu}$ = 788, 864, 888, 936, 992, 1106, 1142, 1178, 1234, 1374, 1412, 1454, 1558, 1692, 1740, 2934, 2980 cm^{-1}.

Preparation of Diisopropyl 2-(3-Hydroxy-3,6-dihydro-2*H*-thiapyranyl)phosphonate (15): A mixture of **14** (322 mg, 1 mmol) and potassium carbonate (276 mg, 2 mmol) in methanol (2 mL) and water (2 mL) was stirred at room temperature for 3 h. The reaction mixture was then extracted with dichloromethane (3 × 10 mL). The organic phase was dried ($MgSO_4$) and the solvents were evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/petroleum ether, 50:50) to give pure **15** (90%) as a white solid (m.p. 124 °C). ^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 21.7 ppm. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.34 (d, J = 5.2 Hz, 6 H, 2 × CH_3), 1.37 (d, J = 6.1 Hz, 6 H, 2 × CH_3), 3.08 (dd, J = 14.5, 3.1 Hz, 1 H, H^6), 3.19 (d, J = 19.5, 3.0 Hz, 1 H, H^2), 3.26 (dd, J = 14.5, 2.0 Hz, 1 H, $H^{6'}$), 3.39 (d, J = 9.5 Hz, 1 H, OH), 4.47 (m, 1 H, H^3), 4.78−4.87 (m, 2 H, 2 × CH−O), 5.95−6.01 (m, 2 H, H^4, H^5) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 23.98 (d, J = 5.9 Hz, CH_3), 24.09 (d, J = 5.0 Hz, CH_3), 24.27 (d, J = 3.5 Hz, CH_3), 24.42 (d, J = 2.5 Hz, CH_3), 26.42 (d, J = 6.4 Hz, C^6), 41.08 (d, J = 149 Hz, C^2), 62.14 (d, J = 3.1 Hz, C^3), 71.97 (d, J = 6.7 Hz, CHOP), 72.35 (d, J = 6.6 Hz, CHOP), 125.40 (s, C^5), 131.51 (d, J = 9.5 Hz, C^4). MS: *m*/*z* (%) = 280 $[M]^+$, 99 (32), 98 (97), 97 (100), 96 (63), 85 (22), 45 (25), 44 (28), 43 (51), 42 (31). IR (KBr): $\tilde{\nu}$ = 536, 632, 664, 692, 740, 774, 860, 892, 946, 1078, 1108, 1146, 1176, 1228, 1294, 1324, 1382, 1408, 1434, 1468, 1654, 2868, 2938, 2982, 3034 cm^{-1}. $C_{11}H_{21}O_4PS$ (280.3): calcd. C 47.13, H 7.55; found C 46.91, H 7.48.

Preparation of Diisopropyl 2-(3,4,5-Trihydroxy-tetrahydrothiapyranyl)phosphonate (16): This compound was obtained by the procedure described above for dihydroxylation (for the preparation of diol **4**), starting from compound **15a**. The pure product was obtained as a white solid (m.p. 132 °C) by crystallization in Et_2O (70% yield). ^{31}P NMR (161.98 MHz, $[D_6]DMSO$): δ = 23.7 ppm. ^1H NMR (400 MHz, $[D_6]DMSO$): δ = 1.23 (d, J = 4.8 Hz, 6 H, 2 × CH_3), 1.25 (d, J = 5.5 Hz, 6 H, 2 × CH_3), 2.14 (m, 1 H, H^6), 2.75 (m, 1 H, $H^{6'}$), 3.31 (dd, J = 19.8, 1.1 Hz, 1 H, H^2), 3.58 (m, 1 H, H^4), 3.89 (m, 1 H, H^5), 4.08 (m, 1 H, H^3), 4.55−4.68 (m, 2 H, 2 × CH−O), 4.79 (d, J = 6.2 Hz, 1 H, OH), 4.95 (d, J = 4.1 Hz, 1 H, OH), 5.05 (d, J = 5.6 Hz, 1 H, OH) ppm. ^{13}C NMR (100.61 MHz, $[D_6]DMSO$): δ = 24.06 (d, J = 5.9 Hz, CH_3), 24.29 (d, J = 4.9 Hz, CH_3), 24.40 (d, J = 3.5 Hz, CH_3), 24.61 (d, J = 2.3 Hz, CH_3), 28.64 (d, J = 10.2 Hz, C^6), 38.13 (d, J = 146.2 Hz, C^2), 66.50 (d, J = 3.1 Hz, C^5), 70.72 (d, J = 5.3 Hz, CHOP), 70.83 (d, J = 6.6 Hz, CHOP), 71.16 (d, J = 5.9 Hz, C^3), 72.13 (d, J = 12.3 Hz, C^4) ppm. MS: *m*/*z* (%) = 314 $[M]^+$, 212 (28), 156 (25), 128 (59), 127 (43), 125 (80), 124 (41), 113 (36), 96 (26), 59 (34), 57 (34), 47 (21), 45 (52), 43 (100). IR (KBr): $\tilde{\nu}$ = 524, 616, 638, 676, 708, 746, 776, 814, 898, 938, 990, 1010, 1086, 1104, 1144, 1180, 1214, 1288, 1326, 1354, 1388, 1450, 2886, 2916, 2982, 3216, 3400 cm^{-1}. $C_{11}H_{23}O_6PS$ (314.3): calcd. C 42.03, H 7.38, S 10.20; found C 41.96, H 7.43, S 10.74.

Preparation of Diisopropyl 2-[2-Methylsulfanyl-3-phenylsulfanyl-3,6-dihydro-2*H*-thiapyranyl]phosphonate (17)

Cycloaddition without Lewis Acid: A mixture of diisopropyl phosphonodithioformate **1** (384 mg, 1.5 mmol) and 1-phenylsulfanyl-1,3-butadiene (486 mg, 3 mmol) in THF (7 mL) was stirred under reflux for 12 h under nitrogen. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on basic silica gel (EtOAc/petroleum ether, 10:90) to give pure **17** as a colorless oil (two diastereoisomers in a 1:1 ratio, yield 95%).

Cycloaddition with Lewis Acid: 1-Phenylsulfanyl-1,3-butadiene (486 mg, 3 mmol) was added to a stirred solution of diisopropyl phosphonodithioformate **1** (384 mg, 1.5 mmol) and ZnCl$_2$ (204 mg, 1.5 mmol) in THF (10 mL) and the mixture was then stirred under nitrogen at room temperature for 72 h. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel (EtOAc/petroleum ether, 10:90) to give pure **17** as a colorless oil (two diastereoisomers in a 1:3 ratio, yield 65%).

Major Diastereoisomer: ^{31}P NMR (161.98 MHz, CDCl$_3$): δ = 19.0 ppm. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.38 (d, J = 5.5 Hz, 3 H, CH$_3$), 1.40 (d, J = 3.7 Hz, 3 H, CH$_3$), 1.41 (d, J = 4.5 Hz, 3 H, CH$_3$), 1.43 (d, J = 5.8 Hz, 3 H, CH$_3$), 2.39 (s, 3 H, SCH$_3$), 2.97 (ddd, J = 17.3, 6.2, 2.9 Hz, 1 H, H^6), 3.41 (dd, J = 17.3, 2.2 Hz, 1 H, H$^{6'}$), 4.77 (m, 1 H, H^3), 4.84−4.98 (m, 2 H, 2 × CH−O), 5.74 (m, 1 H, H^4), 5.79 (m, 1 H, H^5), 7.28−7.34 (m, 3 H, H^{arom}), 7.60−7.62 (m, 2 H, H^{arom}) ppm. ^{13}C NMR (62.9 MHz, CDCl$_3$): δ = 14.77 (s, SCH$_3$), 23.92 (d, J = 6.4 Hz, CH$_3$), 24.11 (d, J = 6.4 Hz, CH$_3$), 24.68 (d, J = 3.6 Hz, C^6), 24.77 (d, J = 2.6 Hz, CH$_3$), 24.98 (d, J = 2.7 Hz, CH$_3$), 51.82 (s, C^3), 56.65 (d, J = 155.0 Hz, C^2), 72.87 (d, J = 7.5 Hz, CHOP), 73.39 (d, J = 7.8 Hz, CHOP), 123.12 (d, J = 1.9 Hz, C^4), 127.86 (s, C^5), 129.28 (s, CH^{arom}), 129.42(s, 2 × CH^{arom}), 133.14 (s, 2 × CH^{arom}), 135.35 (s, C^{arom}) ppm.

Minor Diastereoisomer: ^{31}P NMR (161.98 MHz, CDCl$_3$): δ = 17.2 ppm. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.38 (d, J = 5.5 Hz, 3 H, CH$_3$), 1.40 (d, J = 3.7 Hz, 3 H, CH$_3$), 1.41 (d, J = 4.5 Hz, 3 H, CH$_3$), 1.43 (d, J = 5.8 Hz, 3 H, CH$_3$), 2.41 (s, 3 H, SCH$_3$), 2.99 (m, 1 H, H^6), 3.33 (m, 1 H, H$^{6'}$), 3.71 (m, 1 H, H^3), 4.76−4.87 (m, 2 H, 2 × CH−O), 5.84−6.06 (m, 2 H, H^4, H^5), 7.28−7.34 (m, 3 H, H^{arom}), 7.60−7.62 (m, 2 H, H^{arom}) ppm. ^{13}C NMR (62.9 MHz, CDCl$_3$): δ = 16.39 (s, SCH$_3$), 24.04 (d, J = 3.7 Hz, CH$_3$), 24.20 (d, J = 6.7 Hz, CH$_3$), 24.58 (d, J = 4.9 Hz, C^6), 24.84 (d, J = 4.2 Hz, CH$_3$), 24.97 (d, J = 2.7 Hz, CH$_3$), 49.31 (s, C^3), 55.48 (d, J = 162.5 Hz, C^2), 73.14 (d, J = 8.0 Hz, CHOP), 74.26 (d, J = 6.9 Hz, CHOP), 121.18 (d, J = 1.9 Hz, C^4), 129.17 (s, 2 × CH^{arom}), 129.24 (s, C^5), 129.51 (s, CH^{arom}), 133.48 (s, 2 × CH^{arom}), 135.70 (s, C^{arom}) ppm. MS: m/z (%) = 418 [M]$^+$, 309 (16), 261 (26), 219 (14), 144 (16, 143 (52), 129 (21), 109 (15), 97 (57), 85 (16), 53 (18), 49 (18), 45 (31), 43 (100). IR (NaCl): ṽ = 692, 746, 826, 884, 984−1012, 1066, 1104, 1140, 1176, 1244, 1374, 1384, 1438, 1470, 1582, 1654, 2922, 2978, 3026, 3054 cm^{-1}. C$_{18}$H$_{27}$O$_3$PS$_3$ (418.6): calcd. C 51.65, H 6.50; found C 51.78, H 6.76.

Synthesis of Diisopropyl 2-(6*H*-Thiapyranyl)phosphonate (19): Compound **19** was prepared from **17** using 4 equiv. of Bu$_3$SnH following the procedure mentioned above for desulfanylation (**2** to give **3**). The conversion was quantitative after 5 h and the product was purified by chromatography on silica gel (EtOAc/petroleum ether, 30:70) to give **19** as a colorless oil (60%). ^{31}P NMR (161.98 MHz, CDCl$_3$): δ = 11.6 ppm. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.35 (d, J = 6.1 Hz, 6 H, 2 × CH$_3$), 1.38 (d, J = 6.1 Hz, 6 H, 2 × CH$_3$), 3.25−3.27 (m, 2 H, H^6, H$^{6'}$), 4.66−4.71 (m, 2 H, 2 × CH−O), 5.79 (m, 1 H, H^5), 6.15 (m, 1 H, H^4), 6.99 (dd, J = 18.4, 5.6 Hz, 1 H, H^3) ppm. ^{13}C NMR (101.61 MHz, CDCl$_3$): δ = 24.19 (d, J = 5.1 Hz, 2 × CH$_3$), 24.45 (d, J = 3.8 Hz, 2 × CH$_3$), 24.69 (d, J = 4.1 Hz, C^6), 71.86 (d, J = 5.5 Hz, 2 × CHOP), 119.78 (d, J = 4.0 Hz, C^5), 126.03 (d, J = 192.2 Hz, C^2), 126.12 (d, J = 16.0 Hz, C^4), 131.34 (d, J = 9.2 Hz, C^3) ppm. IR (NaCl): ṽ = 712, 772, 794, 894, 982, 1120, 1038, 1106, 1142, 1178, 1246, 1374, 1386, 1456, 2876, 2934, 2978 cm^{-1}.

Procedure for Cycloaddition under High-Pressure to Prepare Diisopropyl 2-(6-Methoxy-2-methylsulfanyl-3-phenylsulfanyl-3,6-dihydro-2*H*-thiapyranyl)phosphonate (20) and Diisopropyl 2-(3-Methoxy-2-methylsulfanyl-6-phenylsulfanyl-3,6-dihydro-2*H*-thiapyranyl)-phosphonate (21): A solution of phosphonodithioformate **1** (256 mg, 1 mmol) and (*E*,*E*)-1-methoxy-4-phenylsulfanyl-1,3-butadiene (384 mg, 2 mmol) in THF (5 mL) was introduced into a pressure vessel that was placed into a high-pressure apparatus and left under 12 kbar at room temperature for 3 d. After releasing the pressure, the solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel (EtOAc/petroleum ether, 30:70) to give a mixture of **20** and **21** (89% total yield). The characterization of these compounds was possible by analyzing enriched fractions of each component.

20 (one diastereoisomer): Yellow oil. ^{31}P NMR (101.25 MHz, CDCl$_3$): δ = 18.7 ppm. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.38 (d, J = 6.2 Hz, 3 H, CH$_3$), 1.40 (d, J = 7.6 Hz, 3 H, CH$_3$), 1.42 (d, J = 6.4 Hz, 3 H, CH$_3$), 1.47 (d, J = 6.2 Hz, 3 H, CH$_3$), 2.41 (s, 3 H, SCH$_3$), 3.49 (s, 3 H, OCH$_3$), 4.67 (m, 1 H, H^3), 4.81 (m, 1 H, H^6), 4.84−4.97 (m, 2 H, 2 × CH−O), 5.89−5.91 (m, 2 H, H^4 & H^5), 7.26−7.34 (m, 3 H, H^{arom}), 7.57−7.59 (m, 2 H, H^{arom}) ppm. ^{13}C NMR (62.9 MHz, CDCl$_3$): δ = 15.82 (s, SCH$_3$), 23.93 (d, J = 6.8 Hz, CH$_3$), 24.14 (d, J = 6.3 Hz, CH$_3$), 24.70 (d, J = 2.8 Hz, CH$_3$), 25.05 (d, J = 2.5 Hz, CH$_3$), 52.08 (d, J = 1.5 Hz, C^3), 55.32 (d, J = 156.9 Hz, C^2), 57.12 (s, OCH$_3$), 73.00 (d, J = 7.7 Hz, CHOP), 73.89 (d, J = 7.9 Hz, CHOP), 78.07 (d, J = 6.4 Hz, C^6) 124.56 (d, J = 1.7 Hz, C^5), 127.92 (s, CH^{arom}), 129.50 (s, 2 × CH^{arom}), 132.27 (d, J = 10.7 Hz, C^4), 132.97 (s, 2 × CH^{arom}), 135.35 (s, C^{arom}) ppm. IR (NaCl): ṽ = 698, 728, 756, 790, 834, 884, 948, 974, 1002, 1022, 1070, 1088, 1104, 1142, 1186, 1238, 1270, 1320, 1370, 1382, 1438, 1468, 1582, 2820, 2896, 2932, 2980, 3044 cm^{-1}.

21a (minor diastereoisomer): Yellow oil. ^{31}P NMR (101.25 MHz, CDCl$_3$): δ = 19.9 ppm. ^{1}H NMR (250 MHz, CDCl$_3$): δ = 1.34 (d, J = 5.1 Hz, 3 H, CH$_3$), 1.36 (d, J = 7.9 Hz, 3 H, CH$_3$), 1.38 (d, J = 6.3 Hz, 3 H, CH$_3$), 1.40 (d, J = 6.2 Hz, 3 H, CH$_3$), 2.33 (s, 3 H, SCH$_3$), 3.37 (s, 3 H, OCH$_3$), 3.63 (m, 1 H, H^3), 4.60 (d, J = 6.3 Hz, 1 H, H^6), 4.74−4.86 (m, 2 H, 2 × CH−O), 5.99 (m, 1 H, H^4), 6.19 (m, 1 H, H^5), 7.28−7.36 (m, 3 H, H^{arom}), 7.57−7.62 (m, 2 H, H^{arom}) ppm. ^{13}C NMR (100.61 MHz, CDCl$_3$): δ = 15.38 (s, SCH$_3$), 23.74 (d, J = 6.9 Hz, CH$_3$), 24.32 (d, J = 5.0 Hz, CH$_3$), 24.48 (d, J = 3.8 Hz, CH$_3$), 25.04 (d, J = 1.9 Hz, CH$_3$), 45.22 (d, J = 6.2 Hz, C^6), 56.99 (s, OCH$_3$), 59.21 (d, J = 156.9 Hz, C^2), 71.84 (d, J = 3.1 Hz, C^3), 72.10 (d, J = 7.5 Hz, CHOP), 72.98 (d, J = 6.9 Hz, CHOP), 126.51 (d, J = 8.8 Hz, C^4), 128.53 (s, CH^{arom}), 129.18 (s, 2 × CH^{arom}), 131.17 (d, J = 1.8 Hz, C^5), 133.05 (s, C^{arom}), 133.55 (s, 2 × CH^{arom}) ppm. IR (NaCl): ṽ = 744, 896, 936, 992, 1104, 1142, 1178, 1194, 1244, 1374, 1384, 1468, 1582, 1652, 2828, 2932, 2980, 3058 cm^{-1}.

21b (major diastereoisomer): Yellow oil. ^{31}P NMR (101.25 MHz, CDCl$_3$): δ = 18.48 ppm. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.38 (d, J = 5.6 Hz, 3 H, CH$_3$), 1.41 (d, J = 5.2 Hz, 3 H, CH$_3$), 1.43 (d, J = 6.4 Hz, 3 H, CH$_3$), 1.47 (d, J = 6.2 Hz, 3 H, CH$_3$), 2.45 (s, 3 H, SCH$_3$), 3.47 (s, 3 H, OCH$_3$), 4.63 (m, 1 H, H^3), 4.76 (m, 1 H, H^{6}), 4.79−4.96 (m, 2 H, 2 × CH−O), 5.83 (m, 1 H, H^{5}), 6.07 (m, 1 H, H^{4}), 7.27−7.34 (m, 3 H, H^{arom}), 7.52−7.54 (m, 2 H, H^{arom}) ppm. ^{13}C NMR (100.61 MHz, CDCl$_3$): δ = 15.02 (s, SCH$_3$), 23.90 (d, J = 5.5 Hz, CH$_3$), 24.16 (d, J = 6.2 Hz, CH$_3$), 24.74 (2d, J = 2.9 Hz each, 2 × CH$_3$), 49.65 (d, J = 6.2 Hz, C^{6}), 56.34 (d, J = 152.8 Hz, C^{2}), 58.01 (s, OCH$_3$), 72.59 (d, J = 7.2 Hz, CHOP), 73.36 (d, J = 7.8 Hz, CHOP), 78.98 (d, J = 3.1 Hz, C^{3}) 127.42 (d, J = 1.1 Hz, C^{5}), 128.14 (s, CH^{arom}), 128.83 (d, J = 9.7 Hz, C^{4}), 129.53 (s, 2 × CH^{arom}), 132.23 (s, 2 × CH^{arom}), 136.29 (s, C^{arom}) ppm.

Preparation of Diisopropyl 2-(4,5-Dihydroxy-6-methoxy-2-methylsulfanyl-3-phenylsulfanyl-tetrahydrothiapyranyl)phosphonate (22): This compound was obtained by the procedure described above for dihydroxylation (used to prepare diol **4**), starting from compound **20**. The pure product was obtained by chromatography on silica gel (Et$_2$O/petroleum ether, 2:1) as a white solid (m.p. 166 °C) in 70% yield. ^{31}P NMR (101.25 MHz, CDCl$_3$): δ = 18.35 ppm. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.22 (d, J = 6.1 Hz, 3 H, CH$_3$), 1.33 (d, J = 6.2 Hz, 3 H, CH$_3$), 1.38 (d, J = 6.1 Hz, 3 H, CH$_3$), 1.45 (d, J = 6.2 Hz, 3 H, CH$_3$), 2.47 (s, 3 H, SCH$_3$), 2.67 (s, 1 H, OH), 3.54 (s, 3 H, OCH$_3$), 4.12 (s, 1 H, OH), 4.32−4.75 (m, 3 H, H^{3}, H^{4}, H^{5}), 4.75−4.88 (m, 2 H, 2 × CH−O), 4.81 (m, 1 H, H^{6}), 7.24−7.33 (m, 3 H, H^{arom}), 7.60−7.62 (m, 2 H, H^{arom}) ppm. ^{13}C NMR (62.9 MHz, CDCl$_3$): δ = 16.97 (s, SCH$_3$), 23.86 (d, J = 6.8 Hz, CH$_3$), 24.04 (d, J = 5.9 Hz, CH$_3$), 24.40 (d, J = 2.9 Hz, CH$_3$), 25.02 (d, J = 2.3 Hz, CH$_3$), 57.71 (s, C^{3}), 57.94 (s, OCH$_3$), 59.54 (d, J = 153.9 Hz, C^{2}), 70.17 (d, J = 7.6 Hz, C^{4}), 71.08 (s, C^{5}), 73.28 (d, J = 8.0 Hz, CHOP), 76.53 (d, J = 7.9 Hz, CHOP), 84.83 (d, J = 6.4 Hz, C^{6}), 127.48 (s, CH^{arom}), 129.52 (s, 2 × CH^{arom}), 131.23 (s, 2 × CH^{arom}), 136.66 (s, C^{arom}) ppm. MS: m/z (%) = 482 [M]$^{+}$, 373 (11), 347 (16), 327 (27), 319 (11), 317 (13), 257 (10), 249 (29), 237 (25), 223 (13), 215 (52), 209 (16), 208 (15), 193 (12), 187 (26), 181 (12), 173 (27), 169 (11), 167 (17), 156 (14), 110 (15), 109 (11), 103 (24), 91 (17), 87 (32), 85 (18), 59 (14), 49 (12), 47 (18), 45 (60), 43 (100). IR (KBr): $\tilde{\nu}$ = 742, 842, 916, 958, 996, 1072, 1118, 1192, 1220, 1346, 1382, 1448, 1480, 1582, 1638, 2828, 2922, 2978, 3056, 3298, 3442 cm^{-1}. C$_{19}$H$_{31}$O$_6$PS$_3$ (482.6): calcd. C 47.29, H 6.47, S 19.93; found C 47.40, H 6.53, S 19.45.

Synthesis of Diisopropyl 2-(4,5-Dihydroxy-6-methoxy-5,6-dihydro-4*H*-thiapyranyl)phosphonate (23): This compound was prepared from **22** using 4 equiv. of Bu$_3$SnH following the procedure mentioned above for desulfanylation (**2** to **3**). The reaction was complete after 5 h and the product was purified by chromatography on silica gel (EtOAc) to give **23** as a yellow solid (75%, m.p. 82 °C, crystallized from Et$_2$O). ^{31}P NMR (161.98 MHz, CDCl$_3$): δ = 10.38 ppm. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.33 (d, J = 6.2 Hz, 3 H, CH$_3$), 1.35 (d, J = 4.1 Hz, 3 H, CH$_3$), 1.36 (d, J = 6.7 Hz, 6 H, 2 × CH$_3$), 3.06 (d, J = 6.7 Hz, 1 H, OH), 3.48 (s, 3 H, OCH$_3$), 3.82 (d, J = 9.0 Hz, 1 H, OH), 4.10 (m, 1 H, H^{5}), 4.36 (m, 1 H, H^{4}), 4.67−4.72 (m, 2 H, 2 × CH−O), 4.87 (dd, J = 6.3, 4.6 Hz, 1 H, H^{6}), 6.69 (ddd, J = 21.6, 3.2, 1.0 Hz, 1 H, H^{3}) ppm. ^{13}C NMR (100.61 MHz, CDCl$_3$): δ = 23.98 (d, J = 4.8 Hz, CH$_3$), 24.19 (d, J = 4.8 Hz, CH$_3$), 24.38 (d, J = 3.8 Hz, CH$_3$), 24.42 (d, J = 3.8 Hz, CH$_3$), 57.34 (s, OCH$_3$), 65.71 (d, J = 16.7 Hz, C^{4}), 66.72 (d, J = 2.1 Hz, C^{5}), 72.35 (d, J = 5.5 Hz, CHOP), 72.55 (d, J = 5.9 Hz, CHOP), 87.42 (d, J = 6.2 Hz, C^{6}), 123.82 (d, J = 188.2 Hz, C^{2}), 137.73 (d, J = 3.1 Hz, C^{3}) ppm. HRMS calcd. for C$_{12}$H$_{23}$O$_6$PS: 326.0953; found: 326.1032. IR (KBr): $\tilde{\nu}$ = 766, 842, 886, 988, 1076, 1142, 1224, 1386, 1454, 2934, 2982, 3382 cm^{-1}.

Preparation of Diisopropyl 2-(4,5-Dihydroxy-3-methoxy-2-methylsulfanyl-6-phenylsulfanyl-tetrahydrothiapyranyl)phosphonate (24a): This compound was obtained from compound **21a** by the procedure described above for dihydroxylation (used to prepare diol **4**). The pure product was obtained as a white solid (m.p. 91 °C) in 83% yield after chromatography on silica gel (EtOAc/petroleum ether, 1:1). ^{31}P NMR (161.98 MHz, CDCl$_3$): δ = 16.18 ppm. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.33 (d, J = 7.8 Hz, 3 H, CH$_3$), 1.34 (d, J = 2.8 Hz, 3 H, CH$_3$), 1.36 (d, J = 2.6 Hz, 3 H, CH$_3$), 1.38 (d, J = 6.2 Hz, 3 H, CH$_3$), 2.26 (s, 3 H, SCH$_3$), 3.11 (d, J = 7.8 Hz, 1 H, OH), 3.49 (s, 3 H, OCH$_3$), 3.83 (dd, J = 4.9, 3.6 Hz, 1 H, H^{3}), 3.93 (ddd, J = 10.6, 3.4, 9.9 Hz, 1 H, H^{5}), 3.95 (d, J = 9.9 Hz, 1 H, OH), 4.15 (d, J = 10.6 Hz, 1 H, H^{6}), 4.21 (dddd, J = 7.6, 3.6, 3.4, 7.8 Hz, 1 H, H^{4}), 4.71−4.76 (m, 2 H, 2 × CH−O), 7.34−7.36 (m, 3 H, H^{arom}), 7.64−7.66 (m, 2 H, H^{arom}) ppm. ^{13}C NMR (100.61 MHz, CDCl$_3$): δ = 15.18 (s, SCH$_3$), 23.54 (d, J = 6.7 Hz, CH$_3$), 24.19 (d, J = 4.9 Hz, CH$_3$), 24.43 (d, J = 4.1 Hz, CH$_3$), 25.00 (d, J = 1.6 Hz, CH$_3$), 30.02 (d, J = 144.2 Hz, C^{2}), 49.31 (d, J = 7.1 Hz, C^{6}), 59.23 (s, OCH$_3$), 69.63 (s, C^{5}), 71.33 (d, J = 9.4 Hz, C^{4}), 72.47 (d, J = 7.7 Hz, CHOP), 73.51 (d, J = 7.2 Hz, CHOP), 81.69 (d, J = 4.3 Hz, C^{3}), 129.01 (s, CH^{arom}), 129.38 (s, 2 × CH^{arom}), 131.88 (s, C^{arom}), 134.45 (s, 2 × CH^{arom}) ppm. MS: m/z (%) = 482 [M]$^{+}$, 436 (15), 435 (35), 434 (93), 405 (15), 404 (57), 385 (46), 293 (25), 257 (19), 251 (21), 241 (53), 209 (20), 47 (31), 45 (100), 43 (17). IR (KBr): $\tilde{\nu}$ = 692, 738, 842, 990, 1022, 1102, 1140, 1180, 1226, 1384, 1442, 1466, 1480, 2828, 2926, 2980, 3060, 3420 cm^{-1}. C$_{19}$H$_{31}$O$_6$PS$_3$ (482.6): calcd. C 47.29, H 6.47, S 19.93; found C 47.45, H 6.53, S 19.78.

Preparation of Diisopropyl 2-(4,5-Dihydroxy-3-methoxy-2-methylsulfanyl-6-phenylsulfanyl-tetrahydrothiapyranyl)phosphonate (24b): This compound was obtained from compound **21b** by the procedure described above for dihydroxylation (used to prepare diol **4**). The pure product was obtained by chromatography on silica gel (Et$_2$O/petroleum ether, 2:1) as a white solid (m.p. 141 °C) in 70% yield. ^{31}P NMR (101.27 MHz, CDCl$_3$): δ = 20.96 ppm. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.20 (d, J = 6.1 Hz, 3 H, CH$_3$), 1.31 (d, J = 6.1 Hz, 3 H, CH$_3$), 1.36 (d, J = 6.2 Hz, 3 H, CH$_3$), 1.39 (d, J = 6.2 Hz, 3 H, CH$_3$), 2.35 (s, 3 H, SCH$_3$), 3.09 (d, J = 9.2 Hz, 1 H, OH), 3.59 (s, 3 H, OCH$_3$), 3.91 (app. t, J = 4.3, 1 H, H^{3}), 4.02 (ddd, J = 10.2, 3.4, 9.2 Hz, 1 H, H^{5}), 4.15 (app. dt, J = 3.4, 10.9 Hz, 1 H, H^{4}), 4.53 (m, 1 H, CH−O), 4.74 (m, 1 H, CH−O), 4.86 (dd, J = 10.2, 1.3 Hz, 1 H, H^{6}), 5.91 (d, J = 10.9 Hz, 1 H, OH), 7.30−7.32 (m, 3 H, H^{arom}), 7.60−7.62 (m, 2 H, H^{arom}) ppm. ^{13}C NMR (100.61 MHz, CDCl$_3$): 14.69 (s, SCH$_3$), 23.45 (d, J = 7.6 Hz, CH$_3$), 24.14 (d, J = 4.2 Hz, CH$_3$), 24.33 (d, J = 4.7 Hz, CH$_3$), 25.00 (d, J = 1.1 Hz, CH$_3$), 53.41 (s, C^{6}), 55.14 (d, J = 147.7 Hz, C^{2}), 60.61 (s, OCH$_3$), 69.86 (s, C^{5}), 71.31 (s, C^{4}), 73.30 (d, J = 8.4 Hz, CHOP), 76.51 (d, J = 7.9 Hz, CHOP), 84.85 (d, J = 12.6 Hz, C^{3}), 128.51 (s, CH^{arom}), 129.36 (s, 2 × CH^{arom}), 133.18 (s, C^{arom}), 133.82 (s, 2 × CH^{arom}) ppm. MS: m/z (%) = 482 [M]$^{+}$, 387 (9), 386 (24), 385 (74), 384 (100), 307 (8), 301 (8), 269 (9), 257 (14), 251 (8), 241 (19), 215 (8), 213 (8), 47 (13), 45 (54), 43 (63). IR (KBr): $\tilde{\nu}$ = 736, 768, 788, 890, 912, 986, 1008, 1044, 1076, 1108, 1180, 1210, 1300, 1320, 1436, 1452, 1482, 1584, 1632, 2836, 2924, 2976, 3330 cm^{-1}.

Preparation of Diisopropyl 2-(4,5-Dihydroxy-3-methoxy-6-phenylsulfanyl-tetrahydrothiapyranyl)phosphonate (25): This compound was prepared from **24a** or **24b** following the procedure mentioned above for desulfanylation (**2** to **3**) and purified by chromatography on silica gel (EtOAc/petroleum ether, 2:1) to give **25** as a white solid (m.p. 142 °C) in 39% yield. ^{31}P NMR (161.98 MHz, CDCl$_3$): δ = 20.42 ppm. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.34 (d, J = 6.5 Hz, 3 H, CH$_3$), 1.35 (d, J = 4.3 Hz, 6 H, 2 × CH$_3$), 1.36 (d, J = 6.0 Hz, 3 H, CH$_3$), 3.27 (s, 1 H, OH), 3.35 (s, 1 H, OH), 3.52 (s, 3 H, OCH$_3$), 3.76 (dd, J = 21.2, 1.5 Hz, 1 H, H^{2}), 3.89 (dd, J = 10.6, 2.5 Hz, 1 H, H^{5}), 4.01 (ddd, J = 6.0, 4.1, 1.5 Hz, 1 H, H^{3}), 4.27

(dd, J = 4.1, 2.5 Hz, 1 H, H^4), 4.29 (d, J = 10.6 Hz, 1 H, H^6), 4.68–4.76 (m, 2 H, 2 × CH–O), 7.32–7.34 (m, 3 H, H^{arom}), 7.58–7.60 (m, 2 H, H^{arom}) ppm. ^{13}C NMR (100.61 MHz, CDCl$_3$): 23.91 (d, J = 5.9 Hz, CH$_3$), 24.32 (d, J = 4.2 Hz, CH$_3$), 24.42 (d, J = 4.6 Hz, CH$_3$), 24.66 (d, J = 2.6 Hz, CH$_3$), 41.34 (d, J = 145.6 Hz, C^2), 52.10 (d, J = 12.6 Hz, C^6), 58.92 (s, OCH$_3$), 68.69 (d, J = 12.7 Hz, C^4), 70.08 (d, J = 2.1 Hz, C^5), 71.60 (d, J = 6.9 Hz, CHOP), 72.31 (d, J = 6.3 Hz, CHOP), 79.20 (d, J = 5.6 Hz, C^3), 128.64 (s, CH^{arom}), 129.45 (s, 2 × CH^{arom}), 132.58 (s, C^{arom}), 133.15 (s, 2 × CH^{arom}) ppm. MS: m/z (%) = 436 [M]$^+$, 377 (15), 296 (28), 295 (37), 253 (22), 224 (66), 212 (29), 211 (51), 168 (15), 45 (75), 43 (49). IR (KBr): $\tilde{\nu}$ = 704, 752, 788, 846, 906, 944, 992 (P–O–C), 1102, 1142, 1180, 1226, 1306, 1372, 1446, 1466, 2908, 2980, 3314 cm^{-1}. $C_{18}H_{29}O_6PS_2$ (436.5): calcd. C 49.53, H 6.70, S 14.69; found C 49.64, H 6.84, S 14.13.

The preparation of compounds **26a**, **26b**, **27a**, **27b**, **28a**, **28b**, **29a**, **29b** and **30** was described in the supplementary material of our previous communication.[12b]

X-ray Crystallographic Study: CCDC-164889 (**23**), -164890 (**12b**), and 164891 (**4b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

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