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The First Asymmetric Synthesis of α-Sulfanylphosphonates

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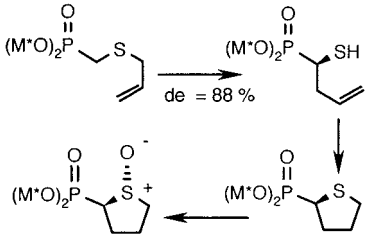
ABSTRACT



Diastereoselectivity of up to 88% was achieved for the synthesis of an α-mercapto γ-unsaturated phosphonate using the readily available chiral dimenthylphosphonyl ester group and a carbanionic [2,3]-sigmatropic rearrangement. Absolute configuration of the newly formed chiral center of this nonracemic thiol was determined, and the corresponding phosphono thiolane and thiolane *S*-oxide were also stereoselectively prepared.

α-Heterosubstituted phosphonates have focused interest due to their potential biological activities[1] (as antibacterial, antiviral, or herbicidal agents) and synthetic applications.[2]

Among these compounds, α-hydroxy and α-amino phosphonates have been extensively studied and their syntheses (racemic or chiral) have been recently reviewed.[3] However, α-mercapto (or sulfanyl) phosphonates have been more scarcely described.[4]

Moreover, to the best of our knowledge, no enantioselective synthesis of chiral α-mercaptophosphonates or sulfides have so far been proposed.

We have previously reported on the preparation of racemic α-mercaptophosphonates via carbanionic [2,3]-sigmatropic rearrangements of (allylthiomethyl)phosphonates.[5] Herein we report an asymmetric version of this rearrangement which allowed us to synthesize the first chiral nonracemic mercaptophosphonate and some of its derivatives including a chiral cyclic sulfoxide (potent useful Wittig−Horner reagent).

[2,3]-Sigmatropic rearrangements which lead to the regioselective formation of carbon−carbon bonds have found wide application in the synthesis of complex organic molecules.[6] Moreover, applications of these rearrangements in the synthesis of chiral compounds usually proceed with a high level of stereo- or enantiocontrol.[6]

Good diastereoselectivities (respectively 99% and 92% de) for the [2,3]-sigmatropic rearrangement of lithiated allyloxymethylphosphonates using additional chiral auxiliaries have been previously reported by both Denmark[7] and our laboratory.[8]

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(1) (a) Engel, R. *Chem. Rev.* **1977**, *77*, 349. (b) Tashma, Z. *J. Org. Chem.* **1982**, *47*, 3012 and cited references. (c) Kafarsky, P.; Lejczak, B. *Phosphorus, Sulfur Silicon* **1991**, *63*, 193.

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(6) (a) Nakaï, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885. (b) Mikami, K.; Nakaï, T. *Synthesis* **1991**, 594. (c) Brükner, R. *Kontakte (French ed.)* **1993**, 3; **1994**, 2.

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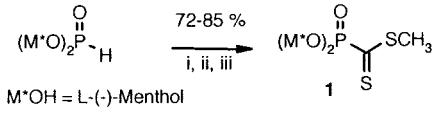
Our successful results in the asymmetric synthesis of an α-hydroxyphosphonate by using a C_2-symmetry dimenthylphosphonyl group incited us to keep this readily accessible and cheap chiral auxiliary in the present study.

Starting from the L-dimenthyl phosphite,[8] we first prepared the easily accessible (yield 72−85% on a 10 g scale) phosphonodithioformate **1** (according to the method of Grisley,[9] Scheme 1) using HK as a base in THF.

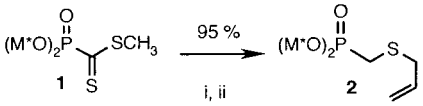
Scheme 1



i : HK / THF ii : CS_2 iii : MeI

The reduction of dithioformate **1** by an excess of sodium borohydride in ethanol followed by addition of allyl bromide led us to (allylsulfanyl)methylphosphonate **2** in 95% yield (Scheme 2).

Scheme 2



i : $NaBH_4$, EtOH ii : CH_2=$CHCH_2Br$

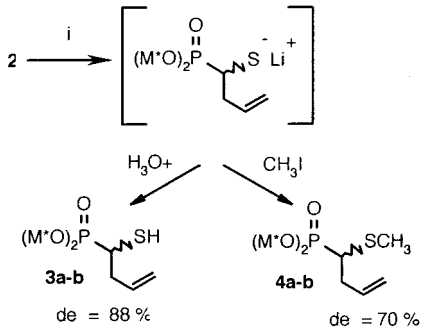
Owing to the dramatic steric effect of the two bulky menthyl groups, the next step of the synthesis required us to find appropriate conditions for the generation and rearrangement of the carbanion α to the phosphorus. Among the bases we have tested,[10] only alkyllithiums were found to be efficient and, at low temperature, a large excess was necessary to obtain a fast and complete deprotonation. The best results were obtained by using 5 equiv of (*sec*-BuLi/HMPA) in THF at −75/−72 °C and with a reaction time of 75 min. After acidic hydrolysis and extraction with pentane, we obtained the rearranged α-mercaptophosphonate **3** (**3a**/**3b**, 94:6) (cf. Scheme 3) with a diastereoisomeric excess of up to 88% (according to ^{31}P NMR) and a yield of 95%.

The thiol was found to be relatively unstable during chromatography (disulfide formation occurred) and thus was used in crude form (purity >90% according to NMR spectra) for subsequent transformations.

Instead of acidic hydrolysis, methyl iodide was also used to trap the intermediate lithiated thiolate. Probably due to the excess of base, a partial racemization occurred and the

(7) Denmark, S. E.; Miller, P. C. *Tetrahedron Lett.* **1995**, *36*, 6631.
(8) Gulea-Purcarescu, M.; About-Jaudet, E.; Collignon, N. *Tetrahedron Lett.* **1995**, *36*, 6635.
(9) Grisley, D. W., Jr. *J. Org. Chem.* **1961**, *26*, 2544.
(10) HNa, HK, HLi, LiHMDS, LDA, and tBuOK/BuLi in various conditions (temperature, solvent, reaction time).

Scheme 3

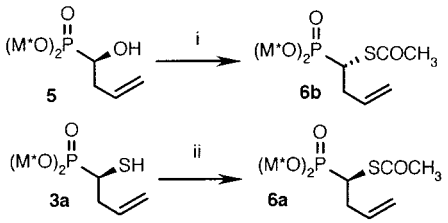


i : 5 equiv (sec-BuLi / HMPA), THF, -75°C, 75 min.

resulting methylsulfanyl derivative **4** was obtained with a lower diastereoisomeric excess (cf. Scheme 3, yield 85%, de = 70%).

We were able to deduce the configuration of the sulfur-substituted carbon (C_1) of the main diastereoisomer **3a** from that of the corresponding alcohol **5** of known configuration.[8] Starting from the α-hydroxy phosphonate **5** (de = 96%, 1*R* from (−)-L-dimenthyl phosphite) and using thiolacetic acid under the Mitsunobu conditions,[11] we prepared the α-acetylsulfanyl phosphonate **6b** with 1*R* configuration (25% yield, de = 96%) with full inversion of configuration (Scheme 4).

Scheme 4



i : DEAD /PPh_3, CH_3COSH ii : $(CH_3CO)_2O$

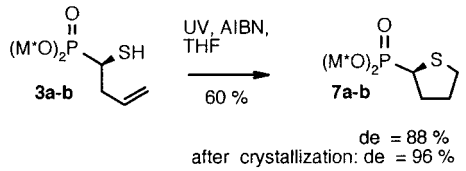
Comparison of the ^{31}P NMR spectra of **6b** (1*R;* ^{31}P = 24.1) and **6a** (^{31}P = 24.2) (obtained by acetylation of the crude thiol **3a**, 94% yield, de = 88%) showed that these compounds are epimers. Therefore, an *S* configuration can be attributed to the α-carbon of **6a** and of its precursor, the major diastereoisomer **3a**.

The radical intramolecular cyclization of crude thiol **3** into the 2-phosphonothiolane **7a**,**b** was then performed (using UV irradiation and a catalytic amount of AIBN).

This cyclization occurred without any epimerization (de = 88%) and the yield was 60% after silica gel chromatography (Scheme 5). Crystallization at −60 °C in pentane allowed us to isolate a nearly pure sample of epimer **7a** (de = 96% by ^{31}P NMR, yield 30%) with an *S* configuration (compound isoster of L-proline esters).

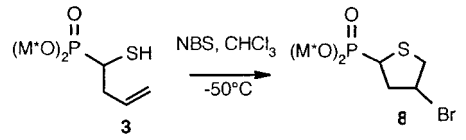
(11) Hughes, D. L. *Org. React.* **1992**, *42*, 335 and cited references.

Scheme 5



Previous work has shown that the addition of *N*-bromosuccinimide to a thiol leads to the formation of a sulfenyl bromide.[12] In particular, when a double bond is present, the sulfenyl bromide spontaneously adds to the double bond and such a reaction was recently used for the preparation of 5- or 6-membered sulfurated rings.[13] Thus, addition of the crude thiol **3** to a solution of *N*-bromosuccinimide in chloroform at −50 °C led to the formation of the 4-bromo-2-phosphothiolane **8** in 65% yield (Scheme 6). As expected[11] and as

Scheme 6



shown by ^{13}C and ^{1}H NMR spectra of the thiolane **8**, the cyclization and bromination reactions were highly stereoselective.

Starting from the thiol **3** (de = 80%), the phosphonobromothiolane **8** (probably *trans* as previously observed in such cyclizations)[12] was isolated with the same diastereomeric excess.

We then performed the oxidation of 2-phosphonothiolane **7a**,**b** (de = 88%) using *m*-chloroperbenzoic acid. The corresponding sulfoxide was obtained quantitatively. The oxidation was found to be totally stereoselective and so allows a complete transfer of the asymmetry from the

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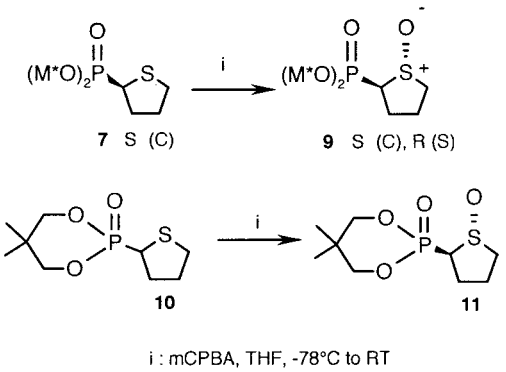
(13) Ren, X.-F.; Turos, E.; Lake, C. H.; Churchill, M. R. *J. Org. Chem.* **1995**, *60*, 6468.

Scheme 7



α-carbon to the sulfur (Scheme 7). The relative configuration of **9** was established by comparison with its racemic analogue, 2-phosphonothiolane *S*-oxide **11**, obtained under the same oxidation conditions from thiolane **10**; the X-ray study of a crystal of this sulfoxide has proven the relative *trans* configuration of the C−P and S−O bonds.[14] Consequently, since the carbon of **9a** is *S*, an *R* configuration can be attributed to the sulfur atom of the major diastereomer **9a**.

In conclusion, this paper describes the first asymmetric synthesis of an α-mercapto γ-unsaturated phosphonate and of its cyclic derivatives **7**, **8**, and **9**. Moreover, owing to the stereoselectivity of the S-oxidation of thiolane **7**, sulfoxide **9** can be considered as a new potential asymmetric Horner−Wadsworth−Emmons reagent for the synthesis of asymmetric vinylic sulfoxides.

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Supporting Information Available: Detailed descriptions of experimental procedures and NMR data for compounds **1**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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