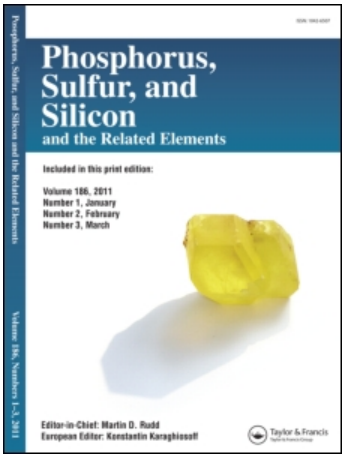

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A new method to prepare enantioenriched sulfinates was developed to obtain optically active ortho-*methylsulfinyl(phenylphosphonates). It consists of a diastereoselective oxidation of sulfenates to sulfinates. Additionally, preliminary results concerning the synthesis of* ortho-*phophonylated benzylic thiol derivatives* via *a new P—S to P—C [1,4]-rearrangement and a first synthetic application of these compounds are also described.*

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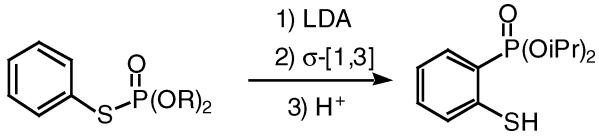
INTRODUCTION

Because of their chelating properties, some *ortho-P,S*-difunctionalized aromatic compounds have found interesting applications: the *ortho*-methylsulfanyl(phenylphosphonic) acid **I** has been involved in the preparation of new *cis*-platinum complexes[1] as candidates for anti-tumor agents and the *ortho*-mercapto(phenylphosphonic) acid **II** is a metallophosphatase inhibitor.[2] Moreover, some of their chiral derivatives such the *ortho*-(arylsulfinyl)phenyl diphenylphosphine **III**[3] and *ortho*-(methylsulfanyl)phenyl phosphoroamidate **IV**[4] have been used as ligands for asymmetric catalysis (Figure 1).

An efficient synthesis of compounds such **I**, **II**, and **IV**, previously mentioned, has been developed by some of us, using the *ortho*-lithiation of arylthio phosphorylated derivatives, followed by a P—S to P—C [1,3]-rearrangement (Scheme 1).[5]



SCHEME 1

We have already directed several studies in the synthesis of their enantiopure sulfoxides derivatives by racemate resolution[6] or by asymmetric oxidation of the corresponding sulfides (using enantiopure oxidants[4] or diastereoselective oxidation in the presence of a chiral phosphorus moiety[5d]). However, some limits, such as the accessibility to only one of the enantiomers, the cost and limited number of commercial enantiopure oxidants, or insufficient ee of the target products caused us to investigate other synthetic routes.

This communication summarizes our recent results of the synthesis of optically active sulfoxides from diastereomeric sulfinic esters. The latter have been prepared by a new diastereoselective oxidation,

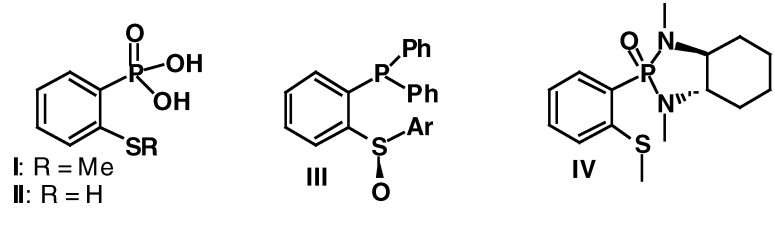


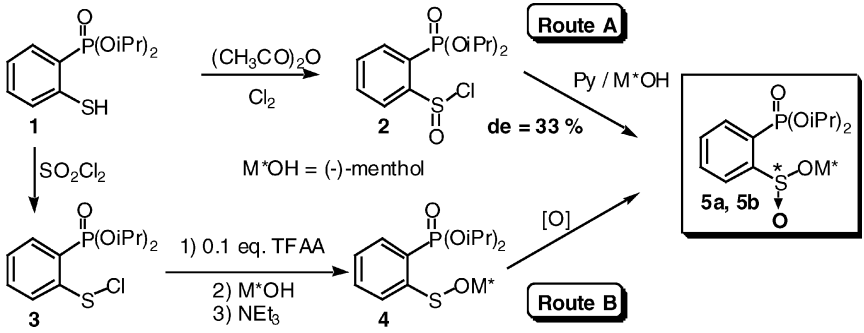
FIGURE 1

of sulfenate to sulfinates. In addition, preliminary results concerning the synthesis of homologue structures of the *ortho-P,S*-difunctionalized aromatic compounds, the *ortho*-(methylsulfanylmethylen)phenyl phosphonates by a new P—S to P—C [1,4] rearrangement, and their first application are also described here.

RESULTS AND DISCUSSION

Diastereoselective Sulfenate to Sulfinate Oxidation

In the first experiment, we followed a classical way[7] to prepare the menthylsulfinate **5**, starting from the *ortho*-mercapto-phenylphosphonate **1**,[5a] which has been converted into the sulfinyl chloride **2** and subsequently reacted with (−)-menthol in pyridine (Scheme 2, route A). The sulfinate ester **5** was obtained with a modest diastereoselectivity (33% de) and separation by column chromatography of the two diastereomers **5a** and **5b** could not be acheived.



SCHEME 2

Therefore we decided to investigate another strategy, mentioned in the literature[8] but, to the best of our knowledge,[9] not really explored, which consists in the preparation of the sulfenate **4**, derived from an enantiopure alcohol, here the (−)-menthol, as a chiral auxiliary and to oxidize it into the corresponding sulfinate **5** (Scheme 2, route B). The synthesis of a relatively stable* sulfanyl chloride **3** seems to be related to the presence of the electron-withdrawing phosphoryl group in the aromatic ring. The catalytic amount (0.1 equivalents) of trifluoroacetic anhydride (TFAA) has been found to be necessary to obtain sulfenate **4** in good yield. To explain this observation, a catalytic cycle has been proposed. Three oxidants were selected: the achiral system NBS/H_2O and

*Usually, sulfanyl chlorides are unstable compounds, decomposing easily to disulfides.

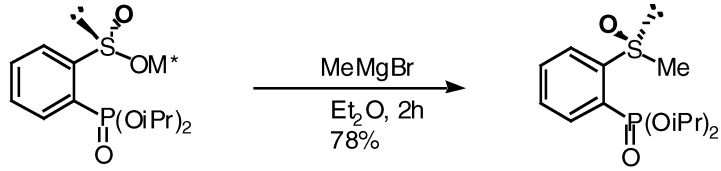
TABLE I Oxidation of Sulfenate 4 into Sulfinate 5

Entry	Oxidant	Solvent	Time (h)	Yield %	dr 5a/5b (%)	de (%)
1	NBS/H_2O	MeCN/H_2O (2/1)	0.5	95[a]	12/88	76
2	(−)-Ox	CCl_4	84	65[b]	17/83	66
3	(+)-Ox	CCl_4	84	65[b]	70/30	40

[a]Crude product with satisfactory purity.
[b]Purified product by column chromatography.

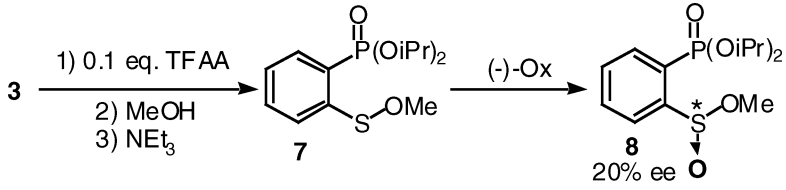
both enantiomers of the (8,8-dichlorocamphorylsulfonyl) oxaziridine,[10] noted here as (−)-Ox and (+)-Ox. The results are summarized in Table I. The best result (76% de) was obtained using the achiral oxidant NBS/H_2O. The oxidation of the (−)-menthyl sulfenate **4** into the corresponding sulfinate **5** by the oxaziridine (−)-Ox gave the "matched" pair (66% de), while the (+)-Ox led to the "mismatched" pair (40% de). Moreover, this effect is accompanied by an inversion of the configuration of the major diastereomer of **5**.

The diastereomeric mixture **5a**/**5b** with 76% de (Table I, entry 1) was treated by methylmagnesium bromide affording, as expected, the methylsulfoxyde **6** with 76% ee (Scheme 3).



SCHEME 3

An independent experiment was carried out for the achiral methyl sulfenate **7** (obtained from sulfanyl chloride **3** and methanol). It was oxidized by the oxaziridine (−)-Ox, giving the chiral methyl sulfinate **8** with an enantiomeric excess of 20% (Scheme 4). This demonstrates the important influence of the bulkiness of the alkoxy group on the enantioselectivity of the considered oxidation.

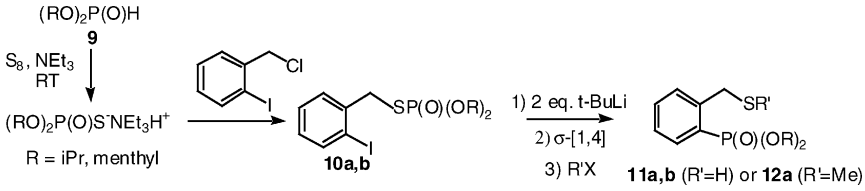


SCHEME 4

This work is in progress to improve the diastereoselectivity of this new sulfenate to sulfinate oxidation using other enantiopure alcohols and different oxidants, especially achiral ones.

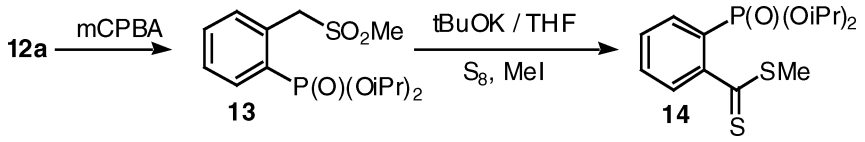
Synthesis of New *P,S*-Difunctionalized Aromatic Compounds *via* a P–S to P–C [1,4] Rearrangement

Compared to the [1,3]-sigmatropic rearrangement of arylthiophosphate into mercaptoarylphosphonate mentioned previously (Scheme 1), no example of the [1,4]-homologue reaction has been described. However, in oxygen series, Li and coworkers described a 1,4-migration of a diaryloxyphosphino group from the benzylic oxygen to the aromatic carbon in *ortho* position.[11] A halogen–metal exchange is needed in this case to generate the carbanion on the aromatic ring of the benzylthiophosphates **10**. The sequence we used, starting from the dialkylphosphite **9**, is given in the Scheme 4. The desired benzylic thiol **11a** and the corresponding methylsulfide **12a** were obtained from benzyl diisopropyl phosphorothioate **10a**. The reaction could be extended to the dimenthylphosphoryl derivative **10b**, and benzylic thiol **11b** bearing the chiral phosphoryl moiety in *ortho* position was also obtained (Scheme 5).



SCHEME 5

The utility of such benzylic sulfenyl derivatives has been examplified by the first synthetic application of sulfide **12a** for the synthesis of the unknown *ortho*-phosphono-dithiobenzoic acid methyl ester **14** (Scheme 6). This procedure is based on a method recently described by some of us[12] involving the intermediate methyl sulfone **13** (the oxidized derivative of **12a**).



SCHEME 6

Further studies will be directed toward the applications of these structures as metal ligands, especially for the *cis*-platinum, leading to new complexes with potential cytotoxic properties.

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