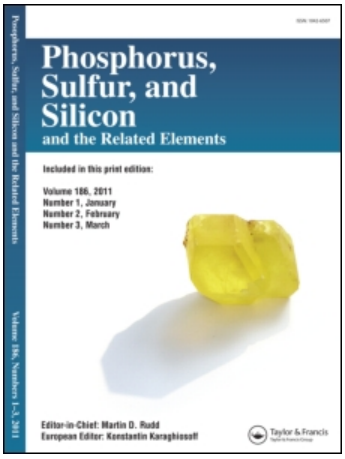

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Asymmetric Cyclopropanation of Optically Active Vinyl Sulfoxides: A New Synthetic Approach to Biologically Active Compounds

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To cite this Article Midura, Wanda H.(2005) 'Asymmetric Cyclopropanation of Optically Active Vinyl Sulfoxides: A New Synthetic Approach to Biologically Active Compounds', Phosphorus, Sulfur, and Silicon and the Related Elements, 180: 5, 1285 — 1290
To link to this Article: DOI: 10.1080/10426500590911593
URL: http://dx.doi.org/10.1080/10426500590911593

Phosphorus, Sulfur, and Silicon, 180:1285–1290, 2005

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500590911593

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Asymmetric Cyclopropanation of Optically Active Vinyl Sulfoxides: A New Synthetic Approach to Biologically Active Compounds

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The influence of adjacent substituents on stereochemical course of cyclopropanation of vinyl sulfoxides with stabilized and nonstabilized ylides, as well as dependence on reaction conditions, was investigated. Application of optically active cyclopropanes obtained in the synthesis of conformationally constrained analogs of L-glutamic acid, the useful pharmacological tools in investigation of excitatory amino acid receptors, is presented.

Keywords Asymmetric synthesis; cyclopropanation; vinyl sulfoxides

One of the most important and general strategies in asymmetric conjugate addition is based on the facial control relying on an appended chiral auxiliary as an electron-withdrawing moiety. Among this type of electron-deficient olefins, optically active α,β-unsaturated sulfoxides have found wide application.

Recently, we designed the new Michael acceptor—optically active (1-diethoxyphosphoryl) vinyl p-tolyl sulfoxide **1**—and found that cyclopropanation of this compound with different sulfonium ylides, as well as diazoalkanes, occurs in a highly diastereoselective manner.[1]

The reaction of 1-diethoxyphosphoryl)vinyl p-tolyl sulfoxide **1** with ethyl (dimethylsulfuranylidene) acetate (EDSA) was also stereoselective; however, all four diastereomers were formed.[2] The stereochemical outcome was strongly dependent on the reaction conditions. The best stereoselection was obtained with the ylide generated *in situ* from sulfonium bromide in the presence of DBU in the nonpolar solvent toluene, affording diastereomeric cyclopropanes with the facial stereoselectivity 12:1 (Scheme 1).

Received July 9, 2004; accepted October 5, 2004.
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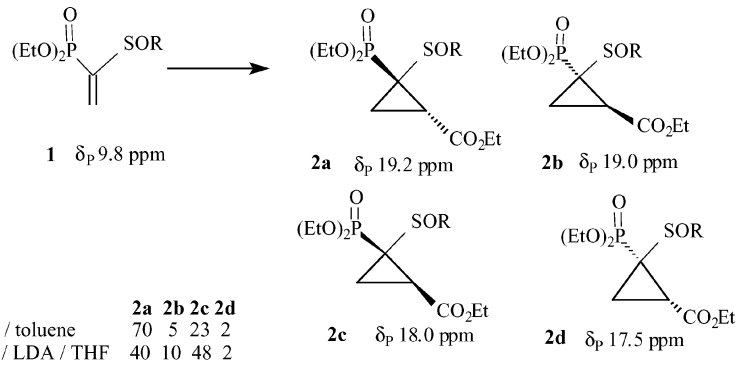
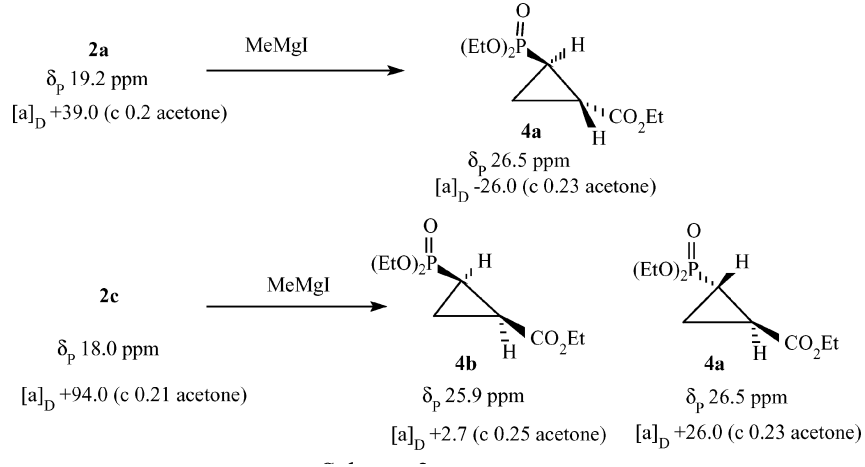


SCHEME 1

The relative configuration was established by comparing the values of $^{3}J_{P\text{-}H}$ and $^{3}J_{C\text{-}P}$ coupling constants, especially for sulfones, where the differences were more evident.

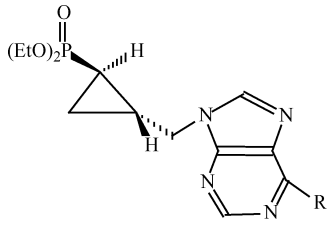
Two major diastereomers were separated by chromatography and desulfurized by treatment with 5 equivalents of methylmagnesium iodide at −40°C. From the isomer *cis*-**2a** only one *trans* (−)-**4a** was obtained. In the case of the isomer *trans* **2c**, two isomers were formed, **4b** and **4a**, the latter as a result of the inversion of the configuration at carbon C1, which affords more stable isomer *trans* (Scheme 2).



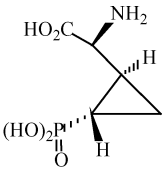
SCHEME 2

After reduction of the carbonyl group, the cyclopropane was coupled with adenine and chloropurine under Mitsunobu reaction conditions (triphenylposphine, diisopropylazidodicarboxylate),

affording the enantiomerically pure cyclopropylphosphonate analogues of nucleotides (Scheme 3).



5a, R=NH$_2$ δ_P 28.3 ppm
5b, R=Cl δ_P 27.8 ppm



6

SCHEME 3

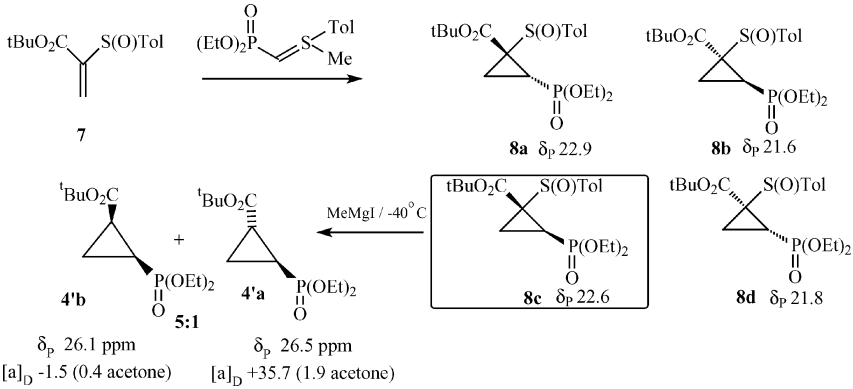
Another type of phosphonate of a great interest is phosphono aminoacids, analogues of natural and synthetic amino acids. Various phosphonic acid analogues of L-glutamic acid act as antagonist at excitatory amino acid (EAA) receptors in the central nervous system, at which L-glutamic acids are thought to be endogenous neurotransmitters. The conformationally restrained cyclic phosphono amino acids have provided much structure and activity information about amino acids receptors.[3] Because the key intermediate in the synthesis of constrained phosphono aminoacid **6** is 1-phosphoryl 2-carboxycyclopropane, we investigated stereochemical course of the cyclopropanation of vinyl sulfoxides to obtain different diastereomers of this structure.

It is known that in the cyclopropanation of vinyl sulfoxides with sulfonium ylides, the transition state involves a nonchelate model in which the dipoles of the sulfinyl and carbonyl group are *anti*-oriented, which determines the facial attack (from the lone pair side) of the ylide.[4] However, in the case of bromomalonate cabanion, different stereochemistry was observed, which was attributed to chelation between the carbonyl and sulfinyl oxygen because of the presence of a complexing metal (counter ion).[5]

The reaction of (1-diethoxyphosphoryl)vinyl p-tolyl sulfone with the bromoacetate carbanion generated by LDA in THF solution leads to the desired cyclopropane, although in moderate yield (46%). The same reaction performed with vinyl p-tolyl sulfoxide **1** gave only a complicated mixture of unidentified products. However, when the reaction was performed in the presence of equal amount of zinc chloride, the cyclopropanation was accomplished in almost 50% of yield. One could expect that the presence of complexing agent as $ZnCl_2$ should change conformation of the vinyl sulfoxide and in consequence the facial stereoselectivity,

but isolated major diastereomers were the same as in the reaction with sulfonium ylide.

Another approach to change the stereochemistry of phosphoryl cyclopropane was performed by exchanging of the reagents, using ^{t}butyl p-tolylsulfinylacrylate as the Michael acceptor and sulfonium ylide stabilized by the phosphoryl group. The phosphorous ylide was obtained according to the Kondo[6] procedure by alkylation of phosphoryl sulfide in the presence of silver perchlorate.

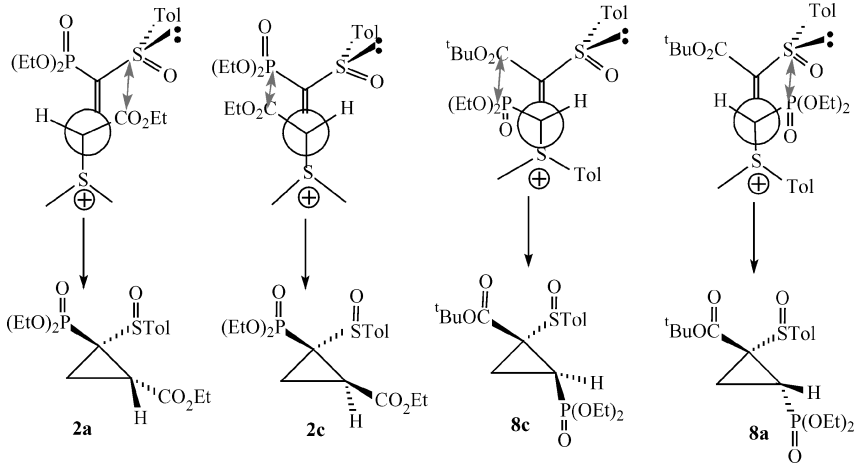


SCHEME 4

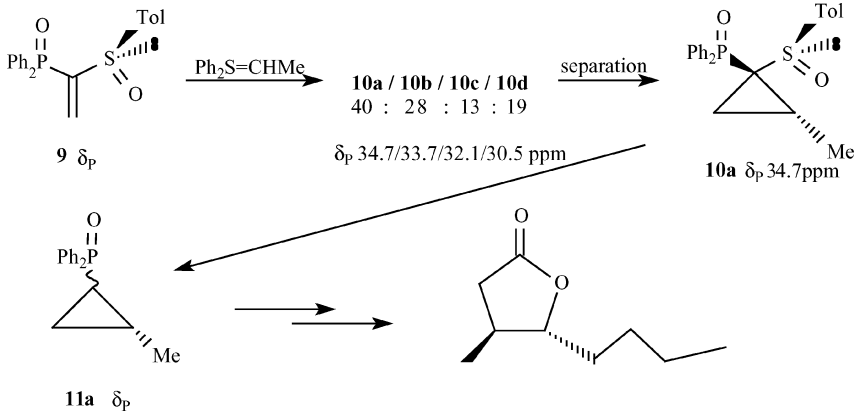
The ratio of diastereomers in this reaction strongly depends on the reaction conditions, mainly on the temperature. The best result was obtained when the reaction was carried at -20°C for 6 h. Relative configuration was assigned, as in the former case, by comparing the coupling constants. Additional proof of our configurational assignment was provided by the desulfurization step. The major product was *cis*-phosphorylcarboxycyclopropane, but of the opposed sign of optical rotation than that obtained in the cyclopropanation of phosphoryl vinyl sulfoxide with EDSA (Scheme 4).

To understand the origin of the observed diastereoselectivities in the cyclopropanation reaction of phosphoryl vinyl sulfoxide, we decided to determine its structure and conformation. Because our reagent is liquid, we synthesized structurally closely related crystalline 1-(diphenylphosphinoyl)vinyl p-tolyl sulfoxide **9**. The X-ray structure revealed that the sulfinyl and phosphoryl groups are *anti*-oriented and the sulfinyl group is *syn* with respect to C=C double bond. Such a conformation is stabilized by intramolecular hydrogen bond between sulfinyl oxygen and vinylic proton. Also the theoretical calculations for the model compound (dimethoxyphosphoryl)vinyl phenyl sulfoxide indicated the same preferred conformation.[7]

In stereochemical outcome of performed reactions we observed high stereoselection caused by optically active sulfinyl group evidently oriented in *s-cis* manner. In the case of (1-diethoxyphosphoryl)vinyl p-tolyl sulfoxide **1** the *cis*/*trans* stereoselection is lower, probably caused by the difference in repulsive action between sulfinyl-carboethoxy vs. phosphoryl-carboethoxy groups. In the case of the phosphoryl ylide approach, the repulsive steric effect between two bulky sulfinyl-phosphoryl groups must be much higher than for phosphoryl-carboalkoxy groups, which determines *trans* configuration of the major isomer (Scheme 5).



SCHEME 5



SCHEME 6

Having in hand 1-(diphenylphosphinoyl)vinyl p-tolyl sulfoxide, we performed cyclopropanation with isopropylidene sulfonium ylide. Although the stereoselection was moderate in this case, diastereomers were easy to separate. The Horner–Wittig reaction on this product leads to alkylidene cyclopropanes, which are optically active intermediates in the synthesis of *quercus lactone*[8] (Scheme 6).

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