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Asymmetric cyclopropanation of chiral (1-phosphoryl)vinyl sulfoxides: A new approach to constrained analogs of biologically active compounds*

Marian Mikolajczyk‡

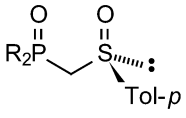
Center of Molecular and Macromolecular Studies, Polish Academy of Sciences, 90-363 Łódź, Sienkiewicza 112, Poland

Abstract: This account outlines the results obtained in the author's laboratory on the asymmetric cyclopropanation of enantiopure 1-phosphorylvinyl *p*-tolyl sulfoxides with sulfur ylides and diazoalkanes. Based on experimental results and theoretical calculations, the transition-state model for asymmetric cyclopropanation is proposed. A great synthetic value of the reaction investigated is exemplified by the total synthesis of constrained analogs of bioactive compounds, namely, enantiopure cyclic analog of phaclofen and cyclopropylphosphonate analogs of nucleotides.

Keywords: Asymmetric cyclopropanation; (1-phosphoryl)vinyl sulfoxides; 2-amino-cyclopropanephosphonic acid; cyclopropylphosphonate analogs of nucleotides; sulfur ylides.

INTRODUCTION

The sulfinyl group has proved to be one of the most efficient chiral auxiliaries because of its extraordinary ability to control stereoselectivity of asymmetric reactions [1–3]. Especially important are chiral, enantiomerically pure vinyl sulfoxides, which have recently found a wide application in numerous asymmetric syntheses.



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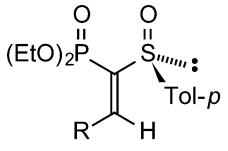

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2a, R=H
2b, R=Ph
2c, R=Me
2d, R=Bu

In continuation of our work on α-phosphoryl sulfoxides **1**, we recently designed a new type of activated enantiomerically pure vinyl sulfoxides, namely, (1-diethoxyphosphoryl)vinyl *p*-tolyl sulfoxide **2a** and its β-substituted analogs [4,5]. Owing to the presence of the two electron-withdrawing groups, phosphoryl and sulfinyl, the carbon–carbon double bond in the vinyl sulfoxides **2** is very reactive. Accordingly, the sulfoxides **2** were found to be good Michael acceptors and reactive Diels–Alder

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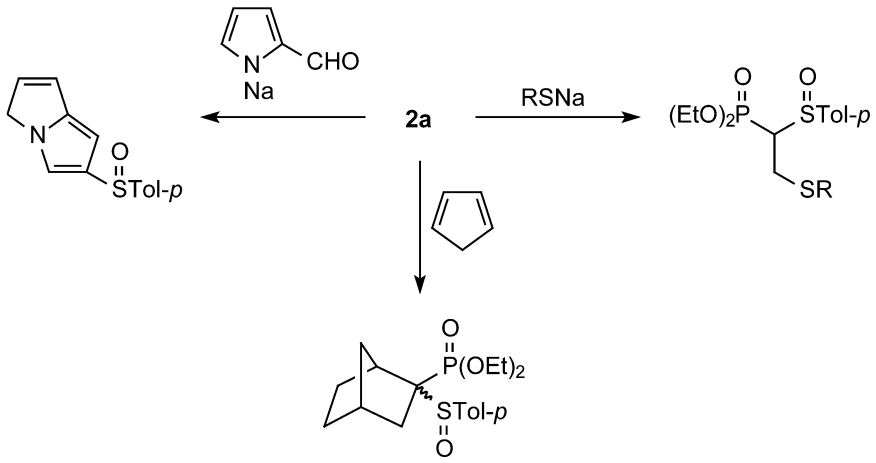
‡E-mail: marmikol@bilbo.cbmm.lodz.pl

dienophiles. They are also key reagents for the construction of monocyclic compounds and condensed carbo- and heterocycles via tandem Michael addition/intramolecular Horner–Wittig reaction. The reactions shown in Scheme 1 illustrate typical reactivity of **2**.

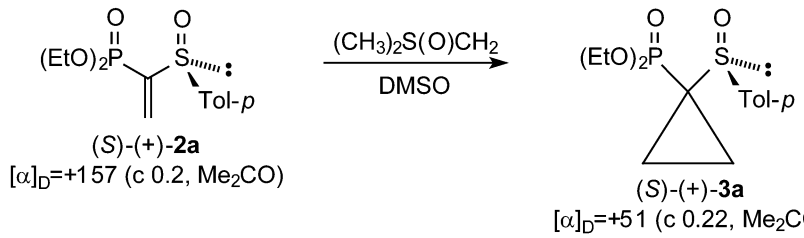


Scheme 1

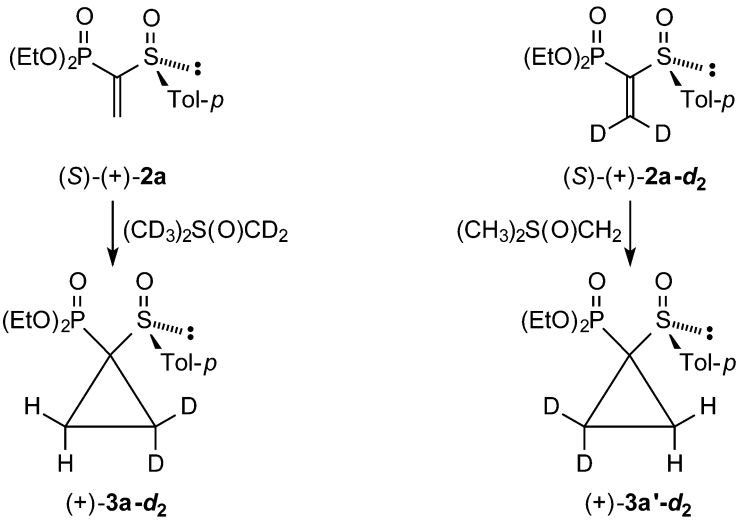
The aim of this short account is to summarize the recent results obtained in the author's laboratory on asymmetric cyclopropanation of the vinyl sulfoxides **2**, as well as to demonstrate the utility of this new cyclopropanation method in the synthesis of selected constrained analogs of biologically active compounds.

ASYMMETRIC CYCLOPROPANATION OF (*S*)-(+)-1-PHOSPHORYLVINYL *p*-TOLYL SULFOXIDE WITH SULFUR YLIDES AND DIAZOALKANES

In the first part of the present study, the reaction of (*S*)-(+)-**2a** with sulfur ylides was examined [6]. Thus, treatment of (*S*)-(+)-**2a** with an excess of dimethyl(oxo)sulfonium methylide gave the expected cyclopropane **3a** in 90 % yield. However, this reaction does not generate a new stereogenic center, and the optical activity of (+)-**3a** is due to the chiral sulfoxide moiety.

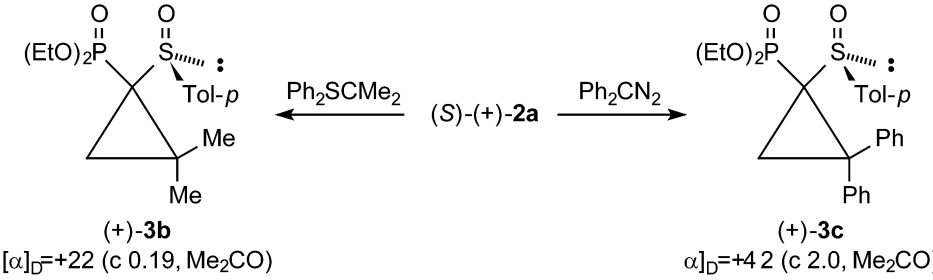


The asymmetric version of this reaction was accomplished by using deuterated sulfur ylide. It resulted in the optically active cyclopropane **3a-d_2** as a major diastereomer in which the new quaternary carbon atom is chiral due to isotopic substitution (CH_2 vs. CD_2). The diastereomer with opposite configuration at this α-carbon atom was obtained starting from 2,2-dideuterio-substituted vinyl sulfoxide (*S*)-(+)-**2a-d_2** [7] (Scheme 2). The diastereomeric ratio in both reactions was found to be ca. 10:1 as determined by integration in the ^{1}H NMR spectra of the methylene protons signals of the diastereomers **3a-d_2** and **3a'-d_2** formed [7].



Scheme 2

More interestingly, treatment of (*S*)-(+)-**2a** with diphenylsulfonium isopropylide or diphenyldiazomethane yielded the corresponding cyclopropanes **3b** and **3c** as single diastereomers (Scheme 3) [7,8].



Scheme 3

Anticipating that the observed high diastereoselectivities in the cyclopropanation reaction of (*S*)-(+)-**2a** are related to the structure and conformation of α-phosphorylvinyl sulfoxides, we determined the crystal and molecular structure of (±)-(1-diphenylphosphinoyl)vinyl *p*-tolyl sulfoxide **4** by X-ray analysis (Fig. 1a). It revealed that both polar sulfinyl and phosphoryl groups adopt an *anti*-orientation. The S=O group is *syn*-coplanar with the ethylenic bond, and its oxygen atom is involved in hydrogen bond with the β-vinylic hydrogen.* Practically, the same conformation of the reactive fragment of 1-phosphorylvinyl sulfoxide resulted from the theoretical calculations of (1-dimethoxyphosphoryl)vinyl phenyl sulfoxide **5** using density functional theory (DFT) at the B3LYP/6-31G* level (Fig. 1b). Moreover, calculations revealed that steric and not thermodynamic factors are responsible for the observed stereoselectivity of the cyclopropanation reaction. An inspection of both conformations, i.e., solid-state conformation of (±)-**4** and gas-phase conformation of (*S*)-**5**, indicates that there are two sterically different diastereotopic faces, the less hindered being occupied by the lone pair of electrons on the sulfur atom and the phosphoryl oxygen.

*For the nature and features of C–H…O interactions, see ref. [9].

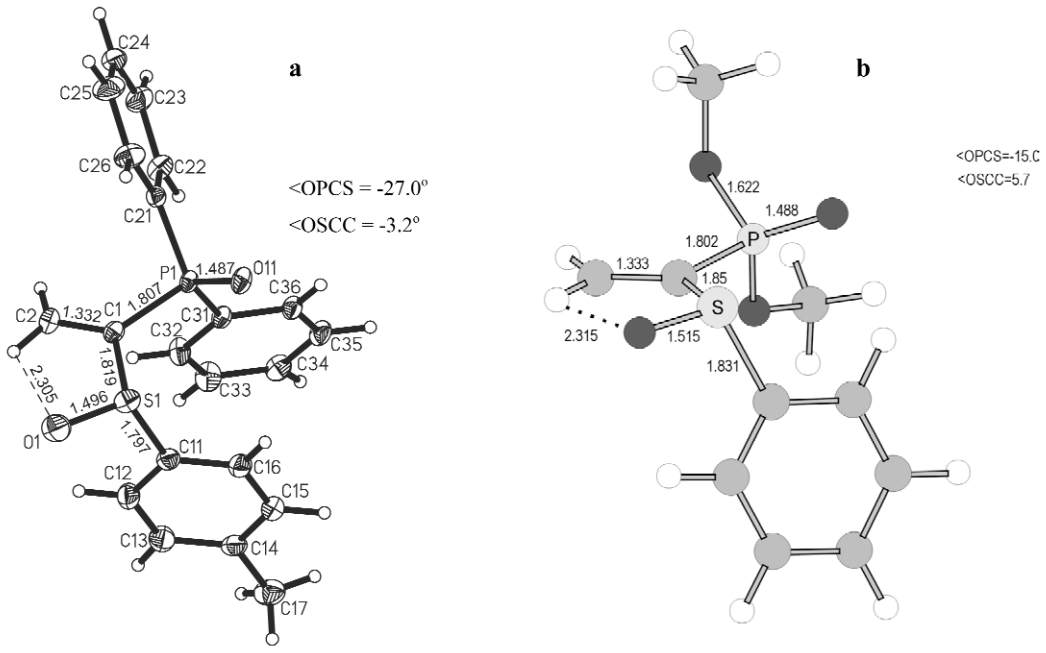
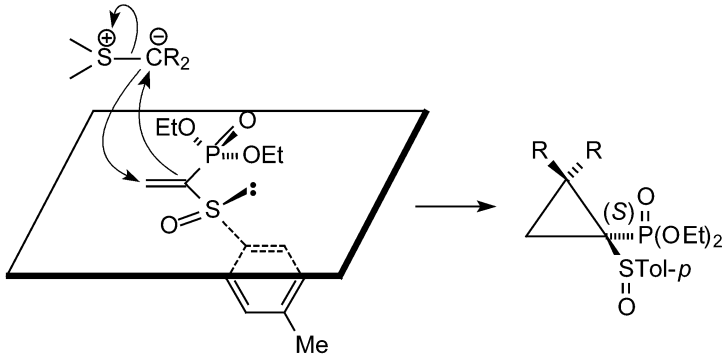


Fig. 1 (a) Solid-state structure of (±)-4 with selected bond lengths; (b) calculated structure of (*S*)-5 with selected bond lengths.

Assuming that the conformation of (1-phosphoryl)vinyl sulfoxides in solution is the same as in the solid state and gas phase, the above results allowed us to propose the transition-state model for the cyclopropanation of chiral sulfoxides **2** (Scheme 4). Hence, sulfur ylide or diazoalkane add to the double carbon–carbon bond in (*S*)-(+)-**2** from the less hindered diastereotopic face occupied by the lone pair of electrons on sulfur (top-face attack). The bottom-face attack of a sulfur ylide is much less probable owing to steric hindrance exerted by the *p*-tolyl group and substituents on phosphorus.



Scheme 4

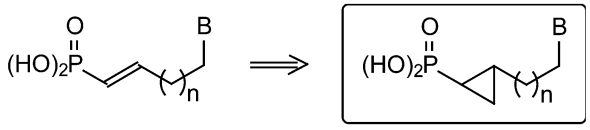
It should be stressed that this model predicts the generation of a new stereogenic α-carbon atom in the cyclopropane ring with the *S* absolute configuration. This was found to be the case for the cyclopropane **3c** (X-ray determination) [8].

The asymmetric cyclopropanation of optically active 1-phosphorylvinyl sulfoxides **2** presented above paved the way to constrained analogs of bioactive compounds. In this context, it should be

pointed out that the design and synthesis of conformationally constrained analogs of bioactive compounds has recently been an important strategy in modern drug discovery [10,11].

ASYMMETRIC SYNTHESIS OF CYCLOPROPYLPHOSPHONATE ANALOGS OF NUCLEOTIDES

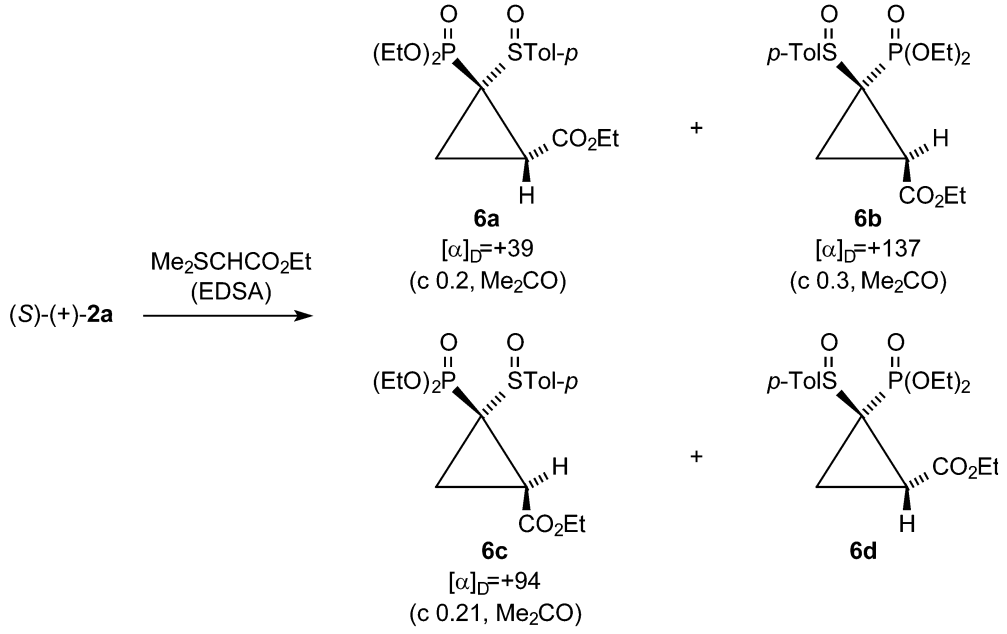
Acyclic nucleotide analogs incorporating the alkenylphosphonic acid group as a phospho-sugar mimic appeared to have great potential for being effective antiviral agents [11]. Since cyclopropyl analogs of nucleotides may be considered as the constrained forms of 1-alkenylphosphonic acid derivatives of purines (see Scheme 5), we decided to synthesize them in enantiomerically pure form utilizing the asymmetric cyclopropanation method discussed above.



B = nucleic acid base

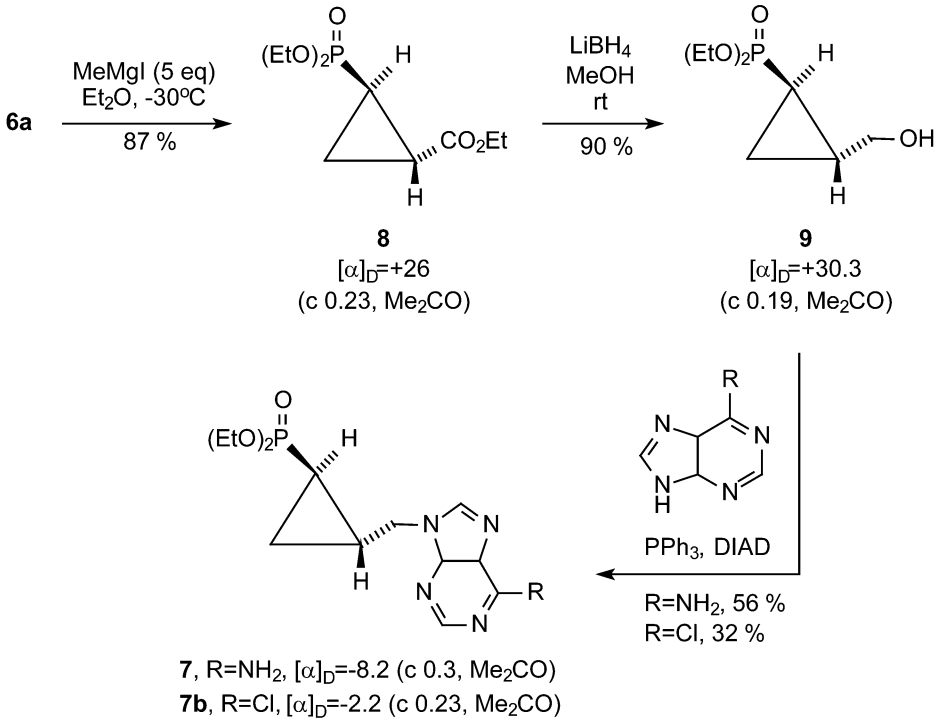
Scheme 5

The reaction of (*S*)-(+)-**2a** with (dimethylsulfuranylidene)acetate (EDSA) gave the corresponding cyclopropane **6** as a mixture of four diastereomers. For example, the reaction with EDSA generated in situ from dimethyl(ethoxycarbonylmethyl)sulfonium bromide in the presence of 1,5-diazabicyclo[5.4.0]undecene-5 (DBU) in toluene afforded in 95 % yield the diastereomeric cyclopropanes **6a**–**d** in a 36:3:12:1 ratio. Also in this case, a high facial stereoselectivity (12:1) was observed. Three dominant diastereomers, **6a**–**c**, were isolated and fully characterized. Moreover, based on spectroscopic NMR analysis and the transition-state model for asymmetric cyclopropanantion of (*S*)-(+)-**2a** the relative and absolute configuration to the cyclopropyl ring in **6a**–**d** have been assigned (Scheme 6).



Scheme 6

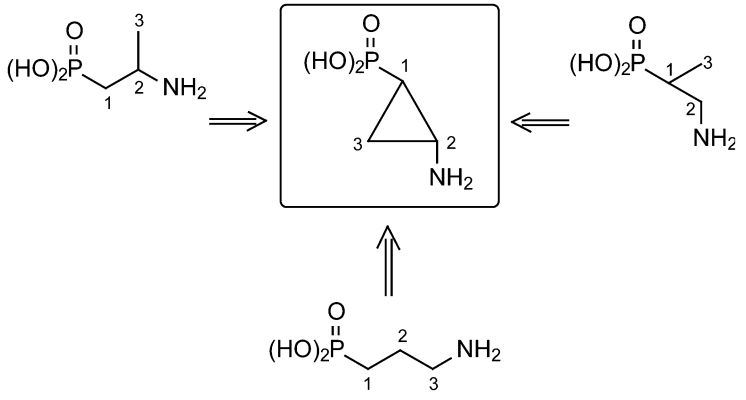
The major diastereomer **6a** was converted in three simple steps involving the fully stereoretentive reaction with Grignard reagent, reduction of the carboethoxy group and Mitsunobu reaction into the desired enantiopure cyclopropylphosphonate analogs of purine nucleotides **7** in reasonably good yields (Scheme 7) [13].



Scheme 7

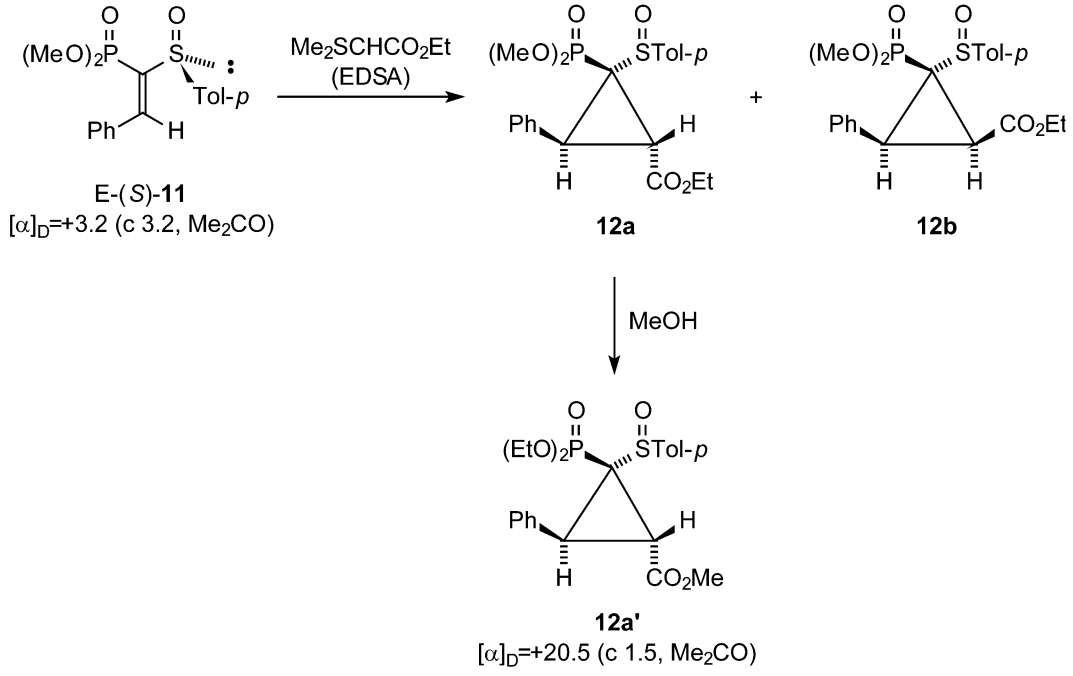
ASYMMETRIC SYNTHESIS OF CONSTRAINED ANALOG OF PHACLOFEN: 2-AMINO-3-PHENYL-1-CYCLOPROPANEPHOSPHONIC ACID

In accord with the concept of conformational constraints, 2-aminocyclopropanephosphonic acids are conformationally constrained analogs of 2- and 3-aminophosphonic acids as schematically depicted in Scheme 8.



Scheme 8

To further demonstrate utility of our cyclopropanation methodology, we decided to synthesize the enantiopure 2-amino-3-phenyl-1-cyclopropanephosphonic acid **10**, which is a constrained analog of the $GABA_B$ antagonist, phaclofen [14]. Thus, E-(*S*)-(1-dimethoxyphosphoryl-2-phenyl)vinyl *p*-tolyl sulfoxide **11** was found to undergo cyclopropanation with EDSA in a highly diastereoselective manner affording instead of eight only two diastereomeric cyclopropanes **12a** and **12b** in an 8:1 ratio. The absolute configuration (S_S,1*S*,2*R*,3*R*) has been assigned to the isolated, major diastereomer **12a**. For synthetic purposes, the latter was converted into the corresponding methyl ester **12a'** (Scheme 9).



E-(*S*)-**11**
$[\alpha]_D$=+3.2 (c 3.2, Me_2CO)

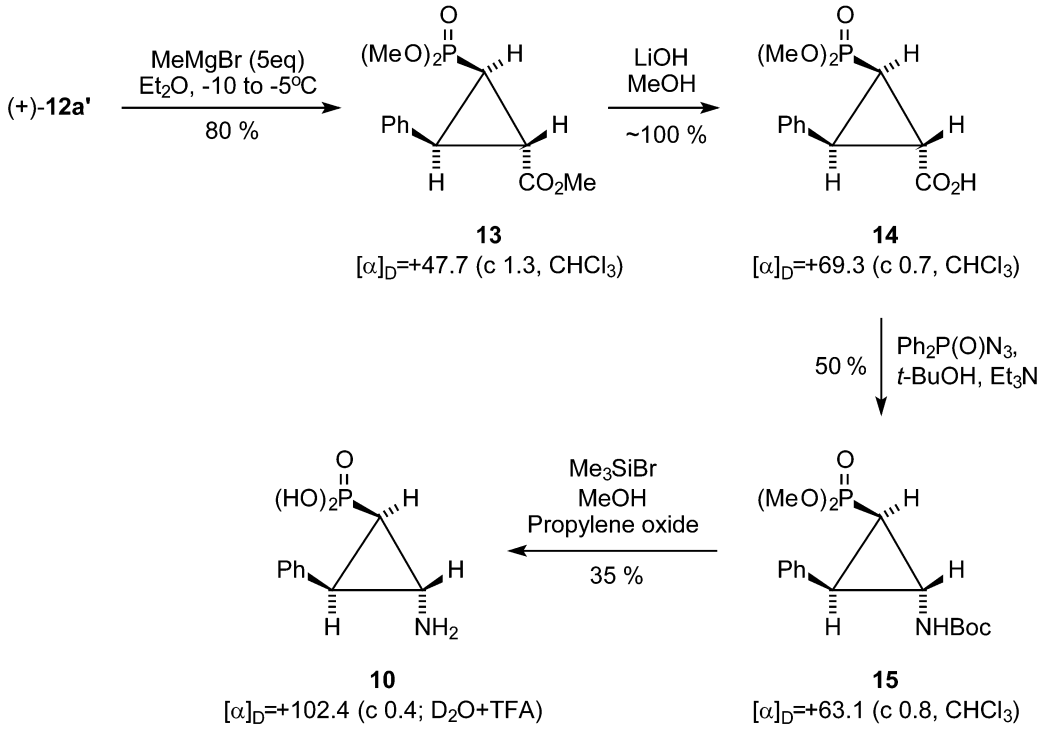
12a **12b**

12a'
$[\alpha]_D$=+20.5 (c 1.5, Me_2CO)

Scheme 9

Starting from the cyclopropane (+)-**12a'**, we could achieve our goal, i.e., the synthesis of **10**, a constrained analog of phaclofen. The desulfinylation of **12a'** has been performed as in the previous case by treatment with methylmagnesium bromide. In the next step, the ester group in the cyclopropane (+)-**13** obtained was hydrolyzed to the carboxylic acid (+)-**14**, which, under modified Curtius reaction conditions, was converted into the N-Boc-protected aminophosphonate (+)-**15**. In the last step of the synthesis under discussion, deprotection of the amino and phosphonate functions afforded the enantiomerically pure (+)-(2*R*)-amino-(3*R*)-phenyl-(1*R*)-cyclopropanephosphonic acid **10** (Scheme 10).

It is interesting to point out that our asymmetric synthesis resulted in the formation of the dextrorotatory enantiomer and is complementary to the asymmetric synthesis of the levorotatory **10** described by Hanessian and coworkers [15].



Scheme 10

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