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The Synthesis of Enantiomerically Pure, Symmetrically Substituted Cyclopropane Phosphonic Acids - A Constrained Analog of the GABA Antagonist Phaclophen

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Abstract: The stereocontrolled conjugate addition of anions derived from chiral α-chlorophosphonamides to α,β-unsaturated esters leads to the corresponding 3-chloro ester adducts which undergo intramolecular expulsion of the chlorine atom to give the corresponding cyclopropanes.

Phosphonic acids play an important role in medicinal chemistry,[1] in agrochemistry[2] and in other areas of chemical interest.[3] For example they are reported to show inhibitory properties towards ESPS synthase,[4] to have antiviral activity,[5] and they also exhibit fungicidal[6] and antibacterial[7] properties. In many instances, phosphonic acids are surrogates for the corresponding carboxylic acids[8] and phosphates,[9] thus avoiding problems associated with metabolic instability. The synthesis of amino phosphonic acids has been of interest in connection with the mimicry of the corresponding amino acids.[10] Since the isolation of 2-aminopropyl phosphonic acid from *ciliate protozoa*[11] and other organisms, there has been much interest in the synthesis of 2- and 3-aminoalkyl phosphonic acids.[12] These have been traditionally obtained by resolution,[13] although some stereoselective syntheses have been devised.[14]

A common practice in the quest for pharmacologically active compounds is the synthesis of conformationally constrained analogs of structures that have proven activity. In this regard, the asymmetric synthesis of constrained phosphonopropionates[15] and aminophosphonic acids[16] in the form of methano analogs presents a challenging area of research.

We report in this Letter the stereocontrolled synthesis of 1,2,3-trisubstituted cyclopropane phosphonic acids utilizing a method that capitalizes on the highly diastereofacial addition of the anion of an α-chloromethylphosphonamide[17] to an α,β-unsaturated ester as shown in Scheme 1. The intermediate γ-chlorophosphonamide esters undergo intramolecular displacement by the incipient enolate to give the corresponding cyclopropanes. Table 1 lists the results of such additions which generally proceeded in preparatively acceptable yields, and with excellent diastereoselectivities. The major or exclusive products had an absolute stereochemistry related to isomer A, as conclusively established by single crystal X-ray analysis in no less than three examples. Although the results in the case of the *t*-butyl acrylate were disappointing, it can be seen that progressive substitution of the β-carbon atom of the *t*-butyl ester with a larger and/or electron withdrawing group had a beneficial effect on the diastereoselectivity of the reaction without affecting the yield. In the case of *t*-butyl sorbate, considerable unreacted starting material remained, which reflects on the diminished reactivity of the ester. Indeed, when the yellow colored reaction mixture was quenched with benzyl

bromide, the α-benzylated α-chloro phosphonamide[17a] was isolated, indicating that the anion was still intact to some extent. The cyclopropanation reaction is of interest from a practical standpoint since several of the major (and even minor) products were crystalline and could be obtained as single isomers. As pointed out before,[18] the *t*-butyl esters proved to afford the best diastereoselectivity among other esters studied.

Scheme 1

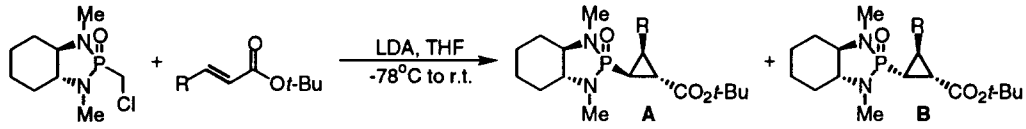


Table 1. Diastereoselective Synthesis of Cyclopropane Phosphonic Acids

Entry	R	Yield[a]	ratio (A:B)[b]	m.p. (°C)	$[\alpha]_D$[c] major isomer	Absolute Stereochemistry
1	H	49 %	1.5 : 1[d]		---	
2	Me[e]	70 %	5 : 2	oil	- 8.9°	X-Ray of **B**
3	*i*-Pr	78 %	21: 1	73-75	-11.9°	X-Ray of **A**
4	cyclohexyl	80 %	60 : 1	121-122	-32.9°	
5	2,4-difluorophenyl	70 %	19 : 1	123-124	-65.0°	
6	trimethylsilyl	75 %	10 : 1	81-82	+ 0.8°	X-Ray of **A**
7	Me-CH=CH	46 %[f]	Single isomer (**A**)	oil	-25.8°	
8	Ph	72 %	Single isomer (**A**)	140-141	-99.0°	X-Ray of **A**

a) Yield of isolated product after chromatography; b) determined by ^{31}P NMR on the crude mixture; c) sample concentration, 1 in $CHCl_3$; d) diastereoisomers were not separable; e) 1.6 equiv. LTMP; f) based on recovered starting material (isolated yield 31%).

Although the addition reaction was highly diastereoselective, the stereochemistry of the products at the α-phosphonamide carbon was found to be opposite to that expected from previous results and predictions.[17a] Thus, engaging the anion of the (*R,R*)-α-chlorophosphonamide in a conjugate addition reaction with α,β-unsaturated esters led to isomer A as the major product, rather than isomer B (Scheme 1). A reversal of this type was observed in another instance where coordination of a heteroatom on the α-alkyl chain with the lithium cation and the phosphoryl group caused a "flip" in the orientation of the alkyl group, which altered the sense of the attack on the electrophile.[14c]

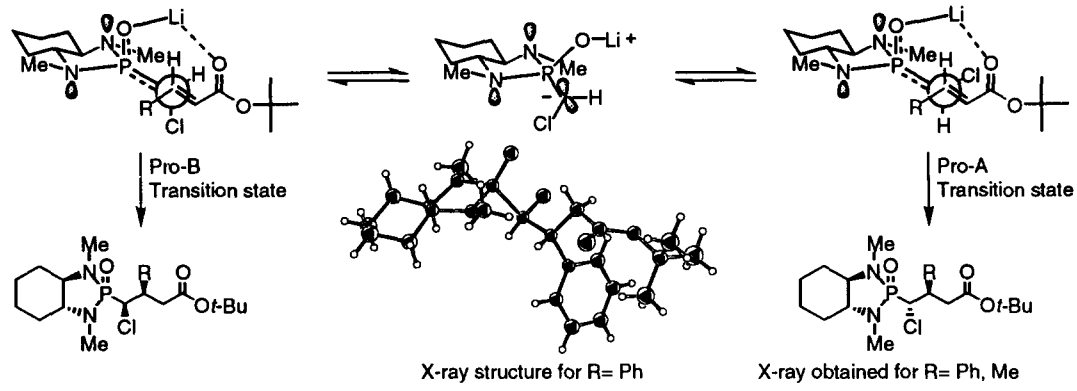
In the present case, attack takes place by an approach of the coordinated enoate in its *s*-cis conformation[19] from the left cleft of the reagent as usual.[18] However, as the steric bulk and/or electronic nature of the β-substituent changes from hydrogen to methyl to phenyl (Table 1, entries 1, 2, 8), increasing repulsive forces with the chlorine atom cause a rotation about the P-C bond,[20] exposing the alternative α-chlorocarbanion rotamer (Scheme 2). Thus in the case of the *t*-butyl acrylate and *t*-butyl methacrylate, the difference in energies between transition states corresponding to pro-A and pro-B may not be significant, and both products A and B are formed, albeit in favor of A in the case of the methacrylate (5:2 ratio, entry 2).

Following this argument it is clear why the larger and more electronically demanding groups such as in entries 3-8, favor the formation of isomer A. It is also possible that the pro-A transition state is stabilized by coordination of the lithium to the electronegative chlorine atom.[21] Energy barriers to attain the antiperiplanar orientation for the ejection of the chlorine atom in the enolate may be lower in transition state pro-A.

We were able to substantiate the nature of the initial adduct with the isolation and X-ray characterization of the α-chloro precursor in a number of cases (Scheme 2). In an effort to explore the influence of the geometry of the α,β-unsaturated ester, we attempted an addition with (*Z*)-*t*-butyl cinnamate. To our surprise,

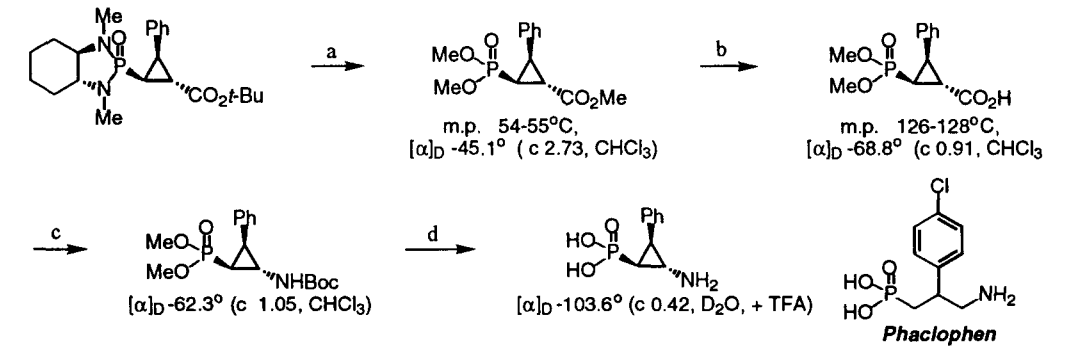
only starting materials were recovered, which may be explained by unfavorable interactions in the transition state.

Scheme 2



The ready availability of the trisubstituted cyclopropanes listed in Table 1, compelled us to consider the synthesis of constrained analogs of 2-aminocyclopropyl phosphonic acids. We chose the phenyl substituted analog because of its similarity to the well known GABA antagonist phaclophen.[22] Thus, the phosphonamide and *t*-butyl ester groups were hydrolyzed to the corresponding acid which was esterified, then subjected to a highly selective cleavage of the methyl ester in the presence of the dimethylphosphonate moiety (Scheme 3). We adopted a modified protocol[23] for the Curtius reaction which called for the isolation of the corresponding acyl azide thereby improving the yields over the conventional procedure.[24] Subsequent treatment with *t*-butanol led to the desired N-Boc derivative in 55% yield. The free (2*S*)-amino-(3*S*)-phenyl-(1*S*)-cyclopropane phosphonic acid was then isolated after hydrolysis with TMS bromide.[25]

Scheme 3



a.1. 1 N HCl, o/n 2.TMSCHN$_2$, MeOH, 0°C to r.t., 1 h., 75%; b. LiOH, MeOH/H$_2$O , 0°C, o.n., quant. c. 1. DPPA, PhMe, 45 min. 2. *t*-BuOH, 100°C, 48 h. 55%; d. 1. 6 eq. TMSBr, CH_2Cl_2, 24 h. 2. 1% aq. MeOH 3. propylene oxide, MeOH, 24 h. 31% after recrystallization.

In summary, we have developed efficient and stereocontrolled syntheses of enantiopure 3-phenyl cyclopropane 2-amino phosphonic acid, as well as the phosphono equivalents of methano succinic acids utilizing phosphonamide anion technology.[17,18] These products, and their derivatives, are useful probes for a number of enzymatic and receptor-based assays with promising therapeutic potential.[26] Results pertaining to these will be reported in due course.

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