Lewis Acid-Promoted [2 + 1] Cycloaddition Reactions of a 1-Seleno-2-silylethene to 2-Phosphonoacrylates: Stereoselective Synthesis of a Novel Functionalized α-Aminocyclopropanephosphonic Acid

Shoko Yamazaki,* Takashi Takada, Tomomi Imanishi, Yumiko Moriguchi, and Shinichi Yamabe

Department of Chemistry, Nara University of Education, Takabatake-cho, Nara 630-8258, Japan

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Stereoselective $SnCl_4$-promoted [2 + 1] cycloaddition reactions of 1-seleno-2-silylethene **1** with 2-phosphonoacrylates **2** lead to highly functionalized cyclopropanephosphonate esters **3** in high yields. The cyclopropane products **3** are potentially versatile starting materials for biologically important compounds. Stereoselective synthesis of a novel functionalized α-aminophosphonic acid derivative, an analogue of (*Z*)-2,3-methanohomoserine **13**, from the cycloadduct **3b** was achieved. Stereoselectivity in the [2 + 1] cycloaddition was explained by consideration of the structure of the **2**−$SnCl_4$ complex.

Introduction

Cyclopropane derivatives play an important role in biological activity[1] and synthetic chemistry.[2] Furthermore, they also function as conformationally constrained amino acid analogues[3] and mechanistic probes to determine reaction pathways.[4] In this regard, development of novel methods of cyclopropanation presents a challenging area of research in current organic chemistry.[5] We have recently reported a novel [2 + 1] cycloaddition strategy involving reaction of (*E*)-1-phenylseleno-2-silylethenes with electrophilic olefins, to afford cyclopropane products with high stereoselectivity in the presence of Lewis acids.[6] This new approach to cyclopropane construction is based on a selenium-stabilized 1,2-silicon migration process that does not occur with the corresponding sulfur analogues.

To enhance the synthetic potential of this [2 + 1] cycloaddition reaction, we are investigating a wide variety of substrates. As part of this effort, electrophilic olefins containing synthetically and potentially biologically useful phosphonate groups were chosen as attractive substrates.[7,8] 2-Phosphonoacrylates **2** were predicted to have high reactivity toward 1-seleno-2-silylethene **1**, since they are isoelectronic analogues of methylenemalonate esters, which have been proven to have effective reactivity toward **1**.[6b] The expected cyclopropanephosphonate ester products are potentially versatile starting materials to access biologically important compounds. For example, α-aminocyclopropanephosphonic acids are of biological interest, in connection with the mimicry of the corresponding amino acids. Although synthesis of the unsubstituted α-aminocyclopropanephosphonic acid has been reported,[9] no general synthetic methods for 2-substituted 1-amino-1-cyclopropanephosphonic acids have appeared yet, probably because suitable starting materials are not readily available in the frame of existing methodology. We now wish to disclose the highly efficient [2 + 1] cycloaddition of 1-seleno-2-silylethene **1** to 2-phosphonoacrylates **2a**−**f** leading to the cyclopropanes **3**[10] and the stereoselective synthesis of a new functionalized α-aminocyclopropanephosphonic acid by transformation of adduct **3b**. In particular, the electro-

(1) For reviews, see: (a) Salaün, J.; Baird, M. S. *Curr. Med. Chem.* **1995**, *2*, 511. (b) Liu, H. W.; Walsh, C. T. Biochemistry of the Cyclopropyl Group. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: New York, 1987; p 959. (c) Elliott, M.; Janes, N. F. *Chem. Soc. Rev.* **1978**, *7*, 473. For recent papers, see: (d) Yoshida, M.; Ezaki, M.; Hashimoto, M.; Yamashita, M.; Shigematsu, N.; Okuhara, M.; Kohsaka, M.; Horikoshi, K. *J. Antibiot.* **1990**, *43*, 748. (e) Kuo, M. S.; Zielinski, R. J.; Cialdella, J. I.; Marschke, C. K.; Dupuis, M. J.; Li, G. P.; Kloosterman, D. A.; Spilman, C. H.; Marshall, V. P. *J. Am. Chem. Soc.* **1995**, *117*, 10629. (f) Gerwick, W. H.; Proteau, P. J.; Nagle, D. G.; Hamel, E.; Blokhin, A.; Slate, D. L. *J. Org. Chem.* **1994**, *59*, 1243. (g) Niwa, H.; Wakamatsu, K.; Yamada, K. *Tetrahedron Lett.* **1989**, *30*, 4543. Kigoshi, H.; Niwa, H.; Yamada, K.; Stout, T. J.; Clardy, J. *Tetrahedron Lett.* **1991**, *32*, 2427. (h) Baertschi, S. W.; Brash, A. R.; Harris, T. M. *J. Am. Chem. Soc.* **1989**, *111*, 5003.

(2) For reviews, see: (a) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165. (b) Goldschmidt, Z.; Crammer, B. *Chem. Soc. Rev.* **1988**, *17*, 229. (c) Paquette, L. A. *Chem. Rev.* **1986**, *86*, 733. (d) de Meijere, A.; Wessjohann, L. *Synlett* **1990**, 20. (e) Trost, B. M. In *Strain and its implications in Organic Chemistry*; de Meijere, A.; Blechert, S., Eds.; Kluwer: Dordrecht, 1989; p 1.

(3) (a) Stammer, C. H. *Tetrahedron* **1990**, *46*, 2231. (b) Burgess, K.; Ho, K.-K.; Pettitt, B. M. *J. Am. Chem. Soc.* **1995**, *117*, 54.

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(5) For reviews, see: (a) *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; John Wiley and Sons: New York, 1987. (b) *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; John Wiley and Sons: New York, 1995; Vol. 2. (c) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Ed.; Pergamon: Oxford, 1991; Vol. 4, pp 951−1067. (d) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (e) Brookhart, M.; Studabaker, W. B. *Chem. Rev.* **1987**, *87*, 411.

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(7) (a) Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73. (b) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(8) For reviews, see: (a) Engle, R. *Chem. Rev.* **1977**, *77*, 349. (b) Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *63*, 193. (c) Kukhar′, V. P.; Svistunova, N. Y.; Soloshonok, V. A. *Russ. Chem. Rev.* **1993**, *62*, 261.

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Table 1. [2 + 1] Cycloadditions of 1 with 2-Phosphonoacrylates (2)[a] in (Eq 2)

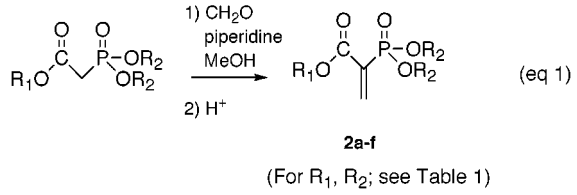
entry	2-phosphonoacrylate	R_1	R_2	time/h	product (yield/%)
1	**2a**	Me	Me	3	**3a** (96)
2	**2b**	Et	Et	6	**3b** (95)
3	**2c**	*t*-Bu	Me	4	**3c** (52)
4	**2d**	CH_2CH_2TMS	Et	4	**3d** (66)[b]
5	**2e**	Et	*i*Pr	4	**3e** (85)[c]
6	**2f**	(*l*)-menthyl	Me	4	**3f** (70)[d]

[a] Reactions were carried out at −78 °C at ∼0.4 M for **1** in CH_2Cl_2. [b] 18% recovered **1**. [c] 14% recovered **1**. [d] 12% recovered **1**.

philic character of **2** has been investigated in detail. In the synthetic transformations, a selenosilylmethyl group in **3b** is employed as aldehyde equivalent via sila-Pummerer rearrangement and a classical Hofmann rearrangement is also used for introduction of an amino group into the α-aminophosphonic acid.

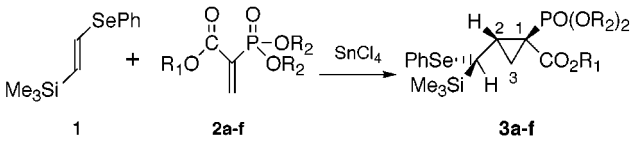
A. [2 + 1] Cycloaddition with 2-Phosphonoacrylates

2-Phosphonoacrylates **2b**−**f** were prepared according to precedented literature procedures from the corresponding phosphonoacetates (eq 1).[11] Table 1 summarizes the [2 + 1] cycloaddition reactions of **1** and **2** (eq 2).



2a-f

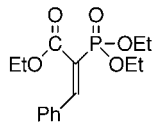
(For R_1, R_2; see Table 1)



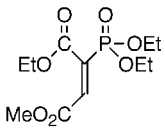
1 **2a-f** **3a-f**

(eq 2)

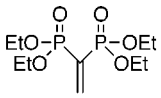
Reaction of **1** (1 equiv) and 2-phosphonoacrylates **2a**−**f** (1.3 equiv) was carried out in the presence of $SnCl_4$ (1.5 equiv) in CH_2Cl_2 at −78 °C for 3−6 h. Quenching with triethylamine (2.6 equiv) gave [2 + 1] cycloadducts **3a**−**f** as single stereoisomeric products in high yields. The increase of the steric bulk in the carboxylate moiety (R_1) resulted in somewhat lower yields, although sterically demanding phosphonate ester groups (R_2) appear to have less effect of the overall yield (entries 3, 5). The ready formation of cyclopropanes bearing *tert*-butyl and trimethylsilylethyl protected carboxyl groups **3c** and **3d** provides suitable handles for further synthetic transformations. No reaction occurred between the donor olefin **1** and the 3-substituted 2-phosphonoacrylates **4**[12] and **5** under these reaction conditions, suggesting steric limitations in the acceptor moiety. We also attempted the reaction of **1** with tetraethyl ethenylidenebis(phosphonate) (**6**)[13] under similar conditions; however, the reaction did not proceed and no cycloadduct was obtained. The carbonyl group of **2** thus seems to exert an important role in this [2 + 1] cycloaddition reaction.



4

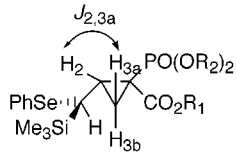


5



6

The structure of the cyclopropane skeleton of **3a** was readily confirmed by the characteristic $^1J_{CH}$ values present in the ^{13}C NMR spectrum (J = 167 (C_2) and 166 (C_3) Hz).[14] Cyclopropanes **3a**−**f** are all single stereoisomers. A NOE cross peak in the 2D-NOESY spectrum, between H_2 and H_{3a}, and the absence of a NOE cross peak between H_2 and H_{3b} in cyclopropanes **3a**, **3c**, and **3f** indicated that the CO_2R_1 and CH(SePh)($SiMe_3$) groups were cis (Figure 1).[15] The stereochemistry of the other cyclopropane products **3b**, **3d**, and **3e** was also assigned as cis from the observed vicinal coupling constants $J_{2,3a}$. The coupling constants of vicinal protons in cyclopropane rings are characteristic of the stereochemistry, and the J values are in the region of cis-vicinal protons (8.9−9.2 Hz for **3a**−**f**).[16]



	$J_{2,3a}$/Hz	$J_{2,3b}$/Hz
3a:	9.0	7.7
3b:	9.2	7.3
3c:	9.0	7.6
3d:	9.1	7.6
3e:	9.0	7.4
3f:	8.9	not determined

The stereochemical outcome of the products may be explained in terms of a Se- - -C_4=O secondary orbital interaction in the first synclinal addition step, as illustrated in Scheme 1.[6] Thus, initially a complex of **2** with $SnCl_4$ is formed, which is then attacked by the selenosilyl nucleophile **1**. Synclinal stereoselective addition (due to a stabilizing secondary orbital interaction, Se- - -C=O, not Se- - -$PO(OR_2)_2$) may cause the observed cis-selectivity regarding CO_2R_1 and CH(SePh)($SiMe_3$) groups. Subsequent 1,2-silicon migration from the first produced zwitterion **X** leads to the second intermediate **Y**. This is followed by generation of a selenium-bridged intermediate **Z** by minimum motion; ring closure then affords cyclopropane **3**. Thus, single-bond rotation of C_1−C_3 as well as C_2−C_3 rotation in **Z** must be a slower process than ring closure. Since the stereochemistry of the original synclinal addition step is retained throughout

(11) **2a** was purchased from Aldrich. (a) Taylor, E. C.; Davies, H. M. L. *J. Org. Chem.* **1986**, *51*, 1537. (b)McIntosh, J. M.; Sieler, R. A. *Can. J. Chem.* **1978**, *56*, 226.

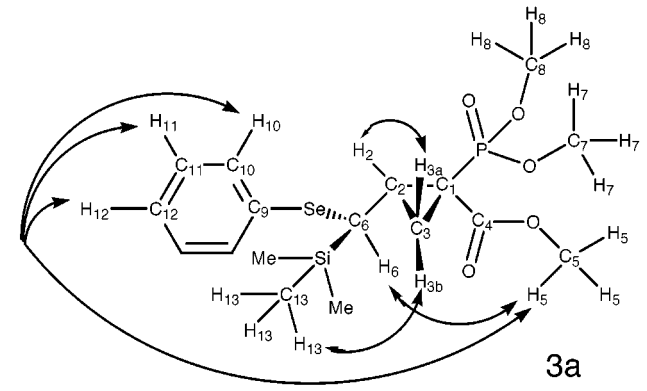
(12) **4** was prepared according to the literature method.[11] The stereochemistry of **4** was assigned as *E* (ca. 90%>). See: (a) Reetz, M. T.; Peter, R.; von Itzstein, M. *Chem. Ber.* **1987**, *120*, 121. (b) Sainz-Díaz, C. I.; Gálvez-Ruano, E.; Hernández-Laguna, A.; Bellanato, J. *J. Org. Chem.* **1995**, *60*, 74.

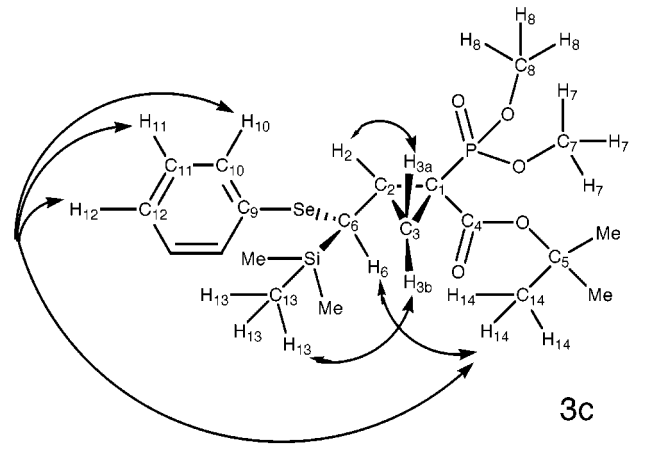
(13) Degenhardt, C. R.; Burdsall, D. C. *J. Org. Chem.* **1986**, *51*, 3488.

(14) Stothers, J. B. *Carbon-13 NMR Spectroscopy*; Academic: New York, 1972.

(15) The relative configuration at C_2 and C_6 was deduced as (*R, R*) or (*S, S*) assuming the same stereochemical course as previously discussed.[6a,b] For **3a** and **3c**, the combination of large vicinal coupling constants ($J_{2,6}$ = 12.5 Hz for **3a**/12.7 Hz for **3c**), which indicate that ∠H_2−C_2−C_6−H_6 is close to 180°, and the observed NOEs (H_{3b}−H_{13}, H_5−H_{10} for **3a**/H_{14}−H_{10} for **3c**, and H_5−$H_{11,12}$ for **3a**/H_{14}−$H_{11,12}$ for **3c**) supports the above assumption.[6b]

(16) (a) Williamson, K. L.; Lanford, C. A.; Nicholson, C. R. *J. Am. Chem. Soc.* **1964**, *86*, 762. (b) Gey, C.; Perraud, R.; Pierre, J. L.; Cousse, H.; Dussourd D′Hinterland, L.; Mouzin, G. *Org. Magn. Reson.* **1977**, *10*, 75. (c) White, J. D.; Jensen, M. S. *J. Am. Chem. Soc.* **1995**, *117*, 6224.





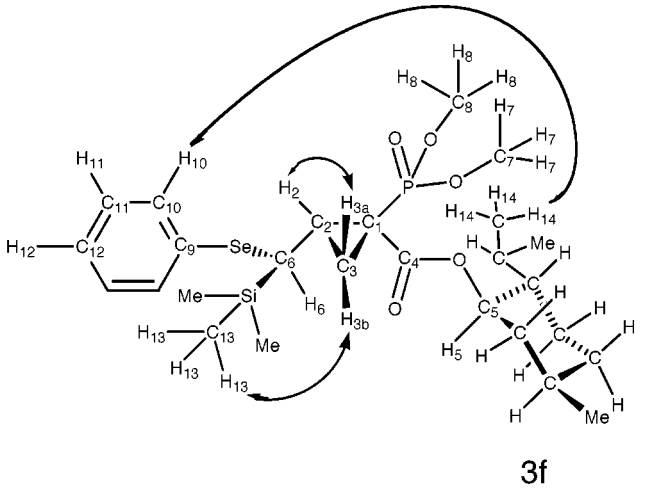


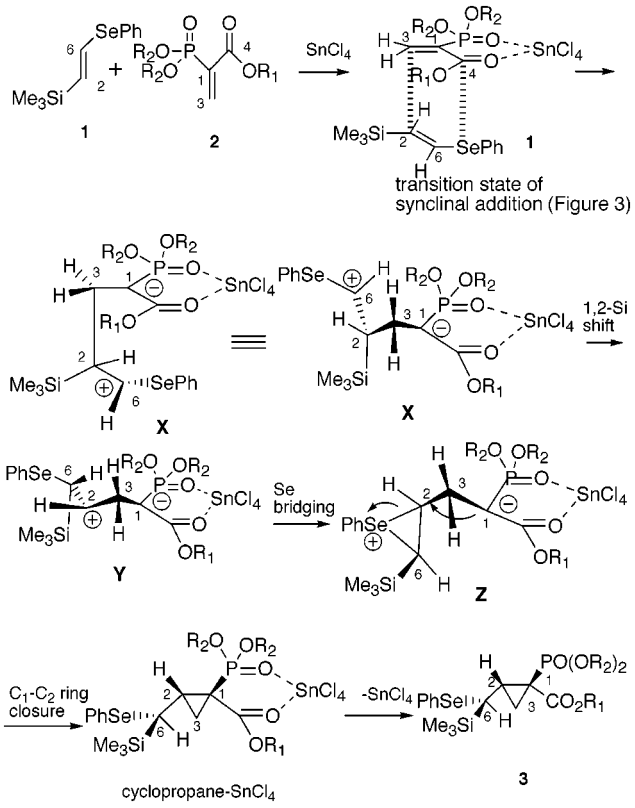
Figure 1. Selected NOEs in the 2D-NOESY spectrum for **3a**, **3c**, and **3f** are indicated. The atom numbering used in the assignment in ref 15 and under Experimental Section is included.

this proposed mechanism, the origin of the observed cis selectivity in **3** arises from a Se−C_4 secondary orbital interaction between **2**−$SnCl_4$ and **1**.

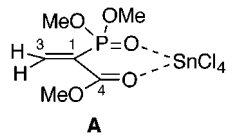
To explain the observed stereochemistry, we have carried out ab initio MO calculations for the possible structures of the complex of **2a** with $SnCl_4$ by using the LANL2MB method.[17] All the ab initio molecular orbital calculations were performed by using Gaussian 94 program packages,[18] and, as a result, the bidentate structure **A** was found to be most stable (Figure 2).[19]

(17) (a) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 270. (b) Wadt, W. R.; Hay, P. J. *J. Chem. Phys.* **1985**, *82*, 284. (c) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299.

Scheme 1. Proposed Reaction Mechanism for Cyclopropanation[a]



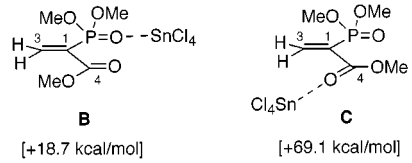
[a] The carbon atom numbering is the same as that in Figure 1.



To investigate the electrophilic sites, the frontier orbital LUMO of the bidentate complex **A** was calculated by STO-3G//LANL2MB. The LUMO shape indicates that the most electrophilic site is the C_3 atom and that the

(18) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. Gaussian *94*, Revision B.1, Gaussian, Inc., Pittsburgh, PA, 1995. MO calculations using Gaussian 94 were made on the CONVEX SPP1200/XA at the Information Processing Center (Nara University of Education).

(19) The geometries of P═O-monocoordinated and C═O-monocoordinated complexes, **B** and **C**, were also optimized, but these species were found to be much less stable than **A** (Figure 2) (in the structure below, energies in square brackets were obtained by ab initio RHF/LANL2MB calculations and are relative ones to that of the complex **A**).



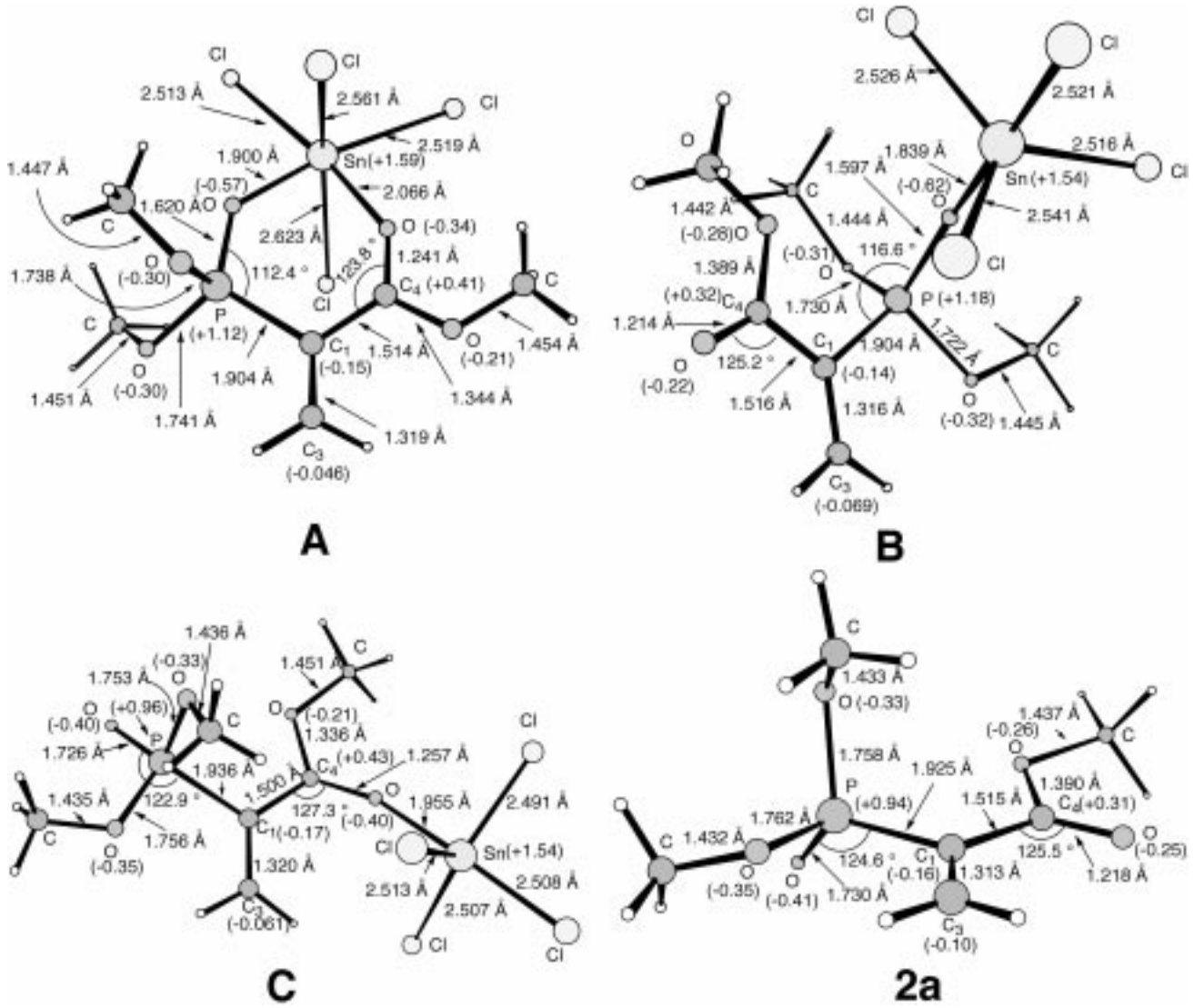


Figure 2. Ab initio RHF/LANL2MB optimized geometries of **A**, **B**, **C**, and **2a**. Numbers in parentheses denote atomic net charges of STO-3G//LANL2MB for **A**, **B**, **C**, and **2a**. Less stable isomers **B** and **C** are described in ref 19.

cofficient of C_4 (−0.558) is larger than that of P (−0.114) (Figure 3). The effective overlap with the HOMO of **1** determines the orientation in the synclinal addition step (Scheme 1). ^{1}H, ^{13}C, and ^{31}P NMR spectra of a **2a**−$SnCl_4$ complex were measured at low temperature (−58 to −63 °C) (Table 2). A solution of **2a** in dichloromethane-d_2 was treated with 1.15 equiv of $SnCl_4$ to form a **2a**−$SnCl_4$ complex. The change in chemical shift of the carbonyl carbon (C_4) in the ^{13}C NMR was +5.8 ppm, which indicates Sn cordination with C═O oxygen. Also, the large downfield shift (144.2 ppm for **2a** and 152.9 ppm for **2a**−$SnCl_4$) of C_3 indicates the significant decrease of electron density on C_3 and the resulting enhanced reactivity as an electrophile. A small change in the chemical shift of the phosphonate P atom (+0.5 ppm) was also observed. Although ^{1}H and ^{13}C NMR studies of Lewis acid carbonyl complexation have been investigated in detail,[20] ^{31}P chemical shift changes by Lewis acid complexation have not been studied systematically.[21,22] The small change in going from **2a** to **2a**−$SnCl_4$ in the ^{31}P chemical shift may be related to the difference in the O═P−C angle between **2a** (124.6 °) and **A** (112.4 °) (see Figure 2). Thus, the difference in angle possibly offsets the ^{31}P downfield shift arising from a decrease in electron density due to P═O−$SnCl_4$ complexation.[23]

Good diastereoselectivity was obtained in the reaction of chiral olefin **2f** (entry 6 in Table 1); no diastereoisomer of **3f** was detected by NMR analysis. To account for the high diastereoselectivity, attack from the *si* face with respect to C_1 (Scheme 2, vide infra) of the $SnCl_4$-coordinated **2f** in the addition step is assumed. The LANL2MB-calculated structure of **2f**−$SnCl_4$ is shown in Figure 4. In Figure 5, the proposed synclinal approaches

(20) (a) Shambayati, S.; Schreiber, S. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, p 283. (b) Childs, R. F.; Mulholland, D. L.; Nixon, A. *Can. J. Chem.* **1982**, *60*, 801.

(21) ^{31}P NMR spectra of $ZnCl_2$-monocoordination to the phosphoryl oxygen of a ketovinylphosphonate was reported and the chemical shift change $\Delta\delta$ was +1.8 ppm. McClure C. K.; Hansen, K. B. *Tetrahedron Lett.* **1996**, *37*, 2149.

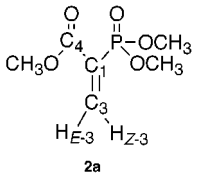
(22) ^{31}P NMR spectra of $SnCl_4$-chelated complex of α-acylphosphonate were shifted 1.1−2.4 ppm downfield of free α-acylphosphonate, while ^{31}P of $SnCl_4$-dimeric complex of α-acylphosphonate [(P═O)$_2$−$SnCl_4$] were shifted 9.67−8.0 ppm upfield. Telan, L. A.; Poon, C.-D.; Evans, S. A., Jr. *J. Org. Chem.* **1996**, *61*, 7455.

(23) (a) Gorenstein, D. G. In *Phosphorus-31 NMR, Principles and Applications*, Gorenstein, D. G., Ed.; Academic Press: London, 1984; p 7. (b) Gorenstein, D. G. *Prog. Nucl. Magn. Reson. Spectrosc.* **1983**, *16*, 1.

Table 2. NMR Chemical Shifts of Methyl 2-Phosphonoacrylate (2a) and 2a−$SnCl_4$[a]

		2a/ppm	**2a**−$SnCl_4$[b]/ppm	$\Delta\delta$[c]/ppm
^{1}H[e]	(*E*)−3[d,g]	6.98, J_{HP} = 42.1 Hz	7.58, J_{HP} = 43.9 Hz	+0.60
	(*Z*)−3[d,g]	6.67, J_{HP} = 20.1 Hz	7.17, J_{HP} = 22.0 Hz	+0.50
	CO_2CH_3	3.71	4.12	+0.41
	$PO(OCH_3)_2$	3.68, J_{HP} = 11.4 Hz	3.97, J_{HP} = 11.9 Hz	+0.29
^{13}C[e]	C_3[d]	144.2	152.9	+8.7
	C_1[d]	129.8, J_{CP} = 187 Hz	121.6, J_{CP} = 196 Hz	−8.2
	C_4[d]	163.0, J_{CP} = 16.8 Hz	168.8	+5.8
	CO_2CH_3	51.7	56.8	+5.1
	$PO(OCH_3)_2$	52.5, J_{CP} = 5.3 Hz	56.2, J_{CP} = 6.1 Hz	+3.7
^{31}P[f]	P	16.7	17.2	+0.5

[a] 0.52 M **2a** in CD_2Cl_2. [b] **2a**−$SnCl_4$ complex was prepared with 1 equiv of **2a** and 1.15 equiv of $SnCl_4$ which was the same as the standard reaction conditions. [c] $\Delta\delta = \delta$(**2a**−$SnCl_4$) − δ(**2a**); positive numbers are downfield shifts. [d] The atom numbering is the same as shown in Scheme 1 and does not follow the IUPAC system. [e] Measured at −58 °C. [f] Measured at −63 °C. [g] The *E*/*Z* stereochemistry of olefin hydrogens was assigned on the basis of the P−H coupling constants.[12]



2a

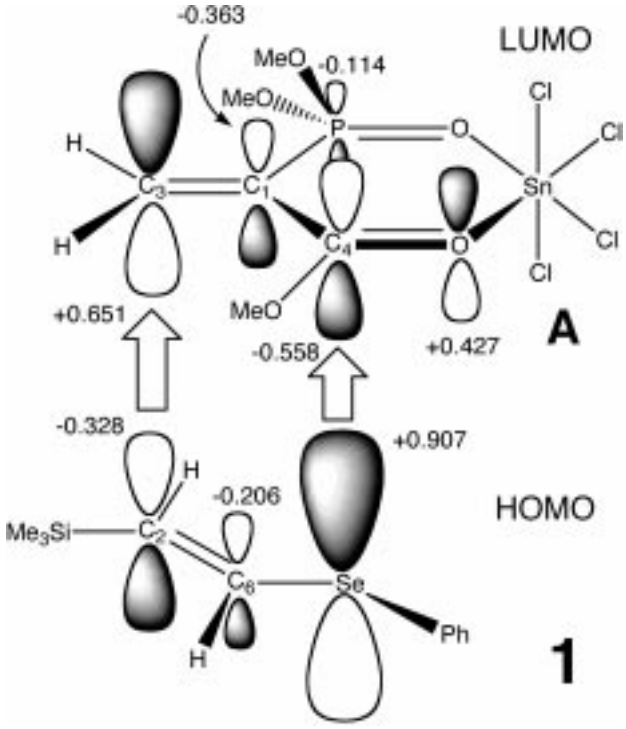
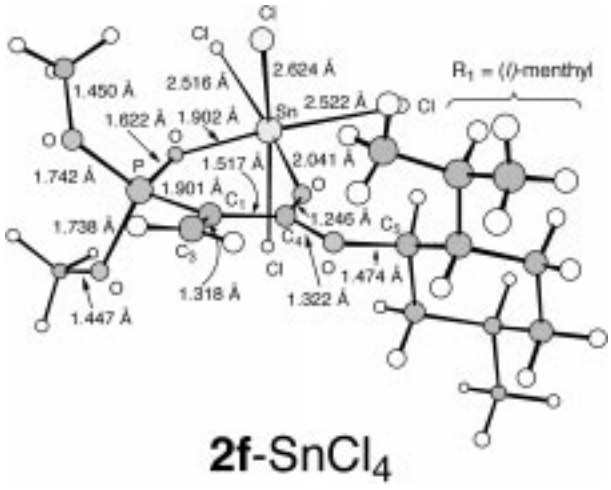


Figure 3. Frontier orbital coefficients of the LUMO of **A** and HOMO of **1**. These coefficients are of STO-3G//LANL2MB.[17,18] Bold upward arrows show the most favorable orbital interaction leading to the synclinal-addition path in Scheme 1.

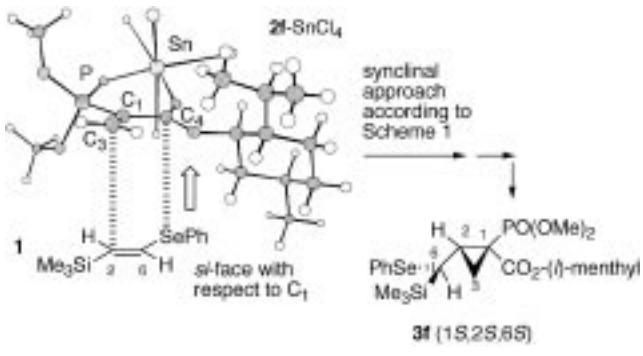
of **1** to **2f**−$SnCl_4$ from the *si* face and *re* face of C_1 are outlined, where C_3- - -C_2 and C_4- - -Se distances are set to ca. 3.0 Å. Approach from the *re* face of C_1 results in the steric repulsion between C_6 and the isopropyl carbon of the menthyl group. This proposed diastereoselection is similar to that observed in asymmetric Diels−Alder reactions involving (*l*)-menthyl acrylates.[24] Thus, attack



2f-$SnCl_4$

Figure 4. Ab initio RHF/LANL2MB optimized geometry of **2f**−$SnCl_4$.

Scheme 2



from the *si* side with respect to C_1 finally leads to (1*S*,2*S*,6*S*)-**3f** according to the mechanism shown in Scheme 1 (vide supra). Experimental determination of the absolute stereochemistry of the product **3f** is currently under way.

This highly efficient [2 + 1] cycloaddition reaction of **1** to 2-phosphonoacrylates **2** may result from the high reactivity of the **2**−$SnCl_4$ complex in the addition step

(24) (a) Katagiri, N.; Haneda, T.; Hayasaka, E.; Watanabe, N.; Kaneko, C. *J. Org. Chem.* **1988**, *53*, 227. (b) Katagiri, N.; Haneda, T.; Watanabe, N.; Hayasaka, E.; Kaneko, C. *Chem. Pharm. Bull.* **1988**, *36*, 3867. (c) Loncharich, R. J.; Schwartz, T. R.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 14.

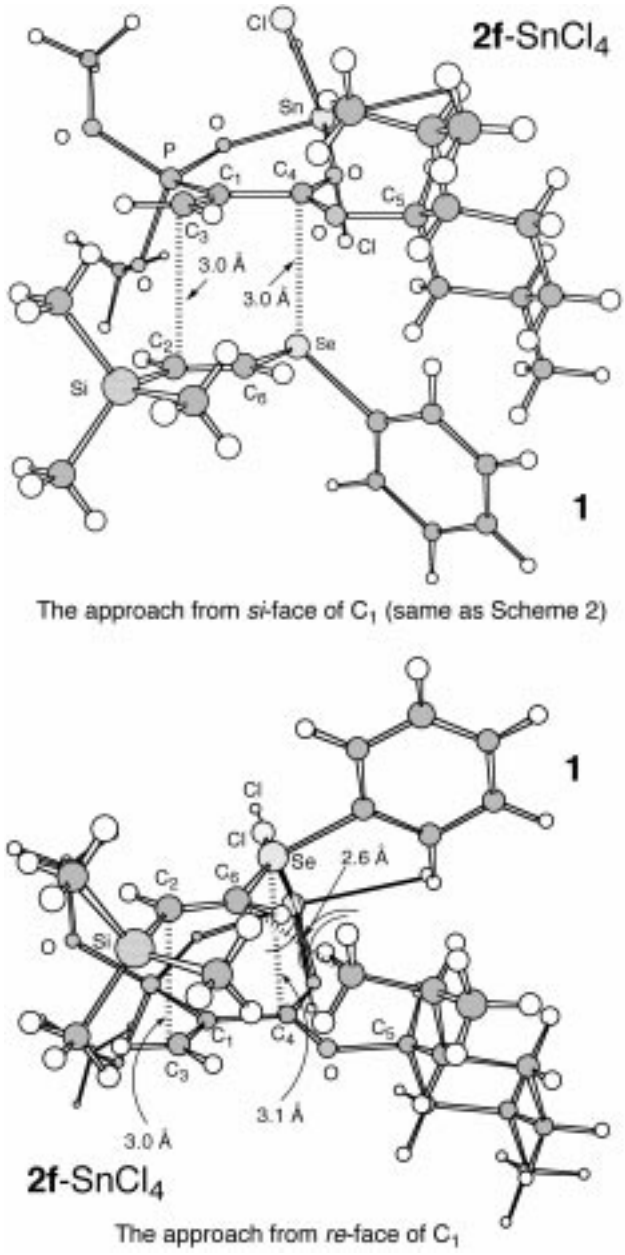
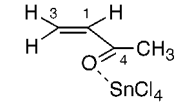


Figure 5. Proposed approaches of **1** to **2f**−$SnCl_4$. For the structure of **1**, RHF/LANL2MB optimized bond lengths and bond angles are used. For the structure of **2f**−$SnCl_4$, RHF/LANL2MB optimized geometry (Figure 4) is used. C_3- - -C_2 and C_4- - -Se distances are set to 3.0−3.1 Å.

(Scheme 1). The higher reactivity of **2**−$SnCl_4$ compared to the corresponding complexes of vinyl ketones with $SnCl_4$, which were originally studied in this [2 + 1] cycloaddition, was examined in terms of both LUMO energy levels and the coefficient of the C_3-carbon where the new C−C bond forms in the LUMO of the electophilic olefin−$SnCl_4$ complex.[25]



methyl vinyl ketone-$SnCl_4$ complex (*s-cis* isomer)

The following frontier orbitals were obtained by STO-3G//LANL2MB.[17,18] The LUMO level of **A** (**2a**−$SnCl_4$) is

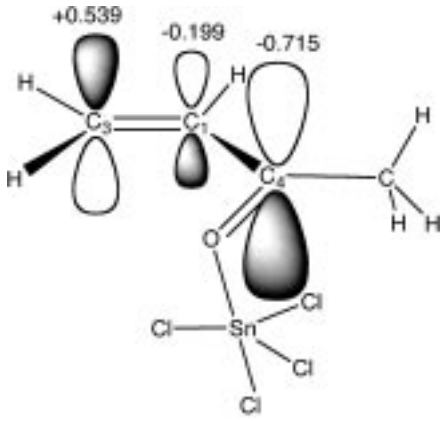


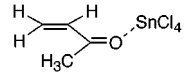
Figure 6. Frontier orbital coefficients of the LUMO of methyl vinyl ketone−$SnCl_4$ complex (s-cis isomer).[25] These coefficients are of STO-3G//LANL2MB.[17,18]

+0.09585 au and that of methyl vinyl ketone−$SnCl_4$ complex (s-cis isomer) is +0.09324 au, which indicates that both complexes have similar LUMO levels and therefore the HOMO−LUMO gaps between **1** (HOMO level, −0.2289 au) and **A** or the methyl vinyl ketone−$SnCl_4$ complex are small enough for efficient reaction. On the other hand, the coefficient of C_3 is 0.651 in **A** (**2a**−$SnCl_4$) and much larger than that in methyl vinyl ketone−$SnCl_4$ complex (0.539) (Figure 6). Thus, the localized coefficient of C_3 seems to contribute to the highly efficient reaction process, and the role of electrophilic olefins **2a**−**f** becomes clearer. In **2**, the phosphonate and carboxylate groups have different functions. The phosphonate group enhances the coefficient of the LUMO at C_3 and accordingly the main (C_2- - -C_3) orbital interaction. On the other hand, the carboxylate group controls the secondary (C_4- - -Se) interaction through the large coefficient of LUMO at C_4. Without the carboxylate group, i.e. the secondary interaction, we could not obtain the [2 + 1] cycloadduct (i.e. from reaction of **1** and **6**). This concept should be useful for the further design of electrophilic olefins in these Lewis acid-mediated reactions.

B. Synthetic Application

In the described [2 + 1] cycloadditions with 2-phosphonoacrylates, the observed chemical yields are very high and the resulting highly functionalized cyclopropanephosphonate ester products are potentially versatile starting materials for biologically important compounds. In this context, synthetic application toward novel aminocyclopropanephosphonic acids, which have attracted much attention recently, was attempted.[9,26] We have

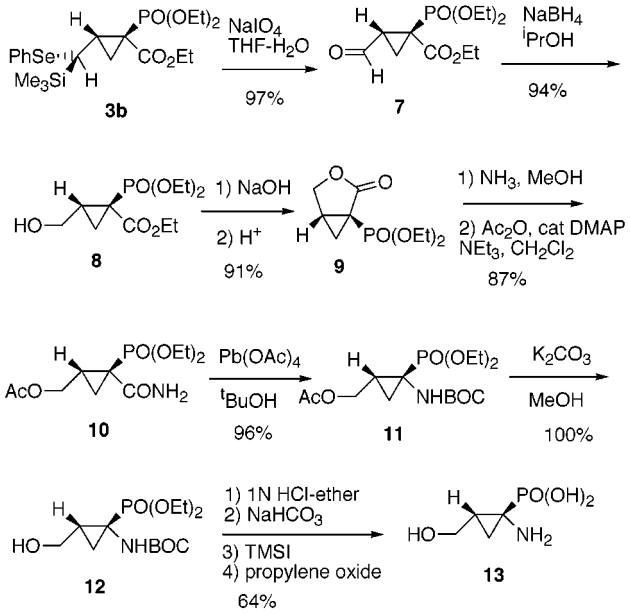
(25) The s-trans isomer of methyl vinyl ketone−$SnCl_4$ complex shown below is 8.7 kcal/mol more unstable than the s-cis isomer by STO-3G//LANL2MB. Therefore, the s-cis isomer is probably the actual electrophile in this reaction.



methyl vinyl ketone-$SnCl_4$ complex (*s-trans* isomer)

(26) (a) Hanessian, S.; Cantin, L.-D.; Roy, S.; Andreotti, D.; Gomtsyan, A. *Tetrahedron Lett.* **1997**, *38*, 1103. (b) Dappen, M. S.; Pellicciari, R.; Natalini, B.; Monahan, J. B.; Chiorri, C.; Cordi, A. A. *J. Med. Chem.* **1991**, *34*, 161. (c) Hanrahan, J. R.; Taylor, P. C.; Errington, W. *J. Chem. Soc., Perkin Trans. 1* **1997**, 493.

Scheme 3. Transformation of the Cycloadduct 3b to α-Aminocyclopropanephosphonic Acid 13



carried out transformation of **3b** to 1-amino-2-(hydroxymethyl)-1-cyclopropanephosphonic acid (Scheme 3). Thus, **3b** was oxidized with $NaIO_4$ in a THF−H_2O solution at room temperature to give the sila-Pummerer product **7** in 97% yield.[27] The aldehyde **7** was then reduced using $NaBH_4$ in 2-propanol to give the alcohol **8** in 94% yield. Hydrolysis of **8** and subsequent acidification provided γ-lactone **9** in 91% yield.[28] The reported synthetic method for (*Z*)-2,3-methanohomoserine was then employed for transformation of **9** to a protected aminocyclopropanephosphonic acid.[29] Treatment of **9** with saturated methanolic ammonia at room temperature and esterification of the resulting alcohol gave amide **10** in 87% yield. Hofmann rearrangement of **10** using lead tetraacetate in refluxing *t*-BuOH gave **11** in 96% yield.[30] Hydrolysis of the acetyl group of **11** gave the alcohol **12** in 100% yield. Deprotection of the *N*-BOC (*N*-*tert*-butoxycarbonyl) group with 1 N HCl in diethyl ether and subsequent deprotection of the phosphonate ester group with iodotrimethylsilane (TMSI) gave 1-amino-2-(hydroxymethyl)-1-cyclopropanephosphonic acid (**13**) in 64% yield. Thus, stereoselective synthesis of **13**, an aminophosphonic acid analogue of (*Z*)-2,3-methanohomoserine,[29] using the cycloadduct **3b** as a starting material was achieved. **13** (and intermediates **11** and **12**) are potential general precursors of a wide variety of (*E*)-2-substituted 1-aminocyclopropanephosphonic acids.

In summary, we have shown that 1-seleno-2-silylethene **1** and 2-phosphonoacrylates **2** undergo $SnCl_4$-promoted [2 + 1] cycloaddition reactions stereoselectively in high yields. The phosphonate and carboxylate groups in **2** provide main and secondary charge accepting sites, respectively. The synthetic application of the cyclopropane products resulting in a novel aminocyclopropane phosphonic acid analogue of (*Z*)-2,3-methanohomoserine was demonstrated. We are currently investigating transformations leading to other aminocyclopropanephosphonic acid derivatives and related biologically interesting compounds. Furthermore, modification of this synthetic approach for asymmetric aminocyclopropanephosphonic acid derivatives utilizing the chiral cyclopropane product **3f** is under way in our laboratory.

Experimental Section

General Methods. Melting points are uncorrected. IR spectra were recorded in the FT-mode. ^{1}H NMR spectra were recorded at 200, 400, 500, or 600 MHz. ^{13}C NMR spectra were recorded at 50.1, 100.6, 125.7, or 150.8 MHz. Chemical shifts are reported in parts per million relative to Me_4Si or residual nondeuterated solvent. ^{13}C chemical shift in D_2O is relative to dioxane as internal reference. ^{31}P NMR spectra were recorded at 161.9 or 202.4 MHz. ^{31}P chemical shifts are relative to 85% H_3PO_4. Mass spectra were recorded at an ionizing voltage of 70 eV by EI or FAB. All reactions were carried out under a nitrogen atmosphere.

Preparation of 2-Phosphonoacrylates. 2-Phosphonoacrylates **2b**−**f** were prepared according to literature procedures from the corresponding phosphonoacetates.[11]

***(l)*-Menthyl 2-(Dimethylphosphono)acrylate (2f).** Paraformaldehyde (1.18 g, 39.2 mmol) was dissolved in methanol (58 mL) containing piperidine (0.116 mL, 1.18 mmol) by refluxing the solution for 0.5 h. (*l*)-Menthyl 2-(dimethylphosphono)acetate (5.73 g, 18.7 mmol) was added and the solution was heated at reflux for 19 h. After evaporation of the methanol, the residue was dissolved in toluene (55 mL). *p*-Toluenesulfonic acid (32 mg, 0.187 mmol) was added and the mixture was refluxed under a Dean−Stark water separator for 8 h. The solvent was removed and the residue purified by column chromatography over silica gel eluting with CH_2Cl_2−ether (1:1) to give **2f** (3.68 g, 68%) (R_f 0.6). **2f**: colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 0.766 (d, J = 6.8 Hz, 3 H), 0.908 (d, J = 7.1 Hz, 3 H), 0.916 (d, J = 6.4 Hz, 3 H), 0.84−1.18 (m, 3 H), 1.39−1.73 (m, 4 H), 1.86−2.10 (m, 2 H), 3.81 (d, J_{HP} = 10 Hz, 6 H), 4.81 (ddd, J = 10.9, 4.4, 4.4 Hz, 1 H), 6.76 (d, J_{HP} = 20.5 Hz, 1 H), 7.12 (d, J_{HP} = 42.5 Hz, 1 H); ^{13}C NMR (50.1 MHz, $CDCl_3$) δ (ppm) 15.11, 19.79, 20.98, 22.30, 24.98, 30.44, 33.19, 39.67, 46.09, 51.96, 74.50, 131.8 (d, J_{CP} = 186 Hz), 142.4, 162.0 (d, J_{CP} = 16 Hz); IR (neat) 2960, 2872, 1721, 1609, 1263 cm^{-1}; MS (EI), *m*/*z* 318; exact mass M^+ 318.1613 (calcd for $C_{15}H_{27}O_5P$ 318.1596); $[\alpha]_D^{16.4}$ −66.8° (*c* = 1.0, $CHCl_3$).

***tert*-Butyl 2-(Dimethylphosphono)acrylate (2c).** Yield 48% (R_f 0.5 (CH_2Cl_2:ether = 2:1)): pale yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.53 (s, 9 H), 3.78 (s, 3 H), 3.84 (s, 3 H), 6.71 (dd, J_{HP} = 20.8 Hz, J_{HH} = 1.7 Hz, 1 H), 7.14 (dd, J_{HP} = 42.7 Hz, J_{HH} = 1.7 Hz, 1 H); ^{13}C NMR (50.1 MHz, $CDCl_3$) δ (ppm) 27.58, 52.63, 52.75, 82.03, 133.2 (d, J_{CP} = 185 Hz), 142.6 (d, J_{CP} = 5.9 Hz), 162.3 (d, J_{CP} = 16 Hz); IR (neat) 2982, 2960, 2856, 1717, 1607, 1259 cm^{-1}; MS (FAB) *m*/*z* 237 (MH^+); Anal. Calcd for $C_9H_{17}O_5P$: C, 45.76; H, 7.35. Found: C, 45.86; H, 7.34.

Isopropyl 2-(Diethylphosphono)acrylate (2e). Yield ca. 67% (including a small amount of impurity) (R_f = 0.6 (CH_2Cl_2:ether = 2:1)): pale yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.29−1.38 (m, 17 H), 4.29 (q, J = 7.1 Hz, 2 H), 4.68−4.85 (m, 2 H), 6.76 (dd, J_{HP} = 20.4 Hz, J_{HH} = 1.9 Hz, 1 H), 6.98 (dd, J_{HP} = 41.8 Hz, J_{HH} = 1.9 Hz, 1 H); ^{13}C NMR (50.1 MHz, $CDCl_3$) δ (ppm) 13.36, 22.94, 23.05, 23.29, 23.34, 60.52, 70.44, 70.56, 133.7 (d, J_{CP} = 186 Hz), 142.0 (d, J_{CP} = 4.4 Hz),

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(28) The synthesis of 3-methyl- and 3,3-dimethylphosphonocyclopropane lactone derivatives was recently reported. Using this method, only trace amounts of 3-unsubstituted derivatives could be obtained. These 3-substituted phosphonocyclopropane lactone derivatives are also promising precursors for 1-aminocyclopropanephosphonic acid derivatives by using the transformations described herein. Töke, L.; Jászay, Z. M.; Petneházy, I.; Clemetis, G.; Vereczkey, G. D.; Kövesdi, I.; Rockenbauer, A.; Kováts, K. *Tetrahedron* **1995**, *51*, 9167.

(29) (a) Pirrung, M. C.; Dunlap, S. E.; Trinks, U. P. *Helv. Chim. Acta* **1989**, *72*, 1301. (b) Aitken, D. J.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1990**, *55*, 2814. (c) Burgess, K.; Ho, K.-K. *J. Org. Chem.* **1992**, *57*, 5931. (d) Koskinen, A. M. P.; Muñoz, L. *J. Org. Chem.* **1993**, *68*, 879.

(30) Baumgarten, H. E.; Staklis, A. *J. Am. Chem. Soc.* **1965**, *87*, 1141.

163.0 (d, J_{CP} = 16 Hz); IR (neat) 2984, 2940, 2880, 1725, 1609, 1259 cm^{-1}; MS (FAB) *m/z* 265 (MH^+).

1-Ethyl 4-Methyl 2-(Diethoxyphosphoryl)butanedioate. Sodium hydride (1.18 g, 60% dispersion in oil, 29.4 mmol, washed 3 times with pentane) was suspended in freshly distilled THF (26.8 mL). After the mixture was cooled to 0 °C, triethyl phosphonoacetate (6.0 g, 26.8 mmol) was added dropwise over 10 min. After 1 h, methyl bromoacetate (4.10 g, 26.8 mmol) was added, and the mixture was stirred for 12 h at 20 °C. The mixture was extracted with ether and the ether extracts were washed with 1 N hydrochloric acid and saturated sodium chloride solution and dried ($MgSO_4$). The solvent was evaporated in vacuo. The residue was purified by column chromatography over silica gel eluting with CH_2Cl_2−ether (4:1) to give the title compound (4.00 g, 76%) (R_f 0.5): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.26−1.37 (m, 9 H), 2.82 (ddd, J = 17.8, 9.2, 3.6 Hz, 1 H), 3.08 (ddd, J = 17.8, 11.1, 6.9 Hz, 1 H), 3.46 (ddd, J = 24.0, 11.1, 3.6 Hz, 1 H), 3.70 (s, 3 H), 4.09−4.26 (m, 6 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.86, 16.07, 16.12, 16.17, 31.09 (d, J_{CP} = 2.3 Hz), 41.15 (d, J_{CP} = 132.0 Hz), 51.90, 61.53, 62.76, 62.82, 168.0 (d, J_{CP} = 5.3 Hz), 171.4 (d, J_{CP} = 18.3 Hz); IR (neat) 2986, 1736, 1259 cm^{-1}; MS (EI) *m/z* 296; exact mass M^+ 296.0998 (calcd for $C_{11}H_{21}O_7P$ 296.1025).

1-Ethyl 4-Methyl 2-(Diethoxyphosphoryl)-2-(phenylseleno)butanedioate. Sodium hydride (0.688 g, 60% dispersion in oil, 16.7 mmol) was washed 3 times with pentane and suspended in freshly distilled THF (20.9 mL). After the mixture was cooled to 0 °C, 1-ethyl 4-methyl 2-(diethoxyphosphoryl)butanedioate (3.65 g, 9.56 mmol) in THF (2.4 mL) was added dropwise and the mixture was stirred for 2 h at 20 °C. Phenylselenyl bromide [11.5 mmol, prepared by adding bromine (0.31 mL, 962 mg, 6.02 mmol) to a stirred solution of diphenyl diselenide (1.80 g, 5.72 mmol) in THF (16.1 mL) at 20 °C followed by further stirring for 10 min] was then added. The mixture was stirred for 12 h at 20 °C and 1 N HCl and dichloromethane were added to the mixture. The organic layer was separated, washed with saturated sodium bicarbonate solution, and dried ($MgSO_4$). The solvent was evaporated in vacuo. The residue was purified by column chromatography over silica gel eluting with CH_2Cl_2−ether (2:1) to give the title compound (2.92 g, 68%) (R_f 0.6): pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.25 (t, J = 7.1 Hz, 3 H), 1.31−1.38 (m, 6 H), 2.67 (dd, J = 17.2, 17.1 Hz, 1 H), 3.19 (dd, J = 17.2, 7.1 Hz, 1 H), 3.61 (s, 3 H), 4.14−4.23 (m, 4 H), 4.25−4.41 (m, 2 H), 7.29−7.33 (m, 2 H), 7.39−7.43 (m, 1 H), 7.76−7.79 (m, 2 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.91, 16.37, 16.43, 16.51, 37.84, 47.38 (d, J_{CP} = 144 Hz), 51.79, 62.28, 63.59 (J_{CP} = 7.6 Hz), 65.03 (d, J_{CP} = 6.9 Hz), 126.3, 128.8, 130.0, 138.8, 168.6, 169.7 (d, J_{CP} = 13.0 Hz); IR (neat) 2986, 1729, 1253 cm^{-1}; MS (EI) *m/z* 452; exact mass M^+ 452.0482 (calcd for $C_{17}H_{25}O_7PSe$ 452.0503).

1-Ethyl 4-Methyl (*E*)-2-(Diethoxyphosphoryl)-2-butenedioate (5). Hydrogen peroxide (30%, 4.64 g) and water (0.97 mL) were added to a stirred solution of 1-ethyl 4-methyl 2-(diethoxyphosphoryl)-2-(phenylseleno)butanedioate (2.69 g, 5.97 mmol) in dichloromethane (28.1 mL) at such a rate the temperature remained above 30 °C. After being stirred for a further 1 h at 20 °C, the mixture was washed with saturated sodium bicarbonate solution and dried over $MgSO_4$, and the solvent was evaporated in vacuo. The residue was purified by column chromatography over silica gel eluting with CH_2Cl_2−ether (2:1) to give **5** (1.223 g, ca. 79%) (R_f 0.6). (A small amount of unidentified inpurity was present). **5**: pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 1.33−1.38 (m, 9 H), 3.79 (s, 3 H), 4.14−4.21 (m, 4 H), 4.34 (q, J = 7.2 Hz, 2 H), 6.81 (d, J_{HP} = 22.0 Hz, 1 H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ (ppm) 13.96, 16.16, 16.21, 52.49, 62.18, 63.46 (d, J_{CP} = 5.2 Hz), 135.1 (d, J_{CP} = 7.3 Hz), 139.1 (J_{CP} = 172 Hz), 163.9 (J_{CP} = 25.9 Hz), 164.4 (J_{CP} = 11.4 Hz); ^{31}P NMR (202.4 MHz, $CDCl_3$) δ (ppm) 11.1; IR (neat) 2960, 2872, 1721, 1607, 1263 cm^{-1}; MS (FAB) *m/z* 295 (MH^+).

A Typical Experimental Procedure in Table 1 (Entry 1). To a solution of **1** (256 mg, 1.00 mmol) in dichloromethane (2.5 mL) was added $SnCl_4$ (0.176 mL, 391 mg, 1.50 mmol), followed by 2-phosphonoacrylate (**2a**) (0.202 mL, 252 mg, 1.30 mmol) at −78 °C. The mixture was stirred at −78 °C for 3 h. The reaction mixture was quenched by triethylamine (0.36 mL, 260 mg, 2.6 mmol) and then saturated aqueous $NaHCO_3$. The mixture was extracted with dichloromethane and the organic phase was washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography over silica gel eluting with CH_2Cl_2−ether (2:1) to give **3a** (430 mg, 96%) (R_f 0.3).

Methyl *r*-1-(Dimethoxyphosphoryl)-*c*-2-[(phenylseleno)(trimethylsilyl)methyl]-1-cyclopropanecarboxylate (3a): pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.105 (s, 9 H, H_{13}), 1.61 (ddd, J = 9.9, 7.7, 4.5 Hz, 1 H, H_{3b}), 1.86 (ddd, J = 14.2, 9.0, 4.5 Hz, 1 H, H_{3a}), 2.24 (dddd, J = 14.1, 12.5, 9.0, 7.7 Hz, 1 H, H_2), 2.59 (d, J = 12.5 Hz, 1 H, H_6), 3.40 (s, 3 H, H_5), 3.80 (d, J = 11.0 Hz, 3 H, H_7), 3.89 (d, J = 11.0 Hz, 3 H, H_8), 7.19−7.24 (m, 3 H, $H_{11,12}$), 7.48−7.52 (m, 2 H, H_{10}) (see numbering in Figure 1); Observed NOEs in the 2D-NOESY spectrum were H_2−H_{3a}, H_2−H_6, H_2−H_{13}, H_{3a}−H_{3b}, H_{3b}−H_6, H_{3b}−H_{13}, H_5−H_6, H_5−H_{10}, H_5−$H_{11,12}$, H_6−H_{10}, H_6−H_{13}, H_{10}−H_{11}, H_{10}−H_{13}; ^{1}H assignments were determined by H−H COSY and NOESY; ^{13}C NMR (50.1 MHz, $CDCl_3$) δ (ppm) −2.114 (J_{CH} = 120 Hz, C_{13}), 23.69 (J_{CH} = 166 Hz, C_3), 25.10 (d, J_{CP} = 190.5 Hz, C_1), 28.69 (d, J_{CH} = 152 Hz, C_6), 33.19 (J_{CH} = 167, 10 Hz, C_2), 52.37 (J_{CH} = 148 Hz, C_5), 53.24 (d, J_{CP} = 5.9 Hz, J_{CH} = 148 Hz, $C_{7\ or\ 8}$), 53.36 (d, J_{CP} = 5.9 Hz, J_{CH} = 148 Hz, $C_{7\ or\ 8}$), 126.9 (J_{CH} = 161, 7.3 Hz, C_{12}), 128.6 (J_{CH} = 160, 5.1 Hz, $C_{10\ or\ 11}$), 130.3 (C_9), 133.5 (J_{CH} = 161 Hz, $C_{10\ or\ 11}$), 168.5 (d, J_{CP} = 7.3 Hz, C_4) (see numbering in Figure 1); IR (neat) 2956, 1721, 1578, 1251 cm^{-1}; MS (EI) *m/z* 450; exact mass M^+ 450.0536 (calcd for $C_{17}H_{27}O_5PSeSi$ 450.0530).

Ethyl *r*-1-(diethoxyphosphoryl)-*c*-2-[(phenylseleno)-(trimethylsilyl)methyl]-1-cyclopropanecarboxylate (3b) (R_f 0.5 (CH_2Cl_2:ether = 2:1)): pale yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 0.079 (s, 9 H), 1.15 (t, J = 7.1 Hz, 3 H), 1.32 (t, J = 7.1 Hz, 3 H), 1.38 (t, J = 7.1 Hz, 3 H), 1.60 (ddd, J = 9.8, 7.3, 4.4 Hz, 1 H), 1.85 (ddd, J = 13.8, 9.2, 4.4 Hz, 1 H), 2.10−2.32 (m, 1 H), 2.61 (d, J = 12.5 Hz, 1 H), 3.70 (dq, J = 10.7, 7.1 Hz, 1 H), 3.96 (dq, J = 10.7, 7.1 Hz, 1 H), 4.09−4.31 (m, 4 H), 7.19−7.29 (m, 3 H), 7.49−7.52 (m, 2 H); ^{13}C NMR (50.1 MHz, $CDCl_3$) δ (ppm) −1.909, 13.92, 16.37, 16.52, 23.84, 25.96 (d, J_{CP} = 189 Hz), 28.72, 32.89, 61.51, 62.65 (d, J_{CP} = 5.9 Hz), 126.9, 128.7, 130.7, 133.6, 168.5 (d, J_{CP} = 7.3 Hz); IR (neat) 2984, 2908, 1717, 1578, 1251 cm^{-1}; MS (EI) *m/z* 492. Anal. Calcd for $C_{20}H_{33}O_5PSeSi$: C, 48.88; H, 6.77. Found: C, 48.68; H, 6.78.

***tert*-Butyl *r*-1-(Dimethoxyphosphoryl)-*c*-2-[(phenylseleno)(trimethylsilyl)methyl]-1-cyclopropanecarboxylate (3c)** (R_f 0.5 (CH_2Cl_2:ether = 2:1)): colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) −0.013 (s, 9 H, H_{13}), 1.43 (s, 9 H, H_{14}), 1.59 (ddd, J = 10.0, 7.6, 4.5 Hz, 1 H, H_{3b}), 1.84 (ddd, J = 14.1, 9.0, 4.5 Hz, 1 H, H_{3a}), 2.11 (dddd, J = 14.2, 12.7, 9.0, 7.6 Hz, 1 H, H_2), 2.66 (d, J = 12.7 Hz, 1 H, H_6), 3.81 (d, J = 11.0 Hz, 3 H, H_7), 3.86 (d, J = 11.0 Hz, 3 H, H_8), 7.18−7.21 (m, 3 H, $H_{11,12}$), 7.50−7.52 (m, 2 H, H_{10}) (see numbering in Figure 1); observed NOEs in the 2D-NOESY spectrum were H_2−H_{3a}, H_2−H_{10}, H_2−H_{13}, H_{3a}−H_{3b}, H_{3b}−H_6, H_{3b}−H_{13}, H_6−H_{13}, H_6−H_{14}, H_7−H_{14}, H_8−H_{14}, H_{10}−$H_{11,12}$, H_{10}−H_{13}, H_{10}−H_{14}, $H_{11,12}$−H_{13}, $H_{11,12}$−H_{14}; ^{13}C NMR (150.8 MHz, $CDCl_3$) δ (ppm) 1.818 (C_{13}), 23.43 (d, J_{CP} = 2.7 Hz, C_3), 26.25 (d, J_{cp} = 188 Hz, C_1), 27.40 (C_6), 28.05 (C_{14}), 31.16 (d, J_{CP} = 2.1 Hz, C_2), 53.19 (J_{cp} = 6.9 Hz, C_7), 53.30 (J_{CP} = 5.7 Hz, C_8), 82.46 (C_5), 126.9 (C_{12}), 128.8 (C_{11}), 130.2 (C_9), 133.4 (C_{10}), 167.1 (d, J_{CP} = 6.3 Hz, C_4); ^{1}H and ^{13}C assignments were determined by NOESY, HMQC, and HMBC spectra; IR (neat) 2958, 1715, 1578, 1251 cm^{-1}; MS (EI) *m/z* 492; exact mass M^+ 492.0992 (calcd for $C_{20}H_{33}O_5PSeSi$ 492.1000).

(2-Trimethylsilyl)ethyl *r*-1-(Diethoxyphosphoryl)-*c*-2-[(phenylseleno)(trimethylsilyl)methyl]-1-cyclopropanecarboxylate (3d) (R_f 0.65 (CH_2Cl_2:ether = 4:1)): colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) −0.032 (s, 9 H), 0.087 (s, 9 H), 0.847−0.953 (m, 2 H), 1.33 (t, J = 7.1 Hz, 3 H), 1.39 (t, J = 7.1 Hz, 3 H), 1.60 (ddd, J = 9.8, 7.6, 4.5 Hz, 1 H), 1.84 (ddd, J = 13.9, 9.1, 4.5 Hz, 1 H), 2.09−2.31 (m, 1 H), 2.63 (d, J = 12.5 Hz, 1 H), 3.68−3.98 (m, 2 H), 4.10−4.35 (m, 4 H),

7.18−7.22 (m, 3 H), 7.47−7.52 (m, 2 H); ^{13}C NMR (50.1 MHz, $CDCl_3$) δ (ppm) −1.909, −1.646, 16.40, 16.52, 17.22, 23.78, 26.00 (d, J_{CP} = 188 Hz), 28.57, 32.89, 62.66 (d, J_{CP} = 7.3 Hz), 63.87, 126.9, 128.7, 130.8, 133.4, 168.6 (d, J_{CP} = 7.3 Hz); IR (neat) 2956, 2904, 1715, 1578, 1251 cm^{-1}; MS (EI) *m*/*z* 564; exact mass M$^+$ 564.1430 (calcd for $C_{23}H_{41}O_5PSeSi_2$ 564.1395).

Ethyl *r*-1-(Diisopropoxyphosphoryl)-*c*-2-[(phenylseleno)(trimethylsilyl)methyl]-1-cyclopropanecarboxylate (3e) (R_f 0.6 (CH_2Cl_2: ether = 2:1)): colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 0.053 (s, 9 H), 1.18 (t, J = 7.1 Hz, 3 H), 1.28−1.41 (m, 12 H), 1.58 (ddd, J = 9.8, 7.4, 4.3 Hz, 1 H), 1.85 (ddd, J = 13.6, 9.0, 4.3 Hz, 1 H), 2.05−2.26 (m, 1 H), 2.58 (d, J = 12.5 Hz, 1 H), 3.78 (dd, J = 10.8, 7.1 Hz, 1 H), 3.97 (dd, J = 10.8, 7.2 Hz, 1 H), 4.66−4.88 (m, 2 H), 7.19−7.22 (m, 3 H), 7.50−7.55 (m, 2 H); ^{13}C NMR (50.1 MHz, $CDCl_3$) δ (ppm) −1.880, 13.95, 23.99, 24.05, 24.13, 26.81 (d, J_{CP} = 189 Hz), 28.60, 32.46, 61.42, 70.97 (d, J_{CP} = 5.9 Hz), 71.07 (d, J_{CP} = 4.4 Hz), 126.9, 128.7, 130.7, 133.7, 168.8 (d, J_{CP} = 5.9 Hz); IR (neat) 2980, 1715, 1578, 1251 cm^{-1}; MS (EI) *m*/*z* 520; exact mass M$^+$ 520.1306 (calcd for $C_{22}H_{37}O_5PSeSi$ 520.1314).

***(l)*-Menthyl *r*-1-(Dimethoxyphosphoryl)-*c*-2-[(phenylseleno)(trimethylsilyl)methyl]-1-cyclopropanecarboxylate (3f)** (R_f 0.75 (CH_2Cl_2:ether = 2:1)): colorless crystals; mp 74−76 °C (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) −0.038 (s, 9 H, H_{13}), 0.482 (d, J = 7.0 Hz, 3 H, H_{14}), 0.822 (d, J = 7.1 Hz, 3 H), 0.910 (d, J = 6.6 Hz, 3 H), 0.776−1.07 (m, 3 H), 1.39−1.51 (m, 2 H), 1.61−1.68 (m, 3 H, including H_{3b}), 1.90 (ddd, J = 14.3, 8.9, 4.3 Hz, H_{3a}), 2.08−2.23 (m, 3 H, including H_2), 2.65 (d, J = 12.8 Hz, 1 H, H_6), 3.81 (d, J = 10.8 Hz, 3 H, H_7), 3.85 (d, J = 10.8 Hz, 3 H, H_8), 4.68 (ddd, J = 10.8, 10.8, 4.5 Hz, 1 H, H_5), 7.18−7.21 (m, 3 H, $H_{11,12}$), 7.51−7.54 (m, 2 H, H_{10}); selected observed NOEs in the 2D-NOESY spectrum were H_2−H_{3a}, H_2−H_6, H_2−H_{13}, H_{3a}−H_{3b}, H_{3b}−H_6, H_{3b}−H_{13}, H_6−H_{10}, H_6−H_{13}, and H_{10}−H_{14}; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) −1.673 (CH_3, J_{CH} = 119 Hz, C_{13}), 16.17 (CH_3, J_{CH} = 124 Hz, C_{14}), 21.11, 22.10, 23.07, 24.12 (J_{cp} = 3.1 Hz, C_3), 25.58, 25.83 (d, J_{CP} = 190 Hz, C_1), 27.40 (C_6), 31.46 (CH, J_{CP} = 2.3 Hz, J_{CH} = 161 Hz, C_2), 31.50 (CH, J_{CH} = 123 Hz), 34.29 (CH_2, J_{CH} = 126 Hz), 40.68 (CH_2, J_{CH} = 125 Hz), 47.22 (CH, J_{CH} = 125 Hz), 53.34 (CH, J_{CP} = 8.4 Hz, J_{CH} = 148 Hz, C_8), 53.42 (CH, J_{CP} = 6.9 Hz, J_{CH} = 148 Hz, C_7), 76.05 (CH, C_6), 127.2 (CH, J_{CH} = 161, 7.3 Hz, C_{12}), 128.9 (CH, J_{CH} = 160 Hz, C_{11}), 130.1 (C, C_9), 134.1 (CH, J_{CH} = 164 Hz, C_{10}), 168.1 (C, J_{CP} = 6.9 Hz, C_4); nondecoupling spectrum was measured at 50.1 MHz and carbon multiplicity was only partially assigned because of complexity; partial ^{1}H and ^{13}C assignments were also determined by COSY, NOESY, HMQC, and TOCSY spectra; IR (KBr) 2960, 2872, 1705, 1578, 1257 cm^{-1}; MS (EI) *m*/*z* 574; exact mass M$^+$ 574.1808 (calcd for $C_{26}H_{43}O_5PSeSi$ 574.1783). Anal. Calcd for $C_{26}H_{43}O_5PSeSi$: C, 54.44; H, 7.56. Found: C, 54.42; H, 7.51; $[\alpha]_D^{22.5}$ −42.3° (*c* = 1.0, $CHCl_3$).

Ethyl *r*-1-(Diethoxyphosphoryl)-*c*-2-formyl-1-cyclopropanecarboxylate (7). To a solution of **3b** (491 mg, 1.0 mmol) in THF (20 mL) and water (10 mL) was added $NaIO_4$ (1.07 g, 5.0 mmol) with vigorous stirring. The mixture was stirred for 4.5 h at room temperature (22 °C). The reaction mixture was concentrated in vacuo and poured into ether (100 mL) and saturated aqueous $NaHCO_3$ solution (50 mL). The organic layer was separated. The water layer was extracted with additional ether (100 mL × 5). The combined organic layer was washed with water, dried ($MgSO_4$), and concentrated in vacuo to give **7** (270 mg, 97%) (R_f 0.4 (ether:methanol = 19:1)). **7**: pale yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.30 (t, J = 7.2 Hz, 3 H), 1.35 (t, J = 7.1 Hz, 6 H), 1.91 (ddd, J = 14.7, 8.7, 5.0 Hz, 1 H), 2.15 (ddd, J = 12.0, 6.6, 5.0 Hz, 1 H), 2.57 (dddd, J = 12.2, 8.7, 6.6, 5.1 Hz, 1 H), 4.11−4.30 (m, 6 H), 9.29 (d, J = 5.1 Hz, 1 H); ^{13}C NMR (50.1 MHz, $CDCl_3$) δ (ppm) 13.83, 16.11, 16.22, 16.89, 29.26 (d, J_{CP} = 183 Hz), 32.43 (d, J_{CP} = 2.9 Hz), 62.24, 63.11 (d, J_{CP} = 5.9 Hz), 63.23 (d, J_{CP} = 5.9 Hz), 166.2 (d, J_{CP} = 4.4 Hz), 196.6; IR (neat) 2988, 1729, 1257 cm^{-1}; MS (EI) *m*/*z* (relative intensity) 279 (5.4, M + 1), 263 (5.4), 233 (25), 205 (100); MS (FAB) *m*/*z* 279 (MH^+).

Ethyl *r*-1-(Diethoxyphosphoryl)-*c*-2-hydroxymethyl-1-cyclopropane carboxylate (8). To a solution of **7** (653 mg, 2.35 mmol) in ^{i}PrOH (13.4 mL) was added $NaBH_4$ (36 mg, 0.94 mmol) in three portions at −78 °C. The mixture was stirred for 2 h at −78 °C. Saturated aqueous Na_2SO_4 solution (2 mL) was added to the reaction mixture. The mixture was extracted with ether (60 mL × 5). The organic phase was dried ($MgSO_4$) and evaporated in vacuo to give **8** (622 mg, 94%) (R_f 0.4 (ether:methanol = 19:1)). **8**: pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.31 (t, J = 7.1 Hz, 3 H), 1.32−1.37 (m, 6 H), 1.47 (ddd, J = 10.4, 7.1, 4.8 Hz, 1 H), 1.60 (ddd, J = 14.3, 8.9, 4.8 Hz, 1 H), 1.73 (brs, 1 H), 2.13 (m, 1 H), 3.48 (dd, J = 12.0, 9.0 Hz, 1 H), 3.96 (dd, J = 12.0 Hz, 5.0 Hz, 1 H), 4.13−4.23 (m, 4 H), 4.25 (q, J = 7.1 Hz, 2 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.11, 16.23 (d, J_{CP} = 3.1 Hz), 16.36, 16.42, 25.01 (d, J_{CP} = 188 Hz), 28.09 (d, J_{CP} = 3.1 Hz), 60.99, 61.94, 62.79 (d, J_{CP} = 6.1 Hz), 62.92 (d, J_{CP} = 6.1 Hz), 168.6 (d, J_{CP} = 6.9 Hz); IR (neat) 3400, 2986, 2918, 1725, 1232 cm^{-1}; MS (EI) *m*/*z* 280; exact mass M$^+$ 280.1107 (calcd for $C_{11}H_{21}O_6P$ 280.1076).

Diethyl 3-Oxabicyclo[3.1.0]hexan-2-one-1-phosphonate (9). To a solution of **8** (756 mg, 2.7 mmol) in EtOH (2.5 mL) was added dropwise a 50% (wt %) aqueous NaOH solution (237 μL) at 0 °C. The resulting solution was stirred for 2 h at 55 °C and then for 0.5 h at 18 °C. The EtOH was evaporated, and the remaining solution was diluted with water (1 mL). The aqueous phase was acidified with $KHSO_4$ and extracted with Et_2O twice. The combined organic extracts were dried ($MgSO_4$) and evaporated to give **9** (577 mg, 91%) (R_f 0.2 (ether:methanol = 19:1)). **9**: pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.31 (ddd, J = 10.4, 4.9, 4.9 H, 1 H), 1.37 (t, J = 7.4 Hz, 3 H), 1.39 (t, J = 7.4 Hz, 3 H), 1.88 (ddd, J = 15.3, 7.8, 4.9 Hz, 1 H), 2.77 (dddd, J = 10.1, 7.8, 4.9, 4.9 Hz, 1 H), 4.20−4.31 (m, 5 H), 4.40 (dd, J = 9.5, 4.9 Hz, 1 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 16.22, 16.28, 17.63 (d, J_{CP} = 3.1 Hz), 22.57 (d, J_{CP} = 209 Hz), 24.66 (d, J_{CP} = 1.5 Hz), 63.64 (d, J_{CP} = 6.9 Hz), 63.66 (d, J_{CP} = 6.1 Hz), 67.73 (d, J_{CP} = 3.1 Hz), 171.5 (d, J_{CP} = 11 Hz); IR (neat) 2988, 2918, 1773, 1255 cm^{-1}; MS (EI) *m*/*z* 234; exact mass M$^+$ 234.0673 (calcd for $C_9H_{15}O_5P$ 234.0658).

***c*-2-(Acetoxymethyl)-*r*-1-(diethoxyphosphoryl)-1-cyclopropanecarboamide (10).** The lactone **9** (640 mg, 2.73 mmol) was dissolved in methanol (10 mL), and methanol saturated with ammonia (ca. 5.8 M, 5.0 mL, 29 mmol) were added and the solution stirred for 17 h at room temperature. The solvent was the evaporated in vacuo and the residue dissolved in dry CH_2Cl_2 (10 mL) and cooled to 0 °C, and triethylamine (326 mg, 3.27 mmol) and (dimethylamino)-pyridine (20 mg) were added to the solution, followed by dropwise addition of acetic anhydride (334 mg, 3.27 mmol). After stirring for 4 h at 0 °C, water was added and the solution was extracted with CH_2Cl_2. The organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography over silica gel eluting with ether−methanol (19:1) to give **10** (698 mg, 87%) (R_f 0.3 (ether:methanol = 19:1)). **10**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.32−1.39 (m, 6 H), 1.43 (ddd, J = 14.1, 9.2, 4.8 Hz, 1 H), 1.73 (ddd, J = 10.1, 7.0, 4.8 Hz, 1 H), 2.05 (s, 3 H), 2.03−2.14 (m, 1 H), 3.96 (dd, J = 11.8, 8.9 Hz, 1 H), 4.11−4.24 (m, 4 H), 4.37 (ddd, J = 11.8, 6.0, 1.2 Hz, 1 H), 5.68 (brs, 1 H), 7.37 (brs, 1 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.40 (J_{CP} = 3.1, J_{CH} = 166 Hz, CH_2), 16.31 (J_{CP} = 6.1, J_{CH} = 127 Hz, CH_3), 16.36 (J_{CP} = 5.3, J_{CH} = 127 Hz, CH_3), 20.76 (J_{CH} = 129 Hz, CH_3), 24.19 (J_{CP} = 2.3, J_{CH} = 167 Hz, CH), 24.90 (J_{CP} = 181 Hz, C), 62.25 (J_{CP} = 1.5, J_{CH} = 150 Hz, CH_2), 63.06 (J_{CP} = 6.1, J_{CH} = 148 Hz, CH_2), 63.23 (J_{CP} = 6.9, J_{CH} = 149 Hz, CH_2), 167.2 (J_{CP} = 9.2 Hz, C), 170.7 (C); IR (neat) 3468, 3202, 2988, 1742, 1676, 1615, 1241 cm^{-1}; MS (EI) *m*/*z* 293; exact mass M$^+$ 293.1046 (calcd for $C_{11}H_{20}O_6NP$ 293.1029).

Diethyl *t*-2-(Acetoxymethyl)-*r*-1-[*N*-(*tert*-butoxycarbonyl)amino]-1-cyclopropanephosphonate (11). A solution of **10** (110 mg, 0.375 mmol) and *t*-BuOH (1.9 mL) was heated to 70 °C. Lead tetraacetate (665 mg, 1.50 mmol) was added and the mixture was heated at reflux for 5 h. After cooling to room temperature, ether (0.9 mL) followed by $NaHCO_3$ (60 mg) were added, and the mixture was stirred for 10 min. The mixture was filtered through a short plug of silica gel and the filtrate evaporated. The residue was purified by column chromatog-

raphy over silica gel eluting with ether−methanol (19:1) to give **11** (132 mg, 96%) (R_f 0.5 (ether:methanol = 19:1)). **11**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.18 (ddd, J = 13.5, 6.8, 6.8 Hz, 1 H), 1.29−1.35 (m, 6 H), 1.45 (s, 9 H), 1.69−1.76 (m, 1 H), 1.78−1.85 (m, 1 H), 3.98 (dd, J = 11.5, 9.6 Hz, 1 H), 4.09−4.25 (m, 4 H), 4.35 (dd, J = 11.5, 2.8 Hz, 1 H), 5.45 (brs, 1 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 16.38, 16.38, 16.50 (d, J_{CP} = 6.1 Hz), 20.97, 21.80, 28.36, 30.71 (d, J_{CP} = 221 Hz), 62.45 (d, J_{CP} = 6.9 Hz), 62.64, 63.02 (d, J_{CP} = 4.7 Hz), 80.04, 155.7, 171.2; IR (neat) 3252, 2984, 2936, 1735, 1721, 1241 cm^{-1}; MS (EI) m/z 365; exact mass M$^+$ 365.1614 (calcd for $C_{15}H_{28}O_7NP$ 365.1604).

Diethyl *r*-1-[*N*-(*tert*-Butoxycarbonyl)amino]-*t*-2-(hydroxymethyl)-1-cyclopropanephosphonate (12). Potassium carbonate (276 mg, 2.0 mmol) was added to a stirred solution of **11** (365 mg, 1.0 mmol) in MeOH (5.6 mL). After the mixture had been heated at 70 °C for 17 h, the MeOH was evaporated, water was added to the residue, and the resulting solution was extracted with ether. The organic layer was dried ($MgSO_4$), and the solvent was evaporated to give **12** (324 mg, 100%). **12**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.632 (ddd, J_{PC} = 12.8, J_{HH} = 6.4, 6.4 Hz, 1 H), 1.30−1.36 (m, 6 H), 1.41−1.49 (m, 1 H), 1.45 (s, 9 H), 1.82 (brs, 1 H), 2.05−2.12 (m, 1 H), 3.17 (dd, J = 11.9, 11.3 Hz, 1 H), 4.00 (bd, J = 11.9 Hz, 1 H), 4.12−4.25 (m, 4 H), 5.17 (brs, 1 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 15.17, 16.34 (d, J_{CP} = 6.1 Hz), 16.50 (d, J_{CP} = 6.1 Hz), 27.11, 28.29, 31.06 (d, J_{CP} = 219 Hz), 60.85, 62.55 (d, J_{CP} = 6.9 Hz), 63.12 (d, J_{CP} = 6.1 Hz), 81.10, 157.1; IR (neat) 3420, 3280, 2984, 2936, 1720, 1696, 1251 cm^{-1}; MS (EI) m/z 323; exact mass M$^+$ 323.1492 (calcd for $C_{13}H_{26}O_6NP$ 323.1497).

***r*-1-Amino-*t*-2-(hydroxymethyl)-1-cyclopropanephosphonic Acid (13).** HCl ether solution, 1 N (14.6 mL, 14.6 mmol), was added to **12** (118 mg, 0.365 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature, stirred for 18 h, and then concentrated in vacuo. The residue was dissolved in water (1.5 mL) and basified with $NaHCO_3$ (ca. 300 mg). The mixture was extracted with CH_2Cl_2 (×10) and the combined organic layer was dried (Na_2SO_4) and concetrated in vacuo to give crude diethyl 2-hydroxymethyl-1-amino-1-cyclopropanephosphonate (66 mg, ca. 80%). To a stirred solution of this aminocyclopropane (66 mg, 0.29 mmol) in CH_2Cl_2 (1.3 mL) at room temperature was added iodotrimethylsilane (0.170 mL, 113 mg, 2.08 mmol). The reaction mixture was stirred for 1 h and then concentrated in vacuo. The residue was dissolved in absolute ethanol (1.4 mL) and treated with propylene oxide (135 μL, 113 mg, 2.08 mmol). After standing overnight at room temperature, the precipitates were separated and washed with ethanol to give **13** (39 mg, 64% from **12**) as a hygroscopic solid. **13**: mp 71−73 °C; ^{1}H NMR (400 MHz, D_2O) δ (ppm) 0.94−1.04 (m, 1 H), 1.16−1.24 (m, 1 H), 1.52−1.60 (m, 1 H), 3.67 (dd, J = 12.3, 6.4 Hz, 1 H), 3.87 (dd, J = 12.3, 4.6 Hz, 1 H); ^{13}C NMR (100.6 MHz, D_2O) δ (ppm) 12.74 (CH_2, J_{CH} = 165 Hz), 21.82 (CH, J_{CH} = 164 Hz), 34.55 (C, J_{CP} = 199 Hz), 58.90 (CH, J_{CH} =145 Hz); IR (KBr) 3400−2600, 1609, 1240 cm^{-1}; MS (FAB) m/z 168 (MH$^+$).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **3d**−**e** and **7**−**13** and 2D-NOESY spectra for compounds **3a**, **3c**, and **3f** (30 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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