Lewis Acid-Catalyzed Intramolecular [2 + 2] Cycloaddition of α-Ester-Substituted Conjugated Dienyl- and Trienylphosphonates. New Synthesis of Functionalized Cyclic Terpenoids

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α-Ester-substituted 1,3-dienylphosphonates **7** and **8**, prepared by the Knoevenagel condensation, underwent intramolecular [2 + 2] cycloaddition in the presence of Lewis acid to form bicyclo[4.2.0] (26−57% yield) and bicyclo[3.2.0]skeleton (14−38% yield), respectively. Similar treatment of homologous 1,3-dienylphosphonate **11** and 1,3,5-trienylphosphonate **12** resulted in the formation of ionone derivatives (30−94% yield). The intramolecular cycloaddition reaction was applicable to several conjugated dienes bearing an ester group.

Vinylphosphonates are of synthetic interest due to their usefulness as electrophiles[1,2] and because of their biological activities.[3] We have recently reported that vinylphosphonates containing an ene component underwent a Lewis acid-catalyzed intramolecular ene reaction to give phosphono group-containing carbocyclic compounds, which are versatile intermediates for the synthesis of bicyclic compounds and of Cadalane and Valerenic acid sesquiterpenoids.[4] Our interest in the further application of vinylphosphonate chemistry led us to explore the reactivity of 1,3-dienyl- and 1,3,5-trienylphosphonates and a new approach to cyclic terpenoids. Although synthesis and synthetic applications of vinylphosphonates have been widely studied,[1] there have been a few simple precedents for their homologue, dienylphosphonates.[5] We now report the synthesis of dienyl- and trienylphosphonates bearing linear monoterpenoid groups, and the Lewis acid-catalyzed reaction of the phosphono-containing unsaturated system to give intramolecular [2 + 2] cycloaddition products. We also describe the reaction of the related 1,3-dienoic acid esters.

Results and Discussion

Synthesis of α-Ester-Substituted 1,3-Dienyl- and 1,3,5-Trienylphosphonates, and the Corresponding Conjugated Dienoic Acid Esters. In an extension of the previously reported procedure for the synthesis of vinylphosphonates,[4,6] 1,3-dienylphosphonate **7a** was prepared from (2*E*)-5,9-dimethyldeca-2,8-dienal (**1**) by the Knoevenagel condensation. Thus, the condensation of **1** with triethyl phosphonoacetate (**5**) in the presence of NaH/ClTi(OEt)$_3$ yields the mixture of ethyl (2*Z*,4*E*)- and (2*E*,4*E*)-2-(diethylphosphono)-7,11-dimethyldodeca-2,4,10-trienoates (**7a**: 74%) and (**7b**: 5%) (Scheme 1) (Table 1, entry 1).

Scheme 1

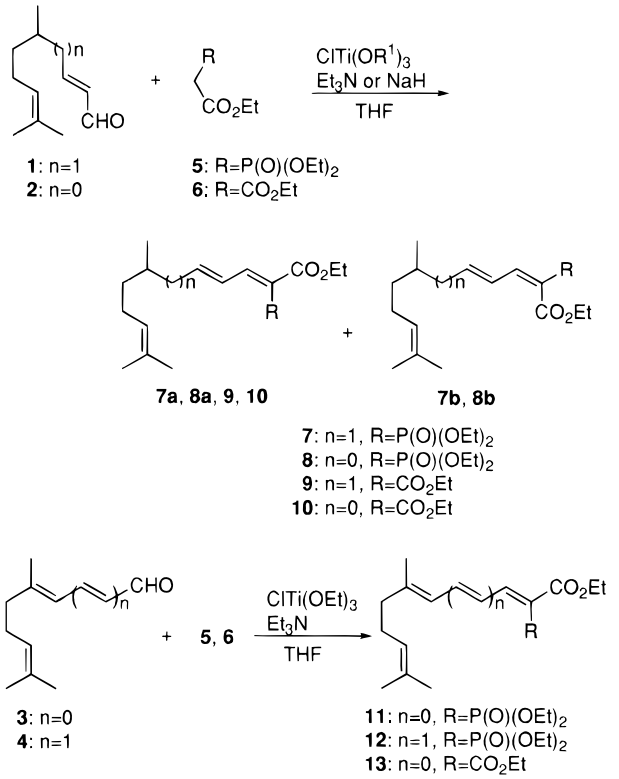

Table 1. Preparation of 1,3-Dienyl- and 1,3,5-Trienylphosphonates and Allylidenemalonates

entry	aldehyde	ester	temp/°C	time/h	products (yield/%)[a]	
1	**1**	**5**	0	6	**7a** (74)	**7b** (5)
2	**2**	**5**	0	6	**8a** (62)	**8b** (10)
3	**3**	**5**	0	6	**11** (76)	
4	**4**	**5**	rt	7	**12** (73)	
5	**1**	**6**	rt	26	**9** (82)	
6	**2**	**6**	rt	24	**10** (83)	
7	**3**	**6**	rt	6	**13** (89)	

[a] Isolated yield.

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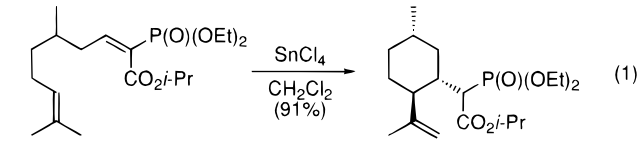
Table 2. Lewis Acid-Catalyzed Cyclization of 7a[a]

entry	Lewis acid (equiv)	temp/°C	time/h	products (yield/%)[b]	
1	$EtAlCl_2$ (2)	−25	3	**16a** (47)	**16b** (10)
2	$EtAlCl_2$ (2)	0	1.5	**16a** (trace)	**16b** (33)
3	$SnCl_4$ (1)	rt	19	**16a** (38)	
4	$TiCl_4$ (1)	rt	9	**16a** (26)	
5	$FeCl_3$ (1)	rt	32	**16a** (26)	

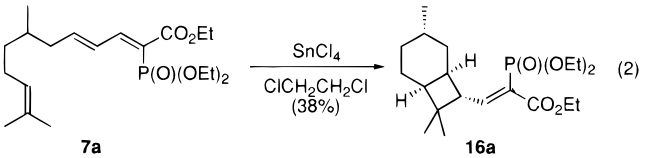
[a] All reactions were carried out in $ClCH_2CH_2Cl$. [b] Isolated yield.

Similar treatment of various conjugated aldehydes **2**, **3**, and **4** with **5** led to a mixture of two stereoisomeric 1,3-dienylphosphonates **8a** (62%) and **8b** (10%), **11** (76%), and a 1,3,5-trienylphosphonate **12** (73%), respectively (Table 1, entries 2−4). The similar titanium-mediated Knoevenagel condensation of conjugated aldehydes **1**−**3** with diethyl malonate (**6**) gave the corresponding condensation products **9**, **10**, **13** in 82−89% yields (Table 1, entries 5−7).

Lewis Acid-Catalyzed Cyclization Reaction of α-Ester-Substituted Conjugated Dienyl- and Trienylphosphonates. We have recently reported that the vinylphosphonates bearing linear monoterpenoid functional groups undergo Lewis acid-catalyzed intramolecular ene reactions under mild conditions.[4] This new and convenient method enabled the construction of functionalized cyclic terpenoids. To compare the reactivity of dienyl- and trienylphosphonates with the vinylphosphonates and to investigate a new approach to cyclic terpenoids, this methodology was applied to the above prepared phosphonates. Although treatment of vinylphosphonate **14** with a Lewis acid ($SnCl_4$) resulted in an ene product (eq 1),[4,7] dienylphosphonate **7a** gave a formal [2 + 2] cycloadduct **16a** in the presence of the same Lewis acid (eq 2). The Lewis acid-catalyzed [2 + 2] cycloaddition using α,β-unsaturated esters or enones has been extensively studied over the last years.[8] On the other hand, cyclobutane formation from 1,3-dienones or their analogues has been rarely observed in synthetic chemistry.[9]



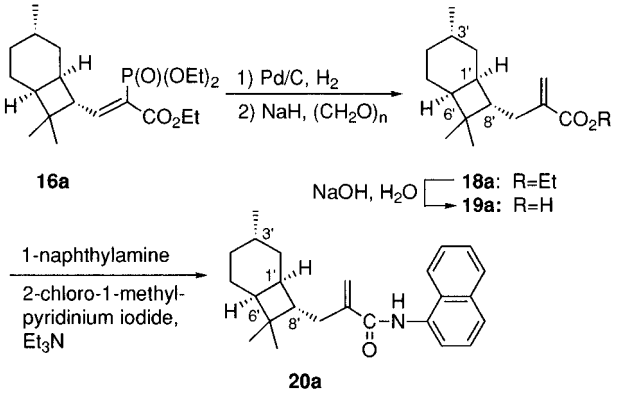
14 **15**



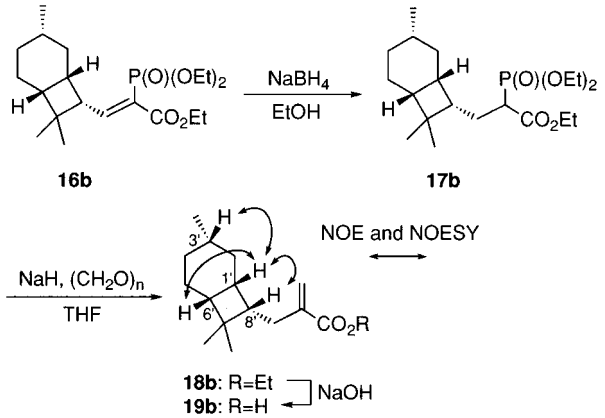
7a **16a**

To improve the yield of **16a**, the dienylphosphonate **7a** was allowed to react in the presence of several Lewis acids such as $EtAlCl_2$, $TiCl_4$, and $FeCl_3$ (Table 2). $EtAlCl_2$ at −25 °C afforded **16a** in 47% yield and its stereoisomer **16b** in 10% yield. Interestingly, **16b** was the major isomer formed (33% yield) by the use of the same aluminum reagent ($EtAlCl_2$) at 0 °C. In contrast to the vinylphosphonates, no ene reaction product was obtained from the dienylphosphonate **7a** regardless of Lewis acids or reaction temperature employed. The resulting [2 + 2] product **16a** was hydrogenated (Pd/C) followed by the Wittig−Horner reaction with paraformaldehyde to give an expected bicyclic sesquiterpene **18a**, containing a novel type of carbon skeleton (Scheme 2).

Scheme 2



Scheme 3



The sesquiterpene **18a** was transformed into amide **20a**, which produced good quality crystals (Scheme 2). The relative configuration of the [2 + 2] cycloadduct **16a** was determined by X-ray crystallography of **20a** (see Figure 1, Supporting Information).

The ^1H NMR spectrum (500 MHz) of the cycloadduct **16b** showed characteristic resonances of the olefinic proton at δ 7.35 (dd, J_{H-H} = 11.9 Hz, $^3J_{P-H}$ = 44.3 Hz) (see Experimental Section). The large coupling (44.3 Hz) between phosphorus and olefinic proton proves that the olefin geometry of **16b** is *Z*.[4] The relative configuration of the bicyclo[4.2.1]skeleton of **16b** was determined by ^1H NMR spectroscopy of **19b** which was derived from **16b** in three steps.[10] As shown in Scheme 3, NOE and NOESY experiments of **19b** showed that H-1′, H-3′, H-6′, and H-8′ on the bicyclo[4.2.1]octane ring have the cis configuration to each other. Accordingly, the structure of the isomer **16b** was assigned as the corresponding (1′*S**,3′*S**,6′*R**,8′*R**)-derivative.

A plausible mechanism for the Lewis acid-catalyzed formal [2 + 2] cycloaddition is shown in Scheme 4. In these annulations, *cis*-fused cycloadducts **16a** and **16b** were generated. This suggested that the reaction could proceed via chairlike zwitterionic transition states **A**−**D**

(7) For the ene reaction of vinylphosphonates, see: (a) Albisetti, C. J.; Fisher, N. G.; Hogsed, M. J.; Joyce, R. M. *J. Am. Chem. Soc.* **1956**, *78*, 2637. (b) Snider, B. B.; Philips, G. B. *J. Org. Chem.* **1983**, *48*, 3685. (c) Sarker, T. K.; Rao, P. S. V. S. *Synth. Commun.* **1989**, *19*, 1281.

(8) Recent papers, see: (a) Brengel, G. P.; Rithner, C.; Meyers, A. I. *J. Org. Chem.* **1994**, *59*, 5144. (b) Knölker, H.-J.; Baum, G.; Graf, R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1612. (c) Monti, H.; Audran, G.; Léandri, G.; Monti, J.-P. *Tetrahedron Lett.* **1994**, *35*, 3073. (d) Narasaka, K.; Hayashi, Y.; Shimazu, H.; Niihata, S. *J. Am. Chem. Soc.* **1992**, *114*, 8869 and references therein.

(9) Majetich, G.; Defauw, J.; Ringold, C. *J. Org. Chem.* **1988**, *53*, 50.

(10) Hydrogenation of **16b** with Pd/C unexpectedly gave a complex mixture, while **17b** was obtained in good yield by using $NaBH_4$.

Scheme 4

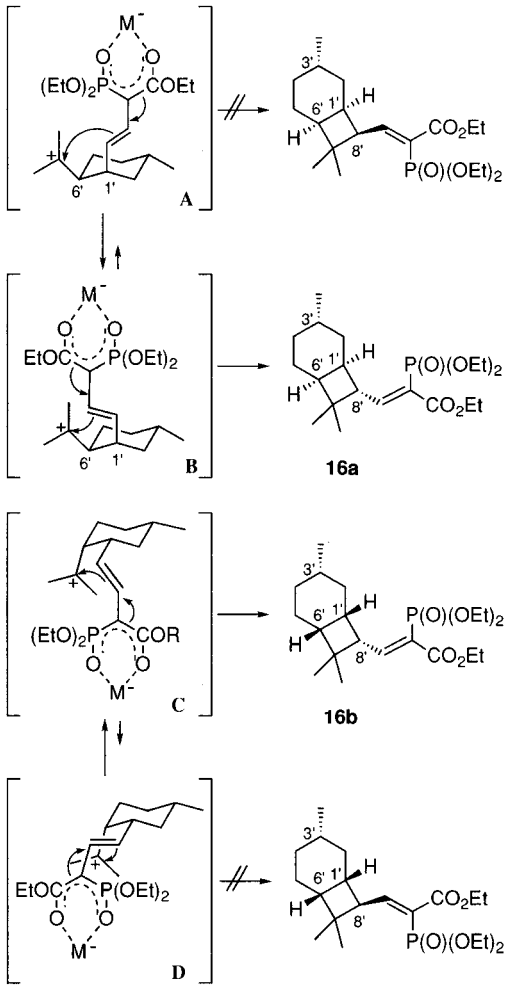


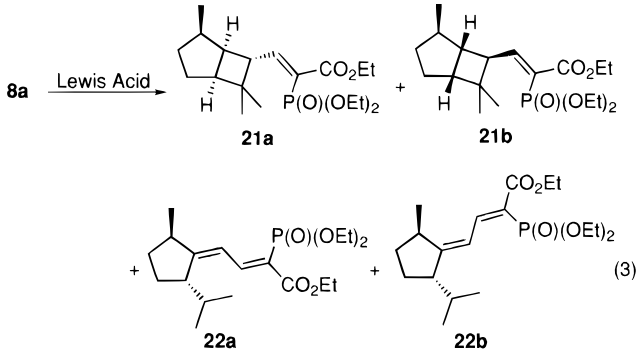
Table 3. Lewis Acid-Catalyzed Cyclization of 1,3-Dienylphosphonate 8a[a]

entry	Lewis acid (equiv)	temp/°C	time/h	products (yield/%)[b]	
1	Me_2AlCl (1.5)	rt	8	**21a** (8)	**21b** (13)
2	$BF_3{\cdot}OEt_2$ (1.5)	rt	1.5	**21a** (5)	**21b** (9)
3	$SnCl_4$ (2)	rt	6.5	**21a** (20)	
4[c]	$SnCl_4$ (2)	reflux	3	**21a** (10)	**21b** (28)
5[c]	$TiCl_4$ (2)	rt	2.5	**22a** (14)	**22b** (13)

[a] All reactions were carried out in $ClCH_2CH_2Cl$ unless otherwise noted. [b] Isolated yield. [c] Reaction was carried out in CH_2Cl_2.

as shown in Scheme 4.[11] Among them, **B** and **C** should be favored, because the π-orbital of the olefin gives a greater overlap with the cation in **B** and **C** than in **A** and **D**.[12] Accordingly, the formation of **16a** and **16b** can be rationalized by intramolecular alkylation via transition states **B** and **C**. However, the temperature dependence of the selectivity between **16a** and **16b** is still not completely elucidated.

Our further interest was focused on examining the influence of the chain length of dienylphosphonates upon the Lewis acid-catalyzed cyclization products. First, treatment of one-carbon contracted (2*Z*,4*E*)-1,3-dienylphosphonate **8a** with several Lewis acids led to the corresponding [2 + 2] cycloadducts **21a** and/or **21b**, albeit in low yields, while the use of $TiCl_4$ as a Lewis acid gave only comparative yield of a mixture of dienylphosphonates **22a** and **22b** as characterizable products (Table 3) (eq 3). The formation of **22a** and **22b** would be explained by two 1,2-hydride shift of the similar zwitterionic intermediates[13] which are reversibly formed by similar complexation of **8a** with $TiCl_4$.



(3)

Next, the homologous dienylphosphonate **11** containing a two-carbon contracted chain system was treated with 4.0 equiv of $SnCl_4$ at room temperature for 24 h to give exclusively an α-ionone derivative, ethyl (*Z*)-2-(diethylphosphono)-3-(2′,6′,6′-trimethyl-2′-cyclohexen-1′-yl)acrylate (**24a**) in 85% yield. In contrast, the use of $BF_3{\cdot}OEt_2$ (3.0 equiv) or TMSOTf (2.0 equiv) as a Lewis acid resulted in a mixture of **24a** (10−22%) and its regioisomer **24b** (40−48%) (Table 4, entries 3, 4) (Scheme 5). Similar treatment of **11** with $TiCl_4$ (2.0 equiv) led to an uncyclized chlorinated product **23** (45%) as a major component in addition to **24a** (30%) (Table 4, entry 2). The isolated compound **24a** was treated with $BF_3{\cdot}OEt_2$ under similar conditions to give only unchanged starting **24a**. This result indicates that the compound **24b** was not formed via **24a**.

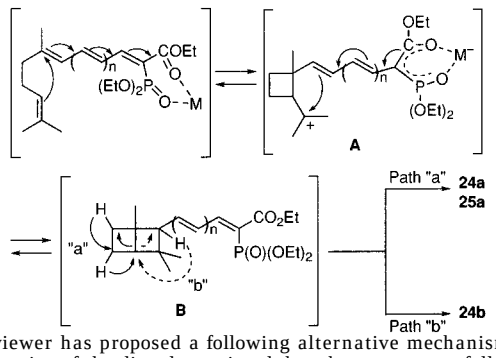
We further applied this Lewis acid-catalyzed cyclization to the 1,3,5-trienylphosphonate **12**. The phospho-

(11) The other set of transition states, in which 3′-methyl group is axial, are negligible, because of their 1,3-diaxial interaction.

(12) A reviewer has proposed a steric argument that **A** is disfavored relative to **B**: the axial substituent at C1′ does not want to be over the cyclohexane ring.

(13) (a) Snider, B. B. In *Selectivities in Lewis Acid Promoted Reactions*; Schinzer, D., Ed.; Kluwer Academic: Dordrecht, 1989; Chapter 8. (b) Snider, B. B.; Rodini, D. J.; van Straten, J. *J. Am. Chem. Soc.* **1980**, *102*, 5872.

(14) For the formation of **24a**, **25a**, and **24b**, we tentatatively propose the following mechanistic possibility: (i) the Lewis acid-catalyzed intramolecular [2 + 2] cycloaddition of dienyl- and trienylphosphonates, **11** and **12**, gives strained bicyclo[2.2.0]hexane intermediates **B** via zwitterionic [2 + 2] cycloadduct intermediates **A**. (ii) Ring opening of a cyclobutane ring, followed by double 1,2-hydride shifts (path a) and/or 1,3-hydride shift (path b) affords **24a**, **25a** and/or **24b**, respectively.



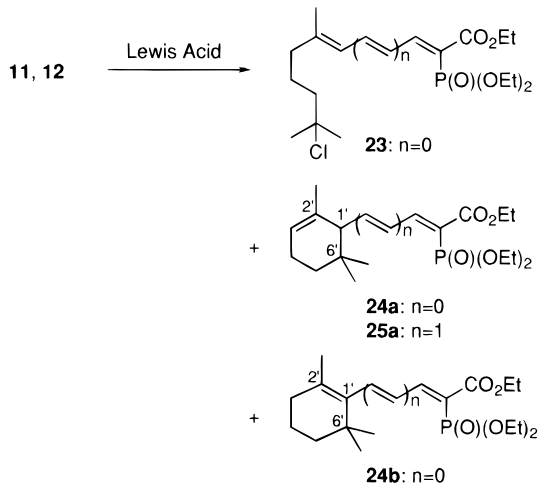
One reviewer has proposed a following alternative mechanism: (i) a deprotonation of the dienyl- or trienylphosphonate occurs, followed by protonation of a prenyl moiety to give a tertiary cation; (ii) this cation cyclizes to **24** and a subsequent deprotonation/reprotonation gives **25**. Another reviewer has explained the mechanism as follows: Lewis acid adds to the terminal trisubstituted double bond in the same manner a proton would. From the acyclic, cationic intermediate so obtained, **23** can result by chloride addition and replacement of the metal fragment by a proton. **24** and **25** are given from a 1,3,3-trimethylcyclohexyl cation formed by a cationic cyclization of this intermediate. We appreciate the suggestion of the reviewers on the possibility of these alternative mechanisms.

Table 4. Lewis Acid-Catalyzed Cyclization of 1,3-Dienylphosphonate 11 and 1,3,5-Trienylphosphonates 12[a]

entry	starting material	Lewis acid (equiv)	temp/ °C	time/ h	products (yield/%)[b]	
1[c]	**11**	$SnCl_4$ (4)	rt	24	**24a** (85)	
2[c]	**11**	$TiCl_4$ (2)	rt	6	**24a** (30)	**23** (45)
3	**11**	$BF_3{\cdot}OEt_2$ (3)	rt	25	**24a** (10)	**24b** (40)
4	**11**	TMSOTf (2)	rt	4.5	**24a** (22)	**24b** (48)
5	**12**	$SnCl_4$ (2)	rt	8	**25a** (94)	

[a] All reactions were carried out in $ClCH_2CH_2Cl$ unless otherwise noted. [b] Isolated yield. [c] Reaction was carried out in CH_2Cl_2.

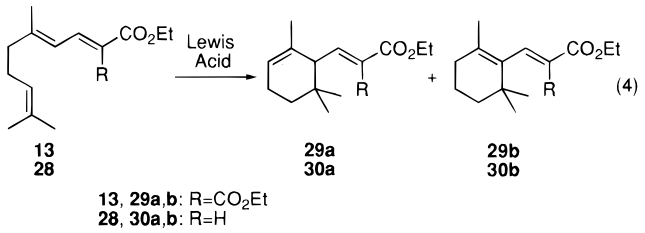
Scheme 5



nate **12** was treated with $SnCl_4$ (2.0 equiv) at room temperature for 8 h to give an expected cyclization product **25a** in excellent yield (94% yield) (Table 4, entry 5) (Scheme 5).[14] The resulting products **24a**,**b** and **25a** can be versatile intermediates for the synthesis of retinol derivatives.

As depicted in Scheme 5, the 2′-cyclohexene derivatives **24a**, **25a**, and its 1′-cyclohexenyl isomer **24b** could result from the following sequence: (i) the Lewis acid-catalyzed intramolecular [2 + 2] cycloaddition of dienyl- and trienylphosphonates, **11** and **12**, gives strained bicyclo[2.2.0]-hexane intermediates **B** via zwitterionic [2 + 2] cycloadduct intermediates **A**. (ii) Ring opening of a cyclobutane ring, followed by double 1,2-hydride shifts (path a) and/or 1,3-hydride shift (path b) affords **24a**, **25a**, and/or **24b**, respectively. The resulting products **24a**,**b** and **25a** can be versatile intermediates for the synthesis of retinol derivatives.

Lewis Acid-Catalyzed Cyclization Reaction of Conjugated Dienoic Acid Esters. To confirm the effect of the phosphono group on the [2 + 2] cycloaddition reaction, we conducted the Lewis acid-catalyzed reaction of allylidenemalonates **9**, **10**, **13**, and a dienoic acid ester **28**. They were similarly treated with several Lewis acids such as $EtAlCl_2$, $SnCl_4$, and $BF_3{\cdot}OEt_2$.



As shown in Scheme 6, eq 4, and Tables 5 and 6, similar cyclized products were obtained, and the effect

Scheme 6

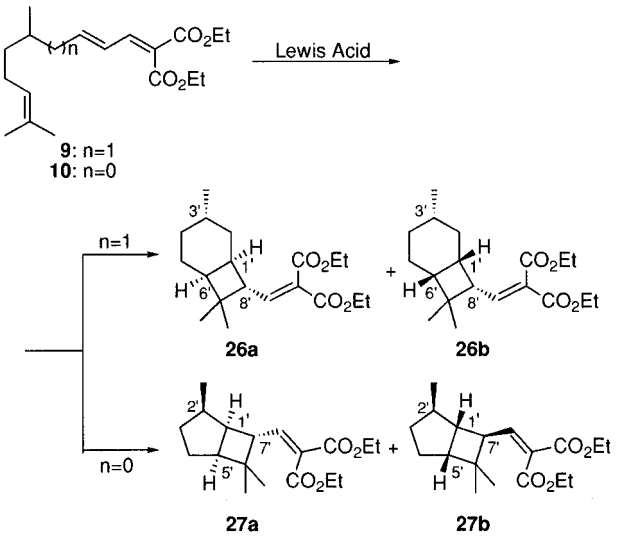


Table 5. Lewis Acid-Catalyzed Cyclization of Allylidenemalonates 9 and 10[a]

entry	starting material	Lewis acid (equiv)	temp/ °C	time/ h	products (yield/%)[b]	
1	**9**	$EtAlCl_2$ (2)	−78	1	**26a** (65)	**26b** (17)
2	**9**	$EtAlCl_2$ (2)	−25	0.5		**26b** (28)
3	**9**	$SnCl_4$ (1)	−78	1	**26a** (76)	
4	**9**	$BF_3{\cdot}OEt_2$ (2)	−25	1.5	**26a** (74)	
5	**9**	$BF_3{\cdot}OEt_2$ (2)	0	0.67	**26a** (52)	**26a** (16)
6	**10**	$BF_3{\cdot}OEt_2$ (1.5)	0	0.67	**27a**+**27b** (59)[c]	

[a] All reactions were carried out in CH_2Cl_2. [b] Isolated yield. [c] Ratio of **27a**:**27b** = 34:66. Determined by ^{1}H-NMR.

Table 6. Lewis Acid-Catalyzed Cyclization of Allylidenemalonate 13 and Dienyl Ester 28[a]

entry	starting material	Lewis acid (equiv)	temp/ °C	time/ h	products	yield/%[b] (ratio[c])
1	**13**	$SnCl_4$ (4)	rt	8	**29a**+**29b**	68 (65:35)
2	**13**	$BF_3{\cdot}OEt_2$ (2)	rt	5	**29a**+**29b**	71 (3:97)
3	**28**	$SnCl_4$ (2)	rt	3	**30a**+**30b**	84 (81:19)
4	**28**	$BF_3{\cdot}OEt_2$ (2)	rt	11	**30a**+**30b**	80 (77:23)

[a] All reactions were carried out in CH_2Cl_2. [b] Isolated yield. [c] Determined by GLC.

of the reaction conditions on the product ratio had a similar trend. These results suggest that conjugated dienes bearing electron-withdrawing groups such as phosphono and ester groups would undergo the [2 + 2] cycloaddition in the presence of Lewis acids.

The two diastereomers **26a** and **26b** thus obtained could be unequivocally assigned as diethyl (1′*R**,3′*S**,6′*S**,8′*R**)-1′,6′,6′-(trimethylbicyclo[4.2.0]octan-8′-yl)-methylenemalonate and its (1′*S**,3′*S**,6′*R**,8′*R**)-diastereomer by comparison of the ^{13}C chemical shift data with those of the corresponding homologues **16a** and **16b** (Table 7). The configuration of **27a** and **27b** was determined in a similar manner.[15]

In conclusion, we note the following results of this investigation: (1) dienylphosphonates have undergone intramolecular [2 + 2] cycloadditions in the presence of Lewis acids; (2) this [2 + 2] cycloaddition is applicable to the conjugated dienes bearing an electron-withdrawing group specifically an ester; (3) the resulting products have the potential to be employed in the synthesis of a new type of sesquiterpene.

(15) Isolation of pure samples of individual **27a** and **27b** was unsuccessful. Fortunately, the main ^{13}C NMR signals were separated to allow us the structure determination of **27a** and **27b** by comparison of the ^{13}C chemical shift data with those of **21a** and **21b**.

Table 7. ^{13}C NMR Data[a] of [2 + 2] Cycloadducts 16a,b, 21a,b, 26a,b, and 27a,b

	^{13}C chemical shifts,[b] ppm									
compd	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′	C-7′	C-8′	Me-2′	Me-3′
16a	35.7	34.6	28.7	32.1	24.6	39.8	40.8	43.9	−	23.0
16b	34.3	32.7	26.5	32.0	25.4	36.8	39.9	33.6	−	19.1
26a	35.2	34.3	28.8	32.0	24.5	39.6	40.4	44.9	−	22.8
26b	34.4	32.4	26.0	31.9	25.4	34.9	37.9	32.8	−	19.0
21a	45.4	37.2	27.0	34.2	46.9	39.7	40.5	−	13.7	−
21b	47.5	37.2	33.5	24.3	45.9	38.5	45.8	−	19.5	−
27a	44.8	36.7	26.8	34.1	46.6	38.9	41.6	−	13.4	−
27b	47.3	37.4	33.4	24.1	45.8	38.0	47.1	−	19.5	−

[a] See Scheme 2 and 6 for carbon labeling. [b] Chemical shifts for $CDCl_3$ solutions with respect to Me_4Si.

Experimental Section

Materials. $TiCl(OEt)_3$ was prepared according to the reported procedure.[16] A commercial 0.93 M solution of $EtAlCl_2$ in hexane was used.

General. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on 500 and 125.7 MHz, respectively, with Me_4Si as an internal standard. Melting points were measured in open capillary tubes and are uncorrected. Gas chromatographic results were obtained on Hicap CBP 10 (Shimadzu capillary column).

Ethyl (2*Z*,4*E*)- and (2*E*,4*E*)-2-(Diethylphosphono)-7,11-dimethyldodeca-2,4,10-trienoate (7a and 7b). To a suspension of NaH (60% dispersion in mineral oil, 0.20 g, 5.0 mmol) in THF (15 mL) was added a phosphonoacetate **5** (5.0 mmol) in THF (15 mL) at room temperature, and the mixture was stirred until an almost clear solution was formed. The solution was cooled to −78 °C and treated with $ClTi(OEt)_3$ (2.5 mL of 2.0 M in THF, 5.0 mmol). After the mixture was stirred at room temperature for 2.5 h, aldehyde **1** (0.45 g, 2.5 mmol) in THF (5 mL) was added to the solution, and the reaction mixture was stirred at 0 °C for 6 h. The reaction mixture was poured onto 4% aqueous HCl and extracted with AcOEt, and the extract was washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on silica gel (AcOEt:hexane = 1:2) to afford **7a** (0.71 g, 74%) and **7b** (0.05 g, 5%). **7a**: colorless oil; IR (neat) 1030, 1240, 1580, 1625, 1715 cm^{-1}; ^1H NMR δ 0.91 (3H, d, J = 6.7 Hz), 1.15−1.23 (1H, m), 1.30−1.39 (1H, m), 1.32 (3H, t, J = 7.1 Hz), 1.33 (6H, t, J = 7.0 Hz), 1.56−1.69 (1H, m), 1.60 (3H, s), 1.68 (3H, s), 1.91−2.06 (2H, m), 2.13 (1H, ddd, J = 14.2, 7.4, 7.4 Hz), 2.29 (1H, ddd, J = 14.2, 6.9, 6.9 Hz), 4.06−4.21 (4H, m), 4.26 (2H, q, J = 7.1 Hz), 5.05−5.11 (1H, m), 6.33−6.41 (1H, m), 7.38−7.46 (1H, m), 7.81 (1H, dd, $^3J_{P-H}$ = 44.3 Hz, J = 11.6 Hz); ^{13}C NMR (125.7 MHz) δ 14.2, 16.3 ($^3J_{P-C}$ = 6.2 Hz), 17.7, 19.5, 25.5, 25.7, 32.7, 36.8, 40.9, 61.2, 62.2 ($^2J_{P-C}$ = 5.2 Hz), 117.8 ($^1J_{P-C}$ = 186.2 Hz), 124.5, 128.6 ($^3J_{P-C}$ = 6.2 Hz), 131.4, 151.9, 157.5 ($^2J_{P-C}$ = 7.2 Hz), 166.1 ($^2J_{P-C}$ = 15.5 Hz); MS m/z 386 (M^+). Anal. Calcd for $C_{20}H_{35}O_5P$: C, 62.16; H, 9.13%. Found: C, 62.36; H, 9.48%. **7b**: colorless oil; IR (neat) 1030, 1255, 1580, 1630, 1720 cm^{-1}; ^1H NMR δ 0.90 (3H, d, J = 6.7 Hz), 1.14−1.23 (1H, m), 1.28−1.39 (1H, m), 1.33 (6H, t, J = 7.0 Hz), 1.34 (3H, t, J = 7.1 Hz), 1.55−1.67 (1H, m), 1.60 (3H, s), 1.68 (3H, s), 1.92−2.05 (2H, m), 2.06−2.13 (1H, m), 2.23−2.30 (1H, m), 4.04−4.20 (4H, m), 4.28 (2H, q, J = 7.1 Hz), 5.05−5.11 (1H, m), 6.37 (1H, ddd, J = 14.7 Hz, J = 7.3 Hz), 7.00−7.09 (1H, m), 7.48 (1H, dd, $^3J_{P-H}$ = 22.0 Hz, J = 11.0 Hz); ^{13}C NMR δ 14.2, 16.3 ($^3J_{P-C}$ = 7.2 Hz), 17.7, 19.5, 25.5, 25.7, 32.6, 36.8, 40.8, 61.0, 62.4 ($^2J_{P-C}$ = 5.2 Hz), 118.3 ($^1J_{P-C}$ = 186.2 Hz), 124.4, 128.0 ($^3J_{P-C}$ = 18.6 Hz), 131.4, 150.8, 155.7 ($^2J_{P-C}$ = 8.3 Hz), 164.8 ($^2J_{P-C}$ = 16.5 Hz); MS m/z 386 (M^+). Anal. Calcd for $C_{20}H_{35}O_5P$: C, 62.16; H, 9.13%. Found: C, 62.00; H, 9.26%.

Synthesis of Dienyl- and Trienylphosphonates and Allylidenemalonates (8−13). General Procedure. To a solution of $ClTi(OEt)_3$ (2.5 mL of 2.00 M in THF, 5.0 mmol), triethylphosphonoacetate **5** or diethyl malonate **6** (5.0 mmol), and an aldehyde **1**−**4** (2.5 mmol) in 30 mL of THF was added Et_3N (0.70 mL, 5.0 mmol) at 0 °C, and then the mixture was stirred for 6−26 h; after similar workup, the residue was chromatographed on silica gel (AcOEt:hexane = 1:2 or 1:9) to afford **8a**,**b**, **9**−**13**. The yields of the products and reaction conditions were summarized in Table 1. The compound **8a** had the following physical properties. The physical properties for compound **8b**−**13** are provided in the Supporting Information.

Ethyl (2*Z*,4*E*)-2-(Diethylphosphono)-6,10-dimethylundeca-2,4,9-trienoate (8a): colorless oil; IR (neat) 1030, 1240, 1580, 1630, 1715 cm^{-1}; ^1H NMR δ 1.06 (3H, d, J = 6.7 Hz), 1.32 (3H, t, J = 7.0 Hz), 1.33 (6H, t, J = 7.2 Hz), 1.36−1.45 (2H, m), 1.58 (3H, s), 1.68 (3H, d, J = 0.9 Hz), 1.96 (2H, dt, J = 7.6, J = 7.6 Hz), 2.35−2.43 (1H, m), 4.08−4.21 (4H, m), 4.26 (2H, q, J = 7.0 Hz), 5.05−5.10 (1H, m), 6.27 (1H, dd, J = 15.0, 8.1 Hz), 7.40 (1H, dd, J = 15.0, 11.6 Hz), 7.81 (1H, dd, $^3J_{P-H}$ = 44.0 Hz, J = 11.6 Hz); ^{13}C NMR δ 14.2, 16.3 ($^3J_{P-C}$ = 7.2 Hz), 17.7, 19.7, 25.7, 25.8, 36.5, 37.2, 61.2, 62.2 ($^2J_{P-C}$ = 4.1 Hz), 117.9 ($^1J_{P-C}$ = 186.2 Hz), 124.1, 125.8 ($^3J_{P-C}$ = 5.2 Hz), 131.8, 157.8 ($^2J_{P-C}$ = 8.3 Hz), 158.4 ($^4J_{P-C}$ = 2.1 Hz), 166.1 ($^2J_{P-C}$ = 14.5 Hz); MS m/z 372 (M^+). Anal. Calcd for $C_{19}H_{33}O_5P$: C, 61.27; H, 8.93%. Found: C, 60.91; H, 9.09%.

Synthesis of Ethyl (2*E*,4*E*)-5,9-Dimethyldeca-2,4,8-trienoate (28). To a suspension of NaH (60% dispersion in mineral oil, 0.10 g, 2.5 mmol) in THF (10 mL) was added triethyl phosphonoacetate (0.56 g, 2.5 mmol) in THF (5 mL) at room temperature and the mixture was stirred until an almost clear solution formed. Geranial (**3**) (0.38 g, 2.5 mmol) in THF (5 mL) was added to the solution, and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was poured onto 4% aqueous HCl and extracted with AcOEt, and the extract was washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on silica gel (AcOEt:hexane = 1:9) to afford **28** (0.45 g, 73%). **28**: pale yellow oil; IR (neat) 1610, 1640, 1720 cm^{-1}; ^1H NMR δ 1.29 (3H, t, J = 7.0 Hz), 1.61 (3H, s), 1.68 (3H, s), 1.89 (3H, s), 2.10−2.20 (4H, m), 4.20 (2H, q, J = 7.0 Hz), 5.07 (1H, brs), 5.78 (1H, d, J = 15.3 Hz), 5.99 (1H, d, J = 11.6 Hz), 7.58 (1H, dd, J = 15.3, 11.6 Hz); ^{13}C NMR δ 14.3, 17.3, 17.6, 25.6, 26.3, 40.2, 60.0, 118.9, 123.2, 123.3, 132.2, 140.9, 149.6, 167.6. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97%. Found: C, 75.63; H, 9.86%.

General Procedure for Intramolecular [2 + 2] Cycloaddition Reaction of Dienylphosphonates, Trienylphosphonates, Allylidenemalonates and Dienoic Acid Ester. To a stirred solution of a dienylphosphonate **7a**, **8a**, **11**, trienylphosphonate **12**, allylidenemalonate **9**, **10**, **13** or dienoic acid ester **28** (1.0 mmol) in $ClCH_2CH_2Cl$ or CH_2Cl_2 (8 mL) was added a Lewis acid under a nitrogen atmosphere. After the reaction mixture was stirred for 0.17−42 h, the reaction was quenched by the slow addition of 4% aqueous HCl. The mixture was extracted with CH_2Cl_2 and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on preparative TLC (silica gel, AcOEt:hexane = 1:1 or 1:9) to afford **16**, **21**−**27**, **29**, and **30**. The yields of the products and reaction conditions were summarized in Tables 2−6. The compounds **16a** and **16b** had the following properties. The physical properties for compound **21**−**27**, **29**, and **30** are provided in the Supporting Information.

Ethyl (1′*R,3′*S**,6′*S**,8′*R**)-(*Z*)-2-(diethylphosphono)-3-(3′,7′,7′-trimethylbicyclo[4.2.0]octan-8′-yl)acrylate (16a)**: colorless oil; IR (neat) 1030, 1255, 1600, 1720 cm^{-1}; ^1H NMR δ 0.64−0.74 (1H, m), 0.86 (3H, d, J = 6.1 Hz), 0.92−1.01 (1H, m), 0.98 (3H, s), 1.18 (3H, s), 1.32 (3H, t, J = 7.0 Hz), 1.34 (6H, t, J = 7.0 Hz), 1.49−1.65 (3H, m), 1.67−1.80

(16) Reetz, M. T.; Westermann, J.; Steinbach, R.; Wenderoth, B.; Peter, R.; Ostarek, R.; Maus, S. *Chem. Ber.* **1985**, *118*, 1421.

(3H, m), 2.38−2.46 (1H, m), 3.95 (1H, dd, J = 11.1, 11.1 Hz), 4.06−4.20 (4H, m), 4.24 (2H, q, J = 7.0 Hz), 7.42 (1H, dd, $^3J_{P-H}$ = 45.8 Hz, J = 11.1 Hz); ^{13}C NMR δ 14.2, 16.4 ($^3J_{P-C}$ = 6.2 Hz), 23.0, 24.1, 24.4, 24.6, 28.7, 32.1, 34.6, 35.7 ($^4J_{P-C}$ = 2.1 Hz), 39.8, 40.8 ($^4J_{P-C}$ = 2.1 Hz), 43.9 ($^3J_{P-C}$ = 4.1 Hz), 61.3, 62.0 ($^2J_{P-C}$ = 6.2 Hz), 124.4 ($^1J_{P-C}$ = 186.2 Hz), 163.3 ($^2J_{P-C}$ = 9.3 Hz), 166.0 ($^2J_{P-C}$ = 16.6 Hz); MS m/z 386 (M^+). Anal. Calcd for $C_{20}H_{35}O_5P$: C, 62.16; H, 9.13%. Found: C, 62.15; H, 9.35%.

Ethyl (1′*S,3′*S**,6′*R**,8′*R**)-(*Z*)-2-(Diethylphosphono)-3-(3′,7′,7′-trimethylbicyclo[4.2.0]octan-8′-yl)acrylate (16b)**: colorless oil; IR (neat) 1030, 1260, 1590, 1715 cm^{-1}; ^{1}H NMR δ 0.68−0.78 (1H, m), 0.85 (3H, d, J = 6.1 Hz), 0.86 (3H, d, J = 6.7 Hz), 0.89−0.96 (1H, m), 0.99 (3H, d, J = 7.0 Hz), 1.24−1.37 (2H, m), 1.30 (3H, t, J = 7.1 Hz), 1.33 (6H, t, J = 7.2 Hz), 1.39−1.48 (3H, m), 1.92−2.03 (2H, m), 2.76 (1H, dd, J = 11.9, 5.2 Hz), 4.07−4.21 (4H, m), 4.22 (2H, q, J = 7.1 Hz), 7.35 (1H, dd, $^3J_{P-H}$ = 44.2 Hz, J = 11.9 Hz); ^{13}C NMR δ 14.2, 16.4 ($^3J_{P-C}$ = 2.0 Hz), 18.2, 19.1, 22.1, 25.1, 26.4, 32.0, 32.7, 33.6 ($^3J_{P-C}$ = 5.2 Hz), 34.3, 36.8, 39.9, 61.0, 61.9 ($^2J_{P-C}$ = 5.2 Hz), 119.0 ($^1J_{P-C}$ = 188.3 Hz), 167.9 ($^2J_{P-C}$ = 15.5 Hz), 167.9 ($^2J_{P-C}$ = 8.3 Hz); MS m/z 386 (M^+). Anal. Calcd for $C_{20}H_{35}O_5P$: C, 62.16; H, 9.13%. Found: C, 62.20; H, 9.52%.

Synthesis of (1′*R,3′*S**,6′*S**,8′*R**)-2-(Ethoxycarbonyl)-3-(3′,7′,7′-trimethylbicyclo[4.2.0]octan-8′-yl)propene (18a).** Hydrogenation of a vinylphosphonate **16a** (0.39 g, 1.0 mmol) was accomplished at 1 atm hydrogen pressure for 12 h in EtOH (8 mL) over Pd−C (10%; 0.20 g). The mixture was filtered through a Celite pad. After evaporation of the solvent in vacuo, the residue was treated with NaH (60% dispersion in mineral oil, 0.032 g, 0.80 mmol) in THF (5 mL) at room temperature. After 0.5 h, paraformaldehyde (0.072 g, 2.4 mmol) was added and was stirred at room temperature for 5.5 h. Then, aqueous NH_4Cl was added, and the mixture was extracted with AcOEt, washed with brine, and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on preparative TLC (silica gel, AcOEt:hexane = 1:24) to afford **18a** (0.186 g, 87%). **18a**: colorless oil; IR (neat) 1600, 1710 cm^{-1}; ^{1}H NMR δ; 0.60−0.71 (1H, m), 0.84−0.97 (1H, m), 0.83 (3H, d, J = 6.4 Hz), 0.90 (3H, s), 1.05 (3H, s), 1.30 (3H, t, J = 6.4 Hz), 1.33−1.43 (1H, m), 1.45−1.55 (3H, m), 1.62−1.71 (2H, m), 2.04−2.13 (2H, m), 2.22 (1H, dd, J = 14.7, 5.8 Hz), 2.32 (1H, dd, J = 14.7, 5.8 Hz), 4.21 (1H, q, J = 7.1 Hz), 4.21 (1H, q, J = 7.1 Hz), 5.52 (1H, d, J = 1.2 Hz), 6.06 (1H, d, J = 1.2 Hz); ^{13}C NMR δ 14.2, 23.0, 23.5, 24.1, 24.7, 28.9, 32.5, 32.6, 34.9, 35.6, 37.4, 40.2, 42.9, 60.5, 124.7, 140.5, 167.5; MS m/z 264 (M^+). Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.23; H, 10.67%. Found: C, 77.19; H, 10.94%.

Synthesis of (1′*S,3′*S**,6′*R**,8′*R**)-2-(Ethoxycarbonyl)-3-(3′,7′,7′-trimethylbicyclo[4.2.0]octan-8′-yl)propene (18b).** To a solution of a vinylphosphonate **16b** (0.39 g, 1.0 mmol) in 2 mL of EtOH was added a solution of $NaBH_4$ (0.019 g, 0.50 mmol) in EtOH (8 mL) at room temperature. The mixture was stirred at room temperature for 1 h. The reaction was quenched by addition of water. After evaporation of the solvent, the residue was extracted with Et_2O, and the extract was washed with 4% aqueous HCl and brine and dried over Na_2SO_4. After evaporation of the solvent in vacuo, the residue gave the crude phosphonoacetate **17b**. To a solution of an in situ-generated carbanion from a crude compound **17b** (0.80 mmol) and NaH (60% dispersion in mineral oil, 0.032 g, 0.80 mmol) in THF (5 mL) at room temperature during 0.5 h was added paraformaldehyde (0.072 g, 2.4 mmol). After the reaction mixture was stirred at room temperature for 3 h, the reaction was quenched with the addition of aqueous NH_4Cl. The mixture was extracted with AcOEt, washed with brine, and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on preparative TLC (silica gel, AcOEt:hexane = 1:24) to afford **18b** (0.161 g, 68%). **18b**: colorless oil; IR (neat) 1630, 1720 cm^{-1}; ^{1}H NMR δ 0.38−0.43 (1H, m), 0.52−0.57 (1H, m), 0.66 (1H, dddd, J = 12.3, 12.3, 12.3, 5.5 Hz), 0.83 (3H, d, J = 6.7 Hz), 0.90 (3H, d, J = 7.0 Hz), 0.92 (3H, d, J = 7.0 Hz), 1.04−1.39 (5H, m), 1.31 (3H, t, J = 7.2 Hz), 1.81−1.88 (1H, m), 1.97 (1H, ddd, J = 14.5, 5.5, 2.7 Hz), 2.13 (1H, dd, J = 16.7, 8.9 Hz), 2.63 (1H, dd, J = 16.7, 5.4 Hz), 4.21 (2H, q, J = 7.1 Hz), 5.61 (1H, t, J = 1.7 Hz), 6.15 (1H, m); ^{13}C NMR δ 14.2, 18.7, 19.5, 22.4, 25.9, 26.5, 26.9, 27.4, 28.6, 30.5, 32.5, 32.8, 33.0, 60.5, 123.7, 141.6, 167.6; MS m/z 264 (M^+). Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.23; H, 10.67%. Found: C, 76.83; H, 10.96%.

Hydrolysis of Acrylic Acid Ester 18a and 18b. General Procedure. A solution of acrylic acid ester **18a** or **18b** (1.0 mmol) in EtOH−water (1:1, 5 mL) containing NaOH (0.10 g, 2.5 mmol) was stirred at reflux for 3 h. After evaporation of the solvent under reduced pressure, the mixture was acidified with 4% aqueous HCl and extracted with Et_2O. The extract was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on preparative TLC (silica gel AcOEt:hexane = 1:2) to give the acid **19a** and **19b**.

(1′*R,3′*S**,6′*S**,8′*R**)-3-(3′,7′,7′-Trimethylbicyclo[4.2.0]-octan-8′-yl)-2-propenecarboxylic acid (19a)**: yield 0.203 g (0.859 mmol, 86%); pale yellow crystal; mp 32.0−34.0 °C; IR (KBr) 1625, 1690 cm^{-1}; ^{1}H NMR δ 0.61−0.70 (1H, m), 0.88−0.96 (1H, m), 0.84 (3H, d, J = 6.1 Hz), 0.92 (3H, s), 1.05 (3H, s), 1.35−1.56 (4H, m), 1.61−1.71 (2H, m), 2.07−2.16 (2H, m), 2.23 (1H, dd, J = 14.7, 5.5 Hz), 2.33 (1H, dd, J = 14.7, 6.1 Hz), 5.67 (1H, d, J = 1.2 Hz), 6.25 (1H, brs); ^{13}C NMR δ 23.0, 23.5, 24.2, 24.6, 28.8, 32.0, 32.5, 34.9, 35.7, 37.4, 40.3, 42.8, 127.3, 139.7, 173.0; MS m/z 236 (M^+). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23%. Found: C, 75.99; H, 10.33%.

(1′*S,3′*S**,6′*R**,8′*R**)-3-(3′,7′,7′-Trimethybicyclo[4.2.0]-octan-8′-yl)-2-propenecarboxylic acid (19b)**: yield 0.215 g (0.910 mmol, 91%); pale yellow viscous oil; IR (neat) 1630, 1690 cm^{-1}; ^{1}H NMR δ 0.39−0.44 (1H, m), 0.57 (1H, ddd, J = 8.7, 5.5, 5.5 Hz), 0.66 (1H, dddd, J = 12.3, 12.3, 12.3, 5.5 Hz), 0.84 (3H, d, J = 6.7 Hz), 0.90 (3H, d, J = 6.7 Hz), 0.92 (3H, d, J = 6.7 Hz), 1.04−1.28 (4H, m), 1.34−1.40 (1H, m), 1.82−1.91 (1H, m), 1.97 (1H, ddd, J = 14.3, 5.5, 2.7 Hz), 2.13 (1H, dd, J = 16.8, 8.9 Hz), 2.64 (1H, dd, J = 16.8, 5.2 Hz), 5.75 (1H, d, J = 1.2 Hz), 6.33 (1H, brs); ^{13}C NMR δ 18.8, 19.5, 22.4, 25.9, 26.5, 26.9, 27.5, 28.5, 30.1, 32.5, 32.9, 33.1, 126.5, 140.8, 173.2; MS m/z 236 (M^+). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23%. Found: C, 76.46; H, 10.16%.

Preparation of *N*-(1-Naphthyl)(1′*R,3′*S**,6′*S**,8′*R**)-3-(3′,7′,7′-trimethylbicyclo[4.2.0]octan-8′-yl)-2-propenecarboxamide (20a).** To a suspension of 2-chloro-1-methylpyridinium iodide (0.307 g, 1.20 mmol) and acid **20a** (0.236 g, 1.00 mmol) in CH_2Cl_2 (3 mL) was added a solution of 1-naphthylamine (0.172 g, 1.20 mmol) and Et_3N (0.33 mL, 2.4 mmol) in CH_2Cl_2 (2 mL) at room temperature. After being stirred overnight, the reaction mixture was washed with 4% aqueous HCl and H_2O. Solvent was removed in vacuo, and the residue was chromatographed on preparative TLC (silica gel AcOEt: hexane = 1:9) to give **20a**: yield 0.152 g (0.420 mmol, 42%); colorless crystal; mp 116.0−118.0 °C; IR (KBr) 1250, 1270, 1500, 1530, 1620, 1650 cm^{-1}; ^{1}H NMR δ 0.61−0.70 (1H, m), 0.83 (3H, d, J = 6.4 Hz), 0.92−1.01 (1H, m), 0.96 (3H, s), 1.10 (3H, s), 1.38−1.54 (3H, m), 1.59−1.73 (3H, m), 2.13−2.21 (2H, m), 2.40 (1H, dd, J = 14.4, 5.6 Hz), 2.51 (1H, dd, J = 14.4, 5.5 Hz), 5.50 (1H, s), 5.80 (1H, s), 7.46−8.00 (8H, m); ^{13}C NMR δ 23.0, 23.5, 24.3, 24.6, 28.9, 32.5, 33.6, 35.1, 35.7, 37.5, 40.3, 42.8, 118.4, 120.3, 120.7, 125.8, 125.8, 126.0, 126.3, 127.1, 128.9, 132.2, 134.1, 146.1, 167.4; MS m/z 361 (M^+). Anal. Calcd for $C_{25}H_{31}NO$: C, 83.06; H, 8.64; N, 3.87%. Found: C, 82.92; H, 8.83; N, 3.80%.

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Supporting Information Available: Spectral and analytical data for compounds **8b**−**13**, **21**−**27**, **29**, and **30** and an ORTEP diagram for amide **20a** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.

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