Thio-Claisen and Cope Rearrangements. A General Method for the Synthesis of α,β,ϵ,ζ-Unsaturated Thioamides

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Abstract: Thio-Claisen rearrangement (α-allylation of α,β-unsaturated thioamides giving α-allylated β,γ-unsaturated thioamides **4**) followed by Cope rearrangement has provided a new method for the preparation of α,β,ϵ,ζ-unsaturated thioamides **9**. A series of α-allylated 3-butenoylthiopyrrolidines (**4a–c**) have rearranged to give **9** together with small amounts of β,γ,ϵ,ζ-unsaturated thioamides (**10–12**). Ethyl lanceolate has been prepared according to this procedure.

In recent years, [3,3]sigmatropic rearrangements have been one of the most actively studied topics both in theoretical[1] and practical fields.[2] From a synthetic point of view various modifications of the Claisen rearrangement, which embody significant substrate flexibility, have been developed and have played an increasingly important role in natural product synthesis owing to their high stereoselectivities.

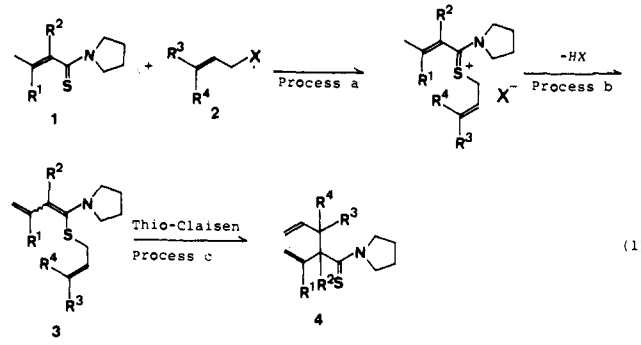
Compared with the Claisen rearrangement, the thio-Claisen rearrangement (with a sulfur atom in place of an oxygen atom) has been less studied.[3,4] Outstanding advancements in this field have been accomplished by Japanese chemists. For example, the stereoselective trisubstituted olefin synthesis reported by Nozaki and co-workers[3d-f] and an α-allylation of thioamides and its application to the indole alkaloid synthesis reported by Takano and co-workers[3h,i] represent a few general applications.

Recently we have reported the first example of the double thio-Claisen (α-allylation of α,β-unsaturated thioamides) and Cope rearrangements (γ-allylation of α,β-unsaturated thioamides),[5] which provide a general method for the synthesis of α,β,ϵ,ζ-unsaturated thioamides possessing a fundamental molecular framework abundantly observed in terpenoid natural products.[6] The present procedure, accompanied by the recent studies on the conversion of thioamides to the ordinary carbonyl compounds[7] (such as esters, ketones, and aldehydes) and some other characteristic reactions of thioamides,[8] will find widespread synthetic use. In this paper the details of our investigations of the thio-Claisen and Cope rearrangements and their application to the synthesis of ethyl lanceolate are described.

Results and Discussion

Thio-Claisen Rearrangement. α-Allylation of α,β-Unsaturated Thioamides. Equation 1 illustrates the procedure of α-allylation of α,β-unsaturated thioamides, which consists of the following three processes: alkylation of thioamides **1** with allylic halides **2** at a sulfur atom (process (a)), dehydrohalogenation to give allyl dienyl sulfides **3** (process (b)), and thio-Claisen rearrangement of **3** (process (c)). Although efforts to isolate allyl dienyl sulfides **3** have so far been unsuccessful owing to their chemical and thermal lability, the intermediacy of **3** is likely as judged from the reaction procedure[9] and the structure of the products.

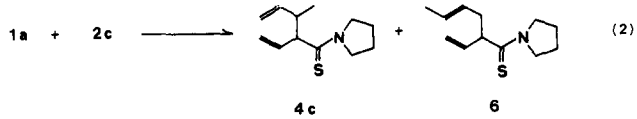
The combination of anhydrous *tert*-butyl alcohol as a solvent and DBU (1,5-diazabicyclo[5.2.0]undecene-5) as a base is found most satisfactory (Table I). Other solvents such as THF or DMF have several drawbacks, the most noticeable of which being the low conversions and low regioselectivity (Table II). Process (a) in eq 1 seems to be an equilibrium, which lies almost exclusively on the right side in protic solvents such as *tert*-butyl alcohol and ethyl alcohol (except for entry 3, Table



(1)

1a; R^1 = R^2 = H 2a; R^3 = R^4 = H, X = Br
1b; R^1 = H, R^2 = Me 2b; R^3 = R^4 = Me, X = Br
1c; R^1 = Me, R^2 = H 2c; R^3 = Me, R^4 = H, X = Cl

I), while in THF or DMF the reverse process becomes significant and the reaction does not attain completion even under forcing conditions especially for the reactions with crotyl chloride (entries 1 and 3, Table II). For such cases sodium tetraphenylborate effected the reaction to attain completion (entry 3, Table I). The reactions with unsymmetric allylic halides (crotyl chloride and prenyl bromide) provide occasionally a mixture of comparable amounts of regioisomers, which stems from the S-alkylations at both allylic termini. With respect to the regioselectivity, *tert*-butyl alcohol was found to be a superior solvent to THF. For example, α-allylation of 2-butenoylthiopyrrolidine (**1a**) with crotyl chloride (**2c**) in *tert*-butyl alcohol provided 3-methyl-2-vinyl-4-pentenoylthiopyrrolidine (**4c**) selectively in 72% yield (entry 3, Table I), while in THF a mixture of **4c** and 2-vinyl-4-hexenoylthiopyrrolidine (**6**) was obtained in a ratio of 59:41 (eq 2, entry 1, Table II).



(2)

4c 6

As a dehydrohalogenation reagent, DBU is a better choice of base than potassium *tert*-butoxide. When potassium *tert*-butoxide is used, yields are generally lower and occasionally this base causes isomerization of the first-formed β,γ-unsaturated thioamides to the conjugated thioamides. For example, **4f** was isomerized completely to 2-allyl-3-methyl-2-butenoylthiopyrrolidine (**7**) under the reaction conditions (room temperature, 1 h; entry 4, Table II).

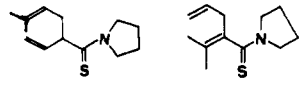


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Table I. α-Allylation of α,β-Unsaturated Thioamides via Thio-Claisen Rearrangement (Reactions in *t*-BuOH Using DBU as a Base)

entry	thioamide[a] 1	halide[a] 2 (equiv)	reaction conditions[b]	product[a] 4	yield,[c] %
1	**1a**	**2a** (1.02)	12, RT; 2.5, RT	**4a**, $R^1 = R^2 = R^3 = R^4 = H$	81 (80)
2	**1a**	**2b** (1.02)	12, RT; 1, 83 °C	**4b**, $R^1 = R^2 = H$; $R^3 = R^4 = Me$	45
				5	10
3	**1a**	**2c** (1.05)	48, RT;[d] 5, RT	**4c**, $R^1 = R^2 = R^4 = H$; $R^3 = Me$	72 (90)
4	**1b**	**2a** (1.02)	17, RT; 2, 75 °C	**4d**, $R^1 = R^3 = R^4 = H$; $R^2 = Me$	78 (84)
5	**1b**	**2c** (1.50)	4, 70 °C; 2, 70 °C	**4e**, $R^1 = R^4 = H$; $R^2 = R^3 = Me$	52 (92)
6	**1c**	**2a** (1.05)	20, RT; 2, RT	**4f**, $R^1 = Me$; $R^2 = R^3 = R^4 = H$	96
7	**1c**	**2b** (1.50)	20, RT; 5, 83 °C	**4g**, $R^1 = R^3 = R^4 = Me$; $R^2 = H$	28
8	**1c**	**2c** (1.10)	2, 75 °C; 1, 75 °C	**4h**, $R^1 = R^3 = Me$; $R^2 = R^4 = H$	93 (89)

[a] For the structures of **1a–c**, **2a–c**, and **4**, see eq 1. [b] The reaction conditions are shown in the following order: S-allylation (h, temp); dehydrohalogenation and thio-Claisen rearrangement (h, temp). [c] Yields refer to the isolated, spectroscopically and chromatographically homogeneous materials, taking into account the recovered materials (conversions are given in parentheses). [d] An equimolar amount of sodium tetraphenylborate was added in order to attain the completion of reaction.

Table II. α-Allylation of α,β-Unsaturated Thioamides via Thio-Claisen Rearrangement (Reactions in THF Using KO-*t*-Bu as a Base)

entry	thioamide[a] 1	halide[a] 2 (equiv)	reaction conditions[b]	product[c] [ratio]	yield,[d] %
1	**1a**	**2c** (1.06)	4, 66 °C; 1, RT	**4c, 6**[e] [59:41]	97 (47)
2	**1b**	**2a** (1.50)	5, 66 °C; 4, 66 °C	**4d**	52 (81)
3	**1b**	**2c** (1.50)	6, 80 °C; 1, 60 °C[f]	**4e**	29 (54)
4	**1c**	**2a** (1.30)	20, RT; 1, RT	**7**[e]	45 (84)

[a] For the structures of **1a–c** and **2a–c**, see eq 1. [b] The reaction conditions are shown in the following order: S-allylation (h, temp); dehydrohalogenation and thio-Claisen rearrangement (h, temp). [c] For the structures of **4c, 4d,** and **4e**, see eq 1 and Table I. [d] Yields refer to the isolated, spectroscopically, and chromatographically homogeneous materials, taking into account the recovered materials (conversion of the starting materials is given in parentheses). [e] See text for the structure. [f] This run was undertaken in DMF.

Table III. γ-Allylation of α,β-Unsaturated Thioamides via Cope Rearrangement

entry	reactant[a]	solvent (time, h)[b]	product[c]	ratio[d]	yield, %[e]
1	**4a**	tetralin (2.0)	**9Aa, 10**	[74:26]	93
2	**4b**	tetralin (1.3)	**9Ab, 11**	[74:26]	91
3	**4c**	tetralin (1.8)	**9Ac, 12**	[77:23]	88
4	**4d**	tetralin (0.8)	**9Ad, 9Bd**	[44:56]	90
5	**4d**	ethylene glycol (0.5)	**9Ad, 9Bd**	[61:39]	88
6	**4d**	VPC[f]	**9Ad, 9Bd**	[71:29]	
7	**4e**	tetralin (0.5)	**9Ae + 9Ce, 9Be + 9De**	[48:52]	95
8	**4e**	DMF (3.0)	**9Ae + 9Ce, 9Be + 9De**	[88:12]	95
9	**4e**	VPC[g]	**9Ae + 9Ce, 9Be + 9De**	[85:15]	
10	**4f**	tetralin (9.0)	**9Af, 9Bf**[h]	[67:33]	75
11	**4g**	tetralin (1.0)	**9Ag, 9Bg**[h]	[65:35]	85
12	**4h**	tetralin (0.5)	**9Ah, 9Dh**[h]	[78:22]	95

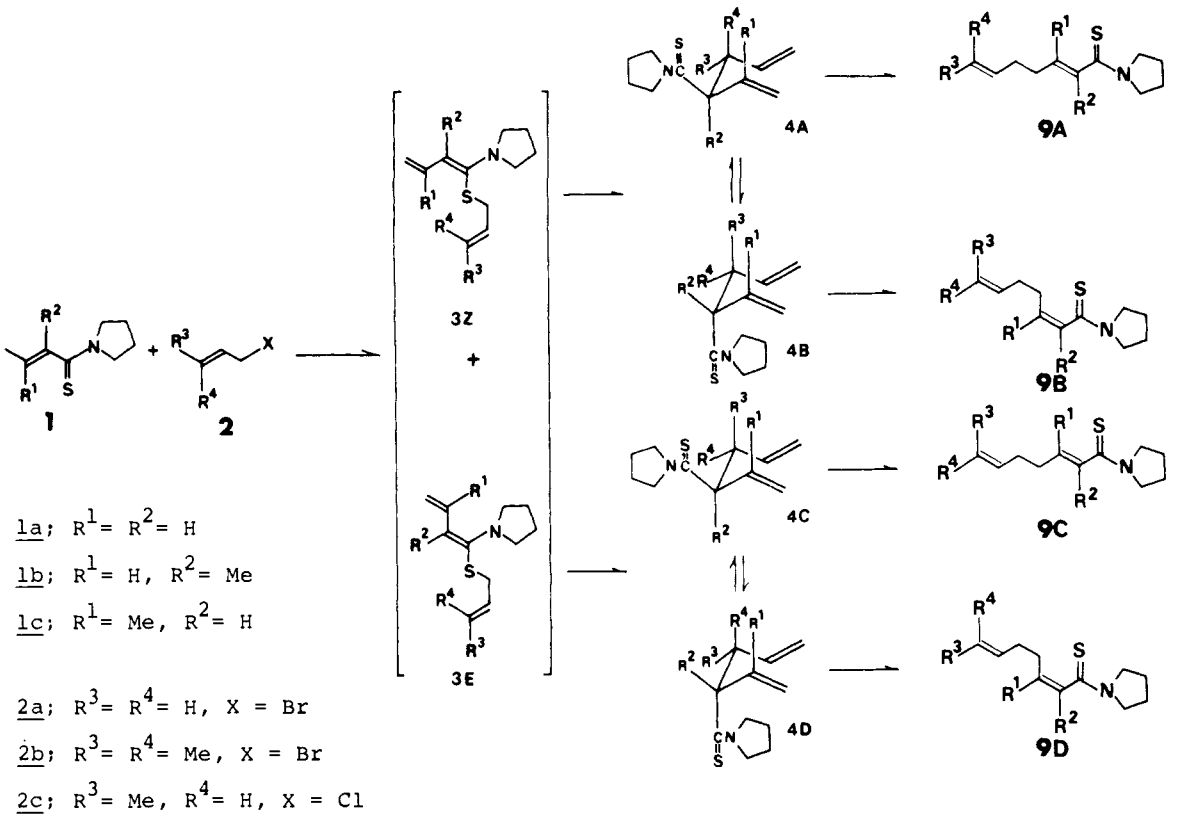
[a] For the structure of **4**, see Table I and eq 1. [b] The reaction was carried out at the refluxing temperature of a solvent under an argon atmosphere. [c] For the structures of **9, 10,** and **12**, see Scheme I. The capital letters **A–D** are meant to differentiate the geometric isomers. The lower case letters **a–h** are meant to differentiate the substituents and correspond to the lower case letters of compounds **4**. [d] Ratio is determined on the basis of area intensities of VPC and ^1H NMR. [e] Yield refers to the mixture isolated by column chromatography. [f] Injection temperature 250 °C, column temperature 220 °C. [g] Injection temperature 275 °C, column temperature 225 °C. [h] Structures of products were determined as the corresponding amides.

First inspection of Table I reveals the correlation between yields and the structures of products: the higher the steric bulk around the newly formed C–C bonds, the lower the yields. No trace of the expected product was obtained for the reaction which forms a bond between tertiary carbons as in the reaction of **1b** with **2b**. However, it should be emphasized that the present procedure permits the allylation of the tertiary carbons α to the thiocarbonyl group (entries 4 and 5, Table I). α-Allylation by the previously reported method[3i] is limited only to the primary or secondary carbons α to the thiocarbonyl group.

It seems pertinent to point out that the present thio-Claisen rearrangement proceeds at much lower temperatures (ranging from ambient temperatures to the refluxing temperature of *tert*-butyl alcohol as opposed to ~200 °C[3c]) even for the reactions leading to C–C bond formation between highly substituted termini, than is required for the rearrangement of allyl vinyl sulfides (with H or alkyl groups in place of the amino group).[3c]

Cope Rearrangement. γ-Allylation of α,β-Unsaturated Thioamides. The thioamides (**4a–h**) possessing the 1,5-hexadienyl moiety obtained by the α-allylation procedure were subjected to Cope rearrangement. Reaction conditions and results are summarized in Table III. The rearrangement was brought to completion within 2 h except for the case of **4f**, which required an exceptionally long reaction time. A total profile of thio-Claisen and Cope rearrangements is illustrated in Scheme I. While α-allylation with allyl bromide or prenyl

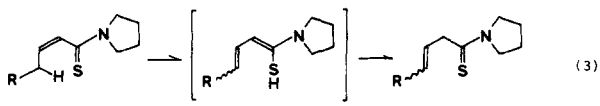
Scheme I. Thio-Claisen and Cope Rearrangements



bromide provides a racemate (**4A** = **4C**), with crotyl chloride α-allylation provides a mixture of diastereoisomers (**4A** and **4C** via **3**-*Z* and **3**-*E*,[10] respectively).[11] Consequently two geometric isomers (**9A** and **9B**) for the former and four geometric isomers (**9A, 9B, 9C,** and **9D**) for the latter are expected as the products of Cope rearrangement.

The result in entry **4** (Table III) suggests that methyl and thioamide groups favor the equatorial position in a similar order of magnitude in tetralin. In ethylene glycol or under VPC measurement conditions (injection temperature 250 °C, column temperature 220 °C, SiDC 550), **4d** rearranged to give **9Ad** preferentially over **9Bd,** which probably reflects the favorable hydrogen bonding or dipole–dipole interaction of the equatorial thioamide group under these conditions.

Thermolysis of a series of α-allylated 3-butenoylthiopyrrolidines (**4a–c**) provided γ-allylated α,β-unsaturated thioamides (**9Aa, 9Ab,** and **9Ac,** respectively) together with small amounts of deconjugated thioamides (**10, 11,** and **12,** respectively). The latter compounds might be derived from α,β-unsaturated thioamides with *Z* configuration (**9Ba, 9Bb,** and **9Dc,** respectively) via dienyl mercaptan intermediates as illustrated in eq 3.



(3)

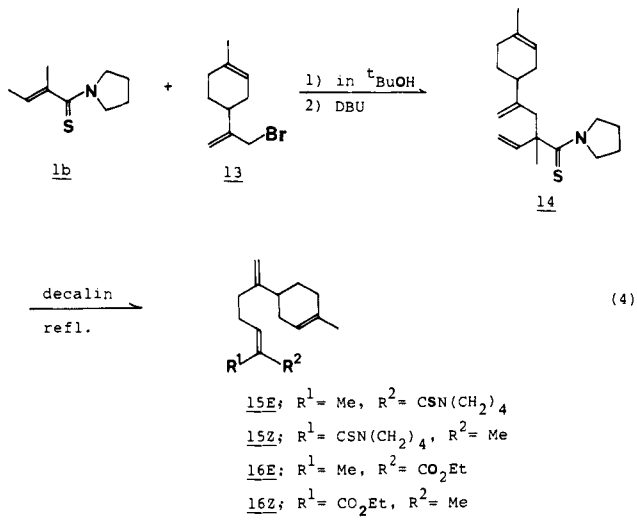
10; R = $CH_2CH{=}CH_2$
11; R = $CH_2CH{=}C(CH_3)_2$
12; R = $CH_2CH{=}CHCH_3$

All the four possible isomers were derived by the thermolysis of **4e** in tetralin, which appeared as a pair of poorly separated double peaks with almost the same area intensities by VPC. A pair of products (**9Ae** and **9Ce**) with *E* configuration with respect to the Δ^2 double bond had longer retention times than another pair of products with *Z* configuration (**9Be** and **9De**). The proportion of the former dramatically increased on thermolysis in refluxing DMF or on subjection of **4e** under the VPC measurement conditions, again probably owing to the favorable equatorial orientation of the thioamide group under these conditions.

Making a contrast to this, only two isomers (**9Ah** and **9Dh**) were obtained for the thermolysis of **4h** , which suggests that conformers **4Ah** and **4Dh** are preferred over **4Bh** and **4Ch,** respectively, owing to the presence of nonbonded interaction between pseudo-1,3-diaxial methyl groups in the latter pair.

The present sequential thio-Claisen and Cope rearrangements seem to have some advantages over the double Claisen and Cope rearrangements initiated by transetherification of allylic alcohols with dienyl ether:[12] (a) Thioamides are readily prepared from the corresponding amides by treatment with phosphorus pentasulfide and they are thermally stable, withstanding shelf storage without noticeable decomposition (see Experimental Section). (b) β,γ-Unsaturated thioamides with allylic substituents at the α position undergo the Cope rearrangement without hydrogen migration to give α,β-unsaturated thioamides which cannot react further.

Synthesis of Ethyl Lanceolate. The present procedure has been applied to the synthesis of ethyl lanceolate (**16**) (eq 4). 2-Methyl-2-butenoylthiopyrrolidine was allylated at the α position as follows. S-Alkylation with 9-bromolimonene, prepared from (+)-limonene according to the method reported by Crawford et al.,[13] in *tert*-butyl alcohol followed by a dehydrohalogenation with DBU provided a diastereoisomeric mixture **14** (3:2) in 76% yield. Without separation, **14** was subjected to Cope rearrangement in refluxing decalin for 3 h. Lanceoylthiopyrrolidine (**15**) was obtained as a mixture of *E* and *Z* isomers (ca. 2:1) in 93% yield, which was transformed to corresponding esters (**16**-*E*:**16**-*Z* = ca. 2:1, (+)-(*E*)-ethyl lanceolate, $[\alpha]^{30}_D$ +44°,[14] (+)-(*Z*)-ethyl lanceolate, $[\alpha]^{30}_D$ +46°)[15] in 72% yield according to the procedure recently established in these laboratories[7] (see Experimental Section). These isomers were separated by means of column chromatography and their structures were identified by comparison of the ^{1}H NMR and IR spectra with those of the authentic samples.[13]



Determination of Stereochemistry of 9. The stereochemistry of all the new compounds **9** was determined unequivocally on the basis of ^{1}H NMR and IR spectra. Spectral data are given in the Experimental Section. The retention times on VCP (SiDC 550) were used supplementarily as a reliable guide for the structural determination of the Δ^2 double bonds. Between a pair of geometric isomers of **9**, the following correlation was found to hold without exception: an *E* isomer has a longer retention time than a *Z* isomer.

In Figure 1 is shown the criterion for the determination of stereochemistry of the Δ^2 double bonds by ^{1}H NMR spectroscopy. The *E* configuration of **9Aa, 9Ab,** and **9Ac** is apparent on the basis of chemical shifts of the olefinic protons (H_β 7.0–7.3, H_α 6.2–6.5 ppm) and coupling constants (J_{H_α,H_β} = 14–15 Hz). Three pairs of isomers (**9Af** and **9Bf, 9Ag** and **9Bg,** and **9Ah** and **9Dh**) showed no significant differences in IR and ^{1}H NMR spectra, and the stereochemistry of this series of compounds was determined as the corresponding amides (**19**). The stereochemistry of the olefins follows from the higher field position of resonance of the vinyl methyl group in **19**-*Z* (δ 1.8) compared with that in **19**-*E* (δ 2.0), the general correlation for β-methyl protons in the α,β-unsaturated amides.[16]

The structural determination of **9d** and **9e** is rather complicated, because both allylic and olefinic protons of one isomer resonate at the deshielded positions more than those of another isomer by 0.2–0.3 ppm. In order to establish the criterion, each of the geometric isomers of **18** (R = CH_3) was transformed to amides independently (without any recognizable geometrical loss as judged from VPC (see Experimental Section). One isomer, which was derived from thioamide with methyl and olefinic protons resonating at lower fields and identified as **18**-*E* (R = CH_3, with an oxygen atom in place of a sulfur atom) by comparison with an authentic sample prepared selectively from tiglic acid, showed again the lower field resonances of methyl and olefinic protons compared with another isomer (**18**-*Z*, R = CH_3, with an oxygen atom in place of a sulfur atom). Consequently, although the reason for this anomaly is not clear, the thioamides **18**, whose allylic and olefinic protons resonate at lower fields, were assigned to be the *E* isomer.

The determination of the stereochemistry of the Δ^6 double bonds is straightforward on the basis of IR spectra except for **9Ac,** whose structure was assigned to be all-trans on the basis of the strong absorption at 960 cm^{-1} (δ_{CH} of trans-Δ^2 and trans-Δ^6).

Experimental Section

Melting points were determined in capillary tubes with a Büchi apparatus and are not corrected. Unless otherwise indicated, short-path (bulb-to-bulb) distillations were carried out in a Kugelrohr apparatus. Microanalyses were performed by the Microanalysis Center of Kyoto University. Analyses agreed with calculated values within ±0.3% unless otherwise noted. Infrared spectra were measured with a Hitachi Model EPI-G3 grating spectrophotometer. Proton magnetic resonance (^{1}H NMR) spectra were determined either at 60 MHz on a JEOL JNM-PMX 60 instrument or at 100 MHz on a Varian HA 100 instrument taking tetramethylsilane as an internal standard. Mass spectra were measured either on a Hitachi Model RMU 6C instrument or on a JEOL JMS-OISG-2 instrument (high-resolution mass spectrophotometer). Optical resolutions were determined on a Yanagimoto OR 50.

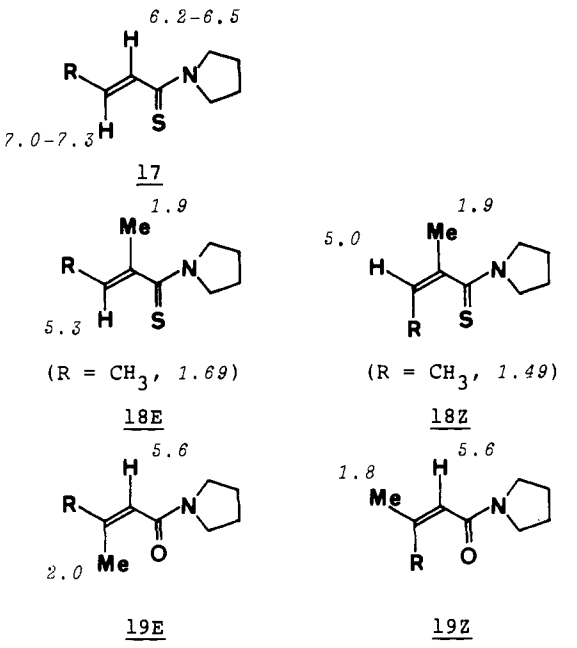


Figure 1. Criterion for structural determination of Δ^2 double bonds of **9** by ^{1}H NMR (δ values taking tetramethylsilane as an internal standard).

Solvents and Reagents. Dimethylformamide (DMF), *tert*-butyl alcohol, tetralin, decalin, and 1,5-diazabicyclo[5.2.0]undecene-5 (DBU) were dried over calcium hydride and distilled under an argon atmosphere. Tetrahydrofuran (THF) was dried and distilled from benzophenone and sodium immediately prior to use. Potassium *tert*-butoxide was purchased from Merck Chemical Co. (+)-Limonene was purchased from Nakarai Chemical Co. and had $[\alpha]^{22}_D$ +115° (*c* 0.43, EtOH).

α,β-Unsaturated Thioamides. 2-Butenoylthiopyrrolidine (**1a**), 2-methyl-2-butenoylthiopyrrolidine (**1b**), and 3-methyl-2-butenoylthiopyrrolidine (**1c**) were prepared as follows. To a stirred solution of a corresponding amide in dimethoxyethane (10 mL/g of amide) cooled with an ice bath was added P_4S_{10} (2–5 equiv with respect to a sulfur atom) portionwise in the presence of a small amount of $NaHCO_3$. The reaction mixture was stirred at the same temperature for 3–5 h with monitoring by TLC (silica gel plate, benzene–ethyl acetate (8:1). The solvent was removed in vacuo under an ambient temperature and the residue was dissolved in ethyl acetate and then washed with ice-cold aqueous NaOH, followed by washing with saturated NaCl. The organic extract was dried over Na_2SO_4 and concentrated to give a viscous oil, which was purified by distillation (and recrystallization). While no significant geometrical isomerization was observed for 2-butenoylpyrrolidine during this procedure, (*E*)-2-methyl-2-butenoylpyrrolidine (>97% geometric purity) isomerized to give (*Z*)-2-methyl-2-butenoylthiopyrrolidine (79%) as a major product together with a small amount of *E* isomer (21%).

(*E*)-2-Butenoylthiopyrrolidine (**1a**): mp 100–101 °C (from EtOH); IR (KBr disk, cm^{-1}) 1640 s, 1470 s, 1315 s, 1260 m, 960 m, and 945 m; ^{1}H NMR (CCl_4) δ 1.87 (d, *J* = 7 Hz, 3 H), 2.0 (m, 4 H), 3.8 (m, 4 H), 6.43 (br d, *J* = 14 Hz, 1 H), and 7.26 (dq, *J* = 14 and 7 Hz, 1 H); mass spectrum *m/e* (rel intensity) 155 (P^+, 77), 140 (41), 122 (10), 94 (54), and 70 (100). Anal. Calcd for $C_8H_{13}NS$: C, 61.89; H, 8.44; N, 9.11. Found: C, 62.10; H, 8.14; N, 9.11.

(*E*)-2-Methyl-2-butenoylthiopyrrolidine (**1b**): bp 88–92 °C (0.07

mmHg); IR (neat film, cm^{-1}) 1465 s, 1440 s, 1320 m, 1260 m, 1030 m, 960 m, 855 m, and 815 m; ^1H NMR (CCl_4) δ 1.69 (dq, J = 6.8 and 1.5 Hz, 3 H), 1.86 (m, 3 H), 2.1 (m, 4 H), 3.6 (m, 4 H), and 5.37 (qq, J = 6.8 and 1.5 Hz, 1 H); mass spectrum *m/e* (rel intensity) 169 (P^+, 96), 154 (100), 121 (68), and 70 (36). Anal. Calcd for $C_9H_{15}NS$: C, 63.85; H, 8.93; N, 8.27. Found: C, 63.58; H, 8.69; N, 8.13.

(*Z*)-2-Methyl-2-butenoylthiopyrrolidine (**1b**): bp 88–92 °C (0.07 mmHg); IR (neat film, cm^{-1}) 1470 s, 1445 s, 1330 m, 1255 m, 1215 m, 960 m, 920 m, and 860 m; ^1H NMR (CCl_4) δ 1.49 (dq, J = 6.8 and 1.2 Hz, 3 H), 1.86 (m, 3 H), 2.1 (m, 4 H), 3.6 (m, 4 H), 5.08 (qq, J = 6.8 and 1.7 Hz, 1 H); mass spectrum *m/e* (rel intensity) 169 (P^+, 100), 154 (92), 121 (52), and 70 (46). Anal. Calcd for $C_9H_{15}NS$: C, 63.85; H, 8.93; N, 8.27. Found: C, 63.60; H, 8.90; N, 8.01.

3-Methyl-2-butenoylthiopyrrolidine (**1c**): bp 95–100 °C (0.05 mmHg); IR (neat film, cm^{-1}) 1650 s, 1460 s, 1445 s, 1260 s, 1215 m, and 845 w; ^1H NMR (CCl_4) δ 1.80 (s, 3 H), 1.83 (s, 3 H), 2.0 (m, 4 H), 3.75 (m, 4 H), 5.99 (br s, 1 H); mass spectrum *m/e* (rel intensity) 169 (P^+, 96), 168 (39), 154 (74), 136 (14), and 70 (100). Anal. Calcd for $C_9H_{15}NS$: C, 63.85; H, 8.93; N, 8.27. Found: C, 64.05; H, 8.66; N, 8.41.

General Procedure for Thio-Claisen Rearrangement. A. Reactions in *t*-BuOH Using DBU as a Base (Table I). To a solution of α,β-unsaturated thioamide **1** (2 mmol) in anhydrous *t*-BuOH (2 mL) was added allylic halide **2** (2.04–3.0 mmol) via a syringe through a septum cap and the solution was stirred under an argon atmosphere at the indicated temperature over a period of time indicated in Table I. Then DBU (2.04–3.0 mmol) was added via a syringe. After the reaction at the indicated temperature and over a period of time indicated, the reaction mixture was poured into water and extracted with ether. Ether extracts were washed with 1 N HCl and then with saturated NaCl and dried over Na_2SO_4. Evaporation of the solvent left faintly red or yellow oil, which was purified by means of column chromatography (silica gel, hexane–benzene gradient). Analytically pure samples were prepared by LC (high-performance liquid chromatography). The physical and spectral data of the products in Table I are as follows.

2-Vinyl-4-pentenoylthiopyrrolidine (**4a**): oil; IR (neat film, cm^{-1}) 3090 m, 1653 m, 1450 s, 1000 s, and 920 s; ^1H NMR ($CDCl_3$) δ 2.0 (m, 4 H), 2.52 (dt, J = 13.0 and 7.0 Hz, 1 H), 2.78 (dt, J = 13.0 and 7.0 Hz, 1 H), 3.50 (dt, J = 7.0 and 7.0 Hz, 1 H), 3.8 (m, 4 H), 5.1 (m, 4 H), and 5.9 (m, 2 H). Anal. Calcd for $C_{11}H_{17}NS$: C, 67.64; H, 8.71; N, 7.17. Found: C, 67.49; H, 8.90; N, 6.98.

3,3-Dimethyl-2-vinyl-4-pentenoylthiopyrrolidine (**4b**): oil; IR (neat film, cm^{-1}) 3075 w, 1630 w, 1440 s, 1005 m, and 915 s; ^1H NMR (CCl_4) δ 1.12 (s, 3 H), 1.16 (s, 3 H), 2.0 (m, 4 H), 3.3 (d, J = 9 Hz, 1 H), 3.8 (m, 4 H), 4.9 (m, 4 H), and 6.1 (m, 2 H). Anal. Calcd for $C_{13}H_{21}NS$: 223.1394. Found: 223.1378.

5-Methyl-2-vinyl-4-hexenoylthiopyrrolidine (**5**): oil, IR (neat film, cm^{-1}) 3025 w, 1660 w, 1625 w, 1450 s, 1000 w, 975 w, and 920 m; ^1H NMR (CCl_4) δ 1.64 (br s, 6 H), 2.0 (m, 4 H), 2.5 (m, 2 H), 3.25 (m, 1 H), 3.7 (m, 4 H), and 4.5–5.5 (m, 4 H). Anal. Calcd for $C_{13}H_{21}NS$: 223.1394. Found: 223.1383.

3-Methyl-2-vinyl-4-pentenoylthiopyrrolidine (**4c**): oil; IR (neat film, cm^{-1}) 1640 w, 1450 s, 1330 m, 1000 w, 970 w, and 920 s; ^1H NMR (CCl_4) δ 0.93 (d, J = 6.0 Hz, 3 H), 2.0 (m, 4 H), 2.95 (m, 1 H), 3.20 (d, J = 9.0 Hz, 1 H), 3.75 (m, 4 H), 4.9–5.1 (m, 4 H), and 5.73 (m, 2 H). Anal. Calcd for $C_{12}H_{19}NS$: 209.1237. Found: 209.1248.

2-Methyl-2-vinyl-4-pentenoylthiopyrrolidine (**4d**): oil; IR (neat film, cm^{-1}) 3080 w, 1640 m, 1430 s, 1380 w, 1000 m, and 920 s; ^1H NMR (CCl_4) δ 1.35 (s, 3 H), 1.9 (m, 4 H), 2.60 (m, 2 H), 3.8 (m, 4 H), 5.0 (m, 4 H), and 5.8 (m, 2 H). Anal. Calcd for $C_{12}H_{19}NS$: 209.1237. Found: 209.1288.

2,3-Dimethyl-2-vinyl-4-pentenoylthiopyrrolidine (**4e**): oil; IR (neat film, cm^{-1}) 3090 w, 1640 m, 1420 s, 960 m, and 920 s; ^1H NMR (CCl_4) δ 0.87, 0.95 (d, J = 8 Hz, 3 H), 1.27, 1.33 (s, 3 H), 1.95 (m, 4 H), 3.30 (dq, J = 16 and 8 Hz, 1 H), 3.83 (m, 4 H), and 4.75–6.3 (m, 6 H). Anal. Calcd for $C_{13}H_{21}NS$: C, 69.90; H, 9.48; N, 6.27. Found: C, 69.96; H, 9.59; N, 6.50.

2-Isopropenyl-4-pentenoylthiopyrrolidine (**4f**): oil; IR (neat film, cm^{-1}) 3080 w, 1640 m, 1480 s, 1445 s, 1340 m, 1000 w, 930 m, and 900 m; ^1H NMR (CCl_4) δ 1.78 (br s, 3 H), 2.0 (m, 4 H), 2.4–3.1 (m, 2 H), 3.37 (t, J = 7 Hz, 1 H), 3.75 (m, 4 H), 4.90, 5.10 (m, 4 H), and 5.7 (m, 1 H). Anal. Calcd for $C_{12}H_{19}NS$: 209.1237. Found: 209.1234.

3,3-Dimethyl-2-isopropenyl-4-pentenoylthiopyrrolidine (**4g**): mp 71–72 °C (MeOH); IR (KBr disk, cm^{-1}) 3090 w, 1635 m, 1445 s, 1010 m, 910 s, and 900 s; ^1H NMR (CCl_4) δ 1.20 (s, 3 H), 1.22 (s, 3 H), 1.92 (s, 3 H), 2.0 (m, 4 H), 3.47 (s, 1 H), 3.85 (m, 4 H), 4.9 (m, 4 H), and 6.43 (dd, J = 11 and 18 Hz, 1 H). Anal. Calcd for $C_{14}H_{23}NS$: 237.1550. Found: 237.1536.

2-Isopropenyl-3-methyl-4-pentenoylthiopyrrolidine (**4h**): mp 51–53 °C (EtOH–hexane); IR (KBr disk, cm^{-1}) 3080 w, 1640 m, 1440 s, 980 w, and 900 m; ^1H NMR (CCl_4) δ 0.93 (d, J = 6 Hz, 3 H), 1.75 (s, 3 H), 2.00 (m, 4 H), 3.18 (m, 1 H), 3.75 (m, 5 H), 4.83, 5.05 (m, 4 H), and 5.65 (m, 1 H). Decouplings at 0.93 and 3.18 ppm changed the multiplets at 3.18 and 5.65 ppm to a doublet (J = 3.5 Hz) and a doublet of doublets (J = 18 and 9 Hz), respectively. Anal. Calcd for $C_{13}H_{21}NS$: 223.1394. Found: 223.1367.

B. Reactions in DMF or THF Using KO-*t*-Bu as a Base (Table II). To a solution of **1** (1 mmol) in anhydrous DMF or THF (1 mL) was added allylic halide (1.0–1.5 mmol) via a syringe through a septum cap and the solution was stirred under an argon atmosphere at an indicated temperature over a period of time indicated in Table II. Then KO-*t*-Bu was added while back-flashing with argon and the solution was stirred at an indicated temperature and over an indicated period of time. Usual extractive workup and purification of the products by column chromatography (silica gel, hexane–benzene gradient) provided **4c, 4d, 4e, 6,** and **7**. Analytically pure materials were obtained by purification with LC.

2-Isopropenylidene-4-pentenoylthiopyrrolidine (**7**): oil; IR (neat film, cm^{-1}) 2980 m, 1450 s, 1330 w, 1010 w, and 920 w; ^1H NMR (CCl_4) δ 1.60 (s, 3 H), 1.73 (s, 3 H), 2.0 (m, 4 H), 3.10 (d, J = 7 Hz, 2 H), 3.6 (m, 4 H), 4.83–5.13 (m, 2 H), and 5.8 (m, 1 H). Anal. Calcd for $C_{12}H_{19}NS$: 209.1237. Found: 209.1283.

General Procedure for Cope Rearrangement (Table III). Under an argon atmosphere was refluxed a solution of **4** (1 mmol) in 1 mL of a solvent over a period of time indicated in Table III. After cooling, the reaction mixture was directly subjected to column chromatography (silica gel, hexane–benzene gradient). For the reactions in DMF, the reaction mixture was subjected to column chromatography after usual extractive workup with ether. The ratio of products was determined on the basis of area intensities on VPC (SiDC 550, 200–240 °C, He), whose components were separated by means of preparative VPC. Thermolyses in VPC equipment were undertaken under the following conditions: injection temperature 250 °C, column temperature 220 °C, He 38 mL/min, SiDC 550 for entry 6; injection temperature 275 °C, column temperature 225 °C, He 38 mL/min, SiDC 550 for entry 9. The products of entries 10, 11, and 12 were separated and characterized as amides, which were prepared as follows. A solution of thioamides in ethanol was exposed to excess methyl iodide (3–5 equiv) for 2–3 h at ambient temperatures and then treated with aqueous Na_2CO_3. Usual extractive workup with ether provided amides quantitatively without noticeable geometrical isomerization. The physical and spectral data of the products in Table III are as follows.

trans-2,6-Heptadienoylthiopyrrolidine (**9Aa**): bp 155 °C (0.01 mmHg); IR (neat film, cm^{-1}) 3050 w, 1635 m, 1435 s, 1320 m, 985 m, 960 m, and 910 m; ^1H NMR ($CDCl_3$) δ 2.0 (m, 4 H), 2.3 (m, 4 H), 3.8 (m, 4 H), 5.05 (m, 2 H), 5.7 (m, 1 H), 6.40 (d, J = 15 Hz, 1 H), and 7.20 (dt, J = 15 and 6 Hz, 1 H).

3,6-Heptadienoylthiopyrrolidine (**10**): bp 155 °C (0.01 mmHg); IR (neat film, cm^{-1}) 1630 m, 1440 s, 990 m, 970 m, and 910 m; ^1H NMR (CCl_4) δ 2.0 (m, 4 H), 2.8 (m, 2 H), 3.4 (m, 2 H), 3.6 (m, 6 H), and 4.8–6.0 (m, 5 H). Anal. (mixture of **9Aa** and **10**) Calcd for $C_{11}H_{17}NS$: C, 67.64; H, 8.71; N, 7.17. Found: C, 67.36; H, 8.59; N, 6.88.

7-Methyl-*trans*-2,6-octadienoylthiopyrrolidine (**9Ab**): bp 175 °C (0.01 mmHg); IR (neat film, cm^{-1}) 1640 m, 1440 s, 960 m, and 840 m; ^1H NMR (CCl_4) δ 1.60 (s, 3 H), 1.67 (s, 3 H), 2.1 (m, 8 H), 3.7 (m, 4 H), 5.03 (m, 1 H), 6.25 (d, J = 14 Hz, 1 H), and 7.0 (dt, J = 15 and 6 Hz, 1 H).

7-Methyl-3,6-octadienoylthiopyrrolidine (**11**): bp 175 °C (0.01 mmHg); IR (neat film, cm^{-1}) 1640 m, 1440 s, 970 s, and 830 w; ^1H NMR (CCl_4) δ 1.60 (s, 3 H), 1.70 (s, 3 H), 2.0 (m, 4 H), 2.7 (m, 2 H), 3.6 (m, 6 H), and 4.9–5.7 (m, 3 H). Anal. (mixture of **9Ab** and **11**) Calcd for $C_{13}H_{21}NS$: C, 69.90; H, 9.48; N, 6.27. Found: C, 70.00; H, 9.53; N, 6.26. Anal. Calcd for $C_{13}H_{21}NS$, 223.1394; found, 223.1397.

trans,trans-2,6-Octadienoylthiopyrrolidine (**9Ac**): oil; IR (neat film, cm^{-1}) 2950 s, 1440 s, 1330 m, 1260 m, and 960 s; ^1H NMR (CCl_4) δ 1.70 (br s, 3 H), 2.03 (m, 4 H), 2.20 (br s, 4 H), 3.80 (m, 4 H), 5.45 (m, 2 H), 6.30 (d, J = 15 Hz, 1 H), and 7.00 (m, 1 H). De-

coupling at 2.20 ppm changed a multiplet at 7.00 ppm into a doublet (J = 15 Hz). Anal. Calcd for $C_{12}H_{19}NS$: 209.1237. Found: 209.1233.

3,*trans*-6-Octadienoylthiopyrrolidine (**12**): oil; IR (neat film, cm^{-1}) 2970 s, 1450 s, 1330 m, 970 m, and 920 w; ^1H NMR (CCl_4) δ 1.70 (br s, 3 H), 2.06 (m, 4 H), 2.80 (m, 2 H), 3.63 (m, 2 H), 3.75 (m, 4 H), and 5.5 (m, 4 H). Anal. Calcd for $C_{12}H_{19}NS$: 209.1237. Found: 209.1268.

2-Methyl-*trans*-2,6-heptadienoylthiopyrrolidine (**9Ad**): oil; IR (neat film, cm^{-1}) 3075 w, 1640 w, 1450 s, 1180 m, and 1000 m; ^1H NMR (CCl_4) δ 1.90 (br s, 3 H), 2.0 (m, 4 H), 2.18 (m, 4 H), 3.65 (m, 4 H), 5.0 (m, 2 H), 5.3 (m, 1 H), and 5.8 (m, 1 H). Anal. Calcd for $C_{12}H_{19}NS$: 209.1237. Found: 209.1321.

2-Methyl-*cis*-2,6-heptadienoylthiopyrrolidine (**9Bd**): oil; IR (neat film, cm^{-1}) 3075 w, 1640 m, 1450 s, 1205 m, 995 m, and 915 m; ^1H NMR (CCl_4) δ 1.90 (br s, 3 H), 2.0 (m, 8 H), 3.52, 3.78 (m, 4 H), 5.0 (m, 3 H), and 5.75 (m, 1 H). Anal. Calcd for $C_{12}H_{19}NS$: 209.1237. Found: 209.1321.

2-Methyl-*trans,trans*-2,6-octadienoylthiopyrrolidine (**9Ae**) and 2-methyl-*trans,cis*-2,6-octadienoylthiopyrrolidine (**9Ce**): oil; IR (neat film, cm^{-1}) 1440 s, 1330 m, 1260 m, and 960 m; ^1H NMR (CCl_4) δ 1.63 (m, 3 H), 1.87 (s, 3 H), 2.00 (m, 4 H), 2.12 (m , 4 H), 3.65 (m, 4 H), 5.30 (m, 1 H), and 5.38 (m, 2 H). Anal. Calcd for $C_{13}H_{21}NS$: 223.1394. Found: 223.1383.

2-Methyl-*cis,trans*-2,6-octadienoylthiopyrrolidine (**9Be**) and 2-methyl-*cis,cis*-2,6-octadienoylthiopyrrolidine (**9De**): oil; IR (neat film, cm^{-1}) 1440 s, 1330 m, 1260 m, and 970 m; ^1H NMR (CCl_4) δ 1.61 (br d, J = 4 Hz, 3 H), 1.89 (br s, 3 H), 2.0 (m, 8 H), 3.5, 3.76 (m, 4 H), 5.04 (m, 1 H), and 5.38 (m, 2 H). Decouplings at 1.61 and 2.0 ppm changed multiplets at 5.38 and 5.04 ppm to broad singlets, respectively. Anal. Calcd for $C_{13}H_{21}NS$: 223.1394. Found: 223.1372.

3-Methyl-*trans*-2,6-heptadienoylthiopyrrolidine (**9Af**): oil; IR (neat film) 3080 w, 1640 m, 1440 s, 1330 m, 1000 w, and 920 m; ^1H NMR (CCl_4) δ 1.80 (s, 3 H), 2.03 (m, 4 **H**), 2.2 (m, 4 H), 3.7 (m, 4 H), 4.90, 5.10 (m, 2 H), 5.7 (m, 1 H), and 5.90 (br s, 1 H).

3-Methyl-*trans*-2,6-heptadienoylpyrrolidine (**9Af,** amide): oil; IR (neat film, cm^{-1}) 1610 s, 1440 s, 1380 w, 1000 w, and 910 m; ^1H NMR (CCl_4) δ 1.9 (m, 4 H), 2.03 (s, 3 H), 2.20 (m, 4 H), 3.41 (m, 4 H), 4.86, 5.10 (m, 2 H), 5.68 (br s, 1 H), and 5.80 (m, 1 H). Anal. Calcd for $C_{12}H_{19}NO$: 193.1466. Found: 193.1472.

3-Methyl-*cis*-2,6-heptadienoylpyrrolidine (**9Bf,** amide): oil; IR (neat film, cm^{-1}) 1610 s, 1420 s, 1350 m, 1000 w, and 910 m; ^1H NMR (CCl_4) δ 1.9 (m, 4 H), 1.83 (s, 3 H), 2.1–2.9 (m, 4 H), 3.40 (m, 4 H), 4.82, 5.03 (m, 2 H), 5.70 (br s, 1 H), and 5.8 (m, 1 H). Anal. Calcd for $C_{12}H_{19}NO$: 193.1466. Found: 193.1449.

3,7-Dimethyl-*trans*-2,6-octadienoylthiopyrrolidine (**9Ag**) and 3,7-dimethyl-*cis*-2,6-octadienoylthiopyrrolidine (**9Bg**): oil; IR (neat film, cm^{-1}) 1645 m, 1440 s, and 845 m; ^1H NMR (CCl_4) δ 1.61 (s, 3 H), 1.67 (s, 3 H), 1.78 (s, 3 H), 2.1 (m, 8 H), 3.60 (m, 4 H), 5.07 (m, 1 H), and 5.80 (br s, 1 H). Anal. Calcd for $C_{14}H_{23}NS$: 237.1550. Found: 237.1506.

3,7-Dimethyl-*trans*-2,6-octadienoylpyrrolidine (**9Ag,** amide): oil; IR (neat film, cm^{-1}) 1630 vs, 1440 vs, 1370 s, and 1340 m; ^1H NMR (CCl_4) δ 1.61 (s, 3 H), 1.68 (s, 3 H), 1.91 (m, 4 H), 2.0–2.2 (m, 7 H, including s at 2.04, 3 H), 3.4 (m, 4 H), 5.1 (m, 1 H), and 5.70 (br s, 1 H). Anal. Calcd for $C_{14}H_{23}NO$: 221.1778. Found: 221.1779.

3,7-Dimethyl-*cis*-2,6-octadienoylpyrrolidine (**9Bg,** amide): oil; IR (neat film, cm^{-1}) 1640 vs, 1440 vs, 1370 s, and 1340 m; ^1H NMR (CCl_4) δ 1.75 (br s, 6 H), 1.8–2.1 (m, 9 H, including s at 1.83, 3 H), 2.5 (m, 2 H), 3.4 (m, 4 H), 5.15 (m, 1 H), and 5.72 (br s, 1 H). Anal. Calcd for $C_{14}H_{23}NO$: 221.1778. Found: 221.1780.

3-Methyl-*trans,trans*-2,6-octadienoylthiopyrrolidine (**9Ah**): oil; IR (neat film, cm^{-1}) 1470 s, 1450 s, 1330 m, 970 m, 920 w, and 850 w; ^1H NMR (CCl_4) δ 1.63 (m, 3 H), 1.78 (s, 3 H), 2.00 (m, 4 H), 2.14 (br s, 4 H), 3.50, 3.75 (m, 4 H), 5.40 (m, 2 H), and 5.82 (br s, 1 H).

3-Methyl-*trans,trans*-2,6-octadienoylpyrrolidine (**9Ah**, amide): oil; IR (neat film, cm^{-1}) 1610 s, 1430 s, 1380 m, 1340 m, 960 m, and 850 w; ^1H NMR (CCl_4) δ 1.66 (m, 3 H), 1.9 (m, 4 H), 2.03 (s, 3 H), 2.13 (br s, 4 H), 3.4 (m, 4 H), 5.40 (m, 2 H), and 5.66 (br s, 1 H). Anal. Calcd for $C_{13}H_{21}NO$: 207.1622. Found: 207.1602.

3-Methyl-*cis,trans*-2,6-octadienoylpyrrolidine (**9Dh,** amide): oil; IR (neat film, cm^{-1}) 1620 s, 1440 s, 1350 m, and 970 m; ^1H NMR (CCl_4) δ 1.65 (m, 3 H), 1.8 (m, 7 H, including s at 1.80, 3 H), 2.1 (m, 2 H), 2.5 (m, 2 H), 3.4 (m, 4 H), 5.40 (m, 2 H), and 5.66 (br s, 1 H). Anal. Calcd for $C_{13}H_{21}NO$: 207.1622. Found: 207.1684.

4-(4-Methyl-3-cyclohexenyl)-2-methyl-2-vinyl-4-pentenoylthiopyrrolidine (14). To a solution of 2-methyl-2-butenoylthiopyrrolidine (548 mg, 3.24 mmol) in 4 mL of anhydrous *t*-BuOH was added (+)-9-bromolimonene (964 mg, 4.48 mmol) via a syringe and the resulting mixture was stirred under an argon atmosphere at an ambient temperature for 16 h. Then DBU (569 mg, 3.73 mmol) was added via a syringe and reacted with stirring for 5 h. Extractive workup with ethyl acetate and subsequent purification by column chromatography (silica gel, benzene–ethyl acetate gradient) provided a diastereoisomeric mixture **14** in 76% yield in a ratio of ca. 3:2 as judged by the ^1H NMR spectra of the mixture. Careful separation by column chromatography provided pure isomers. **14a** (minor portion, R_f 0.6 on silica gel plate, benzene): IR (neat film, cm^{-1}) 3075 w, 1630 m, 1420 vs, 1325 m, 1020 m, 960 m, and 915 m; ^1H NMR (CCl_4) δ 1.1–2.3 (m, 17 H, including 1.67, br s, 3 H), 3.22 (d, J = 12.5 Hz, 1 H), 3.40 (d, J = 12.5 Hz, 1 H), 3.9 (m, 4 H), 4.6–5.1 (m, 4 H), and 6.4 (m, 2 H). **14b** (major portion): IR (neat film, cm^{-1}) 3080 w, 1640 m, 1420 vs, 1330 m, 1020 m, 970 m, 910 m, and 900 m; ^1H NMR (CCl_4) δ 1.2–2.2 (m, 17 H, including s, at 1.46 and br s at 1.64), 2.53 (d, J = 14 Hz, 1 H), 2.81 (d, J = 14 Hz, 1 H), 3.8 (m, 4 H), 4.7–5.5 (m, 5 H), and 6.10 (dd, J = 19 and 10 Hz, 1 H); mass spectrum *m/e* (rel intensity) 303.2073 (P^+, 41; calcd for $C_{19}H_{29}NS$, 303.2021), 168 (100).

Lanceoylthiopyrrolidine (15-*E* and 15-*Z*). A solution of a mixture of **14a** and **14b** (577 mg) in 5 mL of decalin was refluxed under argon for 3 h. After it was allowed to cool, the reaction mixture was directly subjected to column chromatography (silica gel, benzene–ethyl acetate gradient) to give a mixture of **15-*E*** and **15-*Z*** (ca. 2:1) in 93% yield (86% conversion). A mixture of **15-*E*** and **15-*Z***: oil; IR (neat film, cm^{-1}) 3090 w, 1645 m, 1605 w, 1450 s, 1330 m, 1020 m, 960 m, 895 m, and 800 m; mass spectrum *m/e* (rel intensity) 303.2001 (P^+, 100; calcd for $C_{19}H_{29}NS$, 303.2021) and 270 (39).

(+)-(*E*)- and (+)-(*Z*)-Ethyl Lanceolate (16-*E* and 16-*Z*). To a solution of a mixture of **15-*E*** and **15-*Z*** (259 mg) in 3 mL of dry CH_2Cl_2 was added 0.3 mL of methyl iodide and the reaction mixture was stirred under argon overnight at an ambient temperature. Excess methyl iodide and CH_2Cl_2 were removed in vacuo and replaced with 4 mL of anhydrous EtOH. To this solution were added 162 μL of dimethyl sulfate and 236 mg of potassium carbonate, while backflashing with argon, and the solution was stirred for 7 h at an ambient temperature. Usual extractive workup with ethyl acetate provided a colorless oil, which was subjected to distillation (140–145 °C (0.2 mmHg)) to give a mixture of **16-*E*** and **16-*Z***. The separation of this mixture by column chromatography (silica gel, benzene) provided pure **16-*E*** and **16-*Z*** in a ratio of 71:29 (total yield 72%). (+)-(*E*)-Ethyl lanceolate (**16-*E***): $[\alpha]^{30}_D$ +44° (*c* 0.46, EtOH); ^1H NMR ($CDCl_3$) δ 1.28 (t, J = 7 Hz, 3 H), 1.4–2.5 [m, 17 H, including 1.66 (br s) and 1.85 (br s)], 4.19 (q, J = 7 Hz, 2 H), 4.80 (m, 2 H), 5.42 (m, 1 H), and 6.78 (m, 1 H); IR (neat film, cm^{-1}) 3080 w, 1712 s, 1645 m, 1275 s, 1120 m, 892 m, and 800 m; mass spectrum *m/e* (rel intensity) 262 (P^+, 4), 233 (1), 160 (13), 149 (13), 121 (38), 119 (67), 105 (40), 93 (100), 79 (67), and 67 (58). (+)-(*Z*)-Ethyl lanceolate (**16-*Z***): $[\alpha]^{30}_D$ +46° (*c* 0.30, EtOH); ^1H NMR ($CDCl_3$) δ 1.29 (t, J = 7 Hz, 3 H), 1.4–2.8 [m, 17 H, including 1.65 (br s, 3 H) and 1.91 (br s, 3 H)], 4.20 (q, J = 7 Hz, 2 H), 4.79 (m, 2 H), 5.42 (m, 1 H), and 5.94 (m, 1 H); IR (neat film, cm^{-1}) 3080 w, 1715 s, 1645 m, 1183 m, 1125 m, 893 m, and 800 m; mass spectrum *m/e* (rel intensity) 262 (P^+, 7), 233 (3), 160 (19), 149 (74), 121 (50), 119 (86), 105 (49), 93 (100), 79 (78), and 67 (50).

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(7) Conversion of thioamides to esters, ketene *S,S*-acetals, and dihydro-1,3-oxazines will be reported in the near future.

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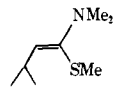
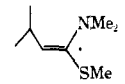
(10) The following observation suggests that **3**-*Z* and **3**-*E* equilibrate under the reaction conditions, i.e., the ratio of a mixture of ketene *S,N*-acetals (**8**-



8-*Z*



8-*E*

E:**8**-*Z* = 6:4), which were generated by the treatment of *N,N*-dimethylthioisovaleroamide with methyl iodide and then with DBU in *tert*-butyl alcohol and distilled carefuly without adopting external heating and contaminated by *tert*-butyl alcohol, changed to a ratio of >9:<1 during storage overnight at an ambient temperature, as observed by ^{1}H NMR spectroscopy. This isomerization may be caused by *tert*-butyl alcohol, whose hydroxyl proton is acidic enough for the protonation of the highly nucleophilic double bonds of ketene *S,N*-acetals [cf. R. Gompper and W. Elser, *Justus Liebigs Ann. Chem.*, **725**, 64 (1969), and ref 8a].

(11) **4e** was obtained as a diastereoisomeric mixture. Although the ratios of diastereomers (**4c** and **4h**) were not able to be determined owing to their poor separation in ^{1}H NMR and LC (high-performance liquid chromatography), the ratios are expected to be reflected in the product ratios of Cope rearrangement (ca. 4:1 for both cases).

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(14) (−)-(*E*)-Ethyl lanceolate, $[\alpha]^{30}_{D}$ −50° (*c* 0.38, EtOH).[13]

(15) (−)-(*Z*)-Ethyl lanceolate, $[\alpha]^{30}_{D}$ −49° (*c* 0.35, EtOH).[13]

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Mass Spectrometry of Phosphate Esters. Phosphoacetoin and Its Methyl Esters

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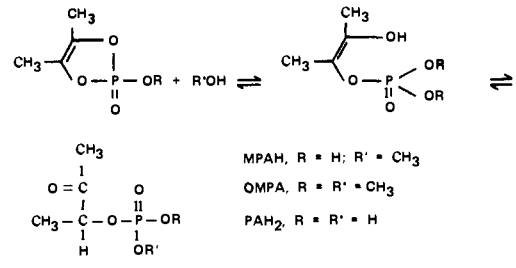
Abstract: The electron-impact (EI) and field-ionization (FI) mass spectra of 3-oxo-2-butyl phosphate (phosphoacetoin, PAH_2) and its mono- and dimethyl esters, MPAH and DMPA, all reveal additional components stemming from thermal reactions that occur both during sample storage and in the instrument. The acidic phosphates, PAH_2 and MPAH, break down thermally to acetoin and monomeric metaphosphoric acid or methyl metaphosphate, respectively. In addition, PAH_2 undergoes thermal dehydration to yield apparently a transient acetoin metaphosphate, which transforms rapidly to a cyclic enediol phosphate. Thermal disproportionation of MPAH into PAH_2 and DMPA takes place via a dimer formed by interaction of the acidic phosphoryl function with the carbonyl group; the neutral DMPA dimerizes by an aldol-type condensation. Ionic decomposition under EI is initiated, for the most part, by two primary processes: (a) loss of the acetyl radical and (b) hydrogen migration and loss of ketene. Process (a) is followed by loss, alternatively, of C_2H_2 or acetaldehyde; (b), by loss of C_2H_4, vinyl radical, or acetaldehyde. The hydrocarbon molecules so eliminated, C_2H_2 and C_2H_4, probably form initially as carbenes, $CH_2{=}C{:}$ and $CH_3CH{:}$, which presumably reorganize rapidly to acetylene and ethylene. A striking feature of the later stages of ionic decomposition of MPAH and DMPA is the loss of formaldehyde, apparently the preferred mode of disposing of methoxy groups in methyl esters of phosphoric and also phosphorous and related acids.

Introduction

The α-ketol phosphate function is present in important biological compounds, e.g., in dihydroxyacetone phosphate and its derivatives, which function as intermediates in gluconeogenesis and in the synthesis of phospholipids of biomembranes.[2] In addition, compounds of this type may be viewed as simple analogues of the sugar phosphates. A few attempts have been made to use mass spectrometry to study sugar phosphates but, without prior derivatization, the resulting spectra were so complex as to defy attempts to extract useful information from them.[3] Choosing to study a few simple α-ketol phosphates, we sought recently to examine the behavior in the mass spectrometer of two 3-oxo-2-butyl phosphates, methyl- (MPAH) and dimethylphosphoacetoins (DMPA), pictured in Scheme I.[4,5] Early in the study, we found that MPAH volatilizes in the spectrometer, at least in part, as dimer, prompting us to work instead with derived salts, from which the desired esters were

Scheme I



then generated thermally in the ionization chamber. We have now returned to direct examination in the mass spectrometer of these phosphoesters and included the corresponding monoester, phosphoacetoin (PAH_2), and the related carboxylic ester, acetoin acetate, $CH_3CO_2CH(CH_3)COCH_3$, as well. We sought in this work to clarify the dimerization reaction(s) that

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