Intramolecular Cycloaddition of the Azomethine Ylides Derived from α-Amino Acids or Esters and 5-Oxo-6-heptenals or 4-Oxo-5-hexenals

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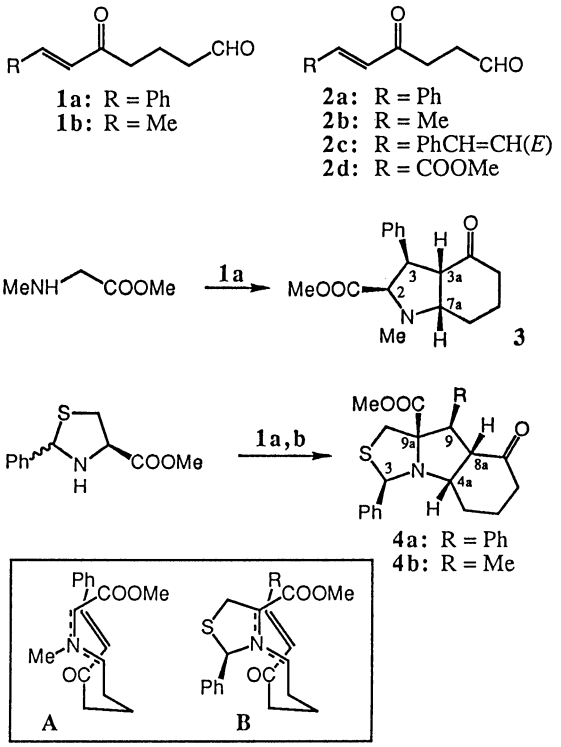
Intramolecular cycloadditions of the azomethine ylides bearing a carbonyl-activated olefinic moiety, generated from α-amino acids or esters and 5-oxo-6-heptenals or 4-oxo-5-hexenals, produce the stereoselective internal cycloadducts either to olefin or carbonyl dipolarophilic function with normal or inverse regioselectivity, depending upon the types of ylides as well as the intervening chain length. Exclusively high diastereofacial selectivity has been achieved when 2-phenyl-4-thiazolidinecarboxylic acid and its methyl ester are utilized.

The condensation of α-amino acids or derivatives with carbonyl compounds offers one of the most direct and convenient generation method of azomethine ylides, both nonstabilized[1-8] and stabilized types.[2b,c,9,10] These methods may be easily extended to an intramolecular methodology simply by employing the carbonyl compounds bearing an internal dipolarophilic moiety, for example olefin aldehydes. Most of the hitherto known examples of intramolecular cycloadditions of the azomethine ylides generated by these methods have been achieved by utilizing the internal olefins either of unsubstituted types[1,2,6] or the ones activated by a terminal functional group.[6] There are only limited numbers of examples known for the use of endocyclic double bond[9] and the internal olefins substituted by an inner substituent.[2b,c]

Synthetic versatility of intramolecular cycloadditions using the azomethine ylides thus generated should depend upon the high stereo- and regioselectivity anticipated in this short step methodology to construct fused nitrogen heterocycles. Its synthetic potential would be properly evaluated if a wide variety of α-amino acids and derivatives are successfully utilized in the condensation with olefin aldehydes.

In the present research, two types of olefin aldehydes have been utilized[11] at the first time, 5-oxo-6-heptenals and 4-oxo-5-hexenals, in the condensation with α-amino acids and esters, where the internal olefinic dipolarophiles of enone types are generated. Several new informations on dipolarophile selectivity, regioselectivity, and diastereofacial selectivity are presented here.



Scheme 1.

Results and Discussion

Heating equimolar amounts of (*E*)-7-phenyl-5-oxo-6-heptenal (**1a**) and methyl sarcosinate, under reflux in toluene with continuous removal of water by the aid of a Dean-Stark trap, afforded the internal cycloadduct **3** as single stereoisomer in 95% yield (Scheme 1). Similarly, cycloadducts **4a,b** were obtained again as single stereoisomers in 90 and 65% yields, respectively, in the reactions of **1a** and (*E*)-5-oxo-6-octenal (**1b**) with methyl 2-phenyl-4-thiazolidinecarboxylate[12] under the equivalent reaction conditions.

Determination of the stereostructures of **3** and **4** was based on the analysis of spectral data of **4a**, especially ^{1}H NMR and NOE spectra: The 9-Ph is cis to 9a-COOMe (δ=3.28) and 4a-H is also cis to 8a-H (NOE). Notable NOEs were observed between 3-H/1-H(α) and 1-H(α)/9-H. Since the *E*-relationship of the starting olefin must be retained in the cycloaddition,[15] the trans configuration between 8a-H and 9-H was suggested, and this was confirmed by a large vicinal coupling constant (J_{8a-9}=13.2 Hz) due to the antiperiplanar arrangement.

The cis ring juncture observed above (between 3a-H/7a-H for **3**; 4a-H/8a-H for **4a,b**) is fully consistent

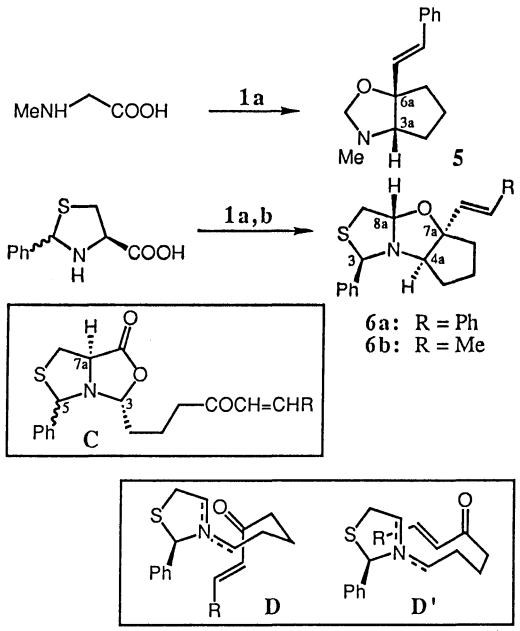
with the precedented examples for the formation of fused five- and six-membered rings in intramolecular 1,3-dipolar cycloadditions of azomethine ylides.[1,2,6,9,16] Since the reversible process of generation of azomethine ylides by the deprotonation route is under a control of thermodynamic stability,[10] ylides **A** and **B** must be *Z,E*- and *Z,Z*-forms, respectively. Thus, there was observed the selective formation of cis geometries between 2-COOMe/7a-H in **3** and 9a-COOMe/4a-H in **4a,b**. The inside location of esteric ylide-stabilizing substituent of **A** is due to the proximate interaction of both ends of the 1,5-dipole as an extended dipolar system.[10]

In contrast with the cases of ester-stabilized ylides, the intramolecular cycloadditions of nonstabilized azomethine ylides generated by the decarboxylative condensation of α-amino acids, instead of α-amino esters, with olefin aldehydes **1** selectively produced isomeric internal cycloadducts. Thus, the reaction of sarcosine with **1a** under reflux in toluene for 9 h afforded **5**, the internal adduct to the carbonyl group, in 82% yield as a single stereoisomer (Scheme 2). Similarly, reactions of 2-phenyl-4-thiazolidinecarboxylic acid with **1a,b** produced **6a,b** also as single stereoisomers in 84 and 70% yields, respectively.

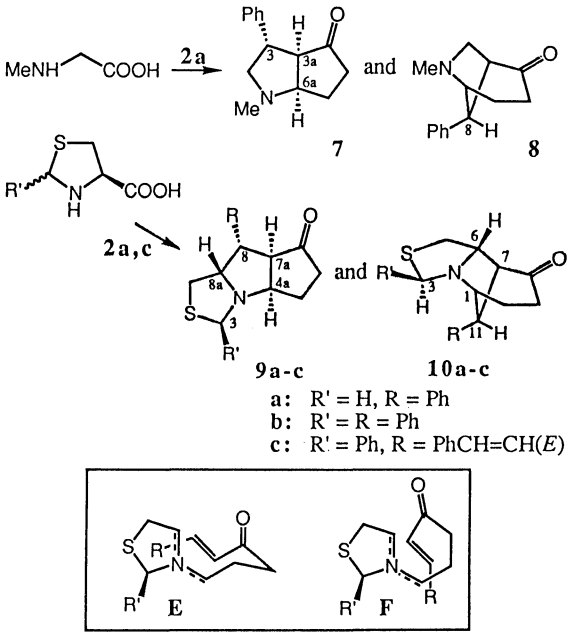
Structural assignments of **5** and **6a,b** were made on the basis of spectral data as shown with the example of **6a**: The existence of the remaining olefin moiety (δ=6.43 and 6.75, each as doublets, *J*=15.9 Hz), no carbonyl absorption in IR spectrum, low field shifts of 8a-H and 8a-C (5.54 in ^{1}H NMR and 98.87 in ^{13}C NMR), and intense NOEs between 3-H/4a-H and 4a-H/α-H of the styryl moiety are all consistent with the proposed structure. The trans configuration between 4a-H and 8a-H is due to the selective participation of the *Z,E*-ylidic form **D** which is derived from the stereospecific decarboxylation of the bicyclic lactone intermediate **C** with a thermodynamically more stable geometry.[3,6] The absolute diastereofacial selectivity is not surprising.

As shown above, the ester-stabilized azomethine ylides such as **A** and **B** undergo smooth cycloadditions at the olefinic moiety, while nonstabilized ones such as **D** react at the carbonyl moiety, both in exclusively selective fashion. One clear structural difference is the geometry of these two azomethine ylides **A**, **B**, and **D** where the intervening methylene chain stretches outside (or exo) and inside (or endo), respectively, as shown in Schemes 1 and 2. The major reason for the difficult formation of the olefin cycloadduct via transition state **D'** would be mainly because of the serious steric repulsion between the terminal olefin substituent R and the *N*-substituent, or more presumably because the azomethine ylides of nonstabilized types having a high-lying HOMO (the highest occupied molecular orbital) would prefer carbonyl moiety as a more electrophilic acceptor with a low-lying LUMO (the lowest unoccupied molecular orbital).[17]

4-Oxo-5-hexenals **2** have the intervening methylene chain one carbon shorter than that of 5-oxo-6-heptenals **1** so that the intramolecular cycloaddition to carbonyl function must become extremely difficult. Thus, the reaction of sarcosine with **2a** under reflux in dioxane[18] for 5 h produced a 4:1 mixture of two regioisomeric internal cycloadducts **7** and **8** (53% of combined yield), both as single stereoisomers (Scheme 3). Although the polarity of **7** was very close to that of **8**, the major product **7** was separated in a pure form through column chromatography on silica gel at the expense of critical weight loss of the both isomers.



Scheme 2.



Scheme 3.

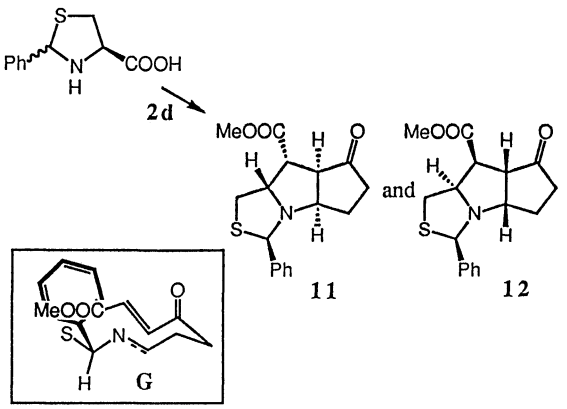
Similar reactions of 4-oxo-5-hexenals **2a,c** with cyclic α-amino acids such as 4-thiazolidinecarboxylic acid and 2-phenyl-4-thiazolidinecarboxylic acid, under reflux in toluene, produced each two stereoisomeric internal cycloadducts **9a—c** and **10a—c** (**9a+10a:** 38% (4:1), **9b+10b:** 38% (3:2), **9c+10c:** 42% (7:1)). The chromatographic separation of **9** and **10** from each other was so difficult that only **9a** and **10a** were separated through column chromatography on silica gel and purified. The isomer ratios were based on the ^{1}H NMR measurement of the crude reaction mixture.

Although the structural assignment will be discussed later, the major products **7** and **9** correspond to the cis-fused internal cycloadducts formed by a normal approach of *E,Z*-ylide **E** and the minor products **8** and **10** are the ones formed by its regioisomeric approach **F**. Since the nonstabilized azomethine ylides **E** (and **F**) are the types bearing one alkyl substituent on each carbon, it is unlikely for these ylides to show high regioselectivity in their cycloaddition. The formation of bicyclic cycloadducts **8** and **10** must be due to both the *E,Z*-geometry of ylides and the steric demand in the transition state.

Structures of the major (**7** and **9**) and minor cycloadducts (**8** and **10**) were confirmed on the basis of ^{1}H and ^{13}C NMR spectra, as shown below with the cases of **9a** and **10a** as typical examples: Strong NOEs were observed between 4a-H/7a-H and 8-H/8a-H of **9a** indicating the cis ring juncture and the 8,8a-cis relationship, respectively, while the trans configuration between 7a-H/8-H was assigned on the ground of no appearance of NOE between them as well as the stereochemical integrity of cycloaddition.[15] On the other hand, its isomer **10a** showed three singlet, or nearly singlet, signals at δ=3.27 (s, 7-H), 3.41 (s, 11-H), and 4.14 (br s, 1-H), indicating that these methine hydrogens are located at the positions so that their dihedral angles to the adjacent hydrogens are 90° or so. The carbonyl moiety of **10a** (210.46) should be in a ring larger than the fused cyclopentanone ring of **9a** (219.75). On the basis of these spectral data together with the molecular model inspection, **10a** was assigned to be the regioisomeric cycloadduct of **9a** as shown in Scheme 3. The configurations at the 6- and 11-positions were based on the only sterically possible approach **F**.

Since the introduction of a substituent at the 2-position of 4-thiazolidinecarboxylic acid added no any isomeric cycloadduct as shown in the reactions leading to **9b,c** and **10b,c**, it is clear that the cycloaddition has undergone via the approches **E** and **F** in which the internal olefinic dipolarophile approaches to the ylidic face from the side opposite to the 2-substituent R′ (R′=Ph). This exclusive diastereofacial selectivity is consistent with the aforementioned case producing **6**.

When the olefin aldehyde bearing an ester group at the terminal olefinic carbon was employed in the condensation with 2-phenyl-4-thiazolidinecarboxylic acid, the stereo- and regioselectivity of reaction changed. Thus, a 1:1 mixture of stereoisomeric cycloadducts **11** and **12** was obtained in 58% yield, no regioisomers being produced (Scheme 4).



Scheme 4.

The structures of **11** and **12** were assigned as shown in Scheme 4 on the basis of the following spectral analysis: 1) Their ^{1}H NMR pattern resembles to that of aforementioned **7** and **9**. 2) The low field carbonyl resonances of **11** (δ=219.39) and **12** (219.52) indicates the existence of fused cyclopentanone skeleton in both cases. 3) The high field shift of 5-Hs (0.75 and 1.35) of **12** compared with those of **11** (2.11) confirms their stereostructures.

The formation of **12** was of our great surprise since this isomer corresponds to the cycloadduct produced by the approach of the internal olefin dipolarophile to the ylidic face from the direction of sterically hindered 2-Ph moiety. Although the 2-Ph moiety is separated by an sp^3 carbon from the ylide conjugation, one plausible explanation for the formation of **12** would be the attractive secondary orbital interaction working between the methoxycarbonyl moiety at the terminal olefinic carbon and the 2-Ph moiety.

In conclusion, the following new informations have been obtained in the present work: 1) The condensation of α-amino acids or esters with olefin aldehydes offers a convenient method for the intramolecular azomethine ylide cycloaddition reactions. 2) Nonstabilized azomethine ylides undergo ready cycloadditions with an internal carbonyl function. 3) In the case of ring-fused azomethine ylides, a chiral center on the ring leads to highly diastereoface-selective cycloadditions. 4) The attractive secondary orbital interaction working between an aryl plane and an ester moiety, located in the same molecule, can overwhelm the repulsive interaction between them.

Experimental

General. Melting points were recorded on a Yanagimoto melting point apparatus and are uncorrected. IR spectra

were taken with JASCO IRA-1 or A-702 spectrometer. ^{1}H and ^{13}C NMR spectra were measured on a Hitachi R-40 (^{1}H NMR: 90 MHz) or a JEOL GSX-270 (270 MHz for ^{1}H NMR and 67.94 MNz for ^{13}C NMR) instrument. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. Mass spectra and high-resolution mass spectra (HRMS) were taken with a JEOL-01SG-2 spectrometer where the ionization energy of 70 eV was employed unless otherwise stated. Elemental analyses were performed on a Hitachi 026 CHN analyzer. For preparative column chromatography, Wakogel C-200, C-300 (Wako), and Silica gel 60 (Merck) were employed. Flash chromatography was carried out on an Eyela EF-10 apparatus using a column (20×180 mm) packed with Silica gel 60 (Merck, size; 0.04—0.063 mm).

Reaction of Methyl Sarcosinate with 1a Leading to 3. A solution of methyl sarcosinate (0.026 g, 0.25 mmol) and (*E*)-7-phenyl-5-oxo-6-heptenal (**1a**, 0.051 g, 0.25 mmol) in toluene (4 ml) was heated under reflux with continuous removal of water by the aid of a Dean-Stark trap for 10.5 h. The solvent was removed in vacuo and the residue was chromatographed on silica gel by using hexane-ethyl acetate (3 : 1 v/v) as an eluent to give **3** (0.068 g, 95%): Colorless liquid; IR (neat) 2960, 1735, 1710, 1455, 1200, and 760 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.4—2.4 (6H, m, 5-, 6-, and 7-H), 2.42 (3H, s, NMe), 3.23 (3H, s, COOMe), 3.43 (1H, dd, $J_{3a\text{-}7a}$=8.7 and $J_{3a\text{-}3}$=8.1 Hz, 3a-H), 3.90 (1H, ddd, $J_{7a\text{-}3a}$=8.7, $J_{7a\text{-}6}$=8.1, and 4.6 Hz, 7a-H), 4.01 (1H, d, $J_{2\text{-}3}$=8.1 Hz, 2-H), 4.06 (1H, t, $J_{3\text{-}2}$=$J_{3\text{-}3a}$=8.1 Hz, 3-H), and 7.1—7.3 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=19.41 (6-C), 26.93 (7-C), 35.25 (5-C), 38.85 (NMe), 47.60 (3a-C), 50.68 (COOMe), 55.25 (3-C), 63.97 (2-C), 71.68 (7a-C), 127.04, 128.19, 138.02 (each Ph), 171.66 (COOMe), and 211.40 (4-C); MS *m/z* (rel intensity, %) 287 (M^+, 14), 229 (20), 228 (base peak), 210 (21), 158 (21), and 58 (33). HRMS Found: *m/z* 287.1522. Calcd for $C_{17}H_{21}NO_3$: M, 287.1520.

General Procedure for the Reaction of Methyl 2-Phenyl-4-thiazolidinecarboxylate with 1a,b Leading to 4a,b. As a typical procedure, the reaction with **1a** is shown: A mixture of methyl 2-phenyl-4-thiazolidinecarboxylate (0.045 g, 0.2 mmol) and **1a** (0.041 g, 0.2 mmol) was heated under reflux in toluene (4 ml) with continuous removal of water by the aid of a Dean-Stark trap for 26 h. The toluene was evaporated in vacuo and the residue was chromatographed on silica gel by using hexane-ethyl acetate (4 : 1 v/v) as an eluent to give **4a** (0.073 g, 90%).

The reaction of the carboxylate (0.056 g, 0.025 mmol) with **1b** (0.035 g, 0.025 mmol) was performed under similar conditions (in toluene (4 ml) for 10 h) and the crude product was purified by silica-gel column chromatography with hexane-ethyl acetate (4 : 1 v/v) to give **4b** (0.056 g, 65%).

4a: Colorless liquid; IR (neat) 2970, 1730, 1700, 1450, 1220, and 730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.4—2.4 (6H, m, 5-, 6-, and 7-H), 3.18 (1H, d, J_{gem}=11.7 Hz, one of 1-H), 3.29 (3H, s, COOMe), 3.69 (1H, d, J_{gem}=11.7 Hz, the other of 1-H), 3.73 (1H, d, $J_{9\text{-}8a}$=13.2 Hz, 9-H), 3.89 (1H, m, 4a-H), 4.18 (1H, dd, $J_{8a\text{-}9}$=13.2 and $J_{8a\text{-}4a}$=7.0 Hz, 8a-H), 5.81 (1H, s, 3-H), and 7.2—7.6 (10H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=22.26 (6-C), 26.06 (5-C), 38.63 (7-C), 40.79 (1-C), 51.86 (COOMe), 54.27 (8a-C), 57.21 (9-C), 61.34 (4a-C), 67.46 (3-C), 86.87 (9a-C), 126.88, 127.80, 128.06, 128.19, 128.38, 128.42, 134.15, 141.10 (each Ph), 172.61 (COOMe), and 209.01 (8-C). MS *m/z* (rel intensity, %) 407 (M^+, 1), 349 (26), 348 (base peak), 226 (18), and 121 (18). HRMS Found: *m/z* 407.1547. Calcd for $C_{24}H_{25}NO_3S$: M, 407.1554.

4b: Colorless liquid; IR (neat) 2970, 1730, 1700, 1450, and 1225 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.95 (3H, d, $J_{Me\text{-}9}$=7.0 Hz, 9-Me), 1.4—2.3 (7H, m, 5-, 6-, 7-, and 9-H), 2.90 (1H, d, J_{gem}=11.4 Hz, one of 1-H), 3.21 (1H, dd, $J_{8a\text{-}9}$=12.4 and $J_{8a\text{-}4a}$=6.9 Hz, 8a-H), 3.69 (1H, d, J_{gem}=11.4 Hz, the other of 1-H), 3.73 (3H, s, COOMe), 3.75 (1H, m, 4a-H), 5.75 (1H, s, 3-H), and 7.2—7.6 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=13.20 (9-Me), 21.67 (6-C), 25.99 (5-C), 38.72 (7-C), 40.73 (1-C), 43.27 (9-C), 52.09 (COOMe), 60.83 (8a-C), 61.24 (4a-C), 67.70 (3-C), 85.45 (9a-C), 126.88, 127.70, 128.29, 141.31 (each Ph), 173.75 (COOMe), and 210.32 (8-C); MS *m/z* (rel intensity, %) 345 (M^+, 1), 286 (25), 169 (32), 164 (40), 162 (46), 160 (30), 137 (71), 117 (76), 91 (55), 88 (68), and 86 (base peak). HRMS Found: *m/z* 345.1392. Calcd for $C_{19}H_{23}NO_3S$: M, 345.1397.

Reaction of Sarcosine with 1a Leading to 5. A mixture of sarcosine (0.015 g, 0.17 mmol) and **1a** (0.034 g, 0.17 mmol) was heated under reflux in toluene (4 ml) with continuous removal of water by the aid of a Dean-Stark trap for 9 h. The toluene was evaporated in vacuo and the residue was chromatographed on silica gel by using hexane-ethyl acetate (4 : 1 v/v) as an eluent to give **5** (0.032 g, 82%): Colorless liquid; IR (neat) 2990, 1495, 1460, 1270, 760, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.43 (3H, s, NMe), 3.04 (1H, dd, $J_{3a\text{-}4}$=6.4 and 2.6 Hz, 3a-H), 4.19, 4.56 (each 1H, d, J_{gem}=4.4 Hz, 2-H), 6.31, 6.67 (each 1H, d, J_{trans}=16.1 Hz, =CH), and 7.2—7.4 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=24.48 (5-C), 32.50, 39.34, 40.06 (NMe, 4-, and 6-C), 75.53 (3a-C), 87.53 (2-C), 91.93 (6a-C), 126.09, 126.35, 127.30, 128.55, 133.72, and 137.02 (Ph and =CH); MS *m/z* (rel intensity, %) 230 (M^+ +1, 10), 229 (M^+, 63), 186 (92), 159 (36), 158 (base peak), 133 (21), 130 (27), 98 (48), and 84 (37). HRMS Found: *m/z* 229.1466. Calcd for $C_{15}H_{19}NO$: M, 229.1466.

General Procedure for the Reaction of 2-Phenyl-4-thiazolidinecarboxylic Acid with 1a,b Leading to 6a,b. As a typical procedure, the reaction with **1a** is shown: A mixture of 2-phenyl-4-thiazolidinecarboxylic acid (0.052 g, 0.25 mmol) and **1a** (0.052 g, 0.25 mmol) was heated under reflux in toluene (4 ml) with continuous removal of water by the aid of a Dean-Stark trap for 5 h. The toluene was evaporated in vacuo and the residue was chromatographed on silica gel by using hexane-ethyl acetate (9 : 1 v/v) as an eluent to give **6a** (0.073 g, 84%).

The reaction of the carboxylic acid (0.031 g, 0.015 mmol) with **1b** (0.022 g, 0.015 mmol) was performed under similar conditions (in toluene (3 ml) for 3 h) and the crude product was purified by silica-gel column chromatography with hexane-ethyl acetate (19 : 1 v/v) to give **6b** (0.03 g, 70%).

6a: Colorless liquid; IR (neat) 2940, 1595, 1480, 1440, and 960 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.5—2.1 (6H, m, 5-, 6-, and 7-H), 3.39 (1H, dd, J_{gem}=11.9 and $J_{1\text{-}8a}$=4.9 Hz, one of 1-H), 3.42 (1H, dd, J_{gem}=11.9 and $J_{1\text{-}8a}$=4.2 Hz, the other of 1-H), 3.52 (1H, dd, $J_{4a\text{-}5}$=9.5 and 4.2 Hz, 4a-H), 5.40 (1H, s, 3-H), 5.54 (1H, dd, $J_{7a\text{-}7}$=5.0 and 2.0 Hz, 7a-H), 6.43, 6.76 (each 1H, d, J_{trans}=15.9 Hz, =CH), and 7.2—7.5 (10H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=24.63 (6-C), 33.68, 35.84, 39.58 (1-, 5-, and 7-C), 72.86, 73.04 (3- and 4a-C), 91.73 (7a-C), 98.87 (8a-C), 126.45, 127.40, 127.58, 128.06, 128.40, 128.59, 134.01, 136.96, and 140.05 (Ph and =CH); MS *m/z* (rel intensity, %) 350 (M^+ +1, 21), 349 (M^+, 69), 302 (50), 227 (23), 186 (32), 170 (64), 169 (42), 149 (35), 145 (27), 141 (47), 131 (28), 130 (31), 105 (40), 104 (34), and 43 (base peak). HRMS Found: *m/z* 349.1501. Calcd for $C_{22}H_{23}NOS$: M, 349.1499.

6b: Colorless liquid; IR (neat) 2950, 1590, 1445, and 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.4—1.9 (6H, m, 5-, 6-, and 7-H), 1.72 (3H, d, J=5.1 Hz, Me), 3.25 (1H, dd, J_{gem}=11.7 and $J_{1\text{-}8a}$=1.8 Hz, one of 1H), 3.36 (1H, m, 4a-H), 3.37 (1H, dd, J_{gem}=11.7 and $J_{1\text{-}8a}$=5.1 Hz, the other of 1-H), 5.38 (1H, s, 3-H), 5.46 (1H, dd, $J_{8a\text{-}1}$=5.1 and 1.8 Hz, 8a-H), 5.72 (1H, d, J_{trans}=15.8 Hz, =CH), 5.80 (1H, dq, J_{trans}=15.8 and J=5.1 Hz, =CHMe), and 7.2—7.5 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=17.77 (Me), 24.45 (6-C), 33.55, 35.82, 38.83 (1-, 5-, and 7-C), 72.58, 72.74 (3- and 4a-C), 91.57 (7a-C), 98.44 (8a-C), 127.57, 128.03, 128.40, 135.29, and 140.21 (Ph and =CH); MS m/z (rel intensity, %) 288 (M^+ +1, 28), 287 (M^+, 96), 165 (34), 108 (base peak), 96 (63), 93 (50), 91 (28), and 83 (52). HRMS Found: m/z 287.1344. Calcd for $C_{17}H_{21}NOS$: M, 287.1343.

Reaction of Sarcosine with 2a Leading to 7 and 8. A mixture of sarcosine (0.089 g, 1 mmol) and (*E*)-6-phenyl-4-oxo-5-hexenal (**2a**, 0.034 g, 0.17 mmol) was heated under reflux in 1,4-dioxane (8 ml) for 5 h. The dioxane was evaporated in vacuo and the residue was chromatographed on silica gel by using hexane-ethyl acetate (4:1 v/v) as an eluent to give a 4:1 mixture (^1H NMR) of **7** and **8** (0.115 g, 53%). Compound **7** was only separated by Lobar column chromatography by hexane-ethyl acetate (4:1 v/v), but **8** was still contaminated by **7**.

7: Colorless liquid; IR (neat) 2930, 1730, 1445, 1150, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.9—2.7 (5H, m, 3a-, 5-, and 6-H), 2.39 (3H, s, NMe), 2.70 (1H, br ddd, $J_{3\text{-}3a}$=5.6, $J_{3\text{-}2}$=4.3, and 1.5 Hz, 3-H), 3.14 (1H, dd, $J_{3a\text{-}6a}$=6.2 and $J_{3a\text{-}3}$=5.6 Hz, 3a-H), 3.4—3.5 (2H, m, 2- and 6a-H), and 7.2—7.4 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=23.34 (6-C), 34.86 (5-C), 39.68 (NMe), 46.26 (3a-C), 60.20 (2-C), 65.69 (3-C), 69.07 (6a-C), 126.48, 127.56, 128.59, 143.38 (each Ph), and 220.60 (4-C); MS m/z (rel intensity, %) 216 (M^+ +1, 13), 215 (M^+, 85), 186 (62), 159 (41), 158 (base peak), and 82 (34). HRMS Found: M, 215.1309. Calcd for $C_{14}H_{17}NO$: M, 215.1309.

8: Since this compound **8** was obtained only as an inseparable mixture with **7**, the partial ^1H spectrum is given as follows: ^1H NMR ($CDCl_3$) δ=1.6—1.9 (2H, m, 4-H), 2.3—2.5 (2H, m, 3-H), 2.61 (3H, s, NMe), 2.7—2.8 (1H, br, one of 7-H), 2.98 (1H, br, 1-H), 3.20 (1H, s, 8-H), 3.33 (1H, dd, J_{gem}=10.6 and $J_{7\text{-}1}$=5.5 Hz, the other of 7-H), 3.59 (1H, br s, 5-H), and 7.2—7.4 (5H, m, Ph).

General Procedure for the Reaction of 4-Thiazolidinecarboxylic Acid or 2-Phenyl-4-thiazolidinecarboxylic Acid with 2a,c Leading to 9a—c and 10a—c. As a typical procedure, the reaction of 4-thiazolidinecarboxylic acid with **2a** is shown: A mixture of 4-thiazolidinecarboxylic acid (0.133 g, 1 mmol) and **2a** (0.282 g, 1.5 mmol) was heated under reflux in dioxane (8 ml) for 3 h. The dioxane was evaporated in vacuo and the residue was chromatographed on silica gel by using hexane-ethyl acetate (4:1 v/v) as an eluent to give a 3:2 mixture of **9a** and **10a** (^1H NMR, 0.098 g, 38%). They were separated by repeated silica-gel column chromatography with the same eluent.

The reaction of 2-phenyl-4-thiazolidinecarboxylic acid (0.084 g, 0.4 mmol) with **2a** (0.1 g, 0.43 mmol) was performed under similar conditions (in toluene (3 ml) for 8 h) and the crude product was purified by silica-gel column chromatography with hexane-ethyl acetate (4:1 v/v) to give an inseparable 2:1 mixture of **9b** and **10b** (0.057 g, 38%).

The reaction of 2-phenyl-4-thiazolidinecarboxylic acid (0.031 g, 0.15 mmol) with **2c** (0.1 g, 0.43 mmol) was performed under similar conditions (in toluene (3 ml) for 4 h) and the crude product was purified by silica-gel column chromatography with hexane-ethyl acetate (4:1 v/v) to give an inseparable 7:1 mixture of **9c** and **10c** (0.023 g, 42%).

9a: Colorless liquid; IR (neat) 2960, 1730, 1455, and 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.0—2.7 (6H, m, 1-, 5-, and 6-H), 3.09 (1H, dd, $J_{8\text{-}8a}$=8.0 and $J_{8\text{-}7a}$=6.5 Hz, 8-H), 3.67 (1H, m, 8a-H), 3.86 (1H, ddd, $J_{4a\text{-}4}$=9.2, 7.2, and $J_{4a\text{-}7a}$=6.5 Hz, 4a-H), 3.96 (1H, t, $J_{7a\text{-}4a}$=$J_{7a\text{-}8}$=6.5 Hz, 7a-H), 4.22, 4.32 (each 1H, d, J_{gem}=9.9 Hz, 3-H), and 7.2—7.4 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=25.64, 32.80, 34.89 (1-, 5-, and 6-C), 48.95 (7a-C), 54.37 (8-C), 57.25 (3-C), 62.81 (4a-C), 75.73 (8a-C), 126.88, 127.76, 128.55, 139.22 (each Ph), and 219.75 (7-C); MS m/z (rel intensity, %) 259 (M^+, base peak), 213 (83), 212 (35), 172 (30), 156 (17), 130 (21), and 128 (24). Found: C, 69.39; H, 6.65; N, 5.14%. Calcd for $C_{15}H_{17}NOS$: C, 69.46; H, 6.61; N, 5.40%.

10a: Colorless liquid: IR (neat) 2960, 1735, 1700, 1440, and 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.80 (1H, m, one of 10-H), 2.06 (1H, dd, J_{gem}=10.6 and $J_{5\text{-}6}$=8.6 Hz, one of 5-H), 2.20 (1H, m, the other of 10-H), 2.44 (1H, br dd, J_{gem}=16.9 and $J_{9\text{-}10}$=7.1 Hz, one of 9-H), 2.66 (1H, dd, J_{gem}=10.6 and $J_{5\text{-}6}$=7.0 Hz, the other of 5-H), 2.76 (1H, dd, J_{gem}=16.9 and $J_{9\text{-}10}$=9.9 Hz, the other of 9-H), 3.27 (1H, s, 7-H), 3.41 (1H, s, 11-H), 3.67 (1H, dd, $J_{6\text{-}5}$=8.6 and 7.0 Hz, 6-H), 4.14 (1H, br s, 1-H), 4.39, and 4.44 (each 1H, d, J_{gem}=8.2 Hz, 3-H); ^{13}C NMR ($CDCl_3$) δ=33.64, 34.93, 36.10 (5-, 9-, and 10-C), 50.44 (7-C), 59.36 (11-C), 61.28 (3-C), 63.96 (1-C) 71.37 (6-C), 126.55, 126.91, 128.59, 138.74 (each Ph), and 210.46 (8-C); MS m/z (rel intensity, %) 259 (M^+, 74), 213 (68), 212 (38), 172 (34), 131 (38), 130 (49), 129 (27), 128 (35), 101 (47), 77 (29), and 73 (base peak). Found: C, 69.29; H, 6.41; N, 5.01%. Calcd for $C_{15}N_{17}NOS$: C, 69.46; H, 6.61; N, 5.40%.

9b and 10b: Pale yellow liquid; IR (neat) 3030, 2960, 1745, 1720, 1500, and 1400 cm^{-1}; ^1H NMR ($CDCl_3$) **9b**: δ=2.1—2.9 (6H, m, 1-, 5-, and 6-H), 3.11 (1H, m, 8-H), 3.87 (1H, m, 8a-H), 4.02 (1H, m, 4a-H), 4.08 (1H, dd, $J_{7a\text{-}4a}$=10.0 and $J_{7a\text{-}8}$=6.2 Hz, 7a-H), 5.71 (1H, s, 3-H), and 7.2—7.5 (10H, m, Ph). **10b**: δ=2.1—2.9 (7H, m, 5-, 7-, 9-, and 10-H), 3.33 (1H, s, 7-H), 3.46 (1H, s, 11-H), 4.02 (1H, overlapping with 4a-H of **9b**, 6-H), 4.21 (1H, br s, 1H), 5.73 (1H, s, 3-H), and 7.2—7.5 (10H, m, Ph); ^{13}C NMR ($CDCl_3$) **9b**: δ=25.73, 34.78, 35.29 (1-, 5-, and 6-C), 48.66 (7a-C), 54.41 (8-C), 64.36 (4a-C), 73.63 (3-C), 74.76 (8a-C), and 219.70 (7-C). **10b**: δ=33.49, 35.20, 38.35 (5-, 9-, and 10-C), 50.76 (7-C), 60.76 (11-C), 62.30 (1-C), 72.29 (6-C), 75.63 (3-C), and 210.23 (8-C). **9b+10b**: 126.19, 126.55, 126.65, 126.89, 127.07, 127.31, 127.80, 128.29, 128.52, 128.56, 128.88, 138.88, 139.31, 143.30, 143.63. MS m/z (rel intensity, %) 335 (M^+, 30), 289 (10), 288 (24), 88 (11), 86 (64), 84 (base peak), and 49 (38). HRMS Found: m/z 335.1348. Calcd for $C_{21}H_{21}NOS$: M, 335.1343.

9c and 10c: Pale yellow liquid; IR (neat) 2950, 1730, 1445, 1150, and 965 cm^{-1}; ^1H NMR ($CDCl_3$) **9c**: δ=2.0—2.1 (2H, m, 5-H), 2.2—3.0 (5H, m, 1-, 6-, and 8-H), 3.45 (1H, m, 8a-H), 3.8—3.9 (2H, m, 4a- and 7a-H), 5.69 (1H, s, 3-H), 6.20 (1H, dd, J_{trans}=15.8 and $J_{CH\text{-}8}$=8.1 Hz, =CH), 6.59 (1H, dd, J_{trans}=15.8 and $J_{CH\text{-}8}$=1.0 Hz, =CH), and 7.2—7.5 (10H, m, Ph). **10c:** δ=3.16, 3.18 (each 1H, s, 1- and 7-H), 3.63 (1H, m, 11-H), 4.12 (1H, m, 6-H), 5.93 (1H, s, 3-H). Other signals are overlapping with those of **9c**; ^{13}C NMR ($CDCl_3$) **9c**: δ=25.92, 34.83, 34.93 (1-, 5-, and 6-C) 47.31 (7a-C), 55.79 (8-C), 64.27 (4a-C), 73.46 (3-C), 74.92 (8a-C), 126.36, 126.55, 127.31, 127.64, 127.86, 128.29, 128.58, 132.72, 143.61 (=CH

and Ph), and 219.53 (7-C). **10c**: δ=33.13, 35.24, 39.32 (5-, 9-, and 10-C), 50.83 (7-C), 63.39 (11-C), 66.54 (1-C), 72.02 (6-C), 74.69 (3-C), 126.27, 127.21, 127.76, 128.00, 128.40, 128.48, 128.75, 131.69, 132.00, 143.41 (=CH and Ph), and 209.50 (8-C); MS *m/z* (rel intensity, %) 361 (M^+, 1), 218 (4), 212 (6), 211 (12), 210 (base peak), and 136 (6). HRMS Found: *m/z* 361.1497. Calcd for $C_{23}H_{23}NOS$: M, 361.1499.

Reaction of 2-Phenyl-4-thiazolidinecarboxylic Acid with 2d Leading to 11 and 12. A mixture of 2-phenyl-4-thiazolidinecarboxylic acid (0.052 g, 0.25 mmol) and methyl (*E*)-6-formyl-4-oxo-2-hexenoate (**1a**, 0.048 g, 0.28 mmol) was heated under reflux in toluene (4 ml) with continuous removal of water by the aid of a Dean-Stark trap for 5 h. The toluene was evaporated in vacuo and the residue was chromatographed on silica gel by using hexane-ethyl acetate (4:1 v/v) as an eluent to give **11** (0.023 g, 29%) and **12** (0.023 g, 29%).

11: Colorless liquid; IR (neat) 2950, 1730, 1430, and 840 cm^{-1}. ^1H NMR ($CDCl_3$) δ=2.11 (2H, m, 5-H), 2.35 (1H, m, one of 6-H), 2.56 (1H, dt, J_{gem}=19.0 and $J_{6\text{-}5}$=9.5 Hz, the other of 6-H), 2.76 (1H, t, J_{gem}=$J_{1\text{-}8a}$=10.2 Hz, one of 1-H), 2.99 (1H, dd, J_{gem}=10.2 and $J_{1\text{-}8a}$=6.6 Hz, the other of 1-H), 3.28 (1H, br dd, $J_{7a\text{-}4a}$=6.5 and $J_{7a\text{-}8}$=3.6 Hz, 7a-H), 3.54 (1H, dd, $J_{8\text{-}8a}$=7.7 and $J_{8\text{-}7a}$=3.6 Hz, 8-H), 3.72 (3H, s, COOMe), 3.74 (1H, m, 4a-H), 3.98 (1H, ddd, $J_{8a\text{-}1}$=10.2, 6.6, and $J_{8a\text{-}8}$=7.7 Hz, 8a-H), 5.67 (1H, s, 3-H), and 7.2—7.4 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=24.92 (5-C), 34.35, 35.03 (1- and 6-C), 48.22 (8-C), 52.37 (COOMe), 53.20 (7a-C), 63.63 (4a-C), 69.96, 73.59 (3- and 4a-C), 126.45, 127.43, 128.35, 143.19 (each Ph), 171.84 (COOMe), and 219.39 (7-C); MS *m/z* (rel intensity, %) 318 (M^+ +1, 20), 317 (M^+, base peak), 286 (22), 284 (28), 271 (41), 235 (23), 212 (78), and 91 (24). HRMS Found: *m/z* 317.1080. Calcd for $C_{17}H_{19}NO_3S$: M, 317.1085.

12: Colorless liquid; IR (neat) 2960, 1725, 1700, and 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.75 (1H, m, one of 5-H), 1.35 (1H, m, the other of 5-H), 2.02 (1H, m, one of 6-H), 2.21 (1H, dt, J_{gem}=18.9 and $J_{6\text{-}5}$=9.5 Hz, the other of 6-H), 2.84 (1H, t, J_{gem}=$J_{1\text{-}8a}$=10.4 Hz, one of 1-H), 2.99 (1H, dd, J_{gem}=10.4 and $J_{1\text{-}8a}$=7.2 Hz, the other of 1-H), 3.31 (1H, br dd, $J_{7a\text{-}4a}$=8.6 and $J_{7a\text{-}8}$=5.5 Hz, 7a-H), 3.48 (1H, dd, $J_{8\text{-}8a}$=7.0 and $J_{8\text{-}7a}$=5.5 Hz, 8-H), 3.76 (3H, s, COOMe), 3.90 (1H, br dd, 4a-H), 4.07 (1H, ddd, $J_{8a\text{-}1}$=10.4, 7.2, and $J_{8a\text{-}8}$=7.0 Hz, 8a-H), 5.95 (1H, s, 3-H), and 7.3—7.7 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=25.23 (5-C), 33.87, 35.13 (1- and 6-C), 47.82 (8-C), 52.44 (COOMe), 53.00 (7a-C), 58.01 (4a-C), 73.43, 74.99 (3- and 4a-C), 128.56, 129.12, 129.56, 134.97 (each Ph), 171.61 (COOMe), and 219.52 (7-C); MS *m/z* (rel intensity, %) 318 (M^+ +1, 27), 317 (M^+, base peak), 316 (31), 286 (26), 284 (38), 271 (47), 235 (33), 224 (21), 212 (86), and 91 (30). Found: C, 64.09; H, 6.03; N, 4.28%. Calcd for $C_{17}H_{19}NO_3S$: C, 64.32; H, 6.03; N, 4.41%.

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