chemistry of 2 had been established by conversion to *O,O'*-dimethylcarnosol[8a] and by total synthesis of both enantiomers of methyl pisiferate.[9] The *O*-methyl ether of 2[4a] and pisiferal[4b] have previously been reported in *S. wiedemannii*.

Pisiferic acid has well-established biological activity as a general cytotoxic agent,[10] and its methyl ether is an important defensive compound.[10,11] In contrast, 1 showed no activity against a variety of bacteria, fungi, and tumor cell lines. Thus 1 this may represent a stored supply of the defensive compound pisiferic acid in the leaves of *S. wiedemannii*.

Experimental Section

General. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 93.94 kG (400 MHz for ^1H, 100 MHz for ^{13}C) in $CDCl_3$ unless otherwise noted using the 7.24 ppm resonance of residual $CHCl_3$ and the 77.0 ppm resonance of $^{13}CDCl_3$ as internal references for ^1H and ^{13}C, respectively. Molecular modeling employed the QUANTA/CHARMm program on a Silicon Graphics work station.

NMR Multipulse Sequences. All 1D and 2D pulse sequences were run using standard Varian software, version 6.1c, except the FLOCK[6] experiment which was added to the sequence library according to Reynolds' program. ^{13}C multiplicities were assigned with the DEPT experiment, and ^{13}C assignments were completed using the HETCOR experiment for one-bond heteronuclear couplings (^1H,^{13}C), and the FLOCK and selective INEPT sequences for two- and three-bond heteronuclear couplings (^1H, ^{13}C). The FLOCK sequence employed two fixed delays of $\Delta1 = 0.072$ s and $\Delta2 = 0.040$ s.[6] Selective INEPT experiments were recorded with the excitation and refocusing delays optimized for different coupling constants according to the formulae $\Delta1 = {}^1/_2\,J$ and $\Delta2 = {}^1/_3\,J$, respectively.[12]

Isolation of 8-Hydroxy-12-oxoabieta-9(11),13-dien-20-oic Acid 8,20-Lactone (1). *S. wiedemannii* Boiss. was collected in the Haymana region of Central Turkey. The air-dried plant (aerial parts, 1.2 kg) was extracted with petroleum ether and then with acetone. The residue from the acetone extract (20 g) was then fractionated on a silica gel column eluting first with petroleum ether and then with a petroleum ether/ethyl acetate step gradient. The fraction eluting with 20% ethyl acetate in petroleum ether contained 1. This crude fraction (500 mg) was purified by chromatography on Sephadex LH-20, eluting with petroleum ether/$CHCl_3$/MeOH (7:4:1), and then by preparative TLC, eluting with $CHCl_3$/acetone (98:2) to give 1 as white crystals (80 mg, 0.0067% dry wt): mp 161-163 °C; $[\alpha]_D$ -167° (0.2 g/100 mL, CH_2Cl_2); CD (CH_3OH) 222 nm ($\Delta\epsilon$ 5.09), 259 (-6.27), 358 (-1.71); IR (KBr) 2920, 1785, 1690, 1640, 1390, 1370 cm^{-1}; UV (MeOH) λ_{max} 248 (ϵ 18190), 337 (ϵ 107); LRMS (EI, 70 eV) *m/z* (relative intensity) 315 ([M + 1]$^+$, 13), 314 (M$^+$, 49), 299 (25), 287 (26), 286 (100), 271 (22), 270 (53), 243 (34), 227 (17), 217 (13), 204 (11), 202 (39), 201 (13), 199 (11), 187 (21), 185 (12); HRMS (EI, 70 eV) *m/z* 314.1854 (M$^+$, calcd for $C_{20}H_{26}O_3$ 314.1882); ^1H and ^{13}C NMR, see Table I.

Reduction of 1 to (+)-Pisiferic Acid (2). To a solution of 1 (5 mg, 0.016 mmol) in glacial acetic acid (3 mL) was added freshly activated zinc powder (100 mg), and the mixture was stirred at rt for 4 h. Saturated brine solution (3 mL) was added, and the mixture was extracted with $CHCl_3$ (4 × 4 mL). The combined $CHCl_3$ extracts were washed with water and dried (Na_2SO_4), and the $CHCl_3$ was evaporated in vacuo. The residue was purified by flash chromatography on silica gel ($CHCl_3$/MeOH, 10:1) to give pure 2 (4 mg, 79% yield) as a white solid: mp 184-186 °C (lit.[8b] mp 185-186 °C); $[\alpha]_D$ +165° (*c* 0.19 g/100 mL, CH_3OH) [lit.[8a] $[\alpha]_D$ +177° (*c* 0.35, CH_3OH)]; CD (CH_3OH) 238 nm ($\Delta\epsilon$ +9.58); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.89 (s, H-14), 6.67 (s, H-11), 3.10 (sept, J = 6.8 Hz, H-15), 2.88 (dd, J = 16.2, 5.9 Hz, H-7β), 2.82-2.76 (2H m, H-7α and H-1β), 2.44 (dddd, J = 13.1, 12.0, 11.0, 5.9 Hz, H-6β), 1.94 (m, H-2β), 1.87 (ddd, J = 11.0, 4.4, 2.8 Hz, H-6α), 1.60 (ddd, J = 13.7, 3.4, 3.2 Hz, H-2α), 1.49 (dd, J = 13.1, 2.8 Hz, H-5), 1.45 (dd, J = 13.1, 3.0 H-3β), 1.22 (2 H, m, H-1α and H-3α), 1.22 (3 H, d, J = 6.8 Hz, H-17), 1.21 (3 H, d, J = 6.8 Hz, H-16), 0.95 (3 H, s, H-19), 0.83 (3 H, s, H-18); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.1 (s, C-20), 150.7 (s, C-12), 138.2 (s, C-9), 133.5 (s, C-13), 129.1 (s, C-8), 127.4 (d, C-14), 112.3 (d, C-11), 52.2 (d, C-5), 41.7 (t, C-3), 36.7 (s, C-10), 34.0 (t, C-1), 32.1 (q, C-19), 29.7 (s, C-4), 29.3 (t, C-7), 26.8 (d, C-15), 22.6 (q, C-16 or C-17), 22.4 (q, C-17 or C-16), 20.3 (t, C-6), 20.1 (q, C-18), 18.5 (t, C-2); LRMS (CI, NH_3, 150 eV) *m/z* (relative intensity) 334 ([M + NH_4]$^+$, 100), 271 ([M - COOH]$^+$, 24); HRMS (CI, NH_3, 150 eV) *m/z* 334.2387 ([M + NH_4]$^+$), calcd for $C_{20}H_{32}NO_3$ 334.2382.[13]

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Supplementary Material Available: ^1H, ^{13}C, and DEPT one-dimensional NMR spectra, DQCOSY (double quantum filtered, phase-sensitive COSY), 2D-NOE, HETCOR, and FLOCK two-dimensional NMR spectra of 1; ^1H, ^{13}C, and APT NMR spectra of 2 (8 pages). Ordering information is given on any current masthead page.

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(10) Antimicrobial activity: (a) Kobayashi, K.; Nishino, C. *Agric. Biol. Chem.* **1986**, *50*, 2405. (b) Kobayashi, K.; Nishino, C.; Fukushima, M.; Shiobara, Y.; Kodama, M. *Agric. Biol. Chem.* **1988**, *52*, 77. Antifungal activity: (c) Kobayashi, K.; Nishino, C.; Shiobara, Y.; Kodama, M. *Agric. Biol. Chem.* **1987**, *51*, 1163. (d) Kobayashi, K.; Nishino, C.; Tomita, H.; Fukushima, M. *Phytochemistry* **1987**, *26*, 3175. Antitumor activity: (e) Kobayashi, K.; Kuroda, K.; Shinomiya, T.; Nishino, C.; Ohya, J.; Sato, S. *Int. J. Biochem.* **1989**, *21*, 463.

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(13) Comparison of the ^1H NMR chemical shifts in $CDCl_3$ with those previously reported for 2 confirmed the structure (refs 8a and 8b). The IR and UV data were also identical. Since the ^{13}C NMR data had not been previously determined, however, we essentially did a complete structure assignment to confirm the structure of 2, thereby enabling assignments of all chemical shifts.

Synthesis of (±)-α-Allokainic Acid via the Zinc Acetate Catalyzed Cyclization of γ-Isocyano Silyl Enolates

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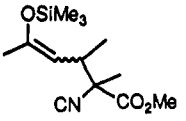
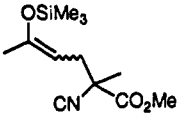
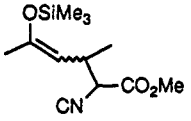
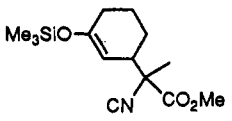
Kainoid amino acids like kainic acid,[1] domoic acid,[2] and acromelic acid[3] have attracted attention because they

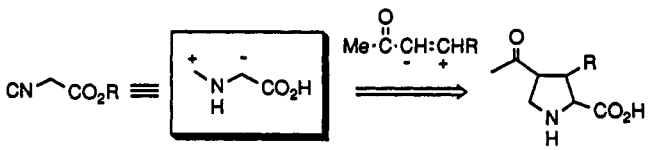
0022-3263/91/1956-7356$02.50/0

Table I. Cyclization of γ-Isocyano Silyl Enolates 1

entry	1	2	yield[a] (%)
1		2a	90
2		2b	76
3		2c	74
4		2d	96

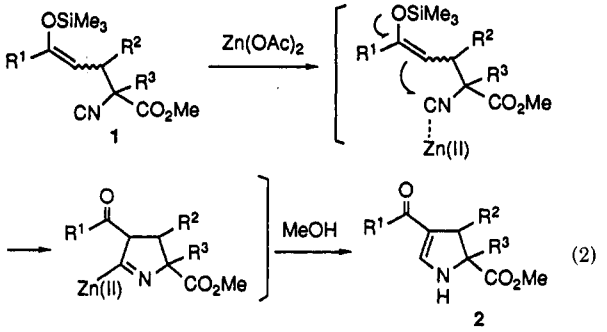
[a] Isolated yields after chromatography

display extremely potent excitotoxic activity.[1-3] These naturally occurring pyrrolidine carboxylic acids and their analogues are important tools for use in the study of neurological diseases.[1-3] Recently, we described a fluoride-catalyzed addition of α-isocyano carboxylates to α,β-unsaturated ketones in the presence of *N,O*-bis(trimethylsilyl)acetamide (BSA) that gives the 1,4-adducts (as the corresponding silyl enolates) in high yield.[4] Now, we describe a versatile synthetic route to pyrrolidine-2-carboxylic acids via the zinc(II) acetate catalyzed cyclization of the 1,4-adducts **1**, and, furthermore, its successful application in a total synthesis of racemic α-allokainic acid. Cyclization via the intramolecular α-addition of nucleophiles to isonitriles has been utilized to synthesize various nitrogen-containing heterocycles.[5] The synthesis of pyrrolidine-2-carboxylic acids described here involves the step-by-step regioselective addition of an α-isocyano carboxylate (which is formally equivalent to an azomethine ylide that bears a carboxyl group[6]) to the carbon–carbon double bond of an enone (eq 1).



(1)

Several metal salts (Cu(I), Sn(II), Pd(II), Ti(IV), Ni(II), Al(III), Sm(III), Zn(II)) were evaluated as promoters of the intramolecular cyclization of γ-isocyano silyl enolates **1**.[4,7] Zinc(II) acetate was found to be the most efficient, and its use led to the 2-pyrroline-5-carboxylates **2** in good yield (Table I). $[Cu(CH_3CN)_4]^+BF_4^-$ and $ZnCl_2$ also showed satisfactory catalytic activity. The other metal salts either showed no catalytic activity or their use led to complex mixtures of products. Activation of the isocyano group by coordination with zinc may have facilitated the intramolecular nucleophilic addition of the silyl enolate moiety. It should be noted that the corresponding α-isocyano-δ-oxo ester, the parent compound of **1**, failed to cyclize under similar conditions. Methanol was indispensable as a proton donor. Cyclization proceeded smoothly in methanol or in dimethyl sulfoxide (DMSO) that contained ca. 2 equiv of methanol. However, in DMSO without added methanol or in other aprotic solvents like THF, compounds **2** were not formed. Cyclization does not equilibrate the diastereomers of **2**; i.e., the two diastereomers are configurationally stable under the reaction conditions.

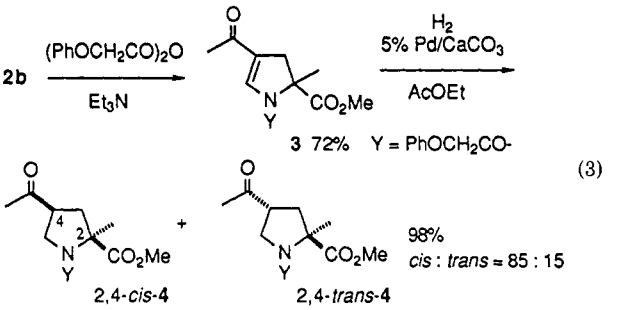


(2)

a) $R^1=R^2=R^3=Me$ c) $R^1=R^2=Me$, $R^3=H$

b) $R^1=R^3=Me$, $R^2=H$ d) $R^1-R^2=-(CH_2)_3-$, $R^3=Me$

The 2-pyrroline-5-carboxylate **2b** so formed was transformed into the corresponding pyrrolidine-2-carboxylic ester **4** via hydrogenation of the N-protected derivative **3**.[8] $Pd/CaCO_3$ (5%) was the catalyst of choice for the selective hydrogenation of the carbon–carbon double bond. The use of other catalysts, e.g., Pd/C, led to concomitant reduction of the carbonyl group. It should be noted that the hydrogenation of **3** in the presence of 5% $Pd/CaCO_3$ preferentially produced **4**, in which the 2-methoxycarbonyl and the 4-acetyl groups are cis to each other (2,4-cis:2,4-trans = 85:15).[9] This indicates that, preferentially, the methoxycarbonyl group is directed away from the surface of the catalyst as the molecule is hydrogenated.



(3)

This method for preparing pyrrolidine-2-carboxylic acids was applied in a total synthesis of racemic α-allokainic acid.[6,10] The starting enone **5** was easily prepared by a

(1) Takano, S.; Sugihara, T.; Satoh, S.; Ogasawara, K. *J. Am. Chem. Soc.* **1988**, *110*, 6467 and references cited therein.
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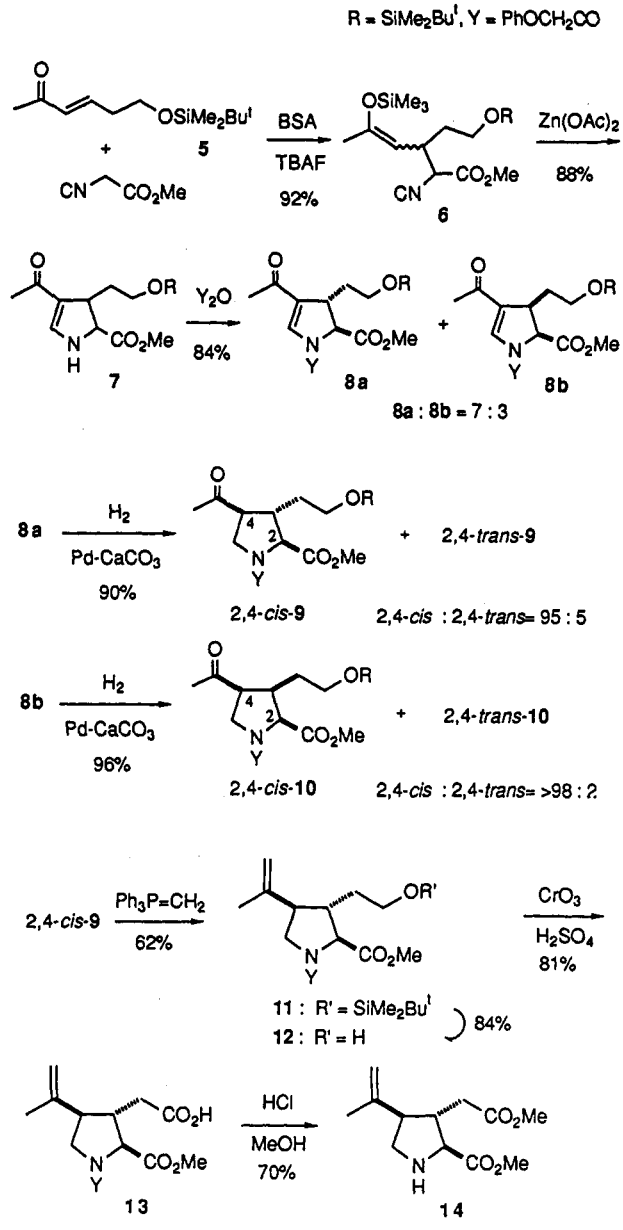
(5) (a) Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 789. (b) Schöllkopf, U. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 339 and references cited therein.
(6) The syntheses of α-allokainic acid by the dipolar cycloaddition of an azomethine ylide to α,β-unsaturated ketone has been reported. See: (a) Kraus, G. A.; Nagy, J. O. *Tetrahedron* **1985**, *41*, 3537. (b) DeShong, P.; Kell, D. A. *Tetrahedron Lett.* **1986**, *27*, 3979.
(7) A mixture of diastereomers was used.
(8) The N-protected 2-pyrroline-5-carboxylate **3** was hydrogenated because **2** is unstable.
(9) The stereochemistry was determined by a ^1H NMR NOE experiment.

known procedure.[11] Methyl isocyanoacetate underwent fluoride-catalyzed 1,4-addition[4] to **5** in the presence of BSA to give **6** (92%). The silyl enolate **6** was cyclized to afford the 2-pyrroline-5-carboxylate **7** as a mixture of diastereomers. After **7** was N-acylated by treatment with phenoxyacetic anhydride, the two diastereomeric amides **8** were separated by HPLC. The ratio of **8a** to **8b** was 7:3. The two diastereomers could also be separated by recrystallization from diisopropyl ether. The stereoselective hydrogenation of each isomer was performed in the presence of 5% $Pd/CaCO_3$. Thus, the pyrroldine-2-carboxylic esters **9**[12] and **10**,[13] in which the 2- and 4-substituents are cis to each other, were selectively produced from **8a** and **8b**, respectively, in high yield. The pyrrolidine-2-carboxylic ester 2,4-*cis*-**9** was converted into the 4-isopropenylpyrrolidine-2-carboxylic ester **11** by Wittig olefination (62%). Removal of the *tert*-butyldimethylsilyl group of **11** (84%) and oxidation of the primary alcohol that resulted (81%) provided the dicarboxylic acid derivative **13**. Subsequent deprotection of the amino acid **13** and esterification afforded the dimethyl ester **14** (70%), which was identical to the dimethyl ester prepared from natural α-allokainic acid. The approach to the synthesis of pyrrolidine-2-carboxylic acids described here provides a new route to kainoids and their analogues (Scheme I).

Scheme I



Experimental Section

General. Unless otherwise noted, materials were obtained from commercial sources. THF and Et_2O were distilled from $LiAlH_4$. CH_2Cl_2, MeOH, DMSO, and EtOAc were destilled from CaH_2. Column chromatography was performed with silica gel 60 (E. Merck, Darmstadt, 230–400 mesh) or with Florisil (60–100 mesh). Preparative thin-layer chromatography was performed with silica gel 60 PF_{254} (E. Merck, Darmstadt). ^1H and ^{13}C NMR spectra of $CDCl_3$ solutions were recorded at 200 and 50 MHz, respectively. High-performance liquid chromatography (HPLC) was performed with a 10 mm × 25 cm Merck LiChrosorb Si 60 column. Na_2SO_4 was used to dry organic solutions after extraction.

6-(*tert*-Butyldimethylsiloxy)-3-hexen-2-one was prepared by the literature procedure.[11]

3-Acetyl-5-(methoxycarbonyl)-4,5-dimethyl-2-pyrroline (2a). The reaction vessel was charged with $Zn(OAc)_2{\cdot}2H_2O$ (8.0 mg, 37 μmol). The salt was dehydrated by heating it in vacuo until it was molten. The vessel was then cooled to rt under N_2. MeOH (7 mg, 0.22 mmol), DMSO (2 mL), and methyl 2-isocyano-2,3-dimethyl-5-(trimethylsiloxy)-4-hexenoate (31.0 mg, 0.115 mmol) were added. Then, the mixture was stirred at 55 °C for 18 h under N_2. Evaporation of DMSO in vacuo, extractive aqueous workup of the residue (AcOEt/H_2O), and column chromatography on Florisil (CH_2Cl_2/MeOH (20:1)) afforded **2a** (20.4 mg, 90%) as a mixture of diastereomers: IR (neat) 3350, 1740, 1576 cm^{-1}; ^1H NMR (the mixture of diastereomers) δ 0.97 and 1.07 (d, J = 6.9 Hz for δ 0.97, J = 7.0 Hz for δ 1.07, 3 H), 1.36 and 1.38 (s, 3 H), 2.07 and 2.08 (s, 3 H), 2.95 and 3.33 (q, J = 6.9 Hz for δ 2.95, J = 7.0 Hz for δ 3.33, 1 H), 3.65 and 3.70 (s, 3 H), 5.40 and 5.59 (br s, 1 H), 7.12 and 7.15 (d, J = 3.0 Hz for δ 7.12, J = 3.4 Hz for δ 7.15, 1 H); ^{13}C NMR (the mixture of diastereomers) δ 13.61, 15.07, 19.13, 25.36, 25.45, 40.66, 45.07, 51.96, 52.55, 70.56, 72.23, 117.98, 120.44, 146.59, 147.98, 172.98, 176.69, 191.39, 191.55. Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.63; H, 7.74; N, 7.05.

3-Acetyl-5-(methoxycarbonyl)-5-methyl-2-pyrroline (2b). In a similar manner, **2b** was prepared in 76% yield from $Zn(OAc)_2{\cdot}2H_2O$ (9.2 mg, 42 μmol), MeOH (9 mg, 0.28 mmol), and methyl 2-isocyano-2-methyl-5-(trimethylsiloxy)-4-hexenoate (37.0 mg, 0.145 mmol): IR (neat) 3240, 1744, 1582 cm^{-1}; ^1H NMR δ 1.49 (s, 3 H), 2.13 (s, 3 H), 2.66 (d, J = 16.6 Hz, 1 H), 3.22 (d, J = 16.6 Hz, 1 H), 3.73 (s, 3 H), 5.15 (br s, 1 H), 7.14 (d, J = 3.1 Hz, 1 H); ^{13}C NMR δ 25.09, 26.18, 38.59, 52.79, 68.00, 112.98, 149.51, 175.58, 192.04. Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.76; H, 7.25; N, 7.64.

3-Acetyl-5-(methoxycarbonyl)-4-methyl-2-pyrroline (2c). In a similar manner, **2c**, a mixture of diastereomers, was prepared in 74% yield from $Zn(OAc)_2{\cdot}2H_2O$ (4.5 mg, 21 μmol), MeOH (7 mg, 0.22 mmol), and methyl 2-isocyano-3-methyl-5-(trimethylsiloxy)-4-hexenoate (30.9 mg, 0.121 mmol): IR (neat) 3300, 1748, 1580 cm^{-1}; ^1H NMR (the mixture of diastereomers) δ 1.05 and 1.28 (d, J = 6.8 Hz, 3 H), 2.14 (s, 3 H), 3.31–3.58 (m, 1 H), 3.73 and 3.77 (s, 3 H), 3.92 and 4.61 (d, J = 3.8 Hz for δ 3.92, J = 10.6 Hz for δ 4.61, 1 H), 4.81 and 4.92 (br s, 1 H), 7.18 and 7.19 (d, J = 2.6 Hz, 1 H); ^{13}C NMR (the mixture of diastereomers) δ 14.31, 20.38, 25.61, 37.54, 39.80, 51.98, 52.45, 65.71, 67.68, 120.04, 120.16, 148.17, 148.24, 171.22, 173.28, 191.37, 191.57; HRMS calcd for

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(11) Vijn, R. J.; Hiemstra, H.; Kok, J. J.; Knotter, M.; Speckamp, W. N. *Tetrahedron* **1987**, *43*, 5019.

(12) The stereochemistry of 2,4-*cis*-**9** was confirmed by that compound's transformation to **14**.

(13) Treatment of 2,4-*cis*-**10** (obtained from the minor isomer **8b**) with DBU in toluene[14] led to epimerization at the C-2-position and gave 2,4-*trans*-**9** quantitatively, which possesses the requisite stereochemistry for α-kainic acid.

(14) Hashimoto, K.; Shirahama, H. *Tetrahedron Lett.* **1991**, *32*, 2625.

$C_9H_{13}NO_3$ m/z 183.0895, found 183.0911.

9-(Methoxycarbonyl)-9-methyl-5-oxo-8-azabicyclo[4.3.0]-non-6-ene (2d). The reaction vessel was charged with $Zn(OAc)_2 \cdot 2H_2O$ (4.0 mg, 18 μmol). The salt was dehydrated by heating it in vacuo until it was molten. The vessel was then cooled to rt under N_2. MeOH (2 mL) and methyl 2-isocyano-2-[3-(trimethylsiloxy)cyclohex-2-enyl]propionate (39.4 mg, 0.140 mmol) were added. The mixture was stirred at 65 °C for 4.5 h under N_2. After evaporation of MeOH, purification of the mixture by column chromatography on Florisil (CH_2Cl_2/MeOH (15:1)) afforded **2d** (28.1 mg, 96%) as a mixture of diastereomers: IR (KBr) 3250, 1738, 1620, 1550 cm^{-1}; ^1H NMR (the mixture of diastereomers) δ 1.27 and 1.60 (s, 3 H), 0.99–2.43 (m, 6 H), 3.00 and 3.27 (ddd, J = 12.6, 4.2, 2.0 Hz for δ 3.00, J = 12.2, 4.4, 2.0 Hz for δ 3.27, 1 H), 3.71 and 3.77 (s, 3 H), 5.17 and 5.24 (br s, 1 H), 7.25–7.38 (m, 1 H); HRMS calcd for $C_{11}H_{15}NO_3$ m/z 209.1052, found 209.1032.

4-Acetyl-2-(methoxycarbonyl)-2-methyl-1-(phenoxyacetyl)pyrrolidine (4). A solution of the N-protected-2-pyrroline **3** (50.7 mg, 0.160 mmol) in EtOAc (3 mL) was hydrogenated in the presence of 5% $Pd/CaCO_3$ (30 mg) at rt for 17 h. The mixture was then filtered through Celite and evaporated. Preparative TLC (AcOEt/*n*-hexane (1:1)) of the residue afforded **4** (49.8 mg, 98%) as a mixture of diastereomers (2,4-*cis*:2,4-*trans* = 85:15). Major diastereomer: IR (neat) 2960, 1740, 1676, 1602 cm^{-1}; ^1H NMR δ 1.58 (s, 3 H), 2.21 (s, 3 H), 2.08–2.33 (m, 2 H), 3.20–3.40 (m, 1 H), 3.64 (s, 3 H), 3.88 (s, 1 H), 3.93 (d, J = 2.9 Hz, 1 H), 4.60 (br s, 2 H), 6.80–7.40 (m, 5 H); ^{13}C NMR δ 21.12, 28.74, 39.70, 47.56, 49.63, 52.35, 66.45, 67.35, 114.53, 121.49, 129.36, 157.70, 166.16, 172.89, 205.10; HRMS calcd for $C_{17}H_{21}NO_5$ m/z 319.1420, found 319.1422.

Methyl 3-[2-(*tert*-Butyldimethylsiloxy)ethyl]-2-isocyano-5-(trimethylsiloxy)-4-hexenoate (6). To a stirred solution of THF (40 mL), 6-(*tert*-butyldimethylsiloxy)-3-hexen-2-one (2.84 g, 12.5 mmol), methyl isocyanoacetate (1.41 g, 14.2 mmol), and BSA (5.29 g, 26.1 mmol) at −78 °C under N_2 was added a solution of TBAF (0.62 mmol) in THF (0.62 mL). After 1 h, n-Bu_3SnCl (0.37 mL, 1.36 mmol) was added. The mixture was warmed to rt and then was subjected to column chromatography on Florisil (Et_2O/*n*-hexane (1:6)) to afford **6** (4.55 g, 92%) as a mixture of diastereomers: IR (neat) 2964, 2152, 1768, 1672, 1256, 1102, 844 cm^{-1}; ^1H NMR (the mixture of diastereomers) δ 0.01–0.04 (m, 6 H), 0.17–0.20 (m, 9 H), 0.86–0.88 (m, 9 H), 1.54–1.80 (m, 5 H), 3.00–3.40 (br, 1 H), 3.40–3.80 (m, 5 H), 4.18–4.55 (m, 2 H); ^{13}C NMR (the mixture of diastereomers) δ −5.45, 0.16, 0.23, 0.75, 18.09, 18.14, 18.31, 18.44, 22.40, 22.52, 25.70, 25.82, 33.13, 33.91, 34.77, 35.02, 35.19, 35.83, 37.11, 52.90, 53.00, 53.08, 59.50, 59.89, 60.28, 60.72, 61.44, 61.51, 103.56, 103.97, 105.03, 105.84, 150.08, 150.59, 152.06, 152.33, 166.63, 166.79, 166.88. Anal. Calcd for $C_{19}H_{37}NO_4Si_2$: C, 57.10; H, 9.33; N, 3.50. Found: C, 56.95; H, 9.63; N, 3.41.

3-Acetyl-4-[2-(*tert*-butyldimethylsiloxy)ethyl]-5-(methoxycarbonyl)-2-pyrroline (7). In a manner similar to that used to prepare **2a**, the title compound, a mixture of diastereomers, was prepared in 88% yield from $Zn(OAc)_2 \cdot 2H_2O$ (100 mg, 0.45 mmol), MeOH (127 mg, 4.0 mmol), and **6** (538 mg, 1.35 mmol): IR (neat) 3288, 2964, 1748, 1582 cm^{-1}; ^1H NMR (the mixture of diastereomers) δ −0.02 and 0.00 (s, 6 H), 0.82 and 0.84 (s, 9 H), 1.55–2.05 (m, 3 H), 2.11 and 2.12 (s, 3 H), 3.35–3.60 (m, 2 H), 3.69 and 3.75 (s, 3 H), 4.42 and 4.58 (d, J = 3.4 Hz for δ = 4.42, J = 11.2 Hz for δ = 4.58, 1 H), 4.89–5.07 (br, 1 H), 7.21–7.22 (s, 1 H); ^{13}C NMR (the mixture of diastereomers) δ −5.50, −5.29, 18.17, 18.26, 25.69, 25.85, 25.91, 33.20, 35.28, 39.39, 42.92, 52.13, 52.40, 53.39, 61.20, 61.64, 65.07, 66.04, 118.69, 119.38, 148.33, 148.77, 171.18, 173.68, 191.35; HRMS calcd for $C_{16}H_{29}NO_4Si$ m/z 327.1866, found 327.1836.

***trans*-3-Acetyl-4-[2-(*tert*-butyldimethylsiloxy)ethyl]-5-(methoxycarbonyl)-1-(phenoxyacetyl)-2-pyrroline (8a).** To a mixture of Et_3N (140 μL, 1.01 mmol), phenoxyacetic anhydride (213 mg, 0.742 mmol), and CH_2Cl_2 (1 mL) was added a solution of **7** (162 mg, 0.495 mmol) in CH_2Cl_2 (1 mL) at rt under N_2. The mixture was stirred for 4 h. Extractive workup (H_2O/CH_2Cl_2) and column chromatography on silica gel (EtOAc/*n*-hexane (1:2)) of the residue afforded a mixture of **8a** and **8b** (192 mg, 84%). Compound **8a** was isolated by HPLC (EtOAc/*n*-hexane (1:4)) as a mixture of two isomeric amide rotamers: IR (neat) 2964, 1754, 1660, 1606, 1218 cm^{-1}; ^1H NMR (the mixture of amide rotamers) δ 0.01 and 0.03 (s, 6 H), 0.86 (s, 9 H), 1.40–2.10 (m, 2 H), 2.24 and 2.27 (s, 3 H), 3.15–3.50 (m, 1 H), 3.60–3.80 (m, 5 H), 4.65–5.22 (m, 3 H), 6.80–7.40 (m, 5 H), 7.79 and 7.88 (s, 1 H); ^{13}C NMR (the major amide rotamer) δ −5.55, 18.14, 25.81, 26.46, 35.56, 42.00, 52.53, 60.53, 64.90, 68.12, 114.57, 122.41, 128.24, 129.83, 138.23, 157.07, 166.02, 169.97, 193.04; ^{13}C NMR (the minor amide rotamer) δ −5.55, 18.14, 25.81, 26.55, 35.22, 45.94, 52.76, 61.27, 64.90, 67.59, 114.38, 122.15, 126.50, 129.67, 139.42, 157.07, 166.89, 170.88, 193.65. Anal. Calcd for $C_{24}H_{35}NO_6Si$: C, 62.44; H, 7.64; N, 3.03. Found: C, 62.26; H, 7.73; N, 3.09.

(2*S,3*S**,4*S**)-4-Acetyl-3-[2-(*tert*-butyldimethylsiloxy)-ethyl]-2-(methoxycarbonyl)-1-(phenoxyacetyl)pyrrolidine (2,4-*cis*-9).** In a manner similar to that used to prepare **4**, the title compound was prepared in 90% yield from **8a** (750 mg, 1.63 mmol) and 5% $Pd/CaCO_3$ (250 mg): IR (neat) 2964, 1750, 1720, 1678 cm^{-1}; ^1H NMR (the mixture of amide rotamers) δ 0.03 (s, 6 H), 0.87 (s, 9 H), 1.50–1.90 (m, 2 H), 2.18 and 2.20 (s, 3 H), 2.70–3.20 (m, 1 H), 3.50–4.40 (m, 9 H), 4.50–4.70 (m, 2 H), 6.80–7.40 (m, 5 H); ^{13}C NMR (the major amide rotamer) δ −4.96, 18.71, 26.33, 29.53, 36.59, 41.31, 48.03, 52.83, 56.97, 60.92, 64.68, 68.23, 115.14, 122.28, 130.09, 158.23, 167.48, 171.81, 205.76; ^{13}C NMR (the minor amide rotamer) δ −4.96, 18.71, 26.33, 29.14, 36.89, 43.53, 48.30, 52.95, 53.79, 61.31, 64.06, 68.66, 114.81, 122.28, 130.09, 157.89, 168.16, 171.92, 206.51; HRMS calcd for $C_{24}H_{37}NO_6Si$ m/z 463.2390, found 463.2402.

(2*S,3*S**,4*R**)-3-[2-(*tert*-Butyldimethylsiloxy)ethyl]-4-isopropenyl-2-(methoxycarbonyl)-1-(phenoxyacetyl)-pyrrolidine (11).** $MePh_3P^+Br^-$ (234 mg, 0.655 mmol) was treated with n-BuLi (1.72 M n-hexane solution, 0.611 mmol) in Et_2O (21 mL) for 15 min at 0 °C under N_2. A solution of 2,4-*cis*-**9** (170 mg, 0.367 mmol) in Et_2O (4 mL) was then added. The mixture was stirred for 14 h. Filtration, concentration of the filtrate, and column chromatography of the residue on silica gel (EtOAc/*n*-hexane (1:3)) gave **11** (105 mg, 62%) as a mixture of two isomeric amide rotamers: IR (neat) 2940, 1750, 1678, 1440 cm^{-1}; ^1H NMR (the mixture of amide rotamers) δ 0.02 (s, 6 H), 0.86 (s, 9 H), 1.60–1.90 (m, 5 H), 2.25–2.55 (m, 1 H), 2.64 (dt, J = 7.3, 10.7 Hz, 1 H), 3.51 (t, J = 10.7 Hz, 1 H), 3.60–3.70 (m, 2 H), 3.71 (s, 3 H), 3.85 (dd, J = 7.6, 10.7 Hz, 1 H), 4.16 (d, J = 8.8 Hz, 1 H), 4.56 and 4.64 (s, 2 H), 4.87 and 4.93 (br s, 2 H), 6.80–7.40 (m, 5 H); ^{13}C NMR (the major amide rotamer) δ −5.46, 18.13, 18.96, 25.80, 34.98, 40.98, 50.54, 52.18, 52.82, 60.04, 65.08, 67.50, 114.28, 114.70, 121.60, 129.48, 141.11, 157.90, 166.65, 172.28; ^{13}C NMR (the minor amide rotamer) δ −5.46, 18.13, 19.37, 25.67, 35.55, 44.25, 49.68, 51.08, 51.73, 60.15, 64.31, 68.06, 113.75, 114.70, 121.72, 129.57, 141.94, 157.32, 167.37, 172.28; HRMS calcd for $C_{25}H_{39}NO_5Si$ m/z 461.2598, found 461.2625.

(2*S,3*S**,4*R**)-3-(2-Hydroxyethyl)-4-isopropenyl-2-(methoxycarbonyl)-1-(phenoxyacetyl)pyrrolidine (12).** The pyrroldine **11** (105 mg, 0.227 mmol) was treated with 3:1:1 AcOH/THF/H_2O (5 mL) at rt for 10 h. Aqueous $NaHCO_3$ was then added, and the mixture was subjected to extractive workup (CH_2Cl_2/aq $NaHCO_3$). Column chromatography on silica gel (AcOEt/*n*-hexane (3:1)) of the residue gave **12** (67 mg, 84%) as a mixture of amide rotamers: IR (neat) 3464, 1740, 1666, 1442, 1240 cm^{-1}; ^1H NMR (the mixture of amide rotamers) δ 1.60–2.00 (m, 5 H), 2.00 (br, 1 H), 2.10–2.50 (m, 1 H), 2.63 (dt, J = 7.3, 11.1 Hz, 1 H), 3.47 (t, J = 10.6 Hz, 1 H), 3.60–3.80 (m, 5 H), 3.89 (dd, J = 7.3, 10.3 Hz, 1 H), 4.27 (d, J = 8.4 Hz, 1 H), 4.58 and 4.64 (s, 2 H), 4.85–5.00 (m, 2 H), 6.80–7.40 (m, 5 H); ^{13}C NMR (the major amide rotamer) δ 19.18, 34.98, 42.01, 50.45, 52.99, 60.17, 64.62, 67.50, 114.25, 114.66, 121.64, 129.48, 140.93, 157.81, 166.79, 172.70; ^{13}C NMR (the minor amide rotamer) δ 19.53, 35.71, 45.29, 50.00, 50.85, 52.43, 60.29, 64.04, 68.18, 113.95, 114.83, 121.81, 129.61, 141.70, 157.26, 167.37, 172.83; HRMS calcd for $C_{19}H_{25}NO_5$ m/z 347.1733, found 347.1740.

(2*S,3*S**,4*R**)-3-(Carboxymethyl)-4-isopropenyl-2-(methoxycarbonyl)-1-(phenoxyacetyl)pyrrolidine (13).** To a solution of **12** (80 mg, 0.23 mmol) in acetone (5 mL) under N_2 was added, drop-by-drop, Jones reagent (8 M solution in acetone) until a red-brown color persisted for 15 min. A few drops of *i*-PrOH were then added to discharge the color. The mixture was diluted with Et_2O and was filtered. After concentration of the filtrate, the residue was diluted with Et_2O and was then extracted with 1 M aq Na_2CO_3. The extract was acidified with concd aq

HCl and was extracted with CH_2Cl_2. The extract was dried. Evaporation of the solvent gave **13** (67 mg, 81%) as a white solid, a mixture of two isomeric amide rotamers: IR (KBr) 3500–2500 (br), 1740, 1602, 1482, 1220 cm^{-1}; ^1H NMR (the mixture of amide rotamers) δ 1.71 (br s, 3 H), 2.40–2.80 (m, 4 H), 3.54 (t, J = 11.0 Hz), 3.57 and 3.67 (s, 3 H), 3.89 and 4.03 (dd, J = 6.9, 10.3 Hz, 1 H), 4.20 and 4.45 (d, J = 8.5 Hz, 1 H), 4.52–4.72 (m, 2 H), 4.84–5.02 (m, 2 H), 6.80–7.40 (m, 5 H), 7.80–8.40 (br, 1 H); ^{13}C NMR (the major amide rotamer) δ 18.80, 34.69, 40.81, 50.17, 51.71, 52.28, 64.35, 67.54, 114.68, 115.70, 121.75, 129.55, 139.91, 157.77, 167.08, 171.36, 175.98; ^{13}C NMR (the minor amide rotamer) δ 18.97, 35.08, 43.69, 48.77, 50.97, 53.70, 63.98, 68.16, 114.14, 115.06, 121.87, 129.84, 140.50, 156.97, 167.87, 171.36, 176.10; HRMS calcd for $C_{19}H_{22}NO_6$ (M − H) m/z 360.1447, found 360.1467.

(±)-α-Allokainic Acid Dimethyl Ester (14). To a solution of **13** (13.6 mg, 37.7 μmol) in MeOH (1 mL) was added concd aq HCl (0.4 mL). The mixture was refluxed for 8 h. The MeOH was then evaporated and the residue was subjected to extrative workup (aq $NaHCO_3/CH_2Cl_2$). Column chromatography of the residue on silica gel (EtOAc) afforded **14** (6.4 mg, 70%), the TLC behavior and ^1H NMR spectrum of which were identical to those of a sample prepared from natural α-allokainic acid.

Acknowledgment. We thank Dr. Y. Ohfune (Suntory Institute for Bioorganic Research) for kindly providing a sample of natural α-allokainic acid.

Registry No. (*R**,*R**)-**1a**, 137007-31-9; (*R**,*S**)-**1a**, 137007-32-0; **1b**, 137007-52-4; (*R**,*R**)-**1c**, 137007-53-5; (*R**,*S**)-**1c**, 137007-54-6; (*R**,*R**)-**1d**, 137007-55-7; (*R**,*S**)-**1d**, 137007-56-8; *cis*-**2a**, 137007-33-1; *trans*-**2a**, 137007-34-2; **2b**, 137007-35-3; *cis*-**2c**, 137007-36-4; *trans*-**2c**, 137007-37-5; *cis*-**2d**, 137007-38-6; *trans*-**2d**, 137007-39-7; **3**, 137007-40-0; *cis*-**4**, 137007-41-1; *trans*-**4**, 137007-42-2; **5**, 103871-65-4; (*R**,*R**)-**6**, 137007-43-3; (*R**,*S**)-**6**, 137007-44-4; *cis*-**7**, 137007-45-5; *trans*-**7**, 137007-46-6; **8a**, 137007-48-8; **8b**, 137007-49-9; 2,4-*trans*-**9**, 137007-47-7; 2,4-*cis*-**9**, 137119-49-4; 2,4-*trans*-**10**, 137119-52-9; 2,4-*cis*-**10**, 137119-51-8; **11**, 137007-50-2; **12**, 137056-95-2; **13**, 137007-51-3; **14**, 137119-50-7; $O(PhOCH_2CO)_2$, 14316-61-1; $MePh_3P^+Br^-$, 1779-49-3; methyl isocyanoacetate, 39687-95-1.

Supplementary Material Available: ^{13}C NMR spectra for **2c**, **4**, **7**, 2,4-*cis*-**9**, **12**, and **13** and ^1H NMR spectra for **2d** and **11** (8 pages). Ordering information is given on any current masthead page.

Additions and Corrections

Vol. 55, 1990

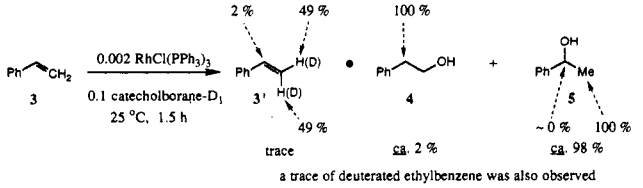
David W. Emerson,* Richard L. Titus,* and Rowena M. González. Evidence for Ketene Intermediates in the Reactions of 2-Oxobutanedioic Acid Diesters with Alcohols and Water.

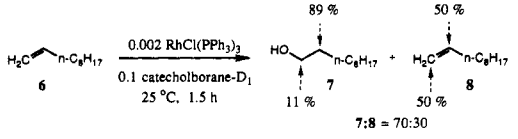
Page 3573. Two important references were omitted and should be included in ref 8: Berkowitz, W. F.; Ozorio, A. A. *J. Org. Chem.* **1971**, *36*, 3787. Leyendecker, F.; Bloch, R.; Conia, J. M. *Tetrahedron Lett.* **1972**, 3703. We thank Prof. Berkowitz for calling his paper to our attention.

Vol. 56, 1991

Kevin Burgess,* Wilfred A. van der Donk, and Alan M. Kook. On Deuterium-Labeling Studies for Probing Rhodium-Catalyzed Hydroboration Reactions.

Page 2949. Deuterioborations of styrene and 1-decene as reported in this paper were performed using commercial (i.e. "aged") Wilkinson's catalyst. We mentioned that differences between these findings and those reported previously could be due to catalyst purity, and this is indeed the case. Repetition of these experiments using catalyst prepared according to the procedure in *Inorganic Syntheses* (X, p 67) gave the following results.





We thank Dr. D. A. Evans (Harvard) for insights which led us to repeat these experiments.

Gregory J. White and Michael E. Garst*. Cyclic Sulfamate from *N*-Substituted-2-amino-3-phenyl-2-propanol and Its Nucleophilic Reactions.

Page 3177. Dr. Lyle and co-workers reported that β-hydroxy triflamides undergo fluoride-induced formation and ring opening of cyclic sulfamates in Lyle, T. A.; Magill, C. A.; Pitzenberger, S. M. *J. Am. Chem. Soc.* **1987**, *109*, 7890–7891. The β-fluoro amino products are similar to those in this paper and occur with inversion at the alcohol center. We are grateful to Dr. Lyle for pointing out his previous work.

David W. Emerson,* Richard L. Titus,* and Rowena M. González. Evidence for Ketene Intermediates in the Decarbonylation of 2,4-Dioxo Acids and Esters and 2-Oxobutanedioic Acid Esters.

Page 5303. Three important references were omitted and should be included in ref 6: Berkowitz, W. F.; Ozorio, A. A. *J. Org. Chem.* **1971**, *36*, 376. Leyendecker, F.; Bloch, R.; Conia, J. M. *Tetrahedron Lett.* **1972**, 3703. Newman, M. S.; Zeuch, E. A. *J. Org. Chem.* **1962**, *27*, 1436, in which IR frequencies of 4.7 μm (2128 cm^{-1}) were reported for two α-carbethoxyketenes. We thank Prof. Berkowitz for calling his paper to our attention.

H. S. Bevinakatti* and A. A. Banerji. Practical Chemoenzymatic Synthesis of Both Enantiomers of Propranolol.

Page 5373, Table II. The stereochemical configurations in column 10 are the opposite of those printed.

William R. Sponholtz, III, Richard M. Pagni,* George W. Kabalka,* James F. Green, and Lay Choo Tan. Reaction of Vinylboronic Acids with Iodine on γ-Alumina.

Pages 5700–5703. In eqs 8–12, $-B^-(OH_3)$ and $-B^-(OH_2)$-O- should be replaced with $-B^-(OH)_3$ and $-B^-(OH)_2$-O-, respectively.