$HCNO_2$), 5.52 (m, 1 H, W = 16.5 Hz, $HCONO_2$). Anal. Calcd for $C_5H_8N_2O_5$: C, 34.10; H, 4.58; N, 15.90. Found: C, 33.94; H, 4.67; N, 16.24.

(ii) 1.9 g (22%) of a mixture of **10** and **13** (ratio 3:1 based on ^{13}C NMR). Rechromatography of this mixture gave 0.025 g of **13** and 1.42 g of **10**. Compound **10**: R_f 0.37; bp 98–101 °C (3–4 mmHg); IR (CCl_4) 1739 (C=O), 1545 (NO_2), 1429, 1365 (NO_2); ^1H NMR (100 MHz, CCl_4) 1.97 (s, 3 H, CH_3COO), 2.0–2.4 (m, 5 H, CH_2 protons), 2.66 (dt, 1 H, J_1 = 5.5 Hz, J_2 = 15.5 Hz, $AcOCCHCNO_2$); ^{13}C NMR 75.10 (COAc), 85.20 (CNO_2). Anal. Calcd for $C_7H_{11}NO_4$: C, 48.55; H, 6.40; N, 8.09. Found: C, 48.71; H, 6.52; N, 8.31. Compound **13** was identified by its spectra and transformation to the nitro cyclopentanol **15**: ^1H NMR (100 MHz, CCl_4) 1.9–2.5 (m, 6 H, CH_2 protons), 2.02 (s, 3 H, CH_3COO), 4.92 (m, 1 H, $HCNO_2$), 5.65 (m, 1 H, HCOAc); ^{13}C NMR (CCl_4) 90.04 (CNO_2), 77.93 (COAc).

(iii) 2.34 g (26%) of **11**, R_f 0.30. Distillation afforded 2.07 g of pure material: bp 85 °C (0.1 mmHg); n^{20}_D 1.4636; IR (CCl_4) 1749, 1560, 1432, 1373; ^1H NMR (360 MHz, CCl_4) 2.00 (m, 5 H, CH_3COO and CH_2), 2.25 (sextet, 1 H), 2.47 (dq, 1 H, J_1 = 6.1 Hz, J_2 = 8.4 Hz, J_3 = 15.5 Hz), 2.55 (m, 3 H, CH_2 protons), 4.86 (m, 1 H, W = 25.4 Hz, $HCNO_2$), 5.12 (m, 1 H, W = 18.8 Hz, HCOAc); ^{13}C NMR 74.61 (COAc), 84.77 (CNO_2). Anal. Calcd for $C_7H_{11}NO_4$: C, 48.55; H, 6.40; N, 8.09. Found: C, 48.63; H, 6.47; N, 8.27.

Hydrolysis of the Nitro Acetates to Nitro Alcohols. H_2SO_4 (0.5 mL) was added to methanol (15 mL) containing 0.7 g of a mixture of **10** and **13**, and the reaction mixture was stirred for 20 h. After the usual workup, column chromatography of the residue (SiO_2, 5/40 μm, hexane:ethyl acetate 1:1) gave 0.39 g of **14** and **15** (ratio 4:1): ^{13}C NMR 72.19 (COH of **14**), 85.36 (CNO_2 of **14**), 73.54 (COH of **15**), 96.40 (CNO_2 of **15**). Further chromatography of the mixture gave pure **14**: IR (C_6H_6) 3580, 3450 (br), 2940, 1530, 1365; ^1H NMR (100 MHz, $CHCl_3$) 1.7–2.5 (m, 6 H, CH_2 protons), 2.73 (s, 1 H, OH), 4.57 (m, 1 H, W = 16.0 Hz, H-COH), 5.12 (m, 1 H, W = 21.2 Hz, $HCNO_2$). Analogous treatment of **11** gave 0.31 g of a nitro alcohol: IR (C_6H_6) 3575, 3400 (br), 2940, 1530, 1370; ^1H NMR (100 MHz, C_6H_6) 1.35–2.4 (m, 6 H, CH_2 protons), 3.16 (s, 1 H, OH), 4.00 (m, 1 H, W = 18.0 Hz, HCOH), 4.32 (septet, 1 H, W = 26.0 Hz, $HCNO_2$).

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Registry No. 1, 88157-56-6; **2a**, 88157-57-7; **2b**, 88157-58-8; **4**, 6925-08-2; **6**, 4883-68-5; **7**, 65283-37-6; **8**, 7053-55-6; **9**, 6925-11-7; **10**, 88157-60-2; **11**, 88157-61-3; **12**, 88157-59-9; **13**, 6925-12-8; **14**, 88157-73-7; **15**, 88157-72-6; **16**, 88157-65-7; **17**, 88157-64-6; **18**, 88157-63-5; **19**, 88157-62-4; **20**, 88157-66-8; **21**, 88157-67-9; **22**, 88157-68-0; **23**, 88157-69-1; **24**, 4734-90-1; **25**, 88157-70-4; **26**, 88157-71-5; **27**, 65283-41-2; **28**, 65283-40-1; $AcONO_2$, 591-09-3; NO_2^+, 14522-82-8; methylenecyclobutane, 1120-56-5; cyclopentene, 142-29-0; cyclohexene, 110-83-8; cyclooctene, 931-88-4; norbornene, 498-66-8.

Supplementary Material Available: Details of the structural assignments to compounds **4** and **6–24** and full experimental details of the reactions of cyclohexene, cyclooctene, methylenecyclobutane, and norbornene (11 pages). Ordering information is given on any current masthead page.

1,3-Asymmetric Induction: Highly Stereoselective Synthesis of 2,4-Trans-Disubstituted γ-Butyrolactones and γ-Butyrothiolactones

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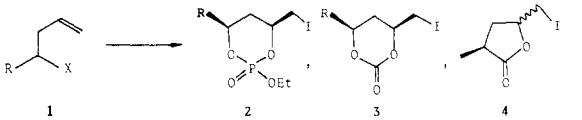
Abstract: A novel 1,3-trans asymmetric induction has been observed for the halolactonization of α- and α,β-substituted γ,δ-unsaturated amides. The 1,3-trans selectivity is lost in the threo diastereomers of amides with a β-OH or β-OAc substituent, due to the 1,2-cis directing ability of these substituents.

Macrolides and ionophores have prompted interest in the development of methods for the control of stereochemistry in acyclic systems.[2] Compared with the extensive work for the 1,2-asymmetric induction, the principal method being, for example, aldol condensation, variations of Claisen rearrangement, and epoxidation of unsaturated alcohols, the work for the remote asymmetric induction is relatively rare. In both 1,2- and remote asymmetric inductions, most of the methodologies seem to rely on a six-membered chairlike transition state, through which a high degree of asymmetry has been induced by virtue of a propensity of the largest numbers of substituents to take the equatorial positions. For example, a high 1,3-asymmetric induction has been observed for the iodocyclization of homoallylic phosphates **1a**[3] and carbonates **1b**,[4] providing 1,3-cis disubstituted cyclic phosphate **2** and carbonates **3**, respectively. For the reactions involving a five-membered cyclic transition state, the number of examples being limited, the 1,3-cis selectivity seems to be general.[5]



1a; X = $OPO(OEt)_2$

1b; X = OCO_2R, R = Li or $-Bu^t$

1c; X = CO_2H

In this paper we describe the first and very novel example of a 1,3-trans asymmetric induction in the halolactonization of

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(1) Present address: Takarazuka Research Center, Sumitomo Chemical Co., Ltd., 4-2-1, Takatsukasa, Takarazuka, Hyogo 665, Japan.
(2) For an excellent review on this subject, see: Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2.
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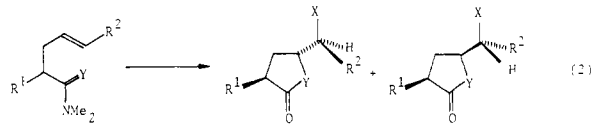
Table I. 1,3-Trans-Selective Lactonization of Amides and Thioamides

entry	amide or thioamide 5[a] compd	R^1	R^2	Y	X[b]	condition[c] (day)	% isolated[d] yield (6 + 7)	product ratio[a,e] 6:7
1	a	Me	H	O	I	A (4)	85	90:10
2	a	Me	H	O	Br	A (3)	75	>99:1
3	a	Me	H	O	Cl	A (3)	60	60:40[f]
4	b	$PhCH_2$	H	O	I	A (4)	84	>99:1
5	c	Me	Me	O	Br	A (1)	74	94:6
6	d	$PhCH_2$	Me	O	I	A (4)	82	>99:1
7	e	Me	H	S	I	B (1)	42	91:9
8	e	Me	H	S	Br	B (1)	24	>99:1
9	e	Me	H	S	H	C (6)	45	92:8
10	f	$PhCH_2$	H	S	I	B (1)	67	>99:1
11	f	$PhCH_2$	H	S	H	C (7)	63	97:3

[a] For the structures of 5–7, see eq 2. [b] As a source of electrophile X, I_2 (X = I, 1.1 equiv), *N*-bromosuccinimide (X = Br, 1.1 equiv), *N*-chlorosuccinimide (X = Cl, 1.1 equiv), or 10-camphorsulfonic acid (X = H, 2.2 equiv) was used. [c] Reaction conditions: A, dimethoxyethane–H_2O (1:1) at room temperature; B, 10 equiv of H_2O in DME at room temperature; C, 15–20 equiv of H_2O in THF at 65 °C. [d] Combined isolated yield of 6 and 7. [e] Determined by ^{13}C NMR of the products. In order to minimize possible effects of relaxation differences (expected to be minor for diastereomeric compounds), the ratios of peak areas were averaged for several well-resolved carbon in each system. [f] Tentative assignment of diastereomers.

α-substituted γ,δ-unsaturated amides **5** (Y = O) and thioamides **5** (Y = S), yielding 2,4-trans substituted γ-(thio)butyrolactones in high selectivity. It is also discussed about the halolactonization of pairs of diastereomers of α,β-disubstituted (thio)amides **8**, which provide 2,3,4-trisubstituted γ-butyro(thio)lactones in high stereoselectivity.

Halolactonization of α-Substituted γ,δ-Unsaturated Amides 5 (Y = O) and Thioamides 5 (Y = S). *N,N*-Dimethyl-2-methyl-4-pentenamide **5a** was treated with 1.1 equiv of I_2 in dimethoxyethane (DME)–H_2O (1:1 vol) at room temperature for 4 days (condition A) to furnish a mixture of *trans*- and *cis*-2-methyl-4-(iodomethyl)-γ-butyrolactones (**6a** and **7a**) in a ratio of 9:1 in 85% isolated yield (eq 2; entry 1, Table I). The stereoselectivity



(2)

5 6 7

was quite dependent on the kind of electrophilic halogen species. With *N*-chlorosuccinimide (NCS), the ratio of **6a** to **7a** was reduced to 3:2 (entry 3), while with *N*-bromosuccinimide (NBS), **6a** was obtained in >99% purity (entry 2). This dependence of selectivity on electrophiles was general for other (thio)amides **5** with an α-methyl substituent, and NBS showed the highest selectivities (cf. entries 7 and 8; see also entry 5). In those cases where $R^1 = PhCH_2$, on the other hand, I_2 gave the satisfactory results, providing trans isomer **6** almost exclusively (entries 4, 6, and 10). The results in entries 5 and 6 demonstrate that the present lactonization is amenable for the asymmetric induction at the two carbon centers at a time. No six-membered lactones were detectable.

The present high 1,3-trans selection makes sharp contrast to a reversed and a moderated 1,3-cis selectivity in the iodolactonization of γ,δ-unsaturated carboxylic acid (3 equiv of I_2 at 0 °C in acetonitrile):[6] 2-methyl- and 2-benzyl-4-pentenoic acids furnished mixtures of **6a** and **7a** (32:68 in 92% yield) and **6c** and **7c** (34:66 in 98% yield), respectively.

The structures of **6a** and **7a** were confirmed by the reduction with *n*-Bu_3SnH to *trans*- and *cis*-2,4-dimethyl-γ-butyrolactones, respectively. The authentic cis isomer was prepared by the similar reduction of *trans,trans*-2-methyl-3-iodo-4-methyl-γ-butyrolactone.[7] Further confirmation was obtained by a base-catalyzed equilibration of both isomers, which showed a slight preference of the cis isomer over the trans isomer (cis:trans = 55:45).[8]

Under condition A, γ,δ-unsaturated thioamide **5f** did not give any characterizable cyclic product, resulting in showing a starting spot on TLC. For the successful halothiolactonization, the amount of water and the kind of solvents were found to be crutial. The optimized condition was I_2 (1.1 equiv) and H_2O (10 equiv) in DME at room temperature (condition B). Compared with condition A, condition B was specified by the use of the reduced amount of water. Under condition B, **6f** was obtained in 67% yield as an essentially single isomer (entry 10). In the presence of 5 and 20 equiv of water in DME, **6f** was isolated in 17 and 45% yields, respectively. All the reactions attempted in acetonitrile, acetic acid, and benzene in the presence of 10 equiv of water were not successful, just providing very polar materials that remain on a starting spot on TLC (benzene–EtOAc, 8:1). Of particular interest is that the thioamides (**5e** and **5f**) underwent protiothiolactonization by treatment with 2.2 equiv of 10-camphorsulfonic acid (CSA) and 15–20 equiv of water in refluxing THF (condition C). Also in these cases 2,4-trans-disubstituted thiolactones (**6e** and **6f**) were obtained with high selectivity (entries 9 and 11). No protiolactonization of amides took place under condition C and the starting materials were recovered completely.

Iodolactonization of α,β-Disubstituted γ,δ-Unsaturated Amides 8. Before proceeding to the halolactonization of α,β-disubstituted γ,δ-unsaturated amides **8**, we examined the effect of β-substituents on the stereochemical course for lactonization. Bartlett et al.[6,9] and Barnes et al.[10] have reported that 3-alkyl-substituted 4-pentenoic acid undergoes the iodolactonization (under the thermodynamic conditions; I_2 in acetonitrile) to furnish *trans*-3-alkyl-4-(iodomethyl)-γ-butyrolactone in 90–95% selectivity. *N,N*-Dimethyl-3-methyl-4-pentenamide, on the other hand, was iodolactonized nonstereoselectively to give a 5:4 mixture of *trans*- and *cis*-3-methyl-4-(iodomethyl)-γ-butyrolactones (condition A, 1.1 equiv of I_2, 4 days, 92% yield). Interestingly, *N,N*-dimethyl-3-hydroxy-4-pentenamide and its 3-acetoxy derivative were cyclized to yield 3,4-cis isomers predominantly in the cis:trans ratios of 92:8 (98%) and 86:14 (82%), respectively. This is in accord with the results reported by Chamberlin et al.,[11] who obtained the cis isomer in 95% selectivity by the iodolactonization of 3-hydroxy-4-pentenoic acid under kinetic conditions (Et_2O–THF, I_2, $NaHCO_3$).

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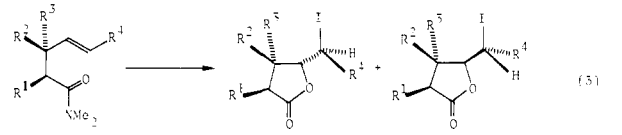
Table II. Stereoselective Iodolactonization of 2,3-Disubstituted *N,N*-Dimethyl-4-penteneamides 8

entry	amide 8[a] compd	R^1	R^2	R^3	R^4	conditions,[b] I_2/h	% isolated yield (9 + 10)	product ratio[a,c] 9:10
1	a	Me	Me	H	H	1.1 equiv/48	63	97:3
2	b	Me	H	Me	H	1.1 equiv/48	63	97:3
3	c	Me	OH	H	H	2 equiv/17	88	20:80
4	d	Me	H	OH	H	2 equiv/17	84	>99:1
5	e	Me	OAc	H	H	2 equiv/17	68	45:55
6	f	Me	H	OAc	H	2 equiv/17	95	>99:1
7	g	Me	OAc	H	Me	2 equiv/17	73[d]	
8	h	Me	H	OAc	Me	2 equiv/17	75	>99:1

[a] For the structures of 8–10, see eq 3. [b] At room temperature in DME–H_2O (1:1). [c] Determined by ^{13}C NMR. [d] *cis,cis,trans*-2,5-Dimethyl-3-acetoxy-4-iodo-δ-valerolactone was obtained.

On the basis of these examples, four pairs of diastereomers (**8a,b**, **8c,d**, **8e,f**, and **8g,h**) were examined (eq 3). The erythro

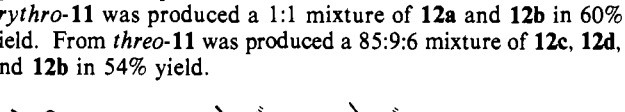


(3)

8 9 10

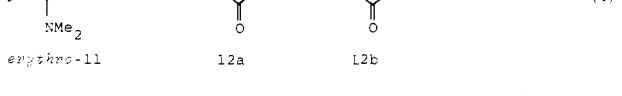
diastereomers **8d**, **8f**, and **8h** were expected to undergo the selective iodolactonization to furnish *trans,cis*-2,3,4-trisubstituted lactones **9d**, **9f**, and **9h**, respectively, because the 1,3-trans directing ability of the α-methyl substituent and the 1,2-cis directing ability of the β-hydroxy and the β-acetoxy groups might cooperate to orient the iodomethyl group in the same direction. Indeed, this proved to be the case and **9d**,[12] **9f**, and **9h** were obtained in 99% selectivity (entries 4, 6, and 8, Table II).

Of particular interest is a pair of results in entries 1 and 2. From *erythro*- (**8a**) and *threo*-*N,N*-dimethyl-2,3-dimethyl-4-pentenamides (**8b**) were obtained *cis,trans*- (**9a**) and *trans,cis*-2,3-dimethyl-4-(iodomethyl)-γ-butyrolacones (**9b**) in the same selectivity of 97%. These results clearly indicate that the α-methyl substituent plays the decisive role in determining the C-4 chirality and the β-methyl group is noninfluential. The previously described nonstereoselective iodolactonization of *N,N*-dimethyl-3-methyl-4-pentenamide is in good accord with these results. The similar stereoselection was observed for the protiothiolactonization of *erythro*-**11** (100% 1,3-trans selectivity, providing **12a** as a single primary product) and *threo*-**11** (94% 1,3-trans selectivity, providing **12c** and **12b** in a 94:6 ratio as primary products; see Experimental Section for detail). The synthetic utility of this protiothiolactonization, however, seems to be diminished owing to a ready epimerization of products under the reaction conditions: From *erythro*-**11** was produced a 1:1 mixture of **12a** and **12b** in 60% yield. From *threo*-**11** was produced a 85:9:6 mixture of **12c**, **12d**, and **12b** in 54% yield.



(4)

erythro-11 12a 12b

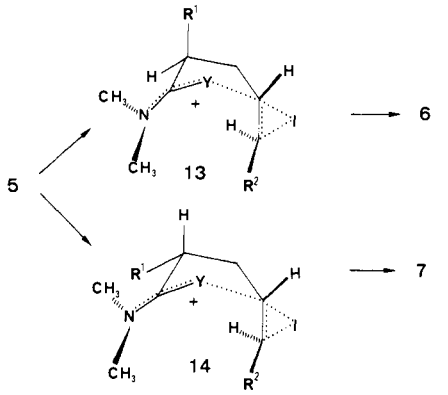


(5)

threo-11 12c 12d 12b

The results in entries 3 and 5 indicate that the 1,2-cis directing ability of the β-hydroxy or β-acetoxy group is greater than or almost equal to the 1,3-trans directing ability of the α-methyl group, respectively. Unexpectedly **8g** was cyclized to give *cis,cis,trans*-2,5-dimethyl-3-acetoxy-4-iodo-δ-valerolactone (ν_{CO} =

Scheme I



1750 cm^{-1}, KBr disk) in 73% yield. The structure of the product was determined on the basis of the coupling constants of ring protons [$J_{C(2)H-C(3)H}$ = 3.4, $J_{C(3)H-C(4)H}$ = 1.7, and $J_{C(4)H-C(5)H}$ = 10.3 Hz].

The structure of **10c** was confirmed by single-crystal X-ray analysis,[13] which indicates that the lactone ring has an envelope conformation with the C(3) atom deviated by 0.538 (3) Å from the least-squares plane formed by the remaining four ring atoms (±0.006 Å). The torsion H–C–C–H angles in a solid state of **10c** are well correlated to the coupling constants in the ^1H NMR spectrum:[14] ∠H(2)–C(2)–C(3)–H(3) = −36.2°, $J_{H(2)-H(3)}$ = 4.88 Hz; ∠H(3)–C(3)–C(4)–H(4) = 44.9°, $J_{H(3)-H(4)}$ = 3.06 Hz; ∠H-(4)–C(4)–C(6)–H(6-1) = −178.3°, $J_{H(4)-H(6\text{-}1)}$ = 9.4 Hz; ∠H-(4)–C(4)–C(6)–H(6-2) = 57.7°, $J_{H(4)-H(6\text{-}2)}$ = 5.92. Interestingly, the molecules are linked through a weak intermolecular hydrogen bond between the hydroxy group and the carbonyl oxygen atom, forming an infinite chain along the *b* axis.[13] The hydrogen-bond parameters are as follows: *d*(O–H) = 0.78 (5) Å; *d*(H···O=) = 2.01 (5) Å; ∠(O–H···O=) = 165 (5)°.

The substitution pattern of **9** and **10** was determined by ^1H NMR (J_{trans} = 0–4.4 Hz, J_{cis} = 3.7–8.5 Hz in the vicinal protons)[14] and ^{13}C NMR (higher field resonances of the vicinal cis substituents compared with the corresponding trans ones).[15] All the γ-butyrolactones examined, except for the ones with the β-hydroxy substituent (**10c** and **9d**), showed the lactone carbonyl absorption at 1770–1780 cm^{-1} in the IR spectra. The lactones **9d** and **10c** showed the anomalously low wavenumbers of carbonyl absorption [1760 (neat) and 1740 (KBr) cm^{-1}, respectively]. The previously discussed X-ray data and the following two experiments indicate that this anomaly stems from the intermolecular hydrogen bonding: First, by acetylation of **9d** [Ac_2O, pyridine, in the presence of a catalytic amount of (dimethylamino)pyridine in

(12) Chamberlin et al. have obtained this compound by the methylation of the dianion of *cis*-3-hydroxy-4-(iodomethyl)-γ-butyrolactone in 93% selectivity: Chamberlin, A. R.; Dezube, M. *Tetrahedron Lett.* **1982**, *23*, 3055.

(13) The ORTEP drawing and packing diagram of **10c** are reported in Figures 1 and 2, and the crystal data, final positional and thermal parameters, bond lengths and angles, torsion angles, and structure factor amplitude are reported in Tables III–IX [supplementary material (see paragraph at end of paper regarding supplementary material)].

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THF] was obtained **9f** in quantitative yield, which shows the normal absorption of γ-butyrolactone (1770 cm^{-1}) in addition to acetoxy absorption (1740 cm^{-1}) in the IR spectrum. Second, both the absorptions of ν_{OH} (3420 cm^{-1}, br) and ν_{CO} (1760 cm^{-1}, br, neat film) of **9d** shifted to the higher wavenumbers in dilutions: 3600 (sharp) and 3450 (br) and 1780 (br) cm^{-1} (8.6×10^{-3} M in CCl_4); 3600 (sharp) and 1785 (sharp) cm^{-1} (8.6×10^{-4} M in CCl_4).

The present unique stereoselectivity may be rationalized as follows. Among possible cyclic transition states, the otherwise most favorable 1,3-di-quasi-equatorial transition state **14** may be discarded owing to an A(1,3) strain[16] between R^1 and *N*-methyl groups, the strain being substantiated by an iminium ion character of $C(sp^2)$–N bond. This strain forces the substituent R^1 to take a quasi-axial orientation and hence the iodomethyl group a quasi-equatorial orientation as in a transition state **13** (Scheme I). Hydrolysis of cyclic intermediate derived from **13** may provide the thermodynamically less stable 1,3-trans lactone **6**. This explanation seems to be supported by the reduced selectivity (**6f**:**7f** = 75:25, X = H; cf. entry 11, Table I) in the protiothiolactonization of the sterically less demanding *N*-pyrrolidino derivative of **5f**.

In conclusion, halolactonization of α-substituted γ,δ-unsaturated (thio)amides provides otherwise scarcely available 2,4-trans-substituted γ-(thio)butyrolactones in high selectivity. The α,β-disubstituted γ,δ-unsaturated amides, both diastereomers of which are readily available in a high purity,[17] were cyclized to 2,4-trans-2,3,4-trisubstituted lactones. The 2,4-trans selectivity is lost in the threo diastereomers of amides with a β-OH or β-OAc substituent, owing to their 1,2-cis directing ability. The present methodology, coupled with the stereoselective epoxide formation[6,11] and carbon–carbon bond-forming reactions,[18] might facilitate the natural product synthesis. Synthetic application to anisomycin[19] and rubrenolide[20] is under investigation.

Experimental Section

Melting points were determined in capillary tubes with a Büchi apparatus and were not corrected. Unless otherwise noted, short-path 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%. Infrared spectra were measured with a Hitachi Model EPI-G3 grating spectrophotometer. Proton magnetic resonance (^1H NMR) spectra were determined either at 60 MHz on a JEOL-PMX 60 instrument, at 100 MHz on a Varian HA 100 instrument, or at 400 MHz on a JEOL-GX400 instrument with tetramethylsilane as an internal standard. ^{13}C NMR spectra were determined at 90 MHz on a JEOL FX 90Q instrument with $CDCl_3$ as an internal standard. Mass spectra were measured either in a Hitachi Model RMU 6C or on a JEOL D-300 instrument (high-resolution mass spectrometer).

Solvents and Reagents. Tetrahydrofuran and ether were dried and distilled from benzophenone and sodium immediately prior to use under an argon atmosphere. Allylic alcohols, tertiary butyl alcohol, triethylamine, and diisopropylamine were distilled over calcium hydride and kept under argon. *n*-Butyllithium and dihydrocinnamic acid were purchased from Aldrich Chemical Co. Allyl bromide, *N*-bromosuccinimide, and 4-toluenesulfonyl chloride were purchased from Wako Pure Chemical Industries, Ltd. *N,N*-Dimethylpropionamide and *N*-chlorosuccinimide were purchased from Tokyo Kasei Kogyo Co., Ltd.

Preparation of γ,δ-Unsaturated (Thio)amides (5, 8, and 11). *erythro*- and *threo*-*N,N*-Dimethyl-2,3-dimethylthiopent-4-enamides (**11e** and **11t**, each diastereomer was contaminated with 3% of another diastereomer) were prepared according to the method reported previously from these laboratories.[16a] *N,N*-Dimethyl-2-methylthiopent-4-enamide (**5e**), *N,N*-dimethyl-2-benzylthiopent-4-enamide (**5f**) and *N,N*-dimethyl-3-methylthiopent-4-enamide were prepared by the thio-Claisen rearrangement of *S*-alkyl ketene *S,N*-acetals.[20] A typical procedure for the preparation is exemplified by the synthesis of **5e**. A mixture of *N,N*-dimethylthiopropionamide (50 mmol) and allyl bromide (75 mmol) in 50 mL of anhydrous *t*-BuOH was stirred overnight at room temperature under an argon atmosphere. After addition of triethylamine (75 mmol) at room temperature, the reaction mixture was refluxed for 3 h. Usual extractive workup, followed by distillation (87 °C/0.9 mmHg), afforded 6.84 g (85.5%) of **5e**. The similar allylation of *N,N*-dimethyl-3-phenylthiopropionamide with allyl bromide and *N,N*-dimethylthioacetamide with crotyl bromide provided **5f** (95%, bp 92–97 °C/0.3 mmHg) and *N,N*-dimethyl-3-methylthiopent-4-enamide (80%, bp 89–90 °C/0.8 mmHg).

N,N-Dimethyl-2-methylpent-4-enamide (**5a**), *N,N*-dimethyl-2-benzylpent-4-enamide (**5b**), and *erythro*- and *threo*-*N,N*-dimethyl-2,3-dimethylpent-4-enamides (**8a** and **8b**) were prepared as follows: To a stirred solution of the corresponding thioamide in THF–H_2O (1:1) was added 5 equiv of methyl iodide and 5 equiv of $NaHCO_3$ at an ambient temperature. After vigorous stirring overnight, the reaction mixture was poured into water and extracted twice with ether. The combined organic layers were washed with saturated NaCl and dried over $MgSO_4$. Evaporation of the solvents followed by a distillation under reduced pressure gave a colorless liquid. In every case, the yield was quantitative.

trans-*N,N*-Dimethyl-2-methylhex-4-enamide (**5c**) was prepared as follows: To a solution of diisopropylamine (5 mmol) in 20 mL of anhydrous THF was added *n*-BuLi (*n*-hexane solution, 5 mmol) at 0 °C and then *N,N*-dimethylpropionamide (4 mmol) dropwise at 0 °C. This homogeneous solution was stirred for 1 h at the same temperature. To this solution was added a THF solution of *trans*-crotyl tosylate (5 mmol), which was prepared beforehand in situ by treatment of *trans*-crotyl alcohol with 1.0 equiv of *n*-BuLi and with 1.0 equiv of toluenesulfonyl chloride, all at −78 °C. The mixture was stirred for 1 h at 0 °C and at room temperature for 2 h and then poured into water. Usual extractive workup and distillation provided **5c** in 63% yield (110 °C/2 mmHg). Allylation with *trans*-crotyl bromide provided **5c** in ca. 50% crude yield, which was contaminated by stereo- and regioisomers and not used for the present study.

trans-*N,N*-Dimethyl-2-benzylhex-4-enamide (**5d**) was prepared in the same procedure as above (70% yield, 130 °C/0.8 mmHg).

threo- (**8c**) and *erythro*-*N,N*-dimethyl-2-methyl-3-hydroxypent-4-enamides (**8d**) were prepared as follows: To a solution of lithium enolate of *N,N*-dimethylpropionamide (4 mmol), generated by the same procedure as the preparation of **5c**, was added acrolein (5 mmol, dried and distilled over $CaCl_2$) in one portion at −78 °C. After the mixture was stirred at −78 °C for 2 min, the reaction was quenched by addition of 3 mL of 2 N HCl. After evaporation of THF, the reaction mixture was diluted with saturated NaCl and extracted successively with ether (30 plus 20 mL) and ethyl acetate (20 mL). After drying over $MgSO_4$ and evaporation of the solvents, the residue was distilled (100–105 °C/0.1 mmHg, 80% yield) to provide a ca. 1:2 mixture of **8c** and **8d**, which were separated by means of column chromatography (silica gel, hexane–ethyl acetate gradient).

threo- (**8e**) and *erythro*-*N,N*-dimethyl-2-methyl-3-acetoxypent-4-enamides (**8f**) were prepared as follows: A solution of **8c** (1 mmol), acetic anhydride (2 mmol), and pyridine (2.2 mmol) in 5 mL of anhydrous THF was stirred at room temperature overnight. The mixture was poured into ether and washed with 1 N HCl and then with 1 N $NaHCO_3$, followed by washing with saturated NaCl. After drying over $MgSO_4$ and evaporation of the solvents, the residue was distilled (87–88 °C/2.5 mmHg) to give **8e** in quantitative yield. According to the same procedure was prepared **8f** in quantitative yield.

threo- (**8g**) and *erythro*-*N,N*-dimethyl-2-methyl-3-acetoxy-*trans*-hex-4-enamides (**8h**) were prepared as follows: To a solution of lithium enolate of *N,N*-dimethylpropionamide (4 mmol) was added crotonaldehyde (5 mmol, dried and distilled over $CaCl_2$) in one portion at −78 °C. After the mixture was stirred for 2 min, acetic anhydride was added at −78 °C. The mixture was allowed to stir for 1 h at −78 °C and then treated with 2 N HCl. Usual extractive workup and distillation (92–97 °C/2.5 mmHg) gave a ca. 1:2 mixture of **8g** and **8h**, which were separated by means of column chromatography (silica gel, hexane–ethyl acetate gradient).

General Procedure for Iodolactonization of Amides (Condition A). To a solution of γ,δ-unsaturated amide **5** or **8** (1 mmol) in DME–H_2O (4 mL, 1:1 vol) was added iodine (1.1–2 equiv) at an ambient temperature. The homogeneous reaction mixture was stirred for the periods of time indicated in Tables I and II. The resultant solution was diluted with ether and treated with saturated $Na_2S_2O_3$ and then extracted twice with ether.

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Ether extracts were washed with saturated $NaHCO_3$ and with saturated NaCl. After drying over $MgSO_4$, the ethereal solution was evaporated and the residue was subjected to preparative TLC (silica gel). Analytically pure samples were prepared by distillation or recrystallization.

***trans*-2-Methyl-4-(iodomethyl)-γ-butyrolactone (6a)**: bp 100 °C/0.3 mmHg; IR (neat film) 3000 (m), 1770 (s), 1170 (s), 1150 (s), 1000 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (d, J = 7.3 Hz, 3 H), 2.10–2.32 (m, 2 H), 2.79 (m, 1 H, coalescing to a triplet J = 8.3 Hz, by irradiation at 1.31), 3.28–3.52 (m, 2 H), 4.61 (dddd, J = 12.5, 9.8, 7.6, 5.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 7.06 (CH_2I), 15.92 (Me), 33.94, 35.20, 76.26 (C-4), 178.7 (C-1); mass spectrum m/z (rel intensity) 240 (M^+, 20), 113 (88), 99 (86), 43 (100). Anal. Calcd for $C_6H_9IO_2$: C, 30.02; H, 3.78; O, 13.33. Found: C, 30.25; H, 3.75; O, 13.47.

***trans*-2-Benzyl-4-(iodomethyl)-γ-butyrolactone (6b)**: bp 150 °C/0.15 mmHg; IR (neat film) 2900 (m), 1770 (s), 1500 (m), 1450 (m), 1150 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04–2.32 (m, 2 H), 2.77–3.28 (m, 5 H), 4.32 (q, J = 6.1 Hz, 1 H), 7.11–7.71 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 7.31 (CH_2I), 32.35 (C-3), 36.36 ($PhCH_2$), 40.85 (C-2), 76.45 (C-4), 126.68, 128.52, 128.68, 137.51 (Ph), 177.38 (C-1); mass spectrum m/z (rel intensity) 316 (M^+, 0.2), 143 (100), 91 (70). Anal. Calcd for $C_{12}H_{13}IO_2$: C, 45.59; H, 4.14; O, 10.12. Found: C, 45.83; H, 4.15; O, 10.35.

***trans*-2-Benzyl-4-(1-iodoethyl)-γ-butyrolactone (6d)**: bp 150 °C/0.08 mmHg; IR (neat film) 1780 (s), 1600 (w), 1150 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.88 (d, J = 6.6 Hz, 3 H), 2.00–2.25 (m, 2 H), 2.71–3.34 (m, 3 H), 3.80–4.25 (m, 2 H), 7.00–7.50 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 24.0 (Me), 28.97 (CHI), 32.44 (C-3), 36.75 ($PhCH_2$), 41.36 (C-2), 81.65 (C-4), 126.84, 128.64, 128.82, 137.68 (Ph), 177.54 (C-1); mass spectrum m/z (rel intensity) 330 (M, 6.6), 203 (39), 157 (100), 91 (71). Anal. Calcd for $C_{13}H_{15}IO_2$: C, 47.29; H, 4.58; O, 9.69. Found: C, 47.40; H, 4.52; O, 9.59.

***cis*- and *trans*-3-Methyl-4-(iodomethyl)-γ-butyrolactones**: bp 120 °C/0.2 mmHg; IR (neat film) 1780 (s), 1170 (s), 980 (s), 930 (s) cm^{-1}; ^{13}C NMR ($CDCl_3$) cis isomer δ 0.42 (CH_2I), 12.5 (Me), 32.4, 37.4, 84.4 (C-4), 175.3 (C-1); ^{13}C NMR ($CDCl_3$) trans isomer δ 6.0 (CH_2I), 17.9 (Me), 35.6, 36.5, 81.6 (C-4), 174.7 (C-1); mass spectrum m/z (rel intensity) 240 (M, 14), 113 (100), 99 (57). Anal. Calcd for $C_6H_9IO_2$: 239.9649. Found: 239.9629.

***cis*,*trans*-2,3-Dimethyl-4-(iodomethyl)-γ-butyrolactone (9a)**: bp 115 °C/0.2 mmHg; IR (neat film) 3000 (m), 1770 (s), 1200 (m), 1160 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (d, J = 7.1 Hz, 3 H), 1.18 (d, J = 7.3 Hz, 3 H), 2.55 (m, 1 H, coalescing to a dd, J = 8.5, 4.4 Hz by irradiation at 1.08), 2.86 (m, 1 H, coalescing to a d, J = 8.5 Hz by irradiation at 1.18), 3.24–3.43 (m, 2 H), 4.13 (ddd, J = 10.3, 5.9, 4.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 5.21 (CH_2I), 10.06 (C-2-Me), 13.47 (C-3-Me), 37.57 (C-2), 38.07 (C-3), 83.20 (C-4), 178.02 (C-1); mass spectrum m/z (rel intensity) 254 (M, 12), 127 (100), 113 (93). Anal. Calcd for $C_7H_{11}IO_2$: C, 33.09; H, 4.36; O, 12.59. Found: C, 33.14; H, 4.49; O, 12.31.

***trans*,*cis*-2,3-Dimethyl-4-(iodomethyl)-γ-butyrolactone (9b)**: bp 115 °C/0.2 mmHg; IR (neat film) 2950 (m), 1770 (s), 1440 (m), 1315 (m), 1140 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (d, J = 6.8 Hz, 3 H), 1.26 (d, J = 6.8 Hz, 3 H), 2.24–2.54 (m, 2 H), 3.29 (m, 2 H), 4.71 (q, J = 6.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 1.38 (CH_2I), 12.3, 13.9 (C-2-Me, C-3-Me), 40.5, 41.1 (C-2, C-3), 79.9 (C-4), 178.1 (C-1); mass spectrum m/z (rel intensity) 254 (M, 28), 128 (13), 127 (100), 114 (4), 113 (63), 99 (30). Anal. Calcd for $C_7H_{11}IO_2$: C, 33.09; H, 4.36; O, 12.59. Found: C, 33.19; H, 4.26; O, 12.45.

***cis*,*cis*-2-Methyl-3-hydroxy-4-(iodomethyl)-γ-butyrolactone (10c)**: mp 85.5–86.0 °C; IR (KBr disk) 3350 (s), 2905 (m), 1740 (s), 1425 (m), 1195 (s), 975 (s) cm^{-1} ^1H NMR ($CDCl_3$) δ 1.29 (d, J = 7.08 Hz, 3 H), 2.41 (d, J = 4.88 Hz, 1 H), 2.77 (dq, J = 4.88, 7.08 Hz, 1 H), 3.20–3.60 (m, 2 H), 4.33 (ddd, J = 3.06, 5.92, 9.40 Hz, 1 H), 4.60 (dt, J = 3.06, 4.88 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ −1.38 (CH_2I), 7.96 (C-2-Me), 42.1 (C-2), 70.75 (C-3), 81.35 (C-4), 177.7 (C-1); mass spectrum m/z (rel intensity) 256 (M, 36), 228 (7), 129 (20), 111 (58), 85 (17), 71 (16), 58 (100). Anal. Calcd for $C_6H_9IO_3$: C, 28.14; H, 3.54; O, 18.75. Found: C, 28.09; H, 3.45; O, 18.67.

***trans*,*cis*-2-Methyl-3-hydroxy-4-(iodomethyl)-γ-butyrolactone (9d)**: bp 145–150 °C/0.1 mmHg; IR (neat film) 3400 (s), 1760 (s), 1170 (s), 980 (s); ^1H NMR ($CDCl_3$) δ 1.35 (d, J = 7.6 Hz, 3 H), 2.77 (dq, J = 7.6, 2.7 Hz, 1 H), 3.27–3.61 (m, 3 H), 4.32 (dd, J = 4.6, 2.7 Hz, 1 H), 4.74 (ddd, J = 11.7, 6.1, 4.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ −0.90 (CH_2I), 13.05 (Me), 44.42 (C-2), 73.81 (C-3), 81.59 (C-4), 178.50 (C-1); mass spectrum m/z (rel intensity) 256 (M, 28), 228 (7), 129 (38), 111 (32), 85 (17), 71 (14), 58 (100). Anal. Calcd for $C_6H_9IO_3$: C, 28.14; H, 3.54; O, 18.75. Found: C, 27.94; H, 3.59; O, 18.58.

***cis*,*cis*- and *cis*,*trans*-2-Methyl-3-acetoxy-4-(iodomethyl)-γ-butyrolactone (9e and 10e)**: bp 130 °C/0.06 mmHg, IR (neat film) 2980 (w), 1780 (s), 1740 (s), 1370 (m), 1220 (m); ^1H NMR ($CDCl_3$) **9e** δ 1.17 (d, J = 7.1 Hz, 3 H), 2.15 (s, 3 H), 2.80 (dq, J = 5.4, 7.1 Hz, 1 H), 3.45 (m, ABM, 2 H), 4.69 (ddd, J = 3.7, 6.1, 9.0 Hz, 1 H), 5.78 (dd, J = 3.7, 5.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) **9e** δ −2.93 (CH_2I), 8.56 (Me), 20.17 (MeCO), 40.88 (C-2), 74.41 (C-3), 81.71 (C-4), 169.34 (MeCO), 175.92 (C-1); ^1H NMR ($CDCl_3$) **10e** δ 1.25 (d, J = 7.3 Hz, 3 H), 2.13 (s, 3 H), 3.18 (quint, J = 7.3 Hz, 1 H), 3.45 (m, ABM, 2 H), 4.48 (dt, J = 1.5, 6.6 Hz, 1 H), 5.32 (dd, J = 7.3, 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) **10e** δ 2.51 (CH_2I), 8.32 (Me), 20.41 (MeCO), 37.47 (C-2), 71.95 (C-3), 79.49 (C-4), 169.76 (MeCO), 176.04 (C-1); mass spectrum m/z (rel intensity) 298 (M, 1), 238 (2), 172 (10), 171 (80), 129 (10), 111 (25), 100 (10), 43 (100). Anal. Calcd for $C_8H_{11}IO_4$: C, 32.23; H, 3.72; O, 21.47. Found: C, 32.03; H, 3.65; O 21.69.

***trans*,*cis*-2-Methyl-3-acetoxy-4-(iodomethyl)-γ-butyrolactone (9f)**: bp 140 °C/0.1 mmHg; IR (neat film) 3000 (w), 1770 (s), 1740 (s), 1365 (m), 1220 (s), 1160 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (d, J = 7.8 Hz, 3 H), 2.13 (s, 3 H), 2.77 (dq, J = 2.2, 7.8 Hz, 1 H), 3.37 (m, ABM, 2 H), 4.82 (ddd, J = 4.6, 6.6, 7.8 Hz, 1 H), 5.20 (dd, J = 2.2, 4.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ −2.69 (CH_2I), 13.17 (Me), 20.53 (MeCO), 42.80 (C-2), 75.42 (C-3), 78.78 (C-4), 169.58 (MeCO), 176.10 (C-1); mass spectrum m/z (rel intensity) 298 (M, 0.1), 238 (1), 172 (8), 171 (70), 129 (15), 111 (35), 43 (100). Anal. Calcd for $C_8H_{11}IO_4$: C, 32.23; H, 3.72; O, 21.47. Found: C, 32.31; H, 3.73; O, 21.30.

By the acetylation, **9d** was converted to **9f**: A mixture of **9d** (1 mmol), acetic anhydride (1 mmol), pyridine (1.1 mmol), and *N*,*N*-dimethylaminopyridine (0.1 mmol) in anhydrous THF (5 mL) was stirred at room temperature overnight under argon. The mixture was diluted with ether and washed with 1 N HCl, with 1 N NaOH, and then with saturated NaCl. After drying over $MgSO_4$, evaporation of the solvents, and distillation under the reduced pressure was isolated **9f** in quantitative yield.

***cis*,*cis*,*trans*-2-Methyl-3-acetoxy-4-iodo-5-methyl-δ-valerolactone**: mp 80.5–81.0 °C; IR (KBr disk) 3000 (w), 1750 (s), 1370 (m), 1220 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (d, J = 6.6 Hz, 3 H), 1.57 (d, J = 6.1 Hz, 3 H), 2.10 (s, 3 H), 3.08 (dq, J = 6.6, 3.4 Hz, 1 H), 3.83 (dd, J = 10.3, 1.7 Hz, 1 H), 4.62 (dd, J = 10.3, 6.1 Hz, 1 H), 5.47 (dd, J = 3.4, 1.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.1 (C-2-Me), 19.1 (C-5-Me), 20.3 (MeCO), 27.54 (C-4), 35.7 (C-2), 78.36 (C-5), 79.1 (C-3), 169.52 (MeCO), 171.8 (C-1); mass spectrum m/z (rel intensity) 312 (M, 1), 252 (7), 208 (11), 185 (20), 143 (16), 125 (100). Anal. Calcd for $C_9H_{13}IO_4$: 311.9860. Found: 311.9884.

***trans*,*cis*-2-Methyl-3-acetoxy-4-(iodoethyl)-γ-butyrolactone (9h)**: mp 87–88 °C; IR (KBr disk) 2950 (w), 1780 (s), 1740 (s), 1370 (m), 1220 (s), 1180 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (d, J = 7.8 Hz, 3 H), 2.09 (d, J = 6.6 Hz, 3 H), 2.11 (s, 3 H), 2.70 (q, J = 7.8 Hz, 1 H), 4.25 (dq, J = 10.7, 6.6 Hz, 1 H), 4.64 (dd, J = 10.7, 3.9 Hz, 1 H), 5.22 (d, J = 3.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.2 (C-1-Me), 18.6 (CHI), 20.6 (MeCO), 25.3 (Me-CH1), 44.0 (C-2), 76.7 (C-3), 83.7 (C-4), 169.4 (MeCO), 176.9 (C-1); mass spectrum m/z (rel intensity) 186 (M, 8), 185 (58), 176 (27), 148 (17), 128 (11), 125 (100). Anal. Calcd for $C_9H_{13}IO_4$: C, 34.63; H, 4.20; O, 20.51. Found: C, 34.51; H, 4.12; O, 20.22.

General Procedure for Halolactonization of Thioamides (Condition B). To a stirred solution of γ,δ-unsaturated thioamide (1 mmol) in DME (2–4 mL) was added iodine (1.1 mmol) and water (10 mmol) at an ambient temperature. The mixture was stirred until TLC monitoring showed the complete disappearance of the starting material (Table I). The reaction mixture was diluted with water and treated with aqueous $Na_2S_2O_3$ and then extracted twice with ether. The ether extracts were washed with saturated $NaHCO_3$ and with saturated NaCl. After drying over $MgSO_4$, the solvents were evaporated and the residue was subjected to preparative TLC (silica gel, benzene–ethyl acetate, 8:1). Analytically pure sample was prepared by distillation.

***trans*-2-Methyl-4-(iodomethyl)-γ-thiobutyrolactone (6e, X = I)**: bp 100 °C/0.2 mmHg; IR (neat film) 2905 (m), 1700 (s), 1450 (m), 960 (m), 880 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (d, J = 6.7 Hz, 3 H), 2.10 (ddd, J = 12.9, 9.8, 5.9 Hz, 1 H), 2.49 (ddd, J = 12.9, 6.9, 3.9 Hz, 1 H, coalescing to a dd, J = 12.9, 6.9 Hz by irradiation at 4.01), 2.82 (m, 1 H, coalescing to a dd, J = 9.8, 6.9 Hz, by irradiation at 1.22), 3.38 (t, J = 10.0 Hz, 1 H), 3.56 (dd, J = 10.0, 5.1 Hz, 1 H), 4.01 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 8.74 (CH_2I), 14.96 (Me), 38.67 (C-3), 44.71 (C-2), 47.29 (C-4), 208.64 (C-1); mass spectrum m/z (rel intensity) 256 (M, 2), 129 (100). Anal. Calcd for C_6H_9IOS: C, 28.14; H, 3.54; O, 6.25. Found: C, 28.39; H, 3.44; O, 6.15.

***trans*-2-Benzyl-4-(iodomethyl)-γ-thiobutyrolactone (6f)**: bp 150 °C/0.8 mmHg; IR (neat film) 2940 (w), 1700 (s), 1600 (w), 1498 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.22 (m, 2 H, coalescing to a d, J = 6.6 Hz by irradiation at 3.94), 2.69–3.27 (m, 3 H), 3.30 (t, J = 9.8 Hz, 1 H), 3.50 (dd, J = 9.8, 5.4 Hz, 1 H), 3.94 (dddd, J = 9.8, 5.4, 4.2, 4.2 Hz, 1 H), 7.10–7.55 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 8.72 (CH_2I), 36.1 (C-3), 36.3 ($PhCH_2$), 47.6 (C-4), 52.0 (C-2), 126.7, 128.6, 129.0, 138.1 (Ph), 207.1 (C-1); mass spectrum m/z (rel intensity) 332 (M, 7), 205 (100), 91 (53). Anal. Calcd for $C_{12}H_{13}IOS$: C, 43.38; H, 3.94; O, 4.82.

Found: C, 43.62; H, 4.10; O, 4.55.

***trans*-2-Methyl-4-(bromomethyl)-γ-thiobutyrolactone (6e, X = Br)**: bp 115–117 °C/1.7 mmHg; IR (neat film) 2950 (w), 1700 (s), 1450 (m), 1195 (m), 960 (m), 860 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (d, J = 6.7 Hz, 3 H), 1.84–2.21 (m, 1 H), 2.50 (ddd, J = 11.3, 6.8, 3.3 Hz, 1 H), 2.89 (ddd, 9.9, 6.8, 6.7 Hz, 1 H), 3.58 (t, J = 10 Hz, 1 H), 3.67 (dd, J = 10, 5.1 Hz, 1 H), 3.93–4.17 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.90 (Me), 34.60 (CH_2Br), 36.81 (C-3), 44.24 (C-2), 46.81 (C-4), 208.0 (C-1); mass spectrum m/z (rel intensity) 209 (M, 2), 129 (100), 115 (53), 69 (98). Anal. Calcd for C_6H_9BrOS: C, 34.46; H, 4.34; O, 7.65; S, 15.53. Found: C, 34.69; H, 4.38; O, 7.77; S, 15.56.

General Procedure for Protiolactonization of Thioamides (Condition C). A solution of γ,δ-unsaturated thioamide (1 mmol), (+)-camphor-10-sulfonic acid (2.2 mmol), and water (15–20 mmol) in THF (2–4 mL) was refluxed until TLC monitoring (silica gel, benzene–ethyl acetate, 8:1) showed the complete disappearance of the starting material (Table I). The reaction mixture was poured into water and extracted with ether twice. The combined ether extracts were washed with saturated $NaHCO_3$ and with saturated NaCl and then dried over $MgSO_4$. Analytically pure sample was prepared by the preparative TLC, followed by diatillation under the reduced pressure.

***trans*-2,4-Dimethyl-γ-thiobutyrolactone (6e, X = H)**: bp 105–115 °C/18 mmHg; IR (neat film) 2907 (m), 1670 (s), 1455 (m), 1380 (w), 960 (m), 875 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (d, J = 7.1 Hz, 3 H), 1.49 (d, J = 6.8 Hz, 3 H), 2.09 (m, 2 H, coalescing to a d, J = 7.6 Hz, by irradiation at 3.90), 2.72 (m, 1 H, coalescing to a t, J = 7.6 Hz, by irradiation at 1.19), 3.90 (m, 1 H, coalescing to a t, J = 5.5 Hz, by irradiation at 1.49); ^{13}C NMR ($CDCl_3$) δ 15.08 (C-2-Me), 22.19 (C-4-Me), 41.31 (C-3, C-4), 45.43 (C-2), 210.58 (C-1); mass spectrum m/z (rel intensity) 130 (M, 53), 70 (46), 60 (42), 55 (100). Anal. Calcd for $C_6H_{10}OS$: C, 55.35; H, 7.74; O, 12.28. Found: C, 55.40; H, 7.73; O, 12.55.

***trans*-2-Benzyl-4-methyl-γ-thiobutyrolactone (6f, X = H)**: bp 130 °C/0.8 mmHg; IR (neat film) 2900 (m), 1685 (s), 1600 (w), 1490 (m), 1445 (m) cm^{-1}; ^1H NMR (CCl_4) δ 1.43 (d, J = 6.8 Hz, 3 H), 1.96 (ddd, J = 10.8, 7.1, 5.6 Hz, 1 H), 2.58 (dd, J = 12.2, 8.8 Hz, 1 H), 2.73–3.01 (m, 2 H), 3.13 (dd, J = 12.2, 3.4 Hz, 1 H), 3.50 (m, 1 H, coalescing to a t, J = 5.6 Hz, by irradiation at 1.43), 7.00–7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 22.22 (Me), 36.14 ($PhCH_2$), 38.58, 41.47 (C-3, C-4), 52.61 (C-2), 126.44, 128.44, 128.82, 138.70 (Ph), 209.33 (C-1); mass spectrum m/z (rel intensity) 206 (M, 41), 178 (45), 118 (57), 117 (72), 58 (100). Anal. Calcd for $C_{12}H_{14}OS$: C, 69.86; H, 6.84; O, 7.76. Found: C, 69.73; H, 6.94; O, 7.55.

2,3,4-Trimethyl-γ-thiobutyrolactone (12) and 1-(Trimethylsiloxy)-2,3,4-trimethyl-3,4-dihydrothiophene: *erythro-N,N*,2,3-Tetramethylthiopent-4-enamide, **11e**, (1 mmol, contaminated with 3% of *threo*-**11t**) was refluxed in 4 mL of DME in the presence of 10-camphorsulfonic acid (2.2 mmol) and water (20 mmol) for 20 h. Usual extractive workup (see the general procedure) and distillation (128–130 °C/22 mmHg) gave in 60% yield a mixture of *cis,trans*- (**12a**, 50%), *trans,trans*- (**12b**, 47%), and *trans,cis*-2,3,4-trimethyl-γ-thiobutyrolactones (**12c**, 3%), whose composition was determined from VPC analysis (PEG, 2 m, 120 °C, He carrier). **12a** and **12b** were separated by means of preparative VPC. It was verified by the following silyl enol ether formation that **12a** and **12b** were the C-2 epimers of each other: Into a solution of lithium isopropylamide (1.2 mmol) in 2.5 mL of anhydrous THF was added a THF solution of the mixture of **12a**, **12b**, and **12c** (1 mmol) obtained as above at −78 °C. After the mixture was stirred for 1 h, trimethylsilyl chloride (1.2 mmol) was added and allowed to stir for 10 min at −78 °C and then at room temperature for 1 h. The mixture was diluted with ether and the organic layer was washed with 1 N HCl and with aqueous $NaHCO_3$ and then dried over $MgSO_4$. Evaporation of the solvents and distillation (85 °C/2.5 mmHg) provided an oil in 89% yield, consisting of 1-(trimethylsiloxy)-2,3,4-trimethyl-3,4-*cis*-dihydrothiophene and its 3,4-*trans*-dihydro isomer (96:4, from VPC and ^1H NMR). Similar protiothiolactonization of **11t** (contaminated with 3% of **11e**, condition C for 46 h) and silyl enol ether formation of the thus obtained mixture of **12** provided a mixture of 2,3,4-(trimethyl)thio-γ-butyrolactones (**12a**:**12b**:**12c**:**12d** = 1:7:84:8) and a mixture of 1-(trimethylsiloxy)-2,3,4-trimethyl-3,4-*cis*-dihydrothiophene and its 3,4-*trans*-dihydro isomer (8:92).

1-(Trimethylsiloxy)-2,3,4-trimethyl-3,4-dihydrothiophene: bp 85–86 °C/2.5 mmHg; IR (neat film) 2960 (s), 1660 (s), 1255 (s), 1220 (s), 1190 (s), 895 (s), 865 (s), 845 (s) cm^{-1}; ^1H NMR ($CDCl_3$) 3,4-trans-dihydro isomer δ 0.21 (s, 9 H), 1.06 (d, J = 7.1 Hz, 3 H), 1.35 (d, J = 6.6 Hz, 3 H), 1.51 (s, 3 H), 2.05–2.45 (m, 1 H), 3.10 (dq, J = 6.6, 5.0 Hz, 1 H); ^1H NMR ($CDCl_3$) 3,4-cis-dihydro isomer δ 0.20 (s, 9 H), 0.97 (d, J = 7.0 Hz, 3 H), 1.27 (d, J = 6.6 Hz, 3 H), 1.53 (s, 3 H), 2.28–2.85 (m, 1 H), 3.61–4.11 (m, coalescing to a d, J = 7.1 Hz, by irradiation at 1.27); mass spectrum m/z (rel intensity) 216 (M, 3), 149 (54), 148 (35), 147 (100), 144 (88). Anal. Calcd for $C_{10}H_{20}OSSi$: C, 55.50; H, 9.32. Found: C, 55.28; H, 9.15.

2,3,4-Trimethyl-γ-thiobutyrolactone (12): bp 128–138 °C/22 mmHg; IR (neat film, as a mixture of isomers) 2970 (m), 2930 (m), 2880 (m), 1700 (s), 1455 (m), 1380 (m), 950 (m) cm^{-1}; ^1H NMR (CCl_4) trans, trans (**12b**) δ 1.10 (d, J = 6.7 Hz, 3 H), 1.17 (d, J = 6.8 Hz, 3 H), 1.45–1.80 (m, 1 H), 1.46 (d, J = 6.6 Hz, 3 H), 2.12 (dq, J = 11.7, 6.7 Hz, 1 H), 3.33 (dq, J = 9.7, 6.6 Hz, 1 H); ^1H NMR (CCl_4) cis, trans (**12a**) δ 1.068 (d, J = 7.4 Hz, 3 H), 1.072 (d, J = 6.6 Hz, 3 H), 1.48 (d, J = 6.8 Hz, 3 H), 2.21 (br sextet, J = 6.6, 6.6, 6.2 Hz, 1 H), 2.66 (br quintet, J = 7.3, 6.6 Hz, 1 H), 3.49 (br quintet, J = 6.8, 6.2 Hz, 1 H); ^1H NMR (CCl_4) trans, cis (**12c**) δ 1.02 (d, J = 6.5 Hz, 3 H), 1.12 (d, J = 6.6 Hz, 3 H), 1.35 (d, J = 6.6 Hz, 3 H), 2.0–2.13 (m, 2 H), 3.67 (m, 1 H, coalescing to a d, J = 6.0 Hz, by irradiation at 1.35); ^1H NMR (CCl_4) cis, cis (**12d**) δ 0.88 (d, J = 6.6 Hz, 3 H), 1.07 (d, J = 6.9 Hz, 3 H), 1.41 (d, J = 6.9 Hz, 3 H), 2.25–2.55 (m, 1 H), 2.72 (m, 1 H, coalescing to a doublet, J = 6.0 Hz), 3.89 (dq, J = 6.9, 4.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) trans, trans (**12b**) δ 13.41, 15.50 (C-2-Me, C-3-Me), 18.50 (C-4-Me), 48.25 (C-4), 49.50 (C-3), 55.43 (C-2); ^{13}C NMR cis, trans (**12b**) δ 10.77, 13.29 (C-2-Me, C-3-Me), 20.23 (C-4-Me), 44.36 (C-3), 48.19 (C-4), 50.58 (C-2); ^{13}C NMR ($CDCl_3$) trans, cis (**12c**) δ 13.23, 14.85 (C-2-Me, C-3-Me), 17.00 (C-4-Me), 43.94 (C-3), 45.01 (C-4), 49.20 (C-2), 209.68 (C-1); mass spectrum m/z (as a mixture of isomers, rel intensity) 144 (M, 96), 84 (40), 69 (100). Anal. Calcd for $C_7H_{12}OS$: C, 58.28; H, 8.39; O, 11.09. Found: C, 58.18; H, 8.64; O, 11.26.

General Procedure for Bromolactonization of Amide (Condition A). To a solution of γ,δ-unsaturated amide (1 mmol) in DME–H_2O (4 mL, 1:1 vol) was added *N*-bromosuccinimide (1.1 equiv) at 0 °C. After being stirred for 5 min at 0 °C, the reaction mixture was allowed to warm to an ambient temperature and stirred for the periods of time indicated in Table I. The mixture was diluted with water and extracted with ether twice. Ether extracts were washed with saturated $NaHCO_3$ and then with saturated NaCl. After being dried over $MgSO_4$, the ethereal solution was evaporated, and the residue was subjected to preparative TLC (silica gel, benzene–ethyl acetate, 8:1). Analytically pure samples were obtained by distillation under the reduced pressures.

***trans*-2-Methyl-4-(bromomethyl)-γ-butyrolactone (6a, X = Br)**: bp 110 °C/1.5 mmHg; IR (neat film) 3000 (w), 1770 (s), 1180 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (d, J = 7.1 Hz, 3 H), 1.94–2.58 (m, ABCM, 2 H), 2.86 (m, 1 H, coalescing to a dd, J = 9.0, 8.3 Hz, by irradiation at 1.30), 3.53 (m, ABM, appearing as a d, J = 5.1 Hz, 2 H), 4.74 (m, 1 H, coalescing to a dd, J = 8.3, 4.2 Hz, by irradiation at 3.53); ^{13}C NMR ($CDCl_3$) δ 15.92 (Me), 33.64, 33.82, 35.58, 75.60 (C-4), 178.68 (C-1); mass spectrum m/z (rel intensity) 192 (M, 2), 179 (10), 177 (10), 149 (85), 174 (87), 121 (16), 67 (100). Anal. Calcd for $C_6H_9BrO_2$: C, 37.31; H, 4.73; O, 16.57. Found: C, 37.30; H, 4.81; O, 16.77.

***trans*-2-Methyl-4-(1-bromoethyl)-γ-butyrolactone (6c, X = Br)**: bp 120 °C/0.9 mmHg; IR (neat film) 3000 (m), 1778 (s), 1445 (m), 1175 (m), 1010 (m), 1000 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (d, J = 7.1 Hz, 3 H), 1.75 (d, J = 6.6 Hz, 3 H), 1.89–2.94 (m, 3 H), 4.18 (m, 1 H, coalescing to a d, J = 6.8 Hz by irradiation at 1.75), 4.89 (ddd, J = 11.5, 6.8, 4.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 16.10 (C-1-Me), 21.73 (Me-CHBr), 33.04 (C-3), 33.88 (C-2), 50.10 (CHBr), 80.21 (C-4), 178.62 (C-1); mass spectrum m/z (rel intensity) 206 (M, 1), 100 (17), 99 (100), 85 (65), 83 (100). Anal. Calcd for $C_7H_{11}BrO_2$: 205.9942. Found: 205.9916.

***cis*- and *trans*-2,4-Dimethyl-γ-butyrolactones**: Into a solution of a mixture of *cis*- and trans-2-methyl-4-iodomethyl-γ-butyrolactones (291 mg, 1.2 mmol; 1:9 mixture prepared in entry 1, Table I) in 10 mL of anhydrous ether was added tri-*n*-butyltin hydride (384 mg, 1.32 mmol) at 0 °C, and this homogeneous mixture was stirred overnight at the same temperature. Usual extractive workup, followed by purification by means of distillation (115–120 °C/2 mmHg) and preparative TLC (silica gel, benzene–ethyl acetate, 8:1), gave a colorless liquid (118 mg, 86% crude yield) that consists of *trans*- and *cis*-2,4-dimethyl-γ-butyrolactones (9:1) and small amount of impurities due to organotin compounds. *trans*-2,4-Dimethyl-γ-butyrolactone was purified by preparative VPC (PEG, 2 m, He carrier at 130 °C). By the similar procedure was obtained *cis*-2,4-dimethyl-γ-butyrolactone (85% crude yield, containing small amount of impurities due to organotin compounds) from *trans,trans*-2,4-dimethyl-3-iodo-γ-butyrolactone.[7] ***trans*-2,4-Dimethyl-γ-butyrolactone**: bp 115–120 °C/2 mmHg; IR (neat film) 1760 (s), 1450 (w), 1170 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (d, J = 7.3 Hz, 3 H), 1.38 (d, J = 6.3 Hz, 3 H), 1.98–2.23 (m, 2 H), 2.52–2.90 (m, 1 H), 4.71 (qdd, J = 7.3, 6.1, 5.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.71 (Me-C-4), 26.34 (Me-C-2), 33.70 (C-2), 36.75 (C-3), 74.29 (C-4), 179.51 (C-1); mass spectrum m/z (rel intensity) 114 (M, 3), 99 (35), 70 (89), 55 (100). Anal. Calcd for $C_6H_{10}O_2$: 114.0680. Found: 114.0662. ***cis*-2,4-Dimethyl-γ-butyrolactone**: bp 115–120 °C/2 mmHg; IR (neat film) 1760

(s), 1450 (w), 1380 (w), 1180 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (d, J = 6.7 Hz, 3 H), 1.41 (d, J = 6.1 Hz, 3 H), 1.53-1.80 (m, 1 H), 2.35-3.05 (m, 2 H), 4.50 (qdd, J = 6.7, 5.3, 3.0 Hz; 1 H); ^{13}C NMR ($CDCl_3$) δ 15.02 (Me-C_2), 20.83 (Me-C-4), 36.27 (C-2), 39.63 (C-3), 74.76 (C-4), 179.34 (C-1); mass spectrum m/z (rel intensity) 114 (M, 1), 99 (34), 71 (33), 70 (100). Anal. Calcd for $C_6H_{10}O_2$: 114.0680. Found: 114.0670.

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Supplementary Material Available: X-ray analysis, ORTEP view, packing diagram, crystal data, positional parameters, anisotropic thermal parameters, bond distances, bond angles, torsional angles, and structure factor amplitudes for **10c** (19 pages). Ordering information is given on any current masthead page.

Synthesis and ^{13}C NMR Analysis of a Series of Bridgehead-Substituted Polycycloalkanes: ^{13}C-Labeled Methyl as the Substituent[1]

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Abstract: The synthesis of eight polycycloalkanes substituted at the bridgehead with a ^{13}C-labeled methyl group is described. Their ^{13}C nuclear magnetic resonance spectra have been measured and the various NMR parameters are reported. It is found that there is no linear correlation between coupling involving directly bonded carbon atoms and the product of the s characters of the bonding orbitals. The experimentally determined values of $^3J(CC)$ are in close agreement with values calculated by using the self-consistent perturbation theory at the INDO level of approximation. In several strained systems, nonbonded interactions provide significant contributions to the vicinal carbon-carbon coupling constants; MO results demonstrate that these interactions oppose through-bond effects. Very good agreement is also noted between the observed $^3J(CC)$ values and those determined from a Karplus relationship; this includes the substrates in which through-space effects are especially important.

Nuclear spin-spin coupling is normally described in terms of the transmission of indirect nuclear spin interactions via the bonding network. The coupling constant, $J(AB)$, is a parameter which provides a measure of the extent of coupling between the nuclei A and B and is considered to be comprised of the following terms:[2]

$$J(AB)_{total} = J(AB)_O + J(AB)_D + J(AB)_C$$

The first, $J(AB)_O$, refers to the interaction between the field produced by the orbiting electrons and the nuclear magnetic moment; the second, $J(AB)_D$, arises from dipole-dipole interaction between the nuclear and electronic magnetic moments; the final (and frequently major) contribution to the coupling, $J(AB)_C$, occurs as a result of interactions between nuclear and electronic spins. $J(AB)_C$ is referred to as the (Fermi) contact term because it depends on the properties of electrons at the nucleus; accordingly, it is concerned with s electron densities.

Of special interest to the organic chemist is the question of coupling involving the carbon-13 nucleus. Evaluation of carbon-carbon coupling constants, $^nJ(CC)$, has captured the attention of both experimental and theoretical chemists over recent years, and, despite the fact that C-C couplings are more difficult to obtain, there currently exists an extensive tabulation of such data.[3-8]

In considering one-bond coupling it is generally believed that the extent of coupling between carbon and hydrogen, for example, bears a direct correlation with the degree of s character of the carbon bonding orbital, i.e., the coupling is governed almost exclusively by Fermi contact. Indeed, the tendency has arisen to regard the value of $^1J(CH)$ as a direct measure of the s content of the carbon orbital, although the need for exercising restraint in too literal an interpretation of this relationship has been emphasised.[9] This correlation has been extended to include carbon-carbon coupling and it is suggested that $^1J(CC)$ values similarly reflect the product of the s electron densities at the nuclei.[6,10] There are, however, some notable exceptions, for instance, when the carbon atoms form part of a strained ring system[11] or if they are multiply bonded.[10b,12]

Undoubtedly, the most intriguing aspect of long-range nuclear spin interactions is the question of vicinal coupling. Generally speaking, three-bond proton-proton coupling in saturated systems obeys a Karplus relationship. Much attention has been paid to establishing a similar correlation between $^3J(CC)$ and the torsional

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