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Diastereoselective Ring-Opening Aldol-Type Reaction of 2,2-Dialkoxycyclopropanecarboxylic Esters with Carbonyl Compounds. 2. Synthesis of *cis*-2,3-Substituted-γ-lactones[1,2]

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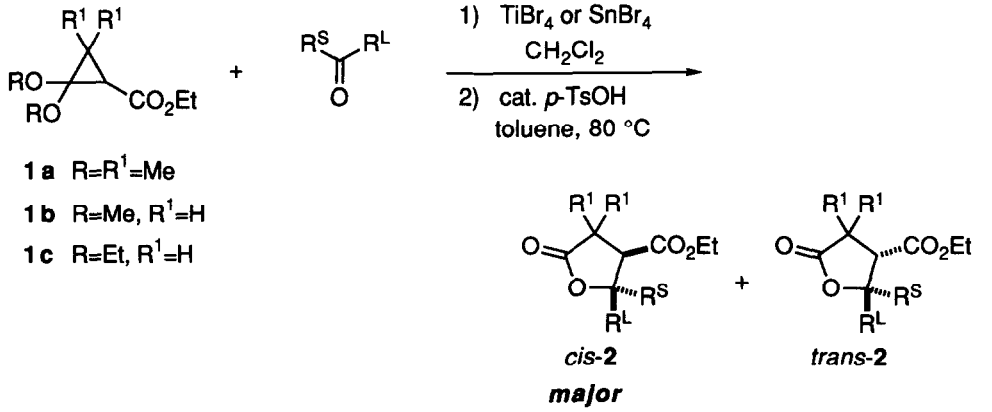
Abstract: The reaction of 3-alkyl-2,2-dialkoxycyclopropanecarboxylic esters **1d-i** with symmetrical ketones and formaldehyde was investigated. Cyclopropanes **1d-i** react with symmetrical ketones and formaldehyde in the presence of $TiCl_4$ to give *cis*-2,3-substituted-γ-lactones in good yields with high diastereoselectivity In the reaction of 3-ethylcyclopropane **1d**, the reaction conditions hardly influenced the diastereoselectivity. Regarding the reaction of 3-methylcyclopropane **1f**, however, the effect of the reaction conditions, especially the solvent, on the diastereoselectivity was observed High chemoselectivity was also observed for the reaction of **1d** with 1,4-cyclohexanedione *mono*-ethylene acetal (**24**). The isomerization of *cis*-γ-lactones by treatment with NaOEt in EtOH gives *trans*-isomers in good yields

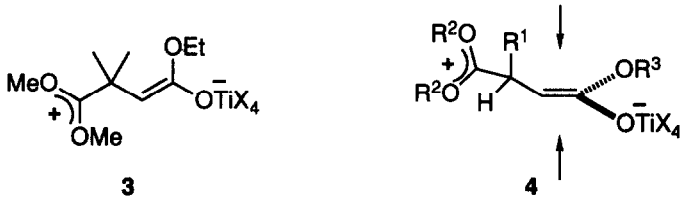
INTRODUCTION

Vicinally donor-acceptor-substituted cyclopropanes are valuable synthetic building blocks in organic synthesis, and are used for the synthesis of many types of compounds, especially five-membered carbo- and heterocycles.[4,5] We recently reported that 2,2-dialkoxycyclopropanecarboxylic esters reacted with various electrophiles[6] and nucleophiles[7] in the presence of a Lewis acid (LA)-catalyst. In the preceding paper of this series,[1] we described a highly diastereoselective synthesis of *cis*-3,4-substituted-γ-lactones by a LA-promoted reaction of ethyl 3,3-dimethyl- or 3-unsubstituted-2,2-dialkoxycyclopropanecarboxylates **1a-c** with aldehydes



Scheme 1

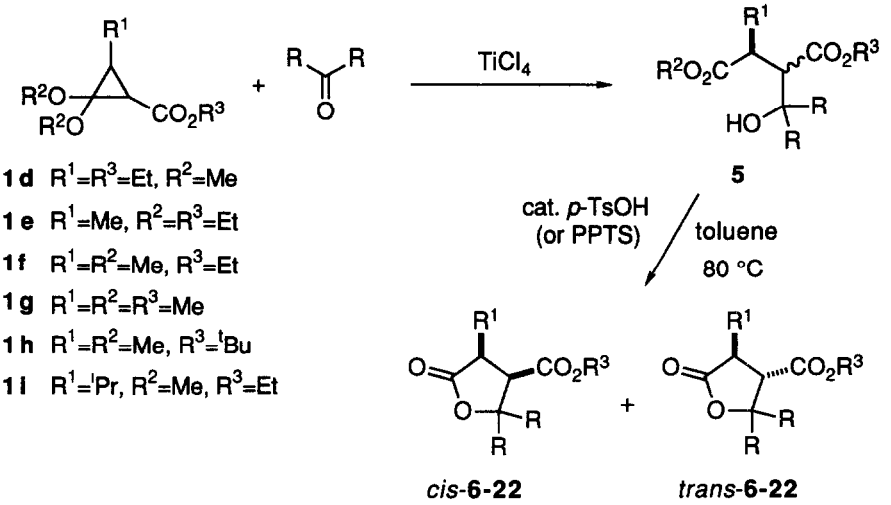
and unsymmetrical ketones (Scheme 1). This reaction is an aldol-type reaction of a ring-opened 1, 3-zwitterion **3** with carbonyl compounds. If 3-monoalkyl-substituted cyclopropanes **1d-i** are employed instead of **1a-c**, zwitterion **4** having a cationic substituent at a chiral center adjacent to the enolate double bond would be formed; it is anticipated that the electronic feature of the cationic substituent would control the facial selectivity in the electrophilic reaction toward **4**. To our knowledge, there has been no example of the electrophilic reaction toward an enolate double bond having a cationic substituent at the neighboring chiral center. In this paper we report on the LA-promoted reaction of 3-alkyl-2,2-dialkoxycyclopropanecarboxylic esters **1d-i** with symmetrical ketones and formaldehyde, resulting in a highly diastereoselective synthesis of *cis*-2,3-substituted-γ-lactones.



3 **4**

RESULTS AND DISCUSSION

The Reaction of Cyclopropanes 1d-i with Symmetrical Ketones and Formaldehyde. Cyclopropanes **1d-i** were synthesized from the corresponding ketene acetals and diazoacetic esters according to a method described in the literature.[8,9] Each **1d-i** was obtained mainly as a *trans*-isomer; the *trans*:*cis*-ratio varied depending on the 3-alkyl substituent.[10] All of **1d-i** were unstable under the conditions of column



1 d R^1=R^3=Et, R^2=Me
1 e R^1=Me, R^2=R^3=Et
1 f R^1=R^2=Me, R^3=Et
1 g R^1=R^2=R^3=Me
1 h R^1=R^2=Me, R^3=^{t}Bu
1 i R^1=^{i}Pr, R^2=Me, R^3=Et

Scheme 2

chromatography; since the isomers could not be separated, we used them as mixtures of *cis*- and *trans*-isomers.

For the reaction of **1a** with aldehydes and unsymmetrical ketones, TiX_4 (X = Cl, Br) generally gave excellent yields of γ-lactones.[1] Therefore, we initially chose $TiCl_4$ as a catalyst and carried out the reaction of 3-ethylcyclopropane **1d** with 4-heptanone. The reaction of **1d** with 4-heptanone smoothly proceeded in the presence of 1.1 equiv of $TiCl_4$ in CH_2Cl_2 at -78 °C. The initial product mainly consisted of hydroxy diesters **5** accompanied by small amounts of γ-lactones **15**. The crude mixture was completely converted into **15** by treatment with a catalytic amount of *p*-toluenesulfonic acid in toluene at 80 °C. To our surprise, GC analysis of the resulting product mixture indicated that only *cis*-γ-lactone *cis*-**15** existed (*cis*:*trans* = >99:1). This high degree of diastereoselectivity might be attributed to an electronic effect of the cationic substituent, as we had expected. Then, the reaction of 3-methylcyclopropane **1e** with 4-heptanone was attempted under the same conditions. The reaction also proceeded smoothly, whereas the diastereoselectivity was considerably depressed (*cis*:*trans* = 72:28). These results indicate that the steric bulkiness of the 3-alkyl substituent of **1** has a significant effect on the diastereoselectivity.

We therefore examined various reaction conditions in order to improve the diastereoselectivity of the reaction of 3-methylcyclopropane. The acetal- and ester-moieties of **1** influenced the diastereoselectivity (Table I). The use of dimethyl acetal **1f** instead of diethyl acetal **1e** slightly improved the *cis*-selectivity, while bulkier ^{t}Bu ester **1h** gave a decreased selectivity. The combination of dimethyl acetal and ethyl ester was found to be

Table I. Reaction of 1e-h with Ketones Promoted by $TiCl_4$[a]

1	ketone	product	yield, %[b]	*cis* : *trans*[c]
1e	4-heptanone	**6**	95	72:28
	cyclohexanone	**7**	98	89:11
1f	4-heptanone	**6**	90	77:23
	cyclohexanone	**7**	92	92: 8
1g	4-heptanone	**8**	97	72:28
	cyclohexanone	**9**	83	85:15
1h	4-heptanone	**10**	quant	62:38
	cyclohexanone	**11**	92	75:25

[a] The reaction was performed in CH_2Cl_2 at – 78°C for 1-2 h 1 . ketone · $TiCl_4$ = 1 1 . 1 · 1 1
[b] Isolated yield [c] Determined by GC

Table II. Effect of Addition Order and Solvent[a]

solvent	method[b]	yield, %[c]	*cis* : *trans*[d]
CH_2Cl_2	A	90	77:23
	B	94	81:19
	C	76	83:17
Toluene	C	64	85:15
CH_3CN	C	68	94: 6

[a] The reaction was performed in CH_2Cl_2 at – 78°C for 1.5-2 h. **1f** · ketone : LA = 1 1 1 1.1.
[b] See text [c] Isolated yield [d] Determined by GC

the best among the four types of combinations examined, namely, **1f** gave the best *cis*-selectivity among **1e-h**. For the reaction of **1f** with 4-heptanone, LAs significantly influenced the yield. Sn(IV) derivatives, such as $SnCl_4$, $SnCl_3(OTf)$, and $SnCl_2(OTf)_2$, were almost ineffective for this reaction.[11] Although $TiCl_2(OTf)_2$ exhibited a slightly improved diastereoselectivity (*cis*:*trans* = 84:16), the yield was disappointing (5%). $TiBr_4$ gave almost the same result (95%, *cis*:*trans* = 76:24) regarding the yield and diastereoselectivity as $TiCl_4$, whereas $TiCl_2(O^iPr)_2$, and $Ti(O^iPr)_4$ did not promote the reaction. On the basis of these results, $TiCl_4$ was chosen as a suitable catalyst.

In Table II are summarized the effects of the addition order of the substrates and solvent. Three types of addition methods (A-C) were examined: In method A, a solution of $TiCl_4$ was added to a mixture of **1** and a ketone; in method B, a solution of a ketone was added to a mixture of **1** and $TiCl_4$; and in method C, a solution of **1** was added to a mixture of a ketone and $TiCl_4$. The addition method slightly affected the diastereoselectivity; among them, method C gave the best selectivity, although the yield decreased slightly. The solvent had a significant effect on the diastereoselectivity; a polar solvent, CH_3CN, exhibited excellent *cis*-selectivity. On the basis of these results, we selected two types of conditions: Conditions I involve addition

Table III. Reaction of 1 with Ketones Promoted by $TiCl_4$

entry	1	ketone	Conditions[a]	product	yield, %[b]	*cis* : *trans*[c]
1	**1f**	4-heptanone	I	**6**	68	94: 6
2			II		90	77:23
3		cyclohexanone	I	**7**	70	94: 6
4			II		92	92: 8
5		acetone	I	**12**	64	89:11
6		cyclopentanone	I	**13**	51	93: 7
7		formaldehyde	[d]	**14**	58	66:34
8	**1d**	4-heptanone	I	**15**	81	98: 2
9			II		78	>99: 1
10		**23**[e]	II	**16**	89	74:26[f]
11		cyclohexanone	I	**17**	91	>99: 1
12			II		73	>99: 1
13		**24**[g]	I	**18**	55	90:10
14			II		61	93: 7
15[h]		cyclopentanone	II	**19**	62	97: 3
16	**1i**	4-heptanone	I	**20**	50	96: 4
17		cyclohexanone	II	**21**	91	98: 2
18[i]		cyclopentanone	II	**22**	43	94: 6

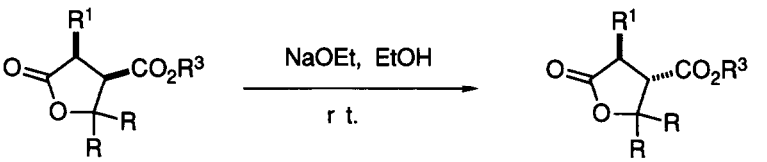
[a] Conditions I: The reaction was performed in CH_3CN at – 45 °C, Addition method C, Reaction time 2 h. Conditions II The reaction was performed in CH_2Cl_2 at – 78 °C, Addition method A, Reaction time 2 h **1** ketone $TiCl_4$ = 1.1 · 1 . 1.1. [b] Isolated yield [c] Determined by GC. [d] Gaseous formaldehyde was bubbled into a mixture of **1f** and $TiCl_4$ in CH_3CN at – 45 °C. [e] **23**. 1,3-Di(benzyloxy)-2-propanone. [f] Determined by ^1H NMR [g] **24**: 1,4-Cyclohexanedione *mono*-ethylene acetal [h] Reaction time: 7 h. [i] Reaction time: 48 h

method C and CH_3CN used as a solvent; Conditions II involve addition method A and CH_2Cl_2 used as a solvent.

Under Conditions I and II the reaction of **1d**, **1f**, and **1i** with various symmetrical ketones and formaldehyde was carried out (Table III). For the reaction of **1f**, Conditions I gave a higher *cis*-selectivity than did Conditions II. However, the reaction of **1f** with formaldehyde, which was performed by bubbling gaseous formaldehyde into a mixture of **1f** and $TiCl_4$, exhibited low selectivity (Table III, entry 7). In the cases of **1d** and **1i**, both Conditions I and II generally exhibited excellent *cis*-selectivity. Moreover, high chemoselectivity was also observed; **1d** reacted with 1,4-cyclohexanedione *mono*-ethylene acetal (**24**) selectively at the ketone function (Table III, entries 13 and 14). No adduct derived from the reaction at the acetal function was detected, although a small amount of 1:2 adduct (dilactone) contaminated by a reaction with 1,4-cyclohexanedione which was probably generated by intermolecular transacetalization under the reaction conditions. Cyclopentanone required a longer reaction time and gave γ-lactones in relatively low yields (Table III, entries 6, 15 and 18). This may be due to a steric effect; the planarity of the cyclopentane ring causes a steric repulsion in a transition state. The reaction of **1d** with 1,3-dibenzyloxy-2-propanone (**23**) gave a significantly low *cis*-selectivity compared with that of other ketones (Table III, entry 10). This result means that the α-ether-oxygen plays an important role in the transition state (vide infra).

Isomerization of *cis*-γ-Lactones to *trans*-γ-Lactones. By the present reaction, *cis*-2,3-substituted-γ-lactones were obtained with high diastereoselectivity. In order to obtain *trans*-γ-lactones, the isomerization reaction of *cis*-γ-lactones was carried out. The reaction conditions employed for the isomerization of *cis*-3,4-substituted-γ-lactones (catalytic NaOEt in EtOH)[1] were also effective in this case, and *trans*-2,3-substituted-γ-lactones were isolated in good yields. The results are summarized in Table IV.

Table IV. Isomerization of *cis*-γ-Lactones to *trans*-γ-Lactones



cis-**6-22** *trans*-**6-22**

γ-lactone	equiv of NaOEt	time, h	*cis* : *trans*[a]	yield / %[b]
6	0.2	0.5	1:99	76
15	0.2	0.7	4:96	90
16	0.2	4	2:98[c]	91
17	0.1	4	2:98	90
18	0.2	1	6:94	82
19	0.2	20	13:87	70
20	0.2	4	1:99	98
22	0.4	4	5:95	82

[a] Determined by GC. [b] Isolated yield of *trans*-isomer [c] Determined by ^1H NMR.

Assignment of the Stereochemistry of γ-Lactones. As mentioned above, the major isomers of **6**, **15-20**, and **22** isomerized to the corresponding minor isomers. This result means that the major isomers of **6**, **15-20**, and **22** are thermodynamically less stable *cis*-isomers.

For **14**, the corresponding methyl ester is a known compound.[12] The ^{1}H NMR chemical shifts of the major and minor isomers of **14** were in good agreement with those of the corresponding *cis* and *trans* isomers of the methyl ester.[13]

For **7-13** and **21**, the ^{1}H NMR data indicated that the major isomers have the same relative stereochemistry as those of **6**, **14-20**, and **22** have. As shown in Table V, $^3J_{2\text{-}3}$s of the major isomers are 7.3-8.9 Hz, while $^3J_{2\text{-}3}$s of the minor isomers are 11.0-11.9 Hz, although for the minor isomers of **16**, **19** and **22** $^3J_{2\text{-}3}$s could not be obtained because of the overlap of H.2 and H.3 signals. In addition, for the major isomers, H.2 was found at a higher field than H.3, except **10-12**. On the other hand, for the minor isomers, H.2 was found at a lower field than H.3 or in a few cases (**16**, **19** and **22**) at the almost same position with H.3. Furthermore, in all cases the GC retention time of the major isomers was longer than that of the corresponding minor isomers, except **16** (the boiling point of **16** is too high to perform GC analysis). On the basis of these results, all of the major isomers have been found to have the same relative stereochemistry, *cis*-configuration.

Table V. Significant ^{1}H NMR Data of γ-Lactones 6 - 22

γ-lactone	*cis* (major)			*trans* (minor)		
	$^3J_{2\text{-}3}$, Hz	δ H.2, ppm	δ H.3, ppm	$^3J_{2\text{-}3}$, Hz	δ H.2, ppm	δ H.3, ppm
6	7.9	3.07	3.13	11.6	3.21	2.94
7	7.9	3.07	3.12	11.9	3.20	2.70
8	8.2	3.09	3.17	11.6	3.21	2.97
9	8.2	3.08	3.15	11.6	3.21	2.72
10	7.9	3.05	2.97	11.6	3.12	2.88
11	7.9	3.02	2.98	11.9	3.13	2.61
12	7.9	3.11	3.09	11.9	3.19	2.81
13	7.9	3.02	3.16	11.6	3.14	3.05
14	9.2	2.92	3.44	10.7	2.87	3.08
15	7.9	2.86	3.16	11.3	3.20	3.05
16	8.9	3.16	3.49	–	3.28-3.36	
17	7.6	2.85	3.14	11.6	3.19	2.78
18	7.6	2.86	3.12	11.6	3.20	2.86
19	7.6	2.80	3.19	–	3.10-3.21	
20	7.3	2.54	3.13	11.0	3.25	3.15
21	7.3	2.54	3.10	11.3	3.25	2.86
22	7.3	2.54	3.17	–	3.18-3.25	

Mechanistic Aspects. In order to detect a zwitterionic species, like **4**, we measured the ^1H and ^{13}C NMR spectra of a 1:1 mixture of **1i** and $TiCl_4$ in CD_2Cl_2 at -78 °C. Although the ^1H and ^{13}C NMR spectra showed the existence of a major species, it was not a ring-opened species but, rather, a $TiCl_4$-chelated species, as observed for the mixture of **1a** and $TiBr_4$.[1,14] Other than the major signals, minor signals were also observed, which might arise from a ring-opened species and/or *cis*-isomer, but could not be assigned. As described in the previous paper,[1] however, the existence of a ring-opened 1,3-zwitterion was strongly supported by the deep brown color of the solution of **1i** and $TiCl_4$.[15] Moreover, the cyclopropane ring-opening is consistent with the reports that the LA-promoted *cis,trans*-isomerization of related vicinally donor-acceptor substituted cyclopropanes proceeds through similar zwitterions.[16] The geometry of the enolate is considered to be *E* by a stereoselective ring-opening of $TiCl_4$-chelated cyclopropanes **1d-i** as described previously.[1] Although there is a possibility of S_E2-type mechanism,[17] we concluded that this reaction proceeded through a ring-opened 1,3-zwitterion also on the basis of the fact that the high *cis*-selectivity and the LA-dependence of diastereoselectivity observed for the reaction of **1a-c** with aldehydes and unsymmetrical ketones could not be well explained by the S_E2 mechanism.[1]

Although there have been several reports concerning the facial selectivity of electrophilic reactions toward α-chiral enolates,[18,19] there has been no report concerning enolates having a cationic substituent at a chiral center, like **4**. For enolates having a donor substituent at a chiral center, highly diastereoselective alkylation reactions have been reported.[19] Regarding these reactions, a perpendicular transition model was proposed (Fig. 1); the high diastereoselectivity was attributed to stereoelectronic and steric effects.[19,20] In this model, the donor-substituent is aligned perpendicularly to the enolate double bond, and an electrophile approaches antiperiplanar to this substituent, since the perpendicularly oriented electron-donating σ orbital makes the enolate more reactive by mixing with the π orbital. Between conformers **I** and **II** (Fig. 1), **I** is favored taking into account the steric repulsion between the R and double-bond moiety.

Upon assuming a perpendicular model to explain the observed diastereoselectivity for the reaction of **1d-i** with ketones, there are six possible conformers **A-F** (Fig. 2). Considering the electron-withdrawing character of the cationic group, conformer **E** is compatible with conformer **I** in Fig. 1. The observed diastereoselectivity, however, is opposite to that predicted from conformer **E**. In this reaction, therefore, another effect would control the diastereoselectivity. That effect may be an electronic effect, such as electronic repulsion between the cationic substituent and the partially positively charged carbonyl carbon of a ketone. Since in conformer **C**, the cationic substituent is aligned antiperiplanar to the approaching ketone, the electronic

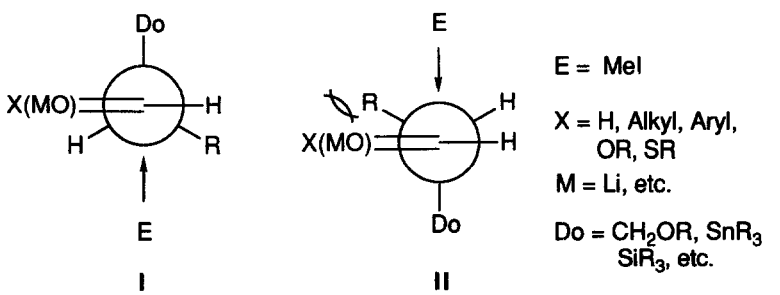


Fig. 1. Perpendicular model proposed for the alkylation reactions of enolates having a donor substituent at the chiral center

repulsion is minimized among conformers **A-C**, which can give the corresponding *cis*-isomer. As mentioned in the previous paper,[1] this reaction is considered to proceed through a cyclic transition state like **25**. The coordination of the ketone toward Ti highly polarizes the carbonyl group, and, consequently, the electronic effect becomes rather serious. Moreover, conformer **C** is favored on the basis of steric effect because the bulkiest cationic substituent occupies the anti-position. Therefore, conformer **C** is the most favorable, which is compatible with the observed diastereoselectivity.[21]

The solvent dependence of the diastereoselectivity observed for the reaction of 3-methylcyclopropane **1f** (Table II) exhibits the importance of the solvation of the cationic substituent. The solvation decreases the cationic character of the substituent while increases the steric bulkiness of the substituent. In the reaction of **1f**

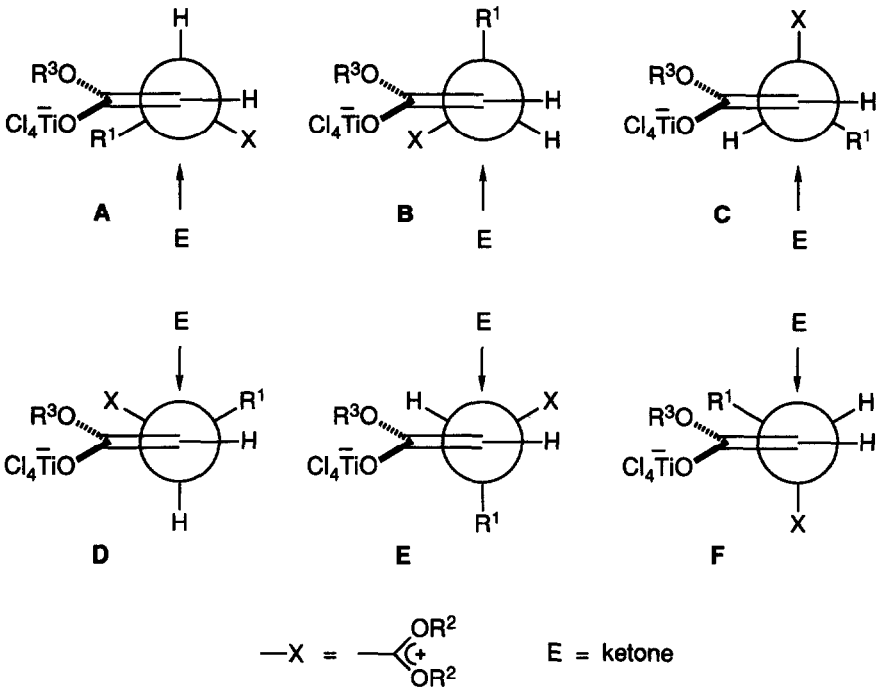
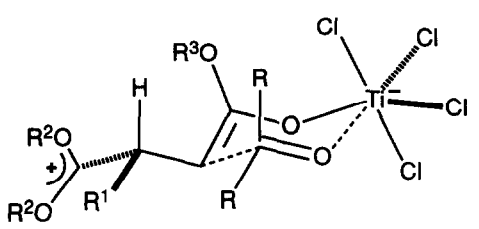
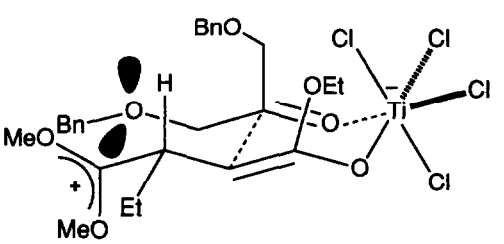


Fig. 2. Perpendicular model for the reaction of **1d-i** with a ketone





in a non-polar solvent, the deference in energy between conformers **C** and **F** is relatively small. In contrast, when the cationic substituent is solvated with a polar solvent, CH_3CN, the increased steric bulkiness of the cationic substituent causes a slight anticlockwise rotation of the chiral center, and makes the steric repulsion between the R^1 and enolate moiety in conformer **F** more serious. Consequently, conformer **C** becomes more favorable, resulting in the higher *cis*-selectivity.

The decreased selectivity in the reaction of **1d** with **23** can be explained by considering the participation of the transition structure **26** to some extent. The lone pair of an ether oxygen of **23** can stabilize the cation center, as depicted in **26**; in this case the preferred face of the enolate double bond becomes opposite to the case of **25**.

CONCLUSION

In summary, it has become clear that the $TiCl_4$-promoted ring-opening aldol-type reaction of 3-alkyl-2,2-dialkoxycyclopropanecarboxylic esters **1d-i** with symmetrical ketones proceeds with high diastereoselectivity to give *cis*-2,3-substituted-γ-lactones in good yields. The diastereoselectivity of the reaction of 3-ethyl- and 3-isopropylcyclopropane, **1d** and **1i**, hardly depends on the reaction conditions, whereas the diastereoselectivity of 3-methylcyclopropane depends on the reaction conditions, especially the solvent. The high diastereoselectivity was attributed to the intermediacy of 1,3-zwitterion **4**; the cationic substituent at the chiral center plays an important role in the transition state. *trans*-γ-Lactones were also obtained in good yields by the isomerization of *cis*-lactones.

EXPERIMENTAL SECTION

General Methods. The given boiling points for γ-lactones refer to the oven temperature (ot) upon bulb-to-bulb distillation. The melting points are not corrected. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ with Me_4Si as an internal standard; *J* values are given in Hz. GC analysis was performed with a 25-m OV-1701 fused silica capillary column.

All moisture-sensitive reactions were carried out under an argon atmosphere. All ketones were purchased from commercial suppliers or synthesized by standard methods. CH_2Cl_2 was distilled from P_2O_5 and then from CaH_2, and stored over MS 4Å. CH_3CN was distilled from CaH_2 and stored over MS 3Å. Toluene was distilled from CaH_2 and stored over Na. Flash column chromatography was performed with E. Merck silica gel 60 (230-400 mesh).

Synthesis of Cyclopropanes 1d-i. Cyclopropanes **1d-i**[8] were similarly prepared as described previously for the preparation of cyclopropane **1a**.[1]

Methyl 2,2-dimethoxy-3-methylcyclopropanecarboxylate (1g). 1,1-Dimethoxypropene[22] (8.5 g, 83 mmol) was allowed to react with methyl diazoacetate (6.4 g, 64 mmol) in the presence of $Cu(acac)_2$ (67 mg, 0.25 mmol) to afford **1g**[9,10] (7.7 g, 69%); bp 55-55.5 °C (1.1 Torr). IR(neat): 2955, 1740, 1170. ***trans*-1g**; ^1H NMR: δ 1.18 (3, d, *J* = 6.4, CH_3.3), 1.65 (1, d, *J* = 6.7, *H*.1), 1.99 (1, quint, *J* = 6.4, *H*.3), 3.36 (3, s, OCH_3), 3.42 (3, s, OCH_3), 3.69 (3, s, CO_2CH_3). EI-MS: *m/z* 174 (M^+, 3), 159 (14), 115 (100), 69 (26), 59 (19). HRMS: calcd for $C_8H_{14}O_4$ 174.0892, found 174.0893.

1,1-Dimethylethyl 2,2-dimethoxy-3-methylcyclopropanecarboxylate (1h). 1,1-Dimethoxypropene[22] (4.0 g, 39 mmol) was allowed to react with 1,1-dimethylethyl diazoacetate (5.0 g, 35 mmol) in the presence of $Cu(acac)_2$ (37 mg, 0.14 mmol) to afford **1h**[9,10] (4.4 g, 58%); bp 47-49 °C (0.4

Torr). IR(neat): 2980, 1730, 1150. ***trans*-1h**; ^{1}H NMR: δ 1.17 (3, d, *J* = 6.4, C*H*$_3$.3), 1.46 (9, s, C(C*H*$_3$)$_3$), 1.57 (1, d, *J* = 6.4, *H*.1), 1.89 (1, quint, *J* = 6.4, *H*.3), 3.35 (3, s, OC*H*$_3$), 3.41 (3, s, OC*H*$_3$). EI-MS: *m/z* 216 (M^+, 1.3), 160 (14), 129 (16), 115 (100), 69 (16), 57 (25). HRMS: calcd for $C_{11}H_{20}O_4$ 216.1362, found 216.1342.

Ethyl 2,2-dimethoxy-3-(1-methylethyl)cyclopropanecarboxylate (1i). 1,1-Dimethoxy-3-methyl-1-butene[23] (1.7 g, 13 mmol) was allowed to react with ethyl diazoacetate (1.1 g, 9.6 mmol) in the presence of Cu(acac)$_2$ (10 mg, 0.04 mmol) to afford **1i**[9,10] (1.0 g, 48%); bp 46-47 °C (0.4 Torr). ^{1}H NMR data for *trans*- and *cis*-isomers were obtained from the spectrum of their mixture. The coupling constant for the signal (δ = 1.03) of the *cis*-isomer could not be determined because one of the doublet peaks overlapped with a signal of the *trans*-isomer. IR(neat): 2960, 1735, 1175, 1160. ***trans*-1i**; ^{1}H NMR: δ 0.99 (3, d, *J* = 6.7, CH(C*H*$_3$)CH$_3$), 1.05 (3, d, *J* = 6.7, CH(CH$_3$)C*H*$_3$), 1.26 (3, t, *J* = 7.2, CO$_2$CH$_2$C*H*$_3$), 1.37-1.48 (1, m, C*H*(CH$_3$)$_2$), 1.67-1.72 (2, m, *H*.1, *H*.3), 3.37 (3, s, OC*H*$_3$), 3.42 (3, s, OC*H*$_3$), 4.14 (2, q, *J* = 7.2, CO$_2$C*H*$_2$CH$_3$). EI-MS: *m/z* 216 (M^+,1), 173 (100), 143 (87), 113 (20). HRMS: calcd for $C_{11}H_{20}O_4$ 216.1362, found 216.1354. ***cis*-1i**; ^{1}H NMR: δ 0.90 (3, d, *J* = 6.4, CH(C*H*$_3$)CH$_3$), 1.03 (3, d, CH(CH$_3$)C*H*$_3$), 1.26 (3, t, *J* = 7.0, CO$_2$CH$_2$C*H*$_3$), 1.34 (1, t, *J* = 10.6, *H*.3), 1.98 (1, d, *J* = 10.4, *H*.1), 2.28 (1, sept d, *J* = 6.7, 10.8, C*H*(CH$_3$)$_2$), 3.33 (3, s, OC*H*$_3$), 3.37 (3, s, OC*H*$_3$), 4.16 (2, q, *J* = 7.2, CO$_2$C*H*$_2$CH$_3$). EI-MS: *m/z* 201 (M^+ - CH$_3$, 3), 173 (100), 143 (75), 113 (30). HRMS: calcd for $C_{11}H_{20}O_4$ 216.1362, found 216.1317.

General Procedure for the Reaction of Cyclopropanes 1d-i with Ketones. Method A; To a stirred 0.2-0.3 M solution of **1d-i** (1.1 equiv)[24] and a ketone (0.3-1.5 mmol) in CH_2Cl_2 was added drop by drop a 0.7-1.5 M solution of $TiCl_4$ (1.1 equiv) in CH_2Cl_2 at -78 °C. After being stirred for 2h, the reaction was quenched at the same temperature by adding a 1:1 mixture of H_2O/THF (1-1.5 ml). The mixture was then stirred vigorously for 15 min. After removing the cooling bath, H_2O (3 ml) was added, and the mixture was allowed to warm up to rt. The solution was extracted with CH_2Cl_2 (3 × 10 ml), and the combined extracts were dried over Na_2SO_4. The mixture was filtered through a short pad of silica gel and then concentrated under reduced pressure to give a crude product, which consisted mainly of hydroxy diester. The crude product was dissolved in dry toluene (5-15 ml); a catalytic amount of *p*-toluenesulfonic acid (TsOH) was added to this solution (for **1h**, pyridinium *p*-toluenesulfonate (PPTS) was used instead of TsOH in order to prevent the cleavage of ^{t}Bu ester). After being stirred for 30 min-1 h at 80 °C, the solvent was removed under reduced pressure. The residue was dissolved in a 1:1 mixture of hexane/EtOAc and filtered through a short pad of aluminum oxide in order to remove TsOH. After evaporation of the solvent, the crude product was subjected to GC analysis to determine the *cis*:*trans* ratio. The crude product was purified by bulb-to-bulb distillation and/or flash column chromatography.

Method B and method C are different only in the addition order of the substrates as described in text.

The reaction in CH_3CN: To a stirred 0.7-1.5 M solution of $TiCl_4$ (1.1 equiv of ketone) in CH_2Cl_2 was added dry CH_3CN (1-3 ml) at rt. The resulting yellow solution was cooled to -45 °C. To this mixture was added a solution of a ketone (0.3-1.5 mmol) in dry CH_3CN (1-3 ml). After being stirred for 10-20 min at the same temperature, a solution of **1** (1.1 equiv) in dry CH_3CN (1-3 ml) was added drop by drop to this mixture. The work-up procedure is the same as that mentioned above.

In all cases, the *trans*-isomer has a higher *Rf* than does *cis*-isomer.

General Procedure for Isomerization of *cis*-γ-Lactones to *trans*-γ-Lactones. To a stirred solution of the *cis*-γ-lactone (0.2-0.3 mmol) in dry EtOH (1-1.5 ml) was added an EtOH solution of NaOEt (0.14 M) at room temperature (the amount of NaOEt and reaction time are listed in Table IV). The reaction

mixture was stirred at room temperature and quenched by adding a saturated solution of NH_4Cl (1 ml). The mixture was extracted by toluene (3 × 10 ml), and the combined extracts were dried over Na_2SO_4. The solution was filtered through a short pad of silica gel and then concentrated under reduced pressure. The crude product was subjected to GC analysis and then purified by flash column chromatography. In the case of **18**, the reaction mixture was diluted with brine (5 ml) and water (5 ml) and extracted by toluene, without quenching with a saturated solution of NH_4Cl.

3-(Ethoxycarbonyl)-2-methyl-4-propyl-4-heptanolide (6). ot 165 °C (1.2 Torr). The isomeric mixture of **6** was separated by column chromatography (5% EtOAc-hexane). ***cis*-6**; mp 62.0-62.5 °C. IR(KBr): 1775, 1725. ^{1}H NMR: δ 0.91 (3, t, J = 7.3, $(CH_2)_2CH_3$), 0.94 (3, t, J = 7.3, $(CH_2)_2CH_3$), 1.24 (3, d, J = 6.7, CH_3.2), 1.29 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.33-1.48 (4, m), 1.50-1.85 (4, m), 3.07 (1, qd, J = 6.7, 7.6, H.2), 3.13 (1, d, J = 7.9, H.3), 4.18-4.24 (2, m, $CO_2CH_2CH_3$). EI-MS: m/z 213 (M^+ - C_3H_7, 42), 185 (36), 71 (100), 69 (51), 43 (57). Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.43; H, 9.29. ***trans*-6**; IR(neat): 1785, 1740. ^{1}H NMR: δ 0.88 (3, t, J = 7.3, $(CH_2)_2CH_3$), 0.96 (3, t, J = 7.3, $(CH_2)_2CH_3$), 1.26 (3, d, J = 7.0, CH_3.2), 1.30 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.34-1.51 (4, m), 1.53-1.66 (2, m), 1.68-1.79 (1, m), 1.84-1.94 (1, m), 2.94 (1, d, J = 11.6, H.3), 3.21 (1, qd, J = 7.3, 11.6, H.2), 4.15-4.26 (2, m, $CO_2CH_2CH_3$). EI-MS: m/z 213 (M^+ - C_3H_7, 45), 185 (46), 71 (100), 69 (55), 43 (63). Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.34; H, 9.32.

Cyclohexanespiro-4'-[3'-(ethoxycarbonyl)-2'-methyl-4'-butanolide] (7). The isomeric mixture of **7** was separated by column chromatography (6% EtOAc-hexane). ***cis*-7**; mp 78-78.5 °C. IR(KBr): 1775, 1720. ^{1}H NMR: δ 1.25 (3, d, J = 6.4, CH_3.2), 1.29 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.51-1.77 (8, m), 1.80-1.90 (2, m), 3.07 (1, qd, J = 7.0, 7.9, H.2), 3.12 (1, d, J = 7.9, H.3), 4.15-4.26 (2, m, $CO_2CH_2CH_3$). EI-MS: m/z 240 (M^+, 5), 167 (17), 142 (25), 69 (100), 55 (48). Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.99; H, 8.45. ***trans*-7**; mp 49.5-50.5 °C. IR(KBr): 1770, 1735. ^{1}H NMR: δ 1.15-1.25 (2, m), 1.26 (3, d, J = 7.0, CH_3.2), 1.32 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.57-1.82 (7, m), 1.88-1.98 (1, m), 2.70 (1, d, J = 11.9, H.3), 3.20 (1, qd, J = 7.0, 11.9, H.2), 4.16-4.32 (2, m, $CO_2CH_2CH_3$). EI-MS: m/z 240 (M^+, 2), 142 (27), 123 (27), 69 (100), 55 (59). HRMS: calcd for $C_{13}H_{20}O_4$ 240.1362, found 240.1387.

3-(Methoxycarbonyl)-2-methyl-4-propyl-4-heptanolide (8). The isomeric mixture of **8** was separated by column chromatography (6% EtOAc-hexane). ***cis*-8**; mp 42.5-43 °C. IR(KBr): 1770, 1735. ^{1}H NMR: δ 0.91 (3, t, J = 7.3, $(CH_2)_2CH_3$), 0.95 (3, t, J = 7.3, $(CH_2)_2CH_3$), 1.23 (3, d, J = 7.0, CH_3.2), 1.25-1.47 (4, m), 1.54-1.63 (2, m), 1.68-1.80 (2, m), 3.09 (1, qd, J = 7.1, 8.1, H.2), 3.17 (1, d, J = 8.2, H.3), 3.73 (3, s, CO_2CH_3). EI-MS: m/z 211 (M^+ - OCH_3, 1), 199 (30), 171 (21), 71 (100), 69 (39), 43 (52), 41 (31). HRMS: calcd for $C_{13}H_{22}O_4$ 242.1518, found 242.1505. ***trans*-8**; IR(neat): 1780, 1740. ^{1}H NMR: δ 0.89 (3, t, J = 7.2, $(CH_2)_2CH_3$), 0.97 (3, t, J = 7.3, $(CH_2)_2CH_3$), 1.26 (3, d, J = 7.0, CH_3.2), 1.28-1.48 (5, m), 1.54-1.63 (1, m), 1.69-1.77 (1, m), 1.86-1.94 (1, m), 2.97 (1, d, J = 11.6, H.3), 3.21 (1, qd, J = 7.0, 11.6, H.2), 3.77 (3, s, CO_2CH_3). EI-MS: m/z 211 (M^+ - OCH_3, 1), 199 (40), 171 (31), 71 (100), 69 (43), 43 (57), 41 (36). HRMS: calcd for $C_{13}H_{22}O_4$ 242.1518, found 242.1514.

Cyclohexanespiro-4'-[3'-(methoxycarbonyl)-2'-methyl-4'-butanolide] (9). The isomeric mixture of **9** was separated by column chromatography (petroleum ether-CH_2Cl_2-EtOAc 20:3:2). ***cis*-9**; mp 115-116 °C. IR(KBr): 1780, 1720. ^{1}H NMR: δ 1.24 (3, d, J = 6.7, CH_3.2), 1.32-1.43 (1, m), 1.50-1.76 (7, m), 1.76-1.91 (2, m), 3.08 (1, qd, J = 7.0, 8.0, H.2), 3.15 (1, d, J = 8.2, H.3), 3.73 (3, s, CO_2CH_3). EI-MS: m/z 226 (M^+, 3), 128 (34), 69 (100), 55 (62), 41 (57). Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.64; H, 7.93. ***trans*-9**; mp 94.5-95.5 °C. IR(KBr): 1765, 1730. ^{1}H NMR: δ 1.15-

1.20 (2, m), 1.27 (3, d, J = 7.0, CH_3.2), 1.58-1.82 (7, m), 1.89-1.97 (1, m), 2.72 (1, d, J = 11.6, H.3), 3.21 (1, qd, J = 7.0, 11.9, H.2), 3.79 (3, s, CO_2CH_3). EI-MS: m/z 226 (M^+, 1.6), 128 (35), 69 (100), 55 (74), 41 (64). HRMS: calcd for $C_{12}H_{18}O_4$ 226.1205, found 226.1172.

3-[(1,1-dimethylethoxy)carbonyl]-2-methyl-4-propyl-4-heptanolide (10). ot 180 °C (1.5 Torr). The isomeric mixture of **10** was separated by column chromatography (3-5% EtOAc-hexane). ***cis*-10**; mp 102-103 °C. IR(KBr): 1780, 1710. ^{1}H NMR: δ 0.92 (3, t, J = 7.3, $(CH_2)_2CH_3$), 0.93 (3, t, J = 7.3, $(CH_2)_2CH_3$), 1.26 (3, d, J = 6.7, CH_3.2), 1.30-1.44 (4, m), 1.49 (9, s, $C(CH_3)_3$), 1.52-1.60 (1, m), 1.63-1.76 (2, m), 1.81-1.90 (1, m), 2.97 (1, d, J = 7.9, H.3), 3.05 (1, qd, J = 6.9, 7.8, H.2). EI-MS: m/z 241 (M^+ - C_3H_7, 2), 185 (31), 69 (37), 57 (100), 41 (33). Anal. Calcd for $C_{16}H_{28}O_4$: C, 67.57; H 9.93. Found: C, 67.45; H, 10.07. ***trans*-10**; mp 52-53 °C. IR(KBr): 1775, 1720. ^{1}H NMR: δ 0.89 (3, t, J = 7.0, $(CH_2)_2CH_3$), 0.96 (3, t, J = 7.3, $(CH_2)_2CH_3$), 1.25 (3, d, J = 7.0, CH_3.2), 1.32-1.54 (5, m), 1.49 (9, s, $C(CH_3)_3$), 1.60-1.68 (1, m), 1.73 (1, ddd, J = 5.3, 11.3, 14.2), 1.86 (1, ddd, J = 4.9, 11.3, 14.2), 2.88 (1, d, J = 11.6, H.3), 3.12 (1, qd, J = 7.0, 11.6, H.2). EI-MS: m/z 241 (M^+ - C_3H_7, 2), 185 (56), 69 (42), 57 (100), 41 (34). Anal. Calcd for $C_{16}H_{28}O_4$: C, 67.57; H 9.93. Found: C, 67.76; H, 10.17.

Cyclohexanespiro-4'-[3'-[(1,1-dimethylethoxy)carbonyl]-2'-methyl-4'-butanolide] (11). ot 190 °C (2 Torr). The isomeric mixture of **11** was separated by column chromatography (5-10% EtOAc-hexane). ***cis*-11**; mp 103.5-104.5 °C. IR(KBr): 1780, 1715. ^{1}H NMR: δ 1.28 (3, d, J = 6.7, CH_3.2), 1.34-1.78 (8, m), 1.49 (9, s, $C(CH_3)_3$), 1.78-1.94 (2, m), 2.98 (1, d, J = 7.9, H.3), 3.02 (1, qd, J = 6.9, 7.8, H.2). EI-MS: m/z 213 (4), 212 (4), 99 (13), 69 (39), 57 (100), 41 (46). Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 66.96; H, 9.20. ***trans*-11**; mp 91-92 °C. IR(KBr): 1770, 1730. ^{1}H NMR: δ 1.10-1.35 (2, m), 1.25 (3, d, J = 7.0, CH_3.2), 1.50 (9, s, $C(CH_3)_3$), 1.58-1.82 (7, m), 1.88-1.97 (1, m), 2.61 (1, d, J = 11.9, H.3), 3.13 (1, qd, J = 7.0, 11.9, H.2). EI-MS: m/z 213 (3), 212 (6), 194 (11), 99 (20), 69 (42), 57 (100), 41 (53). Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 66.81; H, 9.06.

3-(Ethoxycarbonyl)-2,4-dimethyl-4-pentanolide (12). ot 195 °C (9 Torr). The isomeric mixture of **12** was separated by column chromatography (5-16% EtOAc-hexane). ***cis*-12**; IR(neat): 1770, 1730. ^{1}H NMR: δ 1.28 (3, d, J = 6.4, CH_3.2), 1.30 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.47 (6, s, $C(CH_3)_2$), 3.09 (1, d, J = 7.9, H.3), 3.11 (1, qd, J = 6.4, 7.9, H.2), 4.18-4.27 (2, m, $CO_2CH_2CH_3$). EI-MS: m/z 185 (M^+ - CH_3, 6), 83 (60), 69 (100), 43 (78), 41 (42). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.99; H, 8.05. Found: C, 59.78; H, 8.04. ***trans*-12**; IR(neat): 1780, 1730. ^{1}H NMR: δ 1.28 (3, d, J = 7.0, CH_3.2), 1.28 (3, s, $C(CH_3)CH_3$), 1.31 (3, t, J = 7.0, $CO_2CH_2CH_3$), 1.62 (3, s, $C(CH_3)CH_3$), 2.81 (1, d, J = 11.9, H.3), 3.19 (1, qd, J = 7.0, 11.9, H.2), 4.17-4.31 (2, m, $CO_2CH_2CH_3$). EI-MS: m/z 185 (M^+ - CH_3, 9), 83 (80), 69 (100), 43 (71), 41 (49). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.99; H, 8.05. Found: C, 60.27; H, 8.30.

3-(Ethoxycarbonyl)-2-methyl-4-butanolide-4-spirocyclopentane (13). ot 125-130 °C (0.3 Torr). The isomeric mixture of **13** was separated by column chromatography (4-5% acetone-hexane). ***cis*-13**; IR(neat): 1780, 1740. ^{1}H NMR: δ 1.25 (3, d, J = 7.3, CH_3.2), 1.29 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.68-1.80 (4, m), 1.80-1.94 (2, m), 1.96-2.10 (2,m), 3.02 (1, quint, J = 7.3, H.2), 3.16 (1, d, J = 7.9, H.3), 4.18-4.24 (2, m, $CO_2CH_2CH_3$). EI-MS: m/z 226 (M^+, 10), 153 (32), 142 (37), 109 (26), 69 (100). HRMS: calcd for $C_{12}H_{18}O_4$ 226.1205, found 226.1238. ***trans*-13**; IR(neat): 1780, 1740. ^{1}H NMR: δ 1.28 (3, d, J = 7.0, CH_3.2), 1.30 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.51-1.63 (2, m), 1.63-1.75 (2, m), 1.75-1.90 (2, m), 2.00-2.19 (2, m), 3.05 (1, d, J = 11.6, H.3), 3.14 (1, dq, J = 7.0, 11.6, H.2), 4.18-4.27 (2, m, $CO_2CH_2CH_3$). EI-MS: m/z 226 (M^+, 20), 197 (38), 180 (46), 153 (38), 142 (38), 109 (54), 69 (100). HRMS: calcd for $C_{12}H_{18}O_4$ 226.1205, found 226.1192.

3-(Ethoxycarbonyl)-2-methyl-4-pentanolide (14). The isomeric mixture of **14** was separated by column chromatography (petroleum ether-CH_2Cl_2-EtOAc 20:5:2). ***cis*-14**; IR(neat): 1775, 1730. ^{1}H NMR: δ 1.25 (3, d, J = 7.3, CH_3.2), 1.29 (3, t, J = 7.2, $CO_2CH_2CH_3$), 2.92 (1, qd, J = 7.3, 9.2, H.2), 3.44 (1, ddd, J = 4.3, 7.0, 9.2, H.3), 4.19-4.27 (2, m, $CO_2CH_2CH_3$), 4.34 (1, dd, J = 7.0, 9.5, H.4), 4.52 (1, dd, J = 4.3, 9.5, H.4). EI-MS: m/z 172 (M^+, 15), 127 (60), 100 (100), 69 (73), 55 (93). HRMS: calcd for $C_8H_{12}O_4$ 172.0736, found 172.0740. ***trans*-14**; IR(neat): 1780, 1735. ^{1}H NMR: δ 1.30 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.37 (3, d, J = 7.3, CH_3.2), 2.87 (1, qd, J = 7.3, 10.7, H.2), 3.08 (1, ddd, J = 8.5, 9.5, 10.7, H.3), 4.20-4.26 (2, m, $CO_2CH_2CH_3$), 4.27 (1, t, J = 9.7, H.4), 4.49 (1, t, J = 8.9, H.4). EI-MS: m/z 172 (M^+, 4), 127 (35), 100 (26), 69 (39), 55 (100). HRMS: calcd for $C_8H_{12}O_4$ 172.0736, found 172.0741.

3-(Ethoxycarbonyl)-2-ethyl-4-propyl-4-heptanolide (15). The isomeric mixture of **15** was separated by column chromatography (petroleum ether-CH_2Cl_2-EtOAc 20:5:3). ***cis*-15**; mp 52.5-53 °C. IR(KBr): 1770, 1760, 1720. ^{1}H NMR: δ 0.91 (3, t, J = 7.3, $(CH_2)_2CH_3$), 0.94 (3, t, J = 7.3, $(CH_2)_2CH_3$), 1.00 (3, t, J = 7.5, $CHCH_2CH_3$), 1.29 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.30-1.82 (9, m), 1.90-2.01 (1, m), 2.86 (1, ddd, J = 5.5, 7.9, 9.5, H.2), 3.16 (1, d, J = 7.9, H.3), 4.21 (2, q, J = 7.0, $CO_2CH_2CH_3$). EI-MS: m/z 227 (M^+ - C_3H_7, 34), 199 (25), 83 (39), 71 (100), 43 (67). Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69. Found: C, 66.97; H, 9.72. ***trans*-15**; IR(neat): 1775, 1740. ^{1}H NMR: δ 0.88 (3, t, J = 7.0, $(CH_2)_2CH_3$), 0.95 (3, t, J = 7.5, $CHCH_2CH_3$), 0.97 (3, t, J = 7.3, $(CH_2)_2CH_3$), 1.23-1.50 (5, m), 1.30 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.55-1.91 (5, m), 3.05 (1, d, J = 11.3, H.3), 3.20 (1, ddd, J = 5.0, 7.2, 11.3, H.2), 4.18-4.26 (2, m, $CO_2CH_2CH_3$). EI-MS: m/z 242 (M^+ - CH_2=CH_2, 1), 227 (43), 199 (31), 153 (25), 83 (41), 71 (100), 43 (61). Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69. Found: C, 66.45; H, 9.85.

5-(Benzyloxy)-4-(benzyloxy)methyl-3-(ethoxycarbonyl)-2-ethyl-4-pentanolide (16). The isomeric mixture of **16** was separated by column chromatography (3.8-5.7% acetone-hexane). ***cis*-16**; IR(neat): 1790, 1730. ^{1}H NMR: δ 1.00 (3, t, J = 7.5, $CHCH_2CH_3$), 1.17 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.36-1.48 (1, m, $CHCHHCH_3$), 1.82-1.95 (1, m, $CHCHHCH_3$), 3.16 (1, dt, J = 5.5, 9.3, H.2), 3.49 (1, d, J = 8.9, H.3), 3.62 (1, d, J = 9.5), 3.63 (1, d, J = 10.4), 3.76 (1, d, J = 9.2), 3.83 (1, d, J = 10.4), 4.01 (1, qd, J = 7.2, 10.8, CO2CHH), 4.12 (1, qd, J = 7.2, 10.8, CO2CHH), 4.43 (1, d, J = 12.2), 4.45 (1, d, J = 12.2), 4.55 (2, s), 7.22-7.37 (10, m, 2 × Ph). EI-MS: m/z 335 (M^+ - CH_2Ph, 4), 229 (54), 201 (14), 105 (18), 91 (100). Anal. Calcd for $C_{25}H_{30}O_6$: C, 70.40; H, 7.09. Found: C, 70.31; H, 7.34. ***trans*-16**; IR(neat): 1780, 1735. ^{1}H NMR: δ 0.95 (3, t, J = 7.5, $CHCH_2CH_3$), 1.11 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.65-1.88 (2, m, $CHCH_2CH_3$), 3.28-3.36 (2, m, H.2, H.3), 3.58 (1, d, J = 9.8), 3.64 (1, d, J = 10.1), 3.67 (1, d, J = 11.0), 3.76 (1, d, J = 11.0), 3.94-4.08 (2, m, $CO_2CH_2CH_3$), 4.38 (1, d, J = 11.9), 4.46 (1, d, J = 11.9), 4.61 (1, d, J = 12.5), 4.62 (1, d, J = 12.5), 7.22-7.39 (10, m, 2 × Ph). EI-MS: m/z 335 (M^+ - CH_2Ph, 6), 229 (67), 201 (19), 105 (36), 91 (100). Anal. Calcd for $C_{25}H_{30}O_6$: C, 70.40; H, 7.09. Found: C, 70.10; H, 7.12.

Cyclohexanespiro-4'-[3'-(ethoxycarbonyl)-2'-ethyl-4'-butanolide] (17). The isomeric mixture of **17** was separated by column chromatography (petroleum ether-CH_2Cl_2-EtOAc 25:5:3). ***cis*-17**; mp 62-62.5 °C. IR(KBr): 1775, 1735. ^{1}H NMR: δ 1.00 (3, t, J = 7.6, $CHCH_2CH_3$), 1.28 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.35-2.04 (12, m), 2.85 (1, ddd, J = 5.5, 7.9, 9.5, H.2), 3.14 (1, d, J = 7.6, H.3), 4.10-4.25 (2, m, $CO_2CH_2CH_3$). EI-MS: m/z 254 (M^+, 10), 181 (46), 83 (100), 55 (89), 41 (63). Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.17; H, 8.62. ***trans*-17**; mp 52-52.5 °C. IR(KBr): 1775, 1730. ^{1}H NMR: δ 0.95 (3, t, J = 7.4, $CHCH_2CH_3$), 1.14-1.24 (2, m), 1.31 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.55-1.94 (10, m), 2.78 (1, d, J = 11.6, H.3), 3.19 (1, ddd, J = 5.2, 7.6, 11.6, H.2), 4.17-4.30 (2, m,

$CO_2CH_2CH_3$). EI-MS: *m/z* 254 (M^+, 4), 181 (37), 137 (45), 83 (100), 55 (97), 41 (66). Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 65.99; H, 8.77.

4,4-(Ethylenedioxy)cyclohexanespiro-4'-[3'-(ethoxycarbonyl)-2'-ethyl-4'-butanolide] (18). ot 180 °C (0.3-0.4 Torr). The isomeric mixture of **18** was separated by column chromatography (22-33% EtOAc-hexane). ***cis*-18**; mp 80-81 °C. IR(KBr): 1780, 1725. ^{1}H NMR: δ 1.00 (3, t, *J* = 7.5, $CHCH_2CH_3$), 1.28 (3, t, *J* = 7.2, $CO_2CH_2CH_3$), 1.49-1.74 (3, m), 1.80-2.04 (7, m), 2.86 (1, ddd, *J* = 5.5, 7.9, 9.5, *H*.2), 3.12 (1, d, *J* = 7.6, *H*.3), 3.92-4.00 (4, m, $O(CH_2)_2O$), 4.14-4.26 (2, m, $CO_2CH_2CH_3$). EI-MS: *m/z* 312 (M^+, 1), 239 (2), 99 (100), 86 (16), 55 (13). Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.75. Found: C, 61.58; H, 7.64. ***trans*-18**; mp 71-72 °C. IR(KBr): 1760, 1715. ^{1}H NMR: δ 0.96 (3, t, *J* = 7.5, $CHCH_2CH_3$), 1.32 (3, t, *J* = 7.2, $CO_2CH_2CH_3$), 1.54-1.74 (4, m), 1.77-1.95 (4, m), 2.00 (1, dt, *J* = 4.4, 13.5), 2.27 (1, dt, *J* = 4.7, 13.9), 2.86 (1, d, *J* = 11.6, *H*.3), 3.20 (1, ddd, *J* = 5.3, 7.5, 11.4, *H*.2), 3.90-3.98 (4, m, $O(CH_2)_2O$), 4.21 (1, qd, *J* = 7.2, 10.8, CO2CHH), 4.28 (1, qd, *J* = 7.2, 10.8, CO2CH*H*). EI-MS: *m/z* 312 (M^+, 2), 267 (2), 239 (2), 99 (100), 86 (15), 55 (12). HRMS: calcd for $C_{16}H_{24}O_6$ 312.1573, found 312.1556.

3-(Ethoxycarbonyl)-2-ethyl-4-butanolide-4-spirocyclopentane (19). ot 180-185 °C (9 Torr). The isomeric mixture of **19** was separated by column chromatography (5-6% EtOAc-hexane). ***cis*-19**; IR(neat): 1780, 1740. ^{1}H NMR: δ 1.02 (3, t, *J* = 7.4, $CHCH_2CH_3$), 1.28 (3, t, *J* = 7.0, $CO_2CH_2CH_3$), 1.44-1.55 (1, m), 1.61-2.08 (9, m), 2.80 (1, ddd, *J* = 5.3, 7.6, 9.6, *H*.2), 3.19 (1, d, *J* = 7.6, *H*.3), 4.21 (2, q, *J* = 7.1, $CO_2CH_2CH_3$). EI-MS: *m/z* 240 (M^+, 3), 167 (49), 83 (93), 55 (100), 41 (41). HRMS: calcd for $C_{13}H_{20}O_4$ 240.1362, found 240.1332. ***trans*-19**; IR(neat): 1780, 1740. ^{1}H NMR: δ 0.98 (3, t, *J* = 7.6, $CHCH_2CH_3$), 1.30 (3, t, *J* = 7.2, $CO_2CH_2CH_3$), 1.53-2.13 (10, m), 3.10-3.21 (2, m, *H*.2, *H*.3), 4.17-4.28 (2, m, $CO_2CH_2CH_3$). EI-MS: *m/z* 240 (M^+, 3), 167 (38), 83 (82), 55 (100), 41 (40). HRMS: calcd for $C_{13}H_{20}O_4$ 240.1362, found 240.1347.

3-(Ethoxycarbonyl)-2-(1-methylethyl)-4-propyl-4-heptanolide (20). The isomeric mixture of **20** was separated by column chromatography (2% EtOAc-hexane). ***cis*-20**; mp 53-53.5 °C. IR(KBr): 1760, 1715. ^{1}H NMR: δ 0.88 (3, d, *J* = 6.7, $CH(CH_3)CH_3$), 0.90 (3, t, *J* = 7.3, $(CH_2)_2CH_3$), 0.96 (3, t, *J* = 7.3, $(CH_2)_2CH_3$), 1.27 (3, d, *J* = 6.4, $CH(CH_3)CH_3$), 1.29 (3, t, *J* = 7.2, $CO_2CH_2CH_3$), 1.30-1.78 (8, m), 2.03-2.13 (1, m, $CH(CH_3)_2$), 2.54 (1, dd, *J* = 7.3, 10.4, *H*.2), 3.13 (1, d, *J* = 7.3, *H*.3), 4.22 (2, q, *J* = 7.2, $CO_2CH_2CH_3$). EI-MS: *m/z* 241 ($M^+ - C_3H_7$, 48), 213 (25), 97 (37), 71 (100), 43 (77). Anal. Calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.93. Found: C, 67.42; H, 9.69. ***trans*-20**; IR(neat): 1775, 1740. ^{1}H NMR: δ 0.88 (3, t, *J* = 7.2, $(CH_2)_2CH_3$), 0.95 (3, d, *J* = 7.0, $CH(CH_3)CH_3$), 0.96 (3, d, *J* = 7.0, $CH(CH_3)CH_3$), 0.97 (3, t, *J* = 7.3, $(CH_2)_2CH_3$), 1.10-1.90 (8, m), 1.30 (3, t, *J* = 7.2, $CO_2CH_2CH_3$), 2.19-2.29 (1, m, $CH(CH_3)_2$), 3.15 (1, d, *J* = 11.0, *H*.3), 3.25 (1, dd, *J* = 4.3, 11.3, *H*.2), 4.21 (2, q, *J* = 7.2, $CO_2CH_2CH_3$). EI-MS: *m/z* 241 ($M^+ - C_3H_7$, 44), 213 (23), 97 (34), 71 (100), 43 (81). HRMS: calcd for $C_{16}H_{28}O_4$ 284.1988, found 284.1973.

Cyclohexanespiro-4'-[3'-(ethoxycarbonyl)-2'-(1-methylethyl)-4'-butanolide] (21). ot 185 °C (2 Torr). The isomeric mixture of **21** was separated by column chromatography (5% EtOAc-hexane). ***cis*-21**; mp 82.5-83 °C. IR(KBr): 1770, 1725. ^{1}H NMR: δ 0.88 (3, d, *J* = 7.0, $CH(CH_3)CH_3$), 1.26 (3, d, *J* = 6.4, $CH(CH_3)CH_3$), 1.29 (3, t, *J* = 7.0, $CO_2CH_2CH_3$), 1.32-1.44 (1, m), 1.50-1.80 (8, m), 1.84-1.93 (1, m), 2.10 (1, sept d, *J* = 6.6, 10.2, $CH(CH_3)_2$), 2.54 (1, dd, *J* = 7.3, 10.4, *H*.2), 3.10 (1, d, *J* = 7.3, *H*.3), 4.19 (1, qd, *J* = 7.2, 10.8, CO2CHH), 4.23 (1, qd, *J* = 7.2, 10.8, CO2CH*H*). EI-MS: *m/z* 268 (M^+, 3), 127 (67), 97 (72), 55 (78), 41 (100). Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 67.42; H, 8.91. ***trans*-21**; IR(neat): 1775, 1735. ^{1}H NMR: δ 0.92 (3, d, *J* = 6.7, $CH(CH_3)CH_3$), 0.96 (3, d, *J* =

6.4, $CH(CH_3)CH_3$), 1.12-1.23 (2, m), 1.31 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.57-1.90 (8, m), 2.23 (1, d sept, J = 4.6, 6.6, $CH(CH_3)_2$), 2.86 (1, d, J = 11.3, *H*.3), 3.25 (1, dd, J = 4.6, 11.3, *H*.2), 4.22 (2, q, J = 7.2, $CO_2CH_2CH_3$). EI-MS: *m/z* 268 (M^+, 3), 127 (49), 97 (75), 69 (49), 55 (91), 41 (100). HRMS: calcd for $C_{15}H_{24}O_4$ 268.1675, found 268.1652.

3-(Ethoxycarbonyl)-2-(1-methylethyl)-4-butanolide-4-spirocyclopentane (22). ot 170-180 °C (1.2 Torr). The isomeric mixture of **22** was separated by column chromatography (5% EtOAc-hexane). ***cis*-22**; mp 70-71 °C. IR(KBr): 1775, 1725. ^{1}H NMR: δ 0.94 (3, d, J = 6.7, $CH(CH_3)CH_3$), 1.30 (3, d, J = 6.4, $CH(CH_3)CH_3$), 1.32 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.70-2.15 (9, m), 2.54 (1, dd, J = 7.2, 10.2, *H*.2), 3.17 (1, d, J = 7.3, *H*.3), 4.24 (2, q, J = 7.2, $CO_2CH_2CH_3$). EI-MS: *m/z* 212 (M^+ - CH_2=$CHCH_3$, 46), 139 (76), 97 (59), 55 (96), 41 (100). Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.01; H, 8.71. ***trans*-22**; IR(neat): 1780, 1740. ^{1}H NMR: δ 0.96 (3, d, J = 6.7, $CH(CH_3)CH_3$), 0.99 (3, d, J = 7.0, $CH(CH_3)CH_3$), 1.30 (3, t, J = 7.0, $CO_2CH_2CH_3$), 1.48-1.90 (6, m), 2.01-2.09 (2, m), 2.17-2.27 (1, m, $CH(CH_3)_2$), 3.18-3.25 (2, m, *H*.2, *H*.3), 4.22 (2, q, J = 7.2, $CO_2CH_2CH_3$). EI-MS: *m/z* 254 (M^+, 3), 212 (51), 139 (81), 97 (67), 55 (100), 41 (99). HRMS: calcd for $C_{14}H_{22}O_4$ 254.1518, found 254.1499.

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10. *Trans*:*cis* ratio of **1d-i**. **1d**: *trans*:*cis* = ca. 90:10; **1e-h**: *trans*:*cis* = ≥95:5; **1i**: *trans*:*cis* = ca. 70:30.
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