s, 2 H), 4.04 (s, 3 H), 4.01 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 150.0, 149.7, 132.4, 131.2, 130.6, 128.9, 128.8, 127.9, 127.3, 127.1, 126.9, 125.6, 125.5, 123.4, 121.5, 115.9, 101.9 (C_9 and C_{10}), 55.4 (2 OMe's).

Dibenz[*a*,*c*]anthracene (25). Treatment of **15** (0.141 g, 0.64 mmol) and chlorobenzene (0.072 g, 0.64 mmol) in THP (1 mL) with LTMP (2.6 mmol, 6 mL THP) gave **25** as yellow crystals; mp 202–205 °C from EtOH (lit.[23] 205 °C), 0.101 g (55% yield); ^{1}H NMR ($CDCl_3$) δ 9.11 (s, 2 H), 8.8–8.7 (m, 2 H), 8.65–8.55 (m, 2 H), 8.15–8.1 (m, 2 H), 7.7–7.6 (m, 6 H).

Tribenz[*a*,*c*,*h*]anthracene (26). This was made from **15** (0.100 g, 0.45 mmol), 1-bromonaphthalene (0.093 g, 0.45 mmol), THP (1 mL), and LTMP (0.95 mmol, 6 mL THP): yellow crystals of mp 227–228 °C from AcOH (lit.[24] 225–228 °C), 0.100 g (68% yield); ^{1}H NMR ($CDCl_3$) δ 9.90 (s, 1 H), 9.03 (s, 1 H), 8.94 (t, *J* = 8.7 Hz, 2 H), 8.8–8.7 (m, 1 H), 8.7–8.6 (m, 2 H), 8.6–8.0 (m, 9 H).

1,2-Dimethoxy-5-methylanthracene (27) and 1,2-Dimethoxy-8-methylanthracene (28). Reaction of **9** (0.749 g, 4.16 mmol) and 2-chlorotoluene (0.527 g, 4.16 mmol) in THP (5 mL) with LTMP (8.7 mmol, 8 mL THP) gave a mixture (0.439 g of a yellow oil, 42% yield) of **27** and **28** which were inseparable by flash chromatography or HPLC: ^{1}H NMR ($CDCl_3$) δ (isomer ratio 1.3:1) 8.80 (s, 0.44 H), 8.70 (s, 0.56 H), 8.54 (s, 0.56 H), 8.41 (s, 0.44 H), 8.0–7.75 (m, 2 H), 7.4–7.2 (m, 3 H), 4.18 (s, 1.3 H), 4.16 (s, 1.7 H), 4.05 (s, 3 H), 2.88 (s, 1.3 H), 2.82 (s, 1.7 H). An effort to designate **27** and **28** as the major isomer by NOE was inconclusive.

Reaction of 7 and 29 in the Presence of LTMP: *N*,*N*-Diisopropyl-5-chlorofluorenone-1-carboxamide (30). A mixture of **7** (1.00 g, 8.3 mmol) and **29**[16] (2.00 g, 8.3 mmol) in THP (8 mL) was added over 5 min to a refluxing solution of LTMP (17.0 mmol, 20 mL THP). After 30 min, workup, chromatography, and recrystallization from hexane afforded the pure fluorenone **30** as yellow plates; mp 260–261 °C, 0.269 g (19% yield).

Fluorenone **30** also was prepared by adding **29** (0.500 g, 2.10 mmol) in THP (5 mL) to a refluxing solution of LTMP (2.3 mmol, 5 mL THP): 0.133 g (37% yield) of mp 260–261 °C after workup and purification; ^{1}H NMR ($CDCl_3$) δ 8.16 (d, *J* = 7.7 Hz, 1 H), 7.6–7.5 (m, 2 H), 7.43 (d, *J* = 8.0 Hz, 1 H), 7.23 (d, *J* = 8.0 Hz, 1 H), 7.12 (d, *J* = 7.7 Hz, 1 H), 3.7–3.5 (m, 2 H), 1.73 (d, *J* = 6.8 Hz, 3 H), 1.58 (d, *J* = 6.8 Hz, 3 H), 1.10 (d, *J* = 3.2 Hz, 3 H), 1.08 (d, *J* = 3.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 191.3, 167.4, 152.1, 143.5, 140.2, 137.2, 136.3, 135.4, 130.4, 129.8, 129.1, 126.6, 123.8, 122.6, 51.2, 46.0, 20.9, 20.8, 20.4, 19.9.

Pentaphene (31). Reaction of **7** (2.00 g, 16.6 mmol) and *o*-dichlorobenzene (1.16 g, 7.9 mmol) in THP (8 mL) with LTMP (32.5 mmol, 30 mL THP) gave **31** as greenish crystals: mp 256–258 °C from AcOH (lit.[19] 257 °C), 0.439 g (20% yield); ^{1}H NMR ($CDCl_3$) δ 9.27 (s, 2 H), 8.28 (s, 2 H), 8.2–8.15 (m, 2 H), 8.1–8.0 (m, 2 H), 7.66 (s, 2 H), 7.6–7.55 (m, 4 H). The analogous reaction of 1,3,5-trichlorobenzene failed.

Registry No. **7**, 35447-99-5; **8**, 66947-61-3; **9**, 144493-71-0; **10**, 87046-36-4; **11**, 144493-72-1; **13**, 87180-87-8; **14**, 144493-73-2; **15**, 63165-30-0; **16**, 144493-74-3; **17**, 54458-84-3; **18**, 610-48-0; **19**, 144493-75-4; **20**, 144493-76-5; **21**, 144493-77-6; **22**, 142778-09-4; **23**, 56-55-3; **24**, 144493-78-7; **25**, 215-58-7; **26**, 215-26-9; **27**, 144493-79-8; **28**, 144493-80-1; **29**, 35306-66-2; **30**, 144493-81-2; **31**, 222-93-5; LTMP, 38227-87-1; 5,6-dimethoxybenzocyclobutenone, 81447-58-7; 5,6-(methylenedioxy)benzocyclobutenone, 118112-19-9; 9-bromophenanthrene, 573-17-1; ketene diethyl acetal, 2678-54-8; 4,6-dimethoxybenzocyclobutenone, 118112-18-8; 5-chloro-1,3-dimethoxybenzene, 7051-16-3; 3-bromoanisole, 2398-37-0; 2-chlorotoluene, 95-49-8; 2-chloro-1-(trifluoromethyl)benzene, 88-16-4; 4-chloro-3-methoxytoluene, 73909-16-7; 4-bromoveratrole, 2859-78-1; 1-bromonaphthalene, 90-11-9; chlorobenzene, 108-90-7; *o*-dichlorobenzene, 95-50-1.

Supplementary Material Available: Additional spectral (e.g., IR, MS, and HRMS) data, copies of ^{1}H and ^{13}C NMR spectra of new compounds, and details on other experiments noted in discussion (26 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Diastereoselective Ring-Opening Aldol-Type Reaction of 2,2-Dialkoxycyclopropanecarboxylic Esters with Carbonyl Compounds. 1. Synthesis of Cis 3,4-Substituted γ-Lactones[1]

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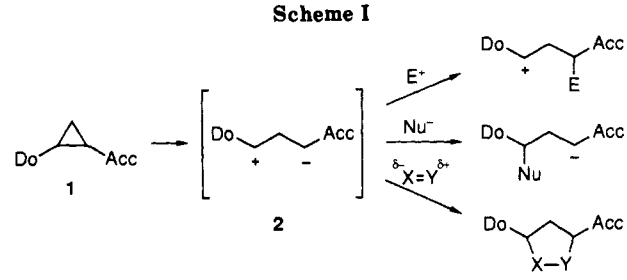
The Lewis acid-promoted reactions of 2,2-dialkoxycyclopropanecarboxylic esters **4a–c** with aldehydes and unsymmetrical ketones to give γ-lactones were investigated. $TiBr_4$ is an excellent catalyst and gives cis 3,4-substituted γ-lactones in good yields with high diastereoselectivity. $SnBr_4$ promotes the reaction of **4a–c** with aldehydes with high cis-selectivity, but does not promote the reaction of **4a** with unsymmetrical ketones. $ZrCl_4$ is moderately trans-selective in the reaction of **4a** with aldehydes, while being moderately cis-selective in the reaction of **4a** with unsymmetrical ketones. Cis γ-lactones can be converted into their trans-isomers by treatment with NaOEt in EtOH.

Introduction

Cyclopropanes activated by an electron-withdrawing or -donating group are susceptible to ring-opening reactions, and many types of activated cyclopropanes are used in organic synthesis as valuable building blocks.[2] Their utility was well demonstrated by their participation as three-carbon units into [3 + 2]-type reactions for syntheses of 5-membered carbo-[3] and heterocycles.[4] Among such activated cyclopropanes, vicinally donor–acceptor-substituted cyclopropane **1** is an equivalent of ring-opened

Scheme I



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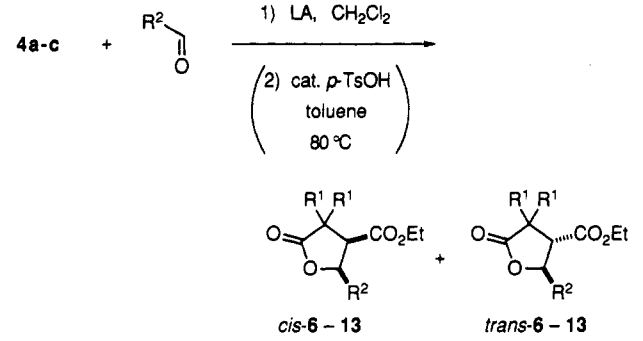
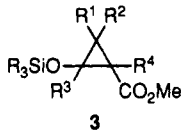
0022-3263/92/1957-7126$03.00/0

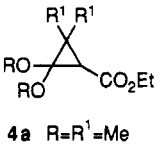
Scheme II



1,3-zwitterion **2**, which is expected to react with both electrophiles and nucleophiles. Although there are many examples of simple solvolytic ring-opening reactions of **1**,[5] relatively few examples are known that utilize **1** for carbon–carbon bond-forming reactions. An exception is the work of Reissig and co-workers, in which 2-[(trialkylsilyl)oxy]cyclopropanecarboxylic esters **3** were used for several types of ring-opening carbon–carbon bond-forming reactions.[5]



3



4a R=R¹=Me

4b R=Me, R¹=H

4c R=Et, R¹=H

In the course of our study to utilize small ring compounds in organic synthesis,[6] we have become interested in the reactivity of 2,2-dialkoxycyclopropanecarboxylic ester **4**. Because **4** has *two* electron-donating groups and one electron-withdrawing group, it is more susceptible to heterolytic ring-cleavage to a 1,3-zwitterion relative to **3**. Recently, we have found that **4** reacts with various carbon-electrophiles[7] and -nucleophiles[8] in the presence of a Lewis acid (LA).[9] In this paper we wish to report on the highly diastereoselective synthesis of 3,4-cis-substituted γ-lactones by the reaction of 3-unsubstituted or 3,3-dimethyl-2,2-dialkoxycyclopropanecarboxylic esters **4a–c** with aldehydes and unsymmetrical ketones.

Table I. Reaction of 4a with 3-Phenylpropanal in the Presence of Various LA[a]

entry	LA	temp (°C)	time (h)	yield[b] (%)	cis:trans[c]
1	$SnBr_4$	−78	4	50	99:1
2	$SnCl_4$	−78 to 0	1	60	97:3
3	$TiBr_4$		1	83	84:16
4	$TiCl_2(OTf)_2$		5	58	83:17
5	$TiCl_4$		0.5	88	78:22
6	$AlCl_3$		4	81	77:23
7	$SbCl_5$		1	*d*	71:29
8	TMSOTf	−78 to rt	50	*d*	69:31
9	$BF_3{\cdot}OEt_2$	−78 to 0	1.5	55	45:55
10	$MgBr_2{\cdot}OEt_2$	−78 to rt	24	9	41:59
11	$ZnBr_2$		6	67	37:63
12	$GaCl_3$	−78 to 0	1	78	36:64
13	$SnCl_2$	−78 to rt	72	*d*	35:65
14	$ZrCl_4$	−78	22	60	32:68
15	Et_2AlCl	−78 to 0	4	37	30:70
16	Bu_2SnBr_2	−78 to rt	10	no reaction	
17	$SiCl_4$		12	no reaction	
18	$GeCl_4$		19	no reaction	
19	$LiClO_4$		24	no reaction	

[a] The reaction was performed in CH_2Cl_2. **4a**:aldehyde:LA = 1.1:1:1.1. [b] Isolated yield. [c] Determined by GC. [d] Not determined.

Table II. Reaction of 4a–c with Aldehydes Promoted by $SnBr_4$, $TiBr_4$, and $ZrCl_4$[a]

4	R^2	LA	time (h)	product	yield[b] (%)	cis:trans[c]
4a	$PhCH_2CH_2$	$SnBr_4$	6	**6**	50	99:1
		$TiBr_4$	2		87	85:15
		$ZrCl_4$	22		60	32:68
	$CH_3(CH_2)_6$	$SnBr_4$	5	**7**	56	99:1
		$TiBr_4$	2		86	89:11
	$(CH_3)_2CH$	$TiBr_4$	2	**8**	87	95:5
	Ph	$SnBr_4$	2	**9**	63	97:3
		$TiBr_4$	2		91	98:2
	trans-PhCH=CH	$TiBr_4$	2	**10**	84	74:26
		$ZrCl_4$	8		53	21:79
4b	$PhCH_2CH_2$	$TiBr_4$	0.7	**11**	89	78:22
		$SnBr_4$	2.5		61	81:19
		$ZrCl_4$	2.5		70	53:47
	$(CH_3)_2CH$	$TiBr_4$	0.7	**12**	88	82:18
		$SnBr_4$	2.5		80	77:23
		$ZrCl_4$	2.5		65	49:51
	Ph	$TiBr_4$	0.7	**13**	87	85:15
		$SnBr_4$	2.5		72	79:21
		$ZrCl_4$	2		87	37:63
4c	$PhCH_2CH_2$	$TiBr_4$	0.5	**11**	91	82:18
	Ph	$TiBr_4$	0.5	**13**	93	80:20
		$SnBr_4$	3		80	88:12

[a] The reaction was performed in CH_2Cl_2 at −78 °C. **4a**:aldehyde:LA = 1.1:1:1.1. **4b** or **4c**:aldehyde:LA = 1.3:1:1.1.[11] [b] Isolated yield. [c] Determined by GC.

Results and Discussion

The Reaction of Cyclopropanes 4 with Aldehydes. Cyclopropanes **4a–c** were synthesized by the reaction of the corresponding ketene acetals with ethyl diazoacetate according to Wenkert's method.[10,11]

(1) A preliminary result of this work has been published: Saigo, K.; Shimada, S.; Hashimoto, Y.; Hasegawa, M. *Chem. Lett.* **1989**, 1293.

(2) For recent reviews, see: (a) Trost, B. M. *Top. Curr. Chem.* **1986**, *133*, 3. (b) Krief, A. *Top. Curr. Chem.* **1987**, *135*, 1. (c) Salaün, J. R. Y. *Top. Curr. Chem.* **1988**, *144*, 1. (d) Baird, M. S. *Top. Curr. Chem.* **1988**, *144*, 137. (e) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165. (f) Kuwajima, I.; Nakamura, E. *Top. Curr. Chem.* **1990**, *155*, 1. (g) Kostikov, R. R.; Molchanov, A. P.; Hopf, H. *Top. Curr. Chem.* **1990**, *155*, 41.

(3) For recent examples, see: (a) Beal, R. B.; Dombroski, M. A.; Snider, B. B. *J. Org. Chem.* **1986**, *51*, 4391. (b) Miura, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 5135. (c) Yamago, S.; Nakamura, E. *J. Am. Chem. Soc.* **1989**, *111*, 7285. (d) Singleton, D. A.; Church, K. M. *J. Org. Chem.* **1990**, *55*, 4780. (e) Komatsu, M.; Suehiro, I.; Horiguchi, Y.; Kuwajima, I. *Synlett* **1991**, 771. (f) Feldman, K. S.; Romanelli, A. L.; Ruckle, R. E., Jr.; Jean, G. *J. Org. Chem.* **1992**, *57*, 100.

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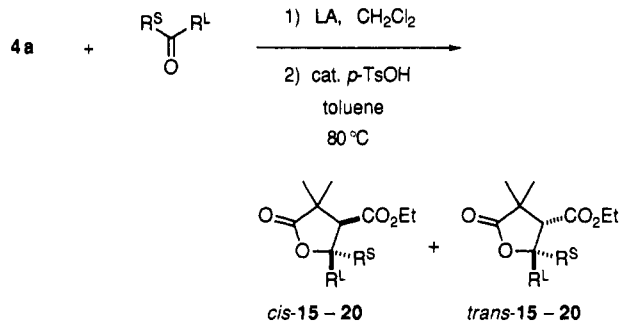
(8) Saigo, K.; Shimada, S.; Shibasaki, T.; Hasegawa, M. *Chem. Lett.* **1990**, 1093.

(9) Thermal ring-opening addition reactions of **4** have been reported. (a) Graziano, M. L.; Iesce, M. R. *J. Chem. Res., Synop.* **1987**, 362; *Miniprint* 2942. (b) Graziano, M. L.; Cimminiello, G. *J. Chem. Res. Synop.* **1989**, 42; *Miniprint* 446. (c) Graziano, M. L.; Chiosi, S. *J. Chem. Res., Synop.* **1989**, 44.

(10) (a) Alonso, M. E.; Jano, P.; Hernandez, M. I.; Greenberg, R. S.; Wenkert, E. *J. Org. Chem.* **1983**, *48*, 3047. (b) Graziano, M. L.; Scarpati, R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 289. (c) Graziano, M. L.; Iesce, M. R. *Synthesis* **1985**, 762.

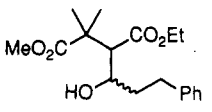
Table III. Reaction of 4a with Unsymmetrical Ketones[a]



entry	R^S	R^L	LA	time (h)	product	yield[b] (%)	cis:trans[c]
1	Me	n-C_8H_{17}	$TiBr_4$	5	15	80	74:26
2			$TiCl_4$	5.5		66	75:25
3		i-Bu	$TiBr_4$	14	16	93	91:9[d]
4			$SnBr_4$	14		0	
5			$ZrCl_4$	21		56	76:24[d]
6		i-Pr	$TiBr_4$	14	17	82	99:1
7			$TiCl_4$	14		59	98:2
8		CH=CH_2	$TiBr_4$	2.5	18	70	93:7
9[e]			$TiBr_4$	4		82	94:6
10			$ZrCl_4$	5.5		68	74:26
11		CH=CMe_2	$TiBr_4$	4.5	19	35	99:1
12[f]	n-Bu	i-Pr	$TiBr_4$	24	20	43	63:37

[a] The reaction was performed in CH_2Cl_2 at −78 °C. 4a:ketone:LA = 1.1:1:1.1. [b] Isolated yield. [c] Determined by GC. [d] Determined by ^1H NMR. [e] The reaction was performed at −94 °C. [f] The reaction mixture was allowed to warm to 0 °C.

When 4a and 3-phenylpropanal were treated with $TiCl_4$ in CH_2Cl_2 at −78 to 0 °C, a distinct color change was observed (dark brown to pale yellow), and γ-lactone 6 was obtained after an aqueous workup (88% yield, cis:trans = 78:22).[12] Although this reaction proceeded efficiently, even at −78 °C without warming to 0 °C, hydroxy diester 14 was obtained as a major product accompanied by a small amount of 6. Hydroxy diester 14 could be easily converted into 6 by treatment with a catalytic amount of p-toluenesulfonic acid in toluene at 80 °C. The diastereoselectivity of this reaction was not dependent on the solvent (toluene and MeCN gave almost the same cis–trans ratio of 6) but was significantly dependent upon the LA used (Table I).[13]



14

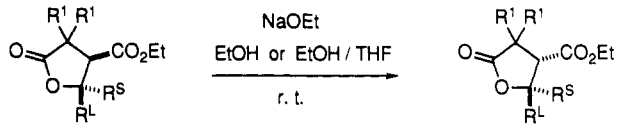
High cis-selectivity was observed for several bidentate LAs. These results indicate the intermediacy of a cyclic transition state for high cis-selectivity (vide infra, see Scheme V). On the basis of the diastereoselectivity and the chemical yield, $SnBr_4$, $TiBr_4$, and $ZrCl_4$ were selected as representative catalysts for the reactions of 4a–c with

(11) Cyclopropane 4a is stable, whereas 4b and 4c are relatively unstable. Unstable 4b and 4c were obtained with the contamination of a small amount of ketene acetal $(RO)_2C{=}CHCH_2CO_2Et$ (5) and gradually isomerized to 5 upon standing even at −20 °C.[10b] However, a small amount of 5 did not affect the reaction. We therefore used 4b and 4c as mixtures with 5 (see Experimental Section), although in the case of 4b most of the contaminated 5 could be removed by careful distillation.

(12) The reaction of 4a with 3-phenylpropanal did not occur under thermal conditions ($ClCH_2CH_2Cl$, reflux; CH_3CH_2CN, reflux; toluene, reflux; and neat, 120 °C).

(13) This reaction required 1 equiv of a LA. As shown in Table I, LAs with low solubility in CH_2Cl_2 were also effective; in these cases the LAs gradually dissolved in CH_2Cl_2 with the progress of the reaction, and the reaction mixtures became almost homogeneous at the end of the reaction.

Table IV. Epimerization of Cis γ-Lactones to Trans γ-Lactones



cis-6 – 13
cis-15 – 20
trans-6 –13
trans-15 –20

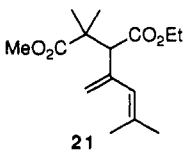
γ-lactone	equiv of NaOEt	time (h)	cis:trans[a]	yield (%)
6	0.2	7	8:92	86[b]
9	0.2	3	3:97	84[b]
10	0.2	3	4:96	83[b]
11	0.2	2	20:80	68[b]
15	4	42	21:79	91[c]
16	0.5	14	18:82[d]	quant[c]
17	3	72	5:95	91[c]
18	0.5	24	73:27	74[c]
19	4	72	59:41	quant[c]
20	5	96	4:96	85[c]

[a] Determined by GC. [b] Isolated yield of trans-isomer. [c] Isolated yield of an isomeric mixture. [d] Determined by ^1H NMR.

various aldehydes. The results are summarized in Table II. In the reaction of 4a, $SnBr_4$ generally exhibited very high cis-selectivity in 50–63% yields. $TiBr_4$ was also highly cis-selective with excellent yields, whereas $ZrCl_4$ showed some trans-selectivity. The reaction of less-congested 4b was generally less selective than that of 4a. The change in the acetal moiety, i.e., from dimethyl acetal 4b to diethyl acetal 4c, slightly affected the selectivity.

The Reaction of Cyclopropane 4a with Unsymmetrical Ketones. $TiBr_4$ was the best catalyst for the reaction of 4a was unsymmetrical ketones, giving cis γ-lactones in excellent yields with high selectivity (Table III). In this case, $ZrCl_4$ was moderately cis-selective (Table III, entries 5 and 10); in contrast, it was moderately trans-selective for the reaction of 4a with aldehydes.

The $TiBr_4$-promoted reaction of 4a could be directly monitored by the color of the reaction mixture. Upon the addition of $TiBr_4$, the reaction mixture became deep reddish brown (this deep color might be attributed to the formation of a ring-opened titanium ester enolate (vide infra)). The deep color faded with the progress of the reaction, and the mixture became pale red at the final stage. On the basis of this color-change monitoring, this reaction seemed to be sensitive to a steric hindrance of the ketones; with an increase of the steric hindrance, it took a longer time for the deep color to fade, resulting in higher selectivity. The limitation was observed in the reaction of butyl isopropyl ketone, which did not react at −78 °C and had to be warmed to 0 °C; low selectivity was observed (Table III, entry 12). It is noteworthy that methyl vinyl ketone, a good Michael acceptor, gave only a 1,2-adduct and that the differentiation between methyl and relatively small vinyl groups was very high. This high selectivity might be due to an electronic effect of the vinyl moiety (vide infra). Mesityl oxide gave cis γ-lactone with high selectivity, accompanied by some dehydration to give diene 21 or 22.



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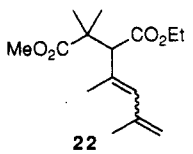


22

Epimerization of Cis γ-Lactones. As mentioned, cis γ-lactones were selectively obtained by the reaction of 4 with aldehydes or unsymmetrical ketones in the presence

Table V. Significant ^{1}H NMR Data of γ-Lactones 6–13

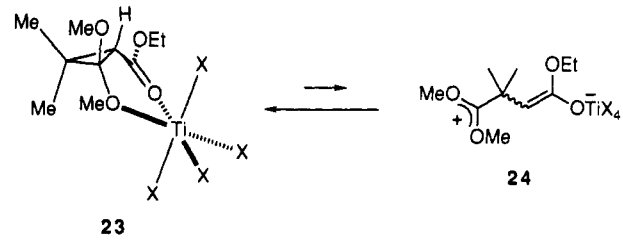
γ-lactone	cis (major)		trans (minor)	
	$^3J_{3-4}$, Hz	δ H.3, ppm	$^3J_{3-4}$, Hz	δ H.3, ppm
6	5.8	2.94	10.0	2.76
7	5.5	2.95	10.1	2.73
8	5.2	2.97	10.1	2.81
9	6.1	3.34	10.1	3.04
10	6.1	3.15	10.1	2.94
11	7.3	3.40	7.3	3.05
12	6.2	3.38	6.9	3.10
13	7.9	3.72	7.0	3.32

of $TiBr_4$ or $SnBr_4$. On the other hand, trans-isomers were not obtained with high selectivity. We therefore examined the epimierzation of cis-isomers. As shown in Table IV, in most cases we examined, the treatment of cis-isomers with NaOEt in EtOH or EtOH/THF gave predominantly epimerized trans-isomers.[14]

Paraconic acid (3-carboxy γ-lactone) is a fundamental skeleton of several natural compounds,[15] and its derivatives are also useful intermediates for the synthesis of natural compounds.[16] For the preparation of paraconic esters, several relatively simple methods have been reported, including the reaction of succinic anhydride[17] or succinic ester[16] with carbonyl compounds under basic conditions, a radical coupling reaction of maleic or fumaric ester with alcohols,[18] a reductive coupling reaction of maleic esters with carbonyl compounds,[19] γ-lactol formation and subsequent oxidation to a γ-lactone,[20] Mn^{3+}-mediated oxidative lactonization,[21] and the addition reaction of enolates of oxetanon-3-yl-acetates with aldehydes.[22] Most of them, however, are low- or nonselective reactions, and only the last one is stereoselective. Regarding the stereoselectivity and generality, the present method may be superior for synthesizing compounds of the paraconic acid family.

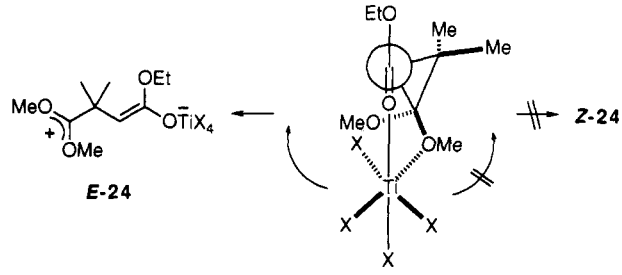
Assignment of the Stereochemistry of γ-Lactones. γ-Lactones 6–10. The major isomers of **6**, **9**, and **10** obtained by $TiBr_4$- or $SnBr_4$-promoted reactions of **4a** with aldehydes were subjected to treatment with a base and epimerized to the corresponding minor isomers. These results indicate that the major products are thermodynamically less stable cis-isomers. As shown in Table V, $^3J_{3-4}$s of the major isomers of **6–10** were 5.2–6.1 Hz, while $^3J_{3-4}$s of the corresponding minor isomers were 10 Hz. In addition, in all cases H.3 of the major isomers was found at a lower field than that of the corresponding minor isomers by >0.16 ppm. The ^{1}H NMR data indicate that the major isomers of **7** and **8** have the same relative stereochemistry as those of the major isomers of **6**, **9**, and **10**.

Scheme III



23 24

Scheme IV



25

This assignment is consistent with that reported for the related γ-lactones by Brückner and Reissig.[20a]

γ-Lactones 11–13. γ-Lactone **13** is a known compound, and the ^{1}H NMR data of the major and minor isomers of **13** are in good agreement with those of cis- and trans-isomers, respectively.[18] The result of an epimerization experiment indicates that the major isomer of **11** is cis. As shown in Table V, the $^3J_{3-4}$ values are meaningless for cis, trans assignment of **11–13**, whereas the chemical shifts of H.3 showed the same tendency as that of **6–10**; the major isomers of **11–13** had the resonance of H.3 at a lower field than the corresponding minor isomers by >0.28 ppm. This means that the major isomer of **12** is also cis.

γ-Lactones 15–20. The epimerization experiments show that the major isomers of **15–17** and **20** are cis. From epimerization experiments, however, the relative stereochemistry of **18** and **19** could not be inferred. We therefore measured the 2D NOESY ^{1}H NMR spectra of **18** (74:26 mixture of major isomer and minor isomer) and the major isomer of **19**. For the major isomer of **18**, strong NOEs were observed between H.3 and two Me groups, Me.4 (δ 1.64, appeared at downfield position relative to two Me.2 groups) and one of the Me.2 (δ 1.41). For the minor isomer of **18**, on the other hand, a strong NOE was observed between H.3 and only one of the Me.2 (δ 1.41). Similarly, for the major isomer of **19**, strong NOEs were observed between H.3 and two Me groups, Me.4 (δ 1.72) and one of the Me.2 (δ 1.38). On the basis of these 2D NOESY ^{1}H NMR, it is concluded that the major isomers of **18** and **19** are cis.

Mechanistic Aspects. When **4** and TiX_4 were mixed in CH_2Cl_2 at −78 °C, the color of this mixture changed to dark brown (for $TiCl_4$) or deep reddish brown (for $TiBr_4$). This color might be attributed to the formation of a titanium ester enolate, namely, ring-opened zwitterion **24**.[23,24] The formation of **24** is strongly supported by a report that the Lewis acid-mediated cis–trans isomerization reaction of 2-[(trialkylsilyl)oxy]- and 2-alkoxycyclopropane-

(14) There are two possible mechanisms for this epimerization reaction; one is a deprotonation–protonation mechanism, and the other is a β-elimination–recyclization mechanism. Although we could not clarify which mechanism is operative in this reaction, a very small amount of β-elimination product was obtained in the case of **11**.

(15) Devon, T. K.; Scott, A. I.; *Handbook of Naturally Occurring Compounds*; Academic Press: New York, 1975; Vol. I, pp 406–408.

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(19) Shono, T.; Hamaguchi, H.; Nishiguchi, I.; Sasaki, M.; Miyamoto, T.; Miyamoto, M.; Fujita, S. *Chem. Lett.* **1981**, 1217.

(20) (a) Brückner, C.; Reissig, H.-U.; *J. Org. Chem.* **1988**, *53*, 2440. (b) Nokami, J.; Ogawa, H.; Miyamoto, S.; Mandai, T.; Wakabayashi, S.; Tsuji, J. *Tetrahedron Lett.* **1988**, *29*, 5181.

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(22) (a) Mulzer, J.; deLasalle, P.; Chucholowski, A.; Blaschek, U.; Brüntrup, G.; Jibril, I.; Huttner, G. *Tetrahedron* **1984**, *40*, 2211. (b) Mulzer, J.; Chucholowski, A. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 655.

(23) A wine-red color has been reported for the reaction of **3** with $TiCl_4$. Reissig, H.-U.; Holzinger, H.; Glomsda, G. *Tetrahedron* **1989**, *45*, 3139.

(24) A deep red color has been reported for the trichlorotitanium enolates of ketones. (a) Nakamura, E.; Shimada, J.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1983**, *24*, 3341. (b) Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1983**, *24*, 3343.

Table VI. ^1H and ^{13}C NMR Chemical Shifts and Chemical Shift Increments for 4a and 4a + $TiBr_4$[a]

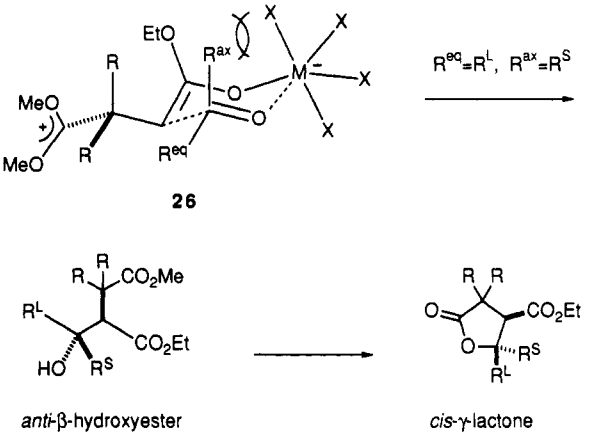
^1H NMR				^{13}C NMR			
	δ, ppm				δ, ppm		
	4a	4a + $TiBr_4$	Δδ, ppm		4a	4a + $TiBr_4$	Δδ, ppm
$CO_2CH_2CH_3$	1.29 (s)	1.56 (q)	0.27	CH_3.3	14.1	14.2	0.1 or 2.3
CH_3.3	1.31 (s)	1.48 (s)	0.17 or 0.06		14.6	16.4	1.8 or −0.4
	1.42 (s)	1.64 (s)	0.22 or 0.33	$CO_2CH_2CH_3$	21.8	22.9	1.1
H.1	1.66 (s)	2.36 (s)	0.70	C.1	33.5	37.8	4.3
OCH_3	3.42 (s)	3.71 (s)	0.29	C.3	35.0	41.1	6.1
		4.13 (s)	0.71	OCH_3	53.9	57.4	3.5 or 9.4
$CO_2CH_2CH_3$	4.12 (q)	4.62 (dq)	0.50		54.2	63.3	8.1 or 3.2
		4.73 (dq)	0.61	$CO_2CH_2CH_3$	60.2	68.7	8.5
				C.2	97.0	100.2	3.2
				$CO_2CH_2CH_3$	169.0	182.2	13.2

[a] The NMR spectra were measured in $CDCl_3$ at −60 °C.

carboxylic esters proceeds through a similar zwitterion.[25] In order to detect such a species, we carried out low-temperature ^1H and ^{13}C NMR experiments. The ^1H and ^{13}C NMR spectra of a 1:1 mixture of **4a** and $TiBr_4$ in $CDCl_3$ at −60 °C showed the predominant existence of a single species. As shown in Table VI, significant downfield shifts were observed for H.1, $CO_2CH_2CH_3$, and only one of the OCH_3 in the ^1H NMR and for C=O, $CO_2CH_2CH_3$, and only one of the OCH_3 in the ^{13}C NMR.[26-28] In addition, from the proton-coupled ^{13}C NMR spectrum, $^1J_{CH}$ of C.1 was 170 Hz, which is characteristic of a cyclopropane carbon.[28,29] On the basis of these data, it is concluded that in the presence of $TiBr_4$ **4a** mainly exists as a $TiBr_4$-chelated cyclopropane form like **23**. However, minor resonances with weak intensity, which could not be identified, were also observed. The minor resonances are considered to arise from enolate zwitterion **24** on the basis of the change in color, as mentioned above, even though the equilibrium between **23** and **24** lies largely to the left side (Scheme III).

The ring-opening of **23** to **24** would proceed in a stereoselective manner, as depicted in Scheme IV. For cleavage of the C.1–C.2 bond, a rotation of the ester group around the C.1–C=O bond would require maximum overlap between the π orbital of the C=O bond and the σ orbital of the C.1–C.2 bond. The right-handed rotation in Scheme IV seems to be preferable, taking into account the steric effect, and the corresponding *E*-enolate would be predominantly formed. Enolate (*E*)-**24** would react with carbonyl compounds through a 6-membered-ring transition state like **26**. The difference in stereoselectivity between $TiBr_4$- and $ZrCl_4$-promoted reactions indicates the importance of the steric repulsion between axial alkyl group R^{ax} of the carbonyl compound and the X group of MX_4. Because the bond length of Ti–O is shorter than that of Zr–O, the steric repulsion between R^{ax} and X of TiX_4 is larger than that of $ZrCl_4$. Therefore, in the TiX_4-promoted reaction, hydrogen or smaller alkyl groups of aldehydes or ketones occupy the axial position, resulting in the selective formation of cis γ-lactones through *anti*-β-hydroxy esters (Scheme V). In contrast, in the $ZrCl_4$-promoted reaction, the steric repulsion between R^{ax} and X is too small to control the reaction course, and the selectivity changes depending on the nature of the substituents of **4** and the carbonyl compounds. The very high selectivity in the reaction of **4a** with methyl vinyl ketone would arise from not only the steric effect but also the electronic effect; the repulsion between the π electrons of the vinyl group and the lone pair of the ether oxygen and/or halogen forces the vinyl group into the equatorial position in **26**. This electronic effect is also influential in the reaction of mesityl oxide.

Scheme V



Conclusion

In summary, a new methodology for the preparation of γ-lactones, based on the LA-promoted ring-opening aldol-type reaction of 2,2-dialkoxycyclopropanecarboxylic esters **4a–c** with carbonyl compounds, has been developed. The diastereoselectivity of the reaction can be controlled by the selection of LA catalyst. In the reaction of **4a** with aldehydes, $TiBr_4$ and $SnBr_4$ were highly cis-selective, while $ZrCl_4$ was moderately trans-selective. $TiBr_4$ and $SnBr_4$ also promoted the reaction of **4b** and **4c** with aldehydes with good cis-selectivity. The reaction of **4a** with unsymmetrical ketones was efficiently promoted by $TiBr_4$, and the cis γ-lactones were obtained with excellent selectivity. The high degree of stereoselection for a quaternary carbon is noteworthy. Trans γ-lactones were also obtained in good yields by the epimerization of cis-isomers.

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 were not corrected. ^1H NMR (400-MHz) and ^{13}C NMR (100-MHz) spectra were recorded in $CDCl_3$ with Me_4Si

(25) (a) Reissig, H.-U.; Böhm, I. *Tetrahedron Lett.* **1983**, *24*, 715. (b) Reference 3e.

(26) Keck et al. have reported a ^1H and ^{13}C NMR study on the $TiCl_4$ complexes of β-alkoxy aldehydes. (a) Keck, G. E.; Castellino, S. *J. Am. Chem. Soc.* **1986**, *108*, 3847. (b) Keck, G. E.; Castellino, S.; Wiley, M. R. *J. Org. Chem.* **1986**, *51*, 5478.

(27) ^1H and ^{13}C NMR data of $TiCl_4$-chelated methyl 3-methyl-4-oxobutyrate have been reported. Kunz, T.; Reissig, H.-U. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 268.

(28) Reissig et al. have reported a chelated species of **3a** ($R^1 = R^3 = R^4 = H$, $R^2 = t$-Bu) with $TiCl_4$. In this case, similar downfield shifts are also observed except for C.2, because the chelated species is a Me_3SiCl-eliminated trichlorotitanium complex; see ref 23.

(29) Rahman, A.-u. *Nuclear Magnetic Resonance*; Springer-Verlag: New York, 1986.

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 Ar. All aldehydes and ketones were purchased from commercial suppliers and distilled from CaH_2. CH_2Cl_2 was distilled from P_2O_5 and then from CaH_2 and stored over MS 4Å. C_6H_6 and toluene were distilled from CaH_2 and stored over Na. Flash column chromatography was performed with E. Merck silica gel 60 (230–400 mesh). Preparative TLC (PTLC) was carried out with Wakogel B-5F.

Cyclopropanes **4b–c** were prepared by a procedure given in the literature[10] by using a smaller amount of ketene acetals (1.3–1.4 equiv, in the literature ~4 equiv were used).

Ethyl 2,2-Dimethoxy-3,3-dimethylcyclopropanecarboxylate (4a). A literature procedure[10] was slightly modified as follows. A solution of 1,1-dimethoxy-2-methylpropene[30] (10.5 g, 90 mmol) and bis(acetylacetonato)copper (64 mg, 0.24 mmol) in dry C_6H_6 (25 mL) was stirred and refluxed at 80 °C while ethyl diazoacetate (7.23 g, 63 mmol) in dry C_6H_6 (30 mL) was added dropwise over 4 h. After the solution was stirred for an additional 30 min at this temperature, the solvent was removed under reduced pressure. The residue was distilled under vacuum to give 8.85 g (67%) of **4a** as a colorless liquid: bp 53–54 °C (0.5 Torr).

Reaction of Cyclopropanes 4 with Aldehydes and Ketones. The general procedure is exemplified with the reaction of **4a** with *trans*-cinnamaldehyde. A solution of **4a** (139 mg, 0.69 mmol) and *trans*-cinnamaldehyde (79.5 mg, 0.60 mmol) in CH_2Cl_2 (2.2 mL) was stirred and cooled to −78 °C while a 0.75 M CH_2Cl_2 solution of $TiBr_4$ (0.90 mL, 0.67 mmol) was added dropwise. After being stirred for 2 h, the reaction was quenched at the same temperature by adding a 1:1 mixture of H_2O/THF (1 mL). The mixture was then stirred vigorously for 15 min. After the cooling bath was removed, H_2O (3 mL) was added, and the mixture was allowed to warm 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 the crude product, which consisted mainly of hydroxy diester. The crude product was dissolved in dry toluene (10 mL), and a catalytic amount of *p*-toluenesulfonic acid (TsOH) was added to this solution. After being stirred for 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 (cis:trans = 74:26). The crude product was purified by PTLC (13% acetone–hexane, twice) to give 34 mg (20%) of *trans*-**10** (higher R_f) and 111 mg (64%) of *cis*-**10**.

$SnBr_4$-promoted reactions were carried out in the same way. The reaction mixture was quenched by adding saturated aqueous $NaHCO_3$; this mixture was then vigorously stirred for 15 min at −78 °C and 1 h at rt. To the mixture were added EtOAc, H_2O, and a small amount of Celite. The mixture was filtered through a pad of Celite; the pad was rinsed with EtOAc. The mixture was separated, and an aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4.

$ZrCl_4$-promoted reactions were carried out as described above with a different order of the addition of substrates; a mixture of **4** and a carbonyl compound in CH_2Cl_2 was added to a stirred suspension of $ZrCl_4$ in CH_2Cl_2.

Although **4b** and **4c** gradually isomerize to **5**, as described,[11] **4b** and **4c** contaminated with **5** (5–12% from ^1H NMR integration) were used without further purification. Subsequently, the reactions of **4b** and **4c** were carried out by using 1.3 equiv of **4b** or **4c**.

Epimerization of Cis γ-Lactones to Trans γ-Lactones. The general procedure is exemplified with the epimerization of *cis*-**9**. A solution of *cis*-**9** (71 mg, 0.27 mmol) in a 2:1 (v/v) mixture of EtOH and THF (3 mL) was stirred as 0.14 M NaOEt in EtOH (0.39 mL, 0.054 mmol) was added. After being stirred for 3 h at rt, the mixture was neutralized by adding saturated aqueous NH_4Cl (1 mL). The mixture was extracted with 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 PTLC (12% EtOAc–hexane) to give 59 mg (84%) of *trans*-**9**.

3-(Ethoxycarbonyl)-2,2-dimethyl-6-phenyl-4-hexanolide (6). The isomeric mixture of **6** was separated by PTLC (8% EtOAc–hexane). The trans-isomer has higher R_f than the cis-isomer. ***cis*-6**: mp 66–68 °C; IR (KBr) 1775, 1765, 1720; ^1H NMR δ 1.27 (3, s, CH_3.2), 1.27 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.33 (3, s, CH_3.2), 1.89 (1, m, $PhCH_2CHH$), 2.17 (1, m, $PhCH_2CHH$), 2.75 (1, m, $PhCHH$), 2.88 (1, m, $PhCHH$), 2.94 (1, d, J = 5.8, H.3), 4.19 (2, m, $CO_2CH_2CH_3$), 4.55 (1, m, H.4), 7.18–7.32 (5, m, Ph); EI-MS m/z 290 (M^+, 15), 203 (59), 171 (28), 157 (43), 129 (46), 91 (100), 83 (52). Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.42; H, 7.75. ***trans*-6**: mp 38–39 °C; IR (KBr) 1780, 1770, 1735; ^1H NMR δ 1.15 (3, s, CH_3.2), 1.28 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.41 (3, s, CH_3.2), 1.91 (1, m, $PhCH_2CHH$), 2.06 (1, m, $PhCH_2CHH$), 2.74 (1, m, $PhCHH$), 2.76 (1, d, J = 10.0, H.3), 2.90 (1, m, $PhCHH$), 4.12–4.30 (2, m, $CO_2CH_2CH_3$), 4.68 (1, dt, J = 3.4, 9.6, H.4), 7.19–7.31 (5, m, Ph); EI-MS m/z 290 (M^+, 17), 203 (55), 171 (21), 157 (36), 129 (38), 91 (100), 83 (44). Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.42; H, 7.48.

3-(Ethoxycarbonyl)-2,2-dimethyl-4-undecanolide (7). ot 180–190 °C (0.8 Torr). The isomeric mixture of **7** was separated by column chromatography (4% EtOAc–hexane). The trans-isomer has higher R_f than the cis-isomer. ***cis*-7**: IR (neat) 1780, 1735. ^1H NMR δ 0.88 (3, t, J = 6.9, $(CH_2)_6CH_3$), 1.20–1.42 (9, m), 1.27 (3, s, CH_3.2), 1.29 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.36 (3, s, CH_3.2), 1.48–1.65 (2, m), 1.78–1.88 (1, m), 2.95 (1, d, J = 5.5, H.3), 4.20 (2 q, J = 7.2, $CO_2CH_2CH_3$), 4.56 (1, td, J = 5.4, 8.5, H.4); EI-MS m/z 284 (M^+, 0.5), 240 (35), 225 (57), 197 (66), 141 (49), 129 (42), 83 (100); HRMS calcd for $C_{16}H_{28}O_4$ 284.1988, found 284.1977. ***trans*-7**: IR (neat) 1780, 1735; ^1H NMR δ 0.88 (3, t, J = 6.7, $(CH_2)_6CH_3$), 1.15 (3, s, CH_3.2), 1.22–1.45 (12, m), 1.40 (3, s, CH_3.2), 1.45–1.77 (3, m), 2.73 (1, d, J = 10.1, H.3), 4.15–4.31 (2, m, $CO_2CH_2CH_3$), 4.65 (1, ddd, J = 4.3, 8.4, 10.0, H.4); EI-MS m/z 284 (M^+, 0.5), 239 (15), 185 (26), 141 (61), 129 (78), 83 (80), 69 (100); HRMS calcd for $C_{16}H_{28}O_4$ 284.1988, found 284.1965.

3-(Ethoxycarbonyl)-2,2,5-trimethyl-4-hexanolide (8). The isomeric mixture of **8** was separated by column chromatography (5% EtOAc–hexane). The trans-isomer has higher R_f than the cis-isomer. ***cis*-8**: mp 51–52 °C; IR (KBr) 1765, 1730; ^1H NMR δ 0.89 (3, d, J = 6.7, $CH(CH_3)CH_3$), 1.13 (3, d, J = 6.4, $CH(CH_3)CH_3$), 1.25 (3, s, CH_3.2), 1.28 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.37 (3, s, CH_3.2), 1.95–2.06 (1, m, H.5), 2.97 (1, d, J = 5.2, H.3), 4.08 (1, dd, J = 5.2, 10.4, H.4), 4.21 (2, q, J = 7.2, $CO_2CH_2CH_3$); EI-MS m/z 185 ($M^+ - CH(CH_3)_2$, 15), 169 (24), 141 (48), 129 (40), 101 (43), 95 (48), 83 (100). Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.02; H, 8.70. ***trans*-8**: IR (neat) 1785, 1740; ^1H NMR δ 0.94 (3, d, J = 6.7, $CH(CH_3)CH_3$), 1.02 (3, d, J = 6.7, $CH(CH_3)CH_3$), 1.16 (3, s, CH_3.2), 1.31 (3, t, J = 7.0, $CO_2CH_2CH_3$), 1.39 (3, s, CH_3.2), 1.84 (1, m, H.5), 2.81 (1, d, J = 10.1, H.3), 4.23 (2, m, $CO_2CH_2CH_3$), 4.50 (1, dd, J = 10.1, H.4); EI-MS m/z 200 ($M^+-CH_2=CH_2$, 1.9), 185 (23), 129 (77), 101 (63), 83 (100). Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.03; H, 8.83.

3-(Ethoxycarbonyl)-2,2-dimethyl-4-phenyl-4-butanolide (9). The isomeric mixture of **9** was separated by PTLC (CH_2Cl_2–hexane–EtOAc (10:10:1)). The trans-isomer has higher R_f than the cis-isomer. ***cis*-9**: mp 118–119 °C; IR (KBr) 1780, 1715; ^1H NMR δ 0.86 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.33 (3, s, CH_3.2), 1.50 (3, s, CH_3.2), 3.34 (1, d, J = 6.1, H.3), 3.74 (2, m, $CO_2CH_2CH_3$), 5.78 (1, d, J = 6.1, H.4), 7.27–7.35 (5, m, Ph); EI-MS m/z 262 (M^+, 5), 156 (41), 145 (23), 128 (26), 83 (100), 77 (19). Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.84; H, 6.83. ***trans*-9**: mp 68–69 °C; IR (KBr) 1775, 1735; ^1H NMR δ 1.27 (3, s, CH_3.2), 1.28 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.47 (3, s, CH_3.2), 3.04 (1, d, J = 10.1, H.3), 4.13–4.30 (2, m, $CO_2CH_2CH_3$), 5.71 (1, d, J = 10.1, H.4), 7.34–7.39 (5, m, Ph); EI-MS m/z 262 (M^+, 8), 234 (20), 145 (53), 129 (65), 105 (88), 83 (100), 77 (37). Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68,72; H, 6.95.

3-(Ethoxycarbonyl)-2,2-dimethyl-6-phenyl-(*E*)-5-hexen-4-olide (10). ***cis*-10**: mp 87–87.5 °C; IR (KBr) 1785, 1730; ^1H NMR δ 1.18 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.32 (3, s, CH_3.2), 1.42 (3, s, CH_3.2), 3.15 (1, d, J = 6.1, H.3), 4.15 (2, m, $CO_2CH_2CH_3$), 5.26 (1, t, J = 6.4, H.4), 6.27 (1, dd, J = 6.6, 16.0, CH=CHPh),

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6.77 (1, d, J = 15.9, CH=C*H*Ph), 7.22–7.42 (5, m, Ph); EI-MS m/z 288 (M^+, 45), 260 (20), 214 (30), 129 (45), 104 (100), 91 (25), 83 (65); HRMS calcd for $C_{17}H_{20}O_4$ 288.1361, found 288.1357. ***trans*-10**: mp 72–73 °C; IR (KBr) 1780, 1735; ^{1}H NMR δ 1.22 (3, s, C*H*$_3$.2), 1.31 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.45 (3, s, C*H*$_3$.2), 2.94 (1, d, J = 10.1, *H*.3), 4.18 (1, qd, J = 7.2, 10.8, CO_2CHH), 4.28 (1, qd, J = 7.2, 10.8, CO_2CHH), 5.28 (1, dd, J = 7.0, 10.1, *H*.4), 6.15 (1, dd, J = 7.0, 15.9, C*H*=CHPh), 6.79 (1, d, J = 15.9, CH=C*H*Ph), 7.22–7.45 (5, m, Ph); EI-MS m/z 288 (M^+, 100), 260 (50), 214 (43), 129 (67), 104 (100), 91 (40), 83 (67); HRMS calcd for $C_{17}H_{20}O_4$ 288.1361, found 288.1331.

3-(Ethoxycarbonyl)-6-phenyl-4-hexanolide (11). ot 160 °C (0.3 Torr). The isomeric mixture of **11** was separated by PTLC (20% EtOAc–hexane). The trans-isomer has higher R_f than the cis-isomer. ***cis*-11**: IR (neat) 1785, 1730; ^{1}H NMR δ 1.28 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.81–1.99, (2, m, CH_2CH_2Ph), 2.65–2.95 (2, m, CH_2CH_2Ph), 2.67 (1, dd, J = 8.5, 17.7, *H*.2), 2.91 (1, dd, J = 5.3, 17.5, *H*.2), 3.40 (1, ddd, J = 5.3, 7.3, 8.7, *H*.3), 4.21 (2, q, J = 7.2, $CO_2CH_2CH_3$), 4.60 (1, ddd, J = 3.9, 7.4, 10.0, *H*.4), 7.18–7.32 (5, m, Ph); EI-MS m/z 262 (M^+, 15), 188 (31), 171 (24), 128 (59), 91 (100), 55 (82); HRMS calcd for $C_{15}H_{18}O_4$ 262.1205, found 262.1176. ***trans*-11**: IR (neat) 1780, 1735; ^{1}H NMR δ 1.26 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.98–2.18 (2, m, CH_2CH_2Ph), 2.71–2.93 (2, m, CH_2CH_2Ph), 2.79 (1, dd, J = 9.5, 17.7, *H*.2), 2.94 (1, dd, J = 9.0, 17.7, *H*.2), 3.05 (1, dt, J = 7.3, 9.2, *H*.3), 4.19 (2, dq, J = 1.3, 7.2, $CO_2CH_2CH_3$), 4.55 (1, ddd, J = 4.0, 7.5, 8.7, *H*.4), 7.19–7.32 (5, m, Ph); EI-MS m/z 262 (M^+, 13), 188 (33), 171 (20), 128 (60), 91 (100), 55 (74); HRMS calcd for $C_{15}H_{18}O_4$ 262.1205, found 262.1182.

3-(Ethoxycarbonyl)-5-methyl-4-hexanolide (12). ot 165 °C (20 Torr). The isomeric mixture of **12** was separated by column chromatography (16% EtOAc–hexane). The trans-isomer has higher R_f than the cis-isomer. ***cis*-12**: mp 66–67 °C; IR (KBr) 1775, 1715; ^{1}H NMR δ 1.00 (3, d, J = 6.7, $CH(CH_3)CH_3$), 1.07 (3, d, J = 6.7, $CH(CH_3)CH_3$), 1.29 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.81–1.94 (1, septet d, J = 6.6, 9.2, *H*.5), 2.71 (1, dd, J = 8.2, 17.4, *H*.2), 2.80 (1, dd, J = 3.1, 17.1, *H*.2), 3.38 (1, ddd, J = 3.1, 6.2, 8.1, *H*.3), 4.15–4.28 (2, m, $CO_2CH_2CH_3$), 4.19 (1, dd, J = 6.1, 9.2, *H*.4); EI-MS m/z 157 ($M^+ - CH(CH_3)_2$, 48), 129 (92), 101 (88), 55 (100). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.81; H, 7.86. ***trans*-12**: IR (neat) 1785, 1735; ^{1}H NMR δ 0.99 (3, d, J = 6.7, $CH(CH_3)CH_3$), 1.02 (3, d, J = 6.7, $CH(CH_3)CH_3$), 1.29 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.89–2.01 (1, m, *H*.5), 2.78 (1, dd, J = 9.9, 17.9, *H*.2), 2.90 (1, dd, J = 8.3, 18.3, *H*.2), 3.10 (1, ddd, J = 6.9, 8.1, 9.9, *H*.3), 4.16–4.28 (2, m, $CO_2CH_2CH_3$), 4.44 (1, t, J = 6.4, *H*.4); EI-MS m/z 172 ($M^+ - CH_2{=}CH_2$, 12), 157 (68), 129 (100), 101 (78), 55 (54). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.70; H, 7.98.

3-(Ethoxycarbonyl)-4-phenyl-4-butanolide (13). ot 170 °C (1.5 Torr). The isomeric mixture of **13** was separated by PTLC (22% EtOAc–hexane). The trans-isomer has higher R_f than the cis-isomer. ***cis*-13**: mp 74–75 °C; IR (KBr) 1770, 1730; ^{1}H NMR δ 0.87 (3, t, J = 7.2, $CO_2CH_2CH_3$), 2.81 (1, dd, J = 8.9, 17.7, *H*.2), 3.09 (1, dd, J = 4.9, 17.7, *H*.2), 3.63–3.83 (3, m, *H*.3, $CO_2CH_2CH_3$), 5.76 (1, d, J = 7.9, *H*.4), 7.20–7.40 (5, m, Ph); EI-MS m/z 234 (M^+, 8), 128 (100), 105 (30), 100 (70), 55 (69). Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.72; H, 5.93. ***trans*-13**: IR (neat) 1790, 1735; ^{1}H NMR δ 1.28 (3, t, J = 7.2, $CO_2CH_2CH_3$), 2.91 (1, dd, J = 9.5, 17.7, *H*.2), 3.00 (1, dd, J = 8.9, 17.7, *H*.2), 3.32 (1, dt, J = 7.2, 9.3, *H*.3), 4.15-4.29 (2, m, $CO_2CH_2CH_3$), 5.66 (1, d, J = 7.0, *H*.4), 7.30–7.50 (5, m, Ph); EI-MS m/z 234 (M^+, 27), 105 (100), 100 (27), 77 (33), 55 (53); HRMS calcd for $C_{13}H_{14}O_4$ 234.0892, found 234.0869.

3-(Ethoxycarbonyl)-2,2,4-trimethyl-4-dodecanolide (15).[31] ot 160 °C (0.5 Torr). ***cis*-15**: IR (neat) 1780, 1745; ^{1}H NMR δ 0.88 (3, t, J = 6.9, $(CH_2)_7CH_3$), 1.20–1.33 (12, m), 1.31 (3, t, J = 7.0, $CO_2CH_2CH_3$), 1.40 (3, s, C*H*$_3$.2), 1.43 (3, s, C*H*$_3$.2), 1.55 (3, s, C*H*$_3$.4), 1.76–1.82 (2, m, $CH_2C_7H_{15}$), 2.98 (1, s, *H*.3), 4.15–4.25 (2, m, $CO_2CH_2CH_3$); EI-MS m/z 253 (1.6), 225 (12), 199 (99), 129 (72), 83 (100). ***trans*-15**: IR (neat) 1780, 1740; ^{1}H NMR δ 0.88 (3, t, J = 6.9, $(CH_2)_7CH_3$), 1.20–1.33 (12, m), 1.31 (3, t, J = 7.0, $CO_2CH_2CH_3$), 1.38 (3, s, C*H*$_3$.2), 1.40 (3, s, C*H*$_3$.2), 1.54 (3, s, C*H*$_3$.4), 1.67–1.85 (2, m, $CH_2C_7H_{15}$), 2.99 (1, s, *H*.3), 4.15–4.26 (2, m, $CO_2CH_2CH_3$); EI-MS m/z 253 (2.3), 225 (6), 199 (75), 129 (54), 83 (100). A mixture of isomers was submitted for elemental analysis. Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32. Found: C, 69.09; H, 10.28.

3-(Ethoxycarbonyl)-2,2,4,6-tetramethyl-4-heptanolide (16).[31] ot 173 °C (6 Torr). ***cis*-16**: IR (neat) 1775, 1740; ^{1}H NMR δ 0.96 (3, d, J = 6.7, $CH(CH_3)CH_3$), 0.99 (3, d, J = 6.7, $CH(CH_3)CH_3$), 1.31 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.40 (3, s, C*H*$_3$.2), 1.43 (3, s, C*H*$_3$.2), 1.59 (3, s, C*H*$_3$.4), 1.71 (2, d, J = 6.1, CH_2iPr), 1.87–1.97 (1, m, *H*.6), 2.96 (1, s, *H*.3), 4.21 (2, q, J = 7.2, $CO_2CH_2CH_3$); EI-MS m/z 241 ($M^+ - CH_3$, 0.6), 199 (34), 129 (50), 83 (100). ***trans*-16**: IR (neat) 1775, 1740; ^{1}H NMR δ 0.95 (3, d, J = 6.4, $CH(CH_3)CH_3$), 1.00 (3, d, J = 6.4, $CH(CH_3)CH_3$), 1.31 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.39 (3, s, C*H*$_3$.2), 1.41 (3, s, C*H*$_3$.2), 1.55 (3, s, C*H*$_3$.4), 1.56 (1, *H*.5), 1.78–1.87 (2, m, *H*.5, *H*.6), 2.99 (1, s, *H*.3), 4.15–4.27 (2, m, $CO_2CH_2CH_3$); EI-MS m/z 241 ($M^+ - CH_3$, 1.6), 199 (24), 129 (38), 83 (100). A mixture of isomers was submitted for elemental analysis. Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.41; H, 9.29.

3-(Ethoxycarbonyl)-2,2,4,5-tetramethyl-4-hexanolide (17). ot 115 °C (2 Torr). The isomeric mixture of **17** was separated by column chromatography (2.5–5% EtOAc–hexane). ***cis*-17**: IR (neat) 1770, 1740; ^{1}H NMR δ 0.79 (3, d, J = 6.7, $CH(CH_3)CH_3$), 1.04 (3, d, J = 6.7, $CH(CH_3)CH_3$), 1.29 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.35 (3, s, C*H*$_3$.2), 1.43 (3, s, C*H*$_3$.2), 1.46 (3, s, C*H*$_3$.4), 2.56 (1, septet, J = 6.7, *H*.5), 2.97 (1, s, *H*.3), 4.11–4.24 (2, m, $CO_2CH_2CH_3$); EI-MS m/z 227 ($M^+ - CH_3$, 2), 199 (79), 129 (100), 83 (69). Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.25; H, 9.15. ***trans*-17**: IR (neat) 1775, 1745; ^{1}H NMR δ 0.91 (3, d, J = 7.0, $CH(CH_3)CH_3$), 0.98 (3, d, J = 6.7, $CH(CH_3)CH_3$), 1.30 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.31 (3, s, C*H*$_3$.2), 1.40 (3, s, C*H*$_3$.2), 1.54 (3, s, C*H*$_3$.4), 1.90 (1, septet, J = 6.9, *H*.5), 2.99 (1, s, *H*.3), 4.13–4.25 (2, m, $CO_2CH_2CH_3$); EI-MS m/z 227 ($M^+ - CH_3$, 3), 199 (68), 129 (100), 83 (68). Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.18; H, 9.09.

3-(Ethoxycarbonyl)-2,2,4-trimethyl-5-hexen-4-olide (18).[31] ot 160–170 °C (15 Torr). ^{1}H NMR data of the trans-isomer were obtained from the spectrum of the cis,trans-mixture (73:27). ***cis*-18**: IR (neat) 1780, 1735; ^{1}H NMR δ 1.29 (3, s, C*H*$_3$.2), 1.32 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.41 (3, s, C*H*$_3$.2), 1.64 (3, s, C*H*$_3$.4), 3.01 (1, s, *H*.3), 4.17–4.29 (2, m, $CO_2CH_2CH_3$), 5.21 (1, d, J = 11.6, CH=C*H*H), 5.42 (1, d, J = 17.4, CH=CH*H*), 6.31 (1, dd, J = 11.0, 17.4, C*H*=CH$_2$); EI-MS m/z 226 (M^+, 0.8), 141 (18), 109 (47), 83 (100); HRMS calcd for $C_{12}H_{18}O_4$ 226.1205, found 226.1216. ***trans*-18**: ^{1}H NMR δ 1.31 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.38 (3, s, C*H*$_3$.2), 1.41 (3, s, C*H*$_3$.2), 1.60 (3, s, C*H*$_3$.4), 3.06 (1, s, *H*.3), 4.16–4.27 (2, m, $CO_2CH_2CH_3$), 5.16 (1, d, J = 10.7, CH=C*H*H), 5.37 (1, d, J = 17.3, CH=CH*H*), 6.05 (1, dd, J = 10.8, 17.3, C*H*=CH$_2$); EI-MS m/z 226 (M^+, 0.5), 109 (46), 83 (100). A mixture of isomers was submitted for elemental analysis. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.41; H, 7.93.

3-(Ethoxycarbonyl)-2,2,4,6-tetramethyl-5-hepten-4-olide (19).[31] ot 120 °C (0.7 Torr). ***cis*-19**: IR (neat) 1780, 1740; ^{1}H NMR δ 1.32 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.34 (3, s, C*H*$_3$.2), 1.38 (3, s, C*H*$_3$.2), 1.72 (3, s, C*H*$_3$.4), 1.72 (3, d, J = 1.2, CH=C-$(CH_3)CH_3$), 1.84 (3, d, J = 1.5, CH=C$(CH_3)CH_3$), 2.91 (1, s, *H*.3), 4.24 (2, q, J = 7.2, $CO_2CH_2CH_3$), 5.52 (1, m, C*H*=CMe$_2$); EI-MS m/z 254 (M^+, 4), 239 (14), 199 (22), 156 (24), 128 (19), 83 (100); HRMS calcd for $C_{14}H_{22}O_4$ 254.1518, found 254.1530. ***trans*-19**: ^{1}H NMR δ 1.31 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.33 (3, s, C*H*$_3$.2), 1.40 (3, s, C*H*$_3$.2), 1.61 (3, s, C*H*$_3$.4), 1.73 (3, d, J = 1.5, CH=C-$(CH_3)CH_3$), 1.79 (3, d, J = 1.2, CH=C$(CH_3)CH_3$), 3.14 (1, s, *H*.3), 4.19–4.27 (2, m, $CO_2CH_2CH_3$), 5.41 (1, m, C*H*=CMe$_2$); EI-MS m/z 254 (M^+, 8), 239 (15), 156 (30), 128 (20), 83 (100); HRMS calcd for $C_{14}H_{22}O_4$ 254.1518, found 254.1540.

3-(Ethoxycarbonyl)-2,2-dimethyl-4-(1-methylethyl)-4-octanolide (20).[31] ot 140 °C (0.6 Torr). ***cis*-20**: ^{1}H NMR δ 0.83 (3, d, J = 6.7, $CH(CH_3)CH_3$), 0.94 (3, t, J = 6.7, $(CH_2)_3CH_3$), 1.01 (3, d, J = 6.7, $CH(CH_3)CH_3$), 1.30 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.34 (3, s, C*H*$_3$.2), 1.46 (3, s, C*H*$_3$.2), 1.23–1.53 (4, m), 1.62–1.86 (2, m), 2.53 (1, septet, J = 6.8, *H*.5), 3.16 (1, s, *H*.3), 4.09–4.24 (2, m, $CO_2CH_2CH_3$); EI-MS m/z 241 ($M^+ - CH(CH_3)_2$, 34), 227 (13), 129 (53), 85 (83), 83 (100), 57 (55), 43 (69). ***trans*-20**: IR (neat) 1770, 1745; ^{1}H NMR δ 0.88 (3, d, J = 7.0, $CH(CH_3)CH_3$), 0.91 (3, d, J = 6.7, $CH(CH_3)CH_3$), 0.91 (3, t, J = 7.0, $(CH_2)_3CH_3$), 1.29 (3, t, J = 7.2, $CO_2CH_2CH_3$), 1.33 (3, s, C*H*$_3$.2), 1.38 (3, s, C*H*$_3$.2),

(31) The cis-trans mixture of **15**, **16**, and **18–20** could not be separated by column chromatography.

1.24–1.56 (4, m), 1.86–1.95 (1, m), 2.09–2.17 (1, m), 2.33 (1, septet, J = 6.9, H.5), 3.13 (1, s, H.3), 4.12–4.24 (2, m, $CO_2CH_2CH_3$); EI-MS m/z 241 (M^+ – $CH(CH_3)_2$, 36), 227 (24), 129 (57), 85 (66), 83 (100), 57 (44), 43 (68). A mixture of isomers was submitted for elemental analysis. Anal. Calcd for $C_{16}H_{28}O_4$: C, 67.53; H, 9.93. Found: C, 67.59; H, 9.90.

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Supplementary Material Available: 2D NOESY ^1H NMR spectra of **18** and *cis*-**19** and low-temperature ^1H and ^{13}C spectra of **4a** and **4a** + $TiBr_4$ (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Remote Diastereoselection in the Asymmetric Synthesis of Pravastatin

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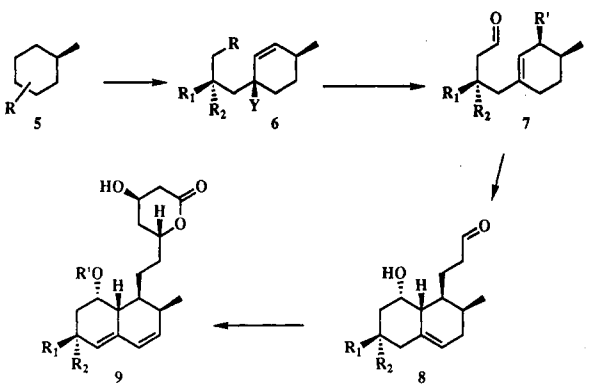
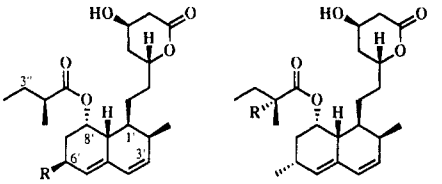
The first total synthesis of pravastatin (**3**) is described. The desymmetrization of 1-methyl-4-methylenecyclohexane (**10**) by an asymmetric ene reaction to form **11a** provided the initial asymmetric framework. The remaining stereogenic centers were introduced sequentially by a series of diastereoselective processes which include the iodolactonization of **11a** to **13**, the Eschenmoser–Claisen rearrangement of **17** to **18**, the stereoselective intramolecular ene reaction of **20** to **21**, and the diastereoselective condensation of aldehyde **27** with diene **28**.

An important new therapeutic strategy in the management of atherosclerosis has emerged from investigations on the mevinic acid family of compounds.[1] Treatment in vivo with these substances, which are competitive inhibitors of HMG-CoA reductase, results in the beneficial alteration of serum lipid levels.[2] The first member of this group, isolated from microbial sources, was mevastatin (**1**),[3-5] which was joined a few years later by the isolation of an even more active inhibitor, lovastatin (**2**). In the course of the clinical development for mevastatin, a more active metabolite, pravastatin (**3**), was isolated as a minor component in the urine of dogs.[6] This 6′-β-hydroxylation of mevastatin is now carried out by a more efficient microbial process.[7] Both lovastatin and pravastatin are currently prescribed for the reduction of serum cholesterol levels.

Scheme I





1 R = H Mevastatin
3 R = OH Pravastatin

2 R = H Lovastatin
4 R = Me Simvastatin

A noteworthy aspect of these inhibitors, in addition to their much higher affinity for the enzyme than the natural

(1) The names for these substances have varied during the course of time and among research groups. We will use the current names for **1**, mevastatin (also referred to as compactin, ML-236B, CS-500), **2**, lovastatin (also referred to as mevinolin, MB-530B, MK-803, Mevacor), **3**, pravastatin (also referred to as eptastatin, CS-514, SQ-3100), and **4**, simvastatin, a semisynthetic derivative of lovastatin (also referred to as synvinolin, MK-733, Zocor).

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