$MgBr_2$-Promoted Addition of Heterosubstituted Methylketene Silyl Acetals to Alkoxy Aldehydes. Diastereoselective Synthesis of 3,4-Syn 2-Methylene- and 2-(Alkoxymethyl)-3-hydroxy-4-alkoxy Esters

Anna Bernardi, Silvia Cardani, Lino Colombo, Giovanni Poli, Giuliana Schimperna, and Carlo Scolastico*

Dipartimento di Chimica Organica e Industriale dell'Università, Centro CNR per lo studio delle Sostanze Organiche Naturali, 20133 Milano, Italy

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The $MgBr_2$-mediated addition of 2- or 3-(methylthio)-substituted ketene silyl acetals **3** and **4** to α-alkoxy and α,β-dialkoxy aldehydes, followed by oxidation and elimination of methanesulfenic acid, gave 3,4-syn 2-methylene-3-hydroxy-4-alkoxy esters **9** and **11** with very high stereoselectivity (up to 100:1) and in good chemical yields. The same diastereofacial selection is at work in the analogous additions of [(benzyloxy)methyl]ketene methyl silyl acetal **5**, which affords 3,4-syn 2-[(benzyloxy)methyl]-3-hydroxy-4-alkoxy esters **12–15**.

The stereocontrolled synthesis of enantiomerically pure polyoxy 2-methylene carbonyl compounds is an attractive target both for the biological properties of this class of molecules[1] and for the synthetic opportunities offered by the methylene moiety, which is particularly suited for the synthesis of branched sugars.[2,3] Our approach to these 2-methylene esters is based on aldol type condensations between optically active α-alkoxy aldehydes and acrylate α-anion equivalents:[4] the stereochemical problem we chose to confront is then the longstanding one of diastereofacial selection on chiral aldehydes.[5] Nucleophilic additions to an α-alkoxy carbonyl group can follow two main stereochemical pathways:[5b,c] (a) when the reagents involved are incapable of bidentate complexation, the Felkin–Anh model pertains and anti diols are formed; (b) a different phenomenon, namely chelation, is also possible, which makes the opposite π face sterically more accessible. In such cases Cram's cyclic model accounts for the stereochemical course of the reaction, which produces syn diols.

We recently described the synthesis of 2-methylene-3-hydroxy-4-alkoxy esters in the 3,4-anti configuration **1** (Chart I) (Felkin–Anh products), using the lithium enolate of *tert*-butyl 3-(dimethylamino)propionate as an acrylate equivalent.[4] We now wish to report the synthesis of 3,4-syn isomers **2** (Chart I) (chelation-controlled products) through a Lewis acid promoted reaction between α-alkoxy and α,β-dialkoxy aldehydes and the 2- or 3-(methylthio)-substituted ketene silyl acetals **3** and **4** (Chart II).[6]

In this context we also investigated the analogous reaction of (alkoxymethyl)ketene silyl acetal **5** (Chart II), which leads to 2-deoxy-2-[(benzyloxy)methyl]xylonic and -lyxonic esters and to their γ-lactones.

Chart I

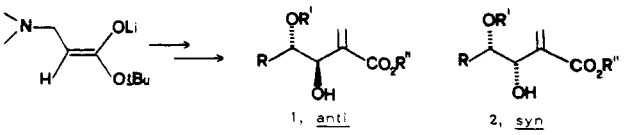
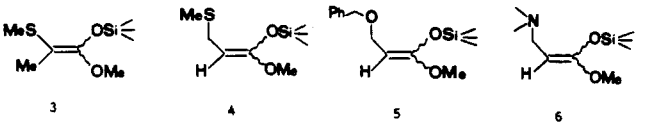
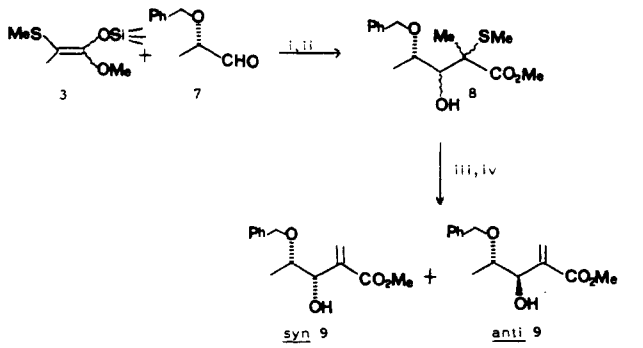


Chart II



Scheme I[a]



[a] Reagents: (i) Lewis acid; (ii) $AcOH/H_2O$; (iii) $NaIO_4/MeOH/H_2O$; (iv) Δ, dioxane.

Results and Discussion

Synthesis of 2-Methylene Esters 9 and 11. It is very well-known that α-alkoxy aldehydes, in the presence of a chelating Lewis acid, react with ketene silyl acetals to give 3,4-syn aldols,[5c] so, on the basis of our previous work, the reaction of [(dimethylamino)methyl]ketene silyl acetal **6** (Chart II) with alkoxy aldehydes was attempted. Unfortunately, 3-amino substitution makes **6** almost unreactive,[7] and we had to turn our attention toward other potential acrylate equivalents.

Though some heterosubstituted ketene silyl acetals have been investigated,[8] little is known about the role played by the additional heteroatom in determining the reaction course. It turned out that **3** and **4**, which could just as well serve our purpose, react much more promptly than **6** with

(1) Müller, J. M.; Fuhrer, H.; Gruner, J.; Vaser, W. *Helv. Chim. Acta* **1976**, *59*, 2506. Hoffman, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94.

(2) Bernardi, A.; Beretta, M. G.; Colombo, L.; Gennari, C.; Poli, G.; Scolastico, C. *J. Org. Chem.* **1985**, *50*, 4442.

(3) Giese, B.; Witzel, T. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 450. Brown, J. M.; Cutting, I. *J. Chem. Soc., Chem. Commun.* **1985**, 578.

(4) Banfi, L.; Bernardi, A.; Colombo, L.; Gennari, C.; Scolastico, C. *J. Org. Chem.* **1984**, *49*, 3784. Banfi, L.; Colombo, L.; Gennari, C.; Scolastico, C. *J. Chem. Soc., Chem. Commun.* **1983**, 1112. A similar approach has been reported: Barbier, P.; Benezra, C. *J. Org. Chem.* **1983**, *48*, 2705. Papageorgiou, C.; Benezra, C. *Ibid.* **1985**, *50*, 157.

(5) (a) Eliel, E. L. In *Asymmetric Synthesis*; Academic: New York, 1983; Vol. 2, Part A, p 125. (b) Gennari, C.; Beretta, M. G.; Bernardi, A.; Moro, G.; Scolastico, C.; Todeschini, R. *Tetrahedron* **1986**, *42*, 893 and references therein. (c) For a review, see: Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.

(6) Bernardi, A.; Cardani, S.; Gennari, C.; Poli, G.; Scolastico, C. *Tetrahedron Lett.* **1985**, 6509.

(7) **6** reacted with a (*S*)-*O*-benzyllactaldehyde (**7**)/Lewis acid complex to give, after β-elimination of NMe_2 group ($MeI/K_2CO_3/MeOH$), aldols **9** in a 94:6 *syn*-**9**/*anti*-**9** ratio with $TiCl_4$, 74:26 with $SnCl_4$, and 100:1 with $MgBr_2$, but the chemical yield did not exceed 20%.

(8) Heathcock, C. H.; Montgomery, S. M. *Tetrahedron Lett* **1985**, 1001. Tokai, K.; Heathcock, C. H. *J. Org. Chem.* **1985**, *50*, 3247. Guanti, G.; Banfi, L.; Narisano, E.; Scolastico, C. *Tetrahedron Lett.* **1985**, 3517. Uenishi, J.-i.; Tomozane, H.; Yamato, M. *Ibid.* **1985**, 3467. Heathcock, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. *J. Org. Chem.* **1986**, *51*, 3027.

0022-3263/87/1952-0888$01.50/0

Table I. Addition of 3 and 4 to *O*-Benzyllactaldehyde

entry	ketene silyl acetal	Lewis acid	condens cond	syn/anti[a]	yield, %
1	3	$TiCl_4$	−78 → 0 °C[b]		
2		$SnCl_4$	−78 °C/1 h	1.1:1	65
3		$ZnCl_2$	−40 °C/3 h	2:1	45
4		$MgBr_2$	−40 °C/3 h	11:1	60
5		$MgBr_2$	−78 °C/8 h	18:1	50
6	4	$MgBr_2$	−78 °C/0.5 h	100:1	78

[a] Determined by HPLC and ^{1}HNMR. [b] The reaction failed to give the expected product. Raising the temperature to 25 °C resulted in extensive decomposition of reactants.

Scheme II[a]

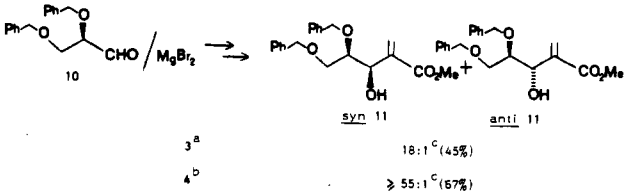
[a] Reagents: (i) $MgBr_2$; (ii) $NaIO_4/MeOH/H_2O$; (iii) Δ, dioxane.

alkoxy aldehydes, probably as a consequence of the lower basicity of the sulfur atom. We first examined the thiolactic acid derivative **3**,[6] which was synthesized as a 75:25 stereoisomeric mixture from methyl 2-(methylthio)propionate,[9] by LDA enolization and Me_3SiCl trapping. Reaction of **3** with (*S*)-*O*-benzyllactaldehyde (**7**) (Scheme I) showed no high 2,3-diastereoselection, regardless of which Lewis acid was used to promote the condensation. However, this is not relevant to our aim, since the stereocenter at C-2 will be lost in the final products. Therefore aldols **8** were submitted without purification to $NaIO_4$ oxidation and methanesulfenic acid was thermally eliminated to give esters **9** (Scheme I). The configuration of *syn*-**9** and *anti*-**9** was unambiguously assigned by NMR spectroscopy,[10] and the diastereomeric ratios were determined by HPLC and ^{1}H NMR (Table I).

As is apparent from the data summarized in Table I, stereoselection depends strongly on the Lewis acid used to promote the condensation. The best results came from $MgBr_2$ (entries 4 and 5), which secured an almost complete α-chelation-controlled diastereofacial preference; on the contrary, and somewhat unexpectedly, $TiCl_4$ failed to promote the reaction, and $SnCl_4$ gave an almost equimolar mixture of *syn*-**9** and *anti*-**9** (entry 2). Although $SnCl_4$ is known to be very efficient as a bidentate complexing agent of α-alkoxy aldehydes,[5c] when an α-heterosubstituted ketene silyl acetal is involved in the reaction 3,4-syn/anti selectivity has been shown to decrease in most cases.[8] Our speculation is that the silyl ether heteroatom can interfere with the formation of a chelate complex between Lewis acids and alkoxy aldehydes, particularly when the metal in such a complex is coordinatively saturated. In fact, better results were obtained with coordinatively unsaturated aldehyde/Lewis acid complexes, such as **7**/$ZnCl_2$ (entry 3) and **7**/$MgBr_2$ (entries 4 and 5).

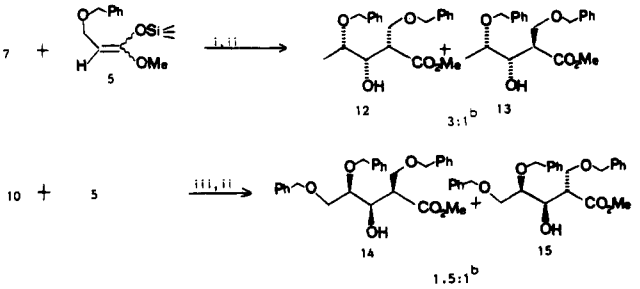
In spite of the good selectivity thus achieved with $MgBr_2$, yields were rather disappointing, so we decided to switch to the less hindered acrylate equivalent **4**. **4** was prepared as an equimolar mixture of isomers by adding methyl 3-(methylthio)propionate to a solution of LDA and

Scheme III



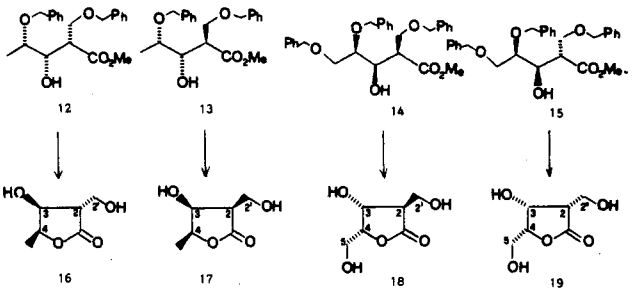
[a] −78 °C → 0 °C, 2 h. [b] −78 °C, 1 h. [c] Syn/anti ratios determined by HPLC, ^{1}H NMR, and ^{13}C NMR.

Scheme IV[a]



[a] Reaction conditions: (i) $MgBr_2$, −78 °C/0.5 h; (ii) $AcOH/H_2O$; (iii) $MgBr_2$, −78 °C/4 h. [b] Determined by HPLC.

Scheme V



Me_3SiCl at −90 °C:[11] this was the only way to prevent SMe β-elimination. $TiCl_4$ and $SnCl_4$ failed to promote the reaction between **4** and **7**, instead decomposition of **4** through β-elimination took place.[12] On the contrary, **4** and **7** underwent smooth condensation in the presence of $MgBr_2$ (Scheme II). A crude sample of condensation product checked by ^{1}H NMR and VPC analyses showed only two aldols, epimers at C-2, in 1:1 ratio. Indeed, demasking of the methylene function afforded, in good yield, ester *syn*-**9** as the only detectable product (Table I, entry 6). Thus **4** appeared to be superior to **3** both in securing high yield and promoting diastereomeric excess. With these encouraging results in hand, we turned our attention toward the addition to α,β-dialkoxy aldehydes.

Although Keck has very recently shown that $MgBr_2$ is also effective in establishing bidentate chelation with β-alkoxy aldehydes,[13] when an α,β-dialkoxy carbonyl compound reacts in the presence of Mg^{2+} salts, products arising from α-chelation tend to prevail.[14] Addition of **3** and **4** to the (*R*)-di-*O*-benzylglyceraldehyde (**10**)/$MgBr_2$ complex

(9) 2-(Methylthio)propionic acid was prepared according to Mooradian et al. (Mooradian, A.; Cavallito, C. J.; Bergman, A. J.; Lawson, E J.; Suter, C. M. *J. Am. Chem. Soc.* **1949**, *71*, 3372) with minor modifications (see Experimental Section).

(10) For the configuration assignments to 2-methylene-3-hydroxy-4-alkoxy esters via ^{13}C and ^{1}H NMR, see: Banfi, L.; Potenza, D.; Ricca, G. S. *Org. Magn. Reson.* **1984**, 224.

(11) Analogous in situ silylations have been reported: Ireland, R. E.; Norbeck, D. W. *J. Am. Chem. Soc.* **1985**, *107*, 3279. Krizan, T. D.; Martin, J. C. *Ibid.* **1983**, *105*, 6155. Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, 495.

(12) The main reaction product (60%) was shown to be the dimethylthio acetal of aldehyde **7**. All attempts to elucidate the pathway of the acid catalyzed–SMe β-elimination by low-temperature ^{1}H NMR were unsuccessfull.

(13) Keck, G. E.; Castellino, S. *J. Am. Chem. Soc.* **1986**, *108*, 3847.

(14) Mead, K.; Macdonald, T. L. *J. Org. Chem.* **1985**, *50*, 422. Danishefky, S. J.; De Ninno, G. B.; Zelle, R. E.; Lartey, P. A. *Tetrahedron* **1986**, *42*, 2809.

Chart III

20 21

Table II. ^{13}C Chemical Shifts (ppm) of γ-Lactones 16–19 (CD_3OD)

compd	C-1	C-2	C-2′	C-3	C-4	C-5
16	181.03	56.05	62.13	74.19	83.49	16.21
17	180.33	52.80	59.56	73.41	83.46	15.87
18	180.72	55.64	61.74	72.87	86.28	63.19
19	179.85	52.35	59.29	71.98	87.20	63.12

conforms to this rule: after the usual oxidation–elimination protocol we isolated esters **11** in very high syn/anti ratio[10] (Scheme III). Here again **4** performed better than **3**.

Synthesis of 2-[(Benzyloxy)methyl] Esters 12–15. Conversion of the methylene function of esters **9** and **11** into a hydroxymethyl group seems to be particularly attractive as an approach to the synthesis of polyhydroxylated compounds.[15] However, since this transformation proved to be difficult, we were urged to investigate condensations of ketene silyl acetal **5** with aldehyde **7** and **10** (Scheme IV). **5** was obtained as a 1:1 diastereomeric mixture from methyl 3-(benzyloxy)propionate[16] by the same procedure described for **4**. As in the case of **4**, reaction with **7** and **10** took place cleanly only under $MgBr_2$ catalysis,[17] affording in good yields aldols **12** + **13** and **14** + **15**. Again, we obtained a complete α-chelation control with both aldehydes, while 2,3 relative induction was rather low (**12**/**13** 3:1, **14**/**15** 1.5:1). Configurational assignments to aldols **12–15** were performed as follows. Esters **12–15** were transformed into the corresponding γ-lactones **16–19** by hydrogenolysis (Pd/C–MeOH) and spontaneous lactonization (Scheme V). Ring closure to **18** and **19** was not complete under these conditions, but when we tried to force cyclization by heating in benzene in the presence of PTS acid, a mixture of γ- and δ-lactones was obtained.

The stereostructures of **16** and **17** were assigned by comparing their ^1H NMR with those of the known lactones **20** and **21** (Chart III).[18] The most diagnostic feature is the resonance for the C-3 proton, which appears as a double doublet with $J_{2,3}$ = 3.36 Hz and $J_{3,4}$ = 5.0 Hz for **16** (**20**, $J_{2,3}$ = 3.4 Hz, $J_{3,4}$ = 5.0 Hz) and $J_{2,3}$ = 5.1 Hz and $J_{3,4}$ = 3.05 Hz for **17** (**21**, $J_{2,3}$ = 4.7 Hz, $J_{3,4}$ = 3.3 Hz). The ^{13}C NMR spectra of lactones **16** and **17** are also useful in confirming the assigned stereostructure. The relevant diagnostic resonance is that due to C-2′, which in lactone **17** is shielded by 2.6 ppm by the cis-hydroxy group at C-3 (see Table II). An anologous shift has been observed by Heathcock.[19] A trend analogous to that reported above was shown by the ^1H NMR spectra of lactones **18** and **19**. We found $J_{2,3}$ = 4.5 Hz and $J_{3,4}$ = 6.3 Hz for **18** and $J_{2,3}$ = 5.03 Hz and $J_{3,4}$ = 3.2 Hz for **19**.

^{13}C NMR resonances are reported in Table II and are consistent with those reported for the lactic derivatives.

Conclusion. The reaction of heterosubstituted ketene silyl acetals **3** and **4** with α-alkoxy and α,β-dialkoxy aldehydes is an efficient, straightforward way to stereoselectively synthesize polyhydroxylated 2-methylene carbonyl compounds in the 3,4-syn configuration.

4 appeared to be superior to **3** both in yield and in stereoselection; $MgBr_2$ proved to be the best promoter for these reactions in that it secures diastereofacial selections up to 100:1 and seems to be the only Lewis acid that **4** is able to withstand.

The same considerations apply to the analogous reactions of 3-[(benzyloxy)methyl]ketene silyl acetal **5**, which leads to 3,4-syn 2-[(benzyloxy)methyl]-3-hydroxy-4-alkoxy esters. The application of these methodologies to the synthesis of lyxo and xylo monosaccharides is under current investigation.

Experimental Section

^1H NMR were recorded with a XL-200 or a Bruker WP-80, while ^{13}C NMR spectra were recorded with a Varian XL-200 or Varian XL-100 instruments in the FT mode with tetramethylsilane as internal standard. Optical rotations were measured in 1-dm cells of 1-mL capacity by using a Perkin-Elmer 241 polarimeter. Elemental analyses were performed with a Perkin-Elmer 240 instrument. Silica gel 60 F_{254} plates (Merck) were used for analytical TLC and 270–400 mesh silica gel (Merck) for flash chromatography. GLC analyses were performed on a Dani 3900 instrument with a capillary OV-1 column using a Hewlett-Packard 3390A integrator. HPLC analyses were performed on a Varian 5000 with a LiChrosorb Column and a UV (254-nm) detector using a Hewlett-Packard 3390A integrator. Organic extracts were dried over Na_2SO_4 and filtered before removal of the solvent under reduced pressure. "Dry" solvents were distilled under dry N_2 just before use: tetrahydrofuran (THF) was distilled from sodium metal in the presence of benzophenone, and CH_2Cl_2 and diisopropylamine were distilled from CaH_2. All reactions employing dry solvents were run under a nitrogen (from liquid N_2) atmosphere.

Methyl 2-(Methylthio)propionate. To a solution of NaOH (7.2 g, 0.180 mol) in 9 mL of water at 0 °C was added dropwise 7.3 mL (0.082 mol) of thiolactic acid. The solution was warmed up to 80 °C, and 7.8 mL (0.082 mol) of Me_2SO_4 was added; the mixture was stirred for 6 h. Sulfuric acid (1 N) was added until pH 2, and the solution was extracted with Et_2O (3 × 10 mL). The organic layers were washed with brine (10 mL) and evaporated under reduced pressure. The crude was purified by distillation, affording 3.7 g (38%) of product [bp 118–120 °C (17mm)].[9] 2-(Methylthio)propionic acid was dissolved in 15 mL of Et_2O, and excess diazomethane was added at 0 °C. Evaporation of the solvent afforded in quantitative yield methyl 2-(methylthio)-propionate: ^1H NMR ($CDCl_3$) δ 1.42 (3 H, d, J = 6.7 Hz), 2.15 (3 H, s), 3.35 (1 H, q), 3.70 (3 H, s). Anal. Found: C 44.73; H, 7.49. Calcd for $C_5H_{10}O_2S$: C, 44.75; H, 7.51.

Methyl(methylthio)ketene Methyl Trimethylsilyl Acetal (3). To a solution of 1.28 mL (9.03 mmol) of diisopropylamine in 15 mL of dry THF at 0 °C was added 5.50 mL (8.21 mmol) of a 1.5 M solution of *n*-butyllithium in hexane. After 10 min the solution was cooled at −78 °C, and methyl 2-(methylthio)-propionate (1 g, 7.46 mmol) in 3.00 mL of THF was added. The mixture was stirred for 30 min, 1.89 mL (14.92 mmol) of Me_3SiCl was added, and the resulting solution was stirred for 5 min at room temperature. The solvent was evaporated, avoiding water quenching, and 7.46 mL of dry CH_2Cl_2 was added in order to store the silyl ether **3** as a 1 M solution. A sample of the crude mixture dissolved in $CDCl_3$ showed two isomers by ^1H NMR in a 75:25 ratio: ($CDCl_3$) δ 0.21 (minor) and 0.25 (9 H, s), 1.79 (minor) and 1.82 (3 H, s), 2.10 (3 H, s), 3.50 and 3.58 (minor) (3 H, s).

Methyl 3-(Methylthio)propionate. This was synthesized as reported above for the corresponding 2-(methylthio)-substituted ester in 80% overall yield [bp 115 °C/(17mm)]: ^1H NMR ($CDCl_3$) δ 2.10 (3 H, s), 2.43–2.88 (4 H, m), 3.68 (3 H, s). Anal. Found: C, 44.78; H, 7.50. Calcd for $C_5H_{10}O_2S$: C, 44.75; H, 7.51. IR (liquid film) ν 2940, 2910, 1735, 1430, 1350, 1240 cm^{-1}.

[(Methylthio)methyl]- and [(Benzyloxy)methyl]ketene Methyl Trimethylsilyl Acetal (4 and 5). To a solution of LDA (5.6 mmol) in 24.0 mL of dry THF at −90 °C was added 2.9 mL

(15) For a review on hydroxymethyl branched sugars, see: Grisebach, H.; Schmid, R. *Angew Chem., Int. Ed. Engl.* **1972**, *11*, 159.
(16) Gresham, T. L.; Jansen, J. E.; Shaver, F. W. *J. Am. Chem. Soc.* **1948**, *70*, 998. Bloomfield, J. J. *J. Org. Chem.* **1962**, *27*, 2742.
(17) Use of $TiCl_4$ and $SnCl_4$ resulted in almost quantitative elimination of $PhCH_2OH$.
(18) Aburaki, S.; Konishi, N.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 1254.
(19) Heathcock, H. C.; Young, D. S.; Hagen, J. P.; Pirrung, M. C.; Withe, C. T.; Van Derveer, D. *J. Org. Chem.* **1980**, *45*, 3846.

(23.2 mmol) of Me_3SiCl dropwise, and after 3 min, 5.2 mmol of the corresponding methyl 3-heterosubstituted propionate was added. The mixture was stirred at room temperature (30 min for **4** and 5 h for **5**), then the solvent was quickly evaporated under reduced pressure, and 5.2 mL of dry CH_2Cl_2 was added. The 1 M solution of ketene silyl acetals **4** and **5** can be stored at least for a week at −20 °C. A sample was dissolved in $CDCl_3$ and submitted to ^1H NMR analysis. Both the silyl ethers were obtained as a 1:1 isomeric mixture.

4: ^1H NMR ($CDCl_3$) δ 0.19 and 0.23 (9 H, s), 2.01 (3 H, s), 3.12 (2 H, d, J = 8.0 Hz), 3.48 and 3.50 (3 H, s), 3.58–3.83 (1 H, m).

5: ^1H NMR ($CDCl_3$) δ 0.22 and 0.30 (9 H, s), 3.54 and 3.56 (3 H, s), 3.70–4.15 (3 H, m), 4.48 and 4.49 (2 H, s), 7.33 (5 H, s).

Lewis Acid Mediated Aldol Condensations. General Procedure. To a mixture of 1.0 mol of aldehyde and 1.1 mol of Lewis acid in 5 mL of CH_2Cl_2 at −78 °C was added 1.5 mol of ketene silyl acetal dropwise. After being stirred at the proper temperature for the required time (see Table I, Schemes III and IV), the mixture was quenched with pH 7 phosphate buffer, extracted with CH_2Cl_2 (3 × 5 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The crude was dissolved in 3 mL of $AcOH/H_2O$ (2/1) and stirred for 30 min at room temperature, then 1 M NaOH was added until pH 5, and the reaction was worked up as usual. In order to determine the C-2/C-3 diastereoselectivity, the crude condensation products were checked by VPC (100 → 190 °C 3 °C/min for aldols **8**; 120 → 180 °C 3 °C/min for the adducts derived from **4** and **7**) and by HPLC (85:15 *n*-hexane/AcOEt, flow 2.5 mL/min for **12** and **13**; 82:18 *n*-hexane/AcOEt, flow 2.5 mL/min for **14** and **15**).

Synthesis of Methylene Esters 9 and 11. Oxidation–Elimination General Procedure. To a solution of the crude condensation product (from **3** and **4** with **7** and **10**) in MeOH (10 mL) at 0 °C was added 2.4 mL of 0.5 M aqueous solution of $NaIO_4$. After being stirred at room temperature for 12 h, the mixture was filtered through a Celite pad. The filtrate was concentrated under reduced pressure, diluted with water, extracted with AcOEt, and evaporated to dryness. The crude was refluxed in 10 mL of 1,4-dioxane for 4 h, and then the solvent was evaporated under reduced pressure. The *syn*-**9**/*anti*-**9** ratio was determined by HPLC (80:20 *n*-hexane/AcOEt, flow 1.5 mL/min) and ^1H NMR analyses; the crude product was purified by flash chromatography (70:30 *n*-hexane/AcOEt). For yields, see Table I.

syn-**9**: ^1H NMR ($CDCl_3/D_2O$) δ 1.22 (3 H, d, J = 6.4 Hz), 3.73 (3 H, s), 3.55–3.85 (1 H, m), 4.35–4.70 (3 H, m), 5.91 (1 H, t, J = 1.2 Hz), 6.31 (1 H, m), 7.30 (5 H, s); IR ($CHCl_3$) ν 3680, 3600, 3540, 2980–2860, 1710, 1595 cm^{-1}. Anal. Found: C, 67.10; H, 7.30. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. $[\alpha]^{25}_D$ +25.4° (*c* 0.3, $CHCl_3$).

anti-**9**: ^1H NMR ($CDCl_3$) δ 1.09 (3 H, d, J = 6.3 Hz), 3.73 (3 H, s), 3.70–4.10 (1 H, m), 4.35–4.70 (3 H, m), 6.00 (1 H, t, J = 1.3 Hz), 6.31 (1 H, m), 7.35 (5 H, s).

The *syn*-**11**/*anti*-**11** ratio was determined by HPLC (80:20 *n*-hexane/AcOEt). For yields, see Scheme III.

syn-**11**: ^1H NMR ($CDCl_3/D_2O$) δ 3.60–3.90 (3 H, m), 3.67 (3 H, s), 4.51 (1 H, d, J = 11.5 Hz), 4.53 (2 H, s), 4.60 (1 H, m), 4.67 (1 H, d, J = 11.5 Hz), 5.96 (1 H, m), 6.33 (1 H, m), 7.25–7.35 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 51.53, 70.60, 70.84, 73.16, 73.28, 78.53, 126.03, 137.92, 140.16, 166.31; IR ($CHCl_3$) ν 3530, 2980–2840, 1700, 1620. Anal. Found: C, 70.68; H, 6.70. Calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.78. $[\alpha]^{25}_D$ −6.8 (*c* 5.4, $CHCl_3$).

anti-**11**: ^1H NMR ($CDCl_3$) δ 3.36 (1 H, br d), 3.60–3.90 (3 H, m), 3.70 (3 H, s), 4.45 (1 H, d, J = 11.5 Hz), 4.52 (1 H, d, J = 11.5 Hz), 4.60 (1 H, m), 4.63 (1 H, d, J = 11.5 Hz), 4.71 (1 H, d, J = 11.5 Hz), 5.94 (1 H, m), 6.30 (1 H, m), 7.25–7.35 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 51.60, 69.61, 71.51, 72.22, 73.42, 79.08, 126.26, 138.14, 139.25, 166.44.

Synthesis of 2-[(Benzyloxy)methyl] Esters 12 and 13. $MgBr_2$-mediated condensation between **7** and **5** was carried out as described above. The crude condensation product was purified by flash chromatography (75:25 *n*-hexane/AcOEt), affording pure **12** (60.7%) and **13** (20.2%).

12: ^1H NMR ($CDCl_3/D_2O$) δ 1.28 (3 H, d, J = 6.4 Hz), 2.90–3.20 (1 H, m), 3.60 (3 H, s), 3.50–3.72 (1 H, m), 3.73–3.98 (3 H, m), 4.51 (2 H, s), 4.37 (1 H, d, J = 10.7 Hz), 4.63 (1 H, d, J = 10.7 Hz), 7.35 (10 H, s); ^{13}C NMR ($CDCl_3$) δ 15.57, 48.78, 51.53, 68.70, 70.95, 73.06, 73.46, 75.03, 126.70, 127.15, 127.38, 127.83, 128.15, 137.88, 140.87, 172.81. Anal. Found: C, 70.41; H, 7.28. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. $[\alpha]^{25}_D$ +30.59° (*c* 1.22, $CHCl_3$); IR (liquid film) ν 3460, 3080, 3060, 3020, 2940, 2860, 1735, 1490, 1450, 1430, 1360, 1190, 1090, 1065, 730, 690 cm^{-1}.

13: ^1H NMR ($CDCl_3/D_2O$) δ 1.30 (3 H, d, J = 6.3 Hz), 2.81–3.05 (1 H, m), 3.58 (3 H, s), 3.44–3.83 (4 H, m), 4.34 (1 H, d, J = 11.7 Hz), 4.49 (2 H, s), 4.64 (1 H, d, J = 11.7 Hz), 7.31 (10 H, s); ^{13}C NMR ($CDCl_3$) δ 15.58, 48.97, 51.54, 68.81, 70.70, 73.17, 73.37, 75.82, 127.48, 127.69, 128.18, 137.82, 138.05, 173.08. Anal. Found: C, 70.42; H, 7.29. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. $[\alpha]^{25}_D$ +20.3° (*c* 1.76, $CHCl_3$); IR (liquid film) ν 3460, 3080, 3060, 3020, 2940, 2860, 1730, 1490, 1450, 1430, 1370, 1240, 1090, 1065, 730, 690 cm^{-1}.

Synthesis of 2-[(Benzyloxy)methyl] Esters 14 and 15. Condensation between **10** and **5** was carried out as described above (see General Procedure). The crude condensation product was purified by flash chromatography (75:25 *n*-hexane/AcOEt), affording **14** (48%) containing 5% of inseparable $PhCH_2OH$ and pure **15** (32%).

14: ^1H NMR ($CDCl_3/D_2O$) δ 2.91–3.22 (1 H, m), 3.51–4.20 (9 H, m), 4.39–4.65 (6 H, m), 7.30 (15 H, br s); ^{13}C NMR (selected data) ($CDCl_3$) δ 48.87, 51.74, 68.80, 70.58, 70.92, 72.98, 73.22, 73.53, 77.49, 172.81.

15: ^1H NMR ($CDCl_3/D_2O$) δ 2.80–3.10 (1 H, m), 3.40–3.80 (8 H, m), 3.90–4.12 (1 H, m), 4.35–4.59 (6 H, m), 7.25 (15 H, br s); ^{13}C NMR (selected data) ($CDCl_3$) δ 47.36, 51.76, 68.74, 70.10, 70.50, 72.58, 73.20, 73.56, 78.53, 173.58. Anal. Found: C, 72.45; H, 6.88. Calcd for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94. $[\alpha]^{25}_D$ −8.7° (*c* 0.93, $CHCl_3$); IR (liquid film) ν 3470, 3080, 3060, 3020, 2940, 2860, 1730, 1490, 1450, 1430, 1360, 1260, 1200, 1165, 1090, 1020, 730, 690 cm^{-1}.

Synthesis of γ-Lactones 16–19. General Procedure. Each of the aldols **12–15** (0.15 mmol) in MeOH (3 mL) was hydrogenated in the presence of 10% Pd/C (4 mg) for 24 h at room temperature. The crude reaction mixture was filtered and the solvent evaporated to give the γ-lactone. **16** and **17** were obtained in quantitative yields.

16: ^1H NMR (CD_3OD) δ 1.39 (3 H, d, J = 6.53 Hz), 2.62–2.68 (1 H, m $J_{2,3}$ = 3.36 Hz), 3.83–3.98 (2 H, m, $J_{2'A,2'B}$ = 10.85 Hz), 4.43–4.47 (1 H, m, $J_{3,4}$ = 5.0 Hz), 4.67–4.80 (1 H, m). Anal. Found: C, 49.33; H, 6.88. Calcd for $C_6H_{10}O_4$: C, 49.31; H 6.90. $[\alpha]^{25}_D$ −63.4° (*c* 1.16, CH_3OH).

17: ^1H NMR (CD_3OD) δ 1.37 (3 H, d, J = 6.41 Hz), 2.85–3.02 (1 H, m, $J_{2,3}$ = 5.1 Hz), 3.84–3.91 (2 H, m), 4.38–4.42 (1 H, m, $J_{3,4}$ = 3.05 Hz), 4.48–4.59 (1 H, m). Anal. Found: C, 49.38; H, 6.95. Calcd for $C_6H_{10}O_4$: C, 49.31; H, 6.90. $[\alpha]^{25}_D$ −85.3° (*c* 1.03, CH_3OH).

18 and **19** were always contaminated by 5% of the corresponding methyl esters.

18: ^1H NMR (CD_3OD) δ 2.67–2.74 (1 H, m, $J_{2,3}$ = 4.5 Hz), 3.78–3.96 (4 H, m), 4.49–4.64 (2 H, m, $J_{3,4}$ = 6.3 Hz).

19: ^1H NMR (CD_3OD) δ 2.90–3.03 (1 H, m, $J_{2,3}$ = 5.03 Hz), 3.83–3.93 (4 H, m), 4.39–4.47 (1 H, m, $J_{3,4}$ = 3.2 Hz), 4.58–4.62 (1 H, m).

^{13}C NMR data are reported in Table II.

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Registry No. (*E*)-**3**, 104699-42-5; (*Z*)-**3**, 104699-47-0; (*E*)-**4**, 106296-38-2; (*Z*)-**4**, 106296-47-3; (*E*)-**5**, 106296-39-3; (*Z*)-**5**, 106296-48-4; **7**, 81445-44-5; *syn*-**9**, 104699-43-6; *anti*-**9**, 104699-44-7; **10**, 20196-70-7; *syn*-**11**, 104699-45-8; *anti*-**11**, 104699-46-9; **12**, 106296-40-6; **13**, 106296-41-7; **14**, 106296-42-8; **15**, 106296-43-9; **16**, 106296-44-0; **17**, 106375-39-7; **18**, 106296-45-1; **18** (methyl ester), 106296-49-5; **19**, 106296-46-2; **19** (methyl ester), 106296-50-8; Me_3SiCl, 75-77-4; $HSCH_2CH_2CO_2H$, 107-96-0; $PhCH_2OCH_2CH_2CO_2Me$, 4126-60-7; $MgBr_2$, 7789-48-2; thiolactic acid, 79-42-5; 2-(methylthio)propionic acid, 58809-73-7; methyl 2-(methylthio)propionate, 1320-73-6; methyl 3-(methylthio)-propionate, 13532-18-8.