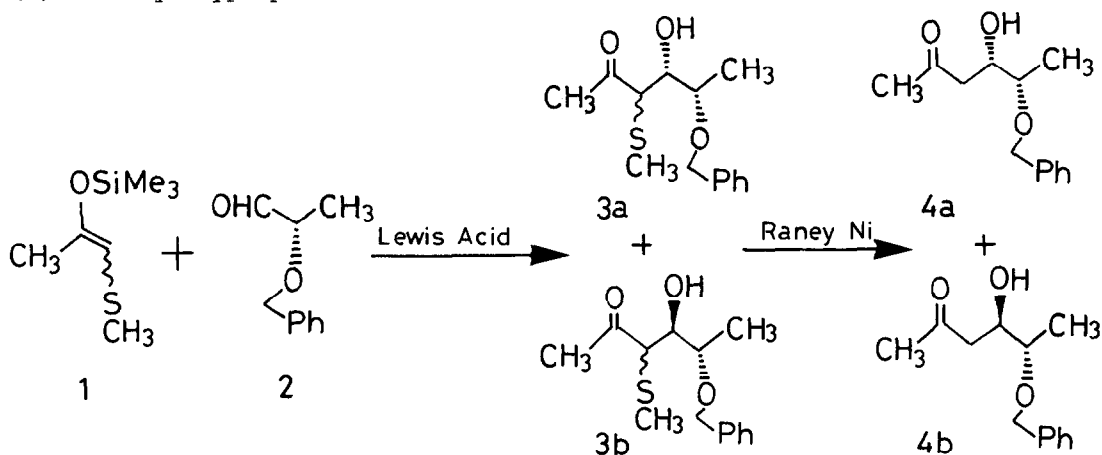


LEWIS ACID MEDIATED 1,2-ASYMMETRIC *Lk*-INDUCTION TO α -ALKOXYALDEHYDE:
SYNTHESIS OF α -NONSUBSTITUTED β, γ -*syn*-DIHYDROXYKETONE AND ESTER

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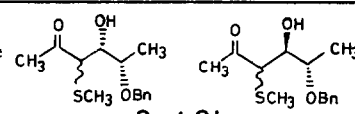
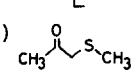
Lewis acid mediated reactions of methylthio substituted silyl enolate or ketene silyl acetal to α -alkoxyaldehyde give *syn* diols. A novel stereocontrolled synthesis of α -nonsubstituted β, γ -dihydroxyketone and ester is described.

Since the pioneering work of Cram¹⁾ in addition stereochemistry to chiral aldehyde, a number of efforts to control the stereochemistry have been paid²⁾. Particularly during the last few years, the diastereoselective addition to α -alkoxyaldehyde³⁾ has attracted much interest in relation to construct acyclic polyhydroxy compounds. Herein we report the stereochemical results of Lewis acid promoted addition of silyl enolate (1) and ketene silyl acetal (5) to (S)- α -benzyloxypropanal (2).



The reaction of the silyl enolate 1⁴⁾ with the aldehyde 2 in the presence of SnCl₄ in CH₂Cl₂ at -78° gave the aldol adducts (3), which contain four

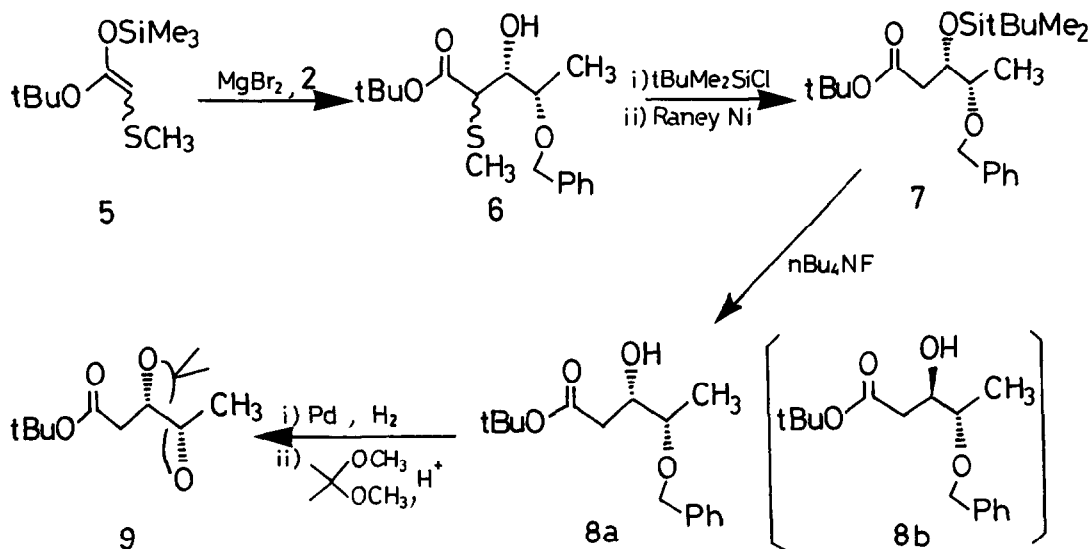
Table I. Stereochemical Results in the reaction of the Silyl Enolate 1 and the Aldehyde 2 with Various Lewis Acids

Entry	Substrate 1	Lewis Acid ^{a, b)}	Solvent	Temp. (°C)	Time (hr)	 3a : 3b	Yield ^{c)} (%)
1	E	SnCl ₄	CH ₂ Cl ₂	-78	0.5	80 : 20	58
2	Z	SnCl ₄	CH ₂ Cl ₂	-78	0.5	82 : 18	53
3	E	SnBr ₂	CH ₂ Cl ₂	0	2.0	24 : 76	34
4	E	MgBr ₂	CH ₂ Cl ₂	0	15.0	99 : 1	70
5	E	ZnCl ₂	CH ₂ Cl ₂	0	1.0	94 : 6	55
6	E	ZnCl ₂	THF	0	24.0	38 : 62	39
7	E	ZnI ₂	CH ₂ Cl ₂	0	0.5	85 : 15	21
8	E	ZrCl ₄	CH ₂ Cl ₂	-78	0.3	60 : 40	18
9	E	BF ₃ ·OEt ₂	CH ₂ Cl ₂	-78	0.3	44 : 56	51
10	E	FeCl ₃	CH ₂ Cl ₂	-78	1.5	83 : 17	54
11 ^{d)}		LDA	THF	-78	0.5	12 : 88	85

a; SnCl₄ and BF₃·OEt₂ were used after distillation. MgBr₂ was freshly prepared by Mg and 1,2-dibromoethane, and other Lewis acids were well dried over P₂O₅ under reduced pressure and used. b; Typical experiment, To a suspension or solution of Lewis acid (1~2 eq) in the solvent (0.2~0.5 M) 2 was added, and the mixture was stirred for 5 to 30 min, then 1 was dropped. c; Isolated yields. d; Basic aldol condition.

diastereomers identified by tlc (rf value; 0.33, 0.35, 0.39 and 0.44, silica gel, hexane:ether, 1:1) and nmr spectra (SCH₃ chemical shifts; 1.92, 2.00, 1.95 and 2.05 ppm). They were separable by flash chromatography on silica gel and desulfurized respectively by Raney Ni to lead diastereomer 4a or 4b. Thus the two isomers having the methylthio group at 1.92 and 1.95 ppm gave the *syn* diol 4a, and the other two at 2.00 and 2.05 ppm *anti* diol 4b. We examined various Lewis acids and their stereochemical results are summarized in Table I. The ratios were determined by integration value of the methylthio group in the nmr, and also confirmed as follow; The crude aldol product was treated with Raney Ni (W-2) carefully. The resultant mixture of 4a and 4b was silylated with *t*-butyldimethylsilyl chloride and then analyzed by gas chromatography. In most of the cases except entries 3, 6 and 9, this Lewis acid

mediated aldol addition preferred *syn* diol 3a, which can be accounted for the cyclic intermediate⁵⁾. Similar highly *syn* selective aldol addition to the same aldehyde 2 by silyl enolate of t-butylmethylketone was reported recently⁶⁾ but this ketone has no proton at α' adjacent to the carbonyl group. The use of $MgBr_2$ or $ZnCl_4$ in CH_2Cl_2 at $0^\circ C$ gave excellent selectivity with satisfactory yields, while that of $ZnCl_4$ in THF gave reversed stereochemistry. $SnBr_2$ and $BF_3 \cdot OEt_2$ showed *anti* preference, of which the results were similar to that observed by the reaction with lithium salt of methylthioacetone.



Although the reaction of lithium salt of t-butyl acetate with 2 gave β -hydroxy- γ -benzyloxyester 8 as *syn* and *anti* diastereomeric mixtures (8a:8b, 2:3)⁷⁾, ketene silyl acetal 5⁸⁾ brought about high *syn* selectivity ($\sim 25:1$). Treatment of 5 and 2 with $MgBr_2$ (2 eq) in CH_2Cl_2 at $0^\circ C$ for 36 hr gave 6 in 55% yield. Silylation of this aldol product followed by desulfurization afforded 7⁹⁾ in 62% yield. Deprotection of the silyl group gave 8a quantitatively as a single isomer.¹⁰⁾ Reductive removal of benzyl group of 8a followed by acid catalyzed reaction with 2,2-dimethoxypropane provided the acetonide 9¹¹⁾ in 82% yield.

These compounds (4, 7, 8 and 9) obtained here are potentially useful as building blocks for construction of complex polyoxo macrolides or ionophores. For example, 3,4-*syn*-dihydroxyvaleric acid is important component on 12-members lactones, Aplysiatoxin or Oscillatoxin¹²⁾

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- 4) b.p. 68-72°/1.3 mmHg, E isomer (E:Z,4:1) was prepared by lithium salt of methylthioacetone and trimethylsilyl chloride in THF at -78°C, and Z isomer (E:Z,1:5) by methylthioacetone and trimethylsilyl chloride with Et₃N and DMAP in CH₂Cl₂ at room temperature.
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- 7) The reaction of methyl acetate with 2 gave 1:1 mixtures; see C.H.Heathcock, S.D.Young, J.P.Hagen, M.C.Pirrung, C.T.White and D.VanDerveer, *J.Org.Chem.*, 45, 3846 (1980). The ratio of 8a and 8b was determined by gas chromatography after leading to the silyl ether.
- 8) b.p. 70-1°/2 mmHg, prepared from t-butyl methylthioacetate and trimethylsilyl chloride in basic condition (LDA, THF, -78°C).
- 9) $[\alpha]_D^{18}$ -19.2 (c 2.0, CHCl₃), NMR (CDCl₃) δ; 7.31 (3H, s), 4.54 (2H, s), 4.27 (1H, m), 3.53 (1H, m), 2.59 (1H, dd J=3.2, 15.4 Hz), 2.25 (1H, dd J=8.0, 15.4 Hz), 1.43 (9H, s), 1.11 (3H, d J=6.3 Hz), 0.84 (9H, s), 0.33 (3H, s), 0.00 (3H, s)
- 10) Direct desulfurization of 6 to 8 was troublesome giving over reduced product.
- 11) $[\alpha]_D^{18}$ -3.5 (c 1.7, CHCl₃), NMR (CDCl₃) δ; 3.87 (1H, m), 3.85 (1H, m), 2.45 (2H, dd J=1.8, 6.3 Hz), 1.46 (9H, s), 1.40 (3H, s), 1.38 (3H, s), 1.28 (3H, d J=5.7 Hz)
- Another isomer 9', NMR (CDCl₃) δ; 4.44 (1H, m), 4.42 (1H, m), 2.49 (2H, dd J=1.8, 6.3 Hz), 1.46 (9H, s), 1.43 (3H, s), 1.34 (3H, s), 1.16 (3H, d J=5.9 Hz)
- The structures of 9 and 9' were determined by NMR shift reagent experiment. When Eu(fod)₃ was added into the mixture, C₄-H of 9 was less moved down than that of 9'. The cis acetonide 9' would take advantage to make contact with Eu(fod)₃ so that the proton (C₄-H) may behave moving larger than that of 9. The structure of 9' was also confirmed to lead (+)-Blastmycinone, J.Uenishi, H.Tomozane and M.Yamato, in press.
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