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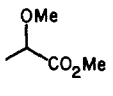
ACYCLIC STEREOSELECTION. 28. USE OF STEREOSELECTIVE ALDOL METHODOLOGY IN THE TOTAL SYNTHESIS OF CLADINOSE.[1]

Clayton H. Heathcock* and Stephen H. Montgomery[2]

Department of Chemistry, University of California
Berkeley, California 94720

Abstract: Reactions of (S)-2-benzyloxypropanal (**4**) with the lithium, magnesium, and zirconium enolates of methyl 2-methoxypropanoate (**1**) and with ketene acetals 2 and 3 have been studied and the stereostructures of the resulting products elucidated. The major stereoisomer resulting from the metal enolate additions has been converted into the branched sugar cladinose (5).

In a recent paper, we reported an investigation of the simple diastereoselection observed in the reactions of the lithium enolates of α-alkoxy esters with achiral aldehydes.[3] One of the compounds studied, methyl 2-methoxypropanoate (**1**), was found to show high stereoselectivity in reactions with α-branched aliphatic aldehydes. In this Letter, we report an investigation of the simple and diastereofacial selectivity of this α-alkoxy ester and its derived silyl ketene acetals 2 and 3 in reactions with (S)-2-benzyloxypropanal (**4**). An application of 1 in a total synthesis of the branched sugar cladinose (**5**)[4,5] is also reported.



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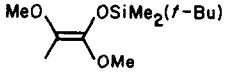

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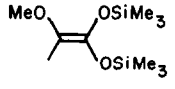

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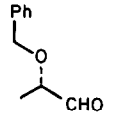

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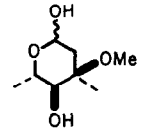

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As shown in Scheme 1, the lithium, magnesium, and zirconium enolates of ester 1 were prepared and allowed to react at -78 °C with aldehyde **4**. In each case, stereoisomeric methyl esters **6a-9a** are produced in the ratios shown in Table 1. In a parallel set of experiments, silyl ketene acetals 2 and 3 were allowed to react with aldehyde **4** in methylene chloride at -78 °C under Lewis acid catalysis. Again, stereoisomeric products are produced, methyl esters **6a-9a** from ketene acetal **2** and carboxylic acids **6b-9b** from ketene acetal **3**. The two series of compounds were correlated by conversion of esters **6a-9a** to the corresponding carboxylic acids **6b-9b** (KOH/CH_3OH). As will be shown, the stereostructure of ester **6a** is vouchsafed by its eventual conversion into cladinose, **5**. The structures of the other three isomers, **7-9** have also been rigorously determined; details will be reported in a forthcoming full paper on the subject.

Scheme 1

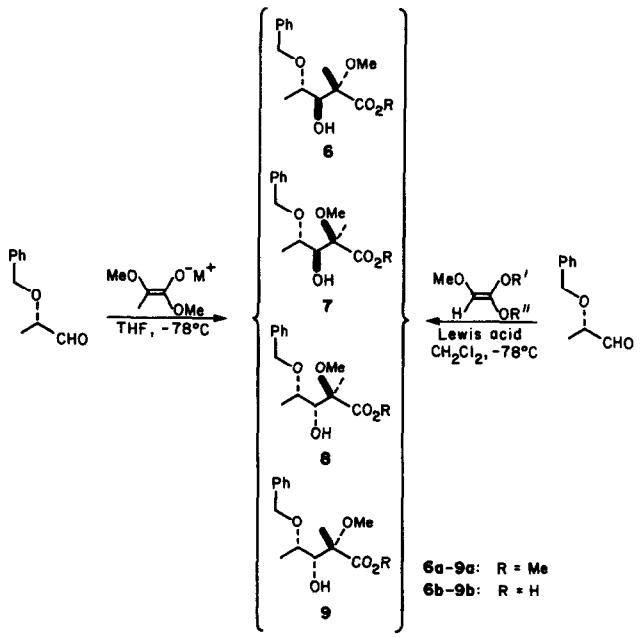


Table 1

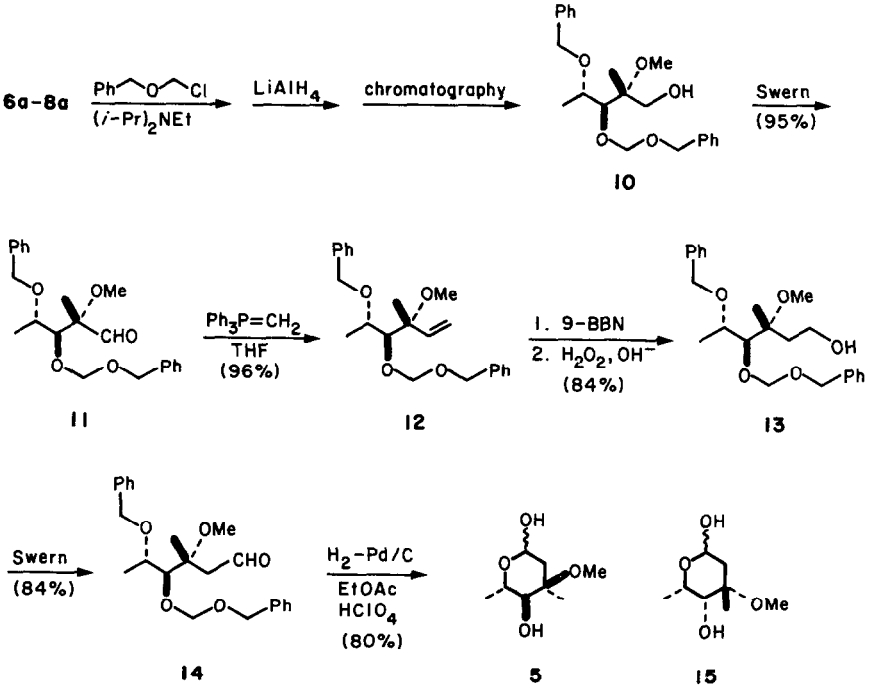
Stereochemistry of Reaction of Aldehyde **4** with Ester **1** and Ketene Acetals 2 and 3

Reactant	Conditions	R	Product Composition 6	7	8	9
1	Li enolate[a]	Me	70	23	7	0
1	Li enolate[b]	Me	63	21	17	0
1	Li enolate[c]	Me	66	25	8	0
1	Mg enolate[d]	Me	50	16	16	16
1	Zr enolate[e]	Me	47	40	13	0
2	$BF_3 \cdot OEt_2$[f]	Me	0	0	67	33
3	$BF_3 \cdot OEt_2$[f]	H	20	30	30	20
3	$SnCl_4$[f]	H	0	0	95	5

(a) Enolate formed with LDA at -78 °C. (b) Enolate formed with LDA at -100 °C. (c) Enolate formed with lithium bis(trimethylsilyl)amide at -78 °C. (d) Enolate formed with bis(cyclohexyl)aminomagnesium bromide at -78 °C. (e) Enolate formed by addition of bis(cyclopentadienyl)zirconium dichloride to the lithium enolate at -78 °C. (f) Reaction carried out by addition of 1.0 mole-equivalent of the indicated Lewis acid to a solution of the aldehyde in CH_2Cl_2 at -78 °C, followed by addition of the silyl ketene acetal.

For the synthesis of cladinose, (S)-2-benzyloxypropanal (**4**) was prepared from commercially-available ethyl (S)-lactate by the procedure of Wuts.[6] As shown in Scheme 2, reaction of **4** with a THF solution of the lithium enolate of ester **1** at -78 °C gives an approximate 7:2:1 mixture of stereoisomeric hydroxy esters **6a**, **7a**, and **8a**. After protection of the secondary hydroxy group with benzyloxymethyl chloride and Hunig's base, the isomeric mixture is reduced by lithium aluminum hydride, and the resulting mixture of alcohols separated by chromatography on silica gel. The major isomer, **10**, is obtained in 54% yield, based on aldehyde **4**. Oxidation of **10** by Swern's procedure[7] provides an aldehyde (**11**), which is subjected to Wittig methylenation to obtain **12**. Hydroboration of the latter substance (9-borabicyclo[3.3.0]nonane)[8] gives primary alcohol **13** in 84% yield. A second Swern oxidation affords aldehyde **14** (84%), which is reduced by hydrogen in ethyl acetate, in the presence of 5% Pd/C and 0.1% $HClO_4$ to obtain L-cladinose (**5**), as a mixture of α- and β-anomers. The synthetic cladinose was identical by ^1H NMR with a sample prepared by acidic hydrolysis of erythromycin A.[4a] Although we have not done so, the same sequence of steps could presumably be used to convert diol **8**, obtained as virtually the only isomer in the $SnCl_4$-mediated reaction of ketene acetal 3 with aldehyde **4**, into the cladinose isomer **15**.

Scheme 2



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References and Notes

1. For part 27, see C.H. Heathcock, K.T. Hug, and L.A. Flippin, Tetrahedron Lett., in press.

2. Current address: Jackson Laboratories, E. I. du Pont de Nemours, Inc., Wilmington, DE 19898.

3. C.H. Heathcock, M.C. Pirrung, S.D. Young, J.P. Hagen, E.T. Jarvi, U. Badertscher, H.-P. Märki, and S.H. Montgomery, J. Am. Chem. Soc., in press.

4. (a) E.H. Flynn, M.V. Sigal, Jr., P.F. Wiley, and K. Gerzon, J. Am. Chem. Soc., **76**, 3121 (1954); (b) P.F. Wiley and O. Weaver, ibid., **78**, 808 (1956); (c) W. Hofheinz, H. Grisebach, and H. Friebolin, Tetrahedron, **18**, 1265 (1962).

5. For previous total syntheses of cladinose, see: (a) D. Lemal, P.D. Pacht, and R.B. Woodward, Tetrahedron, **18**, 1275 (1962); (b) B. Flaherty, W.G. Overend, and N.R. Williams, J. Chem. Soc. (C), 398 (1966); (c) G.B. Howarth and J.K.N. Jones, Can. J. Chem., **45**, 2253 (1967).

6. P.G.M. Wuts and S.S. Bigelow, J. Org. Chem., **48**, 3489 (1983).

7. A.J. Mancuso, S.-L. Huang, and D. Swern, J. Org. Chem., **43**, 2480 (1978).

8. H.C. Brown, E.F. Knight, and C.G. Scouten, J. Am. Chem. Soc., **96**, 7765 (1974).

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