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DIASTEREOSELECTION IN 1,3-O- TO -C-ALKYL MIGRATION REACTION OF 1-ALKENYL ALKYL ACETALS CATALYZED BY BORON TRIFLUORIDE ETHERATE

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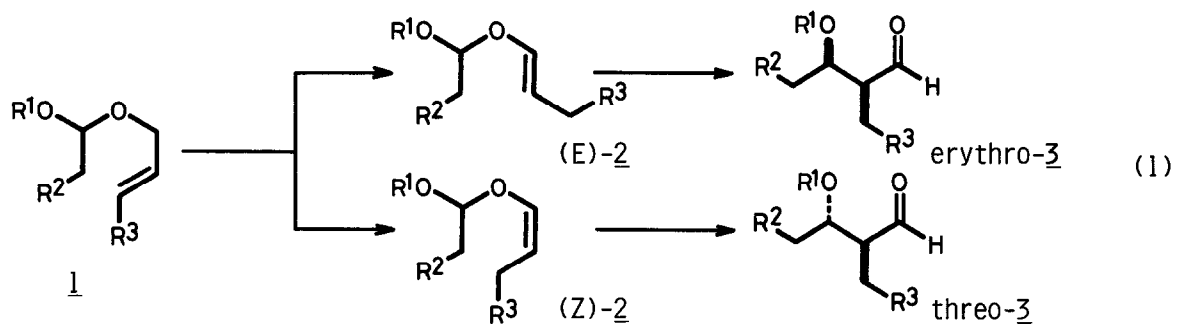
Abstract Remarkable diastereoselection, with (E)-alkenyl alkyl acetal giving selectively the *erythro* α-alkyl-β-alkoxyaldehyde, and (Z)-acetal leading preferentially to the *threo* isomer, is observed in the 1,3-O- to -C-alkyl migration reaction of 1-alkenyl alkyl acetals catalyzed by boron trifluoride etherate.

The aldol condensation reaction is one of the most useful methods of constructing the carbon skeletons with oxygen functionalities in a 1,3-relationship. With the end of the synthesis of macrolide and ionophore antibiotics, stereoselective aldol condensation has intensively been studied in recent years, and a number of methods that attain high stereoselection have been developed [1] In the preceding paper, we reported a novel method for the preparation of α-alkyl-β-alkoxyaldehydes and -ketones via a double bond migration and subsequent 1,3-O- to -C-alkyl migration reaction catalyzed by boron trifluoride etherate.[2] We describe herein a diastereoselective 1,3-O- to -C-alkyl migration reaction of 1-alkenyl alkyl acetals, where (E)-acetals give selectively the *erythro* aldehydes, and (Z)-acetals predominantly afford the *threo* aldehydes (Eq. 1)



(1)

Reactions are carried out by using the selectively prepared (E)- and (Z)-1-alkenyl alkyl acetals[3] as reactants To a stirred solution of 1-alkenyl alkyl acetal in dry dichloromethane was added 0.5 equiv of $BF_3.Et_2O$ at -78°C. The reaction mixture is quenched by the addition of saturated aqueous sodium bicarbonate 3 min after the addition of BF_3 Et_2O. After separation of the layers, the aqueous layer is extracted with dichloromethane and the combined organic layers are washed with water and dried over anhydrous magnesium sulfate Removal of the solvent by

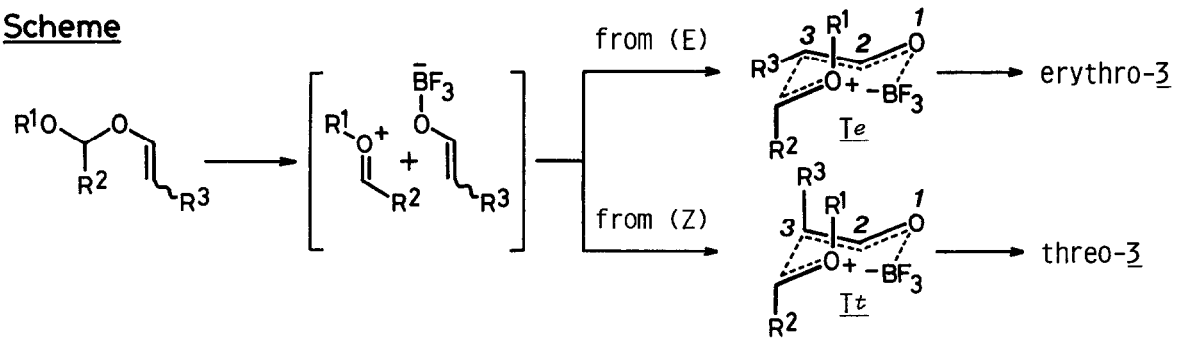
Table 1. Diastereoselective 1,3-O- to -C-Alkyl Migration Reaction of 1-Alkenyl Alkyl Acetals (2) Catalyzed by Boron Trifluoride Etherate[a]

	1-Alkenyl Alkyl Acetal (2)				α-Alkyl-β-alkoxyaldehyde (3)	
	R^1	R^2	R^3	E/Z[b]	isolated yield (%)	erythro/threo[c]
a	Me	H	H	98/2	75	92/8
	Me	H	H	3/97	78	27/73
b	Et	H	H	98/2	95	95/5
	Et	H	H	3/97	94	25/75
c	i-Bu	H	H	98/2	90	95/5
	i-Bu	H	H	3/97	88	26/74
d	Et	H	Me	98/2	85	90/10
e	Et	Me	H	98/2	82	94/6
	Et	Me	H	4/96	79	30/70
f	Bz	Me	H	98/2	90	98/2
	Bz	Me	H	3/97	92	40/60

a; All reactions were conducted in dry dichloromethane in the presence of 0.5 equiv of boron trifluoride etherate at -78°C.
b; Determined by means of GLC.
c; Determined from the aldehyde resonance in the ^{1}H-NMR spectra.

evaporation affords the α-alkyl-β-alkoxyaldehyde (3) in excellent yield. Diastereomer ratio was determined from the aldehyde resonance in the ^{1}H-NMR spectra of the crude α-alkyl-β-alkoxyaldehydes.[4] Typical example is provided by the 1,3-O- to -C-alkyl migration of acetaldehyde ethyl propen-1-yl acetal (2b: E/Z=98/2). The crude product isolated in this reaction (95% yield) consisted of 95% of *erythro* 2-methyl-3-ethoxybutanal (*erythro*-3b) and 5% of *threo* 2-methyl-3-ethoxybutanal (*threo*-3b). In the present case, well-established $J_{threo} > J_{erythro}$ relationship[5] could not be applied to the assignment of the product because of lack of the hydrogen bonded conformation in 3. Therefore, the stereochemistry and the diastereomer ratio of the product, 3b, were determined in comparison with the authentic *threo*-3b derived from tiglic acid.[6] The results of the $BF_3.Et_2O$-catalyzed 1,3-alkyl migration of (E)- and (Z)-1-alkenyl alkyl acetals (2a-2f) are given in Table 1. The results may be summarized as follows: under kinetically controled conditions, (E)-1-alkenyl alkyl acetals are selectively converted to *erythro* α-alkyl-β-alkoxyaldehydes, and (Z)-1-alkenyl alkyl acetals are lead to *threo* α-alkyl-β-alkoxyaldehydes with the diminution of the diastereoselectivity. Diastereoselection attained in the present reaction is different from that observed in the aldol reaction, in which (Z)-lithium enolate gives *erythro* aldol, and (E)-lithium enolate affords *threo* aldol.[1] Such a diastereoselection would be explained by the mechanism illustrated in the following scheme, which involves electrostaically stabilized chair transition state. Cleavage of carbon-oxygen bond of 1-alkenyl alkyl acetal (2) induced by $BF_3.Et_2O$ would generate the intermediary ion-pair of (E)-carboxonium ion[7] and vinyloxyborate. In both transition states, *Te* and *Tt*, R^1 would be forced to occupy the axial position by the $R^2 \leftrightarrow C(3)$ and $R^1 \leftrightarrow BF_3$ interactions. Lowering of the *threo* selection relative to *erythro* one is rationalized by the destabilized *threo* transition state, *Tt*, owing to the $R^1 \leftrightarrow R^3$ interaction.

Scheme



By use of various Lewis acids, such as $ZnCl_2$, $AlCl_3$, Et_2AlCl, $SnCl_4$, $TiCl_4$, $RuCl_3$, $NiCl_2$, $PdCl_2$, and some Pd(II) complexes, similar diastereoselection was attained though the selectivity was lowered to some extent.

The 1,3-O- to -C-alkyl migration reaction of cyclic acetal was also examined. The results of the reaction of (E)- and (Z)-propen-1-yl 2-tetrahydrofuranyl ether, (E)-4 and (Z)-4, and (E)- and (Z)-propen-1-yl 2-tetrahydropyranyl ether, (E)-5 and (Z)-5, with $BF_3.Et_2O$ were given in Table 2. In these cases, *erythro* isomer was preferentially yielded independent of the geometry of alkenyl moiety, and it would be suggested that the 1,3-alkyl migration reaction of the cyclic alkenyl acetal proceeded through somewhat different transition state from that for the acyclic alkenyl acetal.

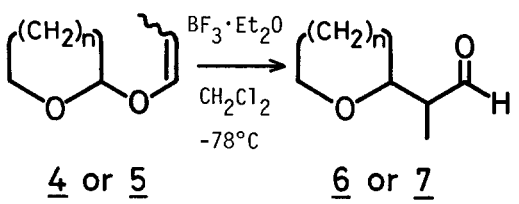


Table 2. 1,3-Alkyl Migration of 4 and 5

Acetal	E/Z	product	Yield(%)	*erythro*/*threo*
4 (n=2)	98/2	6 (n=2)	85	69/31
	5/95		89	70/30
5 (n=3)	97/3	7 (n=3)	85	62/38
	6/94		85	75/25

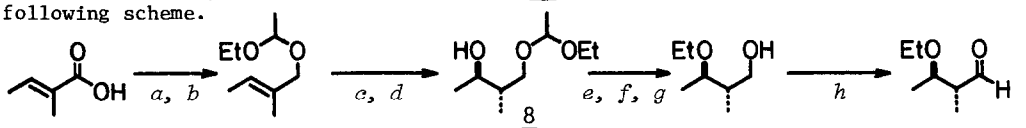
References and Notes

1 C. H. Heathcock, Ch 4, "Stereoselective Aldol Condensation", in *Comprehensive Carbanion Chemistry*, Vol. II, T. Durst and E Buncel, Eds., Elsevier, 1981, and references cited therein.
2. M. Takahashi, H. Suzuki, Y Moro-oka, and T. Ikawa, *Chem. Lett* , 1981, 1435, M. Takahashi, H Suzuki, Y. Moro-oka, and T. Ikawa, *Tetrahedron Lett.*, 23, 1079 (1982).
3 (E)-1-Alkenyl alkyl acetals were prepared from the corresponding allylic acetals (1) via a double bond migration reaction catalyzed by H_2-activated [(cycloocta-1,5-diene)Ir(PPh_2Me)$_2$]PF_6, and (Z)-1-alkenyl alkyl acetals were derived from 1 by heating of 1 in DMSO at 80°C in the presence of potassium *tert*-butoxide
4 *erythro*-3a: ^{1}H-NMR ($CDCl_3$-TMS, ppm) δ1 09(3H, d, J=7), 1 20(3H, d, J=6.5), 2.52(1H, ddq, J=1, 4 2, and 7), 3 36(3H, s), 3.80(1H, dq, J=4 2 and 6.5), 9.68(1H, d, J=1). ^{13}C-NMR ($CDCl_3$-TMS, ppm) δ8 2(q), 16.3(q), 51 3(dd), 56.6(q), 76.4(d), 204.5(d) IR (CCl_4, cm^{-1}) 2716, 1730, 1088. *threo*-3a ^{1}H-NMR ($CDCl_3$-TMS, ppm) δ1 08(3H, d, J=7), 1 18(3H, d, J=6.5), 2.54(1H, ddq, J=2.2, 6 5, and 7), 3 36(3H, s), 3.63(1H, dq, J=6.5 and 6.5), 9.63(1H, d, J=2.2). ^{13}C-NMR ($CDCl_3$-TMS; ppm) δ9.8(q), 16.2(q), 51.3(dd), 51.5(q), 76.4(d), 204.2(d). IR (CCl_4; cm^{-1}) 2716, 1730, 1093. *erythro*-3b ^{1}H-NMR ($CDCl_3$-TMS, ppm) δ1 05(3H, d, J=7), 1.16(3H, t, J=6.5), 2.00(3H, d, J=6.5), 2 50(1H, ddq, J=1.2, 4.5, and 7), 3 50(2H, m), 3 85(1H, dq, J=4.5 and 6.5), 9 64(1H, d, J=1.2). ^{13}C-NMR ($CDCl_3$-TMS; ppm) δ8 5(q), 15 5(q), 17.2(q), 51.6(dd), 64 3(t), 74.7(d), 204.8(d). IR (CCl_4, cm^{-1}) 2713, 1728, 1108.
threo-3b ^{1}H-NMR ($CDCl_3$-TMS, ppm) δ0.97-1.19(9H, m), 2.46(1H, ddq, J=2 2, 6.5, and 7), 3.46(2H,

m), 3.66(1H, dq, J=6.5 and 7), 9.56(1H, d, J=2.2). ^{13}C-NMR ($CDCl_3$-TMS; ppm) δ10.1(q), 15.5(q), 17.1(q), 51.8(dd), 64.2(t), 75.7(d), 204.6(d). IR (CCl_4; cm^{-1}) 2715, 1728, 1106.
erythro-3c: ^{1}H-NMR ($CDCl_3$-TMS; ppm) δ0.92(6H, d, J=6.5), 1.12(3H, d, J=6), 1.19(3H, d, J=6), 1.85(1H, m), 2.52(1H, ddq, J=1.2, 4.5, and 6), 3.22(2H, m), 3.86(1H, dq, J=4.5 and 6), 9.68(1H, d, J=1.2). ^{13}C-NMR ($CDCl_3$-TMS; ppm) δ8.4(q), 17.0(q), 19.4(q), 28.8(d), 51.7(dd), 75.0(d), 75.9(t), 204.9(d). IR (CCl_4; cm^{-1}) 2712, 1728, 1085.
threo-3c: ^{1}H-NMR ($CDCl_3$-TMS; ppm) δ0.92(6H, d, J=6.5), 1.10(3H, d, J=7), 1.12(3H, d, J=6.5), 1.85(1H, m), 3.24(2H, m), 3.68(1H, dq, J=6.5 and 6.5), 9.66(1H, d, J=2.2). ^{13}C-NMR ($CDCl_3$-TMS; ppm) δ10.2(q), 17.0(q), 19.4(q), 28.8(d), 51.9(dd), 75.9(d), 76.3(t), 204.7(d). IR (CCl_4; cm^{-1}) 2711, 1729, 1083.
erythro-3d: ^{1}H-NMR ($CDCl_3$-TMS; ppm) δ0.92(3H, t, J=7), 1.13(3H, d, J=6.5), 1.15(3H, t, J=7), 1.45-1.94(2H, m), 2.35(1H, m), 3.25-3.8(3H, m), 9.65(1H, d, J=2.5). ^{13}C-NMR ($CDCl_3$-TMS; ppm) δ12.1(q), 15.4(q), 17.4(q), 18.1(t), 58.7(dd), 64.3(t), 74.6(d), 205.0(d). IR (CCl_4; cm^{-1}) 2718, 1730, 1117.
erythro-3e: ^{1}H-NMR ($CDCl_3$-TMS; ppm) δ0.96(3H, t, J=7), 1.11(3H, d, J=7), 1.21(3H, d, J=7), 1.60 (2H, m), 2.58(1H, ddq, J=1.0, 4.2, and 7), 3.45-3.75(3H, m), 9.74(1H, d, J=1). ^{13}C-NMR ($CDCl_3$-TMS; ppm) δ8.1(q), 10.4(q), 15.5(q), 24.9(t), 49.6(dd), 65.5(t), 80.4(d), 204.8(d). IR (CCl_4; cm^{-1}) 2718, 1730, 1102.
threo-3e: ^{1}H-NMR ($CDCl_3$-TMS; ppm) δ0.96(3H, t, J=7), 1.08(3H, d, J=7), 1.14(3H, d, J=7), 1.62 (2H, m), 2.59(1H, ddq, J=2, 7, and7), 3.38-3.72(3H, m), 9.70(1H, d, J=2). ^{13}C-NMR ($CDCl_3$-TMS; ppm) δ9.0(q), 10.1(q), 15.5(q), 23.9(t), 49.2(dd), 65.2(t), 81.0(d), 204.7(d). IR (CCl_4; cm^{-1}) 2710, 1731, 1105.
erythro-3f: ^{1}H-NMR ($CDCl_3$-TMS; ppm) δ0.93(3H, t, J=7), 1.13(3H, d, J=6), 1.64(2H, dq, J=6 and 7), 2.56(1H, ddq, J=1, 3.8, and 6), 3.76(1H, dt, J=3.8 and 6), 4.5(2H, s), 7.26(5H, s), 9.62 (1H, d, J=1). ^{13}C-NMR ($CDCl_3$-TMS; ppm) δ8.0(q), 10.2(q), 24.3(t), 49.3(dd), 71.7(t), 79.8(d), 127.7(d), 128.4(d), 138.4(s), 204.7(d). IR (CCl_4; cm^{-1}) 3090, 3070, 3040, 2712, 1730, 1100.
threo-3f: ^{13}C-NMR ($CDCl_3$-TMS; ppm) δ8.9(q), 10.2(q), 23.5(t), 49.0(dd), 71.5(t), 80.4(d), 127.7(d), 128.4(d), 138.2(s), 204.5(d). IR (CCl_4; cm^{-1}) 3090, 3070, 3040, 2715, 1725, 1100.

5. H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, *J. Am. Chem. Soc.*, 95, 3310 (1973).

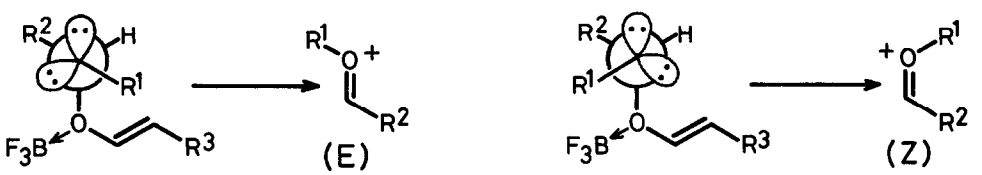
6. Standard *threo* 2-methyl-3-methoxybutanal (*threo*-3b) was derived from tiglic acid as shown in the following scheme.



a: LAH, 10°C, 2h, *b:* $EtOCH{=}CH_2$, PyH.OTs, *c:* 9-BBN, THF, rt, *d:* 0.3N aq.NaOH, H_2O_2, rt, *e:* NaH, THF-HMPA (3:1), -20°C rt, *f:* EtBr, rfx, 2h, *g:* 0.5N-HCl, THF, rt, 36h, *h:* PCC, NaOAc, CH_2Cl_2, rt, 15 min.

Formation of *threo*-8 is rationalized by the cis-addition of 9-BBN and subsequent oxidation giving alcohol in retention of stereochemistry. Moreover, in each step, it was confirmed by ^{1}H-NMR and GLC that the crude product consisted of single diastereomer. The ^{1}H- and ^{13}C-NMR spectra of the major product formed in the reaction of (Z)-2b with $BF_3.Et_2O$ were completely agreed with those of the authentic *threo* 2-methyl-3-ethoxybutanal.

7. The preferential formation of (E)-carboxonium ion would be explicable in terms of the transition state depicted in the following scheme, which took a anti-periplanar arrangement between the breaking C-O bond and the lone pair electrons on the oxygen atom of the alkoxy group. The transition state for forming (Z)-carboxonium ion would be destabilized relative to that for (E)-carboxonium ion owing to $R^1 \leftrightarrow R^2$ interaction.



Furthermore, *ab initio* and CNDO/2 studies indicate that (E)-form is favored than (Z)-form for the structure of the protonated aldehydes in agreement with experiment. (A. C. Hopkinson and I. G. Csizmadia, *Theor. Chim. Acta*, 31, 83 (1973); K. F. Purcell and T. G. M. Dolph, *J. Am. Chem. Soc.*, 94, 2693 (1972).)

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