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COMPLETE DIASTEREOFACE SELECTION IN THE LEWIS ACID-MEDIATED ALDOL REACTIONS OF *C*,*O*-DISILYLATED γ-BUTYROLACTONE ENOLATES WITH ALDEHYDES[1)]

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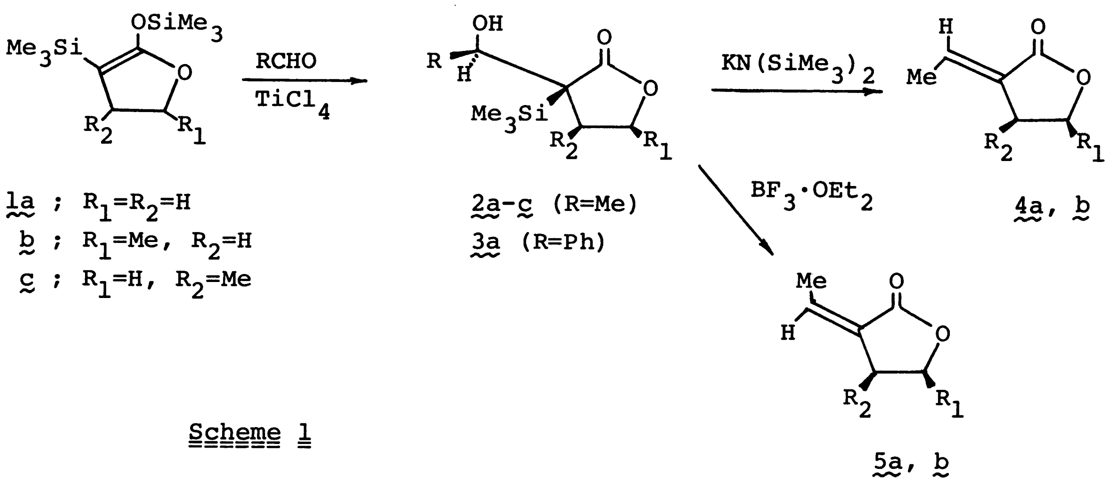
Titanium(IV) chloride-mediated reaction of 4,5-dihydro-5-methyl-2-(trimethylsiloxy)-3-(trimethylsilyl)furan (1b) with acetaldehyde gave diastereomerically pure (3*R**,5*R**,1'*S**)-4,5-dihydro-3-{1'-(hydroxyethyl)}-5-methyl-3-(trimethylsilyl)-2(3*H*)furanone (2b), exhibiting excellent diastereoface selection as well as threo diastereoselection. An anolog with 4-methyl substituent (1c) behaves similarly.

Crossed aldol condensations have been developed in full blast these few years and the aldol stereoselection (diastereoselection[2)]) as a function of both enolate geometry and enolate substituents is well recognized. Also, aldol condensations of chiral enolates with simple aldehydes or with chiral aldehydes to look at the control of stereochemistry (diastereoface selection[2)] and/or consonant Cram rule) in acyclic systems have been the subject of current interest.[3)]

We have reported that titanium(IV) chloride-mediated reaction of 4,5-dihydro-2-(trimethylsiloxy)-3-(trimethylsilyl)furan (1a), which is readily prepared from γ-butyrolactone with two equivalents of trimethylsilyl triflate, with acetaldehyde gives a purely threo aldol adduct (2a).[4,5)] Since the geometry (*Z*-enolate) of this *C*,*O*-bis-trimethylsilylated γ-butyrolactone enolate 1a constitutes so rigidly a five-membered ring framework as to give rise to pure *threo*-adduct 2a, we are interested in extending the reaction to certain substituted γ-butyrolactones and δ-valerolactone.

We wish to report here that the addition of chiral (racemic) *C*,*O*-disilylated enolates obtained from either β-methyl-γ-butyrolactone or γ-valerolactone to acetaldehyde was found to proceed with excellent diastereoface selectivity. The relative configurations of three chiral centers are determined in one step, one diastereomer being formed selectively of the four possible diastereomers (Scheme 1).[6)]

Reaction of 1b with acetaldehyde is representative: Thus, a solution of 1b (2.45 g, 10.0 mmol), prepared from γ-valerolactone, in dry dichloromethane (7.5 mL)



Scheme 1

was slowly added to a cooled (-78 °C) mixture of acetaldehyde (1.10 mL, 20.0 mmol) and titanium(IV) chloride (1.34 mL, 12.0 mmol) dissolved in dichloromethane (7.5 mL) with stirring. The reaction mixture was hydrolyzed in 1 h with aqueous methanol and worked up in a usual manner. The adduct was obtained as white curdy crystals, mp 112-113 °C, in 92% yield. Spectral data of the product: ^{1}H NMR($CDCl_3$, TMS) δ0.18 (s, $\underline{\mathrm{Me}}_3\mathrm{Si}$), 1.27(d, J=6.0 Hz, $\underline{\mathrm{Me}}\mathrm{CH(OH)}$), 1.41(d, J=6.0 Hz, $\underline{\mathrm{Me}}\mathrm{CH}$), 1.79(dd, J=14.4, 8.3 Hz, $\mathrm{CH_AH}$), 2.58(dd, J=14.4, 7.5 Hz, $\mathrm{CHH_B}$), 2.38(d, J=2.8 Hz, OH), 4.15-4.55(br m, $\mathrm{C\underline{H}OH}$), and 4.60 ppm(sym m, $\mathrm{C\underline{H}Me}$). ^{13}C{^{1}H} NMR($CDCl_3$, TMS) δ-3.0(q), 20.4(q), 22.0(q), 33.1(t), 46.7(s), 69.9(d), 76.0(d), and 180.5(s). IR($CHCl_3$) 3600 and 3450 (ν_{OH}) and 1735 cm^{-1}($\nu_{C=O}$). In addition to the requisite spectral data given above, a NOE measurement exhibited that the irradiation at trimethylsilyl protons resulted in a clean increment of integrations of both methyl signals (13% and 18%, respectively). All these data support the adduct to be diastereomerically pure 2b, the NOE being indicative of $Me_3Si \leftrightarrow Me$ syn interactions.

We have already shown a complete *threo*-diastereoselection in the parent adduct 2a on the basis of a base-induced *syn*-elimination of the latter which gave almost pure (E)-α-ethylidene-γ-butyrolactone (4a).[4] Thus, 2b was also subjected to the Peterson olefination. The product was found to be (E)-α-ethylidene-γ-valerolactone (4b),[7] reinforcing that the same stereochemical control operates in the formation of 2b as in 2a.

In the Table are summarized all results obtained for crossed aldol reactions of simple or chiral (racemic) *C,O*-bis-trimethylsilylated γ-butyrolactone enolates, and δ-valerolactone enolate with aldehydes.

As is seen from the Table, complete *threo*-selectivity (based on NMR analysis of the crude product) of the adduct is attained in all cases including a six-membered

Table. Crossed Aldol Reactions of *C*,*O*-Disilylated γ-Butyrolactone Enolates (1a-c) and δ-Valerolactone Enolate (1d) with Aldehydes.

Entry	Substrate	Aldehyde	Product	Yield, %	Erythro : Threo[a]
1	1a	MeCHO	2a	98	0 : 100
2	1a	PhCHO	3a[b]	96	0 : 100
3	1b	MeCHO	2b	92	0 : 100
4	1c	MeCHO	2c	95	0 : 100
5	1d[c]	MeCHO	2d[d]	82	0 : 100

[a] Based on NMR analysis of the crude product (*cf*. ref. 3).

[b] (3*R**,1'*S**)-4,5-Dihydro-3-(α-hydroxybenzyl)-3-(trimethylsilyl)-2(3*H*)furanone.8)

[c] 3,4-Dihydro-6-(trimethylsiloxy)-5-(trimethylsilyl)-2*H*-pyran.

[d] (3*R**,1'*S**)-Tetrahydro-3-(1'-hydroxyethyl)-3-(trimethylsilyl)-2*H*-pyran-2-one.9)

lactone enolate (1d).

It is noteworthy that the present reaction of 1b and 1c with acetaldehyde proceeds with excellent diastereoface-selectivity as well as *threo*-selectivity.6) The titanium(IV) chloride-mediated stereocontrol may be explained by the chelated transition state shown in Scheme 2.

Bicyclic transition state Acyclic extended transition state

Scheme 2

The bicyclic transition state, which disposes the methyl substituent on the chiral center (either C-4 or C-5) *exocyclic*, may well predict the sense of asymmetric induction. Therefore, the relative configurations of 2b and 2c are given unequivocally as indicated in Scheme 1.

Alternatively, the observed threo diastereoselection can be also explained by a consideration of the acyclic transition state (Scheme 2), under the influence of a Lewis acid as simply an activator of a carbonyl group. Based on the assumption that a bulky trimethylsilyl group directs an aldehyde methyl to anti position, it may be postulated that the transition state disposes the smallest ligand (hydrogen) on the chiral center of the lactone *endo*, being consonant with the observed configurations in 2b and 2c.

That 2b and 2c were readily obtained in a diastereomerically pure state appears to implicate some synthetic utility for a 1,4- or 1,3-acyclic stereocontrol by way of reductive ring-opening.[10)]

Despite a high diastereoselectivity in the Lewis acid-mediated aldol reaction of 1a, attempted Michael addition of the latter to certain α,β-unsaturated carbonyl compounds were found to give rather blunt diastereomeric mixtures.

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References

1) Presented at the 46th Fall Meeting of the Chem. Soc. Japan (1982), Abstr. 3D14.
2) The terms 'diastereoselection' and 'diastereoface selection' are used as in ref.3.
3) For an excellent review, see D. A. Evans, J. V. Nelson, and T. R. Taber, Top. Stereochem., 13, pp. 1-115 (1982).
4) K. Yamamoto, Y. Tomo, and S. Suzuki, Tetrahedron Lett., 21, 2861 (1980).
5) According to Noyori's proposal [J. Am. Chem. Soc., 103, 2106 (1981)], the relative configuration of 2a is defined as a threo isomer.
6) Very recently, Mulzer and Chucholowski [Angew. Chem. Intern. Ed., 21, 777 (1982)] have reported that the addition of β-lactone enolates which contain ring substituents to aldehydes proceeds with particularly high diastereoface selectivity, being termed as three-center diastereoselection.
7) ^{1}H NMR data of 4b: (CCl_4, TMS) δ1.38(d, J=6.0 Hz, MeCH), 1.82(dt, J=7.0, 1.7 Hz, MeC=), 2.0-3.3(m, CH_2), 4.2-4.9(m, CH), and 6.67(qt, J=7.0, 1.7 Hz, CH=). IR(neat): 1765($\nu_{C=O}$) and 1680($\nu_{C=C}$). Z-Isomer (5b), which was obtained from a $BF_3 \cdot OEt_2$ induced olefination of 2b very similar to 5a from 2a (see, Scheme 1), has a vinyl methyl signal at 2.09(dt, J=7.2, 2.0 Hz) very diagnostic.
8) ^{1}H NMR($CDCl_3$, TMS) of 3a: δ0.24(s, Me_3Si), 1.8-2.6(m, CH_2 and OH), 3.08-4.54(m, CH_2O), 5.37(s, CHOH), and 6.30(br s, aromatic). IR($CDCl_3$): 3600, 3450, 1740, 1450, 1250, and 840 cm^{-1}.
9) ^{1}H NMR of 2d: δ0.20(s, Me_3Si), 1.21(d, J=6.2 Hz, Me), 1.65-2.25(m, CH_2CH_2), 2.37 (d, J=4.0 Hz, OH), 4.30(br t, J=4.4 Hz, CH_2O), and 4.4-4.9(m, CHOH). IR($CHCl_3$): 3610, 3460, 1680, 1250, 845 cm^{-1}.
10) K. Yamamoto and Y. Tomo, Tetrahedron Lett., in press.

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