

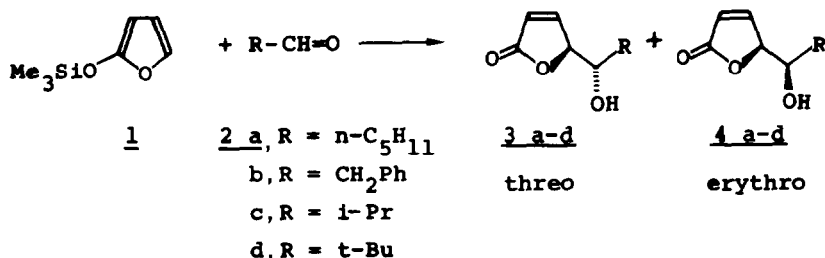
DIASTEREOSELECTIVITY IN THE DIRECTED ALDOL CONDENSATION OF 2-TRIMETHYLSILOXYFURAN WITH ALDEHYDES. A STEREODIVERGENT ROUTE TO *THREO* AND *ERYTHRO* δ -HYDROXY- γ -LACTONES

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Summary: *Threo* and *erythro*- δ -hydroxy- α,β -unsaturated γ -lactones are obtained with useful diastereoselection by condensing 2-trimethylsiloxyfuran and aldehydes by varying the reaction conditions. A stereomechanistic rationale is presented together with a practical two-step synthesis of the *threo* and *erythro* 5-hydroxy-4-decanolides (L factors).

Recent reports on 2-trimethylsiloxyfuran (1) show that it has promise as a masked butenolide.¹⁻⁴ However, in order to exploit 1 in synthesis, the appropriate conditions need to be found for controlling the regio- and diastereoselectivity of carbon-carbon bond formation. Described herein are results of a systematic investigation of the reaction of 1 with aldehydes which demonstrate for the first time how useful diastereoselection can be achieved at will for obtaining predominantly either *threo* (3) or *erythro* (4) δ -hydroxy- α,β -unsaturated- γ -lactones.



The behavior of 1 towards capronaldehyde (2a) is typical.⁵ Lewis acids catalyze condensation to give mainly the *threo* diastereoisomer 3. (entries 1-4, Table). BF₃-Et₂O is the most effective (entry 4). The trityl cation⁶ exerts the same effect (entry 5). However, the highest diastereoselectivities (3a:4a = 82:18) are conferred by trimethylsilyl and triethylsilyl trifluoromethanesulfonates (TMSOTf and TESOTf, entries 6, 7).⁷ The same diastereoselectivity is observed with phenylacetaldehyde (2b), iso-butyraldehyde (2c) and pivalaldehyde (2d) (entries 11, 14 and 17), which with TESOTf furnish predominantly the *threo* diastereoisomers 3.

The persistence of *threo* diastereoselectivity despite different catalysts and aldehydes is only compatible with open transition states. Encounter between the C1 and C5 atoms of the aldehyde and furan respectively can occur on the si faces or the si and re faces. The resulting two pairs of staggered arrangements A,A' and B,B' will produce the *threo* (3) and *erythro* (4) aldols (Scheme).⁸ Although Lewis acids (E) (entries 1-4, Table) will undoubtedly coordinate to the aldehyde with *syn* orientation,⁹ chelation plays no role (cf. entries 5-7).

Table. Condensation of 2-Trimethylsilyloxyfuran (1) with Aldehydes (2) Giving Threo and Erythro 4-(Hydroxymethyl)-2-buten-4-olides (3 and 4)

Entry	<u>2</u> RCH=O	<u>1</u> (eq)	Conditions ^a	Threo (<u>3</u>)/Yield ^c Erythro (<u>4</u>) ratio ^b
1		1.2	SnCl ₄ (0.4 eq) -78°, 2h	76:24 88
2		1.1	ZnBr ₂ (0.4 eq) 0°, 2h	66:34 94
3		1.1	ZnCl ₂ (0.5 eq) 0°, 2h	68:32 82
4		1.1	BF ₃ ·Et ₂ O (0.6 eq) -78°, 2h	81:19 95
5	R=nC ₅ H ₁₁	1.2	TrClO ₄ (0.1 eq) -78+20°, 4h	79:21 92
6		1.2	TMSOTf (0.2 eq) -78°, 2h	82:18 95
7		1.2	TESOTf (0.2 eq) -78°, 2h	82:18 93
8		1.1	CsF (1.3 eq) -78+20°, 4h	27:73 68
9		1.2	nBu ₄ N ⁺ F ⁻ (0.06 eq) -78°, 4h	33:67 74
10		1.2	nBu ₄ N ⁺ F ⁻ (0.06 eq) -78+20°, 6h	22:78 70
11		1.2	TESOTf (0.1 eq) -78°, 1.5h	82:18 92
12	R=CH ₂ Ph	1.2	nBu ₄ N ⁺ F ⁻ (0.06 eq) -78°, 2.5h	19:81 73
13		1.2	nBu ₄ N ⁺ F ⁻ (0.06 eq) -78+20°, 6h	23:77 44
14		1.1	TESOTf (0.04 eq) -78°, 2.5h	81:19 88
15	R=i-Pr	1.2	nBu ₄ N ⁺ F ⁻ (0.06 eq) -78°, 6h	13:87 77
16		1.2	nBu ₄ N ⁺ F ⁻ (0.06 eq) -78+20°, 4.5h	22:78 64
17		1.2	TESOTf (0.04 eq) -78°, 2h	76:24 94
18	R=t-Bu	1.2	nBu ₄ N ⁺ F ⁻ (0.06 eq) -78+-45°, 18h	8:92 48
19		1.2	nBu ₄ N ⁺ F ⁻ (0.06 eq) -78+20°, 23 h	12:88 36

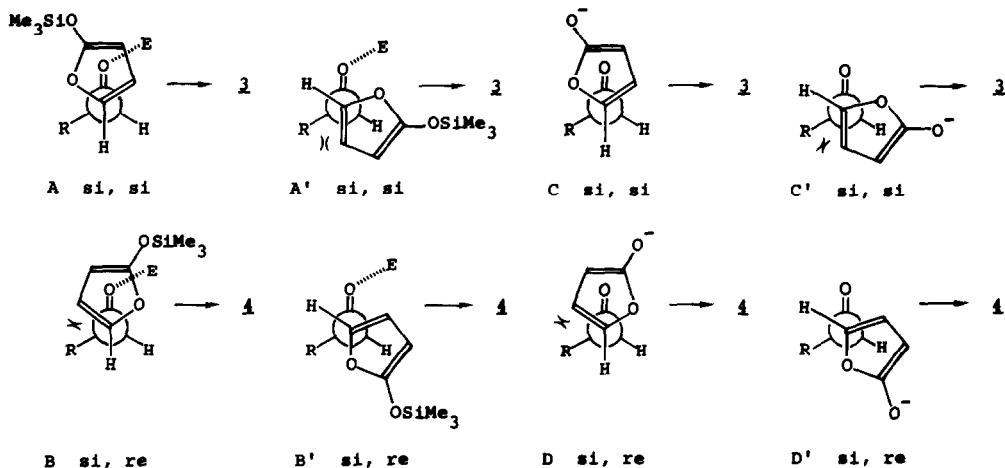
^aTHF was used as solvent for fluorides; CH₂Cl₂ elsewhere. ^bDetermined by ¹H-NMR (360 MHz). ^cReaction mixtures were immediately quenched without warm-up with aqueous 2N HCl, extracted, dried, and chromatographed on SiO₂. Yields are of isolated diastereomeric mixtures.

Consequently, competition between these arrangements will depend just on steric and electronic factors. If the reactants are inclined at *ca.* 110° to adopt the Bürgi-Dunitz trajectory,¹⁰ then the least hindered arrangements appear to be A and B'. Since the former is Diels-Alder-like¹¹ and therefore favored, it accounts for the observed *threo* selectivity.¹²

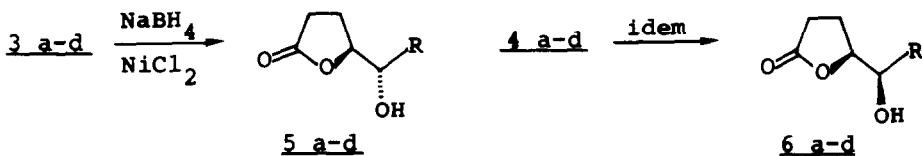
Conversely, if secondary orbital interactions were suppressed, *erythro* selectivity might be enhanced. The anion equivalent of 1 would avoid the Diels-Alder-like arrangements C and D since charge would be better dispersed in C' and D'. However, as D' is sterically favored then kinetic *erythro* selection would be predicted (Scheme). Indeed, the condensation of 1 with aldehydes (2a-d) using fluoride ion for desilylation¹³ leads to marked kinetic *erythro*

selectivity (entries 9, 12, 15 and 18), which is only slightly modified under equilibrating conditions¹³ (entries 8, 10, 13, 16, and 19).

Scheme



In general the yields are high, but less so for *erythro* selection. Furthermore, the diastereoselectivities are sufficiently divergent to be preparatively useful.^{14,15} By way of illustration, the naturally occurring *threo* and *erythro* 5-hydroxy-4-decanolides (L factors; 5a and 6a)¹⁶ are prepared in two steps from 1 in 67 and 48% yields respectively by reducing the lactones 3a and 4a with NaBH₄/NiCl₂.^{17,18}



In view of the natural occurrence^{16,19} and synthetic utility²⁰ of δ -hydroxy- γ -lactones, we believe that the present methodology for the direct stereocontrolled construction of these entities will find practical applications.²¹

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References and Notes

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21. See accompanying letter.

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