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REGIO- AND DIASTEREOSELECTIVITY IN ALDOL REACTIONS OF CYCLOPENT-2-ENONE, 2-(5H)FURANONE AND THEIR DERIVED TRIMETHYLSILYLOXYDIENES

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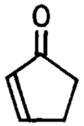
Summary: Differences in erythro/threo-selectivity were assessed for aldol condensations of aldehydes with the lithium salts of cyclopent-2-enone,2-(5H)furanone, and for Lewis acid catalysed condensations with the derived trimethylsilyoxydienes.

Aldol reactions of the anion from cyclopentenone (1) have not been systematically assessed. Earlier studies showed that lithium diisopropylamide mediated alkylations were problematical[1], and suggested that a 3-substituent was desirable for the avoidance of self-condensation processes. We therefore report further studies of the parent system (1) and the derived trimethylsilyloxy diene (2), together with interesting comparisons and differences from the chemistry of (3) and its silyl ether (4).



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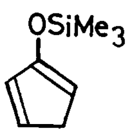

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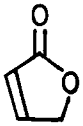

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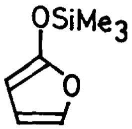

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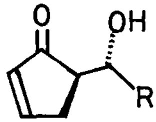

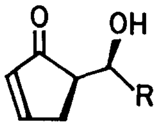

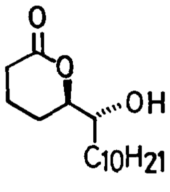

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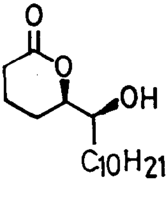


(8)

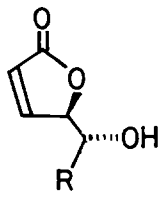
(5a) R = Me (6a)
(5b) R = Et (6b)
(5c) R = ^{i}Pr (6c)
(5d) R = $PhCH_2$ (6d)
(5e) R = $C_{10}H_{21}$ (6e)

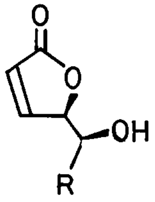
Footnote: The threo assignment is made in the cyclopentenone series on the basis of a staggered carbon chain backbone, where the two substituent groups have anti relationship. In the lactone series threo assignment is made by reference to threose, following the sugar conventions.

The lithium enolate of (1) (LDA,THF,-78°C) reacted with a range of aldehydes, giving *threo* (syn) and *erythro* (*anti*) adducts (5a)-(5e) and (6a)-(6e) in yields ranging from 70% to 85% with marked preference for the *threo* diastereomer (from 70:30 to 95:5, increasing with steric bulk of R.).[3] No 4-substitution was observed. Similar yields, but *reversed* diastereoselectivity, resulted from the zirconium enolates (LDA,$ZrCp_2Cl_2$), as observed for acyclic systems.[4]

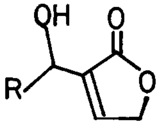
Generally improved stereoselectivity was observed for Lewis acid catalyzed reactions of the trimethylsilyloxy diene (2).[5] A range of Lewis acids and solvents were explored and, optimally, $TiCl_4$/THF gave > 90% *threo* preference with, for example, 2-phenylethanal and 2-methylpropanal, although at the expense of total yield (50%).[2] This stereoselectivity is in accord with postulated transition states for silyl enolates,[6] with R 'exo' to the silyloxycyclopentadiene. [Note that no reaction could be induced by Eu(fod)$_3$ or Pr(fod)$_3$, in contrast to reactions of (4) which will be described] The *threo* preference was established by n.m.r. (δ CHOH 3.7,J=8Hz for *threo*; δ CHOH 4.2,J=2Hz for erythro)[7] and confirmed by reduction of (5a) and (6a) to known cyclopentanones.[7,8] Reversal of diastereoselectivity resulted when *t*-butylammonium fluoride was used to liberate the anion, giving typically a 20: 80 *threo/erythro* mixture.[9]

When (5e) and (6e) were catalytically reduced, and the resultant cyclopentanones subjected to Baeyer-Villiger reaction, the 6-hydroxyalkyl lactones (7) and (8) were isolated in good yields, the latter being related to a known mosquito attractant pheremone.[10] A facile route to such δ-lactones is thus apparent.





(9a)	R = Me	(10a)
(9b)	R = Et	(10b)
(9c)	R = ^{i}Pr	(10c)
(9d)	R = $PhCH_2$	(10d)
(9e)	R = $C_{10}H_{21}$	(10e)



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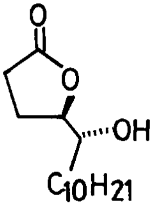

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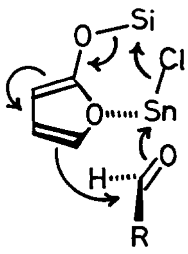

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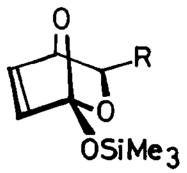

(14)

Interesting comparisons emerged from the corresponding chemistry of 2-(5H)furanone (3) and the derived silyloxydiene (4).[11] Again, these systems have received surprisingly little attention in synthesis,[12] and, in particular regioselectivity and diastereoselectivity have not systematically been explored.

The lithium enolate of (3) (LDA,THF,-78°) reacted with aldehydes to give a mixture of the γ-adducts (9a)-(9e) and (10a)-(10e), together with α-adducts (11), typically in a 1:1:6 ratio. Thus, no significant selectivity was achieved. However, silyloxyfuran (4) reacted with aldehydes in the presence of an extensive range of Lewis acids, the optimal conditions ($SnCl_4$,THF,-78°) affording threo/erythro ratios of 88:12. (In this series, threo is R,R/S,S). It should be noted that fluoride-initiated aldol reactions, although switching the selectivity, did not adequately discriminate between the diastereomers.) Initial assignments came from n.m.r. analysis of coupling constants, and lanthanide-induced shifts. More direct assignment was made by synthesizing a known precursor of the pheremone dispalure.[13] Thus, reactions of (4) with undecanal, and chromatographic separation of the major isomer (threo) gave racemic (9e) which was reduced (H_2,Pd-C) to give 5-hydroxyalkyl γ-lactone (12), spectroscopically identical to the dispalure intermediate. A general route to such γ-lactones, complementing that for the homologous δ-lactones described above, is thus exemplified.

Mechanistically, two explanations are possible for the threo selectivity. Firstly, a novel tricyclic chelate (13) may be invoked. In a concerted process the aldehyde is delivered to the 5-position, with R exo to give the threo products (9). This contrasts with the reaction of (2) in which the methylene group cannot thus be involved. A second mechanism recognises the fact that silyloxybutadienes, catalysed by lanthanides, give Diels Alder adducts.[14] Thus (4) could, via exo adduct (14), lead to threo products (9). Intermediate (14) could not be detected by direct n.m.r. monitoring of the reaction leading to (9a) and (10a), but this does not preclude the route. Interestingly, however, under the Danishefsky conditions[14] [$Eu(fod)_3$,0.5 mol%,$CHCl_3$,RT] no Diels Alder adduct was observed, but a change in regioselectivity of the aldol reaction occurred and good yields of α-adduct (11) were obtained, possibly in consequence of an alternative transition state leading to 2-(3H) furanone adducts and thence (11). Similar regioselectivity was observed for $Pr(fod)_3$.

In summary, 5-lithiocyclopentenone and trimethylsilyloxycyclopentadiene/$TiCl_4$ give predominantly threo 5-hydroxyalkylcyclopent-2-enone aldol adducts although reversal of diastereoselectivity can be achieved from the zirconium enolates or by fluoride-mediated reaction of the silyl enolate. In comparison, 2-trimethylsilyloxyfuran/$SnCl_4$ gives threo 5-hydroxyalkyl 2-(5H)furanones which are the γ-aldol adducts. These products are convertible, respectively, into threo 6-hydroxyalkyl δ-lactones (8) and threo 5-hydroxyalkyl γ-lactones (12).

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2. Yield refers to total diastereomers in the reaction as analysed by g.l.c., using internal standard. Isolated yield (medium pressure column chromatography) gave, typically, 30-50% of total separated diastereomers.

3. For a related cyclopentanone study, see: J.E. Dubois and M. Dubois, J.C.S.Chem.Commun., 1968, 1567. For a review of transition states in aldol reactions see C.M. Heathcock, Asymmetric Synthesis, Vol.III, Academic Press, Orlando, Fl, 1983, 155.

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5. Conveniently prepared from cyclopentenone (LDA,TMSCl,-78°), c.f. earlier Retro Diels Alder route; R. Bloch, Tetrahedron Letters, 1979, 3945.

6. See, for example, T. Mukaiyama, K. Banno and K. Narasaka, J.Amer.Chem.Soc., 1974, 96, 7503; T.H. Chan, T. Aida, P.W.K. Lau, V. Gorys and D.N. Harpp, Tetrahedron Letters, 1979, 4029.

7. See, for example, R. Noyori, I. Nishida and J. Sakata, J.Amer.Chem.Soc., 1983, 105, 1598.

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