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# 6-Methyl-3-benzylidene-5,6-dihydropyran-2,4-diones: Synthesis and Diastereoselectivity[1]

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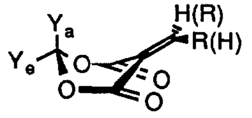
**Abstract:** (*S*)-6-Methyl-(*Z*)-3-benzylidene-5,6-dihydropyran-2,4-diones have been synthesized from (*S*)-6-methyl-5,6-dihydropyran-2,4-dione through Knoevenagel condensation with an arylaldehyde followed by recrystallization from ether. The results of conjugate additions and hetero Diels-Alder reactions of these compounds including an interpretation of the observed diastereoselectivities are described.

Previously, we have reported novel enantioselective synthetic methods by utilizing chiral 1,3-dihetero-4,6-dioxocyclohexanes having an exomethylene group at the 5-position (1[2] and 2[3]). The success of this method is due to fixation of the six-membered ring in a boat conformation. We have proposed novel stereoelectronic effects between hetero atoms in the acetal function and the axial substituent ($Y_a$) at the 2-position as the origin of these unique conformations.[4] In this paper, we would like to report our research concerning the synthesis of the title compounds (3), in which one hetero atom of 1 and 2 is replaced by carbon and their successful utilization in enantioselective synthesis.



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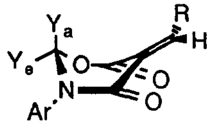

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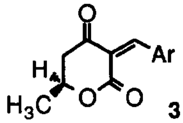
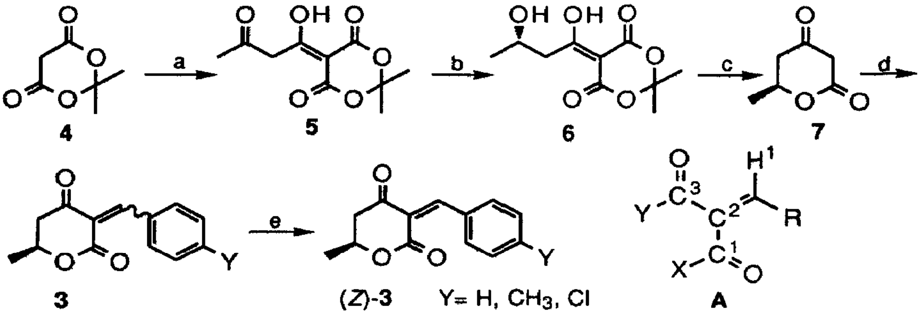


3

a: Ar=$C_6H_4CH_3(p)$
b: Ar=$C_6H_4Cl(p)$

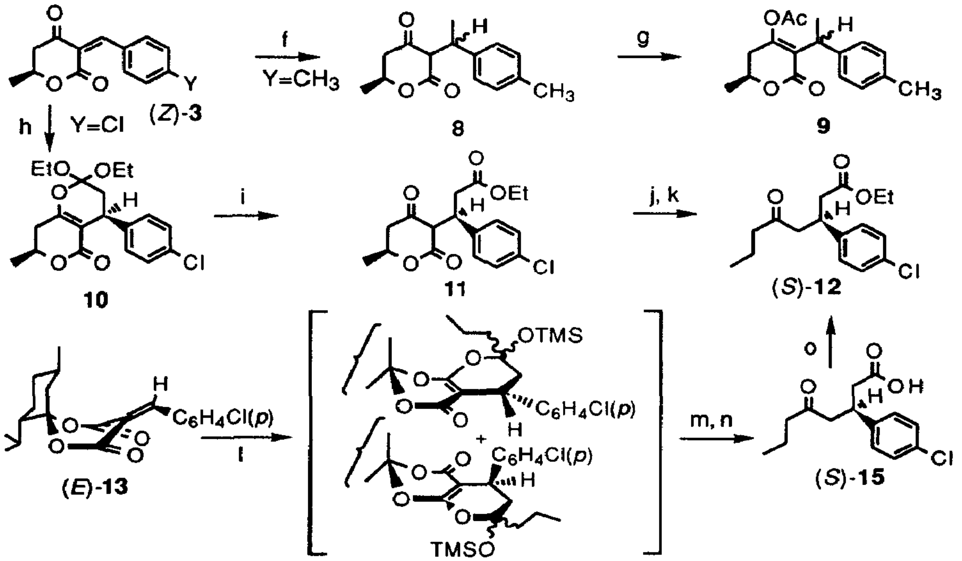
By taking advantage of the finding that acetoacetylated Meldrum's acid (5) was enantioselectively reduced with fermenting baker's yeast to give the corresponding (*S*)-alcohol (6), the pyran (7) has become readily available.[5] For this reason, we chose 3 as the substrate in the present study. Knoevenagel condensation of 7 with *p*-tolualdehyde or 4-chlorobenzaldehyde in the presence of titanium tetrachloride and pyridine in THF gave the benzylidene derivatives as a mixture of two geometrical isomers (*E* and *Z*). The slow recrystallization of each product from diethyl ether afforded the single isomer [(*Z*)-**3a** and (*Z*)-**3b**][6, 7] in nearly quantitative yields. Assignment of these products as having Z-configuration rested on $^{13}C$-NMR spectroscopy according to the method reported by Chaloner, who demonstrated the significant difference ($J_{C\text{-}1,\,H\text{-}1}$ = *ca.* 12 Hz and $J_{C\text{-}3,\,H\text{-}1}$ = *ca.* 5 Hz) between the corresponding coupling constants of the enedione system (A).[8] The $^{13}C$-NMR spectrum of (*Z*)-**3a** showed the coupling constant of 11.47 Hz between the carbon atom in the $CO_2$ group (the chemical shifts of C(2) and C(4) were δ 164.5 and 193.2 ppm, respectively) and the vinylic proton.



a) diketene, $Et_3N$, $CH_2Cl_2$, 0 °C; b) yeast , EtOH, 35 °C; c) toluene, reflux;
d) *p*-Y-$C_6H_4$-CHO, $TiCl_4$, pyridine, THF, 0 °C - r. t.; e) recrystallization from $Et_2O$.

The facile *E*-*Z* isomerization of **3** during the recrystallization fitted well to our expectation. It is because, the demand for coplanarity of the enone function should be much higher than for the α,β-unsaturated ester and hence, the *Z*-isomer is expected to be more stable than the *E*-isomer. Similar *E*-*Z* isomerization has previously been observed in the related benzylidene oxazinediones (*e.g.* **2**: X = NAr).[3, 9]

In order to examine the diastereofacial selectivity of (Z)-**3**, two reactions (conjugate addition with MeMgBr/CuI and Diels-Alder reaction with 1,1-diethoxyethylene) were performed. The first reaction using (±)-(Z)-**3a** gave the expected addition product (**8**) in 72% yield. The de of the reaction determined by 500 MHz $^1$H-NMR analysis of the corresponding acetate (**9**), however, was as low as 20%. On the contrary, the hetero Diels-Alder reaction using (-)-(Z)-**3b** afforded the expected adduct (**10**) in 78% yield. The de of the adduct **10** was determined to be as high as ≥90% by 500 MHz $^1$H-NMR analysis.



f) MeMgBr, CuI, THF, -78 °C; g) $CH_3COCl$, pyridine, $CH_2Cl_2$, 0 °C; h) ketene diethylacetal, $CH_2Cl_2$, -55 °C; i) 1% HCl, $Et_2O$, 0 °C; j) DMSO, $H_2O$, 160 °C(sealed tube); k) $H_2$/10%Pd-C, AcOEt, r. t.; l) 2-trimethylsilyloxy-1-pentene, $CH_2Cl_2$, -30 °C, 1 d; m) conc. HCl, dioxane, reflux; n) xylene, reflux ; o) DCC, DMAP, EtOH, $CH_2Cl_2$, 0 °C - r. t.

In order to determine the preferred face of (Z)-**3b** in the Diels-Alder reaction, the adduct **10** was converted to ethyl 5-oxo-3-(*p*-chlorophenyl)-5-octanoate [**12**: $[\alpha]_D^{23}$ -7.45 in $CHCl_3$ (*c* 0.51)]. The identity of the (-) sign of the specific rotation of **12** with that [$[\alpha]_D^{27}$ -1.50 in $CHCl_3$ (*c* 0.93)][10] of authentic (*S*)-**12** synthesized from the chiral spirocyclic dioxanedione [(*E*)-**13**][2] confirmed that the attack of the dienophile occurs from the side *syn* to the 6-methyl group of (Z)-**3b**.

X-Ray crystallographic analysis of (*S*)-(Z)-**3a** was then carried out. As a result, it was found that the six-membered ring was found to take pseudo-boat conformation with 6-methyl group in an equatorial arrangement (Fig. 1).[11] Hence, it is obvious that the attack of the dienophile (1,1-diethoxyethylene) has occurred from the less hindered bottom side of the boat conformation.

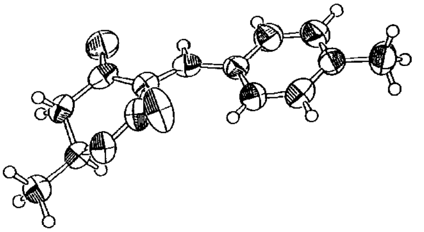


Fig. 1-a. Molecular Structure of (*S*)-(*Z*)-**3a**.

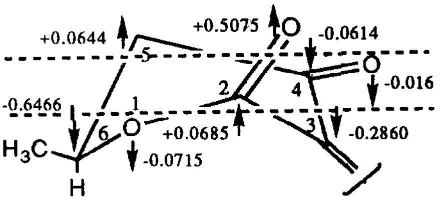
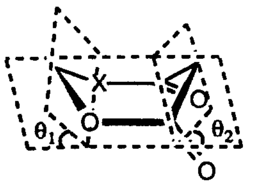


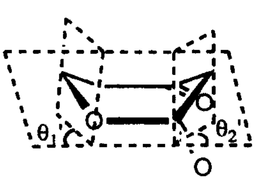
Fig. 1-b. Derivation (in Å unit) of Eight Atoms from the Mean Plane of O(1), C(2), C(4), and C(5).

The fact that (Z)-**3** still has a boat conformation in its six-membered ring is worthy of being stressed. This fact shows clearly that the preference of a boat conformation of 1,3-dioxo six-membered ring (**1** and **2**) is a general phenomenon for compounds having at least one hetero atom at the 4-position. The low de in the reaction of (Z)-**3** to **8** indicates that diastereofacial selectivity of a reaction (e. g. **3**→**8**) is low if the reactive site is restricted only to the terminal $sp^2$ carbon atom in the exomethylene group.

It should be noted, however, that the similar conjugate addition of **2** ($Y_a$ = $CO_2R$ or phenyl) with MeMgBr/CuI has proceeded in high de (>90%).[3] These facts suggest that, though the main factor preventing the upper side attack is surely caused by the bulkiness of the axial substituent ($Y_a$ in **1** and **2** and $C_6$-H in **3**), the actual bulkiness would also depend upon the deepness or shallowness of the boat conformation in the six-membered ring (cf. **B** and **C**). We believe, at present, that the 1-oxa-3-hetero-4,6-dioxo six-membered ring (**B**) has deeper boat conformation than the corresponding 1-oxa ring (**C**) (*i.e.* $\theta_1 > \theta'_1$ and $\theta_2 > \theta'_2$). Experimental verification for this hypothesis as well as understanding of the stereoelectronic effects of the hetero atoms on the fixation of the conformation are under current investigation.



**B**: X=O, NR



**C**

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## References and Notes

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6. All new compounds have been characterized by 500 MHz $^1$H-NMR, IR, and HRMS and/or elemental analysis. **3a**: mp 148-149 °C, $[\alpha]_D^{25}$ -68.0 (*c* 1.23, $CHCl_3$); **3b**: mp 119-121 °C, $[\alpha]_D^{19}$ -151.5 (*c* 1.03, $CHCl_3$).
7. So far, we have synthesized related benzylidene derivatives by using a variety of aryl aldehydes, such as benzaldehyde, α-naphthaldehyde, *etc.* All of the crude products obtained by Knoevenagel condensation reaction are the mixture of *E*- and *Z*-isomers. Recrystallization of them from ether, however, afforded without exception the corresponding Z-isomers.
8. Chaloner, P. A. *J. Chem. Soc. Perkin Trans. 2* **1980**, 1028. See also Kingsbury, C. A.; Cliffton, M.; Looker, J. H. *J. Org. Chem.* **1976**, *41*, 2777.
9. Similar *E-Z* isomerization was first reported for benzylidene oxazepanediones: Tietze, L. F. *J. Heterocyclic Chem.* **1990**, *27*, 47 and references cited therein.
10. It is obvious that **3** having an enone system is much more reactive as the heterodiene in inverse electron demand Diels-Alder reactions than **13** having an acrylate system. As reported,[2] the isomerization between the *E*- and Z-isomers of **13** in an approtic solvent is quite fast resulting in equilibrated mixture within 1 h at 25°C. Hence the low de of the reaction (which did not proceeded below -30 °C) of *E*-**13** with trimethylsilyloxy-1-pentene would be due to the prior *Z-E* isomerization.
11. X-Ray analysis of (*S*)-(*Z*)-**3b**: Monoclinic $P2_1$, a = 5.3074(8) Å, b = 9.0017(7) Å, c = 12.739(1) Å, β = 92.604(6)°, Z = 2, R = 0.034 ($R_W$ =3.6%). Further details have been deposited with the Cambrige Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.

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