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Diastereoselective Michael Addition of (4'*S*)-Ethyl-3-(2',2'-Dimethyl-1',3'-dioxolan-4'-yl) acrylate with Furyl Lithium

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Abstract: Michael addition of the chiral α,β-unsaturated ester **2** with furyl lithium proceeded in *syn* manner with excellent diastereoselectivity. The diastereoselectivity was not affected by the configuration of the double bond in **2**.

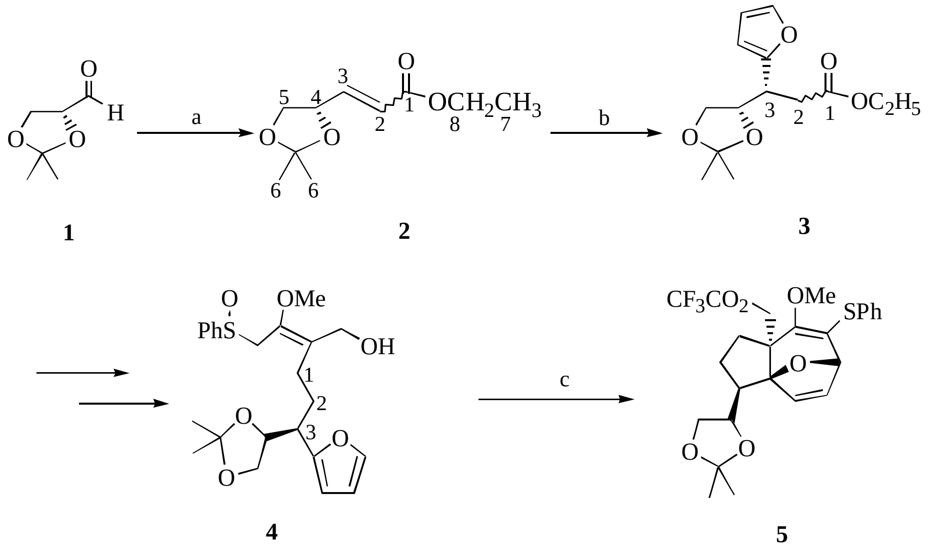
Keywords: Michael addition, configuration determination, *syn* addition.

Recently we reported that the diastereoselective intramolecular [4+3] cycloaddition of **4** led to the formation of cycloadduct **5** as the only isolated isomer in 50% yield. The chiral C-3 of compound **4** could be used to direct the stereochemical course of [4+3] cycloaddition enabling the control of the relative stereochemistry between three contiguous asymmetric centers in adduct **5**[1]. The stereogenic center at C-3 of **4** was constructed by the asymmetric Michael addition of α, β-unsaturated ester **2** with furyl lithium. The configuration of C-3 of adduct **3** was deduced to be R based on the Leonard and others reports[2].

Most recently, we examined the configuration of the newly formed stereogenic C-3 in Michael addition of **2**, particularly with respect to the role of the α, β-unsaturated ester geometry in directing the sense and degree of the diastereoselection in the addition.

A mixture of α, β-unsaturated esters Z-**2** and E-**2** was prepared in excellent yield (98%) and 5:1 ratio by Wittig reaction of D-glyceraldehyde acetonide **1** with ylide **6** using methanol as reaction solvent. Z-**2** and E-**2** were easily separated by chromatography. The Michael addition was performed respectively by treatment of an ether solution of Z-**2** or E-**2** with furyl lithium at -78°C and quenching the resultant anion with aqueous NH_4Cl solution. It is noteworthy that both Z-**2** and E-**2** gave the same adduct **3** as the only product in 70% yield (**Scheme 1**).

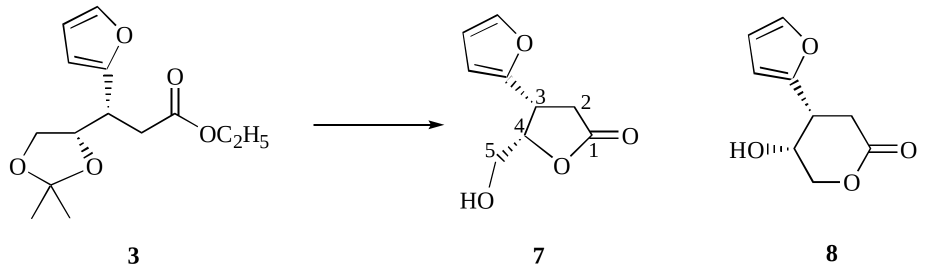
Scheme 1



Reagents and reaction conditions:
a) $Ph_3P{=}CHCO_2C_2H_5$ (**6**), CH_3OH, r.t., overnight, 98%;
b) furyl lithium, Et_2O, -78°C, 2 h, 70%;
c) $(CF_3CO)_2O$, 2,6-lutidine, CH_2Cl_2, r.t., 4 h, 50%.

The stereochemical assignment was made after the conversion of **3** to conforma-tionally restricted lactone **7** or **8** *via* acid-catalyzed transesterification (**Scheme 2**). In homonuclear decoupling experiment, irridiation on hydroxy proton of lactone changed multiplets at δ 3.52 corresponding to two protons at C-5 into doublets of doublets at 3.51(dd, 1H, J = 5.5, J = 12.6Hz) and 3.61 (dd, 1H, J = 3.8, J = 12.6Hz), respectively. This compound also showed a characteristic IR-absorption band of γ-latone at 1778 cm^{-1}. Therefore, the structure of lactone should be **7**.

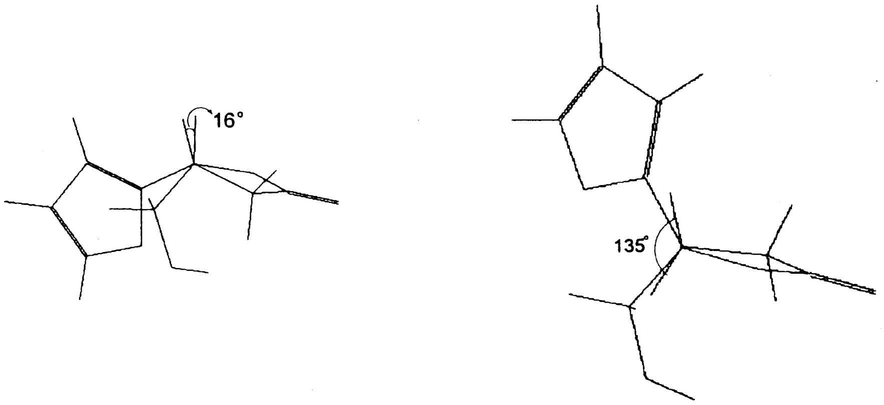
Scheme 2



Reagents and reaction conditions: *p*-TsOH, MeOH, reflux, overnight.

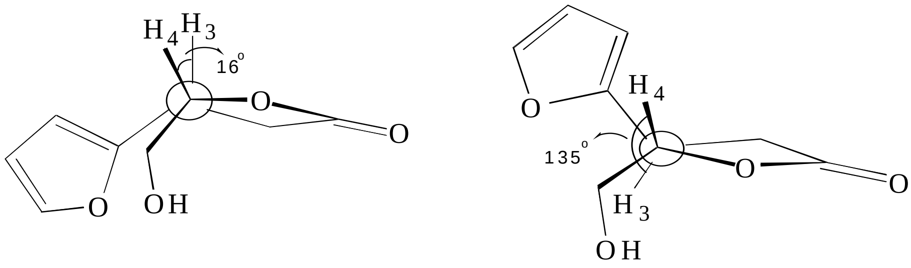
The stereochemistry of lactone **7** was determined based on the coupling constant of H-3,H-4 and *ab initio* calculation of the stable conformations of *cis* 7 and its *trans* isomer. Irridiation on H-2 simplified the signal of H-3 to a doublet at 3.97 (d, 1H, J=6.9Hz). The stable conformations of *cis* **7** and its *trans* isomer were obtained by the optimized geometry of lactones by use of Hartree-Fock method with Guassian 94 program (**Figure 1**). The computational result indicated that in *cis*-form **7** the H_3-C_3-C_4-H_4 dihedral angle was 16° and in *trans*-form, it was 135°. According to Karplus equation, the observed coupling constant (J = 6.9 Hz) of H-3,H-4 is consistent with *cis* stereochemistry. In literature, Abraham *et al.*[3] reported that the *trans* coupling constant of H-3,H-4 in D-ribono-1→4-lactone was <0.5 Hz and the *cis* coupling constant of H-2-H-3 was 5.5 Hz. Therefore, the absolute configuration of C-3 in compound **3** is assigned as R-form, and our initial, tentative assignment of stereochemistry of compounds **3** and **5**[1b] were thus verified.

Figure 1 The stable conformations and Newman projections for *cis*-**7** and its *trans* isomer.



cis-**7**

trans isomer



Newman projection

Newman projection

In summary, the configuration of C-3 in Michael adduct **3** is assigned as R based on the value of coupling constant between H-3 and H-4 in the conformationally restricted lactone **7** with homonuclear decoupling experiment. The results demonstrated that Michael addition of α,β-unsaturated ester **2** with furyl lithium proceeded in *syn* manner and the geometry of α,β-unsaturated ester had not significant effect on stereoselectivity in Michael addition.

Acknowledgment

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References and Notes

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4. Selected data for compound E-**2**: ^{1}HNMR(300Hz, $CDCl_3$, δppm): 1.28 (t, 3H, J = 7.0Hz, H-7), 1.38(s, 3H, H-6), 1.42(s, 3H, H-6), 3.60(dd, 1H, J = 7.1Hz, 8.2Hz, H-5), 4.10-4.25(m, H-3, H-5, H-8), 4.62(m, 1H, H-4), 6.05(d, 1H, J = 15.6Hz, H-2), 6.28(dd, 1H, J = 5.7, 15.6Hz, H-3).
5. Selected data for compound Z-**2**: ^{1}HNMR(300Hz, $CDCl_3$, δppm): 1.29 (t, 3H, J = 7.2Hz, H-7), 1.38(s, 3H, H-6), 1.45(s, 3H, H-6), 3.61(dd, 1H, J=6.9Hz, 8.2Hz, H-5), 4.12(q, 2H, J=7.2Hz, H-8), 4.36(dd, 1H, J=7.2Hz, 8.2Hz, H-5), 5.48(m, 1H, H-4), 5.83(d, 1H, J=11.8Hz, H-2), 6.33(dd, 1H, J=6.9Hz, 11.8Hz, H-3).
6. Selected data for compound **7**: IR(film): 3419, 2916, 1778, 1506, 1175, 1043, 1014, 737 cm^{-1}; ^{1}HNMR(300MHz, $CDCl_3$, δppm): 1.82(br, 1H, OH), 2.86(dd, 1H, J = 9.06, 17.3Hz, H-2), 2.96(dd, 1H, J = 7.97, 17.3Hz, H-2), 3.52(m, 2H, H-5), 3.95(m, 1H, H-3), 4.75(m, 1H, H-4); 6.21(d, 1H, J = 1.9Hz, H-3’), 6.35(m, 1H, H-4’), 7.39(d, 1H, J = 1.4Hz, H-5’); HREIMS for $C_9H_{10}O_4$: calcd: 182.0579; found: 182.0556.

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