

Stereochemistry of Vinyl Cuprate Additions to
Carbohydrate-Derived Enones and α,β -Unsaturated Esters

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Abstract. Vinylic cuprate reagents add with excellent diastereoselectivity (>10:1) to carbohydrate derived enones and α,β -unsaturated esters. The stereochemical outcome of these transformations is consistent with a Felkin-type addition pathway.

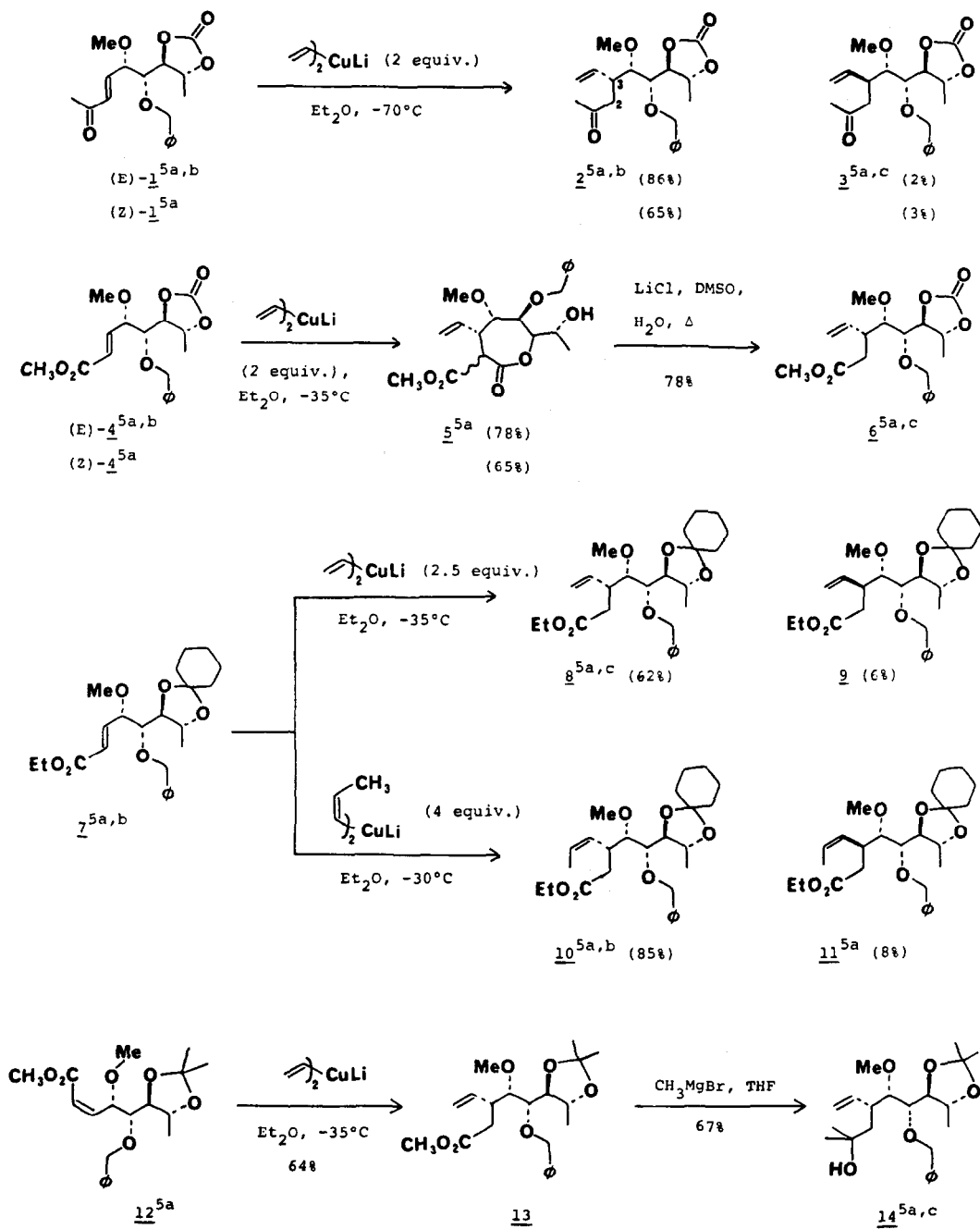
The diastereoselective addition of organometallic reagents to α -alkoxycarbonyl compounds is a powerful method in organic synthesis.² The vinylogous addition of such species to γ -alkoxy- α,β -unsaturated carbonyl systems, however, has received relatively little attention.³ In work directed towards the synthesis of olivin we discovered that vinyl cuprate reagents add to carbohydrate-derived enones and unsaturated esters with excellent (>10:1) diastereoselectivity (Scheme I).^{4,5} We describe herein the results of this study.

All cuprate reagents were generated by using the $\text{CuBr} \cdot \text{Me}_2\text{S}$ complex.⁶ Vinyllithium was prepared in Et_2O from tetravinylltin and n-butyllithium.⁷ Etheral (Z)-propenyllithium was prepared from (Z)-propenyl bromide and Li metal (1% Na).⁸ Reaction times were typically 1.5 h for 1 and 3-5 h for 4 and 7. Reaction temperatures are indicated in the Scheme.

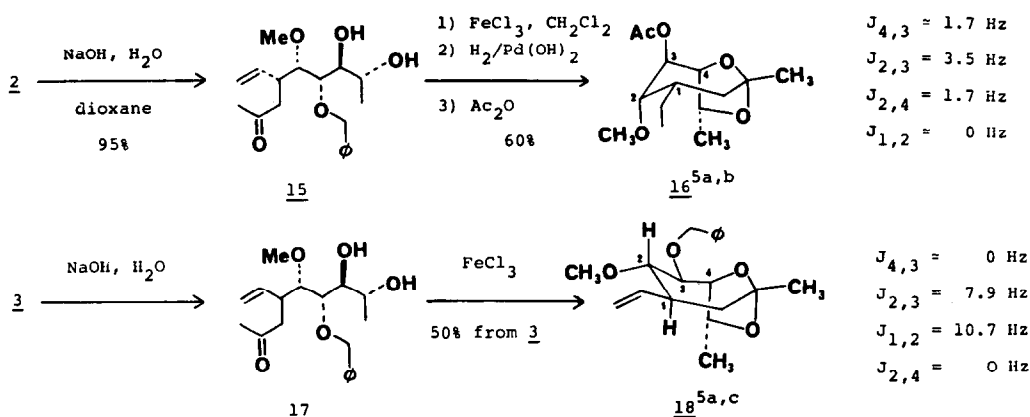
It is noteworthy that the stereochemical outcome of these transformations is independent of the geometry of the starting olefinic systems. Thus, methyl ketone 2 was the major product obtained from either (E)- or (Z)-1 and, similarly, 6 was obtained from each of the olefin isomers of 4.⁹ Although the sense of addition to the enone and enoate substrates is the same (vide infra), the additions to (E,Z)-1 appear to be somewhat more selective. This may be a consequence of the higher reaction temperatures required to promote cuprate addition to the α,β -unsaturated esters.^{9,10}

The stereochemistry of methyl ketones 2 ($[\alpha]_D^{19} -15.6^\circ$ ($c=1.0$, CH_2Cl_2)) and 3 ($[\alpha]_D^{19} +23.2^\circ$ ($c=0.41$, CH_2Cl_2)) were assigned on the basis of the data summarized in Scheme II. Thus, diols 15 and 17 prepared from 2 and 3, respectively, were cyclized by treatment with FeCl_3 in CH_2Cl_2 ¹¹ to afford isomeric bicyclic ketals, the NMR properties of which were strikingly different. The ketal prepared from 15 was transformed to 16¹² by hydrolysis and acylation in order to ensure first-order behavior of the H_2-H_3 and H_3-H_4 spin systems. The observation of a W-couple ($J_{2,4} = 1.7$ Hz) for 16 together with the vicinal coupling constants reported in Scheme II leave little doubt about the conformations and stereochemistry of these compounds. It is evident, therefore, that adduct 2 possesses the wrong stereochemistry for use in our approach to olivin. The assignment of stereochemistry to the enoate adducts rests in large measure on spectroscopic comparisons with 2 and 3,¹³ and by the correlation of 13, the major product of vinyl cuprate addition to 12, with ketone 2 via alcohol 14.¹⁴

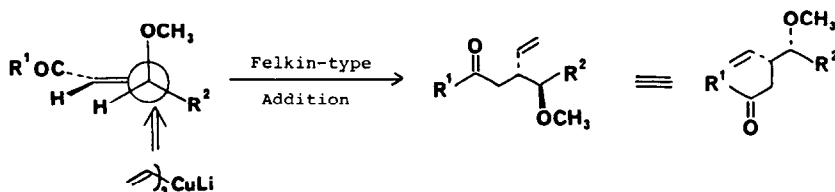
Scheme I



Scheme II



Whereas organolithium reagents add to γ -alkoxy- α,β -unsaturated esters^{3d} and related systems^{3c} by alkoxy-directed (coordinated) pathways, the results summarized in Scheme I are more consistent with the addition of the vinylic cuprate reagents by a Felkin-type transition state¹⁵ in which carbon-carbon bond formation occurs anti to the polar allylic alkoxy substituent.¹⁶ Ziegler has reported an example of a saturated cuprate addition to a



carbohydrate derived enoate, the stereochemical outcome of which is also consistent with the pathway suggested here.^{3a} Allylic cuprate reagents, however, may prove to be an exception to this generalization.^{3a,b}

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4. A highly stereoselective synthesis of **7** has been described (Roush, W.R.; Harris, D.J.; Lesur, B.M. Tetrahedron Lett., preceding paper in this issue). Enones **1** and esters **4** and **12** were synthesized from intermediate **12** of Scheme II of this previous paper. Mixtures of olefin isomers were obtained when the appropriate Wittig reactions were performed with $\text{Ph}_3\text{P}=\text{CHCOCH}_3$ (5:1 mixture of (E)-**1** and (Z)-**1**) or $\text{Ph}_3\text{P}=\text{CHCO}_2\text{CH}_3$ (2:1 mixtures of (E)-**4** and (Z)-**4**) in CH_2Cl_2 . These reactions were more selective for the (Z)-isomers when performed in methanol.
5. (a) The spectroscopic properties (NMR, IR, mass spectrum) of all new compounds are fully consistent with the assigned structures; (b) A satisfactory combustion analysis ($\pm 0.3\%$ for C,H) was obtained for this compound; (c) The elemental composition of this substrate was confirmed by high resolution mass spectroscopy.
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9. The epimer of **6** was not detected in the sequence **4** + **5** + **6**. It may have been separated inadvertently during the purification of **5**.
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12. Physical constants for the alcohol precursor to **16**: m.p. 95.5-96.5°C; $[\alpha]_D + 66.0^\circ$ ($c=0.47$, CH_2Cl_2 , 20°C).
13. One characteristic feature of the NMR spectra of the cuprate adducts is that the resonance for H_3 of **3**, **9**, and **11** is at higher field (0.2-0.3 ppm) than the corresponding signal in **2**, **8**, **10**, and **13**. The ABX patterns for H_2 , H_2 , and H_3 also provided much useful information.
14. Alcohol **14** was synthesized from methyl ketone **2** in 51% overall yield (i) ethylene glycol, pTsOH, C_6H_6 ; (ii) NaOH, H_2O , dioxane; (iii) 2,2-dimethoxypropane, pTsOH; (iv) MeMgCl , Et_2O .
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16. (a) Similar arguments based on the anti-periplanar effect have recently been invoked by Kozikowski and Franck to rationalize the stereochemistry of nitrile oxide and Diels-Alder reactions of alkoxy-functionalized allylic systems: Kozikowski, A.P.; Ghosh, A.K. J. Am. Chem. Soc. **1982**, 104, 5788; Franck, R.W.; John, T.V; Olejniczak, K.; Blount, J.F. J. Am. Chem. Soc. **1982**, 104, 1106. (b) For a theoretical treatment of the anti-periplanar effect, see Caramella, P.; Rondan, N.G.; Paddon-Row, M.N.; Houk, K.N. J. Am. Chem. Soc. **1981**, 103, 2438.

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