lowed by lyophilization gives swainsonine (1) in 84% yield from **21**, mp 140–142 °C (after sublimation), mmp 138–142 °C,[22] $[\alpha]^{25}_D$ −73.8° (*c* 0.21, EtOH)[23] [lit.[1d] mp 144–145 °C, $[\alpha]^{24}_D$ −83.4° (*c* 0.32 EtOH)].

The ^1H and ^{13}C NMR, IR, and TLC behavior[1a,b,d] of our swainsonine matches that published for material from natural sources. When hepatoma HG-2 cells were cultured in the presence of synthetic swainsonine and natural swainsonine, identical effects on the secreted proteins, antitrypsin and antichymotrypsin, were observed.[24]

This synthesis of swainsonine is highly stereoselective in both a relative and an absolute sense and appears to be the first reported noncarbohydrate route to this natural product. Although the synthesis is linear, it is unambiguous. This route also provides for controlled stereochemical variations throughout, allowing selective access to all 16 epimers and/or enantiomers of swainsonine. We are presently working on the synthesis of swainsonine isomers that are epimeric at C-2 and at both C-2 and C-8.[25] By analogy to the proposed mechanism of enzyme inhibition by swainsonine, these isomers might act as inhibitors of glucose and galactose processing enzymes, respectively.

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Supplementary Material Available: Experimental details and physical and spectral data for each isolated compound (20 pages). Ordering information is given on any current masthead page.

(21) Corey, E. J.; Ponder, J. W.; Ulrich, P. *Tetrahedron Lett.* **1980**, *21*, 137.

(22) We thank Dr. G. W. J. Fleet for the authentic sample of swainsonine.

(23) Literature rotation data for (−)-swainsonine is variable ranging from −67.4° (*c* 0.33, MeOH)[5a] to −87.2° (*c* 2.1, MeOH).[1b] Because of the nature of our synthesis, we do not believe that our rotation data is indicative of diminished enantiomeric purity.

(24) We thank Professor H. F. Lodish and N. H. Kong of the M.I.T. Biology Department for performing this biological assay.

(25) **Note Added in Proof**: We have recently completed the syntheses of these two ("gluco" and "galacto") swainsonine isomers.

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Metal Ion Controlled Addition to α,β-Dialkoxy Carbonyl Compounds

Summary: Complementary stereoselection in the addition of carbon and hydride nucleophiles to α,β-dialkoxy carbonyl systems can be obtained with Mg^{2+}-based (syn addition) and Li^+- and Ti^{4+}-based (anti addition) reagents.

Sir: Asymmetric addition to acyclic chiral carbonyl compounds is a valuable synthetic transformation for which several theoretical models have been proposed.[1-6] The chelate model, which requires a suitably positioned internal ligand, can produce highly selective, predictable addition processes, due to the conformationally biased, cyclic nature of the complexed carbonyl.[5,6] The critical role played by the metal counterion in promoting chelate formation in alkoxy carbonyl systems and thus enabling control of the direction of nucleophilic addition was established by Still in 1980[6] and has been more fully defined recently by Reetz,[7] Mulzer,[8] and others.[9] However, in carbonyl compounds with multiple functional groups, several chelate structures are a priori feasible and the relative contributions of the possible chelate structures, as well as of relevant nonchelate models, will presumably influence the stereochemical outcome of addition. We have been attempting to elucidate the critical parameters responsible for directed chelate control in carbonyl compounds with multiple functional groups and present here studies on the nucleophilic addition of organometallic and metal hydride reagents to four closely related α,β-dialkoxy carbonyl systems, 2,3-*O*,*O*-dibenzylglyceraldehyde (1)[10] and 2,3-*O*-

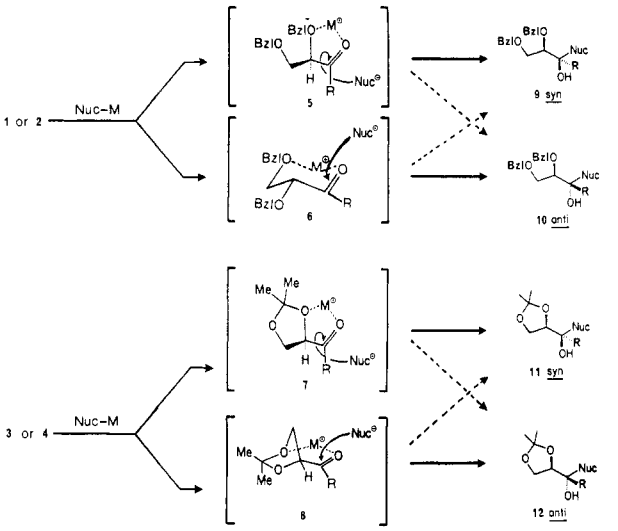

Figure 1. Anticipated stereochemical course of nucleophilic addition via chelated structures. Nucleophilic addition governed by the non-chelate, Felkin model would produce anti products in all cases.

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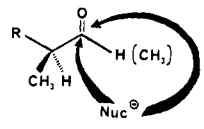
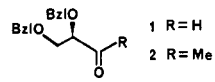
Table I. Reactions of α,β-Dialkoxy Carbonyl Compounds with Nucleophiles

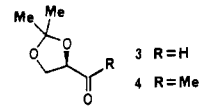
entry	substrate	reagent	solvent	temp, °C	yield, %	product ratio [*syn*/*anti*[a]]
1	1	[MeCu]·$MgBr_2$	Et_2O/SMe_2	−95	83	96/4
2	1	MeMgBr	Et_2O	−95	88	45/55
3	1	$MeTi(O\text{-}i\text{-}Pr)_3$	THF	−45	79	7/93
4	1	Me_2CuLi	Et_2O	−95	84	47/53
5	1	MeLi·LiBr	Et_2O	−95	90	45/55
6	1	[PhCu]·$MgBr_2$	Et_2O/SMe_2	−78	69	96/4
7	1	$PhTi(O\text{-}t\text{-}Pr)_3$	THF	−40	40	17/83
8	1	[BuCu]·$MgBr_2$	Et_2O/SMe_2	−78	78	93/7
9	1	$BuTi(O\text{-}i\text{-}Pr)_3$	THF	−30	81	19/81
10	1	[vinyl-Cu]·$MgBr_2$	Et_2O/SMe_2	−78	80	98/2
11	1	vinyl-$Ti(OiPr)_3$	THF	−78	55	7/93
12	1	[allyl-Cu]·$MgBr_2$	Et_2O/SMe_2	−78	76	68/32
13	1	allyl-Li	Et_2O	−78	81	48/52
14	2	Li(*sec*-Bu_3BH)	THF	−78	88	1/99
15	2	K(*sec*-Bu_3BH)·$MgBr_2$	Et_2O/SMe_2 (THF)	−95	93	95/5
16	2	K(*sec*-Bu_3BH)	Et_2O/SMe_2 (THF)	−95	90	50/50
17	3	[MeCu]·$MgBr_2$	Et_2O/SMe_2	−95	80	35/65
18	3	MeMgBr	Et_2O	−95	84	27/73
19	3	Me_2CuLi	Et_2O	−78	85	82/18
20	3	$MeTi(O\text{-}i\text{-}Pr)_3$	THF	−30	78	30/70
21	4	Li(*sec*-Bu_3BH)	THF	−78	86	6/94
22	4	K(*sec*-Bu_3BH)·$MgBr_2$	Et_2O/SMe_2 (THF)	−78	82	48/52
23	4	K(*sec*-Bu_3BH)	Et_2O/SMe_2 (THF)	−78	85	20/80

[a] All products have been fully characterized by NMR (^1H and ^{13}C), infrared, and mass spectral analysis and their stereochemical assignments confirmed by correlation to materials (11 and 12, R = Me, Bu, Ph, allyl) produced and characterized by Mulzer.[8] Product ratios are reproducible to ±2% and were determined by HPLC (for 9 and 10) and capillary gas chromatography (for 11 and 12) with each sample independently corroborated by high-field proton NMR integration.

isopropylideneglyceraldehyde (3)[11] and their corresponding methyl ketones 2 and 4.







The product stereochemistries anticipated for nucleophilic addition to the chelated structures of 1–4 are illustrated in Figure 1. Importantly, anti adducts 10 and 12 would also be expected on the basis of addition via the nonchelate, Felkin model.[4] The results of addition of a selection of nucleophiles to the carbonyl substrates 1–4 are presented in Table I.

Our results indicate that for addition to 1 and 2 syn products (9) can be obtained with Mg^{2+}-based reagents [RCu·$MgBr_2$] and anti products (10) can be obtained with Li^+-based [LiBH(*sec*-Bu)$_3$] and Ti^{4+}-based [$RTi(O\text{-}i\text{-}Pr)_3$] reagents, when employed in excess (2.0 equiv). Methylation of 1 was investigated in detail with more than 35 agents and condition variations; high syn selectivity was observed with [MeCu]·$MgBr_2$ prepared by addition of ethereal MeMgBr (1.0 equiv) to CuBr·DMS complex (1.0 equiv), and high anti selectivity was observed with $MeTi(O\text{-}i\text{-}Pr)_3$ prepared by addition of MeLi·LiBr (1.0 equiv) to $ClTi(O\text{-}i\text{-}Pr)_3$ (1.0 equiv) at −40 °C. Both solvent and temperature were critical for effective addition by [MeCu]·$MgBr_2$, with strong donor solvents completely inhibiting chelation control and lower temperatures enhancing selectivity. Selectivity with $MeTi(O\text{-}i\text{-}Pr)_3$ was relatively insensitive to solvent, although strongly temperature dependent. The selectivities from both reagents were highly sensitive to the organometallic agent (MeLi, MeMgBr) employed in their synthesis and to metallic "spectator" ion additives. All other methylating agents studied gave poor selectivity, possibly as a consequence of their increased nucleophilicities compared to the $MgBr_2$·MeCu- and MeTi-based reagents, or caused significant substrate decomposition, possibly as a consequence of the enhanced Lewis acidities of the organometallic counterion or additive. Addition of phenyl, *n*-butyl, and vinyl to 1 followed an identical reactivity pattern, with the [RCu]·$MgBr_2$ and $RTi(O\text{-}i\text{-}Pr)_3$ species yielding complementary and good to excellent selectivity and with all other carbon nucleophilic species [e.g., RM, $R_{n+2}CuM_n$, $R_{n+2}ZnM_n$, R_nTiX_{4-n}, etc.] providing a predominant isomer consistent with the Felkin model and in poor selectivity. The low selectivity of allyl addition to 1 under all conditions examined may be explained assuming reaction via a metallo-Claisen transition state which proceeds without a chelate. Reduction of methyl ketone 2 proceeded most stereoselectively and via complementary control with Li(*sec*-Bu_3BH) and K(*sec*-Bu_3BH)·$MgBr_2$.

In comparison with 1, 3 gave little stereoselectivity in nucleophilic additions under identical reaction conditions. In several cases the stereochemistry of the product was opposite to that predicted by a chelate model. The high anti selectivity resulting from reduction of 4 with Li(*sec*-Bu_3BH), although consistent with a β-chelate, we ascribe to hydride addition through the non-chelate, Felkin model (vide infra).

In the reactions of 1 and 2, the Mg^{2+}-based reagents [RCu·$MgBr_2$; K(*sec*-Bu_3BH)·$MgBr_2$] appear to react via α-chelate controlled addition, without competition from β-chelate controlled or Felkin-predicted modes of addition. The high selectivity of Mg^{2+}-based reagents for the α-chelate structures 5 has precedent in monoalkoxy carbonyl systems,[6,9] which also demonstrate a temperature and solvent dependence in addition to aldehydes. Importantly, the magnesium–copper reagents are clearly superior to the corresponding Grignard reagents in producing previously inaccessible high selectivities (>20:1) with aldehydes. We

(11) For references to the synthesis of 3 and its use in the synthesis of carbohydrates and related natural products, see: McGarvey, G. J.; Kimura, M.; Oh, T.; Williams, J. M. *J. Carbohydr. Chem.* **1984**, *3*, 125.

suggest that the depressed reactivity of the carbon nucleophile is responsible for this behavior.

In contrast to the α-chelate controlled syn addition processes, the anti selectivities obtained in addition to **1** and **2** by the lithium [LiBH(*sec*-Bu)$_3$] and titanium [RTi(O-*i*-Pr)$_3$] reagents do not appear to be attributable to β-chelate control. Instead, prior studies by Reetz on monoalkoxy carbonyl systems with these Ti^{4+}-based reagents[7c] and the related selectivities of the LiBH(*sec*-Bu)$_3$ addition to both **2** and **4** argue for the high anti selectivities achieved by these reagents to be a consequence of effective, non-chelate reaction governed by the Felkin model.[12] Thus, although the synthetic utility of these Li^+- and Ti^{4+}-based reagents in addition to α,β-dialkoxy carbonyl systems is established, confirmation of the precise mechanism of addition—via either the β-chelate or the Felkin model—must await further studies.

It is interesting to note that although D-glyceraldehyde derivative **3** has witnessed extensive synthetic utility[11] our work and that of others has not noted predictable, substantial stereoselection in nucleophilic addition to the isopropylidene series **3** and **4** and related systems. We, therefore, conclude that the addition processes of **3** and **4** do not proceed via chelate-controlled addition (cf. ref 8). The inhibition of chelate formation in **3** and **4** may be a consequence of the significant ring strain which would develop in the derived α- and β-chelate structures, of the depressed donor abilities of the acetonide oxygens (relative to an ether oxygen) due to inductive electron withdrawal, and of steric inhibition to chelate formation due to nonbonded interactions between the metal ligands and the acetonide methyl groups.

We have demonstrated that synthetically useful stereoselection in the addition of organometallic and hydride nucleophiles to carbonyl species **1** and **2** can be accomplished. Clearly, chelation in systems such as **1**–**4** is delicately poised and influenced by multiple factors including the size and coordination sphere of the metal counterion and the solvent, as well as the nature of the carbonyl system and of the potential ether ligands. In the enhancement of stereoselective addition to carbonyl compounds, the metal ion appears to be as important in modifying the reactivity of the nucleophile as in orienting the electrophile via chelation. From a preparative standpoint, the Mg^{2+}-counterion-based reagents, which react via α-chelates, appear in general to offer greater nucleophile versatility, stereoselectivity, and yields over the Li^+- and Ti^{4+}-based reagents, which appear to react via the nonchelate model. Our studies also indicate that "open chain" α,β-dialkoxy carbonyl derivatives, such as **1** and **2**, offer enhanced selectivities relative their cyclic acetonide counterparts (**3** and **4**) in nucleophilic addition processes proceeding via both chelate and non-chelate controlled addition modes.

Acknowledgment is made to Dr. Glenn J. McGarvey for helpful discussions of this problem and to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Institutes of Health for support of this research. T.L.M. is a Research Fellow of the Alfred P. Sloan Foundation.

Registry No. **1**, 20196-70-7; **2**, 94278-74-7; **3**, 15186-48-8; **4**, 61821-86-1; [MeCu]·$MgBr_2$, 94278-71-4; MeTi(O-*i*-Pr)$_3$, 18006-13-8; Me_2CuLi, 15681-48-8; MeBr, 74-83-9; [PhCu]·$MgBr_2$, 67501-17-1; PhTi(O-*i*-Pr)$_3$, 16635-23-7; [BuCu]·$MgBr_2$, 62280-51-7; BuTi(O-*i*-Pr)$_3$, 78350-68-2; [vinyl-Cu]·$MgBr_2$, 94294-11-8; vinyl-Ti(C-*i*-Pr)$_3$, 94278-75-8; [allyl-Cu]·$MgBr_2$, 94278-72-5; allyl-Li, 3052-45-7; Li(*sec*-Bu_3BH), 38721-52-7; K(*sec*-Bu_3BH), 54575-49-4.

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(12) For examples of selectivity consistent with α-chelate control in the addition of MeTi(OR)$_3$ to α-hydroxy ketones, see: Reetz, M. T.; Steinbach, R.; Westerman, J.; Urz, R.; Wenderoth, B.; Peter, R. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 135.

(13) For exceptions, see Table I (entry 22), ref 8, and the following:[14] (a) Suzuki, K.; Yuki, Y.; Mukaiyama, T. *Chem. Lett.* **1981**, 1529. (b) Yamaguchi, M.; Mukaiyama, T. *Ibid.* **1981**, 1005. (c) Yamaguchi, M.; Mukaiyama, T. *Ibid.* **1982**, 237. (d) Fronza, G.; Fuganti, C.; Crasselli, P.; Pedrocchi-Fantoni, G.; Zirotti, C. *Tetrahedron Lett.* **1982**, *23*, 4143. (e) Hoffman, R. W.; Endesfelder, A.; Zeiss, H.-J. Carbohydr. *Res.* **1983**, 320.

(14) With the exception of the reaction of **3** with PhTi(O-*i*-Pr)$_3$,[8] all existing examples of nucleophilic addition to **3** producing high ($\gtrsim$90:10) asymmetric induction can be rationalized by assuming reaction via the non-chelate, Felkin model.