

Discorhabdin C (1) represents a new class of potential antitumor agents and is being tested further. Related compounds, isolated from another *Latrunculia* species, are also being studied.

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**Registry No.** 1, 105372-81-4; 1-HCl, 105372-82-5.

**Supplementary Material Available:** Tables of fractional coordinates, thermal parameters, bond distances and bond angles (5 pages). Ordering information is given on any current masthead page.

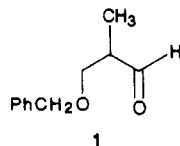
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### Dramatic Effects of Oxygen Substituents on 1,3-Asymmetric Induction in Additions of Allyltriphenylstannane to $\beta$ -Alkoxy Aldehydes: A Chemical and Spectroscopic Investigation

**Summary:** The level of stereoselectivity realized in the Lewis acid mediated additions of allyltriphenylstannane to  $\beta$ -alkoxy aldehydes chiral by virtue of substitution at  $C_3$  depends critically upon the choice of the  $\beta$ -oxygen substituent as well as the choice of Lewis acid. The chemical behavior seen in such addition reactions correlates very well with the solution structures of the Lewis acid complexes formed from such aldehydes and various Lewis acids, as determined by variable-temperature  $^1H$  and  $^{13}C$  NMR spectroscopy.

**Sir:** Recently we reported the results of an NMR investigation of the structures resulting from exposure of the  $\beta$ -alkoxy aldehydes 1 and 2a to  $TiCl_4$ ,  $SnCl_4$ , and  $MgBr_2$ .<sup>1</sup>



The results clearly showed that both  $TiCl_4$  and  $MgBr_2$  afforded a bidentate chelate with 2a in which the methyl substituent occupied an axial (or pseudoaxial) position, which nicely rationalizes the stereoselectivity realized in nucleophilic additions to such chelates. We now report that the choice of O-substituent plays a critical role in determining the conformation of chelates derived from aldehydes such as 2 in solution and that the stereoselectivity realized in the addition of allylstannanes to such

chelates is consistent with predictions based upon the preferred solution conformation of such chelates. Moreover, the reluctance of certain combinations of substrate and Lewis acid to yield conformationally rigid bidentate chelates is also consistent with the chemistry observed with such compounds.

Variable-temperature  $^1H$  and  $^{13}C$  NMR spectroscopy provides a sensitive assay for chelation of aldehydes of general structure 2 with Lewis acids. In this study, we examined via both spectroscopy and reaction chemistry (vide infra) the species derived from reaction of  $\beta$ -alkoxy aldehydes 2a-e with  $MgBr_2$ ,  $TiCl_4$ , and  $SnCl_4$ —Lewis acids that have shown stereoselectivities in Lewis acid mediated nucleophilic additions to  $\beta$ -alkoxy aldehydes consistent with “chelation control”.<sup>2</sup> Information regarding solution conformation is available simply by examination of the coupling constants between protons at  $C_2$  and  $C_3$  for cases where bidentate chelation is established. The most pertinent NMR data is summarized in Table I.<sup>3</sup>

The  $\beta$ -benzyloxy aldehyde 2a with a methyl substituent at  $C_3$  affords a well-behaved bidentate chelate with  $MgBr_2$  over the temperature range of 0–20 °C in which the methyl group occupies an axial position. With  $TiCl_4$ , chelation is again observed (–93 to –70 °C) and the methyl group is again axial. Parallel behavior is observed with 2b, where the methyl substituent is replaced by *n*-hexyl.<sup>4</sup> However, simply changing the O-substituent to methyl (2c) results in a dramatic change in the preferred conformation of such chelates: the *n*-hexyl group at  $C_3$  now occupies an equatorial position in the chelates formed by reaction with  $MgBr_2$  or  $TiCl_4$ . With the *O*-ethyl compound 2d, the *n*-hexyl substituent returns to an essentially axial position in the chelates derived from both Lewis acids. Thus steric effects resulting from the nature of the *O*-substituent are very important in determining the preferred solution conformation of such chelates. The preferred solution conformations as determined by NMR spectroscopy are shown in Figure 1.

A variety of observations suggest that both temperature and steric congestion at and around the ether oxygen are also very important in determining the extent to which chelation can be realized in such systems, particularly with  $SnCl_4$ . While formation of a well-defined bidentate chelate is observed from 1a (in which no alkyl substituent is present at  $C_3$ ) and  $SnCl_4$  by  $^1H$  NMR between –80 and –60 °C, the results obtained with the  $C_3$  substituted materials 2a–c are rather different. The  $^1H$  spectrum from the more sterically demanding *O*-methyl derivative 2c and  $SnCl_4$  at –80 °C contains slightly broadened lines in which the loss of resolution prevents a direct extraction of the solution conformation.<sup>5</sup> The broadened lines suggest the presence

(2) (a) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* 1984, 25, 265. (b) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* 1984, 25, 1879. (c) Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* 1984, 25, 1883. (d) Keck, G. E.; Abbott, D. E.; Wiley, M. R. *Tetrahedron Lett.*, in press. (e) Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron Lett.* 1984, 25, 729. (f) Kiyooka, S.; Heathcock, C. H. *Tetrahedron Lett.* 1983, 23, 4756. (g) Reetz, M. T.; Jung, A. *J. Am. Chem. Soc.* 1983, 105, 4833. (h) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* 1984, 23, 556.

(3) All NMR spectra were recorded on a Varian XL 300 NMR spectrometer operating at 300 MHz for  $^1H$  and 75 MHz for  $^{13}C$  by using 0.1 M solutions of substrates in  $CD_2Cl_2$ . Decomposition of the substrate occurs in the presence of  $TiCl_4$  at temperatures greater than –50 °C. Compound 2b, however, decomposes at temperatures greater than –65 °C. The  $MgBr_2$  chelates were studied between 0 and 20 °C due to the insolubility of some of the chelates at lower temperatures.

(4) In the case of 2b with  $TiCl_4$ , the solution conformation cannot be extracted directly from the observed  $^1H$  spectrum or by decoupling. In this case, the diastereotopic methylenes at  $C_2$  appear as a broad singlet with  $w_{1/2} = 13.4$  Hz. Lineshape analysis in conjunction with spin simulation reveals that no large vicinal coupling to the  $C_3$  methine can be present in this case.

(1) Keck, G. E.; Castellino, S. *J. Am. Chem. Soc.* 1986, 108, 3847.

Table I. NMR Data for Complexes of 2a-e with TiCl<sub>4</sub>, SnCl<sub>4</sub>, and MgBr<sub>2</sub><sup>a</sup>

substrate	Lewis acid; T (°C)	CHO	C <sub>3</sub> -H	C <sub>2</sub> -H	C <sub>2</sub> -H'	OR <sup>b</sup>	C <sub>1</sub> ( <sup>13</sup> C)
2b	TiCl <sub>4</sub> ; -75	-0.46	-0.23	-0.94 <i>w</i> <sub>1/2</sub> = 13.4 Hz		-1.38 -0.25	-17.3
2b	SnCl <sub>4</sub> ; -80	-0.14	-0.09	-0.18		-0.07	
2b	MgBr <sub>2</sub> ; 0	-0.15	-0.03	-0.36 d, <i>J</i> = 4		-0.24 -0.24	-14.3
2c	TiCl <sub>4</sub> ; -80	-0.39	-1.59	-0.85 dd, <i>J</i> = 19, 1		-0.69 dd, <i>J</i> = 19, 10	-14.4
2c	SnCl <sub>4</sub> ; -70	-0.19	-1.37	-0.79		-0.42	-15.0
2c	MgBr <sub>2</sub> ; 10	-0.21	-0.80	-0.76 dd, <i>J</i> = 19, 9		-0.72 dd, <i>J</i> = 19, 2	-13.1
2d	TiCl <sub>4</sub> ; -80	-0.47	-0.99	-1.06 ddd, <i>J</i> = 19, ~4, ~2		-0.94 dd, <i>J</i> = 19, 4	-16.2
2d	SnCl <sub>4</sub> ; -80	-0.19	-0.65	-1.03		0.70 -0.62	
2d	MgBr <sub>2</sub> ; 0	-0.18	-0.24	-0.56 d, <i>J</i> = 4		-0.34	-13.7

<sup>a</sup> Chemical shifts are reported as downfield shifts relative to substrate at the same temperature. <sup>b</sup> Chemical shifts recorded here refer to those for the benzyl protons in 2a and 2b, for the methyl group in 2c, and for the methylene protons of the ethyl group in 2d.

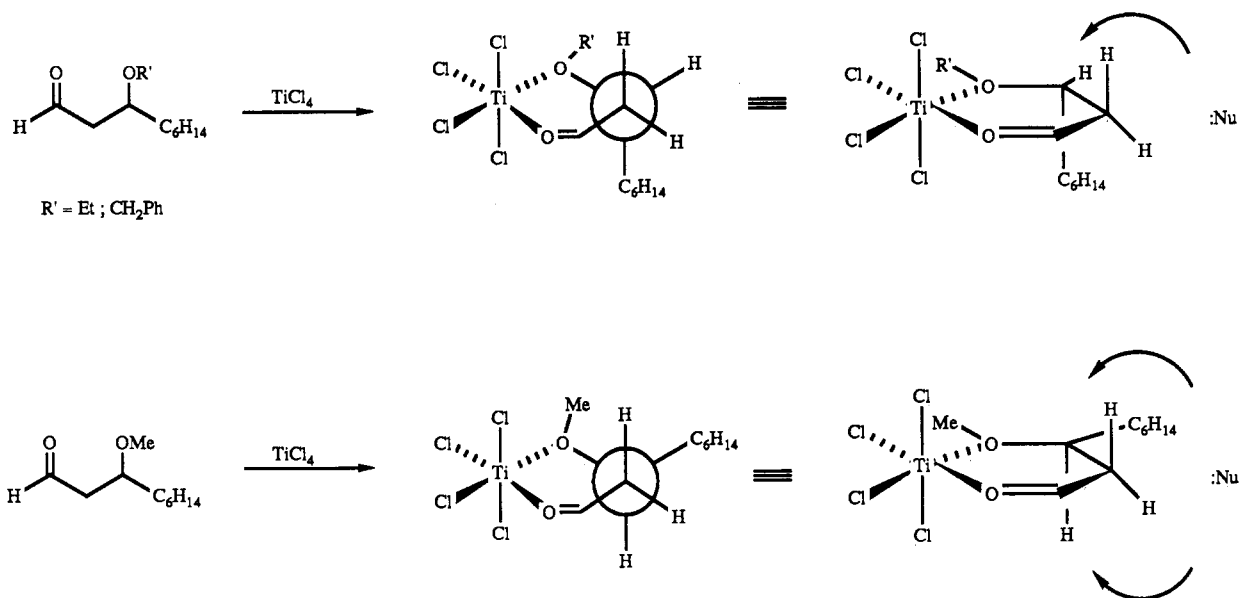


Figure 1.

of dynamic behavior even at -80 °C with respect to the formation of a bidentate chelate. At temperatures greater than -70 °C the resonances become sharper as the temperature increases; in addition, the resonances for the C<sub>3</sub> methine, the C<sub>2</sub> methylene, and the O-methyl protons all shift to higher field with increasing temperature. At 35 °C, the experimental upper limit with respect to temperature, the coupling constants and chemical shifts for these resonances closely approach those observed for 2c alone at the same temperature. It seems clear that equilibration between complexed and uncomplexed materials is occurring rapidly on the NMR time scale in this case and that the equilibrium constant is highly temperature-dependent. A similar trend is observed for 2d and SnCl<sub>4</sub>. In this case, however, the resonances at -80 °C are very broad, suggesting even greater dynamic behavior than that observed with 2c. The <sup>1</sup>H spectra of 2a and 2b, the most sterically

demanding substrates at the ether oxygen, are so broadened that individual resonances are not discernable even at -80 °C.

It is of course crucial to the use of such an approach that the NMR results provide a reliable expectation of chemical events, since the Curtin-Hammett principle can always be invoked in such cases. Fortunately, in all of the cases examined to date, predictions based upon solution structures as examined by NMR are mirrored by the stereoselectivity observed in nucleophilic additions of various allylstannanes to such "complexes". The predictions based upon NMR spectroscopy for the present cases are summarized here: (1) High stereoselectivity for the formation of anti products should be realized for additions to 2a and 2b using TiCl<sub>4</sub> or MgBr<sub>2</sub>, since the axial substituent at C<sub>3</sub> effectively blocks one face of the aldehyde. (2) Low levels of stereoselectivity are expected for 2a and 2b with SnCl<sub>4</sub>, where chelation is much less complete. (3) Low levels of stereoselectivity are expected for 2c with any Lewis acid, since the *n*-hexyl substituent at C<sub>3</sub> is equatorially disposed in the bidentate chelates. (4) Stereoselectivity is expected

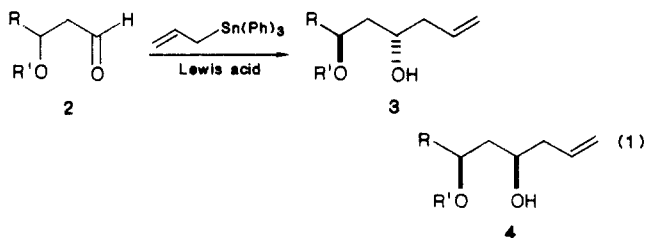
(5) The width at half-height (*w*<sub>1/2</sub>) for the O-methyl singlet is 4.8 Hz at -80 °C for the SnCl<sub>4</sub> case compared to *w*<sub>1/2</sub> = 1.8 Hz for TiCl<sub>4</sub> at -80 °C and *w*<sub>1/2</sub> = 2.6 Hz for MgBr<sub>2</sub> at 10 °C.

Table II

substrate	R	R'	Lewis acid; 3:4 ratio			
			TiCl <sub>4</sub>	MgBr <sub>2</sub>	SnCl <sub>4</sub>	BF <sub>3</sub> ·OEt <sub>2</sub>
2a	CH <sub>3</sub>	PhCH <sub>2</sub>	32:1	8.1:1	3.4:1	3.9:1
2b	<i>n</i> -hexyl	PhCH <sub>2</sub>	96:1	9.7:1	3.3:1	4.9:1
2c	<i>n</i> -hexyl	CH <sub>3</sub>	3.8:1	1.3:1	1.3:3	3.5:1
2d	<i>n</i> -hexyl	CH <sub>3</sub> CH <sub>2</sub>	61:1	3.9:1	3.0:1	4.4:1
2e	<i>n</i> -hexyl	<i>t</i> -BuSiMe <sub>2</sub>	1:1.1	1.7:1	1.7:1	3.4:1

to be high with **2d**, since the *n*-hexyl group is pseudoaxial in the TiCl<sub>4</sub> and MgBr<sub>2</sub> complexes. (5) Low levels of stereoselectivity are again expected with **2e**, which is not expected to form a bidentate complex with any of the Lewis acids examined.<sup>6</sup>

The chemical results are summarized in eq 1 and Table II.<sup>7</sup> In all cases, the stereochemistry assigned to the



products produced was assigned by *chemical correlation* with materials that were independently synthesized by established, unambiguous methods. In particular, the very powerful method of Chamberlin<sup>8</sup> was utilized to secure the anti relationship of oxygenated centers present in the products. Mixtures containing roughly equal amounts of **3** and **4** were prepared via nonselective allyl addition reactions with each of the aldehydes **2a-e**, which then allowed for the development of analytical and/or preparative techniques for the separation of diastereomers. The anti diol (or a simple derivative such as the diacetate) could then be identified via capillary VPC and <sup>13</sup>C NMR comparison with the independently prepared anti material.

Inspection of the data in Table II reveals that the chemical results anticipated based upon the NMR study are in fact realized. For example, with TiCl<sub>4</sub> as Lewis acid, substrate **2b** (R' = benzyl) affords a 96:1 level of stereoselectivity which falls to 3.8:1 with **2c** (R' = CH<sub>3</sub>) and is totally eliminated (1:1.1) in the reaction with **2e** (R' = *t*-BuSiMe<sub>2</sub>), situations in which the group R at C<sub>3</sub> is equatorial, or in which bidentate chelation is not established. With **2d** (R' = ethyl), behavior that parallels that observed with **2b** is observed, consistent with the observation that the C<sub>3</sub> substituents are pseudoaxial in both cases.<sup>9</sup> In no case are high levels of stereoselectivity observed with the monodentate Lewis acid BF<sub>3</sub>·OEt<sub>2</sub> or with SnCl<sub>4</sub> as the Lewis acid. The observed results quite strongly suggest that transmetalation between SnCl<sub>4</sub> and allyltriphenylstannane is faster than, or at least competitive with, the addition of allyltriphenylstannane to the

chelate in this case, and presumably in other cases as well. In fact, "inverse addition" experiments (reaction of substrate with the reagent resulting from reaction of allyltriphenylstannane with Lewis acid) were performed with substrate **2b** by using both SnCl<sub>4</sub> and TiCl<sub>4</sub> and gave 3.1:1 and 1.5:1 stereoselectivities, respectively. Comparison with the data in Table II reveals that the transmetalation hypothesis is quite consistent with this result for the case of SnCl<sub>4</sub> as Lewis acid, but is clearly an unimportant aspect of the reaction of allyltriphenylstannane with the chelate derived from **2b** and TiCl<sub>4</sub>. In general, it seems reasonable to expect that transmetalation possibilities should be considered as possible complications in such reactions with  $\beta$ -alkoxy aldehydes that are rather hindered at or around the ether oxygen, particularly with SnCl<sub>4</sub> as Lewis acid.<sup>10</sup>

In summary, the present investigation provides additional evidence that the sense of asymmetric induction expected in "chelation controlled" nucleophilic additions of allylstannanes to  $\beta$ -alkoxy aldehydes can be predicted by an examination of the solution structures of such chelates and also reveals that rather dramatic changes in solution conformation can result from rather modest changes in substrate structure. Finally, it is of interest to note that rather weak Lewis acids such as MgBr<sub>2</sub> can be much more effective in bidentate chelation than Lewis acids generally regarded as considerably stronger, such as SnCl<sub>4</sub>. Further studies along these and similar lines are in progress and will be reported in due course.<sup>11</sup>

**Registry No.** **2a**, 86272-40-4; **2b**, 105538-80-5; **2c**, 22418-61-7; **2d**, 91243-26-4; **2e**, 105538-81-6; **3a**, 86272-43-7; **3b**, 105538-82-7; **3c**, 105538-83-8; **3d**, 105538-84-9; **3e**, 105538-85-0; **4a**, 86272-50-6; **4b**, 105538-86-1; **4c**, 105538-87-2; **4d**, 105538-88-3; **4e**, 105538-89-4; CH<sub>2</sub>=CHCH<sub>2</sub>Sn(Ph)<sub>3</sub>, 76-63-1.

(10) Keck, G. E.; Abbott, D. E.; Boden, E. P.; Enholm, E. J. *Tetrahedron Lett.* **1984**, 25, 3927.

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### Formation of Quaternary Centers via the Michael Reaction. Electronic Compensation for Steric Congestion

**Summary:** Compensation for steric bulk at the  $\beta$ -terminus of a Michael acceptor may be provided by the attachment of two electron-withdrawing substituents at the  $\alpha$ -terminus. The Michael reaction of ketone and ester enolates is useful for the preparation of contiguous quaternary carbon centers in high yield.

**Sir:** The construction of quaternary carbon centers is one of the more difficult operations in synthetic organic chemistry.<sup>2</sup> We now report methodology that not only provides a simple solution to this problem but is also

(6) (a) Kahn, S. D.; Keck, G. E.; Hehre, W. J. *Tetrahedron Lett.*, in press. (b) Keck, G. E.; Castellino, S. *Tetrahedron Lett.*, in press.

(7) Reactions involving the use of MgBr<sub>2</sub>·OEt<sub>2</sub> as Lewis acid were initiated at -23 °C and allowed to warm slowly to room temperature; those utilizing TiCl<sub>4</sub> or SnCl<sub>4</sub> were conducted at -78 °C. Isolated yields of the products **3** and **4** are typically greater than 85%.

(8) Chamberlin, A. R.; Mulholland, R. L., Jr. *Tetrahedron* **1984**, 40, 2297.

(9) Although we are presently able to make qualitative predictions as to the stereochemical outcome of such reactions based upon preferred solution conformations of intermediate complexes, quantitative predictions as to the level of stereoselectivity expected are much more difficult. For example, the stereoselectivity observed with **2d** and MgBr<sub>2</sub> as Lewis acid is unexpectedly low.

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(2) For an excellent review, see: Martin, S. F. *Tetrahedron* **1980**, 36, 419.