# A Chelate-Controlled Route to Disubstituted and Tetrasubstituted γ-Lactones Stereoselectivity in Lewis Acid Promoted Additions to Chiral Methyl β-Formylcarboxylates

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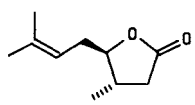
On reaction with allyltrimethylsilane/$TiCl_4$, chiral methyl β-formylcarboxylates **1a–1h** provide disubstituted and tetrasubstituted γ-lactones **3a–3h** with moderate to excellent diastereoselectivities. Other Lewis acids are less selective. The formation of seven-membered ring chelates **1**·$TiCl_4$ has been proven unambiguously by NMR spectroscopy in several cases. Trichloromethyltitanium displays a selectivity pattern similar to the reagent combination allylsilane/$TiCl_4$. Aldehydes **1a–1d**, **1g**, and **1h** give primarily *trans*-γ-lactones, whereas under appropriate conditions **1f** affords an excess of *cis*-γ-lactone **3f**. These results are discussed with regard to the Felkin-Anh model and to chelate formation. Model studies with simpler chiral aldehydes **5** and **7** as well as with acetals **9a/b** and **11a/b** are presented and discussed. They emphasize the importance of chelate control in additions to β-formyl esters **1**.

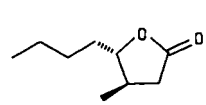
**Ein chelatkontrollierter Weg zu di- und tetrasubstituierten γ-Lactonen – Stereoselektivität von Lewis-Säure-induzierten Additionen an chirale β-Formylcarbonsäure-methylester**

Die chiralen β-Formylcarbonsäure-methylester **1a–1h** liefern mit Allyltrimethylsilan/$TiCl_4$ disubstituierte und tetrasubstituierte γ-Lactone **3a–3h** mit mäßigen bis exzellenten Diastereoselektivitäten. Andere Lewis-Säuren sind weniger selektiv. Die Bildung von siebengliedrigen Chelaten **1**·$TiCl_4$ wurde in einigen Fällen NMR-spektroskopisch eindeutig nachgewiesen. Trichlormethyltitan zeigt ein ähnliches Selektivitätsmuster wie die Reagentienkombination Allylsilan/$TiCl_4$. Die Aldehyde **1a–1d**, **1g** und **1h** werden hauptsächlich in *trans*-γ-Lactone umgewandelt, während **1f** unter geeigneten Bedingungen im Überschuß das *cis*-γ-Lacton **3f** liefert. Diese Ergebnisse werden unter Berücksichtigung des Felkin-Anh-Modells und der Chelatbildung diskutiert. Außerdem werden weitere Modellreaktionen mit den einfacheren chiralen Aldehyden **5** und **7** sowie mit den Acetalen **9a/b** und **11a/b** vorgestellt. Diese unterstreichen die Bedeutung der Chelatkontrolle bei den Additionen an die β-Formylester **1**.

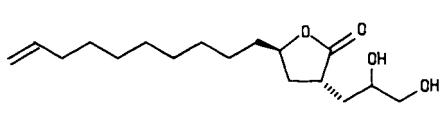
4,5-Disubstituted and 3,5-disubstituted γ-lactones occur frequently as structural units in natural products. Simple examples are the pheromone eldanolide[3], the quercus (oak, whisky) lactone[4], or rubrenolide[5].



Eldanolide



trans-Quercus Lactone



Rubrenolide

Specifically substituted γ-lactones have also been used as templates for stereoselective preparation of complex functionalized acyclic molecules[6–8]. Many interesting and efficient methods for synthesis of this class of heterocycles have therefore been developed quite recently[9]. In this paper[10] we present our entry to this target, involving the *chelate-controlled* addition of allyltrimethylsilane and trichloromethyltitanium to chiral β-formylcarboxylates **1** as the key step.

Chelate-controlled reactions of nucleophiles[11] with carbonyl compounds are usually governed by an α-alkoxy or β-alkoxy group which restricts the conformational freedom of the electrophile by complexation with the metal (Lewis acid). Not much is known concerning γ-functionalized compounds[12] which should form seven-membered ring chelates. In addition, a second carbonyl group has not often been used as ligand for the metal[13]. Therefore, at the outset of our project the following crucial questions arose:

– Are β-formylcarboxylates **1** able to form seven-membered ring chelates?

– Are these chelates effective (rigid) enough to direct the approach of nucleophiles?

– Can chemoselective reagents be found which attack the formyl group exclusively?

## Synthesis of 4,5-Disubstituted γ-Lactones

The readily available[14] methyl β-formylcarboxylates **1** react with allyltrimethylsilane in a Sakurai addition[15] to provide γ-hydroxycarboxylates **2**. However, no attempt to isolate these intermediates was undertaken. Instead, treatment

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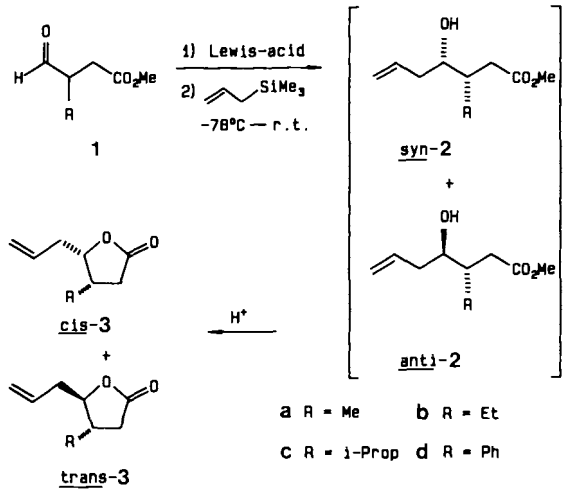
with acid during workup directly afforded 5-allyl-substituted γ-lactones **3** as mixtures of *trans/cis*-isomers. In general yields are good to excellent (Table 1 and 2).




In order to optimize stereoselectivity we examined aldehyde **1a** (R = Me) under various reaction conditions and with different Lewis acids. Table 1 demonstrates that only moderate selectivity – up to 2:1 in favour of the *trans*-γ-lactone – can be attained using titanium tetrachloride (entries 4–7). Other Lewis acids induce even lower (entries 8–10) or negligible (entries 1–3) *trans/cis* selectivity.

Table 1. Additions of allyltrimethylsilane to methyl β-formylcarboxylate **1a** in the presence of Lewis acids under various conditions

| Entry | Lewis Acid | Equivalents | *trans*-**3a**:*cis*-**3a**[a] | Yield[b] |
|---|---|---|---|---|
| 1 | $BF_3$ | 1[c] | 52:48 | 62 |
| 2 | $BF_3$ | 2[c] | 51:49 | 84 |
| 3 | $AlCl_3$ | 1[c] | 52:48 | 71 |
| 4 | $TiCl_4$ | 1[c] | 63:37 | 99 |
| 5 | $TiCl_4$ | 1[d] | 65:35 | 79 |
| 6 | $TiCl_4$ | 1[e] | 69:31 | 66 |
| 7 | $TiCl_4$ | 2[d] | 65:35 | 93 |
| 8 | $ZrCl_4$ | 1[d] | 62:38 | 78 |
| 9 | $HfCl_4$ | 1[d] | 59:41 | 80 |
| 10 | $SnCl_4$ | 1[d] | 56:44 | 92 |

[a] Product distribution after kugelrohr distillation; in individual cases it has been found that ratios in crude **3** are not significantly different. – [b] Yield of purified product. – [c] Complexation with **1a** at −78°C (1 h). – [d] Complexation with **1a** at room temperature (1 h). – [e] Inverse addition: $TiCl_4$ was added to allyltrimethylsilane and **1a** at −78°C.

The approximate 2:1 ratio for **3a** is not significantly different when complexation of aldehyde **1a** with $TiCl_4$ is performed at −78°C and at room temperature (entries 4 and 5). Also, use of *two equivalents* of the Lewis acid does not change the stereochemical outcome (entries 1/2 and 5/7). An inverse procedure – i.e. premixing of **1a** and the silane followed by addition of $TiCl_4$ – causes a slight increase in the *trans/cis* ratio, but the difference between entries 6 and 4 is within the estimated analytical error of ±3% for $^1$H-NMR spectroscopy.

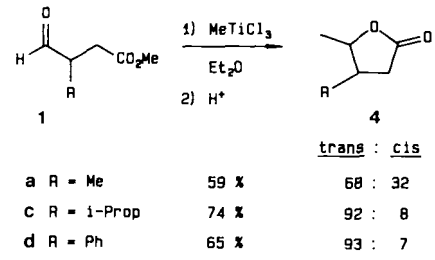
Switching from aldehyde **1a** (R = Me) to substrates **1b–1d** (R = Et, iPr, Ph) remarkably enhances stereoselectivities (Table 2). Again, $BF_3$ is a relatively inefficient promotor in additions of allyltrimethylsilane, while $TiCl_4$ produces *trans*-γ-lactones **3b–3d** in moderate (entry 4) to high excess (entries 6 and 9). Hence, an increase in the steric requirements of the substituent R also strengthens the *trans* selectivity.

Table 2. Additions of allyltrimethylsilane to aldehydes **1a–1d** in the presence of one equivalent of Lewis acid

| Entry | Aldehyde | Lewis Acid | γ-Lactone | *trans*:*cis*[a] | Yield[b] |
|---|---|---|---|---|---|
| 1 | **1a** | $BF_3$[c] | **3a** | 52:48 | 62 |
| 2 | **1a** | $TiCl_4$[d] | **3a** | 63:37 | 99 |
| 3 | **1b** | $BF_3$[c] | **3b** | 50:50 | 58 |
| 4 | **1b** | $TiCl_4$[d] | **3b** | 75:25 | 85 |
| 5 | **1c** | $BF_3$[c] | **3c** | 75:25 | 45 |
| 6 | **1c** | $TiCl_4$[d] | **3c** | 92:8 | 69 |
| 7 | **1d** | $BF_3$[c] | **3d** | 70:30 | 75 |
| 8 | **1d** | $2\,BF_3$[c,e] | **3d** | 72:28 | 65 |
| 9 | **1d** | $TiCl_4$[d] | **3d** | 93:7 | 63 |
| 10 | **1d** | $ZrCl_4$[d] | **3d** | 85:15 | 68 |

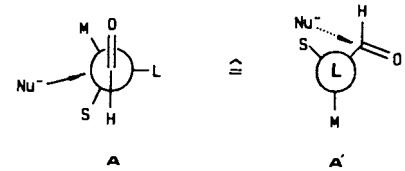
[a–d] See footnotes in Table 1. – [e] Two equivalents of $BF_3$.

As a further example of a highly Lewis acidic nucleophile we examined additions of trichloromethyltitanium[16] to formyl esters **1a**, **1c**, and **1d**. The *trans/cis* ratios determined for γ-lactones **4a**, **4c**, and **4d** are surprisingly close to those obtained in the allylation reaction employing $TiCl_4$ (Table 2). Geometrically similar intermediates and comparable trajectories of attack of the incoming nucleophilic species seem therefore to be involved in both series.



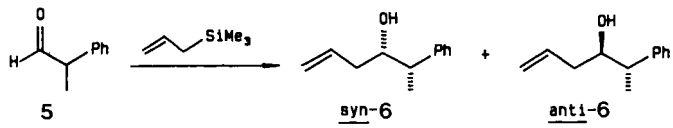

### Interpretation of the 1,2-Asymmetric Induction

The additions of allylsilanes to aldehydes are promoted by coordination of the Lewis acid to the carbonyl group, enhancing the electrophilicity of this moiety. This $S_E$ reaction occurs with a net shift of the double bond, directed by the silyl substituent's β-effect[17]. Reactions with chiral substrates can be qualitatively understood by the Felkin-Anh model[18] – a refinement of the original Cram rule[19].



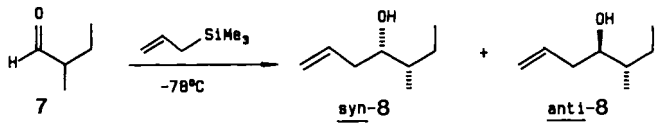
It assumes a reactive conformation with the largest substituent L (or the most electronegative group) antiperiplanar to the carbonyl unit and attack of the nucleophile as shown in **A** (L = large, M = medium, S = small substituent).

This model satisfactorily explains the 1,2-asymmetric induction of allylsilane additions to 2-phenylpropanal (**5**) – the standard substrate for testing diastereoselectivities. An approximate 2:1 ratio of *syn/anti*-isomeric[20] homoallylic alcohols **6** has been reported; only a slight dependence on the Lewis acid employed is observed[21].



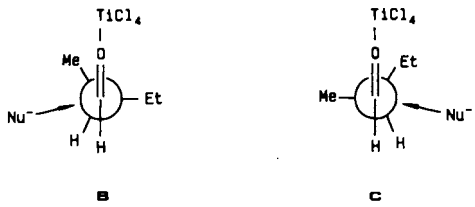

| | | |
|---|---|---|
| $BF_3$ | 67 | 33 |
| $TiCl_4$ | 62 | 38 |
| $SnCl_4$ | 69 | 31 |

For better comparison with chiral aldehydes **1** we also treated 2-methylbutanal (**7**) with allylsilane. With $BF_3$ nonselective addition occurs, giving almost equal amounts of *syn*-**8** and *anti*-**8**, while $TiCl_4$ affords a 62:38 *syn/anti* mixture.




| | | | |
|---|---|---|---|
| $BF_3$ | (49 %) | 53 | 47 |
| $TiCl_4$ | (58 %) | 62 | 38 |

The preference for *syn*-**8** is in accordance with the Felkin-Anh proposal. However, the reason for the higher selectivity with $TiCl_4$ is not clear. Possibly, complexation of **7** with this larger Lewis acid causes a higher population of conformation **B** than **C**. For the less voluminous $BF_3$ this difference might be negligible, since the methyl and ethyl substituents are quite similar.



**B** **C**

Another explanation considers different trajectories of the nucleophile. With larger Lewis acids the nucleophile is forced to be closer to the chiral center, thus enhancing the influence of this moiety on the stereochemical outcome (see **A'**). Experiments with α-chiral thionium ions have recently been explained using this hypothesis[22]. According to this model, changing from $BF_3$ to $TiCl_4$ should result in higher selectivities for **5**; however, this is not the case. This is why we prefer the first proposal at this moment.

The Felkin-Anh model can also be applied to interpret $BF_3$-induced allylsilane additions to aldehydes **1a–1d**. This Lewis acid coordinates at *one* nucleophilic center only. The reactive species will therefore be the monocomplex of the aldehyde, and the potential second ligand can be treated as an "innocent" substituent exerting mainly steric effects.

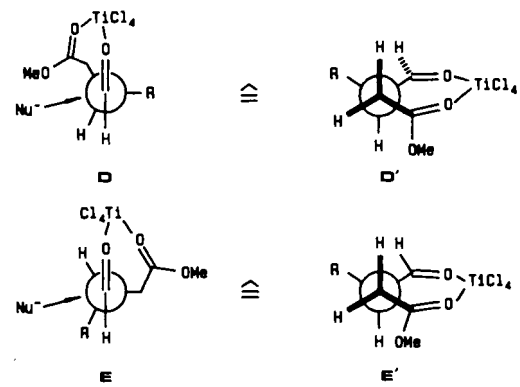
Since both **1a** and **1b** give completely nonselective reactions (Table 2, entries 1 and 3), the methyl, ethyl, and (methoxycarbonyl)methyl groups seem to display rather similar steric requirements in the transition states of the allylation process. These findings are in agreement with those for the $BF_3$-promoted reactions of 2-methylbutanal (**7**). Including the experiments with **1c** and **1d** (Table 2, entries 5 and 7) the following reasonable sequence for the substituents' size[23] can be established:

$$H < Me \approx Et \approx CH_2CO_2Me < iPr \approx Ph$$

Interestingly, rather similar selectivities were obtained for allylations of **1a**, **1c**, and **1d** under conditions involving nucleophilic allyl *radicals* at a metal surface[24]. We propose that these ratios reflect the *inherent selectivity* of chiral aldehydes **1** in reactions with nucleophilic species.

The other Lewis acids used in this study are able to coordinate to two additional ligands, thereby forming octahedral complexes. These seven-membered chelates are formed with β-formylcarboxylates **1** and $TiCl_4$, as unequivocally demonstrated by spectroscopic means (see below). This species, involving *one* equivalent of Lewis acid, should be the reactive intermediate, as suggested by the observation that addition of a second equivalent of $TiCl_4$ has no influence on the stereoselectivity. Therefore, contrary to the $BF_3$-induced allylsilane additions, only a few conformations have to be examined for **1** · $TiCl_4$.

Inspection of molecular models (taking into account the X-ray analysis of a related seven-membered chelate with $TiCl_4$ reported by Helmchen et al.[13c]) suggests that conformers **D** and **E** have to be considered in the formation of *trans*-γ-lactones. In both (idealized) staggered arrangements, the R group avoids *gauche* interactions with the $CH_2-CO_2Me$ bond. Preliminary molecular mechanics calculations support this view. Structures **D** and **E** are similar to the reactive conformation used within the frame of the Felkin-Anh model. The nucleophile's attack should be sterically more favourable in **D**, though stereoelectronic effects might increase the reactivity of **E**[25].



**D** **D'**

**E** **E'**

For compounds with large-sized R only conformation **D** seems to be important, as is demonstrated by the high *trans* selectivities (Table 2 entries 6 and 9). On the other hand, for

Table 3. Selected $^1$H NMR and $^{13}$C NMR values for complexes of **1a** and **1d** with $TiCl_4$ and $BF_3$, respectively (δ, $CD_2Cl_2$)[a]

| | **1a** | **1a** · $TiCl_4$ | Δδ | **1a** · $BF_3$ | Δδ | **1d** | **1d** · $TiCl_4$ | Δδ | **1d** · $BF_3$ | Δδ |
|---|---|---|---|---|---|---|---|---|---|---|
| $^1$H NMR | | | | | | | | | | |
| CHO | 9.70 | 9.82 | 0.12 | 9.66 | −0.04 | 9.66 | 9.86 | 0.20 | 9.65 | −0.01 |
| $CO_2Me$ | 3.69 | 4.14 | 0.45 | 3.69 | 0.00 | 3.62 | 4.10 | 0.48 | 3.63 | 0.01 |
| $^{13}$C NMR | | | | | | | | | | |
| C-1 | 172.1 | 180.9 | 8.8 | 173.3 | 1.2 | 172.2 | 180.9 | 8.5 | 173.1 | 0.7 |
| C-4 | 202.6 | 215.0 | 12.4 | 205.5 | 2.9 | 199.2 | 211.3 | 12.1 | 200.0 | 0.8 |
| OMe | 51.5 | 58.4 | 6.9 | 52.6 | 1.1 | 55.0 | 58.4 | 3.4 | 54.9 | −0.1 |

[a] For the full data set see ref.[1]; for complexes with **1a** also see ref.[10].

small substituents R, like Me or Et, the modest *trans/cis* ratios observed (Table 2) suggest that other conformers have to be considered. However, the *inherent selectivity* of the aldehydes **1a–d** – as discussed above – is significantly surpassed when chelate formation occurs. This enhancement is not just caused by the interchange of the Lewis acids, since the simpler chiral aldehydes **5** and **7**, which are not capable of forming chelates, show a different pattern. For the reaction of **7** and allylsilane promoted by $TiCl_4$, the *syn* isomer of **8** predominates, while **1a** – sterically rather similar to **7** – gives mainly *trans*-**3a**, corresponding to a primary *anti* adduct **2**[26]. Also, reaction of **5** gives a 2:1 *syn/anti* ratio of **6**; the aldehyde **1d** advances selectivity up to 93:7 in favour of *trans*-**3d**! These results unequivocally demonstrate the importance of chelate control in these 1,2-asymmetric inductions. Other bidentate Lewis acids are less effective than $TiCl_4$ as shown in Table 1 and 2. This might be due to longer oxygen metal bonds (increased covalent radii of the central metal[27]) affording less rigid seven-membered chelates and thus lower selectivity.

Trichloromethyltitanium as a nucleophile displays the same selectivity pattern with **1a–1d** as allylsilane/$TiCl_4$. Chelate formation with **1** is therefore very likely with one molecule of $MeTiCl_3$ functioning as Lewis acid[28], while a second one attacks the activated species, following a trajectory similar to that of the allyl reagent.

### Spectroscopic Proof of Chelate Formation

Addition of $TiCl_4$ to aldehydes **1** at −78 °C generates yellow precipitates which dissolve on warming to room temperature, giving an orange-yellow solution of **1** · $TiCl_4$. The IR spectrum of **1a** · $TiCl_4$ (in $CDCl_3$) shows a carbonyl absorption at 1660 $cm^{-1}$, that of **1a** appearing at 1730 $cm^{-1}$. This important weakening of the bond order for *both* C=O bonds suggests chelate formation. Even more convincing arguments arise from NMR spectroscopy, which has successfully been used by others[29] to clarify chelate structures.

Since solutions of **1** · $TiCl_4$ (in $CD_2Cl_2$) do not give well-resolved NMR spectra at low temperature, these have to be recorded at 25 °C. The most significant $^1$H and $^{13}$C NMR values for **1a** and **1d** as well as for their $TiCl_4$ and $BF_3$ complexes are compiled in Table 3. These data unambiguously demonstrate that both carbonyl groups of **1** are involved in complexes with $TiCl_4$. Downfield shifts of approximately 8.5 ppm for C-1 ($CO_2Me$) and 12 ppm for C-4 (CHO) are observed for **1a** · $TiCl_4$ and **1d** · $TiCl_4$, respectively. The $^1$H NMR data are less impressive and, interestingly, display the largest effect for the methoxy signals. $BF_3$ shifts both C=O signals of **1a** or **1d** to lower field. However, the differences from uncomplexed aldehydes are only in the order of 1–3 ppm. The proton signals are essentially unchanged. These findings are in agreement with other recent reports[29], suggesting a weaker interaction of $BF_3$ with carbonyl groups.

### Synthesis of 3,5-Disubstituted and 3,4,4,5-Tetrasubstituted γ-Lactones

α-Chiral β-formyl esters **1e–1h**[14] have been subjected to the Sakurai reaction to examine 1,3-asymmetric induction. As expected, the stereoselectivity observed for **1e** and **1f** is significantly lower than that for aldehydes **1a–1d**. Thus,

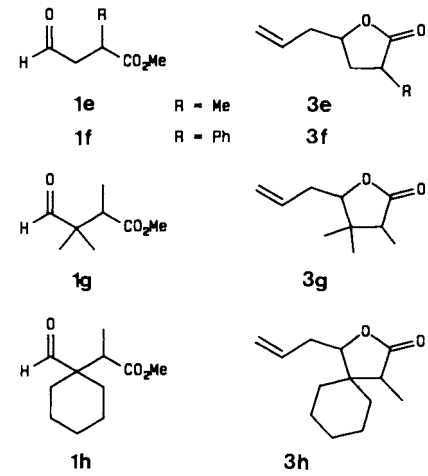



Table 4. Additions of allyltrimethylsilane to aldehydes **1e–1h** in the presence of Lewis acids

| Entry | Aldehyde | Lewis Acid[a] | γ-Lactone | *trans:cis* | Yield[b] |
|---|---|---|---|---|---|
| 1 | **1e** | $BF_3$ | **3e** | 50:50 | 74 |
| 2 | **1e** | $TiCl_4$ | **3e** | 50:50 | 67 |
| 3 | **1f** | $BF_3$ | **3f** | 48:52 | 73 |
| 4 | **1f** | $TiCl_4$ | **3f** | 24:76 | 64 |
| 5 | **1g** | $BF_3$ | **3g** | 50:50 | 60 |
| 6 | **1g** | $TiCl_4$ | **3g** | 90:10 | 61 |
| 7 | **1h** | $TiCl_4$ | **3h** | 88:12 | 70 |

[a] Complexation with one equivalent at −78 °C. – [b] See footnote in Table 1.

the methyl-substituted substrate **1e** gives equal amounts of *trans*- and *cis*-γ-lactones **3e** regardless of whether $BF_3$ or $TiCl_4$ is used as a promoting Lewis acid (Table 4).

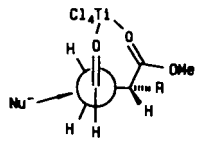
Also, with **1f**, where a sterically more demanding phenyl group is present, $BF_3$ brings about an essentially unselective transformation into **3f**. In contrast, $TiCl_4$ induces a moderate preference for *cis*-**3f** (entry 4). Equilibration experiments[30] reveal that the *trans*/*cis* ratio of approximately 1:3 is not the result of thermodynamic control.

On the other hand, α-chiral β-dialkyl-substituted compounds like **1g** and **1h** provide the corresponding tetrasubstituted γ-lactones **3g** and **3h**, respectively, with a surprisingly high excess (9:1) of the *trans* isomers when $TiCl_4$ is employed (entries 6 and 7). $BF_3$ again yields a completely stereorandom result with aldehyde **1g** (entry 5). The striking difference in the sense of 1,3-asymmetric induction depending on the degree of substitution at the β-carbon was also observed in cuprate additions to **1e**–**1f**[2,31].

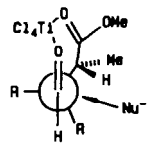
### Interpretation of the 1,3-Asymmetric Induction

The results collected in Table 4 demonstrate that the inherent selectivity of aldehydes **1e**–**1h** is negligible. The $BF_3$-induced additions are not influenced by the stereogenic center β to the carbonyl group attacked (entries 1, 3, and 5).

Chelate formation using $TiCl_4$ as promotor does not raise the stereoselectivity for monosubstituted aldehydes unless the group R is relatively large, e.g. a phenyl group (entries 2 and 4)[32]. In this case we propose a reactive conformer **F** which should lead to the favoured *cis*-**3f**.



**F**



**G**

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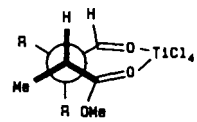
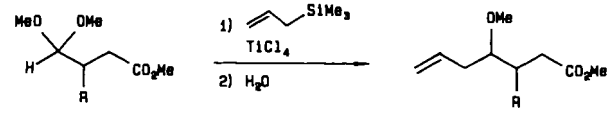


**G'**

For β-dialkyl-substituted β-formyl esters **1g** and **1h** – both providing *trans*-lactones with preference – a different major conformation must be assumed. We speculate that the two additional alkyl groups force a change from **F** to conformation **G**, thereby minimizing repulsive interactions of these substituents with the formyl group. The methyl group might prefer the pseudoequatorial position, as illustrated in **G'**. Thus, the substituents at the stereogenic center in **1f**–**1h** do not directly steer the addition of the nucleophile. Instead, a conformational change must govern this process. The role of large sized chlorine atoms at titanium should also be considered in all these discussions[13c]. Their effect is hard to take into account using molecular models. Consolidation of these speculations by force-field calculations seems to be appropriate.

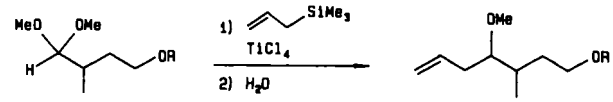
### 1,2-Asymmetric Induction with Chiral Acetals

Having established the effectiveness of chelate-controlled allylsilane additions to chiral β-formyl esters **1**, we wanted to compare these results with those employing the corresponding chiral acetals **9a** and **9b**[14] as electrophiles.



| | | |
|---|---|---|
| **9a** R = Me | 51 % | **10a** syn/anti = 60 : 40 |
| **9b** R = Ph | 99 % | **10b** syn/anti = 40 : 60 |
| | | (60 : 40) |

Using $TiCl_4$ as the promoting Lewis acid with **9a**, a *syn*/*anti* ratio of 60:40 was determined for the isolated homoallylic ether **10a**. Similarly, the phenylsubstituted acetal **9b** gives a 40:60 mixture, though in this case the configurational assignment is uncertain (see below). As expected these transformations, involving highly reactive oxocarbenium ions[33], are much less selective than those of the related aldehydes **1a** and **1d**. Both major products can be explained by applying the Felkin-Anh model to the intermediate. On the other hand, for the lower homologue of **9** – the corresponding α-formyl ester – a 40:60 *syn*/*anti* ratio has been reported, and was interpreted as a consequence of chelate-controlled addition of allylsilane[34]. We do not believe that a chelate accounts for these as well as our own results, since the oxocarbenium ion generated cannot act as a ligand to the Lewis acid[35].



| | | |
|---|---|---|
| **11a** R = $CH_2Ph$ | 94 % | **12a** syn/anti = 60 : 40 |
| **11b** R = $SiMe_2tBu$ | 74 % | **12b** syn/anti = 50 : 50 |

Reactions of allylsilane/$TiCl_4$ with acetals **11a** and **11b** – bearing protected γ-hydroxy functions – also give addition products **12a** and **12b** with low to zero stereoselectivity. These experiments emphasize that the ester group in **9a** is essentially an "inert" substituent, exerting no special effect. In summary, one has to state that the inherent selectivities in these acyclic chiral acetals are quite low.

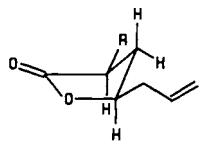
### Configurational Assignments

The determination of the relative configurations in *4,5-disubstituted γ-lactones* **3a**–**d** and **4a**–**d** is straightforward and in accord with comprehensive precedents[36]. The most significant evidence is obtained from $^1H$ NMR spectroscopy, by comparing the chemical shifts of 5-H in the two isomers. Without exception this signal appears at lower field in the *cis*-isomer (δ = 4.5–4.9) than in the corresponding *trans*-γ-lactone (δ = 4.1–4.5). On the other hand, the signal for the 4-methyl group is shifted slightly upfield in *cis* compounds (*cis*-**3a**: δ = 1.05; *trans*-**3a**: δ = 1.14).

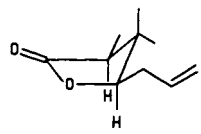
Coupling constants are often not conclusive for five-membered heterocycles. This is also true for substituted γ-lactones, as pointed out by Font et al.[37], who performed force-field calculations and correlated the conformations obtained to observed experimental coupling constants. This is why we did not base our stereochemical assignments on these values even if they were determinable. For **3a** an NOE experiment confirmed the proximity of 5-H to 4-Me in the *trans* compound, while the *cis*-lactone did not display this effect.

$^{13}C$ NMR data fully corroborate our assignments. The signal of 4-$CH_{(2/3)}$ is consistently shifted to lower field (3–4 ppm) in *trans*-lactones. Also, in general *all signals* for ring carbons appear at lower field in *trans*-**3**/**4**, a single exception being recorded for C-4 of **3c**.

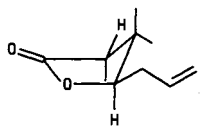
The stereochemistry of *3,5-disubstituted γ-lactones* **3e** and **3f** can be determined by consideration of the coupling constants. For *cis* compounds the conformation having both substituents in pseudoequatorial position should clearly be favoured[37]. Actually, large coupling constants for 3-H *and* 5-H to one of the protons at C-4 are observed for *cis*-**3f** (12 Hz, 10 Hz), whereas *trans*-**3f** displays only small values (5–6 Hz). The chemical shifts for 5-H are at higher field in *cis*-**3e** and *cis*-**3f** than the corresponding signals in the *trans*-lactones. In *cis*-lactones of this pattern the steric compression is smaller than in *trans* compounds – an effect also indicated by lower chemical shifts for C-3 in the $^{13}C$ NMR spectra.



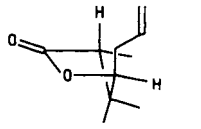
cis-3e,3f



cis-3g



trans-3g



trans-3g

This $^{13}C$ NMR criterium can also be applied to the two tetrasubstituted γ-lactones **3g** and **3h**, where there are no proton couplings to allow stereochemical assignments. $^1H$ NMR signals for 5-H again appear at lower field for *trans* compounds. The chemical shifts for the two 4-methyl groups in *trans*-**3g** are very similar (δ = 1.08, 1.02) compared to those in *cis*-**3g** (δ = 1.18, 0.83). This effect is in agreement with a predominating conformation of *cis*-**3g** having both substituents at C-3 and C-5 in pseudoequatorial positions, as depicted above. For the major *trans* isomer an NOE effect between 5-H and 3-Me as well as to one of the 4-Me groups demonstrates proximity of these substituents. The analogous stereochemical assignment for **3h** has been made by comparison of proton and carbon signals with those of **3g**.

For acyclic addition products **8**, **10**, and **12** the stereochemical assignments are not straightforward. Although *syn* arrangement of substituents in the major isomer of **8** is likely on mechanistic grounds and has been proposed for the related additions of allyl boron reagents to **7**[38], a stereochemical correlation with **3a** was desirable. We converted a *trans*/*cis* mixture of **3a** into the silylated 1,4-diols **13** which were compared with the related compounds **14** and **15**. In **13** the major isomer must have *anti* configuration because of the predominance of *trans*-**3a** in the starting material. Comparison of *O*-silylated compounds was preferred, as it excludes hydrogen bridging effects on the NMR values observed.

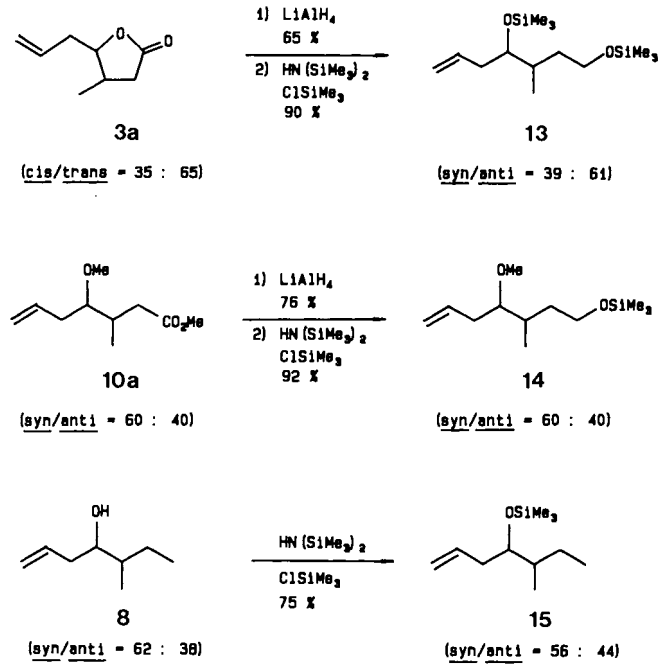



Table 5. Comparison of significant $^{13}C$ NMR and $^1H$ NMR values of 3-methyl substituted 1,4-dioxy compounds **13**, **14**, **12a**, and **12b**, methyl 4-methoxy-6-heptenoates **10a** and **10b**, as well as of homoallylic alcohol derivatives **8** and **15** (δ, $C_6D_6$[a])

| Signal[b] | Compound | **13** | **14** | **15** | **8**[a] | **12a** | **12b** | **10a**[a] | **10b** |
|---|---|---|---|---|---|---|---|---|---|
| 3-Me | *syn* | 15.5 | 14.9 | 14.1 | 13.4 | 14.5 | 14.4 | 14.3 | 135.5[c] |
| | *anti* | 16.1 | 15.9 | 15.4 | 14.6 | 15.4 | 15.4 | 16.9 | 142.3[c] |
| C-4 | *syn* | 76.7 | 85.1 | 76.4 | 73.6 | 84.5 | 84.6 | 83.4 | 83.8 |
| | *anti* | 77.2 | 85.7 | 76.9 | 74.2 | 85.1 | 85.2 | 84.1 | 84.0 |
| C-3 | *syn* | 35.2 | 32.8 | 40.6 | 39.5 | 32.8 | 32.2 | 32.5 | 45.1 |
| | *anti* | 35.7 | 32.8 | 41.0 | 40.6 | 32.8 | 32.2 | 33.2 | 46.3 |
| 4-H[d] | *syn* | 3.7 (m) | 3.08 (3.7/6.2/6.2) | 3.73 (3.5/4.5/7.0) | 3.55 (4.2/4.2/8.5) | 2.98 (3.5/6.5/6.5) | 3.11 (3.8/6.3/6.3) | 3.13 (3.5/5.8/7.1) | |
| | *anti* | 3.47 | 3.01 (5.0/5.0/6.7) | 3.67 (4.8/4.8/6.8) | 3.47 (3.2/5.7/9.0) | 2.91 (5.0/5.0/6.6) | 3.06 (5.0/5.0/6.8) | 3.02 (5.0/6.2/6.2) | |
| ratio | *syn*/*anti* | 39:61 | 60:40 | 56:44 | 62:38 | 60:40 | 50:50 | 60:40 | 40:60 |

[a] Spectra of **8** and **10a** were recorded in $CDCl_3$ as solvent. – [b] To facilitate comparison the same numbering of atoms is applied for all compounds in this table. – [c] Signal for the *ipso*-carbon of the phenyl group. – [d] In parentheses: values of the coupling constants in Hz.

The $^{13}C$ NMR and $^{1}H$ NMR data compiled in Table 5 display relatively small but consistent differences between *syn*- and *anti*-isomeric compounds. Our stereochemical assignments for **14**, **12a**, and **10a** are based on this comparison with **13**. This survey of data also proves that the *syn* isomer of **8** (and **15**) corresponds to the major product as anticipated on mechanistic grounds and literature evidence. The assignment of **10b** is uncertain, but we suggest the *anti* stereochemistry for the predominant isomer to be more likely, considering both the NMR data and the proposal of the Felkin-Anh model.

## Conclusion

In this paper we have demonstrated that disubstituted and tetrasubstituted γ-lactones **3** and **4** can be prepared with a moderate to high excess of one diastereomer. Chelate formation involving two carbonyl groups is the key feature in attaining stereoselectivity. Since several of the aldehydes **1** can be obtained in optically active form[39] this route also opens the possibility of synthesizing enantiomerically pure or enriched γ-lactones[40]. Other Lewis acidic nucleophiles currently investigated display similar behaviour in additions to these chiral aldehydes and even surpass the stereoselectivity achieved for allylsilane/$TiCl_4$ or $MeTiCl_3$[41].

We are very grateful to the *Deutsche Forschungsgemeinschaft*, the *Fonds der Chemischen Industrie*, the *Vereinigung von Freunden der Technischen Hochschule zu Darmstadt*, and the *Karl-Winnacker-Stiftung* (Hoechst AG, Frankfurt). We also thank *Brigitte Suchland*, *Andreas Schmitt*, and *Matthias Rümmler* for experimental help.

## Experimental

IR spectra were recorded with a Perkin-Elmer 1420 Ratio Recording, a Beckman Acculab 4, or a Beckman IR 5a. – $^{1}H$ NMR spectra: Bruker WM 300 (internal reference TMS or $CHCl_3$). – $^{13}C$ NMR spectra: Bruker WM 300 (internal reference $CDCl_3$). – Boiling points of compounds obtained in small-scale experiments refer to the temperature in a Büchi Kugelrohr oven. – Radial chromatography was performed with a "Chromatotron" (Harrison Research, Model 7924) using silica gel plates.

Starting materials: **1a–1f**, **1h**, **9a**, **9b**, **11a**, and **11b** see ref.[14]; **1g** see ref.[42]; allyltrimethylsilane (Fluka, Chemika) was used as obtained; $TiCl_4$ and $Et_2O-BF_3$ were distilled under nitrogen. $Et_2O-BF_3$ was used as source for $BF_3$ in all experiments employing this Lewis acid; dichloromethane was distilled from $CaH_2$ and stored over molecular sieves. All reactions were executed in a flame-dried flask under a slight pressure of dry nitrogen. Solvents and liquid reagents were added by syringe. All chiral products were obtained as racemates.

### Syntheses of γ-Lactones

*General Procedure for Additions of Allyltrimethylsilane to Aldehydes* **1**: To a solution of aldehyde **1** (1.0 equivalent) in dichloromethane (2 ml/1 mmol of **1**) the Lewis acid (1.0–2.0 equivalents, see Table 6) was added. The mixture was stirred for 1 h at −78°C (method A) or for 1 h at room temp. (method B). Allyltrimethylsilane (1.5 equivalents) was added at −78°C. The mixture was stirred for 2 h at −78°C, followed by warm-up to room temp. over a 16-h period, and addition of sulfuric acid (50%, 1 ml/1 mmol of **1**). Dilution with water and extractive workup with dichloromethane provided the crude lactones **3**, which were distilled in a kugelrohr apparatus. Yields refer to reactions performed on 2 to 10-mmol scale. The γ-lactones obtained showed a purity of 90–97% by $^{1}H$ NMR. Major signals of impurities in the $^{1}H$ NMR spectra: δ = 3.8–3.4 (s, $CO_2Me$ of **2** and elimination products derived thereof). Samples for elemental analysis were gained by radial chromatography [$SiO_2$, elution with pentane:ethyl acetate (10:1)].

Table 6. Lewis acid promoted additions of allyltrimethylsilane to aldehyde **1a** (2.00 mmol) according to the general procedure

| Lewis Acid | Equivalents | Method | Yield of **3a** [g] | (%) | *trans:cis* |
|---|---|---|---|---|---|
| $BF_3$ | 1 | A | 0.173 | 62 | 52:48 |
| $BF_3$ | 2 | A | 0.235 | 84 | 51:49 |
| $AlCl_3$ | 1 | A[a] | 0.199 | 71 | 52:48 |
| $TiCl_4$ | 1 | A | 0.279 | 99 | 63:37 |
| $TiCl_4$ | 1 | B | 0.220 | 79 | 65:35 |
| $TiCl_4$ | 1 | A[b] | 0.186 | 66 | 69:31 |
| $TiCl_4$ | 2 | B | 0.260 | 93 | 65:35 |
| $ZrCl_4$ | 1 | B[a] | 0.218 | 78 | 62:38 |
| $HfCl_4$ | 1 | B[a] | 0.225 | 80 | 59:41 |
| $SnCl_4$ | 1 | B | 0.257 | 92 | 56:44 |

[a] Solid Lewis acids were transferred into the reaction flask under a stream of dry nitrogen before adding **1a** and the solvent. – [b] Inverse procedure: $TiCl_4$ was added to a mixture of **1a** and allylsilane.

Table 7. Lewis acid promoted additions of allyltrimethylsilane to aldehydes **1b–1h** according to the general procedure

| Aldehyde (mmol) | Lewis acid[a] | Method | Yield of **3b–h** [g] | (%) | *trans:cis* |
|---|---|---|---|---|---|
| **1b** (2.00) | $BF_3$ | A | 0.178 | 58 | 50:50 |
| **1b** (2.00) | $TiCl_4$ | B | 0.261 | 85 | 75:25 |
| **1c** (1.90) | $BF_3$ | A | 0.144 | 45 | 75:25 |
| **1c** (2.00) | $TiCl_4$ | B | 0.231 | 69 | 92:8 |
| **1d** (2.00) | $BF_3$ | A | 0.305 | 75 | 70:30 |
| **1d** (2.00) | $BF_3$[b] | A | 0.262 | 65 | 72:28 |
| **1d** (2.00) | $TiCl_4$ | B | 0.253 | 63 | 93:7 |
| **1d** (2.00) | $ZrCl_4$ | B | 0.275 | 68 | 85:15 |
| **1e** (3.10) | $BF_3$ | A | 0.321 | 74 | 50:50 |
| **1e** (3.65) | $TiCl_4$ | A | 0.341 | 67 | 50:50 |
| **1f** (3.64) | $BF_3$ | A | 0.584 | 73 | 48:52 |
| **1f** (3.95) | $TiCl_4$ | A | 0.512 | 64 | 24:76 |
| **1g** (5.19) | $BF_3$ | A | 0.521 | 60 | 50:50 |
| **1g** (4.11) | $TiCl_4$ | A | 0.419 | 61 | 90:10 |
| **1h** (3.95) | $TiCl_4$ | A | 0.574 | 70 | 88:12 |

[a] One equivalent of Lewis acid employed. – [b] Two equivalents of $BF_3$ were used in this reaction.

For physical and spectroscopic data of γ-lactones **3a**, **3c**, and **3d** see ref.[24]. For $^{13}C$ NMR data and elemental analyses see Tables 8 and 9.

*5-Allyl-4-ethyl-4,5-dihydro-2(3H)-furanone* (**3b**): Colorless liquid, b.p. 70°C/0.01 Torr. – IR (film): $\tilde{\nu}$ = 3080, 2960, 2930, 2880 $cm^{-1}$ (C–H), 1775 (C=O), 1640 (C=C). – $^{1}H$ NMR ($CDCl_3$): δ = 5.82 ($m_c$, 1H, =CH), 5.24–5.10 (m, 2H, $=CH_2$), 4.56 (dt, *J* = 8.5, 6.5 Hz, 0.25H, *cis*-5-H), 4.19 (td, *J* = 6.5, 5.2 Hz, 0.75H, *trans*-5-H), 2.74–2.08 (m, 4H, 5-$CH_2$, 3-H), 1.58, 1.36 (2 $m_c$, 2H, 4-$CH_2$), 0.94 (t, *J* = 7 Hz, 3H, $CH_3$).

*5-Allyl-4,5-dihydro-3-methyl-2(3H)-furanone* (**3e**): Colorless liquid, b.p. 100°C/0.8 Torr. – IR (film): $\tilde{\nu}$ = 3080–3000,

Table 8. $^{13}C$ NMR data of γ-lactones **3b**, **3e–h**, and **4a–4d** (δ, $CDCl_3$)

| | | C-2 (s) | C-3 | C-4 | C-5 (d) | 4-R or 3-R | 5-R |
|---|---|---|---|---|---|---|---|
| **3b** | *trans* | 176.3 | 38.5 (t)[a] | 41.5 (d) | 84.5 | 25.9 (t), 11.7 (q) | 34.6 (t)[a], 132.4 (d), 118.6 (t) |
| | *cis* | 176.5 | 34.3 (t)[a] | 40.3 (d) | 82.4 | 21.1 (t), 11.9 (q) | 33.9 (t)[a], 133.1 (d), 118.1 (t) |
| **3e** | *trans*[b] | 179.5 | 33.9 (d) | 36.6 (t)[a] | 77.3 | 15.1 (q) | 34.5 (t)[a], 132.2 (d), 119.0 (t) |
| | *cis*[b] | 180.0 | 36.0 (d) | 38.6 (t)[a] | 77.6 | 15.4 (q) | 35.8 (t)[a], 134.5 (d), 118.7 (t) |
| **3f** | *trans* | 177.0 | 45.5 (d) | 39.4 (t)[a] | 77.8 | 137.2 (s), 128.8 (d)[c] | 39.2 (t)[a], 132.0 (d), 119.0 (t) |
| | *cis* | 176.6 | 47.0 (d) | 37.3 (t)[a] | 77.5 | 136.6 (s), 129.0, 128.1, 127.6 (3 d) | 35.5 (t)[a], 131.9 (d), 119.2 (t) |
| **3g** | *trans* | 178.0 | 44.6 (d) | 40.9 (s) | 86.5 | 22.0, 21.9, 9.2 (3 q) | 34.2 (t), 133.5 (d), 117.7 (t) |
| | *cis* | —[c] | 47.0 (d) | 39.0 (s) | 87.7 | 23.2, 15.3, 7.7 (3 q) | 33.0 (t), 133.7 (d), 117.5 (t) |
| **3h** | *trans* | 179.0 | 42.8 (d) | 44.0 (s) | 83.9 | 29.9, 28.8, 25.2, 22.6, 22.4 (5 t), 9.0 (q) | 33.6 (t), 133.8 (d), 117.5 (t) |
| | *cis* | 179.3 | 45.1 (d) | —[c] | 87.8 | 36.0[a], 26.5, 25.1, 22.5, 22.4 (5 t), 12.4 (q) | 37.2 (t)[a], 134.1 (d), 117.2 (t) |
| **4a** | *trans* | 176.2 | 37.1 (t) | 38.0 (d) | 83.3 | 16.5 (q)[a] | 18.8 (q)[a] |
| | *cis* | 176.6 | 36.6 (t) | 33.1 (d) | 79.5 | 13.6 (q)[a] | 15.1 (q)[a] |
| **4c** | *trans* | 176.4 | 32.5 (t) | 49.0 (d) | 80.1 | 30.4 (d), 21.3, 20.7 (2 q)[a] | 19.1 (q)[a] |
| **4d** | *cis* | 175.4 | 37.4 (t) | 49.5 (d) | 83.0 | 138.2 (s), 129.0, 127.7, 127.2 (3 d) | 19.1 (q) |

[a] Signals marked are interchangable within the line. — [b] Due to the 1:1 ratio of diastereomers the assignments of *trans*-**3e** and *cis*-**3e** are uncertain. — [c] Because of the low content of this isomer the signal does not appear.

2990–2880 $cm^{-1}$ (C–H), 1765 (C=O), 1640 (C=C). – $^1H$ NMR ($CDCl_3$): δ = 5.86–5.71 (m, 1H, =CH), 5.20–5.13 (m, 2H, $=CH_2$), 4.58 (dtd, *J* = 5, 6.5, 7.5 Hz, 0.5H, *trans*-5-H), 4.41 (tdd, *J* = 6, 11, 12 Hz, 0.5H, *cis*-5-H), 2.74–2.61 (m, 1H, 3-H), 2.56–2.31 (m, 2.5H, 5-$CH_2$, *cis*-4-H), 2.19 (ddd, *J* = 4.5, 7.5, 13 Hz, 0.5H, *trans*-4-H), 1.99 (td, *J* = 7.5, 13 Hz, 0.5H, *trans*-4-H), 1.59 (ddd, *J* = 11, 12, 13 Hz, 0.5H, *cis*-4-H), 1.28 (d, *J* = 7 Hz, 1.5H, Me), 1.26 (d, *J* = 7 Hz, 1.5H, Me).

*5-Allyl-4,5-dihydro-3-phenyl-2(3H)-furanone* (**3f**): B.p. 140°C/0.01 Torr. – IR (film): ν̃ = 3100–3010, 2980–2900 $cm^{-1}$ (C–H), 1760 (C=O). – $^1H$ NMR ($CDCl_3$): δ = 7.38–7.20 (m, 5H, Ph), 5.90–5.74 (m, 1H, =CH), 5.22–5.12 (m, 2H, $=CH_2$), 4.69 (quint, *J* = 6 Hz, 0.24H, *trans*-5-H), 4.54 (dtd, *J* = 5.5, 6, 12 Hz, 0.76H, *cis*-5-H), 3.88 (dd, *J* = 6, 9 Hz, 0.24H, *trans*-3-H), 3.86 (dd, *J* = 9, 10 Hz, 0.76H, *cis*-3-H), 2.72 (ddd, *J* = 5.5, 9, 13 Hz, 0.76H, *cis*-4-H), 2.64–2.38 (m, 2.5H, 5-$CH_2$, *trans*-4-H), 2.08 (ddd, *J* = 10, 12, 13 Hz, 0.76H, *cis*-4-H).

*5-Allyl-4,5-dihydro-3,4,4-trimethyl-2(3H)-furanone* (**3g**): Colorless liquid, b.p. 70°C/0.01 Torr. – IR (film): = 3080,

Table 9. Elemental analyses obtained for new compounds

| | | | Calcd. C | Calcd. H | Found C | Found H |
|---|---|---|---|---|---|---|
| **3b** | $C_9H_{14}O_2$ | (154.2) | 70.10 | 9.15 | 69.96 | 9.25 |
| **3e** | $C_8H_{12}O_2$ | (140.2) | 68.55 | 8.62 | 68.19 | 8.70 |
| **3f** | $C_{13}H_{14}O_2$ | (202.3) | 77.20 | 6.98 | 76.92 | 7.03 |
| **3g** | $C_{10}H_{16}O_2$ | (168.2) | 71.39 | 9.59 | 71.17 | 9.85 |
| **3h** | $C_{13}H_{20}O_2$ | (208.3) | 74.96 | 9.68 | 74.97 | 9.73 |
| **4c** | $C_8H_{14}O_2$ | (142.2) | 67.57 | 9.92 | 67.15 | 10.10 |
| **4d** | $C_{11}H_{12}O_2$ | (176.2) | 74.98 | 6.86 | 74.34 | 6.88 |
| **8** | $C_8H_{16}O$ | (128.2) | 74.94 | 12.85 | 74.51 | 12.49 |
| **10a** | $C_{10}H_{18}O_3$ | (186.3) | 64.49 | 9.74 | 64.37 | 9.90 |
| **10b** | $C_{15}H_{20}O_3$ | (248.3) | 72.55 | 8.12 | 72.29 | 8.24 |
| **12a** | $C_{16}H_{24}O_2$ | (248.4) | 77.38 | 9.74 | 77.03 | 9.88 |
| **12b** | $C_{15}H_{32}O_2Si$ | (272.5) | 66.11 | 11.84 | 65.56 | 12.02 |
| **14** | $C_{12}H_{26}O_2Si$ | (230.4) | 62.55 | 11.37 | 62.74 | 11.41 |
| **15** | $C_{11}H_{24}OSi$ | (200.4) | 65.93 | 12.07 | 66.50 | 12.19 |

2980–2880 $cm^{-1}$ (C–H), 1770 (C=O), 1640 (C=C). – $^1H$ NMR ($CDCl_3$): δ = 5.87 (tdd, *J* = 7, 10, 17 Hz, 1H, =CH), 5.22–5.12 (m, 2H, $=CH_2$), 4.12 (dd, *J* = 6, 8 Hz, 0.9H, *trans*-5-H), 4.02 (dd, *J* = 4.5, 9 Hz, 0.1H, *cis*-5-H), 2.88–2.42 (m, 3H, 3-H, 5-$CH_2$), 1.12 (d, *J* = 8 Hz, 3H, 3-Me), 1.08, 1.02 (2 s, 5.4H, *trans*-4-Me), 1.18, 0.83 (2 s, 0.3H each, *cis*-4-Me).

*1-Allyl-4-methyl-3-oxo-2-oxaspiro[4.5]decane* (**3h**): B.p. 120°C/0.01 Torr. – IR (film): ν̃ = 3080, 2980–2860 $cm^{-1}$ (C–H), 1760 (C=O), 1640 (C=C). – $^1H$ NMR ($CDCl_3$): δ = 5.90 (tdd, *J* = 6.5, 10, 17 Hz, 1H, =CH), 5.20–5.12 (m, 2H, $=CH_2$), 4.29 (dd, *J* = 4.5, 9 Hz, 0.88H, *trans*-1-H), 4.08 (dd, *J* = 3, 11 Hz, 0.12H, *cis*-1-H), 2.50 (q, *J* = 7 Hz, 1H, 4-H), 2.44–2.24 (m, 2H, 1-$CH_2$), 1.66–1.14 (m, 10H, $CH_2$), 1.14 (d, *J* = 7 Hz, 3H, 4-Me).

*Reactions of Aldehydes* **1** *with Trichloromethyltitanium:* According to ref.[16] 1.14 g (6.00 mmol) of $TiCl_4$ was added to 20 ml of dry diethyl ether at –50°C. This intense yellow solution was treated with 3.66 ml of 1.64 M methyl lithium (in hexane) for 1 h at –50°C. Addition of **1** (2.00 mmol), warm-up to –20°C within 1 h, and further stirring for 3 h at –10°C were followed by treatment with 5 ml of water. After 24 h the mixture was worked up by extraction with diethyl ether. The crude product **4** was distilled in a kugelrohr apparatus and analyzed (purity 90–95%).

*4,5-Dihydro-4,5-dimethyl-2(3H)-furanone* (**4a**): 0.260 g (2.00 mmol) of **1a** gave 0.135 g (59%) of **4a** (*trans*:*cis* = 68:32). – B.p. 60°C/3 Torr (ref.[43] 100°C/15 Torr). – $^1H$ NMR ($CDCl_3$): δ = 4.68 (quint, *J* = 6.5 Hz, 0.32H, *cis*-5-H), 4.15 (dq, *J* = 7.5, 6.1 Hz, 0.68H, *trans*-5-H), 2.75–2.55, 2.30–2.05 (2 m, 3H, 3-H, 4-H), 1.40, 1.14 (2 d, *J* = 6.1 Hz, *J* = 6.3 Hz, 2.05H each, *trans*-5-Me and *trans*-4-Me), 1.29, 1.03 (2 d, *J* = 6.5 Hz, *J* = 6.8 Hz, 0.95H each, *cis*-5-Me and *cis*-4-Me).

*4,5-Dihydro-4-isopropyl-5-methyl-2(3H)-furanone* (**4c**): 0.316 g (2.00 mmol) of **1c** provided 0.211 g (74%) of **4c** (*trans*:*cis* = 92:8). – B.p. 65°C/0.5 Torr. – IR (film): ν̃ = 2950–2870 $cm^{-1}$ (C–H), 1775 (C=O). – $^1H$ NMR ($CDCl_3$): δ = 4.72 ($m_c$, 0.08H, *cis*-5-H), 4.38 (quint, *J* = 6.2 Hz, 0.92H, *trans*-5-H), AB part of an ABX system ($\delta_A$ = 2.63, $\delta_B$ = 2.32, $J_{AB}$ = 18 Hz, $J_{AX}$ = 9.1 Hz, $J_{BX}$ = 8.6 Hz, 1.84H, *trans*-3-H), 1.94 ($m_c$, 1.2H, *cis*-3-H, 4-H), 1.72,

0.95, 0.92 (oct, 2 d, $J$ = 6.7 Hz, 7H, 4-iPr), 1.41, 1.27 (2 d, $J$ = 6.2 Hz, $J$ = 7.0 Hz, 0.92H and 0.08H, *trans*-5-Me and *cis*-5-Me).

*4,5-Dihydro-5-methyl-4-phenyl-2(3H)-furanone* (**4d**): 0.480 g (2.50 mmol) of **1d** afforded 0.286 g (65%) of **4d** (*trans*:*cis* = 93:7). – B.p. 110–125°C/0.02 Torr. – IR (film): $\tilde{\nu}$ = 2970–2930 $cm^{-1}$ (C–H), 1780 (C=O). – $^1H$ NMR ($CDCl_3$): δ = 7.4–7.2 (m, 5H, Ph), 4.90 ($m_c$, 0.07H, *cis*-5-H), 4.55 (dq, $J$ = 8.6, 6.2 Hz, 0.93H, *trans*-5-H), 3.25 (dt, $J$ = 11.1, 8.6 Hz, 0.93H, *trans*-4-H), AB part of an ABX system ($\delta_A$ = 2.92, $\delta_B$ = 2.78, $J_{AB}$ = 17.5 Hz, $J_{AX}$ = 8.6 Hz, $J_{BX}$ = 11.1 Hz, 1.86H, *trans*-3-H), 1.41, 1.00 (2 d, $J$ = 6.2 Hz, $J$ = 6.7 Hz, 2.8H and 0.2H, *trans*-5-Me and *cis*-5-Me); signals for *cis*-4-H and *cis*-3-H are hidden by other signals.

**Further Model Reactions**

*4-Hydroxy-5-methyl-1-heptene* (**8**): 0.688 g (8.00 mmol) of freshly distilled 2-methylbutanal (**7**) was dissolved in 16 ml of dichloromethane and treated at –78°C with 0.810 ml (8.00 mmol) of $TiCl_4$ and 1.400 g (12.00 mmol) of allyltrimethylsilane. After warm-up during a period of 16 h, the mixture was stirred for 1 h with 0.966 g (8.00 mmol) of $Et_3N-HF$[44]. Addition of 30 ml of water, extraction with dichloromethane, and kugelrohr distillation (70°C/7 Torr) provided 0.595 g (58%) of **8** (*syn*/*anti* = 62:38).

Similarly, 0.215 g (2.50 mmol) of **7** and 0.310 g (2.50 mmol) of $Et_2O-BF_3$ gave 0.157 g (49%) of **8** (*syn*/*anti* = 53:47). – IR (film): $\tilde{\nu}$ = 3410 $cm^{-1}$ (OH), 3080, 2980–2870 (C–H), 1640 (C=C). – $^1H$ NMR ($CDCl_3$): δ = 5.83 ($m_c$, 1H, 2-H), 5.18–5.08 (m, 2H, 1-H), 3.55 (dt, $J$ = 8.5, 4.2 Hz, 0.53H, *syn*-4-H), 3.47 (ddd, $J$ = 3.2, 5.7, 9.0 Hz, 0.47H, *anti*-4-H), 2.36–1.93 (m, 3H, 3-H, OH), 1.51 ($m_c$, 2H, 6-H), 1.28–1.11 (m, 1H, 5-H), 0.98–0.86 (m, 6H, 7-H, 5-Me). – $^{13}C$ NMR ($CDCl_3$): *syn* isomer: δ = 135.6 (d, C-2), 117.5 (t, C-1), 73.6* (d, C-4), 39.5 (d, C-5), 39.1 (t, C-3), 25.8 (t, C-6), 13.4, 11.7 (2 q, C-7, 5-$CH_3$); *anti* isomer: δ = 135.5 (d, C-2), 117.7 (t, C-1), 74.2* (d, C-4), 40.6 (d, C-5), 38.2 (t, C-3), 24.8 (t, C-6), 14.6, 11.5 (2 q, C-7, 5-$CH_3$): * signals very similar in intensity, assignment according to ref.[38b].

*5-Methyl-4-trimethylsiloxy-1-heptene* (**15**): A mixture of 0.256 g (2.00 mmol) of **8**, 3 ml of hexamethyldisilazane, and chlorotrimethylsilane (5 drops) was heated to 100°C for 7 h. Distillation (70°C/3 Torr) provided 0.301 g (75%) of **15** as a colorless liquid. For significant NMR data see Table 5, for the full data set see ref.[1].

*General Procedure for Additions of Allyltrimethylsilane to Acetals:* A solution of the acetal (1.0 equivalent) in dichloromethane (5 ml/1 mmol) was treated at –78°C with $TiCl_4$ (1.5 equivalents) and allyltrimethylsilane (3.0 equivalents). After 1 h at this temperature methanol (0.5 ml/1 mmol acetal) was added and the resulting mixture warmed up over approx. 16 h. Addition of water and extraction with dichloromethane afforded the crude product which was purified by kugelrohr distillation.

*Methyl 4-Methoxy-3-methyl-6-heptenoate* (**10a**): Starting with 1.76 g (10.0 mmol) of **9a** we obtained 0.876 g (51%) of **10a** (b.p. 90°C/1 Torr, *syn*/*anti* = 60:40). – IR (film): $\tilde{\nu}$ = 3080, 3040, 2980–2930 $cm^{-1}$ (C–H), 1735 (C=O), 1630 (C=C). – $^1H$ NMR ($CDCl_3$): δ = 5.82 ($m_c$, 1H, 6-H), 5.16–5.00 (m, 2H, 7-H), 3.67, 3.66 (2 s, 3H, $CO_2Me$), 3.35, 3.34 (2 s, 3H, OMe), 3.13 (ddd, $J$ = 3.5, 5.8, 7.1 Hz, 0.6H, *syn*-4-H), 3.02 (dt, $J$ = 5.0, 6.2 Hz, 0.4H, *anti*-4-H), 2.54–2.44, 2.36–2.10 (2 m, 5H, 2-H, 3-H, 5-H), 0.94 (d, $J$ = 6 Hz, 1.2H, *anti*-$CH_3$), 0.93 (d, $J$ = 6.8 Hz, 1.8H, *syn*-$CH_3$). – $^{13}C$ NMR ($CDCl_3$): *syn* isomer: δ = 173.6, 51.7 (s, q, $CO_2Me$), 135.2 (d, C-6), 116.6 (t, C-7), 83.4 (d, C-4), 57.8 (q, OMe), 37.2, 34.8 (2 t, C-2, C-5), 32.5 (d, C-3), 14.3 (q, $CH_3$); *anti* isomer: δ = 134.5 (d, C-6), 116.8 (t, C-7), 84.1 (d, C-4), 57.4 (q, OMe), 51.8 (q, $CO_2Me$), 37.4, 34.5 (2 t, C-2, C-5), 33.2 (d, C-3), 16.9 (q, $CH_3$); the signal of C-1 could not be identified.

Synthesis of *4-methoxy-3-methyl-1-trimethylsiloxy-6-heptene* (**14**) from **10a** by reduction with $LiAlH_4$ (in diethyl ether) and subsequent silylation (as for **15**) is described in full detail in ref.[1]. For significant NMR values see Table 5.

*Methyl 4-Methoxy-3-phenyl-6-heptenoate* (**10b**): Starting with 1.90 g (8.00 mmol) of acetal **9b** we obtained 1.97 g (99%) of **10b** (b.p. 110°C/0.02 Torr, *syn*/*anti* = 40:60). – IR (film): $\tilde{\nu}$ = 3080, 3040, 2980–2930 $cm^{-1}$ (C–H), 1735 (C=O), 1630 (C=C). – $^1H$ NMR ($C_6D_6$): δ = 7.32–7.06 (m, 5H, Ph), 5.76 ($m_c$, 1H, 6-H), 5.13–5.02 (m, 2H, 7-H), 3.47 ($m_c$, 1H, 4-H), 3.33–3.17 (m, 2 s at δ = 3.27, 3.24, 4H, 3-H, $CO_2Me$), 3.14 (s, 1.2H, *syn*-OMe), 3.12 (s, 1.8H, *anti*-OMe), 2.96 (dd, $J$ = 5.4, 15.5 Hz, 0.6H, *anti*-2-H), 2.83 (dd, $J$ = 6.7, 15.7 Hz, 0.4H, *syn*-2-H), 2.70 (dd, $J$ = 8.4, 15.7 Hz, 0.4H, *syn*-2′-H), 2.59 (dd, $J$ = 9.1, 15.5 Hz, 0.6H, *anti*-2′-H), 2.20–2.08, 2.01–1.87 (2 m, 2H, 5-H). – $^{13}C$ NMR ($C_6D_6$): *anti* isomer: δ = 172.4, 50.9 (s, q, $CO_2Me$), 142.3, 129.3, 128.0, 126.9 (s, 3 d, Ph), 134.5 (d, C-6), 117.3 (t, C-7), 84.0 (d, C-4), 57.4 (q, OMe), 46.3 (d, C-3), 37.7, 35.4 (2 t, C-2, C-5); *syn* isomer: δ = 140.8 (s, *i*Ph), 135.5 (d, C-6), 117.0 (t, C-7), 83.8 (d, C-4), 57.9 (q, OMe), 51.1 (q, $CO_2Me$), 45.1 (d, C-3), 36.6, 35.8 (2 t, C-2, C-5); signals for C-1 and *o*-, *m*-, *p*-Ph, respectively, coincide for both isomers.

*1-Benzyloxy-4-methoxy-3-methyl-6-heptene* (**12a**): Starting with 0.476 g (2.00 mmol) of **11a** we obtained 0.465 g (94%) of **12a** (b.p. 110°C/0.02 Torr, *syn*/*anti* = 60:40). – IR (film): $\tilde{\nu}$ = 3080, 3040, 2940–2850 $cm^{-1}$ (C–H). – $^1H$ NMR ($C_6D_6$): δ = 7.31–7.08 (m, 5H, Ph), 5.86 ($m_c$, 1H, 6-H), 5.10–5.00 (m, 2H, 7-H), 4.34 (s, 2H, $CH_2Ph$), 3.39 ($m_c$, 2H, 1-H), 3.15 (s, 1.8H, *syn*-OMe), 3.14 (s, 1.2H, *anti*-OMe), 2.98 (td, $J$ = 6.5, 3.5 Hz, 0.6H, *syn*-4-H), 2.91 (dt, $J$ = 6.6, 5.0 Hz, 0.4H, *anti*-4-H), 2.30–2.09 (m, 2H, 5-H), 1.89 ($m_c$, 2H, 2-H), 1.45 ($m_c$, 1H, 3-H), 0.90, 0.88 (2 d, $J$ = 7 Hz, 3H, $CH_3$). – $^{13}C$ NMR ($C_6D_6$): *syn* isomer: δ = 139.5, 128.4, 127.6, 127.5 (s, 3 d, Ph), 136.2 (d, C-6), 116.3 (t, C-7), 84.5 (d, C-4), 72.9 (t, $CH_2Ph$), 68.7 (t, C-1), 57.4 (q, OMe), 35.5, 33.2 (2 t, C-2, C-5), 32.8 (d, C-3), 14.5 (q, $CH_3$); *anti* isomer: δ = 85.1 (d, C-4), 68.9 (t, C-1), 57.2 (q, OMe), 34.9, 32.5 (2 t, C-2, C-5), 15.4 (q, $CH_3$); signals for $PhCH_2$-, C-3, C-6, and C-7, respectively, coincide for both isomers.

*1-(tert-Butyldimethylsiloxy)-4-methoxy-3-methyl-6-heptene* (**12b**): Starting with 0.525 g (2.00 mmol) of **11b** we obtained after distillation 0.388 g of a mixture of **12b** and the corresponding desilylated material. Silylation with $ClSiMe_2tBu$/imidazole[45] and redistillation (85°C/0.1 Torr) provided 0.405 g (74%) of **12b** (*syn*/*anti* = 50:50). For significant NMR data see Table 5; the full data set is compiled in ref.[1].

Synthesis of *3-methyl-1,4-bis(trimethylsiloxy)-6-heptene* (**13**) from **3a** by reduction with $LiAlH_4$ (in diethyl ether) and subsequent silylation (as for **15**) is described in full detail in ref.[1]. For significant NMR values see Table 5.

**Preparation of 1 – Lewis Acid Complexes for Spectroscopic Investigations**

A solution of 0.50 mmol of **1** in 0.7 ml of $CD_2Cl_2$ was treated at –78°C with the corresponding Lewis acid (1 or 2 equivalents). The suspension or solution was warmed to room temp. and transferred to an NMR tube under a stream of nitrogen. The NMR spectra were recorded at ambient temperature. For significant signals see Table 3; for the full data set see ref.[1]; the NMR parameters for complexes of **1a** were also reported in ref.[10]. Similarly, a solution of **1a**·$TiCl_4$ in $CDCl_3$ was transferred to a $CaF_2$ cuvette to record the IR spectrum.

CAS Registry Numbers

**1a**: 65038-34-8 / **1b**: 40630-07-7 / **1c**: 71464-85-2 / **1d**: 51212-29-4 / **1e**: 13865-21-9 / **1f**: 67031-12-3 / **1g**: 77903-62-9 / **1h**: 121756-45-4 / *trans*-**3a**: 112423-33-3 / *cis*-**3a**: 112423-36-6 / *trans*-**3b**: 121756-24-9 / *cis*-**3b**: 121756-25-0 / *trans*-**3c**: 112423-34-4 / *cis*-**3c**: 112423-37-7 / *trans*-**3d**: 112423-35-5 / *cis*-**3d**: 112423-38-8 / *trans*-**3e**: 121756-26-1 / *cis*-**3e**: 121756-27-2 / *trans*-**3f**: 121756-28-3 / *cis*-**3f**: 121756-29-4 / *trans*-**3g**: 121756-30-7 / *cis*-**3g**: 121756-31-8 / *trans*-**3h**: 121756-32-9 / *cis*-**3h**: 121756-33-0 / *trans*-**4a**: 10150-96-6 / *cis*-**4a**: 10150-95-5 / *trans*-**4c**: 112423-39-9 / *cis*-**4c**: 112423-40-2 / *trans*-**4d**: 92927-63-4 / *cis*-**4d**: 112423-41-3 / 7: 96-17-3 / *syn*-**8**: 121841-87-0 / *anti*-**8**: 121841-88-1 / **9a**: 99097-59-3 / **9b**: 121756-46-5 / *syn*-**10a**: 121756-35-2 / *anti*-**10a**: 121756-36-3 / *syn*-**10b**: 121756-38-5 / *anti*-**10b**: 121756-39-6 / **11a**: 121756-47-6 / **11b**: 121756-48-7 / *syn*-**12a**: 121756-40-9 / *anti*-**12a**: 121756-41-0 / *syn*-**12b**: 121756-42-1 / *anti*-**12b**: 121756-43-2 / *syn*-**13**: 121756-44-3 / *anti*-**13**: 121756-51-2 / *syn*-**14**: 121756-37-4 / *anti*-**14**: 121756-50-1 / *syn*-**15**: 121756-34-1 / *anti*-**15**: 121756-49-8 / $ClSiMe_2tBu$: 18162-48-6 / $BF_3$: 7637-07-2 / $TiCl_4$: 7550-45-0 / $ZrCl_4$: 10026-11-6 / $AlCl_3$: 7446-70-0 / $HfCl_4$: 13499-05-3 / $SnCl_4$: 7646-78-8 / allyltrimethylsilane: 762-72-1 / imidazole: 288-32-4

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[143/89]