Chelate-Controlled Additions of Titanium and Lithium Enolates to Chiral β-Formyl Esters – Diastereofacial and Simple Diastereoselectivity

Hubert Angert[1], Ralf Schumacher, and Hans-Ulrich Reißig*

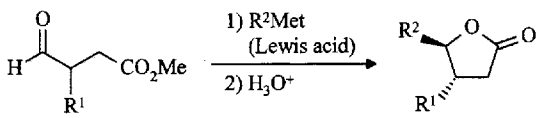
Institut für Organische Chemie der Technischen Universität Dresden,
Mommsenstraße 13, D-01062 Dresden, Germany
Telefax: (internat.) +49(0)351/463-7030
E-mail: reissig@coch01.chm.tu-dresden.de

Received October 9, 1995

Key Words: β-Formyl esters / Titanium enolates / Lithium enolates / Silyl enol ethers / Chelate control

The aldol-type additions of metal enolates **2**-Met derived from pinacolone to the chiral β-formyl carboxylate **1a** were optimized. The highest *trans*:*cis* ratio (86:14) of the products **3** was obtained when the trichlorotitanium enolate **2**-$TiCl_3$ was combined with **1a** precomplexed with one equivalent of $TiCl_4$. The lithium enolate **2**-Li is rather unselective. The simple diastereoselectivity of prochiral enolates **4**-Met was first examined with achiral β-formyl carboxylates **1b** and **1c**. Appropriate reagents made products with high *anti* or with high *syn* selectivity available when the unbranched aldehyde **1b** was the electrophile. In contrast, the sterically more hindered aldehyde **1c** provided *syn* products with all enolates **4**-Met employed. Finally, chiral aldehyde **1a** was combined with prochiral enolates **4**-Met. Conditions could be found which furnished either the *trans*/*anti* or the *trans*/*syn* product **7** with good selectivity. The results are discussed and compared with reactions of related metal enolates with aldehydes capable of chelate formation.

Chelate-controlled additions of Lewis acidic organometallic reagents to alkoxy- or amino-substituted carbonyl compounds very often provide functionalised alcohols with excellent diastereoselectivity[2]. Since not much has been known about the steering effect of other functional groups, we systematically studied reactions of β-formyl carboxylates **1** with allylsilanes/$TiCl_4$[3], $MeTiCl_3$[3], cuprates, and Grignard reagents[4]. For all these reactions the primary addition products were directly cyclised to a mixture of *trans*/*cis* γ-lactones which are synthetically valuable compounds and which also allow rather straightforward structural assignments. The preferential formation of *trans* γ-lactones indicates that seven-membered ring chelates are involved in the addition reaction and that an ester function can serve as a surprisingly effective ligand.



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More recently, the Mukaiyama reaction of silyl enol ethers with **1** in the presence of Lewis acids was investigated[5]. We studied the dependence of the selectivity on the Lewis acid, the β-formyl carboxylate **1**[5], and the silyl enol ether[6] employed and found that *trans* γ-lactones are formed with good to excellent selectivity when chelate control can be assumed. This method could recently be applied to a short and highly diastereoselective synthesis of the pheromone (+)-eldanolide[6] which also proved that no racemisation of enantiomerically enriched β-formyl carboxylates occurs under the Mukaiyama conditions. However, the standard promotor $TiCl_4$, the silyl enol ether **2**-$SiMe_3$ (derived from pinacolone) and the simplest chiral aldehyde of this series **1a** furnished γ-lactone **3** with a rather moderate *trans*:*cis* selectivity of 71:29 (entry 1, next paragraph). In this report we disclose our experiments designed to improve this moderate selectivity. For this purpose other metal enolates were added to **1a**. We also investigated the "simple" diastereoselectivity of prochiral metal enolates when added to achiral aldehydes **1b** and **1c**. Finally, the reactions of chiral aldehyde **1a** with prochiral enolates were studied which combined the problem of simple and facial diastereoselectivity.

Diastereofacial Selectivity with Aldehyde 1a

The tetrachlorotitanium enolate **2**-$TiCl_4^-$ was generated from pinacolone[7] as described by Evans[8] by treating the ketone with $TiCl_4$ and Hünig base[9] at low temperature. Aldehyde **1a** was added to this wine-red solution at −78 °C, and after acidic workup the expected γ-lactone **3** was isolated in 76% yield. However, the addition was essentially unselective giving a *trans*:*cis* ratio of 48:52 (entry 2). This ratio could be dramatically improved when the Nakamura method[10] for the generation of a trichlorotitanium enolate **2**-$TiCl_3$[7] was chosen. Thus, treatment of silyl enol ether **2**-$SiMe_3$ with $TiCl_4$ at room temperature and reaction of the resulting wine-red solution with aldehyde **1a** at −78 °C after acidic workup furnished the γ-lactone **3** with a *trans*:*cis* ratio of 74:26 (entry 3). This selectivity is similar to that of the Mukaiyama method (entry 1); however, it is known that

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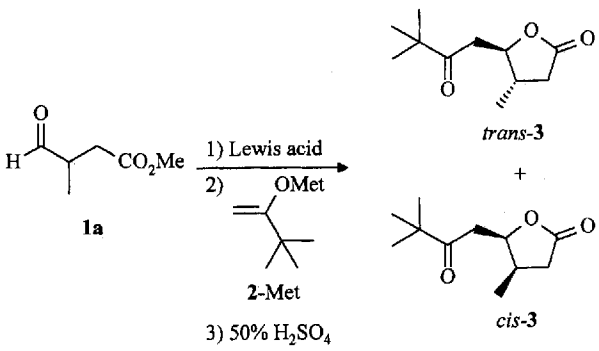


Entry	Lewis Acid	Met	T (°C)	Yield (%)	*trans* : *cis*
1[a]	$TiCl_4$	$SiMe_3$	-40	97	71 : 29
2[b]	-	$TiCl_4^-$	-78	76	48 : 52
3	-	$TiCl_3$	-72	73	74 : 26
4	$TiCl_4$	$TiCl_3$	-40	100	86 : 14
5	-	Li	-78	73	60 : 40

[a] See ref.[6]. - [b] See ref.[5].

under these conditions titanium enolates are usually not involved[11].

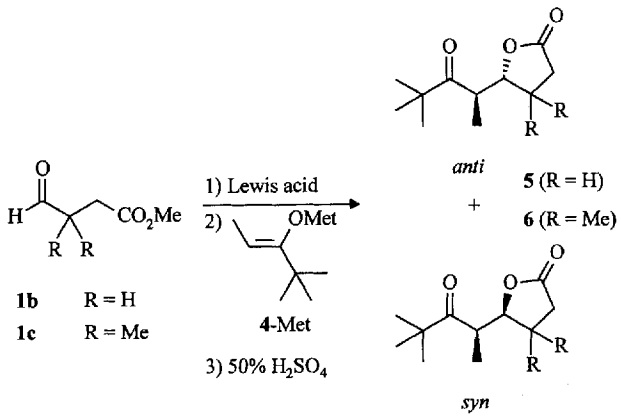
A further remarkable improvement of the diastereofacial selectivity could be achieved when the titanium enolate **2**-$TiCl_3$ was allowed to react with aldehyde **1a** *precomplexed* with one equivalent of $TiCl_4$ (entry 4). This variant provided quantitatively *trans*/*cis*-**3** in a ratio of 86:14[12].

For the highly stereoselective cuprate additions to aldehydes such as **1a** chelate formation involving lithium ions was suggested[4]. Therefore, we were rather surprised that the pinacolone lithium enolate **2**-Li as generated with LDA in tetrahydrofuran reacts with **1a** with very moderate 60:40 *trans*:*cis* selectivity (entry 5). This ratio did not significantly change when diethyl ether was the solvent (61:39), and it increased to 69:31 only with pentane as solvent. However, in the latter case the reaction proceeded not very clean, and a 38% yield of impure product was obtained[1].

Simple Diastereoselectivity with Aldehydes 1b and 1c

Since reactions of chiral aldehydes such as **1a** with prochiral enolates such as **4**-Met give up to four diastereomers (see below) we first investigated additions of these enolates to achiral aldehydes **1b** (R = H) and **1c** (R = Me). Reaction of the silyl enol ether **4**-$SiMe_3$ with **1b** under Mukaiyama conditions in the presence of $TiCl_4$ provided γ-lactone **5** after acidic workup with an excellent *anti*:*syn*[13] ratio of 90:10 (entry 1). Addition of titanium enolate **4**-$TiCl_3$ to precomplexed **1b** afforded **5** with significantly lower simple diastereoselectivity (entry 2). As to be expected[14], the addition reaction with lithium enolate **4**-Li provided γ-lactone **5** with almost complete *syn* selectivity (entry 3). The relative configuration of *anti*-**5** was confirmed by an X-ray crystal structure analysis[15].

The reactivity of dimethyl-substituted aldehyde **1c** was much lower, and the addition of silyl enol ether **4**-$SiMe_3$ to this compound proceeded at room temperature only. Hence, it is likely that not **4**-$SiMe_3$ but transmetallated **4**-$TiCl_3$ is the reactive species under these conditions. This reaction provided γ-lactone **6** with an excellent *anti*:*syn* ratio of 4:96 which is almost identical with that of the reaction of precomplexed **1c** with **4**-$TiCl_3$ (entries 4 and 5). The high *syn* preference was even exceeded when lithium enolate **4**-Li and **1c** were combined (entry 6). An X-ray analysis[15] confirmed the proposed structure of *syn*-**6**.

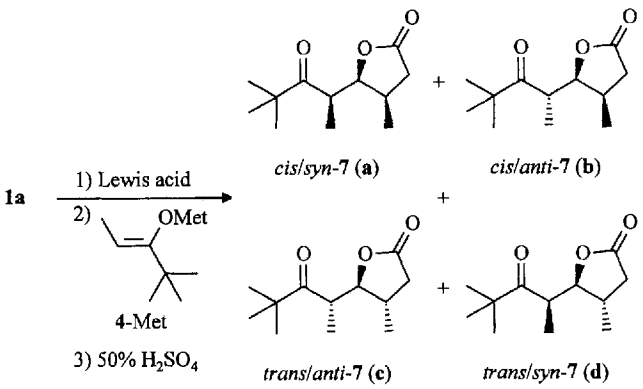


Entry	Lewis Acid	Met	R	T (°C)	γ-Lactone	Yield (%)	*anti* : syn
1	$TiCl_4$	$SiMe_3$	H	-40	**5**	73	90 : 10
2	$TiCl_4$	$TiCl_3$	H	-40	**5**	77	81 : 19
3	-	Li	H	0	**5**	82	3 : 97
4	$TiCl_4$	$SiMe_3$	Me	25	**6**	88	4 : 96
5	$TiCl_4$	$TiCl_3$	Me	25	**6**	86	5 : 95
6	-	Li	Me	0	**6**	76	< 1 : 99

Facial and Simple Diastereoselectivity of Aldehyde 1a

Reactions of **4**-Met with chiral aldehyde **1a** can provide four diastereomers **7a**–**d** since a stereotriade[16] with two new stereogenic centres is generated. All reactions (entries 1–4) are *trans*-selective favouring isomers **7c** and **7d**. Even the BF_3-promoted Mukaiyama reaction (entry 1) gave γ-lactone **7** with a moderate *trans*:*cis* (**c**+**d**:**a**+**b**) ratio of 73:27. This is surprising since no chelate formation can be involved, and therefore we must conclude that silyl enol ether **4**-$SiMe_3$ has an inherent tendency to provide *trans* γ-lactones. This has to be compared with **2**-$SiMe_3$ which adds to **1a** with moderate *cis* selectivity with BF_3 promotion[6]. The $TiCl_4$-promoted Mukaiyama reaction shows a much higher *trans*:*cis* ratio of 90:10 (entry 2). The *anti*:*syn* selectivities (**b**+**c**:**a**+**d**) for these two reactions are 86:14 and 44:56.

The best conditions for the synthesis of diastereomers **7c** and **7d** are described in entries 3 and 4. Thus, addition of $TiCl_4$-precomplexed **1a** to titanium enolate **4**-$TiCl_3$ furnished preferentially **7c**, whereas reaction of **1a** with lithium enolate **4**-Li gave **7d** with a selectivity of 85%. By equili-



Entry	Lewis Acid	Met	T (°C)	Yield of 7 (%)	a : b : c : d
1	$BF_3 \cdot OEt_2$	$SiMe_3$	-78	64	5 : 22 : 64 : 9
2[a]	$TiCl_4$	$SiMe_3$	-40	68	5 : 5 : 39 : 51
3	$TiCl_4$	$TiCl_3$	-40	90	1 : 9 : 85 : 5
4	-	Li	-78	70	15 : 0 : 0 : 85

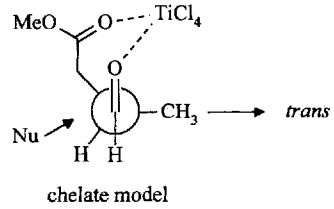
[a] Concd. hydrochloric acid was employed for workup.

bration experiments with acid it could be secured that no *cis-trans* or *syn-anti* isomerisation occurs under the reaction conditions employed and during workup.

Whereas for *trans-cis* assignments the criteria as described earlier could be used, the determination of *anti-syn* configurations was not trivial. However, with the unequivocal structure determination of *anti*-**5** and *syn*-**6** by X-ray analyses their NMR data could be used as reference for the assignments as given to the γ-lactones **7a–d**[1]. These were further corroborated by *anti/syn* selectivities of the reactions of related prochiral enolates with other aldehydes as reported in the literature.

Discussion

The diastereofacial selectivities (*trans*:*cis* ratios of products) of the reaction of aldehyde **1a** with enolates **2**-Met and **4**-Met are collected in Table 1. These ratios reveal that enolates **4**-Met generally have a higher propensity to form *trans* products. Interestingly, three of the reaction pairs reveal differences of $\Delta G^{\neq}$ (as calculated from the product ratio at the reaction temperature) in the order of 2–2.5 kJ/mol. This may be taken as evidence that a common effect is operative, which cannot however be specified at the moment. A similarly clear trend was not observed for the Mukaiyama reactions of **1a** with silyl enol ethers derived from acetophenone, propiophenone, and isobutyrophenone, respectively, which provided the corresponding γ-lactones with *trans*:*cis* selectivities in the range of 90:10 to 96:4[5]. It should be of synthetic importance that a high level of stereoselectivity in the range of 90:10 can be achieved by reaction of precomplexed aldehyde **1a** with the titanium enolates **2**-$TiCl_3$ and **4**-$TiCl_3$. These results emphasize the importance of chelate formation by the strong Lewis acid



chelate model

Table 1. The *trans*:*cis* selectivities of reactions of aldehyde **1a** with enolates **2**-Met and **4**-Met

Met	**2**-Met *trans* : *cis*	**4**-Met *trans* : *cis*	$\Delta\Delta G^{\neq}$ (kJ/mol)[a]
$SiMe_3/BF_3$[b]	34 : 66[c]	73 : 27	2.7
$SiMe_3/TiCl_4$[d]	71 : 29	90 : 10	2.5
$TiCl_3/TiCl_4$[d]	86 : 14	90 : 10	0.7
Li[b]	60 : 40	85 : 15	2.2

[a] $\Delta\Delta G^{\neq} = \Delta G^{\neq}_{cis/trans\text{-}2\text{-Met}} - \Delta G^{\neq}_{cis/trans\text{-}4\text{-Met}}$. – [b] Reaction temperature –78 °C. – [c] From ref.[5]. – [d] Reaction temperature –40 °C.

$TiCl_4$ which fixes the conformation of **1a**. Attack of the titanium enolates on the open side of the chelate leads to preferential formation of *trans* γ-lactones.

The lithium ion of the enolates is apparently not a very efficient Lewis acid to form chelates of similar structure. This is in contrast to the results obtained with cuprates "R_2CuLi" where excellent *trans* selectivities could be obtained. A reason for this striking difference could be the negatively charged enolate oxygen which may "quench" the Lewis acidity of the reagent to a high extent. The simple diastereoselectivities as observed with enolate **4**-Met are more difficult to interpret. For a better comparison the *anti*:*syn* selectivities of the reactions of aldehydes **1b**, **1a**, and **1c** with enolate **4**-Met are collected in Table 2. The general preferential formation of *syn* adducts when lithium enolate **4**-Li was treated with these aldehydes is in perfect accordance with literature examples of (*Z*)-enolates which are supposed to add via cyclic chair-type transition states[14].

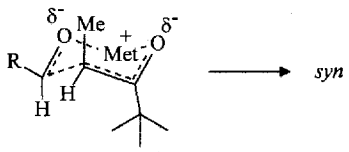
Table 2. The *anti*:*syn* selectivities of reactions of aldehydes **1b**, **1a**, and **1c** with enolate **4**-Met

4-Met Met	**1b** *anti* : *syn*	**1a** *anti* : *syn*	**1c** *anti* : *syn*
$SiMe_3/BF_3$	-	86 : 14	-
$SiMe_3/TiCl_4$	90 : 10	44 : 56	4 : 96
$TiCl_3/TiCl_4$	81 : 19	94 : 6	5 : 95
Li	3 : 97	< 1 : 99	< 1 : 99

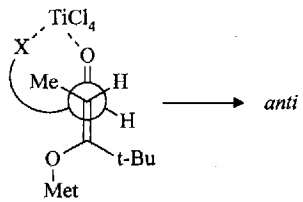
The simple diastereoselectivity of the Mukaiyama aldol reactions strongly depends on the structure of the silyl enol ether and the aldehyde. The fact that **4**-$SiMe_3$ reacts with aldehyde **1b** with excellent *anti* selectivity coincides with its

similarly selective addition to 2-methylpropanal[17]. However, for an α-alkoxy-substituted aldehyde a complete lack of *anti-syn* selectivity was reported although perfect chelate control could be achieved in this example[18]. The gradual change from high *anti* selectivity of the reaction with **1b** via unselective addition to **1a** to excellent *syn* selectivity of the aldehyde **1c** underlines the sensitivity to structural effects which is in accordance with literature experience[17]. Possibly, in the reaction of the sluggishly adding aldehyde **1c** not the silyl enol ether but the corresponding titanium enolate **4**-$TiCl_3$ is the actual reactive species. The fact that aldehyde **1a** and prochiral silyl enol ethers combine with rather low simple diastereoselectivity was already reported for the addition of (*Z*)-1-phenyl-1-(trimethylsiloxy)propene which provided γ-lactones in an *anti*:*syn* ratio of 40:60[5].

Reaction of trichlorotitanium enolate **4**-$TiCl_3$ with aldehydes **1b** and **1a** displays moderate to good *anti* selectivity while sterically more hindered **1c** reacts with excellent *syn* selectivity. This puzzling behaviour has to be compared with related reactions of **4**-$TiCl_3$ with other aldehydes capable of chelate formation. The general tendency of trichlorotitanium enolates to *syn*-selective additions was sustained when **4**-$TiCl_3$ was treated with α-alkoxy aldehydes, however, with no chelate control[18]. This fits our results with aldehyde **1c**. When the α-alkoxy aldehydes were precomplexed with $TiCl_4$ and then allowed to react with **4**-$TiCl_3$ a moderate *anti* selectivity under excellent chelate control was reported[18]. We found *anti*-selective reactions with aldehydes **1b** and **1a**. Possibly, aldehydes that are engaged in chelate formation undergo *anti*-selective reactions with **4**-$TiCl_3$ whereas conditions which allow binding of a Lewis acidic centre to the aldehyde oxygen only support *syn*-selective additions. Chelate formation of **1c** may be disfavoured due to the higher degree of substitution of this aldehyde. The inherent *syn* selectivity of trichlorotitanium (*Z*)-enolates may be explained by a cyclic transition state similar to that of the corresponding lithium enolates. Acyclic transition states may be involved in reactions leading to *anti* products – as usually discussed for Mukaiyama reactions. However, no straightforward explanation reconciling all observed effects can currently be presented.



(Met = Li, $TiCl_3$)



(Met = $SiMe_3$, $TiCl_3$)

Nevertheless, our results with enolates **2**-Met and **4**-Met open the way to stereocontrolled preparation of valuable intermediates. Of particular importance should be the selective synthesis of compound **7c** because the stereotriade[16] incorporated in this γ-lactone is rather difficult to obtain by other methods[19].

Support of this work by the *Deutsche Forschungsgemeinschaft* and the *Fonds der Chemischen Industrie* is most gratefully acknowledged.

Experimental

For general information see ref.[5]. All reactions were performed under nitrogen in a flame-dried flask, and the components were added by means of a syringe. All solvents were dried by standard methods. – Chromatography: silica gel 60 (0.063–0.200 mm, E. Merck). – A Büchi kugelrohr apparatus was used for distillation of small amounts of substances. – ^1H (^{13}C) NMR: Bruker AC 300, 300 (75.5) MHz, internal standards chloroform (δ = 7.26 and 77.0) or tetramethylsilane (δ = 0.00). Missing signals of minor isomers were hidden or too weak. – IR: Perkin-Elmer 325.

Reaction of **1a** *with* **2**-$TiCl_3$: To a solution of 0.345 g (2.00 mmol) of silyl enol ether **2**-$SiMe_3$ in 10 ml of dichloromethane 0.379 g (2.00 mmol) of $TiCl_4$ was added at room temp. After stirring for 30 min at this temp. and cooling to −72°C, 0.390 g (3.00 mmol) of β-formyl carboxylate **1a** was added. The reaction mixture was stirred for 10 min, hydrolyzed with 2 ml of 50% aqueous sulfuric acid, the cooling bath was removed, and stirring was continued for 30 min. Extractive workup (H_2O/CH_2Cl_2), drying (Na_2SO_4), evaporation of solvent, and bulb-to-bulb distillation (110°C/0.02 Torr) of the residue provided 0.291 g (73%) of **3** (*trans*:*cis* = 74:26). For spectroscopic and analytical data of **3** see ref.[5].

Lewis Acid-induced Addition of Titanium Enolates **2**-$TiCl_3$ *and* **4**-$TiCl_3$ *to β-Formyl Carboxylates* **1a–c**. – *General Procedure 1:* To a solution of **1** (2.00 mmol) in 10 ml of dichloromethane $TiCl_4$ (2.00 mmol) was added at temperature T_1 (see individual entries). The mixture was warmed up to temperature T_2 within 15 min, and the titanium enolate (3.00 mmol, generated as described above) was slowly added. After 1 h at T_2 50% aqueous sulfuric acid (2 ml) was added, the cooling bath was removed, and the mixture was stirred for 30 min. Extractive workup (H_2O/CH_2Cl_2), drying (Na_2SO_4), and evaporation of solvent provided the crude products which were further purified by bulb-to-bulb distillation, unless otherwise noted. The ratios of isomers did not significantly change during purification.

Addition of Lithium Enolates **2**-Li *and* **4**-Li *to β-Formyl Carboxylates* **1a–c**. – *General Procedure 2:* A solution of diisopropylamine (2.20 mmol) in 2 ml of tetrahydrofuran was treated with *n*-butyllithium (2.20 mmol, 1.7–2.5 M solution in hexane) at −78°C. After 20 min the ketone (2.00–2.20 mmol, dissolved in 2 ml of THF) was slowly added with stirring. The mixture was further stirred for 20 min at the given reaction temp. before the β-formyl carboxylate **1** (2.00–2.10 mmol) was added. After stirring for 10 min at the same temp. 50% aqueous sulfuric acid (2 ml) was added, and the mixture was worked up as described in general procedure 1 (extraction with diethyl ether).

Lewis Acid-induced Addition of Silyl Enol Ethers **2**-$SiMe_3$ *and* **4**-$SiMe_3$ *to β-Formyl Carboxylates* **1a–c**. – *General Procedure 3:* To a solution of **1** (2.00 mmol) in 10 ml of dichloromethane the Lewis

acid (2.00 mmol) was added at temp. T_1. The mixture was warmed up to temperature T_2 within 15 min, and the silyl enol ether (3.00 mmol, dissolved in 7 ml of dichloromethane) was slowly added. After 1 h at T_2 50% aqueous sulfuric acid (2 ml) was added, and the mixture was worked up as described in general procedure 1.

5-(3,3-Dimethyl-2-oxobutyl)-4,5-dihydro-4-methyl-2(3H)-furanone (**3**): According to general procedure 1 (T_1 = −60, T_2 = −40 °C) the reaction of β-formyl carboxylate **1a** with 3.00 mmol of **2**-$TiCl_3$ furnished 0.395 g (100%) of **3** (*trans*:*cis* = 86:14) as colourless oil with b.p. 100 °C/0.02 Torr. – According to general procedure 2 pinacolone (2.00 mmol) was allowed to react with **1a** (2.00 mmol) at −78 °C affording 0.290 g (73%) of **3** (*trans*:*cis* = 60:40).

4,5-Dihydro-5-(1,3,3-trimethyl-2-oxobutyl)-2(3H)-furanone (**5**): According to general procedure 3 (T_1 = −60, T_2 = −40 °C) the reaction of β-formyl carboxylate **1b** with silyl enol ether **4**-$SiMe_3$ and $TiCl_4$ provided 0.290 g (73%) of **5** (*anti*:*syn* = 90:10) as partially crystalline oil with b.p. 110 °C/0.01 Torr. After recrystallization from diethyl ether crystals were obtained (m.p. 62–64 °C) which could be used for an X-ray analysis (*anti*:*syn* > 97:3). – IR (film): $\tilde{\nu}$ = 2980, 2940, 2920, 2880 cm^{-1} (C–H), 1780, 1700 (C=O). – ^1H NMR (300 MHz), *anti*-**5**: δ = 4.67 (dt, *J* = 6.5/9 Hz, 1H, 5-H), 3.19 (qd, *J* = 7/9 Hz, 1H, 1′-H), 2.58–2.50 (m, 2H, 3-H), 2.37 (m_c, 1H, 4-H), 1.94 (m_c, 1H, 4-H), 1.17 (s, 9H, *t*Bu), 1.05 (d, *J* = 7 Hz, 3H, 1′-CH_3); *syn*-**5**: δ = 4.60 (dt, *J* = 6.5/9 Hz, 1H, 5-H), 3.26 (qd, *J* = 7/9 Hz, 1H, 1′-H), 2.57–2.47 (m, 2H, 3-H), 2.26 (m_c, 1H, 4-H), 1.90 (m_c, 1H, 4-H), 1.27 (d, *J* = 7 Hz, 3H, 1′-CH_3), 1.17 (s, 9H, *t*Bu). – ^{13}C NMR, *anti*-**5**: δ = 216.2 (s, C=O), 176.2 (s, C-2), 81.9 (d, C-5), 44.7, 25.9 (s, q, *t*Bu), 44.5 (d, C-1′), 28.7, 26.1 (2 t, C-3,4), 13.8 (q, 1′-CH_3); *syn*-**5**: δ = 216.9 (s, C=O), 176.5 (s, C-2), 82.6 (d, C-5), 44.9 (d, C-5′), 44.8, 26.1 (s, q, *t*Bu), 28.7, 26.3 (2 t, C-3,4), 16.5 (q, 1′-CH_3). – $C_{11}H_{18}O_3$ (198.3): calcd. C 66.64, H 9.15; found C 66.89, H 9.24.

According to general procedure 1 (T_1 = −60, T_2 = −40 °C) the reaction of **1b** with 3.00 mmol of **4**-$TiCl_3$ furnished 0.305 g (77%) of **5** (*anti*:*syn* = 81:19) as partially crystalline oil.

According to general procedure 2 2,2-dimethyl-3-pentanone (2.20 mmol) was allowed to react with **1b** (2.10 mmol) at 0 °C affording 0.340 g (82%) of **5** (*anti*:*syn* = 3:97) after drying in vacuo (80 °C/1 Torr) with m.p. 36–38 °C.

4,5-Dihydro-4,4-dimethyl-5-(1,3,3-trimethyl-2-oxobutyl)-2(3H)-furanone (**6**): According to general procedure 3 (T_1 = 0, T_2 = 25 °C) the reaction of β-formyl carboxylate **1c** with silyl enol ether **4**-$SiMe_3$ and $TiCl_4$ provided after drying in vacuo (70 °C/0.01 Torr) 0.400 g (88%) of **6** (*anti*:*syn* = 4:96) with m.p. 114–115 °C. – IR (film): $\tilde{\nu}$ = 2970, 2940, 2920, 2880 cm^{-1} (C–H), 1780, 1695 (C=O). – ^1H NMR (300 MHz), *syn*-**6**: δ = 4.54 (d, *J* = 9.5 Hz, 1H, 5-H), 3.26 (qd, *J* = 7/9.5 Hz, 1H, 1′-H), AB system (δ_A = 2.46, δ_B = 2.28, J_{AB} = 17 Hz, 2H, 3-H), 1.28 (d, *J* = 7 Hz, 3H, 1′-CH_3), 1.24 (s, 9H, *t*Bu), 1.09, 1.03 (2 s, each 3H, 4-CH_3); *anti*-**6**: δ = 4.36 (d, *J* = 10.5 Hz, 1H, 5-H), 3.32 (qd, *J* = 7/10.5 Hz, 1H, 1′-H). – ^{13}C NMR, *syn*-**6**: δ = 217.0 (s, C=O), 175.2 (s, C-2), 89.1 (d, C-5), 45.3 (t, C-3), 44.4, 27.8 (s, q, *t*Bu), 41.3 (d, C-1′), 39.4 (s, C-4), 26.1, 22.2 (2 q, 4-CH_3), 16.9 (q, 1′-CH_3); *anti*-**6**: δ = 45.9 (t, C-3), 39.9 (d, C-1′), 20.9 (q, 4-CH_3), 14.9 (q, 1′-CH_3). – $C_{13}H_{22}O_3$ (226.3): calcd. C 69.00, H 9.80; found C 68.95, H 9.86.

According to general procedure 1 (T_1 = 0, T_2 = 25 °C) the reaction of **1c** with 3.00 mmol of **4**-$TiCl_3$ furnished after drying in vacuo (70 °C/0.01 Torr) 0.390 g (86%) of **6** (*anti*:*syn* = 5:95) with m.p. 104–109 °C. After recrystallization from diethyl ether crystals were obtained (m.p. 109–111 °C) which could be used for an X-ray analysis (*anti*:*syn* < 1:99).

According to general procedure 2 2,2-dimethyl-3-pentanone (2.20 mmol) was allowed to react with **1c** (2.10 mmol) at 0 °C affording after drying in vacuo (80 °C/0.1 Torr) 0.360 g (76%) of **6** (*anti*:*syn* < 1:99) with m.p. 111–113 °C.

4,5-Dihydro-4-methyl-5-(1,3,3-trimethyl-2-oxobutyl)-2(3H)-furanone (**7**): According to general procedure 3 (T_1 = −78, T_2 = −78 °C) the reaction of β-formyl carboxylate **1a** with silyl enol ether **4**-$SiMe_3$ and $BF_3 \cdot OEt_2$ provided 0.270 g (64%) of **7** (**a**:**b**:**c**:**d** = 5:22:64:9) with b.p. 120 °C/0.02 Torr. – IR (film): $\tilde{\nu}$ = 2980, 2940, 2920, 2880 cm^{-1} (C–H), 1780, 1700 (C=O). – ^1H NMR (300 MHz): δ = 4.63 (dd, *J* = 5/10 Hz, 0.05H, 5-H, **a**), 4.58 (dd, *J* = 4.5/11 Hz, 0.22H, 5-H, **b**), 4.30 (dd, *J* = 5.5/9.5 Hz, 0.64H, 5-H, **c**), 4.26 (dd, *J* = 5.5/8.5 Hz, 0.09H, 5-H, **d**), 3.27 (qd, *J* = 7/8.5 Hz, 0.09H, 1′-H, **d**), 3.22 (qd, *J* = 7/9.5 Hz, 0.64H, 1′-H, **c**), 2.75 (dd, *J* = 9/17.5 Hz, 0.64H, 3-H, **c**), 2.71 (dd, *J* = 8.5/17.5 Hz, 0.09H, 3-H, **d**), 2.53–2.28 (m, 1H, 4-H), 2.20 (dd, *J* = 7/17.5 Hz, 0.64H, 3-H, **c**), 2.16 (dd, *J* = 6.5/17.5 Hz, 0.09H, 3-H, **d**), 1.24 (d, *J* = 7 Hz, 0.27H, 1′-CH_3, **d**), 1.22 (d, *J* = 8 Hz, 1.92H, 4-CH_3, **c**), 1.18 (s, 0.81H, *t*Bu, **d**), 1.16 (s, 5.76H, *t*Bu, **c**), 1.10 (d, *J* = 7 Hz, 0.27H, 4-CH_3, **d**), 1.09 (d, *J* = 7 Hz, 1.92H, 1′-CH_3, **c**). – ^{13}C NMR, **c**: δ = 215.9 (s, C=O), 175.5 (s, C-2), 88.5 (d, C-5), 44.6, 25.8 (s, q, *t*Bu), 36.5 (t, C-3), 32.7 (d, C-4), 19.9 (q, 1′-CH_3), 14.1 (q, 4-CH_3); **d**: δ = 216.7 (s, C=O), 175.9 (s, C-2), 88.0 (d, C-5), 44.8, 26.0 (s, q, *t*Bu), 44.1 (d, C-1′), 36.3 (t, C-3), 33.5 (d, C-4), 19.5 (q, 1′-CH_3), 16.2 (q, 4-CH_3). – $C_{12}H_{20}O_3$ (212.3): calcd. C 67.89, H 9.50; found C 67.93, H 9.54.

According to general procedure 3 (T_1 = −60, T_2 = −40 °C), the reaction of **1a** with silyl enol ether **4**-$SiMe_3$ and $TiCl_4$ furnished 0.289 g (68%) of **7** (**a**:**b**:**c**:**d** = 5:5:39:51).

According to general procedure 1 (T_1 = −60, T_2 = −40 °C) the reaction of **1a** with 3.00 mmol of **4**-$TiCl_3$ provided 0.380 g (90%) of **7** (**a**:**b**:**c**:**d** = 1:9:85:5).

According to general procedure 2 2,2-dimethyl-3-pentanone (2.20 mmol) was treated with **1a** (2.10 mmol) at −78 °C affording 0.313 g (70%) (**a**:**b**:**c**:**d** = 15:0:0:85).

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