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Stereoselective Conjugate Addition of Lithium and Titanium Enolates to γ - Alkoxy Enones.

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Abstract: The addition of titanium and lithium enolates **1** and **2** to γ-alkoxy enone **4** occurs in good yield with good stereoselectivities. 3,4 syn - 2,3 syn adducts **7** are obtained starting from the lithium enolate **2**, whereas the 3,4 syn - 2,3 anti isomers **9** are formed using the titanium enolate **1**. The levels of selectivity vary with the nature of the oxygen protecting group.

We recently reported that Ti "ate" enolates, obtained by treating the corresponding Li enolates with 1 mol equiv of $Ti(OiPr)_4$, add to unsaturated carbonyl compounds in a 1,4-fashion with high regio- and stereoselectivity.[1] For ester enolates the stereochemical outcome of the addition is reversed on going from Li to Ti. For instance, the Ti enolate of t-butylpropionate **1** adds to *E*-configurated esters and ketones to give *anti* ketoesters with stereoselectivities up to 95%, while the addition of the parent Li enolate **2** is 90-95% *syn* selective (**Figure 1**).[2]

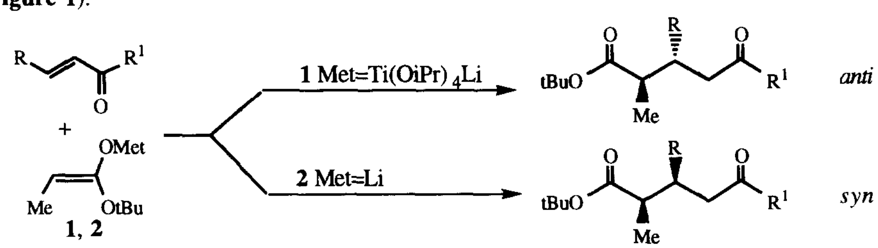


Figure 1. Conjugate addition of propionate enolates **1** and **2**.

The reaction of **1** and **2** with chiral enone **3** was also studied.[3] Both reactions are moderately stereoselective, leading to the synthesis of the *2,3anti-3,4anti* and the *2,3syn-3,4anti* isomers with 78% and 82% selectivity, respectively (**Figure 2**). The addition of **1** appears to take place via an inverse demand Diels-Alder reaction, rather than a conjugate addition, which can explain the different stereochemical behavior of lithium and titanium enolates in the reaction with enones.

In this paper we report on the selectivity observed in the reaction of **1** and **2** to γ-alkoxyketones.

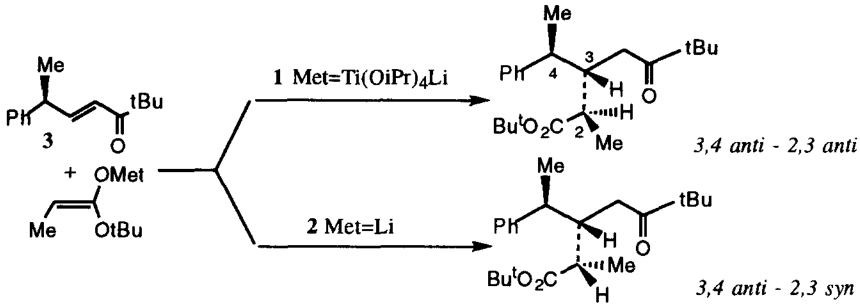
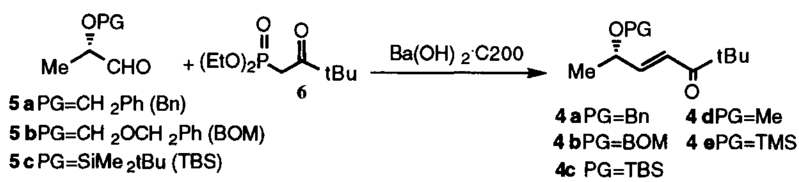


Figure 2. Conjugate addition of **1** and **2** to chiral enone **3**.

RESULTS AND DISCUSSION.

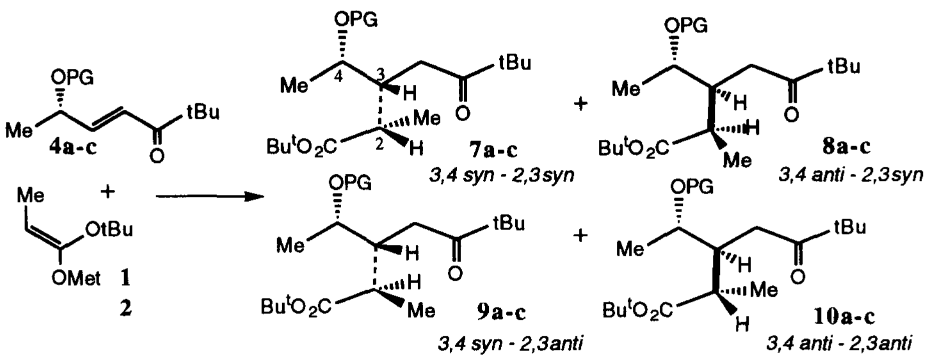
The conjugate addition of nucleophiles to enones bearing an oxygenated allylic stereocenter has received much attention over the past few years.[4] The reaction is often found to occur with synthetically useful levels of selectivity, which vary rather unpredictably depending on the structure of the substrate (type of oxygen protecting group, configuration of the double bond) and of the reagent. However, there are very few reports concerning the conjugate addition of enolates to γ-alkoxy enones. A recent paper by Kanemasa and Nomura[5] has shown that the propionate lithium enolate adds in a non stereoselective fashion to ethyl (2,2-dimethyl-1,3-dioxolan-4-yl)propenoate. On the contrary α-heterosubstituted enolates add to the same substrate with a diastereoisomeric excess (d.e.) which varies from 86 to 96%.[5] The acid catalyzed reaction of 4-silyloxycyclopentenone with silyl ketene acetals has been shown to be *syn* or *anti* selective depending on the substitution pattern of the ketene acetal.[6]

In an effort to clarify the synthetic potential of enolate conjugate addition, we have studied the reaction of lithium enolate **2** and titanium enolate **1** with enones **4a-c**. The enones were synthesized starting from the corresponding protected lactaldehydes **5a-c**[7] and phosphonate **6**[8] (**Scheme 1**) using $Ba(OH)_2$·C200 as a base.[9]



Scheme 1. Synthesis of γ-alkoxy enones **4a-c.**

The addition of propionate enolates **1** (Metal=$Ti(OiPr)_4Li$) and **2** (Metal=Li) to **4** can in principle afford the four different stereoisomers depicted in **Scheme 2.** The experimental results in the presence of different protecting groups (PG) are reported in **Table 1**.



Scheme 2. Addition of t-butyl propionate enolates **1** and **2** to enones **4a-c.**

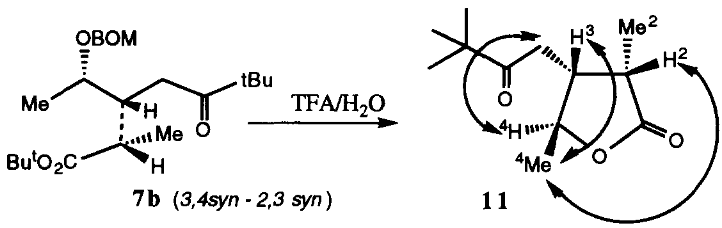
Table 1. Addition of **1** and **2** to **4a-c**.[a]

Entry	Metal	Substr.	PG	**7** (*3,4s-2,3s*)	**8** (*3,4a-2,3s*)	**9** (*3,4s-2,3a*)	**10** (*3,4a-2,3a*)	Yield (%)
1	Li	**4b**	BOM	*55*	19	17	9	90
2	Li	**4a**[b]	Bn	*53*	9	26	12	90
3	Li	**4c**	TBS	*70*	13	17	=	45
4	Li[c]	**4a**[b]	Bn	=	=	*75*	25	50
5	Ti	**4b**	BOM	8	8	*57*	27	95
6	Ti	**4a**[b]	Bn	7	2	*72*	19	98
7	Ti	**4c**	TBS	12	=	*78*	10	63

a) BOM=$PhOCH_2OCH_2$- Bn= $PhCH_2$- TBS= $tBuMe_2Si$. Unless otherwise stated, diastereoisomeric ratios were determined by ^{13}C-NMR spectroscopy.b) Diastereomeric ratios determined by capillary GC. c) *Z* enolate, in the presence of DMPU.

The mixture composition is rather complex, but in all cases 3,4 *syn* selectivity is observed. The 3,4 selectivity tends to increase on going from **4b** to **4a** to **4c**, as the basicity of the allylic oxygen, modulated by the different protecting groups, decreases.[10] The correlation between the level of 3,4 selectivity and the type of protecting group is more pronounced in the case of the titanium enolate **1** (Entries 5-7, *3,4syn : 3,4anti::* **b**: 65:35; **a**: 79:21; **c**: 90:10) than for the lithium enolate **2** (Entries 1-3, *3,4syn : 3,4anti::* **b**: 72:28; **a**: 79:21; **c**: 87:13). As expected, the 2,3 selectivity is *anti for* the titanium enolate **1** and *syn* for the lithium enolate **2**.

In order to determine the product configuration, the reaction mixtures obtained by addition of **1** and **2** to **4b** (**Table 1**, entries 1 and 5) were treated with CF_3COOH/H_2O and converted into the corresponding γ-lactones.[11] From the lithium reaction (**Scheme 3**) the major lactone **11** was isolated by flash chromatography (4:1:1 iPr_2O : hexane : CH_2Cl_2).



Scheme 3. Synthesis of *2,3 cis- 3,4 trans* γ-lactone **11**.

Its configuration was determined to be *2,3 cis-3,4 trans* by the observed nuclear Overhauser effects (see **Scheme 3**). The attribution was confirmed by determining the X-ray structure of **11**, which is reported in **Figure 3**. Thus the most abudant isomer in the lithium mediated condensations was determined to be the *3,4syn - 2,3 syn* compound **7**.

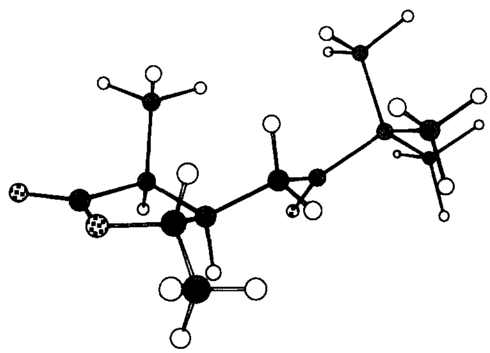
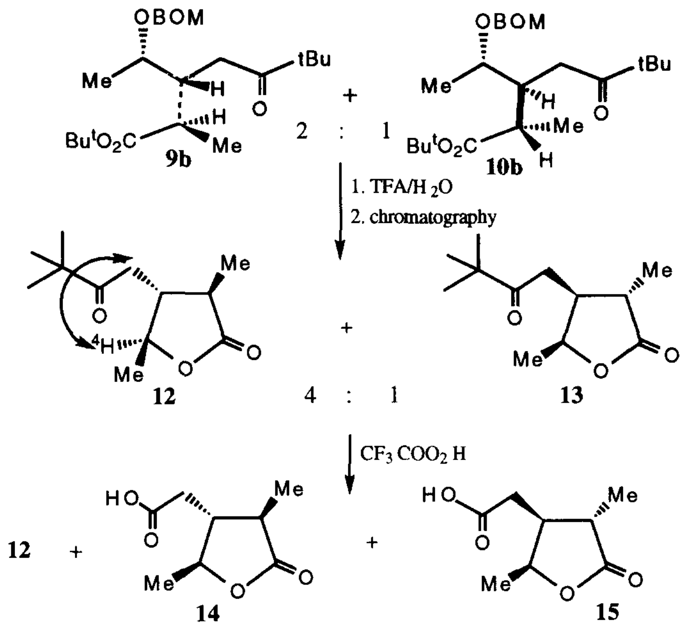


Figure 3. X-ray structure of *2,3cis-3,4trans* γ-lactone **11**.

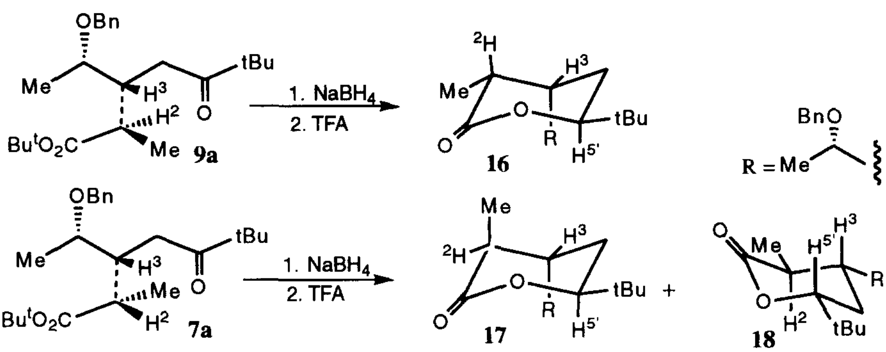
Treatment with CF_3COOH/H_2O of the crude reaction mixture obtained by addition of the titanium enolate **1** to **4b**, followed by flash chromatography afforded a 4:1 mixture of the two γ-lactones **12** and **13** (**Scheme 4**)[11]. The major isomer **12** was finally purified using a selective Bayer-Villiger oxidation with CF_3COO_2H: **12** reacts slowly with the peracid, and is recovered (60%) after the oxidation of **13** is complete. The presence of nuclear Overhauser effect between H_4 and the methylene group (see **Scheme 4**) in the spectrum of **12** reveals a *3,4 trans* configuration in the lactone, which corresponds to *3,4syn* selectivity in the original ketoester **9b**. Since the *3,4syn-2,3syn* configuration has been attributed to **7b**, the major isomer formed in the titanium mediated condensation must be the *3,4syn-2,3anti* isomer **9**.

These attributions were confirmed by transforming the crude products of addition to **4a** (PG=Bn) in the corresponding δ-lactones by $NaBH_4$ reduction of the ketone (**Scheme 5**).

Reduction of **9a** afforded mostly lactone **16**, with a *2,3 cis* relationship, thus confirming the *2,3anti* configuration for the major titanium isomer. Reduction of **7a** gave a ca. 3:1 mixture of 2,3 trans lactones **17** and **18**, in agreement with the *2,3syn* configuration attributed to the major lithium isomer **7**.

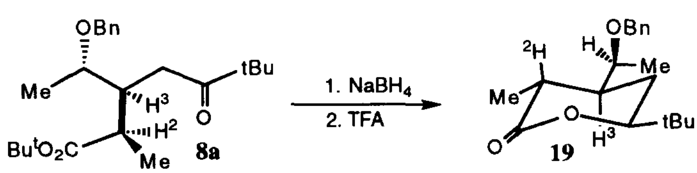


Scheme 4. Isolation of *2,3 trans - 3,4 trans* γ–lactone **12**.



Scheme 5. Determination of relative 2,3 configuration *via* δ-lactones.

The configuration of the minor *3,4anti* adducts **8** and **10** was also determined by reducing **8a** with $NaBH_4$ (**Scheme 6**). This afforded the *2,3 trans* lactone **19**, thus establishing the *2,3syn-3,4anti* configuration for **8a**. The remaining isomer **10a** was then assigned the *2,3anti-3,4anti* configuration.



Scheme 6.

The mechanism of lithium enolate conjugate addition has been studied in some detail by experimental[3] and computational[12] means. The reaction appears to be a nucleophilic addition to the activated double bond and to take place through 8-membered cyclic transition structures. The lowest energy structure is the one reported in **Figure 4** and in the case of *E* enolates like **2**, leads to the formation of *2,3 syn* adducts.[12]

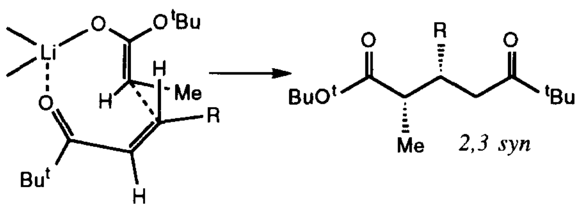


Figure 4. 2,3 selectivity in the conjugate addition of lithium enolate **2**.

The 3,4 selectivity of nucleophilic additions to γ-alkoxy substrates like **4** can be rationalized on the basis of the Felkin-like model reported in **Figure 5**.[13] Formation of products with a *syn* relationship between the nucleophile and the alkoxy group (*3,4 syn* products) is expected on the basis of this model, and observed in the lithium enolate reactions.

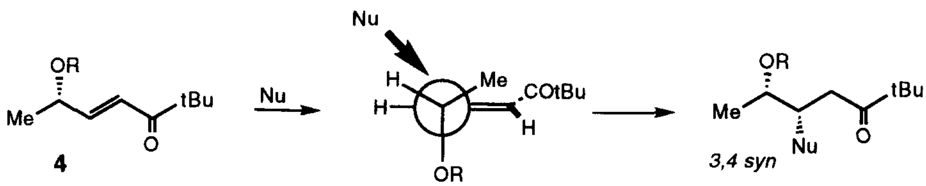


Figure 5. 3,4 selectivity in the conjugate addition of lithium enolate **2**: Felkin-like model for nucleophilic addition to chiral enones.

Based on the above models for 2,3 and 3,4 selectivity, the lowest energy transition structure for the addition of the lithium enolate **2** to **4** is expected to be the one depicted in **Figure 6.** The picture was obtained by graphically adding the appropriate substituents to the calculated lowest energy geometry for the addition of an *E* enolate to an *E* enone.[12] No optimization was attempted.

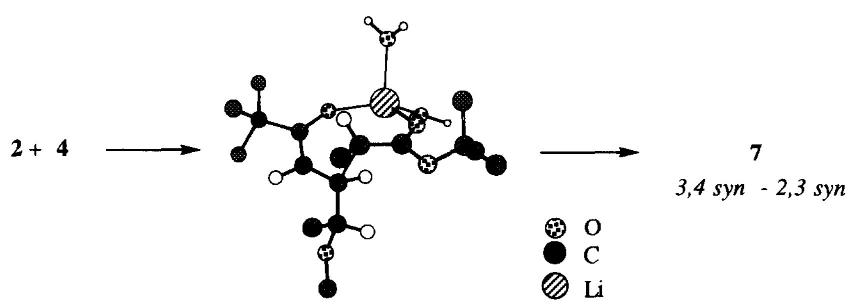


Figure 6. Transition structure for the addition of lithium enolate **2** to **4d** (PG=Me). (Two water molecules mimic ether solvation around the lithium atom).

It has been noted that the level of 3,4 stereoselectivity obtained with the lithium enolate **2** depends on the nature of the allylic oxygen protecting group and slightly increases going from **4b** (*anti: syn* 72:28) to **4a** (79:21) to **4c** (87:13). This is in agreement with recent findings by Gung and coworkers,[14] who have shown by variable temperature NMR that a benzyl protecting group on the hydroxy function of chiral allylic alcohols enhances the CH eclipsed form GS-I (**Figure 7**), whereas silyl ethers enhance the preference for the CO eclipsed conformer GS-II. If these ground state preferences carry over to the transition state, the benzyl group should stabilize the anti Felkin transition structure TS-II (**Figure 7**), which leads to the minor *3,4 anti* isomer.

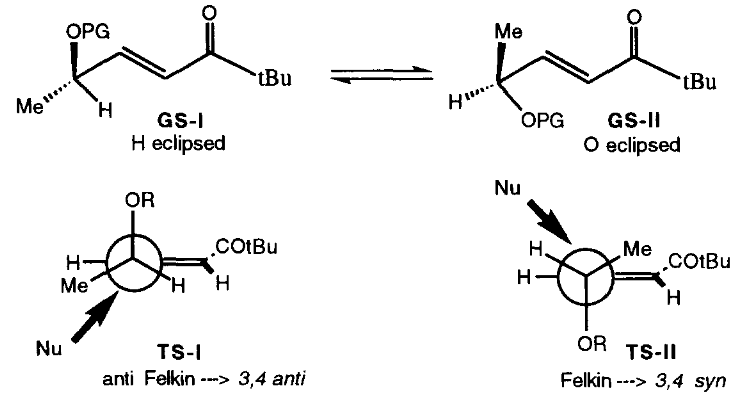


Figure 7.

The formal conjugate addition of the titanium enolate **1** to enones appears to take place *via* an inverse-demand Diels-Alder cycloaddition.[3] The observed *2,3 anti* selectivity can be rationalized on the basis of the 6-membered cyclic transition structure reported in **Figure 8**.

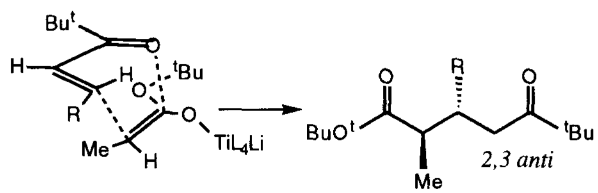


Figure 8. 2,3 selectivity in the conjugate addition of titanium enolate **1**.

The *3,4 syn* selectivity observed in the reaction between **1** and **4** is again of Felkin type. This is not surprising, since the electronic requirements of inverse demand cycloadditions match those of nucleophilic addition reactions, and are similarly related to the stability of the diene LUMO. A few reports in the literature confirm that intermolecular cycloadditions of enol ethers to γ-alkoxy enones afford Felkin type products.[15] The diastereoface selectivity should result from competition between the two enone conformations $\mathbf{H_{in}}$ and $\mathbf{H_{out}}$ depicted in **Figure 9**. Addition to the less hindered diastereoface leads to the anti Felkin type products from $\mathbf{H_{in}}$ and to the Felkin type compound from $\mathbf{H_{out}}$.

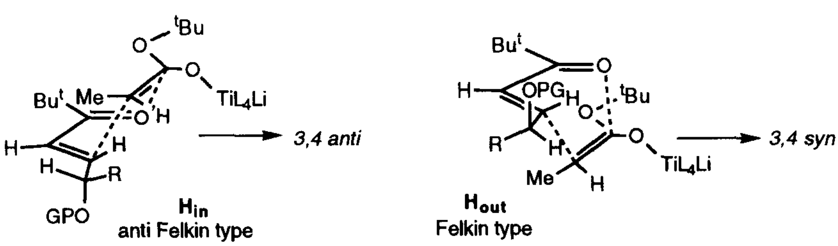


Figure 9. 3,4 selectivity in the addition of **1** to **4**.

The ΔH_f of the two H_{in} and H_{out} conformers for the representative enones **4d** (PG=Me) and **4e** (PG=TMS) are reported in **Table 2**, together with the corresponding LUMO energies, as calculated by MNDO. Although the H_{in} conformers appear to be more stable by 2-4 kcal/mol, the H_{out} rotamers feature the lowest lying LUMO and therefore are expected to determine the steric outcome of the reaction. It should be noted that the largest (H_{out}- H_{in}) LUMO energy difference is calculated for the silyl protected enone **4e**. This is in agreement with the experimental observation that **4c** (PG=TBS) displays the largest diastereoface differentiation among the substrates we have examined (*3,4 syn : 3,4 anti* **4b** 65:35, **4a** 79:21, **4c** 91:9).

Table 2. MNDO calculations of **4d** (PG=Me) and **4e** (PG=TMS).

Compound	PG	ΔH_f (kcal/mol)	LUMO En. (eV)
4d H_{in}	Me	-73.70	0.30874
4d H_{out}	Me	-70.24	0.24192
4e H_{in}	TMS	-142.39	0.3950
4e H_{out}	TMS	-137.94	0.18043

In conclusion, we have shown that the addition of propionate enolates **1** and **2** to chiral enones **4** occurs with useful levels of stereoselectivity and leads to different stereoisomers depending on the enolate counterion.

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EXPERIMENTAL.

Preparation of γ-alkoxy enones 4a-c : A solution of phosphonate **6** (1g) in dry dioxane (3.5 ml) was added to a solution of $Ba(OH)_2$ C200[9] (424 mg,) in dry dioxane (7 ml), at 70° C. After 10 min, a solution of aldehyde **5a-c** (4.2 mmol) in dioxane (3.5 ml) and distilled water (85 μl) was added and the solution was stirred at 70°C. After 15 min the reaction was quenched by adding HCl (10%) to pH 1. The barium salts were filtered, the organic layer was extracted with diethyl ether, dried (Na_2SO_4) and evaporated to give the crude alkoxy enone.

4a: (flash chromatography: hexane/diethyl ether 85:15; 62% yield)
^{1}H-NMR (200 MHz, $CDCl_3$): 1.19 (s, 9H); 1.33 (d, 3H, J=6 Hz); 4.16 (dq, 1H, J=J=6 Hz); 4.45 (d, 1H, J=11.5 Hz); 4.59 (d, 1H, J=11.5 Hz); 6.7 (d, 1H, J=16 Hz); 6.88 (dd, 1H, J=16 Hz, J=6 Hz); 7.32 (m, 5H). ^{13}C-NMR ($CDCl_3$, DEPT): 20.7; 26.0; 70.7; 74.1; 123.3; 127.5; 127.6; 128.35; 147.2. IR ($CHCl_3$, cm^{-1}): 1680 ; 1625 Anal. Calcd. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.17; H, 8.74.
$[\alpha]_D$= - 62° (c=2, $CHCl_3$)

4b: (flash chromatography hexane/ethyl acetate 9:1, 74% yield)
^{1}H-NMR (200 MHz, $CDCl_3$): 1.17 (s, 9H); 1.32 (d, 3H, J=6 Hz); 4.46 (dq, 1H, J=J=6 Hz); 4.63 (AB system, 2H, J=11.44 Hz); 4.79 (AB system, 2H, J=7 Hz); 6.68 (d, 1H, J=16 Hz); 6.82 (dd, 1H, J=16 Hz, J=6 Hz); 7.34 (m, 5H). ^{13}C-NMR ($CDCl_3$, DEPT): 20.6; 26.0; 69.5; 71.55; 92.45; 123.2; 127.68; 127.81; 128.36; 146.7. Anal. Calcd. for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.65; H, 9.06.

4c: (flash chromatography hexane/diethyl ether 95:5, 50% yield)

[1]H-NMR (200 MHz, $CDCl_3$): 0.1 (s, 6H); 0.92 (s, 9H); 1.17 (s, 9H); 1.28 (d, 3H, J=5.4 Hz); 4.49 (ddq, 1H, J=5.4 Hz, J=3.6 Hz, J=2 Hz); 6.72 (dd, 1H, J=14.3 Hz, J=2 Hz); 6.9 (dd, 1H, J=14.3 Hz, J=3.6 Hz). Anal. Calcd. for $C_{15}H_{30}O_2Si$: C, 66.61; H, 11.18. Found: C, 66.77; H, 10.91. $[\alpha]_D= + 3°$ (c=1; $CHCl_3$)

Addition of propionate lithium enolate 2 to 4a-c .

(E enolate)

A solution of BuLi (2.3 eq) in hexane (1.6 M) was added to a solution of iPr_2NH (2.4 eq) in dry THF, under N_2, at 0° C. After 10 min, the solution was cooled to -78°C and *t*-butylpropionate (2 eq) was added and stirred for 30 min. Then, a solution of **4a-c** (1 eq) in dry THF (0.3 ml) was added. The reaction mixture was stirred for 1 h at -78° C and 30 min at 0° C, then was quenched by adding a saturated solution of NH_4Cl. The aqueous layer was extracted with diethyl ether and the combined organic phases were dried and evaporated.

(Z enolate)

To the solution of LDA (2.3 eq) prepared as described above, at -78° C, were added DMPU (0.3 vol. of THF) and *t*-butylpropionate (2 eq). After 20 min, **4a** (1 eq) was added. The reaction mixture was stirred for 1 h at -78° C and 1.5 h at 0° C, then was quenched by adding a saturated solution of NH_4Cl. The aqueous layer was extracted with diethyl ether and the combined organic phases were dried and evaporated.

Addition of propionate titanium enolate 1 to 4a-c : To the solution of E lithium enolate prepared as described above, $Ti(OiPr)_4$ (2eq) was added at -78°C, and the reaction mixture was stirred at -40° C for 30 min. Then, a solution of **4a-c** (1eq) in dry THF (0.3 ml) was added and the solution was allowed to slowly warm to 0° C. After 2.5 h, the reaction was quenched by adding a saturated solution of NH_4F. The aqueous layer was extracted with diethyl ether and the combined organic phases were dried and evaporated

7a : [1]H-NMR (200 MHz, $CDCl_3$): 1.06 (d, 3H, J=6.8 Hz); 1.08 (d, 3H, J=6.8 Hz); 1.14 (s, 9H); 1.4 (s, 9H); 2.4-2.9 (m, 4H); 3.6 (m, 1H); 4.4 (d, 1H, J=11.5 Hz); 4.6 (d, 1H, J=11.5 Hz); 7.32 (m, 5H). [13]C-NMR ($CDCl_3$, DEPT) selected signals: 15.25; 17.00; 34.79; 40.38; 41.72; 70.00; 74.76.

8a [13]C-NMR ($CDCl_3$) selected signals: 35.5; 70.57; 77.14.

9a: [1]H-NMR (200 MHz, $CDCl_3$) selected signals: 1.04 (d,3H, J=6.8 Hz); 1.12 (s,9H); 1.4 (s, 9H); 2.4-2.8 (m, 4H); 3.61 (dq, 1H, J=6.8 Hz, J=3.4 Hz); 4.4 (d, 1H, J=11.4 Hz); 4.53 (d, 1H, J=11.4 Hz); 7.3 (m, 5H). [13]C-NMR ($CDCl_3$, DEPT) selected signals: 14.74; 17.5; 26.7; 27.97; 34.12; 40.5; 41.8; 70.46; 75.86.

10a: [13]C-NMR ($CDCl_3$) selected signals: 14.02; 16.27; 33.8; 38.5; 40.9; 70.16; 75.07.

7b: [13]C-NMR ($CDCl_3$,DEPT) selected signals: 15.48; 18.16; 26.73; 27.93; 34.6;40.80; 41.89; 69.6; 74.04; 93.28; 127.63; 128.29.

8b [13]C-NMR ($CDCl_3$) selected signals: 15.27; 17.45; 34.5; 40.23; 40.50; 69.35; 74.33; 93.23.

9b : [1]H-NMR (200MHz, $CDCl_3$): 1.18 (s, 9H); 1.42 (s, 9H); 2.4-2.8 (m, 4H); 3.7 (dq, 1H, J=7.1 Hz, J=4 Hz); 4.57 (d, 1H, J=12.7 Hz); 4.65 (d, 1H, J=12.7 Hz); 4.72 (d, 1H, J=8.7 Hz); 4.77 (d, 1H, J=8.7 Hz). [13]C-NMR ($CDCl_3$): 14.8; 18.9; 26.74; 28.0; 34.12; 40.87; 41.72; 44.1; 69.45; 74.8; 80; 93.9; 175.1.

10b: [13]C-NMR ($CDCl_3$) selected signals: 14.0; 16.95; 26.7; 27.87; 33.8; 39.2; 69.38; 73.7; 92.7.

7c: [1]H-NMR (200MHz, $CDCl_3$): 0.1 (s, 6H); 0.89 (s, 9H); 1.04 (d, 3H, J=6.4 Hz); 1.12 (d, 3H, J=7 Hz); 1.18 (s, 9H); 1.43 (s, 9H); 2.3-2.5 (m, 3H); 2.88 (m,1H); 3.9 (m, 1H). [13]C-NMR ($CDCl_3$) selected signals: 15.4; 21.7; 34.8; 41.85; 41.9; 67.58.

8c: [13]C-NMR ($CDCl_3$) selected signals: 7.67; 12.64; 34.44; 66.1.

9c: ^{1}H-NMR (300MHz, $CDCl_3$): 0.05 (s, 6H); 0.87 (s, 9H); 1.0 (d, 3H, J=7.6 Hz); 1.01 (d, 3H, J=6 Hz); 1.12 (s, 9H); 1.42 (s, 9H); 2.3-2.5 (m, 3H); 2.7-2.8 (m, 1H); 3.83 (dq, 1H, J=6 Hz, J=2.8 Hz). ^{13}C-NMR ($CDCl_3$) selected signals: 15.06; 22.4; 25.7; 26.8; 33.3; 41.4; 42.3; 69.5; 79.8; 175.6.
10c ^{13}C-NMR ($CDCl_3$) selected signals: 33.5; 40.93; 41.0; 68.96.

Preparation of γ-lactones 11-13 (Scheme 3,4).: The crude of the condensation between **2** and **4b** was dissolved in a solution of 9:1 CF_3COOH/H_2O and stirred for 30 min at 0° C and for 30 min at room temperature, then the solvent was evaporated. The major lactone **11** was isolated by flash chromatography (*i*-Pr_2O/hexane/CH_2Cl_2 4:1:1) and recrystallised from pentane.
11: ^{1}H-NMR (200 MHz, $CDCl_3$): 1.16 (d, 3H, J=7.7 Hz); 1.18 (s, 9H); 1.41 (d, 3H, J=6.4Hz); 2.5-2.78 (m, 3H); 2.97 (dq, 1H, $J_{2,3}$=7.3 Hz, $J_{2,Me2}$=7.7 Hz); 4.18 (dq, 1H, $J_{3,4}$=4.2 Hz, $J_{4,Me4}$=6.4 Hz). ^{1}H-NMR (200 MHz, C_6D_6): 0.85 (d, 3H, $J_{2,Me2}$=7.4Hz); 0.9 (s, 9H); 1.05 (d, 3H, $J_{4,Me4}$= 6.7Hz); 2.06 (d, 2H, 8.2Hz); 2.3 (m, 1H); 2.59 (dq, 1H, $J_{2,3}$=8Hz, $J_{2,Me2}$=7.4Hz); 3.8 (dq, 1H, $J_{3,4}$=4.6Hz, $J_{4,Me4}$= 6.7Hz). ^{13}C-NMR ($CDCl_3$): 10.37; 19.38; 26.43; 34.65; 36.33; 40.56; 44.12; 76.30; 76.94; 77.58; 79.64; 179.17; 191.06. I.R. ($CHCl_3$): 1705cm^{-1}; 1765cm^{-1}. Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.01; H, 9.37.
$[\alpha]_D$= + 9 (c=2, $CHCl_3$).

The same procedure was employed starting with the crude of the condensation between **1** and **4b**. A mixture of **12** and **13** (4:1) was isolated by flash chromatography (*i*-Pr_2O/hexane/CH_2Cl_2 4:1:1)
Purification of 12: (Scheme 4): CF_3CO_3H was prepared *in situ* [16] at 0°C adding $(CF_3CO)_2O$ (24 mmol) to a solution of H_2O_2 (30%, 0.5 g, 44 mmol) in CH_2Cl_2 (3.7 ml). At 0°C, a 4:1 mixture of **12** and **13** (1 eq) was dissolved in CH_2Cl_2 and the solution of CF_3CO_3H (4 eq) was added. The reaction mixture was kept at room temperature for 2 h, then was diluted with H_2O and extracted with CH_2Cl_2. The organic layer (which contains unreacted **12**) was washed, dried (Na_2SO_4) and evaporated.
The acids **14** and **15** were extracted with AcOEt from the aqueous phase and the organic layer was dried (Na_2SO_4) and evaporated. Purification by flash chromatography (ethyl acetate with 3% of acetone) gave a mixture of two acids (**14** and **15**) characterized by a multiplet at 4.44 and 4.80 ppm, respectively, in their ^{1}H-NMR spectra.
12: ^{1}H-NMR (300 MHz, $CDCl_3$): 1.17 (s, 9H); 1.25 (d, 3H, J=6.4 Hz); 1.4 (d, 3H, J=6 Hz); 2.3 (m, 2H); 2.65 (m, 2H); 4.15 (dq, 1H, J=7.8 Hz; J=6Hz). ^{1}H-NMR (500MHz, C_6D_6): 0.89 (s, 9H); 1.13 (d, 6H); 1.7-1.87 (dq, 2H, $J_{2,3}$= 10.52Hz); 1.93-1.98 (m, 2H); 2-2.1 (m, 1H); 3.5-3.65 (dq, 1H, $J_{3,4}$=8.42Hz, $J_{4,Me4}$=7.5Hz). ^{13}C-NMR ($CDCl_3$) selected signals: 14.3; 19.6; 26.03; 37.95; 41.72; 45.5; 79.7; 178.4; 213.46. I.R. (CHCl3): 1710cm^{-1}; 1770cm^{-1}. $[\alpha]_D$= +3.12 (c=2, $CHCl_3$).
13: ^{1}H-NMR (300 MHz, $CDCl_3$): 1.14 (d, 3H, J=6.8 Hz); 1.19 (s, 9H); 1.44 (d, 3H, J=6.4 Hz); 4.95 (dq, J=J=6.8 Hz). ^{13}C-NMR ($CDCl_3$) selected signals: 13.58; 15.19; 26.40; 35.83; 37.87.

Preparation of δ-lactones 16-19. The crude of the condensation between **4a** and **1** or **2** was dissolved in dry MeOH (0.3 M) and $NaBH_4$ (2 eq) was added . After 2.5 h the reaction was quenched with HCl (10%) to pH 5-6. Then water was added and the solution was extracted with diethyl ether. The organic layer was washed, dried and evaporated. The reaction crude (30 mg) was dissolved in CF_3COOH (1 ml) and stirred for 30 min at 0°C, then the solvent was evaporated. Purification by flash chromatography (*i*-Pr_2O/hexane 1:1) allowed the isolation of lactones **16-19**

16: ^{1}H-NMR (200 MHz; $CDCl_3$): 0.99 (s, 9H, tBu); 1.18 (2d, 6H, J=5.8 Hz, $Me_{3'}$, J=7 Hz, Me_2); 1.75 (ddd, 1H, J_{gem}=12 Hz, $J_{4ax,5}$=12 Hz, $J_{3,4ax}$=8 Hz, H_{4ax}); 1.98 (ddd, 1H, J_{gem}=12 Hz, $J_{4eq,5}$=3.5 Hz, $J_{4eq,3}$=7 Hz, H_{4eq}); 2.1 (m, 1H, $J_{3,3'}$=6 Hz, H_3(eq)); 2.75 (dq, 1H, $J_{2,3}$=$J_{2,Me2}$=7 Hz, H_2(ax)); 3.65 (dq, 1H, $J_{3,3'}$=3.6 Hz, $J_{3',Me}$=5.8 Hz, $H_{3'}$); 3.92 (dd, 1H, $J_{5,4ax}$=12 Hz, $J_{5,4eq}$=3.5 Hz, H_5(ax)).

17: ^{1}H-NMR (200 MHz; $CDCl_3$): 0.95 (s, 9H, tBu); 1.22 (d, 3H, J=6.7 Hz, Me_2); 1.25 (d, 3H, J=6.7 Hz, $Me_{3'}$); 1.70 (m, 1H, H_{4ax}); 1.9-2.05 (m, 2H, H_{4eq} e H_3); 2.52 (dq, 1H, J=6.7 Hz, $J_{2,3}$=5 Hz (eq,eq), H_2); 3.82 (dq, 1H, J=6.7 Hz, $J_{3,3'}$=3.6 Hz, $H_{3'}$); 3.95 (dd, 1H, $J_{5,4eq}$=4.3 Hz, $J_{5,4ax}$=11.5 Hz).

18: ^{1}H-NMR (200 MHz; $CDCl_3$): 0.98 (s, 9H, tBu); 1.22 (d, 3H, J=6 Hz, $Me_{3'}$); 1.26 (d, 3H, J=6Hz, Me_2); 1.45-1.60 (m, 2H, $J_{2,3}$=8 Hz (ax,ax), H_3 e H_{4ax}); 1.92 (m, 1H, H_{4eq}); 2.55 (dq, 1H, $J_{2,3}$=8 Hz, $J_{2,Me2}$=6 Hz, H_2); 3.65 (dq, 1H, $J_{3,3'}$=2.5 Hz, $J_{3',Me3'}$=6 Hz, $H_{3'}$); 3.90 (ddd, 1H, $J_{5,4ax}$=11 Hz, $J_{5,4eq}$=$J_{5,3}$=2 Hz, H_5).

19: ^{1}H-NMR (200 MHz; $CDCl_3$): 0.95 (s, 9H, tBu); 1.1 (d, 3H, J=6 Hz, Me_2); 1.25 (d, 3H, J=6 Hz, Me_3); 1.55 (m, 1H, $J_{3,3'}$=2 Hz, H_3); 1.62 (ddd, 1H, J_{gem}=10 Hz, $J_{4ax,5}$=10.8 Hz, $J_{4ax,3}$=10 Hz, H_{4ax}); 2.08 (ddd, 1H, J_{gem}=10 Hz, $J_{3,4eq}$=1-2 Hz, $J_{5,4eq}$=2 Hz, H_{4eq}); 2.72 (dq, 1H, J=6 Hz, $J_{2,3}$=10 Hz, H_2); 3.93 (dq, 1H, J=6 Hz, $J_{3,3'}$=2 Hz, $H_{3'}$); 4.05 (dd, 1H, $J_{4,5}$=10 Hz, $J_{5,4eq}$=2 Hz, H_5).

X-Ray diffraction of (11)

$C_{12}H_{20}O_3$, Orthorhombic $P2_12_12_1$, a=10.545(2) Å, b=12.436(3) Å, c=19.303(3) Å, V=2531.35(87) Å^3, $d_{calc.}$=1.114 gcm^{-3}, μ(Mo Kα)=0.08 mm^{-1}. Diffractometer *Siemens P4*, Mo Kα radiation, λ=0.71073 Å; cell parameters from 15 reflections in the range 4.20°<2θ<13.26°. A number of 2519 reflections in the range 3.5°<2θ<45.0° (-1≤h≤11, -1≤k≤13, -1≤l≤20) were collected by ω-scan technique, scan width=$\Delta\omega_{K\alpha1-K\alpha2}$±0.8°, scan speed=2°/min. R_{merge}= 0.020.

Structure solution by program *SIR92*[17] revealed the presence of two independent molecules in the asymmetric unit. All non hydrogen atoms appeared in the first E-map. The enantiomorph was chosen on the basis of the known configuration at C4.

Refinement was conducted on 1584 F^2 having F>2σ(F), employing program *SHELX93*[18], with weights w= $1/(\sigma^2(F_o^2)+(0.44P)^2+0.17P)$, where $P=(\max(F_o^2,0)+2F_c^2))/3$. Anisotropic atomic displacement parameters (ADP's) were refined on C and O atoms, except for the $COC(CH_3)_3$ moiety of molecule 2, whose ADP's were retained isotropic. H atoms were fixed in idealized positions (d_{CH}=0.98 Å for tertiary C atoms, d_{CH}=0.96 Å for methyls, HCX angles all equal to 109.45°), conformation of methyl groups were initially determined by a difference Fourier synthesis, then refined at each cycle. Isotropic ADP's were refined for Hs attached to tertiary carbons, while for methyl H atoms their values were constrained to 1.2 times the U_{iso} of the bearing carbon atom. Conformational disorder around C29-C30 in the $COC(CH_3)_3$ moiety of molecule B was modelled by refining two sets of atomic positions, labelled A and B respectively (except for C30, which was not splitted) and their site occupancy factors, the sum of which was constrained to 1: the final value was 0.514(10) for s.o.f. of conformer 2A. The final model counted up to 204 variables. $\Delta\rho_{max}$=0.16 e Å^{-3}, wR(F^2)=0.1224, G.o.F. = 1.225 (wR(F^2)=0.0637 and G.o.F. = 1.183 on 1210 F^2 having F>4σ(F)).

Rms distance of all non-H nuclei of molecule 2 from the corresponding nuclei of molecule 1 amounts to 0.924 Å for conformer 2A (0.905 Å for conformer 2B). Main differences between molecules 1 and 2 arise in the conformation of the disordered $COC(CH_3)_3$ moiety: the torsion angles about the exocyclic Cα-CO bond are $\tau_{C23-C29-C30-O31A}$ = 15.5° and $\tau_{C23-C29-C30-O31B}$ = -18.1°; t-But groups of 2A and 2B show two different conformations, with torsion angles around OC-C32A(B) about 60° apart. The rest of the molecule has geometry remarkably similar in 1 and 2, rms distance between non-H nuclei excluding the atoms of the $COC(CH_3)_3$ moiety amounting to 0.074 Å.

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