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Enantioselective Conjugate Additions of Silylketene acetals to 2-Carboxycyclopentenones Promoted by Chiral Ti Complexes.#

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Abstract: The conjugate addition of silylketeneacetals to 2-carbalkoxycyclopentenones **1** promoted by TADDOL-$TiCl_2$ complexes was studied. The reactions are highly *syn* selective. The enantioselectivity depends on the size of the substrate ester group, with the methyl ester **1b** being more enantioselective than the ethyl ester **1a**. E.e. up to 47% are achieved. The absolute configuration of the major product was established by chemical correlation to the known (+)-isodehydroiridodiol. The reaction of representative doubly activated alkenes was studied: good results were obtained with cyclopentenones and γ-butenolides. © 1997 Published by Elsevier Science Ltd.

The Mukaiyama version of the Michael reaction[1] is a versatile process for the construction of carbon-carbon bonds and is frequently used to obtain 1,5-dicarbonyl compounds. In 1974 Mukaiyama and coworkers[2] found that silyl enolethers and silyl keteneacetals add to enones and enoates at low temperatures, in the presence of certain Lewis acids (LA). The reaction occurs under formally acidic conditions, and shows a very high level of 1,4 regioselectivity. The process has been thoroughly investigated and a great number of LA promoters have been developed and employed in stoichiometric or catalytic amounts.[1,3]

In general, the reaction between prochiral donors and / or acceptors is only moderately diastereoselective. In most instances the configuration of the enol silane has only a limited effect, if any, on the stereochemistry of the process. The reaction of ketone silyl enol ethers is generally *anti* selective.[1,4] On the contrary, the addition of ester silyl keteneacetals leads to *syn* products with moderate diastereomeric excess (d.e.).[1,4] The stereoselectivity observed with thiolester keteneacetals is usually higher: good levels of *anti* selectivity have been achieved with acyclic acceptors,[1] whereas, in some examples, exceptionally high *syn* selectivity has been reported with properly substituted cyclic acceptors.[5] The unsatisfactory stereochemical outcome observed with silyl keteneacetals was proven to result from the coexistence of two quite distinct processes: a LA - mediated conjugate addition and a Single Electron Transfer (SET) process, which is stereorandom.[6] The suppression of this second path may be achieved by an appropriate choice of (bulky) protective groups on both reactants, and by the use of a strongly oxophilic LA. Under these conditions, an excellent *syn* selectivity can be obtained in the addition of silyl keteneacetals to α,β–unsaturated ketones.[6]

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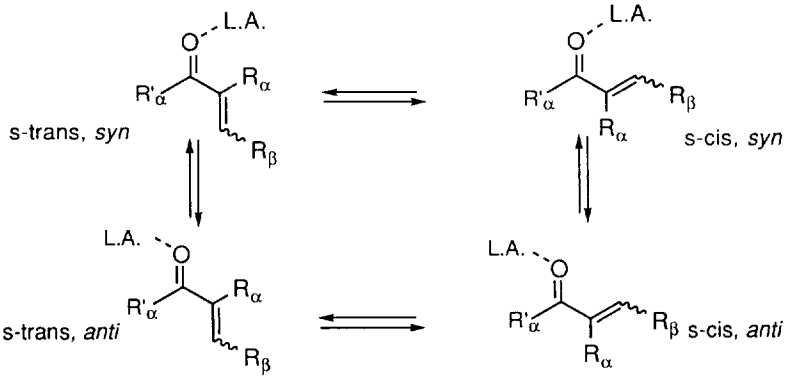
# *This paper is dedicated to Prof. D. Seebach on his 60th birthday.*

We are currently interested in the enantioselective version of the Mukaiyama-Michael reaction between achiral donors and acceptors, promoted by chiral LA.[7] The enantioselective Michael reaction of malonate-type enolates has been described using catalytic amounts of various chiral additives.[8] Tin(II) enolates of dithioacetates give moderate to high enantioselectivity in the addition to benzalacetone in the presence of a chiral diamine and TMSOTf.[9a,b] Prior to our studies,[10] only two examples had been reported in the literature concerning the enantioselective Mukaiyama-Michael reaction mediated by chiral promoters not covalently bound to the reactants.[9c,d] These reactions are catalytic in the LA and can afford good enantiomeric excess, but they both are restricted to the use of thio- or dithio-acetates. However, so far no general enantioselective methods have been described for simple ester enolates.

Thus much less progresses have been made toward the control of enantioselectivity by means of chiral LA in the Mukaiyama-Michael reaction than in the LA promoted aldol and Diels - Alder reactions. Indeed, the stereocontrol of the conjugate addition reaction is complicated by various factors. First of all, during a conjugate addition the LA is further away from the site of formation of the new stereocenters, compared to the LA promoted aldol and Diels - Alder reactions. Furthermore, the intermediate acceptor - LA complex (and the likely extended chain open TS) are highly flexible. The most relevant degrees of conformational freedom reside in the relative disposition of the C=O and C=C bonds, that can be either s-cis or s-trans, and in the mode of coordination of the LA to the carbonyl group, which can be either *syn* or *anti* with respect to the unsaturated residue (**Scheme 1**).



Scheme 1. The four conformers of LA-coordinated α,β-unsaturated compounds.

In the absence of external LA, the s-cis/s-trans equilibrium of unsaturated carbonyl compounds, depends on their substitution pattern.[11] The s-trans conformer prevails when $R_\alpha \neq H$, the s-cis prevails for Z olefins and when R'_α is bulky. In all other cases, conformational mixtures are observed. Coordination of a LA is generally found to stabilize the s-trans conformation, at least for unsaturated esters.[11] The *syn* coordination of the LA to the double bond of an enone may be imposed by the presence of a bulky carbonyl substituent R'_α (Figure 1, R'_α=tBu, $NAlk_2$ etc).[12] *Syn* coordination is also favored in the case of enoates (R'_α=OR).[12]

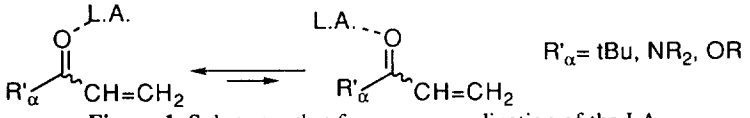


Figure 1. Substrates that favor *syn* coordination of the LA

These considerations guided us to the selection of substrates in which the above-mentioned degrees of freedom would be restricted. The s-cis / s-trans equilibrium can be blocked by working with appropriate cyclic enones. If these structures possess also a second functionality capable of complexation with a bidentate chiral LA, the formation of conformationally rigid complexes can be achieved, and eventually lead to a more efficient control of the enantioselectivity in the 1,4 addition reactions. To this end the substrates shown in **Figure 2** were chosen as appropriate models. They are expected to form complexes of the s-trans, *syn* type with bidentate Lewis acids. In this paper the results of L*$TiCl_2$ promoted Mukaiyama - Michael additions to these substrates are reported.[10a]

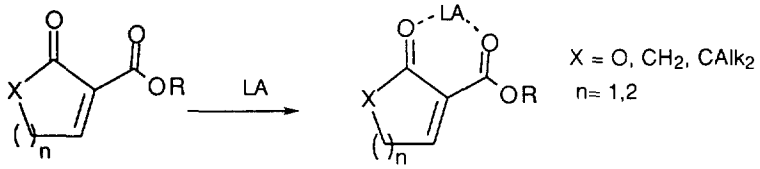
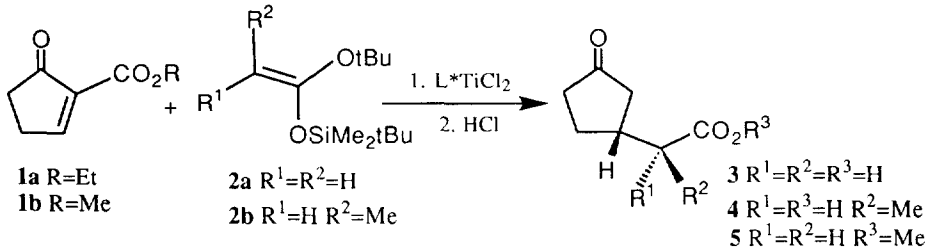


Figure 2. Conformationally restricted substrates for the Mukaiyama - Michael reaction.

Results and discussion.

The 2-carboxycyclopentenones **1**[13] and the silyl keteneacetals **2**[14] were synthesized following literature procedures. The addition reactions (**Scheme 2**) were conducted at -78° in CH_2Cl_2 solutions, and in the presence of 1 mol equiv of the chiral LA L*$TiCl_2$. A list of the ligands **7-9** used is given in **Chart 1.** The TADDOL ligands **8a-g** were synthesized following literature procedures.[15]

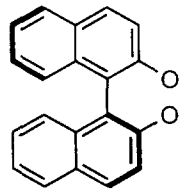


1a R=Et
1b R=Me

2a R^1=R^2=H
2b R^1=H R^2=Me

3 R^1=R^2=R^3=H
4 R^1=R^3=H R^2=Me
5 R^1=R^2=H R^3=Me
6 R^1=H R^2=R^3=Me

Scheme 2. Addition of **2** to **1** promoted by L*$TiCl_2$.



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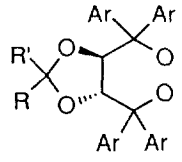

8 **a** R = R' = Me, Ar = Ph
b R = R'= Me, Ar = α–naphthyl
c R = R'= Me, Ar = β–naphthyl
d R = R'= Ph , Ar = Ph
e R = R'= Me, Ar = 2,5-xylyl
f R = R'= Me, Ar = 3,5-xylyl
g R = Ph, R' = H, Ar = Ph

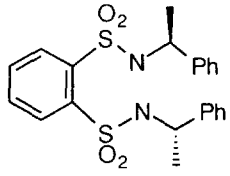

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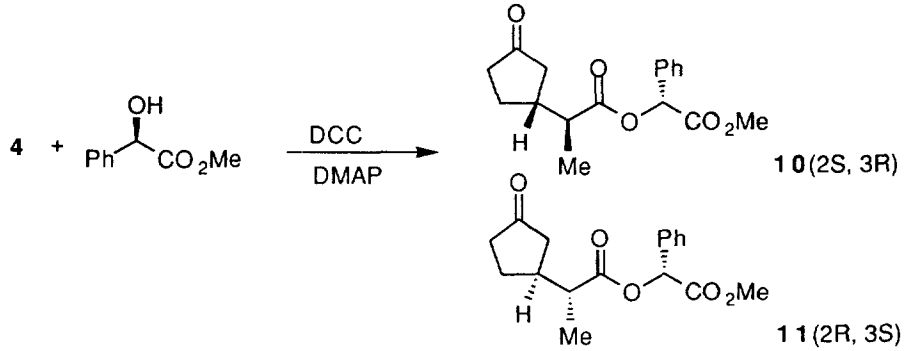
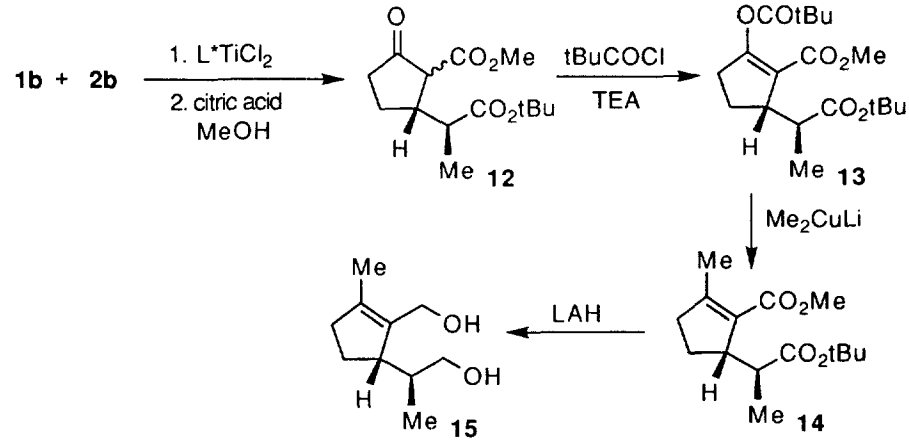
Chart 1. The L* ligands.

The complexes were prepared from equimolar solutions of the bidentate ligand L* and of $(iPrO)_2TiCl_2$, either in the presence of 4Å molecular sieves (method A),[16] or by removing iPrOH by azeotropic distillation with toluene (method B). After the Michael addition, the TADDOL-type ligands **8** were recovered by precipitation with hexane. The filtrates were treated with refluxing HCl and the acids **3** and **4** were isolated by flash chromatography. Treatment with diazomethane in Et_2O yielded the corresponding methyl esters **5** and **6**. The e.e. of **5** was then determined by ^{1}H-NMR in the presence of Eu(hfc)$_3$, and the d.e. of **6** was determined by capillary GC. The e.e. of the propionate derived acid **4** was determined after reaction with (R)-methylmandelate[17] (**Scheme 3**) by integration of the benzyl proton signals of **10** and **11**.



Scheme 3. Determination of the e.e. of **4**.

The absolute configuration of **3** was determined to be (R) by comparison of its optical rotation with literature data.[18] The *syn* configuration was assigned to the propionate-derived acid **4** on the basis of its ^{13}C NMR spectra.[19] The (2S, 3S) absolute configuration was determined by transforming the condensation product into the known (+)-(3S, 8S)-isodehydroiridodiol **15**[20] according to **Scheme 4**. Thus the crude reaction product, which consists of the ketoester **12** and the corresponding silyl enol ether, was treated with citric acid in MeOH[21] followed by tBuCOCl/TEA to give the enolpivalate **13**.[22] Reaction with Me_2CuLi,[22] followed by LAH reduction of **14** gave (3S, 8S)-isodehydroiridodiol **15**.[20]



Scheme 4. Determination of the absolute configuration of **4**. Synthesis of (S,S)-isodehydroiridodiol.

A preliminary set of experiments were conducted on the ethyl ester **1a** (**Scheme 2**), and the results are collected in **Table 1**.

Table 1. Additions of **2a-b** to **1a** promoted by L*$TiCl_2$ (L*=**8a**).[a]

Entry	Reagent	L*	Solvent	Complex Formation[b]	Product	Yield (%)	*syn:anti*[c]	e.e. (%)
1	**2a**	**7**	CH_2Cl_2	A	**3**	9		5[d]
2	**2a**	**9**	CH_2Cl_2	A	=	=		=
3	**2a**	**8a**	CH_2Cl_2	A	**3**	25		10[d]
4	**2a**	**8a**	CH_2Cl_2	B	**3**	34		8[d]
5	**2b**	**8a**	CH_2Cl_2	A	**4**	28	11:1	11[e]
6	**2b**	**8a**	CH_2Cl_2	f	**4**	40		7[e]
7	**2b**	**8a**	toluene	A	**4**	34	26:1	17[e]
8	**2b**	**8a**	EtCN	A	**4**	20		12[e]
9	**2b**	**8a**	$EtNO_2$[g]	A	4	13	18:1	0[e]

a. Reactions in the indicated solvent, at -78°C, 5h, using 2 mol equiv of **2**. b. A: 100 mg of 4Å molecular sieves / 0.1 mmol of $TiCl_2(OiPr)_2$ 1M in CH_2Cl_2. B: azeotropic distillation of iPrOH/toluene. c. determined by GC of methyl ester **6**. d. Determined by Eu(hfc)$_3$ NMR of **5**. e. Determined as **10**: **11** ratio after reaction with (R)-methyl mandelate. f. No sieves added. g. Reaction run at -20°C.

Using the chiral complexes obtained from binaphthol **7** or the bis-sulfonamide **9** in CH_2Cl_2 little or no reaction occurred (**Table 1**, Entries 1 and 2) between **1a** and the acetate equivalent **2a**. In the presence of the TADDOL ligand **8a** the same reaction occurs with low yields and enantioselectivity (Entry 3), which are not dramatically improved by azeotropic removal of iPrOH from the promoter before the addition (Entry 4). The same results are obtained in the addition of propionate **2b** to **1a** (Entry 5). However, this reaction displays an interesting diastereoselectivity (*syn:anti* 11:1). A significant yield improvement (up to 40%) and an almost twofold reduction of the e.e. are obtained if the molecular sieves are not introduced in the reaction mixture (Entry 6). This is likely due to incomplete formation of the TADDOLate complex and thus to the presence of residual $Cl_2Ti(OiPr)_2$, which is a better promoter for the Mukaiyama-Michael reaction than **8a**$TiCl_2$.[23] Toluene (Entry 7) appears to be the solvent of choice for the condensation of **1a** and **2b**, yielding **4** with 26:1 diastereoselectivity and 17% e.e. No improvement was achieved in EtCN (Entry 8) or $CH_3CH_2NO_2$ (Entry 9).

The methyl ester **1b** proved to be a much better substrate than the ethyl ester **1a** for the condensation with **2b** (**Table 2**).

Table 2. Additions of **2b** to **1b** promoted by L*TiX_2.[a]

Entry	L*	X	Solvent	Yields[b] (%)	*syn:anti*[c]	e.e.[d] (%)
1	**7**	Cl	toluene	16		15
2	**8a**	Cl	toluene	38	31:1	43
3	**8a**	Br	toluene	27		36
4	**8a**	Cl	Et_2O	15		33
5	**8a**	Cl	CH_2Cl_2	35		43
6	**8b**	Cl	toluene	50	41:1	47
7	**8b**	Cl	tol./CH_2Cl_2[e]	32		39
8	**8c**	Cl	toluene	10		27
9	**8d**	Cl	toluene	35		25
10	**8e**	Cl	toluene	18		17
11	**8f**	Cl	toluene	37		16
12	**8g**	Cl	toluene	48	19:1	4

a. Reactions run for 5h in the indicated solvent, at -78 °C, using 2 eq. of **2b**. Catalyst formed by method A. b. Yields of ketoacid **4**. c. Determined by GC of methyl ester **6**. Where the value is not indicated, a single isomer was revealed by 200 MHz ^{1}H-NMR spectroscopy. d. Determined as **10**:**11** ratio by ^{1}H-NMR spectroscopy. e. 1:1 ratio

Thus the reaction between **2b** and **1b** promoted by **8a**-$TiCl_2$ (**Table 2**, Entry 2) occurs in toluene to give a 31:1 diastereomeric ratio and 43% e.e, which represents an almost threefold increase over the reaction with **1a** (**Table 1**, Entry 7). The same selectivity is achieved in CH_2Cl_2 (**Table 2**, Entry 5). The use of **8a**-$TiBr_2$ as a promoter (**Table 2**, Entry 3) leads to lower yields, possibly due to starting material decomposition with this stronger LA. Of the various TADDOLs tried as ligands, **8b** (Ar=α-naphthyl) gave the best results, leading to **4** with 50% overall yields, 41:1 diastereomeric ratio and 47% enantioselectivity (**Table 2**, Entry 6). All other variations were detrimental. It is worth noting that a dimethyl substitution in the dioxolane moiety appears to be superior to a diphenyl substitution (compare Entries 2 and 9), and that all C_2 symmetric ligands **7** and **8a-f** gave better e.e.s than the C_1 symmetric TADDOL **8g** (Entry 12).

The scope of the method was explored by studying the reactions of substrates **16-20** (**Chart 2**).

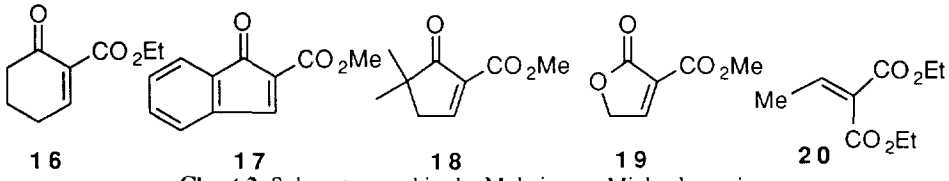
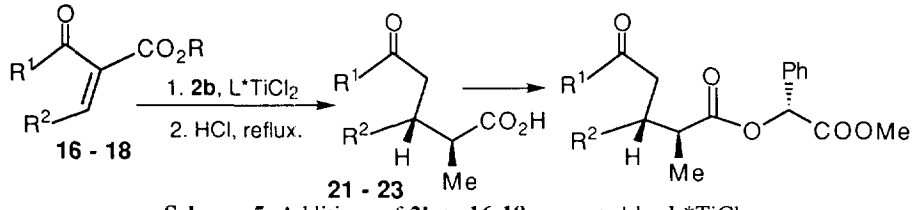


Chart 2. Substrates used in the Mukaiyama-Michael reaction.

The results with the ketoesters **16-18** are summarized in **Table 3.** In all cases, the crude condensation mixtures were decarboxylated with refluxing HCl, and yields and d.e. were measured on the resulting acids **21-23**, whereas the e.e. were determined by ^{1}H-NMR analysis of the mandelates (**Scheme 5**).



Scheme 5. Additions of **2b** to **16-18** promoted by L*$TiCl_2$.

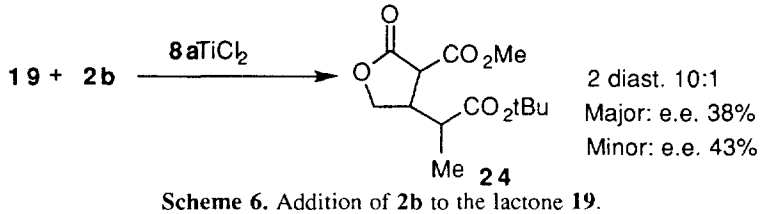
Table 3. Additions of **2b** to **16-18** promoted by L*$TiCl_2$.[a]

Entry	Substrate	L*	Product	Yields (%)b	*syn*:*anti*[c]	e.e. (%)[d]
1	**16**	**8b**	**21**	36	11:1	0
2	**17**	**8a**	**22**	11	3:1	9
3	**17**[e]	**8a**	**22**	25	4:1	20
4	**18**	**8a**	**23**	54	59:1[f]	22
5	**18**	**8b**	**23**	33	g	21

a. Reactions run in toluene for 5h, at -78°C. b. Determined after decarboxylation. c. Unless otherwise noted, d.e.s were determined by ^{13}C-NMR of the acids. d. Determined by ^{1}H-NMR of the mandelates. e. Reaction run in the presence of 1.6 eq of 1,4-dinitrobenzene. f. Determined by GC of the methyl ester. g. Single isomer by 200 MHz ^{1}H-NMR.

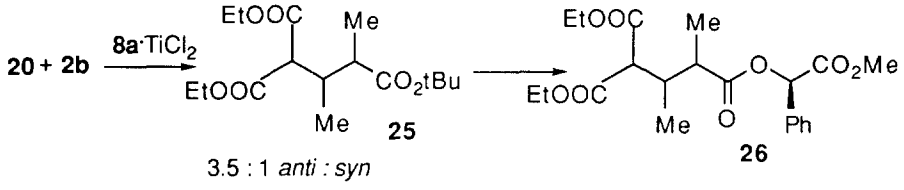
Surprisingly, the addition to the cyclohexenone **16** (Entry 1) did not afford any enantio selectivity, and led to the racemic *syn* adduct.[24] Reaction of the indenone **17** occurred with low yields and selectivity (Entry 2), and could be only moderately improved by suppressing the SET mechanism[6] with the addition of 1,4-dinitrobenzene (Entry 3).[25] The 5,5-dimethyl cyclopentenone **18** reacts with good yields and very high *syn* diastereoselectivity, but the e.e.s are low, using either **8a** (Entry 4) or **8b** (Entry 5) as ligands.[26]

The reaction of **2b** with **19** promoted by **8a**·$TiCl_2$ affords **24** as a 10:1 mixture of two of the four possible diastereoisomers[27] (**Scheme 6**). Eu(hfc)$_3$ spectroscopy of **24** established a 38% e.e for the major isomer and a 43% e.e. for the minor one.



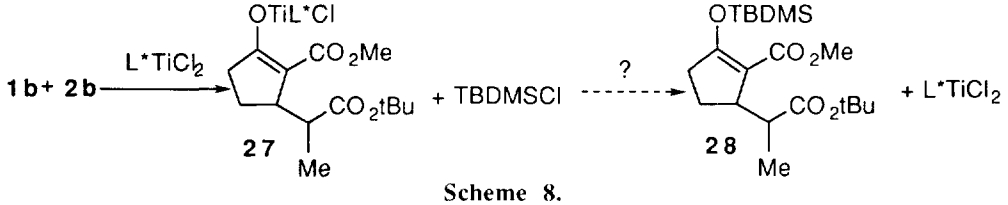
Scheme 6. Addition of **2b** to the lactone **19**.

A lower selectivity was observed with the acyclic substrate **20** (**Scheme 7**). In this case the major product is ***anti*** - **25**[28], which is obtained with 12% e.e., as measured by ^{1}H-NMR spectroscopy of the mandelates **26.**



Scheme 7. Addition of **2b** to the ester **20**.

Finally, an attempt was made to promote the reaction using catalytic quantities of the chiral LA. However, in the presence of 20% **8a** $TiCl_2$ the addition of **2b** to **1b** takes place with only 10% yield (*vs.* 50% yield in the stoichiometric reaction. **Table 2**, Entry 6). Assuming that the initial products of the condensation are the Ti enolate **27** and TBDMSCl (**Scheme 8**), this result suggests that either **27** can not react with TBDMSCl to form the silyl enol ether **28** and recycle the catalyst, or that the Si/Ti exchange does take place, but the LA is then strongly coordinated by the reaction product and is not available for further reaction.[29]



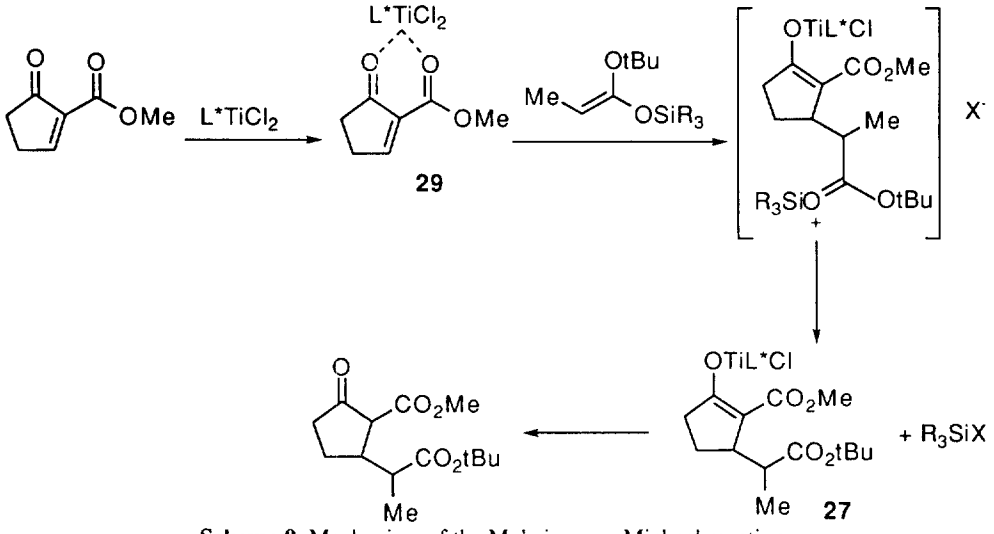
Scheme 8.

An interesting implication of the above considerations is that very likely TBDMSCl is not a promoter of the conjugate addition of **2b** to **1b**. Indeed, when **1b** and **2b** were mixed in the presence of 1 equiv of TBDMSCl for 5h at -78°C, no reaction occured. Silicon promoted processes have been found to compete effectively with titanium promoted ones in the Mukaiyama-aldol reaction,[30] and are often suspected to depress the enantioselectivity of reactions catalyzed by chiral LA. The foregoing result shows that the modest enantioselectivity observed in the TiTADDOLate promoted Mukaiyama-Michael addition is not a result of competition by achiral Si based promoters[31] and suggests that the silicon promoted pathways can be

suppressed, possibly also in other reactions, by fine tuning the silicon substituents on the enolether, and the LA counterion.[32]

Reaction Mechanism.

The Mukaiyama-Michael reaction is generally accepted to occur *via* nucleophilic addition of the enolsilane to the enone- LA complex, according to **Scheme 9.**[1]



Scheme 9. Mechanism of the Mukaiyama - Michael reaction.

Stereorandom reactions *via* a SET mechanism have also been observed.[6] The SET path can be inhibited by a proper choice of oxophilic promoters and bulky substituents on both reaction partners.[6c] The combination of the oxophilic titanium LA **8a**·$TiCl_2$ and the sterically crowded ketene acetal **2b** results in highly diastereoselective additions to substrates **1**, **16**, and **18-20**. Addition of 1,4-dinitrobenzene as single electron trap[25] has no effect on the reaction beetween **1b** and **2b**, and only a limited effect on the addition of **2b** to the indenone **17** (compare Entries 2 and 3 in **Table 3**). Thus we can safely rule out the electron transfer mechanism as a major pathway for our reactions.

A second possible alternative to the nucleophilic addition pathway proposed in **Scheme 9** is the formation of a titanium enolate *via* Si/Ti exchange prior to the conjugate addition. Although NMR studies suggest that the titanium promoted Mukaiyama reaction takes place faster than ligand metathesis,[33] formation of titanium enolates from enolsilanes was shown to occur in a few cases.[34] To assess this point, the addition of **2b** to **18**[35] promoted by **8a**·$TiCl_2$ was carried out varying the mode of addition of the reagents (**Table 4**). Yields, e.e. and diastereomeric ratios are essentially the same either when the enone is precomplexed with the LA for 10 min at -78°C before the addition of **2b** (**Table 4**, Entry 1; 54% y., 22% e.e.), or when **2b** is precomplexed with the LA before adding the enone (**Table 4**, Entry 3; 45% y., 21% e.e.). A very similar result is also obtained premixing **18** and **2b** and adding **8a**·$TiCl_2$ at -78°C (**Table 4**, Entry 5; 59% y.; 19% e.e.). Forcing the reaction between **2b** and the LA by increasing the temperature to 0°C before adding the enone (**Table 4**, Entry 4) leads to an unreactive species. Taken together these results suggest that the real intermediate in this reaction is the enone/LA complex, rather than a titanium enolate.[36]

Table 4. Various modes of addition in the reaction between **2b** and **18**.[a]

Entry	Reaction Conditions	Yields of **23** (%)	*syn:anti*	e.e. (%)
1	**18**+**8a**$TiCl_2$ 10', -78°C then **2b**	54	59:1	22
2	**18**+**8a**$TiCl_2$ 1h, -78°C then **2b**	37	42:1	21
3	**2b**+**8a**$TiCl_2$ 10', -78°C then **18**	45	b	21
4	**2b**+**8a**$TiCl_2$, -78°C --> 0°C then **18**	no rxn.		
5	**8a**$TiCl_2$, -78°C then (**2b** + **18**)	59	b	19

a. All reactions were run for 5h at -78°C. b. Single isomer by ^1H NMR

The origin of enantioselectivity and the nature of the active species in TADDOLate Lewis acid catalysis has recently been the subject of much discussion.[37] Ti·TADDOL complexes of acryloyloxazolidinones have been observed both in the solid state[38] and in solution.[39] The X-ray structure of the cinnamoyloxazolidinone complex[38] is octahedral, with the chiral diol and the alkene in the equatorial plane, and the two chloride ligands in the axial position (Figure 3, structure **A**, R=Ph). This structure does not show any obvious discrimination of the alkene enantiofaces and it has been argued that it represents the most stable, but not the most reactive species in solution.[39] Indeed, three rapidly interconverting diastereomeric adducts (out of the five possible ones) have been observed in low temperature NMR studies of the heptenoyloxazolidinone complex (Figure 3, R=Bu).[39a] The most abundant species is complex **A.** The two less abundant species have been assigned structures **B** and **C**, and they were shown to be consumed twice as fast as **A** in the Diels-Alder reaction with a highly reactive diene.[39b] Addition to complex **C** accounts for the observed selectivity in the cycloaddition. More recently, Seebach has suggested that a cationic complex of structure **D** could best explain the steric course of TADDOL·$TiCl_2$ catalyzed Diels-Alder reactions and account for the observed non-linearity of ee%.[37]

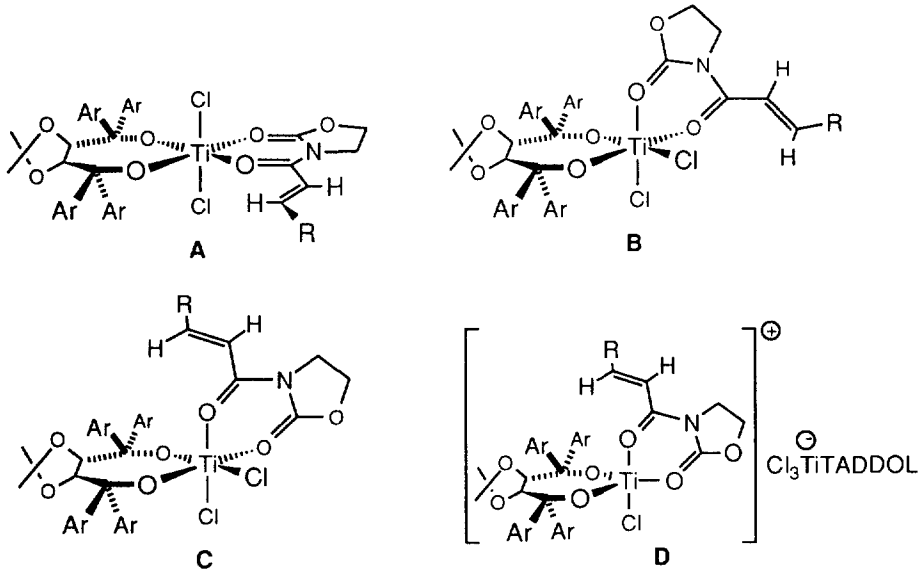


Figure 3. Proposed structures of the reactive TADDOL·$TiCl_2$ complexes of acryloyloxazolidinones (From *ref 37-40*).

The different degrees of reactivity of the complexes **A-C** can be rationalized by comparing the electron donating properties and the relative positions of ligands in the coordination sphere of titanium.[40] In the most abundant complex, the enone is bound opposite to the strongest electron donor, the alkoxide, and thus it experiences the least LA activation. In the less abundant adducts **B** and **C** the alkene is coordinated opposite to one alkoxy ligand and one chlorine ligand, which is a weaker electron donor than the alkoxide. This results in a stronger activation in **B** and **C** compared to **A**. The greater deshielding of the β carbon observed in the ^{13}C-NMR of **B** and **C** compared to **A** is in agreement with the aforementioned hypothesis.[39]

Analogous considerations on the complex between **1b** and **8a**·$TiCl_2$ lead to the two diasteroisomeric structures **E** and **F** as the most likely reactive intermediates in the Mukaiyama-Michael reaction. Both structures feature the more basic ester carbonyl[41] in the apical position, trans to one chlorine atom. The close proximity of this position to one of the pseudo-axial TADDOL substituents explains the striking sensitivity of the reaction to the size of the ester group (compare **Table 1** and **Table 2**). In structure **E** the enone is coordinated proximal to a pseudoequatorial phenyl group on the cyclooxatitanate, whereas in **F** the enone is proximal to a pseudoaxial substituent. Attack on the less hindered *Re* face of the enone in complex **E** accounts for the enantioselectivity observed in the addition of **2b**.

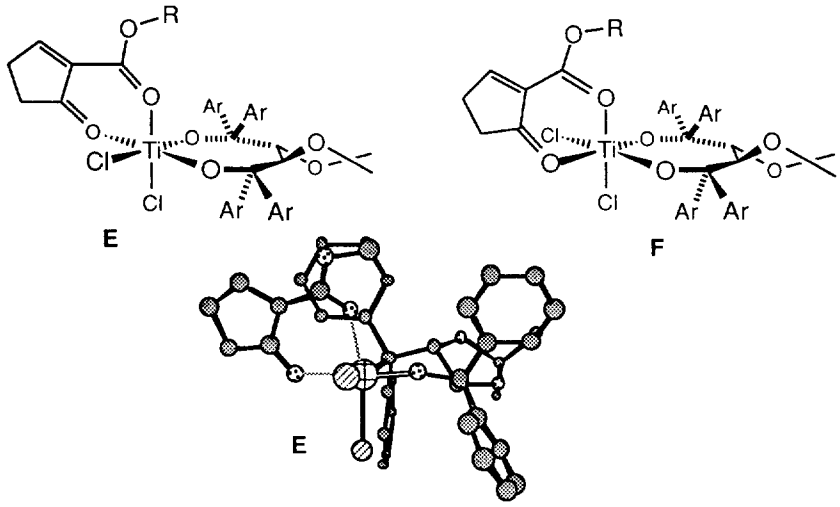


Figure 4. Reactive diastereomers of the complex between **1b** and **8a**·$TiCl_2$.

In conclusion, the Mukaiyama-Michael addition of propionate silylketene acetals to bisactivated olefins promoted by $TiCl_2$TADDOLates appears to be a viable route to the synthesis of 1,5-dicarbonyl compounds with good to excellent diastereoselectivity and moderate e.e.. Although its synthetic scope appears to be limited to cyclopentenones and γ-butenolides, this is the first method which allows the acid catalyzed conjugate addition of simple propionates in excellent d.e. and fair e.e. in the presence of a chiral activator.

Experimental.

^1H-NMR spectra were recorded at 200 or 300 MHz and ^{13}C-NMR spectra were recorded at 50 and 75 MHz. Chemical shifts are reported in ppm relative to tetramethylsilane; coupling constants are reported in Hz. All

solvents were dried before use: THF and Et_2O using Na-benzophenone; toluene using Na; CH_2Cl_2, triethylamine, diisopropylamine and disopropylethylamine using CaH_2.

Synthesis of 2-carbomethoxyindanone.[42] 1 g (7.6 mmol, 1 eq.) of indanone is dissolved in 17 ml. of DMSO and 2.3 ml. of a 30% NaOH solution are added. The yellow solution turns brown. After cooling at 5°C, 483 µl of CS_2 (8.0 mmol, 1.05 eq.) and 2 ml. of Me_2SO_4 (21 mmol, 2.7 eq.) are added. The solution is stirred at 5°C for 1h, then NaOH (3.0 g, 7.6 mmol, 1 eq.) in MeOH (30 ml.) is added. The resulting solution is warmed at 50°C for 1h, then 10% HCl (30 ml) is added, and the reaction is extracted with AcOEt. The organic phase is washed with brine and dried with Na_2SO_4. The solvent is evaporated and the resulting brown solid is purified by flash chromatography (benzene, followed by 8:2 hexane/AcOEt) to yield 821 mg (57%) of pure **17**.
^{1}H-NMR ($CDCL_3$, 200 MHz): 3.32-3.68 (m, 2H); 3.72-3.80 (m, 1H); 3.82 (s, 3H); 7.30-7.85 (m, 4H).

Synthesis of 5,5-dimethyl-2-carbomethoxycyclopentanone.[43] 1.12 g of 60% NaH (27.9 mmol, 3.1 eq.) were suspended in dry THF (6 ml) and 2.1 g of dimethylcarbonate (22.3 mmol, 2.5 eq.) are added. The suspension is warmed to reflux and a few drops of 2,2-dimethylcyclopentanone are added. After 2 min a 35% suspension of KH in mineral oil is quickly added (33.9 mg of KH, 0.8 mmol, 0.095 eq.), then the remaining ketone (1.000 g, 8.9 mmol, 1 eq.) in 2 ml of dry THF is added dropwise during 15 min. The solution is refluxed for 1h, then cooled to 0°C and the reaction is quenched with 3M AcOH, followed by brine. The mixture is extracted with $CHCl_3$, the organic layer dried with Na_2SO_4 and the solvent evaporated at reduced pressure and at room temperature. The product is purified by distillation (b.p. 140°C, 15 mmHg) to yield 894 mg (59%) of 5,5-dimethyl-2-carbomethoxycyclopentanone.
^{1}H-NMR ($CDCl_3$, 200 MHz): 1.10 (s, 3H); 1.14 (s, 3H); 1.65-2.10 (m, 2H); 2.10-2.46 (m, 2H); 3.28 (t, J = 8.6, 1H); 3.75 (s, 3H).

Synthesis of the unsaturated β-ketoesters.[13] A solution of 2.69 mmol (1.05 eq) of PhSeCl in 50 ml of CH_2Cl_2 is cooled to 0°C and 230 µl of pyridine (2.82 mmol, 1.1 eq.) are added. After 15 min, 2.56 mmol (1 eq.) of the ß-ketoester in 6 ml of dry CH_2Cl_2 are added. The orange solution is stirred at 0°C until reaction completion (TLC), then extracted twice with 10% HCl (2 x 10 ml.). The organic phase is cooled to 0°C and 30% H_2O_2 (600 µl, 18 mmol, 6.9 eq.) is added in three portions, during 0.5 h and under stirring. After 10 min the clear solution is quenched with H_2O, the organic phase is washed with $NaHCO_3$ and H_2O, dried with Na_2SO_4 and the solvent evaporated. The crude reaction products are used without purification.
1a (89% yield):
^{1}H-NMR ($CDCl_3$, 200 MHz): 1.35 (t, J = 6.9, 3H); 2.52-2.60 (m, 2H); 2.70-2.80 (m, 2H); 4.30 (q, J = 6.9, 2H); 8.40 (t, J = 3.4, 1H).
1b (76% yield):
^{1}H-NMR ($CDCl_3$, 200 MHz): 2.45-2.55 (m, 2H); 2.65-2.75 (m, 2H); 3.80 (s, 3H); 8.40 (t, J = 3.1).
16 (91% yield):
^{1}H-NMR ($CDCl_3$, 200 MHz): 1.33 (t, J = 7.0, 3H); 2.06 (m, 2H); 2.55 (m, 4H); 4.27 (q, J = 7.0, 2H); 7.67 (t, J = 4.3, 1H).
17 (85% yield):
^{1}H-NMR ($CDCl_3$, 80 MHz): 3.84 (s, 3H); 7.15-7.85 (m, 4H); 8.30 (s, 1H).

18 (75% yield);
^{1}H-NMR ($CDCl_3$, 200 MHz): 1.15 (s, 6H); 2.60 (d, J = 3.6, 2H); 3.85 (s, 3H); 8.35 (t, J = 3.6).
19 (34% yield):
^{1}H-NMR ($CDCl_3$, 200 MHz): 3.90 (s, 3H); 4.97 (d, J = ca. 2.0, 2H); 8.33 (t, J = 2, 1H).

TADDOL·TiCl$_2$ Promoted Addition to Ketones 1 and 16-18: General Procedure. To a suspension of triturated 4Å molecular sieves (500 mg) and TADDOL (0.5 mmol, 1 eq) in 3 ml of dry toluene a 1M solution of $TiCl_2(OiPr)_2$ in CH_2Cl_2 (500 µl, 0.5 mmol, 1 eq) is added. The reaction is stirred for 1h at room temperature under a nitrogen atmosphere, then the mixture is cooled to -78°C, and 0.5 mmol of β–ketoester in 1 ml of toluene are added. After 5 min, a solution of **2** (1.25 mmol. 2.5 eq) in 1 ml of toluene is added dropwise. The reaction is stirred for 5h at -78°C, then quenched with H_2O or a sat. NH_4F solution and the mixture is filtered on a Celite cake. The filtrate is extracted with CH_2Cl_2, the organic phase washed with H_2O and dried with Na_2SO_4, then the solvent is evaporated. The crude reaction product is suspended in hexane and TADDOLs **8a-c** are recovered by filtration (70% average recovery). The filtrate is not purified at this stage, but directly submitted to HCl hydrolysis. Thus the crude is suspended in 3 ml of 37% HCl and refluxed for 5h, then extracted with AcOEt. The organic phase is washed with H_2O, dried with Na_2SO_4 and evaporated. The products are purified by flash chromatography (1:1 hexane:AcOEt with 0.8% AcOH)
3:
^{1}H-NMR ($CDCl_3$, 200 MHz): 1.50-2.60 (m, 9H); 7.80 (s, broad, 1H).
^{13}C-NMR ($CDCl_3$, 200 MHz): *selected signals:* 29.1; 33.1; 38.2; 44.4.
IR ($CDCl_3$): 3640-2440, 1750, 1720, 1420, 1250, 1225, 1195, 1165.
(Found C, 59.31, H, 6.98; $C_7H_{10}O_3$ requires C, 59.14, H. 7.09)
$[\alpha]_D$ = + 11.7° (*c* 1.16, $CHCl_3$) for a sample having 10% e.e, prepared as in Table 1, Entry 3.
Lit.[44] *$[\alpha]_D$ = - 116.5° (c 6.99, $CHCl_3$) for the 3S enantiomer.*
4:
^{1}H-NMR ($CDCl_3$, 200 MHz): 1.28 (d, J = 6.6, 3H); 1.50-2.56 (m, 8H); 8.70 (br. s, 1H).
^{13}C-NMR ($CDCl_3$, 200 MHz): *major isomer (syn):* 14.9; 27.0; 38.5; 39.6; 43.3; 44.1, 181, 215. *minor isomer (anti):* 15.6; 27.6; 38.6; 39.8; 42.5.
(Found C, 61.25, H, 7.61; $C_8H_{12}O_3$ requires C, 61.52, H. 7.74)
$[\alpha]_D$ = -45.2° (*c* = 0.6, $CHCl_3$) for a sample having 43% e.e.
21:
^{1}H-NMR ($CDCl_3$, 200 MHz): 1.20 (d, J = 6.7, 3H); 1.30-2.55 (m, 10H); 7.50 (br.s, 1H).
^{13}C-NMR ($CDCl_3$, 200 MHz): *major (syn):* 13.6; 24.8; 27.8; 41.0; 44.3; 45.5; 180.8; 193.9.
minor (anti): 13.5; 41.1; 44.5.
22:
^{1}H-NMR ($CDCl_3$, 200 MHz): *major:* 1.22 (d, J = 7.2, 3H); 2.52-3.23 (m, 3H); 3.85 (m, 1H); 7.20-7.35 (m, 4H). *minor:* 0.94 (d); 3.98 (m).
23:
^{1}H-NMR ($CDCl_3$, 200 MHz): 1.05 (s, 3H); 1.12 (s, 3H); 1.26 (d, J = 6.4, 3H); 1.32-1.50 (m, 1H); 1.95-2.12 (m, 2H); 2.30-2.70 (m, 3H).
^{13}C-NMR ($CDCl_3$, 200 MHz): *major: (syn)* 14.9; 23.9; 24.1; 35.3; 42.4; 42.7; 44.7; 46.0. *minor (anti)* : 15.7.

(Found C, 65.40, H, 8.69; $C_{10}H_{16}O_3$ requires C, 65.19, H. 8.75)

TADDOL·TiCl$_2$ Promoted Addition to Esters 19 and 20: General Procedure. To a suspension of triturated 4Å molecular sieves (500 mg) and TADDOL (0.5 mmol, 1 eq) in 2 ml of dry toluene a 1M solution of $TiCl_2(OiPr)_2$ in CH_2Cl_2 (500 µl, 0.5 mmol, 1 eq) is added. The reaction is stirred for 1h at room temperature under a nitrogen atmosphere, then the mixture is cooled to -78°C, and 0.5 mmol of the ester in 1 ml of CH_2Cl_2 are added. After 5 min, a solution of **2** (1.25 mmol, 2.5 eq) in 1 ml of toluene is added dropwise. The reaction is stirred for 4h at -78°C, then quenched with H_2O and the mixture is filtered on a Celite cake. The filtrate is extracted with AcOEt, the organic phase washed with H_2O and dried with Na_2SO_4, then the solvent is evaporated. The crude reaction product is suspended in hexane and TADDOL **8a** is recovered by filtration (90% recovery). The filtrate is purified by flash chromatography

24 (52% yield, flash chromatography 7:3 hexane : AcOEt):
^{1}H-NMR ($CDCl_3$, 300 MHz): *major:* 1.17 (d, J = 7.4, 3H); 1.42 (s, 9H); 2.43 (m, 1H); 3.18 (m, 1H); 3.44 (d, J = 8.2, 1H); 3.78 (s, 3H); 4.05 (dd, J = 8.2, 1H); 4.51 (dd, J = 8.6, 1H). *minor:* 1.43 (s); 2.96 (m); 3.65 (d); 4.18 (dd); 4.42 (t).
^{13}C-NMR ($CDCl_3$, 300 MHz): *major:* 15.2; 28.5; 42.5; 42.8; 50.8; 53.6; 70.4; 82.3; 168.7; 172.3; 173.4. *minor:* 16.2; 30.2; 50.3; 71.2.
(Found C, 57.12, H, 7.27; $C_{13}H_{20}O_6$ requires C, 57.34, H. 7.40)
25 (79% yield, flash chromatography 9:1 hexane: AcOEt):
^{1}H-NMR ($CDCl_3$, 200 MHz): *major(anti):* 0.98 (d, J = 7.9, 3H); 1.08 (d, J = 7.9, 3H); 1.30 (t, J = 7.2); 1.46 (s, 9H); 2.46 (m, 1H); 2.70 (m, 1H); 3.35 (d, J = 8.7, 1H); 4.18 (q, J = 7.0, 4H). *minor (syn):* 1.00 (d); 1.18 (d); 1.32 (t); 1.54 (s); 2.40 (m); 3.50 (d); 4.08 (q).

Synthesis of the Methyl Esters 5 and 6. To a Et_2O solution of the acids **3**or **4** an ethereal solution of CH_2N_2 is added at 0°C. After 0.5h, AcOH is added to quench excess CH_2N_2 and the solvent is evaporated. The products are purified by flash chromatography (8:2 hexane : AcOEt).
5:
^{1}H-NMR ($CDCl_3$, 200 MHz): 1.45-2.70 (m, 9H); 3.70 (s, 3H).
6:
^{1}H-NMR (C_6D_6, 200 MHz): 0.88 (d, J = 6.6, 3H); 1.20-2.25 (m, 8H); 3.30 (s, 3H).
^{1}H-NMR ($CDCl_3$, 200 MHz): 1.25 (d, J = 6.6, 3H); 1.40-2.60 (m, 8H); 3.72 (s, 3H).
^{13}C-NMR ($CDCl_3$, 50 MHz): *major (syn) selected signals* 15.0; 27.1; 38.4; 39.9; 43.3; 44.3; 51.6. *minor (anti):* 15.8; 27.6; 38.5; 42.6.
G.C.: $T_{inj.}$= 200°C; 100°C 4 min; 5°C/min. to 150°C; T_r (*syn*) = 8.85; T_r (*anti*) = 8.39.
(Found C, 63.38, H, 8.29; $C_9H_{14}O_3$ requires C, 63.51, H. 8.29)

Synthesis of the Mandelates 10 and 11.[17] To a solution of 0.16 mmol (1 eq) of the acid **3** or **4** and 0.5 mg of DMAP in 1 ml of CH_2Cl_2 at -10°C, 36 mg of DCC (1.1 eq) and 29 mg (1.1 eq) of (R)-methylmandelate are added. The solution is refluxed for 3h, then DCU is filtered off. The filtrate is washed with 5% HCl and H_2O. The organic phase is dried with Na_2SO_4 and the solvent evaporated.

^{1}H-NMR (C_6D_6, 200 MHz) **10**: 0.95 (d, J = 7.0, 3H); 1.20-2.60 (m, 8H); 6.00 (s, 1H); 7.05-7.40 (m, 5H).**11** (*selected*) 1.05 (d); 6.04 (s).
^{13}C-NMR ($CDCl_3$, 200 MHz): **10** *(selected):* 14.7; 27.0; 38.4; 39.8; 43.2; 43.9; 52.5; 74.2. **11** (*selected*): 15.0; 27.0; 38.5; 40.0; 44.5; 52.9; 74.5.

Synthesis of the isodehydroiridodiol 15.

Synthesis of 13.[21,22] 280 mg of **1b** (2 mmol) were reacted with **2b**, using TADDOL **8a** as ligand, according to the general procedure, to yield 900 mg of crude that still contains ca. 30% of TADDOL. The crude is stirred for 20 min in a 1M solution of citric acid in MeOH (20 ml) at room temperature, then the solvent is evaporated, Et_2O is added and the organic phase is washed with H_2O and a 10% solution of $NaHCO_3$,and evaporated to dryness. The ketoester **12** may be purified from the TADDOL hydrolysis byproducts at this stage by flash chromatography (hexane/AcOEt 9:1, then 8:2. 205 mg of **12**, 38% yield from **1b**), but the next step is more conveniently carried out on the crude reaction mixture. Thus the crude is dissolved in 13 ml of dry DMPU and 234 µl of dry triethylamine are added. The solution is cooled to 0°C, and 207 µl of freshly distilled pivaloylchloride are added dropwise. The solution is stirred under nitrogen for 2.5 h, then quenched with phosphate buffer and diluted with Et_2O. The organic phase is washed with H_2O and dried, and the solvent is evaporated. The product is isolated by flash chromatography (85:15 Et_2O : hexane) to yield 212 mg of **13** (79% from **12**).
^{1}H-NMR ($CDCl_3$, 200 MHz): 1.02 (d, J = 7.2, 3H); 1.30 (s, 9H); 1.48 (s, 9H); 1.65-2.15 (m, 2H); 2.35-2.75 (m, 2H); 3.05 (qd, J = 7.2, J= 3.4, 1H); 3.60 (m, 1H); 3.70 (s, 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz): 10.5; 21.5; 27.6; 27.8; 33.5; 39.7; 42.0; 44.7; 51.7; 81.0; 119.6; 161.7; 164.3; 175.3; 175.6.

Synthesis of 14.[22] To a suspension of CuI (280 mg, 1.47 mmol, 2 eq.) in 4 ml.of dry Et_2O at -5°C and under a nitrogen atmosphere, MeLi is added (2.1 ml of a 1.6 M solution, 2.95 mmol, 4 eq). The resulting clear solution is cooled to -78°C, **13** is added (261.0 mg, 0.74 mmol, 1 eq.), and the reaction stirred for 30 min at this temperature then for 1.5 h at room temperature. The reaction is quenched with $NH_4Cl.NH_3$ buffer (pH = 8-9), the product is extracted with Et_2O, and the organic phase is repeatedly washed with the buffer, then with H_2O. The product is isolated by flash chromatography (88:12 hexane : Et_2O) to yield 87 mg of **14** (44%):
^{1}H-NMR ($CDCl_3$, 200 MHz): 0.88 (d, J = 7.0, 3H); 1.45 (s, 9H); 1.60-2.10 (m, 2H); 2.10 (d, J = 1.5, 3H); 2.35-2.60 (m, 2H); 3.00 (qd, J = 7.0, J= 3.2, 1H); 3.60 (m, 1H); 3.75 (s, 3H).
^{13}C-NMR ($CDCl_3$, 50 MHz): 9.8; 16.4; 22.9; 28.0; 39.9; 41.5; 47.8; 50.8; 79.7; 127.9; 157.4; 166.2; 175.0.
$[\alpha]_D$ = - 13.4° (*c* 1, $CHCl_3$).

Synthesis of 15.[20] To a suspension of $LiAlH_4$ (24 mg, 0.63 mmol, 2.6 eq.) in dry Et_2O (2.5 ml) a solution of **14** (65 mg, 0.24 mmol, 1 eq.) in dry Et_2O (2 ml) is added dropwise at 0°C. The mixture is stirred at room temperature under nitrogen for 30 min, then the reaction is quenched by adding 24 µl of H_2O, 24 µl of 15% NaOH and 48 µl of H_2O. The resulting suspension is filtered washing with Et_2O, the filtrate dried with Na_2SO_4 and evaporated. The diol is isolated by flash chromatography (15:85 hexane :AcOEt) to yield 37 mg of **15** (90%).

^{1}H-NMR ($CDCl_3$, 200 MHz): 0.73 (d, J = 7.2, 3H); 1.50-1.70 (m, 1H); 1.72 (d, J = 1.1, 3H); 1.72-1.93 (m, 1H); 2.03 (br. m, exch.); 2.28 (br. t, J = 7.8, 2H); 3.05-3.20 (br m, 1H); 3.52-3.55 (m, 2H); 4.06-4.30 (AB system , 2H, J_{AB} = 11.7).
^{13}C-NMR ($CDCl_3$, 50 MHz): 10.9; 14.0; 21.8; 36.5; 37.9; 45.8; 57.3; 67.0; 135.2; 137.3.
$[\alpha]_D$ = + 5.2° (*c* = 0.76, $CHCl_3$) (lit.[20] for (3R, 8R) = - 15.3° (*c* 0.78, $CHCl_3$)).

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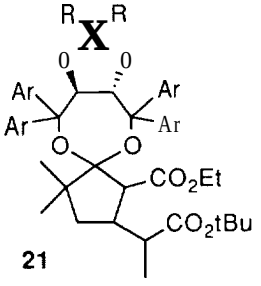

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27. Although the configuration of these compounds was not rigorously established they are likely to be the cis and trans isomers on the cyclopentenone ring, since the reaction of 19 with the acetate equivalent **2a** also gives two isomers in 6: 1 ratio.

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complex. To rule out the intervention of such acidic species, the addition of **2b** to **1b** was carried out using 1 equiv of **8a**·$TiCl_2$ in the presence of 1 equiv of DIPEA, or filtering off the molecular sieves immediately after the formation of the Ti TADDOLate. In both cases the e.e. of the product was unaffected.

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