Siamyl Glyoxylate as an Efficient Enophile in the Lewis Acid Mediated Glyoxylate Ene-Reaction with Allylic Ethers. Application to the Synthesis of a Taxol A-Ring Subunit

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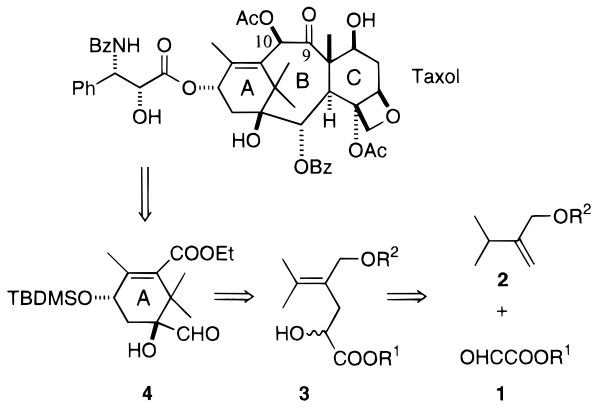
In contrast to other simple alkyl glyoxylates, siamyl glyoxylate (**1a**) proved to be an effective enophile in the glyoxylate ene-reaction with the allylic ether **2a**, which we earlier used for the synthesis of the A-ring subunit of taxol.

Introduction

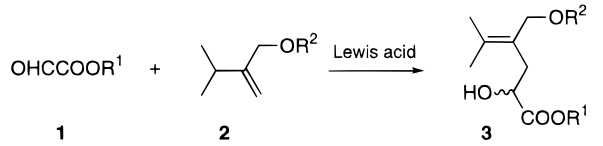
The thermal and Lewis acid induced glyoxylate ene reaction was introduced more than 30 years ago by Klimova and Arbuzov *et al.*[1−6] and was further developed by several research groups (Achmatowicz et al.,[7] Snider et al.,[8,9] Whitesell et al.,[10] and Mikami *et al.*[11,12]). In particular, the asymmetric induction achieved by using chiral glyoxylate esters[7,10,13−15] and the catalysis with BINOL−Lewis acid complexes developed by Mikami *et al.*[11,12] were major achievements. In our efforts to synthesize the taxol A-ring building block **4** (Scheme 1), we previously used the $SnCl_4$-catalyzed asymmetric ene reaction of 8-phenylmenthyl glyoxylate **1** (R^1 = (−)-8-phenylmenthyl) and the ene-component **2a** (R^2 = PMB).[16] This reaction resulted in a high yield of the ene-product **3** with a high enantiomeric purity (>98% ee).

There were, however, several drawbacks (to be discussed below), and the need for larger amounts of precursor **3** required a more suitable method. We therefore abandoned the asymmetric ene reaction and instead used the $(iPrO)_2TiCl_2$-catalyzed reaction of the easily available **1d** and **2a** (Scheme 2) to produce racemic **3d**. Ethyl glyoxylate **1d** was used in 5 molar excess over **2a**. Relatively good yields of **3d** were obtained in 1-g scales but the yields dropped when the scale was increased. In one such large scale experiment "catalyzed" by 2 equiv of $(iPrO)_2TiCl_2$ we obtained 40 g (40%) of **3d**. This amount of material lasted for some time. To our dismay we could not repeat this reaction with a reasonable accuracy at a later date. A large number of experiments were run applying many different conditions, but, statistically, less than one out of 10 experiments were successful i.e., gave yields of up to 40%. In the other nine experiments there was no conversion of the allylic ether. We therefore decided to further investigate this reaction, and we here report the successful solution to this problem by using siamyl glyoxylate.

Scheme 1. Partial Retrosynthetic Scheme for the Synthesis of Taxol



Scheme 2



Results and Discussion

Lewis Acids. A number of standard Lewis acids such as $TiCl_4$, $SnCl_4$, Et_2AlCl, $BF_3{\cdot}OEt_2$, BINOL·$TiCl_2$, and BINOL·$AlCl_3$ were previously tried in the glyoxylate ene reactions involving ethyl glyoxylate **1d** and **2a** without success.[16] As mentioned, $TiCl_2(OiPr)_2$ did not work well with **1d**, although in some small scale experiments yields of up to 80% of **3d** could be achieved, but most often no product was formed at all. Application of two other Lewis acids particularly recommended for the ene reaction, $FeCl_3$[8] and $ZnCl_2$,[17] gave only intractable reaction products (Table 1, entries 17 and 18). Curiously, the PMB-grouping migrated to give **5** when the ene-reaction was

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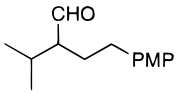
Table 1. Lewis Acid Catalyzed Glyoxylate Ene Reactions of 1a−d and 2a−c

entry	R^1(**1**)	R^2(**2**)	catalyst	ratio **1**:cat.:**2**	cond[a]	product (yield %)
1	Sia (**1a**)	PMB (**2a**)	$(iPro)_2TiCl_2$	5:2:1	A	**3a** (97−99)
2	**1a**	**2a**	$(iPrO)_2TiCl_2$	1:1:1	B	**3a** (30)
3	**1a**	**2a**	$(iPrO)_2TiCl_2$	2:1:1	B	**3a** (47)
4	**1a**	**2a**	$(iPrO)_2TiCl_2$	2:0.1:1	B	−(0)[b]
5	**1a**	**2a**	$(iPrO)_2TiCl_2$/BINOL	5:2:1	B	(+)-**3a** (95, 95% ee)
6	Et (**1d**)	**2a**	$(iPrO)_2TiCl_2$	5:2:1	A	**3d** (0−40)[c]
7	**1d**	**2a**	$(iPrO)_2TiCl_2$	2:0.1:1	A	**3d** (9)
8	**1a**	Bn (**2b**)	$(iPrO)_2TiCl_2$	5:2:1	A	**3g** impure
9	**1d**	**2b**	$(iPrO)_2TiCl_2$	1:1:1	A	**3e** (0)
10	**1d**	TBDMS (**2c**)	$(iPrO)_2TiCl_2$	1:1:1	A	*d*
11	**1d**	**2a**	$(iPrO)_2TiCl_2$	1:1:1	A	**3d** (0)[e]
12	Cy (**1b**)	**2a**	$(iPrO)_2TiCl_2$	1:1:1	A	**3b** (57)[f]
13	2-MeCy (**1c**)	**2a**	$(iPrO)_2TiCl_2$	1:1:1	A	**3c** (65)[f]
14	**1c**	**2a**	$SnCl_4$	1:1:1	C	**3c** (63)[f]
15	**1a**	**2a**	$SnCl_4$	1:1:1	C	**3a** (30)
16	**1b**	**2a**	$SnCl_4$	1:1:1	C	**3b** (58)[f]
17	**1d**	**2a**	$FeCl_3$	1:1:1	D	*g*
18	**1d**	**2a**	ZnI_2	1:1:1	A	*g*

[a] Conditions; A: 48 h, −17 °C; B: 96 h, −17 °C; C: 5 min., −78 °C; D: 20 min., −25 °C. [b] All of the starting material **2a** was recovered. [c] In most cases no reaction at all took place. [d] The product deteroriated during chromatography on silica. [e] The reaction was performed in toluene. [f] Yields after reesterfication to the corresponding ethyl esters. [g] A large number of compounds were formed.

attempted with $BF_3{\cdot}OEt_2$ as Lewis acid or in the presence of zeolite-β. This rearrangement is the subject of a separate investigation.[18]



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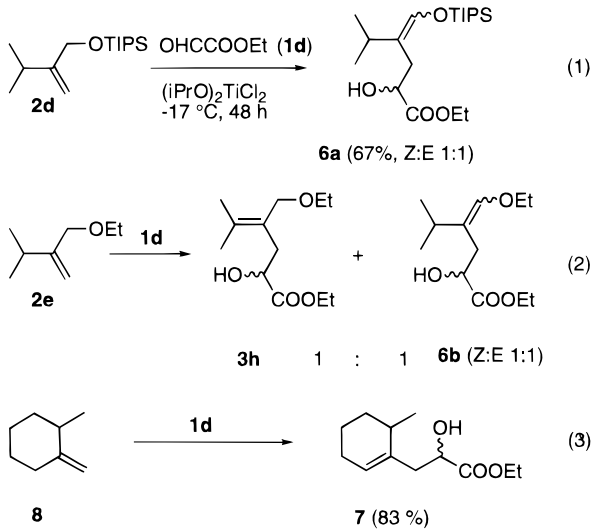
Thus, even if $(iPrO)_2TiCl_2$ only worked sporadically it was still the only Lewis acid that gave at least some ene-product. It was therefore used in the further testing of other allylic ethers as ene components and glyoxylates as enophiles.

Protecting Group of the Ene Component. We initially chose the PMB-ether protection of the allylic alcohol since the PMB-group may be conveniently removed in high yields later in the reaction sequence.[16] However, Lewis acid interactions with the PMB group may have contributed to the problems related to the unreproducibility of the ene reaction. Therefore we also tested the reaction between **1d** and allylic ethers carrying the benzyl, ethyl, TIPS, and TBDMS groups. The TBDMS and benzyl protective groups in the ene-component were reported to be compatible with the glyoxylate ene reaction conditions ($SnCl_4$, −78 °C).[19] It was mentioned, however, that the benzyl ether of 2-buten-1-ol did not give any ene product, which was also true in our experiment with **1d** and benzyl ether **2b** (entry 9). The TBDMS allyl ether **2c**[20] gave a green spot and retention on TLC, characteristic of the expected ene product, but the product was too unstable to allow isolation in the pure state (entry 10). On the other hand the TIPS allyl ether **2d** gave a fair yield of ene product **6a** (Scheme 3, eq 1). Thus, the oxy-methylene hydrogens were more reactive than the methine hydrogen. For comparison we also tried the ethyl allyl ether **2e**, which gave a 1:1 mixture of the two ene products **3h** and **6b** (Scheme 3, eq 2). In this case the reactivities of the different allylic hydrogens were obviously identical. In other cases there may be a certain degree of unselectivity; e.g. oxomalonate gave a completely unselective reaction with substrate **8**.[21] However, for *allyloxy* systems such lack of regioselectivity has previously only been reported for allylic acetates and trifluoro acetates.[11,19]

Scheme 3



It should be mentioned that we checked our technique and reagents by repeating some relevant cases of Mikami et al.,[19] which could be perfectly reproduced.

Apparently, our ene-substrate has two more or less equally reactive hydrogen sites, which of course may be a complicating factor, even if this is reportedly not the case with other closely related allyl ether substrates.[19] We could verify an earlier observation[9] that methine hydrogens are less reactive than methylene hydrogens in some carbonyl ene-reactions (Scheme 3, eq 3).

It seems reasonable to take into account the coordination of the Lewis acid to the allylic ether oxygen. In the TIPS ether it is likely that the nucleophilicity of the silicon-carrying oxygen is lowered both due to steric hindrance and to the low availability of the oxygen

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n-electrons for complexation.[22−24] Thus, the effective bulk at the oxymethylene hydrogens would be smaller in the TIPS ether **2d** as compared with the corresponding benzyl (**2b**), PMB (**2a**), and ethyl (**2e**) ethers. As a consequence the oxymethylene hydrogens would be more available in **2d**. In the less sterically demanding **2e** the bulk of the Lewis acid complex is probably intermediate at the region of the oxymethylene hydrogens, making the methine and the methylene hydrogens equally reactive.

If this reasoning is correct, the coordination of the Lewis acid at the allylic ether oxygen of the PMB ether **2a** builds up too much steric hindrance for the oxymethylene hydrogens to be available for the reaction. Apparently, allylic ethers of the general stucture **2** are particularly difficult ene components, which may give regiounselective reactions as well as the 1,4-rearrangement mentioned.

Glyoxylates. As is seen in Table 1 (entries 6, 7, 11, 17, 18) ethyl glyoxylate (**1d**) was inferior in the Lewis acid induced ene-reactions with **2a** as were the *n*-butyl, isopropyl, and methyl glyoxylates (not shown). It should also be mentioned that the thermal noncatalyzed reaction did not give an ene product at all. The more bulky glyoxylates such as **1** (R^1 = 8-phenylmenthyl, 2-phenylcyclohexyl,[16] 2-methylcyclohexyl (entries 13, 14) or cyclohexyl (entry 12, 16) gave on the other hand repeatedly moderate to good yields of the corresponding ene products. However, there were serious drawbacks by using these bulky glyoxylates. First, taking the 8-phenylmenthyl case as an example, the yields dropped drastically when the scale was increased to more than ca. 1 gram of substrate; second, the bulk of the ester function prevented further reaction at the carbonyl carbon of the ene product **3** by the enolate of ethyl acetate, and therefore the ester function had to be replaced by a smaller one; third, the asymmetric auxiliary by necessity must be present in stoichiometric amounts, and fourth, the resulting ene products **3**, carrying bulky ester groups, were not stable enough to make the method reliable. As we earlier observed, these compounds readily decomposed on standing or on contact with silica gel used for their purification,[16] while the ene products carrying smaller ester groups (Me and Et) were more stable. Details of this decomposition have not been investigated. Unfortunately, only traces of ene product could be detected in the (*S*)-BINOL−$TiCl_2$ catalyzed reaction between **2a** and ethyl glyoxylate **1d**.[16] Thus, it was necessary to find a more suitable glyoxylate.

NMR spectra of a series of glyoxylates in $CDCl_3$ showed that the free aldehyde content was negligible for the lower alkyl glyoxylates but increased with larger ester groups. For example, methyl and ethyl glyoxylate had a free aldehyde content of less than 1%, while butylglyoxylate had 21%, cyclohexyl 22%, 2-methylcyclohexyl 41%, and 8-phenylmentyl glyoxylate >98%. A plausible explanation for this is that the lower alkyl glyoxylates tend to form trimers and hydrates to a larger extent than the more bulky ones. Mechanistically, the ene-reaction requires that the free aldehyde is the reacting species, and consequently the larger glyoxylates were expected to be better than the smaller ones. Even if it has been shown that aldehyde trimers revert to monomer in the presence of protic acids[25] little is known about glyoxylates in this respect. One may speculate that, e.g., trimeric cyclic glyoxylates, having many electron rich oxygens, may trap the Lewis acid by forming less reactive complexes. We therefore argued that the use of glyoxylates of sufficient bulk to increase the chances that the monomer is present under the reaction conditions would be desirable.

Despite that its drawbacks were essentially as described for 8-phenylmenthyl glyoxylate **1c** still gave the reproducibly highest yields (entries 13 and 14). We therefore reasoned that a structurally similar ester unit, generated by removing two of the methylene groups of the cyclohexane ring of **1c** to create the siamyl group, would be worth testing. The siamyl group has the branching points as in the 2-methylcyclohexyl group but is of course more flexible.

We were very satisfied to find that **1a** (5 equiv) gave reliably very high yields of **3a** using 2 equiv of $(^iPrO)_2TiCl_2$ as a catalyst and 1 equiv of the allylic PMB-ether **2a** (entry 1). The reaction gave consistently 97−99% yields of **3a** in a 1 mmol scale. Other stoichiometries gave lower yields, and in the presence of only 0.1 equiv of the Lewis acid there was essentially no reaction with **1a** (entry 4), and a very inefficient reaction with **1d** (entry 7). As seen in Table 1 the 1:1:1 ratio was not optimal but was used for screening purposes since it gave yields high enough to be of diagnostic value. In large scale experiments (250 mmol of **2a**) we used 3 equiv of the glyoxylate, which gave 80−85% yields of **3a**, repeatedly. The excess of the glyoxylate **1a** was recovered by distillation at reduced pressure and could be reused several times. Even the previously unreactive benzyl protected ether **2b** gave a product with **1a** (entry 8) using the 5:2:1 conditions that by TLC analysis indicated it to be the expected one (characteristic green spot by anisaldehyde spray). However, it could not be obtained sufficiently pure by silica gel chromatography to give an interpretable NMR spectrum.

A reasonable explanation for the "siamyl effect" on this ene reaction has not yet been found. We have hitherto only been able to dismiss some possible mechanistic details, such as ester exchange between the glyoxylate and the titanium isopropoxides, product catalysis, and induction period. Nor has any NMR spectroscopic evidence been obtained of a complex between the Lewis acid and the glyoxylates.

Initially, we believed that the quality and/or the mode of preparation of the glyoxylates were critical, but this turned out to be not that important for **1a**. Our preferred synthesis of glyoxylates is the periodate cleavage of of tartrates followed by distillation from P_2O_5.[26] Siamyl glyoxylate can be stored at 22 °C for several weeks without loosing its efficiency in the ene reaction. Its NMR spectrum revealed the presence of substantial amounts (37%) of the free aldehyde.

Application to the Synthesis of a Taxol A-Ring Subunit. We earlier found that the 4*S*,6*R* and the 4*S*,6*S* isomers of epoxyallylsilane **12** (Scheme 4) underwent different reactions when treated with $BF_3{\cdot}Et_2O$. The 4*S*,6*R* isomer cyclized to give compound (+)-**13** while the 4*S*,6*S* isomer rearranged to ketone (−)-**14**.[27,28] It would

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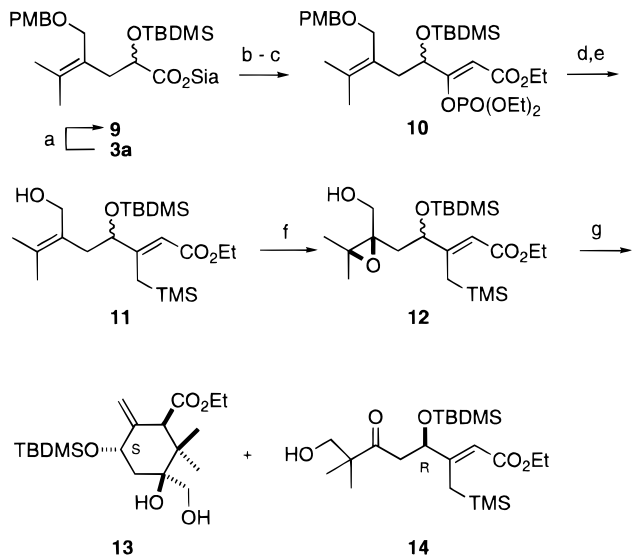
Scheme 4[a]



[a] Reactions conditions: (a) TBDMSCl, imidazole, 95%; (b) $(TMS)_2NLi$, TMEDA, EtOAc, −78 °C to 0 °C, 95%; (c) KOtBu, $ClPO_3Et_2$, 60%; (d) $TMSCH_2MgCl$, $Ni(acac)_2$, 65%; (e) DDQ, 85%; (f) D-(−)-DIPT, $Ti(OiPr)_4$, TBHP, −40 °C, 87%; (g) $BF_3{\cdot}Et_2O$, 0 °C, 36%.

therefore be possible to use racemic **11** and then introduce the epoxide stereoselectively by the use of the Sharpless asymmetric epoxidation reaction for the synthesis of optically active **12**.[29] Thus, racemic **9** was treated with the enolate of ethyl acetate, followed by diethyl chlorophosphate to give phosphoenolate **10**. We were delighted to find that the enolate reaction resulted in a very high yield (95%) of the chain extended β-keto carboxylate.

Subsequent Ni-catalyzed coupling with $TMSCH_2MgCl$ and deprotection with DDQ)[16] gave racemic **11**. Sharpless epoxidation[29] of **11** using D-(−)-diisopropyl tartrate (D-(−)-DIPT) gave a diastereomeric mixture of **12**, which was treated with $BF_3{\cdot}Et_2O$ to give the cyclized derivative (+)-**13** and the rearranged derivative (−)-**14**. These compounds were easily separated by silica gel chromatography. The absolute configuration of the major enantiomer of (+)-**13** was confirmed by comparison with an authentic sample.[27] Based on the optical rotation and on NMR analysis of the Mosher ester of (+)-**13**, the ee was determined to be 80−85%. Although this eight-step route to (+)-**13** gave material with lower enantiomeric purity than was previously obtained via the more tedious routes,[16,27] we believe that it is advantageous especially on a larger scale.

Optically active **3a** would be the ideal starting material for the construction of **13** and should be obtainable by the use of the *asymmetric* catalytic carbonyl-ene reaction as described by Mikami et al. who used 5 mol % of optically active BINOL·$TiCl_2$ as a catalyst.[11,30] Satisfactorily, application of this complex to **1a** and **2a** gave (+)-**3a** of 95% ee in 95% yield (Table 1, entry 5). However, it was necessary to use 2 equiv of the Ti−BINOL complex; a catalytic amount (5 mol %) gave no conversion. Due to the relatively high cost of optically active BINOL, large scale synthesis of the taxol A-ring subunit (+)-**13** was not as attractive as we first imagined. As already mentioned, the Ti−BINOL catalyst did not produce any ene product (essentially no reaction took place) together with **2a** and ethyl glyoxylate **1d** despite several variations of the reaction conditions.[16]

In conclusion, we solved the problem with the erratic glyoxylate reaction of **2a** by using siamyl glyoxylate **1a** together with $(iPrO)_2TiCl_2$ as a Lewis acid. The now reliable and high yielding synthesis of the ene-product **3a** made it practical to synthesize the optically active taxol A-ring derivative (+)-**13** in only eight steps from PMB ether **2a** (Scheme 4). Optically active (+)-**3a** could be obtained by the use of 2 equivalents of BINOL·$Ti(OiPr)_2$ as promoter in the *siamyl* glyoxylate ene reaction. We previously reported the syntesis of a seco taxane derivative starting from (+)-**13**,[31] and the ample supply of this compound allows us to resume our work toward the synthesis of taxanes.

Experimental Section

General. GC analyses were performed with a DBwax (J&W Scientific) capillary column (30 m, 0.25 mm i.d., 0.25 μm stationary phase) and with a Beta-DEX 120 chiral column for determination of enantiomeric compositions. NMR spectra were recorded at 300 MHz using $CDCl_3$ ($CHCl_3$ δ 7.26 (^1H) and 77.0 (^{13}C)) as solvent. Chromatographic separations were performed on Matrex Amicon normal phase silica gel 60 (0.035−0.070 mm), and for thin-layer chromatography we used Merck precoated TLC-plates Silica gel 60 F-254, 0.25 mm. After elution, the TLC-plates were sprayed with a solution of *p*-methoxybensaldehyde (26 mL), glacial acetic acid (11 mL), concentrated sulfuric acid (35 mL), and 95% ethanol (960 mL), and the compounds were visualized upon heating. Unless otherwise stated, reagent grade chemicals were used, and the reactions were perfomed in septum-capped, oven-dried flasks under an atmospheric pressure of argon. THF was distilled under N_2 from sodium−benzophenone ketyl, and CH_2Cl_2 was distilled from P_2O_5 prior to use. Molecular sieves were activated at 400 °C for 3 h and all organic extracts were dried using $MgSO_4$. The cyclohexyl[32] and ethyl[26] glyoxylates, **1b** and **1d**, respectively, were prepared according to literature procedures as was 2-isopropyl-2-propenol.[33]

3-Methyl-2-butyl Glyoxylate (1a). The procedure of Kelly et al.[26] was adopted. Paraperiodic acid (11.4 g, 50.0 mmol) was added in portions during 1 h to an ice-cooled solution of bis(3-methyl-2-butyl) tartrate (14.5 g, 50.0 mmol) in ether (300 mL). The mixture was stirred for another 1 h and was then decanted from the solid residue. The ether solution was dried with 4A molecular sieves and filtered. Evaporation of the solvent at reduced pressure gave a pale yellow oil (13.5 g) which was distilled to give **1a** (10.8 g, 75%) as a colorless oil: bp 85−88 °C/20 mbar; IR: (film) 3430, 1735 cm^{-1}; ^1H NMR δ 9.41 (s, <1H), 5.30 (m, <1H), 4.86 (m, 1H), 3.60 (broad s, exch. with D_2O), 1.87 (m, 1H), 1.25 (d, J = 6.5 Hz, 3H), 0.91 (d, J = 6.9 Hz, 6H); ^{13}C NMR δ 184.3, 156.4, 87.2, 32.7, 17.9, 16.8. Anal. HRMS Calcd for $C_7H_{16}O_3N$ [M + NH_4]: 162.1130. Found: 162.1129.

Asymmetric Ene Reaction Catalyzed by (*S*)-BINOL·$TiCl_2$. Preparation of 3′-Methyl-2′-butyl (2*S*)-2-Hydroxy-4-[[(4-methoxybenzyl)oxy]methyl]-5-methyl-4-hexenoate ((+)-3a). A solution of $(i\text{-}PrO)_2TiCl_2$ (237 mg, 1.00 mmol) in CH_2Cl_2 (2 mL) was added to a mixture of (*S*)-BINOL (286 mg, 1.00 mmol) and pulverized activated 4A molecular sieves (4 g) in CH_2Cl_2 (25 mL) at 0 °C under an argon atmosphere.

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After 15 min, the temperature was raised to 20 °C, and the stirring was continued for 1 h. The reaction mixture was then cooled to −78 °C, and **2a** (110 mg, 0.50 mmol) in CH_2Cl_2 (1 mL) was added followed by glyoxylate **1a** (362 mg, 2.50 mmol) in CH_2Cl_2 (1 mL). After 48 h at −17 °C, the mixture was diluted with ether and washed with a saturated aqueous $NaHCO_3$ and brine. The organic extract was dried, and then the solvent was evaporated at reduced pressure. Chromatography of the residue (heptane−EtOAc, 3:1) gave (+)-**3a** (173 mg, 95%): $[\alpha]^{21}_D$ +0.2° (*c* 2, $CDCl_3$). The ee was determined to be 95% by GC and ^{1}H NMR analysis of the corresponding Mosher ester.[34]

General Procedure for Ene Reactions Catalyzed by (i-PrO)$_2$TiCl$_2$. Preparation of 3′-Methyl-2′-Butyl-2-hydroxy-4-[[(4-methoxybenzyl)oxy]methyl]-5-methyl-4-hexenoate ((±)-3a). The reaction conditions were varied according to Table 1. Glyoxylate **1a** (1.81 g, 12.5 mmol) in CH_2Cl_2 (2.5 mL) was added to a solution of (i-PrO)$_2$TiCl$_2$ (1.18 g, 5.00 mmol) in CH_2Cl_2 (10 mL) at −78 °C and under Ar followed by addition of PMB-ether **2a** (0.550 g, 2.50 mmol) in CH_2Cl_2 (2.5 mL). The reaction mixture was kept at −17 °C for 48 h and was then diluted with ether and washed with saturated aqueous $NaHCO_3$ and brine. The organic extract was dried, and then the solvent was evaporated at reduced pressure. Chromatography of the residue (heptane-EtOAc, 3:1) gave **3a** (0.90 g, 99%) as a mixture of diastereomers: IR: (film) 3450, 1735 cm^{-1}; ^{1}H NMR δ 7.28 (d, 2H, J = 8.7 Hz), 6.88 (d, 2H, J = 8.7 Hz), 4.80 (m, 1H), 4.45 (s, 2H), 4.25−4.05 (m, 2H), 3.98−3.89 (m, 1H), 3.80−3.68 (m, 1H), 3.79 (s, 3H), 2.73 (m 1H), 2.45 (m, 1H), 1.91−1.71 (m, 1H), 1.75 (s, 3H), 1.72 (s, 3H), 1.18 (dd, J = 6.4 Hz, J = 3.1 Hz, 3H), 0.90 (dd, J = 4.8 Hz, J = 2.0 Hz, 6H); ^{13}C NMR δ 174.6, 159.3, 142.7, 135.1, 130.0, 130.0, 129.5, 125.2, 125.2, 113.8, 76.3, 76.3, 72.2, 70.8, 70.7, 69.6, 69.6, 55.3, 37.1, 36.9, 32.6, 32.6, 21.0, 20.7, 18.1, 18.0, 16.7, 16.6. Anal. HRMS Calcd for $C_{21}H_{33}O_5$ [M + H] 365.2328. Found: 365.2330.

This procedure was used for the preparation of the following compounds in a 1 mmol scale.

Ethyl 2-Hydroxy-4-(2-propyl)-5-[(triisopropylsilyl)oxy]-4-pentenoate (6a). Yield: 241 mg (67%) starting from **2d**. IR: (film) 1740 cm^{-1}; ^{1}H NMR δ 4.95 (s, <1H), 4.84 (s, <1H), 4.21 (m, 4H), 2.98 (m, 1H), 2.83 (m, 1H), 1.78 (m, 1H), 1.41 (s, 3H), 1.32 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H), 1.11−1.05 (m, 3H), 1.05 (s, 18H); ^{13}C NMR δ 172.4, 153.7, 142.7, 104.6, 83.5, 74.1, 61.1, 36.5, 28.1, 17.7, 14.2, 12.3. Anal. Calcd for $C_{19}H_{38}O_4Si$: 358.2539. Found: 358.2533

Ethyl 5-Ethoxy-2-hydroxy-4-(2-propyl)-4-pentenoate (6b *Z*:*E* 1:1). Yield 84 mg (36%) starting from **2e**. R_f = 0.21; IR (film) 1735 cm^{-1}; ^{1}H NMR δ 5.87 (s, <1H), 5.41 (s, <1H), 4.31 (q, J = 7.1 Hz, 2H), 4.27−4.07 (m, 1H), 3.92−3.71 (m, 1H), 3.51 (q, J = 7.0 Hz, 2H), 2.85−2.68 (m, 1H), 2.48−2.32 (m, 1H), 1.81 (m, 1H), 1.33 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.0 Hz, 3H), 0.92 (d, J = 6.8 Hz, 6H); ^{13}C NMR δ 172.5, 153.7, 142.7, 70.6, 66.0, 61.1, 37.3, 20.9, 20.7, 15.0, 14.2. Calcd for $C_{12}H_{22}O_4$: 230.1518. Found: 230.1520.

In this experiment the following was also formed:

Ethyl 2-Hydroxy-4-(ethoxymethyl)-5-methyl-4-hexenoate (3h). Yield: 86 mg (37%); R_f = 0.43; IR: (film) cm^{-1}: 1740; ^{1}H NMR δ 4.20 (q, J = 7.2 Hz, 2H), 4.12 (m, 1H), 4.07 (s, 2H), 3.86 (m, 1H), 3.51 (q, J = 7.0 Hz, 2H), 2.76 (m, 1H), 2.42 (m, 1H), 1.76 (s, 3H), 1.74 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H), 1.24 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 174.1, 135.2, 124.9, 70.8, 70.6, 65.9, 61.0, 37.1, 20.8, 20.4, 14.8, 14.4. Anal. Calcd for $C_{12}H_{22}O_4$ 230.1518. Found: 230.1511.

Ethyl 2-Hydroxy-3-(6-methyl-1-cyclohexenyl)propanoate (7, mixture of diastereomers). Yield: 176 mg (83%) starting from **8**. IR: (film) 3470, 1730 cm^{-1}; ^{1}H NMR δ 5.51 (s, 1H), 4.24 (q, J = 7.1 Hz, 2H), 4.29−4.20 (m, 1H), 2.68−2.60 (d, J = 13.0 Hz, 1H), 2.52−2.30 (m, 1H), 2.23−2.07 (m, 2H), 2.03−1.92 (m, 2H), 1.77−1.27 (m, 4H), 1.25 (t, J = 7.1 Hz, 3H), 1.07 (d, J = 7.0 Hz, 3H); ^{13}C NMR δ 174.9, 137.3, 125.6, 69.1, 61.5, 40.3, 31.3, 30.8, 25.7, 19.6, 19.5, 14.2. Anal. Calcd for $C_{12}H_{21}O_3$ [M + H]: 213.1491. Found: 213.1498

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General Procedure for Ene Reactions Catalyzed by SnCl$_4$. Preparation of Cyclohexyl 2-Hydroxy-4-[[(4-methoxybenzyl)oxy]methyl]-5-methyl-4-hexenoate (3b) and Derivatization to Its Corresponding Ethyl Ester. A solution of **2a** (220 mg, 1.00 mmol) in CH_2Cl_2 (5 mL) was added to a solution of **1b** (156 mg, 1.00 mmol) in CH_2Cl_2 (5 mL) at −78 °C under an argon atmosphere, followed by dropwise addition of $SnCl_4$ (118 μL, 1.00 mmol). The dark red reaction mixture was stirred for 5 min and was then diluted with ether and washed with saturated aqueous $NaHCO_3$ and brine. The organic extract was dried, and then the solvent was evaporated at reduced pressure which gave 280 mg of opalescent oil. The product decomposed on silica and could therefore not be properly purified for spectroscopic analysis. Instead it was transformed to its corresponding ethyl ester in the following manner. Crude **3b** (280 mg, 0.74 mmol) was hydrolyzed by refluxing for 8 h in a mixture of THF (5 mL), MeOH (10 mL), and 1 M NaOH (5 mL). The mixture was extracted with heptane whereafter the aqueous phase was acidified with 1 M HCl (to pH = 2) and extracted with ether. The collected ethereal extract was washed with brine (15 mL) and dried, and the solvent was evaporated at reduced pressure to give the crude hydroxy acid, which was dissolved in benzene (5 mL) containing DBU (0.37 mL, 5.0 mmol) and EtBr (0.40 mL, 10 mmol). This mixture was refluxed for 5 h, diluted with ether and washed with 1 M HCl, saturated $NaHCO_3$ solution, and brine. The ethereal extract was dried, and the solvent was then evaporated at reduced pressure. Chromatography of the residue (heptane−EtOAc, 1:1) gave **3b** (187 mg, 58%). NMR data were identical with those earlier reported.[16]

3′-Methyl-2′-butyl 2-[(*tert*-butyldimethylsilyl)oxy]-4-[[(4-methoxybenzyl)oxy]methyl]-5-methyl-4-hexenoate (9). A solution of **3a** (1.00 g, 2.70 mmol), imidazole (0.43 g, 6.30 mmol), and TBDMSCl (0.475 g 3.15 mmol) in DMF (7 mL) was stirred overnight under Ar. The reaction mixture was then diluted with ether and washed with 1 M HCl, saturated aqueous $NaHCO_3$, and brine. The organic extract was dried, and the solvent was evaporated at reduced pressure. Chromatography of the residue (heptane−EtOAc, 3:1) gave **9** (1.28 g, 92%) as a mixture of diastereoisomers: IR: (film) 1740 cm^{-1}; ^{1}H NMR δ 7.24 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 4.80 (m, 1H), 4.39 (s, 2H), 4.26 (m, 1H), 4.00 (s, 2H), 3.79 (s, 3H), 2.57 (m, 1H), 2.34 (s, 1H), 1.95−1.75 (m, 1H), 1.74, 1.69 (2s, 6H), 1.18 (dd, J = 6.4 Hz, J = 1.4 Hz, 3H), 0.90 (m, 6H), 0.85 (s, 9H), 0.09, −0.02 (2s, 6H); ^{13}C NMR δ 173.8, 129.3, 113.9, 75.8, 72.1, 72.0, 69.5, 55.1, 36.7, 36.6, 32.7, 32.6, 25.7, 21.2, 20.6, 18.3, 18.1, 18.0, 17.9, 16.7, 16.6. Anal. Calcd for $C_{27}H_{46}O_5Si$: C, 67.7; H 9.7. Found: C, 67.4; H, 9.3. HRMS Calcd for $C_{27}H_{47}O_5Si$ [M + H]: 479.3192. Found: 479.3200.

Ethyl (2*Z*)-4-[(*tert*-Butyldimethylsilyl)oxy]-3-[(diethoxyphosphoryl)oxy]-6-[[(4-methoxybenzyl)oxy]methyl]-7-methyl-2,6-octadienoate (10). n-BuLi (1.6 M solution in hexane, 2.2 mL, 3.5 mmol) was added to a solution of hexamethyl-disilazane (0.80 mL, 3.8 mmol) in THF (3 mL) at 0 °C under an argon atmosphere. The mixture was cooled at −78 °C, and EtOAc (0.17 mL, 1.8 mmol) was then added dropwise. After stirring this mixture for 10 min a solution of **9** (0.57 g, 1.2 mmol) and TMEDA (0.52 mL, 3.5 mmol) in THF (0.75 mL) was added. The cooling bath was removed, and the mixture was stirred for 30 min at rt. Ether (15 mL) was added, and the resulting mixture was washed with 1 M HCl and brine. The organic layer was dried, and the solvent was evaporated at reduced pressure. The crude β-keto ester was dissolved in THF (3 mL) followed by addition of t-BuOK (136 mg, 1.2 mmol). The resulting mixture was stirred for 3 min followed by addition of diethyl chlorophosphate (0.21 mL, 1.7 mmol). Stirring was continued for another 15 min, and then ether (15 mL) was added followed by washing with saturated NH_4Cl solution and water. The etheral extract was dried, and the solvent was evaporated under reduced pressure. Chromatography of the residue (heptane−EtOAc, 1:1) gave **10** (0.42 g, 58%): ^{1}H NMR and ^{13}C NMR are identical with those earlier reported.[16]

Ethyl (4*RS*,6*R*)-(2*Z*)-4-[(*tert*-Butyldimethylsilyl)oxy]-6,7-epoxy-6-(hydroxymethyl)-7-methyl-3-[(trimethylsilyl-)methyl]-2-octenoate (12). The same two-step procedure as

described earlier[16,27] was used for the synthesis of **12** from **10** including nickel catalyzed coupling of **10** and [(trimethylsilyl-)methyl]magnesium chloride to give **11**, followed by Sharpless asymmetric epoxidation using D-(−)-diisopropyl tartrate. After chromatography (heptane:EtOAc, gradient 10:1 → 5:1) **12** (11.0 g, 87%) was isolated as a mixture of diastereomers (R_f (heptane:EtOAc 3:1) 0.30) as indicated by the ^{1}H NMR spectrum, which showed two sets of signals as earlier described for the separate compounds.[27]

Ethyl (1*R*,3*S*,5*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-3-hydroxy-3-(hydroxymethyl)-2,2-dimethyl-6-methylenecyclohexanecarboxylate (13). A solution of BF_3·OEt_2 (3.4 mL, 27.6 mmol) in CH_2Cl_2 (12 mL) was added to a solution of **12** (11.0 g, 26.3 mmol) in dry CH_2Cl_2 (1300 mL) under an argon atmosphere at 0 °C. The reaction mixture was then stirred for 10 min followed by addition of aqueous $NaHCO_3$ (sat., 220 mL) and ether (300 mL). The organic phase was washed with brine and dried. Evaporation of the solvent at reduced pressure followed by column chromatography (heptane: EtOAc, gradient 10:1 → 3:1) of the crude product gave (+)-**13** (3.0 g, 36%) as a clear oil. $[\alpha]^{21}_D = +64$ (c 2.39, $CDCl_3$) corresponding to 80% ee based on the literature value[27] $[\alpha]^{21}_D$ +81 (*c* 1.10, $CDCl_3$). Its NMR data were identical with those earlier reported. The Mosher ester gave ^{1}H signals at 5.0 and 5.3 ppm suitable for determination of the ee, which with this method was found to be 85%. Compound (+)-**13** was eluted before (−)-**14**. A small sample of pure (−)-**14** was obtained; $[\alpha]^{20}_D = -21$ (c 1.10, $CDCl_3$), having ^{1}H NMR data as described.[27]

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Supporting Information Available: ^{13}C NMR spectra for all compounds with high-resolution mass spectra and experimental details for bis(1,2-dimethylpropyl)tartrate, bis(2-methylcyclohexyl)tartrate, **1c**, **2b**−**e**, and large scale preparation of **3a** (15 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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