Stereoselective Reactions. Part 23.[1] Asymmetric Michael Reaction of α-Alkyl β-Keto Esters *via* Chiral Enamines. Dependence of the Diastereofacial Selection on the Combination of Solvents and Additives

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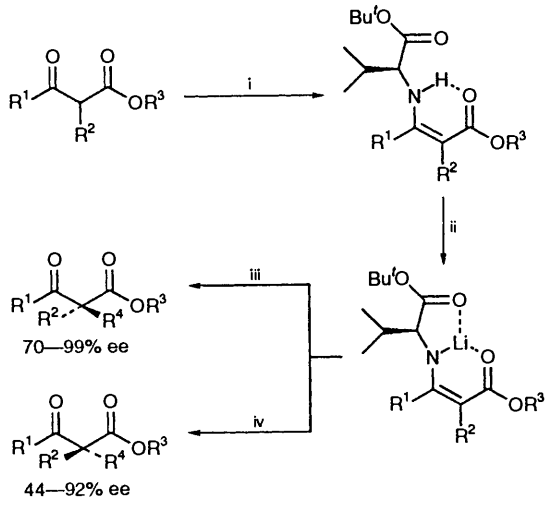
Asymmetric Michael reaction of the chiral enamines prepared from α-alkyl β-keto esters and (*S*)-valine *tert*-butyl ester is described. The diastereoselectivity of this reaction is highly sensitive to the solvent system. The lithiated chiral enamines react with di-*tert*-butyl methylenemalonate in toluene–HMPA to give α,α-dialkylated β-keto esters in 87–92% ee after hydrolysis. On the other hand, the reactions in THF give the corresponding antipodes in 84–95% ee.

Carbon–carbon-bond formation *via* Michael reaction occupies a central niche in synthetic organic chemistry.[2] The importance of this process has prompted numerous searches for procedures to effect Michael reaction with high asymmetric induction. These efforts focused on the following strategies utilizing either (i) chiral α,β-unsaturated carbonyl derivatives,[3a,b] (ii) chiral nucleophiles,[3a,c] or (iii) external chiral catalysts.[3d] However, there have been only a few asymmetric Michael reactions which provide either product enantiomer from the same starting materials.[4]

In previous papers,[5] we have reported that the chiral enamines, derived from α-alkyl β-keto esters and (*S*)-valine *tert*-butyl ester, react with alkyl halides *via* their lithioenamines to give, after hydrolysis, either (*R*)- or (*S*)-α,α-dialkyl β-keto esters depending on the combination of solvents and additives used (Scheme 1). Since the dependence of the diastereofacial selection on the solvent system is of both mechanistic and synthetic interest, we further studied asymmetric Michael reactions of the same substrates. In a preliminary paper,[6] we reported a highly diastereoselective Michael reaction of chiral enamines **1** and **4** with di-*tert*-butyl methylenemalonate **2**. Now we would like to describe the details of this asymmetric Michael reaction of α-alkyl β-keto esters *via* chiral lithioenamines.

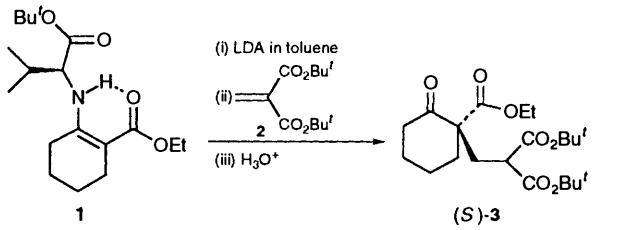


Scheme 1 *Reagents:* i, (*S*)-valine *tert*-butyl ester, BF_3·OEt_2; ii, LDA, toluene; iii, R^4X, HMPA; iv, R^4X, THF or dioxolane or Me_3N

Results

Chiral enamines **1** and **4** were prepared from the corresponding β-keto esters and (*S*)-valine *tert*-butyl ester in the presence of a catalytic amount of BF_3·OEt_2 under azeotropic conditions. In analogy with our asymmetric alkylation study of chiral enamines,[5] enamine **1** was lithiated with lithium diisopropylamide (LDA) (1.1 mol equiv.) in toluene. The resulting lithioenamine was treated with a weakly activated Michael acceptor, such as ethyl acrylate or methyl vinyl ketone, in the presence of 1 mol equiv. of hexamethylphosphoric triamide (HMPA). Unfortunately, the reactions failed to afford any products.† So we tried to use a highly reactive Michael acceptor, di-*tert*-butyl methylenemalonate **2**.[8]‡ The lithioenamine reacted with diester **2** in toluene at −78 °C to afford, after hydrolysis, keto ester (*R*)-**3** in 33% enantiomeric excess (ee) as shown in entry 1 (Table 1). Addition of 1 mol equiv. of HMPA dramatically changed the stereochemical course of the reaction to afford keto ester (*S*)-**3**

Table 1 Asymmetric Michael reaction of enamine **1** with diester **2** in toluene in the presence of HMPA



1 (*S*)-**3**

Entry	HMPA (mol equiv.)	Temp. (*T*/°C)	Yield (%)	ee (%)	Config.
1[a]		−78	59 (71)[b]	33	*R*
2	1	−78	80 (94)	58	*S*
3[a]	2	−78	75 (93)	56	*S*
4	2	−78	77	68	*S*
5	4	−78	86 (100)	72	*S*
6	8	−78	82	75	*S*
7	4	−95	73	92	*S*

[a] Compound **2** was added during 3 min. In other runs, diester **2** was added during 15 min. [b] Yield based on consumed compound **1** in parentheses.

† Later we found the reaction was promoted by Lewis acids.[7]

‡ Diethyl methylenemalonate was too reactive to allow control of both the reaction with enamine **1** and the stereochemistry of the Michael adduct. Although reaction of diethyl methylenemalonate with enamine **1** gave the (*R*)-adduct (81% ee) in tetrahydrofuran (THF) and the (*S*)-adduct (18% ee) in toluene–HMPA respectively, at best, the reproducibility of the reaction was poor and the adduct was accompanied by many polymeric compounds, which could act as additives.

in 58% ee. Increasing the amount of HMPA was found to improve the stereoselectivity, providing product (*S*)-**3** in 75% ee by the use of 8 mol equiv. of HMPA at −78 °C (entry 6), but in this case HMPA was not completely dissolved in toluene. An increase in the addition period of diester **2** resulted in increased diastereoselectivity (3 min addition, 56% ee *vs.* 15 min addition, 68% ee) (entries 3 and 4). These results show that the reaction is too fast to be perfectly controlled at −78 °C. Indeed, keto ester **3** of 92% ee was obtained when the reaction was conducted at −95 °C in the presence of 4 mol equiv. of HMPA. All the chemical yields are high and the corrected yields show that the reaction is clean and highly stereoselective.

In striking contrast to these results, the reaction in toluene in the presence of THF did not change the stereochemical course of the reaction and just increased the selectivity. That is, the reaction of the chiral enamine **1** with diester **2** in the presence of 2 mol equiv. of THF in toluene solvent gave compound (*R*)-**3** in 72% ee at −78 °C (entry 2 in Table 2). Further increase of the amount of THF (up to 8 mol equiv.) did not improve the optical yield. Even at −95 °C, only a slight improvement of enantiomeric excess was attained (76% ee) (entry 5).

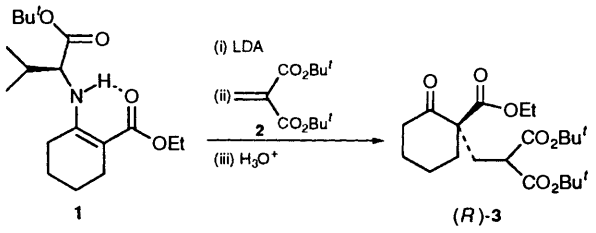
Next we used THF as the solvent. The lithioenamine was prepared in THF and treated with diester **2** to give compound (*R*)-**3** in 80% ee at −78 °C. Finally, at −105 °C, compound (*R*)-**3** of 95% ee was obtained in high yield (entry 7). On the other hand, when the Michael reaction of compound **1** with diester **2** was performed in the presence of HMPA (8 mol equiv.) in THF as solvent, compound (*S*)-**3** was obtained in only 17% ee (entry 8). This result shows that HMPA and THF have opposite effects and complement each other just as in the case of the alkylation study.[5]

The acyclic enamine **4** was also treated with diester **2** under the same conditions as for the cyclic enamine **1** (Table 3). When 4 mol equiv. of HMPA were added as an additive into a toluene solution of the lithioenamide derived from substrate **4**, keto ester (*S*)-**5** of 87% ee was obtained at −95 °C (entry 1). On the other hand, the use of 8 mol equiv. of THF as an additive afforded the enantiomer (*R*)-**5** in 66% ee at −95 °C. In THF solvent at −105 °C, the optical purity of product (*R*)-**5** was improved to 84% ee (entry 3).

Discussion

These results for this asymmetric Michael reaction are comparable to the results of our alkylation study.[5] That is, the powerful ligand HMPA in toluene as solvent favours top-side attack, and the weaker ligand THF, either as a solvent or as an additive in toluene solvent, favours bottom-side attack

Table 2 Asymmetric Michael reaction of enamine **1** with diester **2** in the presence of THF

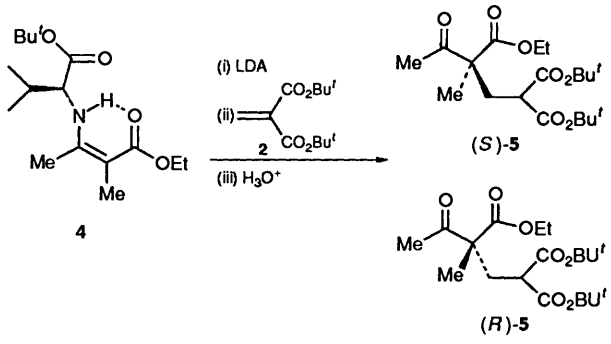


1 (*R*)-**3**

Entry	Solvent	THF (mol equiv.)	Temp. (*T*/°C)	Yield (%)	ee (%)	Config.
1	toluene		−78	59 (71)[a]	33	*R*
2	toluene	2	−78	75 (94)	72	*R*
3	toluene	4	−78	80	71	*R*
4	toluene	8	−78	78	72	*R*
5	toluene	8	−95	87	76	*R*
6	THF		−78	83 (95)	80	*R*
7	THF		−105	86	95	*R*
8	THF	HMPA(8)	−78	86	17	*S*

[a] Yield based on consumed compound **1** in parentheses.

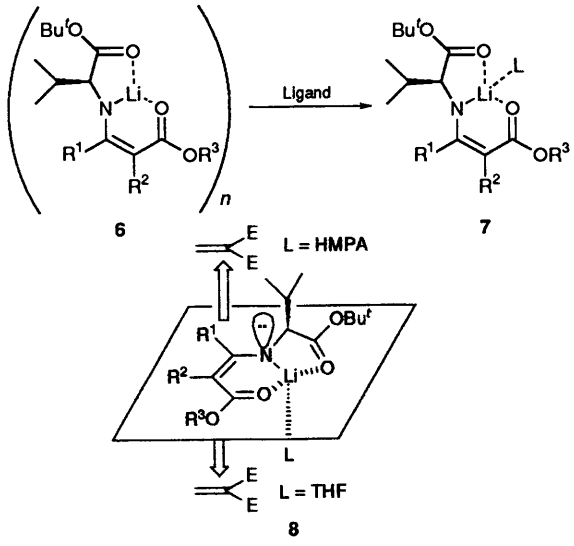
Table 3 Asymmetric Michael reaction of enamine **4** with diester **2**



4

Entry	Solvent/additive	Temp. (*T*/°C)	Yield (%)	ee (%)	Config.
1	toluene/HMPA (4 mol equiv.)	−95	82	87	*S*
2	toluene/THF (8 mol equiv.)	−95	58	66	*R*
3	THF	−105	86	84	*R*

(structure **8** in Scheme 2). The best results were obtained by using THF as solvent or 4 mol equiv. of HMPA in toluene solvent. These results contrast with those of the asymmetric alkylations in which an excess of THF or HMPA reduced the diastereofacial selectivity.[5]

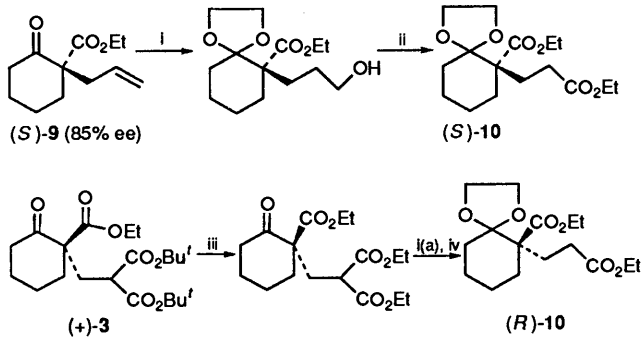


6 **7** **8**

Scheme 2

It is of interest to speculate on the reaction mechanism of this novel asymmetric Michael reaction. The results may be explained by the *trans*-fused chelated structure **8** proposed in the alkylation of the lithioenamides with alkyl halides. The lithioenamides probably exist as a mixture of aggregates **6** in toluene solvent. On addition of an electron-donating additive, they would be converted into species **7** bearing an additive as the ligand for the lithium cation, *i.e.* structure **8**. The bulky and powerful ligand HMPA would coordinate to the lithium cation to satisfy its coordination sphere and this coordination would increase the nucleophilicity of the enamine system, block bottom-side attack, and result in top-side attack. Since di-*tert*-butyl methylenemalonate itself is a better ligand for the lithium cation than alkyl halides, some ligand exchange might be responsible for the low ee when 1 mol equiv. of HMPA was used. On the other hand, the weak ligand THF would not completely convert aggregate **6** into monomer **7** (L = THF) in toluene solvent before the addition of diester **2**. Owing to its strong reactivity, diester **2** would react not only with complex **7** but also with aggregate **6** to give moderate selectivity (~ 72% ee). In THF solvent, the enamine would be lithiated with LDA to give directly the monomer **7** (L = THF). From complex **7**, THF would be smoothly replaced by diester **2**, which reacts from the bottom side of structure **8**. Snyder has reported the asymmetric oxidation of β-keto esters with benzoyl peroxide (BPO) using our lithioenamide procedure and mentioned that the stereoselectivity was optimized by using THF as the solvent rather than as the ligand in toluene and the stereochemistry was not changed by use of HMPA in toluene.[9] Since BPO should be a better ligand than diester **2**, their results are similar to ours from this asymmetric Michael reaction and support the above mechanistic considerations.

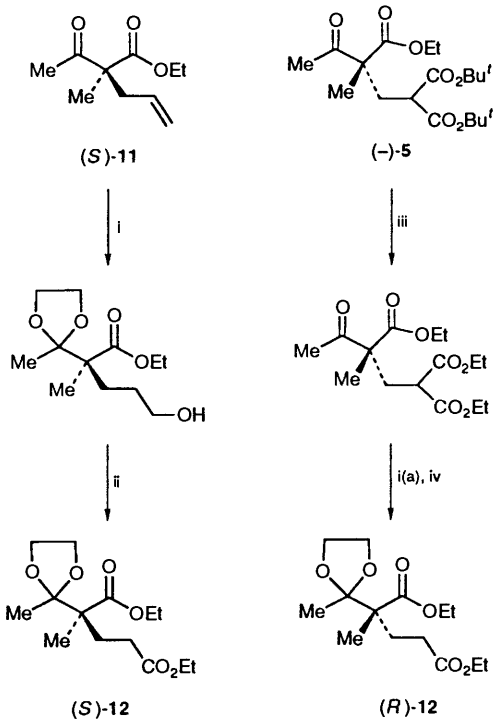
Determination of the Absolute Configuration and Optical Purities.—Since the chiral Michael adducts reported here had not been previously described in enantiomerically pure form and since this asymmetric Michael reaction was mechanistically interesting, it was very important to establish rigorously not only the degree of asymmetric induction but also the absolute configuration of the Michael adducts. The absolute configurations of the chiral Michael adducts **3** and **5** were determined by the chemical correlation with the known allyl compounds **9**[10] and **11**.[11] Hence, treatment of (*S*)-**9** (85% ee), which was obtained by our alkylation study,[5] with ethylene glycol-*p*-TsOH followed by BH_3-THF, H_2O_2–NaOH, Jones reagent, and diazoethane, provided acetal ester **10** which proved to be identical, with the exception of enantiomeric purity and absolute configuration, with the sample prepared by trans-esterification, acetalization, and de-ethoxycarbonylation[12] of keto ester (+)-**3** (Scheme 3). Compound **5** was submitted to the



(*S*)-**9** (85% ee) (*S*)-**10** (+)-**3** (*R*)-**10**

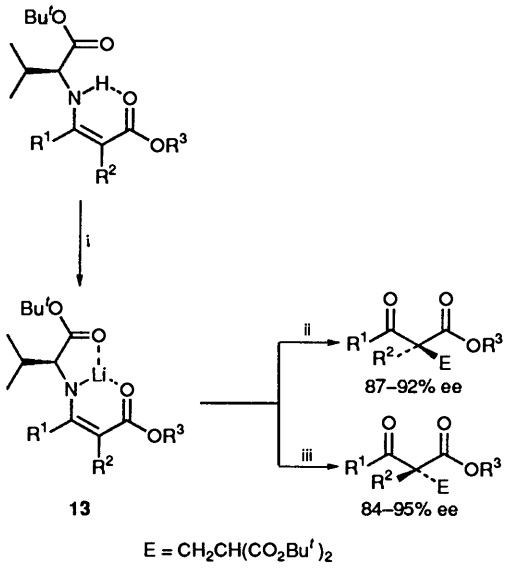
Scheme 3 *Reagents and conditions:* i, (a) $HOCH_2CH_2OH$, TsOH; (b) BH_3-THF; then H_2O_2, NaOH; ii (a) Jones reagent; (b) $MeCHN_2$; iii, TFA; then $MeCHN_2$; iv, NaCN, DMSO, 160 °C

same procedure to give acetal ester **12**, whose absolute stereochemistry had been assigned by correlation with compound **11** by using the identical procedure (Scheme 4). The optical purities were further confirmed by ^1H NMR analysis in the presence of the chiral shift reagent europium trisheptafluorobutyrylcamphorate [Eu(hfc)$_3$].



(*S*)-**11** (−)-**5** (*S*)-**12** (*R*)-**12**

Scheme 4 *Reagents and conditions:* i (a) $HOCH_2CH_2OH$, TsOH; (b) BH_3-THF; then H_2O_2, NaOH; ii (a) Jones reagent; (b) $MeCHN_2$; iii, TFA; then $MeCHN_2$; iv, NaCN, DMSO, 160 °C



Scheme 5 *Reagents:* i, LDA; ii, **2**, HMPA; iii, **2**, THF

Conclusions.—Asymmetric Michael reaction of chiral enamines prepared from α-alkyl β-keto esters and (*S*)-valine *tert*-butyl ester has led to α,α-dialkyl β-keto esters having an (*R*)- or an (*S*)-quaternary centre depending on the solvent system used (Scheme 5). That is, the reaction of the enamines **1** and **4** with di-*tert*-butyl methylenemalonate **2** in toluene in the presence of HMPA takes place preferentially from the front side of the lithioenamide **13**, while in THF solvent it takes place from the back side of complex **13**. This method provides a procedure for the synthesis of both enantiomers of α,α-dialkyl β-keto esters with a predictable absolute configuration in high enantiomeric purity starting from the same chiral enamine. Current work has expanded the scope and the utility of our procedure.

Experimental

All dry solvents were distilled under argon. Toluene and THF were distilled from sodium/benzophenone just before use. Diisopropylamine was distilled from calcium hydride. All reactions were conducted under argon unless otherwise stated. B.p.s and m.p.s (capillaries) were uncorrected. Kugelrohr distillation b.p.s refer to the external air-bath temperature. Column chromatography was performed on SiO_2. The ^1H NMR spectra were recorded in $CDCl_3$ at 100 MHz (JNM-PS) or 60 MHz (Hitachi R-24B); the chemical shifts are expressed in ppm relative to tetramethylsilane, and *J* values are given in Hz. Optical rotations were measured on a JASCO DIP-181 Digital Polarimeter, and $[\alpha]_D$-values are given in units of 10^{-1} deg cm^2 g^{-1}. Areas of (*R*)- and (*S*)-proton signals in the presence of Eu(hfc)$_3$ were determined by cutting and weighing expanded spectra.

Michael Reaction of N-[2-(*Ethoxycarbonyl*)*cyclohex*-1-*enyl*]-L-*valine* tert-*Butyl Ester* **1** *with Di*-tert-*butyl Methylenemalonate* **2**.—(*Entry* 7 *of Table* 1) (*procedure A*). An LDA solution was prepared from diisopropylamine (0.19 cm^3, 1.36 mmol) in toluene (1.5 cm^3) and 1.6 mol dm^{-3} BuLi in hexane (0.85 cm^3, 1.36 mmol) at −78 °C for 30 min. This LDA solution was added to a solution of compound **1**[5] (0.402 g, 1.24 mmol) in toluene (3.5 cm^3) at −78 °C and the mixture was stirred for 30 min. After treatment with HMPA (0.95 cm^3, 5.46 mmol) for 30 min, the mixture was cooled to −95 °C by using a pentane–liquid N_2-bath. A solution of diester **2** (0.32 cm^3, 1.36 mmol) in toluene (1.5 cm^3) was added to this over a period of 15 min and the mixture was stirred for 1 h at −95 °C. The reaction was quenched by 2 mol dm^{-3} HCl (20 cm^3) and the whole mixture was stirred vigorously at 0 °C for 1 h and was then extracted with diethyl ether (30 cm^3 × 3). The combined extracts were washed successively with aq. $NaHCO_3$, water and brine, dried ($MgSO_4$), and concentrated. Column chromatography [hexane–AcOEt (15:1)] provided the *Michael adduct* (S)-**3** (0.357 g, 73%) as an oil; $[\alpha]_D^{25}$ −45.1 (*c* 1.26 in $CHCl_3$) (92% ee) (Found: C, 63.3; H, 8.7. $C_{21}H_{34}O_7$ requires C, 63.3; H, 8.6%); ν_{max}(neat)/cm^{-1} 1750, 1730 and 1716; δ_H 1.23 (3 H, t, *J* 7), 1.42 (18 H, s), 1.43–2.70 (10 H, m), 3.25 (1 H, t, *J* 5.7) and 4.13 (2 H, q, *J* 7); *m*/*z* 398 (M$^+$), 342 and 286.

(*Entry* 7 *of Table* 2) (*procedure B*). An LDA solution was prepared from diisopropylamine (0.19 cm^3, 1.34 mmol) in THF (1.5 cm^3) and 1.6 mol dm^{-3} BuLi in hexane (0.84 cm^3, 1.34 mmol) at −78 °C for 30 min. This LDA solution was added to a solution of compound **1** (0.398 g, 1.22 mmol) in THF (3.5 cm^3) at −78 °C and the mixture was stirred for 30 min. The resulting mixture was cooled to −105 °C by using a pentane–liquid N_2-bath and a solution of diester **2** (0.32 cm^3, 1.34 mmol) in THF (1.5 cm^3) was added to this over a period of 15 min. After being stirred for 1 h at −105 °C, the reaction mixture was worked up in the same way as entry 7 of Table 1 to give compound (*R*)-**3** (0.420 g, 86%) as an oil; $[\alpha]_D^{25}$ +46.6 (*c* 1.24 in $CHCl_3$) (95% ee).

Michael Reaction of N-[2-(*Ethoxycarbonyl*)-1-*methylprop*-1-*enyl*]-L-*valine* tert-*Butyl Ester* **4** *with Diester* **2**.—(*Entry* 1 *of Table* 3). This reaction was performed by procedure A by using the enamine **4**[5a] to give *compound* (S)-**5** (82%) as an oil; $[\alpha]_{365}^{25}$ +6.72 (*c* 1.16 in $CHCl_3$) (87% ee) (Found: C, 61.0; H, 8.7. $C_{19}H_{32}O_7$ requires C, 61.3; H, 8.7%); ν_{max}(neat)/cm^{-1} 1743, 1728 and 1715; δ_H 1.27 (3 H, t, *J* 7), 1.33 (3 H, s), 1.45 (18 H, s), 2.15 (3 H, s), 2.46 (2 H, d, *J* 6), 3.15 (1 H, t, *J* 6) and 4.17 (2 H, q, *J* 7); *m*/*z* 372 (M$^+$).

(*Entry* 3 *of Table* 3). This reaction was performed by procedure B by using the enamine **4** to give compound (*R*)-**5** (86%) as an oil; $[\alpha]_{365}^{25}$ −6.48 (*c* 1.20 in $CHCl_3$) (84% ee).

Conversion of (S)-**9** *into* (S)-**10**.—To a solution of ethyl (*S*)-1-allyl-2-oxocyclohexanecarboxylate (*S*)-**9** (85% ee) (1.51 g, 7.18 mmol) in benzene (70 cm^3) were added ethylene glycol (0.80 cm^3, 14.4 mmol) and toluene-*p*-sulfonic acid monohydrate (0.274 g, 1.44 mmol) and the mixture was refluxed in a Dean–Stark apparatus for 90 min. This mixture was washed successively with aq. $NaHCO_3$ and brine, and dried ($MgSO_4$). Removal of the solvent and column chromatography [hexane–AcOEt (10:1)] provided the ketal (1.65 g, 90%) along with the starting material (*S*)-**9** (0.056 g, 4% recovery). The ketal was an oil; $[\alpha]_D^{25}$ −32.0 (*c* 1.47 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 1725 and 1640; δ_H 1.27 (3 H, t, *J* 7), 1.35–3.05 (10 H, m), 3.93 (4 H, s), 4.14 (2 H, q, *J* 7) and 4.80–6.07 (3 H, m); *m*/*z* 254 (M$^+$) (Found: M$^+$, 254.1516. $C_{14}H_{22}O_4$ requires M, 254.1516).

To a solution of the above ketal (0.653 g, 2.57 mmol) in THF (2.5 cm^3) was added 1 mol dm^{-3} BH_3·THF (3.08 cm^3, 3.08 mmol) over a period of 5 min. After the mixture had been stirred at 0 °C for 1 h, water (0.6 cm^3), 3 mol dm^{-3} NaOH (2.7 cm^3) and 35% aq. H_2O_2 (1.3 cm^3, 13 mmol) were added to the mixture which was then stirred for 1 h. After addition of brine, the mixture was extracted with diethyl ether (30 cm^3 × 3). The combined extracts were washed successively with 5% aq. $Na_2S_2O_3$ and brine, and dried ($MgSO_4$). Removal of the solvent followed by column chromatography [hexane–AcOEt (3:1)] gave the *alcohol ketal* (0.538 g, 77%) (see Scheme 3) and the starting ketal (0.035 g, 5% recovery). The alcohol was an oil; $[\alpha]_D^{25}$ −4.96 (*c* 1.49 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3430 and 1726; δ_H 1.27 (3 H, t, *J* 7), 1.20–2.25 (13 H, m), 3.61 (2 H, t, *J* 6), 3.93 (4 H, s) and 4.17 (2 H, q, *J* 7); *m*/*z* 272 (M$^+$) (Found: M$^+$, 272.1666. $C_{14}H_{24}O_5$ requires M, 272.1624).

The above alcohol ketal (0.435 g, 1.60 mmol) was oxidized by 1.87 mol dm^{-3} Jones reagent (1.19 cm^3, 2.23 mmol) in acetone at 0 °C. After 45 min, the reaction was quenched by Pr^iOH (2 drops) and water (30 cm^3). This mixture was extracted with diethyl ether (50 cm^3 × 3) and the combined extracts were washed with brine and dried ($MgSO_4$). After removal of the solvent, the crude acid was treated with diazoethane prepared from *N*-nitroso-*N*-ethylurea (3.74 g, 32 mmol) and 50% aq. KOH (20 cm^3) in diethyl ether at 0 °C. The mixture was stirred for 1 h at room temperature and the excess of diazoethane was destroyed by 3 mol dm^{-3} AcOH. The ethereal layer was washed successively with aq. $NaHCO_3$ and brine, and dried ($MgSO_4$). Removal of the solvent followed by column chromatography [hexane–AcOEt (15:1)] provided *diethyl ester* (S)-**10** (0.339 g, 68%) as an oil; $[\alpha]_D^{25}$ −9.83 (*c* 1.48 in $CHCl_3$) (Found: C, 61.3; H, 8.4. $C_{16}H_{26}O_6$ requires C, 61.1; H, 8.3%); ν_{max}(neat)/cm^{-1} 1732 and 1085; δ_H 1.25 (3 H, t, *J* 7), 1.28 (3 H, t, *J* 7), 1.05–2.56 (12 H, m), 3.98 (4 H, s), 4.15 (2 H, q, *J* 7) and 4.23 (2 H, q, *J* 7); *m*/*z* 314 (M^+), 269 and 241.

Conversion of Keto Ester **3** *into Ketal* **10**.—The Michael adduct (+)-**3** {$[\alpha]_D^{25}$ +16.4 (*c* 1.30 in $CHCl_3$)} (0.105 g, 0.265 mmol) was treated with trifluoroacetic acid (TFA) (0.5 cm^3) at 0 °C for 90 min. After evaporation, the residue was treated with excess of diazoethane in diethyl ether at 0 °C for 30 min. The excess of reagent was destroyed by 3 mol dm^{-3} AcOH and the ethereal layer was washed successively with aq. $NaHCO_3$ and brine, and dried ($MgSO_4$). Removal of the solvent followed by column chromatography [hexane–AcOEt (15:1)] provided the *triethyl ester* (0.062 g, 69%) (see Scheme 3) as an oil; $[\alpha]_D^{25}$ +23.1 (*c* 1.24 in $CHCl_3$) (Found: C, 59.4; H, 7.7. $C_{17}H_{26}O_7$ requires C, 59.6; H, 7.7%); ν_{max}(neat)/cm^{-1} 1753, 1729 and 1707; δ_H 1.28 (9 H, t, *J* 7), 1.45–2.70 (10 H, m), 3.41 (1 H, t, *J* 6) and 4.17 (6 H, q, *J* 7); *m*/*z* 342 (M^+) and 297.

The enantiomeric sample of the triethyl ester {$[\alpha]_D^{25}$ −17.8 (*c* 1.71 in $CHCl_3$)} (0.215 g, 0.628 mmol) in benzene (13 cm^3) was refluxed with ethylene glycol (0.15 cm^3, 1.3 mmol) and *p*-TsOH·H_2O (0.050 g, 0.13 mmol) by using a Dean–Stark apparatus for 3 h. Aqueous work-up and column chromatography [hexane–AcOEt (8:1)] provided the corresponding ketal (0.174 g, 72%) along with the starting triethyl ester (0.021 g, 10% recovery). The *ketal* was an oil; $[\alpha]_D^{25}$ −3.29 (*c* 1.46 in $CHCl_3$) (Found: C, 58.8; H, 7.9. $C_{19}H_{30}O_8$ requires C, 59.05; H, 7.8%); ν_{max}(neat)/cm^{-1} 1748, 1732 and 1719; δ_H 1.24 (9 H, t, *J* 7), 1.23–2.20 (8 H, m), 2.30 (1 H, dd, *J* 7 and 14), 2.67 (1 H, dd, *J* 5 and 14), 3.44 (1 H, dd, *J* 5 and 7), 3.88 (4 H, s), 4.08 (2 H, q, *J* 7) and 4.11 (4 H, q, *J* 7); *m*/*z* 386 (M^+), 341, 313 and 214.

A solution of the above ketal (0.073 g, 0.19 mmol), NaCN (0.013 g, 0.24 mmol) and water (0.01 cm^3, 0.6 mmol) in dimethyl sulfoxide (DMSO) (3 cm^3) was heated at 160 °C for 6 h. After addition of water (10 cm^3), the mixture was extracted with diethyl ether (25 cm^3 × 3) and the combined extracts were washed with brine and dried ($MgSO_4$). Removal of the solvent followed by column chromatography [hexane–AcOEt (15:1)] provided compound (*S*)-**10** (0.047 g, 80%) as an oil; $[\alpha]_D^{25}$ −2.98 (*c* 1.57 in $CHCl_3$); the other spectral data were identical with those of compound (*S*)-**10** derived from keto ester (*S*)-**9**.

Conversion of Keto Ester (S)-**11** *into Diester* (S)-**12**.—Ethyl (*S*)-2-acetyl-2-methylpent-4-enoate (*S*)-**11** (93% ee) was submitted to the same procedure as the conversion of keto ester (*S*)-**9** into ketal (*S*)-**10**. The *ketal* (72%) was an oil; $[\alpha]_D^{23.5}$ −13.4 (*c* 2.00 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 1725 and 1640; δ_H 1.18 (3 H, s), 1.25 (3 H, t, *J* 7), 1.34 (3 H, s), 2.14 (1 H, dd, *J* 8 and 13), 2.82 (1 H, dd, *J* 7 and 13), 3.97 (4 H, s), 4.18 (2 H, q, *J* 7), 5.05 (1 H, m), 5.07 (1 H, m) and 5.50–6.00 (1 H, m); *m*/*z* 228 (M^+) and 213 (Found: M^+, 228.1346. $C_{12}H_{20}O_4$ requires M, 228.1359).

Hydroboration then gave the *ketal alcohol* (66%) (see Scheme 4) as an oil; $[\alpha]_D^{23.5}$ +14.7 (*c* 1.00 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3600–3000 and 1720; δ_H 1.21 (3 H, s), 1.26 (3 H, t, *J* 7), 1.32 (3 H, s), 1.20–2.30 (4 H, m), 2.41 (1 H, s), 3.40–3.70 (2 H, m), 3.95 (4 H, s) and 4.15 (2 H, q, *J* 7); *m*/*z* 246 (M^+), 231 and 185 (Found: M^+, 246.1470. $C_{12}H_{22}O_5$ requires M, 246.1467).

Oxidation and esterification finally gave the *diester* (*S*)-**12** (44%) as an oil; $[\alpha]_D^{23.5}$ +10.5 (*c* 2.00 in $CHCl_3$) (93% ee) (Found C, 58.1; H, 8.4. $C_{14}H_{24}O_6$ requires C, 58.3; H, 8.4%); ν_{max}(neat)/cm^{-1} 1725; δ_H 1.21 (3 H, s), 1.25 (3 H, t, *J* 7), 1.27 (3 H, t, *J* 7), 1.35 (3 H, s), 1.70–2.50 (4 H, m), 3.96 (4 H, s), 4.13 (2 H, q, *J* 7) and 4.17 (2 H, q, *J* 7); *m*/*z* 288 (M^+) and 273.

Conversion of Triester **5** *into Ketal* **12**.—The Michael adduct (−)-**5** {$[\alpha]_{365}^{25}$ −6.48 (*c* 1.20 in $CHCl_3$)} (84% ee) was transesterificated by the same procedure as the conversion of its cyclic analogue **3** into compound **10**. The intermediate *triethyl ester* (91%) (see Scheme 4) was an oil; Kugelrohr distillation (170 °C/0.04 mmHg); $[\alpha]_{365}^{23}$ +16.5 (*c* 2.12 in $CHCl_3$) (Found: C, 56.65; H, 7.7. $C_{15}H_{24}O_7$ requires C, 56.95; H, 7.65%); ν_{max}(neat)/cm^{-1} 1750, 1730 and 1713; δ_H 1.27 (9 H, t, *J* 7), 1.35 (3 H, s), 2.16 (3 H, s), 2.49 (1 H, dd, *J* 6 and 15), 2.53 (1 H, dd, *J* 6 and 15), 3.40 (1 H, t, *J* 6) and 4.19 (6 H, q, *J* 7); *m*/*z* 316 (M^+) and 271.

The enantiomeric triethyl ester {$[\alpha]_{365}^{23.5}$ +15.6 (*c* 2.00 in $CHCl_3$)} was submitted to acetalization and de-ethoxycarbonylation by the same procedure as for the second part of the conversion of compound **3** into ketal diester **10**. Along with the starting triethyl ester (17% recovery), the *ketal triester* (74%) was obtained as an oil; $[\alpha]_{365}^{23.5}$ −25.5 (*c* 1.00 in $CHCl_3$) (Found: C, 56.7; H, 7.6. $C_{17}H_{28}O_8$ requires C, 56.7; H, 7.8%); ν_{max}(neat)/cm^{-1} 1725; δ_H 1.20 (3 H, s), 1.26 (9 H, t, *J* 7), 1.35 (3 H, s), 2.29 (1 H, dd, *J* 7 and 14), 2.65 (1 H, dd, *J* 5 and 14), 3.40 (1 H, dd, *J* 5 and 7), 3.96 (4 H, s), 4.15 (2 H, q, *J* 7), 4.17 (2 H, q, *J* 7) and 4.19 (2 H, q, *J* 7); *m*/*z* 345 ($M^+ - CH_3$).

Further elaboration gave diester (*S*)-**12** (54%) as an oil; $[\alpha]_D^{23.5}$ −8.21 (*c* 2.00 in $CHCl_3$); the other spectral data were identical with those of compound (*S*)-**12** derived from keto ester (*S*)-**11**.

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