An Expeditious Enantioselective Synthesis of Methyl *trans*-Chrysanthemate

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Dedicated to Professor Dieter Seebach on the occasion of his 65th birthday with extremely great appreciation for his invaluable contribution to organic synthesis.

Abstract: Methyl *trans*-chrysanthemate has been prepared in few steps from isopropylidenediphenylsulfurane and methyl (*E*)-3-(3,3-dimethyloxiran-2-yl)prop-2-enoate. The latter was obtained from methyl 4-oxobutenoate or 3-methylbut-2-en-1-ol. The Sharpless catalytic epoxidation reaction allows an asymmetric version of this transformation.

Key words: sulfur ylides, cyclopropanation, asymmetric induction, Sharpless epoxidation

Several years ago we reported that methyl chrysanthemate can be synthesized in a single pot from 4-oxobutenoate (**1**) and isopropylidenetriphenylphosphorane (**2a**) (2 equiv, Scheme 1).[1a] It was later established that the reaction takes place first on the aldehyde carbonyl group (already at –78 °C) of **1** and that the cyclopropanation occurs (around –30 °C) prior to any decomposition of the betaine **3**.[2]

We also described that 'protection' of the aldehyde group as a 'functionalized ether' **5** allows inversion of the order of construction of the carbon-carbon double bond and of the cyclopropane ring (Scheme 2).[1,3–5]

The second approach is less expeditious than the first because it requires a second deprotection step, but it offers the following advantages: it reaches the (1*R*)-*trans* **4′**, the most 'active' enantiomer, by taking advantage of the presence on **5** of a chiral center close to the site of attack of the incoming ylide; and it allows the choice of cyclopropanating agents such as isopropylidenediphenylsulfurane (**2b**).

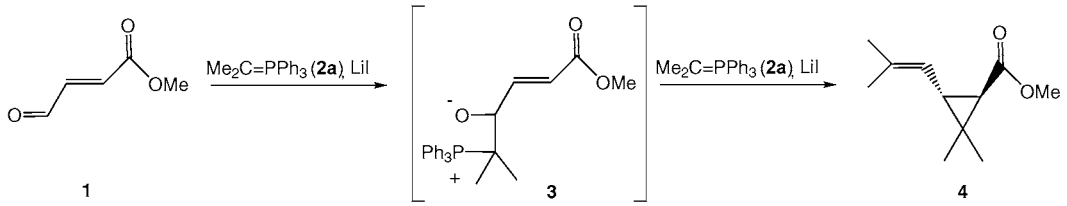
Particularly good results have been obtained from α,β-unsaturated esters bearing an acetal **5a**,[3] a hemi-aminal **5b**,[3,4f,h] a protected diol **5c**[3,4a–e,4g–i] or a thionocarbonate **5d**[5] in a suitable position (Figure 1).

Good to extremely good asymmetric induction was achieved using isopropylidenetriphenylphosphorane (**2a)** or better, isopropylidenediphenylsulfurane (**2b**), but it was found that whereas the former reagent mainly attacks (*E*)-**5c′** from the *Si*-face (de 72 %), the second one enters almost exclusively from the *Re*-face (de >98 %) (Scheme 3).[4]

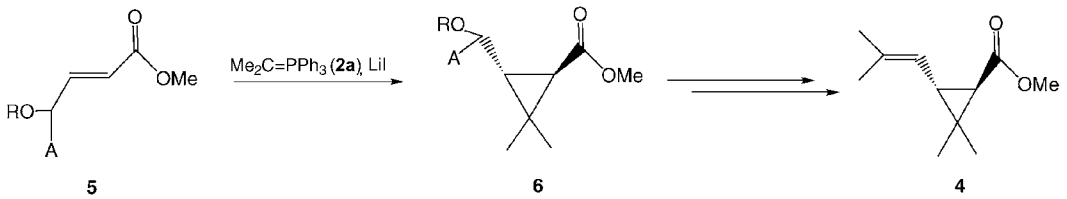
We now disclose two related sequences, which allow an efficient enantioselective catalytic version of these transformations.

Synthesis of Methyl (dl)-trans-Chrysanthemate

Following the work described in Scheme 1, we found that reaction of methyl 4-oxobutenoate (**1**) and isopropylidenediphenylsulfurane (**2b**) (2 equiv, DME, –78 °C, 2 h



Scheme 1



Scheme 2

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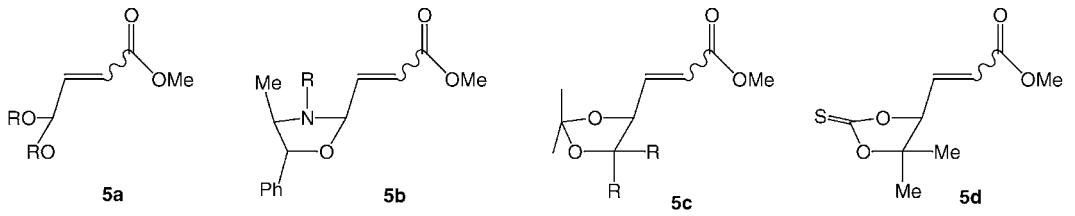
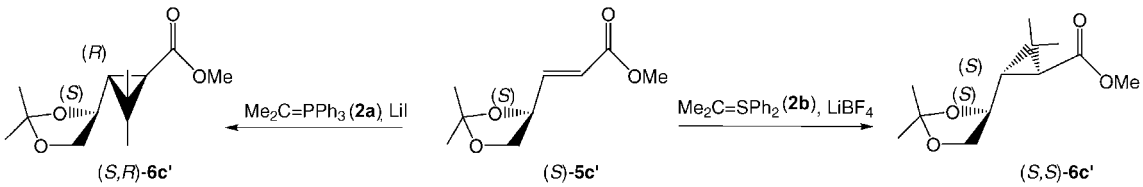


Figure 1 The structures of protected substrates **5a**–**d**



Scheme 3

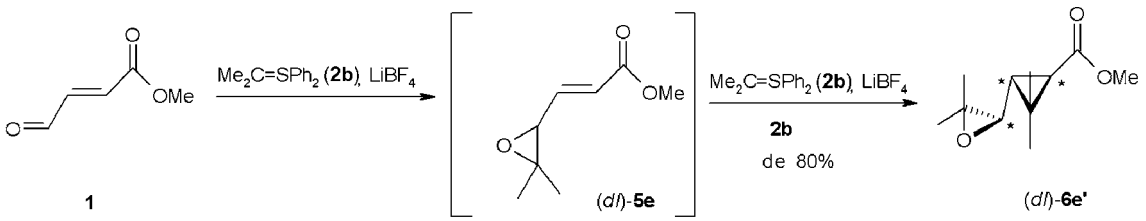
then 20 °C, 1 h) leads to the racemic methyl epoxychrysanthemate (*dl*)-**6e′** in good yield (70 %) and reasonably good stereocontrol at the three stereogenic centers (de 80 %) (Scheme 4).

The same process can be carried out stepwise providing first methyl (*E*)-3-(3,3-dimethyloxiran-2-yl)prop-2-enoate [(*dl*)-(*E*)-**5e**] by reaction of the first equivalent of ylide **2b** with **1** (DME, –78 °C, 2 h, then 20 °C, 1 h, 73% yield) followed by subsequent reaction of a second equivalent of the same ylide (DME, –78 °C, 2 h, then 20 °C, 1 h) with (*dl*)-**5e** to give (*dl*)-**6e′** in 88 % yield (de 94 %, Scheme 5, entry a).

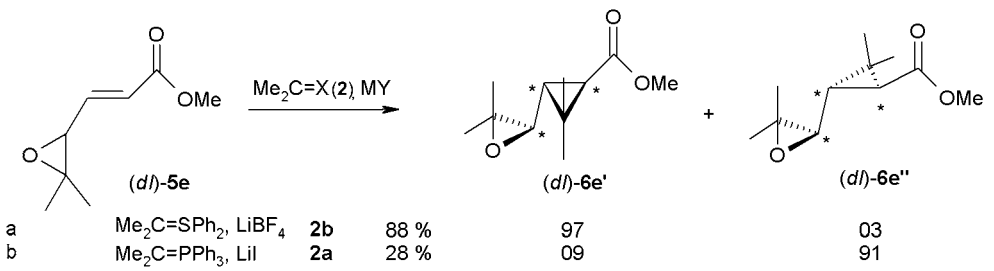
The higher relative stereocontrol systematically obtained in the stepwise reaction suggests that the cyclopropanation might take place, at least in part, on the betaine precursor of (*dl*)-(*E*)-**5e**.

Interestingly, a different diastereoisomer (*dl*)-**6e″**, resulting from the attack of (*dl*)-**5e** from the other face, is obtained in modest yield if the reaction is performed instead with isopropylidenetriphenylphosphorane (**2a**) (THF, 0 °C, 1 h, then 20 °C, 1 h, 28 % yield; **6e″**/**6e′** = 9:91, de 82%, Scheme 5, entry b).[4] Therefore (*dl*)-**5e** behaves as the other members of the γ-alkoxy-α,β-unsaturated esters family **5c**,**d** since all these compounds provide cyclopropyl esters **6** in which the relative stereochemistry is similar within the same family of reagents but different between the two families (**2a** and **2b**, Scheme 3).[3–5]

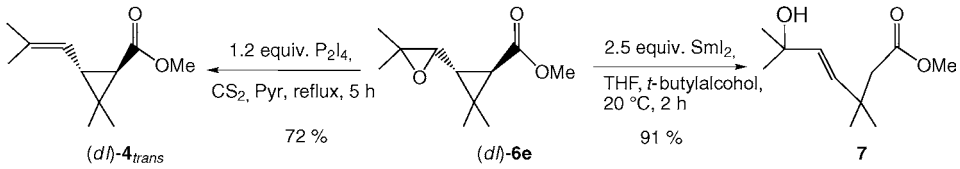
We have unambiguously confirmed the *trans*-relationship of (*dl*)-**6e′** and (*dl*)-**6e″** by comparing their ^{1}H NMR data to those of **6e** obtained as a stereoisomeric mixture (*dl*)-**6e′**/(*dl*)-**6e″** = 54:46) by epoxidation of methyl (*dl*)-*trans*-chrysanthemate [(*dl*)-*trans*-**4**] with *m*-CPBA (1.5 equiv, CH_2Cl_2, 20 °C, 1 h, 87 % yield).



Scheme 4



Scheme 5



Scheme 6

Finally, reduction of (dl)-**6e** to methyl (dl)-trans-chrysanthemate [(dl)-trans-**4**] has been effectively achieved by reaction with P_2I_4 (1.2 equiv, CS_2, pyridine, reflux, 5 h, 72 %, de ~100 %, Scheme 6).[6] It is interesting to note that SmI_2, which is usually able to reduce epoxides to olefins,[7] does not provide even a trace of the desired product but instead the allyl alcohol **7** resulting from reductive cyclopropane ring opening (Scheme 6).[8]

Enantioselective Synthesis of Methyl (1R)-trans-Chrysanthemate [(1R)-4]*

An enantioselective version of this reaction was achieved from the *trans*-γ,δ-epoxy-α,β-unsaturated ester (*E*)-**5e*** prepared, using the Sharpless asymmetric epoxidation reaction,[9] from 3-methylbut-2-en-1-ol (**8**) and (*l*)-diisopropyl tartrate to produce first the required (*S*)-(3,3-dimethyloxiran-2-yl)methanol (**9***) (Scheme 7).

The most straightforward synthesis of (*E*)-**5e*** entails the direct 'Parikh–von Doering oxidation'[10] of the crude mixture obtained from the Sharpless epoxidation reaction (1.2 equiv pyridine·SO_3, Et_3N, DMSO, 20 °C, 3 h) leading to the crude aldehyde **10*** which is in turn subjected, without purification, to the Wittig olefination reaction using α-methoxycarbonyltriphenylphosphorane in DMSO (1 equiv, DMSO, 20 °C, 4 h, 59%).[4d,11] A single chromatographic purification (silica gel, pentane–Et_2O, 80:20 v/v) allows, separation of the small amount (4%) of the *Z*-stereoisomer (*Z*)-**5e*** concomitantly produced. The enantiomeric excess recorded for methyl epoxy-*trans*-chrysanthemate [(1*R*)-*trans*-**6e***] resulting from the reaction of isopropyldiphenylsulfonium tetrafluoroborate was rather moderate (74 %) due to the modest enantiomeric excess with which **9*** is obtained (75%).[9]

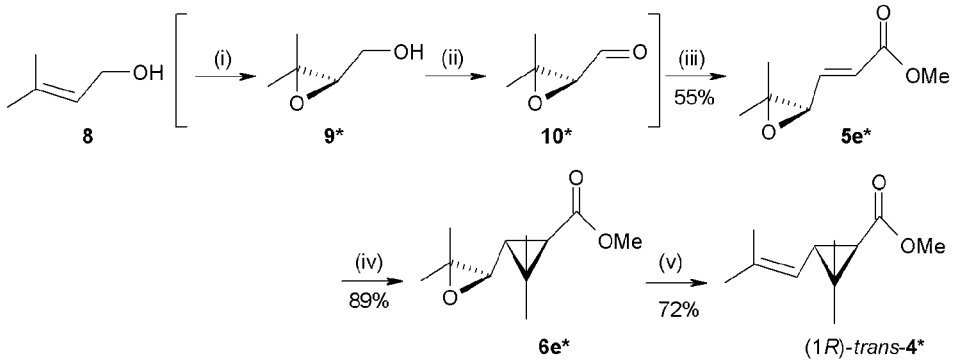
Almost complete stereocontrol of methyl (*E*)-3-[(2*R*)-3-3-dimethyloxiran-2-yl]prop-2-enoate {**5e***; ee >98%, $[\alpha]_D^{20}$ –30.64 (*c* = 1.155, $CHCl_3$)}, methyl epoxychrysanthemate {**6e***; ee 98%; $[\alpha]_D^{20}$ +16.02 (*c* = 0.945, $CHCl_3$)} and methyl *trans*-chrysanthemate {(1*R*)-*trans*-**4***; ee 98%; $[\alpha]_D^{20}$ +20.28 (*c* = 1.140, $CHCl_3$)} was nevertheless achieved by a single crystallization from diethyl ether of the nitrobenzoate of **9e***[9b,c] from which the enantiopure (*S*)-(3,3-dimethyloxiran-2-yl)methanol (**9e***) was obtained by biphasic ester hydrolysis using a phase transfer catalyst (4.1 equiv of an aq 9.6 N KOH solution, 0.2 equiv benzyltributylammonium chloride, CH_2Cl_2, 20 °C, 12 h).

Spectroscopic data (IR, ^1H NMR) of methyl (1*R*)-*trans*-chrysanthemate [(1*R*)-*trans*-**4***] obtained in this work are identical to those of an authentic sample.[4d]

Work is now in progress to adapt the reported strategy to the synthesis of deltamethrin.

Methyl (*E*)-3-[(2*R*)-3,3-dimethyloxiran-2-yl]prop-2-enoate (5e*)

Method 1: Crushed, activated 3 Å molecular sieves (1.5 g) were introduced into a flame-dried flask filled with argon. CH_2Cl_2 (100 mL) was added and the flask was cooled to –20 °C. D-(–)-Diisopropyl tartrate (702 mg, 3.0 mmol), 3-methylbut-2-en-1-ol (**8**; 4.3 g, 50.0 mmol, stored over molecular sieves), and Ti(*i*-PrO)$_4$ (710 mg, 2,5 mmol) were added sequentially. The stirring was maintained for 0.5 h at –20 °C, whereupon a 3.7 M solution of *tert*-butyl hydroperoxide (TBHP) in toluene (27 mL, 100 mmol) was added via a syringe and the stirring was continued for a further 3 h at the same temperature. Careful quenching of the excess TBHP was accomplished by the slow addition of dimethyl sulfide (12.4 g, 200 mmol), taking care that the temperature did not rise above –20 °C. After stirring at –20 °C, for 0.7 h, CH_2Cl_2 was evaporated under vacuum



Scheme 7 (i) TBHP, Ti(OPr-*i*)$_4$, (*l*)-DIPT, CH_2Cl_2, –20 °C, 3 h, Me_2S; (ii) Pyridine·SO_3, Et_3N, DMSO, 20 °C, 3 h; (iii) $Ph_3P{=}CHCO_2Me$, 20 °C, 4h; (iv) $Me_2C{=}SPh_2$, $LiBF_4$, DME, –78 °C, 2 h then 20 °C, 1 h; (v) P_2I_4, CS_2, pyridine, 5 h, reflux

(15 mbar, under 20 °C). The resulting mixture, still containing some CH_2Cl_2, was dissolved in DMSO (60 mL) and Et_3N (55 mL) and subjected to the 'Parikh–von Doering oxidation' reaction using a solution of pyridine·SO_3 complex (9.54 g, 60 mmol) in DMSO (70 mL) which was slowly added (3 h) at 20 °C temperature. Olefination reaction of the crude aldehyde was carried out with α-methoxycarbonyltriphenylphosphorane (16.7 g, 50 mmol)[11] at r.t. After stirring the resulting mixture for 4 h at r.t., H_2O (20 mL) was added and the mixture was extracted twice with Et_2O, washed with H_2O and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude material was purified by column chromatography on silica gel (pentane–Et_2O, 80:20 v/v, R_f 0.38) to yield 4.27 g (55%) of (*E*)-**5e***.

Method 2: Alternatively oxidation of **8** was performed similarly, but with TBHP in CH_2Cl_2 (15 mL of a 6.8 M solution, 100 mmol). The reaction mixture was stirred at –20 °C for 2.5 h, then the excess of TBHP was reduced by trimethyl phosphite (19 mL, 75.0 mmol) in 0.75 h taking care that the temperature did not rise above –20 °C. The synthesis of the related nitrobenzoate was achieved by adding Et_3N (8.5 mL, 60 mmol) followed by a solution of *p*-nitrobenzoyl chloride (9.3 g, 50 mmol) in CH_2Cl_2 (15 ml). This mixture was stirred at 0 °C for 1 h, filtered through a pad of Celite, and the filtrate was washed with 10% aq tartaric acid (2 × 15 mL), aq sat. $NaHCO_3$ (3 ×15 mL), and brine (2 × 15 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated. The solid was recrystallized twice from Et_2O to give [(2*R*)-3,3-dimethyloxiran-2-yl] 4-nitrobenzoate, as fine pale yellow needles (3.62 g; 31%; ee >98%; 3.12 g; 26%; ee >90%). An aq solution of NaOH (2.69 g in 5 mL of H_2O, 9.6 N, 48 mmol) containing benzyltributylammonium chloride (700 mg, 2.4 mmol) was added dropwise at 20 °C to the [(2*R*)-3,3-dimethyloxiran-2-yl] 4-nitrobenzoate (2.89 g, ee >98%, 11.5 mmol) dissolved in CH_2Cl_2 (30 mL). After stirring for 12 h at 20 °C, the mixture was extracted with Et_2O and dried (Na_2SO_4). CH_2Cl_2 was evaporated at 20 °C under 15 mbar and the resulting mixture was diluted with DMSO (15 mL) containing Et_3N (13 mL) and reacted with pyridine·SO_3 complex (2.2 g, 13.8 mmol) dissolved in the same solvent (15 mL). The mixture was stirred at r.t. for 2 h and subjected to the olefination reaction using the α-methoxycarbonyltriphenylphosphorane (3.84 g, 11.5 mmol)[11] at 20 °C. After stirring at this temperature for 4 h, the mixture was hydrolyzed with H_2O (10 mL) and extracted with Et_2O, washed with H_2O and dried (Na_2SO_4). The solvents were removed under reduced pressure. The crude material was purified by column chromatography on silica gel (pentane–Et_2O, 80:20, R_f 0.38) to yield 0.933 g (52 %) of (*E*)-**5e***.

IR (film): 2999, 2958, 2926, 1725, 1658, 1438, 1381, 1320, 1296, 1265, 1194, 1173, 1115, 1042, 981 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.30 and 1.42 (2 s, 6 H, 2 CH_3), 3.34 (dd, *J* = 6.4, 1.2 Hz, 1 H, Me_2COCH), 3.76 (s, 3 H, CO_2CH_3), 6.12 (dd, *J* = 15.6, 1.2 Hz, 1 H, $CHCO_2Me$), 6.85 (dd, *J* = 6.4, 15.6 Hz, HC=$CHCO_2Me$).

Methyl *trans*-3-(3,3-Dimethyloxiran-2-yl)-2,2,dimethylcyclopropane Carboxylate (Methyl *trans*-Epoxychrysanthemate, 6e*)

A solution of LDA (0.58 N, 3.1 mL) was added dropwise, under argon and at –78 °C, to a well stirred solution of isopropyldiphenylsulfonium tetrafluoroborate (569 mg, 1.8 mmol)) in anhyd DME (10 mL) containing freshly distilled CH_2Cl_2 (0.12 mL, 1.8 mmol). The resulting yellow solution was then stirred for an additional 0.3 h at –78 °C. A solution of **5e*** (234 mg, 1.5 mmol) in DME (1 mL) was added dropwise to the above mixture. After stirring for 2 h at –78 °C and 1 h at 20 °C, the mixture was hydrolyzed by the addition of aq sat. NH_4Cl solution, and extracted with Et_2O. The Et_2O extract was washed with brine, dried (Na_2SO_4),and the Et_2O was removed under reduced pressure. The crude material was purified by column chromatography on silica gel (pentane–Et_2O, 85:15 v/v, R_f 0.49) to yield 266 mg (89 %) of **6e***.

IR (film): 2991, 2957, 2931, 1730, 1441, 1403, 1381, 1341, 1287, 1225, 1174, 1118, 1061, 1027, 997 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.26–1.37 (m, 13 H, 4 CH_3, 3 s at 1.37, 1.33 and 1.26 with 3 H each and 1 H, m, $CHCHCO_2Me$), 1.54 (d, *J* = 5.2 Hz, 1 H, $CHCO_2Me$), 2.51 (d, *J* = 8.4 Hz, 1 H, Me_2COCH), 3.70 (s, 3 H, CO_2CH_3).

Methyl *trans*-Chrysanthemate [(1*R*)-*trans*-4*]

A solution of **6e*** (297 mg, 1.5 mmol) and pyridine (1.5 mL) in CS_2 (3 mL) was added at 20 °C to a solution of P_2I_4 (1.026 g, 1.8 mmol) in CS_2 (5 mL). The resulting dark brown solution was refluxed for 5 h, hydrolysed with H_2O (5 mL) and extracted with Et_2O. The organic extracts were washed with aq sat. solution of $Na_2S_2O_3$ prior to the usual workup. Purification by column chromatography on silica gel (pentane–Et_2O, 90:10 v/v, R_f 0.78) afforded the methyl *trans*-chrysanthemate [(1*R*)-*trans*-**4***] in 72 % yield. Its IR and ^{1}HNMR spectrum were identical to those of an authentic sample.[4d]

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