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Enantioselective synthesis of 1(*R*)-*trans*-chrysanthemic acid

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Abstract—1(*R*)-*trans*-Chrysanthemic acid has been prepared in four steps from methyl 5-methyl-2,4-hexadienoate and isopropylidene diphenylsulfurane.

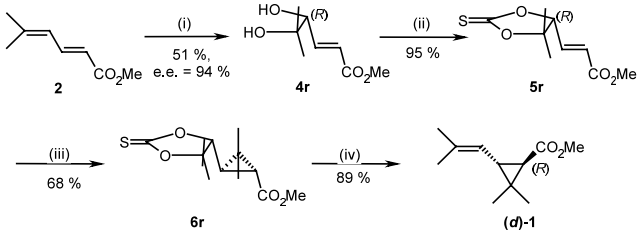
We report a short and efficient enantioselective synthesis of methyl 1(*R*)-*trans*-chrysanthemate (*d*)-**1**, whose corresponding acid is the constituent of one of the most active natural pyrethroid insecticides.[1] This has been achieved in four steps from methyl 5-methyl-2,4-hexadienoate **2**[2] and isopropylidene diphenylsulfurane **3**[3] which provide the complete carbon skeleton (7+3) present on methyl chrysanthemate (Scheme 1).

Interestingly our approach uses the same starting materials and the same key step (cyclopropanation of an α,β-unsaturated ester) as originally described by Corey for the synthesis of the racemate (Scheme 2)[3] and can therefore be viewed as one of its asymmetric versions.

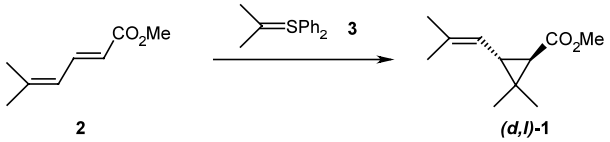
The proposed transformation takes into account (i) the high propensity of AD-mix β to perform the enantioselective dihydroxylation of C,C double bond using catalytic amounts of its chiral ligand,[4] (ii) the high asymmetric induction which is usually associated to the cyclopropanation of chiral γ-alkoxy-α,β-unsaturated esters by sulfur ylides,[1,5] and (iii) the proper choice of the thiono carbonate which plays the role of 'the diol protecting group' in the cyclopropanation step and delivers the trisubstituted C,C double bond present on methyl chrysanthemate **1** on further reductive elimination reaction.[6]

The reaction between methyl 5-methyl-2,4-hexadienoate **2** and AD-mix β[4] leads to a 8/2 mixture of regioisomeric diols in 88% overall yield. Purification affords 2,3-dihydroxy-5-methyl-2-hexenoate **4r** in 51% yield (e.e. 94%) which has been then transformed to the corresponding thionocarbonate **5r** on reaction with thiophosgene (DMAP, 0°C, 2 h, 95%).[6]

Cyclopropanation went smoothly from **5r** and isopropylidene diphenyl sulfurane [prepared from isopropyldiphenyl sulfonium tetrafluoroborate and LDA (1.2 equiv.), DME, −78°C, 0.5 h in the presence of dichloromethane (DCM, 1.2 equiv.)] and affords the functionalized cyclopropyl ester **6r** in good yield and with almost complete asymmetric induction (68% yield d.e.>98%).



Scheme 1. Synthesis of 1(*R*)-*trans*-chrysanthemic acid using isopropylidene diphenyl sulfurane. (i) (a) AD-mix β, *t*-BuOH/H_2O (1/1); (b) $MeSO_2NH_2$, 20°C, 20 h; (ii) $Cl_2C{=}S$, DMAP, CH_2Cl_2, 0°C, 2 h; (iii) $Me_2C{=}SPh_2$ **3**, $LiBF_4$, DME, −78°C, 2 h, −78°C to 20°C, 1 h; (iv) $(CH_2NMe)_2P$-Ph, neat, 40°C, 6 h.



Scheme 2. Synthesis of (*R*,*S*)-*trans*-chrysanthemic acid as originally described by E.J. Corey.

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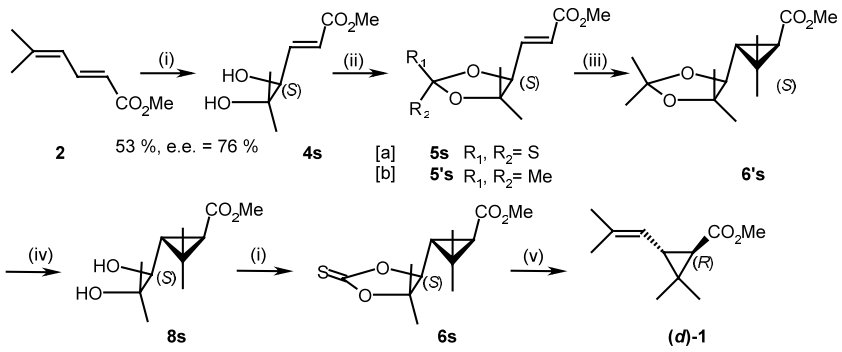

Scheme 3. Proposed alternative route to 1(*R*)-*trans*-chrysanthemic acid using isopropylidene triphenyl phosphorane. (i) AD-mix α; (ii) (a) $Cl_2C{=}O$; (b) acetone, H^+; (iii) $Me_2C{=}PPh_3$; (iv) H_3O^+; (v) $(CH_2NMe)_2PPh$.

Removal of the thiocarbonate moiety has been achieved under mild conditions using trisaminophosphine (3 equiv., neat, 40°C, 6 h)[6a] to produce methy1 1(*R*)-*trans*-chrysanthemate **1** (89% yield, e.e. 95%, compared to an authentic sample).[5a,7]

The synthesis reported here could appear as trivial since each of the individual steps was previously known. We will now show that successful synthesis of **1** requires adequate synthetic planning and proper choice of reagents.

What would have happened if we had made a different choice? Let us look at a different scenario which would have taken place if isopropylidene triphenyl phosphorane would have been used in place of its sulfur analogue.[1,5]

AD-mix α is now required since phosphoranes and sulfuranes are known to react by the opposite face with γ-alkoxy-*E*-α,β-unsaturated esters.[1,5] Stereocontrol is much poorer at both the dihydroxylation stage[4] (e.e. 76% instead of 94% with AD-mix β) and at the cyclopropanation reaction[5,8] (d.e. 75% instead of 98% with AD-mix β, compare Scheme 3 to Scheme 1). Moreover isopropylidene triphenyl phosphorane leads, on reaction with the unsaturated the thionocarbonate **5′** (1.2 equiv., THF, 0°C to 20°C), to an intractable mixture of compounds in which the cyclopropyl ester **6′** is missing.

The synthesis of methyl 1(*R*)-*trans*-chrysanthemate **1** could have been nevertheless achieved from the diol **4s** using the dioxolane protecting group as already described for a related case[1,5,7] (**5s**, Scheme 3). This is a quite lengthy route (seven instead of four steps) which will produce **1** with poor enantioselection (e.e. <56%= 75×75) and will offer no advantages over the route reported in Scheme 1. We have not pursued our work towards these lines.

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