

NOVEL STEREOSELECTIVE SYNTHESSES OF VINYL CYCLOPROPANE CARBOXYLIC ESTERS.

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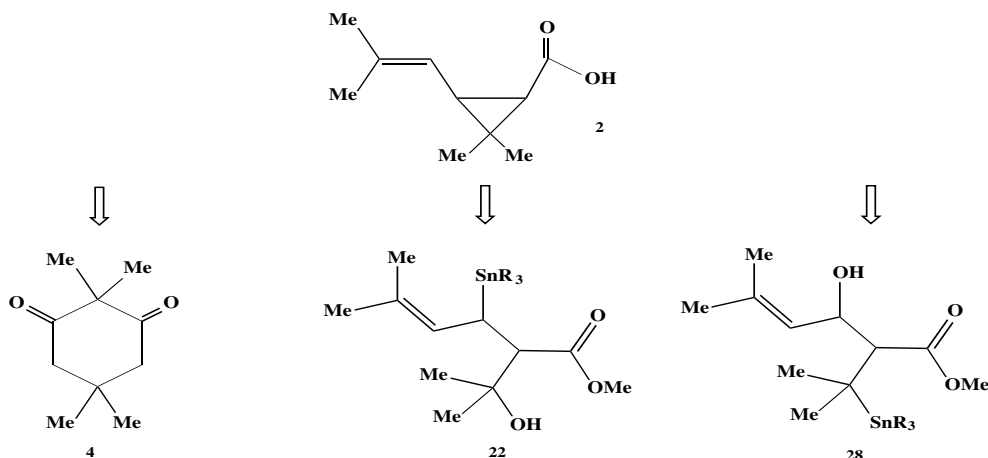
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Abstract

Vinyl cyclopropane carboxylic esters including chrysanthemates **1**, the most powerful commercially available insecticides,¹ have been prepared from dimethyl dimedone **4** or γ -hydroxyalkyl stannanes **22** and **28** themselves easily prepared from unsaturated esters and trialkylstannylolithiums (Scheme 1).

Scheme 1

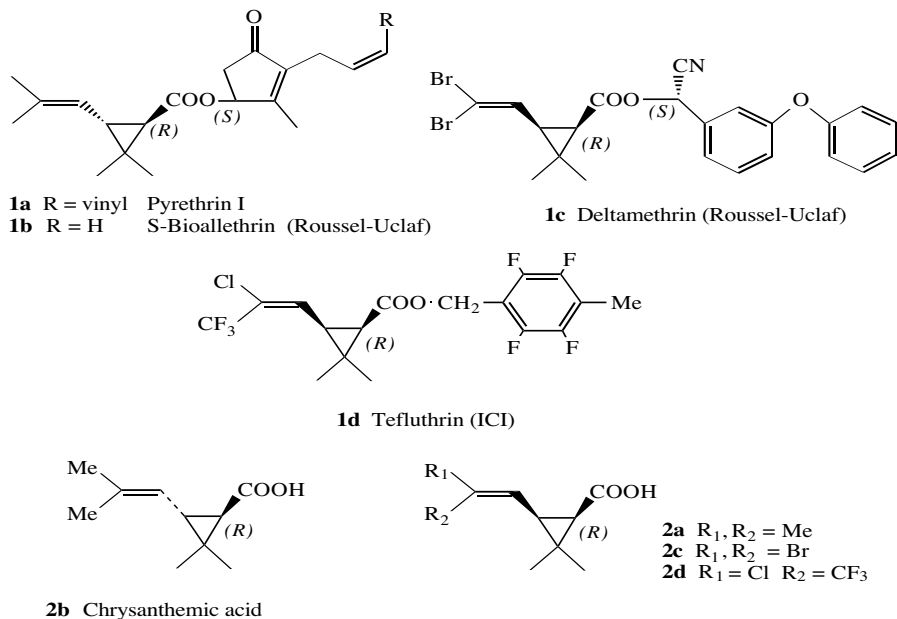


We have been interested over the past twenty years in the synthesis of this fascinating small molecule belonging to the diterpene family which concentrates on its C-10 carbon skeleton all the features of the complex molecules : three inter-reactive functional groups (olefin, ester, cyclopropane) and stereochemical problems (relative and absolute stereochemistry).^{1a,b}

S-Bioallethrin **1b**,¹ deltamethrin **1c** ^{1,2a} and tefluthrin **1d** ^{1b,c} are valuable insecticides belonging to this family of compounds, commercially available for domestic and agricultural uses against flying and soil insects respectively.

possesses the *trans*-stereochemistry found in the natural pyrethrin I **1a**, the others possess a *cis*-relationship between the two substituents on the cyclopropane ring and bear two halogens on the vinylic carbon which are required to enhance their photostability in the fields.

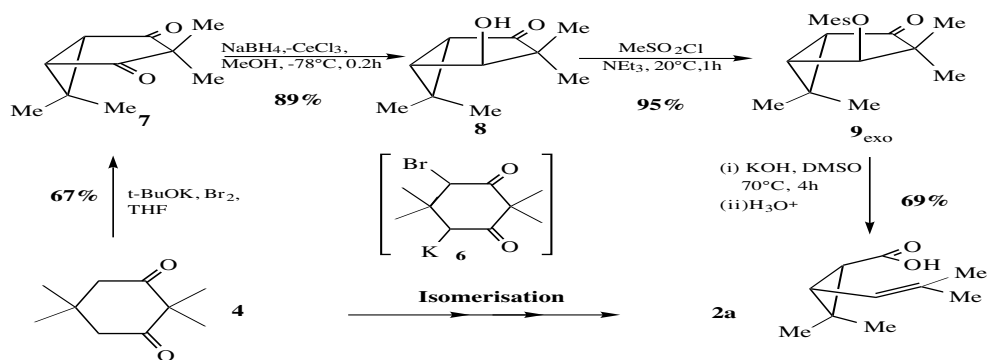
Scheme 2



We have first designed ^{1,3} a novel stereoselective synthesis of 1-(*R,S*)-*cis*-chrysanthemic acid **2a** from dimethyl dimedone **4** which uses cheap reagents compatible with industrial requirements and have extended it to the synthesis of optically active (*1R*)-*cis*-chrysanthemic acid **2a*** precursor of deltamethrin and of (*1R*)-*trans*-chrysanthemic acid **2b*** precursor of the natural pyrethrin I **1a**.

Dimethyl dimedone **4**, readily prepared by di-methylation of dimedone **3** (4 equiv. K₂CO₃, 2.5 equiv. MeI, EtOH-H₂O, 70°C, 4h, 63% yield),⁴ was chosen as the starting material since it possesses not only the same formula as chrysanthemic acid **2a** (C₁₀H₁₆O₂) but also the carbon framework and the functionalities placed in suitable positions to allow, in a minimum number of steps, the functional group modifications required for the desired transformation. The key steps of this process are beyond doubt (i) the cyclopropanation reaction which produced the bicyclo [3.1.0]hexa-2,4-dione ⁵ **7** and (ii) the Grob fragmentation ⁶ on the mesylate **9** derived from β-keto alcohol **8** itself resulting from the mono-reduction of **7**. The stereochemical outcome of each individual step which is important for the success of the whole process is depicted in Scheme 3.

Scheme 3



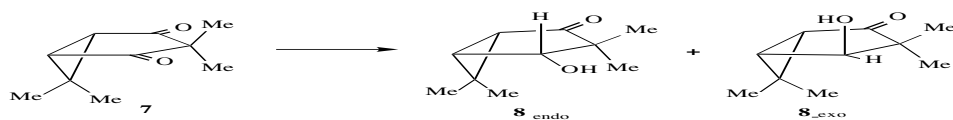
The synthesis of the 3,3,6,6-tetramethyl-bicyclo[3.1.0]hexa-2,4-dione **7** was efficiently achieved (67% yield) in one pot from 2,2,5,5-tetramethyl-cyclohexa-1,3-dione **4** on sequential reaction with potassium *tert*-butoxide (2.2 equiv., THF, -78°C to 40°C) and bromine (1.6 equiv., pentane, 40°C , 1h). This one pot transformation offers an original solution to our problem since the 6-bromo-4-potassio-2,2,5,5-tetramethyl-cyclohexa-1,3-dione **6** intermediary formed is immediately cyclised under these conditions rather than to further react with bromine. This avoids the difficulties we encountered when the transformation was performed in a two-step reaction. An even more efficient method involves the reaction of the dione **4** with two equivalents of LDA to deliver the dianion which is further oxidatively cyclised^{3c} by copper (II) chloride ((i) 2 equiv. LDA, THF, -78°C , 0.5h, (ii) 2 equiv. CuCl_2 , -78°C , 0.5h then 20°C , 1h, 81% yield). It is interesting to note that such reaction cannot be achieved if potassium *tert*-butoxide, which is probably not strong enough to allow the dianion formation, is used instead.

The chemoselective mono-reduction of this bicyclic dione **7** was achieved by a large array of reducing agents^{6,7} but most of them delivered, exclusively or mainly, the *endo* alcohol **8_{endo}** resulting from the attack of the hydride from the least hindered face of **7**.^{3a,b} Unfortunately however, this quite hindered cyclopropyl carbinol, which produced the corresponding mesylate **9_{endo}** in fair yield on further reaction with mesyl chloride (1 equiv. MsCl , NEt_3 , CH_2Cl_2 , 0°C , 6h, >95% yield), decomposed to 5-isopropylidene-2,2-dimethyl cyclopenten-3-one-1 resulting from cyclopropane ring opening at higher temperature (20°C) or when it was reacted with a base.

After different unsuccessful attempts, we have found that a dramatic change in the *exo/endo* ratio can be achieved when the reaction is carried out at 20°C with one molar equivalent of NaBH_4 in methanol in the presence of one molar equivalent of cerium trichloride (Luche's reagent, Scheme 4).^{9,10} Interestingly exclusive *endo* attack leading to **8_{exo}** was observed (Scheme 4) when the reaction was carried out at

Changing one of several parameters in the above mentioned reaction ^{3b} decreases the ratio of the desired *exo*-stereoisomer ((i) different solvents : such as ethers or alcohols, (ii) different lanthanide salts (Ce(NO₃)₄NH₄, SmI₂, SmI₃) or (iii) different hydrides (LiBH₄, NaHB(OMe)₃, ClCe(BH₄)₂, Ce(BH₄)₃). We have also found that this change of stereoselectivity can be achieved with catalytic amounts of CeCl₃ (up to 0.1 equiv.) ; the regioselectivity was then poorer than when one molar equivalent of CeCl₃ was used (Scheme 4).

Scheme 4



Conditions

Overall yield

Ratio

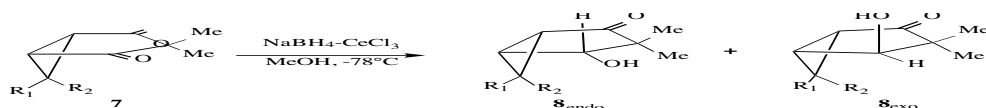
endo/exo

1 mol. equiv. NaBH ₄ , methanol, 20°C	89%	80/20
1 mol. equiv. NaBH ₄ , 1 mol. equiv. CeCl ₃ , methanol, 20°C	88%	22/78
1 mol. equiv. NaBH ₄ , 1 mol. equiv. CeCl ₃ , methanol, -78°C	85%	0/100
1 mol. equiv. NaBH ₄ , 0.5 mol. equiv. CeCl ₃ , methanol, -78°C	81%	23/77

This reversal of stereoselectivity was accounted from a pre-complexation by CeCl₃ of the bicyclic diketone **7** from its least hindered *exo*-face and reaction of the hydride from the *endo* face of the complexed diketone. The presence of the *endo* methyl group proved to be crucial for the stereoselective reduction since it hinders the *endo*-face allowing thus a more complete discrimination, by CeCl₃, of the two faces of the bicyclic-diketone **7**.

We in fact found ^{3c} that (i) the reduction with NaBH₄-CeCl₃ of the bicyclic diketones **7'** and **7''** possessing no *endo* methyl group is less selective. But very high selectivity is observed when bicyclic diketone **7'''**, possessing an *endo* methyl group, is reacted with the same reducing system (1 equiv. NaBH₄, 1 equiv. CeCl₃, MeOH, -78°C, Scheme 5).

Scheme 5



STARTING DIKETONE
7' R₁ = Me, R₂ = H
7'' R₁ = H, R₂ = H
7''' R₁ = H, R₂ = Me

PRODUCT YIELD (ENDO/EXO)
8' 94% (43 / 57)
8'' 89% (50 / 50)
8''' 93% (07 / 93)

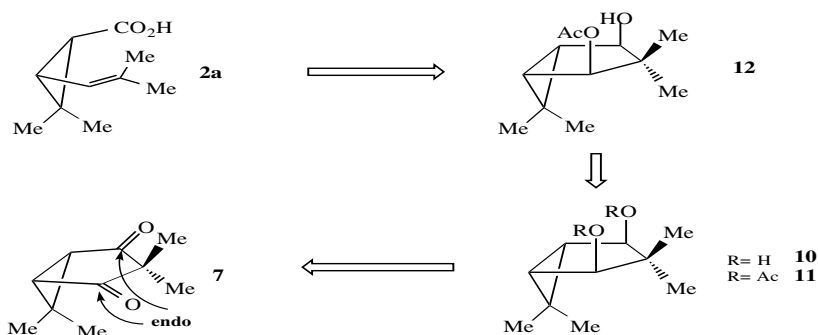
The synthesis of (*d,l*)-*cis*-chrysanthemic acid **2a** was achieved ² (Scheme 3) from the *exo* alcohol **8_{exo}** in two steps which involve its mesylation (MsCl, NEt₃, CH₂Cl₂, 20°C, 1h, 95% yield) and the reaction of the resulting mesylate **9_{exo}** with

Modification of the synthetic scheme discussed above (Scheme 3) allowed the stereoselective synthesis of the (1*R*)-*cis*-chrysanthemic acid **2a***. The stereo differentiation should have been best achieved at the earliest stage of the synthesis by the enantioselective reduction of the prochiral diketone **7** but this should have required the selective reduction of its pro-*R* carbonyl group by its most hindered face. This could have been achieved by a chiral reducing agent or by using a chiral lanthanide salt. It was not easy to propose a practical solution for the former objective since the class of reagents able to perform such reaction are bulky and their use seems to be incompatible with the stereofacial differentiation required. Furthermore the poor knowledge of (i) the intimate mechanism by which the lanthanide salts work and (ii) the role of various parameters on the stereochemical course of their reaction towards **7** led us to postpone this approach.

We have tried to perform the enantioselective reduction of **7** using baker yeast or *Curvularia lunata* under conditions which proved to be successful for the enantioselective reduction of related dimethyl dimedone **10** and 2,2,5,5-tetramethyl-1,4-hexadione **11** respectively but the reductions of **7** were too slow by both methods to be of practical use (10 and 20% yield after 5 days and 48h respectively).

We decided therefore to adopt a different strategy which is depicted in Scheme 6 and whose success lies on (i) the stereoselective di-reduction of **7** to the prochiral diol **10** (ii) the di-acetylation of **10** to **11** and (iii) further enantioselective mono de-acetylation ¹² of **11** to **12** which was expected to deliver (1*R*)-*cis*-chrysanthemic acid **2a*** after proper group manipulations (Scheme 6).

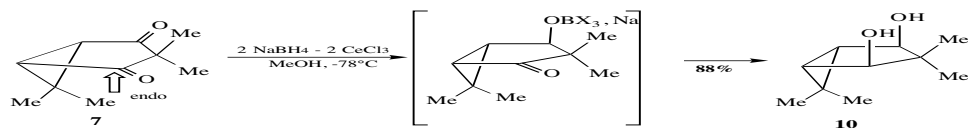
Scheme 6



The stereoselective synthesis of the di-*exo* diol **10**_{diexo} required the reduction of **7** twice by its most hindered face and was expected to be successfully achieved using the NaBH₄-CeCl₃ reagent already successfully used for its mono-reduction to **8**_{exo}. We took advantage of this work to also study the selective reduction of **7** to its di-*endo* prochiral stereoisomer **10**_{diendo} or to the *exo-endo* diol **10**_{exo-endo}. The reduction of **7** to the di-*exo* diol **10**_{diexo} was almost completely stereoselectively achieved by using an excess of NaBH₄-CeCl₃ (2.4 equiv) NaBH₄ (2 equiv) CeCl₃

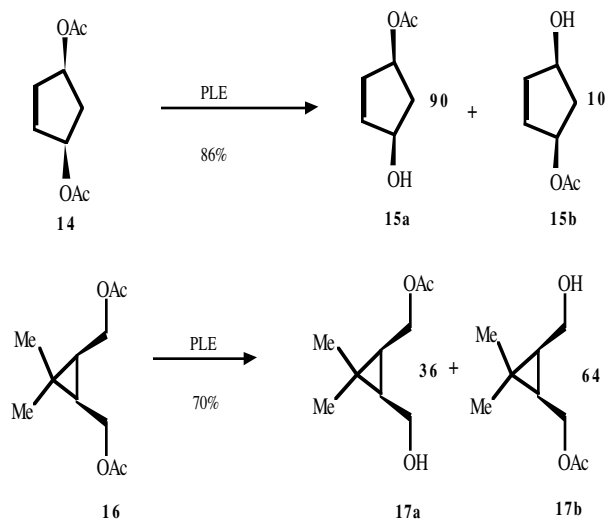
contrast with the results we described above for the selective mono reduction of **7** to **8_{exo}**.

Scheme 7



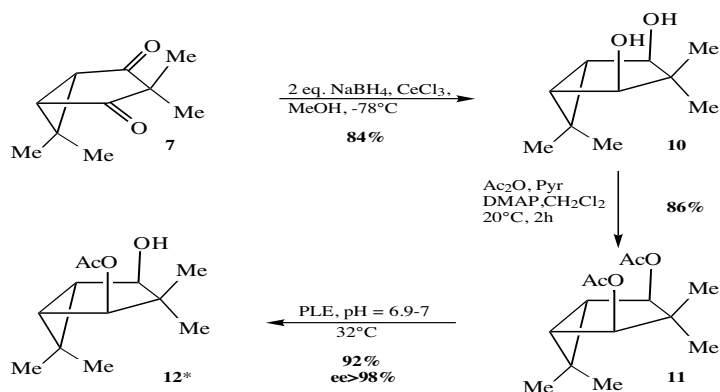
The di-*exo* diol **10** was readily transformed to its diacetate **11** on reaction with acetic anhydride (excess Ac₂O, Pyr., DMAP, CH₂Cl₂, 20°C, 2h, 86% yield). The next step was again a crucial one since it should involve the enantioselective hydrolysis of one of the two diacetates. We decided to use a lipase for such purpose. Several reports deal with the stereoselective hydrolysis of prochiral diols.¹² The lipase induced hydrolysis of the *cis*-cyclopentene-1,3-diacetate **14** was reported^{12a,b} to deliver the *cis*- γ -acetoxy alcohol **15a** in very good yield and very high enantioselectivity (Scheme 8) whereas the *cis*-cyclopropyl di-carbinol diacetate **16** was described^{12b,c} to produce the δ -acetoxy alcohol **17b** which possesses the reversed stereochemistry as compared as **15a** and with a much poorer enantioselectivity (Scheme 8). Interestingly both of the structural features located in **14** and **15** are present in the bicyclic diacetate **11_{diexo}**.

Scheme 8



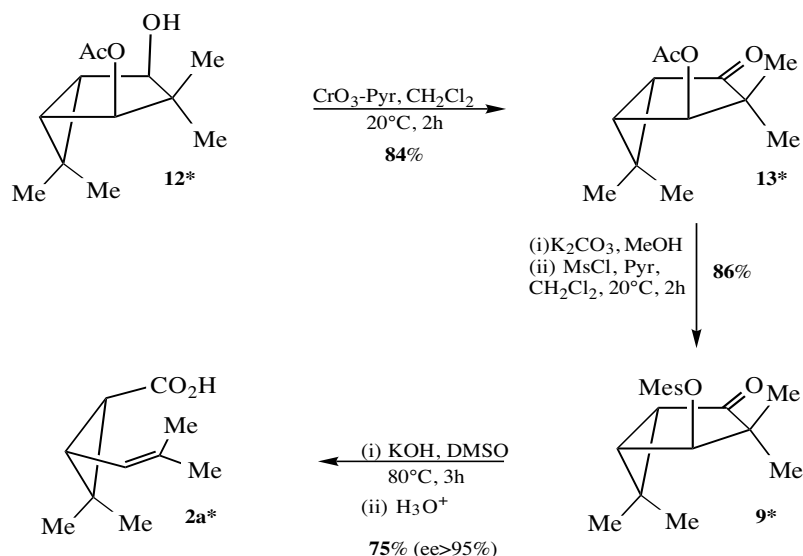
We have found that the di-*exo* diacetate **11** is transformed to the corresponding γ -acetoxy alcohol **12*** in very good yield and very high enantioselectivity using pig liver esterase (PLE, pH= 6.9-7, 32°C, 8h, 92%, e.e. > 98%, Scheme 9).

Scheme 9



The synthesis of (1*R*)-*cis*-chrysanthemic acid **2a*** has been achieved from **12*** in good overall yield by oxidation with the Corey-Suggs reagent to the β-ketoacetate **13*** (1.5 equiv. CrO₃-2 Pyr., CH₂Cl₂, 20°C, 2h, 84%). Mild basic hydrolysis of this compound (excess K₂CO₃, MeOH, 20°C) followed by mesylation of the corresponding hydroxyketone (1 equiv. MsCl, NEt₃, 20°C, 2h) led to the β-mesyloxyketone **9*** in 84% overall yield. **9*** was then transformed to the (1*R*)-*cis*-chrysanthemic acid **2a*** by the same sequence of reactions used for racemic **9** (6 equiv. KOH, DMSO-H₂O, 80°C, 3h, 75% yield, ee > 95%, Scheme 10).

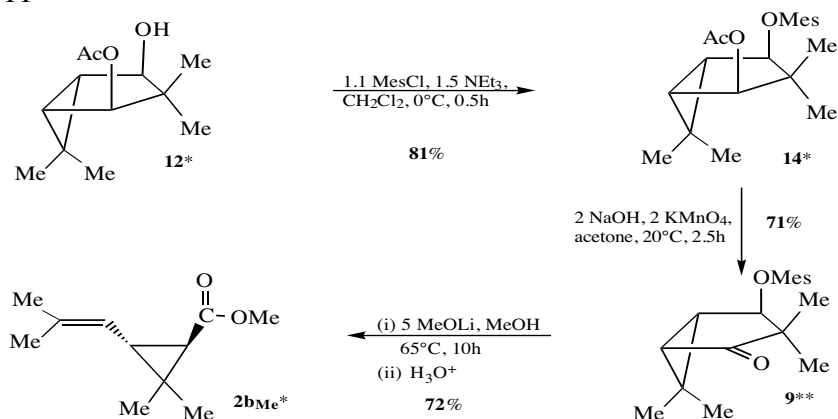
Scheme 10



Alternatively, the synthesis of (1*R*)-*trans*-chrysanthemic acid **2b*** has been achieved in good overall yield and with high enantioselectivity from the γ-acetoxy alcohol **12*** by slight changes in the synthetic scheme described for the synthesis of (1*R*)-*cis*-chrysanthemic acid **2a*** (Scheme 11). It in fact involves (i) the modification of the reactions sequence used which produced (1*S*)-*cis*-chrysanthemic acid **2a*** and (ii) an additional step which will allow the stereoselective epimerisation of its (1*S*) to (1*R*) center (Scheme 11). Thus mesylation of γ-acetoxy alcohol **12*** led to the β-acetoxymesylate **14*** (1.1 equiv. MsCl, 1.5 equiv. NEt₃, 0°C, 0.5h, 81% yield) whose protected hydroxyl group was concomitantly deacetylated and further oxidized on reaction with potassium permanganate in basic

(1*R*)-*trans*-chrysanthemate in good yield and with high dia- and enantioselection (5 equiv. MeOLi, MeOH, 65°C, 10h, 72% yield, e.e. > 95%). These conditions proved better than the ones implying potassium *t*-butoxide in THF for the isomerisation of alkyl *cis*- to *trans*-chrysanthemate.

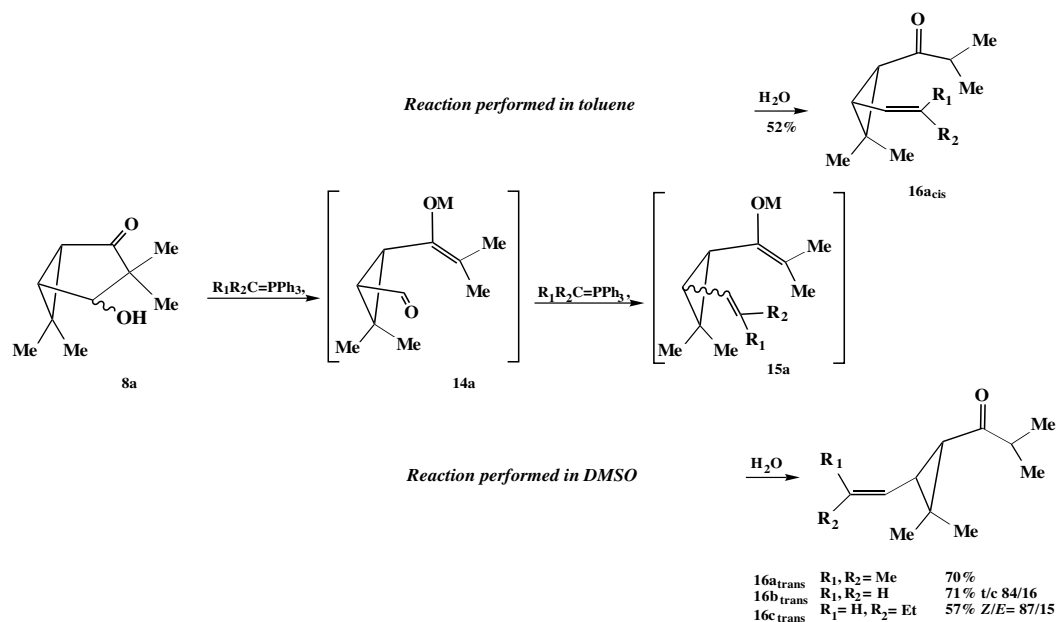
Scheme 11



In conclusion, we have disclosed a new method which allows the synthesis of enantiomerically pure (1*R*)-*cis* - as well as (1*R*)-*trans*-chrysanthemic acids from a common intermediate namely the γ -acetoxy alcohol **12***. The synthesis of such key intermediate as been in turn achieved in few steps from the cheap and commercially available dimethyl dimedone. A particularly interesting observation was made during this work : the Luche's reagent (NaBH₄-CeCl₃-MeOH) is able to reduce some hindered ketones by their most hindered face.

The synthetic scheme disclosed cannot be easily extended to the direct synthesis of chrysanthemic acid analogues bearing substituents on the vinyl group different from two alkyls. For example those bearing even one hydrogen there, due to the elimination which is expected to compete favorably with the required Grob fragmentation reaction. We therefore devised a modified synthetic scheme (Scheme 12) which allows the synthesis of chrysanthemic acid and analogues bearing different substituents on the vinyl group not only from the *exo*-keto alcohol **8** but also from its *endo*-stereoisomer from which they were not previously available.

Scheme 12



This new synthesis takes advantage of the unique structure of the β -keto alcohol **8** bearing two alkyl groups on β -carbon which make it an ideal candidate for a retro-aldol reaction.⁷

We have in fact tried for long to epimerise the hydroxyl group from the *endo* to the *exo*-side. Although the epimerisation effectively took place on reaction with bases, the *exo/endo* ratio was modest (60/40 at much) and never reached our expectations. The yields were often poor or miserable probably due to competitive polymerisation.

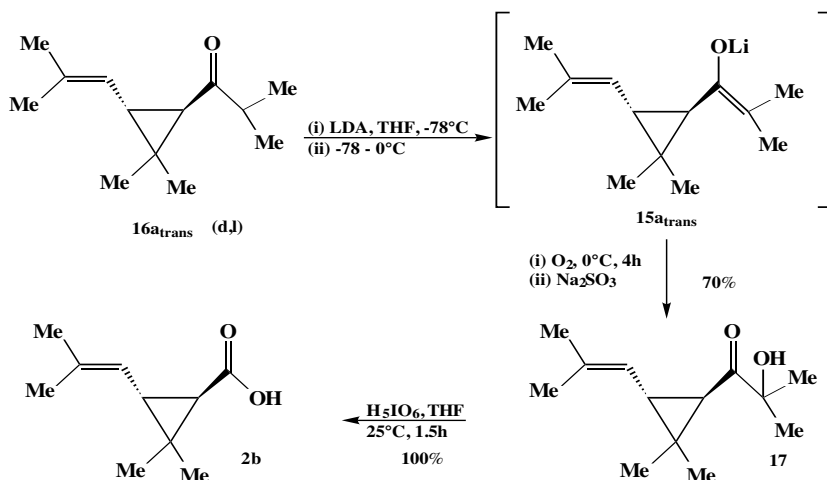
We now achieved the desired goal using an excess of phosphorous ylide playing both the role of a base and of a scavenger of the intermediate aldehyde (Scheme 12). The reaction required specific conditions to produce after hydrolysis the isopropyl ketone **16**. The usual conditions which involve the ylide generated in THF from the corresponding phosphonium salts and butyllithium did not effect the desired transformation.^{13a} The "salt free" conditions however involving the reaction of isopropyltriphenylphosphonium iodide with dimethylsodium in DMSO (2.5 equiv. Me₂CH-PPh₃ I, 2.5 equiv. NaH, DMSO, 0°-20°C, then 20°C, 1 h)^{13b} or generated in toluene from isopropyltriphenylphosphonium bromide and *n*-BuLi (3 equiv. Me₂CH-Ph₃ Br, 3 equiv. *n*-BuLi, toluene, 80°C, 5h)^{13c} produces the desired isopropyl ketone **16**. The later two conditions led to different results : the *trans*-stereoisomers **16** were unexpectedly formed in DMSO whereas the *cis*-derivatives **16** were obtained from toluene.

We have not yet determined the epimerisation site on the cyclopropane ring (at the carbon attached to the ester group or at the one bearing the aldehyde).

The synthesis of *trans*-chrysanthemic acid **2b** was achieved from the isopropyl

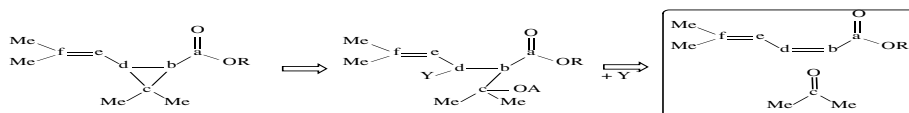
(iii) O₂, 0°C, 4 h (iv) Na₂SO₃ 70% yield in **2b** or **2a**) and their further oxidation with periodic acid (H₅IO₆, THF, 20°C, 1 h, 100%, Scheme 13).

Scheme 13



In a parallel work we have devised a "three components" synthesis of vinyl cyclopropane carboxylic acids of chrysanthemic esters which involves the formal condensation of alkyl 5-methyl-hexa-2,4-dienoates and acetone and produces sequentially the "b-c" and "d-c" bonds (Scheme 14).¹⁴

Scheme 14

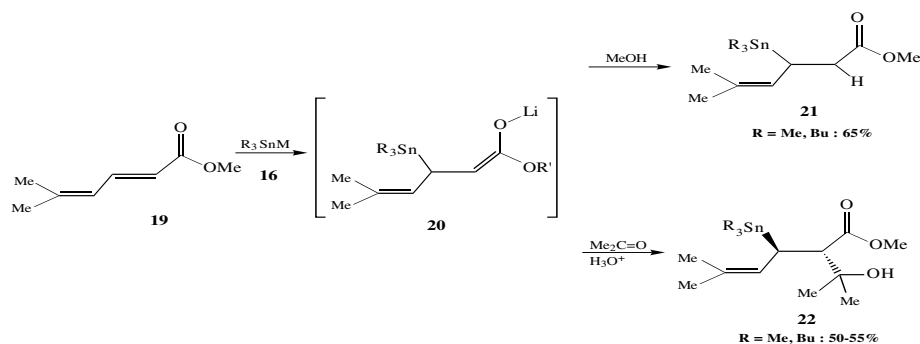


The synthetic strategy planned involves (i) the 1,4-addition of silyl-¹⁵ and stannyl^{16,17} metals **18** across the C,C double bond of dienoate **19** and trapping of the resulting enolates **20** with acetone (ii) 1,3-elimination of the silyl- or stannyl moiety and the hydroxyl group on the resulting γ -hydroxyalkyl allyl stannanes **17** and -silanes **17** **22** to produce the functionalised cyclopropane ring.

To be successful, this synthetic scheme nevertheless requires : (i) the regioselective addition of **18** at the β - and not at the δ -position of the dienoates **19** (ii) reaction of the allyl silanes or -stannanes **22** from their α - and not as usual from their γ -position ¹⁹ and (iii) 1,3-elimination of "Si-OH" or "Sn-OH" and not for example a series of 1,2-shifts of hydrogens leading finally to rearranged products.^{18,20}

We found that trimethylsilyl-¹⁷ or better dilithium bis(trimethylsilyl) cyano cuprate²¹ and trialkylstannyl- lithiums¹⁶ **18** add regioselectively at the C-3 site of methyl 5-methyl-hexa-2,4-dienoate **19** and provide, after methanolysis or reaction with acetone the corresponding esters **21** or **22** in moderate to good yields (Scheme 15).

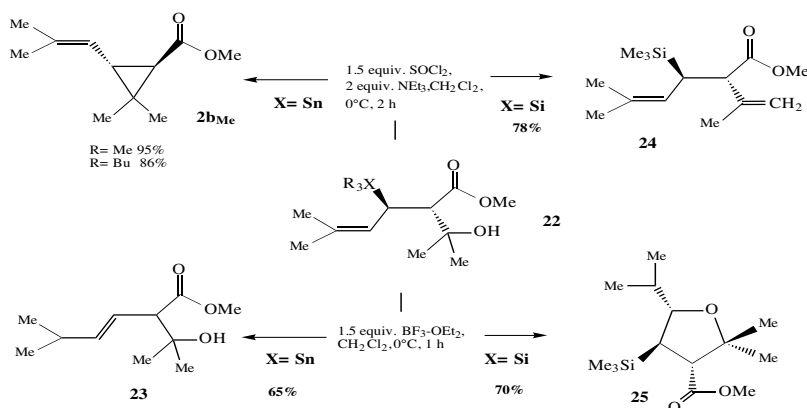
Scheme 15



We expected to form the cyclopropane ring by transforming the hydroxyl group in **22** to a better leaving group.^{17,22} This was indeed the case when the stannyl derivatives **22** (R= Me or Bu) were reacted with thionyl chloride in the presence of triethylamine. Methyl *trans*-chrysanthemate **2b**_{Me} was obtained stereoselectively and in very good yield (1.5 equiv. SOCl₂, 2 equiv. NEt₃, CH₂Cl₂, 0°C, 2 h, R= Me 95%, R= Bu 86%). These conditions proved to be crucial for the success of this transformation since 3-carbomethoxy-2-hydroxy-6-methyl-hept-4-ene **23**, resulting probably from a "protodestannylation"²³ is instead produced when the reaction is carried out with BF₃.OEt₂ (1.5 equiv. BF₃.OEt₂, CH₂Cl₂, 0°C, 1.5h, 65%, Scheme 16). Compound **23** was also present in small amounts (10%) besides methyl *trans*-chrysanthemate **2b**_{Me} (40%) when the reaction is instead performed with BF₃.OEt₂, NEt₃ or MsCl, NEt₃.

The silyl analogues exhibit completely different behaviour since we have not yet been able to achieve the construction of the cyclopropane ring (Scheme 16). Elimination of water leading to 3-carbomethoxy-2,6-dimethyl-4-trimethylsilyl-hepta-1,5-diene **24** was observed when the reaction was carried out with thionyl chloride-triethylamine ((i) 2 equiv. NEt₃, CH₂Cl₂, 0°C, 0.1h (ii) 1.5 equiv. SOCl₂, CH₂Cl₂, 0.5h, 0°C, 78% yield) under conditions which proved successful for the generation of the cyclopropane ring from the stannyl analogues.

Scheme 16



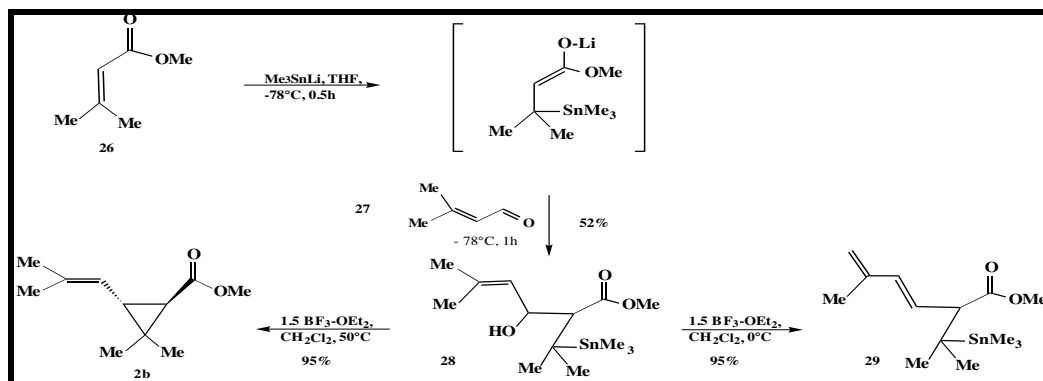
Performing the reaction with BF₃.OEt₂ or HF dramatically changes the course of

It is well established from previous work ¹⁸ that γ -hydroxyalkyl silanes possess a high propensity to rearrange in the presence of $\text{BF}_3 \cdot 2\text{AcOH}$. Formation of a cyclopropane has been nevertheless observed at the express condition that a carbomethoxy group is present in β -position and with the correct stereochemical arrangement to produce the *cis*-cyclopropane derivative.

Finally we have been able to produce methyl *trans*-chrysanthemate **2b**_{Me} in a different way than reported in Scheme 16 which involves the same set of reactions but performed on different starting materials (methyl dimethyl acrylate and dimethyl acrolein) even more easily available than the ones we already used (Scheme 17).

The γ -hydroxyalkyl allyl stannane resulting from the sequential reaction of trimethylstannyllithium with methyl dimethyl acrylate **26** and dimethyl acrolein **27** (THF, -78°C , 0.5 h, 70/30 stereoisomeric mixture) does not lead to methyl *trans*-chrysanthemate **2b**_{Me} on further reaction with thionyl chloride- NEt_3 , the reagent which successfully allowed the cyclopropanation of the isomeric γ -hydroxyalkyl allyl stannane **22**. Surprisingly however, $\text{BF}_3 \cdot \text{OEt}_2$ which was inefficient with **22** proved to be a very good reagent for the desired synthesis of **2b**_{Me} from **28**. But the reaction, to be successful, must be carried out at least at 40°C , otherwise, an elimination of water takes place leading mainly to the diene **29**. Work is now in progress to understand the reason of such behaviour.

Scheme 17



Acknowledgements

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