Tetrahedron: Asymmetry Vol. 4, No. 3, pp. 289-292, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

Novel Enantioselective Syntheses of Optically Active (1R)-cis- and (1R)-trans-Chrysanthemic Acids.

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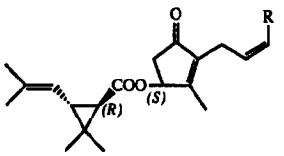
(*Received in UK* 8 *December* 1992; *accepted* 14 *January* 1993)

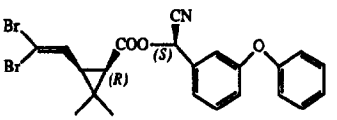
Dimethyl dimedone, a non chiral and cheap compound, has been converted to the optically actives 1-(R)-cis- and 1-(R)-trans-chrysanthemic acids possessing high economic value. These processes involve as the key steps (i) a cyclopropanation reaction (ii) a Grob fragmentation and (iii) a lipase monitored hydrolysis of a prochiral diacetate.

Pyrethroids such as S-Bioallethrin [1a,b] **1b**, deltamethrin [1a-d] **1c** and tefluthrin [1e,f] **1d** are esters of (1R)-trans- or (1R)-cis-2,2-dimethyl-3-vinyl cyclopropane carboxylic acids **2** which proved to be valuable commercially available insecticides, for domestic and agricultural uses, against flying and soil insects respectively (Scheme 1).

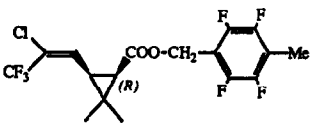
Scheme 1



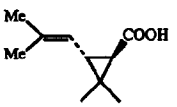
1a R = vinyl Pyrethrin I
1b R = H S-Bioallethrin (Roussel-Uclaf)



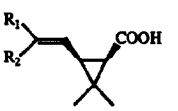
1c Deltamethrin (Roussel-Uclaf)



1d Tefluthrin (ICI)



2b Chrysanthemic acid

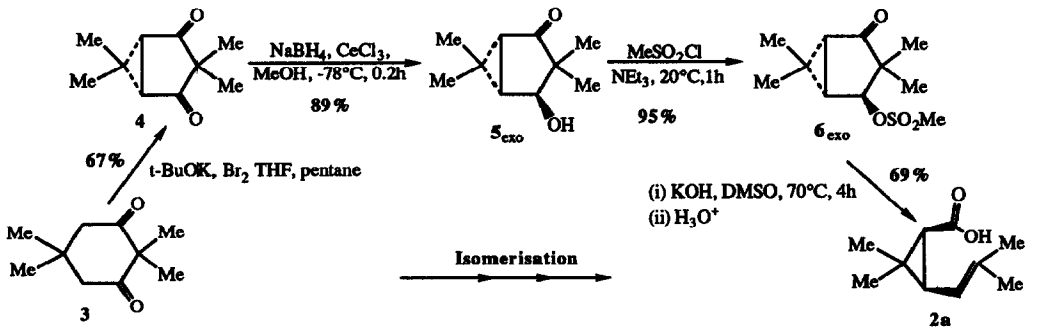


2a R_1, R_2 = Me
2c R_1, R_2 = Br
2d R_1 = Cl R_2 = CF_3

We recently designed [2] a novel stereoselective synthesis of 1-(R,S)-cis-chrysanthemic acid **2a** which started from dimethyl dimedone **3** and cheap reagents compatible with industrial requirements. The key steps of this process are without doubt (i) the cyclopropanation reaction which produced the bicyclo [3.1.0] hexan-2,4-dione **4** and (ii) the Grob's fragmentation which was achieved on the keto mesylate **6** [KOH, aq. DMSO, 70°C, 4h, 69% yield]. This resulted from the mono reduction of **4** followed by sulfonation of the corresponding β-keto alcohol **5** [MesCl, NEt_3, CH_2Cl_2, 20°C, 1h, 95% yield]. The stereochemical outcome of each individual step proved to be, as expected, particularly important for the success of the whole process which is disclosed in the Scheme 2.

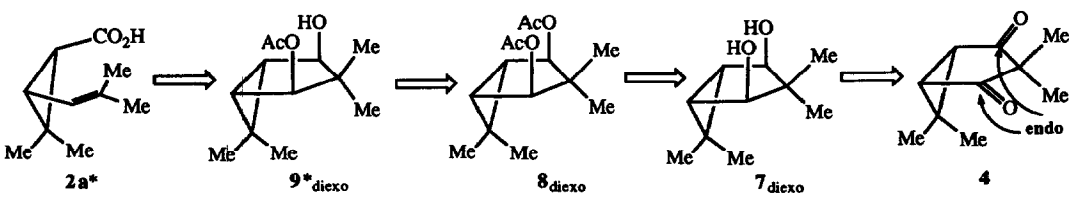
We indeed found that the exo mesylate $\mathbf{6}_{exo}$ was the only one which led to the Grob fragmentation and its synthesis therefore required the chemoselective mono-reduction of this bicyclic dione **4**. Most of the reducing agents, including $NaBH_4$ in methanol, delivered exclusively or mainly the endo alcohol $\mathbf{5}_{endo}$ resulting from the attack of the bicyclic diketone from its less hindered face.[2a,b] We found however that this stereoisomer $\mathbf{5}_{exo}$ was stereoselectively produced [2a,b] on reaction with Luche'reagent [3] ($NaBH_4$-$CeCl_3$, 1 equiv. each, MeOH, -78°C) and observed that the percentage of the endo-product was still very high even when catalytic amounts [up to 0.1 equiv.] of $CeCl_3$ were used.

Scheme 2



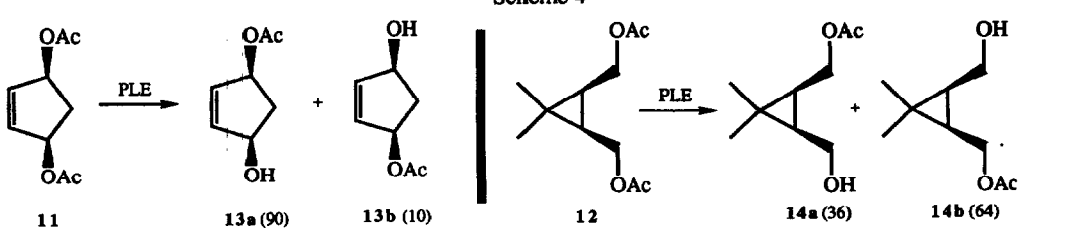
Modification of this synthetic scheme should allow the stereoselective synthesis of 1-(R)-cis-chrysanthemic acid **2a*** and 1-(S)-cis-chrysanthemic acid **2a**** whose isomerisation at the C-1 site would allow the formation of 1-(R)-trans-chrysanthemic acid **2b***. The stereo differentiation should have been best performed at an early stage of the synthesis, for example, by an enantio- and stereoselective reduction of the prochiral diketone **4** on its pro-R carbonyl group and from its most hindered face. This could have been achieved by using a chiral reducing agent, perhaps an enzymic one, or a chiral lanthanide salt. Baker's yeast or Curvularia lunata, under conditions which proved to be successful for the enantioselective reduction of the related dimethyl dimedone [4] and 2,2,5,5-tetramethyl-1,4-hexanedione [5] respectively, proved to be too slow 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 3 and whose success lies on (i) stereoselective di-reduction of **4** to the prochiral diol **7** (ii) its di-acetylation to **8** and (iii) enantioselective mono de-acetylation [6] of **8** to **9***.

Scheme 3



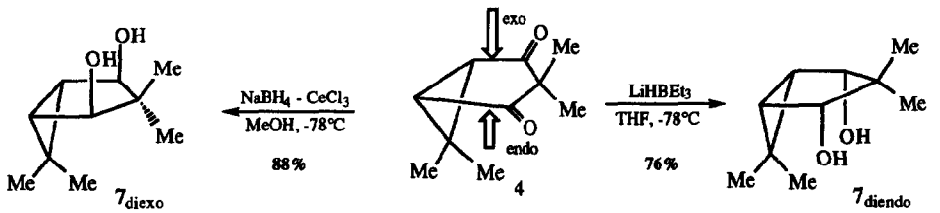
Nevertheless this crucial step was problematic since the lipase induced hydrolysis of the cis-cyclopentane-1,3-diol diacetate **11** [6a,b] and the cis-cyclopropyl di-carbinol diacetate **12**,[12b,c] whose structural features are present in the bicyclic diacetate **8a**$_{diexo}$, proved to be inconsistent.[6a-c] The former diacetate **11** delivered in fact the cis-γ-acetoxy alcohol **13a** in very good yield and very high enantioselectivity whereas **12** was found to produce the δ-acetoxy alcohol **14b** possessing the reversed stereochemistry as compared as **13a** with a much poorer enantioselectivity (Scheme 4).

Scheme 4



The stereoselective synthesis of the di-exo diol 7_{diexo}, which required the reduction of **4** twice on by its most hindered face, was successfully achieved by using an excess of $NaBH_4$-$CeCl_3$ [2 equiv. $NaBH_4$, 2 equiv. $CeCl_3$, MeOH, -78°C, 4h, 88% yield, Scheme 5]. In this case however the presence of at least two equivalents of $CeCl_3$ is required for the success of this transformation and for example the diastereoselection, in contrast with the results described for the mono reduction of **4**, was poor when lower amounts of $CeCl_3$ are used.

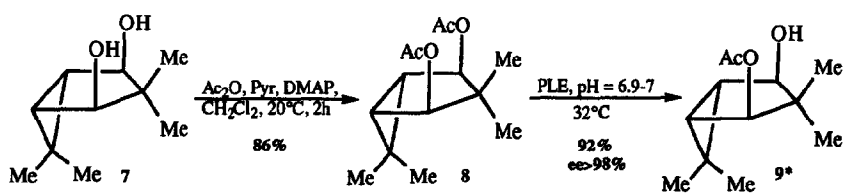
Scheme 5



We took the opportunity in this study also to perform the stereoselective synthesis of the di-endo- 7_{diendo} and of the exo-endo- $7_{exo\text{-}endo}$ diols from the diketone **4**. The synthesis of the former diol was efficiently achieved using the bulky lithium triethyl borohydride [2 equiv. $LiBHEt_3$, THF, -78°C, 4h, 76% yield, Scheme 5] whereas the synthesis of $7_{exo\text{-}endo}$ proved to be a little more complicated and required the use either of β-keto alcohol 5_{endo} [7] or 5_{exo}.[2] β-Keto alcohol 5_{endo} could not be reduced from its exo face by $NaBH_4$-$CeCl_3$ [7] and was recovered unchanged whereas the reduction exo stereoisomer 5_{exo} occured stereoselectively from its endo face with lithium triethyl borohydride thus producing the desired diol $7_{exo\text{-}endo}$ in reasonably good yield [2 equiv. $LiBHEt_3$, -78°C, 4h, 68% yield].

The di-exo diol 7_{diexo} was readily transformed to its diacetate 8_{diexo} on reaction with acetic anhydride [excess Ac_2O, Pyr., DMAP, CH_2Cl_2, 20°C, 2h, 86% yield] and hydrolysed with pig liver esterase [6] to the corresponding γ-acetoxy alcohol 9_{diexo} in very good yield and very high chemo and enantioselectivity [PLE, pH= 6.9-7, 32°C, 92% yield, e.e.> 95%, Scheme 6].

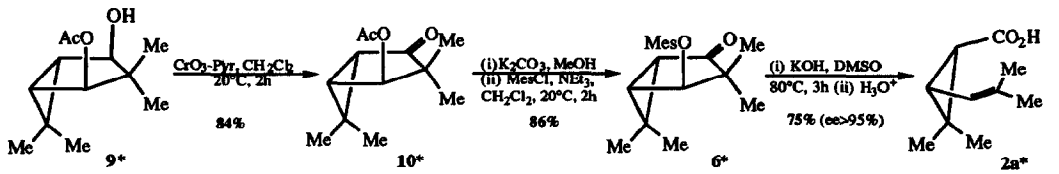
Scheme 6



The synthesis of 1-(R)-cis-chrysanthemic acid **2a*** from **9*** has been achieved in good overall yield (Scheme 7) via its oxidation by the Corey-Suggs reagent to the β-ketoacetate **10*** [1.5 equiv. CrO_3-2 Pyr., CH_2Cl_2, 20°C, 2h, 84%]. Mild basic hydrolysis of this compound [excess K_2CO_3, MeOH] followed by mesylation of the resulting β-keto alcohol 5^*_{exo} [1 equiv. MesCl, NEt_3, 20°C, 2h] led to the β-keto mesylate **6*** in 84% overall yield, which was then transformed to 1-(R)-cis-chrysanthemic acid **2a*** by using the same sequence of reactions already used on racemic **6** [KOH, DMSO-H_2O, 80°C, 3h, 75% yield, e.e.= 90%].[2a]

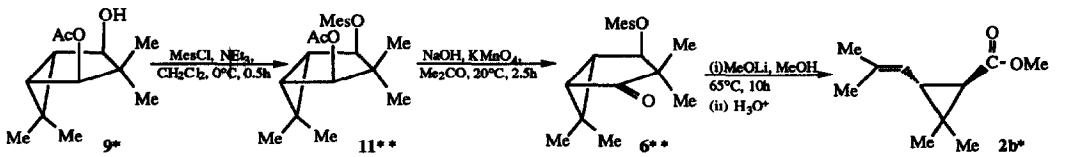
Alternatively the synthesis of 1-(R)-trans-chrysanthemic acid **2b*** has been achieved in good overall yield and with high enantioselectivity from the β-acetoxy alcohol 9^*_{diexo} by slight changes in the synthetic scheme described for **2a*** (Scheme 8).

Scheme 7



It in fact involved (i) the modification of the sequence of reactions used which will produce 1-(S)-cis-chrysanthemic acid **2a**** and (ii) an additional step implying the stereoselective epimerisation at C-1 (Scheme 8).

Scheme 8



Thus mesylation of β-acetoxy alcohol $\mathbf{9}^{**}_{diexo}$ led to the β-acetoxy mesylate $\mathbf{11}^{**}_{diexo}$ [1.1 equiv. MesCl, 1.5 equiv. NEt_3, 0°C, 0.5h, 81% yield] which was concomitantly deacetylated and oxidised with potassium permanganate in basic media to the keto mesylate **6**** [2 equiv. NaOH, 2 equiv. $KMnO_4$, aq. acetone, 20°C, 2.5h, 71% yield]. Reaction of the latter with an excess of lithium methoxide in methanol allows the stepwise Grob fragmentation and cis-trans isomerisation leading to the required methyl 1-(R)-trans-chrysanthemate **2b*** in good yield and with high diastereo- and enantioselection [5 equiv. MeOLi, MeOH, 65°C, 10h, 72% yield, ee>95%]. These conditions proved to be better for isomerisation of alkyl cis to trans-chrysanthemates than thoses imploying potassium t-butoxide in THF.

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 $\mathbf{9}_{diexo}$. The synthesis of such a key intermediate has been in turn achieved in few steps from the cheap and commercially available dimethyl dimedone. Work is now in progress to extend the reported synthetic scheme to the synthesis of the more complex tefluthrin **1d**.

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7. This reagent, when used in equimolar amounts, was already found to reduce stereoselectively **4** to the β-keto alcohol $\mathbf{5}_{endo}$ by its exo face.