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DIASTEREOSELECTIVE EPOXIDATION OF COMPOUND BEARING A CYCLOHEX-3-ENOL MOIETY: APPLICATION TO THE ENANTIOSELECTIVE SYNTHESIS OF (1*R*)-*TRANS*-CHRYSANTHEMIC ACID AND (1*R*)-*CIS*-DELTAMETRINIC ACID

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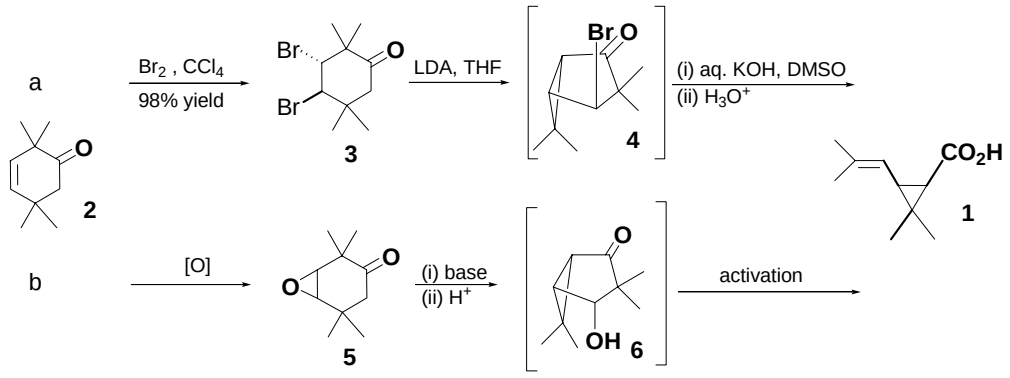
To Prof. Ryoji Noyori on the occasion of his 70th Birthday, with great appreciation

Abstract – We disclose the synthesis of enantiomeric (1*S*)-*cis*- and (1*R*)-*cis*-chrysanthemic acids precursors of S-bioallethrin and deltamethrin the most active indoor and outdoor insecticides respectively. It involves an original strategy which takes advantage of the complete stereocontrolled epoxidation of an homoallylalcohol and the synthesis in the same pot of precursors of each of the two enantiomers of *cis*-chrysanthemic acid, bearing functional groups possessing similar reactivity but having different structural behavior which allow their easy separation.

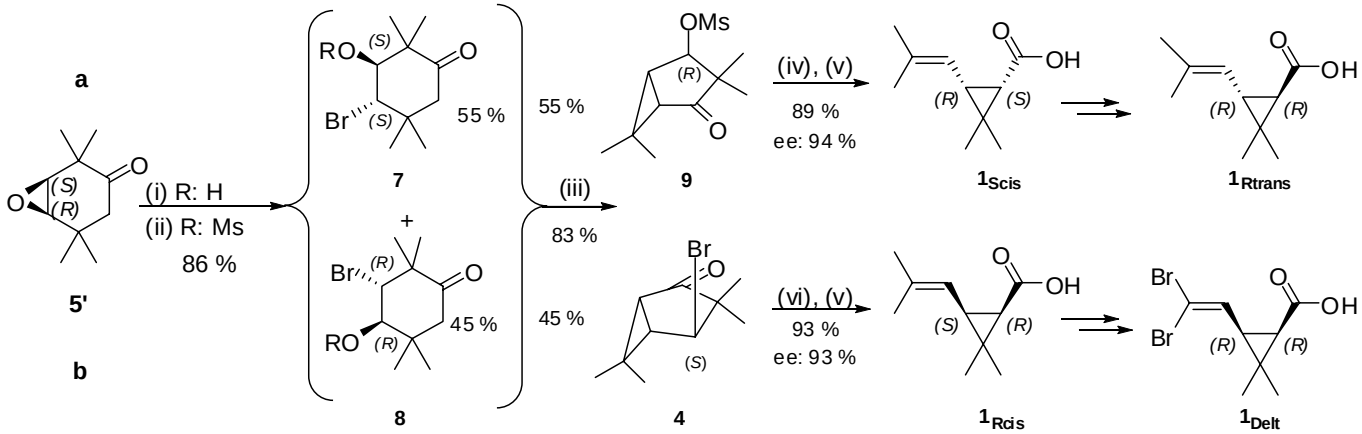
We recently wanted to extend to 2,2,5,5-tetramethyl-7-oxabicyclo[4.1.0]heptan-3-one **5** possessing the 3,4-epoxy-cyclohexanone skeleton (Scheme 1, entry b), the strategy we described[1] for the synthesis of (*d,l*)-*cis*-chrysanthemic acid **1** from 3,4-dibromo-2,2,5,5-tetramethylcyclohexone **3** (Scheme 1, entry a). The new approach is challenging since (i) epoxidation of **2** could compete with the Bayer-Villiger reaction[2] and (ii) transannular alkylation[3] which has been already achieved on 4,5-epoxycyclooctanone,[3a] was expected to be much harder on the more strained 3,4-epoxycyclohexanone **5**. Finally even if successful the process is expected to produce the endo-alcohol **6** which has not yet been transformed to **1**.[4]



Scheme 1

The epoxidation of 2,2,5,5-tetramethylcyclohex-3-enone **2** with m-CPBA in methylene dichloride proved successful but we have been unable to achieve the required acid or base promoted transannular alkylation reaction leading to **6**.

We report a novel strategy, disclosed in Scheme 2, which allows the synthesis of each of the two enantiomeric (*1S*)-*cis*-chrysanthemic acid $\mathbf{1_{Scis}}$ and (*1R*)-*cis*-chrysanthemic acid $\mathbf{1_{Rcis}}$ from the common scalemic γ-epoxy-ketone **5'**. The $\mathbf{1_{Scis}}$ derivative can be transformed, using known procedures, to (1*R*)-*trans*-chrysanthemic acid $\mathbf{1_{Rtrans}}$ (Scheme 2, entry a)[5,6] precursor of the natural pyrethrin I and of *S*-bioallethrin, the most used commercially available domestic insecticide whereas its enantiomer $\mathbf{1_{Rcis}}$ has been transformed to (*1R*)-*cis*-dibromovinylchrysanthemic acid $\mathbf{1_{Delt}}$ (deltamethrinic acid) which upon esterification with the suitable alcohol produces deltamethrin the most active commercially available insecticide for outdoor purposes.



(i) 0.5 eq. $TiBr_4$, CH_2Cl_2, 20 °C, 2 h (ii) 1.2 eq. MsCl, 1.5 eq. NEt_3, CH_2Cl_2, -10 to 0 °C, 5 h (iii) 1.2 eq. KHMDS, THF, 0°C, 1 h (iv) *t*-BuOK-H_2O (7.6-2.3), DMSO, 20 °C, 0.6 h (v) aq. HC l (vi) *t*-BuOK-H_2O (7.6-2.3), THF, 20 °C, 0.6 h

Scheme 2

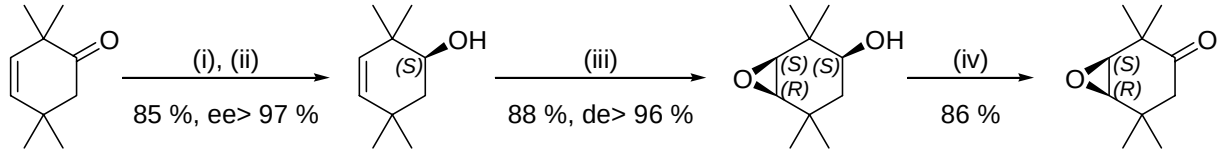
This approach takes into account the formation of almost equal amounts of the two regioisomeric bromohydrins $\mathbf{7_H}$ and $\mathbf{8_H}$, from the epoxide ring opening in **5'** (Scheme 2). It also takes advantage of:

(i) Easy separation, by chromatography on silicagel, of the two "pseudo enantiomeric" 4-mesyloxy-

and 4-bromo-3,3,6,6-tetramethylbicyclo[3.1.0]hexan-2-ones **9** and **4** which bear groups of different polarity (mesyloxy and bromine),

(ii) Efficient transformation in a single step of **9**[4b] and **4**[1a] to (*1S*)-*cis*- $\mathbf{1_{Scis}}$ and (*1R*)-*cis*- $\mathbf{1_{Rcis}}$ chrysanthemic acids respectively (Scheme 2).

Since we have been unable to achieve enantioselective epoxidation of prochiral 2,2,5,5-tetramethylcyclohex-3,4-enone **2**,[8] we decided to adopt a more elaborated strategy disclosed in Scheme 3. It (i) takes advantage of the enantioselective reduction of **2** leading to **10**, we already achieved using (-)-B-chlorodiisopinocampheylborane[1b,c] (neat, 25 °C, 48h, 85% yield, ee >97%), and (ii) requires (a) face selective epoxidation of the C,C double bond and (b) oxidation of the cyclohexanol moiety (Scheme 3).



2 **10** **11'** **5'**

(i) 1.05 eq. (-) Ipc_2BCl, neat, 25 °C, 48 h (ii) 2.2 eq. diethanolamine, Et_2O, 25 °C (iii) 1.5 eq. *t*-BuO_2H, 0.015 eq. $Mo(CO)_6$, C_6H_6, 80 °C, 2 h (iv) PDC, CH_2Cl_2, 20 °C, 0.33 h

Scheme 3

Stereoselective the synthesis of **11'** has been achieved in good yield (88 %) and very high diastereoselection (**11'**/**11''**: 98/2) using molybdenum hexacarbonyl catalyzed epoxidation of **10** by *t*-butylhydroperoxide. It takes advantage of the delivery of the "oxygen" from the same side as the hydroxyl group and can be rationalized by coordination of the catalyst to the hydroperoxy moiety as well as to the hydroxyl group present on **10** (1.5 eq. *t*-BuOOH, 0.015 eq. $Mo(CO)_6$, C_6H_6, 80 °C, 2 h, Scheme 3).[9a]

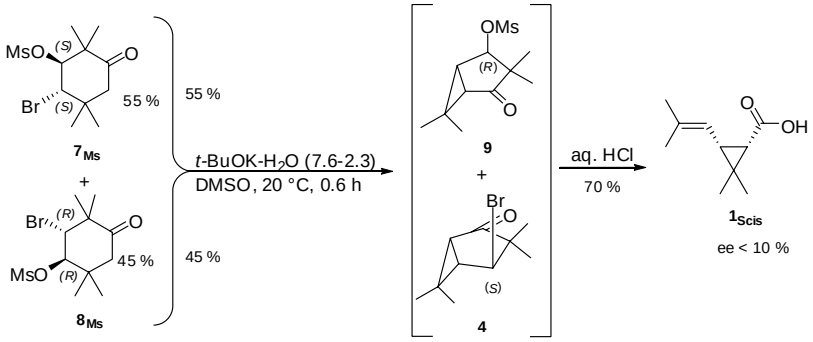
Among the various reagents tested, *m*-CPBA proved to be completely unselective whereas Hydrogen peroxide /carbodiimide[10] (8.8 eq. H_2O_2, 2 eq. DCC, 2 eq. $KHCO_3$, MeOH, 20 °C, 23 h, 25 %, de: 94) and *t*-butylhydroperoxide/$VO(acac)_2$[9] (1.5 eq. *t*-BuOOH, 0.015 eq. $VO(acac)_2$, C_6H_6, 80 °C, 5 h, 26 % yield, de: 98), produce almost exclusively **11'** but in poor yield due to a low conversion rate in the first case and competing oxidation of the alcohol leading to the epoxy-ketone **5**. Such type of side reaction has been reported in the case of unsaturated alcohols whose hydroxyl group lies in equatorial position.[9b,c]

Oxidation of 3(*S*),4(*R*)-epoxy-cyclohexanol **11'** was efficiently achieved by PDC[11] to afford the scalemic 3,4-epoxy-cyclohexan-2-one **5'** (1.5 eq. PDC, MS 4A°, CH_2Cl_2, 0 to 20 °C, 18 h, 86 % yield, Scheme 3).

However the reagents tested to effect the epoxide ring opening of **5'** ($TiCl_4$,$TiBr_4$, Me_3SiI) did it, whatever the conditions used, in good yield but unselectively (1 eq. $TiBr_4$, CH_2Cl_2, 20 °C, 96 % yield in $\mathbf{7_H}$+$\mathbf{8_H}$, $\mathbf{7_H}$/$\mathbf{8_H}$ ratio: 55/45). Separation of the two regioisomers proved to be difficult and it was also the case of the corresponding β-bromo mesylates $\mathbf{7_{Ms}}$ and $\mathbf{8_{Ms}}$ which have been obtained as a 55/45

regioisomeric mixture on reaction with mesyl chloride (1.2 eq. MsCl, 1.5 eq. NEt_3, CH_2Cl_2, -10 to 0 °C, 5 h, 83 % yield, $\mathbf{7_{Ms}}$ /$\mathbf{8_{Ms}}$: 55/45).

Treatment of this mixture with the "Gassman reagent"[4b,12] effects in the same pot the transannular alkylation reaction producing the [3.1.0] carbon framework then the subsequent Grob type fragmentation reaction leading to *cis*-chrysanthemic acid **1** after acid hydrolysis (7.6 eq. *t*-BuOK, 2.3 eq. H_2O, THF, 20 °C, 2.5 h, then aq. HCl, 70 % yield, Scheme 4). As expected its enantiomeric excess (ee < 10 %) was negligible.



Scheme 4

Following the strategy proposed initially, we have reacted the $\mathbf{7_{Ms}}$+$\mathbf{8_{Ms}}$ mixture with potassium hexamethyldisilazide **(**1.2 eq. KHMDS, THF, 0°C, 1 h, Scheme 2). It leads to the mixture of bicyclic [3.1.0]cyclohexanone **9**+**4** which has been successfully separated into its constituents **9** and **4** using column chromatography on silicagel (**4**, rf: 0.52, pentane-ether: 95-5, ee 92 %[13a] and **9,** rf: 0.19, pentane-ether: 60-40, ee 94 %).[13b]

The fragmentation reaction has been carried out with the "Gassman reagent".[4b,12] on each of the two bicyclic [3.1.0]cyclohexanones **9** and **4**. The first reaction delivers, as already described, (1*S*)-*cis*-chrysanthemic acid $\mathbf{1_{Scis}}$ when carried out in DMSO as the solvent ((i) *t*-BuOK-H_2O (7.6-2.3), 20 °C, 0.6 h (ii) aq. HCl, 89 % yield, ee: 94 %,[13c] Scheme 2, entry a). The reaction implying the bromo derivative **4** had never been carried out with the "Gassman reagent". It is however best achieved using THF instead of DMSO as the solvent and delivers (1*R*)-*cis*-chrysanthemic acid $\mathbf{1_{Rcis}}$ ((i) *t*-BuOK-H_2O (7.6-2.3), THF, 20 °C, 0.6 h, $\mathbf{1_{Rcis}}$: 93 %, ee: 93 %,[13d] Scheme 2, entry b).

In conclusion we have devised an efficient and high yielding route to valuable insecticides which are produced from the same scalemic starting material **5'**, by taking advantage of an easy purification of the mixture of 4(*S*)-bromo-3,3,6,6-tetramethylbicyclo[3.1.0]hexan-2-one and 3,3,6,6-tetramethyl-4(*R*)-oxobicyclo[3.1.0]hexan-2-yl methanesulfonate just before the last stage.

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13. (a) $[\alpha]_D^{20}$ +16.3 (c 1.0 in $CHCl_3$). (b) $[\alpha]_D^{20}$ -51.7 (c 1.14 in $CHCl_3$). (c) $[\alpha]_D^{20}$ -77.5 (c 1.0 in $CHCl_3$). (d) $[\alpha]_D^{20}$ +77.1 (c 1.0 in $CHCl_3$).