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Novel Stereoselective Route to Cis-Chrysanthemic Acid

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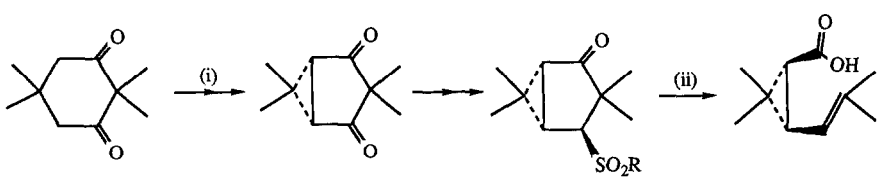
The stereoselective synthesis of cis- chrysanthemic acid has been achieved from 2,2-dimethyl dimedone by a short sequence of efficient reactions.

We report on a novel highly convergent synthesis of chrysanthemic acid[1] 7 which allows the completely stereoselective preparation of the cis-stereoisomer.

2,2,5,5-tetramethyl cyclohexa-1,3-dione 1, readily prepared by dimethylation of dimedone[2] (4 equiv. K_2CO_3, EtOH-H_2O, 2.5 equiv. MeI, 70°C, 4h, 63 % yield in 1), was choosen as the starting material since it not only possesses the same formula as chrysanthemic acid ($C_{10}H_{16}O_2$) but also the carbon framework and the functionalities placed in suitable positions to allow, in a minimum of steps, the functional group transformations required for the desired 1 to 7 isomerisation (Scheme 1).

The key steps of this transformation are without doubt **(i)** the cyclopropanation reaction which produces the prochiral bicyclo [3.1.0] hexa-2,4-dione 4 and **(ii)** the Grob's type fragmentation [3] achieved on the sulfonates 6 resulting from its reduction-sulfonylation (Scheme 1).

Scheme 1

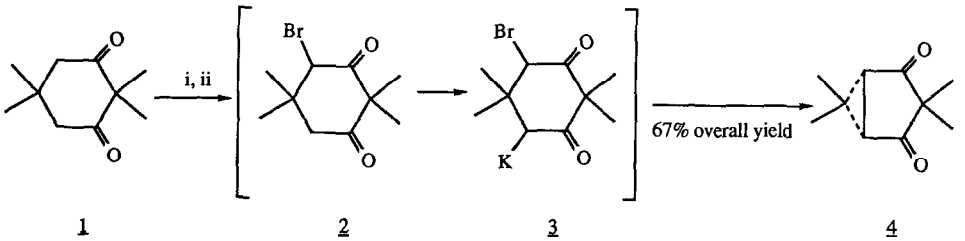


1 $C_{10}H_{16}O_2$ 4 6 7 $C_{10}H_{16}O_2$

The synthesis of the bicyclo [3.1.0] hexa-2,4-dione [4] 4 was efficiently achieved (67 % yield) from 2,2,5,5-tetramethyl cyclohexa-1,3-dione on sequential reaction with potassium tert-butoxide (2.2 equiv. in

THF from -78°C to + 40°C) and bromine (1.6 equiv. in 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 3 intermediary formed is immediately cyclized under these conditions rather than to further react with bromine. This avoids the difficulties we uncountered when the transformation was performed stepwise. In the later case we have been unable to perform selectively the required monobromination reaction [4,5] (bromine in CCl_4, 20°C). The monobromo derivative [4] 2 (mp : 98°C), although produced in good yield (75 %) proved particularly difficult to remove from the starting material and / or from the dibromo derivatives 8 concomitantly present if the reaction is performed with lower or higher amounts of bromine than the one required by the stoechiometry. [1 / 2 / 8 ratio (number of equiv. of Br_2 used) : 11 / 77 / 12 (0.85), 7 / 78 / 15 (1), 5 / 75 / 20 (1.25), 0 / 65 / 35 (1.45)].

Scheme 2

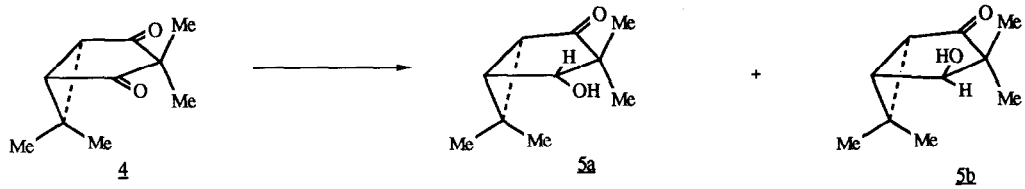


1 2 3 4

i : 2.2 equiv. t -BuOK, THF, -78°C to +40°C, **ii** : 1.6 equiv. Br_2, pentane, 40°C,1h.

Although, chemioselective monoreduction of the bicyclic dione 4 was achieved by a large array of reducing agents [5] even when used in a fourth fold excess, the stereoselective synthesis of the exo alcohol 5b was tremendously more complex. This stereochemical outcome in very important since not only the exo alcohol is the only stereoisomer which leads to a sulfonate [6] 6 but also the later possesses the antiperiplanar arrangement required for the Grob's fragmentation to occur.[3] Lithium aluminum hydride in THF, sodium borohydride in methanol-ether and lithium borohydride in DMF, THF or ethanol (Scheme 3 entries a-f,i) lead predominantly to the endo alcohol 5a resulting from the attack of the diketone 4 by the less hindered convex face. This one can even be exclusively obtained if lithium triethylborohydride is instead used (Scheme 3, entry h). The aproach of the reducing agent by the concave face seems to be particularly difficult due to the committant presence of two methyl groups adjacent to the carbonyl group and of the endo methyl group on the cyclopropane ring. All the trials involving a Lewis acid which would act as a carbonyl activator expected to allow the production of the more stable exo alcohol 5b by favoring a late transition state were unsuccessful [7] (see for example Scheme 3, entry g). Performing the reduction with sodium borohydride in methanol at +20°C as before but in the presence of cerium trichloride [8] dramatically increases the amount of the desired stereoisomer 5b (Scheme 3, entry j). The later reaction proved particularly sensitive both to the temperature and to the amount of $CeCl_3$ used (Scheme 3, compare entries j,k,l) and delivers exclusively the desired alcohol 5b when the reaction is carried out with one equivalent of $CeCl_3$ at -78°C (scheme 3, entry k).

Scheme 3



4 → 5a + 5b

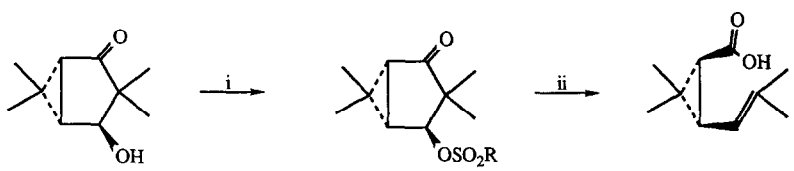
Entries	Reagent	Conditions	Overall yield	Ratio 5a / 5b
a	1 mol. equiv. $LiBH_4$	THF, 20°C	86	65 / 35
b	1 mol. equiv. $LiBH_4$	DMF, 20°C	87	70 / 30
c	1 mol. equiv. $LiBH_4$	Ethanol, 20°C	88	75 / 25
d	0.5 mol. equiv. $LiBH_4$	THF, 20°C	92	50 / 50
e	0.25 mol. equiv. $LiBH_4$	THF, 20°C	93	45 / 55
f	0.5 mol. equiv. $LiAlH_4$	THF, 20°C	89	90 / 10
g	0.5 mol. equiv. $LiAlH_4$ / 1 mol equiv BF_3-Et_2O	THF, 20°C	90	75 / 25
h	1 mol. equiv. $LiBHEt_3$	THF, 20°C	92	98 / 02
i	1 mol. equiv. $NaBH_4$	Ether / Methanol, 20°C	89	80 / 20
j	1 mol. equiv. $NaBH_4$ / 1 mol equiv. $CeCl_3$	Ether / Methanol, 20°C	88	22 / 78
k	1 mol. equiv. $NaBH_4$ / 1 mol equiv. $CeCl_3$	Ether / Methanol, -78°C	85	0 / 100
l	1 mol. equiv. $NaBH_4$ / 0.5 mol equiv. $CeCl_3$	Ether / Methanol, -78°C	81	23 / 77

Further reaction of 5b with mesylchloride-triethylamine leads to quantitative formation of the exo mesylate $6b_1$ (1.1 equiv. MsCl, 1.5 equiv. NEt_3, CH_2Cl_2, 20°C, 1.5 h, $6b_1$: 88% yield) . Alternatively the synthesis of the corresponding tosylate has been also achieved (Scheme 4). Althought the tosylation is much slower than the mesylation reaction when performed under closely related conditions (1.1 equiv. TsCl., 0.2 equiv. 4-dimethylamino-pyridine, 4 equiv. pyridine, CH_2Cl_2, 20°C, 16h), it offers the advantage to produce a crystaline material ($6b_2$ mp :106°C, ether, 93% yield)

Finally, the synthesis of the cis-chrysanthemic acid 7 has been achieved from the exo mesylate $6b_1$ or tosylate $6b_2$ and potassium hydroxide in DMSO (6 equiv. KOH, DMSO / H_2O, 70°C; 4h, 69% yield from $6b_1$; 2.5 h, 82% yield from $6b_2$). Under these conditions the original cis-stereochemistry is completely retained (Scheme 4).

Application of a similar sequence of reactions to the endo alcohol 5a is under way. However two difficult problems have to be solved in this specific case. They are related to unfavorable steric interactions which disfavor the sulfonylation of 5a as well as the antiperiplanar arrangement required for the Grob's fragmentation reaction.

Scheme 4



5b → (i) → OSO_2R → (ii) → 7

R = Me 88% $6b_1$ 69%
R = 4-MeC_6H_4 93% $6b_2$ 82%

i : 1.1 equiv. MsCl, 4.5 equiv. NEt_3, 20°C, 1h or 1.1 equiv.TsCl, 0.2 equiv.4-dimethylaminopyridine, 4 equiv. pyridine, 20°C, 16h ; ii : 6 equiv. KOH, DMSO-H_2O, 70°C.

The synthetic approach which is described in the scheme 4 requires further comments. To our knowledge, cis-chrysanthemic acid is not part of a biologically active compound. It can be however easily transformed to its cis-dihalogenovinyl analog[10] or isomerized to its trans stereoisomer [11] whose suitable esters are among the most potent insecticides actually available[1].

Other interesting features of this approach ly (i) in its potentiality to allow a more direct synthesis of cis-dihalogeno vinyl chrysanthemic acids from for example the readily available 2,2-dichloro-5,5-dimethyl cyclohexa-1,3-dione [12] and (ii) from the prochiral nature of our key intermediate 4 which renders formally possible an asymetric synthesis of the 1R enantiomers, whose suitable esters are indubitably the most biologically active compounds.[1,10,11] Work is in progress toward this end.

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4. (a) This compound has been already synthesized by Nozaki [4b]. However the problem lies in the preparation of 4-bromo -2,2,5,5-tetramethylcyclohexa-1,3-dione 2 which we were unable to perform selectively under various experimental conditions. Under the conditions cited by Nozaki [4b] (ref. to Stetter's work) and using NBS, the bromination is very slow and provides a mixture of products from which the desired pure product 2 can be isolated in low yield by crystallisation. (b) T.Okada, K. Kamogawa, M. Kawanisi and H. Nozaki Bull. Chem. Soc. Jpn., 43, 2908 (1970).

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6. Further reaction of the mixture of the two stereoisomers 5a and 5b (arising from the reduction of 4 with $LiBH_4$ in THF) with mesylchloride-triethylamine leads to quantitative formation of the exo mesylate $6b_1$ (1.1 equiv. MsCl, 1.5 equiv. NEt_3, CH_2Cl_2, 20°C, 1.5 h, $6b_1$, 45 % yield) which is readily separated by TLC from the unreacted endo alcohol 5a (quantitative recovery). Alternatively the synthesis of the corresponding tosylate has been also achieved (1.1 equiv. TsCl., 0.2 equiv. 4-dimethylamino-pyridine, 4 equiv. pyridine, CH_2Cl_2, 20°C, 16h). It offers the advantage to produce a crystaline material wich can be separated fron 5a by simple crystallisation (6b2 mp :106°C, ether, 48% yield).

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