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Isomerisation of 2,2-dimethyl dimedone to (D,L) *cis*-chrysanthemic acid†

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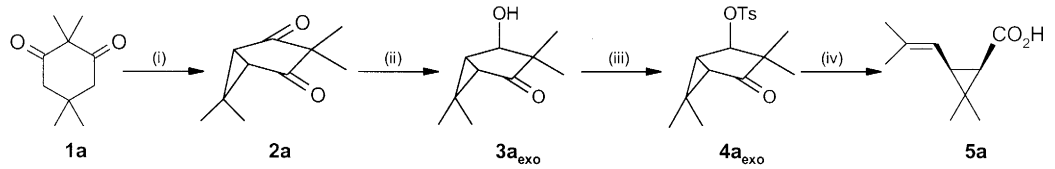
Abstract

(D,L) *cis*-Chrysanthemic acid has been obtained in four steps from 2,2-dimethyl dimedone which involves Bamford–Stevens olefination and tandem cyclization–Grob fragmentation reactions.

Keywords: Bamford–Stevens reaction; cyclopropanes; hydrazones; olefin bromination.

Some time ago, we showed that 2,2-dimethyl dimedone **1a** can be transformed in a few steps into chrysanthemic acid **5a** (Scheme 1).[1,2] This transformation involves the production of the bicyclo[3.1.0]hexane dione **2a** and its *exo*-β-ketosulfonate **4a**$_{exo}$ which is then subjected to Grob fragmentation.[1,3] The key step of this transformation is indubitably the formation of the β-ketoalcohol **3a**$_{exo}$ which required the stereoselective reduction of the dione **2a** by its more hindered face.



Scheme 1. Previous synthesis of *cis*-chrysanthemic acid from dimethyl dimedone. (i) *t*-BuOK, Br_2, THF–pentane; (ii) $NaBH_4$–$CeCl_3$, ethanol; (iii) Ts–Cl, Pyr., CH_2Cl_2; (iv) KOH, DMSO–H_2O

We show in this paper our results concerning the synthesis of chrysanthemic acid **5a** (R_1, R_2=Me) as well as its analogues **5b** (R_1=H, R_2=Me) and **5c** (R_1, R_2=H) from cyclohexanediones **1a**–**c** through β-keto-olefins **7a**–**c** and bicyclic ketones **9a**–**c** according to the strategy disclosed in Scheme 2.

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† Dedicated with great appreciation to Prof. Pierre Sinay on the occasion of his 62nd birthday.

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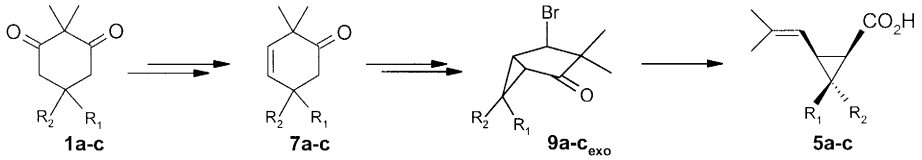
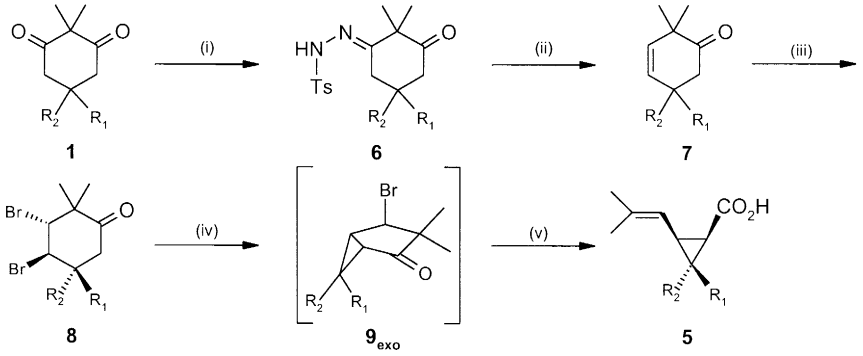


Scheme 2. Novel synthesis of *cis*-chrysanthemic acid and homologues from dimedones

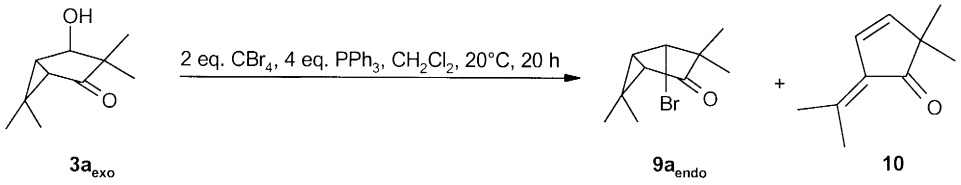
The transformation of **1a** to **8a**, using the Bamford–Stevens reaction,[4] was known to occur in very poor yield (<20%)[5,6] due to the concomitant formation of bis-tosylhydrazone, besides the desired β-ketohydrazone **6a** from **1a** and *N*-tosylhydrazine.[7] Careful investigation of this reaction shows that the β-ketohydrazone **6a** is in equilibrium with the bis-tosylhydrazone and the β-diketone **1a**.[8] We have found that **6a** can be chemoselectively obtained by performing the reaction in ethanol taking advantage of its insolubility in this solvent (1 equiv. $TsNHNH_2$, EtOH, 20°C, 4 h, 84% yield, Scheme 3). The synthesis of the β-keto-olefin **7a** was then achieved in very good yield using the Bamford–Stevens reaction (5 equiv. $HOCH_2CH_2ONa$, ethyleneglycol, 180°C, 0.5 h, 80% yield). Bromination of the C,C double bond was chemoselectively performed with bromine in the presence of acetamide as an acid scavenger[9] (1 equiv. Br_2, 0.1 equiv. $AcNH_2$, CCl_4, 0°C, 98% yield) and transformation of the resulting **8a** to **5a** was achieved in a single step using the conditions we previously set up[1] for the transformation of **4a** to **5a** (6 equiv. KOH, DMSO:H_2O (4:1), 70°C, 2 h, 87%).



Scheme 3. Synthesis of *cis*-chrysanthemic acid and lower homologues. R_1, R_2=Me: (i) 1 equiv. $TsNHNH_2$, EtOH, 20°C, 4 h, **6a**: 84% yield; (ii) 5 equiv. $HOCH_2CH_2ONa$, ethyleneglycol, 180°C, 0.5 h, **7a**: 80% yield; (iii) 1 equiv. Br_2, 0.1 equiv. $AcNH_2$, CCl_4, 0°C, **8a**: 98% yield (iv+v) 6 equiv. KOH, DMSO:H_2O (4:1), 70°C, 2 h, **5a**: 87% yield. R_1=H, R_2=Me; R_1, R_2=H: (i+ii) 1 equiv. $TsNHNH_2$, THF, 20°C, 4 h, then 5 equiv. $HOCH_2CH_2ONa$, ethyleneglycol, 180°C, 0.5 h, **7b** and **7c**: 30% yield each; (iii) 1 equiv. Br_2, CH_2Cl_2, −78°C, **8b**: 74% yield, **8c**: 81% yield; (iv) 1 equiv. LDA, THF, −78°C, 1 h, **9b**: 74% yield, **9c**: 91% yield; (v) 6 equiv. KOH, DMSO:H_2O (4:1), 70°C, 2 h, **5b**: 94% yield, **5c**: 83% yield

We have proved, in separate experiments, using lithium diisopropylamide or potassium *t*-butoxide, that the first step of the reaction **8a** to **9a** involves the stereoselective synthesis of the bicyclic *exo*-β-bromoketone **9a**$_{exo}$ (1 equiv. LDA, THF, −78°C, 1 h, 86% yield or 2 equiv. *t*-BuOK, 23°C, 2 h, 94% yield). It is interesting to notice that we have not previously been able to obtain compound **9a**$_{exo}$ from **3a**$_{endo}$ and that, for example CBr_4–PPh_3 (2 equiv. CBr_4, 4 equiv. PPh_3, CH_2Cl_2, 20°C, 20 h)[10a] and its *exo*-stereoisomer **9a**$_{exo}$ has been produced along with some *exo*-isopropylidene cyclopentenone **10** when **3a**$_{exo}$ was used instead (Scheme 4).[10b]

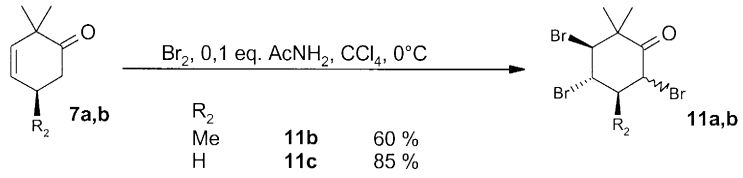
The synthesis of desmethyl or didesmethyl derivatives **5b** and **5c** from the related cyclohexadiones **1b**[11] and **1c** was achieved according the same strategy but some differences were noticed. We have not been able to find a solvent in which the β-ketohydrazones **6b**,**c** could selectively precipitate. Since separation of the mixture of the three products (**1**, **6** and the bis-tosylhydrazones) could not be achieved efficiently,



Scheme 4. Synthesis of *endo* β-bromoketone **9a**$_{endo}$

we decided to perform the Bamford–Stevens reaction directly on the crude product obtained from the reaction of the cyclohexadiones **1b**,**c** with tosylhydrazine (i) 1 equiv. $TsNHNH_2$, THF, 20°C, 4 h; (ii) 5 equiv. $HOCH_2CH_2ONa$, ethyleneglycol, 180°C, 0.5 h, 30% yield each) thus accepting the modest overall yield in **7b**,**c**.

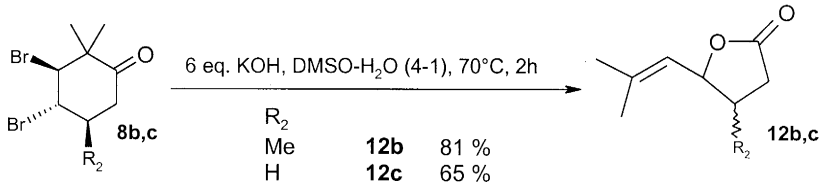
Bromination of **7b** and **7c** using the conditions already used for the higher homologue **7a** was not successful since the tribromides **11b**,**c** involving competing bromination alpha to the ketone were produced besides the starting materials **7b**,**c** and the desired dibromides **8b–c**, and increasing the amount of bromine in order to completely remove **7b**,**c** led to the formation of **11b–c** in very good yields (Scheme 5).



Scheme 5. Synthesis of tribromocyclohexanones **7b**,**c**

We nevertheless found that the synthesis of the dibromides **8b**,**c** could be chemoselectively achieved by performing the reaction of bromine on **7b**,**c** at low temperature without any additive (1 equiv. Br_2, CH_2Cl_2, −78°C; **8b** and **8c** in 74 and 81% yield, respectively, Scheme 3).[12] Under the same conditions **8a** was quantitatively formed from **7a**. The formation of the single stereoisomer **8b** from **7b** is worthwhile to note.

Reaction of **8b** and **8c** with potassium hydroxide using the conditions already used for the transformation of the higher homologue **8a** to **5a** did not lead to the desired derivatives **5b** and **5c** but instead produce the lactones **12b**,**c** resulting from the Grob fragmentation[1,3] without prior cyclization to **9b**,**c** (Scheme 6). The more efficient cyclization of **9a** can therefore be accounted for by the Thorpe–Ingold effect.



Scheme 6. Reaction of dibromocyclohexanones **8b**,**c** with potassium hydoxide.

Anyhow, the desired transformation can be achieved in two steps involving first the synthesis of the cyclopropane ring leading to the bicyclic *exo*-β-bromoketones **9b**,**c** (1 equiv. LDA, THF, −78°C, 1 h, **9b**,**c** in 74 and 91% yield, respectively, Scheme 3) and their further reaction with potassium hydroxide in DMSO for achieving the Grob fragmentation reaction (6 equiv. KOH, DMSO:H_2O (4:1), 70°C, 2 h, **5b** and **5c** in 94 and 83% yield, respectively, Scheme 3).

Finally, we have described a short, efficient and stereoselective synthesis of *cis*-chrysanthemic acid from easily available dimethyl dimedone and very simple reagents. Although the strategy used applies to the synthesis of lower homologues bearing one or even no methyl group on the cyclopropane ring, the individual reactions used in the case of chrysanthemic acid can no longer be applied.

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8. Under other conditions the bis-tosylhydrazone is formed concommitantly (conditions, dimethyl dimedone:mono-tosylhydrazone:bis-tosylhydrazone ratio (1% HCl, ethanol, reflux, 0.5 h, 8:54:36; benzene, 20°C, 4 h, 68:27:5; THF, 20°C, 4 h, 33:33:33; methanol, 20°C, 4 h, 30:57:13).
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