Fragmentation of 4-Sulfonylbicyclo[3.1.0]hexan-2-ones as the Key Step in the Enantioselective Synthesis of (1*R*)-*cis*-Chrysanthemic Acid Involving Desymmetrization of 3,3,6,6-Tetramethylbicyclo[3.1.0]hexane-2,4-dione

Alain Krief,* Adrian Kremer

Laboratoire de Chimie Organique de Synthèse, Facultés Universitaires N.-D. de la Paix, 61 Rue de Bruxelles, Namur 5000, Belgium
Fax +32(81)724536; E-mail: alain.krief@fundp.ac.be

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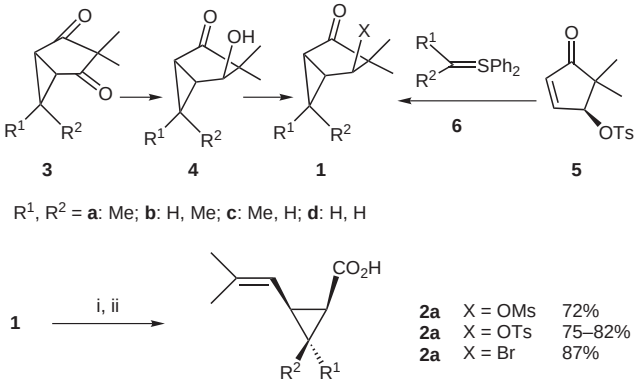
Abstract: *t*-BuOK–H_2O (7.6:2.3) in THF or DMSO allows the efficient Grob-type fragmentation of 4-sulfonyl-bicyclo[3.1.0]hexan-2-ones which cannot be achieved by potassium hydroxide in DMSO as we originally described.

Key words: ring opening, retro-aldol, nucleophiles, lithiation, chirality

Grob-type fragmentation of bicyclo[3.1.0]hexan-2-ones **1**, bearing a leaving group in 4-position, proved to be a valuable synthetic strategy to produce *cis*-vinyl cyclopropane carboxylic acids **2** (Scheme 1). For example, it has been efficiently used in our laboratory as a key step in the synthesis of *cis*-chrysanthemic acid (**2a**) in racemic form[1] or as a single enantiomer[1c,2,3a] from 3,3,6,6-tetramethylbicyclo[3.1.0]hexane-2,4-dione (**3a**)[1,2] or from 4-tosyloxy-5,5-dimethylcyclopent-2-enone (**5**)[3] (Scheme 1).



Scheme 1 *Reagents and conditions*: (i) KOH (6 equiv), DMSO–H_2O (4:1), 70 °C, 2–4 h; (ii) H_3O^+.

It has been also successfully used for the synthesis of related (*d*,*l*)-*cis*-2-desmethyl- (**2b**,**c**) and 2,2-di-desmethyl chrysanthemic acids (**2d**).[4] The published conditions involve the reaction of aqueous potassium hydroxide solution in DMSO on the 4-mesylate,[1] 4-tosylate,[1,3] and 4-bromide[5] $\mathbf{1}_{exo}$ [conditions A: 6 equiv KOH, DMSO–H_2O (4:1), 1 M solution, 70 °C, 2–4 h,].

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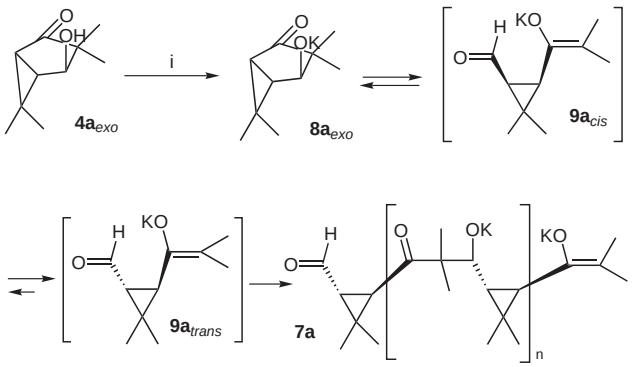
The transformation of **4** to **2** is not general. For example **4a** and **4b** which possess an *endo*-methyl group are very unstable.[1a,4] Thus the effect of the stereochemistry on the Grob-type fragmentation which is known to require an antiperiplanar arrangement of the atoms involved in the process[6] has not been systematically tested.[1a,4]

A few years ago Prof. N. Simpkins informed us that he was unable to repeat[7] the fragmentation of the 4-mesylate $\mathbf{1a}_{exo}$ to **2a** we previously published[1a] and we confirmed his finding. In fact *cis*-chrysanthemic acid (**2a**) is effectively produced under conditions A, but in minute amount (2–7%, 15 runs) beside large quantities of unidentified polymeric material **7a** (Scheme 2).



Scheme 2 *Reagents and conditions*: (i) KOH (6 equiv), DMSO–H_2O (4:1), 70 °C, 2–4 h.

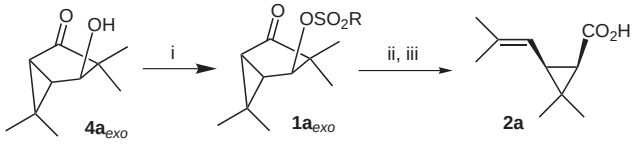
We have systematically performed the reaction between the mesylate and tosylate $\mathbf{1a}_{exo}$ and potassium hydroxide in DMSO under different conditions. We have changed the temperature (50–100 °C), the concentration of the reagent (0.1–1 M in DMSO), the amount of water (0–50%) and of potassium hydroxide (2.5–10 equiv) used, and achieved little or no success. We for example observed that the sulfonates $\mathbf{1a}_{exo}$ do not react at an appreciable rate when the temperature is lower than 50 °C under conditions A and that **2a** can be obtained in 23% yield from the tosylate $\mathbf{1a}_{exo}$ by performing the reaction with 12 equivalents of potassium hydroxide at 100 °C in DMSO–H_2O (4:1).

However, we were surprised to find that the above observations do not apply to the whole series of compounds **1**.[8] For example, conditions A works on some desmethyl

derivatives (**1c**$_{endo}$ and **1d**$_{endo}$)[1b,4] and especially on the 4-*exo*-bromo-3,3,6,6-tetramethylbicyclo[3.1.0]hexan-2-one **1a**$_{exo}$ which produced **2a** in up to 87% yield as originally described (5/5 successful runs).[5]

We suspected, after comparing the dramatic difference of reactivity between the sulfonates and the bromide **1a**$_{exo}$, that the failure of potassium hydroxide to produce **2a** from the sulfonates was due to a competing reaction on the electrophilic sulfur atom of the sulfonates. This instead produces the potassium 4-*exo*-oxy-3,3,6,6-tetramethylbicyclo[3.1.0]hexan-2-one **8a**$_{exo}$ intermediate which then polymerizes. We effectively found, in a separate experiment, that **8a**$_{exo}$ prepared from 4-*exo*-hydroxy-3,3,6,6-tetramethylbicyclo[3.1.0]hexan-2-one **4a**$_{exo}$ and potassium hydroxide in anhydrous or wet DMSO, provides a polymeric material postulated as **7a** once heated around 70 °C, as the result of a tandem retro-aldol–*cis*/*trans*-isomerization reaction. Those steps are tentatively disclosed in Scheme 2.

The first strategy we tried was therefore expected to prevent the attack of the hydroxide ion on the sulfur atom of the sulfonate. It was achieved by increasing steric hindrance there using 2,4,6-trimethyl benzenesulfonate **1a**$_{exo}$ [R = 2,4,6-$(Me)_3C_6H_2$] or 2,4,6-triisopropylbenzenesulfonate **1a**$_{exo}$ [R = 2,4,6-$(i\text{-}Pr)_3C_6H_2$], and proved to be quite successful since chrysanthemic acid (**2a**) is produced in up to 50% yield. Nevertheless, it was of poor synthetic value since it required too long of a reaction time and access to the 'sterically hindered sulfonates' from the ketoalcohol **4a**$_{exo}$ was far from easy (Scheme 3, Table 1, entries 3–5 compared to entries 1 and 2).

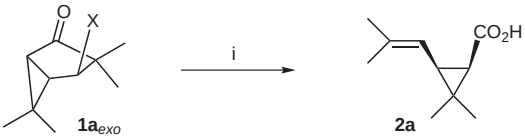


Scheme 3 *Reagents and conditions*: (i) RSO_2Cl (1 equiv), CH_2Cl_2;(ii) KOH (70 equiv), DMSO–H_2O (2:1), 55 °C; (iii) H_3O^+.

The second strategy, which involves the use of a more carbophilic reagent, proved to be more successful.

Although neither lithium, sodium or tetrabutyl ammonium hydroxides in DMSO allow the desired transformation of the mesylate or tosylate **1a**$_{exo}$ to **2a**, we found the 'Gassman reagent',[9] prepared from potassium *tert*-butoxide and water (3.3:1), particularly efficient when used in excess (sulfonates **1a**$_{exo}$–*t*-BuOK–H_2O, 1:7.6:2.3).

The reaction proceeds at room temperature in less than 1 hour on all the *exo*-sulfonates **1a**$_{exo}$ so far tested either in anhydrous DMSO (conditions B: Scheme 4, Table 2 entries 1, 3, 8, 10) or in anhydrous THF (conditions C: Scheme 4, Table 2 entries 2, 4, 9) and produces after acid hydrolysis *cis*-chrysanthemic acid (**2a**) in more than 80% yield. Conditions B, which uses DMSO proved to be more efficient than conditions C, which involves instead THF (Scheme 4, Table 2 compare entries 1 to 2 and 3 to 4). Surprisingly, however, the reverse has been observed with the 'hindered' 2,4,6-trimethylbenzenesulfonate **1a**$_{exo}$ (Scheme 4, Table 2, compare entry 8 to 9).



Scheme 4 *Reagents and conditions*: (i) *t*-BuOM–H_2O, solvent, 22 °C; (ii) H_3O^+.

The ratio of starting materials and the solvent (anhyd DMSO) used by Gassman to successfully cleave non-enolizable cyclopropyl ketones[9a–c] and hydrolyze 'hindered esters'[9d] to the corresponding carboxylic acids proved to be the most efficient combination (Table 2, entries 1–4, 8, 9). Changing the sulfonate/'Gassman reagent' ratio (Table 2, compare entries 5 to 4), the potassium *tert*-butoxide/water ratio (Table 2, compare entries 6, 7, 4) or the *tert*-butoxide counter ion (K to Na or Li) proved to be highly detrimental (22 °C, metal, solvent, time, yield in **2a**: Na, DMSO, 8 h, 72%; Na, THF, 36 h, 0%; Li, DMSO, 72 h, 2%).

We took advantage of the efficient fragmentation reaction described above and of the recent discovery of N. Simpkins[10,11a] that the scalemic ketomesylate **4a**$_{exo}$ can be easily prepared (80% yield, >98% ee, Scheme 5) by asymmetric desymmetrization of 3,3,6,6-tetramethylbicyclo[3.1.0]hexane-2,4-dione (**3a**) with scalemic lithium (*R*,*R*)-bis(1-phenylethyl)amide in the presence of lithium chloride (1.2 equiv) and trimethylsilyl chloride (10 equiv, –78 °C to 20 °C, 5 h), to devise a novel efficient enantioselective synthesis of (1*R*)-*cis*-chrysanthemic acid (**2a**).

Table 1 Reaction of Compounds **4a**$_{exo}$ to **1a**$_{exo}$ and **2a**$_{exo}$ under Various Conditions

Entry	R	Conditions	Yield of **1a**$_{exo}$ (%)	Yield of **4a**$_{exo}$ (%)	Time (h)	Yield of **2a** (%)
1	Me	1.5 equiv Et_3N, –10 °C, 0.75 h	86	–		
2	Ph	2.5 equiv Py, 0.2 equiv DMAP, 20 °C, 24 h	83	–		
3	2,4,6-$(Me)_3C_6H_2$	2.5 equiv Py, 0.2 equiv DMAP, 20 °C, 168 h	76	20	30	33
4	2,4,6-$(i\text{-}Pr)_3C_6H_2$	2.5 equiv Py, 0.2 equiv DMAP, 20 °C, 108 h	25	50		
5	2,4,6-$(i\text{-}Pr)_3C_6H_2$	2.5 equiv py, 0.2 equiv DMAP, 45 °C, 108 h	35	–	48	52

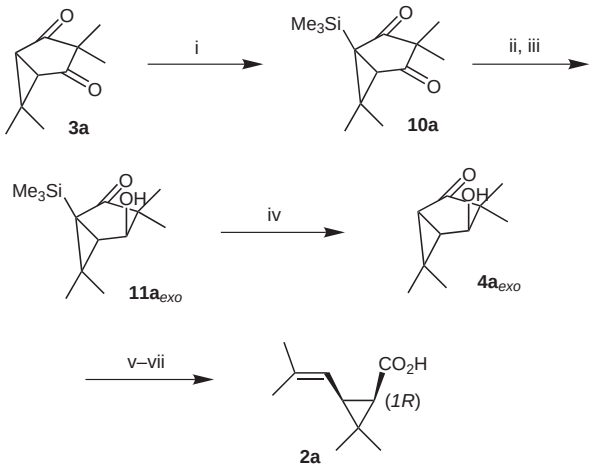
Table 2 Reaction of Compounds $\mathbf{1a}_{exo}$ to $\mathbf{2a}_{exo}$ Using THF and DMSO as Solvents

Entry	X	Ratio of **1a**:*t*-BuOM:H_2O	Solvent	Time (h)	Yield of **2a** (%)	Yield of $\mathbf{1a}_{exo}$ (%)
1	$MeSO_2O$	1:7.6:2.3	DMSO	0.4	90	
2	$MeSO_2O$	1:7.6:2.3	THF	0.3	60	
3	*p*-$TolSO_2O$	1:7.6:2.3	DMSO	0.3	86	
4	*p*-$TolSO_2O$	1:7.6:2.3	THF	1	84	
5	*p*-$TolSO_2O$	1:3.6:1.1	THF	4	64	08
6	*p*-$TolSO_2O$	1:4.4:2.2	THF	24	60	06
7	*p*-$TolSO_2O$	1:2.2:2.2	THF	52	07	64
8	2,4,6-$(Me)_3C_6H_2SO_2O$	1:7.6:2.3	DMSO	0.8	80	
9	2,4,6-$(Me)_3C_6H_2SO_2O$	1:7.6:2.3	THF	0.5	95	
10	2,4,6-(*i*-Pr)$_3C_6H_2SO_2O$	1:7.6:2.3	DMSO	0.8	83	

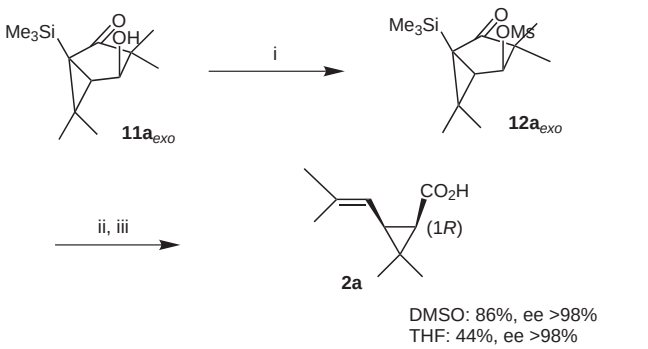
Reduction of the resulting α-trimethylsilyl diketone **10a**[11a] by sodium borohydride in the presence of cerium trichloride leads to the aldol $\mathbf{11a}_{exo}$[11b] bearing a trimethylsilyl group at the ring junction in α-position to its carbonyl group. This reaction occurs not only regioselectively on the carbonyl carbon the farest from the trimethylsilyl group but also stereoselectively, as on related **3a**,[1] from the most hindered *endo*-face of the bicyclic dione. These features have been unambiguously established by an X-ray crystallography analysis of its *p*-nitrobenzoate.[12]

Desilylation of **11a** {1.1 equiv [(*n*-Bu)$_4$NF·3H_2O], THF, 0–20 °C, 60 h}, followed by fragmentation of the corresponding mesylate **1a**,[11c] using conditions B, as disclosed above affords (1*R*)-*cis*-chrysanthemic acid (**2a**)[11d] in up to 76% yield almost as a single enantiomer (ee >98%). This correlation unambiguously establishes the stereochemistry attributed[10] to scalemic **10a** resulting from the enantioselective desymmetrization of **3a** (Scheme 5).

(1*R*)-*cis*-Chrysanthemic acid has been synthesized even more efficiently from the aldol $\mathbf{11a}_{exo}$[11b] by changing the order of reactions described above. Mesylation of $\mathbf{11a}_{exo}$ leads to the ketomesylate $\mathbf{12a}_{exo}$[11e] still bearing the trimethylsilyl group [1.1 equiv $MeSO_2Cl$ (0.15 M), 1.5 equiv Et_3N, CH_2Cl_2, –20 °C, 0.75 h, 86%].[1a,2] Treatment of $\mathbf{12a}_{exo}$ with the 'Gassman reagent' in DMSO (conditions B) followed by acid treatment, directly generates scalemic (1*R*)-*cis*-chrysanthemic acid (**2a**),[11f] in a single-pot domino reaction in which the reagent has performed the desilylation as well as the fragmentation reactions (86% yield, ee >98%, Scheme 6).



Scheme 5 *Reagents and conditions*: (i) lithium (*R*,*R*)-bis(1-phenylethyl)amide (1.2 equiv), LiCl (1.2 equiv), Me_3SiCl (10 equiv), THF, –78 °C to 20 °C, 5 h, 80%, ee >98%; (ii) $CeCl_3·7H_2O$ (1 equiv), MeOH; (iii) $NaBH_4$ (1 equiv), MeOH, –78 °C, 5 h, 95%; (iv) $Bu_4NF·3H_2O$ (1.1. equiv), THF, 0–20 °C, 60 h, 98%; (v) MsCl (1.1 equiv), Et_3N (1.5 equiv), CH_2Cl_2, –20 °C, 0.75 h; (vi) *t*-BuOK–H_2O (7.6:2.3), DMSO, 22 °C, 0.4 h; (vii) H_3O^+; 85–91%, >98% ee.



Scheme 6 *Reagents and conditions*: (i) MsCl (1.1 equiv), 1.5 Et_3N, CH_2Cl_2, –20 °C, 0.75 h, 86%; (ii) *t*-BuOK–H_2O (7.6:2.3), DMSO, 20 °C, 0.5 h; or THF, 20 °C, 0.75 h; (iii) H_3O^+.

We suspected that the desilylation reaction occurs first but were unable to prove it since, even when the temperature was lowered, **2a** was the only product formed whether the reaction was carried out in anhydrous DMSO or THF. The former conditions proved to be in this case by far the best.

Nevertheless, we have been able to isolate the desilylated mesylate **1a**$_{exo}$ in more than 93% on reaction of **12a**$_{exo}$ with potassium hydroxide [6 equiv, DMSO–H_2O (4:1), 22 °C, 0.75 h]. As expected degradation of **1a**$_{exo}$ takes place if the reaction is instead performed at 70 °C for four hours.

The reasons why conditions A are not reproducible when applied to sulfonates **1a**$_{exo}$ still remain unanswered since some related compounds deliver the corresponding vinyl cyclopropane carboxylic acids. Anyhow, we have found a particularly efficient reagent (K_2O supported on *t*-BuOK?) and conditions, which proved smoother than the previous ones. We are investigating and reinvestigating systematically the reactivity of the whole series of regioisomeric **1** under conditions A–C to better understand the scope and limitations of this fragmentation reaction.

Typical Experiment

H_2O (42 mg, 2.3 mmol) was added at r.t., under an atmosphere of argon, to a solution of freshly sublimed *t*-BuOK (851 mg, 7.6 mmol) in anhyd DMSO (4.0 mL). The solution was stirred for 10 min before adding 4-*exo*-mesyloxy-3,3,6,6-tetramethylbicyclo[3.1.0]hexan-2-one (**1a**, 246 mg, 1.0 mmol) in one portion (yellow coloration appeared). The reaction mixture was then stirred at r.t. and monitored by TLC. After 45 min, the reaction mixture was poured into an Erlenmeyer flask containing 10 mL of Et_2O and 2 mL of ice and acidified to pH 2 with an aq solution of HCl (10%; discoloration). After decantation and extraction with Et_2O (4×10 mL), the combined organic extracts were washed with H_2O (2×2 mL), dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure to give a crude product. Purification by column chromatography (*n*-pentane–Et_2O, 60:40) gives the *cis*-chrysanthemic acid (**2a**) as a white solid (153 mg, 91%).

References and Notes

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(7) Once we found a good method for the fragmentation reaction, we performed the synthesis of scalemic **2a** as originally planned by Prof. Nigel Simpkins and informed him. We thank Prof. Nigel Simpkins, School of Chemistry, University of Nottingham, University Park, Nottingham, NG7 2RD, UK for his kindness.

(8) These results as well as those on the whole series of stereoisomers disclosed on Scheme 1 will be reported later. For example, we confirmed that the very labile *endo*-mesylate **1a**$_{Ms\text{-}endo}$ does not produce chrysanthemic acid **2a** neither under conditions A nor optimized conditions B or C.[1a,4]

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(11) (a) Compound **10a**: $[\alpha]_D^{20}$ –20 (*c* 1.20, $CHCl_3$).
(b) Compound **11a**$_{exo}$: $[\alpha]_D^{20}$ +12.5 (*c* 1.22, $CHCl_3$).
(c) Compound **1a**$_{Ms\text{-}exo}$: $[\alpha]_D^{20}$ +55.1 (*c* 1.11, $CHCl_3$).
(d) Compound **2a**: $[\alpha]_D^{20}$ +81.7 (*c* 1.0, $CHCl_3$).
(e) Compound **12a**$_{exo}$: $[\alpha]_D^{20}$ +4.9 (*c* 1.32, MeOH).
(f) Compound **2a**: $[\alpha]_D^{20}$ +82.2 (*c* 1.0, $CHCl_3$).

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