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Competing cyclopropane over epoxide formation from γ-halogeno-δ-hydroxy-ketones

Alain Krief *, Adrian Kremer

Department of Chemistry, Facultés Universitaires N.-D. de la Paix, 61 Rue de Bruxelles, Namur B-5000, Belgium

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ABSTRACT

Carbocyclization has been selectively achieved over epoxide formation from a γ-chloro-δ-hydroxy-ketone in the presence of a lithiumamide or using a different strategy in which the related silyloxyenol ether bearing an iodine atom at gamma-position and a silyloxy group in delta-position is reacted with tetrabutylammonium fluoride. These approaches take advantage of (i) the poor reactivity of the intermediate β-halogeno lithiumalkoxide first formed in the former case and (ii) the poorer ability of the fluoride ion to desilylate a silyl ether over a silylenol ether.

We report an original approach to scalemic (1*S*)-*cis*-chrysanthemic acid **1a**, precursor of (1*R*)-*trans*-chrysanthemic acid **1b**,[1,2] from scalemic (1*S*,6*R*)-2,2,5,5-tetramethyl-7-oxabicyclo[4.1.0]heptan-3-one **2** (Scheme 1).[2] It involves as a key-step intramolecular annelation of (3*S*,4*S*)-4-chloro-3-hydroxy-2,2,5,5-tetramethylcyclohexanone **3a**″, whose synthesis has been achieved by high yielding epoxide ring opening using beryllium dichloride (Scheme 1).

However the latter reaction occurs with modest selectivity delivering also the regioisomeric chlorohydrin **3a**′ as a by-product. For this purpose we have devised an original and simple strategy which allows to recycle **3a**′ to the epoxide **2** and at the same time favors the carbocyclization of the major isomer **3a**″ to the bicyclic [3.1.0] cyclopentanone **4** bearing an *exo*-hydroxyl group and precursor of (1*S*)-*cis*-chrysanthemic acid **1a** (Scheme 1).[3] It also takes advantage of the difference of polarity between the epoxide **2** and the keto-alcohol **4** which allows to achieve their efficient separation by chromatographic techniques (SiO_2).

It implies the apparent contradictory requirement to find the proper conditions which favor the transformation of **3a**′ to **2** and, at the same time, avoid its synthesis from 3**a**″ (Scheme 2).

It relies on (i) the expertise we previously gained on producing **4**, resulting from a C-alkylation reaction, from LiTMP and the related γ-bromo-δ-hydroxy-cyclohexanone **3b**″[2a] at the expense of the epoxide **2** which should have resulted from a competing O-alkylation reaction, (ii) the extremely poor capacity of β-chloro lithium-alcoholates **6a** to generate **2** (Table 1, entries a, b) and (iii) the high propensity of the alcoholate **6a**″, to generate **4** either through an equilibrated process leading to the enolate **7a**″ (Scheme 2, entry b; Table 1, entry b) or even better after a further metallation involving the dianion **8a**″ (Scheme 2, entry a; Table 1, entry b).

We have finally achieved the in situ transformation of the lithium-alcoholate **8a**′ to the epoxide **2** by taking advantage of the lithium–potassium exchange which occurs on reacting potassium *t*-butoxide (2 equiv, Scheme 1, entry d, compare to entry c).

The transformation reported above is far from obvious since we have been unable to apply it to the related bromo- and iodohydrin mixtures which arise from the ring opening of epoxide **2** by titanium tetrabromide (**3b**″/**3b**′: 43/57) or trimethylsilyl iodide[4,5] followed by hydrolysis of the resulting β-iodotrimethylsilyloxy ketone since in both cases the epoxide **2** is mainly formed in low yield indistinctly from both regioisomers.[2]

We have nevertheless achieved the same goal using a related strategy (Scheme 3), in which the crucial steps that involve epoxide ring opening and enolate formation have been carried out in a different order. For that purpose we have first synthesized the 'protected' silyl enolate **10** from the epoxy-ketone **2** ((i) 1 equiv LiHMDS, THF, −78 °C (ii) 2 equiv Me_3SiCl, −78 to 20 °C) and achieved the epoxide ring opening using trimethylsilyl iodide[4,5] (1 equiv Me_3SiI, THF, −78 to 20 °C). Although the latter reaction is high yielding, it provides an almost one to one mixture of the two regioisomeric β-silyloxyalkyl iodides **11c** (Scheme 3, entry a) from which the regioisomer **11c**″ has been selectively transformed to the bicyclic [3.1.0] cyclopentanone **4** and its regioisomer **11c**′ recycled via the epoxide **2**.

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* Corresponding author. Tel.: +32 474 318181; fax: +32 81 724 536.
E-mail address: alain.krief@fundp.ac.be (A. Krief).

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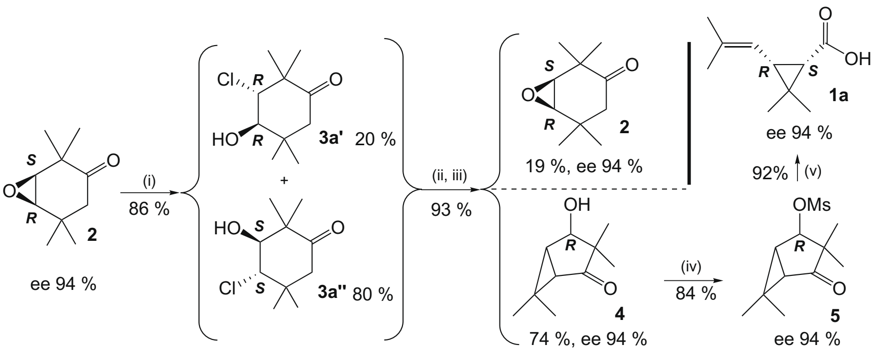
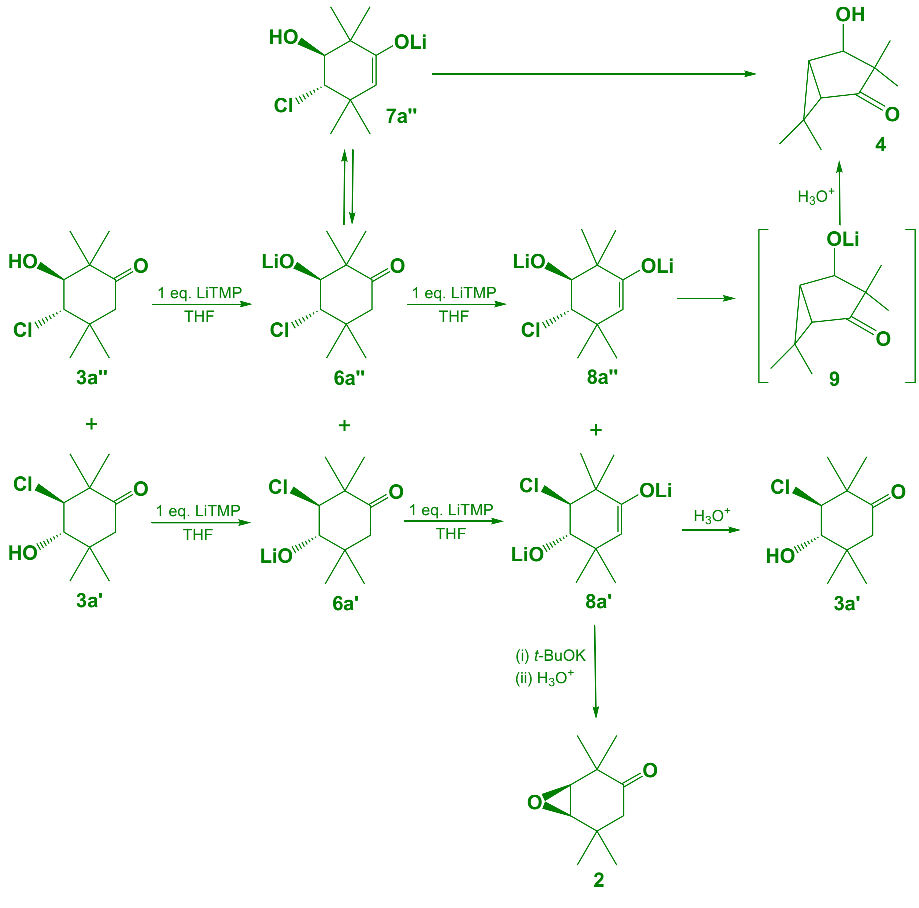


Scheme 1. Reagents and conditions: (i) 5 equiv $BeCl_2$, CH_2Cl_2, 20 °C; (ii) (a) 2 equiv LiTMP; (b) 2 equiv *t*-BuOK; (c) H_3O^+ (see entry d of the table); (iii) separation on chromatography on SiO_2; (iv) 1.2 equiv MsCl CH_2Cl_2, −10 °C, 2 h; (v) 6 equiv *t*-BuOK-3 equiv H_2O, THF, 20 °C, 1 h.



Scheme 2.

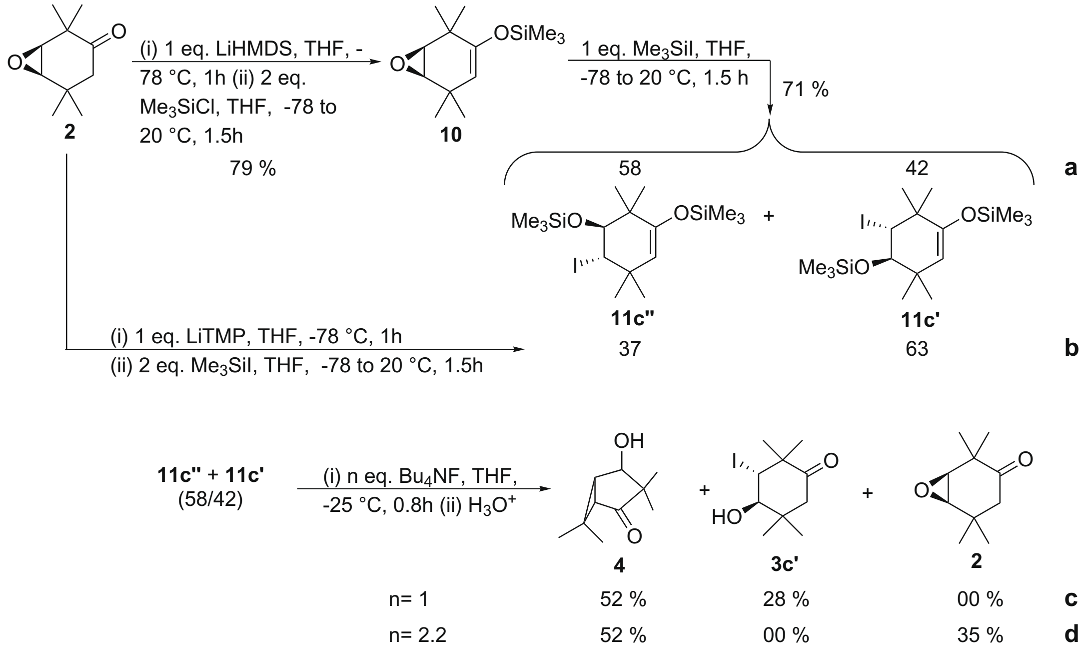
This has been efficiently achieved on reacting the **11c** mixture with tetrabutylammonium fluoride (2.2 equiv, THF, −25 to 20 °C, 0.8 h, then acidic workup, Scheme 3, entry d) taking advantage of the faster desilylation of the silylenolate moiety over that of the silylether. It allows the exclusive carbocyclization of **11c**″ leading to **4** at the expense of epoxide formation which would have left the epoxy-ketone **2** instead and the quantitative formation of the latter from the regiosiomeric **11c**′ (Scheme 3, entry d). This proposal has been assessed by the fact that bicyclic [3.1.0] cyclopentanone **4** has been produced along with the β-iodotrimethylsilyloxy ketone (transformed to **3c**′ after acidic workup) when using a single equivalent of tetrabutylammonium fluoride instead (Scheme 3, entry c).

In a related approach, the whole process has been carried out in a single pot using trimethylsilyl iodide to achieve sequentially both

Table 1

	3a″/**3a**′ ratio	Reagent (equiv/addit.[a])	*T* (°C)	*t* (h)	**4**/**2**/**3a**″/**3a**′ ratio	**4**/**2** isol.
a	80/20	LiTMP (1/N)	−25	1	21/0/58/21	20/—
b	80/20	LiTMP (1/N)	20	0.5	67/8/8/16	66/—
c	80/20	LiTMP (2/R)	−25	1	80/0/0/20	68/—
d	80/20	LiTMP (2/R) then *t*-BuOK (2/N)	−25	1.5	80/20/0/0	74/19

[a] N = addition of the base to **3a**; R = addition of **3a** to the base.



Scheme 3.

the in situ silylation of the lithium enolate resulting from metallation of the epoxy-ketone **2** with LiTMP, and the epoxide ring opening (Scheme 3, entry b).

Although this approach is very short, especially when the next step involving ammonium fluoride is carried in the same pot and it uses a single equivalent of base as compared to that using the ‘beryllium dichloride**’** instead (Scheme 1), the poor **11c**″/**11c**′ ratio of the β-silyloxyalkyl iodides formed precludes its synthetic use unless that ratio is greatly improved.

References and notes

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5. Trimethylsilyl chloride and bromide are unable to perform the opening of the epoxide ring of **2** and **9** even when used in excess and under harsher conditions.