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Stereochemical issues on the fragmentation of non-enolisable β-heterosubstituted-cyclopentanones with wet and anhydrous potassium hydroxide

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ABSTRACT

Tandem Haller–Bauer-*scission*/Grob-*fragmentation* reaction of cyclopentanone bearing a leaving group in β-position involves antiperiplanar arrangements which can be also achieved from epimeric derivatives, probably due to the high flexibility of the five-membered ring. We have observed that epimeric compounds react at different rates if the leaving group is a halogen and leads to very different types of compounds when it is a mesyl group.

Several years ago we devised[1] an original route to *cis*-chrysanthemic acid **1a**, which takes advantage of the tandem Haller–Bauer-*scission*[2]/Grob-*fragmentation*[3] reaction performed in aqueous DMSO with potassium hydroxide on the *exo*-β-keto-mesylate **4a**.

We were surprised 20 years later to be unable to reproduce[4] the yield we originally reported for the last step. We got instead a polymeric material resulting from competing attack of the hydroxide ion onto the sulfur atom of the mesylate (6 equiv KOH, DMSO–H_2O (4:1) 'WPH', 70 °C; Method A;[1,4,5] 6% instead of 80%[1] yield).[4]

We however found that the desired transformation can be achieved, in almost quantitative yield and under very mild conditions, using 'anhydrous' potassium hydroxide 'APH' [6] (mixture of potassium hydroxide, potassium *t*-butoxide, and *t*-butanol) prepared by the addition of water to an excess of potassium *t*-butoxide in DMSO (Method B)[4–6] or THF (Method C)[4–6] ((i) **4a**/*t*-BuOK/H_2O (1:7.6:2.3 ratio), 20 °C, <1 h, Scheme 1, entry a, Table 1, entry a).

We decided to extend these reactions to the synthesis of desmethyl-**1b**, **1c** and didesmethyl-**1d** *cis*-chrysanthemic acids from the corresponding β-keto-mesylates bearing an *exo*-mesyloxy group **4** as well as their *endo*-stereoisomers **6** any time they were available (Scheme 2).

We found that 'APH' efficiently transforms the *exo*-β-keto-mesylate **4b** to the corresponding desmethyl *cis*-chrysanthemic acid **1b** especially if the reaction is performed in DMSO (Method B, compare to Method C; Scheme 2, Table 1, entry b). We also found that **4b** behaves like **4a** which also bears an *endo*-methyl group on the cyclopropane ring since **1b** is obtained in very poor yield if the reaction is instead carried out with 'WPH' (Method A, compare to Methods B and C; Scheme 2, Table 1, entry b, compare to entry a).[7a,b]

'APH' however reacts sluggishly with the related *exo*-β-keto-mesylates **4c** and **4d** both of which miss the methyl group in *endo*-4-position. These reactions lead to desmethyl-**1c** and didesmethyl-**1d** *cis*-chrysanthemic acids in extremely poor yields besides large quantities of polymeric material whatever THF or DMSO is used as the solvent (Table 1; entries c and d; Methods B and C). We have surprisingly observed, in control experiments, that 'WPH' in DMSO behaves similarly but delivers **1c** and **1d** in slightly better yields after acidic work-up (Table 1; entries c and d; Method A).[8]

We however found that the synthesis of desmethyl-**1c** and didesmethyl-**1d** *cis*-chrysanthemic acids can be efficiently achieved by 'APH' using instead their epimeric *endo*-β-keto-mesylates **6c** and **6d** as starting materials (Table 1, entries e and f, Methods B and C; compare to entries c and d). In such case 'WPH'[7a,c] is also able to achieve the same transformation but it requires higher temperature, longer time, and delivers **1c** and **1d** in poorer yields (40 °C instead of 20 °C, Table 1, entries e and f, compare Method A to Methods B and C).

Accordingly we have been able to propose two different strategies to achieve the stereoselective synthesis of the whole set of *cis*-vinyl cyclopropane carboxylic acids **1** differently substituted at C-6 on the cyclopropane ring from the 3,3-dimethylbicyclo[3.1.0]hexane-2,4-diones **2**, both of which use the efficiency of 'APH' to pro-

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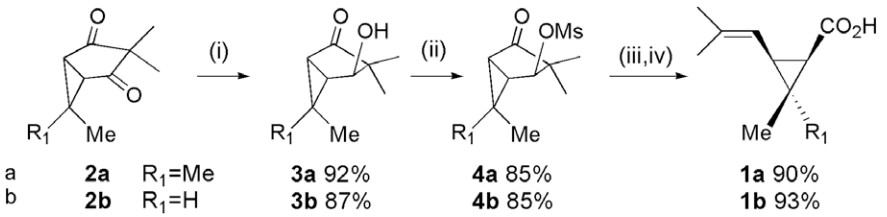
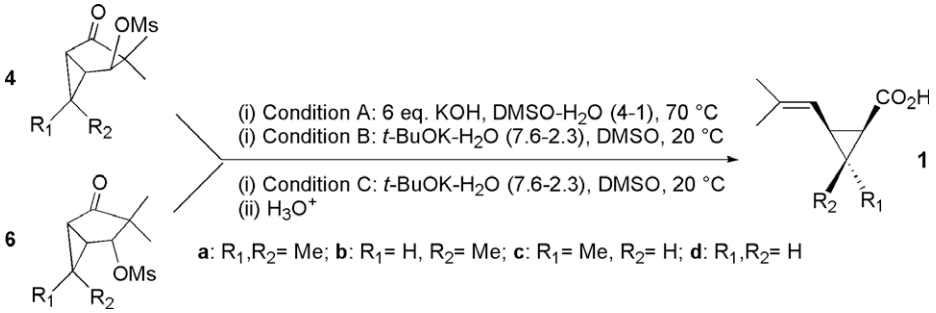


Scheme 1. Reagents and conditions: (i) 1 equiv $NaBH_4$, 1 equiv $CeCl_3{\cdot}7H_2O$, −78 °C, 1.5 h; (ii) MsCl, NEt_3, CH_2Cl_2, −10 °C, 1 h; (iii) *t*-BuOk–H_2O (7.6–2.3), DMSO, 20 °C; (iv) aq HCl.

Table 1
Reaction of 4-mesyloxy-3,3-dimethylbicyclo[3.1.0]hexan-2-ones **4** and **6** with potassium hydroxide

	R_1	R_2	Leaving group	**4**/**6**	**1**%[a] (h) Method A[5]	**1**%[a] (h) Method B[5]	**1**%[a] (h) Method C[5]
a	Me	Me	OMs	**4a**	6 (6)	90 (0.4)	60 (0.3)
b	H	Me	OMs	**4b**	18 (6)	93 (0.5)	54 (0.5)
c	Me	H	OMs	**4c**	14 (1.5)	5 (0.5)	<5 (0.5)
d	H	H	OMs	**4d**	21 (2)	9 (0.5)	3 (0.5)
e	Me	H	OMs	**6c**	55 (0.8)[b]	70 (0.3)	90 (0.3)
f	H	H	OMs	**6d**	65 (0.8)[b]	73 (0.3)	76 (0.3)

[a] The yields reported refer to isolated analytically pure compounds.
[b] These reactions have been carried out at 40 °C.



Scheme 2.

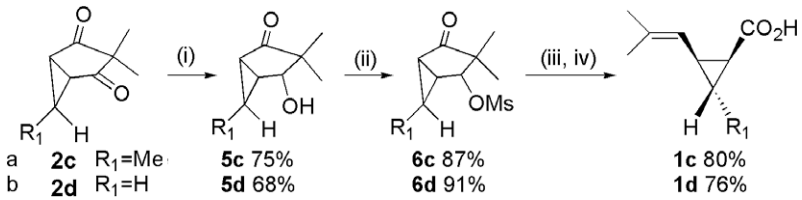
mote the tandem Haller–Bauer-*scission*[2]/Grob-*fragmentation*[3] reaction reported above (Schemes 1 and 3).

The synthesis of desmethyl *cis*-chrysanthemic acid **1b**, as that of *cis*-chrysanthemic acid **1a** we already published,[4] can only be achieved from the *exo*-β-keto-mesylate **4b** and 'APH', DMSO being the best solvent. The synthesis of the mesylates requires the stereoselective reduction of the diketone **2b** possessing an *endo*-methyl group at C-6, by its most hindered face. This has been efficiently achieved using Luche's reagent ($NaBH_4$–$CeCl_3{\cdot}7H_2O$, MeOH, −78 °C, Scheme 1, entry b compare to entry a).[9]

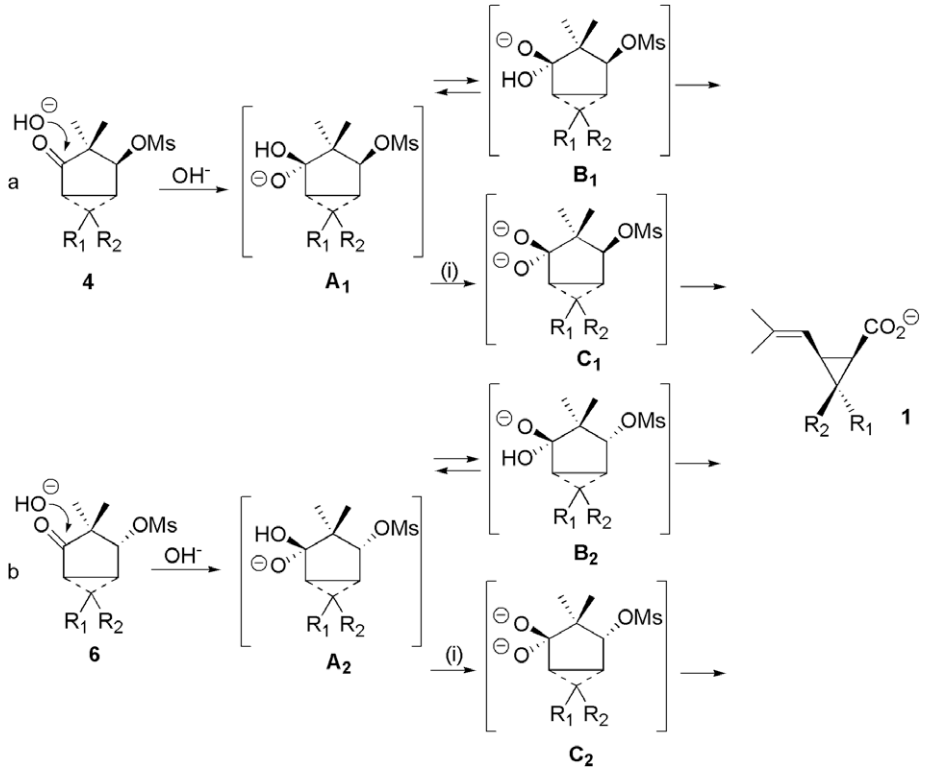
The synthesis of desmethyl *cis*-chrysanthemic acid **1c** and didesmethyl *cis*-chrysanthemic acid **1d** however is best achieved on the reaction of 'APH' in THF with *endo*-mesylates **6c** and **6d** (Method C, Scheme 3, entries a and b). The synthesis of the latter requires the stereoselective reduction of the diones **2c** and **2d** possessing an *endo*-hydrogen at C-6, by their least hindered faces. It has been efficiently achieved with sodium borohydride in methanol at −78 °C or better with lithium triethyl borohydride in THF at the same temperature.[9]

All steps involved in the two strategies are not interchangeable. We have been lucky that 'APH' allows the fragmentation of the mesylates **4b** as **4a** since the related epimers **6b** as **6a** are thermally unstable and decompose around −10 °C extremely rapidly. This prevents their use for the synthesis of the corresponding cyclopropane carboxylic acids **1b** and **1a**. We have been also extremely lucky that 'APH' fragments efficiently the *endo*-keto-mesylates **6c** and **6d** and not their epimers **4c** and **4d** which cannot be produced stereoselectively from β-diketones **2c** and **2d** using the Luche's reagent since it produces at best almost 1:1 epimeric mixtures of **4c**/**6c** and **4d**/**6d**.[9]

The transformations reported above involve a stepwise mechanism which implies addition of the hydroxide ion to the carbonyl of **4** and **6** followed by the fragmentation of the resulting intermediate **A** (Scheme 4). The former step is expected to be better achieved



Scheme 3. Reagents and conditions: (i) 1 equiv $LiBhEt_3$, THF, −78 to 20 °C, 0.3 h; (ii) MsCl, NEt_3, CH_2Cl_2, −10 °C, 1 h; (iii) *t*-BuOK–H_2O (7.6–2.3), THF, 20 °C; (iv) aq HCl.



Scheme 4. Reagents: (i) *t*-BuOK, *t*-BuOH from 'APH'.

with 'APH' rather than with 'WPH' because it involves the more reactive naked hydroxide ion and because the excess of potassium *t*-butoxide present beside potassium hydroxide is able to promote the formation of the α,α-dialkoxides **C**[6] more prone to release the unfavorable electronic interactions by fragmentation than **B**.

Furthermore it is well documented that an antiperiplanar arrangement of atoms and bonds usually favors smooth fragmentation reactions.[3,10] This could be apparently achieved from some of the 4-oxobicyclo[3.1.0]hexan-2-yl methanesulfonates depending on the orientation of the mesyloxy group and the substitution at carbon-6 on the cyclopropane ring fused to the flexible five-membered ring.

Apparently the conformation leading to the antiperiplanar arrangement cited above can be achieved from **4a** and **4b** bearing an *endo*-methyl group and an *exo*-mesyloxy group. However the top face attack of the hydroxide ion could be hampered by the presence of the 'bulky' mesyloxy group thus favoring competitive attack on its sulfur atom which finally leads to polymeric material.[4] The less 'hindered' and more reactive naked hydroxide ion from 'APH' and the formation of the dialkoxide $\mathbf{C_1}$ (R_1, R_2: Me for example) which is expected to be more prone to fragment than $\mathbf{A_1}$ or $\mathbf{B_1}$ (R_1, R_2 = Me for example) might be responsible for the difference of reactivity observed between 'APH' and 'WPH'.

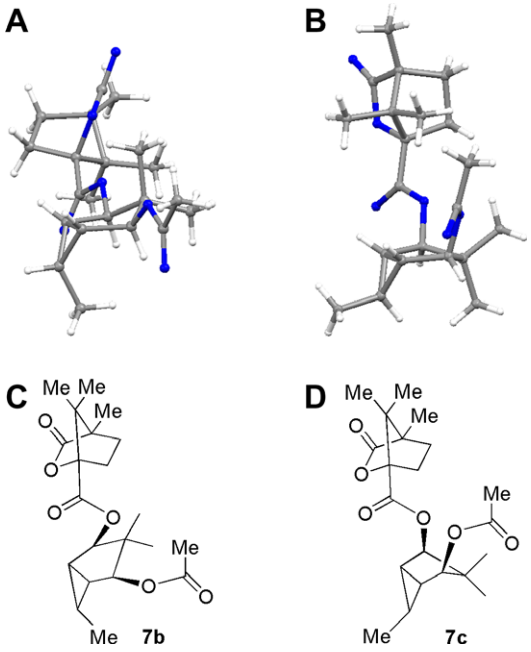


Figure 1.

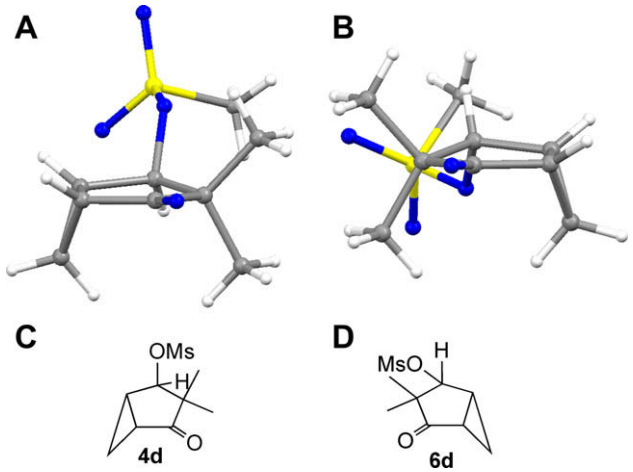
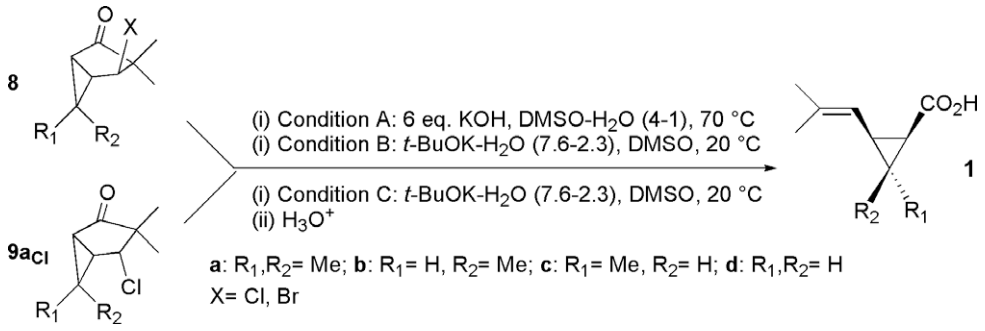


Figure 2.



Scheme 5.

The difference of reactivity observed between the *exo*-mesylates **4a** and **4b** bearing the *endo*-methyl group and their related regioisomers **4c** and **4d** missing it (Table 1, compare entries c and d to a and b) could be related to the change of preferred conformation in the transition state due to the flexibility of the five-membered ring. This not only brings the mesyloxy group in axial position which favors, as described above for **4a** and **4b**, the formation of polymeric material but also at the same time does not favor the antiperiplanar arrangement suitable for fragmentation. Therefore both 'WPH' and 'APH' behave similarly and do not allow the fragmentation reaction leading to **1c** and **1d**, respectively (Table 1, entries c and d).

X-ray crystallographic data of the two isomeric di-*exo*-acetoxycamphenoates possessing the *endo*-methyl group **7b** or missing it **7c** (Fig. 1),[11] which could be related to the transition states of the two type of reactions described above, clearly show that the antiperiplanar arrangement present in the former is no longer present in the latter. These results tend to support the hypotheses presented above.

Finally the successful synthesis of desmethyl-**1c** and didesmethyl-**1d** *cis*-chrysanthemic acids **1c** and **1d** from keto-mesylates epimers **6c** and **6d** both missing the *endo*-methyl group on the cyclopropane ring and bearing an *endo*-mesyloxy group could account from the conformation of the starting material in which the mesyloxy group lies in equatorial position (see X-ray data[12] for **6d**, Fig. 2). It allows, at the same time, the top face attack of any type of hydroxide ion on to its carbonyl group, avoiding the competing attack on the sulfur atom of the mesyloxy group and favors the achievement of the antiperiplanar arrangement in the transition state of the fragmentation step.

In order to delineate the role of each of the factors reported above, we have carried out the reaction of 'AHP' toward the related β-keto-halides **8** and **9** (Scheme 5) missing the mesyloxy group present on the related β-keto-mesylates **4** and **6**, which is particularly 'bulky' and possesses an extra electrophilic site on sulfur.

We found that the fragmentation is efficiently achieved from all the *exo*-β-keto-bromides $\mathbf{8_{Br}}$ possessing or not the *endo*-methyl group and whether 'AHP' or even 'WHP' is used (Table 2, entries a–c).[13] This suggests that the impact of the mesyloxy group and of its direction on the reactivity of β-keto-mesylates **4** and maybe **6** is far more important than the access to the antiperiplanar arrangement.

An even better insight on the mechanism of these transformations arises from the reaction of potassium hydroxide toward the couple of β-chloro-ketones $\mathbf{8a_{Cl}}$ and $\mathbf{9a_{Cl}}$.

The *exo*-β-chloro-ketone $\mathbf{8a_{Cl}}$ whose reaction with potassium hydroxide is expected to easily proceed through an antiperiplanar arrangement provides *cis*-chrysanthemic acid **1a** in good yield (Method A and C, Table 2, entry d) and at the same rate than that of the related *exo*-β-bromo-ketone $\mathbf{8a_{Br}}$ (Table 2, compare entries c and d) even as the leaving group ability of the chloride is much poorer than that of the bromide.

The epimeric *endo*-β-chloro-ketone $\mathbf{9a_{Cl}}$, whose reaction with potassium hydroxide is not expected to achieve so easily the antiperiplanar arrangement, leads to a polymeric material on reaction with 'WPH' at 70 °C (Method A, Table 2, entry e). It reacts extremely slowly with 'APH' to produce *cis*-chrysanthemic acid **1a** in poor yield if the reaction is carried out at 20 °C (Method C, Table 2, entry e) and in much better yield if it is instead performed at 60 °C for quite a long time (Method C, Table 2, entry f).

In conclusion cyclopentanones **4**, **6**, **8**, and **9** fused in α′,β′-position to a cyclopropane ring and bearing a leaving group in β-position react with potassium hydroxide to produce vinylcyclopropane carboxylates **1** by fragmentation reaction. This reaction is best achieved with those compounds bearing an *exo*-halogen atom **8**. This has been rationalized by assuming an access to a periplanar arrangement of those atoms and bonds involved in the process favored by the flexibility of the cyclopentane skeleton.[14]

In the related mesylates **4** and **6**, the formation of polymers often compete in those derivatives bearing this group in *exo*-position due to competing attack of the hydroxide ion on its sulfur atom leading then to a retroaldol fragmentation reaction if the nucleophile is not strong enough or the antiperiplanar arrangement is difficult to reach.[4] Thus 'APH' proved to be the reagent of choice owing the nucleophilic-

Table 2
Reaction of some 4-halogeno-3,3-dimethylbicyclo[3.1.0]hexan-2-ones **8** and **9** with potassium hydroxide

	R_1	R_2	Leaving group	**8**/**9**	**1**%[a] (h) Method A	**1**[a]% (h) Method B	**1**[a]% (h) Method C
a	Me	H	Br	$\mathbf{8c_{Br}}$	95 (0.3)[13]	—	95 (0.3)
b	H	H	Br	$\mathbf{8d_{Br}}$	83 (0.3)[13]	—	86 (0.3)
c	Me	Me	Br	$\mathbf{8a_{Br}}$	87 (0.8)[4,13]	53 (0.3)[4]	94 (0.5)[4]
d	Me	Me	Cl	$\mathbf{8a_{Cl}}$	75 (0.8)	—	91 (0.5)
e	Me	Me	Cl	$\mathbf{9a_{Cl}}$	0 (3.5)	—	22 (216)[b]
f	Me	Me	Cl	$\mathbf{9a_{Cl}}$	—	—	72 (72)[c,d]

[a] The yields reported refer to isolated analytically pure compounds.
[b] 75% of $\mathbf{9a_{Cl}}$ recovered.
[c] Reaction carried out at 60 °C.
[d] 15% of $\mathbf{9a_{Cl}}$ recovered.

ity of the naked hydroxide ion and the aptitude fragmentation of the dialkoxide intermediates **C** to fragment (Scheme 4).[6a]

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5. Method A: **4** or **6** (1 mmol, neat) is added to a solution of potassium hydroxide (6 mmol) in DMSO–water mixture (4:1, 3 mL) at 70 °C and stirred at the temperature for the time required (Table 1). Acidification and usual work-up lead to **1** (Table 1); Method B: **4** or **6** (1 mmol, neat) is added at room temperature to a slurry resulting from the addition of water (2.3 mmol) to a solution of *t*-BuOK (7.6 mmol) in dry DMSO (4 mL). After the time required (Table 1), acidification and usual work-up, **1** is produced (Table 1); Method C: A solution of **4** or **6** (1 mmol) in THF (4 mL) is added at room temperature to a suspension resulting from the addition of water (2.3 mmol) to a solution of *t*-BuOK (7.6 mmol) in dry THF (8 mL). After the time required (Table 1), acidification and usual work-up, **1** is produced (Table 1).
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7. (a) Krief, A.; Surleraux, D.; Robson, M. J. *Synlett* **1991**, 276–278; (b) The yield of **1b** resulting from the fragmentation reaction of **4b** using 'WPH' is much poorer than the one reported in Ref. 7a; (c) These results are in accordance with those reported using 'WPH' in Ref. 7a. However the statement that the *exo*-mesylate **4d** is more reactive toward 'WPH' than is *endo*-isomer **6d** is wrong.[7a]
8. Original work.
9. (a) The proof of structure of those compounds have already been published[9b]; (b) Krief, A.; Surleraux, D. *Synlett* **1991**, 273–275.
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14. Most of the reactions involving 'Grob-type fragmentation reaction' so far reported have been carried out on rigid six-membered cyclic derivatives[2,3,10] where change in the stereochemistry of one of the group involved in the process changes, in an expected manner, the outcome of the reaction.