

# Lithium naphthalenide induced reductive cleavage of $\alpha,\beta$ -epoxy ketones: an efficient procedure for the preparation of $\beta$ -hydroxy ketones

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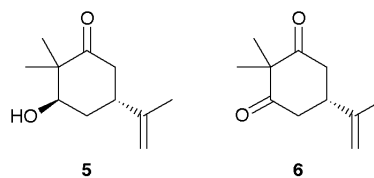
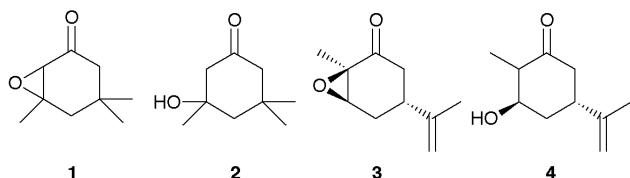
**Lithium naphthalenide presents itself as a mild and efficient reagent for the cleavage of  $\alpha,\beta$ -epoxy ketones to give the corresponding  $\beta$ -hydroxy ketones in good yields.**

$\beta$ -Hydroxy ketones and the closely related 1,3-diol group are important functionalities, which are found in prostaglandins,<sup>1</sup> taxol and congeners,<sup>2</sup> and many other interesting natural products.  $\beta$ -Hydroxy ketones are commonly prepared by an aldol condensation reaction<sup>3</sup> or by reductive cleavage of an  $\alpha,\beta$ -epoxy ketone. The aldol process proved to be highly useful for the preparation of 'acyclic'  $\beta$ -hydroxy ketones. For cyclic  $\beta$ -hydroxy ketones, however, this method cannot be generally applied efficiently due to the lack of stereo- and regio-control in general, side reactions such as the intermolecular aldol, and further reactions (e.g. dehydration) of the desired products. Many reagents have been found to be effective for the reductive cleavage of  $\alpha,\beta$ -epoxy ketones, which are readily accessible from conjugated enones and allylic alcohols with stereocontrol and possible asymmetric induction, including alkali metal in liquid ammonia,<sup>4</sup> zinc in acetic acid,<sup>5</sup> samarium diiodide,<sup>6</sup> aluminium amalgam,<sup>7</sup> chromous salts in alcohol,<sup>8</sup> organoselenium borate complex,<sup>9</sup> sodium hydrogen telluride,<sup>10</sup> sodium iodide in conjunction with sodium acetate,<sup>11</sup> and the combination of palladium, formic acid and triethylamine.<sup>12</sup> It has also been shown that the reductive cleavage can be carried out electrochemically.<sup>13</sup> The yields of the desired  $\beta$ -hydroxy ketones, however, are often inconsistent by the use of many of the existing procedures. This is mainly because of the intrinsic instability of the  $\beta$ -hydroxy ketone system which may undergo facile dehydration or retro-aldol reaction even under weakly acidic or basic conditions at somewhat higher temperature over somewhat longer reaction time. Herein we describe an efficient and apparently general procedure for the reductive cleavage of  $\alpha,\beta$ -epoxy ketones to the corresponding  $\beta$ -hydroxy ketones under very mild conditions, which minimize the side reactions.

The new procedure, which is operationally simple, makes use of lithium naphthalenide (LN) as the reducing agent. This reagent, which can be easily prepared as a stable stock solution by mixing equal parts of lithium metal and naphthalene in THF at room temperature,<sup>14</sup> was found to be highly effective for the selective cleavage of the  $\alpha,\beta$ -epoxy ketone system. ‡ In a typical experiment, a solution of epoxy ketone **1** (49 mg, 0.32 mmol) in THF (2 ml) was added to a 0.34 M solution of LN in THF (2.8

ml) at  $-78$  °C. The resulting solution was stirred at  $-78$  °C under an atmosphere of argon for 10 min. Then water (1 ml) was added, and the resulting solution was allowed to warm up to room temperature, diluted with water (4 ml) and extracted with Et<sub>2</sub>O (15 ml). Usual work-up of the ethereal solution gave the  $\beta$ -hydroxy ketone **2** in 78% yield after flash chromatography on silica gel (prewashed with a 1% solution of Et<sub>3</sub>N in hexanes), eluting with a 15% solution of EtOAc in hexanes containing a small amount of Et<sub>3</sub>N (5 drops in 100 ml of solution). The generality of this procedure is evident from the results obtained for a number of  $\alpha,\beta$ -epoxy ketones examined (Table 1). In all cases, products were obtained in synthetically useful yields, many of which are superior to those obtained using other reducing agents. For example, the reduction of epoxide **3** derived from (*R*)-carvone was found to be ineffective with samarium diiodide.<sup>6</sup> With lithium in liquid ammonia, it gave only 35% yield of the desired product **4**.<sup>4b</sup> In the present case with LN, a considerably higher yield of **4** (62%) was realized. As another example, many attempts previously made to introduce the  $\beta$ -hydroxy ketone moiety to steroidal compounds often met with undesirable results.<sup>4c,d,8</sup> Again, by the use of LN under the described conditions, two isomeric steroidal epoxy ketones (entries 8 and 9) were readily reduced to the corresponding  $\beta$ -hydroxy ketones.

In light of its generality, operational simplicity, good yield in product formation, and the mild reaction conditions under which many functional groups are known to be unaffected towards LN,<sup>14</sup> the aforementioned procedure promises to be a method of choice for the synthesis of  $\beta$ -hydroxy ketones *via* reductive cleavage of the corresponding epoxy ketones. As illustrated by the following experimental results, this procedure can be extended to facilitate the preparation of  $\alpha,\alpha$ -disubstituted  $\beta$ -hydroxy ketones *via* alkylation of the ensuing enolate produced from the reductive cleavage of the epoxy ring and of 2,2-disubstituted 1,3-diones by subsequent oxidation. Treatment of epoxy ketone **3** with LN in tetrahydrofuran under the standard conditions (*vide supra*) for 30 min, followed by addition of MeI (5 equiv.) and warming up to room temperature resulted in the formation of  $\beta$ -hydroxy ketone **5** in 70% yield.

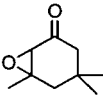
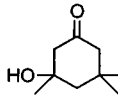
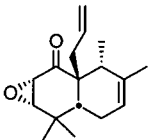
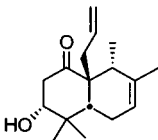
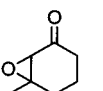
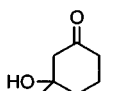
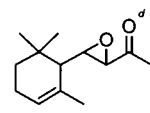
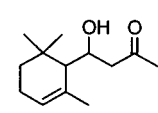
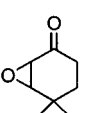
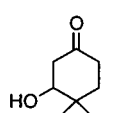
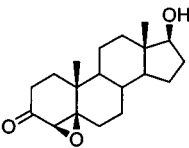
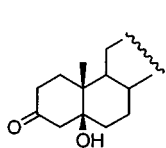
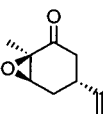
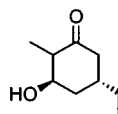
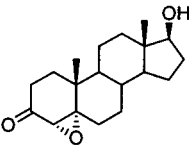
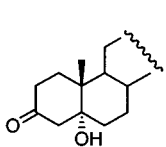
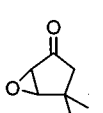
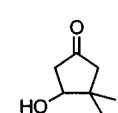


When hydroxy ketone **5** was subjected to oxidation [PCC (5 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, 20 °C, 8 h], diketone **6** was formed in 78% yield.

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**Table 1** Reductive cleavage of  $\alpha,\beta$ -epoxy ketones with lithium naphthalenide to the corresponding  $\beta$ -hydroxy ketones

Entry	$\alpha,\beta$ -Epoxy ketone <sup>a</sup>	t/min	Product	Yield <sup>b</sup> (%)	Entry	$\alpha,\beta$ -Epoxy ketone <sup>a</sup>	t/min	Product	Yield <sup>b</sup> (%)
1		10		78	6		20		88
2		15		78	7		60		65 <sup>d</sup>
3		15		71	8		30°		77
4		30		62 <sup>c</sup>	9		30°		87
5		25		68					

<sup>a</sup> The  $\alpha,\beta$ -epoxy ketones used for the present study were prepared by treatment of the corresponding enones with LiOH (0.5 equiv.), 30% H<sub>2</sub>O<sub>2</sub> (1.5–2.0 equiv.) in MeOH (4 ml per 1 mmol of enone) at room temperature for 0.5–2 h. <sup>b</sup> Yields are for isolated products. <sup>c</sup> An inseparable mixture of two diastereomers was obtained in a ratio of 11 : 1. The stereochemistry of these compounds remains to be determined. <sup>d</sup> A single stereoisomer was obtained. Its stereochemistry remains to be determined. <sup>e</sup> In each of these cases, 4 equiv. of LN was used.

## Notes and references

‡ The reductive cleavage of epoxides derived from alkenes with aromatic radical anions has been studied previously by Bartmann (ref. 15) and Cohen *et al.* (ref. 16). To the best of our knowledge, however, this procedure has never been applied to  $\alpha,\beta$ -epoxy ketones to facilitate the preparation of 1,3-ketols.

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