Lithium–potassium superbases as key reagents for the base-catalysed isomerisation of some terpenoids

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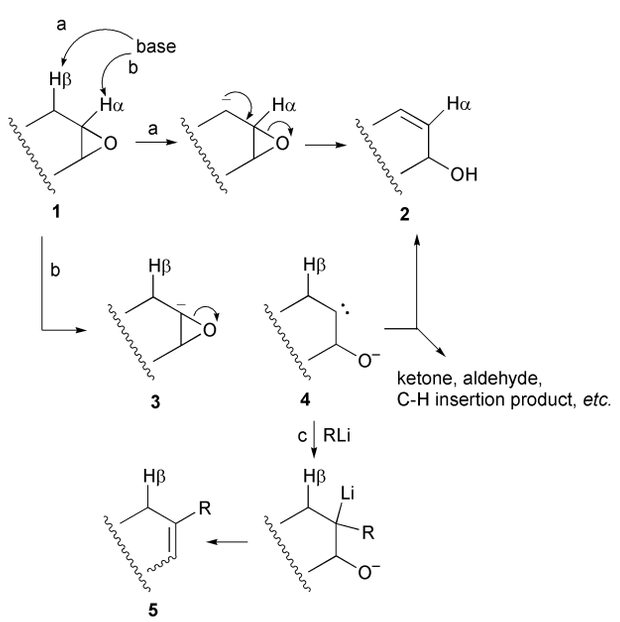
Received (in Cambridge, UK) 1st August 2001, Accepted 17th September 2001
First published as an Advance Article on the web 17th October 2001

Some representative monoterpenes have been isomerised under the influence of Schlosser's lithium–potassium mixed superbases, promoting β-elimination reactions. The results are compared with those obtained with butyllithium and LDA. Different selectivities and different reaction yields are achieved as a function of the base employed. These results confirm the particular reactivity of bimetallic reagents. In this paper it is proposed that the observed selectivities might depend on the conformational features of the substrate, on the strength of the organometallic reagent, as well as on steric requirements of the elimination reaction.

Introduction

Monoterpenes can be considered relatively inexpensive building blocks, simple and efficacious structural elaboration of which should be possible by base-induced isomerisation. Oxiranes are versatile compounds that can be easily isomerised both under acidic[1] and basic[2] conditions to give useful derivatives such as aldehydes, ketones and allylic alcohols. From the literature data it can be seen that aliphatic oxiranes react in strong basic milieu according to several pathways, depending on their structure and the reaction conditions (Scheme 1).



Scheme 1 Base-promoted reactions of epoxides.

First of all the oxirane **1** undergoes isomerisation to the allylic alcohol **2** (path *a*). Moreover, metalation may occur at a position adjacent to the heterocyclic oxygen atom (path *b*). By this route an oxiran-2-yl anion intermediate **3** results, which rearranges to α-oxido carbenoid **4** by α-elimination. The produced carbenoid undergoes various reactions such as isomerisation to carbonyl compounds, backbone rearrangement, and C–H insertion reaction. In particular, the insertion reaction may involve the carbon–lithium bond of a lithium reagent molecule (path *c*), affording alkene **5**.

The first base-promoted isomerisation of an oxirane was reported by Heilbron, Jones, Haynes and Sondheimer when they treated 2-benzyloxirane with sodium amide in liquid ammonia and isolated cinnamyl alcohol (in 80% yield).[3] The metalation and the ring opening of oxiranes promoted by alkyllithium reagents[4] and by mixed bases[5] have been reported and used in various syntheses. Crandall and co-workers have extensively studied various base-promoted isomerisations of oxiranes,[2] and in particular have described from the synthetic point of view, among other reactions, the isomerisation of α-pinene oxide to *trans*-pinocarveol.[6] The isomerisation described by these authors was carried out in the presence of lithium diethylamide in anhydrous diethyl ether at reflux temperature. We were interested in investigating the feasibility of base-induced isomerisation of terpenic structures containing an oxirane ring, resorting to the use of Schlosser's lithium–potassium mixed bases.[7] Moreover, simple and efficacious structural elaboration should be also possible in terpenes containing five- and six-membered heterocyclic rings, resorting to the particular reactivity of lithium–potassium mixed superbases that are more effective than a metal amide alone. Previous examples of ring opening of functionalised tetrahydrofuran structures have been reported.[8]

Results and discussion

The isomerisations have been studied and the obtained structures have been assigned by 200 and 400 MHz ^{1}H NMR spectra either on the crude mixture or on purified samples. We have examined the influence of different basic reagents on the isomerisation reaction of α-pinene oxide, β-pinene oxide, 3-carene oxide, 1,4-cineole and 1,8-cineole (Chart 1), and the obtained results are presented below according to the starting material. In particular, we started our study by considering the isomerisation of α-pinene oxide and β-pinene oxide in the presence of Schlosser bases, since the behaviour of these terpenes with LDA (also termed LIDA in this paper: see below) has been deeply investigated in previous works of other authors and the results clearly reported in the literature.[3]

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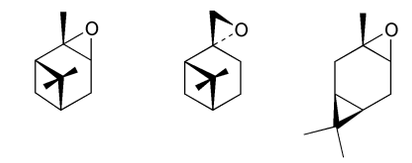
 DOI: 10.1039/b106906c

Table 1 Effect of the base on the isomerisation of α-pinene oxide[a] (see Scheme 2)

Entry	Base (equiv.)	**6** : **7** Ratio[b]	Reaction time (reaction temp. *T*/°C)	Yield (%)[c]
1	BuLi (2.5)	50 : 50	24 h (25)	80
2	LDA (2.5)	100 : 0	24 h (25)	90
3	LIC–KOR (1.0)	66 : 33	30 min (−95)	25
4	LIC–KOR (2.5)	66 : 33	30 min (−95)	90
5	LIDA–KOR (2.0)	90 : 10	30 min (−95)	90
6	LIDA–KOR (2.5)	93 : 7	30 min (−95)	90
7	LITMP–KOR (2.5)[d]	95 : 5	30 min (−95)	90

[a] Substrate: 2.0 mmol; solvent: THF. [b] On the basis of separated products by column chromatography. [c] Isolated and purified products. [d] 2,2,6,6-Tetramethylpyperidine was used.



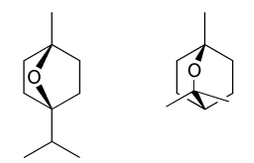
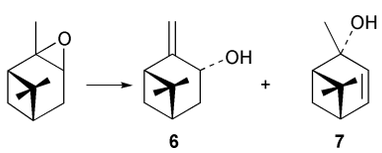


Chart 1

α-Pinene oxide

The influence of the base has been examined by considering the isomerisation shown in Scheme 2, and the results are



Scheme 2 Base-promoted isomerisation of α-pinene oxide.

reported in Table 1. As can be seen from the data in Table 1 lithium–potassium mixed bases LIDA–KOR (LIDA = lithium diisopropylamide, KOR = potassium *tert*-butoxide) and LITMP–KOR (LITMP = lithium 2,2,6,6-tetramethylpiperidide, KOR = potassium *tert*-butoxide) react with a selectivity comparable to that shown by LDA and reported by Crandall and Crawley.[6] In addition, the mixed bases are greatly more reactive than the amide alone and high reaction yields are indeed achieved in a very much shorter reaction time working at −95 °C (compare entry 2 with entries 5, 6 and 7 in Table 1). Butyllithium alone and LIC–KOR (LIC = butyllithium, KOR = potassium *tert*-butoxide) that afford a mixture of exocyclic (**6**) and endocyclic (**7**) alkenes appear to be less selective. Therefore, a clear control of the deprotonation site of α-pinene oxide takes place upon a simple change of the base. The structures of alkyllithium reagents and bimetallic superbase in solution are of course quite different, and this parameter is probably highly relevant in understanding this problem. However, these results could be tentatively explained by considering the conformation of α-pinene oxide proposed in Fig. 1.

It has been recognised that β-elimination in oxiranes prefers a *syn*-periplanar arrangement between the deprotonation site and the leaving oxirane oxygen.[9] α-Pinene oxide can be metalated at two sites of comparable acidity (H^a and H^b in Fig. 1), thus undergoing β-elimination. On the other hand, the two sites differ from a stereochemical point of view. The H^a site is expected to be the preferred deprotonation target, being free of

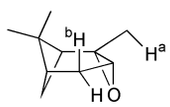


Fig. 1 α-Pinene oxide.

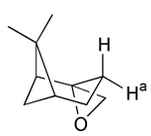
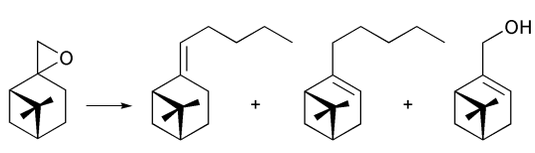


Fig. 2 β-Pinene oxide.

steric encumbrance (actually, alcohol **6** has been selectively produced, or predominates in most cases reported in Table 1), while the H^b site suffers due to its 'wrong' geometry with respect to the correct *syn*-periplanar arrangement. Despite this, product **7** was obtained, even if as the minor isomer (a 50 : 50 mixture was obtained only when using BuLi: see Table 1). From a mechanistic point of view it cannot be excluded that α-metalation and α-elimination of the oxirane ring could take place, and that the subsequent isomerisation of the resulting carbenoid species might contribute to the formation of compound **7**. This hypothesis has been previously formulated in the case of the base-promoted isomerisation of *cis*-1,2-epoxycyclodecane.[3]

β-Pinene oxide

The influence of the base has been examined by considering the isomerisation shown in Scheme 3, and the results are reported



Scheme 3 Base-promoted reaction of β-pinene oxide.

in Table 2. In the case of β-pinene oxide three compounds were obtained and the ratio among the products strongly depends on the nature of the basic reagent. Working with butyllithium only the two isomeric structure **8** and **9** were obtained, and the allylic alcohol **10** was not produced. On the other hand, in the presence of LIDA–KOR mixed base the allylic alcohol **10** was selectively obtained in quantitative yield (compare entries 1 and 2 in Table 2). This compound clearly derives from the β-elimination mechanism reported in path *a* of Scheme 1, while the formation of the isomeric products **8** and **9** can be readily rationalised by considering path *c* of Scheme 1. Other comments can be made from consideration of the conformation of β-pinene shown in Fig. 2. The stronger bimetallic superbase is able to react with the H^a site (Fig. 2), promoting β-elimination according to the *syn*-periplanar fashion, while in the case of the weaker butyllithium, α-metalation successfully competes, and therefore only path *c* can take place.

Table 2 Effect of the base on the isomerisation of β-pinene oxide[a] (see Scheme 3)

Entry	Base (equiv.)	**8** : **9** : **10** Proportions[b]	Reaction time (reaction temp. *T*/°C)	Yield (%)[c]
1	BuLi (2.5)	40 : 60 : 0	1 h (−95) ⟶ 1 h (25)	30
2	LDA (2.5)	0 : 0 : 100	2 h (25)	70
3	LIDA–KOR (2.5)	0 : 0: 100	30 min (−95)	99

[a] Substrate: 2.0 mmol; solvent: THF. [b] On the basis of separated products by column chromatography. [c] Isolated and purified products.

Table 3 Effect of the base on the isomerisation of 3-carene oxide[a] (see Scheme 4)

Entry	Base (equiv.)	**11** : **12** Ratio[b]	Reaction time (reaction temp. *T*/°C)	Yield (%)[c]
1	BuLi (2.5)	50 : 50	1 h (−95) ⟶ 1 h (25)	70
2	LDA	70 : 30	1 h (−95) ⟶ 1 h (25)	75
3	LIC–KOR	94 : 6	30 min (−95)	75
4	LIDA–KOR (2.5)	>99 : <1	30 min (−95)	80

[a] Substrate: 2.0 mmol; solvent: THF. [b] On the basis of separated products by column chromatography. [c] Isolated and purified products.

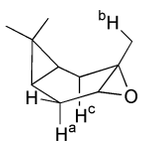


Fig. 3 3-Carene oxide.

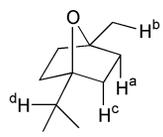
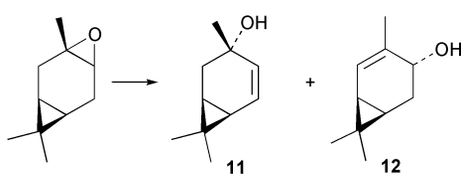


Fig. 4 1,4-Cineole.

3-Carene oxide‡

The influence of the base has been examined by considering the isomerisation shown in Scheme 4, and the results are reported



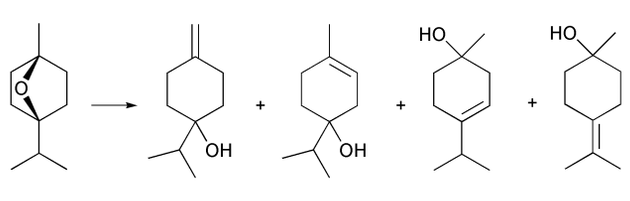
Scheme 4 Base-promoted isomerisation of 3-carene oxide.

in Table 3. Three metalation sites of comparable acidity are present in 3-carene oxide, *i.e.* H^a, H^b and H^c (Fig. 3). In spite of this, upon treatment with LIDA–KOR reagent 3-carene oxide selectively (and partly also with LIC-KOR) affords compound **11**,§ while butyllithium alone gives a mixture of the isomeric allylic alcohols **11** and **12**¶ (compare entry 1 with entry 2 in Table 3). The rationalisation of this result can be tentatively understood after considering that the H^a, H^b, and H^c sites enjoy the correct arrangement that allows *syn*-periplanar elimination. However, what is more, only H^a and H^c sites are constrained with the right *syn*-periplanar arrangement (Fig. 3). This fact could favour metalation at these positions, which furthermore leads to endocyclic alkenes by β-elimination reaction. The encumbering bimetallic reagent selects the H^a target that does not suffer the hindrance of the methyl substituent at the α position of the oxirane ring. By contrast, the less encumbering butyllithium, and partly also LDA, afford, in addition, the isomer **12**.

We then extended the study to 1,4-cineole and 1,8-cineole in order to control the feasibility of base-promoted isomerisation without resorting to the assistance of ring strain that provides sufficient driving force to overcome the reluctance of the ether oxygen to act as a nucleofugal leaving group in β-elimination reactions. In these compounds the basic reagent induces an eliminative ring opening in five- and six-membered rings that does not benefit from relief of ring strain. Notwithstanding this, we have considered that it is well known that alkylamides are endowed with an exceptionally high 'kinetic basicity' (velocity of proton abstraction).[10] What is more, working with a lithium–potassium mixed base, the potassium metal would confer high basicity to its anionic counterpart, thereby facilitating deprotonation, while the lithium metal, through its electrophilic properties, could efficaciously promote ring opening by interaction with the oxygen atom. We have indeed found a noticeable difference between the reactivity of butyllithium and that of bimetallic reagents, and the results obtained are gathered in the Schemes and Tables.

1,4-Cineole

Four metalation targets of comparable acidity are present in 1,4-cineole, *i.e.* H^a, H^b, H^c, and H^d (Fig. 4). The deprotonation reaction of these sites should lead to compounds **14**, **13**, **15**, and **16**, respectively. In spite of this, the elimination product **14** has been selectively recovered in fairly good yield. This result can be tentatively explained by considering the conformation of 1,4-cineole shown in Fig. 4, which points out the constrained right *anti*-periplanar geometry of the H^a and H^c protons. Moreover, the H^a proton is more free with respect to H^c, which suffers the hindrance of the more encumbering isopropyl substituent. Possible products obtainable from 1,4-cineole are presented in Scheme 5. Results of the elimination are given in Table 4.



Scheme 5 Base-promoted isomerisation of 1,4-cineole.

1,8-Cineole

Scheme 6 shows the three products **17**, **18** and **19** (60% overall yield) obtained starting from 1,8-cineole by reaction with 4.0

‡ Irradiation of C(4)H (*δ* 2.70) does not cause an NOE effect at C(1)H or at C(6)H (*δ* 0.38 and 0.42).
§ Irradiation of the C(3)Me group (*δ* 1.19) does not cause an NOE effect at C(1)H or at C(6)H (*δ* 0.95–1.08).
¶ Irradiation of the C(4)H (*δ* 3.67) does not cause an NOE effect on C(1)H or on C(6)H (*δ* 0.92–1.10).

Table 4 Effect of the base on the isomerisation of 1,4-cineole[a] (see Scheme 5)

Entry	Base (equiv.)	**13** : **14** : **15** : **16** Proportions[b]	Reaction time (reaction temp. *T*/°C)	Yield (%)
1	BuLi (2.0)		40 h (25)	0
2	BuLi (2.0)	0 : 100 : 0 : 0	7 d (60)	20[c]
3	LIC–KOR (2.0)	0 : 100 : 0 : 0	40 h (60)	50[c]
4	LIDA–KOR (2.5)	0 : 100 : 0 : 0	15 h (60)	50[c]

[a] Substrate: 2.0 mmol; solvent: hexane. [b] By GC analysis. [c] Isolated and purified products.

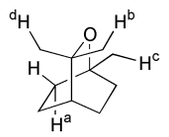
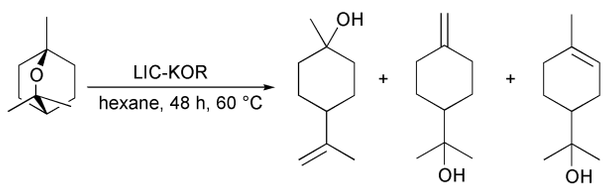


Fig. 5 1,8-cineole.



17 (13%) **18** (15%) **19** (72%)

Scheme 6 Base-promoted isomerisation of 1,8-cineole.

mole equivalents of LIC–KOR superbase. All the other conditions we experimented with [BuLi (4.0 equiv.), 3 days at 60 °C in hexane; $KNSiMe_3$ (4.0 equiv.), 3 days at 60 °C in hexane; LIC–KOR/HMPA (2.5 equiv.), 4 days at 60 °C in hexane; LIC–KOR 60 h at 25 °C in hexane] are ineffective. These results strongly stress the important role of ring strain in oxirane ring opening: only a large excess of the bimetallic superbase LIC–KOR in hexane, at the reflux temperature, effectively metalates the substrate, promoting ring fission by β-elimination reaction. Four sites of deprotonation, that is H^a, H^b, H^c, and H^d, endowed with comparable acidity, are present in 1,8-cineole (Fig. 5). Notwithstanding this isomer **19** is the major one. On the basis of the conformation shown in Fig. 5 we can consider that the H^a proton adopts an axial orientation, giving to the dihedral angle between H^a and the leaving oxygen a value of about 180°. Isomer **19** could also predominate owing to its superior thermodynamic stability.

Conclusions

In summary these base-mediated isomerisations of some terpenoids indicate that interesting structures can be obtained using easily accessible starting materials. Moreover, a few features can be clearly recognised. In particular, butyllithium is unselective and gives poor yields, while, depending on substrate, LIC–KOR, LIDA–KOR or LDA give best results. Moreover, two major conclusions can be drawn. First, even if methylene groups are sterically and electronically more shielded than methyl groups, both compete as centres of deprotonation in β-elimination. The regioselectivity outcome depends on the H–C–C–O dihedral angles (the elimination mode being *syn*-periplanar[5,9]). Second, ring strain, as present in oxiranes, facilitates the elimination reaction but is not a prerequisite. Also, five- and six-membered oxygen-containing rings are opened by strong bases, although under more severe conditions.

Experimental

General

Reactions were performed in flame-dried glassware under an argon atmosphere. The temperature of slush liquid nitrogen–acetone is indicated as −95 °C, and 'room temperature' as 25 °C. THF was distilled from sodium benzophenone ketyl.[11] BuLi (Aldrich) was used as 1.6 M solution in hexanes, *t*-BuOK was sublimed *in vacuo* (0.1 mmHg), and diisopropylamine was distilled from calcium hydride. β-Pinene oxide, 1,4-cineole, 1,8-cineole, and all other commercially available reagents were used as received. α-Pinene oxide and 3-carene oxide were synthesized according to standard procedure.[12] Purification by column chromatography was performed on Merck silica gel 60 as stationary phase and diethyl ether–light petroleum (distillation range 40–60 °C) as eluent. ^1H and ^{13}C NMR spectra were recorded at 400 and 100.4 MHz, respectively and were recorded out at the Dipartimento IFM (Università di Torino). Coupling constants (*J*) are given in Hz. Mass spectra were obtained on a mass-selective detector HP 5970 B instrument operating at an ionising voltage of 70 eV connected to an HP 5890 GC, cross-linked methyl silicone capillary column (25 m × 0.2 mm × 0.33 μm film thickness).

Reactions of α-pinene oxide, β-pinene oxide, and 3-carene oxide with organometallic basic reagents. General procedures

Method A. BuLi (2.5 ml, 4.0 mmol) was added dropwise with stirring to a solution of the selected substrate (0.30 g, 2.0 mmol) in anhydrous THF (5.0 ml). The solution was stirred at −95 °C for 1.5 h, and whenever no reaction was observed at this temperature the cooling bath was removed and the reaction mixture allowed to reach 25 °C. After the time indicated in Tables 1–3, the reaction was quenched with an aqueous solution of THF (5.0 ml). The two phases were separated, the aqueous one was extracted with diethyl ether (3 × 10 ml), and the collected organic phases were washed with brine (2 × 10 ml) and dried (Na_2SO_4). After evaporation of the solvent the crude residue was purified by column chromatography.

Method B (LDA). Diisopropylamine (0.40 g, 4.0 mmol) and BuLi (2.5 ml, 4.0 mmol) were added at 0 °C to anhydrous THF (5.0 ml). After 10 min the mixture was cooled to −95 °C, and then the reaction proceeds in accordance with the procedure above described.

Method C (LIC–KOR). Sublimed *t*-BuOK (0.45 g, 4.0 mmol), substrate (0.30 g, 2.0 mmol), and BuLi (2.5 ml, 4.0 mmol) were consecutively added to cooled (−95 °C) anhydrous THF (5.0 ml). Afterwards the reaction and the work-up conditions were the same as described in Method A.

Method D (LIDA–KOR; LITMP–KOR). At 0 °C, diisopropylamine (0.40 g, 4.0 mmol) (or 2,2,6,6-tetramethylpiperidine, 0.56 g, 4.0 mmol) and sublimed *t*-BuOK (0.45 g, 4.0 mmol) were consecutively added to a solution of BuLi (2.5 ml, 4.0 mmol) in dry THF (5.0 ml). After 15 min of vigorous stirring the temperature was decreased to −95 °C, and the substrate (0.30 g, 2.0 mmol) was added; the method proceeds then according to that specified in Method A.

***trans*-Pinocarveol 6.**[13] Purification by column chromatography (90 : 10, light petroleum–diethyl ether). Colourless oil, δ_H ($CDCl_3$) 0.65 (s, 3 H), 1.24 (s, 3 H), 1.69 (br s, 1 H), 1.71 (d, *J* 9.8, 1 H), 1.81 (dd, *J* 14.6, 4.3, 1 H), 2.00 (ddd, *J* 12.6, 5.8, 2.3, 1 H), 2.25 (ddt, *J* 14.7, 7.6, 2.3, 1 H), 2.38 (dtd, *J* 12.6, 5.5, 2.3, 1 H), 2.50 (t, *J* 5.5, 1 H), 4.40 (d, *J* 7.6, 1 H), 4.81 (s, 1 H),

5.00 (s, 1 H); δ_C ($CDCl_3$) 22.0, 25.8, 27.5, 34.5, 39.9, 40.5, 50.6, 66.9, 111.5, 156.0; *m/z* (EI, 70 eV, rel. int.) 134 ($M^+ - H_2O$, 2%), 55 (83), 43 (46), 41 (100), 39 (70).

***trans*-Pin-3-en-2-ol 7.**[14] Purification by column chromatography (90 : 10, light petroleum–diethyl ether). Colourless oil, δ_H ($CDCl_3$) 0.85 (s, 3 H), 1.27 (s, 3 H), 1.32 (s, 3 H), 1.45 (d, *J* 9.9, 1 H), 2.00 (m, 1 H), 2.17 (m, 1 H), 2.35 (m, 1 H), 2.40 (br s, 1 H), 5.46 (dd, *J* 8.8, 1.2, 1 H), 6.22 (dd, *J* 8.8, 6.4, 1 H); δ_C ($CDCl_3$) 24.2, 25.9, 27.5, 33.4, 42.7, 47.0, 54.0, 74.3, 129.9, 138.1; *m/z* (EI, 70 eV, rel. int.) 137 (M^+ − Me, 5%), 67 (86), 43 (98), 41 (100), 39 (73).

6,6-Dimethyl-2-pentylidenebicyclo[3.1.1]heptane 8. Purification by column chromatography (light petroleum). Colourless oil, ν_{max} (film)/cm^{-1} 2990, 1663; δ_H ($CDCl_3$) 0.71 (s, 3 H), 0.89 (t, *J* 8.2, 3 H), 1.28 (s, 3 H), 1.25–1.38 (m, 6 H), 1.47 (d, *J* 9.7, 1 H), 1.75–2.10 (m, 4 H), 2.25–2.38 (m, 2 H), 2.79 (t, *J* 5.5, 1 H), 5.13 (td, *J* 5.5, 1.8, 1 H); δ_C ($CDCl_3$) 14.1, 21.8, 22.4, 24.0, 24.1, 25.0, 26.1, 26.3, 32.7, 41.0, 45.1, 52.6, 121.7, 140.8; *m/z* (EI, 70 eV, rel. int.) 192 (M^+, 1%), 93 (41), 79 (27), 69 (50), 41 (100).

6,6-Dimethyl-2-pentylbicyclo[3.1.1]hept-2-ene 9. Purification by column chromatography (light petroleum). Colourless oil, ν_{max} (film)/cm^{-1} 2995, 1660: δ_H ($CDCl_3$) 0.71 (s, 3 H), 0.89 (t, *J* 8.2, 3 H), 1.21 (s, 3 H), 1.20–1.35 (m, 6 H), 1.65–2.05 (m, 4 H), 2.10 (dd, *J* 16.5, 8.4, 2 H), 2.32 (m, 1 H), 2.56 (dtt, *J* 16.5, 8.2, 2.2, 1 H), 4.94 (tt, *J* 5.8, 2.2, 1 H); δ_C ($CDCl_3$) 14.3, 19.8, 21.8, 24.1, 25.9, 26.1, 26.1, 26.2, 28.0, 32.5, 40.9, 45.1, 121.8, 141.7; *m/z* (EI, 70 eV, rel. int.) 192 (M^+, 1%), 93 (43), 69 (50), 41 (100), 39 (37).

Myrtenol 10.[15] Purification by column chromatography (90 : 10, light petroleum–diethyl ether). Colourless oil, ν_{max} (film)/cm^{-1} 3345, 2960; δ_H ($CDCl_3$) 0.81 (s, 3 H), 1.15 (d, *J* 9.2, 1 H), 1.19–1.25 (m, 1 H), 1.26 (s, 3 H), 2.10 (qm, *J* 5.3, 2 H), 2.21 (dm, *J* 15.2 1 H), 2.29 (br d, *J* 15.2, 1 H), 2.38 (dt, *J* 9.2, 5.2, 1 H), 3.95 (s, 2 H), 5.45 (br s, 1 H); δ_C ($CDCl_3$) 21.2, 26.2, 31.2, 31.7, 38.0, 41.0, 43.4, 65.9, 117.8, 147.9; *m/z* (EI, 70 eV, rel. int.) 152 (M^+, 5%), 108 (26), 91 (47), 79 (100), 67 (18).

(+)-Car-4-en-3-ol 11.[16] Purification by column chromatography (70 : 30, light petroleum–diethyl ether). Colourless oil, ν_{max} (film)/cm^{-1} 3384, 1639; δ_H ($CDCl_3$) 0.85 (s, 3 H), 0.95–1.08 (m, 2 H), 1.10 (s, 3 H), 1.19 (s, 3 H), 1.40 (dd, *J* 15.2, 5.1, 1 H), 1.88 (br s, 1 H), 2.06 (ddd, *J* 15.2, 9.2, 0.7, 1 H), 5.76 (ddd, *J* 9.7, 2.4, 0.7 1 H), 5.80 (br d, *J* 9.7, 1 H); δ_C ($CDCl_3$) 14.8, 18.3, 22.5, 23.5, 27.7, 28.9, 34.5, 65.7, 128.9, 136.5; *m/z* (EI, 70 eV, rel. int.) 137 (M^+ − Me, 10%), 119 (73), 109 (61), 91 (64), 43 (100).

(+)-*cis*-2-Caren-4-ol 12.[17] Purification by chromatography (70 : 30, light petroleum–diethyl ether). δ_H ($CDCl_3$) 0.80 (s, 3 H), 0.92–1.10 (m, 2 H), 1.01 (s, 3 H), 1.06 (s, 3 H), 1.77–1.94 (m, 2 H), 3.33 (br s, 1 H), 3.67 (br s, 1 H), 5.53 (br s, 1 H); δ_C ($CDCl_3$) 15.0, 18.5, 20.2, 22.6, 22.8, 27.1, 27.6, 64.2, 121.7, 136.8; *m/z* (EI, 70 eV, rel. int.) 152 (M^+, 2%), 109 (100), 43 (58), 41 (45), 39 (39).

Reaction of 1,4-cineole and 1,8-cineole with organometallic basic reagents. General procedure

BuLi (2.5 ml, 4.0 mmol) was added dropwise to a cooled (−95 °C) and stirred solution of sublimed *t*-BuOK (0.45 g, 4.0 mmol) and of substrate (0.31 g, 2.0 mmol) in dry hexane (5.0 ml). The solution was heated to 60 °C, and after the time reported in Table 4 and in the text and the reaction was quenched with water (1.5 ml). The two phases were separated and the aqueous one was extracted with Et_2O (3 × 10 ml). The collected organic phases were washed with brine (2 × 10 ml), dried (Na_2SO_4), and concentrated to give the crude reaction product.

4-Terpineol 14.[18] Purification by column chromatography (60 : 40, light petroleum–diethyl ether). Colourless oil, ν_{max} (film)/cm^{-1} 3421, 1377, 1070; δ_H ($CDCl_3$) 0.86 (d, *J* 6.9, 3 H), 0.92 (d, *J* 6.9, 3 H), 1.52–1.60 (m, 2 H), 1.61–1.68 (m, 5 H), 1.85–1.94 (m, 2 H), 2.10–2.16 (m, 2 H), 5.28 (br d, *J* 2.7, 1 H); δ_C ($CDCl_3$) 16.8, 16.9, 23.3, 27.1, 30.9, 34.5, 36.8, 71.8, 118.5, 133.7; *m/z* (EI, 70 eV, rel. int.) 154 (M^+, 1%), 71 (99), 55 (37), 43 (100), 41 (75).

α-Terpineol 19.[19] Purification by column chromatography (50 : 50, light petroleum–diethyl ether). Colourless oil, δ_H ($CDCl_3$) 1.08 (d, *J* 6.5, 6 H), 1.30–1.50 (m, 2 H), 1.60 (br s, 3 H), 1.65–1.95 (m, 2 H), 1.90–2.10 (m, 3 H), 2.27 (s, 1 H), 5.36 (br s, 1 H); δ_C ($CDCl_3$) 22.7, 24.0, 25.9, 26.8, 27.0, 31.6, 45.1, 71.0, 121.0, 133.3; *m/z* (EI, 70 eV, rel. int.) 136 ($M^+ - H_2O$, 30%), 121 (38), 93 (52), 59 (100), 43 (48).

Acknowledgements

This work was supported by grants from Italian MURST and CNR. We thank Professor Manfred Schlosser for useful suggestions.

References and notes

1 A. S. Rao, S. K. Paknikar and J. C. Kirtane, *Tetrahedron*, 1983, **39**, 2323.
2 J. K. Crandall and M. Apparu, *Org. React. (N.Y.)*, 1983, **29**, 345.
3 L. H. Haynes, I. Heilbron, E. H. R. Jones and F. Sondheimer, *J. Chem. Soc.*, 1947, 1583.
4 M. Lautens, E. Fillion and M. Sampat, *J. Org. Chem.*, 1997, **62**, 7080; D. M. Hodgson and I. D. Cameron, *Org. Lett.*, 2001, **3**, 441; D. M. Hodgson and S. L. M. Norsikian, *Org. Lett.*, 2001, **3**, 461.
5 A. Mordini, E. Ben Rayana, C. Margot and M. Schlosser, *Tetrahedron*, 1990, **46**, 2401; P. Saravanan, A. DattaGupta, D. Bhuniya and V. K. Singh, *Tetrahedron*, 1997, **53**, 1855; P. O'Brien and J. J. Tournayre, *Tetrahedron*, 1997, **53**, 17527; A. Mordini, S. Bindi, A. Capperucci, D. Nistri, G. Reginato and M. Valacchi, *J. Org. Chem.*, 2001, **66**, 3201 and references therein.
6 J. K. Crandall and L. H. Chang, *J. Org. Chem.*, 1967, **32**, 435; J. K. Crandall and L. C. Crawley, *Org. Synth.*, 1988, **Coll Vol. 6**, p. 948.
7 M. Schlosser, *J. Organomet. Chem.*, 1967, **8**, 9; M. Schlosser, F. Faigl, L. Franzini, H. Geneste, G. Katsoulos and G. Zhong, *Pure Appl. Chem.*, 1994, **66**, 1439; A. Mordini, in *Comprehensive Organometallic Chemistry II*, ed. E. W. Abel, F. G. A. Stone and G. Wilkinson (vol. ed. A. McKillop), Pergamon Press, Oxford, 1995, vol. 11, p. 93; L. Lochmann, *Eur. J. Inorg. Chem.*, 2000, 1115.
8 F. Cominetti, A. Deagostino, C. Prandi and P. Venturello, *Tetrahedron*, 1998, **54**, 14603.
9 R. P. Thummel and B. Rickborn, *J. Am. Chem. Soc.*, 1970, **92**, 2064; G. A. Molander and K. Mautner, *J. Org. Chem.*, 1989, **54**, 4042.
10 Huisgen and Sauer were the first to report that phenyllithium converts piperidine instantaneously and quantitatively into lithium piperidide. Despite its weaker thermodynamic basicity, the latter reagent brings about the dehydrohalogenation of bromobenzene almost 100 times faster than its organometallic precursor, see R. Huisgen and J. Sauer, *Angew. Chem.*, 1960, **72**, 91; R. Huisgen and J. Sauer, *Chem. Ber.*, 1959, **92**, 192.
11 W. Schlenk and E. Bergann, *Justus Liebigs Ann. Chem.*, 1928, **464**, 22.
12 H. Hubbert and P. Burt, *Org. Synth.*, 1921, **Coll. Vol. 1**, 494.
13 J. K. Crandall and L. C. Crawley, *Org. Synth.*, 1973, **53**, 17; J. M. Coxon and E. Dansted, *Org. Synth.*, 1976, **56**, 25.
14 M. K. Lajunen, T. Maunula and A. M. P. Koskinen, *Tetrahedron*, 2000, **56**, 8167.
15 H. Heikman, P. Baeckström and K. Torssell, *Acta Chem. Scand.*, 1968, **22**, 2034; C. Filliatre, J.-J. Villenav and J. Prévot, *Bull. Soc. Chim. Fr.*, 1979, **II**, 473.
16 M. H. Shastri, D. G. Patil, V. D. Patil and Sukh Dev, *Tetrahedron*, 1985, **41**, 3083; G. Rücker and K. Frey, *Liebigs Ann. Chem.*, 1987, 389.
17 T. Satoh, T. Okuda, Y. Kaneko and K. Yamakawa, *Chem. Pharm. Bull.*, 1984, **32**, 1401.
18 K. N. Gurudutt, M. A. Pasha, B. Ravindranath and P. Srinivass, *Tetrahedron*, 1984, **40**, 1629; F. Delay and G. Ohloff, *Helv. Chim. Acta*, 1979, **62**, 2168.
19 N. Bluthe, J. Ecoto, M. Fetizon and S. Lazare, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1747; M. Bertrand, B. Waegell and J. P. Zahra, *Bull. Soc. Chim. Fr.*, 1991, **128**, 904.