

Connective (C–C) Route to Hindered Epoxides and Olefins from Hindered Ketones

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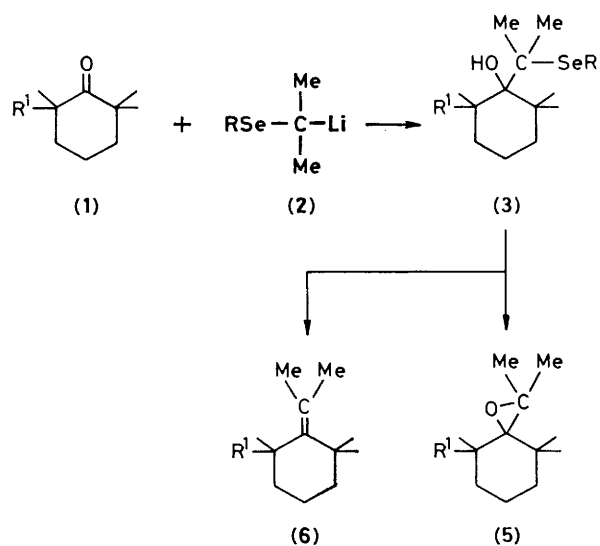
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Hindered ketones have been transformed into hindered epoxides (**5**) and olefins (**6**) with the concomitant formation of new carbon–carbon bonds using β -hydroxyselenides as key intermediates; the unusual reactivity of such crowded molecules is reported.

The regioselective synthesis of olefins and epoxides from hindered carbonyl compounds is a problem often encountered during the synthesis of natural products for which a general solution has not yet been found.¹ *E.g.*, sulphur² and phosphorus ylides,^{1b,3} even those derived from methylene groups, do not produce the corresponding epoxides and olefins from hindered carbonyl compounds such as 2,2,6,6-tetramethyl- and 2,2,6-trimethyl-cyclohexanones under normal conditions.^{4†}

The discovery that epoxides and olefins can be formed in high yield from β -hydroxyselenides⁶ (readily prepared from α -selenoalkyl-lithium and carbonyl compounds) led us to investigate these reactions with the hindered carbonyl compound (**1**) as a model (Scheme 1).

We found that 2-lithio-2-selenopropanes⁷ (**2**) (R = Me or Ph), readily available from 2,2-bis-selenopropanes and



Scheme 1

† Other α -heterosubstituted organometallic compounds bearing a non-charged heteroatom such as α -thioalkyl-lithiums and α -trimethylsilylalkyl-lithiums⁶ have been successfully used for epoxide^{2b,6a} and olefin^{1b,5b-c} synthesis from hindered carbonyl compounds.

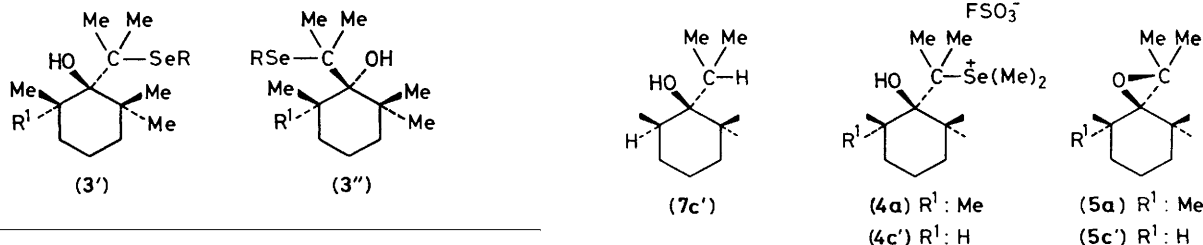


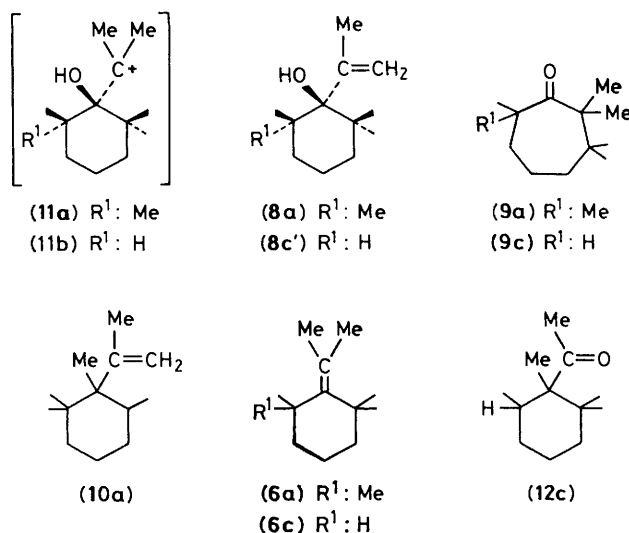
Table 1

	R	R ¹	Conditions	Yield as (3), % (3':3'')
(3a)	Me	Me	THF, -45 °C, 3h	77
			Ether, -78 °C, 4h	83
(3b)	Ph	Me	THF, -78 °C, 3h	00
			Ether, -78 °C, 4h	60
(3c)	Me	H	THF, -45 °C, 4h	48 (33:67)
			Ether, -78 °C, 1h	85 (95:5)
(3d)	Ph	H	THF, -78 °C, 1h	00
			Ether, -78 °C, 0.5h	84 (95:5)

butyl-lithium,[‡] exhibit an unusual nucleophilicity towards the hindered carbonyl compound (1). The methyl-seleno derivative was found to be the best reagent § producing the corresponding β -hydroxymethylselenide (3) (R = Me) in good yield (*ca.* 80%) if the reaction is conducted in ether-pentane (1:1) instead of tetrahydrofuran (THF)-hexane as reported previously⁵ (Table 1). The right choice of solvent was found to be even more important[‡] for phenyl-selenoalkyl-lithiums for which no reaction was detected in THF-hexane whereas modest to good yields were obtained in ether-pentane.

Equatorial attack leading to (3') predominates in the case of trimethylcyclohexanone. However the ratio of the two stereoisomers differs with the solvent used (Table 1). We have purified the two stereoisomers (3') and (3'') by preparative layer chromatography (SiO₂, Merck, pentane-ether, 95:5, *R_F* 0.6 and 0.55 respectively) and we have correlated the stereoisomers (3') of different origins (R = Me, Ph) by reducing their selenyl moieties with tributyltin hydride in the presence of 10% azobisisobutyronitrile⁸ [80 °C, 0.2 h, quantitative yield as (7)]. The stereochemistry of the isomer (3c') has been unambiguously ascertained by an X-ray crystallographic study on a related derivative.[¶]

The methods we have reported for the synthesis of epoxides and olefins from β -hydroxyselenides were found unsuitable for the synthesis of compounds (5) and (6) from the hindered methylseleno-derivatives (3a) and (3c'). Thus the β -hydroxyselenonium salts (4a) and (4c') needed for the synthesis of epoxides are not produced on reaction with MeI^{7b} but require the more electrophilic methyl fluorosulphonate (1 equiv., ether, -78 °C, 0.5 h, then -78 °C to 0 °C, 1 h). These salts are particularly unstable when liberated from ether and rearrange immediately in Me₂SO or CH₂Cl₂ (the solvents used for further transformation to epoxide).^{7b} Thus (4a) leads to an 80:20 mixture of the allyl alcohol (8a) and the ring-enlarged ketone (9a) in Me₂SO (20 °C, 0.9 h) and a 66:34 mixture of the same ketone (9a) and the diene (10a) in CH₂Cl₂ (20 °C, 0.3 h). Under the latter conditions, the β -hydroxyselenonium salt



(4c') only produces the ketone (9c), by exclusive migration of the dimethyl-substituted carbon atom.

Compounds (8), (9), and (10) can be formed by the loss of dimethyl selenide from (4) which reduces the strain present and leads to a particularly well stabilized carbenium ion (11); this should produce (8) by loss of a proton and (9) by migration of one side of the six-membered ring (related to the Demjanov or pinacol rearrangements).⁹ These reactions produce fluorosulphonic acid which can account for the formation of the diene **(10a)** by protonation of the hydroxy-moiety of either (4a) or (8a).

In agreement with these proposals we found that the allyl alcohol (8a), prepared¹¹ from the β -hydroxyselenide (3a) [Bu^tO₂H (4 equiv.), basic alumina (8 equiv.), THF, 55 °C, 3 h, 95% yield] rearranges to the diene (10a) on reaction with catalytic amounts of fluorosulphonic acid (CH₂Cl₂, -40 °C, 0.2 h, 85% yield). The less hindered allyl alcohol (8c') [from (3c), Bu^tO₂H, basic alumina, tetrahydrofuran, 55 °C, 3 h, 86% yield] is recovered unchanged after the same treatment.

The synthesis of the desired epoxides (5a) and (5c') was finally achieved in high yield (95%) by the reaction of the corresponding selenonium salts (4a) and (4c') suspended in ether with a 10% aqueous solution of KOH (0 °C, 1 h). We found that they behave differently in acid media. The epoxide (5a) derived from tetramethylcyclohexanone exclusively produces the ring-enlarged ketone (9a) on reaction with BF₃·OEt₂ [CH₂Cl₂ (0.5 equiv.), -78 °C, 0.1 h; 0 °C, 0.3 h, 95%]; the epoxide (5c') under similar conditions leads to the rearranged (12c) and the ring-enlarged (9c) ketones [(12c): (9c), 90:10] in 62% overall yield.

[‡] These reactions have been performed at -78 °C for 0.5 h with BuⁿLi in THF-hexane or with Bu^tLi in ether-pentane.

[§] These findings seem to be general. For example, 1-selenoethyl-lithium and selenomethyl-lithium behave similarly with these two ketones.

[¶] Details will be reported in the full paper.

** A closely related rearrangement has been described by Trost¹⁰ for a β -hydroxycyclopropyl sulphide derived from tetramethylcyclohexanone.

The synthesis of the olefins (**6a**) and (**6c**) was the last objective and from the results just described a rearrangement of the type (**3a**) → (**10a**) should occur when the hydroxy-group of (**3**) is transformed into a better leaving group, and the hindered carbon-carbon double bond in the expected olefins (**6c**) could migrate readily.

Our previously described method¹² (SOCl₂, NEt₃, CH₂Cl₂, 20 °C, 4 h) applied to (**3**) leads to a moderate yield (63%) of the required olefin (**6**). This is not formed if POCl₃¹³ is used instead of SOCl₂. We discovered however that PI₃ (1 equiv., CH₂Cl₂, NEt₃, 20 °C, 0.5 h) reacts instantaneously and allows the synthesis of (**6a**) (95%) and (**6c**) (84%) in very high yield.

The reactions described here show how versatile the β-hydroxyselenides are for the selective syntheses of various selenium-free molecules.

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