Transformation of the Geraniol Skeleton into the Fragranol and Grandisol Skeletons

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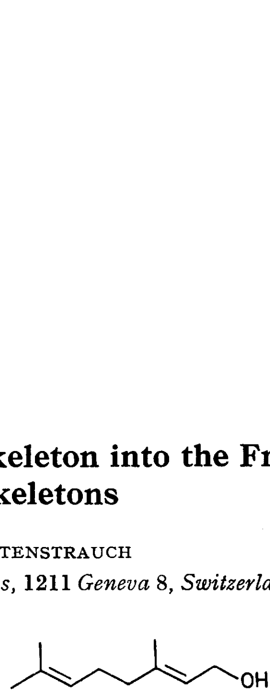
Summary Racemic 6,7-epoxygeranyl t-butyl sulphide (**2**) was lithiated [butyl-lithium–1,2-bis(dimethylamino)-ethane] at C(1) to give the (1*E*)-epoxyallyl-lithium (**10**) which cyclised to give the alcoholates of the (racemic) cyclobutyl carbinols (**4**) and (**5**) (fragranol and grandisol skeletons) and of a single (racemic) cyclopentanol, (**6**) or (**7**).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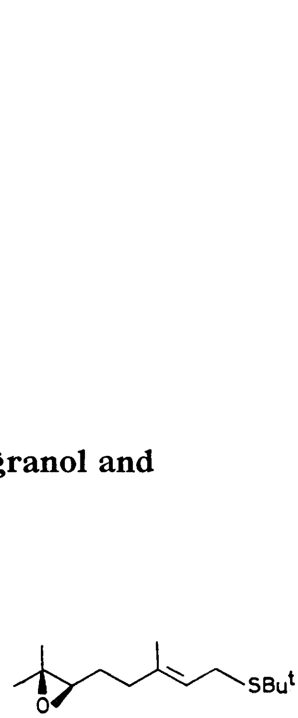

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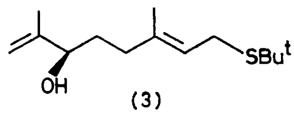

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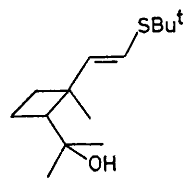

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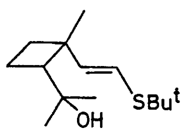

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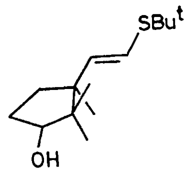

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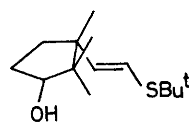

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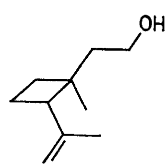

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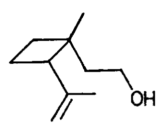


(9)

Extreme cyclisations which involve displacement (exo- and endo-cyclic displacements) are of current interest.[1,2] I report cyclisations of a geraniol (**1**) derivative to give racemic fragranol (**8**)† and grandisol (**9**)† derivatives,[3] *via* displacement of an epoxide O-atom by a stabilized allyl anion generated by abstraction of a proton. This principle, previously used by Itô[4] to cyclise farnesol (→ 10-membered ring) and geranylgeraniol (→14-membered ring) derivatives, is a useful anionic counterpart of the 'corresponding'‡ biological and biomimetic cyclisations. Stork's[5] epoxy-nitrile cyclisations are related.[6]

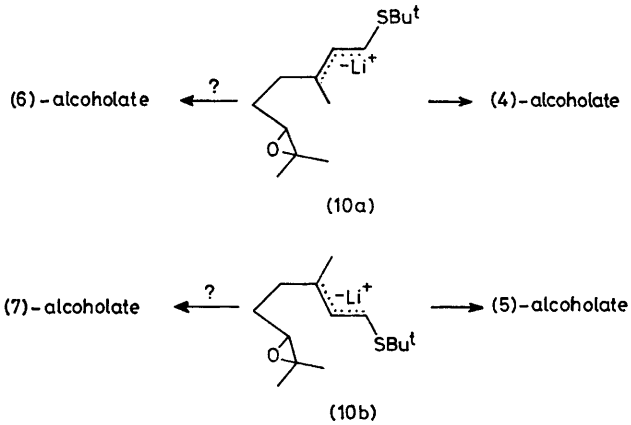
Geranyl and neryl chloride, as a mixture, were transformed into the corresponding t-butyl sulphides which were epoxidized at the C(6)–C(7) double bond[7] and racemic 6,7-epoxygeranyl t-butyl sulphide (**2**)† was isolated by g.l.c. The sulphide (**2**) was added at once to excess of butyl-lithium–1,2-bis(dimethylamino)ethane (5 equiv. of each) in tetrahydrofuran (THF)–hexane [*ca.* −75 °C, 0·08—0·09 M initial concentration of (**2**) in THF–hexane (*ca.* 2·4 : 1 v/v)] and the resulting yellow solution was kept at *ca.* −75 °C for 3 h and then at *ca.* 5 °C for 2 h. Hydrolysis, work up, and distillation afforded a mixture (g.l.c.) of two (racemic) cyclobutyl carbinols, (**4**)† (*ca.* 43%, fragranol skeleton) and

† One enantiomer is depicted, which, in the case of (**9**), is (+)-grandisol.

‡ Cyclisation *via* addition of a cation, generated by opening of an epoxide, to a double bond.

(**5**)† (*ca.* 29%, grandisol skeleton), a single (racemic) cyclopentanol, (**6**)† or (**7**)† [*ca.* 25%, <*ca.* 1% of the isomer, (**7**) or (**6**), present], and the (racemic) open-chain alcohol (**3**)† (*ca.* 3%), in *ca.* 64% combined yield.

At *ca.* −75 to *ca.* −25 °C under otherwise the same conditions, (**2**) was deprotonated at C(1) (*ca.* 75% conversion within 10 min at *ca.* −25 °C) and the cyclisations of the resulting anion were slow, quenching with D_2O giving [1-^{2}H]-(**2**). The geometry (1*E*)[2] of the anion (**10**)† (Scheme),



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follows from that of the derived cycles. Apart from the stereochemistry with respect to the rings, structures (**4**), (**5**), and (**6**) or (**7**) [and (**8**)] were deduced from the spectra [^{1}H n.m.r. spectrum ($CDCl_3$) of (**4**): δ 1·09, 1·20, 1·38 (s, 3H each), 1·33 (s, 9H), 1·5—2·4 (m, 6H), and 6·04 (AB, δ_{AB} 0·06 p.p.m., *J* 15 Hz); (**5**): δ 1·04, 1·19, 1·29 (s, 3H each), 1·36 (s, 9H), 1·5—2·4 (m, 6H), and 6·28 (AB, δ_{AB} 0·27 p.p.m., *J* 16 Hz); (**6**) or (**7**): δ 0·84, 0·87, 1·07 (s, 3H each), 1·34 (s, 9H), 1·4—2·4 (m, 5H), 3·8—4·0 (br. m, 1H), and 5·98 (AB, δ_{AB} very small]. That (**4**) is *trans*- and (**5**) is *cis*-substituted at the ring (as drawn) was shown by ^{1}H n.m.r. spectrometry using $Eu(fod)_3$ complexation. The analogous distinction between (**6**) or (**7**) has not yet been made.

I interpret the results as follows (see Scheme). In the epoxyallyl-lithium (**10**), intramolecular displacement of the epoxide O-atom at C(6) or C(7), by the distal C(1) (to give a *trans*-cyclohexene and -cycloheptene, respectively) is not geometrically feasable, but such displacement is feasible by the proximate C(3), and is more favourable than an intermolecular displacement. Exocyclic displacement[1,2] by C(3) at C(6) within folded conformers of type (**10a**)† and (**10b**)† gives the lithium alcoholates of (**4**) and (**5**), respectively, and endocyclic displacement[1,2] by C(3) at C(7) within these types of conformers would give the lithium alcoholates of (**6**) and (**7**), respectively. Molecular models show that the displacement leading to (**7**), although sterically quite hindered, is sterically more favourable, and structure (**7**) is therefore more likely.

The sulphide function stabilizes the allyl-lithium (**10**) and facilitates its selective formation from (**2**) and butyllithium; attack at C(8) to give the alcoholate of (**3**) is minimal. The t-butyl group was introduced to protect the sulphur atom during epoxidation. Synthetically, these particular choices lead to an impasse since the cyclisations are neither regio- nor stereo-selective and since the t-butylthio function in (**4**) and (**5**) turns out to block liberation of the latent aldehyde functions, but they provide a well characterized model for further, systematic studies, which are under way.

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