Stereoselective One-step Syntheses of *trans*-β-Ocimene and α-Farnesene

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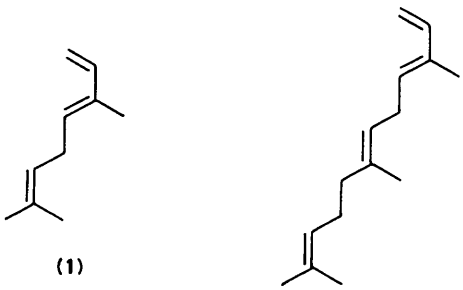
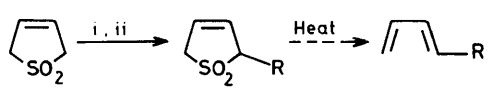
Protected forms of *trans*-β-ocimene and α-farnesene were synthesized in one step by direct deprotonation of 2,5-dihydro-3-methylthiophene-1,1-dioxide (**6**) followed by alkylation with suitable allylic bromides; this approach provides a regioselective and stereoselective introduction of an isoprene unit onto a pre-existing skeleton.

The monoterpene *trans*-β-ocimene (**1**) and the sesquiterpene α-farnesene (**2**) occur in many essential oils. The structures of these two natural products contain terminal 1-connected isoprene units. Two of the problems that need to be solved for their synthesis are the formation of the acid-sensitive terminal conjugated double bonds and the stereoselective introduction of the *trans* configuration in the C(3)–C(4) double bonds. We now describe an attractive one-step synthesis of the acid-stable protected forms of (**1**) and (**2**), the easy deprotections of which lead stereoselectively to the desired C(3)–C(4) *trans* configurations.

We have been interested in the direct deprotonation and alkylation of the 3-sulpholene (**3**) in the preparation of substituted 3-sulpholenes (**4**) (Scheme 1). It was discovered that under the right reaction conditions (**4**) could be prepared without the problem of ring-opening.[1] Since 3-sulpholenes are known to undergo cheleotropic thermal extrusion of SO_2[2] in a regioselective manner to yield the corresponding terminal substituted butadienes (**5**), 3-methyl-3-sulpholene (**6**), the key compound in our synthetic route, was expected to be an ideal precursor for the introduction of terminal isoprene. We thus studied the regioselectivity of the deprotonation and alkylation reaction of (**6**) and discovered that the reaction took place exclusively at the 2-position, presumably *via* the intermediate anion (**7**). Although reaction with alkyl iodides proceeded smoothly,[1b] the reaction with alkyl bromides was rather sluggish and dirty. However, allylic bromides proved excellent alkylating reagents in this step. Thus, when 2.5 equiv. of (**6**) reacted with 1 equiv. of allyl bromide in tetrahydrofuran (THF) at 0 °C, (**8a**) was produced in 75% yield (Scheme 2). Following the same sequence and using prenyl bromide or geranyl bromide[3] as alkylating reagents, (**8b**) (75%) and (**8c**) (68%) were produced.† Compounds (**8b**) and (**8c**) are the acid



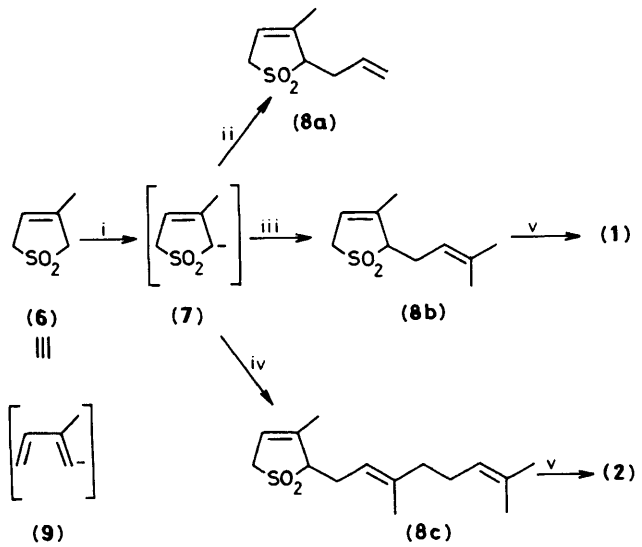
(**1**) (**2**)



(**3**) (**4**) (**5**)

Scheme 1. i, NaH–dimethylformamide or $LiN(SiMe_3)_2$–THF; ii, RI.

† All new compounds gave satisfactory spectroscopic (n.m.r., i.r., and mass) and analytical data.



Scheme 2. i, $LiN(SiMe_3)_2$–THF; ii, allyl bromide; iii, prenyl bromide; iv, geranyl bromide; v, thermolysis.

and air-stable, SO_2-protected forms of *trans*-β-ocimene (**1**) and α-farnesene (**2**), respectively. Indeed, thermolysis of (**8b**) by preparative g.l.c. (on an OV 101 column, injection temperature 240 °C, oven temperature 150 °C) gave a single product for which the n.m.r., i.r., and mass spectral data were identical with those reported earlier[4] for *trans*-β-ocimene. Thermolysis of (**8c**) under the same conditions yielded exclusively α-farnesene which was confirmed as (**2**) by comparison of n.m.r., i.r., and mass spectra with those reported earlier.[5] No attempts were made to deprotect the sulpholenes (**8b**) and (**8c**) by methods other than preparative g.l.c.

In summary, 3-methyl-3-sulpholene (**6**) can be used as an isoprene 1-anion equivalent (**9**) and introduced at the terminal position of a carbon chain. This one-step synthesis is not only regioselective, efficient, and short, but also is favourable because the normally unstable target molecules are prepared directly in their protected forms. The deprotection step is also clean and stereoselective.

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