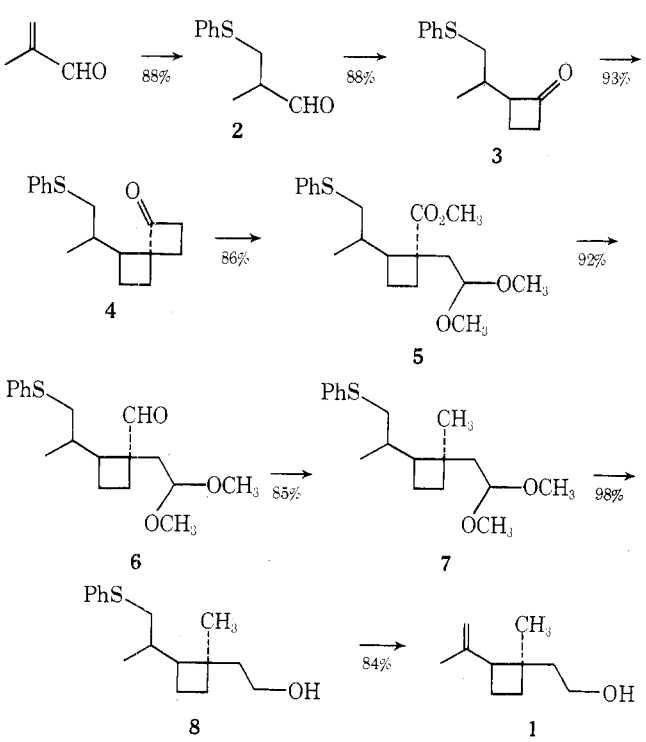
New Synthetic Methods. Secoalkylative Approach to Grandisol

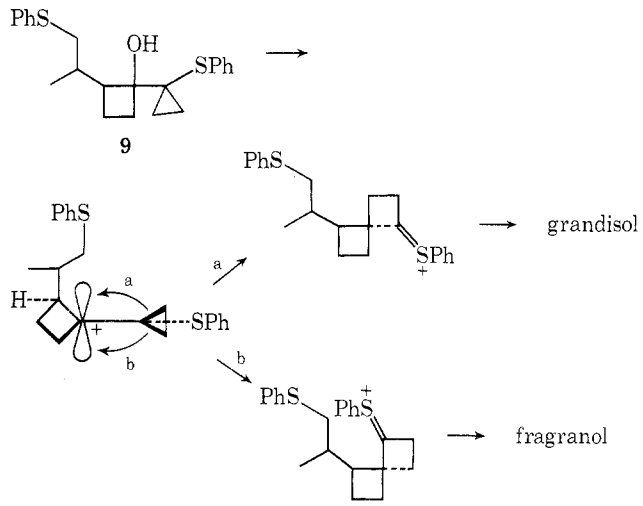
Summary: A stereoselective synthesis of a constituent of the boll weevil sex pheromone using a double cyclobutyl annelation and a new isopropenylation procedure is reported.

Sir: We wish to report a flexible synthesis of racemic grandisol (**1**), one of the four components of the sex attractant released by the male boll weevil.[1,2] This approach illustrates the new cyclobutyl annelation using 1-lithiocyclopropyl phenyl sulfide[3,4] in secoalkylation[5,6] and develops a new way for the introduction of an isopropenyl group based on the sulfoxide elimination.[7]

Scheme I outlines the sequence. Conjugate addition of thiophenol to methacrolein (triethylamine, neat, 0°) gave aldehyde **2**:[8] bp 103° (0.1 mm); ir 1720 cm^{-1}; NMR δ 9.6 (s, 1 H), 1.05 (d, J = 6 Hz, 3 H). Addition of 1-lithiocyclopropyl phenyl sulfide (THF, −78°) followed by acid-catalyzed rearrangement (TsOH, PhH, water, reflux) gave cyclobutanone **3**:[8] bp 109° (0.1 mm); ir 1777 cm^{-1}; NMR, two doublets for diasteromeric methyl group, δ 1.05 (d, J = 6 Hz), 1.15 (d, J = 6 Hz). Repetition of the sequence led to the spiro[3.3]heptan-1-one **4**:[8] bp 115° (0.05 mm); ir 1772 cm^{-1}; NMR, two doublets centered at δ 1.0 (J = 8 Hz, 3 H). Bromination of **4** (pyridinium bromide perbromide, HOAc, 50°), ring cleavage (sodium methoxide, methanol, 25°), and silver ion assisted solvolysis (silver nitrate, methanol, 25°) gave **5**[8] without purification of any intermediates [**5**: ir 1731 cm^{-1}; NMR δ 3.18, 3.22 (6 H), 3.62 (s, 3 H), 4.26 (m, 1 H)]. Reduction of the ester to the alcohol ($LiAlH_4$, THF, reflux) followed by Moffatt oxidation[9] (pyridine–sulfur trioxide, DMSO, triethylamine, 25°) gave the aldehyde **6**[8] [ir 1720 cm^{-1}; NMR δ 9.45 (s, 1 H), 3.19, 3.21 (6 H), 0.95 (d, J = 6 Hz, 3 H), 4.25 (d of d, J = 7 Hz, 1 H)] which, in turn, was subjected to the Wolff–Kishner reduction (hydrazine hydrate, ethylene glycol, KOH, 210°) to produce the methylcyclobutane **7**[8] [NMR δ 0.95 (m, 3 H, 1.16 (s, 3 H), 3.35 (s, 6 H), 4.3 (d of d, J = 6 Hz, 1 H)]. Acetal hydrolysis (1:1 THF–water, HCl) and reduction ($LiAlH_4$, ether, 25°) gave the requisite precursor **8**:[8] ir 3620 cm^{-1}, 3410 cm^{-1}; NMR δ 1.05 (s, 3 H), 1.15 (s, 3 H), 3.6 (m, 2 H). The creation of the isopropenyl substituent involved oxidation of sulfur to the sulfoxide (MCPBA, methylene chloride, −78°) followed by thermolysis (decalin, calcium carbonate, 180°).[7] It is important to note that no isomerization of the double bond occurred—a fact that makes this method a useful one for introduction of an isopropenyl unit. The ir, NMR, and mass spectra of **1** correspond to the published data.[2]

Scheme I
Secoalkylative Approach to Grandisol





The saturated methyl region in the NMR spectrum (δ 1.17 and 0.92) revealed that the product was an 80:20 mixture of grandisol[1] and fragranol.[10] The stereoselectivity is determined in the rearrangement of the cyclopropylcarbinol **9**.[4] Ring expansion of the presumed carbonium ion intermediate by path a involves less steric crowding of the largest groups than the alternative, path b. This route provided grandisol in ~32% overall yield from α-methylacrolein.

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References and Notes

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