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TOTAL SYNTHESIS OF IONONES AND IRONES FROM 2-HYDROXYMETHYL-4-PHENYLTHIO-1-BUTENE

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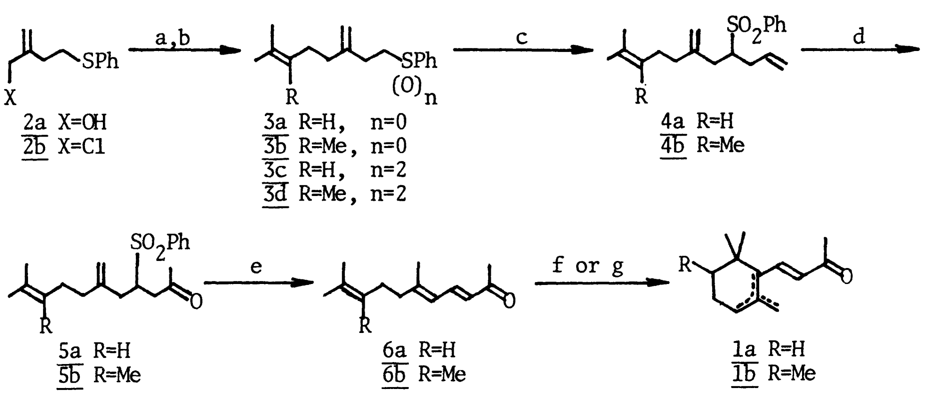
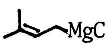
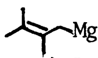
A sequence of allylation, the Wacker reaction, and desulfonylation of homoallyl sulfones provided a new synthetic method for the α,β,γ,δ-unsaturated ketone system often encountered in natural products. This procedure was successfully applied to ionone and irone synthesis.

Ionones (1a) are well known as important fragrant components. The β-isomer, in particular, is one of the most promising intermediates for the synthesis of vitamin A and other carotenoids. Natural irones (1b) consisting of four isomers (α-trans, α-cis, β, and γ-cis), are also important odorous constituents isolated from orris root. A number of synthetic studies on both ionones$^{1)}$ and irones$^{2)}$ has been made so far, many of which involve pseudoionone (6a) and 9-methylpseudoionone (6b) as precursors.

We have recently disclosed$^{3,4)}$ that 2-hydroxymethyl-4-phenylthio-1-butene (2a) can be a versatile building block for several acyclic terpenoids through the utilization of the functionalities involved in 2a. In the course of our studies on this key compound 2, we have found that the homoallyl sulfide moiety is convertible to the α,β,γ,δ-unsaturated ketone system and report here a new approach to 6a and 6b. Our synthetic plan is based on both the carbon elongation at primary allylic site of 2b (step a) and the formation of α,β,γ,δ-unsaturated ketone system by acetonylation of 3c and 3d (step c and d) and subsequent desulfonylation of 5 (step e). The procedures are outlined in the following scheme.

Scheme



a)  MgCl,  MgCl, CuI, α,α'-dipyridyl b) t-BuOOH, cat. V_2O_5 c) n-BuLi, $CH_2=CHCH_2Br$
d) $PdCl_2$-CuCl-O_2 e) DBU, CH_2Cl_2 f) H_2SO_4-HOAc-ether g) H_3PO_4

The Grignard coupling[5] of 2b with prenyl chloride was performed by the dropwise addition of prenyl magnesium chloride to a mixture of 2b (5.0 mmol), CuI (0.5 mmol), and α,α'-dipyridyl (0.5 mmol) in THF at 0° C over 15 min followed by stirring at room temperature for 1 hr. The product was isolated by column chromatography (silica gel, hexane) in 95 % yield based on 2b. In the same manner, the sulfide 3b was obtained in 92 % yield. Oxidation of 3a and 3b was carried out by treatment with t-BuOOH in the presence of a catalytic amount of V_2O_5[6] in ethyl acetate at room temperature for 48 hr to give 3c and 3d in 79 % and 75 % yield, respectively. The sulfones 3c and 3d were treated with n-BuLi in THF at -78° C and with allyl bromide for 1 hr (-78° C~r.t.) to give 4a and 4b in 80 % yields. Selective oxidation of the terminal double bond in 4a and 4b by the Wacker reaction[7] was successfully achieved in aqueous DMF containing catalytic $PdCl_2$ (10 mol %) and CuCl (1 equiv.) under an oxygen atomosphere at room temperature for 12 hr. The ketosulfones 5a and 5b were isolated by column chromatography (silica gel, hexane-ether 10:1) in 73 % and 76 % yield, respectively. Desulfonylation of 5a and 5b was carried out in refluxing CH_2Cl_2 in the presence of DBU (1.5 equiv.) for 1hr to give the α,β,γ,δ-unsaturated ketones, which showed three peaks (a mixture of cis-cis and cis-trans, trans-cis, and trans-trans) in GLC (SE-30, 6a, 2:55:43, 6b, 2:45:53), in quantitative yields.[8] The final step of the synthesis is acid-catalyzed cyclization of 6a and 6b. Treatment of 6a with a mixture of H_2SO_4-HOAc-ether (5:1:5) at 0° C for 1.5 hr[9] provided exclusively β-ionone (98 %) in 85 % yield. All the spectral data were fully identical with those of the authentic sample. Transformation of 6b to irones was accomplished by treatment with H_3PO_4 at 45° C for 1.5 hr without solvent[9] to give a mixture of α-trans, α-cis, and β-irones (80:3:17) in 80 % yield. The spectral data of the isolated isomers by preparative GLC were consistent with those of the authentic specimens. NMR data (δ in ppm referred to an internal TMS standard in CCl_4): 3a) 1.55 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 1.85-2.10 (m, 4H, allylic), 2.25 (t, 2H, allylic), 2.95 (t, 2H, CH_2S), 4.70 (bs, 2H, CH_2=), 5.00 (t, 1H, olefinic), and 6.90-7.35 (m, 5H, aromatic). 3b) 1.60 (s, 9H, CH_3), 2.05 (s, 4H, allylic), 2.30 (t, 2H, allylic), 2.95 (t, 2H, CH_2S), 4.70 (bs, 2H, CH_2=), and 6.90-7.30 (m, 5H, aromatic). 5a) 1.50 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.81 (s, 2H, allylic), 1.85 (d, 2H, allylic), 2.00 (s, 3H, CH_3CO), 2.13-2.40 (m, 2H, allylic), 2.65 (dd, 1H, J_1=2.0 Hz, J_2=18 Hz), 3.00 (dd, 1H, J_1=6.0 Hz, J_2= 18 Hz), 3.80 (m, 1H, $CHSO_2$), 4.63 (bs, 2H, CH_2=), 4.85 (t, 1H, olefinic), and 7.30-7.65 (m, 3H, aromatic), and 7.65-7.90 (m, 2H, aromatic). 5b) 1.50, 1.58 (s, 9H, CH_3), 1.85 (bs, 4H, allylic), 2.05-2.50 (m, 2H, allylic), 2.05 (s, 3H, CH_3CO), 2.64 (dd, 1H, J_1=2.0 Hz, J_2=18 Hz), 3.02 (dd, 1H, J_1=6.0 Hz, J_2=18 Hz), 3.80 (m, 1H, $CHSO_2$), 4.66 (bs, 2H, CH_2=), 7.30-7.60 (m, 3H, aromatic), and 7.60-7.90 (m, 2H, aromatic).

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References and Note

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