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2-HYDROXYMETHYL-4-PHENYLTHIO-1-BUTENE AS A KEY COMPOUND FOR TOTAL SYNTHESIS OF ACYCLIC TERPENOIDS

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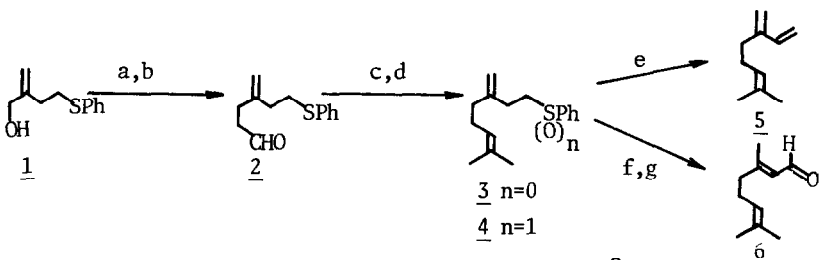
A new total synthesis of myrcene, citral, squalane, and isophytol employing 2-hydroxymethyl-4-phenylthio-1-butene as a starting material is described.

We have recently reported a convenient synthetic method for some functionalized isoprenes by thermolysis of 2-functionalized-4-phenylsulfinyl-1-butene (X⌒⌒SOPh, X = CH_2Cl, CH_2OH, CO_2Et) and their application to limonene analog synthesis by the Diels-Alder reaction with methyl vinyl ketone.[1] In connection with our interest in terpenoid synthesis employing the functionalized isoprenes, we have disclosed that 2-hydroxymethyl-4-phenylthio-1-butene (1) is a versatile building block for some acyclic terpenoids. The compound 1 involves three functionalities; that is, i) the allylic alcohol moiety allows two carbon elongation by the Claisen rearrangement, ii) homoallyl phenyl sulfide system is synthetically equivalent to α,β-unsaturated aldehyde (the Pummerer reaction of the corresponding sulfoxide and subsequent hydrolysis of the resulting acetate), and iii) thiophenyl function allows both alkylation at the active methylene of the corresponding sulfone and thermolytic generation of a double bond from its sulfoxide.

First we carried out the synthesis of myrcene and citral according to the procedure outlined in Scheme I. The alcohol 1[1] was converted to vinyl ether[2] which was subjected to the Claisen rearrangement to give the aldehyde 2 (82 %): NMR (CCl_4) δ 2.28 (m, 6H), 2.95 (t, 2H), 4.70 (bs, 2H), 7.10 (m, 5H), and 9.45 (t, 1H). The aldehyde 2 thus obtained was treated with isopropylidene triphenylphosphorane to give the sulfide 3 (81 %). Myrcene (5) was given in a quantitative yield by distillative thermolysis of the sulfoxide 4. Citral (6) was provided as a mixture of two geometric isomers (E/Z = 6:4) by the Pummerer reaction of 4 followed by hydrolysis of the resulting acetate (68 %). The spectral data were identical with those of authentic samples.[3]

Scheme I

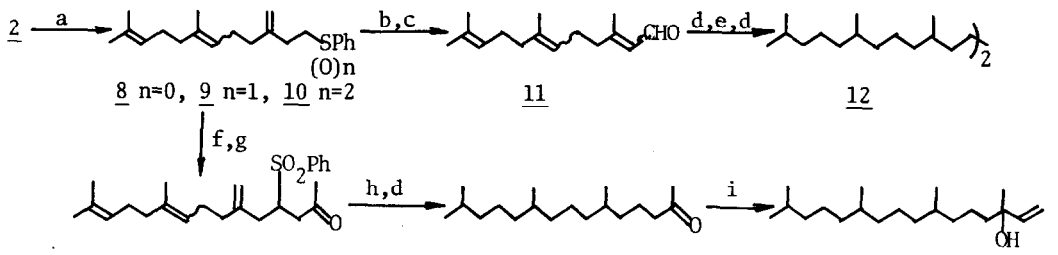


1 2 3 n=0 4 n=1 5 6

a) CH_2=$CHOCH_2CH_3$, $Hg(OAc)_2$, reflux, 24 hr b) xylene, 140°, 3 hr c) $(CH_3)_2C$=PPh_3, THF, reflux, 2 hr d) $NaIO_4$-acetone-H_2O e) △ f) Ac_2O-cat.$(CF_3CO)_2O$, r.t., 48 hr g) EtOH-1N NaOH, r.t., 0.5 hr.

Synthesis of squalane and isophytol is shown in Scheme II. Condensation of 2 with the ylide 7[4] gave the sulfide 8 as a mixture of two geometric isomers (E/Z = 6:4) (62 %): NMR (CCl_4) δ 1.55, 1.62 (s, 9H), 1.88-2.55 (m, 10H), 2.95 (t, 2H), 4.71 (bs, 2H), 5.02 (t, 2H), and 7.13 (m, 5H). The Pummerer reaction of the sulfoxide 9 and subsequent hydrolysis of the resulting acetate provided farnesal (11)[5] consisted of three geometric isomers in GLC analysis (65 %). Catalytic hydrogenation of 11 and coupling of the resulting saturated aldehyde by low valent titanium[6] afforded a symmetrical olefin which was led to squalane (12) by catalytic hydrogenation (63 %).[7] Oxidation of 8 to the sulfone 10 was achieved by t-BuOOH in the presence of V_2O_5 (79 %). Alkylation of 10 with allyl bromide followed by the selective oxidation[9] of terminal double bond afforded the ketosulfone 13 (70 %): NMR (CCl_4) δ 1.55, 1.62 (s, 9H), 1.80-2.50 (m, 10H), 2.00 (s, 3H), 2.73 (dd, 1H), 3.10 (dd, 1H), 3.80 (m, 1H), 4.65 (bs, 2H), 4.90 (t, 2H), and 7.35-7.90 (m, 5H). Desulfonylation followed by catalytic hydrogenation led to phyton (14) (92 %) which was converted to isophytol (15).[10] The spectral data were fully consistent with those of an authentic specimen.

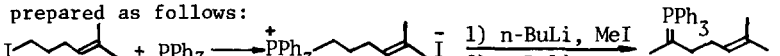
Scheme II



a) Ph_3P=CHCH=CMe$_2$ 7, THF, reflux, 2 hr b) Ac_2O-cat.$(CF_3CO)_2O$, r.t., 48 hr c) EtOH-1N NaOH d) Pd/C, H_2, EtOH e) Mg(Hg)-$TiCl_4$, THF, r.t., 12 hr f) n-BuLi, THF, CH_2=$CHCH_2Br$, -78°, 1 hr g) $PdCl_2$-CuCl-O_2, DMF, H_2O, r.t., 12 hr h) DBU, CH_2Cl_2, reflux, 1 hr i) CH_2=CHMgBr

References and Notes

1) T. Mandai, H. Yokoyama, T. Miki, H. Fukuda, H. Kobata, M. Kawada, and J. Otera, Chem. Lett., 1057 (1980).
2) W. G. Dauben and T. J. Dietsche, J. Org. Chem., 37, 1212 (1972).
3) The authentic citral obtained by oxidation (pyridinium dichromate-CH_2Cl_2) of geraniol inherently shows two peaks in GLC due to E and Z isomers.
4) The ylide 7 was prepared as follows:



Cf. E. Bertele and P. Schudel, Helv. Chim. Acta, 50, 2445 (1967).
5) Three peaks were observed in GLC of commercial farnesol (Aldrich Chemical Co.). The spectral data and GLC analysis of 11 were consistent with those of the authentic sample derived from this farnesol.
6) E. J. Corey, R. L. Danheiser, and S. Chandrasekaran, J. Org. Chem., 41, 260 (1976).
7) Reductive coupling of 11 by either $LiAlH_4$-$TiCl_3$ (J. E. McMurry and M. P. Fleming, J. Am. Chem. Soc., 96, 4708 (1974)) or Mg(Hg)-$TiCl_4$ have not given successful results yet.
8) L. Kuhnen, Angew. Chem., 78, 937 (1966).
9) J. Tsuji and T. Mandai, Tetrahedron Lett., 1817 (1978).
10) K. Suga, S. Watanabe, and Y. Yamaguchi, Yukagaku, 20, 356 (1971).

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