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A NOVEL TERMINAL FUNCTIONALIZATION OF FARNESOL AND RELATED POLYISOPRENOIDS. APPLICATION TO THE SYNTHESIS OF SOLANESOL

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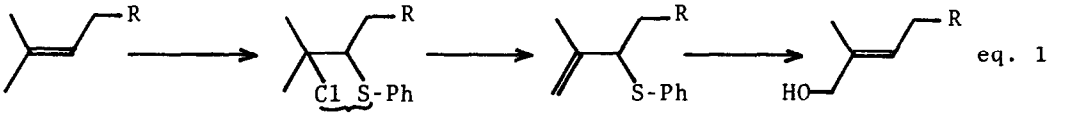
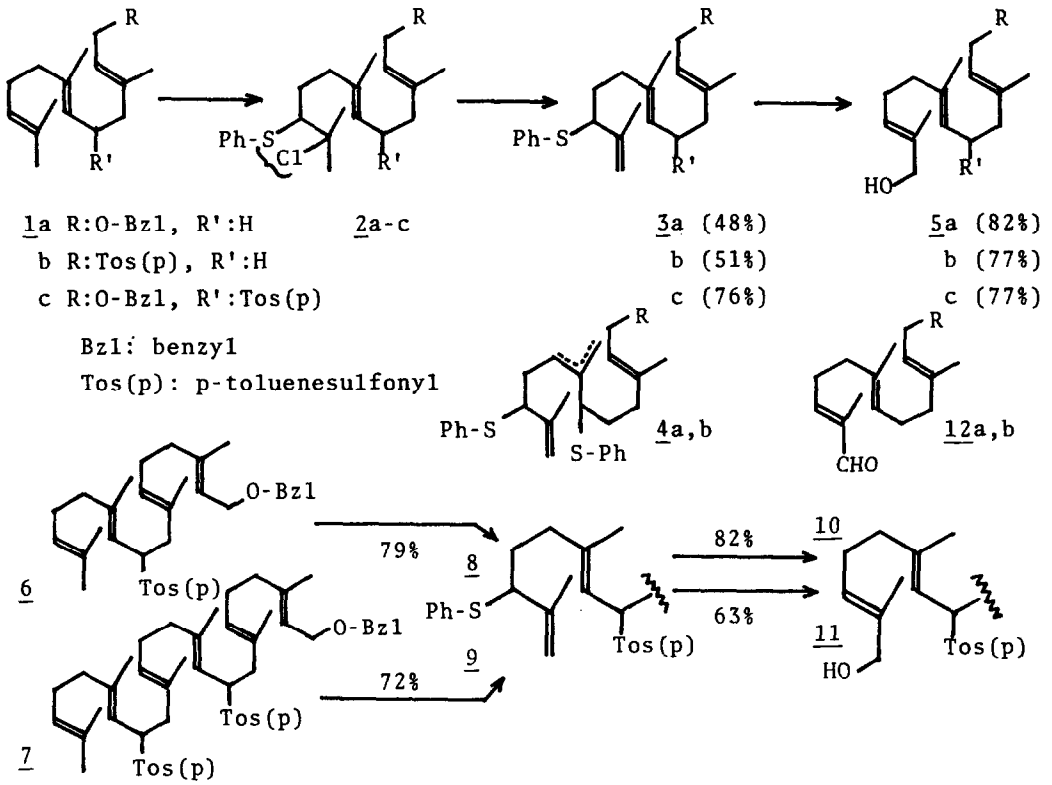
Terminal functionalizations of isoprenoids have received considerable attention particularly from the viewpoint of linear terpenoid synthesis.[1] In our synthetic projects of physiologically active polyprenylquinones, e.g., vitamin(s) K and ubiquinones we required facile synthetic methods for preparation of terminally functionalized polyisoprenoids. In the previous communication[2] we reported the high yield terminal functionalization of isoprenoids by way of benzenesulfenyl chloride addition represented by equation (1), which could be fully applied to various monoterpenes.



eq. 1

Here we describe an extension of the method to a novel terminal functionalization of farnesol and related polyisoprenoids, and also a highly stereoselective synthesis of solanesol (15),[3] naturally occuring all trans nonaprenyl alcohol using the triprenyl synthons obtained.

Treatment of E,E-farnesol benzyl ether (1a) with an equivalent of benzenesulfenyl chloride in CH_2Cl_2 at -78° for 10 min followed by evaporation of the solvent gave a crude adduct (2a), which was warmed for 20 hr at 60° in DMF containing triethylamine to give the desired methallylic sulfide (3a)[4] in 48% yield [1.60(6H, s), 1.77(3H, s), 3.48(1H, t, J:6.5), 3.90(2H, d, J:6.5), 4.39(2H, s), 4.53, 4.65(each 1H, bs), 4.95-5.48(2H, br)], mass M/e 420. Under similar conditions the methallylic sulfide (3b) was obtained from farnesyl sulfone (1b) in 51% yield. In each case formation of undesirable disulfides (4a) and (4b) to certain extent less than 20% together with inevitable recovery of respective starting materials (1a) and (1b) was observed. Although conditions have not been optimized, the above results imply that the positional selectivity of benzenesulfenyl chloride addition to relatively longer isoprenoids was not so high as to monoterpenes such as geraniol and nerol. Enhancement of the selectivity was expected by using polyisoprenoid substrates bearing bulky blocking group(s) at the appropriate position(s) in the carbon chain. That was the case when a farnesol derivative (1c)[5] bearing a p-toluenesulfonyl group closely to the inner double bond was chosen as substrate. Thus, the methallylic sulfide (3c) was



obtained in 76% yield from 1c under similar conditions. Analogous transformation of long polyisoprenoids (6) and (7)[5] to the corresponding terminal methallylic sulfides (8)(79%) and (9)(72%) was realized respectively.

Stereospecific conversion of the terminal methallylic sulfides (3, 8, 9) to the corresponding terminal trans allylic alcohols (5, 10, 11)(5a {1.62(9H, s), 1.82(1H, s, disapp. by D_2O), 3.81(2H, s), 3.92(2H, d, J:6.5), 4.41(2H, s), 4.80-5.50(3H, br), 7.25(5H, s)}, mass M/e 328) via the sulfoxides was achieved by the Evans' procedure[6] in high yields shown in the figure. The trans stereohomogeneity was confirmed by nmr analysis[7] of the corresponding α,β-unsaturated aldehydes (12a,b) derived from active manganese dioxide oxidation of the allylic alcohols (5a,b).

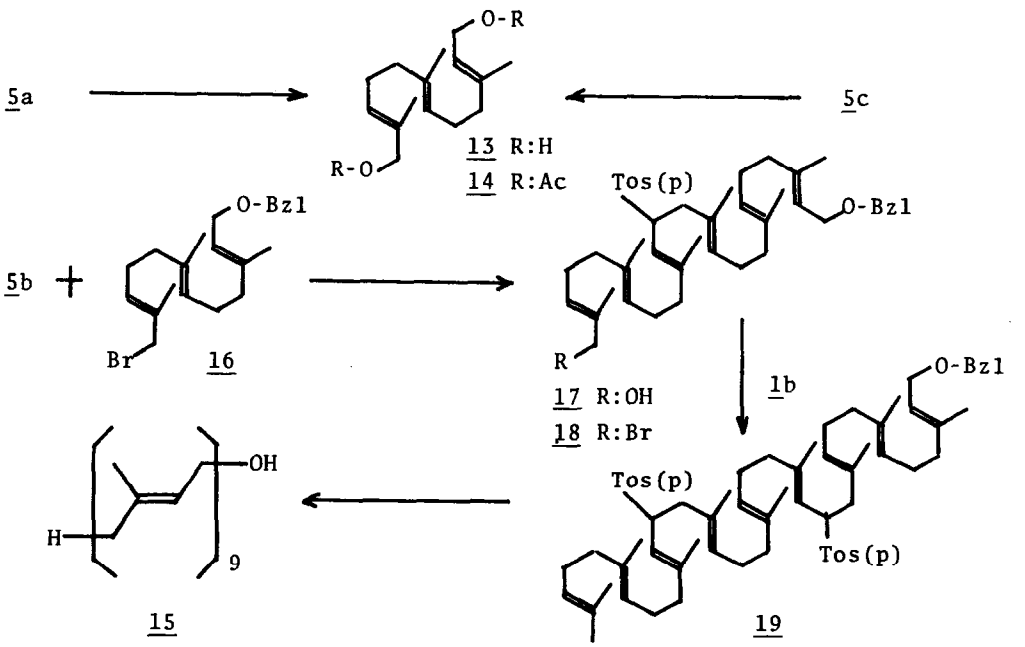
The terminal trans allylic alcohols thus obtained are useful key intermediates for natural polyisoprenoid syntheses, that were demonstrated herein by their successful application to the syntheses of terminal trans hydroxyfarnesol (13) and its diacetate (14),[8] very recently isolated sesquiterpene from Tanacetum odessanum and also to the highly stereoselective synthesis of solanesol (15).

The sesquiterpene diol (13) was easily obtained by the Birch reduction of 5a and 5c with lithium in ethylamine at -78° for 30 min followed by quenching with 1,3-butadiene respectively in 95% and 88% yield. Acetylation of the diol (13) with Ac_2O in pyridine gave the natural product diacetate (14)(95%){1.63, 1.65

1.73, 1.97, 2.00(each 3H, s) 4.36(2H, s), 4.47(2H, d, J:6.5), 4.90-5.50(3H, br)], mass M/e 322.

The all trans nonaprenyl skeleton of solanesol (15) was constructed by combining three farnesol units. Thus, the dianion[9] made by treatment of the hydroxy sulfone (5b) with 2.5 equivalent of n-BuLi in THF containing a trace of HMPA at -78° for 30 min was submitted to carbon-carbon coupling by addition of the bromide (16) prepared from 5a followed by gradual warming the mixture up to 0° (ca. 1 hr) to afford the hexaprenyl alcohol (17) in 45% yield. The alcohol (17) was treated with PBr_3 in Et_2O at 0° to give the bromide (18)(97%), which was coupled with farnesyl sulfone (1b) under the similar condition above also using 2.5 equivalent of n-BuLi to lead to formation of the disulfone (19)(65%) possessing the whole carbon skeleton of solanesol (15) including the stereochemistry of double bonds. Solanesol (15) was obtained in 75% yield by the above Birch reduction of 19. By spectral comparison (nmr, ir, mass and glc) the synthetic solanesol was fully identified with the authentic natural one.

The existing syntheses of solanesol[10] and related polyisoprenoids[11] except Altman's synthesis of geranylgeraniol[1a] suffered inevitable contamination of stereoisomers due to the low stereoselectivity of reactions used and required troublesome separation of stereoisomers. It is worth noting that in our method described above no separation of stereoisomers were necessary because the double bonds of the starting isoprenoid synthons remained intact throughout the chain assembly. The synthetic strategy combining the terminal oxygenation method presented in this communication appears to be promising generally for syntheses of polyisoprenoids without undesirable double bond stereoisomers.



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References and Notes

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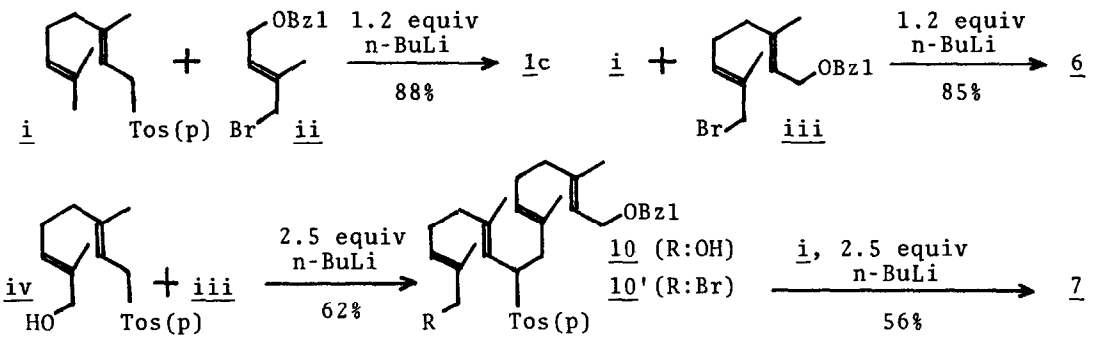
4. Satisfactory nmr and ir spectra were obtained for all compounds, some of which gave reasonable mass spectra. Nmr spectra were taken in CCl_4 at 60 MHz and chemical shifts are reported in δ and coupling constants in hertz.
5. The polyisoprenoids (1c, 6, 7) were prepared highly stereoselectively as depicted in the following scheme. Reaction condition: solvent THF-HMPA, temp. -78-0°, time 1-1.5 hr.



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7. Each aldehyde proton signal appeared at 9.28 ppm. No signal corresponding to cis-β-substituted methacrolein, which generally appears at 10.0-10.1 ppm was observed.
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