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A FACILE FUNCTIONALIZATION OF THE ISOPROPYLIDENE TERMINUS OF ISOPRENOIDS. APPLICATION TO THE SYNTHESIS OF TERMINAL TRANS ALLYLIC ALCOHOLS

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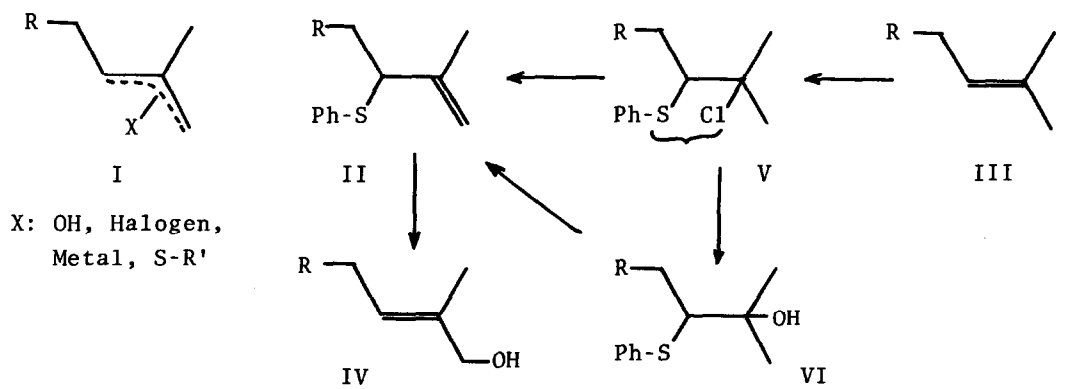
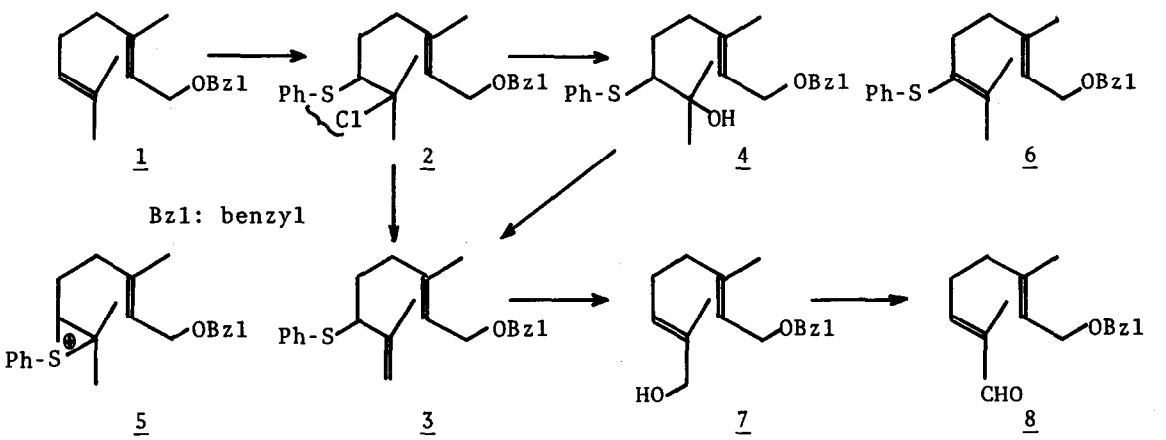
In the synthetic strategies for the acyclic terpenoids containing trisubstituted double bonds, the potential utility of terminally functionalized olefins of type I has received much attention from the viewpoint of carbon-carbon bond formation with highly geometrical and positional control.[1] From our synthetic interest in polyisoprenoids, we required a facile and high yield synthetic method for the preparation of terminal methallylic sulfides of type II, a synthetic potential for construction of trisubstituted olefinic linkages by [2,3] sigmatropic rearrangements via sulfoxides or sulfonium ylides.[2] Here we describe a facile terminal functionalization[3] that enables isoprenoids of type III which contain the isopropylidene terminus in the molecule to be converted direcly into II with high chemoselectivity. Also a simple transformation of the latter to terminal trans allylic alcohols of type IV, an important building block in terpenoid syntheses, is reported. The overall synthetic sequence involves (1) addition of benzenesulfenyl chloride[4] to olefins III to make adducts of type V, (2) formation of terminal methallylic sulfides II by direct dehydrochlorination of V or by silica gel treatment of V leading to terminal β-hydroxy sulfides of type VI followed by acid catalized dehydration, and (3) stereospecific transformation of II to terminal trans allylic alcohols IV by the Evans' procedure.[2b]



The terminal functionalization developed is exemplified by geranylbenzyl ether (1). Treatment of 1 with an equivalent of benzenesulfenyl chloride in CH_2Cl_2 at -20° within 10 min led to quantitative formation of a pair of regio-isomeric adducts (2). The preference for the isopropylidene terminus in the attack of sulfenium cation (Ph-S$^{\oplus}$) was expected on the bases of reactions of linear polyisoprenoids with electrophiles such as N-bromosuccinimide.[3c] Nmr analysis confirmed that Δ^2-E-double bond was intact; the olefinic proton attached to C-2 [5.37 bt, J:6.5], and the methylene protons to C-1 [3.94 d, J:6.5] were observed. The adduct (2) was warmed at 60° in DMF for 20 hr to give only desired terminal methallylic sulfide (3)[5] (88%)[1.59, 1.77(each 3H, s), 3.47(1H, t, J: 7.0), 3.88(2H, d, J:7.0), 4.35(2H, s), 4.50, 4.60(each 1H, bs), 5.30(1H, bt, J: 7.0)]. The adduct (2) was converted to terminal β-hydroxy sulfide (4) (68%) [1.16, 1.23(each 3H, s), 1.55(3H, bs), 2.91(1H, dd, J:10.5, 2.5), 3.80(2H, d, J:6.5), 4.30(2H, s), 5.11(1H, bt, J:6.5)] by simple running through a silica gel columun in hexane followed by elution with hexane/ether (1:1). The sulfide (3) was also obtained by warming 4 with D-10-camphorsulfonic acid in benzene at 40-50° for 2 days in 80% yield.



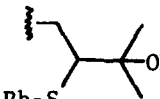
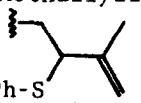
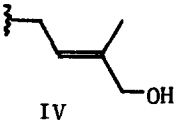
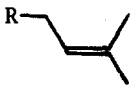
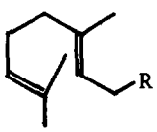
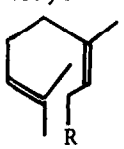
1 2 4 6

5 3 7 8

It is worth noting that no purification nor separation of the crude isomeric mixture of adducts (2) is neccessary for the requisite transformation to the sulfide (3); the behavior of the adduct (2) in the above conversion is understandable on the bases of intermediacy of episulfonium cation (5),[4] and also that the use of neutral (DMF or toluene) or rather weakly basic condition (in the presence of triethylamine) in the dehydrochlorination to 3 is crucial because vinyl sulfide (6) was obtained in 63% yield from the adduct (2) by treatment with potassium tert-butoxide in DMSO at room temperature.[6]

The versatility of the terminal functionalization method mentioned above was demonstrated on the various isoprenoids including protected hydroxyl groups (Table). Basic conditions were neccessary for dehydrochlorination of adducts V which contain acid-labile hydroxyl protecting groups such as O-THP and O-CH_2OCH_3,

Table. Transformation of Isoprenoids III to Terminal β-Hydroxy Sulfides VI, Terminal Methallylic Sulfides II, and Terminal Trans Allylic Alcohols IV via Benzenesulfenyl Chloride Addition.

Isoprenoid	R*1	% Yield Terminal β-Hydroxy Sulfide  VI	% Yield Terminal Methallylic Sulfide  II Dehydrochlorination*2 of Adduct V	Dehydration*3 of VI	% Yield*4 Terminal Trans Allylic Alcohol  IV
Prenyl 	H	94	75[b]	73[d]	79 (59)
	O-Bzl		89[b]		86 (77)
	O-Ac		77[b]		87 (67)
Geranyl 	O-Bzl	68	88[a,b]	80[d]	87 (76)
	Ts(p)	79	74[a,b]	85[e]	92 (68)
	O-Ac	74	73[a,b]	73[e]	79 (58)
	O-THP		89[b]		89 (79)
	O-MTM		76[b]		72 (55)
Neryl 	O-Bzl	65	84[b]	79[d]	95 (80)
	Ts(p)	84	70[c]	98[e]	86 (70)
	O-Ac	85	74[c]	68[d]	75 (55)
	O-THP		86[b]		85 (73)
Myrcene			68[b]		69 (47)
Linalyl acetate			86[b]		79 (68)

*1. Bzl: benzyl, Ts(p): p-toluenesulfonyl, MTM: methoxymethyl.

*2. Conditions for dehydrochlorination: a. DMF, 60-80°, 20 hr; b. DMF, triethylamine, 60-80°, 20 hr; c. toluene, triethylamine, 120°, 20 hr.

*3. Conditions for dehydration: d. D-(10)-camphorsulfonic acid, benzene, 40-50°, 2-3 days; e. p-toluenesulfonic acid, benzene, 40-50°, 4-6 hr.

*4. Yields from II are listed and the values shown in parentheses represent overall yields from the starting isoprenoids III.

and silica gel treatment was not efficient to afford β-hydroxy sulfide VI because of decomposition due to liberated hydrochloric acid. The acid catalysis in dehydration of VI was also effective by p-toluenesulfonic acid.[6,7]

Transformation of allylic sulfides to allylic alcohols is much more general and efficient.[2b,c,7] Thus the sulfide (3) was oxidized with sodium meta-periodate to give intermediate sulfoxide which was treated with trimethyl phosphite in MeOH at room temperature to lead to stereospecific formation of trans-10-hydroxygeranyl benzyl ether (7)[1d] (87%, and 76% overall yield from 1). The structure and stereohomogeneity of the alcohol (7) was confirmed by identification with that obtained directly from 1 (33%) by the known procedure (SeO_2),[1d] and by nmr analysis[8] of trans α,β-unsaturated aldehyde (8) [6.33(t, olefinic β-proton), 9.30(s, aldehyde proton)], derived from active manganese dioxide oxidation of 7. Analogous stereospecific transformation to terminal trans allylic alcohols IV was carried out on various sulfides II in high yields (Table).

The overall sequence described here presents an useful alternative route to terminal trans allylic alcohols IV from various isoprenoids III containing the isopropylidene terminus in the molecule.

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References and Notes

1. a) D. J. Faulkner, Synthesis, 175 (1971) and references cited therein; b) B. M. Trost and L. Weber, J. Org. Chem., 40, 3617 (1975); c) K. Sato, S. Inoue and S. Morii, Chem. Lett., 747 (1975); d) L. J. Altman, L. Ash and S. Marson, Synthesis, 129 (1974); e) P. A. Grieco, D. Boxler and K. Hiroi, J. Org. Chem., 38, 2572 (1973).
2. a) B. M. Trost and L. S. Melvin, Jr., "Sulfur Ylides" Emerging Synthetic Intermediates, Academic Press (1975); b) D. A. Evans, G. C. Andrews, T. T. Fujimoto and D. Wells, Tetrahedron Lett., 1385, 1389 (1973); c) P. A. Grieco, J. Chem. Soc., Chem. Commun., 702 (1972).
3. For existing terminal oxygenations and metallation of isopropylidene terminus see: a) N. Rabjohn, "Organic Reactions", Vol. 24, 261 (1976); b) R. W. Denny and A. Nickon, ibid., Vol. 20, 133 (1973); c) E. E. van Tamelen, Accounts Chem. Res., 1, 111 (1968); T. Inoue, T. Uchimaru and T. Mukaiyama, Chem. Lett., 1215 (1977) and references cited therein; d) ref. 1b.
4. M. H. Mueller and P. E. Butler, J. Am. Chem. Soc., 90, 2075 (1968); P. B. Hopkins and P. L. Fuchs, J. Org. Chem., 43, 1208 (1978).
5. Satisfactory nmr, mass, ir, tlc and glc data were obtained for all compounds. Nmr spectra were obtained in CCl_4 at 60 MHz and chemical shifts are reported in δ and coupling constants in hertz.
6. B. M. Trost, K. Hiroi and S. Kurozumi, J. Am. Chem. Soc., 97, 438 (1975).
7. P. Brownbridge and S. Warren, J. Chem. Soc., Perkin I, 1131 (1977).
8. No aldehyde proton signal corresponding to cis-β-substituted methacrolein, which generally appears at 10.0-10.1 ppm, was observed.

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