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A STEREOSELECTIVE FORMATION OF (Z)-2-METHYL-2-ALKENOL BY THE WITTIG REACTION: ITS APPLICATION TO A SYNTHESIS OF NERYLACETONE AND (Z,Z)-FARNESYLACETONE

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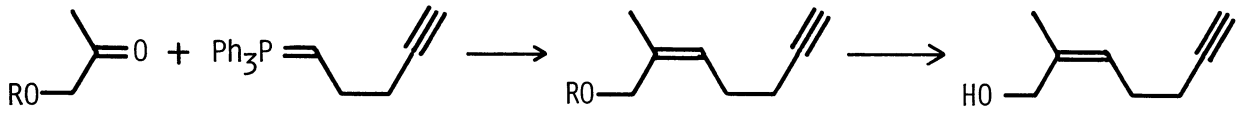
The Wittig reaction of benzyloxyacetone or tetrahydropyranyloxyacetone with 4-pentynylidenetriphenylphosphorane in salt-free conditions followed by removal of the protecting group afforded (Z)-2-methylhept-2-en-6-yn-1-ol in 95-96 % stereoselectivity. After conversion of the allylic alcohol to the corresponding bromide, the latter was coupled with prenyl or neryl p-tolyl sulfone, followed by reductive desulfonation and hydration of the acetylenic bond, to give nerylacetone and (Z,Z)-farnesylacetone, respectively.

In recent years much effort has been devoted to the stereoselective synthesis of biologically active isoprenoid compounds.[1,2] One of the most important and essential problems in this synthesis is a stereoselective construction of polyprenyl carbon framework with requisite E and/or Z configuration. In this respect many methods have been reported for the stereoselective synthesis of trisubstituted (E)-olefins[3] and all-trans polyprenyl compounds.[2,4,5]

On the contrary a limited number of methods have been reported for the stereoselective synthesis of trisubstituted (Z)-olefins,[6] and there have been few reports so far on the synthesis of cis polyprenyl compounds.[7] Here we wish to report a stereoselective Wittig reaction of alkoxyacetone leading to (Z)-2-methyl-2-alkenol which can serve as a cisoid isoprenoid synthon and its application to a stereoselective synthesis of (Z)-polyprenylacetones.

Previously we reported[8] that the Wittig reaction of benzyloxyacetone (1a) with 4-pentynylidenetriphenylphosphorane (2)[9] afforded 7-benzyloxy-6-methylhept-

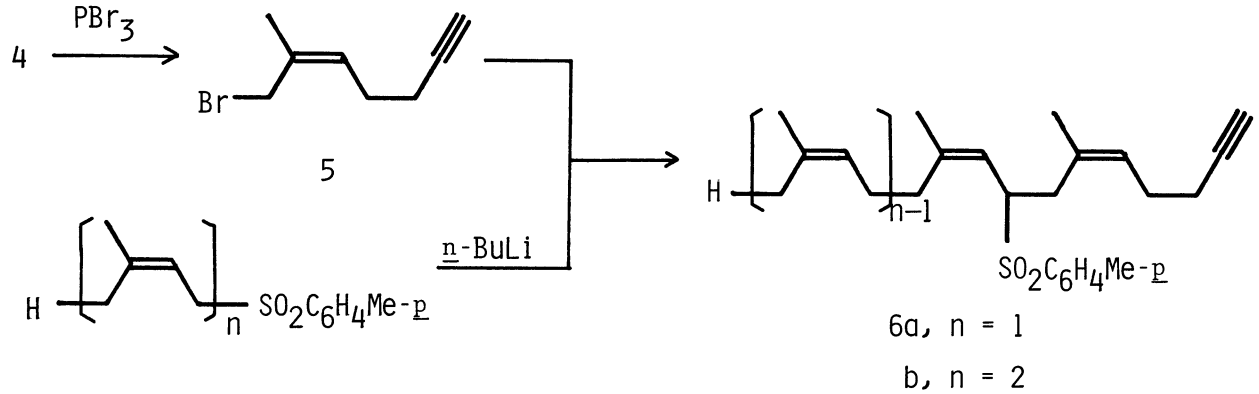


1a, R = $PhCH_2$ 2 3a, R = $PhCH_2$ 4

b, R = THP b, R = THP

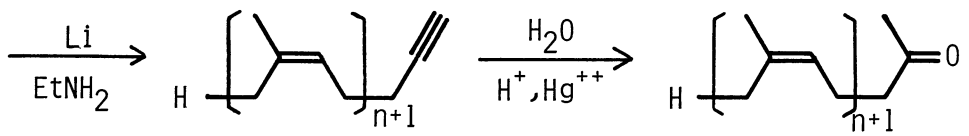
5-en-1-yne (3a) in which the Z isomer was formed predominantly (Z/E = 95/5). Recently Still and Mitra[6b] reported the cis-stereoselective Wittig reaction of unstabilized ylids with α-alkoxyketones. In our hand the reaction of tetrahydropyranyloxyacetone (1b) with 2 gave 3b (Z/E = 96/4) in 95 % yield. Lithium/ethylamine reduction of 3a or acid-catalyzed hydrolysis of 3b led to (Z)-2-methylhept-2-en-6-yn-1-ol (4) in high yields. The stereochemistry of our products was confirmed by ^1H- and ^{13}C-NMR spectroscopy of the primary product (3a),[10] the allylic alcohol (4)[11] and an aldehyde obtained by oxidation of 4 with active manganese dioxide.[12]

The allylic alcohol (4) was treated with phosphorus tribromide in ether at 0 °C to afford allylic bromide 5 without stereochemical and positional isomerization. The bromide (5) was coupled with prenyl p-tolyl sulfone[13] or neryl p-tolyl sulfone[13] in THF–HMPA at −78 °C using n-butyllithium as base, affording the coupling products 6a and 6b respectively, in 70–80 % yields, which were subjected to reductive desulfonation with lithium/ethylamine to give the desired



6a, n = 1

b, n = 2



7a, n = 1 8a, n = 1

b, n = 2 b, n = 2

hydrocarbons 7a and 7b in good yields. The removal of an allylic sulfonyl group by reductive fission was inevitably accompanied with formation of a conjugate reduction product in a ratio of 1:10 in the synthesis of all-trans polyprenoids.[5] It should be noted that in the present reaction of cis series, the conjugate reaction took place only to the same extent as in the trans series.

Finally hydration of the en-yne compounds 7a and 7b in aqueous methanol in the presence of a catalytic amount of mercury(II) sulfate and sulfuric acid furnished nerylacetone (8a) and (Z,Z)-farnesylacetone (8b). The stereochemistry of the final products was confirmed by the comparison of NMR spectra and GLC retention times with authentic specimens prepared from nerol and (Z,Z)-farnesol.

As terminal methyl ketones and, preferentially, terminal acetylenic compounds were reported to serve as the precursors for cis trisubstituted allylic alcohols[14] or trans ones,[15] the present results appear to offer an efficient procedure to the selective synthesis of all-cis or partially-cis polyprenyl compounds. Active investigation is now being undertaken on this field in these laboratories.

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10) ^{1}H-NMR (CCl_4): δ 1.65 and 1.77 (each s, 1H, 5:95, CH_3), 2.13 (m, 5H, CH_2CH_2 and HC≡C), 3.83 and 3.93 (each s, 2H, 5:95, $OCH_2\overset{|}{C}=$), 4.38 (s, 2H, CH_2Ph), 5.35 (t, 1H, =CH-), 7.23 (s, 5H, C_6H_5).

11) ^{1}H-NMR (CCl_4): δ 1.64 and 1.78 (each s, 3H, 4:96, CH_3), 1.85 (t, 1H, HC≡C), 2.20 (m, 4H, CH_2CH_2), 2.90 (bs, 1H, OH), 3.87 and 4.00 (each s, 2H, 4:96, $OCH_2\overset{|}{C}=$), 5.23 (t, 1H, =CH-).[16]

12) A mixture of 4 (200 mg, 3.2 mmol) and active manganese dioxide (5.57 g) in hexane (55 ml) was stirred at 0 °C for 1.5 hr. Filtration and evaporation of the solvent under reduced pressure gave (Z)-2-methylhept-2-en-6-ynal (198 mg, quant.), homogeneous on TLC (R_f 0.5, silica gel/hexane–ethyl acetate 4:1); ^{1}H-NMR ($CDCl_3$): δ 1.81 (s, 3H, CH_3), 2.02 (t, J = 2.6 Hz, 1H, HC≡C), 2.39 (dt, J = 2.6 and 7 Hz, 2H, $CH_2C\equiv$), 2.80 (q, J = 7 Hz, 2H, $CH_2CH=$), 6.54 (t, J = 7 Hz, 1H, =CH-), and 10.14 (s, 1H, CHO) (a small but clear singlet peak was observed at δ 9.43 due to the formyl proton of the trans isomer); ^{13}C-NMR ($CDCl_3$): δ 16.5 (C-5), 18.6 (C-4), 25.4 (CH_3), 70.0 (C-7), 82.3 (C-6), 137.5 (C-2), 146.1 (C-3), and 190.9 (CHO).[16]

The (Z)-aldehyde completely isomerized to the (E)-isomer on standing the $CDCl_3$ solution at room temperature for a week; ^{13}C-NMR ($CDCl_3$): δ 9.3 (C-5), 17.7 (CH_3), 27.8 (C-4), 69.5 (C-7), 82.7 (C-6), 140.4 (C-2), 151.6 (C-3), and 195.0 (CHO).[16]

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