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STEREOSELECTIVE SYNTHESIS OF A CISOID C_{10} ISOPRENOID BUILDING BLOCK AND SOME ALL-CIS-POLYPRENOLS

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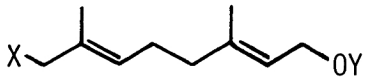
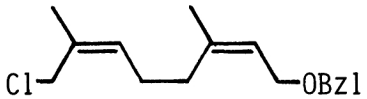
As the key compound for the construction of cisoid terpenoids, (2Z,6Z)-8-benzyloxy-1-chloro-2,6-dimethylocta-2,6-diene was synthesized stereoselectively via the Wittig reaction starting from nerol. The ten-carbon building block was coupled with prenyl or neryl p-tolyl sulfone to afford, after reductive desulfonylation, (Z,Z)-farnesol and (Z,Z,Z)-nerylnerol, respectively.

Several syntheses of all-trans-polyprenyl compounds have been reported utilizing such bifunctional ten-carbon building blocks as 1a[1] and 1b[2] possessing trans-trisubstituted double bonds, whereas the synthesis of polyprenols with specifically positioned cis-trisubstituted olefinic bonds has scarcely been reported because of difficult availability of cisoid isoprenoid synthons.[3] Here we report a stereoselective synthesis of the cisoid ten-carbon building block 2, which can be served as a key compound for the construction of the cis-polyprenyl skeleton 3.



1a, X = Cl, Y = Bzl
b, X = Br, Y = Ac



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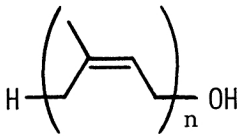
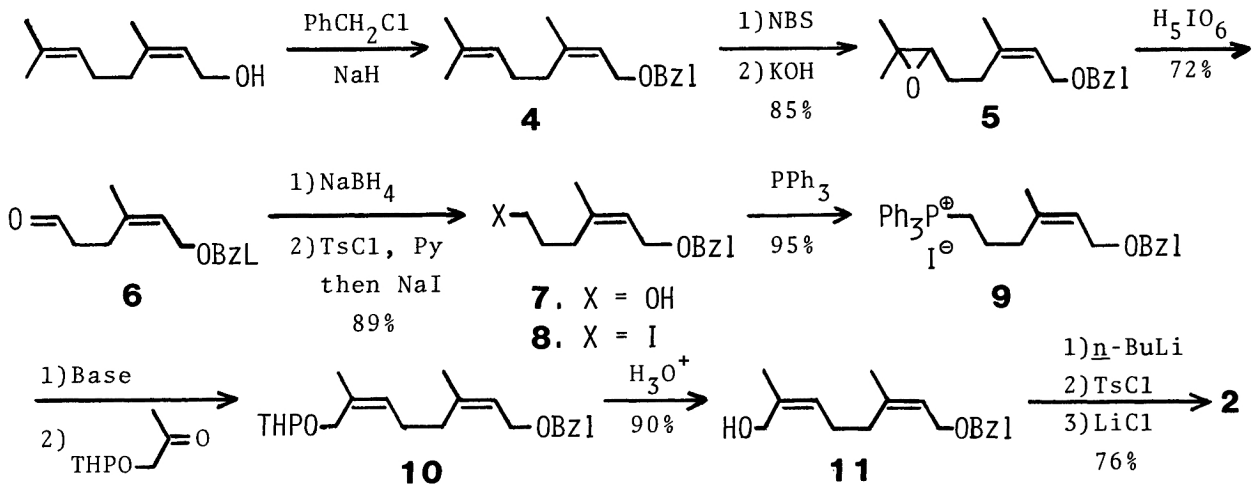


3

Recently, Still and coworkers[4] and we[5] reported that the Wittig reaction of various α-alkoxyketones with unstabilized ylids led to protected trisubstituted allylic alcohols of Z configuration. Now we applied this reaction to the stereoselective construction of 2 as depicted in the following scheme.

Neryl benzyl ether (4) was treated with NBS in aq 1,2-dimethoxyethane at −10~0 °C for 5 h to give a bromohydrin which, without further purification, was converted to epoxide 5 by treatment with potassium hydroxide in methanol at 0 °C for 2 h. The epoxide 5 was oxidatively cleaved with periodic acid in aq dioxane at r. t. for 5 h to give aldehyde 6. This was converted into alcohol 7 with sodium borohydride in a good yield, from which was obtained iodide 8 via the corresponding tosylate. The triphenylphosphonium iodide 9, mp 138–139 °C (lit.[6] mp 134.5–135.5 °C was obtained in 95% yield by the reaction of 8 with triphenylphosphine in benzene at reflux for 20 h. The Wittig reaction between tetrahydropyranyloxyacetone



and the ylid derived from 9 produced the desired olefinic ether 10 with Z configuration in an acceptable yield. The stereoselectivity of the Wittig reaction was generally high but the yield was varied with the reaction conditions empolyed as shown in the Table.

Table. The Wittig Reaction of Tetrahydropyranyloxyacetone and 9

Base	Solvent	conditions[a]	yield[b] (%)	Z/E[c]
n-BuLi	THF	−70 °C, 3h	77	95:5
t-BuOK	THF	0 °C, 2h	32	95:5
n-BuLi	10% HMPA/THF	−70 °C, 2h	45	98:2

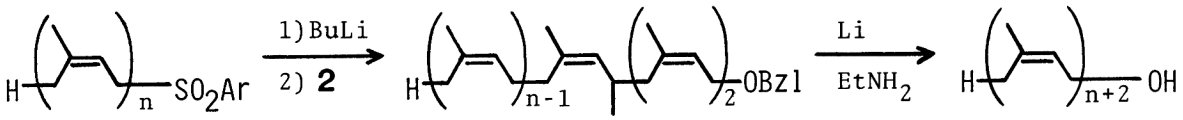
a) Conditions refered to the ylid formation from 9. Tetrahydropyranyloxyacetone was added to the ylid solution and the mixture was allowed to gradually warm up to room temperature for 15 h, forming the desired product 10. b) Isolated yield after column chromatography (silica gel, 10–15% isopropyl ether/hexane or 10% ethyl ether/hexane. c) The ratio Z/E was determined by GLC of the TMS ether of the alcohol 11.

The pure Z isomer 10 was isolated by careful chromatography on silica gel column. Deprotection of 10 with p-TsOH in methanol at room temperature for 27 h provided alcohol 11[7] in 90% yield. The stereochemistry of 11 was confirmed by NMR spectroscopy[8] of the alcohol itself and an aldehyde[9] obtained therefrom by active manganese dioxide oxidation, and also by the fact that (Z,Z)-farnesol was obtained by the prenylation of 11 (vide infra).

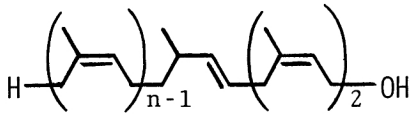
Finally the alcohol 11 in ether–HMPA (3:1) was treated successively with n-butyllithium (1 eq., −60 °C), tosyl chloride (1.2 eq., −30~−10 °C), and lithium chloride (1.5 eq., −10 °C~r.t.) to afford a chloride 2[10] in 76% yield after purification by silica gel column (5% isopropyl ether/hexane). The HPLC analysis of 2 showed that the stereochemistry of the allylic moiety was completely retained during the chlorination.

The above sequence of reactions constitutes the first practical method of stereoselective Z-functionalization of the isopropylidene terminus of acyclic monoterpenoids. As the regioselective bromohydrination of polyolefins is attainable,[11] the present process seems applicable to various isoprenoids.

Having accomplished our initial goal of preparing the cisoid ten-carbon building block **2**, we next investigated the utility of this synthon for the synthesis of cisoid terpenoids. Prenyl p-tolyl sulfone (**12**)[12] was deprotonated (n-BuLi/THF–HMPA, −40~−30 °C) and reacted with **2** (−60~0 °C) to give the coupling product **13**[13] in 83% yield. The reductive removal of the sulfonyl and benzyl groups (Li/$EtNH_2$) afforded (Z,Z)-farnesol (**14**), in 86% yield, which coincided with an authentic sample on GLC and exhibited characteristic signals on NMR identical with those reported in the literature.[14] The product contained a very minor amount (ca. 5%) of isomer **15** which arose from conjugate reduction. As the byproduct **15** contains a disubstituted E-olefinic bond, it is separable from the desired product **14** by careful column chromatography.



12, n = 1 **13**, n = 1 **14**, n = 1
16, n = 2 **17**, n = 2 **18**, n = 2



15, n = 1
19, n = 2

In a similar manner, the coupling reaction between the anion of neryl p-tolyl sulfone[12] (**16**) (100% Z) and the ten-carbon block **2** (95% Z) afforded the desired product **17**[15] (95% stereochemical purity by HPLC) in 86% yield, which was subjected to Li/$EtNH_2$ reduction to give nerylnerol (**18**)[16] in 85% yield after column chromatography on silica gel. GLC analysis revealed the presence of two minor components (2.6% each) which corresponded to the conjugate reduction product **19** and (6E)-isomer of **18**.

In summary, it should be noted that the present successful procedure of Z-functionalization of isoprenoid terminals opens a promising methodology of stereoselective synthesis of various natural polyprenols. Further investigation is in progress in these laboratories.

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7) IR (neat): 3400, 1670, 1005, 740, 700 cm^{-1}; ^{1}H-NMR (CCl_4): δ 1.73 (s, 6H), 2.04 (m, 4H), 2.59 (s, 1H), 3.89 (d, 2H), 3.91 (s, 2H), 4.36 (s, 2H), 5.14 (t, 1H), 5.33 (t, 1H), 7.18 (s, 5H).
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9) The ^{1}H-NMR spectrum of the aldehyde (CCl_4 solution) exhibited a singlet at 10.01 assignable to the formyl proton of the Z-aldehyde. On standing the CCl_4 solution at room temperature, a new singet developed at δ 9.29 assignable to the formyl proton of the E-isomer with concurrent decrease of the former signal.
10) IR (neat): 1670, 1070, 740, 700 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.79 (bs 6H), 2.10 (m, 4H), 3.92 (d, 2H), 3.95 (s, 2H), 4.44 (s, 2H), 5.32 (t, 1H), 5.45 (t, 1H), 7.26 (s, 5H).
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13) IR (neat): 1660, 1300, 1140, 740, 700 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.17 (s, 3H), 1.59 (s, 3H), 1.65 (s, 3H), 1.75 (s, 3H), 2.03 (m, 4H), 2.40 (s, 3H), 2.3–2.9 (m, 2H), 3.72 (sextet, 1H), 3.95 (d, 2H), 4.47 (s, 2H), 4.94 (d, 1H), 5.16 (t, 1H), 5.40 (t, 1H), 7.30 (s, 5H), 7.27 and 7.70 (ABq, 4H).
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15) IR (neat): 1650, 1595, 1495, 1310, 1300, 1290, 1145, 1085 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.51 (s, 3H), 1.64 (bs, 13H), 1.72 (s, 3H), 1.99 (m, 4H), 2.41 (s, 3H), 2.25–2.73 (m, 2H), 3.75 (dt, 1H), 3.93 (d, 2H), 4.45 (s, 2H), 4.97 (m, 3H), 5.36 (t, 1H), 7.26 (s, 5H), 7.24 and 7.64 (ABq, 4H).
16) IR (neat): 3325, 1665, 1000 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.59 (s, 3H), 1.66 (s, 9H), 1.72 (s, 3H), 2.00 (m, 12H), 2.08 (s, 1H), 3.99 (d, 2H), 5.05 (bs, 3H), 5.32 (t, 1H).

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