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GENERAL METHOD OF STEREOSPECIFIC SYNTHESIS OF NATURAL POLYPRENOLS. SYNTHESIS OF BETULAPRENOL-6, -7, -8, AND -9

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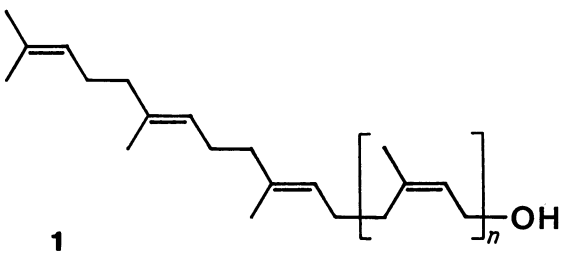
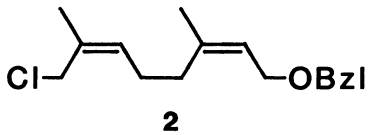
A stereoselective synthesis of (Z,Z,Z)-12-benzyloxy-1-chloro-2,6,10-trimethyldodeca-2,6,10-triene (**3**) was achieved starting from (Z,Z)-farnesol. All the components of betulaprenols were synthesized using the C_{15} block **3** and its lower homologue (C_{10} block) as the key building blocks for the cisoid polyprenyl skeletone.

In recent years several kinds of polyprenols such as betulaprenols (**1**),[1,2] ficaprenols,[3] undecaprenol,[4] dolichols,[5] and others[6] have been isolated from plant and animal tissues and microorganisms. Much attention has been given to these polyprenols since phosphorylated esters of undecaprenol and dolichols have been shown to participate as carbohydrate carriers in the biosynthesis of bacterial cell wall polysaccharides and in the biosynthesis of lipopolysaccharides, peptidoglycans, and glycoproteins in prokaryotes and eukaryotes.[7] As natural sources of polyprenols are extremely scarce, an efficient method of synthesis of these compounds is strongly desired. The only practicable method reported so far is a stepwise cis-C_5 homologation,[8] however, the creation and usage of much longer building blocks, i.e., cis,cis-C_{10} (**2**)[9] and all-cis-C_{15} isoprenoid blocks (**3**) and so on, would be obviously preferable. Here we wish to report an effective general method of synthesis of these potential polyprenols using **2** and **3** as the key building blocks.



1

a(n=3), **b**(n=4), **c**(n=5), **d**(n=6)



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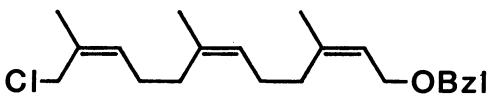
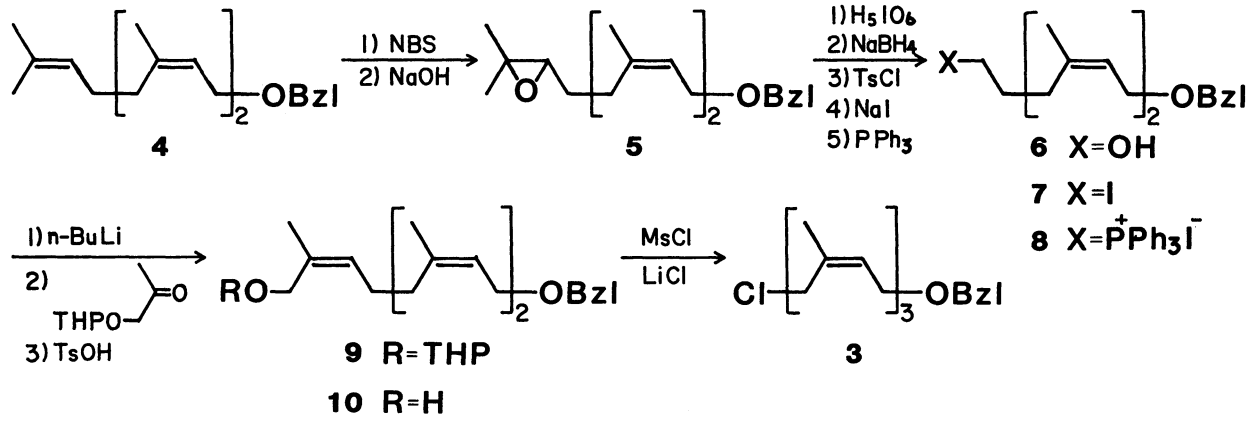


3

Based on our previous finding on the stereoselective Wittig reaction,[10] (Z,Z)-farnesol was successfully transformed into a key C_{15} building block **3** as depicted in Scheme 1 which essentially followed the synthesis of the C_{10} homologue **2**.[9] (Z,Z)-Farnesyl benzyl ether (**4**) was converted via the bromohydrin into the epoxide

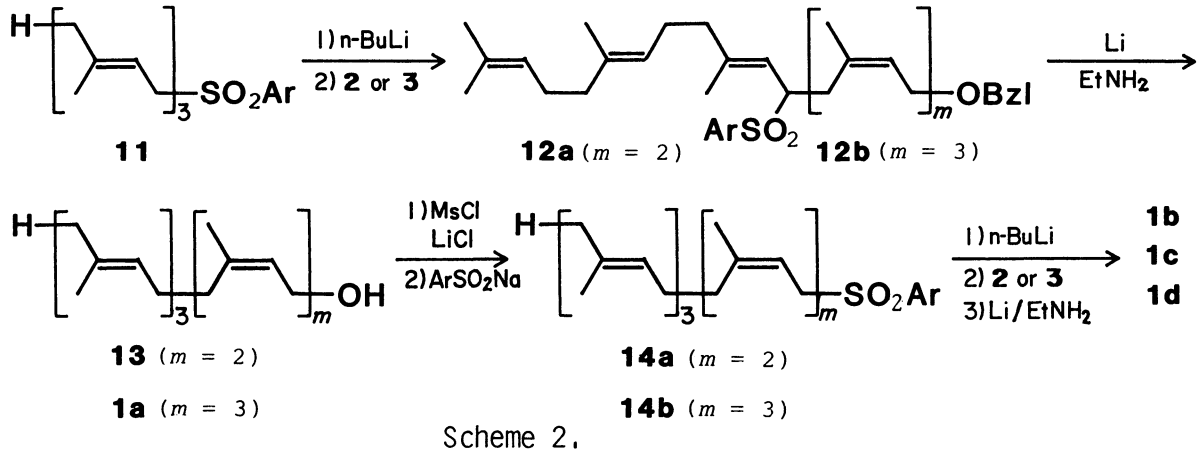


Scheme 1.

5 (59%), which was oxidatively cleaved with periodic acid in aq dioxane and the crude aldehyde was reduced yielding the alcohol **6**[11] as a clear liquid in 77% yield. The alcohol **6** was converted *via* the tosylate into the iodide **7** in 88% yield, which was reacted with triphenylphosphine in benzene at reflux to give the phosphonium salt **8**[11] in 90% yield, mp 70–72 °C. The Wittig reaction between the ylide derived from **8** and tetrahydropyranyloxyacetone was conducted in THF at −70 °C to yield the all-cis-bisether **9**[11] in 75% yield in 95% stereoselectivity (HPLC). Removal of the THP protecting group afforded the alcohol **10**[12,13] in 94% yield. The final step of the synthesis of the key C_{15} building block **3** was constituted by treatment of **10** with methanesulfonyl chloride in the presence of *s*-collidine and lithium chloride in DMF at 0 °C yielding the chloride **3**[12] (85%), which was purified by silica gel column chromatography and could be stored in a freezer for a few weeks without significant isomerization and decomposition.

The stereospecific synthesis of betulaprenol-6 (**1a**) was achieved as follows. (*E*,*E*)-Farnesyl *p*-tolyl sulfone (**11**)[14] (327 mg, 0.91 mmol) was lithiated with *n*-butyllithium (0.9 mmol) in THF–HMPA (4:1, 5 ml) at −76 °C, then a solution of **3** (210 mg, 0.61 mmol) in THF (3 ml) was added and the mixture was stirred at −76 – −55 °C for 2 h. The product **12b**[11] (364 mg, 90%) was isolated by silica gel column chromatography and the unreacted sulfone **11** was recovered (110 mg). The coupling product **12b** (970 mg, 1.45 mmol) in ether (15 ml) was treated with a solution of lithium (298 mg, 43 mmol) in ethylamine (20 ml) at −76 °C for 1.7 h. The reaction was quenched with successive addition of isoprene and methanol, and the crude product was purified on silica gel column (10% ethyl acetate/hexane) to give betulaprenol-6 (**1a**)[12] (542 mg, 88%). The structure of the product was confirmed on the basis of ^{1}H- and ^{13}C-NMR spectra, which were in good agreement with the reported ones.[8,15]

A very similar procedure was applied for the synthesis of (*Z*,*Z*,*E*,*E*)-pentaprenol (**13**)[12] by the coupling of **11** with the chloride **2** (86%) followed by reductive treatment (84%). Pentaprenol **13** was then converted *via* the corresponding chloride into the sulfone **14a**[11] in 71% overall yield. The sulfone was again coupled with **2** (64%) and the resulting coupling product was treated with lithium/ethylamine, furnishing betulaprenol-7 (**1b**)[12] in 77% yield. The IR and NMR spectra of **1b** were in good agreement with the reported ones for the natural product.[2]



Scheme 2.

In order to elaborate a longer cisoid polyprenyl skeletone, betulaprenol-6 (**1a**) was converted to the sulfone **14b**[11] (78%), which was lithiated and coupled with **2**. The coupling product (91%) was treated with lithium in ethylamine – ether, giving betulaprenol-8 (**1c**)[12] (88%). Analogously betulaprenol-9 (**1d**)[12] was prepared using **3** in place of **2** (88%). It should be mentioned that each of betulaprenols prepared as above contained a few per cent of the conjugate reduction products by IR and NMR spectrometry and HPLC analyses, and these contaminants could be eliminated by chromatographic purification of the product using silver nitrate-impregnated silica gel.[16]

In conclusion, stereoselective synthesis of **3** as well as **2** made it possible to attain the first total synthesis of betulaprenols-7, -8, and -9, and a greatly improved synthesis of betulaprenol-6. The present methodology as exemplified above is obviously applicable to the stereocontrolled synthesis of various kinds of natural polyprenols. Further investigation is being undertaken in these laboratories.

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11) All the new compounds were satisfactorily characterized by MS, IR, and ^{1}H-NMR spectra.
12) Spectral data for the selected compounds are as follows.
10: IR(neat) 3350, 1660, 1070, 1000, 740, and 700 cm^{-1}; ^{1}H NMR(CCl_4) δ 1.65 (3H,s), 1.74 (6H,s), 1.95–2.25 (9H,m), 3.92 (2H,d), 3.96 (2H,s), 4.44 (2H,s), 5.07 (1H,bs), 5.15 (1H,bs), 5.35 (1H,t), and 7.21 (5H,s).
3: IR(neat) 1660, 1070, 740, and 700 cm^{-1}; ^{1}H NMR($CDCl_3$) δ 1.67 (3H,s), 1.75 (3H,s), 1.80 (3H,s), 2.07 (8H,s), 3.99 (2H,d), 4.03 (2H,s), 4.49 (2H,s), 5.10 (1H,bs), 5.24 (1H,bs), 5.34 (1H,t) and 7.31 (5H,s).
1a: IR(neat) 3300, 1660, 1000, and 830 cm^{-1}; ^{1}H NMR($CDCl_3$) δ 1.60 (9H,s), 1,69 (9H,s), 1.75 (3H,s), 2.07 (21H,m), 4.09 (2H,d), 5.11 (5H,bs), and 5.45 (1H,t); ^{13}C NMR($CDCl_3$) δ 16.0, 17.7, 23.4, 25.7, 26.3, 26.7, 32.0, 32.2, 39.8, 59.1, 124.2, 124.5, 131.3, 135.0, 135.3, 136.3, and 139.9.
1b: IR(neat) 3320, 1660, 1000, and 830 cm^{-1}; ^{1}H NMR($CDCl_3$) δ 1.60 (9H,s), 1.68 (12H,s), 1.74 (3H,s), 2.05 (25H,m), 4.09 (2H,d), 5.11 (6H,bs), and 5.39 (1H,t); ^{13}C NMR($CDCl_3$) δ 16.0, 17.8, 23.4, 25.7, 26.3, 26.7, 32.0, 32.2, 39.8, 58.9, 124.2, 124.5, 124.9, 131.2, 134.9, 135.3, 136.0, and 139.8; MS(FD) m/z 494(M^+).
1c: IR(neat) 3300, 1665, 1450, 1380, 1000, and 835 cm^{-1}; ^{1}H NMR($CDCl_3$) δ 1.60 (9H,s), 1.68 (15H,s), 1.74 (3H,s), 2.07 (29H,m), 4.08 (2H,d), 5.11 (7H,bs), and 5.42 (1H,t).
1d: IR(neat) 3300, 1660, 1450, 1380, 1000, and 835 cm^{-1}; ^{1}H NMR($CDCl_3$) δ 1.60 (9H,s), 1.68 (18H,s), 1.74 (3H,s), 2.04 (33H,m), 4.09 (2H,d), 5.12 (8H,bs), and 5.44 (1H,t).
13) The stereochemistry of the alcohol **10** was determined[17] by ^{1}H NMR (δ 1.74, CH_3 and 3.96, CH_2) and ^{13}C NMR (δ 61.1, $\underline{C}H_2OH$; cf. δ 65.8 for the (E,Z,Z) isomer), and further confirmed by the ^{1}H-NMR spectrum of the corresponding aldehyde obtained by the oxidation of **10** with active manganese dioxide in hexane at 0 °C (quant.); ^{1}H NMR(CCl_4) δ 1.73 (9H,s), 1.95–2.30 (6H,m), 2.57 (2H,q), 3.89 (2H,d), 4.40 (2H,s), 5.14 (2H,m), 5.35 (1H,t), 6.31 (1H,t), 7.21 (5H,s), and 10.00 (1H,s).
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