Stereospecific Synthesis of (*Z,Z,Z,Z,Z,Z,Z,Z,E,E*)-Undecaprenol (Bacterialprenol) using an all-*cis*-Diterpene Building Block

Kikumasa Sato,* Osamu Miyamoto, Seiichi Inoue, Yasusuke Matsuhashi, Shingo Koyama, and Toshihiko Kaneko

Department of Applied Chemistry, Faculty of Engineering, Yokohama National University, Tokiwadai, Hodogaya-ku, Yokohama 240, Japan

Base-induced coupling of two monoterpene building blocks (**6**) and (**7**) followed by functional group transformations afforded an all-*cis*-diterpene building block (**4**), which was used to effect C_{20} homologation of (*E,E*)-farnesol and (*Z,Z,Z,Z,E,E*)-heptaprenol (betulaprenol-7) (**9**) *via* the corresponding *p*-tolyl sulphones; thus the title undecaprenol (**1**) was synthesised stereospecifically in short steps.

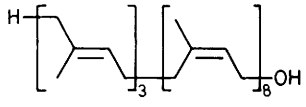
Significant attention has been given to natural polyprenols such as plant polyprenols,[1] bacterialprenol (**1**),[2] and dolichols[3] from biogenetic and biochemical points of view. General synthetic methodology has, however, not been established for these polyprenols except plant polyprenols possessing a relatively short *cis*-polyprenyl backbone.[4,5] Here we report a synthesis of a *cisoid* diterpene building block (**4**) as a synthon of the *cis*-polyisoprene moiety and the first total synthesis of bacterialprenol (**1**).

(*Z,Z*)-8-Benzyloxy-1-tetrahydropyranyloxy-2,6-dimethylocta-2,6-diene (**5**)[6] was deprotected (Na, NH_3, −60 °C, 10 min, 89%) and converted, *via* the chloride [$MeSO_2Cl$, LiCl, *s*-collidine, dimethylformamide (DMF), 0 °C, 2 h], into the sulphone (**6**) (*p*-$MeC_6H_4SO_2Na$, DMF, room temp., 89%), which was coupled with (*Z,Z*)-8-benzyloxy-1-chloro-2,6-dimethylocta-2,6-diene (**7**)[6] [Bu^nLi, tetrahydrofuran–hexamethylphosphoramide (THF–HMPA), −70 °C, 1 h] to give (**2**) in 85% yield. Removal of the tetrahydropyranyl protective group of (**2**) (MeOH, *p*-$MeC_6H_4SO_2OH$, room temp., 5 h, 91%), followed by chlorination ($MeSO_2Cl$, LiCl, *s*-collidine, DMF, 0 °C, 4 h, 87%) afforded the desired chloride (**4**) which was purified by column chromatography on silica gel with isopropyl ether–hexane as eluant.

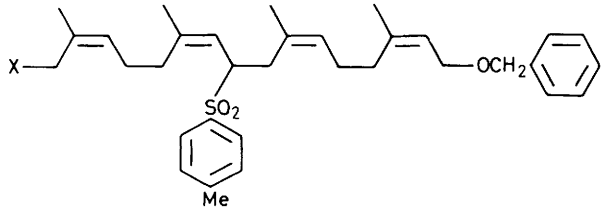
(*E,E*)-Farnesyl *p*-tolyl sulphone (**8**)[7] was lithiated (Bu^nLi, THF–HMPA, −65 °C, 2 h) and then reacted with (**4**) (−65 °C, 1 h) to give the coupling product in 92% yield, which was treated with lithium in ethylamine–diethyl ether (−78 °C, 1 h) affording (*Z,Z,Z,Z,E,E*)-heptaprenol (betulaprenol-7) (**9**)[5,8] in 79% yield. The product was contaminated by the conjugate reduction products[9] ($\Delta^{9,10}$- and $\Delta^{17,18}$-isomers, *ca.* 15%) according to g.c. analysis and n.m.r. spectra. Therefore the alcohol so obtained was purified by column chromatography of the corresponding benzoate ester on silica gel impregnated with silver nitrate. Pure betulaprenol-7 was obtained upon saponification of the purified ester and characterised by the following spectral properties: i.r. (neat) 3300, 1665, 1000, and 830 cm^{-1}; n.m.r. ($CDCl_3$) δ 1.60 (s, 9H, 3 × Me), 1.68 (s, 12H, 4 × Me), 1.74 (s, 3H, 3-Me), 2.03 (br.s, 25H, 6 × CH_2–CH_2 and OH), 4.08 (d, 2H, *J* 7 Hz, CH_2–O), 5.11 (br.s, 6H, vinyl H), and 5.44 (t, 1H, *J* 7 Hz, vinyl 2-H); mass spectrum (field desorption) *m/z* 494 (M^+).

The synthesis of undecaprenol (**1**) from (**9**) was accomplished in a similar reaction sequence to the synthesis of (**9**). The alcohol (**9**) was converted *via* the chloride into the sulphone (**10**) (*p*-$MeC_6H_4SO_2Na$, DMF, 60 °C, 14 h, 90%), which was lithiated and then reacted with (**4**). The coupling product (93%) was subjected to reductive elimination of a benzyl and two *p*-tolylsulphonyl groups to afford undecaprenol (**1**) (78%). The alcohol was purified by medium pressure liquid chromatography of the corresponding benzyl ether on silica gel (Lobar column, Merck) with 2% isopropyl ether–hexane as eluant. Pure undecaprenol (**1**) was regenerated upon reductive fission (Na, NH_3, −70 °C, 10 min) and characterised by the following spectral data: i.r. (neat) 3300, 1660, 1000, and 830 cm^{-1}; n.m.r. ($CDCl_3$) δ 1.60 (s, 9H, 3 × Me), 1.68 (s, 24H, 8 × Me), 1.74 (s, 3H, 3-Me), 2.03 (br.s, 41H, 10 × CH_2CH_2 and OH), 4.09 (d, 2H, *J* 6 Hz, CH_2–O), 5.12 (br. s, 10 H, vinyl H), and 5.45 (t, 1H, *J* 6 Hz, vinyl 2-H); mass spectrum (field desorption) *m/z* 766 (M^+).

The two step reaction sequence described above offers an extremely convenient route for the construction of *cis*-



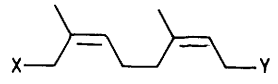
(**1**)



(**2**) X = 

(**3**) X = HO

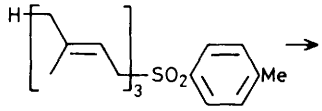
(**4**) X = Cl



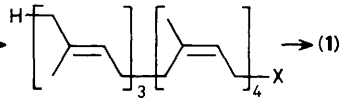
(**5**) X =  , Y = OCH_2Ph

(**6**) X =  , Y = $SO_2C_6H_4Me$-*p*

(**7**) X = Cl, Y = OCH_2Ph



(**8**)



(**9**) X = OH

(**10**) X = $SO_2C_6H_4Me$-*p*

polyisoprene compounds and may find application in the synthesis of dolichols.

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