Stereoselective Total Synthesis of (*S*)-(−)-Dolichol-20

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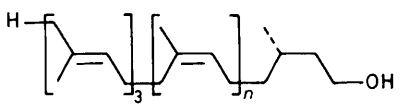
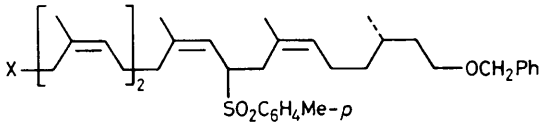
A stereoselective synthesis of (*S*)-(−)-dolichol-20 (**1a**) was achieved using (*Z,Z,Z,Z,Z,Z,Z,Z,E,E*)-undecaprenol (**11**), the C_{20} block (**5**), and the optically active C_{25} block (**3**) as the key building blocks.

Dolichols (**1**)[1,2] have been isolated from yeast and various mammalian tissues, and shown to participate as carbohydrate carriers in the biosynthesis of glycoproteins. In particular (*S*)-(−)-dolichol-20 (**1a**) is the main component of dolichols obtained from human tissue. Here we report a synthesis of the optically active C_{25} block (**3**) and the first total synthesis of (*S*)-(−)-dolichol-20 (**1a**) by a convergent strategy utilizing the C_{20} (**5**) and the C_{25} (**3**) building blocks.

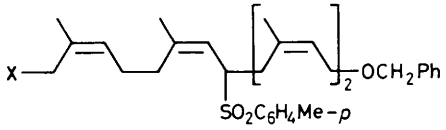
We have already reported the synthesis of undecaprenol (**11**),[5] in which the polyprenyl backbone was constructed by



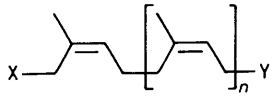
(1) n = 9-18
(1a) n = 16, (S)-(-)-dolichol-20



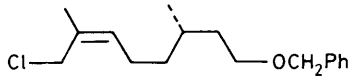
(2) X = THPO
(3) X = Cl



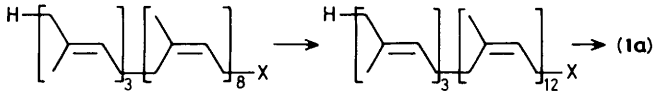
(4) X = THPO
(5) X = Cl



(6) n = 1, X = THPO, Y = $SO_2C_6H_4Me$-p
(7) n = 1, X = Cl, Y = OCH_2Ph
(8) n = 2, X = THPO, Y = OCH_2Ph
(9) n = 2, X = THPO, Y = $SO_2C_6H_4Me$-p



(10)



(11) X = OH
(12) X = $SO_2C_6H_4Me$-p
(13) X = OH
(14) X = $SO_2C_6H_4Me$-p

the conventional coupling reaction between allylic sulphones and allylic halides using n-butyl-lithium at low temperature. In this paper we exploit the usefulness of a phase transfer-catalysed coupling reaction for various terpenoid building blocks. Thus, the sulphone (**6**)[5] was treated with the chloride (**7**)[3] in the presence of tetra-n-butyl ammonium bromide (TBAB) (5 mol% with respect to sulphone) and 50% aqueous sodium hydroxide at room temperature for 6 h to give (**4**) in 88% yield.

The optically active C_{10} block (**10**) was prepared from (*S*)-(−)-citronellol (94% enantiomeric excess, e.e.) by a similar route to (**7**). The C_{15} block (**8**)[4] was deprotected (Na, NH_3, −65 °C, 5 min, 88%) and converted *via* the chloride [$MeSO_2Cl$, LiCl, *s*-collidine, dimethylformamide (DMF), 0—5 °C, 2.5 h] into the sulphone (**9**) (p-$MeC_6H_4SO_2Na$, DMF, room temp., 19 h) in 63% yield, which was coupled with (**10**) (TBAB, 50% aq. NaOH, room temp., 1 h) to give (**2**) in 70% yield. Removal of the tetrahydropyranyl (THP) protecting group of (**2**) (MeOH, p-$MeC_6H_4SO_2OH$, room temp., 23 h, 89%), giving the corresponding alcohol, $[\alpha]_D^{18}$ −1.22° (*c* 0.98, $CHCl_3$), followed by chlorination ($MeSO_2Cl$, LiCl, *s*-collidine, DMF, 2—4 °C, 5 h) afforded the desired chloride (**3**), which was used without purification in the next reaction.

(*Z*,*Z*,*Z*,*Z*,*Z*,*Z*,*Z*,*Z*,*E*,*E*)-Undecaprenol (**11**)[5] was converted *via* the chloride ($MeSO_2Cl$, LiCl, *s*-collidine, DMF, 3—6 °C, 5 h) into the sulphone (**12**) (p-$MeC_6H_4SO_2Na$, DMF, room temp., 14 h) in 68% overall yield. This sulphone (**12**) was treated with the C_{20} block (**5**)[5] (TBAB, 50% aq. NaOH, room temp., 1 h) to give the coupling product in 79% yield, which was treated with lithium in ethylamine–diethyl ether (−70 °C, 1.5 h) affording (*Z*,*Z*,*Z*,*Z*,*Z*,*Z*,*Z*,*Z*,*Z*,*Z*,*Z*,*E*,*E*)-pentadecaprenol (**13**) in 75% yield.

The synthesis of dolichol-20 (**1a**) from (**13**) was accomplished in a similar reaction sequence to the synthesis of (**13**). The alcohol (**13**) was converted *via* the chloride into the sulphone (**14**) in 60% overall yield, which was treated with the optically active C_{25} block (**3**) (TBAB, 50% aq. NaOH, room temp., 1 h) to give the coupling product in 71% yield. The coupling product was subjected to reductive elimination of a benzyl and two p-tolylsulphonyl groups to afford (*S*)-(−)-dolichol-20 (**1a**) (68%). The dolichol-20 obtained was characterized by the following spectral properties: i.r. (neat) 3300, 1660, 1040, and 830 cm^{-1}; n.m.r. ($CDCl_3$) δ 0.89 (d, 3H, *J* 6 Hz), 0.90—1.70 (m, 5H), 1.59 (s, 9H), 1.66 (s, 51H), 2.01 (br.s., 75H), 3.66 (t, 2H, *J* 7 Hz), and 5.11 (br.s, 19H); mass spectrum (field desorption) *m/z* 1380 (M^+).

In conclusion, the use of the C_{20} block (**7**) and the optically active C_{25} block (**3**) as the key building blocks and the use of the phase transfer catalyst made it possible to elaborate the *cis*-polyprenyl frameworks effectively in a stereospecific manner and attain the first stereoselective total synthesis of (*S*)-(−)-dolichol-20. This methodology is obviously applicable to the stereocontrolled syntheses of various kinds of natural polyprenols.

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