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NOVEL APPROACH TO THE STEREOSELECTIVE SYNTHESIS OF POLYPRENOLS VIA DIRECTED ALDOL CONDENSATION. PREPARATION OF HEPTAPRENOLS ωtttcccOH AND ωtttcctOH.

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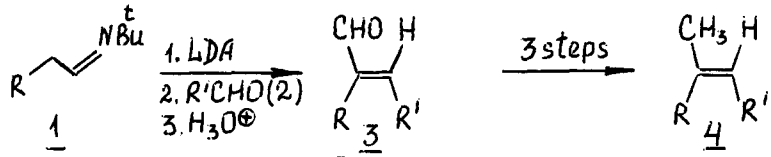
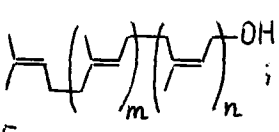
Abstract. New convenient and stereoselective route to linear isoprenoids including the construction of Z-trisubstituted double bond is elaborated based on directed aldol condensation.

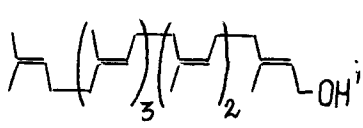
We have previously reported[1] that the directed aldol condensation[2] of α-lithated aldimines 1 with aldehydes 2 is highly stereoselective, even when R and R' are longchain alkyles, due to the thermodynamic preference of E-disubstituted acroleins 3[3,4]



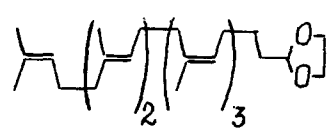
Keeping in mind well documented[5] reductive transformation of aldehydes 3 into hydrocarbons 4 we supposed that suitably chosen components of the sequence 1 + 2 → 3 → 4 will permit to elaborate new, convenient and stereoselective route to linear isoprenoids containing Z-trisubstituted double bonds. Here we reported the adaptation of this approach for the synthesis of polyprenols 5[6], the membrane soluble carbohydrate carriers essential for the biosynthesis of bacterial polysaccharides as well as of pro- and eucariotic glycoproteins. This communication deals with the synthesis of heptaprenol ωtttcccOH 5a, its Δ^2-isomer (5b) and protected aldehyde 6 which can be used as a substrate for the synthesis of higher polyprenols according to this approach.



5 m = 2,3; n ≥ 3.
5a m = n = 3.



5b



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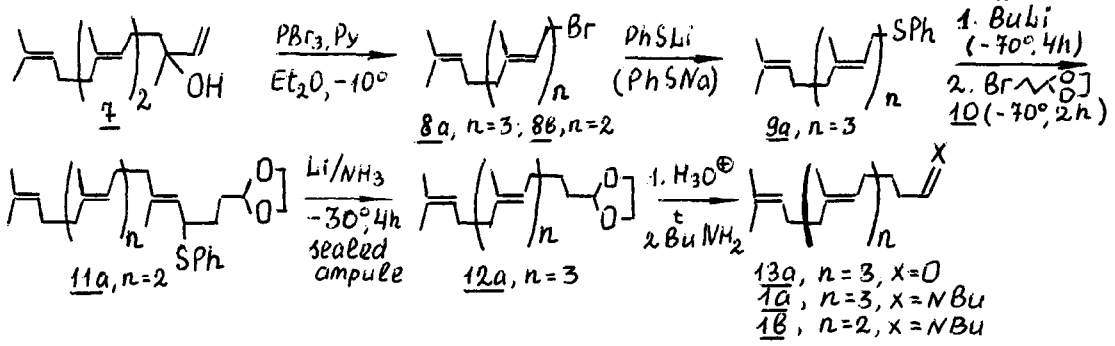
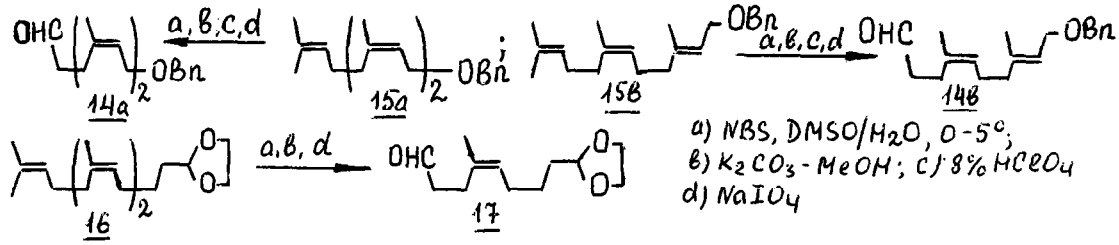
Scheme 1 outlines the sequence of reactions leading to aldimine 1a starting from geranyllinalool 7. The transformation of 7 into primary bromide 8a[7a] proved to be not stereoselective contrary to the earlier claims [7,8]. We obtained 8a (80%) as the 3:1 mixture of E:Z- Δ^2-isomers[9] and this ratio could not be changed by the variations of temperature, solvent and reagent addition order. The reaction of 8a with PhSLi or PhSNa produced (87%) the 3:1 mixture of E:Z-Δ^2-isomers of sulfide 9a[11] which was enriched by carefull flash-column chromatography up to the ratio 9:1.[13] The treatment of α-lithated 9a with 10 yielded 87% of acetal 11a.[16,17] Its further desulfurisation (without double bond shift, PMR), hydrolysis of resulting acetal 12a[16,17] and amination of the aldehyde 13a[16] lead to aldimine 1a[16] with overall yield (from 7) about 50%. Aldimine 1b was prepared similarly from E,E-farnesylbromide 8b.

Scheme 1



In order to obtain aldehydes 14a,b, the aldehyde components for synthesis of 5a,b, the respective benzyl farnesols 15a,b were oxidised with good yield using the modified van Tamelen's procedure.[18] Similarly, acetal 16 (obtained from Z,Z-farnesylbromide in the same manner as 12a from 8a) was transformed into aldehyde 17, the aldehyde component for synthesis of 6 (Scheme 2).

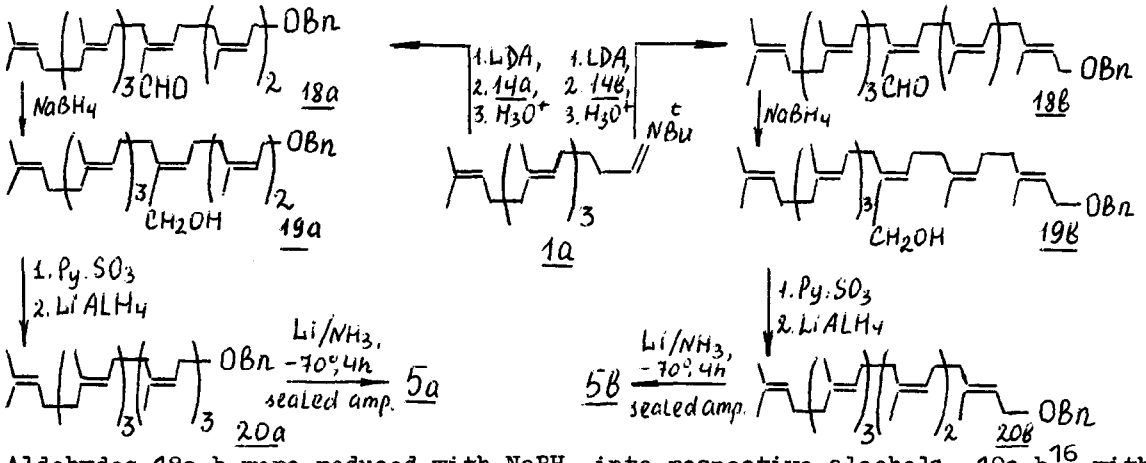
Scheme 2



The crucial steps of the 5a,b synthesis were performed according to scheme 3. Thus, the treatment of aldimine 1a freshly prepared from 11mM 13a with 11mM of LDA in ether-hexan (3:1) solution (1h at -20°, then 1h at 0°, Ar) followed by one-pot reaction of α-Li-1a with 8mM of etheral 14a (2,5h at-70°, then 2h at -30°) gave after hydrolysis of the reaction mixture (5% aqueous oxalic acid), usual treatment and purification by the flash-column chromatography on silica gel (elution from hexan to ether up to 5 vol % of the latter)

the key intermediate 18a[16] in about 55% yield and stereochemical purity > 95% (^1H and ^{13}C NMR data, cf[3]). Aldehyde 18b[16] was obtained (52%) in the similar manner starting from 1a and 14b

Scheme 3



Aldehydes 18a,b were reduced with $NaBH_4$ into respective alcohols 19a,b[16] with about 90% yield. Their hydrogenolysis according to[5a] furnished benzylic ethers 20a,b[16] smoothly debenzilated into desired 5a and 5b. The total yield of the latters was 12-14% starting from geranyllinalool 7. Analogously, condensation of α-Li-aldimine 1b with 17 followed by above transformation of CHO-group to methyl gave 6, a useful synthon for the construction of higher polyprenols according to our scheme.

Thus, the discussed approach might be regarded as an effective route to regular and modified polyprenols for their further biochemical investigations.

References and notes

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13. Fortunately the complete resolution of Δ^2-E:Z - mixture of 9a is not necessary. The Δ^2-Z-contamination in 9a resulted only in ωttccccOH-contamination in the desired heptaprenol ωtttcccOH. This admixture should not affect the biochemical properties of the latter compound, since, according to V.N.Shibaev and others[14], the moraprenol (5, m=3, n=7)is effectively incorporated in the biosynthesis of polyprenols by Salmonella enzymes whose own prenols have structure 5 (m=2, n=8).
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