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SYNTHESIS OF MAMMALIAN DOLICHOLS FROM PLANT POLYPRENOLS

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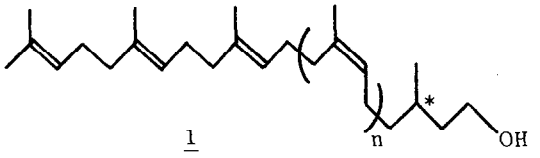
Abstract: Both natural (S)- and unnatural (R)-mammalian dolichols were synthesized for the first time from the mixture of novel polyprenols isolated from *Ginkgo biloba*.

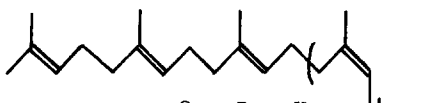
Mammalian dolichols (1) are the mixture of α-saturated optically active (S)-polyprenols,[1] which are present in various mammalian tissues at low concentration (0.04 - 3000 ppm).[2] The nature of 1 and their derivatives as sugar carrier in the biosynthesis of glycoprotein has been well established.[3] For a further biological evaluation, however, the synthesis of optically active dolichols has been longed.



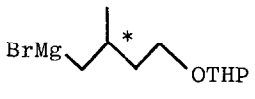
1

n = 12 - 18

We describe herein the first synthesis of 1 starting from a mixture of novel polyprenols 2a isolated from the leaves of *Ginkgo biloba*.[4] The synthesis was achieved by the addition of the optically active saturated isoprene unit to the polyprenyl acetate 2b using a Grignard coupling reaction. In preliminary experiments with a model compound, we found the coupling reaction between neryl acetate and the Grignard reagent 3 proceeded with complete retention of stereo- and regiochemistry of the (Z)-trisubstituted double bond system, when the reaction was carried out in the presence of Li_2CuCl_4 (4 mol% for neryl acetate), at 0°C and in tetrahydrofuran (THF).[5]



2a R = H
2b R = Ac
n = 12-18



3

The alkaline hydrolysis (KOH-MeOH) of the extract (acetone-hexane) of the dried leaves (3.2 kg) collected from *Ginkgo biloba* in November provided the polyprenols 2a (64.2 g) after purification on silica gel column chromatography.[6] The polyprenols 2a were converted to the acetates 2b in 84% yield, which were submitted to the coupling reaction with the Grignard reagent (R)-3 in the following way. To a mixture of a solution of 2b (6.42 g) in THF (15 ml) and 0.1 M solution of Li_2CuCl_4 in THF (2 ml) was added a solution of (R)-3[7], prepared from (R)-2-(4-bromo-3-methylbutoxy)tetrahydro-2H-pyran[8] (2.51 g) and magnesium (0.32 g), in THF (60 ml) at 0°C under argon. The mixture was stirred for 2 h at 0°C and the usual work-up of the reaction mixture afforded the coupling product, which was deprotected with PPTS[9] to give (S)-mammalian dolichols (1) (5.64 g), $[\alpha]_D^{25}$ -0.51° (neat), in 85% yield from the acetates 2b.

The HPLC analyses of the synthetic (S)-1 and 1 isolated from pig liver showed a similar distribution of peaks as shown in Figure 1. These peaks were assigned to the α-saturated polyprenols having different numbers of (Z)-isoprene residues (n) by the field-desorption mass analysis. ^{1}H-NMR, ^{13}C-NMR and IR spectra of the synthetic (S)-1 were entirely identical with those of the pig liver origin.

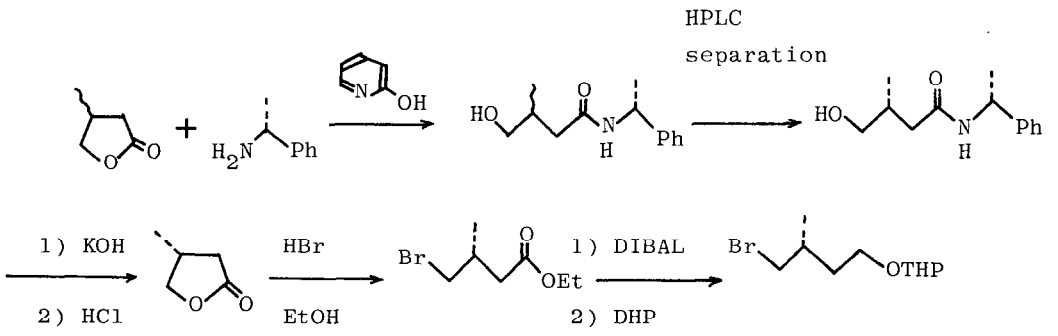
By the same procedure as described above, the unnatural (R)-mammalian dolichols (1), $[\alpha]_D^{25}$ +0.53° (neat), were synthesized using the Grignard reagent (S)-3[10] in 81% yield from the acetates 2b.

The biological activities of these synthetic dolichols are now under investigation.

References and Notes:

1. W. L. Adair, Jr., S. Robertson, *Biochem. J.*, 189, 441 (1980).
2. J. Burgos, F. W. Hemming, J. F. Pennock, R. A. Morton, *ibid.*, 88, 470 (1963).
K. K. Carroll, A. Vilim, M. C. Woods, *Lipids*, 8, 246 (1973).
I. A. Tavares, T. Coolbear, F. W. Hemming, *Arch. Biochem. Biophys.*, 207, 427 (1981).
3. For recent review articles see, *e.g.*
F. W. Hemming, *Bioscience Report*, 2, 203 (1982).
R. J. Staneloni, L. F. Leloir, *CRC Critical Reviews in Biochemistry*, 289

(1982).
J. T. Mills, A. M. Adamany, *International Reviews of Cytology*, 103 (1981).
4. K. Ibata, M. Mizuno, T. Takigawa, Y. Tanaka, *Biochem. J.*, 213, 305 (1983).
5. S. Suzuki, M. Shiono, Y. Fujita, to be published.
6. The chain length distribution of the polyprenols 2a were not changed by the purification procedure.
7. Optical purity of the Grignard reagent was determined 97.6% e.e. by HPLC diastereomer separation of the amide obtained from (R)-(+)-methylbenzylamine, $[\alpha]_D^{20}$ +41.0° (neat), and the citronellic acid which was prepared by the coupling reaction of (R)-3 and prenyl acetate, followed by deprotection and oxidation.
8. This bromide was prepared as follows (Scheme 1): HPLC separation[11] of two diastereomeric amides obtained from (R)-(+)-methylbenzylamine, $[\alpha]_D^{20}$ +40.3° (neat), and β-methyl-γ-butyrolactone was conducted by Waters System 500 on semipreparative column (Prep PAK-500) using EtOAc:*i*-PrOH = 97:3 as an eluent. The less polar amide was subjected to alkaline hydrolysis, followed by acid treatment to give (R)-β-methyl-γ-butyrolactone, b.p. 96-98°C at 24 Torr, $[\alpha]_D^{26}$ +25.7° (c = 4.0, MeOH), which was converted to the bromide by successive treatment with HBr-EtOH, *i*-Bu_2AlH and dihydropyran[12].
9. M. Miyashita, A. Yoshikoshi, P. A. Grieco, *J. Org. Chem.*, 42, 3772 (1977).
10. This Grignard reagent was prepared from (S)-β-methyl-γ-butyrolactone, $[\alpha]_D^{26}$ -25.0° (c = 4.0, MeOH), {lit.[13] $[\alpha]_D^{20}$ -24.7° (c = 4.0, MeOH)}, by the same procedure as described above.
11. G. Helmchew, G. Nill, *Angew. Chem. Int. Ed. Engl.*, 18, 65 (1979).
12. M. Schmid, R. Barner, *Helv. Chim. Acta*, 62, 464 (1979).
13. H. G. W. Leusenberger, W. Boguth, R. Barner, M. Schmid, R. Zell, *ibid.*, 62, 455 (1979).
14. Chromatographic conditions: Column: Nucleosil 5 C_{18}, 10 mm i.d. × 300 mm. Solvent: acetone:methanol = 9:1. Flow rate: 3 ml/min. Detector: RI.



Scheme 1 Preparation of (R)-2-(4-bromo-3-methylbutoxy)tetrahydro-2H-pyran

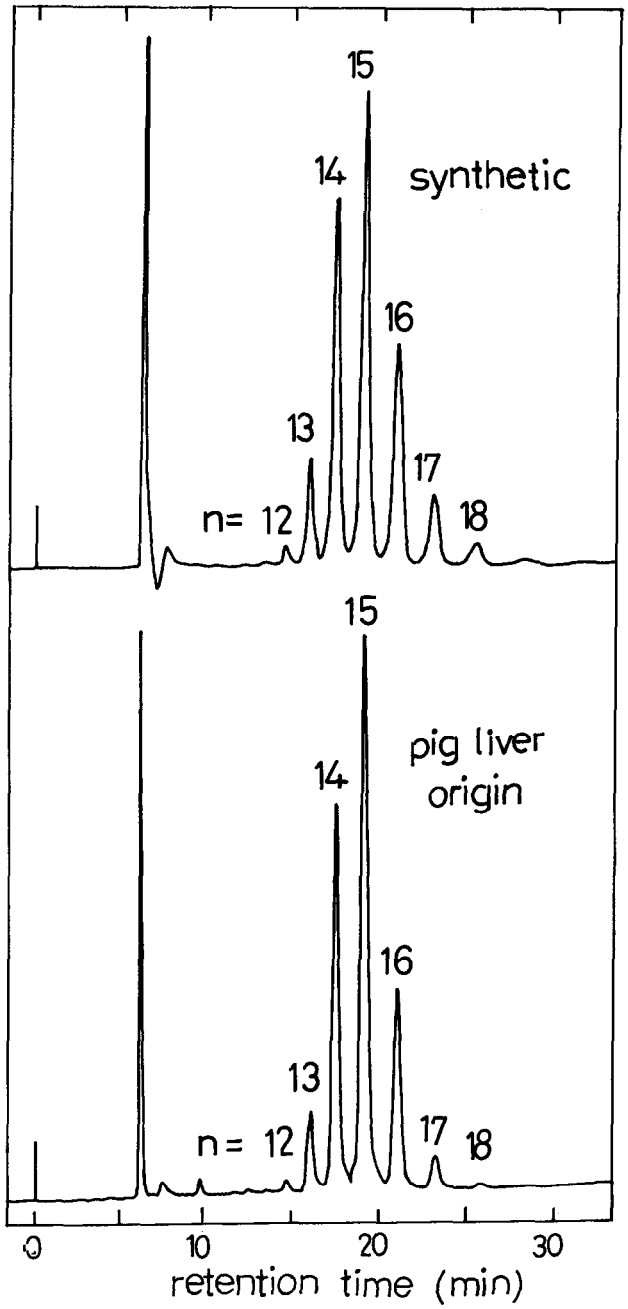


Figure 1 Chromatograms of the dolichols[14]

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