SYNTHESIS OF 3-DESMETHYLHEXAPRENOL WT_3C_2OH

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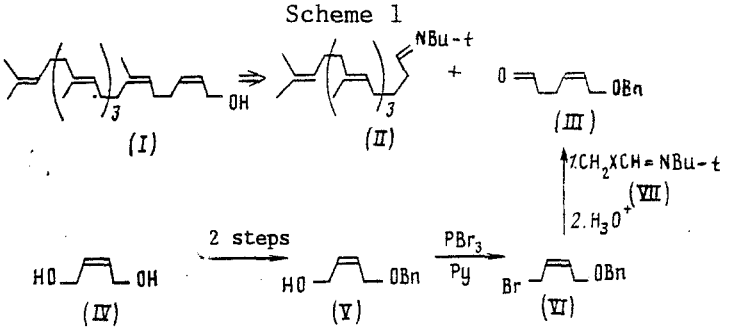
A six-step synthesis of 3-desmethylhexaprenol WT_3C_3OH was carried out in continuation of studies of the relationship between the structure of polyprenols and their biological properties.

In the present article, in continuation of studies of the synthesis of natural and modified polyprenols [1], the preparation of 3-nor-analog (I) of hexaprenol WT_3C_2OH is discussed, which is of interest for investigating the relationship between the structure and the biological activity of polyprenols [2].

In accordance with our previously developed "block" scheme for the synthesis of this group of natural compounds, suitable starting compounds for building up the molecule of (I) are the known aldimine (II) [3] and aldehyde (III). The latter was obtained by an in situ hydrolysis of its corresponding tert-butylimine, a product of alkylation of aldimine (VII; X = H → X = Li) by bromide (VI), which in turn is prepared by a three-step transformation of but-4Z-ene-1,4-diol (IV) via the monobenzyl ether (V) [4] (Scheme 1).

Scheme 1



The retention of the Z-configuration of the disubstituted C=C bond on transition from glycol (IV) to bromide (VI) and further to aldehyde (III) was reliably confirmed by PMR method: the SSCC of the vinyl protons was found to be typical for Z-olefins in its value [5]: J = 10.8 for (VI) and 11.0 Hz for (III). A detailed analysis of the fairly complex spectra of (III), (IV), and (VI) and related compounds will be presented separately.

The condensation of aldehyde (III) with aldimine (II), deprotonated by means of lithium diisopropylamide (LDA), under the previously found conditions [3], leads, after the hydrolytic splitting of the intermediate aldol to E-acrolein (VIII) in a yield of 30%. The stereochemical purity of the latter exceeds 95%, as follows from a comparison of the integral intensities of the CHO group signals of the E- and Z-isomers (δ 9.35 and 10.1 ppm, respectively) in the PMR spectrum (cf. [6]). The stereospecific reduction of (VIII) according to [7], via the stage of the allyl alcohol (IX) into the benzyl ether (X) and debenzylation of the latter brings the synthesis of the desired alcohol (I) to a conclusion, the overall yield of which is 16%, based on aldehyde (III) (Scheme 2).

The structure of the previously unknown compounds (I), (VIII)-(X) was confirmed spectrally, particularly by means of the NMR method. It was thus shown that the spectral parameters of the fragment containing trisubstituted C=C bonds correspond well to those for related structures [3, 8, 9]. The interpretation of the signals of the HC=CH fragment given in the experimental section is based for the protonic spectra on the results of the analysis

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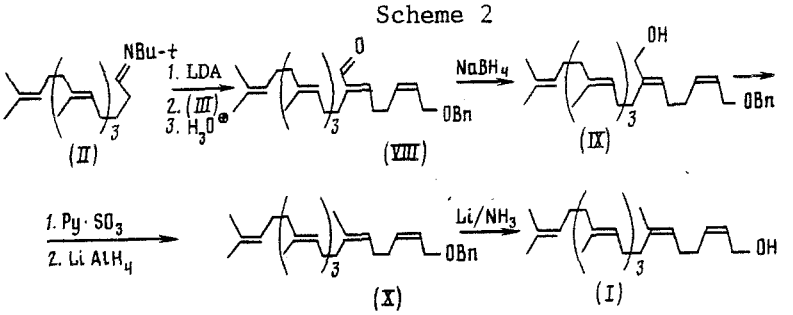
Scheme 2



of (III) and (VI) (see above), and for the carbon spectra, on a comparison of the data for the compounds under consideration and related compounds with an α-isopropene unit [10], taking into account the additive constant of the CH_3 group in olefins.

EXPERIMENTAL

The IR spectra were obtained on a Perkin–Elmer 577 spectrophotometer in thin layer or (for alcohols) in CCl_4 solutions. The mass spectra were measured on a Varian MAT Ch-6 spectrometer at 70 eV, the ^1H NMR spectra in $CDCl_3$ relative to TMS on a Bruker WM-250 spectrometer. The ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer with a working frequency of 75.5 Hz. The preparative chromatography was carried out in a flash variant on silica gel L (40-100 μm), TLC on Silufol plates (CSSR) in a hexane–ether (4:1) system. All the experiments were carried out in an Ar atmosphere, using freshly distilled solvents.

Benzyl Ether of 4-Bromo-2Z-buten-1-ol (VI). A solution of 3.3 ml (34.8 mmoles) of PBr_3 in 20 ml of ether was added in the course of 20 min to a solution of 14.34 g (80.5 mmoles) of (V) [4] and 2 ml (25 mmoles) of C_5H_5N in 160 ml of a hexane–ether (3:1) mixture, stirred without access of light at −10°C. The reaction mixture was allowed to stand for 1 h at −10°C, then was heated to ~20°C, held for another 2 h, and then poured into ice water. After stirring for 15 min, the aqueous layer was separated and extracted with ether. The product (16.33 g), isolated by usual treatment from the combined extracts, was distilled under vacuum. Yield 13.58 g (70%) of (VI) in the form of a colorless oil; bp 78°C (0.02 mm). IR spectrum (ν, cm^{-1}); 3090, 3070, 3040, 2925, 2860, 1500, 1460, 1390, 1345, 1310, 1210, 1100, 1080, 1030, 1015, 950, 910, 890, 820, 740, 705, 615. PMR spectrum* (δ, ppm, J, Hz): 4.01 br. d (2H, J = 8.2, HC^4), 4.18 d.d (2H, J = 6.4 and −1.5 HC^1), 4.56 s (2H, CH_2Ph), 5.79 d.t (1H, J = 10.8 and 6.4 HC^2), 5.93 d.t.t (1H, J = 10.8, 8.2, and −1.5 HC^3), 7.38 m (5H, Ph), ^{13}C NMR spectrum (δ, ppm): 26.52 (C^4), 64.83 (C^1), 72.28 (CH_2Ph), 127.62 (C^3), 131.01 (C^2), 127.62, 128.22, 128.30, 137.85 (Ph). Mass spectrum (m/z): 242, 241 (M^+), 240, 161, 160, 159, 143, 131, 130, 108, 107, 106, 105, 93, 92, 91, 90, 89, 79, 78, 77, 65, 55, 54, 53, 41, 39, 32, 28, 27. Found, %: C 55.36, H 5.60, Br 32.73. $C_{11}H_{13}BrO$. Calculated, %: C 54.79, H 5.43, Br 33.14; mol. wt. 241.1.

6-Benzyloxy-4Z-hexen-1-al (III). A solution of 5.94 g (60 mmoles) of (VII, X = H) in 10 ml of THF was added in the course of 20 min to a solution of LDA (freshly prepared at −15°C from 58 ml of a 1.3 M solution of BuLi (75 mmoles) in hexane and 7 g (70 mmoles) of diisopropylamine and 11 g (60 mmoles) of HMPA in 50 ml of THF, stirred at −5°C. After 45 min, the reaction mixture was cooled to −70°C, then treated in the course of 20 min with a solution of 13.58 g (56.4 mmoles) of (VI) in 20 ml of THF, and stirred for 1 h. After raising the temperature of the mixture to −50°C, it was stirred for another 1 h, and was then decomposed at 0°C with 200 ml of a 10% solution of tartaric acid in water. The reaction mixture was stirred for 45 min at 0°C, and then the aqueous layer was separated and extracted with ether. After the usual treatment of the combined extracts, 12.8 g of an oily product was obtained, which was chromatographed on 200 g of SiO_2. Gradient elution from hexane to ether (up to 30% of the latter) gave 8.39 g (73%) of (III), bp 85-86°C (0.015 mm). IR spectrum (ν, cm^{-1}): 3090, 3060, 3020, 2920, 2890, 2860, 2830, 2720, 1725, 1495, 1455, 1410, 1390, 1350, 1310, 1250, 1200, 1090, 1075, 1030, 940, 905, 850, 740, 700, 605. PMR spectrum (δ, ppm, J, Hz): 2.37 m (2H, HC^3), 2.50 m (2H, HC^2), 4.11 d.d (2H, J = 6.5 and −1.1, HC^6), 4.52 s (2H, CH_2Ph), 5.57 d.t.t (1H, J = 11.0, 7.0, and −1.1, HC^4), 5.68 d.t.t (J = 11.0, 6.5, and −1.1, HC^5), 7.34 m (5H, Ph), 9.72 t (1H, J = 1.5, HC^1). ^{13}C NMR spec-

*A detailed analysis of the PMR spectra of compounds (III), (VI), and related compounds will be given in a special article.

trum (δ, ppm): 20.05 (C^3), 43.07 (C^2), 65.28 (C^8), 71.88 (CH_2Ph), 127.31 (C^5), 130.83 (C^4), 127.31, 127.42, 128.06, 138.08 (Ph), 201.05 (C^1). Mass spectrum (m/z): 204 (M^+), 161, 160, 159, 134, 113, 108, 107, 106, 105, 104, 98, 96, 95, 93, 92, 91, 90, 89, 85, 83, 81, 80, 79, 78, 77, 69, 68, 67, 65, 57, 55, 54, 53, 52, 51, 45, 44, 43, 42, 41, 39, 32, 29, 28, 27, 18, 17, 16. Found, %: C 76.32, H 7.88. $C_{13}H_{16}O_2$. Calculated, %: C 76.44, H 7.89; mol. wt. 204.3.

Benzyl Ether of 11,15,19,23-Tetramethyl-7-formyltetraeicosa-2Z,6E,10E,14E,18E,22-hexaen-1-ol (VIII). A solution of 5.39 g (14 mmoles) of (II) [3] in 10 ml of ether was added in the course of 20 min to a solution of LDA (18 mmoles) in 108 ml of an ether–hexane (5:1) mixture, stirred at −5°C. After 45 min, the mixture was cooled to −70°C and was reacted for 20 min with a solution of 2.45 g (12 mmoles) of (III) in 5 ml of ether. The reaction mixture was stirred for 2.5 h at −70°C, and then after bringing the temperature in the course of 40 min to −10°C, it was cautiously poured into a mixture of 100 ml of ether and a solution of 8.4 g (67 mmoles) of $(COOH)_2 \cdot 2H_2O$ in 160 ml of water, cooled to 5°C. After 1.5 h, the aqueous layer was separated and extracted with ether. By the usual treatment of the combined extracts, 7.27 g of an oily product was obtained, which was chromatographed on 150 g of SiO_2. Gradient elution from hexane to ether (up to 20% of the latter) gave 1.94 g (30%) of (VIII), bp (bath) 215-217°C (0.018 mm). IR spectrum (ν, cm^{-1}): 3090, 3060, 3020, 2960, 2920, 2850, 2705, 1690, 1640, 1490, 1450, 1380, 1330, 1310, 1250, 1200, 1140, 1090, 1070, 1030, 835, 735, 700. UV spectrum (EtOH): λ_{max} 230 nm (log ε 4.053). PMR spectrum (δ, ppm, J, Hz): 1.57 s (3H, CH_3C^{11}), 1.61 s (9H, cis-CH_3), 1.70 s (3H, trans-CH_3–C^{23}), 2.05 m (14H, CH_2), 2.27 m (4H, $HC^{4,8}$), 2.43 m (2H, HC^5), 4.09 d (2H, J = 6.5, HC^1), 4.52 s (2H, CH_2Ph), 5.12 m (4H, HC=C), 5.66 br.d.t (1H, J = 11.0 and 7.0 HC^3), 5.72 br.d.t (1H, J = 11.0 and 6.5, HC^2), 6.42 t (1H, J = 7.5, HC^6), 7.32 m (5H, Ph), 9.35 s (1H, CHO). ^{13}C NMR spectrum (δ, ppm): 16.03 ($\underline{C}H_2$–$C^{11,15,19}$), 17.71 (cis-$\underline{C}H_3$–C^{23}), 24.30 (C^8), 25.72 (trans-$\underline{C}H_3$–C^{23}), 26.68, 26.78 ($C^{9,13,17,21}$), 26.97 (C^5), 28.79 (C^4), 39.76 ($C^{12,16,20}$), 65.62 (C^1), 72.38 (CH_2Ph), 123.29, 124.20, 124.32, 124.48 ($C^{10,14,18,22}$), 128.50 (C^3), 131.40 (C^{23}), 131.72 (C^2), 127.76, 127.82, 128.50, 138.00 (Ph), 134.98, 136.21 ($C^{11,15,19}$), 143.84 (C^7), 153.74 (C^6), 195.08 (CHO). Mass spectrum (m/z): 517, 516 (M^+), 499, 498, 473, 447, 425, 409, 408, 407, 379, 339, 337, 297, 284, 283, 279, 273, 271, 257, 253, 243, 229, 217, 215, 213, 211, 204, 191, 189, 161, 149, 137, 136, 135, 123, 121, 119, 109, 107, 105, 95, 93, 92, 91, 81, 79, 77, 69, 68, 67, 57, 55, 43, 41, 32, 29, 28, 18. Found, %: C 83.73, H 10.13. $C_{36}H_{52}O_2$. Calculated, %: C 83.70, H 10.14; mol. wt. 516.8.

Benzyl Ether of 7-Hydroxymethyl-11,15,19,23-tetramethyltetraeicosa-2Z,6E,10E,14E,18E,22-heaen-1-ol (IX). A 0.133 g portion (3.5 mmoles) of $NaBH_4$ was added in the course of 10 min to a solution of 1.52 g (2.94 mmoles) of (VIII) in 90 ml of EtOH, stirred at 0°C. The mixture was allowed to stand at ~20°C for 1.5 h, and was then decomposed at 0°C with 0.1 g (1.6 mmoles) of AcOH. Following the usual treatment, 1.46 g (96%) of (IX) was obtained in the form of a colorless oil. R_f 0.12. IR spectrum (ν, cm^{-1}): 3620, 3090, 3070, 3035, 2970, 2930, 2915, 2860, 2735, 1665, 1500, 1450, 1380, 1370, 1310, 1245, 1205, 1110, 1090, 1070, 1030, 1010, 945, 845, 780, 700. PMR spectrum (δ, ppm, J, Hz): 1.60 s, 12H, cis-CH_3), 1.70 s (3H, trans-CH_3), 2.15 m (20H, CH_2), 3.99 s (2H, $C\underline{H}_2OH$), 4.04 d (2H, J = 5.5, HC^1), 5.10 m (4H, HC=C), 5.37 t (1H, J = 7.5, HC^6), 5.57 and 5.62 m (2H, J_{HC^2,HC^3} = 11.0, HC^2, HC^3), 7.35 m (5H, Ph). ^{13}C NMR spectrum (δ, ppm): 16.03 (CH_3–$C^{11,15,19}$), 17.69 (cis-$\underline{C}H_3$–C^{23}), 25.70 (trans-$\underline{C}H_3$–C^{23}), 26.87, 26.79, 27.02, 27.30, 27.70, ($C^{5,9,13,17,21}$), 28.28 (C^4), 39.74 ($C^{12,16,20}$) 65.71 (C^1), 67.03 (CH_2OH), 72.21 (CH_2Ph), 123.86, 124.11, 124.26, 124.43 ($C^{10,14,18,22}$), 125.87 (C^6), 126.57 (C^2), 127.63, 127.80, 128.37, 138.30 (Ph), 131.21 (C^{23}), 132.90 (C^3), 134.90, 135.03, 135.62 ($C^{11,15,19}$), 139.73 (C^7). Mass spectrum (m/z): 518 (M^+), 500, 431, 427, 410, 409, 393, 392, 349, 341, 339, 323, 321, 282, 273, 271, 255, 192, 191, 189, 187, 183, 177, 176, 175, 173, 163, 161, 159, 149, 145, 143, 137, 136, 135, 133, 123, 121, 119, 107, 105, 95, 93, 92, 91, 81, 79, 77, 70, 69, 68, 57, 55, 53, 43, 41, 32, 28, 18.

Benzyl Ether of 7,11,15,19,23-Pentamethyltetraeicosa-2Z,6Z,10E,14E,18E,22-hexaen-1-ol (X). A 0.72 g portion (4.5 mmoles) of Py·SO_3 [11] was added in the course of 15 min to a solution of 1.4 g (2.7 mmoles) of (IX) in 45 ml of THF, stirred at 0°C. The reaction mixture was allowed to stand for 2 h at 0°C, and then was reacted for 20 min at −30°C with a 1.6 M solution of $LiAlH_4$ in THF (13.1 ml, 21 mmoles). After stirring at ~20°C for 3 days, the reaction mixture was treated as described in [3]. Yield 1.11 g of an oily product, which was chromatographed on 60 g of SiO_2. Gradient elution from hexane to ether (up to 5% of the latter) gave 0.89 g (65.5%) of (X); R_f 0.86. IR spectrum (ν, cm^{-1}): 3090, 3060,

3030, 2960, 2920, 2850, 1660, 1490, 1450, 1375, 1350, 1310, 1200, 1110, 1090, 1070, 1030, 835, 735, 695. PMR spectrum (δ, ppm, J, Hz): 1.62 s (12H, cis-CH_3), 1.71 s (6H, trans-CH_3), 2.1 m (20H, CH_2), 4.10 d (2H, J = 5.0, HC^1), 5.11 m (5H, HC=C), 5.56 m (2H, J_{HC^2,HC^3} = 11.0, HC^2, HC^3), 7.35 m (5H, Ph). ^{13}C, NMR spectrum (δ, ppm): 16.09 ($\underline{C}H_3$–$C^{11,15,19}$), 17.77 (cis-$\underline{C}H_3$–C^{23}), 25.53 (trans-$\underline{C}H_3$–C^{23}), 25.79 ($\underline{C}H_3$–C^7), 26.64, 26.73, 26.85, 27.84 ($C^{5,9,13,17,21}$), 28.15 (C^4), 32.08 (C^8), 39.82 ($C^{12,16,20}$), 65.68 (C^1), 72.15 (CH_2Ph), 124.17, 124.30, 124.44, 124.49 ($C^{6,10,14,18,22}$), 126.40 (C^2), 127.63, 127.83, 128.44, 138.8 (Ph), 131.32 (C^{23}), 133.43 (C^3), 134.97, 135.06, 135.30, 136.00 ($C^{7,11,15,19}$). Mass spectrum (m/z): 503, 502 (M^+), 433, 412, 411, 394, 383, 382, 365, 325, 282, 257, 191, 189, 175, 173, 163, 161, 159, 149, 147, 137, 136, 135, 133, 123, 121, 119, 109, 108, 107, 105, 95, 93, 91, 81, 79, 70, 69, 68, 67, 57, 55, 53, 43, 41, 28.

7,11,15,19,23-Pentamethyltetraeicosa-2Z,6Z,10E,14E,18E,22-hexaen-1-ol (I). A solution of 0.86 g (1.7 mmoles) of (X) in 2 ml of ether was added in the course of 2 min to a solution of 0.2 g (28.6 mg-at) of Li in 100 ml of NH_3, stirred at −35°C. The reaction mixture was held at the above temperature for 5 h, and after adding excess of NH_4Cl and NH_3, it was evaporated. Following the usual treatment of the residue, 0.68 g of an oily product was isolated, which was chromatographed on 50 g of SiO_2. Elution from hexane to ether (up to 20% of the latter) gave 0.58 g (82%) of (I), bp (bath) 198°C (0.018 mm). IR spectrum (ν, cm^{-1}): 3630, 3020, 2970, 2935, 2925, 2860, 2735, 1670, 1450, 1380, 1330, 1310, 1180, 1150, 1110, 1080, 1030, 990, 980, 930, 910, 845. PMR spectrum (δ, ppm, J, Hz): 1.60 s (12H, cis-CH_3), 1.70 s (6H, trans-CH_3), 2.0 m (20H, CH_2), 4.18 d (2H, J = 6.0, HC^1), 5.1 m (5H, HC=C), 5.52 and 5.63 m (2H, JHC^2 HC^3 = 11.0, HC^2, HC^3). ^{13}C NMR spectrum (δ, ppm): 16.05 ($\underline{C}H_3$–$C^{11,15,19}$), 17.73 (cis-$\underline{C}H_3$–C^{23}), 23.46 ($\underline{C}H_3$–C^7), 25.73 (trans-$\underline{C}H_3$–C^{23}), 26.43, 26.60, 26.82, 27.77, 27.90 ($C^{4,5,9,13,17,21}$), 32.06 (C^9), 39.79 ($C^{12,16,20}$), 58.56 (C^{-1}), 124.10, 124.20, 124.31, 124.46 ($C^{6,10,14,18,22}$), 128.82 (C^2), 131.28 (C^{23}), 132.59 (C^3), 134.94, 135.03, 135.31, 136.24 ($C^{7,11,15,19}$). Mass spectrum (m/z): 413, 412 (M^+), 394, 369, 344, 343, 341, 325, 301, 285, 275, 273, 272, 259, 257, 233, 231, 229, 217, 215, 204, 191, 189, 177, 175, 163, 161, 149, 147, 137, 136, 135, 133, 123, 121, 119, 109, 107, 105, 95, 93, 91, 81, 79, 77, 70, 69, 68, 67, 57, 55, 53, 43, 41, 32, 28. Found, %: C 83.98, H 11.51. $C_{29}H_{48}O$. Calculated, %: C 84.40, H 11.72.

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