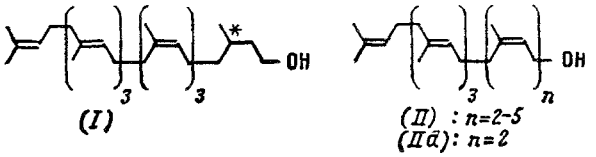
STEREOSELECTIVE SYNTHESIS OF A DOLICHOL-LIKE OCTAPRENOL (S)-WT_3C_3SOH

N. Ya. Grigor'eva, O. A. Pinsker,
E. D. Daeva, and A. M. Moiseenkov

UDC 541.63:542.91:541.64:547.366

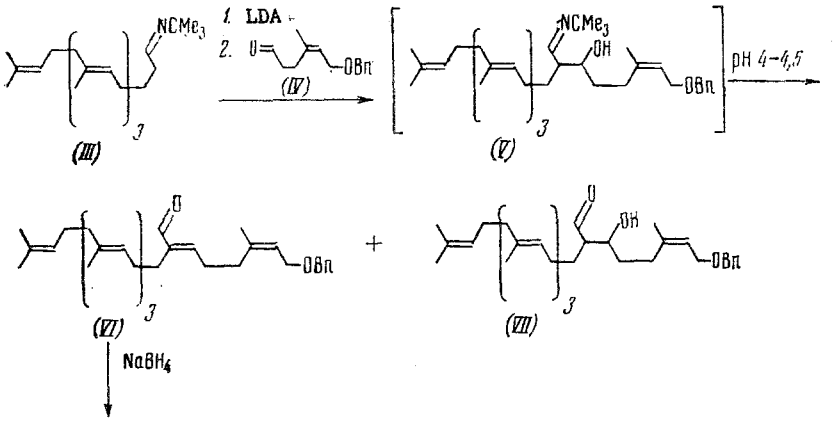
In accordance with the previously developed block method of constructing polyprenol molecules, a new stereospecific synthesis was carried out of their natural representative WT_3C_2OH, which was then converted in nine steps into the above chiral octaprenol. At the same time the synthesis of the racemate of the latter has been improved.

We have previously reported on the synthesis of racemic octa-(WT_3C_3SOH) and nonaprenol WT_3C_4SOH, related to dolichols of mammals [1]. The present article is devoted to the construction of an octaprenol molecule WT_3C_3SOH (I) with the natural (S)-configuration of the saturated α-unit. Recent reports [2] on the high pharmacological activity of the group of polyprenols of the general formula (II) isolated from a palm juice Serenoa repens, prompted us to carry out the synthesis of (I) via the stage of hexaprenol WT_3C_2OH (IIa).



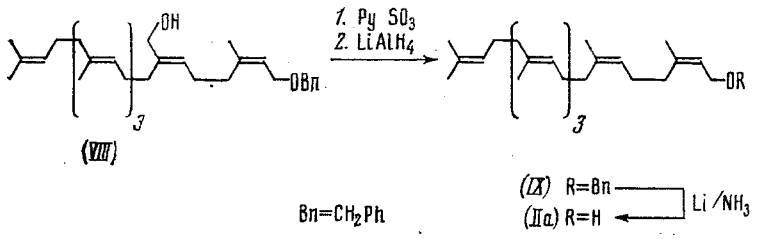
(I) (II): n=2-5 (IIa): n=2

The latter was obtained using the block method of synthesis of polyprenols that we have developed [3-5] starting, from aldimine (III) [3] and aldehyde (IV) [6] (scheme 1). Thus, the condensation of aldimine (III), deprotonated by the action of lithium diisopropyl amide (LDA), with (IV) leads, after weak acid treatment of the intermediate β-oximine (V) (oxalate buffer, pH 4-4.5) to a chromatographically readily separable mixture of E-acrolein (VI) and β-hydroxyaldehyde (VII) in a ratio of ≈4:3. The use of more acidic (1% HCl) conditions of splitting (V) makes it possible to minimize the proportion of (VII) in the mixture, and to isolate the E-acrolein (VI) in a 58% yield and with a stereochemical purity of >95% with respect to the newly formed C=C bond, as follows from comparison in the PMR spectrum of (VI) of the integral intensity of the CHO group signals for its E and Z isomers, δ 9.35 and 10.1 ppm, respectively (cf. [7]). By reductive transformation of E-acrolein (VI) according

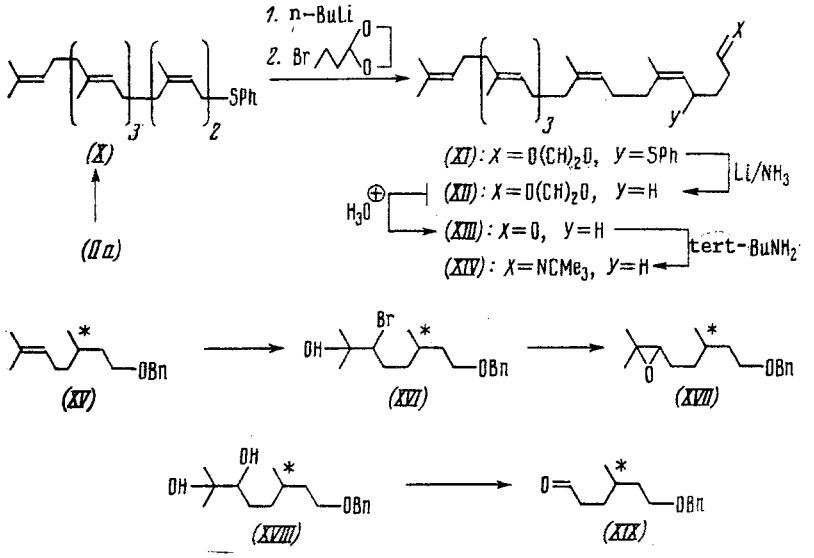


N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 10, pp. 2325-2333, October, 1991. Original article submitted March 12, 1991.

0568-5230/91/4010-2037$12.50



to Corey [8] via the stage of the E-allyl alcohol (VIII) and its corresponding sulfonate, the benzyl ether (IX) was obtained with complete retention of the configuration of the Δ^6 double bond. Ether (IX) was smoothly debenzylated by means of Li in NH_3 into the desired hexaprenol WT_3C_2OH (IIa), identical in its spectral characteristics to a sample of this compound previously prepared in accordance with the stepwise scheme described in [4]. The transformation of (IIa) into allyl sulfide (X) and its subsequent C_3 homologization by means of 3-bromopropionaldehyde ethyleneacetal leads to thioether (XI), the reductive desulfurization of which gave acetal (XII), which, in turn, by a standard sequence of transformations was converted into aldehyde (XIII) and subsequently into aldimine (XIV) (scheme 2).

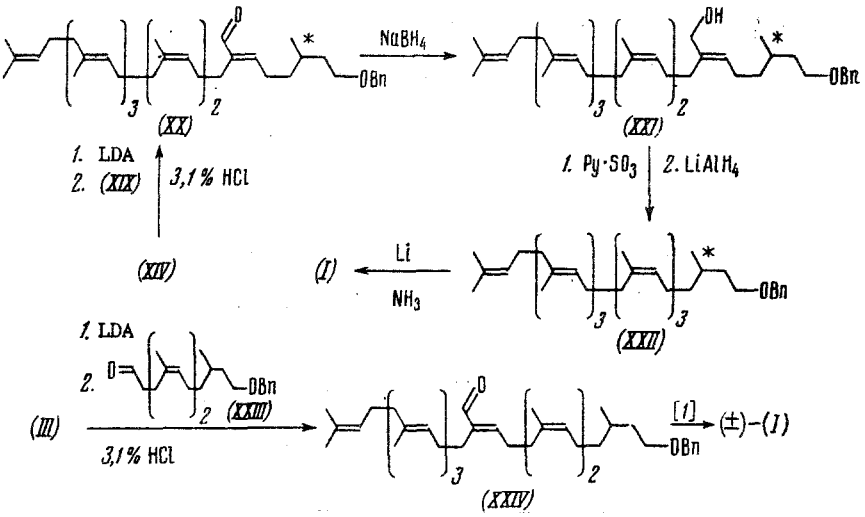


The (S)-C_7-aldehyde block synthone (XIX), complementary to aldimine (XIV) in the synthesis of the molecule of (S)-octaprenol (I) according to the adopted block scheme, was prepared (scheme 2) by the oxidative splitting of the benzyl ether of (S)-citronellol (XV) [9], according to van Tamelen [10] via the stages of bromohydrin (XVI), epoxide (XVII) and diol (XVIII) in an overall yield of 53%.

The final step in the synthesis of the chiral prenol (I) consists in the condensation of aldimine (XIV), deprotonated by means of LDA, with aldehyde (XIX) (scheme 3) as a result of which E-acrolein (XX) was obtained in a 40% yield, with a stereochemical purity of ≥95% with respect to the Δ^6 double bond (PMR data). Its further reductive transformation via the steps of E-allyl alcohol (XXI), its corresponding sulfonate, and finally the benzyl ether (XXII), gives, as described above for (IIa), the desired (S)-octaprenol (I) in an overall yield of 12.5%, based on hexaprenol (IIa) (see scheme on following page).

The structure of the previously undescribed compounds (I), (VI)-(XIV), (XVI), (XVIII), (XX)-(XXII), discussed in schemes 1-3 was reliably confirmed by the whole set of spectral data found for them and partially presented in Tables 1 and 2, and conforms well with the data previously found for such structures (cf. [1, 4, 11-13]).

In conclusion, we must note that the application of the fairly rigorous conditions of the hydrolytic splitting of β-oximines of type (V) in the presence of 1% HCl found in the present work, made it possible to improve considerably our previously reported synthesis of (±)-octaprenol (I) [1]. Thus (scheme (3)), under the above conditions, the yield of E-acrolein (XXIV) by the condensation of aldimine (III) with aldehyde (XXIII) could be raised to 40%, compared with 8% when an oxalate buffer was used.



EXPERIMENTAL

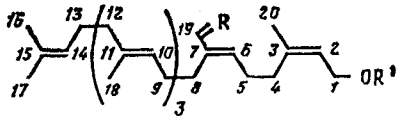
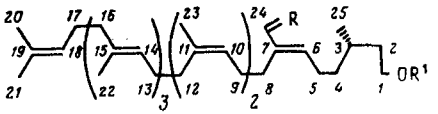
The IR spectra of the solutions in CCl_4 or $CHCl_3$ were obtained on a Perkin-Elmer 577 spectrophotometer, the UV spectra of the alcoholic solutions on a Specord UV-VIS spectrophotometer, the mass spectra at a ionizing voltage of 70 eV on a Varian MAT-CH-6 spectrometer. The ^1H NMR spectra were measured in $CDCl_3$ on a Bruker WM-250 spectrometer with reference to TMS, and the ^{13}C NMR spectra on a Bruker AM-300 spectrometer (75.5 MHz). The spectra of compounds (I), (IIa), (VI), (VIII), (IX), (XX)-(XXII) are given in Table 1, and of compounds (X)-(XIII) in Table 2. The preparative chromatography was carried out in a flash variant on silica gel L (40-100 μm) from the firm "Chemapol". The R_f values are given for a stationary layer of SiO_2 brand "Silufol" from the same firm in an ether–hexane system (1:1), unless otherwise indicated. The high performance liquid chromatography (HPLC) was carried out on a Armopher Si1 column 10.150 × 4 (10 μm) using heptane/ethyl acetate (up to 1.5% of the latter) as eluent, and PIDK-102 detector. The $[\alpha]_D$ values were determined in $CHCl_3$ solutions by means of the Jasco DIP-360 polarimeter.

Benzyl Ether of 3,11,15,19,23-Pentamethyl-7-formyltetraeicosa-2Z,6E,10E,14E,18E,22-hexaen-1-ol (VI) and Benzyl Ether of 6-Hydroxy-3,11,15,19,23-pentamethyl-7-formyltetraeicosa-2Z,10E,14E,18E,22-pentaen-1-ol (VII). A solution of 13.3 g (40 mmoles) of (III) [3] in 35 ml of ether was added in the course of 20 min to a stirred solution at −20°C in an argon atmosphere of LDA (42 mmoles) in an ether–hexane mixture (8:1). The reaction mixture was held for 2 h at 0°C and then was treated at −70°C with a solution of 7.6 g (34.7 mmoles) of (IV) [6] in 20 ml of ether. The mixture was then stirred at this temperature for 2.5 h, warmed in the course of 2 h to ~20°C, allowed to stand overnight, and then was transferred to a mixture of 150 ml of ether and a solution of 13 g of $(COOH)_2 \cdot 2H_2O$ in 150 ml of water cooled to 5°C. The mixture was stirred for 2 h at ~20°C and extracted with ether. The subsequent usual treatment of the extract gave 22 g of an oily product, which was chromatographed on 200 g of SiO_2. Gradient elution from hexane to ether (up to 20% of the latter) gave 5.8 g (32%) of (VI) and 4.3 g (24%) of (VII), both in the form of a colorless oil.

Acrolein (VI). R_f 0.53. IR spectrum (ν, cm^{-1}): 3090, 3060, 3020, 3010, 2960, 2920, 2860, 2720, 1690, 1640, 1490, 1450, 1380, 1360, 1220, 1200, 1140, 1100, 1070, 1030, 720, 700. UV spectrum: λ_{max} 232 nm (log ε 4.07). PMR spectrum (δ, ppm, J, Hz): 1.58 s (3H, Me–C^{11}), 1.6 br. s (9H, cis-Me), 1.69 s (3H, trans-Me–C^{23}), 1.8 s (3H, trans-Me–C^3), 2.05 m (14H, CH_2C=C), 2.25 m (4H, H_2C^8, H_2C^4), 2.45 d.t (2H, H_2C^5, $J_1 = J_2 = 7$), 4.0 d (2H, CH_2OBn, J = 6.8), 4.5 s (2H, CH_2Ph), 5.1 m (4H, HC=C), 5.52 t (1H, HC^2, J = 6.8), 6.4 t (1H, HC^6, J = 7), 7.35 m (5H, Ph), 9.32 s (1H, CHO). Mass spectrum (m/z): 531 (M^+), 530, 512, 487, 461, 439, 422, 374, 353, 305, 285, 271, 243, 204, 136, 108, 91, 68.

Aldol (VII). R_f 0.29. IR spectrum (ν, cm^{-1}): 3485, 3020, 2960, 2920, 2860, 2720, 1720, 1660, 1520, 1450, 1380, 1250, 1210, 1120, 1040, 1020, 960, 940, 910, 840, 730, 660. PMR spectrum (δ, ppm, J, Hz): 1.5 m (4H, CH_2), 1.6 br. s (12H, cis-Me), 1.68 s (3H, trans-Me–C^{23}), 1.75 s (3H, trans-Me–C^3), 2.06 m (16H, CH_2C=C), 2.38 m (1H, HC^7), 3.85 m (1H, CHOH), 4.0 m (2H, CH_2OBn), 4.5 s (2H, CH_2Ph), 5.1 m (4H, HC=C), 5.5 m (1H, HC^2), 7.35 m (5H, Ph), 9.68 d and 9.72 d (1H, CHO, $J_1 \approx 3.5$, $J_2 \approx 3$).

TABLE 1. ^{13}C NMR Spectra of Compounds (I), (IIa), (VI), (VIII), (IX), (XX)-(XXII)

C atom No.					C atom No.				
	R=O R^1=Bn[a] (VI)	R=H, OH R^1=Bn[a] (VIII)	R=H, H R^1=Bn[a] (IX)	R=H, H R^1=H (IIa)		R=O R^1=Bn[a] (XX)	R=H, OH R^1=Bn[a] (XXI)	R=H, H R^1=Bn[a] (XXII)	R=H, H R^1=H (I)
1	66,2	66,2	66,5	59,0	1	68,4	68,9	68,8	61,4
2	123,2[b]	122,1	121,9	124,2[b]	2	36,2[b]	36,7[b]	36,8[b]	40,2
3	136,4	138,4	140,5	139,9	3	29,8	29,7[b]	29,7[b]	29,7
4	31,1	32,1	32,2	31,9	4	36,7[b]	37,1	37,6	37,7
5	27,45[c]	27,6[c]	26,5[c]	26,7[c]	5	26,5[c]	26,5[c]	25,4	25,4
6	153,9	125,8[b]	124,1[b]	124,2[b]	6	155,5	124,4[d]	124,3[c]	124,5[b]
7	143,5	139,9	134,8[d]	134,8[d]	7	143,2	138,6	134,9[d]	135,1[c]
8	24,3	28,2	32,5	32,2	8	24,5	28,4	32,0	32,2
9[e]	27,1[c]	27,0[c]	26,7[c]	26,6[c]	9[f]	26,7[c]	26,6[c]	26,2[g]	26,6[d]
10[e]	123,4[b]	123,8[b]	124,3[b]	124,4[b]	10[f]	124,3[d]	124,2[d]	124,3[c]	124,5[b]
11[e]	135,5	134,9	135,2[d]	134,9[d]	11[f]	135,0[g]	135,0[f]	135,0[d]	135,1[c]
12[e]	39,6	39,7	39,7	39,7[c]	12[f]	32,1	32,1	32,3	32,2
13	26,8[c]	26,7[c]	26,7[c]	26,6[b]	13[e]	26,6[c]	26,7[c]	26,5[g]	26,8[d]
14	124,5[b]	123,8[b]	124,6[b]	125,0[b]	14[e]	124,4[d]	124,3[d]	124,5[c]	124,6[b]
15	131,5	131,4	131,4	131,4	15[e]	135,1[g]	135,1[f]	135,0[d]	135,1[c]
16	17,7	17,6	17,7	17,7	16[e]	40,1[c]	39,8	39,8	39,9
17	25,7	25,8	25,8	25,8	17	26,6[c]	26,8[c]	26,7[g]	26,8[d]
18[e]	16,1	16,0	16,0	15,9	18	125,0[d]	124,9[d]	125,6[c]	125,3[b]
19	194,1	66,9	23,5	23,4	19	131,3	131,3	131,3	131,4
20	23,35	23,4	23,4	23,4	20	17,7	17,7	17,7	17,7
					21	25,7	25,7	25,7	25,7
					22[e]	16,1	15,9	16,1	16,1
					23[f]	23,5	23,5	23,5	23,5
					24	195,2	67,3	23,5	23,5
					25	19,4	19,5	19,6	19,6

[a] The spectra also contain signals of the benzyl group.
[b-d, g] Signals marked by the same letters in the same column may be interchanged.
[e] Signals of these atoms have a tripled intensity.
[f] Signals of these atoms have a doubled intensity.

The reaction mixture obtained as described above was added dropwise to a mixture of 240 ml of 1% HCl and 100 ml of THF cooled to 0°C. The mixture was stirred for 2.5 h at ~20°C, and then was extracted with ether. The subsequent usual treatment and chromatography gave 10.6 g (58%) of (VI). Aldol (VII) was not observed under these conditions.

Benzyl Ether of 7-Hydroxymethyl-3,11,15,19,23-pentamethyl-tetraeicosa-2Z,6E,10E,14E,18E,22-hexaen-1-ol (VIII). Sodium borohydride ($NaBH_4$), 1.2 g, (30.0 mmoles) was added in portions to a stirred solution at 0°C of 10.4 g (19.5 mmoles) of (VI) in 380 ml of EtOH. The reaction mixture was held for 20 min at ~20°C (TLC monitoring), and then was decomposed at 0°C in 4 ml of AcOH, and the mixture was evaporated in vacuo to dryness. The residue was treated with 100 ml of water and extracted with ether. By the usual treatment of the extract, 8.5 g of an oily product was obtained, which was chromatographed on 100 g of SiO_2. Gradient elution from hexane to ether (up to 20% of the latter) gave 9.3 g (90%) of (VIII) in the form of a colorless oil. R_f 0.32. IR spectrum (ν, cm^{-1}): 3620, 3450, 3090, 3070, 2970, 2920, 2860, 1660, 1500, 1450, 1380, 1370, 1200, 1100, 1060, 1030, 1000, 945, 845, 730, 700, 665. PMR spectrum (δ, ppm, J, Hz): 1.62 br. s (12H, cis-Me), 1.70 s (3H, Me–C^{23}), 1.78 s (3H, Me–C^3), 2.05 m (20H, $CH_2C{=}C$), 4.0 d (2H, CH_2OBn, J = 6.8), 4.08 s (2H, CH_2OH), 4.5 s (2H, CH_2Ph), 5.12 m (4H, HC=C), 5.42 m (2H, HC^6, HC^2), 7.35 m (5H, Ph). Mass spectrum (m/z): 533 (M^+), 532, 514, 513, 500, 440, 432, 405, 354, 336, 286, 268, 218, 204, 136, 108, 91, 68.

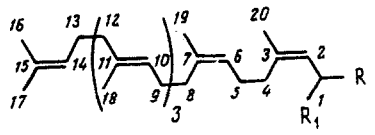
Benzyl Ether of 3,7,11,15,19,23-Hexamethyltetraeicosa-2Z,6Z,10E,14E,18E,22-hexaen-1-ol (IX). $Py{\cdot}SO_3$ (5.6 g, 35.2 mmoles) was added in portions to a stirred solution at 0°C in an Ar atmosphere of 9.3 g (17.6 mmoles) of (VIII) in 180 ml of THF. The mixture was held at 0°C for 2 h, and then was treated dropwise at −30°C with 158.5 ml of a 1 M solution of $LiAlH_4$ in THF (15.85 mmoles) and the mixture was stirred for 48 h at ~20°C. The subsequent usual treatment gave 7 g of an oily product, which was chromatographed on 100 g of SiO_2. Elution with a hexane–ether mixture (98:2) gave 6 g (67%) of (IX) in the form of a colorless oil, R_f 0.67. PMR spectrum (δ, ppm, J, Hz): 1.62 br. s (12H, cis-Me), 1.72 s (6H, trans-Me), 1.80 s (3H, Me–C^3), 2.08 m (20H, $CH_2C{=}C$), 4.00 d (2H, CH_2OBn, J = 6.8), 4.5 s (2H, CH_2Ph), 5.15 m (5H, HC=C), 5.45 t (1H, HC^2, J = 6.8), 7.35 m (5H, Ph). Mass spectrum (m/z): 517 (M^+), 516, 448, 447, 409, 408, 379, 339, 272, 244, 204, 176, 137, 136, 108, 91, 69, 68.

3,7,11,15,19,23-Hexamethyltetraeicosa-2Z,6Z,10E,14E,18E,22-hexaen-1-ol, hexaprenol WT_3C_2OH (IIa). Lithium (0.7 g, 100 mmoles) was added in portions to a stirred solution at −35°C in an Ar atmosphere of 3 g (5.8 mmoles) of (IX) in 300 ml of NH_3. The reaction mixture was held at this temperature for 2.5 h, and then was decomposed by an excess of NH_4Cl and subjected to the usual treatment. Thus, 2.5 g of an oily product was obtained, which was chromatographed on 80 g of SiO_2. Gradient elution from hexane to ether (up to 15% of the latter) gave 1.98 g (80%) of (IIa) in the form of a colorless oil, R_f 0.41, the spectral characteristics of which were identical with those published for a natural [2] and synthetic [4] samples of this compound.

Phenyl Ether of 3,7,11,15,19,23-hexamethyltetraeicosa-2Z,6Z,10E,14E,18E,22-hexaen-1-thiol (X). A 13 ml portion of a 1.5 M hexane solution of n-BuLi (19.5 mmoles) was added dropwise to a stirred solution at 0°C in an Ar atmosphere of 6.3 g (14.7 mmoles) of (IIa) in 50 ml of HMPA and 160 ml of ether and then a solution of 3.3 g (17.3 mmoles) of TsCl in 25 ml of HMPA was added. The reaction mixture was stirred for 2.5 h at 0°C, treated with a solution of PhSLi, obtained from 0.13 g of Li and 1.94 g of thiophenol in 45 ml of HMPA, stirred for another 2 h at ~20°C, and then poured into a mixture of water and ice, and extracted with ether. After the usual treatment, 7.5 g of an oily product was obtained, which was chromatographed on 160 g of SiO_2. Elution with hexane gave 6.25 g (82%) of (X), R_f 0.75. IR spectrum (ν, cm^{-1}): 3100-2860, 1660, 1585, 1480, 1450, 1440, 1380, 1330, 1300, 1230-1200, 1150, 1100, 1090, 1060, 1025, 970, 925, 840, 690. PMR spectrum (δ, ppm, J, Hz): 1.62 br. s (12H, cis-Me), 1.70 s (6H, trans-Me), 1.73 s (3H, Me–C^3), 2.05 m (20H, $CH_2C{=}C$), 3.56 d (2H, CH_2SPh, J = 7), 5.13 m (5H, HC=C), 5.34 t (1H, HC^2, J = 7). Mass spectrum (m/z): 519 (M^+), 518, 410, 409, 408, 340, 272, 204, 136, 109, 69, 68.

Ethyleneacetal of 6,10,14,18,22,26-Hexamethyl-4-phenylthioheptaeicosa-5Z,9Z,13E,17E,21E,25-hexaen-1-al (XI). A 9 ml portion of a 1.3 M solution of n-BuLi (11.7 mmoles) in hexane was added in the course of 30 min to a stirred solution at −70°C in an Ar atmosphere of 4.0 g (7.7 mmoles) of (X) in 120 ml of THF. The mixture was held for 3 h at −70°C, and then 2.78 g (15.4 mmoles) of 3-bromopropionaldehyde ethyleneacetal [12] in 20 ml of THF was added in the course of 20 min. The reaction mixture was held for 1.5 h at −70°C, and

TABLE 2. ^{13}C NMR Spectra of Compounds (X)-(XIII)

C atom No.				
	R=H R¹=SPh (X)	R=CH₂CH₂CH(OCH₂)₂ (21 22 23 24)		R=CH₂CH₂CHO (21 22 23) R¹=H (XIII)
		R¹=SPh (XI)	R¹=H (XII)	
1	31,9 a	46,9	27,7 a	27,1
2	124,3 b	126,2	124,2 a	124,2 a
3	139,9	138,6	134,8 b	135,0 b
4	32,1 a	32,2 a	32,1 c	32,0 c
5	26,4 c	26,2 b	26,4 d	26,4 a
6	124,3 b	124,2 c	124,3 a	124,3 a
7	134,5	133,8	134,9 b	135,1 b
8	32,3 a	32,4 a	32,3 c	32,3 c
9 e	26,7 c	26,4 b	26,7 d	26,5 d
10 e	124,4 b	124,4 c	124,4 a	124,5 a
11 e	134,5	133,8	134,9 b	135,3 b
12 e	39,9	39,6	39,7	39,8
13	26,8 c	26,7 b	26,8 d	26,2 d
14	124,6 b	124,8 c	125,0 a	125,0
15	134,4	131,4	131,4	131,4
16	17,6	17,7	17,7	17,7
17	25,8	25,8	25,8	25,8
18 e	16,1	16,1	16,1	16,1
19	23,5	23,2	23,4	23,5
20	23,5	23,5	23,5	23,5
21		29,7	24,5	22,5
22		31,7 a	33,6	43,5
23		104,4	104,7	202,8
24		65,0	64,7	

a-d Signals marked by the same letters in the same column may be interchanged.

e The signals of these atoms have a tripled intensity.

was then decomposed with 10 ml of an MeOH–ether mixture (1:1), poured into a mixture of ice water and ether (1:1), the aqueous layer was separated and extracted with ether. After the usual treatment of the combined organic layer, the excess of bromoacetal was distilled in vacuo, and the residue was chromatographed on 100 g of SiO_2. Gradient elution from hexane to ether (up to 20% of the latter) gave 3.15 g (66.5%) of (XI) in the form of a colorless oil. R_f 0.24 (hexane–ether, 9:1). IR spectrum (ν, cm^{-1}): 3010-2860, 1660, 1580, 1470, 1450, 1440, 1380, 1330, 1300, 1230-1200, 1140, 1030, 1025, 970, 940, 910, 860, 840, 690. PMR spectrum (δ, ppm, J, Hz): 1.62 br. s (12H, cis-Me), 1.66 m (2H, CH_2), 1.69 m (9H, trans-Me), 1.8 m (2H, CH_2), 2.04 m (20H, $CH_2C{=}C$), 3.9 m (5H, CH_2O, CHS), 4.83 t (1H, OCHO, J = 4.5), 5.1 m (6H, $HC{=}C$), 7.35 m (5H, Ph). Mass spectrum (m/z): 619 (M^+), 618, 510, 509, 447, 204, 136, 109, 68.

Ethyleneacetal of 6,10,14,18,22,26-Hexamethylheptaeicosa-5Z,9Z,13E,17E,21E,25-hexaen-1-al (XII). Lithium (0.25 g, 35.7 mmoles) was added in portions to a stirred solution at −35 to −40°C in an Ar atmosphere of 3.15 g (5.1 mmoles) of (XI) in 80 ml of NH_3 and the mixture was held at this temperature for 3 h. It was then decomposed with an excess of NH_4Cl and NH_3 was evaporated. After the usual treatment of the residue, 2.5 g of an oily product was obtained, which was chromatographed on 80 g of SiO_2. Gradient elution from hexane to ether (up to 5% of the latter) gave 2.15 g (82%) of (XII) in the form of a colorless oil. R_f 0.3 (hexane–ether, 9:1). IR spectrum (ν, cm^{-1}): 3010-2860, 1660, 1450, 1410, 1380, 1230-1200, 1140, 1130, 1050-1030, 970, 940, 910, 840, 720, 650. PMR spectrum (δ, ppm, J, Hz): 1.47 m (2H, CH_2), 1.62 br. s (12H, cis-Me), 1.64 m (2H, CH_2), 1.68 br. s (9H, trans-Me), 2.04 m (22H, $CH_2C{=}C$), 3.9 m (4H, CH_2O), 4.85 t (1H, OCHO, J = 4.5), 5.13 m (6H, $HC{=}C$). Mass spectrum (m/z): 511 (M^+), 510, 443, 442, 375, 307, 238, 204, 137, 68.

6,10,14,18,22,26-Hexamethylheptaeicosa-5Z,9Z,13E,17E,21E,25-hexaen-1-al (XIII). A solution of 2.15 g (4.2 mmoles) of (XII) in 200 ml of an acetone–H_2O mixture (4:1), containing 0.04 ml of concentrated H_2SO_4 was boiled for 6 h (HPLC monitoring), and then was

neutralized with $NaHCO_3$ at ~20°C. Acetone was evaporated and the residue was extracted with ether. After the usual treatment of the extract, 1.97 g (~100%) of (XIII) was obtained, the admixture of (XII) which did not exceed 2% according to the HPLC data. The aldehyde (XIII) obtained, R_f 0.68, was used further without additional purification. IR spectrum (ν, cm^{-1}): 3010-2860, 2720, 1730, 1660, 1450, 1410, 1380, 1230-1200, 1140, 1130, 1110-1070, 1040, 970, 890, 850, 840. PMR spectrum (δ, ppm, J, Hz): 1.62 br. s (12H cis-Me), 1.70 m (11H, trans-Me, H_2C^3), 2.02 m (22H, CH_2C=C), 2.4 d.t, H_2C^2, J_1 = 1, J_2 = 8), 5.12 m (6H, HC=C), 9.76 t (1H, CHO, 1 = 1). Mass spectrum (m/z): 467 (M^+), 439, 424, 398, 330, 272, 204, 137, 136, 69, 68.

tert-Butylimine of 6,10,14,18,22,26-Hexamethylpentaeicosa-5Z,9Z,13E,17E,21E,25-hexaen-1-al (XIV). A solution of 1.5 g (20.6 mmoles) of tert-$BuNH_2$ in 10 ml of ether was added in the course of 10 min to a stirred solution at −10 to −5°C of 1.97 g (4.1 mmoles) of (XIII) in 30 ml of ether. The mixture was stirred for 3 h, and then was treated with 0.6 g of KOH, and stirred for another 20 min. The organic layer was separated, dried over K_2CO_3, and evaporated in vacuo. Yield, 2.05 g (97%) of (XIV) in the form of light-yellow oil, which was dried for 5 h at ~20°C (1 mm Hg), and then dissolved in 5 ml of ether. The solution was allowed to stand for 12 h over molecular sieves (4 Å) at ~20°C and was used further without additional purification. PMR spectrum (δ, ppm, J, Hz): 1.1 s (9H, Me_3C), 1.6 br. s (12H, cis-Me), 1.7 br. s (11H, trans-Me, H_2C^3), 2.2 m (24H, CH_2C=C, CH_2C=N), 5.1 m (6H, HC=C), 7.6 t (1H, CH=N, J = 4).

Benzyl Ether of 6(R,S)-Bromo-7-hydroxy-3(S),7-dimethyloctan-1-ol (XVI). N-Bromosuccinimide (4.5 g, 25 mmoles) was added in portions to a stirred mixture at −10 to −5°C of 5.8 g (23.5 mmoles) of (XV) [9], 45 ml of DMSO and 8 ml of H_2O. The mixture was stirred for 1 h at −5 to 0°C, and then was treated with a saturated solution of $NaHCO_3$ and extracted with ether. After the usual treatment of the extract, 7.8 g of an oily product was obtained, which was chromatographed on 100 g of SiO_2. Gradient elution from hexane to ether (up to 10% of the latter) gave 7.0 g (87%) of (XVI) in the form of a yellow oil. R_f 0.3, $[\alpha]_D^{28}$ −18.66° (C 3.29). PMR spectrum (δ, ppm, J, Hz): 0.92 d (3H, Me−C^3, J = 6), 1.35 s and 1.37 s (3H, Me−C^7 in each case), 1.7 m (7H, CH_2, HC^3), 2.12 br. s (1H, OH), 3.5 t (2H, CH_2OBn, J = 7), 4.0 m (1H, HC^6), 4.5 br. s (2H, CH_2Ph), 7.35 m (5H, Ph).

Benzyl Ether of 3(S),7-Dimethyl-6(R,S)-7-epoxyoctan-1-ol (XVII). A suspension of 7.0 g (20.4 mmoles) of (XVI) and 14 g of K_2CO_3 in 140 ml of MeOH was stirred for 20 min at ~20°C, then was filtered, and the precipitate was washed with MeOH. The filtrate was evaporated in vacuo, the residue was dissolved in ether and the ether solution was washed with a saturated Na_2SO_4 solution. The subsequent usual treatment gave 5.6 g of an oily product, which was chromatographed on 90 g of SiO_2. Gradient elution from hexane to ether (up to 8% of the latter) gave 5.1 g (96%) of (XVII). R_f 0.45, $[\alpha]_D^{31}$ −2.64° (C 3.5). The spectral characteristics of epoxide (XVII) were identical with those given in [11] for its racemate.

Benzyl Ether of 3(S),7-Dimethyloctane-1,6-(R,S),7-triol (XVIII). A solution of 4.7 g (17.8 mmoles) of (XVII) and 2.8 ml of a 5% $HClO_4$ in 65 ml of a THF−H_2O mixture (3:2) was stirred for 2 h at ~20°C (TLC monitoring), and then was neutralized with $NaHCO_3$ and extracted with ether. After the usual treatment of the extract, 5 g of an oily product was obtained, which was chromatographed on 90 g of SiO_2. Gradient elution from hexane to ether (up to 50% of the latter) gave 4.1 g (82%) of (XVIII), R_f 0.1, $[\alpha]_D^{31}$ −1.04° (C 2.65). PMR spectrum (δ, ppm, J, Hz): 0.89 d and 0.92 d (3H, Me−C^3, J_1 = J_2 = 7), 1.14 s and 1.2 s (3H, Me−C^7), 1.54 m (6H, CH_2), 2.42 br. s (2H, OH), 3.3 m (1H, HC^6), 3.5 t and 3.52 t (J_1 = J_2 = 7, CH_2OBn), 4.5 br. s (2H, CH_2Ph), 7.35 m (5H, Ph).

6-Benzyloxy-4(S)-methylhexan-1-al (XIX). A solution of 3.8 g (13.5 moles) of (XVIII) in 60 ml of THF, stirred at ~20°C, was treated with a solution of 5.7 g of $NaIO_4$ in 85 ml of H_2O. The mixture was held for 4 h at ~20°C (TLC monitoring) and then was extracted with ether. The usual treatment of the extract gave 2.9 g of an oily product, which was distilled in vacuo. Yield, 2.3 g (78%) of (XIX), bp 98-100°C/0.04 m Hg. R_f 0.35, $[\alpha]_D^{30}$ −1.96° (C 2.95). The spectral characteristics of the aldehyde (XIX) were identical with those given in [11] for its racemate.

Benzyl Ether of 3(S),11,15,19,23,27,31-heptamethyl-7-formylditriaconta-6E,10Z,14Z,18E,-22E,26E,30-heptaen-1-ol (XX). As described above for (VI), from 2.05 g (3.9 mmoles) of (XIV) and 0.78 g (3.4 mmoles) of (XIX), 0.95 g (40%) of E-acrolein (XX) was obtained in the form of a colorless oil, R_f 0.61, $[\alpha]_D^{25}$ −0.44° (C 1.34). IR spectrum (ν, cm^{-1}): 3010-2860, 2720, 1680, 1640, 1450, 1380, 1100, 1080, 1050, 840, 700. UV spectrum: λ_{max} 230 nm

(log ε 4.02). PMR spectrum (δ, ppm, J, Hz): 0.92 d (3H, Me–C^3, J = 7), 1.2-1.7 m (5H, CH_2, HC^3), 1.62 br. s (12H, cis-Me), 1.7 br. s (9H, trans-Me), 2.05 m (22H, $CH_2C{=}C$), 2.3 m (4H, $H_2C^{5,8}$) 3.5 t (2H, CH_2OBn, J = 7.0), 4.5 br. s (2H, CH_2Ph), 5.12 m (6H, HC=C), 6.45 t (1H, HC^6, J = 7), 7.35 m (5H, Ph), 9.37 br. s (1H, CHO). Mass spectrum (m/z): 669 (M^+), 651, 626, 600, 578, 532, 397, 272, 204, 136, 68. In a similar way, from 2.10 g (6.3 mmoles) of aldimine (III) and 1.19 g (3.34 mmoles) of aldehyde (XXIII) [1], 0.96 g (40%) of acrolein (XXIV) was obtained, which was completely identical with the sample of this compound described in [1].

Benzyl Ether of 7-Hydroxymethyl-3(S),11,15,19,23,27,31-heptamethylditriaconta-6E,10Z,-14Z,18Z,22E,26E,30-heptaen-1-ol (XXI). As described above for (VIII), from 0.95 g (1.42 mmoles) of (XX), 0.83 g (87%) of (XXI) was obtained in the form of a colorless oil. R_f 0.41, $[\alpha]_D^{22}$ −0.67° (C 1.78). IR spectrum (ν, cm^{-1}): 3620, 3520, 3020, 2990-2860, 1660, 1455, 1380, 1100, 1030, 840, 700. PMR spectrum (δ, ppm, J, Hz): 0.91 d (3H, Me–C^3, J = 7), 1.3-1.7 m (5H, CH_2, HC^3), 1.6 br. s (12H, cis-Me), 1.7 br. s (9H, trans-Me), 2.05 m (26H, CH_2-C=C), 3.5 t (12H, CH_2OBn, J = 7.0), 4.01 br. s (2H, CH_2OH), 4.5 s (2H, CH_2Ph), 5.12 m (6H, HC=C), 5.4 t (1H, HC^6, J = 7), 7.35 m (5H, Ph). Mass spectrum (m/z): 671 (M^+), 653, 603, 584, 580, 562, 516, 448, 408, 398, 380, 340, 313, 272, 204, 136, 68.

Benzyl Ether of 3(S),7,11,15,19,23,27,31-Octamethylditriaconta-6Z,10Z,14Z,18E,22E,26E,30-heptaen-1-ol (XXII). As described above for (IX), from 0.83 g (1.24 mmoles of (XXI), 0.69 g (85%) of (XXII) was obtained in the form of colorless oil, R_f 0.68, $[\alpha]_D^{25}$ −0.39° (C 1.78). IR spectrum (ν, cm^{-1}): 3000, 2960, 2920, 2860, 1660, 1630, 1450, 1380, 1150, 1090, 1025, 1010, 980, 830. PMR spectrum (δ, ppm, J, Hz): 0.92 d (3H, Me–C^3, J = 7), 1.3-1.7 m (5H, CH_2, HC^3), 1.62 br. s (12H, cis-Me), 1.69 br. s (12H, trans-Me), 2.05 m (26H, $CH_2C{=}C$), 3.52 t (2H, CH_2OBn, J = 7), 4.52 s (2H, CH_2Ph), 5.12 m (7H, HC=C), 7.32 m (5H, Ph). Mass spectrum (m/z): 655 (M^+), 564, 517, 382, 313, 272, 107, 91, 69, 68.

3(S), 7,11,15,19,23,27,31-Octamethylditriaconta-6Z,10Z,14Z,18E,22E,26E,30-heptaen-1-ol, octaprenol $WT_3C_3S^*OH$ (I). As described above for (IIa), from 0.69 g (1.05 mmoles) of (XXII), 0.53 g (90%) of (I) was obtained in the form of colorless oil, R_f 0.40, $[\alpha]_D^{27}$ −0.66° (C 0.9). IR spectrum (ν, cm^{-1}): 3640, 3520, 3030, 2970-2860, 1665, 1450, 1380, 1160, 850. PMR spectrum (δ, ppm, J, Hz): 0.92 d (3H, Me–C^3, J = 7), 1.4 m (5H, CH_2, HC^3), 1.62 br. s (12H, cis-Me), 1.69 br. s (12H, trans-Me), 2.05 m (26H, $CH_2C{=}C$), 3.68 m (2H, CH_2OH), 5.12 m (7H, HC=C). Mass spectrum (m/z): 565 (M^+), 564, 547, 496, 428, 427, 409, 341, 272, 204, 136, 68.

LITERATURE CITED

1. N. Ya. Grigor'eva, O. A. Pinsker, V. N. Odinokov, et al., Izv. Akad. Nauk SSSR, Ser. Khim., No. 7, 1546 (1987).
2. G. Jommi, L. Verotta, P. Garibordi, et al., Gazz. Chim. Ital., 118, No. 12, 823 (1988).
3. N. Ya. Grigor'eva (Grigorieva), I. M. Avrutov, and A. V. Semenovskii (Semenovsky), Tetrahedron Lett., 24, No. 49, 5531 (1983).
4. A. V. Semenovskii, N. Ya. Grigor'eva, I. M. Avrutov, et al., Izv. Akad. Nauk SSSR, Ser. Khim., No. 1, 152 (1984).
5. N. Ya. Grigor'eva, I. M. Avrutov, O. A. Pinsker, et al., Izv. Akad. Nauk SSSR, Ser. Khim., No. 8, 1824 (1985).
6. K. Sato, O. Migamoto, S. Inoue, et al., Chem. Lett., No. 5, 725 (1983).
7. N. Ya. Grigor'eva, E. P. Prokof'ev, and A. V. Semenovskii, Dokl. Akad. Nauk SSSR, 245, No. 2, 366 (1979).
8. E. J. Corey and K. J. Akiwa, J. Org. Chem., 34, No. 11, 3667 (1969).
9. K. Mori and T. Sugai, Synthesis, No. 10, 752 (1982).
10. E. E. van Tamelen and T. J. Curphey, Tetrahedron Lett., No. 1, 121 (1962).
11. A. S. Shashkov, N. Ya. Grigor'eva, I. M. Avrutov, et al., Izv. Akad. Nauk SSSR, Ser. Khim., No. 2, 388 (1979).
12. M. Y. Kim, J. E. Starrett, and S. M. Weinreb, J. Org. Chem., 46, No. 26, 5383 (1981).
13. G. Büchi and H. Wüest, J. Org. Chem., 34, No. 4, 1122 (1969).