STEREOSPECIFIC SYNTHESIS OF OCTAPRENOLS WT_3C_4OH AND WT_3C_3TOH

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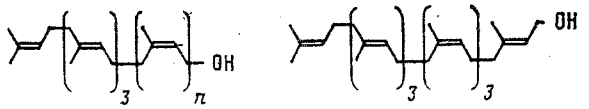
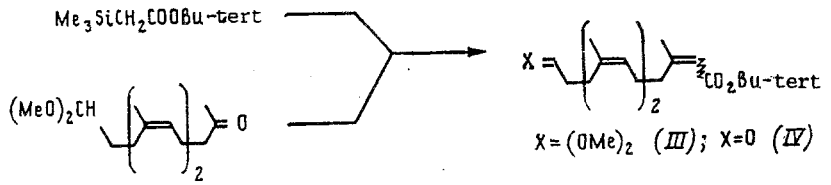
A total synthesis of the above prenols has been carried out.

The development of methods of synthesis of plant polyprenols (Ia-d) is of interest in connection with their high effectivity [1] in treating functional disturbances related to hypertrophy of the prostate giand. Using two different methods, we have previously obtained the hexa- (Ia) [2, 3] and heptaprenols (Ib) [4, 5]. In the present work we used a block method [3-7] to carry out a total synthesis of octaprenol WT_3C_4OH (Ic) as well as its 2E-isomer (Ie), which is required for biological investigations (cf. [8]).



(I): n = 2(a); 3(b); 4(c); 5(d) (Ie)

The aldehyde block-synthones were prepared starting from ketoacetal (II), a readily available product of selective ozonolysis of a cyclodimer of isoprene, or extensive ozonolysis of natural rubber [9, 10]. The olefination of (II) according to Peterson by means of α-trimethylsilyl acetates leads in high yield to esters (III), obtained in the form of a mixture of isomers (2Z/2E ≈ 3:2) the ratio of which is practically the same for ethyl (cf. [11]) and tert-butyl esters. The great difference in the chromatographic mobility of the latter made it possible to practically quantitatively separate them by means of flash-chromatography. The stereochemical purity of Z and E isomers (IIIa, b) is 97 and ~100%, according to the intensity ratio of the PMR spectra of the singlet signals of the Me_3–C^3 group at δ 1.86 (Z isomer) and 2.16 ppm (E isomer) (cf. [11]). The acid-catalyzed hydrolytic splitting of acetals (IIIa, b) readily gives the aldehydo-esters (IVa, b) with the above-indicated stereochemical purity (scheme 1).



(II)

The condensation of aldehydes (IV) with the known aldiminic block synthone (V) [5] deprotonated by the action of lithium diisopropyl amide (LDA), and subsequent acid treatment of the reaction mixture gives with a 50% yield and ≥95% stereospecificity (PMR data, cf. [3, 12]) the key E-acroleins (VIa, b) (scheme 2). The reductive transformation of the tert-butyl esters (VI) via the intermediate stages of allyl alcohols (VIIa, b) and their corresponding sulfonates under earlier developed conditions for related ethyl esters [6] unexpectedly gives, together with the desired octaprenols (Ic, e), up to 50% of the known [11] dolichol-like alcohols (VIII). Reagents and conditions: 1) LDA/Et_2O, −20°C; 2) (IVa/b)/Et_2O, −70°C; 3) H_3O^+; 4) $NaBH_4$/EtOH; 5) Py·SO_3/THF, 0°C; 6) AlH_3/Et_2O, −5°C; 7) $LiAlH_4/Et_2O$, −30°C.

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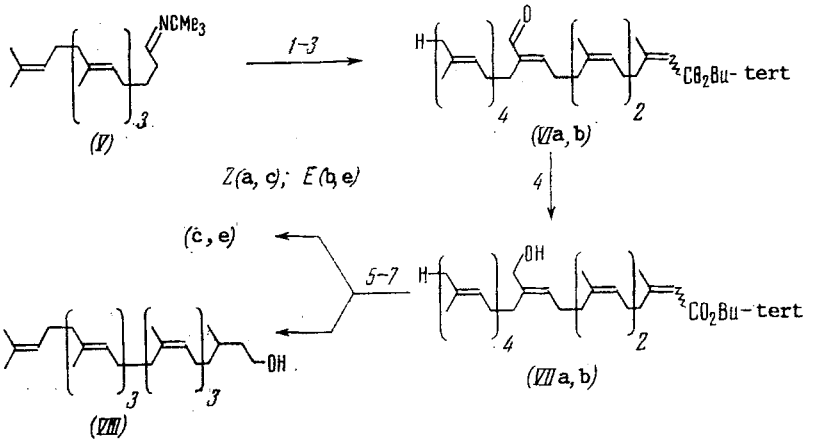


The content of the latter in the mixture can be lowered to 5-8% by carrying out the reduction in two stages: first by a treatment with AlH_3 [13] for the saturation of the ester group and then, in the same reaction vessel with $LiAlH_4$ – for the hydrogenolysis of the allyl sulfate residue. At the end, the total yield of alcohols (Ic) and (Ie), additionally purified by HPLC was ~15 and 25% (not optimized) based on (IVa) and (IVb), respectively.

The structure of all the previously undescribed compounds (III), (IV), (VI), (VII) was confirmed by the ^{13}C NMR data (Tables 1, 2), which were interpreted taking into account the data for the previously found related structures [3, 11, 14].

EXPERIMENTAL

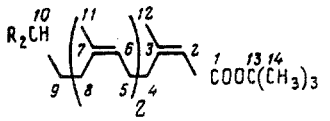
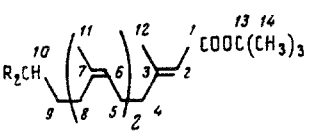
The IR spectra of the solutions in CCl_4 or $CHCl_3$ were obtained on a Perkin-Elmer 577 spectrophotometer, the mass spectra at an ionizing voltage of 70 eV on a Varian MAT-CH-6 spectrometer, the ^1H NMR spectra on a Bruker WM-250 spectrometer in $CDCl_3$ with reference to TMS, and the ^{13}C NMR spectra on a Bruker AM-300 spectrometer (75.5 MHz). The preparative chromatography was carried out by a flash variant on silica gel L (40-100 μm) from the firm "Chemapol". The R_f values are given for a stationary "Silufol" brand SiO_2 layer from the same firm in a hexane–ether system (1:1). The HPLC was carried out on a column with "Silasorb 600" sorbent (7.5 μm), using a heptane–ethyl acetate mixture (up to 5% of the latter), as the eluent and a refractometric detector.

tert-Butyl Esters of 14,14-Dimethoxy-3,7,11-trimethyltetradeca-2Z,6Z,10Z- (IIIa) and -2E,6Z,10Z-trienoic (IIIb) Acids. A solution of 11.1 g (59 mmoles) of tert-butyltrimethylsilyl acetate [15] in 10 ml of THF was added dropwise to a stirred solution at −78°C in an Ar atmosphere of LDA (59 mmoles) in 350 ml of a THF–hexane mixture (6:1). The mixture was held for 1.5 h at −78°C, and then was treated at the same temperature with a solution of 8.9 g (32 mmoles) of ketoacetal (II) [9, 10]. After stirring the mixture for another 1.5 h, it was warmed in the course of 1 h to ~20°C and after 30 min was decomposed with 11 g of $NaHSO_4 \cdot H_2O$. The precipitate was filtered and washed with ether. Subsequent usual treatment of the filtrate gave 13 g of an oily product, which was chromatographed on 250 g of SiO_2. Gradient elution from hexane to ether (up to 5% of the latter) gave 10.0 g (87%) of (III) in the form of a mixture of isomers (IIIa)/(IIIb) ≈ 3:2 (according to PMR).

A portion of this mixture (1 g) was chromatographed again on 250 g of SiO_2. Elution with a hexane–ether mixture (97:3) gave 0.7 g of (IIIa) containing 18% of (IIIb) and 0.3 g (IIIb) containing ~2% of (IIIa) (according to PMR). The fraction enriched with (IIIa) was chromatographed once again under the above-described conditions to yield 0.58 g of (IIIa), containing ~3% of (IIIb). In a similar way, from fractions enriched with (IIIb), 0.37 g of (IIIb) was isolated, without an admixture of (IIIa) (PMR data).

Acetal (IIIa) – colorless oil with R_f 0.52. IR spectrum (ν, cm^{-1}): 3010-2830, 1715, 1660, 1450, 1390, 1380, 1370, 1290, 1230, 1140, 1080, 1060, 960, 880, 860. PMR spectrum (δ, ppm, J, Hz): 1.48 br. s (9H, CMe_3), 1.60 m (2H, HC^{13}), 1.68 br. s (6H, trans-Me), 1.86 d (3H, Me–C^3, J = 1.6), 2.05 m (6H, $HC^{8,9,12}$), 2.16 m (2H, HC^5), 2.6 t (2H, HC^4, J = 8), 3.3 s (6H, MeO), 4.32 t (1H, HC^{14}, J = 6), 5.12 m (2H, HC=C), 5.6 br. s (1H, HC^2). Mass spectrum (m/z): 350 (M^+), 349, 319, 291, 260, 192, 161, 135, 93, 68.

TABLE 1. ^{13}NMR Spectra of Compounds (IIIa, b); (IVa, b)

C atom No.				
	R=OCH$_3$ (IIIa)	R$_2$=O (IIIb)	R=OCH$_3$ (IVa)	R$_2$=O (IVb)
1	166,5	166,5	166,5	166,5
2	118,1	118,1	117,4	117,4
3	157,8	157,8	157,9	157,9
4	33,3	33,3	41,2	41,1
5[a]	26,8	25,9	26,8	25,9
6[a]	124,5	124,5	124,5	124,5
7[a]	135,5	135,5	135,9	135,6
8[a]	32,1	32,1	32,1	32,0
9	30,8	42,3	30,9	42,3
10	104,1	201,9	104,1	201,9
11[a]	23,2[c]	23,2[c]	23,3	23,3
12	23,3[c]	23,3[c]	16,5	16,6
13	79,3	79,3	79,3	79,3
14[b]	28,3	28,3	28,3	28,3
15[a]	52,5		52,5	

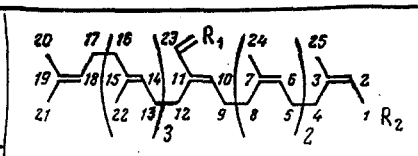
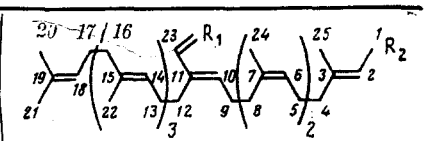
[a] The signals have doubled intensity.
[b] The signals have tripled intensity.
[c] The signals may be interchanged.

Acetal (IIIb) – colorless oil with R_f 0.51. IR spectrum (ν, cm^{-1}): 3010-2830, 1715, 1660, 1450, 1390, 1380, 1370, 1320, 1280, 1220, 1150, 1080, 1060, 960, 925, 860. PMR spectrum (δ, ppm, J, Hz): 1.48 br. s (9H, CMe_3), 1.6 m (2H, HC^{13}), 1.68 br. s (6H, trans-Me), 2.05 m (6H, $HC^{8,9,12}$), 2.16 s (3H, Me–C^3), 2.05-2.20 m (4H, $HC^{4,5}$), 3.34 s (6H, MeO), 4.32 t (1H, HC^{14}, J = 6), 5.12 m (2H, HC=C), 5.6 br. s (1H, HC^2). Mass spectrum (m/z): 350 (M^+), 349, 319, 291, 260, 192, 161, 135, 93, 68.

tert-Butyl Esters of 14-Oxo-3,7,11-trimethyltetradeca-2Z,6Z,10Z-(IVa) and -2E,6Z,10Z-trienoic (IVb) Acids. A solution of 7.2 g (19 mmoles) of (IIIa) and 0.5 g of TsOH·H_2O in 150 ml of a 60% aqueous acetone was boiled for 4 h, and then neutralized with Na_2CO_3, concentrated in vacuo and the residue was extracted with ether. The usual treatment of the extract gave 6.0 g (95%) of (IVa) in the form of a colorless liquid, bp 142°C (0.2 mm). IR spectrum (ν, cm^{-1}): 3080, 3020, 2970, 2920, 2860, 2720, 1730, 1715, 1660, 1450, 1390, 1380, 1370, 1250, 1150, 1050, 960, 850. PMR spectrum (δ, ppm, J, Hz): 1.48 br. s (9H, CMe_3), 1.62 br. s (6H, trans-Me), 1.80 d (3H, Me–C^3, J = 1.6), 2.05 m (4H, $HC^{8,9}$), 2.16 m (2H, HC^5), 2.3 t (2H, HC^{12}, J = 7), 2.45 d.t (2H, HC^{13}, J_1 = 1, J_2 = 7), 2.55 t (2H, HC^4, J = 8), 5.12 m (2H, HC=C), 5.52 s (1H, HC^2), 9.72 t (1H, CHO, J = 1.0). In a similar way, from 1.15 g (3.04 mmoles) of (IIIb), 0.96 g (95%) of (IVb) was obtained in the form of a colorless liquid, R_f 0.52. IR spectrum (ν, cm^{-1}): 3090, 3070, 3020, 2965, 2930, 2915, 2855, 2720, 1730, 1715, 1660, 1450, 1390, 1380, 1370, 1245, 1140, 1060, 960, 930, 860. PMR spectrum (δ, ppm, J, Hz): 1.44 br. s (9H, CMe_3), 1.64 br. s (6H, trans-Me), 2.02 m (4H, $HC^{8,9}$), 2.16 s (3H, Me–C^3), 2.05-2.20 m (4H, $HC^{4,5}$), 2.3 t (2H, HC^{12}, J = 7), 2.45 d.t (2H, HC^{13}, J_1 = 1, J_2 = 7), 5.12 m (2H, HC=C), 5.5 s (1H, HC^2), 9.75 t (1H, CHO, J = 1).

tert-Butyl Esters of 3,7,11,19,23,27,31-Heptamethyl-15-formylditriaconta-2Z,6Z,10Z,-14E,18E,22E,26E,30- (VIa) and -2E,6Z,10Z,14E,18E,22E,26E,30-octaenoic (VIb) Acids. A solution of 7.6 g (19.5 mmoles) of (V) [5] in 20 ml of ether was added in the course of 15 min to a stirred solution at –20°C in an Ar atmosphere of LDA (20.6 mmoles) in 150 ml of an ether–hexane mixture (6:1). The mixture was held for 2 h at 0°C, treated at –70°C with a solution of 5.0 g (15 mmoles) of (IVa) in 15 ml of ether, and held at this temperature for 2.5 h. Then it was warmed in the course of 2 h to ~20°C and allowed to stand overnight. The reaction mixture was poured carefully into a vigorously stirred and cooled to 5°C mixture of 80 ml of ether and a solution of 10 g of $(COOH)_2 \cdot 2H_2O$ in 80 ml of H_2O. The stirring was continued for 2 h at ~20°C, and then the aqueous layer was separated and extracted with ether. The subsequent usual treatment of the combined organic layers gave 8 g of a product, which was chromatographed on 160 g of SiO_2. Gradient elution from hexane to ether

TABLE 2. ^{13}C NMR Spectra of Compounds (Ie), (VIa, b), (VIIa, b)

C atom No.	 R_1=O R_2=CO_2Bu-tert[a] (VIa)	R_1=H, OH R_2=CO_2Bu-tert[a] (VIIa)	 R_1=O R_2=CO_2Bu-tert[a] (VIb)	R_1=H, CH R_2=$COBu$-tert[a] (VIIb)	R_1=H, H R_2=CH_2OH (Ie)
1	166,5	166,5	166,5	166,5	59,3
2	118,4	118,4	117,4	117,4	123,4
3	158,1	158,1	157,7	157,7	139,4
4	33,4	33,4	41,2	41,2	39,8
5[b]	25,8[c]	25,3[c]	25,3[c]	25,3[c]	26,3[c]
6[b]	124,4[d]	124,4[d]	124,4[d]	124,4[d]	124,3[d]
7[b]	134,8[e]	134,9[e]	134,8[e]	134,8[e]	134,9[e]
8[b]	32,1	32,0	32,2	32,0	32,0[f]
9	26,3[c]	26,4[c]	26,3[c]	26,3[c]	26,4[c]
10	154,2	126,7	154,4	126,7	124,5[d]
11	143,3	139,1	143,7	139,1	134,9
12	24,2	28,6	24,2[c]	28,3[c]	32,4[f]
13[g]	26,7[c]	26,5[c]	26,6[c]	26,5[c]	26,6[c]
14[g]	123,4[d]	124,3[d]	123,3[d]	124,3[d]	124,6[d]
15[g]	134,9[e]	135,5[e]	134,9[e]	135,6[e]	135,0[e]
16[g]	40,0	39,8	40,0	39,8	39,8
17	26,7[c]	26,8[c]	26,7[c]	26,8[c]	26,7[c]
18	124,8[d]	125,4[d]	124,8[d]	125,4[d]	125,1
19	131,1	131,2	131,2	131,4	131,1
20	17,7	17,6	17,7	17,7	17,6
21	25,7	25,7	25,8	25,7	25,7
22[g]	16,1	16,1	16,0	16,1	16,0
23	195,8	67,3	195,1	67,3	23,4
24[b]	23,4	23,5	23,4	23,3	23,4
25	23,4	23,4	16,0	16,5	16,3

[a] The spectra also contain signals of the tert-butyl group.
[b] The signals have doubled intensity.
[c-f] The signals marked by the same letters in the same column may be interchanged.
[g] The signals have tripled intensity.

(up to 2% of the latter) gave 4.65 g (48%) of (VIa) in the form of a colorless oil. R_f 0.68. IR spectrum (ν, cm^{-1}): 3090, 3060, 3020, 2960, 2920, 2850, 2720, 1715, 1690, 1640, 1450, 1390, 1380, 1370, 1245, 1140, 970, 925, 860. PMR spectrum (δ, ppm, J, Hz): 1.48 br. s (9H, CMe_3), 1.58 s (3H, Me–C^{19}), 1.60 br. s (9H, cis-Me), 1.68 br. s (6H, trans-Me), 1.70 s (3H, Me–C^{11}), 1.84 d (3H, Me–C^3, J = 1.6), 2.05 m (20H, H_2C), 2.27 m (4H, $HC^{12,16}$), 2.45 d.t (2H, HC^{13}, $J_1 = J_2 = 7$), 2.6 t (2H, HC^4, J = 8), 5.12 m (6H, HC=C), 5.56 s (1H, HC^2), 6.44 t (1H, HC^{14}, J = 7), 9.35 s (1H, CHO). Mass spectrum (m/z): 647 (M^+), 646, 628, 590, 572, 558, 529, 490, 461, 441, 423, 354, 286, 204, 136, 68.

In a similar way, from 0.95 g (2.2 mmoles) of (V) and 0.55 g (1.65 mmoles) of (IVb), 0.5 g (47%) of (VIb) was obtained in the form of a colorless oil. R_f 0.67. IR spectrum (ν, cm^{-1}): 3070, 3020, 2960, 2920, 2860, 2720, 1715, 1690, 1640, 1450, 1390, 1380, 1370, 1240, 1140, 970, 860. PMR spectrum (δ, ppm, J, Hz): 1.48 br. s (9H, CMe_3), 1.58 s (3H, Me–C^{19}), 1.60 br. s (9H, cis-Me), 1.68 br. s (6H, trans-Me), 1.70 s (3H, Me–C^{11}), 2.05 m (18H, H_2C), 2.16 s (3H, Me–C^3), 2.0-2.2 m (4H, $HC^{4,5}$), 2.27 m (4H, $HC^{12,16}$), 2.45 d.t (2H, HC^{13}, $J_1 = J_2 = 7$), 5.0 m (6H, HC=C), 5.58 s (1H, HC^2), 6.43 t (1H, HC^{14}, J = 7), 9.35 (1H, CHO). The mass spectrum of (VIb) was identical with that given above for (VIa).

tert-Butyl Esters of 15-Hydroxymethyl-3,7,11,19,23,27,31-heptamethylditriaconta-2Z,-6Z,10Z,14E,18E,22E,26E,30- (VIIa) and -2E,6Z,10Z,14E,18E,22E,26E,30-octaenoic (VIIb) Acids. Sodium borohydride (0.43 g, 10.8 mmoles) was added in portions to a stirred solution at 0°C of 4.65 g (7.2 mmoles) of (VIa) in 150 ml of EtOH. The mixture was held for 20 min at ~20°C (TLC), and then was decomposed at 0°C with 1.2 ml of AcOH, and the mixture was evaporated in vacuo to dryness. The residue was treated with 30 ml of H_2O and extracted with ether. By the usual treatment of the extract, 5 g of a 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 4.2 g (90%) of (VIIa) in the form of a colorless oil. R_f 0.45. IR spectrum (ν, cm^{-1}): 3620, 3520, 3010, 2970, 2940, 2860, 1715, 1650, 1450, 1390, 1380, 1370, 1250, 1160, 1110, 1050, 960, 930, 860. PMR spectrum (δ, ppm, J, Hz): 1.48 br. s (9H, CMe_3), 1.6 br. s (12H, cis-Me), 1.70 br. s (9H, trans-Me), 1.84 d (3H, Me—C^3, J = 1.6), 2.08 m (26H, H_2C), 2.6 t (2H, HC^4, J = 8), 4.03 br. s (2H, CH_2OH), 5.12 m (6H, HC=C), 5.42 t (1H, HC^{14}, J = 6), 5.5 br. s (1H, HC^2). Mass spectrum (m/z): 649 (M^+), 576, 560, 476, 356, 339, 293, 272, 204, 136, 135, 68.

In a similar way, from 0.5 g (0.78 mmole) of (VIb), 0.46 g (90%) of (VIIb) was obtained in the form of a colorless oil, R_f 0.45. IR spectrum (ν, cm^{-1}): 3600, 3500, 2970, 2920, 2860, 1715, 1650, 1450, 1390, 1380, 1370, 1250, 1140, 1050, 950, 920, 860. PMR spectrum (δ, ppm, J, Hz): 1.48 br. s (9H, CMe_3), 1.62 br. s (12H, cis-Me), 1.70 br. s (9H, trans-Me), 2.02-2.2 m (28H, H_2C), 2.13 s (3H, Me—C^3), 4.03 br. s (2H, CH_2OH), 5.12 m (2H, HC=C), 5.42 t (1H, HC^{14}, J = 6), 5.58 br. s (1H, HC^2). The mass spectrum (m/z) of (VIIb) was identical with that given above for (VIIa).

3,7,11,15,19,23,27,31-Octamethylditriaconta-2Z,6Z,10Z,14Z,18E,22E,26E,30-octaen-1-ol, octaprenol WT_3C_4OH (Ic), and -2E,6Z,10Z,14Z,18E,22E,26E,30-octaen-1-ol, octaprenol WT_3C_3TOH (Ie). $Py \cdot SO_3$ (1.08 g, 6.4 mmoles) was added in portions to a solution of 2.12 g (3.27 mmoles) of (VIIa) in 90 ml of THF stirred at −5°C in an Ar atmosphere. The mixture was held at 0°C for 2 h and was added dropwise to a solution cooled at −5°C of AlH_3 (6.4 mmoles), prepared at −5°C (Ar) from a solution of 0.21 g (1.6 mmole) of $AlCl_3$ in 40 ml of ether and 20 ml of a 0.24 M solution of $LiAlH_4$ (4.8 mmoles) in ether. The reaction mixture was warmed in the course of 30 min to ~20°C, held for another 30 min, and then treated dropwise at −30°C with 26 ml of a 1 M solution of $LiAlH_4$ in ether. The mixture was warmed in the course of 20 min to ~20°C, and then was stirred for another 48 h. The subsequent usual treatment gave 3 g of a product, which was chromatographed on 70 g of SiO_2. Gradient elution from hexane to ether (up to 20% of the latter) gave 0.56 g (30%) of (Ic), containing according to the HPLC data ~5% of (VIII) [11]. The admixture was separated by means of preparative HPLC. Octaprenol (Ic) was obtained in the form of a colorless oil, R_f 0.3. IR spectrum (ν, cm^{-1}): 3600, 3450, 3010, 2960, 2920, 2860, 1670, 1450, 1380, 1230, 1030, 980, 840. Mass spectrum (m/z): 563, (M^+), 562, 544, 494, 477, 476, 409, 408, 341, 340, 272, 204, 136, 135, 68. The ^1H and ^{13}C NMR spectra were identical with those given in [1]. In a similar way, from 0.46 g (0.7 mmole) of (VIIb) 0.22 g (45%) of a mixture of (Ie)/(VIII) ≈ 92:8 was obtained, from which a pure (Ie) was isolated by the same method in the form of a colorless oil. R_f 0.30. PMR spectrum of (Ie) (δ, ppm, J, Hz): 1.62 br. s (12H, cis-Me), 1.70 br. s (15H, trans-Me, Me—C^3), 2.06 m (28H, H_2C), 4.18 d (2H, H_2C^1, J = 7), 5.13 m (7H, HC=C), 5.43 t (1H, HC^2, J = 7). The mass spectrum (m/z) of (Ie) was identical with that obtained above for (Ic).

LITERATURE CITED

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SYNTHESIS OF α,β-DISUBSTITUTED ALDEHYDES INVOLVING METALLATED 1-AZA-1,3-BUTADIENES IN THE PRESENCE OF PHOSPHINE COMPLEXES OF PALLADIUM

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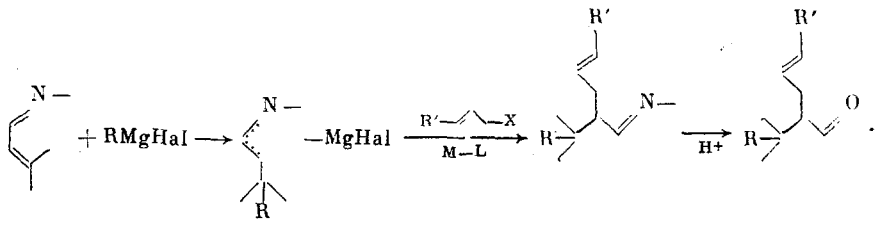
A novel catalytic method was developed for the synthesis of α,β-disubstituted aldehydes by the reaction of N-, O-, and S-containing allyl electrophiles with magnesium azaenolates obtained by metallation of α,β-unsaturated imines by Grignard reagents. The reaction is carried out with high regio- and stereoselectivity in the presence of phosphine complexes of palladium.

As a rule, the alkylation of ketones and aldehydes with the introduction of a new carbon–carbon bond in the α and β positions to the carbonyl group via a step of enolation of the corresponding keto group has been studied for the case of the simplest organic halides and carbonyl compounds [1-4]. At the time of our investigations, there was virtually no published information on the possibility of simultaneous introduction of two structurally different alkyl, alkenyl, and alkadienyl substituents in the α and β positions of α,β-unsaturated aldehydes using functionally substituted allyl compounds.

We assumed that the 1,4 addition of Grignard reagents to 1-azadienes would afford substituted magnesium azaenolates, whose subsequent catalytic reaction with allyl compounds and aryl halides would enable synthesis of α,β-disubstituted aldehydes of various structures according to the following scheme:



We chose as the model reaction the coupled 1,4-addition of EtMgBr to 1-methyl-4-phenyl-1-aza-1,3-butadiene [5], affording the 1-azaallyl anion (I), more stable than the 2-azaallyl anion [6]. The reaction of the reagent (I) with 1-methoxy-2,7-octadiene in the presence of 5 mole % $Pd(acac)_2$ + $2Ph_3P$ in an ether solution for 6 h at 38-40°C gave α,β-unsaturated imine (II), the treatment of which with a 10% HCl solution gave a mixture of threo- and erythro-α-(2E,7-octadienyl)-β-ethylhydrocinnamaldehydes (III) in 86% yield. The structure of stereoisomers (III) was established by spectral methods without their preliminary separation (Table 1).

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