SYNTHESIS OF IRREGULAR LAVANDULYL SERIES ISOPRENOIDS BASED ON 4-PHENYLTHIO-3-METHYLBUT-2Z-EN-1-OL

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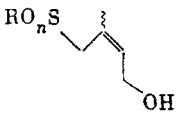
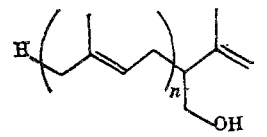
The three-stage cis- or trans-C_5 homologization of linear terpenols with the aid of the appropriate Z-(Ia), Z-(Ib), or E-blocks (Ic) is a convenient method for the stereospecific synthesis of regular isoprenoid chains, which are used in the biomimetic synthesis of polyprenols and some of their analogs [1-6]. We have developed a related technique using the newly available hydroxysulfide (Id) [7] to obtain irregular lavandulol-type (IIa) structures [8]. This is illustrated in the present communication by the synthesis of sesqui- (IIb) and triterpene (IIc) isoprenol derivatives of compound (IIa). These compounds are racemic forms of sesquilavandulol [9] (found in Peucedanum palustre) and ulmoprenol [10] (identified in Eucommia ulmoides), respectively.



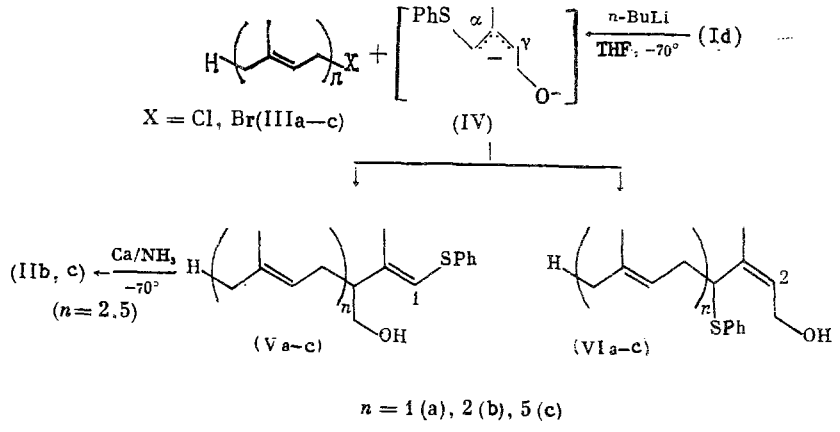
$n = 2$; R = $N(CH_2)_4O$; Z(Ia); $n = 2$; R = Ph; Z(Ib); $n = 2$, R = Ph; E(Ic); $n = 0$, R = Ph, Z(Id).



$n = 1$ (IIa); 2 (IIb); 5 (IIc)

The stepwise synthesis was begun with C-alkylation of ambidentate dianion (IV) with the appropriate allyl halide (III); the former is readily generated from hydroxysulfide (Id) under conditions developed earlier for the synthesis of related sulfonyl derivatives (Ia-c) [1-6]. Considering the well-known preference of electrophilic attack on the γ-center of allyl sulfide carbanions compared to α-attack for allylsulfonyl ions [11], in the case of compound (IV) we expected the vinyl sulfide alkylation product (V) to predominate over the allyl sulfide product (VI).

Treatment of dilithium derivative (IV) with prenyl chloride (IIIa) at −70°C in THF in the presence of HMPA gave the regioisomeric mixture (Va):(VIa) ≈ 1:2. Geranyl bromide (IIIb) gave the ratio (Vb):(VIb) ≈ 3:2; sesterterpenyl bromide (IIIc) gave an even higher ratio – (Vc):(VIc) ≈ 2:1. Compound (IIIc) was obtained via a standard reaction sequence including chain elongation of diterpenyl bromide (IIId) by one E-isoprene unit with the aid of hydroxysulfone



$n = 1$ (a), 2 (b), 5 (c)

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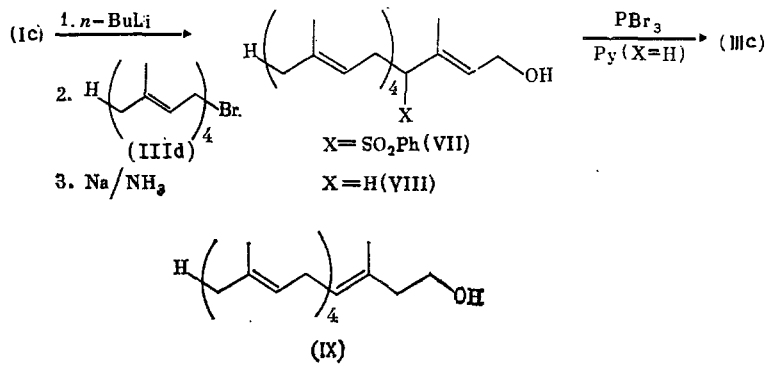
(Id) to give sulfone (VII) and its reductive desulfonation to yield geranyl-E,E,E-farnesol (VIII), previously observed in waxy secretions of Ceroplastes albolineatus and synthesized by another method [12]. It should be noted that the allyl alcohol (VIII) thus obtained contained (according to PMR data) up to 20% of the homoallyl compound (IX) [3], which decomposed when compound (VIII) was converted to bromide (IIIc) (cf. [1-4]).



The hydroxysulfide (Id) alkylation product ratios (C_α/C_γ) shown above are based on PMR spectral measurements of the sum of compounds (V) + (VI), purified by chromatography on SiO_2: integral intensities and intensities of triplet ($\delta \approx 5.5$ ppm and singlet ($\delta \approx 6.1$ ppm) signals belonging to olefin protons HC^2 and HC^1, respectively, of allyl alcohols (VI) and vinyl sulfides (V). These oily mixtures were subjected to further separation in order to extract the sesqui- and triterpene components (Vb, c) needed for the final stage of synthesis. Chromatographic separation of the mixture of regioisomers (Vb) and (VIb) proved very difficult. The mixture therefore was subjected to the modified Bouveault–Blanc reduction [13], which resulted in the selective decomposition of allyl sulfide (VIb). Consequently, vinyl sulfide (Vb) was easily isolated in an overall yield of 40%. The pair (Vc), (VIc) was separated into individual components without difficulty by flash chromatography on SiO_2.

The structures of the previously unknown compounds (Vb, c) and (VIc) were determined by a combination of data based on elemental and spectral analysis. The E-configuration of the α-isoprene unit of vinyl disulfides (Vb, c) was established on the basis of NER experimental data, which show a spatial proximity between protons HC^1 and CH_2O in these molecules. Reductive cleavage of the C–S bond in compounds (Vb, c) by reaction of Ca in NH_3 at −70°C, based on available information about related reactions [14], yielded the appropriate homoallyl alcohols (IIb, c) in good yield. The spectral properties of (IIc) were almost identical to the published data for this natural product [10].

Thus we have found a simple method for obtaining irregular lavanduloi-type isoprenoid chains based on a two-stage homologization of prenyl halides with the aid of Z-C_5 syntone (Id).

EXPERIMENTAL

IR spectra in $CHCl_3$ were recorded on a UR-20 instrument. ^1H and ^{13}C NMR spectra (62.89 MHz) were measured in $CDCl_3$ relative to TMS on a Bruker WM-250 spectrometer. Mass spectra were obtained on a Varian MAT CH-6 instrument at 70 eV. R_f values are given for a fixed SiO_2 (Silufol) layer in ether–hexane (1:1), unless specified otherwise.

1-Phenylthio-3-hydroxymethyl-2,6-dimethylhepta-1E,5-diene (Va) and 4-Phenylthio-3,7-dimethylocta-2Z,6-dien-1-ol (VIa). A 1.1-ml portion of 2 M n-BuLi in hexane (2.2 mmoles) and, 20 min later, 0.15 g (1.43 mmoles) of compound (IIIa) in 2 ml THF were added to a mixed (at −70°C) solution containing 0.21 g (1.08 mmoles) of compound (Id) in 5 ml THF and 1 ml HMPA (Ar). The reaction mixture was kept at −70°C for 15 min, was heated to 10°C over 30 min, and treated with ether and water. The aqueous layer was separated, neutralized with 20% H_2SO_4, and extracted with ether. The pooled organic extract was washed with water, dried with $MgSO_4$, and evaporated in a vacuum. This afforded 0.4 g of product, which was chromatographed on 20 g SiO_2. Gradient elution from hexane to ether (up to 30% of the latter) yielded 0.2 g (71%) of the mixture (Va):(VIa) ≈ 1:2 as a colorless oil with a R_f of 0.46. Found: C 73.53; H 8.59; S 12.19%. M^+ 262. $C_{16}H_{22}OS$. Calculated: C 73.23; H 8.45; S 12.22%. Molecular mass 262.4. PMR spectrum of (Va) (δ, ppm): 1.60, 1.71 and 1.79 br. s (9H, CH_3), 2.0-2.4 m (3H, HC^3, HC^4), 3.56 d (2H, CH_2O, J = 7 Hz), 5.1 m (1H, HC^5), 6.02 br. s (1H, HC^1), 7.1-7.5 m (5H, C_6H_5).

PMR spectrum of (VIa) (δ, ppm): 1.60, 1.67, and 1.79 br.s (9H, CH_3), 2.2-2.5 m (2H, HC^5), 3.7 m (2H, HC^1), 4.06 d.d (1H, HC^4, J = 6.5 and 15.5 Hz), 5.1 m (1H, HC^6), 5.40 br. t (1H, HC^2, J = 8 Hz), 7.2-7.5 m (5H, C_6H_5).

1-Phenylthio-3-hydroxymethyl-2,6,10-trimethylundeca-1E,5E,9-triene (Vb). As described above for compounds (Va) and (VIa), 3.03 g (15.6 mmoles) of (Id), 15.6 ml of 2 M n-BuLi in hexane (31.2 mmoles), and 3.4 g (15.66 mmoles) of (IIIb) in 50 ml THF and 3 ml HMPA afforded 6 g of product, which was chromatographed on 200 g SiO_2. Gradient elution from hexane to ether (up to 50% of the latter) yielded 3.36 g (65%) of the mixture (Vb):(VIb) = 3:2 (PMR) as a colorless oil with a R_f of 0.38. This mixture was dissolved in 15 ml THF and 5 ml ethanol and treated, with vigorous mixing, at 10-15°C with 0.8 g (34.8 mg-atom) Na for 4 h. The reaction mass was then diluted with 100 ml ether and 15 ml water. The aqueous layer was separated, neutralized with 20% H_2SO_4, and extracted with ether. Standard treatment of the pooled organic layer and chromatography of the residue (3 g), as described in the previous experiment, yielded 2.08 g (40%) of compound (Vb) as a colorless oil with a R_f of 0.39. IR spectrum (ν, cm^{-1}): 825, 880, 1035, 1090, 1245, 1380, 1440, 1480, 1585, 1620, 1670, 2850, 2920, 2960, 3010, 3060, 3450, 3620. PMR spectrum (δ, ppm): 1.61, 1.62, 1.68, and 1.83 br. s (12H, CH_3), 2.0-2.3 m (6H, CH_2), 2.45 m (1H, HC^3), 3.62 br. d (2H, CH_2O, J = 7.5 Hz), 5.1 m (2H, HC^5, HC^9), 6.07 br. s (1H, HC^1), 7.1-7.4 m (5H, C_6H_5). Found: C 76.50; H 9.15; S 9.79%. M^+ 330. $C_{21}H_{30}OS$. Calculated: C 76.31; H 9.15; S 9.70%. Molecular mass, 330.5.

(±)-Sesquilavandulol (IIb). A 0.3-g portion (0.91 mmole) of compound (Vb) in 3 ml THF was added to a vigorously mixed (at −70°C) solution (Ar) containing 0.24 g (6 mg-atom) Ca in 10 ml NH_3. The reaction mixture was kept at −70°C for 40 min. It was then decomposed with excess NH_4Cl, the NH_3 was evaporated, and the residue was treated with hexane and water. Standard treatment of the extract afforded 0.2 g of product, which was chromatographed on 15 g SiO_2. Elution with hexane–ether (4:1) yielded 70 mg (31%) of compound (IIb) as a colorless liquid with a bp of 79-80°C (0.05 mm), n_D^{20} 1.4855. IR spectrum (ν, cm^{-1}): 840, 900, 985, 1040, 1110, 1190, 1245, 1330, 1375, 1445, 1645, 1670, 2860, 2920, 2970, 3015, 3075, 3570, 3620. PMR spectrum (δ, ppm): 1.56, 1.64, and 1.66 br. s (12H, CH_3), 2.0 m (6H, CH_2), 2.25 m (1H, HC^3), 3.50 m (2H, CH_2O), 4.80 and 4.91 br. s (2H, HC^1), 5.10 m (2H, HC^5, HC^9). ^{13}C NMR spectrum (δ, ppm): 16.2 ($\underline{C}H_3$–C^6), 17.7 (cis-$\underline{C}H_3$–C^{10}), 19.7 ($\underline{C}H_3$–C^2), 25.7 (trans-$\underline{C}H_3$–C^{10}), 26.7 (C^8), 28.5 (C^4), 39.8 (C^7), 50.1 (C^3), 63.8 ($\underline{C}H_2O$), 113.0 (C^1), 122.1 (C^5), 124.3 (C^9), 131.4 (C^{10}), 136.4 (C^6), 145.6 (C^2). Found: C 81.28; H 11.90%; M^+ 222. $C_{15}H_{26}O$. Calculated: C 81.02; H 11.79%. Molecular mass 222.4.

4-Phenylsulfonyl-3,7,11,15,19-pentamethyleicosa-2E,6E,10E,14E,18-pentaen-1-ol (VII). A 3-ml portion of 2 M n-BuLi in hexane (6 mmoles) was added to a mixed (at −70°C) solution containing 0.67 g (2.96 mmoles) of compound (Ic) [15] in 20 ml THF (Ar); after 20 min bromide (IIId), freshly prepared from 0.96 g (3.3 mmoles) geranyllinalool [2] in 5 ml THF and 0.5 ml HMPA, was added. The reaction mixture was kept at −70°C for 30 min; it was then heated to 15°C for 1 h and decomposed with ether and water. Standard treatment of the organic layer afforded 2 g of product, which was chromatographed on 60 g SiO_2. Gradient elution from hexane to ether (up to 70% of the latter) yielded 1 g (61%) of compound (VII) as a colorless oil with a R_f of 0.38 (ether–hexane, 2:1). IR spectrum (ν, cm^{-1}): 890, 945, 1000, 1090, 1150, 1305, 1385, 1450, 1590, 1665, 2860, 2930, 2975, 3520, 3615. PMR spectrum (δ, ppm, J, Hz): 1.55, 1.58, 1.65, and 1.69 br. s (18H, CH_3), 2.0-2.8 m (14H, CH_2), 3.50 d.d (1H, HC^4, J = 4.5 and 11), 4.04 br. d (2H, HC^1, J = 6), 4.88 br. t (1H, HC^6, J = 6.5), 5.1 m (3H, HC=C), 5.37 br. t (1H, HC^2, J = 6), 7.5-7.9 m (5H, C_6H_5). ^{13}C NMR (δ, ppm): 14.5 ($\underline{C}H_3$–C^3), 16.0, 16.3 (CH_3–C^7, $\underline{C}H_3$–C^{11} $\underline{C}H_3$–C^{15}), 17.7 (cis-CH_3–C^{19}), 24.6, 26.6, 26.7, 26.8 (C^5, C^9, C^{13}, C^{17}), 25.7 (trans-$\underline{C}H_3$–C^{19}), 39.7 (C^8, C^{12}, C^{16}), 59.1 (C^1), 73.7 (C^4), 118.4 (C^6), 123.8, 124.2, 124.5 (C^{10}, C^{14}, C^{18}), 131.2 (C^{19}), 133.6 (C^2), 134.6, 135.0, 135.3 (C^7, C^{11}, C^{15}), 138.9 (C^3), 128.9, 129.0, 134.6, 138.2 (C_6H_5). Found: C 75.01; H 9.50, S 6.42%. M^+ 498. $C_{31}H_{46}O_3S$. Calculated: C 74.65; H 9.30; S 6.43%. Molecular mass 498.8.

Geranyl-E,E,E-farnesol (VIII). A 50-ml portion of hexane, 0.46 g (1.28 mmoles) dibenzo-18-crown-6, and, after 20 min, 3.15 g (6.32 mmoles) of compound (VII) in 10 ml THF were added, with vigorous mixing (at −70°C), to a solution containing 1.5 g (65.25 mg-atom) Na in 50 ml NH_3 (Ar). The reaction mass was mixed at −70°C for 30 min; it was then decomposed with excess NH_4Cl, NH_3 was evaporated, and the residue was treated with hexane and water. Standard treatment of the organic layer afforded 2.3 g of product, which was chromatographed on 80 g SiO_2. Elution with hexane–ether (7:3) yielded 1.26 g (56%) of compound (VIII) [12] as a colorless oil with a R_f of 0.47. PMR spectrum (δ, ppm; J, Hz): 1.61 and 1.70 br. s (18H, CH_3), 1.9-2.2 m (16H, CH_2), 4.16 br. d (2H, HC^1, J = 7), 5.1 m (4H, HC=C), 5.43 br. t (1H, HC_2), J = 7).

1-Phenylthio-3-hydroxymethyl-2,6,10,14,18,22-hexamethyltricosa-1E,5E,9E,13E,17E,21-hexene (Vc) and 4-Phenylthio-3,7,11,15,19,23-hexamethyltetracosa-2Z,6E,10E,14E,18E,22-hexaen-1-ol (VIc). As described above for compounds (Va) and (VIa), 0.45 g (2.32 mmoles) of compound (Id), 2.32 ml of 2 M n-BuLi in hexane (4.64 mmoles), and bromide (IIIc), freshly prepared from 0.4 g (1.12 mmoles) of compound (VIII) in 15 ml THF and 1 ml hexamethanol (Ar), afforded 0.3 g of product, which was chromatographed on 30 g SiO_2. Gradient elution from hexane to ether (up to 30% of the latter) yielded 60 mg (10%) of compound (VIc) and 120 mg (20%) of compound (Vc).

Hydroxysulfide (Vc) is a colorless oil with a R_f of 0.55. IR spectrum (ν, cm^{-1}): 990, 1030, 1095, 1160, 1320, 1385, 1450, 1485, 1585, 1665, 2850, 2930, 2975, 3040, 3625. PMR spectrum (δ, ppm): 1.60, 1.70, and 1.83 br. s (21H, CH_3), 1.9-2.2 m (18H, CH_2), 2.4 m (1H, HC^3), 3.63 br. d (2H, CH_2O, J = 7 Hz), 5.1 m (5H, HC=C), 6.08 br. s (1H, HC^1), 7.2-7.4 m (5H, C_6H_5). Found: C 80.76; H 10.58; S 5.78%. M^+ 534. $C_{36}H_{54}OS$. Calculated: C 80.84; H 10.18; S 5.99%. Molecular mass 534.9.

Hydroxysulfide (VIc) is a colorless oil with a R_f of 0.57. IR spectrum (ν, cm^{-1}): 920, 960, 995, 1030, 1090, 1110, 1160, 1240, 1385, 1440, 1590, 1665, 2860, 2935, 2975, 3025, 3580, 3620. PMR spectrum (δ, ppm, J, Hz): 1.63, 1.71 and 1.84 br. s (21H, CH_3), 2.0-2.2 m (16H, CH_2), 2.3-2.6 m (2H, HC^5), 3.7 m (2H, HC^1), 4.10 d.d (1H, HC^4, J = 6.5 and 9), 5.1 m (5H, HC=C), 5.44 br. t (1H, HC^2, J = 7), 7.2-7.5 m (5H, C_6H_5). Mass spectrum (m/z): 534 (M^+), 516 ($-H_2O$), 465, 425, 398, 329, 203, 201, 193, 174, 165, 151, 149, 137, 135, 123, 109, 107, 95, 93, 83, 79.

(±)-Ulmoprenol (IIc). As described above for compound (IIb), 0.15 g (0.28 mmole) of compound (Vc) and 0.11 g (2.74 mg-atom) Ca in 10 ml NH_3 and 2 ml THF afforded 0.1 g of product, which was chromatographed on 20 g SiO_2. Elution with hexane–ether (4:1) yielded 50 mg (42%) of compound (IIc) as a colorless oil with a R_f of 0.58. PMR spectrum (δ, ppm): 1.60, 1.68 and 1.71 br. s (21H, CH_3), 1.9-2.2 m (1H, CH_2), 2.3 m (1H, HC^3), 3.55 m (2H, CH_2O), 4.82 and 4.93 br. s (2H, HC^1), 5.1 m (5H, HC=C).

CONCLUSIONS

1. The dianion that is generated by a strong base from 4-phenylthio-3-methylbut-2Z-en-1-ol undergoes a predominantly γ-alkylation in the presence of terpenyl halides.

2. A simple method was found for synthesizing irregular isoprenoids of the lavandulol series.

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