tional bands characteristic for 1,3 disubstituted benzene). Weak bands at 3300 cm^{-1} (−C≡H) and 2100 cm^{-1} (−C≡C−) were associated with residual (I) in the analyzed mixture.

The proton NMR spectra were recorded on a WH-360 spectrometer. Spectrum of Z-(I) (CD_3OD): 360 MHz, δ, ppm, TMS; J, Hz: 1.86 d (3H, $-CH_3$, J = 1.46) 3.30, 3.34, (1H, OH),* 3.55 s (1H, C≡CH), 4.24 dd (2H, $-CH_2-$, J_1 = 6.84, J_2 = 1.5), 5.88 tq (1H, =CH, J_1 = 6.84, J_2 = 1.46). The proton NMR spectrum of (II) (same conditions): 2.04 d (3H, CH_3, J_2 = 1.46), 2.31 s (3H, CH_3), 3.30, 3.34 (1H, OH),* 3.97 dd (2H, CH_2, J_1 = 6.84, J_2 = 1.5), 5.62 tq (1H, =CH, J_1 = 6.84, J_2 = 1.46); protons of the benzene ring: 6.92 d (1H), 6.98 s (1H), 7.05 d (1H), 7.16 t (1H).

Formaldehyde was determined by passing the evolved reaction gas through a solution of chromotropic acid [7].

The authors express their gratitute to A. F. Bochkov and A. B. Gagarinov for helpful discussions on the results of this work, and also to A. D. Pershin for recording the proton NMR spectra.

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SYNTHESIS OF DOLICHOL-TYPE (S)-HEXA- AND (S)-HEPTAPRENOLS

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UDC 542.91:547.366

(R)-1-Phenysulfonyl-2-methylbutan-4-ol has been used as starting material for the stepwise synthesis of the dolichol-related hexa- and heptaprenols (S)-3,7,11,15,19,23-hexamethyltetraeicosa-6Z,10Z,14E,18E,22-pentaene-1-ol and (S)-3,7,11,15,19,23,27-heptamethyloctaeicosa-6Z,10Z,14E,18E,22E,26-hexaen-1-ol.

The membrane-active polyprenols (dolichols) found in the cellular tissues of mammals have been identified as monochiral(S)-alcohols saturated at the α-isoprene moiety (I) [1]. A reliable source for these low molecular weight bioregulants is by homologization of the regular isoprenoid chains in the much more readily available [2] alcohols (IV) of plant origin, using suitable saturated bifunctional C_5-synthons such as (VII) or (VIII) [3]. Such a method has recently been employed [4] for the total synthesis of dolichols (I) from an appropriate mixture of plant polyprenols (IV) and the rather inaccessible chiral precursor (VII) [5]. We here consider the possibility of using the (R)-hydroxysulfone (VIII) as a novel chiral C_5 unit, as illustrated by its use to obtain the novel dolichol-type (S)-hexaprenol (WT_2C_2SOH) (II) and (S)-heptaprenol (WT_3C_2SOH) (III) from the sester- (V) [6] and diterpenol (VI) [7] respectively.

*The proton signals of the alcohol group consisted of two peaks, one of which corresponded to the OH signal of methyl alcohol, and the combined integrated intensity corresponded to 1H. Apparently, there was an exchange between the OH of (I) or (II) and OD of CD_3OD.

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Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 9, pp. 2052-2056, September, 1989. Original article submitted July 1, 1988.

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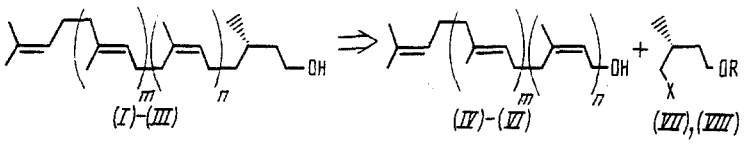


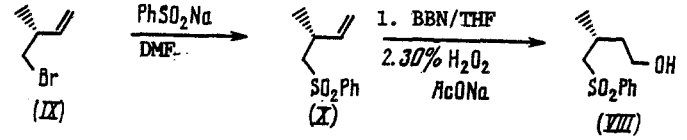
(I)-(III) (IV)-(VI) (VII),(VIII)

$m = 2, 3, n \geqslant 3$ (I), (IV); $m = n = 2$ (II), (V); $m = 3, n = 2$ (III), (VI);
R = THP, X = Br (VII); R = H, X = SO_2Ph (VIII).

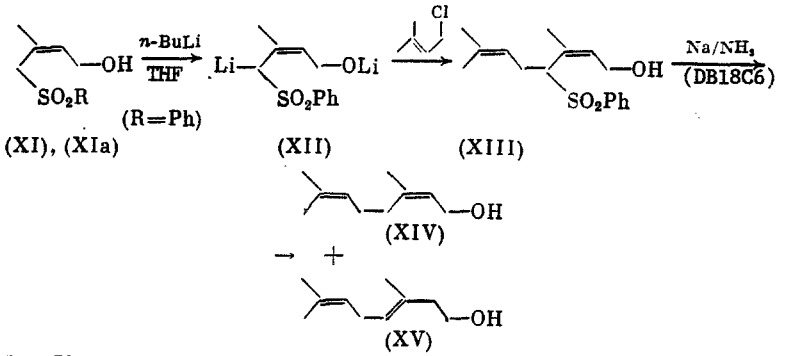
The hydroxysulfone (VIII) required for this purpose was obtained in three steps from the recently described [8] homoallyl bromide (IX), which is readily available from a by-product in the synthesis of semisynthetic steroids [9]. Treatment of (IX) with $PhSO_2Na$ in DMF affords the unsaturated sulfone (X). Anti-Markovnikov hydration of this compound, using 9-borabicyclo·[3.3.1]nonane (BBN) at the hydroboration stage, gave the required chiral intermediate (VIII) in an overall yield of ∿35%. The spectral properties of this compound were identical with those reported for (±)-(VIII) [10].

The norisoprenologs (V) and (VI) required for the preparation of the terpenols (II) and (III) were obtained by stepwise cis-C_5-homologation [3, 6, 7, 11] of the appropriate oligoprenyl halides. In the cases described below, the Z-hydroxysulfone (XI) [12] rather than the previously used, less readily accessible Z-hydroxysulfonamide (XIa) [6, 7] was employed to obtain the sesterterpenol (V).

Alkylation of the lithium derivative (XII) of the hydroxysulfone (XI) with prenyl chloride proceeded smoothly to give the allyl sulfone (XIII). The latter served as a convenient model for establishing the conditions required for the Birch reductive cleavage of these compounds at the C–S bond with minimum allyl migration of the C=C bond, and especially the need to use dibenzo-18-crown-6 (DB18C6) in this reaction, which was found to be useful



(IX) (X) (VIII)



(XI), (XIa) (R=Ph) (XII) (XIII) (XIV) (XV)

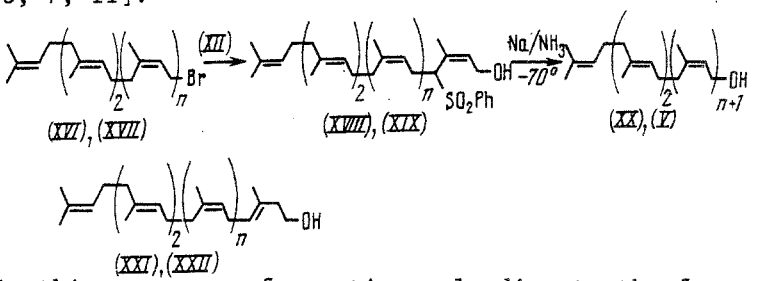
R = Ph (XI), $N(CH_2)_4O$ (XIa).

in the case of the sulfonamide analog (XIII) [13], but less so in its higher prenologs [6, 7, 11]. It was found that treatment of (XIII) with alkali metals in amines under the usual conditions (cf. [13]) for such cases (controlled temperatures, addition of cosolvent, DB18·C6, etc.) gave in virtually the same yield (70-80%) a mixture of the known alcohols (XIV)/(XV) ≈ 9/1.

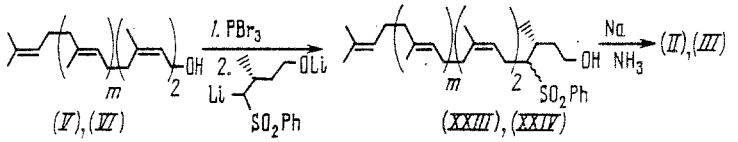
Alkylation of (XII) with farnesyl bromide (XVI) gave the sulfone (XVIII), the structure of which was confirmed spectrally. Reductive desulfurization of (XVIII) with sodium in ammonia at −70°C afforded the known [14] diterpenol (XX). Repetition of these latter operations via the bromide (XVII), obtained from (XX) and freshly distilled but without further purification, and the hydroxysulfone (XIX) gave the required sesterterpenol (V).

Reductive cleavage of the C–S bond in the allyl sulfones (XVIII) and (XIX) under the conditions described, including the presence of catalytic amounts of DB18C6, resulted in the formation of ≥10% (PMR) of the isogeraniol (XV) related homoallyl alcohols (XXI) and (XXII) respectively, identified previously by PMR spectroscopy in the mixed reduction products of the allylsulfonamides corresponding to the sulfones (XVIII) and (XIX) [6]. It may be pointed out here that the (XXI) and (XXII) present as impurities are removed under the conditions used for the conversion of the allyl alcohols (XX) and (V) into the corres-

sponding allyl bromides and n = 0 (XVI), (XVIII), (XX), (XXI); n = 1 (V), (XVII), (XIX), (XXII), did not prevent the use of the latter in the next stage of the stepwise route to the linear terpenols [3, 6, 7, 11].



The final step in this sequence of reactions, leading to the formation of the required (S)-terpenols (II) and (III), was by alkylating the dilithium derivative of the (R)-hydroxysulfone (VIII) with allyl bromides freshly prepared from the alcohols (V) and (VI), carried out in accordance with the two-step method previously developed by the authors for the preparation of related racemic compounds [11]. The structures of the diastereoisomeric sulfones (XXIII) and (XXIV) obtained in the first step, like the products of their reductive desulfurization (II) and (III), were confirmed by comparison of their spectral properties with those found for the corresponding racemates.



$m = 2$ (V), (XXIII), $m = 3$ (VI), (XXIV).

Thus, the two-step C_5-homologation of regular, linear terpenols with the (R)-hydroxysulfone (VIII) is a reliable method for the synthesis of dolichol-type compounds with the natural (S)-configuration at the sole chiral center.

EXPERIMENTAL

IR spectra were obtained on a UR-20 in CCl_4. The PMR spectra of solutions in $CDCl_3$ were obtained on a Bruker WM-250 spectrometer, and mass spectra on a Varian MAT CH-6 at 70 eV. The optical rotation was measured on a Perkin-Elmer 141 polarimeter. The R_f values given are for bound layers of Silufol silica.

(R)-1-Phenylsulfonyl-2-methyl-3-butene (X). A suspension of 4.5 g (27.4 mmoles) of $PhSO_2N$ and 2.1 g (13.8 mmoles) of (IX) [8] in 5 ml of DMF was stirred at 50°C for 10 h, then diluted with water and extracted with ether. The combined organic layers were washed with water, dried over $MgSO_4$, evaporated under reduced pressure, and the residue (1.8 g) chromatographed on 60 g of silica. Gradient elution from hexane to ether (up to 50% of the latter) gave 1.38 g (48%) of (X) as a colorless oil, R_f 0.49 (hexane–ether, 1:1), $[\alpha]_D^{20}$ +2.4° (c 4, $CHCl_3$). IR spectrum (ν, cm^{-1}): 925, 1000, 1085, 1150, 1240, 1310, 1380, 1400, 1450, 1590, 1645, 2885, 2940, 2985, 3040, 3080. PMR spectrum (δ, ppm): 1.13 d (3H, CH_3, J = 7 Hz), 2.5-3.3 m (3H, CH_2S, HC^2), 4.7-5.2 m (2H, $H_2C{=}C$), 5.7 m (1H, $HC{=}C$), 7.3-7.8 m (5H, C_6H_5). Found: C 62.85; H 6.96; S 15.47%. $C_{11}H_{14}O_2S$. Calculated: 62.83; H 6.71; S 15.24%.

(R)-1-Phenylsulfonyl-2-methylbutan-4-ol (VIII). To a stirred suspension of 0.98 g (8 mmoles) of BBN on 10 ml of THF under argon was added at 10°C a solution of 0.8 g (3.8 mmoles) of (X) in 5 ml of THF. After 20 min, the solution was warmed to 25°C, kept at this temperature for 30 min, cooled to 0°C, and a solution of 1.65 g (20.1 mmoles) of AcONa in 5 ml of water added, followed by 4.5 g of 50% H_2O_2 (39.7 mmoles), and the mixture kept at 20°C for 12 h. It was then treated with ether and water, and the aqueous layer separated and extracted with ether. The combined extracts were worked up in the usual way to give 1.9 g of material which was chromatographed on 100 g of SiO_2. Gradient elution from hexane to ether (up to 80% of the latter) gave 0.6 g (69%) of (VIII) as a viscous oil, R_f 0.32 (ether), $[\alpha]_D^{23}$ −7.0° (c 9, EtOH), the spectral characteristics of which (IR, PMR) were similar to those reported previously [10] for (±)-(VIII).

4-Phenylsulfonyl-3,7-dimethylocta-2Z,6-dien-1-ol (XIII). To a solution of 1 g (4.42 mmoles) of (XI) [12] in 20 ml of THF and 1 ml of HMPA was added with stirring at −70°C under argon 5.5 ml of a 1.61 M solution of n-BuLi in hexane (8.86 mmoles) over five minutes, then

after 20 min at −70°C a solution of 0.6 g (5.74 mmoles) of prenyl chloride in 5 ml of THF was added over five minutes. The mixture was kept at −70°C for 30 min, then warmed to 10°C for one hour and treated with ether and water. The aqueous layers was separated, neutralized with 50% sulfuric acid, and extracted with ether. The combined organic layers were washed with water, dried over $MgSO_4$, evaporated under reduced pressure, and the residue (1.2 g) chromatographed on 40 g of silica. Gradient elution from hexane to ether (up to 50% of the latter) gave 1.13 g (87%) of (XIII) as a colorless oil, R_f 0.34 (ether–hexane, 2:1). IR spectrum (ν, cm^{-1}): 840, 865, 960, 1000, 1020, 1085, 1140, 1240, 1300, 1385, 1450, 1590, 1660, 2880, 2930, 2970, 3010, 3510, 3610. PMR spectrum (δ, ppm): 1.47, 1.53, and 1.74 br. s (9H, CH_3), 2.5 m (2H, HC^5), 3.8 m (2H, CH_2O), 4.06 d.d (1H, CHS, J = 7 and 12 Hz), 4.7 m (1H, HC^6), 5.77 br. t (1H, HC^2, J = 7 Hz), 7.4-7.8 m (5H, C_6H_5). Found: C 65.41; H 7.49; S 10.39%; M^+ 294. $C_{16}H_{22}O_3S$. Calculated: C 65.27; H 7.53; S 10.89%; mol. mass 294.4.

Nerol (XIV) and Isogeraniol (XV). To a vigorously stirred solution of 0.28 g (12.2 mg·atom) of Na in 50 ml of ammonia was added at −70°C under argon over five minutes a solution of 0.5 g (1.7 mmoles) of (XIII) in 5 ml of THF. The mixture was kept at −70°C for 30 min, then decomposed with an excess of ammonium chloride, the ammonia evaporated, and the residue treated with water and extracted with hexane. Workup of the extract in the usual way gave 0.35 g of material which was chromatographed on 20 g of silica. Gradient elution from hexane to ether (up to 50% of the latter) gave 0.21 g (80%) of a mixutre of (XIV) and (XV) in a ratio of ∿9:1, found by comparison (GLC and PMR) with samples of mixtures of these compounds obtained previously [13].

4-Phenylsulfonyl-3,7,11,15-tetramethylhexadeca-2Z,6E,10E,14-tetraen-1-ol (XVIII). To a solution of 2.2 g (9.7 mmoles) of (XI) in 20 ml of THF and 1.5 ml of HMPA was added with stirring at −70°C under argon 9.8 ml of a 2 M solution of n-BuLi in hexane (19.6 mmoles), followed after 20 min at −70°C by a solution in 7 ml of THF of the bromide (XVI), freshly prepared as described in [15] from 2 g (9.1 mmoles) of E, E-farnesol, over 10 min. The mixture was kept at −70°C for 30 min, then warmed to 10°C over 1 h, and treated with ether and water. The aqueous layer was separated, neutralized with 50% sulfuric acid, and extraced with ether. The combined organic layers were washed with water, dried over $MgSO_4$, evaporated under reduced presure, and the residue (∿4 g) chromatographed on 200 g of silica. Gradient elution from hexane to ether (up to 80% of the latter) gave 2.71 g (69%) of (XVIII) as a colorless oil, R_f 0.38 (ether–hexane, 2:1). IR spectrum (ν, cm^{-1}): 965, 1000, 1085, 1150, 1245, 1305, 1385, 1450, 1590, 1665, 2860, 2930, 2975, 3020, 3520, 3615. PMR spectrum (δ, ppm): 1.50, 1.52, 1.56, 1.64, and 1.80 br. s (15H, CH_3), 1.8-2.1 m (8H, CH_2), 2.6 m (2H, HC^5), 3.84 br. d (2H, CH_2O, J = 7.5 Hz), 4.13 d.d (1H, HC^4, J = 7 and 9 Hz), 4.78 br. t (1H, HC^6, J = 7 Hz), 5.0 m (2H, HC=C), 5.88 br. t (1H, HC^2, J = 7.5 Hz), 7.5-7.9 m (5H, C_6H_5). Found: S 7.42%; M^+ 430. $C_{26}H_{38}O_3S$. Calculated: S 7.44%; of mol. mass 430.6.

Diterpenol (XX). To a solution of 0.16 g (6.96 mg·atom) of sodium in 10 ml of ammonia at −70°C were added successively with vigorous stirring under argon 10 ml of hexane, followed after 5 min by a solution of 0.34 g (0.79 mmole) of (XVIII) in 3 ml of THF. The mixture was kept at −70°C for 15 min, then decomposed with an excess of ammonium chloride, the ammonia evaporated, and the residue treated with water and extracted with hexane. The usual workup of the extract gave 0.3 g of material which was chromatographed on 15 g of silica. Gradient elution from hexane to ether (up to 20% of the latter) gave 0.15 g (65%) of (XX), R_f 0.44 (ether–hexane, 1:1), containing ∿10% (by PMR) of the homoallyl alcohol (XXI). The spectral characteristics (IR and PMR) were similar to those reported previously [6, 14] for this compound.

Hydroxysulfone (XIX). As described for (XVIII), from 0.7 g (3.1 mmoles) of (XI), 3.1 ml of 2 M n-BuLi in hexane (6.2 mmoles), and the bromide (XVII), freshly prepared from 0.61 g (2.1 mmoles) of (XX), in 10 ml of THF and 1 ml of HMPA, there was obtained 1.3 g of material which was chromatographed on 60 g of silica. Gradient elution from hexane to ether (up to 50% of the latter) gave 0.49 g (47%) of (XIX), R_f 0.38 (ether–hexane, 2:1), identical (IR and PMR) with the sample of this compound obtained previously [11].

Sesterterpenol (V). As described for (XX), from 0.42 g (0.84 mmole) of (XIX), 0.16 g (6.96 mg·atom) of sodium in 20 ml of ammonia, 10 ml of hexane, and 5 ml of THF there was obtained 0.3 g of material which was chromatographed on 20 g of silica. Gradient elution from hexane to ether (up to 20% of the latter) gave 0.17 g (56%) of (V), R_f 0.47 (ether–hexane, 1:1), containing ~10% (by PMR) of the homoallyl alcohol (XXII). Its spectral characteristics (IR and PMR) were similar to those reported previously [6] for this compound.

Hydroxysulfone (XXIII). To a stirred solution of 0.46 g (2 mmoles) of (VIII) in 10 ml of THF and 1 ml of HMPA was added at −50°C under argon over five minutes 2.05 ml of a 2 M solution of n-BuLi in hexane (4.1 mmoles). The mixture was kept at −50°C for 15 min, then treated over five minutes at −30°C with a solution of the bromide, freshly prepared from 0.29 g (0.8 mmole) of (V), in 4 ml of THF. The mixture was stirred for 30 min at −30°C, then warmed to 10°C over one hour and treated with ether and water. The aqueous layer was separated, neutralized with 50% sulfuric acid, and extracted with ether. The combined extracts were washed with water, dried over $MgSO_4$, evaporated under reduced pressure, and the residue (0.6 g) chromatographed on 50 g of silica. Gradient elution from hexane to ether (up to 70% of the latter) gave 0.11 g (24%) of (XXIII) as a colorless oil, R_f 0.48 (ether–hexane, 3:1), identical (IR and PMR) with a sample of racemic (XXIII) obtained previously [11].

(S)-Hexaprenol (II). To a solution of 40 mg (1.74 mg·atom) of sodium in 10 ml of ammonia at −60°C under argon was added over five minutes with stirring a solution of 0.11 g (0.19 mmoles) of (XXIII) in 4 ml of THF. The mixture was kept at −60°C for 20 min, then decomposed with an excess of ammonium chloride, the ammonia evaporated, and the residue treated with ether and water. The combined extracts were washed with water, dried over $MgSO_4$, and evaporated under reduced pressure to give 0.1 g of material which was chromatographed on 10 g of silica. Gradient elution from hexane to ether (up to 20% of the latter) gave 36.5 mg (45%) of (II) as a colorless oil, R_f 0.50 (ether–hexane, 1:1), $[\alpha]_D^{20}$ −2.0° (c 3.5, EtOH), identical (PMR and IR) with a sample of (±)-(II) reported previously [11].

Hydroxysulfone (XXIV). As described for (XXIII), from 0.6 g (2.6 mmoles) of (VIII), 2.65 ml of 2 M n-BuLi in hexane (5.3 mmoles), and the bromide freshly prepared from 0.63 g (1.5 mmoles) of (VI) [7], in 20 ml of THF and 1 ml of HMPA there was obtained 1.3 g of product which was chromatographed on 70 g of silica. Gradient elution from hexane to ether (up to 70% of the latter) gave 0.11 g (12%) of (XXIV) as a colorless oil, R_f 0.45 (ether–hexane, 3:1), identical (IR and PMR) with a previously described sample of racemic (XXIV).

(S)-Heptaprenol (III). As described in (II), from 0.11 g (0.17 mmoles) of (XXIV), 30 mg (1.3 mg·atom) of sodium in 10 ml of ammonia, and 3 ml of THF there was obtained 0.11 g of product which was chromatographed on 10 g of silica. Gradient elution from hexane to ether (up to 20% of the latter) gave 49.7 mg (59%) of (III) as a colorless oil, R_f 0.62 (ether–hexane, 1:1), $[\alpha]_D^{20}$ −1.2° (c 5, EtOH), identical (IR and PMR) to a previously described sample [11] of (±)-(III).

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