SYNTHESIS OF 17E- AND 17Z-CHEILANTHENE-13α,19-DIOLS

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cis- and trans-Cheilanthene-3α,19-diols — structurally close analogues of the parent of the cheilanthane sesterterpenoids cheilantha-6α,13α,19-triol and substances related to it — have been synthesized.

One of the carbon skeletons upon which the sesterterpenoids are based is represented by the hypothetical tricyclic hydrocarbon cheilanthane (I). So far, a single compound belongs to this type of structure — cheilanthatriol (II), which was isolated by Suk Dev et al. [1, 2] from Cheilanthea farinosa. This substance has not been synthesized.

In the present paper we describe the synthesis of 17E- and 17Z-cheilanthene-13α,19-diols, (III) and (IV), which are close analogues of cheilanthatriol (II), from 15-bishomoisoagatha-13α,22-diol (V), the synthesis of which from sclareol we have performed previously [3]. The diol (V) was acetylated selectively with acetic anhydride in pyridine to the hydroxyacetate (VI), the hydroxy group of which was then protected in the form of the tetrahydropyranyl ether. The ether-ester (VII) was saponified with alcoholic alkali to the hydroxyether (VIII). The same product was formed on the reduction of the ether-ester (VII) with lithium tetrahydroaluminate in ether.

Oxidation of the hydroxyether (VIII) with chromium trioxide in pyridine led to the aldehydoether (IX), which reacted with methylmagnesium iodide to form the hydroxyether (X). This was oxidized with chromium trioxide in pyridine to the keto ether (XI), giving on reaction with methyl trimethylsilylacetate in the presence of lithium diisopropylamide in tetrohydrofuran a mixture (~1.3:1) of the 17E- and 17Z-esters (XII) and (XIII). It was separated by chromatography on a column of silica gel under pressure. As was to be expected, the cis-ester (XIII) was eluted from the column first. The configurations of the esters (XII) and (XIII) at the trisubstituted double bond were established on the basis of their PMR spectra: in the cis-ester (XIII) the methyl group at C17 resonated in a stronger field (1.90 ppm) than in the trans-ester (XI) (2.13 ppm), which is in agreement with literature information [4]. The ether-esters (XII) and (XIII) were reduced, respectively, to the hydroxy ethers (XIV) and (XV) with lithium tetrahydroaluminate in the presence of cerium trichloride in tetrahydrofuran [5]. The tetrahydropyranyl groups in the ether-ester (XII) and (XIII) were eliminated by hydrolysis with sulfuric acid in methanol.

The structures and stereochemistries of the hydrolysis products — 17E- and 17Z-cheilanthene-13α,19-diols (III) and (IV) were confirmed by their IR and PMR spectra. In particular, in agreement with literature information [6], the methyl group at C17 in the trans-diol (III) resonated in a stronger field than in the cis-diol (IV) (1.33 and 1.38 ppm, respectively).

It must be mentioned that in the synthesis of 17E- and 17Z-cheilanthene-13α,19-diols (III) and (IV) the yields of products proved to be fairly high (~80-90%) at all stages.

Thus, we have effected a 9-stage synthesis of 17E- and 17-cheilanthene-13α,19-diols (III) and (IV) from the bishomoisoagathanediol (V) with an overall yield of 31%.

EXPERIMENTAL

For the general part, see [3].

The Hydroxyacetate (VI). At room temperature, 0.3 ml of acetic anhydride was added to a solution of 500 mg of the diol (V) [3] in 7 ml of dry pyridine, and the mixture was left

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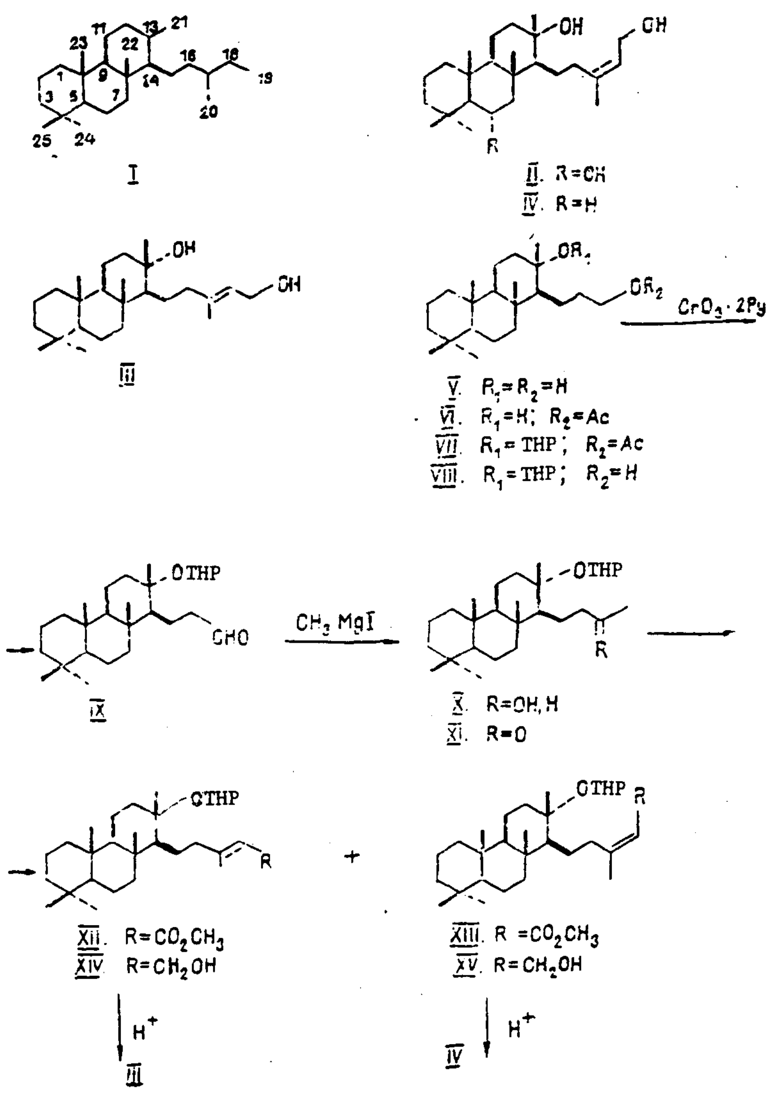

at the ordinary temperature for 10 h. After the usual working up, 527.2 mg (93.7%) of the hydroxyacetate (VI) was obtained: mp 83-84°C (from petroleum ether); $[\alpha]_D^{22}$ −29° (c 2.2). IR spectrum (cm^{-1}): 1235, 1733 (OAc), 1150, 3470, 3600 (OH group). PMR spectrum ($CDCl_3$, ppm): 0.73 (s, 12H, CH_3 at C4, C8 and C10), 1.08 (s, 3H, CH_3 at C13); 1.98 (s, 3H, CH_3COO—), 4.02 (m, 2H, —CH_2O—). Found %: C 75.96; H 11.23. $C_{24}H_{42}O_3$. Calculated %: C 76.14; H 11.18.

The Ether-Ester (VII). A solution of 4.2 g of the hydroxyacetate (VI) in 50 ml of dry benzene was treated with 3 ml of freshly distilled dihydropyran and 27 mg of p-toluenesulfonic acid, and the mixture was stirred at room temperature for 2 h. Then a 1% solution of KOH (10 ml) was added to the mixture and it was worked up in the usual way. The reaction product (4.92 g) was chromatographed on a column containing 85 g of silica gel. A 9:1 mixture of petroleum ether and ethyl acetate eluted 4.67 g (91% with allowance for the initial hydroxy acetate recovered) of the ether-ester (VII): mp 78.5-80°C (from petroleum ether); $[\alpha]_D^{20}$ −7.7° (c 4.2).

IR spectrum (cm^{-1}): 980, 1020, 1070, 1124 (O—THP group), 1238, 1735 (OAc). PMR spectrum (ppm): 0.75 (s, 9H, CH_3 at C4, C8 and C10), 0.81 (s, 3H, CH_3 at C4), 1.88 (s, 3H, CH_3COO—), 3.92 (m, 2H, CH_2—O—), 3.38 (m, 2H) and 4.70 (m, 1H) (α-protons of the tetrahydropyranyl group). Found %: C 75.28; H 10.72. $C_{29}H_{50}O_4$. Calculated %: C 75.28; H 10.89. A 4:1 mixture of petroleum ether and ethyl acetate eluted 0.14 g of the initial hydroxyacetate (VI).

The Hydroxyether (VIII). a) A solution of 1.12 g of the ether-ester (VII) and 2.2 ml of ethanol was treated with 15 ml of a 5% alcoholic solution of KOH, and the mixture was left at room temperature for 3 h. After the usual working up, 0.98 g of reaction product was obtained which was chromatographed on a column containing 20 g of silica gel.

A 49:1 mixture of petroleum ether and ethyl acetate eluted 27 mg of the initial ether-ester (VII), and a 17:3 mixture of the same solvents eluted 943 mg of the hydroxyether (VIII) (yield 92% allowing for the initial compound (VII) recovered): mp 76.5-78°C (from petroleum ether): $[\alpha]_D^{22}$ −47.5° (c 2.7). IR spectrum (cm^{-1}): 980, 1025, 1072, 1130 (O—THP group), 3455, 3600 (OH group). PMR spectrum (ppm): 0.73 (s, 9H, CH_3 at C4, C8 and C10), 0.81 (s, 3H, CH_3 at C4), 1.03 (s, 3H, CH_3 at C13), 2.28 (br. s, 1H, OH), 3.92 (m, 2H, $-CH_2O-$), 3.42 (m, 2H) and 4.65 (m, 1H) (α-H's of a tetrahydropyranyl group). Found %: C 77.33, H 11.59. $C_{27}H_{48}O_3$. Calculated %: C 77.09; H 11.50.

b) A solution of 60 mg of the ether-ester (VII) in 5 ml of absolute ether was treated with 24 mg of $LiAlH_4$, and the mixture was left at room temperature for 2.5 h. After the usual working up, 50.2 mg of the hydroxy ether (VIII), identical with the product described above, was obtained.

The Aldehydoether (IX). A solution of 3 g of the hydroxyether (VIII) in 25 ml of dry pyridine was treated with 3.3 g of the complex $CrO_3 \cdot 2C_5H_5N$, the mixture was stirred at room temperature for 5 h and was filtered, and the filtrate was worked up in the usual way. This gave 2.78 g of a reaction product, which was chromatographed on a column containing 50 g of Al_2O_3. A 9:1 mixture of petroleum ether and ethyl acetate eluted 1.68 g of the aldehydoether (IX) (85% with allowance for the initial compound (VIII) recovered); colorless viscous liquid, $[\alpha]_D^{22}$ −28.4° (c 2.3).

IR spectrum (cm^{-1}): 1725, 2710 (CHO), 985, 1020, 1073, 1128 (O—THP group). PMR spectrum (PPM): 0.80 (s, 12H, CH_3 at C4, C8 and C10), 1.07 (s, 3H, CH_3 at C13), 3.43 (m, 2H) and 4.77 (m, 1H) (α-H's of a tetrahydropyranyl group), 9.60 (s, 1 H, CHO). Found %: C 77.24; H 11.01. $C_{27}H_{46}O_3$. Calculated %: C 77.46; H 11.07. A 4:1 mixture of the same solvents eluted 1.02 g of the initial hydroxyether (VIII).

The Alcohol (X). With stirring, a solution of 230 mg of the aldehyde (IX) in 1.5 ml of absolute ether was added to a solution of methylmagnesium iodide obtained from 35 mg of magnesium turnings and 0.8 ml of methyl iodide in 4.5 ml of absolute ether. The mixture was stirred for 45 min and was worked up in the usual way. This gave 228 mg of a reaction product which was chromatographed on a column containing 5.5 g of Al_2O_3. Petroleum ether eluted 27 mg of the initial aldehyde (IX), and a 19:1 mixture of petroleum ether and ethyl acetate eluted 190 mg of the alcohol (X) (~80% with allowance for the aldehyde (IX) recovered), a colorless viscous liquid. IR spectrum (cm^{-1}): 985, 1024, 1076, 1126 (O—THP group), 1100, 3460, 3616 (OH group). Found %: C 77.18; H 11.49. $C_{28}H_{50}O_3$. Calculated %: C 77.36; H 11.59.

The Ketoether (XI). A solution of 480 mg of the alcohol (X) in 5 ml of dry pyridine was treated with 450 mg of the complex $CrO_3 \cdot 2C_5H_5N$ and the mixture was stirred at room temperature for 12 h. It was worked up in the usual way, giving 450 mg of a product, which was chromatographed on a column containing 12 g of Al_2O_3. Petroleum ether eluted 15 mg of a mixture of weakly polar substances which was not investigated, and a 19:1 mixture of petroleum ether and ethyl acetate eluted 305 mg of the ketoether (XI) (84%, allowing for the initial compound (X) recovered); colorless viscous liquid: $[\alpha]_D^{20}$ +33.2° (c 2.1).

IR spectrum (cm^{-1}): 985, 1020, 1073, 1128 (O—THP group), 1716 (>C=O). PMR spectrum (ppm): 0.73 (s 12.1, CH_3 at C4, C8 and C10), 1.03 (s, 3H, CH_3 at C13), 1.97 (s, 3H, $-COCH_3$), 3.99 (m, 2H) and 4.72 (m, 1H) (α-H's of a tetrahydropyranyl group). Found %: C 77.92; H 11.03. $C_{28}H_{48}O_3$. Calculated %: C 77.72; H 11.18. A 4:1 mixture of the same solvents eluted 117 mg of the initial alcohol (X).

The Cheilanthene Esters (XII) and (XIII). In an atmosphere of argon at −20°C with stirring, 5.3 ml of a 1.4 N solution of n-butyllithium in hexane was added dropwise to a stirred solution of 400 mg of diisopropylamine in 5 ml of dry tetrahydrofuran. The mixture was stirred at the same temperature for 30 min and was then cooled to −78°C, and 0.8 ml of methyl trimethylsilylacetate was added to it. The resulting mixture was stirred at −78°C for 40 min, and 400 mg of the ketone (XI) in 5 ml of tetrahydrofuran was added to it dropwise. The temperature of the reaction mixture was raised to that of the room gradually, over 10 min, and it was stirred for another 40 min and was then neutralized with a saturated solution of NH_4Cl and was worked up to give 433 mg of reaction product. This was chromatographed on a column containing 10 g of silica gel (5 μm) under high pressure (200 atm). A

19:1 mixture of petroleum ether and ethyl acetate eluted 86 mg of the ester (XII), a colorless viscous liquid: $[\alpha]_D^{22}$ −26.5° (c 3.9).

IR spectrum (cm^{-1}): 980, 1018, 1068, 1124 (O—THP group), 1712 (CO_2CH_3), 847, 1638 ($>C=C<_H$). PMR spectrum ($CDCl_3$, ppm): 0.77 (s, 9H, CH_3 at C4, C8 and C10), 0.82 (s, 3H, CH_3 at C4), 1.06 (s, 3H, CH_3 at C13), 1.90 (s, 3H, CH_3 at C17), 3.62 (s, 3H, CO_2CH_3), 3.90 (m, 2H) and 4.75 (m, 1H) (α-H's of a tetrahydropyranyl group). 5.56 (br.s, 1H, $>C=C<_H$). Found %: C 76.34; H 10.56. $C_{31}H_{52}O_4$. Calculated %: C 76.18; H 10.72.

Then the same solvent eluted 192 mg of a mixture (~1:1) of the esters (XII) and (XIII) and 143 mg of the ester (XII): mp 101-102.5°C (from petroleum ether) $[\alpha]_D^{20}$ −8.6° (c 2.3). IR spectrum (cm^{-1}): 978, 1016, 1068, 1123 (O—THP group), 857, 1640 ($>C=C<_H$), 1715 (CO_2CH_3). PMR spectrum ($CDCl_3$, ppm): 0.73 (s, 9H, CH_3 at C4, C8 and C10), 0.81 (s 3H, CH_3 at C4), 1.05 (s, 3H, CH_3 at C13), 2.13 (s, 3H, CH_3 at C17), 3.55 (s, 3H, CO_2CH_3), 3.88 (m, 2H) and 4.73 (m, 1H) (α-H's of a tetrahydropyranyl group), 5.52 (br. s, 1H, $>C=C<_H$). Found %: C 76.29; H 10.78. $C_{31}H_{52}O_4$. Calculated %: C 76.18; H 10.72.

The Hydroxyether (XIV). With stirring, at room temperature, 72 mg of dry cerium chloride and 70 mg of $LiAlH_4$ were added to a solution of 70 mg of the ester (XII) in 5 ml of absolute tetrahydrofuran. The mixture was stirred at room temperature for 20 min and was worked up. This gave 58.5 mg (86%) of the hydroxyether (XIV); viscous liquid. IR spectrum (cm^{-1}): 982, 1020, 1070, 1125 (O—THP group), 853, 1654 ($>C=C<_H$), 3475, 3614 (OH group). Found%: C 78.04; H 11.41. $C_{30}H_{52}O_3$. Calculated %: C 78.20; H 11.38.

The Hydroxyether (XV). A solution of 70 mg of the ester (XIII) in 5 ml of absolute tetrahydrofuran was treated with 70 mg of $CeCl_3$ and 62 mg of $LiAlH_4$, and the mixture was stirred at room temperature for 20 min and was worked up. This gave 59 mg (89%) of the hydroxyether (XV); viscous liquid. IR spectrum (cm^{-1}): 980, 1012, 1070, 1132 (O—THP group), 857, 1654 ($>C=C<_H$) 3452, 3610 (OH group). Found %: C 77.96; H 11.27. $C_{30}H_{52}O_3$. Calculated %: C 78.20; H 11.38.

17E-Cheilanthene-13α,19-diol (III). A solution of 61 mg of the tetrahydropyranyl ether of 17E-cheilanthene-13α,19-diol (XIV) in 1 ml of methanol was treated with 1 ml of a 0.023 M methanolic solution of H_2SO_4 and the mixture was stirred at room temperature for 45 min and was worked up to give 46 mg of reaction product which was chromatographed on a column containing 1.1 g of Al_2O_3. A 19:1 mixture of petroleum ether and ethyl acetate eluted 2.8 mg of a mixture of weakly polar substances, and a 3:1 mixture of the same solvents eluted 43.5 mg (87%) of 17E-cheilanthene-13α,19-diol (III): mp 95-97.5°C (from petroleum ether), $[\alpha]_D^{20}$ −48.2° (c 2.1).

IR spectrum (cm^{-1}): 0.72 (s, 9H, CH_3 at C4, C8 and C10), 0.78 (s, 3H, CH_3 at C4), 1.02 (s, 3H, CH_3 at C4), 1.02 (s, 3H, CH_3 at C13), 1.33 (s, 3H, CH_3 at C17), 4.06 (m, 2H, $-CH_2O-$), 5.36 (m, 1H, $>C=C<_H$). Found %: C 79.54; H 11.62. $C_{25}H_{44}O_2$. Calculated %: C 79.73; H 11.78.

17Z-Cheilanthene-13α,19-diol (IV). With stirring at room temperature, 1 ml of a 0.023 M methanolic solution of H_2SO_4 was added to a solution of 54 mg of the 17Z-cheilanthenediol tetrahydropyranyl ether (XV) in 1 ml of methanol, and the resulting solution was stirred for 40 min and was worked up. The reaction products (42 mg) were chromatographed on a column containing 1 g of Al_2O_3. A 19:1 mixture of petroleum ether and ethyl acetate eluted 2.1 mg of a mixture of weakly polar substances, and a 4:1 mixture of the same solvents eluted 37.3 mg (84%) of 17Z-cheilanthene-13α,19-diol (IV); viscous oil: $[\alpha]_D^{20}$ −12.1° (c 2.7).

IR spectrum (cm^{-1}): 840, 1652 ($>C=C<_H$), 3400, 3588 (OH group). PMR spectrum ($CDCl_3$, ppm): 0.74 (s, 9H, CH_3 at C4, C8 and C10), 0.78 (s, 3H, CH_3 at C4), 1.01 (s, 3H, CH_3 at C13), 1.38 (s, 3H, CH_3 at C17), 4.02 (m, 2H, $-CH_2O-$), 5.33 (M, 1H, $>C=C<_H$). Found %: C 79.58; H 11.73. $C_{25}H_{44}O_2$. Calculated %: C 79.73; H 11.78.

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AVAROL AND ISOAVAROL FROM A PACIFIC OCEAN SPONGE Dysidea SP.

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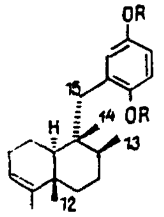
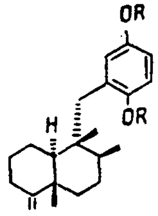
Two hydroquinone-group-containing terpenoids have been isolated from a Pacific Ocean sponge *Dysidia*, sp. One of them has been identified by physicochemical methods as the previously known avarol. The second, isoavarol, obtained for the first time, differs from avarol by the 4(11)-position of the double bond.

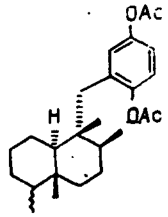
Continuing investigations of sponge metabolites [1], from an alcoholic extract of *Dysidia* sp. we have isolated by column chromatography on silica gel a difficultly separable mixture of two hydroquinone-group-containing terpenoids (I) and (II). We obtained the individual compounds by acetylating the mixture and using HPLC for separating the acetates (Ia) and (IIa). The acetate (Ia) was converted into the dimethyl ether (Ib). A comparison of the ^{1}H and ^{13}C NMR spectra and the physical constants of this compound with literature information for the dimethyl ether of avarol [2] enabled (I) to be identified as avarol.



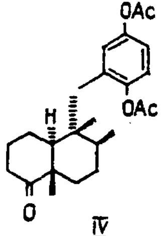
I. R = H
Ia. R = Ac
Ib. R = CH_3



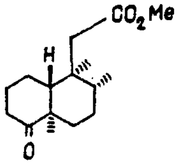
II. R = H
IIa. R = Ac
IIb. R = CH_3



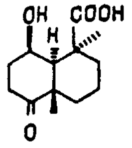
III a,b



IV



V



VI

The mass spectrum of (IIa) was close to the spectrum of (Ia), but their ^{1}H and ^{13}C NMR differed substantially. The ^{1}H NMR spectrum of (IIa) lacked the signal of the olefinic protons at C3 present in the spectrum of (Ia) but, at the same time, there were two signals in the form of triplets at 4.40 and 4.46 ppm, which are characteristic for the protons of an exomethylene group. Correspondingly, in the ^{13}C NMR spectrum of (IIa) the signals of an exocyclic double bond appeared in the form of a singlet at 159.3 and a triplet at 103.0 ppm.

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