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SYNTHESIS OF (±)-RECIFEIOLIDE

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A description is given of the directed synthesis of (±)-recifeiolide (VI), starting from cyclooctene and 1-chlorobutan-3-ol. The ozonolysis of cyclooctene gave 7-formylheptanoic acid, the methyl ester of which (II) was condensed with the ylide of (3-hydroxybut-1-yl)triphenylphosphonium iodide (I) synthesized from 1-chlorobutan-3-ol. The lactonization of the 11-hydroxydodec-8(E)-enoic acid so obtained gave (VI). The IR, PMR, and mass spectra of (VI) are presented.

The total synthesis of natural macrolides has recently been attracting ever-increasing attention [1-3]. The synthesis of one of the representatives of this broad class of compounds, recifeiolide, in both the racemic and the optically active forms has been reported by a number of authors [4-6]. One of the most promising routes envisages as the key stage the synthesis of 11-hydroxydodec-8(E)-enoic acid (III) by the Wittig reaction [6].

We propose a simpler scheme based on readily available substances. 1-Chlorobutan-3-one, obtained from acetyl chloride, ethylene and $AlCl_3$ [7], was selectively reduced with $LiAlH_4$ in ether at −78°C to 1-chlorobutan-3-ol. The subsequent replacement of the chlorine atom by iodine gave 1-iodobutan-3-ol. Boiling this with triphenylphosphine in benzene led to the crystalline phosphonium salt (I) with a yield of 70%.

The second fragment (II) was synthesized from the readily available butadiene dimer cycloocta-1,5-diene. Its selective hydrogenation with hydrogen in hexane in the presence of 5% Pd/C (5% on the weight of the cyclooctadiene) at room temperature and atmospheric pressure until one equivalent of hydrogen had been absorbed permitted cyclooctene to be obtained with a yield of 95%. Ozonolysis of the cyclooctene in cyclohexane in the presence of acetic acid followed by hydrolytic cleavage of the ozonolide with acetic anhydride—sodium acetate gave 7-formylheptanoic acid, the treatment of which with diazomethane in ether gave (II) with a yield of 75-80% (after distillation).

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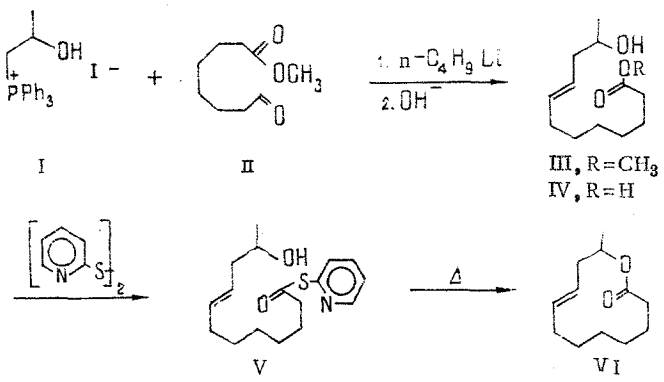

Condensation of the aldehydo ester (II) and the ylide obtained by treating the phosphonium salt (I) with two equivalents of n-butyllithium gave methyl 11-hydroxydodec-8-enoate (III) in the form of a mixture of isomers [6]. (Diphenyl disulfide)-initiated cis-trans isomerization under the action of ultraviolet light permitted the mixture to be enriched with the required trans isomer.

The saponification of this ester with an aqueous methanolic solution of KOH gave the acid (IV) with a yield of 90%. The cyclization of (IV) was carried out with the use of dipyrid-2-yl disulfide as activator via the thio ester (V) under thermal conditions. The yield of (VI) was 50% after purification on a column of silica gel.

EXPERIMENTAL

PMR spectra were taken on a Tesla BS-480B instrument in CCl_4, using hexamethyldisiloxane as internal standard.

IR spectra were recorded on a UR-20 spectrometer in a thin layer. Mass spectra were measured on an MKh-1303 instrument at an ionizing voltage of 70 V and a temperature of the ionization chamber of 75-100°C. GLC analysis was carried on a Chrom-41 instrument with a flame-ionization detector using a 2.4 m × 3 mm column containing 5% of SE-30 Chromaton N-AW, with helium as the carrier gas.

The results of elementary analysis corresponded to the calculated figures.

1-Chlorobutan-3-ol. A solution of 10.7 g (0.1 mole) of 1-chlorobutan-3-one [7] in 20 ml of ether was added dropwise to a stirred suspension of 1.9 g (0.05 mole) of $LiAlH_4$ in 100 ml of ether at −78°C. The mixture was stirred at this temperature for 1 h and then at −10°C for another 1 h. Then it was hydrolyzed by the addition of a saturated solution of ammonium chloride. The precipitate of $Al(OH)_3$ that had deposited was dissolved by the addition of dilute, 2 N, hydrochloric acid solution. The ethereal layer was separated off, and the aqueous layer was extracted with ether (2 × 50 ml). The combined organic layers were dried with Na_2SO_4 and the ether was evaporated off. This gave 10 g (92%) of 1-chlorobutan-3-ol, pure according to GLC.

1-Iodobutan-3-ol. To a solution of 17 g (0.113 mole) of anhydrous NaI in 100 ml of acetone was added 9.8 g (0.090 mole) of 1-chlorobutan-3-ol, and the reaction mixture was boiled for 5-6 h. After the usual working up, 16.7 g (90%) of a substance with bp 50-56°C (2 mm) was obtained. PMR spectrum (δ, ppm): 1.16 (d, 3 H); 1.86 (q, 2 H); 3.20 (t, 2 H); 4.45 (s, 1 H); 3.80 (q, 1 H).

(3-Hydroxy-but-1-yl)triphenylphosphonium Iodide (I). A mixture of 12 g (0.060 mole) of 1-iodobutan-3-ol and 20 g (0.076 mole) of triphenylphosphine in 50 ml of anhydrous benzene was boiled for 5-6 h. The phosphonium salt that had deposited was filtered and was washed twice with anhydrous benzene. This gave 20 g (70%) of the phosphonium salt (I) with mp 226-227°C (according to the literature [6]: mp 219-221°C (decomp.)).

7-Formylheptanoic Acid. With stirring, ozone-containing oxygen was passed through a mixture of 12.1 g (110 mmole) of cyclooctene, 110 ml of cyclohexane (purified by passage through a column of Al_2O_3), and 15.4 ml (270 mmole) of glacial acetic acid cooled to +5°C. Then the reaction mixture was purged with argon, the solvent was decanted off, and the residual ozonide was dissolved in 20 ml of acetic anhydride. The mixture was stirred at a temperature not exceeding +15°C, and finely ground sodium acetate (8.6 g) in 40 ml of glacial

acetic acid was added, the temperature being kept below +30°C. Stirring at this temperature was continued for 30 min and then 47 ml of water was added and the mixture was heated on the water bath for about another hour. The acetic acid was distilled off at a bath temperature of 40-50°C and a residual pressure of 20-30 mm Hg. The residue was dissolved in the minimum amount of water and the solution was extracted with chloroform three or four times (100-200 ml each). The organic layers were washed with saturated aqueous NaCl solution and dried with Na_2SO_4, and the chloroform was evaporated off in vacuum. After distillation, 15 g (80%) of the aldehydo acid with bp 130-134°C (0.1 mm) was obtained. IR (ν, cm^{-1}): 1710, 1720, 2740, 2500-3600.

Methyl 7-Formylheptanoate (II). A solution of 15 g (0.094 mole) of 7-formylheptanoic acid in 50 ml of ether and 50 ml of methylene chloride was treated with an ethereal solution of diazomethane until a permanent yellow coloration appeared. The excess of diazomethane was neutralized by the addition of 1-2 ml of acetic acid. The ethereal solution was washed with saturated NaCl solution, dried with Na_2SO_4, and evaporated. The residue was distilled in vacuum. This gave 13 g (80%) of methyl 7-formylheptanoate (II) with bp 90-93°C (0.05 mm). IR (ν, cm^{-1}): 1720, 1740, 2740. PMR spectra (δ, ppm): 1.30-2.10 (m, 12 H); 3.40 (s, 3 H); 9.54 (d, 1 H).

Methyl 11-Hydroxydodec-8(E)-enoate (III). At 25°C with stirring, 20 ml of a 1.1 N solution of n-butyllithium in hexane was added over 30 min to a suspension of 10 g (21.6 mmole) of (3-hydroxybut-1-yl)triphenylphosphonium iodide in 150 ml of absolute ether. After another 7 min, 3 g (17.3 mmole) of methyl 7-formylheptanoate was added dropwise to the red suspension. The mixture was stirred for another 20 min, and then 10 ml of water was added and the ethereal layer was decanted off. The residue was extracted with another 100 ml of ether. The ethereal extracts were evaporated, and the residue was chromatographed on a column of silica gel with hexane–ether (3:2) as the eluent. This gave 1 g (30%) of a mixture of the cis and trans isomers of compound (III). In solution in 150 ml of a mixture of pentane and benzene (3:1), 0.7 g of the mixture of isomers together with 30 mg of diphenyl disulfide was irradiated with a PRK lamp for 2 h. Then the solvent was evaporated off. The preparative thin-layer chromatography of the residue on plates coated with a layer of silica gel impregnated with 10% of $AgNO_3$ gave 0.5 g of the trans ester (III). IR (ν, cm^{-1}): 3240-3600 (OH); 1740 (COOMe); 985 (trans-HC=CH). PMR spectrum (δ, ppm): 1.05 (d, 3 H, J = 6 Hz); 1.25 (br.m, 8 H); 1.82-2.3 (br.m, 7 H); 3.4 (t, 1 H); 3.5 (s, 3 H); 5.3 (m, 2 H).

11-Hydroxydodec-8(E)-enoic Acid (IV). A mixture of 0.5 g of methyl 11-hydroxydodec-8(E)-enoate (III) and 15 ml of 2 N aqueous KOH in 15 ml of methanol was boiled for 1.5 h. The methanol was evaporated off in vacuum, and the residue was extracted with ether. The aqueous layer was acidified with hydrochloric acid and was then extracted with ether (3 × 50 ml). The ethereal extracts were dried with Na_2SO_4 and evaporated. This gave 0.43 g (92%) of compound (IV). IR (ν, cm^{-1}): 980, 1710, 2500-3500.

Lactone of 11-Hydroxydodec-8(E)-enoic Acid — (±)-Recifeolide (V). A mixture of 0.43 g (1.9 mmole) of the hydroxy acid (IV), 0.68 g (2.9 mmole) of dipyrid-2-yl disulfide, and 0.82 g (3.3 mmole) of triphenylphosphine was dissolved in 10 ml of anhydrous oxygen-free xylene and was stirred in a current of argon at room temperature for 5 h. The reaction mixture, containing the pyridine-2-thiol ester (V), was diluted with 10 ml of anhydrous xylene, the resulting solution was added dropwise to boiling anhydrous xylene (100 ml) in a current of argon over 15 h, and the mixture was boiled for another 20 h. After this, the xylene was distilled off the and residue was chromatographed on a column of silica gel with elution by petroleum ether–diethyl ether (4:1). This gave 0.18 g (50%) of the lactone (VI). IR (ν, cm^{-1}): 980 (trans-HC=CH); 1730 (lactone). PMR spectrum (δ, ppm): 1.13 (d, 3 H, J = 6.5 Hz); 1.1-1.5 (m, 4 H); 1.8-2.25 (m, 10 H); 4.83-5.04 (m, 3 H). Mass spectrum, m/z: 196 (M^+); 152 ($M^+ - CO_2$).

SUMMARY

A convenient route for the synthesis of the lactone of 11-hydroxydodec-8(E)-enoic acid, (±)-recifeiolide, a natural macrolide, has been developed using as the starting materials cyclooctene and 1-chlorobutan-3-one.

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^{13}C NMR SPECTRA AND STRUCTURE OF BUNGEIDIOL AND ITS TRANSFORMATION PRODUCTS

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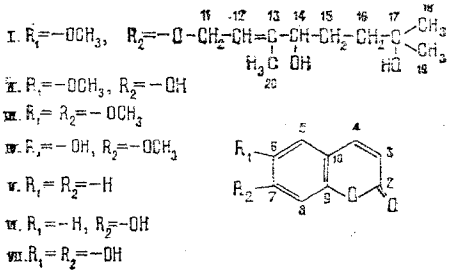
The results are given of a study of the ^{13}C NMR spectra of the new terpenoid coumarin bungeidiol (I) and of the products of its transformation (II) and (III) and some model compounds (IV-VII). On the basis of the results obtained from these ^{13}C NMR spectra and with the use of additive contributions depending on the nature and positions of various substituents (hydroxy and methoxy groups) in the aromatic ring, the structure (I) has been confirmed and a complete assignment of the signals of all the carbon atoms both in the coumarin ring and in the aliphatic part of the molecule of (I) has been made.

Previously, in a study of the coumarin composition of *Haplophyllum bungei* Trautv., we isolated a new terpenoid coumarin with the composition $C_{20}H_{26}O_6$, mp 108-109°C, $[\alpha]_D^{20}$ +42.8° (c 3.55, ethanol). On the basis of a detailed study of the proton magnetic resonance spectra and its chemical transformations, structure (I) was established for it.

In the present paper we give the results of an investigation of the ^{13}C NMR spectra of compound (I), and its transformation products (II and III), and some model compounds (IV-VIII) with the aim of confirming the proposed structure (I) and elucidating the correlation between the ^{13}C chemical shifts and additive contributions depending on the natures and positions of various substituents (hydroxy and methoxy groups) in the aromatic ring of the coumarin nucleus [1, 2]. The ^{13}C NMR spectra of compounds (V-VII) have been studied previously by other authors [1, 3, 4].



As can be seen from the chemical shifts and spin-spin coupling constants in the ^{13}C NMR spectra of the substances investigated (I-VII) (Table 1 and Figs. 1-5), the signals of all the carbon atoms appear clearly and in number and multiplicity they correspond completely to structures (I-VII). The assignment of the signals in the ^{13}C NMR spectra was made in the light of the degree of hybridization of the carbon atoms, the number of protons attached to the corresponding carbon atoms [5], and literature information on ^{13}C NMR spectra of analogs of the compounds under investigation (V-VII) [1, 3, 4]. To determine the chemical shifts of the signals, the spectra of compounds (I-VII) were taken in the regime of complete decoupling

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