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OXIDATION OF TRITERPENES DERIVED FROM 18-LUPENE AND 18,19-SECOLUPANE WITH RUTHENIUM TETROXIDE BY AN IMPROVED PROCEDURE

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A convenient preparative procedure for the oxidation with ruthenium tetroxide of 18-lupene derivatives to 18,19-secolupane-18,19-dione derivatives in an ethyl acetate—water system has been developed. It has been found that 3β,28-diacetoxy-18,19-secolupane-18,19-dione can be obtained from its 19-(ethylene acetal) or 19-oxime by reaction with ruthenium tetroxide.

The problem of the rational use of betulin (3β,28-dihdyroxy-20(29)-lupene), a widely available triterpenoid of the lupane series is still far from exhausted [1]. One of the interesting routes of the chemical transformation of triterpenes of this series is their conversion into derivatives of tetracyclic triterpenes of the baccharane (18,19-secolupane) series [2]. Triterpenes with the skeleton of 18,19-secolupane have been proposed as an intermediate link between the dammarane series and the lupane and shionane series in the scheme of biogenetic transformations of triterpenes [3]. They have been synthesized from lupeol [4] and have been obtained in the skeletal rearrangement of the so-called baccharis oxide (hence their name – baccharanes), isolated from the roots of Baccharis halimifolia L. [5]. Only two examples of the isolation of native baccharanes from plants are known [6].

In this paper we give results relating to the development of a preparative method for synthesizing baccharane derivatives via the ruthenium tetroxide oxidation of a betulin isomerization product.

Betulin diacetate (I) was converted in dry benzene into 3β,28-diacetoxy-18-lupene (II) by the action of a mixture of the reagents HBr, Ac_2O, and AcOH in the optimum molar ratio (1:1.3:4.7) according to [7]. We raised the concentration of (I) in the reaction mixture 10- to 15-fold in comparison with [7], which made this procedure more suitable for preparative purposes (by making it cheaper and decreasing the total amount of wastes), in spite of the fact that the reaction time increased by a factor of 1.5-3, and the yield of product (II) fell from 87 to 74-80%.

The action of NaOH on a solution of (II) in EtOH–C_6H_6 gave 3β,28-dihydroxy-18-lupene (III) from which, by reactions with succinic and glutaric anhydride in pyridine the bis(hydrogen succinate) and bis(hydrogen glutarate) of 3β,28-dihydroxy-18-lupene (IV and VI) were synthesized, these being characterized in the form of their methyl esters (V) and (VII).

The procedure for the ruthenium tetroxide oxidation of 18-lupene derivatives was developed with compound (II) as an example. We first reproduced the known procedure [2] for oxidizing (II) to a baccharane derivative – 3β,28-diacetoxy-18,19-secolupane-18,19-dione (VIII). The reaction was performed in a H_2O–CCl_4 two-phase system with a catalytic amount of $RuO_2 \cdot xH_2O$ from which, in the aqueous phase under the action of $NaIO_4$ the RuO_4 that had oxidized the substrate in the CCL_4 phase was regenerated and was again converted into RuO_2. This procedure for the oxidation of organic compounds by RuO_4 has been used most frequently [8]. However, to complete the reaction even with 2 mmoles of (II) required vigorous stirring for 20 h [2]. The reason for the prolonged course of oxidation by

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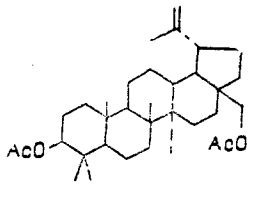

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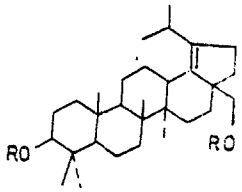
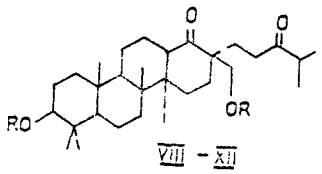
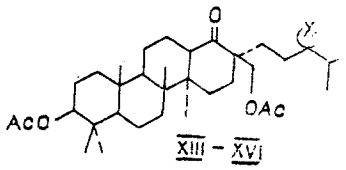


II - VII



VIII - XII



XIII - XVI

II. R=Ac
III. R=H
IV. R=$COCH_2CH_2COOH$
V. R=$COCH_2CH_2COOMe$
VI. R=$CO(CH_2)_3COOH$
VII. R=$CO(CH_2)_3COOMe$

VIII. R=Ac
IX. R=$COCH_2CH_2COOH$
X. R=$COCH_2CH_2COOMe$
XI. R=$CO(CH_2)_3COOH$
XII. R=$CO(CH_2)_3COOMe$

XIII. X=OCH_2CH_2O
XIV. X=OCH_2CH_2S
XV. X=SCH_2CH_2S
XVI. X=NOH

this procedure is the gradual deactivation of the ruthenium catalyst in the course of the process [9], which we observed particularly clearly on the repeated use of the RuO_2 isolated after an analogous reaction. In a review [8] it is mentioned that only the hydrated form of RuO_2 is readily oxidized in RuO_4. According to later results [10], samples of $RuO_2 \cdot xH_2O$ containing 24-26% of H_2O are readily oxidized to RuO_4, while samples containing less than 20% of H_2O are oxidized to RuO_4 only partially, and if the H_2O content is less than 10% no tetroxide whatever is formed. The deactivation of the catalyst was prevented by the use of the H_2O–CH_2CN–CCl_4 (3:2:2 by volume) solvent system [9]. An active form of RuO_2 can be obtained from the inactive form by fusing it with a mixture of NaOH and $NaClO_3$ followed by dissolution in water and treatment with alcohol [11].

Another problem in the oxidation of organic compounds with RuO_4 is the contamination of the products obtained with part of the RuO_2, which forms a colloidal solution in the organic phase. Purification is usually carried out either by chromatographing the product on a short column of silica gel [2] or by treating an alcoholic solution of the product with activated carbon of a suitable type (for example, Norite) [12].

We have found that an activated ruthenium catalyst can be obtained in aqueous solution containing such an oxidant as $K_2S_2O_8$ or $NaIO_4$ by alkalinizing the solution to pH 10 and stirring. Under these conditions the black precipitate of RuO_2 gradually dissolves and an orange or red solution containing ruthenate ions is formed. Subsequent neutralization of the solution with dilute H_2SO_4 leads to the precipitation of a deposit of the active form $RuO_2 \cdot xH_2O$. Using the oxidation of (II) as an example, we have established that such activation of the ruthenium catalyst can be carried out directly in a reaction mixture with the H_2O–CCl_4 system. Since on alkalinization of the stirred reaction mixture complete decoloration of the CCl_4 layer was observed, we began to use it after the completion of the oxidation of compound (II) as a convenient method for eliminating impurities of colloidal RuO_2 from the organic phase containing the product (VIII), provided that an excess of $NaIO_4$ was present in the aqueous phase. In this process, no saponification of the diacetate (VIII) or appreciable alkaline decomposition of the CCl_4 was observed. This method of freeing the products of the oxidation of organic compounds by RuO_4 from contamination with colloidal RuO_2 is apparently applicable in all cases when compounds insoluble in an alkaline aqueous solution are formed. It must be mentioned that the best results of purification were obtained in CCl_4 as a non-aqueous phase, while if a mixture of CH_3CN with CCl_4 or $CHCl_3$ was used extraction of the oxidant by an alkaline aqueous solution led to fairly stable emulsions.

For the case of the RuO_4 oxidation of cyclic derivatives of amino acids it has been shown that on the use of the EtOAc–H_2O two-phase solvent system the reaction took place 3-5 times faster than in the H_2O–CH_3CN–CCl_4 system and 5-7 times faster than in the H_2O–CCl_4 system [13]. We have successfully used the EtOAc–H_2O system for the oxidation of (II) to (VIII) by RuO_4 with the use of $NaIO_4$ as co-oxidant. Under these conditions, the reaction with 7 mmoles of (II) was complete in 6 h and no fall in the activity of the ruthenium catalyst was

TABLE 1. ^{13}C NMR Chemical Shifts of the 18-Lupene Derivatives (II-VII) (δ, ppm)

Atom C[a]	II [17]	II	III	IV	V	VI	VII
1	38,3	38,7	39,2	38 6	38,6	38,6	38,7
2	23,4	23.7	27,2	23,7	23,7	23 7	23 8
3	80,4	81,0	78,8	81,6	81,3	81,1	81,0
4	37,5	37,8	39,0	37,9	37,8	37,8	37,9
5	55,2	55.6	55,7	55,6	55,5	55,5	55'6
6	17 9	18,2	18.5	18,2	18,2	18,1	18,2
7	34,4	34 6	34,2	34,4	34,4	34,4	34.5
8	40,5	40,9	41,0	40,9	40.9	40,8	40,9
9	50 7	51,1	51.3	51,0	51,0	51,1	51,6
10	36,8	37,2	37.4	37,2	37,1	37,1	37,2
11	21,4	21,6	22,2	21,6	21.6	21,6	21,6
12	28,0	28,3	28,0	28,2	28,2	28,2	28,3
13	40,6	40,9	41,0	40,9	40,9	40,8	40,9
14	43.0	43,4	43,7	43,4	43,4	43,4	43,4
15	28,0[b]	28,3[b]	28,3[b]	28,2[b]	28,2	28,2	28,3
16	32,2[b]	32,5[b]	32,4[b]	32,4[b]	32,3[b]	32,4[b]	32,5[b]
17	51,9	52,2	54,3	52,3	52,2	52.2	52.2
18	133,6	134,1	134,5	133,9	134,0	134.0	134,1
19	143.1	143,6	144,2	143.5	143,6	143,5	143,6
20	26,3	26,6	26,8	22,6	26,6	26,6	26,6
21	29,1	29,4	29,7	29,4	29,1	29,4	29,4
22	34,7[b]	35,0[b]	35,3[b]	35,0[b]	35,0[b]	35,0[b]	35.0[b]
23	27,6	27,9	28,5	27,9	27,9	27,7	28,1
24	16,6	16,8	15,5	16,3	16,8	16,8	16 8
25	16,3	16,6	16,8[c]	16,6	16,5	16,6	16,6
26	16,3	16,6	16,6[c]	16,6	16,5	16,6	16,6
27	15,3	15,5	15,5	15,6	15,6	15,5	15,6
28	66,6	67,0	65,6	67,3	67,1	67,0	66,9
29	21,4[d]	21,6[d]	21,9[d]	21,6[d]	21,6[d]	21,6[d]	21,6[d]
30	21,9[d]	22,2[d]	21,7[d]	22,1[d]	22,1[d]	22,1[d]	22,2[d]
1′	170,2[e]	170,9[e]	—	171,6[e]	172,0[e]	173,1[e]	172,7
1″	170,6[e]	171,3[e]	—	172,0[e]	172,1[e]	172,7[e]	172,7
2′	20,7[f]	21,0[f]	—	29,6	29,7	33,7[f]	33,8[f]
2″	21,0[f]	21,3[f]	—	29,6	29,7	33,4[f]	33,5[f]
3′, 3″	—	—	—	29,1	29,3	19,9	20,3
4′, 4″	—	—	—	177,8	171,9	33,1	33,2
5′, 5″	—	—	—	—	—	179,0	173,2
Me′, Me″	—	—	—	—	51,8	—	51,1

[a]C-1′–C-5′ and Me′ – carbon atoms of the 3-OR group; C-1″–C-5″ and Me″ – carbon atoms of the 28-OR group. [b-f]Assignment of the signals ambiguous.

observed. To eliminate impurities of colloidal RuO_2 from the solution in EtOAc we used extraction with an alkaline solution of $NaIO_4$. Since the alkaline aqueous solution was fairly rapidly neutralized as the result of the hydrolysis of the EtOAc and the oxidation of the EtOH, the extraction and separation of the aqueous layer had to be done fairly rapidly so that the aqueous layer continued to remain alkaline. Two or three extractions gave a fairly pure product (VIII).

We used the oxidation of (IV) and (VI) with RuO_4 in the EtOAc–H_2O system for the synthesis of the corresponding baccharane derivatives (IX and XI), which were characterized in the form of their methyl esters (X and XII).

Compound (VIII) was brought into reaction with excesses of the reagents: ethylene glycol in C_6H_6 in the presence of p-TsOH [2], 2-mercaptoethanol or 1,2-dimercaptoethanol in 1,4-dioxane in the presence of fused $ZnCl_2$ [14], and hydroxylamine in ethanol [15]. In all cases practically the only products of the reactions were derivatives of (VIII) at the 19-CO group: respectively, the 19-(ethylene acetal) (XIII) [2], the 19-(ethylene monothioacetal) (XIV), the 19-(ethylene dithioacetal) (XV), and the 19-oxime (XVI). The action of RuO_4 in EtOAc–H_2O on compounds (XIII-XVI) led to the regeneration of the diketone (VIII). The reaction took place slowly only with the ethylene acetal (XIII). In three cases, (VIII) was the only product, while in the case of (XV) it was isolated with a yield of 30% from a mixture of several products. Thus, in the absence of other functional groups labile to oxidation the reaction with RuO_4 can be used for removing ethylene acetal and oxime protections of keto groups.

TABLE 2. ^{13}C Chemical Shifts of the Baccharanes (VIII), (X), and (XII-XVI) (δ, ppm)*

Atom C	a	VIII	X	XII	XIII	XIV[b]	XV[c]	XVI[d]
1	36,4	38,4	38,2	38,6	38,7	38,7	38,7 t	38,7
2	26,4	23,5	23,4	23,7	23,7	23,7	23,7 t	23,7
3	80,4	80,3	81,1	80,6	80,7	80,6	80,6 d	80,7
4	38,5	37,6	37,9	37,8	37,9	37,9	37,9 s	37,9
5	54,9	55,4	55,5	55,5	55,6	55,7	55,6 d	55,6
6	17,6	18,0	19,1	18,1	18,2	18,7	18,2 t	18,2
7	33,1	33,9	34,0	34,0	34,2	34,2	34,1 t	34,1
8	41,3	40,8	41,0	40,8	41,1	41,1	41,1 s	41,1
9	51,6	50,5	50,8	50,8	50,8	50,8	50,8 d	50,8
10	37,6	37,0	37,2	37,2	37,2	37,3	37,3 s	37,3
11	22,2	19,7	20,0	20,3	20,0	20,1	20,0 t	20,6
12	23,8	22,0	22,1	22,2	22,3	22,3	22,2 t	22,2
13	51,7	48,9	48,9	49,1	49,1	49,1	49,0 d	49,2
14	46,5	46,2	46,5	46,4	46,3	46,3	46,3 s	46,3
15	28,6	26,8	26,9	27,0	27,2	27,2	27,1 t	27,1
16	32,5	29,5	29,1	29,7	29,7	32,3	30,1 t	29,5
17	47,2	50,0	50,2	50,2	50,0	50,1	50,2 s	50,6
18	212,8	213,8	213,8	213,7	213,8	213,4	213,5 s	213,6
19		213,2	214,2	214,5	113,8	102,9	77,9 s	165,4
20		40,6	38,2	41,0	29,9	33,7	37,9 d	33,6
21		34,8	35,0	35,0	34,2	30,0	36,1 t	29,5
22		27,7	27,7	27,9	27,9	28,1	30,3 t	29,5
23	24,4	27,7	27,9	27,9	27,9	28,0	27,9 q	27,9
24	17,8	16,5	16,7	16,2	16,7	16,7	16,6 q	16,6
25	17,1	16,0	16,4	16,2	16,5	16,5	16,5 q	16,5
26	14,6	16,3	16,4	16,3	16,3	16,3	16,3 q	16,2
27	16,5	15,9	16,1	16,1	16,1	16,2	16,1 q	16,2
28	66,2	67,1	67,3	67,3	67,3	67,0	67,0 t	67,0
29		18,2	18,4	18,3	17,1	17,6	19,7 q	20,0
30		18,2	18,7	18,3	17,1	18,2	19,7	20,0
—X—		—	—	—	65,4	71,2 36,0	39,8	—

*Assignment of the signals approximate.
[a]Values for 3β,28-dihydroxy-18,19-secolupan-18-one.
[b]Spectrum of a mixture of 19-epimers in which the signals of the C-21, C-28, and 19-SC atoms appear in the form of doublets with secondary values of 30.1, 67.3, and 36.2, respectively.
[c]The multiplicities of the signals were determined from the spectrum with incomplete decoupling.
[d]Values are given for the predominating isomer in the mixture.

The structures of the new 18-lupene derivatives (IV-VI) obtained were confirmed by the results of IR spectroscopy, mass spectrometry (V, VII), and a comparison of their PMR and ^{13}C NMR spectra with those of previously described compounds (II) [7] and (III) [16]. The assignment of the signals in the ^{13}C NMR spectra of compounds (II-VII) given in Table 1 was made by analogy with those known for (II) [17], with the use for (IV-VII) of results for succinic and glutaric acid derivatives [18].

The structures of the new baccharane derivatives (IX-XII) and (XIV-XVI) were confirmed by the results of IR spectroscopy and mass spectrometry (XIII-XVI) and by their PMR and ^{13}C NMR spectra in comparison with the spectra of the known compounds (VIII) and (XIII). Table 2 gives the assumed assignments of the ^{13}C chemical shifts of compounds (VIII), (X), and (XII-XVI). The chemical shifts of rings A and B and of the substituents at C-3 and C-28 in these compounds are close to those for (II-VII). The assignment of the ^{13}C signals of rings C and D of the baccharanes was made on the basis of semiempirical calculations according to [19] performed for the structure of 3β,28-dihydroxy-18,19-secolupan-18-one with the aid of a Dreiding model. The assignment of the ^{13}C signals of the side chain at C-17 was made by analogy with literature figures for similar fragments. Thus, good agreement was observed of the ^{13}C chemical shifts of the C-19 atoms and those of the isopropyl groups of the 18,19-diones (VIII, X, and XII) and of the 19-oxime (XVI) with the shifts of the analogous atoms in the spectra of 2-methylpentan-3-one and its oximes [20]. It followed from the ^{13}C NMR spectrum of the oxime (XVI) that the sample obtained was a mixture of isomers in which the anti-oxime probably predominated. The ethylene monothioacetal (XIV) was a mixture of equimolar amounts of the 19-epimers in which the chemical shifts differed for the C-28 atom (67.0 and 67.3) and for the C-atom of the thioacetal fragment $-S-CH_2-$.

EXPERIMENTAL

NMR spectra were taken on a Bruker WM-250 spectrometer with a working frequency of 250 MHz for ^1H and 62.9 MHz for ^{13}C and a Bruker HX-90E spectrometer with a working frequency of 22.63 MHz for ^{13}C at 30°C in $CDCl_3$. The chemical shifts are expressed in the δ scale relative to TMS. The accuracy of the measurement amounted to ±0.15 Hz for ^1H and ±1.5 Hz for ^{13}C. Mass spectra were recorded on a MKh-1303 instrument with a system for the direct introduction of the specimen into the ion source at ionizing energies of 15 and 70 eV. IR spectra were recorded on IR-75 and Specord M-80 spectrometers for solutions in $CHCl_3$. Optical rotations were determined on a Perkin-Elmer 141 instrument in cells 10 cm long at 20°C in $CHCl_3$ at a concentration of the substances of 1 g/liter. Melting points were determined on the Boetius stage.

The monitoring of the course of the reactions and of the purity of the compounds was carried out with the aid of TLC on 25 × 75 mm Silufol plates (Czechoslovakia) and (in one case) on the same plates impregnated with $AgNO_3$. The plates were immersed for 2-5 min in a saturated solution of $AgNO_3$ in MeOH, dried for 1 h in a drying chest at 70°C, and stored in dark packing in a desiccator. As the solvent for TLC on the impregnated plates we used CH_2Cl_2, and in other cases the C_6H_6–$CHCl_3$–Me_2CO (5:5:1 or 3:3:1) and $CHCl_3$–EtOAc (10:1 or 4:1) systems. Visualization and TLC were carried out by brief immersion of the plates in a saturated solution of $SbCl_3$ in $CHCl_3$ followed by heating at 100-120°C for 3-5 min.

Betulin was isolated from evaporated $CHCl_3$ extracts of birches of the species Betula pendula and B. pubescens by fractional recrystallization from C_6O_6–EtOH (2:1) and was acetylated with a Ac_2O–C_5H_5N mixture to betulin diacetate (I), mp 224°C. According to the literature [1]: mp 223°C.

3β-28-Diacetoxy-18-lupene (II). A solution of 13.18 g (25 mmoles) of (I) in 50 ml of dry C_6H_6 was treated with 57 g of a mixture containing 114 mmoles of anhydrous HBr, 148 mmoles of Ac_2O, and 536 mmoles of glacial AcOH. The reaction mixture was left at room temperature for a month in a tightly sealed flask, the process being monitored by TLC on impregnated plates, and it was then diluted with 100 ml of C_6H_6 and was washed twice with cold water and with saturated $NaHCO_3$ solution. The benzene layer was dried over calcined granulated silica gel and was evaporated to dryness, and the residue was recrystallized from 300 ml of EtOH–$CHCl_3$ (5:1). This gave 8.46 g and, after partial evaporation of the mother solution, another 1.30 g of (II). Yield 74%; mp 213-214°C, $[\alpha]_D^{20}$ +14.2° (c 1.0; $CHCl_3$). According to the literature [7]: mp 215°C, $[\alpha]_D$ +16° (c 1.0; $CHCl_3$).

3β-28-Dihydroxy-18-lupene (III). A mixture of 6.40 g (12.2 mmoles) of (II) and 1.98 g (35 mmoles) of KOH in 150 ml of EtOH–C_6H_6 (1:1) was boiled for 7 h, cooled, neutralized with KU-2-8 cation-exchange resin, filtered, and concentrated in a rotary evaporator. This gave 5.21 g of (III). Yield 97%; mp 220°C. According to the literature [16]: mp 220°C.

Bis(hydrogen succinate) of 3,28-Dihydroxy-18-lupene (IV). A mixture of 1.00 g (2.26 mmoles) of (III) and 1.5 g (15 mmoles) of succinic anhydride in 30 ml of dry C_5H_5N was boiled for 10 h, cooled, and poured onto ice, and the resulting mixture was acidified with dilute H_2SO_4, and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated to dryness. This gave 1.17 g of (IV). Yield 80%; amorphous. IR spectrum (ν_{max}, cm^{-1}): 3524, 2500-3300 (OH), 1716 (C=O), 1616 (C=C). PMR: 0.838 (6H, s), 0.898 (6H, s), 0.908 (d, J = 6.5 Hz, CH_3-29), 0.996 (d, J = 6.5 Hz, CH_3-30), 1.058 (3H, s), 2.65 (8H, m), 3.134 (1H, m, J = 6.5 Hz, H-20), 4.04 (2H, s, H-28), 4.514 (1H, m, H-3), 1.1-2.5 (remaining Hs).

Samples of the acidic compounds (IV, VI, IX, and XI) were treated with a solution of diazomethane in ether, and the corresponding methyl esters (V, VII, X, and XII) were obtained with yields of 96-98%.

Bis(methyl succinate) of 3β,28-Dihydroxy-18-lupene (V). mp 120-124°C (EtOH); $[\alpha]_D^{20}$ +4.1° (c 1.0; $CHCl_3$). IR spectrum (ν_{max}, cm^{-1}): 1726 (C=O), 1620 (C=C). PMR: 0.834 (3H, s), 0.843 (3H, s), 0.894 (6H, s), 0.905 (d, J = 6.7 Hz, CH_3-29), 0.991 (d, J = 6.7 Hz, CH_3-30), 1.057 (3H, s), 2.64 (8H, d), 3.14 (1H, m, J = 6.7 Hz, H-20), 3.700 (6H, s, 2 × Me), 4.04 (2H, q, J = 10.6 Hz, H-28), 4.52 (1H, m, H-3), 1.2-2.0 (remaining Hs).

Bis(hydrogen glutarate) of 3β,28-Dihydroxy-18-lupene (VI). A mixture of 3.50 g (7.9 mmoles) of (III) and 8.7 g (76 mmoles) of glutaric anhydride in 50 ml of C_5H_5N was boiled for 12 h and was worked up as described above. This gave 4.1 g of (VI). Yield 77%; amor-

phous. IR spectrum (ν_{max}, cm^{-1}): 3424, 2500-3300 (OH), 1712 (C=O), 1630 (C=C). PMR: 0.855 (6H, s), 0.910 (6H, s), 0.916 (d, J = 5.8 Hz, CH_3-29), 1.005 (d, J = 5.8 Hz, $CH_3$30), 1.078 (3H, s), 1.958 (6H, m), 2.417 (11H, m), 3.133 (1H, m, J = 5.8 Hz, H-20), 4.02 (2H, q, H-28), 4.478 (1H, m, H-3), 1.2-1.8 (remaining Hs).

Bis(methyl glutarate) of 3β,28-Dihydroxy-18-lupene (VII). mp 63-65°C (EtOH); $[\alpha]_D^{20}$ +3.2° (c 1.0; $CHCl_3$). Found, %: C 71.24; H 9.42; M^+, m/z: 698. $C_{42}H_{66}O_8$. Calculated: M 698.98; for $C_{42}H_{66}O_8 \cdot 0.5C_2H_6O$ %: C 71.53; H 9.63. IR spectrum (ν_{max}, cm^{-1}): 1725 (C=O), 1620 (C=C). PMR: 0.835 (3H, s), 0.839 (6H, s), 0.897 (6H, s), 0.902 (d, J = 6.8 Hz, CH_3-29), 0.992 (d, J = 6.8 Hz, CH_3-30), 1.064 (3H, s), 3.142 (1H, m, J = 6.8 Hz, H-20), 3.675 (3H, s), 3.683 (3H, s), 4.025 (2H, q, J = 10.8 Hz, H-28), 4.502 (1H, m, H-3), 1.2-2.5 (remaining Hs).

Initial Ruthenium Compounds. A solution containing Na_2RuO_4 was obtained from a powder of Ru metal in 4 M aqueous NaOH by the action of powdered $K_2S_2O_8$ according to [21], or from the inactive form of RuO_2 by treatment with an alkaline aqueous solution of $NaIO_4$. Before use in synthesis, portions of the ruthenate solution were neutralized with dilute H_2SO_4. A commercial reagent $Ru(OH)Cl_3$, "ch" ["pure"], and active $RuO_2 \cdot xH_2O$ isolated after synthesis in the EtOAc—H_2O system were also used.

Oxidation of Compound (II) with RuO_4 in H_2O—CCl_4. A solution of 1.103 g (2.09 mmoles) of (II) in 50 ml of CCl_4, 1.0 g (4.6 mmoles) of $NaIO_4$ in 50 ml of water, and ~0.2 mmoles of a Ru compound was stirred with an efficient magnetic stirrer in a flask sealed with a glass stopper for 20 h. The CCl_4 layer was separated off and was extracted twice with a $NaIO_4$ + NaOH solution. The washwater, neutralized with H_2SO_4, and the aqueous phase of the reaction mixture were treated with 1 ml of iso-PrOH and the black powder of $RuO_2 \cdot xH_2O$ was filtered off. The CCl_4 layer was dried over $CaCl_2$ and evaporated to dryness, and the residue was recrystallized for EtOH. This gave 0.885 g of 3β,28-diacetoxy-18,19-secolupane-18,19-dione (VIII). Yield 78%; mp 163-164.5°C, $[\alpha]_D^{20}$ +49.6° (c 1.0; $CHCl_3$). According to the literature [2]: mp 166°C, $[\alpha]_D$ +38.7°. PMR: 0.802 (3H, s), 0.846 (6H, s), 0.901 (6H, s), 1.096 (6H, d, J = 7.0 Hz, CH_3-29, CH_3-30), 1.126 (3H, s), 2.025 (3H, s), 2.049 (3H, s), 2.474 (2H, m), 2.632 (1H, m, J = 7.0 Hz, H-20), 2.698 (1H, q), 4.018 d and 4.435 d (2H, J = 11.0 Hz, H-28), 4.479 (1H, m, H-3).

General Procedure for Oxidizing Triterpenoids with Ruthenium Tetroxide. A flat-bottomed flask was charged with 1 mmoles of a triterpenoid, 15-30 ml of EtOAc, 0.1-0.5 mmole of a ruthenium compound, 3-6 mmoles of $NaIO_4$ and 10-20 ml of water. The flask was closed with a glass stopper and the mixture was stirred with an efficient magnetic stirrer until the reaction was complete [1-6 h in the oxidation of (II, IV, VI), and (XIV-XVI) and 25 h for (XIII)]. The excess of oxidant was destroyed by the addition of 1-3 ml of iso-PrOH or EtOH. The organic and aqueous phases were separated and were filtered from the deposit of $RuO_2 \cdot xH_2O$. To eliminate the colloidal RuO_2, the EtOAc layer was twice extracted rapidly with an aqueous solution of $NaIO_4$ + NaOH with the separation of the aqueous layer before it had time to be neutralized. The decolorized EtOAc solution was dried over anhydrous $CaCl_2$, $MgSO_4$, or Na_2SO_4 and was evaporated to dryness. The residue was recrystallized from EtOH. In this way, VIII was obtained with a yield of 80-90% from (II, XIII, XIV, and XVI) and with a yield of 30% from (XV). In the case of the oxidation of the acidic esters (IV) and (VI), after the separation of the layer the aqueous phase was extracted with EtOAc, the extract was combined with the EtOAc layer and the combined solution was dried over Na_2SO_4 and evaporated to dryness. The residue was dissolved in ethanol, and the solution was decolorized with activated carbon and evaporated to dryness. This gave (IX) or (XI) with a yield of 73-75%.

Bis(hydrogen succinate) of 3β,28-Dihydroxy-18,19-secolupane-18,19-dione (IX). Amorphous. IR spectrum (ν_{max}, cm^{-1}): 3515, 2800-3300 (OH), 1712 (C=O). PMR: 0.813 (3H, s), 0.858 (6H, s), 0.909 (3H, s), 1.104 (d, J = 7.0 Hz, CH_3-29 , CH_3-30), 1.128 (3H, s), 4.090 (1H, d, J = 11.0 Hz, H-28), 4.430 (1H, d, J = 11.0 Hz, H=28), 4.500 (1H, m, H-3), 1.2-2.8 (remaining Hs).

Bis(methyl succinate) of 3β,28-Dihydroxy-18,19-secolupane-18,19-dione (X). mp 102-105°C, $[\alpha]_D^{20}$ +10.2° (c 1.0; $CHCl_3$). IR spectrum (ν_{max}, cm^{-1}): 1732 (C=O). PMR: 0.796 (3H, s), 0.850 (6H, s), 0.898 (3H, s), 1.094 (d, J = 7.0 Hz, CH_3-29, CH_3-30), 1.124 (3H, s), 3.700 (6H, s), 4.057 (1H, d, J = 11.0 Hz, H-28), 4.452 (1H, d, J = 11.0 Hz, H-28), 4.500 (1H, m, H-3), 1.2-2.7 (remaining Hs).

Bis(hydrogen glutarate) of 3β,28-Dihydroxy-18,19-secolupane-18,19-dione (XI). Amorphous. IR spectrum (ν_{max}, cm^{-1}): 3512, 2800-3300 (OH), 1730, 1712 (C=). PMR: 0.801 (3H, s), 0.848

(6H, s), 0.905 (3H, s), 1.096 (d, J = 7.0 Hz, CH_3-29, CH_3-30), 1.129 (3H, s), 4.011 (1H, d, J = 11.0 Hz, H-28), 4.487 (1H, d, J = 11.0 Hz, H-28), 4.510 (1H, m, H-3), 6.15-6.55 (2H, m, OH), 1.1-2.7 (remaining Hs).

Bis(methyl glutarate) of 3β,28-Dihydroxy-18,19-secolupane-18,19-dione (XII). mp 86-90°C; $[\alpha]_D^{20}$ +6.4° (c 1.0; $CHCl_3$). IR spectrum (ν_{max}, cm^{-1}): 1732 (C=O). PMR: 0.800 (3H, s), 0.841 (6H, s), 0.900 (3H, s), 1.094 (d, J = 6.8 Hz, CH_3-29, CH_3-30), 1.127 (3H, s), 3.677 (3H, s), 3.683 (3H, s), 4.031 (1H, d, J = 11.2 Hz, H-28), 4.484 (1H, d, J = 11.2 Hz), 4.500 (1H, m, H-3), 1.1-2.7 (remaining Hs).

19-(Ethylene acetal) of 3β,28-Diacetoxy-18,19-secolupane-18,19-dione (XIII) was obtained as described in [2]. mp 191-193°C; $[\alpha]_D^{20}$ +44.4° (c 1.0; $CHCl_3$); M^+, m/z: 602. According to the literature [2]: mp 192°C $[\alpha]_D$ +43°.

19-(Ethylene thioacetal)s of 3β-28-Diacetoxy-18,19-secolupane-18,19-dione (XIV and XV). A mixture of 1 mmole of (VIII), 10 mmoles of 2-mercaptoethanol or 1,2-dimercaptoethane, 1 g of freshly fused $ZnCl_2$, and 2 g of $CaCl_2$ in 10 ml of dry 1,4-dioxane was stirred for 5-10 h and was then poured into cold water and extracted with $CHCl_3$. The extract was washed 3-5 times with water, dried over $CaCl_2$, and evaporated to dryness. The residue was recrystallized from EtOH, giving (XIV) or (XV) with yields of 70-85%.

Ethylene Monothioacetal (XIV). mp 205-208°C; $[\alpha]_D^{20}$ +40.6° (c 1.0; $CHCl_3$). Found, %: C 69.91; H 9.62; M^+, m/z: 6.8. $C_{36}H_{58}O_6S$. Calculated, %: C 69.86; H 9.45; M 618.91. IR spectrum (ν_{max}, cm^{-1}): 1723, 1712 (C=O). PMR: 0.798 (3H, s), 0.846 (6H, s), 0.898 (311, s), 0.981 (d, J = 6.7 Hz, CH_3-29), 0.991 (d, J = 6.7 Hz, CH_3-30), 1.121 (3H, s), 2.026 (3H, s), 2.048 (3H, s), 2.168 (1H, m), 2.730 (1H, q), 2.93 (2H, m, 19-SCH_2), 4.008 d and 4.065 d (1H, J = 11 Hz, H-28 of the epimers), 4.07 m and 4.23 m (2H, 19-OCH_2 of the epimers), 4.448 (1H, m, H-3), 0.450 d and 4.488 d (1H, J = 11 Hz, H-28 of the epimers), 1.2-1.8 (remaining Hs).

Ethylene Dithioacetal (XV). mp 229-230°C; $[\alpha]_D^{20}$ +35.0° (c 1.0; $CHCl_3$). Found, %: C 68.04; H 9.28; M^+, m/z: 634. $C_{36}H_{58}O_5S_2$. Calculated, %: C 68.10; H 9.21; M 634.97. IR spectrum (ν_{max}, cm^{-1}): 1723 (C=O). PMR: 0.816 (3H, s), 0.858 (6H, s), 0.913 (3H, s), 1.098 (d, J = 6.7 Hz, CH_3-29), 1.117 (d, J = 6.7 Hz, CH_3-30), 1.137 (3H, s), 2.030 (3H, s), 2.050 (3H, s), 2.182 (1H, m, J = 6.7 Hz, H-20), 2.750 (1H, q), 3.22 (4H, s), 4.050 (1H, d, J = 11.2 Hz, H-28), 4.453 (1H, d, J = 11.2 Hz, H-28), 4.484 (1H, m, H-3), 1.2-1.9 (remaining Hs).

3β,28-Diacetoxy-19-hydroxyimino-18,19-secolupan-18-one (XVI). A mixture of 363 mg (0.65 mmole) of (VIII), 448 mg (6.3 mmoles) of $NH_2OH \cdot HCl$, and 180 mg (4 mmoles) of NaOH in 30 ml of EtOH was stirred for 3 h and was then poured into water, and the product was filtered off and recrystallized from EtOH. This gave 300 mg of (XVI). Yield 80%; mp 192-195°C; $[\alpha]_D^{20}$ +46.5° (c 1.0; $CHCl_3$). Found, %: C 70.45; H 9.62; N 2.27; M^+, m/z: 573. $C_{34}H_{55}NO_6$. Calculated, %: C 71.17; H 9.66; N 2.44; M 573.81. IR spectrum (ν_{max}, cm^{-1}): 3586, 3100-3400 (OH), 1722 (C=O). PMR: 0.807 (3H, s), 0.839 (6H, s), 0.903 (3H, s), 1.124 (d, J = 6.7 Hz, CH_3-29, CH_3-30), 1.131 (3H, s), 2.016 (3H, s), 2.045 (3H, s), 2.537 (1H, m, J = 6.7 Hz, H-20), 2.74 (1H, m), 4.079 (1H, d, J = 10.7 Hz, H-28), 4.487 (1H, d, J = 10.7 Hz, H-28), 4.490 (1H, m, H-3), 8.2 (1H, NOH), 1.15-1.86 (remaining Hs).

SUMMARY

1. A convenient preparative method for the oxidation with ruthenium tetroxide of 18-lupene derivatives to 18,19-secolupane-18,19-dione derivatives has been developed.

2. It has been found that 3β,28-diacetoxy-18,19-secolupane-18,19-dione can be regenerated from its 19-(ethylene acetal) or 19-oxime by reaction with ruthenium tetroxide.

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SYNTHESIS OF 24-ETHYLCHOLESTA-7,22E-DIENE-3β,5α,6β-TRIOL – A NATURAL TRIHYDROXYSTEROID FROM THE BRYOZOAN Myriapora truncata

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24-Ethylcholesta-7,22E-diene-3β,5α,6β-triol – a natural trihydroxysteroid from the bryozoan Myriapora truncata – has been synthesized from stigmasterol.

Bryozoa are among the little-studied marine invertebrates. Five 3β,5α,6β-trihydroxy-7,8-dehydrosteroids having untransformed sterol side chains have been isolated from the Mediterranean bryozoan Myriapora truncata Pallas [1]. Eight trihydroxysteroids proving to be identical or close in structure to the polyhydroxysteroids of M. truncata have been isolated from the Mediterranean sponge Spongionella gracilis [2]. The 3β,5α,6β-trihydroxy-7,8-dehydrosteroids mentioned form a new and unique group of natural compounds the biological value of which, and also their distribution in the animal and, possibly, vegetable kingdoms, is yet to be elucidated.

Since these compounds are present in natural materials in only small amounts, for an all-sided study of their biological activity the development of methods for obtaining them by chemical synthesis from accessible natural sterols is necessary. With this aim, we have for the first time effected the synthesis of one of the trihydroxysteroids of M. truncata, 24-ethylcholesta-7,22E-diene-3β,5α,6β-triol (I), which was identified by Cafieri et al. [1] in

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