SYNTHESIS OF 20-DEOXOLUTEONE

P. F. Vlad, N. D. Ungur,
and Nguyen Van Hung

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20-Deoxoluteone has been synthesized from sclareol. Sclareol was brominated with phosphorus tribromide to form a mixture of primary allyl bromides, from which, by the malonic synthesis, a mixture of bicyclogeranylgeranylacetic acids was obtained which was cyclized with fluorosulfonic acid to form a mixture of two diastereomeric δ-lactones. The predominating lactone was converted by successive reduction with lithium tetrahydroaluminate, oxidation with oxalyl chloride in dimethyl sulfoxide, reaction with methylmagnesium iodide, and oxidation by the chromium trioxide/pyridine complex into 20-deoxyluteone.

We have previously [1] reported the synthesis of the deoxo analogues (I) and (II) with the Δ^{12} and Δ^{13} double bonds of luteone (III). However, it was not possible to obtain 20-deoxoluteone (IV) in this investigation.

In the present communication we describe a structure-selective and stereoselective synthesis of 20-deoxoluteone (IV) from sclareol (V). The latter was converted by a known procedure [2] into a mixture of primary allyl bromides (VI) which, as the result of a malonic synthesis, gave a mixture of esters of bicyclogeranylgeranylmalonic acids (VII) isomeric at the Δ^{13}-double bond and also with respect to the position of the ethylene bond in ring B. When they were heated with sodium chloride in dimethyl sulfoxide [3] an ethoxycarbonyl group was split out with the formation of a mixture of isomeric esters (VIII), which was saponified with alkali to form a mixture of the corresponding acids (IX). The 13E- isomer predominated in this mixture since the corresponding isomer was the predominant component of the initial mixture of bromides (VI). The cyclization of this mixture of acids with fluorosulfonic acid in 2-nitropropane led with ~95% yield to a mixture of the 1,5-lactones (X) and (XI). When this was recrystallized from petroleum ether, the predominating lactone (XI) was obtained. The lactone (X), isomeric with it, was isolated by chromatographing the mother liquors from crystallization on silica gel.

The molecules of compounds (X) and (XI) contained no double bonds and, consequently they contained three carbocycles in addition to the lactone ring. These compounds were δ-lactones, since their IR spectra contained maxima at 1708 and 1740 cm^{-1}, respectively. The PMR spectrum of each of these substances contained the signals of four methyl groups at quaternary carbon atoms and of a methyl group at a carbon atom linked to an oxygen atom. The structure of lactone (XI) was also confirmed by its mass spectrum. In this spectrum there were the fairly intense peak of the molecular ion with m/z 322 and peaks of ions with m/z 317 $(M - CH_3)$, 288 $(M - CO_2)$, 273 $(M - CH_3CO_2H)$, 260 $(M - (CH_2)_2CO_2H)$, 245 $(M - (CH_2)_2CO_2H{-}CH_3)$, 191 (an ion formed on the cleavage of the C9—C11 and the C8—C14 bonds) and 136 (an ion formed on the cleavage of the C9—C10 and C6—C7 bonds).

According to the principle of stereospecific trans-antiparallel addition in the electrophilic cyclization of 1,5-dienic compounds [4, 5], lactones (X) and (XI) should differ by the configuration at C—14; namely, the first of them should have the 14R-, and the second the 14S-, configuration. The structure and sterochemistry of lactone (XI) were shown strictly as the result of its correlation with a substance of known structure and stereochemistry — the isoagathane diol (XII).

To carry out this correlation it was necessary to introduce a double bond into the α-position with respect to the carbonyl group of lactone (XI). However, this proved to be a fairly inert substance; it did not react with lead tetraacetate on boiling in benzene [6],

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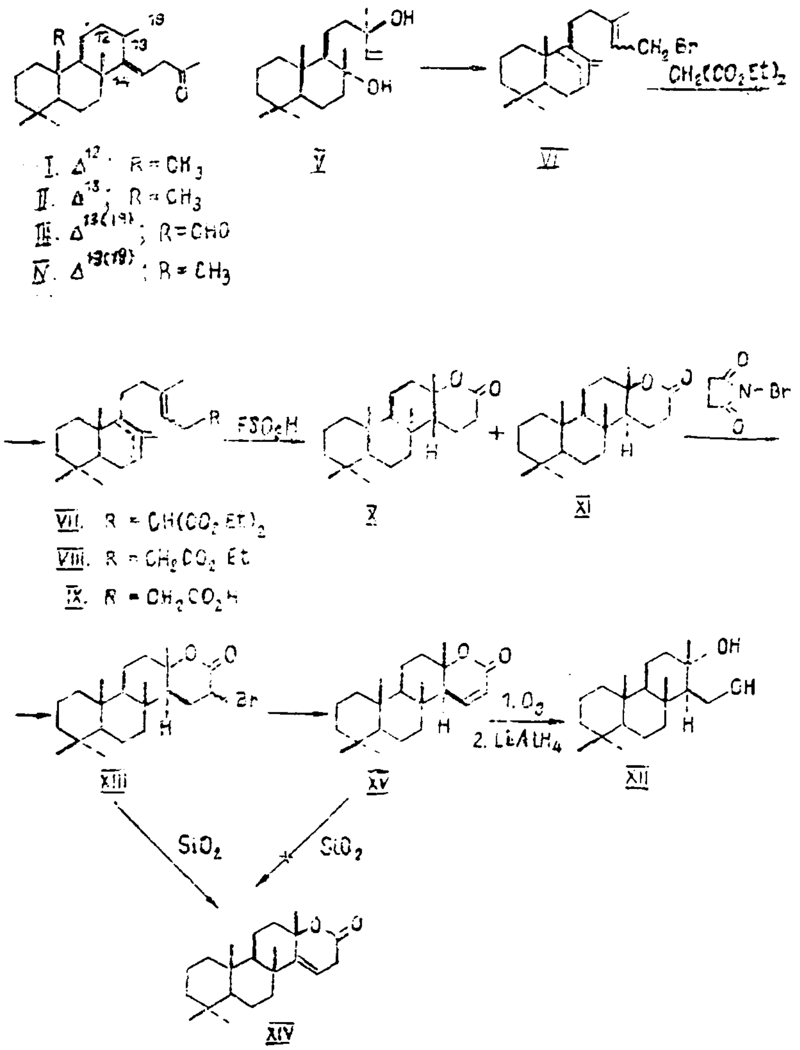


Scheme 1

with fluorotrimethylsilane in the presence of lithium diisopropylamide [7], and with N-bromosuccinimide on boiling in the presence of benzoyl peroxide in methylene chloride or carbon tetrachloride [8]. And only on prolonged boiling of lactone (XI) with N-bromosuccinimide and benzoyl peroxide in dichloroethane was the bromolactone (XIII) formed in low yield; however, this could not be isolated in the individual state since on chromatography of the reaction product in a silica gel column it split out hydrogen bromide and, judging from the PMR spectrum, gave the unsaturated lactone (XIV). In actual fact, this spectrum contained multiplet signals of one vinyl proton and of a methylene group attached to a lactone group but no signals characteristic for the two vinyl protons of structure (XV). Therefore, subsequently, the bromination product of lactone (XI), without purification, was heated with quinoline, and the resulting mixture of substances was separated by chromatography on a silica gel column. As a result of the chromatography, the unsaturated lactone (XV) was isolated in low yield (~14%), its structure following from its spectral characteristics. Its IR spectrum contained the maxima of an α,β-unsaturated δ-lactone group (1700 cm^{-1}) and of a double bond conjugated with it (845, 1649 cm^{-1}), while its PMR spectra contained the doublets of doublets of two cis-located vinyl protons at 5.90 and 6.71 ppm. In its mass spectrum in the region of high mass numbers there were the peaks of ions with m/z 330 (molecular ion), 315 (M − CH$_3$), 260 (M − CH=CH—CO$_2$, the ion formed on the cleavage of the C13—O and C14—C15 bonds), 128 (the ion formed on the cleavage of the C12—C13 and C9—C14 bonds with the transfer of two hydrogen atoms to it), 192 (an ion arising on the cleavage of the C9—C11 and C8—C14 bonds) and 191 (an ion formed on the cleavage of the same bonds, C9—C11 and C8—C14, with the transfer of one hydrogen atom), confirming its structure.

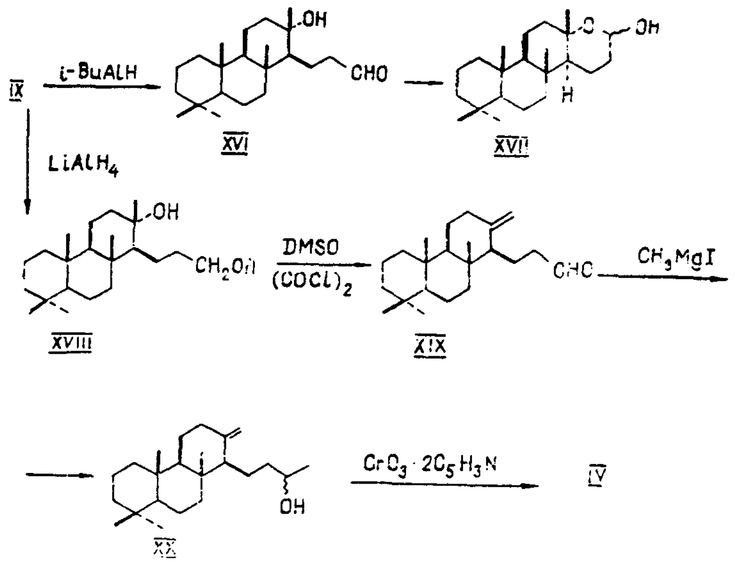
It is interesting to note that when it was chromatographed on a column of silica gel, lactone (XV) did not isomerize into lactone (XIV). This possibly shows that the elimination of hydrogen bromide from the bromolactone (XIII) on silica gel takes place as a 1,3-elimination process with the detachment of a proton from C14 and the subsequent migration of a hydride ion from C15 to C16.

When lactone (XV) was ozonized in methylene chloride in the presence of pyridine and the ozonization product was then reduced with lithium tetrahydroaluminate, the known (14S)-isoagathane-13α, 15-diol (XII) [9] was obtained. This unambiguously showed the structures and stereochemistries of lactones (XI) and (XIV), and (XV) and confirmed that the cyclization of the unsaturated acids (IX) had taken place stereospecifically in the manner of a trans-antiparallel addition, since the ratio of the lactones (X) and (XI) (1:5) approximately reflected the ratio of the 13Z- and 13E- isomers in the mixtures of bromides (IV).

To construct the carbon side chain characteristic for luteone (III) we attempted to bring lactone (XI) into reaction with methyllithium or with methylmagnesium bromide, but unsuccessfully. It was impossible to obtain the hydroxy acid corresponding to lactone (XI) even under mild conditions because of its ready and rapid conversion into the initial lactone. For this reason it was also impossible to obtain the methyl ester of this hydroxy acid, while when its sodium salt was treated with methyllithium in THF the initial lactone was again recovered. When the latter was reduced with diisobutylaluminum hydride in THF, judging from spectral characteristics, the corresponding hydroxyaldehyde (XVI), existing in the form of the cyclic semiacetal (XVII) arose. This likewise did not take part in a reaction with methyllithium or with methylmagnesium bromide.

The following route led to the desired result. When the product of the reduction of lactone (XI) with lithium tetrahydroaluminate – the diol (XVIII) – was oxidized with dimethyl sulfoxide and oxalyl chloride by Swern's method [10], in addition to the smooth conversion of the primary hydroxy group into an aldehyde group, the tertiary hydroxy group was split out and the sole reaction product, the yield of which was ~79%, was the unsaturated aldehyde with a semicyclic double bond (XIX). The splitting out of the tertiary hydroxy group of the diol (XVIII) took place regioselectively, since the isomers of aldehyde (XIX) with Δ^{12} and Δ^{14} double bonds could not be detected either by TLC or GLC or by PMR spectroscopy. The structure of aldehyde (XIX) followed from the results of elementary analysis and also those of IR and PMR spectroscopy: its molecule contained an aldehyde group and a semicyclic double bond and no hydroxy group.

The reaction of the unsaturated aldhyde (XIX) with methylmagnesium iodide formed, with an ~80% yield, the unsaturated alcohol (XX), which was smoothly oxidized (81% yield) by the chromium trioxide/pyridine complex to 20-deoxoluteone (IV). Its structure was shown by its IR and PMR spectra (it contained a semicyclic double bond and the methyl ketone group) and was confirmed by its mass spectrum, which contained together with others, the intense peak of the molecular ion with m/z 330 and the peaks of ions with m/z 315 (M – CH_3), 287



Scheme 2

($M - COCH_3$), 273 ($M - CH_2COCH_3$), 259 ($M - CH_2CH_2COCH_3$), the presence of which confirmed the structure of the side chain of ketone (IV), and also the peaks of ions with m/z 204 (formed on the cleavage of the C11–C12 and C8–C14 bonds) and 191 (the 100% ion, formed by the cleavage of the C9–C11 and C8–C14 bonds), the appearance of which agrees with the presence of a semicyclic double bond at C13.

Thus, we have effected a nine-stage structure-selective and stereoselective synthesis of 20-deoxoluteone (IV) from sclareol (V) based on two fortunate synthetic findings: 1) the highly effective stereospecific superacid cyclization of a mixture of the acids (IX) into a mixture of the lactones (X) and (XI), and 2) the oxidation of the diol (XVIII) with simultaneous regiospecific dehydration by Swern's reagent to the aldehyde (XIX). It must be mentioned that lactone (XI) is a convenient synthon for the synthesis of other polycyclic terpenoids, as well.

EXPERIMENTAL

For the general part, see [1].

Mixture of the Acids (IX). With stirring, a solution of 6 g of the mixture of bromides (V) [2] in 0.9 ml of dimethylformamide, 2.8 ml of acetone, and 0.15 g of benzyltriethylammonium chloride were added to a suspension of 2.7 g of potassium carbonate in 2 ml of dry malonic ester. The mixture was stirred at +75 to 78°C for 20 h and was diluted with water (15 ml) and extracted with ether (3 × 10 ml), and the extract was washed with water to neutrality, dried, filtered, and evaporated. The residue (6.88 mg) was chromatographed on a column containing 140 g of silica gel. Petroleum ether eluted 243 mg of a mixture of hydrocarbons which was not investigated further.

A mixture of petroleum ether and ethyl acetate (9:1) eluted from the column 5.65 g (77%) of the mixture of diesters (VII) in the form of a viscous liquid. IR spectrum (cm^{-1}): 1734, 1750 ($CO_2C_2H_5$), 1362, 1382 [$C(CH_3)_2$], 858, 1667 ($>C=C<_H$), 885, 1642 ($>C=CH_2$).

A solution of 20 g of the mixture of diesters (VII) in 53 ml of dimethyl sulfoxide was treated with 3.5 ml of water and 4.3 g of sodium chloride. The resulting mixture was stirred at 155-160°C for 26 h. The solvent was distilled off in vacuum, and the residue (17.8 g) was chromatographed on a column containing 180 g of silica gel. Petroleum ether eluted 0.62 g of a mixture of weakly polar substances, which were not investigated further, and a mixture of petroleum ether with ethyl acetate (19:1) eluted 13.4 g (~83%) of a liquid mixture of esters (VIII). IR spectrum (cm^{-1}): 1728 ($CO_2C_2H_5$), 1361, 1377 [$C(CH_3)_2$], 848, 1655 ($>C=C<_H$), 880, 1632 ($>C=CH_2$).

A solution of 12.5 g of the mixture of esters (VIII) in 10 ml of ethanol was treated with 30 ml of a 10% alcoholic solution of caustic potash, and the solution was boiled under reflux for 5 h. The alcohol was distilled off in vacuum, and the reaction mixture was worked up in the usual way. This gave 10.6 g (89.5%) of the mixture of isomeric acids (IX). IR spectrum (cm^{-1}): 1710 (COOH), 1734, 1382 [$C(CH_3)_2$]. PMR spectrum (δ, ppm): 0.82 (s, 3H, CH_3 – at C10), 0.88 (s, 6H, CH_3 at C4), 1.38 (s, 1.5H, CH_3 at C8), 1.53 (s, 3H, CH_3 at C13), 2.33 (m, 2H, $-CH_2COO-$), 4.50 (m) and 4.78 (m) (1H, $>C=CH_2$) and 5.08 (br. s, 1H, 14-H), 5.30 (br. s, 0.3H, 7-H). Found %: C 79.24; H 10.98. $C_{22}H_{36}O_2$. Calculated %: C 79.46; H 10.91.

The Mixture of Lactones (X) and (XI). With stirring, a solution of 7 g of the mixture of acids (IX) in 47 ml of 2-nitropropane was added at –80 to –82°C to a solution of 23.6 g of fluorosulfonic acid in 127 ml of 2-nitropropane cooled to the same temperature. The reaction mixture was stirred at this temperature for 20 min and was frozen with liquid nitrogen, after which, on thawing, it was added dropwise with stirring to a solution of 26 g of caustic potash in 55 ml of water. The reaction product was extracted with ether (3 × 25 ml). The extract was washed with water to neutrality, dried, and filtered, and the solvent was distilled off. This gave 6.7 g (95%) of a crystalline product, which was recrystallized from petroleum ether. The yield of lactone (XI) was 3.8 g; mp 132-133; $[\alpha]_D^{22}$ + 12.8° (c 1.1; $CHCl_3$). IR spectrum (cm^{-1}): 1708 ($-COO-$), 1366, 1381 [$C(CH_3)_2$]. PMR spectrum (δ, ppm): 0.80 (s, 9H, CH_3 at C4 and C10), 0.85 (s, 3H, CH_3 at C8), 1.15 (s, 3H, CH_3 at C13), 2.33 (m, 2H, $-CH_2COO-$). Mass spectrum m/z (%): 332 (M^+, 31), 317(29), 260(62), 245(18), 204(29), 191(63), 136(96), 123(44), 104(47), 69(100). Found %: C 79.32; H 10.83. $C_{22}H_{36}O_2$. Calculated %: C 79.46; H 10.91.

The mother liquors from the crystallization of the lactone (XI) (2.85 g) were chromatographed on a column containing 75 g of silica gel. Petroleum ether eluted 56 mg of a mixture of weakly polar substances which was not investigated, and a mixture of petroleum ether and ethyl acetate (9:1) eluted 354 mg of lactone (X), mp 34-36.5°C (from petroleum ether); $[\alpha]_D^{22}$ −23.5° (c 1.9; $CHCl_3$). IR spectrum (cm^{-1}): 1740 (—COO—), 1357, 1376 $[C(CH_3)_2]$. PMR spectrum (δ, ppm): 0.77 (s, 6H, CH_3 at C4 and C10), 0.92 (s, 6H, CH_3 at C4 and C8), 1.25 (s, 3H, CH_3 at C13), 2.23 (m, 2H, $-CH_2COO-$). Found %: C 79.61; H 10.84. $C_{22}H_{36}O_2$. Calculated %: C 79.46; H 10.91.

Then a 4:1 mixture of the same solvents eluted from the column 2.3 g of a mixture of lactones (X) and (XI) (~1:2).

The Unsaturated Lactone (XIV). A solution of 400 mg of the lactone (XI) in 6.5 ml of dichloroethane was treated with 10 mg of benzoyl peroxide, and the mixture was boiled under reflux for 20 h and was then cooled and was worked up in the usual way. This gave 0.57 g of a reaction product containing the initial lactone (XI) and the α-bromolactone (~4:1). It was chromatographed on a column containing 11 g of silica gel. A mixture of petroleum ether and ethyl acetate (19:1) eluted 60 mg of a mixture of weakly polar substances, which was not investigated, and a 9:1 mixture of the same solvents eluted 0.38 g of the initial lactone (XI). A 5:1 mixture of the same solvents eluted 98 mg of the lactone (XIV), a viscous colorless liquid. IR spectrum (cm^{-1}): 1700 (—COO group). PMR spectrum (δ, ppm): 0.77 (s, 6H, CH_3 at C4 and C10), 0.81 (s, 6H, CH_3 at C4 and C8), 1.25 (s, 3H, CH_3 at C13), 2.25 (m, 2H, $-CH_2COO-$) and 5.17 (m), 1H, $>C=C<_H$). Found %: C 79.72; H 10.25, $C_{22}H_{34}O_2$. Calculated %: C 79.95; H 10.37.

The α,β-Unsaturated Lactone (XV). A solution of 1 g of lactone (XI) in 6 ml of 1,2-dichloroethane was treated with 640 mg of N-bromosuccinimide and 9 mg of benzoyl peroxide, and the mixture was boiled under reflux for 25 h and was then cooled and worked up to give 0.97 g of a reaction product containing the initial lactone (XI) and the α-bromolactone (XIII) (~4:1). This was dissolved in 5 ml of quinoline and the solution was heated at 180-190°C for 3 h. Then it was cooled and worked up in the usual way to give 0.83 g of reaction product which was chromatographed on a column containing 18 g of silica gel.

A 19:1 mixture of petroleum ether and ethyl acetate eluted 110 mg of a mixture of weakly polar substances, which was not investigated; a 17:3 mixture of the same solvents eluted 563 mg of the initial lactone (XI); and a 4:1 mixture eluted 140 mg of the α,β-unsaturated lactone (XV). IR spectrum (cm^{-1}): 1700 (—COO—), 845, 965, 1649 ($_H>C=C<_H$). PMR spectrum (δ, ppm): 0.73 (s, 3H, CH_3 at, C10), 0.77 (s, 9H, CH_3 at C4 and C8), 1.20 (s, 3H, CH_3 at C13), 5.90 (dd, J_1=2 Hz, J_2=7 Hz, 1H, 16-H) and 6.71 (dd J_1=2 Hz, J_2=7 Hz, 1H, 15-H). Mass spectrum, m/z (%): 330 (M^+, 4), 315(30), 260(58), 218(15), 192(20), 191(50), 177(32), 136(62), 69(93), 43(100).

Isogathane-13α,15-diol (XII). A current of ozonized oxygen was passed through a solution of 100 mg of lactone (XV) in 10 ml of methylene chloride and 0.6 ml of dry pyridine cooled to −70°C until it was saturated (20 min). Then the solution was acidified with 10% sulfuric acid and was worked up in the usual way. The product (86.2 mg) was dissolved in 5 ml of absolute ether, 50 mg lithium tetrahydroaluminate was added to the solution, and the mixture was kept a room temperature for 2.5 h and was worked up in the usual way. The reaction product (63.5 g) was chromatographed on a column containing 1.2 g of silica gel. A 17:3 mixture of petroleum ether and ethyl acetate eluted 21.6 g of a mixture of weakly polar substances, and a 3:1 mixture of the same solvent eluted 30.2 mg of the diol (XII), mp 187-190°C (from petroleum ether), identical with an authentic sample [9].

The Diol (XVIII). A solution of 1.9 g of lactone (XI) in 10 ml of tetrahydrofuran was treated with 324 mg of lithium tetrahydroaluminate, and the mixture was left at room temperature for 3.5 h. The excess of tetrahydroaluminate was decomposed with ethyl acetate, and the mixture was acidified with sulfuric acid and worked up in the usual way. This gave 1.6 g (83%) of the diol (XVIII), mp 167-168.5°C (from ether): $[\alpha]_D^{22}$ + 10.9° (c 1.9; $CHCl_3$). IR spectrum ($CHCl_3$, cm^{-1}): 1362, 1384 $[C(CH_3)_2]$, 1130, 3380, 3600 (OH groups). PMR spectra ($CDCl_3$, δ, ppm): 0.78 (s, 9H, CH_3 at C4, C8 and C10), 0.85 (s, 3H, CH_3 at C4), 1.25 (s, 3H, CH_3 at C13), 3.58 (m, 2H, $-CH_2-O-$). Found %: C 78.62; H 11.86, $C_{22}H_{40}O_2$. Calculated %: C 78.51; H 11.98.

The Aldehyde (XIX). With stirring, a solution of 220 mg of dimethyl sulfoxide in 0.7 ml of methylene chloride was added to a solution of 200 mg of oxalyl chloride in 3 ml of methylene chloride cooled to –(60-62)°C. The resulting solution was stirred for 5 min, and then a solution of 100 mg of the diol (XVIII) in 0.7 ml of methylene chloride was added to it and the mixture was stirred at the same temperature for 45 min, after which 1 ml of triethylamine was added, and then, with stirring, the temperature of the reaction mixture was raised to that of the room. The mixture was extracted with ether, and the extract was washed with water to neutrality, dried, filtered, and evaporated. The residue (89 mg) was chromatographed on a column containing 1.9 g of silica gel. A 19:1 mixture of petroleum ether and ethyl acetate eluted 74 mg (~79%) of the unsaturated aldehyde (XIX), a colorless viscous liquid: $[\alpha]_D^{22}$ +20.2 (c 1.8; $CHCl_3$). IR spectrum (cm^{-1}): 1720, 2707 (CHO), 883, 1636 ($>C=CH_2$), 1357, 1380 [$C(CH_3)_2$]. PMR spectrum (δ, ppm): 0.80 (s, 12 H, 4 methyl groups at quaternary carbon atoms), 4.33 (m and 4.70 (m) (2H, $>C=CH_2$)), 9.67 (s, 1H, CHO). Found %: C 83.34; H 11.42. $C_{22}H_{36}O$. Calculated %: C 83.48; H 11.46.

The Unsaturated Alcohol (XX). With stirring at room temperature, a solution of 130 mg of the aldehyde (XIX) in 1 ml of ether was added to a solution of methylmagnesium iodide obtained from 24 mg of magnesium turnings and 0.6 ml of methyl iodide in 2 ml of absolute ether. The mixture was stirred for another 30 min and was decomposed by the addition of ice and a solution of ammonium chloride to neutralization, and was then extracted with ether (3 × 10 ml). The ethereal extract was washed with water, with saturated sodium bicarbonate solution, and with water again and was dried, filtered, and evaporated. The residue (127 mg) was chromatographed on a column containing 1.7 g of silica gel. A 17:3 mixture of petroleum ether and ethyl acetate eluted 109 mg (~80%) of the unsaturated alcohol (XX), a colorless viscous liquid: $[\alpha]_D^{22}$ +9.9° (c 2.9; $CHCl_3$). IR spectrum (cm^{-1}): 884, 1640 ($>C=CH_2$), 1364, 1380 [$C(CH_3)_2$], 1128, 3455, 3620 (OH group). PMR spectrum (δ, ppm): 0.80 (s, 12 H, 4 CH_3 groups at quaternary carbon atoms), 3.58 (m, 1H, $>CH-OH$), 4.45 (m) and 4.72 (m) (2H, $>C=CH_2$). Found %: C 82.94; H 12.10, $C_{23}H_{40}O$. Calculated %: C 83.06; H 12.12.

20-Deoxyluteone (IV). A solution of 66 mg of the alcohol (XX) in 4.5 ml of dry methylene chloride was treated with 250 mg of the complex $CrO_3 \cdot 2C_5H_5N$, and the mixture was stirred at room temperature for 4 h. The precipitate was filtered off and was washed with methylene chloride and with ether, and the solvents were distilled off. The distillation residue (61 mg) was chromatographed on a column containing 0.8 g of silica gel. A 9:1 mixture of petroleum ether and ethyl acetate eluted 53 mg (~81%) of 20-deoxyluteone (IV), a colorless viscous liquid: $[\alpha]_D^{22}$ –21.3° (c 1.9; $CHCl_3$). IR spectrum (cm^{-1}): 1710 ($COCH_3$), 880, 1636 ($>C=CH_2$), 1352, 1374 [$C(CH_3)_2$]. PMR spectrum (δ, ppm): (s, 9H, CH_3 at C4 and C16), 0.79 (s, 3H, CH_3 at C8), 1.93 (s, 3H, $COCH_3$), 4.23 (m, 4.68 (m) (2H, $>C=CH_2$). Found %: C 83.64; H 11.52, $C_{23}H_{38}O$. Calculated %: C 83.57; H 11.59.

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