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SYNTHESIS OF THE ENANTIOMERS OF UMBELACTONE. CONFIGURATIONAL ASSIGNMENT OF THE NATURAL PRODUCT.

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Summary.- Both (+)- and (-)-umbelactone have been synthetized from (R)-γ-hydroxymethyl-γ-butyrolactone and D-ribonolactone, respectively. The absolute configuration of the natural product has shown to be R-(+).

INTRODUCTION

(+)-Umbelactone, (+)-1, is an example of naturally occurring structurally simple α,β-butenolides which was isolated from Memycelon Umbelatum Burm.[1] The crude extracts of this plant showed activity against Ranikhe disease virus and exhibited spasmolytic and antiamphetamine activity.[2]

Structural elucidation of 1 was made from its spectral data and elemental analysis[1] and was later confirmed by synthetizing the racemic form.[3] However, its absolute configuration remained unknown.

We have achieved the unequivocal syntheses of the enantiomeric umbelactones (+)-1 and (-)-1 in order to clarify their configuration, being (R)-γ-hydroxymethyl-γ-butyrolactone,[4] 2, and D-ribonolactone, 3, respectively, the chiral starting materials.

RESULTS AND DISCUSION

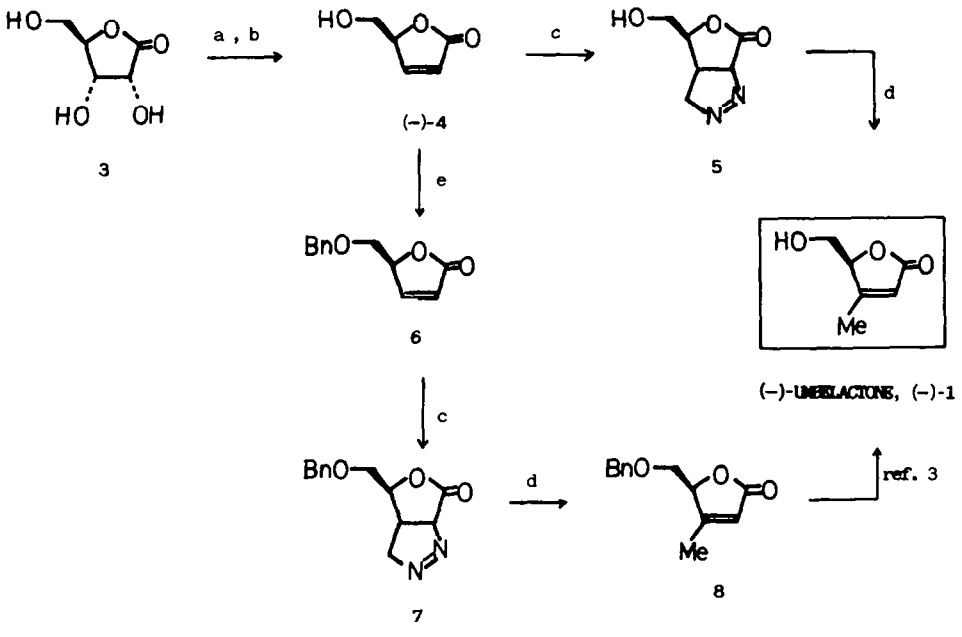
The two synthetic sequences followed to prepare (+)-1 and (-)-1 have enantiomeric γ-hydroxymethyl-α,β-butenolides, 4, as intermediates.

The enantiomer (-)-(S)-4 was easily obtained from D-ribonolactone, 3, by reaction with ethyl ortoformate and subsequent pyrolysis[5] (Scheme 1). Reaction of α,β-butenolides with diazoalkanes is a known method to obtain either cyclopropane derivatives[6] or β-alkylbutenolides,[7] depending on the reaction conditions. Thus, introduction of the methyl group in (-)-4 was accomplished by allowing it to react with 5 moles of diazomethane in ether-THF for 60 h at room temperature. The resulting pyrazoline 5 is a very insoluble solid, that was identified by its mass spectrum: m/e 156 (M), 138 (M - H_2O), 110 (138 - N_2), 95 (110- CH_3), and used in the next step without purification. Thus, crude 5 was subjected to pyrolysis in refluxing dioxane to afford (-)-(S)-umbelactone, (-)-1, $\{\alpha\}^{20}_D$ = -11.86° (c = 1.57, chloroform), in 33 % overall yield from (-)-4.

In order to prevent the possible influence of the free hydroxyl group of (-)-4 in the overall yield reported hereupon, we protected it as a benzyl ether, hydrogenolysis of this function in racemic 8 being reported to occur in good yield.[3] Thus, reaction of the known[5] benzyloxymethylbutenolide 6 with diazomethane gave the pyrazoline 7, identified from its spectral data. The

mass spectra showed loss of nitrogen (m/e 218 (M-28)), and characteristic absorptions at δ 5.58 (=N-C<u>H</u>-CO-) and δ 4.71 (-C<u>H</u>$_2$-N=) were observed in its ^{1}H NMR spectrum . Attempts to purify 7 by column chromatography resulted in decomposition of the product. Therefore, crude 7 was pyrolyzed to afford the β-methylbutenolide 8, $\{\alpha\}_D^{20}$ = -46.50° (c = 1.60, chloroform), in 55 % yield (40 % overall yield from (-)-4).

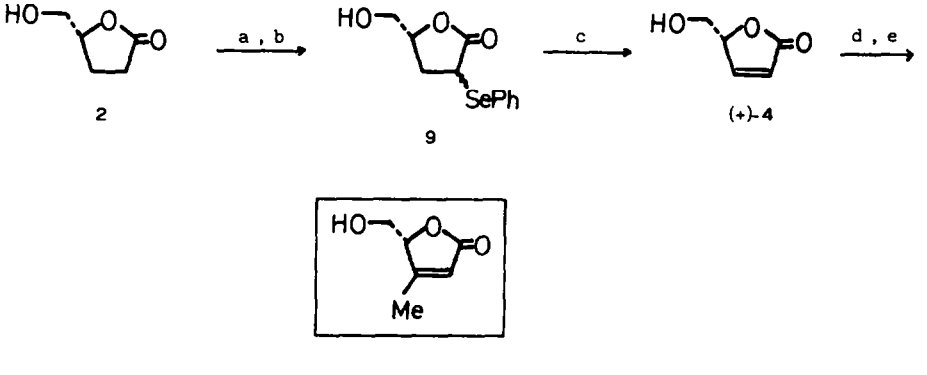
Although the methylene insertion step occurs actually in a higher yield, the increase in the number of steps and their overall yield do not advantage the direct route from (-)-4 to (-)-1.



Reagents.- a: $HC(OEt)_3$; b: 220°/40 torr; c: CH_2N_2; d: dioxane, reflux; e: BnCl, Ag_2O.

Scheme 1

Since natural umbelactone is described to be dextrorotatory,[1] and we had obtained the <u>levo</u> enantiomer from <u>D</u>-ribonolactone, 3, we decided to synthetize (+)-umbelactone starting from (<u>R</u>)-γ-hydroxymethyl-γ-butyrolactone, 2. The synthetic way passes through the new enantiomer (+)-(<u>R</u>)-γ-hydroxymethyl-α,β-butenolide (+)-4. (Scheme 2).



Reagents.- a: LDA, -78°; b: PhSeBr, -78°; c: 30 % aq H_2O_2, HAcO, THF; d: CH_2N_2; e: dioxane, reflux.

Scheme 2

Treatment of the lithium enolate of 2 with phenylselenyl bromide, gave the diastereoisomeric mixture 9 as a syrup. Oxidation with hydrogen peroxide, and pyrolysis in situ of the resulting selenoxide afforded (+)-4 as a solid, m.p. 37-39°, $\{\alpha\}_D^{25}$ = +136.09 (c = 1.69, water), in 45 % overall yield from 2.

In a similar manner as described above, (+)-(R)-4 was converted into (+)-(R)-umbelactone, m.p. 62-64°, $\{\alpha\}_D^{20}$ = +11.67 (c = 1.84, chloroform).(Lit[1] $\{\alpha\}_D$ = + 5.2°).

Thus, the absolute configuration of the natural product is shown to be R, and a more accurate specific rotation is given.

EXPERIMENTAL SECTION

Melting points have been determined on a Kofler hot stage and are uncorrected. Optical rotations were obtained on a Propol polarimeter, model Dr. Kernchen. Distillation of small amounts were effected on a rotational distillator Büchi, model KRV 65/30 (only external or oven temperature given). The 70 eV electron impact mass spectra were recorded with a Hewlett-Packard apparatus, model 5985 B. The infrared spectra were recorded on a Perkin-Elmer spectrophotometer, model 1310. The 80 MHz ^{1}H and 20 MHz ^{13}C NMR spectra were recorded on a Bruker Spectrometer, model WP 80 SY; chemical shifts are given in parts per million relative to TMS (δ scale).

(-)-(S)-Benzyloxymethyl-4-methyl-2(5H)-furanone, 8.

To an ice-cooled solution of 6 (250 mg, 1.23 mmol) in 1 ml of anhydrous THF under argon, 5 ml of a 0.5 M ethereal solution of diazomethane (2.5 mmol) were added. The light-protected mixture was stirred for 45 h at r.t. Then, the solvent was evaporated, and the residue poured into 15 ml of dioxane and heated to reflux for 50 h. The solvent was removed and the residue chromatographed on silica gel (ethyl acetate-hexane as eluent) to afford 8 (148 mg, 55 % yield) as a liquid, b.p. 130°/-0.08 torr, $\{\alpha\}_D^{20}$ = -46.50° (c = 1.60, chloroform). ^{1}H NMR ($CDCl_3$) 2.09 (m, 3H); 3.75 (d, J=4.0 Hz, 2H); 4.75 (s, 2H); 4.93 (m, 1H); 5.87 (m, 1H); 7.27 (complex absorption, 5H); ^{13}C NMR ($CDCl_3$) 13.8, 68.4, 73.6, 83.6, 117.7, 127.5 (2 C), 127.7, 128.3 (2 C), 137.4, 166.3, 172.6; IR (film) 3060, 3040, 2920, 2860, 1760, 1645, 1495, 1450, 1440, 1360, 1290, 1150, 1120, 1065 cm^{-1}; MS, m/e 219 (M+1, 0.5), 218 (1), 188 (2), 91 (100), 77 (5), 65 (16), 51 (6), 43 (14).

Diastereoisomeric mixture of (3R,5R)- and (3S,5R)-phenylseleno-5-methyldihydro-2(3H)-furanone, 9.

To a stirred solution of diisopropylamine (2.2 ml, 15.6 mmol) in anhydrous THF (17 ml) cooled at -78° under argon, 11 ml (17.6 mmol) of a 1.6 M solution of butyllithium in hexane were added. After 30 min a solution of 2 (550 mg, 4.7 mmol) in THF (19 ml) was added over a 15 min period and the mixture was stirred for 45 min. Then phenylselenyl bromide (5.7 mmol, prepared from 886 mg of diphenyldiselenide and 456 mg of bromine) in 16 ml of THF was added. After stirring for 3 h at -78° the mixture was hydrolyzed with 17 ml of 2 M hydrochloric acid, allowed to reach r.t. and diluted with ethyl acetate (250 ml). The layers were separated and the organic layer was washed with sat aq NaCl (55 ml) and dried over sodium sulfate. The solvents were removed at reduced pressure and the residue was chromatographed on silica gel (mixtures ef ethyl acetate-hexane as eluents) to afford 9 as a mixture of diastereoisomers (596 mg, 46 % yield), recovering 12 % of unaltered 2. ^{1}H NMR ($CDCl_3$) 1.63 (broad signal, 1H); 1.98-2.89 (complex absorption, 2H); 3.48 (dd, J = 12.5 Hz, J' = 5.1 Hz, 1H); 3.78 (dd, J = 12.5 Hz, J' = 3.8 Hz, 1H); 4.03 (dd, J = J' = 9.5 Hz, 1H); 4.51 (m, 1H); 7.19-7.80 (complex absorption, 5H); IR (film) 3680-3090 (broad), 3040, 2925, 2860, 1750, 1565, 1465, 1435, 1335, 1175, 1090, 1055, 1015, cm^{-1}; MS, m/e 272 (M, 3), 169 (45), 117 (31), 105 (51), 99 (48), 91 (32), 85 (43), 84 (54), 83 (44), 77 (50), 71 (37), 57 (41), 55 (84), 51 (31), 45 (32), 43 (100), 41 (58). Anal. Calc. for $C_{11}H_{12}O_3Se$: C, 48.72; H, 4.46. Found: C, 48.49; H, 4.53.

(+)-(R)-5-Hydroxymethyl-2(5H)-furanone, (+)-4.

To an ice-cooled solution of diastereoisomeric mixture 9 (550 mg, 2.0 mmol) in 18 ml of THF some drops of acetic acid and 30 % aq hydrogen peroxide (1.4 ml, 12.5 mmol) were successively added and the mixture stirred for 30 min. Then, the solution was neutralized to pH slightly basic with sat aq sodium bicarbonate. The aqueous layer was extracted with ethyl acetate, the combined organic layers dried on sodium sulfate and the solvents removed under reduced pressure. The residue was chromatographed on silica gel (mixtures of methylene chloride-ether as eluents) to give butenolide (+)-4 (192 mg, 83 % yield) as a solid, m.p. 37-39°(from methylene chloride-ether), b.p. 88°/0.01 torr, $\{\alpha\}_D^{25}$ = +136.09° (c =1.69, water).(Lit[5] $\{\alpha\}_D^{20}$ = -143° (c = 1.14, water) for the enantiomer). ^{1}H NMR($CDCl_3$) 2.13 (broad, 1H);3.79 (dd, J = 11.5 Hz, J' = 4.6 Hz, 1H); 4.03 (dd, J = 11.5 Hz, J' = 3.8 Hz, 1H); 5.19 (m, 1H); 6.20 (dd, J = 6.6 Hz, J' = 2.0 Hz, 1H); 7.52 (dd, J = 6.6 Hz, J' = 1.3 Hz, 1H).

(+)-(R)-Umbelactone, (+)-1.

To an ice-cooled solution of (+)-4 (140 mg, 1.2 mmol) in 1 ml of anhydrous THF under argon, a 0.52 M ethereal solution of diazomethane (7 ml) was added. The light-protected mixture was stirred for 45 h at 5-7°. Then, 2 further ml of diazomethane solution were added. After stirring for 15 h, the solvent was evaporated, and the residue poured into 12 ml of dioxane and heated to reflux for 50 h. The solvent was removed and the residue was washed several times with chloroform. Evaporation of the solvent under reduced pressure afforded 133 mg of a crude that was chromatographed on

silica gel (methylene chloride-ether as eluent) to give (+)-**1** (50 mg, 32 % yield) as a solid, m.p. 62-64° (from methylene-chloride-ether), b.p. 95°/0.06 torr, $\{\alpha\}_D^{20}$ = +11.67° (c = 1.84, chloroform).(Lit[1] m.p. 65°, $\{\alpha\}_D$ = +5.2). ^{1}H NMR ($CDCl_3$) 2.11 (m, 3H); 2.37 (broad signal, 1H); 3.75 (dd, J = 12.5 Hz, J' = 4.4 Hz, 1H); 4.08 (dd, J = 12.5, J' = 3.1 Hz, 1H); 4.91 (m, 1H); 5.87 (m, 1H); ^{13}C NMR ($CDCl_3$) 13.7, 60.8, 85.4, 117.6, 166.8, 173.6; IR ($CHCl_3$) 3610, 3570-3180 (broad), 3020, 2950, 1760, 1650, 1440, 1385, 1310, 1180, 1150, 1100, 1045, 935 cm^{-1}; MS, m/e 129 (M+1, 40), 111 (8), 98 (84), 97 (28), 83 (8), 69 (36), 43 (14), 42 (30), 41 (100), 40 (17).

(-)-(S)-Umbelactone, (-)-1.

In a similar manner as described above, (-)-**1** was prepared from (-)-**4** in 33 % yield; $\{\alpha\}_D^{20}$ = -11.86° (c = 1.57, chloroform).

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