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STUDIES ON STRUCTURALLY SIMPLE α,β-BUTENOLIDES. III. BEHAVIOUR OF (-)-(S)-δ-HETEROSUBSTITUTED γ-METHYL-α,β-BUTENOLIDES TOWARDS NUCLEOPHILES. PROTOANEMONIN AS INTERMEDIATE IN AN ELIMINATION-ADDITION MECHANISM.

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Abstract.- The reactivity of the title compounds with different nucleophiles has been checked and it was shown that products from reaction with sodium phenylthiolate result from an elimination-addition process in which protoanemonin is the key intermediate. The synthesis of (-)-(R)-β-angelica lactone is reported for the first time.

In part II of this series[1], we have recently reported the synthesis of optically active γ-methyl-α,β-butenolides possesing good leaving groups as substituents at the δ-position, namely (-)-(S)-5-p-toluenesulfonyloxymethyloxol-3-en-2-one, 1, (-)-(S)-5-methanesulfonyloxymethyloxol-3-en-2-one, 2, and (-)-(S)-5-iodomethyloxol-3-en-2-one, 3. Attempts to prepare ether derivatives by S_N2 reactions on these substrates were fruitless due to the competitiveness of the other functional groups present in the molecule, mainly the allylic proton. We have studied now the reactivity of these compounds with several weakly basic nucleophiles, allowing us to propose a unified mechanism.

Reaction of tosylate 1 and iodide 3 with cyanide ion did not give the desired nitrile. Instead, protoanemonin 4 was the only product detected when the reaction was done in heterophase (CH_2Cl_2/CN^-) or under phase transfer conditions. On the other hand, reaction of 3 with KCN in methanol gave methyl 2-methoxy-4-pentanoate, 5, as the only isolated product, formed in very low yield.

Attempts to prepare δ-nitrogen derivatives of γ-methyl-α,β-butenolides by reaction of mesylate 2 and iodide 3 with very weakly basic nitrogen anions like pyrrolide, azide or phthalimide, yielded only protoanemonin 4 as the main crude component.

Reactions of the very strong nucleophile and weakly basic phenylthiolate anion with the mentioned substrates (1, 2 and 3) as well as the new (-)-(S)-5-bromomethyloxol-3-en-2-one, 6, have been studied and the results are given on Table 1. With this nucleophile we have found good yields of reaction products: (±)-5-phenylthiomethyloxol-3-en-2-one, (±)-7, 5-phenylthiomethyloxol-4-en-2-one, 8, and (±)-3-phenylthio-5-phenylthiomethyloxolan-2-one, (±)-9, together with 20 % of unaltered, optically pure, starting material. The presence of this last product is explained not only by the use of a 5 % defect of PhS^- but also by the oxidative dimerization of PhS^- to diphenyl disulfide (15 %) during the reaction. In fact, operating with 1 eq. of PhS^- under argon, the starting material was not recovered and some Michael adduct (±)-9 was now obtained. However, the recovery of unchanged 1, 2, 3 or 6 gave us the clue for the proposed mechanism.

We believe that abstraction of the allylic proton by basic or weakly basic nucleophiles is the fastest performed reaction on the title substrates, (only halides react giving the expected substitution products), followed by rapid Y^- elimination when Y is a good leaving group, giving protoanemonin 4. Once this product is formed, only very soft nucleophiles (e.g. PhS^-) can give 1,6-conjugate addition product (8), while other nucleophiles cannot; in this last case, 4 either reacts giving open-chain compounds (e.g. 5) or, as is well known, dimerizes and polymerizes[2].

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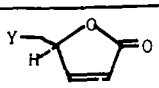
Table 1

Experiment[a]	Substrate	eq. PhS^-	Reaction time	% yield[b]	Molar ratio [c]			
					Starting material	(±)-7	8	(±)-9
(1)	Y=Br, 6	0.95	14 h	55	1.6	1.0	3.8	0
(2)	Y=I, 3	0.95	14 h	62	0.3	1.0	0.5	0
(3)	Y=TsO, 1	0.95	14 h	69	1.0	1.0	2.0	0
(4)	1	0.95	1 h	67	1.2	1.0	1.4	0
(5)	1	0.95	10 min	60	0.6	1.0	0.9	0
(6)	1	1	10 min	63	0	1.0	0	0.3
(7)	Y=Mso, 2	0.95	14 h	46	---	1.0	0.1	0.2
(8)[d]	4	catal.	10 min	64	0	1.0	0	4.0
(9)[d]	4	catal.	2.2 h	64	0	1.0	0	4.0
(10)[d]	4	------	10 min	--	recov.	0	0	0

(a) Only the experiment (6) was performed under argon atmosphere.

(b) Calculated from the equivalents of added PhS^-, except in experiments (8)-(10) where it was calculated from PhSH.

(c) Calculated on the basis of isolated products (column chromatography), except in experiments (4), (9) and (10), where it was calculated from the PMR spectrum of the crude reaction mixture.

(d) In the presence of 1 eq. of PhSH.

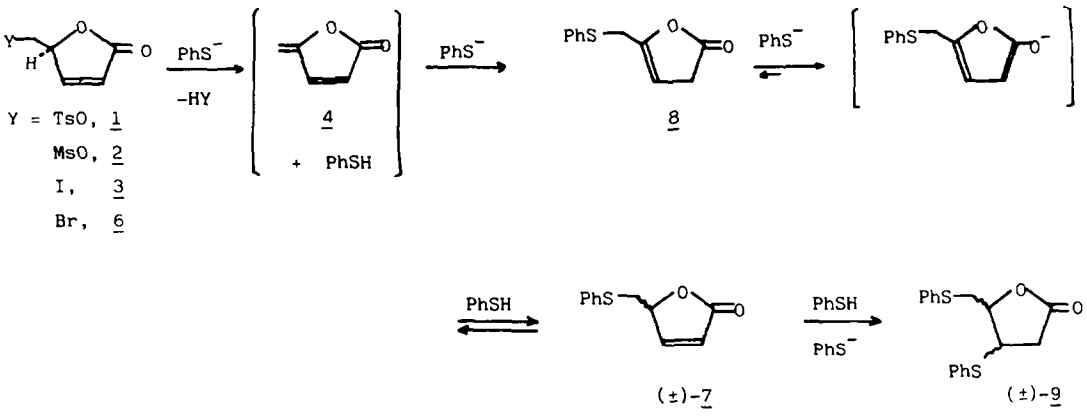
In agreement with the rôle of protoanemonin as intermediate, 4 (prepared independently[3]) was made to react with 1 eq. of PhSH and a catalytic amount of PhS^- in the conditions shown in Table 1, giving a 64 % yield of a mixture of (±)-7 and (±)-9 in a 1:4 ratio. To our knowledge this is the first reported 1,6-addition to protoanemonin, although similar 1,6-additions have been recently reported with other γ-iliden-α, β-butenolides[5].

The ratio between conjugated, (±)-7, and deconjugated, 8, butenolides depends upon the concentration of the pair PhS^-/PhSH in the reaction conditions. In fact, (±)-7 is the thermodynamically more stable and is quantitatively obtained from 8 by treatment with catalytic PhS^- or when 8 is allowed to stand in a silica gel column for several hours. Moreover, reaction of 8 with p-TsOH results in ring opening of the enol lactone. However, both silica gel and p-TsOH let optically active 7 unaltered and treatment with catalytic PhS^- showed instantaneous racemization (reaction carried out in a polarimeter cell) but neither double bond deconjugation nor elimination (PMR control) were detected, due to the poor nucleofugacity of the phenylthio group.

The Michael adduct (±)-9 results unambigously -as has been indepently verified- from base catalyzed addition of PhSH over (±)-7. The amount of (±)-9 in the reaction mixture is also sensitive to the concentration of the pair PhS^-/PhSH. (Scheme 1 summarizes the proposed mechanism).

The base catalyzed isomerization of β,γ-butenolides to the corresponding conjugated systems, had earlier been reported for 5-methyl and 5-tert-butyloxol-4-en-2-one [4], and a trident anion was postulated as intermediate. In our case, PMR provided evidence of a hydroxyfuran anion (δ 6.5 and 6.7, AB system, J_{AB} = 6.6 Hz), when the spectrum of a solution of a mixture of (±)-7 and 8 in DMSO-d_6 containing 1 eq. t-BuONa, was recorded. In fact, such an anion can be the intermediate in the conjugation of 8 to (±)-7 in basic media. Nevertheless, the sulfur derivatives (±)-7 and 8 are completely stable in neutral conditions (polarimetry and PMR control).

We have synthesized, as far as we know,



Scheme 1

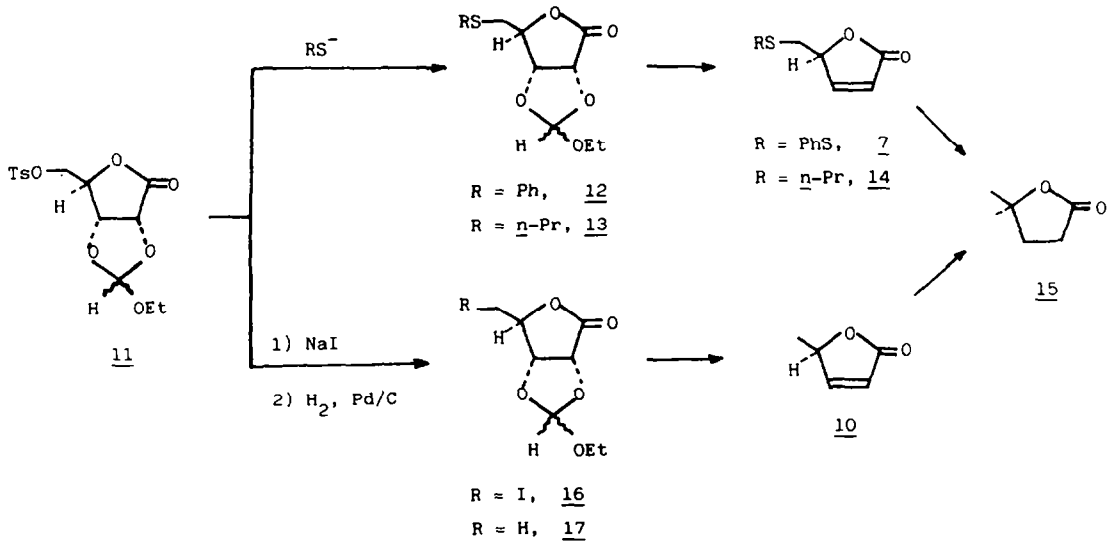
for the first time, (-)-(R)-5-methyloxol-3-en-2-one, 10, (optically active β-angelica lactone),(by pyrolysis of 2,3-O-ethoxymethylene-5-deoxy-γ-D-ribonolactone, 17) and it does not racemize in neutral conditions.

Therefore, we can conclude that a tautomeric equilibrium for these systems does not exist in neutral media.

The alternative synthetic route to prepare optically active δ-sulfur derivatives of γ-methyl-α,β-butenolides consisted in the substitution of the tosylate group in 11 (Scheme 2) prior to the creation of the C-C double bond by pyrolysis of the orthoester, method described by us in part II[1]. Thus, (-)-(S)-5-phenylthiomethyloxol-3-en-2-one, 7 and (-)-(S)-5-n-propylthiomethyloxol-3-en-2-one, 14, have been synthesized in good yield from D-ribonolactone, through the orthoesters 5-deoxy-2,3-O-ethoxymethylene-5-phenylthio-γ-D-ribonolactone, 12, and 5-deoxy-2,3-O-ethoxymethylene-5-n-propylthio-γ-D-ribonolactone, 13, respectively.

However, reaction of 11 with pyrrolide or phthalimide anions gave unidentified products. Thus, the synthesis of δ-N-substituted γ-methyl-α,β-butenolides is still unsolved.

The enantiomeric purity of the compounds 1, 2, 3, 6, 7, 10 and 14 has been established by chemical correlation with the known (+)-(R)-5-methyloxolan-2-one, 15[6].



Scheme 2

EXPERIMENTAL PART

M. ps have been determined on a Kofler hot stage and are uncorrected. Optical rotations were obtained on a Bellingham-Stanley P-10 polarimeter. Distillation of small amounts were effected on a rotational distillator Büchi, Mod. KRV 65/30 (only external or oven temp. given). MS spectra were recorded with a Hewlett-Packard apparatus, model 5930A working at 70 eV. The IR spectra were recorded on a Perkin-Elmer Spetrophotometer, model 720. The PMR spectra were recorded on a Perkin-Elmer Spectrometer, model R-12 A; chemical shifts are given in ppm relative to TMS (δ scale).

(-)-(S)-5-bromomethyloxol-3-en-2-one, 6

A solution of 1 (250 mg, 0.92 mmol) and lithium bromide (400 mg, 4.62 mmol) in 1 ml of anh DMSO was magnetically stirred for 3 hr at 60º, then diluted with 4 ml of H_2O and extracted with ether. The combined extracts were washed with brine and dried with anh Na_2SO_4. The solvents were removed at reduced pressure and the residue chromatographed through silica gel, using CH_2Cl_2 as eluent, to give 6 (120 mg, 74 % yield) as an undistillable liquid. $[\alpha]_D^{20}$=-150º, c=2.94 in $CHCl_3$. PMR ($CDCl_3$), 3.70 (m, 2H); 5.37 (m, 1H); 6.34 (dd, J=6.0, J'=2.0; 1H); 7.67 (dd, J=6.0, J'=1.4; 1H); IR ($CHCl_3$), 3050, 1780, 1610, 1330, 1160, 1030 and 895 cm^{-1}. Found: C, 34.29; H, 2.94. $C_5H_5O_2Br$ requires: C, 33.93; H, 2.84%.

(-)-(S)-5-phenylthiomethyloxol-3-en-2-one, 7

To a stirred and ice-cooled solution of 2,3-O-ethoxymethylene-5-O-tosyl-γ-D-ribonolactone, 11; (4.01 g, 11.2 mmol) in 20 ml of anh DME, a solution of NaPhS, prepared from PhSH and NaH, (1.48 g, 11.20 mmol) in 20 ml of anh DME was added slowly and the mixture was allowed to stand at 4º for 14 hr. Filtration, washing of the solid with 30 ml of anh DME and evaporation of the solvent at reduced pressure, afforded 3.2 g of a syrup, which chromatographed through silica gel (3:2 hexane-CH_2Cl_2) yielded the diastereoisomeric 5-deoxy-2,3-O-ethoxymethylene-5-phenylthio-γ-D-ribonolactone, 12, (3.02 g, 91 % yield) as a syrup, b.p. 160º/0.2 torr. PMR ($CDCl_3$), 1.15 and 1.24 (two t, J=7.3; 3H); 3.20-3.40 (complex abs, 2H) 3.60 and 3.64 (two q, J=7.3; 2H); 4.55-5.15 (complex abs, 3H); 6.00 (s, 1H) and 7.25-7.65 (complex abs, 5H); IR (film), 3100, 3020, 2970, 1790, 1580, 1480, 1435, 1340, 1250, 1170, 1100, 1060 and 1020 cm^{-1}; MS, m/e (%) 296 (M^+, 11), 251 (47), 222 (20), 187 (15), 176 (12), 174 (17), 173 (12), 160 (9), 159 (7), 123 (100), 110 (7), 109 (19), 79 (9), 78 (20), 77 (32) and 45 (80). Found: C, 57.01; H, 5.25; S, 10.50. $C_{14}H_{16}O_5S$ requires: C, 56.74; H, 5.44; S, 10.82 %.

A 10 ml flask, containing 12 (3.02 g, 10.2 mmol) was connected to a rotary microdistillation apparatus and heated at 220º/1 atm for 2 hr. Then, the ethanol formed during the pyrolysis was eliminated in vacuo to give 1.53 g of a residue, which chromatographed through 30 g of silica gel, using hexane-ethyl acetate (9:1), afforded 1.03 g of 7 (49 % yield). B.p. 160º/14 torr; $[\alpha]_D^{20}$=-34.48º, c=0.58 in $CHCl_3$. PMR ($CDCl_3$), 3.00 (dd, J=14, J'=8; 1H); 3.45 (dd, J=14, J'=5.3; 1H); 5.14 (m, 1H); 6.11 (dd, J=6, J'=1.7; 1H); 7.14-7.65 (complex abs, 6H); IR (film), 3100, 2950, 1750, 1600, 1580, 1480, 1440, 1320, 1160, 1100, 1060 and 1020 cm^{-1}; MS, m/e (%) 206 (M^+, 7), 154 (4), 126 (7), 125 (7.5), 124 (11), 123 (100), 110 (12), 109 (28), 85 (19), 84 (16), 83 (30), 79 (16), 78 (12), 77 (22) and 45 (43). Found: C, 64.28; H, 5.02; S, 15.79. $C_{11}H_{10}O_2S$ requires: C, 64.05; H, 4.88; S, 15.54 %.

(-)-(S)-5-n-propylthiomethyloxol-3-en-2-one, 14

Diastereoisomeric 5-deoxy-2,3-O-ethoxymethylene-5-n-propylthio-γ-D-ribonolactone, 13, was prepared from 11 and Na(n-Pr)S (from n-PrSH and NaH) in 69 % yield, by the method described above. B.p. 150º/0.05 torr. PMR ($CDCl_3$), 0.80-2.00 (complex abs, 8H); 2.60 (t, J=6.7; 2H); 2.92 (d, J=4, 2H); 3.62 and 3.66 (two q, J=7.3; 2H); 4.57-5.20 (complex abs, 3H) and 6.00 (s, 1H); IR (film), 2990, 2950, 2900, 1780, 1450, 1370, 1350, 1300, 1250, 1180 and 1060 cm^{-1}; MS, m/e (%) 262 (M^+, 23), 217 (58), 189 (6), 188 (5), 187 (17), 179 (10), 177 (38), 175 (22), 147 (100), 145 (32), 144 (19), 143 (43), 129 (39), 101 (25), 89 (31) and 68 (12). Found: C, 50.62; H, 7.18; S, 11.97. $C_{11}H_{18}O_5S$ requires: C, 50.36; H, 6.91; S, 12.22 %.

In a similar way as above, pyrolysis of

13 at 245°/1 atm, followed by chromatography of the crude through 10 g of silica gel, using a mixture of CH_2Cl_2-hexane (4:1) as eluent, afforded 14 in 73 % yield. B.p. 100°/0.02 torr; $[\alpha]_D^{21}$=-87.3°, c=1.18 in $CHCl_3$. PMR ($CDCl_3$), 1.0 (t, J=7.3; 2H); 2.75-3.20 (complex abs, 2H); 5.2 (m, 1H); 6.24 (dd, J=6, J'=1.8; 1H); 7.62 (dd, J=6, J'=1.3; 1H); IR (film), 3100, 2990, 2950, 2900, 1760, 1460, 1380, 1330, 1240, 1160, 1100 and 1020 cm^{-1}; MS, m/e, (%) 172 (M^+, 12), 145 (1), 144 (1), 130 (2), 129 (2.5), 113 (2), 101 (15), 97 (5.5), 89 (100), 85 (14), 83 (17), 61 (60), 55 (34) and 43 (61). Found: C, 55.65; H, 6.91; S, 18.70. $C_8H_{12}O_2S$ requires: C, 55.78; H, 7.12; S, 18.59 %.

Reaction of (-)-(S)-5-p-toluenesulfonyloxymethyloxol-3-en-2-one, 1, with NaPhS: obtention of (±)-5-phenylthiomethyloxol-3-en-2-one, (±)-7 and 5-phenylthiomethyloxol-4-en-2-one, 8.

To a stirred and ice-cooled solution of 1 (840 mg, 3.14 mmol) in 45 ml of anh DME, a solution of NaPhS (390 mg, 2.98 mmol) in 27 ml of anh DME was added slowly. The mixture was allowed to stand at 0° for 10 min, then diluted with $CHCl_3$ and washed with water. The aqueous layer was extracted with $CHCl_3$ and the combined organic liquors dried with anh Na_2SO_4. The solvents were removed at reduced pressure to give 640 mg of a residue, which by column chromatography through silica gel, using a 9:1 mixture of hexane-ethyl acetate as eluent, afforded 148 mg of recovered starting material 1, 194 mg of (±)-7 (32 % yield) and 174 mg of 8 (28 % yield). The spectroscopic data of (±)-7 were identical to those of optically active 7. The spectroscopic data of 8 were the following: PMR ($CDCl_3$), 3.18 (m, 2H); 3.70 (m, 2H); 5.26 (m,1H); 7.16-7.59 (complex abs, 5H); IR ($CHCl_3$), 3050, 2950, 1805, 1800, 1590, 1480, 1440 and 1100 cm^{-1}.

The experiments (1), (2), (3), (4) and (7), listed on Table 1, were carried out in a similar way as described above.

(±)-3-phenylthio-5-phenylthiomethyloxolan-2-one, (±)-9.

Operating as before, but under argon atmosphere, from 1 (2.0 g, 10 mmol) and NaPhS (0.99 g, 10 mmol) in 130 ml of anh DME at 0° for 30 min, 1.40 g of a crude mixture were obtained. Column chromatography through silica gel, with hexane-ethyl acetate from 9:1 to 2:3 ratio as eluent, afforded 0.64 g of (±)-7 (41 % yield) and 0.25 g of (±)-9 (22 % yield), m.p. 75.5-76.5°. PMR ($CDCl_3$), 2.50 (dd, J=18.7, J'=6.7; 1H), 3.06 (dd, J=18.7, J'=8; 1H); 3.19 (d, J=5.3; 2H); 3.79 (m, 1H); 4.60 (q, J=5.3; 1H); 7.4 (complex abs, 10H); IR ($CHCl_3$), 3050, 1790, 1590, 1490, 1445, 1170, 1030 and 995 cm^{-1}; MS, m/e (%) 316 (M^+, 1.5), 218 (2), 207 (2), 206 (5), 147 (5.5), 134 (4), 136 (4), 135 (5), 125 (11.5), 124 (12.5), 123 (100), 115 (12.5), 110 (24), 109 (42), 101 (9), 99 (10), 97 (11), 96 (17), 91 (12), 79 (25), 77 (35), 69 (32), 65 (31), 55 (31) and 45 (46). Found: C, 64.52; H, 5.13; S, 10.13. $C_{17}H_{16}O_2S_2$ requires: C, 64.52; H, 5.09; S, 10.11 %.

Reaction of protoanemonin, 4, with PhSH

To a stirred and ice-cooled solution of 4 (125 mg, 1.3 mmol) in 18 ml of anh DME a solution of PhSH (143 mg, 1.3 mmol) and a catalytic amount of NaPhS was added. The mixture was allowed to stand at 0° for 10 min, then diluted with $CHCl_3$ and washed with H_2O. The combined organic liquors were dried with anh Na_2SO_4 and the volatile materials evaporated at reduced pressure to give 206 mg of a crude. The PMR spectrum of this crude showed a mixture of (±)-7 and (±)-9 in 1:4 ratio, as the only products.

(+)-(R)-5-methyloxolan-2-one, 15, from 3.

Powdered $NaHCO_3$ (400 mg, 4.76 mmol) and Raney-Ni W-4 (1.5 g) were added to a solution of 3 (632 mg, 2.82 mmol) in 10 ml of abs EtOH and the mixture was stirred for 2 hr, then filtered and the catalyst washed with 25 ml of abs EtOH, taking care of the solid becoming dry. The solvent was removed at reduced pressure and the residue was distilled to give 15 (178 mg, 63 % yield). B.p. 110°/18 torr; $[\alpha]_D^{21}$=+27, c=1.33 in CH_2Cl_2. (Lit[6], b.p. 105°/35 torr, $[\alpha]_D^{20}$=+30.1, c=0.85 in CH_2Cl_2). PMR ($CDCl_3$), 1.47 (d, J=6.3; 3H); 1.6-2.7 (complex abs, 4H) and 4.51 (m, 1H); IR (film), 3020, 2950, 1780, 1460, 1420, 1390, 1350, 1300, 1280, 1230, 1200, 1180, 1125, 1100, 1060, 1000 and 950 cm^{-1}. Found: C, 59.82; H, 7.87. $C_5H_8O_2$ requires: C, 59.98; H, 8.05 %.

In a similar way, the compounds 1, 2,

6, 7, 10 and 14 were correlated to 15.

(-)-(R)-5-methyloxol-3-en-2-one ((-)-(R)-β-angelica lactone), 10

The iodo derivative 16, prepared according to ref. 1, (1.26 g, 4.01 mmol) dissolved in 25 ml of ethyl acetate, was hydrogenated using 10 % Pd/C (126 mg) as catalyst, in the presence of K_2CO_3 (1.1 g, 8 mmol), at 3.4 atm and r.t. The solvent was removed at reduced pressure and the residue boiled with 50 ml of $CHCl_3$ and filtered. Evaporation of the $CHCl_3$ afforded 698 mg of crude diastereoisomeric 2,3-O-ethoxymethylene-5-deoxy- γ-D-ribonolactone, 17, which by column chromatography through silica gel, using a mixture of CH_2Cl_2-hexane (1:7) as eluent, gave pure 17 (627 mg, 83 % yield). PMR ($CDCl_3$), 1.00-1.30 (complex abs, 3H); 1.45 (d, J=7.3; 3H); 3.25-3.70 (complex abs, 2H); (4.38-4.90 (complex abs, 4H) and 5.87 (s, 1H); IR (film), 3000, 1780, 1350, 1190, 1060 and 980 cm^{-1}; MS, m/e (%) 178 (M^+, 2), 177 (10), 145 (7), 144 (23), 143 (100), 119 (5), 117 (5), 99 (32), 97 (20), 89 (9), 88 (17), 87 (23), 85 (9), 83 (9), 76 (13), 75 (100), 73 (15), 72 (7), 71 (100), 70 (100) and 69 (68).

A 10 ml flask containing 17 (587 mg, 312 mmol) was connected to a rotary microdistillation apparatus and heated at 220º/1 atm. The crude from the pyrolysis was distilled to afford 10 (226 mg, 87 % yield); b.p. 100º/14 torr; $\{\alpha\}_D^{20}$=-95.89, c=0.73 in $CHCl_3$. PMR ($CDCl_3$), 1.48 (d, J=6; 3H); 5.20 (d, J=6, 1H); 6.17 (dd, J=6, J'=2.6; 1H) and 7.57 (dd, J=6, J'=1.3; 1H); IR (film), 3025, 3000, 1780, 1350, 1190, 1070 and 980 cm^{-1}.

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