Tetrahedron Vol. 38, No. 15, pp. 2395 to 2402, 1982
Printed in Great Britain.

0040-4020/82/152395-08$03.00/0

STUDIES ON STRUCTURALLY SIMPLE α,β-BUTENOLIDES—II

(−)-(*S*)-γ-HYDROXYMETHYL-α,β-BUTENOLIDE AND DERIVATIVES FROM D-RIBONOLACTONE EFFICIENT SYNTHESIS OF (−)-RANUNCULIN

P. CAMPS,† J. CARDELLACH, J. FONT*, R. M. ORTUÑO and O. PONSATI
Departamento de Química Orgánica, Universidad Autónoma de Barcelona, Bellaterra, Spain

(*Received in U.K. 4 January 1982*).

Abstract—A short synthesis of the title compound, **16**, from D-ribonolactone is described. Two alternative approaches differing in the timing of the C=C double bond creation are used to prepare some chiral derivatives of **16**. (−)-Ranunculin, a glycoside present in *Ranunculaceae*, has been synthesized for the first time.

In part I of this series[1] we presented exhaustive and good synthetic methods to prepare racemic δ-heterosubstituted γ-methyl-α,β-butenolides. However, in order to use these substances as synthons for more complex natural molecules, an easy entry to their chiral forms was needed.

We have recently published[2] as a preliminary communication, a short and high yielding synthesis of (−)-(*S*)-γ-hydroxymethyl-α,β-butenolide, **16**, and some derivatives such as (−)-(*S*)-γ-benzyloxymethyl-α,β-butenolide, **15**, and (−)-(*S*)-γ-trityloxymethyl-α,β-butenolide, **18**, from D-ribonolactone, **1**. Compounds **15** and **18** were prepared by Koga *et al.*[3,4] in moderate yields by a six-step sequence starting from L-glutamic acid and used for the asymmetric total synthesis of the antileukaemic lignans (+)-*trans*-burseran,[4] (−)-isostegane[4] and (+)-steganacin.[5] The great potential of **16**, the synthesis of which is reported here in its complete form for the first time, and its O-derivatives for the synthesis of chiral compounds, and a renewed interest in the field of α,β-butenolides,[6] led us to study the various possibilities of converting D-ribonolactone into **16** and its O-derivatives. As a result, the first synthesis of (−)-ranunculin, a glucoside present in many plants of the family *Ranunculaceae*, has been achieved.

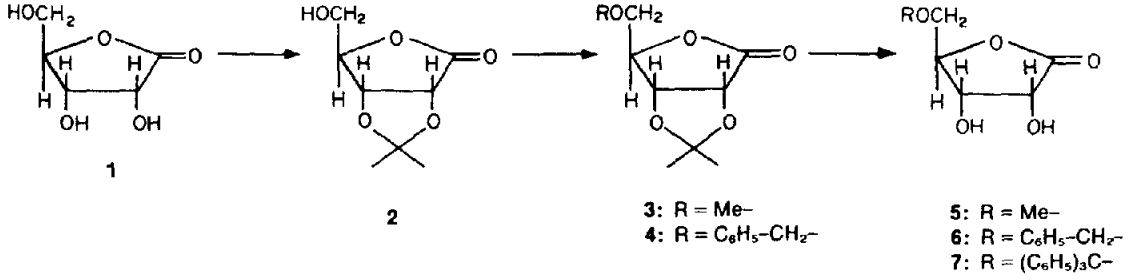
The comparison of the structure of D-ribonolactone and **16** or its O-derivatives, shows that two transformations have to be carried out: (a) alkylation of the hydroxyl at C_5, that might need protection of the secondary hydroxyl functions, and (b) introduction of a carbon–carbon double bond at C_2–C_3, by elimination of the hydroxyls at these carbon atoms. The order of these transformations can be interchanged.

Our first approach followed the sequence (a)+(b), therefore we prepared (+)-5-O-methyl-D-ribonolactone,[7] **5**, and (+)-5-O-benzyl-D-ribonolactone, **6**, by the sequence depicted in Scheme 1. The preparation of (+)-5-O-trityl-D-ribonolactone, **7**, was carried out, however, by direct tritylation of **1**.

The elimination of the *cis*-diol function at C_2–C_3 in order to introduce the C=C double bond was firstly tried on compound **5**. There are many methods to carry out this kind of transformation. Among them, we choosed the Corey–Winter method.[8] The reaction of **5** with thiocarbonyldiimidazole gave the corresponding 5-O-methyl-2,3-O-thiocarbonyl-D-ribonolactone, **8**, in 67% yield. However, the reaction of **8** with trimethyl phosphite did not yield the expected (*S*)-γ-methoxymethyl-α,β-butenolide, **9**. Also, the Hanessian method[9] did not give satisfactory results. Reaction of **5** with *N,N*-dimethylformamide dimethyl acetal followed by reaction with methyl iodide and pyrolysis gave a complex mixture that contained no more than 8% of **9** (NMR). Finally, the reaction of **5** with triethyl orthoformate gave quantitatively 2,3-O-ethoxymethylene-5-O-methyl-D-ribonolactone, **11**, as a mixture of two stereoisomers, that on heating at 176° for 14 h in the absence of solvent and catalyst gave **9** in 66.5% yield.

In the same way, **6** was converted into (−)-(*S*)-γ-benzyloxymethyl-α,β-butenolide, **15**, in 66% overall yield. In this case the pyrolysis was carried out by heating a solution of the stereoisomeric mixture of cyclic orthoformates **12** in diglyet for 7 h at 200° in the presence of a trace of AcOH as catalyst. By heating **12** at different

†Present address: Departamento de Química Orgánica, Facultad de Química de San Sebastián, Universidad de País Vasco, Alza, San Sebastián, Spain.



Scheme 1.

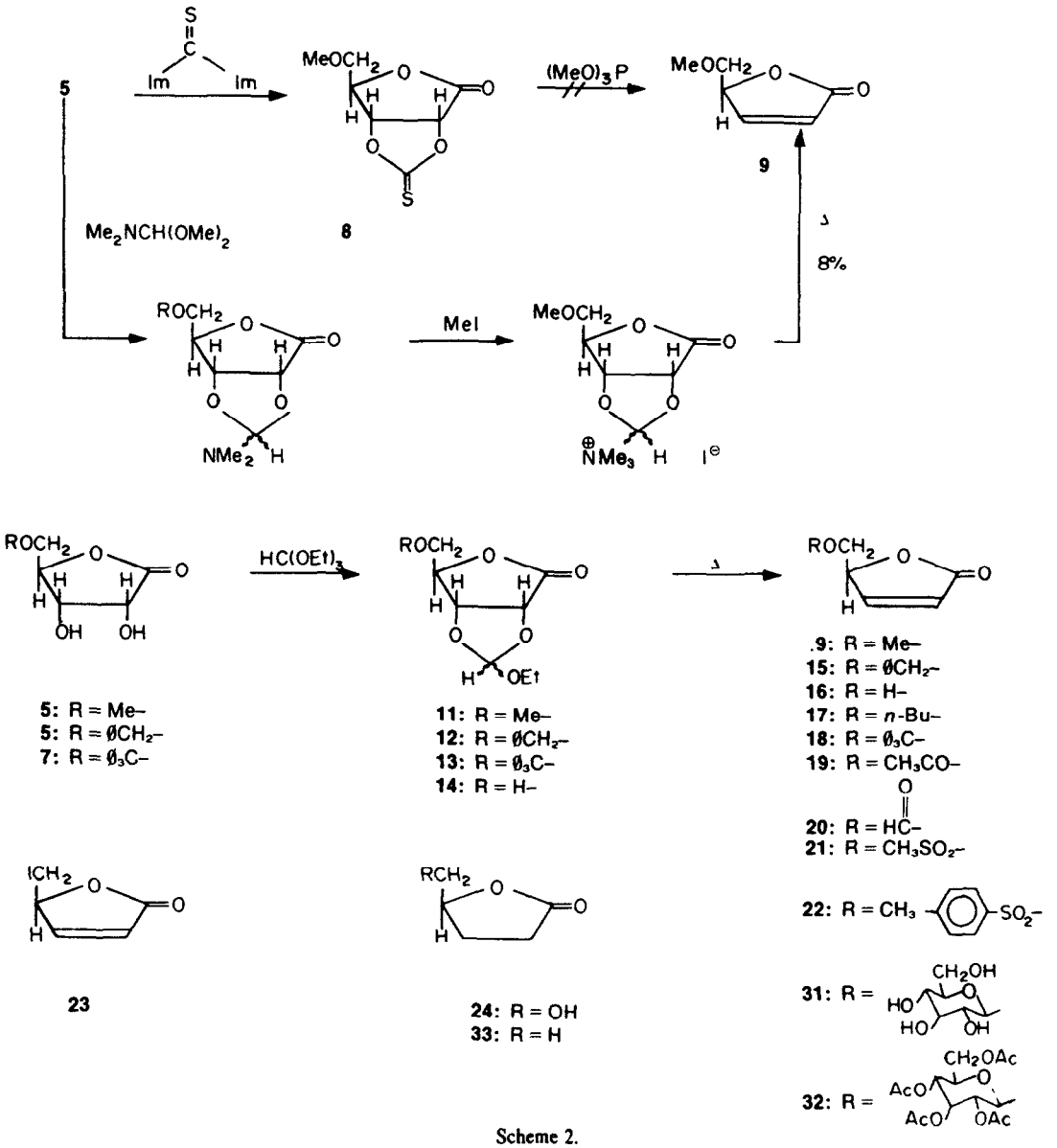
temperatures in the absence of solvent and catalyst, no defined products were obtained.

The reaction of the trityl derivative **7** with triethyl orthoformate without catalyst gave the mixture of the corresponding cyclic othoformates **13**, but all attempts to pyrolize **13** were fruitless, probably because of the instability of the trityl ether towards the pyrolysis conditions. Thus, this approach is limited to the preparation of O-derivatives of the butenolide **16** that are stable under the pyrolytic conditions.

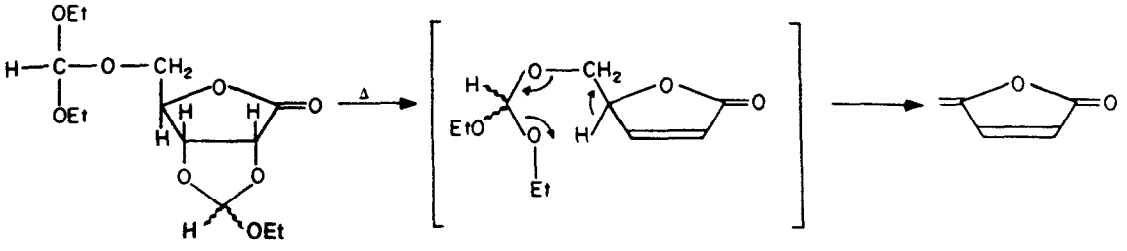
In order to develop a more general method we tried to prepare **16**, following the sequence (b) + (a), from which O-derivatives might easily be prepared. After much experimentation, **16** could be obtained from **1** in 68% yield by reaction with 1.0 equiv. of triethyl orthoformate in the absence of acid catalyst, followed by pyrolysis of the stereoisomeric mixture of cyclic orthoformates, **14**, in a rotary microdistillation apparatus in such conditions that the butenolide **16** was distilled as it was formed. The yield of this pyrolysis decreased in large scale operations probably due to decomposition of the reaction product before distillation. Probably, for the same reason, pyrolysis of **14** in the presence of AcOH as catalyst did not give **16**.

When **1** was treated with two or more equiv. of triethyl orthoformate the hydroxyl at C_5 was also orthoesterified and pyrolysis of this crude mixture, **25**, did not give the desired product, and protoanemonin, **26** was detected. Probably, after the formation of the C=C double bond, an elimination reaction such as that depicted in Scheme 3 might take place.

Compound **16** obtained by the above described method has the same specific rotation as that obtained by acid hydrolysis of natural (−)-ranunculin, **31**, from which it is the aglycone. Therefore, no epimerization at C_γ takes place during the pyrolysis. Moreover, hydrogenation of **16** over 10% Pd/C at atmospheric pressure gave (+)-(*S*)-γ-hydroxymethylbutanolide, **24**, whose specific rotation agrees with that described by Koga[3] for this product, prepared from L-glutamic acid.



Scheme 2.



25 26

Scheme 3.

Etherification of the hydroxyl function of **16** should be carried out avoiding the use of strong bases. Reaction of **16** with methyl iodide, benzyl bromide or *n*-butyl iodide and silver oxide gave the corresponding ethers in moderate to good yields depending on the reactivity of the alkyl halide. Similarly, reaction of **16** with trityl chloride in pyridine gave **18** in 65% yield.

Benzyl derivative **15** had the same specific rotation as that obtained from 5-O-benzyl-D-ribonolactone. Moreover, the specific rotations of **15** and **18** prepared by our method agree with those described by Koga[4] for the same compounds prepared from L-glutamic acid.

Acyl derivatives of **16** were also easily prepared. Thus, reaction of **16** with Ac_2O gave (−)-(*S*)-γ-acetoxymethyl-α,β-butenolide, **19**, in 79% yield, and reaction with ethyl formate under acid catalysis gave (−)-(*S*)-γ-formyloxymethyl-α,β-butenolide, **20**, in 74% yield. This compound was identical to a by-product isolated in low yield from a 16 g scale preparation of **16**.

The two procedures so far described to transform D-ribonolactone into O-derivatives of **16** have the common feature that the CH_2–O bond is not broken. In order to study the possibility of preparing ethers of **16** in which the original CH_2–O bond had to be broken, **16** was treated with methanesulfonyl chloride to give (−)-(*S*)-γ-methanesulfonyloxymethyl-α,β-butenolide, **21**, in 79% yield as an unstable liquid that should be used immediately. Its reaction with sodium *n*-butoxide did not give the substitution product **17**, as expected. In contrast, reaction of **16** with *p*-toluenesulfonyl chloride gave the corresponding (−)-(*S*)-γ-*p*-toluenesulfonyloxymethyl-α,β-butenolide, **22**, as a stable solid in 71% yield. The reaction of **22** with sodium iodide in acetone gave (−)-(*S*)-γ-iodomethyl-α,β-butenolide, **23**, in 63% yield, as an unstable liquid that could not be distilled but could be chromatographed through silica gel. Several attempts to obtain **17** by reaction of **23** with *n*-butanol and Ag_2O failed. Reduction of the iododerivative **23** with Ni–Ra afforded (+)-(*R*)-γ-methylbutyrolactone which showed the described optical specific rotation,[10] therefore no epimerization at C_γ occurred during the tosylate displacement.

Substitution reactions on compounds **21**, **22** and **23** must be difficult because of the acidity of the hydrogen at C_γ which makes elimination very favorable, particularly when the nucleophiles to be used are hard bases. In order to circumvent this problem we developed the alternative sequence depicted in Scheme 4.

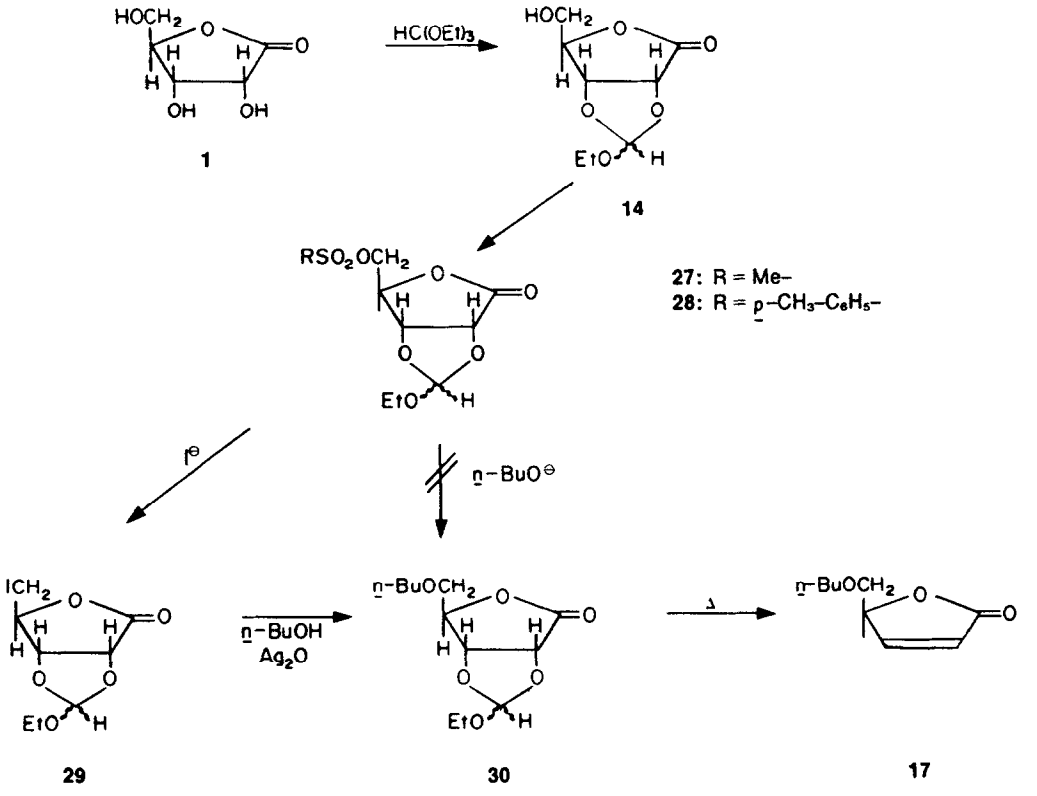
The salient features of this sequence are: (i) The use of the cyclic orthoformates as a protecting group and as precursor of the C=C double bond; (ii) the low acidity of the C_4 proton in the substrates in which the substitution reactions are made, and (iii) the possibility of obtaining by this procedure a wide variety of chiral δ-heterosubstituted γ-methyl-α,β-butenolides.

The reaction of the diasteroisomeric mixture **14** with methanesulfonyl chloride gave quantitatively a crude product whose NMR spectrum agreed with that expected for **27** and was used without further purification. In a similar way, **28** was prepared and could be purified by silica gel column chromatography to give a solid. Reaction of **27** with sodium *n*-butoxide did not give the desired substitution product, but both **27** and **28** were converted in high yield into the iodide **29** by reaction with sodium iodide in acetone and reaction of **29** with *n*-butanol and Ag_2O gave a crude product whose NMR spectrum showed it to be essentially the substitution product **30**. Pyrolysis of this crude material gave the butoxy derivative **17** in 27% yield of purified product from **29**.

Therefore, the more general method of preparing O-derivatives of (−)-(*S*)-γ-hydroxymethyl-α,β-butenolide, **16**, from D-ribonolactone implies, first, the formation of the C=C double bond and then alkylation of the hydroxyl function under non basic conditions. Less general is the alkylation of the protected D-ribonolactone followed by the introduction of the C=C double bond. However, the preparation of γ-methylsubstituted-α,β-butenolides that implies breaking of the CH_2–O bond, should be carried out in such a way that the C=C double bond is generated in the last step of the sequence. We are now investigating by this way the obtention of a variety of γ-heterosubstituted (sulfur, nitrogen...) derivatives.

Finally, we have used the more general method to the synthesis of (−)-ranunculin, **31**, the precursor of the vesicant substance (protoanemonin, **26**) formed when tissues of several *Ranunculaceae* are crushed. Hill and van Heyningen[11] isolated for the first time this compound and proposed it to be the β-glucoside of γ-hydroxymethyl-α,β-butenolide. Independently, Benn and Yelland[12] and Boll[13] determined the configuration of the aglycone to be *S*. However, to the best of our knowledge, **31** had not yet been synthesized.

Reaction of **16** with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide[14] and Ag_2O in anydrous, ethanol-free $HCCl_3$ gave ranunculin tetraacetate, **32**, in 88.4% yield, identical with that obtained by acetylation of natural **31**.[11] Acid hydrolysis of **32** gave **31** in 95% yield, identical (IR, 200 MHz PMR, 50 MHz ^{13}C NMR spectra, m.p. and specific rotation) with an authentic sample. Noteworthy are the stability of the acetal function of **31** towards the acid hydrolysis and its instability towards bases. The knowledge of the chemical behaviour of natural **31**[15] was of great importance in choosing the appropriate protection for the hydroxyl functions of the glucosylating agent. The chemical shift for the anomeric carbon atom



1 14 29 30 17

Scheme 4.

(103.4 ppm from TMS) confirms the assigned β-configuration[16] of the glucoside.

EXPERIMENTAL

M.ps have been determined on a Kofler hot-stage and are uncorrected. Optical rotations were obtained on a Bellingheam-Stanley P-10 polarimeter. Distillation of small amounts were effected on a rotational distillator Buchi, Mod. KRV 65/30 (only external or oven temp. given). MS spectra were recorded with a Hewlett-Packard apparatus, model 5930 A, working at 70 ev. The IR spectra were recorded on a Perkin-Elmer Spectrophotometer, model 720. All the PMR spectra were recorded on a Perkin-Elmer Spectrometer, model R-12 A, and only in a few stated cases a Varian Spectrometer, model XL-200 was used to register 200 MHz PMR and 50 MHz ^{13}C NMR spectra. Chemical shifts are given in ppm relative to TMS (δ scale).

5-O-*Methyl*-2,3-O-*thiocarbonyl*-D-*ribonolactone*, 8

A mixture of 5 (2.02 g, 12.4 mmole), thiocarbonyldiimidazole (2.22 g, 12.4 mmole) and 25 ml anh. toluene was heated to reflux for 30 min under N_2 atmosphere. The solvent was removed at reduced pressure and the residue was filtered through 20 g silica gel, eluting with ether, to give 1.7 g of 8 as a syrup (8.3 mmole, 67% yield). IR ($CHCl_3$), 1800 cm^{-1}; MS, *m/e* (%) 204 (M^+), 189 (3), 173 (10), 172 (19), 159 (100), 95 (30), 67 (10) and 45 (60); PMR ($CDCl_3$), 3.32 (s, 3H), 3.71 (d, J = 3, 2H) and 4.20–5.00 (complex abs, 3H).

Reaction of 8 *with trimethyl phosphite*

A mixture of 8 (0.5 g, 2.4 mmole) and 25 ml trimethyl phosphite was boiled under reflux for 70 h under Ar atmosphere. The volatile products were removed at reduced pressure and the residue was chromatographed through silica gel. No defined product was isolated.

2,3-O-*Dimethylaminomethylene*-5-O-*methyl*-D-*ribonolactone*, 10

A mixture of 5 (1.3 g, 8.02 mmole), *N,N*-dimethylformamide dimethyl acetal (954 mg, 8.02 mmole) and 25 ml anh. CH_2Cl_2 was stirred for 1 h at r.t. under N_2 atmosphere. The solvent was removed at reduced pressure to give essentially pure 10 quantitatively. PMR ($CDCl_3$), 2.30 and 2.34 (two s, 6H), 3.34 (s, 3H), 3.62 (d, J = 2.3, 2H), 4.54–5.93 (complex abs, 3H) and 5.94 (s, 1H).

(−)-(*S*)-5-O-*Methoxymethyloxol*-3-*en*-2-*one*, 9, *from* 10

A solution of 10 (1.74 g, 8.02 mmole) in 20 ml anh toluene and 20 g methyl iodide was heated under reflux for 2 h. During this time a white precipitated appeared. Excess methyl iodide was removed by distillation and the mixture heated under reflux for an additional 4 h (CO_2 evolution was observed). Toluene was removed at reduced pressure and the residue was chromatographed through 25 g of silica gel using mixtures CH_2Cl_2–hexane as eluent, affording 82 mg of 9 (0.64 mmole, 8% yield) and 900 mg of a complex mixture that by acid hydrolysis gave 5 (543 mg). Physical and spectroscopic characteristics of 9 are described later.

2,3-O-*Ethoxymethylene*-5-O-*methyl*-D-*ribonolactone*, 11

A mixture of 5 (1.11 g, 6.86 mmole), 15 ml of triethyl orthoformate and a drop of satd. methanolic HCl was stirred for 24 h at r.t. The reaction mixture was neutralized with solid K_2CO_3 and filtered. Evaporation of the volatile products at reduced pressure gave 1.43 g of 11 (6.55 mmole, 95.3% yield), as a mixture of two stereoisomers, m.p. 63–70°. IR ($CHCl_3$), 1785 cm^{-1}; MS, *m/e* (%) 219 ($M^+ + 1$), 218 (M^+), 203 (1), 187 (4), 173 (20), 85 (30), 61 (20), 57 (100), 47 (30) and 43 (55); PMR ($CDCl_3$), 1.15 and 1.20 (two t, J = 7, 3H), 3.32 (s, 3H), 3.54 and 3.60 (two q, J = 7, 2H), 3.64 (m, 2H), 4.72 (complex abs, 3H) and 5.92 (s, 1H). Found: C, 49.39; H, 6.27. $C_9H_{14}O_6$ requires: C, 49.54; H, 6.47%.

(−)-(*S*)-5-*Methoxymethyloxol*-3-*en*-2-*one*, 9

In a 5 ml flask fitted with a reflux condenser, 1.33 g (6.08 mmole) of 11 was placed and the flask was immersed in an oil bath at 176° for 14 h. Then the flask was connected to a rotary

microdistillation apparatus and the product distilled to give 0.54 g of **9** (4.26 mmole, 70% yield) as a liquid b.p. 140°/14 torr, $\{\alpha\}_D^{20} = -91.3$, c = 5.42 in CCl_4. IR ($CHCl_3$), 3040, 1760 and 1600 cm^{-1}; MS *m/e* (%), 129 ($M^+ + 1$), 128 (M^+), 98 (8), 83 (11), 55 (33), 45 (100) and 39 (38); PMR ($CDCl_3$), 3.39 (s, 3H), 3.65 (d, $J = 5.3$, 2H), 5.16 (m, 1H), 6.18 (dd, $J = 6$, $J' = 2$; 1H), 7.53 (dd, $J = 6$, $J' = 1.3$; 1H). Found: C, 56.39; H, 6.24. $C_7H_8O_3$ requires: C, 56.30; H, 6.30%.

(+)-5-O-*Benzyl*-D-*ribonolactone*, **6**

In a 100 ml light-protected flask, a mixture of 2,3-O-isopropylidene-D-ribonolactone, **2**, (10 g, 53.2 mmole) in 40 ml anh. DMF, benzyl bromide (13 ml, 18.8 g, 100 mmole) and Ag_2O (9.76 g, 42 mmole), was introduced. The flask was stoppered and the mixture magnetically stirred for 48 h at r.t., then filtered and the precipitate washed with 200 ml $CHCl_3$. The combined filtrate and washing $CHCl_3$ solns were cooled in a refrigerator and the precipitated AgBr filtered off. To this filtrate, 20 ml of pyridine was added and the mixture was succesively washed with water, aq 10% HCl and water. After drying the soln over anh. Na_2SO_4, the solvents were removed at reduced pressure to give **4** contaminated with dibenzylether. This residue was boiled under reflux with 150 ml of a mixture of dioxane–aq 10% HCl (6:4) for 90 min. The dioxane was distilled at reduced pressure and the aqueous soln was extracted with $CHCl_3$ (2 × 100 ml). The chloroform extracts were washed with aq $NaHCO_3$ and water. After drying with anh. Na_2SO_4 the solvent was removed at reduced pressure to give a solid. Crystallization from ether–hexane afforded 9.74 g of **6** (40.9 mmole, 76.8% yield), m.p. 105–6°, $\{\alpha\}_D^{20} = +17.5$, c = 7 in $CHCl_3$. IR ($CHCl_3$), 3600, 3050 and 1780 cm^{-1}; MS, *m/e* (%) 239 ($M^+ + 1$), 238 (M^+), 107 (38), 92 (27), 91 (100) and 65 (25); PMR (DMSO-d_6), 3.67 (d, $J = 3.6$, 2H), 4.02–4.58 (complex abs, 3H), 4.49 (s, 2H), 5.38 (d, $J = 3.6$, 1H), 5.75 (d, $J = 7.3$, 1H) and 7.32 (s, 5H). Found: C, 60.48; H, 5.80. $C_{12}H_{14}O_4$ requires: C, 60.56; H, 5.93%.

(−)-5-O-*Benzyl*-2,3-O-*isopropylidene*-D-*ribonolactone*, **4**

A sample of pure **4** was obtained by reaction of **6** (300 mg) with 5 ml of 2,2-dimethoxypropane and a trace of *p*-toluenesulfonic acid, 24 h at r.t. The solution was neutralized with solid K_2CO_3, filtered and the volatile products removed at reduced pressure to give quantitatively **4** as a syrup, pure by tlc $\{\alpha\}_D^{20} = -50$, c = 0.8 in $CHCl_3$. IR ($CHCl_3$), 1790 cm^{-1}; MS, *m/e* (%) 279 ($M^+ + 1$), 278 (M^+), 263 (2.5), 92 (12), 91 (100), 85 (18), 79 (6), 77 (6), 70 (10), 65 (15) and 59 (20); PMR ($CDCl_3$), 1.37 (s, 3H), 1.47 (s, 3H), 3.69 (d, $J = 2.4$, 2H), 4.51 (s, 2H), 4.52–4.85 (complex abs, 3H), 7.28 (s, 5H). Found: C, 64.67; H, 6.42. $C_{15}H_{18}O_4$ requires: C, 64.81; H, 6.53%.

(−)-(*S*)-5-O-*Benzyloxymethyloxol*-3-*en*-2-*one*, **15**

A mixture of **6** (4.2 mmole), 20 ml of triethyl orthoformate and a drop of satd methanolic HCl was stirred for 24 h at r.t. After neutralizing with solid K_2CO_3, the mixture was filtered and the volatile products removed at reduced pressure to give 1.29 g (quantitative yield) of a syrup, mixture of two stereoisomers of 5-O-benzyl-2,3-O-ethoxymethylene-D-ribonolactone, **12**. IR ($CHCl_3$), 1790 cm^{-1}; MS, *m/e* (%) 295 ($M^+ + 1$), 294 (M^+), 249 (12), 235 (18), 107 (12), 91 (100), 79 (7), 77 (8) and 57 (42); PMR ($CDCl_3$), 1.17 and 1.22 (two t, $J = 6.9$, 2H), 3.62 (two q, $J = 6.9$, 2H), 3.68 (d, $J = 2$, 2H), 4.5 (s, 2H), 4.7–4.9 (complex abs, 3H), 5.91 (s, 1H) and 7.28 (s, 5H).

A solution of **12** (500 mg, 2.1 mmole) in 10 ml anh. diethyleneglycol diethyl ether and a trace of glacial acetic acid was heated in a sealed pyrex tube at 200° for 7 h. After cooling, the tube was open, the solvent was removed at reduced pressure and the residue distilled in a rotary microdistillation apparatus to give 282 mg of liquid **15** (1.38 mmole, 65.7% yield), b.p. 140°/0.03 torr, $\{\alpha\}_D^{20} = -10.7$, c = 1.6 in EtOH (lit.[4] $\{\alpha\}_D^{20} = -10.7$ in EtOH); IR (film), 3120, 3050, 1750 and 1600 cm^{-1}; MS, *m/e* (%) 205 ($M^+ + 1$), 204 (M^+), 107 (44), 91 (100), 85 (30), 79 (12), 77 (23) and 55 (10); PMR (CCl_4), 3.60 (dd, $J = 5.3$, $J' = 2.4$; 2H), 4.50 (s, 2H), 5.00 (m, 1H), 6.03 (dd, $J = 5.7$, $J' = 2$; 1H), 7.25 (s, 5H), 7.43 (dd, $J = 5.7$, $J' = 1.6$; 1H). Found: C, 70.72; H, 5.91. $C_{12}H_{12}O_2$ requires: C, 70.65; H, 5.93%.

(+)-5-O-*Trityl*-D-*ribonolactone*, **7**

5 g of D-ribonolactone (33.7 mmole) and 9.7 g of trityl chloride (33.7 mmole) were dissolved in 40 ml anh. pyridine. The solution was magnetically stirred for 1 h and kept for 2 days at r.t., then filtered and the pyridinium chloride washed with 7 ml of pyridine. The solvent was removed at reduced pressure, the residue dissolved in CH_2Cl_2 and the insoluble part filtered off. Addition of hexane afforded a white precipitate, that recrystallized from benzene–hexane yielded 8.02 g of **7** (20.5 mmole, 61% yield), m.p. 170–172°, $\{\alpha\}_D^{20} = +50$, c = 3.8 in CH_2Cl_2. IR ($CHCl_3$), 1785 cm^{-1}; MS, *m/e* (%) 390 (M^+) (5), 243 (39), 184 (29), 165 (92), 105 (100), 77 (48), 73 (22), 60 (20) and 43 (18); PMR (DMSO-d_6), 3.00–4.50 (complex abs, 5H), 4.80 (s, 2H), 7.22 (s, 15H). Found: C, 73.90; H, 5.76. $C_{24}H_{22}O_5$ requires: C, 73.83; H, 5.68%.

2,3-O-*Ethoxymethylene*-5-O-*trityl*-D-*ribonolactone*, **13**

A solution of **7** (1.16 g, 3 mmole) in 18 ml of triethyl orthoformate was magnetically stirred at 60–70° overnight. Evaporation of unreacted triethyl orthoformate at reduced pressure yielded quantitatively 1.2 g of **13** as a stereoisomeric mixture. PMR (DMSO-d_6), 1.24 (t, 3H), 3.22–3.90 (complex abs, 4H), 4.55–5.0 (complex abs, 3H), 5.40 (s, 1H) and 7.34 (complex abs, 15H). The crude mixture **13** was pyrolized without affording **18** (see below).

(+)-2,3-O-*Ethoxymethylene*-D-*ribonolactone*, **14**

A mixture of **1** (4 g, 27.0 mmole), triethyl orthoformate (4.2 g) and 80 ml anh. THF was heated to reflux for 12 h. The volatile products were removed under reduced pressure to give 5.54 g of **14** (quantitative yield) as a mixture of stereoisomers in 3:2 ratio. After standing for a week, one of the stereoisomers crystallized. A pure sample had m.p. 84–86°, $\{\alpha\}_D^{20} = +18$, c = 1 in $CHCl_3$, and PMR ($CDCl_3$), 1.15 (t, $J = 6.4$, 3H), 3.54 (q, $J = 6.4$, 2H), 3.81 (complex abs, 3H), 4.50–5.00 (complex abs, 3H) and 5.90 (s, 1H). Spectroscopic data of the mixture were: IR (film), 3500 (broad), 2920 and 1780 cm^{-1}; MS, *m/e* (%) 204 (M^+), 117 (11), 85 (36), 75 (38), 73 (40), 71 (45), 61 (62), 57 (100), 47 (76) and 43 (71); PMR ($CDCl_3$), 1.15 and 1.20 (two t, $J = 6.4$, 3H), 3.54 and 3.60 (two q, $J = 6.4$, 2H), 3.81 (complex abs, 3H), 4.50–5.00 (complex abs, 3H) and 5.90 (s, 1H). Found: C, 47.01; H, 5.81. $C_8H_{12}O_6$ requires: C, 47.06; H, 5.92%.

(−)-(S)-5-*Hydroxymethyloxol*-3-*en*-2-*one*, **16**

A 10 ml flask, containing 410 mg of **14** (2.0 mmole), was connected to a rotary microdistillation apparatus and heated at 220°/40 torr in such a way that **14** could not distill and **16** distilled as soon as formed. The distillate was chromatographed through 3 g of silica gel using mixtures of CH_2Cl_2–ether as eluent. By distilling the fraction eluted with 4:1 CH_2Cl_2–ether (170 mg), pure **16** was obtained (156 mg, 1.36 mmole, 68% yield). B.p. 130°/0.3 torr, m.p. 37–39°, $\{\alpha\}_D^{20} = -143$, c = 1.14 in H_2O (lit[13] $\{\alpha\}_D^{25} = -145$, c = 0.13 in H_2O). IR (film), 3700–3200 (broad), 3125, 1750 and 1600 cm^{-1}; MS, *m/e* (%) 114 (M^+), 98 (2), 96 (3), 85 (20), 84 (100), 58 (10), 56 (25) and 55 (50); PMR ($CDCl_3$), 3.57–4.16 (complex abs, 3H), 5.19 (m, 1H), 6.20 (dd, $J = 6.7$, $J' = 2$; 1H), 7.60 (dd, $J = 6.7$, $J' = 1.3$; 1H); PMR ($CDCl_3 + D_2O$), 3.74 (dd, $J = 11.5$, $J' = 4.6$; 1H) and 4.01 (dd, $J = 11.5$, $J' = 4$; 1H). Found: C, 52.42; H, 5.08. $C_5H_6O_3$ requires: C, 52.63; H, 5.30%.

(+)-(S)-5-*Hydroxymethyloxolan*-2-*one*, **24**

A solution of **16** (749 mg, 6.57 mmole) in 15 ml of ethyl acetate was hydrogenated at atmospheric pressure in 3 min using 75 mg of 10% Pd on charcoal as catalyst. The mixture was filtered and the solvent removed at reduced pressure to give **24** quantitatively, $\{\alpha\}_D^{21} = +32.3$, c = 3.56 in ethanol (lit[3] $\{\alpha\}_D^{26} = +31.30$, c = 2.92 in EtOH). IR (film), 3450, 2950 and1750 cm^{-1}; MS, *m/e* (%) 117 ($M^+ + 1$), 116 (M^+), 98 (2.3), 86 (16), 85 (100), 57 (22), 55 (70); PMR ($CDCl_3$), 1.80–2.90 (complex abs, 4H), 3.55 (dd, $J = 12.6$, $J' = 4.6$; 1H), 3.96 (dd, $J = 12.6$, $J' = 3$; 1H), 3.98 (s, 1H), 4.69 (m, 1H). Found: C, 51.51; H, 7.09. $C_5H_8O_3$ requires: C, 51.72; H, 6.94%.

(−)-(S)-5-*Methoxymethyloxol*-3-*en*-2-*one*, **9**, *from* **16**

A light-protected mixture of **16** (0.21 g, 1.86 mmole), Ag_2O (0.40 g, 1.86 mmole) and 10 ml of freshly distilled methyl iodide

was stirred for 48 h at r.t. The mixture was filtered, the unreacted methyl iodide removed at reduced pressure and the residue distilled to give 0.16 g of **9** (1.25 mmole, 67.2% yield). Its spectrocopic data and specific rotation were the same as for the product obtained by pyrolysis of **11**.

(−)-(S)-5-*Benzyloxymethyloxol-3-en-2-one*, **15**, *from* **16**

A light-protected mixture of **16** (300 mg, 2.63 mmole), 3 ml anh. DMF, Ag_2O (463 mg, 2.0 mmole) and benzyl bromide (940 mg, 5.5 mmole) was stirred for 48 h at r.t., then diluted with 30 ml $CHCl_3$ and filtered. After standing for 14 h in a refrigerator, pyridine (2 ml) was added and the solution washed with 10% aq HCl, aq $NaHCO_3$ and H_2O, and dried with anh. Na_2SO_4. The solvents were removed at reduced pressure and the residue was filtered through a 10 g silica gel column and distilled at 140°/0.06 torr to give 393 mg of **15** (1.92 mmole, 73% yield). Its spectroscopic data and specific rotation were the same as for the product obtained from pyrolysis of **12**.

(−)-(S)-5-*Butoxymethyloxol-3-en-2-one*, **17**

To a magnetically stirred and light-protected mixture of **16** (300 mg, 2.6 mmole), Ag_2O (620 mg, 2.6 mmole), *n*-butyl iodide (8 ml) and anh. CH_2Cl_2 (1 ml), more Ag_2O (930 mg) was added in several portions during 9 days. Then, the mixture was filtered and the filtrate concentrated at reduced pressure and chromatographed through 5 g of silica gel using mixtures of CH_2Cl_2–hexane as eluent. Eluting with CH_2Cl_2, **17** was obtained (180 mg, 1.05 mmole, 40% yield), b.p. 100°/0.1 torr, $\{\alpha\}_D^{20} = -126.7$, c = 3.0 in $CHCl_3$. IR (film), 1760 and 1600 cm^{-1}; PMR ($CDCl_3$), 0.61–2.86 (complex abs, 7H), 3.49 (t, $J = 5.5$, 2H), 3.66 (d, $J = 5.5$, 2H), 5.17 (m, 1H), 6.18 (dd, $J = 6$, $J' = 2.7$; 1H) and 7.60 (dd, $J = 6$, $J' = 1.3$; 1H). Found: C, 63.25; H, 8.63. $C_9H_{14}O_3$ requires: C, 63.51; H, 8.29%.

(−)-(S)-5-*Trityloxymethyloxol-3-en-2-one*, **18**

A mixture of **16** (187 mg, 1.64 mmole) in 5 ml anh. pyridine and recrystallized trityl chloride (457 mg, 1.64 mmole) was magnetically stirred for 20 min until complete solution, allowed to stand for 72 h at r.t. and then filtered. The filtrate was concentrated at reduced pressure and chromatographed through 15 g of silica gel using mixtures CH_2Cl_2–hexane as eluent, to afford 409 mg of a solid. Crystallization from benzene gave 379 mg of **18** (1.06 mmole, 64.7% yield), m.p. 152–154°, $\{\alpha\}_D^{20} = -95.1 \pm 0.7$, c = 3.42 in $CHCl_3$ (lit[5] m.p. 153–154°, $\{\alpha\}_D^{20} = -95.9$, c = 1.03 in $CHCl_3$). IR (film), 3120, 3100, 3050, 1750 and 1600 cm^{-1}; MS, *m/e* (%) 356 (M^+), 279 (13), 244 (20), 243 (65), 239 (15), 183 (17), 166 (23), 165 (100), 105 (69), 97 (42), 83 (77), 78 (51), 77 (51), 69 (31) and 55 (26); PMR ($CDCl_3$), 3.48 (d, $J = 4.7$, 2H), 5.13 (m, 1H), 6.21 (dd, $J = 6$, $J' = 1.8$, 1H), and 7.18–7.58 (complex abs, 16H). Found: C, 80.59; H, 5.51. $C_{24}H_{20}O_3$ requires: C, 80.88; H, 5.66%.

(−)-(S)-5-*Acetoxymethyloxol-3-en-2-one*, **19**

A solution of **16** (300 mg, 2.63 mmole), acetic anhydride (402 mg, 3.95 mmole) and pyridine (312 mg, 3.95 mmole) in 20 ml anh CH_2Cl_2 was allowed to stand for 14 h at r.t., then washed with 1% aq HCl and water and dried. The volatile products were removed at reduced pressure and the residue distilled to give 324 mg of **19** (2.07 mmole, 79% yield), b.p. 125°/0.2 torr, $\{\alpha\}_D^{20} = -123.6$, c = 3.68 in $CHCl_3$. IR (film) 3120, 3050, 1760 (broad) and 1600 cm^{-1}; MS, *m/e* (%) 157 ($M^+ + 1$), 126 (7), 97 (5), 96 (2), 84 (7), 83 (6), 73 (4), 55 (9), 54 (8), 53 (5), 50 (6) and 43 (100); PMR ($CDCl_3$), 2.08 (s, 3H), 4.34 (d, $J = 4.7$, 2H), 5.26 (m, 1H), 6.23 (dd, $J = 6$, $J' = 2$; 1H) and 7.50 (dd, $J = 6$, $J' = 1.6$; 1H). Found: C, 53.75; H, 5.23. $C_7H_8O_4$ requires: C, 53.85; H, 5.16%.

(−)-(S)-5-*Formyloxymethyloxol-3-en-2-one*, **20**

A mixture of **16** (519 mg, 4.55 mmole), methyl formate (25 ml), 4 drops of conc H_2SO_4 and 5 g of 4 Å molecular sieves was boiled under reflux for 5 h. The solution was decanted and the molecular sieves washed with CH_2Cl_2 (10 ml). After neutralizing with solid $NaHCO_3$, the volatile products were removed at reduced pressure and the residue chromatographed through 20 g of silica gel using CH_2Cl_2 as eluent, to afford 479 mg of **20** (3.37 mmole, 74% yield). B.p. 100–110°/0.1 torr, $\{\alpha\}_D^{21} = -132.3$, c = 5.6 in $CHCl_3$. IR (film), 3150, 1760, 1725 and 1600 cm^{-1}; PMR ($CDCl_3$), 4.46 (d, $J = 4.7$, 2H), 5.3 (m, 1H), 6.22 (dd, $J = 6$, $J' = 2$; 1H), 7.5 (dd, $J = 6$, $J' = 1.3$; 1H) and 8.04 (s, 1H). Found C, 50.50; H, 4.36. $C_6H_6O_4$ requires: C, 50.71; H, 4.26%.

(−)-(S)-5-*Methanesulfonyloxymethyloxol-3-en-2-one*, **21**

To an ice-cooled solution of **16** (1.29 g, 11.28 mmole) and pyridine (1.78 g, 22.57 mmole) in 25 ml CH_2Cl_2, a solution of methanesulfonyl chloride (2.58 g, 22.57 mmole) in 10 ml CH_2Cl_2 was added dropwise. The mixture was stirred for 30 min and allowed to stand in a refrigerator for 14 h, then washed with 0.1 *N* aq HCl (2 × 20 ml) and water (1 × 20 ml), and dried. The volatile products were removed at reduced pressure to give 1.71 g of **21** (8.91 mmole, 79% yield). The product could neither be chromatographed nor distilled and the crude was used in further reactions. $\{\alpha\}_D^{21} = -73.2$, c = 2.8 in CH_2Cl_2. IR (film), 3120, 3050, 1750 and 1350 cm^{-1}; MS, *m/e* (%) 192 (M^+), 162 (9), 120 (4), 109 (11), 97 (9), 95 (9), 83 (79), 79 (100), 65 (28), 55 (79), 50 (29), 48 (29), 45 (30), 43 (28), 41 (29) and 39 (74); PMR ($CDCl_3$), 3.12 (s, 3H), 3.38 (dd, $J = 7.3$, $J' = 4.6$; 1H), 3.68 (dd, $J = 7.3$, $J' = 3.6$; 1H), 5.40 (m, 1H), 6.33 (dd, $J = 6$, $J' = 2$; 1H) and 7.65 (dd, $J = 6$, $J' = 1.6$; 1H). Found: C, 37.24; H, 3.96; S, 16.37. $C_6H_8O_5S$ requires: C, 37.50; H, 4.19; S, 16.68%.

(−)-(S)-5-p-*Toluenesulfonyloxymethyloxol-3-en-2-one*, **22**

To an ice-cooled solution of 1.08 g of **16** (9.5 mmole) and 1.5 g anh pyridine (19 mmole) in 12 ml CH_2Cl_2, *p*-toluenesulfonyl chloride (3.62 g, 19 mmole) was added. The mixture was magnetically stirred for 14 h at r.t., diluted with 10 ml CH_2Cl_2, washed with 1% aq HCl (3 × 5 ml) and water, and dried over anh. Na_2SO_4. Evaporation of the volatile products at reduced pressure gave a residue which was chromatographed through 25 g silica gel, using mixtures CH_2Cl_2–hexane as eluent, to afford 1.81 g of **22** (6.75 mmole, 71% yield). A sample recrystallized from CH_2Cl_2–hexane had m.p. 64–65° and $\{\alpha\}_D^{20} = -56$, c = 7.5 in $CHCl_3$. IR ($CHCl_3$), 3050, 1765, 1600 and 1370 cm^{-1}; PMR, ($CDCl_3$), 2.45 (s, 3H), 4.27 (d, $J = 4.7$, 2H), 5.22 (m, 1H), 6.22 (dd, $J = 6$, $J' = 2$; 1H), 7.46 (complex abs, 3H) and 7.84 (d, $J = 8.7$, 2H); MS, *m/e* (%) 268 (M^+), 155 (48), 97 (25), 91 (100), 83 (26), 69 (15), 65 (34), 55 (13) and 39 (16). Found: C, 53.70; H, 4.46; S, 12.05. $C_{12}H_{12}O_5S$ requires: C, 53.72; H, 4.50; S, 11.95%.

(−)-(S)-5-*Iodomethyloxol-3-en-2-one*, **23**

A mixture of **22** (0.43 g, 1.6 mmole), NaI (3.6 g, 24 mmole) and anh. acetone (20 ml) was boiled under reflux for 8 h, then filtered and the solvent removed at reduced pressure. The organic residue was dissolved in 25 ml ether, washed with aq $Na_2S_2O_3$ and brine, and dried. Evaporation of the solvent gave 0.30 g of a residue which was chromatographed through 3.5 g silica gel, using 1:1 CH_2Cl_2–hexane as eluent, to afford 0.23 g of pure **23** (1.03 mmole, 63% yield). $\{\alpha\}_D^{20} = -113$, c = 5 in $CHCl_3$. IR (film), 1750 and 1600 cm^{-1}; PMR ($CDCl_3$), 3.42 (m, 2H), 5.15 (m, 1H), 6.32 (dd, $J = 5.3$, $J' = 2$; 1H), 7.59 (dd, $J = 5.3$; $J' = 1.3$; 1H). Found: C, 27.07; H, 2.28. $C_5H_5O_2I$ requires: C, 26.80; H, 2.23%).

(+)-(R)-5-*Methyloxolan-2-one*, **33**

To a soln of **23** (632 mg, 2.82 mmole) in 10 ml abs. ethanol 200 mg of $CaCO_3$ and 1.5 g of freshly prepared Ni–Ra W-4, were added. The mixture was stirred for 2 h and filtered. The catalyst was exhaustively washed with abs. ethanol and the solvent removed at reduced pressure. The residue was dissolved in CH_2Cl_2, the insoluble material filtered off and the solvent evaporated at reduced pressure to give a crude which, distilled at 110°/18 torr, afforded 178 mg of **33** (1.78 mmole, 63% yield). $\{\alpha\}_D^{21} = +27$, c = 1.33 in CH_2Cl_2 (lit.[10] $\{\alpha\}_D^{23} = +30.1$, c = 0.85 in CH_2Cl_2). IR (film), 1780 cm^{-1}; PMR ($CDCl_3$), 1.38 (d, $J = 6$, 3H), 1.6–2.7 (complex abs, 4H) and 4.61 (m, 1H). Found: C, 59.82; H, 7.87. $C_5H_6O_2$ requires: C, 59.98; H, 8.05%.

Attempts to obtain **17** *from* **23**

(a) *With a large excess of* n-*butanol.* To a magnetically stirred and light-protected mixture of **23** (0.19 g, 0.87 mmole), 15 ml anh. *n*-butanol and 0.20 g of Ag_2O (0.87 mmole), 0.3 g of Ag_2O (1.31 mmole) was added in small portions during 9 days. Then,

the mixture was filtered, the *n*-butanol removed at reduced pressure and the residue chromatographed through 2 g silica gel, using CH_2Cl_2 as eluent. A small quantity (12 mg) of a *n*-butyl ester, probably *n*-butyl (*Z*)-4-oxo-2-pentenoate was isolated as the only defined product. IR (film), 1720, 1710 and 1620 cm^{-1}; PMR ($CDCl_3$), 0.65–2.05 (complex abs, 7H), 2.35 (s, 3H), 4.19 (t, $J = 6$, 2H), 6.05 (d, $J = 11.3$, 1H) and 6.53 (d, $J = 11.3$, 1H).

(b) *With 1 equivalent of* n-*butanol.* The reaction was carried out as before, except for the use of only 1 eq of *n*-butanol and 10 ml of CH_2Cl_2 as solvent. After the work-up only starting material and protoanemonin **26** were detected (PMR).

*2,3-O-Ethoxymethylene-5-O-methanesulfonyl-*D*-ribonolactone,* **27**

To a solution of **14** (4.26 g, 20.9 mmole) in 25 ml anh. CH_2Cl_2, a soln of 2.39 g of methanesulfonyl chloride (20.9 mmole) and 4.95 g of anh. pyridine (62.5 mmole) in 10 ml anh. CH_2Cl_2 was added slowly. The mixture was allowed to stand for 8 h at r.t. and filtered. The volatile products were removed from the filtrate to give 5.30 g of essentially pure **27** (100% yield) that was used without further purification because of its instability towards silica gel chromatography and distillation. IR (film), 1780 cm^{-1}; PMR ($CDCl_3$), 1.14 and 1.17 (two t, $J = 6.6$, 3H), 3.10 (s, 3H), 3.60 and 3.64 (two q, $J = 6.6$, 2H), 4.31 (m, 2H), 4.80–5.00 (complex abs, 3H) and 5.96 (s, 1H).

*2,3-O-Ethoxymethylene-5-O-p-toluenesulfonyl-*D*-ribonolactone,* **28**

To a solution of 4.12 g of **14** (20.1 mmole) and 2.39 g of pyridine (30.3 mmole) in 15 ml anh. CH_2Cl_2, 3.85 g of *p*-toluenesulfonyl chloride (20.2 mmole) in 15 ml anh. CH_2Cl_2 was added dropwise, and the mixture allowed to stand for 75 h at r.t. The consumption of *p*-toluenesulfonyl chloride was followed by tlc. The reaction mixture was filtered and the solvent removed at reduced pressure. The residue was chromatographed through 80 g silica gel, eluting with mixtures CH_2Cl_2–hexane, to afford 5.49 g of **28** (14.7 mmole, 73% yield) as a mixture of stereoisomers, m.p. 85–92°. IR (KBr), 1780 cm^{-1}; PMR ($CDCl_3$), 1.15 (t, $J = 7.3$, 3H), 2.49 (s, 3H), 3.59 (q, $J = 7.3$, 2H), 4.22 (dd, $J = 10.6$, $J' = 2.6$, 1H), 4.44 (dd, $J = 10.6$, $J' = 2$, 1H), 4.70–5.00 (complex abs, 3H), 5.98 (s, 1H), 7.41 (d, $J = 8$, 2H) and 7.82 (d, $J = 8$, 2H).

*5-Deoxy-2,3-O-ethoxymethylene-5-iodo-*D*-ribonolactone,* **29** *from* **27**

A mixture of crude **27** (870 mg, 3.08 mmole), NaI (6 g, 40 mmole) and 25 ml acetone was heated to reflux for 6 h. The solvent was removed at reduced pressure and the residue chromatographed through 25 g silica gel eluting with mixtures CH_2Cl_2–hexane to afford 793 mg of **29** (2.52 mmole, 82% yield) as a mixture of stereoisomers, m.p. 54–60°. IR (film), 1790 cm^{-1}; MS, *m/e* (%) 315 ($M^+ + 1$), 314 (M^+), 270 (29), 269 (100), 225 (19), 187 (29), 169 (29), 143 (72), 141 (25), 127 (34), 71 (31), 70 (28), 69 (84) and 57 (28); PMR ($CDCl_3$), 1.16 and 1.22 (two t, $J = 6.7$, 3H), 3.46 (d, $J = 4$, 2H), 3.54 and 3.58 (two q, $J = 6.7$, 2H), 4.44–5.13 (complex abs, 3H) and 5.90 (s, 1H).

Preparation of **29** *from* **28**

A mixture of **28** (354 mg, 0.99 mmole) and NaI (2.0 g, 13.3 mmole) in 15 ml anh. acetone was magnetically stirred for 2 days at r.t., then filtered and the solid washed with 40 ml CH_2Cl_2. The filtrate was washed with aq $Na_2S_2O_3$ and water, and dried. Elimination of the solvent gave 281 mg of **29** (0.89 mmole, 90.5% yield). Its spectroscopic data agreed with those of the product obtained from **27**.

(−)-(S)-5-Butoxymethyloxol-3-en-2-one, **17**, *from* **29**

A light-protected mixture of **29** (937 mg, 2.98 mmole), *n*-butanol (220 mg, 2.98 mmole) and Ag_2O (1.38 g) in 15 ml $CHCl_3$ was magnetically stirred for 9 days. Two additional portions of Ag_2O (total 1.38 g, 5.96 mmole) were added over this period. The mixture was filtered and the solid washed with $CHCl_3$. The combined washing and filtrate solns were washed with aq $Na_2S_2O_3$ and water, and dried. The chloroform was removed at reduced pressure to give a residue (473 mg) that showed it to be essentially pure 5-O-butyl-2,3-O-ethoxymethylene-D-ribonolactone, **30**. PMR ($CDCl_3$), 0.70–2.00 (complex abs, 10H), 3.30–5.20 (complex abs, 9H) and 5.98 (s, 1H).

Pyrolysis of **30** without further purification was carried out by heating it at 225°/18 torr in rotary microdistillation apparatus. The distillate (198 mg) was chromatographed through silica gel, eluting with mixtures of CH_2Cl_2–hexane to afford 137 mg of pure **17** (27% yield from **29**). Its spectroscopic data and specific rotation agreed with those of the product obtained by butylation of **16**.

(−)-Ranunculin tetraacetate, **32**

To a light-protected mixture of **16** (283 mg, 2.48 mmole), Ag_2O (629 mg, 2.72 mmole), anh. $CaSO_4$ (1.7 g) and iodine (125 mg) in 5 ml anh. and ethanol-free chloroform, a solution of 1.02 g of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (2.48 mmole) in 8 ml anh. and ethanol-free chloroform was slowly added and the resulting mixture magnetically stirred for 86 h at r.t. After 24, 48 and 72 h stirring, portions of 315 mg Ag_2O (1.35 mmole) and 510 mg (1.47 mmole) of the alkylating agent in 5 ml $CHCl_3$ were added. The reaction was followed by tlc. The reaction mixture was filtered, the filtrate washed with aq $Na_2S_2O_3$ and water, and the volatile products removed at reduced pressure. The residue was chromatographed through 30 g silica gel, using mixtures $CHCl_3$–ether as eluent, to afford 844 mg of **32** (1.90 mmole, 77% yield), m.p. 136–138° from ethanol (lit[11] 136–137°); mixed m.p. with a sample obtained from natural ranunculin showed no depression. $\{\alpha\}_D^{20} = -24.2$, $c = 3.82$ in $CHCl_3$. IR (film) 1750 cm^{-1}; MS, *m/e* (%) 444 (M^+), 43 (100); 200 MHz PMR ($CDCl_3$), 2.02 (s, 3H), 2.04 (s, 3H), 2.09 (s, 3H), 2.10 (s, 3H), 3.64–3.80 (complex abs, 2H), 3.77 (dd, $J = 11$, $J' = 7.5$; 1H), 4.03 (dd, $J = 11$, $J' = 4.7$; 1H), 4.17 (dd, $J = 12.5$, $J' = 2.5$; 1H), 4.28 (dd, $J = 12.5$, $J' = 4.3$; 1H), 4.62 (d, $J = 8$, 1H), 4.98–5.30 (complex abs, 3H), 6.20 (dd, $J = 7$, $J' = 2.5$; 1H) and 7.47 (dd, $J = 7$, $J' = 2$; 1H).

(−)-Ranunculin, **31**

A solution of **32** (300 mg, 0.67 mmole) in 1 ml dioxane and 5 ml 1.5% aq HCl was heated under reflux for 5 h. The volatile products were removed by steam distillation at reduced pressure and the residue was left in a dessicator with P_2O_5 until it solidified (14 days). Crystallization from methanol gave 159 mg of pure **31** (0.57 mmole, 85% yield), m.p. 138–140°, mixed m.p. with a sample of natural ranunculin showed no depression; $\{\alpha\}_D^{20} = -81$, $c = 2$ in H_2O (lit[12] m.p. 140–141°, $\{\alpha\}_D^{24} = -77$, $c = 2$ in H_2O). IR (KBr), 3380 (broad), 1750 and 1580 cm^{-1}; MS, no detectable; 200 MHz PMR (DMSO-d_6), 2.90–3.80 (complex abs, 6H), 3.66 (dd, $J = 11.6$, $J' = 6$; 1H), 4.03 (dd, $J = 12$, $J' = 4$; 1H), 4.22 (d, $J = 8$, 1H) 4.54 (t, 1H), 4.98 (d, 1H), 5.02 (d, 1H), 5.08 (d, 1H), 5.35 (m, 1H), 6.28 (dd, $J = 8.5$, $J' = 2.5$; 1H), 7.83 (dd, $J = 8.5$, $J' = 2$; 1H); 50 MHz ^{13}C NMR (DMSO-d_6), butenolide part: 173.3 (C=O), 121.8 (C_α), 156.1 (C_β), 82.9 (C_γ), 68.8 (C_δ); glucoside part: 103.4 (C_1), 73.5 (C_2), 77.2 (C_3 or C_5), 70.2 (C_4), 76.9 (C_5 or C_3) and 61.4 (C_6).

Acknowledgements—A fellowship from I.N.A.P.E., Ministerio de Educación y Ciencia to O.P. is gratefully acknowledged. We thank the Comisión Asesora de Investigación Científica y Técnica for financial support.

REFERENCES

[1]J. Cardellach, C. Estopá, J. Font, M. Moreno-Mañas, R. M. Ortuño, F. Sánchez-Ferrando, S. Valle and L. Vilamajó, *Tetrahedron* **38**, 2377 (1982).
[2]P. Camps, J. Font and O. Ponsatí, *Tetrahedron Letters* **22**, 1471 (1981).
[3]M. Taniguchi, K. Koga and S. Yamada, *Tetrahedron* **30**, 3547 (1974).
[4]K. Tomioka, T. Ishiguro and K. Koga, *J. Chem. Soc. Chem. Comm.* 652 (1979).
[5]K. Tomioka, T. Ishiguro and K. Koga, *Tetrahedron Letters* **21**, 2973 (1980).
[6]See preceding paper and references therein.
[7]L. Hough, J. K. N. Jones and D. L. Mitchell, *Can. J. Chem.* **36**, 1720 (1958).

[8a]E. J. Corey and Roland A. E. Winter, *J. Am. Chem. Soc.* **85**, 2677 (1963); [b]E. J. Corey and Roland A. E. Winter, *Ibid.* **87**, 934 (1965).
[9]S. Hanessian, A. Bargiotti and M. La Rue, *Tetrahedron Letters* 737 (1978).
[10]K. Mori, *Tetrahedron* **31**, 3011 (1975).
[11]R. Hill and R. van Heyningen, *Biochem. J.* **49**, 332 (1951).
[12]M. H. Benn and L. J. Yelland, *Can. J. Chem.* **46**, 729 (1968).
[13]M. Boll, *Acta Chem. Scand.* **22**, 3245 (1968).
[14]C. E. Redemann and C. Niemann, *Org. Synth. Coll.* III, 11 (1955).
[15]J. Font and J. Pascual, *Anales de Fís. y Quím.* **62B**, 705 (1966).
[16]E. Breitmaier and W. Woelter, *^{13}C NMR Spectroscopy*, 2nd Edn. Verlag Chemie, Weinheim (1978).