Microbial Metabolites. Part XI.[1] Total Synthesis and Absolute Configuration of (*S*)-Carlosic Acid (4-Butyryl-2,5-dihydro-3-hydroxy-5-oxofuran-2-acetic Acid) and Conversion of (*R*)-5-Methyltetronic Acid into (*R*)-Carolic Acid {3,4-Dihydro-8-methylfuro[3,4-*b*]oxepin-5,6(2*H*,8*H*)-dione}

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Syntheses of (*S*)-2,5-dihydro-3-hydroxy-5-oxofuran-2-acetic acid (5) and its methyl ester are described. Biomimetic acylations of the ester and of (*R*)-3-hydroxy-2-methylfuran-2(5*H*)-one[(*R*)-γ-methyltetronic acid] (1) to produce (*S*)-carlosic acid (3) and (*R*)-carolic acid (2), respectively, are described. The absolute configuration of carlosic acid from *Penicillium charlesii* NRRL 1887 has been established as *S*.

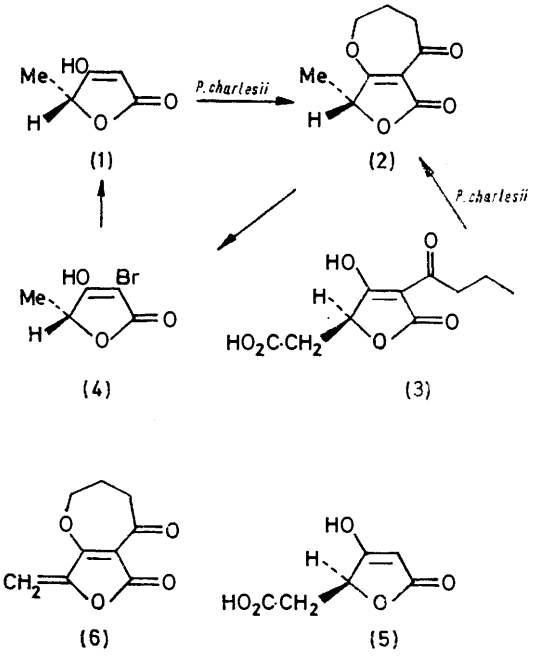
THE considerable recent interest in the synthesis of racemic tetronic acids of natural type [2-9] prompts us to report our own studies in the optically active series.

One of the primary objectives in our studies on mould tetronic acids has been the identification of the biogenetic intermediates involved and the development of methods for their synthesis, especially methods adaptable to isotopic labelling studies.

At the inception of these studies the absolute configurations of carolic and carlosic acids were not known, and a number of fundamental questions regarding the biogenetic relationship of γ-methyltetronic acid (1) to carolic acid (2) and carlosic acid (3) had not been answered. Other workers subsequently established the configuration of the acid (1) to be *R* as shown.[10]

The incorporation of both γ-methyltetronic acid (1) and carlosic acid (3) into carolic acid (2) in *Penicillium charlesii* NRRL 1887 was demonstrated by isotope competition experiments against [U-^{14}C]glucose, and subsequently by feeding [U-^{14}C]-(1) and [U-^{14}C]-(3) to the organism. The latter compounds were prepared as follows. Feeding [U-^{14}C]glucose to the organism gave carolic acid (2) and carlosic acid (3), both uniformly labelled. The former was converted *via* the bromide (4) into [U-^{14}C]-γ-methyltetronic acid (1) by previous methods.[11] Both the uniformly labelled precursors were incorporated in good yield.

From these biosynthetic studies [12] it was apparent that dual metabolic pathways to (2) existed and that development of a procedure for the acylation of tetronic acids in the 3- (or α-) position would be not only biomimetic but also potentially applicable to the synthesis of all known mould tetronic acids from two simple α-unsubstituted precursors, *viz.* (1) and (5) [didehydrocarolic acid (6) being an exception owing to the anticipated lability of the vinyl ether group].



As a model for our acylation studies we selected (*RS*)-(1), readily prepared by two general methods of tetronic acid synthesis, *viz.* the closure of γ-bromo-esters of type (8) [13,14] and the cyclisation of acetoacetates of lactic esters, described below.[15] The former synthesis, though, has thus far been limited to racemic materials.

[1] (*a*) J. L. Bloomer, S. M. H. Zaidi, J. T. Strupczewski, C. S. Brosz, and L. A. Gudzyk, *J. Org. Chem.*, 1974, **39**, 3615 should be considered as Part X. For preliminary communications see J. L. Bloomer and F. E. Kappler, (*b*) *Tetrahedron Letters*, 1973, 163; (*c*) *J. Org. Chem.*, 1974, **39**, 113. For previous papers in the series see (*d*) J. L. Bloomer, W. R. Eder, and W. F. Hoffman, *Chem. Comm.*, 1968, 354; J. L. Bloomer and W. F. Hoffman, *Tetrahedron Letters*, 1969, 4339; J. L. Bloomer, M. A. Gross, F. E. Kappler, and G. N. Pandey, *Chem. Comm.*, 1970, 1030; J. L. Bloomer, W. R. Eder, and W. F. Hoffman, *J. Chem. Soc.* (*C*), 1970, 1848; J. L. Bloomer, W. R. Eder, and W. F. Hoffman, *Bryologist*, 1970, **73**, 586; J. L. Bloomer, F. E. Kappler, and G. N. Pandey, *Chem. Comm.*, 1972, 243; J. L. Bloomer and F. E. Kappler, *ibid.*, p. 1047.

[2] F. H. Andresen, A. Svendsen, and P. M. Boll, *Acta Chem. Scand.*, 1974, **28B**, 130.

[3] S. Gelin and A. Galliaud, *Compt. rend.*, 1972, **275C**, 897.

[4] S. Gelin and P. Pollet, *Compt. rend.*, 1974, **279C**, 345.

[5] J. V. Greenhill and T. Tomassini, *Tetrahedron Letters*, 1974, 2683.

[6] T. P. C. Mulholland, R. Foster, and D. B. Haydock, *J.C.S. Perkin I*, 1972, 1225.

[7] A. Svendsen and P. M. Boll, *Tetrahedron*, 1973, **29**, 4251.

[8] A. Svendsen and P. M. Boll, *J. Org. Chem.*, 1975, **40**, 1927.

[9] M. Omo and N. Kawabe, *Japan Kokai*, 1974, **69**, 659 (*Chem. Abs.*, 1974, **71**, 15,1976w).

[10] P. M. Boll, E. Sorensen, and K. Balieu, *Acta Chem. Scand.*, 1968, **22**, 3251.

[11] P. W. Clutterbuck, H. Raistrick, and F. Reuter, *Biochem. J.*, 1935, **29**, 300.

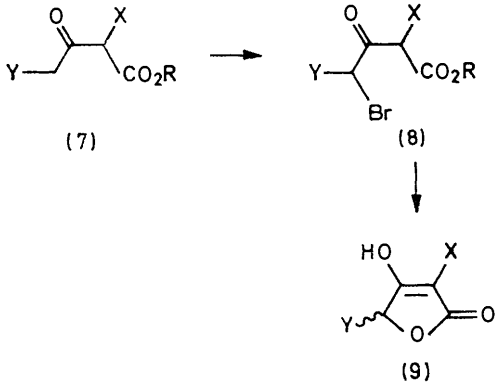
[12] J. L. Bloomer, F. E. Kappler, and G. N. Pandey, *J.C.S. Chem. Comm.*, 1972, 243.

[13] M. E. DeMarcay, *Compt. rend.*, 1879, **88**, 126.

[14] L. Wolff, *Annalen*, 1896, **291**, 226.

[15] R. N. Lacey, *J. Chem. Soc.*, 1954, 832.

As models for α-acylation, tetronic acids were prepared by the classical methods,[13,14] whereby β-oxo-esters of type (7) were brominated and rearranged to γ-bromo-β-oxo-esters (8), which were then cyclised to the racemic



(7) (8) (9)

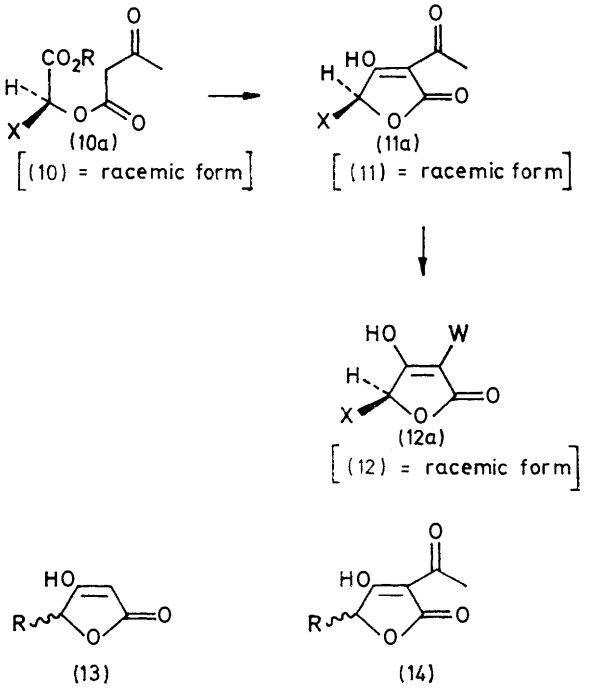
tetronic acids (9) (in the original studies R = Et, X = Me, Y = H [13] and R = Et, X = Br, Y = H [14]). With the γ-bromoacetoacetic ester (8; R = Et, X = Y = H) closure to the α-unsubstituted parent tetronic acid (9; X = Y = H) could not be effected, and in order to prepare the required α-unsubstituted tetronic acids (9; X = H) it was necessary to reduce the α-bromotetronic acids (9; X = Br) or to prepare the α-ethoxycarbonyltetronic acids (9; X = CO_2Et) *via* cyclisation of γ-bromoacylmalonates. For example, acylation of malonic ester with α-bromopropionyl chloride gave the γ-bromo-ester (8; R = Et, X = CO_2Et, Y = Me), cyclisation of which afforded the α-ethoxycarbonyltetronic acid (9; X = CO_2Et, Y = Me); [16] this could be de-ethoxycarbonylated.

A more convenient synthesis of (8; R = Et, X = CO_2Et, Y = Me) involves bromination and rearrangement of the propionylmalonic ester (7; R = Et, X = CO_2Et, Y = Me). The availability of both propionyl chloride and diethyl malonate in several isotopically labelled forms with both ^{14}C and ^{13}C makes this approach very useful for labelling studies.

The acyclic bromo-esters were best cyclised by use of dilute alkali rather than thermally, a result which has recently been reported independently.[7] The α-ethoxycarbonyltetronic acid (9; X = CO_2Et, Y = Me) was converted by dilute alkali, acidification, and warming into γ-methyltetronic acid (9; X = H, Y = Me), presumably *via* the carboxylic acid (9; X = CO_2H, Y = Me).

Acetylmalonic ester [17] (7; R = Et, X = CO_2Et, Y = H) was converted into the bromo-ester (8; R = Et, X = CO_2Et, Y = H); cyclisation then gave the α-ethoxycarbonyltetronic acid (9; X = CO_3Et, Y = H) and de-ethoxycarbonylation afforded tetronic acid (9; X = Y = H). Phenylacetylmalonic ester (7; R = Et, X = CO_2Et, Y = Ph) [18] was similarly converted into γ-phenyltetronic acid (9; X = H, Y = Ph). The ethoxycarbonylpropionylmalonic ester (7; R = Et, X = CO_2Et, Y = $EtO_2C{\cdot}CH_2$) was also prepared [19] but attempts to cyclise the derived bromo-compound to the α-ethoxy carbonyltetronic acid (9; X = CO_2Et, Y = $MeO_2C{\cdot}CH_2$) failed, presumably owing to the ease or elimination of HBr, since a considerable quantity of maleic acid was isolated on the usual work-up.

The second major synthetic approach to the tetronic acid nucleus, *viz.* the cyclisation of acetoacetates, was due to Lacey,[15] who cyclised the ester (10; R = Et, X = Me) to the tetronic acid (11; X = Me). The latter could be converted into the α-unsubstituted tetronic acid (*RS*)-(1) *via* bromination [to the α-bromotetronic acid (12; W = Br, X = Me)], and catalytic reduction of the bromo-group.[11] The bromination and reduction steps were high-yielding, but cyclisation by use of sodium as reported gave only a 20—30% yield of the tetronic acid (11; X = Me). However, use of potassium t-butoxide in t-butyl alcohol improved the yield to 95%.



(10a) [(10) = racemic form] (11a) [(11) = racemic form] (12a) [(12) = racemic form]

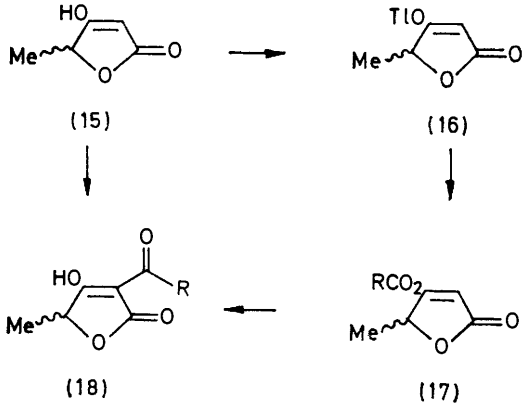
(13) (14)

Although Haynes [20] had reported α-acylation of γ-phenyltetronic acid (13; R = Ph) to (14; R = Ph) by use of acetyl chloride–tin(IV) chloride, the method did not give significant quantities of α-acylated material when applied to γ-methyltetronic acid (15) [*i.e.* (*RS*)-(1)].

Since the *O*-acylation of thallium enolates with acyl chlorides had been reported for phenols,[21] we investigated the application of this reaction to the tetronic acids. The thallium enolate (16) was prepared from the tetronic acid (15) in essentially quantitative yield with thallium(I)

[16] E. Benary, *Ber.*, 1911, **44**, 1759.
[17] A. Ogata, Y. Nosaki, and K. Takagi, *J. Pharm. Soc. Japan*, 1939, **59**, 105 (*Chem. Abs.*, 1939, **33**, 4230[7]).
[18] W. Borsche and U. Wannagat, *Chem. Ber.*, 1952, **85**, 193.
[19] U. Eisner, J. A. Elvidge, and R. P. Linstead, *J. Chem. Soc.*, 1950, 2223.
[20] L. J. Haynes and J. Jamieson, *J. Chem. Soc.*, 1958, 4132.
[21] E. C. Taylor, G. H. Hawks, tert., and A. McKillop, *J. Amer. Chem. Soc.*, 1968, **90**, 2422.

ethoxide in benzene. Although an attempted *C*-acylation failed with acyl fluorides, the acid chlorides PhCOCl, PrCOCl, and $MeO_2C{\cdot}CH_2{\cdot}CH_2COCl$ [22] converted the thallium salt into the corresponding *O*-acylated



(15) (16) (18) (17)

tetronic acids (17; R = Ph, Pr, or $MeO_2C{\cdot}CH_2$) in yields of 94, 89, and 99%, respectively.

We next attempted the conversion of the *O*-acylated tetronic acids into *C*-acylated derivatives *via* Fries-type arrangements. Though the yields were disappointing [a 29% yield of α-butyryl-γ-methyltetronic acid (18; R = Pr) by $TiCl_4$ in $PhNO_2$ at 50 °C], we were able to extend the process to a synthesis of (*RS*)-carolic acid (2) *via* γ-bromobutyronitrile [23] and γ-bromobutyric acid.[24] The γ-bromo-acid was converted into the acid chloride in the usual manner and used to form the *O*-acylated tetronic acid, which was then taken directly for rearrangement. The intermediate, presumably the bromobutyryltetronic acid (18; R = $BrCH_2{\cdot}CH_2{\cdot}CH_2$), was best converted directly into (*RS*)-carolic acid (2) by dilute alkali. The overall yield was 22% from the enolate (16).

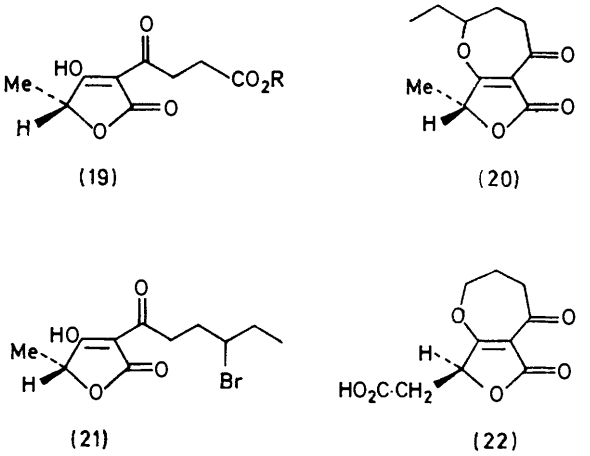
In an attempt to prepare terrestric acid, a homologue of carolic acid, 4-bromohexanoyl chloride was prepared as follows. The Doebner modification of the Knoevenagel reaction [25] on butyraldehyde gave hex-2-enoic acid, which was converted into γ-caprolactone [26] and 4-bromohexanoic acid [27] as previously reported. The acid was converted into the chloride and thence into the *O*-acyl derivative (17; R = $MeCH_2{\cdot}CHBr{\cdot}CH_2{\cdot}CH_2$) as described above in 92% yield. Attempts to rearrange and and cyclise this material as for the carolic acid series were not successful.

The α-acylation reaction was considerably improved by omitting the thalliation step. Thus treatment of the α-unsubstituted tetronic acid (15) directly with PrCOCl and $TiCl_4$ in $PhNO_2$ at 50 °C gave a 72% yield of the α-butyryltetronic acid (18; R = Pr). Likewise a similar acylation with $BrCH_2{\cdot}CH_2{\cdot}CH_2{\cdot}COCl$ followed by the dilute alkali treatment described above gave a 53% yield of (*RS*)-carolic acid (2). Attempts to extend the procedure to the carolinic ester (19; R = Me) were not successful, possibly because $MeO_2C{\cdot}CH_2{\cdot}CH_2{\cdot}COCl$ cyclised intramolecularly under even these mild conditions. Attempts to extend the synthesis to terrestric acid (20) from the 4-bromohexanoyl chloride described above were not successful, possibly owing to the greater difficulty in achieving the intramolecular cyclisation to the final product, which would presumably require the S_N2 displacement of a secondary rather than primary halide by a tetronate anion.

In order to test whether the stereochemical integrity of position 5 in the tetronic acid nucleus was maintained, the tetronic acid (1) obtained from natural carolic acid (2) as described above [11] was used to resynthesise carolic acid (2). The yield was comparable and the product, of 97% optical purity, was identical in m.p. and i.r. and n.m.r. spectra with the natural carolic acid.

Since our biosynthetic studies suggested that carolinic acid (19; R = H) and terrestric acid (20) were metabolic termini rather than intermediates, the syntheses of (19; R = H) *via* the ester (19; R = Me) and of (20) *via* (21) were not pursued, but our efforts were directed instead to the synthon (5).

In addition to the biogenetic and synthetic advantages outlined above, the synthon (5) offered the added possibility of establishing the absolute configuration of carlosic acid (3), a point of considerable importance in elucidating the detailed biogenesis of carolic acid (2).



(19) (20) (21) (22)

The acetoacetate (10; X = Me) of ethyl (*RS*)-lactate could be prepared and cyclised by sodium as reported by Lacey,[15] but the yield of the cyclisation step was low. The yield of the cyclisation product, α-acetyl-γ-methyltetronic acid (11; X = Me) was improved to 95% by use of potassium t-butoxide in t-butyl alcohol at reflux.

(*RS*)-Malic acid was readily esterified and converted by treatment with keten dimer and triethylamine into the triester (10; R = Me, X = $MeO_2C{\cdot}CH_2$); however, application of the above cyclisation conditions resulted in almost total elimination of the equivalent of acetoacetic acid, to give dimethyl fumarate. In the t-butoxide system the lowest temperature which could be

[22] J. Cason, *Org. Synth.*, Coll. Vol. III, 1955, p. 169.
[23] C. G. Derick and R. W. Hess, *J. Amer. Chem. Soc.*, 1918, **40**, 537.
[24] C. S. Marvel and E. K. Birkheimer, *J. Amer. Chem. Soc.*, 1929, **51**, 260.
[25] S. E. Boxer and R. P. Linstead, *J. Chem. Soc.*, 1931, 740.
[26] R. P. Linstead, *J. Chem. Soc.*, 1932, 115.
[27] J. F. Lane and H. W. Heine, *J. Amer. Chem. Soc.*, 1951, **73**, 1348.

used was *ca.* 0 °C, giving a 39% yield of the tetronic acid (11; X = $MeO_2C{\cdot}CH_2$). Doubtless, use of other bases and lower temperature could improve this yield, but this was not pursued since the starting materials were inexpensive and all subsequent steps were simple and high-yielding. Conversion of the α-acetyltetronic acid (11; X = $MeO_2C{\cdot}CH_2$) into the corresponding α-bromotetronic acid (12; W = Br, X = $MeO_2C{\cdot}CH_2$) by bromination and thence into the α-unsubstituted tetronic acid (12; W = H, X = $MeO_2C{\cdot}CH_2$) by reduction was carried out as in the γ-methyl series discussed above.[11,28] As in the γ-methyl series, modification of the bromination by use of less bromine allowed the isolation of the intermediate α-bromoacetyltetronic acid (12; W = $CO{\cdot}CH_2$-Br, X = $MeO_2C{\cdot}CH_2$).

Treatment of the α-acetyltetronic acid (11; X = $MeO_2C{\cdot}CH_2$) with dilute alkali saponified the aliphatic ester group to give the carboxylic acid (11; X = $HO_2C{\cdot}CH_2$). As in the ester series, bromination gave the α-bromotetronic acid bearing a free carboxy-group (12; W = Br, X = $HO_2C{\cdot}CH_2$), and catalytic reduction then gave the α-unsubstituted tetronic acid (12; W = H, X = $HO_2C{\cdot}CH_2$), which is the *RS* form of the synthon (5).

Attempts to convert the synthon (*RS*)-(5) directly into carlosic acid were not successful. Difficulty was also encountered when attempts were made to *O*-acylate the thallium salt of the ester (12; W = H, X = $MeO_2C{\cdot}CH_2$) with butyryl chloride. Spectroscopic evidence indicated that an *O*-butyryl derivative had been formed, but the yield was low. However direct α-acylation of the ester (12; W = H, X = $MeO_2C{\cdot}CH_2$) with butyryl chloride and $TiCl_4$ in nitrobenzene followed by gentle saponification gave (*RS*)-carlosic acid [(*RS*)-(3)] in 59% overall yield.

Similarly, natural (*S*)-malic acid was converted into its methyl ester and thence into the acyclic acetoacetate (10a; X = $MeO_2C{\cdot}CH_2$, R = Me), which was cyclised to the tetronic acid (11a; X = $MeO_2C{\cdot}CH_2$). Saponification of the ester group gave the acid (11a; X = $HO_2C{\cdot}CH_2$), from which the α-acetyl group could be removed by bromination [to give the α-bromotetronic acid (12a; W = Br, X = $HO_2C{\cdot}CH_2$)] and catalytic hydrogenation [to yield the α-unsubstituted tetronic acid (12a; W = H, X = $HCO_2C{\cdot}CH_2$), *i.e.* (5)]. The last two compounds were identical with materials derived from carlosic acid (3) [28] in i.r. and n.m.r. properties and closely similar in m.p. and optical rotation, thus establishing the absolute configuration of (3) to be *S* as shown.

The stereochemical result was unexpected, as a simple decarboxylation of (3) in the organism should have given (2) with the same, rather than opposite, stereochemistry at position 5. This biosynthetic problem is under investigation.

The ester (12; W = H, X = $MeO_2C{\cdot}CH_2$) was acylated as in the methyl series to (12; W = COPr, X = $MeO_2C{\cdot}CH_2$) which was converted by gentle saponification into (*RS*)-carlosic acid (3). Repetition with the optically active ester (12a) gave carlosic acid (3) of the appropriate absolute configuration.

The synthetic procedures described should be especially suitable for the production of (3) with specific isotopic labels for biosynthetic studies. Extension of these studies to specifically labelled viridicatic acid (12a; W = $CO{\cdot}[CH_2]_4{\cdot}CH_3$, X = $HO_2C{\cdot}CH_2$) *via* the methyl ester (12a; W = $CO{\cdot}[CH_2]_4{\cdot}CH_3$, X = $MeO_2C{\cdot}CH_2$) should be particularly easy and should allow us to test whether viridicatic acid plays a critical role in the biosynthesis of terrestric acid (20) similar to that of carlosic acid (3) in the biosynthesis of carolic acid (2).

Conversion of (12; W = H, X = $MeO_2C{\cdot}CH_2$), obtained by an alternative synthetic route, into methyl (*RS*)-carlate [(*RS*)-(22)] has been reported,[8] under conditions essentially the same as ours except for the substitution of 4-chlorobutyroyl chloride for the 4-bromo-material. Our combined studies constitute a formal synthesis of carlic acid (22) in its correct absolute configuration.

The only synthetic limitation to our direct α-acylation procedure for tetronic acids involved the use of a labile acylating agent, *viz.* β-methoxycarbonylpropionyl chloride which, when treated under the standard conditions described with γ-methyltetronic acid (15), allowed the latter to be recovered unchanged. Substitution of a suitably masked carboxy-function in the acylating reagent should allow synthesis of carolinic acid (19; R = H), though we have not pursued this further owing to our limited biosynthetic interest in this material.

EXPERIMENTAL

I.r. spectra were recorded with a Beckman IR-5A or a Perkin-Elmer Infracord spectrophotometer, and n.m.r. spectra with a Varian A-60A or XL-100 spectrophotometer (Me_4Si as internal standard). I.r. and n.m.r. data for compounds marked with an asterisk are available as Supplementary Publication No. SUP 21747 (4 pp.).* M.p.s were measured with a Kofler hot-stage apparatus. Microanalyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, New York. Analytical t.l.c. was performed with Eastman Chromagram sheets coated with fluorescent silica gel, and preparative t.l.c. with glass plates (20 cm × 20 cm × 2 mm) coated with fluorescent silica gel (Brinkmann GF_{254}). For column chromatography Woelm silica gel was used (activity II unless otherwise specified). Optical rotations were measured with a Bendix-NPL automatic polarimeter. Organic solutions were dried prior to evaporation by addition of sodium sulphate (5—10% w/w) unless otherwise specified. Solvents were evaporated off at 30—40 °C and 20—30 mmHg.

Ethyl 2,5-Dihydro-4-hydroxy-5-methyl-2-oxofuran-3-carboxylate (9; X = CO_2Et, Y = Me).—The ester (7; R = Et, X = CO_2Et, Y = Me) was prepared from propionyl chloride and diethyl ethoxymagnesiomalonate by the procedure used for the ester (7; R = Et, X = CO_2Et, Y = H) (below). Bromine (5 ml) was added over 45 min to a stirred solution of the ester (21.6 g) in carbon disulphide (25 ml). After a further 10 min the mixture was evaporated and the residue poured into N-sodium hydroxide (300 ml). After 12 h at room

* For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1975, Index issue.

[28] P. W. Clutterbuck, H. Raistrick, and F. Reuter, *Biochem. J.*, 1935, **29**, 871.

temperature the mixture was poured onto ice (100 g) and concentrated hydrochloric acid (25 ml). Extraction with chloroform and evaporation afforded a residue which was taken up in ether; the solution was slowly concentrated until crystallisation commenced, then set aside to give the tetronic acid (9; X = CO_2Et, Y = Me) * (14.1 g, 76%) (from ethyl acetate), m.p. 91—91.5° (lit.,[16] 89—90°).

4-Hydroxy-5-methylfuran-2(5H)-one (9; X = H, Y = Me).—The ester (9; X = CO_2Et, Y = Me) (14 g) was refluxed in 2N-sodium hydroxide (100 ml) for 45 min; the mixture was cooled, acidified, and extracted with ether to give the tetronic acid (9; X = H, Y = Me) * (8.3 g, 100%), m.p. 119—120° (from ethyl acetate) (lit.,[16] 117—119°).

4-Hydroxy-5-phenylfuran-2(5H)-one (9; X = H, Y = Ph).—The ester in the corresponding phenyl series (7; R = Et, X = CO_2Et, Y = Ph) [18,*] (27.8 g) was brominated in chloroform as for the Y = Me series and cyclised as above to give the α-ethoxycarbonyltetronic acid (9; X = CO_2Et, Y = Ph) * (22.5 g, 91%), m.p. 140—141° (lit.,[29] 140°). De-ethoxycarbonylation as in the methyl series gave the γ-phenyltetronic acid (9; X = H, Y = Ph) * (86%), m.p. 127° (lit.,[29] 127.5—128.5°).

4-Hydroxyfuran-2(5H)-one (9; X = Y = H).—Alcohol-free diethyl ethoxymagnesiomalonate was treated with 1 equiv. of acetyl chloride in ether. The mixture was refluxed for 2 h, acidified with sulphuric acid, and extracted with ether, and the extract was distilled to give diethyl acetylmalonate * (7; R = Et, X = CO_2Et, Y = H) [17] in 66% yield. This ester (20.2 g) was brominated in carbon disulphide as for the Y = Me series. Evaporation of the solvent left a residue which was heated at 130 °C (50 mmHg) for 1.5 h, cooled, and triturated with ether to give the α-ethoxycarbonyltetronic acid * (9; X = CO_2Et, Y = H) (10.2 g) (twice recrystallised from EtOAc), m.p. 122—123° (lit.,[30] 124—125°). De-ethoxycarbonylation as in the Y = Me series, with 2N-sodium hydroxide, gave the tetronic acid (9; X = Y = H) (4.8 g; 80% from acetonitrile), m.p. 140—141° (lit.,[30] m.p. 141°).

Improved Procedure for 3-Acetyl-4-hydroxy-5-methylfuran-2(5H)-one (11; X = Me).—The ester (10; R = Et, X = Me) [15,*] (8 g) was stirred under reflux with t-butyl alcohol (10 ml) and potassium t-butoxide (4.5 g) for 2 h. The cooled solution was acidified (6N-HCl), water was added (to dissolve KCl), and the acidified solution was extracted with ether and chloroform. The extracts were evaporated and the residue treated with ether and chilled to −78 °C to give the product (11; X = Me) * (5.9 g, 95%), m.p. 51—53° (from ether–hexane) (lit.,[15] 52—54°).

Thallium Salt (16) *of 4-Hydroxy-5-methylfuran-2(5H)-one* (15).—The tetronic acid (15) (114 mg) was stirred with benzene (2 ml), ethanol (0.5 ml), and thallium(I) ethoxide (0.07 ml, 0.25 g), for 15 min. The salt (16) was filtered off and washed with benzene and hexane; yield 296—317 mg (93—100%); m.p. 175—177°, $\nu_{max.}$ (Nujol) 1 670 cm^{-1}, and was used for the experiments below without further characterisation.

4-Benzoyloxy-5-methylfuran-2(5H)-one (17; R = Ph).—The thallium salt (16) (317 mg, 1 mmol), benzoyl chloride (140 mg), and benzene (20 ml) were refluxed for 2 h; the mixture was then cooled and the thallium chloride filtered off. The benzene solution was washed with saturated sodium hydrogen carbonate and water, dried, and evaporated to give the *product* (17; R = Ph) (204 mg, 94%), m.p. 115—116°, $\nu_{max.}$ (Nujol) 1 760, 1 740 (C=O), and 1 625 cm^{-1} (C=C); $\delta_H(CDCl_3)$ 1.61 (3 H, d, *J* 7 Hz, CH_3·CH·O), 5.14 (1 H, m, CH_3·C*H*·O), 6.27 (1 H, d, *J* 1.5 Hz, :CH), and 7.55—8.27 (5 H, m, Ph) (Found: C, 65.75; H, 4.55. $C_{12}H_{10}O_4$ requires C, 66.05; H, 4.2%), M^+ 218. Haynes [20] has claimed to have prepared this compound, but gives m.p. 39—43°.

4-Butyryloxyl-5-methylfuran-2(5H)-one (17; R = Pr).—The thallium salt (16) (296 mg), ether (5 ml), and butyryl chloride (0.1 ml) were stirred for 30 min. Thallium chloride was filtered off, and the ether solution was washed with saturated sodium hydrogen carbonate and water, dried, and evaporated to give the *product* (17; R = Pr) as a pale yellow oil (153 mg, 89%); $\nu_{max.}$ (film) 2 940 (C–H), 1 790, 1 760 (C=O), and 1 625 cm^{-1} (C=C); $\delta_H(CDCl_3)$ 1.02 (3 H, t, *J* 6 Hz, CH_3·CH_2), 1.47 (3 H, d, *J* 7 Hz, CH_3·CH·O), 1.77 (2 H, m, CH_2), 2.59 (2 H, t, *J* 6 Hz, CH_2·CH_2·CO), 4.97 (1 H, m, CH·O), and 6.00 (1 H, d, *J* 1.5 Hz, vinylic) (Found: C, 58.5; H, 6.5. $C_9H_{12}O_4$ requires C, 58.7; H, 6.55%).

2,5-Dihydro-2-methyl-5-oxo-3-furyl β-Methoxycarbonylpropionate (17; R = MeO_2C·CH_2·CH_2).—β-Methoxycarbonylpropionyl chloride (1.32 g) was treated as butyryl chloride above to give the *diester* (17; R = MeO_2C·CH_2·CH_2) (1.9 g, 99%), m.p. 40—41°; $\nu_{max.}$ (Nujol) 1 790, 1 755, 1 725 (C=O), and 1 625 cm^{-1} (C=C); $\delta_H(CDCl_3)$ 1.40 (3 H, d, *J* 7 Hz, CH_3), 2.72 (4 H, m, CH_2·CH_2), 3.70 (3 H, s, CH_3O), 4.95 (1 H, q, *J* 7 Hz, CH_3·C*H*·O), and 6.15 (1 H, d, *J* 1.5 Hz, vinylic) (Found: C, 52.45; H, 5.2. $C_{10}H_{12}O_6$ requires C, 52.65; H, 5.3%).

2,5-Dihydro-2-methyl-5-oxo-3-furyl 4-Bromohexanoate (17; R = EtCHBr·CH_2·CH_2).—4-Bromohexanoic acid * (23.9 g) and thionyl chloride (15 ml) were heated on a steam-bath for 1 h. The excess of reagent was removed, and the residue distilled to give the acid chloride (20.2 g, 73%), b.p. 111—114° at 34 mmHg, $\nu_{max.}$ 1 790 cm^{-1} (C=O), which was taken directly for the subsequent step without further characterisation. The acid chloride (1.26 g) was treated with the thallium salt (16) as for butyryl chloride to give the ester (17; R = EtCHBr·CH_2·CH_2) (yellow oil; 1.6 g, 92%), $\nu_{max.}$ (film) 1 780, 1 755 (C=O), and 1 625 cm^{-1} (C=C); δ_H ($CDCl_3$) 1.13 (3 H, t, *J* 7 Hz, CH_3·CH_2), 1.72—3.0 (6 H, m, alkyl chain), 4.05 (1 H, m, CH_2·C*H*Br·CH_2), 4.92 (1 H, q, *J* 7 Hz, CH_3·C*H*·O), and 6.04 (1 H, d, *J* 1.5 Hz, vinylic).

3-Butyryl-4-hydroxy-5-methylfuran-2(5H)-one (18; R = Pr).—(A) via *Fries rearrangement of the ester* (17; R = Pr). The ester (17; R = Pr) (153 mg), nitrobenzene (2 ml), and titanium tetrachloride (0.3 ml) were stirred and heated at 50 °C for 35 min. The mixture was then cooled to 0 °C and acidified (3M-HCl). The organic layer was separated and the aqueous phase extracted with ether and chloroform. The combined extracts were washed with water, and extracted with saturated sodium hydrogen carbonate; this solution was in turn extracted with ether (25 ml), acidified (conc. HCl), and extracted with chloroform. Evaporation of the chloroform solution gave a residue (85 mg), which was chromatographed on preparative silica gel plates (twice) in chloroform–acetic acid (9 : 1) to give the product (18; R = Pr) (45 mg, 29%) as pale yellow crystals, m.p. 58—60°.

(B) via *Direct acylation of γ-methyltetronic acid* (15). The tetronic acid (15) (114 mg), butyryl chloride (110 mg), nitrobenzene (5 ml), and titanium tetrachloride (0.3 ml) were stirred and heated at 50 °C for 2.5 h. The cooled solution was poured over ice and concentrated hydrochloric acid and the aqueous phase was extracted with chloroform. The acidic material was extracted with sodium hydrogen

[29] R. Anschutz and R. Böcker, *Annalen*, 1909, **368**, 53.
[30] E. Benary, *Ber.*, 1907, **40**, 1079.

carbonate, and this solution was washed with chloroform, acidified, and extracted with chloroform. This last extract was dried and evaporated to give the product (18; R = Pr) (130 mg, 72%), identical with the material from method (A).

3,4-*Dihydro*-8-*methylfuro*[3,4-b]*oxepin*-5,6(2H,8H)-*dione* [(RS)-*Carolic Acid* (2)].—(*A*). The thallium salt (16) was suspended in ether (50 ml), γ-bromobutyryl chloride (1.6 g) was added, and the solution was stirred at room temperature for 30 min. The thallium chloride was removed by filtration, and the ethereal solution was washed with water (2 × 20 ml) and saturated sodium hydrogen carbonate (2 × 20 ml), dried, and evaporated to give a liquid ester (2 g). The ester was dissolved in carbon disulphide (15 ml) and added dropwise to a refluxing solution of carbon disulphide (40 ml) and titanium tetrachloride (2 ml). The solution turned orange, and a viscous red oil separated. Refluxing was continued for 1 h. The solution was then cooled in ice and N-hydrochloric acid (40 ml) was added. The carbon disulphide layer was separated, and the aqueous phase was extracted with chloroform (3 × 50 ml). The organic extracts were combined and extracted with 2N-sodium hydroxide (2 × 50 ml). The basic extracts were washed with ether, acidified with concentrated hydrochloric acid, and extracted with chloroform (1 × 50 ml; 3 × 25 ml). The chloroform layer was extracted with saturated sodium hydrogen carbonate (5 ml), washed with water (10 ml), dried, and evaporated to give crude carolic acid (510 mg). Recrystallisation from ethanol gave (*RS*)-(2) (32 mg, 22%), m.p. 114—116° (lit.,[31] 113°), identical with the natural product in i.r. and n.m.r. spectra.

(*B*). The tetronic acid (*RS*)-(1) (114 mg, 1 mmol), γ-bromobutyryl chloride * (187 mg), nitrobenzene (5 ml), and titanium tetrachloride (0.3 ml) were stirred and heated at 50 °C for 2.5 h. After cooling, the solution was poured over ice and concentrated hydrochloric acid. The aqueous phase was extracted with chloroform. The chloroform was evaporated off and the residue stirred with 2N-sodium hydroxide (10 ml) at room temperature for 30 min. After acidification with 3M-hydrochloric acid, the solution was extracted with chloroform, which was back-extracted with saturated sodium hydrogen carbonate (2 ml), dried, and evaporated to leave crude carolic acid, (*RS*)-(3) (135 mg). Recrystallization from ethanol gave (*RS*)-(2) (97 mg, 53%), m.p. 114—116°, identical in i.r. and n.m.r. spectra with the natural material.

Repetition of the above procedure with the *R*-isomer (1) [derived degradatively [11] from natural carolic acid (2)] gave carolic acid (2) (117 mg) identical in i.r. and n.m.r. spectra with the natural material. For optical activity determination this material was chromatographed on silica gel plates (R_F 0.53 in acetone–hexane, 3 : 2); the product (80 mg) had m.p. 124—128° [129—130° when thrice recrystallised from ethanol (yield 15 mg)], $[\alpha]_D^{21}$ +81.90 (*c* 1.26) {lit.,[32] $[\alpha]_D^{20}$ +84.0° (*c* not given)}.

Dimethyl Malate.—A solution of (*RS*)-malic acid (27 g) in methanol (100 ml) was treated with gaseous hydrogen chloride until homogeneous and then stirred for 18 h. Removal of solvent and distillation gave (*RS*)-dimethyl malate * (2.38 g, 74%), b.p. 110—116° at 4.5 mmHg (lit.,[33] 116° at 11 mmHg).

Repetition with (*S*)-malic acid gave (*S*)-dimethyl malate (79%), b.p. 105—108° at 2.5 mmHg (lit.,[34] 90—92° at 2 mmHg), $[\alpha]_D^{21}$ −9.2° (*c* 1.31 in MeOH) {lit.,[34] $[\alpha]_D^{21}$ −8.9° (*c* 6.37 in MeOH)}.

Acetoacetate (10; R = Me, X = $MeO_2C{\cdot}CH_2$) *of* (RS)-*Dimethyl Malate*.—(*RS*)-Dimethyl malate (16.2 g), benzene (50 ml), and triethylamine (0.1 ml) were stirred and heated to reflux. Keten dimer (50 ml) was added dropwise, and stirring and refluxing were continued for 1 h. The benzene was removed under reduced pressure, and the residue passed through alumina (90 g) (ether as eluant) to yield the triester (10; R = Me, X = $MeO_2C{\cdot}CH_2$) (19.7 g, 80%). (Attempted distillation of this, even in high vacuum, yielded dimethyl fumarate as the only identified product.) Subsequent chromatography over alumina (90 g; ether as eluant) gave the product (10; R = Me, X = $MeO_2C{\cdot}CH_2$) (19.2 g, 78%); $\nu_{max.}$ (film) 3 485 (C–H) and 1 725 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 2.25 (3 H, s, MeCO), 2.90 (2 H, d, *J* 6 Hz, $CO{\cdot}CH_2{\cdot}CH$), 3.50 (2 H, s, $CO{\cdot}CH_2{\cdot}CO$), 3.67 (3 H, s, CH_3O), 3.72 (3 H, s, CH_3O), and 5.47 (1 H, t, *J* 6 Hz, $CH_2{\cdot}CH{\cdot}O$).

Because of its lability this material was not purified further but taken directly for the subsequent step. Repetition with (*S*)-dimethyl malate gave (10a; R = Me, X = $MeO_2C{\cdot}CH_2$), $[\alpha]_D^{21}$ 21.6° (*c* 1.45).

Methyl 4-*Acetyl*-2,5-*dihydro*-3-*hydroxy*-5-*oxofuran*-2-*acetate* (11; X = $MeO_2C{\cdot}CH_2$).—To the ester (10; R = Me, X = $MeO_2C{\cdot}CH_2$) (5.17 g) was added t-butyl alcohol (60 ml), by distillation directly from calcium hydride into the reaction vessel. The flask was cooled in ice and stirred under nitrogen. Potassium t-butoxide (25 g) was added rapidly in 2 g portions during 10—15 min. Stirring at 0 °C was continued for 1 h. The mixture was allowed to warm to room temperature and stirred for an additional 30 min, then warmed on a steam-bath for 20 min, cooled again to 0 °C, and acidified with 4N-hydrochloric acid (60 ml). Stirring was continued for 30 min, and the precipitate was filtered off and washed with ether (150 ml). The filtrate was shaken and the ether layer removed. The aqueous phase was then extracted with ether (2 × 150 ml). The ethereal extracts were then combined and dried. Solvents were removed at 25—30° under reduced pressure. The water aspirator was replaced with an oil pump to remove the last traces of solvent. This gave a viscous orange residue which was dissolved in ether (40 ml) and chilled to yield yellow crystals. More ether (50 ml) was added, and the solid was crushed, filtered off, powdered, and washed with ether to give the *ester* (11; X = $MeO_2C{\cdot}CH_2$) (16.6 g, 39%), m.p. 54—55°. Sublimation at 50 °C and 2 × 10^{-3} mmHg gave material of m.p. 58—58.5°; $\nu_{max.}$ (Nujol) 1 750, 1 725 (C=O), 1 665, and 1 615 cm^{-1} (C=C); $\delta_H(CDCl_3)$ 2.38 (3 H, s, $CH_3{\cdot}CO$), 2.72—2.80 (2 H, m, $CO{\cdot}CH_2{\cdot}CH$), 3.60 (3 H, s, CH_2O), and 4.57—4.75 (1 H, m, $CH_2{\cdot}CH{\cdot}O$) (in this and some of the following spectra, multiplicities of the $CH_2{\cdot}CH{\cdot}O$ and $CH_2{\cdot}CH{\cdot}O$ signals are increased owing to restricted rotation) (Found: C, 50.1; H, 4.75. $C_9H_{10}O_6$ requires C, 50.05; H, 4.65%). Repetition with (10a; R = Me, X = $MeO_2C{\cdot}CH_2$) gave (11a; X = $MeO_2C{\cdot}CH_2$), m.p. 86—87°, $[\alpha]_D^{21}$ −54.4° (*c* 1.21).

Methyl 4-*Bromoacetyl*-2,5-*dihydro*-3-*hydroxy*-5-*oxofuran*-2-*acetate* (12; X = $MeO_2C{\cdot}CH_2$, W = $CO{\cdot}CH_2Br$).—To a solution of the ester (11; X = $MeO_2C{\cdot}CH_2$) (2.14 g) in acetic acid (5 ml) at 40 °C was added bromine in acetic acid (1M;

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[32] P. W. Clutterbuck, W. N. Haworth, H. Raistrick, G. Smith, and M. Stacey, *Biochem. J.*, 1934, **28**, 94.

[33] H. Havekoss, O. Bayer, and H. Wolz, Ger. P. 738,922/1943 (*Chem. Abs.*, 1945, **39**, 308[7]).

[34] H. Arakawa, *Naturwiss.*, 1963, **50**, 441 (*Chem. Abs.*, 1963, **59**, 7419e).

10 ml) over 1 h. The acetic acid was evaporated off (25 °C; 2.5 mmHg) to leave a viscous oil which crystallised when triturated with ether. Filtration gave the product (12; X = $MeO_2C{\cdot}CH_2$, W = $CO{\cdot}CH_2Br$) [1.7 g from ethyl acetate–hexane (twice recrystallized)], m.p. 95.5—97.5°; $\nu_{max.}$ (Nujol) 1 740 (C=O), 1 665, and 1 610 cm^{-1} (C=C); $\delta_H[(CD_3)_2CO]$ 3.02 (2 H, m, $CO{\cdot}CH_2{\cdot}CH{\cdot}O$), 3.67 (3 H, s, CH_3O), 4.57 (2 H, s, $CO{\cdot}CH_2Br$), 4.90 (1 H, s, enol), and 5.24 (1 H, m, $CH_2{\cdot}CH{\cdot}O$).

Methyl 4-Bromo-2,5-dihydro-3-hydroxy-5-oxofuran-2-acetate (12; X = $MeO_2C{\cdot}CH_2$, W = Br).—To a solution of the ester (11; X = $MeO_2C{\cdot}CH_2$) (2.14 g) in acetic acid (5 ml) at 40 °C was added bromine in acetic acid (1M; 10 ml) over 1 h. Water (10 ml) was added, followed by a second portion of the bromine solution (1M; 10 ml) at room temperature. Solvents were removed at 25—30 °C and 2.5 mmHg to give a white solid, which was triturated with ether (20 ml), broken up, and filtered off. The precipitate was further powdered in the funnel and washed with ether (50 ml) and hexane (20 ml). This gave *compound* (12; X = $MeO_2C{\cdot}CH_2$, W = Br) (1.14 g). Concentration of the washings gave an additional 0.63 g. This was recrystallised from ethyl acetate–hexane; yield 1.35 g (54%), m.p. 114—116°. Sublimation at 96 °C and 1.5×10^{-3} mmHg gave material of m.p. 115—117°; $\nu_{max.}$ (Nujol) 2 590 (O–H), 1 730, 1 720 (C=O), and 1 655 cm^{-1} (C=C); $\delta_H[(CD_3)_2SO]$ 2.44—3.24 (2 H, m, $CO{\cdot}CH_2{\cdot}CH{\cdot}O$), 3.60 (3 H, s, CH_3O), 5.10—5.32 (1 H, m, $CH_2{\cdot}CH{\cdot}O$), and 7.42br (1 H, s, enol) (Found: C, 33.35; H, 2.75; Br, 31.6. $C_7H_7BrO_5$ requires C, 33.45; H, 2.8; Br, 31.85%). Repetition with (11a; X = $MeO_2C{\cdot}CH_2$) gave (12a; X = $MeO_2C{\cdot}CH_2$, W = Br), m.p. 119—121°.

Methyl 2,5-Dihydro-3-hydroxy-5-oxofuran-2-acetate (12; X = $MeO_2C{\cdot}CH_2$, W = H).—Compound (12; X = $MeO_2C{\cdot}CH_2$, W = Br) (100 mg) dissolved in 50% aqueous acetic acid (8 ml) containing 10% palladium–carbon (20 mg) was hydrogenated at room temperature and atmospheric pressure. The catalyst was removed and the filtrate extracted with ether (3 × 10 ml). The extracts were dried and evaporated to a white solid. Recrystallization from toluene gave the product (12; X = $MeO_2C{\cdot}CH_2$, W = H) (45 mg, 26%), m.p. 112—114° (lit.,[35] 116—118°); $\nu_{max.}$ (Nujol) 2 690 (O–H), 1 740, 1 695 (C=O), and 1 640 cm^{-1} (C=C); $\delta_H[CDCl_3–5\%\ (CD_3)_2SO]$ 2.46—3.31 (2 H, m, $CO{\cdot}CH_2{\cdot}CH{\cdot}O$), 3.72 (3 H, s, CH_3O), 4.99 (1 H, s, vinylic), and 5.10 (1 H, m, $CH_2{\cdot}CH{\cdot}O$). Repetition with (12a; X = $MeO_2C{\cdot}CH_2$, W = Br) gave (12a; X = $MeO_2C{\cdot}CH_2$, W = H), m.p. 116—117°.

4-Acetyl-2,5-dihydro-3-hydroxy-5-oxofuran-2-acetic Acid (11; X = $HO_2C{\cdot}CH_2$).—The ester (11; X = $MeO_2C{\cdot}CH_2$) (462 mg) was dissolved in 6N-sodium hydroxide (1 ml) and stirred at room temperature for 36 h. The resulting yellow solution was poured over ice (2 g) and concentrated sulphuric acid (0.5 ml). This solution was then continuously extracted with ether for 18 h. The extract was dried and evaporated, and the residue recrystallised from ethyl acetate–hexane (2 ×) to give the *acid* (11; X = $HO_2C{\cdot}CH_2$) (260 mg), m.p. 174—176°. Sublimation at 140 °C and 3.5×10^{-3} mmHg raised the m.p. to 177—178°; $\nu_{max.}$ (Nujol) 3 355 (O–H), 1 755, 1 695 (C=O), 1 670, and 1 615 cm^{-1} (C=C); $\delta_H[(CD_3)_2CO]$ 2.49 (3 H, s, $CH_3{\cdot}CO$), 2.90—3.17 (2 H, m, $CO{\cdot}CH_2{\cdot}CH{\cdot}O$), 5.05 (1 H, t, *J* 5 Hz, $CH_2{\cdot}CH{\cdot}O$), 7.92 (1 H, s, CO_2H), and 10.3 (1 H, s, enol) (Found: C, 47.8; H, 4.25. $C_8H_8O_6$ requires C, 48.0; H, 4.05%). Repetition with (11a; X = $MeO_2C{\cdot}CH_2$) gave (11a; X = $HO_2C{\cdot}CH_2$), m.p. 182—184°, $[\alpha]_D^{21}$ −10.3° (*c* 1.93).

4-Bromo-2,5-dihydro-3-hydroxy-5-oxofuran-2-acetic Acid (12; X = $HO_2C{\cdot}CH_2$, W = Br).—The acid (11; X = $HO_2C{\cdot}CH_2$) (65 mg) was dissolved in 50% acetic acid (1 ml). Bromine (106 mg) in 50% acetic acid (1 ml) was added. The solution was swirled and set aside for 5 min, then evaporated to dryness at 25—30 °C and 2 mmHg. The residue was sublimed at 120 °C and 5×10^{-3} mmHg to give the product (12; X = $HO_2C{\cdot}CH_2$, W = Br) (42 mg, 53%), m.p. 198—199°; $\nu_{max.}$ (Nujol) 2 680 (O–H), 1 720, 1 700 (C=O), and 1 655 cm^{-1} (C=C); $\delta_H[(CD_3)_2SO]$ 2.52—3.29 (2 H, m, $CH_2{\cdot}CH{\cdot}O$), 5.18—5.37 (1 H, m, $CH_2{\cdot}CH{\cdot}O$), 9.60br (2 H, s, CO_2H plus enol OH) (Found: C, 31.05; H, 2.4; Br, 33.7. Calc. for $C_6H_5BrO_5$: C, 30.4; H, 2.1; Br, 33.75%). Repetition with (11a; X = $HO_2C{\cdot}CH_2$) gave (12a; X = $HO_2C{\cdot}CH_2$, W = Br), m.p. 190—192°, $[\alpha]_D^{21}$ −107.4° (*c* 2.15) {lit.,[28] m.p. 194°; $[\alpha]_D$ −117° (*c* not given)}.

2,5-Dihydro-3-hydroxy-5-oxofuran-2-acetic Acid (12; X = $HO_2C{\cdot}CH_2$, W = H) [(RS)-(5)].—Compound (12; X = $HO_2C{\cdot}CH_2$, W = Br) (200 mg) was dissolved in 2N-sodium hydroxide (5 ml) and shaken in hydrogen over 5% palladium–carbon (25 mg). After reduction was complete, the catalyst was removed and the filtrate acidified with dilute sulphuric acid and extracted with ether (5 × 5 ml). The extract was dried and evaporated to give material (130 mg) which on recrystallisation from ethyl acetate–hexane afforded the acid (*RS*)-(5) (116 mg, 88%), m.p. 185—187°; $\nu_{max.}$ (Nujol) 2 665 (O–H), 1 725, 1 695 (C=O), and 1 620 cm^{-1} (C=C); $\delta_H[(CD_3)_2CO]$ 2.38—3.30 (2 H, m, $CO{\cdot}CH_2{\cdot}CH{\cdot}O$), 4.98 (1 H, s, vinylic), 5.18—5.37 (1 H, m, $CH_2{\cdot}CH{\cdot}O$), and 10.28br (2 H, s, CO_2H plus enol OH) (Found: C, 45.6; H, 4.05. Calc. for $C_6H_6O_5$: C, 45.6; H, 4.0%). Repetition with (12a; X = $HO_2C{\cdot}CH_2$, W = Br) gave (12a; X = $HO_2C{\cdot}CH_2$, W = H) [*i.e.* (5)], m.p. 180—181°, $[\alpha]_D^{21}$ −41.6° (*c* 1.86) {lit.,[28] m.p. 182°; $[\alpha]_D$ −52° (*c* not given)}.

4-Butyryl-2,5-dihydro-3-hydroxy-5-oxofuran-2-acetic Acid [(RS)-*Carlosic Acid*, (RS)-(3)].—To the ester (12; X = $MeO_2C{\cdot}CH_2$, W = H) (180 mg) and butyryl chloride (110 mg) in nitrobenzene (5 ml), was added titanium tetrachloride (0.3 ml). The solution was stirred and heated at 50 °C for 2.5 h, then cooled and poured over ice and hydrochloric acid. The mixture was extracted with chloroform, which in turn was extracted with saturated sodium hydrogen carbonate. Acidification of the aqueous extract followed by extraction with chloroform gave the crude ester (193 mg), which was dissolved in chloroform and passed through a silica gel column (1 × 10 cm) (chloroform as eluant) to afford a pale yellow oil (151 mg). This was dissolved in 5N-sodium hydroxide (15 ml); the solution was swirled for 30 min, cooled in ice, and acidified. Extraction of the aqueous solution with ether gave (*RS*)-carlosic acid [(*RS*)-(3)] (135 mg, 59%), m.p. 169—172°. Recrystallisation from ethyl acetate (2 ×) raised the m.p. to 178—179°. I.r., n.m.r., and t.l.c. properties were identical with those of natural carlosic acid. Repetition with (12a; X = $MeO_2C{\cdot}CH_2$, W = H) gave (*S*)-carlosic acid (3), m.p. 174—176° [17] {lit.,[28] m.p. 181°, $[\alpha]_D^{21}$ −137° (*c* 1.21); lit.,[28] $[\alpha]_D$ −160° (*c* 0.21)}.

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