Dioxolanones as Synthetic Intermediates. Part 4.† Biomimetic Synthesis of Multicolanic Acid

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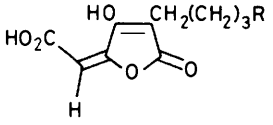
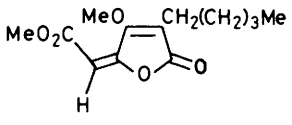
Regiospecific cyclisation of the intermediate formed by reaction of the dioxolanone (**9**) with methyl α-lithioheptanoate gave (*Z*)-t-butyl multicolanate (**13**) in 53% yield. Photochemical stereomutation of (**13**) gave (*E*)-t-butyl multicolanate (**16**) which was converted by trifluoroacetic acid into (*E*)-multicolanic acid (**3**), a metabolite of *P. multicolor*. In the same way, reaction of (**9**) with methyl α-lithiophenylacetate and, if desired, subsequent photochemical irradiation, provided (*Z*)- and (*E*)-4-carboxymethylene-2-phenyltetronic acids (**21**) and (**23**).

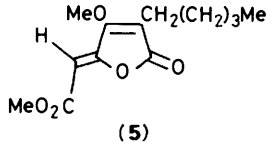
In 1974, Holker and co-workers reported the isolation and structure elucidation of multicolic (**1**) and multicolosic (**2**) acids from *Penicillium multicolor*.[1] The isolation of multicolanic acid (**3**), as methyl-*O*-methylmulticolanate (**4**), was later reported.[2] The (*E*)-geometry at the exocyclic double bond in all three metabolites was demonstrated by spectral studies, the synthesis of methyl (*E*)- and (*Z*)-*O*-methylmulticolanates (**4**) and (**5**)[3] and



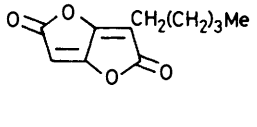
(**1**) R = CH_2OH
(**2**) R = CO_2H
(**3**) R = Me



(**4**)



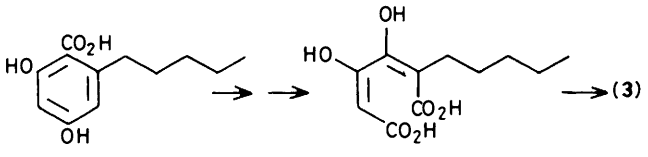
(**5**)



(**6**)

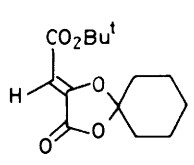
the observation that synthetic multicolanic acid could be converted into the bis-lactone (**6**) which can only arise from the (*E*)-isomer (**3**).[4]

Holker also demonstrated the intermediacy of the acetate-derived 6-pentylresorcylic acid (**7**) in the biosynthesis of these metabolites in *P. multicolor* and proposed that oxidative fission of (**7**) would lead to the di-acid (**8**) which could then cyclise to multicolanic acid (**3**) (Scheme 1).[2] It was suggested that oxidation of the pentyl side-chain to give multicolic (**1**) and multicolosic (**2**) acids occurred late in the biosynthetic sequence.[2] The strategy adopted by us for the synthesis of multicolanic acid (**3**) depended on this proposed biosynthetic pathway, particularly with reference to the intermediate (**8**) which bears a striking resemblance to the postulated intermediates in the biosynthesis of pulvinic acids.[5] It is interesting that the latter series of natural products are derived from aromatic α-amino acids whereas multicolanic acid (**3**) utilises the acetate pathway.[5]

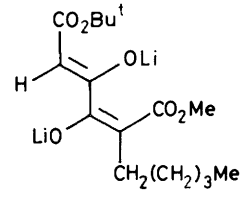


(**7**) (**8**)

Scheme 1.



(**9**)



(**10**)

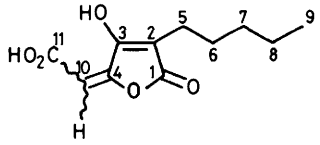
Our previous work with dioxolanones as synthetic intermediates suggested that attack of methyl α-lithioheptanoate on the dioxolanone (**9**) would provide the intermediate (**10**) which is directly analogous to the proposed biosynthetic intermediate (**8**) and which would be expected to cyclise regiospecifically at the methoxycarbonyl group.[6] The Wittig reaction between anhydrous t-butyl glyoxylate and the previously reported phosphorane (**12**)[7] in toluene led to formation of the (*Z*)-dioxolanone (**9**) in 56% yield after distillation. The u.v. spectrum of (**9**) which exhibited a maximum at 259 nm (ε 11 200) is analogous to the u.v. spectrum of the (*Z*)-dioxolanone (**11**) ($\lambda_{max.}$ 269, ε 11 000) of known geometrical configuration.[6] In this latter example the phenyl ring would be expected to play a minor role in determining the position of the u.v. maximum since it is twisted out of the plane of conjugation. Treatment of (**9**) with methyl α-lithioheptanoate (2.2 equiv.) in tetrahydrofuran (THF) gave, as a result of regiospecific cyclisation of the intermediate (**10**), t-butyl (*Z*)-multicolanate (**13**) as a colourless solid in 54% yield after purification. The (*Z*)-geometry at the exocyclic double bond was assigned on the basis of the spectral properties of the ester (**13**). The chemical shift (δ 5.61) of the vinylic proton resonance was very similar to that observed[3] for the corresponding proton (δ 5.63) in methyl (*Z*)-*O*-methylmulticolanate (**5**), whereas the resonance of the more deshielded vinylic proton in the (*E*)-ester (**4**) is observed at δ 5.83. The hydroxy proton of (**13**) is seen as a broad singlet centred about δ 8.9; this is comparable with the broad hydroxy resonance previously reported for the (*Z*)-t-butyl ester (**14**), and different from the sharp singlet seen at

† Part 3, preceding paper.

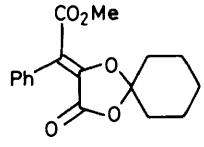
Table. ^{13}C N.m.r. data for (*E*)- and (*Z*)-multicolanic acids, the t-butyl esters, and permethylated derivatives

Atom	(13)[a]	(16)[a]	(17)[b]	(3)[b]	(5)[b]	(5)[c]	(4)[c]	(4)[d]	Mult
1	170.3	170.0	169.0	172.6	169.3	169.0	168.7	168.6	s
11	164.7	168.0	164.6	167.8	163.6	164.0	164.4	164.3	s
3	162.3	161.2	162.1	161.7	162.1	161.6	161.1	160.9	s
4	152.6	158.0	153.4	159.5	153.1	152.3	150.9	150.7	s
2	106.8	108.0	106.7	107.8	107.3	107.3	110.6	110.4	s
10	96.7	101.8	94.5	100.2	94.4	95.0	101.1	101.0	d
8	31.3	31.1	31.5	31.4	31.6	31.6	31.6	31.6	t
6	27.3	26.6	27.5	26.9	29.8	29.9	29.7	29.7	t
7	22.2	21.9	22.3	22.3	23.2	23.4	23.5	23.5	t
5	21.3	20.7	21.4	21.4	22.4	22.3	22.3	22.4	t
9	13.7	13.5	13.5	13.5	13.6	13.9	13.9	13.9	q
12[e]	82.7s	84.7s			59.7q		59.7q		
13[e]	27.9	27.5			51.2		52.1		q

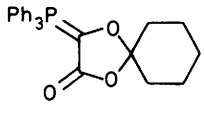
[a] In $CDCl_3$; shifts relative to $^{13}CDCl_3$ at 76.9. [b] In $(CD_3)_2CO$; shifts relative to $(^{13}CD_3)_2CO$ septet at 29.2. [c] Values for product quoted in ref. 3. [d] Values for naturally derived product quoted in ref. 3. [e] In structures (**13**) and (**16**) atoms 12 and 13 relate to the t-butyl carbon atoms whereas in structures (**4**) and (**5**) atoms 12 and 13 are the two methyl carbon atoms of the ester and enol ether functions respectively.



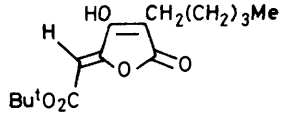
δ 14.13 for the (*E*)-t-butyl ester (**15**).[6] These hydroxy proton resonances show the chemical shift and peak width differences expected for inter- and intra-molecular hydrogen bonded systems. U.v. irradiation of a solution of the (*Z*)-ester (**13**) in ethanol for 12 h gave 76% conversion into t-butyl (*E*)-multicolanate (**16**) which was separated from the remaining (**13**) by differential solubility in light petroleum. The progress of the stereomutation could be monitored by u.v. spectroscopy since a reproducible absorption at 313 nm for the (*E*)-ester (**16**) replaced the variable absorption at 305—352 nm of the (*Z*)-ester (**13**). The vinylic proton of the (*E*)-ester (**16**) resonated at δ 5.86 and the hydroxy proton was seen as a sharp singlet (δ 12.81); these observations confirm the (*E*)-stereochemistry at the exocyclic double bond.



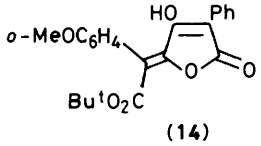
(**11**)



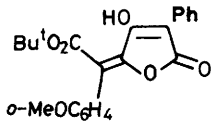
(**12**)



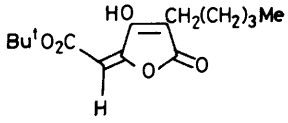
(**13**)



(**14**)

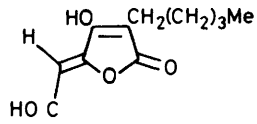


(**15**)

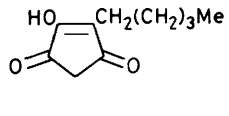


(**16**)

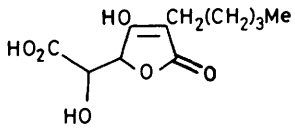
The (*Z*)- and (*E*)-t-butyl esters, (**13**) and (**16**), were efficiently converted into the corresponding (*Z*)- and (*E*)-multicolanic acids (**17**) and (**3**) by anhydrous trifluoroacetic acid (TFA) with complete retention of stereochemistry at the exocyclic double bond in each case. The ^1H n.m.r. spectrum of (*Z*)-multicolanic acid (**17**) in $(CD_3)_2SO$ showed the vinylic proton resonance at δ 5.65 and a broad singlet (δ 3.0—5.0) for the two hydroxy protons. Attempted recrystallisation of (**17**) from water led to near quantitative formation of the trione (**18**) which has been previously reported[4] as a by-product in the preparation of multicolanic acid (**3**) *via* dehydration of the intermediate tetronic acid (**19**). The (*E*)-acid (**3**) was identical in all respects with an authentic sample of multicolanic acid. Methylation of (*Z*)-multicolanic acid (**17**) using ethereal diazomethane gave



(**17**)



(**18**)



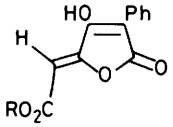
(**19**)

methyl (*Z*)-*O*-methylmulticolanate (**5**) which showed the reported spectral characteristics.[3] Diazomethane treatment of (*E*)-multicolanic acid (**3**) gave methyl (*E*)-*O*-methylmulticolanate (**4**) as a colourless oil which had spectral properties identical with those previously reported.[3] It was observed that, with time, the (*E*)-isomer (**4**) underwent partial rearrangement to the (*Z*)-isomer (**5**) at room temperature: this rearrangement has been noted previously.[2]

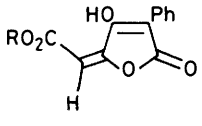
It is noteworthy that the ^{13}C resonances of C-4 and C-10 of compounds (**3**), (**4**), (**13**), (**16**), and (**17**) have chemical shifts

dependent on the geometry of the exocyclic double bond (see Table) consistent with the conclusions drawn from the ^{1}H n.m.r. spectra.

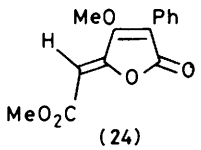
By a similar series of reactions the dioxolanone (**9**) has been used to prepare 4-carboxymethylene-2-phenyltetronic acids, a series of compounds which are structurally similar to pulvinic acids[5] but which lack the extra phenyl ring on the exocyclic double bond. The dioxolanone (**9**) was treated with methyl α-lithiophenylacetate (3 equiv.) in THF at −78 °C and the mixture was allowed to attain room temperature before dilution with water. The aqueous layer was washed with ether and carefully acidified with sulphuric acid. Chromatography of the crude material isolated by extraction of the aqueous layer gave a moderate (22%) yield of the (*Z*)-t-butyl ester (**20**) which showed the ^{1}H n.m.r. vinylic proton resonance at δ 5.77. The unexpected isolation of the (*Z*)-acid (**21**) from this reaction indicated that the ester (**20**) was unstable to the acidic conditions used in the work-up.



(**20**) R = Bu^t
(**21**) R = H



(**22**) R = Bu^t
(**23**) R = H



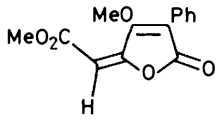
(**24**)

U.v. irradiation of the (*Z*)-ester (**20**) in ethanol for 6.5 h gave efficient conversion to the (*E*)-t-butyl ester (**22**). However, when the reaction was scaled up, substantial quantities of the (*Z*)-ester (**20**) were recovered, and partial deprotection to the (*Z*)-acid (**21**) also occurred. The vinylic proton of the (*E*)-ester (**22**) was observed at δ 5.92 in the ^{1}H n.m.r. spectrum and the strongly intramolecularly bound hydroxy proton was seen as a sharp singlet at δ 13.67.

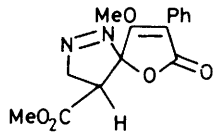
Treatment of the (*Z*)- and (*E*)-t-butyl esters (**20**) and (**22**) with anhydrous TFA gave high yields of the corresponding (*Z*)- and (*E*)-acids (**21**) and (**23**) with complete retention of stereochemistry at the exocyclic double bond in both cases. The vinylic proton resonance in the (*Z*)-acid (**21**) was observed at δ 5.92; that in the (*E*)-acid at δ 6.08. The (*E*)-acid (**23**) also showed the usual low field (δ 13.24) sharp singlet for the intramolecularly hydrogen bonded hydroxy proton.

Treatment of the (*Z*)-acid (**21**) with an excess of diazomethane gave the expected (*Z*)-dimethyl derivative (**24**). However, reaction of the (*E*)-acid (**23**) under the same conditions gave a mixture (*ca.* 1:1) of the (*E*)-dimethyl derivative (**25**) and a by-product which we believe to be the Δ^1-pyrazoline (**26**). Preparative chromatography failed to separate (**25**) from the pyrazoline (**26**). Examination of the material isolated from the column showed partial rearrangement of (**25**) to its (*Z*)-isomer (**24**). This rearrangement is analogous to that reported above for the 2-n-pentyltetronates (**4**) and (**5**).

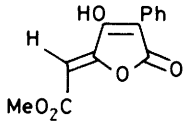
In another synthesis of 4-ylidenetetronic acids the structure (**27**) has been assigned to the product from cyclisation of (**28**).[8] Comparison of spectral data of (**20**) and (**22**) with those reported for (**27**) suggest that the structure (**27**) has been misassigned. Furthermore, methylation of a sample of purported (**27**), kindly supplied by Dr. Weinstock, gave a product which was different from both (**24**) and (**25**). We suggest that an alternative structure for the product from cyclisation of (**28**) is the pyrone (**29**).



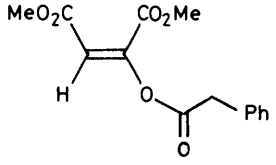
(**25**)



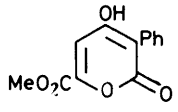
(**26**)



(**27**)



(**28**)



(**29**)

Experimental

I.r. spectra, calibrated against polystyrene film at 1 603 cm^{-1}, were recorded on a Perkin-Elmer 197 spectrophotometer. 60 MHz ^{1}H N.m.r. spectra were recorded on Perkin-Elmer R12 and R20A spectrometers, 80 MHz on a Bruker WP80, 90 MHz on a Perkin-Elmer R32, 220 MHz on a Perkin-Elmer R34 and 300 MHz on a Varian SC300 spectrometer; chemical shifts are relative to internal $SiMe_4$ at 0.00 p.p.m. ^{13}C N.m.r. spectra were recorded at 21.1 MHz on a Bruker WP80; chemical shifts are relative to $^{13}CDCl_3$ at 76.9 p.p.m. or $(^{13}CD_3)_2CO$ at 29.2 p.p.m. U.v. spectra were recorded on a Varian Cary 118X or Pye Unicam SP8-100 spectrophotometer. Mass spectra were recorded on A.E.I. MS 902 and Kratos MS 45 spectrometers with an ionisation potential of 70 eV. Microanalyses were made on a Perkin-Elmer 240 Elemental Analyser. Melting points were determined on a Buchi 510 and are uncorrected as are boiling points. T.l.c. was carried out on Eastman Chromogram Sheet 6060 and examined by u.v. light at 254 and 366 nm or by staining in iodine vapour. Preparative chromatography was performed on silica gel 60 (70—230 mesh ASTM) (Merck). Photochemical irradiation was carried out in an Hanovia 300 ml photochemical reactor. Unless stated otherwise all reactions were carried out at room temperature (18—24 °C). Commercially available solvents were dried by standard procedures and distilled prior to use. Tetrahydrofuran (THF) was distilled from potassium benzophenone ketyl immediately before use. Petroleum refers to the fraction boiling in the range 40—60 °C. Nitrogen was purified by passing it successively through Fieser's solution, saturated aqueous lead(II) acetate, concentrated sulphuric acid, and potassium hydroxide pellets.

(*Z*)-*5′-t-Butoxycarbonylmethylenecyclohexanespiro-2′-(1′,3′-dioxolan)-4′-one* (**9**).—A freshly prepared solution of anhydrous t-butyl glyoxylate (9.13 g, 61.6 mmol) in benzene (80 ml), obtained by azeotropic distillation of a benzene solution of the

monohydrate,[9] was added over 0.5 h to the phosphorane (**12**)[5] (61.6 mmol) in toluene (300 ml). The mixture was stirred for 1 h, cooled to ambient temperature, and filtered. The residue was washed with toluene (2 × 50 ml) and the combined washings and filtrate were evaporated under reduced pressure to afford an *oil which* was shaken with ether (300 ml). The solid triphenylphosphine oxide so formed was filtered off and washed with ether (2 × 50 ml). Evaporation of the combined filtrate and washings under reduced pressure yielded an orange oil which was extracted with boiling petroleum (4 × 100 ml). The combined extracts were evaporated under reduced pressure and the residue chromatographed on silica gel (300 g) with $CHCl_3$ as eluant. The fractions containing the product were combined, evaporated under reduced pressure, and distilled to yield cyclohexanespiro-2′-(1′,3′-dioxolan)-4′-one (2.93 g, 30%), b.p. 106—108 °C (16 mmHg) and the t-butyl ester (**9**) (9.3 g, 56%), b.p. 121.5—122.5 °C (0.03 mmHg) which solidified with time, m.p. 58—61 °C. Recrystallisation from methanol–water at 0 °C provided colourless prisms of (Z)-*5′-t-butoxycarbonylmethylenecyclohexanespiro-2′-(1′,3′-dioxolan)-4′-one* (**9**), m.p. 64.5—65.5 °C (Found: C, 62.4; H, 7.8. $C_{14}H_{20}O_5$ requires C, 62.7; H, 7.5%); $\lambda_{max.}$(EtOH) 258 nm (ε 11 200); $\nu_{max.}$(film) 3 070w, 2 988m, 2 946m, 2 872m, 1 808s, 1 724s, and 1 672m cm^{-1}; $\nu_{max.}$(Nujol) 3 062w, 1806s, 1 724s, 1 676m, and 1 136s cm^{-1}; $\nu_{max.}$(CCl_4) 2 980m, 2 945m, 2 870w, 1 808s, 1 718s, and 1 662 cm^{-1}; δ_H($CDCl_3$) 1.47 (9 H, s, Bu^t), 1.58—1.81 [10 H, m, $(CH_2)_5$], and 5.71 (1 H, s, =CH); δ(^{13}C) ($CDCl_3$) 22.2, 23.5, 27.4, 35.7, 81.2, 103.0, 111.7, 145.2, 158.0, and 162.4; *m/z* 268 (M^+, 0.1%).

(Z)-3-*n-Pentyl-5-t-butoxycarbonylmethylenefuran*-2,4-(3H,5H)-*dione* [2-*n-Pentyl*-(Z)-4-*t-butoxycarbonylmethylene-tetronic Acid*; *t-Butyl* (Z)-*Multicolanate*] (**13**).—Lithium diisopropylamide (LDA) was prepared under nitrogen by the addition of n-butyl-lithium (111 mmol) in n-hexane (55 ml) to di-isopropylamine (11.22 g, 111 mmol) in THF (120 ml) at −78 °C. After 20 min a solution of methyl heptanoate (16.0 g, 111 mmol) in THF (120 ml) was added followed 20 min later by a solution of the dioxolanone (**9**) (13.4 g, 49.8 mmol) in THF (50 ml). The mixture was allowed to warm to room temperature, left for 16 h, and then heated to reflux for 3 h. After cooling the volatiles were removed by evaporation under reduced pressure and the residue was shaken with water (750 ml), washed with ether (2 × 200 ml), and cooled to 0 °C. Careful acidification (to moist litmus paper) with concentrated H_2SO_4 and extraction with ethyl acetate (2 × 300 ml), washing of the extracts with brine (2 × 150 ml), drying (Na_2SO_4), and evaporation of the solvent under reduced pressure yielded a viscous, orange oil. This was chromatographed on silica gel (200 g) with $CHCl_3$ as eluant and triturated with petroleum (50 ml; b.p. 60—80 °C) to afford a colourless solid (7.6 g, 54%). Recrystallisation ($CHCl_3$–petroleum, *ca.* 1:10) provided colourless needles of the *dione* (**13**) (7.48 g, 53%), m.p. 104—105 °C [decomp., eliminates 2-methylpropene to form (Z)-multicolanic acid (**17**), m.p. and mixed m.p. 174—175.5 °C] (Found: C, 64.0; H, 8.0. $C_{15}H_{22}O_5$ requires C, 63.8; H, 7.85%); $\lambda_{max.}$(EtOH) 262 (ε 17 450) and *ca.* 305infl. (7 400)–352 (6 000) (isosbestic point at 320 nm); $\lambda_{max.}$(EtOH + 1 drop 2M NaOH) 261 (ε 18 950) and 353 nm (6 350); $\nu_{max.}$(Nujol) 3 085br, 1 795s, 1 690s, 1 680m, 1 670m, 1 658s, and 1 642s cm^{-1}; $\nu_{max.}$($CHCl_3$) 3 080br, 1 790s, 1 692s, and 1 642s cm^{-1}; δ_H($CDCl_3$) 0.87 (3 H, t, *J* 6.5 Hz, CH_3), 1.1—1.6 [6 H, m, $(CH_2)_3$], 1.53 (9 H, s, Bu^t), 2.33 (2 H, t, *J* 7.5 Hz, $=CCH_2$), 5.61 (1 H, s, =CH), and 7.8—9.9 (1 H, br s, exchanges with D_2O); *m/z* 282 (M^+, 0.1%).

(E)-3-*n-Pentyl-5-t-butoxycarbonylmethylenefuran*-2,4-(3H,5H)-*dione* [2-*n-Pentyl*-4-*t-butoxycarbonylmethylene-tetronic Acid; t-Butyl* (E)-*Multicolanate*)] (**16**).—A deoxygenated solution of the (Z)-t-butyl ester (**13**) (826 mg, 2.92 mmol) in ethanol (250 ml) was irradiated in a Pyrex apparatus using a 125 W medium-pressure mercury lamp for 12 h. Samples were withdrawn periodically and examined by u.v. spectroscopy to follow the progress of the stereomutation. The solvent was evaporated under reduced pressure to afford a viscous oil (828 mg) which was triturated with light petroleum (15 ml) and left overnight at −10 °C. The insoluble, unchanged (Z)-ester (**13**) was filtered off and washed with petroleum. The combined filtrate and washings were evaporated under reduced pressure to yield the *ester* (**16**) (612 mg, 74%) as a pale yellow oil (Found: C, 63.5; H, 8.1. $C_{15}H_{22}O_5$ requires C, 63.8; H, 7.85%); $\lambda_{max.}$(EtOH) 261 (ε 15 600) and 313 nm (6 350); $\lambda_{max.}$ (EtOH + 1 drop 2M-NaOH) 258 (ε 16 250) and 348 nm (4 900); $\nu_{max.}$ (neat or in CH_2Cl_2) 2 958s, 2 935s, 2 870m, 2 858m, 2 700w, 2 650w, 1 794s (or 1 784s in CH_2Cl_2), 1 692s, and 1 642s cm^{-1}; δ_H($CDCl_3$) 0.89 (3 H, t, *J* 6.5 Hz, CH_3), 1.2—1.6 [6 H, m, $(CH_2)_3$], 1.54 (9 H, s, Bu^t), 2.32 (2 H, t, *J* 7.5 Hz, $=CCH_2$), 5.86 (1 H, s, =CH), and 12.76 (1 H, s, exchanges with D_2O); *m/z* 282 (M^+, 1%). The (E)-ester (**16**) could not be purified by chromatography since this led to regeneration of the (Z)-ester (**13**) in high yield.

(Z)-3-*Phenyl-5-t-butoxycarbonylmethylenefuran*-2,4-(3H,5H)-*dione* [(Z)-*Phenyl*-4-*t-butoxycarbonylmethylene-tetronic Acid*] (**20**). A solution of LDA prepared from n-butyl-lithium (100 mmol) in hexane (50 ml) and di-isopropylamine (10.12 g, 100 mmol) in THF (120 ml) at −78 °C was treated with methyl phenylacetate (15.02 g, 100 mmol) in THF (120 ml) and stirred at −78 °C for 20 min. A solution of the (Z)-dioxolanone (**9**) (8.945 g, 33.3 mmol) in THF (60 ml) was added. The mixture was allowed to warm to ambient temperature and was then left overnight. The oily mass was stirred vigorously with water (750 ml) and the solution was washed with ether (2 × 200 ml), cooled to 0 °C, acidified (pH 2) with concentrated H_2SO_4, and extracted with ethyl acetate (2 × 300 ml). The combined extracts were washed with brine (2 × 150 ml), dried (Na_2SO_4), and evaporated under reduced pressure to yield an orange oil (16.6 g). Chromatography on silica gel (200 g) with chloroform as eluant yielded the (Z)-ester (**20**) together with phenylacetic acid. The combined fractions were evaporated under reduced pressure and triturated with chloroform–petroleum (1:1; 50 ml). The crystals which formed were separated and washed with chloroform (2 × 10 ml) to provide the (Z)-acid (**21**) (0.792 g, 10%), m.p. 201—202 °C (decomp.). The combined solution and washings were evaporated under reduced pressure and the residue triturated with CCl_4–petroleum (1:1; 50 ml) to afford a yellow solid which was filtered off and washed with CCl_4 to afford the (Z)-*t-butyl ester* (**20**) (2.06 g, 22%), m.p. 120—123 °C [decomp., eliminating 2-methylpropene to form the (Z)-acid (**21**), m.p. and mixed m.p. 206—207.5 °C] (Found: C, 66.9; H, 5.4. $C_{16}H_{16}O_5$ requires C, 66.7; H, 5.6%); $\lambda_{max.}$(EtOH) 270 (ε 45 600) and 337 (10 500)–385 nm (7 700); $\lambda_{max.}$ (EtOH + 1 drop 2M-NaOH) 269 (ε 59 600) and 384 nm (7 800); $\nu_{max.}$(Nujol) 3 110m, 1 774m, 1 728m, 1 722m, 1 674s, 1 642m, and 1 625m cm^{-1}; $\nu_{max.}$($CHCl_3$) 3 030w, 2 975m, 2 930w, 1 778s, 1 688s, 1 642s, and 1 600w cm^{-1}; δ_H($CDCl_3$) 1.54 (9 H, s, Bu^t), 5.77 (1 H, s, =CH), 7.32—7.50 (3 H, m, ArH), 7.67—7.85 (2 H, m, ArH), OH not detected; *m/z* 288 (M^+, 1%). Deprotection of the residue from evaporation of the combined washings and filtrates with TFA (10 ml, 130 mmol) as below afforded a residue which upon being stirred with $CHCl_3$ (20 ml) for 1 h yielded more of the (Z)-acid (**21**) (0.95 g, 12%).

(E)-3-*Phenyl-5-t-butoxycarbonylmethylenefuran*-2,4-(3H,5H)-*dione* [(*E*)-4-*t-Butoxycarbonylmethylene*-2-*phenyl-tetronic Acid*] (**22**).—Irradiation, as above, of the (Z)-t-butyl

ester (**20**) (125 mg, 0.434 mmol) in ethanol (250 ml) for 6.5 h, followed by evaporation of the solvent under reduced pressure and trituration with ice-cold ethanol (10 ml) afforded a yellow solid which was separated and recrystallised from ethanol to yield yellow plates of the (E)-*t-butyl ester* (**22**) (102 mg, 82%), m.p. 143—145 °C [decomp., eliminates 2-methylpropene forming the (*E*)-acid (**23**), m.p. and mixed m.p. 219—221 °C] (Found: C, 66.5; H, 5.6. $C_{16}H_{16}O_5$ requires C, 66.7; H, 5.6%); $\lambda_{max.}$(EtOH) 236 (ε 14 050), 272 (19 200), and 363 nm (13 100); $\lambda_{max.}$ (EtOH + 1 drop 2M-NaOH) 268 (ε 31 000) and 370 nm (7 100); $\nu_{max.}$(Nujol) 3 072w, 3 040w, *ca.* 2 500br w, 1 772s, 1 676w, 1 642s, 1 598m, 1 582m, and 1 566m cm^{-1}; $\nu_{max.}$($CHCl_3$) 2 980w, 2 930w, *ca.* 2 535br w, 1 776m, 1 680m, 1 638s, 1 600w, and 1 588m cm^{-1}; δ_H($CDCl_3$) 1.54 (9 H, s, Bu^t), 5.92 (1 H, s, =CH), 7.25—7.60 (3 H, m, ArH), 8.00—8.25 (2 H, m, ArH), and 13.67 (1 H, s, exchanges with D_2O); *m/z* 288 (M^+, 1%).

Conversion of 4-*t-Butoxycarbonylmethylenetetronic Acids into* 4-*Carboxymethylenetetronic Acids: General Procedure.*—Anhydrous TFA (5 ml, 65 mmol) was added in one portion to the t-butyl ester (1.5 mmol) at room temperature and stirred for 3 h. Excess of TFA was removed by evaporation under reduced pressure and toluene [for the (*E*)-acids] or 1,4-dioxane [for the (*Z*)-acids] (3 × 20 ml), was thrice added and removed in the same way. Trituration with petroleum [for the (*E*)-acids] or chloroform [for the (*Z*)-acids] (25 ml) gave the crude product which was separated and recrystallised as follows.

(i) (Z)-5-*Carboxymethylene*-3-*n-pentylfuran*-2,4(3H,5H)-*dione* [(*Z*)-4-carboxymethylene-2-n-pentyltetronic acid: (Z)-multicolanic acid] (**17**) crystallised as colourless needles from ethyl acetate–petroleum (580 mg, 98%), m.p. 174—175.5 °C (decomp.) (Found: C, 58.3; H, 6.3. $C_{11}H_{14}O_5$ requires C, 58.4; H, 6.2%); $\lambda_{max.}$(EtOH) 261 (ε 17 200) and 302infl. (7 950)—350 nm (6 000) (isosbestic point at 318 nm); $\lambda_{max.}$ (EtOH + 1 drop 2M-NaOH) 255 (ε 16 750) and 335 nm (7 700); $\nu_{max.}$(Nujol) 3 125m, 1 732s, 1 710s, 1 668m, and 1 633s cm^{-1}; $\nu_{max.}$(1,4-dioxane) 1 795s, 1 706m, and 1 652s cm^{-1}; δ_H[$(CD_3)_2SO$] 0.88 (3 H, t, *J* 6 Hz, CH_3), 1.1—1.6 [6 H, m, $(CH_2)_3$], 2.27 (2 H, t, $=CCH_2$), 3.0—5.0 (2 H, s, exchanges with D_2O), and 5.65 (1 H, s, =CH); *m/z* 226 (M^+, 0.4%). Crystallisation of the acid from water gave, near quantitatively, 1-hydroxy-2-n-pentylcyclopent-1-ene-3,5-dione (**18**) as the monohydrate, m.p. 76.5—78 °C (lit.,[10] 76—77 °C) which was identical with an authentic sample supplied by Dr. J. S. E. Holker.

(ii) (E)-5-*Carboxymethylene*-3-*n-pentylfuran*-2,4(3H,5H)-*dione* [(*E*)-4-carboxymethylene-2-n-pentyltetronic acid: (*E*)-multicolanic acid] (**3**) (360 mg, 83%), had m.p. (petroleum or CCl_4–petroleum) 109—110.5 °C (lit.,[9] 109—110.5 °C), identical with an authentic sample supplied by Dr. J. S. E. Holker (Found: C, 58.5; H, 6.5. Calc. for $C_{11}H_{14}O_5$: C, 58.4; H, 6.2%); $\lambda_{max.}$(EtOH) 259 (ε 15 100) and 315 nm (5 550); $\lambda_{max.}$ (EtOH +1 drop 2M-NaOH) 258 (ε 14 750) and 325 nm (7 500); $\nu_{max.}$(Nujol) 3 160m, 3 070m, 2 620w, 2 540w, 1 753s, 1 700m, 1 642s, 1 635s, and 1 600m cm^{-1}; $\nu_{max.}$($CHCl_3$) 3 030m, 2 953m, 2 928m, 2 855w, 2 650w, 1 783s, 1 695m, and 1 640s cm^{-1}; δ_H($CDCl_3$) 0.89 (3 H, t, *J* 6 Hz, CH_3), 1.15—1.67 [6 H, m, $(CH_2)_3$], 2.35 (2 H, t, *J* 7.5 Hz, $=CCH_2$), 6.02 (1 H, s, =CH), 6.4 (1 H, br s, exchanges with D_2O), and 12.13 (1 H, s, exchanges with D_2O); *m/z* 226.0839 (M^+, 43%, dev. 0.0001).

(iii) (Z)-5-*Carboxymethylene*-3-*phenylfuran*-2,4(3H,5H)-*dione* [(*Z*)-4-carboxymethylene-2-phenyltetronic acid] (**21**) crystallised as yellow needles from chloroform (257 mg, 90%), m.p. 201—202 °C (Found: C, 62.0; H, 3.7. $C_{12}H_8O_5$ requires C, 62.1; H, 3.5%); $\lambda_{max.}$(EtOH) 269 (ε 41 000) and 338 (7 400)—382 nm (7 400) (isosbestic point at 369 nm); $\lambda_{max.}$ (EtOH + 1 drop 2M-NaOH) 266 (ε 34 000) and 362 nm (8 800); $\nu_{max.}$(Nujol) 3 070w, 1 733m, 1 692s, 1 665m, 1 622m, and 1 598m cm^{-1}; $\nu_{max.}$(1,4-dioxane) 3 100—2 700, 1 790s, 1 707s, 1 649s, and 1 605w cm^{-1}; δ_H [300 MHz, $(CD_3)_2SO$] 5.92 (1 H, s, =CH), 7.31 (1 H, t, *J* 7.5 Hz), 7.44 (2 H, t, *J* 8 Hz), 7.97 (2 H, d, *J* 8 Hz), OH not detected; *m/z* 232 (M^+, 1%).

(iv) (E)-5-*Carboxymethylene*-3-*phenylfuran*-2,4(3H,5H)-*dione* [(*E*)-4-carboxymethylene-2-phenyltetronic acid] (**23**) as lemon-yellow needles from water (164 mg, 81%), m.p. 219—221 °C (decomp.) (Found: C, 62.1; H, 3.2. $C_{12}H_8O_5$ requires C, 62.1; H, 3.5%); $\lambda_{max.}$(EtOH) 243infl. (ε 18 250), 263 (26 750), and 363 nm (9 250); $\lambda_{max.}$(EtOH + 1 drop 2M-NaOH) 267 (ε 40 550) and 346 nm (7 800); $\nu_{max.}$(Nujol) 3 250m, 3 078w, 3 048w, 2 400br, 1 765m, 1 756m, 1 685m, 1 632s, 1 598w, 1 581m, and 1 567m, cm^{-1}; $\nu_{max.}$($CHCl_3$) 2 550br, 1 775m, 1 685w, 1 638s, and 1 582m cm^{-1}; δ_H($CDCl_3$) 6.08 (1 H, s, =CH), 7.33—7.60 (3 H, m, ArH), 8.05—8.20 (2 H, m, ArH), and 13.24 (1 H, s, exchanges with D_2O); *m/z* 232 (M^+, 30%).

(Z)-4-*Methoxy*-5-*methoxycarbonylmethylene*-3-*n-pentylfuran*-2(5H)-*one* [*Methyl* (Z)-4-*Methoxycarbonylmethylene*-2-*n-pentyltetronate: Methyl* (Z)-O-*Methylmulticolanate*] (**5**).—An ice-cold solution of diazomethane (3 mmol) in ether (10 ml) was added to a stirred suspension of the (*Z*)-acid (**17**) (232 mg, 1.024 mmol) in ether (10 ml). After 0.5 h the mixture was filtered and the filtrate was evaporated under reduced pressure. Recrystallisation of the residue from chloroform (*ca.* 2 ml) gave colourless needles of (**5**) (170 mg, 65%), m.p. 73—73.5 °C (lit.,[3] 72—73 °C) (Found: C, 61.3; H, 7.4. Calc. for $C_{13}H_{18}O_5$: C, 61.4; H, 7.1%); $\lambda_{max.}$(EtOH) 266 nm (ε 18 800); $\nu_{max.}$(Nujol) 1 800m, 1 706s, 1 662w, and 1 643m cm^{-1}; $\nu_{max.}$($CHCl_3$) 1 788s, 1 708s, 1 674m, and 1 642s cm^{-1}; δ_H($CDCl_3$) 0.90 (3 H, t, *J* 6 Hz, CH_3), 1.1—1.4 (4 H, m), 1.58 (2 H, t, *J* 6 Hz), 2.53 (2 H, t, *J* 8 Hz, $=CCH_2$), 3.82 (3 H, s, CO_2Me), 4.18 (3 H, s, =COMe), and 5.62 (1 H, s, =CH); *m/z* 254 (M^+, 36%). A further crop (86 mg, 33%) of (**5**) was obtained by evaporation of the mother liquor under reduced pressure and recrystallisation of the residue from petroleum.

(E)-4-*Methoxy*-5-*methoxycarbonylmethylene*-3-*n-pentylfuran*-2(5H)-*one* [*Methyl* (E)-4-*Methoxycarbonylmethylene*-2-*n-pentyltetronate: Methyl* (E)-O-*Methylmulticolanate*] (**4**).—An ice-cold solution of diazomethane (0.4 mmol) in ether (10 ml) was added to a solution of the (*E*)-acid (**3**) (35.6 mg 0.157 mmol) in ether (10 ml). After 30 min the volatile components were removed by evaporation under reduced pressure and the residual oil was chromatographed on silica gel (20 g) with petroleum–chloroform (3:1) as eluant. The first eluate was methyl (*E*)-*O*-methylmulticolanate (**4**) (36.2 mg, 91%) (t.l.c. R_F 0.56 in $CHCl_3$), a colourless mobile oil, $\nu_{max.}$(film) 2 955m, 2 930m, 2 870w, 2 860w, 1 785s, 1 738s, 1 666m, and 1 640s cm^{-1}; δ_H($CDCl_3$) 0.90 (3 H, t, *J* 6 Hz, CH_3), 1.1—1.7 [6 H, m, $(CH_2)_3$], 2.50 (2 H, t, *J* 8 Hz, $=CCH_2$), 3.77 (3 H, s, CO_2Me), 4.13 (3 H, s, =COMe), and 5.87 (1 H, s, =CH) which slowly rearranged to the (*Z*)-isomer (**5**) (t.l.c. R_F 0.38 in $CHCl_3$). There was a second eluate which was probably the mono-methylated product (R_F 0.49 in $CHCl_3$); δ_H($CDCl_3$) 3.90 (3 H, s, CO_2Me), 5.93 (1 H, s, =CH), and 12.49 (1 H, s, exchanges with D_2O).

(Z)-4-*Methoxy*-5-*methoxycarbonylmethylene*-3-*phenylfuran*-2(5H)-*one* [*Methyl* (Z)-4-*Methoxycarbonylmethylene*-2-*phenyltetronate*] (**24**).—An ice-cold solution of diazomethane (2.81 mmol) in ether (15 ml) was added to a stirred suspension of the (*Z*)-acid (**21**) (200 mg, 0.86 mmol) in ether (10 ml). After 15 min the solution was filtered and evaporated under reduced pressure. The solid residue was recrystallised from ethyl acetate–petroleum to give pale yellow needles of the *ester* (**24**) (164 mg, 73%), m.p. 88.5—91 °C (Found: C, 64.8; H, 4.4. $C_{14}H_{12}O_5$ requires C, 64.6; H, 4.65%); $\lambda_{max.}$(EtOH) 266 (ε 19 950) and *ca.* 310infl. nm (11 000); $\lambda_{max.}$ (EtOH + 1 drop 2M-NaOH) 259 nm (ε 57 050); $\nu_{max.}$(Nujol) 1 785s, 1 718m, 1 700s, 1 678m, 1 644s,

and 1 603m cm^{-1}; $\nu_{max.}$($CHCl_3$) 1 788s, 1 708s, 1 672m, 1 642s, and 1 600w cm^{-1}; δ_H($CDCl_3$) 3.85 (6 H, s, CO_2Me and =COMe), 5.77 (1 H, s, =CH), and 7.47 (5 H, m, Ph); *m/z* 260 (M^+, 61%).

(E)-4-*Methoxy*-5-*methoxycarbonylmethylene*-3-*phenylfuran*-2(5H)-*one* [*Methyl* (E)-4-*Methoxycarbonylmethylene*-2-*phenyltetronate*] (**25**).—An ice-cold solution of diazomethane (3.36 mmol) in ether (10 ml) was added to a solution of the (*E*)-acid (**23**) (102 mg, 0.44 mmol) in ether (10 ml). After 2 h the volatiles were removed by evaporation under reduced pressure to yield a pale yellow oil which, when examined by t.l.c. and ^1H n.m.r. spectroscopy, proved to be a mixture (*ca.* 1:1) of the desired tetronate (**25**) (t.l.c. R_F 0.28 in petroleum–$CHCl_3$ (1:1) and 0.48 in CH_2Cl_2); δ_H (220 MHz, $CDCl_3$) 3.80 (3 H, s, OMe), 3.82 (3 H, s, OMe), 6.04 (1 H, s, =CH), and 7.44 (5 H, m, Ph) and a second component to which we assign the structure of the Δ^1-pyrazoline (**26**) [t.l.c. R_F 0.11 in petroleum–$CHCl_3$ (1:1) and 0.29 in CH_2Cl_2]; δ_H (220 MHz, $CDCl_3$) 3.33 (1 H, ABM, *J* 8 Hz), 3.65 (3 H, s, OMe), 3.77 (3 H, s, OMe), 4.97 and 5.16 (2 H, ABM, *J* 18 Hz), and 7.44 (5 H, m, Ph). The (*E*)-tetronate (**25**) rearranged to the (*Z*)-isomer (**24**) on chromatography as shown by ^1H n.m.r. spectroscopy. The partial rearrangement, coupled with the fact that the methoxy and methoxycarbonyl groups of the (*Z*)-isomer (**24**) possess near-identical chemical shifts, permitted unambiguous assignment of the singlet signals at 3.80, 3.82, and 6.04 p.p.m. to be those of the (*E*)-tetronate (**25**) and the singlets at 3.65 and 3.77 p.p.m. to be those of the pyrazoline (**26**).

1-*Hydroxy*-2-*n-pentylcyclopent*-1-*ene*-3,5-*dione* (**18**) *as the Monohydrate*.—The (*Z*)-acid (**17**) (289 mg, 1.28 mmol) was dissolved in water (30 ml) by boiling. Charcoal (*ca.* 100 mg) was added, the mixture boiled for a few minutes more, and filtered. The filtrate was concentrated by evaporation under reduced pressure to *ca.* 15 ml and allowed to cool yielding pale yellow needles of 1-hydroxy-2-n-pentylcyclopent-1-ene-3,5-dione (**18**) as the monohydrate (195 mg, 76%), m.p. 76.5—78 °C (lit.,[10] 76—77 °C) (Found: C, 59.4; H, 8.0. Calc. for $C_{10}H_{14}O_3 \cdot H_2O$: C, 60.0; H, 8.0%); $\lambda_{max.}$(EtOH) 276 nm (ε 14 750); $\lambda_{max.}$(EtOH + 1 drop 2M-NaOH) 232 (ε 10 100) and 327 nm (11 150); $\nu_{max.}$(Nujol) 3 490m, 3 360m, 2 600m, 1 736m, 1 678s, and 1 648s cm^{-1}; $\nu_{max.}$($CHCl_3$) 3 680w, 3 460m, 2 995m, 2 930m, 2 870m, 2 860m, 1 746m, 1 692s, 1 666m, 1 656m, and 1 602w cm^{-1}; δ_H (80 MHz, $CDCl_3$) 0.87 (3 H, t, 6 Hz, CH_3), 1.16—1.68 [6 H, m, $(CH_2)_3$], 1.82 (2 H, s, exchanges with D_2O), 2.41 (2 H, t, *J* 7.5 Hz, $=CCH_2$), 2.91 (2 H, s, CH_2CO), and 7.29 (1 H, br s, exchanges with D_2O); *m/z* 182 (M^+, 3%).

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