Directed Metallations of 4-Ethylidenetetronic Acid O-Methyl Ether and its Derivatives as a Synthetic Entry to Natural 4-Oxyfuran-2-ones

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Lithium di-isopropylamide removes the C-2(α-)-protons from the O-methyl tetronates (11) and (20) in a regioselective manner leading to the corresponding novel anions e.g. (18). The vinyl anions then react with a range of electrophiles providing a preparatively useful procedure for the synthesis of a range of 2-substituted O-methyl tetronates e.g. (13), (15), (16), (22), and (25). Alkylation of the vinyl anion (18) with trimethylsilyl chloride leads to the 2-silyl derivative (26) which on treatment with lithium di-isopropylamide followed by alkylation (MeI and PhCHO) gives the product [(27) and (28)] resulting from addition at C-4 in (11). Acylation of the anion derived from (26) under different reaction conditions, produces either the 4-acetoxy derivative (29) or the furan enol acetate (30). The 2'-substituted carbinol (34) is produced when the enolate derived from (26) is quenched with n-propanal.

The directed metallations of (11) and its derivatives provide access to a range of 4-oxyfuran-2-one analogues found amongst natural products.

Treatment of (11) with N-bromosuccinimide followed by triphenylphosphine produces the corresponding phosphonium salt (37b) which reacts with benzaldehyde and isovaleraldehyde to give the polyene O-methyl tetronates (38) and (39) respectively.
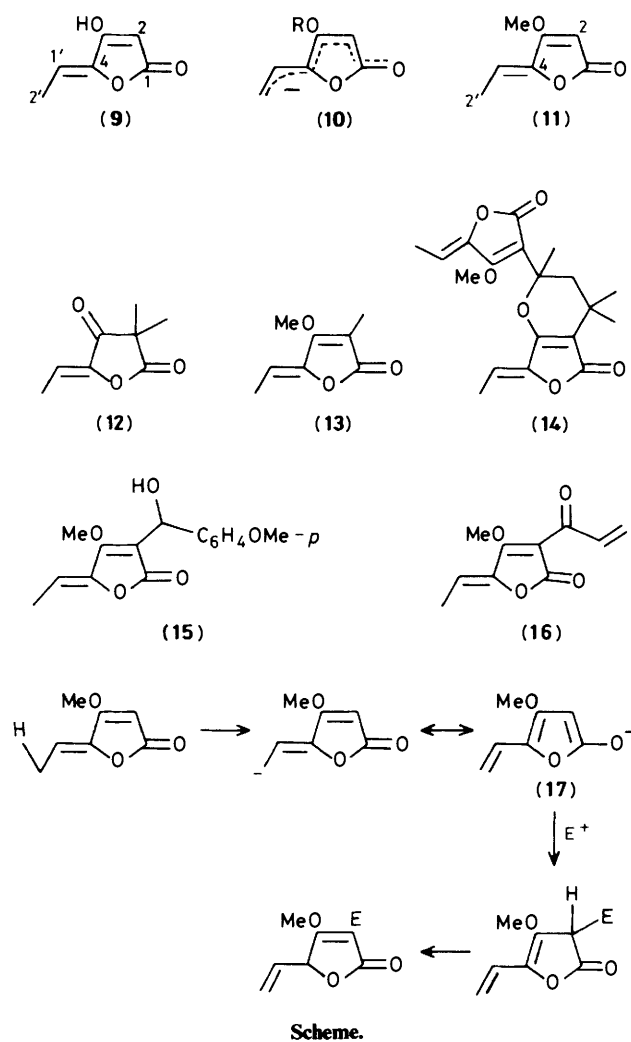
Ylidenetetronic acids are widely distributed in Nature and several members, e.g. vulpinic acid (1), piperolide (2), multicolosic acid (3), show a useful spectrum of biological activity.[1] Closely related structurally to the ylidenetetronic acids are the natural 4-oxyfuran-2-ones aspertetronin A (4),[2] obtusilactone (5),[3] and allamandin (6).[4] In previous studies we have demonstrated that ylidenebutenolides can function as useful synthons in the construction of other molecules of biological interest, e.g. isomerisation of the butenolide (7) leads to calythrone (8) found in *Calythrix tetragona*.[5] In this paper we show how it is possible to control α-(C-2), γ-(C-4), and ε-(C-2') substitution within the readily available ethylidenetetronic acid O-methyl ether (11) leading to derivatives containing the 4-oxyfuran-2-one substitution patterns found in compounds (2), (4), and (5).[6] In the accompanying paper, we describe the extension of this study to a total synthesis of the structure (4) proposed for the aspertetronin family of antimicrobial fungal metabolites present in *Aspergillus* and *Cephalosporium* sp.

In the preceding paper[7] it was shown that ethylidenetetronic acid (9) reacts with a variety of carbonyl compounds in the presence of weak bases leading to products resulting from exclusive attack at C-2 in (9). We reasoned that one way of effecting reaction at C-4 and at C-2' in (9), leading to related 4-oxy-γ-butyrolactones of the type (2), and (4), was first to protect the enol grouping in (9), and then to produce an extended enolate via deprotonation at C-2' [viz. (10)]. Although the enol grouping in (9) could be protected in a number of ways,[8] in view of the incidence of O-methyl tetronates in Nature, we elected to protect the enol as its methyl ether (11).

The O-methyl ether (11) was most conveniently prepared in high yield (>92%) by methylation of the tetrabutylammonium salt of ethylidenetetronic acid with dimethyl sulphate.[9] Alternative procedues e.g. MeI–K₂CO₃ or Me₂SO₄–K₂CO₃ in acetone, invariably produced C-methylation products i.e. (12) and (13) and 'dimeric' products, e.g. (14),[7] in addition to the O-methyl ether (11). To our initial surprise, metallation of the O-methyl ether (11) using lithium di-isopropylamide in tetrahydrofuran at −78 °C, followed by reaction with a variety of electrophiles led exclusively to products resulting from substitution at C-2 in (11). Thus, methylation with methyl iodide led to (13) (58%), alkylation with 4-methoxybenzaldehyde led to

(1)

(2)

(3)

(4)

(5)

(6)

(7)

(8)
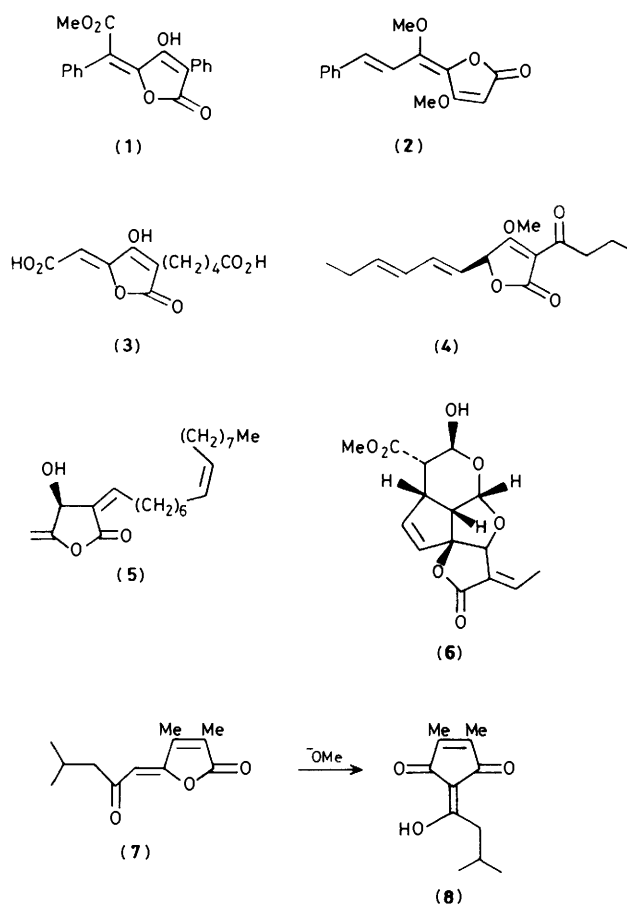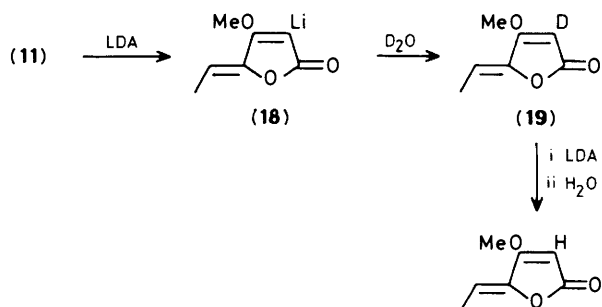
the crystalline carbinol (15) (68%), and acylation with methyl acrylate produced the product (16) of 1,2-addition in 20% yield. In no case did we obtain evidence for geometrical isomerisation about the exocyclic Z-double bond in (11), which was surprising

(9)

(10)

(11)

(12)

(13)

(14)

(15)

(16)

(17)

(18)

(19)

Scheme.

lithium di-isopropylamide was occurring regioselectively at C-2, leading to the vinyl anion (18).

In contemporaneous studies Dean[10] and Staunton[11] and their respective co-workers described similar observations with closely related O-heterocyclic systems, and the novel deprotonation of (11) was to become a key feature of our synthesis of the structures proposed for the aspertetronin family of 4-methoxy-γ-butyrolactones, described in the following paper. Indeed in a related series of reactions using the 5,5-dimethyltetronate (20),[12] which is a clear model for the aspertetronins [cf. (4)], deprotonation followed by alkylation and acylation led to the analogous 2-substitution products (21) and (22). Interestingly, we were unable to prepare the corresponding 2-aminotetronate (25) by direct amination of the anion derived from (20), using a range of aminating agents. This amine was instead obtained by a more circuitous route, involving Curtius rearrangement of the azide (24) derived from the carboxy tetronate (23).
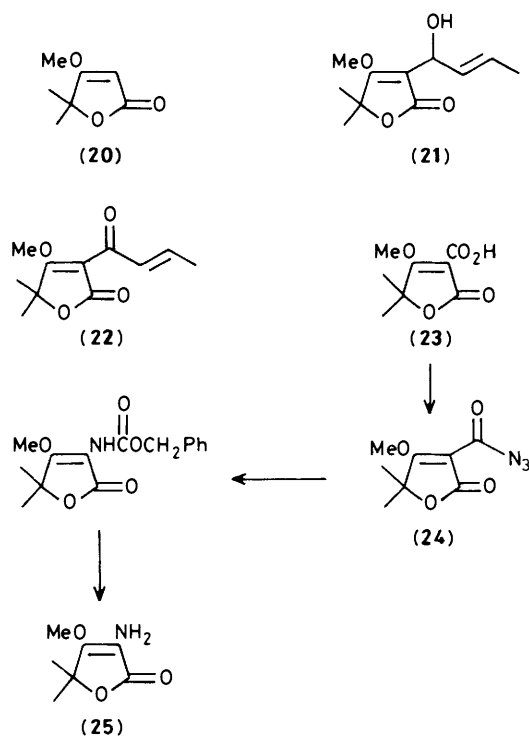
(20)

(21)

(22)

(23)

(24)

(25)

had the mechanism for its substitution at C-2 proceeded via initial deprotonation at C-2' according to the Scheme.

Suspecting that the intermediate anion was not the extended enolate (17) but rather the vinyl-lithium species (18), the metallated tetronate was quenched with deuterium oxide, whereupon we isolated the mono-deuteriated derivative (19) in high yield containing >90% deuterium. The deuteriated sample (19) retained the resonances associated with the (Z)-ethylidene side chain, and furthermore, on treatment with lithium di-isopropylamide at −90 °C followed by quenching with water it gave the ¹H-tetronate (11) containing less than 5% deuterium by ¹H n.m.r. spectroscopy. These experiments demonstrated conclusively that the deprotonation of (11) in the presence of

(11) —LDA→ (18) —D₂O→ (19)

i LDA
ii H₂O

Although the vinyl-lithium species (18) provided a novel and regioselective entry to a variety of 2-substituted 4-methoxyfuranones from the parent ethylidenetetronate (11), at the same time it precluded any possibility of direct substitution at either C-4 or C-2' in (11). To circumvent this problem, and provide more scope for the ethylidenetetronate in synthesis we elected to employ a protection–deprotection sequence of the C-2 position in (11) using the trimethylsilyl derivative (26). Thus, metallation of the O-methyl ether, in the usual manner, followed by alkylation with trimethylsilyl chloride gave, as expected, the C-2 trimethylsilyl derivative (26) exclusively, which was isolated as a crystalline solid in 71% yield. Sequential treatment of (26) with lithium di-isopropylamide and then methyl iodide in the presence of hexamethylphosphoric triamide, followed by workup gave a low yield of the product (27) of substitution at C-4 in (26) as a labile oil. In a similar manner, alkylation of the anion derived from (26) using benzaldehyde produced the 4-substituted carbinol (28) (60%). The carbinol (28) could not be purified by chromatography, and when stored over short

(26)　(27)

(26) ⇌ (28)
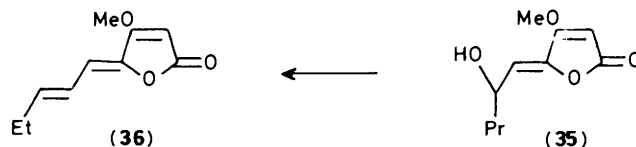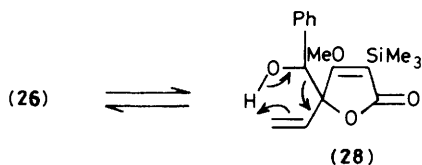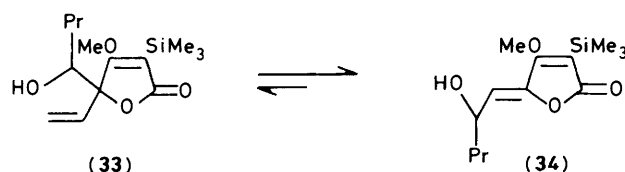
periods, decomposed to the *O*-methyl ether (26). The facility of this reversion may possibly be due to a retro-ene reaction.

Acylation of the anion derived from (26) using acetyl chloride, under slightly differing conditions led to either of the two products (29) and (30). Thus, acylation of the anion at −78 °C for 5 min, followed by warming to 20 °C and immediate quenching produced largely the 5-acetyl derivative (29). By contrast, when the acylation was carried out at −78 °C (0.5 h) followed by storage at room temperature for 2 h, chromatography gave only the novel furan enol-acetate (30) (76%). The isomers (29) and (30) were easily distinguished in their i.r. spectra where the enol acetate (30) showed a single strong carbonyl absorption at 1 790 cm^{-1}, whereas (29) exhibited two carbonyl stretching frequencies at $\nu_{max.}$ 1 750 and 1 720 cm^{-1}. Furthermore, when the furan enol acetate (30) was heated in benzene in the presence of dimethyl acetylenedicarboxylate, a high yield of the corresponding Diels–Alder adduct (31) was produced. In a similar manner, acylation of the anion derived from (26) with benzoyl chloride led to the corresponding enol benzoate (32).

(29)　(30)

(31)　(32)
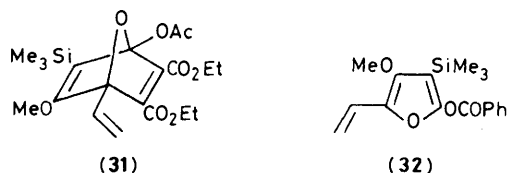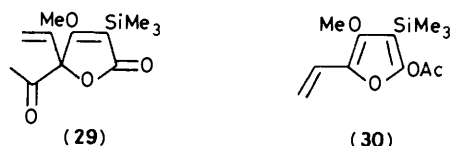
Having achieved substitution at both C-2 and C-4 in the tetronate (11) by appropriate choice of reaction conditions and electrophile we were pleased to find that when the enolate derived from (26) was quenched with n-propanal, the major product isolated was the 2′-substituted carbinol (34). We were unable to obtain evidence for the co-formation of products resulting from simultaneous substitution at either C-2 or C-4 in this reaction. We suggest that in this case, the carbinol (34) is the thermodynamic product of the condensation, produced from the thermodynamically unstable kinetic product (33) by retroaldol–realdolisation. Upon treatment of the silane (34) with dilute hydrochloric acid in tetrahydrofuran, clean protodesilylation occurred to give the tetronate (35), which on further treatment with sulphuric acid in tetrahydrofuran could be converted into the conjugated ylidenetetronate (36).

As a corollary to the metallation studies of (11) and its

(33) ⇌ (34)

(36) ← (35)

derivatives, we also examined the direct activation of the 2′-position in (11) *via* free-radical bromination using *N*-bromosuccinimide. This approach provided a more satisfactory entry to the synthesis of the 'extended' polyene tetronates like (36), found in natural products similar to piperolide (2). Thus, treatment of (11) with *N*-bromosuccinimide in hot carbon tetrachloride produced the bromide (37a) as a crystalline solid (60%) which was converted into the stable phosphonium salt (37b).

(37)　(38)　(39)
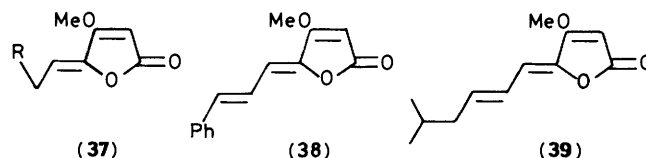
a; R = Br
b; R = $\overset{+}{P}Ph_3Br^-$

Deprotonation of (37b) using potassium t-butoxide at −78 °C followed by quenching with benzaldehyde produced a mixture of *Z*- and *E*-isomers, about the newly formed double bond of the phenylpropenylidenefuranone (38) in a combined yield of 23%. In a similar manner, a 1:1 mixture of *Z*- and *E*-isomers of the polyene (39) was produced from isovaleraldehyde and the ylide derived from (37b).

Experimental

For general experimental details see ref. 7.

5-*Ethylidene*-4-*methoxyfuran*-2(5H)-*one* (11).—A solution of 5-ethylidene-4-hydroxyfuran-2(5*H*)-one (ethylidenetetronic acid) (6.3 g) and 0.1m-tetrabutylammonium hydroxide in toluene–methanol (500 cm^3) was kept at 25 °C for 1 h and then evaporated to near dryness under reduced pressure. The residue was treated with light petroleum (b.p. 60—80 °C) and the precipitated solid was filtered off and washed with ethyl acetate to leave the tetrabutylammonium salt of (9) (17.7 g, 96%) as a white powder, m.p. 138—140 °C. The salt (7.3 g) was stirred with a solution of dimethyl sulphate (2.52 g) in dichloromethane (50 cm^3) at 25 °C for 2 h, and the mixture was then evaporated to dryness under reduced pressure. The residue was dissolved in ether, and the ether extract was then washed with water, dried, and evaporated. Crystallisation of the residue (2.71 g) from n-hexane gave the *methoxyfuranone* (2.4 g, 90%) as white

needles, m.p. 68—69 °C, $\lambda_{max.}$(EtOH) 258 nm (16 000); $\nu_{max.}$(KBr) 1 760, 1 605 cm^{-1}, δ 1.85 (d, J 7.5, =CMe), 3.88 (OMe), 5.13 (=CH), and 5.41 (q, J 7.5, =CHMe) (Found: C, 59.9; H, 5.7. C$_7$H$_8$O$_3$ requires C, 60.0; H, 5.8%).

Methylation of the tetronic acid (9) using dimethyl sulphate in acetone in the presence of anhydrous potassium carbonate also gave the O-methyl ether (11), (82%), but this was sometimes contaminated with the methyl ether bis-tetronic acid (14), (*ca.* 10%, *cf.* ref. 7); prisms, m.p. 133—137 °C (ethyl acetate), $\lambda_{max.}$(EtOH) 269 nm; $\nu_{max.}$(KBr) 1 757, 1 675, and 1 640 cm^{-1}; δ 1.07 (Me), 1.28 (Me), 1.68 (d, J 15, 1 H), 2.71 (Me), 1.92 (d, J 7.5, 2 × =CHMe), 2.67 (d, J 15, 1 H), 3.88 (OMe), 5.41 (q, J 7.5, =CHMe), and 5.53 (q, J 7.5, =CHMe) (Found M^+, 346.1420. C$_{19}$H$_{22}$O$_6$ requires M, 346.1416).

Methylation of the tetronic acid (9) using methyl iodide in acetone in the presence of potassium carbonate led to a complex mixture of products which were separated by chromatography (silica; 4:1 ether–hexane) to give: (*a*) 5-ethylidene-3,3-dimethyl-furan-2,4(3H,5H)-dione (12) (eluted first; 15%), m.p. 51—55 °C (hexane), $\lambda_{max.}$(EtOH) 254 nm; $\nu_{max.}$(film) 1 810, 1 740, 1 660, and 1 620 cm^{-1}; δ 1.65 (CMe$_2$), 1.89 (d, J 7.5, =CHMe), and 5.91 (q, J 7.5, =CHMe), (*b*) the methyl ether bis-tetronic acid (14) (eluted second; 16%) showing spectral data identical with those described above, (*c*) 5-ethylidene-4-methoxy-3-methylfuran-2(5H)-one (13) (eluted third; 8%) showing spectral data identical with those described below, and (*d*) the methoxy-furanone (11) (eluted last; 43%).

Metallation and Substitution of 5-Ethylidene-4-methoxyfuran-2(5H)-one (11).—*General procedure.* A solution of 5-ethylidene-4-methoxyfuran-2(5H)-one (1.25 g) in dry tetrahydrofuran (5 cm^3) was added dropwise over 10 min to a solution of lithium di-isopropylamide (1.1 equiv.) in dry tetrahydrofuran (35 cm^3) maintained at −78 °C under a nitrogen atmosphere. A lemon yellow solution of the metallated furanone was obtained almost immediately. The solution was stirred at −78 °C for 0.25 h and then a solution of the electrophile (1.2 equiv.) in dry tetra-hydrofuran (1 cm^3) was introduced dropwise over 5 min. The resulting mixture was stirred at −78 °C for 0.5 h, then allowed to warm to 10 °C when it was quenched by the addition of saturated aqueous ammonium chloride, and diluted with ether. The ether layer was separated, washed with brine, and dried. Evaporation of the ether left a residue which was purified by chromatography or by recrystallisation.

5-Ethylidene-4-methoxy-3-methylfuran-2(5H)-one (13).—By the general procedure, alkylation of the anion derived from (11) with methyl iodide, followed by recrystallisation of the crude product gave the 3-*methylfuranone* (58%) as colourless needles, m.p. 64—65 °C (n-hexane), $\lambda_{max.}$(CHCl$_3$) 268 nm; $\nu_{max.}$(KBr) 1 750, 1 687, and 1 640 cm^{-1}; δ 1.85 (d, J 7.5, =CHMe), 2.07 (= CMe) 4.1 (OMe), and 5.34 (q, J 7.5, =CHMe) (Found: C, 62.5; H, 6.55. C$_8$H$_{10}$O$_3$ requires C, 62.3; H, 6.5%).

5-Ethylidene-3-(α-hydroxy-4-methoxybenzyl)-4-methoxy-furan-2(5H)-one (15).—By the general procedure alkylation of the anion derived from (11) with 4-methoxybenzaldehyde, followed by chromatography (silica; dichloromethane) and crystallisation gave the 3-substituted *furanone* (68%) as pale yellow cubes, m.p. 120—121 °C (ethyl acetate–cyclohexane), $\lambda_{max.}$(EtOH) 227 (16 000) and 267 nm (21 000); $\nu_{max.}$(CHCl$_3$) 3 400, 2 900, 1 740, 1 695, 1 620, and 1 510 cm^{-1}; δ 1.85 (d, J 7.5; =CHMe), 3.63 (ArOMe), 3.9 (OH), 3.91 (OMe), 5.49 (q, J 7.5, =CHMe), 5.88 (CHOH), 6.8 (d, J 9, 2 H), and 8.27 (d, J 9, 2 H); (Found: C, 64.8; H, 5.9. C$_{15}$H$_{16}$O$_5$ requires C, 65.2; H, 5.8%).

5-Ethylidene-(α-hydroxy-3,4-dimethoxybenzyl)-4-methoxy-furan-2(5H)-one.—By the general procedure, alkylation of the

anion derived from (11) with 3,4-dimethoxybenzaldehyde, followed by chromatography (silica, ethyl acetate) and crystallisation gave the 3-substituted *furanone* (40%) as pale yellow cubes, m.p. 111—112 °C (tetrahydrofuran–hexane), $\lambda_{max.}$(EtOH) 237 (18 500) and 269 nm (25 000); $\nu_{max.}$(KBr) 3 395, 1 725, 1 688, 1 605, and 1 508 cm^{-1}; δ 1.92 (d, J 7.5, =CHMe), 3.93 (2 × ArOMe), 4.05 (OMe), 4.06 (d, J 8.5, OH), 5.66 (q, J 7.5, =CHMe), 6.03 (d, J 8.5, CHOH), 6.93 (2 H), and 7.16 (1 H) (Found: C, 62.6; H, 5.6. C$_{16}$H$_{18}$O$_6$ requires C, 62.75; H, 5.9%).

3-Acryloyl-5-ethylidene-4-methoxyfuran-2(5H)-one (16).—By the general procedure, acylation of the anion derived from (11) with methyl acrylate (3 equiv.), followed by chromatography (silica, dichloromethane) and crystallisation gave the 3-*acryloyl-furanone* (48%) as colourless needles, m.p. 82—83 °C (light petroleum, b.p. 60—80 °C), $\lambda_{max.}$(EtOH) 239 and 294 nm; $\nu_{max.}$(CHCl$_3$) 1 765, 1 665, 1 610, and 1 585 cm^{-1}; δ 1.9 (d, J 7.5, =CHMe), 4.11 (OMe), 5.76 (q, J 7.5, =CHMe), 5.85 (dd, J 10 and 1.8, HC=CHH), 6.31 (dd, J 17 and 1.8, HC=CHH), and 7.08 (dd, J 17 and 10, HC:CH$_2$) (Found: C, 62.1; H, 5.4%; M^+, 194.0582. C$_{10}$H$_{10}$O$_4$ requires C, 61.85; H, 5.2%; M, 194.0579).

2-Deuterio-4-ethylidene-4-methoxyfuran-2(5H)-one (19).—By the general procedure deuteriation of the anion derived from (11) with deuterium oxide, followed by recrystallisation from n-hexane gave the deuteriofuranone (70%) as colourless needles, m.p. 66—68 °C (Found: M^+, 141.0519. C$_7$DH$_7$O$_3$ requires M, 141.0535). Inspection of the intensity of absorption at δ 5.13 (=CH) relative to that at 3.88 (OMe) in the ^{1}H n.m.r. spectrum of the crude product showed 92% deuterium incorporation at C-2. Addition of the deuteriofuranone to a solution of lithium di-isopropylamide in tetrahydrofuran at −90 °C followed by quenching with water and work-up, gave the *furanone* (11) containing < 5% deuterium at C-2 (by ^{1}H n.m.r. spectroscopy).

Metallation and Substitution of 4-Methoxy-5,5-dimethylfuran-2(5H)-one (20).—*General procedure.* The general procedure used for the metallation and substitution of 5-ethylidene-4-methoxyfuran-2(5H)-one, described above, was followed with the exception that hexamethylphosphoric triamide (3.7 cm^3) was added to the solution of lithium di-isopropylamide prior to the introduction of the electrophile.

3-(1-Hydroxyethyl)-5,5-dimethyl-4-ethoxyfuran-2(5H)-one.
—By the general procedure, alkylation of the anion derived from (20) with acetaldehyde, followed by chromatography (flash silica deactivated with Et$_3$N; 3:2 ether–pentane) gave the *alcohol* (43%) as a colourless oil, $\nu_{max.}$(film) 3 400, 1 750 and 1 660 cm^{-1}; δ 1.43 (CMe$_2$), 1.45 (d, J 7, CHMe), 4.33 (OMe), and 4.91 (q, J 7, CHMe) (Found: M^+, 186.0830. C$_9$H$_{14}$O$_4$ requires M, 186.0888).

[1-Hydroxy-(E)-but-2-enyl]-4-methoxy-5,5-dimethylfuran-2(5H)-one (21).—By the general procedure, alkylation of the anion derived from (20), with crotonaldehyde, followed by chromatography (flash silica deactivated with Et$_3$N; 3:2 ether–pentane) gave the *alcohol* (80%) as a colourless oil, b.p. 75 °C at 0.01 mmHg; $\nu_{max.}$(film) 3 450, 1 740, 1 610, and 1 615 cm^{-1}; δ 1.46 (CMe$_2$), 1.72 (d, J 7, CHMe), 4.21 (OMe), 5.21—5.36 (m, :CH), and 5.68—5.87 (m, :CH); m/z 197 (M^+ − Me).

(E)-3-Crotonyl-4-methoxy-5,5-dimethylfuran-2(5H)-one (22).—By the general procedure, acylation of the anion derived from (20) with methyl crotonate, followed by chromatography (flash silica; 7:3 pentane–ether) and crystallisation gave the *furanone* (40%) as colourless crystals, m.p. 67—68 °C (pentane–ether), $\lambda_{max.}$(EtOH) 219 (12 000) and 258 nm (9 000);

$v_{max.}$(Nujol) 1 750, 1 640, and 1 620 cm^{-1}; δ 1.47 (CMe$_2$), 1.92 (d, J 7, =CMe), 4.04 (OMe), and 6.61—7.32 (m, 2 × CH); δ$_C$ 187.2, 184.1, 169.0, 145.8 (d), 131.6 (d), 102.5, 81.4, 62.6 (q), 24.5 (q), and 18.4 (q) (Found: C, 62.9; H, 6.7. C$_{11}$H$_{14}$O$_4$ requires C, 62.85; H, 6.7%).

The same furanone was also obtained (83%) by oxidation of 5,5-dimethyl-β-[1-hydroxy-(E)-but-2-enyl]-4-methoxyfuran-2(5H)-one with manganese dioxide in dichloromethane (25 °C; 24 h).

3-Carboxy-4-methoxy-5,5-dimethylfuran-2(5H)-one (23).—

By the general procedure carboxylation of the anion derived from (20), with dry carbon dioxide, followed by extraction and crystallisation, gave the carboxylic acid (51%) as almost colourless needles, m.p. 108—109 °C (ether), $\lambda_{max.}$(EtOH) 231 (7 900) and 224 nm (8 800); $v_{max.}$(Nujol) 1 770, 1 670, and 1 605 cm^{-1}; δ 1.57 (CMe$_2$), and 4.68 (OMe) (Found: C, 51.7; H, 5.4. C$_8$H$_{10}$O$_5$ requires C, 51.6; H, 5.4%).

3-Amino-4-methoxy-5,5-dimethylfuran-2(5H)-one (25).—

Diphenylphosphoryl azide (0.9 g) was added to a solution of 3-carboxy-4-methoxy-5,5-dimethylfuran-2(5H)-one (0.61 g) in dry dioxane (10 cm^3) containing dry triethylamine (0.33 g), and the resulting mixture was stirred at 23 °C for 18 h, when gas evolution had ceased. Benzyl alcohol (0.35 g) was added, and the mixture was kept at 23 °C for 24 h and then evaporated to dryness under reduced pressure. The residue was dissolved in 0.5M-hydrochloric acid (10 cm^3) and then extracted with ether (3 × 15 cm^3). The combined ether extracts were washed successively with aqueous sodium hydrogen carbonate, water, and brine, then dried and evaporated under reduced pressure. Chromatography of the residue on flash silica using pentane–ether (1:1) as the eluant gave the carbamate (0.52 g, 55%) which crystallised from toluene–hexane as white crystals, m.p. 88—89 °C, $\lambda_{max.}$(EtOH) 221sh (9 300) and 209 nm (13 300); $v_{max.}$(Nujol) 3 250, 1 760, 1 680, and 1 530 cm^{-1}; δ 1.47 (CMe$_2$), 4.13 (OMe), 5.21 (PhCH$_2$), 6.61 (NH), and 7.42 (5 H) (Found: C, 61.9; H, 5.95; N, 4.8%; M$^+$, 291.1134. C$_{15}$H$_{17}$NO$_5$ requires C, 61.85; H, 5.9; N, 4.8%; M, 291.1107).

A solution of the carbamate (0.16 g) in ethanol (5 cm^3) containing 2M-hydrochloric acid (0.3 cm^3) was shaken in the presence of hydrogen and 5% palladium-on-charcoal (30 mg) until no more hydrogen was absorbed (1 h), and then filtered. The filtrate was evaporated to dryness, and the residue was then dissolved in 2M-sodium hydroxide (5 cm^3). The resulting solution was extracted with dichloromethane (3 × 3 cm^3) and the combined extracts were then washed with brine, dried and evaporated under reduced pressure, to leave a solid residue. Crystallisation from n-hexane gave the amine (74 mg, 86%) as colourless crystals, m.p. 60—61 °C, $\lambda_{max.}$(EtOH) 265 (4 200) and 285 nm (4 950); $v_{max.}$(Nujol) 3 350, 3 300, 1 735, and 1 670 cm^{-1}; δ 1.43 (CMe$_2$), 3.06 (NH$_2$), and 4.19 (OMe) (Found: C, 53.3; H, 7.4; N, 9.1%; M$^+$, 157.0762. C$_7$H$_{11}$NO$_3$ requires C, 53.5; H, 7.05; N, 8.9%; M, 157.0739).

5-Ethylidene-4-methoxy-3-trimethylsilylfuran-2(5H)-one

(26).—By the general procedure, alkylation of the anion derived from (11) with trimethylsilyl chloride, followed by chromatography (flash silica; dichloromethane) and crystallisation gave the silyl furanone (71%) as colourless needles, m.p. 47—48 °C (light petroleum, b.p. 40—60 °C), $\lambda_{max.}$(EtOH) 271 nm; $v_{max.}$(film) 1 740, 1 675, and 1 605 cm^{-1}; δ 0.31 (SiMe$_3$), (d, J 7, =CHMe), 3.97 (OMe), and 5.36 (q, J 7, =CHMe) (Found: C, 56.5; H, 7.7%; M$^+$, 212.0880. C$_{10}$H$_{16}$O$_3$Si requires C, 56.6; H, 7.6%; M, 212.0869).

4-Methoxy-5-methyl-3-trimethylsilyl-5-vinylfuran-2(5H)-one

(27).—Hexamethylphosphoric triamide (0.82 cm^3) was added

dropwise to a stirred solution of lithium di-isopropylamide (1.1 equiv.) in dry tetrahydrofuran (10 cm^3) maintained at −78 °C under nitrogen and the resulting mixture was stirred at −78 °C for 0.5 h. A solution of 5-ethylidene-4-methoxy-3-trimethylsilyl-furan-2(5H)-one (1 g) in dry tetrahydrofuran (2 cm^3) was added over 0.5 h, and after a further 0.5 h methyl iodide (0.4 ml) was added. The reaction was kept at −78 °C for 6 h and then allowed to warm to 23 °C over 18 h. The mixture was evaporated to dryness under reduced pressure to leave a brown semi-solid which was dissolved in ether (15 cm^3) and filtered. The filtrate was evaporated to dryness to leave a dark brown oil which was purified by flash column chromatography on silica (40 g) using n-hexane and ethyl acetate (9:1) as the eluant to give the methylfuranone (0.2 g, 20%) as an orange coloured oil, $\lambda_{max.}$(EtOH) 272 (5 000) and 208 nm (22 000); $v_{max.}$(film) 1 730 and 1 590 cm^{-1}; δ 0.29 (SiMe$_3$), 1.59 (Me), 4.0 (OMe), 5.23 (dd, J 12 and 2, HC=CHH), 5.46 (dd, J 16 and 2, HC=CHH), and 5.94 (dd, J 16 and 12, HC=CH$_2$); δ$_C$ 189.1, 174.85, 136.6 (d), 116.4 (q), 97.0, 83.3, 60.8 (q), 22.9 (q), and 0.61 (q) (Found: M$^+$, 226.1029. C$_{11}$H$_{18}$O$_3$Si requires M, 226.1025).

5-(α-Hydroxybenzyl)-4-methoxy-3-trimethylsilyl-5-vinyl-furan-2(5H)-one (28).—

By the general procedure, alkylation of the anion derived from (26) with benzaldehyde followed by extraction and evaporation gave the carbinol (ca. 60%) as an unstable oil, δ 0.27 (SiMe$_3$), 3.81 (OMe), 4.88 [Ph CH(OH)], 5.29 (dd, J 10.5 and 2, HC=CHH), 5.5 (dd, J 16.5 and 2, HC=CHH), 6.09 (dd, J 16.5 and 10.5, HC=CH$_2$), and 7.2 (ArH). Attempted purification of the carbinol led only to recovery of the starting material.

In a similar manner, alkylation of the anion derived from (26) with 4-nitrobenzaldehyde and with 4-methoxybenzaldehyde led to the corresponding 5-hydroxybenzyl derivatives which underwent decomposition to the starting furan-2(5H)-one on brief storage in ether and an attempted purification by chromatography.

Metallation and Substitution of 5-Ethylidene-4-methoxy-3-trimethylsilylfuran-2(5H)-one (26).—General procedure.

The general procedure used for the metallation and substitution of 5-ethylidene-4-methoxyfuran-2(5H)-one, described above, was followed.

5-Acetyl-2-methoxy-3-trimethylsilyl-5-vinylfuran-2(5H)-one

(29).—By the general procedure acylation of the anion derived from (26) with acetyl chloride (−78 °C, 5 min, then allowed to warm to 25 °C) followed by chromatography [flash silica, 9:1 light petroleum (b.p. 40—60 °C)–ether] gave the acetylfuranone (43%) as an unstable orange oil, $\lambda_{max.}$ 336 (2 700) and 276 nm (2 500); $v_{max.}$(film) 1 750, 1 720, and 1 600 cm^{-1}; δ 0.32 (SiMe$_3$), 2.24 (COMe), 3.98 (OMe), 5.25 (d, J 10, HC=CHH), 5.48 (d, J 16, HC=CHH), and 6.2 (dd, J 16 and 10, HC=CH$_2$). A small amount (ca. 20%) of the isomeric furan (30) was also recovered by chromatography.

4-Methoxy-3-trimethylsilyl-5-vinylfuran-2-ylacetate (30).—

By the general procedure, acylation of the anion derived from (26) with acetyl chloride (−78 °C, 0.5 h; then 23 °C for 2 h), followed by chromatography (silica, dichloromethane) gave the acetate (76%) as a pale yellow oil, $\lambda_{max.}$(EtOH) 272 nm 12 700; $v_{max.}$(film) 1 790, 1 615, and 1 580 cm^{-1}; δ 0.2 (SiMe$_3$), 2.2 (OCOMe), 3.7 (OMe), 4.9 (dd, J 12 and 2, HC=CHH), 5.27 (dd, J 16 and 2, HC=CHH), and 6.45 (dd, J 16 and 12, HC=CH$_2$); δ$_C$ 168.2, 151.3, 149.4, 134.8, 122.1 (d), 109.0 (t), 99.2, 61.7 (q), 20.4 (q), and −1.03 (q) (Found: M$^+$, 254.0952. C$_{12}$H$_{18}$O$_4$Si requires M, 254.0974).

1-Acetoxy-5-methoxy-6-trimethylsilyl-4-vinyl-7-oxabicyclo-[2.2.1]hepta-2,5-diene-2,3-dicarboxylic Acid Dimethyl Ester (**31**).—A solution of 5-ethenyl-4-methoxy-3-trimethylsilylfuran-2-ylacetate (2 g) and dimethyl acetylenedicarboxylate (2.2 g) in dry benzene (5 cm^3) was heated under reflux in a nitrogen atmosphere for 18 h. The solvent was removed under reduced pressure to leave a brown oil which was purified by flash column chromatography on silica (80 g) using petroleum ether (b.p. 40—60 °C) and ether (4:1) as the eluant to give the *adduct* (1.6 g, 51%) as a pale yellow unstable oil, $v_{max.}$(film) 1 770, 1 720, and 1 590 cm^{-1}; δ 0.24 (SiMe$_3$), 2.15 (COMe), 3.71 (Me), 3.74 (Me), 3.77 (Me), 5.34 (dd, *J* 12 and 2, HC:C*H*H), 5.5 (dd, *J* 16 and 2, HC:CH*H*), and 6.32 (dd, *J* 16 and 12, *H*C:CH$_2$); δ$_C$ 167.7, 163.9, 151.2, 149.7, 127.2 (d), 120.0 (t), 60.5 (q), 52.3 (q), 52.1 (q), 21.3 (q), and 0.59 (q) (Found: *m/z* 337.1106. C$_{18}$H$_{24}$O$_8$Si requires $M^+ - CO_2Me$, 337.1098).

4-Methoxy-3-trimethylsilyl-5-vinylfuran-2-ylbenzoate (**32**).— By the general procedure, benzoylation of the anion derived from (**26**) with benzoyl chloride (− 78 °C for 0.5 h, then 23 °C for 17 h) followed by chromatography (silica, dichloromethane) gave the *benzoate* (44%) as a yellow oil, $v_{max.}$(film) 1 750, 1 715, 1 685, 1 632, and 1 600 cm^{-1}; δ 0.3 (SiMe$_3$), 4.02 (OMe), 5.4—5.7 (:CH$_2$), 6.35 (dd, *J* 17 and 10.5, HC:CH$_2$), 7.5 (m, 3 H), and 7.99 (dd, *J* 8 and 1.5, 2 H) (Found: M^+, 316.1162. C$_{17}$H$_{20}$O$_4$Si requires *M*, 316.1132).

5-(2-Hydroxypentylidene)-4-methoxy-3-trimethylsilylfuran-2(5H)-one (**34**).—By the general procedure, alkylation of the anion derived from (**26**), with propanal, followed by chromatography (silica; 4:1 methylene dichloride–ethyl acetate) and distillation gave the *furanone* (17%) as an oil, b.p. 150 °C (oven temperature) at 0.07 mmHg, $\lambda_{max.}$(EtOH) 274 nm; $v_{max.}$(film) 3 450, 1 740, and 1 600 cm^{-1}; δ 0.3 (SiMe$_3$), 0.96 (t, *J* 7, *Me*CH$_2$), 1.52 (m, 2 H), 1.74 (OH, exchanges with D$_2$O), 2.52 (m, 2 H), 3.72 (m, C*H*OH), and 4.04 (OMe), 5.6 (t, *J* 8, =CH) (Found: M^+, 270.1296. C$_{13}$H$_{22}$O$_4$Si requires *M*, 270.1287).

5-(2-Hydroxypentylidene)-4-methoxyfuran-2-(5H)-one (**35**).—Concentrated hydrochloric acid (0.2 cm^3) was added to a solution of the silane (**34**) (34 mg) in methanol (2.5 cm^3), and the mixture was kept at 23 °C for 7 days and then evaporated to dryness under reduced pressure. The residue was diluted with water (5 cm^3) and then extracted with ether. Evaporation of the dried ether extracts left the furanone (19.5 mg, 80%) as an oil, $\lambda_{max.}$(EtOH) 262 nm; $v_{max.}$(film) 3 430, 1 758, and 1 610 cm^{-1}; δ 0.95 (t, *J* 7, CH$_2$*Me*), 1.5 (m, 2 H), 1.9 (OH), 2.47 (m, 2 H), 3.68 (m, C*H*OH), 3.9 (OMe), 5.2 (=C*H*), and 5.58 (t, *J* 8, CH$_2$CH=); *m/z* 181 ($M^+ - OH$) and 140 ($M^+ - C_3H_6O$). Further treatment with concentrated sulphuric acid in tetrahydrofuran led to the polyene (**36**), $\lambda_{max.}$(EtOH) 293 nm [*cf.* analogue (**2**)].

5-(2-Bromoethylidene)-4-methoxyfuran-2(5H)-one (**37a**).—A stirred mixture of *N*-bromosuccinamide (2.5 g) and 5-ethylidene-4-methoxyfuran-2(5*H*)-one (2 g) in carbon tetrachloride (30 cm^3) was heated under reflux in a nitrogen atmosphere and irradiated with a Phillips 300 W lamp for 24 h. The mixture was filtered and the filtrate was then evaporated to dryness under reduced pressure to leave the *bromofuranone* (2 g, 60%) as a yellow solid which recrystallised from cyclohexane as pale yellow crystals, m.p. 105—109 °C, $v_{max.}$(KBr) 1 780, 1 640, and 1 600 cm^{-1}; δ 3.9 (OMe), 4.2 (d, *J* 8, CH$_2$Br), 5.34 (=CH), and 5.71 (t, *J* 8, =C*H*CH$_2$Br) (Found: C, 38.6; H, 3.6. C$_7$H$_7$BrO$_3$ requires C, 38.4; H, 3.2%).

2-(2,5-Dihydro-5-oxo-4-methoxyfuran-1-ylidenemethyl)-triphenylphosphonium Bromide (**37b**).—A solution of triphenyl-phosphine (3.6 g) in dry benzene (25 cm^3) was added to a solution of 5-(2-bromoethylidene-4-methoxyfuran-2(5*H*)-one (2 g) in dry benzene (25 cm^3). The solution was kept at 23 °C for 5 days, and then the supernatant liquid was decanted off. The solid residue was stirred with ether, filtered off, and dried to give the *phosphonium salt* (2.8 g, 68%) as a cream powder, m.p. 126—127 °C, $v_{max.}$(mull) 1 755, 1 610, and 1 460 cm^{-1}; δ 3.87 (OMe), 4.88 (dd, *J* 15 and 7, C*H$_2$*P̄Ph$_3$), 5.33 (=CH), 5.5 (m, =C*H*CH$_2$P̄), and 7.45—8.05 (m, 15 H) (Found: C, 57.9; H, 4.6. C$_{25}$H$_{22}$BrO$_3$P·2H$_2$O requires C, 58.0; H, 5.0%).

Z,Z/E,Z-4-Methoxy-5-(3-Phenylprop-2-enylidene)furan-2(5H)-one (**38**).—A solution of potassium t-butoxide (0.37 g) in dry tetrahydrofuran (3 cm^3) was added dropwise to a suspension of the phosphonium salt (**38**) (1.5 g) in dry tetrahydrofuran (10 cm^3) maintained at − 78 °C under nitrogen. After 0.5 h a solution of benzaldehyde (0.35 g) in dry tetrahydrofuran (3 cm^3) was added dropwise over 5 min. The mixture was kept at − 78 °C for 2 h and then allowed to warm to 23 °C when it was poured into water (20 cm^3). The mixture was extracted with ether (3 × 10 cm^3), and the combined extracts were washed with water and brine, and then dried (MgSO$_4$). Evaporation of the solvent under reduced pressure left a brown oil which was purified by flash column chromatography on silica (40 g) using acetone and n-hexane (1:19) as the eluant to give (*a*) the *Z,Z-isomer* (83 mg, 11%) (eluted first) as a pale yellow solid, m.p. 99—100 °C, $\lambda_{max.}$(EtOH) 331 (21 500) and 246 nm (4 600); $v_{max.}$(mull) 3 110, 1 765, and 1 600 cm^{-1}; δ 3.9 (OMe), 5.28 (=CH), 6.41—6.9 (m, 3 × =CH), and 7.4 (Ar=CH) (Found: M^+, 228.0782. C$_{14}$H$_{12}$O$_3$ requires *M*, 228.0786) and (*b*), the *Z,E-isomer* (90 mg, 12%) (eluted second) as a pale orange solid which recrystallised from n-hexane to give pale orange crystals, m.p. 112—114 °C, $\lambda_{max.}$(EtOH) 341 (12 000), 256 (5 000), and 246 nm (2 700); $v_{max.}$(mull) 3 120, 1 765, 1 750, and 1 600 cm^{-1}; δ 3.9 (OMe), 5.24 (=CH), 6.07—7.2 (m, 3 × =CH), and 7.23—7.6 (m, Ar=CH) (Found: C, 73.7; H, 5.4%; M^+, 228.0792. C$_{14}$H$_{12}$O$_3$ requires C, 73.7; H, 5.3%; *M*, 228.0786).

Z,Z/E,Z-4-Methoxy-5-(5-methylhex-2-enylidene)furan-2(5H)-one (**39**).—A solution of the phosphonium salt (**38**) (2.05 g) in dry dimethyl sulphoxide (5 cm^3) was added to a solution of dimsyl sodium in dimethyl sulphoxide [prepared from sodium hydride (0.11 g) and dry dimethyl sulphoxide (5 cm^3)] at 23 °C under nitrogen. After 1 h at 23 °C solution of isovaleraldehyde (0.4 g) in dry dimethyl sulphoxide (2 cm^3) was added dropwise over 5 min and the mixture was then kept at 23 °C for 18 h. The mixture was poured into 2м-hydrochloric acid, and then extracted with ether (3 × 15 cm^3). The combined ether extracts were washed with water and brine and then dried (MgSO$_4$). Evaporation of the solvent under reduced pressure left a brown oil which was purified by flash column chromatography on silica (25 g) using n-pentane and ether (2:3) as the eluant to give a 1:1 mixture of isomers of the *alkene* (0.41 g, 43%) as a colourless liquid showing $\lambda_{max.}$(EtOH) 305 nm; $v_{max.}$ 3 120, 2 950, 1 780, and 1 610 cm^{-1}; δ 0.89 (d, *J* 2 CH*Me*$_2$), 1.03 (d, *J* 2, CH*Me*$_2$), 1.72 (m, Me$_2$C*H*CH$_2$), 2.13 (m, 2 H), 3.96 (OMe), 3.98 (OMe), 5.27 (:CH), 5.29 (:CH), and 5.71—6.55 (m, 3 × :CH); δ$_C$ 170.4, 170.3, 168.2, 168.1, 142.9, 141.3, 140.7 (d), 137.8, 123.7 (d), 121.3 (d), 108.9 (d), 103.9 (d), 89.1, 88.8, 59.2, 42.6 (t), 37.2 (t), 28.6 (d), 28.4 (d), and 22.3 (q) (Found: M^+, 208.1086. C$_{12}$H$_{16}$O$_3$ requires *M*, 208.1099).

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