Cannabis. Part 29.[1] Synthesis of Four Benzofuro[6,7-*c*][2]benzopyrans Related to Cannabinol

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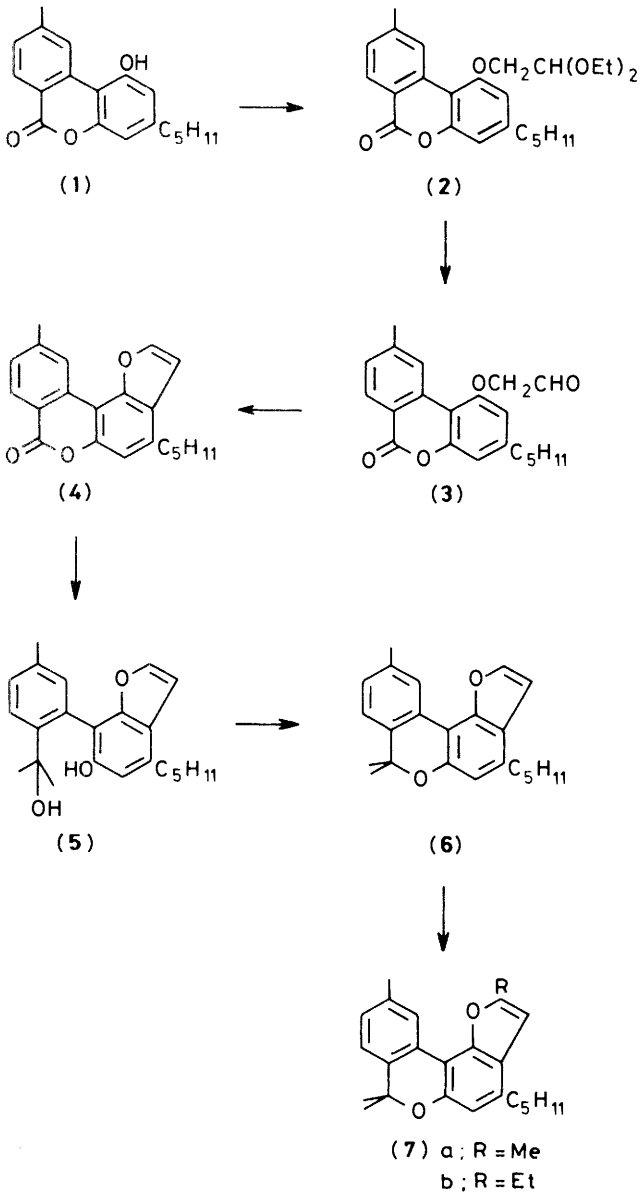
Four cannabinoids, the furan (**6**), the 2-methylfuran (**7a**), the 2-ethylfuran (**7b**), and the 2,3-dimethylfuran (**11**), related to cannabinol have been totally synthesized for the first time. The structures of two of three benzofuro[*3,2-b*][1]benzopyrans, the furan (**6**) and the 2-methylfuran (**7a**), recently isolated from cannabis resin smoke, were thereby confirmed. The earlier proposed structure of the third furan, as being the 2,3-dimethylfuran (**11**), was shown to be incorrect. The structure of 2-ethylfuran (**7b**) is now proposed for this cannabinoid. The key step in the syntheses of the furan (**6**) and the 2,3-dimethylfuran (**11**) was an internal site-specific base-catalysed cyclization of the intermediate aryloxyacetaldehyde (**3**) and 3-aryloxybutan-2-one (**8**), respectively. The 2-alkylated furans (**7a**) and (**7b**) have been synthesized in good yield by a highly selective lithiation of the furan (**6**) followed by treatment with an alkyl iodide.

In a recent study[2] three new cannabinoids, the furan (**6**), the 2-methylfuran (**7a**), and the 2,3-dimethylfuran (**11**), have been identified in the sublimate of cannabis resin smoke. The structure determination was based on the spectroscopic data and gas chromatography–mass spectral (gc–ms) analysis, and the structure of the 2,3-dimethylfuran (**11**) was proposed from the gc–ms data alone. Since these furans represent a hitherto unique structure, an unambiguous proof of the structure by synthesis was required.

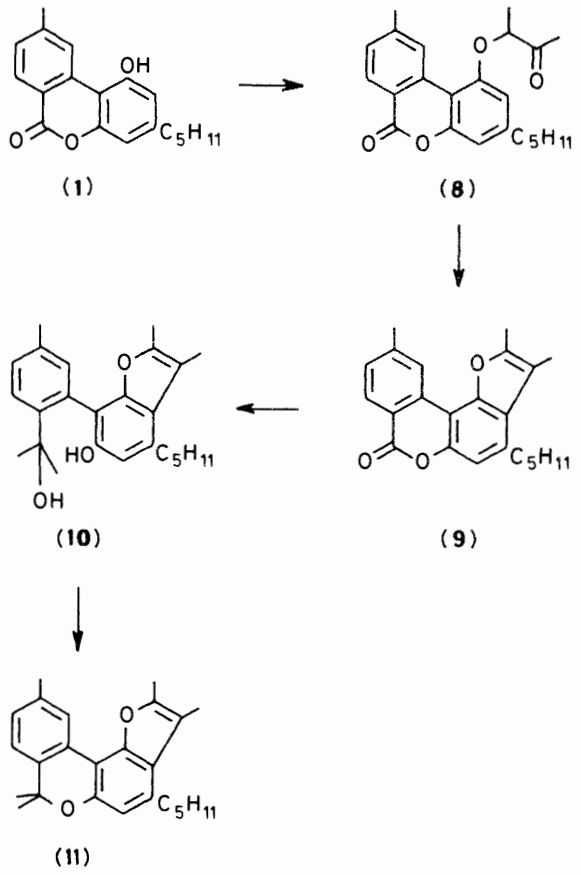
The close relationship of the new furans to cannabinol suggested that this compound or a derivative thereof should be the most useful starting compound. None of the methods available for the transformation of a phenol to a benzofuran was satisfactory. According to a comprehensive review,[3] the most direct method is still the Stoermer synthesis,[4–6] *i.e.* the cyclization of an aryloxyacetaldehyde acetal; however, this gives impractically low yields. Two methods from the more recent literature[7,8] proceed *via* the 2-chloroallyl and the propargyl ether of a phenol, respectively, but give 2-methylbenzofurans only. A simplified method, but with the same limitation, using the $TiCl_4$-mediated rearrangement of the 2-bromoallyl ether was reported recently.[9]

The known syntheses of another group of related natural compounds, the furocoumarins (from hydroxycoumarins) were more helpful. Most of these approaches are derived from the conversion of phenols into benzofurans, and most involve a Claisen rearrangement.[10–16] A potentially shorter route using milder conditions was discovered by Lahey and MacLeod.[17] 7-(2-Oxoethyl)coumarin, prepared from geiparvarin, undergoes a site-specific cyclization under basic conditions to give the furocoumarin psoralen in 30% yield. The mechanism was described [18] as an intramolecular Aldol condensation in which the phenoxide ion, formed on base hydrolysis of the pyrone ring, promotes attack at the exocyclic carbonyl function through the resonance-stabilized carbanion generated at the position *para* to the phenoxide ion.

With this base-catalysed cyclization as the key step, we used the lactone (**1**), available from earlier work,[19] as the starting compound in our reaction sequence (Scheme 1) leading to the furan (**6**). This lactone was etherified with bromoacetaldehyde diethyl acetal to give the acetal ether (**2**). The acetal was subsequently converted into the corresponding aldehyde (**3**) by heating it a dilute solution of hydrochloric acid in acetone. The cyclization to the furo-lactone (**4**) was carried out in aqueous ethanolic KOH in unexpectedly high yield (91%). Treatment of this lactone with an excess of methylmagnesium iodide followed



Scheme 1.



Scheme 2.

by acid-catalysed cyclization gave the crystalline furan (**6**), which was identical (^{1}H n.m.r., gc–ms) with the isolated[2] oily compound, thereby confirming the proposed structure.

The synthesis of the 2-methylfuran (**7a**) was achieved very simply and in high yield by adapting the α-lithiation of furan, known since 1962.[20] The furan (**6**) was selectively lithiated with butyl-lithium in hexane–tetrahydrofuran, and then methylated by subsequent treatment with methyl iodide, affording the crystalline 2-methylfuran (**7a**). This was identical (^{1}H n.m.r., gc–ms) with the isolated oily compound, thus establishing the proposed structure.

The synthetic route to the dimethylated furan (**11**) (Scheme 2) was derived from that in Scheme 1, giving products which included the furan (**6**). The lactone (**1**) was etherified with 3-chlorobutan-2-one to the ether lactone (**8**) which was cyclized under basic conditions to the furo-lactone (**9**). Treatment with methylmagnesium iodide followed by cyclization gave the crystalline 2,3-dimethylfuran (**11**); however, this differed significantly from the isolated compound. The gas chromatographic relative retention time [SE-30; 250 °C, relative R_t of (**6**):1.91, relative R_t of cannabidiol:1] of the synthetic compound was 3.12, while 2.55 was reported for the isolated compound.[21] We therefore considered the 2-ethylfuran (**7b**) as a possible structure. This compound was synthesized in the same way as the 2-methylfuran (**7a**) from the furan (**6**), using ethyl iodide in place of methyl iodide. The gas chromatogram of this product showed a relative R_t value (2.54) practically identical with that of the isolated material. The mass spectral data of the isolated compound, the 2-ethylfuran, and the 2,3-dimethylfuran were, as expected, almost identical. Consequently, we propose the 2-ethylfuran structure (**7b**) for this compound.

Experimental

General.—See the directions in the previous part.[1]

9-Methyl-6-oxo-3-pentyl-6H-dibenzo[b,d]pyran-1-yloxyacetaldehyde Diethyl Acetal (**2**).—A mixture of the lactone[19] (**1**) (0.30 g), bromoacetaldehyde diethyl acetal (0.22 g), potassium carbonate (0.15 g), and *N,N*-dimethylformamide (0.5 ml) was stirred and refluxed for 90 min, then cooled, diluted with water (10 ml), and extracted with ethyl acetate (2 × 20 ml). The extracts were washed twice with water, dried, and evaporated under reduced pressure to yield the crystalline ether acetal (**2**) (0.39 g, 93%), m.p. 121 °C (from ethyl acetate); δ_H [$(CD_3)_2SO$] 0.85 (3 H, t, ω-Me), 1.15 (6 H, t, *J* 7 Hz, 2 × OCH_2CH_3), 1.1—1.8 (6 H, m, 3 × CH_2), 2.5 (3 H, s, ArMe), 2.65 (2 H, t, *J* 7.5 Hz, benzylic CH_2), 3.7 (4 H, m, 2 × OCH_2CH_3), 4.2 (2 H, d, *J* 5 Hz, CH_2CH), 5.1 (1 H, t, *J* 5 Hz, CH_2CH), 6.85br (1 H, s, ArH), 6.95br (1 H, s, ArH), 7.45br (1 H, d, *J* 8 Hz, ArH), 8.15 (1 H, d, *J* 8 Hz, ArH), and 8.95br (1 H, s, ArH); δ_C($CDCl_3$) 13.6 (q), 15.0 (q, 2 C), 22.1 (q and t, 2 C), 30.2 (t), 31.0 (t), 35.6 (t), 61.7 (t, 2 C), 68.2 (t), 99.5 (d), 105.8 (s), 107.7 (d), 109.8 (d), 117.8 (s), 127.3 (d), 128.3 (d), 129.5 (d), 134.3 (s), 145.1 (s), 145.3 (s), 152.2 (s), 156.6 (s), and 161.3 p.p.m. (s).

9-Methyl-6-oxo-3-pentyl-6H-dibenzo[b,d]pyran-1-yloxyacetaldehyde (**3**).—Aqueous 2M-HCl (0.3 ml) was added to a solution of the acetal (**2**) (0.3 g) in acetone (4 ml). The resulting solution was refluxed for 4 h, cooled, diluted with water (10 ml), and extracted with ethyl acetate (2 × 15 ml). The extracts were washed with water, dried, and evaporated to give the crystalline aldehyde (**3**) (0.22 g, 89%), m.p. 178—179 °C (from toluene); δ_H[$(CD_3)_2SO$] 0.85 (3 H, t, ω-Me), 1.15—1.8 (6 H, m, 3 × CH_2), 2.6 (3 H, s, ArMe), 2.65 (2 H, t, *J* 7.5 Hz, benzylic CH_2), 5.2 (2 H, s, OCH_2), 6.85 (1 H, s, ArH), 6.9 (1 H, s, ArH), 7.45br (1 H, d, *J* 8 Hz, ArH), 8.2 (1 H, d, *J* 8 Hz, ArH), 9.2br (1 H, s, ArH), and 9.85 (1 H, s, CHO).

10-Methyl-4-pentylbenzofuro[6,7-c][2]benzopyran-7-one (**4**).—To a hot solution of the aldehyde (**3**) (2.2 g) in ethanol (200 ml) was added hot 0.1M-NaOH solution (400 ml). The mixture was refluxed for 30 min, then cooled, acidified with 10% H_3PO_4, and extracted with ethyl acetate (2 × 150 ml). The extracts were washed twice with water, dried, and concentrated under reduced pressure. Crystallization from methanol afforded the off-white furo-lactone (**4**) (1.9 g, 91%), m.p. 103—104 °C; δ_H($CDCl_3$) 0.9 (3 H, t, ω-Me), 1.15—1.85 (6 H, m, 3 × CH_2), 2.6 (3 H, s, ArMe), 2.85 (2 H, t, *J* 7.5 Hz, benzylic CH_2), 6.85 (1 H, d, *J* 2 Hz, β-furo-H), 7.05 (1 H, s, ArH), 7.35 (1 H, d, *J* 8 Hz, ArH), 7.8 (1 H, d, *J* 2 Hz, α-furo-H), 8.3 (1 H, d, *J* 8 Hz, ArH), and 8.65 (1 H, s, ArH); δ_C($CDCl_3$) 13.8 (q), 22.2 (q), 22.3 (t), 29.6 (t), 31.4 (t), 32.9 (t), 103.0 (s), 105.1 (d), 112.1 (d), 117.9 (s), 123.5 (s), 125.7 (d), 129.2 (d), 129.9 (d), 133.0 (s), 137.7 (s), 144.6 (d), 145.8 (s), 149.3 (s), 150.3 (s), and 161.3 p.p.m. (s).

6-Hydroxy-7-[2-(1-hydroxy-1-methylethyl)-5-methylphenyl]-4-pentylbenzofuran (**5**).—To a stirred solution of methylmagnesium iodide prepared from methyl iodide (0.65 ml) and magnesium (0.25 g) in diethyl ether (5 ml) was added dropwise a solution of the lactone (**4**) (0.30 g) in tetrahydrofuran (THF) (10 ml). The mixture was refluxed and stirred for 70 min, then cooled and poured into saturated aqueous ammonium chloride (35 ml). The mixture was extracted with diethyl ether (2 × 25 ml) and the extracts were washed with water, dried, and concentrated under reduced pressure at room temperature to yield the alcohol (**5**) as an almost colourless, viscous oil (0.31 g, 94%). The product was used directly for the next step.

7,7,10-Trimethyl-4-pentyl-7H-benzofuro[6,7-c][2]benzopyran (**6**).—Trifluoroacetic acid (0.05 ml) was added to a stirred solution of the alcohol (**5**) (0.26 g) in chloroform (3.5 ml). After 30 min at room temperature, the greenish brown solution was

diluted with diethyl ether, washed with water, dried, and evaporated to dryness to give the pure (gas chromatography) furocannabinol (**6**) (100%), m.p. 86—87 °C (from heptane), b.p. 185 °C/0.18 mmHg (M^+, 334.1940. Calc. for $C_{23}H_{26}O_2$: *M*, 334.1933); the ^{1}H n.m.r. data were identical with the published values;[2] δ_C[$(CD_3)_2CO$] 13.7 (q), 20.8 (q), 22.5 (t), 27.1 (q, 2 C), 30.3 (t), 31.7 (t), 33.0 (t), 77.6 (s), 105.5 (d), 106.2 (s), 113.6 (d), 121.9 (s), 123.2 (d), 125.9 (d), 126.6 (s), 128.6 (d), 136.5 (s), 136.6 (s), 137.1 (s), 144.1 (d), 151.2 (s), and 151.7 p.p.m. (s); *m/z* 334 (M^+, 22%), 319 (100), 277 (2), 275 (4), 262 (18), and 247 (9).

2,7,7,10-*Tetramethyl*-4-*pentyl*-7H-*benzofuro*[6,7-c][2]-*benzopyran* (**7a**).—To a solution of 1.5M-butyl-lithium in hexane (5 ml) was added a solution of the furan (**6**) (2.5 g) in THF (9 ml) dropwise at −15 °C and stirring was continued for 4 h at −15 °C. A solution of methyl iodide (0.53 ml) in THF (0.5 ml) was added to the resulting yellow mixture at −25 °C. The temperature was allowed to rise to room temperature in 1 h. Water (10 ml) was added and the mixture was extracted with diethyl ether (2 × 40 ml). The extracts were washed twice with water, dried, and concentrated to yield a yellow oil (2.48 g), the ^{1}H n.m.r. spectrum of which showed a conversion of 89%. Crystallization from heptane at −20 °C gave the pure (gas chromatography) 2-methylfuran (**7a**) (2.0 g, 77%), m.p. 56—57 °C (M^+, 348.2084. Calc. for $C_{24}H_{28}O_2$: *M*, 348.2089); ^{1}H n.m.r. data were identical with the published values;[2] δ_C($CDCl_3$) 13.9 (q), 14.1 (q), 21.4 (q), 22.4 (t), 27.3 (q, 2 C), 29.9 (t), 31.5 (t), 33.1 (t), 77.3 (s), 101.0 (d), 105.8 (s), 112.8 (d), 122.6 (d), 123.0 (s), 125.9 (d), 126.7 (s), 127.9 (d), 135.1 (s), 136.2 (s), 136.9 (s), 150.0 (s), 151.1 (s), and 153.5 p.p.m. (s); *m/z* 348 (M^+, 26%), 333 (100), 291 (3), 289 (4), 276 (15), and 261 (11).

2-*Ethyl*-7,7,10-*trimethyl*-4-*pentyl*-7H-*benzofuro*[6,7-c][2]-*benzopyran* (**7b**).—This compound was prepared in the same way as 2-methylfuran (**7a**) except for that ethyl iodide was used instead of methyl iodide. Starting with 0.68 g of the furan (**6**), 0.67 g of the product was obtained, as a yellow oil containing (^{1}H n.m.r. spectrum) 9% of the unconverted starting furan (**6**). The product was chromatographed on a silica-gel column using a mixture of hexane–diethyl ether (99 : 1) as eluant; the fractions were monitored by gas chromatography (SE-30; 250 °C), relative R_t: 2.54, relative R_t of (**6**): 1.91. The pure (gas chromatography) 2-ethylfuran (**7b**) was an almost colourless *oil* (M^+, 362.2243. $C_{25}H_{30}O_2$ requires *M*, 362.2246), δ_H($CDCl_3$) 0.9 (3 H, t, ω-Me), 1.4 (3 H, t, *J* 7.5 Hz, furo-CH_2CH_3), 1.6 (6 H, s, 2 × Me), 1.1—1.8 (6 H, m, 3 × CH_2), 2.4 (3 H, s, ArMe), 2.6—3.0 (4 H, m, $ArCH_2$ and furo-CH_2CH_3), 6.35 (1 H, s, β-furo-H), 6.65 (1 H, s, ArH), 7.1 (2 H, s, 2 × ArH), and 8.3 (1 H, s, ArH); δ_C($CDCl_3$) 12.0 (q), 13.9 (q). 21.4 (q), 21.8 (t), 22.4 (t), 27.3 (q, 2 C), 29.8 (t), 31.6 (t), 33.1 (t), 77.3 (s), 99.3 (d), 105.8 (s), 112.7 (d), 122.5 (d), 122.8 (s), 126.0 (d), 126.7 (s), 127.9 (d), 135.3 (s), 136.2 (s), 136.8 (s), 150.0 (s), 151.0 (s), and 159.1 p.p.m. (s); *m/z* 362 (M^+, 31%), 347 (100), 305 (3), 303 (3), 290 (14), and 275 (10).

9-*Methyl*-1-(1-*methyl*-2-*oxopropoxy*)-3-*pentyldibenzo*[b,d]-*pyran*-6-*one* (**8**).—A mixture of the lactone (**1**) (0.336 g), 3-chlorobutan-2-one (0.12 ml), potassium carbonate (0.18 g), and acetone (10 ml) was stirred and refluxed for 24 h. The cooled mixture was evaporated to dryness and dissolved in ethyl acetate (60 ml), and the solution was washed with water, dried, and concentrated to yield the crystalline ether (**8**) (0.40 g, 96%), m.p. 144—145 °C (from toluene); δ_H[$(CD_3)_2SO$] 0.85 (3 H, t, ω-Me), 1.1—1.8 (6 H, m, 3 × CH_2), 1.6 (3 H, d, *J* 7 Hz, $CHCH_3$), 2.25 (3 H, s, COMe), 2.5 (3 H, s, ArMe), 2.6 (2 H, t, benzylic CH_2), 5.4 (1 H, q, *J* Hz, $CHCH_3$), 6.75 (1 H, s, ArH), 6.85 (1 H, s, ArH), 7.45 (1 H, d, *J* 8 Hz, ArH), 8.2 (1 H, d, *J* 8 Hz, ArH), and 9.1 (1 H, s, ArH); δ_C($CDCl_3$) 13.8 (q), 17.4 (q), 22.3 (q and t, 2 C), 24.4 (q), 30.2 (t), 31.1 (t), 35.6 (t), 79.9 (d), 106.1 (s), 108.1 (d), 110.6 (d), 118.2 (s), 127.2 (d), 128.6 (d), 130.0 (d), 134.3 (s), 145.3 (s), 145.6 (s), 152.8 (s), 155.5 (s), 161.1 (s), and 208.5 p.p.m. (s).

2,3,10-*Trimethyl*-4-*pentylbenzofuro*[6,7-c][2]*benzopyran*-7-*one* (**9**).—The ether (**8**) (0.90 g) was dissolved in ethanol (50 ml) and 1M-KOH solution (200 ml) and refluxed for 16 h. After being cooled, the solution was acidified with 10% aqueous phosphoric acid and extracted with ethyl acetate (2 × 100 ml). Work-up gave the crystalline furo-lactone (**9**) (100%), m.p. 131—132 °C (from ethyl acetate); δ_H[$(CD_3)_2CO$] 0.9 (3 H, t, ω-Me), 1.2—1.9 (6 H, m, 3 × CH_2), 2.35 (3 H, s, β-furo-CH_3), 2.5 (3 H, s, α-furo-CH_3), 2.6 (3 H, s, ArMe), 3.0 (2 H, t, *J* 7.5 Hz, benzylic CH_2), 7.0 (1 H, s, ArH), 7.5 (1 H, d, *J* 8 Hz, ArH), 8.25 (1 H, d, *J* 8 Hz, ArH), and 8.75 (1 H, s, ArH); δ_C($CDCl_3$) 10.3 (q), 11.7 (q), 13.9 (q), 22.3 (q), 22.4 (t), 31.2 (t), 31.5 (t), 32.4 (t), 102.2 (s), 109.7 (s), 112.0 (d), 118.0 (s), 124.4 (s), 125.8 (d), 128.8 (d), 129.9 (d), 133.3 (s), 137.8 (s), 145.6 (s), 148.2 (s), 149.6 (s), 150.6 (s), and 161.5 p.p.m. (s).

6-*Hydroxy*-7-[2-(1-*hydroxy*-1-*methylethyl*)-5-*methylphenyl*]-2,3-*dimethyl*-4-*pentylbenzofuran* (**10**).—To a stirred solution of methylmagnesium iodide prepared from methyl iodide (1.3 ml) and magnesium (0.48 g) in diethyl ether (10 ml) was added dropwise a solution of the lactone (**9**) (0.80 g) in THF (20 ml). The mixture was stirred and refluxed for 70 min and worked up as for compound (**5**) to yield the alcohol (**10**) (0.83 g, 95%), which slowly crystallized. The product was used directly for the next step.

2,3,7,7,10-*Pentamethyl*-4-*pentyl*-7H-*benzofuro*[6,7-c][2]*benzopyran* (**11**).—Trifluoroacetic acid (0.16 ml) was added to a stirred solution of the alcohol (**10**) (0.83 g) in chloroform (16 ml). After 30 min at room temperature, the mixture was worked up as for compound (**6**) to give the pure (gas chromatography) 2,3-dimethylfuran (**11**) (100%), m.p. 107—108 °C (from acetone) (M^+, 362.2251. $C_{25}H_{30}O_2$ requires *M*, 362.2246); relative R_t: 3.12; δ_H($CDCl_3$) 0.9 (3 H, t, ω-Me), 1.2—1.8 (6 H, m, 3 × CH_2), 1.6 (6 H, s, 2 × Me), 2.3 (3 H, s, β-furo-CH_3), 2.5 (6 H, s, α-furo-CH_3 and ArMe), 2.85 (2 H, t, *J* 7.5 Hz, benzylic CH_2), 6.6 (1 H, s, ArH), 7.1 (2 H, s, 2 × ArH), and 8.25 (1 H, s, ArH); δ_C[$(CD_3)_2CO$] 10.0 (q), 11.0 (q), 13.7 (q), 20.9 (q), 22.6 (t), 27.1 (q, 2 C), 31.8 (t), 32.0 (t), 32.5 (t), 77.3 (s), 105.6 (s), 110.0 (s), 113.7 (d), 122.8 (s), 123.1 (d), 126.1 (d), 126.9 (s), 128.3 (d), 136.7 (s, 2 C), 137.0 (s), 149.4 (s), 150.2 (s), and 151.0 p.p.m. (s); *m/z* 362 (M^+, 29%), 347 (100), 305 (3), 303 (3), 290 (12), and 275 (6).

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