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Synthesis of Tricyclic Aryl Spiroacetals Related to the Papulacandins

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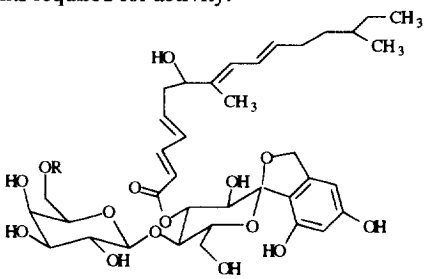
Abstract: A convenient synthesis of aryl spiroacetals related to the antifungal agents, the papulacandins, is reported. The synthetic methodology involves the addition of ortho-lithiated diethylbenzamides to lactones followed by acid catalysed cyclization of the resultant keto-alcohols.

INTRODUCTION

Spiroacetals are an important structural feature in many biologically active compounds such as the polyether antibiotics, marine and plant toxins, insect pheromones and antiparasitic agents.[1] The papulacandins A **1**, B **2**, C **3**, D, **4** and E are a group of C-arylglycosyl spiroacetal antifungal agents isolated from *Papularia spherosperma*[2] which exhibit potent *in vitro* activity against *Candida albicans* and related microorganisms[3,4] More recently, the common opportunistic infection in AIDS patients, *Pneumoocystis carinii* pneumonia, has been effectively overcome by newer members of the papulacandin family, Mer-WF3010 5 and L-687-781 6.[5] Papulacandin D **4** which lacks the short fatty acid and the galactose residue exhibits antifungal activity, hence, less complex molecules may result in enhanced biological activity or provide a better understanding of the elements required for activity.



papulacandin D **4**

papulacandin A **1** R =

papulacandin B **2** R =

papulacandin C **3** R =

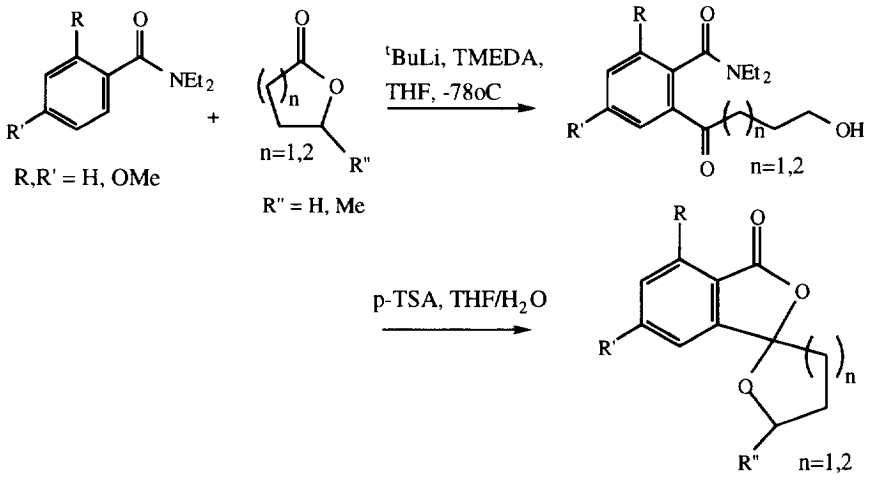
Mer-WF3010 **5** R =

L-687,781 **6** R =

The tricyclic C-arylglycosyl spiroacetal nucleus has been assembled *via* a Diels-Alder reaction[6], a palladium (0) catalysed coupling of an aryl halide with a stannyl glucal[7,8,9] and the reaction of a 2-bromobenzyl ether with an appropriately protected gluconolactone.[10,11,12] We now wish to report an efficient two step synthesis of a range of aryl spiroacetals related to the papulacandins, *via* the addition of ortho-lithiated tertiary benzamides to lactones followed by acid-catalyzed cyclization of the resultant keto alcohols (Scheme).

DISCUSSION

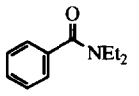
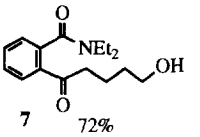
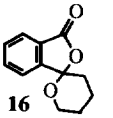
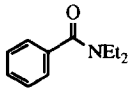
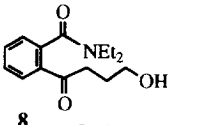
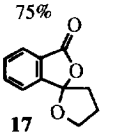
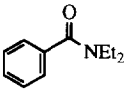
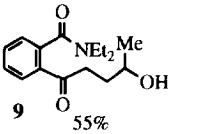
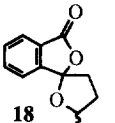
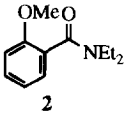
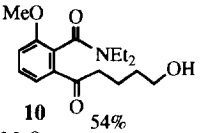
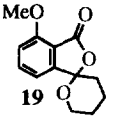
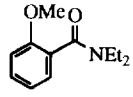
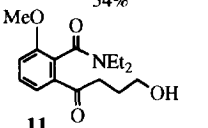
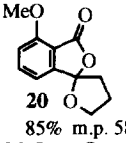
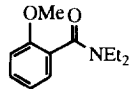
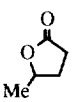
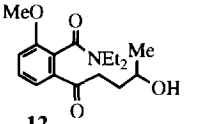
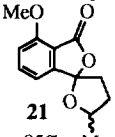
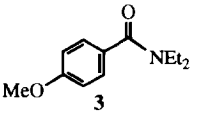
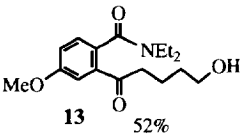
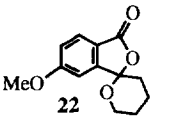
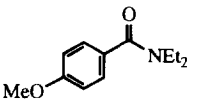
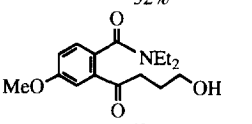
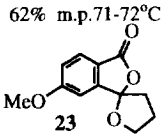
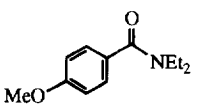
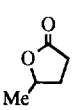
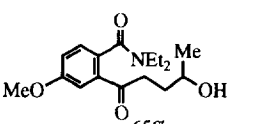
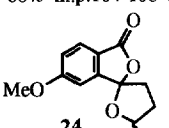
Our initial work focused on the use of *N,N'*-diisopropylbenzamides, however, the resultant keto-alcohol products proved to be very resistant towards the desired cyclization. Use of the corresponding *N,N'*-diethylbenzamides, however, provided keto-alcohol products which underwent facile cyclization to the desired spiroacetals. The diethylbenzamides **1**,**2**,**3** underwent *ortho*-lithiation upon treatment with *tert*-butyllithium (1.1 equiv.) at -78°C in THF containing TMEDA (1.1 equiv.). Coupling to the lactones proceeded readily upon addition of the appropriate lactone to the lithiated amide and allowing the reaction mixture to warm to room temperature. Use of δ-valerolactone **4**, γ-butyrolactone **5** and γ-valerolactone **6** provided keto-alcohol products in good yield and no evidence for formation of the corresponding cyclic hemiacetals was found upon analysis of the NMR and IR spectra of the crude products.



Scheme

The ^{1}H NMR spectra of the keto-alcohols exhibited two triplets assigned to the methyl groups of the amide and two resonances for the CH_2N group. The non-equivalence of the CH_3CH_2N group is attributed to a significant contribution to the structure from the resonance form with a double bond between the carbonyl carbon and the nitrogen atoms thereby imparting considerable rigidity to the amide linkage. Doubling up of the signals is due to the slowness of rotation around the C-N bond on the NMR time scale. Furthermore in the

Table. Synthesis of Aryl Spiroacetals from Benzamides and Lactones (Scheme)

Benzamide	lactone	keto-alcohol	spiroacetal
 **1**	 **4**	 **7** 72%	 **16** 75%
 **1**	 **5**	 **8** 56%	 **17** 70%
 **1**	 **6**	 **9** 55%	 **18** 90% Me
 **2**	 **4**	 **10** 54%	 **19** 73% m.p. 74-76°C
 **2**	 **5**	 **11** 60%	 **20** 85% m.p. 58-60°C
 **2**	 **6**	 **12** 70%	 **21** 95% Me
 **3**	 **4**	 **13** 52%	 **22** 62% m.p.71-72°C
 **3**	 **5**	 **14** 50%	 **23** 80% m.p.104-106°C
 **3**	 **6**	 **15** 65%	 **24** 70% Me

^{13}C NMR spectra of the keto-alcohols, two resonances were observed for several of the individual carbons as a result of this restricted rotation.

After purification of the keto-alcohols by flash chromatography cyclization to the aryl spiroacetals was effected by heating a solution of the keto-alcohol in THF:H_2O (1:1) under reflux with a catalytic quantity of *p*-toluenesulphonic acid. Attempts to effect cyclization of the keto-alcohols using a variety of other acidic conditions met with little success (e.g TFA, perchloric acid, HCl). A summary of the spiroacetals prepared is given in the Table with the yields for the individual steps. Spiroacetals **18**, **21**, **24** were formed from keto-alcohols **9**,**12**,**15** as inseparable 1:1 isomeric mixtures. Subsequent treatment of these isomeric mixtures with trifluoroacetic acid in toluene under reflux for 10 days did not alter the ratio of isomers.

The methodology presented herein is limited to the use of benzamides bearing a methoxy group at the *ortho* and *para* positions in that use of 3-methoxy-*N*,*N*'-diethylbenzamide failed to give significant quantities of the keto-alcohol products in the lithiation step. This is attributed to steric hindrance, whereby the bulky lactone is hindered from reaction when the anion is generated between the amide and the methoxy groups. Quenching the organolithium species with deuterium oxide led to complete incorporation at C-2 thereby establishing that anion formation had taken place and that reaction with the lactone electrophile was problematic.

In the published syntheses of the papulacandins wherein the arylspiroacetal ring was assembled *via* ortholithiation of benzyl ethers[10,11,12] the addition products were only formed in low yield using gluconolactones as electrophiles. The work presented herein provides an efficient entry to a range of aryl spiroacetals related to the papulacandins and suggests that the low yields observed in the reported syntheses of the papulacandins using similar methodology is attributed to steric hindrance in the reaction of an aryllithium with a lactone electrophile when it is flanked by a neighbouring methoxy group.

EXPERIMENTAL

General Methods

Infrared spectra were recorded on a Perkin Elmer 1600 Series FTIR spectrometer as Nujol mulls or thin films between sodium plates. ^1H nmr spectra were obtained at 200.13 MHz using a Bruker AC200B spectrometer ^{13}C nmr spectra were obtained at 50 MHz using a Bruker AC200B spectrometer. Microanalyses were performed at the microanalytical laboratory, University New South Wales, Sydney. Mass spectra were recorded on an AEI model MS902 double focusing magnetic sector mass spectrometer with an ionization potential of 70eV. Merck Kieselgel 60 (230-400 mesh) was used for flash chromatography. All solvents were purified and dried before use.

General Procedure for Preparation of Benzamides[13]

The appropriate benzoyl chloride (0.02 mol) was slowly added to a cooled and stirred (0^0C) solution of diethylamine (0.04 mol) in dichloromethane (25 cm^3) using a pressure equilising dropping funnel. The reaction mixture was stirred for 1 h under nitrogen at room temperature after the acid chloride had been added. Cold water (15 cm^3) was then added to dissolve the diethylamine hydrochloride that had precipitated. The reaction mixture was poured into dichloromethane (100 cm^3) and washed with 5% HCl (2 x 100 cm^3), H_2O (50 cm^3), 5% NaOH (50 cm^3), brine (50 cm^3) and dried ($MgSO_4$). The dichloromethane was removed at

reduced pressure to afford a pale yellow oil. Purification by flash chromatography using 1:1 hexane / ethyl acetate as eluent afforded the diethylbenzamide.

General Procedure for the Preparation of Keto-alcohols

To a stirred solution of the appropriate benzamide (1.5-4.0 mmol) in dry tetrahydrofuran (15 cm^3) under argon at -78°C, was added *tert*-butyllithium (1.1 equiv.) dropwise. Tetramethylethylenediamine (1.1 equiv., freshly distilled from calcium hydride) was then added and the reaction mixture stirred for 1 h at -78°C. The appropriate lactone (1.1 equiv.) was then added and the reaction mixture allowed to warm to room temperature. After quenching with saturated aqueous ammonium chloride solution (10 cm^3), tetrahydrofuran was removed under reduced pressure. The residue was extracted with ethyl acetate (3 x 50 cm^3), washed with water (10 cm^3) and dried ($MgSO_4$). Removal of solvent at reduced pressure afforded an orange-yellow oil that was purified by flash chromatography using hexane : ethyl acetate as eluent [gradient elution (1:1) to (1:2)] affording the keto-alcohol.

N,N-*Diethyl-2-(5'-hydroxy-1'-oxopentyl)benzamide* (**7**). The *title compound* (**7**) (0.79 g, 72%) was prepared as a pale yellow oil from *N,N*-diethylbenzamide (**1**) (0.7 g, 4 mmol) and δ-valerolactone (**4**) (0.44 g, 4.4 mmol) following the general procedure given above (Found: M^+, 277.1640. $C_{16}H_{23}NO_3$ requires M, 277.1678); υ_{max} (thin film) / cm^{-1} 3380 (br, OH), 1687 (s, C=O, ketone) 1617 (s, C=O, amide); δ_H (200 MHz; $CDCl_3$) 1.06 (3 H, t, *J* 7.0, Me), 1.30 (3 H, t, *J* 7.0, Me), 1.61 (2 H, m, 3'-H), 1.84 (2 H, m, 4'-H), 1.95 (1 H, br, OH), 2.99 (2 H, t, *J* 6.8, 2'-H), 3.14 (2 H, q, *J* 7.1, CH_2N), 3.59 (2 H, q, *J* 7.1, CH_2N), 3.62 (2 H, t, *J* 6.0, 5'-H),7.29 (1 H, dd, $J_{5,6}$ 7.5, $J_{4,6}$ 1.6, 6-H), 7.49 (1 H, td, J_{ortho} 7.5, $J_{5,3}$ 1.5, 5-H), 7.55 (1 H, td, J_{ortho} 7.5, $J_{4,6}$ 1.6, 4-H), 7.81 (1 H, dd, $J_{3,4}$ 7.5, $J_{3,5}$ 1.5, 3-H); *m/z* (%) 277 (M^+, 31), 259 ($M-H_2O$, 29), 204 ($M-HNEt_2$, 43), 187 ($M-H_2O-NEt_2$, 95), 159 (63), 146 (22), 131 (20), 105 (20), 72 (NEt_2, 100).

N,N-*Diethyl-2-(4'-hydroxy-1'-oxobutyl)benzamide* (**8**). The *title compound* (**8**) (213 mg, 56%) was prepared as a pale yellow oil from *N,N'*-diethylbenzamide (**1**) (0.26 g, 1.5 mmol) and γ-butyrolactone (**5**) (0.15 g, 1.7 mmol) following the general procedure given above (Found: $M-H_2O$, 245.1523. $C_{15}H_{19}NO_2$ requires $M-H_2O$, 245.1416); υ_{max} (thin film) / cm^{-1} 3402 (br, OH), 1682 (s, C=O, ketone) 1612 (s, C=O, amide); δ_H (200 MHz; $CDCl_3$) 1.05 (3 H, t, *J* 7.0, Me), 1.29 (3 H, t, *J* 7.0, Me), 1.91 (2 H, p, *J* 6.0, 3'-H), 3.00-3.18 (4 H, m, 2'-H, CH_2N), 3.23 (1 H, br, OH), 3.52-3.69 (4 H, m, 4'-H, CH_2N), 7.28 (1 H, dd, $J_{5,6}$ 7.4, $J_{4,6}$ 1.4, 6-H), 7.43 (1 H, td, J_{ortho} 7.5, $J_{5,3}$ 1.5, 5-H), 7.53 (1 H, td, J_{ortho} 7.4, $J_{4,6}$ 1.3, 4-H), 7.80 (1 H, dd, $J_{3,4}$ 7.4, $J_{3,5}$ 1.4, 3-H); *m/z* (%) 263 (M^+, 1), 245 ($M-H_2O$, 45), 233 (65), 204 (43), 173 ($M-H_2O-NEt_2$, 90), 72 (NEt_2, 100).

N,N-*Diethyl-2-(4'-hydroxy-1'-oxopentyl)benzamide* (**9**). The *title compound* (**9**) (0.21 g, 55%) was prepared as a yellow oil from *N,N'*-diethylbenzamide (**1**) (0.27 g, 1.5 mmol) and γ-valerolactone (**6**) (0.17 g, 1.7 mmol) following the general procedure given above (Found: $M-H_2O$, 259.1537. $C_{16}H_{21}NO_2$ requires M, 277.1678); υ_{max} (thin film) / cm^{-1} 3401 (br, OH), 1687 (s, C=O, ketone) 1622 (s, C=O, amide); δ_H (200 MHz; $CDCl_3$) 1.05 (3 H, t, *J* 7.1, CH_2CH_3), 1.20 (3 H, d, *J* 6.3, Me) 1.29 (3 H, t, *J* 7.1, CH_2CH_3), 1.65-1.97 (2 H, m, 3'-H), 2.99 (2 H, t, *J* 6.8, 2'-H), 3.12 (2 H, q, *J* 7.2, CH_2N), 3.33 (1 H, br, OH), 3.56 (2 H,q, *J* 6.8, CH_2N),

3.75-3.91 (1 H, m, C*H*OH),7.20 (1 H, dd, $J_{5,6}$ 6.7, $J_{4,6}$ 1.9, 6-H), 7.44 (1 H, td, J_{ortho} 7.4, $J_{5,3}$ 1.6, 5-H), 7.53 (1 H, td, J_{ortho} 7.4, $J_{4,6}$ 1.4, 4-H), 7.82 (1 H, dd, $J_{3,4}$ 7.5, $J_{3,5}$ 1.5, 3-H); *m/z* (%) 277 (M^+, 2), 259 (M-H_2O, 10), 204 (M-$HNEt_2$, 35), 187 (M-H_2O-NEt_2, 90), 176 (10), 159 (10), 146 (90), 72 (NEt_2, 100).

N,N-*Diethyl-2-(5'-hydroxy-1'-oxopentyl)- 6-methoxybenzamide* (**10**). The *title compound* (**10**) (181 mg, 54%) was prepared as a pale yellow oil from 2-methoxy-*N,N'*-diethylbenzamide (**2**) (0.23 g, 1.1 mmol) and δ-valerolactone (**4**) (0.12 g, 1.2 mmol) following the general procedure given above (Found: M-H_20, 289.1657. $C_{17}H_{23}NO_3$ requires M-H_20, 289.1677); υ_{max} (thin film) / cm^{-1} 3382 (br, OH), 1687 (s, C=O, ketone) 1615 (s, C=O, amide); δ_H (200 MHz; $CDCl_3$) 1.05 (3 H, t, *J* 7.3, Me), 1.27 (3 H, t, *J* 7.2, Me) 1.58-1.98 (4 H, m, 3'-H, 4'-H), 2.37 (1 H, br, OH), 2.90-3.02 (2 H, m, 2'-H), 3.12 (2 H, q, *J* 7.1, CH_2N), 3.45-3.71 (4 H, m, 5'-H, CH_2N), 3.82 (3 H, s, OMe), 7.07 (1 H, dd, $J_{4,5}$ 7.5, $J_{5,3}$ 1.6, 5-H), 7.35 (1 H, dd, $J_{3,4}$ 7.5, $J_{3,5}$ 1.6, 3-H), 7.39 (1 H, t, *J* 7.5, 4-H); *m/z* (%) 307 (M^+, 2), 289 (M-H_2O, 8), 234 (M-$HNEt_2$, 4), 217 (M-H_2O-NEt_2,9), 177 (10), 135 (10), 105 (10), 72 (NEt_2, 100).

N,N-*Diethyl-2-(4'-hydroxy-1'-oxobutyl) -6-methoxybenzamide* (**11**). The *title compound* (**11**) (0.25 g, 60%) was prepared as a pale yellow oil from 2-methoxy-*N,N'*-diethylbenzamide (**2**) (0.3 g, 1.5 mmol) and γ-butyrolactone (**5**) (0.15 g, 1.7 mmol) following the general procedure given above (Found: M-H_2O, 275.1482. $C_{16}H_{21}NO_3$ requires M, 275.1521); υ_{max} (thin film) / cm^{-1} 3402 (br, OH), 1692 (s, C=O, ketone) 1617 (s, C=O, amide); δ_H (200 MHz; $CDCl_3$) 1.04 (3 H, t, *J* 7.3, Me), 1.27 (3 H, t, *J* 7.2, Me) 1.92 (2 H, m, 3'-H), 2.99 (2 H, t, *J* 6.9, 2'-H), 3.28 (2 H, q, *J* 7.1, CH_2N), 3.45-3.73 (4 H, m, 4'-H, CH_2N), 3.82 (3 H, s, OMe), 7.08 (1 H, dd, $J_{4,5}$ 5.8, $J_{5,3}$ 3.4, 5-H), 7.34-7.59 (2 H, m, 3-H, 4-H); *m/z* (%) 293 (M^+, 3), 234 (M-$HNEt_2$, 15), 203 (M-H_2O-NEt_2, 80), 177 (20) 72 (NEt_2, 100).

N,N-*Diethyl-2-(4'-hydroxy-1'-oxopentyl)- 6-methoxybenzamide* (**12**). The *title compound* (**12**) (0.52 g, 70%) was prepared as a yellow oil from 2-methoxy-*N,N'*-diethylbenzamide (**2**) (0.5 g, 2.4 mmol) and γ-valerolactone (**6**) (0.26 g, 2.6 mmol) following the general procedure given above (Found: M-H_2O, 289.1779. $C_{17}H_{23}NO_3$ requires M, 289.1678); υ_{max} (thin film) / cm^{-1} 3402 (br, OH), 1682 (s, C=O, ketone) 1617 (s, C=O, amide); δ_H (200 MHz; $CDCl_3$) 1.05 (3 H, t, *J* 7.3, CH_2CH_3), 1.16 (3 H, d, *J* 6.2, Me), 1.27 (3 H, t, *J* 7.2, CH_2CH_3) 1.61-1.98 (2 H, m, 3'-H), 2.97-3.18 (4 H, m, CH_2N, 2'-H), 3.44-3.79 (4 H, m, CH_2N, 4'-H, OH), 3.82 (3 H, s, OMe), 7.02-7.09 (1 H, m, 5-H), 7.34-7.40 (2 H, m, 3-H, 4-H); *m/z* (%) 307 (M^+, 3), 289 (M-H_20, 15), 234 (M-$HNEt_2$, 15), 217 (M-H_2O-NEt_2, 100), 176 (50), 72 (NEt_2, 80).

N,N-*Diethyl-2-(5'-hydroxy-1'-oxopentyl)-4-methoxybenzamide* (**13**). The *title compound* (**13**) (0.39 g, 52%) was prepared as a pale yellow oil from 4-methoxy-*N,N'*-diethylbenzamide (**3**) (0.5 g, 2.4 mmol) and δ-valerolactone (**4**) (0.26 g, 2.6 mmol) following the general procedure given above (Found: M^+, 307.1732. $C_{17}H_{25}NO_4$ requires M, 307.1784); υ_{max} (thin film) / cm^{-1} 3401 (br, OH), 1692 (s, C=O, ketone) 1607 (s, C=O, amide); δ_H (200 MHz; $CDCl_3$) 1.06 (3 H, t, *J* 7.1, Me), 1.28 (3 H, t, *J* 7.1, Me), 1.55-1.82 (4 H, m, 3'-H, 4'-H), 2.60 (1 H, br, OH), 2.94 (2 H, t, *J* 6.9, 2'-H), 3.15 (2 H, q, *J* 6.5, CH_2N), 3.49-3.62 (4 H, m, 5'-H, CH_2N), 3.86 (3 H, s, OMe), 7.01 (1 H, dd, $J_{5,6}$ 8.1, $J_{5,3}$ 2.6, 5-H), 7.20 (1 H, d, *J* 8.4, 6-H), 7.25 (1 H, d, $J_{3,5}$ 2.4, 3-H); *m/z* (%) 307 (M^+, 2), 289 (M-H_20, 30), 234 (M-$HNEt_2$, 25), 217 (M-H_2O-NEt_2, 100), 189 (30), 72 (NEt_2, 100).

N,N-*Diethyl-2-(4'-hydroxy-1'-oxobutyl)-4-methoxybenzamide* (**14**). The *title compound* (**14**) (0.35 g, 50%) was prepared as a pale yellow oil from 4-methoxy-*N,N'*-diethylbenzamide (**3**) (0.5g, 2.4 mmol) and γ-butyrolactone (**5**) (0.22 g, 2.6 mmol) following the general procedure given above (Found: M-H_2O, 275.1487. $C_{16}H_{21}NO_3$ requires M, 275.1521); υ_{max} (thin film) / cm^{-1} 3402 (br, OH), 1687 (s, C=O, ketone) 1607 (s, C=O, amide); δ_H (200 MHz; $CDCl_3$) 1.07 (3 H, t, *J* 7.1, Me), 1.27 (3 H, t, *J* 7.0, Me) 1.90-2.00 (2 H, m, 3'-H), 3.02 (2 H, t, *J* 6.7, 2'-H), 3.18 (2 H, q, *J* 7.1, CH_2N), 3.54 (2 H, q, *J* 7.1, CH_2N), 3.68 (2 H, t, *J* 6.0, 4'-H), 3.86 (3 H, s, OMe), 7.04 (1 H, dd, $J_{5,6}$ 8.4, $J_{5,3}$ 2.4, 5-H), 7.21 (1 H, d, *J* 8.4, 6-H), 7.27 (1 H, d, *J* 2.5, 3-H); *m/z* (%) 293 (M^+, 1), 275 (M-H_2O, 5) 234 (M-$HNEt_2$, 40), 203 (M-H_2O-NEt_2, 100), 72 (NEt_2, 42).

N,N-*Diethyl-2-(4'-hydroxy-1'-oxopentyl)-4-methoxybenzamide* (**15**). The *title compound* (**15**) (0.48 g, 65%) was prepared as a yellow oil from 4-methoxy-*N,N'*-diethylbenzamide (**3**) (0.5g, 2.4 mmol) and γ-valerolactone (**6**) (0.26 g, 2.6 mmol) following the general procedure given above (Found: M-H_2O, 289.1785. $C_{17}H_{23}NO_3$ requires M, 289.1678); υ_{max} (thin film) / cm^{-1} 3402 (br, OH), 1692 (s, C=O, ketone) 1612 (s, C=O, amide); δ_H (200 MHz; $CDCl_3$) 1.06 (3 H, t, *J* 7.1, CH_2CH_3), 1.21 (3 H, d, *J* 6.3, Me), 1.27 (3 H, t, *J* 7.1, CH_2CH_3), 1.63-2.10 (2 H, m, 3'-H), 2.22 (1 H, br, OH), 3.02 (2 H, m, 2'-H), 3.16 (2 H, q, *J* 7.1, CH_2N), 3.53 (2 H, q, *J* 7.0, CH_2N), 3.80-3.92 (1 H, m, C*H*OH), 3.85 (3 H, s, OMe), 7.01 (1 H, dd, $J_{5,6}$ 8.4, $J_{5,3}$ 2.6, 5-H), 7.20 (1 H, d, *J* 8.4, 6-H), 7.26 (1 H, d, $J_{3,5}$ 2.8, 3-H); *m/z* (%) 307 (M^+, 1), 289 (M-H_2O, 4), 234 (M-$HNEt_2$, 40), 217 (M-H_2O-NEt_2, 100), 135 (20), 72 (NEt_2, 60).

General Procedure for the Preparation of Spiroacetals.

The appropriate keto-alcohol (0.2-1.8 mmol) was dissolved in 1:1 THF / H_2O (5 cm^3). 4-Toluenesulfonic acid (catalytic quantity) was added and the solution heated gently under reflux for 3-26 h. TLC analysis was performed at regular intervals to determine the completion of the reaction. The solvent was removed at reduced pressure and the reaction mixture extracted with ethyl acetate (3 x 5 cm^3). The organic extract was washed with water (5 cm^3), dried ($MgSO_4$) and concentrated at reduced pressure. Purification of the residue by flash chromatography using hexane : ethyl acetate as eluent afforded the spiroacetal.

Spiro[isobenzofuran-1(3 H), 2'-tetrahydropyran]-3-one (**16**). A solution of keto-alcohol (**7**) (0.2 g, 0.7 mmol) in 1:1 THF / H_2O (5 cm^3) was heated under reflux for 18 h and purified by flash chromatography to afford *spiroacetal* (**16**) as a colourless oil (0.11 g, 75%) (Found: M^+, 204.0793. $C_{12}H_{12}O_3$ requires M, 204.0786); υ_{max} (thin film) / cm^{-1} 1772 (s, C=O); δ_H (200 MHz; $CDCl_3$) 1.79-2.42 (6H, m, 3'-H, 4'-H, 5'-H), 3.98 (1 H, ddd, J 11.4, 4.8, 2.7, 6'-Heq), 4.17 (1 H, ddd, *J* 12.6, 11.4, 2.7, 6'-Hax), 7.54 (1 H, dd, $J_{7,6}$ 7.6, $J_{7,5}$ 0.8, 7-H), 7.58 (1 H, td, J_{ortho} 7.5, $J_{6,4}$ 0.9, 6-H), 7.70 (1 H, td, J_{ortho} 7.5, $J_{6,4}$ 1.1, 5-H), 7.92 (1 H, dd, $J_{4,5}$ 7.6, $J_{4,6}$ 0.8, 4-H); δ_C (50 MHz; $CDCl_3$) 19.3 (CH_2, C-4'), 24.3 (CH_2, C-5'), 33.6 (CH_2, C-3'), 65.3 (CH_2, C-6'), 106.4 (quat., C-2'), 122.0 (CH, C-5), 125.5 (CH, C-7), 126.4 (quat., C-7a), 130.5 (CH, C-7), 134.4 (CH, C-6), 149.2 (quat., C-3a), 168.5 (quat., C=O); *m/z* (%) 204 (M^+, 7), 176 (M-CO, 5), 160 (M-CO_2, 54), 149 (100), 146 (13), 132 (37), 104 (70).

Spiro[isobenzofuran-1-(3 H), 2'-tetrahydrofuran] -3-one (**17**). A solution of keto-alcohol (**8**) (0.13 g, 0.5 mmol) in 1:1 THF / H_2O (5 cm^3) was heated under reflux for 18 h and purified by flash chromatography to afford *spiroacetal* (**17**) as a pale yellow oil (65 mg, 70%); (Found: M^+, 190.0633. $C_{11}H_{10}O_3$ requires M,

190.0630); υ_{max} (thin film) / cm^{-1} 1764 (s, C=O); δ_H (200 MHz; $CDCl_3$) 2.23-2.50 (4 H, m, 3'-H, 4'-H), 4.27-4.35 (2 H, m, 5'-H), 7.53 (1 H, dt, $J_{7,6}$ 7.5, $J_{7,5}$ 0.9, 7-H), 7.58 (1 H, td, J_{ortho} 7.5, $J_{6,4}$ 0.9, 6-H), 7.70 (1 H, td, J_{ortho} 7.5, $J_{6,4}$ 1.1, 5-H), 7.87 (1 H, d, *J* 7.7, 4-H); δ_C (50 MHz; $CDCl_3$) 24.3 (CH_2, C-4'), 37.4 (CH_2, C-3'), 70.8 (CH, C-5'), 114.0 (quat., C-2'), 122.6 (CH, C-5), 125.3 (CH, C-6), 127.7 (quat., C-7a), 130.6 (CH, C-7), 134.1 (CH, C-4), 146.5 (quat., C-3a), 168.0 (quat., C=O); *m/z* (%) 190 (M^+, 5), 171 (M-H-H_2O, 5), 160 (10), 149 (48), 146 (M-CO_2, 71), 105 (100).

Spiro[isobenzofuran-1-(3 H), 5-methyl-2'-tetrahydrofuran] -3-one (**18**). A solution of keto-alcohol (**9**) (80 mg, 0.28 mmol)) in 1:1 THF / H_2O (5 cm^3) was heated under reflux for 18 h and purified by flash chromatography to afford *spiroacetal* (**18**) as a pale yellow oil (55 mg, 90%) (Found: $(M+H)^+$, 205.0867 $C_{12}H_{12}O_3$ requires M+H, 205.0865); υ_{max} (thin film) / cm^{-1} 1765 (s, C=O); δ_H (200 MHz; $CDCl_3$) 1.39 (1.5 H, d, *J* 6.2, Me), 1.46 (1.5 H, d, *J* 6.2, Me), 1.52-2.68 (4 H, m, 3'-H, 4'-H), 4.61 (1 H, m, 5'-H), 7.51 (1 H, dd, $J_{7,6}$ 7.6, $J_{7,5}$ 0.8, 7-H),7.57-7.70 (2 H, m, 5-H, 6-H),7.85 (1 H, dd, $J_{4,5}$ 7.6, $J_{4,6}$ 0.9, 4-H); δ_C (50 MHz; $CDCl_3$) 21.8, 22.8 (Me), 32.4, 32.2 (CH_2, C-4'), 36.8, 38.9 (CH_2, C-3'), 79.7, 80.8 (CH, C-5'), 114.0 (quat., C-2'), 122.3 (CH, C-5), 125.3 (CH, C-6), 127.5 (quat., C-7a), 130.5 (CH, C-7), 134.3 (CH, C-4), 146.8 (quat., C-3a), 168.1 (quat., C=O); *m/z* (%) 205 (MH^+, 9), 203 (M-H, 10), 183 (12), 160 (M-CO_2, 64), 149 (100), 105 (149-CO_2, 83).

Spiro[4-methoxyisobenzofuran-1-(3 H), 2'-tetrahydropyran]-3-one (**19**). A solution of keto-alcohol (**10**) (0.1 g, 0.34 mmol) in 1:1 THF / H_2O (5 cm^3) was heated under reflux for 26 h and purified by flash chromatography to afford *spiroacetal* (**19**) as a colourless solid (58 mg, 73%), m.p. 74-76 ^{0}C (Found: C, 66.54; H, 5.91; M^+, 234.0875. $C_{13}H_{14}O_4$ requires C, 66.66; H, 6.02; M, 234.0892); υ_{max} (thin film) / cm^{-1} 1763 (s, C=O); δ_H (200 MHz; $CDCl_3$) 1.69-2.12 (6H, m, 3'-H, 4'-H, 5'-H), 3.88-4.12 (1 H, m, 6'-Heq), 3.99 (3 H, s, OMe), 4.16 (1 H, ddd, *J* 11.5, 11.5, 3.3, 6'-Hax), 6.98 (1 H, d, *J* 8.0, 5-H), 7.06 (1 H, d, *J* 7.2, 7-H), 7.62 (1 H, t, *J* 8.0, 6-H); δ_C (50 MHz; $CDCl_3$) 19.2 (CH_2, C-4'), 24.3 (CH_2, C-5'), 33.6 (CH_2, C-3'), 56.1 (OMe), 65.1 (CH_2, C-6'), 104.8 (quat., C-2'), 112.2 (CH, C-5), 113.7 (CH, C-7), 128.7 (quat., C-7a), 136.6 (CH, C-6), 151.7 (quat., C-3a), 158.1 (quat., C-4), 168.2 (quat., C=O); *m/z* (%) 234 (M^+, 23), 216 (M-H_2O, 10) 205 (M-CHO, 18), 179 (85), 149 (100), 104 (22), 76 (35), 57 (36), 41 (34).

Spiro[4-methoxyisobenzofuran-1- (3 H), 2'-tetrahydrofuran] -3-one (**20**). A solution of keto-alcohol (**11**) (0.53 g, 1.8 mmol) in 1:1 THF / H_2O (5 cm^3) was heated under reflux for 26 h and purified by flash chromatography to afford *spiroacetal* (**20**) as a colourless solid (0.34 g, 85%), m.p. 58-60 ^{0}C (Found: C, 65.32; H, 5.31; M^+, 220.0735. $C_{12}H_{12}O_4$ requires C, 65.45; H, 5.49; M, 220.0736); υ_{max} (thin film) / cm^{-1} 1767 (s, C=O); δ_H (200 MHz; $CDCl_3$) 2.29-2.49 (4 H, m, 3'-H, 4'-H), 3.99 (3 H, s, OMe), 4.17-4.38 (2 H, m, 5'-H), 6.99 (1 H, d, *J* 8.7, 5-H), 7.04 (1 H, d, *J* 8.1, 7-H), 7.64 (1 H, t, *J* 7.3, 6-H); δ_C (50 MHz; $CDCl_3$) 24.2 (CH_2, C-4'), 37.3 (CH_2, C-3'), 56.0 (OMe), 70.5 (CH, C-5'), 112.2 (CH, C-5), 112.5 (quat., C-2'), 113.9 (CH, C-7), 114.4 (quat., C-7a), 136.6 (CH, C-4), 149.1 (quat., C-3a), 159.0 (quat., C-6), 165.4 (quat., C=O); *m/z* (%) 234 (M^+, 23), 216 (M-H_2O, 10), 205 (M-CHO, 18), 179 (85), 149 (100), 104 (22), 76 (35), 57 (36), 41 (34).

Spiro[4-methoxyisobenzofuran-1- (3 H), 5'-methyl-2'-tetrahydrofuran] -3-one (**21**). A solution of keto-alcohol (**12**) (0.90 mg, 0.3 mmol) in 1:1 THF / H_2O (5 cm^3) was heated under reflux for 22 h and purified

by flash chromatography to afford *spiroacetal* (**21**) as a pale yellow oil (65 mg, 95%) (Found: M^+, 234.0895. $C_{13}H_{14}O_4$ requires M, 234.0892); υ_{max} (thin film) / cm^{-1} 1767 (s, C=O); δ_H (200 MHz; $CDCl_3$) 1.37 (1.5 H, d, *J* 6.4, Me), 1.43 (1.5 H, d, *J* 6.4, Me), 1.88-2.55 (4 H, m, 3'-H, 4'-H), 3.98 (3 H, s, OMe), 4.50-4.71 (1 H, m, 5'-H), 6.99 (1 H, d, *J* 8.3, 5-H), 7.05 (1 H, d, *J* 7.1, 7-H), 7.65 (1 H, t, *J* 7.6, 6-H); δ_C (50 MHz; $CDCl_3$) 21.8, 22.7 (Me), 32.1, 32.8 (CH_2, C-4'), 37.4, 39.6 (CH_2, C-3'), 56.7 (OMe), 78.8, 80.6 (CH, C-5'), 112.9 (CH, C-5), 113.2 (quat., C-2'), 114.6 (CH, C-7), 116.4 (quat., C-7a), 137.2 (CH, C-6), 150.2 (quat., C-3a), 158.7 (quat., C-4), 166.8 (quat., C=O); *m/z* (%) 234 (M^+, 25), 192 (100), 179 (65), 162 (100), 135 (25), 104 (35), 76 (33), 56 (15), 43 (10).

Spiro[6-methoxyisobenzofuran-1-(3 H*), 2'-tetrahydropyran]-3-one* (**22**). A solution of keto-alcohol (**13**) (55 mg, 0.18 mmol) in 1:1 THF / H_2O (5 cm^3) was heated under reflux for 3 h and purified by flash chromatography to afford *spiroacetal* (**22**) as a colourless solid (26 mg, 62%), m.p. 71-72 ^0C ^0C (Found: C, 66.51; H, 5.83; M^+, 234.0875. $C_{13}H_{14}O_4$ requires C, 66.66; H, 6.02; M, 234.0892); υ_{max} (thin film) / cm^{-1} 1762 (s, C=O); δ_H (200 MHz; $CDCl_3$) 1.71-2.12 (6 H, m, 3'-H, 4'-H, 5'-H), 3.79-3.99 (1 H, m, 6'-Heq), 3.91 (3 H, s, OMe), 4.18 (1 H, ddd, *J* 11.8, 11.7, 2.7, 6'-Hax), 6.95 (1 H, d, *J* 2.1, 7-H), 7.06 (1 H, dd, $J_{5,4}$ 8.4, $J_{5,7}$ 2.3, 5-H), 7.75 (1 H, d, *J* 8.4, 4-H); δ_C (50 MHz; $CDCl_3$) 19.9 (CH_2, C-4'), 24.9 (CH_2, C-5'), 34.3 (CH_2, C-3'), 56.5 (OMe), 65.8 (CH_2, C-6'), 106.1 (quat., C-2'), 106.6 (CH, C-5), 118.4 (CH, C-7), 119.2 (quat., C-7a), 127.7 (CH, C-4), 152.6 (quat., C-3a), 165.6 (quat., C-6), 168.9 (quat., C=O); *m/z* (%) 234 (M^+, 45), 216 (M-H_2O, 5) 190 (M-CO_2, 35), 179 (100), 135 (87), 134 (92), 106 (45), 77 (C_6H_7, 36), 63 (45), 55 (30).

Spiro[6-methoxyisobenzofuran-1- (3 H*), 2'-tetrahydropyran] -3-one* (**23**). A solution of keto-alcohol (**14**) (60 mg, 0.2 mmol) in 1:1 THF / H_2O (5 cm^3) was heated under reflux for 3 h and purified by flash chromatography to afford *spiroacetal* (**23**) as a colourless solid (35 mg, 80%), m.p. 104-106 ^0C (Found: C, 65.39; H, 5.38; M^+, 220.0735. $C_{12}H_{12}O_4$ requires C, 65.45; H, 5.49; M, 220.0736); υ_{max} (thin film) / cm^{-1} 1758 (s, C=O); δ_H (200 MHz; CDCl3) 2.20-2,49 (4 H, m, 3'-H, 4'-H), 3.91 (3 H, s, OMe), 4.19-4.39 (2 H, m, 5'-H), 6.94 (1 H, d, $J_{5,7}$ 2.2, 7-H), 7.06 (1 H, dd, $J_{5,4}$ 8.4, $J_{5,7}$ 2.1, 5-H), 7.75 (1 H, d, *J* 8.4, 4-H); δ_C (50 MHz; $CDCl_3$) 24.2 (CH_2, C-4'), 37.3 (CH_2, C-3'), 56.5 (OMe), 70.6 (CH, C-5'), 106.2 (CH, C-5), 113.0 (quat., C-2'), 117.8 (CH, C-7), 119.7 (quat., C-7a), 126.7 (CH, C-4), 149.2 (quat., C-3a), 165.1 (quat., C-6), 168.9 (quat., C=O); *m/z* (%) 220 (M^+, 35) 190 (10), 176 (M-CO_2, 50), 135 (100), 106 (20), 77 (C_6H_7, 10), 63 (25).

Spiro[6-methoxyisobenzofuran-1-(3 H*)-one, 5-methyl-2'-tetrahydropyran]-3-one* (**24**). A solution of keto-alcohol (**15**) (0.17 g, 0.55 mmol) in 1:1 THF / H_2O (5 cm^3) was heated under reflux for 2 h and purified by flash chromatography to afford *spiroacetal* (**24**) as a pale yellow oil (90 mg, 70%) (Found: M^+, 234.0888. $C_{13}H_{14}O_4$ requires M, 234.0892); υ_{max} (thin film) / cm^{-1} 1760 (s, C=O); δ_H (200 MHz; CDCl3) 1.39 (1.5 H, d, *J* 6.2, Me), 1.49 (1.5 H, d, *J* 6.2, Me), 1.76-2.58 (4 H, m, 3'-H, 4'-H), 3.91 (3 H, s, OMe), 4.51-4.71 (1 H, m, 5'-H), 6.92 (1 H, t, *J* 2.9, 7-H), 7.05 (1 H, dd, $J_{5,4}$ 8.4, $J_{5,7}$ 2.1, 5-H), 7.75 (1 H, d, *J* 8.4, 4-H); δ_C (50 MHz; $CDCl_3$) 21.8, 22.8 (Me), 32.1, 32.8 (CH_2, C-4'), 37.5, 39.5 (CH_2, C-3'), 56.5 (OMe), 78.9, 80.8 (CH, C-5'), 106.8, 107.0 (CH, C-5), 113.8, 113.9 (quat., C-2'), 118.2, 118.5 (CH, C-7), 120.2, 120.5 (quat., C-7a), 127.4 (CH, C-4), 150.2 (quat., C-3a), 165.3 (quat., C-6), 168.5 (quat., C=O); *m/z* (%) 234 (M^+, 30), 190 (M-CO_2, 70), 179 (65), 135 (100), 106 (20), 71 (35), 63 (30), 57 (55), 43 (40).

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