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Directed *Ortho* Metalations of Tertiary Benzamides Using Lactones as Electrophiles

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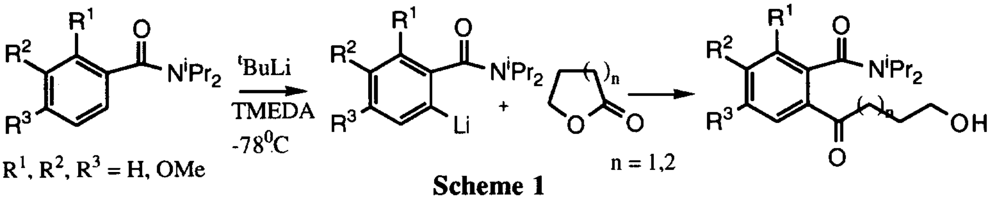
Abstract: Directed *ortho* metalation of oxygenated tertiary benzamides using *tert*-butyllithium in THF / TMEDA at -78°C followed by the addition of a range of lactones afforded *ortho*-substituted keto-alcohols in good yield.

INTRODUCTION

The efficient and regiospecific synthesis of polysubstituted aromatic compounds has been aided significantly by the advances made in the use of directed *ortho* metalation reactions. This approach involves deprotonation of a site *ortho* to a heteroatom-containing directed metalating group (DMG) by a strong base, normally an alkyllithium reagent, leading to an *ortho*-lithiated species which upon treatment with electrophilic reagents yield 1,2-disubstituted products.[1] The addition of a range of carbon electrophiles has been investigated including ketones, aldehydes, acyl halides and alkyl halides, carbamoyl chlorides, carbon dioxide and dimethyl formamide. Ester and lactone electrophiles have been less widely used.[1] In the latter case only a few examples have been reported using lactones derived from a carbohydrate with the use of an ether as the directed metalating group.[2,3]

DISCUSSION

The work described herein reports the directed *ortho*-lithiation of tertiary benzamides using common lactones as electrophiles (Scheme 1). This *ortho* metalation reaction not only provides a milder alternative to Friedel-Crafts acylation but also has the advantage of providing two new functional groups at the position *ortho* to the directed metalating group which can be used in further synthetic manipulations.



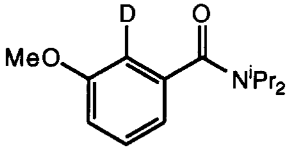
Scheme 1

A range of oxygenated *di*-isopropylbenzamides were prepared from the corresponding acid via treatment of the derived acid chloride with the appropriate amine. Directed *ortho*-lithiation of these amides was then effected using *tert*-butyllithium (1.2-2.0 equiv.) in THF / TMEDA (1.2-2.0 equiv.) at -78°C for 0.2-0.5 h.

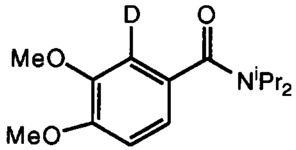
Subsequent addition of the lactone electrophile afforded the keto-alcohol products (Table) with no trace of tertiary alcohol products resulting from double addition of the aryl anion to the ketone products.

The generality of the reaction was tested using both the five membered lactones, γ-butyrolactone and γ-valerolactone, and the six membered lactone, δ-valerolactone. As a comparison, transmetalation of several of the amides bearing a bromide at the position *ortho* to the amide was effected using butyllithium, however very little difference in yield was obtained using this method.

In most cases the lactone added in good yield to the position *ortho* to the amide directing group. The notable exception being entries 10 and 11 where only poor yields of the lactone addition products were observed. In these cases, lithiation of amides (**4**) and (**3**) followed by the addition of deuterium oxide afforded the C-2 deuteriated amides (**17**) and (**18**) respectively, in quantitative yield.



(**17**)



(**18**)

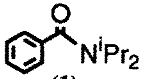
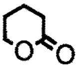
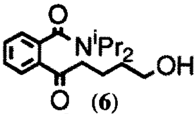
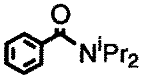
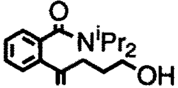
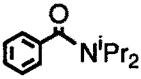
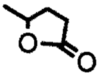
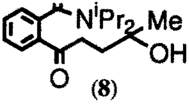
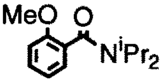
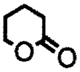
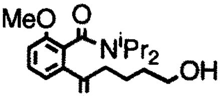
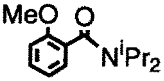
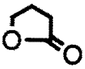
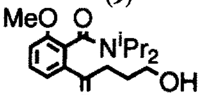
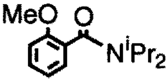
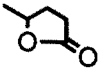
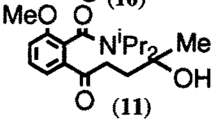
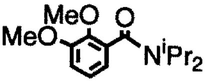
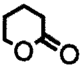
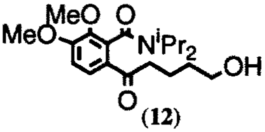
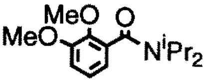
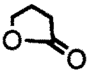
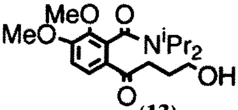
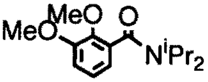
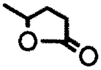
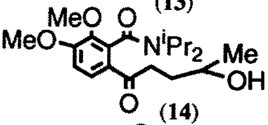
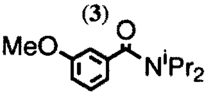
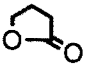
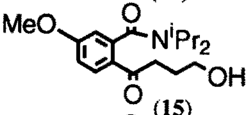
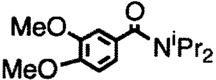
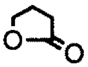
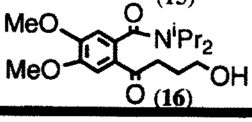
The low yield of lactone addition products was therefore attributed to the difficulty in adding the more bulky lactone electrophile to a position crowded by both an amide and a methoxy group in the *ortho* positions. This was supported by the fact that the only lactone addition products isolated (albeit in low yield) were those wherein addition occurred at the position *ortho* only to the amide group.

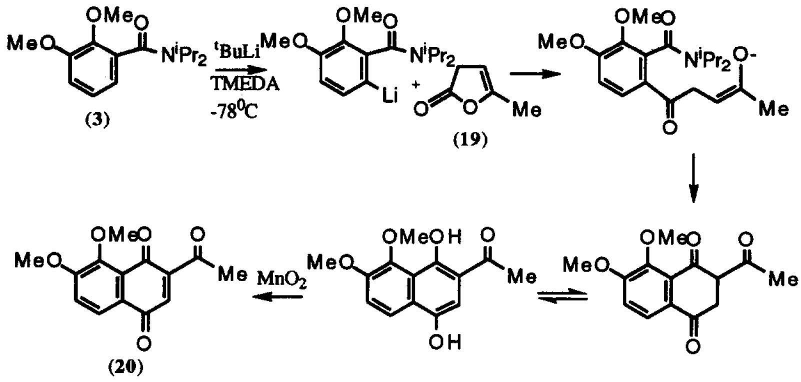
The regiochemistry of the addition products in all cases was easily determined by the coupling patterns of the aromatic protons in the ^{1}H n.m.r spectra. The only notable feature of the ^{1}H n.m.r. spectra was the observation in several instances of considerable broadening of the resonances assigned to the isopropyl groups due to restricted rotation about the CO-N bond. In several cases [e.g. keto-alcohols (**8**) and (**15**)] two resonances were observed in the ^{1}H and ^{13}C n.m.r. spectra due to the presence of conformational isomers.

Our initial intention for this work was to provide an efficient synthesis of naphthoquinone (**20**) *via* directed *ortho*-lithiation of amide (**3**) followed by treatment with α-angelicalactone (**19**) (Scheme 2). Naphthoquinone (**20**) is a key intermediate in our synthesis of the pyranonaphthoquinone antibiotic, arizonin, and has only been prepared to date in moderate yield.^{4} An efficient synthesis of naphthoquinone (**20**) has yet to be achieved since in the present work we have been unable to effect the desired reaction of any of the aryllithiums with α-angelicalactone (**19**). Starting material was recovered in all cases. Use of ceric chloride^{5,6} not only to increase the oxyphilic character of the lactone but also to reduce the basicity of the aryllithium also met with little success.

Whilst our initial goal to prepare naphthoquinone (**20**) was not realized, nevertheless, the present work illustrates the use of directed *ortho*-lithiation of tertiary amides and reaction with saturated lactones as a method to introduce two new functional groups at the position ortho to the amide group.

Table. Orthometalation of Benzamides with Lactones (Scheme 1)

Entry	Amide	Lactone	Keto-alcohol	Yield	m.p. (°C)
1	 (1)		 (6)	80%	74-76
2	 (1)		 (7)	83%	72-75
3	 (1)		 (8)	71%	105-108
4	 (2)		 (9)	76%	110-112
5	 (2)		 (10)	81%	97-100
6	 (2)		 (11)	69%	107-110
7	 (3)		 (12)	80%	139-141
8	 (3)		 (13)	62%	123-125
9	 (3)		 (14)	62%	118-121
10	 (4)		 (15)	4%	oil
11	 (3)		 (16)	14%	oil



Scheme 2

EXPERIMENTAL

General Methods.

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Infrared spectra were recorded on a BIO-RAD FTS-7 or a BIO-RAD FTS-40 spectrophotometer as Nujol mulls or thin films between sodium chloride plates. ^{1}H NMR spectra were obtained at 400 MHz using a Bruker AM400 spectrometer, at 270 MHz using a Jeol GX270 spectrometer or at 60 MHz using a Hitachi R-1200 spectrometer. ^{13}C NMR were obtained at 100 MHz using a Bruker AM400 spectrometer or at 67.8 MHz using a Jeol GX270 spectrometer. Microanalyses were performed at the microanalytical laboratory, University of Otago, Dunedin. Mass spectra and accurate mass measurements were recorded on a Varian VG70-250S double focussing magnetic sector mass spectrometer with an ionization potential of 70 eV. Merck Kieselgel 60 (230-400 mesh) was used for flash chromatography. All solvents and reagents were purified and dried if necessary before use.

Preparation of amides.

General procedure. The amides were prepared by addition of a cold (0^{o}C) solution of the amine in benzene to a cold (0^{o}C) solution of the acid chloride in benzene. After the addition was complete, the reaction mixture was allowed to warm to ambient temperature for 3 h. Extractive workup (EtOAc) afforded the crude amide which was recrystallized from ethyl acetate. The acid chlorides were prepared from the acid by reaction with excess SOCl$_2$ at reflux, followed by removal of excess SOCl$_2$ by distillation. The crude acid chlorides were used without further purification. Spectroscopic and analytical data for new compounds are given below.

2,3-Dimethoxy-N,N-bis-(methylethyl)benzamide (3). Prepared from thionyl chloride (3.0 ml, 41 mmol), 2,3-dimethoxybenzoic acid (5 g, 27 mmol), and anhydrous diisopropylamine (7.69 ml, 54 mmol). Recrystallisation from ethyl acetate afforded colourless crystals (6.85g, 94%), m.p. 113-114^{o}C (Found : C, 67.95; H, 8.9; N, 5.3. C$_{15}$H$_{23}$NO$_3$ requires C, 67.9; H, 8.7; N, 5.3%); ν_{max}(Nujol)/cm^{-1}1628s (C=O, amide); δ_H (270 MHz; CDCl$_3$) 1.04 (3 H, d, *J* 6.6, Me), 1.16 (3 H, d, *J* 6.6, Me), 1.55 (3 H, d, *J* 6.9, Me), 1.57 (3 H, d, *J* 6.9, Me), 3.50 (1 H, septet, *J* 6.6, CHN), 3.70 (1 H, septet, *J* 6.6, CHN), 3.86 (3 H, s, 3-OMe), 3.88 (3 H, s, 2-OMe), 6.76 (1 H, d, *J* 7.3, 4-H), 6.89 (1 H, d, *J* 7.3, 6-H), 7.06 (1 H, t, *J* 7.3, 5-H); δ_C (67.8 MHz; CDCl$_3$)

20.1, 20.5, 20.6, 20.7 (q, 4xMe), 45.5 (d, CHN), 51.0 (d, CHN), 55.7 (q, 3-OMe), 61.4 (q, 2-OMe), 111.8 (d, C-4), 118.2 (d, C-6), 124.6 (d, C-5), 134.0 (s, C-1), 144.1 (s, C-3), 152.5 (s, C-2), 167.9 (s, C=O, amide); *m/z* 265 (M^+, 24), 222 (M-CH$(CH_3)_2$, 28), 165 (M-N[CH$(CH_3)_2$]$_2$, 100), 43 (CH$(CH_3)_2$, 9).

3,4-Dimethoxy-N,N-bis-(methylethyl)benzamide (5). Prepared from thionyl chloride (3.0 ml, 41 mmol), 3,4-dimethoxybenzoic acid (5 g, 27 mmol) and anhydrous diisopropylamine (7.69 ml, 54 mmol). Recrystallisation from ethyl acetate afforded colourless crystals (7.28g, 100%), m.p. 69-72°C; (Found : C, 67.7; H, 8.5; N, 5.3. $C_{15}H_{23}NO_3$ requires C, 67.9; H, 8.7; N, 5.3%); ν_{max}(Nujol)/cm^{-1}1628s (C=O, amide); δ_H (270 MHz; $CDCl_3$) 1.25-1.50 (12 H, br.s, Me), 3.90 (6 H, s, 2xOMe), 6.86-6.90 (3 H, m, ArH); δ_C (67.8 MHz; $CDCl_3$) 20.8 (q, Me), 40.8 (br.s, 2xCHN), 55.9 (q, 2xOMe), 109.6 (d, C-5), 110.5 (d, C-2), 118.2 (d, C-6), 131.4 (s, C-1), 148.8 (s, C-3), 149.3 (s, C-4), 170.8 (s, C=O, amide); *m/z* 265 (M^+, 22), 222 (M-CH$(CH_3)_2$, 28), 165 (M-N[CH$(CH_3)_2$]$_2$, 100), 77 (Ph, 7), 43 (CH$(CH_3)_2$, 5).

Preparation of keto-alcohols.

General procedure. To a stirred solution of the benzamide (1.8 mmol) in dry tetrahydrofuran (15 ml) under argon at -78°C was added *tert*-butyllithium (2.0 mmol) dropwise. Tetramethylethylenediamine (2.0 mmol) was added and the reaction mixture stirred for 0.33 h. at -78°C. The appropriate lactone (2.2 mmol) was added and the mixture allowed to warm to room temperature. After quenching with saturated ammonium chloride solution the solvent was removed at reduced pressure. Standard ethyl acetate workup and purification by flash chromatography, using hexane : ethyl acetate as eluent afforded the keto-alcohol which was recrystallised from ethyl acetate.

*2-(5'-Hydroxy-1'-oxopentyl)-*N,N-bis-*(methylethyl)benzamide (6)* - colourless needles (80%), m.p. 74-76°C; (Found: C, 70.7; H, 8.9; N, 4.5. $C_{18}H_{27}NO_3$ requires C, 70.8; H, 8.8; N, 4.6%); (Nujol)/cm^{-1} 3342br (OH), 1689s (C=O, ketone), 1614s (C=O, amide); δ_H (270 MHz; $CDCl_3$) 1.15 (6 H, d, *J* 6.7, Me), 1.58 (6 H, d, *J* 6.7, Me), 1.62-1.86 (4 H, m, 2xCH_2), 2.98 (2H, m, $C\underline{H_2}CO$), 3.53 (1 H, septet, *J* 6.7, CHN), 3.60 (2 H, t, *J* 5.8, 5'-H), 3.60 (1 H, septet, *J* 6.7, CHN), 7.39 (1 H, d, *J* 7.5, 3-H), 7.41, 7.49 (1 H, t, *J* 7.5, 4-H, 5-H), 7.74 (1 H, d, *J* 7.5, 6-H); δ_C (67.8 MHz; $CDCl_3$) 20.1, 20.2, 20.4, 20.5 (q, 4xMe), 20.5, 31.7 (t, C-3', C-4'), 39.7 (t, C-2'), 45.7 (d, CHN), 51.3 (d, CHN), 61.9 (t, C-5'), 126.2, 128.1 (d, C-4, C-5), 128.5, 131.7 (d, C-3, C-6), 136.0 (s, C-2), 138.9 (s, C-1), 170.6 (s, C=O, amide), 202.1 (s, C-1'); *m/z* 305 (M^+, 2), 287 (M-H_2O, 10), 187 (M-H_2O-N[CH$(CH_3)_2$], 100), 159 (M-H_2O-C(O)N[CH$(CH_3)_2$]$_2$, 35), 100 (N[CH$(CH_3)_2$]$_2$, 75), 43 (CH$(CH_3)_2$, 10).

*2-(4'-Hydroxy-1'-oxobutyl)-*N,N-bis-*(methylethyl)benzamide (7)* - yellow solid (83%), m.p. 72-75°C; (Found: C, 70.1; H, 8.6; N, 4.83. $C_{17}H_{25}NO_3$ requires C, 70.1; H, 8.65; N, 4.8%); ν_{max}(Nujol)/cm^{-1} 3432br (OH), 1692m (C=O, ketone), 1631s (C=O, amide); δ_H (270 MHz; $CDCl_3$) 1.13 (6 H, d, *J* 6.6, 2xMe), 1.57 (6 H, d, *J* 6.6, 2xMe), 1.87 (2 H, p, *J* 6.6, C-3'), 3.00 (2H, t, *J* 7.0, $C\underline{H_2}CO$),3.53 (2 H, septet, *J* 6.6, 2xCHN), 3.53 (2 H, t, *J* 7.0, 4'-H), 7.20 (1 H, d, *J* 6.2, 3-H), 7.40, 7.49 (1 H, t, *J* 6.2, 4-H, 5-H), 7.79 (1 H, d, *J* 6.2, 6-H); δ_C (67.8 MHz; $CDCl_3$) 20.1 (q, Me), 26.8 (t, C-3'), 36.3 (t, C-2'), 45.5 (d, CHN), 51.1 (d, CHN), 60.8 (d, t-4'), 126.0, 128.0, 128.6, 131.6 (d, ArH), 135.4 (s, C-2), 138.5 (s, C-1), 170.5 (s, C=O, amide), 201.6 (s, C-1'); *m/z* 291 (M^+, 2), 273 (M-H_2O, 15), 173 (M-H_2O-N[CH$(CH_3)_2$]$_2$, 100), 100 (N[CH$(CH_3)_2$]$_2$, 55).

2-(4'-Hydroxy-1'-oxopentyl)-N,N-bis(methylethyl)benzamide (8) - colourless solid (71%), m.p. 105-108°C; (Found : M^+, 305.1985. $C_{18}H_{27}NO_3$ requires M^+, 305.1991); υ_{max} (Nujol)/cm^{-1} 3393 (OH), 1689 (C=O, ketone), 1616 (C=O, amide); δ_H (400 MHz; $CDCl_3$) 1.26 (9H, m, 2xMe, 5'-Me), 1.56 (6H, 2xd, *J* 6.6, 2xMe), 1.67, 1.84 (2H, m, 3'-H), 3.02 (2H, t, *J* 7.3, 2'-H), 3.50, 3.60 (2H, septet, *J* 6.6, 2xCHN), 3.73 (1H, m, 4'-H), 7.19 (1H, dd, *J* 7.5, 1.1, H-3), 7.39 (1H, td, *J* 7.5, 1.1, H-4), 7.48 (1H, td, *J*7.5, 1.1, H5), 7.79 (1H, d, *J* 7.5, H-6); δ_C (100 Mhz; $CDCl_3$) 19.95, 20.0 (q, Me), 23.3 (q, C-5'), 33.0 (t, C-3'), 36.2 (t, C-2'), 45.4, 51.0 (d, CHN), 66.2 (d, C-4'), 125.9 (d, C-3), 128.0 (d, C-4), 128.6 (d, C-6), 131.5 (d, C-5), 135.5 (s, C-2), 138.5 (s, C-1), 170.4 (s, C=O, amide), 201.7 (s, C=O, ketone); m/z 305 (M^+, 1), 287 ($M-H_2O$, 8), 187 (287-$N[CHMe_2]_2$, 100), 146 (64), 100 ($N[CH(CH_3)_2]_2$, 57).

*2-(5'-Hydroxy-1'-oxopentyl)-6-methoxy-*N,N-bis-*(methylethyl)benzamide (9)* - colourless solid (76%), m.p. 110-112°C; (Found: M^+, 335.2092, $C_{19}H_{29}NO_4$ requires M^+, 335.2097); ν_{max}(Nujol)/cm^{-1} 3409br (OH), 1689s (C=O, ketone), 1622s (C=O, amide); δ_H (270 MHz; $CDCl_3$) 1.12 (3 H, d, *J* 6.7, Me), 1.17 (3 H, d, *J* 6.7, Me), 1.54 (3 H, d, *J* 6.7, Me), 1.58 (3 H, d, *J* 6.7, Me), 1.75-1.83 (2 H, m, CH_2), 2.86-3.12 (2 H, m, $C\underline{H}_2CO$), 3.51-3.61 (4 H, m, 2xCHN and $C\underline{H}_2OH$), 3.82 (3H, s, OMe), 7.01 (1 H, d, *J* 8.0, C-5), 7.29 (1 H, t, *J* 8.0, C-4), 7.33 (1 H, d, *J* 8.0, C-3); δ_C (67.8 MHz; $CDCl_3$) 19.9, 20.0, 20.3, 20.4, (q, 4xMe), 20.4, 31.6 (t, C-3', C-4'), 40.2 (t, C-2'), 45.8 (d, CHN), 51.4 (d, CHN), 55.7 (q, OMe), 61.8 (t, C-5'), 113.9 (d, C-5), 120.3 (d, C-4), 127.5 (s, C-1), 128.9 (d, C-3), 137.6 (s, C-2), 155.6 (s, C-6), 167.3 (s, C=O, amide), 202.6 (s, C-1'); *m/z* 335 (M^+, 2), 317 ($M-H_2O$, 10), 217 ($M-H_2O-N[CH(CH_3)_2]$, 98), 189 ($M-H_2O-C(O)N[CH(CH_3)_2]_2$, 40), 100 ($N[CH(CH_3)_2]_2$, 100), 43 ($CH(CH_3)_2$, 20).

*2-(4'-Hydroxy-1'-oxobutyl)-6-methoxy-*N,N-bis-*(methylethyl)benzamide (10)* - colourless solid (81%), m.p. 97-100°C; (Found: $M-H_2O$ 303.1832 $C_{18}H_{27}NO_4$ requires $M-H_2O$ 303.1834); ν_{max}(Nujol)/cm^{-1} 3373br (OH), 1693s (C=O, ketone), 1612s (C=O, amide); δ_H (270 MHz; $CDCl_3$) 1.12 (3 H, d, *J* 6.6, Me), 1.15 (3 H, d, *J* 6.6, Me), 1.53 (3 H, d, *J* 6.6, Me), 1.58 (3 H, d, *J* 6.6, Me), 1.86 (2 H, p, *J* 6.2, CH_2), 2.95-2.99 (2H, m, $C\underline{H}_2CO$), 3.47-3.59 (4 H, m, 2xCHN and $C\underline{H}_2OH$), 3.81 (3H, s, OMe), 7.02 (1 H, d, *J* 6.6, 5-H), 7.30-7.33 (2 H, m, 3-H, 4-H); δ_C (67.8 MHz; $CDCl_3$) 19.8, 20.0, 20.2, 20.3 (q, 4xMe), 26.8 (t, C-3'), 37.0 (t, C-2'), 45.7 (d, CHN), 51.3 (d, CHN), 55.5 (q, OMe), 60.8 (t, C-4'), 113.8 (d, C-5), 120.2 (d, C-4), 127.2 (s, C-1), 128.9 (d, C-3), 137.5 (s, C-2), 155.4 (s, C-6), 167.3 (s, C=O, amide), 202.3 (s, C-1'); *m/z* 303 ($M-H_2O$, 10), 203 ($M-H_2O-N[CH(CH_3)_2]_2$, 100), 176 ($M-H_2O-C(O)N[CH(CH_3)_2]_2$, 17), 100 ($N[CH(CH_3)_2]_2$, 43).

6-Methoxy-2-(4'-Hydroxy-1'-oxopentyl)-N,N-bis(methylethyl)benzamide (11) - colourless solid (69%), m.p. 107-110°C; (Found : M^+, 335.2098. $C_{18}H_{27}NO_3$ requires M^+, 335.2097); υ_{max} (Nujol)/cm^{-1} 3369 (OH), 1692 (C=O, ketone), 1614 (C=O, amide); δ_H (400 MHz; $CDCl_3$) 1.13 (9H, m, 2xMe, 5'-Me), 1.53, 1.59 (6H, 2xd, *J* 6.7, 2xMe), 1.65, 1.87 (2H, m, 3'-H), 2.99 (2H, t, *J* 7.3, 2'-H), 3.50, 3.60 (2H, septet, *J* 6.7, 2xCHN), 3.76 (1H, m, 4'-H), 3.80, 3.81 (3H, s, OMe), 7.03 (1H, dd, *J* 7.5, 1.3, H-5), 7.31 (1H, td, *J* 7.5, 1.3, H-3), 7.31 (1H, td, *J*7.5, 1.3, H-4); δ_C (100 MHz; $CDCl_3$) 19.7, 19.8, 19.9, 20.1, 20.2, 20.25 (q, Me), 23.2, 23.4 (q, C-5'), 33.0, 33.1 (t, C-3'), 36.8, 37.0 (t, C-2'), 45.6, 45.7 (d, CHN), 51.1, 51.2 (d, CHN), 55.4, 55.5 (q, OMe), 65.8, 66.8 (d, C-4'), 113.6, 114.0 (d, C-5), 119.9, 120.5 (d, C-4), 126.9, 127.5 (s, C-1), 128.7, 128.9 (d, C-3), 137.0, 137.9 (s, C-2), 155.3, 155.5 (s, C-6), 167.0, 167.2 (s, C=O, amide), 202.1, 202.7 (s, C=O, ketone); m/z 335 (M^+, 1), 317 ($M-H_2O$, 12), 217 (317-$N[CHMe_2]_2$, 100), 176 (65), 100 ($N[CH(CH_3)_2]_2$, 54).

*2,3-Dimethoxy-6-(5'-hydroxy-1'-oxopentyl)-*N,N-bis-*(methylethyl)-benzamide (12)* - colourless solid (80%), m.p. 139-141°C; (Found: $M-H_2O$ 347.2094 $C_{20}H_{24}NO_5$ requires $M-H_2O$ 347.2097); ν_{max}(Nujol)/cm^{-1} 3320br (OH), 1669s (C=O, ketone), 1611s (C=O, amide); δ_H (270 MHz; $CDCl_3$) 1.07 (6 H, d, *J* 6.7, Me), 1.49(3 H, d, *J* 6.7, Me), 1.57 (3 H, d, *J* 6.7, Me), 1.42-1.75 (4 H, m, 2xCH_2), 2.62-2.91 (2H, m, $C\underline{H}_2CO$), 3.50 (2 H, m, 2xCHN), 3.75 (3H, s, 3-OMe), 3.87 (3H, s, 2-OMe), 3.83-4.13 (2H, m, $C\underline{H}_2OH$), 6.82 (1 H, d, *J* 8.8, 4-H), 7.51 (1 H, d, *J* 8.8, 5-H); δ_C (67.8 MHz; $CDCl_3$) 19.7, 20.0, 20.2, 20.5 (q, 4xMe), 20.6, 31.8 (t, C-3', C-4'), 39.2 (t, C-2'), 45.6 (d, CHN), 51.5 (d, CHN), 55.9 (q, 3-OMe), 61.5 (q, 2-OMe), 61.6 (t, C-5'), 110.3 (d, C-4), 126.2 (d, C-5), 128.5 (s, C-6), 134.3 (s, C-1), 145.0 (s, C-3), 155.0 (s, C-2), 166.9 (s, C=O, amide), 199.9 (s, C-1'); *m/z* 365 (M^+, 2), 347 ($M-H_2O$, 7), 247 ($M-H_2O-N[CH(CH_3)_2]_2$, 100), 219 ($M-C(O)N[CH(CH_3)_2]_2$, 36), 100 ($N[CH(CH_3)_2]_2$, 89), 43 ($CH(CH_3)_2$, 19).

*2,3-Dimethoxy-6-(4'-hydroxy-1'-oxobutyl)-*N,N-bis-*(methylethyl)benzamide (13)* - colourless solid (62%), m.p. 121-123°C; (Found: $M-H_2O$ 333.1940 $C_{19}H_{22}NO_5$ requires $M-H_2O$ 333.1940); ν_{max}(Nujol)/cm^{-1} 3342, 3464br (OH), 1675s (C=O, ketone), 1619s (C=O, amide); δ_H (270 MHz; $CDCl_3$) 1.12 (3 H, d, *J* 6.6, Me), 1.13 (3 H, d, *J* 6.6, Me), 1.56 (3 H, d, *J* 6.6, Me), 1.63 (3 H, d, *J* 6.6, Me), 1.94 (2 H, p, *J* 6.2, CH_2), 3.01 (2H, m, $C\underline{H_2}CO$), 3.51-3.55 (2 H, m, 2xCHN), 3.67 (2 H, t, *J* 5.9, $C\underline{H_2}OH$), 3.82 (3H, s, 3-OMe), 3.94 (3H, s, 2-OMe), 6.88 (1 H, d, *J* 8.4, 4-H), 7.61 (1 H, d, *J* 8.4, 5-H); δ_C (67.8 MHz; $CDCl_3$) 19.8, 20.1, 20.3, 20.6 (q, 4xMe), 27.3 (t, C-3'), 36.3 (t, C-2'), 45.6 (d, CHN), 51.5 (d, CHN), 56.0 (q, 3-OMe), 61.5 (q, 2-OMe), 61.7 (t, C-4'), 110.4 (d, C-4), 126.4 (d, C-5), 128.4 (s, C-6), 134.5 (s, C-1), 145.1 (s, C-3), 156.1 (s, C-2), 166.8 (s, C=O, amide), 199.8 (s, C-1'); *m/z* 351 (M^+, 2), 333 ($M-H_2O$, 8), 233 ($M-H_2O-N[CH(CH_3)_2]$, 100), 100 ($N[CH(CH_3)_2]_2$, 57), 43 ($CH(CH_3)_2$, 8).

5,6-Dimethoxy-2-(4'-Hydroxy-1'-oxopentyl)-N,N-bis(methylethyl)benzamide (14) - colourless solid (62%), m.p. 118-121°C; (Found : M^+, 365.2206. $C_{20}H_{31}NO_5$ requires M^+, 365.2202); υ_{max} (Nujol)/cm^{-1} 3398 (OH), 1680 (C=O, ketone), 1619 (C=O, amide); δ_H (400 MHz; $CDCl_3$) 1.11-1.16 (9H, m, 2xMe, 5'-Me), 1.55 1.63 (6H, 2xd, *J* 6.7, 2xMe), 1.71, 1.88 (2H, m, 3'-H), 3.00 (2H, t, *J* 7.6, 2'-H), 3.51 (2H, septet, *J* 6.7, 2xCHN), 3.79 (1H, m, 4'-H), 3.81, 3.82 (3H, s, OMe), 3.93 (3H, s, OMe), 6.67 (1H, d, *J* 8.7, H-4), 7.63 (1H, d, *J* 8.7, H-4), 7.63 (1H, td, *J* 8.7, H-3); δ_C (100 MHz; $CDCl_3$) 19.7, 19.8, 19.9, 20.0, 20.2, 20.5 (q, Me), 23.4, 23.6 (q, C-5'), 33.4, 33.5 (t, C-3'), 35.7, 36.0 (t, C-2'), 45.4, 45.5 (d, CHN), 51.3, 51.4 (d, CHN), 55.8 (q, OMe), 61.4 (q, OMe), 66.6, 67.0 (d, C-4'), 110.35, 110.4 (d, C-4), 126.4, 126.6 (d, C-3), 127.9, 128.3 (s, C-2), 134.2, 134.5 (s, C-1), 144.9, 145.0 (s, C-6), 156.0, 156.2 (s, C-6), 166.7, 166.8 (s, C=O, amide), 199.5, 199.8(s, C=O, ketone); m/z 365 (M^+, 1), 347 ($M-H_2O$, 11), 247 ($347-N[CHMe_2]_2$, 100), 206 (64), 100 ($N[CH(CH_3)_2]_2$, 52).

*6-(4'-Hydroxy-1'-oxobutyl)-3-methoxy-*N,N-bis-*(methylethyl)benzamide (15)* - colourless oil (4%),; (Found: M^+ 321.1941 $C_{18}H_{27}NO_4$ requires M^+ 321.1940); ν_{max}(Nujol)/cm^{-1} 3395 (OH), 1680 (C=O, ketone), 1605s (C=O, amide); δ_H (400 MHz; $CDCl_3$) 1.12 (6 H, br. s, 2 x Me), 1.59 (6 H, br. s, 2 x Me), 1.97 (2 H, p, *J* 6.4, CH_2), 3.04 (2H, t, $C\underline{H_2}CO$), 3.51 (1 H, septet, *J* 7 Hz, CHN), 3.57 (1 H, septet, *J* 7 Hz, CHN), 3.86 (3H, s, OMe), 6.68 (1 H, d, *J* 2.6, 6-H), 6.88 (1 H, dd, *J* 8.7, 2.6, 4-H), 7.81 (1H, d, *J* 8.7, H-3); δ_C (100 MHz; $CDCl_3$) 20.3 (q, 4xMe), 27.3 (t, C-3'), 36.2 (t, C-2'), 45.7 (d, CHN), 51.1 (d, CHN), 55.6 (q, OMe), 62.0 (t, C-4'), 112.1(d, C-6), 113.0 (d, C-4), 127.6 (s, C-1), 131.3 (d, C-3), 141.5 (s, C-2), 162.5 (s, C-5), 170.2 (s, C=O, amide), 199.8 (s, C-1'); *m/z* 321 (M^+, 3), 303 ($M-H_2O$, 11), 221($M-N[CH(CH_3)_2]_2$, 25), 203 ($221-H_2O$, 100), 100 ($N[CH(CH_3)_2]_2$, 48).

*4,5-Dimethoxy-2-(4'-hydroxy-1'-oxobutyl)-*N,N-bis-*(methylethyl)benzamide (16)* - colourless solid (14%), m.p. 123-125°C; (Found: M^+, 331.2052, $C_{19}H_{29}NO_5$ requires M^+, 331.2046); ν_{max}(Nujol)/cm^{-1} 3409br (OH), 1674s (C=O, ketone), 1616s (C=O, amide); δ_H (270 MHz; $CDCl_3$) 1.11 (6 H, d, *J* 6.2, Me), 1.59 (6 H, d, *J* 6.6, Me), 1.98 (2 H, p, *J* 6.2, CH_2), 3.06 (2 H, t, *J* 5.9, $C\underline{H_2}CO$), 3.49-3.60 (2 H, m, 2xCHN), 3.70 (2 H, t, *J* 5.9, $C\underline{H_2}OH$), 3.93 (3 H, s, OMe), 3.95 (3 H, s, OMe), 6.65 (1 H, s, 6-H), 7.31 (1 H, s, 3-H); δ_C (67.8 MHz; $CDCl_3$) 20.3 (q, Me), 27.2 (t, C-3'), 36.5 (t, C-2'), 45.8 (d, CHN), 51.2 (d, CHN), 56.2 (q, 2xOMe), 61.7 (t, C-4'), 108.9, 111.6 (d, C-3, C-6), 127.6 (s, C-2), 133.1 (s, C-1), 148.1, 152.0 (s, C-4, C-5), 170.4 (s, C=O, amide), 200.0 (s, C-1'); *m/z* 351 (M^+, 2), 333 ($M-H_2O$, 8), 233 ($M-H_2O-N[CH(CH_3)_2]$, 100), 100 ($N[CH(CH_3)_2]_2$, 57), 43 ($CH(CH_3)_2$, 8).

Deuteriation of the aryllithiums derived from amides (4) and (3).

General procedure. To a stirred solution of the benzamide (1.8 mmol) in dry tetrahydrofuran (15 ml) under argon at -78°C was added *tert*-butyllithium (2.0 mmol) dropwise. Tetramethylethylenediamine (2.0 mmol) was added and the reaction mixture stirred for 0.33 h. at -78°C. Deuterium oxide (2.2 mmol) was added and the mixture allowed to warm to room temperature. Standard ethyl acetate workup and purification by flash chromatography, using hexane : ethyl acetate as eluent afforded the deuteriated amide.

3-Methoxy-N,N-bis-(methylethyl)benzamide-2-^{2}H (17) - colourless oil (100%); (Found : M^+, 236.1632. $C_{14}H_{20}DNO_2$ requires M^+, 236.1635); υ_{max} (thin film)/cm^{-1} 1631 (C=O, amide); δ_H (400 MHz; $CDCl_3$) 1.16 (6 H, br. d, 2xMe), 1.51 (6 H, br. d, 2xMe), 3.50 (2 H, br. m, 2xCHN), 3.80 (3 H, s, OMe), 6.85 (1 H, d, *J* 7.4, 4-H or 6-H), 6.87 (1 H, d, *J* 7.4, 6-H or 4-H), 7.26 (1 H, t, *J* 7.4, 5-H); δ_C (100 MHz; $CDCl_3$) 20.4 (q, 4xMe), 45.5, 50.5 (d, 2xCHN), 55.0 (q, OMe), 110.5 (t, C-2), 114.3 (d, C-4), 117.4 (d, C-5), 129.3 (d, C-6), 139.8 (s, C-1), 159.3 (s, C-3), 170.4 (s, C=O); *m/z* 236 (M^+, 20), 221 (M-Me, 5), 193 ($M-CHMe_2$, 20), 136 [$M-N(CHMe_2)_2$, 100]

3,4-Dimethoxy-N,N-bis-(methylethyl)benzamide-2-^{2}H (18) - colourless oil (100%); (Found : M^+, 266.1739. $C_{15}H_{22}DNO_3$ requires M^+, 266.1741); υ_{max} (thin film)/cm^{-1} 1628 (C=O, amide); δ_H (400 MHz; $CDCl_3$) 1.31 (12 H, br., 4xMe), 3.70 (2 H, br. m, 2xCHN), 3.84, 3.85 (6 H, s, 2 x OMe), 6.82 (1 H, d, *J* 7.4, 5-H or 6-H), 6.84 (1 H, d, *J* 7.4, 6-H or 5-H); δ_C (100 MHz; $CDCl_3$) 20.5 (q, 4xMe), 48.9 (d, 2xCHN), 55.6 (q, 2 x OMe), 109.0 (t, C-2), 110.4 (d, C-5), 118.0 (d, C-6), 131.0 (s, C-1), 148.6, 149.2 (s, C-3, C-4), 170.5 (s, C=O); *m/z* 266 (M^+, 18), 251 (M-Me, 2), 223 ($M-CHMe_2$, 20), 166 [$M-N(CHMe_2)_2$, 100]

REFERENCES

1. For a recent review on directed *ortho* metalations see : Snieckus, V. *Chem. Rev.*, 1990, **90**, 879.
2. Rosenblum S. B.; Bihovsky, R. *J. Amer. Chem. Soc.*, 1990, **112**, 2746.
3. Tatsuka, K.; Ozeki, H.; Yamaguchi, M.; Tanaka, M.; Okui, T. *Tetrahedron Lett.*, 1990, **38**, 5495.
4. Brimble M. A.; Phythian, S. J. *Tetrahedron Lett.*, 1993, **34**, 5813.
5. Mudryk, B.; Shook, C.A.; Cohen, T. *J.Amer.Chem. Soc.*, 1990, **112**, 6389.
6. Bartroli, G.; Marcantoni, E.; Petrini, M. *Angew. Chem. Int. Ed. Engl.*, 1993, **32**, 1061.

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