Intermolecular Dearomatising Addition of Organolithium Compounds to *N*-Benzoylamides of 2,2,6,6-Tetramethylpiperidine

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Dedicated to Professor Marc Julia on the occasion of his 80th birthday

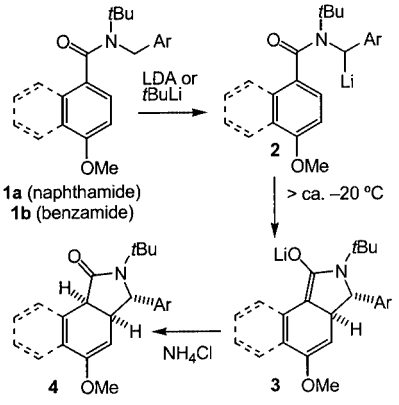
Keywords: Organolithium compounds / Amides / Dearomatisation / Steric hindrance / Cyclohexadienes

N-Benzoylamides of 2,2,6,6-tetramethylpiperidine are not ortholithiated by organolithium compounds but instead undergo nucleophilic addition of the organolithium compound to the aromatic ring in the manner of a conjugate addition. The resulting dearomatised enolates may be protonated or alkylated, and yield substituted cyclohexadienes in yields of up to 76%. Deprotection of the piperidine ring is possible under acidic conditions.

Introduction

Few methods in alicyclic chemistry match the regiocontrol available with aromatic functionalisation, whether by classical electrophilic substitution methods or by directed metallation. Dearomatisation reactions therefore provide a valuable link from the flat but regiocontrolled world of aromatic chemistry to the stereocontrolled world of saturated and partially saturated ring systems.[1−3] Dearomatisation of electron-rich or electron-poor aromatic rings can be achieved reductively by Birch reduction with an electrophilic quench;[4,5] a rather more select group of aromatic systems can be dearomatised by attack of a nucleophile. For the electron-deficient heterocycles, nucleophilic attack is facile, and often complicates other reactions, such as lithiation, which must therefore be carried out with hindered, non-nucleophilic bases.[6−8] Regio- and stereocontrolled nucleophilic attack on pyridines is a useful synthetic method for the synthesis of piperidines.[9−11] Naphthalenes may similarly undergo nucleophilic attack by organolithium compounds,[12] though dearomatisation of a naphthalene rings requires additional activation in the form of an electron-withdrawing substituent.[13] Naphthalenecarboxamides,[14] naphthalenecarboxylic acids[15] and their esters,[16,17] naphthalenimines,[18,19] and most importantly naphthyloxazolines[20−23] all accept nucleophiles, losing aromaticity in one ring and providing valuable synthetic intermediates.

We discovered a few years ago that naphthalenecarboxamides bearing *N*-benzyl substituents, such as **1a**, are susceptible to intramolecular nucleophilic attack in the form of a cyclisation reaction[24−29] which can be interpreted as an electrocyclic ring closure[30] of the organolithium compound **2** to the enolate **3** (Scheme 1). Comparable dearomatising cyclisation reactions onto naphthyloxazolines,[13] naphthyl sulfones[31] and naphthylphosphonamides[32] have also been reported.



Scheme 1

Benzenoid aromatic rings are much harder to dearomatise by nucleophilic addition. Benzamide analogues of the amide cyclisations of **1a** are an exception,[33] and enolates **3b** form via **2b** on treatment of **1b** with *t*BuLi or LDA.[34−38] Benzene rings have also been dearomatised by nucleophilic cyclisations of sulfones,[39] sulfonamides[40−43] and phosphonamides.[44]

In the intramolecular sense, complexation of the ring with a transition metal, such as chromium, manganese or osmium[45−48] withdraws sufficient electron density to allow dearomatising nucleophilic attack to take place. A number of research groups have used such reactions in the synthesis

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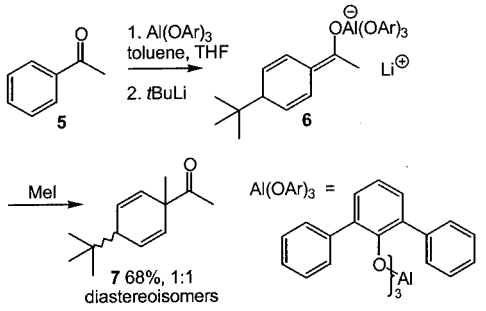
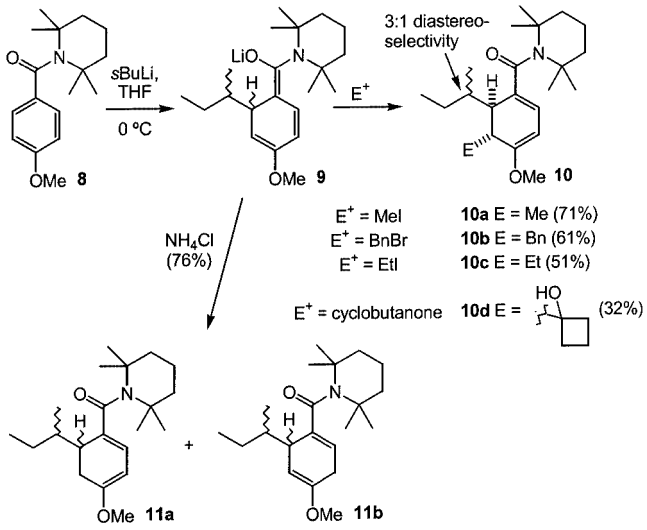
of partially saturated ring systems with regio- and stereocontrol,[49] especially since the planar chirality of the complexes ring can be exploited, for example, by asymmetric lithiation.[50−52] Coordination to a palladium atom can also lead to remarkable dearomatising substitution reactions.[53]

The problem with most electron-withdrawing groups as activators of an only reluctantly electrophilic aromatic ring is that the activating groups themselves are susceptible to attack by the nucleophile. In the amide cyclisation shown in Scheme 1, a bulky alkyl group is needed at the nitrogen atom at least in part to protect the carbonyl group from attack.[34] Yamamoto has shown that very bulky aluminium-based Lewis acids can perform a similar role with aromatic aldehydes and ketones, blocking attack at the carbonyl group of **5** and leading to conjugate or homoconjugate additions to give **6** and hence **7** (Scheme 2).[54−56]

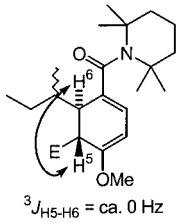


Scheme 2

orientated at an approximately perpendicular dihedral angle in both compounds.



Scheme 3



Scheme 4

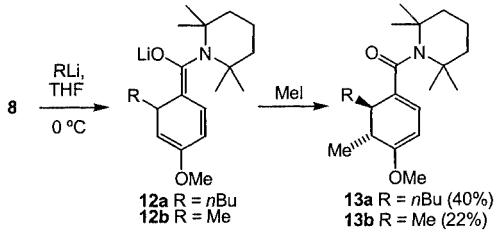
Results and Discussion

Dearomatising Additions

Steric hindrance to attack at C=O is behind the use of *N*,*N*-diethyl- and *N*,*N*-diisopropylcarboxamides as substrates for directed metallation reactions with alkyllithium compounds,[57−59] and as part of a project in which we aimed to study conformational properties[60] of even more hindered amides, we attempted an ortholithiation of *N*-anisoyl-2,2,6,6-tetramethylpiperidide (**8**). Treatment with *s*BuLi at −78 °C and then methyl iodide gave, instead of the expected[61] *ortho*-methylated product, the dearomatised compound **10a** as a mixture of diastereoisomers at the stereogenic centre of the *sec*-butyl group (Scheme 3). Increasing the temperature to 0 °C resulted in a yield of 71% of **10a**. Nucleophilic addition to the *ortho* position of the aromatic ring takes place in preference to deprotonation, forming an extended enolate **9** which alkylates at its terminus. The addition of the organolithium compound is rather non-stereoselective (3:1), but the alkylation is fully stereoselective for the *trans* product and gives only two of the possible four diastereoisomers of **10a**. Stereochemistry is assigned to **10** on the basis that the coupling between 5-H and 6-H is essentially zero for both diastereoisomers (Scheme 4), indicating they have the same relative stereochemistry and are

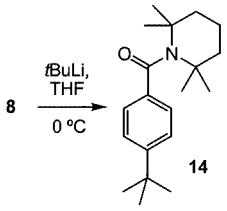
Other alkylating agents react with the enolate in a similar way to give good yields of benzylated **10b** or ethylated products **10c** with complete regioselectivity, and a dearomatising aldol reaction with cyclobutanone gave the adduct **10d**. Only protonation gave a mixture of regioisomers **11a** and **11b**, possibly due to double bond migration in the products.

Reactions with other organolithium compounds were variable in terms of yield and selectivity. *n*-Butyllithium was less reactive than *s*-butyllithium and gave a moderate yield of a single diastereoisomer of **13a** on addition to the amide's *ortho* position and methylation (Scheme 5). Methyllithium was even less reactive but nonetheless produced some of the dimethylated product **13b** after methyl iodide quench of the intermediate enolate **12b**.



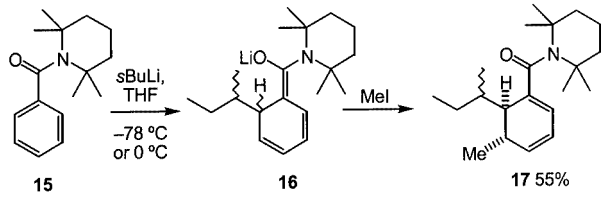
Scheme 5

tert-Butyllithium behaved quite differently, attacking the *para* position of **8** instead of the *ortho* position. A substitution reaction ensued, giving **14** in low yield (Scheme 6). Presumably, despite its greater reactivity, it is too bulky to approach close to the amido substituent, and is therefore forced to the *para* position. However, it cannot be ruled out that a change in mechanism − involving radical intermediates − is operating. *tert*-Butyllithium is particularly prone to nucleophilic substitution reactions with aromatic electrophiles.[62]



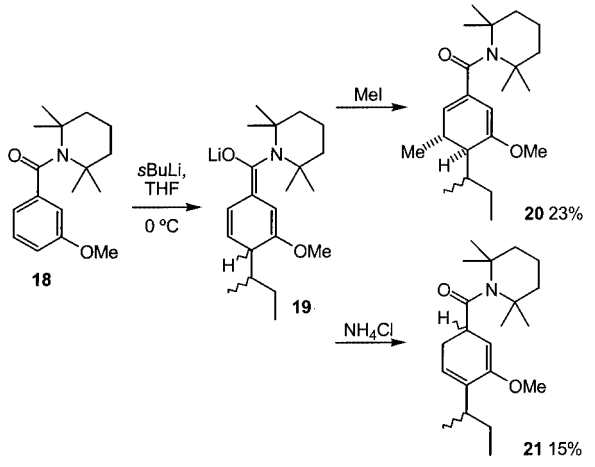
Scheme 6

A *p*-methoxy substituent must contribute to the stability of the products, being "more conjugated" with the carbonyl group in **10** and **13** than in the starting material **8** (see below). However, a *p*-methoxy substituent is not necessary for successful reaction. Treatment of the simple benzamide **15** with *s*BuLi dearomatises it to **16** and MeI stereoselectively generates compound **17** (Scheme 7).

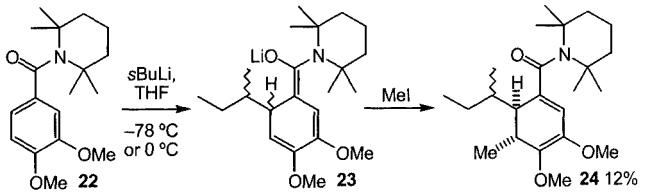


Scheme 7

The *meta*-substituted benzamide **18** is also dearomatised by *s*BuLi, but this time by addition to the *para* position rather than the *ortho* position. Methylation of **19** gives **20**; protonation leads to the regioisomer **21** (Scheme 8). With the *para* position blocked, addition returns to the *ortho* position, though the product **24** from **22** is formed in only poor yield. (Scheme 9).

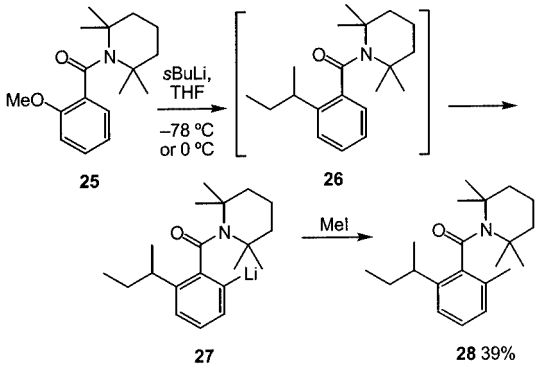


Scheme 8



Scheme 9

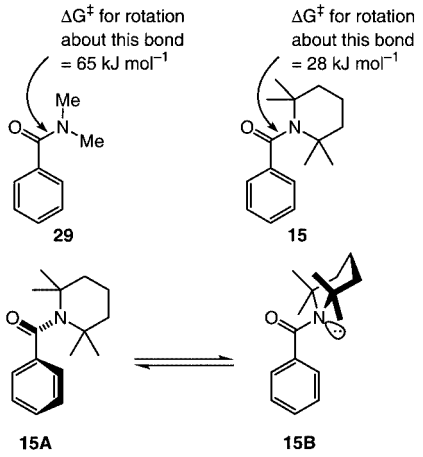
Attack by *s*BuLi on the *ortho* position of the *ortho*-substituted amide **25** resulted in a substitution reaction to give **26**. Nucleophilic substitution by organolithium compounds of methoxy substituents *ortho* to electron-withdrawing groups, in particular oxazolines, has been observed before.[63] Interestingly, the excess *s*BuLi was then able to ortholithiate this compound to give **27**; a methyl iodide quench generated the product **28** (Scheme 10). The transformation of **26** to **27** is the only time we have been able to observe the reaction we initially aimed to achieve, ortholithiation of a TMP amide.



Scheme 10

Amides of 2,2,6,6-tetramethylpiperidine (TMP amides) have some conformational features which manifest themselves in their NMR spectrum and which may contribute to the unexpected reactivity of these compounds towards attack on the ring. The C−N bonds of most tertiary amides rotate sufficiently slowly that at the very least the conformers are distinguishable by NMR.[64] Not so for amides of 2,2,6,6-tetramethylpiperidine.[65] Despite its extreme steric hindrance, which is often a factor increasing barriers to rotation,[61] the C−N bond of **15** has been shown to have a very low barrier to rotation (Scheme 11). Similar observations − where increased steric hindrance leads to decreased rotational barriers − have been ascribed to destabilisation of a ground state conformer with a consequent lowering of the energy required to reach the transition state conformation.[66−69] In the case of **15**, which we take as representative of the TMP amides, the ground state is expected to have a conformation approximating to that shown in **15A** (Scheme 11), in which there is some degree of twisting about the Ar−CO axis to avoid steric clashes between the *ortho*-protons of the benzamide ring and the nitrogen substituents.[70] The proximity of the *gem*-dimethyl pair *trans* to the oxygen atom and the aromatic ring raises the energy of this conformer. C−N rotation in **15** would

pass through a transition state approximating to **15B**; the N lone pair is now co-planar with the C=O bond (and presumably antiperiplanar to maximise n−σ* interactions), and the C=O bond has the opportunity to gain coplanarity with the aromatic ring. A geared rotation probably having a comparable transition state takes place in other hindered tertiary amides.[71−73]



Scheme 11

As the conformation approaches **15B**, the aromatic ring becomes more susceptible to attack by nucleophiles: Conjugation is achieved with an electron-deficient carbonyl group whose π* orbital can no longer accept electron density from the nitrogen lone pair. At the same time, the carbonyl group remains protected from attack by the methyl groups of the TMP ring (compare the role of the Lewis acid in Scheme 2). We propose that **15B** approximates to the most reactive conformation of the TMP amides, explaining the lack of willingness for TMP amides to undergo lithiation and also their relative susceptibility to attack on the ring.

Support for the existence of a twisted ground state is provided by the X-ray crystal structure of **8**, shown in Figure 1, which manifests features both of **15A** and **15B**. Not only is the amide system twisted out of the plane of the aromatic ring by 48.0°, but the amide itself is also twisted, leading to a dihedral angle of 45.6° between the carbonyl group and the nitrogen substituents. The tetramethylpiperidine ring assumes a twist-boat conformation with two methyl groups pseudoaxial and two methyl groups pseudoequatorial.

Hydrolysis of the TMP Ring

The tetramethylpiperidine ring is susceptible to cleavage under acidic conditions, and we found that the cleanest method for achieving the ring opening to dearomatised compounds of potential synthetic usefulness was by treatment with iodotrimethylsilane in the dark. Thus, **10a** underwent cleavage of both the enol ether and the TMP ring, with concomitant migration of the double bond into conjugation with the amide to give the secondary cyclohexenamide **30** (Scheme 12) in 50% yield.

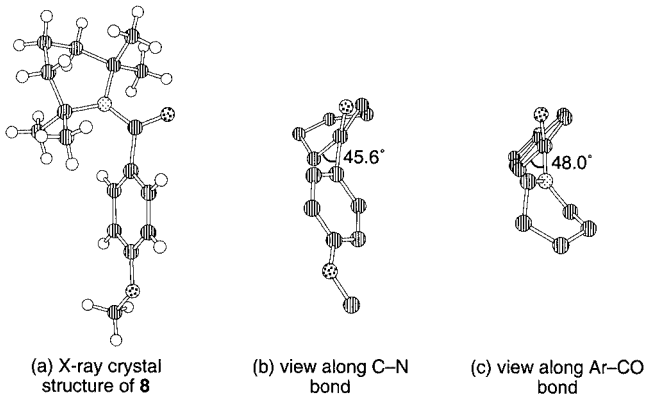
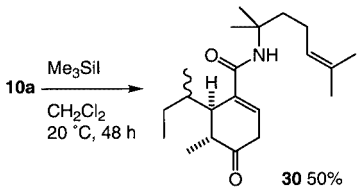


Figure 1. X-ray crystal structure of a TMP amide; for clarity, H atoms and Me groups are omitted from (b) and (c)



Scheme 12

Synthesis of the Amides 8, 15, 18, 22 and 25

The amides of TMP are slow to form from 2,2,6,6-tetramethylpiperidine and the appropriate acyl chloride under normal conditions, but on treatment with sodium hydride in refluxing toluene acceptable yields of the amides can be obtained. The sensitivity of the TMP ring to strong acid meant that acid/base workup procedures had to be avoided, and we found that the best way to avoid contamination of the product by acyl chloride or carboxylic acid was to quench the reaction with ethanol, forming the ethyl ester of the unchanged carboxylic acid. Base hydrolysis and extraction yielded the amide, free of unchanged acid or acyl chloride.

Conclusion

Treatment of hindered amides with strong bases is well established as a method for the synthesis of aromatic compounds by *ortho*-lithiation.[62] This reaction appears to place some limits of the types of amides which may be successfully *ortho*-lithiated, but it also opens up new prospects for the use of aromatic rings as precursors of substituted cyclohexane derivatives without the need for recourse to transition metal chemistry.

Experimental Section

General Remarks: Except where noted otherwise, reagents and starting materials were obtained from commercial sources and used as received. Tetrahydrofuran (THF) was dried with sodium and distilled from sodium benzophenone ketyl immediately prior to use.

Dichloromethane (CH_2Cl_2) and toluene were dried and distilled by standard procedures. Other reaction solvents, and all chromatographic and workup solvents were spectroscopic grade and used as received. Flash chromatography was carried out by the method of Still, Kahn and Mitra.[74] Infrared spectra were recorded with an ATI Matson Genesis Series FTIR spectrometer using an evaporated film on sodium chloride plate and are reported in wavenumbers (cm^{-1}). Low-resolution mass spectra (chemical ionisation) were recorded with a Fisons VG Trio 2000 quadrupole mass spectrometer. High-resolution mass spectra (accurate mass measurement) were recorded with a Kratos Concept-IS mass spectrometer. ^1H NMR and ^{13}C were recorded with a Varian Inova (300 MHz for ^1H NMR and 75 MHz for ^{13}C NMR) spectrometer. Chemical shifts (δ_H and δ_C) are in ppm and all coupling constants (J) are in Hz. Deuteriochloroform was employed as solvent. Reactions were monitored by thin layer chromatography (TLC) using available pre-coated aluminium plates (Merck silica Kieselgel 60F245). TLC plates were inspected under UV light and developed by spraying with potassium permanganate.

Synthesis of Amides

1-(4-Methoxybenzoyl)-2,2,6,6-tetramethylpiperidine (8): 2,2,6,6-Tetramethylpiperidine (14 mL, 1.5 equiv.) was added to a solution of 60% sodium hydride (4.42 g, 2 equiv.) in dry toluene (75 mL) at room temperature under nitrogen. After stirring for 10 min, *p*-anisoyl chloride (7.5 mL, 55.2 mmol) was slowly added to the reaction mixture and the solution was heated at reflux for 24 h. The reaction was quenched by slow addition of ethanol (40 mL). The solution was washed with brine (150 mL) and the resulting solution was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried with magnesium sulfate and concentrated under reduced pressure to afford the product as brown oil. The product was dissolved in ethanol (100 mL) and 2 M sodium hydroxide (2 equiv.) was added. After stirring for 40 h (to convert the ester to carboxylic acid), the solution was washed with sodium hydrogen carbonate (2 × 20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried with magnesium sulfate and concentrated under reduced pressure. The crude yellow product was purified by flash chromatography [EtOAc/petroleum ether (b.p. 40−60 °C), 1:14] to provide the benzamide **8** (4.13 g, 27%) as white crystals, m.p. 80−84 °C. ^1H NMR ($CDCl_3$): δ = 1.39 (s, 12 H, 4 × CH_3), 1.80 (s, 6 H, 3 × CH_2), 3.85 (s, 3 H, OCH_3), 6.88 (d, J = 8.8 Hz, 2 H, 3-H & 5-H), 7.45 (d, J = 8.8 Hz, 2 H, 2-H & 6-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.1 (*C*H_2), 30.5 [2 × C(*C*H_3)$_2$], 37.1 (2 × CH_2), 55.2 [2 × *C*(CH_3)$_2$], 56.2 (O*C*H_3), 113.0 (*C*-3 & *C*-5), 129.5 (*C*-2 & *C*-6), 135.8 (*C*−C=O), 160.7 (*C*−OCH_3), 177.1 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 1607 cm^{-1} (C=O). *m*/*z* (CI): 276 (100%) [M + H^+]; found M = 276.1962; $C_{17}H_{25}NO_2 + H^+$ requires M = 276.1963.

1-Benzoyl-2,2,6,6-tetramethylpiperidine (15):[65] In the same way, 2,2,6,6-tetramethylpiperidine (4.4 mL, 1.5 equiv.), 60% sodium hydride (1.49 g, 2 equiv.), toluene (40 mL) and benzoyl chloride (2 mL, 17.23 mmol) gave a crude product was purified by flash chromatography [ethyl acetate/petroleum ether (b.p. 40−60 °C), 1:9] to afford the benzamide **15** (1.19 g, 28%) as white crystals, m.p. 89−92 °C.[65] ^1H NMR ($CDCl_3$): δ = 1.40 (s, 12 H, 4 × CH_3), 1.82 (s, 6 H, 3 × CH_2), 7.37 (m, 3 H, 3-H & 4-H & 5-H), 7.45 (m, 2 H, 2-H & 6-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.8 (*C*H_2), 30.5 [2 × C(*C*H_3)$_2$], 36.9 (2 × *C*H_2), 56.4 [2 × *C*(CH_3)$_2$], 127.6 (*C*-2 & *C*-6), 127.7 (*C*-3 & *C*-5), 129.2 (*C*-4), 143.2 (*C*−C=O), 176.3 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 1620 cm^{-1} (C=O). *m*/*z* (CI): 246 (100%) [M + H^+].

1-(3-Methoxybenzoyl)-2,2,6,6-tetramethylpiperidine (18): In the same way, 2,2,6,6-tetramethylpiperidine (4.59 mL, 1.5 equiv.), 60% sodium hydride (1.45 g, 2 equiv.), dry toluene (60 mL) and *m*-anisoyl chloride (2.55 mL, 18.15 mmol) gave a crude product was purified by flash chromatography [EtOAc/petroleum ether (b.p. 40−60 °C), 1:14] to provide the benzamide **18** (0.83 g, 17%) as yellow solid, m.p. 70−74 °C. ^1H NMR ($CDCl_3$): δ = 1.40 (s, 12 H, 4 × CH_3), 1.80 (s, 6 H, 3 × CH_2), 3.80 (s, 3 H, OCH_3), 6.94 (dd, J = 8.2, 0.9 Hz, 1 H, 4-H), 7.02 (s, 1 H, 2-H), 7.05 (dd, J = 7.5, 0.9 Hz, 1 H, 6-H), 7.27 (t, J = 7.8 Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.8 (*C*H_2), 30.4 [2 × C(*C*H_3)$_2$], 36.9 (2 × *C*H_2), 55.2 [2 × *C*(CH_3)$_2$], 56.5 (O*C*H_3), 113.0 (*C*-2), 115.3 (*C*-4), 120.1 (*C*-6), 128.7 (*C*-5), 144.4 (*C*−C=O), 159.1 (*C*−OCH_3), 176.2 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 1625 cm^{-1} (C=O). *m*/*z* (CI): 276 (100%) [M + H^+]; found M = 275.1885; $C_{17}H_{25}NO_2$ requires M = 275.1885.

1-(3,4-Dimethoxybenzoyl)-2,2,6,6-tetramethypiperidine (22): Thionyl chloride (60 mL) was added to 3,4-dimethoxybenzoic acid (7.22 g, 35.9 mmol) and the mixture was heated at reflux for 2.5 h under nitrogen. The excess thionyl chloride was removed under reduced pressure to afford 3,4-dimethyoxybenzoyl chloride (5.78 g). By the method used for **8**, 2,2,6,6-tetramethylpiperidine (7.29 mL, 1.5 equiv.), 60% sodium hydride (2.33 g, 2 equiv.), toluene (70 mL) and the crude 3,4-dimethoxybenzoyl chloride (5.78 g, 28.8 mmol) gave a crude product which was purified by flash chromatography [EtOAc/petroleum ether (b.p. 40−60 °C), 1:14] to provide the benzamide **22** (1.07 g, 12%) as a brown solid, m.p. 138−142 °C. ^1H NMR ($CDCl_3$): δ = 1.38 (s, 12 H, 4 × CH_3), 1.79 (s, 6 H, 3 × CH_2), 3.91 (s, 6 H, 2 × OCH_3), 6.81 (d, J = 8.8 Hz, 1 H, 5-H), 7.05 (m, 2 H, 6-H & 2-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.0 (*C*H_2), 30.4 [2 × C(*C*H_3)$_2$], 37.0 (2 × *C*H_2), 55.9 [2 × *C*(CH_3)$_2$], 56.4 (2 × O*C*H_3), 109.5 (C-2), 111.1 (C-5), 120.9 (C-6), 135.7 (*C*−C=O), 148.6 (2 × *C*−OCH_3), 177.0 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 1602 cm^{-1} (C=O). *m*/*z* (CI): 306 (100%) [M + H^+]; found M = 305.1977; $C_{18}H_{27}NO_3$ requires M = 305.1991.

1-(2-Methoxybenzoyl)-2,2,6,6-tetramethylpiperidine (25): As for compound **8**, 2,2,6,6-tetramethylpiperidine (3.15 mL, 1.5 equiv.), 60% sodium hydride (1.16 g, 2 equiv.), toluene (40 mL) and *o*-anisoyl chloride (2.14 mL, 14.38 mmol) gave a crude product which was purified by flash chromatography [EtOAc/petroleum ether (b.p. 40−60 °C), 1:14] to provide the benzamide **25** (1.33 g, 34%) as a white solid, m.p. 85−89 °C. ^1H NMR ($CDCl_3$): δ = 1.41 (s, 12 H, 4 × CH_3), 1.80 (s, 6 H, 3 × CH_2), 3.86 (s, 3 H, OCH_3), 6.91 (m, 2 H, 3-H & 5-H), 7.17 (d, J = 7.3 Hz, 1 H, 6-H), 7.31 (t, J = 7.9 Hz, 1 H, 4-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.8 (*C*H_2), 30.3 [2 × C(*C*H_3)$_2$], 37.1 (2 × CH_2), 55.4 [2 × *C*(CH_3)$_2$], 56.5 (O*C*H_3), 111.2 (Ar-C), 119.3 (Ar-C), 128.3 (Ar-C), 129.7 (Ar-C), 132.4 (Ar-C), 156.1 (*C*−OCH_3), 172.6 (*C*=O) ppm. IR: $\tilde{\nu}_{max}$ = 1620 cm^{-1} (C=O). *m*/*z* (CI): 276 (100%) [M + H^+]; found M = 275.1882; $C_{17}H_{25}NO_2$ requires M = 275.1885.

Additions of Alkyllithium Compounds

(5*RS*,6*SR*)-1-(6-*sec*-Butyl-4-methoxy-5-methylcyclohexa-1,3-dienyl)carbonyl-2,2,6,6-tetramethylpiperidine (10a): *sec*-Butyllithium (1.3 M in hexane, 0.68 mL, 1.2 equiv.) was slowly added to a solution of the benzamide **8** (0.20 g, 0.74 mmol) in dry THF (7 mL) at 0 °C under nitrogen and the solution was stirred for 1 h. Iodomethane (0.14 mL, 3 equiv.) was added and the mixture was stirred for further 45 min. The mixture was allowed to warm to room remperature and a saturated solution of ammonium chloride (15 mL) was added. The mixture was extracted with ethyl acetate (2 × 20 mL). The combined organic phases were then washed with brine (2 × 20 mL) and dried with magnesium sulfate. The solution

was concentrated under reduced pressure to yield the crude product as yellow oil. Purification by flash chromatography [EtOAc/petroleum ether (b.p. 40−60 °C), 1:14] gave a 3:1 mixture of diastereoisomers of the dearomatised product **10a** (0.19 g, 71%) and the starting material **8** (12 mg). ^{1}H NMR ($CDCl_3$): δ = 0.73 (d, *J* = 7.0 Hz, 3 H, CHC*H*$_3$), 0.96 (t, *J* = 7.6 Hz, 3 H, CH_2C*H*$_3$), 1.04 (d, *J* = 7.1 Hz, 3 H, CHC*H*$_3$), 1.26 (m, 12 H, 4 × CH_3 on piperidine ring), 1.36 (m, 2 H, CH_2), 1.46−1.53 (m, 6 H, 3 × CH_2 of piperidine ring), 1.74 (m, 1 H), 2.29 (q, *J* = 7.3 Hz, 1 H, 5-H), 2.60 & 2.70 (1 H, 2 × d, *J* = 2.3, 2.7 Hz, 6-H), 3.66 (s, 3 H, OCH_3), 4.96 (d, *J* = 6.6 Hz, 1 H, 3-H), 7.40 (d, *J* = 6.7 Hz, 1 H, 2-H) ppm. IR: $\tilde{\nu}_{max}$ = 1625 cm^{-1} (C=O). *m*/*z* (CI): 349 (100%) [M + H$^+$]; found *M* = 348.2903; $C_{23}H_{38}NO_2$ requires *M* = 348.2902.

(5*RS*,6*SR*)-1-(5-Benzyl-6-*sec*-butyl-4-methoxycyclohexa-1,3-dienyl)carbonyl-2,2,6,6-tetramethylpiperidine (10b): *sec*-Butyllithium (1.3 M in hexane, 1.71 mL, 3 equiv.) was slowly added to a solution of the benzamide **8** (0.20 g, 0.74 mmol) in dry THF (7 mL) at 0 °C under nitrogen and the mixture was stirred for 1 h. Benzyl bromide (0.26 mL, 3 equiv.) was added to the solution at 0 °C in the ice bath and the mixture was allowed to warm to room temperature overnight. The usual workup gave the crude product as yellow oil, which was purified by flash chromatography [EtOAc/petroleum ether (b.p. 40−60 °C), 1:14] to provide a 3:1 mixture of diastereoisomers of the dearomatised product **10b** (0.19 g, 61%) as yellow oil, and starting material **8** (9 mg). ^{1}H NMR ($CDCl_3$): δ = 0.60 (t, *J* = 7.3 Hz, 3 H, CH_2C*H*$_3$), 0.71 (m, 3 H, CHC*H*$_3$), 1.04 (m, 2 H, CH_2), 1.29 (s, 12 H, 4 × CH_3 on the piperidine ring), 1.56 (t, *J* = 6.0 Hz, 6 H, 3 × CH_2 of piperidine ring), 1.64 (m, 1 H), 2.44 (q, *J* = 4.0 Hz, 1 H, 5-H), 2.82 (m, 2 H, CH_2), 2.92 (d, *J* = 2.6 Hz, 1 H, 6-H), 3.65 (s, 3 H, OCH_3), 5.06 (d, *J* = 6.4 Hz, 1 H, 3-H), 7.22 (m, 5 H, Ar−H on aromatic ring), 7.52 (d, *J* = 6.6 Hz, 1 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.6, 15.1, 17.7, 24.0, 26.3, 37.9, 38.8, 39.2, 40.5, 41.0, 54.2, 55.2, 92.0, 126.0, 128.2, 129.5, 131.6, 138.3, 141.7, 168.7, 184.9 ppm. IR: $\tilde{\nu}_{max}$ = 1624 cm^{-1} (C=O). *m*/*z* (CI): 424 (100%) [M + H$^+$]; found *M* + H$^+$ = 424.3214; $C_{28}H_{42}NO_2$ requires *M* = 424.3215.

(5*RS*,6*SR*)-1-(6-*sec*-Butyl-5-ethyl-4-methoxycyclohexa-1,3-dienyl)carbonyl-2,2,6,6- tetramethylpiperidine (10c): *sec*-Butyllithium (1.3 M in hexane, 2.14 mL, 3 equiv.) was added slowly to a solution of the benzamide **8** (0.26 g, 0.93 mmol) in dry THF (7 mL) at 0 °C and the mixture was stirred for 1 h. Iodoethane (0.22 mL, 3 equiv.) was added and the mixture was left to warm to room temperature overnight. A saturated solution of ammonium chloride (15 mL) was added. The usual workup gave a crude product which was purified by flash chromatography [EtOAc/petroleum ether (b.p. 40−60 °C), 1:14] to provide a 3:1 mixture of diastereoisomers of the dearomatised product **10c** (0.17 g, 51%) and starting material **8** (19 mg). ^{1}H NMR ($CDCl_3$): δ = 0.73 (d, *J* = 6.9 Hz, 3 H, CHC*H*$_3$), 0.92 (m, 6 H, Me × 2), 1.21 (s, 12 H, 4 × CH_3 on piperidine ring), 1.34 to 1.47 (m, 6 H, 3 × CH_2 of piperidine ring), 1.50 (m, 4 H), 1.71 (m, 1 H), 2.07 (t, *J* = 6.8 Hz, 1 H, 5-H), 2.76 & 2.85 (1 H, 2 × d, *J* = 2.6, 3.0 Hz, 6-H), 3.65 (s, 3 H, OCH_3), 4.97 (d, *J* = 6.6 Hz, 1 H, 3-H), 7.38 (d, 1 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.1, 12.2, 15.5, 17.6, 23.9, 27.1, 30.5, 37.9, 38.3, 39.9, 41.7, 54.1, 55.1, 91.6, 131.9, 138.2, 169.5, 184.9 ppm. IR: $\tilde{\nu}_{max}$ = 1623 cm^{-1} (C=O). *m*/*z* (CI): 362 (100%) [M + H$^+$]; found *M* = 361.2989; $C_{23}H_{39}NO_2$ requires *M* = 361.2981.

(5*RS*,6*SR*)-1-[6-*sec*-Butyl-5-(1-hydroxycyclobutyl)-4-methoxycyclohexa-1,3-dienyl]carbonyl-2,2,6,6-tetramethylpiperidine (10d): *sec*-Butyllithium (1.3 M in hexane, 1.61 mL, 3 equiv.) was slowly added to a solution of the benzamide **8** (0.19 g, 0.69 mmol) in dry THF (7 mL) at 0 °C. After 2 h, cyclobutanone (0.16 mL, 3 equiv.) was added and the mixture was stirred for further 1 h. A saturated solution of ammonium chloride (15 mL) was added at 0 °C. The usual workup up gave a crude product which was purified by flash chromatography [EtOAc/petroleum ether (b.p. 40−60 °C), 1:14] to afford a 3:1 mixture of diastereoisomers of the dearomatised product **10d** (91 mg, 32%) and starting material **8** (24 mg). ^{1}H NMR ($CDCl_3$): δ = 0.76 (d, *J* = 7.0 Hz, 3 H, CHC*H*$_3$), 0.96 (t, *J* = 7.5 Hz, 3 H, CH_2C*H*$_3$), 1.10 to 2.90 (m, 28 H), 2.97 and 3.05 (1 H, 2 × s, 6-H), 3.64 (s, 3 H, OCH_3), 5.15 (d, *J* = 6.4 Hz, 1 H, 3-H), 7.11 (d, *J* = 6.4 Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.5, 15.0, 16.8, 16.9, 23.1, 26.4, 29.3, 33.5, 37.4, 39.3, 44.9, 55.1, 57.3, 79.6, 94.3, 133.2, 136.2, 164.2, 182.8 ppm. IR: $\tilde{\nu}_{max}$ = 1622 cm^{-1} (C=O). *m*/*z* (CI): 404 (100%) [M + H$^+$]; found *M* = 404.3165; $C_{25}H_{41}NO_3$ + H$^+$ requires *M* = 404.3164.

1-(6-*sec*-Butyl-4-methoxycyclohexa-1,3-dienyl)carbonyl-2,2,6,6-tetramethylpiperidine (11a) and 1-(6-*sec*-Butyl-4-methoxycyclohexa-1,4-dienyl)carbonyl-2,2,6,6-tetramethylpiperidine (11b): *sec*-Butyllithium (1.27 M in hexane, 0.69 mL, 1.2 equiv.) was added slowly to a solution of the benzamide **8** (0.20 g, 0.73 mmol) in dry THF (7 mL) at 0 °C under nitrogen. After 1.5 h, a saturated solution of ammonium chloride (30 mL) was added. The usual workup gave a crude product which was purified by flash chromatography [EtOAc/petroleum ether (b.p. 40−60 °C), 1:14] to provide a 3:1 mixture of diastereoisomers of the regioisomers **11a** and **11b** (0.15 g, 76%) and the starting material **8** (39 mg). ^{1}H NMR ($CDCl_3$): δ = 0.70 to 1.06 (m, 12 H), 1.14 to 2.00 (m, 42 H), 2.20−2.70 (m, 2 H, 5-H), 2.67 and 2.74 (2 H, 2 × t, *J* = 4.1, 4.6 Hz, 3′-H), 2.80 to 3.00 (m, 2 H, 6-H & 6′-H), 3.60 (s, 3 H, OCH_3′), 3.66 (s, 3 H, OCH_3), 4.62 (dd, *J* = 5.1, 1.9 Hz, 1 H, 5′-H), 4.98 (dd, *J* = 6.5, 2.1 Hz, 1 H, 3-H), 6.04 (dd, *J* = 5.1, 2.3 Hz, 1 H, 2′-H), 7.00 (d, *J* = 6.4 Hz, 1 H, 2-H) ppm. IR: $\tilde{\nu}_{max}$ = 1623 cm^{-1} (C=O). *m*/*z* (CI): 335 (100%) [M + 2 H$^+$], 334 (25%) [M + H$^+$]; found *M*[M + H$^+$] = 334.2748; $C_{21}H_{36}NO_2$ requires *M* = 334.2746.

(5*RS*,6*SR*)-1-(6-Butyl-4-methoxy-5-methylcyclohexa-1,3-dienyl)-carbonyl-2,2,6,6-tetramethylpiperidine (13a): *n*-Butyllithium (2.35 M in pentane, 0.37 mL, 1.2 equiv.) was slowly added to a solution of the benzamide **8** (0.20 g, 0.72 mmol) in dry THF (7 mL) at 0 °C under nitrogen. After 50 min, iodomethane (0.13 mL, 3 equiv.) was added. After a further 40 min, a saturated solution of ammonium chloride (10 mL) was added at room temperature. The usual workup gave a crude product which was purified by flash chromatography [EtOAc/petroleum ether (b.p. 40−60 °C), 1:14] to provide the dearomatised product **13a** (0.10 g, 40%) and the starting material **8** (48 mg). ^{1}H NMR ($CDCl_3$): δ = 0.90 (m, 3 H, CH_2C*H*$_3$), 1.02 (d, *J* = 7.1 Hz, 3 H, CHC*H*$_3$), 1.25 (m, 14 H), 1.38 (m, 4 H), 1.47−1.53 (m, 6 H, 3 × CH_2), 2.29 (q, *J* = 7.1 Hz, 1 H, 5-H), 2.53 (dd, *J* = 8.7, 0.8 Hz, 1 H, 6-H), 3.68 (s, 3 H, OCH_3), 5.03 (d, *J* = 6.4 Hz, 1 H, 3-H), 7.14 (d, *J* = 6.6 Hz, 1 H, 2-H) ppm. IR: $\tilde{\nu}_{max}$ = 1624 cm^{-1} (C=O). *m*/*z* (CI): 349 (100%) [M + 2 H$^+$], 348 (75%) [M + H$^+$]; found *M*[M + H$^+$] = 348.2903; $C_{22}H_{38}NO_2$ requires *M* = 348.2902.

(5*RS*,6*SR*)-1-(4-Methoxy-5,6-dimethylcyclohexa-1,3-dienyl)carbonyl-2,2,6,6-tetramethylpiperidine (13b): Methyllithium (1.6 M in diethyl ether, 0.59 mL, 1.2 equiv.) was slowly added to a solution of the benzamide **8** (0.22 g, 0.79 mmol) in dry THF (7 mL) at 0 °C under nitrogen and the mixture was stirred for 1 h. Iodomethane (0.14 mL, 3 equiv.) was added. After 50 min, a saturated solution of ammonium chloride (20 mL) was added at room temperature. The usual workup gave a crude product which was purified by flash chromatography [EtOAc/petroleum ether (b.p. 40−60 °C), 1:14] to provide the dearomatised product **13b** (54 mg, 22%) and the start-

ing material **8** (0.11 g). ^{1}H NMR ($CDCl_3$): δ = 0.94 (d, *J* = 7.1 Hz, 3 H, CHC*H*$_3$), 1.00 (d, *J* = 7.0 Hz, 3 H, CHC*H*$_3$), 1.18 (s, 12 H, 4 × CH_3), 1.41 to 1.48 (m, 6 H, 3 × CH_2), 1.98 (q, *J* = 7.1 Hz, 1 H, 5-H), 2.55 (1 H, qd, *J* = 7 and 1.6, 6-H), 3.59 (s, 3 H, OCH_3), 4.94 (d, *J* = 6.5 Hz, 1 H, 3-H), 6.87 (d, *J* = 6.6 Hz, 1 H, 2-H) ppm. IR: $\tilde{\nu}_{max}$ = 1622 cm^{-1} (C=O). *m*/*z* (CI): 306 (100%) [M + H$^+$]; found *M*[M + H$^+$] = 306.2429; $C_{19}H_{32}NO_2$ requires *M* = 306.2433.

1-(4-*tert*-Butylbenzoyl)-2,2,6,6-tetramethylpiperidine (14): *tert*-Butyllithium (1.27 M in pentane, 0.43 mL, 1.2 equiv.) was added slowly to a solution of the benzamide **8** (0.20 g, 0.74 mmol) in dry THF (7 mL) at 0 °C under nitrogen and the solution was stirred for 1 h. Iodomethane (0.13 mL, 3 equiv.) was added, and after a further 1 h at 0 °C, a saturated solution of ammonium chloride (20 mL) was added. The usual workup gave a crude product which was purified by flash chromatography [EtOAc/petroleum ether (b.p. 40−60 °C), 1:9] to yield the substitution product **14** (19 mg, 8.7%) and the staring material **8** (90 mg). ^{1}H NMR ($CDCl_3$): δ = 1.35 (s, 9 H, 3 × CH_3), 1.41 (s, 12 H, 4 × CH_3), 1.82 (m, 6 H, 3 × CH_2), 7.38 (m, 4 H, 4 × Ar−H) ppm. IR: $\tilde{\nu}_{max}$ = 1625 cm^{-1} (C=O). *m*/*z* (CI): 302 (100%) [M + H$^+$]; found *M*[M + H$^+$] = 302.2494; $C_{20}H_{32}NO$ requires *M* = 302.2484.

(5*RS*,6*SR*)-1-(6-*sec*-Butyl-5-methylcyclohexa-1,3-dienyl)carbonyl-2,2,6,6-tetramethylpiperidine (17): *sec*-Butyllithium (1.25 M in hexane, 0.71 mL, 1.2 equiv.) was added to a solution of the benzamide **15** (0.18 g, 0.74 mmol) in dry THF (7 mL) at 0 °C. After 2 h, iodomethane (0.14 mL, 3 equiv.) was added and the mixture allowed to warm to room temperature. A saturated solution of ammonium chloride (10 mL) was added, and the usual workup gave a crude product which was purified by flash chromatography [EtOAc/petroleum ether (b.p. 40−60 °C), 1:14] to provide a 3:1 mixture of the diastereoisomers of the dearomatised product **17** (0.13 g, 55%) and benzamide **15** (12 mg). ^{1}H NMR ($CDCl_3$): δ = 0.60−1.10 (m, 6 H, 8-H & 10-H), 1.10−2.10 (m, 21 H), 2.30 (m, 1 H), 2.40−2.60 (2 × d, 1 H), 2.70 (m, 1 H), 2.90 (quint, *J* = 7, 1 H), 3.10 (m, 1 H), 5.40 (m, 2 H), 6.80 (m, 2 H) ppm. IR: $\tilde{\nu}_{max}$ = 1623 cm^{-1} (C=O). *m*/*z* (CI): 319 (100%) [M + H$^+$], 318 (17%) [M$^+$]; found *M*[M + H$^+$] = 318.2797; $C_{21}H_{36}NO$ requires *M* = 318.2797.

(4*RS*,5*SR*)-1-(4-*sec*-Butyl-3-methoxy-5-methylcyclohexa-1,5-dienyl)carbonyl-2,2,6,6-tetramethylpiperidine (20): *sec*-Butyllithium (1.25 M in hexane, 0.74 mL, 1.2 equiv.) was added slowly to a solution of benzamide **18** (0.21 g, 0.77 mmol) in dry THF (7 mL) at 0 °C under nitrogen. After 2 h, iodomethane (0.14 mL, 3 equiv.) was added. After a further 1 h, a saturated solution of ammonium chloride (10 mL) was added. The usual workup gave a crude product what was purified by flash chromatography [EtOAc/petroleum ether (b.p. 40−60 °C), 1:14] to provide a 3:1 mixture of the diastereoisomers of the dearomatised product **20** (0.52 g, 23%) and the starting material **18** (41 mg). ^{1}H NMR ($CDCl_3$): δ = 0.90 (m, 3 H), 0.99 (m, 3 H), 1.04 (dd, 3 H, *J* = 7.2, 2.0 Hz, CHC*H*$_3$), 1.42 (s, 12 H, 4 × CH_3), 1.48 (m, 6 H, 3 × CH_2), 1.60 to 1.80 (m, 3 H), 2.48 (quint, *J* = 6.8, 1 H, 5-H), 3.63 (s, 3 H, OCH_3), 5.20 (d, *J* = 1.8 Hz, 1 H, 2-H), 5.46 (d, *J* = 5.9 Hz, 1 H, 6-H) ppm. IR: $\tilde{\nu}_{max}$ = 1621 cm^{-1} (C=O). *m*/*z* (CI): 348 (100%) [M + H$^+$]; found *M* = 347.2827; $C_{22}H_{37}NO_2$ requires *M* = 347.28241.

1-(4-*sec*-Butyl-3-methoxycyclohexa-2,4-dienyl)carbonyl-2,2,6,6-tetramethylpiperidine (21): *sec*-Butyllithium (1.30 M in hexane, 0.74 mL, 1.2 equiv.) was added slowly to ta solution of benzamide **18** (0.17 g, 0.62 mmol) in dry THF (7 mL) at 0 °C under nitrogen. After 1.5 h, a saturated solution of ammonium chloride (10 mL) was added. The usual workup gave a crude product which was purified by flash chromatography [EtOAc/petroleum ether (b.p. 40−60 °C), 1:14] to yield the dearomatised product **21** (31 mg, 15%) as a mixture of diastereoisomers and the starting material **18** (38 mg). ^{1}H NMR ($CDCl_3$): δ = 0.69−1.13 (m, 6 H, 2 × Me), 1.16−2.00 (m, 15 H), 2.84 (m, 2 H, 6-H), 3.53 (s, 3 H, OCH_3), 4.76 (br. d, 1 H, 2-H), 6.20 (br. d, 1 H, 5-H) ppm. IR: $\tilde{\nu}_{max}$ = 1620 cm^{-1} (C=O). *m*/*z* (CI): 335 (100%) [M + H$^+$]; found *M*[M$^+$] = 334.2750; $C_{21}H_{36}NO_2$ requires *M* = 334.2746.

(5*RS*,6*SR*)-1-(6-*sec*-Butyl-3,4-dimethoxy-5-methylcyclohexa-1,3-dienyl)carbonyl-2,2,6,6-tetramethylpiperidine (24): *sec*-Butyllithium (1.27 M in hexane, 0.67 mL, 1.2 equiv.) was added slowly to a solution of the benzamide **22** (0.21 g, 0.71 mmol) in dry THF (7 mL) at 0 °C under nitrogen. After 1.5 h, iodomethane (0.13 mL, 3 equiv.) was added, and after a further 45 min, a saturated solution of ammonium chloride (20 mL) was added at room temperature. The usual workup gave a crude product which was purified by flash chromatography [EtOAc/petroleum ether (b.p. 40−60 °C), 1:14] to provide a mixture of diastereoisomers of the dearomatised product **24** (32 mg, 12%) and starting amide **22** (95 mg). ^{1}H NMR ($CDCl_3$): δ = 0.84 (d, *J* = 7.0 Hz, 3 H, CHC*H*$_3$), 0.99 (t, *J* = 7.3 Hz, 3 H, CH_2C*H*$_3$), 1.05 (d, *J* = 7.0 Hz, 3 H, CHC*H*$_3$), 1.28 (s, 12 H, 4 × CH_3), 1.39 (m, 2 H, 9-H), 1.59 (m, 6 H, 3 × CH_2), 1.75 (m, 1 H, 7-H), 2.46 (q, *J* = 7.3 Hz, 1 H, 5-H), 2.58 and 2.67 (2 × d, *J* = 2.7, 3.3 Hz, 1 H, 6-H), 3.61 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 7.30 (s, 1 H, 2-H) ppm. IR: $\tilde{\nu}_{max}$ = 1627 cm^{-1} (C=O). *m*/*z* (CI): 378 (100%) [M + H$^+$]; found *M*[M + H$^+$] = 378.3012; $C_{23}H_{40}NO_3$ requires *M* = 378.3008.

1-(2-*sec*-Butyl-6-methylbenzoyl)-2,2,6,6-tetramethylpiperidine (28): *sec*-Butyllithium (1.30 M in pentane, 1.88 mL, 3 equiv.) was slowly added to a solution of the benzamide **25** (0.23 g, 0.82 mmol) in dry THF (7 mL) at 0 °C. After 2 h, iodomethane (0.15 mL, 3 equiv.) was added and the reaction mixture was left to warm to room temperature overnight. A saturated solution of ammonium chloride (10 mL) was added. The usual workup gave a crude product which was purified by flash chromatography [EtOAc/petroleum ether (b.p. 40−60 °C), 1:14] to yield substitution product **28** (0.10 g, 39%) and the starting material **25** (0.12 g). ^{1}H NMR ($CDCl_3$): δ = 0.80 to 1.20 (m, 6 H, 2 × CH_3), 1.20 to 2.00 (m, 21 H), 6.97 (d, *J* = 7.4 Hz, 1 H, 5-H), 7.07 (d, *J* = 7.7 Hz, 1 H, 3-H), 7.16 (m, 1 H, 4-H) ppm. IR: $\tilde{\nu}_{max}$ = 1613 cm^{-1} (C=O). *m*/*z* (CI): 316 (100%) [M + H$^+$]; found *M*[M + H$^+$] = 316.2631; $C_{21}H_{34}NO$ requires *M* = 316.2640.

(5*RS*,6*SR*)-5-Methyl-6-(1-methylpropyl)-4-oxo-*N*-(1,1,5-trimethylhex-4-en-1-yl)cyclohex-1-ene-1-carboxamide (30): The amide **10a** (0.13 g, 0.36 mmol) was dissolved in CH_2Cl_2 (0.18 mL) under nitrogen. Iodotrimethylsilane (0.1 mL, 1.3 equiv.) was added and the mixture was stirred for 40 h at room temperature and poured into 4 equiv. of methanol. The volatile compounds were removed under reduced pressure and the remaining was extracted with diethyl ether (2 × 10 mL) and washed with sodium bisulfite, brine, water and then dried with magnesium sulfate. The combined organic phases were concentrated under reduced pressure to afford the crude product as brown oil. The crude product was purified by flash chromatography [EtOAc/petroleum ether (b.p. 40−60 °C), 1:2] to provide the secondary amide **30** (60 mg, 50%). ^{1}H NMR ($CDCl_3$): δ = 0.64 (d, *J* = 6.9 Hz, 3 H, CHC*H*$_3$), 0.80 (t, *J* = 7.3 Hz, 3 H, CH_2C*H*$_3$), 1.19 (d, *J* = 7.3 Hz, 3 H, CHC*H*$_3$), 1.20−2.30 (m, 19 H), 2.55 (q, 2 H, 5-H), 2.86 (d, *J* = 3.2 Hz, 1 H, 3-H^a), 2.90−2.95 (m, 2 H, 6-H and 3-H^b), 5.13 (t, *J* = 7.0 Hz, 1 H, CH=C), 5.67 (br. s, 1 H, NH), 6.33 (t, *J* = 4.3 Hz, 1 H, 2-H). *m*/*z* (CI): 334 (100%) [M + H$^+$].

X-ray Crystal Structure of 8: The crystallographic data for compound **8** in this paper has been deposited with the Cambridge Crys-

tallographic Data Centre, reference CCDC-192191. These data can be obtained free of charge from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.

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