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PAPER

Synthesis of quaternary stereogenic centres *via* stereoselective intermolecular Friedel–Crafts reactions†

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Highly stereoselective Friedel–Crafts reactions have been performed using a chiral anthracene template to control the selectivity of the reaction. In the case of additions to fully substituted *N*-acyliminium ions, competitive elimination and condensation reactions were observed. Retro-Diels–Alder reaction of one of the reaction products led to a precursor that could be used for the construction of pyroglutamic acids bearing quaternary stereogenic centres.

Introduction

In recent years, chiral anthracenes have been shown to undergo highly diastereoselective Diels–Alder cycloadditions with a range of dienophiles such as *N*-methylmaleimide and maleic anhydride,[1] and more recently *p*-benzoquinone.[2] These cycloadducts are then able to undergo further transformations utilising the anthracene template to control the stereoselectivity, followed by a retro-Diels–Alder reaction to liberate a product with high enantiopurity. In 2005, Snyder *et al.* demonstrated the addition of allyltrimethylsilane to fully substituted *N*-acyliminium ions derived from maleimide cycloadducts to form quaternary stereocentres used for the synthesis of bicyclic alkaloidal systems.[1f] However, attempts to add other carbon nucleophiles, such as Grignard reagents, to these species led to deprotonation and formation of *N*-acyl enamines. It was therefore surmised that a non-basic C–C bond process, such as a Friedel–Crafts reaction, may give superior results. Intra-molecular variants of this process have been previously reported,[3] and recent work from our own laboratory has used this strategy with chiral anthracene templates.[1a] Several reports have detailed the stereoselective inter-molecular Friedel–Crafts reaction of un-substituted *N*-acyl iminium ions leading to products with tertiary stereogenic centres using chiral pool[4] or catalytic methods.[5] However, there are fewer reports of performing an inter-molecular reaction that would lead to products bearing quaternary stereogenic centres.[6] Having recently established a strategy to construct pyroglutamic acids using an inter-molecular Friedel–Crafts reaction of un-substituted *N*-acyliminium ions with furan,[7] we now report our findings of the generality of this process and application to the synthesis of quaternary stereogenic centres.

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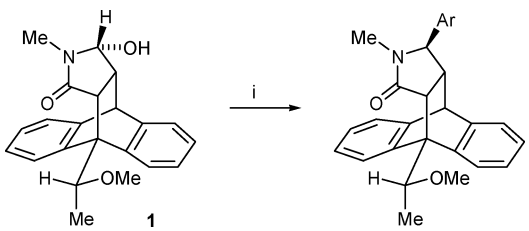
Results & Discussion

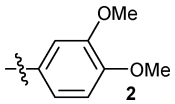
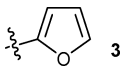
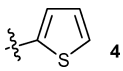
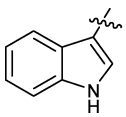
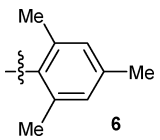
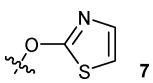
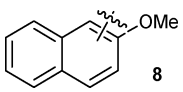
Hydroxy-lactam **1** was prepared in 2 steps from (*R*)-9-(methoxyethyl)anthracene as previously reported.[1a] Treatment of this with TFA and an aromatic nucleophile led to formation of a single diastereoisomer in nearly every case studied (Scheme 1, Table 1). The identity of these isomers was confirmed by the small coupling constant of the proton of the tertiary stereocentre (around $J \approx 3$), that correlates with the modelled dihedral angle and coupling constant for this isomer (135° and 6.0 Hz, respectively).[8] The modelled dihedral angle of the other isomer (27°) would have resulted in a larger coupling constant ($J \approx 9.6$ Hz). This data is therefore in-line with previous studies and confirms that the nucleophile attacks the Si face of the *N*-acyliminium ion (Fig. 1).



Scheme 1 *Reagents and conditions*: i. TFA, ArCH, CH_2Cl_2.

1,3,5-Trimethylbenzene did not react under these conditions, but $TiCl_4$ provided the desired product in moderate yield (Table 1, entry 5). Addition of 2-ethoxythiazole gave the somewhat unexpected result of an *O*-aryl product (Table 1, entry 6). Under the acidic conditions of the reaction, the 2-ethoxy thiazole is most likely protonated ($pK_{aH} \sim 2.5$), rendering this extremely electron deficient. Under equilibrating conditions, the more thermodynamically stable (*S*)-configured hydroxy-lactam is formed which then undergoes nucleophilic attack at the 2-position of a thiazolium intermediate (Scheme 2). Attempts to extend this chemistry to other related heterocyclic aromatics such as 2-methoxy-pyridines or their *N*-oxides were unsuccessful both under Brønsted acid

Table 1 Friedel–Crafts reactions of hydroxy-lactam **1**

Entry	Ar	Yield (%)
1	 **2**	48
2	 **3**	100
3	 **4**	98
4	 **5**	97
5	 **6**	54[a]
6	 **7**	68
7	 **8**	59[b]

[a] Reaction conditions: $TiCl_4$ (2 eq), CH_2Cl_2, −78 °C. [b] Reaction yielded an inseparable mixture of isomers.

conditions (TFA) and Lewis acid conditions ($TiCl_4$). In these cases, it is likely that they are too electron deficient to undergo the Friedel–Crafts reaction, yet not sufficiently electrophilic to perform nucleophilic aromatic substitution as in the case of the thiazole. Addition of 2-methoxynaphthalene gave an inseparable mixture of isomers (about 2 : 1 ratio) in good yield (Table 1, entry 7).[9]

This approach was extended to the Grignard addition adducts **9** and **10** where successful introduction of another carbon-carbon bond would allow generation of a quaternary stereogenic centre (Scheme 3).[10] Hydroxy-lactam **9** was prepared as previously reported,[1a] the *N*-allyl analogue **10** also being prepared by application of the same procedure.

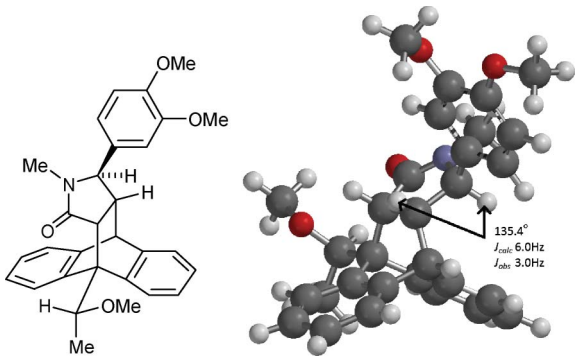
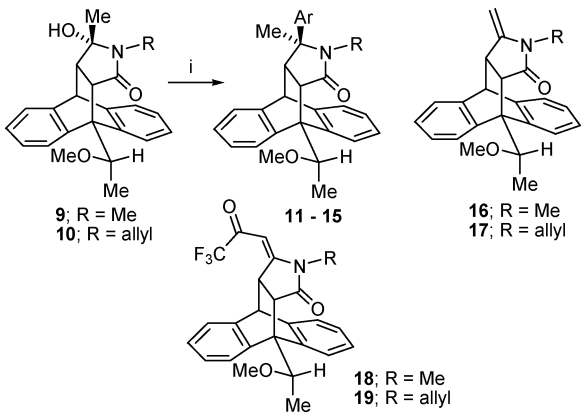


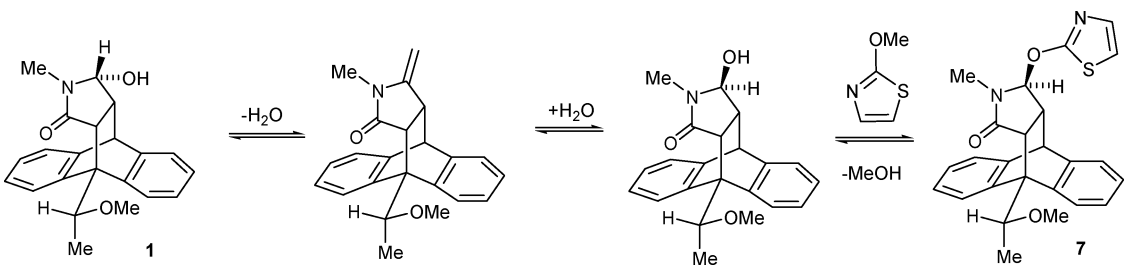
Fig. 1 Modelled dihedral angles and observed *J* values for product **2**.



Scheme 3 *Reagents and conditions.* i. TFA, ArH, CH_2Cl_2, reflux 24 h.

Application of the Friedel–Crafts methodology described above, gave good yields and selectivities for furan and indole (Table 2, entries 1–3), but in the case of other aromatic species, side-products were observed. Attempted addition of 1,2-dimethoxybenzene to hydroxy-lactam **9** or **10** using TFA or $TiCl_4$ resulted in elimination product **16** and **17** being formed, respectively. Re-subjecting this isolated product to the reaction conditions did not lead to the desired product. Reaction of hydroxy-lactams **9** and **10** with thiophene gave a 1 : 1 mixture of desired products **14** and **15** and the unexpected (*E*)-trifluoroacetyl products **18** and **19**.[11]

Presumably, the extended reaction times for this process must generate small quantities of trifluoroacetic anhydride that can then undergo condensation with the *N*-acyl-enamine. Similar products have also been observed by Rashatasakhon and Padwa in transformations of related hydroxy-lactams, although in their study, the authors note that direct use of trifluoroacetic anhydride



Scheme 2 Proposed mechanism of formation of hydroxy-lactam **7**.

Table 2 Friedel–Crafts reactions of hydroxy-lactams **9** and **10**

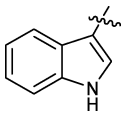
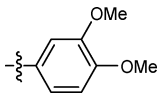
			Component, yield (%)		
Entry	R	Ar	**11–15**	**16/17**	**18/19**
1	Me		**11**, 100	0	0
2	Allyl		**12**, 99	0	0
3	Allyl		**13**, 98	0	0
4	Me		0	**16**, 80	0
5	Allyl		0	**17**, 44	0
6	Me		**14**, 50	0	**18**, 50
7	Allyl		**15**, 52	0	**19**, 48

Table 3 Formation of products as a function of time from reaction of hydroxy-lactam **9** with thiophene

		Product distribution (%)[a]		
Entry	Time (h)	**14**	**16**	**18**
1	1	11	89	0
2	4	10	85	5
3	9	11	78	11
4	12	23	54	23
5	27	52	0	48

[a] Ratio's obtained by integration of the appropriate signals in the ^{1}H-NMR spectrum of the crude reaction mixture.

to effect this transformation leads to a different by-product.[12] To further investigate the formation of product **18**, a study was conducted to monitor the progress of the reaction of hydroxy-lactam **9** with thiophene with time (Table 3 and Fig. 2).

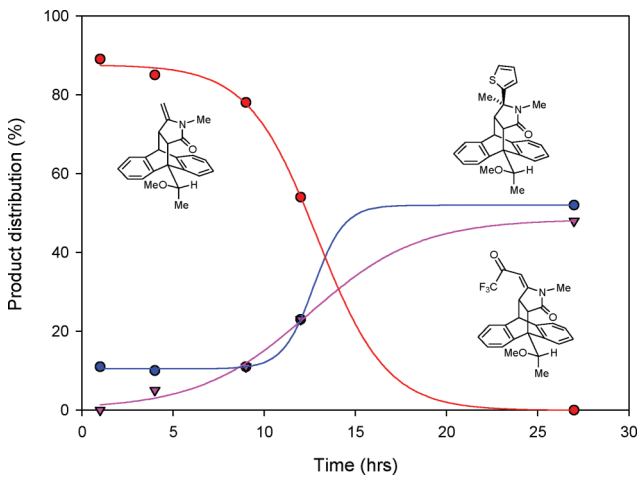
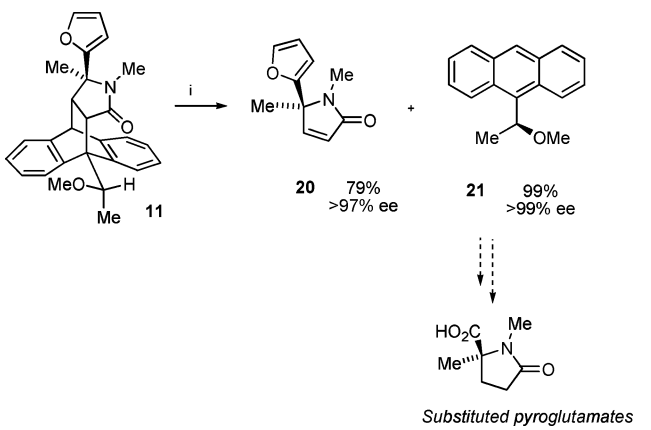


Fig. 2 Graphical representation of data in Table 3.

From this data, it appears that the formation of the *N*-acyl enamine **16** is incredibly fast during this reaction as after one hour, essentially all starting material has been consumed. Formation of the desired Friedel–Crafts product **14** then slowly increases with time, but at a very similar rate to the formation of the trifluoroacetyl adduct **18**. This implies that there is a limit to the quantity of desired product that may be prepared under these reaction conditions with less reactive aromatics, since the competing formation of the trifluoroacetyl compound removes starting material at approximately the same rate as that which provides the product.

In order to complete the cycle and free the chiral anthracene template from the transformed product, a retro-Diels–Alder was performed using flash vacuum pyrolysis (FVP). Recent work within our group has found that if a substrate with a tertiary stereocentre has an acidic proton in this position, racemisation may occur in the product during the FVP process.[1a,7] In order to thus exemplify the process with a substrate bearing a quaternary stereogenic centre, the retro-Diels–Alder reaction of cycloadduct **11** was carried out, providing substituted maleimide **20** in high yield and ee, the latter confirmed by HPLC (Scheme 4). Auxiliary **21** was also regenerated in high yield with no loss in enantiopurity; $[\alpha]_D^{22}$ –45 (*c* 1 in $CHCl_3$ ee >99%) before Diels–Alder cycloaddition and $[\alpha]_D^{22}$ –45 (*c* 1 in $CHCl_3$) after FVP. This methodology is particularly applicable for the preparation of enantiomerically enriched substituted pyroglutamic acid analogues by application of our previously reported methodology for the synthesis of pyroglutamates by transforming the furan into a carboxylic acid group.[7] This still retains the alkene may that can be further functionalised to prepare more complex derivatives.



Scheme 4 *Reagents and conditions.* i. FVP (180 °C inlet, 510 °C furnace, 0.02 mmHg).

Conclusions

We have reported a method to combine intermolecular Friedel–Crafts reactions to *N*-acyliminium ions derived from maleimide cycloadducts and a Diels–Alder/retro-Diels–Alder methodology to prepare quaternary stereocentres in high yield and enantiopurity. Further work into demonstrating the applicability to preparing pyroglutamic acid analogues containing quaternary stereocentres is now being undertaken.

Experimental

All solvents were obtained dry from a Grubbs dry solvent system. When required, glassware was flame-dried and cooled under vacuum. All other reagents were used as supplied without any purification unless stated. Column chromatography was carried out on Silica Gel 40–63u 60A (Fluorochem Ltd.) and thin layer chromatography on Merck aluminium sheets coated with silica gel 60 F_{254}. ^{1}H NMR and ^{13}C NMR spectra were measured using $CDCl_3$ as a solvent unless otherwise stated, on a Bruker AC250 machine and an AC400 with automated sample changers. Chemical shifts for carbon and hydrogen are given on the δ scale relative to TMS (tetramethylsilane, δ = 0 ppm). *J* values are given in Hz. ^{13}C NMR spectra were recorded using the JMOD method. Optical rotations were performed on an Optical Activity Ltd. AA-10 automatic polarimeter at 589 nm (Na D-Line) and measured at 20 °C unless otherwise stated. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded on a Perkin–Elmer 1600 FT-IR machine using KBr discs. Low resolution mass spectra (*m*/*z*) were recorded on Kratos MS 25 or MS 80 spectrometer supported by DS 55 system, operating in EI, CI or FAB mode. High resolution mass spectra (HRMS) recorded for accurate mass analysis, were performed on either MicroMass LCT operating in Electrospray mode (TOF ES); or a MicroMass Prospec operating in either FAB, EI or CI mode. HPLC was carried out using a Spectra Physics Analytical system (consisting of a P4000 pump, a UV2000 detector and using PC 1000 version 2.0 software). Compounds **1** and **9** were prepared by established literature methods.[1a]

General procedure A for the synthesis of substituted malemide cycloadducts *via N*-acyliminium ions

Trifluoroacetic acid (0.11 mL, 1.43 mmol) was added to a stirred solution of hydroxy-lactam **1** (100 mg, 0.29 mmol) and aromatic compound (0.57 mmol) in dichloromethane (2 mL) and heated to reflux for 4 h. The reaction was followed by LCMS, cooled and quenched with a saturated aqueous solution of Na_2CO_3 (5 mL), extracted with CH_2Cl_2 (3 × 5 mL), washed with brine (3 × 5 mL) and dried (Na_2SO_4). The solvent was removed to give the crude material. Purification was carried out as detailed in individual experiments.

(3a*R*,9a*R*,3*R*)-2,3,3a,4,9,9a-Hexahydro-4-[(1*R*)-1-methoxyethyl]-3-(3,4-dimethoxyphenyl)-2-methyl-4,9-[1′,2′]benzeno-1*H*-benz[*f*]isoindol-1-one 2. The title compound was prepared according to general procedure A and purified by recrystallisation from CH_2Cl_2/petroleum ether (40–60) to give a white solid (65 mg, 48%); $[\alpha]_D^{22}$ −67.6 (*c* 1 in $CHCl_3$); mp 135 °C [from CH_2Cl_2/petroleum ether (40–60)]; ν_{max}(ATR)/cm^{-1} 3058, 2937, 2835, 1674, 1594 and 1516; δ_H (400 MHz; $CDCl_3$) 1.87 (3 H, d, *J* 6.4, C*H*$_3$CH), 2.12 (3 H, s, NC*H*$_3$), 2.57 (1 H, dt, *J* 9.9 and 3.0, COCHC*H*), 3.61 (1 H, d, *J* 9.9, COC*H*CH), 3.65 (1 H, d, *J* 3.0, NC*H*), 3.76 (3 H, s, OC*H*$_3$), 3.82 (3 H, s, OC*H*$_3$), 3.86 (3 H, s, OC*H*$_3$), 4.25 (1 H, d, *J* 3.0, 10-H), 5.50 (1 H, q, *J* 6.4, CH$_3$C*H*), 6.52 (1 H, d, *J* 2.0, ArC*H*), 6.69–6.75 (1 H, m, ArC*H*), 6.77–6.83 (1 H, m, ArC*H*), 7.05–7.17 (2 H, m, ArC*H*), 7.18–7.33 (4 H, m, ArC*H*), 7.42–7.44 (1 H, m, ArC*H*) and 7.87 (1 H, d, *J* 7.2, ArC*H*); δ_C (100 MHz; $CDCl_3$) 17.0 (*C*H$_3$CH), 27.5 (NC*H*$_3$), 48.3 (*C*H), 48.5 (*C*H), 49.2 (*C*H), 54.7 (9-C), 56.0 (2 × OC*H*$_3$), 57.2 (OC*H*$_3$), 67.0 (*C*H), 73.5 (*C*HOCH$_3$), 108.6 (ArCH), 111.0 (ArCH), 119.3 (ArCH), 123.4 (ArCH), 124.1 (ArCH), 125.1 (ArCH), 125.5 (ArCH), 125.8 (ArCH), 125.9 (ArCH), 126.3 (ArCH), 126.7 (ArCH), 134.2 (Ar*C*), 139.5 (Ar*C*), 139.9 (Ar*C*), 140.3 (Ar*C*), 143.7 (Ar*C*), 149.0 (Ar*C*), 149.8 (Ar*C*) and 172.6 (*C*O); *m*/*z* (EI) 469.2273 (M$^+$. $C_{30}H_{31}NO_4$ requires 469.2253), 454 (20%), 234 (100), 221 (40), 205 (25) and 178 (23).

(3a*R*,9a*R*,3*R*)-2,3,3a,4,9,9a-Hexahydro-4-[(1*R*)-1-methoxyethyl]-3-(2-furanyl)-2-methyl-4,9-[1′,2′]benzeno-1*H*-benz[*f*]isoindol-1-one 3. The title compound was prepared according to general procedure A and purified by recrystallisation from CH_2Cl_2/petroleum ether (40–60) to give a brown solid (114 mg, 100%); $[\alpha]_D^{22}$ −57.5 (*c* 1 in $CHCl_3$); mp 152–154 °C; ν_{max}(ATR)/cm^{-1} 2936, 2821 and 1681; δ_H (400 MHz; $CDCl_3$) 1.86 (3 H, d, *J* 6.4, C*H*$_3$CH), 2.57 (3 H, s, NC*H*$_3$), 2.75 (1H, dt, *J* 9.9 and 3.0, COCHC*H*), 3.58 (1 H, d, *J* 9.9, COC*H*CH), 3.74 (3 H, s, OC*H*$_3$), 3.84 (1 H, d, *J* 3.0, C*H*), 4.24 (1 H, d, *J* 3.0, C*H*), 5.45 (1 H, q, *J* 6.4, CH$_3$C*H*), 6.18 (1 H, d, *J* 3.1, ArC*H*), 6.29 (1 H, dd, *J* 3.1 and 1.9, ArC*H*), 7.04–7.41 (8 H, m, ArC*H*) and 7.87–7.92 (1H, m, ArC*H*); δ_C (100 MHz; $CDCl_3$) 17.0 (*C*H$_3$CH), 27.4 (NC*H*$_3$), 45.0 (*C*H), 48.0 (*C*H), 49.1 (*C*H), 54.7 (9-C), 57.3 (OC*H*$_3$), 59.8 (*C*H), 73.4 (*C*HOCH$_3$), 107.6 (ArCH), 110.2 (ArCH), 123.4 (ArCH), 124.1 (ArCH), 124.9 (ArCH), 125.6 (ArCH), 125.8 (ArCH), 125.9 (ArCH), 126.4 (ArCH), 126.8 (ArCH), 139.2 (Ar*C*), 139.9 (Ar*C*), 140.3 (Ar*C*), 142.8 (ArCH), 143.6 (Ar*C*), 153.3 (Ar*C*) and 172.4 (*C*O); *m*/*z* (EI) 399.1846 (M$^+$. $C_{26}H_{25}NO_3$ requires 399.1834), 384 (27%), 236 (84), 221 (52), 205 (26), 178 (31), 164 (100) and 152 (7).

(3a*R*,9a*R*,3*R*)-2,3,3a,4,9,9a-Hexahydro-4-[(1*R*)-1-methoxyethyl]-3-(2-thienyl)-2-methyl-4,9-[1′,2′]benzeno-1*H*-benz[*f*]isoindol-1-one 4. The title compound was prepared according to general procedure A. A viscous, colourless oil was obtained which solidified upon standing to give a white solid (117 mg, 98%); $[\alpha]_D^{22}$ −61.9 (*c* 1 in $CHCl_3$); mp 216–217 °C; ν_{max}(ATR)/cm^{-1} 3044, 2979, 2939, 2820, 1681 and 1468; δ_H (400 MHz; $CDCl_3$) 1.86 (3 H, d, *J* 6.4, C*H*$_3$CH), 2.17 (3 H, s, NC*H*$_3$), 2.70 (1 H, dt, *J* 9.9 and 3.0, COCHC*H*), 3.60 (1 H, d, *J* 9.9, COC*H*CH), 3.75 (3 H, s, OC*H*$_3$), 4.03 (1 H, d, *J* 3.0, C*H*), 4.27 (1 H, d, *J* 3.0, C*H*), 5.47 (1 H, q, *J* 6.4, CH$_3$C*H*), 6.89–6.96 (2 H, m, ArC*H*), 7.04–7.31 (7H, m, ArC*H*), 7.39–7.41 (1 H, m, ArC*H*) and 7.88 (1 H, d, *J* 7.5, ArC*H*); δ_C (100 MHz; $CDCl_3$) 17.0 (*C*H$_3$CH), 27.5 (NC*H*$_3$), 47.8 (*C*H), 49.0 (2 × *C*H), 54.7 (9-C), 57.3 (OC*H*$_3$), 62.2 (*C*H), 73.4 (*C*HOCH$_3$), 123.5 (ArCH), 124.1 (ArCH), 125.0 (ArCH), 125.3 (ArCH), 125.6 (ArCH), 125.7 (ArCH), 125.9 (ArCH), 126.0 (ArCH), 126.4 (ArCH), 126.8 (2 × ArCH), 139.2 (Ar*C*), 139.9 (Ar*C*), 140.2 (Ar*C*), 143.5 (Ar*C*), 145.9 (Ar*C*) and 172.1 (*C*O); *m*/*z* (EI) 415.1592 (M$^+$. $C_{26}H_{25}NO_2{}^{32}S$ requires 415.1606), 400 (17%), 236 (96), 221 (77), 205 (37), 180 (100), 178 (49) and 84 (16).

(3a*R*,9a*R*,3*R*)-2,3,3a,4,9,9a-Hexahydro-4-[(1*R*)-1-methoxyethyl]-3-(3-indolyl)-2-methyl-4,9-[1′,2′]benzeno-1*H*-benz[*f*]isoindol-1-one 5. The title compound was prepared according to general procedure A as a yellow solid (132 mg, 100%); $[\alpha]_D^{22}$ −56.6 (*c* 1 in $CHCl_3$); mp >230 °C (decomp.); ν_{max}(ATR)/cm^{-1} 3450, 3059, 2929, 1660 and 1551; δ_H (400 MHz; $CDCl_3$) 1.88 (3 H, d, *J* 6.4, C*H*$_3$CH), 2.16 (3 H, s, NC*H*$_3$), 2.83 (1 H, dt, *J* 10.1 and 3.0, COCHC*H*), 3.70 (1 H, d, *J* 10.1, COC*H*CH), 3.80 (3 H, s, OC*H*$_3$), 4.02 (1 H, d, *J* 3.0, C*H*), 4.26 (1 H, d, *J* 3.0, C*H*), 5.53 (1 H, q, *J* 6.4, CH$_3$C*H*), 7.02–7.15 (3 H, m, ArC*H*), 7.16–7.29 (5 H, m, ArC*H*), 7.28–7.48 (4 H, m, ArC*H*), 7.89 (1 H, d, *J* 7.5, ArC*H*)

and 8.12 (1 H, br s, N*H*); δ_C (100 MHz; $CDCl_3$) 17.0 (*C*H_3CH), 27.4 (N*C*H_3), 47.2 (*C*H), 48.9 (*C*H), 49.2 (*C*H), 54.8 (9-C), 57.3 (O*C*H_3), 59.7 (*C*H), 73.6 (*C*HOCH_3), 111.4 (Ar*C*H), 116.2 (Ar*C*), 119.0 (Ar*C*H), 120.2 (Ar*C*H), 122.6 (Ar*C*H), 122.8 (Ar*C*H), 123.5 (Ar*C*H), 124.1 (Ar*C*H), 124.9 (Ar*C*), 125.2 (Ar*C*H), 125.5 (Ar*C*H), 125.8 (Ar*C*H), 125.9 (Ar*C*H), 126.3 (Ar*C*H), 126.6 (Ar*C*H), 136.9 (Ar*C*), 139.9 (Ar*C*), 140.2 (Ar*C*), 140.4 (Ar*C*), 143.8 (Ar*C*) and 172.2 (*C*O); *m/z* (EI) 448.2165 (M^+. $C_{30}H_{28}N_2O_2$ requires 448.2151), 433 (23%), 236 (65), 221 (52), 213 (100), 205 (23), 178 (18) and 83 (23).

(3a*R*,9a*R*,3*R*)-2,3,3a,4,9,9a-Hexahydro-4-[(1*R*)-1-methoxyethyl]-3-(2,4,6-trimethylphenyl)-2-methyl-4,9-[1′,2′]benzeno-1*H*-benz[*f*]isoindol-1-one 6. The title compound was prepared according to general procedure A as a white solid after purification by column chromatography on silica gel eluting with 10% ethyl acetate/90% hexane to 40% ethyl acetate/60% hexane (70 mg, 54%); $[\alpha]_D^{22}$ −63.2 (*c* 1 in $CHCl_3$); mp 251–253 °C; ν_{max}(ATR)/cm^{-1} 3060, 2937, 2834, 1681, 1594 and 1516; δ_H (400 MHz; $CDCl_3$) 1.86 (3 H, d, *J* 6.4, C*H*$_3$CH), 2.02 (3 H, s, C*H*$_3$), 2.08 (3 H, s, C*H*$_3$), 2.25 (3 H, s, C*H*$_3$), 2.48 (3 H, s, NC*H*$_3$), 2.70 (1 H, ddd, *J* 10.3, 3.1 and 4.4, COCHC*H*), 3.52 (1 H, d, *J* 10.3, COC*H*CH), 3.76 (3 H, s, OC*H*$_3$), 4.22 (1 H, d, *J* 3.1, C*H*), 4.31 (1 H, d, *J* 4.4, C*H*), 5.47 (1 H, q, *J* 6.4, CH$_3$C*H*), 6.80 (1H, s, ArC*H*), 6.90 (1H, s, ArC*H*), 7.04–7.24 (5 H, m, ArC*H*), 7.28–7.33 (1 H, m, ArC*H*), 7.40–7.46 (1 H, m, ArC*H*) and 7.88 (1 H, d, *J* 7.2, ArC*H*); δ_C (100 MHz; $CDCl_3$) 17.0 (*C*H$_3$CH), 19.7 (*C*H$_3$), 20.8 (*C*H$_3$), 21.5 (*C*H$_3$), 27.1 (N*C*H$_3$), 46.3 (*C*H), 49.0 (*C*H), 50.1 (*C*H), 54.5 (9-C), 57.2 (O*C*H$_3$), 61.0 (*C*H), 73.4 (*C*HOCH$_3$), 123.7 (Ar*C*H), 124.2 (Ar*C*H), 125.1 (Ar*C*H), 125.5 (Ar*C*H), 125.9 (2 × Ar*C*H), 126.4 (Ar*C*H), 126.5 (Ar*C*H), 129.6 (Ar*C*H), 131.7 (Ar*C*H), 132.8 (Ar*C*), 136.8 (2 × Ar*C*), 137.5 (Ar*C*), 140.2 (Ar*C*), 140.3 (Ar*C*), 140.4 (Ar*C*), 143.5 (Ar*C*) and 172.4 (*C*O); *m/z* (EI) 451.2499 (M^+. $C_{31}H_{33}NO_2$ requires 451.2511), 436 (33%), 236 (55), 221 (47), 216 (100), 205 (23), 178 (20) and 96 (8).

(3a*R*,9a*R*,3*R*)-2,3,3a,4,9,9a-Hexahydro-4-[(1*R*)-1-methoxyethyl]-3-(2-thiazolyloxy)-2-methyl-4,9-[1′,2′]benzeno-1*H*-benz[*f*]isoindol-1-one 7. The title compound was prepared according to general procedure A as a colourless oil after purification by column chromatography on silica gel eluting with 50% ethyl acetate, 50% petroleum ether (82 mg, 68%); $[\alpha]_D^{22}$ −59.0 (*c* 1 in $CHCl_3$); ν_{max}(ATR)/cm^{-1} 3026, 2934, 1678 and 1515; δ_H (400 MHz; $CDCl_3$) 1.87 (3 H, d, *J* 6.4, C*H*$_3$CH), 2.22 (3 H, s, NC*H*$_3$), 2.58 (1 H, dt, *J* 9.4 and 2.2, COCHC*H*), 3.61 (1 H, d, *J* 9.4, COC*H*CH), 3.74 (3 H, s, OC*H*$_3$), 4.47 (1 H, d, *J* 2.2, H-10), 5.22 (1 H, d, *J* 2.2, NC*H*), 5.38 (1 H, q, *J* 6.4, CH$_3$C*H*), 6.15 (1 H, d, *J* 5.4, ArC*H*), 6.26 (1 H, d, *J* 5.4, ArC*H*), 7.14–7.24 (5 H, m, ArC*H*), 7.32–7.36 (1 H, m, ArC*H*), 7.48–7.51 (1 H, m, ArC*H*) and 7.88–7.90 (1 H, m, ArC*H*); δ_C (100 MHz; $CDCl_3$) 16.8 (*C*H$_3$), 26.8 (*C*H$_3$), 46.8 (*C*H), 47.6 (*C*H), 48.1 (*C*H), 54.7 (9-C), 57.2 (O*C*H$_3$), 71.4 (N*C*H), 73.2 (*C*HOCH$_3$), 103.4 (NC*H*O), 119.7 (Ar*C*H), 123.7 (Ar*C*H), 124.0 (Ar*C*H), 125.2 (Ar*C*H), 125.8 (Ar*C*H), 126.2 (Ar*C*H), 126.5 (Ar*C*H), 126.7 (Ar*C*H), 126.8 (Ar*C*H), 138.5 (Ar*C*), 139.4 (Ar*C*), 139.6 (Ar*C*), 143.0 (Ar*C*), 171.8 (S*C*═N) and 172.7 (*C*O); *m/z* (TOF EI$^+$) 471 (M^++K, 5%), 433.1565 (MH^+. $C_{25}H_{25}N_2O_3{}^{32}S$ requires 433.1586), 332 (12).

(3a*R*,9a*R*,3*R*)-2,3,3a,4,9,9a-Hexahydro-4-[(1*R*)-1-methoxyethyl]-3-(2-methoxy-1-naphthalenyl)-2-methyl-4,9-[1′,2′]benzeno-1*H*-benz[*f*]isoindol-1-one and (3a*R*,9a*R*,3*R*)-2,3,3a,4,9,9a-hexahydro-4-[(1*R*)-1-methoxyethyl]-3-(2-methoxy-3-naphthalenyl)-2-methyl-4,9-[1′,2′]benzeno-1*H*-benz[*f*]isoindol-1-one 8. The title compound was prepared according to general procedure A. Attempted purification by flash column chromatography (30% ethyl acetate, 70% hexane followed by 50% ethyl acetate, 50% hexane) gave an inseparable mixture of isomers as a pale yellow oil in a 2 : 1 ratio (41 mg, 59%); ν_{max}(ATR)/cm^{-1} 3027, 2932, 1678, 1592 and 1515; δ_H (400 MHz; $CDCl_3$) *Major isomer*: 2.04 (3 H, s, NC*H*$_3$), 2.93 (1 H, dt, *J* 10.0 and 3.0, COCHC*H*), 3.62 (1 H, d, *J* 10.0, COC*H*CH), 3.82 (3 H, s, OC*H*$_3$), 3.85 (3 H, s, OC*H*$_3$), 4.26 (1 H, d, *J* 3.0, 10-H) and 4.86 (1 H, d, *J* 3.0, NC*H*); *Minor isomer*: 2.12 (3 H, s, NC*H*$_3$), 2.93 (1 H, ddd, *J* 10.5, 4.9 and 3.0, COCHC*H*), 3.78–3.82 (1 H, m, COC*H*), 3.84 (3 H, s, OC*H*$_3$), 4.12 (3 H, s, OC*H*$_3$), 4.30 (1 H, d, *J* 3.0, 10-H) and 5.06 (1 H, d, *J* 4.9, NC*H*); *Both isomers*: 1.92 (3 H, d, *J* 6.4, C*H*$_3$CH), 5.52–5.60 (1 H, m, CH$_3$C*H*), 7.04–8.17 (14 H, m, ArC*H*); δ_C (100 MHz; $CDCl_3$) *Major isomer*: 17.2 (*C*H$_3$CH), 27.0 (N*C*H$_3$), 46.7 (*C*H), 49.5 (*C*H), 50.3 (*C*H), 54.7 (*C*-9), 56.3 (O*C*H$_3$), 57.1 (O*C*H$_3$), 58.4 (N*C*H), 73.7 (*C*HOCH$_3$), 113.1 (Ar*C*H), 119.9 (Ar*C*), 144.0 (Ar*C*), 156.0 (Ar*C*) and 173.3 (*C*O); *Minor isomer*: 17.0 (*C*H$_3$CH), 27.4 (N*C*H$_3$), 46.4 (*C*H), 48.5 (*C*H), 49.7 (*C*H), 54.6 (*C*-9), 57.1 (O*C*H$_3$), 57.2 (O*C*H$_3$), 57.4 (N*C*H), 73.6 (*C*HOCH$_3$), 113.2 (Ar*C*H), 119.5 (Ar*C*), 143.7 (Ar*C*), 156.1 (Ar*C*) and 172.6 (*C*O); *Both isomers*: 120.78 (Ar*C*H), 122.4 (Ar*C*H), 123.4 (Ar*C*H), 123.5 (Ar*C*H), 123.7 (Ar*C*H), 123.9 (Ar*C*H), 124.1 (Ar*C*H), 124.2 (Ar*C*H), 125.0 (Ar*C*H), 125.4 (Ar*C*H), 125.7 (Ar*C*H), 125.9 (Ar*C*H), 126.3 (Ar*C*H), 126.5 (Ar*C*H), 127.4 (Ar*C*H), 128.8 (Ar*C*), 129.0 (Ar*C*H), 129.2 (Ar*C*H), 129.7 (Ar*C*), 130.3 (Ar*C*H), 130.6 (Ar*C*H), 131.8 (Ar*C*), 133.5 (Ar*C*), 140.3 (Ar*C*), 140.5 (Ar*C*), 140.6 (Ar*C*) and 140.8 (Ar*C*); *m/z* (TOF ES$^+$) 490.2369 (MH^+. $C_{33}H_{32}NO_3$ requires 490.2382).

Preparation of (3*R*,3a*R*,9a*R*)-2,3,3a,4,9,9a-Hexahydro-3-hydroxy-9-[(1*R*)-1-methoxyethyl]-2-(2-propen-1-yl)-3-methyl-4,9[1′,2′]-benzeno-1*H*-benz[*f*]isoindol-1-one 10. Prepared by application of known literature procedures in three steps as outlined below.

***N*-Allyl maleimide.** Allylamine (1.30 mL, 17.5 mmol) and maleic anhydride (3.43 g, 35.0 mmol) were heated to reflux in toluene (15 mL) for 2 h. Acetic acid (30 mL, 525 mmol) was then added and the reaction heated to reflux for 5 h. The resulting mixture was cooled to RT and the solvent removed. Water (50 ml) was added and the mixture extracted with CH_2Cl_2 (3 × 50 mL), dried ($MgSO_4$) and solvent was removed to give a yellow oil. This was purified by flash column chromatography on silica gel eluting with (20% ethyl acetate, 80% hexane) to give a white solid (735 mg, 31%) as the title compound; mp 42–44 °C (Lit.[13] 42–44 °C); ν_{max}(ATR)/cm^{-1} 3459, 3162, 3087, 2925, 1771, 1707 and 1651; δ_H (400 MHz; $CDCl_3$) 4.13 (2 H, dt, *J* 5.6, 1.4, NC*H*$_2$), 5.12–5.24 (2 H, m, C═C*H*$_2$), 5.73–5.88 (1H, m, C*H*═CH$_2$) and 6.72 [2 H, s, C(O)C*H*].

(3a*R*,9a*R*)-3a,4,9,9a-Tetrahydro-4-[(1*R*)-1-methoxyethyl]-2-(2-propen-1-yl)-4,9-[1′,2′]benzeno-1*H*-benz[*f*]isoindole-1,3-(2*H*)-dione. 9-(1*R*)-Methoxyethyl anthracene[1] (300 mg, 1.27 mmol) and *N*-allylmaleimide (174 mg, 1.27 mmol) were dissolved in CH_2Cl_2 (15 mL) and heated to reflux for 9 h. The reaction mixture was allowed to cool to RT and the solvent was removed to give a pale yellow solid. This was recrystallised from CH_2Cl_2/petroleum

ether (40–60) to give a white solid as the title compound (435 mg, 92%); mp 175–176 °C (from CH_2Cl_2/petroleum ether); $[\alpha]_D^{22}$ −34.0 (*c* 1 in $CHCl_3$); ν_{max} (ATR)/cm^{-1} 2934, 2825, 1770, 1699 and 1645; δ_H (400 MHz; $CDCl_3$) 1.86 (3 H, d, *J* 6.4, CH_3CH), 3.13 (1 H, dd, *J* 8.3 and 3.1, COCHC*H*), 3.62 (1 H, d, *J* 8.3, COC*H*CH), 3.65–3.68 (2 H, m, CH_2), 3.71 (3 H, s, OCH_3), 4.55 (1 H, app. dd, *J* 17.0 and 1.3, 1 × C=CH_2), 4.72 (1 H, d, *J* 3.1, 10-H), 4.81 (1 H, app. dd, *J* 10.2 and 1.3, 1 × CH=CH_2), 4.93 (1 H, ddt, *J* 17.0, 10.2 and 4.4, C*H*=CH$_2$), 5.12 (1 H, q, *J* 6.4, CH_3C*H*), 7.12–7.21 (5 H, m, ArC*H*), 7.28–7.33 (1 H, m, ArC*H*), 7.35–7.40 (1 H, m, ArC*H*) and 7.84–7.90 (1 H, m, ArC*H*); δ_C (100 MHz; $CDCl_3$) 16.9 (*C*H$_3$), 40.5 (*C*H$_2$), 46.4 (*C*H), 46.9 (*C*H), 48.7 (*C*H), 54.7 (9-C), 57.1 (O*C*H$_3$), 73.8 (*C*HOCH$_3$), 117.6 (HC=*C*H$_2$), 123.8 (Ar*C*H), 123.9 (Ar*C*H), 125.3 (Ar*C*H), 125.9 (Ar*C*H), 126.4 (Ar*C*H), 126.7 (Ar*C*H), 126.8 (2 × Ar*C*H), 130.2 (H*C*=CH$_2$), 138.5 (Ar*C*), 139.0 (Ar*C*), 139.4 (Ar*C*), 142.5 (Ar*C*), 175.9 (*C*O) and 176.4 (*C*O); *m*/*z* (EI) 373.1680 (M$^+$. $C_{24}H_{23}NO_3$ requires 373.1678), 358 (18), 235 (100), 221 (85), 205 (50), 178 (42) and 59 (24).

(3a*R*,9a*R*,3*R*)- 3a,4,9,9a-Tetrahydro-4-[(1*R*)-1-methoxyethyl]-2-(2-propen-1-yl)-3-hydroxy-3-methyl-4,9-[1′,2′]benzeno-1*H*-benzo[*f*]isoindole-1-(1*H*)-one 10. MeMgBr (0.9 ml, 2.68 mmol, 3 M in THF) was added to the *N*-allyl cycloadduct (prepared above) (200 mg, 0.54 mmol) in THF (10 mL) at 0 °C. The reaction was stirred at 0 °C for 30 min then allowed to warm to RT and stirred for 18 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was dried (Na_2SO_4) and the solvent was removed to give a white solid as the title compound (198 mg, 95%); mp 130 °C; $[\alpha]_D^{22}$ +39.0 (*c* 1 in $CHCl_3$); ν_{max}(ATR)/cm^{-1} 3373, 2941, 2820, 1665 and 1456; δ_H (400 MHz; $CDCl_3$) 1.36 (3 H, s, CH_3), 1.86 (3 H, d, *J* 6.4, CH_3CH), 2.34 (1 H, d, *J* 1.0, O*H*), 2.61 (1 H, dd, *J* 9.8 and 2.6, COCHC*H*), 3.30 (1 H, dd, *J* 15.7 and 5.9, 1 × CH_2), 3.55 (1 H, d, *J* 9.8, COC*H*CH), 3.72 (3 H, s, OCH_3), 3.75–3.77 (1 H, m, 1 × CH_2), 4.41 (1 H, dd, *J* 17.4 and 1.3, C=CH*H*), 4.64 (1 H, d, *J* 2.6, 10-H), 4.75 (1 H, dd, *J* 10.3 and 1.3, C=C*H*H), 5.09–5.18 (1 H, m, C*H*=CH$_2$), 5.49 (1 H, q, *J* 6.4, CH_3C*H*), 7.15–7.24 (4 H, m, ArC*H*), 7.31–7.40 (3 H, m, ArC*H*) and 7.86–7.89 (1 H, m, ArC*H*); δ_C (100 MHz; $CDCl_3$) 17.1 (*C*H$_3$CH), 28.4 (*C*H$_3$), 41.0 (*C*H$_2$), 45.6 (*C*H), 48.0 (*C*H), 51.1 (*C*H), 55.0 (*C*-9), 57.2 (O*C*H$_3$), 73.8 (*C*HOCH$_3$), 89.0 (*C*OH), 115.7 (CH=*C*H$_2$), 123.2 (Ar*C*H), 124.2 (Ar*C*H), 125.2 (Ar*C*H), 125.6 (Ar*C*H), 126.0 (Ar*C*H), 126.4 (Ar*C*H), 126.8 (Ar*C*H), 126.9 (Ar*C*H), 134.0 (*C*H=CH$_2$), 140.0 (Ar*C*), 140.6 (Ar*C*), 141.5 (Ar*C*), 144.1 (Ar*C*) and 171.0 (*C*O); *m*/*z* (TOF ES$^+$) 390.2063 (MH$^+$, $C_{25}H_{28}NO_3$ requires 390.2069).

General procedure B to synthesise quaternary stereocentres *via* *N*-acyliminium ions

Trifluoroacetic acid (0.32 mL, 4.13 mmol) was added to hydroxy-lactam **9** or **10** (0.83 mmol) and aromatic (0.83 mmol) in dichloromethane (2 mL) and heated to reflux for 24 h. The reaction was quenched with saturated Na_2CO_3 (4 mL), extracted with CH_2Cl_2 (3 × 5 mL), washed with brine (3 × 5 mL) and dried (Na_2SO_4). The solvent was removed to give the target compound which was purified as appropriate.

(3a*S*,9a*S*,3*S*)-3a,4,9,9a-Tetrahydro-4-[(1*S*)-1-methoxyethyl]-2-methyl-3-(2-furanyl)-3-methyl-4,9-[1′,2′]benzeno-1*H*-benzo[*f*]-isoindole-1-(1*H*)-one 11. Using general procedure B with hydroxy-lactam **9** and furan afforded a white solid as the title compound (341 mg, 100%); $[\alpha]_D^{22}$ +19 (*c* 1 in $CHCl_3$); mp 205 °C; ν_{max}(ATR)/cm^{-1} 3050, 2980, 2942, 2819, 1681 and 1502; δ_H (400 MHz; $CDCl_3$) 1.72 (3 H, s, CH_3), 1.89 (3 H, d, *J* 6.4, CH_3CH), 2.23 (3 H, s, NCH_3), 2.58 (1 H, dd, *J* 9.3 and 2.1, COCHC*H*), 3.76 (3 H, s, OCH_3), 3.89 (1 H, d, *J* 9.3, COC*H*CH), 4.47 (1 H, d, *J* 2.1, 10-H), 5.60 (1 H, q, *J* 6.4, CH_3C*H*), 6.06 (1 H, dd, *J* 3.2 and 0.7, ArC*H*), 6.21 (1 H, dd, *J* 3.2 and 1.7, ArC*H*), 7.08–7.25 (5H, m, ArC*H*), 7.25–7.29 (2 H, m, ArC*H*), 7.33–7.39 (1 H, m, ArC*H*) and 7.86–7.88 (1 H, m, ArC*H*); δ_C (100 MHz; $CDCl_3$) 17.2 (*C*H$_3$), 17.3 (*C*H$_3$), 24.8 (*C*H$_3$), 46.5 (*C*H), 47.6 (*C*H), 50.0 (*C*H), 54.9 (9-C), 57.5 (O*C*H$_3$), 61.4 (N*C*CH$_3$), 73.9 (*C*HOCH$_3$), 105.3 (Ar*C*H), 109.8 (Ar*C*H), 122.9 (Ar*C*H), 124.3 (Ar*C*H), 125.4 (Ar*C*H), 125.6 (2 × Ar*C*H), 125.7 (Ar*C*H), 125.8 (Ar*C*H), 126.9 (Ar*C*H), 140.0 (Ar*C*), 140.1 (Ar*C*), 141.3 (Ar*C*), 142.2 (Ar*C*H), 145.2 (Ar*C*), 157.8 (Ar*C*) and 173.8 (*C*O); *m*/*z* (EI) 413.2008 (M$^+$, $C_{27}H_{27}NO_3$ requires 413.1991), 398 (38), 236 (35), 221 (32), 205 (20), 178 (100), 147 (10) and 110 (12).

(3a*R*,9a*R*,3*R*)-3a,4,9,9a-Tetrahydro-4-[(1*R*)-1-methoxyethyl]-2-(2-propen-1-yl)-3-(2-furanyl)-3-methyl-4,9-[1′,2′]benzeno-1*H*-benzo[*f*]isoindole-1-(1*H*)-one 12. Using general procedure B with hydroxy-lactam **10** (150 mg, 0.39 mmol) and furan gave an orange oil which solidified upon standing. This was recrystallised from CH_2Cl_2/petroleum ether (40–60) giving an orange solid (359 mg, 99%) as the title compound; $[\alpha]_D^{22}$ −26 (*c* 1 in $CHCl_3$); mp 170–173 °C; ν_{max}(ATR)/cm^{-1} 3069, 3040, 2970, 2940, 2818, 1679 and 1502; δ_H (400 MHz; $CDCl_3$) 1.71 (3 H, s, CH_3), 1.89 (3 H, d, *J* 6.4, CH_3CH), 2.59 (1 H, dd, *J* 9.5 and 2.1, COCHC*H*), 2.95 (1 H, dd, *J* 16.6 and 5.6, 1 × CH_2), 3.75 (3 H, s, OCH_3), 3.77–3.83 (2 H, m, COC*H*CH and 1 × CH_2), 4.07 (1 H, dd, *J* 17.3 and 1.9, 1 × C=CH_2), 4.48 (1 H, d, *J* 2.1, 10-H), 4.65 (1H, dd, *J* 10.5 and 1.9, 1 × C=CH_2), 5.02 (1 H, dddd, *J* 17.3, 10.5, 5.6 and 4.3, C*H*=CH$_2$), 5.60 (1 H, q, *J* 6.4, CH_3C*H*), 6.05 (1 H, dd, *J* 3.3 and 0.7, ArC*H*), 6.21 (1 H, dd, *J* 3.3 and 1.7, ArC*H*), 7.10–7.32 (7 H, m, ArC*H*), 7.37–7.42 (1 H, m, ArC*H*), and 7.84–7.89 (1 H, m, ArC*H*); δ_C (100 MHz; $CDCl_3$) 17.3 (*C*H$_3$CH), 17.9 (*C*H$_3$), 42.2 (*C*H$_2$), 46.5 (*C*H), 47.4 (*C*H), 50.1 (*C*H), 54.9 (9-C), 57.5 (O*C*H$_3$), 62.2 (N*C*CH$_3$), 73.8 (*C*HOCH$_3$), 105.3 (Ar*C*H), 109.8 (Ar*C*H), 115.0 (C=*C*H$_2$), 122.9 (*C*=CH$_2$), 124.5 (Ar*C*H), 125.5 (Ar*C*H), 125.7 (Ar*C*H), 125.8 (2 × Ar*C*H), 125.9 (Ar*C*H), 126.9 (Ar*C*H), 133.5 (Ar*C*H), 140.1 (2 × Ar*C*), 141.6 (Ar*C*), 142.2 (Ar*C*H), 145.2 (Ar*C*), 158.3 (Ar*C*) and 174.2 (*C*O); *m*/*z* (EI) 439.2160 (M$^+$, $C_{29}H_{29}NO_3$ requires 439.2147), 424 (45), 236 (34), 221 (30), 204 (100), 178 (24), 147 (16), 136 (8), 91 (10) and 59 (8).

(3a*R*,9a*R*,3*R*)-3a,4,9,9a-Tetrahydro-4-[(1*R*)-1-methoxyethyl]-2-(2-propen-1-yl)-3-(indol-3-yl)-3-methyl-4,9-[1′,2′]benzeno-1*H*-benzo[*f*]isoindole-1-(1*H*)-one 13. Using general procedure B with hydroxy-lactam **10** and indole afforded the title compound as a yellow solid (395 mg, 98%); $[\alpha]_D^{22}$ −29 (*c* 1 in $CHCl_3$); mp 230 °C; ν_{max}(ATR)/cm^{-1} 3418, 3286, 3058, 2982, 2944 and 1661; δ_H (400 MHz; $CDCl_3$) 1.88–1.91 (6 H, m, CH_3 and CH_3CH), 2.74 (1 H, dd, *J* 9.3 and 1.9, COCHC*H*), 3.20 (1 H, dd, *J* 16.1 and 6.0, 1 × CH_2), 3.60 (1 H, d, *J* 9.5, COC*H*CH), 3.71 (3 H, s, OCH_3), 4.09–4.15 (1 H, m, 1 × CH_2), 4.18 (1 H, dd, *J* 17.1 and 1.4, 1 × C=CH_2), 4.67 (1 H, d, *J* 1.9, 10-H), 4.70 (1 H, dd, *J* 10.3 and 1.2, 1 × C=CH_2), 4.91–5.01 (1 H, dddd, *J* 17.1, 10.3, 6.0 and 4.3, C*H*=CH$_2$), 5.65 (1 H, q, *J* 6.4, CH_3C*H*), 6.67 (1 H, d, *J* 2.7, ArC*H*), 7.07–7.36 (9 H, m, ArC*H*), 7.45–7.48 (1H, m,

ArC*H*), 7.60 (1 H, d, *J* 7.8, ArC*H*), 7.80–7.82 (1 H, m, ArC*H*) and 8.14 (1 H, s, ArC*H*); δ_C (100 MHz; $CDCl_3$) 17.3 (*C*H_3CH), 21.1 (*C*H_3), 43.2 (*C*H_2), 47.1 (*C*H), 47.3 (*C*H), 52.0 (*C*H), 54.9 (9-*C*), 57.4 (O*C*H_3), 63.7 (N*C*CH_3), 73.8 (*C*HOCH_3), 111.6 (ArC*H*), 115.1 (C=*C*H_2), 119.5 (Ar*C*H), 119.9 (Ar*C*H), 120.2 (Ar*C*H), 122.2 (Ar*C*H), 122.8 (*C*=CH_2), 124.0 (2 × Ar*C*), 124.1 (Ar*C*H), 125.2 (Ar*C*H), 125.6 (Ar*C*H), 125.8 (Ar*C*H), 125.9 (Ar*C*H), 126.1 (Ar*C*H), 126.9 (Ar*C*H), 133.9 (Ar*C*H), 137.3 (Ar*C*), 140.0 (Ar*C*), 140.5 (Ar*C*), 141.7 (Ar*C*), 145.6 (Ar*C*) and 174.1 (*C*O); *m*/*z* (TOF ES$^+$) 489.2556 (MH^+, $C_{33}H_{33}N_2O_2$ requires 489.2542).

(3a*S*,9a*S*,3*S*)-3a,4,9,9a-Tetrahydro-4-[(1*S*)-1-methoxyethyl]-2-methyl-3-(2-thienyl)-3-methyl-4,9-[1′,2′]benzeno-1*H*-benzo[*f*]isoindole-1-(1*H*)-one 14. Using general procedure B with hydroxy-lactam **9** and thiophene afforded the title compound as a white solid after column chromatography on silica gel eluting with 20% ethyl acetate, 80% hexane as a white solid (177 mg, 50%); $[\alpha]_D^{22}$ +20 (*c* 1 in $CHCl_3$); mp 184–185 °C; ν_{max}(ATR)/cm^{-1} 3041, 2979, 2941, 2818, 1681 and 1502; δ_H (400 MHz; $CDCl_3$) 1.84 (3 H, s, CH_3), 1.89 (3 H, d, *J* 6.4, CH_3CH), 2.32 (3 H, s, NCH_3), 2.58 (1 H, dd, *J* 9.3 and 2.0, COCHC*H*), 3.72–3.75 (4 H, m, OCH_3 and COC*H*CH), 4.51 (1 H, d, *J* 2.0, 10-H), 5.61 (1 H, q, *J* 6.4, CH_3C*H*), 6.70 (1 H, dd, *J* 3.4 and 1.0, ArC*H*), 6.86 (1H, dd, *J* 3.9 and 3.7, ArC*H*), 7.08–7.21 (5 H, m, ArC*H*), 7.27–7.30 (2 H, m, ArC*H*), 7.36–7.38 (1 H, m, ArC*H*) and 7.83–7.85 (1 H, m, ArC*H*); δ_C (100 MHz; $CDCl_3$) 17.3 (*C*H_3), 20.3 (*C*H_3), 25.1 (*C*H_3), 46.7 (*C*H), 46.8 (*C*H), 53.6 (*C*H), 54.9 (9-C), 57.5 (O*C*H_3), 63.6 (N*C*CH_3), 73.9 (*C*HOCH_3), 122.7 (Ar*C*H), 122.9 (Ar*C*H), 124.4 (2×Ar*C*H), 125.4 (Ar*C*H), 125.6 (2 × Ar*C*H), 125.7 (Ar*C*H), 125.8 (Ar*C*H), 126.8 (Ar*C*H), 126.9 (Ar*C*H), 139.9 (Ar*C*), 140.0 (Ar*C*), 141.3 (Ar*C*), 145.1 (Ar*C*), 152.5 (Ar*C*) and 173.2 (*C*O); *m*/*z* (TOF ES$^+$) 430.1855 (MH^+, $C_{27}H_{28}NO_2{}^{32}S$ requires 430.1841).

(3a*R*,9a*R*,3*R*)-3a,4,9,9a-Tetrahydro-4-[(1*R*)-1-methoxyethyl]-2-(2-propen-1-yl)-3-(2-thienyl)-3-methyl-4,9-[1′,2′]benzeno-1*H*-benzo[*f*]isoindole-1-(1*H*)-one 15. Using general procedure B with hydroxy-lactam **10** and thiophene afforded a yellow solid. This was purified by column chromatography on silica gel (5% ethyl acetate, 95% hexane to 20% ethyl acetate, 80% hexane) giving a white solid as the title compound (18 mg, 52%); $[\alpha]_D^{22}$ −27 (*c* 1 in $CHCl_3$); mp 191 °C; ν_{max}(ATR)/cm^{-1} 3071, 2979, 2939, 2819 and 1681; δ_H (400 MHz; $CDCl_3$) 1.80 (3 H, s, CH_3), 1.86 (3 H, d, *J* 6.4, CH_3CH), 2.56 (1 H, dd, *J* 9.3 and 2.1, COCHC*H*), 2.95 (1 H, dd, *J* 16.4 and 5.9, 1 × CH_2), 3.72–3.74 (4 H, m, OCH_3 and COC*H*CH), 3.91–3.96 (1 H, m, 1 × CH_2), 4.05 (1 H, dd, *J* 17.1 and 1.3, 1 × C=CH_2), 4.50 (1 H, d, *J* 2.1, 10-H), 4.63 (1 H, app. dd, *J* 12.0 and 4.0, 1 × C=CH_2), 4.98 (1 H, dddd, *J* 17.1, 12.0, 5.9 and 4.1, C*H*=CH_2), 5.59 (1 H, q, *J* 6.4, CH_3C*H*), 6.68 (1 H, dd, *J* 3.5 and 1.1, ArC*H*), 6.83 (1 H, dd, *J* 5.0 and 3.5, ArC*H*), 7.03–7.21 (5 H, m, ArC*H*), 7.24–7.32 (2 H, m, ArC*H*), 7.34–7.42 (1 H, m, ArC*H*) and 7.78–7.84 (1H, m, ArC*H*); δ_C (100 MHz; $CDCl_3$) 17.3 (*C*H_3CH), 21.3 (*C*H_3), 42.9 (*C*H_2), 46.6 (*C*H), 46.8 (*C*H), 53.6 (*C*H), 54.9 (9-C), 57.5 (O*C*H_3), 64.7 (N*C*–CH_3), 73.7 (*C*HOCH_3), 115.1 (C=*C*H_2), 122.7 (Ar*C*H), 122.9 (*C*=CH_2), 124.5 (Ar*C*H), 124.6 (Ar*C*H), 125.4 (Ar*C*H), 125.7 (Ar*C*H), 125.8 (Ar*C*H), 125.9 (Ar*C*H), 126.0 (Ar*C*H), 126.8 (Ar*C*H), 126.9 (Ar*C*H), 133.4 (Ar*C*H), 140.0 (2 × Ar*C*), 141.5 (Ar*C*), 145.1 (Ar*C*), 153.4 (Ar*C*) and 173.6 (*C*O); *m*/*z* (EI) 455.1938 (M^+, $C_{29}H_{29}NO_2S$ requires 455.1919), 440 (45), 236 (43), 220 (100), 205 (27), 178 (25), 163 (15) and 136 (14).

(3a*S*,9a*S*)-3a,4,9,9a-Tetrahydro-4-[(1*S*)-1-methoxyethyl]-2-methyl-3-methylene-4,9-[1′,2′]benzeno-1*H*-benzo[*f*]isoindole-1-(1*H*)-one 16. Using general procedure B with hydroxy-lactam **9** and 1,2-dimethoxy benzene afforded a white solid as the title compound (0.225 mg, 80%); $[\alpha]_D^{22}$ +63 (*c* 1 in $CHCl_3$); mp 180 °C; ν_{max}(ATR)/cm^{-1} 2938, 1699 and 1661; δ_H (400 MHz; $CDCl_3$) 1.87 (3 H, d, *J* 6.4, CH_3CH), 2.43 (3 H, s, NCH_3), 3.23 (1 H, ddt, *J* 9.2, 2.9 and 1.8, C*H*CHCO), 3.45 (1 H, d, *J* 9.2, CHC*H*CO), 3.74 (3 H, s, OCH_3), 4.09 (1 H, app. t, *J* 1.8, C=CH*H*), 4.29 (1 H, app. t, *J* 1.8, C=C*H*H), 4.31 (1 H, d, *J* 2.9, 10-H), 5.32 (1 H, q, *J* 6.4, CH_3C*H*), 7.09–7.23 (6 H, m, ArC*H*), 7.36–7.38 (1 H, m, ArC*H*) and 7.88–7.91 (1 H, m, ArC*H*); δ_C (100 MHz; $CDCl_3$) 17.0 (*C*H_3CH), 25.6 (N*C*H_3), 44.7 (*C*H), 47.0 (*C*H), 50.7 (*C*H), 54.5 (9-*C*), 57.2 (O*C*H_3), 73.8 (*C*HOCH_3), 83.5 (C=*C*H_2), 123.4 (Ar*C*H), 123.6 (Ar*C*H), 125.4 (Ar*C*H), 125.6 (Ar*C*H), 125.8 (Ar*C*H), 126.0 (2 × Ar*C*H), 126.7 (Ar*C*H), 139.1 (Ar*C*), 139.4 (Ar*C*), 139.9 (Ar*C*), 143.2 (Ar*C*), 149.0 (*C*=CH) and 173.6 (*C*O); *m*/*z* (TOF ES$^+$) 346.1803 (MH^+, $C_{23}H_{24}NO_2$ requires 346.1807).

(3a*R*,9a*R*)-3a,4,9,9a-Tetrahydro-4-[(1*R*)-1-methoxyethyl]-2-(2-propen-1-yl)-3-methylene-4,9-[1′,2′]benzeno-1*H*-benzo[*f*]isoindole-1-(1*H*)-one 17. Using general procedure B with hydroxy-lactam **10** and 1,2-dimethoxy benzene afforded a pale orange solid after recrystallisation from CH_2Cl_2–hexane as the title compound (0.133 mg, 43%); $[\alpha]_D^{22}$ −78 (*c* 1 in $CHCl_3$); mp 147 °C (from CH_2Cl_2–hexane); ν_{max}(ATR)/cm^{-1} 3061, 3020, 2933, 1709 and 1660; δ_H (400 MHz; $CDCl_3$) 1.85 (3 H, d, *J* 6.4, CH_3CH), 3.20–3.23 (1 H, m, COCHC*H*), 3.38 (1 H, dd, *J* 16.1 and 5.6, NC*H*H), 3.46 (1 H, d, *J* 9.4, COC*H*CH), 3.71 (3 H, s, OCH_3), 3.93 (1 H, ddt, *J* 16.1, 5.6 and 1.3, 1 × NCH*H*), 4.08 (1 H, s, 10-H), 4.27–4.33 (2 H, m, NC=CH_2), 4.37 (1 H, app. dd, *J* 17.1 and 1.3, C=C*H*H), 4.79 (1 H, app. dd, *J* 10.3 and 1.3, C=CH*H*), 4.85–4.97 (1 H, m, C*H*=CH_2), 5.29 (1 H, q, *J* 6.4 CH_3C*H*), 7.07–7.24 (6 H, m, ArC*H*), 7.31–7.37 (1 H, m, ArC*H*), 7.84–7.89 (1 H, m, ArC*H*); δ_C (100 MHz; $CDCl_3$) 17.0 (*C*H_3), 42.0 (*C*H_2), 44.8 (*C*H), 46.9 (*C*H), 50.7 (*C*H), 54.5 (9-C), 57.2 (O*C*H_3), 73.7 (*C*HOCH_3), 84.5 (*C*H_2), 116.4 (C=*C*H_2), 123.6 (2×Ar*C*H), 125.6 (*C*=CH_2), 125.7 (Ar*C*H), 125.9 (Ar*C*H), 126.0 (Ar*C*H), 126.1 (Ar*C*H), 126.7 (Ar*C*H), 130.7 (C=*C*H_2), 139.3 (Ar*C*H), 139.7 (Ar*C*), 140.0 (Ar*C*), 143.5 (Ar*C*), 147.5 (Ar*C*) and 173.4 (*C*O); *m*/*z* (TOF ES$^+$) 372.1951 (MH^+, $C_{25}H_{26}NO_2$ requires 372.1964).

(3*E*,3a*S*,9a*S*)-3a,4,9,9a-Tetrahydro-4-[(1*S*)-1-methoxyethyl]-2-(methyl)-3-(3,3,3-trifluoro-2-oxopropylidene)-4,9-[1′,2′]benzeno-1*H*-benzo[*f*]isoindole-1-(1*H*)-one 18. Using general procedure B, with hydroxy-lactam **9** and thiophene and heating to reflux for 24 h afforded a white solid as the title compound after purification by silica gel eluting with 20% ethyl acetate, 80% hexane (183 mg, 50%); $[\alpha]_D^{22}$ +169 (*c* 0.5 in $CHCl_3$); mp 195–196 °C; ν_{max}(ATR)/cm^{-1} 2982, 2937, 2825, 1744, 1691 and 1568; δ_H (400 MHz; $CDCl_3$) 1.90 (3 H, d, *J* 6.4, CH_3CH), 2.57 (3 H, s, NCH_3), 3.60 (1 H, d, *J* 8.3, COC*H*CH), 3.71 (3 H, s, OCH_3), 3.97–3.99 (1 H, m, COCHC*H*), 4.87 (1 H, d, *J* 2.7, 10-H), 5.20 (1 H, q, *J* 6.4, CH_3C*H*), 5.64 [1 H, s, C*H*C(O)CF_3], 7.13–7.25 (6 H, m, ArC*H*), 7.55–7.57 (1 H, m, ArC*H*) and 7.88–7.89 (1 H, m, ArC*H*); δ_C (100 MHz; $CDCl_3$) 16.7 (*C*H_3), 26.6 (*C*H_3N), 46.3 (*C*H), 46.5 (*C*H), 47.2 (*C*H), 54.1 (9-C), 54.8 (*C*H_3O), 73.4 (*C*HOCH_3), 90.7 (C*H*=C), 116.66 (q, J_{C-F} 291.8, *C*F_3), 123.3 (ArC*H*), 124.4 (ArC*H*), 125.1 (ArC*H*), 125.9 (ArC*H*), 126.5 (ArC*H*), 126.6 (2 × ArC*H*), 126.8, 143.0 (Ar*C*), 139.0 (Ar*C*), 138.9 (Ar*C*), 138.5 (Ar*C*), 169.1 (N*C*=CH), 175.1

(*C*O) and 178.2 (q, J_{C-F} 34.0, CF_3CO); δ_F (235 MHz; $CDCl_3$) –77.94 (CF_3); *m*/*z* (TOF ES$^+$) 442.1617 (MH^+, $C_{25}H_{23}F_3NO_3$ requires 442.1630).

(3*E*,3a*R*,9a*R*)-3a,4,9,9a-Tetrahydro-4-[(1*R*)-1-methoxyethyl]-2-(2-propen-1-yl)-3-(3,3,3-trifluoro-2-oxopropylidene)-4,9-[1′,2′]benzeno-1*H*-benzo[*f*]isoindole-1-(1*H*)-one 19. Using general procedure B with hydroxy-lactam **10** and thiophene and heating to reflux for 27 h afforded a yellow solid that was purified by column chromatography on silica gel (5% ethyl acetate, 95% hexane to 20% ethyl acetate, 80% hexane) giving a white solid as the title compound (184 mg, 48%); mp 187–188 °C; $[\alpha]_D^{22}$ –124 (*c* 1 in $CHCl_3$); ν_{max}(ATR)/cm^{-1} 2936, 2827, 1742, 1692 and 1567; δ_H (400 MHz; $CDCl_3$) 1.88 (3 H, d, *J* 6.4, CH_3CH), 3.48 (1 H, dd, *J* 16.0 and 6.1, 1 × NCH_2), 3.58 (1 H, d, *J* 8.3, COC*H*CH), 3.70 (3 H, s, OCH_3), 3.96 (1 H, dd, *J* 8.3 and 1.3, COCHC*H*), 4.06 (1 H, dd, *J* 16.0 and 4.6, 1 × NCH_2), 4.57 (1 H, d, *J* 17.1, 1 × C=CH_2), 4.75–4.90 (2 H, m, 10-H and C*H*=CH_2), 4.90–4.99 (1 H, m, 1 × C=CH_2), 5.19 (1 H, q, *J* 6.4, CH_3CH), 5.64 [1 H, s, C*H*C(O)CF_3], 7.08–7.29 (6 H, m, ArC*H*), 7.49–7.57 (1 H, m, ArC*H*) and 7.80–7.91 (1 H, m, ArC*H*); δ_C (100 MHz; $CDCl_3$) 16.8 (CH_3CH), 42.7 (CH_2), 46.3 (*C*H), 46.5 (*C*H), 47.1 (*C*H), 54.8 (9-*C*), 57.2 (OCH_3), 73.4 (*C*HOCH_3), 91.5 (C*H*=C), 118.5 (CH=CH_2), 116.6 (q, J_{C-F} 178.2, CF_3), 123.5 (Ar*C*H and *C*H=CH_2), 124.4 (Ar*C*H), 125.4 (Ar*C*H), 125.9 (Ar*C*H), 126.5 (2 × Ar*C*H), 126.6 (Ar*C*H), 128.7 (Ar*C*H), 138.7 (Ar*C*), 139.2 (2 × Ar*C*), 143.1 (Ar*C*), 168.1 (*C*=CH), 174.9 (*C*O), 178.4 (q, J_{C-F} 34.2, CF_3CO); δ_F (377 MHz; $CDCl_3$) –78.1 (CF_3); *m*/*z* (TOF ES$^+$) 468.1804 (MH^+, $C_{27}H_{25}F_3NO_3$ requires 468.1787).

(*S*)-5-(Furan-2-yl)-1,5-dimethyl-1*H*-pyrrol-2(5*H*)-one 20. A 50 cm quartz thermolysis tube was connected to a 25 mL flask containing cycloadduct **11** (190 mg, 0.46 mmol), and the other end to a cold trap. The thermolysis tube was heated at 510 °C under vacuum (0.02 mmHg) and the starting material was then heated to 180 °C for 0.5 h. The system was then allowed to cool to room temperature. The crude material was collected from the U-tube (100% conversion) and the desired compound **20** was separated from the auxiliary **21** by flash column chromatography on silica gel (50% ethyl acetate, 50% petroleum ether) affording pale yellow crystals (64 mg, 79%); (Found: C, 67.87; H, 6.31; N, 7.75. $C_{10}H_{11}NO_2$ requires C, 67.78; H, 6.26; N, 7.90%); $[\alpha]_D^{22}$ –268 (*c* 1 in $CHCl_3$, ee 97%); mp 38–39 °C; ν_{max}(ATR)/cm^{-1} 3116, 2984, 2936, 1690 and 1594; δ_H (400 MHz; $CDCl_3$) 1.64 (3 H, s, CH_3), 2.76 (3 H, s, NCH_3), 6.17 (1 H, d, *J* 5.8, C*H*=CH), 6.23 (1 H, dd, *J* 3.3 and 0.9, ArC*H*), 6.33 (1 H, dd, *J* 3.3 and 1.8, ArC*H*), 7.02 (1 H, d, *J* 5.8, C*H*=CH) and 7.36 (1 H, dd, *J* 1.8 and 0.9, ArC*H*); δ_C (100 MHz; $CDCl_3$) 20.0 (CH_3), 24.4 (NCH_3), 65.5 (CH_3C), 107.6 (*C*H), 110.4 (*C*H), 125.9 (*C*H), 142.9 (*C*H), 150.5 (*C*H), 151.2 (Ar*C*) and 170.2 (*C*O); *m*/*z* (TOF ES$^+$) 178.0863 (MH^+, $C_{10}H_{12}NO_2$ requires 178.0868); Chiral HPLC, Phenomenex Lux 3 μm Cellulose-1, 10% IPA in hexane, flow rate 1 mL min^{-1}, t_R (*S*) enantiomer 10.3 min (*R*) enantiomer 11.5 min.

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8 Dihedral angles were measured from molecular models obtained using Spartan 06 (1.0.2) using the B3LYP functional method and the 6-311+G** basis set. Coupling constants were then modelled with the Smith-Barfield equation using MestReJ v1.1, freely available from http://mestrelab.com/software/mestrej/.

9 A variable temperature ^{1}H NMR experiment to determine the nature of these isomers (regioisomers or atropisomers) gave no significant change in the ratios of signals upon heating that unfortunately precludes any closure on this matter.

10 Note that for these transformations, the opposite enantiomer of anthracene template was employed to prepare the *N*-methyl series. The absolute stereochemistry of the *N*-allyl series is the same as depicited in Scheme 1.

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