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Spiro cyclisations of *N*-acyliminium ions involving an aromatic π-nucleophile

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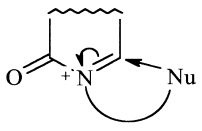
Abstract—Spiro 2-pyrrolidin-5-ones were obtained from *N*-substituted succinimides by a two-step procedure, involving 5- or 6-*endo-trig* cyclisation of *N*-acyliminium ion intermediates with a tethered aromatic π-nucleophile.

The importance of *N*-acyliminium ion chemistry in organic synthesis is attested by numerous reviews.[1,2] In the common type of intramolecular reaction of *N*-acyliminium ions represented by **1**, the nucleophile may be heteroatom, alkene, alkyne or aromatic groups; from cyclic iminium ions, fused bicyclic or polycyclic products are obtained. Much less common are intramolecular reactions of the type represented by **2**, which lead to the formation of spiro products. Prior to our work in this area, the only examples of such α,α-cyclisations involved alkene nucleophiles.[3] The reaction was applied in two syntheses of perhydrohistrionicotoxin[4] via the key intermediate 6,6-spiro lactam **3**. Recent examples of spiro cyclisation via *N*-acyliminium ions include two syntheses of lepadiformine.[5]



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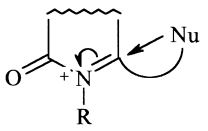

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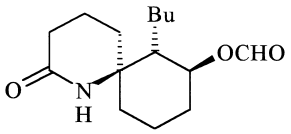

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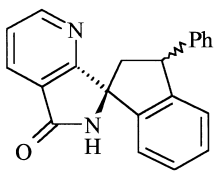

4

Our own interest in spiro lactams was stimulated by elucidation of the unexpected formation of **4** via a different route,[6] which prompted us to examine the possibility of α,α-cyclisations **2** with an aromatic ring as the π-nucleophile.[7] Two examples of this type were reported in the context of a tandem thionium/*N*-acyliminium ion cascade cyclisation sequence.[8] Although an erythrinane synthesis achieved via iminium ion cyclisation also involves the formation of a spiro structure,[9] the cyclisation step in this case corresponds to type **1**, not **2**.

1. Results and discussion

The required cyclisation was first demonstrated with the hydroxy lactam **7a**, which afforded the 5,5-spiro lactam **9a** in 69% yield by dehydration in refluxing trifluoroacetic acid (TFA). In the same way, the homologous hydroxy lactam **7b** was the intermediate in a two-step synthesis of the 5,6-spiro lactam **9b** (Scheme 1). ^{13}C NMR DEPT spectra showed the appropriate signals for CH_3, CH_2 (×4 in **9a**, ×5 in **9b**) and crucially for quaternary carbon (δ 74.2 in **9a**, δ 65.8 in **9b**). Grignard addition to *N*-benzylsuccinimide **6**, followed by cyclisation in refluxing TFA, similarly afforded the *N*-benzyl spiro lactams **10a**,**b**, which showed the corresponding ^{13}C NMR resonances for quaternary carbon at δ 74.9 and 67.1, respectively. However, we sought additional evidence to confirm the spiro structures in these two cases and specifically to exclude the alternative fused tricyclic structures **11a**,**b**, which could result from the intermediates **8a**,**b** via the alternative *N*-acyliminium ion cyclisation **1** involving the *N*-benzyl group. Although these would be relatively disfavoured 5-*endo-trig* cyclisations, there are precedents in the formation of **12** and **13**.[10,11] The non-equivalence of the *N*–CH_2 signals in the ^{1}H NMR spectra (two doublets, δ 3.85 and 4.67 in **10a** and δ 3.65 and 4.88 in

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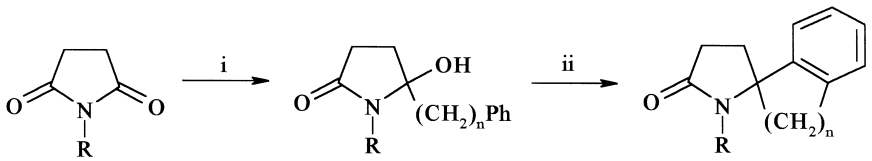


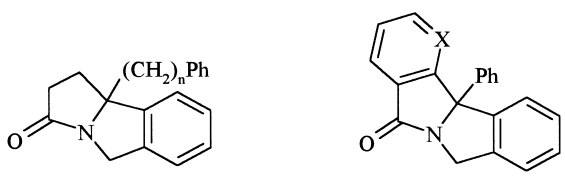
5 R = Me
6 R = CH_2Ph

7 a R = Me, *n* = 2
b R = Me, *n* = 3
8 a R = CH_2Ph, *n* = 2
b R = CH_2Ph, *n* = 3

9 a R = Me, *n* = 2
b R = Me, *n* = 3
10 a R = CH_2Ph, *n* = 2
b R = CH_2Ph, *n* = 3

Scheme 1. *Reagents*: (i) $Ph(CH_2)_nMgBr$ (ii) TFA, reflux.

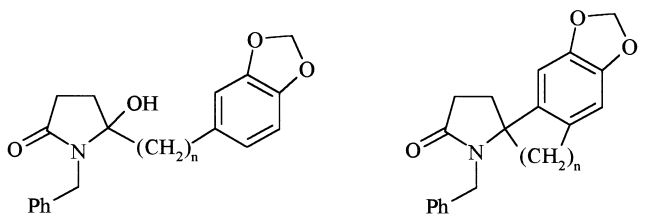
10b) might have been interpreted as evidence for the fused tricyclic structures **11a**,**b**.



11 a *n* = 2
b *n* = 3

12 X = CH
13 X = N

In the first place, and in order to develop applications of these spiro cyclisations towards natural product targets, we examined the cyclisation into a 3,4-methylenedioxy substituted benzene ring. This involved the preparation of bromides **19a**,**b** as outlined in Scheme 2. Grignard reagents made from **19a**,**b** were then added to *N*-benzyl succinimide **6** to give hydroxy lactams **20a**,**b** and, in one case, the by-product **22** from aldol condensation of **6**. Heating of **20a**,**b** in TFA achieved cyclodehydration to give the spiro lactams **21a**,**b**, which showed ^{13}C resonances for quaternary carbon at δ 74.7 and 67.1, respectively. ^1H NMR Spectra of **21a**,**b** included two singlets for aryl H adjacent to the OCH_2O substituent, which provides evidence to confirm the spiro structures rather than fused tricyclic structures analogous to **11**.

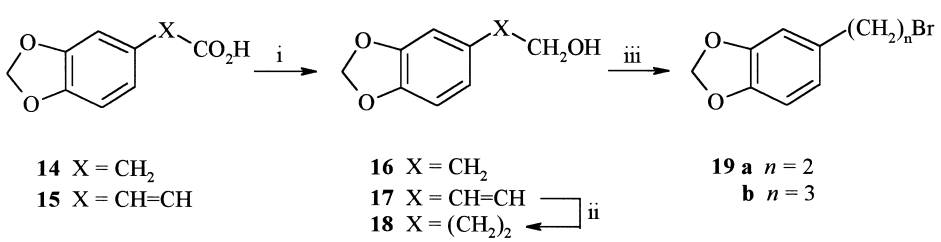


20 a *n* = 2
b *n* = 3

21 a *n* = 2
b *n* = 3

A second approach to prove the correct assignment of spiro structures **10a**,**b** involved cyclisation of derivatives of **8a**,**b** with substituents in both *ortho* positions of the *N*-benzyl group, which served to block the alternative cyclisation to **11**. The hydroxy lactam **26** obtained in low yield from *N*-(2,6-difluorobenzyl)succinimide **24** was incompletely separated from by-products, but on heating in TFA it afforded the 5,5-spiro lactam **28**. Attempted Grignard addition to the more sterically hindered succinimide **25** was unsuccessful, and only the aldol condensation product **23** was obtained. However, the alternative route shown in Scheme 3 afforded, instead of the hydroxy lactam **27**, the enamide **30**. On heating this in TFA the desired spiro product **29** was obtained, although the reaction was slower than in other cases and still incomplete after 4 days. Attempted debenzylation of **29** with hydrogen and palladium resulted only in hydrodehalogenation[12] to give the *N*-benzyl spiro lactam **10a**. This series of experiments thus provides conclusive proof of the correct assignment of spiro structures **10a**,**b**.

A variety of chiral control elements has been employed in reactions via *N*-acyliminium ions.[2] Among the simplest of these is a chiral 1-arylethyl substituent on nitrogen, which controls the stereochemistry of intermolecular additions to *N*-acyliminium ions,[13–15] although the changes in stereoselectivity resulting from changes in substituent, reactant or conditions are not always understood. Hence, we were also interested to explore the corresponding cyclisations of hydroxy lactam precursors with a chiral *N*-substituent for the possibility of stereochemical control of formation of the spiro carbon centre. For this purpose, we took (*R*)-*N*-(1-phenylethyl)succinimide **31**, but found that steric hindrance reduced the reactivity towards Grignard addition onto a succinimide carbonyl group, while the basicity of the Grignard reagent resulted in aldol-type dimerisation of **31** to give **36**. This problem was circumvented by using a cerium-moderated Grignard reagent of lower basicity,[16] whereby the ketoamide **32** and enamide **33b** were obtained if the Grignard reagent was prepared from $Ph(CH_2)_nBr$ (*n*=2 or 3), respectively. Treatment of **32** with TFA under very mild conditions achieved recyclisation to the enamide **33a**. In

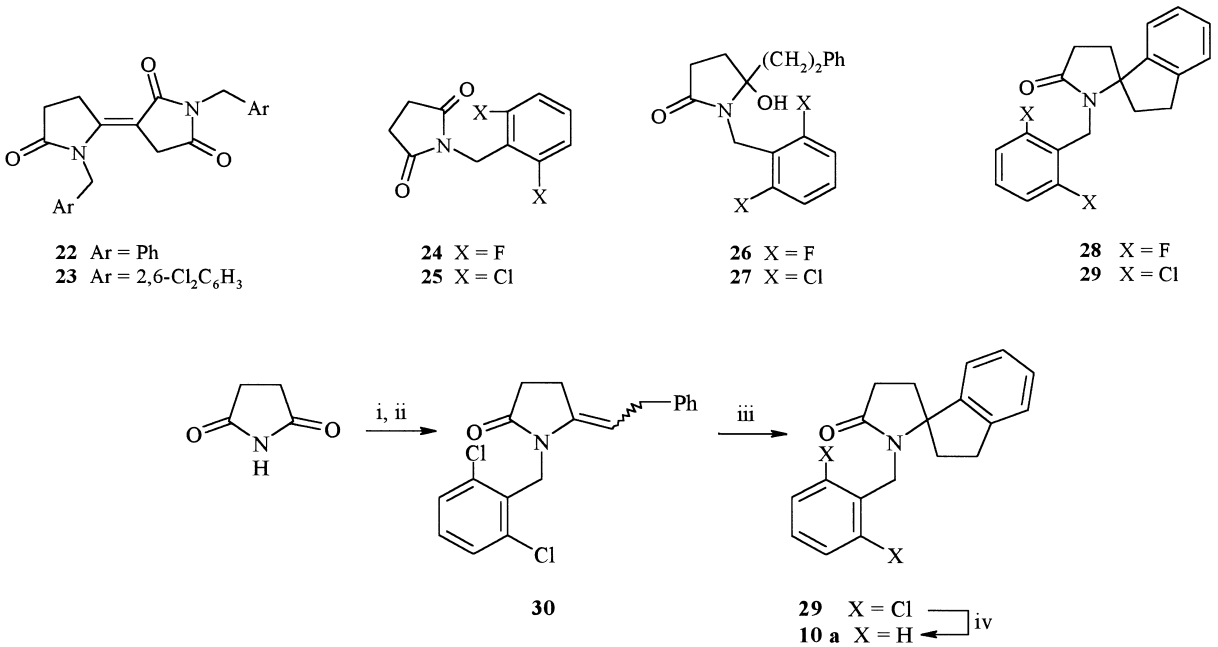


14 X = CH_2
15 X = CH=CH

16 X = CH_2
17 X = CH=CH
18 X = $(CH_2)_2$

19 a *n* = 2
b *n* = 3

Scheme 2. *Reagents*: (i) $LiAlH_4$/THF; (ii) H_2/Pd; (iii) PPh_3+CBr_4/MeCN.

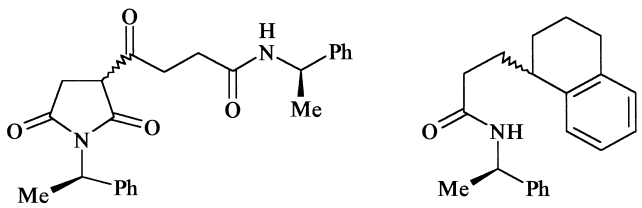


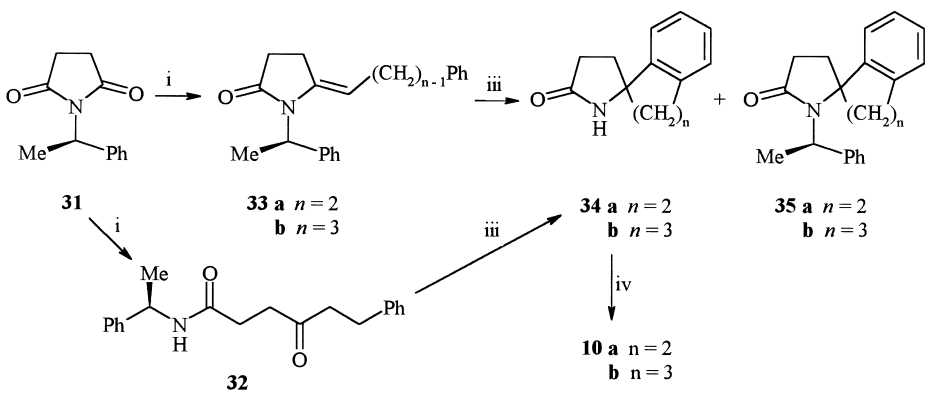
Scheme 3. *Reagents*: (i) $PhCH_2CH_2MgBr/THF$; (ii) $2,6\text{-}Cl_2C_6H_3CH_2Br/Cs_2CO_3/MeCN$; (iii) TFA, reflux; (iv) $H_2/Pd(OH)_2-C/MeOH$.

refluxing TFA **32** and **33a** were separately converted into the spiro lactam **34a**, but with loss of the chiral *N*-substituent (Scheme 4). TLC was used to monitor the progress of reaction in TFA at lower temperatures, but this did not indicate the formation of other spiro products (**35a**). Moreover, and disappointingly, the product **34a** was racemic, implying that this debenzylation of the *N*-acyliminium ion intermediate had occurred prior to spiro cyclisation.

More interestingly, the corresponding cyclisation of homologous enamide **33b** in refluxing TFA resulted in formation of a mixture of NH and *N*-substituted 5,6-spiro lactams **34b** and **35b**, in 58 and 25% yield, respectively; **34b**, like **34a**, was racemic and **35b** was a ca. 3:1 mixture of diastereoisomers, inseparable by chromatography. Spiro lactam **34b** was prepared independently in two steps by Grignard addition to succinimide, followed by cyclisation in refluxing TFA. Benzylation of **34a**,**b** gave *N*-benzyl derivatives (Scheme 4), which were identical with the spiro lactams **10a**,**b** obtained previously.

Spiro lactam **35b** contains two benzylic groups attached to nitrogen and it was problematic whether the side chain 1-phenylethyl group could be removed selectively. In fact, no debenzylation of **35b** was observed under the usual conditions of hydrogen with palladium or Pearlman's catalyst, with or without addition of acid. In a small scale experiment with sodium and liquid ammonia, **35b** was reduced with unexpected cleavage of the endocyclic benzylic bond to give amide **37**. This appeared to be a single diastereoisomer (^{13}C NMR spectrum[7]) and some of **35b** remained (tlc analysis), which suggested that ring-opening of **35b** had occurred diastereoselectively.





Scheme 4. *Reagents*: (i) $Ph(CH_2)_nMgBr/CeCl_3/THF$; (ii) $TFA/CH_2Cl_2/0^{\circ}C$; (iii) TFA, reflux; (iv) $PhCH_2Br/Cs_2CO_3/MeCN$.

In conclusion, we have demonstrated the formation of spiro lactams by cyclisation of *N*-acyliminium ion intermediates reacting intramolecularly with an arene π-nucleophile. In subsequent work we have found that some of the cyclisations, e.g. to **10a**,**b**, can be achieved using aluminium trichloride in 1,2-dichloroethane. We have also developed a stereoselective approach[17] to spiro lactams based on the use of phenylglycinol as chiral auxiliary and a regioselective debenzylation procedure[18] to remove the side chain from nitrogen.

2. Experimental

2.1. General

Optical rotations were recorded for solutions in dichloromethane (DCM) at 22°C (Perkin–Elmer 141 polarimeter). IR Spectra were recorded for solutions in chloroform (Perkin–Elmer 1420 spectrophotometer). ^{1}H NMR Spectra were recorded at 90 MHz (JEOL FX90Q) or at 300 MHz (Bruker MSL300) and ^{13}C NMR spectra at 22.5 MHz (JEOL FX90Q spectrometer) for solutions in deuteriochloroform (unless stated otherwise) with tetramethylsilane as internal standard. In ^{13}C NMR spectra lines enclosed in | | are due to ^{19}F splittings. Mass spectra were obtained by electron impact at 70 eV (VG Autospec). Flash chromatography[19] was performed using silica gel 60 (230–400 mesh) purchased from Camlab. Acetonitrile, diethyl ether and THF were dried before use. DCM refers to dichloromethane.

2.2. *N*-Substituted succinimides 6, 24, 25 and 31

N-Benzylsuccinimide **6** was prepared by dropwise addition of benzylamine (16.5 g, 150 mmol) to a stirred solution of succinic anhydride (15.0 g, 150 mmol) in THF (150 mL). The mixture was heated under reflux for 2 h, then cooled and the solvent removed in vacuo. Acetic anhydride (150 mL) was added and the mixture again heated under reflux for 2 h, then cooled and poured onto crushed ice and stirred. The precipitated solid was collected and recrystallised to give the imide **6**, mp 101–103°C (methanol) (lit.[20] mp 103.5–105°C).

(*R*)-(+)-*N*-(1-Phenylethyl)succinimide **31** was prepared in the same way from (*R*)-(+)-1-phenylethylamine and succinic anhydride. After pouring the acetic anhydride solution onto crushed ice, the mixture was extracted three times with DCM. The combined extracts were washed with saturated sodium hydrogen carbonate solution, then with brine, then dried ($MgSO_4$), and the solvent evaporated to afford a colourless oil. This was chromatographed on silica, from which DCM eluted the imide **31** as a colourless oil (60% yield) which crystallised after trituration with ether, mp 64–65°C (HREIMS Found M^+ *m/z* 203.0945. $C_{12}H_{13}NO_2$ requires *M* 203.0946); $[\alpha]_D$+91.9 (*c* 4.0, DCM); IR ν_{max}/cm^{-1} 3000, 1775, 1700, 1600, 1580, 1490, 1450 and 1430; ^{1}H NMR (90 MHz) δ 1.81 (3H, d, *J* 7.4 Hz, CHC*H*$_3$), 2.62 (4H, s, 2×ring CH_2), 5.42 (1H, q, *J* 7.4 Hz, C*H*CH$_3$) and 7.25–7.50 (5H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 16.6 (CH_3), 28.1 (CH_2), 50.3 (CH), 127.6 (CH), 127.8 (CH), 128.4 (CH), 139.7 (C) and 177.0 (C═O); MS *m/z* 203 (M^+, 50%), 188 (6), 160 (100), 146 (9), 132 (6), 120 (7), 104 (24) and 77 (22). (*S*)-(−)-**31** has been reported:[13,21] mp 39–41°C, 67–68.5°C; $[\alpha]_D$−79.8, −68.9 (EtOH).

N-(2,6-Difluorobenzyl)succinimide **24** was prepared from succinimide (2.39 g) and 2,6-difluorobenzyl bromide (5.0 g) dissolved in acetonitrile (30 mL) and stirred with caesium carbonate (10.0 g) for 24 h. The solution was filtered, the solvent evaporated and the residue recrystallised to give the imide **24** (4.22 g, 77%) as colourless platelets, mp 112–113°C (methanol) (HREIMS Found M^+ *m/z* 225.0600. $C_{11}H_9F_2NO_2$ requires *M* 225.0601); IR ν_{max}/cm^{-1} 1780 and 1710 (C═O); ^{1}H NMR (90 MHz) δ 2.70 (4H, s, 2×ring CH_2), 4.74 (2H, s, NCH_2) and 6.72–7.39 (3H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 28.1 (CH_2), |30.6, 30.8, 31.0| (CH_2), |110.8, 111.9| (CH), |129.3, 129.7, 130.2| (CH), |155.7, 156.1, 166.8, 167.2| (CF) and 176.3 (C═O); MS *m/z* 225 (M^+, 100%), 196 (10), 169 (12), 140 (64) and 127 ($ArCH_2^+$, 51).

N-(2,6-Dichlorobenzyl)succinimide **25** was obtained in the same way (36% yield) using 2,6-dichlorobenzyl bromide; mp 116–118°C (methanol) (HRCIMS Found M·NH_4^+ *m/z* 275.0356. $C_{11}H_{13}{}^{35}Cl_2N_2O_2$ requires 275.0354); IR ν_{max}/cm^{-1} 1780 and 1710 (C═O); ^{1}H NMR (90 MHz) δ 2.67 (4H, s, 2×ring CH_2), 4.89 (2H, s, NCH_2) and 7.12–7.28 (3H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 27.7 (CH_2), 38.5 (CH_2), 128.1 (CH), 129.3 (CH), 129.8 (C), 135.8 (C) and 176.3 (C═O); MS *m/z* 261, 259 and 257 (M^+, all <1%), 224 (31), 222 (M−Cl, 100), 172 (7), 161 (8), 159 (12) and 141 (21).

2.3. 2-(3,4-Methylenedioxyphenyl)ethanol 16 and 1-bromo-2-(3,4-methylenedioxy-phenyl)ethane 19a; 3-(3, 4-methylenedioxyphenyl)propan-1-ol 18 and 1-bromo-3-(3,4-methylenedioxyphenyl)propane 19b

3,4-Methylenedioxyphenylacetic acid (5.0 g) was reduced with aluminium lithium hydride (2.3 g) in THF at room temperature. Aqueous work-up afforded the alcohol **16** (4.6 g) as a colourless oil. This was dissolved in acetonitrile (50 mL) together with triphenylphosphine (6.9 g), to which was added carbon tetrabromide (9.2 g) in portions, followed by stirring overnight. The solvent was evaporated in vacuo and the residue chromatographed on silica, from which DCM eluted the bromide **19a** (5.1 g, 80% over 2 steps), colourless oil (HREIMS Found M^+ 227.9815. $C_9H_9{}^{79}BrO_2$ requires *M* 227.9786); ^{1}H NMR (90 MHz) δ 3.05 (2H, br t, *J* 7.3 Hz, ArC*H*$_2$CH$_2$), 3.50 (2H, br t, *J* 7.3 Hz, CH_2Br), 5.91 (2H, s, OCH_2O) and 6.57–6.80 (3H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 33.2 (CH_2), 39.1 (CH_2), 101.0 (CH_2), 108.4 (CH), 109.0 (CH), 121.7 (CH), 132.7 (C), 146.5 (C) and 147.7 (C); MS *m/z* 230 and 228 (M^+, 25%), 149 (M−Br, 20), 135 ($ArCH_2^+$, 100), 119 (9), 91 (16) and 77 (11).

3,4-Methylenedioxycinnamic acid (3.0 g) was dissolved in THF (100 mL) and cooled to 0°C during addition of aluminium hydride (1.5 g) with stirring. The mixture was allowed to warm to room temperature, then heated under reflux for 24 h. Aqueous work-up afforded a mixture of saturated and unsaturated alcohols **17** and **18**, which was redissolved in methanol (50 mL) and stirred overnight with

palladium on charcoal under an atmosphere of hydrogen. The solution was filtered, the solvent evaporated, and the residue chromatographed on silica, from which DCM eluted 3-(3,4-methylenedioxyphenyl)propan-1-ol **18** (1.5 g, 53%), colourless oil (HREIMS Found M^+ 180.0787. $C_{10}H_{12}O_3$ requires *M* 180.0787); IR ν_{max}/cm^{-1} 3605 (OH); ^1H NMR (90 MHz) δ 1.72–1.96 (2H, m, $ArCH_2CH_2CH_2$), 2.43 (1H, s, OH), 2.51–2.68 (2H, m, $ArCH_2CH_2$), 3.61 (2H, t, *J* 6.4 Hz, CH_2OH), 5.88 (2H, s, OCH_2O) and 6.54–6.76 (3H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 31.7 (CH_2), 34.3 (CH_2), 61.8 (CH_2), 100.7 (CH_2), 108.1 (CH), 108.8 (CH), 121.1 (CH), 135.7 (C), 145.6 (C) and 147.5 (C); MS *m/z* 180 (M^+, 66%), 162 (5), 136 (60), 135 ($ArCH_2^+$, 100), 106 (10), 91 (8) and 77 (17).

Alcohol **18** (1.3 g) and triphenylphosphine (1.8 g) were dissolved in acetonitrile (20 mL) and stirred during addition of carbon tetrabromide (2.4 g) in portions. Stirring was continued overnight, after which the solvent was evaporated in vacuo and the residue chromatographed on silica, from which DCM eluted 1-bromo-3-(3,4-methylenedioxyphenyl)-propane **19b** (1.25 g, 71%), colourless oil (HREIMS Found M^+ 243.9901. $C_{10}H_{11}{}^{81}BrO_2$ requires *M* 243.9902); IR O–H absorption absent; ^1H NMR (90 MHz) δ 1.92–2.28 (2H, m, $ArCH_2CH_2CH_2$), 2.69 (2H, t, *J* 7.3 Hz, $ArCH_2CH_2$), 3.37 (2H, t, *J* 6.3 Hz, CH_2Br), 5.92 (2H, s, OCH_2O) and 6.56–6.82 (3H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 32.9 (CH_2), 33.7 (CH_2), 34.3 (CH_2), 100.8 (CH_2), 108.2 (CH), 108.9 (CH), 121.4 (CH), 134.2 (C), 145.9 (C) and 147.7 (C); MS *m/z* 244 and 242 (M^+, 19%), 162 (5), 135 ($ArCH_2^+$, 100), 105 (5) and 77 (15).

2.4. General procedures for Grignard reactions and for cyclisations in TFA

The Grignard reagent was freshly prepared from the required bromide in ether with an equimolar quantity of magnesium; reaction was initiated, if necessary, by addition of a small crystal of iodine and completed by heating under reflux for 1 h. The required imide dissolved in THF was added to the Grignard reagent in ether at room temperature with stirring and the mixture stirred overnight. Saturated aqueous ammonium chloride was added and the mixture extracted with 2 portions of chloroform. The combined extracts were washed 3 times with brine, then dried ($MgSO_4$); the solution was filtered, the solvent evaporated in vacuo, and the residue purified by flash chromatography on silica to yield hydroxy lactam and other products described below.

The hydroxy lactam was dissolved in TFA and heated under reflux for 1–3 days. The solution was cooled and poured dropwise into saturated $NaHCO_3$ solution in presence of an excess of solid $NaHCO_3$. The mixture was extracted twice with chloroform, the extracts washed with brine, then dried ($MgSO_4$); the solution was filtered, the solvent evaporated in vacuo, and the residue purified by flash chromatography on silica to yield spiro products described below.

2.4.1. Hydroxy lactam 7a,b and spiro products 9a,b derived from *N*-methylsuccinimide. The Grignard reagent was prepared from 1-bromo-2-phenylethane (3.7 g, 20 mmol) and reacted with *N*-methylsuccinimide (1.0 g, 8.8 mmol) according to the general procedure. The crude product was a yellow oil (3.3 g) which by flash chromatography on silica and elution with a solvent gradient (ether/DCM 40:60 to methanol/ether/DCM 2:40:58) afforded 5-hydroxy-1-methyl-5-(2-phenylethyl)pyrrolidin-2-one **7a** (1.01 g, 52%) as a pale yellow foam (HREIMS Found M^+ 219.1244. $C_{13}H_{17}NO_2$ requires *M* 219.1259); R_f 0.20 (methanol/chloroform 1:9); IR ν_{max}/cm^{-1} 3580 (O–H), 3000, 1675 (C=O), 1600, 1490, 1455 and 1410; ^1H NMR (90 MHz) δ 2.75 (3H, s, CH_3), 1.83–2.90 (8H, m, 4×CH_2), 5.26 (1H, br, s, OH) and 7.11–7.40 (5H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 24.1 (CH_3), 29.3 (CH_2), 30.1 (CH_2), 31.6 (CH_2), 39.9 (CH_2), 91.6 (spiro C), 126.1 (CH), 128.2 (CH), 128.5 (CH), 141.0 (C) and 175.0 (C=O); MS *m/z* 219 (M^+, 2%), 201 ($M-H_2O$, 100), 200 (45), 186 (3), 172 (12), 124 (42), 114 (32) and 91 (51).

After heating the hydroxy lactam **7a** (500 mg, 2.28 mmol) in TFA (20 mL) under reflux for 48 h, the mixture was worked up to afford a crude product of a yellow oil (425 mg) and after flash chromatography and elution with ether/DCM (5:95) *2,3-dihydro-1′-methylspiro[1H-indene-1,2′-pyrrolidin]-5′-one* **9a** (318 mg, 69%) as colourless needles, mp 44–45°C (from methanol) (Found: C, 77.6; H, 7.5; N, 7.0. $C_{13}H_{15}NO$ requires C, 77.6; H, 7.5; N, 6.9%); R_f 0.27 (ether/chloroform 1:9); IR ν_{max}/cm^{-1} 3000, 1670 (C=O), 1475, 1450, 1435, 1420 and 1395; ^1H NMR (90 MHz) δ 1.94–2.58 (6H, m, 3×CH_2), 2.58 (3H, s, CH_3), 2.96 (2H, t, *J* 7.1 Hz, $ArCH_2$) and 7.01–7.26 (4H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 25.3 (CH_3), 29.4 (CH_2), 30.2 (CH_2), 33.8 (CH_2), 34.9 (CH_2), 74.2 (spiro C), 122.7 (CH), 125.0 (CH), 127.2 (CH), 128.3 (CH), 142.7 (C), 144.2 (C) and 174.7 (C=O); MS *m/z* 201 (M^+, 100%), 200 (37), 186 (8), 172 (30), 158 (34), 144 (29), 129 (16) and 115 (16).

The Grignard reagent was prepared from 1-bromo-3-phenylpropane (3.7 g, 20 mmol) and reacted with *N*-methylsuccinimide (1.0 g, 8.8 mmol) according to the general procedure. The crude product was a yellow oil (3.05 g) which by flash chromatography on silica and elution with a solvent gradient (ether/DCM 10:90 to methanol/ether/DCM 2:10:88) afforded the hydroxy lactam **7b** (536 mg) [R_f 0.44 (ether/chloroform 1:9)] contaminated by some baseline material. This product was dissolved in TFA (15 mL) and heated under reflux for 48 h. The usual work-up procedure afforded 1,2,3,4-tetrahydro-1′-methylspiro[naphthalene-1,2′-pyrrolidin]-5′-one **9b** as a colourless oil (474 mg, 25% from *N*-methylsuccinimide) (HREIMS Found M^+ 215.1318. $C_{14}H_{17}NO$ requires *M* 215.1310); R_f 0.39 (ether/chloroform 1:9); IR ν_{max}/cm^{-1} 3000, 1670 C=O), 1490, 1450, 1420 and 1400; ^1H NMR (90 MHz) δ 1.75–2.50 (8H, m, 4×CH_2), 2.57 (3H, s, CH_3), 2.65–2.90 (2H, m, $ArCH_2$) and 7.00–7.24 (4H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 20.0 (CH_2), 25.7 (CH_3), 29.3 (CH_2), 29.5 (CH_2), 32.2 (CH_2), 35.8 CH_2), 65.8 (spiro C), 126.0 (CH), 126.7 (CH), 127.2 (CH), 129.3 (CH), 137.6 (C), 139.1 (C) and 175.1 (C=O); MS *m/z* 215 (M^+, 100%), 200 (29), 186 (60), 172 (44), 158 (24), 144 (19), 124 (19), 115 (17) and 91 (9).

2.4.2. Hydroxy lactam 8a,b and 20a,b and spiro products 10a,b and 21a,b derived from *N*-benzylsuccinimide. The Grignard reagent was prepared from 1-bromo-2-phenylethane (5.3 mmol) and reacted with *N*-benzylsuccinimide **6**

(0.77 g, 4.1 mmol) according to the general procedure. The crude product was a yellow oil (1.4 g) which by flash chromatography on silica and elution with a solvent gradient (ether/DCM 40:60 to methanol/ether/DCM 2:40:58) afforded *1-benzyl-5-hydroxy-5-(2-phenylethyl)pyrrolidin-2-one* **8a** (0.81 g, 67%) as a colourless oil (HREIMS Found M^+ 295.1570. $C_{19}H_{21}NO_2$ requires *M* 295.1572); R_f 0.53 (methanol/chloroform 1:9); IR ν_{max}/cm^{-1} 3575, 3000, 1675 (C═O), 1600, 1490, 1455, 1410 and 1355; ^1H NMR (90 MHz) δ 1.75–2.80 (8H, m, 4×CH_2), 3.67 (1H, br s, OH), 4.30 and 4.64 (each 1H, apparent s, outer lines of AB system not seen, NCH_2) and 7.28–7.88 (10H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 29.2 (CH_2), 30.2 (CH_2), 32.5 (CH_2), 41.0 (CH_2), 42.5 (CH_2), 92.7 (C), 126.1 (CH), 127.4 (CH), 128.2 (CH), 128.5 (CH), 128.7 (CH), 138.4 (C), 140.9 (C) and 175.6 (C═O); MS *m/z* 295 (M^+, 2%), 277 ($M-H_2O$, 84), 248 (16), 186 (65), and 91 (100).

The hydroxy lactam **8a** (100 mg) was dissolved in TFA and heated under reflux for 72 h. After the usual work-up, flash chromatography on silica and elution with ether/DCM (5:95) afforded *1′-benzyl-2,3-dihydrospiro[1H-indene-1:2′-pyrrolidin]-5′-one* **10a** (35 mg, 37%) as a colourless oil (HREIMS Found M^+ 277.1498. $C_{19}H_{19}NO$ requires *M* 277.1467); R_f 0.54 (ether/chloroform 1:9); IR ν_{max}/cm^{-1} 3000, 2950, 1670, 1600, 1490, 1450, 1430, 1400 and 1355; ^1H NMR (90 MHz) δ 1.95–2.30 (4H, m, 2×CH_2), 2.50–2.90 (4H, m, CH_2CO and CH_2Ph), 3.85 and 4.67 (each 1H, d, *J* 15.4 Hz, NCH_2) and 6.95–7.25 (9H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 29.4 (CH_2), 30.1 (CH_2), 34.8 (CH_2), 37.1 (CH_2), 43.9 (CH_2), 74.9 (spiro C), 123.2 (CH), 125.1 (CH), 127.0 (CH), 127.1 (CH), 127.7 (CH), 128.3 (CH), 128.5 (CH), 138.5 (C), 143.0 (C), 144.2 (C) and 175.5 (C═O); MS *m/z* 277 (M^+, 100%), 248 (13), 200 (8), 186 (10), 146 (23), 130 (32) and 91 (50).

The Grignard reagent was prepared from 1-bromo-3-phenylpropane (1.85 g, 10 mmol) and reacted with *N*-benzylsuccinimide **6** (1.50 g, 7.94 mmol) with stirring overnight. Work-up according to the general procedure gave a crude product as a yellow oil (3.75 g) and flash chromatography on silica and elution with a solvent gradient (ether/DCM 50:50 to methanol/ether/DCM 5:50:45) afforded *1-benzyl-5-hydroxy-5-(3-phenylpropyl)pyrrolidin-2-one* **8b** (1.55 g, 50%) as a pale yellow oil (HREIMS Found M^+ 309.1704. $C_{20}H_{23}NO_2$ requires *M* 309.1732); R_f 0.50 (methanol/chloroform 1:9); IR ν_{max}/cm^{-1} 3575, 3000, 1675 (C═O), 1600, 1490, 1455, 1410 and 1355; ^1H NMR (90 MHz) δ 1.02–1.61 (10H, m, 5×CH_2), 4.15–4.60 (2H, m, NCH_2) and 6.92–7.25 (10H, m aryl H); ^{13}C NMR (22.5 MHz) δ 25.8 (CH_2), 29.0 (CH_2), 32.0 (CH_2), 35.6 (CH_2), 38.9 (CH_2), 42.4 (CH_2), 92.8 (C), 125.9 (CH), 127.3 (CH), 128.2 (CH), 128.3 (CH), 128.5 (CH), 138.5 (C), 141.7 (C) and 175.5 (C═O); MS *m/z* 309 (M^+, <1%), 291 ($M-H_2O$, 2%), 200 (100) and 91 (55).

The hydroxy lactam **8b** (240 mg) was dissolved in TFA and heated under reflux for 72 h. After the usual work-up, flash chromatography on silica and elution with ether/DCM (5:95) afforded 1′-benzyl-1,2,3,4-tetrahydrospiro[naphthalene-1:2′-pyrrolidin]-5′-one **10b** (80 mg, 35%) as a colourless oil (HREIMS Found M^+ 291.1632. $C_{20}H_{21}NO$ requires *M* 291.1623); R_f 0.52 (ether/chloroform 1:9); IR ν_{max}/cm^{-1} 3000, 2950, 1670, 1600, 1485, 1450, 1430, 1405 and 1355; ^1H NMR (90 MHz) δ 1.62–1.87 (4H, m, 2- and 3–CH_2), 2.13 and 2.20 (each 1H, dt, *J* 13.0, 8.0 Hz, 3′–CH_2), 2.63 (2H, t, *J* 8.0 Hz, 4′–CH_2), 2.71–2.77 (2H, m, 4–CH_2), 3.65 and 4.88 (each 1H, d, *J* 15.6 Hz, NCH_2Ph) and 7.03–7.27 (9H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 20.1 (CH_2), 29.3 (2 lines, CH_2), 35.4 (CH_2), 36.3 (CH_2), 44.5 (CH_2), 67.1 (spiro C), 125.9 (CH), 126.6 (CH), 127.0 (CH), 127.4 (CH), 128.4 (CH), 128.8 (CH), 129.6 (CH), 137.8 (C), 138.7 (C), 139.3 (C) and 176.3 (C═O); MS *m/z* 291 (M^+, 1%), 248 (15), 200 (10), 163 (35), 146 (35), 106 (30) and 91 (83).

The Grignard reagent was prepared from 1-bromo-2-(3,4-methylenedioxyphenyl)ethane **19a** (1.0 g, 4.4 mmol) and reacted with *N*-benzylsuccinimide **6** (0.28 g, 1.5 mmol) according to the general procedure. After flash chromatography on silica and elution with ether/DCM (1:9) 1-benzyl-5-hydroxy-5-{2-(3,4-methylenedioxyphenyl)ethyl}pyrrolidin-2-one **20a** (0.43 g, 85%) was obtained as a pale yellow foam; R_f 0.42 (methanol/chloroform 1:9); ^1H NMR (90 MHz) δ 1.85–2.85 (8H, m, 4×CH_2), 3.20 (1H, br, OH), 4.28–4.85 (2H, m, NCH_2), 5.88 (2H, s, OCH_2O), 6.28–6.70 (3H, m, aryl H) and 7.25 (5H, br, aryl H); ^{13}C NMR (22.5 MHz) δ 21.3 (CH_2), 28.1 (CH_2), 28.8 (CH_2), 32.2 (CH_2), 43.7 (CH_2), 100.8 (CH_2), 108.1 (CH), 108.5 (CH), 120.5 (CH), 127.1 (CH), 127.3 (CH), 128.6 (CH), 134.7 (C), 136.0 (C), 139.9 (C), 145.7 (C), 147.6 (C) and 175.5 (C═O); MS *m/z* M^+ absent, 321 ($M-H_2O$, 80%), 292 (4), 230 (41), 186 (55), 135 (34), 91 (100) and 77 (10). This hydroxy lactam **20a** (0.26 g) was dissolved in TFA (10 mL) and heated under reflux for 24 h. After work-up, flash chromatography on silica and elution with ether/DCM (1:9) afforded *1′-benzyl-5,6-methylenedioxy-2,3-dihydrospiro[1H-indene-1:2′-pyrrolidin]-5′-one* **21a** (70 mg, 28%) as a colourless foam (HREIMS Found M^+ 321.1364. $C_{20}H_{19}NO_3$ requires *M* 321.1365); R_f 0.45 (ether/chloroform 1:9); ^1H NMR (90 MHz) δ 1.96–2.23 (4H, m, 2×CH_2), 2.52–2.77 (4H, m, 2×CH_2), 3.92 and 4.56 (each 1H, d *J* 15.3 Hz, NCH_2), 5.90 (2H, s, OCH_2O), 6.37 and 6.63 (each 1H, s, H-4 and H-7) and 7.04–7.28 (5H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 29.3 (CH_2), 30.0 (CH_2), 34.6 (CH_2), 37.5 (CH_2), 43.6 (CH_2), 74.7 (spiro C), 101.2 (CH_2), 103.3 (CH), 104.9 (CH), 126.9 (CH), 127.6 (CH), 128.1 (CH), 136.3 (C), 136.7 (C), 138.5 (C), 147.2 (C), 148.3 (C) and 175.0 (C═O); MS *m/z* 321 (M^+, 92%), 292 (15), 264 (18), 230 (7), 187 (34), 174 (100) and 91 (42). A repeat of the experiment using a less pure sample of hydroxy lactam **20a** gave, in addition to the spiro compound **21a**, a small quantity of *N-benzyl-3-(1-benzyl-5-oxopyrrolidin-5-ylidene)succinimide* **22** as a colourless foam (HREIMS Found M^+ 360.1477. $C_{22}H_{20}N_2O_3$ requires *M* 360.1474); R_f 0.35 (ether/chloroform 1:9); IR ν_{max}/cm^{-1} 3000, 1740 and 1690 (C═O), 1625 and 1430; ^1H NMR (300 MHz) δ 2.69–2.74 and 3.44–3.49 (each 2H, m, CH_2CH_2), 3.26 (2H, br s, CH_2), 4.64 and 4.94 (each 2H, s, NCH_2), 7.03–7.06 (2H, m, aryl H) and 7.25–7.38 (8H, m, aryl H); ^{13}C NMR (75 MHz) δ 25.5 (CH_2), 27.6 (CH_2), 33.0 (CH_2), 42.0 (CH_2), 44.5 (CH_2), 92.2 (C), 125.1 (CH), 127.6 (CH), 127.7 (CH), 128.6 (CH), 128.8 (CH), 129.3 (CH), 135.8 (C), 136.1 (C), 152.4 (C), 170.9 (C═O), 173.5 (C═O) and 177.6 (C═O); MS *m/z* 360 (M^+, 40%), 269 (16), 241 (10), 198 (7), 171 (7), 149 (8), 137 (20) and 91 (100).

The Grignard reagent was prepared from 1-bromo-3-(3,4-methylenedioxyphenyl)propane **19b** (0.63 g, 2.6 mmol) and reacted with *N*-benzylsuccinimide **6** (0.35 g, 1.85 mmol) according to the general procedure. After flash chromatography on silica and elution with a solvent gradient [ether/DCM (1:9) to methanol/ether/DCM (2:10:88)] *1-benzyl-5-hydroxy-5-[3-(3,4-methylenedioxyphenyl)propyl]pyrrolidin-2-one* **20b** (125 mg, 19%) was obtained as a pale yellow foam (HREIMS Found *m/z* 353.1614. $C_{21}H_{23}NO_4$ requires *M* 353.1627); R_f 0.30 (methanol/chloroform 1:9); IR ν_{max}/cm^{-1} 3575 (OH), 3000, 2920, 1670 (C=O), 1600, 1500 and 1485; ^{1}H NMR (90 MHz) δ 1.15–2.65 (10H, m, 5×CH_2), 3.74 (1H, s, OH), 4.14–4.63 (2H, m, NCH_2), 5.88 (2H, s, OCH_2O), 6.37–6.74 (3H, m, aryl H) and 7.27 (5H, s, aryl H); ^{13}C NMR (22.5 MHz) δ 26.0 (CH_2), 29.0 (CH_2), 32.0 (CH_2), 35.3 (CH_2), 38.7 (CH_2), 42.4 (CH_2), 92.8 (C), 100.7 (CH_2), 108.0 (CH), 109.0 (CH), 121.1 (CH), 127.1 (CH), 128.1 (CH), 128.5 (CH), 135.5 (C), 138.5 (C), 145.6 (C), 147.5 (C) and 175.5 (C=O); MS *m/z* 353 (M^+, 1%), 335 ($M-H_2O$, 5), 200 (95), 148 (30) and 91 (100).

The hydroxy lactam **20b** (80 mg) was dissolved in TFA (10 mL) and heated under reflux for 48 h. After the usual work-up, flash chromatography on silica and elution with ether/DCM (20:80) afforded *1′-benzyl-6,7-methylenedioxy-1,2,3,4-tetrahydrospiro[naphthalene-1,2′-pyrrolidin]-5′-one* **21b** (24 mg, 32%) as a pale yellow foam (HREIMS Found 335.1540. $C_{12}H_{21}NO_3$ requires *M* 335.1521); R_f 0.68 (ether/chloroform 1:9); IR ν_{max}/cm^{-1} 3000, 1780, 1710, 1585, 1570, 1440, 1400, 1350 and 1330; ^{1}H NMR (90 MHz) δ 1.62–1.87 (4H, m, 2×CH_2), 2.01–2.26 (2H, m, CH_2), 2.47–2.88 (4H, m, 2×CH_2), 3.72 and 4.80 (each 1H, d *J* 15.5 Hz, NCH_2), 5.89 (2H, s, OCH_2O), 6.47 and 6.55 (each 1H, s, H-5 and H-8) and 7.15–7.26 (5H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 20.4 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 35.1 (CH_2), 36.1 (CH_2), 44.3 (CH_2), 67.1 (spiro C), 101.0 (CH_2), 105.8 (CH), 108.7 (CH), 125.3 (CH), 126.9 (CH), 127.9 (CH), 128.3 (CH), 131.4 (C), 132.4 (C), 138.7 (C), 146.4 (C), 146.9 (C) and 175.9 (C=O); MS *m/z* 335 (M^+, 70%), 292 (30), 278 (9), 202 (8), 188 (100), 174 (8), 163 (19), 149 (12) and 91 (83).

2.4.3. Enamide 30 and spiro products 28 and 29 derived from *N*-2,6-difluoro- and *N*-2,6-dichlorobenzylsuccinimide. The Grignard reagent was prepared from 1-bromo-2-phenylethane (3.3 g, 18 mmol) and reacted with *N*-(2,6-difluorobenzyl)succinimide **24** (1.0 g, 4.4 mmol) according to the general procedure. The crude product was a complex mixture. Flash chromatography on silica and elution with a solvent gradient (ether/DCM 1:9 to methanol/ether/DCM 2:10:88) afforded a mixture of low-running components as a yellow oil (250 mg). This was dissolved in TFA and heated under reflux for 48 h. After the usual work-up and flash chromatography on silica, elution with ether/DCM (1:9) afforded 2,3-dihydro-1′-(2,6-difluorobenzyl)spiro[1H-indene-1,2′-pyrrolidin]-5′-one **28** (52 mg), mp 62–66°C (DCM) (HREIMS Found M^+ 313.1287. $C_{19}H_{17}F_2NO$ requires *M* 313.1278); R_f 0.50 (ether/chloroform 1:9); IR ν_{max}/cm^{-1} 3000, 1675 (C=O), 1630, 1595, 1470 and 1400; ^{1}H NMR (300 MHz) δ 2.05–2.45 (4H, m, 2×CH_2), 2.55–2.65 (2H, m, CH_2CO), 2.85–2.95 (2H, m, (CH_2Ar), 4.30–4.70 (2H, m, NCH_2), 6.62 (1H, t, *J* 8.0 Hz, aryl H) and 6.60–7.30 (6H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 30.7 (CH_2), 31.2 (CH_2), |32.6, 32.8, 33.0| (CH_2), 36.5 (CH_2), 36.6 (CH_2), 76.7 (spiro C), |111.8, 112.1, 113.0, 113.2| (CH), |113.8, 114.5, 115.2| (C), 124.5 (CH), 126.2 (CH), 127.1 (C), 128.1 (CH), 129.7 (CH), |130.5, 131.0, 131.5| (CH), 144.5 (C), |157.4, 157.6, 168.4, 168.8| (CF) and 177.6 (C=O); MS *m/z* 313 (M^+, 51%), 186 (14), 143 (89), 142 (86), and 127 (100).

The Grignard reagent was prepared from 1-bromo-2-phenylethane (2.2 g, 12 mmol) and reacted with *N*-(2,6-dichlorobenzyl)succinimide **25** (1.0 g, 3.9 mmol) according to the general procedure. The crude product was again a complex mixture, from which flash chromatography on silica and elution with a solvent gradient (ether/DCM 1:4 to methanol/ether/DCM 2:20:78) separated a mixture of low-running components as a yellow oil (0.33 g). This was dissolved in TFA and heated under reflux for 48 h. After the usual work-up and flash chromatography on silica, elution with ether/DCM (1:19) afforded *N-(2,6-dichlorobenzyl)-2-[1-(2,6-dichlorobenzyl)-5-oxopyrrolidin-5-ylidene]succinimide* **23** (33 mg), mp 185–188°C (HREIMS Found $[M-Cl]^+$ 461.0009. $C_{22}H_{16}{}^{35}Cl_3N_2O_3$ requires 461.0015); IR ν_{max}/cm^{-1} 3000, 1740 and 1690 (C=O), 1620, 1570, 1550, 1430 and 1390; ^{1}H NMR (300 MHz) δ 2.51–2.56 (2H, m, CH_2), 3.36–3.39 (4H, m, 2×CH_2), 4.98 and 5.13 (each 2H, s, NCH_2), 7.14–7.21 (2H, m aryl H) and 7.29–7.33 (4H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 25.8 (CH_2), 27.4 (CH_2), 33.1 (CH_2), 38.7 (CH_2), 42.6 (CH_2), 95.9 (C), 128.4 (CH), 129.3 (CH), 130.5 (C), 130.6 (C), 134.9 (C), 136.2 (C), 153.0 (C) and 170.3, 172.5 and 177.7 (C=O); MS M^+ peaks absent, *m/z* 465/463/461 (M−Cl, 30/91/91%), 234 (25), 232 (77), 161 (64), 159 (100), 123 (15) and 91 (20).

The Grignard reagent was prepared from 1-bromo-2-phenylethane (1.5 g, 8 mmol) and reacted with succinimide (0.20 g, 2 mmol) according to the general procedure. The crude product was a brown oil (0.40 g), which was redissolved in acetonitrile and stirred with caesium carbonate (4.0 g) during addition of 2,6-dichlorobenzyl bromide (2.0 g) and for further 4 days. The mixture was filtered, the filtrate evaporated in vacuo, and the residue chromatographed on silica, from which ether/DCM (1:19) eluted *1-(2,6-dichlorobenzyl)-5-(2-phenylethylidene)-pyrrolidin-2-one* **30**, colourless oil (0.53 g, 77% from succinimide), as a mixture of stereoisomers (HREIMS Found M^+ 345.0687. $C_{19}H_{17}{}^{35}Cl_2NO$ requires 345.0687); R_f 0.69 (ether/chloroform 1:9); IR ν_{max}/cm^{-1} 3010, 1710, 1675, 1605, 1580, 1520, 1495, 1475, 1440 and 1405; ^{1}H NMR (90 MHz) δ 2.50–2.85 (4H, m, 2×ring CH_2), 3.24 (2H, t, *J* 7.7 Hz, PhCH_2CH), 4.51–5.01 (3H, m, PhCH_2C*H* and NCH_2) and 6.82–7.34 (8H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 21.1 (CH_2), 28.8 (CH_2), 32.4 (CH_2), 40.0 (CH_2), 100.4 (CH), 125.7 (CH), 127.6 (CH), 128.2 (CH), 128.3 (CH), 128.8 (CH), 129.1 (CH), 13.9 (C), 135.8 (C), 136.3 (C), 139.5 (C), 140.8 (C) and 175.3 (C=O); MS *m/z* 349/347/345 (M^+, 1/8/13%), 312/310 (M−Cl, 22/66), 224/222 (15/46), 220/218 (19/55), 186 (9), 161 (44), 159 (68), 143 (8), 141 (18), 123 (15) and 91 (100). Additional ^{13}C NMR signals attributable to the minor stereoisomer δ 28.0, 29.6, 38.8, 136.6 and 176.2.

The enamide **30** (140 mg) was dissolved in TFA (15 mL) and heated under reflux for 4 days. The usual work-up was

followed by flash chromatography on silica and elution with ether/DCM (1:19) to give 2,3-dihydro-1′-(2,6-dichlorobenzyl)spiro[1H-indene-1,2′-pyrrolidin]-5′-one **29**, colourless oil (38 mg, 27%), together with recovered starting material **30** (35 mg). Data for **29**: (HREIMS Found $[M-Cl]^+$ 310.0995, $C_{19}H_{17}{}^{35}ClNO$ requires 310.0999); R_f 0.57 (ether/chloroform 1:9); IR ν_{max}/cm^{-1} 3000, 1710, 1675, 1580, 1560, 1440 and 1390; ^1H NMR (90 MHz) δ 1.96–2.87 (8H, m, 4×ring CH_2), 4.55 and 5.03 (each 1H, d, J 15.0 Hz, NCH_2) and 6.68–7.26 (7H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 29.3 (CH_2), 29.9 (CH_2), 33.4 (CH_2), 35.4 (CH_2), 39.0 (CH_2), 74.9 (spiro C), 123.2 (CH), 124.6 (CH), 126.2 (CH), 127.8 (CH), 128.1 (CH), 128.7 (CH), 132.7 (C), 136.4 (C), 142.6 (C), 143.2 (C) and 174.9 (C═O); MS M^+ peaks absent, m/z 312/310 (M−Cl, 34/100%), 201 (7), 163 (9), 159 (14), 151 (24) and 113 (20).

The spiro compound **29** (30 mg) was dissolved in methanol (10 mL) and shaken with Pearlman's catalyst (palladium hydroxide on charcoal) under an atmosphere of hydrogen for 24 h. After filtration and removal of solvent, the residue was flash chromatographed on silica. Elution with ether/DCM (1:19) afforded the chlorine-free *N*-benzyl spiro lactum **10a** (17 mg), which was identical by tlc and ^1H NMR spectrum with the sample obtained by cyclisation of **8a**.

2.4.4. Ketoamide 32, hydroxy lactum 33a,b and spiro products 34a,b and 35b derived from *N*-(1-phenylethyl)-succinimide. The Grignard reagent was prepared from 1-bromo-2-phenylethane (0.74 g, 4 mmol) and reacted with *N*-(1-phenylethyl)succinimide **31** (0.30 g, 1.5 mmol) according to the general procedure. After the usual work-up, flash chromatography on silica eluted with a solvent gradient (ether/DCM 5:95 to methanol/ether/DCM 2:5:93) afforded the dimer *N-(1-phenylethyl)-4-[1-(1-phenylethyl)-2,5-dioxopyrrolidin-3-yl]-4-oxobutanamide* **36** (0.25 g, 84%) as a pale yellow foam (HREIMS Found M^+406.1900. $C_{24}H_{26}N_2O_4$ requires M 406.1893); R_f 0.59 (methanol/chloroform 1:9); IR ν_{max}/cm^{-1} 3000, 1775, 1700, 1675, 1600, 1500, 1450 and 1400; ^1H NMR (90 MHz) δ 1.44 (3H, d, J=6.8 Hz, NCH(CH_3)Ph), 1.75 (3H, dd, J=6.8, 2.4 Hz, NHCH(CH_3)Ph), 2.15–2.61 (4H, m, 2×CH_2), 2.97–3.15 (2H, m, CH_2CH), 3.80–4.00 (1H, m, CH_2CH), 5.03 (1H, apparent quintet, J 7.2 Hz, NHCH(CH_3)Ph), 5.36 (1H, q, J 6.8 Hz, NCH(CH_3)Ph), 5.98 (1H, br d, J 7.2 Hz, NH) and 7.05–7.49 (10H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 16.4 (CH_3), 21.8 (CH_3), 30.0 (CH_2), 35.9 (CH_2), 38.0 (CH_2), 49.0 (CH), 50.7 (CH), 52.8 (CH), 126.1 (CH), 127.3 (CH), 127.9 (CH), 128.5 (CH), 128.6 (CH), 139.1 (C), 143.2 (C), 170.3 (C═O), 172.5 (C═O), 175.4 (C═O) and 201.5 (C═O); MS m/z 406 (M^+, 6%), 285 (3), 219 (19), 201 (9), 160 (15), 120 (91) and 105 (100).

Anhydrous cerium(III) chloride was prepared from the trihydrate (373 mg, 1.0 mmol) in a 3-neck flask equipped with a magnetic stirring bar suspended above the solid by means of a second magnet external to the flask. The flask was heated to 135–140°C and evacuated to 2 mm Hg pressure. After 1 h the external magnet was removed to free the internal stirring bar and the solid was stirred for further 2 h to afford a free-flowing white powder. The flask was cooled to −20°C and dry THF (2 mL) added via syringe with rapid stirring. After stirring for 30 min, the cerium chloride was further activated by sonication for 1 h at room temperature.[22] The Grignard reagent was prepared from 1-bromo-2-phenylethane (185 mg, 1.0 mmol) in ether (3 mL) and added to the flask containing cerium chloride, which was stirred for 2 h, then cooled to −78°C. *N*-(1-Phenylethyl)succinimide **31** (101 mg, 0.50 mmol) in dry THF (6 mL) was added with stirring and the mixture was allowed to warm slowly to room temperature with stirring overnight. After the usual work-up, a colourless oil (188 mg) was obtained, which was flash chromatographed on silica. Elution with a solvent gradient (DCM to ether/DCM 1:9) separated *N-(1-phenylethyl)-4-oxo-6-phenylhexanamide* **32** (94 mg, 61%), unreacted succinimide **31** (17 mg) and still unresolved mixture of these two (42 mg). Data for **32**: (HREIMS Found M^+ 309.1740. $C_{20}H_{23}NO_2$ requires M 309.1729); R_f 0.35 (ether/chloroform 1:9); IR ν_{max}/cm^{-1} 3430, 3080, 3060, 3000, 1710, 1665, 1600, 1510, 1455, 1420 and 1375; ^1H NMR (90 MHz) δ 1.44 (3H, d, J 7.0 Hz, CHCH_3), 2.32–2.95 (8H, m, 4×CH_2), 5.06 (1H, dq, J 7.3, 7.0 Hz, CHCH$_3$), 6.17 (1H, br d, J 7.3 Hz, NH) and 7.13–7.28 (10H, m aryl H); ^{13}C NMR (22.5 MHz) δ 21.9 (CH_3), 29.7 (CH_2), 30.0 (CH_2), 37.8 (CH_2), 44.2 (CH_2), 48.8 (CH), 126.1 (CH), 127.3 (CH), 128.2 (CH), 128.5 (CH), 128.6 (CH), 140.9 (C), 143.3 (C), 170.9 (C═O) and 209.1 (C═O); MS m/z 309 (M^+, 50%), 208 (22), 188 (10), 177 (10), 161 (9), 152 (29), 133 (7), 121 (74), 107 (94), 106 (100), 101 (15), 92 (79), 79 (15), 78 (23) and 57 (13).

The ketoamide **32** (31 mg) was dissolved in dry chloroform (5 mL) and treated with successive addition of small quantities of TFA, with monitoring by tlc. With 5 equiv. of TFA (40 μL) slow appearance of a new product was observed. The solution was worked up after 3 days at room temperature and a pale yellow oil is obtained (31 mg). Flash chromatography of this on silica, eluting with a solvent gradient (ether/DCM 5:95 to methanol/ether/DCM 2:5:95), separated (*R*)-1-(1-phenylethyl)-5-(2-phenylethylidene)pyrrolidin-2-one **33a** (11 mg, 39%) as a mixture of *E* and *Z* stereoisomers and unreacted ketoamide **32** (18 mg). Data for **33a**: (HREIMS Found M^+ 291.1623. $C_{20}H_{21}NO$ requires M 291.1623); R_f 0.63 (ether/chloroform 1:9); IR ν_{max}/cm^{-1} 3000, 2940, 1700, 1660, 1520, 1490, 1450 and 1400; ^1H NMR (90 MHz) δ 1.74 (3H, d, J 7.2 Hz, CHCH_3), 2.61 (4H, br s, 2×ring CH_2), 3.22 (2H, d, J 7.7 Hz, CHCH_2), 4.66 (1H, br t, J 7.7 Hz, CHCH$_2$), 5.71 (1H, q, J 7.2 Hz, CHCH$_3$) and 6.82–7.49 (10H, m aryl H); ^{13}C NMR (22.5 MHz) δ 15.6 (CH_3), 21.4 (CH_2), 29.0 (CH_2), 32.8 (CH_2), 49.1 (CH), 102.2 (CH), 125.9 (CH), 126.6 (CH), 127.0 (CH), 127.9 (CH), 128.3 (CH), 128.5 (CH), 138.4 (C), 139.8 (C), 141.0 (C) and 175.9 (C═O), and additional lines due to the minor stereoisomer δ 16.6 (CH_3), 28.2 (CH_2), 50.4 (CH) and 97.3 (CH); MS m/z 291 (M^+, 28%), 203 (26), 200 (7), 187 (41), 160 (46), 105 (100), 91 (55), 84 (36) and 77 (43).

The ketoamide **32** (60 mg) was dissolved in TFA (10 mL) and heated under reflux for 48 h. After work-up, yellow oil was obtained (57 mg) and flash chromatographed on silica. Elution with ether/DCM afforded *2,3-dihydrospiro[1H-indene-1,2′-pyrrolidin]-5′-one* **34a** (25 mg, 69%), colourless cubic crystals, mp 131–132°C (methanol) (Found: C, 77.0; H, 7.0; N, 7.5. $C_{12}H_{13}NO$ requires C, 77.0; H, 7.1; N,

7.4%); R_f 0.18 (ether/chloroform 1:9); IR ν_{max}/cm^{-1} 3430 (N–H), 3000, 1690 (C═O), 1600, 1520, 1480, 1460, 1400 and 1350; ^1H NMR (300 MHz) δ 2.13–2.38 (4H, m, 2×CH_2), 2.49–2.54 (2H, m, 4′-CH_2), 2.89–2.95 (2H, m, 3-CH_2), 6.36 (1H, br s, NH) and 7.22–7.30 (4H, m, aryl H); ^{13}C NMR (75 MHz) δ 29.1 (CH_2), 30.6 (CH_2), 35.1 (CH_2), 40.3 (CH_2), 69.6 (spiro C), 122.3 (CH), 124.9 (CH), 127.2 (CH), 128.2 (CH), 142.1 (C), 146.3 (C) and 177.6 (C═O); MS *m/z* 187 (M, 100%), 158 (42), 144 (77), 131 (71), 115 (23), 103 (15), 91 (12), 86 (29), 84 (54), 77 (17) and 49 (60). In another experiment the enamide **33a** (21 mg) was dissolved in TFA and changes monitored by tlc. No reaction was observed over 3 days at room temperature, so the solution was heated at 50°C for 48 h and then at 70°C for 48 h, when conversion to the spiro compound **34a** was complete. After flash chromatography **34a** (13 mg, 92%) was isolated and shown to be identical to the sample obtained directly from the ketoamide **32**.

Anhydrous cerium(III) chloride was prepared from the trihydrate (5.4 g, 14.5 mmol) as before, suspended in dry THF (20 mL) and further activated by sonication.[22] The Grignard reagent was prepared from 1-bromo-3-phenylpropane (2.0 g, 10 mmol) in ether (10 mL) and added to the cerium chloride suspension, which was stirred at room temperature for 2 h, then cooled to −78°C. *N*-(1-Phenylethyl)succinimide **31** (1.01 g, 5 mmol) in THF (20 mL) was added dropwise with stirring, the mixture was allowed to warm slowly to room temperature and stirred overnight. After the usual work-up procedure involving some troublesome separation of precipitated solids, then flash chromatography on silica eluting with a solvent gradient (ether/DCM 5:95 to methanol/ether/DCM 5:5:90) afforded *(R)-1-(1-phenylethyl)-5-(3-phenylpropylidene)pyrrolidin-2-one* **33b**, colourless oil (0.38 g, 25%). The aqueous phase from work-up together with precipitates was acidified to pH 1 by addition of hydrochloric acid (6 M) and extracted with chloroform. The extract afforded further crude material (0.60 g) from which flash chromatography on silica eluting with a solvent gradient (DCM to ether/DCM 5:95) separated more of the enamide **33b** (0.10 g, total yield 32%) and unreacted imide **31** (225 mg). Data for **33b**: (HREIMS Found M^+ 305.1781. $C_{21}H_{23}NO$ requires *M* 305.1780); R_f 0.77 (ether/chloroform 1:9); $[\alpha]_D$+23.1 (*c*=4.0, DCM); IR ν_{max}/cm^{-1} 3050, 2980, 2300, 1700, 1665, 1600, 1520, 1470 and 1420; ^1H NMR (90 MHz) δ 1.65 (3H, d, *J* 7.2 Hz, C*H*$_3$CH), 2.08–2.53 (8H, m, 4×CH_2), 4.41 (1H, br t, *J* 7.6 Hz, C*H*CH_2), 5.62 (1H, q, *J* 7.2 Hz, CH_3C*H*) and 6.86–7.37 (10H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 15.6 (CH_3), 21.0 (CH_2), 28.9 (CH_2), 29.2 (CH_2), 36.1 (CH_2), 48.8 (CH), 102.7 (CH), 125.6 (CH), 126.5 (CH), 126.8 (CH), 128.0 (CH), 128.2 (CH), 128.5 (CH), 137.6 (C), 139.7 (C), 141.5 (C) and 175.7 (C═O); MS *m/z* 305 (M^+, 3%), 214 (37), 110 (100), 105 (78), 91 (13) and 77 (13).

The enamide **33b** (227 mg) was dissolved in TFA (10 mL) and heated under reflux for 48 h. The usual work-up was followed by flash chromatography on silica, eluting with a solvent gradient (DCM to ether/DCM 1:9 to methanol/ether/DCM 5:10:85), to afford *1′-(1-phenylethyl)-1,2,3,4-tetrahydrospiro[naphthalene-1,2′-pyrrolidin]-5′-one* **34b** (38 mg, 25%) and *1,2,3,4-tetrahydrospiro[naphthalene-1,2′-pyrrolidin]-5′-one* **35b** (57 mg, 58%). Data for **34b**: colourless oil (HREIMS Found M^+ 201.1161. $C_{13}H_{15}NO$ requires *M* 201.1154); R_f 0.58 (methanol/chloroform 1:9); $[\alpha]_D$0.0; IR ν_{max}/cm^{-1} 3420 (N–H), 3000, 2940, 2870, 1690, 1600, 1520, 1490, 1420, 1400 and 1340; ^1H NMR (90 MHz) δ 1.86–2.56 (8H, m, 4×CH_2), 2.72–2.78 (2H, m, 4–CH_2), 6.57 (1H, br s, NH) and 7.04–7.41 (4H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 20.2 (CH_2), 29.2 (CH_2), 29.9 (CH_2), 36.8 (CH_2), 37.1 (CH_2), 60.8 (spiro C), 126.1 (CH), 126.5 (CH), 127.2 (CH), 129.0 (CH), 136.7 (C), 141.2 (C) and 177.6 (C═O); MS *m/z* 201 (M^+, 86%), 173 (100), 158 (19), 144 (66), 130 (45), 117 (33), 105 (18), 91 (15) and 77 (15). Data for **35b**: colourless oil; ca. 3:1 mixture of two diastereoisomers; R_f 0.60 (ether/chloroform 1:9); IR ν_{max}/cm^{-1} 3000, 2940, 2300, 1670, 1600, 1520, 1450, 1420 and 1350; ^1H NMR (300 MHz) (minor distereoisomer in italics) δ 1.67 and 1.80 (3H, d, *J* 7.2 Hz, C*H*$_3$CH), 1.64–2.27 (6H, m, 3×CH_2), 2.49–2.62 (2H, m, 4′-CH_2), 2.73–2.85 (2H, m, 4-CH_2), 3.92 and 4.22 (1H, q, *J* 7.2 Hz, CH_3C*H*) and 6.90–7.38 (9H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 20.3 and 20.7 (CH_2), 20.1 and 21.1 (CH_3), 29.5 and 29.7 (CH_2), 30.4 and 30.5 (CH_2), 33.5 and 35.1 (CH_2), 36.4 and 36.6 (CH_2), 54.2 and 55.0 (CH), 68.5 and 68.8 (spiro C), 125.9 and 126.6 (CH), 126.7 (CH), 126.8 (CH), 127.0 and 127.1 (CH), 127.4 and 127.7 (CH), 128.3 (CH), 128.8 and 129.5 (CH), 137.7 and 138.0 (C), 139.3 and 140.2 (C), 142.7 and 144.3 (C) and 175.7 and 176.1 (C═O); MS *m/z* 305 (M^+, 100%), 214 (8), 200 (12), 185 (10), 173 (14), 161 (53), 160 (52), 146 (37), 129 (27), 128 (26), 120 (32), 105 (81), 91 (13) and 77 (27).

Spiro lactam **35b** (31 mg) was dissolved in TFA (10 mL) and heated under reflux overnight. Tlc analysis indicated that no more than a trace amount of the debenzylated lactam **34b** was formed.

The Grignard reagent prepared from magnesium (1.94 g) and 1-bromo-3-phenylpropane (15.92 g, 80 mmol) in dry THF was added to succinimide (1.98 g, 20 mmol) in THF. The mixture was stirred for 3 days at room temperature before work-up, which gave a crude product contaminated with 1-phenylpropane and unreacted 1-bromo-3-phenylpropane. This crude material was dissolved in TFA (25 mL) and heated under reflux for 62 h, then cooled and worked up in the usual way. The crude product was washed with light petroleum and the residue recrystallised to afford *1′-(1-phenylethyl)-1,2,3,4-tetrahydrospiro[naphthalene-1,2′-pyrrolidin]-5′-one* **34b** (2.28 g, 57% from succinimide), mp 166–168°C (from ethanol), identical (tlc, ^1H NMR and mass spectra) with the sample obtained above from **33b**.

Spiro lactam **34b** (40 mg, 0.20 mmol) was dissolved in acetonitrile and stirred with caesium carbonate (750 mg) during addition of benzyl bromide (500 mg). The mixture was heated under reflux for 48 h, then cooled, filtered, and the filtrate evaporated in vacuo. The residue was flash chromatographed on silica, eluting with ether/DCM (1:9), to give the *N*-benzyl spiro lactam **10b** identical (by TLC and ^1H NMR spectrum) with the material obtained previously by cyclisation of hydroxy lactam **8b**.

Spiro lactam **35b** (15 mg) was dissolved in THF (1 mL) and added to liquid ammonia (10 mL). Freshly cut sodium (23 mg) was added in small portions with stirring to maintain a blue colouration for 1 h. Solid ammonium

chloride was then added to quench the reaction, and the ammonia allowed to evaporate. Brine was added to the residue, which was then extracted with ethyl acetate; the organic extract was dried ($MgSO_4$), filtered, and the filtrate evaporated to give yellow oil. Flash chromatography on silica eluting with a solvent gradient (DCM to ether/DCM 1:9) afforded *N-(1-phenylethyl)-3-(1,2,3,4-tetrahydronaphth-1-yl)propanamide* **37** as a colourless oil (9 mg, 59%) (HREIMS Found M^+ 307.1929. $C_{20}H_{25}NO$ requires *M* 307.1936); R_f 0.71 (methanol/chloroform 1:9); IR ν_{max}/cm^{-1} 3425, 3000, 2925, 2860, 1660, 1600, 1500, 1450, 1420 and 1375; ^1H NMR (90 MHz) δ 1.48 (3H, d, *J* 6.8 Hz, C*H*$_3$CH), 1.62–2.81 (11H, m, 5×CH_2 and CH), 5.14 (1H, dq, *J* 7.6, 6.8 Hz, CH_3C*H*NH), 5.65 (1H, br d, *J* 7.6 Hz, NH) and 7.05–7.36 (9H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 19.8 (CH_2), 21.7 (CH_3), 27.5 (CH_2), 29.6 (CH_2), 32.2 (CH_2), 34.5 (CH_2), 37.1 (CH), 48.6 (CH), 125.6 (CH), 125.7 (CH), 126.2 (CH), 127.4 (CH), 128.7 (2 lines, CH), 129.1 (CH), 137.1 (C), 140.2 (C), 143.2 (C) and 171.9 (C═O); MS *m*/*z* 307 (M^+, 15%), 202 (3), 176 (13), 163 (91), 143 (10), 131 (22), 115 (13), 105 (100), 91 (21), 77 (15) and 59 (24). As **37** was a single diastereoisomer (^{13}C NMR spectrum), the yield is effectively 79% (from the major diastereoisomer of **35b**). Tlc analysis showed the presence of unreacted **35b** (the minor diastereoisomer?) in the crude product before chromatography.

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