Abualnaja M, Waddell PG, Clegg W, Hall MJ.

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Synthesis of pentacyclic pyrrolo[3,4-*a*]carbazole-1,3(2*H*)-diones via an intermolecular Diels-Alder, intramolecular carbonyl-ene reaction strategy

Matokah Abualnaja, Paul G. Waddell, William Clegg and Michael J. Hall*

School of Chemistry, Newcastle University, Newcastle upon Tyne, NE1 7RU, UK.
Email: michael.hall@ncl.ac.uk
Telephone: +44 (0) 191 208 7321
Fax: +44 (0) 191 208 6929

Abstract

Pentacyclic pyrrolo[3,4-*a*]carbazole-1,3(2*H*)-diones are accessed via two key synthetic steps, an intermolecular Diels-Alder (D-A) reaction between an *N*-protected 3-vinyl-1*H*-indole and *N*-methyl-maleimide, and a Lewis acid-catalysed intramolecular carbonyl-ene cyclisation reaction. Cyclopentyl- or cyclohexyl-containing scaffolds can be formed through variation in the length of the alkyl tether, whilst the observed stereospecificity of carbonyl-ene cyclisation supports a concerted mechanism.

Introduction

Pentacyclic tetrahydrocarbazoles are common scaffolds in a wide range of synthetic and naturally occurring bioactive molecules,[1] which has led to the development of a number of synthetic strategies for the derivatisation of indoles towards these targets.[2] In particular the D-A reactions of alkenyl-substituted heteroaromatics have been used extensively in synthesis of saturated carbazoles[3] and related molecules,[4] with recent examples including enantioselective[5] and multicomponent variants.[6] In this work we report a diastereoselective approach to the synthesis of polycyclic saturated carbazoles through an intermolecular Diels-Alder (D-A)/intramolecular carbonyl-ene reaction strategy.[7] We envisaged that an intermolecular D-A reaction of a substituted 3-alkenyl-1*H*-indole **1** would result in a reactive 2,3,9,9a-tetrahydro-1*H*-carbazole intermediate **2** capable of undergoing a further cyclisation, via a facially selective intramolecular carbonyl-ene reaction. Variation of the length of the alkyl chain bearing the aldehyde **2** would allow access to either cyclopentyl or cyclohexyl

rings **3**, whilst the stereochemistry of the alkene in the initial D-A reaction would determine the facial selectivity of the final cyclisation (Figure 1).

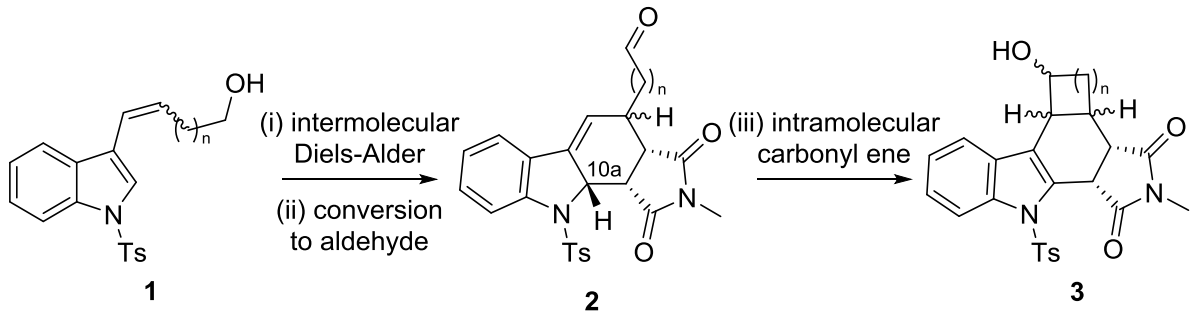
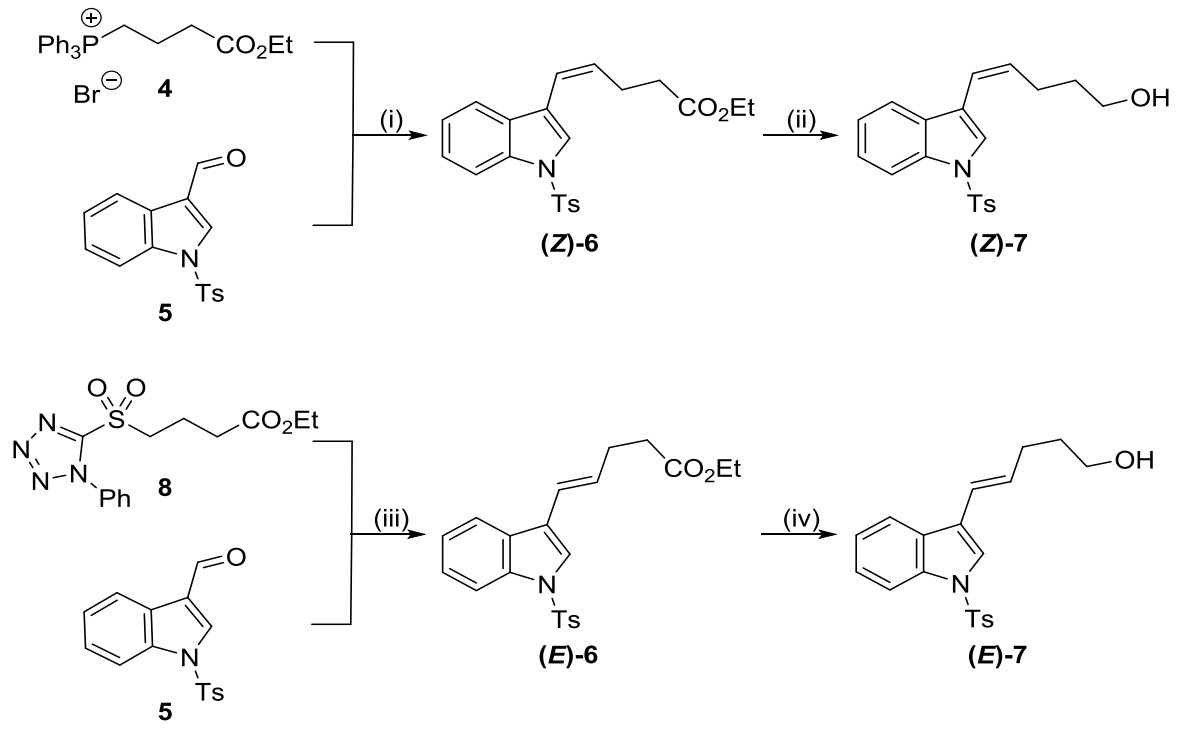


Figure 1. Proposed intermolecular Diels-Alder (D-A)/intramolecular carbonyl-ene reaction strategy for the diastereoselective synthesis of pentacyclic saturated carbazoles.

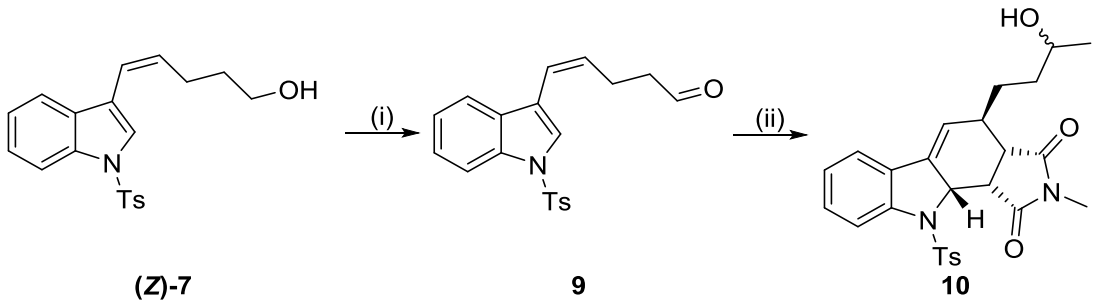
Results and discussion

We commenced our investigation with the synthesis of a number of (*E*)- and (*Z*)-3-alkenyl-1*H*-indoles as precursors for our planned intermolecular D-A/intramolecular carbonyl ene reactions. Thus protected indole-3-carbaldehyde **5** was reacted with ethyl 4-(triphenyl-λ^5-phosphanylidene)butanoate (generated *in situ* via the deprotonation of (4-ethoxy-4-oxobutyl)triphenylphosphonium bromide **4** by NaHMDS) to give, after chromatography, a 60% yield of (*Z*)-ethyl 5-(1-tosyl-1*H*-indol-3-yl)pent-4-enoate **6**. Subsequent DIBAL-H mediated reduction then gave the corresponding alcohol **7** in 87% yield. To access the corresponding *E*-isomer a Julia–Kocienski olefination was employed,[8] reacting the sodium salt of phenyltetrazolylsulfonyl ester **8**[9] with protected indole-3-carbaldehyde **5** to give ethyl 5-(1-tosyl-1*H*-indol-3-yl)pent-4-enoate **6** with excellent (*E*)-selectivity. Finally, reduction of ester with DIBAL-H gave the alcohol **7** as the (*E*)-isomer in a 96% isolated yield (Scheme 1).



Scheme 1. Reagents and conditions: (i) **4**, NaHMDS, -78 °C to 0 °C, 2 h, THF then **5**, r.t., 48 h, 60%; (ii) DIBAL-H, toluene, -78 °C, 3 h, 87%; (iii) **8**, NaHMDS, -78 °C to 0 °C, 2 h, THF then **5**, r.t. 14 h, 71%; (iv) DIBAL-H, toluene, -78 °C, 3 h, 96%.

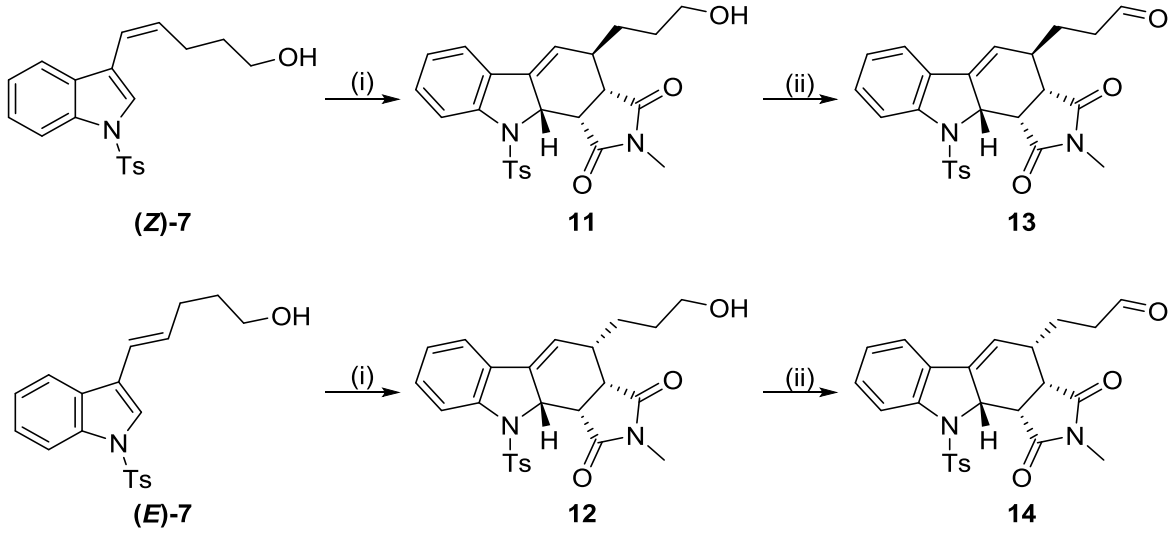
Preliminary examination of the proposed D-A reaction between **(*Z*)-7** or **(*E*)-7** and *N*-methylmaleimide gave no D-A cycloadducts under thermal conditions (DCM, *i*-PrOH or toluene at reflux for up to 5 days) or through thiourea-mediated organocatalysis (Schreiner's cat. 20% mol, DCM).[10] However the use of aluminium-based Lewis acids proved promising, with the corresponding D-A cycloadducts being formed in the presence of Me_2AlCl in refluxing DCM without the appearance of undesirable rearomatisation products. Thus we envisaged that a "one-pot" intermolecular D-A/intramolecular ene reaction might be feasible, employing Me_2AlCl to catalyse both steps. Therefore **(*Z*)-7** was oxidised under Swern conditions to give the corresponding aldehyde **9** and subsequently reacted with *N*-methylmaleimide in the presence of Me_2AlCl in refluxing DCM. Unfortunately, rather that the desired D-A/ene product we instead obtained alcohol **10** as a 3:2 mixture of diastereoisomers, resulting from a D-A reaction followed by an undesired preferential alkylation of the aldehyde by Me_2AlCl (Scheme 2).[11]



(*Z*)-7 **9** **10**

Scheme 2. Reagents and conditions: (i) DMSO, $C_2O_2Cl_2$, DCM, -78 °C to r.t., 3 h, 70%; (ii) 2 eq. Me_2AlCl, *N*-methylmaleimide, DCM, -78 °C to 40 °C, 48 h, 52%.

Since the aldehyde functionality was not well tolerated under the D-A reaction conditions, we decided to pursue a stepwise strategy in which the aldehyde would be masked as the corresponding primary alcohol during the D-A step and then revealed in a subsequent oxidation step. Thus 3-alkenyl-1*H*-indoles **(*Z*)-7** and **(*E*)-7** were reacted with *N*-methylmaleimide, in the presence of two equivalents of Me_2AlCl in refluxing DCM, to give high yields of the corresponding diastereomeric D-A cycloadducts **11** and **12**, followed by Swern oxidation to give aldehydes **13** and **14** in 69% and 75% respectively (Scheme 3).



(*Z*)-7 **11** **13**

(*E*)-7 **12** **14**

Scheme 3. Reagents and conditions: (i) 2 eq. Me_2AlCl, *N*-methylmaleimide, DCM, (**11**, 48 h, reflux, 75%; **12**, 5 h, reflux, 89%); (ii) DMSO, $C_2O_2Cl_2$, DCM, -78 °C to r.t. (**13**, 69%; **14**, 75%).

Single-crystal X-ray analysis was performed for D-A cycloadducts **11** and **12**, confirming that the relative stereochemistry was consistent with an *endo*-selective D-A reaction in both cases (Figure 2).

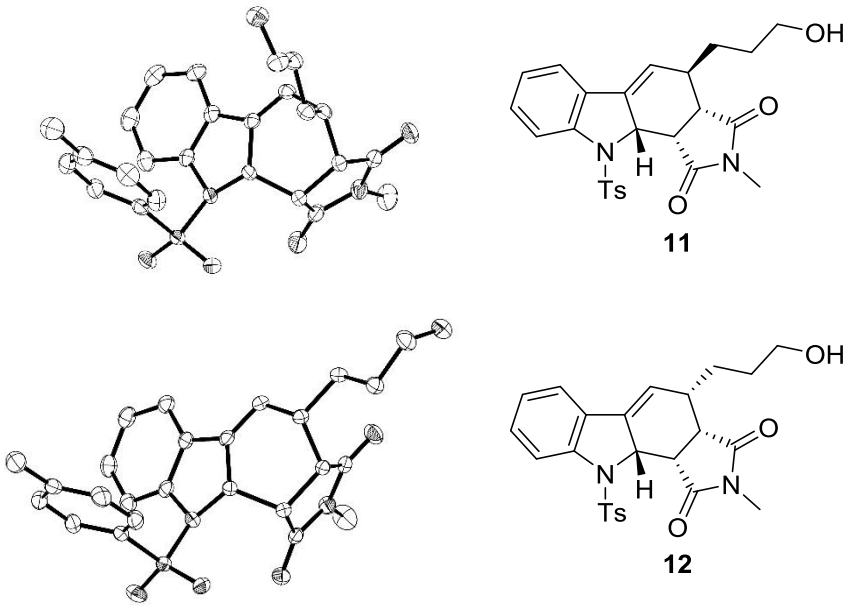
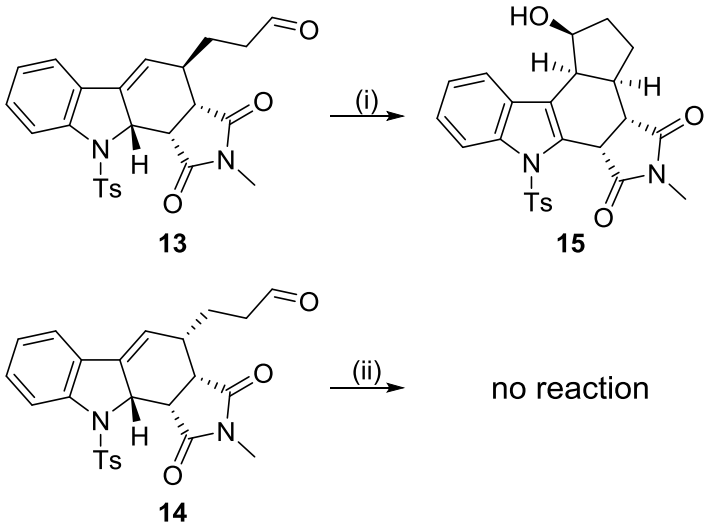


Figure 2. Crystallographically determined structures of D-A cycloadducts **11** and **12** (50% displacement ellipsoids; H atoms omitted for clarity).

When 2,3,9,9a-tetrahydro-1*H*-carbazole **13** was exposed to Me_2AlCl at low temperature (DCM, -78 °C, 30 min) a rapid carbonyl-ene cyclisation reaction occurred, with concurrent rearomatisation of the indole, to give the target pentacyclic carbazole **15** in 89% yield and as a single diastereomer, the *endo*-selectivity of the carbonyl-ene reaction being confirmed by single-crystal X-ray analysis (Scheme 3, Figure 3). Interestingly, exposure of the epimeric 2,3,9,9a-tetrahydro-1*H*-carbazole **14** to Me_2AlCl under a range of conditions, including refluxing in DCM for 3 days, showed no formation of carbonyl-ene cyclisation products, with only starting material recovered (Scheme 3).



Scheme 3. Reagents and conditions: (i) Me_2AlCl, DCM, -78 °C, 30 min, 89%; (ii) Me_2AlCl, DCM, reflux, 72 hr.

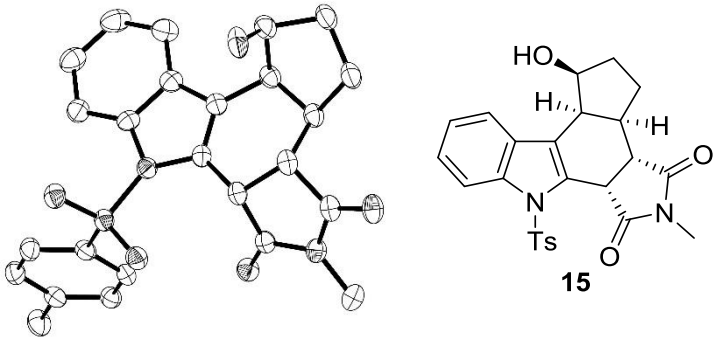


Figure 3. Crystallographically determined structure of pentacyclic carbazole **15** (50% displacement ellipsoids; H atoms omitted for clarity).

This large difference in reactivity between the two epimeric substrates **13** and **14** indicates a high degree of facial selectivity in the cyclisation, supporting a concerted carbonyl-ene reaction mechanism rather than a potentially more facially promiscuous stepwise addition/elimination mechanism. This hypothesis is further supported by the observed *endo*-selectivity in the cyclisation of 2,3,9,9a-tetrahydro-1*H*-carbazole **13** to the desired pentacyclic carbazole **15** (Figure 4).

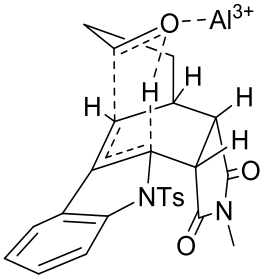
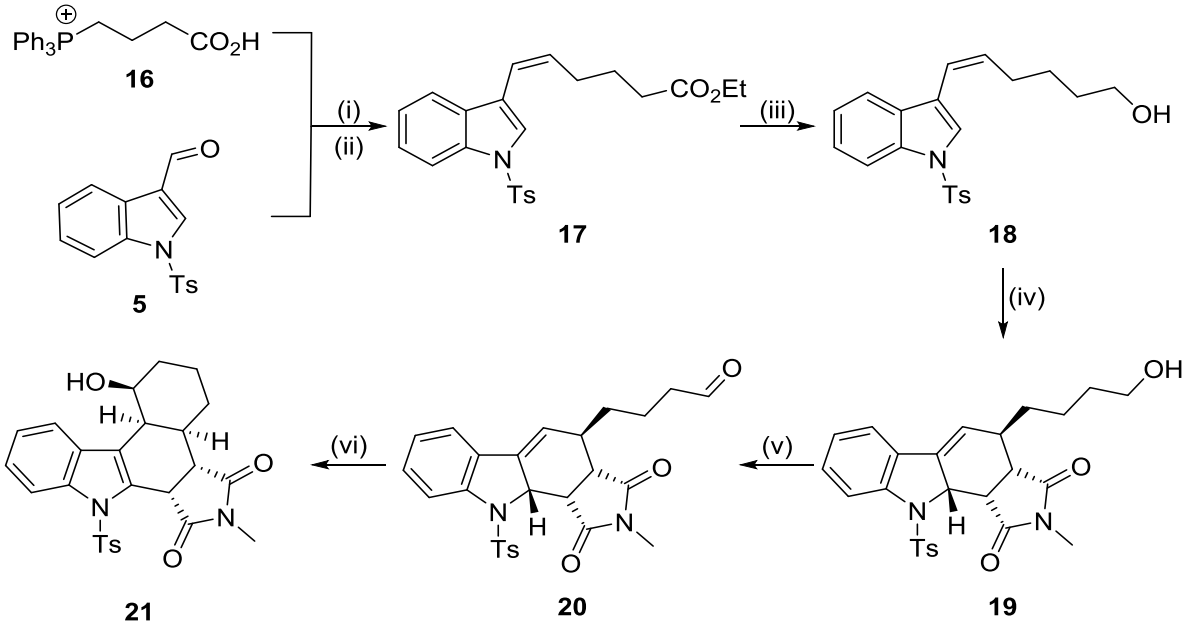


Figure 4. Proposed *endo*-transition state for the concerted intramolecular ene-reaction of **13**.

Finally we examined the possibility of forming pentacyclic carbazoles containing a cyclohexyl ring, through elongation of the alkyl tether. Thus treatment of indole-3-carbaldehyde **5** with the ylide prepared by reaction of (4-carboxybutyl)triphenylphosphonium bromide **16**[13] with NaHMDS gave an inseparable 4:1, (Z):(*E*) mixture of 6-(1-tosyl-1*H*-indol-3-yl)hex-5-enoic acid. Acid-catalysed esterification to the ethyl ester subsequently allowed the isolation of (*Z*)-3-alkenyl-

1*H*-indole **17** as a single geometrical isomer. DIBAL-H reduction then gave target alcohol **18**, which underwent a D-A reaction with *N*-methylmaleimide in the presence of Me_2AlCl to give the *endo*-D-A cycloadduct **19**, followed by Swern oxidation to access aldehyde **20** in good overall yield. Treatment of **20** with Me_2AlCl at low temperatures gave no reaction; however, warming the reaction to room temperature resulted in the formation of the target cyclohexyl-containing pentacyclic tetrahydrocarbazole **21** as a single diastereomer arising from an *endo*-carbonyl ene reaction, as confirmed by single crystal X-ray analysis (Scheme 4, Figure 5).



Scheme 4. Reagents and conditions: (i) **16**, 2 eq. NaHMDS, -78 to 0 °C, 1h, THF then **5** -78 to 0 °C, 4 h, 64%; (ii) H_2SO_4, EtOH, reflux, 1.5 h, 56%; (iii) DIBAL-H, toluene, -78 °C, 3 h, 94%; (iv) 2 eq. Me_2AlCl, *N*-methylmaleimide, DCM, reflux, 48 h, 78%; (v) DMSO, $C_2O_2Cl_2$, DCM, -78 °C to r.t., 3 h, 79%; (vi) Me_2AlCl, DCM, r.t., 3 h, 54%.

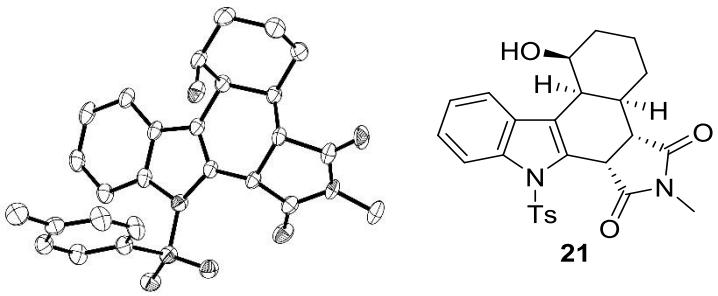


Figure 5. Crystallographically determined structure of pentacyclic carbazole **21** (50% displacement ellipsoids; H atoms omitted for clarity).[14]

Conclusions

In conclusion we have demonstrated an intermolecular D-A/intramolecular carbonyl-ene reaction strategy for the diastereoselective synthesis of pentacyclic saturated carbazoles and have confirmed the concerted nature of the ene reaction under these conditions. Future work will include focus on the introduction of enantioselective D-A and ene-reaction steps to direct the formation of enantio-enriched bioactive pentacyclic carbazoles.

Acknowledgments

The authors thank Newcastle University and EPSRC (EP/I033959/1) for funding, Umm al-Qura University for a PhD scholarship (MA), EPSRC for X-ray crystallography facilities at Newcastle (EP/F03637X/1), Diamond Light Source for access to beamline I19, and Prof. W. McFarlane and Dr C. Wills (Newcastle) for NMR support. Mass spectrometry data was acquired at the EPSRC UK National Mass Spectrometry Facility at Swansea University.

Experimental

^{1}H and ^{13}C NMR spectra were recorded directly with a Jeol Lambda 500 MHz, Jeol ECS-400 MHz or Bruker Avance 300 MHz. HRMS data were provided by the EPSRC National Mass Spectrometry Service (University of Swansea). X-ray diffraction data for compounds **11**, **12** and **15** were obtained on an Oxford Diffraction Gemini, whilst data for compound **21** were collected on the I19 beamline at Diamond Light Source. IR spectra were obtained from neat samples using a Varian 800 FTIR Scimitar Series spectrometer scanning from 4000 to 600 cm^{-1}. Melting points were obtained using a Stuart SMP3 melting point machine. THF was distilled from sodium/benzophenone and used directly. DCM was distilled from calcium hydride and used directly. Compounds **4**, **5**, **(*Z*)-6**, **8** and **16** were prepared according to literature procedures.

Ethyl (*E*)-5-(1-tosyl-1*H*-indol-3-yl) pent-4-enoate ((*E*)-6)

NaHMDS (1.0 M in THF, 1.48 mL, 1.48 mmol) was added to a solution of ethyl 4-((2-phenyl-2*H*-tetrazol-5-yl)sulfonyl)butanoate (0.49 g, 0.34 mmol) in THF (10 mL) at -78 ^{o}C. The mixture was stirred at -78 ^{o}C for 30 min. In a separate round-bottomed flask, 1-(toluene-4-sulfonyl)–1*H*-indol-3-carboxaldehyde (0.3 g, 1.30 mmol) was dissolved

in dry THF (5 mL) and transferred via cannula into the reaction solution. The reaction mixture was warmed slowly to r.t. over 4 h and stirred for a further 14 h. The solution was quenched into saturated $NH_4Cl_{(aq)}$ (5 mL), extracted with EtOAc (2 x 80 mL), washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The resulting colourless oil was purified by flash chromatography (petrol/ethyl acetate 10:1) to give ethyl (*E*)-5-(1-tosyl-1*H*-indol-3-yl) pent-4-enoate in (0.198 g, 0.49 mmol, 39%) as colourless oil and a further fraction containing a 5:1 mixture of ethyl (*E*) and (*Z*)-5-(1-tosyl-1*H*-indol-3-yl) pent-4-enoate in (0.17 g, 0.42 mmol, 33%).

R_f: 0.65 (petrol/ethyl acetate 7:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.99 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 7.9 Hz, 1H), 7.53 (s, 1H), 7.31 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.28 – 7.22 (m, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.49 (d, *J* = 16.0 Hz, 1H), 6.27 (dt, *J* = 16.0, 6.3 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 2.62 – 2.46 (m, 4H), 2.31 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 173.0, 145.0, 135.5, 135.2, 130.2, 130.0, 129.2, 126.9, 124.9, 123.5, 123.2, 121.5, 120.7, 120.4, 113.8, 77.2, 60.5, 34.2, 28.9, 21.6, 14.4. IR (neat): ν_{max}/cm^{-1} 1727, 1597. MS (pNSI): 398.1 (100%, $[M+H]^+$), 415.2 (98%, $[M+NH_4]^+$), 812.3 (26%, $[2M+NH_4]^+$). HRMS (pNSI): calcd $C_{22}H_{24}NO_4S$ $[M+H]^+$: 398.1421; observed: 398.1417.

(*Z*)-(1-tosyl-1*H*-indol-3-yl)pent-4-en-1-ol ((Z)-7)

DIBAL-H (1.0 M in toluene, 11.45 mL, 11.45 mmol) was added to a solution of ethyl (*Z*)-5-(1-tosyl-1*H*-indol-3-yl) pent-4-enoate (1.300 g, 3.27 mmol) in dry toluene (20 mL) at -78 ^{o}C under nitrogen. The reaction mixture was stirred at room temperature for 3 h and then quenched into $HCl_{(aq)}$ (1.0 M, 20 mL). The organic layer was extracted with EtOAc (2 x 100 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give a crude oil which was purified by column chromatography (petrol/ethyl acetate 2:1) to give the product as a clear colourless oil (1.009 g, 2.83 mmol, 87 %).

R_f: 0.26 (petrol/ethyl acetate 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.99 (dt, *J* = 8.3, 0.8 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.61 (s, 1H), 7.55 – 7.48 (m, 1H), 7.33 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.24 (ddd, *J* = 8.2, 7.3, 1.1 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.43 (dq, *J* = 11.3, 1.7 Hz, 1H), 5.83 (dt, *J* = 11.4, 7.1 Hz, 1H), 3.70 (t, *J* = 6.4 Hz, 2H), 2.43 (qd, *J* = 7.3, 1.9 Hz, 2H), 2.30 (s, 3H), 1.77 (pt, *J* = 6.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 145.1, 135.1, 134.6, 133.8, 130.9, 130.0, 126.9, 125.0, 123.6,

123.4, 119.6, 119.1, 118.2, 113.7, 62.3, 32.4, 26.1, 21.6. IR (neat): ν_{max}/cm^{-1} 3335, 2972. MS (p NSI): 356.1 (63%, $[M+H]^+$), 373.2 (100 %, $[M+NH_4]^+$). HRMS (p NSI): calcd $C_{20}H_{25}N_2O_3S$ $[M+NH_4]^+$: 373.1580; observed: 373.1581.

(*E*)-5-(1-tosyl-1*H*-indol-3-yl)pent-4-en-1-ol ((*E*)-7)

DIBAL-H (1.0 M in toluene, 1.5 mL, 1.5 mmol) was added to a solution of ethyl (*E*)-5-(1-tosyl-1*H*-indol-3-yl) pent-4-enoate (0.170 g, 0.43 mmol) in dry toluene (10 mL) at -78 ^oC under nitrogen. The reaction mixture was stirred at room temperature for 3 h and quenched into $HCl_{(aq)}$ (1.0 M, 20 mL). The organic layer was extracted with EtOAc (2 x 100 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give a colourless oil which was purified by column chromatography (petrol/ ethyl acetate 1:1) to give the product as a colourless oil (0.1461 g, 0.41 mmol, 96%).

R_f: 0.3 (petrol/ethyl acetate 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.99 (d, *J* = 7.8 Hz, 1H), 7.75 (d, *J* = 8.2 Hz, 2H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.52 (s, 1H), 7.35 – 7.28 (m, 1H), 7.28 – 7.21 (m, 1H), 7.19 (d, *J* = 8.2 Hz, 2H), 6.47 (d, *J* = 16.0 Hz, 1H), 6.28 (dt, *J* = 16.0, 6.6 Hz, 1H), 3.72 (t, *J* = 6.6 Hz, 2H), 2.38 – 2.29 (m, 2H), 2.31 (s, 3H), 1.81 – 1.72 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 145.0, 135.6, 135.3, 131.9, 130.0, 129.4, 126.9, 124.9, 123.5, 123.0, 121.0, 120.9, 120.4, 113.9, 62.5, 32.4, 29.9, 21.7. IR (neat): ν_{max}/cm^{-1} 3335, 2972. MS (p NSI): 356.1 (54%, $[M+H]^+$), 373.2 (100 %, $[M+NH_4]^+$). HRMS (p NSI): calcd $C_{20}H_{25}N_2O_3S$ $[M+NH_4]^+$: 373.1580; observed: 373.1580.

(3a*S,4*R**,10a*S**,10b*S**)-4-(3-hydroxypropyl)-2-methyl-10-tosyl-4,10,10a,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (11)**

Dimethyl aluminium chloride (1.0 M in hexane, 1.8 mL, 1.8 mmol) was added dropwise at -78 ^oC to a solution of *N*-methylmaleimide (0.100 g, 0.90 mmol) in dry DCM (10 mL). The mixture was stirred for 10 min followed by the addition of (*Z*)-5-(1-tosyl-1*H*-indol-3-yl) pent-4-en-1-ol (0.32 g, 0.90 mmol) in dry DCM (10 mL). The reaction mixture was refluxed for 48 h and then quenched with saturated $NaHCO_{3\,(aq)}$ (25 mL). The organic layer was extracted with DCM (1 X 50 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the crude white solid which purified by column chromatography (gradient elution

from petrol/ethyl acetate 1:1 to 100% ethyl acetate) to give the product as a colourless crystalline solid in (0.313 g, 0.67 mmol, 75 %).

Mp. 112 – 114 ^{o}C. R_f: 0.3 (petrol/ethyl acetate 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.80 (d, *J* = 8.3 Hz, 2H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.29 – 7.17 (m, 4H), 6.97 (td, *J* = 7.5, 0.9 Hz, 1H), 6.15 (dd, *J* = 7.4, 3.3 Hz, 1H), 4.86 (dd, *J* = 7.5, 3.4 Hz, 1H), 4.15 (dd, *J* = 8.7, 7.5 Hz, 1H), 3.66 (t, *J* = 5.9 Hz, 2H), 3.16 – 3.10 (m, 1H), 3.07 (d, *J* = 8.8 Hz, 1H), 2.83 (s, 3H), 2.36 (s, 3H), 1.76 – 1.49 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 179.0, 174.2, 144.7, 144.2, 135.9, 134.2, 130.5, 130.0, 127.7, 127.0, 124.0, 121.0, 117.6, 115.5, 62.4, 60.0, 44.3, 43.2, 37.6, 31.6, 29.9, 25.3, 21.7. IR (neat): ν_{max}/cm^{1}: 3657, 1639. MS (pNSI): 467.16 (100%, $[M+H]^+$), 484.18 (50%, $[M+Na]^+$). HRMS (p NSI): calcd $C_{25}H_{27}N_2O_5S$ $[M+H]^+$: 467.1635; observed: 467.1628.

(3a*S,4*S**,10a*S**,10b*S**)-4-(3-hydroxypropyl)-2-methyl-10-tosyl-4,10,10a,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (12)**

Dimethyl aluminium chloride (1.0 M in hexane, 0.82 mL, 0.82 mmol) was added dropwise to a solution of *N*-methylmaleimide (0.046 g, 0.41 mmol) in dry DCM (5 mL) at -78 ^{o}C. The mixture was stirred for 30 min followed by the addition of (*E*)-5-(1-tosyl-1*H*-indol-3-yl)pent-4-en-1-ol (0.146 g, 0.41mmol) in DCM (7 mL). The reaction mixture was warmed to reflux for 5 h, quenched with saturated $NaHCO_{3\,(aq)}$ (25 mL), extracted with DCM (2 x 50 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the crude product which was purified by column chromatography (gradient elution from petrol/ethyl acetate 1:1 to 100% ethyl acetate) to give the product as a white solid in (0.1699 g, 0.36 mmol, 89 %).

Mp. 207 – 209 ^{o}C. R_f: 0.33 (petrol/ethyl acetate 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.78 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 1H), 7.28 – 7.25 (m, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.99 (td, *J* = 7.5, 0.8 Hz, 1H), 5.88 (t, *J* = 3.7 Hz, 1H), 4.55 (ddd, *J* = 7.2, 3.3, 1.8 Hz, 1H), 4.02 (dd, *J* = 8.4, 7.3 Hz, 1H), 3.76 (t, *J* = 6.3 Hz, 2H), 3.19 (dd, J = 8.5, 6.5 Hz, 1H), 2.77 (s, 3H), 2.36 (s, 3H), 2.30 – 2.21 (m, 1H), 2.16 – 2.07 (m, 1H), 2.03 – 1.93 (m, 1H), 1.87 – 1.74 (m, 2H), 1.69 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 176.5, 173.8, 144.5, 136.8, 134.4, 133.9, 130.4, 129.9, 127.3, 126.0, 123.8, 121.0, 118.0, 115.3, 62.64, 61.79, 43.98, 40.39, 37.96, 31.24, 27.53, 24.88, 21.60. IR (neat): ν_{max}/cm^{-1} 3553, 1659. MS (p NSI): 484.18 (100%, $[M+NH_4]^+$), 467.16 (90%,

$[M+H]^+$). HRMS (p NSI): calcd $C_{25}H_{26}N_2O_5SNa$ $[M+Na]^+$: 489.1455; observed: 489.1446.

3-((3a*S,4*R**,10a*S**,10b*S**)-2-methyl-1,3-dioxo-10-tosyl-1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanal (13)**

DMSO (0.04 mL, 0.69 mmol) was added dropwise at -78 °C to a stirred solution of oxalyl chloride (0.02 mL, 0.33 mmol) in dry DCM (2 mL). After 30 min, a solution of 3-((3a*S**,4*R**,10a*S**,10b*S**)-2-methyl-1,3-dioxo-10-tosyl-1,2,3,3a,4,10,10a,10b octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanal (0.130 g, 0.27 mmol) in dry DCM (8 mL) was added. The reaction mixture was stirred for 30 min at -78 °C followed by the addition of triethylamine (0.15 mL, 1.11 mmol). The reaction mixture was warmed to room temperature, stirred for 2 h and quenched with saturated $NaHCO_{3\,(aq)}$ (10 mL). The organic layer was extracted with DCM (1 x 50 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the crude product as a yellow solid which was purified by column chromatography (petrol/ethyl acetate 1:1) to give the product as a white solid in (0.086 g, 0.185 mmol, 69 %).

Mp. 135 – 137 °C. R_f: 0.30 (petrol/ethyl acetate 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.76 (s, 1H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.25 – 7.22 (m, 4H), 6.97 (td, *J* = 7.6, 0.8 Hz, 1H), 6.09 (dd, *J* = 7.4, 3.3 Hz, 1H), 4.86 (dd, *J* = 7.6, 3.4 Hz, 1H), 4.17 (dd, *J* = 8.4, 8.0 Hz, 1H), 3.11 (dt, *J* = 9.9, 7.0 Hz, 1H), 3.05 (d, *J* = 8.7 Hz, 1H), 2.82 (s, 3H), 2.74 – 2.45 (m, 2H), 2.35 (s, 3H), 1.98 – 1.68 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 201.1, 178.5, 174.0, 144.7, 144.3, 136.8, 133.9, 130.7, 130.0, 127.6, 126.7, 123.9, 121.1, 116.3, 115.5, 59.9, 44.2, 43.0, 42.7, 37.1, 25.3, 25.2, 21.7. IR (neat): ν_{max}/cm^{-1} 2925, 1697. MS (p NSI): 465.1 (16%, $[M+H]^+$), 497.2 (100%, $[M+MeOH+H]^+$), 514.2 (80%, $[M+MeOH+NH_4]^+$), 519.2 (100%, $[M+MeOH+Na]^+$). HRMS (p NSI): calcd $C_{25}H_{25}N_2O_5S$ $[M+H]^+$: 465.1479; observed: 465.1486.

3-((3a*S,4*S**,10a*S**,10b*S**)-2-methyl-1,3-dioxo-10-tosyl-1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanal (14)**

DMSO (0.02 mL, 0.33 mmol) was added dropwise at -78 °C to a stirred solution of oxalyl chloride (0.01 mL, 0.15 mmol,) in dry DCM (2 mL). After 30 min, a solution of (3a*S**,4*S**,10a*S**,10b*S**)-4-(3-hydroxypropyl)-2-methyl-10-tosyl-4,10,10a,10b-

tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (0.062 g, 0.13 mmol) in dry DCM (5 mL) was added. The reaction mixture was stirred for 30 min at -78 °C followed by the addition of triethylamine (0.10 mL, 0.53 mmol). The reaction mixture was warmed to r.t. and stirred for 2 h, quenched with saturated $NaHCO_{3\,(aq)}$ (10 mL), extracted with DCM (1 x 50 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the crude product as a yellow solid which was purified by column chromatography (petrol/ethyl acetate 1:1) to give the product as a white solid in (0.045 g, 0.097 mmol, 75 %).

Mp: 139 – 141 °C. R_f: 0.2 (petrol/ethyl acetate 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 9.86 (s, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.70 (d, *J* = 8.9 Hz, 1H), 7.31 – 7.21 (m, 4H), 6.99 (td, *J* = 7.6, 0.9 Hz, 1H), 5.83 (t, *J* = 3.4 Hz, 1H), 4.51 (ddd, *J* = 7.2, 3.2, 1.4 Hz, 1H), 4.03 (dd, *J* = 8.5, 7.3 Hz, 1H), 3.17 (dd, *J* = 8.6, 5.5 Hz, 1H), 2.85 – 2.72 (m, 2H), 2.78 (s, 3H), 2.36 (s, 3H), 2.40 – 2.23 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C δ 201.7, 176.2, 173.4, 145.0, 144.6, 137.3, 134.3, 130.6, 129.9, 127.3, 125.8, 123.9, 121.0, 117.0, 115.3, 61.7, 43.9, 42.1, 40.0, 37.0, 24.9, 23.7, 21.6. IR (neat): ν_{max}/cm^{-1} 2925, 1697. MS (p APCI): 279.1 (100%), 293.1 (41%), 300.1 (15%), 465.1 (65%, $[M+H]^+$). HRMS (p APCI): calcd $C_{25}H_{25}N_2O_5S$ $[M+H]^+$: 465.1479; observed: 465.1485.

(3a*R,3b*S**,6*R**,6a*S**,11b*R**)-6-hydroxy-2-methyl-11-tosyl-3a,3b,4,5,6,6a,11,11b-octahydro-1*H*-cyclopenta[*c*]pyrrolo[3,4-*a*]carbazole-1,3(2*H*)-dione (15)**

Dimethyl aluminum chloride (1.0 M in hexane, 0.09 mL, 0.09 mmol) was added dropwise at -78 °C to a solution of 3- (3a*R**,4*S**,10b*S**)-2-methyl-1,3-dioxo-10-tosyl-1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanal (0.045 g, 0.09 mmol) in dry DCM (5 mL). The reaction mixture was stirred for 30 min, quenched with saturated $NaHCO_{3\,(aq)}$ (5mL). The organic layer was extracted with DCM (1 x 20 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the crude product as a white solid which was purified by column chromatography (petrol/ethyl acetate 1:1) to give the product as a white solid (0.038 g, 0.08 mmol, 89 %).

Mp. 240 – 242 °C. R_f: 0.6 (petrol/ethyl acetate 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.92 (d, *J* = 8.2 Hz, 1H), 7.86 (d, *J* = 7.6 Hz, 2H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.7 Hz, 1H), 7.27 – 7.18 (m, 3H), 4.95 (d, *J* = 7.2 Hz, 1H), 4.51 (t, *J* = 3.8 Hz, 1H), 3.31 (dd, *J* = 11.2, 7.2 Hz, 1H), 3.18 (dd, *J* = 7.3, 4.1 Hz, 1H), 3.03 (s, 3H), 2.41 –

2.35 (m, 1H), 2.34 (s, 3H), 2.25 – 2.03 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 178.5, 174.1, 145.1, 137.4, 135.5, 130.7, 129.9, 128.6, 127.2, 125.5, 124.0, 118.9, 117.4, 115.5, 77.5, 77.2, 76.8, 73.6, 46.5, 44.3, 41.9, 38.9, 33.4, 27.7, 25.2, 21.8. IR (neat): ν_{max}/cm^{-1} 3655, 2980. MS (p NSI): 465.1 (100 %, $[M+H]^+$), 482.2 (75 %, $[M+NH_4]^+$). HRMS (p NSI): calcd $C_{25}H_{25}N_2O_5S$ $[M+H]^+$: 465.1479; observed: 465.1484.

Ethyl (*Z*)-6-(1-tosyl-1*H*-indol-3-yl)hex-5-enoate (17)

In a Schlenk flask, (4-carboxybutyl)triphenylphosphonium bromide (3.60 g, 8.12 mmol) was dissolved in dry THF (20 mL) and cooled to -78 ^{o}C. Sodium bis(trimethylsilyl)amide (1.0 M in THF, 16.24 mL, 16.24 mmol) was added dropwise over 10 min. The reaction mixture was warmed to 0 ^{o}C and stirred for 1 h. In a separate round-bottomed flask, 1-(toluene-4-sulfonyl)–1*H*-indol-3-carboxaldehyde (1.69 g, 7.38 mmol) was dissolved in dry THF (10 mL) and transferred via cannula to the reaction solution. The resulting reaction mixture was stirred at room temperature for 4 h, quenched with water (20 mL). The aqueous layer was acidified to pH 1 with $HCl_{(aq)}$ (2.0 M, 20 mL) and was extracted with EtOAc (3 x 100 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give an oil which was purified by column chromatography (petrol/ethyl acetate 7:3) to give a 4:1 mixture of *(Z)* and *(E)*-6-(1-tosyl-1*H*-indol-3-yl)hex-5-enoic acid as a colourless oil in (1.8122 g, 4.72 mmol, 64 %).

A 4:1 mixture of *(Z)* and *(E)*-6-(1-tosyl-1*H*-indol-3-yl)hex-5-enoic acid (0.516 g, 1.34 mmol) was dissolved in anhydrous EtOH (35 mL). Concentrated $H_2SO_{4(aq)}$ (0.2 mL) was added, the solution was refluxed for 1.5 h, quenched into saturated $NaHCO_{3(aq)}$ (15 mL) and extracted with EtOAc (2 x 75 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give an orange solid which was purified by column chromatography in (petrol/ethyl acetate 10:1) to give the product as yield as a colourless oil in (0.308 g, 0.82 mmol, 56 %).

R_f: 0.7 (petrol / ethyl acetate 7:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.90 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.43 (s, 1H), 7.43 – 7.39 (m, 1H), 7.23 (ddd, *J* = 8.4, 7.2, 1.4 Hz, 1H), 7.19 – 7.14 (m, 1H), 7.11 (d, *J* = 7.9 Hz, 2H), 6.34 (dq, *J* = 11.4, 1.8 Hz, 1H), 5.70 (dt, *J* = 11.4, 7.0 Hz, 1H), 4.03 (q, *J* = 7.1 Hz, 2H), 2.29 (qd, *J* = 7.3, 1.8 Hz, 2H), 2.26 (t, *J* = 7.4 Hz, 2H), 2.22 (s, 3H), 1.74 (p, *J* = 7.5 Hz, 2H),

1.14 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 173.5, 145.0, 135.2, 134.7, 133.4, 130.9, 130.0, 126.9, 125.0, 123.5, 123.4, 119.6, 119.1, 118.5, 113.7, 60.4, 33.8, 29.1, 24.8, 21.6, 14.3. MS (p NSI): 412.2 (63%, $[M+H]^+$), 429.2 (100%, $[M+NH_4]^+$), 840.3 (15%, $[2M+NH_4]^+$); HRMS (p NSI): calcd $C_{23}H_{26}NO_4S$ $[M+H]^+$: 412.1577; observed: 412.1575.

(*Z*)-6-(1-Tosyl-1*H*-indol-3-yl)hex-5-en-1-ol (18)

DIBAL-H (1.0 M in toluene, 3.40 mL, 3.40 mmol) was added under nitrogen to a solution of ethyl (*Z*)-6-(1-tosyl-1*H*-indol-3-yl)hex-5-enoate (0.400 g, 0.97 mmol) in dry toluene (20 mL) at -78 ^{o}C. The reaction mixture warmed to rt and stirred for 3 h, quenched with $HCl_{(aq)}$ (1.0 M, 5 mL), extracted with EtOAc (2 x 100 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the product as a colourless oil in (0.1533 g, 0.41 mmol, 94 %) with no further purification required.

R_f*:* 0.27 (petrol/ethyl acetate 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.99 (d, *J* = 8.2 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.54 (s, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.36 – 7.28 (m, 1H), 7.26 – 7.20 (m, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.41 (dq, *J* = 11.4, 1.8 Hz, 1H), 5.82 (dt, *J* = 11.4, 7.1 Hz, 1H), 3.66 (t, *J* = 6.2 Hz, 2H), 2.35 (qd, *J* = 7.3, 1.7 Hz, 2H), 2.30 (s, 3H), 1.69 (br s, 1H), 1.69 – 1.52 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 145.0, 135.1, 134.6, 134.3, 130.9, 129.9, 126.8, 124.9, 123.4, 123.3, 119.6, 119.2, 117.8, 113.6, 62.5, 32.3, 29.4, 25.6, 21.5. IR (neat) ν_{max}/cm^{-1} 3435, 2972. MS (p NSI): 370.1 (28%, $[M+H]^+$), 387.2 (100%, $[M+NH_4]^+$), 392.1 (18%, $[M+Na]^+$), 756.3 (45%, $[2M+NH_4]^+$). HRMS (p NSI): calcd $C_{21}H_{27}N_2O_3S$ $[M+NH_4]^+$: 387.1737; observed: 387.1738.

(3a*S,4*R**,10a*S**,10b*S**)-4-(4-hydroxybutyl)-2-methyl-10-tosyl-4,10,10a,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (19)**

Dimethyl aluminium chloride (1.0 M in hexane, 0.58 mL, 0.58 mmol) was added dropwise at -78 ^{o}C to a solution of *N*-methylmaleimide (0.0325 g, 0.29 mmol,) in dry DCM (5 mL). The mixture was stirred for 10 min followed by the addition of (*Z*)-6-(1-tosyl-1*H*-indol-3-yl)hex-5-en-1-ol (0.108 g, 0.29 mmol) in dry DCM (5 mL). The reaction mixture was heated to reflux for 48 h, quenched with saturated $NaHCO_{3\ (aq)}$ (10 mL), extracted with DCM (2 x 25 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give a white solid

which was purified by column chromatography (gradient elution from petrol/ethyl acetate 1:1 to 100% ethyl acetate) to give the product as a white solid yield in (0.1093 g, 0.23 mmol, 78 %).

Mp. 189 – 201 ^{o}C. R_f: 0.26 (petrol/ethyl acetate 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.79 (d, *J* = 8.3 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.30 – 7.18 (m, 3H), 7.01 – 6.92 (m, 1H), 6.14 (dd, *J* = 7.4, 3.3 Hz, 1H), 4.84 (dd, *J* = 7.5, 3.3 Hz, 1H), 4.13 (dd, *J* = 8.5, 7.6 Hz, 1H), 3.63 (t, *J* = 6.0 Hz, 2H), 3.17 – 3.08 (m, 1H), 3.06 (d, *J* = 8.7 Hz, 1H), 2.83 (s, 3H), 2.36 (s, 3H), 1.64 – 1.40 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 179.0, 174.2, 144.7, 144.3, 135.8, 134.3, 130.5, 130.0, 127.6, 127.1, 124.0, 121.0, 117.7, 115.5, 62.7, 60.0, 44.4, 43.1, 37.9, 33.5, 32.6, 25.3, 25.1, 21.7. IR (neat): ν_{max}/cm^{-1} 3636, 2981, 1727. MS (p NSI): 481.2 (100%, $[M+H]^+$), 498.2 (15%, $[M+NH_4]^+$), 503.2 (35%, $[M+Na]^+$), 983.3 (5%, $[2M+Na]^+$). HRMS (p NSI): calcd $C_{26}H_{29}N_2O_5S$ $[M+H]^+$: 481.1792; observed: 481.1786.

4-((3a*S,4*R**,10a*S**,10b*S**)-2-methyl-1,3-dioxo-10-tosyl-1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)butanal (20)**

DMSO (0.07 mL, 1.04 mmol) was added dropwise at -78 ^{o}C to a stirred solution oxalyl chloride (0.1 mL, 0.49 mmol) in dry DCM (2 mL). After 30 min a solution of 3a*S**,4*R**,10a*S**,10b*S**)-4-(4-hydroxybutyl)-2-methyl-10-tosyl-4,10,10a,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (0.200 g, 0.42 mmol) in DCM (8 mL) was added. The reaction mixture was stirred for 30 min at -78^{o}C followed by the addition of triethylamine (0.23 mL, 1.68 mmol). The reaction mixture was warmed to r.t., stirred for 2 h, quenched with saturated $NaHCO_{3(aq)}$ (10 mL), extracted with DCM (2 x 25 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give a yellow solid which was purified by column chromatography (petrol/ethyl acetate 1:1) to give the product as a white solid (0.1588 g, 0.33 mmol, 79 %).

Mp. 171 – 173 ^{o}C. R_f: 0.3 (petrol/ethyl acetate 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 9.76 (s, 1H), 7.80 (d, *J* = 8.3 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.30 – 7.19 (m, 4H), 6.97 (t, *J* = 7.5 Hz, 1H), 6.14 (dd, *J* = 7.4, 3.3 Hz, 1H), 4.84 (dd, *J* = 7.5, 3.3 Hz, 1H), 4.19 – 4.10 (m, 1H), 3.13 (q, *J* = 7.7 Hz, 1H), 3.05 (d, *J* = 8.7 Hz, 1H), 2.84 (s, 3H), 2.49 (t, *J* = 6.8 Hz, 2H), 2.37 (s, 3H), 1.80 – 1.67 (m, 2H), 1.62 – 1.47 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 201.7, 178.8, 174.1, 144.7, 144.3, 136.1, 134.1, 130.6, 130.0, 127.6, 126.9, 124.0, 121.0, 117.1, 115.5, 60.0, 44.3, 43.6, 43.1, 37.6, 32.8,

25.3, 21.7, 21.0. MS (p NSI): 478.2 (42%, $[M\text{-}H_2O+NH_4]^+$), 496.2 (21%, $[M+NH_4]^+$), 511.2 (74%, $[M+MeOH+H]^+$), 528.2 (100%, $[M+MeOH+NH_4]^+$), 533.2 (48%, $[M+MeOH+Na]^+$). IR (neat): ν_{max}/cm^{-1} 2944, 1773, 1699. HRMS (p NSI): calcd $C_{26}H_{27}N_2O_5S$ $[M+H]^+$: 496.1901; observed: 496.1891.

(3a*S,3b*R**,7*S**,7a*S**,12b*S**)-7-hydroxy-2-methyl-12-tosyl-3b,4,5,6,7,7a,12,12b-octahydrobenzo[c]pyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (21)**

Dimethyl aluminum chloride (1.0 M in hexane, 0.06 mL, 0.06 mmol) was added dropwise at -78 °C to a solution of 4-((3a*S**,4*R**,10a*S**,10b*S**)-2-methyl-1,3-dioxo-10-tosyl-1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)butanal (0.03 g, 0.06 mmol) in dry DCM (5 mL). The reaction mixture was stirred for three hours at 25 °C before being quenched with saturated $NaHCO_{3\,(aq)}$ (5mL), extracted with DCM (1 x 20 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give a white solid which was purified by column chromatography (petrol/ethyl acetate 1:1) to give the product as a white solid in (0.0165 g, 0.034 mmol, 54 %).

Mp: 265 – 267 °C. R_f: 0.6 (petrol/ethyl acetate 1:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.00 (d, *J* = 8.2 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 7.7 Hz, 1H), 7.34 – 7.27 (m, 1H), 7.25 – 7.19 (m, 1H), 7.19 (d, *J* = 8.3 Hz, 2H), 4.96 (d, *J* = 7.2 Hz, 1H), 4.12 – 4.00 (m, 1H), 3.80 (dd, *J* = 12.4, 7.2 Hz, 1H), 3.07 (dd, *J* = 5.0, 2.7 Hz, 1H), 3.01 (s, 3H), 2.44 (d, *J* = 14.0 Hz, 1H), 2.33 (s, 3H), 2.10 – 1.83 (m, 3H), 1.81 – 1.47 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 177.9, 174.3, 145.1, 137.9, 135.3, 130.3, 129.8, 128.2, 126.9, 125.4, 124.0, 121.7, 118.7, 116.1, 67.8, 43.4, 42.4, 38.8, 34.4, 32.2, 26.8, 25.2, 21.7, 14.6. IR (neat): ν_{max}/cm^{-1} 3655, 2980. MS (p NSI): 479.2 (100%, $[M+H]^+$), 501.1 (85%, $[M+Na]^+$). 496.2 $[M+NH_4]^+$). HRMS (p NSI): calcd $C_{26}H_{27}N_2O_5S$ $[M+H]^+$: 479.1635; observed: 479.1629.

Table 1: Crystal data and structure refinement for **11**

Identification code	mjh140033
Empirical formula	$C_{25.95}H_{26.95}Cl_{2.85}N_2O_5S$ ($CHCl_3$ solvate)
Formula weight	579.94
Temperature/K	150.01(10)
Crystal system	monoclinic

Space group	$P2_1/c$
a/Å	10.33568(16)
b/Å	31.6318(5)
c/Å	8.57183(13)
α/°	90
β/°	106.4841(16)
γ/°	90
Volume/Å^3	2687.25(7)
Z	4
ρ_{calc}mg/mm^3	1.433
μ/mm^{-1}	4.015
F(000)	1204.0
Crystal size/mm^3	0.37 × 0.27 × 0.2
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection	5.588 to 133.572
Index ranges	-12 ≤ h ≤ 12, -35 ≤ k ≤ 37, -9 ≤ l ≤ 10
Reflections collected	37079
Independent reflections	4756 [R_{int} = 0.0365, R_{sigma} = 0.0164]
Data/restraints/parameters	4756/45/349
Goodness-of-fit on F^2	1.033
Final R indexes [I>=2σ (I)]	R_1 = 0.0412, wR_2 = 0.1029
Final R indexes [all data]	R_1 = 0.0444, wR_2 = 0.1054
Largest diff. peak/hole / e Å^{-3}	0.83/-0.43

Table 2: Crystal data and structure refinement for **12**.

Identification code	mjh140032_fa
Empirical formula	$C_{25}H_{26}N_2O_5S$
Formula weight	466.54
Temperature/K	150.01(10)
Crystal system	monoclinic
Space group	$P2_1/n$

a/Å	11.80720(1)
b/Å	11.35230(1)
c/Å	16.4724(2)
α/°	90
β/°	94.7820(1)
γ/°	90
Volume/Å^3	2200.26(4)
Z	4
ρ_{calc}g/cm^3	1.408
μ/mm^{-1}	1.654
F(000)	984.0
Crystal size/mm^3	0.38 × 0.11 × 0.06
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.874 to 133.532
Index ranges	-14 ≤ h ≤ 14, -13 ≤ k ≤ 13, -19 ≤ l ≤ 19
Reflections collected	59078
Independent reflections	3905 [R_{int} = 0.0517, R_{sigma} = 0.0161]
Data/restraints/parameters	3905/0/304
Goodness-of-fit on F^2	1.038
Final R indexes [I>=2σ (I)]	R_1 = 0.0344, wR_2 = 0.0884
Final R indexes [all data]	R_1 = 0.0403, wR_2 = 0.0933
Largest diff. peak/hole / e Å^{-3}	0.26/-0.42

Table 3: Crystal data and structure refinement for **15**

Identification code	mjh140006
Empirical formula	$C_{26}H_{26}N_2O_5SCl_2$
Formula weight	549.45
Temperature/K	150.01(10)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	12.9390(2)

b/Å	16.4953(3)
c/Å	24.2101(5)
α/°	90
β/°	96.0290(17)
γ/°	90
Volume/Å^3	5138.64(16)
Z	8
ρ_{calc}mg/mm^3	1.420
m/mm^{-1}	3.374
F(000)	2288.0
Crystal size/mm^3	0.37 × 0.25 × 0.05
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection	6.496 to 132.868°
Index ranges	-13 ≤ h ≤ 15, -18 ≤ k ≤ 19, -27 ≤ l ≤ 28
Reflections collected	42625
Independent reflections	8988 [R_{int} = 0.0491, R_{sigma} = 0.0346]
Data/restraints/parameters	8988/3/658
Goodness-of-fit on F^2	1.020
Final R indexes [I>=2σ (I)]	R_1 = 0.0443, wR_2 = 0.1103
Final R indexes [all data]	R_1 = 0.0561, wR_2 = 0.1198
Largest diff. peak/hole / e Å^{-3}	0.74/-0.74

Table 4: Crystal data and structure refinement for **21**

Identification code	mjh150010
Chemical formula (moiety)	$C_{26}H_{26}N_2O_5S·0.5CH_2Cl_2$
Chemical formula (total)	$C_{26.5}H_{27}ClN_2O_5S$
Formula weight	521.01
Temperature	100(2) K
Radiation, wavelength	synchrotron, 0.6889 Å
Crystal system, space group	monoclinic, $P2_1/c$
Unit cell parameters	a = 13.119(3) Å, α = 90°

	b = 16.319(3) Å, β = 100.030(2)°
	c = 22.882(5) Å, γ = 90°
Cell volume	4823.9(18) Å^3
Z	8
Calculated density	1.435 g/cm^3
Absorption coefficient μ	0.231 mm^{-1}
F(000)	2184
Crystal colour and size	colourless, 0.070 × 0.010 × 0.010 mm^3
Reflections for cell refinement	6929 (θ range 2.2 to 25.5°)
Data collection method	Rigaku Saturn 724+ on kappa diffractometer wide-frame ω scans
θ range for data collection	1.5 to 25.8°
Index ranges	h –16 to 16, k –20 to 17, l –28 to 28
Completeness to θ = 24.4°	99.9 %
Reflections collected	42956
Independent reflections	10111 (R_{int} = 0.0955)
Reflections with $F^2>2\sigma$	6291
Absorption correction	none
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.1315, 7.9105
Data / restraints / parameters	10111 / 67 / 664
Final R indices [$F^2>2\sigma$]	R_1 = 0.0838, wR_2 = 0.2270
R indices (all data)	R_1 = 0.1379, wR_2 = 0.2582
Goodness-of-fit on F^2	1.073
Extinction coefficient	0.0093(11)
Largest and mean shift/su	0.003 and 0.000
Largest diff. peak and hole	0.81 and –1.12 e Å^{-3}

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14) CCDC 1437386-1437389 contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.