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Sequential oxopyridinium betaine cycloaddition–palladium catalysed cyclisation–anion capture processes

Mark R. Fielding,[a] Ronald Grigg,[a,*] Visuvanathar Sridharan,[a] Mark Thornton-Pett[a] and Christopher J. Urch[b]

[a]*Molecular Innovation, Diversity and Automated Synthesis (MIDAS) Centre, School of Chemistry, Leeds University, Leeds LS2 9JT, UK*
[b]*Syngenta, Jealott's Hill Research Station, Bracknell, Berkshire RG42 6EY, UK*

Dedicated to Professor K. Undheim on the occasion of his 70th birthday

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Abstract—Katritzky's oxopyridinium betaine cycloaddition is employed to generate bridged bicyclic substrates suitable for our palladium(0) catalysed cyclisation–anion capture methodology. A variety of polycyclic heterocycles have been synthesised via mono-cyclisation–organotin(IV) capture with or without incorporation of carbon monoxide. Sequential cycloaddition–cyclisation can be performed as a one pot process to deliver substantial gain in molecular complexity. © 2001 Elsevier Science Ltd. All rights reserved.

The 1,3-dipolar cycloaddition of oxopyridinium betaines, pioneered by Katritzky et al.,[1–3] is a versatile synthetic procedure for the construction of [3.2.1]-azabridged bicyclic enones. In this reaction a 3-hydroxypyridinium salt is treated with base in the presence of a suitable dipolarophile to afford a mixture of *endo*- and *exo*-cycloadducts via a cyclic azomethine ylide. A variety of activated alkenes[1] serve as dipolarophiles for this cycloaddition. Applications of this chemistry have been reported by a number of authors[4–7] and manipulation of the enone moiety has been used to modify of the azabicyclic scaffold. The quaternary salts of the cycloadducts can also be converted into tropones[1] under Hofmann elimination conditions.

Hart[8] has applied Katritzky's cycloaddition to the synthesis of a range of substrates suitable for radical mediated cyclisations with tri-*n*-butyltin hydride. The intramolecular version of the cycloaddition was reported[9] in 1976 and has since been used in the synthesis of polycyclic enones.[10,11] A similar approach was adopted by Kozikowski et al.[12,13] in their preparation of 'back bridged' cocaine-like analogues.

Our group has reported extensively on palladium(0) catalysed cyclisation–anion capture.[14–16] This has been developed into a powerful method for the construction of complex heterocycles in which one or more rings are created in a single step. In these reactions a capture reagent[17] is required in order to make the final bond (C–C, C–N, C–H, etc.) and thus allow regeneration of the Pd(0) catalyst. We have employed a range of such reagents in mono-, bis- and tris-cyclisations.[14–17] Organotin(IV) reagents are particularly attractive due to their ease of preparation and tolerance of air and moisture. The sequential Tactical Combination of the oxopyridinium betaine cycloaddition with our cyclisation–anion capture methodology provides the opportunity for linking two disparate ring forming reactions to engineer highly efficient and selective protocols allowing one-pot access to target molecules possessing a high degree of complexity which would otherwise require tedious and/or technically demanding multistep syntheses. We have previously reported examples of such Tactical Combinations which combined azomethine ylide–cycloaddition cascades with palladium(0) catalysed cyclisation reactions.[18,19] A similar approach was employed by our group in the synthesis of bicyclic β-lactams.[20] Herein, we demonstrate the first examples of palladium-catalysed cyclisation–stannane capture applied to oxopyridinium betaine cycloadducts which utilise the cycloadduct enone moiety as terminating species. The products from these reactions are similar to the 'front bridged' cocaine analogues reported by Kozikowski et al.[12,13] and serve as an interesting series for biological evaluation.

1. Cycloadditions of 3-hydroxypyridinium salts (Katritzky's cycloaddition)

Heating 3-hydroxypyridine in the presence of 2-iodo-

Keywords: palladium catalysis; cyclisation; 1,3-dipolar cycloaddition; molecular queuing.

* Corresponding author. Tel./fax: +44-113-233-6501; e-mail: r.grigg@chem.leeds.ac.uk

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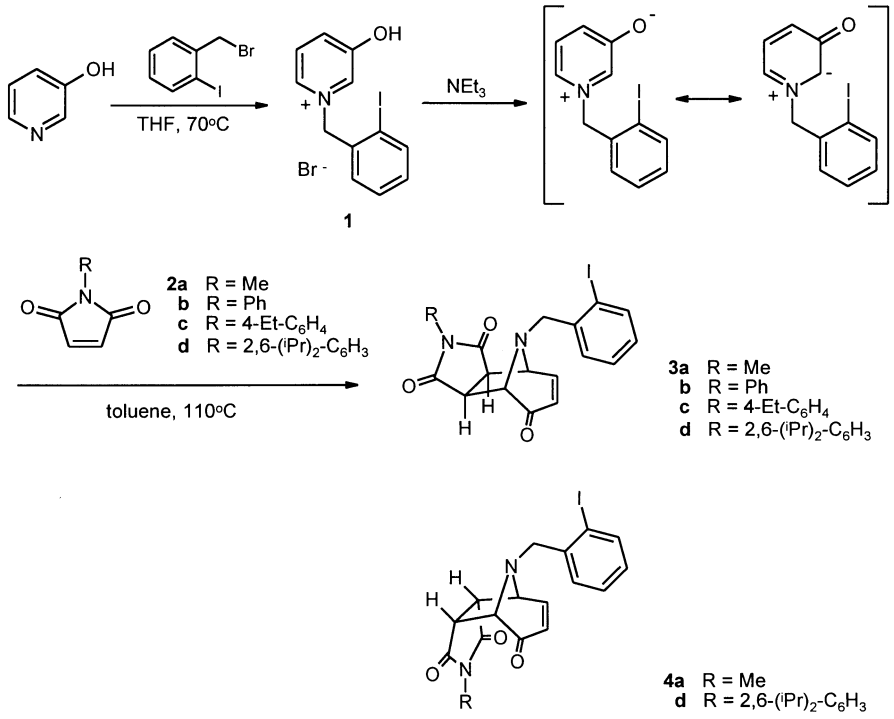


Scheme 1.

Table 1. Cycloaddition between 3-hydroxy-*N*-(2-iodobenzyl)pyridinium bromide and **2a–d**

Maleimide	Time (h)	Products (%)[a]	
2a	16	**3a** (62)	**4a** (10)
2b	17	**3b** (84)	–
2c	28	**3c** (67)	–
2d[b]	39	**3d** (30)	**4d** (33)

All reactions were carried out with 2.5 equiv. NEt_3 at 110°C in toluene.
[a] Isolated yields.
[b] Reaction went to 82% completion.

benzyl bromide afforded **1** in 90% yield. The desired *exo*-cycloadducts[†] **3a–d** were prepared from the reaction of **1** with maleimides **2a–d** and triethylamine in toluene at 110°C (Scheme 1; Table 1). The use of maleimides **2a** and **2d** resulted in the formation of *endo*-cycloadducts **4a** and **4d** in addition to **3a** and **3d** (Table 1).

The cycloaddition of maleimide **2a** occurred in good overall yield affording a 6:1 ratio of *exo*-/*endo*-cycloadducts **3a** and **4a**. Maleimides **2b** and **2c**, on the other hand, exclusively reacted in the *exo* sense to yield **3b** and **3c**, respectively. Reaction of **2d** with the oxopyridinium betaine afforded ca. 1:1 mixture of *exo*-/*endo*-cycloadducts. In this particular case, the reaction only went to 82% completion after 39 h in boiling toluene. Such a slow conversion can be attributed to the bulky *ortho* isopropyl groups on the maleimide. Maleimide **2d** was synthesised using established methods[21] from 2,6-diisopropylaniline.

[†] Cycloadducts **3a–d** are deemed to be *exo* due to the relationship of the maleimide with the enone bridge (*trans*). These adducts can also be considered to be *endo* by virtue of the *endo* approach of the maleimide to the 1,3-dipole.

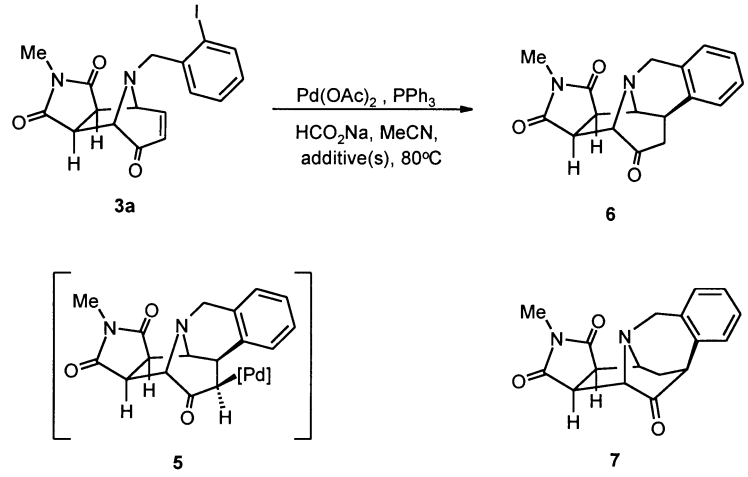
2. Palladium catalysed cyclisation–anion capture

2.1. Non-carbonylative processes

2.1.1. Cyclisation–hydride capture. Cycloadduct **3a** (Scheme 1) was selected to evaluate palladium(0) catalysed cyclisation–hydride capture employing sodium formate[22] as the source of hydride ion (Scheme 2; Table 2). Scheme 2 highlights the advantage of using Katritzky's cycloadducts as cyclisation substrates because β-hydride elimination of **5** is not possible, allowing capture of an external 'anion'. In all cases we isolated a mixture of **6** (via **5**) and **7** resulting from competitive 6-*exo*- and 7-*endo-trig* processes, respectively. The structure of **7** was confirmed by single crystal X-ray analysis (Fig. 1).[23]

In the absence of additives, cyclisation–hydride capture of **3a** was found to be very slow and a very poor yield of **6** was obtained. The addition of 1 equiv. of tetraethyl-ammonium chloride,[22–26] allowed the reaction to go to completion affording **6** and **7** in 90% combined yield. The ratio of **6**/**7** was improved by the addition of zinc chloride to the reaction mixture, presumably due to polarisation of the enone upon Lewis acid coordination to the enone carbonyl group.

2.1.2. Organotin(IV) capture agents. Organostannanes have proved versatile anion capture agents for our catalytic cascade cyclisation–anion capture methodology.[14–17,27] The organostannanes can be pre-formed or, in many instances, generated in situ by hydrostannylation of appropriate alkynes[16,17,27] or allenes.[28] Tributylstannanes serve as excellent nucleophilic components in the Stille[29,30] cross-coupling reaction. Treatment of **3a** with commercially available tributylvinylstannane was evaluated in boiling toluene (Scheme 3; Table 3).



Scheme 2.

Table 2. Effect of additives on cyclisation-hydride capture of **3a** with sodium formate

Time (h)	Additive (equiv.)	Equiv. HCO_2Na	Products (%)[a]	
15	–	1.1	**6** (6)	**7** (0)
21.5	Et_4NCl (1)	3	**6** (46)	**7** (44)
16	Et_4NCl (1) $ZnCl_2$ (1)	1.1	**6** (51)	**7** (28)

Reaction carried out at 80°C in acetonitrile. Catalyst system: 10 mol% $Pd(OAc)_2$ and 20 mol% PPh_3.
[a] Isolated yields.

In all cases a mixture of **8**, **9** and **10** was isolated in the reaction of **3a** with tributylvinylstannane (Scheme 3). Compound **9** is formed by direct capture[22] of the vinyl group from tin by the arylpalladium iodide species whilst **6** arises from hydride capture by **5** (Scheme 2). We have not been able to suppress formation of **6** completely. There are many instances of unwanted hydride capture in the literature.[29] In the absence of additives (Table 3) at 85°C in toluene, product **8** was formed in 71% yield. The addition of 1 equivalent of tetraethylammonium chloride and a reaction temperature 110°C had a detrimental effect on the efficiency of the reaction. Silver(I) acetate as additive was essentially neutral in effect. The best conditions (Table 3) employed a 4:1 ratio of phosphine/palladium and no additives when **8** was formed in 85% yield. At this point it was decided to assess the reactivity of **4a** (*endo*-cycloadduct, Scheme 1) towards palladium(0) catalysed cyclisation–anion capture with tributylvinylstannane (Scheme 4).

Treatment of **4a** with 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3 and 3.5 equiv. of the stannane in boiling toluene afforded direct capture byproduct **10** in 68% yield. This result shows that in substrate **4a**, cyclisation is slower than direct capture of the vinyl group. Such a remarkable difference in reactivity is attributed to the buttressing effect of the maleimide group in the *exo*-cycloadduct substrates (Fig. 2).

The *exo*-cycloadduct **3a** has restricted inversion about the nitrogen atom due to the buttressing of the aryl moiety by the maleimide group. This effect, which is absent in the

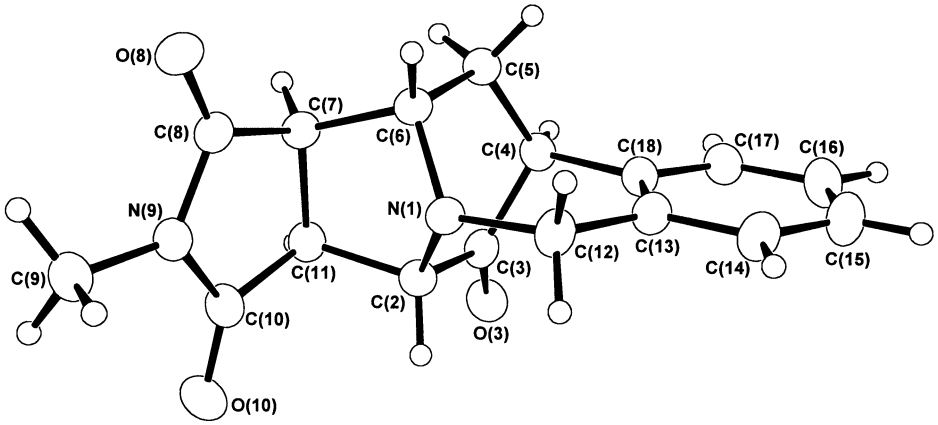
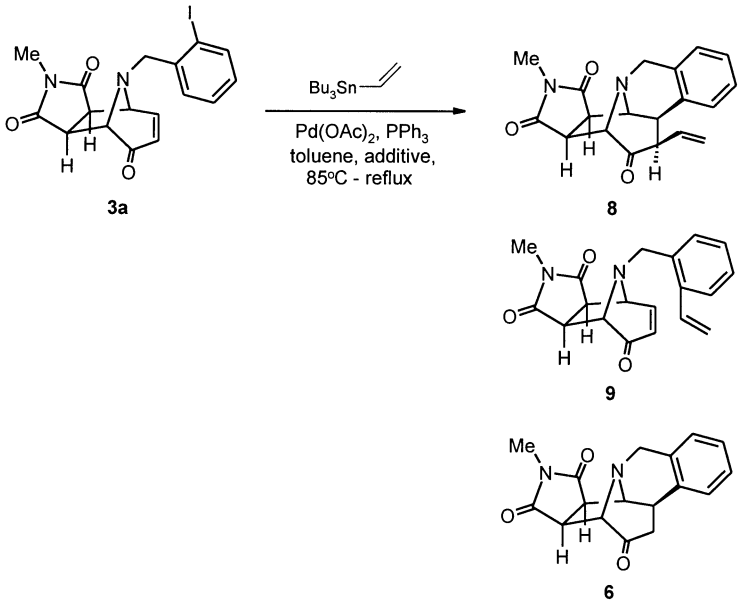


Figure 1. ORTEP[24] representation of the molecular structure of **7**. Note that the structural asymmetric unit contains two almost identical molecules. In the interests of brevity only one molecule is shown.

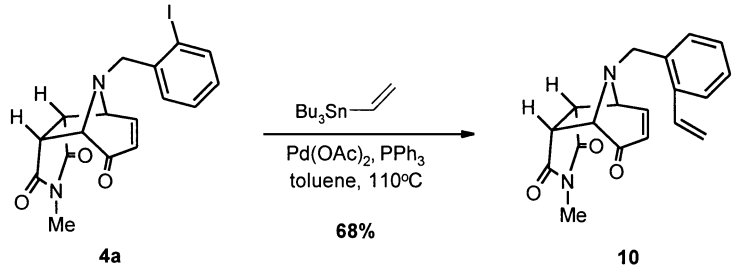


Scheme 3.

Table 3. Cyclisation–vinyl capture of **3a** with tributylvinylstannane (3.5 equiv.)

Time (h)	Temperature (°C)	Ratio Pd/PPh_3	Additive (equiv.)	Products (%)[a]		
24	85	1:2	–	**8** (71)	**9** (14)	**6** (14)
47	110	1:2	NEt_4Cl(1)	**8** (42)	**9** (10)	**6** (24)
14	110	1:2	AgOAc(1)	**8** (74)	**9** (16)	**6** (8)
14	110	1:4	-	**8** (85)	**9** (6)	**6** (7)

Reactions carried out in toluene. Catalyst system: 10 mol% $Pd(OAc)_2$ and 20–40 mol% PPh_3.
[a] Isolated yields.



Scheme 4.

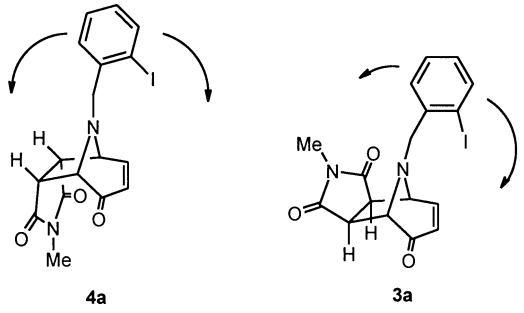
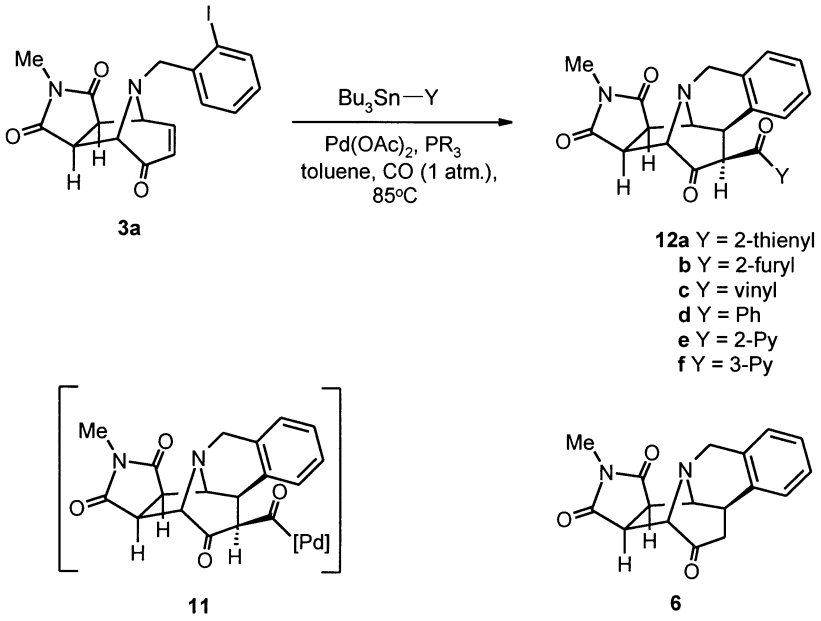


Figure 2.

endo-cycloadduct **4a**, facilitates the desired cyclisation in **3a**.

2.2. Carbonylative processes

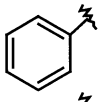
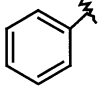
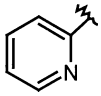
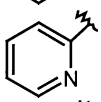
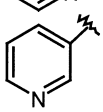
Certain reactants, of which carbon monoxide and allenes are prime examples, allow extension of the relay phase of cyclisation–anion capture processes and offer the opportunity to switch the cascade between inter- and intramolecular processes. These reactants we have termed relay switch components.[31] Use of carbon monoxide (CO) as a relay switch offers access to aldehydes,[14] ketones,[31] esters, amides, etc.



Scheme 5.

We have studied the combination of CO, organostannanes and oxopyridinium betaines as a route to ketones. Cycloadduct **3a** was employed as the substrate for palladium(0) catalysed cyclisation–carbonylation–anion capture employing a range of tributylstannanes as capture reagents (Scheme 5; Table 4).

Table 4. Cyclisation–carbonylation–organostannane capture of **3a** catalyst system

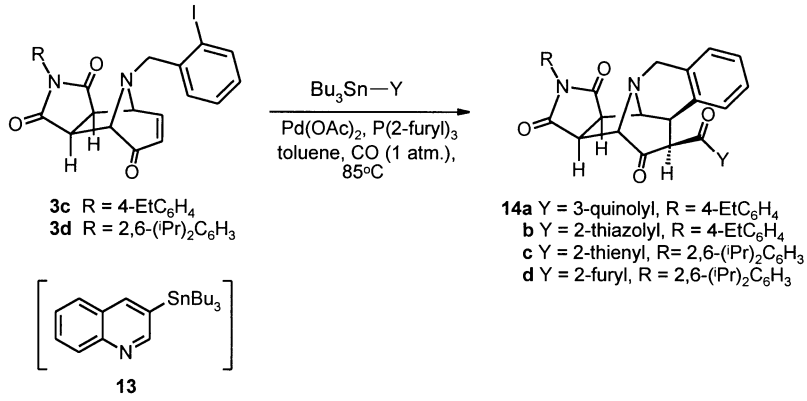
Time (h)	PR_3	Bu_3SnY (Y=)	Products (%)[a]
4	$P(Ph)_3$		**12a** (66), **6** (13)
5	TFP[b]		**12a** (80), **6** (9)
5	$P(Ph)_3$		**12b** (70), **6** (14)
3	$P(Ph)_3$		**12c** (51), **6** (16)
15	$P(Ph)_3$		**12d** (55), **6** (13)
14	TFP		**12d** (86), **6** (10)
14	$P(Ph)_3$		**12e** (51), **6** (19)
15	TFP		**12e** (62), **6** (22)
15	TFP		**12f** (57), **6** (18)

Reactions carried out in toluene at 85°C with CO (1 atm) and Bu_3SnY (2 equiv.). Catalyst system: 10 mol% $Pd(OAc)_2$ and 20 mol% PR_3.
[a] Isolated yields.
[b] TFP=tris(2-furyl)phosphine.

In all cases (Table 4) a mixture of **12** (via **11**, Scheme 5) and **6** was isolated from the reactions. Initially, we employed a triphenylphosphine–palladium acetate catalyst system. This promoted cyclisation–carbonylation–capture of 2-thienyl-(**12a**)- and 2-furyl-(**12b**)-tributylstannane in 66 and 70% yield, respectively. Vinyl group transfer was successful but **12c** was isolated in a lower yield (51%). Aryl/heteroaryl stannanes were also found to be effective capture reagents with phenyl- and 2-pyridyl-tributylstannane reacting with **3a** to afford **12d** and **12e**, respectively (Table 4). These last two reactions, however, required a longer time to achieve complete conversion. Changing the catalyst to tris(2-furyl)phosphine[32]-palladium acetate effected a marked improvement in the yield of **12a** (80%) and **12d** (86%) but only a slight improvement in the yield of **12e** (62%) (Table 4). The cyclisation–carbonylation–capture of tributyl(3-pyridyl)stannane under the new conditions afforded **12f** in 57% yield. The aldehyde corresponding to hydride capture of **11** (Scheme 5) was not detected.

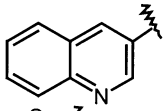
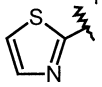
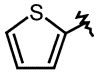
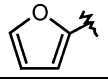
Analogous reactions were carried out with **3c** and **3d** using the $Pd(OAc)_2$–TFP catalyst system (Scheme 6; Table 5).

Substrate **3c** was subjected to palladium(0) catalysed cyclisation–carbonylation–anion capture using 3-quinolyl-(**13**) and 2-thiazolyl-tributylstannane, which were synthesised by known methods.[33] The transfer of bicyclic aromatics was successful as exemplified by the formation of **14a** in good yield (Table 5). Aromatic groups containing two heteroatoms also serve as effective capture reagents. Thus, **14b** was isolated in 54% yield when 2-thiazolyl tributylstannane was employed. Under identical conditions, substrate **3d** was subjected to cyclisation–carbonylation–anion capture. Reaction of **3d** with tributyl(2-thienyl)tin afforded **14c** in 84% yield whereas the 2-furyl stannane gave **14d** in a significantly lower yield (51%) (Table 5).



Scheme 6.

Table 5. Cyclisation–carbonylation–organostannane capture reactions of **3c** and **3d**

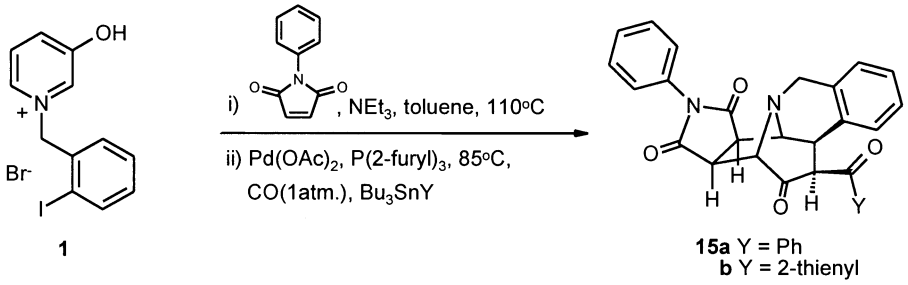
Time (h)	Substrate	Bu_3SnY (Y=)	Products (%)[a]
13	**3c**		**14a** (75)
4	**3c**		**14b** (54)
6	**3d**		**14c** (84)
7	**3d**		**14d** (51)

Reactions carried out in toluene at 85°C with CO (1 atm) and Bu_3SnY (2 equiv.). Catalyst system: 10 mol% $Pd(OAc)_2$ and 20 mol% TFP.
[a] Isolated yields.

We have demonstrated that a wide range of tributylstannane capture reagents readily partake in the cyclisation–carbonylation–anion capture of substrates **3a**, **3c** and **d**. Also, that direct capture byproducts were not detected in the reactions carried out in the presence of CO suggesting that 6-*exo-trig* processes in these substrates is rapid.

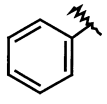
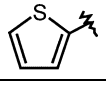
2.2.1. Sequential one-pot cycloaddition–palladium catalysed cyclisation–carbonylation–anion capture. Our cyclisation methodology was combined with Katritzky's oxopyridinium betaine cycloaddition in a two step, one pot process (Scheme 7; Table 6).

N-Phenylmaleimide was the dipolarophile selected for these one pot reactions due to the excellent yield and *exo*-selectivity observed in its cycloadditions with oxopyridinium betaines (Scheme 1; Table 1). Employing



Scheme 7.

Table 6. Sequential one-pot cycloaddition–palladium(0) catalysed cyclisation–carbonylation–anion capture of **1** via **3b**

Time (h)[a]	Bu_3SnY (Y=)	Products (%)[b]
22		**15a** (52)
8		**15b** (61)

Reactions carried out in two steps: (i) **1** was reacted with NEt_3 (2.5 equiv.) and *N*-phenylmaleimide (1 equiv.) at 110°C in toluene; (ii) after cooling to rt catalyst, CO (1 atm) and Bu_3SnY (2 equiv.) were added and the reaction heated to 85°C. Catalyst system (for second step): 10 mol% $Pd(OAc)_2$ and 20 mol% $P(2\text{-furyl})_3$.
[a] Overall time for the two step procedure.
[b] Isolated yields.

phenyl- or 2-thienyl-tributylstannane as capture reagents gave products **15a** (52%) and **15b** (61%) (Table 6). Whilst there is no improvement in the overall yield for the sequential one pot processes, purification of the cycloadduct intermediate has been avoided and a substantial increase in molecular complexity has been achieved involving formation of 2 rings, 5 bonds and 6 stereocentres regio- and stereo-selectively in a one pot protocol.

In summary, we have shown that Katritzky's oxopyridinium betaine cycloadducts serve as excellent substrates for our palladium(0) catalysed cyclisation–anion capture methodology. In the absence of CO, hydride and vinyl capture from organotin(IV) occurred in excellent yield using *exo*-cycloadduct **3a**. Cyclisation of the corresponding *endo*-cycloadduct **4a** was found to be very slow. Reactions

performed in the presence of CO were generally efficient and were successful for a broad range of organotin(IV) reagents. Performing such reactions as a sequential, one pot process affords the desired 1,3-diketones whilst bypassing the need for time consuming intermediate purification.

3. Experimental

3.1. General

Melting points were determined on a Reichert apparatus and are uncorrected. Mass spectral data were obtained from a VG Autospec mass spectrometer operating at 70 eV. Nuclear magnetic resonance spectra spectra were recorded on Bruker DPX250, QE300, AM 400 and DRX 500 machines operating at 250, 300, 400 and 500 MHz, respectively. Unless otherwise specified, deuterochloroform was used as solvent with tetramethylsilane as internal standard. Microanalyses were obtained using a Carlo Erba MOD 11016 instrument and all IR spectra were obtained as films on a Nicolet Magna FT-IR 560 spectrometer. Thin layer chromatography was carried out on Whatman PESIL G/UV polyester plates coated with a 0.2 mm layer of silica gel 60 (Merck 9385). Column chromatography was performed with silica gel 60 (Merck 9385). Petroleum ether refers to the fraction with bp 40–60°C. Anhydrous toluene was commercially available (Aldrich), MeCN was distilled from calcium hydride, THF was distilled from sodium and petroleum ether was distilled prior to use. Non-commercially available organo(IV) compounds and *N*-(2,6-diisopropylphenyl)maleimide were synthesised according to known methods.[21,33] All compounds are named according to the IUPAC system and were determined using the ACD/ILAB web service (http://www.acdlabs.com).

3.1.1. 3-Hydroxy-*N*-(2-iodobenzyl)pyridinium bromide (1). 3-Hydroxypyridine (3.8 g, 0.04 mol) and 2-iodobenzyl bromide (12 g, 0.04 mol) were added to dry THF (200 mL) and heated under reflux for 18 h. The solution was then reduced in volume to ca. 100 mL and filtered to afford **1** (14.07 g, 90%) as a colourless, non-crystalline solid, mp 172–174°C. (Found: C, 36.8; H, 2.8; N, 3.65. $BrC_{12}H_{11}INO$ requires: C, 36.75; H, 2.8; N, 3.55%.) ν_{max} 3385, 1653, 1576, 1540, 1507, 1497, 1457 and 1437 cm^{-1}. δ (d_6-DMSO) 8.57–8.54 (m, 2H, ArH), 8.04–8.00 (m, 3H, ArH), 7.51 (dt, 1H, *J*=7.5, 1.1 Hz, ArH), 7.23 (t, 2H, *J*=7.9 Hz, ArH) and 5.86 (s, 2H, $ArCH_2$). *m/z* (%) 312 ($(M-Br)^+$, 100) and 217 (19).

3.1.2. *N*-(2,6-Diisopropylphenyl)maleimide (2d). A solution of 2,6-diisopropylaniline (9.04 g, 5 mmol) in diethyl ether (10 mL) was added dropwise to a stirred solution of maleic anhydride (5 g, 5 mmol) in diethyl ether (65 mL) and stirring continued for 1 h at rt. The solution was cooled to 10°C (ice) and the resulting solid filtered off and added to a mixture of acetic anhydride (17.1 mL) and sodium acetate (1.66 g, 25.2 mmol). The mixture was heated to 100°C for 40 min, allowed to cool to rt, poured into ice-water (60 mL) and the precipitate filtered off, washed with water (2×50 mL) and petroleum ether (100 mL) and dried under vacuum at 60°C. Crystallisation from hexane afforded the *product* (5.53 g, 51%) as colourless prisms, mp 111–114°C. (Found: C, 74.45; H, 7.6; N, 5.15. $C_{16}H_{19}NO_2$ requires: C, 74.7; H, 7.6; N, 5.15%.) ν_{max} 1712, 1457, 1390, 1375, 1155, 833 and 802 cm^{-1}. δ 7.43 (t, 1H, *J*=7.3 Hz, ArH), 7.26 (d, 2H, *J*=7.8 Hz, ArH), 6.88 (s, 2H, COC*H*=C*H*CO), 2.62 (quin., 2H, *J*=6.9 Hz, $ArCH(CH_3)_2$) and 1.16 (d, 12H, *J*=6.9 Hz, $ArCH(CH_3)_2$). *m/z* (%) 258 ($(M+H)^+$, 100), 214 (51) and 174 (82).

3.2. General procedure for 1,3-dipolar cycloaddition between 1 and 2a–d

A mixture of **1** (15.2 mmol), the *N*-substituted maleimide (15.2 mmol) and triethylamine (5.3 mL, 38 mmol) in toluene (110 mL) were heated under reflux for 16–39 h. After cooling to room temperature, the solvent was removed under vacuum and the residue purified by column chromatography to yield a mixture of *exo*- and *endo*-cycloadducts as pale yellow solids.

3.2.1. (+/−)-*exo*(and *endo*)-4-Methyl-11-(2-iodobenzyl)-4,11-diaza-tricyclo[5.3.1.$0^{2,6}$]undec-9-ene-3,5,8-trione (3a and 4a). Obtained from **1** (5.88 g, 15 mmol) and maleimide **2a** (1.67 g, 15 mmol) after column chromatography eluting with 1:20, 1:15 and 1:10 v/v EtOAc/petroleum ether. The *exo isomer* **3a** (3.91 g, 62%) was obtained as pale yellow rods from EtOAc, mp 150–151°C and the *endo isomer* **4a** (0.71 g, 10%) as pale yellow prisms from EtOAc, mp 148–149°C. **3a**: (Found: C, 48.55; H, 3.85; N, 6.45. $C_{17}H_{13}IN_2O_3$ requires: C, 48.35; H, 3.55; N, 6.65%). ν_{max} 1697, 1436 and 1289 cm^{-1}. δ 7.80 (d, 1H, *J*=7.9 Hz, ArH), 7.30–7.24 (m, 1H, ArH), 7.13 (dd, 1H, *J*=9.9, 4.8 Hz, COCH=C*H*), 7.04–6.99 (m, 1H, ArH), 6.95 (dd, 1H, *J*=7.6, 1.6 Hz, ArH), 6.22 (dd, 1H, *J*=9.9, 1.4 Hz, COC*H*=CH), 4.06 (d, 1H, *J*=4.8 Hz, NC*H*CH=), 3.84 (s, 1H, NCH), 3.81, 3.74 (2×d, 2H, *J*=13.2 Hz, NCH_2Ar), 3.30, 3.11 (2×d, 2H, *J*=7.2 Hz, 2×NCOCH) and 3.05 (s, 3H, NCH_3). *m/z* (%) 422 (M^+, 34), 393 (45), 295 (38), 217(62), 205 (100) and 90 (48). **4a**: (Found: C, 48.15; H, 3.5; N, 6.5. $C_{17}H_{13}IN_2O_3$ requires: C, 48.35; H, 3.55; N, 6.65%). ν_{max} 1733, 1702, 1457, 1435, 1380 and 1284 cm^{-1}. δ 7.84 (dd, 1H, *J*=7.9, 1.1 Hz, ArH), 7.34 (dd, 1H, *J*=7.6, 1.1 Hz, ArH), 7.27 (td, 1H, *J*=7.4, 1.1 Hz, ArH), 7.04 (dd, 1H, *J*=9.8, 5.1 Hz, COCH=C*H*), 7.00–6.96 (m, 1H, ArH), 6.17 (dd, 1H, *J*=9.8, 0.7 Hz, COC*H*=CH), 4.20–4.15 (m, 1H, NCH), 4.03–3.89 (m, 3H, NCH, 2×NCOCH), 3.82, 3.75 (2×d, 2H, *J*=13.7 Hz, NCH_2Ar) and 2.88 (s, 3H, NCH_3). *m/z* (%) 422 (M^+,17), 393 (28), 295(30), 217(75), 205(100) and 90(46).

3.2.2. (+/−)-*exo*-4-Phenyl-11-(2-iodobenzyl)-4,11-diaza-tricyclo[5.3.1.$0^{2,6}$]undec-9-ene-3,5,8-trione (3b). Obtained from **1** (392 mg, 1 mmol) and maleimide **2b** (173 mg, 1 mmol) after column chromatography eluting with 1:15 and 1:10 v/v EtOAc/petroleum ether. The *product* **3b** (407 mg, 84%) was obtained as pale yellow prisms from EtOAc, mp 208–210°C dec. (Found: C, 54.25; H, 3.45; N, 5.5. $C_{22}H_{17}IN_2O_3$ requires: C, 54.55; H, 3.5; N, 5.8%.) ν_{max} 1713, 1701, 1684, 1389, 1203 and 1192 cm^{-1}. δ 7.81 (d, 1H, *J*=7.5 Hz, ArH), 7.49–7.37 (m, 3H, ArH), 7.35–7.27 (m, 3H, ArH), 7.20 (dd, 1H, *J*=9.7, 4.8 Hz, COCH=C*H*), 7.12 (d, 1H, *J*=7.6 Hz, ArH), 6.99 (t, 1H, *J*=7.5 Hz, ArH), 6.28 (dd, 1H, *J*=9.8, 1.3 Hz, COC*H*=CH), 4.23 (d, 1H,

J=4.8 Hz, NC*H*CH=), 4.00 (s, 1H, NCH), 3.90, 3.82 (2×d, 2H, J=13.3 Hz, NCH_2Ar) and 3.48, 3.29(2×d, 2H, J=7.4 Hz, 2×NCOCH). *m/z* (%) 485($(M+H)^+$, 15), 357 (9), 339 (28), 312 (26) and 283 (33).

3.2.3. (+/−)-*exo*-4-(4-Ethylphenyl)-11-(2-iodobenzyl)-4,11-diaza-tricyclo[5.3.1.$0^{2,6}$]undec-9-ene-3,5,8-trione (3c). Obtained from **1** (5.59 g, 14.3 mmol) and maleimide **2c** (2.87 g, 14.3 mmol) after column chromatography eluting with 1:10 v/v EtOAc/petroleum ether. The *product* (4.9 g, 67%) was obtained as pale yellow rods from EtOAc, mp 187–188°C. (Found: C, 55.95; H, 4.2; N, 5.2. $C_{24}H_{21}IN_2O_3$ requires: C, 56.25; H, 4.1; N, 5.45%.) ν_{max} 1711, 1685, 1514, 1388, 1206 and 1190 cm^{-1}. δ 7.36–6.93 (m, 8H, ArH), 4.25 (d, 1H, J=4.7 Hz, NCH), 4.01 (s, 1H, NCH), 3.92, 3.82 (2×d, 2H, J=14.1 Hz, NCH_2Ar), 3.48, 3.28 (2×d, 2H, J=7.6 Hz, 2×NCOCH), 2.71 (q, 2H, J=7.7 Hz, $ArCH_2CH_3$) and 1.27 (t, 3H, J=7.6 Hz, $ArCH_2CH_3$). *m/z* (%) 512 (M^+, 15), 484 (40), 311 (24), 295 (34), 217 (100), 201 (51) and 186 (81).

3.2.4. (+/−)-*exo*(and *endo*)-4-(2,6-Diisopropylphenyl)-11-(2-iodobenzyl)-4,11-diaza-tricyclo[5.3.1.$0^{2,6}$]undec-9-ene-3,5,8-trione (3d and 4d). Obtained from **1** (5.06 g, 12.9 mmol) and maleimide **2d** (3.32 g, 12.9 mmol) after column chromatography eluting with 1:10, 1:5 and 1:1 v/v EtOAc/petroleum ether. The *exo isomer* **3d** (2.20 g, 30%) was obtained as colourless rods from EtOAc, mp 130–135°C and the *endo isomer* **4d** (2.46 g, 33%) as colourless rods from EtOAc, mp 182–184°C. **3d**: (Found: C, 59.05; H, 5.35; N, 4.6. $C_{28}H_{29}IN_2O_3$ requires: C, 59.15; H, 5.1; N, 4.9%). ν_{max} 2966, 1712, 1685, 1465, 1457, 1375 and 1187 cm^{-1}. δ 7.83 (dd, 1H, J=7.9, 1.0 Hz, ArH), 7.43 (t, 1H, J=7.8 Hz, ArH), 7.34–7.23 (m, 4H, ArH), 7.15 (dd, 1H, J=9.9, 4.8 Hz, COCH=C*H*), 6.97 (td, 1H, J=7.8, 1.9 Hz, ArH), 6.25 (dd, 1H, J=9.9, 1.5 Hz, COC*H*=CH), 4.37 (d, 1H, J=4.8 Hz, NC*H*CH=), 4.16 (d, 1H, J=1.1 Hz, NCH), 4.04, 3.93 (2×d, 2H, J=14.5 Hz, NCH_2Ar), 3.60, 3.40 (2×d, 2×1H, J=7.7 Hz, 2×NCOCH), 2.77 (spt, 1H, J=6.7 Hz, $ArCH(Me)_2$), 2.55 (spt, 1H, J=6.8 Hz, $ArCH(Me)_2$) and 1.17–1.03 (m, 12H, J=6.8 Hz, $ArCH(CH_3)_2$). *m/z* (%) 569 ($(M+H)^+$, 33), 441 (15), 351 (54), 334 (29), 312 (100), 217 (96) and 73 (52). **4d**: (Found: C, 59.05; H, 5.3; N, 4.7. $C_{28}H_{29}IN_2O_3$ requires: C, 59.15; H, 5.1; N, 4.9%). ν_{max} 1712, 1685, 1365 and 1181 cm^{-1}. δ 7.86 (dd, 1H, J=7.9, 1.0 Hz, ArH), 7.68–7.19 (m, 6H, ArH, COCH=C*H*), 7.01 (td, 1H, J=7.8, 2.1 Hz, ArH), 6.27 (dd, 1H, J=9.8, 1.4 Hz, COC*H*=CH), 4.29–4.16 (m, 3H, 2×NC*H*, NCOC*H*), 4.12–4.09 (m, 1H, NCOCH), 3.87, 3.81 (2×d, 2H, J=13.7 Hz, NCH_2Ar), 2.49 (spt, 2H, J=6.9 Hz, $ArCH(CH_3)_2$) and 1.17–1.09 (m, 12H, $ArCH(CH_3)_2$). *m/z* (%) 569 ($(M+H)^+$, 36), 351 (56), 312 (100) and 217 (75).

3.3. General procedure for cyclisation–hydride capture with sodium formate

3a (106 mg, 0.25 mmol), palladium(II) acetate (5.6 mg, 10 mol%), triphenyl phosphine (13.2 mg, 20 mol%), additive (NEt_4Cl or $ZnCl_2$, 0.25 mmol) and sodium formate (18.7 mg, 0.275 mmol) were added to MeCN (10 mL) and heated under reflux for 15–21.5 h. The mixture was evaporated to dryness and chromatographed to afford a mixture of **6** and **7**as colourless solids.

3.3.1. (+/−)-*exo*-16-Methyl-2,16-diazapentacyclo[8.8.0.$0^{2,13}$.$0^{4,9}$.$0^{14,18}$]octadeca-4,6,8-triene-12,15,17-trione (6) and (+/−)-*exo*-15-methyl-2,15-diazapentacyclo-[8.7.1.$0^{2,12}$.$0^{4,9}$.$0^{13,17}$]octadeca-4,6,8-triene-11,14,16-trione (7). Obtained from **3a** (101 mg, 0.25 mmol) after column chromatography eluting with 1:9, 1:5 and 1:1 v/v EtOAc/petroleum ether. The *6-membered ring product* **6** (34 mg, 46%) was obtained as fine needles from diethyl ether-hexane, mp 200–201°C dec. and the 7-membered ring product **7** (33 mg, 44%) was obtained as colourless prisms from diethyl ether, mp 230–232°C. **6**: (Found: C, 68.7; H, 5.65; N, 9.45. $C_{17}H_{16}N_2O_3$ requires: C, 68.9; H, 5.4; N, 9.45%). ν_{max} 1734, 1696, 1436, 1386, 1289, 1128 and 1004 cm^{-1}. δ (C_6D_6) 6.96–6.89 (m, 2H, ArH), 6.57 (d, 1H, J=7.1 Hz, ArH), 6.41 (d, 1H, J=6.6 Hz, ArH), 3.88 (d, 1H, J=1.6 Hz, NCH), 3.82, 3.61 (2×d, 2H, J=18.7 Hz, NCH_2Ar), 3.50 (d, 1H, J=1.9 Hz, NCH), 2.65 (s, 3H, NCH_3), 2.53–2.51 (m, 1H, ArC*H*CH_2), 2.48, 2.30 (2×d, 2H, J=7.7 Hz, 2×NCOCH) and 2.07–1.96 (m, 2H, $ArCHCH_2$). *m/z* (%) 296 (M^+, 39), 284 (37), 268 (100), 149 (30), 117 (100), 91 (83), 57 (30) and 39 (33). **7**: (Found: C, 68.65; H, 5.45; N, 9.55. $C_{17}H_{16}N_2O_3$ requires: C, 68.9; H, 5.4; N, 9.45%). ν_{max} 1733, 1695, 1437, 1296, 1239 1133 and 1115 cm^{-1}. δ (C_6D_6) 6.88–6.86 (m, 2H, ArH), 6.79–6.77 (m, 1H, ArH), 6.47–6.45 (m, 1H, ArH), 3.85 (s, 1H, NCH), 3.84, 3.74 (2×d, 2H, J=18.2 Hz, NCH_2Ar), 3.51 (d, 1H, J=8.9 Hz, NC*H*CH), 3.18 (d, 1H, J=7.5 Hz, ArCHCO), 2.71 (dd, 1H, J=7.2, 1.9 Hz, NCOCH), 2.61 (s, 3H, NCH_3), 2.08 (m, 1H, NCOCH), 1.95 (dd, 1H, J=10.2, 9.1 Hz, $COCHCH_2$) and 1.39–1.33 (m, 1H, $COCHCH_2$). *m/z* (%) 297 ($(M+H)^+$, 20), 268 (90), 117 (100) and 91 (45).

3.4. General procedure for cyclisation–vinyl capture with tributyl(vinyl)stannane

3a or **4a** (106 mg, 0.25 mmol), palladium(II) acetate (5.6 mg, 10 mol%), the phenylphosphine (20–40 mol%) and tributyl(vinyl)stannane (1–3.5 equiv.) in toluene (2.5–5 mL) were rapidly heated to reflux for 14–47 h. The reaction mixture was allowed to cool to rt, evaporated to dryness, dissolved in MeCN (10 mL), washed with hexane (3×20 mL) and the MeCN layer separated and evaporated to dryness. The residue was chromatographed to afford mixtures of **8**, **9** and **6**.

3.4.1. (+/−)-*exo*-16-Methyl-11-vinyl-2,16-diazapentacyclo[8.8.0.$0^{2,13}$.$0^{4,9}$.$0^{14,18}$]octadeca-4,6,8-triene-12,15,17-trione (8) and (+/−)-*exo*-4-methyl-11-(2-vinylbenzyl)-4,11-diaza-tricyclo[5.3.1.$0^{2,6}$]-undec-9-ene-3,5,8-trione (9). Obtained from **3a** (422 mg, 1 mmol) after column chromatography eluting with 1:5, 1:3 and 3:2 v/v EtOAc/petroleum ether. The *product* **8** (274 mg, 85%) was obtained as colourless prisms from EtOAc/petroleum ether, mp 180–183°C and the *direct capture byproduct* **9** (19.3 mg, 6%) was obtained as colourless prisms from EtOAc/petroleum ether, mp 157–160°C. **8**: (Found: C, 70.7; H, 5.6; N, 8.5. $C_{19}H_{18}N_2O_3$ requires: C, 70.8; H, 5.6; N, 8.7%). δ 7.30–7.11 (m, 2H, ArH), 7.02 (t, 2H, J=7.3 Hz, ArH), 5.45–5.35 (m, 1H, H_2C=C*H*), 5.10 (d, 1H, J=16.0 Hz, H_2C=CH), 4.98 (d, 1H, J=10.0 Hz, H_2C=CH), 4.50, 4.40 (2×d, 2H, J=18.1 Hz, NCH_2Ar), 4.01 (s, 1H, NC*H*CH), 3.73 (s, 1H, NCHCO), 3.55 (d, 1H, J=7.0 Hz, ArCH), 3.25, 3.05 (2×d,

2H, J=8.0 Hz, 2×NCOCH), 3.02 (s, 3H, NCH_3) and 2.84 (t, 1H, J=7.0 Hz, COC*H*(CH=CH_2)). *m/z* (%) 323((M+H)$^+$, 33), 81 (37), 69 (62) and 55 (100). **9**: (Found: C, 70.55; H, 5.55; N, 8.4. $C_{19}H_{18}N_2O_3$ requires: C, 70.8; H, 5.6; N, 8.7%). δ 7.49 (d, 1H, J=7.4 Hz, ArH), 7.28–7.13 (m, 2H, ArH), 7.05–6.96 (m, 2H, ArH, C*H*=CHCO), 6.77 (dd, 1H, J=15.6, 11.0 Hz, ArC*H*=CH_2), 6.18 (d, 1H, J=9.4 Hz, COC*H*=CH), 5.55 (d, 1H, J=15.6 Hz, ArCH=CH_2), 5.12 (d, 1H, J=11.0 Hz, ArCH=CH_2), 3.92 (d, 1H, J=4.7 Hz, NC*H*CH=), 3.80–3.73 (m, 3H, NCH_2Ar, NCH), 3.24, 3.08 (2×d, 2H, J=7.7 Hz, 2×NCOCH) and 2.97 (s, 3H, NCH_3). *m/z* (%) 322 (M$^+$, 13), 294 (32), 268 (81), 115 (100) and 91(60).

3.4.2. (+/−)-*endo*-4-Methyl-11-(2-vinylbenzyl)-4,11-diazatricyclo[5.3.1.0^{2,6}]undec-9-ene-3,5,8-trione (10). Obtained from **4a** (422 mg, 1 mmol) after column chromatography eluting with 1:5, 1:3 and 1:1 v/v EtOAc/petroleum ether. The *direct capture byproduct* **10** (219 mg, 68%) was obtained as a pale yellow, non-crystalline solid, mp 87–89°C. (Found: C, 70.65; H, 5.85; N, 8.4. $C_{19}H_{18}N_2O_3$ requires: C, 70.8; H, 5.6; N, 8.7%.) δ 7.54 (d, 1H, J=7.6 Hz, ArH), 7.30 (t, 1H, J=7.5 Hz, ArH), 7.23 (t, 1H, J=7.6 Hz, ArH), 7.12 (d, 1H, J=7.6 Hz, ArH), 7.04–6.92 (m, 2H, ArC*H*=CH_2, COCH=C*H*), 6.15 (d, 1H, J=9.3 Hz, COC*H*=CH), 5.64 (d, 1H, J=16.9 Hz, ArCH=CH_2), 5.29 (d, 1H, J=10.2 Hz, ArCH=CH_2), 4.05 (t, 1H, J=5.6 Hz, NC*H*CH=), 4.01–3.92 (m, 3H, NCH, NCH_2Ar), 3.87 (d, 1H, J=7.1 Hz, NCOCH), 3.82–3.79 (m, 1H, NCOCH) and 2.86 (s, 3H, NCH_3). *m/z* (%) 323 ((M+H)$^+$, 25), 212 (47), 205 (38), 149 (47) and 117 (100).

3.5. General procedure for cyclisation–CO insertion–anion capture with tributyl-stannanes

3a, **3c** or **3d** (0.25 mmol), palladium(II) acetate (5.6 mg, 10 mol%), the trisubstituted phosphine (20 mol%) and the trialkylstannane (2 equiv.) in toluene* (2.5 mL) were rapidly heated to 85°C for 3–15 h under 1 atm of carbon monoxide (balloon). On cooling to rt the reaction mixture was evaporated to dryness, dissolved in MeCN (10 mL), washed with hexane (3×20 mL), the MeCN layer separated and evaporated to dryness. The residue was chromatographed to afford mixtures of **12a–f** and **6**. [* CO gas was bubbled through the solvent at rt for 5 min prior to reagent addition.]

3.5.1. (+/−)-*exo*-11-(2-Thienoyl)-16-methyl-2,16-diazapentacyclo[8.8.0.0^{2,13}.0^{4,9}.0^{14,18}]-octadeca-4,6,8-triene-12,15,17-trione (12a). Obtained from **3a** (106 mg, 0.25 mmol) after column chromatography eluting with 1:4 and 1:1 v/v EtOAc/petroleum ether. The *product* **12a** (82 mg, 80%) was obtained as colourless plates from EtOAc/petroleum ether, mp 251–252°C dec. (Found: C, 63.5; H, 4.4; N, 6.65. $C_{22}H_{18}N_2O_4S{\cdot}0.5H_2O$ requires: C, 63.6; H, 4.6; N, 6.75%.) ν_{max} 1733, 1716, 1698, 1668, 1662, 1558, 1436 and 1290 cm^{-1}. δ 7.66–7.64 (m, 2H, ArH), 7.20–7.14 (m, 2H, ArH), 7.02 (d, 1H, J=7.6 Hz, ArH), 6.93 (t, 1H, J=7.5 Hz, ArH), 6.53 (d, 1H, J=7.7 Hz, ArH), 4.73, 4.35 (2×d, 2H, J=18.5 Hz, NCH_2Ar), 4.62 (s, 1H, NCH), 4.11 (s, 1H, NCH), 4.02, 3.98 (2×d, 2H, J=7.2 Hz, COC*HCH*), 3.33 (d, 1H, J=7.4 Hz, NCOCH) and 3.09–3.06 (m, 4H, NCH_3, NCOCH). *m/z* (%) 407 ((M+H)$^+$, 100), 378 (65), 267 (77) and 111 (34).

3.5.2. (+/−)-*exo*-11-(2-Furoyl)-16-methyl-2,16-diazapentacyclo[8.8.0.0^{2,13}.0^{4,9}.0^{14,18}]-octadeca-4,6,8-triene-12,15,17-trione (12b). Obtained from **3a** (422 mg, 1 mmol) after column chromatography eluting with 1:4 and 1:1 v/v EtOAc/petroleum ether. The *product* **12b** (273 mg, 70%) was obtained as colourless prisms from DCM/petroleum ether, mp 249–251°C dec. (Found: C, 62.3; H, 4.45; N, 6.45. $C_{22}H_{18}N_2O_5{\cdot}0.5CH_2Cl_2$ requires: C, 62.4; H, 4.4; N, 6.45%.) ν_{max} 1698, 1675, 1466, 1437, 1290, 1117, 1028 and 880 cm^{-1}. δ 7.59 (d, 1H, J=1.0 Hz, ArH), 7.15 (t, 1H, J=8.7 Hz, ArH), 7.12–6.99 (m, 2H, ArH), 6.94 (t, 1H, J=8.1 Hz, ArH), 6.59 (d, 1H, J=7.1 Hz, ArH), 6.54 (dd, J=3.7, 1.8 Hz, 1H, ArH), 4.69, 4.33 (2×d, 2H, J=19.1 Hz, NCH_2Ar), 4.65 (s, 1H, NCH), 4.20, 3.95 (2×d, 2H, J=7.1 Hz, COC*HCH*), 4.11 (s, 1H, NCH), 3.31, 3.05 (2×d, 2H, J=7.4 Hz, 2×NCOCH) and 3.06 (s, 3H, NCH_3). *m/z* (%) 391 ((M+H)$^+$, 100), 362 (63), 267 (68) and 73 (31).

3.5.3. (+/−)-*exo*-11-Acryloyl-16-methyl-2,16-diazapentacyclo[8.8.0.0^{2,13}.0^{4,9}.0^{14,18}]octadeca-4,6,8-triene-12,15, 17-trione (12c). Obtained from **3a** (422 mg, 1 mmol) after column chromatography eluting with 1:4 and 1:1 v/v EtOAc/petroleum ether. The *product* **12c** (179 mg, 51%) was obtained as colourless prisms from EtOAc-petroleum ether, mp 127–129°C. (Found: C, 68.15; H, 5.15; N, 8.0. $C_{20}H_{18}N_2O_4$ requires: C, 68.55; H, 5.15; N, 8.0%.) ν_{max} 1698, 1436, 1290, 1136, 1117 and 996 cm^{-1}. δ 7.19 (t, 1H, J=7.4 Hz, ArH), 7.08 (t, 1H, J=7.4 Hz, ArH), 7.00 (d, 1H, J=7.6 Hz, ArH), 6.92 (d, 1H, J=7.4 Hz, ArH), 6.27 (dd, 1H, J=17.4, 10.3 Hz, COC*H*=CH_2), 6.09 (d, 1H, J=16.9 Hz, COCH=CH_2), 5.79 (d, 1H, J=10.8 Hz, COCH=CH_2), 4.62, 4.31 (2×d, 2H, J=16.9 Hz, NCH_2Ar), 4.58 (s, 1H, NCH), 4.08 (s, 1H, NCH), 3.92, 3.54 (2×d, 2H, J=7.0 Hz, COC*HCH*), 3.28, 2.98 (2×d, 2H, J=7.4 Hz, 2×NCOCH) and 3.05 (s, 3H, NCH_3). *m/z* (%) 351 ((M+H)$^+$, 100), 322 (63), 267 (97) and 182 (15).

3.5.4. (+/−)-*exo*-11-Benzoyl-16-methyl-2,16-diazapentacyclo[8.8.0.0^{2,13}.0^{4,9}.0^{14,18}]octadeca-4,6,8-triene-12,15,17-trione (12d). Obtained from **3a** (212 mg, 0.5 mmol) after column chromatography eluting with 1:4 and 1:1 v/v EtOAc/petroleum ether. The *product* **12d** (172 mg, 86%) was obtained as colourless rods from DCM/petroleum ether, mp 167–169°C. (Found: C, 70.45; H, 5.0; N, 6.9. $C_{24}H_{20}N_2O_4{\cdot}0.25H_2O$ requires: C, 70.4; H, 5.15; N, 6.85%.) ν_{max} 1733, 1699, 1653, 1436, 1386, 1289, 1247 and 1117 cm^{-1}. δ 8.06–7.54 (m, 3H, ArH), 7.42 (t, 2H, J=7.4 Hz, ArH), 7.14 (dt, 1H, J=7.5, 1.2 Hz, ArH), 7.01 (d, 1H, J=6.9 Hz, ArH), 6.84 (dt, 1H, J=7.6, 1.2 Hz, ArH), 6.29 (dd, 1H, J=7.6, 0.8 Hz, ArH), 4.73 (s, 1H, NCH), 4.71, 4.34 (2×d, 2×H, J=18.4 Hz, NCH_2Ar), 4.13, 3.91 (2×d, 2H, J=7.1 Hz, COC*HCH*), 4.10 (s, 1H, NCH), 3.34 (d, 1H, J=7.3 Hz, NCOCH) and 3.11–3.07 (m, 4H, NCH_3, NCOCH). *m/z* (%) 401 ((M+H)$^+$, 75), 372 (37), 267 (100) and 105 (55).

3.5.5. (+/−)-*exo*-11-(2-Pyridoyl)-16-methyl-2,16-diazapentacyclo[8.8.0.0^{2,13}.0^{4,9}.0^{14,18}]-octadeca-4,6,8-triene-12,15,17-trione (12e). Obtained from **3a** (422 mg, 1 mmol)

after column chromatography eluting with 0:0:1, 0.5:1:98 and 0.5:3:96 v/v NEt_3/MeOH/DCM. The *product* **12e** (249 mg, 62%) was obtained as colourless prisms from EtOAc/petroleum ether, mp 242–246°C. (Found: C, 68.5; H, 4.8; N, 10.75. $C_{23}H_{19}N_3O_4$ requires: C, 68.8; H, 4.7; N, 10.5%.) ν_{max} 1774, 1697, 1437, 1289, 1244, 1117 and 997 cm^{-1}. δ 8.70 (m, 1H, ArH), 7.74 (t, 1H, *J*=7.7 Hz, ArH), 7.59 (d, 1H, *J*=7.8 Hz, ArH), 7.50 (m, 1H, ArH), 7.11 (t, 1H, *J*=7.6 Hz, ArH), 7.00 (d, 1H, *J*=7.1 Hz, ArH), 6.82 (t, 1H, *J*=7.2 Hz, ArH), 6.34 (d, 1H, *J*=7.0 Hz, ArH), 4.69, 4.35 (2×d, 2H, *J*=18.4 Hz, NCH_2Ar), 4.67 (s, 1H, NCH), 4.59, 4.39 (2×d, 1H, *J*=7.0 Hz, 2×COC*H*C*H*), 4.10 (s, 1H, NCH), 3.34, 3.11 (2×d, 2H *J*=7.4 Hz, 2×NCOCH) and 3.07 (s, 3H, NCH_3). *m/z* (%) 402 ($(M+H)^+$, 100), 373 (45), 308 (9) and 267 (38).

3.5.6. (+/−)-*exo*-11-(3-Pyridoyl)-16-methyl-2,16-diazapentacyclo[8.8.0.0^{2,13}.0^{4,9}.0^{14,18}]-octadeca-4,6,8-triene-12,15,17-trione (12f). Obtained from **3a** (422 mg, 1 mmol) after column chromatography eluting with 0:0:1, 0.5:1:98 and 0.5:3:96 v/v NEt_3/MeOH/DCM. The *product* **12f** (229 mg, **57%**) was obtained as colourless prisms from EtOAc/petroleum ether, mp 183–185°C. (Found: C, 68.35; H, 4.85; N, 10.65. $C_{23}H_{19}N_3O_4{\cdot}0.25H_2O$ requires: C, 68.06; H, 4.81; N, 10.36%.) ν_{max} 1734, 1717, 1699, 1686 and 1653 cm^{-1}. δ 8.83–8.79 (m, 2H, ArH), 7.79 (dd, 1H, *J*=7.9, 2.0 Hz, ArH), 7.38 (dd, 1H, *J*=8.0, 4.9 Hz, ArH), 7.17 (t, 1H, *J*=7.6 Hz, ArH), 7.03 (d, 1H, *J*=7.7 Hz, ArH), 6.87 (t, 1H, *J*=7.5 Hz, ArH), 6.31 (d, 1H, *J*=7.7 Hz, ArH), 4.74 (s, 1H, NCH), 4.69, 4.35 (2×d, 2H, *J*=18.5 Hz, NCH_2Ar), 4.12 (s, 1H, NCH), 4.09 (m, 1H, COC*H*CH), 3.89 (d, 1H, *J*=7.1 Hz, COCHC*H*), 3.35 and 3.11 (2×d, 2H, *J*=7.4 Hz, 2×NCOCH) and 3.08 (s, 3H, NCH_3). *m/z* (%) 402 ($(M+H)^+$, 100), 373 (31), 267 (48) and 220 (5).

3.5.7. 3-(Tributylstannyl)quinoline (13). Butyl lithium (9.37 mL, 1.6 M in hexanes, 15 mmol) was added dropwise to a cooled (−78°C) stirred solution of 3-bromoquinoline (3.12 g, 15 mmol) in dry diethyl ether (100 mL) such that the temperature did not exceed −70°C. The solution was left at −78°C for a further hour when tributyltin chloride (4.07 mL, 15 mmol) in diethyl ether (20 mL) was added dropwise and stirring continued for 1 h. The mixture was allowed to warm to rt and water (80 mL) then carefully added to the mixture. The organic phase was separated and the aqueous layer extracted with diethyl ether (3×50 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was chromatographed eluting with diethyl ether–pentane mixtures to afford the *product* (3.89 g, 62%) as a colourless oil. (Found: C, 60.05; H, 7.8; N, 3.35. $C_{21}H_{33}NSn$ requires: C, 60.30; H, 7.9; N, 3.35%.) ν_{max} 2957, 2926, 2871, 2853, 1559, 1488 and 1457 cm^{-1}. δ_H 8.92 (d, 1H, *J*=1.5 Hz, ArH), 8.24 (s, 1H, ArH), 8.07 (d, 1H, *J*=8.4 Hz, ArH), 7.78 (d, 1H, *J*=8.1 Hz, ArH), 7.69 (td, 1H, *J*=8.4, 1.5 Hz, ArH), 7.54 (td, 1H, *J*=8.0, 1.1 Hz, ArH), 1.62–1.54 (m, 6H, $SnBu_3$), 1.39–1.31 (m, 6H, *J*=7.1 Hz, $SnBu_3$), 1.20–1.14 (m, 6H, *J*=7.8 Hz, $Sn(CH_2CH_2CH_2CH_3)_3$) and 0.89 (t, 9H, *J*=7.8 Hz, $Sn(CH_2CH_2CH_2CH_3)_3$). *m/z* (%, major isotope) 420 ($(M+H)^+$, 100), 362 (18), 248 (45) and 130 (27).

3.5.8. (+/−)-*exo*-11-(3-Quinoloyl)-16-(4-ethylphenyl)-2,16-diazapentacyclo-[8.8.0.0^{2,13}.0^{4,9}.0^{14,18}]octadeca-4,6,8-triene-12,15,17-trione (14a). Obtained from **3c** (256 mg, 0.5 mmol) after column chromatography eluting with 0:0:1, 0.5:1:98 and 0.5:3:96 v/v NEt_3/MeOH/DCM. The *product* **14a** (203 mg, 75%) was obtained as colourless prisms from EtOAc/petroleum ether, mp 188–189°C. (Found: C, 73.95; H, 5.05; N, 7.5. $C_{34}H_{27}N_3O_4{\cdot}0.5H_2O$ requires: C, 74.2; H, 5.1; N, 7.6%.) ν_{max} 1733, 1708, 1684, 1653, 1559, 1515, 1506, 1387 and 1186 cm^{-1}. δ 8.95 (d, 1H, *J*=2.2 Hz, ArH), 8.45 (d, 1H, *J*=2.0 Hz, ArH), 8.18 (d, 1H, *J*=8.5 Hz, ArH), 7.95–7.86 (m, 2H, ArH), 7.69 (t, 1H, *J*=7.0 Hz, ArH), 7.36–7.21 (m, 4H, ArH), 7.16 (d, 1H, *J*=7.1 Hz, ArH), 7.07 (d, 1H, *J*=7.3 Hz, ArH), 6.82 (t, 1H, *J*=6.8 Hz, ArH), 6.26 (d, 1H, *J*=7.3 Hz, ArH), 4.92 (s, 1H, NCH), 4.84, 4.46 (2×d, 2H, *J*=18.5 Hz, NCH_2Ar), 4.32–4.28 (m, 2H, NCH, COC*H*CH), 4.00 (d, 1H, *J*=7.1 Hz, COCHC*H*), 3.53, 3.31 (2×d, 2H, *J*=7.6 Hz, 2×NCOCH), 2.70 (q, 2H, *J*=7.7 Hz, $ArCH_2CH_3$) and 1.26 (t, 3H, *J*=7.6 Hz, $ArCH_2CH_3$). *m/z* (%) 542 ($(M+H)^+$, 100), 357 (96), 285 (55), 207 (30), 179 (65), 147 (70) and 133 (35).

3.5.9. (+/−)-*exo*-11-(2-Thiazolyl)-16-(4-ethylphenyl)-2,16-diazapentacyclo-[8.8.0.0^{2,13}.0^{4,9}.0^{14,18}]octadeca-4,6,8-triene-12,15,17-trione (14b). Obtained from **3c** (246 mg, 0.48 mmol) after column chromatography eluting with 1:5 and 1:1 v/v EtOAc/petroleum ether. The *product* **14b** (131 mg, 54%) was obtained as colourless prisms from DCM/petroleum ether, mp 162–165°C. (Found: C, 61.55; H, 4.35; N, 7.5. $C_{28}H_{23}N_3O_4S{\cdot}0.75CH_2Cl_2$ requires: C, 61.5; H, 4.35; N, 7.5%.) ν_{max} 1709, 1685, 1514, 1386, 1183 and 945 cm^{-1}. δ 8.06 (d, 1H, *J*=2.9 Hz, ArH), 7.68 (d, 1H, *J*=3.0 Hz, ArH), 7.33, 7.24 (2×d, 4H, *J*=8.4 Hz, ArH), 7.15 (t, 1H, *J*=7.4 Hz, ArH), 7.03 (d, 1H, *J*=7.5 Hz, ArH), 6.89 (t, 1H, *J*=6.8 Hz, ArH), 6.50 (d, 1H, *J*=7.5 Hz, ArH), 4.78 (s, 1H, NCH), 4.76 (d, 1H, *J*=18.5 Hz, NCH_2Ar), 4.51–4.39 (m, 3H, NCH_2Ar, COC*H*C*H*), 4.24 (s, 1H, NCH), 3.48, 3.25 (2×d, 2H, *J*=7.5 Hz, 2×NCOCH), 2.69 (q, 2H, *J*=7.6 Hz, $ArCH_2CH_3$) and 1.26 (t, 3H, *J*=7.6 Hz, $ArCH_2CH_3$). *m/z* (%) 498 ($(M+H)^+$, 45), 357 (100), 182 (55) and 73 (77).

3.5.10. (+/−)-*exo*-11-(2-Thienoyl)-16-(2,6-diisopropylphenyl)-2,16-diazapentacyclo-[8.8.0.0^{2,13}.0^{4,9}.0^{14,18}]octadeca-4,6,8-triene-12,15,17-trione (14c). Obtained from **3d** (284 mg, 0.5 mmol) after column chromatography eluting with 1:5 and 1:1 v/v EtOAc/petroleum ether. The *product* **14c** (233 mg, 84%) was obtained as a colourless, non-crystalline solid, mp 220–225°C dec. (Found: C, 71.7; H, 6.0; N, 4.8. $C_{33}H_{32}N_2O_4S$ requires: C, 71.75; H, 5.8; N, 5.05%.) ν_{max} 1709, 1684, 1662, 1653, 1414, 1381 and 1206 cm^{-1}. δ 7.68–7.66 (m, 2H, ArH), 7.41 (t, 1H, *J*=7.7 Hz, ArH), 7.28–7.15 (m, 4H, ArH), 7.07 (d, 1H, *J*=7.2 Hz, ArH), 6.97 (t, 1H, *J*=7.6 Hz, ArH), 6.58 (d, 1H, *J*=7.5 Hz, ArH), 4.87, 4.45 (2×d, 2H, *J*=18.4 Hz, NCH_2Ar), 4.74 (s, 1H, NCH), Hz. HHH 4.28 (s, 1H, NCH), 4.09–4.03 (m, 2H, COC*H*C*H*), 3.58, 3.32 (2×d, 2H, *J*=7.4 Hz, 2×NCOCH), 2.91 (m, 1H, *J*=6.7 Hz, $ArCH(CH_3)_2$), 2.64 (m, 1H, *J*=6.8 Hz, $ArCH(CH_3)_2$) and 1.26–1.14 (m, 12H, $ArCH(CH_3)_2$). *m/z* (%) 553 ($(M+H)^+$, 9), 413 (28), 177 (45), 91 (39) and 69 (64).

3.5.11. (+/−)-*exo*-11-(2-Furoyl)-16-(2,6-diisopropylphenyl)-2,16-diazapentacyclo-[8.8.0.0^{2,13}.0^{4,9}.0^{14,18}]octadeca-4,6,8-triene-12,15,17-trione (14d). Obtained from **3d** (267 mg, 4.7 mmol) after column chromatography eluting with 1:5 and 1:1 v/v EtOAc/petroleum ether. The *product* **14d** (130 mg, 51%) was obtained as colourless rods from EtOAc/petroleum ether, mp 245°C dec. (Found: C, 73.85; H, 6.15; N, 5.05. $C_{33}H_{32}N_2O_5{\cdot}0.25H_2O$ requires: C, 73.9; H, 5.95; N, 5.2%.) ν_{max} 1712, 1685, 1652, 1458, 1378, 1208 and 1193 cm^{-1}. δ 7.61 (m, 1H, ArH), 7.50–7.11 (m, 2H, ArH), 7.10–7.01 (m, 4H, ArH), 6.97 (t, 1H, *J*=7.2 Hz, ArH), 6.62 (d, 1H, *J*=7.3 Hz, ArH), 6.51 (d, 1H, *J*=1.0 Hz, ArH), 4.82, 4.43 (2×d, 2H, *J*=18.2 Hz, NCH_2Ar), 4.77 (s, 1H, NCH), 4.25 (s, 1H, NCH), 4.09–3.99 (m, 2H, COC*H*C*H*Ar), 3.58, 3.30 (2×d, 2H, *J*=7.4 Hz, 2×NCOCH), 2.92 (m, 1H, *J*=6.8 Hz, ArC*H*$(CH_3)_2$), 2.67 (m, 1H, *J*=6.8 Hz, ArC*H*$(CH_3)_2$) and 1.30–1.09 (m, 12H, ArCH(CH_3)$_2$). *m/z* (%) 537 ((M+H)$^+$, 100), 185 (52), 129 (19) and 73 (26).

3.6. General procedure for sequential, one pot cycloaddition–cyclisation–CO insertion–anion capture with tributyl-stannanes

A mixture of **1** (1 mmol), *N*-phenylmaleimide (173 mg, 1 mmol) and triethylamine (0.348 mL, 2.5 mmol) in toluene (10 mL) were heated under reflux for 4 h. After cooling to room temperature, palladium(II) acetate (5.6 mg, 10 mol%), the trisubstituted phosphine (20 mol%) and the trialkylstannane (2 equiv.) were added and the solution was rapidly heated to 85°C for 3–15 h under 1 atm of carbon monoxide (balloon). On cooling to rt the reaction mixture was evaporated to dryness, dissolved in MeCN (10 mL), washed with hexane (3×20 mL), the MeCN layer separated and evaporated to dryness. The residue was chromatographed to afford **15a–b**.

3.6.1. (+/−)-*exo*-11-Benzoyl-16-phenyl-2,16-diazapentacyclo[8.8.0.0^{2,13}.0^{4,9}.0^{14,18}]octadeca-4,6,8-triene-12,15,17-trione (15a). Obtained from **1** (392 mg, 1 mmol) after column chromatography eluting with 1:5 and 1:1 v/v EtOAc/petroleum ether. The *product* **15a** (240 mg, 52%) was obtained as a colourless, non-crystalline solid from EtOAc/petroleum ether, mp 266°C dec. (Found: C, 75.2; H, 4.7; N, 6.05. $C_{29}H_{22}N_2O_4$ requires: C, 75.3; H, 4.8; N, 6.05%.) ν_{max} 1712, 1684, 1497, 1387, 1206 and 1183 cm^{-1}. δ 7.60 (d, 2H, *J*=8.0 Hz, ArH), 7.56–7.34 (m, 8H, ArH), 7.16 (t, 1H, *J*=7.7 Hz, ArH), 7.03 (d, 1H, *J*=7.5 Hz, ArH), 6.86 (t, 1H, *J*=7.8 Hz, ArH), 6.32 (d, 1H, *J*=7.6 Hz, ArH), 4.87 (s, 1H, NCH), 4.80, 4.43 (2×d, 2H, *J*=18.5 Hz, NCH_2Ar), 4.24 (s, 1H, NCH), 4.18, 3.96 (2×d, 2H, *J*=7.0 Hz, COC*H*C*H*) and 3.50, 3.25 (2×d, 2H, *J*=7.5 Hz, 2×NCOCH). *m/z* (%) 463 ((M+H)$^+$, 26) 434 (18) 391 (74) and 329 (32).

3.6.2. (+/−)-*exo*-11-(2-Thienoyl)-16-phenyl-2,16-diazapentacyclo[8.8.0.0^{2,13}.0^{4,9}.0^{14,18}]-octadeca-4,6,8-triene-12,15,17-trione (15b). Obtained from **1** (392 mg, 1 mmol) after column chromatography eluting with 1:5 and 1:1 v/v EtOAc/petroleum ether. The *product* **15b** (285 mg, 61%) was obtained as an amorphous, colourless solid from EtOAc/petroleum ether, mp 267°C dec. (Found: C, 69.2; H, 4.25; N, 6.0. $C_{27}H_{20}N_2O_4S$ requires: C, 69.2; H, 4.3; N, 6.0%.) ν_{max} 1733, 1714, 1653, 1558, 1387 and 1184 cm^{-1}. δ 7.68–7.66 (m, 2H, ArH), 7.51–7.43 (m, 3H, ArH), 7.35 (d, 2H, *J*=8.5 Hz, ArH), 7.19–7.15 (m, 2H, ArH), 7.05 (d, 1H, *J*=6.7 Hz, ArH), 6.95 (t, 1H, *J*=8.2 Hz, ArH), 6.56 (d, 1H, *J*=7.0 Hz, ArH), 4.83, 4.45 (2×d, 2H, *J*=18.2 Hz, NCH_2Ar), 4.76 (s, 1H, NCH), 4.25 (s, 1H, NCH), 4.05–3.99 (m, 2H, COC*H*C*H*) and 3.49, 3.23 (2×d, 2H, *J*=7.5 Hz, 2×NCOCH). *m/z* (%) 469 (M+H$^+$, 9), 440 (7), 359 (11) and 330 (10).

3.7. Single crystal X-ray diffraction analysis of 7

Crystallographic data were measured at 150 K on a Nonius KappaCCD diffractometer using a mixture of area-detector ω- and ϕ-scans. The structure was solved by direct methods using SHELXS-86[34] and was refined by full-matrix least-squares (based on F^2) using SHELXL-97.[35] The weighting scheme used $w = [\sigma^2(F_0^2) + (0.0661P)^2 + 0.2027P]^{-1}$ where $P = (F_0^2 + 2F_c^2)/3$. All non-hydrogen atoms were refined with anisotropic displacement parameters whilst hydrogen atoms were constrained to predicted positions using a riding model. The residuals wR_2 and R_1, given below, are defined as $wR_2 = (\sum[w(F_0 - F_c^2)^2]/\sum[w(F_c^2)^2])^{1/2}$ and $R_1 = \sum||F_0| - |F_c||/\sum|F_0|$.

Crystal data for **7**. $C_{17}H_{16}N_2O_3$, 0.66×0.36×0.24 mm^3, *M*=296.32, monoclinic, space group $P2_1$, *a*=12.0734(2), *b*=6.7271(1), *c*=17.8912(3) Å, β=104.3700(11), *V*=1407.64(4) Å^3, *Z*=4, D_c=1.4 mg m^{-3}, μ=0.097 mm^{-1}, *F*(000)=624, *T*=150 K.

Data collection. Graphite monochromated Mo-K$_\alpha$ radiation, λ=0.71073 Å, $2.0<2\theta<27.5°$; Of 34688 data collected, 5502 were unique and 5138 with $F_0>4.0\ \sigma(F_0)$ were considered 'observed'.

Structure refinement. Number of parameters=400, goodness of fit, *s*=1.045; wR_2 (all data)=0.1085, R_1 ('observed' data)=0.0398.

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