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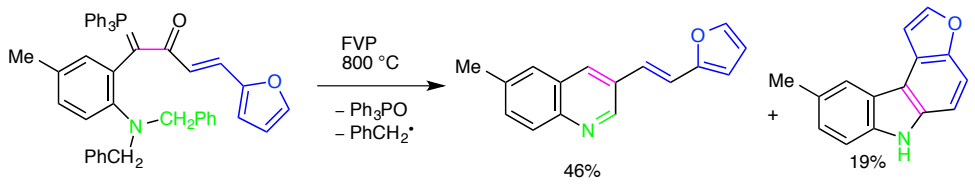

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Gas-phase domino cyclisation of phosphonium ylides leading to the total synthesis of Eustifoline D

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ABSTRACT

Six stabilised phosphonium ylides bearing *ortho*-benzylaminophenyl and cinnamoyl (or a heterocyclic analogue) groups have been prepared and upon flash vacuum pyrolysis at 800 °C were found to undergo cascade cyclization processes to give mainly 3-styrylquinolines but also in some cases ring-fused carbazoles and other fused-ring heterocyclic products. By starting with an appropriate ring-methylated precursor the natural product Eustifoline D was obtained in 19% yield in the pyrolysis in addition to the 3-(2-furylethenyl)quinoline (46%).

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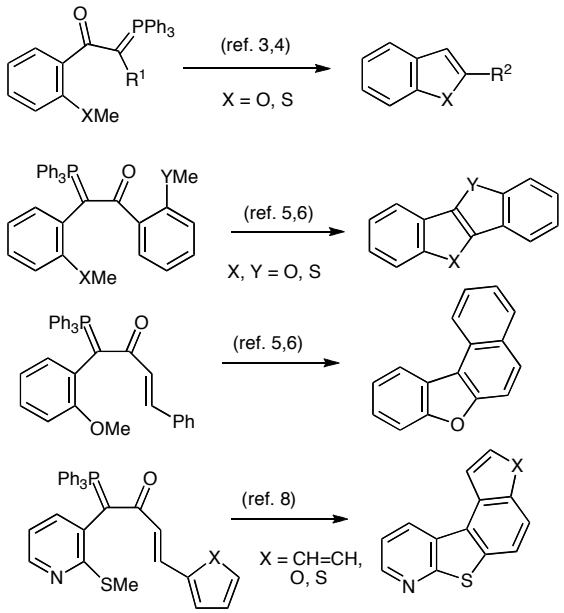
There has been considerable recent interest in the application of flash vacuum pyrolysis (FVP) to the synthesis of a wide range of heterocyclic compounds,[1] and despite a common misapprehension that the technique involves overly harsh conditions which are incompatible with sensitive functional groups, it has been used in natural product synthesis in a few cases.[2] In previous work, we have combined the pyrolytic generation of an alkyne functional group from an oxo-stabilised phosphonium ylide with the generation of an *ortho* phenoxy or phenylthio radical, leading to intramolecular cyclization to give benzofurans and benzothiophenes (Scheme 1).[3,4] This was later extended to domino cyclization methods leading to tri- and tetra-cyclic fused ring heterocycles.[5,6] More recent developments have included the observation of an eight-stage cascade process,[7] the synthesis of thieno[2,3-*b*]pyridines,[8] and an application of this approach to the formation of benzopyranones.[9] However all these studies have involved O or S as the cyclizing atom and the corresponding process involving cyclization of N to give indoles is much less developed. There is only one report of this process, and it shows that the situation is complicated in the case of *N*-methyl ylides by the possibility of N to C transfer of the reactive centre leading to quinoline products rather than the expected *N*-methylindoles in some cases.[10] Despite this problem, ring-fused carbazoles were obtained and among these was *N*-methylfuro[2,3-*c*]carbazole **1** (Scheme 2) which was obtained in 65% yield by FVP of the appropriate ylide at 700 °C.

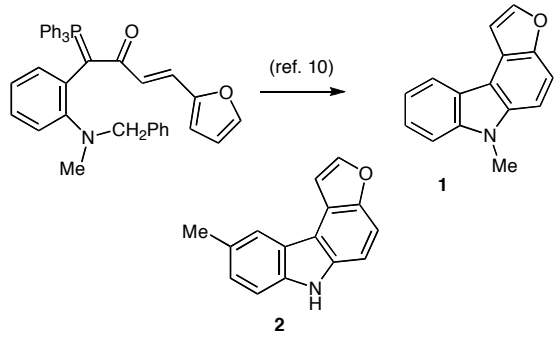
We noticed that this was isomeric with the natural product Eustifoline D, **2** isolated in 1990 by Furukawa and co-workers[11] from the shrub *Murraya euchrestifolia* Hayata along with many other carbazole alkaloids, some of which possess useful medicinal activity. This activity has attracted a good deal of synthetic interest in such carbazole alkaloids,[12] but to date there have only been two



Scheme 1. Summary of previous cyclizations with OMe and SMe as the radical-generating group

previous syntheses of **2**.[13,14] These both involve initial carbazole synthesis followed by installation of the furan ring in the last steps. Herein, we report a new and conceptually distinct synthesis of **2** in which the two central rings of the target

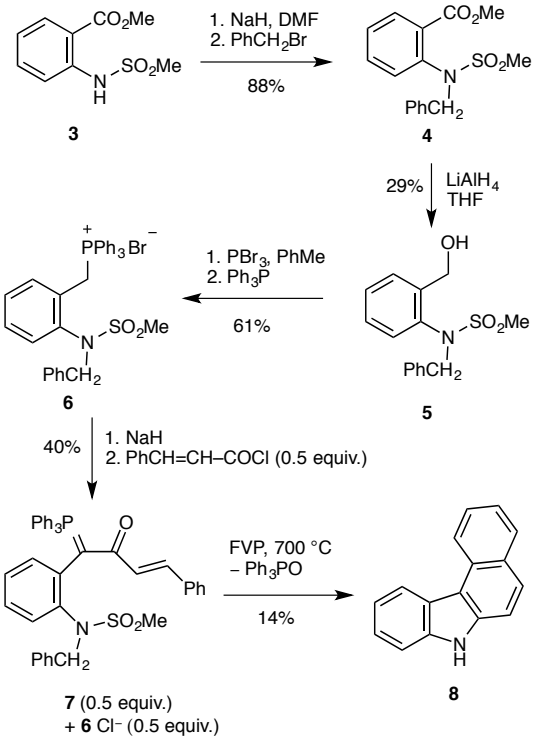
compound are formed by cyclization onto an alkyne in a single gas-phase step from a precursor already containing the remaining benzene and furan rings. Similar cascade cyclization processes



Scheme 2. Structures of previously obtained **1** and the isomeric natural product target **2**

leading to tetracyclic fused ring products have recently been reported for alkynes containing aromatic OMe groups with cyclizations initiated by a carbodiimide,[15] isocyanate[16] or iodine,[17] SMe groups and iodination with[18] or without[19] a gold catalyst, and NMe_2 groups with iodine[20] or a palladium or copper catalyst.[21]

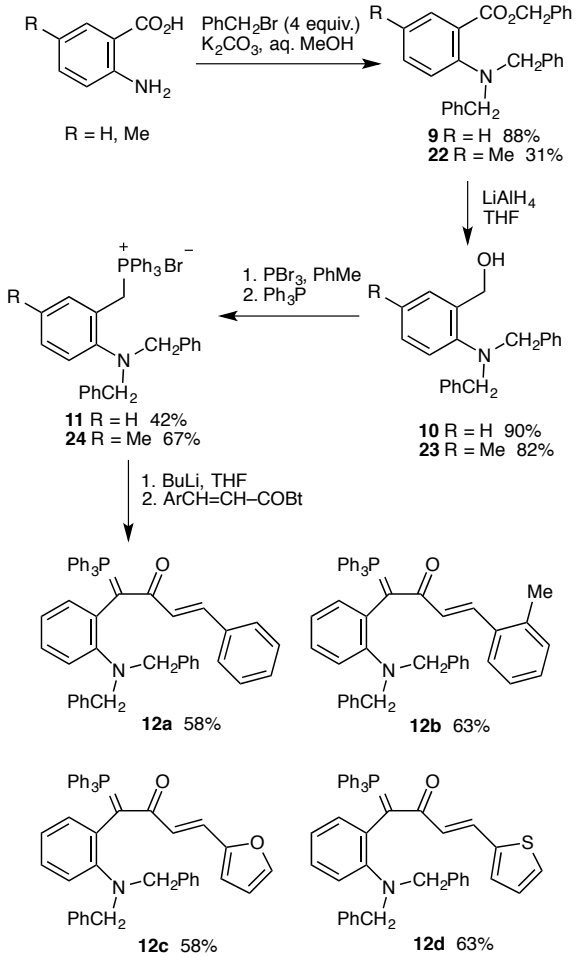
In our previous work,[10] there was always an *N*-methyl group present, but it was found that either *N*-methanesulfonyl or *N*-benzyl could act as a suitable radical-generating leaving group. To test whether having both of these groups present might lead to an aminyl radical for cyclization and ultimate loss of the other group to form the NH product, ylide **7** was prepared as shown in Scheme 3.



Scheme 3. Synthesis and FVP of ylide **7**

When this was subjected to FVP at 700 °C, the required benzo[*c*]carbazole **8** was formed albeit in only 14% yield.

The presence of the *N*-methanesulfonyl group led to competitive deprotonation when using the typical base, *n*-butyllithium, with phosphonium salt **6** and we had to resort to the less convenient sodium hydride. This route also suffers from the drawback that half of the phosphonium salt is wasted in the inevitable "transylidation"[22] that accompanies the use of an acid chloride for acylation, effectively absorbing HCl from the initially formed acylphosphonium salt to regenerate 0.5 equiv. of the chloride corresponding to **6**. Substituting the appropriate *N*-



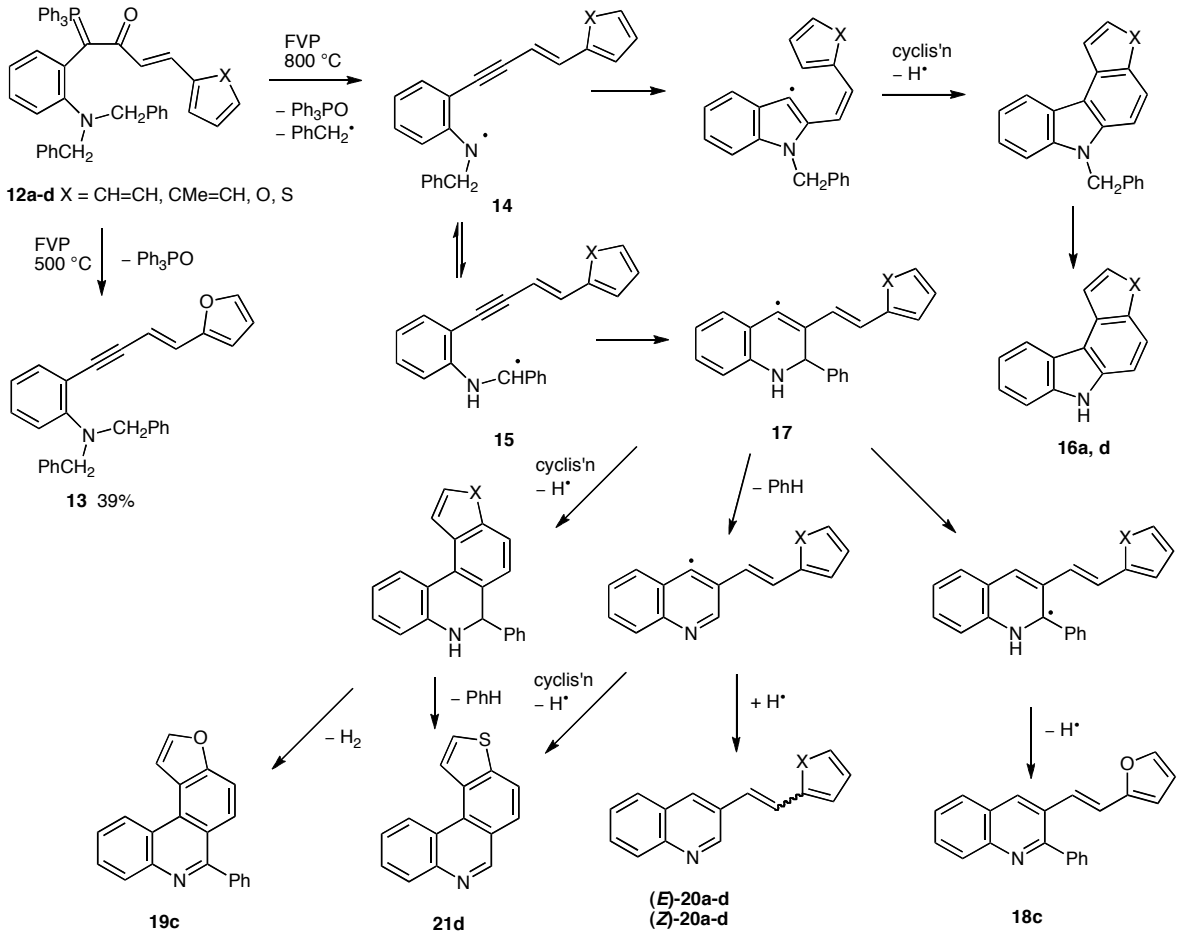
Scheme 4. Synthesis of the model ylides **12a-d** and ring-methylated phosphonium salt **24**

acylbenzotriazole, as first applied in synthesis of peptide-derived ylides,[23] overcomes this problem. An improved synthetic route (Scheme 4) was thus developed and used to access the four model ylides **12a-d**, which were designed to explore the viability of the cascade cyclization to give tetracyclic NH carbazole products as well as the compatibility with the presence of a ring methyl substituent (**12b**). These compounds were obtained as stable highly crystalline solids but their analysis by NMR spectroscopy was difficult due to restricted rotation, meaning that satisfactory ^{13}C NMR data could only be obtained at 55 °C. Once this data was obtained however, the highly consistent pattern of ^{31}P coupling provided good confirmation of the structures, and the low value of 6 Hz for $^{2}J_{P-CO}$ meant that the Ph_3PO elimination was likely to be successful.[24,25]

When ylides **12a–d** were subjected to FVP, the desired elimination of Ph_3PO readily occurred but the pattern of heterocyclic products obtained was more complex than expected. At the low temperature of 500 °C, FVP of furyl compound **12c**

Table 1. Products from the FVP of ylides **12a-d** at 800 °C

Comp		Isolated		Yield	(%)		
ound	X	**16**	**18**	**19**	***E*-20**	***Z*-20**	**21**
12a	CH=CH	18	–	–	35	9	–
12b	CMe=CH	–	–	–	31	21	–
12c	O	–	10	25	39	2	–
12d	S	15	–	–	35	6	5



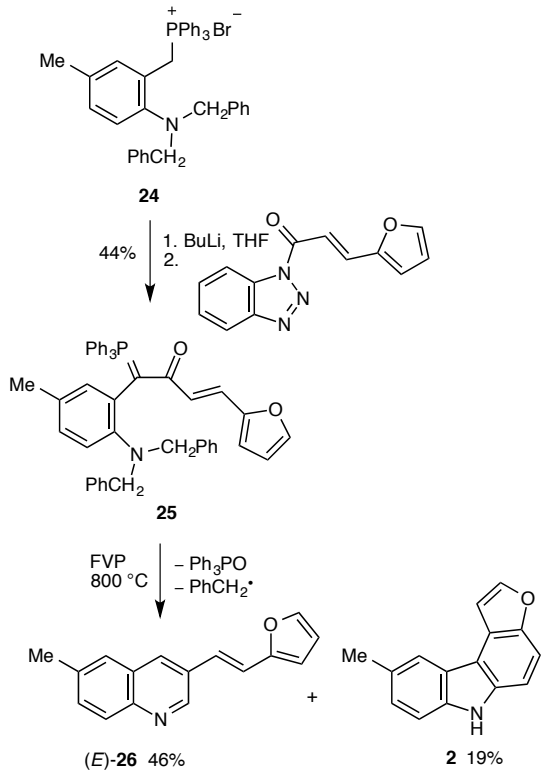
Scheme 5. Proposed mechanisms for the pyrolysis of **12a-d** to give **13**, **16**, **18**, **19**, **20** and **21**

gave a moderate yield of enyne **13**, thus confirming the occurrence of the desired initial step. When the temperature was increased, complete reaction was achieved at 800 °C to give Ph_3PO, bibenzyl and a variety of heterocyclic products (Scheme 5, Table 1).

It appears that the initially formed aminyl radical **14** equilibrates with the isomeric benzylic *C*-centred radical **15**, and in fact the latter is favoured compared to the corresponding situation with *N*-methyl.[10] Thus, although some cyclization of **14** leading to the ring-fused carbazoles **16** was observed for the phenyl **12a** and thienyl **12d** substituted compounds, the major products in all four cases were the (*E*)- and (*Z*)-3-alkenylquinolines **20**. Perhaps the most surprising observation is that these are generally formed with loss of the 2-phenyl group and only for the furyl **12c** case are products **18** and **19** obtained in which the phenyl group is retained. It appears that the initial cyclization product **17** generally prefers to eliminate benzene and only in the furyl case do the alternative routes with retention of the phenyl dominate. Only for **12d** is a further cyclization with loss of benzene observed to give a low yield of the novel thieno[2,3-*k*]phenanthridine **21d**.

Despite the rather unpromising outcome of these model studies, we proceeded with synthesis of the ring-methylated phosphonium salt **24** required for Eustifoline D, as shown in Scheme 3, starting from 5-methylanthranilic acid.[26,27] Treatment of this salt with *n*-butyllithium followed by the (furylethenoyl)benzotriazole gave ylide **25** (Scheme 6). To our pleasant surprise, and in contrast to the behaviour of **12c**, FVP at 800 °C gave a mixture of two compounds, which were readily separable by chromatography: *E*-3-alkenyl-6-methylquinoline **26** (46%) and Eustifoline D **2** (19%). The latter showed ^{1}H NMR data which was in close agreement with the naturally-derived material (Table 2).[11]

In summary, the FVP at 800 °C of 2-(*N,N*-dibenzylamino)phenylcinnamoyl ylides **12** proceeds mainly



Scheme 6. Synthesis and FVP of ylide **25**

to give the corresponding (*E*)- and (*Z*)-3-styrylquinolines **20**, although ring-fused carbazoles **16** are also formed in some cases as well as other products such as thieno[2,3-*k*]phenanthridine **21**. Only for the furan-derived compound **12c** is there retention of one *N*-benzyl-derived phenyl group in the products **18** and **19**. Addition of a 5-methyl substituent unexpectedly alters the behaviour and gives the (*E*)-3-alkenylquinoline **26** together with the desired natural product **2** which is thus formed in five steps from 5-methylanthranilic acid.

Table 2. Comparison of experimental and literature ^{1}H NMR data for **2** (400 MHz, $CDCl_3$)

Signal	Observed	Lit.[11]
H-1	7.33 (dd, *J* = 2, 1 Hz)	7.23 (dd, *J* = 2, 1 Hz)
H-2	7.81 (d, *J* = 2 Hz)	7.81 (d, *J* = 2 Hz)
H-4	7.58 (dd, *J* = 9, 1 Hz)	7.58 (dd, *J* = 9, 1 Hz)
H-5	7.36 (d, *J* = 9 Hz)	7.35 (d, *J* = 9 Hz)
NH	8.12 (br)	8.12 (br)
H-7	7.40 (d, *J* = 8 Hz)	7.40 (d, *J* = 8 Hz)
H-8	(under $CHCl_3$)	7.26 (dd, *J* = 8, 2 Hz)
Me	2.58 (s)	2.58 (s)
H-10	7.97 (br s)	7.97 (br s)

Acknowledgments

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Supplementary data

Supplementary data associated with this article (full experimental and characterisation details and copies of NMR spectra) can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017

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27. Typical experimental procedures:
Benzyl 2-(*N,N*-dibenzylamino)-5-methylbenzoate 22
Potassium carbonate (23.77 g, 171.9 mmol) and 2-amino-5-methylbenzoic acid (6.50 g, 43.0 mmol) were added to a stirred mixture of methanol:water (5:1, 240 mL) and benzyl bromide (23.53 g, 16.36 mL, 137.7 mmol) was added. The mixture was heated under reflux for 3 h and the solvent mixture was removed by evaporation. Water (150 mL) was added to the residue and the mixture was extracted using ethyl acetate (2 × 100 mL). The combined organic fractions were washed with water, dried and evaporated to give a dark brown oil which was triturated with diethyl ether. The solid was filtered off and found to be 2-(*N,N*-dibenzylamino)-5-methylbenzoic acid (4.39 g, 31%) mp 141–142 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34 (m, 2 H), 7.29–7.25 (m, 6 H), 7.19–7.17 (m, 4 H), 7.07 (d, *J* = 8 Hz, 1 H, H-3), 4.15 (s, 4 H, 2 × CH_2N), 2.36 (s, 3 H, Me). The filtrate was evaporated to give a mixture of desired product, benzyl bromide and tribenzylamine by ^{1}H NMR. The oil was kugelrohr distilled to give benzyl bromide (bp 90 °C/3 Torr), tribenzylamine (bp 150 °C/3 Torr) and the desired product **22** was obtained as the residue (6.95 g, 39%). IR: 1721 (CO), 1487, 1364, 1126, 1066, 952, 689 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.17 (m, 16 H), 7.02 (ddd, *J* = 8, 2, 1 Hz, 1 H, H-4) 6.80 (d, *J* = 8 Hz, 1 H, H-3), 5.34 (s, 2 H, OCH_2), 4.13 (s, 4 H, 2 NCH_2), 2.21 (s, 3 H, Me). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.3 (CO), 148.2 (C), 138.1 (2 C), 135.9 (C), 132.4 (CH), 131.3 (CH), 130.7 (C), 128.51 (CH), 128.48 (CH), 128.3 (6 CH), 128.1 (4 CH), 126.8 (2 CH), 125.6 (C), 121.7 (2 CH), 66.7 (OCH_2), 57.2 (2 NCH_2), 20.4 (Me). MS (ESI$^+$): *m/z* (%) = 443.98 (100) $[M+Na]^+$, 422.05 (20) $[M+H]^+$. HRMS (ESI$^+$): *m/z* calcd for $C_{29}H_{28}NO_2$ $[M+H]^+$: 422.2120; found: 422.2110.
2-(*N,N*-Dibenzylamino)-5-methylbenzyl alcohol 23
Under a nitrogen atmosphere, a solution of **22** (8.00 g, 19.0 mmol) in dry THF (70 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (0.79 g, 20.8 mmol) in dry THF (10 mL) and the resulting mixture was stirred at room temperature for 18 h. To destroy the excess of $LiAlH_4$, water (0.80 mL) in THF (5.6 mL) was added to the mixture followed by a 15% sodium hydroxide solution (0.80 mL) and finally water (2.40 mL). The suspension was stirred for 0.5 h and $MgSO_4$ was added and stirred overnight. The mixture was filtered through celite, the solid washed with ethyl acetate and the combined filtrate and washings evaporated to give **23** (4.69 g, 82%) as a pale yellow oil. IR: 3379 (OH), 1601, 1501, 1358, 1191, 1036 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.18 (m, 10 H), 7.13 (d, *J* = 8 Hz, 1 H, H-4 of Ar), 7.03 (dd, *J* = 8, 2 Hz, 1 H, H-3 of Ar), 6.97 (d, *J* = 2 Hz, 1 H, H-6 of Ar), 4.60 (s, 2 H, CH_2O), 4.26 (br s, 1 H, OH), 4.03 (s, 4 H, 2 NCH_2), 2.28 (s, 3 H, Me). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.5 (C), 137.5 (2 C), 136.7 (C), 134.7 (C), 129.3 (4 CH), 129.2 (CH), 128.5 (CH), 128.3 (4 CH), 127.3 (2 CH), 123.5 (CH), 63.9 (CH_2O), 58.6 (2 NCH_2), 20.9 (Me). MS (EI): *m/z* (%) = 317.18 (5) $[M]^+$, 226.11 (100) [M–

$CH_2Ph]^+$. HRMS (ESI$^+$): *m/z* calcd for $C_{22}H_{23}NO$ $[M]^+$: 317.1780; found: 317.1783.

(2-(*N,N*-Dibenzylamino)-5-methylbenzyl)triphenylphosphonium bromide 24

A stirred solution of alcohol **23** (4.00 g, 12.6 mmol) in toluene (50 mL) was heated to 60 °C and phosphorus tribromide (1.19 g, 0.42 mL, 4.4 mmol) was added dropwise over 0.5 h. The solution was stirred at 60 °C for 2 h and at rt for 16 h. The mixture was added to water (30 mL) and the organic layer separated, washed with water (2 × 20 mL) and dried. The dried organic solution was heated at reflux with triphenylphosphine (3.30 g, 12.6 mmol) for 8 h. The precipitate was filtered off, washed with diethyl ether and oven dried to give **24** (4.5 g, 67%) as a white powder, mp 201–203 °C. IR: 1430, 1373, 1107, 739, 690 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79 (t, *J* = 8 Hz, 3 H), 7.63 (td, *J* = 8, 3 Hz, 6 H), 7.48–7.38 (m, 6 H), 7.56–7.17 (m, 6 H), 7.11 (br dd, *J* = 8, 2 Hz, 1 H, H-3 of Ar), 6.94 (d, *J* = 8 Hz, 1 H, H-4 of Ar), 6.89-6.85 (m, 4 H), 6.56 (br d, *J* = 2 Hz, 1 H, H-6 of Ar), 4.75 (d, *J* = 14 Hz, 2 H, CH_2P), 3.65 (s, 4 H, 2 NCH_2), 2.05 (s, 3 H, Me). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.9 (d, *J* = 7 Hz, C-2 of Ar), 136.9 (C), 136.7 (2 C), 135.4 (d, *J* = 2 Hz, C-4 of PPh), 135.3 (CH), 134.1 (CH), 134.0 (d, *J* = 9 Hz, C-2 of PPh), 130.4 (d, *J* = 12 Hz, C-3 of PPh), 129.1 (4 CH), 128.2 (4 CH), 127.5 (2 CH), 125.4 (CH), 124.1 (d, *J* 7, C-1 of Ar), 117.9 (d, *J* = 86 Hz, C-1 of PPh), 57.8 (2 NCH_2), 25.0 (d, *J* = 50 Hz, CH_2P), 20.8 (Me). ^{31}P NMR (162 MHz, $CDCl_3$): δ = +21.6. MS (ESI$^+$): *m/z* (%) 562.15 (100) $[M–Br]^+$. HRMS (ESI$^+$): *m/z* calcd for $C_{40}H_{37}NP$ $[M–Br]^+$: 562.2664; found: 562.2675. Anal. Calcd for $C_{40}H_{37}BrNP$: C, 74.76; H, 5.80; N, 2.18. Found: C, 74.54; H, 6.45; N, 2.24.

[(2-(*N,N*-Dibenzylamino)-5-methylphenyl)(3-(2-furyl)propenoyl)methylene]triphenylphosphorane 25

A suspension of salt **24** (3.00 g, 4.67 mmol) in THF (10 mL) was stirred under nitrogen while a solution of *n*-BuLi in hexanes (0.23 mL, 2.04 M, 4.67 mmol) was added. The resulting brightly coloured solution was stirred for 2 h and a solution of *N*-(3-(2-furyl)propenoyl)benzotriazole (1.12 g, 4.67 mmol) in THF (5 mL) was added and the mixture stirred for a further 18 h. Water (20 mL) was added to the solution and the mixture was extracted using ethyl acetate (2 × 20 mL). The combined extracts were washed with water, dried and evaporated. The resulting solid was recrystallised (Et_2O/EtOAc) to give **25** (1.49 g, 44%) as yellow crystals, mp 203–204 °C. IR: 1724, 1630, 1540, 1339, 1090, 739 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75–7.28 (m, 15 H), 7.23–7.06 (m, 10 H), 7.02 (d, *J* = 15 Hz, 1 H, C*H*=CH), 6.87–6.79 (m, 4 H), 6.47 (d, *J* = 8 Hz, 1 H, H-3 of Ar), 6.25 (dd, *J* = 3, 2 Hz, 1 H, furyl H-4), 6.23 (d, *J* = 3 Hz, 1 H, furyl H-3), 4.11 (d, *J* = 14 Hz, 2 H, NCH_2), 3.94 (d, *J* = 14 Hz, 2 H, NCH_2), 2.19 (s, 3 H, Me); ^{13}C NMR (300 MHz, $CDCl_3$): δ (55 °C) = 179.2 (d, *J* = 6 Hz, CO), 153.4 (furyl C-2), 151.4 (d, *J* = 5 Hz, Ar C-2), 142.5 (furyl C-5), 139.2 (d, *J* = 5 Hz, CH), 137.1 (2 C), 133.9 (br d, *J* = 10 Hz, C-2 of PPh), 132.2 (d, *J* = 10 Hz, Ar C-1), 131.5 (br d, *J* = 3 Hz, C-4 of PPh), 129.6 (4 CH), 128.3 (br d, *J* = 12 Hz, C-3 of PPh), 127.7 (4 CH), 127.9 (d, *J* = 2 Hz, CH), 126.3 (2 CH), 127.1 (d, *J* = 90 Hz, C-1 of PPh), 125.5 (d, *J* = 13 Hz, CO-*C*H), 124.3 (CH), 122.6 (d, *J* = 2 Hz, CH), 122.5 (d, *J* = 2 Hz, CH), 111.5 (furyl CH), 111.0 (furyl CH), 74.3 (d, *J* = 107 Hz, C=P), 54.5 (2 NCH_2), 20.4 (CH_3). ^{31}P NMR (162 MHz, $CDCl_3$): δ = +16.5. MS (ESI$^+$): *m/z* (%) = 682.02 (100) $[M+H]^+$. HRMS (ESI$^+$): *m/z* calcd for $C_{47}H_{41}NO_2P$ $[M+H]^+$: 682.2875; found: 682.2888.

FVP of ylide 25 to give 26 and Eustifoline D

Ylide **25** (154 mg, 0.32 mmol) was subjected to FVP at 800 °C and 2–3 × 10^{-2} torr. NMR analysis of the crude product showed a mixture of Ph_3PO, bibenzyl and other products. The mixture was purified by preparative TLC (50:50 diethyl ether:petroleum ether) to give (*E*)-3-(2-(2-furyl)ethenyl)-6-methylquinoline **26** (24.4 mg, 46%) as dark brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.00 (d, *J* = 2 Hz, 1 H, H-2), 8.01 (d, *J* = 2 Hz, 1 H, H-4), 7.96 (d, *J* = 8 Hz, 1 H, H-8), 7.55 (br s, 1 H, furyl), 7.49 (dd, *J* = 8, 2 Hz, 1 H, H-7), 7.44 (d, *J* = 2 Hz, 1 H, H-5), 7.16 and 7.09 (AB pattern, *J* = 16 Hz, 2 H), 6.67–6.43 (m, 2 H, furyl), 2.53 (s, 3 H, Me). MS (ESI$^+$): *m/z* (%) = 236.07 (100) $[M+H]^+$. HRMS (ESI$^+$): *m/z* calcd for $C_{16}H_{14}NO$ $[M+H]^+$: 236.1075; found: 236.1068.

Also isolated was 9-methylfuro[2,3-*c*]carbazole **2** (Eustifoline D) as a brown oil (9.5 mg, 19%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (br s, 1 H, NH), 7.97 (br s, 1 H, H-10), 7.81 (d, *J* = 2 Hz, 1 H, H-2), 7.58 (dd, *J* = 9, 1 Hz, 1 H, H-4), 7.40 (d, *J* = 8 Hz, 1 H, H-7), 7.36 (d, *J* = 9 Hz, 1 H, H-5), 7.33 (dd, *J* = 2, 1 Hz, 1 H, H-1), [under chloroform, from lit.,[11] 7.26 (dd, *J* = 8, 1 Hz, 1 H, H-8)], 2.58 (s, 3 H, Me).