Domino Reactions – New Concepts in the Synthesis of Indole Alkaloids and Other Polycyclic Indole Derivatives

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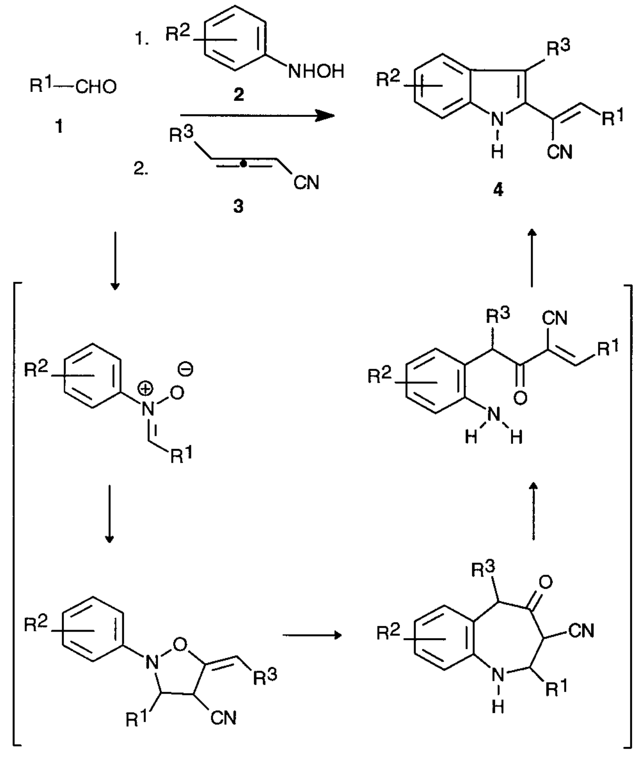
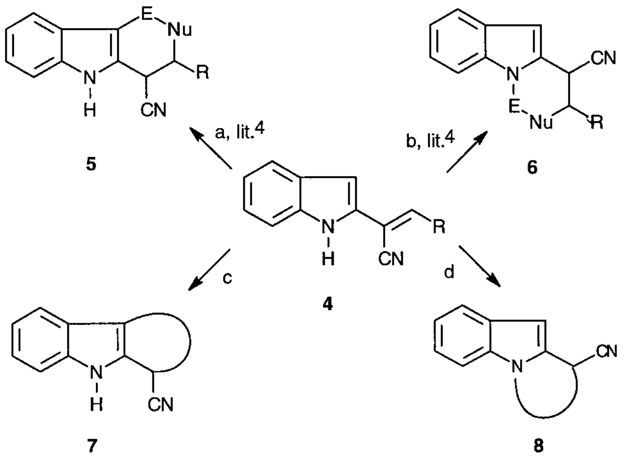
2-Vinylindoles, which are easily accessible via a domino process, are useful synthons for a variety of applications. Subsequent Diels–Alder reactions yield tetrahydrocarbazoles which can be dehydrated to carbazoles such as derivatives of olivacine or elipticine. Cycloadditions with enamine intermediates lead to the synthesis of epi-dasycarpidone.

Domino processes often offer attractive possibilities for building up several bonds in a single step.[1] Based on our investigations of hetero-Cope rearrangements we developed such a process for the synthesis of 2-vinylindoles of type **4**.[2] Starting from aldehydes **1**, phenylhydroxylamines **2** and cyanoallenes **3**, a wide variety of indoles is available with high stereoselectivity. Recently we were able to show that even substituted cyanoallenes can be used. This reaction also tolerates various functional groups.[3] According to our experience the only limitation to this method is the availability of the nitrones. The formation of some nitrones is very slow. Aliphatic and enolizable nitrones are often unstable due to their tendency to undergo dimerization. However, isolation and purification of these nitrones is not necessary. In most cases they can be captured by addition of cyanoallene and transformed into 2-vinylindoles of higher stability in a one-pot process. Thus, a variety of differentially substituted vinylindoles is easily accessible by a simple synthetic route (Scheme 1). In the following, we report the extension of the developed reaction cascade to 2-vinylindoles by a Diels–Alder reaction and consecutive hydrogen shift as well as other ring annullations.

Compounds of type **4** should be flexible building blocks, especially for the synthesis of alkaloids and other heterocycles. The acceptor-substituted double bond can be used for nucleophilic addition reactions and thus makes available a broad variety of 2-substituted indoles.[4] The use of nucleophiles (Nu, Scheme 2) which contain a suitable electrophilic centre (E, Scheme 2) also allows ring-closure reactions of type a or b by consecutive intramolecular reaction with the indole. Previously, we published examples for this type of reaction.[4] In connection with studies towards the synthesis of indole alkaloids we also investigated cyclization reactions of types c and d. In these cases an electrophilic centre contained in R should react with the indole after reduction of the vinylic double bond.



Scheme 1

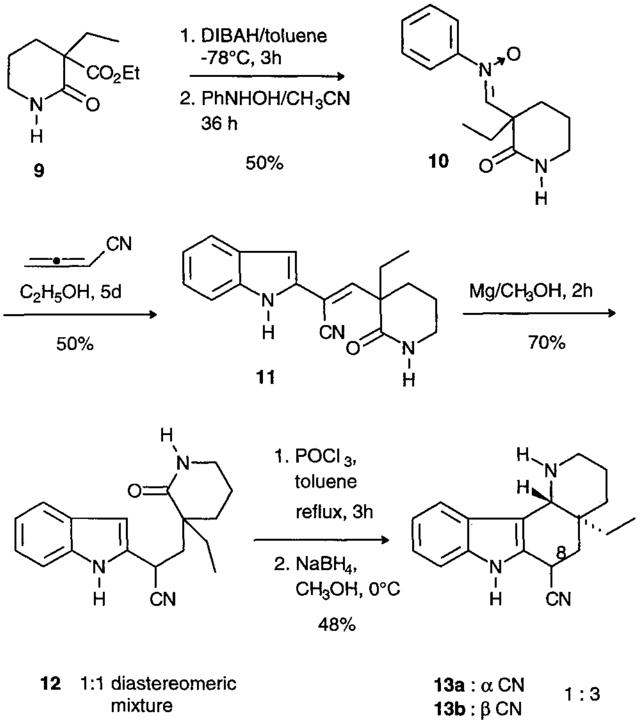


Scheme 2

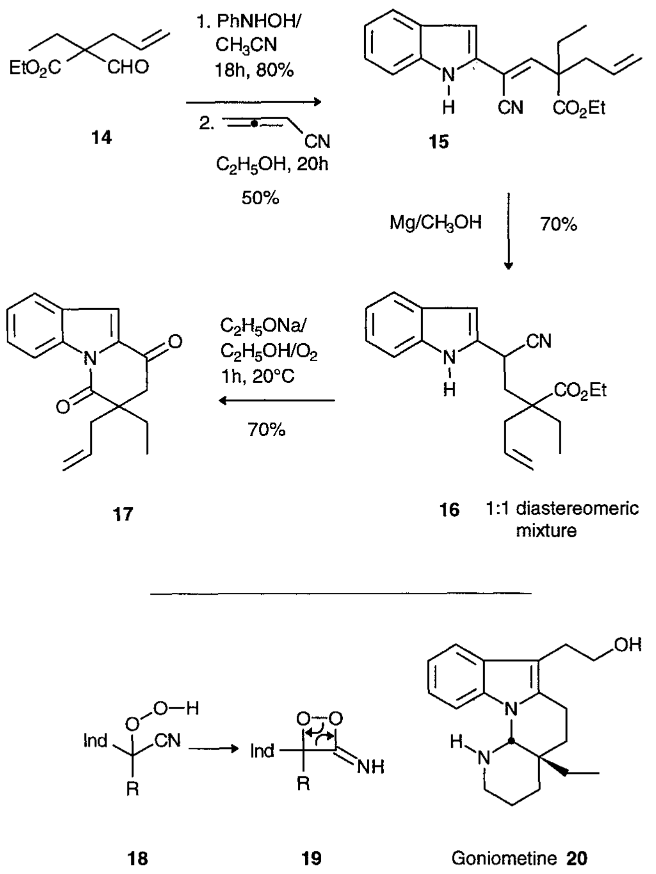
Electrophilic Ring Closure

In order to verify ring closure path c (Scheme 2), 2-vinylindole **11** was synthesized as a model compound with regard to aspidosperma alkaloids. Using diisobutylaluminum hydride (DIBAH) ester **9** was reduced to the corresponding aldehyde which was directly converted into nitrone **10** by reaction with *N*-phenylhydroxylamine in acetonitrile at room temperature. A complete conversion could not be reached in spite of addition of water binding agents, e.g., molecular sieves or magnesium sulfate. Here, addition of Al_2O_3, which proved to be successful elsewhere, led to decomposition, as did increase of temperature. Subsequent conversion of the nitrone with an excess of cyanoallene in dry ethanol at room temperature gave the *Z*-configurated 2-vinylindole **11**. The long reaction time of 5 days for **11** is an exception.

In most cases, indole formation takes place within half an hour. The stereochemistry of the vinylindoles can be assigned on the basis of ^3J ^{13}C–^1H NMR coupling constants. Following chromatographic purification on silica gel, the vinylic double bond was reduced with magnesium/methanol to yield the saturated nitrile **12** as a 1:1 diastereomeric mixture. The following electrophilic cyclization was successfully carried out with phosphorus oxychloride ($POCl_3$) in boiling toluene.[5] The resulting iminium salt was reduced immediately after evaporation of the solvent by reaction with sodium borohydride in methanol to give the *trans*-linked tetracyclic compound **13**. In this case the C–H acidity at C-8 (carbazole numbering) resulted in a 3:1 mixture of diastereoisomers. *trans*-Annullation was deduced by comparison with ^{13}C NMR data of similar compounds. Furthermore, an NOE between H-8 and the ethyl group of **13b** verifies a 1,3-diaxial interaction between these substituents which is possible only in the case of a transannulation of rings C and D. The stereochemistry of **13a** can be deduced from the vicinal ^1H coupling constants. The cyclization with the indole nitrogen (path d, Scheme 2) is of interest for the synthesis of other types of alkaloids. In principle, this reaction should be feasible, but was not observed.



Scheme 3



Scheme 4

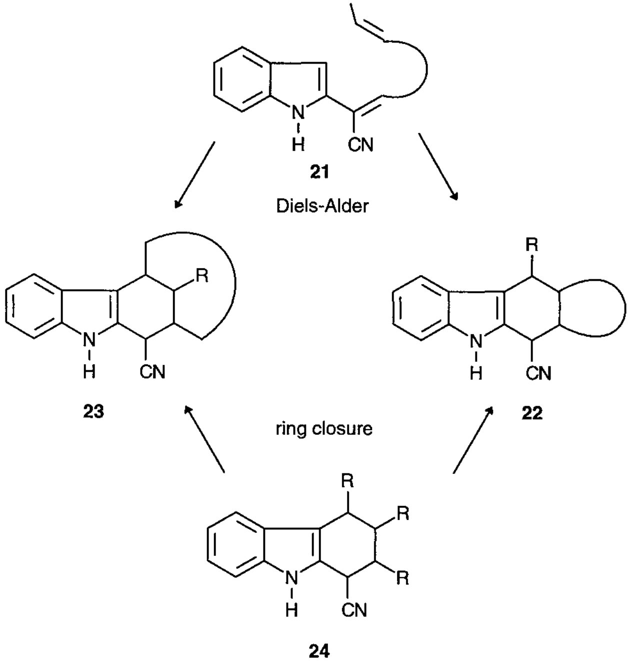
Biographical Sketch

Siegfried Blechert, born in Aalborg, Denmark in 1946. He obtained his Ph.D. under the supervision of E. Winterfeldt at the University of Hannover in 1974. After a postdoctorate in Gif-sur-Yvette with P. Portier he completed his habilitation in 1983. From 1986 to 1990 he was professor for organic chemistry at the Universität Bonn. In 1990 he moved to the Technische Universität Berlin where he is presently director of the Department of Organic Chemistry. His research interests centre around the development of novel methods and strategies in synthetic organic chemistry and their application in the total synthesis of natural products as well as transition metal induced carbon–carbon bond formations.

In connection with the synthesis of the tetracyclic indole alkaloid goniometine **20** we were interested in cyclization reactions involving the indole nitrogen.[6] As a suitable starting material for the construction of a tetracyclic compound of this type we selected aldehyde **14**.[7] Reaction with phenylhydroxylamine in acetonitrile gave the desired nitrone in 80% yield after chromatographic purification on silica gel. Reaction with cyanoallene furnished the *Z*-configured vinylindole **15** in 60% yield. For the planned cyclization we reduced the double bond with magnesium/methanol as described above. Cyclization into the 1-position of the indole and removal of the redundant cyano group was necessary for the synthesis of goniometine. This was achieved by stirring **16** with sodium ethoxide in ethanol at room temperature in an oxygen atmosphere. Formation of the indole nitrogen amide and oxidative removal of the cyano group afforded **17** within one hour. The removal of the cyano group can be explained by a radical formation of hydroperoxide **18**, which yields a dioxetane **19** by cyclization to a four-membered ring with the cyano group or an imino ether. A subsequent cycloreversion leads to the carbonyl group. In principle, the transformation of **17** into goniometine **20** should be feasible by a route reminiscent of the one developed by Takano et al.[8]

Diels–Alder Reactions

Numerous indole alkaloids contain a carbazole or a tetrahydrocarbazole moiety with different substituents in ring C.[9] In order to synthesize compounds of that type, Diels–Alder reactions with 2-vinylindoles are of special interest.[10] The regioselectivity and stereospecificity of this cycloaddition should provide a simple route to tetrahydrocarbazoles with substituents of defined regio- and stereochemistry. By subsequent dehydrogenation, carbazoles would be easily accessible. Therefore we investigated inter- and intramolecular Diels–Alder reactions with our 2-vinylindoles. Intramolecular cyclization reactions should provide either linear annulated carbazole derivatives of type **22** or bridged annulated compounds of type **23**, depending on the regioselectivity of the cycloaddition (see Scheme 5). Both structural variations are found in different indole alkaloids.[11] Application of a bimolecular Diels–Alder reaction can be used for the synthesis of these compounds. In this case, the initially generated tetrahydrocarbazoles **24** have to be transformed subsequently into tetracycles using adequate functionalities R.

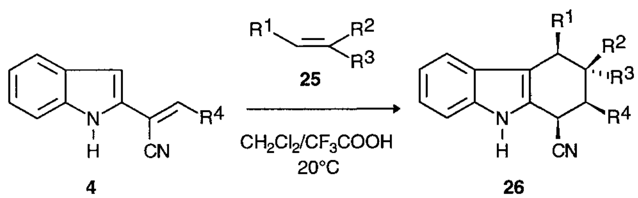


Scheme 5

Proton-Induced Diels–Alder Reactions

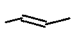
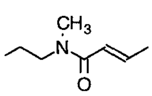
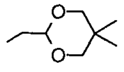
Thermally induced bimolecular Diels–Alder reactions could not be carried out in spite of the thermal stability of **4**. Application of Lewis acids did not show an improvement. However, the desired cycloaddition could be brought about by reaction with electron-deficient dienophiles at room temperature in mixtures of chloroform or dichloromethane with trifluoroacetic acid (TFA). A wide range of differentially functionalized tetrahydrocarbazoles are accessible by Diels–Alder reactions with a subsequent aromatization (see Scheme 6). The TFA-induced Diels–Alder reaction can also be successfully applied to 3-substituted vinylindoles. In cases where a subsequent hydrogen shift is not possible, the *endo*-products are formed with high selectivity. The relative stereochemistry was confirmed by NOE experiments and by comparison of ^{1}H NMR coupling constants. In cases of C–H acidity, acceptor substituents can be isomerized to the thermodynamically more stable products under base catalysis and thus offer a high stereochemical flexibility. The examples shown in Table 1 illustrate that a wide range of dienophiles and 2-vinylindoles can be used in this reaction. The synthesis and spectroscopic data of the vinylindoles have been published earlier with exception of **4b,c**.[2]

In the case of higher conjugated 2-vinylindoles (e.g., **4b**) the double bond of the indole moiety is part of the reacting diene. Under these conditions, no intramolecular Diels–Alder reaction of **4c** was observed. High concentrations of 2-vinylindole cause the formation of dimers of type **26g**. In these cycloadditions, TFA can be replaced by the acidic ion exchanger montmorillonite.[12] The advantage of this modification is that undesired dimerization can be suppressed even at high concentrations of the diene.

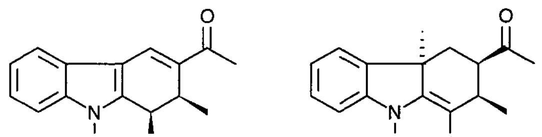


Scheme 6

Table 1. Synthesis of tetrahydrocarbazoles **26**

Product	R^1	R^2	R^3	R^4	yield (%)
26 a	$-H$	$-COCH_3$	$-H$	$-CH_3$	90
26 b	$-H$	$-COCH_3$	$-H$		60
26 c	$-H$	$-COCH_3$	$-H$		57
26 d	$-H$	$-COCH_3$	$-H$		81
26 e	$-CH_2-(CH_2)_2-CO-$		$-H$	$-CH_3$	50
26 f	$-H$	$-CHO$	$-CH_2CH_3$	$-CH_3$	60
26 g	$-CH_3$	$-CN$	2-indolyl	$-CH_3$	60

Examples **27** and **28** (Scheme 7) show that triple bonds or 3-substituted vinylindoles can also be used in this reaction. Using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), products of type **26a–g** or **27** can be transformed to carbazoles in good yields.



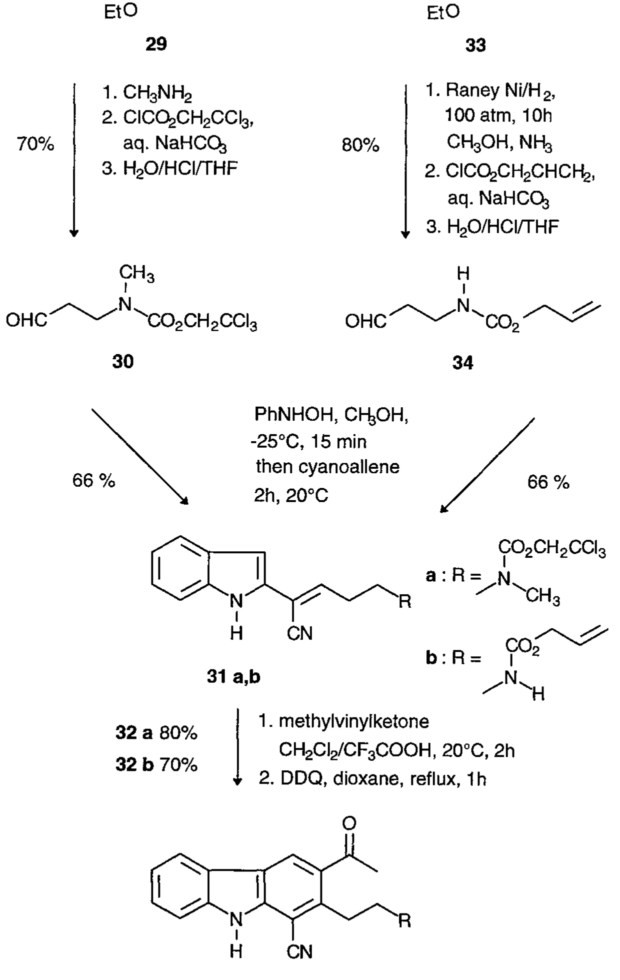
27 **28**

Scheme 7

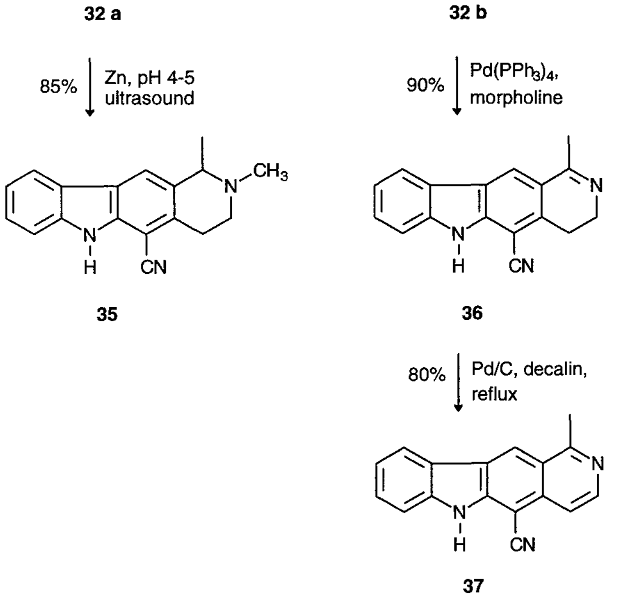
The proton-induced Diels–Alder reactions presented above are restricted to electron-deficient dienophiles. However, 2-vinylindoles of type **4** can be encouraged to react with electron-rich substituted dienophiles (e.g., *β*-enamido esters or nitriles) by a photo- or electrochemically induced cycloaddition. Linear and angular six-membered ring annulations are feasible. Depending on reaction conditions and substrates carbazoles or pyrido[1,2-*a*]indoles are obtained, as we recently demonstrated.[13]

Synthesis of Olivacine Derivatives

Carbazole structures are found in various alkaloids.[8] Due to their biological activities, ellipticine and olivacine types are of great interest.[14] We were interested in a general approach leading to derivatives of these structures via 2-vinylindoles. Therefore, we synthesized suitably functionalized carbazoles and introduced ring D by an intramolecular reaction of an amine with a carbonyl group. The flexibility of this concept is demonstrated by the following two examples. Starting from the *β*-chloropropionketal **29**, aldehyde **30** was synthesized in three steps (see Scheme 8). 2-Vinylindole **31a** can be obtained by the domino process presented above in a one-pot process, without isolation of the nitrone in 66 % yield. The proton-induced Diels–Alder reaction yields a tetrahydrocarbazole which was dehydrogenated with DDQ in boiling dioxane. After crystallization from ethanol, **32a** was obtained in 80 % yield. In the same manner we synthesized carbazole **32b** from aldehyde **34**, which is easily accessible from the commercially available nitrile **33**. **32b** was purified by flash column chromatography on silica gel. The different protecting groups of **32a** and **32b** offer the possibility for selective synthesis of dihydro- and tetrahydropyridine derivatives. Removal of the 2,2,2-trichloroethyloxycarbonyl protecting group and subsequent reductive amination with zinc in tetrahydrofuran/water at pH 4–5 yields 5-cyanoguatambuine **35** with the saturated ring D. On the other hand, palladium-catalyzed release of the amine transforms **32b** into cyanodihydroolivacine **36** with the unsaturated ring D, from which cyanoolivacine **37** can be easily prepared by dehydrogenation (Scheme 9). The methyl group of ring D, which is characteristic for the olivacine derivatives **35** and **36**, was introduced using methyl vinyl ketone as a dienophile in the above reaction sequence. Therefore, the substitution pattern of the ellipticine type, with a methyl group in ring C, can be obtained using the same synthetic concept with methacrolein as dienophile.



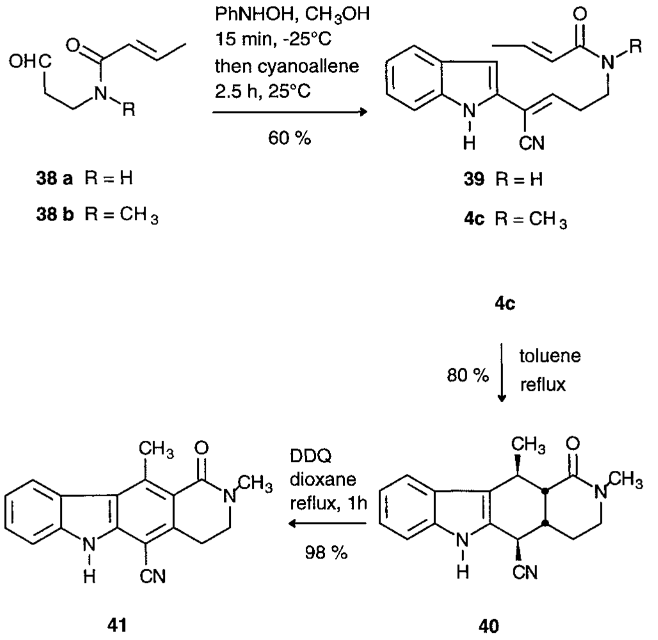
Scheme 8 **32 a,b**



Scheme 9

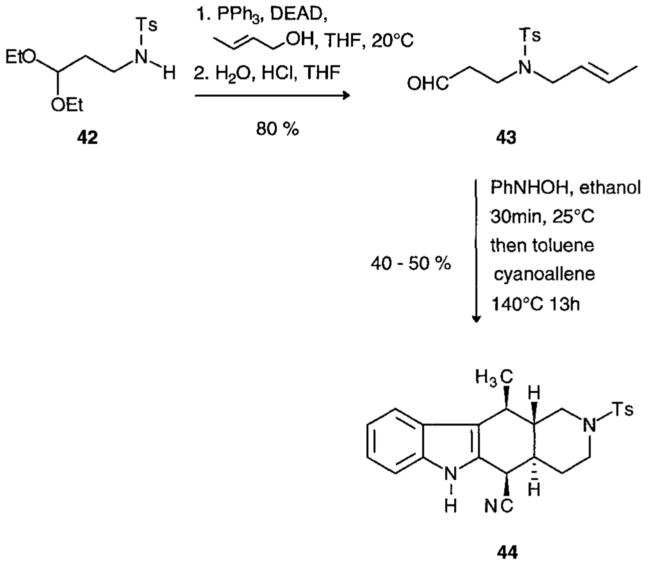
Synthesis of Ellipticine Derivatives

In addition to the bimolecular Diels–Alder reactions described above, we were interested in intramolecular variations providing tetracyclic indole derivatives by a shorter route. According to the strategy shown in Scheme 5 (**21** → **22**), we attempted to build up ellipticine derivatives in this way. Starting from **33** we synthesized the amine by hydrogenation with Raney nickel, which was then transformed into the amide using crotonyl chloride. A subsequent deketalization and purification by flash column chromatography yielded aldehyde **38a** (Scheme 10), which was reacted with phenylhydroxylamine at − 25 °C in methanol. Within 12 minutes the corresponding nitrone was formed quantitatively; this could then be captured with an excess of cyanoallene in methanol giving 2-vinylindole **39** in 60 % yield. The desired intramolecular Diels–Alder reaction could not be realized. Even heating in xylene for several days with addition of radical inhibitors did not lead to any reaction. When using higher boiling solvents merely decomposition was observed. The principle of the proton-induced Diels–Alder reaction mentioned above could not be applied to the intramolecular case. Bimolecular cycloadditions however were feasible. We envisaged that an *N*,*N*-dialkylated amide might lead to an amide conformation with a more favourable geometry for the planned Diels–Alder reaction. In order to test this presumption we synthesized aldehyde **38b** from β-chloropropionitrile **29** by substitution with methylamine, amide formation with crotonyl chloride and hydrolysis of the ketal. Aldehyde **38b** could be transformed into 2-vinylindole **4c** in a one-pot process in 60 % yield. **4c** undergoes proton-induced bimolecular cycloadditions, as shown in Table 1. Unlike **39**, purely thermal Diels–Alder reactions are also possible. Heating of **4c** in a sealed tube in an argon atmosphere to 150 °C afforded two diastereomeric cycloaddition products in a 2:1 ratio. If the reaction was carried out under milder conditions in boiling toluene the *endo*-product **40** was obtained in 80 % yield. The spectroscopic data are identical to those of the main product formed at 150 °C. The *cis*-linkage of rings C and D can be deduced from the ^{1}H coupling constants. **40**, or its diastereomeric mixture, gave the tetrahydroellipticine derivative **41** in nearly quantitative yield by reaction with DDQ (Scheme 10).



Scheme 10

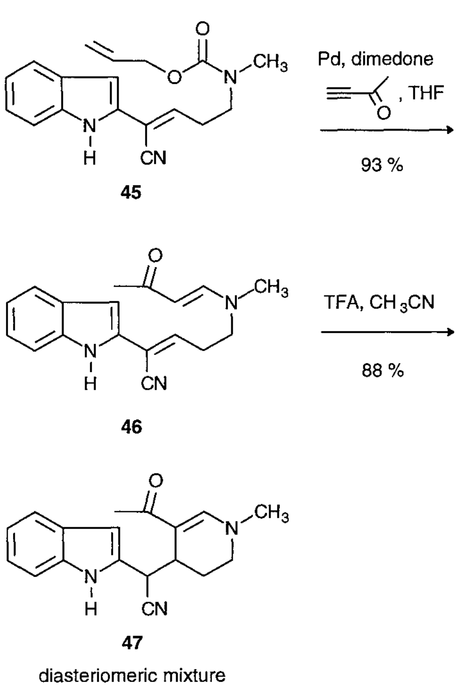
Next we investigated the influence of the amide group on the stereochemical outcome of the Diels–Alder reaction. In that context we found that *N*-allyl-substituted tertiary amides also undergo intramolecular Diels–Alder reactions leading to C,D-*trans*-annulated tetracycles. The synthesis of the requisite 2-vinylindoles is not directly feasible from the corresponding aminoaldehydes but requires the application of protecting groups and thus a longer synthetic route. This can be avoided by using *N*-tosylated amides, as demonstrated in the following example. **42** was generated from nitrile **33** by hydrogenation and *N*-tosylation. A modified Mitsunobu reaction with crotyl alcohol and subsequent ketal hydrolysis gave aldehyde **43** in good yield.[15] The *N*-tosylated aldehyde could be converted directly to the *Z*-configurated 2-vinylindole in a one-pot process. Heating in toluene furnished the *trans*-annulated tetracyclic compound **44**. The addition of radical inhibitors to this reaction, and all other examples investigated, proved to be beneficial and led to improved yields.[16] The isolation of the 2-vinylindole is not essential for further transformations, as we were able to show in other cases. If aldehydes such as **43** or **38b** are reacted with phenylhydroxylamine until complete formation of the nitrone, followed by addition of cyanoallene in toluene, the desired tetracycles are formed directly after heating of this solution. Thus, **43** can be transformed into **44** in 40–50 % yield in one pot using a domino process (Scheme 11). In summary, we have established a highly chemo-, regio- and stereoselective process which combines a 1,3-dipolar cycloaddition, a [3,3]-sigmatropic rearrangement, a retro-Michael reaction, formation of an indole, a Diels–Alder reaction and a hydrogen shift in a domino process starting from a nitrone. The yield is satisfactory, taking into account the number of bonds being formed and cleaved in this process.



Scheme 11

Synthesis of (±)-3-*epi*-Dasycarpidone

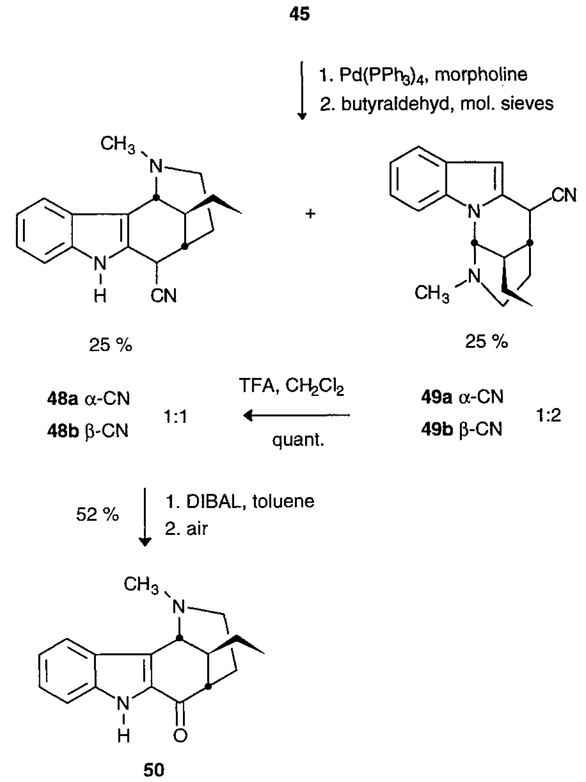
Following the successful synthesis of linear annulated carbazole derivatives by an intramolecular Diels–Alder reaction, we were interested in the preparation of bridged annellated compounds. Structures of this type are found in many alkaloids, e.g., the uleine alkaloids.[17] Having seen that amides (see **4c**) are suitable for intramolecular cycloadditions, we envisaged that by using a vinylogous amide we could reverse the regioselectivity of the reaction. To test this proposal we first synthesized the 2-vinylindole **45** in analogy to the synthesis of **31a**. Deprotection in the presence of 2-butynone gave the desired vinylogous amide **46** in one step. The planned thermal cyclization of **46** could not, however, be carried out. The attempt to perform a proton-catalyzed cycloaddition with TFA/dichloromethane yielded the tetrahydropyridine **47** as a diastereomeric mixture, but cyclization into the 3-position of the indole was not feasible (Scheme 12).



Scheme 12

The route via the vinylogous amide did not lead to uleine alkaloids. We therefore modified the above reaction sequence by introducing a more reactive enamine as dienophile. For this purpose, we deprotected **45** with $Pd(PPh_3)_4$/morpholine. The crude product was purified by flash column chromatography and was reacted with a large excess of butyric aldehyde in acetonitrile in the presence of molecular sieves at room temperature. The formation of four products was observed. The two more polar products were isolated in 25% combined yield. Spectroscopic analysis revealed that these products are the diastereomeric *epi*-uleine derivatives **48a,b** which were formed in a 1:1 ratio. The two less polar compounds proved to be a 1:2 mixture of **49a,b**. The formation of these products can be rationalized by another domino process consisting of enamine formation, Michael addition and Mannich reaction. The ring closure of the intermediate iminium salt with the indole nitrogen leads to the undesired cyclization reaction, but **49** can be transformed almost quantitatively into **48** with TFA.[18] This is also possible with the crude reaction mixture. Thus, **45** can be transformed into the cyano-*epi*-uleine **48a,b** in 52% yield. The oxidative decyanation of **48a,b** (by the same method as described for the preparation of **17**) yielded *epi*-dasycarpidone **50**, but only in poor yield. The spectroscopic data of **50** are fully consistent with those of the natural product. The initial step of the reaction sequence leading to the decyanation is an attack of oxygen at a C–H acidic position. This primary step should therefore be favored if the C–H acidity in this position is increased. In order to test this presumption, **48** was reduced with DIBAH and worked up in the presence of air. The desired (±)-3-*epi*-dasycarpidone was obtained in 52% yield and no traces of the aldehyde intermediate were found (Scheme 13).

In conclusion, we have demonstrated that 2-vinylindoles are easily prepared from aldehydes in one step and are valuable building blocks for organic synthesis. The new proton-induced Diels–Alder reactions of 2-vinylindoles yield a wide variety of tetrahydrocarbazoles with defined stereochemistry. These can easily be transformed into carbazoles. Intramolecular thermal cycloadditions of 2-vinylindoles are also feasible. Such reactions can be integrated into a domino process and thus allow a very short synthesis of tetracyclic indole derivatives. This new method can be successfully applied to the synthesis of natural products, as we have shown in selected examples, e.g., olivacine derivatives, ellipticine derivatives and *epi*-dasycarpidone.



Scheme 13

¹H NMR spectra were measured in $CDCl_3$ with $CHCl_3$ ($\delta = 7.26$ ppm) as internal standard on a Bruker AM 400 (400 MHz) spectrometer. ¹³C NMR spectra were recorded on a Bruker AM 400 (100.6 MHz), a Bruker AM 270 (67.5 MHz) or a Bruker AC 200 (50.1 MHz) spectrometer. Infrared spectra were obtained on a Perkin-Elmer model 881 spectrophotometer. Mass spectra were recorded on a Varian MAT 711 mass spectrometer (70 eV) using a direct inlet. Elemental analyses were performed on a Perkin-Elmer CHNO/S-analysator model 2400 series II. *t*-Butyl methyl ether (MTBE), diethyl ether and petroleum ether (PE, boiling point range 30–70 °C) were purified by distillation. Tetrahydrofuran (THF) was freshly distilled from potassium, toluene from sodium and dichloromethane from calcium hydride. Satisfactory microanalyses were obtained for compounds **4c**, **31a,b** and **44**: $C \pm 0.26$, $H \pm 0.32$, $N \pm 0.31$.

Reduction of Ethyl 3-Ethyl-2-oxopiperidine-3-carboxylate (9):[19]

To a solution of ester **9** (5 mmol) in dry toluene (60 mL) was added dropwise a 1.5 M solution of DIBAH in toluene (3.4 mL, 5.1 mmol) at −78 °C under Ar. After 3 h the reaction was quenched with MeOH. The reaction mixture was poured into H_2O and was acidified with HCl. The aqueous layer was extracted with CH_2Cl_2, the solvent removed and the crude product was used for the next step without further purification.

Synthesis of Nitrones; General Procedure:

The aldehyde (2 mmol) and *N*-phenylhydroxylamine (2 mmol) were dissolved in EtOH or CH_3CN (10 mL) and stirred at r.t. under Ar. In the case of less reactive aldehydes, dry $MgSO_4$ was added to absorb the formed water. The reaction was monitored by TLC; the reaction times were in the range of 1 min for acetaldehyde and 36 h for nitrone **10**. $MgSO_4$ was removed by filtration. The crude product was either purified by flash column chromatography or the solution of the nitrone was directly used for the synthesis of 2-vinylindoles.

C-[3-(3-Ethylpiperidin-2-one)]-N-phenylnitrone (**10**): obtained in 50 % yield after flash column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) as a yellow oil.

¹H NMR (400 MHz, $CDCl_3$): $\delta = 7.72$–7.39 (5 H, m); 7.29 (1 H, s); 5.92 (1 H, br s); 3.59 (1 H, dt, $J = 5$, 10 Hz); 3.35–3.24 (1 H, m); 2.58–1.78 (6 H, m); 1.08 (3 H, t, $J = 8$ Hz).

MS: *m/z* (%) = 246 (86, $M^{+\cdot}$); 229 (83); 200 (52); 176 (94); 158 (46); 127 (70); 112 (90); 104 (74); 93 (51); 77 (100).

HRMS: Calc. for $C_{14}H_{18}N_2O_2$ 246.1364. Found: 246.1368.

2-Vinylindoles; General Procedure:

A solution of the nitrone (2 mmol) in EtOH (10 mL), or the crude product from the reaction of an aldehyde and a *N*-phenylhydroxylamine, was treated with cyanoallene (20 mmol) at r.t. under Ar. If very reactive nitrones were used, 1.5 equiv of cyanoallene were sufficient. The reaction could also be carried out in CH_3CN, CH_2Cl_2 or toluene. The reaction was monitored by TLC; reaction times were in the range of between 10 min and 5 d (for **10**). The solvent was removed by distillation. The solution of the cyanoallene in EtOH could be recovered. The crude product was purified by crystallization or flash column chromatography.

3-[3-(3-Ethylpiperidin-2-one)]-2-(indol-2-yl)acrylonitrile (**11**): obtained as a yellow wax after flash column chromatography (silica gel, CH_2Cl_2/MeOH 10:1); yield: 50 %.

¹H NMR (400 MHz, $CDCl_3$): $\delta = 9.18$ (1 H, s); 7.59 (1 H, d, $J = 8$ Hz), 7.29 (1 H, d, $J = 8$ Hz), 7.19 (1 H, t, $J = 8$ Hz), 7.10 (1 H, s); 7.09 (1 H, t, $J = 8$ Hz); 6.79 (1 H, br s); 6.22 (1 H, br s); 3.39 (2 H, m); 2.50–2.40 (1 H, m); 2.38–2.28 (1 H, m); 2.16–1.75 (4 H, m); 1.02 (3 H, t, $J = 8$ Hz).

¹³C NMR (100 MHz, $CDCl_3$): $\delta = 144.9$ (CH); 137.6, 132.6, 128.0 (3 × C); 123.5, 121.0, 120.2 (3 × CH); 115.9 (C); 111.1, 103.8 (2 × CH); 42.2, 27.2, 24.0, 20.0 (4 × CH_2); 8.1 (CH_3).

The signals of three quaternary carbon atoms were too small to be observed.

IR ($CHCl_3$): $\nu = 3400$, 2229, 1654 cm^{-1}.

MS: *m/z* (%) = 293 (53, $M^{+\cdot}$); 264 (16); 184 (32); 127 (78); 112 (100); 103 (71); 98 (57).

HRMS Calc. for $C_{18}H_{19}N_3O$ 293.1524. Found: 293.1528.

1,4-Reduction of 2-Vinylindoles; General Procedure:

A solution of the 2-vinylindole (1 mmol) in MeOH (20 mL) was treated with Mg turnings (30–50 equiv) at r.t. until the reaction was complete (TLC). The reaction time was in the range of 1 to 3 h. The reaction mixture was poured into H_2O and acidified with aq HCl. The solution was extracted with CH_2Cl_2 and the solvent evaporated. The crude product was purified by flash column chromatography.

3-(3-Ethyl-2-oxopiperidin-3-yl)-2-(indol-2-yl)propionitrile (**12**): obtained as a colourless wax; yield: 70 % after flash column chromatography (silica gel, EtOAc); 1:1 mixture of diastereoisomers.

¹H NMR (400 MHz, $CDCl_3$): $\delta = 9.26/8.89$ (2 H, s); 7.57 (2 H, d, $J = 8$ Hz); 7.34 (2 H, dd, $J = 3$, 8 Hz); 7.18 (2 H, m); 7.09 (2 H, td, $J = 8$, 3 Hz); 6.59/6.52 (2 H, br s); 5.91/5.82 (2 H, br s); 4.73 (1 H; dd, $J = 7$, 4 Hz); 3.92 (1 H, dd, $J = 7$, 2 Hz); 3.48–3.20 (6 H, m); 2.59 (1 H, dd, $J = 15$, 2 Hz); 2.42 (1 H, dd, $J = 15$, 7 Hz); 2.20–1.40 (12 H, m); 1.00 (3 H, t, $J = 8$ Hz); 0.90 (3 H, t, $J = 8$ Hz).

¹³C NMR (100 MHz, $CDCl_3$): $\delta = 136.7/136.5$, 133.3/133.2, 127.8/127.6 (6 × C); 122.2 (2 × CH); 120.7 (2 × C); 120.4/120.0/119.8, 111.1, 100.9/100.5 (8 × CH); 42.3/42.4, 41.8/41.5, 31.2/31.2, 28.2 (8 × CH_2); 28.0/26.7 (2 × CH); 18.9/18.8 (2 × CH_2); 8.2/8.0 (2 × CH_3).

IR ($CHCl_3$): $\nu = 3400$, 2248, 1648 cm^{-1}.

MS: *m/z* (%) = 295 (44, $M^{+\cdot}$); 168 (26); 155 (44); 127 (100); 112 (99); 98 (38).

HRMS: calc. for $C_{18}H_{21}N_3O$ 295.1680. Found: 295.1684.

2-(Indol-2-yl)hexa-2,4-dienenitrile (**4b**): yellow crystals; yield: 44 % after flash column chromatography (silica gel, CH_2Cl_2); mp 177–178 °C (CH_2Cl_2).

¹H NMR (200 MHz, d_6-acetone): $\delta = 1.92$ (3 H, dd, $J = 6.8$, 1.5 Hz); 6.35 (1 H, dqd, $J = 15$, 6.8, 0.8 Hz); 6.65 (1 H, ddq, $J = 15$,

10.8, 1.5 Hz); 6.74 (1 H, s); 7.00 (1 H, ddd, J = 7.8, 7.0, 1.8 Hz); 7.14 (1 H, ddd, J = 7.8, 7.0, 1.2 Hz); 7.32 (1 H, ddd, J = 7.8, 1.8, 0.8 Hz); 7.40 (1 H, dd, J = 10.8, 0.8 Hz); 7.55 (1 H, ddd, J = 7.8, 1.2, 0.8 Hz); 10.62 (1 H, s).

^{13}C NMR (22.6 MHz, d_6-DMSO): δ = 141.0, 139.3 (2 × CH); 137.7, 132.5 (2 × C); 128.2 (CH); 127.9 (C); 123.2, 120.6, 119.9 (3 × CH); 116.0 (C); 111.2, 102.9 (2 × CH); 102.6 (C); 18.8 (CH$_3$).

IR (CHCl$_3$): ν = 3440, 2215, 1625 cm^{-1}.

MS: m/z (%) = 208 (61, M$^{+\cdot}$); 193 (100); 192 (35); 180 (12).

HRMS: calc. for $C_{14}H_{12}N_2$ 208.1000. Found: 208.0983

4a-Ethyl-2,3,4,4a,5,6,7,11c-octahydro-1*H*-pyrido[3,2-*c*]carbazole-6-carbonitrile (13a,b):

A solution of amide **12** (1 mmol) and POCl$_3$ (3 mmol) in toluene (20 mL) was heated under reflux for 3.5 h. The solvent was removed under reduced pressure. The crude product was dissolved in MeOH (20 mL) and treated with NaBH$_4$ (3 mmol) at r.t. for 1 h. The reaction mixture was poured into sat. aq. NH$_4$Cl and extracted with CH$_2$Cl$_2$. The crude product was purified by flash column chromatography (silica gel, CH$_2$Cl$_2$/MeOH 10:1); and obtained as a pale yellow wax; yield: 16% **(13a)** and 32% **(13b)**.

Spectroscopic data, **13a**:

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.07 (1 H, s); 8.01 (1 H, d, J = 8 Hz); 7.33 (1 H, d, J = 8 Hz); 7.18 (1 H, t, J = 8); 7.07 (1 H, t, J = 8 Hz); 4.05 (1 H, d, J = 7 Hz); 3.91 (1 H, d, J = 1.5 Hz); 3.30 (1 H, dd, J = 13, 5 Hz); 2.88 (1 H, td, J = 13, 4 Hz); 2.27 (1 H, d, J = 14 Hz); 1.92 (1 H, m); 1.79 (1 H, ddd, J = 14, 7, 1.5 Hz); 1.72 (1 H, q, J = 7.5 Hz); 1.70 1 H, m); 1.46 (1 H, q, J = 7.5 Hz); 1.50–1.40 (1 H, m); 1.20 (1 H, td, J = 13, 8 Hz); 0.97 (1 H, t, J = 7.5).

^{13}C NMR (50 MHz, CDCl$_3$): δ = 136.3, 126.0, 123.6 (3 × C); 122.3, 121.3, 119.6 (3 × CH); 119.5, 113.4 (2 × C); 110.7, 62.8 (2 × CH); 46.6 (CH$_2$); 35.4 (C); 34.0, 32.7, 21.7, 16.7 (4 × CH$_2$); 7.0 (CH$_3$).

IR (CHCl$_3$): ν = 3450, 2239, 1459 cm^{-1}.

MS: m/z (%) = 279 (100, M$^{+\cdot}$); 278 (57); 277 (87); 250 (28); 249 (33); 248 (43); 210 (73); 197 (40); 183 (45); 181 (92); 169 (23).

HRMS: calc. for $C_{18}H_{21}N_3$ 279.1731. Found: 279.1735.

Spectroscopic data, **13b**:

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.23 (1 H, s); 7.97 (1 H, d, J = 8 Hz); 7.33 (1 H, d, J = 8 Hz); 7.17 (1 H, t, J = 8 Hz); 7.07 (1 H, t, J = 8 Hz); 4.03 (2 H, m); 3.31 (1 H, dd, J = 13, 5 Hz); 2.92 (1 H, td, J = 13, 4 Hz); 2.26 (1 H, dd, J = 14, 5 Hz); 1.90–1.60 (4 H, m); 1.48 (1 H, m); 1.30 (1 H, td, J = 13, 4 Hz); 1.13–1.02 (1 H, m); 0.85 (3 H, t, J = 7.5 Hz).

^{13}C NMR (50 MHz, CDCl$_3$): δ = 136.4, 126.4, 124.4 (3 × C); 122.4, 121.3 (2 × CH); 119.8 (CH); 119.8, 113.2 (2 × C); 111.0 (CH); 63.2, 47.0 (2 × CH$_2$); 36.2 (C); 36.3, 32.3, 22.0, 16.6 (4 × CH$_2$); 7.3 (CH$_3$).

IR (CHCl$_3$): ν = 3457, 2243, 1463 cm^{-1}.

MS: m/z (%) = 279 (100, M$^{+\cdot}$); 278 (56); 277 (31); 250 (20); 249 (18); 210 (82); 197 (46); 183 (52); 182 (44); 169 (25).

HRMS: calc. for $C_{18}H_{21}N_3$ 279.1731. Found: 279.1735.

C-[2-(1-Ethoxycarbonyl-2-ethylpent-4-enyl)]-*N*-phenylnitrone:

The nitrone was obtained from aldehyde **14**[7] in 80% yield after flash column chromatography (silica gel, CH$_2$Cl$_2$/MeOH 10:1).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.65–7.61 (2 H, m); 7.45–7.42 (3 H, m); 7.28 (1 H, s); 5.72 (1 H, ddt, J = 17, 10, 7 Hz); 5.16 (1 H, m); 5.07 (1 H, m); 4.25 (2 H, q, J = 7 Hz); 3.01 (1 H, dd, J = 14, 7 Hz); 2.91 (1 H, dd, J = 14, 7 Hz); 2.34–2.24 (1 H, m); 2.06–1.95 (1 H, m); 1.29 (3 H, t, J = 7 Hz); 0.91 (3 H, t, J = 7 Hz).

^{13}C NMR (50 MHz, CDCl$_3$): δ = 172.4, 147.9 (C); 139.0, 133.4, 130.0, 129.0, 121.7 (5 × CH); 118.4, 61.1 (2 × CH$_2$); 52.2 (C); 35.3, 26.2 (2 × CH$_2$); 14.3, 9.1 (2 × CH$_3$).

MS: m/z (%) = 276 (7); 275 (38, M$^{+\cdot}$); 258 (12); 230 (13); 202 (28); 186 (24); 184 (18); 158 (14); 156 (32); 147 (75); 146 (100); 144 (20); 130 (14); 119 (29); 118 (32); 104 (58); 93 (27); 81 (18); 77 (78).

HRMS: calc. for $C_{16}H_{21}NO_3$ 275.1516. Found: 275.1521

3-[2-(1-Ethoxycarbonyl-2-ethylpent-4-enyl)]-2-(indol-2-yl)acrylnitrile (15):

15 was obtained from **14** in 50% yield (reaction time: 20 h; flash column chromatography: silica gel, MTBE/PE 1:5) as a yellow wax.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.34 (1 H, s); 7.61 (1 H, d, J = 8 Hz); 7.36 (1 H, d, J = 8 Hz); 7.25 (1 H, td, J = 8, 1 Hz); 7.14 (1 H, td, J = 8, 1 Hz); 7.12 (1 H, s); 6.84 (1 H, d, J = 2 Hz); 5.66 (1 H, ddd, J = 17, 10, 7 Hz); 5.13 (1 H, m); 5.07 (1 H, m); 4.28 (2 H, q, J = 7 Hz); 2.96 (1 H, dd, J = 14, 7 Hz); 2.80 (1 H, dd, J = 14, 7 Hz); 2.34–2.24 (1 H, m); 2.14–2.04 (1 H, m); 1.33 (3 H, t, J = 7 Hz); 0.90 (3 H, t, J = 7 Hz).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 173.5 (C); 143.1 (CH); 137.0 (C); 132.5 (CH); 132.1, 128.2 (2 × C); 123.9, 121.2, 120.8 (3 × CH); 119.1 (CH$_2$); 115.4 (C); 111.0 (CH); 108.0 (C); 103.7 (CH); 61.6 (CH$_2$); 53.8 (C); 41.8, 30.7 (2 × CH$_2$); 14.2, 9.5 (2 × CH$_3$).

IR (CHCl$_3$): ν = 3470, 2240, 1750, 1620 cm^{-1}.

MS: m/z (%) = 323 (20); 322 (84, M$^{+\cdot}$); 282 (22); 281 (100); 275 (29); 249 (26); 209 (23); 208 (35); 207 (91); 193 (20); 170 (30); 146 (37); 118 (29); 104 (18); 77 (36).

HRMS: calc. for $C_{20}H_{22}N_2O_2$ 322.1676. Found: 322.1681.

Ethyl 2-[2-Cyano-2-(indol-2-yl)ethyl]-2-ethylpent-4-enoate (16):

16 was prepared according to the general procedure for the 1,4-reduction of 2-vinylindoles and obtained as a colourless wax; yield: 70%, 1:1 mixture of diastereoisomers.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.59/8.57 (2 H, s); 7.57 (2 H, d, J = 8 Hz); 7.37 (2 H, d, J = 8 Hz); 7.21 (2 H, t, J = 8 Hz); 7.12 (2 H, t, J = 8 Hz); 6.53 (2 H, s); 5.74–5.90 (1 H, m); 5.60–5.72 (1 H, m); 5.08–5.30 (4 H, m); 4.18–4.06 (6 H, m); 2.56 (2 H, d, J = 8 Hz); 2.44 (2 H, d, J = 8 Hz); 2.24–2.38 (4 H, m); 1.70–1.98 (1 H, m); 1.22–1.36 (1 H, m); 1.29 (1 H, t, J = 7 Hz); 1.25 (1 H, t, J = 7 Hz); 0.99 (3 H, t, J = 7 Hz); 0.84 (3 H, t, J = 7 Hz).

^{13}C NMR (50 MHz, CDCl$_3$): δ = 175.6/175.7, 136.4/136.5 (4 × C); 132.5 (2 × CH); 132.3, 127.7 (4 × C); 122.5, 120.2/120.5 (6 × CH); 119.7 (C); 119.3/119.5 (2 × CH$_2$); 111.0, 101.2/101.5 (4 × CH); 61.2 (2 × CH$_2$); 49.1 (2 × C); 37.9/38.4, 38.7/38.9, 27.3/28.7 (6 × CH$_2$); 27.0/27.1 (CH); 14.1, 8.3/8.6 (4 × CH$_3$).

IR (CHCl$_3$): ν = 3470, 2260, 1725 cm^{-1}.

MS: m/z (%) = 325 (8); 324 (38, M$^{+\cdot}$); 279 (15); 209 (15); 196 (10); 170 (28); 169 (100); 168 (74); 156 (47); 155 (98); 144 (33); 142 (34); 141 (50); 131 (66); 128 (26); 117 (18); 113 (36); 101 (20); 95 (16).

HRMS: calc. for $C_{20}H_{24}N_2O_2$ 324.1832. Found: 324.1838.

7-Allyl-7-ethyl-7,8-dihydropyrido[1,2-*a*]indol-6,9-dione (17):

A solution of indole **16** (120 mg, 0.37 mmol) in EtOH (5 mL) was treated with a solution of NaOEt (prepared from 100 mg Na and 5 mL EtOH) in an atmosphere of oxygen. The reaction was monitored by TLC. After complete decyanation (1–3 h) the reaction mixture was poured into H$_2$O (100 mL). The solution was acidified with dil. HCl and extracted with MTBE (3 × 40 mL). The combined extracts were dried (MgSO$_4$) and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, PE/MTBE 10:1) and obtained as a colourless wax; yield: 69 mg (70%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.56 (1 H, dd, J = 8, 1 Hz); 7.73 (1 H, m); 7.57 (1 H, ddd, J = 8, 8, 1 Hz); 7.39 (1 H, ddd, J = 8, 8, 1 Hz); 7.26 (1 H, s); 5.83–5.71 (1 H, m); 5.16–5.09 (2 H, m); 3.00 (1 H, d, J = 17 Hz); 2.83 (1 H, d, J = 17 Hz); 2.75 (1 H, dd, J = 14, 8 Hz); 2.31 (1 H, dd, J = 14, 8 Hz); 1.97–1.86 (1 H, m); 1.75–1.63 (1 H, m); 0.94 (3 H, t, J = 7 Hz).

^{13}C NMR (50 MHz, CDCl$_3$): δ = 188.6, 171.7, 135.9, 133.9, 128.5 (5 × C); 132.4, 129.0, 125.0, 123.2, 117.0, 112.3 (6 × CH); 120.2 (CH$_2$); 49.2 (C); 45.8 (CH$_2$); 41.2, 31.2 (2 × CH$_2$); 8.7 (CH$_3$).

IR (CHCl$_3$): ν = 1700, 1715, 1555 cm^{-1}.

MS: m/z (%) = 268 (19); 267 (100, M$^{+\cdot}$); 239 (25); 238 (25); 226 (13); 210 (30); 198 (44); 170 (10); 154 (11); 144 (82); 143 (46); 115 (50).

HRMS: calc. for $C_{17}H_{17}NO_2$ 267.1255. Found: 267.1259.

Proton-induced Diels–Alder Reactions; General Procedure:
To a solution of 2-vinylindole (1.0 mmol) in CH_2Cl_2 (25 mL) were added dienophile (15 mmol) and TFA (0.5–1.0 mL). After stirring for 30–60 min in the dark (monitored by TLC) the reaction mixture was neutralized with sat. aq $NaHCO_3$ and extracted with MTBE. The solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography on silica gel.

All compounds **26a–g** were fully characterized and gave either correct elemental analysis (CHN ± 0.25%) or HRMS (± 0.0015 *m/z*).

3-Acetyl-2-methyl-1,2,3,4-tetrahydro-9H-carbazole-1-carbonitrile (**26a**): colourless solid, mp 202–205 °C (Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.53$ (1 H, d, $J = 8$ Hz); 7.39 (1 H, d, $J = 8$ Hz); 7.25 (1 H, t, $J = 8$ Hz); 7.16 (1 H, t, $J = 8$ Hz); 4.41 (1 H, dt, $J = 5, 2$ Hz); 3.06 (1 H, ddq, $J = 2.4, 5, 7$ Hz); 2.98 (1 H, ddd, $J = 16, 7, 2$ Hz); 2.96 (1 H, ddd, $J = 16, 9.6, 2.4$ Hz); 2.47 (1 H, ddd, $J = 9.6, 7, 2.4$ Hz); 2.32 (3 H, s); 1.11 (3 H, d, $J = 7$ Hz).

IR ($CHCl_3$): $\nu = 3450, 2240, 1710$ cm^{-1}.

3-Acetyl-2-propenyl-1,2,3,4-tetrahydro-9H-carbazole-1-carbonitrile (**26b**): colourless wax.

^{1}H NMR (200 MHz, d_6-acetone): $\delta = 1.57$ (3 H, dd, $J = 6.5, 1.6$ Hz); 1.72 (1 H; ddd, $J = 10, 5.2, 2.5$ Hz); 2.22 (3 H, s); 2.77 (1 H, ddd, $J = 15, 5.2, 2$ Hz); 2.91 (1 H, ddd, $J = 15, 10, 2$ Hz); 3.57 (1 H, ddd, $J = 10, 5, 2.5$ Hz); 4.73 (1 H, dt, $J = 5, 2$ Hz); 5.31 (1 H, ddq, $J = 15.3, 10, 1.6$ Hz); 5.80 (1 H, dq, $J = 15.3, 6.5$ Hz); 7.05 (1 H, dd, $J = 7, 7$ Hz); 7.14 (1 H, dd, $J = 7, 7$ Hz); 7.38 (1 H, d, $J = 7$ Hz); 7.47 (1 H, d, $J = 7$ Hz); 10.24 (1 H, s).

IR ($CHCl_3$): $\nu = 2480, 2270, 1725$ cm^{-1}.

Methyl 1-Cyano-2-[2-(1-oxobut-2-enylamino)ethyl]-1,2,3,4-tetrahydro-9H-carbazole-3-carboxylate (**26c**): amorphous colourless solid.

^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.55$ (1 H, br s); 7.49 (1 H, d, $J = 8$ Hz); 7.34 (1 H, d, $J = 8$ Hz); 7.20 (1 H,t $J = 8$ Hz); 7.10 (1 H, t, $J = 8$ Hz); 6.90 (1 H, dq, $J = 14, 7$ Hz); 6.34 (1 H, m); 4.33 (1 H, m); 3.75 (1 H, m); 3.38 (1 H, m); 3.2–2.8 (4 H, m); 3.00 (3 H, br s); 2.30 (3 H, s), 1.88 (3 H, dd, $J = 7, 1$ Hz); 1.75 (2 H, m).

IR ($CHCl_3$): $\nu = 3450, 2240, 1710, 1660, 1600$ cm^{-1}.

3-Acetyl-2-[5,5-dimethyl-(1,3-dioxan-2-ylmethyl)]-1,2,3,4-tetrahydro-9H-carbazole-1-carbonitrile (**26d**): colourless solid, mp 171 °C (Et_2O).

^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.70$ (3 H, s); 1.15 (3 H, s); 1.80 (1 H, ddd, $J = 14.5, 7.5, 6.5$ Hz); 1.99 (1 H, ddd, $J = 14.5, 6, 4.8$ Hz); 2.28 (3 H, s); 2.77 (1 H, ddd, $J = 10, 5, 2.5$ Hz); 2.90 (1 H, ddd, $J = 16, 10, 1.5$ Hz); 3.05 (1 H, ddd, $J = 16, 10, 2.2$ Hz); 3.24 (1 H, dddd, $J = 7.5, 6, 5.5, 2.5$ Hz); 3.36 (2 H, d, $J = 11$ Hz); 3.53 (2 H, d, $J = 11$ Hz); 4.38 (1 H, dt, $J = 5.5, 1.7$ Hz); 4.57 (1 H, dd, $J = 6.5, 4.8$ Hz); 7.13 (1 H, dd, $J = 7.5, 7$ Hz); 7.20 (1 H, dd, $J = 7.5, 7$ Hz); 7.35 (1 H, d, $J = 7.5$ Hz); 7.51 (1 H, d, $J = 7.5$ Hz); 8.31 (1 H, s).

IR ($CHCl_3$): $\nu = 3350, 2240, 1700, 1132$ cm^{-1}.

5-Methyl-4-oxo-2,3,4,4a,5,6,7,11c-octahydro-1H-benzo[c]carbazole-6-carbonitrile (**26c**): amorphous colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.45$ (1 H, s); 7.40 (1 H, m); 7.37 (1 H, ddd, $J = 8, 0.8, 0.8$ Hz); 7.20 (1 H, td, $J = 8, 0.8$ Hz); 7.10 (1 H, td, $J = 8, 0.8$ Hz); 4.24 (1 H, dd, $J = 6.8, 2$ Hz); 3.55 (1 H, m); 2.78 (1 H, ddd, $J = 6, 3, 0.8$ Hz); 2.55 (3 H, m); 2.30 (2 H, m); 1.88 (2 H, m); 1.48 (2 H, d, $J = 7$ Hz).

IR ($CHCl_3$): $\nu = 3460, 2260, 1720, 1470$ cm^{-1}.

3-Ethyl-3-formyl-2-methyl-1,2,3,4-tetrahydro-9H-carbazole-1-carbonitrile (**26f**): data corresponded to that in reference 12.

3-(2-Indol-2-yl)-2,4-dimethyl-1,2,3,4-tetrahydro-9H-carbazole-1,3-dicarbonitrile (**26g**): amorphous colourless solid.

^{1}H NMR (200 MHz, $CDCl_3/CD_3OD$): $\delta = 10.50$ (1 H, s); 10.29 (1 H, s); 7.64 (2 H, m); 7.43 (2 H, d, $J = 8$ Hz); 7.28–7.08 (4 H, m); 6.72 (1 H, d, $J = 1.5$ Hz); 4.41 (1 H, dd, $J = 6.5, 1.5$ Hz); 3.66 (1 H, qd, $J = 7, 1.5$ Hz); 2.87 (1 H, qd, $J = 7, 6.5$ Hz); 1.63 (3 H, d, $J = 7$ Hz); 1.25 (3 H, d, $J = 7$ Hz).

IR (KBr): $\nu = 3340, 2220, 1440$ cm^{-1}.

3-Acetyl-2-methyl-1,2-dihydro-9H-carbazole-1-carbonitrile (**27**): yield: 40%.

^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 9.42$ (1 H, s); 7.73 (1 H, s); 7.67 (1 H, m); 7.27 (2 H, m); 4.43 (1 H, d, $J = 6.8$ Hz); 3.67 (1 H, qd, $J = 7, 6.8$ Hz); 2.46 (3 H, s); 1.19 (3 H, d, $J = 7$ Hz).

IR (KBr): $\nu = 3300, 2250, 1640, 1620, 1600$ cm^{-1}.

MS: *m/z* (%) = 250 (33, M$^{+}\cdot$); 235 (30); 207 (30); 193 (27); 192 (29); 43 (100).

HRMS: calc. for $C_{16}H_{14}N_2O$ 250.1106. Found: 250.1097.

3-Acetyl-1-cyano-2,4-dimethyl-2,3,4,4a-tetrahydro-9H-carbazole (**28**): amorphous colourless solid; yield: 38%; mp 158–160 °C.

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.76$ (3 H, d, $J = 7$ Hz); 1.53 (3 H, s); 2.28 (5 H, m); 3.12 (1 H, m); 3.67 (1 H, dt, $J = 13, 3.5$ Hz); 5.58 (1 H, s); 7.30 (3 H, m); 7.67 (1 H, d, $J = 8$ Hz).

^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 208.5, 179.4, 151.5, 146.5$ (4 × C); 128.1, 127.0, 121.9, 121.4 (4 × CH); 118.2, 75.4, 53.6 (3 × C); 45.4, 43.8 (CH); 33.0 (CH_2); 28.7, 21.9, 10.2 (3 × CH_3).

IR ($CHCl_3$): $\nu = 3670, 3567, 2245, 1709, 1456$ cm^{-1}.

MS: *m/z* (%) = 266 (5, M$^{+}\cdot$); 196 (30); 185 (79); 147 (100).

HRMS: calc. for $C_{17}H_{18}N_2O$ 266.1419. Found: 266.1419.

2,2,2-Trichloroethyl-*N*-methyl-*N*-(1-oxoprop-3-yl)carbamate (30):
3-Chlorodiethoxypropane (**29**) was reacted with $MeNH_2$ following the protocol of Wohl and Losanitsch.[20] The secondary amine (10 mmol) was dissolved in the two-phase system MTBE (20 mL)/ sat. aq $NaHCO_3$ (20 mL). Under vigorous stirring, 2,2,2-trichloroethyl chloroformate (10 mmol) was added dropwise at r.t. After 15 min the organic layer was decanted and the aqueous layer was extracted with MTBE. The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The crude product was purified by Kugelrohr distillation (bp 130 °C, 0.1 mbar); yield: 90%.

The obtained carbamate (9 mmol) was dissolved in THF (20 mL)/ 2 N HCl (7 mL) and stirred for 1 h at r.t. The solution was neutralized with sat. aq $NaHCO_3$ and extracted with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The crude product was purified by Kugelrohr distillation (bp 150 °C, 0.5 mbar) and obtained as a colourless oil; yield: 96%.

^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 2.70$ (2 H, t, $J = 6$ Hz); 2.95 (3 H, s); 3.55 (2 H, t, $J = 6$ Hz); 4.63 (2 H; s); 9.74 (1 H, s).

IR ($CHCl_3$): $\nu = 1715, 1129$ cm^{-1}.

MS: *m/z* (%) = 261 (1, M$^{+}\cdot$); 86 (13); 70 (100).

HRMS: calc. for $C_7H_{10}{}^{35}Cl_3NO_3$ 260.9726. Found: 260.9700.

(*Z*)-2,2,2-Trichloroethyl-*N*-4-cyano-4-(indol-2-yl)but-3-enyl-*N*-methylcarbamate (31a):
31a was prepared according to the general procedure for the synthesis of 2-vinylindoles from aldehyde **30** and obtained as colourless crystals; yield: 66%; mp 150 °C (CH_2Cl_2).

^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.88$ (2 H, m); 3.09 (3 H, s); 3.60 (2 H, m); 4.74 (2 H, s); 6.65 (1 H, t, $J = 7.5$ Hz); 6.77 (1 H, br s); 7.10 (1 H, dd, $J = 8, 7.5$ Hz); 7.23 (1 H, dd, $J = 8, 7.5$ Hz); 7.35 (1 H, d, $J = 8$ Hz); 7.60 (1 H, d, $J = 8$ Hz); 8.35 (1 H, s).

^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 155.1$ (C); 139.2 (CH); 137.2, 131.2, 128.3 (C); 123.9, 121.3, 120.8 (3 × CH); 115.4 (C); 111.1 (CH); 110.4 (C); 103.7 (CH); 95.6 (C); 75.1, 48.0 (2 × CH_2); 34.2 (CH_3); 30.6 (CH_2).

IR (KBr): $\nu = 3250, 2200, 1675$ cm^{-1}.

3-Acetyl-1-cyano-2-(*N*-methyl-*N*-2,2,2-trichloroethyloxycarbonyl)-aminoethylcarbazole (32a):
TFA (0.6 mL) was added to a solution of 2-vinylindole **31a** (403 mg, 1.0 mmol) and methyl vinyl ketone (3.5 mL, 42 mmol) in CH_2Cl_2 (45 mL) at 0 °C. The mixture was stirred at r.t. for 80 min. The solution was neutralized with sat. aq $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined ex-

tracts were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The crude tetrahydrocarbazole was dissolved in dioxane (50 mL). DDQ (2.3 mmol) was added and the mixture was heated under reflux for 1 h. The reaction mixture was poured into sat. aq $NaHCO_3$ and extracted with CH_2Cl_2. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (silica gel, CH_2Cl_2/EtOAc 15:1) and obtained as a colourless solid; yield: 370 mg (80%); mp 201 °C (EtOH).

^{1}H NMR (200 MHz, d_6-DMSO): $\delta = 2.73$ and 2.76 (3 H, s, amide mesomerism); 2.89 and 3.00 (3 H, s, amide mesomerism); 3.51 (2 H, m); 3.65 (2 H, dt, $J = 14.2$, 6.1 Hz); 4.53 and 4.69 (2 H, s, amide mesomerism); 7.34 (1 H, dd, $J = 8$, 7.5 Hz); 7.53 (1 H, dd, $J = 8$, 7.5 Hz); 7.62 (1 H, d, $J = 8$ Hz); 8.31 (1 H, d, $J = 8$ Hz); 9.08 and 9.10 (1 H, s, amide mesomerism); 12.39 (1 H, s).

IR (KBr): $\nu = 3245$, 2219, 1689, 1668 cm^{-1}.

MS: m/z (%) = 465 (0.4, $M^{+\cdot}$); 451 (3); 449 (13); 276 (28); 260 (100); 222 (28); 220 (90); 218 (96); 135 (22); 133 (70); 131 (75).

HRMS: calc. for $C_{21}H_{18}{}^{35}Cl_3N_3O_3$ 465.0446. Found: 465.0430.

Allyl-*N*-(3-oxopropyl)carbamate (34):

3,3-Dimethoxypropionitrile (**33**, 13 mmol) was dissolved in MeOH (500 mL) and the solution saturated with NH_3. Raney nickel was added (2 g) and the mixture heated in an autoclave to 50 °C under an atmosphere of H_2 (100 atm) for 10 h. After filtration the solvent was evaporated under reduced pressure. The crude product was reacted with allylchloroformate, hydrolyzed and purified as described for aldehyde **30**; colourless oil; yield: 80%.

^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 2.63$ (1 H, t, $J = 6$ Hz); 3.39 (2 H, dt, $J = 6$, 6 Hz); 4.46 (2 H, d, $J = 5.8$ Hz); 5.12 (1 H, d, $J = 10$ Hz); 5.18 (1 H, br s); 5.19 (1 H, d, $J = 17$ Hz); 5.85 (1 H, ddt, $J = 17$, 10, 5.8 Hz); 9.73 (1 H, s).

IR ($CHCl_3$): $\nu = 3442$, 1713, 1509 cm^{-1}.

MS: m/z (%) = 157 (0.5, $M^{+\cdot}$); 112 (13); 62 (100); 43 (77).

HRMS: calc. for $C_7H_{11}NO_3$ 157.0739. Found: 157.0720.

(*Z*)-Allyl-*N*-4-cyano-4-(indol-2-yl)but-3-enyl-*N*-methylcarbamate (31b):

31b was prepared according to the general procedure for the synthesis of 2-vinylindoles from aldehyde **34** and obtained as colourless crystals; yield: 59%; mp 153 °C (CH_2Cl_2).

^{1}H NMR (200 MHz, d_6-DMSO): $\delta = 2.68$ (2 H, dt, $J = 7.3$, 6.4 Hz); 3.25 (2 H, dt, $J = 6.4$, 6.4 Hz); 4.47 (2 H, d, $J = 5.3$ Hz); 5.13 (1 H, d, $J = 10.5$); 5.25 (1 H, d, $J = 17$ Hz); 5.89 (1 H, ddt, $J = 17$, 10.5, 5.3 Hz); 6.61 (1 H, s); 7.03 (1 H, dd, $J = 8$, 7.5 Hz); 7.07 (1 H, t, $J = 7.3$ Hz); 7.16 (1 H, dd, $J = 8$, 7.5 Hz); 7.17 (1 H, d, $J = 8$ Hz); 7.46 (1 H, m); 7.57 (1 H, d, $J = 8$ Hz); 11.60 (1 H, s).

^{13}C NMR (50 MHz, d_6-DMSO): $\delta = 156.0$ (C); 141.4 (CH); 137.4 (C); 133.7 (CH); 132.0, 127.6 (C); 123.0, 120.7, 119.7 (3 × CH); 116.9 (CH_2); 115.6 (C); 111.2 (CH); 108.9 (C); 102.2 (CH); 64.1, 37.9, 32.3 (3 × CH_2).

IR (KBr): $\nu = 3389$, 3270, 2242, 1693, 1590 cm^{-1}.

3-Acetyl-1-cyano-2-[2-(*N*-allyloxycarbonyl)aminoethyl]carbazole (32b):

Prepared analogously to **32a** and obtained as an amorphous colourless solid; yield: 70%.

^{1}H NMR (200 MHz, d_6-DMSO): $\delta = 2.75$ (3 H, s); 3.25–3.50 (4 H, m); 4.41 (1 H, d, $J = 5$ Hz); 5.10 (1 H, d, $J = 10.4$ Hz); 5.22 (1 H, d, $J = 17$ Hz); 5.85 (1 H, ddt, $J = 17$, 10.4, 5 Hz); 7.30 (1 H, br s); 7.32 (1 H; dd, $J = 8$, 7.5 Hz); 7.52 (1 H, dd, $J = 8$, 7.5 Hz); 7.62 (1 H, d, $J = 8$ Hz); 8.30 (1 H, d, $J = 8$ Hz); 9.03 (1 H, s); 12.35 (1 H, s).

^{13}C NMR (50 MHz, d_6-DMSO): $\delta = 200.2$, 155.9, 142.1, 141.2, 140.8 (5 × C); 133.9 (CH); 129.2 (C); 127.6, 127.2 (2 × CH); 122.2, 121.4 (C); 120.9 (CH); 120.6 (CH); 116.8 (CH_2); 116.1 (C); 112.2 (CH); 96.3 (C); 64.2, 41.6, 32.8 (CH_2); 30.0 (CH_3).

IR (KBr): $\nu = 3300$, 3192, 2218, 1684, 1603, 1600, 1231 cm^{-1}.

MS: m/z (%) = 361 (3, $M^{+\cdot}$); 302 (14); 260 (100); 245 (53); 233 (70); 219 (32); 204 (38).

HRMS: calc. for $C_{21}H_{19}N_3O_3$ 361.1434. Found: 361.1430.

5-Cyanoguatambuine (35):

Carbazole **32a** (465 mg, 1 mmol) was deprotected following the general protocol by Just and Grotzinger.[21] The mixture was poured into sat. aq Na_2CO_3 (200 mL) and extracted with MTBE. The solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (silica gel, EtOAc/MeOH 5:1) to give pale yellow crystals; yield: 233 mg (85%); mp 214 °C (EtOAc).

^{1}H NMR (200 MHz, d_6-DMSO): $\delta = 1.40$ (3 H, d, $J = 6.7$ Hz); 2.41 (3 H, s); 2.76 (1 H, m); 3.05 (3 H, m); 3.76 (1 H, q, $J = 6.7$ Hz); 7.21 (1 H, dd, $J = 8$, 7.5 Hz); 7.44 (1 H, dd, $J = 8$, 7.5 Hz); 7.54 (1 H, d, $J = 8$ Hz); 8.15 (1 H, d, $J = 8$ Hz); 8.28 (1 H, s); 11.90 (1 H, s).

^{13}C NMR (22.6 MHz, d_6-DMSO): $\delta = 140.5$, 139.8, 135.7, 131.4 (4 × C); 126.5, 123.8 (2 × CH); 122.0, 121.9 (C); 120.5, 119.7 (2 × CH); 116.4 (C); 111.6 (CH); 92.0 (C); 58.3 (CH); 47.3 (CH_2); 42.4 (CH_3); 27.2 (CH_2); 19.3 (CH_3).

5-Cyano-3,4-dihydroolivacine (36):

A solution of carbazole **32b** (52 mg, 0.2 mmol) in dry THF (20 mL) was treated with morpholine (0.1 mL) and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) at r.t. for 3 h. The solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (silica gel, EtOAc/MeOH 50:1) to give a pale yellow amorphous solid; yield: 47 mg (90%); mp 240 °C (decomposition).

^{1}H NMR (200 MHz, d_6-DMSO): $\delta = 2.45$ (3 H, s); 2.97 (2 H, t, $J = 7$ Hz); 3.62 (2 H, t, $J = 7$ Hz); 7.29 (1 H, dd, $J = 8$, 7 Hz); 7.48 (1 H, dd, $J = 8$, 7 Hz); 7.58 (1 H, d, $J = 8$ Hz); 8.27 (1 H, d, $J = 8$ Hz); 8.69 (1 H, s); 12.31 (1 H, s).

^{13}C NMR (22.6 MHz, d_6-DMSO): $\delta = 162.3$, 140.8, 140.3, 139.6 (4 × C); 126.8, 122.8 (2 × CH); 122.4, 122.0, 121.2 (3 × C); 120.7, 120.3 (2 × CH); 115.7 (C); 111.9 (CH); 92.1 (C); 45.6, 25.2 (2 × CH_2); 23.3 (CH_3).

IR (KBr): $\nu = 3460$, 2220, 1620, 1602 cm^{-1}.

MS: m/z (%) = 259 (91, $M^{+\cdot}$); 258 (100); 230 (15); 216 (14).

HRMS: calc. for $C_{17}H_{13}N_3$ 259.1109. Found: 259.1103.

5-Nor-5-cyanoolivacine (37):

To a solution of imine **36** (47 mg, 0.18 mmol) in decaline (15 mL) was added Pd-on-charcoal (20 mg). The mixture was degassed by bubbling Ar through for several minutes. The mixture was heated under reflux for 12 h. The catalyst was removed by filtration and the solvent was evaporated under reduced pressure (0.01 Torr). The crude product was purified by preparative TLC (silica gel, EtOAc/PE 1:1) to give a yellow amorphous solid; yield: 38 mg (80%); mp 265 °C (decomposition).

^{1}H NMR (200 MHz, d_6-DMSO): $\delta = 3.07$ (3 H, s); 7.37 (1 H, m); 7.60 (2 H, m); 7.80 (1 H, d, $J = 6$ Hz); 8.48 (1 H, d, $J = 6$ Hz); 8.50 (1 H, d, $J = 8$ Hz); 9.40 (1 H, s); 12.45 (1 H, s).

^{13}C NMR (50 MHz, d_6-DMSO): $\delta = 159.7$, 144.3 (C); 143.1 (CH); 142.4, 134.4 (2 × C); 128.8 (CH); 126.0 (C); 123.6 (CH); 122.0 (C); 121.9, 120.8 (2 × CH); 120.8, 116.1 (2 × C); 114.8, 111.7 (2 × CH); 84.1 (C); 22.9 (CH_3).

IR (KBr): $\nu = 3460$, 2248, 1630 cm^{-1}.

MS: m/z (%) = 257 (100, $M^{+\cdot}$); 242 (3); 230 (8); 215 (4).

HRMS: calc. for $C_{17}H_{11}N_3$ 257.0953. Found: 257.0960.

***N*-3-Oxopropylcrotonylamide (38a):**

Prepared analogously to aldehyde **30**. **38a** was obtained in 75% yield after flash column chromatography (silica gel, MTBE/PE 1:1).

^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 1.77$ (3 H, dd, $J = 7$, 1.5 Hz); 1.91 (3 H, dd, $J = 7$, 1.5 Hz); 2.71 (2 H, t, $J = 5.5$ Hz); 3.53 (2 H, m); 5.71 (2 H, m); 6.05 (1 H, br s); 6.88 (1 H, dq, $J = 16$, 7 Hz); 9.91 (1 H, s).

IR ($CHCl_3$): $\nu = 3440$, 1722, 1670, 1632, 1510 cm^{-1}.

MS: m/z (%) = 129 (0.1, $M^{+}\cdot$); 86 (100); 69 (51).

HRMS: calc. for $C_7H_{11}NO_2$ 129.0789. Found: 129.0780.

N-[(4-Cyano-4-indol-2-yl)but-3-enyl]prop-1-enecarboxamide (39):
39 was prepared according to the general procedure for the synthesis of 2-vinylindoles from **38a** (reaction time 2.5 h). Obtained as a colourless solid; yield: 60 %; mp 173 °C (decomposition); crystallized from Et_2O/MeOH 10:1.

^1H NMR (200 MHz, d_6-DMSO): δ = 1.78 (3 H, dd, J = 7, 1.5 Hz); 2.68 (2 H, m); 3.35 (2 H, m); 5.89 (1 H, dq, J = 15, 1.5 Hz); 6.60 (1 H, br s); 6.61 (1 H, dq, J = 15, 7 Hz); 7.01 (1 H, dd, J = 8, 7.5 Hz); 7.07 (1 H, t, J = 7.5 Hz); 7.17 (1 H, dd, J = 8, 7.5 Hz); 7.37 (1 H, d, J = 8 Hz); 7.56 (1 H, d, J = 8 Hz); 8.13 (1 H, br s); 11.60 (1 H, s).

IR ($CHCl_3$): ν = 3421, 3280, 2218, 1663, 1622, 1505 cm^{-1}.

MS: m/z (%) = 279 (24, $M^{+}\cdot$); 194 (100); 69 (41).

HRMS: calc. for $C_{17}H_{17}N_3O$ 279.1372. Found: 279.1340.

N-Methyl-N-3-oxopropylcrotonylamide (38b):
38b was prepared as described for aldehyde **34**. **38b** was obtained as a colourless oil; yield: 85 % after flash column chromatography (silica gel, MTBE/PE 5:1).

^1H NMR (90 MHz, $CDCl_3$): δ = 1.87 (3 H, dd, J = 1, 7 Hz); 2.77 (2 H, t, J = 6.5 Hz); 3.08 (3 H, m); 3.76 (2 H, t, J = 6.5 Hz); 6.22 (1 H, dq, J = 15, 1 Hz); 6.89 (1 H, dq, J = 15, 7 Hz); 9.80 (1 H, s).

IR ($CHCl_3$): ν = 2740, 1728, 1665, 1612 cm^{-1}.

MS: m/z (%) = 169 (15, $M^{+}\cdot$); 128 (100); 114 (30); 103 (63); 84 (51); 75 (67); 69 (30).

HRMS: calc. for $C_9H_{15}NO_2$ 169.1102. Found: 169.1103.

N-[(4-Cyano-4-indol-2-yl)but-3-enyl]-N-methylprop-1-enecarboxamide (4c):
4c was prepared according to the general procedure for the synthesis of 2-vinylindoles and obtained as colourless crystals; yield: 60 %; mp 105 °C (Et_2O/MeOH 10:1).

^1H NMR (200 MHz, d_6-DMSO): δ = 1.77 and 1.82 (3 H, d, J = 6.5 Hz, amide mesomerism); 2.76 (2 H, m); 2.91 and 3.08 (3 H, s, amide mesomerism); 3.61 (2 H, m); 6.44 (1 H, d, J = 16 Hz); 6.60 (2 H, m); 7.11 (3 H, m); 7.38 (1 H, d, J = 8 Hz); 7.57 (1 H, d, J = 8 Hz); 11.62 (1 H, s).

IR ($CHCl_3$): ν = 3470, 2225, 1658, 1600, 962 cm^{-1}.

MS: m/z (%) = 293 (15, $M^{+}\cdot$); 194 (20); 193 (21); 112 (32); 69 (100); 50 (35).

5-Cyano-N-methyl-1-oxo-1,2,3,4,4a,5,11,11a-octahydroellipticine (40):
A solution of 2-vinylindole **4c** (293 mg, 1.0 mmol) in toluene (20 mL) was degassed by bubbling Ar through the solution under sonication. After heating to 110 °C for 10 h under an atmosphere of Ar the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, MTBE/MeOH 15:1) to give colourless crystals; yield: 235 mg (80 %); mp 257–258 °C (CH_2Cl_2).

^1H NMR (300 MHz, d_6-DMSO/$CDCl_3$): δ = 1.47 (3 H, d, J = 6.5 Hz); 1.86 (1 H, ddt, J = 12.5, 7.5, 7.3 Hz); 1.99 (1 H, ddt, J = 12.5, 3.8, 4.8 Hz); 2.39 (1 H, dd, J = 3.8, 7.8 Hz); 2.75 (1 H, dddd, J = 3.8, 3.8, 5, 7.5 Hz); 2.83 (3 H, s); 3.23 (1 H, ddq, J = 1, 7.8, 6.5 Hz); 3.41 (2 H, dd, J = 4.8, 7.3 Hz); 4.68 (1 H, dd, J = 1, 5 Hz); 6.96 (1 H, dd, J = 8, 8 Hz); 7.07 (1 H, dd, J = 8, 8 Hz); 7.35 (1 H, d, J = 8 Hz); 7.50 (1 H, d, J = 8 Hz); 11.15 (1 H, s).

^{13}C NMR (75 MHz, d_6-DMSO/$CDCl_3$): δ = 170.3, 136.5, 126.2, 125.8 (4 × C); 121.8, 119.5, 118.8 (3 × CH); 118.4, 115.1 (2 × C); 111.6 (CH); 47.6 (CH_3); 47.5 (CH_2); 35.9 (CH); 34.4 (CH_3); 30.6, 29.8 (2 × CH); 27.1 (CH_2); 23.9 (CH).

IR (KBr): ν = 3269, 2239, 1631 cm^{-1}.

MS: m/z (%) = 293 (76, $M^{+}\cdot$); 278 (93); 251 (14); 219 (7); 193 (35); 182 (15); 167 (9); 155 (9); 138 (13); 122 (100); 112 (36).

HRMS: calc. for $C_{18}H_{19}N_3O$ 293.1528. Found: 293.1526.

5-Cyano-N-methyl-1-oxo-1,2,3,4-tetrahydroellipticine (41):
41 was prepared analogously to **32a**. The crude product was purified by crystallization from EtOH; yield: 98 %; mp 330 °C (decomposition).

^1H NMR (200 MHz, d_6-DMSO): δ = 8.25 (1 H, d, J = 8 Hz); 7.62 (1 H, d, J = 8 Hz); 7.50 (1 H, t, J = 8 Hz); 7.30 (1 H, t, J = 8 Hz); 3.60 (2 H, t, J = 6.5 Hz); 3.25 (2 H, t, J = 6.5 Hz); 3.20 (3 H, s); 3.10 (3 H, s).

IR (KBr): ν = 3220, 2200, 1620, 1590, 1570 cm^{-1}.

MS: m/z (%) = 289 (70, $M^{+}\cdot$); 246 (100); 218 (40).

N-(3,3-Dimethoxypropyl)-p-toluenesulfonamide (42):
33 (1.215 g, 5 mmol) was hydrogenated analogously to **34**. The crude product was dissolved in Et_2O (20 mL) and treated with dimethylaminopyridine (0.6 g, 5 mmol). A solution of p-toluenesulfonyl chloride (0.96 g, 5 mmol) in Et_2O (20 mL) was added dropwise over 1 h at r.t. The solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (silica gel, PE/MTBE 2:1) to give a colourless oil; yield: 1.17 g (78 %).

^1H NMR (90 MHz, $CDCl_3$): δ = 1.02 (3 H, t, J = 7 Hz); 1.61 (2 H, dt, J = 6.4, 5.8 Hz); 2.30 (3 H, s); 2.93 (2 H, m); 3.35 (2 H, q, J = 7 Hz); 4.38 (1 H, t, J = 5.8 Hz); 5.20 (1 H, br s); 7.20 (2 H, d, J = 8.2 Hz); 7.65 (2 H, d, J = 8.2 Hz).

IR ($CHCl_3$): ν = 3308, 1602, 1331 cm^{-1}.

MS: m/z (%) = 301 ($M^{+}\cdot$, 1); 282 (13); 255 (15); 184 (63); 155 (88); 103 (100); 100 (89); 91 (95); 85 (91); 82 (96).

(HRMS): calc. for $C_{14}H_{23}NO_4S$ 301.1347. Found: 301.1347.

N-(2-Butenyl)-N-(3-oxopropyl)-p-toluenesulfonamide (43):
42 (1.0 g, 3.32 mmol) was reacted with but-2-enol (220 mg, 2.5 mmol) in THF (20 mL) following the protocol of Weinreb.[15] After flash column chromatography (silica gel, PE/MTBE 10:1) the purified product was hydrolyzed with dil. HCl (7 mL)/THF (20 mL) according to the protocol given for the preparation of **30** to give a colourless oil; yield: 560 mg (80 %).

^1H NMR (90 MHz, $CDCl_3$): δ = 1.56 (3 H, dd, J = 6, 1 Hz); 2.36 (3 H, s); 2.70 (2 H, t, J = 7 Hz); 3.33 (2 H, t, J = 7 Hz); 3.64 (1 H, d, J = 6.4 Hz); 5.15 (1 H, dtq, J = 15, 6.4, 1 Hz); 5.46 (1 H, dq, J = 15, 6 Hz); 7.25 (2 H, d, J = 8 Hz); 7.63 (2 H, d, J = 8 Hz); 9.58 (1 H, s).

IR ($CHCl_3$): ν = 1725, 1600, 1162 cm^{-1}.

MS: m/z (%) = 281 (1, $M^{+}\cdot$); 184 (47); 155 (98); 126 (100); 91 (93).

HRMS: calc. for $C_{14}H_{19}NO_3$ 281.1086. Found: 281.1094.

5-Cyano-N-tosyl-1,2,3,4,4a,5,11,11a-octahydroellipticine (44):
43 (140 mg, 0.5 mmol) and phenylhydroxylamine (55 mg, 0.5 mmol) were dissolved in EtOH (5 mL). When the formation of the corresponding nitrone was completed (TLC, ca. 30 min), cyanoallene (0.6 mL) and toluene (20 mL) were added. The mixture was heated in an autoclave to 140 °C for 13 h. The solvent was removed by distillation and the crude product was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH gradient with increasing polarity). Colourless crystals were obtained; yield: 105 mg (50 %); mp 217 °C. [Several experiments gave yields in the range of 40 to 50 %. Best yields were obtained when di(3-*tert*-butyl-4-hydroxy-5-methylphenyl)sulfide (2 mol %) was added.[16]]

^1H NMR (400 MHz, d_6-DMSO): δ = 1.65 (1 H, dddd, J = 12, 12, 12, 4 Hz); 1.80 (1 H, dddd, J = 12, 12, 4.5, 4.5 Hz); 1.97 (1 H, dd, J = 12, 4.5 Hz); 2.14 (1 H, dd, J = 12, 12 Hz); 2.33 (1 H, ddd, J = 12, 12, 2.5 Hz); 2.39 (3 H, s); 2.57 (1 H, dq, J = 9, 6.5 Hz); 3.81 (1 H, d, J = 12 Hz); 4.07 (1 H, ddd, J = 12, 4.5, 1.5 Hz); 4.28 (1 H, d, J = 4.5 Hz); 7.07 (1 H, dd, J = 7.8, 7 Hz); 7.09 (1 H, dd, J = 7.8, 7 Hz); 7.33 (1 H, d, J = 7.8 Hz); 7.45 (2 H, d, J = 8 Hz); 7.53 (1 H, d, J = 7.8 Hz); 7.71 (2 H, d, J = 8 Hz); 11.18 (1 H, s).

^{13}C NMR (50 MHz, d_6-DMSO): δ = 143.6, 136.2, 132.9 (3 × C); 129.9 (CH); 127.7 (C); 127.4 (CH); 126.2 (C); 121.6, 119.5 (2 × CH); 118.0 (C); 118.0 (CH); 113.2 (C); 111.5 (CH); 49.3, 45.3 (2 × CH_2); 41.9, 36.6, 30.7, 29.9 (4 × CH); 28.7 (CH_2); 21.0, 19.2 (2 × CH_3).

IR (KBr): ν = 3392, 2247, 1600, 1350 cm^{-1}.

MS: m/z (%) = 419 (82, M$^{+\cdot}$); 404 (35); 392 (5); 377 (5); 264 (10); 249 (30); 91 (100); 65 (19).

Allyl-*N*-methyl-*N*-(3-oxopropyl)carbamate:
The aldehyde was prepared analogously to aldehyde **30**; yield: 78 %.

^{1}H NMR (90 MHz, CDCl$_3$): δ = 2.71 (2 H, dt, J = 1, 6.5 Hz); 2.93 (3 H, s); 3.59 (2 H, t, J = 6.5 Hz); 5.25 (2 H, m); 5.92 (1 H, m); 9.80 (1 H, d, J = 1 Hz).

IR (CHCl$_3$): ν = 2745, 1730, 1700, 1410 cm^{-1}.

MS: m/z (%) = 170 (2, M$^{+\cdot}$); 143 (12); 130 (10); 128 (15); 115 (27); 114 (6); 86 (16); 84 (14); 72 (26); 58 (50); 42 (100).

HRMS: calc. for $C_8H_{12}NO_3$ 170.0817. Found: 170.0813.

Allyl-*N*-[4-cyano-4-(indol-2-yl)but-2-enyl]-*N*-methylcarbamate (45):
45 was obtained from allyl-*N*-methyl-*N*-(3-oxopropyl)carbamate following the general procedure for the synthesis of 2-vinylindoles. After flash column chromatography (silica gel, MTBE/PE 3:1); yield: 55 %; colourless crystals; mp 105 °C (Et$_2$O/MeOH 10:1).

^{1}H NMR (300 MHz, CDCl$_3$/CD$_3$OD): δ = 2.85 (2 H, dt, J = 8, 6 Hz); 3.08 (3 H, s); 3.51 (2 H, t, J = 6 Hz); 4.53 (2 H, d, J = 5 Hz); 5.00 (1 H, d, J = 10 Hz); 5.17 (1 H, m); 5.81 (1 H, m); 6.71 (1 H, t, J = 8 Hz); 6.73 (1 H, s); 7.01 (1 H, dd, J = 8, 8 Hz); 7.19 (1 H, dd, J = 8, 8 Hz); 7.25 (1 H, d, J = 8 Hz); 7.63 (1 H, d, J = 8 Hz); 9.85 (1 H, s).

^{13}C NMR (75 MHz, CDCl$_3$/CD$_3$OD): δ = 156.2 (C); 138.8 (CH); 137.5 (C); 132.3 (CH); 131.9, 127.9 (2 × C); 123.2, 120.8, 120.0 (3 × CH); 117.2 (CH$_2$); 115.4, 110.9 (2 × CH); 110.2 (C); 103.3 (CH); 66.1 (CH$_2$); 47.3 (CH$_2$); 33.6 (CH$_3$); 30.3 (CH$_2$).

IR (KBr): ν = 3310, 2225, 1685 cm^{-1}.

MS: m/z (%) = 309 (10, M$^{+\cdot}$); 193 (10); 181 (9); 154 (17); 128 (88); 94 (56); 47 (100).

HRMS: calc. for $C_{18}H_{19}N_3O_2$ 309.1477. Found: 309.1476.

2-(Indol-2-yl)-5-[*N*-methyl(3-oxobut-1-enyl)amino]pent-2-enenitrile (46):
A mixture of **45** (185 mg, 0.6 mmol), dimedone (335 mg, 1.14 mmol) and Pd(PPh$_3$)$_4$ (68 mg, 0.06 mmol) in THF (20 mL) was treated with butynone (78 mg, 1.14 mmol). After stirring for 90 min at r.t. the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (silica gel, Et$_2$O/MeOH 10:1) to give **46**; yield: 163 mg (93 %); colourless crystals; mp 159–161 °C (Et$_2$O/MeOH 10:1).

^{1}H NMR (300 MHz, d_6-DMSO): δ = 1.92 (3 H, s); 2.81 (5 H, m); 3.56 (2 H, br s); 4.98 (1 H, d, J = 14 Hz); 6.63 (1 H, s); 7.05 (1 H, dd, J = 8, 8 Hz); 7.11 (1 H, t, J = 8 Hz); 7.19 (1 H, dd, J = 8, 8 Hz); 7.41 (1 H, d, J = 8 Hz); 7.50 (1 H, d, J = 14 Hz); 7.57 (1 H, d, J = 8 Hz); 11.66 (1 H, s).

IR (CHCl$_3$): ν = 3240, 2230, 1647, 1621, 1555, 1365 cm^{-1}.

MS: m/z (%) = 293 (9, M$^{+\cdot}$); 193 (10); 138 (67); 112 (100); 96 (13); 84 (20); 70 (18).

HRMS: calc. for $C_{18}H_{19}N_3O$ 293.1528. Found: 293.1526.

2-(5-Acetyl-1-methyl-1,2,3,4-tetrahydropyrid-4-yl)-2-(indol-2-yl)-carbonitrile (47):
To a solution of amide **46** (140 mg, 0.47 mmol) in CH$_3$CN (20 mL) was added dropwise TFA (0.3 mL) at r.t. After stirring at r.t. for 2 h the solution was neutralized with sat. aq NaHCO$_3$. The aqueous layer was extracted with CH$_2$Cl$_2$. The solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (silica gel, Et$_2$O/MeOH 10:1) to give a colourless solid; yield: 124 mg (88 %); mp 184–186 °C (Et$_2$O/MeOH 10:1).

^{1}H NMR (200 MHz, d_6-DMSO): δ = 1.57 (2 H, m); 2.14 (3 H, s); 3.05 (4 H, br s); 3.27 (2 H, m); 5.04 (1 H, d, J = 4 Hz); 6.45 (1 H, s); 6.98 (1 H, dd, J = 8, 5.3 Hz); 7.08 (1 H, dd, J = 8, 5.3 Hz); 7.36 (1 H, d, J = 8 Hz); 7.50 (1 H, d, J = 8 Hz); 7.83 (1 H, s); 10.45 (1 H, s).

IR (CHCl$_3$): ν = 3240, 2247, 1630, 1571, 1355 cm^{-1}.

MS: m/z (%) = 293 (6, M$^{+\cdot}$); 275 (3); 139 (100).

HRMS: calc. for $C_{18}H_{19}N_3O$ 293.1528. Found: 293.1528.

1-Cyano-3-*epi*-uleine (48):
A mixture of 2-vinylindole **45** (160 mg, 0.518 mmol), Pd(PPh$_3$)$_4$ (30 mg, 0.026 mmol) and morpholine (0.5 mL, 5.5 mmol) in dry THF (20 mL) was stirred at r.t. for 1 h under Ar. The solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (silica gel, EtOAc/MeOH/Et$_2$NH 10:1:0.1) within 15 min. The obtained product was dissolved in CH$_3$CN (10 mL) immediately after the purification. Butyraldehyde (1 mL) and 3 Å molecular sieves were added and the mixture was stirred for 12 h at 4 °C in the dark. TFA (0.5 mL) was added and stirring was continued for 1 h. The mixture was poured into sat. aq NaHCO$_3$ and extracted several times with CH$_2$Cl$_2$. The solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (silica gel, EtOAc/MeOH 50:1) to give a 1:1 mixture of diastereoisomers (α-CN, β-CN); yield: 76 mg (63 %). This diastereomeric mixture was directly used for the synthesis of **50**.

For characterization of the intermediates formed in the reaction of **45** with butyraldehyde, the reaction was carried out as described above with the exception that no TFA was added. After flash column chromatography (silica gel, hexane/Et$_2$O 5:1 followed by EtOAc/MeOH 50:1) 12 mg of the aminal **49a**, 24 mg of the aminal **49b** and 18 mg each of α- and β-cyanouleine **48a** and **48b** were obtained, all amorphous colourless solids.

Spectroscopic data of α-1-cyano-3-*epi*-uleine (**48a**):

^{1}H NMR (200 MHz, CDCl$_3$): δ = 1.80–2.30 (4 H, m); 2.27 (3 H, s); 2.42 (1 H, d, J = 6.5 Hz); 2.48 (1 H, d, J = 2.5 Hz); 3.95 (1 H, d, J = 1.5 Hz); 4.02 (1 H, d, J = 1.5 Hz); 7.13 (1 H, dd, J = 8, 8 Hz); 7.21 (1 H, dd, J = 8, 8 Hz); 7.37 (1 H, d, J = 8 Hz); 7.56 (1 H, d, J = 8 Hz); 8.40 (1 H, s).

IR (CHCl$_3$): ν = 3468, 2247 cm^{-1}.

MS: m/z (%) = 279 (29, M$^{+\cdot}$); 264 (5); 239 (16); 222 (100); 193 (43); 124 (9).

(HRMS): calc. for $C_{18}H_{21}N_3$ 279.1735. Found: 279.1734.

Spectroscopic data of β-1-cyano-3-*epi*-uleine (**48b**):

^{1}H NMR (200 MHz, CDCl$_3$): δ = 1.02 (3 H, t, J = 7.2 Hz); 1.70 (2 H, m); 1.87–2.30 (4 H, m); 2.28 (3 H, s); 2.40 (1 H, m); 2.49 (1 H, m); 4.00 (1 H, d, J = 1.5 Hz); 4.34 (1 H, d, J = 6 Hz); 7.13 (1 H, dd, J = 8, 8 Hz); 7.21 (1 H, dd, J = 8, 8 Hz); 7.38 (1 H, d, J = 8 Hz); 7.55 (1 H, d, J = 8 Hz); 8.42 (1 H, s).

^{13}C NMR (55 MHz, CD$_3$OH): δ = 138.2, 130.5, 128.8 (3 × C); 123.1, 120.7, 119.8 (3 × CH); 119.7 (C); 112.3 (CH); 109.3 (C); 55.2 (CH); 47.0 (CH$_2$); 45.1 (CH$_3$); 44.6, 42.7, 32.6 (3 × CH); 24.8, 24.5 (2 × CH$_2$); 12.4 (CH$_3$).

IR (CHCl$_3$): ν = 3468, 2247 cm^{-1}.

MS: m/z (%) = 279 (29, M$^{+\cdot}$); 264 (5); 239 (16); 222 (100); 193 (43); 124 (9).

HRMS: calc. for $C_{18}H_{21}N_3$ 279.1735. Found: 279.1734.

Spectroscopic data of 13-ethyl-2,3,4,5-tetrahydro-2-methyl-1,5-methano[1,3]diazocino[1,8-*a*]indol-6-nitrile (**49a**):

^{1}H NMR (200 MHz, CDCl$_3$): δ = 1.05 (3 H, t, J = 7.5 Hz); 1.55–2.28 (6 H, m); 2.29 (3 H, s); 2.38–2.47 (2 H, m); 4.48 (1 H, d, J = 4.2 Hz); 5.17 (1 H, d, J = 3 Hz); 6.59 (1 H, s); 7.09 (1 H, dd, J = 8, 7.5 Hz); 7.19 (1 H, dd, J = 8, 7.5 Hz); 7.44 (1 H, d, J = 8 Hz); 7.57 (1 H, d, J = 8 Hz).

IR (CHCl$_3$): ν = 2238 cm^{-1}.

MS: m/z (%) = 279 (2, M$^{+\cdot}$); 125 (10); 124 (100); 95 (4).

HRMS: calc. for $C_{18}H_{21}N_3$ 279.1735. Found: 279.1735.

Spectroscopic data of 13-ethyl-2,3,4,5-tetrahydro-2-methyl-1,5-methano[1,3]diazocino[1,8-*a*]indol-6-nitrile (**49b**):

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.07 (3 H, t, J = 7.5 Hz); 1.57 (1 H, d, J = 14 Hz); 1.73 (1 H, dq, J = 10, 7.5 Hz); 1.98 (1 H, m); 1.99 (1 H, dq, J = 10, 7.5 Hz); 2.20 (1 H, d, J = 14 Hz); 2.29 (1 H, m); 2.30 (3 H, s); 2.44 (1 H, m); 2.49 (1 H, br s); 4.28 (1 H, t, J = 1 Hz); 5.20 (1 H, br s); 6.56 (1 H; s); 7.10 (1 H, dd, J = 7.5 Hz);

7.19 (1 H, dd, $J = 8$, 7.5 Hz); 7.45 (1 H, d, $J = 8$ Hz); 7.57 (1 H, d, $J = 8$ Hz).

^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 137.2$, 129.2, 127.8 (3 × C); 121.8, 120.5 (2 × CH); 120.3 (C); 120.2, 110.5, 100.6, 69.6 (4 × CH); 45.3 (CH_2); 45.1 (CH_3); 40.6, 33.1, 32.6 (3 × CH); 26.4, 23.4 (2 × CH_2); 11.6 (CH_3).

IR ($CHCl_3$): $\nu = 2238\ cm^{-1}$.

MS: m/z (%) = 279 (2, $M^{+\cdot}$); 125 (10); 124 (100); 95 (4).

HRMS: calc. for $C_{18}H_{21}N_3$ 279.1735. Found: 279.1735.

3-*epi*-Dasycarpidone (50):

A 1 : 1 diastereomeric mixture of **48** (70 mg, 0.25 mmol) was dissolved in dry toluene (20 mL) and cooled to − 78 °C. A 1.5 M solution of DIBAH in toluene (0.5 mL, 0.75 mmol) was added and the mixture stirred for 3 h at − 78 °C. The reaction was quenched with H_2O. The organic layer was washed with sat. aq $NaHCO_3$ and the solvent was evaporated under reduced pressure. The crude product was purified by preparative thin layer chromatography (silica gel, EtOAc/MeOH 50 : 1); yield: 35 mg (52 %); colourless solid; mp 161 °C (Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.01$ (3 H, t, $J = 7.5$ Hz); 1.66 (1 H, m); 1.73 (1 H, dq, $J = 15$, 7 Hz); 2.03 (1 H, m); 2.20–2.31 (2 H, m); 2.27 (3 H, s); 2.50 (1 H, dd, $J = 12$, 5 Hz); 2.64 (1 H, dt, $J = 5$, 2.5 Hz); 4.19 (1 H, br s); 7.18 (1 H, dd, $J = 8$, 8 Hz); 7.38 (1 H, dd, $J = 8$, 8 Hz); 7.52 (1 H, d, $J = 8$ Hz); 7.70 (1 H, d, $J = 8$ Hz); 9.92 (1 H, s).

^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 195.4$ (C); 138.2 (CH); 133.5 (C); 126.9 (CH); 126.8, 124.3 (2 × C); 122.1, 121.0, 112.9, 54.9 (4 × CH); 46.3 (CH_3); 46.2 (CH_2); 45.1, 44.6 (2 × CH); 24.0, 23.4 (2 × CH_2); 11.8 (CH_3).

IR (KBr): $\nu = 3268$, $1639\ cm^{-1}$.

MS: m/z (%) = 268 (100, $M^{+\cdot}$); 239 (32); 211 (67); 198 (42); 183 (29); 168 (23); 130 (9); 97 (6).

HRMS: calc. for $C_{17}H_{20}N_2O$ 268.1576. Found: 268.1577.

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