NEW DIELS-ALDER REACTIONS OF OXY-FUNCTIONALIZED 3-VINYLINDOLES WITH CARBODIENOPHILES

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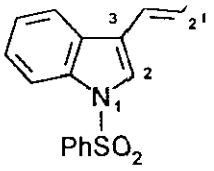
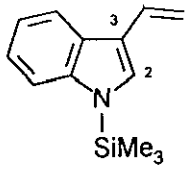
Abstract — Some new Diels-Alder reactions of oxy-functionalized 3-vinylindoles (**1**, **2**) with carbodienophiles are described. In most cases, functionalized carbazoles (**4 - 6** ,**10** and **11**) were formed regio- and/or *endo*-selectively. The product spectrum is characterized by [4+2] cycloadditions, elimination and ene reaction.

INTRODUCTION

Selectively functionalized 2- and 3-vinylindoles have become versatile building blocks for regio- and stereoselective syntheses of a range of [b]anellated indoles including physiologically active compounds by procedures in which a Diels-Alder reaction constitutes the key step.[1-5] However, the synthetic application of vinylindoles bearing directly a heteroatom substituted onto the vinyl function should be of general interest in carbazole and carbazole alkaloid chemistry[6,7] leading directly to heteroatom functionalized carbazoles. In continuation of our investigations on vinylindole cycloadditions,[4,5] we report some new Diels-Alder reactions of *(E)*-ß-methoxy-3-vinylindole (**1**) and of the 1-trimethylsilyloxy-1-indol-3-ylethene (**2**)[11] with some carbodienophiles.



(E)-**1**



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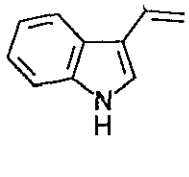

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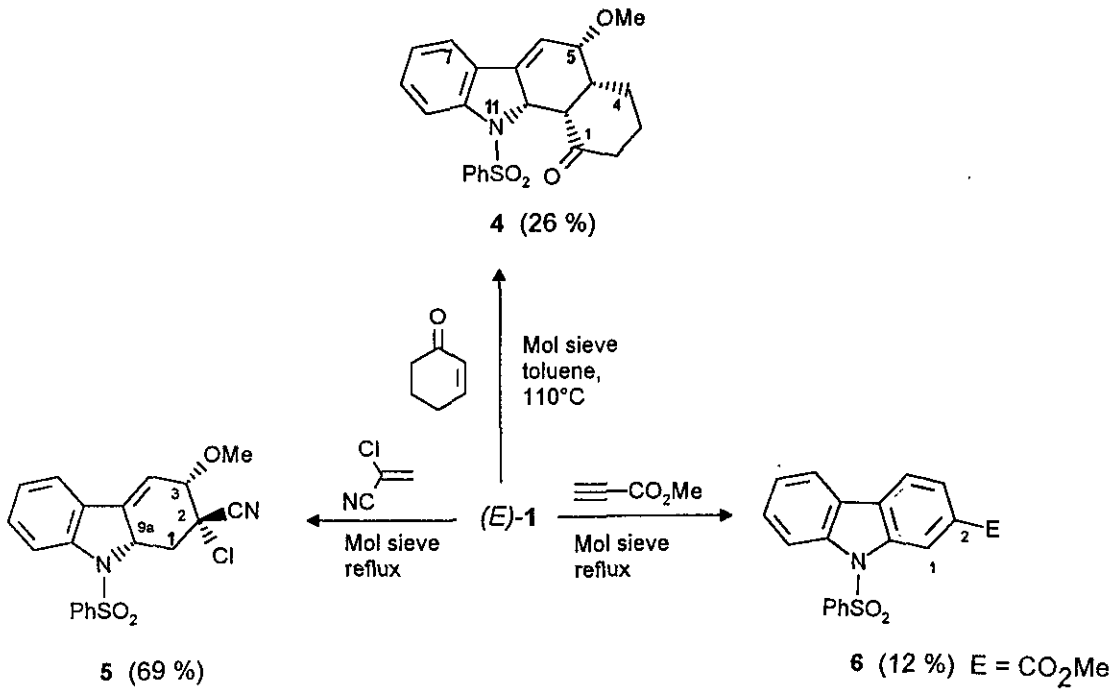
RESULTS AND DISCUSSION

Synthetic Aspects

The readily available 3-vinylindole (**1**)[8] reacts with 2-cyclohexenone in the presence of molecular sieves (4 Å) in boiling toluene (5 days) almost quantitatively to form the *endo*-cycloadduct (**4**) (tlc monitoring) (Scheme 1). However, the isolated yield of analytically pure compound was only 26 %. A significant loss of substance unfortunately occurred during chromatographic work up. According to predictions of the FMO concept on the basis of a HOMO*(diene)*-LUMO*(dienophile)* interaction (AM1 calculations[9]), the *"endo"*-regioisomer bearing the carbonyl-function at the 4 position should be favored. Concerning the product stability AM1 calculations of the heat of formation of both *"endo"*-regioisomers revealed that the isolated cycloadduct (**4**) is about 3.7 kcal/mol more stable than the alternative *"endo"* regioisomer.

Scheme 1

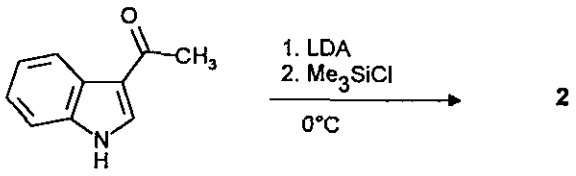


3-Vinylindole (**1**) reacts with α-chloroacrylnitrile regioselectively and "chloro-endo"-selectively to form analytically pure tetrahydrocarbazole (**5**) in 69 % yield (Scheme 1). The regiochemistry and the given *"chloro-endo"* stereochemistry are fully compatible with the predictions of the FMO concept on the basis of AM1 calculations.[9,10] In an analogous way, diene (**1**) reacts with methyl propiolate regioselectively to form 2-methoxycarbonyl-substituted carbazole (**6**), probably *via* elimination of methanol from the cycloadduct initially formed (Scheme 1). Tlc monitoring of the reaction mixture

revealed only one single isomer. The poor yield of 12 % is due to significant loss of substance during work up by flash chromatography. In this case the frontier orbital concept as well as the charge control both predict the given orientation of reactants to form compound (**6**) (Scheme 1).[10]

1'-Oxy-functionalized 3-vinylindoles should be interesting electron-rich dienes for synthesis of 4-oxo- or 4-hydroxy-functionalized carbazoles. We have reported several successful [4+2] cycloadditions of highly reactive indolyl-enol ether (**3**) generated *in situ*.[5] In continuation of these results, we studied the Diels-Alder reactivity of the formerly described[11] trimethylsilyloxy derivative (**2**), which bears a further trimethylsilyl group at the indole nucleus. In contrast to generation of **3**, the silyl enol ether (**2**) is preparatively available[11] as an oily, relatively unstable compound from 3-acetylindole (**7**) by deprotonation and O-silylation as is outlined in Scheme 2.

Scheme 2



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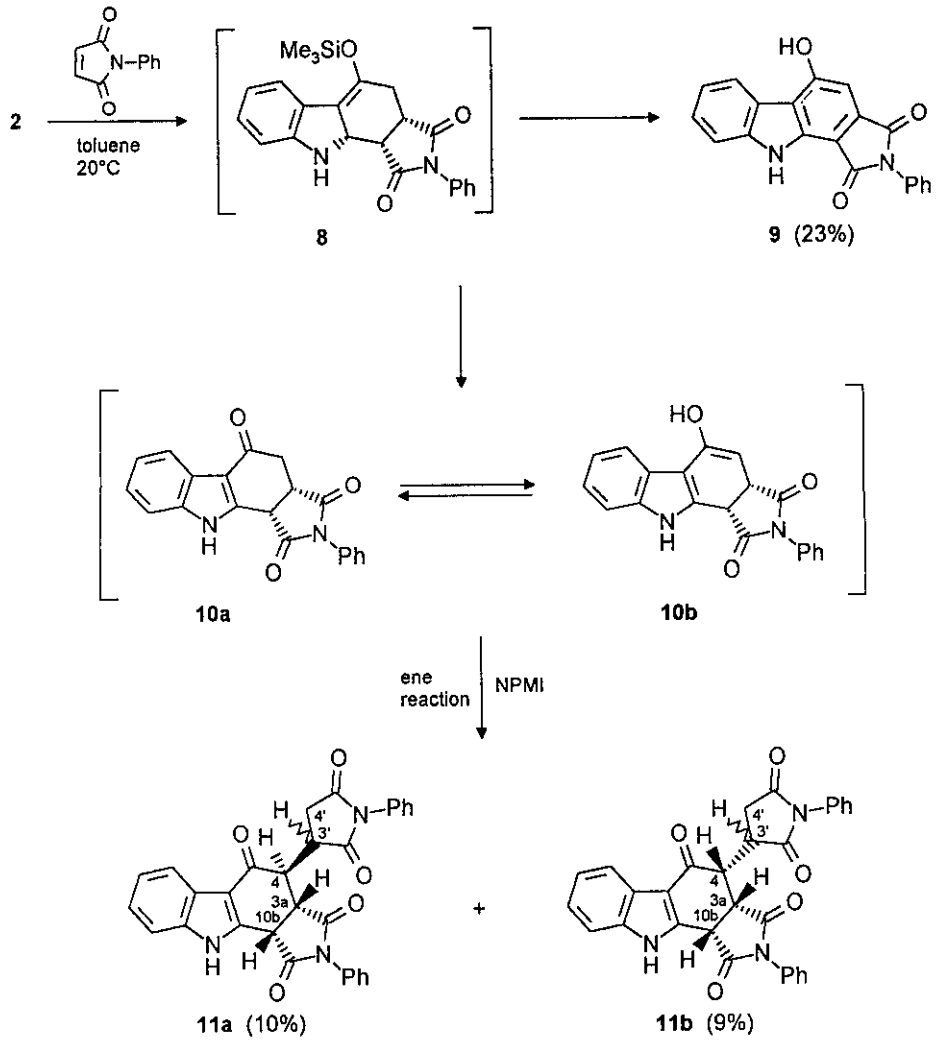
According to AM1 calculations 3-vinylindole (**2**) is predestinated to be involved in HOMO*(diene)*-LUMO*(dienophile)*-controlled cycloadditions.[10] We reinvestigated the reaction of **2** with a variety of dienophiles.[11] However, only the cycloaddition with *N*-phenylmaleimide was successful in our hands. 3-Vinylindole (**2**) reacts with this dienophile at room temperature to form three products (Scheme 3) which were isolated by flash chromatography. The pyrrolo[3,4-*a*]anellated carbazole (**9**) is probably immediately formed from cycloadduct (**8**) by a desilylation and dehydrogenation step, *respectively. Dehydrogenation reactions in cycloaddition procedures* with vinylindoles were frequently observed.[4] The other two products are a diastereomeric mixture of the anellated carbazoles (**11a**, **11b**), possibly formed by a hetero-ene reaction (or a conjugate addition reaction) of carbazole intermediates (**10a**, **10b**) with *N*-phenylmaleimide. All three compounds were obtained analytically pure.

Scheme 3

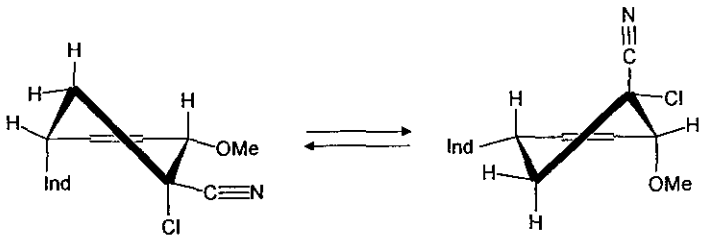


Structural Aspects

The analysis of the relative configuration of the cycloadduct (**4**) (four ß-oriented hydrogen atoms H_{11a}, H_{11b}, H_{4a}, H_5 at the anellated cyclohexene unit) and the regiochemistry were unambiguously performed by 400 MHz $^1H,^1H$-NOE measurements and several $^1H,^1H$-decoupling experiments (SFD-technique). In the same manner, the constitution of carbazole (**5**) was established. However, the analysis of the configuration of **5** at the 2 position is more difficult. The methoxy group resonates in comparison to other methoxy-substituted tetrahydrocarbazoles[4] about 0.4 ppm at significantly lower field (δ = 3.65 ppm in $CDCl_3$). This paramagnetic shift can be induced by the influence of an anisotropy effect of the nitrile function in the energetically favored conformation I with pseudoequatorial position of the methoxy group and equatorial position of the vicinal nitrile function

(see Scheme 4 for the conformational equilibrium of **5**). In the alternative C2-epimer, these effects are absent on inspection of Dreiding models.

Scheme 4



Ind = anellated indolenine system

I II

The constitution of **6** was clarified by $^1H,^1H$-NOE measurements and the pyrrolo[3,4-*a*]anellated carbazole(**9**)by routine nmr spectroscopy. In the case of the two isolated pure fractions of **11a** and **11b** the existence of maximal four diastereomers (epimeric mixture of **11a**, epimeric mixture of **11b**) is to be expected. However, the 400 MHz ^1H nmr data revealed only one set of signals for **11a** and only one set of signals for **11b**. If we rule out any incidental signal coincidences by the "epimeric pairs" of fraction **11a**, **11b**, then compounds (**11a**, **11b**) are two diastereomers. The H,H-COSY spectra gave detailed insight into the 10bH, 3aH, 4H, 3'H spin system of "both" isomers. The vicinal coupling constant 3a*H*-4*H* of 8.80 Hz (*trans*) for **11a** and of 4.20 Hz (*cis*) for **11b** is mostly indicative. However, diagnostic $^1H,^1H$-NOE and INDOR effects (Figure 1) at the stereocenters in the cyclohexenone unit support unambiguously the stereochemistry at C10b, C3a and C4. However, the configuration at the stereocenter in the pyrrole ring (C3') in "both" compounds could not be clarified so far because of the high complexity of the spin systems in the resonance area of the protons H3' and H4', respectively.

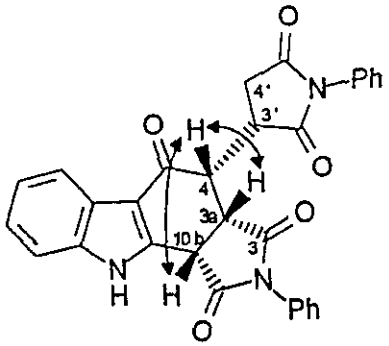


Figure 1. *Diagnostically relevant* $^1H,^1H$-NOE and INDOR effect of Diels-Alder ene adduct (**11b**).

EXPERIMENTAL

^{1}H Nmr spectra were recorded at 200 and 400 MHz with Bruker 200 and 400 spectrometers. The EI (70 eV) and FD mass spectra were recorded on a Varian MAT 7 spectrometer. Elemental analysis were performed using Carlo Erba Strumentazione 1106 apparatus. Melting points were measured with an Electrothermal 8200 instrument. Flash chromatography was performed on Merck 60 silica gel (particle size: 0.040 - 0.063 mm). The petroleum ether used had the boiling range of 40 - 60 °C. All reactions were performed in highly pure, anhydrous solvents. The yields given refer to analytically pure compounds. Some product loss occurred during chromatograhic work up. In the case of the racemates, the nomenclature of one enantiomer is given.

5α-Methoxy-11-phenylsulfonyl-1,2,3,4,4aß,5ß,11aß,11bß-octahydro-11*H*-benzo[*a*]carbazol-1-one (**4**). A mixture of 3-vinylindole (**1**) (190 mg, 0.61 mmol) ,[8] 2-cyclohexen-1-one (1.0 ml, 12 4 mmol) and 12 g of activated molecular sieve 4 Å in 40 ml of toluene was refluxed for 120 h. Then, the molecular sieves were separated by filtration and after concentration of the mixture the residue was worked up by flash chromatography (petroleum ether/ethyl acetate 5/2). Yield : 64 mg (26%), mp 163 - 164 °C; ^{1}H nmr (400 MHz, $CDCl_3$): δ 1.45 (dq, ^3J = 3.88 and 8.87 Hz, 1H, 4-Hß), 1.72 (m, 1H, 3-H), 1.90 (*pseudo*-d, ^3J = 12.86 Hz, 1H, 4-H$_\alpha$), 2.03 (m, 1H, 3-H), 2.51 (m, 2H, 2-H$_\alpha$ and 2-Hß), 2.82 (*pseudo*-t, $^3J_{11bHß,11aHß}$ = 6.11 Hz, 1H, 11b-Hß), 2.89 (m, 1H, 4a-Hß), 3.31 (s, 3H, OCH_3), 3.97 (m, 1H, 11a-Hß), 4.03 (m, 1H, 5-Hß), 6.05 (*pseudo*-t, $^3J_{6H,5Hß}$ = 2.99 Hz, 1H, 6-H), 7.01 - 7.05 (1H, aromatic H), 7.26 - 7.33 (m, 2H, aromatic H), 7.42 (*pseudo*-t, ^3J = 7.74 Hz, 2H, aromatic H), 7.54 (*pseudo*-t , ^3J = 7.46 Hz, 1H, aromatic H), 7.75 (d, $^3J_{2'H,3'H}$ = $^3J_{5'H,6'H}$ = 7.26 Hz, 2H, 2'- and 6'-H), 7.85 (d, ^3J = 8.42 Hz, 1H, aromatic H); EI-ms *m/z* (rel. int %) 409 (M^+ ,2), 313 (M^+ - C_6H_8O , retro Diels-Alder, 40), 43 (100). Anal. Calcd for $C_{23}H_{23}NO_4S$: C, 67.46; H, 5.66; N, 3.42; S, 7.83. Found: C, 67.64; H, 5.78; N, 3.30; S, 7.69.

2α-Chloro-2β-cyano 3α-methoxy-9-phenylsulfonyl-1,2,3ß,9aß-tetrahydro-9*H*-carbazole (5).

A mixture of 3-vinylindole (**1**) (110 mg, 0.35 mmol), α-chloroacrylonitrile (10 ml, 114 mmol) and 5.0 g of activated molecular sieves 4 Å were refluxed at 80 °C for 48 h. Then , the molecular sieve was filtered off and the residue purified by flash chromatography (petrol ether/ethyl acetate 3/1); the oily fraction was crystallized several times from dichloromethane/n-hexane to give colorless crystals of **5**. Yield: 97 mg (69%); mp 149 °C; ^{1}H nmr (400 MHz, $CDCl_3$): δ 2.59 (dd, $^2J_{1Hα,1Hß}$ = 13.28 Hz, $^3J_{1Hß,9aHß}$ = 10.11 Hz, 1H, 1-Hß), 3.39 (dd, $^2J_{1Hα,1Hß}$ = 13.27 Hz, $^3J_{1Hα,9aHß}$ = 4.85 Hz, 1H, 1-Hα), 3.65 (s, 3H, OCH_3), 4.09 (dd, $^3J_{4H,3Hß}$ = 3.52 Hz, $^5J_{9aHß,3Hß}$ = 1.87 Hz, 1H, 3-Hß), 4.33 - 4.43 (m, 1H, 9a-Hß), 5.87 (*pseudo*-t, $^3J_{4H,3Hß}$ = 3.52 Hz, 1H, 4-H), 7.07 (*pseudo*-t, ^3J = 7.44 Hz,

1H, 6- or 7-H), 7.30 - 7.37 (m, 1H, aromatic H), 7.42 - 7.62 (m, 3H, aromatic H), 7,79 - 7.87 (m, 3H, aromatic H); FD-ms *m/z* (rel. int. %) 402.2 (M^+, isotope peak, 41), 400.1 (M^+, 100). Anal. Calcd for $C_{20}H_{17}N_2O_3ClS$: C, 59.92; H, 4.27; N, 6.99; S, 8.00; Cl, 8.84. Found; C, 60.05; H, 3.90; N, 6.78; S, 8.30; Cl, 8.87.

Methyl 9-phenylsulfonyl-9*H*-carbazole-2-carboxylate (6) . A mixture of 3-vinylindole (**1**) (260 mg, 0.83 *mmol*), *methyl propiolate* (510 mg, 6.00 mmol) and 7.0 g of activated molecular sieves 4 Å in 20 ml of toluene was refluxed for 12 h. The molecular sieves were filtered off and the mixture concentrated. The residue obtained was purified by flash chromatography (petrol ether/ethyl acetate 4/1). Yield : 35 mg (12 %); mp 198 °C (dichloromethane/ n-hexane); ^1H nmr (200 MHz, CD_2Cl_2): δ 3.95 (s, 3H, CO_2CH_3), 7.45 - 7.70 (m, 5H, aromatic H), 7.82 - 7.85 (m, 2H, aromatic H), 8.02 - 8.06 (d, ^3J = 7.98 Hz, 1H, 3-H or 4-H), 8.22 - 8.32 (m, 3 H, aromatic H), 8.88 (s, 1H, aromatic H1.); FD-ms *m/z* (rel. int. %) 402.2 (M^+, isotope peak, 41), 400.1 (M^+ , 100). Anal. Calcd for $C_{20}H_{15}NO_4S$: C, 65.74; H, 4.14; N, 3.83; S, 8.77. Found: C, 65.48; H, 3.98; N, 3.66; S, 8.47.

1-Trimethylsilyloxy-1-(1-trimethylsilylindol-3-yl)ethene (2)[11]. In a special glass ware apparatus, described by us,[12] 3-acetylindole (320 mg, 2.01 mmol) was dissolved in 20 ml of tetrahydrofuran and cooled to 0 °C. Then, *trimethylsilyl chloride (0.8 ml, 6.30 mmol) and lithium diisopropyl amide* (2 molar solution in tetrahydrofuran, 2.5 ml, 5.00 mmol) were added slowly using a syringe. The mixture was stirred for 1 h at 0 °C, then it was warmed to room temperature. After filtering, the liquid was concentrated in vacuum. The obtained oily compound (**2**) is highly susceptible to air and moisture and was subsequently used for the Diels-Alder reactions. ^1H Nmr (400 MHz,CD_2Cl_2): δ 0.37 (s, 9H, $Si(CH_3)_3$) , 0.62 (s, 9H, $Si(CH_3)_3$), 4.50 (d, ^2J = 1.26 Hz, 1H, 2-H_A), 4.89 (d, ^2J = 1.28 Hz, 1H, 2-H_B), 7.35 - 7.21 (m, 2H, indole H), 7.43 (s, 1H, indole 2'-H), 7.56 (d, ^3J = 6.79 Hz, 1H, indole H), 7.92 (d, ^3J = 6.96 Hz, 1H, indole H).

Diels-Alder reaction of 2 with *N*-phenylmaleimide.

The whole amount of subsequently obtained oily compound (**2**) was dissolved in 4 ml of toluene and mixed with a solution of *N*-phenylmaleimide (420 mg, 2.43 mmol) in 5 ml of toluene. The mixture was stirred at room temperature for 2 h, and then a drop of hydrochloric acid (18 %) was added and the mixture poured onto ice. The crude products were extracted with several portions with ether. The organic layer was concentrated and the residue obtained separated by flash chromatography (petrol ether/ ethyl acetate 1/1).

5-Hydroxy-2-phenyl-1,2,3,10-tetrahydropyrrolo[3,4-*a*]carbazole-1,3-dione (9). Yield: 23%; mp 356 °C (petrol ether/ethyl acetate); ^{1}H nmr (200 MHz, DMSO-D_6): δ 7.09 (s, 1H, 4-H), 7.27 (*pseudo*-t, ^3J = 7.22 Hz, 1H, aromatic H), 7.40 - 7.64 (m, 7H, H-aromatic H), 8.26 (d, ^3J = 7.67 Hz, 1H, aromatic H), 11.72 and 12.12 (2s, NH or OH, exchangeable); EI-ms *m/z* (rel. int. %) 328 (M^+, 100), 284 (M^+ - C_2H_4O, 45). Anal. Calcd for $C_{20}H_{12}N_2O_3$: C, 73.16 ; H, 3.68; N, 8.53. Found: C, 72.98; H, 3.62; N, 8.47.

4ß-[2,5-Dioxo-1-phenylpyrrolidin-3-yl]-2-phenyl-1,2,3,3aß,4α,5,10,10bß-octahydropyrrolo[3,4-*a*]carbazole-1,3,5-trione (11a). Yield: 10%; mp 276 - 278 °C ($CHCl_3$) ; ^{1}H nmr (400 MHz, CD_2Cl_2): δ 2.70 (dd, $^2J_{4'H\alpha,4'H\beta}$ = 16.38 Hz, ^3J = 7.23 Hz, 1H, 4'-H), 2.96 - 3.04 (m, 2H, 3a-Hß and 3'-H), 3.44 (dd, $^4J_{10bH\beta,4H\alpha}$ = 1.41 Hz, $^3J_{10bH\beta,3aH\beta}$ = 10.79 Hz, 1H, 10b-Hß), 3.52 (d-*pseudo*-t, ^3J = 7.62 Hz, ^3J = 7.46 Hz, $^4J_{4H\alpha,10bH\beta}$ = 1.47 Hz, 1H, 4-Hα), 4.48 (dd, $^3J_{4'H,3'H}$ = 7.62 Hz, ^2J = 7.24 Hz, 1H, 4'-H), 7.25 - 7.27 (m, 2H, aromatic H), 7.32 - 7.55 (m, 11H, aromatic H), 8.26 (d, ^3J = 7.66 Hz, 1H, aromatic H), 9.44 (br s , 1H, NH, exchangeable); FD-ms *m/z* (rel. int. %) 503.4 (M^+,100). Anal. Calcd for $C_{30}H_{21}N_3O_5$: C, 71.56; H, 4.20; N, 8.35. Found: C, 71.35; H, 4.24; N, 8.33.

4α-[2,5-Dioxo-1-phenylpyrrolidin-3-yl]-2-phenyl-1,2,3,3aß,4ß,5,10,10bß-octahydropyrrolo[3,4-*a*]carbazole-1,3,5-trione (11b). Yield: 9%; mp 299 °C ($CHCl_3$); ^{1}H nmr (400 MHz, CD_2Cl_2): δ 2.53 (dd, $^2J_{4'H\alpha,4'H\beta}$ = 18.38 Hz, ^3J = 7.23 Hz, 1H, 4'-H), 2.80 - 3.04 (m, 2H, 3a-Hß and 3'-H), 3.43 (dd, $^4J_{10bH\beta,4H\beta}$ = 1.41 Hz, $^3J_{10bH\beta,3aH\beta}$ = 9.89 Hz, 1H, 10b-Hß), 3.52 (d-*pseudo*-t, ^3J = 8.89 Hz, ^3J = 4.20 Hz, $^4J_{4H,10bH\beta}$ = 1.47 Hz, 1H, 4-H), 4.51 (dd, $^3J_{4'H,3'H}$ = 9.74 Hz, ^2J = 7.24 Hz, 1H, 4'-H), 7.20 - 7.27 (m, 2H, aromatic H), 7.37 - 7.55 (m, 11H, aromatic H), 8.36 (d, ^3J = 7.66 Hz, 1H, aromatic H), 9.50 (br s, 1H , NH, exchangeable); EI-ms *m/z* (rel. int. %) = 503.4 (M^+, 84) , 183 (100). Anal. Calcd for $C_{30}H_{21}N_3O_5$: C, 71.56; H, 4.20; N, 8.31. Found: C, 71.45; H, 4.17; N, 8.21.

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10. MO calculation details of geometry optimized structures. The 3-vinylindoles were calculated in the *s-cis* conformation: **1** : E*(HOMO)* = - 8.33 eV; *HOMO* coefficients at C2 = - 0.3725, C1 = -O.3523, C3' = 0.4036, C2' = 0.4704; netto atomic charge at C2 = -0.03, C1 = 0.17, C3' = -0.06, C2' = -0.06. 2-Cyclohexenone : E*(LUMO)* = 0.03 eV; *LUMO* coefficients at C2 = 0.4449, C3 = -0.6119; netto atomic charge at C2 = -0.23, C3 = -0.09. α-Chloroacetonitrile : E*(LUMO)* = -0.34 eV; *LUMO* coefficients at C2 = 0.5575, C3 = -0.6906, netto atomic charge at C2 = -0.02, C3 = -0.15. Methyl propiolate : E*(LUMO)* = 0.02 eV; *LUMO* coefficients at C2 = 0.4192, C3 = -0.5155; netto atomic charge at C2 = -0.23, C3 = -0.09. 3-Vinylindole **2**: E*(HOMO)* = -8.09 eV; *HOMO* coefficients at C2 = -0.3778, C1 = -0.2039, C3' = 0.4564, C2' = 0.3650.
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