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Diastereodivergence and appendage diversity in the multicomponent synthesis of aryl-pyrrolo-tetrahydrocarbazoles

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ABSTRACT

A one-pot approach using a subsequent Cu(II)/Cu(I) catalysis and a highly diastereodivergent three-component reaction allow an easy access to various aryl-pyrrolo-tetrahydrocarbazoles with the control of up to four variable fragments and two different diastereoselectivities.

1. Introduction

Multicomponent reactions (MCR) are powerful approaches for the rapid access to large libraries of compounds,[1] in particular for those involving many variable reactants. Each variable reactant can introduce a new appendage that, combined with each other, would greatly increase the potentiality of fragment combinations. When these reactions create and control multiple stereogenic centres,[2] complex three-dimensional architectures can be made. Among multistereogenic MCR, the multicomponent [4+2] cycloaddition reactions can potentially generate up to four stereogenic sp^3 carbon centres in a single step and have proven to be highly diastereoselective.[3] According to the Diversity-Oriented Synthesis (DOS) concept,[4] reactions that would be able to diverge towards a new diastereoselection should thus extend the libraries into new three-dimensional molecular diversities.[5]

Several years ago, an efficient three-component [4+2] cycloaddition reaction involving a 2-substituted indole **1** with an aromatic aldehyde **2** and a maleimide **3** was described to yield a single diastereomeric aryl-pyrrolo-tetrahydrocarbazole **4** in racemic form (Scheme 1).[6,7] Only one relative configuration was accessible. The central rigid core can be regarded as a suitable scaffold for elaborating a small molecules library that mimics podophyllotoxin, a natural product well-known as an inhibitor of protein–protein interaction at tubulin level.[8] Moreover, molecules having an aryl-pyrrolo-tetrahydrocarbazole structure have been reported to be cytotoxic against cancer cell lines.[9]

To meet the practice-oriented synthesis criteria and to rapidly expand our chemical library, we now report reaction optimisations that allow two distinct configurations to be selectively obtained. In addition, we will describe the beneficial use of $CuSO_4 \cdot 5H_2O$ as the catalyst of choice in this MCR approach. Indeed, a subsequent Huisgen 1,3-dipolar cycloaddition ('click' methodology[10]) can be performed in the same flask by the ability of Cu(II) to be regenerated in situ to Cu(I).[11,12] These processes have the potential to extensively increase the diversification of the chemical library.

2. Results and discussion

We began our study by the preparation of various 2-substituted indoles **1a–h**, readily obtained in two steps from **6** (Scheme 2) using an improved Moody's approach.[13]

The three-component coupling of **1**, **2** and **3** (Scheme 3) requires a catalyst (Table 1, entry 1), presumably to activate the initial Friedel–Crafts addition of the indole **1** to the aldehyde **2**. The thermal condition should favour a subsequent 1,4-elimination process, generating the reactive indole-2,3-quinodimethane species.[14]

Our initial study used the Brønsted acid 10-camphorsulfonic acid (CSA) as catalyst. However, a low yield was observed with the electron-donating aromatic aldehyde **2a** (entry 2). We found that the unexpensive Lewis acid $CuSO_4 \cdot 5H_2O$ (10 mol %) proved to be more efficient (entry 3) and allowed through combination of various indoles **1a–h** with the aldehydes **2a–d** and the maleimides **3a–c** the synthesis of a wide range of new cycloadduct **4** or **5** ranging from 44% to 90% yield. Remarkably, for each combination

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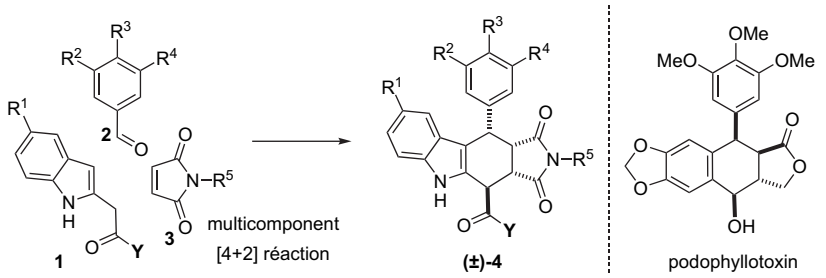
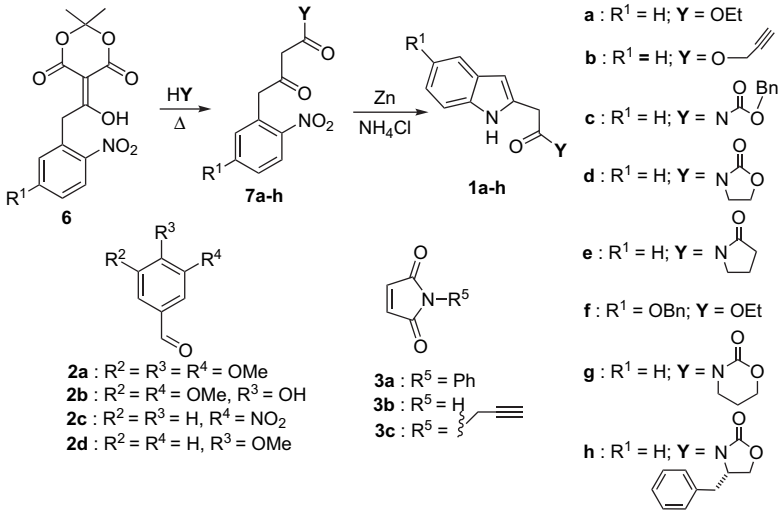
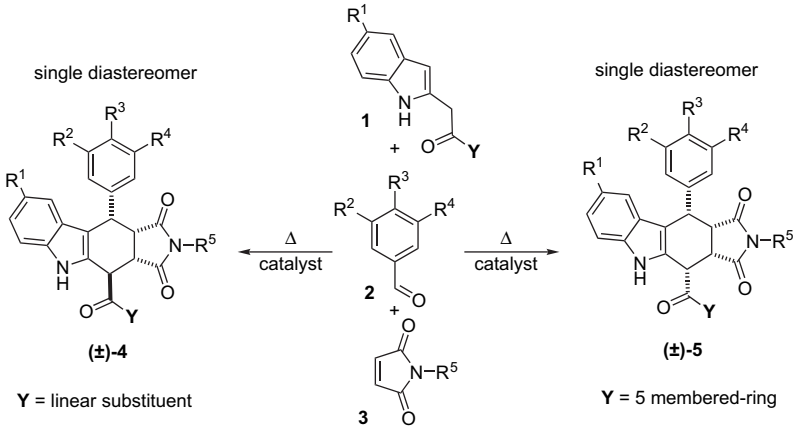


Scheme 1. Lévy-3CR for the synthesis of indolo-podophyllotoxin analogues.



Scheme 2. Synthesis of 2-substituted indoles **1a**–**h**.



Scheme 3. Highly diastereodivergent [4+2] Lévy-3CR.

with the indoles **1a**–**f**, only one diastereomer in racemic form was isolated, either **4** or **5**. It is noteworthy that every indole having an acyclic **Y**-substituent (**1a**–**c**) gives the configuration **4** (entries 2–11), whereas those having a five-membered ring at the **Y**-substituent position (**1d**,**e**) end up with the configuration **5** (entries 12–17). The only detectable and competing side product was the self-condensed indole-2,3-quinodimethane dimer.[15]

This reaction condition was tolerant with the unprotected phenol **2b**, the simple maleimide **3b** and the terminal alkynes (entries 10 and 11). It was easy from the ^{1}H NMR spectra to distinguish the diastereomers **4** from **5** by their typical chemical shifts and by their coupling constants from the protons set on the cyclohexene. Interestingly, when the reaction was carried out with the indole **1g** having a six-membered ring at the **Y**-substituent position (entry 18), the diastereoselection was less efficient and both configurations **5g** and **4g** were obtained as an inseparable mixture in 59% yield. The configuration of the major diastereomer remains the cycloadduct **5g** in the ratio of 9:1 compared with **4g** as shown by the ^{1}H NMR spectra.

At the **Y**-substituent position, we also evaluated the impact of the chiral *N*-acyl-benzyloxazolidinone (five-membered ring) in discriminating the facial selectivity (Scheme 4). The reaction of

Table 1
Stereoselectives [4+2] Lévy-3CR

Entry	Reactants[a]	Condition[b]	Product	Yield (%)
1	**1a**+**2a**+**3a**	No catalyst[c]	—	0
2	**1a**+**2a**+**3a**	A	**4a**	38
3	**1a**+**2a**+**3a**	B	**4a**	74
4	**1a**+**2b**+**3a**	B	**4b**	65
5	**1a**+**2a**+**3b**	B	**4c**	52
6	**1a**+**2b**+**3b**	C	**4d**	44
7	**1f**+**2a**+**3a**	B	**4e**	47
8	**1c**+**2a**+**3a**	B	**4f**	56
9	**1a**+**2c**+**3a**	B	**4g**	90
10	**1a**+**2d**+**3c**	B	**4h**	76
11	**1b**+**2b**+**3a**	B	**4i**	69
12	**1d**+**2a**+**3a**	B	**5a**	73
13	**1e**+**2a**+**3a**	B	**5b**	68
14	**1d**+**2b**+**3a**	B	**5c**	63
15	**1d**+**2a**+**3b**	B	**5d**	66
16	**1d**+**2b**+**3b**	C	**5e**	54
17	**1d**+**2c**+**3a**	B	**5f**	77
18	**1g**+**2a**+**3a**	B	**5g**/**4g** (9:1)	59

[a] Reactants: **1** (1 equiv)+**2** (1.5 equiv)+**3** (3 equiv).
[b] Condition A: 10 mol % CSA, reflux in toluene for 20 h. Condition B: 10 mol % $CuSO_4{\cdot}5H_2O$, reflux in toluene for 16–36 h. Condition C: 10 mol % $CuSO_4{\cdot}5H_2O$, reflux in chlorobenzene for 16–36 h.
[c] Reflux in toluene for 18 h.

indole (+)-**1h** with the aldehyde **2b** and the phenylmaleimide **3a** gave two separable products (−)-**8** (27%) and (+)-**9** (45%), albeit with a weak facial selectivity (2:3).

Gratifyingly, compounds (±)-**4a** and (+)-**9** formed single crystals suitable for X-ray diffraction (Fig. 1).[16,17] Hence, the relative configurations of products **4** and **5** and the absolute stereochemistries for (−)-**8** and (+)-**9** were unambiguously assigned. The cycloadduct (+)-**9** is a typical Diels–Alder *endo*-isomer, whereas cycloadduct **4a** shows an inversion on the stereogenic centre bearing the acyl-**Y**-substituent.[18] In addition, the reduction of the imide group of **5a** with 6 equiv of $LiEt_3BH$ in THF (Scheme 5) gave regioselectively the hydroxy lactam **10** (71%), whereas the reduction of **4a** in the same condition led to the isolation of the diastereomeric product **11** (74%). Interestingly, the resulting hydroxy lactam group holds potential for further transformations into various substructures.[19]

To circumvent the need for extensive purifications and to rapidly increase the diversity of our library, we thought that the Cu(II) catalyst used for our MCR, i.e., $CuSO_4{\cdot}5H_2O$, could be 'recycled' into Cu(I) catalyst by simple addition of sodium ascorbate to promote a subsequent Huisgen 1,3-dipolar cycloaddition in a one-pot process.

As proof of concept, the indole **1a**, the aldehyde **2d** and the maleimide **3c** (only 1.5 equiv of **3c** was used) were first heated in toluene with 10 mol % $CuSO_4{\cdot}5H_2O$ for 24 h (Scheme 6). The resulting mixture containing the newly formed product **4i** was split into two equal parts. From each vessel were added sodium ascorbate and a new fragment having an azide group. Both mixtures were stirred overnight at room temperature to yield two new arylpyrrolo-tetrahydrocarbazoles **12** (68%) and **13** (62%).[20] This approach extends truly the diversification potential of our product in a very short and efficient way.

Two products **14** and **15** (Fig. 2) gave additional examples of possible variations on this scaffold using this stereoselective and stereodivergent one-pot route.

3. Conclusion

In summary, an one-pot approach can selectively unite in one molecular entity four different and variable fragments with two kinds of diastereoselectivities, using the copper catalyst twice in two different oxidation degrees. The high stereoselectivity observed in the formation of **4** (with acyclic **Y**-substituents) and **5** (with five-membered ring **Y**-substituents) is still unclear considering that it cannot be ascribed to the hindrance of the **Y**-substituent, nor be related to their functional moieties. Further investigations are now underway to clarify the highly selective formation of these two distinct diastereomers **4** and **5**. Their potency to inhibit protein–protein interactions are now under evaluation. These results will be reported shortly.

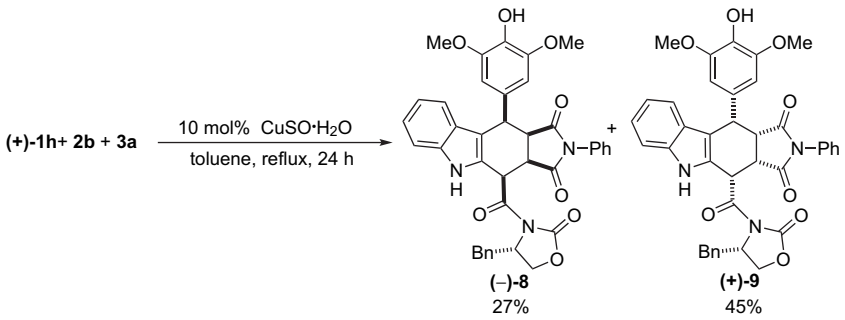
4. Experimental

4.1. General informations

Melting points were performed on Reichert Thermovar hot-stage apparatus. IR (film and KBr) spectra were measured with a Bormem FTIR instrument. UV spectra were obtained with a UNICAM 8700 UV/Vis spectrophotometer in MeOH. ^{1}H NMR (300 MHz and 400 MHz) and ^{13}C NMR (75 MHz and 100 MHz) spectra were acquired on a Bruker AC 300 and AC 400 spectrometer with TMS as internal standard or relative to the deuterated solvent [^{13}C: δ ($CDCl_3$)=77 ppm, δ (DMSO-d_6)=39.51 ppm, δ (CD_3OD)=49.2 ppm]. Optical rotations were recorded on a Perkin–Elmer 341. Mass spectra (LRMS and HRMS) were recorded with a VG Autospec, Micromass GCT and apparatus NERMAG R1010C (EI, CI, DCI, FAB). ESI mass spectra were recorded with ZQ Waters and MALDI, Autoflex, Bruker. Elemental analyses were carried out by the Microanalysis Service of the University of Reims. Flash chromatography was performed on silica gel (Merck, 40–63 μm). Reactions were monitored by Thin-layer chromatography, with Merck TLC aluminium sheets (Silica gel $60F_{254}$). Zinc dust (<325 mesh) was purchased from Aldrich Chemical. $CuSO_4{\cdot}5H_2O$ was crushed as a powder prior to use.

4.2. 1-Prop-2-ynylpyrrole-2,5-dione (3c)[21]

Triphenylphosphine (2.7 g, 10.3 mmol) in dry THF (70 mL) was cooled to −78 °C. DEAD (1.63 mL) was injected dropwise over



Scheme 4. Weak diastereoselectivity induced by the chiral *N*-acyl-benzyloxazolidinone in [4+2] 3CR.

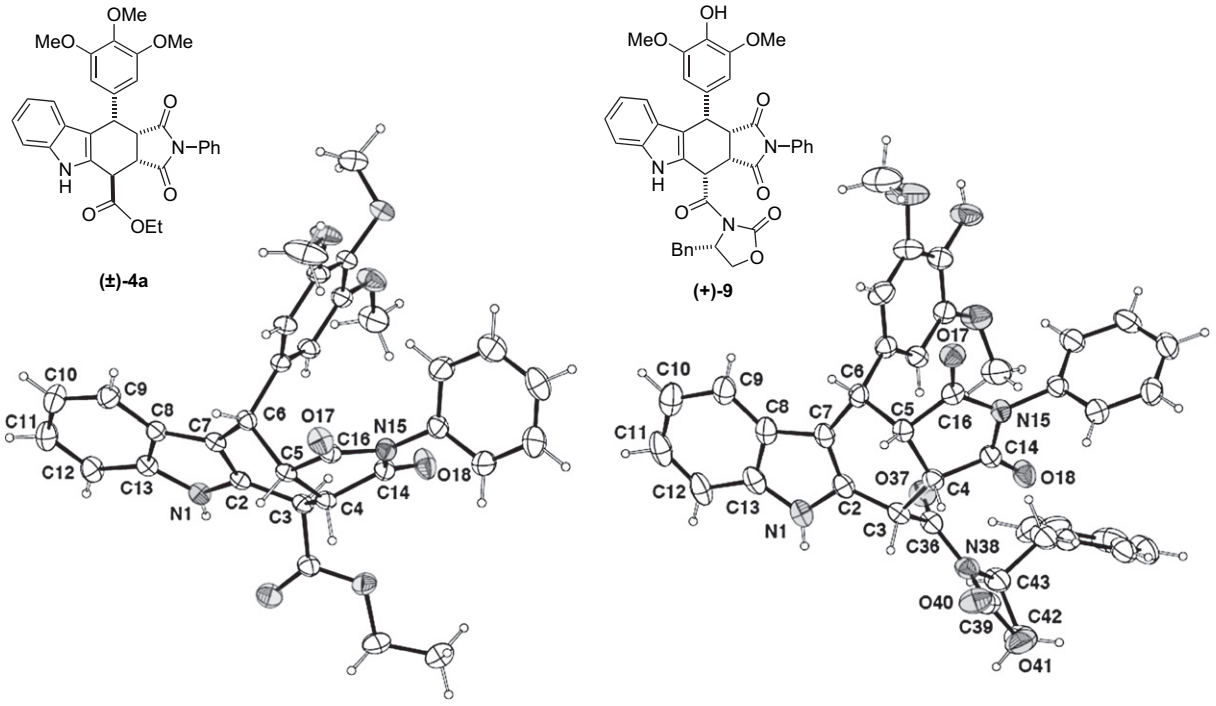
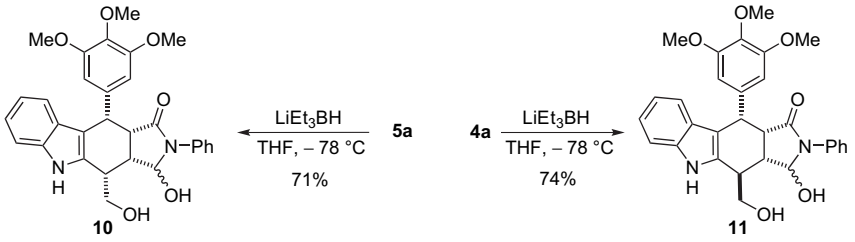
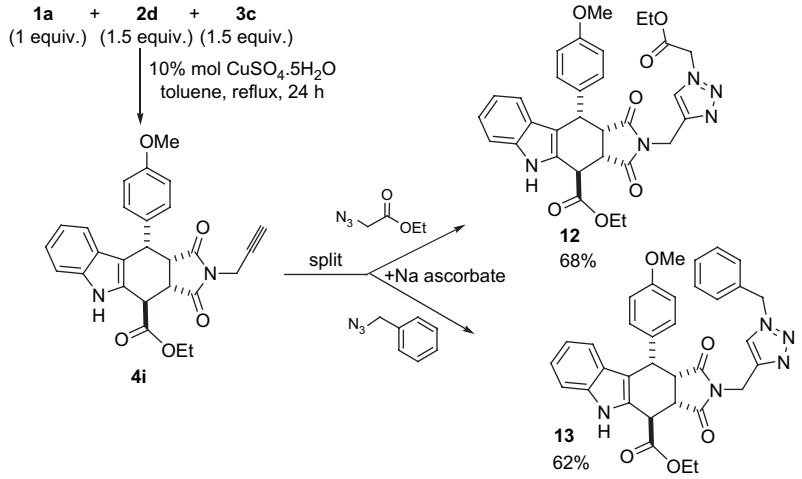


Figure 1. ORTEP drawing of molecules **4a** (left hand side) and **9** (right hand side). Displacement ellipsoids are shown at the 30% probability level.



Scheme 5. Regioselective reduction of **5a** and **4a**.



Scheme 6. Dual Cu(II)/Cu(I) catalysis in the one-pot, four-component assembling.

2 min. The yellow mixture was stirred for 5 min after which the propargyl alcohol (633 mg, 11.3 mmol) was added over 1 min. After stirring for 5 min, the maleimide **3b** (1.0 g, 10.3 mmol) was poured in one portion. The resulting mixture was stirred for 5 min at −78 °C and at ambient temperature overnight. The solvent was removed in vacuo and the product directly purified by flash chromatography (silica gel, 1:4 EtOAc/cyclohenaxe) to give the product **3c** (722 mg, 52%) as a colourless oil; R_f=0.14 (1:4 EtOAc/

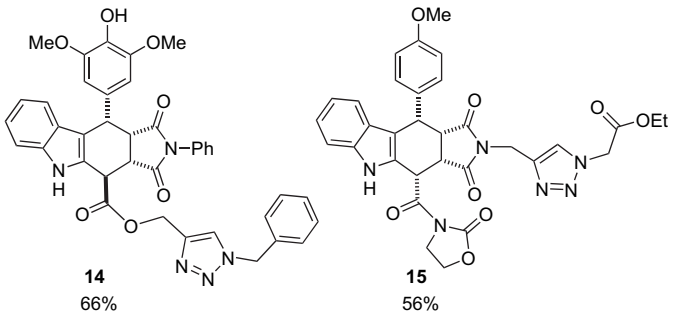


Figure 2. Additional examples of product obtained in the one-pot diastereodivergent [4+2] MCR/[3+2] cycloaddition.

cyclohexane); IR: ν_{max} (film): 3054, 1718, 1428, 1265, 1153, 738 cm^{-1}; UV: 328, 296, 285, 205 nm; ^1H NMR (400 MHz, $CDCl_3$): δ=2.31 (t, J=2.6 Hz, 1H), 4.29 (d, J=2.6 Hz, 2H), 6.83 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=26.6 (CH_2), 71.4 (C), 76.9 (CH), 134.3 (2×CH), 169.1 (2×C); LRMS (EI, 70 eV): m/z (%): 135 (37) $[M]^+$, 107 (72), 54 (100); HRMS (EI): calcd for $C_7H_5N_2O_2$: 135.0320, found: 135.0319.

4.3. 2-[1-Hydroxy-2-(2-nitrophenyl)-ethylidene]-malonic acid dimethyl ester (6a)[13]

To a solution of 2-nitrophenyl-acetic acid (25.0 g, 0.138 mol) in dry CH_2Cl_2 (250 mL) under N_2 was injected oxalyl chloride $(COCl)_2$ (15 mL, 1.25 equiv) via syringe followed by six drops of DMF (gas evolution). The mixture was stirred at rt for 4 h. Then, the solvent and excess of $(COCl)_2$ were evaporated in vacuo to give the corresponding acyl chloride as a clear brown oil. In meantime, Hünig's base (47 mL, 2 equiv) was added dropwise to a solution of Meldrum's acid (19.9 g, 0.138 mol, 1 equiv) in dry CH_2Cl_2 (150 mL) cooled with an ice bath. The previous freshly prepared acyl chloride in dry CH_2Cl_2 (50 mL) was added dropwise to the mixture at 0 °C. After stirring for 1 h at 0 °C and 30 min at rt, the mixture was acidified with an aqueous solution of HCl (1 M). The two layers were separated and the compound was extracted from the aqueous layer with CH_2Cl_2. The combined organic solution was dried ($MgSO_4$) and evaporated. The resulting yellow solid was suspended in ethanol (minimum volume) and placed in fridge overnight. After quick filtrations and washings with cold ethanol and with cold ether, the product **6a** (36.85 g, 87%) was obtained as a white solid, mp 114–116 °C (ether/cyclohexane); R_f=0.13 (2.5% MeOH/CH_2Cl_2); IR ν_{max} (KBr): 3451, 2999, 1736 cm^{-1}; UV: 260, 240 nm; ^1H NMR (300 MHz, $CDCl_3$): δ=1.69 (s, 6H), 4.55 (s, 2H), 7.29 (d, J=6.7 Hz, 1H), 7.40 (dd, J=8.0, 6.6 Hz, 1H), 7.54 (dd, J=6.7, 6.6 Hz, 1H), 8.00 (d, J=8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=26.7 (2×CH_3), 41.2 (CH_2), 91.4 (C), 105.5 (C), 125.3 (CH), 129.0 (CH), 129.1 (C), 133.7 (CH), 133.8 (CH), 148.4 (C), 160.4 (C), 170.7 (C), 193.0 (C); LRMS (FAB^+): m/z (%): 308 (100) $[M+H]^+$, 292 (45). Elemental analysis calcd (%) for $C_{14}H_{13}O_7N$: C 54.71, H 4.27, N 4.56; found: C 54.53, H 4.06, N 4.49.

4.4. 5-[2-(5-Benzyloxy-2-nitrophenyl)-1-hydroxy-ethylidene]-2,2-dimethyl-[1,3]dioxane-4,6-dione (6f)

Following the same condition as described for **6a**, the product **6f** (15.2 g, 67%) was obtained as a white solid, mp 100 °C (ether/cyclohexane); R_f=0.24 (1:1 EtOAc/CH_2Cl_2); IR: ν_{max} (film): 3435, 1735, 1661, 1579, 1511, 1420, 1332, 1261, 1028, 918, 733 cm^{-1}; UV: 309, 255, 240, 210 nm; ^1H NMR (400 MHz, $CDCl_3$): δ=1.8 (s, 6H), 4.77 (s, 2H), 5.17 (s, 2H), 6.93 (d, J=2.8 Hz, 1H), 7.02 (dd, J=9.2, 2.8 Hz, 1H), 7.35–7.43 (m, 5H), 8.24 (d, J=9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=26.8 (2×CH_3), 42.1 (CH_2), 70.7 (CH_2), 91.4 (C), 105.6 (C), 114.0 (CH), 119.9 (CH), 127.5 (2×CH), 128.2 (CH), 128.6 (CH), 128.8 (2×CH), 132.1 (C), 135.2 (C), 141.4 (C), 160.6 (C), 162.7 (C), 170.7 (C), 193.1 (C); LRMS (DCI, NH_3+isobutane): m/z (%): 414 (4) $[M+H]^+$, 370 (72), 286 (100); HRMS (ESI) calcd for $C_{21}H_{18}O_8NNa_2$ $[M-H+2Na]^+$: 458.0828, found: 458.0815.

4.5. 4-(2-Nitrophenyl)-3-oxobutyric acid ethyl ester (7a)[13]

Compound **6a** (10.0 g, 32.6 mmol) in absolute ethanol (100 mL) was refluxed for 5 h (oil bath: T=130 °C). Ethanol was evaporated in vacuo and the resulting solid was purified by flash chromatography (silica gel, 1:4 EtOAc/cyclohenaxe) to give the ester **7a** (7.36 g, 90%) as a white crystals, mp 53–54 °C; R_f=0.34 (CH_2Cl_2); IR: ν_{max} (KBr): 3439, 3073, 2992, 2942, 1749, 1724 cm^{-1}; UV: 260, 208 nm; ^1H NMR (300 MHz, $CDCl_3$): δ=1.30 (t, J=7.2 Hz, 3H), 3.62 (s, 2H), 4.23 (q, J=7.2 Hz, 2H), 4.25 (s, 2H), 7.30 (d, J=7.6 Hz, 1H), 7.47 (dd, J=8.2, 7.6 Hz, 1H), 7.50 (dd, J=7.6, 7.6 Hz, 1H), 8.11 (d, J=7.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.0 (CH_3), 47.7 (CH_2), 49.2 (CH_2), 61.5 (CH_2), 125.2 (CH), 128.6 (CH), 129.6 (C), 133.6 (CH), 133.7 (CH), 148.4 (C), 166.9 (C), 198.1 (C); LRMS (DCI, NH_3+isobutane): m/z (%): 269 (20) $[M+NH_4]^+$, 252 $[M+H]^+$ (100), 206 (41), 164 (90). Elemental analysis calcd (%) for $C_{12}H_{13}O_5N$: C 57.37, H 5.22, N 5.58; found: C 57.21, H 5.10, N 5.51.

4.6. 4-(2-Nitrophenyl)-3-oxobutyric acid prop-2-ynyl ester (7b)

A solution of compound **6a** (1.5 g, 4.9 mmol) and propargyl alcohol (410 mg, 7.32 mmol) in dry THF (10 mL) was warmed at 100 °C for 3 h. THF was evaporated in vacuo and the resulting solid was purified by flash chromatography (silica gel, 3:7 EtOAc/heptane) to give the ester **7b** (1.23 g, 96%) as a colourless crystal, mp 54–55 °C; R_f=0.27 (3:7 EtOAc/cyclohexane); IR: ν_{max} (film): 2949, 1751, 1722, 1525, 1408, 1347, 1313, 1196, 1151, 1067, 1000, 730 cm^{-1}; UV: 260, 205 nm; ^1H NMR (400 MHz, $CDCl_3$): δ=2.55 (t, J=2.4 Hz, 1H), 3.70 (s, 2H), 4.25 (s, 2H), 4.74 (d, J=2.4 Hz, 2H), 7.31 (dd, J=7.6, 1.2 Hz, 1H), 7.47 (ddd, J=7.6, 7.6, 1.2 Hz, 1H), 7.59 (ddd, J=7.6, 7.6, 1.2 Hz, 1H), 8.09 (d, J=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=47.5 (CH_2), 48.5 (CH_2), 52.5 (CH_2), 75.4 (C), 76.9 (CH), 125.0 (CH), 128.5 (CH), 129.3 (C), 133.6 (CH), 133.7 (CH), 148.1 (C), 165.9 (C), 197.6 (C); LRMS (FAB^+): m/z (%): 262 (100) $[M+H]^+$, 206 (75). Elemental analysis calcd (%) for $C_{13}H_{11}O_5N$: C 59.77, H 4.24, N 5.36; found: C 59.55, H 4.21, N 5.35.

4.7. [4-(2-Nitrophenyl)-3-oxobutyryl]-carbamic acid benzyl ester (7c)

Starting from **6a** (502 mg, 3.32 mmol) and following the same condition as described for **7b**, the product **7c** (1.06 g, 89%) was isolated as a white solid, mp 98 °C; R_f=0.18 (3:7 EtOAc/cyclohexane); IR: ν_{max} (film): 3288, 2965, 1757, 1729, 1703, 1524, 1346, 1202, 1069 cm^{-1}; UV: 291, 266, 205 nm; ^1H NMR (400 MHz, $CDCl_3$): δ=4.03 (s, 2H), 4.24 (s, 2H), 4.25 (s, 2H), 5.15 (s, 2H), 7.31–737 (m, 5H), 7.46 (dd, J=8.0, 7.6 Hz, 1H), 7.59 (dd, J=7.6, 7.6 Hz, 1H), 8.10 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=47.8 (CH_2), 50.6 (CH_2), 68.1 (CH_2), 125.2 (CH), 128.3 (CH), 128.6 (4×CH), 129.4 (C), 133.6 (CH), 133.8 (CH), 134.6 (C), 148.5 (C), 151.7 (C), 167.2 (C), 198.9 (C); LRMS (DCI, NH_3+isobutane): m/z (%): 374 $[M+NH_4]^+$ (18), 357 $[M+H]^+$ (100), 152 (63); HRMS (ESI) calcd for $C_{18}H_{16}O_6N_2Na$ $[M+Na]^+$: 379.0906, found: 379.0906.

4.8. 4-(2-Nitrophenyl)-1-(2-oxo-oxazolidin-3-yl)-butane-1,3-dione (7d)

Starting from **6a** (2.0 g, 6.5 mmol) and 2-oxazolidinone (567 mg, 6.5 mmol) and following the same condition as described for **7b**, the product **7d** (1.56 g, 82%) was obtained as white needles, mp 110 °C (EtOAc/cyclohexane); R_f=0.28 (1:1 EtOAc/cyclohexane); IR: ν_{max} (KBr): 3435, 3387, 2978, 2928, 1771, 1723, 1699, 1522, 1391, 1341 cm^{-1}; UV: 260, 212 nm; ^1H NMR (300 MHz, $CDCl_3$): δ=4.01 (t, J=7.8 Hz, 2H), 4.16 (s, 2H), 4.26 (s, 2H), 4.40 (t, J=7.8 Hz, 2H), 7.37 (dd, J=7.6, 1.3 Hz, 1H), 7.47 (ddd, J=8.2, 7.6 Hz, 1.3, 1H), 7.60 (ddd, J=7.6, 7.6, 1.3 Hz, 1H), 8.08 (dd, J=8.2, 1.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=41.9 (CH_2), 47.3 (CH_2), 49.9 (CH_2), 62.2 (CH_2), 124.9 (CH), 128.4 (CH), 129.2 (C), 133.5 (CH), 133.6 (CH), 148.4 (C), 153.7 (C), 165.7 (C), 198.6 (C); LRMS (EI, 70 eV): m/z (%): 292 (1) $[M]^+$, 156 (100). Elemental analysis calcd (%) for $C_{12}H_{12}O_6N_2$: C 53.43, H 4.14, N 9.59; found: C 53.14, H 4.01, N 9.47.

4.9. 4-(2-Nitrophenyl)-1-(2-oxopyrrolidin-1-yl)-butane-1,3-dione (7e)

Starting from **6a** (700 mg, 2.28 mmol) and pyrrolidin-2-one (233 mg, 2.74 mmol) and following the same condition as described for **7b**, the product **7e** (500 mg, 76%) was obtained as yellow solid, mp 102 °C; R_f=0.19 (1:1 EtOAc/cyclohexane); IR: ν_{max} (film): 2950, 1733, 1691, 1525, 1402, 1346, 1248, 1198, 1068, 732 cm^{-1}; UV: 290, 260, 207 nm; ^1H NMR (400 MHz, $CDCl_3$): δ=1.95 (tt, J=8.0, 7.5 Hz, 2H), 2.48 (t, J=8.0 Hz, 2H), 3.74 (t, J=7.5 Hz, 2H), 4.04 (s, 2H), 4.20 (s, 2H), 7.29 (dd, J=7.6, 1.3 Hz, 1H), 7.37 (ddd, J=7.9, 7.6, 1.3 Hz, 2H), 7.51 (ddd, J=7.6, 7.6, 1.3 Hz, 1H), 8.00 (dd, J=7.9, 1.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=16.8 (CH_2), 33.1 (CH_2), 45.1 (CH_2), 47.5 (CH_2), 51.3 (CH_2), 124.9 (CH), 128.4 (CH), 129.5 (C), 133.5 (CH), 133.7 (CH), 148.5 (C), 166.4 (C), 175.7 (C), 198.9 (C); LRMS (DCI, NH_3+isobutane): m/z (%): 308 (7) $[M+NH_3]^+$, 291 (100) $[M+H]^+$, 246 (7), 154 (14). Elemental analysis calcd (%) for $C_{14}H_{14}O_5N_2$: C 57.93, H 4.86, N 9.65; found: C 57.75, H 4.63, N 9.55.

4.10. 4-(5-Benzyloxy-2-nitrophenyl)-3-oxobutyric acid ethyl ester (7f)

Starting from **6f** (2.0 g, 4.8 mmol) in absolute ethanol (38 mL) and following the same condition as described for **7a**, the product **7f** (1.67 g, 97%) was obtained as a white amorphous solid, mp 96 °C; R_f=0.21 (CH_2Cl_2); IR: ν_{max} (film): 2982, 2943, 1732, 1715, 1604, 1592, 1521, 1412, 1333, 1252, 1073, 1034, 842, 743 cm^{-1}; UV: 308, 397, 231, 211 nm; ^1H NMR (400 MHz, $CDCl_3$): δ=1.29 (t, J=7.2 Hz, 3H), 3.64 (s, 2H), 4.21 (s, 2H), 4.22 (q, J=7.2 Hz, 2H), 5.11 (s, 2H), 6.83 (d, J=2.8 Hz, 1H), 6.95 (dd, J=9.2, 2.8 Hz, 1H), 7.33–7.42 (m, 5H), 8.17 (d, J=9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.0 (CH_3), 48.3 (CH_2), 49.3 (CH_2), 61.4 (CH_2), 70.5 (CH_2), 113.8 (CH), 119.6 (CH), 127.5 (2×CH), 128.0 (CH), 128.4 (CH), 128.7 (2×CH), 132.7 (C), 135.3 (C), 141.2 (C), 162.6 (C), 167.0 (C), 198.2 (C); LRMS (DCI, NH_3+isobutane): m/z (%): 375 $[M+NH_4]^+$ (63), 358 $[M+H]^+$ (100), 312 (30), 266 (9); HRMS (TOF EI$^+$): calcd for $C_{19}H_{19}O_6N$: 357.1212, found: 357.1214.

4.11. 4-(2-Nitrophenyl)-1-(2-oxo-[1,3]oxazinan-3-yl)-butane-1,3-dione (7g)

Starting from **6a** (4.0 g, 13 mmol) and [1,3]oxazinan-2-one (1.3 g, 13 mmol) and following the same condition as described for **7b**, the product **7g** (2.4 g, 61%) was obtained as a white solid, mp 104 °C; R_f=0.25 (1:1 EtOAc/cyclohexane); IR: ν_{max} (film): 3425, 2921, 1730, 1700, 1523, 1478, 1407, 1347, 1276, 1170, 1070, 989, 727 cm^{-1}; UV: 300, 265, 210 nm; ^1H NMR (400 MHz, $CDCl_3$): δ=2.06 (m, 2H), 3.76 (t, J=6.4 Hz, 2H), 4.26 (s, 2H), 4.29 (t, J=5.4 Hz, 2H), 6.42 (s, 1H); 7.37 (d, J=7.6 Hz, 1H), 7.45 (dd, J=8.2, 7.6 Hz, 1H), 7.37 (d, J=7.6 Hz, 1H), 7.45 (dd, J=8.2, 7.6 Hz, 1H), 7.59 (dd, J=7.6, 7.6 Hz, 1H), 8.07 (d, J=8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=21.2 (CH_2), 42.3 (CH_2), 47.2 (CH_2), 52.9 (CH_2), 67.6 (CH_2), 124.8 (CH), 128.3 (CH), 129.5 (C), 133.5 (CH), 133.7 (CH), 148.4 (C), 151.6 (C), 168.9 (C), 198.9 (C); LRMS (ESI): m/z (%): 329 (85) $[M+Na]^+$, 124 (100); HRMS (ESI): calcd for $C_{14}H_{14}N_2O_6Na$ $[M+Na]^+$: 329.0750, found: 329.0746.

4.12. (*S*)-(+)-1-(4-Benzyl-2-oxo-oxazolidin-3-yl)-4-(2-nitrophenyl)-butane-1,3-dione (7h)

Starting from **6a** (3.46 g, 11.3 mmol) and (*S*)-(+)-4-benzyloxazolidin-2-one (1.6 g, 9.0 mmol) and following the same condition as described for **7b**, the product **7h** (2.6 g, 75%) was isolated as a white amorphous solid, mp 92–93 °C; R_f=0.28 (1:1 EtOAc/cyclohexane); $[\alpha]_D^{28}$ +38.0 (*c* 1.0, $CHCl_3$); IR: ν_{max} (KBr): 3412, 3032, 2981, 2924, 1782, 1726, 1701, 1528, 1395, 1356, 1202 cm^{-1}; UV: 204, 261, 231, 210 nm; ^1H NMR (300 MHz, $CDCl_3$): δ=2.74 (dd, J=13.5, 9.8 Hz, 1H), 3.25 (dd, J=13.5, 3.3 Hz, 1H), 4.06–4.20 (m, 4H), 4.24 (s, 2H), 4.64 (m, 1H), 7.12–7.32 (m, 5H), 7.38 (dd, J=7.6, 1.2 Hz, 1H), 7.52 (dd, J=8.2, 8.0 Hz, 1H), 7.61 (dd, J=8.2, 7.6 Hz, 1H), 8.02 (d, J=8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=37.0 (CH_2), 47.2 (CH_2), 50.1 (CH_2), 54.5 (CH), 66.1 (CH_2), 124.7 (CH), 126.9 (CH), 128.3 (CH), 128.5 (2×CH), 129.1 (2×CH), 129.2 (C), 133.4 (CH), 133.5 (CH), 134.8 (C), 148.2 (C), 153.5 (C), 165.6 (C), 198.8 (C); LRMS (EI, 70 eV): m/z (%): 382 (66) $[M]^+$, 246 (63), 178 (100). Elemental analysis calcd (%) for $C_{20}H_{18}O_6N_2$: C 62.82, H 4.74, N 7.33; found: C 62.69, H 4.90, N 7.30.

4.13. (1*H*-Indol-2-yl)-acetic acid ethyl ester (1a)[13]

To a biphasic solution of compound **7a** (925 mg, 3.68 mmol) in THF (40 mL) and an aqueous solution of saturated NH_4Cl (39 mL) was added zinc dust (21 g) under vigorous stirring. The reaction mixture was stirred for 2 h and then quenched with an aqueous solution of saturated $KHCO_3$. The solid residue was removed by filtration (Celite). The product was extracted with EtOAc and dried ($MgSO_4$). After evaporation and flash chromatography (silica gel, CH_2Cl_2), the product **1a** (710 mg, 95%) was isolated as an oil, which solidified by standing in fridge, mp 32 °C; R_f=0.70 (CH_2Cl_2); IR: ν_{max} (KBr): 3399, 3055, 2982, 1726 cm^{-1}; UV: 289, 281, 272, 221 nm; ^1H NMR (400 MHz, $CDCl_3$): δ=1.27 (t, J=7.2 Hz, 3H), 3.78 (s, 2H), 4.19 (q, J=7.2 Hz, 2H), 6.33 (m, 1H), 7.07 (dd, J=8.0, 7.5 Hz, 1H), 7.12 (dd, J=8.2, 8.0 Hz, 1H), 7.29 (d, J=8.2 Hz, 1H), 7.54 (d, J=7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.1 (CH_3), 33.9 (CH_2), 61.3 (CH_2), 101.7 (CH), 110.8 (CH), 119.7 (CH), 120.0 (CH), 121.6 (CH), 128.1 (C), 130.6 (C), 136.3 (C), 170.6 (C); LRMS (FAB$^+$): m/z (%): 204 (25) $[M+H]^+$, 203 (40), 130 (100). Elemental analysis calcd (%) for $C_{12}H_{13}O_2N$: C 70.92, H 6.45, N 6.89; found: C 70.67, H 6.63, N 6.90.

4.14. (1*H*-Indol-2-yl)-acetic acid prop-2-ynyl ester (1b)

Starting from compound **7b** (845 mg, 3.23 mmol) and following the same condition as described for **1a**, except vigorous stirring with zinc dust only for 30 min, the product **1b** (521 mg, 76%) was isolated as an oil, which solidified by standing in fridge, mp 55 °C; R_f=0.14 (1:4 ether/cyclohexane); IR: ν_{max} (film): 3400, 3286, 3058, 2925, 1738, 1456, 1289, 1158, 1024, 748, 640 cm^{-1}; UV: 289, 272, 218 nm; ^1H NMR (400 MHz, $CDCl_3$): δ=2.47 (t, J=2.6 Hz, 1H), 3.76 (s, 2H), 4.28 (d, J=2.6 Hz, 2H), 6.32 (m, 1H), 7.07 (ddd, J=7.6, 7.6, 1.2 Hz, 1H), 7.12 (ddd, J=7.6, 7.6, 1.2 Hz, 1H), 7.24 (dd, J=7.6, 1.2 Hz, 1H), 7.52 (dd, J=7.6, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=33.5 (CH_2), 52.6 (CH_2), 75.4 (C), 77.1 (CH), 102.0 (CH), 110.8 (CH), 119.8 (CH), 120.1 (CH), 121.7 (CH), 128.0 (C), 129.7 (C), 136.3 (C), 169.6 (C); LRMS (DCI, NH_3+isobutane): m/z (%): 214 (32) $[M+H]^+$, 144 (45), 131 (100). Elemental analysis calcd (%) for $C_{13}H_{11}O_2N$: C 73.23, H 5.20, N 6.57; found: C 72.93, H 5.17, N 6.50.

4.15. (2-1*H*-Indol-2-yl-acetyl)-carbamic acid benzyl ester (1c)

Starting from **7c** (474 mg, 1.33 mmol) and following the same condition as described for **1a**, the product **1c** (352 mg, 86%) was isolated as a white solid, mp 135 °C; R_f=0.30 (1:19 EtOAc/CH_2Cl_2); IR: ν_{max} (film): 3345, 2930, 1765, 1693, 1513, 1499, 1455, 1204, 1028 cm^{-1}; UV: 288, 289, 274 nm; ^1H NMR (400 MHz, $CDCl_3$): δ=4.24 (s, 2H), 5.19 (s, 2H), 6.41 (s, 1H), 7.08 (ddd, *J*=8.0, 7.0, 0.8 Hz, 1H), 7.15 (ddd, *J*=7.0, 7.0, 1.2 Hz, 1H), 7.31 (dd, *J*=8.0, 1.2 Hz, 1H), 7.35–7.38 (m, 5H), 7.55 (dd, *J*=7.0, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=35.6 (CH_2), 68.2 (CH_2), 102.6 (CH), 110.9 (CH), 119.8 (CH), 120.2 (CH), 121.9 (CH), 128.1 (C), 128.5 (2×CH), 128.7 (2×CH), 128.8 (CH), 130.1 (C), 134.6 (C), 136.3 (C), 151.6 (C), 170.8 (C); LRMS (ESI): *m*/*z* (%): 331 (100) $[M+Na]^+$, 309 (40) $[M+H]^+$, 265 (35), 220 (35); HRMS (TOF EI+) calcd for $C_{18}H_{16}O_3N_2$: 308.1161, found: 308.1160.

4.16. 3-[1*H*-Indol-2-yl-acetyl]-oxazolidin-2-one (1d)

Starting from **7d** (865 mg, 2.96 mmol) and following the same condition as described for **1a**, the product **1d** (614 mg, 85%) was isolated as white crystals, mp 174 °C; R_f=0.19 (CH_2Cl_2); IR: ν_{max} (KBr): 3353, 3000, 2934, 1765, 1686, 1404, 1391, 1294, 1225, 1125 cm^{-1}; UV: 289, 286, 271, 219 nm; ^1H NMR (300 MHz, $CDCl_3$): δ=4.02 (dd, *J*=8.4, 7.8 Hz, 2H), 4.42 (dd, *J*=8.4, 7.8 Hz, 2H), 4.45 (s, 2H), 6.46 (m, 1H), 7.07 (ddd, *J*=8.0, 7.0, 0.8 Hz, 1H), 7.15 (ddd, *J*=7.0, 7.0, 1.2 Hz, 1H), 7.34 (dd, *J*=8.0, 1.2 Hz, 1H), 7.55 (dd, *J*=7.0, 0.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=34.3 (CH_2), 42.7 (CH_2), 62.2 (CH_2), 102.7 (CH), 110.8 (CH), 119.8 (CH), 120.2 (CH), 121.9 (CH), 128.2 (C), 130.2 (C), 136.2 (C), 153.9 (C), 169.6 (C); LRMS (EI, 70 eV): *m*/*z* (%): 244 (27) $[M]^+$, 189 (26), 157 (95), 130 (100). Elemental analysis calcd (%) for $C_{13}H_{12}O_3N$ (244): C 63.91, H 4.95, N 11.47; found: C 63.51, H 4.96, N 11.27.

4.17. 1-(2-1*H*-Indol-2-yl-acetyl)-pyrrolidin-2-one (1e)

Starting from **7e** (360 mg, 1.24 mmol) and following the same condition as described for **1a**, the product **1e** (224 mg, 75%) was isolated as a white powder, mp 183 °C; R_f=0.19 (CH_2Cl_2); IR: ν_{max} (film): 3345, 1724, 1682, 1452, 1355, 1293, 1226, 743 cm^{-1}; UV: 289, 281, 273, 218, 210 nm; ^1H NMR (400 MHz, acetone-d_6): δ=2.05 (m, 2H), 2.61 (t, *J*=8.0 Hz, 2H), 3.78 (t, *J*=7.2 Hz, 2H), 4.40 (s, 2H), 6.30 (m, 1H), 6.96 (ddd, *J*=7.0, 7.0, 1.2 Hz, 1H), 7.04 (ddd, *J*=7.0, 7.0, 1.2 Hz, 1H), 7.37 (dd, *J*=7.0, 1.2 Hz, 1H), 7.46 (dd, *J*=7.0, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6): δ=17.8 (CH_2), 34.1 (CH_2), 36.4 (CH_2), 46.4 (CH_2), 102.2 (CH), 111.8 (CH), 119.9 (CH), 120.5 (CH), 121.7 (CH), 129.6 (C), 133.2 (C), 137.7 (C), 170.8 (C), 176.6 (C); LRMS (DCI, NH_3+isobutane): *m*/*z* (%): 243 (100) $[M+H]^+$, 157 (62). Elemental analysis calcd (%) for $C_{14}H_{14}O_2N_2$: C 69.41, H 5.82, N 11.56; found: C 69.24, H 5.57, N 11.43.

4.18. (5-Benzyloxy-1*H*-indol-2-yl)-acetic acid ethyl ester (1f)

Starting from **7f** (2.19 g, 6.13 mmol) and following the same condition as described for **1a**, the product **1g** (1.75 g, 92%) was isolated as a white solid, mp 92 °C; R_f=0.28 (CH_2Cl_2); IR: ν_{max} (film): 3393, 2982, 1729, 1589, 1485, 1453, 1179, 1026, 736 cm^{-1}; UV: 305, 294, 287, 274, 212 nm; ^1H NMR (400 MHz, $CDCl_3$): δ=1.28 (t, *J*=7.2 Hz, 3H), 3.78 (s, 2H), 4.19 (q, *J*=7.2 Hz, 2H), 5.08 (s, 2H), 6.25 (br s, 1H), 6.89 (dd, *J*=8.6, 2.4 Hz), 7.08 (d, *J*=2.4 Hz, 1H), 7.21 (d, *J*=8.6 Hz, 1H), 7.29 (m, 1H), 7.36 (m, 2H), 7.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.1 (CH_3), 35.7 (CH_2), 62.4 (CH_2), 72.6 (CH_2), 101.6 (CH), 103.7 (CH), 111.5 (CH), 112.5 (2×CH), 127.5 (CH), 127.7 (CH), 128.4 (2×CH), 128.6 (C), 131.4 (C), 131.7 (C), 138.2 (C), 154.0 (C), 171.0 (C); LRMS (DCI, NH_3+isobutane): *m*/*z* (%): 310 (100) $[M+H]^+$, 218 (33); HRMS (TOF EI^+); calcd for $C_{19}H_{19}N0_3$: 309.1365, found: 309.1342.

4.19. 3-(2-1*H*-Indol-2-yl-acetyl)-[1,3]oxazinan-2-one (1g)

Starting from **7g** (1.8 g, 5.9 mmol) and following the same condition as described for **1a**, the product **1g** (1.03 g, 68%) was isolated as a white solid, mp 144 °C; R_f=0.26 (1:1 EtOAc/cyclohexane); IR: ν_{max} (film): 1735, 1700, 1548, 1478, 1458, 1422, 1266, 1175, 994, 742 cm^{-1}; UV: 287, 272, 217, 200 nm; ^1H NMR (400 MHz, $CDCl_3$): δ=2.03 (m, 2H), 3.70 (t, *J*=6.5 Hz, 2H), 4.27 (t, *J*=5.4 Hz, 2H), 4.45 (s, 2H), 6.42 (s, 1H), 7.05 (dd, *J*=7.8, 7.8 Hz, 1H), 7.12 (dd, *J*=8.0, 7.8, 1H), 7.31 (d, *J*=8.0 Hz, 1H), 7.53 (d, *J*=7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=21.6 (CH_2), 37.5 (CH_2), 42.9 (CH_2), 67.6 (CH_2), 102.4 (CH), 110.8 (CH), 119.6 (CH), 120.1 (CH), 121.6 (CH), 128.1 (C), 131.4 (C), 136.1 (C), 152.0 (C), 172.9 (C); LRMS (ESI): *m*/*z* (%): 281 (28) $[M+Na]^+$, 216 (38), 102 (100); HRMS (ESI): calcd for $C_{14}H_{14}N_2O_3Na$ $[M+Na]^+$: 281.0902, found: 281.0894.

4.20. (*S*)-(+)-4-Benzyl-3-[1*H*-indol-2-yl-acetyl]-oxazolidin-2-one (1h)

Starting from **7h** (2.34 g, 6.13 mmol) and following the same condition as described for **1a**, the product **1h** (1.59 g, 78%) was isolated as an amorphous white solid, mp 112 °C; R_f=0.39 (CH_2Cl_2); $[\alpha]_D^{28}$ +119.5 (*c* 1.0, $CHCl_3$); IR: ν_{max} (KBr): 3390, 3316, 3028, 2976, 2924, 1767, 1699, 1456, 1395, 1362, 1217, 1186 cm^{-1}; UV: 289, 282, 274, 217 nm; ^1H NMR (300 MHz, $CDCl_3$): δ=2.80 (dd, *J*=13.6, 8.5 Hz, 1H), 3.09 (dd, *J*=13.6, 3.2 Hz, 1H), 4.10–4.20 (m, 2H), 4.37 (d, *J*=15.0 Hz, 1H), 4.52 (d, *J*=15.0 Hz, 1H), 4.65 (m, 1H), 6.49 (m, 1H), 6.98 (d, *J*=7.1 Hz, 2H), 7.05–7.22 (m, 4H), 7.34 (d, *J*=8.0 Hz, 1H), 7.57 (d, *J*=7.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=34.8 (CH_2), 37.3 (CH_2), 55.0 (CH), 66.2 (CH_2), 102.6 (CH), 110.9 (CH), 119.8 (CH), 120.2 (CH), 121.8 (CH), 127.3 (CH), 128.2 (C), 128.8 (2×CH), 129.3 (2×CH), 130.2 (C), 134.5 (C), 136.1 (C), 153.9 (C), 169.4 (C); LRMS (EI, 70 eV): *m*/*z* (%): 334 (24) $[M]^+$, 157 (73), 130 (100). Elemental analysis calcd (%) for $C_{20}H_{18}O_3N_2$ (334): C 71.83, H 5.43, N 8.38; found: C 71.81, H 5.47, N 8.37.

4.21. General procedure for the three-component coupling reaction

Method A. The indole **1** (1 mmol), the aldehyde **2** (1.5 mmol), the dienophile **3** (3 mmol) and D-(+)-10-camphorsulfonic acid (23 mg, 0.1 mmol) in dry toluene (15 mL) were warmed up to 130 °C for 20 h under N_2. After cooling, the black solution was neutralised with saturated aqueous $NaHCO_3$. The compound was extracted with EtOAc and dried ($MgSO_4$). After evaporation, the product was applied to flash chromatography (silica gel).

Method B. The indole **1** (1 mmol), the aldehyde **2** (1.5 mmol), the dienophile **3** (3 mmol) and $CuSO_4 \cdot 5H_2O$ (25 mg, 0.1 mmol) in dry toluene (15 mL) were warmed up to 130 °C for 16–36 h under N_2. The mixture was filtered (paper filter) to remove the catalyst, which was washed once with CH_2Cl_2 or methanol. After evaporation, the product was applied to flash chromatography (silica gel).

Method C. Same condition as method B by using chlorobenzene instead of toluene and by warming up to 150 °C for 16–36 h.

4.21.1. (±)-(4S,5S*,10S*,10aS*)-1,3-Dioxo-2-phenyl-10-(3,4,5-trimethoxyphenyl)-1,2,3,3a,4,5,10,10a-octahydropyrrolo-[3,4-b]carbazole-4-carboxylic acid ethyl ester (**4a**)*

Method A, 24 h, 210 mg (38%), method B, 24 h, 410 mg (74%), flash chromatography with eluent 2:3 EtOAc/cyclohexane, isolated as clear yellow needles, mp 263 °C (yellow needles, EtOAc/cyclohexane); R_f=0.37 (1:1 EtOAc/cyclohexane); IR: ν_{max} (KBr): 3360, 2940, 1736, 1717, 1589, 1503, 1387, 1198, 1125 cm^{-1}; UV: 291, 283, 271, 219, 209 nm; ^1H NMR (300 MHz, $CDCl_3$): δ=1.46 (t, *J*=7.1 Hz, 3H), 3.64 (s, 6H), 3.75 (s, 3H), 3.82 (dd, *J*=8.7, 7.6 Hz, 1H), 4.38 (dd, *J*=8.7, 3.0 Hz, 1H), 4.44 (q, *J*=7.1 Hz, 2H), 4.83 (d, *J*=3.0 Hz, 1H), 4.91

(d, J=7.6 Hz, 1H), 6.22 (s, 2H), 6.57 (m, 2H), 7.05 (dd, J=7.5, 7.5 Hz, 1H), 7.20 (dd, J=7.5, 7.5 Hz, 1H), 7.25–7.33 (m, 3H), 7.34 (d, J=7.5 Hz, 1H), 7.38 (d, J=7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.4 (CH_3), 36.4 (CH), 38.9 (CH), 41.0 (CH), 45.3 (CH), 56.0 (2×CH_3), 60.7 (CH_3), 63.0 (CH_2), 106.0 (2×CH), 111.0 (CH), 112.1 (C), 118.6 (CH), 120.1 (CH), 123.0 (CH), 125.8 (C), 126.0 (2×CH), 127.1 (C), 128.6 (CH), 128.9 (2×CH), 131.3 (C), 134.8 (C), 136.3 (C), 137.4 (C), 153.2 (2×C), 170.4 (C), 175.7 (C), 177.1 (C); LRMS (EI, 70 eV): m/z (%): 554 (27) $[M]^+$, 508 (100), 308 (20), 167 (25). Elemental analysis calcd (%) for $C_{32}H_{30}O_7N_2$: C 69.30, H 5.45, N 5.05; found: C 68.95, H 5.67, N 4.83.

4.21.2. (±)-(4S*,5S*,10S*,10aS*)-10-(4-Hydroxy-3,5-dimethoxyphenyl)-1,3-dioxo-2-phenyl-1,2,3,3a,4,5,10,10a-octahydropyrrolo[3,4-b]carbazole-4-carboxylic acid ethyl ester (**4b**)

Method A, 24 h, 243 mg (45%), method B, 24 h, 350 mg, (65%), flash chromatography with eluent 2:3 EtOAc/cyclohexane, isolated as an amorphous white solid, mp 254 °C (EtOAc/cyclohexane); R_f=0.32 (1:1 EtOAc/cyclohexane); IR: ν_{max} (film): 3395, 2940, 1713, 1614, 1517, 1500, 1459, 1356, 1299, 1214, 1196, 1112, 1027 cm^{-1}; UV: 290, 279, 270, 216 nm; ^{1}H NMR (400 MHz, DMSO-d_6, TMS): δ=1.33 (t, J=7.0 Hz, 3H), 3.52 (s, 6H), 3.75 (dd, J=8.7, 8.0 Hz, 1H), 4.32 (m, 2H), 4.38 (dd, J=8.7, 3.2 Hz, 1H), 4.65 (d, J=3.2 Hz, 1H), 4.84 (d, J=8.0 Hz, 1H), 6.19 (s, 2H), 6.54 (m, 2H), 6.90 (dd, J=8.0, 7.5 Hz, 1H), 7.07 (dd, J=8.0, 7.5 Hz, 1H), 7.25 (d, J=8.0 Hz, 1H), 7.27–7.33 (m, 3H), 7.40 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, TMS): ^{13}C NMR (100 MHz, DMSO-d_6, TMS): δ=14.0 (CH_3), 36.7 (CH), 37.8 (CH), 41.6 (CH), 44.7 (CH), 55.9 (2×CH_3), 61.9 (CH_2), 106.7 (2×CH), 111.0 (C, CH), 118.3 (CH), 118.7 (CH), 121.7 (CH), 125.3 (C), 126.4 (2×CH), 128.2 (C, CH), 128.6 (2×CH), 130.3 (C), 131.9 (C), 135.0 (C), 136.7 (C), 147.5 (2×C), 171.1 (C), 175.4 (C), 177.3 (C); LRMS (EI, 70 eV): m/z (%): 540 (7) $[M]^+$, 495 (32), 294 (51), 57 (100). Elemental analysis calcd (%) for $C_{31}H_{28}O_7N_2$: C 68.88, H 5.22, N 5.18; found: C 68.60, H 5.20, N 5.00.

4.21.3. (±)-(4S*,5S*,10S*,10aS*)-1,3-Dioxo-10-(3,4,5-trimethoxyphenyl)-1,2,3,3a,4,5,10,10a-octahydropyrrolo-[3,4-b]carbazole-4-carboxylic acid ethyl ester (**4c**)

Method A, 24 h, 120 mg (25%), method C, 24 h, 249 mg (52%), flash chromatography with eluent 1:1 EtOAc/cyclohexane, isolated as an amorphous white solid, mp 235 °C; R_f=0.19 (1:1 EtOAc/cyclohexane); IR: ν_{max} (film): 3263, 2939, 1777, 1718, 1591, 1506, 1459, 1330, 1234, 1125, 1019 cm^{-1}; UV: 292, 279, 270, 219 nm; ^{1}H NMR (400 MHz, DMSO-d_6, TMS): δ=1.31 (t, J=7.2 Hz, 3H), 3.56 (dd, J=8.8, 8.4 Hz, 1H), 3.58 (s, 3H), 3.63 (s, 6H), 4.08 (dd, J=8.8, 3.6 Hz, 1H), 4.28 (m, 2H), 4.52 (d, J=3.6 Hz, 1H), 4.76 (d, J=8.4 Hz, 1H), 6.23 (s, 2H), 6.89 (dd, J=8.0, 7.6 Hz, 1H), 7.06 (dd, J=8.0, 7.6 Hz, 1H), 7.22 (d, J=8.0 Hz, 1H), 7.38 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, TMS): δ=14.1 (CH_3), 36.9 (CH), 38.1 (CH), 42.6 (CH), 45.6 (CH), 55.6 (2×CH_3), 59.9 (CH_3), 61.8 (CH_2), 106.1 (2×CH), 111.4 (CH), 111.5 (C), 118.4 (CH), 118.8 (CH), 121.7 (CH), 125.5 (C), 128.5 (C), 136.2 (C), 136.5 (C), 136.6 (C), 152.2 (2×C), 171.1 (C), 177.8 (C), 179.4 (C); LRMS (EI, 70 eV): m/z (%): 478 (19) $[M]^+$, 432 (100), 308 (62). Elemental analysis calcd (%) for $C_{26}H_{26}O_7N_2$: C 65.27, H 5.48, N 5.86; found: C 65.36, H 5.76, N 5.66.

4.21.4. (±)-(4S*,5S*,10S*,10aS*)-10-(4-Hydroxy-3,5-dimethoxyphenyl)-1,3-dioxo-1,2,3,3a,4,5,10,10a-octahydropyrrolo[3,4-b]carbazole-4-carboxylic acid ethyl ester (**4d**)

Method C, 36 h, 204 mg (44%), flash chromatography with eluent 1:1 EtOAc/cyclohexane, isolated as an amorphous white solid, mp 296 °C; R_f=0.16 (3:1 EtOAc/cyclohexane); IR: ν_{max} (KBr): 3377, 3182, 3064, 1779, 1712, 1617, 1518, 1460, 1364, 1334, 1300, 1276, 1213, 1192, 1114, 746 cm^{-1}; UV: 328, 296, 285, 205 nm; ^{1}H NMR (400 MHz, DMSO-d_6, TMS): δ=1.30 (t, J=7.2 Hz, 3H), 3.53 (dd, J=8.8, 8.4 Hz, 1H), 3.61 (s, 6H), 4.04 (dd, J=8.8, 3.2 Hz, 1H), 4.28 (m, 2H), 4.50 (d, J=3.2 Hz, 1H), 4.69 (d, J=8.4 Hz, 1H), 6.17 (s, 2H), 6.88 (dd, J=8.0, 7.6 Hz, 1H), 7.05 (dd, J=8.0, 7.6 Hz, 1H), 7.18 (d, J=8.0 Hz, 1H), 7.48 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, TMS): δ=14.1 (CH_3), 36.9 (CH), 37.9 (CH), 42.6 (CH), 45.9 (CH), 55.8 (2×CH_3), 61.8 (CH_2), 106.4 (2×CH), 111.5 (CH), 111.7 (C), 118.5 (CH), 118.7 (CH), 121.6 (CH), 125.5 (C), 128.5 (C), 130.6 (C), 134.5 (C), 136.7 (C), 147.3 (2×C), 171.2 (C), 177.8 (C), 179.5 (C); LRMS (FAB$^+$): m/z (%): 465 (15) $[M+H]^+$, 265 (100). Elemental analysis calcd (%) for $C_{25}H_{24}O_7N_2$: C 64.65, H 5.21, N 6.03; found: C 64.46, H 5.26, N 5.87.

4.21.5. (±)-(4S*,5S*,10S*,10aS*)-8-Benzyloxy-1,3-dioxo-2-phenyl-10-(3,4,5-trimethoxyphenyl)-1,2,3,3a,4,5,10,10a-octahydropyrrolo[3,4-b]carbazole-4-carboxylic acid ethyl ester (**4e**)

Method B, 48 h, 200 mg (47%) as an amorphous solid, mp 239 °C, R_f=0.17 (3:7 EtOAc/cyclohexane); IR: ν_{max} (film): 2953, 1711, 1592, 1498, 1459, 1390, 1182, 1123 cm^{-1}; UV: 308, 277, 222, 210 nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.43 (t, J=7.2 Hz, 3H), 3.66 (s, 6H), 3.76 (s, 3H), 3.78 (dd, J=8.8, 7.6 Hz, 1H), 4.36 (dd, J=8.8, 2.8 Hz, 1H), 4.40 (q, J=7.2 Hz, 2H), 4.81 (d, J=2.8 Hz, 1H), 4.82 (d, J=7.6 Hz, 1H), 5.0 (s, 2H), 6.20 (s, 2H), 6.55 (m, 2H), 6.84 (s, 1H), 6.92 (d, J=8.8 Hz, 1H), 7.23–7.30 (m, 5H), 7.33 (dd, J=8.2, 7.2 Hz, 2H), 7.39 (d, J=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.3 (CH_3), 36.4 (CH), 38.8 (CH), 41.0 (CH), 45.3 (CH), 56.0 (2×CH_3), 60.7 (CH_3), 62.9 (CH_2), 70.8 (CH_2), 102.5 (CH), 105.9 (2×CH), 111.7 (CH), 113.2 (CH), 126.0 (2×CH), 126.2 (C), 127.5 (2×CH), 127.8 (CH), 128.4 (2×CH), 128.5 (CH), 128.9 (2×CH), 131.2 (C), 131.6 (C), 134.7 (C2), 137.2 (C9), 137.4 (C), 153.1 (2×C), 153.4 (C), 170.3 (C), 175.7 (C), 177.1 (C); LRMS (FAB$^+$): m/z (%): 661 (25) $[M+H]^+$, 614 (100); HRMS (ESI): calcd for $C_{39}H_{36}O_8Na$ $[M+Na]^+$: 683.2369, found: 683.2359.

4.21.6. (±)-(4S*,5S*,10S*,10aS*)-[1,3-Dioxo-2-phenyl-10-(3,4,5-trimethoxyphenyl)-1,2,3,3a,4,5,10,10a-octahydropyrrolo[3,4-b]-carbazole-4-carbonyl]-carbamic acid benzyl ester (**4f**)

Method B, 18 h, 163 mg (56%), as an amorphous solid, mp 218 °C; R_f=0.21 (2:3 EtOAc/cyclohexane); IR: ν_{max} (film): 3353, 2958, 1783, 1714, 1590, 1504, 1456, 1385, 1327, 1188, 1124 cm^{-1}; UV: 291, 282, 274, 220, 211 nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.59 (s, 6H), 3.76 (s, 3H), 3.77–3.30 (m, 2H), 4.83 (m, 1H), 4.94 (m, 1H), 5.16 (d, J=11.8 Hz, 1H), 5.22 (d, J=11.8 Hz, 1H), 6.22 (s, 2H), 6.64 (m, 2H), 7.04 (dd, J=7.6, 7.6 Hz, 1H), 7.16 (dd, J=7.6, 7.6 Hz, 1H), 7.30–7.37 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=38.7 (CH), 39.1 (CH), 43.0 (CH), 47.0 (CH), 56.1 (2×CH_3), 60.7 (CH_3), 68.2 (CH_2), 106.0 (2×CH), 111.6 (CH), 113.1 (C), 118.4 (CH), 120.0 (CH), 122.9 (CH), 125.4 (C), 126.1 (2×CH), 128.1 (C), 128.7 (2×CH), 128.8 (2×CH), 128.8 (CH), 129.1 (2×CH), 130.8 (C), 134.0 (C), 134.6 (C), 136.8 (C), 137.5 (C), 151.0 (C), 153.3 (2×C), 170.2 (C), 175.3 (C), 179.0 (C); LRMS (ESI): m/z (%): 682 (100) $[M+Na]^+$; HMRS (ESI): calcd for $C_{38}H_{33}N_3O_8Na$ $[M+Na]^+$: 682.2165, found: 682.2168.

4.21.7. (±)-(4S*,5S*,10S*,10aS*)-10-(3-Nitrophenyl)-1,3-dioxo-2-phenyl-1,2,3,3a,4,5,10,10a-octahydropyrrolo[3,4-b]carbazole-4-carboxylic acid ethyl ester (**4g**)

Method B, 18 h, 338 mg, 90%, flash chromatography with eluent 3:7 EtOAc/cyclohexane, isolated as a white solid, mp 225 °C; R_f=0.21 (3:7 EtOAc/cyclohexane); IR: ν_{max} (film): 3413, 3057, 1713, 1528, 1382, 1349, 1184, 736 cm^{-1}; UV: 289, 282, 267, 218, 196 nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.46 (t, J=7.2 Hz, 3H), 3.93 (dd, J=8.6, 8.2 Hz, 1H), 4.41 (dd, J=8.6, 3.2 Hz, 1H), 4.44 (q, J=7.2 Hz, 2H), 4.89 (d, J=3.2 Hz, 1H), 5.07 (d, J=8.2 Hz, 1H), 6.50 (m, 2H), 7.02 (dd, J=8.0, 7.6 Hz, 1H), 7.16 (d, J=8.0 Hz, 1H), 7.20 (dd, J=7.6, 7.6 Hz, 1H), 7.25–7.27 (m, 3H), 7.33–7.42 (m, 3H), 7.90 (br s, 1H), 8.05 (br d, J=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.4 (CH_3), 36.5 (CH), 38.3 (CH), 40.9 (CH), 44.5 (CH), 63.1 (CH_2), 110.6 (C), 111.3 (CH), 118.3 (CH), 120.3 (CH), 122.6 (CH), 123.2 (CH), 123.7 (CH), 125.4 (C), 125.5 (2×CH), 127.8 (C), 128.6 (CH), 128.9 (2×CH), 129.5 (CH), 130.9 (C), 135.0 (CH), 136.4 (C), 141.8 (C), 148.3 (C), 170.1 (C), 175.1 (C), 176.4 (C); LRMS (ESI): m/z (%): 548.1 (15) $[M+K]^+$, 532 (100) $[M+Na]^+$;

HRMS (ESI): calcd for $C_{29}H_{30}N_3O_6Na$ $[M+Na]^+$: 532.1485, found: 532.1483.

4.21.8. (±)-(4S,5S*,10S*,10aS*)-10-(4-Methoxyphenyl)-1,3-dioxo-2-prop-2-ynyl-1,2,3,3a,4,5,10,10a-octahydropyrrolo[3,4-b]-carbazole-4-carboxylic acid ethyl ester (**4h**)*

Method B, 24 h, 205 mg (76%), flash chromatography eluent 1:4 EtOAc/cyclohexane, isolated as an amorphous white solid, mp 148 °C; R_f=0.27 (3:7 EtOAc/cyclohexane); IR: ν_{max} (film): 3390, 3300, 2992, 1713, 1510, 1460, 1395, 1251, 1178, 1030, 735 cm^{-1}; UV: 330, 290, 281, 221, 202 nm; ^1H NMR (400 MHz, $CDCl_3$): δ=1.39 (t, J=7.2 Hz, 3H), 2.01 (t, J=2.4 Hz, 1H), 3.59 (dd, J=17.4, 2.4 Hz, 1H), 3.64 (s, 3H), 3.67 (dd, J=17.4, 2.4 Hz, 1H), 3.68 (dd, J=8.8, 7.6 Hz, 1H), 4.15 (dd, J=8.8, 3.2 Hz, 1H), 4.36 (q, J=7.2 Hz, 2H), 4.76 (d, J=3.2 Hz, 1H), 4.80 (d, J=7.6 Hz, 1H), 6.61 (d, J=8.4 Hz, 2H), 6.79 (d, J=8.4 Hz, 2H), 6.97 (dd, J=7.8, 7.6 Hz, 1H), 7.12 (dd, J=8.2, 7.6 Hz, 1H), 7.19 (d, J=7.6 Hz, 1H), 7.34 (d, J=8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.2 (CH_3), 26.9 (CH_2), 36.2 (CH), 37.6 (CH), 40.7 (CH), 45.4 (CH), 54.9 (CH_3), 62.7 (CH_2), 71.1 (C), 76.2 (CH), 110.9 (CH), 111.9 (C), 113.5 (2×CH), 118.5 (CH), 119.8 (CH), 122.6 (CH), 125.6 (C), 127.0 (C), 129.4 (2×CH), 130.8 (C), 136.2 (C), 158.7 (C), 170.3 (C), 175.4 (C), 176.5 (C); LRMS (DCI, NH_3+isobutane): m/z (%): 474 (8) $[M+NH_4]^+$, 457 (100) $[M+H]^+$, 410 (81), 349 (68). Elemental analysis calcd (%) for $C_{27}H_{24}O_5N_2$: C 71.04, H 5.30, N 6.14; found: C 70.87, H 5.11, N 6.05.

4.21.9. (±)-(4S,5S*,10S*,10aS*)-10-(4-Hydroxy-3,5-dimethoxyphenyl)-1,3-dioxo-2-phenyl-1,2,3,3a,4,5,10,10a-octahydropyrrolo[3,4-b]carbazole-4-carboxylic acid prop-2-ynyl ester (**4i**)*

Method B, 20 h, 103 mg, (69%), flash chromatography eluent 1:49 EtOAc/CH_2Cl_2, isolated as an amorphous white solid, mp 231 °C; R_f=0.23 (2:3 EtOAc/cyclohexane); IR: ν_{max} (film): 3420, 1744, 1713, 1617, 1517, 1459, 1386, 1273, 1214, 1112, 735 cm^{-1}; UV: 289, 281, 217, 207 nm; ^1H NMR (400 MHz, $CDCl_3$): δ=2.62 (t, J=2.6 Hz, 1H), 3.64 (s, 6H), 3.81 (dd, J=8.6, 7.1 Hz, 1H), 4.33 (dd, J=8.6, 3.0 Hz, 1H), 4.88 (dd, J=15.7, 2.3 Hz, 1H), 4.89 (d, J=3.0 Hz, 1H), 4.90 (d, J=7.1 Hz, 1H), 6.21 (s, 2H), 6.53 (m, 2H), 7.03 (dd, J=8.0, 7.9 Hz, 1H), 7.19 (dd, J=8.1, 7.9 Hz, 1H), 7.23–7.33 (m, 4H), 7.38 (d, J=8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=36.3 (CH), 38.6 (CH), 41.0 (CH), 45.4 (CH), 53.9 (CH_2), 56.3 (2×CH_3), 76.5 (CH), 76.6 (C), 105.8 (2×CH), 111.1 (CH), 112.5 (C), 118.6 (CH), 120.1 (CH), 123.1 (CH), 125.7 (C), 126.0 (2×CH), 126.4 (C), 128.5 (CH), 128.9 (2×CH), 129.9 (C), 131.1 (C), 134.4 (C), 136.4 (C), 146.9 (2×C), 169.8 (C), 175.7 (C), 176.9 (C); LRMS (DCI, NH_3+isobutane): m/z (%): 551 (4) $[M+H]^+$, 494 (21), 316 (54), 288 (100). Elemental analysis calcd (%) for $C_{32}H_{26}O_7N_2$: C 69.81, H 4.76, N 5.09; found: C 69.53, H 4.60, N 5.01.

4.21.10. (±)-(4S,5S*,10S*,10aR*)-4-(2-Oxo-oxazolidine-3-carbonyl)-2-phenyl-10-(3,4,5-trimethoxyphenyl)-4,5,10,10a-tetrahydro-3aH-pyrrolo[3,4-b]carbazole-1,3-dione (**5a**)*

Method B, 24 h, 434 mg, 73%, flash chromatography with eluent 3:2 EtOAc/cyclohexane, isolated as needles, mp 233 °C (EtOAc/cyclohexane); R_f=0.18 (3:2 EtOAc/cyclohexane); IR: ν_{max} (film): 3340, 2958, 2928, 1775, 1714, 1591, 1504, 1461, 1389, 1237, 1123 cm^{-1}; UV: 290, 284, 279, 216 nm; ^1H NMR (400 MHz, DMSO-d_6, TMS): δ=3.57 (s, 9H), 3.78 (dd, J=8.0, 7.8 Hz, 1H), 3.98 (ddd, J=9.6, 9.6, 9.0 Hz, 1H), 4.10 (m, 1H), 4.49–4.56 (m, 2H), 4.61 (dd, J=11.6, 8.0 Hz, 1H), 4.82 (d, J=7.6 Hz, 1H), 5.55 (d, J=11.6 Hz, 1H), 6.43 (m, 2H), 6.69 (s, 2H), 6.92 (dd, J=7.6, 7.6 Hz, 1H), 7.07 (dd, J=7.6, 7.6 Hz, 1H), 7.26–7.31 (m, 3H), 7.33 (d, J=7.6 Hz, 1H), 7.34 (d, J=7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, TMS): δ=36.2 (CH), 38.4 (CH), 39.0 (CH), 43.0 (CH_2), 46.2 (CH), 56.0 (2×CH_3), 59.8 (CH_3), 62.7 (CH_2), 107.0 (2×CH), 110.9 (CH), 111.5 (C), 118.1 (CH), 118.5 (CH), 121.6 (CH), 125.3 (C), 126.6 (2×CH), 128.3 (CH), 128.6 (2×CH), 130.8 (C), 131.7 (C), 136.2 (C), 136.4 (C), 136.5 (C), 152.5 (2×C), 154.0 (C), 171.5 (C), 174.8 (C), 176.4 (C); LRMS (ESI): m/z (%): 595 (100) $[M+H]^+$, 131 (87). Elemental analysis calcd (%) for $C_{33}H_{29}O_8N_3$: C 66.53, H 4.91, N 7.06; found: C 66.18, H 4.75, N 6.86.

4.21.11. (±)-(4S,5S*,10S*,10aR*)-4-(2-Oxopyrrolidine-1-carbonyl)-2-phenyl-10-(3,4,5-trimethoxyphenyl)-4,5,10,10a-tetrahydro-3aH-pyrrolo[3,4-b]carbazole-1,3-dione (**5b**)*

Method B, 18 h, 81 mg (68%), flash chromatography (silica gel) with eluent 1:1 EtOAc/cyclohexane, isolated as an amorphous white powder, mp 224 °C; R_f=0.18 (3:2 EtOAc/cyclohexane); IR: ν_{max} (film): 3346, 2938, 1715, 1697, 1590, 1503, 1461, 1383, 1248, 1197, 1123 cm^{-1}; UV: 292, 280, 220, 211 nm; ^1H NMR (400 MHz, $CDCl_3$): δ=2.00 (m, 2H), 2.62 (t, J=8.0 Hz, 2H), 3.67 (s, 6H), 3.75 (s, 3H), 3.80 (dd, J=7.5, 7.1 Hz, 1H), 3.90 (t, J=7.8 Hz, 2H), 4.44 (dd, J=10.6, 7.1 Hz, 1H), 4.89 (d, J=7.5 Hz, 1H), 5.55 (d, J=10.6 Hz, 1H), 6.50 (m, 2H), 6.62 (s, 2H), 7.04 (dd, J=7.5, 7.5 Hz, 1H), 7.17 (dd, J=7.5, 7.5 Hz, 1H), 7.22–7.28 (m, 3H), 7.30 (d, J=7.5 Hz, 1H), 7.35 (d, J=7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=16.9 (CH_2), 33.7 (CH_2), 38.6 (CH), 39.0 (CH), 39.6 (CH), 46.2 (CH_2), 46.7 (CH), 56.3 (2×CH_3), 60.6 (CH_3), 106.7 (2×CH), 110.9 (CH), 112.8 (C), 118.4 (CH), 119.7 (CH), 122.8 (CH), 125.5 (C), 126.2 (2×CH), 128.6 (CH), 128.9 (2×CH), 130.0 (C), 131.0 (C), 134.8 (C), 137.0 (2×C), 153.0 (2×C), 171.3 (C), 175.1 (C), 175.8 (C), 176.5 (C); LRMS (FAB^+): m/z (%): 616 (25) $[M+Na]^+$, 594 (95) $[M+H]^+$, 508 (100). Elemental analysis calcd (%) for $C_{34}H_{31}O_7N_3$: C 68.79, H 5.26, N 7.08; found: C 68.40, H 5.18, N 6.91.

4.21.12. (±)-(4S,5S*,10S*,10aR*)-10-(4-Hydroxy-3,5-dimethoxyphenyl)-4-(2-oxo-oxazolidine-3-carbonyl)-2-phenyl-4,5,10,10a-tetrahydro-3aH-pyrrolo[3,4-b]carbazole-1,3-dione (**5c**)*

Method A, 24 h, 99 mg, 17%, method B, 24 h, 366 mg, 63%, flash chromatography with eluent 3:2 EtOAc/cyclohexane, isolated as an amorphous solid, mp 232 °C; R_f=0.14 (3:2 EtOAc/heptane); IR: ν_{max} (film): 3351, 2958, 2920, 1762, 1708, 1515, 1459, 1389, 1202, 1110, 1031 cm^{-1}; UV: 291, 283, 274, 208 nm; ^1H NMR (400 MHz, DMSO-d_6, TMS): δ=3.69 (s, 6H), 3.44–3.80 (m, 4H), 4.22 (ddd, J=9.6, 9.6, 9.2 Hz, 1H), 4.10 (m, 1H), 4.52 (m, 1H), 4.58 (m, 1H), 4.76 (d, J=7.6 Hz, 1H), 5.53 (d, J=11.6 Hz, 1H), 6.43 (m, 2H), 6.62 (s, 2H), 6.90 (dd, J=8.0, 7.2 Hz, 1H), 7.06 (dd, J=8.0, 7.2 Hz, 1H), 7.24–7.33 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6, TMS): δ=36.5 (CH), 38.5 (CH), 39.3 (CH), 43.3 (CH_2), 46.8 (CH), 56.4 (2×CH_3), 63.0 (CH_2), 107.5 (2×CH), 111.2 (CH), 112.1 (C), 118.4 (CH), 118.7 (CH), 121.9 (CH), 125.6 (C), 127.0 (2×CH), 128.5 (CH), 128.8 (2×CH), 130.5 (C), 131.0 (C), 132.0 (C), 135.1 (C), 136.8 (C), 147.8 (2×C), 154.3 (C), 171.8 (C), 175.2 (C), 176.7 (C); LRMS (DCI, NH_3+isobutane): m/z (%): 599 (2) $[M+NH_4]^+$, 581 (2) $[M]^+$, 428 (4), 183 (100); HRMS (ESI): calcd for $C_{32}H_{27}N_3O_8Na$ $[M+Na]^+$: 604.1696, found: 604.1695.

4.21.13. (±)-(4S,5S*,10S*,10aR*)-4-(2-Oxo-oxazolidine-3-carbonyl)-10-(3,4,5-trimethoxyphenyl)-4,5,10,10a-tetrahydro-3aH-pyrrolo[3,4-b]carbazole-1,3-dione (**5d**)*

Method B, 24 h, 343 mg, 66%, flash chromatography with eluent 3:1 EtOAc/cyclohexane, isolated as an amorphous solid, mp 253 °C (EtOAc/cyclohexane); R_f=0.20 (3:1 EtOAc/cyclohexane); IR: ν_{max} (film): 3350, 2945, 2920, 1772, 1701, 1589, 1506, 1457, 1357, 1320, 1224, 1123, 1036 cm^{-1}; UV: 291, 281, 270, 213 nm; ^1H NMR (400 MHz, DMSO-d_6, TMS): δ=3.54 (dd, J=8.8, 7.6 Hz, 1H), 3.55 (s, 3H), 3.63 (s, 6H), 4.00 (ddd, J=10.8, 9.2, 9.2 Hz, 1H), 4.10 (ddd, J=10.8, 8.8, 5.2 Hz, 1H), 4.28 (dd, J=11.8, 8.8 Hz, 1H), 4.51 (dd, J=9.2, 8.8 Hz, 1H), 4.55 (ddd, J=9.2, 8.8, 5.2 Hz, 1H), 4.69 (d, J=7.6 Hz, 1H), 5.39 (d, J=11.8 Hz, 1H), 6.61 (s, 2H), 6.89 (dd, J=8.0, 7.2 Hz, 1H), 7.04 (dd, J=8.0, 7.2 Hz, 1H), 7.30 (dd, J=8.0, 7.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, TMS): δ=36.0 (CH), 38.2 (CH), 39.7 (CH), 43.1 (CH_2), 47.3 (CH), 55.8 (2×CH_3), 59.8 (CH_3), 62.7 (CH_2), 106.7 (2×CH), 110.9 (CH), 111.7 (C), 118.1 (CH), 118.4 (CH), 121.5 (CH), 125.3 (C), 130.8 (C), 136.0 (C), 136.3 (C), 136.5 (C), 152.1 (2×C), 154.0 (C), 171.7

(C), 177.1 (C), 178.6 (C); LRMS (DCI, NH_3+isobutane): *m/z* (%): 520 (53) $[M+H]^+$, 352 (100); HRMS (ESI): calcd for $C_{27}H_{25}N_3O_8Na$: 542.1539 $[M+Na]^+$, found: 542.1539.

4.21.14. (±)-(4S*,5S*,10S*,10aR*)-10-(4-Hydroxy-3,5-dimethoxyphenyl)-4-(2-oxo-oxazolidine-3-carbonyl)-4,5,10,10a-tetrahydro-3aH-pyrrolo[3,4-b]carbazole-1,3-dione (**5e**)

Method C, 36 h, 273 mg, 54%, flash chromatography with eluent 3:2 EtOAc/cyclohexane, isolated as an amorphous solid, mp >325 °C (ether/CH_2Cl_2); R_f=0.1 (3:1 EtOAc/cyclohexane); IR: ν_{max} (film): 3362, 2941, 1772, 1718, 1610, 1513, 1463, 1392, 1329, 1217, 1112 cm^{-1}; UV: 330, 291, 285, 210 nm; ^1H NMR (400 MHz, DMSO-d_6, TMS): δ=3.50 (dd, *J*=8.8, 7.6 Hz, 1H), 3.61 (s, 6H), 4.01 (ddd, *J*=9.6, 9.2, 9.2 Hz, 1H), 4.10 (m, 1H), 4.25 (dd, *J*=11.6, 8.8 Hz, 1H), 4.50 (m, 1H), 4.56 (m, 1H), 4.64 (d, *J*=7.6 Hz, 1H), 5.36 (d, *J*=11.6 Hz, 1H), 6.57 (s, 2H), 6.88 (dd, *J*=8.0, 7.2 Hz, 1H), 7.04 (dd, *J*=8.0, 7.2 Hz, 1H), 7.30 (d, *J*=8.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, TMS): δ=36.1 (CH), 38.0 (CH), 39.8 (CH), 43.1 (CH_2), 47.6 (CH), 55.9 (2×CH_3), 62.7 (CH_2), 106.8 (2×CH), 110.9 (CH), 112.0 (C), 118.1 (CH), 118.3 (CH), 121.5 (CH), 125.4 (C), 130.5 (C), 130.8 (C), 134.2 (C), 136.5 (C), 147.2 (2×C), 171.7 (C), 177.2 (C), 178.6 (C); LRMS (FAB^+): *m/z* (%): 506 (10) $[M+H]^+$, 277 (90), 244 (100). Elemental analysis calcd (%) for $C_{26}H_{23}O_8N_3$: C 61.78, H 4.59, N 8.32; found: C 61.34, H 4.80, N 7.91.

4.21.15. (±)-(4S*,5S*,10S*,10aR*)-10-(3-Nitrophenyl)-4-(2-oxo-oxazolidine-3-carbonyl)-2-phenyl-4,5,10,10a-tetrahydro-3aH-pyrrolo[3,4-b]carbazole-1,3-dione (**5f**)

Method B, 18 h, 260 mg, 77%, flash chromatography with eluent 1:1 EtOAc/cyclohexane, isolated as a white solid, mp 217–218 °C; R_f=0.25 (3:2 EtOAc/cyclohexane); IR: ν_{max} (film): 3372, 3045, 1766, 1697, 1523, 1393, 1350, 1258, 734 cm^{-1}; UV: 290, 284, 268, 219, 198 nm; ^1H NMR (400 MHz, DMSO-d_6): δ=3.95 (dd, *J*=8.6, 8.2 Hz, 1H), 4.00–4.16 (m, 2H), 4.47–4.66 (m, 2H), 5.17 (d, *J*=8.2 Hz, 1H), 5.67 (d, *J*=11.6 Hz, 1H), 6.37 (m, 2H), 6.89 (dd, *J*=7.6, 7.6 Hz, 1H), 7.07 (dd, *J*=7.6, 7.6 Hz, 1H), 7.24–7.30 (m, 4H), 7.35 (d, *J*=8.0 Hz, 1H), 7.49 (dd, *J*=8.0, 8.0 Hz, 1H), 7.89 (d, *J*=8.0 Hz, 1H), 8.04 (br d, *J*=8.0 Hz, 1H), 8.32 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=35.9 (CH), 37.3 (CH), 38.9 (CH), 43.0 (CH_2), 45.3 (CH), 62.7 (CH_2), 110.4 (C), 111.1 (CH), 117.9 (CH), 118.7 (CH), 121.8 (CH), 122.0 (CH), 124.1 (CH), 125.0 (C), 126.2 (2×CH), 128.3 (CH), 128.6 (2×CH), 129.3 (CH), 131.3 (C), 131.4 (C), 136.0 (CH), 136.5 (C), 143.2 (C), 147.6 (C), 154.0 (C), 171.5 (C), 174.7 (C), 175.9 (C); LRMS (ESI): *m/z* (%): 573 (100) $[M+Na]^+$; HRMS (ESI): calcd for $C_{30}H_{29}N_4O_7Na$ $[M+Na]^+$: 573.1386, found: 573.1390.

4.21.16. 4-(2-Oxo-[1,3]oxazinane-3-carbonyl)-2-phenyl-10-(3,4,5-trimethoxyphenyl)-4,5,10,10a-tetrahydro-3aH-pyrrolo-[3,4-b]carbazole-1,3-dione (**5g**/**4g**)

Method B, 36 h, 100 mg, 59%, flash chromatography with eluent 1:1 EtOAc/cyclohexane, isolated as a white solid; R_f=0.12 (1:1 EtOAc/cyclohexane); IR: ν_{max} (film): 3345, 2931, 1715, 1591, 1505, 1458, 1386, 1274, 1184, 1123, 1004, 738 cm^{-1}; UV: 291, 285, 217, 203 nm; LRMS (ESI): *m/z* (%): 632 (100) $[M+Na]^+$, 341 (50); HRMS (ESI): calcd for $C_{34}H_{31}N_3O_8Na$ $[M+Na]^+$: 632.2009, found: 632.2003.

NMR data for the major diastereomer **5g**: ^1H NMR (400 MHz, $CDCl_3$): δ=1.82–2.04 (m, 2H), 3.68 (s, 6H), 3.74 (s, 3H), 3.74–3.82 (m, 3H), 4.15 (m, 1H), 4.23 (m, 1H), 4.48 (dd, *J*=10.8, 8.5 Hz, 1H), 4.89 (d, *J*=7.6 Hz, 1H), 5.66 (d, *J*=10.8 Hz, 1H), 6.50 (m, 2H), 6.67 (s, 2H), 7.03 (dd, *J*=7.5, 7.5 Hz, 1H), 7.15 (dd, *J*=7.5, 7.5 Hz, 1H), 7.20–7.30 (m, 4H), 7.35 (d, *J*=7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=21.4 (CH_2), 39.0 (CH), 39.9 (CH), 40.4 (CH), 43.3 (CH_2), 46.7 (CH), 56.3 (2×CH_3), 60.6 (CH_3), 67.6 (CH_2), 106.7 (2×CH), 110.9 (CH), 112.5 (C), 118.3 (CH), 119.6 (CH), 122.7 (CH), 125.5 (C), 126.2 (2×CH), 128.6 (CH), 128.9 (2×CH), 130.7 (C), 131.1 (C), 135.1 (C), 136.9 (C), 151.8 (C), 152.9 (2×C), 174.3 (C), 175.1 (C), 176.1 (C).

4.21.17. (−)-(4S,5S,10S,10aS,4′S)-4-(4-Benzyl-2-oxo-oxazolidine-3-carbonyl)-10-(4-hydroxy-3,5-dimethoxyphenyl)-2-phenyl-4,5,10,10a-tetrahydro-3aH-pyrrolo[3,4-b]carbazole-1,3-dione (**8**)

As a white powder, mp 180 °C, $[\alpha]_D^{28}$ −32.2 (*c* 1.5, $CHCl_3$); R_f=0.16 (2:3 EtOAc/cyclohexane); IR: ν_{max} (film): 3364, 2920, 1770, 1712, 1516, 1461, 1389, 1217, 1112, 740 cm^{-1}; UV: 292, 283, 210, 206 nm; ^1H NMR (400 MHz, DMSO-d_6, TMS): δ=3.00 (dd, *J*=13.6, 8.8 Hz, 1H), 3.38 (dd, *J*=13.6, 3.2 Hz, 1H), 3.60 (s, 6H), 3.77 (dd, *J*=8.4, 7.2 Hz, 1H), 4.27 (dd, *J*=9.2, 4.0 Hz, 1H), 4.37 (dd, *J*=9.2, 8.8 Hz, 1H), 4.57 (dd, *J*=11.4, 8.4 Hz, 1H), 4.70 (m, 1H), 4.80 (d, *J*=7.2 Hz, 1H), 5.64 (d, *J*=11.4 Hz, 1H), 6.45 (m, 2H), 6.66 (s, 2H), 6.94 (dd, *J*=8.0, 7.2 Hz, 1H), 7.10 (dd, *J*=8.0, 7.2 Hz, 1H), 7.25–7.40 (m, 10H); ^{13}C NMR (100 MHz, DMSO-d_6, TMS): δ=36.8 (CH), 37.8 (CH_2), 38.2 (CH), 38.9 (CH), 46.6 (CH), 55.6 (CH), 56.1 (2×CH_3), 66.6 (CH_2), 107.3 (2×CH), 111.0 (CH), 112.1 (C), 118.1 (CH), 118.5 (CH), 121.6 (CH), 125.3 (C), 126.7 (2×CH), 126.9 (CH), 128.2 (CH), 128.6 (2×CH), 128.7 (2×CH), 129.4 (2×CH), 130.2 (C), 130.6 (C), 131.7 (C), 134.9 (C), 136.2 (C), 136.7 (C), 148.1 (2×C), 154.1 (C), 171.6 (C), 174.9 (C), 176.6 (C); LRMS (DCI, NH_3+isobutane): *m/z* (%): 689 $[M+NH_4]^+$, 672 (15) $[M+H]^+$, 518 (46), 494 (65), 178 (100); HRMS (ESI): calcd for $C_{39}H_{33}N_3O_8Na$ $[M+Na]^+$: 694.2164, found: 694.2170.

4.21.18. (+)-(4R,5R,10R,10aR,4′S)-4-(4-Benzyl-2-oxo-oxazolidine-3-carbonyl)-10-(4-hydroxy-3,5-dimethoxyphenyl)-2-phenyl-4,5,10,10a-tetrahydro-3aH-pyrrolo[3,4-b]carbazole-1,3-dione (**9**)

As a white powder, mp 185 °C, $[\alpha]_D^{28}$ +23.7 (*c* 1.0, acetone); R_f=0.10 (2:3 EtOAc/cyclohexane); IR: ν_{max} (film): 3362, 1770, 1713, 1517, 1457, 1388, 1213, 1111, 741 cm^{-1}; UV: 290, 282, 205 nm; ^1H NMR (400 MHz, DMSO-d_6, TMS): δ=2.77 (dd, *J*=13.6, 10.8 Hz, 1H), 3.41 (dd, *J*=13.6, 4.2 Hz, 1H), 3.59 (s, 6H), 3.78 (dd, *J*=8.2, 7.8 Hz, 1H), 4.30 (dd, *J*=8.8, 2.0 Hz, 1H), 4.42 (dd, *J*=8.8, 8.0 Hz, 1H), 4.66 (dd, *J*=11.4, 8.2 Hz, 1H), 4.68 (m, 1H), 4.78 (d, *J*=7.8 Hz, 1H), 5.49 (d, *J*=11.4 Hz, 1H), 6.45 (m, 2H), 6.74 (s, 2H), 6.92 (dd, *J*=8.0, 7.2 Hz, 1H), 7.07 (dd, *J*=8.0, 7.2 Hz, 1H), 7.22–7.35 (m, 10H); ^{13}C NMR (100 MHz, DMSO-d_6, TMS): δ=36.3 (CH), 36.4 (CH_2), 38.3 (CH), 40.5 (CH), 46.5 (CH), 55.9 (2×CH_3), 56.2 (CH), 66.8 (CH_2), 107.3 (2×CH), 110.9 (CH), 111.8 (C), 118.1 (CH), 118.4 (CH), 121.6 (CH), 125.3 (C), 126.7 (2×CH), 126.8 (CH), 128.2 (CH), 128.6 (2×CH), 128.7 (2×CH), 129.2 (2×CH), 130.2 (C), 131.0 (C), 131.8 (C), 134.8 (C), 136.4 (C), 136.6 (C), 147.6 (2×C), 153.6 (C), 171.4 (C), 175.0 (C), 176.3 (C); LRMS (FAB^+): *m/z* (%): 672 (100) $[M+H]^+$. Elemental analysis calcd (%) for $C_{39}H_{33}O_8N_3$: C 69.72, H 4.95, N 6.26; found: C 69.32, H 4.97, N 6.12.

4.21.19. (±)-(4S*,5R*,10S*,10aR*)-3-Hydroxy-4-hydroxymethyl-2-phenyl-10-(3,4,5,-trimethoxyphenyl)-3,3a,4,5,10,10a-hexahydro-2H-pyrrolo[3,4-b]carbazol-1-one (**10**)

To a suspension of **5a** (50 mg, 84 μmol) in dry CH_2Cl_2 (2 mL) cooled at −78 °C was injected dropwise $LiEt_3BH$ (0.59 mL, 1 M in THF, 0.59 mmol, 7 equiv) under argon. The solution was stirred for 6 h at −78 °C. After addition of MeOH (2 mL), the solution was warmed up to rt. The solvent was removed in vacuo and brine was added. The product was extracted with EtOAc and the combined organic solvent was dried over $MgSO_4$. After evaporation and flash chromatography (3:97 MeOH/CH_2Cl_2), the product **10** (32 mg, 74%) was isolated as yellow solid, mp 180–182 °C; R_f=0.28 (5:95 MeOH/CH_2Cl_2); IR: ν_{max} (film): 3054, 1704, 1588, 1423, 1267, 1124, 890 cm^{-1}; UV: 290, 283, 277, 221, 196 nm; ^1H NMR (400 MHz, DMSO-d_6): δ=2.92 (dd, *J*=8.0, 7.4 Hz, 1H), 3.37 (s, 3H), 3.49 (s, 6H), 3.58 (m, 1H), 3.88 (dd, *J*=7.6, 7.4 Hz, 1H), 4.35 (m, 1H), 4.41 (m, 1H), 4.58 (d, *J*=8.0 Hz, 1H), 5.27 (d, *J*=7.2 Hz, 1H), 6.40 (br s, 2H), 6.77 (dd, *J*=7.6, 7.6 Hz, 1H), 6.90 (d, *J*=7.6 Hz, 1H), 6.96 (dd, *J*=8.0, 7.6 Hz, 1H), 7.02 (m, 2H), 7.16 (m, 2H), 7.34 (d, *J*=8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=35.6 (CH), 39.2 (CH), 41.4 (CH), 44.7 (CH), 56.0 (2×CH_3), 60.7 (CH_3), 63.0 (CH_2), 86.4 (CH), 106.6 (2×CH), 110.9 (CH), 111.3 (C),

118.6 (CH), 119.2 (CH), 121.9 (CH), 122.5 (2×CH), 126.2 (CH), 126.3 (C), 128.8 (2×CH), 133.3 (C), 136.4, 136.7 (4×C), 152.9 (2×C), 175.3 (C); LRMS (FAB$^+$): *m*/*z* (%): 537 (10) [M+Na]$^+$, 515 (100) [M+H]$^+$, 497 (45) [M−OH], 484 (45); HRMS (ESI): calcd for $C_{30}H_{30}N_2O_6Na$ [M+Na]$^+$: 537.2002; found: 537.2003.

4.21.20. (±)-(4S,5R*,10S*,10aS*)-3-Hydroxy-4-hydroxymethyl-2-phenyl-10-(3,4,5,-trimethoxyphenyl)-3,3a,4,5,10,10a-hexahydro-2H-pyrrolo[3,4-b]carbazol-1-one (**11**)*

Following the same condition as described for **10** and starting from **4a** (156 mg, 0.28 mmol), the product **11** (102 mg, 71%) was isolated as a white amorphous solid, mp 214–215 °C; R_f=0.25 (5:95 MeOH/CH_2Cl_2); IR: ν_{max} (film): 3444, 3055, 1705, 1584, 1420, 1258, 1124, 890 cm^{-1}; UV: 291, 283, 276, 223, 207 nm; ^{1}H NMR (400 MHz, DMSO-d_6): δ=2.89 (dd, *J*=7.8, 7.5 Hz, 1H), 3.30 (m, 3H), 3.50 (s, 6H), 3.60 (dd, *J*=7.8, 2.0 Hz, 1H), 3.67 (m, 1H), 3.78 (m, 1H), 3.91 (m, 1H), 4.57 (d, *J*=7.5 Hz, 1H), 5.30 (d, *J*=6.7 Hz, 1H), 6.27 (br s, 2H), 6.80 (dd, *J*=8.0, 7.5 Hz, 1H), 6.97 (dd, *J*=8.0, 7.5 Hz, 1H), 7.00 (dd, *J*=8.0, 7.5 Hz, 1H), 7.04–7.08 (m, 3H), 7.13–7.18 (m, 2H), 7.31 (d, *J*=8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=33.5 (CH), 38.1 (CH), 40.6 (CH), 43.1 (CH), 55.6 (2×CH_3), 59.7 (CH_3), 64.6 (CH_2), 85.3 (CH), 106.3 (2×CH), 110.9 (CH), 117.7 (CH), 118.1 (CH), 120.6 (2×CH), 124.2 (CH), 125.9 (C), 128.1 (2×CH), 134.4 (C), 135.8 (C), 136.4 (C), 137.8 (C), 138.0 (C), 152.1 (2×C), 174.8 (C); LRMS (FAB$^+$): *m*/*z* (%): 537 (10) [M+Na]$^+$, 515 (100) [M+H]$^+$, 496 (20) [M−H_2O]$^+$; HRMS (TOF EI$^+$): calcd for $C_{30}H_{30}N_2O_6$: 514.2104, found: 514.2144.

4.21.21. (±)-(4S,5S*,10S*,10aS*)-10-(4-Hydroxy-3,5-dimethoxyphenyl)-1,3-dioxo-2-phenyl-1,2,3,3a,4,5,10,10a-octahydropyrrolo[3,4-b]carboxylic acid 1-benzyl-1H-[1,2,3]triazol-4-ylmethyl ester (**14**)*

A solution of indole **1g** (95 mg, 0.45 mmol), 3,5-dimethoxy-4-hydroxy-benzaldehyde **2b** (121 mg, 0.67 mmol, 1.5 equiv), *N*-phenylmaleimide **3a** (231 mg, 1.3 mmol, 3 equiv) and $CuSO_4 \cdot 5H_2O$ (11 mg, 0.045 mmol) in toluene (5 mL) was stirred and refluxed for 24 h. After cooling, $CHCl_3$ (0.5 mL), EtOH (0.5 mL) and water (0.5 mL) were added followed by benzyl azide (77 mg, 0.58 mmol) in $CHCl_3$ (0.5 mL) and the L-ascorbic acid sodium salt (10 mg, 0.049 mmol) and the mixture was stirred for 18 h at rt. EtOAc was added (10 mL) and the mixture was dried over $MgSO_4$. After filtration and solvent evaporation, flash chromatography (silica gel, 45:55 EtOAc/cyclohexane) gave the product **14** (201 mg, 66%) as yellow solid, mp 211 °C; R_f=0.11 (1:1 EtOAc/cyclohexane); IR: ν_{max} (KBr): 3465, 3375, 1734, 1707, 1614, 1519, 1499, 1459, 1428, 1384, 1330, 1214, 1176, 1117, 734 cm^{-1}; UV: 300, 292, 218, 207 nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.65 (s, 6H), 3.75 (dd, *J*=8.6, 7.5 Hz, 1H), 4.31 (dd, *J*=8.6, 3.9 Hz, 1H), 4.86 (d, *J*=3.9 Hz, 1H), 4.91 (d, *J*=7.5 Hz, 1H), 5.28 (d, *J*=13.0 Hz, 1H), 5.51 (d, *J*=14.8 Hz, 1H), 5.56 (d, *J*=14.8 Hz, 1H), 5.73 (d, *J*=13.0 Hz, 1H), 6.24 (s, 2H), 6.52 (m, 2H), 7.05 (dd, *J*=7.5, 7.5 Hz, 1H), 7.20 (dd, *J*=7.5, 7.5 Hz, 1H), 7.24–7.38 (m, 9H), 7.50 (s,1H), 7.51 (d, *J*=7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=36.9 (CH), 38.7 (CH), 41.1 (CH), 45.9 (CH), 54.4 (CH_2), 56.3 (2×CH_3), 59.0 (CH_2), 105.6 (2×CH), 111.6 (CH), 112.1 (C), 118.2 (CH), 119.8 (CH), 122.5 (CH), 122.8 (CH), 125.6 (C), 126.1 (2×CH), 126.7 (CH), 127.0 (C), 128.1 (2×CH), 128.5 (CH), 128.7 (CH), 129.0 (2×CH), 129.2 (2×CH), 129.9 (C), 131.2 (C), 134.0 (C), 134.3 (C), 136.7 (C), 142.3 (C), 146.9 (2×C), 170.3 (C), 175.9 (C), 177.2 (C); LRMS (DCI, NH_3+isobutane): *m*/*z* (%): 684 (53) [M+H]$^+$, 174 (100). Elemental analysis calcd (%) for $C_{39}H_{33}O_7N_5$: C 68.51, H 4.86, N 10.24; found: C 68.36, H 4.75, N 9.91.

4.22. Procedure for the 'one flask' Cu(II)/CuI catalysed reactions

A solution of indole **1a** (240 mg, 1.18 mmol), 4-anisaldehyde **2c** (241 mg, 1.77 mmol, 1.5 equiv), *N*-propynylmaleimide **3c** (240 mg, 1.77 mmol, 1.5 equiv) and $CuSO_4 \cdot 5H_2O$ (29 mg, 0.12 mmol) in toluene (5 mL) was stirred and refluxed for 24 h. After cooling, $CHCl_3$ (1 mL), EtOH (1 mL) and water (1 mL) were added. The mixture was checked for homogenisation and split into equal shares. To the first flask, the azido-acetic acid ethyl ester (168 mg, 1.18 mmol, 2 equiv) in $CHCl_3$ (1 mL) and the L-ascorbic acid sodium salt (14 mg, 0.07 mmol) were added and the mixture was stirred for 18 h at rt. To the second flask, the benzyl azide (160 mg, 1.18 mmol, 2 equiv) in $CHCl_3$ (1 mL) and the L-ascorbic acid sodium salt (14 mg, 0.07 mmol) were added and the mixture was stirred for 18 h at rt. The solvent of each flask was removed in vacuo. EtOAc was added and the resulting solution was dried ($MgSO_4$) and filtered. The solvent was removed in vacuo prior to flash chromatography.

4.22.1. (±)-(4S,5S*,10S*,10aS*)-2-(1-Ethoxycarbonylmethyl-1H-[1,2,3]triazol-4-ylmethyl)-10-(4-methoxyphenyl)-1,3-dioxo-1,2,3,3a,4,5,10,10a-octahydropyrrolo[3,4-b]carbazole-4-carboxylic acid ethyl ester (**12**)*

Flash chromatography eluent 3:2 EtOAc/cyclohexane, 234 mg (68%), isolated as an amorphous white solid, mp 160 °C; R_f=0.3 (4:1 EtOAc/cyclohexane); IR: ν_{max} (film): 3380, 2992, 1738, 1708, 1510, 1445, 1400, 1250, 1236, 1216, 1180, 1027, 734 cm^{-1}; UV: 290, 280, 276, 226, 208 nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.27 (t, *J*=7.2 Hz, 3H), 1.39 (t, *J*=7.2 Hz, 3H), 3.64 (s, 3H), 3.68 (dd, *J*=9.0, 7.6 Hz, 1H), 4.16 (dd, *J*=9.0, 3.4 Hz, 1H), 4.22 (q, *J*=7.2 Hz, 2H), 4.25 (d, *J*=14.4 Hz, 1H), 4.36 (q, *J*=7.2 Hz, 2H), 4.37 (d, *J*=14.4 Hz, 1H), 4.73 (d, *J*=3.4 Hz, 1H), 4.80 (d, *J*=7.6 Hz, 1H), 5.03 (s, 2H), 6.50 (dd, *J*=7.6 Hz, 2H), 6.76 (d, *J*=7.6 Hz, 2H), 6.95 (dd, *J*=8.0, 7.6 Hz, 1H), 7.13 (dd, *J*=8.0, 7.6 Hz, 1H), 7.18 (d, *J*=8.0 Hz, 1H), 7.27 (s, 1H), 7.33 (d, *J*=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.9 (CH_3), 14.2 (CH_3), 33.2 (CH_2), 36.5 (CH), 37.5 (CH), 40.7 (CH), 45.0 (CH), 50.6 (CH_2), 54.9 (CH_3), 62.2 (CH_2), 62.7 (CH_2), 110.9 (CH), 112.2 (C), 113.2 (2×CH), 118.4 (CH), 119.7 (CH), 122.6 (CH), 124.5 (CH), 125.6 (C), 127.2 (C), 129.5 (2×CH), 130.9 (C), 136.2 (C), 141.7 (C), 158.2 (C), 166.2 (C), 170.4 (C), 176.1 (C), 177.2 (C); LRMS (FAB$^+$): *m*/*z* (%): 586 (65) [M+H]$^+$, 539 (78), 512 (40), 307 (100); HRMS (TOF EI$^+$): calcd for $C_{32}H_{35}N_5O_6$: 585.2223, found: 585.2206.

4.22.2. (±)-(4S,5S*,10S*,10aS*)-2-(1-Benzyl-1H-[1,2,3]triazol-4-ylmethyl)-10-(4-methoxyphenyl)-1,3-dioxo-1,2,3,3a,4,5,10,10a-octahydropyrrolo[3,4-b]carbazole-4-carboxylic acid ethyl ester (**13**)*

Flash chromatography eluent 2:3 EtOAc/cyclohexane, 215 mg (62%), isolated as an amorphous white solid, mp 188–190 °C; R_f=0.22 (1:1 EtOAc/cyclohexane); IR: ν_{max} (film): 3392, 2989, 2937, 1750, 1713, 1506, 1458, 1241, 1180, 1030, 1024 cm^{-1}; UV: 290, 284, 279, 214, 193 nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.40 (t, *J*=7.2 Hz, 3H), 3.66 (m, 1H), 3.67 (s, 3H), 4.11 (m, 1H), 4.12 (d, *J*=15.2 Hz, 1H), 4.28 (d, *J*=15.2 Hz, 1H), 4.38 (q, *J*=7.2 Hz, 2H), 4.72 (d, *J*=2.4 Hz, 1H), 4.79 (d, *J*=7.6 Hz, 1H), 5.41 (s, 2H), 6.56 (d, *J*=8.0 Hz, 2H), 6.77 (d, *J*=8.0 Hz, 2H), 6.97 (dd, *J*=7.6, 7.2 Hz, 1H), 7.10–7.40 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.3 (CH_3), 33.2 (CH_2), 36.4 (CH), 37.6 (CH), 40.7 (CH), 45.2 (CH), 53.9 (CH_2), 55.0 (CH_3), 62.8 (CH_2), 110.9 (CH), 112.2 (C), 113.3 (2×CH), 118.5 (CH), 119.9 (CH), 122.7 (CH), 122.9 (CH), 125.7 (C), 127.2 (C), 128.01 (2×CH), 128.6 (CH), 129.0 (2×CH), 129.6 (2×CH), 130.8 (C), 134.5 (C), 136.2 (C), 158.4 (C), 170.4 (C), 176.2 (C), 177.2 (C); LRMS (ESI): *m*/*z* (%): 612 (10) [M+Na]$^+$, 590 (100) [M+H]$^+$; HRMS (ESI): calcd for $C_{34}H_{32}N_5O_5$[M+H]$^+$: 590.2403, found: 590.2404.

4.22.3. (±)-(4S,5S*,10S*,10aR*)-{4-[10-(4-Methoxyphenyl)-1,3-dioxo-4-(2-oxo-oxazolidine-3-carbonyl)-3,3a,4,5,10,10a-hexahydro-1H-pyrrolo[3,4-b]carbazol-2-ylmethyl]-[1,2,3]-triazol-1-yl}-acetic acid ethyl ester (**15**)*

A solution of indole **1a** (200 mg, 0.8 mmol), 4-anisaldehyde **2d** (166 mg, 1.2 mmol, 1.5 equiv), *N*-propynyl-maleimide **3c** (166 mg, 1.2 mmol, 1.5 equiv) and $CuSO_4 \cdot 5H_2O$ (20 mg, 0.08 mmol) in toluene

(5 mL) was stirred and refluxed for 24 h. After cooling, $CHCl_3$ (1 mL), EtOH (1 mL) and water (1 mL) were added followed by the azidoacetic acid ethyl ester (234 mg, 1.81 mmol) in $CHCl_3$ (1 mL) and the L-ascorbic acid sodium salt (18 mg, 0.09 mmol) and the mixture was stirred for 18 h at rt. EtOAc was added (15 mL) and the mixture was dried over $MgSO_4$. After filtration and solvent evaporation, flash chromatography (silica gel, 1:99 MeOH/CH_2Cl_2) gave the product **15** (288 mg, 56%) as an amorphous white solid, mp 203 °C; R_f=0.17 (1:1 EtOAc/cyclohexane); IR: ν_{max} (film): 3400, 2985, 1770, 1706, 1510, 1426, 1391, 1245, 1223, 1115, 1029, 738 cm^{-1}; UV: 291, 282, 220, 205 nm; ^1H NMR (400 MHz, $CDCl_3$): δ=1.25 (t, J=7.2 Hz, 3H), 3.61 (s, 3H), 3.64 (dd, J=9.0, 8.2 Hz, 1H), 3.92 (m, 1H), 4.04 (m, 1H), 4.12 (dd, J=10.3, 9.0 Hz, 1H), 4.19 (q, J=7.2 Hz, 2H), 4.20–4.34 (m, 2H), 4.25 (d, J=15.0 Hz, 1H), 4.37 (d, J=15.0 Hz, 1H), 4.80 (d, J=8.2 Hz, 1H), 4.92 (s, 2H), 5.57 (d, J=10.3 Hz, 1H), 6.54 (d, J=8.9 Hz, 2H), 6.91 (dd, J=7.8, 7.2 Hz, 2H), 7.03–7.15 (m, 5H), 7.27 (d, J=8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.9 (CH_3), 33.2 (CH_2), 37.2 (CH), 37.6 (CH), 40.3 (CH), 43.0 (CH_2), 45.7 (CH), 50.5 (CH_2), 54.9 (CH_3), 62.2 (CH_2), 62.7 (CH_2), 111.1 (CH), 112.8 (C, 2×CH), 118.3 (CH), 119.5 (CH), 122.5 (CH), 124.4 (CH), 125.3 (C), 129.1 (C), 130.7 (2×CH), 131.0 (C), 136.7 (C), 141.8 (C), 154.4 (C), 158.1 (C), 166.3 (C), 170.9 (C), 175.7 (C), 176.2 (C); LRMS (DCI, NH_3+isobutane): m/z (%): 627 (11) $[M+H]^+$, 344 (17), 512 (40), 105 (100). Elemental analysis calcd (%) for $C_{32}H_{30}O_8N_6$: C 61.34, H 4.83, N 13.41; found: C 61.38, H 4.63, N 13.35.

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17. Crystal data for **9**: $C_{39}H_{33}N_3O_8 \cdot 2H_2O$, M=707.72, monoclinic, a=19.516(8), b=9.894(4), c=20.266(8) Å, U=3510(2) $Å^3$, T=293(2) K, space group $C2$, Z=4, D_c=1.339 Mg m^{-3}, reflection collected/unique 15,516/6753[R_{int}=0.0310, wR_2=0.1672 for all data]; CCDC 651346.
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