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# Synthesis of spiro{pyrrolidine-3,1'-pyrrolo[3,4-*c*]pyrrole} basic framework *via* multicomponent 1,3-dipolar cycloaddition

Asmaa Belabbes,[a] Verónica Selva,[a] Francisco Foubelo,[a] Mª de Gracia Retamosa,[a] José M. Sansano.[a]*

**Abstract:** The synthesis of complex spiro{pyrrolidine-3,1'-pyrrolo[3,4-c]pyrrole} skeleton employing mild conditions is presented. The order of addition of a primary amine, two equivalents of the corresponding maleimide and finally, the aldehyde is of a paramount importance to obtain these final compounds in very high yields. The mechanism is studied performing very simple tests, the Michael type addition of the amine onto the maleimide being the key step. Interestingly, the hybrid scaffold is prepared by sequential addition of two different maleimides. In addition, a more interesting architecture is prepared through a metathesis reaction between allylic residues bonded in the molecule precursor.

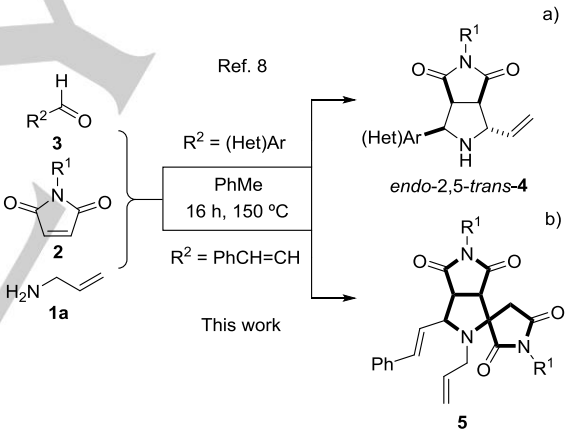
*Dedicated to the memory of Prof. Ron Grigg*

## Introduction

Multicomponent reactions (MCRs) diminish the operational difficulties and increase the atom economy of the processes involved.[1] Many synthetic subjects, in which three or more reactants come together in a single reaction vessel to form a product containing substantial elements of all the reactants, take advantage of this strategy as, for example, the synthesis of bioactive compounds,[2] in asymmetric synthesis,[3] in organometallic chemistry,[4] in combination with microwave chemistry process,[5] etc. Frequently, very complex structures are readily accessible using MCRs (by Nature or through synthetic procedures), especially those involving 1,3-dipolar cycloadditions (DCs)[6] (also called Huisgen reaction).[7]

The ability to generate azomethine ylides using several routes open new perspectives to run efficiently this domino processes. During our study of MC-thermal 1,3-DC of unactivated azomethine ylides derived from allylamine **1a** and aromatic or heteroaromatic aldehydes **3** with maleimides **2**, affording *endo*-2,5-*trans*-cycloadducts **4** (Scheme 1a),[8] we observed the generation of an unexpected major product (impurified with its corresponding adduct **5**) when cinnamaldehyde was employed as aldehyde. This structure obeyed to the general pattern assigned for compound **5** (Scheme 1b). The spiro{pyrrolidine-3,1'-pyrrolo[3,4-c]pyrrole} scaffold present in molecules **5** is not new. In 1986 Schiff's bases derived from 5-nitro-thiophene-2-carboxaldehyde or 5-nitrofurfural and anilines reacted with maleimides in modest yields at 170 ºC to obtain final compounds similar to **5** with promising antibiotic properties.[9] In this case, there was no option to form the thermal-induced 1,2-prototropy to generate the corresponding azomethine ylide.[10] In addition, thermal reaction with aromatic aldimines, derived from methylamine, gave very poor results. However, just in a particular case of the reaction of arylidene benzylamines in xylenes at 140 ºC, involving sterically hindered *o*-(dimethylamino)benzylidene *o*-(dimethylamino)benzylamine, Grigg's group isolated the corresponding compound **5** incorporating two units of *N*-phenylmalemide (NPM) in 82% yield (2:1 *dr*).[11]

So, in this work, we study the origin of this unexpected behavior, the scope of the reaction and the search of a new Diversity-Oriented Synthesis (DOS) (Scheme 1).[12]




**Scheme 1**. DOS of compounds **4** or **5** using different reaction conditions.

## Results and Discussion

The synthesis of the spiro{pyrrolidine-3,1'-pyrrolo[3,4-c]pyrrole} **5** was observed using allylamine (**1a**), *N*-methylmaleimide (NMM, **2a**) and cinnamaldehyde (**3a**) in this precise order and at 120 ºC in toluene (sealed tube) for 17 h. The diastereomeric ratio of **5a** was 2:1 in 88% yield (Table 1, entry 1). The addition order was crucial for the development of the reaction because when aldehyde **3a** and allylamine (**1a**) were added followed by NMM, the reaction gave poor conversions (<40%) of both the corresponding compound **5a** and the *endo*-2,5-*trans*-**4a** (Table 1, entry 2). The reaction was complete in 8 h at 120 ºC and even at 50 ºC but increasing the reaction time up to 17 h (Table 1, entries 3 and 4, respectively). A higher diasteroselectivity was detected at lower temperatures (3:1 *dr* at 50 ºC). However, we realized that the reaction was complete after 24 h at room temperature, and with almost total diastereoselectivity (>95:5,

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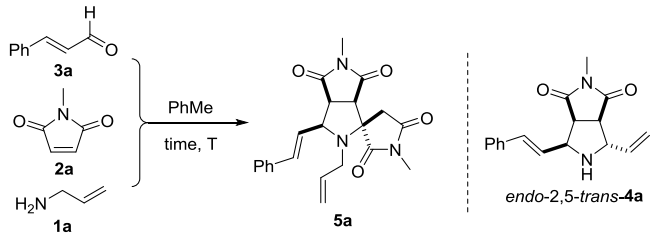
Table 1, entry 5). These exact conditions were assayed in the presence of THF affording a lower conversion (78%), whilst dichloromethane and chloroform afforded identical results than the reported with toluene. Methylbenzene was finally selected because of lower toxicity and with the aim to scale the process to a pilot plant level. The diastereomeric ratios in this three-component domino sequence were determined from the $^1$H NMR spectra of the crude mixtures, which possessed a high purity.

**Table 1.** Optimization of the synthesis of cycloadduct **5a**.[a]




| Entry | T (º C)[b] | Time (h) | Yield (%)[c] | *dr*[d] |
|---|---|---|---|---|
| 1 | 120 | 17 | 88 | 2:1 |
| 2[e] | 120 | 17 | < 40[f] | --- |
| 3 | 120 | 8 | 89 | 2:1 |
| 4 | 50 | 17 | 88 | 3:1 |
| 5 | rt | 24 | 87 | >95:5 |

[a] Reaction conditions: **1a** (1 mmol), **2a** (2 mmol) and **3a** (1 mmol) were dissolved in toluene (5 mL) and stirred at temperatures and times depicted in the table. [b] Oil bath temperature. [c] Isolated after flash chromatography (silica-gel). [d] Determined by $^1$H NMR analysis of the crude mixtures. [e] The addition order was **1a**, **3a**, **2a.** [f] A 1:1 mixture of **4a** and **5a** was observed.

At this point, in order to determine the relative configuration of the main isolated diastereoisomer in this reaction, a careful study of the nOe experiments of **5a** was done. Negative population increments were detected between hydrogen atoms (b) and (c) when hydrogens (a) were irradiated. However, a very small effect was observed (in the same experiment) with both methyl groups. Moreover, hydrogens (d), (c) and (b) possessed, unambiguously, relative *cis*-arrangement in the final structure **5a** after selective irradiation of each one of them. The proposed relative configuration did not match with the analogous one reported previously by Grigg and co-workers after reaction at 130 ºC.[11] This aspect is clearly confirmed by the $^1$H NMR shift of the two diastereotopic hydrogens (a) which appear as doublets with 19.5 Hz coupling constant and with a chemical shift difference of 1.5 ppm.

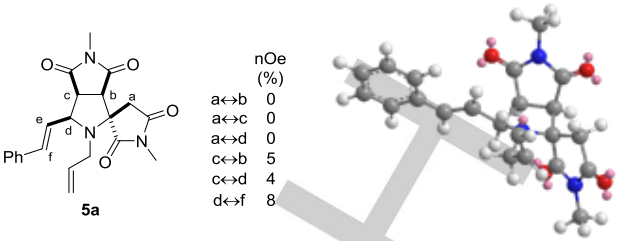
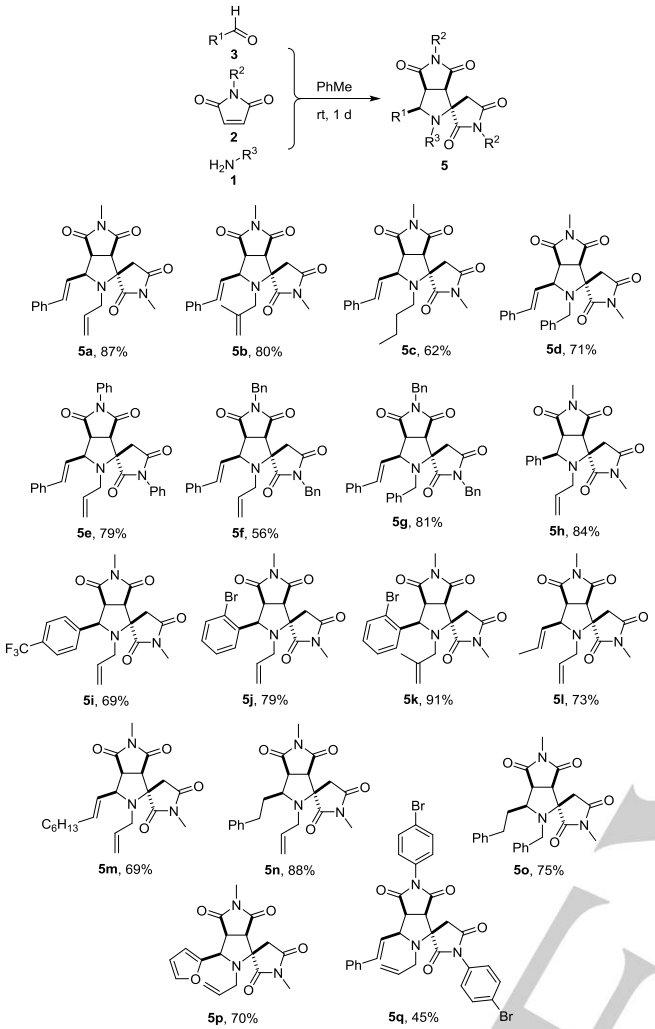



**Figure 1**. Relative configuration assigned for **5a** and lowest energy conformation calculated at B3LYP basic level.

The analysis of the scope of the reaction was carried out at room temperature for 24 h, adding (in this order) the amine **1**, followed by the two equiv of the corresponding maleimide **2**, and, after 10 min, the aldehyde **3** (Scheme 2). In general, the chemical isolated yields of products **5** were very notable in a range between 62 and 91%. Allyl-, methallyl-, *n*-butyl- and benzyl-amines were successfully attempted. Maleimides, such as NMM, NPM and *N*-benzylmaleimide (NBM) (**2a**-**2c**, respectively) also worked satisfactorily giving compounds **5a**, **5e-5g**. Next, the nature of the aldehyde was assessed finding that benzaldehyde, 4-(trifluoromethyl)benzaldehyde and 2-bromobenzaldehyde furnished compounds **5h**-**5k** in very high yields. Another conjugated aldehydes (different from cinnamaldehyde) as crotonaldehyde and (*E*)-non-2-enal, and an aliphatic one as dihydrocinnamaldehyde were appropriate components to complete the reaction in very high yields. Heteroaromatic aldehydes (furfural) or other aryl-substituted maleimides [*N*-(4-bromophenyl)maleimide] afforded the corresponding spirocycles **5o** and **5q** in moderate yields (Scheme 2). In each reaction crude of compounds **5** the diastereomeric ratio observed was >95:5 (crude $^1$H NMR) except in the example of **5g** and **5q** which were isolated as almost 1:1 mixture of diastereosisomers. In these two examples, the second diastereoisomer corresponded to the structure **8** (by comparison with the reported experimental data) depicted in Scheme 5 but following a different reaction course (see below).




**Scheme 2**. Scope of the multicomponent synthesis of spirobicycles **5**.

The X-ray diffraction analysis of compound[13] could be obtained confirming the previous relative configuration deduced from nOe experiments (Figure 2).

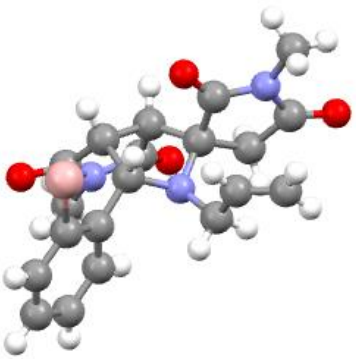
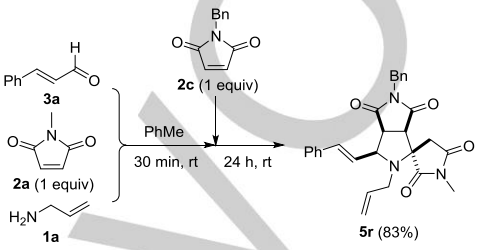


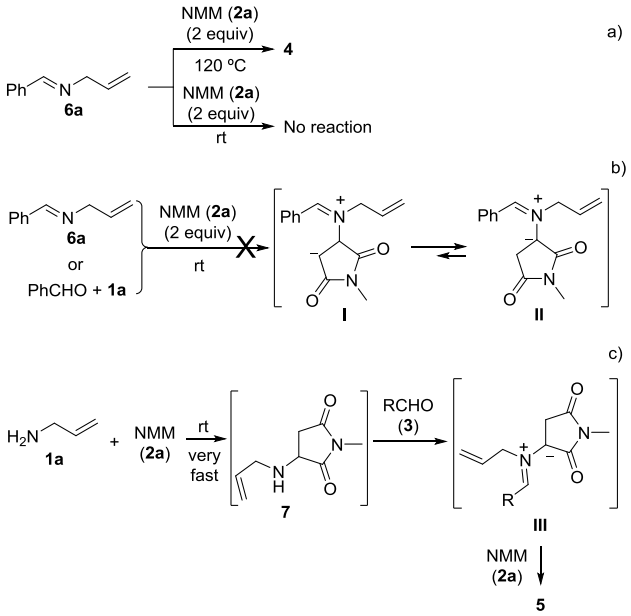
**Figure 2**. X-ray diffraction pattern determined for product **5j**.

Unlike the previous published methods, this methodology allowed the incorporation of two different maleimide units, that means, the first maleimide would form the spirocyclic moiety, whilst a second (different) maleimide would complete the 1,3-DC stage in a 4-component domino reaction. For example, a mixture of allylamine (**1a**) with one equiv of NMM (**2a**) in toluene was stirred for 5 min, and then, 1 equiv of cinnamaldehyde (**3a**), was added. After stirring this final solution for 30 min, 1 equiv of a different maleimide [in this case NBM (**2c**)] was added, leaving the reaction 24 h at room temperature, obtaining only one diastereoisomer (>95:5 by $^1$H NMR) of spirocycloadduct **5r** in 83% yield (Scheme 3).



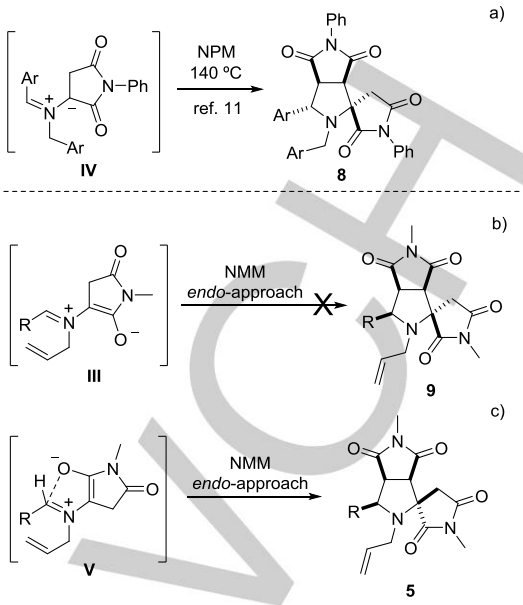

**Scheme 3**. Synthesis of the hybrid spirocycloadduct **5r**.

Unfortunately, Michael-type acceptors as acrylates, acrylamides, dimethyl maleate or fumarate, maleic anhydride, benzoquinone, 1,1-bis(phenylsulfonyl)ethylene and (*E*)-1,2-bis(phenylsulfonyl)ethylene did not react under the optimized reaction conditions. This exclusive behavior of maleimides moved us to run several $^1$H NMR tests with the idea of clarifying the mechanism of this multicomponent domino reaction. It was clear that starting from preformed imine **6a** the reaction proceeded to give cycloadduct **4** upon heating at 120 ºC, but the reaction was cleaner by mixing allylamine and benzaldehyde first and followed by the addition of maleimide. In this case, the formation of the imine **6a** occurred preferentially (Scheme 4a).[8] This imine did not give the expected spirocyclic compound **5a** after reaction with 2 equiv of NMM (Scheme 4a) at room temperature. In contrast, imine **6a** did not form the corresponding betaines **I** and **II**, respectively,[14] such as it was suggested in the publications involving thermal generation of substances **5** reported previously.[10,11] No product was found whether benzaldehyde and amine **1a** were mixed previously to the addition of NMM (Scheme 4b). It was observed the very fast Michael-type addition of allylamine **1a** onto NMM giving intermediate **7** (observed by $^1$H NMR but not characterized, see the corresponding spectra of the reaction course in the supporting experimental section), which would afford the iminium salt, and the corresponding 1,3-dipole **III**, promoting the formation of the expected compound **5** (Scheme 4c). None of the above-mentioned electron-rich alkenes [acrylates, acrylamides, dimethyl maleate or fumarate, maleic anhydride, benzoquinone, 1,1-bis(phenylsulfonyl)ethylene and (*E*)-1,2-bis(phenylsulfonyl)ethylene] underwent the Michael-type addition of the allylamine (**1a**). So, this is the key factor to trigger the multicomponent domino process. In two examples, **5g** and **5q**, diastereoisomer **8** was detected and presumably originated by the *exo*-approach of the corresponding maleimide to dipole **V**.




**Scheme 4**. Designed experiments for the study of the mechanism of the formation of spirocycloadducts **5**.

The stereochemical outcome of the structures **5** obeyed to a plausible generation of the 1,3-dipole **V**, which reacted with NMM through an *endo*-approach (Scheme 5c). *All-cis*-arrangement drawn in skeleton **9**, originated by the existence of the 1,3-dipole **III** (Scheme 5b), did not correspond with the experimental nOe found. In this line, an intense nOe should be observed in the C3-hydrogen upon irradiation of the methylene group, such as it was documented for the compound **8** (this one generated at 140 ºC, Scheme 5a).[11] In addition, the NMR signals of the synthesized compounds **5** differed from the signals observed for molecules **8**. It seems that steric hinderance would favor azomethine ylide **III** but the strong O···C=N$^+$ electronic interaction represented in fleeting intermediate **V** move it to a more stable (2.8 kcal·mol$^{-1}$, calculated at B3LYP basic level) species (Scheme 5c). This control of the geometry in **V** explained the high diastereoselectivity achieved. All these hypothesis were confirmed by a simple analysis of the slightly asynchronous transition states of the three dipoles (**IV**, **III** and **V**) with NMM (Figure 3). The large energy gap of the most energetic **IV-NMM TS** can justify its arrangement at very high temperatures unlike the **V-NMM TS**, which requires room temperature to proceed.




**Scheme 5**. Designed experiments for the study of the mechanism of the formation of spirocycloadducts **5**.

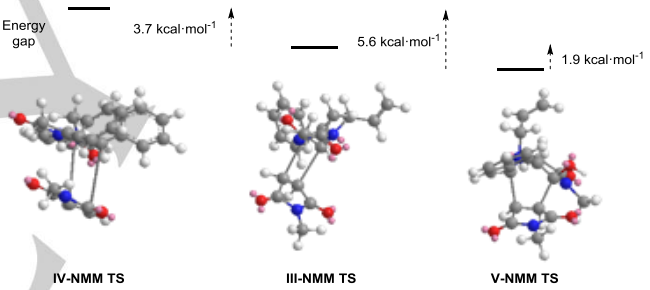
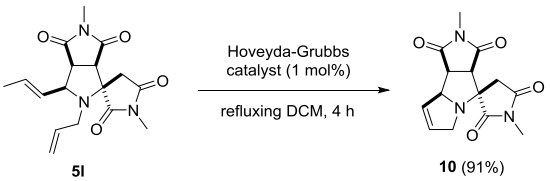



**Figure 3**. Relative energies of **IV-NMM TS**, **III-NMM TS** and **I-NMM TS** calculated at B3LYP basic level.

More sophisticated structure **10**, with another condensed cycle, could be achieved from spirocycloadduct **5l** after ring-closing metathesis reaction employing the Hoveyda-Grubbs' catalyst (1 mol%) in refluxing dichloromethane for 4 h. This catalyst was also employed by our group[8] in the synthesis of biologically active compounds.[15] The crude product was very clean and the purification (flash chromatography) gave almost quantitative yield (91%) (Scheme 6).




**Scheme 6**. Spirotricyclic structure **10** isolated after ring-closing metathesis reaction.

## Conclusions

In conclusion, the novel diastereoselective three- or four-component domino reaction, generating spiro{pyrrolidine-3,1'-pyrrolo[3,4-c]pyrroles}, is controlled by an initial Michael type addition of the amine onto the maleimide, followed by the iminium salt→azomethine ylide, and final 1,3-DC. The four-component version involves the employment of two different maleimides. Maleimides are the unique electron-deficient alkenes able to promote these processes. The reaction is very versatile incorporating components with several structures and operating at room temperature. According to Scheme 1, a valuable DOS methodology is accomplished to obtain different scaffolds in very high yields, just by controlling the addition order of the reagents, and the reaction temperature. In this particular example, a very complex architecture is smoothly achieved

## Experimental Section

**General:** Melting points were determined with a Marienfeld melting-point meter (MPM-H2) apparatus and are uncorrected. For flash chromatography, silica gel 60 (40–60 μm) was employed. $^1$H NMR (300, 400 MHz) and $^{13}$C NMR (75 or 101 MHz) spectra were recorded with Bruker AV300, and Bruker AV400, respectively, with $CDCl_3$ as solvent and TMS as internal standard for $^1$H NMR spectra, and the chloroform signal for $^{13}$C NMR spectra; chemical shifts are given in ppm. Low-resolution electron impact (DIP-EI) mass spectra were obtained at 70 eV with an Agilent 6890N Network GC system and an Agilent 5973Network Mass Selective Detector. High-resolution mass spectra (DIP-EI) were recorded with a QTOF Agilent 7200 instrument for the exact mass and Agilent 7890B for the GC. Analytical TLC was performed using ALUGRAM® Xtra SIL G/UV254 silica gel plates, and the spots were detected under UV light (λ=254 nm).

**General procedure for the synthesis of compounds 5**: In a flask with a magnetic bar, containing 3 mL of toluene, was added the corresponding maleimide (2 mmol), and the amine (1 mmol) in this order. After 5 min, the aldehyde (1 mmol) was added dropwise to the solution, and the resulting mixture stirred for 1 d. The solvent was evaporated, and the residue was purified by flash chromatography (flash silica-gel) eluting with 3/1 *n*-hexane:ethyl acetate affording pure compounds **5**.

(3*R**,3'*S**,3a'*S**,6a'*R**)-2'-Allyl-1,5'-dimethyl-3'-[(*E*)-styryl]tetrahydro-4'*H*-spiro{pyrrolidine-3,1'-pyrrolo[3,4-*c*]pyrrole}-2,4',5,6'(5'*H*)-tetraone (**5a**): Colourless prisms (342 mg, 87% yield); mp 173-175 ºC ($Et_2O$); IR (neat) $\upsilon_{max}$: 1684, 1434, 1385, 1277, 1132, 1068, 985, 752, 695 cm$^{-1}$. $^1$H NMR (400 MHz) δ: 2.64 (d, *J* = 19.4 Hz, 1H, $CCH_2CO$), 2.98 (s, 3H, $CH_3$), 3.04 (s, 3H, $CH_3$), 3.05-3.11 (m, 1H, N*C*$H_2$CH=$CH_2$), 3.25 (d, *J* = 8.1 Hz, 1H, NCCHCO), 3.36 (ddt, *J* = 15.7, 6.4, 1.6 Hz, 1H, N*C*$H_2$CH=$CH_2$), 3.63 (dd, *J* = 8.8, 8.1 Hz, 1H, N*C*HCHCO), 4.02 (d, *J* = 19.4 Hz, 1H, $CCH_2CO$), 4.46 (dd, *J* = 9.5, 8.8 Hz, 1H, PhCH=CHC*H*), 4.93-5.06 (m, 2H, $NCH_2CH=CH_2$), 5.72-5.84 (m, 1H, $NCH_2CH=CH_2$), 5.87 (dd, *J* = 15.7, 9.5 Hz, 1H, PhCH=C*H*), 6.69 (d, J = 15.7 Hz, 1H, PhC*H*=CH), 7.28-7.41 (m, 5H, Ar*H*). $^{13}$C NMR (100 MHz) δ: 24.4, 25.4 (2x$CH_3$), 35.2 (C$CH_2$C=O), 47.6, 48.1 (2x*C*HCO), 50.0 (N$CH_2$CH=C), 65.3 (NCHCH=CH), 69.2 (NCCO), 117.8 (CH=$CH_2$), 126.6, 127.0, 128.2, 128.7, 133.9, 135.3, 136.4 (ArC, CH=CH, *C*H=$CH_2$), 174.7, 175.4, 176.0, 178.5 (4xCO). MS (EI) *m/z*: 393 (M$^+$, 2%), 353 (21), 352 (100), 302 (14), 115 (16). HRMS calculated for $C_{22}H_{23}N_3O_4$: 393.1689; found: 393.1679.

(3*R**,3'*S**,3a'*S**,6a'*R**)-(*E*)-1,5'-Dimethyl-2'-(2-methylallyl)-3'-styryltetrahydro-4'*H*-spiro{pyrrolidine-3,1'-pyrrolo[3,4-*c*]pyrrole}-2,4',5,6'(5'*H*)-tetraone (**5b**): Colourless needles (326 mg, 80% yield); mp 172-174°C (*n*-hexane/ethyl acetate); IR (neat) $\nu_{max}$:1681, 1434, 1380, 1280, 1130, 1076, 975, 744 cm$^{-1}$; $^1$H NMR (400 MHz) δ: 1.61 (br s, 3H, C*H*$_3$C); 2.56 (d, *J* = 19.4 Hz, 1H, $CCH_2CO$), 2.74 (d, *J* = 15.5 Hz, 1H, $CH_2C$=C), 3.04 (s, 6H, 2x$CH_3$N), 3.15 (d, *J* = 15.5 Hz, 1H, $CH_2C$=C), 3.24 (d, *J* = 8.1 Hz, 1H, NCCHCO), 3.60 (dd, *J* = 9.1, 8.4 Hz, 1H NCCHCO), 3.92 (d, *J* = 19.4 Hz, 1H, $CCH_2CO$), 4.34 (dd, *J* = 9.4, 9.1 Hz, 1H), 4.70, 4.74 (2m, 2H, $CH_2$=C), 5.80 (dd, J = 15.7, 9.4 Hz, 1H, PhCH=C*H*), 6.65 (d, J = 15.7 Hz, 1H PhC*H*=CH), 7.38–7.22 (m, 5H, Ar*H*); $^{13}$C NMR (75 MHz) δ: 20.7 ($CH_3$C=C), 24.3, 24.4 (2x$CH_3$N), 34.2 (C$CH_2$CO), 47.6, 48.2 (2x*C*HCO), 53.7 (N$CH_2$), 67.3 (NCHCH=CH), 70.1 (NCCO), 113.46 (CH=$CH_2$),126.9, 126.9, 128.1, 128.7, 135.0, 136.5, 142.9 (Ar*C*, CH=CH, *C*H=$CH_2$), 174.8, 175.4, 176.0, 178.4 (4xCO). MS (EI) *m/z*: 407 (M$^+$, 5%), 353 (22), 352 (100), 316 (17), 115 (23), 91 (11), 55(14.46). HRMS calculated for $C_{23}H_{25}N_3O_4$: 407.1845; found 407.1846.

(3*R**,3'*S**,3a'*S**,6a'*R**)-2'-Butyl-1,5'-dimethyl-3'-[(*E*)-styryl]{tetrahydro-4'*H*-spiro[pyrrolidine-3,1'-pyrrolo[3,4-c]pyrrole}-2,4',5,6'(5'*H*)-tetraone (**5c**): Pale yellow prisms (254 mg, 62% yield); mp 169-170°C (*n*-hexane/ethyl acetate); IR (neat) $\nu_{max}$: 1681, 1434, 1380, 1280, 971, 748 cm$^{-1}$; $^1$H NMR (400 MHz) δ: 0.75 (t, *J* = 7.2 Hz, 3H, C*H*$_3$CH$_2$); 1.00–1.45 (m, 4H, C$H_2$C$H_2$CH$_3$), 2.32 (ddd, *J* = 14.2, 9.5, 6.3 Hz, 1H, C$H_2$N), 2.49 (m with d, *J* = 19.3 Hz, 2H, $CCH_2CO$ and C$H_2$N), 3.03 (s, 6H, 2x$CH_3$N), 3.22 (d, *J* = 8.1 Hz, 1H), 3.59 (t, *J* = 9.2, 8,1, 1H, NCCHCO), 4.02 (d, *J* = 19.3 Hz, 1H, $CCH_2CO$), 4.39–4.33 (m, 1H, NCHC=C), 5.85 (d, *J* = 9.5 Hz, 1H, PhCH=C*H*), 6.68 (d, J = 15.7 Hz, 1H, PhC*H*=CH), 7.46–7.18 (m, 5H, Ar*H*); $^{13}$C NMR (75 MHz) 13.3 (*C*H$_3$CH$_2$), 20.6 (CH$_3$*C*H$_2$CH$_2$), 24.6, 25.4 (2xCH$_3$N), 31.0 (*C*H$_2$CH$_2$N), 35.3 (C*C*H$_2$C=O), 47.2 (CH$_2$*C*H$_2$N), 47.9, 48.0 (2xCHCO), 66.3 (NCHCH=C), 69.6 (NCCO), 126.9, 127.5, 128.1, 128.7, 134.1, 136.5 (ArC, CH=CH), 174.9, 175.5, 176.1, 178.3 (4xCO); MS(EI) *m/z*: 409 (M$^+$, 23%), 367 (11), 366 (17), 352 (100), 318 (39), 117 (20), 115 (24), 91 (17); HRMS calculated for $C_{25}H_{29}NO_4$: 409.2002; found 409.2010.

(3*R**,3'*S**,3a'*S**,6a'*R**)-(*E*)-2'-Benzyl-1,5'-dimethyl-3'-styryltetrahydro-4'*H*-spiro{pyrrolidine-3,1'-pyrrolo[3,4-*c*]pyrrole}-2,4',5,6'(5'*H*)-tetraone (**5d**): Colourless prisms (315 mg, 71% yield); mp 205-209 °C (*n*-hexane/ethyl acetate); IR (neat) $\nu_{max}$: 1765, 1683, 1437, 1382, 1281, 1124, 1069, 980, 735 cm$^{-1}$; $^1$H NMR (400 MHz) δ: 2.35 (d, *J* = 19.4 Hz, 1H, $CCH_2CO$), 3.06, 3.01 (2xs, 6H, 2x$CH_3$N), 3.26 (d, *J* = 8.1 Hz, 1H, NCCHCO), 3.45 (d, *J* = 15.1 Hz, 1H, $CH_2$N), 3.63 (dd, *J* = 8.8, 8.1, 1H, NCHC*H*CO), 3.80 (d, *J* = 15.1 Hz, 1H, $CH_2$N), 3.88 (d, *J* = 19.4 Hz, 1H, $CCH_2CO$), 4.51 (dd, *J* = 9.5, 8.8 Hz, 1H, N*C*HCH=CH), 5.68 (dd, *J* = 15.7, 9.5 Hz, 1H, CH=C*H*CHN), 6.67 (d, *J* = 15.7 Hz, 1H, C*H*=CHCHN), 7.05 (dd, *J* = 7.8, 1.7 Hz, 2H, Ar*H*), 7.28–7.14 (m, 8H, Ar*H*); $^{13}$C NMR (75 MHz) δ: 24.5, 25.4 (2x$CH_3$N), 34.7 (C$CH_2$C=O), 47.6, 48.2 (2xCHCO), 51.5 (N$CH_2$), 67.2 (NCHCH=CH), 69.9 (NCCO), 113.5, 126.9, 127.1, 127.6, 128.0, 128.1, 128.5, 135.2, 136.3, 138.1 (Ar*C*, CH=CH), 174.4, 175.3, 176.0, 178.1 (4xCO). MS (EI) *m/z*: 443 (M$^+$, 2%), 353 (21), 352 (100), 91 (25). HRMS calculated for $C_{26}H_{25}N_3O_4$: 443.1845; found: 443.1850.

(3*R**,3'*S**,3a'*S**,6a'*R**)-(*E*)-2'-Allyl-1,5'-diphenyl-3'-styryltetrahydro-4'*H*-spiro{pyrrolidine-3,1'-pyrrolo[3,4-*c*]pyrrole]-2,4',5,6'(5'*H*)-tetraone (**5e**): Colourless prims (408 mg, 79% yield); mp 53-55 °C (*n*-hexane/ethyl acetate); IR (neat) $\nu_{max}$: 1704, 1500, 1380, 1141, 829, 755, 690 cm$^{-1}$; $^1$H NMR (400 MHz) δ: 2.86 (d, *J* = 19.5 Hz, 1H, $CCH_2CO$), 3.50, 3.25 (2m, 3H, NCC*H*CO, N$CH_2$), 3.82 (dd, *J* = 8.9, 8.2 Hz, 1H, NCHC*H*CO), 4.23 (d, *J* = 19.5 Hz, 1H, $CCH_2CO$), 4.54 (dd, *J* = 9.5, 8.8 Hz, 1H, N*C*HCH=CH), 5.17–5.06 (m, 2H, C*H*=$CH_2$), 5.92–5.81 (m, 1H, C*H*=$CH_2$), 5.97 (dd, *J* = 15.7, 9.0 Hz, 1H, CH=C*H*CHN), 6.73 (d, *J* = 15.7 Hz, 1H, C*H*=CHCHN), 7.50–7.22 (m, 15H, Ar*H*); $^{13}$C NMR (75 MHz) δ: 35.3 (C$CH_2$CO), 47.6, 48.5 (2x*C*HCO), 50.3 (N$CH_2$), 66.0 (NCHCH=CH), 69.7 (NCCO), 118.3, 126.2, 126.4, 126.5, 127.5, 128.3, 128.7, 129,1, 129.2, 129.4, 129.5,

131.3, 131.6, 134.5, 135.3, 136.3, (CH=CH, CH=$CH_2$, Ar*C*), 173.5, 174.4, 175.1, 177.2 (4xCO); MS (EI) *m/z*: 517 ($M^+$, 40%), 477 (29), 476 (84), 426 (35), 397 (54), 371 (29), 370 (100), 369 (32), 279 (41), 253 (55), 222 (30), 197 (35), 196 (31), 182 (37), 173 (39), 168 (29), 167 (26), 141 (39), 130 (28), 129 (45), 128 (34), 119 (51), 117 (30), 115 (84), 106 (29), 91 (70), 77 (31), 57 (38), 43 (67), 41 (42); HRMS calculated for $C_{32}H_{27}N_3O_4$: 517.2002; found: 517.1999.

(3*R**,3'*S**,3a'*S**,6a'*R**)-(*E*)-2'-Allyl-1,5'-dibenzyl-3'-styryltetrahydro-4'*H*-spiro{pyrrolidine-3,1'-pyrrolo[3,4-c]pyrrole}-2,4',5,6'(5'*H*)-tetraone (**5f**): Colourless needles (305 mg, 56% yield); mp 119-120 °C (*n*-hexane/ethyl acetate); IR (neat) $\nu_{max}$: 1689, 1392, 1342, 1068, 979, 929, 694 $cm^{-1}$; $^1H$ NMR (300 MHz) δ: 2.59 (d, *J* = 19.5 Hz, 1H, $CCH_2CO$), 2.78, 3.15 (2m, 2H, $NCH_2CH=CH_2$), 3.18 (d, *J* = 9 Hz, 1H, NCC*H*CO), 3.59 (dd, *J* = 9.0, 7.9 Hz, 1H, NCC*H*CO), 3.97 (d, *J* = 19.5 Hz, 1H, $CCH_2CO$), 4.33 (deform t, *J* = 9.2 Hz, 1H, NC*H*CH=CH), 4.80–4.48 (m, 6H, 2x$CH_2$Ph, $CH_2$=CH), 5.46 (m, 1H, $CH_2$=C*H*), 5.56 (dd, *J* = 15.7, 9.2 Hz, 1H, C*H*=CHPh), 6.56 (d, *J* = 15.7 Hz, 1H, CH=C*H*Ph), 7.38–7.35 (m, 15H, Ar*C*); $^{13}C$ NMR (75 MHz): 42.4, 42.5 (2x$NCH_2$Ph), 43.7 ($CCH_2CO$), 47.4, 48.2 (2x*C*CHCO), 49.8 ($NCH_2$ C=C), 66.1 (NCHCH=CH), 69.5 ($CCH_2CO$), 126.6 ($CH_2$=CH), 126.8, 128.1, 128.1, 128.3, 128.4, 128.6, 128.7, 128.8, 128.9, 129.3, 134.3, 134.9, 135.4, 135.5, 136.2 (CH=CHPh, $CH_2$=*C*H, ArC), 174.2, 174.9, 175.5, 177.9 (4xCO); MS (EI) *m/z*: 545 ($M^+$, 3%), 505 (33), 504 (100), 115 (13), 91 (78); HRMS calculated for $C_{34}H_{31}N_3O_4$: 545.2315; found 545.2311.

(*E*)-1,2',5'-Tribenzyl-3'-styryltetrahydro-4'*H*-spiro{pyrrolidine-3,1'-pyrrolo[3,4-*c*]pyrrole}-2,4',5,6'(5'*H*)-tetraone (**5g**) (1:1 mixture of diastereoisomers): Colourless prims (352 mg, 81% yield); mp 84-87 °C (*n*-hexane/ethyl acetate); IR (neat) $\nu_{max}$:1685, 1434, 1380, 1322, 1114, 829 $cm^{-1}$; $^1H$ NMR (400 MHz) δ: 2.24 (d, *J* = 19.4 Hz, 0.5H), 2.84, 2.95 (2d, *J* = 16.0 Hz, 1H), 3.16 (d, *J* = 16.0 Hz, 0.5H), 3.25 (d, *J* = 7.8 Hz, 0.5H), 3.34 (d, *J* = 8.8 Hz, 0.5H), 3.42 (d, *J* = 14.0 Hz, 0.5H), 3.45-3.55 (m, 1H), 3.80-3.89 (m, 1H), 4.21 (d, *J* = 8.8, 0.5H), 4.60-4.84 (m, 5H), 5.42, 5.89 (2xdd, *J* = 16.0, 6.0 Hz, 1H), 6.36, 6.56 (2d, *J* = 16 Hz, 1H), 6.90-7.55 (m, 20H); $^{13}C$ NMR (75 MHz) δ: 34.6, 34.7, 38.9, 39.0, 42.4, 42.5, 42.7, 42.8, 43.0, 47.4, 47.9, 48.0, 50.3, 50.8, 55.2, 55.3, 125.8, 126.7, 126.8 (m), 127.2 (m), 127.5, 127.8, 127.9 (m), 128.1, 128.2, 128.4 (m), 128.6 (m), 129.3, 128.8, 128.9 (m), 129.1, 129.3 (m), 129.5 (m), 134.9, 134.9, 135.0, 135.4, 135.7, 136.1, 137.4, 138.4, 172.8, 173.8, 174.0, 174.4, 174.8, 175.2, 175.4, 177.4; MS (EI) *m/z*: 595 ($M^+$, 1%), 394(22), 349 (36), 323 (14), 228 (14), 212 (11), 91 (100), 77 (50); HRMS calculated for $C_{38}H_{33}N_3O_4$: 595.6990; found: 595.6995.

(3*R**,3'*S**,3a'*S**,6a'*R**)-2'-Allyl-1,5'-dimethyl-3'-phenyltetrahydro-4'*H*-spiro{pyrrolidine-3,1'-pyrrolo[3,4-*c*]pyrrole}-2,4',5,6'(5'*H*)-tetraone (**5h**): Colourless needles (308 mg, 84% yield); mp: 124-126 °C (*n*-hexane/ethyl acetate); IR (neat) $\nu_{max}$: 1689, 1434, 1380, 1280, 1130, 1068, 698 $cm^{-1}$. $^1H$ NMR (400 MHz) δ: 2.78 (d, J = 19.5 Hz, 1H, $CCH_2CO$), 2.85 (s, 3H, $CH_3N$), 2.95-3.01 (m with s at 3.00, 5H, NC*H*Ph, $CH_3N$, 1H $NCH_2$), 3.12-3.28 (m with d, *J* = 7.8 Hz, 2H, NCC*H*CO, 1H $NCH_2$), 3.81 (dd, *J* = 10.0, 7.8 Hz, 1H, NCHC*H*CO), 4.20 (d, *J* = 19.4 Hz, 1H, $CCH_2CO$), 4.97–4.83 (m, 4H, C$H_2$=CH), 5.74–5.62 (m, 1H, $CH_2$=C*H*), 7.53–7.16 (m, 5H, Ar*H*); $^{13}C$ NMR (75 MHz) δ: 24.3, 25.0 (2x$CH_3$), 34.9 ($CCH_2CO$), 48.5, 48.5 (2xCHCO), 50.6 ($NCH_2$), 67.1 (NCHPh), 69.51 (NCCO), 118.1 (CH=$CH_2$), 127.6, 128.7, 128.8, 129.1, 133.4, 137.0 (Ar*C*, *C*H=$CH_2$), 174.9, 175.1, 175.8, 178.6 (4xCO); MS (EI) *m/z*: 367 ($M^+$, 40%), 366 (22), 327 (19), 326 (100), 282 (26), 281 (64), 267 (15), 255 (37); HRMS calculated for $C_{20}H_{21}N_3O_4$: 367.1532; found: 367.1534.

(3*R**,3'*S**,3a'*S**,6a'*R**)-2'-Allyl-1,5'-dimethyl-3'-[4-(trifluoromethyl)phenyl]tetrahydro-4'*H*-spiro{pyrrolidine-3,1'-pyrrolo[3,4-c]pyrrole}-2,4',5,6'(5'*H*)-tetraone (**5i**): Pale yellow prisms (300 mg, 69% yield); mp 105-109 °C (*n*-hexane/ethyl acetate); IR (neat) $\nu_{max}$: 1689, 1434, 1380, 1322, 1284, 1114, 1064, 852 $cm^{-1}$; $^1H$ NMR (400 MHz, major diastereoisomer) δ: 2.78 (d, *J* = 19.5 Hz, 1H, $CCH_2CO$), 2.86 (s, 3H, $CH_3N$), 2.95-3.04 (m with s at 3.02, 5H, NC*H*Ar, $CH_3N$, 1H $NCH_2$), 3.14-3.29 (m with d, *J* = 8.0 Hz, 2H, NCC*H*CO, 1H $NCH_2$), 3.84 (dd, *J* = 9.9, 8.0 Hz, 1H, NCHCHCO), 4.21 (d, *J* = 19.4 Hz, 1H, $CCH_2CO$), 4.86-5.01 (m, 2H, C$H_2$=CH), 5.64 (m, 1H, $CH_2$=C*H*), 7.33 (m, 2H, Ar*H*), 7.58-7.70 (m, 3H, Ar*H*); $^{13}C$ NMR (75 MHz, major diastereoisomer) 24.4, 25.1 (2x$CH_3$), 34.8 (C$CH_2CO$), 48.4, 48.5 (2xCHCO), 50.7 (NC$H_2$CH=C), 66.7 (NC*H*CH=CH), 69.6 (NCCO), 118.6 (CH=C$H_2$), 125.7 ($CF_3$), 127.9, 128.1, 130.6, 132.9, 134.1 (ArC, *C*H=$CH_2$), 174.6, 174.8, 175.6, 178.4 (4xCO); $^{19}F$ NMR (400 MHz) δ: 64.9 ppm; MS (EI) *m/z*: 435 ($M^+$, 19%), 395 (21), 394 (100), 375 (11), 350 (20), 349 (47), 347 (11), 335 (14), 323 (25), 265 (12), 264 (18), 238 (11), 224 (15), 212 (18), 191 (36), 183 (11), 172 (11), 171 (10), 151 (11), 115 (10), 43 (14), 41(27); HRMS calculated for $C_{21}H_{20}F_3N_3O_4$: 435.1406; found: 435.1410.

(3*R**,3'*S**,3a'*S**,6a'*R**)-2'-Allyl-3'-(2-bromophenyl)-1,5'-dimethyltetrahydro-4'*H*-spiro{pyrrolidine-3,1'-pyrrolo[3,4-*c*]pyrrole}-2,4',5,6'(5'*H*)-tetraone (**5j**): Colourless needles (352 mg, 79% yield); mp 168-172 °C (*n*-hexane/ethyl acetate); IR (neat) $\nu_{max}$; 1689, 1430, 1380, 1284, 1133, 763 $cm^{-1}$; $^1H$ NMR (400 MHz) δ: 2.77 (d, *J* = 19.5 Hz, 1H, $CCH_2CO$), 2.79 (s, 3H, $CH_3N$); 2.96–3.02 (m with s at 3.01, 4H, $CH_3N$, 1H $NCH_2C$=C), 3.19 (m, 1H, $NCH_2C$=C), 3.21 (d, *J* = 8.0 Hz, 1H, NCC*H*CO), 3.99 (dd, *J* = 9.9, 8.0 Hz, 1H, NCHC*H*CO), 4.21 (d, *J* = 19.5 Hz, 1H, $CCH_2CO$), 4.89 (dd, *J* = 17.0, 1.5 Hz, 1H, C$H_2$=CH), 4.99 (dd, *J* = 8.0, 1.5 Hz, 1H, C$H_2$=CH), 5.01 – 4.97 (m, 1H), 5.31 (d, J = 9.9 Hz, 1H, NC*H*Ar), 5.77 – 5.65 (m, 1H, $CH_2$=C*H*), 7.17–7.20 (m, 2H, Ar*H*), 7.23 (m, 1H, Ar*H*), 7.60 (d, *J* = 8.1 Hz, 1H); $^{13}C$ NMR (75 MHz) δ: 24.9, 24.4 (2x$CH_3$), 35.2 (C$CH_2$C=O), 46.4, 48.4 (2xCHCO), 51.0 (N$CH_2$CH=C), 65.9 (NCHAr), 69.6 (NCCO), 118.5 (CH=C$H_2$), 125.4, 127.5, 127.6, 129.8, 133.2, 133.2, 136.4 (Ar*C*, *C*H=$CH_2$), 174.6, 174.8, 175.72, 178.1 (4xCO); MS (EI) *m/z*: 445 ($M^+$, 0.28%), 267 (24), 366 (100), 281 (18), 41 (12); HRMS calculated for $C_{17}H_{15}BrN_3O_4$ [$M^+$-C3H5]: 404.0246; found 404.0248.

(3*R**,3'*S**,3a'*S**,6a'*R**)-3'-(2-Bromophenyl)-1,5'-dimethyl-2'-(2-methylallyl)tetrahydro-4'*H*-spiro{pyrrolidine-3,1'-pyrrolo[3,4-*c*]pyrrole}-2,4',5,6'(5'*H*)-tetraone (**5k**): Colourless prisms (418 mg, 91% yield); mp 172-175 °C (*n*-hexane/ethyl acetate); IR (neat) $\nu_{max}$: 1770, 1685, 1434, 1380, 1280, 1130, 960, 755, 659 $cm^{-1}$; $^1H$ NMR (300 MHz) δ: 1.72 (br s, 3H, $CH_3C$), 2.74 (d, *J* = 19.5 Hz, 1H, $CCH_2CO$), 2.80 (s, 3H, $CH_3N$), 2.83, 2.99 (2d, *J* = 15 Hz, 2H, $CH_2N$), 3.06 (s, 3H, $CH_3N$), 3.23 (d, *J* = 8.0 Hz, 1H, NCC*H*CO), 3.97 (dd, *J* = 10.1, 8.0 Hz, 1H, NCHC*H*CO), 4.16 (d, *J* = 19.5 Hz, 1H, $CCH_2CO$), 4.64, 4.73 (2 br s, 2H, $CH_2$=C), 5.23 (d, J = 10.1 Hz, 1H, NC*H*Ar), 7.11, 7.30, 7.59 (3m, 5H, Ar*C*); $^{13}C$ NMR (75 MHz) δ: 14.3 (*C*$H_3$C), 21.1, 29.8 (2x$CH_3$N), 35.0 (C*C*H2CO), 47.4, 48.2 (2xCHCO), 49.6 ($NCH_2$), 66.1 (NCHAr), 69.5 ($NCCH_2$), 117.4 (C=*C*$H_2$), 126.6, 126.9, 128.0, 127.6, 129.8, 133.2, 136.4 (ArC, *C*=$CH_2$), 174.6, 174.8, 175.7, 178.4 (4xCO); MS (EI) *m/z*: 459 ($M^+$, 0.20%), 381 (25), 380 (100), 295 (12), 55 (13); HRMS calculated for $C_{21}H_{22}BrN_3O_4$: 459.0794; found: 461.0791.

(3*R**,3'*S**,3a'*S**,6a'*R**)-(*E*)-2'-Allyl-1,5'-dimethyl-3'-(prop-1-en-1-yl)tetrahydro-4'*H*-spiro{pyrrolidine-3,1'-pyrrolo[3,4-*c*]pyrrole}-2,4',5,6'(5'*H*)-tetraone (**5l**): Colourless prisms (242 mg, 73% yield); mp 135-137 °C (*n*-hexane/ethyl acetate); IR (neat) $\nu_{max}$: 1681, 1434, 1380, 1280, 1133, 1072, 975 $cm^{-1}$; $^1H$ NMR (400 MHz) δ: 1.76 (deform. d, *J* = 6.6 Hz, 3H, $CH_3C$), 2.55 (d, *J* = 19.3 Hz, 1H, $CCH_2CO$), 2.95, 3.01 (2xs, 6H, 2x$CH_3N$), 3.02 (m, 1H, $CH_2N$), 3.15 (d, *J* = 8.0 Hz, 1H, NCC*H*CO), 3.27 (ddt, J = 15.8, 6.4, 1.6 Hz, 1H, $CH_2N$), 3.53 (dd, *J* = 9.2, 8.0 Hz, 1H NCHC*H*CO), 3.98 (d, *J* = 19.3 Hz, 1H, $CCH_2CO$), 4.21 (dd, *J* = 9.2, 9,2 Hz, 1H, NC*H*CH=CH), 5.07 (m, 3H, C$H_2$=CH, C*H*=CHCH$_3$), 5.68–5.88 (m, 2H, $CH_2$=C*H*, C*H*=C*H*CH$_3$); $^{13}C$ NMR (75 MHz) δ: 18.0 (*C*$H_3$C) 24.2, 25.2 (2x$CH_3$N), 35.1 ($CCH_2CO$), 47.2, 48.0 (2xCHCO), 49.6 (N$CH_2$CH), 65.1 (NC*H*CH=CH), 68.9 (NCCO), 117.4 (CH=*C*$H_2$), 128.0 ($CH_3$CH=*C*H), 132.4 ($CH_2$=C*H*), 134.0 (NCH*C*H=C), 174.8, 175.6, 176.0, 178.5 (4xCO);

MS (EI) *m/z*: 331 ($M^+$, 5%), 317 (11), 316 (58), 291 (17), 290 (100), 245 (13), 231 (43), 219 (15), 205 (18), 191 (16), 120 (15), 79 (12), 41 (24); HRMS calculated for $C_{17}H_{21}N_3O_4$: 331.1532; found: 331.1528.

(3*R**,3'*S**,3a'*S**,6a'*R**)-(*E*)-2'-Allyl-1,5'-dimethyl-3'-(oct-1-en-1-yl)tetrahydro-4'*H*-spiro{pyrrolidine-3,1'-pyrrolo[3,4-*c*]pyrrole}-2,4',5,6'(5'*H*)-tetraone (**5m**): Colourless needles (277 mg, 69% yield); mp 108-112°C (*n*-hexane/ethyl acetate); IR (neat) $\nu_{max}$: 1685, 1434, 1380, 1280, 1133, 1072, 975 $cm^{-1}$; $^1H$ NMR (300 MHz) δ: 0.92–0.85 (m, 3H, $CH_3$C), 1.40–1.22 [m, 8H, $CH_3(CH_2)_4$], 2.15–2.02 (m, 2H, CC$H_2$CH=CH), 2.55 (d, *J* = 19.4 Hz, 1H, $CCH_2CO$), 2.95, 3.00 (2m, 6H, 2x$CH_3$N), 3.07–3.02 (m, 1H, $CH_2$N), 3.15 (d, *J* = 8.0 Hz, 1H, NCC*H*CO), 3.32–3.23 (m, 1H, $CH_2$N), 3.52 (dd, J = 9.0, 8.0 Hz, 1H, NCHC*H*CO), 3.98 (d, *J* = 19.4 Hz, 1H, $CCH_2CO$), 4.20 (t, *J* = 9.2 Hz, 1H, NC*H*CH=C), 5.10–4.89 (m, 3H, C$H_2$=CH, CH=C*H*CN), 5.86–5.65 (m, 2H, CH=C*H*$CH_2$, C*H*=$CH_2$); $^{13}C$ NMR (75 MHz) δ: 14.1 ($CH_3CH_2$), 22.6 ($CH_3CH_2$), 24.2, 25.2 (2x$NCH_3$), 28.8, 28.9, 31.0, 32.2 ($CH_2CH_2CH_2CH_2$CH=C), 35.0 (C*C*$H_2$CO), 47.2, 48.0 (2x*C*HCO), 49.5 (N$CH_2$CH=C), 65.0 (N*C*HCH=CH), 68.9 (N*C*CO), 117.4 (CH=*C*$H_2$), 126.6 ($CH_2$*C*H=CHC), 133.9 (NCH*C*H=$CH_2$), 137.7 (NCH*C*H=CH) 174.7, 175.4, 176.0, 178.5 (4xCO); MS (EI) *m/z*: 401 ($M^+$, 2%), 361 (14), 360 (66), 317 (21), 316 (100), 231 (19), 41 (20); HRMS calculated for $C_{22}H_{31}N_3O_4$: 401.2315; found: 401.2314.

(3*R**,3'*S**,3a'*S**,6a'*R**)-2'-Allyl-1,5'-dimethyl-3'-phenethyltetrahydro-4'*H*-spiro{pyrrolidine-3,1'-pyrrolo[3,4-*c*]pyrrole}-2,4',5,6'(5'*H*)-tetraone (**5n**): Colourless prisms (347 mg, 88% yield): mp 132-134 °C (*n*-hexane/ethyl acetate); IR (neat) $\nu_{max}$: 1685, 1434, 384, 1280, 1130, 1072, 744, 694; $^1H$ NMR (300 MHz) δ: 1.73–1.57, 2.06–1.92 (2m, 2H, C$H_2CH_2$Ph), 2.47 (d, *J* = 19.3 Hz, 1H, $CCH_2CO$), 2.70–2.52 (m, 1H, C$H_2$Ph), 2.95, 3.02 (2s, 6H, 2x$CH_3$N), 3.25–3.12 (m, 4H, 1H of C$H_2$Ph, $CH_2$N, NCC*H*CO), 3.62 (dd, *J* = 8.2, 8.2 Hz, 1H, NCHC*H*CO), 3.85 (ddd, *J* = 11.0, 8.2, 2.8 Hz, 1H, NC*H*$CH_2$), 3.94 (d, *J* = 19.3 Hz, 1H, $CCH_2CO$), 5.07–4.97 (m, 2H, C$H_2$=CH), 5.77–5.62 (m, 1H, $CH_2$=C*H*), 7.34–7.16 (m, 5H, Ar*H*); $^{13}C$ NMR (75 MHz) δ:, 24.4, 25.2 (2x$CH_3$N), 32.3 ($CH_2CH_2$Ph), 32.5 (*C*$H_2$Ph), 35.1 ($CCH_2CO$), 45.8, 47.7 (2xCHCO), 48.95 ($NCH_2$), 61.9 (N*C*H$CH_2$), 69.1 (NCCO), 117.6 (CH=*C*$H_2$), 126.0, 128.3, 128.6, 133.8, 142.0 (Ar*C*, *C*H=$CH_2$), 174.77, 175.97, 176.01, 178.54 (4xCO); MS (EI) *m/z*: 395 ($M^+$, 18%), 380 (13), 354 (13), 304 (48), 290 (100), 283 (36), 206 (12), 207 (13), 191 (11), 172 (34), 120 (16), 91 (55), 80 (11), 41 (40); HRMS calculated for $C_{22}H_{25}N_3O_4$: 395.1845; found: 395.1844.

(3*R**,3'*S**,3a'*S**,6a'*R**)-2'-Benzyl-1,5'-dimethyl-3'-phenethyltetrahydro-4'*H*-spiro{pyrrolidine-3,1'-pyrrolo[3,4-*c*]pyrrole}-2,4',5,6'(5'*H*)-tetraone (**5o**): Colourless prisms (334 mg, 75% yield); mp 172-174 °C (*n*-hexane/ethyl acetate); IR (neat) $\nu_{max}$: 1681, 1434, 1380, 1280, 1130, 1076, 975, 744 $cm^{-1}$; $^1H$ NMR (400 MHz) δ: 1.53–1.62, 1.70–1.90 (2m, 2H, C$H_2CH_2$Ph), 2.34 (d, *J* = 19.4 Hz, 1H, $CCH_2CO$), 2.57 (m, 1H, C$H_2$Ph), 2.97, 3.05 (2s, 6H, 2x$CH_3$N), 3.12 (m, 1H, C$H_2$Ph), 3.24 (d, J = 8.1 Hz, 1H, NCC*H*CO), 3.51 (d, *J* = 16.2 Hz, 1H, $NCH_2$), 3.64-3.70 (m, 2H, 1H of $NCH_2$, NCHC*H*CO), 3.90 (m with d at 3.87, *J* = 19.4 Hz, 2H, NC*H*$CH_2$, $CCH_2CO$), 7.03–7.29 (m, 10H, Ar*H*); $^{13}C$ NMR (75 MHz) δ: 24.5, 25.3 (2x$CH_3$N), 32.6 (Ph$CH_2CH_2$), 33.1 (Ph$CH_2$), 34.2 (C*C*$H_2$CO), 46.1, 48.1 (2xCHCO), 51.1 ($NCH_2$), 64.4 (NCH$CH_2$), 70.2 (NCCO), 126.0, 127.18, 127.6, 128.3, 128.4, 128.6, 128.7, 138.8, 141.8 (Ar*C*), 174.5, 175.9, 176.0, 178.1 (4xCO); MS (EI) *m/z*: 445 ($M^+$, 6%), 355 (12), 354 (53), 333 (13), 91 (100); HRMS calculated for $C_{26}H_{27}N_3O_4$: 445.2002; found: 445.1999.

(3*R**,3'*R**,3a'*S**,6a'*R**)-2'-Allyl-3'-(furan-2-yl)-1,5'-dimethyltetrahydro-4'*H*-spiro{pyrrolidine-3,1'-pyrrolo[3,4-*c*]pyrrole}-2,4',5,6'(5'*H*)-tetraone (**5p**): White solid (75 mg, 70% yield); mp: 144-150 °C (*n*-hexane/ethyl acetate); IR (neat) $\nu_{max}$: 1689.34, 1434.78, 1384.64, 1280.5, 1133.94, 1068.37 $cm^{-1}$. $^1H$ NMR (400 MHz) δ: 2.70 (d, *J* = 19.5 Hz, 1H, $CCH_2CO$), 3.04–2.88 (m with two s at 2.96 and 2.97, 7H, 2x$CH_3$N, 1H NCC*H*CO), 3.24–3.09 (m, 2H, $NCH_2$), 3.72 (dd, *J* = 9.7, 8.0 Hz, 1H, NCHC*H*CO), 4.14 (d, *J* = 19.5 Hz, 1H, $CCH_2CO$), 5.02–4.79 (m, 3H, C$H_2$=CH and NC*H*furyl), 5.68–5.45 (m, 1H, $CH_2$=C*H*), 6.35–6.26 (m, 2H, furyl-H), 7.34 (dd, *J* = 1.8, 0.9 Hz, 1H, furyl-H). $^{13}C$ NMR (75 MHz) δ: 24.4, 25.4 (2x$CH_3$), 34.5 (C$CH_2$CO), 46.7, 48.2 (2xCHCO), 50.5 ($NCH_2$), 61.0 (NCHPh), 68.9 (NCCO), 110.6 (furyl-*C*H), 118.60 (CH=*C*$H_2$), 133.1, 143.2, (furyl-*C*H), 149.5 (furyl-*C*), 174.8, 175.4, 175.6, 178.5 (4xCO); MS (EI) *m/z*: 357($M^+$, 2%), 317 (18), 316 (100), 191 (25), 57 (12), 43 (22), 41 (19); HRMS calculated for $C_{18}H_{19}N_3O_5$[$M^+$] 357.1325; found: 357.1317.

(3*R**,3'*S**,3a'*S**,6a'*R**)-(2'-Allyl-1,5'-bis(4-bromophenyl)-3'-{(*E*)-styryl)tetrahydro-4'*H*-spiro[pyrrolidine-3,1'-pyrrolo[3,4-*c*]pyrrole}-2,4',5,6'(5'*H*)-tetraone (**5q**):Mixture of diasteroisomers: 55:45. White solid (88 mg, 45% yield); mp 63-70 °C (*n*-hexane/ethyl acetate); IR (neat) $\nu_{max}$: 1704.76, 1488.78, 1384.64, 1191.79, 817.67, 752.102 $cm^{-1}$. $^1H$ NMR (400 MHz) δ: 2.79 (d, *J* = 18.1 Hz, 1H), 3.03 (dd, *J* = 14.3, 8.9 Hz, 1H), 3.24–3.14 (m, 1H), 3.37–3.25 (m, 3H), 3.49–3.41 (m, 2H), 3.59–3.49 (m, 2H), 3.73–3.59 (m, 2H), 3.85 (dd, *J* = 9.6, 7.2 Hz, 1H), 4.36 (dd, *J* = 8.7, 6.6 Hz, 1H), 5.34–4.96 (m, 4H), 5.83–5.68 (m, 1H), 5.98–5.83 (m, 1H), 6.08 (dd, *J* = 15.7, 8.6 Hz, 1H), 6.40 (dd, *J* = 15.7, 9.6 Hz, 1H), 6.72 (t, *J* = 15.8 Hz, 2H), 7.16–7.07 (m, 3H), 7.37–7.19 (m, 11H), 7.47–7.38 (m, 4H), 7.68–7.53 (m, 8H).$^{13}C$ NMR (101 MHz) δ: 36.5, 41.6, 48.7, 49.4, 50.9, 51.2, 54.3, 56.3, 68.6, 70.6, 71.7, 118.4, 118.5, 121.8, 123.1, 123.1, 123.2, 125.7, 126.9, 127.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.5, 128.8, 128.8, 130.2,130.6, 130.7, 132.0, 132.6, 132.7, 135.1, 135.1, 135.6, 135.8, 136.0, 136.1,171.8, 172.5, 173.2, 174.3, 174.7, 174.8, 175.9, 176.9. MS (EI) *m/z*: 673 ($M^+$, 5%), 636 (28), 364 (51), 632 (26), 450 (32), 448 (33), 222 (25), 212 (26), 182 (59), 180 (27), 171 (23), 170 (33), 169 (25), 168 (27), 167 (28), 141 (39), 132 (31), 130 (35), 129 (40), 128 (37), 118 (21), 117 (25), 116 (26), 115 (100), 91 (49), 90 (28), 41 (52); HRMS calculated for $C_{32}H_{25}Br_2N_3O_4$: 673.0212; found: 673.0204.

(3*R**,3'*S**,3a'*S**,6a'*R**)-2'-Allyl-5'-benzyl-1-methyl-3'-[(*E*)-styryl]tetrahydro-4'*H*-spiro{pyrrolidine-3,1'-pyrrolo[3,4-*c*]pyrrole}-2,4',5,6'(5'*H*)-tetraone. (**5r**): Colourless prisms (389 mg, 83% yield); mp: 129-131 °C (*n*-hexane/ethyl acetate); IR (neat) $\nu_{max}$: 1689, 1430, 1392, 1284, 1187, 1133, 979, 694 $cm^{-1}$; $^1H$ NMR (400 MHz) δ: 2.56 (d, *J* = 19.4 Hz, 1H, $CCH_2CO$), 2.97 (s, 3H, $CH_3$N), 3.01 (m, 1H, $CH_2$N), 3.19 (d, *J* = 7.9 Hz, 1H, NCC*H*CO), 3.26 (ddt, *J* = 16.1, 6.1, 1.6 Hz, 1H, $CH_2$N), 3.61 (dd, *J* = 8.9, 7.9 Hz, 1H, NCHC*H*CO), 3.97 (d, *J* = 19.4 Hz, 1H, $CCH_2CO$), 4.39 (dd, *J* = 8.9, 8.9 Hz, 1H, NC*H*CH=CH), 4.67, 4.71 (2d, *J* = 12.7 Hz, 2H, $CH_2$Ph), 4.86–5.00 (m, 2H, C$H_2$=CH), 5.61 (dd, *J* = 15.7, 9.4 Hz, 1H, NCHC*H*=CH), 5.68 (m, 1H, CH=C$H_2$), 6.60 (d, *J* = 15.7 Hz, 1H, PhC*H*=CH), 7.20–7.40 (m, 10H, Ar*H*); $^{13}C$ NMR (75 MHz) δ: 24.3 ($CH_3$), 35.1 ($NCH_2$Ph), 42.7, 47.53 (2x*C*HCO), 48.1 (N$CH_2$CH=$CH_2$), 49.8 (C$CH_2$CO), 65.6 (N*C*HCHCO), 69.3 (*C*$CH_2$CO), 117.5 (*C*$H_2$=CH), 126.5, 126.9, 128.1, 128.6, 128.6, 128.7, 128.8, 133.8, 134.1, 135.0, 135.5, 136.2 (CH=CH, $CH_2$=C*H*, Ar*C*), 174.7, 175.0, 175.6, 178.3 (4xCO); MS (EI) *m/z*: 469 ($M^+$, 3%), 429 (28), 428 (100), 378 (14), 115 (16), 91 (50); HRMS calculated for $C_{28}H_{27}N_3O_4$: 469.2002; found: 469.1998.

**Synthesis of compound 10**: In a flask with a magnetic bar, containing 3 mL of dichoromethane, was added the corresponding spirobicycle **5l** (165 mg, 0.5 mmol), and the Hoveyda-Grubbs catalyst (3 mg, 0.005 mmol). The solution was refluxed for 4 h. Then, the solvent was evaporated and the residue was purified by flash chromatography (flash silica-gel), eluting with 3/1 *n*-hexane:ethyl acetate, affording pure (3*R**,3a'*R**,8a'*S**,8b'*S**)-1,2'-Dimethyl-3a',6',8a',8b'-tetrahydro-1'*H*-spiro{pyrrolidine-3,4'-pyrrolo[3,4-*a*]pyrrolizine}-1',2,3',5(2'*H*)-tetraone (**10**): Colourless needles (131 mg, 91% yield); mp 150-159 °C (*n*-hexane/ethyl acetate); IR (neat) $\nu_{max}$: 1681, 1434, 1380, 1280, 1122, 964, 721 $cm^{-1}$. $^1H$ NMR (300 MHz) δ: 2.87 (s, 3H, $CH_3$N), 2.95 (d, J = 18.8 Hz, 1H, $CCH_2CO$), 3.02 (s, 3H, $CH_3$N), 3.32 (d, *J* = 7.8 Hz, 1H, NCCHCO), 3.40, 3.75 (2m, 2H, $CH_2$N), 3.80 (dd, *J* = 9.1, 7.8 Hz, 1H, NCHC*H*CO), 4.05 (d, J = 18.8 Hz, 1H, $CCH_2CO$), 4.94 (m, 1H, NCH), 5.75, 5.96 (2m, 2H, CH=CH); $^{13}C$ NMR (75 MHz) δ: 25.0, 25.2 (2x$CH_3$N), 33.6 (C$CH_2$CO),

51.2, 57.4 (2xCHCO), 70.9 ($NCH_2$), 71.7 (NCH), 74.5 ($CCH_2CO$), 127.0, 128.8 (CH=CH), 174.3, 176.6, 176.7, 177.3 (4xCO); MS (EI) *m/z*: 289 ($M^+$, 17%), 203 (11), 183 (34), 178 (21), 177 (22), 152 (15), 145 (10), 119 (15), 118 (32), 117 (17), 108 (16), 107 (100), 93 (29), 92 (12), 67 (11); HRMS (ESI) calculated for $C_{14}H_{15}N_3O_4$: 289.1063; found: 289.1066.

See supporting information for additional details.

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**Keywords:** Amines, Azomethine ylide, Dipolar Cycloaddition, Maleimides, Multicomponent, Spirocycles

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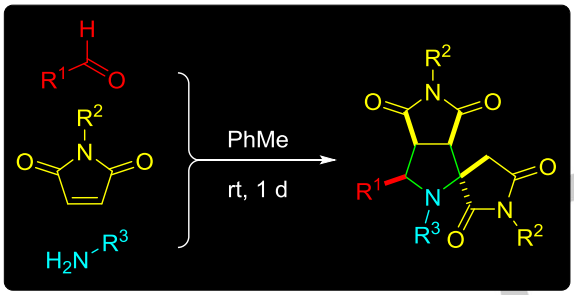
FULL PAPER

**Synthesis of spiro{pyrrolidine-3,1'-pyrrolo[3,4-*c*]pyrrole} basic framework *via* multicomponent 1,3-dipolar cycloaddition**

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