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Graphical Abstract

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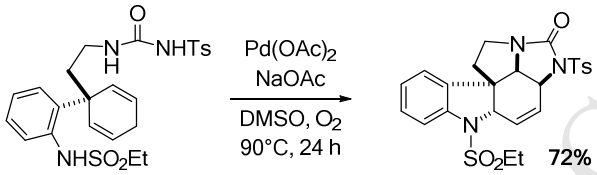
University of Bordeaux, Institute of Molecular Sciences (ISM), CNRS-UMR 5255, F-33400 Talence, France.



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Palladium-mediated Domino Oxidative Amination of Cyclohexadienes as an Entry to Indole Alkaloids.

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Dedicated with respect to Prof. Leon Ghosez

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ABSTRACT

A palladium-mediated double oxidative amination reaction on cyclohexa-2,5-dienes has been developed, leading to the tetracyclic indoline skeleton of *aspidosperma* and *strychnos* alkaloids. The allyl-palladium intermediate, generated after the double oxidative amination, could be trapped by an internal nucleophile to allow the construction of 3 rings in a single step. Approaches to the synthesis of strychnine and mossambine is finally reported.

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1. Introduction

Cascade (or Domino) reactions constitute a powerful tool for the construction of complex natural products as several C-C or C-heteroatom bonds may be created in one pot with an increase of the structural complexity.[1] The desymmetrization of cyclic dienes,[2] when applicable, also constitutes an efficient strategy in organic synthesis[3] as, at least two new stereogenic centers are formed, including in some cases, the creation of a chiral quaternary stereocenter.[4] Combining these two approaches then allows a straightforward access to the synthesis of a broad range of natural products. Applying this strategy to the synthesis of alkaloids, and especially indole alkaloids, requires the development of efficient C-N bond forming reactions (Figure 1).

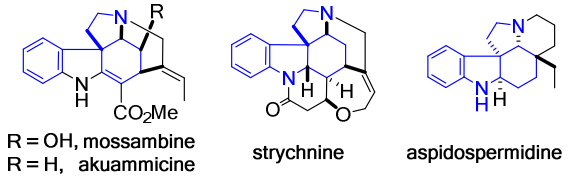
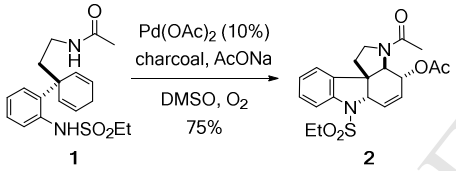


Figure 1. Indoles alkaloids sharing a common tetracyclic backbone.

Aza-Michael reactions[5] have been successfully used in asymmetric desymmetrization of cyclohexadienones as an access to tetracyclic indolines,[6] including the Büchi ketone,[7] a key intermediate in the synthesis of *aspidosperma* and *strychnos* alkaloids. Few years ago, our group has also developed a Pd(II)-catalyzed double oxidative amination of cyclohexadienes with the trapping of the final allyl-palladium by an acetate forming a highly functionalized cyclohexene as a single diastereoisomer (Scheme 1).[8]



Scheme 1. Pd(II)-catalyzed double oxidative amination cascade.

We wish to report herein an extension of this methodology with the formation of a third ring by an intramolecular trapping of the Pd-π allyl intermediate (Figure 2) and some attempts to complete the synthesis of mossambine, a *strychnos* alkaloid.

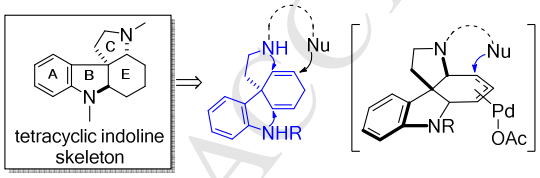
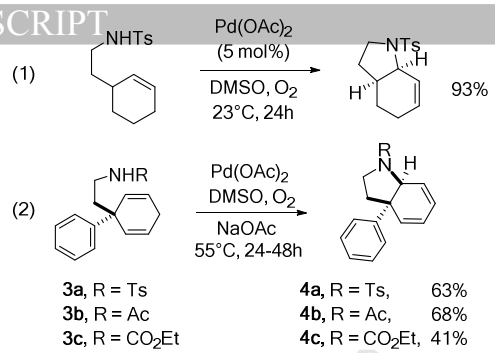


Figure 2. Triple cascade addition onto cyclohexadienes

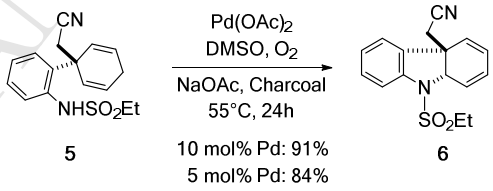
2. Results and discussion

Bäckvall *et al.* first explored the Pd(II)-catalyzed cyclization of sulfonamides onto cyclohexene in DMSO with dioxygen as a reoxidant (Scheme 2, eq. 1).[9] We demonstrated that the cyclization could also be performed on a cyclohexa-1,4-diene with various protecting groups on the nitrogen (Scheme 2, eq. 2). The somewhat lower yields obtained are due to a partial overoxidation of the final diene into an enone.



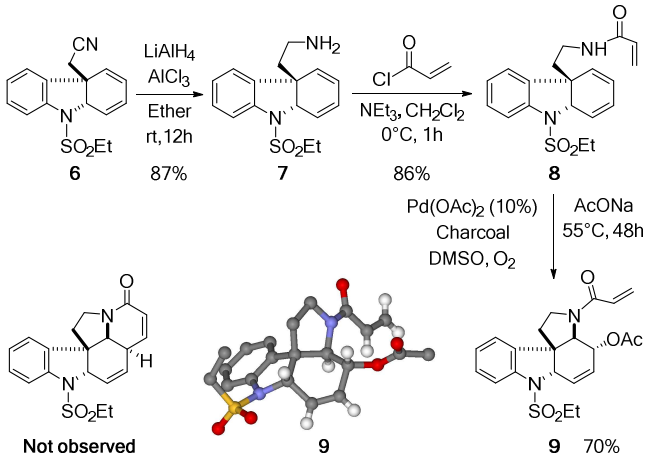
Scheme 2. Pd(II)-catalyzed oxidative amination.

We then attempted a cyclization starting from an aromatic sulfonamide **5**, available in two steps from 2-aminobiphenyl through a Birch reductive alkylation[10] (after the protection of the aniline). Oxygen concentration was found to be a critical factor, indicating that Pd^0 reoxidation is the turnover limiting step of the process.[11] Inefficient reoxidation of Pd^0 into Pd^{II} leads to aggregation of Pd^0 and precipitation of Pd metal, a process which could be prevented by addition of charcoal.[12] The presence of stoichiometric NaOAc as a base also enhanced the yield of these reactions (Scheme 3).[13] It should also be noticed that Zhu *et al.* have developed recently an elegant palladium oxidative amination on cyclohexadienes using chiral ligands, allowing the extension of our strategy to an enantioselective version.[14]



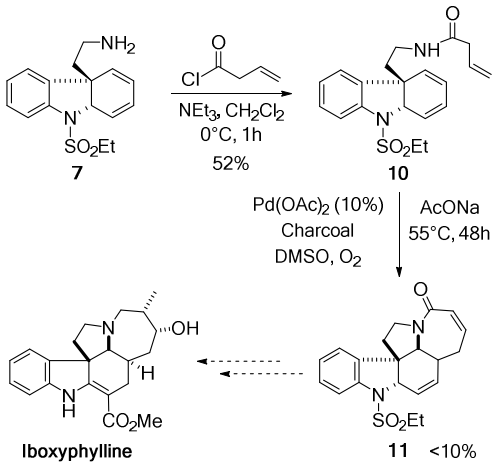
Scheme 3. Oxidative amination of aromatic sulfonamide.

At this stage, a sequential double addition confirmed the formation of the acetate insertion product as a unique diastereoisomer, identical to that obtained through the one pot process (Scheme 1 and 4). However, when the reaction was run with an acrylamide (*e.g.* **8**), instead of an acetate, only the tetracyclic product **9** was formed with no trace of the desired pentacyclic system, resulting from an insertion (and elimination) of the intermediate palladium species into the double bond in a Heck-type fashion.



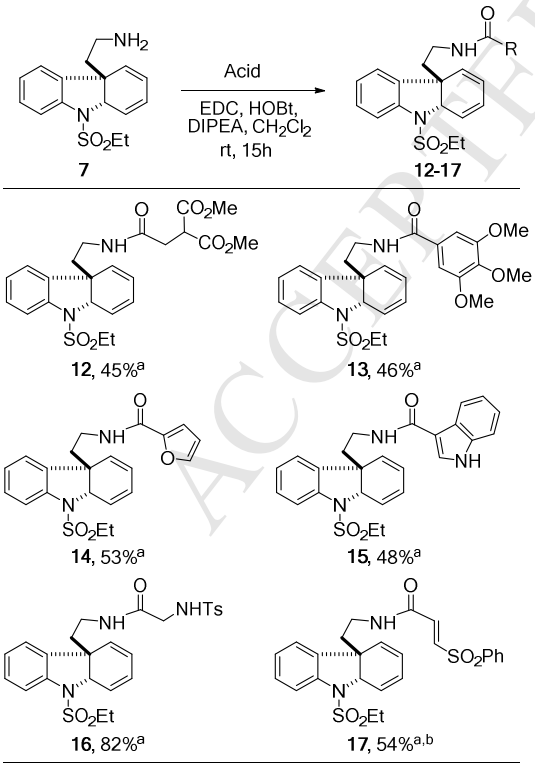
Scheme 4. Sequential double oxidative amination.

The double bond of the acrylamide being quite far away from the palladium center in the putative allyl-Pd intermediate, an amide **10** with a longer arm was then synthesized (Scheme 5). Unfortunately, if the desired tricyclic product **11**, an advanced intermediate in the synthesis of iboxyphylline, an *aspidosperma* alkaloid,[15] was effectively formed, yields were always low and the reaction difficult to reproduce. The faster oxidation of the terminal double bond of **10** (through a Wacker type process) or a competing 6-exo carbopalladation followed by an oxidation of the exocyclic double bond might explain the low yield of **11**, the only compound stable to overoxidation.



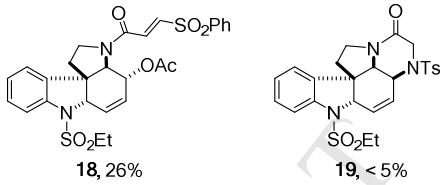
Scheme 5. Double oxidative amination and insertion.

In the search for a nucleophile that would stand the harsh oxidative conditions, different acyl groups bearing electron-rich aromatics, a malonate, a tosylamine... were then introduced on the primary amine (Scheme 6). Amides **12-16** were thus isolated in good overall yield (in 2 steps from **6**), except amide **17** formed after sulfone elimination.



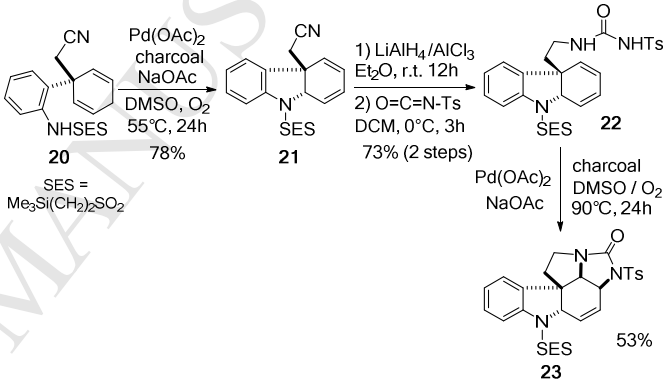
Scheme 6. Acid coupling

When the palladium oxidative amination was performed on the six amides above, only two cyclized products were observed. Starting from **17**, low amount of tetracyclic acetate **18** was isolated. However, when the reaction was carried out on tosylamine **16**, pentacyclic **19** could be observed, albeit in very low yield (Scheme 7).



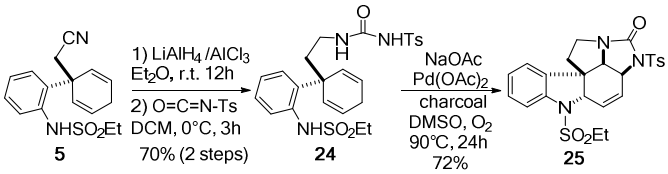
Scheme 7. Oxidative amination on substrates **16** and **17**.

From these failures, it appeared that sulfonamides, stable under the harsh oxidative conditions, would constitute suitable nucleophiles. Carbamate **22**, formed through addition of a N-tosyl isocyanate to the corresponding amine, was thus submitted to the oxidative amination protocol, affording the pentacyclic compound **23**, formed in satisfying yield (Scheme 8).



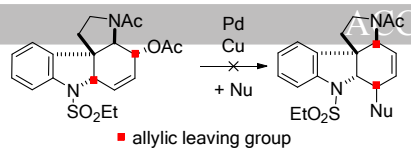
Scheme 8. Formation of pentacyclic compound **23**.

To demonstrate further the efficiency of the strategy, a one-pot triple oxidative amination protocol was then attempted with success on precursor **24**, leading to pentacyclic **25** in a remarkable 72% yield (Scheme 9), in only five steps and 30% overall yield from commercially available 2-amino biphenyl.



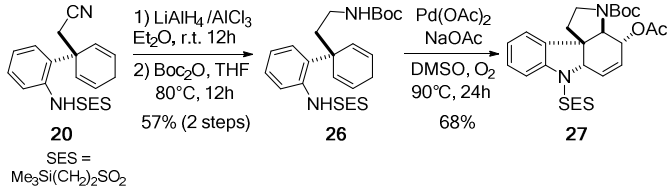
Scheme 9. One-pot triple oxidative amination.

In order to complete the synthesis of indole alkaloids, including that of strychnine, we also thought using the allylic acetate **2** formed after the double cyclization (Scheme 1). Unfortunately, despite extensive efforts and whatever the organometallic protocol (Pd or Cu) used for the SN_2' type reactions (Scheme 10), only starting material or degradation were observed. This may be ascribed to the presence of the allylic sulfonamide which may enter into a competition with the acetate leaving group in the allylic substitution reaction.



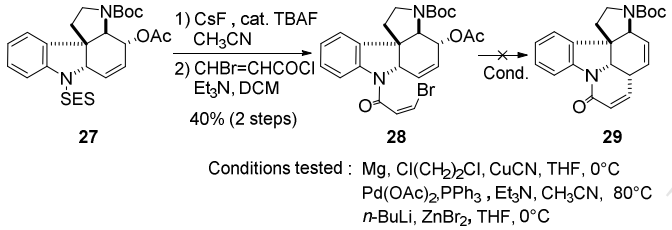
Scheme 10. Failures in the intermolecular SN_2' reactions

An intramolecular version was then envisaged to avoid the allylic leaving group problems mentioned above. For this purpose, precursor **27**, having a SES protecting group, was prepared with the same strategy (Scheme 11).



Scheme 11. Synthesis of the SES-protected precursor.

The aromatic nitrogen was then unprotected with a fluoride source and coupled with a bromoacryloyl chloride to give **28**. Unfortunately, as before, the various organometallic conditions tested gave rise to degradation products and no trace of the desired pentacyclic skeleton **29** (Scheme 12).



Scheme 12. Failures in the intramolecular SN_2' reactions

In the meantime we also envisaged to target mossambine (see Fig. 1), for which only one total synthesis was achieved by the group of Kuehne.[16] An intramolecular Heck reaction, inspired by Rawal in his synthesis of dehydrotubifoline,[17] was chosen for the formation of the alkaloid D-ring (Figure 3).

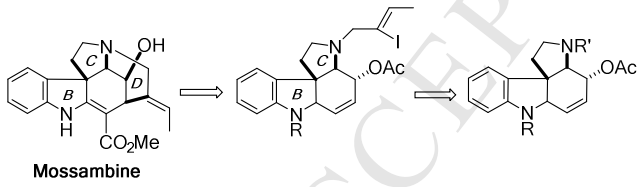
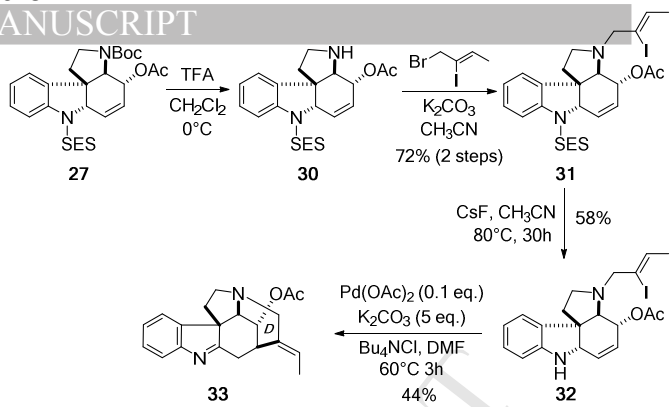


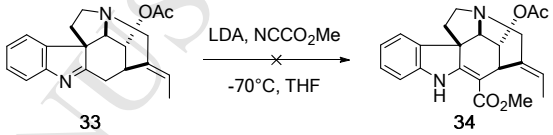
Figure 3. Mossambine retrosynthesis

For that purpose, the derivative **27**, bearing appropriate orthogonal protecting groups on both nitrogens, *i.e.* Boc and SEM substituents, was used. An iodo-butenyl chain was then installed, after Boc removal, on the key intermediate **27** (Scheme 13). The SES protecting group was then removed in order to direct the Heck reaction on the correct position.[17b] Compound **33**, which can be seen as an acetoxy-dehydrotubifoline derivative,[18] was thus formed in a moderate 44% yield and only 9 steps from 2-amino biphenyl.



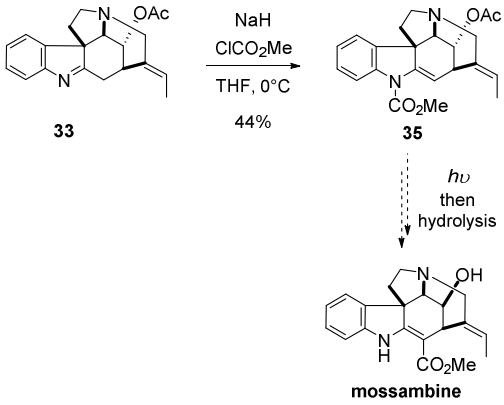
Scheme 13. Synthesis of the mossambine precursor.

To complete the synthesis of mossambine, the installation of a carbomethoxy group was then required. A common and general strategy exploited by many groups,[19] for the elaboration of the *aspidosperma* skeletons relies on the use of a combination of LDA (or *n*-BuLi) and Mander's reagent $NCCO_2Me$,[20] a soft reagent known to favor C- over N-alkylation (Scheme 14).



Scheme 14. Mander's reagent approach to mossambine

Despite extensive efforts to find suitable reaction conditions, including variation of the amount of base and reagent or of the temperature, we were not able to adapt this reaction to the formation of the *strychnos* skeleton. On similar compounds of the *strychnos* family, as for example for the transformation of dehydrotubifoline into akuammicine (Figure 1), Bonjoch, Bosch *et al.* have used the carbomethoxylation of the nitrogen center, followed by a photochemical rearrangement.[21] N-carbomethoxylation of substrate **33** was performed to afford **35**, albeit in moderate yield, but the photochemical rearrangement of the latter never provided the expected rearranged product, probably due to the presence of the acetoxy group (Scheme 15).



Scheme 15. Photochemical rearrangement approach

3. Conclusion

As a summary, our palladium-mediated double oxidative amination reaction constitutes an attractive and straightforward strategy for the functionalization of cyclohexa-2,5-dienes,

leading to the tetracyclic and pentacyclic indoline skeletons of *aspidosperma* and *strychnos* alkaloids. Combined with the enantioselective method developed by Zhu and co-workers,[14] this strategy offers a valuable entry for a rapid access to *aspidosperma* and *strychnos* alkaloids. Finally, we also showed that the allyl-palladium intermediate, formed after the double oxidative amination, could also be trapped in an intramolecular fashion with a third internal sulfonamide to afford the construction of 3 rings and 3 C-N bond in a single step.

4. Experimental

4.1. Materials and apparatus

Commercial reagents were used without purification. DMSO, Acetonitrile, CH_2Cl_2 and $(i\text{-}Pr)_2NH$ were distilled under CaH_2. THF and Et_2O were distilled from sodium and benzophenone. ^1H NMR and ^{13}C NMR were recorded on Brüker AC-250FT (^1H: 250 MHz, ^{13}C: 62.9 MHz), a Brüker Avance-300FT (^1H: 300 MHz, ^{13}C: 75.5 MHz) or a Brüker DPX-400FT (^1H: 400 MHz, ^{13}C: 100.2 MHz) apparatus using $CDCl_3$ as internal reference. Mass spectra were recorded on a Nermag R10-10 C. High resolution mass spectra were recorded on a FT-IRC mass spectrometer Brüker 4.7T BioApex II. InfraRed (IR) spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer. Melting points were not corrected and determined by using a Büchi-Totolli apparatus and Stuart Scientific apparatus (SMP3). Compound 1, 2, 6, 7, 8, 9 have already been described.[8]

4.2. General protocol for amide synthesis

In a two-necked round-bottom flask was introduced $AlCl_3$ (178 mg, 1.33 mmol) in ether (8 mL) at 0°C. A solution of $LiAlH_4$ (1.0M in ether, 1.33 mL, 1.33 mmol) was added dropwise and the mixture was allowed to stirr for 30 min at room temperature. To the solution, was added 9-Ethanesulfonyl-9,9a-dihydro-carbazol-4a-yl)-acetonitrile **6** (400 mg, 1.33 mmol; in 8 mL of ether) dropwise at 0°C and the media was stirred at room temperature for an additional 4h. Water (1 mL) was cautiously added followed by the addition of a 10% aqueous sodium hydroxide solution and the media was stirred for another 30 min. Filtration of the solid residue over celite, washing generously with AcOEt, separation of the two layers, drying of the organic layer over sodium sulfate and evaporation of the solvent gave **7** as an oily product (350 mg, 87%). The product was, in general, sufficiently pure to be used in the next step without further purification. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.31-7.28 (m, 1H), 7.03-7.01 (m, 2H), 6.94-6.91 (m, 1H), 5.88 (m, 2H), 5.78-5.74 (m, 1H), 5.60 (dd, J = 1.6 Hz, 1H), 4.95(d, J = 1.60 Hz), 3.01 (q, J = 7.5 Hz, 2H), 2.68 (m , 2H), 2.95-1.80 (m, 2 H), 1.27 (t, J = 7.50 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 140.4 (C), 137.2 (C), 130.2 (CH), 127.8 (CH), 124.4 (CH), 123.7 (C), 123.7 (CH), 123.5 (CH), 120.5 (CH), 113.9 (CH), 65.59 (CH), 46.8 (C), 46.5 (CH_2), 46.1 (CH_2), 45.4 (CH_2), 37.4 (CH_2), 7.7 (CH_3).

Crude amine **7** (1 eq.) was dissolved in CH_2Cl_2 (0.1M). The carboxylic acid (1.1 eq.), EDAC (1.5 eq.) and HOBt (1.3 eq.) were added to this mixture. Finally the base (DIPEA, 0.16 ml, 3 eq.) was added and the reaction mixture was stirred 30h at room temperature. The reaction was then stopped by addition of $NaHCO_3$ and extracted with EtOAc. The combined organic layers were washed with brine, dried over sodium sulfate, concentrated *in vacuo* and the product purified by silica gel chromatography giving amides **12**-**17**.

*4.2.1. Dimethyl 2-(2-(2-((4aS,9aS)-9-(ethylsulfonyl)-9,9a-dihydro-4aH-carbazol-4a-yl)ethylamino)-2-oxoethyl)malonate (**12**)*

Starting from **7** (100 mg, 0.328 mmol, 1 eq.) and 2-methoxycarbonyl-succinic acid 1-methyl ester, the crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate, 70/30) to give **12** (70 mg, 0.1470 mmol, 45% over 2 steps) as a colorless oil**.** R_f = 0.79 (EtOAc: 100%). IR (film, NaCl): ν= 2951, 1783, 1707, 1596, 1476, 1346, 1235, 1153, 757 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.41-7.02 (m, 5H), 6.03 (d, 1H, J = 3 Hz), 5.94-5.89 (m, 1H), 5.70-5.67 (m, 1H), 5.05 (s, 1H), 3.96 (t, 1H, J = 3 Hz), 3.75 (s, 6H), 3.28 (d, 1H, J = 3.4 Hz), 3.20-3.11 (m, 2H), 2.74-2.71 (m, 2H), 2.06-2.02 (m, 2H), 1.89-1.81 (m, 2H), 1.39 (t, 3H, J = 4.14 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 169.6 (C=O), 169.3 (C=O), 140.7 (C), 136.8 (C), 130.2 (CH), 128.2 (CH), 124.7 CH), 124.1 (CH), 123.5 (CH), 121.3 (CH), 114.3 (CH), 65.4 (CH), 52.9 (CH_3), 47.6 (CH), 46.7 (CH_2), 45.9 (CH), 41.7 (CH_2), 35.7 (CH_2), 34.8 (CH_2), 7.8 (CH_3). MS (ESI) *m/z* (%):499 $[M+Na]^+$ (100), 477 $[M+H]^+$ (18). HRMS (ESI): $[M+Na]^+$ $C_{23}H_{28}N_2O_7NaS$: calcd. 499.1520, found 499.1520.

*4.2.2. N-(2-((4aS,9aS)-9-(ethylsulfonyl)-9,9a-dihydro-4aH-carbazol-4a-yl)ethyl)-3,4,5-trimethoxybenzamide. (**13**)*

Starting from **7** (100 mg, 0.328 mmol, 1 eq.) and 3,4-dimethoxy-benzoic acid, the crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate, 70/30 then 50/50) to give **13** (75 mg, 0.15 mmol, 46% over 2 steps) as a white solid. M.p. = 74.2-75.9°C. R_f = 0.86 (petroleum ether/ethyl acetate: 50/50). IR (solid, KBr): ν = 2924, 1638, 1583, 1498, 1338, 1234, 1127, 697 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.32 (d, 1H, J = 7.9 Hz), 7.07-7.04 (m, 2H), 6.96-6.87 (m, 3H), 6.27 (t, 1H, J = 3 Hz), 5.97-5.96 (m, 2H), 5.90- 5.84 (s, 1H), 5.69 (d, 1H, J = 9.4 Hz), 5.09 (d, 1H, J = 3 Hz), 3.81 (s, 9H), 3.49-3.35 (m, 2H), 3.12 (q, 2H, J = 7.1 Hz), 2.11-1.95 (m, 2H), 1.33 (t, 3H, J=7.5 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 167.2 (C), 153.1 (C), 140.5 (CH), 136.8 (CH), 130.4 (C), 129.7 (CH), 128.1 (CH), 124.7 (CH), 123.8 (CH), 123.8 (CH), 123.5 (CH), 121.2 (CH), 114.2 (CH), 104.2 (CH), 65.3 (CH), 60.9 (CH_3), 56.2 (CH_3), 46.7 (CH), 46.3 (CH_2), 41.5 (CH_2), 36.1 (CH_2), 7.8 (CH_3). MS (ESI) *m/z* (%):521 $[M+Na]^+$ (100), 499 $[M+H]^+$ (45). HRMS (ESI): $[M+Na]^+$ $C_{26}H_{30}N_2O_6NaS$: calcd. 521.1716, found 521.1721.

*4.2.3. N-(2-((4aS,9aS)-9-(ethylsulfonyl)-9,9a-dihydro-4aH-carbazol-4a-yl)ethyl)furan-3-carboxamide. (**14**)*

Starting from **7** (100 mg, 0.328 mmol, 1 eq.) and furan-2-carboxylic acid, the crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate, 70/30 then 50/50) to give **14** (174 mg, 0.4370 mmol, 53% over 2 steps) as a white solid. M.p. = 52.2-54.5 °C. R_f = 0.48 (petroleum ether/ethyl acetate: 50/50). IR (solid, KBr): ν = 3370, 2928, 1651, 1528, 1476, 1343, 1170, 1009, 722, 697 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) = .43-7.42 (m, 2H), 7.27-7.15 (m, 2H), 7.09-7.02 (m, 2H), 6.52-6.48 (m, 2H), 6.07-6.06 (s, 2H), 5.97-5.94 (m, 1H), 5.74 (d, 1H, J = 9.4 Hz), 5.10 (s, 1H), 3.50 (q, 2H, J = 7.1 Hz), 3.22-3.12 (m, 2H), 2.23-1.95 (m, 2H), 1.42 (t, 3H, J =7.5 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 158.4 (C), 147.8 (C), 143.9 (CH), 140.7 (C), 136.7 (C), 130.2 (CH), 128.2 (CH), 124.7 (CH), 123.9 (CH), 123.9 (CH), 123.5 (CH), 121.3 (CH), 114.2 (CH), 114.1 (CH), 112.1 (CH), 65.4 (CH), 46.7 (C), 45.8 (CH_2), 41.8 (CH_2), 35.1 (CH_2), 7.8 (CH_3). MS (ESI) *m/z* (%):399 $[M+H]^+$ (100), 421 $[M+Na]^+$ (54). HRMS (ESI): $[M+H]^+$ $C_{21}H_{23}N_2O_4S$: calcd. 399.1373, found 399.1380.

*4.2.4. N-(2-((4aS,9aS)-9-(ethylsulfonyl)-9,9a-dihydro-4aH-carbazol-4a-yl)ethyl)-1H-indole-3-carboxamide. (**15**)*

Starting from **7** (100 mg, 0.328 mmol, 1 eq.) and 1H-indole-3-carboxylic acid, the crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate, 70/30 then 50/50) to give **15** (105 mg, 0.2348 mmol, 48% over 2 steps) as a white solid. M.p = 126.6-127.7 °C. R_f = 0.65 (petroleum ether/ethyl acetate: 50/50). IR (solid, KBr): ν = 3401, 1618, 1542, 1457, 1339, 1150, 1009, 749 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 9.77 (s, 1H), 7.94-7.91 (m, 1H), 7.62 (s, 1H), 7.29-7.25 (m, 2H), 7.09-7.01 (m, 3H), 6.88-6.86 (m, 2H), 6.46-6.42 (t, 1H, *J* = 5.3 Hz), 5.84-5.83 (m, 2H), 5.74-5.70 (m, 1H), 5.50 (d, 1H, *J* = 9.4 Hz), 5.04-5.03 (s, 1H), 3.34-3.32 (m, 2H), 3.10-2.97 (m, 2H), 2.03-1.79 (m, 2H), 1.21 (t, 3H, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 166.1 (C), 140.4 (C), 137.1 (C), 136.5 (C), 130.2 (CH), 128.1 (CH), 127.9 (CH), 125.1 (C), 124.7 (CH), 124.1 (CH), 123.8 (CH), 123.6 (CH), 122.8 (CH), 121.5 (CH), 121.1 (CH), 120.2 (CH), 114.2 (CH), 112.2 (CH), 111.5 (C), 65.5 (CH), 46.8 (C), 45.8 (CH_2), 42.2 (CH_2), 35.4 (CH_2), 7.7 (CH_3). MS (ESI) *m/z* (%): 470 $[M+Na]^+$ (100), 448 $[M+H]^+$ (50). HRMS (ESI): $[M+Na]^+$ $C_{25}H_{25}N_3O_3NaS$: calcd. 470.1662, found 470.1662.

*4.2.5. N-(2-((4aS,9aS)-9-(ethylsulfonyl)-9,9a-dihydro-4aH-carbazol-4a-yl)ethyl)-2-(4-methylphenylsulfonamido)acetamide (**16**)*

Starting from **7** (100 mg, 0.328 mmol, 1 eq.) and (toluene-4-sulfonylamino)-acetic acid, the crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate, 80/20 then 50/50) afforded **16** (349 mg, 0.6774 mmol, 82 % over 2 steps) as a white solid. M.p. = 143.4-144.0°C. R_f = 0.48 (petroleum ether/ethyl acetate: 50/50). IR (solid, KBr): ν = 2284, 1658, 1458, 1339, 1152, 763 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.92-7.89 (m, 2H), 7.70 (d, 2H, *J*= 8.1 Hz), 7.39-7.32 (m, 4H), 7.24 (t, 1H, *J*= 6.8 Hz), 7.11 (t, 1H, *J*= 14.8 Hz), 6.06-6.01 (m, 1H), 5.96-5.85 (m, 3H), 5.10 (d, 1H, *J*= 3.4 Hz), 3.36 (d, 2H, *J*= 7.1 Hz), 3.24-3.12 (m, 2H, CH_2), 3.09-2.53 (m, 2H), 2.34 (s, 3H), 2.01-1.91 (m), 1.70-1.60 (m), 1.27 (t, 3H, *J*= 7.3 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 162.1 (C), 140.6 (C), 139.8 (CH), 138.7 (C), 136.6 (C), 134.4 (C), 133.9 (CH), 130.1 (CH), 129.7 (CH), 128.3 (C), 128.2 (CH), 124.8 (C), 124.1 (CH), 123.9 (CH), 123.6 (C), 121.5 (CH), 114.3 (C), 65.4 (CH), 46.7 (C), 46.3 (CH_2), 41.2 (CH_2), 36.1 (CH_2), 7.9 (CH_3). MS (ESI) *m/z* (%): 538 $[M+Na]^+$ (100), 615 $[M+H]^+$ (56). HRMS (ESI): $[M+Na]^+$ $C_{25}H_{29}N_3O_5NaS_2$: calcd. 538.1446, found 538.1452.

*4.2.6. (E)-N-(2-((4aS,9aS)-9-(ethylsulfonyl)-9,9a-dihydro-4aH-carbazol-4a-yl)ethyl)-3-(phenylsulfonyl)acrylamide (**17**)*

Starting from **7** (100 mg, 0.328 mmol, 1 eq.) and 3,3-bis-benzenesulfonyl-propionic acid, the crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate, 80/20 then 50/50) to give **17** (195 mg, 0.3915 mmol, 54 % over 2 steps) as a white solid. M.p. = 147.1-148.9°C. R_f = 0.48 (petroleum ether/ethyl acetate: 50/50). IR (solid, KBr): ν = 3231, 1671, 1476, 1343, 1148, 656 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.55 (d, 2H, *J*= 7.5 Hz), 7.33-7.30 (m), 7.25-7.20 (m, 2H), 7.04 (d, 1H, *J*= 8.1 Hz), 6.94-6.82 (m, 2H), 6.80 (t, 1H, *J*= 8.1 Hz), 6.71-6.67 (m), 6.64-6.58 (m), 6.33 (t, 1H, *J*= 5.4 Hz), 5.66-5.58 (m, 2H), 5.55-5.53 (m), 5.33 (d, 1H, *J*= 9.6 Hz), 4.69 (d, 1H, *J*= 2.6 Hz), 3.06-2.97 (m, 2H), 2.84-2.72 (m, 2), 1.83-1.69 (m, 1H), 1.58-1.49 (m, 1H), 1.05 (t, 3H, *J*= 7.3 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 162.1 (C), 140.6 (C), 139.8 (CH), 138.7 (C), 136.6 (C), 134.4 (C), 133.9 (CH), 130.1 (CH), 129.7 (CH), 128.3 (C), 128.2 (2 CH), 124.8 (C), 124.1 (CH), 123.9 (CH), 123.6 (C), 121.5 (CH), 114.3 (C), 65.4 (CH), 46.7 (C), 46.3 (CH_2), 41.2 (CH_2), 36.1 (CH_2), 7.9 (CH_3). MS (ESI) *m/z* (%):521 $[M+Na]^+$ (100), 499 $[M+H]^+$ (11). HRMS (ESI): $[M+Na]^+$ $C_{25}H_{26}N_2O_5NaS_2$: calcd. 521.1175, found 521.1192.

4.3. Other amide precursors

*4.3.1. 4-methyl-N-(2-((4aS,9aS)-9-(2-(trimethylsilyl)ethylsulfonyl)-9,9a-dihydro-4aH-carbazol-4a-yl)ethylcarbamoyl)benzenesulfonamide (**22**)*

In a 100 ml two-necked round bottom flask, $AlCl_3$ (1.142 g, 8.56 mmol, 3 eq.) was dissolved in Et_2O (12 mL) at 0°C, then $LiAlH_4$ (433 mg, 11.42 mmol, 4 eq.) was added. The reaction mixture was then stirred at room temperature for 30 min. Nitrile **21** (1.062 g, 2.855 mmol, 1 eq.) was dissolved in Et_2O (3 mL) and THF (3 mL), and added dropwise at 0°C. The reaction mixture was stirred at room temperature for 18h then the reaction stopped by addition of ice then NaOH 10% (40 mL) was added and the reaction mixture was stirred for 1h. Ether was added. The reaction mixture was filtered through celite and extracted with DCM. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated *in vacuum* affording the amine as a yellow oil. To a solution of the crude amine (703 mg, 1.869 mmol, 1 eq.) in CH_2Cl_2 (20 mL) at 0°C was added the *p*-toluene sulfonyl isocyanate (368 mg, 1.869 mmol, 1 eq.). The reaction was warmed to r.t. and stirred while monitoring the consumption of the amine by TLC (2-16h). The reaction mixture was evaporated directly without extraction. Purification by silica gel chromatography (petroleum ether/ethyl acetate, 70/30) afforded **22** (786 mg, 1.371 mmol, 73% over 2 steps) as a white solid. M.p. = 86.8-88.1°C. R_f = 0.58 (petroleum ether/ ethyl acetate: 70/30). IR (solid, KBr): ν = 3353, 2950, 1672, 1547, 1345, 1250, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.75 (broad s, 1H), 7.77 (d, 2H, *J* = 8.3 Hz), 7.38 (d, 1H, *J* = 8.1 Hz), 7.30-7.16 (m, 2H), 7.14-7.09 (m, 2H), 7.02-6.97 (m, 1H), 6.54-6.52 (m, 1H), 6.03(d, 2H, *J* = 3.4 Hz), 5.93-5.87 (m, 1H), 5.65 (d, 1H, *J* = 9.6 Hz), 5.00 (s, 1H), 3.28-3.20 (m, 2H), 3.08-2.99 (m, 2H), 2.40 (s, 3H), 2.12-2.02 (m, 1H), 1.87-1.77 (m, 1H), 1.08-0.99 (m, 2H), -0.01 (s, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 151.9 (C), 144.9 (C), 141.2 (C), 136.8 (C), 136.2 (C), 130.4 (CH), 130.1 (CH), 128.3 (CH), 127.1 (CH), 125.3 (CH), 123.7 (CH,), 123.6 (CH), 123.3 (CH), 121.4 (CH), 114.1 (CH), 65.2 (CH), 49.2 (C), 46.6 (CH_2,), 41.4 (CH_2), 36.2 (CH_2), 21.8 (CH_3), 9.9 (CH_2), -1.9 (CH_3). MS (ESI) *m/z* (%): 596 $[M+Na]^+$ (100). HRMS (ESI): $[M+Na]^+$ $C_{27}H_{35}N_3O_5NaSiS_2$: calcd. 596.1679, found 596.1683.

*4.3.2. N-(2-(1-(2-(ethylsulfonamido)phenyl)cyclohexa-2,5-dienyl)ethylcarbamoyl)-4-methylbenzenesulfonamide (**24**)*

In a 100 ml two-necked round bottom flask, $AlCl_3$ (966 mg, 7.25 mmol, 3 eq.) was dissolved in Et_2O (20 mL) at 0°C, then $LiAlH_4$ (365 mg, 9.64 mmol, 4 eq.) was added. The reaction mixture was stirred at room temperature for 30 min. Product **5** (700 mg, 2.41 mmol, 1 eq.) was dissolved in Et_2O (5 mL) and THF (5 mL), and added dropwise at 0°C. The reaction mixture was stirred at room temperature for 18h, then the reaction was stopped by addition of ice. NaOH 10% (40 mL) was then added and the reaction mixture stirred for 1h. After addition of ether the reaction mixture was filtered through celite and extracted with DCM. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated in vacuum, affording the intermediate amine as a viscous oil. To a solution of crude amine (1 eq.) in DCM (0.1M) at 0°C was added the *p*-toluene sulfonyl isocyanate (1 eq.). The reaction was warmed to r.t. and

stirred while monitoring the consumption of the amine by TLC (2-16h). The reaction mixture was evaporated directly without extraction. Purification by silica gel chromatography (petroleum ether/ ethyl acetate, 70/30) afforded **24** (376 mg, 0.747 mmol, 70% over 2 steps) as a white solid. M.p. = 92.1-93.4°C. R_f = 0.26 (petroleum ether/ethyl acetate: 70/30). IR (solid, KBr): ν = 3347, 1672, 1453, 1335, 1148, 1090, 887 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.48 (broad s, 1H), 7.45 (d, 2H, *J* = 8.3 Hz), 7.23 (d, 1H, *J* = 7.9 Hz), 7.02-6.90 (m, 5H), 6.35 (t, 1H, *J*= 5.7 Hz), 5.77 (d, 2H, *J* = 10.2 Hz), 5.15 (d, 2H, *J* = 10.2 Hz), 3.01-2.93 (m, 2H), 2.81 (q, 2H, *J* = 7.3 Hz), 2.65 (AB_{system}, 2H, J_{AB} = 8.3 Hz), 2.08 (s, 3H), 1.75-1.70 (m, 2H), 0.99 (t, 3H, *J* = 7.3 Hz,). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 151.9 (C), 144.9 (C), 137.6 (C), 136.8 (C), 132.4 (C), 130.1 (CH), 130.1 (CH), 128.6 (CH), 126.9 (CH), 126.8 (CH), 126.2 (CH), 123.9 (CH), 119.3 (CH), 46.5 (CH_2), 41.7 (C), 38.8 (CH_2), 36.7 (CH_2), 25.8 (CH_2), 21.7 (CH_3), 8.1 (CH_3). MS (ESI) *m/z* (%): 526 $[M+Na]^+$ (100), 504 $[M+H]^+$ (6). HRMS (ESI): $[M+Na]^+$ $C_{24}H_{29}N_3O_5NaS_2$: calcd. 526.1440, found 526.1450.

*4.3.3. Tert-butyl 2-(1-(2-(2-(trimethylsilyl)ethylsulfonamido)phenyl)cyclohexa-2,5-dienyl)ethylcarbamate (**26**)*

To a solution of the amine[5a] (380 mg, 1.005 mmol, 1 eq.) in THF (10 mL), was added (*t*-Boc)$_2$O (263 mg, 1.206 mmol, 1.2 eq.). The resulting solution was refluxed at 80°C for 12 h. The reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. Purification by silica gel chromatography (petroleum ether/ ethyl acetate, 80:20) afforded **26** (275 mg, 0.5750 mmol, 57% over 2 steps) as a white solid. M.p. = 58.3-60.5°C. R_f = 0.51 (petroleum ether/ ethyl acetate: 80/20). IR (solid, KBr): ν = 3350, 2954, 1713, 1495, 1336, 1251, 1147, 861, 757 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.58-7.55 (m, 1H), 7.42-7.39 (m, 1H), 7.30-7.25 (m, 1H), 7.15-7.12 (m, 1H), 6.12 (d, 2H, *J* = 9.4 Hz), 5.55 (d, 2H, *J* = 9.78 Hz), 4.70 (broad s, 2H), 3.22- 3.20 (m, 2H), 3.07-3.01 (m, 2H), 2.94-2.80 (m, 2H), 2.14-2.09 (m, 2H), 1.47 (s, 9H) 1.04-0.98 (m, 2H), 0.00 (s, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 158.1 (C), 139.8 (C), 134.7 (C), 132.4 (CH), 130.4 (CH), 128.5 (CH), 128.3 (CH), 125.9 (CH), 121.4 (CH), 81.4 (C), 50.5 (CH_2), 43.7 (C), 41.3 (CH_2), 38.9 (CH_2), 30.5 (CH_3), 27.8 (CH_2), 12.1 (CH_2), 0.0 (CH_3). MS (ESI) *m/z* (%):501 $[M+Na]^+$ (100), 479 $[M+H]^+$ (46), 379 $[(M+H)-Boc]^+$ (73). HRMS (ESI): $[M+Na]^+$ $C_{24}H_{38}N_2O_4NaSSi$: calcd. 501.2361, found 501.2361.

4.4. General procedure for palladium oxidative amination

Starting material (1 eq.) and sodium acetate (2 eq.) were dissolved in DMSO (0.1M) and the solution was flushed with dioxygen. $Pd(OAc)_2$ (0.1 eq.) and charcoal (approx. same mass as $Pd(OAc)_2$) were added and the resulting solution was stirred for 24h at 55-90°C. The reaction mixture was diluted with a large volume of water and was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure before purification by silica gel chromatography.

*4.4.1. (3aR,4R,6aS,11a1R)-7-(ethylsulfonyl)-3-((E)-3-(phenylsulfonyl)acryloyl)-2,3,3a,4,6a,7-hexahydro-1H-pyrrolo[2,3-d]carbazol-4-yl acetate (**18**)*

Starting from **17** (169 mg, 0.338 mmol, 1 eq.), the reaction was run 24h at 55°C. The crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate, 80:20) to give **18** (49 mg, 0.0881 mmol, 26%) as an oily product. R_f = 0.48 (petroleum ether/ ethyl acetate: 80/20). IR (solid, KBr): ν = 2981, 1739, 1648, 1420, 1348, 1151, 671 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.69-7.64 (m, 2H), 7.57-7.52 (m, 1H), 7.44-7.38 (m, 2H), 7.33-7.26 (m, 3H), 7.03 (t, 1H, *J* = 7.5 Hz), 6.80 (d, 1H, *J* = 7.7 Hz), 6.34 (d, 1H, *J* = 10.3 Hz), 5.84 (d, 1H, *J* = 7.7 Hz), 3.30 (d, 1H, *J* = 10.3 Hz), 5.22 (d, 1H, *J* = 8.6 Hz), 4.65 (s, 1H), 4.11-4.01 (m, 1H), 3.94 (d, 1H, *J* = 9.03 Hz), 3.75-3.68 (m, 1H), 3.16 (q, 2H, *J* = 7.3 Hz), 2.40-2.20 (m, 2H), 2.08 (s, 3H), 1.42 (t, 3H, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 170.3 (C), 161.9 (C), 141.6 (CH), 140.2 (C), 138.8 (C), 135.2 (C), 134.4 (C), 131.1 (CH), 129.9 (CH), 129.7 (CH), 128.3 (CH), 128.2 (CH), 127.7 (C) 125.1 (CH), 123.1 (C), 114.7 (CH), 70.1 (CH), 65.1 (CH), 64.1 (CH), 52.1 (C), 44.8 (CH_2), 43.8 (CH_2), 36.3 (CH_2), 21.1 (CH_3), 7.8 (CH_3). MS (ESI) *m/z* (%): 579 $[M+Na]^+$ (100). HRMS (ESI): $[M+Na]^+$ $C_{27}H_{28}N_2O_7NaS_2$: calcd. 579.1230, found 579.1244.

*4.4.2. 2-((4aS,9aS)-9-(2-(trimethylsilyl)ethylsulfonyl)-9,9a-dihydro-4aH-carbazol-4a-yl)acetonitrile (**21**)*

Starting from **20**[5a] (1.8 g, 4.813 mmol, 1 eq.), the reaction was run 24h at 55°C. The crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate: 80/20) to give **21** (1.40 g, 3.762 mmol, 78%) as a white solid. M.p. = 92.4-93.3°C. R_f = 0.16 (petroleum ether/ethyl acetate: 90/10). IR (solid, KBr): ν = 2958, 1595, 1478, 1342, 1250, 1152, 984, 838, 738, 650 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.42-7.39 (m, 1H), 7.25-7.20 (m, 2H), 7.08-7.04 (m, 1H), 6.07 (s, 2H), 6.01-5.97 (m, 1H), 5.74 (d, 1H, *J* = 9.4 Hz), 5.00 (s, 1H), 3.17-2.97 (m, 2H), 2.82 (AB_{system}, 2H, J_{AB} = 25.59 Hz), 1.11-1.04 (m, 2H), 0.0002 (s, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 141.5 (C), 133.2 (C), 129.3 (CH), 127.7 (CH), 124.4 (CH), 124.2 (CH), 123.6 (CH), 123.6 (CH), 122.6 (CH), 116.4 (C), 114.3 (CH), 65.4 (CH), 48.2 (C), 45.6 (CH_2), 29.4 (CH_2), 9.7 (CH_2), -1.9 (CH_3). MS (ESI) m/z (%): 395 $[M+Na]^+$ (100). HRMS (ESI): $[M+Na]^+$ $C_{19}H_{24}N_2O_2NaSiS$: calcd. 395.1219, found 395.1224.

*4.4.3. Product (**23**)*

Starting from **22** (152 mg, 0.264 mmol, 1 eq.), the reaction was run 24h at 55°C. The crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate, 90/10), affording **23** (80 mg, 0.140 mmol, 53%) as a white solid. M.p. = 239.3-241.1°C. R_f = 0.63 (petroleum ether/ ethyl acetate: 80/20). IR (solid, KBr): ν = 2924, 1737, 1478, 1348, 1164, 840, 663 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.98 (d, 2H, *J* = 8.3 Hz), 7.29 (m, 4H), 7.10-7.09 (m, 1H), 7.08-7.06 (m, 1H), 6.10-5.97 (m, 2H), 4.92-4.88 (m, 1H), 4.61 (d, 1H, *J* = 8.3 Hz), 4.40 (s, 1H), 3.51-3.37 (m, 2H), 3.11-3.05 (m, 2H), 2.47-2.41 (m, 1H), 2.40 (s, 3H), 2.23-1.11 (m, 1H), 1.10-1.04 (m, 2H), 0.02 (s, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 151.7 (C), 144.8 (C), 140.5 (C), 136.6 (C), 131.7 (C), 130.3 (CH), 129.7 (CH), 129.6 (CH), 128.2 (CH), 124.5 (CH), 124.3 (CH,), 122.9 (CH), 114.8 (CH), 62.7 (CH), 57.4 (CH), 52.1 (CH), 50.2 (C), 49.6 (CH_2), 42.8 (CH_2), 41.9 (CH_2), 21.8 (CH_3), 10.3 (CH_2), -1.9 (CH_3). MS (ESI) *m/z* (%): 594 $[M+Na]^+$ (100), 572 $[M+H]^+$ (8). HRMS (ESI): $[M+Na]^+$ $C_{27}H_{35}N_3O_5NaSiS_2$: calcd. 594.1523, found 594.1546.

*4.4.4. Product (**25**)*

Starting from **24** (150 mg, 0.298 mmol, 1 eq.), the reaction was run 24h at 55°C. The crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate, 90/10), affording **25** (107 mg, 0.214 mmol, 72%) as a white solid. M.p. = 217.7-219.1°C. R_f = 0.48 (petroleum ether/ ethyl acetate: 50/50). IR (solid, KBr): ν = 2972, 1734, 1478, 1384, 1154, 763, 663 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.87 (d, 2H, *J* = 8.3 Hz), 7.28-7.18 (m, 4H), 7.15-7.10 (m, 1H), 7.04 (t, 1H, *J* = 7.3 Hz), 6.01 (t, 2H, *J* = 14.3 Hz), 4.84-4.81 (m, 1H), 4.55 (d, 1H, *J* = 8.3 Hz), 4.33 (s, 1H), 3.43-3.29 (m, 2H), 3.16 (q, 2H, *J* = 7.4

Hz), 2.40-2.38 (m, 1H), 2.35 (s, 3H), 2.21-2.10 (m, 1H), 1.36 (t, 3H, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 151.6 (C), 144.8 (C), 140.2 (C), 136.7 (C), 131.7 (C), 130.4 (CH), 129.7 (CH), 129.6 (CH), 128.2 (CH), 124.5 (CH), 124.3 (CH), 123.1 (CH), 114.8 (CH), 62.7 (CH), 57.5 (CH), 52.1 (CH), 50.1 (C), 47.2 (CH_2), 43.1 (CH_2), 41.8 (CH_2), 21.7 (CH_3), 8.2 (CH_3). MS (ESI) *m/z* (%): 522 $[M+Na]^+$ (100), 500 $[M+H]^+$ (10). HRMS (ESI): $[M+Na]^+$ $C_{24}H_{25}N_3O_5NaS_2$: calcd. 522.1127, found 522.1144.

*4.4.5. (3aR,4R,6aS,11a1R)-tert-butyl 4-acetoxy-7-(2-(trimethylsilyl)ethylsulfonyl)-3a,4,6a,7-tetrahydro-1H-pyrrolo[2,3-d]carbazole-3(2H)-carboxylate (**27**)*

Starting from **26** (1.070 g, 2.248 mmol, 1 eq.), the reaction was run 24h at 55°C. The crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate 90:10) to give **27** (0.880 mg, 1.647 mmol, 72%) as a colorless oil. R_f = 0.41 (petroleum ether/ ethyl acetate: 80/20). IR (film, NaCl): ν = 3354, 2814, 1668, 1478, 1171, 1055, 844, 766 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.32-7.22 (m, 2H), 7.05-6.99 (m, 2H), 6.27-6.16 (m, 1H), 6.10-6.04 (m, 1H), 5.52 (s, 1H), 4.61 (s, 1H), 4.21 (s, 1H), 3.63 (broad s, 2H), 3.03-2.97 (m, 2H), 2.16-2.07 (m, 2H), 1.62 (s, 3H), 1.50 (s, 9H), 1.06-1.01 (m, 2H), 0.00 (s, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 169.8 (C), 154.4 (C), 154.1 (C), 141.4 (CH), 137.9 (C), 137.3 (C), 128.8 (CH), 123.9 (CH), 122.3 (C), 113.7 (CH), 80.4 (C), 68.7 (CH), 67.5 (CH), 60.1 (CH), 53.7 (C), 47.8 (CH_2), 43.8 (CH_2), 40.3 (CH_2), 28.5 (CH_3), 20.30 (CH_3), 9.9 (CH_2), -2.0 (CH_3). MS (ESI) m/z (%): 557 $[M+Na]^+$(100). HRMS (ESI): $[M+Na]^+$ $C_{26}H_{38}N_2O_6$ NaSSi: calcd.557.2112, found 557.2108.

4.5. Synthesis of strychnos skeleton

*4.5.1. (3aR,4R,6aS,11a1S)-tert-butyl 4-acetoxy-7-((Z)-3-bromoacryloyl)-3a,4,6a,7-tetrahydro-1H-pyrrolo[2,3-d]carbazole-3(2H)-carboxylate (**28**)*

3-bromoacryloyl chloride (206 mg, 1.216 mmol, 1.5 eq) was added to the crude amine (300 mg, 0.810 mmol, 1 eq) in CH_2Cl_2 (10 mL), then triethylamine (1.5 eq), EDAC (1.5 eq) was added to this mixture. The reaction mixture was stirred for 6h at room temperature. Then the reaction was stopped by addition of H_2O (20 mL), extracted with EtOAc. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The crude reaction mixture was purified by silica gel chromatography (petroleum ether/ethyl acetate 70:30) to provide **28** (162 mg, 0.3226 mmol, 40%) as a yellow solid. M.p. = 92.9-94.6°C. R_f = 0.41 (petroleum ether/ethyl acetate: 80/20). IR (solid, KBr): 2976, 1739, 1696, 1480, 1391, 1239, 1170, 932, 753, 659 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.72 (d, 1H, J = 9.6 Hz), 7.28-7.24 (m, 2H), 7.10-7.02 (m, 3H), 5.92 (s, 2H), 5.50 (s, 1H), 4.72 (s, 1H), 4.06 (s, 1H), 3.76 (s, 1H), 3.50 (s, 1H), 2.16 (s, 2H), 1.94 (s, 3H), 1.48 (s, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 170.5 (C), 161.8 (C), 155.2 (C), 140.22 (C), 136.5 (C), 129.4 (CH), 128.9 (CH), 128.6 (C), 126.6 (C), 125.4 (CH), 122.9 (CH), 80.6 (C), 69.03 (CH), 64.02 (CH), 63.3 (CH), 52.1 (C), 45.03 (CH_2), 38.7 (CH_2), 28.6 (CH_3), 21.1 (CH_3). HRMS (ESI): $[M+Na]^+$ $C_{24}H_{27}N_2O_5$ Br Na: calcd. 525.1001, found 525.0997.

*4.5.2. (3aR,4R,6aS,11a1R)-3-((Z)-2-iodobut-2-enyl)-7-(2-(trimethylsilyl)ethylsulfonyl)-2,3,3a,4,6a,7-hexahydro-1H-pyrrolo[2,3-d]carbazol-4-yl acetate (**31**)*

To a solution of crude **30** (160 mg, 0.37 mmol, 1 eq.) in CH_3CN (6 mL) were added anhydrous K_2CO_3 (110 mg, 0.74 mmol, 2 eq.) and (*Z*)-1-bromo-2-iodo-2-butene (193 mg, 0.74 mmol, 2 eq.). The mixture was stirred at r.t. for 3 h. The solvent was removed *under vacuum*, and the residue was partitioned between H_2O and CH_2Cl_2. The dried organic extracts were concentrated under vacuum. Purification by silica gel chromatography (Hexane/ethyl acetate: 8/2) afforded **31** (164 mg, 0.267 mmol, 72% over 2 steps) as a white solid. M.p. = 134.3-135.6°C. R_f = 0.65 (petroleum ether/ ethyl acetate: 80/20). IR (solid, KBr): ν = 2950, 1731, 1476, 1340, 1232, 1100, 970, 840, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.33-7.25 (m, 1H), 7.16-7.11 (m, 1H), 7.05-7.00 m, 1H), 6.08-6.04 (m, 1H), 5.90 (q, 1H, J = 6.03 Hz), 5.81-5.76 (m, 1H), 5.23 (s, 1H), 4.59 (s, 1H), 3.93 (AB $_{system}$, 2H, J_{AB} = 140.1 Hz), 3.29 (d, 1H, J = 3.8 Hz), 3.20-3.12 (m, 1H), 3.09-3.02 (m, 2H), 2.69-2.61 (m, 1H), 2.10-1.91 (m, 2H), 1.85 (s, 3H), 1.77 (d, 3H, J = 6.4 Hz), 1.10-1.04 (m, 2H), 0.00 (s, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 170.4 (C), 140.1 (C), 135.8 (C), 130.9 (CH), 130.2 (CH), 128.6 (CH), 125.7 (CH), 123.8 (CH), 123.6 (CH), 114.3 (CH), 109.4 (C), 67.9 (CH), 66.5 (CH), 66.4 (CH_2), 66.1 (CH), 51.4 (C), 50.1 (CH_2), 48.4 (CH_2), 40.1 (CH_2), 21.6 (CH_3,, 20.9 (CH_3) 10.1 (CH_2), -1.9 (CH_3). MS (ESI) m/z (%):615 $[M+H]^+$ (100), 637 $[M+Na]^+$ (70). HRMS (ESI): $[M+H]^+$ $C_{25}H_{36}IN_2O_4SSi$: calcd. 615.1209, found 615.1216.

*4.5.3. (3aR,4R,6aS,11a1S)-3-((Z)-2-iodobut-2-enyl)-2,3,3a,4,6a,7-hexahydro-1H-pyrrolo[2,3-d]carbazol-4-yl acetate. (**32**)*

CsF (1.854 g, 13.9 mmol, 15 eq.) was added to a solution of product **31** (0.5 g, 0.814 mmol, 1 eq.) in CH_3CN (40 mL). The resulting suspension was heated at 80°C for 30h. After cooling to r.t., the solvent was removed *under vacuum.* Purification by silica gel chromatography (deactivated silica gel, DCM/methanol: 95/5) afforded **32** (214 mg, 0.475 mmol, 58%) as a brown oil. R_f = 0.26 (petroleum ether/ ethyl acetate: 80/20). IR (film, NaCl): ν = 3368, 1731, 1606, 1484, 1369, 1238, 1022, 969, 743 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.10-7.06 (m, 2H), 6.77 (t, 1H, J = 7.5 Hz), 6.68 (d, 1H, J = 7.8 Hz), 5.97 (q, 1H, J = 6.4 Hz), 5.79-5.70 (m, 2H), 5.30 (s, 1H), 4.01 (s, 1H), 3.95 (d, 1H, J = 14.3 Hz), 3.89 (s, 1H), 3.51 (d, 1H, J= 14.3 Hz), 3.23 (d, 1H, J = 4.1 Hz), 3.14-3.07 (m, 1H), 2.72-2.64 (m, 1H), 2.16-2.07 (m, 2H), 1.96 (s, 3H), 1.82 (d, 3H, J= 6.4 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 170.8 (C), 148.7 (C), 133.9 (C), 131.52 (CH), 130.6 (CH), 128.05 (CH), 125.5 (CH), 123.7 (CH), 119 (CH) 110.2 (C), 109.9 (CH), 69.7 (CH), 67.1 (CH), 66.7 (CH_2), 62.1 (CH), 52.7 (C), 50.3 (CH_2), 38.7 (CH_2), 21.7 (CH_3), 21.3 (CH_3). MS (ESI) m/z (%):451 $[M+H]^+$ (100), 473 $[M+Na]^+$ (12), 391 $[(M+H)-OAc]^+$ (11). HRMS (ESI): $[M+H]^+$ $C_{20}H_{24}IN_2O_2$: calcd. 451.0877, found 451.0882.

*4.5.4. Product (**33**)*

A solution of **32** (190 mg, 0.422 mmol, 1 eq.), $Pd(OAc)_2$ (9 mg, 0.0411 mmol, 0.1 eq.), K_2CO_3 (284 mg, 2.055 mmol, 5 eq.) and Bu_4NCl (1165 mg, 0.419 mmol, 1 eq.) in DMF (4 mL) was warmed at 60°C for 3 h. After cooling to room temperature, Et_2O was added and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. Purification by silica gel chromatography (Diethyl ether/triethylamine: 98/2) afforded **33** (60 mg, 0.186 mmol, 44%) as a yellow solid. R_f = 0.48 (Diethyl ether /triethylamine: 95/5). M.p. = 104.7-105.9°C. IR (solid, KBr): ν = 3368, 1731, 1606, 1484, 1369, 1238, 1022, 969, 743 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.55 (d, 1H, J = 7.9 Hz), 7.32-7.28 (m, 2H), 7.20-7.15 (m, 1H), 5.49 (q, 1H, J = 6.8 Hz), 5.09 (t, 1H, J = 3.4 Hz), 4.17 (d, 1H, J = 2.6 Hz), 3.80 (d, 1H, J = 15.5 Hz), 3.43 (s, 1H), 3.39-3.19 (m, 4H), 2.81 (d, 1H, J = 13.5 Hz), 2.26-2.17 (m, 1H), 2.12-2.03 (m, 1H), 1.69 (d, 3H, J = 6.8 Hz), 1.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 187.2 (C), 169.5 (C), 154.5 (C), 144.2 (C), 139.4 (C), 127.4 (CH), 124.9 (CH), 120.9 (CH), 120.6 (CH), 119.6 (CH) 69.2 (CH), 67.2 (CH), 63.2 (C), 55.2 (CH_2), 52.9

(CH_2), 35.9 (CH_2), 34.1 (CH), 33.4 (CH_2), 19.8 (CH_3), 12.8 (CH_3). MS (ESI) m/z (%): 345 $[M+Na]^+$, 323 $[M+H]^+$, 263 $[M-Ac+H]^+$. HRMS (ESI): $[M+Na]^+ C_{20}H_{22}N_2O_2Na$: calcd. 345.1579, found 345.1600.

*4.5.5. Product (**35**)*

To a solution of NaH (7.5 mg, 0.3105 mmol, 2 eq.) in THF (2 mL) cooled at 0°C was added dropwise a solution of the imine **33** (50 mg, 0.1552 mmol, 1 eq.) in THF (1 mL) over 25 min. After 40 min, methyl chloroformate (0.02 mL, 0.0.465 mmol, 3 eq.) was added over 5 min. The resulting mixture was stirred at -20°C for 12h and then poured into brine (20 mL). The organic layer was separated, and the aqueous layer was extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in *vacuo*. The crude reaction mixture was purified by silica gel chromatography (diethyl ether/triethylamine 99:1 then 95:5) to provide **35** (26 mg, 0.0686 mmol, 44%) as a white solid. M.p. = 143.4-144.7°C. R_f = 0.41 (petroleum ether/ ethyl acetate: 80/20). IR (solid, KBr) ν= 3456, 2962, 1733, 1474, 1360, 1230, 1059, 757, 603 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.75 (d, 1H, J = 5.85 Hz), 7.07-7.01 (m, 1H), 7.01 (d, 1H, J = 4.74 Hz), 6.99 (t, 1H, J = 4.74 Hz), 6.07 (d, 1H, J = 6.06 Hz), 5.45-5.39 (q, 1H, J = 5.13 Hz), 5.25 (t, 1H, J = 2.64 Hz), 4.17-4.16 (m, 1H), 3.91 (s, 3H), 3.61 (d, 2H, J = 11.19 Hz), 3.57-2.96 (m, 1H), 2.95-2.93 (m, 1H), 2.82-2.75 (m, 1H), 2.26-2.20 (m, 1H), 1.82-1.75 (m, 1H), 1.70 (d, 3H, J = 5.13 Hz), 1.46 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 170.4 (C), 153.2 (C), 145.5 (C), 140.7 (C), 135.7 (C), 134.3 (C), 127.3 (C), 123.7 (CH), 121.8 (C), 119.8 (CH), 115.2 (CH), 108.5 (CH), 69.1 (CH), 60.2 (CH), 52.9 (CH_3), 52.8 (C), 52.4 (CH_2), 52.1 (CH_2), 41.1 (CH_2), 35.7 (CH), 20.57 (CH_3, OAc), 13.2 (CH_3). MS (ESI) m/z (%): 381$[M+H]^+$(100). HRMS (ESI): $[M+H]^+ C_{22}H_{25}N_2O_4$: calcd. 381.1808, found 381.1808.

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