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OXIDATION OF 1-ARYLCYCLOHEXA-2,5-DIENES AND SUBSEQUENT DOUBLE MICHAEL ADDITION. A RAPID ACCESS TO THE BÜCHI KETONE AND THE PENTACYCLIC CORE OF ASPIDOSPERMA ALKALOIDS≠

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Abstract – The Pd-catalyzed oxidation of 1-arylcyclohexa-2,5-dienes, resulting from a Birch reductive alkylation, leads to the corresponding arylcyclohexadienones. A careful choice of the substituents on the starting biaryl affords arylcyclohexadieonones, which may then enter into a double Michael addition, opening an access to the tetracyclic core of terpene indole alkaloids of the aspidosperma family. This strategy was used to prepare the Büchi ketone, a key-intermediate in the synthesis of this class of alkaloids, in 6 synthetic operations and 17% overall yield from commercially available 2-aminobiphenyl.

INTRODUCTION

Terpene indole alkaloids, including their dimeric forms constitute a family of more than 3000 members,[1] in which only a few exhibit physiological effects on mammals,[2] including vincristine and vinblastine, isolated for *Catharanthus roseus*, and used respectively in the treatment of leukemia and Hodgkin's disease. Vindoline, the constituent of the lower half of vincristine and vinblastine, and a key component in the biosynthesis and the preparation of these antitumor drugs,[3] but also vindorosine and strychnine share the same tetracyclic skeleton, which may be accessible through a common intermediate, known as the Büchi ketone **1** (Figure 1). Since its first synthesis by Büchi in 1971,[4] this ketone has aroused great interest and led to many synthetic developments.[5] We describe here an access to **1**, based

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≠ Dedicated with respect to Prof. Kiyoshi Tomioka on the occasion of his 70th birthday on a strategy (called “BRAD” for Birch Reductive Alkylation – Desymmetrization),[6] which includes as a key-step the desymmetrization of a cyclohexadienone **I** through a double-Michael addition process.[7] The dienone is itself prepared from a simple biaryl precursor **III**, through a Birch reductive alkylation,[8] followed by the controlled oxidation of the cyclohexa-1,4-diene **II** into the dienone **I**. Our efforts to develop further the methodology and to access the pentacyclic core of vindorosine is also discussed.

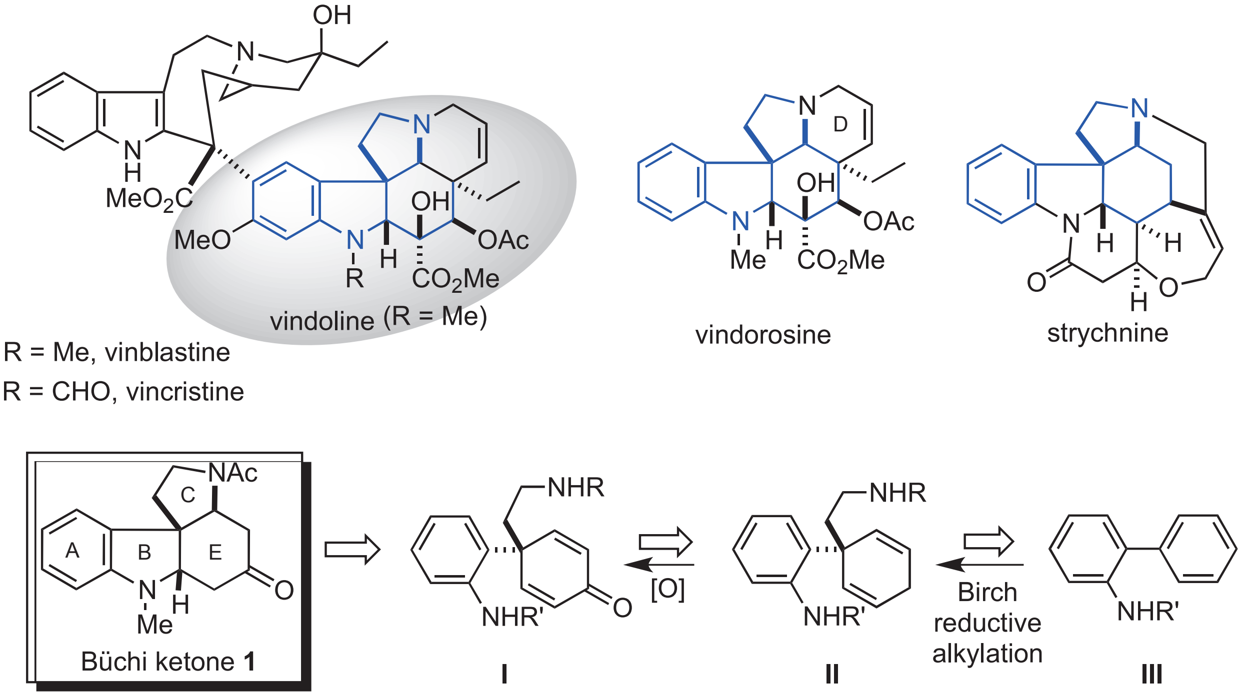
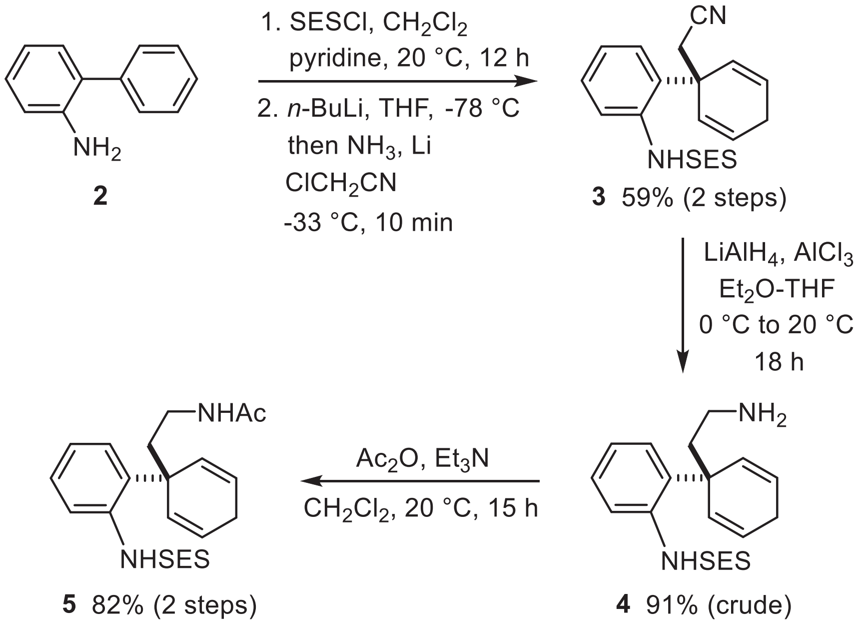


Figure 1. Some terpene indole alkaloids and their synthetic precursor, the Büchi ketone 1

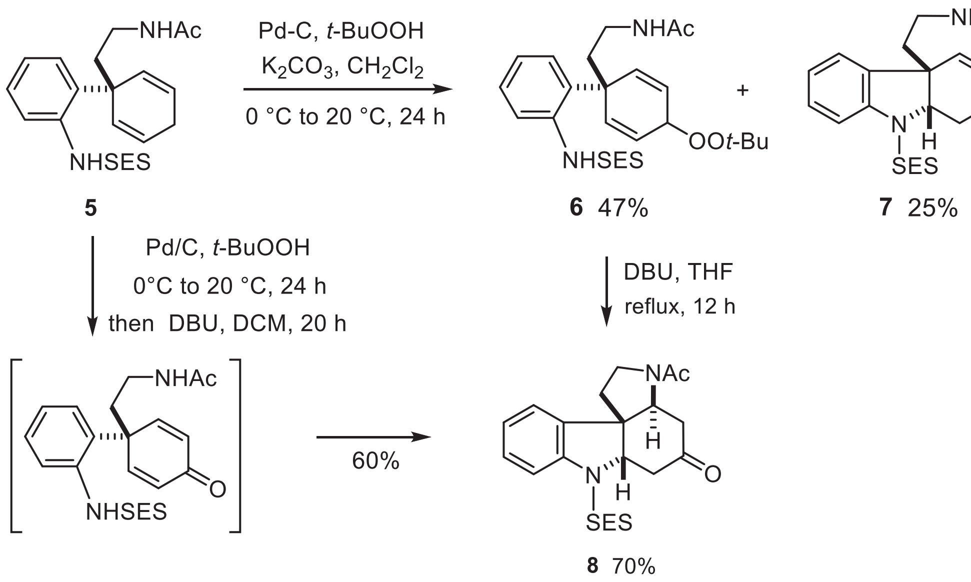
RESULTS AND DISCUSSION

Our preliminary studies showed that the choice of the R’ substituent on the biaryl amine **III** strongly influenced the regioselectivity of the Birch reductive alkylation.[8c,9] Best results were thus obtained with electron-deficient substituents, including sulfonamides (R’= SO_2Ar). Although the origin of this observation is not yet clear, it is believed that the acidic NH is removed during the Birch reduction, leading to a sulfonamide anion and thus an increase of the electron density on the arylsulfonamide ring, which would favor the regioselective reduction of the non-substituted phenyl ring. Sulfonamides thus appear as ideal protecting groups,[10] but anticipating a tedious deprotection step at the end of the synthesis with the NHTs substituent, we turned our attention to the more labile NHSES group (SES for 2-(trimethylsilyl)ethanesulfonamide; $Me_3Si(CH_2)_2SO_2$),[11] which can be readily removed using mild and orthogonal conditions (generally a fluorine source). Therefore, the synthesis started with 2-aminobiphenyl **2**, the protection of which with SESCl was followed by our standard Birch reductive alkylation,[8c] furnishing diene **3** in 59% overall yield from **2** (Scheme 1). Reduction of the nitrile was then easily carried out using a mixture of $LiAlH_4$ and $AlCl_3$, leading to **4** in good yield (crude).[6a] Our attempt at purifying **4** invariably leading to an important loss of material (~ 50%) upon chromatography, **4** was thus directly acetylated into **5** without further purification.



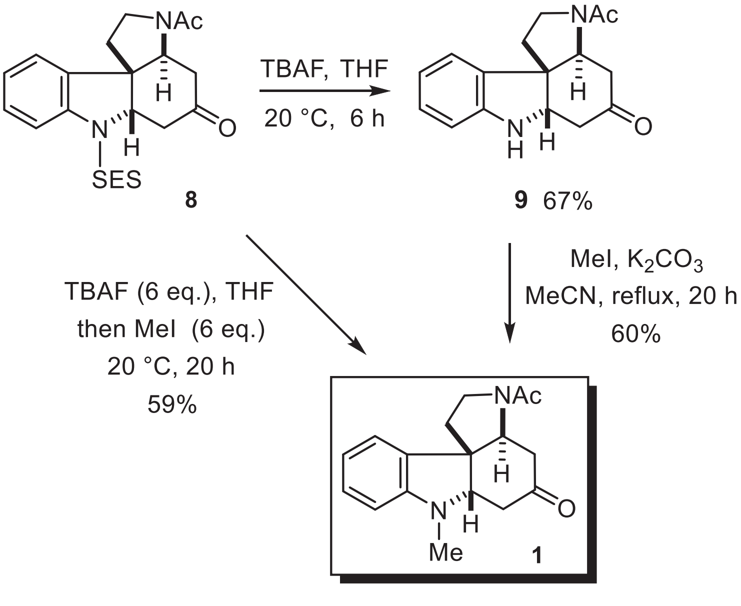
Scheme 1

With diene **5** in hand, we then studied its oxidation to generate the desired dienone of type **I**. Previous investigations showed that oxidation of dienes such as **II**, using Pd(0) and *t*-BuOOH readily produced dienone **I**,[6a] which stability depends on the nature of the substituents on the aryl group. In the absence of a NHR' substituent, **I** was shown to afford directly the Michael addition product and could not be isolated. In contrast, with a NHTs substituent, **II** was detected and a base required to trigger the Michael addition. Preliminary oxidation experiments on **5** using Pd-C and *t*-BuOOH[12] led to peroxide **6** and monocyclized product **7** (Scheme 2). Weakly basic conditions employed in this reaction are likely insufficient to trigger the Kornblum-De la Mare (KDM) rearrangement[13] of the peroxide **6** into the desired dienone of type **I**. **6** was thus heated in THF under reflux in the presence of a stronger base such as DBU, which afforded, in good yield, tetracyclic **8** resulting from a tandem KDM rearrangement/double Michael addition. Compound **8** was finally obtained, in a single-pot operation, through a sequential addition of the reagents as outlined in Scheme 2. Interestingly, the cyclohexadienone formed initially, could not be isolated and reacted spontaneously to provide the double Michael addition product **8** in 60% overall yield.



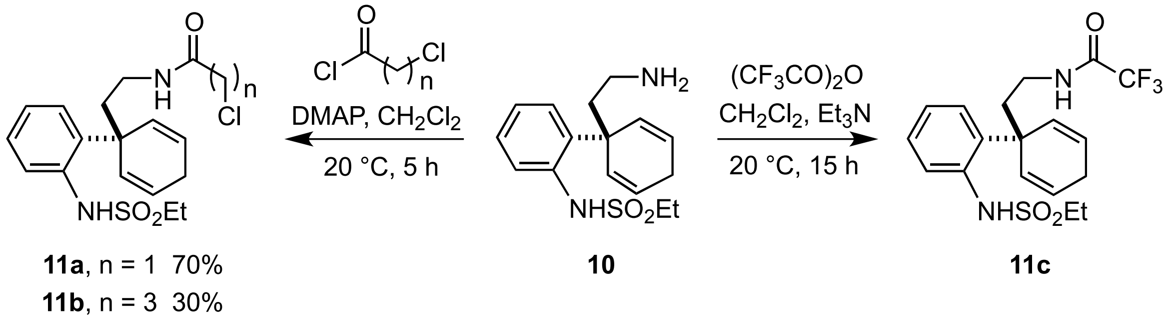
Scheme 2

The final stage of the synthesis of the Büchi ketone **1** finally required the SES deprotection and the methylation of the indole nitrogen center. This was readily accomplished through treatment of **8** with TBAF in THF,[14] which led to the deprotected indole **9** in satisfying yield (Scheme 3). The final methylation of **9** using standard MeI conditions finally provided the desired ketone **1**.[5d-f] The deprotection-methylation sequence could also be carried out in a single pot with sequential addition of the reagents, providing Büchi ketone **1** in only 6 synthetic operations from commercially available 2-aminobiphenyl **2** and 17% overall yield.



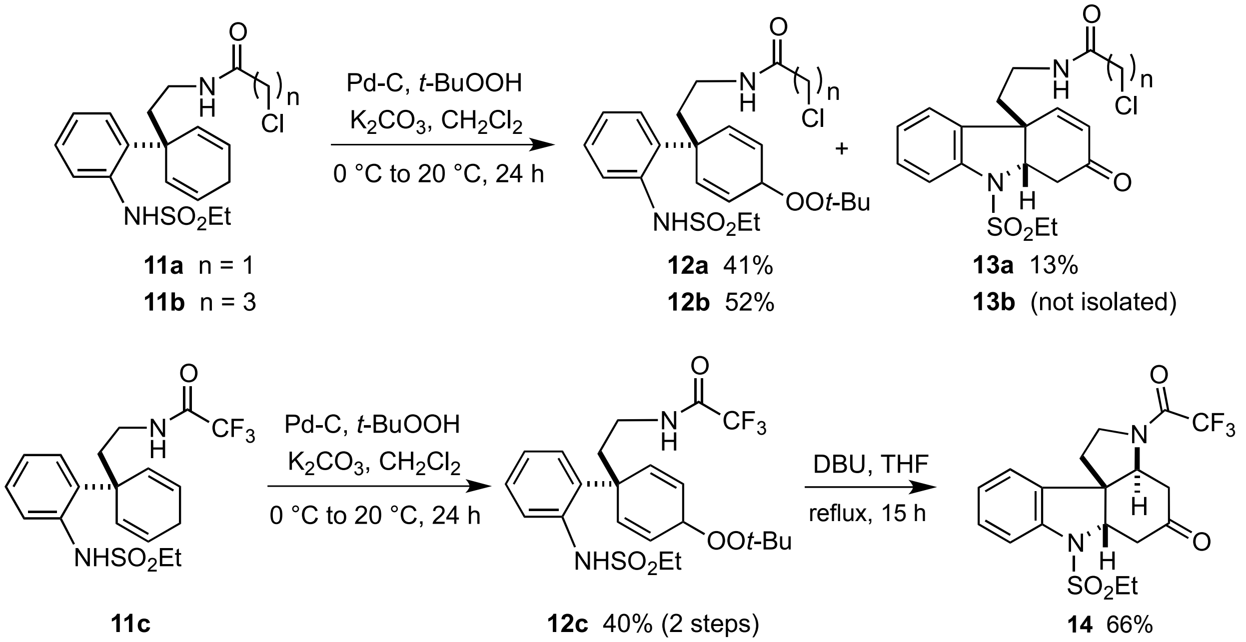
Scheme 3

Based on these premises, we then explored the possibility to access more functionalized substrates through our double Michael reaction. For instance, the presence of a suitably functionalized amide chain on substrates such as **8** should allow further functionalization, including the formation of additional rings.[15] We thus prepared a series of functionalized amides **11a-c** from amine **10**, using standard acylation conditions (Scheme 4). **11a-b** were obtained in moderate to good yields, while the sensitive trifluoracetylated analogue **11c** was used in the next step without further purification.



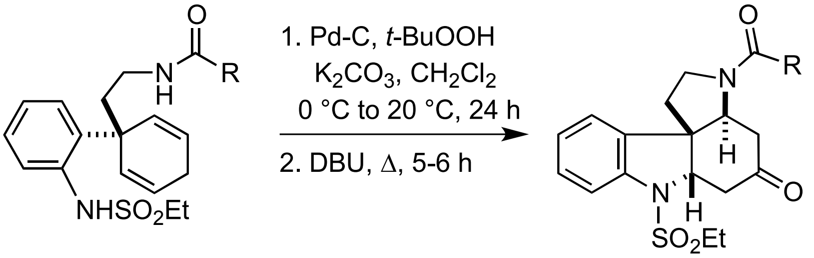
Scheme 4

These were then subjected to the Pd-catalyzed oxidation above to form the corresponding peroxides or Michael addition products. As mentioned for closely related amide **5**, treatment of **11a-c** with Pd-C and *t*-BuOOH led to both the corresponding peroxides **12a-c** and the monocyclized products **13a-b** (Scheme 5). While **13a** was isolated in low yield, **13b** could not be purified, although it was unambiguously observed through ^{1}H NMR. The Michael addition product was also not observed with more sensitive trifluoroacetamide **11c**.[10] Only the peroxide **12c** was isolated in this case, albeit in moderate yield. **12c** was finally converted into **14** through a tandem KDM rearrangement/double Michael addition reaction.



Scheme 5

These results prompted us to extend the one-pot conditions developed for the preparation of **8** (Scheme 2). Under these conditions, **11a** led essentially to degradation products, while **11b-c** afforded the double Michael addition products **14-15** in moderate yields (Scheme 6). With **11b**, we did not observe products resulting from a tandem double Michael addition-alkylation, but only **15**. Further deprotection of the labile $COCF_3$ substituent in **14** also met with failure. Amongst the many attempts, deprotection using K_2CO_3 in MeOH[16] led to trace amount of the desired tetracyclic aminoketone, which was too sensitive to be purified. A Robinson-type annulation to install ring D of vindorosine (Figure 1), as reported by Büchi on a similar compound,[4] was finally tried on **14**, relying on an *in situ* trapping of the amino-ketone with acrolein (MeONa-MeOH, acrolein, 20 °C). Unfortunately, this led to extensive degradation and no trace of pentacyclic system.

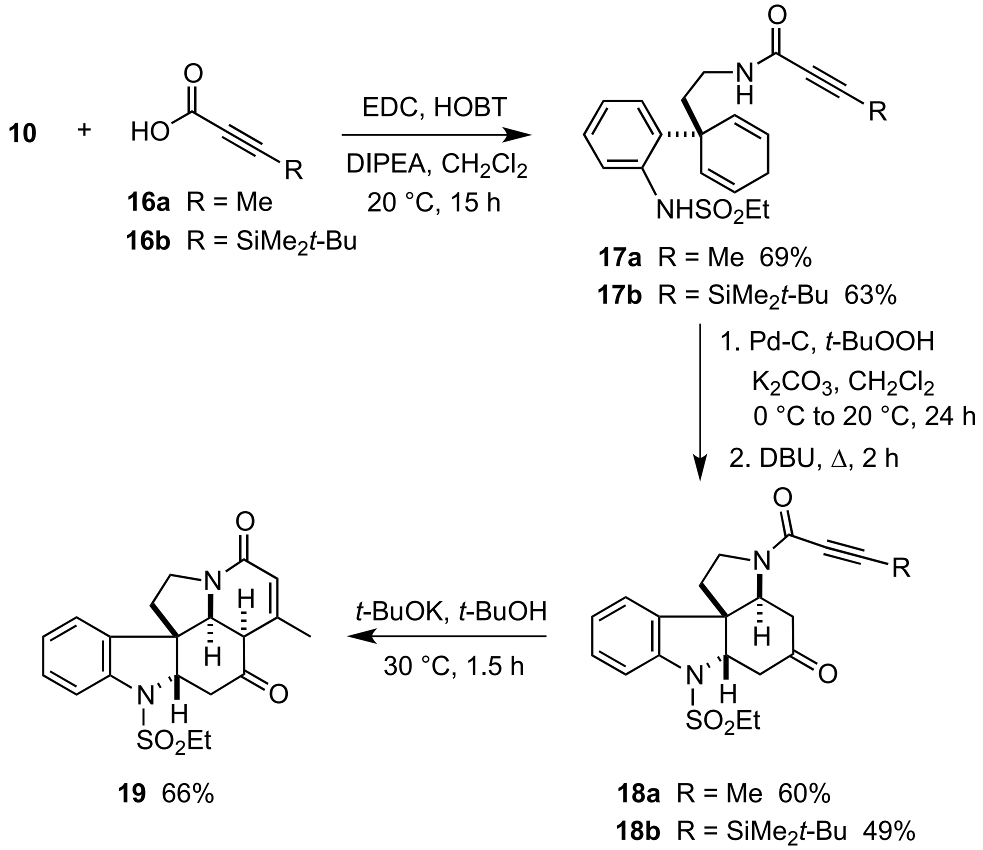


11b R = $(CH_2)_3Cl$
11c R = CF_3

15 R = $(CH_2)_3Cl$ 40%
14 R = CF_3 46% (2 steps)

Scheme 6

Considering the failures during tandem Michael addition-alkylation above, we envisioned developing instead a domino KDM rearrangement-double Michael addition-6-*endo*-dig cyclization, starting from alkynylamides **17a-b**, accessible from amine **10** and the corresponding alkynoic acids **16a-b**, using standard peptide coupling methods[17] (Scheme 7). Base-catalyzed 6-e*ndo*-dig cyclization are not so common,[18] but would allow a straightforward formation of the D ring present in vindoline, vindorosine and more generally in aspidosperma alkaloids (Figure 1). Oxidation of dienes **17a-b** as before led to the corresponding ketones **18a-b**, resulting from the double conjugate addition, but these conditions (DBU) were not suitable to trigger the final 6-*endo*-trig cyclization onto the alkynone. Several bases (LDA in THF, EtONa-EtOH) were thus tested to perform the desired cyclization on **18a**. After extensive investigations, *t*-BuOK in *t*-BuOH was found to be the best choice, affording pentacyclic system **19** in satisfying yield as a single diastereomer, having the *cis*-stereochemistry as unambiguously shown by ^1H NMR studies (NOESY). Surprisingly, under similar conditions, the silylated analogue **18b** led to degradation and no trace of the desired polycyclic system.



Scheme 7

In summary, we reported here on the further development of our BRAD strategy,[6] based on the functionalization of 1-arylcyclohexa-2,5-dienes through a tandem Pd-catalyzed allylic oxidation-double Michael addition. This approach provides a straightforward access to the Büchi ketone **1**, in a limited number of step. A careful choice of the substituents on both nitrogen centers ultimately allows further manipulation such as the elaboration of the D ring present in several key terpene indole alkaloids of the aspidosperma family. The pentacyclic skeleton of these alkaloids is thus accessible with the stereoselective incorporation of four stereogenic centers in no more than seven steps.

EXPERIMENTAL

All reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials. Commercial reagents were used without purification, unless otherwise stated. Silica gel 60M (230-400 mesh ASTM) was used for flash chromatography. In some cases, silica gel was preliminary deactivated by mixing with 5% (v/v) of triethylamine. CH_2Cl_2 and (i-Pr)$_2$NH were distilled under CaH_2. THF and Et_2O were distilled from sodium and benzophenone. In some cases, THF, Et_2O, CH_2Cl_2, MeOH, and toluene were dried on a MBraun SPS-800 (Grubbs columns). For Birch reductions, lithium wire (3.2 mm diameter, 0.01% sodium) was cut into small pieces and hammered before use. NH_3 gas was dried by passing through potassium hydroxide pellets. ^1H NMR and ^{13}C NMR were recorded on Brüker DPX-200 FT (^1H: 200 MHz, ^{13}C: 50.2 MHz), Brüker AC-250 FT (^1H: 250 MHz, ^{13}C: 62.9 MHz), Brüker Avance-300 FT (^1H: 300 MHz, ^{13}C: 75.5 MHz) and Brüker DPX-400 FT (^1H: 400 MHz, ^{13}C: 100.2 MHz) apparatus using $CDCl_3$ as internal reference unless otherwise indicated. The chemical shifts (δ) and coupling constants (*J*) are expressed in ppm and Hz respectively. Mass spectra were recorded on a Nermag R10-10C. 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 uncorrected and determined by using a Büchi-Totolli apparatus and Stuart Scientific apparatus (SMP3).

***N*-(2-(1-(Cyanomethyl)cyclohexa-2,5-dienyl)phenyl)-2-(trimethylsilyl)ethanesulfonamide (3).** To a solution of 2-aminobiphenyl **2** (2 g, 11.83 mmol, 1 eq) in dry CH_2Cl_2 (50 mL) were added pyridine (3.84 mL, 47.32 mmol, 4 eq) and 2-(trimethylsilyl)ethanesulfonyl chloride (SESCl) (5 mL, 26.03 mmol, 2.2 eq) at room temperature under nitrogen. The stirring was continued for 12 h at the same temperature. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude reaction mixture was purified by silica gel chromatography (pentane/EtOAc 98:2) to provide SES-protected-2-aminobiphenyl (3.879 g, 11.63 mmol, 98%) as a yellow oil. $R_f = 0.2$ (petroleum ether/EtOAc 95/5). IR (film, NaCl): ν = 3357, 2952, 1581, 1481, 1396, 1250, 1147, 841, 754, 567 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): *δ* (ppm) = 7.73-7.71 (m, 1H), 7.56-7.49 (m, 3H), 7.43-7.38 (m, 3H), 7.32-7.26 (m, 2H), 5.57 (br s), 2.94-2.88 (m, 2H), 0.82-0.75 (m, 2H), 0.00 (s, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): *δ* (ppm) = 139.7, 136.2, 135.1, 132.8, 131.6, 131.1, 130.5, 126.8, 122.2, 50.2, 12.2, 0.0. MS (ESI) *m/z* (%): 356 $[M+Na]^+$ (100). HRMS (ESI): $[M+Na]^+$ $C_{17}H_{23}NO_2NaSiS$: calcd. 356.1111, found 356.1112.

In an oven dried three-necked round bottom flask equipped with a dry-ice condenser was introduced, under nitrogen, the SES-protected 2-aminobiphenyl (1.7 g, 5.10 mmol, 1 eq) in THF (40 mL, 0.03 M). *n*-BuLi (2 M solution in hexane, 2.75 mL, 5.61 mmol, 1.1 eq) was added dropwise at -20 °C and the solution was stirred for 15 min. The flask was then cooled to -78 °C and ammonia (approx. 80 mL) was condensed. Lithium wire (89 mg, 12.75 mmol, 2.5 eq) was added. The media turned rapidly brown and finally brick red. The solution was stirred at -78 °C for 30 min then at -33 °C for 1 h. The red mixture was then cooled to -78 °C and chloroacetonitrile (1.155 g, 15.30 mmol, 3 eq) in THF (10 mL) was added in one portion. The mixture turned immediately brown. After 10 min, ammonia was let to evaporate and a half-saturated aqueous ammonium chloride solution was added. After extraction with EtOAc, the reaction media was washed with brine, dried over Na_2SO_4 and the organic solvents were concentrated under vacuum to provide a brown paste. The crude product was then submitted to silica gel flash chromatography (petroleum ether/ EtOAc 90/10 → 80/20) to afford **3** (1.14 g, 3.04 mmol, 60%, 2 steps) as a yellow oil. $R_f = 0.46$ (petroleum ether/EtOAc 80/20). IR (film, NaCl): ν = 3347, 2953, 1581, 1495, 1410, 1337, 1251, 1170, 842, 758 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.54 (d, 1H, J = 7.9 Hz), 7.34-7.18 (m, 1H), 7.17-7.13 (m, 2H), 6.25-6.22 (m, 2H), 5.64 (d, 2H, J = 7.9 Hz), 3.07-2.95 (m, 6H), 1.03-0.97 (m, 2H), 0.00 (s, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 139.4, 132.1, 131.2, 130.7, 130.3, 127.3, 126.1, 121.8, 118.9, 50.9, 43.2, 32.6, 27.9, -0.06. MS (ESI) *m/z* (%): 397 $[M+Na]^+$ (100). HRMS (ESI): $[M+Na]^+$ $C_{19}H_{26}N_2O_2NaSSi$: calcd. 397.1376, found 397.1373.

***N*-(2-(1-(2-Aminoethyl)cyclohexa-2,5-dienyl)phenyl)-2-(trimethylsilyl)ethanesulfonamide (4).** In a 100 mL two-necked round bottom flask, $AlCl_3$ (1.54 g, 11.55 mmol, 3 eq) was dissolved in Et_2O (25 mL) at 0 °C, then $LiAlH_4$ (0.58 g, 15.40 mmol, 4 eq) was added. The reaction mixture is stirred at rt for 30 min. Nitrile **3** (1.440 g, 3.85 mmol, 1 eq) was dissolved in Et_2O (15 mL) and THF (8 mL), and added dropwise at 0 °C. The reaction mixture is stirred at rt for 18 h then the reaction was stopped by addition of ice then 10% aqueous NaOH (40 mL) was added and the reaction mixture stirred for 1 h. Et_2O was added. The reaction mixture was filtered through celite and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuum. The crude material was pure enough to be used without further purification in the next step. However, purification by silica gel chromatography (silica gel deactivated CH_2Cl_2/MeOH 95:5) afforded **4** (577 mg, 1.5257 mmol, 40%) as a yellow oil. $R_f = 0.23$ (CH_2Cl_2/MeOH 95:5). IR (film, NaCl): ν = 3347, 2952, 1493, 1336, 1251, 1169, 1147, 889, 758 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.57-7.55 (m, 1H), 7.45-7.35 (m, 1H), 7.30-7.25 (m, 1H), 7.15-7.09 (m, 1H), 6.10 (d, 2H, J = 10.17 Hz), 5.54 (d, 2H, J = 10.17 Hz), 3.63 (br s, 3H), 3.07-3.01 (m, 2H), 2.94-2.88 (m, 2H), 2.86-2.78 (m, 2H), 2.19-2.11 (m, 2H), 1.04-0.98 (m, 2H), -0.006 (s, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 137.5, 132.5, 130.3, 128.2, 126.1, 125.9, 123.6, 119.1, 48.3, 41.9, 41.6, 37.5, 25.6, 9.9, -2.3. MS (ESI) *m/z* (%): 379 $[M+H]^+$ (100). HRMS (ESI): $[M+H]^+$ $C_{19}H_{31}N_2O_2SSi$: calcd. 379.1870, found 379.1873.

***N*-(2-(1-(2-(2-(Trimethylsilyl)ethylsulfonamido)phenyl)cyclohexa-2,5-dienyl)ethyl)acetamide (5).** The amine **4** (671 mg, 1.78 mmol, 1 eq) was dissolved in CH_2Cl_2 (25 mL). Triethylamine (0.27 g, 2.67 mmol, 1.5 eq) was added dropwise at 0 °C followed by acetic anhydride (0.22 g, 2.136 mmol, 1.2 eq). The solution was stirred over night at rt saturated aqueous NH_4Cl was added then the reaction mixture extracted with CH_2Cl_2. The organic layers were washed with brine then dried over Na_2SO_4. The solvent was evaporated *in vacuo*. Purification by silica gel chromatography (petroleum ether/EtOAc 70/30 then EtOAc 100%) afforded **5** (366 mg, 0.870 mmol, 51% (2 steps from **3**)) as a yellow oil. $R_f = 0.35$ (petroleum ether/EtOAc 80/20). IR (Film, NaCl): ν = 3340, 2952, 1651, 1548, 1335, 1251, 1146, 842, 758 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.56-7.53 (m, 1H), 7.41-7.36 (m, 2H), 7.30-7.24 (m, 1H), 7.13-7.08 (m, 1H), 6.12-6.09 (m, 2H), 5.98 (br s, 1H), 5.54-5.51 (m, 2H), 3.37-3.30 (m, 2H), 3.07-3.01 (m, 2H), 2.94-2.88 (m, 2H), 2.16-2.11 (m, 2H, 1.99 (s, 3H), 1.01-0.98 (m, 2H), 0.00 (s, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 172.3, 139.8, 134.6, 132.4, 130.5, 128.6, 127.1, 125.9, 121.4, 50.6, 43.8, 40.9, 37.9, 27.9, 25.4, 12.2, 0.003. MS (ESI) *m/z* (%): 443 $[M+Na]^+$ (100), 421 $[M+H]^+$ (53). HRMS (ESI): $[M+Na]^+$ $C_{21}H_{32}N_2O_3NaSSi$: calcd. 443.1795, found 443.1789.

***N*-(2-(4-*(tert*-Butylperoxy)-1-(2-(2-(trimethylsilyl)ethylsulfonamido)phenyl)cyclohexa-2,5-dienyl)-ethyl)acetamide (6) and *N*-(2-((4aS,9aS)-2-Oxo-9-(2-(trimethylsilyl)ethylsulfonyl)-2,4a,9,9a-tetrahydro-1*H*-carbazol-4a-yl)ethyl)acetamide (7).** To a suspension of 3% Pd/C (0.0319 g, 0.009 mmol, 0.025 eq) in CH_2Cl_2 (3 mL) were added at 0 °C, K_2CO_3 (0.0124 g, 0.09 mmol, 0.25 eq) and *tert*-butyl hydroperoxide in decane (5M) (0.4 mL, 1.8 mmol, 5 eq). Diene **5** (0.150 g, 0.36 mmol, 1 eq) was dissolved in CH_2Cl_2 (2 mL) and then added to the reaction media. The mixture was stirred at 0 °C during 8 h and then at rt overnight. The mixture was filtered through a pad of silica gel and washed with CH_2Cl_2 to remove the excess of *tert*-butyl hydroperoxide. Silica was then washed with EtOAc. The solvent was concentrated *in vacuo*. Purification by silica gel chromatography (EtOAc 100%) afforded **6** (85 mg, 0.870 mmol, 47%) as a colorless oil and **7** (40 mg, 0.09 mmol, 25%) as a colorless oil.

(**6**): R_f = 0.25 (EtOAc 100%). IR (Film, NaCl): ν = 3354, 2953, 1658, 1548, 1453, 1336, 1251, 1195, 1146, 860 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.29-7.27 (m, 3H), 7.24-7.14 (m, 1H), 7.12-7.09 (m, 1H), 6.32-6.27 (m, 2H), 6.19 (br s, 1H), 5.91-5.88 (m, 2H), 5.12 (s, 1H), 3.36 (q, 2H, *J* = 6.4 Hz), 3.06-3.00 (m, 2H), 2.26 (t, 2H, *J* = 6.7 Hz), 1.93 (s, 3H), 1.28 (s, 9H), 1.01-0.98 (m, 2H), -0.00 (s, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 172.1, 139.3, 139.1, 133.2, 130.8, 129.1, 127.8, 126.6, 122.1, 82.8, 74.7, 51.2, 45.6, 39.1, 37.9, 28.5, 25.4, 12.3, 0.02. MS (ESI) *m/z* (%): 531 $[M+Na]^+$ (100), 419 $[(M+H)\text{-}OOt\text{-}Bu]^+$ (53). HRMS (ESI): $[M+Na]^+$ $C_{25}H_{40}N_2O_5NaSSi$: calcd. 531.2324, found 531.2324.

(**7**): R_f = 0.20 (EtOAc 100%). IR (film, NaCl): ν = 3350, 2948, 1652, 1456, 1347, 1148, 860, 757 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.23-7.18 (m, 1H), 7.17-7.06 (m, 2H), 7.04-7.01 (m, 1H), 6.70 (d, 1H, *J* = 10.2 Hz), 6.02 (d, 1H, *J* = 10.2 Hz), 5.82 (br s, 1H), 4.75 (t, 1H, *J* = 5.2 Hz), 3.28-3.11 (m, 2H), 3.05-2.96 (m, 2H), 2.91-2.78 (m, 2H), 2.05-1.99 (m, 2H), 1.85 (s, 3H,), 1.06-0.98 (m, 2H), 0.00 (s, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 195.8, 170.1, 148.2, 140.7, 132.5, 129.1, 127.6, 123.9, 123.4, 114.8, 64.6, 50.3, 47.9, 40.1, 37.7, 35.5, 22.9, 9.8, -2.1. MS (ESI) *m/z* (%): 457 $[M+Na]^+$ (100), 435 $[M+H]^+$ (22). HRMS (ESI): $[M+Na]^+$ $C_{21}H_{30}N_2O_4NaSSi$: calcd. 457.1587, found 457.1589.

(3aS,6aS,11a1R)-3-Acetyl-7-(2-(trimethylsilyl)ethylsulfonyl)-2,3,3a,4,6a,7-hexahydro-1*H*-pyrrolo-[2,3-*d*]carbazol-5(6*H*)-one (8). To a suspension of 3% Pd/C (93 mg, 0.03 mmol, 0.025 eq) in CH_2Cl_2 (14 mL) were added at 0 °C, K_2CO_3 (41 mg, 0.3 mmol, 0.25 eq) and *tert*-butyl hydroperoxide in decane (5M) (1.04 mL, 5.2 mmol, 5 eq). Diene **5** (0.435 g, 1.04 mmol, 1 eq) was dissolved in CH_2Cl_2 (5 mL) and then added to the reaction media. The mixture was stirred for 8 h at 0 °C, and then at rt overnight. DBU (0.31 mL, 2.08 mmol, 2 eq) was added and the mixture was heated for 20 h under reflux. After cooling at rt, the reaction mixture was filtered through a pad of silica gel and the residue was washed with CH_2Cl_2 to remove the excess of *tert*-butyl hydroperoxide. Silica was then washed with a mixture of AcOEt/MeOH (96/4). The organic solvents were removed under *vacuum*. Purification by silica gel chromatography (AcOEt/MeOH 99/1) afforded **8** (270 mg, 0.6218 mmol, 60%) as a white solid. Mp 230.1-231.8 °C. R_f = 0.37 (EtOAc 100%). IR (solid, KBr): ν = 3354, 2918, 1722, 1643, 1414, 1348, 1250, 1150, 843, 759 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.34-7.27 (m, 2H), 7.06-7.04 (m, 2H), 4.55-4.50 (m, 1H), 4.46-4.42 (m, 1H), 3.77-3.74 (m, 2H), 3.05-2.94 (m, 2H), 2.60-2.51 (m, 2H), 2.43-2.39 (m, $2H_2$), 2.36-2.26 (m, 2H), 2.13 (s, 3H), 1.19-0.97 (m, 2H), -0.00 (s, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 207.5, 171.6, 141.7, 137.1, 131.5, 126.4, 125.1, 116.6, 67.7, 61.1, 54.5, 50.6, 47.5, 45.7, 43.4, 39.8, 24.6, 11.9, -0,2. MS (ESI) *m/z* (%): 457 $[M+Na]^+$ (100), 435 $[M+H]^+$ (21). HRMS (ESI): $[M+Na]^+$ $C_{21}H_{30}N_2O_4NaSSi$: calcd. 457.1587, found 457.1586.

(3aS,6aS,11a1S)-3-Acetyl-2,3,3a,4,6a,7-hexahydro-1*H*-pyrrolo[2,3-d]carbazol-5(6*H*)-one (9). To a solution of ketone **8** (151 mg, 0.35 mmol, 1 eq) in THF (4 mL) was added a 1 M solution of *n*-Bu_4NF (TBAF) in THF (737 μL, 1.4 mmol, 4 eq). The resulting solution was stirred for 15 min and then diluted with Et_2O (18 mL). The organic layer was washed with water, followed by saturated aqueous $NaHCO_3$ (10 mL), dried, and concentrated *in vacuo*. Purification by silica gel chromatography (CH_2Cl_2/MeOH 95/5) afforded **9** (63 mg, 0.2332 mmol, 67%) as a yellow solid. Mp 62.3-64.1 °C. R_f = 0.43 (CH_2Cl_2/MeOH 95:5). IR (solid, KBr): ν = 3354, 2924, 1716, 1635, 1486, 1417, 1362, 1261, 749 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.06-6.95 (m, 2H), 6.73-6.68 (m, 1H), 6.59-6.56 (m, 1H), 4.17-4.13 (m, 1H), 4.04-4.02 (m, 1H), 4.01-3.92 (br s, 1H), 3.73-3.61 (m, 2H), 2.86-2.77 (m, 2H), 2.65-2.52 (m, 2H), 2.50-2.38 (m, 2H), 2.04 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 210.2, 172.1, 151.6, 133.6, 131.1, 125, 121.6, 112.1, 65.8, 64.5, 55.1, 49.1, 45.5), 42.1, 39.6, 25.3. MS (ESI) *m/z* (%): 293 $[M+Na]^+$ (100), 271 $[M+H]^+$ (10). HRMS (ESI): $[M+Na]^+$ $C_{16}H_{18}N_2O_2Na$: calcd. 293.1260, found 293.1258.

(3aS,6aS,11a1S)-3-Acetyl-7-methyl-2,3,3a,4,6a,7-hexahydro-1*H*-pyrrolo[2,3-d]carbazol-5(6*H*)-one (1). To a mixture of **9** (74 mg, 0.272 mmol, 1eq) and potassium carbonate (31 mg, 0.0272 mmol, 0.1 eq) in MeCN (3 mL) was added MeI (0.08 mL, 1.632 mmol, 6 eq) in one portion. The reaction mixture was stirred under reflux for 20 h, then diluted with CH_2Cl_2 (20 mL) and quenched by addition of water (20 mL). The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers dried over $MgSO_4$, then evaporated under vacuum. Purification by silica gel chromatography (CH_2Cl_2/MeOH 50/1) afforded **1** (46 mg, 0.1618 mmol, 60%) as a white solid. Mp 186.3-187.7 °C (Litt.[4a]: Mp 195-197 °C). R_f = 0.52

(CH_2Cl_2/MeOH 95:5). IR (solid, KBr): ν = 2924, 1716, 1646, 1488, 1362, 1296, 1261, 1233, 1111, 756 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.14 (t, 1H, J = 7.9 Hz), 6.99-6.97 (m, 1H), 6.73 (t, 1H, J = 7.5 Hz), 6.47-6.44 (m, 1H), 4.10 (t, 1H, J = 4.1 Hz), 3.78-3.64 (m, 1H), 3.62-3.52 (m, 2H), 3.03-2.95 (m, 1H), 2.70-2.69 (m, 1H), 2.63 (s, 3H), 2.58-2.52 (m, 2H), 2.49-2.42 (m, 1H), 2.09-2.07 (m, 1H), 2.03 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 208.1, 170.1, 152.1, 131.3, 129.4, 122.6, 119.1, 108.3, 71.1, 63.2, 52.4, 47.3, 39.9, 39.3, 37.8, 33.3, 23.4. MS (ESI) *m/z* (%): 307 [M+Na]$^+$ (100), 285 [M+H]$^+$ (13). HRMS (ESI): [M+Na]$^+$ $C_{17}H_{20}N_2O_2Na$: calcd. 307.1416, found 307.1404.

2-Chloro-*N*-(2-(1-(2-(ethylsulfonamido)phenyl)cyclohexa-2,5-dienyl)ethyl)acetamide (11a). The amine **10** (361 mg, 1.18 mmol, 1 eq) was dissolved in CH_2Cl_2 (12 mL), then Et_3N (0.33 mL, 2.36 mmol, 2 eq), DMAP (cat.) and chloroacetyl chloride (0.14 mL, 1.77 mmol, 1.5 eq) were added at 0 °C. The reaction mixture was stirred at rt for 5 h. The reaction was then quenched with a saturated aqueous solution of NH_4Cl and the two layers separated. The aqueous layer was extracted with CH_2Cl_2 and the organic layer washed with a saturated aqueous solution of NaCl, then dried over Na_2SO_4. Solvent was removed to give the crude product which was purified through silica gel chromatography (petroleum ether/EtOAc 40/60), affording **11a** (314 mg, 0.82 mmol, 70%) as a pale yellow oil. IR (film, KBr): ν = 3334, 2943, 1650, 1537, 1331, 1144, 752 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.53-7.52 (m, 1H), 7.50-7.21 (m, 3H) 7.09-7.02 (m, 1H), 7.86 (br s, 1H), 6.09-6.05 (m, 2H), 5.49-5.46 (d, 2H, J = 8.7 Hz), 3.99 (d, 2H, J = 3 Hz), 3.36-3.35 (m, 2H), 3.08-3.04 (qd, 2H, J = 2.6, 7.5 Hz), 2.88-2.83 (m, 2H), 2.14-2.09 (m, 2H), 1.29-1.23 (td, 3H, J = 3, 7.5 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 165.9, 137.5, 132.4, 130.2, 128.4, 126.6, 126.2, 123.9, 119.1, 46.4, 42.7, 41.7, 38.4, 36.1, 25.7, 8.0. MS (EI) *m/z* (%): 405 [M+Na]$^+$ (100). HRMS (LSIMS): [M+Na]$^+$ $C_{18}H_{23}ClN_2O_3SNa$: calcd. 405.1015, found 405.1011 (0.9 ppm).

4-Chloro-*N*-(2-(1-(2(ethylsulfonamido)phenyl)cyclohexa-2,5-dienyl)ethyl)butanamide (11b). The amine **10** (600 mg, 1.96 mmol, 1 eq) was dissolved in CH_2Cl_2 (20 mL), then Et_3N (0.55 mL, 3.92 mmol, 2 eq), DMAP (cat.) and chlorobutanoyl chloride (0.26 mL, 2.352 mmol, 1.2 eq) were added at 0 °C. The reaction mixture was stirred at rt for 5 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl and the two layers separated. The aqueous layer was extracted with CH_2Cl_2 and the organic layer washed with a saturated aqueous solution of NaCl, then dried over Na_2SO_4. Solvents were removed to give the crude product which was purified on silica gel chromatography (petroleum ether/EtOAc 40/60) providing **11b** (243 mg, 0.59 mmol, 30%) as a colorless oil. IR (film, KBr): ν = 3330, 3255, 2944, 1654, 1634, 1557, 1339, 1151, 922, 746 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.54 (dd, 1H, J = 1.1, 8.3 Hz), 7.39-7.23 (m, 3H) 7.11-7.05 (m, 1H), 6.10-6.07 (d, 2H, J = 10.5 Hz), 5.82 (br s, 1H), 5.50 (d, 2H, J = 10.5 Hz), 3.59 (t, 2H, J = 6.0 Hz), 3.35-3.29 (m, 2H), 3.10 (q, 2H, J = 7.2 Hz), 2.91-2.85 (m, 2H), 2.34

(t, 2H, $J = 7.2$ Hz), 2.10 (m, 4H), 1.29 (t, 3H, $J = 7.2$ Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 171.8, 137.6, 132.6, 130.4, 128.5, 126.6, 126.4, 124.0, 119.3, 46.6, 44.6, 41.8, 38.9, 36.0, 33.3, 28.2, 25.9, 8.1. MS (LSIMS) *m/z* (%): 433 $[M+Na]^+$ (100). HRMS (LSIMS): $[M+Na]^+$ $C_{20}H_{27}ClN_2O_3SNa$: calcd. 433.1328, found 433.1330.

***N*-(2-(4-(*tert*-Butylperoxy)-1-(2-(ethylsulfonamido)phenyl)cyclohex-2,5-dienyl)ethyl-2,2,2-trifluoroacetamide (11c) and (12c).** The amine **10** (470 mg, 1.53 mmol, 1 eq) was dissolved in CH_2Cl_2 (15 mL), then Et_3N (0.32 mL, 2.295 mmol, 1.5 eq) and trifluoroacetic anhydride (0.26 mL, 1.836 mmol, 1.2 eq) were added at 0 °C. The reaction mixture was stirred at room temperature overnight. The reaction was quenched with a saturated aqueous NH_4Cl solution and the two layers separated. The aqueous layer was extracted with CH_2Cl_2 and the organic layer washed with a saturated aqueous solution of NaCl, then dried over Na_2SO_4. Evaporation of the solvents gave **11c** (604 mg). The product was used in the next step without further purification. Pd/C (3%wt, 25 mg, 7×10^{-3} mmol, 0.025 eq) was placed into a flask and CH_2Cl_2 (2 mL) was added at 0 °C, then K_2CO_3 (10 mg, 0.07 mmol, 0.25 eq) and *t*-BuOOH (5 M in decane) (0.28 mL, 1.4 mmol, 5 eq) were added. **11c** (115 mg, 0.28 mmol, 1 eq) was dissolved in CH_2Cl_2 (1 mL) and added in the reaction mixture. The mixture was stirred at 0 °C for 8 h, then at room temperature overnight. The reaction mixture was filtered on a short pad of celite, and washed with EtOAc. Solvents were removed to give a crude product which was purified by silica gel chromatography (petroleum ether/EtOAc 75/25) to give **12c** (56 mg, 0.11 mmol, 40% 2 steps) as a yellow oil. IR (film, NaCl): ν = 3353, 2979, 1719, 1559, 1335, 1146 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.46-7.12 (m, 4H), 6.87 (s, 1H), 6.35 (dd, 2H, $J = 10.17, 3.75$ Hz), 5.88 (dd, 2H, $J = 10.17, 1.14$ Hz), 5.12 (m, 1H), 3.53 (q, 2H, $J = 6.03$ Hz), 3.11 (q, 2H, $J = 7.53$ Hz), 2.32 (t, 2H, $J = 6.03$ Hz), 1.32 (t, 3H, $J = 7.53$ Hz), 1.25 (s, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 157.0, 137.2, 137.0, 130.7, 129.1, 126.9, 126.6, 124.7, 120.0, 116.0, 81.1, 72.5, 47.1, 43.5, 36.3, 36.1, 26.4, 8.2. GC-MS *m/z* (%): 68.9 (100), 417.2 $[M-Ot\text{-}Bu]^+$ (10).

***N*-(2-(4-(*tert*-Butylperoxy)-1-(2-(ethylsulfonamido)phenyl)cyclohexa-2,5-dienyl)ethyl)-2-chloroacetamide (12a) and 2-Chloro-*N*-(2-(9-(ethylsulfonyl)-2-oxo-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-4a-yl)ethyl)acetamide (13a).** Pd/C (3%wt, 47 mg, 0.013 mmol, 0.025 eq) was placed into a flask, CH_2Cl_2 (3 mL) was added at 0 °C, then K_2CO_3 (18 mg, 0.13 mmol, 0.25 eq) and *t*-BuOOH (5 M in decane) (0.53 mL, 2.65 mmol, 5 eq) were added. **11a** (203 mg, 0.53 mmol, 1 eq) was dissolved in CH_2Cl_2 (2 mL) and added in the reaction mixture. The mixture was stirred at 0 °C for 10 h, then at room temperature overnight. The reaction mixture was filtered on a short pad of celite, and washed with EtOAc. Solvents were removed to give a crude product which was purified by silica gel chromatography (petroleum ether/ EtOAc 80/20 to 40/60) to provide two products, **12a** (102 mg, 0.22 mmol, 41%) as a colorless oil and **13a** (28 mg, 0.07 mmol, 13%) as a colorless oil.

(**12a**): IR (film, KBr): ν = 3348, 2977, 2931, 1651, 1547, 1459, 1345, 1152, 758 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm) = 7.45-7.39 (m, 2H), 7.25-7.04 (m, 4H), 6.92 (s, 1H), 6.32 (dd, 2H, *J* = 2.4, 9.1 Hz), 5.83 (d, 2H, *J* = 9.1 Hz), 5.07 (br s, 1H), 3.98 (s, 2H), 3.42 (q, 2H, *J* = 6.4 Hz), 3.12 (q, *J* = 7.3 Hz), 2.23 (t, 2H, *J* = 6.4 Hz), 1.30-1.20 (m, 12H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 165.8, 137.2, 136.5, 130.9, 128.9, 126.8, 126.7, 124.5, 119.8, 80.6, 72.4, 46.9, 43.5, 42.6, 36.9, 35.9, 26.5, 8.1. MS (LSIMS) *m/z* (%): 381 [M-OOt-Bu]$^+$ (100), 493 [M+Na]$^+$ (51). HRMS (LSIMS): [M+Na]$^+$ $C_{22}H_{31}ClN_2O_5SNa$: calcd. 493.1539, found 493.1556.

(**13a**): IR (film, NaCl): ν = 2928, 1720, 1653, 1476, 1418, 1345, 1268, 1152 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.36-7.08 (m, 4H), 6.81 (br s, 1H), 6.72 (d, 1H, *J* = 10.2 Hz), 6.04 (d, 1H, *J* = 10.2 Hz), 4.75 (t, 1H, *J* = 6.2 Hz), 3.95 (s, 2H), 3.37 (m, 2H), 3.19 (m, 2H), 2.95 (dd, 2H, *J* = 19.4, 6.6 Hz), 2.10 (m, 2H), 1.40 (t, 3H, *J* = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) =195.9, 166.3, 148.1, 140.7, 132.6, 129.4, 128.0, 124.3, 123.6, 115.1, 64.9, 48.0, 47.6, 42.6, 40.4, 37.8, 36.1, 7.9. MS (ESI) *m/z* (%): 397.11 [M+H]$^+$ (13), 419.08 [M+Na]$^+$ (100). HRMS (ESI): [M+Na]$^+$ $C_{18}H_{23}ClN_2O_4SNa$: calcd. 419.0808, found 419.0811.

***N*-(2-(4-(*tert*-Butylperoxy)-1-(2-ethylsulfonamido)phenyl)cyclohexa-2,5-dienyl)ethyl)-4-chlorobutanamide (12b).** Pd/C (3%wt, 15 mg, 4.25 10^{-3} mmol, 0.025 eq) was placed into a flask, CH_2Cl_2 (1 mL) was added at 0 °C, then K_2CO_3 (6 mg, 0.0425 mmol, 0.25 eq) and *t*-BuOOH (5 M in decane) (0.17 mL, 0.85 mmol, 5 eq) were added. Compound **11b** (70 mg, 0.17 mmol, 1 eq) was dissolved in CH_2Cl_2 (1 mL) and added in the reaction mixture. The mixture was stirred at 0 °C for 10 h, then at room temperature overnight. The reaction mixture was filtered on a short pad of celite, and washed with EtOAc. Solvents were removed to give a crude product which was purified by silica gel chromatography (petroleum ether/EtOAc 50/50 → 20/80) to provide **12b** (44 mg, 0.09 mmol, 52%) as a colorless oil. IR (film, KBr): ν = 3335, 3257, 2948, 1658, 1637, 1557, 1460, 1348, 1151, 922, 746 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.44 (d, 2H, *J* = 8.3 Hz), 7.30-7.25 (m, 1H) 7.17-7.15 (m, 1H), 6.97 (br s, 1H), 6.31 (dd, 2H, *J* = 3.8, 10.2 Hz), 6.19 (br s, 1H), 5.88 (d, 2H, *J* = 10.2 Hz), 5.09 (br s, 1H), 3.57 (t, 2H, *J* = 6.0 Hz), 3.37 (q, 2H, *J* = 6.0 Hz), 3.10 (q, 2H, *J* = 7.5 Hz), 2.30-2.24 (m, 4H), 2.10-2.02 (m, 2H), 1.28-1.20 (m, 12H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 171.6, 137.3, 137.2, 131.1, 128.9, 126.9, 125.9, 124.7, 119.9, 80.8, 72.7, 47.0, 44.6, 43.6, 37.1, 36.0, 33.3, 28.2, 26.6.

7-(Ethylsulfonyl)-3-(2,2,2-trifluoroacetyl)-2,3,3a,4,6a,7-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazol-5(6*H*)-one (14). Pd/C (3%wt, 41 mg, 0.0115 mmol, 0.025 eq) was placed into a flask, CH_2Cl_2 (3 mL) was added at 0 °C, then K_2CO_3 (16 mg, 0.115 mmol, 0.25 eq) and *t*-BuOOH (5M in decane) (0.46 mL, 2.3 mmol, 5 eq) were added. **11c** (187 mg, 0.46 mmol, 1 eq) was dissolved in CH_2Cl_2 (2 mL) and added in the reaction mixture. The mixture was stirred at 0 °C for 8 h, then at rt overnight. DBU (137 μL, 0.92 mmol, 2 eq) was added and the mixture was refluxed for 6 h. After cooling to ambient, the reaction mixture was filtered on a short pad of celite, and washed with EtOAc. Solvents were removed to give a crude product, which was purified by silica gel chromatography (petroleum ether/EtOAc 70/30) to give **14** (90 mg, 0.22 mmol, 46% 2 steps) as a colorless oil. IR (film, NaCl): ν = 2963, 1694, 1477, 1455, 1349, 1259, 1152, 799 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.43-7.29 (m, 2H), 7.14-7.03 (m, 2H), 4.59-4.51 (m, 2H), 4.02-3.99 (m, 2H), 3.17-3.12 (m, 2H), 3.05-2.96 (m, 1H), 2.87-2.62 (m, 2H), 2.49-2.37 (m, 3H), 1.63-1.35 (m, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 204.29, 156.15, 139.98, 134.18, 130.23, 125.03, 125.22, 115.26, 116.05, 65.80, 61.69, 52.16, 46.91, 45.07, 43.92, 40.48, 38.19, 8.03. GC MS *m/z* (%): 156.0 (100), 267.1 $[M-SO_2Et-3F]^+$ (12), 359.2 $[M-3F]^+$ (10), 416.3 $[M]^+$ (52). HRMS (ESI): $[M+Na]^+$ $C_{18}H_{19}F_3N_2O_4SNa$: calcd. 439.0915, found 439.0914 (-0.3042 ppm).

3-(4-Chlorobutanoyl)-7-(ethylsulfonyl)-2,3,3a,4,6a,7-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazol-5(6*H*)-one (15). Pd/C (3%wt, 15 mg, 4.25x10^{-3} mmol, 0.025 eq) was placed into a flask, CH_2Cl_2 (1 mL) was added at 0 °C, then K_2CO_3 (6 mg, 0.0425 mmol, 0.25 eq) and *t*-BuOOH (5 M in decane) (0.17 mL, 0.85 mmol, 5 eq) were added. Compound **11b** (70 mg, 0.17 mmol, 1 eq) was dissolved in CH_2Cl_2 (1 mL) and added in the reaction mixture. The mixture was stirred at 0 °C for 10 h, then at rt overnight. DBU (52 μL, 0.34 mmol, 2 eq) was added, the mixture was then refluxed for 5.5 h. After cooling to room temperature, the reaction mixture was filtered on a short pad of celite, and washed with EtOAc. Solvents were removed to give a crude product which was purified by silica gel chromatography (petroleum ether/EtOAc 40/60), affording **15** (29 mg, 0.068 mmol, 40%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.42-7.29 (m, 2H), 7.09-7.04 (m, 2H), 4.58-4.43 (m, 2H), 3.81-3.78 (m, 2H), 3.68-3.65 (m, 2H), 3.16-3.12 (m, 2H), 3.08-2.79 (m, 2H), 2.65-2.10 (m, 8H), 1.39 (t, 3H, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 205.7, 171.1, 139.8, 135.3, 129.9, 124.9, 123.4, 115.1, 66.1, 59.7, 52.6, 46.8, 45.1, 44.8, 44.6, 44.7, 38.2, 31.4, 27.3, 8.1. MS (ESI) *m/z* (%): 321.1 $[M-CO(CH_2)_3Cl+H]^+$ (100), 343.1 $[M-CO(CH_2)_3Cl+Na]^+$ (20).

***N*-(2-(1-(2-(Ethylsulfonamido)phenyl)cyclohexa-2,5-dienyl)ethyl)but-2-ynamide (17a).** The amine **10** (100 mg, 0.32 mmol, 1 eq) was dissolved in CH_2Cl_2 (3 mL). 2-Butynoic acid (30 mg, 0.352 mmol, 1.1 eq) was added, followed by *N*-hydroxybenzotriazole (56 mg, 0.416 mmol, 1.3 eq), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC.HCl) (92 mg, 0.48 mmol, 1.5 eq) and diisopropylethylamine (0.16 mL, 0.96 mmol, 3 eq). The reaction mixture was stirred at rt overnight. A saturated aqueous NH_4Cl solution was added. The two layers were separated, then the aqueous layer was extracted with CH_2Cl_2 and the combined organic layers washed with a saturated aqueous NaCl solution and dried over Na_2SO_4. Evaporation of the solvent gave the crude product which was purified by silica gel chromatography (petroleum ether/EtOAc 80/20 → 60/40) to give **17a** (83 mg, 0.22 mmol, 69%) as a colorless oil. IR (film, NaCl): ν = 3342, 1635, 1540, 1332, 1146, 668 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300

MHz): δ (ppm) = 7.54-7.52 (m, 1H), 7.36-7.33 (m, 1H), 7.23-7.20 (m, 1H), 7.09-7.06 (m, 1H), 6.11-6.07 (m, 3H, NH), 5.51-5.46 (m, 2H), 3.38-3.30 (m, 2H), 3.12-3.05 (m, 2H), 2.90-2.84 (m, $2H_2$), 2.10 (t, 2H, J = 7.7 Hz), 1.89 (s, 3H), 1.31-1.25 (m, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 153.6, 137.6, 132.5, 130.2, 128.5, 126.7, 126.2, 124.0, 119.3, 83.3, 75.0, 46.5, 41.7, 38.5, 36.1, 25.8, 8.1, 3.7. GC MS *m/z* (%): 66.9 $[COC{\equiv}CMe]^+$ (100), 111.0 $[(CH_2)_2NHCOC{\equiv}CMe]^+$ (85), 261.0 $[\text{biaryl}]^+$ (5), 343.1 $[M\text{-}Et]^+$ (3), 372.1 $[M]^+$ (4). HRMS (ESI): $[M+Na]^+$ $C_{20}H_{24}N_2O_3SNa$: calcd. 395.1405, found 395.1406 (0.1660 ppm).

3-(*tert*-Butyldimethylsilyl)-*N*-(2-(1-(2-(ethylsulfonamido)phenyl)cyclohexa-2,5-dienyl)ethyl)propiloamide (17b). The amine **10** (300 mg, 0.98 mmol, 1 eq) was dissolved in CH_2Cl_2 (6 mL). 3-(*tert*-Butyldimethylsilyl)propiolic acid (199 mg, 1.078 mmol, 1.1 eq) was dissolved in CH_2Cl_2 (4 mL) and added to the mixture, followed by *N*-hydroxybenzotriazole (172 mg, 1.274 mmol, 1.3 eq), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC.HCl) (282 mg, 1.47 mmol, 1.5 eq) and diisopropylethylamine (0.5 mL, 2.94 mmol, 3 eq). The reaction mixture was stirred at rt overnight and a saturated aqueous NH_4Cl solution was added. The two layers were separated, then the aqueous layer extracted with CH_2Cl_2 and the combined organic layers washed with a saturated aqueous NaCl solution and dried over Na_2SO_4. Evaporation of the solvent gave the crude product which was purified by silica gel chromatography (petroleum ether/EtOAc 90/10 → 70/30) to give **17b** (294 mg, 0.62 mmol, 63%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.57-7.54 (m, 1H), 7.38-7.37 (m, 1H), 7.25-7.23 (m, 1H), 7.11-7.06 (m, 1H), 6.12-6.08 (m, 2H), 5.50 (d, 2H, J = 10.2 Hz), 3.40-3.33 (m, 2H), 3.10 (q, 2H, J = 7.5 Hz), 2.89 (q, 2H, J = 19 Hz), 2.16-2.11 (m, 2H), 1.33-1.24 (m, 3H), 0.95 (s, 9H), 0.13 (s, 6H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 152.8 (C=O), 137.7, 132.5, 130.2, 128.6, 126.9, 126.3, 124.0, 119.4, 98.6, 90.0, 46.5, 41.8, 38.5, 36.3, 26.1, 25.9, 16.6, 8.1. MSMS (ESI) *m/z* (%): 170 (100), 197 $[M\text{-}SO_2Et\text{-}NHCOC{\equiv}CTBDMS]^+$ (35), 288 $[M\text{-}ArNHSO_2Et]^+$ (66), 380 $[M\text{-}SO_2Et]^+$, 473 $[M+H]^+$ (30). HRMS (ESI): $[M+Na]^+$ $C_{25}H_{36}N_2O_3SSiNa$: calcd. 495.2108, found 495.2086 (-4.4722 ppm).

3-But-2-ynoyl-7-(ethylsulfonyl)-2,3,3a,4,6a,7-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazol-5(6*H*)-one (18a). Pd/C (3%wt, 11 mg, 3.10^{-3} mmol, 0.025 eq) was placed into a flask, CH_2Cl_2 (1 mL) was added at 0 °C, then K_2CO_3 (4 mg, 0.03 mmol, 0.25 eq) and *t*-BuOOH (5 M in decane) (0.12 mL, 0.6 mmol, 5 eq) were added. **17a** (46 mg, 0.12 mmol, 1 eq) was dissolved in CH_2Cl_2 (1 mL) and added in the reaction mixture. The mixture was stirred at 0 °C for 8 h and then at rt overnight. DBU (35 µL, 0.24 mmol, 2 eq) was added and the mixture refluxed for 2 h. After cooling to ambient, the reaction mixture was filtered on a short pad of celite, and washed with EtOAc. Solvents were removed to give a crude product, which was purified by silica gel chromatography (petroleum ether/EtOAc 40/60) to give **18a** (28 mg, 0.072 mmol, 60%) as a colorless oil. IR (film, NaCl): ν = 1721, 1622, 1411, 1347, 1153 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.45-7.26 (m, 4H), 7.14-7.01 (m, 4H), 4.54-4.41 (m, 4H), 3.97-3.92 (m, 2H), 3.81-3.77 (m, 2H), 3.16-3.07 (m, 4H), 3.02-2.79 (m, 4H), 2.67-2.54 (m, 2H), 2.48-2.28 (m, 6H), 2.01 (d, 6H, *J* = 17 Hz), 1.42-1.35 (m, 6H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): (2 rotamers are observed at room temperature): δ (ppm) = 205.2, 205.0, 153.4, 152.9, 139.9, 139.3, 135.6, 134.8, 130.0, 129.9, 125.3, 124.8, 123.4, 115.2, 115.1, 89.5, 89.3, 74.1, 73.7, 66.1, 65.7, 60.7, 59.4, 53.8, 53.2, 46.9, 46.3, 46.1, 44.7, 44.1, 44.0, 43.7, 41.1, 37.6, 37.2, 8.1, 4.2. GC MS *m/z* (%): 66.9 [COC≡CMe]$^+$, 386.2 [M]$^+$ (1.2). HRMS (ESI): [M+H]$^+$ $C_{20}H_{23}N_2O_4S$: calcd. 387.1378, found 387.1375 (-0.9151 ppm). [M+Na]$^+$ $C_{20}H_{22}N_2O_4SNa$: calcd. 409.1197, found 409.1192.

3-(3-(*tert*-Butyldimethylsilyl)propioloyl)-7-(ethylsulfonyl)-2,3,3a,4,6a,7-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazol-5(6*H*)-one (18b). Pd/C (3%wt, 19 mg, 5.25x10^{-3} mmol, 0.025 eq) was placed into a flask. CH_2Cl_2 (1 mL) was added at 0 °C, then K_2CO_3 (7 mg, 0.0525 mmol, 0.25 eq) and *t*-BuOOH (5 M in decane) (0.21 mL, 1.05 mmol, 5 eq) were added. Compound **17b** (100 mg, 0.21 mmol, 1 eq) was dissolved in CH_2Cl_2 (1 mL) and added in the reaction mixture, which was stirred at 0 °C for 8 h, then at rt overnight. DBU (63 μL, 0.42 mmol, 2 eq) was added and the mixture refluxed for 1.5 h. After cooling to ambient, the reaction mixture was filtered on a short pad of celite, and washed with EtOAc. Solvents were removed to give a crude oil, which was purified by silica gel chromatography (petroleum ether/EtOAc 70/30) to give **18b** (50 mg, 0.103 mmol, 49%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.42-7.30 (m, 2H), 7.13-7.04 (m, 2H), 4.57-4.42 (m, 2H), 3.98-3.93 (m, 1H), 3.80-3.78 (m, 1H), 3.17-3.08 (m, 3H), 3.01-2.93 (m, 1H), 2.81-2.65 (m, 1H), 2.52-2.30 (m, 3H), 1.41-1.38 (m, 3H), 0.92 (d, 9H), 0.16 (d, 6H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): (2 rotamers are observed at room temperature): δ (ppm) = 205.1, 204.1, 152.7, 152.1, 139.9, 139.3, 135.6, 134.7, 130.1, 130.0, 125.3, 124.9, 123.5, 123.4, 115.2, 115.1, 97.2, 97.1, 96.5, 66.2, 65.7, 61.0, 59.6, 54.0, 53.2, 46.9, 46.6, 46.3, 44.4, 44.2, 44.0, 43.8, 41.0, 37.7, 37.1, 26.1, 16.6, 8.1, -5.0, -5.1. MSMS (ESI) *m/z* (%): 337 [M-SO_2Et-*t*-Bu+H]$^+$ (100), 394 [M-SO_2Et]$^+$ (28), 429 [M-*t*-Bu]$^+$ (20), 487 [M+H]$^+$ (27). HRMS (ESI): [M+H]$^+$ $C_{25}H_{35}N_2O_4SSi$: calcd. 487.2081, found 487.2081.

6-(Ethylsulfonyl)-3-methyl-3a^1,5,5a,6,11,12-hexahydro-1*H*-indolizino[8,1-*cd*]carbazole-1,4(3a*H*)-dione (19). Compound **18a** (95 mg, 0.24 mmol, 1 eq) was dissolved in *tert*-butanol (5 mL) and heated to 30 °C. *t*-BuOK (55 mg, 0.484 mmol, 2 eq) was added and the yellow mixture stirred for 1.5 h. Water was added to the orange mixture, which was extracted with EtOAc. The organic layer was washed with a saturated aqueous solution of NaCl and dried over $MgSO_4$. Solvent was removed to give a yellow oil, which was purified through silica gel chromatography (EtOAc 100%) to give **19** (62 mg, 0.16 mmol, 66%) as a white powder. Mp 238.5-239.4 °C. IR (film, NaCl): ν = 2921, 1717, 1665, 1616, 1457, 1345, 1152 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.32-7.12 (m, 4H), 5.83 (s, 1H), 4.62 (t, 1H, *J* = 5.67 Hz), 4.35 (d, 1H, *J* = 5.28 Hz), 3.98-3.93 (m, 1H), 3.61-3.54 (m, 1H), 3.17 (qd, 2H, *J* = 2, 9 Hz), 2.9 (d, 2H, J_{AB} = 32 Hz, *J* = 5 Hz), 2.80 (d, 1H, *J* = 5 Hz), 2.33-2.29 (m, 2H), 1.99 (s, 3H_3), 1.41 (t, 3H, *J* = 7 Hz).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 203.4, 163.3, 148.1, 141.7, 130.6, 130.0, 124.5, 123.2, 122.1, 115.0, 68.4, 64.7, 52.7, 48.8, 47.3, 44.0, 42.5, 37.8, 23.2, 7.9. MSMS (ESI) *m/z* (%): 316 $[M-SO_2Et+Na]^+$ (23), 409 $[M+Na]^+$(100). HRMS (ESI): $[M+Na]^+$ $C_{20}H_{22}N_2O_4SNa$: calcd. 409.1192, found 409.1195.

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