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A diversity oriented four-component approach to tetrahydro-β-carbolines initiated by Sonogashira coupling

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A consecutive four-component synthesis of highly-substituted tetrahydro-β-carbolines **6** can be achieved by a coupling-aminatio-aza-annulation-Pictet–Spengler (CAAPS) sequence creating five new σ-bonds and four new stereocenters in a one-pot fashion. The structures were unambiguously supported by X-ray structure analyses.

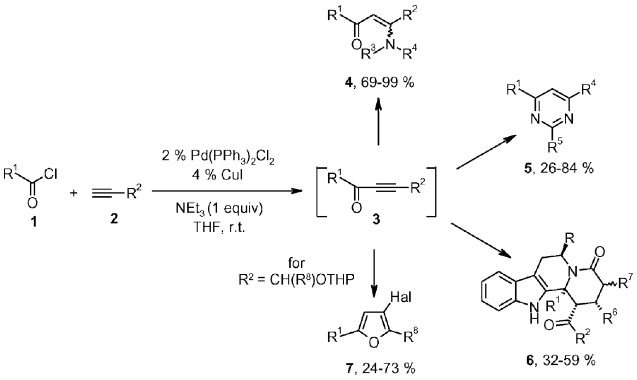
Introduction

Tetrahydro-β-carbolines not only constitute subunits in numerous alkaloids[1] but they are also templates for drug discovery and have been used as scaffolds for combinatorial libraries. They display a pronounced antitumor and antiviral activity[2] and some of them have been shown to efficiently inhibit monoamine oxidase A[3] and bind with nanomolar affinity to serotonin receptors in the central nervous system.[4] Hence, the development of concise and modular syntheses of this class of heterocycles is a highly rewarding methodological challenge for the rapidly evolving field of diversity oriented synthesis.

In particular, multi-component reactions and sequential one-pot processes address very fundamental principles of synthetic efficiency and reaction design[5] and are steadily gaining a considerable and increasing academic, economic and ecological interest. Additionally, the modular aspect of one-pot reactions can be readily expanded into combinatorial and solid phase syntheses[5,6] promising manifold opportunities for developing novel lead structures of pharmaceuticals, catalysts and even novel molecule based materials. Thus, the concept of integrating modern cross-coupling methodology, such as Sonogashira coupling,[7,8] and well-established Michael addition chemistry into a one-pot consecutive process has been an ongoing focus in our group.[9]

Recently, we have demonstrated that Sonogashira coupling of acid chlorides **1** and terminal alkynes **2** under extremely mild conditions, *i.e.* using only one equivalent of triethylamine as the base,[10] furnishes ynones **3** that represent extremely versatile building blocks in heterocyclic chemistry[11–14] due to their highly activated triple bond which lends itself to Michael addition. Therefore, they can directly and without isolation be transformed into β-enaminones **4**,[15] pyrimidines **5**,[10,15] tetrahydro-β-carbolins **6**[16] and halofurans **7**[17] in a one-pot fashion (Scheme 1).

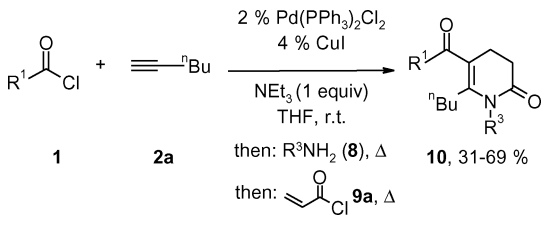
In particular, the synthesis of tetrahydro-β-carbolines **6** most clearly demonstrates the potential of this methodology for the rapid construction of highly-substituted, complex heterocycles where 5 new σ-bonds and 4 new stereocenters can be installed in a sequence of consecutive one-pot transformations. Here we report details and mechanistic studies on the facile synthesis of tetrahydro-β-carbolines **6** by a coupling-amination-aza-annulation-Pictet–Spengler (CAAPS) sequence.



Scheme 1 One-pot syntheses of enaminones and heterocycles initiated by Sonogashira coupling of acid chlorides.

Results and discussion

According to the basic principles of multi-component reactions the products of consecutive transformations should preferentially contain substantial fragments of all starting materials, thus providing a high degree of atom-efficiency. As a consequence, the use of β-enaminones **4** in the heterocyclic synthesis as synthetic equivalents of 1,3-dicarbonyl compounds would only result in an additional step in a reaction sequence, since ynones react with binucleophiles as well giving rise to the same products. On the other hand, it could be even more useful to take advantage of the unique electronically amphoteric reactivity of β-enaminones **4** trying to conserve all atoms in the final product, including the enamino nitrogen atom. As a major consequence of our modified Sonogashira conditions,[10] the reaction medium after the first cross-coupling and the stoichiometric amine addition steps is essentially neutral. Therefore, we decided to apply α,β-unsaturated chlorides **9** as a fourth component, thus probing the compatibility of a subsequent aza-annulation reaction[18] with the conditions of the coupling–amination (CA) sequence (Scheme 2, Table 1).



Scheme 2 One-pot four-component coupling-amination-aza-annulation (CAA) sequence.

Hence, after performing the CA reaction with acid chlorides **1**, 1-hexyne (**2a**), and benzyl amine (**8a**) or homoveratryl amine (**8b**), acryloyl chloride (**9a**) was added and after gentle heating the intermediate enaminones were smoothly converted into 5-acyl dihydropyrid-2-ones **10** that were isolated in moderate to good yield as yellow or colorless oils. Interestingly, the use of

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Table 1 One-pot four component coupling-amination-aza-annulation (CAA) sequence

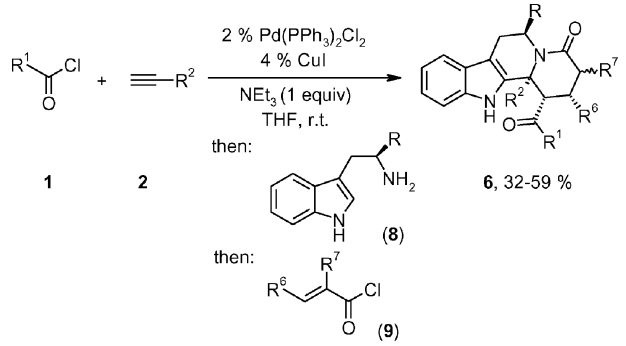
Entry	Acid chloride **1**	Amine **8**	5-Acyl dihydropyrid-2-one **10**
1	R^1 = 2-thienyl (**1a**)	R^3 = Bn (**8a**)	**10a** (R^1 = 2-thienyl, R^3 = Bn, 31%)[a]
2	R^1 = *p*-$MeOC_6H_4$ (**1b**)	**8a**	**10b** (R^1 = *p*-$MeOC_6H_4$, R^3 = Bn, 63%)[b]
3	**1a**	R^3 = $(MeO)_2C_6H_3CH_2CH_2$ (**8b**)	**10c** (R^1 = 2-thienyl, R^3 = $(MeO)_2C_6H_3CH_2CH_2$, 69%)[c]

[a] 1.2 Equiv of benzyl amine (**8a**) and 1.2 equiv of acryloyl chloride (**9a**) were used. [b] 1.2 Equiv of benzyl amine (**8a**) and 1.5 equiv of acryloyl chloride (**9a**) were used. [c] 1.2 Equiv of homoveratryl amine (**8b**) and 2.1 equiv of acryloyl chloride (**9a**) were used.

a slight excess of acryloyl chloride (**9a**) leads to the significant increase of the yield (compare entries 1 and 2).

The structure of the lactams **10** is unambiguously supported by the spectroscopic data. Characteristically, in the ^{1}H NMR spectra the resonances of two CH_2 groups are found at δ 2.39–2.69 either as distinct singlets (**10a**, **10c**) or as two multiplets (**10b**). Accordingly, in the ^{13}C NMR spectra the carbon resonances of dihydropyrid-2-one systems can be unambiguously assigned at δ 30.3–32.0 for the two CH_2 groups, at δ 118.2–119.5 and δ 144.5–145.0 for two quaternary olefinic carbons, and at δ 170.6–171.1 for the quaternary amide carbon. In addition, the mass spectrometric and IR spectroscopic data corroborate the suggested molecular structure of these aza-annulation products.

However, upon applying tryptamine (**8c**) or L-tryptophane methylester (**8d**) as primary amines in the CAA sequence the lactams **10** were not the final reaction products, but as a result of a subsequent Pictet–Spengler reaction,[19] only the indolo[2,3-*a*] quinolizin-4-ones **6** were isolated in moderate to good yields as colorless crystals (Scheme 3, Table 2).



Scheme 3 One-pot four-component coupling-amination-aza-annulation-Pictet–Spengler (CAAPS) sequence.

Thus, a Pictet–Spengler cyclization,[20] *i.e.* an *N*-acyliminium cyclization,[21] terminates the CAA reaction in the sense of a four-component coupling-aza-annulation-Pictet–Spengler (CAAPS) sequence and generates a maximum of structural complexity and diversity in a one-pot fashion.

The results show that the CAAPS sequence proceeds with good yields for electron deficient (entry 2) and electron rich (entry 3) aromatic acid chlorides. Heteroaromatic (entries 1, 4–10) and even aliphatic (entry 11) acid chlorides can be introduced into the sequence. The substitution pattern on the alkyne **2** component is also highly flexible. In the case of phenylacetylene (**2b**) the prolongation of heating is required to complete the reaction. For example, after 3 h of reflux the desired product **6d** was obtained in only 27%, and 32% of an uncyclized aza-annulation product was isolated. After 24 h of reflux, 41% of **6d** was obtained, while no traces of the aza-annulation product were detected. This sluggish reaction is presumably caused by the steric hindrance of the phenyl substituent.

It is worth mentioning that for the complete conversion of the ynone to the β-enaminone, 2 equiv of the amine **8c** were required, due to a partial conversion to the hydrochloride (entries 1–9). However, this amount can be reduced to 1.1 equiv simply by adding 1.0 equiv of DBU as a strong, non-nucleophilic base to the reaction mixture in the second step (entries 10–11).

Interesting, however, is the excellent diastereoselectivity of the CAAPS sequence where the R^2, acyl-R^1, and R^6 substituents are exclusively placed in a *syn–syn* arrangement (Table 2, entries 1–5, 7–11), whereas with a substituent R^7 other than hydrogen, epimers are formed with moderate selectivity (entry 6, dr = 4.5 : 1). Most surprisingly, with (*S*)-(-)-tryptophan methyl ester (**8d**) as a tryptamine derivative the only cyclization product isolated in 45% yield is the tetrahydro-β-carboline **6h** (entry 8, Fig. 1) that is formed as a single diastereomer.

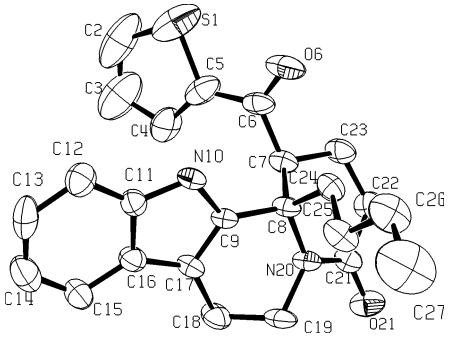


Fig. 1 ORTEP plot of **6a** (R^1 = 2-thienyl, R^2 = ^{n}Bu, R = R^6 = R^7 = H, hydrogen atoms were omitted for clarity).

The successful formation of the indolo[2,3-*a*] quinolizin-4-one core and the relative stereochemistry is unambiguously supported by numerous X-ray structure analyses (for **6a**, **6b**, **6c**, **6e**, **6f** and **6h** see Figs 1–6).†

† Crystal data for **6a–c,e–f,h,l**. Data were collected on a Bruker Smart CCD diffractometer for **6a**, **6b**, **6c**, **6e**, **6f**, **6l**, and on a Bruker APEX diffractometer at for **6h**. Mo K_α radiation was used in all cases and the intensities were corrected for absorption effects using SADABS[25] based on the laue symmetry of the reciprocal space. The structures were solved by direct methods and refined against F^2 with a full matrix least square algorithm by using the SHELXTL[25] software package. Hydrogen atoms were refined isotropically for **6h** and in several cases where they were attached to heteroatoms, in all other cases they were considered at calculated positions and refined using appropriate riding models. In the case of **6c** slight disorder had to be considered for the last atom of the butyl chain, in **6f** the thiophen rings occur in two alternative orientations, additionally some electron density of severe disordered solvent was found. **6a**: $C_{24}H_{26}N_2O_2S \times CH_2Cl_2$, M = 491.45, orthorhombic, space group $Pna2_1$, a = 24.218(1), b = 14.582(1), c = 14.204(1) Å, V = 5016.0(3) Å^3, T = 200(2) K, Z = 8, ρ_{calc} = 1.302 g cm^{-3}, crystal dimensions 0.34 × 0.34 × 0.18 mm^3, Θ_{max} = 21.96 deg, 31357 reflections measured, 6126 unique (R_{int} = 0.0396), 5352 observed ($I > 2\sigma(I)$), μ = 0.37 mm^{-1}, T_{min} = 0.89, T_{max} = 0.94, 578 parameters refined, R_1 = 0.059 and $wR2$ = 0.153 for observed reflections, residual electron density −0.49 to 0.59 e Å^{-3}. **6b**: $C_{26}H_{27}N_3O_4$, M = 445.5, monoclinic, space group $P2_1/c$, a = 11.762(1), b = 13.007(1), c = 14.732(1) Å, β = 97.724(1)°, V = 2233.3(1) Å^3, T = 200(2) K, Z = 4, ρ = 1.325 g cm^{-3}, crystal dimensions 0.40 × 0.34 × 0.11 mm^3, Θ_{max}= 27.46 deg, 22678 reflections measured, 5107 unique (R_{int} = 0.0294), 3941 observed ($I > 2\sigma(I)$), μ = 0.09 mm^{-1}, T_{min} = 0.96, T_{max} = 0.99, 298 parameters refined, $R1$ = 0.041 and $wR2$ = 0.100 for observed reflections, residual electron density −0.27 to 0.33 e Å^{-3}. **6c**: $C_{27}H_{30}N_2O_3$, M = 430.5, monoclinic,

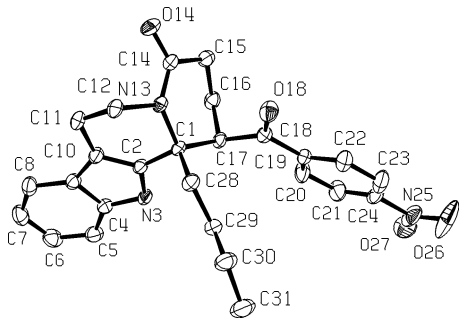


Fig. 2 ORTEP plot of **6b** ($R^1 = p\text{-}O_2NC_6H_4$, $R^2 = {}^n\text{Bu}$, $R = R^6 = R^7 = H$, hydrogen atoms were omitted for clarity).

In addition, in the ^{1}H NMR spectra a single set of signals corresponding to 1,2,3,6,7-H protons of quinolizin-4-one is found in a range of δ 1.96–5.52 (Fig. 7).

First, the equatorial proton 6-H_a appearing at δ 4.76–5.25 can be unambiguously assigned due to its characteristic downfield shift by the deshielding of the adjacent amide carbonyl group. Usually, it appears as a doublet of doublets of doublets with coupling constants of ^2J = 12.7–12.8 Hz, ^3J = 4.6–4.8 Hz (equatorial–axial, *cf.* dihedral angle from X-ray of 43–54°) and ^3J = 1.3–1.8 Hz (equatorial–equatorial, *cf.* dihedral angle from X-ray of 65–75°). For compound **6h** where the ester group adopts an equatorial position the resonance at δ 5.52 can be assigned to 6-H_α and gives rise to a doublet of doublets with coupling constants of ^3J = 6.8 Hz (axial–axial) and ^3J = 2.7 Hz (axial–equatorial). The other signals were readily assigned though NOESY and COSY experiments. The resonances of 6-H_β are detected at δ 2.91–3.41 as doublets of triplets with coupling constants of ^2J = 12.0–12.7 Hz and ^3J = 3.4–4.7 Hz.

space group $C2/c$, a = 15.691(1), b = 16.534(1), c = 18.142(1) Å, β = 99.574(1)°, V = 4641.2(1) Å^3, T = 298(2) K, Z = 8, ρ = 1.232 g cm^{-3}, crystal dimensions 0.46 × 0.32 × 0.30 mm^3, Θ_{max} = 27.47 deg, 23712 reflections measured, 5323 unique (R_{int} = 0.0371), 2835 observed ($I > 2\sigma(I)$), μ = 0.08 mm^{-1}, T_{min} = 0.96, T_{max} = 0.98, 300 parameters refined, $R1$ = 0.049 and $wR2$ = 0.120 for observed reflections, residual electron density −0.18 to 0.22 e Å^{-3}. **6e**: $C_{25}H_{28}N_2O_2S \times CH_3OH$, M = 452.61, monoclinic, space group $P2_1/n$, a = 9.892(1), b = 10.392(1), c = 23.113(1) Å, β = 95.472(1)°, V = 2365.2(1) Å^3, T = 200(2) K, Z = 4, ρ = 1.271 g cm^{-3}, crystal dimensions 0.46 × 0.28 × 0.08 mm^3, Θ_{max} = 27.45 deg, 23864 reflections measured, 5407 unique (R_{int} = 0.0363), 3937 observed ($I > 2\sigma(I)$), μ = 0.167 mm^{-1}, T_{min} = 0.94, T_{max} = 0.99, 300 parameters refined, $R1$ = 0.041 and $wR2$ = 0.103 for observed reflections, residual electron density −0.50 to 0.25 e Å^{-3}. **6f**: $C_{25}H_{28}N_2O_2S$, M = 420.6, monoclinic, space group $P2_1/n$, a = 8.624(1), b = 22.051(1), c = 13.223(1) Å, β = 100.164(1)°, V = 2475.1(1) Å^3, T = 200(2) K, Z = 4, ρ = 1.129 g cm^{-3}, crystal dimensions 0.50 × 0.26 × 0.22 mm^3, Θ_{max} = 27.50 deg, 25612 reflections measured, 5688 unique (R_{int} = 0.0437), 3739 observed ($I > 2\sigma(I)$), μ = 0.15 mm^{-1}, T_{min} = 0.93, T_{max} = 0.97, 324 parameters refined, $R1$ = 0.068 and $wR2$ = 0.191 for observed reflections, residual electron density −0.58 to 0.65 e Å^{-3}. **6h**: $C_{26}H_{28}N_2O_4S \times CH_2Cl_2$, M = 549.5, monoclinic, space group $P2_1$, a = 12.022(1), b = 14.950(1), c = 14.663(1) Å, α = 90.0°, β = 94.869(2)°, γ = 90.0°, V = 2625.9(4) Å^3, T = 100(2) K, Z = 4, ρ = 1.390 g cm^{-3}, crystal dimensions 0.21 × 0.15 × 0.12 mm^3, Θ_{max} = 26.37 deg, 23151 reflections measured, 10561 unique (R_{int} = 0.0423), 9120 observed ($I > 2\sigma(I)$), μ = 0.36 mm^{-1}, T_{min} = 0.93, T_{max} = 0.96, 877 parameters refined, $R1$ = 0.050 and $wR2$ = 0.107 for observed reflections, residual electron density −0.24 to 0.46 e Å^{-3}. **6l**: $C_{18}H_{20}N_2O_3$, M = 312.4, monoclinic, space group $P2_1/c$, a = 11.526(1), b = 12.965(1), c = 10.742(1) Å, β = 94.770(1)°, V = 1599.6(1) Å^3, T = 200(2) K, Z = 4, ρ = 1.297 g cm^{-3}, crystal dimensions 0.42 × 0.22 × 0.16 mm^3, Θ_{max} = 27.47 deg, 16235 reflections measured, 3648 unique (R_{int} = 0.0298), 3011 observed ($I > 2\sigma(I)$), μ = 0.09 mm^{-1}, T_{min} = 0.96, T_{max} = 0.99, 288 parameters refined, $R1$ = 0.036 and $wR2$ = 0.089 for observed reflections, residual electron density −0.24 to 0.19 e Å^{-3}. CCDC reference numbers 281672 (**6a**), 281673 (**6b**), 281674 (**6c**), 281675 (**6e**), 281676 (**6f**), 235421 (**6h**), and 281677 (**6l**). For crystallographic data in CIF or other electronic format see DOI: 10.1039/b511861a

Table 2 Coupling-amination-aza-annulation-Pictet–Spengler (CAAPS) sequence to indolo[2,3-*a*] quinolizin-4-ones **6**

Entry	Acid chloride **1**	Alkyne **2**	Tryptamine **8**	α,β-Unsaturated acid chloride **9**	Tetrahydro-β-carboline **6** (yield)
1[a]	R^1 = 2-thienyl (**1a**)	$R^2 = {}^n\text{Bu}$ (**2a**)	R = H (**8c**)	$R^6 = R^7$ = H (**9a**)	**6a** (R^1 = 2-thienyl, $R^2 = {}^n\text{Bu}$, R = $R^6 = R^7$ = H, 52%)
2[a]	$R^1 = p\text{-}O_2NC_6H_4$ (**1c**)	**2a**	**8c**	**9a**	**6b** ($R^1 = p\text{-}O_2NC_6H_4$, $R^2 = {}^n\text{Bu}$, R = $R^6 = R^7$ = H, 43%)
3[a]	$R^1 = p\text{-}MeOC_6H_4$ (**1b**)	**2a**	**8c**	**9a**	**6c** ($R^1 = p\text{-}MeOC_6H_4$, $R^2 = {}^n\text{Bu}$, R = $R^6 = R^7$ = H, 59%)
4[a]	**1a**	R^2 = Ph (**2b**)	**8c**	**9a**	**6d** (R^1 = 2-thienyl, R^2 = Ph, R = $R^6 = R^7$ = H, 41%)
5[a]	**1a**	**2a**	**8c**	$R^6 = CH_3$, R^7 = H (**9b**)	**6e** (R^1 = 2-thienyl, $R^2 = {}^n\text{Bu}$, R = R^7 = H, $R^6 = CH_3$, 50%)
6[a]	**1a**	R^2 = TMS (**2c**)	**8c**	R^6 = H, $R^7 = CH_3$ (**9c**)	**6f** (R^1 = 2-thienyl, $R^2 = {}^n\text{Bu}$, $R = R^6$ = H, $R^7 = CH_3$, 54%, *syn–syn* : *syn–anti* = 4.5 : 1)[b]
7[a]	**1a**	**2a**	**8c**[c]	**9a**	**6g** (R^1 = 2-thienyl, $R^2 = R = R^6 = R^7$ = H, 32%)
8[d]	**1a**	**2a**	R = CO_2CH_3 (**8d**)[e]	**9a**	**6h** (R^1 = 2-thienyl, $R^2 = {}^n\text{Bu}$, R = CO_2Me, $R^6 = R^7$ = H, 45%)
9[a]	**1a**	$R^2 = CH_2OTBS$ (**2d**)	**8c**	**9a**	**6i** (R^1 = 2-thienyl, $R^2 = CH_2OTBS$, R = $R^6 = R^7$ = H, 30%)
10[a]	R^1 = *N*-(phenylsulfonyl)-3-indolyl (**1d**)	**2a**	**8c**	**9a**	**6j** (R^1 = *N*-(phenylsulfonyl)-3-indolyl, $R^2 = {}^n\text{Bu}$, $R = R^6 = R^7$ = H, 36%)
11[a]	R^1 = isopropyl (**1e**)	**2a**	**8c**	**9a**	**6k** (R^1 = isopropyl, $R^2 = {}^n\text{Bu}$, R = $R^6 = R^7$ = H, 36%)

[a] In THF. [b] The mixture of diastereomers was separated by column chromatography. [c] After the coupling step 1.00 mmol of an aqueous TBAF solution was added and the reaction mixture was stirred for 5 min prior to the addition of **8a**. [d] In toluene. [e] Together with 2.00 mmol of **8b** (as a hydrochloride), 0.28 mL (2.00 mmol) of triethylamine were added.

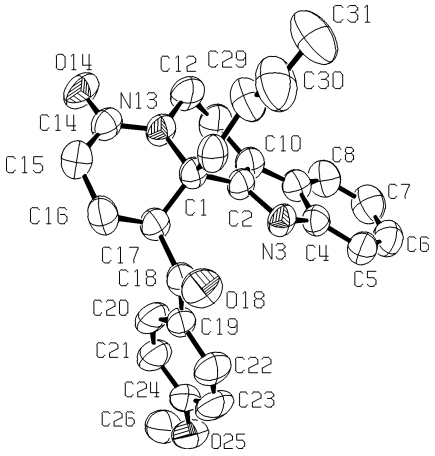


Fig. 3 ORTEP plot of **6c** (R^1 = *p*-$MeOC_6H_4$, R^2 = ^{n}Bu, R = R^6 = R^7 = H, hydrogen atoms were omitted for clarity).

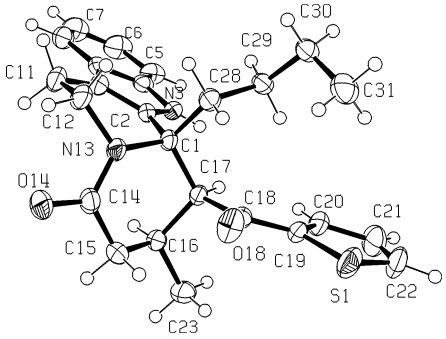


Fig. 4 ORTEP plot of **6e** (R^1 = 2-thienyl, R^2 = ^{n}Bu, R = R^7 = H, R^6 = CH_3).

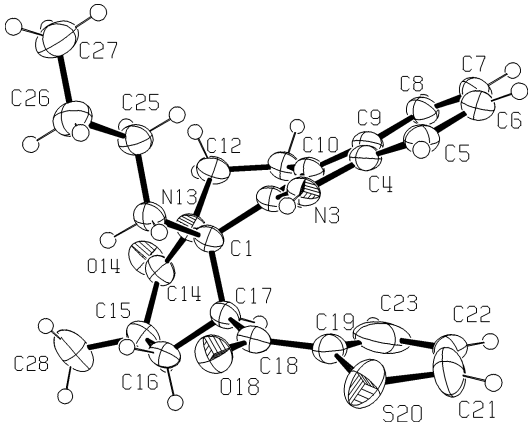


Fig. 5 ORTEP plot of **6f** (R^1 = 2-thienyl, R^2 = ^{n}Bu, R = R^6 = H, R^7 = CH_3), major diastereomer.

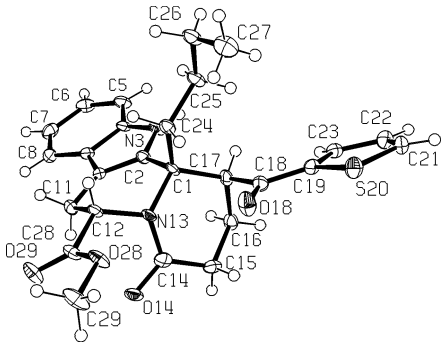


Fig. 6 ORTEP plot of **6h** (R^1 = 2-thienyl, R^2 = ^{n}Bu, R = CO_2CH_3, R^6 = R^7 = H).

The resonances of 7-H are identified in the region of δ 2.66–2.93 and overlap with the butyl protons, but for **6d** they are found as a doublet of triplets with coupling constants of ^2J = 15.1 Hz and ^3J = 5.6 Hz and a doublet of doublets with coupling constants of ^2J = 14.9 Hz and ^3J = 4.2 Hz. For **6e** the resonances of 7-H give rise to a doublet of doublets of doublets at δ 2.80 with coupling constants of ^2J = 15.6 Hz, ^3J = 11.5 Hz (axial–axial) and ^3J = 6.9 Hz (axial–equatorial) and a doublet of doublets at δ 2.55 with coupling constants of ^2J = 15.6 Hz and ^3J = 5.0 Hz (equatorial–axial). Accordingly, the resonances of 1-H, which usually adopts an axial position, are found at δ 3.16–4.90 appearing as doublets of doublets with coupling constants of ^3J = 13.1–13.5 Hz (axial–axial, *cf.* dihedral angle from X-ray of 170–173°) and 5.0–6.0 Hz (axial–equatorial, *cf.* dihedral angle from X-ray of 52–54°) and can be unambiguously assigned by the cross-peak of ^1CH carbon and ^{1}H proton in HMBC spectra, since usually only one CH group is present in compounds. Finally, 2-H resonances can be detected at δ 1.88–2.62 and 3-H resonances at δ 2.31–2.93, which can be readily assigned from the COSY experiments.

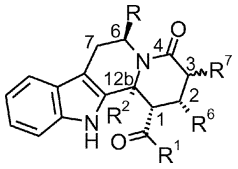
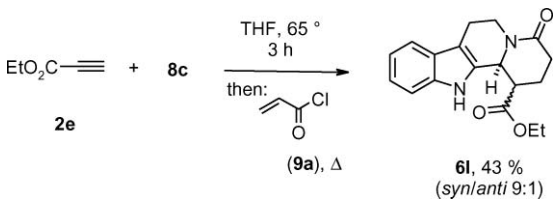


Fig. 7 Numeration of quinolizinone core.

For compound **6g** the most interesting information stems from the coupling constant of 1-H and 12b-H resonances. The resonance of 12b-H gives rise to a doublet at δ 5.44 with a coupling constant of ^3J = 10.0 Hz (axial–axial coupling, confirming a *trans*-relationship), the resonance of 1-H appears as a doublet at δ 3.60 with coupling constants of ^3J = 12.0 Hz (axial–axial), ^3J = 10.0 Hz (axial–axial coupling, confirming a *trans*-relationship) and ^3J = 3.2 Hz (axial–equatorial) coupling.

For alkynes bearing an electron withdrawing group this sequence can be performed without the first cross-coupling step in a three-component fashion (Scheme 4).



Scheme 4 One-pot three-component amination–aza-annulation-Pictet–Spengler sequence (AAPS).

This time, since triethylammmonium hydrochloride is absent from the reaction mixture, only 1.0 equiv of tryptamine **8c** is sufficient to complete the β-enaminone formation. Hence, this one-pot three-component amination-aza-annulation-Pictet–Spengler (AAPS) sequence provides additional flexibility in the tetrahydro-β-carboline substitution pattern. The structure of the major diastereomer is unambiguously supported by X-ray structure analysis (for **6l** see Fig. 8).†

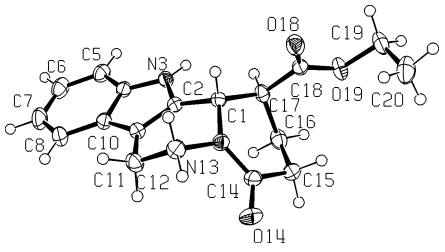
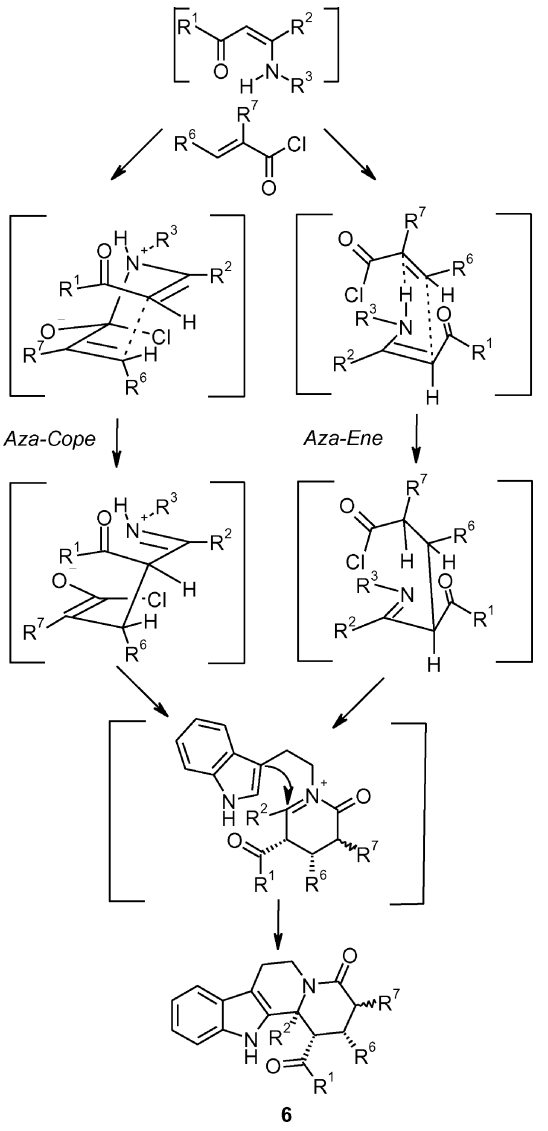


Fig. 8 ORTEP plot of **6l** (R^2 = OEt, R^1 = R = R^6 = R^7 = H), major diastereomer.

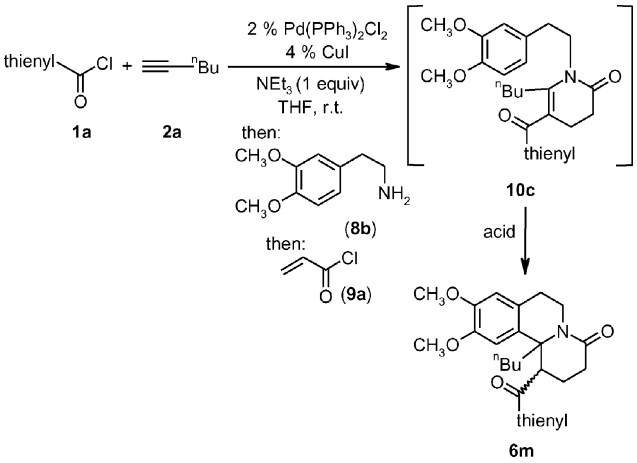
In order to rationalize the exclusive diastereoselectivity of the CAAPS sequence two mechanistic pathways were proposed (Scheme 5).



Scheme 5 Plausible mechanistic pathways.

First, the addition of tryptamine to ynones results in the formation of a (*Z*)-configured β-enaminone, which reacts with an α,β-unsaturated acid chloride either *via* a cationic aza–Cope-type rearrangement or *via* an aza–ene reaction.[22] In the first pathway a chair-like transition state is preferred, while in the latter case the transition state has an envelope conformation with an *endo*-electron withdrawing group lying over the fold of the envelope.[23] Both mechanisms rationalize the mutual *syn*-orientation of the R^6 and the carbonyl substituents. Finally, for the resulting acyliminium species an intramolecular nucleophilic attack by the indole can be expected to occur predominantly *anti* with respect to the more bulky carbonyl group, leading mainly to the *syn* diastereomer (with respect to R^2 and carbonyl substituents). Two diastereomers observed in the reaction with methacryloyl chloride ($R^7 = CH_3$) were formed most probably *via* epimerization.

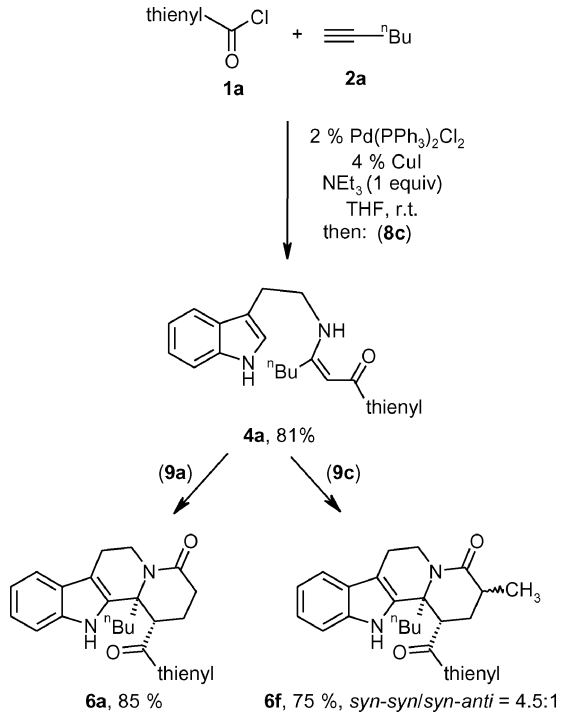
Next, we turned our attention to the case of the homoveratryamine **8b** that gave rise to the aza-annulation product **10c** (Scheme 2, Table 1). We reasoned that the aromatic ring of the homoveratryl amine carries activating substituents providing the electronic character for the annulation to occur. However, it seems as if the dimethoxyphenyl substituent is less nucleophilic in comparison to indole. Therefore, we decided to test a range of Lewis and Brønsted acids to enhance the electrophilicity of the acyliminium salt and to induce the Pictet–Spengler cyclization (Scheme 6).



Scheme 6 CAAPS sequence for homoveratryl amine (**8b**).

By applying strong Brønsted acids such as CH_3SO_3H, CF_3SO_3H or CF_3CO_2H the desired product **6m** was obtained in 55, 66 or 70% yields, respectively, but with low diastereoselectivity (dr 1–1.4 : 1). After addition of weak Lewis acids such as BF_3, trifluoroacetic anhydride or TMSCl, only the aza-annulation product **10c** was detected by TLC. Upon using stronger Lewis acids such as $TiCl_4$, $SnCl_4$ and $POCl_3$ the formation of a black tar was observed. Finally, TMSOTf was the superior Lewis acid resulting in the formation of **6m** in 65% with a dr of 1.6 : 1.

In order to compare our consecutive approach with the stepwise splitting protocol, we synthesized the β-enaminone **4a** in 81% yield *via* the coupling–amination sequence[15] and subjected it to the aza-annulation–PS sequence with acryloyl **9a** or methacryloyl **9c** chlorides (Scheme 7).



Scheme 7 CAAPS sequence as a splitting protocol.

Indolo[2,3-*a*] quinolizin-4-ones **6a** and **6f** were obtained in 85% and 75% yields, respectively. The overall yields for this splitting protocol lie in the same range as for the CAAPS sequence. However, avoiding the isolation and purification of

the intermediate β-enaminone favors the application of the direct CAAPS approach.

In conclusion, the four-component CAAPS sequence, where five bonds and four stereocenters are formed in a one-pot reaction, proceeds with reasonable yields and delivers, starting from electronically diverse acid chlorides and aliphatic, aromatic alkynes as well as (TMS)acetylene and a broad variety of tetrahydro-β-carbolines **6**. In addition, applying TMSOTf as a Lewis acid the enaminone of homoveratrylamine (**8b**) can be involved in a Pictet–Spengler cyclization again in a one-pot fashion. This synthesis provides a rapid access to highly-substituted subunits of numerous alkaloids. Further studies are currently in progress.

Experimental

All reactions were carried out in screw cap pressure vessels under a nitrogen atmosphere. The solvents were dried according to standard procedures[24] and were distilled prior to use. Column chromatography: silica gel 60 M (mesh 230–400) Macherey–Nagel. Thin layer chromatography (TLC): silica gel layered aluminium foil (60 F_{254} Merck, Darmstadt). Melting points (uncorrected): Reichert–Jung Thermovar and Büchi Melting Point B-540. $Pd(PPh_3)_2Cl_2$, CuI, acid chlorides **1**, hexyne (**2a**), phenylacetylene (**2b**), (trimethylsilyl)acetylene (**2c**), amines **8** and α,β-unsaturated chlorides **9** were purchased from ACROS or Merck and were used without further purification. ^1H and ^{13}C NMR, DEPT-, NOESY-, COSY-, HMQC-, and HMBC spectra were recorded on Bruker DRX 300 or Bruker DRX 500 spectrometers with $CDCl_3$ or DMSO-d_6 as solvents. The assignments of quaternary C, CH, CH_2 and CH_3 were made on the basis of DEPT spectra. IR: Bruker Vector 22 FT-IR spectrophotometer. MS: Jeol JMS-700 and Finnigan TSQ 700. Elemental analyses were carried out in the microanalytical laboratory of the Organisch-Chemisches-Institut der Universität Heidelberg.

General procedure for the CAA sequence

In a screw cap pressure vessel 14 mg (0.02 mmol) of $Pd(PPh_3)_2Cl_2$, and 7 mg (0.04 mmol) of CuI were dissolved in 5 mL of degassed THF. Then 0.14 mL (1.00 mmol) of triethylamine, as well as 1 mmol of acid chloride **1** and 0.12 mL (1.05 mmol) of hexyne **2a** were successively added to the solution. The reaction mixture was stirred for 2 h at room temperature until the conversion was complete (monitored by TLC). Afterwards 1.2 mmol of amine **8** were added and the reaction mixture was heated at 70 °C for 24 h. After complete conversion of the ynone to the enaminone (TLC), acryloyl chloride **9a** (1.2–2.1 mmol) was added and the reaction mixture was heated at 70 °C for 3 h. After cooling to room temperature the reaction mixture was diluted with methanol, stirred for 10 min, evaporated and applied to column chromatography on silica gel eluting with hexane–ethyl acetate 2 : 1 (**10a,b**) or ether (**10c**), to give the analytically pure 5-acyl dihydropyrid-2-ones **10** as oils (for experimental details, see Table 3).

1-Benzyl-6-butyl-5-(thiophene-2-carbonyl)-3,4-dihydro-1*H*-pyridin-2-one (10a). Colorless oil; (Found: 353.1470. $C_{21}H_{23}NO_2S$ requires 353.1444); ν_{max} (thin film)(cm^{-1}) 2957, 2930, 1683, 1634, 1515, 1454, 1412, 1373, 1286, 1180, 843 and 729; δ_H ($CDCl_3$, 300 MHz) 0.73 (t, J = 7.2 Hz, 3 H; CH_3), 1.10–1.23 (m, 2 H), 1.28–1.40 (m, 2 H), 2.12–2.18 (m, 2 H), 2.57 (s, 4 H; dihydropyrid-2-one CH_2CH_2), 4.89 (s, 2 H; PhCH_2), 6.94 (dd, J = 4.9 Hz, J = 3.8 Hz, 1 H), 7.09–7.28 (m, 6 H) and 7.51 (dd, J = 4.9 Hz, J = 1.1 Hz, 1 H); δ_C ($CDCl_3$, 75 MHz) 13.6 (CH_3), 22.2 (CH_2), 23.6 (CH_2), 29.5 (CH_2), 31.1 (CH_2; dihydropyrid-2-one), 31.9 (CH_2; dihydropyrid-2-one), 44.0 (CH_2; benzyl), 119.2 (C_{quat}), 126.3 (CH), 127.2 (CH), 127.9 (CH), 128.7 (CH), 132.6 (CH), 133.9 (CH), 137.7 (C_{quat}), 144.5 (C_{quat}), 145.7 (C_{quat}), 171.1 (C_{quat}; amide) and 188.3 (C_{quat}; ketone); m/z (EI^+) 353 (M^+, 37%), 320 ((M^+ − HS), 100) and 111 ((2-ThCO^+), 32).

1-Benzyl-6-butyl-5-(*p*-methoxybenzoyl)-3,4-dihydro-1*H*-pyridin-2-one (10b). Yellow oil; (Found: 377.1988. $C_{24}H_{27}NO_3$ requires 377.1991); ν_{max} (thin film)(cm^{-1}) 2957, 2931, 1679, 1599, 1372, 1257, 1143 and 1029; δ_H ($CDCl_3$, 300 MHz) 0.80 (t, J = 7.4 Hz, 3 H), 1.14–1.27 (m, 2 H), 1.33–1.46 (m, 2 H), 2.15 (t, J = 7.7 Hz, 2 H), 2.49–2.57 (m, 2 H), 2.61–2.69 (m, 2 H), 3.83 (s, 3 H; CH_3O), 4.98 (s, 2 H; PhCH_2), 6.84 (d, J = 8.8 Hz, 2 H), 7.19–7.39 (m, 5 H) and 7.61 (d, J = 8.8 Hz, 2 H); δ_C ($CDCl_3$, 75 MHz) 13.7 (CH_3), 22.3 (CH_2), 23.6 (CH_2), 29.4 (CH_2), 31.1 (CH_2; dihydropyrid-2-one), 32.0 (CH_2; dihydropyrid-2-one), 44.1 (CH_2; benzyl), 55.5 (CH_3; CH$_3$O), 113.8 (CH), 119.5 (C_{quat}), 126.5 (CH), 127.3 (CH), 128.8 (CH), 130.4 (C_{quat}), 131.2 (CH), 137.7 (C_{quat}), 144.7 (C_{quat}), 163.2 (C_{quat}), 171.1 (C_{quat}; amide) and 195.5 (C_{quat}; ketone); m/z (EI^+) 377 (M^+, 576), 360 (M^+ − OH, 36), 334 (M^+ − C_3H_7, 56) and 135 (*p*-$CH_3OC_6H_4CO^+$, 100).

1-[3,4-Dimethoxyphenylethyl]-6-butyl-5-(thiophene-2-carbonyl)-3,4-dihydro-1*H*-pyridin-2-one (10c). Colorless oil (~90% pure); R_f (product) 0.65 (neat diethyl ether); δ_H ($CDCl_3$, 250 MHz) 0.84 (t, J = 7.1 Hz, 3 H), 1.05–1.35 (m, 4 H), 2.16–2.24 (m, 2 H), 2.39 (s, 4 H; dihydropyrid-2-one CH_2CH_2), 2.70–2.78 (m, 2 H), 3.72 (s, 3 H; CH_3O), 3.75 (s, 3 H; CH_3O), 3.79–3.87 (m, 2 H), 6.64–6.70 (m, 3 H), 7.00 (dd, J = 4.9 Hz, J = 3.8 Hz, 1 H), 7.20 (dd, J = 3.8 Hz, J = 1.2 Hz, 1 H) and 7.54 (dd, J = 4.9 Hz, J = 1.2 Hz, 1 H); δ_C ($CDCl_3$, 75 MHz) 13.3 (CH_3), 21.8 (CH_2), 23.2 (CH_2), 28.7 (CH_2), 30.3 (CH_2), 31.4 (CH_2; dihydropyrid-2-one), 36.8 (CH_2; dihydropyrid-2-one), 42.1 (CH_2), 55.4 (CH_3; CH$_3$O), 55.5 (CH_3; CH$_3$O), 110.9 (CH), 111.8 (CH), 118.2 (C_{quat}), 120.5 (CH), 127.6 (CH), 130.5 (C_{quat}), 132.3 (CH), 133.6 (CH), 144.1 (C_{quat}), 145.0 (C_{quat}), 147.4 (C_{quat}), 148.5 (C_{quat}), 170.6 (C_{quat}; amide) and 188.0 (C_{quat}; ketone).

General procedure for the CAAPS sequence

In a screw cap pressure vessel 14 mg (0.02 mmol) of $Pd(PPh_3)_2Cl_2$, and 7 mg (0.04 mmol) of CuI were dissolved in 5 mL of degassed THF or toluene. Then 0.14 mL (1.00 mmol) of triethylamine, as well as 1 mmol of acid chloride **1** and 1.05 mmol of alkyne **2** were successively added to the solution. The reaction mixture was stirred for 2 h at room temperature until the conversion was complete (monitored by TLC). Afterwards 2.0 mmol of amine **8c** or **8d** were added (for **6j** and **6k** the amount of **8c** was reduced to 1.1 mmol, adding 0.15 mL (1.00 mmol) of DBU at the same time) and the reaction mixture was heated at 70 °C (THF) or 100 °C (toluene) for 10 h. After complete conversion of ynone to enaminone (TLC), an α,β-unsaturated acid chloride **9** (5.0 mmol) was added and the reaction mixture was heated at 70 °C for 3 h. After cooling to r.t. the reaction mixture was diluted with methanol, stirred for 10 min, evaporated and applied to column chromatography on

Table 3 Experimental details for the CAA sequence

Acid chloride **1**	Amine **8**	Acryloyl chloride (**9a**)	Product (yield%)
147 mg (1.00 mmol) of **1a**	0.13 mL (1.20 mmol) of **8a**	0.10 mL (1.20 mmol)	110 mg (31%) of **10a**
171 mg (1.00 mmol) of **1b**	0.13 mL (1.20 mmol) of **8a**	0.12 mL (1.50 mmol)	238 mg (63%) of **10b**
147 mg (1.00 mmol) of **1a**	0.20 mL (1.20 mmol) of **8b**	0.17 mL (2.10 mmol)	295 mg (69%) of **10c**

Table 4 Experimental details for the CAAPS sequence

Acid chloride **1**	Alkyne **2**	Amine **8**	α,β -Unsaturated chloride **9**	Product (yield%)
147 mg[a] (1.00 mmol) of **1a**	0.12 mL (1.05 mmol) of **2a**	320 mg (2.00 mmol) of **8c**	0.41 mL (5.00 mmol) of **9a**	210 mg (52%) of **6a**
186 mg[a] (1.00 mmol) of **1c**	0.12 mL (1.05 mmol) of **2a**	320 mg (2.00 mmol) of **8c**	0.41 mL (5.00 mmol) of **9a**	192 mg (43%) of **6b**
171 mg[a] (1.00 mmol) of **1b**	0.12 mL (1.05 mmol) of **2a**	320 mg (2.00 mmol) of **8c**	0.41 mL (5.00 mmol) of **9a**	254 mg (59%) of **6c**
147 mg[a] (1.00 mmol) of **1a**	0.11 mL (1.05 mmol) of **2b**	320 mg (2.00 mmol) of **8c**	0.41 mL (5.00 mmol) of **9a**	175 mg (41%) of **6d**
147 mg[a] (1.00 mmol) of **1a**	0.12 mL (1.05 mmol) of **2a**	320 mg (2.00 mmol) of **8c**	0.48 mL (5.00 mmol) of **9b**	210 mg (50%) of **6e**
147 mg[a] (1.00 mmol) of **1a**	0.12 mL (1.05 mmol) of **2a**	320 mg (2.00 mmol) of **8c**	0.48 mL (5.00 mmol) of **9c**	185 mg (44%) of **6f** and 40 mg (10%) of **6f**
147 mg[a] (1.00 mmol) of **1a**	0.14 mL (1.05 mmol) of **2c**	320 mg[c] (2.00 mmol) of **8c**	0.41 mL (5.00 mmol) of **9a**	140 mg (32%) of **6g**
147 mg[b] (1.00 mmol) of **1a**	0.12 mL (1.05 mmol) of **2a**	510 mg[d] (2.00 mmol) of **8d**	0.80 mL (9.76 mmol) of **9a**	210 mg (45%) of **6h**
147 mg[a] (1.00 mmol) of **1a**	179 mg (1.05 mmol) of **2d**	320 mg (2.00 mmol) of **8c**	0.41 mL (5.00 mmol) of **9a**	148 mg (30%) of **6i**
318 mg[a] (1.00 mmol)of **1d**	0.12 mL (1.05 mmol) of **2a**	175 mg[e] (1.10 mmol) of **8c**	0.41 mL (5.00 mmol) of **9a**	206 mg (36%) of **6j**
107 mg[a] (1.00 mmol) of **1e**	0.12 mL (1.05 mmol) of **2a**	175 mg[e] (1.10 mmol) of **8c**	0.41 mL (5.00 mmol) of **9a**	130 mg (36%) of **6k**

silica gel, to give the analytically pure tetrahydro-β-carbolines **6** as solids (for experimental details, see Table 4).

***rac*-12*b*-Butyl-1-(thiophene-2-carbonyl)-2,3,6,7,12,12*b*-hexahydro-1*H*-indolo[2,3-*a*] quinolizin-4-one (6a).** Colorless crystals; mp 250–251 °C; R_f (product) 0.37 (neat diethyl ether); (Found: C, 70.64; H, 6.44; N, 6.92. $C_{24}H_{26}N_2O_2S$ requires C, 70.91; H, 6.45; N, 6.89%); ν_{max} (KBr)(cm^{-1}) 2955, 2869, 1626 (C=O), 1413, 1238 and 731; δ_H ($CDCl_3$, 500 MHz) 0.83 (t, J = 7.4 Hz, 3 H; Bu), 1.02–1.11 (m, 1 H), 1.22–1.37 (m, 3 H), 2.10–2.23 (m, 2 H), 2.35–2.44 (m, 1 H; 2-H), 2.72–2.88 (m, 5 H), 2.98 (dt, J = 12.4 Hz, J = 3.8 Hz, 1 H; 6-H), 3.73 (dd, J = 13.4 Hz, J = 5.0 Hz, 1 H; 1-H), 5.22 (ddd, J = 12.8 Hz, J = 4.8 Hz, J = 1.5 Hz, 1 H; 6-H), 6.90 (dd, J = 4.9 Hz, J = 3.7 Hz, 1 H), 7.03–7.09 (m, 2 H), 7.13–7.16 (m, 1 H), 7.38 (dd, J = 3.7 Hz, J = 1.1 Hz, 1 H), 7.44–7.49 (m, 1 H), 7.54 (dd, J = 4.9 Hz, J = 1.1 Hz, 1 H) and 8.00 (s, 1 H; indole-N*H*); δ_C ($CDCl_3$, 125 MHz) 13.9 (CH_3; Bu), 20.1 (CH_2; 7-C), 21.8 (CH_2; 2-C), 23.3 (CH_2; Bu), 27.2 (CH_2; Bu), 29.6 (CH_2; 3-C), 35.9 (CH_2; Bu), 40.0 (CH_2; 6-C), 55.0 (CH; 1-C), 61.9 (C_{quat}; 12b-C), 110.0 (CH), 118.2 (CH), 119.5 (CH), 122.2 (CH), 126.0 (C_{quat}), 128.5 (CH), 132.5 (CH), 133.9 (C_{quat}), 135.2 (CH), 135.8 (C_{quat}), 143.9 (C_{quat}), 145.2 (C_{quat}), 169.6 (C_{quat}; amide) and 195.5 (C_{quat}; ketone); m/z (FAB) 407 [(M + H)$^+$, 100] and 349 [(M + H)$^+$ − C_4H_9, 90].

***rac*-12*b*-Butyl-1-(4-nitrophenyl-1-carbonyl)-2,3,6,7,12,12*b*-hexahydro-1*H*-indolo[2,3-*a*] quinolizin-4-one (6b).** Yellow crystals; mp 195–197 °C; R_f (product) 0.26 (neat diethyl ether); (Found: C, 69.79; H, 6.05; N, 9.41. $C_{24}H_{27}N_3O_4$ requires C, 70.10; H, 6.11; N, 9.43%); ν_{max} (KBr)(cm^{-1}) 2957, 2868, 1618 (C=O), 1527, 1347, 1235 and 746; δ_H ($CDCl_3$, 500 MHz) 0.85 (t, J = 7.1 Hz, 3 H; Bu), 1.01–1.18 (m, 1 H), 1.22–1.41 (m, 3 H), 2.00 (ddd, J = 18.4 Hz, J = 9.0 Hz, J = 4.4 Hz, 1 H), 2.21 (dt, J = 18.4 Hz, J = 4.4 Hz, 1 H), 2.29–2.39 (m, 1 H), 2.65 (dt, J = 18.0 Hz, J = 4.0 Hz, 1 H), 2.74–2.85 (m, 3 H), 2.90 (ddd, J = 15.1 Hz, J = 3.3 Hz, J = 1.3 Hz, 1 H), 2.98 (dt, J = 12.4 Hz, J = 3.4 Hz, 1 H; 6-H), 3.92 (dd, J = 13.4 Hz, J = 5.0 Hz, 1 H; 1-H), 5.24 (ddd, J = 12.7 Hz, J = 4.7 Hz, J = 1.3 Hz, 1 H; 6-H), 7.03–7.08 (m, 3 H), 7.47–7.50 (m, 1 H), 7.68 (d, J = 9.0 Hz, 2 H), 7.83 (s, 1 H; indole-N*H*) and 8.05 (d, J = 9.0 Hz, 2 H); δ_C ($CDCl_3$, 125 MHz) 14.0 (CH_3; Bu), 21.0 (CH_2; 7-C), 21.1 (CH_2; 2-C), 23.3 (CH_2; Bu), 27.0 (CH_2; Bu), 29.3 (CH_2; 3-C), 35.5 (CH_2; Bu), 40.1 (CH_2; 6-C), 54.1 (CH; 1-C), 61.8 (C_{quat}; 12*b*-C), 110.1 (C_{quat}), 111.6 (CH), 118.2 (CH), 119.8 (CH), 122.4 (CH), 123.6 (CH), 125.9 (C_{quat}), 128.6 (CH), 133.4 (C_{quat}), 135.6 (C_{quat}), 141.1 (C_{quat}), 150.1 (C_{quat}), 169.1 (C_{quat}) and 201.8 (C_{quat}; ketone); m/z (FAB) 446 [(M + H)$^+$, 100] and 388 [(M + H)$^+$ − C_4H_9, 75].

***rac*-12*b*-Phenyl-1-(thiophene-2-carbonyl)-2,3,6,7,12,12*b*-hexahydro-1*H*-indolo[2,3-*a*] quinolizin-4-one (6c).** Colorless crystals; mp 201–202 °C; R_f (product) 0.25 (neat diethyl ether); (Found: C, 74.93; H, 7.01; N, 6.46. $C_{27}H_{30}N_2O_3$ requires C, 75.32; H, 7.02; N, 6.51%); ν_{max} (KBr)(cm^{-1}) 2957, 2868, 1600 (C=O), 1426, 1261, 1173, 1029, 843, 745, 593 and 505; δ_H ($CDCl_3$, 500 MHz) 0.85 (t, J = 7.0 Hz, 3 H; Bu), 1.05–1.20 (m, 1 H), 1.24–1.40 (m, 3 H), 1.96–2.12 (m, 1 H), 2.20–2.40 (m, 2 H), 2.75–2.90 (m, 5 H), 2.98 (dt, J = 12.0 Hz, J = 4.0 Hz, 1 H; 6-H), 3.74 (s, 3 H; C*H*$_3$O), 3.93 (dd, J = 13.2 Hz, J = 4.9 Hz, 1 H; 1-H), 5.27 (ddd, J = 12.8 Hz, J = 4.8 Hz, J = 1.5 Hz, 1 H; 6-H), 6.74 (d, J = 9.0 Hz, 2 H), 7.04–7.17 (m, 3 H), 7.46–7.52 (m, 1 H), 7.66 (d, J = 9.0 Hz; 2 H) and 8.27 (s, 1 H; indole-N*H*); δ_C ($CDCl_3$, 125 MHz) 13.9 (CH_3; Bu), 20.9 (CH_2; 7-C), 21.5 (CH_2; 2-C), 23.2 (CH_2; Bu), 27.2 (CH_2; Bu), 29.6 (CH_2; 3-C), 35.7 (CH_2; Bu), 39.8 (CH_2; 6-C), 52.6 (CH; 1-C), 55.3 (CH_3; *C*H$_3$O), 62.0 (C_{quat}; 12*b*-C), 110.7 (C_{quat}), 111.0 (CH), 113.7 (CH), 118.0 (CH), 119.3 (CH), 121.8 (CH), 125.9 (C_{quat}), 129.4 (C_{quat}), 130.3 (CH), 134.3 (C_{quat}), 135.7 (C_{quat}), 163.7 (C_{quat}), 169.6 (C_{quat}; amide) and 201.5 (C_{quat}; ketone); m/z (EI$^+$) 430 (M$^+$, 13), 373 (32), 135 (4-MeOPhCO$^+$, 100).

***rac*-12*b*-Phenyl-1-(thiophene-2-carbonyl)-2,3,6,7,12,12*b*-hexahydro-1*H*-indolo[2,3-*a*] quinolizin-4-one (6d).** Colorless crystals; mp 315–316 °C; (Found: C, 72.55; H, 5.26; N, 6.52. $C_{26}H_{22}N_2O_2S$ requires C, 73.21; H, 5.20; N, 6.57%); ν_{max} (KBr)(cm^{-1}) 1651 (C=O), 1611, 1456, 1413, 1351, 1236, 1215, 745 and 702; δ_H (DMSO-d$_6$, 500 MHz) 1.80–1.90 (m, 1 H; 2-H), 1.92–1.99 (m, 1 H; 2-H), 2.26 (dd, J = 17.7 Hz, J = 5.4 Hz, 1 H; 3-H), 2.41 (dd, J = 14.9 Hz, J = 4.2 Hz, 1 H; 7-H), 2.78 (ddd, J = 17.7 Hz, J = 12.9 Hz, J = 6.8 Hz, 1 H; 3-H), 2.91 (dt, J = 15.1 Hz, J = 5.6 Hz, 1 H; 7-H), 2.99 (dt, J = 12.1 Hz, J = 4.4 Hz, 1 H; 6-H), 4.66 (dd, J = 12.7 Hz, J = 5.6 Hz, 1 H; 6-H), 4.81 (t, J = 3.6 Hz, 1 H; 1-H), 6.98–7.03 (m, 2 H), 7.10–7.18 (m, 4 H), 7.27 (d, J = 7.6 Hz, 2 H), 7.38 (d, J = 7.6 Hz, 1 H), 7.52 (d, J = 8.3 Hz, 1 H), 7.87 (dd, J = 4.9 Hz, J = 1.1 Hz, 1 H), 8.06 (dd, J = 3.9 Hz, J = 1.1 Hz, 1 H) and 11.76 (s, 1 H; indole-N*H*); δ_C (DMSO-d_6, 125 MHz) 19.8 (CH_2; 7-C), 21.8 (CH_2; 2-C), 28.9 (CH_2; 3-C), 39.0 (CH_2; 6-C), 47.2 (CH; 1-C), 66.7 (C_{quat}; 12*b*-C), 109.5 (C_{quat}), 111.4 (CH), 118.1 (CH), 119.0 (CH), 121.8 (CH), 126.6 (C_{quat}), 126.9 (CH), 127.0 (CH), 127.8 (CH), 128.3 (CH), 134.0 (CH), 135.8 (C_{quat}), 136.0 (CH), 136.1 (C_{quat}), 141.3 (C_{quat}), 144.7 (C_{quat}), 171.7 (C_{quat}; amide) and 192.1 (C_{quat}; ketone); m/z (EI$^+$) 426 (M$^+$, 100), 349 (M$^+$ − Ph, 18) and 111 (2-ThCO$^+$, 70).

***rac*-12*b*-Butyl-2-methyl-1-(thiophene-2-carbonyl)-2,3,6,7,12,12*b*-hexahydro-1*H*-indolo[2,3-*a*] quinolizin-4-one (6e).** Colorless crystals; mp 301–302 °C; R_f (product) 0.32 (hexane–ethyl acetate; 1 : 1); (Found: C, 70.60; H, 6.68; N, 6.66. $C_{25}H_{28}N_2O_2S\cdot$ 0.4 CH_3OH requires C, 70.40; H, 6.88; N, 6.46%); ν_{max} (KBr)(cm^{-1}) 2958, 1615 (C=O), 1415, 1233 and 742; δ_H (DMSO-d$_6$, 500 MHz) 0.50 (t, J = 7.8 Hz, 3 H; Bu), 0.77 (d, J = 6.9 Hz, 3 H; C*H*$_3$), 0.85 (dd, J = 14.7 Hz, J = 7.3 Hz, 1 H), 0.94–1.04 (m, 1 H), 1.08–1.18 (m, 1 H), 1.24–1.34 (m, 1 H), 1.82 (dt, J = 12.8 Hz, J = 3.6 Hz, 1 H), 1.88–1.96 (m, 1 H; 2-H), 2.07–2.24 (m, 3 H), 2.55 (dd, J = 15.6 Hz, J = 5.0 Hz, 1 H; 7-H), 2.80 (ddd, J = 15.6 Hz, J = 11.5 Hz, J = 6.9 Hz, 1 H; 7-H), 3.41 (dt, J = 12.4 Hz, J = 5.0 Hz, 1 H; 6-H), 4.66 (d, J = 3.7 Hz,

1 H; 1-H), 4.76 (dd, $J = 13.7$ Hz, $J = 6.9$ Hz, 1 H; 6-H), 6.97 (t, $J = 7.4$ Hz, 1 H), 7.10 (t, $J = 7.4$ Hz, 1 H), 7.35–7.43 (m, 3 H), 8.11 (dd, $J = 5.0$ Hz, $J = 0.9$ Hz, 1 H), 8.53 (dd, $J = 3.7$ Hz, $J = 0.9$ Hz, 1 H) and 11.16 (s, 1 H; indole-N*H*); δ_C (DMSO-d_6, 75 MHz) 13.9 (CH_3; Bu), 19.0 (CH_3; *C*H_3), 19.5 (CH_2; 7-C), 21.9 (CH_2; Bu), 26.2 (CH_2; 3-C), 27.0 (CH; 2-C), 35.5 (CH_2; Bu), 36.1 (CH_2; Bu), 38.4 (CH_2; 6-C), 48.8 (CH; 1-C), 63.0 (C_{quat}; 12*b*-C), 107.0 (C_{quat}), 110.9 (CH), 117.5 (CH), 118.4 (CH), 121.0 (CH), 126.8 (C_{quat}), 128.7 (CH), 134.4 (CH), 135.3 (C_{quat}), 136.5 (C_{quat}), 137.4 (CH), 147.3 (C_{quat}), 170.2 (C_{quat}; amide) and 192.7 (C_{quat}; ketone); *m*/*z* (EI$^+$) 420 (M^+, 28), 363 ($M^+ - C_4H_9$, 100) and 111 (2-ThCO$^+$, 29).

***rac*-12*b*-Butyl-3-methyl-1-(thiophene-2-carbonyl)-2,3,6,7,12,12*b*-hexahydro-1*H*-indolo[2,3-*a*] quinolizin-4-one major diastereomer 6f (*syn–syn* : *syn–anti* = 4.5 : 1).** Colorless crystals; mp 209–210 °C; R_f (product) 0.35 (hexane–ethyl acetate; 2 : 1); (Found: C, 71.11; H, 6.68; N, 6.67. $C_{25}H_{28}N_2O_2S$ requires C, 71.40; H, 6.71; N, 6.66%); ν_{max} (KBr)(cm^{-1}) 3439, 3281, 2957, 2930, 1644 (C=O), 1462, 1414, 1351, 1301, 1237, 742 and 729; δ_H ($CDCl_3$, 500 MHz) 0.82 (t, $J = 7.0$ Hz, 3 H; Bu), 1.04–1.16 (m, 1 H), 1.22–1.36 (m, 3 H), 1.39 (d, $J = 7.0$ Hz, 3 H; C*H*$_3$), 1.84 (ddd, $J = 14.1$ Hz, $J = 5.7$ Hz, $J = 4.4$ Hz, 1 H; 2-H), 2.31 (ddd, $J = 14.5$ Hz, $J = 12.4$ Hz, $J = 4.2$ Hz, 1 H), 2.62 (dt, $J = 13.7$ Hz, $J = 9.8$ Hz, 1 H; 2-H), 2.68–2.78 (m, 2 H), 2.81–2.88 (m, 2 H), 2.96 (dt, $J = 12.4$ Hz, $J = 3.7$ Hz, 1 H; 6-H), 3.75 (dd, $J = 13.1$ Hz, $J = 6.0$ Hz, 1 H; 1-H), 5.23 (ddd, $J = 12.8$ Hz, $J = 4.8$ Hz, $J = 1.6$ Hz, 1 H; 6-H), 6.91 (dd, $J = 4.9$ Hz, $J = 3.9$ Hz, 1 H), 7.03–7.10 (m, 2 H), 7.14–7.16 (m, 1 H), 7.38 (dd, $J = 3.9$ Hz, $J = 1.0$ Hz, 1 H), 7.47 (d, $J = 7.0$ Hz, 1 H), 7.54 (dd, $J = 4.9$ Hz, $J = 1.0$ Hz, 1 H) and 7.99 (s, 1 H; indole-N*H*); δ_C ($CDCl_3$, 125 MHz) 14.0 (CH_3; Bu), 19.7 (CH_3; *C*H_3), 21.0 (CH_2; 7-C), 23.3 (CH_2; Bu), 27.2 (CH_2; Bu), 30.9 (CH_2; 2-C), 33.9 (CH; 3-C), 35.4 (CH_2; Bu), 40.1 (CH_2; 6-C), 53.9 (CH; 1-C), 62.4 (C_{quat}; 12*b*-C), 111.0 (C_{quat}), 111.1 (CH), 118.1 (CH), 119.5 (CH), 122.1 (CH), 126.1 (C_{quat}), 128.4 (CH), 132.5 (CH), 134.5 (C_{quat}), 135.0 (C_{quat}), 135.1 (CH), 143.9 (C_{quat}), 173.0 (C_{quat}; amide) and 195.4 (C_{quat}; ketone); *m*/*z* (EI$^+$) 420 (M^+, 5), 363 ($M^+ - C_4H_9$, 100) and 111 (2-ThCO$^+$, 43).

Minor diastereomer 6f′

Colorless crystals; mp 213–214 °C; R_f (product) 0.30 (hexane–ethyl acetate; 2 : 1); (Found: C, 71.04; H, 6.92; N, 6.53. $C_{25}H_{28}N_2O_2S$ requires C, 71.40; H, 6.71; N, 6.66%); ν_{max} (KBr)(cm^{-1}) 2957, 2931, 1627 (C=O), 1463, 1414, 1350, 1237, 744 and 728; δ_H ($CDCl_3$, 300 MHz) 0.83 (t, $J = 7.2$ Hz, 3 H; Bu), 0.86–0.92 (m, 1 H), 1.00–1.37 (m, 4 H), 1.42 (d, $J = 6.0$ Hz, 3 H; C*H*$_3$), 2.08–2.32 (m, 3 H), 2.70–2.90 (m, 3 H), 3.02 (t, $J = 11.3$ Hz, 1 H; 6-H), 3.77 (dd, $J = 11.7$ Hz, $J = 3.7$ Hz, 1 H; 1-H), 5.22 (d, $J = 12.1$ Hz, 1 H; 6-H), 6.92–6.98 (m, 1 H), 6.96–7.12 (m, 2 H), 7.13–7.18 (m, 1 H), 7.40–7.50 (m, 2 H), 7.58 (d, $J = 4.5$ Hz, 1 H) and 7.95 (s, 1 H; indole-N*H*); δ_C ($CDCl_3$, 75 MHz) 13.9 (CH_3), 19.3 (CH_3; *C*H_3), 24.8 (CH_2), 24.9 (CH_2), 27.6 (CH_2), 30.8 (CH_2), 36.1 (CH), 37.8 (CH_2), 40.0 (CH_2; 6-C), 54.8 (CH; 1-C), 62.0 (C_{quat}; 12*b*-C), 110.8 (C_{quat}), 111.0 (CH), 118.2 (CH), 119.5 (CH), 122.1 (CH), 126.0 (C_{quat}), 128.5 (CH), 132.5 (CH), 134.4 (C_{quat}), 135.0 (CH), 135.6 (C_{quat}), 143.6 (C_{quat}), 172.9 (C_{quat}; amide) and 195.5 (C_{quat}; ketone); *m*/*z* (EI$^+$) 420 (M^+, 11), 363 ($M^+ - C_4H_9$, 100) and 111 (2-ThCO$^+$, 80).

***rac*-1-(Thiophene-2-carbonyl)-2,3,6,7,12,12*b*-hexahydro-1*H*-indolo[2,3-*a*] quinolizin-4-one (6g).** Yellow crystals; mp 133–134 °C; R_f (product) 0.48 (neat ethyl acetate); (Found: C, 58.04; H, 4.66; N, 6.48; S, 7.31; Cl, 16.51. $C_{20}H_{18}N_2O_2S{\cdot}CH_2Cl_2$ requires C, 57.93; H, 4.63; N, 6.43; S, 7.37; Cl, 16.29%); ν_{max} (KBr)(cm^{-1}) 3372, 1641 (C=O), 1413, 1251, 1235, 1061 and 753; δ_H ($CDCl_3$, 500 MHz) 2.02–2.11 (m, 1 H; 2-H), 2.24–2.30 (m, 1 H; 2-H), 2.55–2.90 (m, 5 H), 3.60 (ddd, $J = 12.0$ Hz, $J = 10.0$ Hz, $J = 3.2$ Hz, 1 H; 1-H), 5.13–5.19 (m, 1 H; 6-H), 5.29 (s, 2 H (CH_2Cl_2)), 5.44 (d, $J = 10.0$ Hz, 1 H; 12b-H), 7.06 (dt, $J = 7.9$ Hz, $J = 1.2$ Hz, 1 H), 7.06 (dt, $J = 7.4$ Hz, $J = 1.2$ Hz, 1 H), 7.15–7.19 (m, 2 H), 7.45 (d, $J = 7.6$ Hz, 1 H) and 7.74–7.77 (m, 3 H); δ_C ($CDCl_3$, 125 MHz) 21.2 (CH_2), 26.4 (CH_2; 2-C), 31.9 (CH_2), 40.7 (CH_2; 6-C), 50.7 (CH; 1-C), 55.0 (CH; 12*b*-C), 111.3 (CH), 118.3 (CH), 119.9 (CH), 122.4 (CH), 126.5 (C_{quat}), 128.4 (CH), 132.0 (C_{quat}), 133.3 (CH), 135.8 (CH), 136.2 (C_{quat}), 142.2 (C_{quat}), 155.8 (C_{quat}), 168.3 (C_{quat}; amide) and 197.0 (C_{quat}; ketone); *m*/*z* (EI$^+$) 350 (M^+, 77), 239 (M^+ − 2-ThCO, 100) and 111 (2-ThCO$^+$, 25).

(6*S*, 4*S*, 12*bS*)-12*b*-Butyl-4-oxo-1-(thiophene-2-carbonyl)-1,2,3,4,6,7,12,12*b*-octahydro-indolo-[2,3-*a*]quinolizin-6-carboxylic acid methyl ester (6h). Colorless crystals; mp 139–140 °C; R_f (product) 0.45 (neat ether); $[\alpha]_D^{24}$ +178° (c 2.0, CH_2Cl_2); (Found: C, 62.72; H, 5.77; N, 5.52; S, 6.32; Cl, 6.99. $C_{26}H_{28}N_2O_4S{\cdot}0.5\ CH_2Cl_2$ requires C, 62.72; H, 5.78; N, 5.36; S, 6.39; Cl, 7.18%); ν_{max} (KBr)(cm^{-1}) 3428, 2955, 2931, 1739, 1650 (C=O), 1414, 1239, 1060 and 741; δ_H ($CDCl_3$, 500 MHz) 0.60–0.70 (m, 1 H; Bu), 0.76 (t, $J = 7.1$ Hz, 3 H; Bu), 1.14–1.25 (m, 3 H; Bu), 2.24 (dt, $J = 14.0$ Hz, $J = 4.0$ Hz, 1 H; Bu), 2.31–2.37 (m, 2 H; 2-H), 2.61–2.66 (m, 1 H; Bu), 2.82–2.86 (m, 2 H; 3-H), 3.10 (dd, $J = 15.8$ Hz, $J = 6.9$ Hz, 1 H; 7-H), 3.45 (dd, $J = 15.8$ Hz, $J = 2.7$ Hz, 1 H; 7-H), 3.67 (s, 3H; CO_2CH_3), 4.90 (t, $J = 9.9$ Hz, 1 H; 1-H), 5.29 (s, 1 H (CH_2Cl_2)), 5.52 (dd, $J = 6.8$ Hz, $J = 2.7$ Hz, 1 H; 6-H), 7.05–7.13 (m, 3 H), 7.18–7.19 (m, 1 H), 7.45 (dd, $J = 6.3$ Hz, $J = 1.8$ Hz, 1 H), 7.68 (dd, $J = 4.9$ Hz, $J = 1.0$ Hz, 1 H), 7.79 (dd, $J = 3.8$ Hz, $J = 1.0$ Hz, 1 H) and 8.16 (s, 1 H; indole-N*H*); δ_C ($CDCl_3$, 75 MHz) 13.9 (CH_3; Bu), 22.5 (CH_2; 7-C), 22.7 (CH_2; 2-C), 23.0 (CH_2; Bu), 25.5 (CH_2; Bu), 30.0 (CH_2; 3-C), 37.3 (CH_2; Bu), 52.0 (CH; 1-C), 52.6 (CH_3; CO_2CH_3), 54.8 (CH; 6-C), 62.9 (C_{quat}; 12*b*-C), 107.6 (C_{quat}), 111.3 (CH), 118.2 (CH), 119.6 (CH), 122.4 (CH), 125.2 (C_{quat}), 128.9 (CH), 133.9 (CH), 134.1 (C_{quat}), 135.9 (CH), 136.1 (C_{quat}), 144.4 (C_{quat}), 172.8 (C_{quat}; amide or ester), 172.9 (C_{quat}; amide or ester) and 197.9 (C_{quat}; ketone); *m*/*z* (EI$^+$) 464 (M^+, 10), 407 ($M^+ - C_4H_9$, 100) and 111 (2-ThCO$^+$, 57).

***rac*-12*b*-(*tert*-Butyl-dimethyl-silanyloxymethyl)-1-(thiophene-2-carbonyl)-2,3,6,7,12,12*b*-hexahydro-1*H*-indolo[2,3-*a*] quinolizin-4-one (6i).** Colorless crystals; mp 288–289 °C; R_f (product) 0.45 (hexane–ethyl acetate; 2 : 1); (Found: C, 65.23; H, 6.87; N, 5.78. $C_{27}H_{34}N_2O_3SSi$ requires C, 65.55; H, 6.93; N, 5.66%); ν_{max} (KBr)(cm^{-1}) 2953, 2855, 1623 (C=O), 1412, 1253, 1103, 841 and 742; δ_H ($CDCl_3$, 500 MHz) 0.01 (s, 3 H; TBS), 0.04 (s, 3 H; TBS), 0.84 (s, 9 H; TBS), 2.00–2.10 (m, 1 H; 2-H), 2.65–2.87 (m, 5 H), 2.95 (dt, $J = 12.0$ Hz, $J = 4.2$ Hz, 1 H; 6-H), 3.80–3.88 (m, 1 H; 1-H), 4.08 (d, $J = 10.6$ Hz, 1 H; TBSOC*H*$_2$), 4.97 (d, $J = 10.6$ Hz, 1 H; TBSOC*H*$_2$), 5.17 (dd, $J = 12.8$ Hz, $J = 3.3$ Hz, 1 H; 6-H), 7.02–7.12 (m, 3 H), 7.17 (d, $J = 7.8$ Hz, 1 H), 7.45 (d, $J = 7.5$ Hz, 1 H), 7.58 (d, $J = 3.5$ Hz, 1 H), 7.65 (d, $J = 4.6$ Hz, 1 H) and 7.95 (s, 1 H; indole-N*H*); δ_C ($CDCl_3$, 125 MHz) −5.8 (CH_3; TBS), −5.7 (CH_3; TBS), 18.2 (C_{quat}; *tert*-Bu), 21.2 (CH_2), 23.7 (CH_2; 2-C), 25.8 (CH_3; *tert*-Bu), 31.3 (CH_2), 36.7 (CH_2; 6-C), 52.6 (CH; 1-C), 62.3 (C_{quat}; 12*b*-C), 65.0 (CH_2; TBSO*C*H$_2$), 110.6 (C_{quat}), 111.2 (CH), 118.4 (CH), 119.8 (CH), 122.4 (CH), 126.0 (C_{quat}), 128.6 (CH), 132.8 (CH), 133.7 (C_{quat}), 135.3 (CH), 135.8 (C_{quat}), 143.6 (C_{quat}), 170.2 (C_{quat}; amide) and 196.4 (C_{quat}; ketone); *m*/*z* (EI$^+$) 494 (M^+, 4), 349 (M^+ − $TBSOCH_2$, 100) and 111 (2-ThCO$^+$, 25).

***rac*-1-(1-Benzenesulfonyl-1*H*-indole-3-carbonyl)-12*b*-butyl-2,3,6,7,12,12*b*-hexahydro-1*H*-indolo[2,3-*a*] quinolizin-4-one (6j).** Colorless crystals; mp 286–288 °C; (Found: C, 70.06; H, 5.65; N, 7.28; S, 5.58. $C_{34}H_{33}N_3O_4S$ requires C, 70.44; H, 5.74; N, 7.25; S, 5.53%); ν_{max} (KBr)(cm^{-1}) 2960, 2932, 1844, 1619 (C=O), 1535, 1448, 1381, 1235, 1188, 1172, 748 and 732; δ_H ($CDCl_3$, 500 MHz) 0.83 (t, $J = 7.4$ Hz, 3 H; Bu), 1.03–1.12 (m, 1 H; Bu), 1.24–1.40 (m, 3 H; Bu), 2.06–2.14 (m, 1 H; 2-H), 2.20–2.27 (m, 1 H; Bu), 2.37–2.47 (m, 1 H; 2-H), 2.71–2.93 (m, 5 H), 2.99 (dt, $J = 12.0$ Hz, $J = 4.0$ Hz, 1 H; 6-H), 3.67 (dd, $J = 13.4$ Hz, $J = 5.4$ Hz, 1 H; 1-H), 5.25 (dd, $J = 12.7$ Hz, $J = 4.4$ Hz,

1 H; 6-H), 6.97 (d, $J = 8.0$ Hz, 1 H), 7.02 (dt, $J = 8.4$ Hz, $J = 1.3$ Hz, 1 H), 7.08 (dt, $J = 7.0$ Hz, $J = 1.0$ Hz, 1 H), 7.30–7.37 (m, 4 H), 7.48–7.53 (m, 2 H), 7.57 (dd, $J = 8.7$ Hz, $J = 1.0$ Hz, 2 H), 7.73 (dd, $J = 7.0$ Hz, $J = 1.3$ Hz, 1 H), 7.81 (s, 1 H; $PhSO_2$-indole-2-*H*), 7.92 (s, 1 H; indole-N*H*) and 8.31 (dd, $J = 6.4$ Hz, $J = 1.3$ Hz, 1 H); δ_C ($CDCl_3$, 75 MHz) 14.0 (CH_3; Bu), 21.0 (CH_2; 7-C), 21.7 (CH_2; 2-C), 23.3 (CH_2; Bu), 27.2 (CH_2; Bu), 29.6 (CH_2; 3-C), 36.0 (CH_2; Bu), 40.0 (CH_2; 6-C), 55.7 (CH; 1-C), 61.9 (C_{quat}; 12*b*-C), 111.0 (CH), 111.2 (C_{quat}), 113.0 (CH), 118.4 (CH), 119.6 (CH), 120.8 (C_{quat}), 122.2 (CH), 122.7 (CH), 125.0 (CH), 125.9 (CH), 126.1 (C_{quat}), 127.0 (CH), 127.3 (C_{quat}), 129.7 (CH), 131.8 (CH), 134.3 (C_{quat}), 134.5 (CH), 134.6 (C_{quat}), 135.7 (C_{quat}), 136.9 (C_{quat}), 169.7 (C_{quat}; amide) and 198.6 (C_{quat}; ketone); *m*/*z* (EI^+) 579 (M^+, 22), 522 ($M^+ - C_4H_9$, 64), 284 ($PhSO_2Ind$-3-CO^+, 100).

***rac*-12*b*-Butyl-1-isobutyryl-2,3,6,7,12,12*b*-hexahydro-1*H*-indolo[2,3-*a*] quinolizin-4-one (6k).** Colorless crystals; mp 194–196 °C; (Found: C, 71.61; H, 7.89; N, 7.27; Cl, 1.61. $C_{23}H_{30}N_2O_2 \cdot 0.2\ CH_2Cl_2$ requires C, 72.66; H, 7.99; N, 7.30; Cl, 3.70%); ν_{max} (KBr)(cm^{-1}) 3267, 2960, 2932, 2871, 1708, 1624 (C=O), 1466, 1433, 1405 and 744; δ_H ($CDCl_3$, 500 MHz) 0.69 (d, $J = 6.7$ Hz, 3 H; iso-Pr-CH_3), 0.80 (t, $J = 7.2$ Hz, 3 H; Bu), 0.94 (d, $J = 7.0$ Hz, 3 H; iso-Pr-CH_3), 0.97–1.07 (m, 1 H; Bu), 1.20–1.32 (m, 3 H; Bu), 1.96 (ddd, $J = 18.1$ Hz, $J = 9.0$ Hz, $J = 4.7$ Hz, 1 H; 2-H), 2.08 (dt, $J = 14.2$ Hz, $J = 4.0$ Hz, 1 H; Bu), 2.13–2.21 (m, 1 H; 2-H), 2.28 (spt, $J = 7.0$ Hz, 1 H; iso-Pr-C*H*), 2.60 (dt, $J = 12.4$ Hz, $J = 3.4$ Hz, 1 H; Bu), 2.66–2.76 (m, 3 H), 2.83 (ddd, $J = 15.4$ Hz, $J = 3.4$ Hz, $J = 1.6$ Hz, 1 H; 7-H), 2.91 (dt, $J = 12.4$ Hz, $J = 3.7$ Hz, 1 H; 6-H), 3.16 (dd, $J = 13.7$ Hz, $J = 5.0$ Hz, 1 H; 1-H), 5.16 (ddd, $J = 12.7$ Hz, $J = 4.8$ Hz, $J = 1.5$ Hz, 1 H; 6-H), 7.11 (dt, $J = 8.0$ Hz, $J = 1.0$ Hz, 1 H), 7.16 (dt, $J = 7.7$ Hz, $J = 1.0$ Hz, 1 H), 7.26 (d, $J = 8.0$ Hz, 1 H), 7.49 (d, $J = 7.7$ Hz, 1 H) and 7.70 (s, 1 H; indole-N*H*); δ_C ($CDCl_3$, 125 MHz) 13.9 (CH_3; Bu), 17.5 (CH_3; iso-Pr-*C*H_3), 20.4 (CH_2; 2-C), 20.9 (CH_2; 7-C), 23.2 (CH_2; Bu), 27.0 (CH_2; Bu), 29.4 (CH_2; 3-C), 35.4 (CH_2; Bu), 39.9 (CH_2; 6-C), 42.4 (CH; iso-Pr-*C*H), 56.8 (CH; 1-C), 61.4 (C_{quat}; 12*b*-C), 110.9 (CH), 111.1 (C_{quat}), 118.3 (CH), 119.7 (CH), 122.4 (CH), 126.2 (C_{quat}), 134.0 (C_{quat}), 135.8 (C_{quat}), 169.4 (C_{quat}; amide) and 218.3 (C_{quat}; ketone); *m*/*z* (EI^+) 366 (M^+, 16), 309 ($M^+ - C_4H_9$, 72) and 239 ($M^+ - C_4H_9 - {}^iPrCO$, 100).

***rac*-4-Oxo-1,2,3,4,6,7,12,12*b*-octahydro-indolo[2,3-*a*] quinolizine-1-carboxylic acid ethyl ester (6l).** In a screw cap pressure vessel 0.2 mL (2.00 mmol) of ethyl propiolate **2e**, and 320 mg (2.00 mmol) of tryptamine **8c** were dissolved in 10 mL of THF. The reaction mixture was heated at 65 °C for 3 h. After complete conversion 0.18 mL (2.20 mmol) of acryloyl chloride **9a** was added and the reaction mixture was heated at 70 °C for 6 h. After cooling to room temperature the reaction mixture was diluted with methanol, stirred for 10 min, evaporated and applied to column chromatography on silica gel eluting with neat diethyl ether → neat ethyl acetate to give the analytically pure quinolizinone **6l** as colorless crystals (135 mg, 43%). Crystallization was achieved from pentane–CH_2Cl_2.

Syn : *anti* = 9 : 1 (^{1}H NMR, minor diastereomer not listed). Colorless crystals; mp 186–187 °C; R_f (product) 0.50 (neat ethyl acetate); (Found: C, 68.19; H, 6.41; N, 8.81. $C_{18}H_{20}N_2O_3$ requires C, 69.21; H, 6.45; N, 8.97%); ν_{max} (KBr)(cm^{-1}) 2930, 1723, 1619 (C=O), 1467, 1444, 1327, 1299, 1160 and 739; δ_H ($CDCl_3$, 500 MHz) 1.40 (t, $J = 7.1$ Hz, 3 H; $CO_2CH_2CH_3$), 2.02–2.12 (m, 1 H), 2.22–2.28 (m, 1 H), 2.42–2.49 (m, 1 H), 2.65 (ddd, $J = 17.6$ Hz, $J = 4.9$ Hz, $J = 2.9$ Hz, 1 H), 2.74 (d, $J = 11.2$ Hz, 1 H), 2.80–2.90 (m, 3 H), 4.39 (q, $J = 7.1$ Hz, 2 H; $CO_2CH_2CH_3$), 5.10–5.15 (m, 2 H), 7.11 (dt, $J = 7.8$ Hz, $J = 1.0$ Hz, 1 H), 7.18 (dt, $J = 8.3$ Hz, $J = 1.0$ Hz, 1 H), 7.31 (d, $J = 8.3$ Hz, 1 H), 7.49 (d, $J = 7.8$ Hz, 1 H) and 8.50 (s, 1 H; indole-N*H*); δ_C ($CDCl_3$, 125 MHz) 14.2 (CH_3; $CO_2CH_2CH_3$), 21.0 (CH_2), 23.8 (CH_2), 31.5 (CH_2), 41.0 (CH_2), 46.1 (CH), 55.3 (CH), 62.0 (CH_2; $CO_2CH_2CH_3$), 111.9 (C_{quat}), 111.2 (CH), 118.4 (CH), 119.8 (CH), 122.3 (CH), 126.5 (C_{quat}), 132.5 (C_{quat}), 136.1 (C_{quat}), 168.5 (C_{quat}; amide) and 174.8 (C_{quat}; ester); *m*/*z* (EI^+) 312 (M^+, 100), 256 ($M^+ - C_4H_9$, 100), 256 ($M^+ - CH_2CH_2CO$, 80) and 239 ($M^+ - CO_2Et$, 36).

11*b*-Butyl-9,10-dimethoxy-1-(thiophene-2-carbonyl)-1,2,3,6,7,11*b*-hexahydro-pyrido[2,1-*a*] isoquinolin-4-one (6m). In a screw cap pressure vessel 14 mg (0.02 mmol) of $Pd(PPh_3)_2Cl_2$, and 7 mg (0.04 mmol) of CuI were dissolved in 5 mL of degassed toluene. Then 0.14 mL (1.00 mmol) of triethylamine, 147 mg (1.00 mmol) of thiophene acid chloride **1a** and 0.12 mL (1.05 mmol) of hexyne **2a** were added. The reaction mixture was stirred for 3 h at room temperature until consumption of alkyne (that was verified by TLC HE–EA 9 : 1). Afterwards 0.2 mL (1.20 mmol) of homoveratryl amine **8b** were added and the reaction mixture was heated at 100 °C for 10 h. After complete conversion of alkynone to enaminone (TLC hexane–ethyl acetate 4 : 1; for alkynone R_f 0.7, for enaminone R_f 0.2) acryloyl chloride **9a** 0.17 mL (2.00 mmol) was added and the reaction mixture was heated at 70 °C for 3 h (TLC neat diethyl ether; for the aza-annulation product **10c** R_f 0.65). Afterwards 0.30 mL (4.00 mmol) of CF_3CO_2H was added and the reaction mixture was heated until the aza-annulation product was consumed **10c** (TLC in neat ethyl acetate; for **6m** R_f 0.5, for both diastereomers). The reaction mixture was quenched with K_2CO_3 solution, extracted with CH_2Cl_2, dried, evaporated and applied to column chromatography eluting with neat ethyl acetate to give the analytically pure quinolizinone **6m** as yellow solid (300 mg, 70%).

dr = 1.4 : 1 (^{1}H NMR). Yellow solid; mp 67–68 °C; R_f (product) 0.50 (neat ethyl acetate). (Found: 427.1788. $C_{24}H_{29}NO_4S$ requires 427.1817); ν_{max} (KBr)(cm^{-1}) 3440, 2955, 2934, 2870, 1737, 1562, 1414, 1260, 1221 and 726; major diastereomer: δ_H ($CDCl_3$, 300 MHz) 0.84 (t, $J = 7.3$ Hz, 3 H; Bu), 1.04–1.14 (m, 1 H), 1.20–1.34 (m, 4 H), 1.80–2.15 (m, 3 H), 2.44–2.92 (m, 6 H), 3.50 (s, 3 H; OCH_3), 3.76 (s, 3 H; OCH_3), 5.04–5.14 (m, 1 H), 6.42 (s, 1 H), 6.55 (s, 1 H), 6.80–6.85 (m, 1 H), 6.95–7.02 (m, 1 H) and 7.46–7.51 (m, 1 H). minor diastereomer: δ_H ($CDCl_3$, 300 MHz) 3.63 (s, 3 H; OCH_3), 3.75 (s, 3 H; OCH_3), 6.46 (s, 1 H) and 6.59 (s, 1 H); major diastereomer: δ_C ($CDCl_3$, 75 MHz) 13.9 (CH_3; Bu), 20.2 (CH_2), 23.2 (CH_2), 26.6 (CH_2), 28.9 (CH_2), 30.0 (CH_2), 35.4 (CH_2), 39.6 (CH_2), 54.8 (CH), 55.6 (CH_3; OCH_3), 55.8 (CH_3; OCH_3), 64.5 (C_{quat}; 12b-C), 109.8 (CH), 111.7 (CH), 128.5 (C_{quat}), 128.6 (CH), 129.5 (C_{quat}), 132.0 (CH), 134.9 (CH), 145.6 (C_{quat}), 147.3 (C_{quat}), 169.6 (C_{quat}; amide) and 194.4 (C_{quat}; carbonyl); minor diastereomer: δ_C ($CDCl_3$, 75 MHz) 13.8 (CH_3; Bu), 19.9 (CH_2), 23.3 (CH_2), 27.3 (CH_2), 27.4 (CH_2), 28.6 (CH_2), 37.2 (CH_2), 43.6 (CH_2), 51.0 (CH), 55.7 (CH_3; OCH_3), 56.1 (CH_3; OCH_3), 62.7 (C_{quat}; 12*b*-C), 108.9 (CH), 111.5 (CH), 128.4 (C_{quat}), 129.0 (CH), 129.4 (C_{quat}), 132.1 (CH), 133.5 (CH), 144.0 (C_{quat}), 147.6 (C_{quat}), 169.4 (C_{quat}; amide) and 192.1 (C_{quat}; ketone); *m*/*z* (EI^+) 427 (M^+, 6), 370 ($M^+ - C_4H_9$, 100), 111 (2-$ThCO^+$, 66).

Splitting protocol

(*Z*)-3-[2-(1*H*-Indol-3-yl)-ethylamino]-1-thiophen-2-yl-hepten-one (4a). In a Schlenk flask a stirred mixture of 140 mg (0.20 mmol) of $Pd(PPh_3)_2Cl_2$, and 70 mg (0.40 mmol) of CuI in 30.0 mL of THF was degassed for 5 min. Then 1.40 mL (10.0 mmol) of triethylamine, 1.07 mL (10.0 mmol) of thiophene acid chloride **1a** and 1.2 mL (10.5 mmol) of hexyne **2a** were added. The reaction mixture was stirred for 2 h under nitrogen at room temperature until the hexyne was completely consumed (monitored by TLC). Then 1.92 g (12.0 mmol) of tryptamine **8c** and 30.0 mL of methanol were added. The reaction mixture was heated to reflux temperature for 3 h until the conversion was complete (monitored by TLC). The solvents were evaporated and the residue was chromatographed on silica gel (hexane–ethyl acetate, 2 : 1) to afford 2.86 g (81%) of the enaminone **4a** as a yellow oil.

Yellow oil; R_f (product) 0.50 (hexane–ethyl acetate; 2 : 1); δ_H ($CDCl_3$, 300 MHz) 0.99 (t, J = 7.2 Hz, 3 H; Bu), 1.36–1.48 (m, 2 H; Bu), 1.51–1.62 (m, 2 H; Bu), 2.26 (t, J = 7.6 Hz, 2 H; Bu), 3.12 (t, J = 6.8 Hz, 2 H; tryptamine-CH_2), 3.65 (q, J = 6.6 Hz, 2 H; tryptamine-CH_2), 5.68 (s, 1 H; olefinic), 7.06–7.11 (m, 2 H), 7.18–7.26 (m, 2 H), 7.31–7.36 (m, 1 H), 7.43 (d, J = 5.1 Hz, 1 H), 7.63–7.67 (m, 2 H), 9.12 (s, 1 H; indole-2-H) and 11.40 (t, J = 5.5 Hz, 1 H; indole-NH); δ_C ($CDCl_3$, 75 MHz): 13.5 (CH_3; Bu), 22.4 (CH_2), 25.9 (CH_2), 29.7 (CH_2), 31.8 (CH_2), 43.3 (CH_2), 90.5 (CH; olefinic), 111.0 (C_{quat}), 111.4 (CH), 117.8 (CH), 118.8 (CH), 121.4 (CH), 122.9 (CH), 126.6 (C_{quat}), 126.8 (CH), 127.4 (CH), 129.1 (CH), 136.2 (C_{quat}), 147.0 (C_{quat}), 168.8 (C_{quat}; olefinic) and 180.3 (C_{quat}; ketone).

Synthesis of indolo[2,3-a]quinolizin-4-ones 6a or 6f *via* aza-annulation-PS sequence

In a screw cap pressure vessel 353 mg (1.00 mmol) of enaminone **4a** was dissolved in 5 mL of degassed THF. Then α,β-unsaturated chloride **9a** or **9c** (1.2 mmol) was added and the reaction mixture was heated at 70 °C for 3 h. After cooling to room temperature the reaction mixture was diluted with 5 mL of methanol, stirred for 10 min, evaporated and applied to column chromatography on silica gel eluting with neat diethyl ether (compound **6a**) or hexane–ethyl acetate 2 : 1 (compounds **6f**) to give 345 mg (85%) of compound **20a** as colorless crystals or 312 mg (75%) of compound **6f** (the ratio of diastereomers 4.5 : 1, the diastereomers were separated by column chromatography) (crystallization was achieved from pentane–CH_2Cl_2). For the characterization, see the CAAPS sequence.

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