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Tandem enlargement of the tetrahydropyridine ring in 1-aryl-tetrahydroisoquinolines using activated alkynes—a new and effective synthesis of benzoazocines

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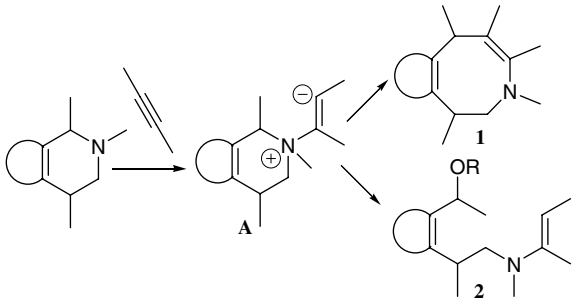
Abstract—Tetrahydroisoquinolines **3a**–**e** underwent piperidine ring enlargement under the action of activated alkynes, giving benzoazocines **4**, **5** and **7**–**11** in high yields.

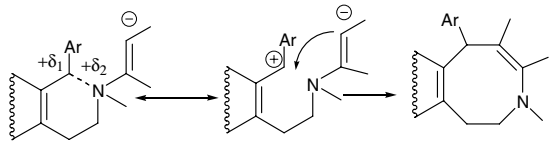
It is known that transformations of the tetrahydropyridine (THP) ring in pyrrolo[3,2-*c*]pyridines, tetrahydro-β- and γ-carbolines under the action of activated alkynes begin with the formation of the intermediate zwitterion **A**, resulting from Michael addition of the piperidine nitrogen to the triple bond of the activated alkyne.[1] This zwitterion undergoes further transformations via two different pathways, both of which are controlled by the reactivity of the anionic centre, the electronic effects of the substituent and the nature of the solvent (Scheme 1).



Scheme 1.

The final products of these tandem transformations in aprotic solvents are azocines **1**: pyrrolo[2,3-*d*]azocines,[1] azocino[4,5-*b*]-and [5,4-*b*]indoles,[2] whereas in the case of alcohols as the solvent—alkoxyalkyl-substituted pyrroles and indoles **2**, result.[2,3] In some cases, the formation of mixtures of azocines and alkoxy-substituted pyrroles or indoles in different proportions occurs. As a rule, the most efficient solvent for synthesizing the azocines **1** is acetonitrile, and for the alkoxy-substituted **2** is methanol or ethanol.

Analysis of the data obtained led us to presume that the presence of an Ar-substituent, providing additional delocalization of the partial positive charge $+\delta_1$ appearing on C-1 of the intermediate zwitterion, would facilitate cleavage of the C-1–N bond, thus favouring the formation of azocines via the intramolecular S_N1-process (Scheme 2). To check this assumption, we studied the tandem interaction of 1-aryl-6,7-dimethoxy-2-ethyl-1,2,3,4-tetrahydroisoquinolines **3a**–**d** with dimethyl acetylene dicarboxylate (DMAD), methyl propiolate, acetylacetylene and *p*-tosylacetylene[4] in methanol and acetonitrile.



Scheme 2.

Keywords: Tetrahydroisoquinoline; Azocines; Glaucine; Alkyne; Tandem reactions.
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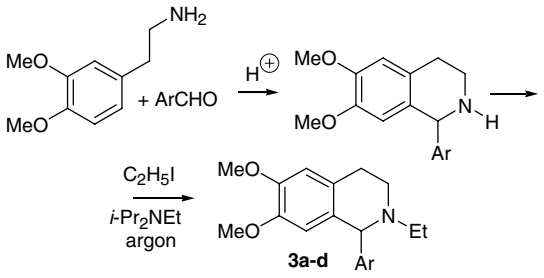
According to Scheme 2, starting materials having a benzhydryl fragment with differently substituted Ar radicals attached to the C-1 position should have different reactivities in S_N1 reactions, subject to the electronic properties of the substituents on the Ar rings. It is well known that the S_N1 reactivity dramatically increases for the benzhydryl and trityl derivatives having additional substituents with electron-donating resonance effects in the *para*-positions.[5]

The starting *N*-ethyl substituted isoquinolines **3a**–**d** were obtained by Pictet–Spengler condensation of 2-(3,4-dimethoxyphenyl)ethanamine with the appropriate aldehydes,[6] followed by N-ethylation of the intermediate *N*H-isoquinolines with ethyl iodide[7] (Scheme 3 and Table 1). The methods for preparing the starting tetrahydroisoquinolines, described in the literature,[8] were unsuccessful in our case. After the addition of the cyclizing agent (usually HCl), hydrolysis of the imines occurred and none of the desired products were obtained. Modifying the method to use H_3PO_4 instead of HCl avoided this problem. Isoquinoline **3e** was synthesized by the well-known Bischler–Napieralski[9] reaction of *N*-benzoylphenethylamine, followed by N-ethylation of the intermediate *N*H-isoquinolines with ethyl iodide (Scheme 4).

Isoquinoline **3a** reacted with methyl propiolate at 25 °C both in acetonitrile and in methanol to form azocine **4** in high yields[10] (Scheme 5 and Table 2).

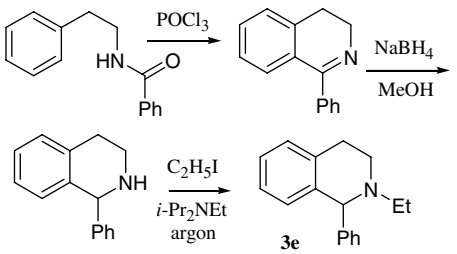
Benzoazocine **5** was the sole product from the reaction of isoquinoline **3a** with DMAD in acetonitrile; but in methanol, a mixture of azocine **5** and the product of tandem cleavage of the tetrahydropyridine ring—the substituted diarylmethane **6** was formed (ratio 1:1; derived from ^{1}H NMR data). Similar results were obtained in the case of tetrahydropyrrolopyridines and tetrahydrocarbolines.[1,2] This is presumably due to the lower reactivity (higher stability) of the anionic centre in the intermediate zwitterion caused by the additional negative charge delocalization between the two ester groups.



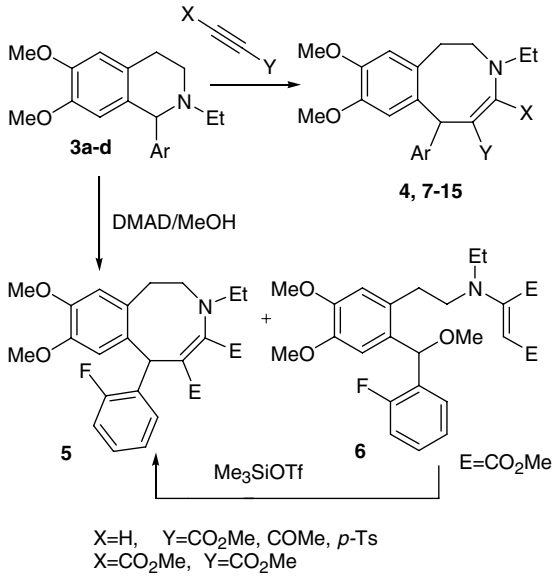
Scheme 3.

Table 1. Yields of tetrahydroquinolines **3a**–**e**

3	a	b	c	d	e
Ar	*o*-F–C_6H_4	*p*-F–C_6H_4	*p*-MeO–C_6H_4	*p*-CF_3–C_6H_4	Ph
Yield (%)	81	69	75	77	74



Scheme 4.



Scheme 5.

Compound **6** was converted into azocine **5** by the action of trimethylsilyltriflate. The only products isolated from the reactions of **3a** with methyl propiolate or *p*-tosylacetylene in acetonitrile were azocines **7** and **8**, respectively.

Analogously, the reactions of isoquinoline **3c** with methyl propiolate, DMAD and acetylacetylene gave benzoazocines **9**–**11** in high yield. In the case of reactions in acetonitrile, the yields were higher than in methanol; this may arise from the higher nucleophilicity and the lower steric factor of acetonitrile. The reaction of **3b** with methyl propiolate gave azocine **12**, the yield of which was again higher in acetonitrile than in methanol.

The structure of compound **8** was investigated by X-ray diffraction.[15] Suitable crystals were obtained by recrystallization from ethyl acetate by slow evaporation at room temperature. The refined X-ray crystal structure of **8** is shown in Figure 1. The conformation of the 8-membered ring is a twisted boat with the planes of the isoquinoline dimethoxy phenyl fragment and C-1-aryl being mutually perpendicular.

To see whether the presence of methoxy groups on the isoquinoline are mandatory for the transformation of the tetrahydropyridine ring, we carried out the reaction

Table 2. Yields of azocines and reaction time

Product	Ar	X, Y	Yields (%)	Time (h)
4	*o*-F–C_6H_4	X = H, Y = CO_2CH_3	72 (MeCN)	38 (MeCN)
			88 (MeOH)	41 (MeOH)
5	*o*-F–C_6H_4	X = Y = CO_2CH_3	36 (MeOH)	39
7	*o*-F–C_6H_4	X = H, Y = $COCH_3$	87 (MeCN)	41
8[11]	*o*-F–C_6H_4	X = H, Y = *p*-Ts	65 (MeCN)	36
9	*p*-MeO–C_6H_4	X = H, Y = CO_2CH_3	90 (MeCN)	37 (MeCN)
			75 (MeOH)	39 (MeOH)
10	*p*-MeO–C_6H_4	X = H, Y = $COCH_3$	85 (MeCN)	40
11[12]	*p*-MeO–C_6H_4	X = Y = CO_2CH_3	70 (MeCN)	42 (MeCN)
			55 (MeOH)	40 (MeOH)
12[13]	*p*-F–C_6H_4	X = H, Y = CO_2CH_3	88 (MeCN)	37 (MeCN)
			77 (MeOH)	38 (MeOH)
13	*p*-CF_3–C_6H_4	X = H, Y = CO_2CH_3	88 (MeCN)	41
14[14]	*p*-CF_3–C_6H_4	X = H, Y = $COCH_3$	76 (MeCN)	42
15	*p*-CF_3–C_6H_4	X = H, Y = *p*-Ts	67 (MeCN)	39

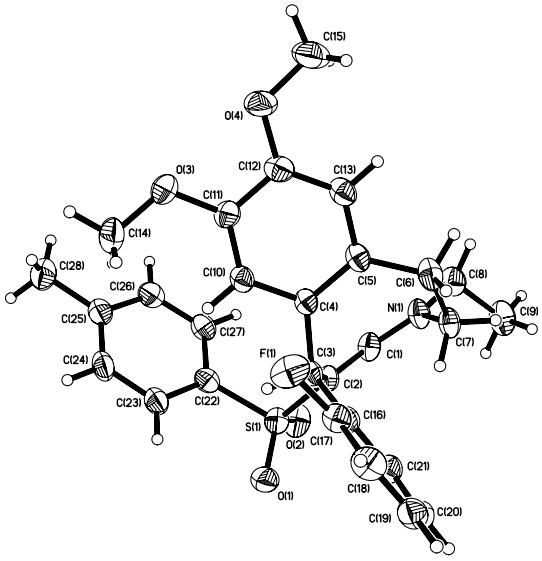


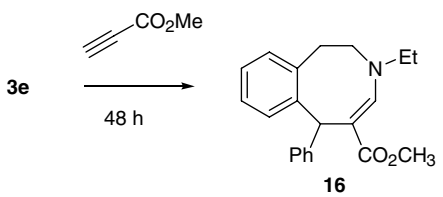
Figure 1. X-ray crystal structure of **8**.

of isoquinoline **3e** with methyl propiolate. The reaction occurs at room temperature, giving azocine **16**[16] in a yield of 50% (Scheme 6).

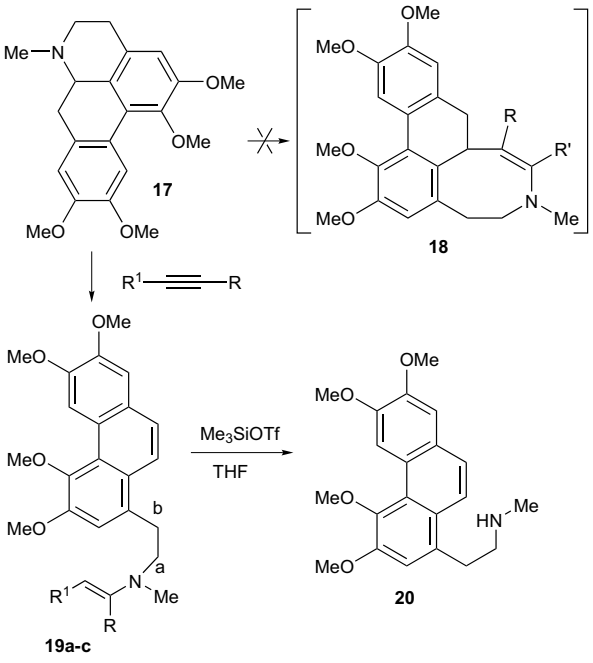
The ease of transformation of isoquinolines **3a**–**e** into benzoazocines **4** and **7**–**15** encouraged us to study the transformation of the alkaloid glaucine **17** under the action of activated alkynes. Glaucine **17** is used in medicine as an anti-tussive agent (Scheme 7).

However, the tandem transformations of glaucine **17** under the action of DMAD, methyl propiolate and 2-propynal both in acetonitrile and in methanol[17] led neither to the desired azocine **18** nor to the formation of alkoxy-alkyl-substituted derivatives of type **2**.

In all cases, the formation of the intermediate zwitterions was followed by a Hoffman-like cleavage of the tetrahydropyridine ring and the formation of phenanthrenes **19a**–**c**.[18–20] According to ^{1}H NMR data, compound **19c** exists as a mixture of isomers (presumably, s-*cis* and s-*trans* conformers). A detailed study of the stereochemistry is underway and will be reported elsewhere. Our attempts to carry out the cyclization of **19b** into azocine **18** by the action of $AlCl_3$ and trimethylsilyltriflate were also unsuccessful. From the reaction with $AlCl_3$, the starting compound was isolated. Using trimethylsilyltriflate in THF, amine **20**[21] was obtained in 52% yield (Scheme 7).



Scheme 6.



19a R=H, R'=CO_2Me, **c** R=H, R'=CHO
b R=R'=CO_2Me

Scheme 7.

In conclusion, we have elaborated an effective single-step synthetic protocol towards benzoazocine derivatives, based on a new tandem cleavage–cyclization reaction of tetrahydroisoquinoline derivatives. The data obtained shows that the reaction rate is not influenced by the substituents on the phenyl rings. A more detailed study on the reaction mechanism is underway and will be reported elsewhere.

Acknowledgement

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.04.151.

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6. *General procedure for the synthesis of tetrahydroisoquinolines*: To a flask equipped with a Dean–Stark apparatus, amine (0.06 mol), aldehyde (0.065 mol) and toluene (70 ml) were added and refluxed until all the water had been extracted. Then the mixture was allowed to cool to room temperature and 85% phosphoric acid (50 ml) was added. The resulting mixture was boiled for 3 h and then cooled to room temperature. The organic layer was decanted, the residue poured into a mixture of water and ice and the pH adjusted to 9–10 (NaOH). The resulting solution was extracted with CH_2Cl_2. The solvent was evaporated under reduced pressure to give the target isoquinolines.
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9. See e.g. (a) Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 74–150; (b) Wender, P. A.; Smith, T. E. *J. Org. Chem.* **1996**, *61*, 824–825.
10. *General synthetic procedure for the synthesis of benzoazocines* **5**, **7**–**16**: DMAD, methyl propiolate, acetylacetylene or *p*-tosylacetylene (1.2 mmol) was added to a solution of the isoquinoline derivative **3a**–**e** (1 mmol) in methanol or acetonitrile (10 ml). The reaction mixture was stirred for 36–42 h at 25 °C (TLC monitoring). The solvent was evaporated under reduced pressure and the residue was recrystallized (ethyl acetate/hexane) to give benzoazocines **4**, **7**–**16**. In the case of the reaction of isoquinoline **3a** with DMAD, a mixture (1:1 according to ^{1}H NMR data) of azocine **5** and the product of the tandem cleavage of the tetrahydropyridine ring **6** were formed. The mixture (0.15 g) was dissolved in acetonitrile (10 ml) and a few drops of trimethylsilyltriflate was added. The reaction was kept for a week (TLC monitoring). The solvent was evaporated under reduced pressure and the resulting residue purified by column chromatography with ethyl acetate as eluent to give benzoazocine **5**.
11. *3-Ethyl-6-(2-fluorophenyl)-8,9-dimethoxy-5-(4-methylphenylsulfonyl)-1,2,3,6-tetrahydrobenzo[d]azocine* **8**: Yield 65% white crystals, mp 202–204 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.11$ (t, $J = 7.1$ Hz, 3H, –CH_2–CH_3), 2.39 (s, 3H, –CH_3(*p*-Ts)), 2.62 (dd, $J = 5.4$, $J = 15.8$, 1H, CH_2-1), 2.68–2.78 (m, 1H, CH_2-1), 2.98 (dd, $J = 7.4$, $J = 15.8$, 1H, CH_2-2), 3.18–3.28 (m, 2H, –CH_2–CH_3), 3.42 (s, 3H, OCH_3), 3.73–3.79 (m, 4H, OCH_3 and 2-CH_2), 5.06 (s, 1H, 6-H), 5.71 (s, 1H, 10-H), 6.74 (s, 1H, 7-H), 6.84 (dd, $J = 8.1$, $J = 11.0$ Hz, 1H, CH–Ar), 7.09 (t, $J = 8.1$ Hz, 1H, CH–Ar), 7.15–7.20 (m, 1H, CH–Ar), 7.24 (d, $J = 7.8$ Hz, 2H, 2CH-Ts), 7.62 (t, $J = 8.1$ Hz, 1H, CH–Ar), 7.68 (s, 1H, 4-H), 7.70 (d, $J = 7.8$ Hz, 2H, 2CH-Ts) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 15.1$, 21.4, 35.4, 46.8, 49.7, 51.8, 55.0, 55.7, 102.8, 114.3, 115.3, 115.9 (d, $^2J = 22$ Hz), 124.2 (d, $^4J = 2$ Hz), 127.9 (2C), 128.5, 129.1 (d, $^3J = 8$ Hz), 130.1 (2C), 131.5, 131.7 (d, $^3J = 3$ Hz), 131.9 ($^2J = 10$.Hz), 140.7, 142.8, 146.8, 146.9, 153.2, 160.5 (d, $^1J = 242$ Hz) ppm. IR (KBr): $\nu = 1728$, 1608 cm^{-1}. EI MS: m/z (%) = 495 (15) [M$^+$], 340 (100), 324 (5), 207 (20), 164 (10), 133 (15), 109 (20), 91 (85), 77 (15), 65 (57), 58 (45), 39 (20). $C_{28}H_{30}FNO_4S$ (495.19): calcd C 67.86, H 6.10, F 3.83, N 2.83, O 12.91, S 6.47; found C 67.90, H 6.12, F 3.84, N 2. 82, O 12.92, S 6.43.
12. *Dimethyl 3-ethyl-6-(p-methoxyphenyl)-8,9-dimethoxy-1,2,3,6-tetrahydrobenzo[d]azocine-4,5-dicarboxylate* **11**: Yield 55% in methanol (70% in acetonitrile) white crystals mp 188–190 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J = 7.2$ Hz, 3H, –CH_2–CH_3), 2.58 (ddd, $J = 0.7$, $J = 5.3$, $J = 7.0$ Hz, 1H, CH_2-1), 2.71–2.81 (m, 2H, –CH_2–CH_3 and 1-CH_2), 2.96 (qd, $J = 7.2$, $J = 14.3$ Hz, 1H, CH_2–CH_3), 3.19 (ddd, $J = 1.8$, $J = 7.3$, $J = 15.1$, 1H, CH_2-2), 3.36–3.44 (m, 1H, CH_2-2), 3.72 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 5.82 (s, 1H, 6-H), 6.60 (s, 1H, 10-H), 6.77 (d, $J = 8.4$ Hz, 2H, H–Ar), 6.80 (s, 1H, 7-H), 6.99 (d, $J = 8.4$ Hz, 2H, H–Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.4$, 34.2, 45.6, 50.3, 50.9, 51.6, 52.3, 55.1, 55.8, 55.8, 102.4, 113.4 (2C), 114.1, 116.6, 127.3 (2C), 129.6, 131.2, 137.0, 147.0, 147.3, 155.6, 157.5, 167.3, 169.8. IR (KBr): $\nu = 1728$, 1678, 1558 cm^{-1}. EI MS: m/z (%) = 469 (5) [M$^+$], 410 (20), 398 (100), 382 (15), 350 (20), 339 (25), 283 (15), 59 (12). $C_{26}H_{31}NO_7$ (469.21): calcd C 66.51, H 6.65, N 2.98, O 23.85; found C 66.53, H 6.63, N 3.00, O 23.87.
13. *Methyl 3-ethyl-6-(p-fluorophenyl)-8,9-dimethoxy-1,2,3,6-tetrahydrobenzo[d]azocine-5-carboxylate* **12**: Yield 77% in methanol (88% in acetonitrile) white crystals, mp 74–76 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.08$ (t, $J = 7.2$ Hz, 3H, –CH_2–CH_3), 2.74–2.87 (m, 3H, CH_2-1 and CH_2-2), 3.13–3.23 (m, 2H, –CH_2–CH_3), 3.42–3.50 (m, 1H, CH_2-2), 3.75 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 5.81 (s, 1H, 6-H), 6.64 (s, 1H, 10-H), 6.77 (s, 1H, 7-H), 6.93 (t, $J = 8.7$ Hz, 2H, 2CH–Ar), 7.05–7.12 (m, 2H, 2CH–Ar), 7.67 (s, 1H, 4-H) ppm. IR (KBr): $\nu = 1670$, 1605 cm^{-1}. ESI MS 400

(M^++1) $C_{23}H_{26}FNO_4$ (399.18): calcd C 69.16, H 6.56, F 4.76, N 3.51, O 16.02; found C 69.15, H 6.58, F 4.74, N 3.52, O 16.00.

14. *1-[3-Ethyl-8,9-dimethoxy-6-(4-trifluoromethyl-phenyl)-1,2,3,6-tetrahydrobenzo[d]azocine-5-yl]-1-ethanone* **14**: Yield 76% white crystals (ethyl acetate/hexane) mp 126–128 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.14$ (t, $J = 7.0$ Hz, 3H, –CH_2–CH_3), 2.36 (s, 3H, $COCH_3$), 2.79 (dd, $J = 5.4$, $J = 15.0$ Hz, 1H, 1-CH_2), 2.90 (qd, $J = 7.0$, $J = 13.6$ Hz, 2H, –CH_2–CH_3), 3.24 (dd, $J = 6.7$, $J = 13.8$ Hz, 2H, 1-CH_2 and 2-CH_2), 3.37–3.46 (m, 1H, 2-CH_2), 3.83 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.24 (s, 1H, 6-H), 6.65 (s, 1H, 7-H), 6.73 (s, 1H, 10-H), 7. 14 (d, $J = 7.8$ Hz, 2H, CH–Ar), 7.48 (d, $J = 7.8$ Hz, 2H, CH–Ar), 7.53 (s, 1H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 10.2$, 20.3, 31.7, 42.4, 44.2, 47.5, 51.3, 51.4, 107.9, 109.9, 111.8, 120.6 (q, $^3J_{C,F} = 4$ Hz, 2C), 121.7 (2C), 122.8 (q, $^2J_{C,F} = 32$ Hz), 123.5 (q, $^1J_{C,F} = 280$ Hz), 123.6, 126.6, 142.3, 142.9, 146.7, 150.6, 189.7 ppm. IR (KBr): $\nu = 1613$, 1571 cm^{-1}. EI MS: m/z (%) = 433 (47) [M^+], 414 (9), 404 (7), 391 (24), 390 (100), 376 (12), 374 (6), 363 (13), 362 (50), 348 (6), 347 (21), 346 (23), 345 (5), 334 (6), 333 (18), 321 (7), 320 (8), 319 (320), 290 (6), 275 (5), 219 (6), 218 (13), 202 (6), 164 (9), 72 (7), 58 (72), 43 (11). $C_{24}H_{26}F_3NO_3$ (433.19): calcd C 66.50, H 6.05, F 13.15, N 3.23, O 11.07; found C 66.59, H 6.01, F 13.13, N 3.21, O 11.09.
15. Crystal structure analysis for **8**: $C_{28}H_{30}FNO_4S$, $M_r = 495.59$ g mol^{-1}, orthorhombic, space group *Pbca*, $a = 14.2575(10)$ Å, $b = 16.6195(10)$, $c = 21.2819(10)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 5042.8(5)$ Å^3, $Z = 8$, $\rho = 1.306$ g cm^3, $\mu = 1.490$ mm^{-1}, $F(000) = 2096$, crystal size: $0.80 \times 0.40 \times 0.20$ mm. Crystal data were collected on a Cad-4 diffractometer (λCu K_α radiation, graphite monochromator; ω scanning). A total of 5151 reflections ($4.58 < \theta < 69.49°$) were collected of which 4687 were unique (R(int) = 0.0771). The structure was solved with the program SHELXS-97[22] and refined using SHELXL-97[23] to $R_1 = 0.0695$ and $wR(F^2) = 0.2057$ for 3367 reflections with $I > 2\sigma(I)$; max\min residual electron density 0.535 and −0.523 e Å^{-3}. Crystallographic data (excluding structure factors) for compound **8** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 298845.
16. *Methyl 3-ethyl-6-phenyl-1,2,3,6-tetrahydro benzo[d]azocine-5-carboxylate* **16**: Yield 50% white crystals mp 108–109 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.05$ (t, $J = 7.2$ Hz, 3H, –CH_2–CH_3), 2.80–2.97 (m, 3H, 1-CH_2 and 2-CH_2), 3.08–3.22 (m, 2H, –CH_2–CH_3), 3.51–3.61 (m, 1H, 2-CH_2), 3.74 (s, 3H, OCH_3), 6.00 (s, 1H, 6-H), 7.12–7.30 (m, 9H, Ar), 7.67 (s, 1H, 4-H) ppm. IR (KBr): $\nu = 1675$, 1605 cm^{-1}. ESI MS 322 (M^++1). $C_{21}H_{23}NO_2$ (321.17): calcd C 78.47, H 7.21, N 4.36, O 9.96; found C 78.50, H 7.19, N 4.37, O 9.98.
17. *General synthetic procedure for the synthesis of phenanthrenes* **19a–c**: DMAD or methyl propiolate (1.2 mmol) was added to a solution of glaucine **17** (1 mmol) in methanol or acetonitrile (10 ml) (TLC monitoring). The reaction mixture was kept for 2–3 days at room temperature. The solvent was evaporated under reduced pressure and the residue was recrystallized (ethyl acetate/hexane) to give phenanthrenes **19a–c**.
18. *Methyl (E)-3-methyl-[2-(3,4,6,7-tetramethoxy-1-phenanthryl)ethyl]amino-2-propenoate* **19a**: Yield 73% in methanol (85% in acetonitrile) white crystals mp 131–133 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.73$ (s, 3H, N–CH_3), 3.31 (t, 2H, $J = 6.9$ Hz, CH_2-β), 3.52 (t, 2H, $J = 6.9$ Hz, CH_2-α), 3.66 (s, 3H, O–CH_3), 3.92 (s, 3H, O–CH_3), 4.01 (s, 3H, O–CH_3), 4.04 (s, 3H, O–CH_3), 4.07 (s, 3H, O–CH_3), 4.59 (d, 1H, $J = 12.9$ Hz, =CH), 7.10 (s, 1H, CH-2), 7.22 (s, 1H, CH-8), 7.45 (d, 1H, $J = 12.9$ Hz, N–CH=), 7.58 (d, 1H, $J = 9.2$ Hz, CH-9), 7.67 (d, 1H, $J = 9.2$ Hz, CH-10), 9.27 (s, 1H, CH-5). IR (KBr): $\nu = 1685$, 1611 cm^{-1}. EI MS: m/z (%) = 439 (40) [M^+], 408 (10), 324 (15), 311 (100), 265 (10), 128 (75), 45 (10). $C_{25}H_{29}NO_6$ (439.2): calcd C 68.32, H 6.65, N 3.19, O 21.84; found C 68.33, H 6.68, N 3.20, O 21.87.
19. *Dimethyl (E)-2-methyl-[2-(3,4,6,7-tetramethoxy-1-phenanthryl)ethyl]amino-2-butendioate* **19b**: Yield 58% in methanol (72% in acetonitrile) yellow crystals mp 109–110 °C (ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.71$ (s, 3H, N–CH_3), 3.34 (t, 2H, $J = 6.8$ Hz, CH_2-β), 3.48 (t, 2H, $J = 6.8$ Hz, CH_2-α), 3.66 (s, 3H, O–CH_3), 3.90 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 4.07 (s, 3H, OCH_3), 4.65 (s, 1H, =CH) 7.12 (s, 1H, CH-2), 7.21 (s, 1H, CH-8), 7.56 (d, 1H, $J = 9.1$ Hz, CH-9), 7.71 (d, 1H, $J = 9.0$ Hz, CH-10), 9.27 (s, 1H, CH-5). IR (KBr): $\nu = 1739$, 1689, 1574 cm^{-1}. EI MS: m/z (%) = 497 (5) [M^+], 186 (100), 82 (30), 45 (25). $C_{27}H_{31}NO_8$ (497.20): calcd C 65.18, H 6.28, N 2.82, O 27.73; found C 65.20, H 6.31, N 2.25, O 27.77.
20. *(E)-3-Methyl-[2-(3,4,6,7-tetramethoxy-1-phenanthryl)ethyl]amino-2-propenal* **19c**: Propargyl aldehyde (10 mmol) was added to a solution of glaucine **17** (1 mmol) in methanol (10 ml). The reaction mixture was kept for 10 days at 30 °C (TLC monitoring). The solvent was evaporated under reduced pressure and hexane was added to the residue, causing precipitation of **19c** (241 mg, 59%); pink crystals mp 168–170 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.84$ (s, 2H, N–CH_3 maj), 2.85 (br s, 1H, N–CH_3 min), 3.35 (m, 2H, CH_2-β), 3.55 (m, 0.66 H, CH_2-α min), 3.65 (m, 1.34H, CH_2-α maj), 3.92 (s, 3H, O–CH_3), 4.02 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 4.07 (s, 3H, OCH_3), 5.10 (m, 0.66H, =C*H*–CHO maj), 5.10 (m, 0.34H, =C*H*–CHO min), 6.80 (m, 0.66H, N–C*H*=-maj), 7.10 (s, 1H, CH-2), 7.12 (m, 0.34H, N–C*H*=-min), 7.23 (s, 1H, CH-8), 7.61 (d, 1H, $J = 8.9$ Hz, CH-9), 7.71 (br d, 1H, $J = 8.9$ Hz, CH-10), 8.90 (br d, 0.66 H, –CHO maj), 9.12 (br d, 0.34H, –CHO min), 9.30 (s, 1H, CH-5). IR (KBr): $\nu = 1604$, 1515 cm^{-1}. EI MS: m/z (%) = 409 (20) [M^+], 324 (45), 311 (95), 265 (20), 98 (100). $C_{24}H_{27}NO_5$ (409.48): calcd C 70.40, H 6.65, N 3.42, O 19.54; found C 70.43, H 6.67, N 3.41, O 19.55.
21. *Methyl [2-(3,4,6,7-tetramethoxy-1-phenanthryl)ethyl]-amine* **20**: To a solution of phenanthrene **19a** (100 mg, 0.23 mmol) in acetonitrile (5 ml), three drops of trimethylsilyltriflate was added. The reaction mixture was kept for 3 days at 30 °C (TLC monitoring). The solvent was evaporated under reduced pressure, the residue was treated with a 30% aqueous solution of Na_2CO_3 (10 ml) and extracted with ether (3×25 ml). The organic layer was dried over $MgSO_4$. The solvent was evaporated under reduced pressure and hexane was added to the residue, causing precipitation of **20** (43 mg, 52%); yellow crystals, mp 94–96 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.48$ (s, 3H, N–Me), 3.00 (t,2H, $J = 7.1$ Hz, CH_2-β), 3.32 (t, 2H, $J = 7.1$ Hz, CH_2-α), 3.91 (s, 3H, O–CH_3), 4.03 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 4.08 (s, 3H, OCH_3), 7.21 (s, 1H, CH-2), 7.23 (s, 1H, CH-8), 7.54 (d, 1H, $J = 9.0$ Hz, CH-9), 7.80 (d, 1H, $J = 9.0$ Hz, CH-10), 9.27 (s, 1H, CH-5). EI MS: m/z (%) = 355 (10) [M^+], 312 (40), 297 (10), 58 (10), 44 (100). $C_{21}H_{25}NO_4$ (355.18): calcd C 70.96, H 7.09, N 3.94, O 18.01; found C 70.99, H 7.06, N 3.95, O 17.99.
22. Sheldrick, G. M. SHELXS, Program for Crystal Structure Solution, University of Göttingen, Germany, 1997.
23. Sheldrick, G. M. shelxl, Program for Crystal Structure Refinement, University of Göttingen, Germany, 1997.