A New Route to Acridines: Pauson–Khand Reaction on Quinoline-Bearing 1-En-7-ynes Leading to Novel Tetrahydrocyclopenta[*c*]acridine-2,5-diones

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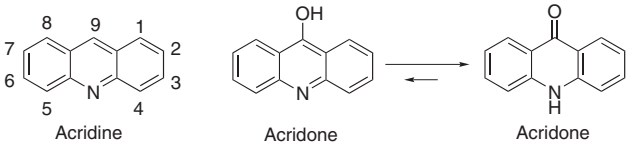
This paper is dedicated to Pr. Marco A. Ciufolini.

Abstract: Efficient Pauson–Khand reactions on quinolines bearing 1-en-7-ynes features gave tetrahydrocyclopenta[*c*]acridine derivatives. The quinoline intermediates were obtained in two steps: a Sonogashira reaction with functionalized alkynes (TMS, Bu, Ph, CHB_2OTHP) followed by a Grignard reaction with allylmagnesium bromide. The sequence provides new acridine structures in four high yielding steps from commercially available quinolines.

Key words: quinoline, acridine, enynes, intramolecular Pauson–Khand reaction, cyclopenta[*c*]acridine

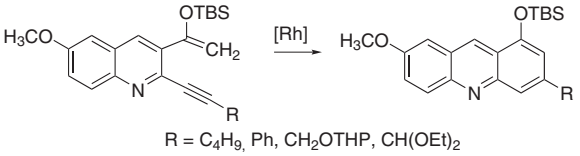
Acridines are interesting heteroaromatic structures (Scheme 1), they have been known since the 19th century as pigments and dyes,[1] and are in use in clinics for their antibacterial properties (acriflavine, aminacrine, ethacridine).[1,2] Also, their biological activities against parasite infections (malaria, trypanosomiasis or leishmaniasis) result in clinical applications (quinacrine, acranil).[2]Antitumoral treatments have also been developed (nitracrine, amsacrine)[3] and are of considerable contemporary importance due to the current vigorous search for inhibitors of telomerase and topoisomerases.[2a]



Scheme 1 Acridine and acridone structures and numbering

Following our recent work,[4] we are still looking for alternative synthetic pathways to reach functionalized acridines. Reasons for that are the usual harsh conditions needed for synthesizing acridines through the acridone intermediates (Scheme 1), which are obtained by heating diphenylamine-2-carboxylic acids[5] in strong acidic media. [6] Acridines are then reached by harsh reductive (e.g. sodium amalgam)[1,7] and oxidative (e.g. nitric acid)[8] conditions. Other methods include the Bernthsen reaction[9] (heating diphenylamines and organic acids with $ZnCl_2$ between 200 °C and 270 °C), the cyclization of diphenylamine-2-carboxaldehyde (TFA, H_2SO_4 and/or high temperature)[10] or the adaptation of the Pfitzinger quinoline synthesis (heating isatine and 1,3,5-trihydroxy-benzene in NaOH solution).[11]

Our previous work[4] on quinolines bearing a TBS-protected enol-ether at position 3 and an internal alkyne chain at position 2 (i.e., 1-en-5-yne structures), allowed us to obtain 1,3,7-trisubstituted acridines via a 6-*endo-dig* cyclization process catalyzed by a rhodium (I) complex $[Rh(CO)_2Cl]_2$ (Scheme 2).



Scheme 2 Previous work

We were interested in finding an alternative approach to acridines that could also provide new tetracyclic structures. For this purpose, Pauson–Khand reaction (PKR)[12] on 1-en-7-yne heteroaromatic structures, such as **A** (Scheme 3), appeared to suit us since it could open the way to new structures such as tetrahydro-2*H*-cyclopenta[*c*]acridine-2,5-diones.

To our knowledge, this is the first application of the PKR in order to access acridine derivatives. PKR[13] has become a very useful tool in the synthesis of natural products,[14] and the classical cobalt reagent $[Co_2(CO)_8]$ has been used with different initiators in stoechiometric or catalytic versions,[15] and even in an asymmetric fashion.[14] The intramolecular PKR applied on enynes connected through an aromatic usually gives moderate yields, although some good results are obtained when using PKR promoted by molecular sieves and trimethylamine *N*-oxide.[16]

We first started our work by synthesizing the 1-en-7-yne features (Compound **A**, Scheme 3) from commercially available 2-chloro-3-quinoline carboxaldehyde. These derivatives were obtained in two simple and high yielding steps (Scheme 4): Sonogashira reaction[17] on the chlorinated quinoline[18] with various functionalized alkynes (**1a**–**1d**, 95–98% yield), followed by Grignard addition of allylmagnesium bromide (**2a**–**2d**, 80–93% yield).

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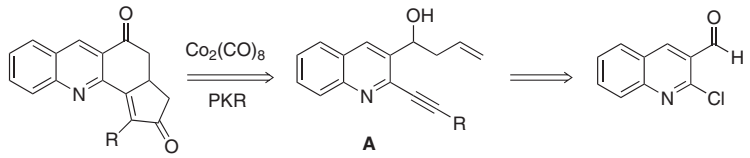
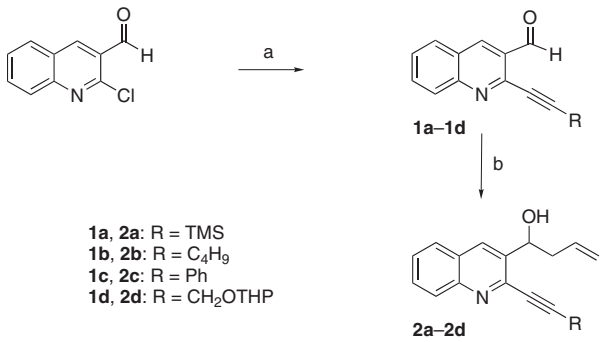


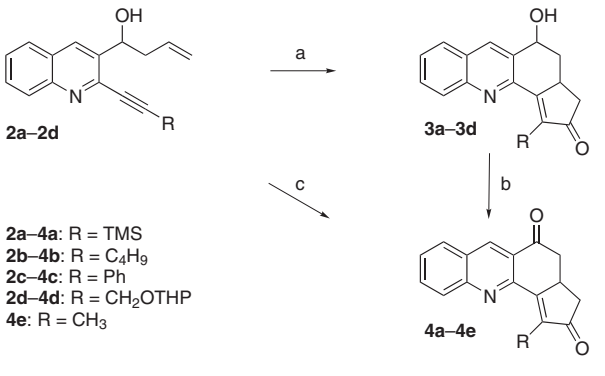
Scheme 3 Retrosynthetic analysis



Scheme 4 *Reagents and conditions*: (a) 1-alkyne, $PdCl_2(PPh_3)_2$ (0.05 equiv), CuI (0.05 equiv), Et_3N (4.15 equiv), DMF, r.t., **1a** (95%), **1b** (98%), **1c** (97%), **1d** (98%); (b) AllylMgBr (1.3 equiv), THF, –78 °C, **2a** (85%), **2b** (93%), **2c** (80%), **2d** (84%)

So, the next reaction is the key step of our methodology and we were comforted in our choice for intramolecular PKR on aromatic compounds bearing 1-en-7-yne features by recent and interesting work of Pérez–Castells group on aromatic enynes derivatives[16b,19] and indoles.[16a] It is noteworthy that in both cases, yields are moderate to good and the compound issued from the PKR can be accompanied by isomeric double-bond products and/or also a *trans*/*cis* diastereomeric mixture. We used the classical non-thermal conditions for our PKR, i.e. the $Co_2(CO)_6$-alkyne complex was treated with *N*-methyl morpholine *N*-oxide (NMO) at room temperature (Scheme 5).

We observed the formation of only one diastereomer (**3a**–**3d**, 70% quant) in all cases.[20] The relative stereochemistry of the stereogenic carbons was assigned by NOE experiments. On compound **3b** no stereochemical assignment could be made, so we methylated the free hydroxyl function of **3b** (NaH, MeI, THF, r.t.) and new NOE experiments revealed that the trio OCH_3-Hb-Hd is on the same side of the ring (**3b**-CH_3, Figure 1), proving that the unique stereoisomers seen were the *trans* isomer (i.e. Ha and Hd are *trans*). This result is in accordance with observed directed Pauson–Khand reactions.[21,22]



Scheme 5 *Reagents and conditions*: (a) Enynes **2a**–**2d**, $Co_2(CO)_8$ (1.3 equiv), CH_2Cl_2, r.t., 2 h; NMO (10 equiv), r.t. overnight, **3a** (70%), **3b** (quant), **3c** (81%), **3d** (75%); (b) DMP (1.72 equiv), CH_2Cl_2, r.t., **4a** (93%), **4b** (94%), **4c** (98%), **4d** + **4e** (50% + 43%). (c) Enyne **2a**, $Co_2(CO)_8$ (1.3 equiv), CH_2Cl_2, r.t., 2 h; NMO (10 equiv), r.t. overnight; TPAP (0.1 equiv) and 4 Å MS, **4a** (43%)

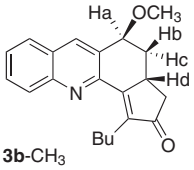


Figure 1 Stereochemical assignment

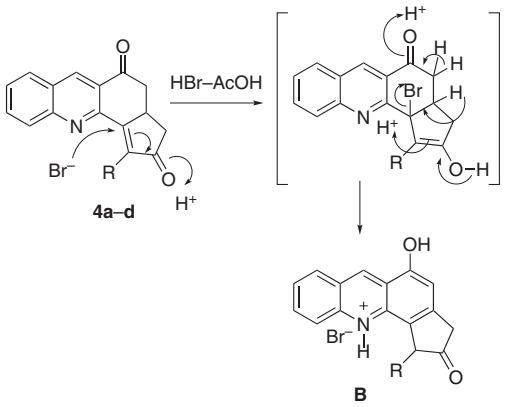
The PKR products (**3a**–**3d**) were then oxidized with Dess–Martin periodinane[23] (DMP) to form the tetrahydro-2*H*-cyclopenta[*c*]acridine-2,5-dione derivatives (**4a**–**4c**, 93–98%, Scheme 5). We tried to achieve the transformation with a one-pot process from enyne **2a** to compound **4a** using the excess of NMO to operate the well-known oxidation reaction developed by Ley and coworkers.[24] Even after optimization, we could not obtain more than 43% of the desired compound, which remains less efficient than our two-step procedure.

Intriguingly, compound **3d** gave the desired oxidized product (**4d**, 50%) accompanied with a methylated derivative (**4e**, 43%). In order to explain the formation of this compound under oxidative conditions, we propose an activation for the disruption of the OTHP part by chelation with hypervalent iodine in the DMP reagent (Scheme 6).

An acetate anion may deprotonate at the benzylic position, which provides a E_2' type elimination reaction of the OTHP portion. The *exo* methylene unit formed can then be protonated by a tautomeric exchange to yield compound **4e**. This reaction (**4e**, 43%) appeared to be in competition with the regular oxidation reaction (**4d**, 50%) since an excess of DMP does not affect the **4e**/**4d** ratio.

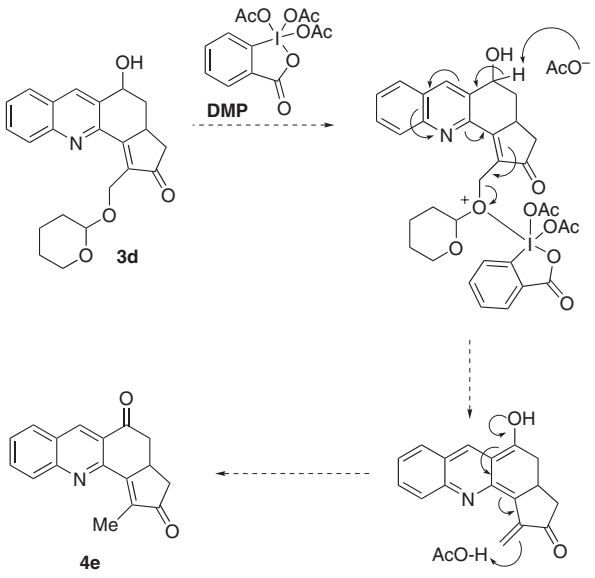
Preliminary studies were also performed in order to reach cyclopenta[*c*]acridine-2,5-diones (**B**, Scheme 7). In order to do so, isomerization of the double-bond formed during the PKR is necessary. Interestingly, we never observed, with our quinolines systems, isomerization of the emerging double bond during the PKR. Moreover, attempts to isomerize the double-bond for aromatization using classical methodologies failed (*p*-TsOH, TfOH, DBU). These

conditions furnished only the starting materials and heating up to 120 °C only led to decomposition of the reaction mixture. But, the use of HBr in AcOH gave the good products as salts. The NMR data are in accordance with the desired structures, but the products are accompanied with their enols, and the mixture is not separable. Addition of Et_3N in the NMR tube shows the free base-**B** product, which quickly decomposes. Work is still underway to obtain cleanly theses compounds, which are not stable.



Scheme 7 Aromatization

In conclusion, we have applied successfully Pauson–Khand reaction for the synthesis of tetrahydroacridine scaffold. The original tetracyclic structures are a new entry in the family of nitrogen-heterocycles, which are widely known for their broad biological properties. Preliminary studies are promising for the obtention of the real acridine nucleus. Also, we have observed an unusual formation of a methylated compound R^1-CH_3 by transformation of a R^1-CH_2OTHP protecting group under a Dess–Martin periodinane oxidation process. Development of our methodology to broaden these structural panels will be published in due course.



Scheme 6 Possible formation mechanism for **4e**

Melting points were determined on a Büchi B-540 apparatus. IR spectra were recorded on an FTIR spectrometer Perkin Elmer 1720, as thin films or directly with solids. ^1H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively, in $CDCl_3$ solutions on a ALS300 Brüker instrument. Chemical shifts are reported in ppm on the δ scale. Multiplicities are described as s (singlet), d (doublet), dd, ddd, etc. (doublet of doublets, doublet of doublets of doublets, etc.), t (triplet), q (quartet), m (multiplet), and further qualified as app (apparent), br (broad), c (complex). Coupling constants, *J*, are reported in Hz. Low and high-resolution mass spectra (*m*/*z*) were measured on a Thermo-Finnigan Mat 95XL spectrometer, with different techniques: Chemical Ionization mode (CI, isobutane as the reagent gas) or LSIMS (Liquid Secondary Ion Mass Spectrometry). Low resolution was also performed with ESI (ElectroSpray Ionization). Mass Analyses were done by Ms L. Rousset-Arzel and Dr. D. Bouchu. Flash column chromatography purifications were performed with Geduran® Si 60 from Merck (particle size 60–200 μm), and PTLC on Analtech 1000 μm or 250 μm.

When necessary, reactions were performed under Ar atmosphere and in dried flasks. THF was freshly distilled from sodium benzophenone ketyl under N_2 and CH_2Cl_2 was distilled from CaH_2.

Synthesis of 2-(2-Trimethylsilyl-1-ethynyl)-3-quinolinecarbaldehyde (1a) via Sonogashira Coupling Reaction; Typical Procedure

To a stirred solution of the aldehyde (3.00 g, 15.54 mmol) in anhyd DMF (15.0 mL) were added $Pd(PPh_3)Cl_2$ (540 mg, 0.78 mmol), CuI (150.0 mg, 0.78 mmol), Et_3N (9.0 mL, 64.5 mmol) and (trimethylsilyl)acetylene (17.19 mmol) at r.t. and under Ar, and the mixture was stirred at the same temperature overnight. After filtration through a short pad of silica and elution with EtOAc, the filtrate was concentrated to the crude product, which was chromatographed. Elution with mixture of cyclohexane–EtOAc (3:1) afforded the aldehyde (3.75 g, 95%) as yellow scales; mp 125 °C.

IR (neat): 2954, 2850, 2359, 2338, 1694, 1579, 1369, 1149, 1096 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.34 [s, 9 H, $Si(CH_3)_3$], 7.63 (ddd, *J* = 1.0, 6.9, 8.1 Hz, 1 H), 7.86 (ddd, *J* = 1.5, 6.9, 8.4 Hz, 1 H), 7.96 (dd, *J* = 1.5, 8.1 Hz, 1 H), 8.16 (dd, *J* = 1.0, 8.4 Hz, 1 H), 8.72 (s, 1 H), 10.71 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –0.4 (3 × CH_3), 100.0 (C), 102.4 (C), 126.5 (C), 128.3 (CH), 128.8 (C), 129.3 (CH), 129.6 (CH), 132.9 (CH), 136.7 (CH), 143.6 (C), 150.0 (C), 190.9 (CHO).

MS: *m*/*z* (%) = 286 (81) [MNa^+], 254 (100) [MH^+], 180 (17) [MH^+ – TMS].

HRMS: *m*/*z* [MH^+] calcd for $C_{15}H_{15}NOSi$: 254.1001; found: 254.0997.

2-(1-Hexynyl)-3-quinolinecarbaldehyde (1b)

Yield: 98%; mp 49–50 °C.

IR (neat): 2956, 2861, 2216, 1690, 1580, 1358, 1110 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.5 Hz, 3 H), 1.36–1.52 (m, 2 H), 1.72 (tt, *J* = 7.5, 15.3 Hz, 2 H), 2.59 (t, *J* = 7.5 Hz, 2 H), 6.58 (s, 1 H), 7.55 (ddd, *J* = 1.2, 6.9, 8.1 Hz, 1 H), 7.84 (ddd, *J* = 1.5, 6.9, 8.4 Hz, 1 H), 7.93 (d, *J* = 8.4 Hz, 1 H), 8.06 (d, *J* = 8.1 Hz, 1 H), 9.06 (s, 1 H), 10.68 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.3 (CH_3), 19.0 (CH_2), 21.9 (CH_2), 29.9 (CH_2), 77.2 (C), 97.8 (C), 125.9 (C), 127.5 (CH), 128.4 (C), 128.8 (CH), 129.3 (CH), 132.5 (CH), 136.4 (CH), 144.1 (C), 149.7 (C), 190.7 (CHO).

MS: *m*/*z* (%) = 238 (100) [MH^+].

HRMS: *m*/*z* [MH^+] calcd for $C_{16}H_{15}NO$: 238.1232; found: 238.1235.

2-(2-Phenyl-1-ethynyl)-3-quinolinecarbaldehyde (1c)
Yield: 97%; mp 126 °C.

IR (neat): 3047, 2853, 2208, 1691, 1581, 1372, 1168, 1087 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.48 (m, 3 H), 7.64 (ddd, *J* = 1.2, 7.2, 8.4 Hz, 1 H), 7.68–7.75 (m, 2 H), 7.88 (ddd, *J* = 1.5, 7.2, 8.7 Hz, 1 H), 7.98 (d, *J* = 7.8 Hz, 1 H), 8.18 (d, *J* = 8.7 Hz, 1 H), 8.76 (s, 1 H), 10.82 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 86.0 (C), 95.9 (C), 121.8 (C), 126.8 (C), 128.6 (CH), 129.0 (2 × CH), 129.2 (C), 129.7 (CH), 130.1 (CH), 130.3 (CH), 132.7 (2 × CH), 133.4 (CH), 137.5 (CH), 144.3 (C), 150.6 (C), 191.2 (CHO).

MS: *m*/*z* (%) = 258 (100) [MH^+].

HRMS: *m*/*z* [MH^+] calcd for $C_{18}H_{11}NO$: 258.0919; found: 258.0919.

2-(3-Tetrahydro-2*H*-2-pyranyloxy-1-propynyl)-3-quinolinecarbaldehyde (1d)
Yield: 98%; mp 77 °C.

IR (neat): 3050, 2939, 2869, 1690, 1580, 1371, 1115, 1013, 967 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.44–1.92 (m, 6 H), 3.50–3.62 (m, 1 H), 3.81–3.94 (m, 1 H), 4.55–4.70 (m, 2 H), 4.92 (t, *J* = 3.3 Hz, 1 H), 7.60 (ddd, *J* = 1.2, 6.9, 8.1 Hz, 1 H), 7.83 (ddd, *J* = 1.5, 6.6, 8.1 Hz, 1 H), 7.92 (d, *J* = 7.8 Hz, 1 H), 8.10 (d, *J* = 8.1 Hz, 1 H), 8.69 (s, 1 H), 10.6 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.7 (CH_2), 25.1 (CH_2), 30.0 (CH_2), 54.4 (CH_2), 61.8 (CH_2), 81.7 (C), 91.8 (C), 97.1 (CH), 126.2 (C), 128.0 (CH), 128.5 (C), 129.0 (CH), 129.3 (CH), 132.7 (CH), 136.7 (CH), 143.0 (C), 149.7 (C), 190.3 (CHO).

MS: *m*/*z* (%) = 296 (100) [MH^+], 212 (41) [MH^+ – THP].

HRMS: *m*/*z* [MH^+] calcd for $C_{18}H_{17}NO_3$: 296.1285; found: 296.1287.

Grignard Reaction; Typical Procedure
1-[2-(2-Trimethylsilyl-1-ethynyl)-3-quinolyl]-3-buten-1-ol (2a)
To a stirred solution of the aldehyde (2.0 g, 7.90 mmol) in THF (40 mL) at –78 °C under Ar was added dropwise allylmagnesium bromide (10.0 mL, 1 M in THF, 10.0 mmol). The solution was allowed to stir at r.t. until complete disappearance of the starting material (monitored by TLC). The mixture was then poured into sat. aq NH_4Cl solution and then extracted with EtOAc. The organic layer was washed with sat. aq NaCl solution, dried and evaporated to leave the crude product, which was chromatographed. Elution with a mixture of cyclohexane–EtOAc (3:1) gave the desired compound (1.98 mg, 85%), as a yellow solid; mp 111 °C.

IR (neat): 3232, 3074, 2958, 2899, 2161, 1247, 1060 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.32 [s, 9 H, $Si(CH_3)_3$], 2.36–2.50 (m, 2 H), 2.80–2.92 (m, 1 H), 5.20–5.28 (m, 2 H), 5.34 (dt, *J* = 3.6, 8.1 Hz, 1 H), 5.82–5.95 (m, 1 H), 7.54 (ddd, *J* = 1.0, 6.6, 8.0 Hz, 1 H), 7.69 (ddd, *J* = 1.2, 6.6, 8.4 Hz, 1 H), 7.81 (d, *J* = 8.4 Hz, 1 H), 8.09 (d, *J* = 8.0 Hz, 1 H), 8.30 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –0.3 (3 × CH_3), 42.7 (CH_2), 70.0 (CH), 100.4 (C), 101.9 (C), 118.9 (CH_2), 127.4 (CH), 127.6 (CH), 129.0 (CH), 129.7 (CH), 132.5 (CH), 133.2 (C), 134.2 (CH), 138.6 (C), 141.0 (C), 147.1 (C).

MS: *m*/*z* (%) = 296 (100) [MH^+], 255 (18).

HRMS: *m*/*z* [MH^+] calcd for $C_{18}H_{21}NOSi$: 296.1474; found: 296.1474.

1-[2-(1-Hexynyl)-3-quinolyl]-3-buten-1-ol (2b)
Yield: 93%; mp 56 °C.

IR (neat): 3263, 3059, 2956, 2930, 2870, 2227, 1596, 1491, 1407, 1057 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.5 Hz, 3 H), 1.40–1.68 (m, 4 H), 2.42 (dd, *J* = 8.1, 14.1 Hz, 1 H), 2.50 (t, *J* = 6.6 Hz, 2 H), 2.72–2.86 (m, 1 H), 5.14–5.24 (m, 2 H), 5.30 (dd, *J* = 3.0, 8.1 Hz, 1 H), 5.81–5.98 (m, 1 H), 7.48 (ddd, *J* = 1.2, 6.6, 8.4 Hz, 1 H), 7.64 (ddd, *J* = 1.5, 6.6, 8.4 Hz, 1 H), 7.73 (d, *J* = 8.4 Hz, 1 H), 8.03 (d, *J* = 8.7 Hz, 1 H), 8.24 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.5 (CH_3), 19.2 (CH_2), 22.1 (CH_2), 30.3 (CH_2), 42.6 (CH_2), 70.0 (CH), 78.7 (C), 96.3 (C), 118.6 (CH_2), 126.9 (CH), 127.1 (C), 127.5 (CH), 128.7 (CH), 129.5 (CH), 132.4 (CH), 134.3 (CH), 138.3 (C), 141.9 (C), 147.1 (C).

MS: *m*/z (%) = 280 (100) [MH^+], 262 (17) [$MH^+ – H_2O$].

HRMS: *m*/*z* [MH^+] calcd for $C_{19}H_{21}NO$: 280.1701; found: 280.1701.

1-[2-(2-Phenyl-1-ethynyl)-3-quinolyl]-3-buten-1-ol (2c)
Yield: 80%; mp 117 °C.

IR (neat): 3255, 3057, 2892, 2854, 2209, 1489, 1056, 936 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.49 (dt, *J* = 7.8, 14.4 Hz, 1 H), 2.78–2.90 (m, 1 H), 3.05–3.50 (br s, 1 H), 5.11–5.23 (m, 2 H), 5.43 (dd, *J* = 3.6, 8.4 Hz, 1 H), 5.94 (ddt, *J* = 7.2, 10.2, 17.1 Hz, 1 H), 7.28–7.41 (m, 3 H), 7.45 (ddd, *J* = 1.2, 6.9, 8.1 Hz, 1 H), 7.54 (dd, *J* = 1.5, 8.1 Hz, 1 H), 7.62 (dd, *J* = 1.5, 8.7 Hz, 1 H), 7.67 (t, *J* = 8.1 Hz, 1 H), 8.05 (d, *J* = 8.4 Hz, 1 H), 8.28 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 42.8 (CH_2), 70.0 (CH), 86.9 (C), 94.2 (C), 118.6 (CH_2), 121.7 (C), 127.2 (CH), 127.2 (C), 127.6 (CH), 128.4 (2 × CH), 128.6 (CH), 129.3 (CH), 129.6 (CH), 132.0 (2 × CH), 132.7 (CH), 134.3 (CH), 138.8 (C), 141.3 (C), 147.0 (C).

MS: *m*/*z* (%) = 300 (100) [MH^+], 282 (16) [$MH^+ – H_2O$].

HRMS: *m*/*z* [MH^+] calcd for $C_{21}H_{17}NO$: 300.1388; found: 300.1389.

1-[2-(3-Tetrahydro-2*H*-2-pyranyloxy-1-propynyl)-3-quinolyl]-3-buten-1-ol (2d)
Yield: 84%; brown oil.

IR (neat): 3348, 2975, 2925, 1595, 1490, 1343, 1064, 915 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.44–1.88 (m, 6 H), 2.44 (dd, *J* = 7.2, 14.4 Hz, 1 H), 2.68–2.82 (m, 1 H), 3.18 (br s, 1 H), 3.47–3.60 (m, 1 H), 3.84 (ddd, *J* = 3.6, 9.0, 10.8 Hz, 1 H), 4.48–4.57 (m, 2 H), 4.87 (t, *J* = 3.3 Hz, 1 H), 5.08–5.21 (m, 2 H), 5.28 (dd, *J* = 3.9, 8.7 Hz, 1 H), 5.88 (ddt, *J* = 7.2, 10.2, 17.1 Hz, 1 H), 7.47 (ddd, *J* = 1.2, 6.6, 7.8 Hz, 1 H), 7.63 (ddd, *J* = 1.5, 6.6, 8.1 Hz, 1 H), 7.72 (d, *J* = 7.8 Hz, 1 H), 8.00 (d, *J* = 8.4 Hz, 1 H), 8.24 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.9 (CH_2), 25.2 (CH_2), 30.1 (CH_2), 42.6 (CH_2), 54.5 (2 × CH_2), 62.0 (CH_2), 69.8 (CH), 69.9 (CH), 83.2 (C), 90.3 (C), 97.0 (CH), 97.1 (CH), 118.5 (CH_2), 127.2 (CH), 127.3 (C), 127.5 (CH), 128.7 (CH), 129.6 (CH), 132.7 (CH), 134.1 (CH), 138.5 (C), 140.8 (C), 147.0 (C).

MS: *m*/*z* (%) = 338 (100) [MH^+], 320 (7) [$MH^+ – H_2O$], 254 (19) [MH^+ – THP], 236 (25) [MH^+ – THP – H_2O].

HRMS: *m*/*z* [MH^+] calcd for $C_{21}H_{23}NO_3$: 338.1756; found: 338.1756.

Pauson–Khand Reaction; Typical Procedure
5-Hydroxy-1-trimethylsilyl-3,3a,4,5-tetrahydro-2*H*-cyclopenta[*c*]acridin-2-one (3a)
$Co_2(CO)_8$ (450 mg, 1.32 mmol) was added to a solution of enyne (295 mg, 1.0 mmol) in CH_2Cl_2 (30 mL) at r.t. under Ar. After the mixture was stirred for 2 h, NMO (1.17 g, 10.0 mmol) was added and the mixture was further stirred overnight. After filtration through a short pad of silica and elution with EtOAc, the filtrate was concentrated to dryness. Chromatography of the residue with a mixture of cyclohexane–EtOAc (3:1) afforded cyclopentenone (225 mg, 70%) as a yellow solid with some starting material (69 mg, 23%); mp 182 °C.

IR (neat): 3244, 3073, 2957, 2899, 2162, 1248, 1060, 857 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.32 [s, 9 H, $Si(CH_3)_3$], 1.90 (dt, *J* = 3.3, 13.5 Hz, 1 H), 2.22 (dd, *J* = 4.2, 18.0 Hz, 1 H), 2.48 (ddd, *J* = 2.4, 4.2, 14.7 Hz, 1 H), 2.78 (dd, *J* = 6.9, 18.0 Hz, 1 H), 2.87 (br s, 1 H), 3.64 (ddt, *J* = 1.8, 6.3, 12.9 Hz, 1 H), 5.15 (t, *J* = 2.7 Hz, 1 H), 7.56 (ddd, *J* = 1.2, 6.6, 7.8 Hz, 1 H), 7.74 (ddd, *J* = 1.5, 6.9, 8.1 Hz, 1 H), 7.82 (d, *J* = 8.1 Hz, 1 H), 8.09 (d, *J* = 8.0 Hz, 1 H), 8.20 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.7 (3 × CH_3), 35.2 (CH), 37.7 (CH_2), 43.5 (CH_2), 67.3 (CH), 127.7 (CH), 127.8 (CH), 128.2 (C), 129.3 (CH), 130.3 (CH), 132.6 (C), 137.3 (CH), 142.3 (C), 147.4 (C), 149.7 (C), 179.9 (C), 212.1 (C).

MS: *m*/*z* (%) = 324 (68) [MH^+], 306 (100) [$MH^+ – H_2O$].

HRMS: *m*/*z* [MH^+] calcd for $C_{19}H_{21}NO_2Si$: 324.1420; found: 324.1422.

1-Butyl-5-hydroxy-3,3a,4,5-tetrahydro-2*H*-cyclopenta[*c*]acridin-2-one (3b)
Yield: (100%); mp 47 °C.

IR (neat): 3327, 2925, 2854, 1702, 1661, 1489, 1027, 914 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.2 Hz, 3 H), 1.40–1.74 (m, 4 H), 1.86 (dt, *J* = 3.0, 13.2 Hz, 1 H), 2.06–2.12 (br s, 1 H), 2.20 (dd, *J* = 3.0, 18.6 Hz, 1 H), 2.51 (ddd, *J* = 2.4, 3.9, 13.5 Hz, 1 H), 2.86 (dd, *J* = 6.3, 18.3 Hz, 1 H), 2.88–3.10 (m, 2 H), 3.55–3.68 (m, 1 H), 5.18 (m, 1 H), 7.58 (ddd, *J* = 1.2, 6.9, 8.4 Hz, 1 H), 7.75 (ddd, *J* = 1.5, 6.9, 8.1 Hz, 1 H), 7.82 (d, *J* = 8.1 Hz, 1 H), 8.10 (d, *J* = 8.4 Hz, 1 H), 8.19 (s, 1 H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5 (CH_3), 23.6 (CH_2), 24.1 (CH_2), 31.0 (CH_2), 33.2 (CH), 38.0 (CH_2), 41.4 (CH_2), 68.2 (CH), 127.9 (CH), 128.0 (C), 128.1 (CH), 130.4 (CH), 130.5 (CH), 133.0 (C), 137.6 (CH), 144.5 (C), 148.5 (C), 151.0 (C), 162.9 (C), 209.5 (C).

MS: *m*/*z* (%) = 308 (100) [MH^+], 290 (7) [$MH^+ – H_2O$].

HRMS: *m*/*z* [MH^+] calcd for $C_{20}H_{21}NO_2$: 308.1651; found: 308.1656.

5-Hydroxy-1-phenyl-3,3a,4,5-tetrahydro-2*H*-cyclopenta[*c*]acridin-2-one (3c)
Yield: (81%); mp 98 °C.

IR (neat): 3364, 3056, 2908, 2359, 1676, 1487, 1224, 1151, 1034 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.99 (dt, *J* = 3.6, 13.5 Hz, 1 H), 2.35 (dd, *J* = 3.6, 18.9 Hz, 1 H), 2.54 (ddd, *J* = 2.4, 3.9, 13.5 Hz, 1 H), 2.96 (dd, *J* = 6.6, 18.6 Hz, 1 H), 3.64–3.76 (m, 1 H), 5.15 (m, 1 H), 7.37–7.53 (m, 6 H), 7.55–7.65 (m, 2 H), 7.73 (d, *J* = 8.4 Hz, 1 H), 8.14 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.9 (CH_2), 37.8 (CH), 41.4 (CH), 67.3 (CH_2), 127.1 (CH), 127.2 (CH), 127.7 (CH), 127.8 (CH), 128.0 (C), 130.0 (CH), 130.3 (CH), 131.7 (C), 132.6 (C), 137.2 (CH), 140.7 (C), 147.4 (C), 148.9 (C), 162.9 (C), 209.5 (C).

MS: *m*/*z* (%) = 328 (100) [MH^+], 310 (8) [$MH^+ – H_2O$].

HRMS: *m*/*z* [MH^+] calcd for $C_{22}H_{17}NO_2$: 328.1337; found: 328.1330.

5-Hydroxy-1-tetrahydro-2*H*-2-pyranyloxymethyl-3,3a,4,5-tetrahydro-2*H*-cyclopenta[*c*]acridin-2-one (3d)
Yield: (75%); mp 70–71 °C.

IR (neat): 3363, 2920, 2361, 1681, 1228, 1020, 917 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.30–1.85 (m, 6 H), 2.06 (dt, *J* = 3.0, 18.6 Hz, 1 H), 2.28–2.44 (m, 3 H), 2.60–2.75 (m, 1 H), 3.38–3.95 (m, 3 H), 4.63 (d, *J* = 10.5 Hz, 1 H), 4.76–5.08 (m, 2 H), 5.30 (d, *J* = 10.5 Hz, 1 H), 7.42–7.52 (m, 1 H), 7.60–7.73 (m, 2 H), 7.78–8.12 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.0 (CH), 19.0 (CH_2), 19.1 (CH_2), 30.3 (CH_2), 30.4 (CH_2), 32.7 (CH), 33.2 (CH), 37.2 (CH_2), 37.3 (CH_2), 37.4 (CH_2), 40.6 (CH_2), 40.9 (CH_2), 58.1 (CH_2), 58.4 (CH_2), 61.8 (CH_2), 67.1 (CH), 67.2 (CH), 98.9 (CH), 99.4 (CH), 127.4 (2 × CH), 127.7 (CH), 127.9 (2 × C), 129.7 (CH), 129.8 (2 × CH), 129.9 (CH), 130.0 (CH), 132.6 (C), 132.9 (C), 137.2 (CH), 137.4 (CH), 137.9 (C), 138.2 (C), 139.0 (C), 147.7 (C), 149.5 (2 × C), 150.7 (C), 162.6 (C), 166.7 (2 × C), 207.8 (C), 207.9 (C), 209.2 (C).

MS: *m*/*z* (%) = 366 (71) [MH^+], 282 (100) [MH^+ – THP], 264 (9) [MH^+ – THP – H_2O].

HRMS: *m*/*z* [MH^+] calcd for $C_{22}H_{23}NO_4$: 366.1705; found: 366.1710.

DMP Oxidation; Typical Procedure
1-Trimethylsilyl-3,3a,4,5-tetrahydro-2*H*-cyclopenta[*c*]acridine-2,5-dione (4a)
A solution of 15 w% DMP in CH_2Cl_2 (3.5 mL, 1.72 mmol) was added to a solution of alcohol (323 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) at r.t. under Ar. After 2 h of stirring, the reaction mixture was diluted with EtOAc and a mixture of aq 10% $Na_2S_2O_3$ and sat. $NaHCO_3$ solution (in 1:1 ratio) was added. The mixture was then stirred until the phases were homogeneous (15 min). Extraction with EtOAc, drying and evaporation gave the crude material, which was purified by chromatography. Elution with a mixture of cyclohexane–EtOAc (3:1) afforded the aldehyde (300 mg, 93%) as a yellow solid; mp 167–168 °C.

IR (neat): 2968, 2950, 2894, 1686, 1273, 1157, 8567 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.37 [s, 9 H, $Si(CH_3)_3$], 2.37 (dt, *J* = 3.9, 18.3 Hz, 1 H), 2.70 (dd, *J* = 13.5, 16.5 Hz, 1 H), 2.91 (dd, *J* = 6.9, 18.3 Hz, 1 H), 3.27 (dd, *J* = 5.1, 16.5 Hz, 1 H), 3.55–3.66 (m, 1 H), 7.68 (ddd, *J* = 1.2, 6.9, 8.4 Hz, 1 H), 7.90 (ddd, *J* = 1.5, 6.9, 8.4 Hz, 1 H), 8.02 (dd, *J* = 1.8, 8.4 Hz, 1 H), 8.16 (dd, *J* = 1.2, 8.4 Hz, 1 H), 8.93 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.2 (3 × CH_3), 39.6 (CH), 43.3 (CH_2), 45.5 (CH_2), 126.4 (C), 127.6 (C), 128.4 (CH), 129.4 (CH), 129.8 (CH), 132.9 (CH), 137.1 (CH), 145.0 (C), 149.4 (C), 152.9 (C), 176.4 (C), 195.1 (C), 210.2 (C).

MS: *m*/*z* (%) = 322 (100) [MH^+], 306 (72) [$MH^+ – CH_4$].

HRMS: *m*/*z* [MH^+] calcd for $C_{19}H_{20}NO_2Si$: 322.1263; found: 322.1263.

1-Butyl-3,3a,4,5-tetrahydro-2*H*-cyclopenta[*c*]acridine-2,5-dione (4b)
Yield: (94%); mp 128 °C.

IR (neat): 2929, 2857, 1681, 1581, 1463, 1367, 1174, 1096, 935 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 6.9 Hz, 3 H), 1.39–1.80 (m, 4 H), 2.31 (dd, *J* = 3.0, 18.6 Hz, 1 H), 2.62 (dd, *J* = 14.4, 16.2 Hz, 1 H), 2.90 (dd, *J* = 6.6, 17.2 Hz, 1 H), 2.90–3.05 (m, 2 H), 3.23

(dd, *J* = 5.4, 16.5 Hz, 1 H), 3.47–3.60 (m, 1 H), 7.63 (ddd, *J* = 0.9, 6.9, 8.1 Hz, 1 H), 7.86 (ddd, *J* = 1.8, 6.9, 8.4 Hz, 1 H), 7.96 (d, *J* = 8.4 Hz, 1 H), 8.14 (d, *J* = 8.7 Hz, 1 H), 8.89 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 23.1 (CH_2), 23.5 (CH_2), 30.5 (CH_2), 36.8 (CH), 41.2 (CH_2), 45.5 (CH_2), 126.5 (C), 127.1 (C), 128.2 (CH), 129.6 (CH), 130.0 (CH), 132.6 (CH), 137.1 (CH), 145.9 (C), 150.0 (C), 153.2 (C), 159.7 (C), 195.3 (C), 207.3 (C).

MS: *m*/*z* (%) = 306 (100) [MH^+].

HRMS: *m*/*z* [MH^+] calcd for $C_{20}H_{19}NO_2$: 306.1494; found: 306.1495.

1-Phenyl-3,3a,4,5-tetrahydro-2*H*-cyclopenta[*c*]acridine-2,5-dione (4c)
Yield: (98%); mp 195 °C.

IR (neat): 3047, 2359, 1699, 1683, 1583, 1491, 1308, 1159, 1129 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.49 (dd, *J* = 2.7, 19.2 Hz, 1 H), 2.77 (dd, *J* = 13.8, 16.8 Hz, 1 H), 3.06 (dd, *J* = 6.6, 19.2 Hz, 1 H), 3.32 (dd, *J* = 4.8, 16.5 Hz, 1 H), 3.60–3.73 (m, 1 H), 7.34–7.43 (m, 3 H), 7.48–7.62 (m, 3 H), 7.70–7.77 (m, 2 H), 7.91 (d, *J* = 8.1 Hz, 1 H), 8.88 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.1 (CH), 41.4 (CH_2), 45.5 (CH_2), 126.4 (C), 127.3 (CH), 127.5 (C), 128.3 (CH), 128.4 (CH), 129.4 (CH), 130.0 (CH), 130.1 (CH), 130.5 (C), 132.6 (CH), 137.1 (CH), 142.3 (C), 149.4 (C), 152.0 (C), 161.3 (C), 194.9 (C), 205.4 (C).

MS: *m*/*z* (%) = 326 (100) [MH^+].

HRMS: *m*/*z* [MH^+] calcd for $C_{22}H_{15}NO_2$: 326.1181; found: 326.1188.

1-Tetrahydro-2*H*-2-pyranyloxymethyl-3,3a,4,5-tetrahydro-2*H*-cyclopenta[*c*]acridine-2,5-dione (4d)
Yield: 50% + 43% **4e**; mp 141–143 °C.

IR (neat): 3366, 2920, 2359, 1683, 1009, 969 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40–1.95 (m, 6 H), 2.39 (dd, *J* = 3.0, 18.9 Hz, 1 H), 2.74 (dd, *J* = 14.1, 16.5 Hz, 1 H), 2.95 (dd, *J* = 6.9, 18.9 Hz, 1 H), 3.28 (dd, *J* = 5.4, 16.8 Hz, 1 H), 3.41–3.70 (m, 2 H), 3.80–4.00 (m, 0.5 H), 4.02–4.20 (m, 0.5 H), 4.68 (dd, *J* = 1.5, 10.5 Hz, 1 H), 4.88 (t, *J* = 3.0 Hz, 0.5 H), 5.41 (d, *J* = 10.5 Hz, 0.5 H), 7.67 (ddd, *J* = 1.2, 7.5, 8.4 Hz, 1 H), 7.88 (ddd, *J* = 1.5, 6.9, 8.1 Hz, 1 H), 8.00 (d, *J* = 8.1 Hz, 1 H), 8.18 (d, *J* = 8.7 Hz, 1 H), 8.94 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0 (CH_2), 19.1 (CH_2), 25.3 (CH_2), 25.4 (CH_2), 30.3 (CH_2), 30.5 (CH_2), 37.2 (CH), 41.3 (CH_2), 45.1 (CH_2), 57.9 (CH_2), 58.1 (CH_2), 61.7 (CH_2), 61.8 (CH_2), 99.0 (CH), 99.5 (CH), 126.6 (C), 127.5 (C), 128.6 (CH), 129.7 (CH), 130.0 (C), 130.1 (CH), 132.8 (CH), 137.3 (CH), 140.2 (C), 140.5 (C), 149.9 (C), 152.4 (C), 163.7 (C), 163.8 (C), 194.8 (C), 206.0 (C), 206.1 (C).

MS: *m*/*z* (%) = 364 (22) [MH^+], 280 (100) [MH^+ – THP].

HRMS: *m*/*z* [MH^+] calcd for $C_{22}H_{22}NO_4$: 364.1549; found: 364.1551.

1-Methyl-3,3a,4,5-tetrahydro-2*H*-cyclopenta[*c*]acridine-2,5-dione (4e)
Yield: (43%); mp 186–187 °C.

IR (neat): 2919, 1681, 1581, 1489, 1299, 1225, 1171, 1080, 969 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.34 (dd, *J* = 2.4, 18.6 Hz, 1 H), 2.45 (s, 3 H), 2.64 (dd, *J* = 14.4, 16.2 Hz, 1 H), 2.93 (dd, *J* = 6.6, 19.2 Hz, 1 H), 3.25 (dd, *J* = 5.1, 16.8 Hz, 1 H), 3.50–3.65 (m, 1 H), 7.65 (ddd, *J* = 1.2, 7.5, 8.4 Hz, 1 H), 7.88 (ddd, *J* = 1.5, 6.9, 8.1 Hz, 1 H), 7.99 (d, *J* = 7.5 Hz, 1 H), 8.19 (d, *J* = 8.4 Hz, 1 H), 8.93 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.8 (CH_3), 36.8 (CH), 41.0 (CH_2), 45.3 (CH_2), 126.5 (C), 127.0 (C), 128.2 (CH), 129.6 (CH), 129.9 (CH), 132.6 (CH), 137.1 (CH), 141.1 (C), 149.8 (C), 153.4 (C), 159.6 (C), 195.0 (C), 207.4 (C).

MS: *m*/*z* (%) = 264 (100) [MH^+].

HRMS: *m*/*z* [MH^+] calcd for $C_{17}H_{14}NO_2$: 264.1025; found: 264.1025.

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