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Synthesis of the Azaoxoaporphine Alkaloid Sampangine and Ascididemin-Type Pyridoacridines through TMPMgCl·LiCl-Mediated Ring Closure

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We report the synthesis of the azaoxoaporphine alkaloid sampangine (**4**) and a series of ring A analogues and isomers of the marine pyridoacridine alkaloid ascididemin (**2**). This approach starts from readily available 1-bromo[2,7]naphthyridine (**12**) or 4-bromobenzo[*c*][2,7]naphthyridine (**5**), and the ring A scaffold bearing an ester moiety is introduced by a Suzuki or Negishi cross-coupling reaction. The final cyclization step was achieved through a directed remote ring metallation with the Knochel–Hauser base (TMPMgCl·LiCl; TMP = 2,2,6,6-tetramethylpiperidinyl), followed by intramolecular trapping of the ester group.

Introduction

The pyridoacridine family represents an important class of natural products isolated from marine organisms such as sponges, tunicates, corals, and bryozoa.[1,2] Since the isolation and identification of amphimedine (**1**) in 1983 by Schmitz et al.,[3] more than 100 of these polycyclic heteroaromatic alkaloids have been isolated,[1–3] and based on biosynthetic considerations, a number of "undiscovered" pyridoacridines have been predicted.[4] Besides a few hepta- and octacyclic compounds, tetra-, penta-, and hexacyclic compounds form the largest group of pyridoacridine alkaloids. Among the most prominent types of pentacyclic pyridoacridines are the amphimedine (**1**) and ascididemin (**2**) type subclasses, which differ in the connection of rings A and B (Figure 1).[4] Almost all the natural pyridoacridines are rich in biological activity, and this has attracted many groups to work towards the total synthesis of these alkaloids and their analogues.[1]

Besides their high cytotoxicity, many of these alkaloids show also antiviral, antibacterial, antifungal, and insecticidal profiles.[1] Furthermore, antiparasitic activities against *Plasmodium*, *Leishmania*, and *Trypanosoma* species have been reported.[5] Concerning the cytotoxic effects of this class of natural compounds, various modes of action have been described. Among the predominant effects are the formation of reactive oxygen species and the inhibtion of topoisomerase II.[2,6] The induction of apoptosis as a molecular mechanism of cell killing has been demonstrated for

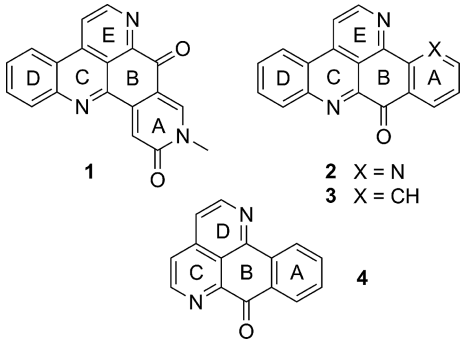

Figure 1. Marine pyridoacridine alkaloids amphimedine (**1**) and ascididemin (**2**), biologically active deaza analogue **3**, and azaoxoaporphine alkaloid sampangine (**4**).

ascididemin (**2**).[7] Deazaascididemin (**3**; also named AK 37) shows reduced cytotoxicity, but in contrast to ascididemin (**2**), which is a topoisomerase II inhibitor, only topoisomerase I is inhibited. Synthetic analogue **3** stabilizes the DNA–topoisomerase-I cleavable complex, but it does not obviously act through the generation of harmful reactive-oxygen species.[8] Furthermore, the observed bioactivities[9] and a QSAR (quantitative structure–activity relationship) study by Debnath et al.[10] of ring-A analogues of **3** have also confirmed the importance of ring A for antitumor activity.

The first total synthesis of ascididemin (**2**) has been reported by one of us.[11] The strategy used for this synthesis, which was subsequently applied to the syntheses of many related pyridoacridine alkaloids and their analogues, involves an oxidative amination of quinoline-5,8-dione, followed by an acid-catalyzed cyclization, and a final annulation to form ring E.[11] Other synthetic approaches towards ascididemin (**2**) and its analogues were published by different groups.[9b,12,13]

The azaoxoaporphine alkaloid sampangine (**4**) has a close structural relationship with the pyridoacridine family,

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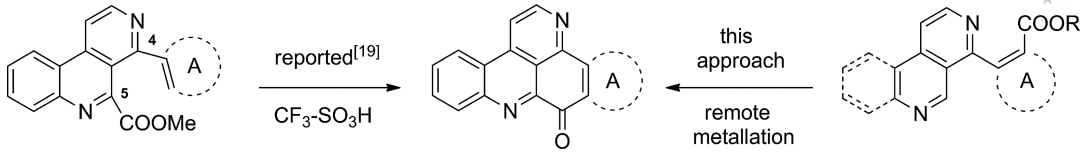


Figure 2. New and reported[19] strategies for the synthesis of azaoxoaporphines and pyridoacridines with high variability in ring A.

especially the ascididemin subclass. Sampangine (**4**) was isolated by Rao et al.[14] from the stem bark of *Cananga odorata* (Annonaceae) in 1986. This alkaloid shows broad and potent antiproliferative activities against human cancer cell lines, fungal pathogens, malaria parasites, and mycobacteria.[15] The antiproliferative activity is caused by the inhibition of heme biosynthesis, which leads to higher levels of reactive oxygen species.[16] The first total synthesis of sampangine (**4**), using a hetero-Diels–Alder-cycloaddition step followed by annulation of ring D, was reported by our group.[17] Another synthetic approach was reported by Kitahara et al.[18]

Recently, we developed a new approach to ring A analogues of ascididemin (**2**).[19] The synthetic strategy involved a high-yielding Minisci-type homolytic methoxycarbonylation at C-5 of a 4-bromobenzo[*c*][2,7]naphthyridine building block, followed by introduction of the ring A scaffold through a Suzuki cross-coupling reaction at C-4, and then trifluoromethanesulfonic-acid-aided Friedel–Crafts-type intramolecular acylation (Figure 2). Unfortunately, this Friedel–Crafts protocol does not allow the introduction of electron-deficient carbocyclic and heterocyclic ring A equivalents.

In this communication, we report the development of a new approach to the pyridoacridine and azaoxoaporphine ring systems in which (hetero)areneboronic acids bearing an ester moiety in the *ortho* position serve as sources for ring A. We envisaged that the synthesis (Figure 3) would start from readily available 1-bromo[2,7]naphthyridine (**12**)[20] or 4-bromobenzo[*c*][2,7]naphthyridine (**5**).[21] Suzuki or Negishi cross-coupling reactions should permit the introduction of various ring A equivalents bearing an ester moiety, and finally, the tetra- or pentacyclic ring system should be obtained via TMPMgCl·LiCl (TMP = 2,2,6,6-tetramethylpiperidinyl) mediated ring closure (Figure 3). This final intramolecular cyclization step was inspired by our recently published synthesis of the alkaloid demethyldeoxyamphimedine, in which the key step was a directed ring metallation of a 5-substituted benzo[*c*][2,7]naphthyridine, followed by intramolecular trapping of an ester group.[22] In contrast to our previous approach to ring A analogues of ascididemin,[19] this synthetic strategy is compatible with electron-deficient (hetero)aromatic ring A equivalents.

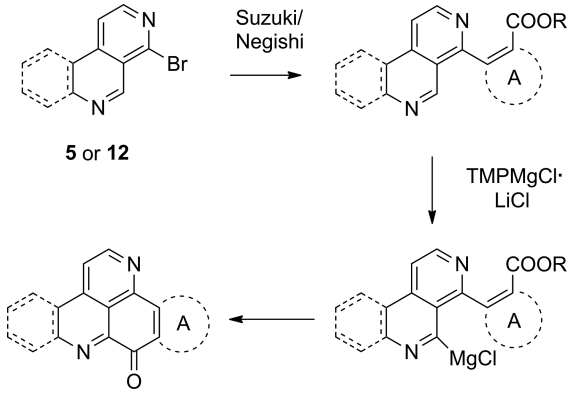


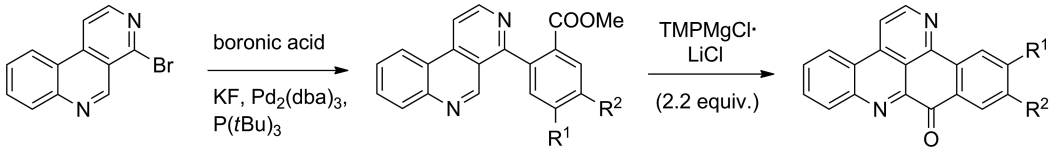
Figure 3. Strategy envisaged for the synthesis of azaoxoaporphine alkaloids and ascididemin-type alkaloids involving a Suzuki or Negishi cross-coupling reaction followed by directed remote ring metallation and intramolecular trapping of the ester group.

Results and Discussion

For the development of this new route to ascididemin- and sampangine-type scaffolds, we chose deazaascididemin (**3**) and sampangine (**4**) as the first target molecules, since we had authentic samples of these compounds in hand from previous investigations.[17,19,23] The synthesis of deazaascididemin (**3**) started with the Suzuki cross-coupling[24] of 4-bromobenzo[*c*][2,7]naphthyridine (**5**) and commercially available 2-methoxycarbonylphenylboronic acid to give biaryl carboxylate **6a** in 90% yield (Scheme 1). Analogously to our recently published synthesis of demethyldeoxyamphimedine,[22] we supposed that direct metallation with Knochel's TMPMgCl·LiCl[25] should take place regioselectively at the *peri* position (C-5) of the benzo[*c*][2,7]-naphthyridine scaffold without affecting the ester group, and avoiding undesired nucleophilic addition reactions to the naphthyridine ring system (Figure 3). As expected, treatment of ester **6a** with TMPMgCl·LiCl (2.2 equiv.) at 0 °C for 2 h and subsequent intramolecular trapping of the ester group at room temperature within 16 h gave the desired pentacyclic compound (i.e., **3**) in 27% yield. Side-reactions were not observed, and 51% of the starting material (i.e., **6a**) was recovered.

In order to improve this yield, modifications of the reaction conditions were examined. According to our previous experience,[22] negligible conversion took place if only 1.1 equiv. of the base was used, and an increase of the amount of the metallating agent to 3.3 equiv. did not further improve the yield of **3**. Other temperatures (25 and –20 °C) and longer metallation times (4 h) did not improve the yield of pentacycle **3**.

Cyclization experiments under the optimized conditions described above gave rise to an appreciable number of new ascididemin-type compounds (Scheme 1). Areneboronic acids bearing an ester moiety in the *ortho* position served as precursors of ring A of the desired pyridoacridines, and



5

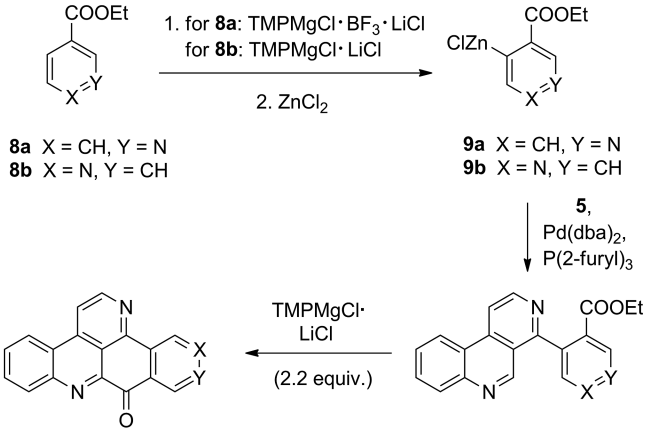
6a R^1 = H, R^2 = H (90%)
6b R^1 = Cl, R^2 = H (86%)
6c R^1 = F, R^2 = H (87%)
6d R^1 = OMe, R^2 = OMe (73%)

3 R^1 = H, R^2 = H (27%)
7b R^1 = Cl, R^2 = H (39%)
7c R^1 = F, R^2 = H (31%)
7d R^1 = OMe, R^2 = OMe (33%)

Scheme 1. Synthesis of ascididemin-type analogues **3** (deazaascididemin) and **7b**–**7d** from biaryl esters **6a**–**6d**. dba = dibenzylideneacetone.

they were coupled with **5** to give biaryl carboxylates **6b**–**6d** in good yields (73–87%; Scheme 1). Biaryl esters **6b**–**6d** were cyclized using TMPMgCl·LiCl (2.2 equiv.) to give **7b**–**7d** in poor to modest yields (31–39%). Again, appreciable amounts of the starting materials were recovered.

For the synthesis of structural isomers **11a** and **11b** of the marine alkaloid ascididemin (**2**), ethyl nicotinate (**8a**) and ethyl isonicotinate (**8b**) served as ring A precursors (Scheme 2). The first step of the synthesis of 9*H*-quinolino[4,3,2-*de*][1,8]phenanthrolin-9-one (**11a**) was the regioselective direct metallation at C-4 of ethyl nicotinate (**8a**) using TMPMgCl·BF_3·LiCl, and subsequent transmetallation with $ZnCl_2$ to give **9a**,[26] following Knochel's protocol.[26] Subsequent palladium-catalyzed Negishi cross-coupling with **5** gave biaryl carboxylate **10a** in 71% yield. Later, we found that metallation of **8a** can be performed equally well with TMPMgCl·LiCl. Isomeric ester **10b** was synthesized in an analogous manner. Thus, ethyl isonicotinate (**8b**) was metallated directly at C-3 with TMPMgCl·LiCl. Transmetallation with $ZnCl_2$, followed by Negishi cross-coupling with **5** gave **10b** in 76% yield (Scheme 2). Ascididemin isomers **11a** and **11b** were then formed by treatment of biaryl carboxylates **10a** and **10b** with Knochel–Hauser base (TMPMgCl·LiCl, 2.2 equiv.) under the conditions described above in yields of 31 and 34%, respectively (Scheme 2). The spectroscopic data of **11a** and **11b** were fully consistent with those reported previously by Delfourne[27] and Kristensen.[12d]



8a X = CH, Y = N
8b X = N, Y = CH

9a X = CH, Y = N
9b X = N, Y = CH

11a X = CH, Y = N (31%)
11b X = N, Y = CH (34%)

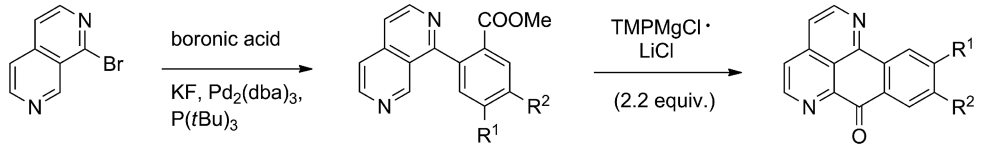
10a X = CH, Y = N (71%)
10b X = N, Y = CH (76%)

Scheme 2. Synthesis of ascididemin isomers **11a** and **11b**.

The synthesis of sampangine (**4**) started with the Suzuki cross-coupling of 1-bromo-2,7-naphthyridine (**12**)[20] and 2-methoxycarbonylphenylboronic acid to give biaryl carboxylate **13a** in 85% yield (Scheme 3). Cyclization of **13a** with TMPMgCl·LiCl gave alkaloid **4** in 35% yield. Sampangine analogue **14** was prepared by Suzuki cross-coupling of **12** with [4,5-dimethoxy-2-(methoxycarbonyl)-phenyl]boronic acid to give **13b** in 77% yield, followed by treatment of **13b** with TMPMgCl·LiCl to give **14** in 36% yield (Scheme 3).

Conclusions

In conclusion, we have developed a new approach to the azaoxoaporphine alkaloid sampangine (**4**) and one analogue, and various ring-A-modified analogues of ascididemin-type pyridoacridine alkaloids. Although the yields of the final cyclization step were modest, this protocol enables us to carry out new structural variations on a critical part of the pentacyclic ring system, since the ring whose variation is of special pharmacological interest is ring A.[9,10] This new and flexible approach, which is also compatible with electron-deficient aromatic ring A equivalents, provides a



12

13a R^1 = H, R^2 = H (85%)
13b R^1 = OMe, R^2 = OMe (77%)

4 R^1 = H, R^2 = H (35%)
14 R^1 = OMe, R^2 = OMe (36%)

Scheme 3. Total synthesis of sampangine (**4**) and dimethoxy analogue **14**.

collection of new synthetic and natural compounds for in-depth investigations of structure–activity relationships in the sampangine and pyridoacridine alkaloid classes.

Experimental Section

General Information: All reactions were carried out under a nitrogen atmosphere with flame-dried glassware, unless otherwise noted. Chemical reagents were purchased from Sigma–Aldrich (Schnelldorf, Germany), ABCR (Karlsruhe, Germany), and Acros (Geel, Belgium). Anhydrous $ZnCl_2$ solution (1 M) was prepared by drying $ZnCl_2$ (3.41 g, 25 mmol) under high vacuum (1 mbar) for 5 h at 140 °C. After cooling to 25 °C, dry THF (25 mL) was added, and the mixture was stirred until the salt had dissolved. Solvents used were of HPLC grade or p.a. grade, and/or were purified according to standard procedures. IR measurements were carried out with a Perkin–Elmer FTIR Paragon 1000 spectrometer. Melting points were determined by the open tube capillary method with a Büchi melting point B-450 apparatus. NMR spectra were recorded with Jeol J NMR GX 400 (400 MHz), Jeol J NMR GX 500 (500 MHz), and Avance III HD 500 MHz Bruker BioSpin spectrometers with tetramethylsilane as an internal standard. The spectra were recorded in deuterated solvents, and chemical shifts are reported in parts per million (ppm). *J* values are given in Hertz. Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, m = multiplet. Signal assignments were carried out based on ^1H, ^{13}C, HMBC, HMQC, and COSY spectra. NMR spectra were analyzed with the NMR software MestReNova, Version 5.1.1–3092 (Mestrelab Research S.L.). HRMS spectra were measured using the electron impact (EI) method at 70 eV with a Finnigan MAT 95 or a Jeol GCmate II spectrometer. Microwave-promoted syntheses were carried out using a single-mode microwave reactor (Discover) equipped with an IR temperature sensor from CEM (Kamp-Lintfort, Germany). All reactions were monitored by thin-layer chromatography (TLC) using precoated plastic sheets POLYGRAM® SIL G/UV254 from Macherey–Nagel (Düren, Germany). Compounds on TLC plates were detected under UV light at 254 nm and 366 nm. Chromatographic purification of products was achieved using flash column chromatography on Merck silica gel 60 as the stationary phase. Solutions were concentrated in vacuo with a Heidolph rotary evaporator. The purity of all synthesized compounds was >95%, as determined by HPLC with a Merck Hitachi LaChrom HPLC system equipped with a Poroshell 120 EC-C18 column (3.0 × 100 mm), using acetonitrile/water/THF (700:298:2) eluent and UV detection at 210 and 254 nm.

General Procedure A (Suzuki Cross-Coupling): 4-Bromobenzo[*c*][2,7]naphthyridine (**5**; 0.258 g, 1.00 mmol) or 1-bromo[2,7]-naphthyridine (**12**; 0.208 g, 1.00 mmol), the appropriate boronic acid (1.3 equiv.), $Pd_2(dba)_3$ (0.064 g, 0.070 mmol, 7 mol-%), P(*t*Bu)$_3$ (0.020 g, 0.10 mmol, 10 mol-%), and KF (0.192 g, 3.30 mmol, 3.3 equiv.) were put into a dry and nitrogen-flushed microwave vessel equipped with a magnetic stirrer bar. The flask was purged with nitrogen, and THF (3 mL) was added. The reaction was carried out in a single-mode microwave reactor under a nitrogen atmosphere at a maximum output of 150 W, a maximum temperature of 80 °C, and a reaction time of 30 min. After cooling, the mixture was poured into water (25 mL), and extracted with dichloromethane (3 × 30 mL). The combined organic phases were dried with Na_2SO_4, and concentrated under vacuum. The residue was purified by flash column chromatography (dichloromethane/ethyl acetate, 3:1).

General Procedure B (Direct Metallation Followed by Negishi Cross-Coupling): TMPMgCl·LiCl (1.0 M in THF; 1.07 mL, 1.07 mmol) was put into a dry and nitrogen-flushed Schlenk flask (25 mL) equipped with a magnetic stirrer bar, and the flask was then cooled to –40 °C. Freshly distilled $BF_3{\cdot}Et_2O$ (0.130 mL, 1.07 mmol) was added dropwise, and the mixture was stirred for 10 min at the same temperature ($BF_3{\cdot}Et_2O$ was only used for the metallation of ethyl nicotinate). Ethyl nicotinate or ethyl isonicotinate (0.147 g, 0.970 mmol) was dissolved in dry THF (3 mL) under a nitrogen atmosphere, and then this solution was added dropwise over 2 min to the stirred reaction mixture. The mixture was stirred at –40 °C for 20 min, and then anhydrous $ZnCl_2$ (1.0 M in THF; 1.07 mL, 1.07 mmol) was added. The mixture was stirred at the same temperature for 30 min, and then a solution of $Pd(dba)_2$ (0.029 g, 0.050 mmol, 5 mol-%) and P(2-furyl)$_3$ (0.023 g, 0.10 mmol, 10 mol-%) in dry THF (2 mL) was transferred to the reaction mixture, directly followed by the addition of a solution of 4-bromobenzo[*c*][2,7]naphthyridine (**5**; 0.200 g, 0.780 mmol), in dry THF (6 mL). The reaction mixture was slowly warmed to room temperature and stirred at that temperature for 24 h. Then the mixture was quenched with satd. aqueous NH_4Cl solution (10 mL), and extracted with ethyl acetate (3 × 40 mL). The combined organic phases were dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (dichloromethane/ethyl acetate, 3:1).

General Procedure C (Ring Closure with TMPMgCl·LiCl): TMPMgCl·LiCl (1.0 M in THF; 2.2 equiv.) was put into a dry and nitrogen-flushed Schlenk flask (25 mL) equipped with a magnetic stirrer bar, and the flask was then cooled to 0 °C. The appropriate 4-arylbenzo[*c*][2,7]naphthyridine (**6a**–**6d**, **10a**, **10b**) or 1-aryl-2,7-naphthyridine (**13a**, **13b**) was dissolved in dry THF (7 mL), and then this solution was added dropwise to the reaction mixture over 2 min. The mixture was stirred for 2 h at 0 °C, then it was warmed to room temperature, and the stirring was continued for 16 h. The mixture was quenched with satd. aqueous NH_4Cl solution (10 mL), and extracted with dichloromethane (3 × 30 mL). The combined organic phases were dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (dichloromethane/ethyl acetate, 1:1).

9*H*-Benzo[*b*]pyrido[4,3,2-*mn*]acridin-9-one (3):[19,23] This compound was prepared following general procedure C from **6a** (0.080 g, 0.255 mmol) with TMPMgCl·LiCl (1.0 M in THF; 0.550 mL, 0.550 mmol, 2.2 equiv.) to give **3** (0.019 g, 27%) as a yellow solid, m.p. 260–262 °C (ref.[19] m.p. 256–258 °C, ref.[23] m.p. 254 °C). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.98 (d, *J* = 5.7 Hz, 1 H), 8.79 (dd, *J* = 1.0, *J* = 7.9 Hz, 1 H), 8.59–8.51 (m, 2 H), 8.45 (dd, *J* = 1.0, *J* = 7.9 Hz, 1 H), 8.31 (d, *J* = 5.7 Hz, 1 H), 7.93 (ddd, *J* = 1.4, *J* = 7.1, *J* = 8.4 Hz, 1 H), 7.87–7.77 (m, 2 H), 7.65 (td, *J* = 1.3, *J* = 7.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 182.1, 150.4, 148.9, 146.8, 145.7, 137.7, 136.0, 134.9, 133.0, 132.4, 131.5, 131.1, 130.3, 128.7, 125.7, 123.4, 122.8, 116.9, 115.4 ppm. IR: $\tilde{\nu}$ = 2441, 3058, 1677, 1593, 1422, 1262, 1054, 945, 778, 735, 613 cm^{-1}. HRMS (EI): calcd. for $C_{19}H_{10}N_2O$ 282.0793; found 282.0778. Recovered starting material (0.041 g, 51%) was also isolated.

7*H*-Naphtho[1,2,3-*ij*][2,7]naphthyridin-7-one (4, Sampangine):[17] This compound was prepared following general procedure C from **13a** (0.180 g, 0.682 mmol) with TMPMgCl·LiCl (1.0 M in THF; 1.50 mL, 1.50 mmol, 2.2 equiv.) to give **4** (0.055 g, 35%) as a dark yellow solid, m.p. 212–214 °C (ref.[17] m.p. 216–218 °C). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.14 (d, *J* = 5.5 Hz, 1 H), 8.89 (d, *J* = 5.7 Hz, 1 H), 8.82 (d, *J* = 7.9 Hz, 1 H), 8.47 (d, *J* = 7.9 Hz, 1 H), 7.93 (d, *J* = 5.5 Hz, 1 H), 7.88–7.80 (m, 1 H), 7.76–7.66 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 182.1, 151.3, 148.5, 148.0, 147.4, 138.7, 135.5, 134.7, 132.4, 131.4, 128.6, 125.4, 123.5, 119.8,

119.2 ppm. IR: ṽ = 3431, 3045, 1671, 1612, 1594, 1381, 1325, 1273, 1227, 877, 756, 722, 595 cm^{-1}. HRMS (EI): calcd. for $C_{15}H_8N_2O$ 232.0637; found 232.0633.

Methyl 2-(Benzo[*c*][2,7]naphthyridin-4-yl)benzoate (6a): This compound was prepared following general procedure A from **5** (0.258 g, 1.00 mmol) and 2-(methoxycarbonyl)phenylboronic acid (0.234 g, 1.30 mmol) to give **6a** (0.283 g, 90%) as a pale brown solid, m.p. 154–156 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.08 (s, 1 H), 8.96 (d, J = 5.8 Hz, 1 H), 8.64 (dd, J = 1.2, J = 8.2 Hz, 1 H), 8.42 (d, J = 5.8 Hz, 1 H), 8.28–8.12 (m, 2 H), 7.88 (ddd, J = 1.3, J = 7.1, J = 8.3 Hz, 1 H), 7.78 (ddd, J = 1.3, J = 7.1, J = 8.3 Hz, 1 H), 7.72 (td, J = 1.4, J = 7.5 Hz, 1 H), 7.65 (td, J = 1.4, J = 7.7 Hz, 1 H), 7.53 (dd, J = 1.3, J = 7.5 Hz, 1 H), 3.54 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.6, 160.0, 149.4, 145.6, 143.4, 137.5, 135.5, 130.1, 129.1, 128.8, 128.7, 128.5, 128.3, 127.1, 125.7, 120.9, 120.2, 117.8, 112.4, 50.0 ppm. IR: ṽ = 3426, 2945, 1723, 1587, 1436, 1281, 1246, 1177, 1097, 1024, 767, 749 cm^{-1}. HRMS (EI): calcd. for $C_{20}H_{14}N_2O_2$ 314.1055; found 314.1056.

Methyl 2-(Benzo[*c*][2,7]naphthyridin-4-yl)-4-chlorobenzoate (6b): This compound was prepared following general procedure A from **5** (0.258 g, 1.00 mmol) and 5-chloro-2-(methoxycarbonyl)phenylboronic acid (0.278 g, 1.30 mmol) to give **6b** (0.299 g, 86%) as a brown solid, m.p. 126–128 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.06 (s, 1 H), 8.96 (d, J = 5.8 Hz, 1 H), 8.63 (d, J = 8.2 Hz, 1 H), 8.43 (d, J = 5.8 Hz, 1 H), 8.22 (d, J = 8.2 Hz, 1 H), 8.16 (d, J = 8.5 Hz, 1 H), 7.88 (ddd, J = 1.4, J = 7.1, J = 8.3 Hz, 1 H), 7.78 (ddd, J = 1.4, J = 7.1, J = 8.3 Hz, 1 H), 7.62 (dd, J = 2.1, J = 8.5 Hz, 1 H), 7.54 (d, J = 2.1 Hz, 1 H), 3.54 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 160.6, 151.1, 147.7, 145.5, 141.3, 138.8, 137.7, 132.3, 131.4, 131.2, 130.5, 129.5, 128.8, 127.9, 123.1, 122.2, 119.8, 115.0, 52.4 ppm. IR: ṽ = 3432, 2953, 1725, 1605, 1558, 1430, 1286, 1100, 847, 762 cm^{-1}. HRMS (EI): calcd. for $C_{20}H_{13}N_2O_2Cl$ 348.0666; found 348.0659.

Methyl 2-(Benzo[*c*][2,7]naphthyridin-4-yl)-4-fluorobenzoate (6c): This compound was prepared following general procedure A from **5** (0.258 g, 1.00 mmol) and 5-fluoro-2-(methoxycarbonyl)phenylboronic acid (0.257 g, 1.30 mmol) to give **6c** (0.289 g, 87%) as a pale brown solid, m.p. 125–127 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.05 (s, 1 H), 8.96 (d, J = 5.9 Hz, 1 H), 8.64 (d, J = 8.2 Hz, 1 H), 8.44 (d, J = 5.9 Hz, 1 H), 8.28–8.18 (m, 2 H), 7.88 (ddd, J = 1.3, J = 7.2, J = 8.3 Hz, 1 H), 7.78 (ddd, J = 1.3, J = 7.2, J = 8.3 Hz, 1 H), 7.33 (ddd, J = 2.6, J = 7.9, J = 8.8 Hz, 1 H), 7.25 (dd, J = 2.6, J = 8.6 Hz, 1 H), 3.53 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 163.7, 160.7, 151.0, 147.7, 145.6, 142.6, 137.7, 133.6, 131.0, 130.5, 127.9, 126.7, 123.0, 122.2, 119.8, 118.7, 116.4, 115.0, 52.3 ppm. IR: ṽ = 3420, 3051, 2953, 1722, 1603, 1583, 1430, 1272, 1272, 1121, 889, 835, 765, 623 cm^{-1}. HRMS (EI): calcd. for $C_{20}H_{13}N_2O_2F$ 332.0961; found 332.0962.

Methyl 2-(Benzo[*c*][2,7]naphthyridin-4-yl)-4,5-dimethoxybenzoate (6d): This compound was prepared following general procedure A from **5** (0.258 g, 1.00 mmol) and 4,5-dimethoxy-2-(methoxycarbonyl)phenylboronic acid (0.312 g, 1.30 mmol) to give **6d** (0.273 g, 73%) as a pale yellow solid, m.p. 170–172 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.07 (s, 1 H), 8.96 (d, J = 5.7 Hz, 1 H), 8.64 (d, J = 8.1 Hz, 1 H), 8.41 (d, J = 5.7 Hz, 1 H), 8.21 (d, J = 8.1 Hz, 1 H), 7.87 (t, J = 7.6 Hz, 1 H), 7.77 (t, J = 7.6 Hz, 1 H), 7.72 (s, 1 H), 6.97 (s, 1 H), 4.06 (s, 3 H), 3.93 (s, 3 H), 3.49 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.0, 162.1, 152.1, 151.6, 148.9, 147.6, 145.4, 137.5, 133.8, 130.8, 130.3, 127.7, 123.0, 122.3, 122.2, 120.1, 114.4, 113.4, 113.0, 56.3, 56.2, 51.9 ppm. IR: ṽ = 3400, 3015, 2946, 1709, 1600, 1556, 1518, 1429, 1359, 1274, 1212, 1024, 991, 753, 620 cm^{-1}. HRMS (EI): calcd. for $C_{22}H_{18}N_2O_4$ 374.1267; found 374.1252.

12-Chloro-9*H*-benzo[*b*]pyrido[4,3,2-*mn*]acridin-9-one (7b): This compound was prepared following general procedure C from **6b** (0.135 g, 0.388 mmol) with TMPMgCl·LiCl (1.0 M in THF; 0.854 mL, 0.854 mmol, 2.2 equiv.) to give **7b** (0.048 g, 39%) as a yellow solid, m.p. 339–341 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.10 (d, J = 5.7 Hz, 1 H), 8.90 (d, J = 2.1 Hz, 1 H), 8.71–8.61 (m, 2 H), 8.50–8.43 (m, 2 H), 8.02 (ddd, J = 1.4, J = 7.1, J = 8.3 Hz, 1 H), 7.94 (ddd, J = 1.4, J = 7.1, J = 8.3 Hz, 1 H), 7.66 (dd, J = 2.1, J = 8.3 Hz, 1 H) ppm. A ^{13}C NMR spectrum could not be recorded due to the extremely poor solubility of the compound. MS (APCI): m/z = 317.2 [M + H]$^+$. IR: ṽ = 3427, 3057, 1681, 1599, 1585, 1438, 1384, 1307, 1258, 1145, 1049, 881, 763 cm^{-1}. HRMS (EI): calcd. for $C_{19}H_9N_2OCl$ 316.0403; found 316.0398.

12-Fluoro-9*H*-benzo[*b*]pyrido[4,3,2-*mn*]acridin-9-one (7c): This compound was prepared following general procedure C from **6c** (0.085 g, 0.256 mmol) with TMPMgCl·LiCl (1.0 M in THF; 0.563 mL, 0.563 mmol, 2.2 equiv.) to give **7c** (0.024 g, 31%) as a yellow solid, m.p. 328–330 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.07 (d, J = 5.6 Hz, 1 H), 8.68–8.58 (m, 2 H), 8.57–8.49 (m, 2 H), 8.44 (d, J = 6.0 Hz, 1 H), 8.05–7.88 (m, 2 H), 7.40–7.32 (m, 1 H) ppm. A ^{13}C NMR spectrum could not be recorded due to the extremely poor solubility of the compound. MS (CI): m/z = 301 [M + H]$^+$ (100), 281 (5), 210 (30), 145 (5), 113 (5), 103 (20). IR: ṽ = 3426, 2923, 1680, 1605, 1594, 1578, 1448, 1387, 1319, 1260, 1233, 1190, 1049, 886, 764, 751, 603 cm^{-1}. HRMS (EI): calcd. for $C_{19}H_9N_2OF$ 300.0699; found 300.0692.

11,12-Dimethoxy-9*H*-benzo[*b*]pyrido[4,3,2-*mn*]acridin-9-one (7d): This compound was prepared following general procedure C from **6d** (0.119 g, 0.318 mmol) with TMPMgCl·LiCl (1.0 M in THF; 0.704 mL, 0.704 mmol, 2.2 equiv.) to give **7d** (0.036 g, 33%) as an orange solid, m.p. 295–297 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.85 (d, J = 5.7 Hz, 1 H), 8.55 (dd, J = 1.0, J = 8.3 Hz, 1 H), 8.51 (dd, J = 1.0, J = 8.3 Hz, 1 H), 8.19 (d, J = 5.7 Hz, 1 H), 8.14 (s, 1 H), 7.93 (ddd, J = 1.4, J = 7.0, J = 8.3 Hz, 1 H), 7.83 (ddd, J = 1.4, J = 7.0, J = 8.3 Hz, 1 H), 7.80 (s, 1 H), 4.11 (s, 3 H), 4.08 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 180.9, 154.7, 151.6, 150.4, 148.6, 147.1, 145.8, 137.5, 132.9, 131.4, 131.3, 130.1, 126.8, 123.3, 122.8, 116.5, 114.8, 109.6, 106.8, 56.5, 56.4 ppm. IR: ṽ = 3441, 2922, 1635, 1588, 1513, 1373, 1311, 1249, 1214, 1026, 767, 751 cm^{-1}. HRMS (EI): calcd. for $C_{21}H_{14}N_2O_3$ 342.1004; found 342.0995.

Ethyl 4-(Benzo[*c*][2,7]naphthyridin-4-yl)nicotinate (10a): This compound was prepared following general procedure B from ethyl nicotinate (0.147 g, 0.970 mmol), BF_3·Et_2O (0.130 mL, 1.07 mmol), and **5** (0.200 g, 0.780 mmol) to give **10a** (0.182 g, 71%) as a brown solid, m.p. 128–130 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.42 (s, 1 H), 9.02 (s, 1 H), 8.97 (d, J = 8.1 Hz, 2 H), 8.64 (d, J = 8.1 Hz, 1 H), 8.47 (d, J = 5.6 Hz, 1 H), 8.23 (d, J = 8.1 Hz, 1 H), 7.90 (t, J = 7.6 Hz, 1 H), 7.80 (t, J = 6.9 Hz, 1 H), 7.50 (d, J = 4.7 Hz, 1 H), 4.02 (q, J = 7.1 Hz, 2 H), 0.89 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.8, 159.2, 152.8, 151.9, 150.4, 147.6, 147.0, 145.4, 137.6, 131.1, 130.5, 128.1, 126.2, 125.2, 122.9, 121.9, 119.4, 115.3, 61.4, 13.6 ppm. IR: ṽ = 3433, 2925, 1715, 1600, 1592, 1363, 1230, 1077, 785, 761, 621 cm^{-1}. HRMS (EI): calcd. for $C_{20}H_{15}N_3O_2$ 329.1164; found 329.1150.

Ethyl 3-(Benzo[*c*][2,7]naphthyridin-4-yl)isonicotinate (10b): This compound was prepared following general procedure B with ethyl isonicotinate (0.147 g, 0.970 mmol) and **5** (0.200 g, 0.780 mmol) to give **10b** (0.195 g, 76%) as a brown solid, m.p. 134–136 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.09 (s, 1 H), 8.99 (dd, J = 5.4, J =

9.4 Hz, 2 H), 8.88 (s, 1 H), 8.66 (d, J = 8.3 Hz, 1 H), 8.48 (d, J = 5.8 Hz, 1 H), 8.24 (d, J = 8.3 Hz, 1 H), 8.02 (d, J = 5.1 Hz, 1 H), 7.91 (ddd, J = 1.4, J = 7.1, J = 8.3 Hz, 1 H), 7.81 (ddd, J = 1.3, J = 7.2, J = 8.3 Hz, 1 H), 4.01 (q, J = 7.1 Hz, 2 H), 0.86 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1, 158.4, 151.8, 151.2, 150.8, 147.8, 145.5, 138.4, 137.8, 133.3, 131.2, 130.6, 128.1, 123.6, 123.0, 122.0, 120.3, 115.2, 61.8, 13.7 ppm. IR: $\tilde{\nu}$ = 3416, 2983, 1719, 1601, 1561, 1365, 1298, 1255, 1101, 845, 774, 668 cm^{-1}. HRMS (EI): calcd. for $C_{20}H_{15}N_3O_2$ 329.1164; found 329.1153.

9*H*-Quinolino[4,3,2-*de*][1,8]phenanthrolin-9-one (11a):[27] This compound was prepared following general procedure C from **10a** (0.120 g, 0.365 mmol) with TMPMgCl·LiCl (1.0 M in THF; 0.803 mL, 0.803 mmol, 2.2 equiv.) to give **11a** (0.032 g, 31%) as a yellow solid, m.p. 310–312 °C (ref.[27] m.p. >260 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.66 (s, 1 H), 9.13 (d, J = 5.8 Hz, 1 H), 9.06 (d, J = 5.2 Hz, 1 H), 8.70–8.59 (m, 3 H), 8.53 (d, J = 5.8 Hz, 1 H), 8.02 (ddd, J = 1.4, J = 7.1, J = 8.3 Hz, 1 H), 7.95 (ddd, J = 1.4, J = 7.1, J = 8.3 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 181.6, 155.2, 150.7, 149.1, 148.2, 146.0, 145.7, 142.4, 137.9, 133.3, 132.0, 130.9, 126.2, 123.2, 122.9, 118.5, 118.1, 117.3 ppm. IR: $\tilde{\nu}$ = 3426, 2854, 1677, 1608, 1593, 1571, 1422, 1392, 1262, 1054, 945, 778, 734 cm^{-1}. HRMS (EI): calcd. for $C_{18}H_9N_3O$ 283.0746; found 283.0747.

9*H*-Quinolino[4,3,2-*de*][1,9]phenanthrolin-9-one (11b):[12d] This compound was prepared following general procedure C from **10b** (0.168 g, 0.511 mmol) with TMPMgCl·LiCl (1.0 M in THF; 1.12 mL, 1.12 mmol, 2.2 equiv.) to give **11b** (0.049 g, 34%) as a yellow solid, m.p. 314–316 °C (ref.[12d] m.p. >308 °C). ^{1}H NMR (500 MHz, [D$_4$]methanol/$CDCl_3$, 3:1): δ = 10.16 (s, 1 H), 9.17 (d, J = 5.7 Hz, 1 H), 8.99 (d, J = 5.1 Hz, 1 H), 8.78 (d, J = 8.2 Hz, 1 H), 8.61 (d, J = 2.8 Hz, 2 H), 8.28 (d, J = 5.1 Hz, 1 H), 8.08 (ddd, J = 1.3, J = 7.1, J = 8.4 Hz, 1 H), 8.02 (ddd, J = 1.3, J = 7.1, J = 8.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.4, 151.8, 149.3, 148.7, 148.5, 145.7, 145.6, 138.3, 137.2, 132.7, 132.3, 131.4, 129.7, 123.9, 123.3, 120.3, 117.3, 116.6 ppm. IR: $\tilde{\nu}$ = 3425, 2923, 1735, 1677, 1593, 1571, 1421, 1392, 1262, 945, 777, 734, 716, 606 cm^{-1}. HRMS (EI): calcd. for $C_{18}H_9N_3O$ 283.0746; found 283.0732.

Methyl 2-(2,7-Naphthyridin-1-yl)benzoate (13a): This compound was prepared following general procedure A from **12** (0.208 g, 1.00 mmol) and 2-(methoxycarbonyl)phenylboronic acid (0.234 g, 1.30 mmol) to give **13a** (0.224 g, 85%) as a pale yellow solid, m.p. 146–148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.06 (s, 1 H), 8.75 (d, J = 5.8 Hz, 1 H), 8.71 (d, J = 5.8 Hz, 1 H), 8.18 (dd, J = 1.0, J = 7.8 Hz, 1 H), 7.73–7.60 (m, 4 H), 7.51 (dd, J = 1.0, J = 7.8 Hz, 1 H), 3.54 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7, 162.5, 152.2, 146.7, 145.9, 139.4, 138.8, 132.3, 131.0, 130.9, 130.6, 129.3, 122.8, 119.4, 118.5, 52.2 ppm. IR: $\tilde{\nu}$ = 3429, 2924, 1725, 1604, 1557, 1429, 1286, 1265, 1100, 847, 762, 756, 527 cm^{-1}. IR: $\tilde{\nu}$ = 3429, 2924, 1725, 1604, 1557, 1429, 1286, 1265, 1100, 847, 762, 756, 527 cm^{-1}. HRMS (EI): calcd. for $C_{16}H_{12}N_2O_2$ 264.0899; found 264.0898.

Methyl 4,5-Dimethoxy-2-(2,7-naphthyridin-1-yl)benzoate (13b): This compound was prepared following general procedure A from **12** (0.208 g, 1.00 mmol) and 4,5-dimethoxy-2-(methoxycarbonyl) phenylboronic acid (0.312 g, 1.30 mmol) to give **13b** (0.249 g, 77%) as a brown solid, m.p. 172–174 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.03 (s, 1 H), 8.75 (d, J = 5.8 Hz, 1 H), 8.71 (d, J = 5.8 Hz, 1 H), 7.70 (t, J = 2.4 Hz, 2 H), 7.66 (d, J = 5.8 Hz, 1 H), 6.94 (s, 1 H), 4.05 (s, 3 H), 3.93 (s, 3 H), 3.49 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.0, 162.5, 152.2, 152.1, 149.0, 146.6, 145.8, 138.6, 133.5, 123.1, 122.3, 119.2, 118.4, 113.2, 112.9, 56.3, 56.2, 51.9 ppm. IR: $\tilde{\nu}$ = 3412, 2963, 1715, 1614, 1597, 1520, 1364, 1271, 1206, 1004, 850, 774, 635 cm^{-1}. HRMS (EI): calcd. for $C_{18}H_{16}N_2O_4$ 324.1110; found 324.1102.

9,10-Dimethoxy-7*H*-naphtho[1,2,3-*ij*][2,7]naphthyridin-7-one (14): This compound was prepared following general procedure C from **13b** (0.210 g, 0.648 mmol) with TMPMgCl·LiCl (1.0 M in THF; 1.43 mL, 1.43 mmol, 2.2 equiv.) to give **14** (0.068 g, 36%) as a dark yellow solid, m.p. 291–293 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.10 (d, J = 5.5 Hz, 1 H), 8.80 (d, J = 5.8 Hz, 1 H), 8.21 (s, 1 H), 7.90–7.84 (m, 2 H), 7.65 (d, J = 5.8 Hz, 1 H), 4.15 (s, 3 H), 4.09 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.0, 154.6, 151.8, 151.3, 148.4, 148.3, 147.2, 138.5, 130.6, 126.8, 123.3, 119.4, 118.7, 109.6, 106.6, 56.5, 56.5 ppm. IR: $\tilde{\nu}$ = 3426, 2965, 1668, 1614, 1585, 1509, 1374, 1284, 1212, 1110, 1008, 878, 772 cm^{-1}. HRMS (EI): calcd. for $C_{17}H_{12}N_2O_3$ 292.0848; found 292.0849.

Supporting Information (see footnote on the first page of this article): Copies of ^{1}H and ^{13}C NMR spectra for all compounds.

Acknowledgments

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[1] K. M. Marshall, L. R. Barrows, *Nat. Prod. Rep.* **2004**, *21*, 731–754.
[2] E. Delfourne, J. Bastide, *Med. Res. Rev.* **2003**, *23*, 234–252.
[3] F. J. Schmitz, S. K. Agarwal, S. P. Gunasekera, *J. Am. Chem. Soc.* **1983**, *105*, 4835–4836.
[4] D. Skyler, C. H. Heathcock, *J. Nat. Prod.* **2002**, *65*, 1573–1581.
[5] B. R. Copp, O. Kayser, R. Brun, A. F. Kiderlen, *Planta Med.* **2003**, *69*, 527–531.
[6] N. Dias, H. Vezin, A. Lansiaux, C. Bailly, *Top. Curr. Chem.* **2005**, *253*, 89–108.
[7] V. Dirsch, S. O. Kirschke, M. Estermeier, B. Steffan, A. M. Vollmar, *Oncogene* **2004**, *23*, 1586–1593.
[8] K. M. Marshall, J. A. Holden, A. Koller, Y. Kashman, B. R. Copp, L. R. Barrows, *Anticancer Drugs* **2004**, *15*, 907–913.
[9] a) D. R. Appleton, A. N. Pearce, B. R. Copp, *Tetrahedron* **2010**, *66*, 4977–4986; b) M. Alvarez, L. Feliu, W. Ajana, J. A. Joule, J. L. Fernandez-Puentes, *Eur. J. Org. Chem.* **2000**, 849–855; c) E. Delfourne, R. Kiss, L. Le Corre, J. Merza, J. Bastide, A. Frydman, F. Darro, *Bioorg. Med. Chem.* **2003**, *11*, 4351–4356; d) B. S. Lindsay, L. Barrows, B. R. Copp, *Bioorg. Med. Chem. Lett.* **1995**, *5*, 739–742.
[10] B. Debnath, S. Gayen, S. Bhattacharya, S. Samanta, T. Jha, *Bioorg. Med. Chem.* **2003**, *11*, 5493–5499.
[11] a) F. Bracher, *Heterocycles* **1989**, *29*, 2093–2095. For the related total synthesis of the alkaloids 2-bromoleptoclinidinone and neocalliactine acetate, see: b) F. Bracher, *Liebigs Ann. Chem.* **1990**, 205–206; c) F. Bracher, *Liebigs Ann. Chem.* **1992**, 1205–1207.
[12] a) A. Koller, A. Rudi, G. M. Garcia, Y. Kashman, *Molecules* **2001**, *6*, 300–322; b) J. M. Cuerva, D. J. Cardenas, A. M. Echavarren, *J. Chem. Soc. Perkin Trans. 1* **2002**, 1360–1365; c) C. J. Moody, C. W. Rees, R. Thomas, *Tetrahedron* **1992**, *48*, 3589–3602; d) I. N. Petersen, F. Crestey, J. L. Kristensen, *Chem. Commun.* **2012**, *48*, 9092–9094.
[13] I. N. Petersen, J. L. Kristensen, *Synthesis* **2014**, *46*, 1469–1474.
[14] J. U. M. Rao, G. S. Giri, T. Hanumaiah, K. V. J. Rao, *J. Nat. Prod.* **1986**, *49*, 346–347.
[15] a) J. Kluza, A. M. Clark, C. Bailly, *Ann. N. Y. Acad. Sci.* **2003**, *1010*, 331–334; b) J. Kluza, R. Mazingghien, K. Degardin, A. Lansiaux, C. Bailly, *Eur. J. Pharmacol.* **2005**, *525*, 32–40; c) I. Muhammad, D. C. Dunbar, S. Takamatsu, L. A. Walker, A. M. Clark, *J. Nat. Prod.* **2001**, *64*, 559–562; d) J. R. Peterson, J. K.

Zjawiony, S. Lin, C. D. Hufford, A. M. Clark, R. D. Rogers, *J. Med. Chem.* **1992**, *35*, 4069–4077.
[16] Z. Huang, K. Chen, T. Xu, J. Zhang, Y. Li, W. Li, A. K. Agarwal, A. M. Clark, J. D. Phillips, X. Pan, *Eukaryotic Cell* **2011**, *10*, 1536–1544.
[17] F. Bracher, *Liebigs Ann. Chem.* **1989**, 87–88.
[18] Y. Kitahara, M. Mochii, M. Mori, A. Kubo, *Tetrahedron* **2003**, *59*, 2885–2891.
[19] A. Plodek, S. Raeder, F. Bracher, *Tetrahedron* **2013**, *69*, 9857–9864.
[20] E. C. Glazer, Y. Tor, *Angew. Chem. Int. Ed.* **2002**, *21*, 4022–4026; *Angew. Chem.* **2002**, *114*, 4194–4198.
[21] N. D. Tyrrell, N. Tremayne, G. R. Evans, US 2009/0221828 A1, **2009**.
[22] B. Melzer, A. Plodek, F. Bracher, *J. Org. Chem.* **2014**, *79*, 7239–7242.
[23] S. Raeder, F. Bracher, *Arch. Pharm. Chem. Life Sci.* **2012**, *345*, 822–826.
[24] A. F. Littke, C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028.
[25] A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958–2961; *Angew. Chem.* **2006**, *118*, 3024–3027.
[26] M. Jaric, B. Haag, A. Unsinn, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 5451–5455.
[27] C. Brahic, F. Darro, M. Belloir, J. Bastide, R. Kiss, E. Delfourne, *Bioorg. Med. Chem.* **2002**, *10*, 2845–2853.

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