Intramolecular Michael-type addition of azadienes to 1,4-naphthoquinones instead of Aza-Diels–Alder cycloaddition: a synthesis of ascididemin

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α,β-Unsaturated hydrazones tethered by an amino group to 1,4-naphthoquinone or quinoline-5,8-dione do not react by intramolecular aza-Diels–Alder cycloaddition. Instead, these substrates cyclize to form benzo[*b*]acridine-6,11-dione or pyrido[2,3-*b*]acridine-5,12-dione derivatives, respectively. This route leads to a highly concise synthesis of the pyridoacridine alkaloid ascididemin.

Introduction

Pyridoacridine alkaloids of marine origin, such as amphimedine, meridine, and ascididemin (**1b**),[1,2] have attracted much attention due to their structural novelty and cytotoxic properties.[3,4] Strategies based on Diels–Alder azacycloadditions are amongst the most conceptually simple and potentially general approaches for the synthesis of these heterocycles.[2] Indeed, although low yielding, azacycloadditions of 4-substituted 1-azadienes to quinoline quinones allow for the ready access to the ascididemin family of natural products.[5,6,7] Recently, high pressure aza-Diels–Alder reaction has been used for the synthesis of **1b** and its regioisomer **2**.[8,9]

We reported in a preliminary communication that α,β-unsaturated hydrazones tethered by an amino group synthesised from aza-diene **3** and **4a** or **4b** led to the corresponding cycloadducts, which subsequently rearranged to give linear tetracycles. These tetracycles were later transformed into pentacycles **1a** (benzosampangine) and a triazaderivative for which we assigned structure **2**.[10] This assignment was based on comparison of its NMR spectra with that of ascididemin **1b**. Although the NMR spectra were similar, small differences were found which led to the proposal of the non-natural structure **2** for this compound.[11] However, independent reinvestigation of these results by Delfourne demonstrated that our route actually provided ascididemin **1b** instead of **2**. We have examined our previous assignments by comparison with NMR provided by Delfourne[12] and indeed have found that the synthesis that starts from **3** and **4b** gives rise to **1b**. The differences found in the ^{1}H (H-1 and H-6 chemical shifts) and ^{13}C NMR spectra between the natural and the synthetic material, which led to the wrong assignment of the regiochemistry of the triazapentacycle and the wrong mechanistic proposal, were probably due to the presence of acid in the solvent ($CDCl_3$) used for recording some of the NMR spectra and/or differences in the composition of the NMR solvent (mixtures of $CDCl_3$ and d_4-methanol).

Herein we report in full the corrected results on the synthesis of pentacycle **1a**[13,14] and ascididemin (**1b**) from the products of condensation of **3** and **4a**–**b** (Scheme 1), and related substrates. We also provide an alternative mechanistic rationale for the cyclization that allows for the formation of the tetracyclic heterocycles.

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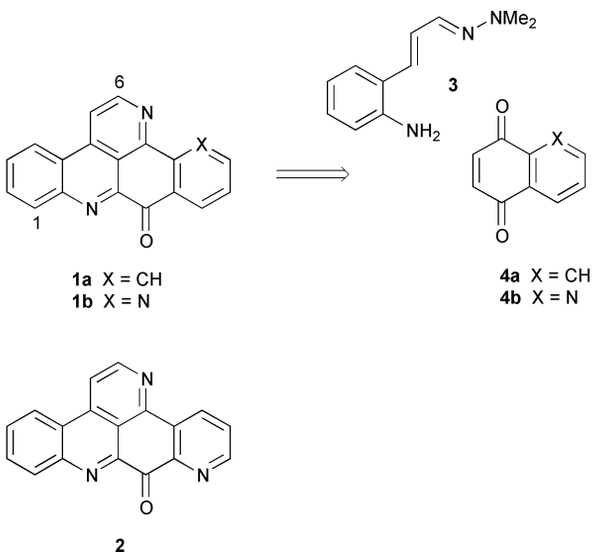

Scheme 1

Results and discussion

Synthesis of pentacycle 1a

The starting aminoquinones were readily available by the addition of substituted anilines to 1,4-naphthoquinones in MeOH at 23 °C with $CeCl_3 \cdot 7H_2O$ (0.1 equiv.) as a Lewis acid, in the presence of air to oxidise the Michael-adducts. Thus, addition of **3**[5] to 1,4-naphthoquinone (**4a**) gave **8a** (70% yield) (Scheme 2). Similarly, reaction of **5** with **4a** gave **6** in 70% yield. Oxidation of the allylic alcohol of **6** with PCC gave **7** (66%), which was condensed with *N*-phenylhydrazine, *N,N*-diphenylhydrazine, and methoxylamine to furnish hydrazones **8b** (77%) and **8c** (56%), and methoxime **8d** (86%), respectively.

Treatment of **8a** (NaH, TFAA, 3 equiv. each, THF, 23 °C) followed by replacement of THF by CH_2Cl_2 and addition of excess TFA (23 °C, 1 h) gave **9** in 45% yield (Scheme 3). Surprisingly, treatment of **9** with HCl led to known[15] benzo[*b*]acridine-6,11-dione **10** in 94% yield by aromatization of the dihydropyridine ring and loss of the side chain.

Scheme 4 indicates a possible mechanism for this remarkable transformation in which, at least formally, trifluoroacetyl dimethylhydrazine and acetylene are lost under relatively mild

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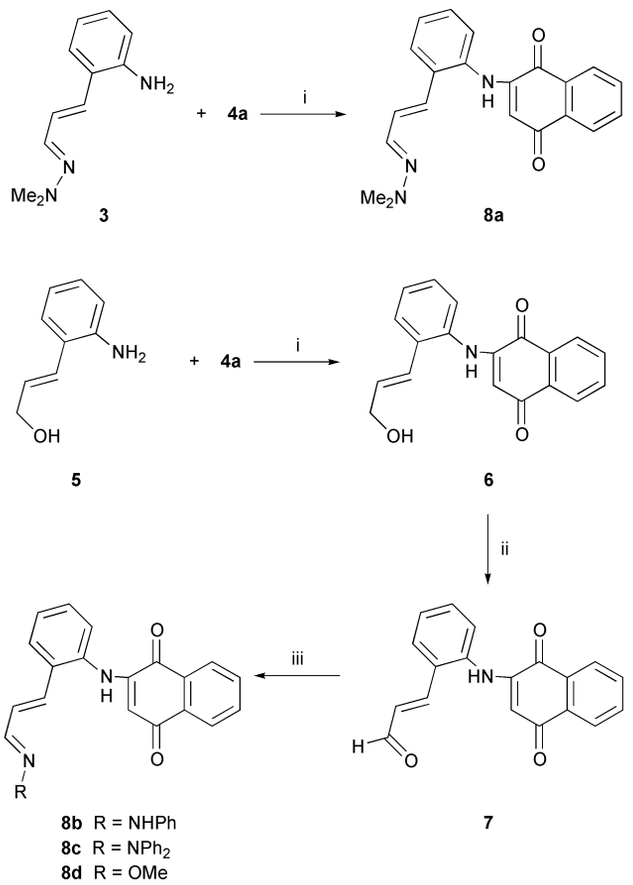
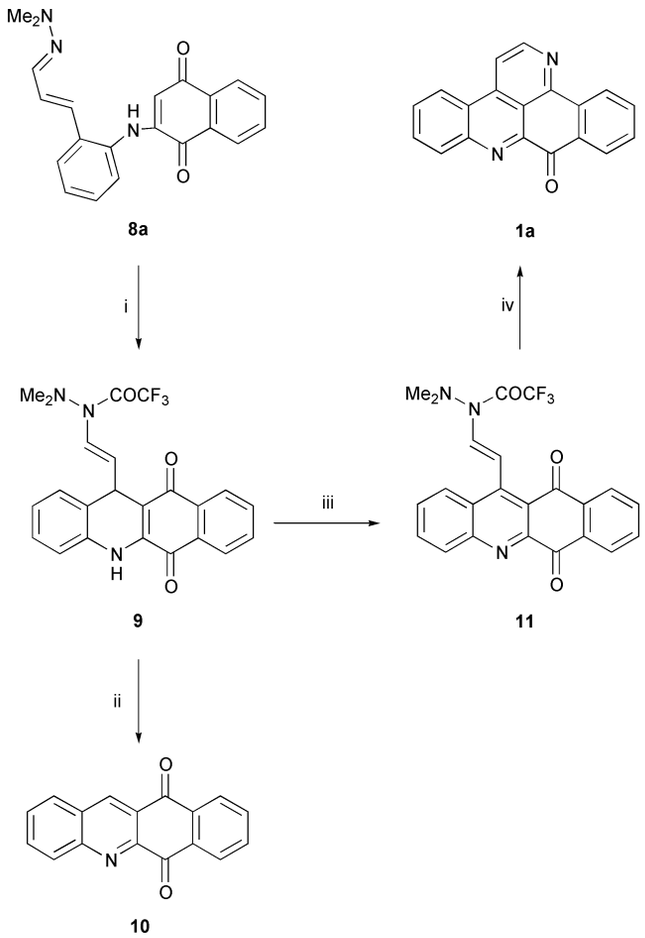
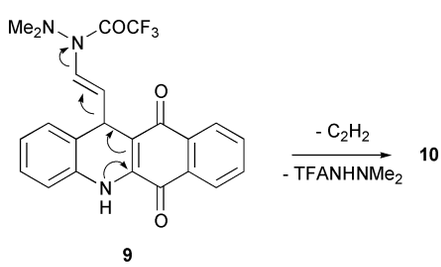


Scheme 2 *Reagents and conditions*: i, $CeCl_3 \cdot 7H_2O$, O_2, MeOH, 23 °C (70% for **6** and **8a**); ii, PCC, CH_2Cl_2, 23 °C (66%); iii. $RNH_2 \cdot HCl$, DMAP, EtOH, 23 °C (**8b**: 77%; **8c**: 56%; **8d**, 86%).



Scheme 3 *Reagents and conditions*: i, NaH, TFAA, THF, 23 °C; TFA, CH_2Cl_2 (45%); ii, 10% aq HCl–1,4-dioxane, reflux (94%); iii, MnO_2, CH_2Cl_2, 23 °C (quantitative); iv, NH_4Cl, NaOAc, EtOH, reflux (93%).



Scheme 4

conditions by a Grob-type fragmentation. When **9** was heated in a sealed NMR tube in a 3 : 1 mixture of benzene-d_6 and TFA-*d* at 50–55 °C, **10** was quantitatively formed, along with *N,N*-dimethylhydrazine. In this experiment, a signal was also observed at 1.8 ppm, which was attributable to dissolved acetylene.

Treatment of **9** with excess MnO_2 in CH_2Cl_2 at 23 °C smoothly led to tetracycle **11** in quantitative yield as a single isomer. A *trans* configuration was assigned for the alkenyl portion of these derivatives on the basis of a vicinal coupling constant of 15.5 Hz. However, the configuration around the enamine nitrogen was not rigorously assigned. The oxidation of **9** also proceeds with DDQ or CAN as the oxidants, although the yields were lower. Reaction of **11** with NH_4Cl and NaOAc in ethanol under refluxing conditions gave pentacycle **1a**[15] (93%).

Interestingly, thermolysis of phenylhydrazone **8b** in refluxing xylene gave directly **1a** in 40% yield, along with cleavage product **10** (10%) (Scheme 5). However, tetracycle **10** was the only product isolated upon treatment of **8a**–**d** with trifluoroacetic acid. Heating of **7** with aniline in benzene also gave **10** (32%), presumably by cyclization of the corresponding imine followed by a fragmentation such as that shown in Scheme 4.

Synthesis of ascididemin (1b)

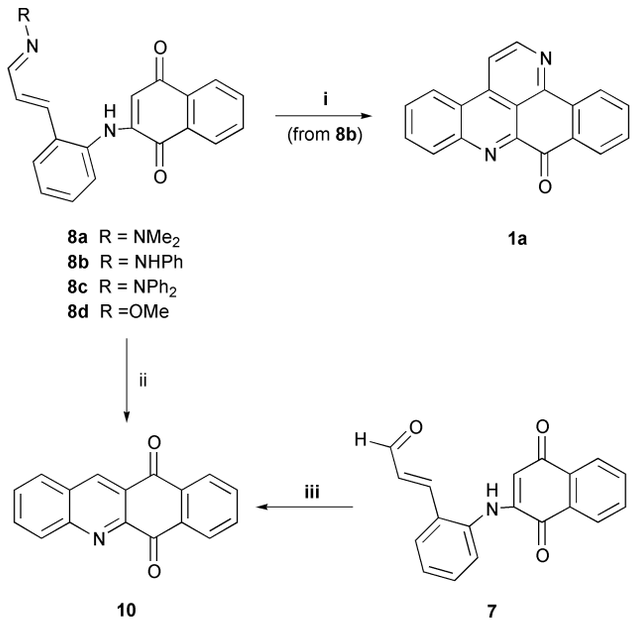
A similar set of transformations takes place from **12**, prepared from hydrazone **3** and quinoline-1,4-dione (**4b**) as shown in Scheme 6. The addition of aniline **3** proceeded regioselectively by attack of the nucleophile at the more electrophilic site of **4b** (C-6),[16] as shown by the observation of a long range ^1H–^{13}C coupling between H-7 and C-8a in Michael adduct **12**.

Cyclization of **12** afforded **13** in 36% yield (47% based on unrecovered starting material) under the conditions developed for the transformation of **8a** into **9** (Scheme 7). Similarly, reaction of **12** with aqueous HCl in 1,4-dioxane under refluxing conditions gave pyrido[2,3-*b*]acridine-5,12-dione (**14**) in 43% yield (66% corrected for conversion). Oxidation of **13** with MnO_2 furnished **15** quantitatively, which reacted with NH_4Cl and NaOAc in ethanol to give ascididemin (**1b**) in 84% yield.

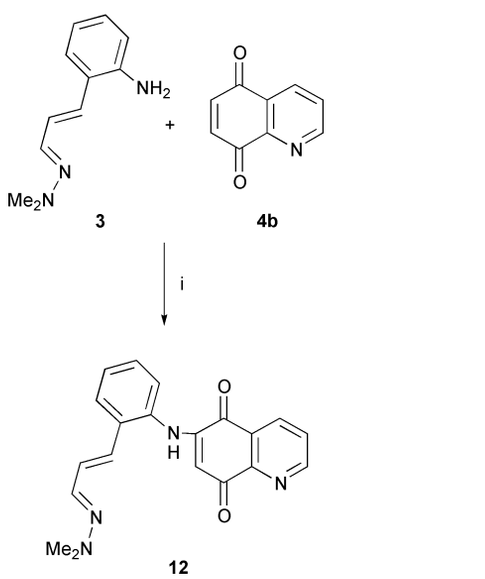
A more concise synthesis of **1b** was realised in just two steps as shown in Scheme 8. Heating of **12** in xylene under reflux for 4 h gave hydrazone **16** (54%). Longer reaction times led to tetracycle **14** as the major product. A similar transformation from **8a**, which bears a less reactive quinone, required prolonged heating in xylene and led only to tetracycle **10**. Heterocyclization of **16** with NH_4Cl and NaOAc in ethanol gave ascididemin (**1b**) in 64% yield, along with **14** (17%).

Conclusion

α,β-Unsaturated hydrazones tethered by an amino group such as **8a** and **12** do not react by an intramolecular Diels–Alder pathway to afford adducts **17a**–**b** (Scheme 9), as we previously proposed.[10] Instead, acylation reaction of **8a** and **12** with TFAA at the imine nitrogen presumably promotes a cyclization



Scheme 5 *Reagents and conditions*: i, xylene, reflux (40%); ii. TFA (68% from **8a**); iii. aniline, benzene, reflux (32%).



Scheme 6 *Reagents and conditions*: i, $CeCl_3 \cdot 7H_2O$, O_2, MeOH, 23 °C (52%).

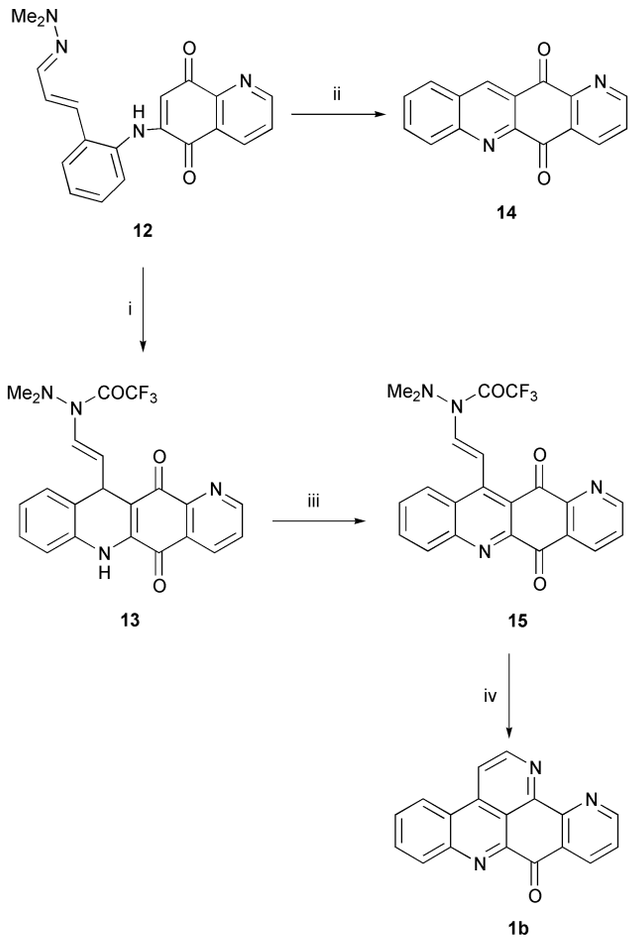
reaction to give **18a**–**b**. These intermediates would subsequently isomerise to give **9** or **13**. An alternative mechanistic interpretation based on the attack of the nucleophilic terminus of the unsaturated *N,N*-dimethylhydrazone at C-7 of the quinone appears less likely since substrates bearing hydrazone or imine functions also undergo cyclisation reactions (Scheme 5). This route provides benzosampangine (**1a**) and ascididemin (**1b**) in a highly concise manner from readily available starting materials.

Experimental

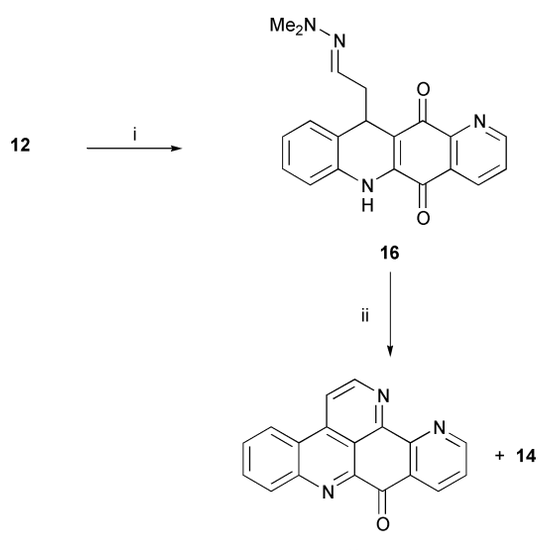
The following starting compounds were prepared according to the described procedures: (*E*)-3-(2-nitrophenyl)prop-2-en-1-ol (*o*-nitrocinnamyl alcohol),[17a] *o*-aminocinnamaldehyde *N,N*-dimethylhydrazone (**3**),[5] and quinoline-5,8-dione (**4b**).[18]

3-(2-Aminophenyl)prop-2-en-1-ol (5)[17b]

A mixture of *o*-nitrocinnamyl alcohol (200 mg, 1.17 mmol) and $FeSO_4 \cdot 7H_2O$ (2.50 g, 9.09 mmol) in a mixture of methanol (12 mL), conc. aqueous ammonium hydroxide (10 mL), and

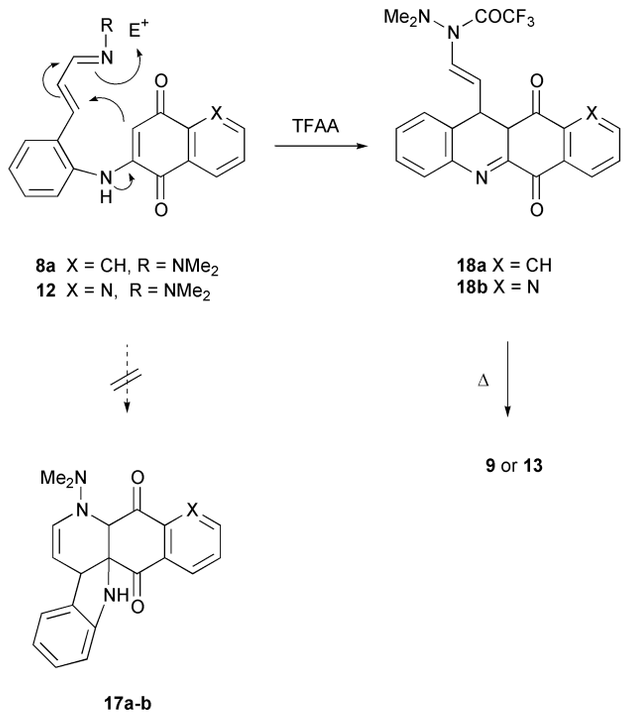


Scheme 7 *Reagents and conditions*: i, NaH, TFAA, THF, 23 °C; TFA, CH_2Cl_2 (36%); ii, 10% aq HCl–1,4-dioxane, reflux (43%); iii, MnO_2, CH_2Cl_2, 23 °C (quantitative); iv, NH_4Cl, NaOAc, EtOH, reflux (84%).



Scheme 8 *Reagents and conditions*: i, xylene, reflux (54%); ii, NH_4Cl, NaOAc, EtOH, reflux (64%).

water (3 mL) was heated at 80 °C for 3 h. The mixture was diluted with EtOAc, washed with water, dried ($MgSO_4$), and evaporated. The residue was chromatographed (3 : 7 hexane–EtOAc) to give **5** (130 mg, 77%) as a light brown solid: mp 78–80 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.23 (d, J = 7.5 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 6.82–6.60 (m, 3H), 6.21 (dt, J = 15.6, 5.5 Hz, 1H), 4.30 (d, J = 5.5 Hz, 2H), 3.75 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.62, 130.25, 128.61, 127.47, 126.53, 119.02, 116.15, 63.80, (one carbon signal was not observed).



Scheme 9

(*E*)-*N*-[2-(3-Hydroxyprop-1-enyl)phenyl]-2-amino-1,4-naphthoquinone (6)

A solution of **5** (295 mg, 1.98 mmol), naphthoquinone (**4a**) (300 mg, 1.98 mmol), and $CeCl_3 \cdot 7H_2O$ (150 mg, 0.40 mmol) in MeOH (10 mL) was stirred at 23 °C for 24 h. The mixture was evaporated and the residue was chromatographed (1 : 1 hexane–EtOAc) to give **6** (420 mg, 70%) as a reddish solid: mp 128–130 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.12–8.05 (m, 2H), 7.78–7.59 (m, 4H), 7.40–7.29 (m, 3H), 6.67 (d, J = 16 Hz, 1H), 6.37 (dt, J = 16.0, 5.3 Hz, 1H), 5.95 (s, 1H), 4.31 (t, J = 5.3 Hz, 2H), 2.00–1.65 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.72, 181.98, 145.99, 134.87, 134.25, 133.24, 132.79, 132.62, 132.28, 130.36, 128.61, 127.37, 127.09, 126.41, 126.13, 125.34, 125.11, 103.68, 63.46; EI-MS *m*/*z* 305 (M^+, 16%), 287 (39), 274 (62), 260 (100). Anal. calc. for $C_{19}H_{15}NO_2$: C, 74.74; H, 4.95; N, 4.59. Found: C, 73.89; H, 4.930; N, 4.59%.

(*E*)-*N*-[2-(3-Oxoprop-1-enyl)phenyl]-2-amino-1,4-naphthoquinone (7)

A mixture of **6** (102 mg, 0.33 mmol) and PCC (144 mg, 0.69 mmol) in CH_2Cl_2 (10 mL) was stirred at 23 °C for 2 h. The mixture was diluted with Et_2O, filtered through Celite, and the solvent was evaporated. The residue was chromatographed (9 : 1 hexane–EtOAc) to give **7** (67 mg, 66%) as an orange solid: mp 148–150 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.67 (d, J = 7.5 Hz, 1H), 8.18 (dd, J = 5.6, 1.6 Hz, 1H), 8.12 (dd, J = 5.9, 1.3 Hz, 1H), 7.85–7.70 (m, 4H), 7.59 (d, J = 16.1 Hz, 1H), 7.60–7.28 (m, 3H), 6.74 (dd, J = 16.1, 7.4 Hz, 1H), 5.91 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.26, 183.56, 181.67, 146.21, 146.07, 136.34, 135.00, 133.03, 132.51, 132.17, 130.72, 130.27, 130.23, 128.10, 127.66, 126.50, 126.47, 126.23, 104.42; EI-MS *m*/*z* 303 (M^+, 23%), 274 (71), 260 (100). Anal. calc. for $C_{19}H_{13}NO_2$: C, 75.24; H, 4.32; N, 4.62. Found: C, 75.35; H, 4.20; N, 4.84%.

(*E*)-*N*-[2-(3-*N*′,*N*′-Dimethylhydrazonoprop-1-enyl)phenyl]-2-amino-1,4-naphthoquinone (8a)

A solution of **3** (90 mg, 0.48 mmol), naphthoquinone (**4a**) (75 mg, 0.48 mmol), and $CeCl_3 \cdot 7H_2O$ (18 mg, 0.05 mmol) in MeOH (5 mL) was stirred at 23 °C for 48 h. The solvent was evaporated and the residue was chromatographed (7 : 3 hexane–EtOAc) to give **8a** (115 mg, 70%) as a brown solid: mp 138–140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (dd, J = 7.6, 1.4 Hz, 1H), 8.08 (dd, J = 7.6, 1.4 Hz, 1H), 7.75 (dt, J = 7.5, 1.3 Hz, 1H), 7.65 (dt, J = 7.5, 1.5 Hz, 1H), 7.66–7.63 (m, 1H), 7.36 (br s, 1H), 7.25–7.10 (m, 3H), 7.06 (d, J = 8.9 Hz, 1H), 6.94 (dd, J = 15.5, 8.9 Hz, 1H), 6.60 (d, J = 15.5 Hz, 1H), 5.96 (s, 1H), 2.92 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.57, 182.10, 150.33, 146.14, 134.84, 133.97, 133.80, 133.43, 132.21, 130.67, 130.42, 128.09, 127.26, 126.32, 126.17 (2C), 125.63, 124.28, 103.62, 42.56. Anal. calc. for $C_{21}H_{19}N_3O_2$: C, 73.03; H, 5.54; N, 12.17. Found: C, 73.06; H, 5.73; N, 12.18%.

(*E*)-*N*-[2-(3-*N*′-Phenylhydrazonoprop-1-enyl)phenyl]-2-amino-1,4-naphthoquinone (8b)

A solution of **7** (30 mg, 0.10 mmol), phenylhydrazine hydrochloride (22 mg, 0.15 mmol) and DMAP (18 mg, 0.15 mmol) in EtOH (5 mL) was stirred at 23 °C for 30 min. The mixture was diluted with Et_2O, washed with H_2O, dried (Na_2SO_4) and evaporated. The residue was chromatographed (7 : 3 hexane–EtOAc) to give **8b** (30 mg, 77%) as a brown solid (mixture of *syn*–*anti* isomers); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16–8.07 (m, 2H), 7.81–7.60 (m, 4H), 7.50 (d, J = 9.4 Hz, 1H), 7.40–7.20 (m, 6H), 7.15–6.80 (m, 4H), 6.69 (d, J = 15.5 Hz, 1H), 5.96 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.61, 182.03, 146.10, 143.95, 139.05, 134.93, 134.59, 134.14, 133.29, 132.84, 132.33, 131.04, 130.36, 129.29, 128.95, 128.78, 127.37, 127.03, 126.52, 126.41, 126.19, 125.73, 120.38, 112.76, 103.79, (several C signals were not observed). EI-MS *m*/*z* 393 (M^+, 8%), 285 (45), 260 (100), 77 (32). Anal. calc. for $C_{25}H_{19}N_3O_2 \cdot \frac{1}{2}H_2O$: C, 74.6; H, 4.96; N, 10.44. Found: C, 75.00; H, 4.98; N, 10.60%.

(*E*)-*N*-[2-(3-*N*′,*N*′-Diphenylhydrazonoprop-1-enyl)phenyl]-2-amino-1,4-naphthoquinone (8c)

A solution of **7** (20 mg, 0.07 mmol), *N*,*N*-diphenylhydrazine hydrochloride (18 mg, 0.08 mmol) and DMAP (12 mg, 0.10 mmol) in EtOH (5 mL) was stirred at 23 °C for 2 h. The mixture was diluted with Et_2O, washed with H_2O, dried ($MgSO_4$), and evaporated. The residue was chromatographed (9 : 1 hexane–EtOAc) to give **8c** (18 mg, 56%) as a brown solid (mixture of *syn*–*anti* isomers); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16–8.07 (m, 2H), 7.80–7.63 (m, 4H), 7.45–7.15 (m, 14H), 7.07 (dd, J = 14.5, 9.1 Hz, 1H), 6.53 (d, J = 14.5 Hz, 1H), 5.95 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.58, 182.05, 146.16, 143.23, 137.34, 134.89, 134.00, 133.27, 133.16, 132.24, 130.37, 130.12, 129.79, 129.28, 128.56, 127.30, 126.77, 126.44, 126.36, 126.16, 125.80, 124.74, 122.45, 103.71, (several C signals were not observed); EI-MS *m*/*z* 469 (M^+, 2%), 260 (100), 169 (49).

(*E*)-*N*-[2-(3-Methoxyiminoprop-1-enyl)phenyl]-2-amino-1,4-naphthoquinone (8d)

A solution of **7** (55 mg, 0.18 mmol), methoxylamine hydrochloride (31 mg, 0.36 mmol) and DMAP (27 mg, 0.22 mmol) in EtOH (5 mL) was stirred at 23 °C for 30 min. The mixture was diluted with Et_2O, washed with H_2O, dried (Na_2SO_4) and evaporated. The residue was chromatographed (7 : 3 hexane–EtOAc) to give **8d** (52 mg, 86%) as an orange solid (3 : 1 *anti*–*syn*); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.12–8.05 (m, 2H), 7.90–7.60 (m, 4H), 7.50–7.20 (m, 4H), 6.92–6.80 (m, 2H), 5.92 (s, 1H), 3.92 (s, 3H, minor isomer), 3.88 (s, 3H, major isomer); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.56, 181.82, 149.99, 147.34, 146.10, 134.87, 134.70, 133.12, 132.31, 132.17, 131.94, 130.25, 130.14, 129.63, 127.37, 127.27, 126.79, 126.36, 126.13, 125.96, 124.83, 118.74, 103.91, 61.96 (several C signals were not observed); EI-MS *m*/*z* 332 (M^+, 1%), 301 (55), 286 (47), 260 (100).

12-(*E*)-[2-(*N*′,*N*′-Dimethylamino-*N*-trifluoroacetylamino)-ethenyl]-5,12-dihydrobenzo[*b*]acridine-6,11-dione (9)

A solution of **8a** (280 mg, 0.81 mmol) and NaH (60% in mineral oil, 57 mg, 2.43 mmol) in THF (5 mL) was stirred at

23 °C for 5 min. The resulting blue mixture was treated with TFAA (510 mg, 2.43 mmol) yielding a yellow solution. After 15 min, the solvent was evaporated under high vacuum and the residue was dissolved in CH_2Cl_2 (10 mL). TFA (0.20 mL, 10.00 mmol) was added to give a purple solution. After being stirred for 1 h, the crude mixture was chromatographed (1 : 4 EtOAc–CH_2Cl_2) to give the crude product that was triturated with 7 : 3 hexane–EtOAc to give **9** (160 mg, 45%) as a dark solid: mp 224–226 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.11 (dd, J = 8.7, 1.0 Hz, 1H), 8.08 (dd, J = 7.6, 1.2 Hz, 1H), 7.75 (dt, J = 7.4, 1.4 Hz, 1H), 7.65 (dt, J = 7.4, 1.4 Hz, 1H), 7.54 (br s, 1H), 7.26–7.20 (m, 2H), 7.10 (dt, J = 8.5, 1.2 Hz, 1H), 6.95 (d, J = 8.3 Hz, 1H), 6.24 (d, J = 14.6 Hz, 1H), 6.13 (dd, J = 14.6, 7.2 Hz, 1H), 5.09 (d, J = 7.2 Hz, 1H), 2.65 (s, 3H), 2.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.43, 181.13, 138.94, 134.94, 134.83, 133.17, 132.41, 130.27, 130.05, 128.19, 126.30, 126.16, 124.82, 124.04, 121.95, 120.71, 116.09, 114.51, 43.86, 43.64, 36.75 (the signals corresponding to CF_3CO were not observed); EI-MS m/z 441 (M^+, 3%), 396 (21), 285 (100). Anal. calc. for $C_{23}H_{18}N_3O_3F_3 \cdot \frac{1}{2}H_2O$: C, 61.4; H, 4.22; N, 9.34. Found: C, 61.53; H, 4.20; N, 9.68%.

Benzo[*b*]acridine-6,11-dione (10)

Method a. A solution of **9** (20 mg, 0.06 mmol) in a 1 : 1 mixture of 10% HCl and 1,4-dioxane (5 mL) was heated under refluxing conditions for 1 day. The mixture was treated with 5% aqueous $NaHCO_3$ and extracted with CH_2Cl_2, dried (Na_2SO_4), and evaporated. The residue was chromatographed (7 : 3 hexane–EtOAc) to give **10** (14 mg, 94%) as a brown solid: mp > 250 °C, lit. mp [15a,b] 304–305 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.47 (d, J = 9.1 Hz, 1H), 8.49–8.45 (m, 1H), 8.41–8.36 (m, 1H), 8.09 (br d, J = 9.4 Hz, 1 H), 7.94 (ddd, J = 8.5, 6.9, 1.4 Hz, 1H), 7.88–7.83 (m, 2H), 7.75 (ddd, J = 8.1, 6.9, 1.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ IR (KBr, cm^{-1}) 1687, 1669, 1577, 1344, 1274, 976, 757; EI-MS m/z 298 (0.003%), 259 (100), 231 (66), 203 (48.5).

Method b. A solution of **8a** (167 mg, 0.49 mmol) in xylene (15 mL) was heated under refluxing conditions for 10 days. The solvent was evaporated and the residue was chromatographed to give **10** (70 mg, 55%).

Method c. A solution of **8a** (20 mg, 0.06 mmol) in TFA (2 mL) was stirred at 23 °C for 48 h. The mixture was treated with 5% aqueous $NaHCO_3$ and then was extracted with CH_2Cl_2, dried (Na_2SO_4), and evaporated. The residue was chromatographed to give **10** (10 mg, 68%).

12-(*E*)-[2-(*N*′,*N*′-Dimethylamino-*N*-trifluoroacetylamino)-ethenyl]benzo[*b*]acridine-6,11-dione (11)

A mixture of **9** (75 mg, 0.17 mmol) and MnO_2 (300 mg, 3.44 mmol) in CH_2Cl_2 (25 mL) was stirred at 23 °C for 2 h. The mixture was filtered through Celite and evaporated to give **11** (75 mg, quantitative) as yellow solid: mp > 285 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.50 (d, J = 8.6 Hz, 1H), 8.46–8.41 (m, 2H), 8.36–8.30 (m, 1H), 7.96 (td, J = 6.9, 1.4 Hz, 1H), 7.86–7.83 (m, 2H), 7.80 (d, J = 15.5 Hz, 1H), 7.77 (t, J = 5.9 Hz, 1H), 6.95 (d, J = 15.5 Hz, 1H), 3.17 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.97, 181.83, 149.90, 148.03, 147.23, 134.73, 134.67, 134.31, 133.31, 132.87, 132.08, 129.89, 128.16, 127.72, 127.58, 127.37, 123.56, 115.37, 43.85, (the signals of CF_3CO and another C signal were not observed); EI-MS m/z 284 (100); IR (KBr, cm^{-1}) 1686, 1595, 1462, 1273, 1043. Anal. calc. for $C_{23}H_{16}N_3O_3F_3$: C, 62.87; H, 3.67; N, 9.56. Found: C, 62.59; H, 3.79; N, 9.18%.

9*H*-Benzo[*b*]pyrido[4,3,2-*mn*]acridin-9-one (benzosampangine) (1a)

Method a. A mixture of **11** (75 mg, 0.17 mmol), NH_4Cl (182 mg, 3.41 mmol) and NaOAc (280 mg, 3.41 mmol) in EtOH (5 mL) was heated under refluxing conditions for 1 h. The mixture was evaporated, the residue was dissolved in EtOAc, washed with 5% aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated. The residue was chromatographed (1 : 2 hexane–EtOAc) to give **1a** (45 mg, 93%) as a pale yellow solid: mp 258–260 °C, lit mp [13] 262 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.04 (d, J = 5.4 Hz, 1H), 8.86 (dm, J = 8.0 Hz, 1H), 8.62 (dm, J = 5.4 Hz, 1H), 8.60 (dm, J = 5.7 Hz, 1H), 8.48 (dm, J = 7.3 Hz, 1H), 8.37 (d, J = 5.8 Hz, 1H), 7.98 (td, J = 7.0, 1.5 Hz, 1H), 7.88 (td, J = 6.9, 1.2 Hz, 1H), 7.83 (td, J = 6.5, 1.4 Hz, 1H), 7.68 (dt, J = 7.4, 1.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.36, 150.52, 148.86, 146.84, 145.78, 137.80, 134.84, 132.97, 132.44, 131.48, 131.10, 130.21, 128.66, 125.65, 123.40, 122.76, 116.98, 115.38, (one C signal overlaps); IR (KBr, cm^{-1}) 1679, 1593, 1420, 1262, 764, 736. Anal. calc. for $C_{19}H_{10}N_2O \cdot \frac{1}{2}H_2O$: C, 78.34; H, 4.12; N, 9.62. Found: C, 78.14; H, 3.96; N, 9.62%.

Method b. A solution of **8b** (34 mg, 0.09 mmol) in xylene (10 mL) was heated under refluxing conditions 24 h. The solvent was evaporated and the residue was chromatographed to give **1a** (14 mg, 40%) and **10** (*ca.* 1 mg).

(*E*)-*N*-{2-[3-(*N*′,*N*′-Dimethylhydrazono)prop-1-enyl]phenyl}-6-aminoquinoline-5,8-dione (12)

A solution of **3** (270 mg, 1.45 mmol), quinoline-5,8-dione (**4b**) (230 mg, 1.45 mmol) and $CeCl_3 \cdot 7H_2O$ (53 mg, 0.015 mmol) in MeOH (15 mL) was stirred at 23 °C for 16 h. The mixture was evaporated, the residue was dissolved in EtOAc and washed with H_2O, dried (Na_2SO_4) and evaporated. The residue was chromatographed (EtOAc) to give **12** (260 mg, 52%) as a brown solid: mp 174–176 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.00 (dd, J = 4.7, 1.6 Hz, 1H), 8.38 (dd, J = 7.9, 1.5 Hz, 1H), 7.67–7.53 (m, 2H), 7.38 (br s, 1H), 7.30–7.20 (m, 3H), 6.98 (br d, J = 8.6 Hz, 1H), 6.89 (dd, J = 14.9, 8.6 Hz, 1H), 6.47 (d, J = 14.9 Hz, 1H), 6.06 (s, 1H), 2.86 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.83, 181.80, 155.18, 148.96, 145.76, 134.21, 133.61, 133.50, 133.25, 131.01, 128.12, 127.61, 127.32, 126.31 (2C), 125.58, 123.89, 104.66, 42.54; HMQC (75 MHz, $CDCl_3$) shows the following ^{1}H–^{13}C correlations: H-4 (8.38 ppm) with C-8a (148.96 ppm) and C-2 (155.18 ppm), H-7 (6.06 ppm) with C-8a (148.96 ppm), H-2 (9.00 ppm) with C-8a (148.96 ppm). Anal. calc. for $C_{20}H_{18}N_4O_2 \cdot \frac{1}{2}H_2O$: C, 67.53; H, 5.62; N, 15.75. Found: C, 67.89; H, 5.35; N, 15.42%.

12-(*E*)-[2-(*N*′,*N*′-Dimethylamino-*N*-trifluoroacetylamino)-ethenyl]-6,11-dihydropyrido[2,3-*b*]acridine-5,12-dione (13)

A mixture of **12** (43 mg, 0.12 mmol) and NaH (60% in mineral oil, 9 mg, 0.37 mmol) in THF (5 mL) was stirred at 23 °C for 10 min. The resulting purple mixture was treated with TFAA (52 mg, 0.25 mmol) at this temperature and was stirred for 15 min yielding a yellow solution. The mixture was evaporated under high vacuum and the residue was dissolved in CH_2Cl_2 (10 mL). TFA (0.10 mL, 10.00 mmol) was added to give a purple solution. After being stirred 1 h, the crude mixture was diluted with CH_2Cl_2, washed with 5% aqueous $NaHCO_3$, dried (Na_2SO_4), the solvent was evaporated and the residue was chromatographed (EtOAc) to give unchanged starting material and **13** (20 mg, 36%, 47% based on unrecovered starting material) as a dark solid: mp > 285 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.01 (dd, J = 4.9, 1.6 Hz, 1H), 8.41 (dd, J = 7.5, 1.6 Hz, 1H), 7.60 (dd, J = 7.5, 4.9 Hz, 1H), 7.54 (br s, 1H), 7.30–7.20 (m, 2H), 7.12 (t, J = 7.5 Hz, 1H), 6.97 (d, J = 7.5 Hz, 1H), 6.33 (d, J = 14.5 Hz, 1H), 6.22 (dd, J = 14.5, 7.0 Hz, 1H), 5.16 (d, J = 7.0 Hz, 1H), 2.68 (s, 3H), 2.64 (s, 3H). Anal. calc. for $C_{22}H_{17}N_4O_3F_3 \cdot \frac{1}{2}H_2O$: C, 58.48; H, 3.98; N, 12.40. Found: C, 58.54; H, 3.84; N, 12.20%.

Pyrido[2,3-*b*]acridine-5,12-dione (14)

A solution of **12** (47 mg, 0.14 mmol) in TFA (2 mL) was stirred at 23 °C for 24 h. The mixture was treated with 5% aqueous

$NaHCO_3$ and extracted with CH_2Cl_2, dried (Na_2SO_4), and evaporated. The residue was chromatographed (EtOAc) to give starting material and **14** (16 mg, 43%, 66% based on unrecovered starting material) as a brown solid: mp > 285 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.33 (s, 1H), 9.19 (dd, J = 4.8, 2.1 Hz, 1H), 8.83 (dd, J = 8.1, 2.1 Hz, 1H), 8.50 (d, J = 8.6 Hz, 1H), 8.13 (d, J = 8.1 Hz, 1H), 7.99 (ddd, J = 8.6, 7.0, 1.6 Hz, 1H), 7.86–7.76 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.27, 180.91, 155.58, 150.28, 148.95, 146.97, 138.77, 136.39, 133.66, 131.61, 131.60, 130.21, 129.71, 129.06, 128.32, 127.21; IR (KBr, cm^{-1}) 1692, 1612, 1574, 1342, 1286, 977, 762; EI-MS *m*/*z* 260 (M^+, 100%), 232 (86), 204 (67).

11-(*E*)-[2-(*N*′,*N*′-Dimethylamino-*N*-trifluoroacetylamino)-ethenyl]pyrido[2,3-*b*]acridine-5,12-dione (15)

A mixture of **13** (19 mg, 0.04 mmol) and MnO_2 (200 mg, 2.29 mmol) in CH_2Cl_2 (15 mL) was stirred at 23 °C for 2 h. The mixture was filtered through Celite and evaporated to give **15** (19 mg, quantitative) as a yellow solid: mp 254–256 °C (dec); ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.17 (dd, J = 4.6, 1.8 Hz, 1H), 8.78 (dd, J = 6.9, 1.7 Hz, 1H), 8.50 (dd, J = 6.9, 4.6 Hz, 1H), 7.99 (ddd, J = 8.4, 6.9, 1.3 Hz, 1H), 7.85–7.75 (m, 3H), 7.72 (d, J = 15.7 Hz, 1H), 7.11 (d, J = 15.5 Hz, 1H), 3.23 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.47, 181.38, 158.57, 155.80, 149.99, 149.50, 148.15, 147.21, 135.98, 133.38, 132.12, 130.38, 130.20, 128.54, 128.19, 127.59, 123.34, 114.00, 43.87, (the signal of CF_3CO was not observed). Anal. calc. for $C_{22}H_{15}N_4O_3F_3$: C, 60.00; H, 3.43; N, 12.72. Found: C, 59.96; H, 3.42; N, 12.82%.

6,11-Dihydro-11-[2-(*N*,*N*-dimethylhydrazono)ethyl]pyrido-[2,3-*b*]acridine-5,12-dione (16)

A solution of **12** (120 mg, 0.35 mmol) in xylene (5 mL) was heated under refluxing conditions for 4 h. The solvent was evaporated and the residue was chromatographed (9 : 1 EtOAc–MeOH) to give **16** (65 mg, 54%) as a brown solid: mp 204–206 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.00 (br d, J = 4.9 Hz, 1H), 8.37 (d, J = 7.0 Hz, 1H), 7.58 (dd, J = 7.0, 4.9 Hz, 1H), 7.51 (br s, 1H), 7.25–7.13 (m, 3H), 6.94 (t, J = 8.1 Hz, 1H), 6.57 (t, J = 6.0 Hz, 1H), 4.68 (t, J = 6.0 Hz, 1H), 2.55 (s, 6H), 2.60–2.50 (m, 2H); EI-MS *m*/*z* 346 (M^+, 1%), 261 (100), 232 (53), 204 (43), 85 (25). This compound slowly decomposed on standing to give **14**.

Ascididemin (1b)

Method a. A mixture of **15** (29 mg, 0.07 mmol), NH_4Cl (73 mg, 1.36 mmol) and NaOAc (111 mg, 1.36 mmol) in EtOH (5 mL) was heated under refluxing conditions for 20 min. The solvent was evaporated and the residue was dissolved in EtOAc, washed with 5% aqueous $NaHCO_3$ dried (Na_2SO_4), and evaporated. The residue was chromatographed (4 : 1 EtOAc–MeOH) to give **1b** (16 mg, 84%) as a pale yellow solid: mp > 285 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.29 (d, J = 5.6 Hz, 1H), 9.19 (dd, J = 4.6, 1.8 Hz, 1H), 8.80 (dd, J = 8.0, 1.8 Hz, 1H), 8.73–8.62 (m, 2H), 8.56 (d, J = 5.6 Hz, 1H), 8.03 (td, J = 7.2, 1.8 Hz, 1H), 7.95 (td, J = 8.0, 1.8 Hz, 1H), 7.68 (dd, J = 7.8, 4.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.15, 155.58, 149.77, 145.76, 138.03, 136.62, 133.18, 131.88, 130.87, 129.06, 125.62, 123.48, 122.91, 116.82 (four carbon signals were not observed); EI-MS *m*/*z* 283 (100%), 255 (99.5).

Method b. A mixture of **16** (23 mg, 0.07 mmol), NH_4Cl (70 mg, 1.32 mmol) and NaOAc (109 mg, 1.32 mmol) in EtOH (10 mL) was heated under refluxing conditions for 20 min. The solvent was evaporated and the residue was dissolved in EtOAc, washed with 5%, aqueous $NaHCO_3$, and dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed to give **1b** (12 mg, 64%) and **14** (3 mg, 17%).

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