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Total Synthesis of Quebrachamine through Macrolactamization

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The total synthesis of quebrachamine was achieved through the macrolactamization of *cis*-2-alkenylated indole **17**, which was prepared by a Sonogashira reaction between indole **5b** and piperidine **11** followed by *cis*-hydrogenation. We found that stoichiometric copper(I) iodide limited the undesired Glaser-type homocoupling of alkyne **11** that would otherwise take place during the Sonogashira coupling. This direct approach allowed the total synthesis in ten linear steps starting from commercially available chemicals. Conditions for the reduction of lactam **19** by lithium aluminiumhydride were adjustable, so that either (±)-quebrachamine or the analogue (±)-kopsiyunnanine D was prepared.

Introduction

Quebrachamine (**1**) and related indole alkaloids (Figure 1), isolated from *Aspidospermaquebracho* tree bark,[1] have received considerable and sustained attention from chemists due to their structural complexity and biological activities.[2] Indeed, quebrachamine and its related or derived alkaloids have continually been found in various plants.[3] Since Stork and Dolfini utilized the Fischer indole synthesis and subsequent reductive ring opening to achieve the first synthesis of quebrachamine,[4] fragmentation of fused or bridged 5- to 6-membered ring systems has been the dominant method used to access the nine-membered ring of quebrachimine as shown in many clever formal and total syntheses developed to the preparation of strained compounds for the essential fragmentation/ring opening.[5,6] Recently, Pagenkopf's group reported their synthesis of quebrachimine, in which the direct formation of the challenging nine-membered ring was accomplished by chloroacetamide-promoted Witkop photocyclization, rather than the conventional fragmentation.[7,8] This direct formation of the medium-sized ring is attractive because the necessity to prepare the strained intermediates for fragmentations is circumvented and a more straightforward, efficient synthesis becomes possible. Here we report our studies based on this direct approach to construction of the nine-membered ring of quebrachimine by the lactamization of an amino acid bearing a *cis*-olefin. A recently discovered quebrachamine-derived alkaloid, kopsiyunnanine D,[3b] was also prepared by the direct conversion of the indolyl carbamate to the hemiaminal ether.

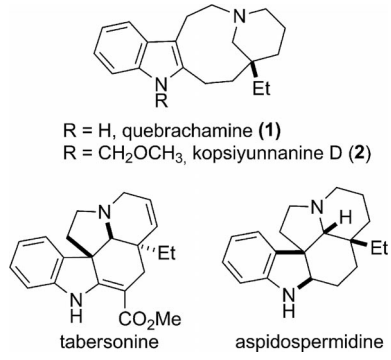

Figure 1. Some *Aspidosperma* alkaloids.

Results and Discussion

The retrosynthetic analysis of quebrachamine is shown in Scheme 1. With the lactamization to generate the nine-membered ring in mind, we envisioned the synthesis of (±)-quebrachamine (**1**) from the amino acid **A**, which was expected to be assembled from the Sonogashira coupling reaction of 2-iodo-1*H*-indol-3-ylacetic acid **B** and piperidine **C**. The latter could be prepared from the inexpensive diethyl ethylmalonate and acrylonitrile.

The synthesis started with the iodination of ethyl and benzyl indol-3-ylacetates (**3a** and **3b**, respectively)[9] to provide the iodides **4a** and **4b**,[10] which were further protected as the ethyl carbamates **5a** and **5b** (Scheme 2). The preparation of the alkynyl component for the Sonogashira cross-coupling started with the 1,4-addition between acrylonitrile and diethyl ethylmalonate to give the spiro compound **7** (Scheme 3).[11] Subsequent reduction of the cyano group by H_2/PtO_2 and condensation generated the lactam **8**, which

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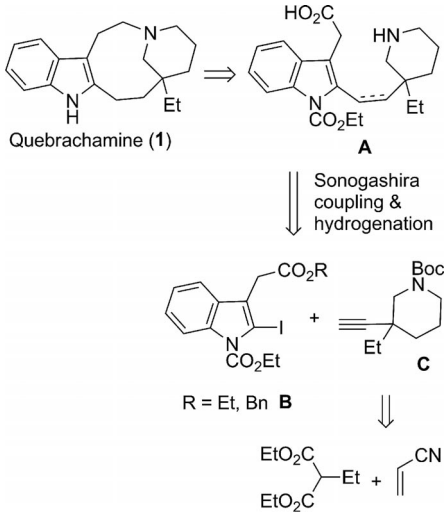
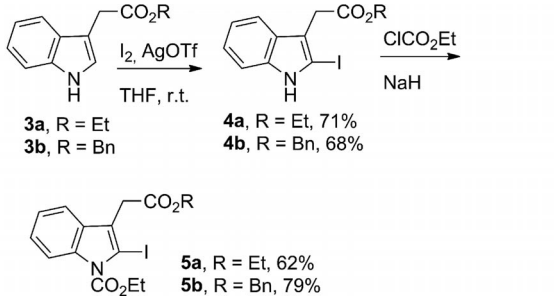
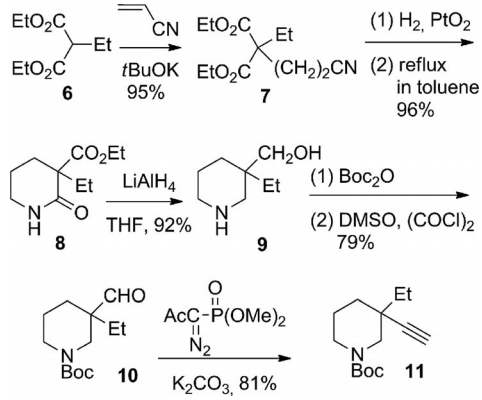


Scheme 1. Retrosynthetic analysis of quebrachamine.

was further reduced to the piperidinyl alcohol **9**, protected with a *tert*-butoxycarbonyl (Boc) group and oxidized to the aldehyde **10**. The Seyferth–Gilbert homologation was applied with dimethyl (1-diazo-2-oxopropyl)phosphonate to generate the terminal alkyne **11**.[12]



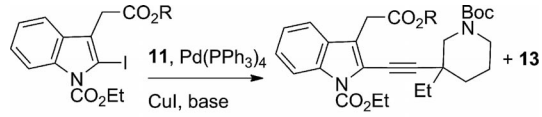
Scheme 2. Synthesis of indole **5**.



Scheme 3. Synthesis of alkyne **11**.

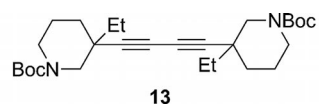
Although 2-haloindoles have been used as substrates for Sonogashira cross-coupling,[10,13] different reactivities towards alkynes containing nitrogen atoms were observed.[13a] Our results for the Sonogashira cross-coupling reaction to link iodides **5a** or **5b** with **11** are summarized in Table 1. Preliminary screening of the bases (Entries 1–3) and reaction temperatures (Entries 4 and 5) with substrate **5a** showed that the best yield was obtained with the tertiary amine (NEt_3) at 80 °C. In addition to the desired heterocoupling product **12**, a notable amount of the Glaser-type homocoupling product **13** was also produced under these reaction conditions, which made the isolation of **12** arduous.[14] We found that this competing pathway could be effectively suppressed by increasing the amount of cuprous iodide. Thus, the ratios of **12/13** were improved from ca. 2:1 to 20:1 (Entries 6–8 and 10). The transmetallation between palladium complex and copper acetylide is believed to be the rate-determining step of Sonogashira cross-coupling.[15] Pretreatment of **11** with a stoichiometric amount of CuI and excess Et_3N should consume the terminal alkyne to give the corresponding copper acetylide, which might speed up the transmetallation process to make the Sonogashira cross-coupling product **12** dominant. The lack of free terminal alkyne **11** might also slow down the homocoupling process. For the reaction of benzyl ester **5b**, more palladium catalyst (30 mol-%) was required to obtain a good yield (Entries 9 vs. 10).

Table 1. Preparation of **12** by Sonogashira cross-coupling.[a]

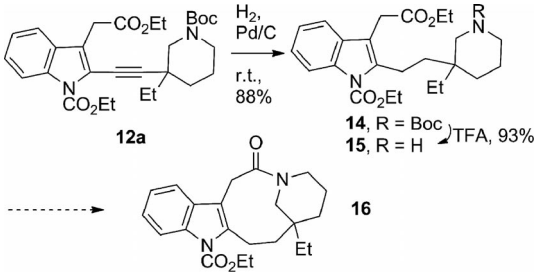


Entry	Substrate	Base	Temp. [°C]	Cu [mol-%]	Yield [%][b][c]
1	**5a**	Et_3N	50	20	49 (5.0:1)
2	**5a**	$(iPr)_2NH$	50	20	17 (1.3:1)
3	**5a**	$nBuNH_2$	50	20	0
4	**5a**	Et_3N	80	20	73 (4.8:1)
5	**5a**	Et_3N	100	20	0
6	**5a**	Et_3N	80	50	75 (2.1:1)
7	**5a**	Et_3N	80	100	90 (3.5:1)
8	**5a**	Et_3N	80	150	95 (11:1)
9	**5b**	Et_3N	80	150	43 (5.8:1)
10	**5b**	Et_3N	80	150	95 (20:1)[d]

[a] The reactions were carried out with $Pd(PPh_3)_4$ (10 mol-%) and **11** (1.2 equiv.) in toluene under nitrogen for 6 h. [b] Yields of **12**. [c] The ratios of **12/13** are shown in parentheses, based on ^1H NMR spectroscopic integration. [d] $Pd(PPh_3)_4$ (30 mol-%).

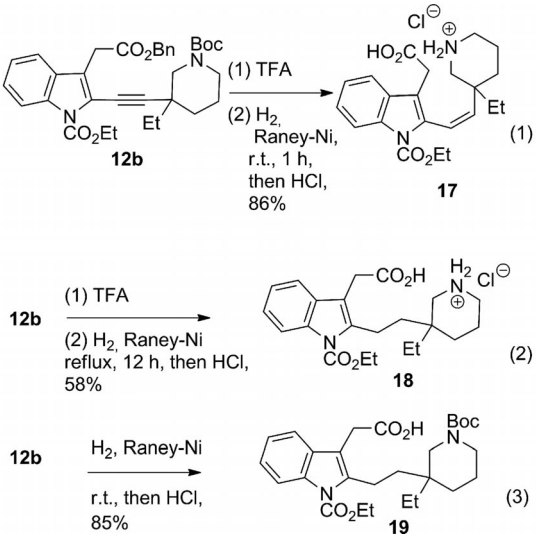


Hydrogenation of **12a** with palladium on charcoal gave 2-alkylindole **14**, and subsequent treatment with trifluoroacetic acid (TFA) removed the Boc protective group to give amine **15**. However, the intramolecular condensation of **15** intended to give the lactam **16** was unsuccessful (Scheme 4).[16]

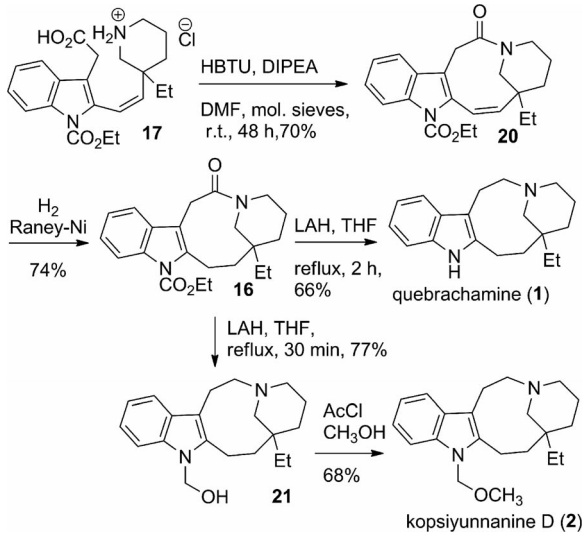


Scheme 4. Failed lactamization with **15**.

Fortunately, we found that the Raney-nickel-catalyzed hydrogenation and hydrogenolysis of **12b** (after removal of the Boc group) provided the partially reduced product **17** containing a *cis* olefin [Equation (1)]. Use of an elevated reaction temperature (80 °C) completely reduced the internal alkyne to afford the 2-alkylindole **18** [Equation (2)]. It is also interesting to note that without removal of the Boc group, the alkynyl moiety was completely reduced to afford **19** [Equation (3)]. Previous studies by Fukuyama's and Baran's groups suggested that the partial *cis* hydrogenation of 2-alkynylindoles was directed by the *N*-Boc group.[10,13b] However, our results with the ethyl-carbamate-protected indoles **12a** and **12b** indicate that the presence of the carboxylate group and the secondary amine is essential to give the *cis* olefin here. We also noticed that Raney-Ni provided a better selectivity for the *cis* hydrogenation than Pd/C.[17]



Lactamization of 2-alkenylindole **17** was successfully carried out with *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU) under mild conditions, to give compound **20** (70% yield, Scheme 5). In contrast, the corresponding reaction of the 2-alkylindole **18** did not yield any lactam under various reaction conditions. The *cis* olefin system, furnishing the conformationally more restricted **17**, should be the key factor for the ring closure to give the nine-membered lactam ring. Further hydrogenation of **20** generated the lactam **16** smoothly. Quebrachamine (**1**) was synthesized after the reduction of the amide group and the removal of the ethyl carbamate, both effected with lithium aluminiumhydride in one step. Our previous reaction conditions (25 °C) reduced 1-indolyl carbamates to hemiaminals but kept amides intact.[18] Here, both the amide and the carbamate groups of **16** were reduced at the higher reaction temperature (65 °C). The hemiaminal **21** was harvested by shortening the reaction time (30 min) and was converted into kopsiyunnanine D (**2**) under anhydrous acidic conditions. The ^{1}H NMR and ^{13}C NMR spectra of the synthetic quebrachamine and kopsiyunnanine D are consistent with the reported data.[6g,3b] A nucleophilic substitution reaction between the alkali quebrachamine anion and methoxymethyl chloride (MOMCl) was applied in the previous semisynthesis of kopsiyunnanine D.[3b] In this work, the protective ethyl carbamate group was utilized to generate the *N*-methoxymethyl substituent of kopsiyunnanine D.



Scheme 5. Lactamization and synthesis of **1** and **2**.

Conclusions

Incorporation of conformationally restricted *cis*-alkenes as key components for forming macrocycles has been demonstrated in several natural product syntheses, in which the intramolecular Mitsunobu or Horner–Wadsworth–Emmons reactions were utilized for the cyclization.[10,13b,13c] This synthesis of quebrachamine demonstrates that the typical amide formation, although rarely utilized for macrocyclization,[8a] can also benefit from the presence of an internal *cis*-alkene to generate the medium rings. This direct approach simplified the synthetic design, and the quebrachamine was prepared in ten linear steps with 9% total yield. The competition between the Glaser-type homocoupling and the Sonogashira coupling was conveniently adjusted by varying the amount of CuI. The method developed to transform carbamates into hemiaminals and the corresponding ethers should be applicable to the preparation of the compounds with these functional groups.

Experimental Section

Ethyl 2-(2-Iodo-1*H*-indol-3-yl)acetate (4a):[10] A solution of iodine (1.78 g, 7.0 mmol) in THF (15 mL) was added slowly at 25 °C to a solution of **3a** (1.44 g, 7.1 mmol) and silver triflate (2.36 g, 9.2 mmol) in THF (35 mL). The reaction mixture was stirred for 5 min, treated with satd. sodium thiosulfate$_{(aq)}$ (25 mL) and extracted with ethyl acetate (50 mL×2). The organic layers were combined, washed with satd. NaCl$_{(aq.)}$ (25 mL), dried with Na_2SO_4 and concentrated. The crude product was further purified by column chromatography (SiO_2, EtOAc/hexanes 1:9; R_f 0.35) to give **4a** (1.61 g, 4.9 mmol, 71%) as a viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.22 (br., 1 H), 7.54–7.52 (m,1 H), 7.24–7.21 (m, 1 H), 7.13–7.05 (m, 2 H), 4.15 (q, J = 7.2 Hz, 2 H), 3.71 (s, 2 H), 1.24 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.2, 138.7, 127.4, 122.4, 120.1, 118.2, 115.2, 110.4, 79.8, 61.0, 33.2, 14.2 ppm.

Benzyl 2-(2-Iodo-1*H*-indol-3-yl)acetate (4b): A solution of iodine (1.27 g, 5.0 mmol) in THF (12.5 mL) was added at 25 °C to a solution of **3b** (1.02 g, 5 mmol) and silver triflate (1.67 g, 6.5 mmol) in THF (29 mL). The reaction mixture was stirred for 5 min, treated with satd. sodium thiosulfate$_{(aq.)}$ (20 mL) and extracted with ethyl acetate (40 mL × 2). The organic layers were combined, washed with satd. NaCl$_{(aq.)}$ (20 mL), dried with Na_2SO_4 and concentrated. The crude product was further purified by column chromatography (SiO_2, EtOAc/hexanes 1:9; R_f 0.35) to give **4b** (1.27 g, 3.25 mmol, 68%) as a viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.16 (br., 1 H), 7.54 (d, J = 7.0 Hz, 1 H), 7.32 (m, 5 H), 7.24–7.20 (m, 1 H), 7.09 (m, 2 H), 5.15 (s, 2 H), 3.78 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.0, 138.7, 135.8, 128.4, 128.1, 127.3, 122.4, 120.1, 118.1, 144.9, 110.4, 79.9, 66.6, 33.1 ppm. HRMS (FAB): calcd. for $C_{17}H_{14}NO_2I$ [M]$^+$ 391.0069; found 391.0063.

Ethyl 3-[(Ethoxycarbonyl)methyl]-2-iodo-1*H*-indole-1-carboxylate (5a): A solution of **4a** (1.24 g, 3.78 mmol) in THF (10 mL) was added at 0 °C to a suspension of sodium hydride (302 mg, 7.56 mmol) in THF. The reaction mixture was treated with ethyl chloroformate (540 μL, 5.67 mmol), stirred for another 2 h at 25 °C, quenched with water (5 mL) and extracted with ethyl acetate (15 mL × 2). The combined organic layers were dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes 1:9; R_f 0.5) to give **5a** (940 mg, 2.34 mmol, 62%) as a white solid, m.p. 81.5–84.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08 (d, J = 6.7 Hz, 1 H), 7.47 (d, J = 5.8 Hz, 1 H), 7.22 (dt, J = 6.7, J = 5.8 Hz, 2 H), 4.53 (q, J = 7.2 Hz, 2 H), 4.15 (q, J = 7.2 Hz, 2 H), 3.71 (s, 2 H), 1.51 (t, J = 7.2 Hz, 3 H), 1.23 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.0, 150.7, 137.8, 129.6, 124.7, 123.8, 123.1, 118.4, 115.7, 80.6, 63.6, 61.0, 34.2, 14.3, 14.1 ppm. HRMS (ESI): calcd. for $C_{15}H_{16}NO_4NaI$ [M + Na]$^+$ 424.0022; found 424.0022.

Ethyl 3-{[(Benzyloxy)carbonyl]methyl}-2-iodo-1*H*-indole-1-carboxylate (5b): A solution of **4b** (1.36 g, 3.46 mmol) in THF (7 mL) was added at 0 °C to a suspension of sodium hydride (280 mg, 6.93 mmol) in THF. The reaction mixture was treated with ethyl chloroformate (500 μL, 5.2 mmol), stirred for another 2 h at 25 °C, quenched with water (5 mL) and extracted with ethyl acetate (15 mL × 2). The combined organic layers were dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes 1:9; R_f 0.5) to give **5b** (1.27 g, 2.73 mmol, 79%) as a white solid, m.p. 74.5–76.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.9 (d, J = 7.7 Hz, 1 H), 7.45 (d, J = 7.1 Hz, 1 H), 7.32–7.30 (m, 5 H), 7.23 (dt, J = 7.7, J = 7.1 Hz, 2 H), 5.14 (s, 2 H), 4.54 (q, J = 7.2 Hz, 2 H), 3.85 (s, 2 H), 1.52 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.7, 150.5, 137.7, 135.5, 129.5, 128.3, 128.0, 127.9, 124.6, 123.5, 123.0, 118.3, 115.6, 80.7, 66.6, 63.5, 34.1, 14.2 ppm. HRMS (ESI): calcd. for $C_{20}H_{18}NO_4NaI$ [M + Na]$^+$ 486.0178; found 486.0177.

Diethyl 2-(Cyanomethyl)-2-ethylmalonate (7): Potassium *tert*-butoxide (596 mg, 5.31 mmol) was added at 0 °C to a solution of diethyl ethylmalonate (20.0 g, 106 mmol) in *tert*-butyl alcohol (40 mL). A solution of acrylonitrile (11 mL, 166 mmol) in *tert*-butyl alcohol (40 mL) was added to the above solution. The reaction mixture was stirred at 25 °C for 1 h, concentrated, diluted with ethyl acetate (200 mL) and washed with water (50 mL), satd. $NaHCO_{3(aq.)}$ (50 mL) and satd. NaCl$_{(aq.)}$ (50 mL). The organic layer was dried with Na_2SO_4 and concentrated to give **7** (24.2 g, 0.1 mol, 95%) as a colourless solid, m.p. 43.5–45.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.17 (q, J = 7.2 Hz, 4 H), 2.39–2.29 (m, 2 H), 2.22–2.13 (m, 2 H), 1.91 (q, J = 7.5 Hz, 2 H), 1.22 (t, J = 7.2 Hz, 6 H), 0.82 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 119.1, 61.6, 57.0, 28.2, 26.2, 14.0, 12.9, 8.4 ppm. HRMS (FAB): calcd. for $C_{12}H_{20}NO_4$ [M + H]$^+$ 242.1392; found 242.1388.

Ethyl 3-Ethyl-2-oxopiperidine-3-carboxylate (8): A suspension of compound **7** (2.8 g, 11.6 mmol), platinum(IV) oxide (131 mg, 0.58 mmol) and acetic acid (40 mL) was stirred under hydrogen (100 psi) for 10 h. The reaction mixture was concentrated, treated with water (20 mL), basified with KOH$_{(aq.)}$ and extracted with ethyl acetate (20 mL × 3). The combined organic layers were dried with Na_2SO_4 and concentrated. The crude amine was redissolved in toluene (40 mL), heated at reflux for 2 h and concentrated to give **8** (2.22 g, 11.1 mmol, 96%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.89 (br., 1 H), 4.11 (q, J = 7.2 Hz, 2 H), 3.43–3.05 (m, 2 H), 2.13–2.01 (m, 1 H), 1.99–1.64 (m, 5 H), 1.18 (t, J = 7.2 Hz, 3 H), 0.86 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.9, 171.2, 61.1, 54.0, 42.1, 28.9, 28.3, 19.5, 14.0, 8.9 ppm. HRMS (FAB): calcd. for $C_{10}H_{18}O_3N$ [M + H]$^+$ 200.1287; found 200.1289.

(3-Ethylpiperidin-3-yl)methanol (9): Compound **8** (760 mg, 2.78 mmol) in THF (40 mL) was added at 0 °C to a solution of lithium aluminiumhydride (422 mg, 11.1 mmol) in THF (20 mL). After the addition, the reaction mixture was heated to reflux for 2 h and quenched with satd. $Na_2CO_{3(aq.)}$ (4 mL). The clear solution was decanted, dried with Na_2SO_4 and concentrated to give **9** (360 mg, 2.51 mmol, 92%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.59 (br., 2 H), 3.45 (d, J = 10.8 Hz, 1 H), 3.36 (d, J = 10.8 Hz, 1 H), 2.78, 2.68 (m, 1 H), 2.72 (d, J = 12.2 Hz, 1 H), 2.56, 2.45 (m, 1 H), 2.35 (d, J = 12.2 Hz, 1 H), 1.65, 1.48 (m, 1 H), 1.48, 1.31 (m, 2 H), 1.24, 1.03 (m, 3 H), 0.68 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 67.2, 53.6, 46.5, 35.7, 31.3, 28.0, 22.4, 7.1 ppm. HRMS (ESI): calcd. for $C_{13}H_{25}NO_3Na$ [M + Na]$^+$ 266.1732; found 266.1738.

***tert*-Butyl 3-Ethyl-3-formylpiperidine-1-carboxylate (10):** Di-*tert*-butyl dicarbonate (2.2 g, 10.2 mmol) in THF (17 mL) was added to a solution of **9** (1.46 g, 10.2 mmol) in THF (17 mL). The reaction mixture was stirred at 25 °C for 16 h and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes 1:3; R_f 0.63) to give the carbamate (1.96 g, 8.16 mmol, 80%) as a viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.64 (br., 1 H), 3.40–2.89 (m, 4 H), 2.76 (br., 1 H), 2.61–2.31 (m, 1 H), 1.48–1.25 (m, 4 H), 1.32 (s, 9 H), 1.25–0.96 (m, 2 H), 0.71 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.9, 154.7, 79.5, 64.4, 62.3, 50.1, 49.4, 45.4, 43.8, 37.9, 30.0, 28.2, 27.5, 25.3, 21.2, 20.8, 7.1 ppm. HRMS (ESI): calcd. for $C_{13}H_{25}NO_3Na$ [M + Na]$^+$ 266.1732; found 266.1738. Dimethyl sulfoxide (2.9 mL, 40.6 mmol) was added at –78 °C to a solution of oxalyl chloride (1.8 mL, 20.3 mmol) in dichloromethane (19 mL). After having

been stirred for 30 min at –78 °C, the reaction mixture was treated with the solution of the above Boc-carbamate (1.98 g, 8.12 mmol) in dichloromethane (55 mL), stirred for 1 h at –78 °C, treated with triethylamine (18 mL, 130 mmol) and allowed to warm up to room temp. The solution was washed with satd. $NH_4Cl_{(aq.)}$ (20 mL × 3) and satd. $NaCl_{(aq.)}$ (20 mL), dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes 1:3; R_f 0.67) to give **10** (1.88 g, 7.8 mmol, 96%) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.45 (s, 1 H), 4.42–3.74 (m, 1 H), 3.63 (br., 1 H), 3.20–2.60 (m, 2 H), 1.97 (br., 1 H), 1.59–1.45 (m, 3 H), 1.45–1.30 (m, 3 H), 1.40 (s, 9 H), 0.78 (t, J = 7.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.2, 154.6, 79.8, 50.2, 48.3, 44.3, 43.8, 28.7, 28.4, 26.4, 26.1, 21.8, 7.8 ppm. HRMS (ESI): calcd. for $C_{13}H_{24}NO_3$ $[M + H]^+$ 242.1756; found 242.1755.

***tert*-Butyl 3-Ethyl-3-ethynylpiperidine-1-carboxylate (11):** Ohira–Bestmann reagent (1.9 g, 9.744 mmol) was added to a solution of **10** (1.96 g, 8.12 mmol) and potassium carbonate (2.25 g, 16.24 mmol) in methanol (60 mL). The reaction mixture was stirred at 25 °C for 6 h, diluted with diethyl ether (30 mL), washed with sat, $NaHCO_{3(aq.)}$ (30 mL), dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes 1:3; R_f 0.7) to give **11** (1.56 g, 6.6 mmol, 81%) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.93–3.72 (br., 2 H), 2.90–2.69 (br., 2 H), 2.05 (s, 1 H), 1.82–1.73 (m, 2 H), 1.52–1.35 (m, 13 H), 0.98 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.6, 87.1, 79.2, 70.5, 52.9, 43.4, 36.6, 35.5, 30.3, 28.2, 21.7, 8.4 ppm. IR (neat): $\tilde{\nu}$ = 3307, 3249, 2971, 2858, 2109, 1695, 1427, 1366, 1274, 1162, 1106, 1002, 877, 767, 632 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{23}NO_2Na$ $[M + Na]^+$ 260.1626; found 260.1628.

Ethyl 2-{2-[1-(*tert*-Butoxycarbonyl)-3-ethylpiperidin-3-yl]ethynyl}-3-[(ethoxycarbonyl)methyl]-1*H*-indole-1-carboxylate (12a): A solution of compound **5a** (56 mg, 0.14 mmol), compound **11** (40 mg, 0.17 mmol), triethylamine (1 mL) and toluene (2 mL) was added to a flask containing tetrakis(triphenylphosphine)palladium(0) (16 mg, 0.014 mmol) and copper(I) iodide (40 mg, 0.21 mmol). The reaction mixture was stirred for 6 h at 80 °C under nitrogen, treated with satd. $NH_4Cl_{(aq.)}$ (2 mL) and extracted with ethyl acetate (5 mL). The organic layer was separated, washed with satd. $NaCl_{(aq.)}$ (2 mL), dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes 1:9; R_f 0.2) to give **12a** (68 mg, 0.13 mmol, 95%) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (d, J = 8.2 Hz, 1 H), 7.49 (d, J = 7.3 Hz, 1 H), 7.31 (dd, J = 8.2, J = 7.5 Hz, 1 H), 7.22 (dd, J = 7.3, J = 7.5 Hz, 1 H), 4.50 (q, J = 7.2 Hz, 2 H), 4.11 (q, J = 7.2 Hz, 2 H), 3.79 (s, 2 H), 3.79–3.52 (br., 2 H), 3.27–2.98 (br., 2 H), 1.97–1.83 (m, 2 H), 1.64–1.58 (m, 4 H), 1.46 (t, J = 7.2 Hz, 3 H), 1.39 (s, 9 H), 1.20 (t, J = 7.2 Hz, 3 H), 1.11 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 154.8, 151.0, 135.5, 128.8, 125.6, 123.2, 122.9, 121.2, 119.8, 119.1, 115.6, 103.1, 79.4, 74.0, 63.1, 60.9, 52.5, 43.7, 37.9, 35.6, 31.4, 30.6, 28.3, 22.0, 14.5, 14.2, 8.9 ppm. HRMS (ESI): calcd. for $C_{29}H_{38}N_2O_6Na$ $[M + Na]^+$ 533.2628; found 533.2626.

Ethyl 3-{[(Benzyloxy)carbonyl]methyl}-2-{2-[1-(*tert*-butoxycarbonyl)-3-ethylpiperidin-3-yl]ethynyl}-1*H*-indole-1-carboxylate (12b): A solution of compound **5b** (1.43 g, 3.09 mmol), compound **11** (880 mg, 3.7 mmol), triethylamine (8 mL) and toluene (22 mL) was added to a flask containing tetrakis(triphenylphosphine)palladium(0) (1.07 g, 0.92 mmol) and copper(I) iodide (882 mg, 4.64 mmol). The reaction mixture was stirred for 6 h at 80 °C under nitrogen, treated with satd. $NH_4Cl_{(aq.)}$ (10 mL) and extracted with ethyl acetate (50 mL). The organic layer was separated, washed with satd. $NaCl_{(aq.)}$ (10 mL), dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes 1:9; R_f 0.2) to give **12b** (1.68 g, 2.94 mmol, 95%) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (d, J = 8.4 Hz, 1 H), 7.46 (d, J = 7.5 Hz, 1 H), 7.32 (s, 5 H), 7.28 (dt, J = 8.4, J = 7.5 Hz, 2 H), 5.11 (s, 2 H), 4.49 (q, J = 7.2 Hz, 2 H), 3.85 (s, 2 H), 3.73–3.53 (m, 2 H), 3.27–2.86 (m, 2 H), 1.89–1.69 (m, 2 H), 1.58–1.48 (m, 7 H), 1.38 (s, 9 H), 1.07 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.2, 154.7, 150.9, 135.7, 135.4, 132.1, 128.6, 128.5, 128.1, 125.6, 123.2, 120.9, 119.8, 119.0, 115.6, 103.2, 79.4, 73.9, 66.6, 63.1, 52.6, 43.5, 37.9, 35.4, 31.2, 29.6, 28.3, 21.6, 14.5, 8.9 ppm. HRMS (ESI): calcd. for $C_{34}H_{40}N_2O_6Na$ $[M + Na]^+$ 595.2784; found 595.2779.

Ethyl 2-{2-[1-(*tert*-Butoxycarbonyl)-3-ethylpiperidin-3-yl]ethyl}-3-[(ethoxycarbonyl)methyl]-1*H*-indole-1-carboxylate (14): A suspension of **11a** (46 mg, 0.089 mmol), palladium on activated charcoal (10%, 20 mg, 0.018 mmol) and methanol (4 mL) was stirred for 16 h at 25 °C under hydrogen (1 atm), filtered with a plug of celite and concentrated to give **14** (40.3 mg, 0.078 mmol, 88%) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (d, J = 7.4 Hz, 1 H), 7.47 (d, J = 7.2 Hz, 1 H), 7.22 (dt, J = 7.4, J = 7.2 Hz, 2 H), 4.50 (q, J = 7.2 Hz, 2 H), 4.11 (q, J = 7.2 Hz, 2 H), 3.64 (s, 2 H), 3.64–3.32 (br., 2 H), 3.18–2.87 (m, 4 H), 1.52–1.45 (m, 7 H), 1.42–1.24 (m, 10 H), 1.23–1.15 (m, 6 H), 0.88 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.9, 155.1, 151.7, 139.7, 135.5, 129.7, 123.8, 122.8, 118.3, 115.7, 111.9, 79.1, 63.0, 60.9, 52.5, 43.9, 35.9, 35.6, 33.6, 30.4, 29.6, 28.4, 21.1, 20.5, 14.5, 14.2, 7.5 ppm. HRMS (ESI): calcd. for $C_{29}H_{42}N_2O_6Na$ $[M + Na]^+$ 537.2941; found 537.2938.

3-{2-[3-(2-Ethoxy-2-oxoethyl)-1-(ethoxycarbonyl)-1*H*-indol-2-yl]-ethyl}-3-ethylpiperidinium Triflate (15): Trifluoroacetic acid (24 μL, 0.31 mmol) was added to a solution of **14** (20 mg, 0.039 mmol) and dichloromethane (1 mL). The reaction mixture was stirred at 25 °C for 16 h and concentrated. The crude product was further purified by column chromatography (SiO_2, EtOAc/hexanes 1:5; R_f 0.5) to give **15** (19.0 mg, 0.36 mmol, 93%) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.68 (br., 1 H), 7.98 (d, J = 8.8 Hz, 1 H), 7.54 (d, J = 8.7 Hz, 1 H), 7.26 (dt, J = 8.8, J = 8.7 Hz, 2 H), 4.51 (q, J = 6.5 Hz, 2 H), 4.11 (q, J = 7.0 Hz, 2 H), 3.67 (s, 2 H), 3.43–3.36 (m, 2 H), 3.04–2.94 (m, 2 H), 2.90–2.82 (m, 2 H), 1.85–1.64 (m, 4 H), 1.57–1.47 (m, J = 6.5 Hz, 5 H), 1.34–1.19 (m, 5 H), 1.01 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.9, 152.1, 138.5, 135.2, 129.5, 124.3, 123.2, 118.4, 115.9, 112.6, 63.7, 61.5, 50.3, 44.5, 34.6, 32.0, 30.4, 29.7, 28.2, 20.5, 18.3, 14.3, 14.0, 6.6 ppm. HRMS (ESI-TOF): calcd. for $C_{24}H_{35}N_2O_4$ $[M + H]^+$ 415.2597; found 415.2596.

(*Z*)-3-{2-[3-(Carboxymethyl)-1-(ethoxycarbonyl)-1*H*-indol-2-yl]-vinyl}-3-ethylpiperidinium Chloride (17): Trifluoroacetic acid (310 μL, 4.06 mmol) was added to a solution of **12b** (129.4 mg, 0.23 mmol) and dichloromethane (2 mL). The reaction mixture was stirred at 25 °C for 16 h and concentrated. The residue was redissolved in methanol (10 mL) and treated with Raney nickel (50% slurry in water, 5 mL). The reaction mixture was stirred at 25 °C for 1 h under hydrogen, filtered with a plug of celite, acidified with $HCl_{(aq.)}$ (1 N, 0.5 mL) and concentrated to give **17** (98.6 mg, 0.19 mmol, 86%) as a colourless oil. ^{1}H NMR (300 MHz, [D$_6$]-DMSO): δ = 9.01 (br., 2 H), 8.02 (d, J = 7.8 Hz, 1 H), 7.47 (d, J = 7.4 Hz, 1 H), 7.28 (dd, J = 7.8, J = 7.15 Hz, 1 H), 7.22 (dd, J = 7.4, J = 7.15 Hz, 1 H), 6.39 (d, J = 12.6 Hz, 1 H), 5.71 (d, J = 12.6 Hz, 1 H), 4.37 (q, J = 6.6 Hz, 2 H), 3.59 (s, 2 H), 2.84–2.68 (m, 4 H), 1.55–1.42 (m, 5 H), 1.37–1.32 (m, 4 H), 0.77 (t, J =

5.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.8, 147.8, 137.1, 131.9, 129.3, 126.1, 121.5, 119.9, 117.7, 116.5, 112.0, 111.0, 60.5, 46.4, 45.1, 35.9, 27.7, 26.7, 24.7, 15.0, 11.2, 5.1 ppm. HRMS (ESI): calcd. for $C_{22}H_{29}N_2O_4$ $[M]^+$ 385.2127; found 385.2129.

Ethyl (*Z*)-7-Ethyl-2-oxo-4,5,6,7-tetrahydro-1*H*-3,7-methano[1]azacycloundecino[5,4-*b*]indole-10(2*H*)-carboxylate (20): *N*,*N*-Diisopropylethylamine (91 μL, 0.522 mmol) was added to a mixture of **17** (67 mg, 0.174 mmol), *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluroniumhexafluorophosphate (131 mg, 0.348 mmol), molecular sieves (3 Å, 40 mg) and DMF (17 mL). The reaction mixture was stirred at 25 °C for 48 h and treated with citric $acid_{(aq.)}$ (1 N, 5 mL) and ethyl acetate (10 mL). The organic layer was separated, washed with satd. $NaHCO_{3(aq.)}$ (5 mL) and sat, $NaCl_{(aq.)}$ (5 mL), dried with Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (SiO_2, MeOH/$CHCl_3$ 1:1; R_f 0.5) to give **20** (44.6 mg, 0.12 mmol, 70%) as a light yellow solid, m.p. 145.5–150.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 8.0 Hz, 1 H), 7.37–7.21 (m, 3 H), 6.57 (d, *J* = 12.9 Hz, 1 H), 5.44 (d, *J* = 12.9 Hz, 1 H), 4.61 (d, *J* = 12.8 Hz, 1 H), 4.45 (q, *J* = 7.2 Hz, 2 H), 4.26 (d, *J* = 13.5 Hz, 1 H), 3.93–3.76 (m, 2 H), 2.75 (d, *J* = 13.5 Hz, 1 H), 2.57–2.48 (dd, *J* = 12.8, *J* = 3.5 Hz, 1 H), 1.87–1.82 (m, 2 H), 1.59–1.54 (m, 1 H), 1.43 (t, *J* = 7.2 Hz, 3 H), 1.30–1.20 (m, 3 H), 0.78 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.6, 151.5, 137.6, 135.3, 130.7, 128.9, 124.9, 123.7, 123.0, 118.1, 115.5, 113.7, 63.1, 55.9, 43.6, 43.5, 38.1, 34.9, 32.6, 21.1, 14.3, 7.8 ppm. IR (neat): $\tilde{\nu}$ = 2933, 1733, 1646, 1459, 1375, 1326, 1228, 1143, 1027, 750 cm^{-1}. HRMS (FAB): calcd. for $C_{22}H_{27}N_2O_3$ $[M + H]^+$ 367.2022; found 367.2017.

Ethyl 7-Ethyl-2-oxo-4,5,6,7,8,9-hexahydro-1*H*-3,7-methano[1]azacycloundecino[5,4-*b*]indole-10(2*H*)-carboxylate (16): A mixture of **20** (26 mg, 0.07 mmol), ethanol (2 mL) and Raney nickel (50% slurry in water, 4 mL) was heated to reflux for 12 h under hydrogen, filtered with a plug of celite and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes 1:1; R_f 0.55) to give **16** (55 mg, 0.15 mmol, 74%) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 6.9 Hz, 1 H), 7.71 (d, *J* = 5.7 Hz, 1 H), 7.23 (dt, *J* = 6.9, 5.7 Hz, 2 H), 4.59–4.54 (m, 1 H), 4.46 (q, *J* = 7.2 Hz, 2 H), 4.43–4.41 (m, 1 H), 3.99 (d, *J* = 13.8 Hz, 1 H), 3.48 (d, *J* = 13.8 Hz, 1 H), 3.47–3.44 (m, 1 H), 2.83–2.78 (m, 1 H), 2.71–2.65 (m, 1 H), 2.47–2.42 (m, 1 H), 1.86–1.83 (m, 1 H), 1.62–1.56 (m, 2 H), 1.48 (t, *J* = 7.2 Hz, 3 H), 1.45–1.40 (m, 3 H), 1.23–1.21 (m, 2 H), 0.89 (t, *J* = 7.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.3, 152.0, 140.4, 135.1, 130.2, 123.8, 123.2, 118.6, 115.3, 114.0, 63.0, 54.5, 43.3, 39.8, 34.2, 31.6, 30.1, 27.9, 20.7, 19.8, 14.3, 7.3 ppm. HRMS (FAB): calcd. for $C_{22}H_{28}N_2O_3Na$ $[M + Na]^+$ 391.1998; found 391.1997.

Quebrachamine (1):[6g] Compound **16** (31 mg, 0.085 mmol) in THF (3 mL) was added at 0 °C to a solution of lithium aluminiumhydride (16 mg, 0.425 mmol) in THF (3 mL). After the addition, the reaction mixture was heated to reflux for 2 h, quenched with satd. $NH_4Cl_{(aq.)}$ (1 mL) and extracted with diethyl ether (3 mL). The organic layer was separated, dried with Na_2SO_4 and concentrated to give quebrachamine (15.0 mg, 0.053 mmol, 66%) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (br., 1 H), 7.47 (d, *J* = 6.0 Hz, 1 H), 7.26 (d, *J* = 5.3 Hz, 1 H), 7.09–7.04 (dt, *J* = 6.0, *J* = 5.3 Hz, 2 H), 3.25–3.21 (m, 1 H), 2.93–2.83 (m, 2 H), 2.72–2.66 (m, 2 H), 2.46–2.40 (m, 2 H), 2.39–2.34 (m, 1 H), 2.32–2.23 (m, 1 H), 1.95–1.87 (m, 1 H), 1.60–1.50 (m, 2 H), 1.49–1.47 (m, 1 H), 1.26–1.13 (m, 3 H), 1.11–1.01 (m, 2 H), 0.82 (t, *J* = 7.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.9, 134.8, 128.9, 120.2, 118.7, 117.4, 110.0, 108.7, 56.7, 55.1, 53.3, 37.1, 34.8, 33.5, 32.1, 22.7, 22.5, 22.0, 7.8 ppm. IR (neat): $\tilde{\nu}$ = 3407, 2923, 1645, 1459, 1301, 1133, 1028, 735, 701, 542 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{27}N_2$ $[M + H]^+$ 283.2174; found 283.2180.

[7-Ethyl-4,5,6,7,8,9-hexahydro-1*H*-3,7-methano[1]azacycloundecino[5,4-*b*]indol-10(2*H*)-yl]methanol (21): Compound **16** (80 mg, 0.217 mmol) in THF (10 mL) was added at 0 °C to a solution of lithium aluminiumhydride (42 mg, 1.08 mmol) in THF (5 mL). After the addition, the reaction mixture was heated to reflux for 30 min and quenched with satd. $NH_4Cl_{(aq.)}$ (1 mL). The organic layer was decanted and concentrated to give **21** (52.7 mg, 0.169 mmol, 77%) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 8.4 Hz, 1 H), 7.35 (d, *J* = 7.8 Hz, 1 H), 7.15–7.09 (dt, *J* = 8.4, *J* = 7.8 Hz, 2 H), 5.63–5.57 (m, 2 H), 3.38–3.33 (m, 1 H), 2.89–2.78 (m, 3 H), 2.68–2.66 (m, 1 H), 2.46–2.30 (m, 2 H), 2.29–2.23 (m, 2 H), 2.20 (br., 1 H), 1.89–1.81 (m, 1 H), 1.66–1.47 (m, 3 H), 1.30–1.19 (m, 3 H), 1.17–1.10 (m, 2 H), 0.86 (t, *J* = 7.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.1, 135.4, 128.7, 120.7, 119.5, 117.6, 110.4, 108.4, 66.4, 56.5, 55.2, 53.0, 37.6, 34.7, 32.6, 31.9, 22.6, 22.3, 18.6, 7.8 ppm. HRMS (FAB): calcd. for $C_{20}H_{29}N_2O$ $[M + H]^+$ 313.2280; found 313.2275.

Kopsiyunnanine D (2):[3b] Acetyl chloride (50 μL, 0.7 mmol) was added at 0 °C to a flask containing molecular sieves (3 Å, 100 mg) and methanol (1.5 mL). Compound **21** (12.1 mg, 0.038 mmol) in methanol (0.5 mL) was added to the above flask at 25 °C. The reaction mixture was stirred for 16 h, concentrated, diluted with ethyl acetate (3 mL), washed with satd. $NaHCO_{3(aq.)}$ (3 mL), dried with Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (SiO_2, ethyl acetate/hexanes 1:9; R_f 0.15) to give **2** (7.8 mg, 0.12 mmol, 68%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 6.9 Hz, 1 H), 7.38 (d, *J* = 7.5 Hz, 1 H), 7.10 (dt, *J* = 7.5, *J* = 6.9 Hz, 2 H), 5.47–5.38 (m, 2 H), 3.36–3.32 (m, 1 H), 3.24 (s, 3 H), 2.89–2.80 (m, 3 H), 2.64–2.56 (m, 1 H), 2.46–2.30 (m, 2 H), 2.44–2.22 (m, 2 H), 1.83–1.77 (m, 1 H), 1.66–1.47 (m, 3 H), 1.30–1.19 (m, 3 H), 1.17–1.10 (m, 2 H), 0.85 (t, *J* = 7.5 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.8, 136.8, 128.4, 120.5, 119.2, 117.4, 110.2, 108.8, 73.8, 56.5, 55.6, 55.2, 53.0, 37.5, 34.7, 32.5, 31.8, 22.6, 22.3, 18.5, 7.8 ppm. HRMS (FAB): calcd. for $C_{21}H_{31}N_2O$ $[M + H]^+$ 327.2436; found 327.2442.

Supporting Information (see footnote on the first page of this article): Experimental procedures for compounds **13**, **18** and **19** and copies of the ^{1}H NMR and ^{13}C NMR spectra for the new and key compounds.

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[1] a) J. E. Saxton, in: *The Alkaloids*, vol. 51 (Ed.: G. A. Cordell), Academic Press, New York, **1998**, Chapt. 1; b) G. A. Cordell, in: *The Alkaloids*, vol. 17 (Ed.: R. H. F. Manske, R. G. A. Rodrigo), Academic Press, New York, **1979**, p. 199.

[2] a) J. A. Joule, in: *The Alkaloids*, vol. 1 (Ed.: J. E. Saxton), The Chemical Society, London, **1971**, p. 178; b) H. F. Deutsch, M. A. Evenson, P. Drescher, C. Sparwasser, P. O. Madsen, *J. Pharm. Biomed. Anal.* **1994**, *12*, 1283.

[3] a) M. A. Beniddir, M.-T. Martin, M.-E. T. H. Dau, P. Grellier, P. Rasoanaivo, F. Guéritte, M. Litaudon, *Org. Lett.* **2012**, *14*, 4162; b) Y. Wu, M. Suehiro, M. Kitajima, T. Matsuzaki, S.

Hashimoto, M. Nagaoka, R. Zhang, H. Takayama, *J. Nat. Prod.* **2009**, *72*, 204.
[4] G. Stork, J. E. Dolfini, *J. Am. Chem. Soc.* **1963**, *85*, 2872.
[5] a) I. Coldham, A. J. M. Burrell, L. E. White, H. Adams, N. Oram, *Angew. Chem. Int. Ed.* **2007**, *46*, 6159; *Angew. Chem.* **2007**, *119*, 6271; b) A. J. M. Burrell, I. Coldham, L. Watson, N. Oram, C. D. Pilgram, N. G. Martin, *J. Org. Chem.* **2009**, *74*, 2290; c) W. H. Pearson, A. Aponick, *Org. Lett.* **2006**, *8*, 1661; d) E. S. Sattely, S. J. Meek, S. J. Malcolmson, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2009**, *131*, 943.
[6] a) J. E. Nidhiry, K. R. Prasad, *Tetrahedron* **2013**, *69*, 5525; b) A. G. H. Wee, Q. Yu, *Tetrahedron* **1998**, *54*, 13435; c) T. Fujimura, H. Nakashima, H. Sakagami, T. Taniguchi, K. Ogasawara, *Tetrahedron Lett.* **2002**, *43*, 97; d) S. Takano, M. Yonaga, K. Ogasawara, *J. Chem. Soc., Chem. Commun.* **1981**, 1153; e) S. B. Mandal, V. S. Giri, M. S. Sabeena, S. C. Pakrashi, *J. Org. Chem.* **1988**, *53*, 4237; f) M. Node, H. Nagasawa, K. Fuji, *J. Org. Chem.* **1990**, *55*, 517; g) M. Amat, O. Lozano, C. Escolano, E. Molins, J. Bosch, *J. Org. Chem.* **2007**, *72*, 4431; h) O. Temme, S.-A. Taj, P. G. Andersson, *J. Org. Chem.* **1998**, *63*, 6007; i) Y. Ban, K. Yoshida, J. Goto, T. Oishi, *J. Am. Chem. Soc.* **1981**, *103*, 6990; j) S. A. Kozmin, T. Iwama, Y. Huang, V. H. Rawal, *J. Am. Chem. Soc.* **2002**, *124*, 4628.
[7] B. Bajtos, B. L. Pagenkopf, *Eur. J. Org. Chem.* **2009**, 1072.
[8] For reviews on the formation of medium-sized heterocycles, see: a) U. Nubbemeyer, in: *Topics in Current Chemistry* (Ed.: P. Metz), Springer, Berlin, Heidelberg, **2001**, vol. 216, p. 125–196; b) H. M. C. Ferraz, I. Bombonato, L. S. Longo Jr., *Synthesis* **2007**, 3261; c) P. A. Evans, A. B. Holmes, *Tetrahedron* **1991**, *47*, 9131; d) S. K. Chattopadhyay, S. Karmakar, T. Biswas, K. C. Majumdar, H. Rahaman, B. Roy, *Tetrahedron* **2007**, *63*, 3919.
[9] D. E. Levy, D.-X. Wang, Q. Lu, Z. Chen, J. Perumattam, Y.-j. Xu, A. Liclican, J. Higaki, H. Dong, M. Laney, B. Mavunkel, S. Dugar, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2390.
[10] a) P. S. Baran, R. A. Shenvi, *J. Am. Chem. Soc.* **2006**, *128*, 14028; b) S. Soto, E. Vaz, C. Dell'Aversana, R. Álvarez, L. Altucci, Á. R. de Lera, *Org. Biomol. Chem.* **2012**, *10*, 2101.
[11] a) X. Hong, J. M. Mejía-Oneto, S. France, A. Padwa, *ARKIVOC* **2007**, 125; b) A. Padwa, A. T. Price, *J. Org. Chem.* **1998**, *63*, 556; c) T. R. Govindachari, S. Rajeswari, *Indian J. Chem. Sect. B: Org. Chem. Incl. Med. Chem.* **1983**, *22*, 531; d) C. F. Koelsch, *J. Am. Chem. Soc.* **1943**, *65*, 2458.
[12] a) D. Seyferth, R. S. Marmor, P. Hilbert, *J. Org. Chem.* **1971**, *36*, 1379; b) J. C. Gilbert, U. Weerasooriya, *J. Org. Chem.* **1982**, *47*, 1837; c) S. Müller, B. Liepold, G. Roth, H. J. Bestmann, *Synlett* **1996**, 521.
[13] a) P. J. Black, E. A. Hecker, P. Magnus, *Tetrahedron Lett.* **2007**, *48*, 6364; b) S. Sumi, K. Matsumoto, H. Tokuyama, T. Fukuyama, *Org. Lett.* **2003**, *5*, 1891; c) S. Sumi, K. Matsumoto, H. Tokuyama, T. Fukuyama, *Tetrahedron* **2003**, *59*, 8571; d) P. S. Baran, R. A. Shenvi, C. A. Mitsos, *Angew. Chem. Int. Ed.* **2005**, *44*, 3714; *Angew. Chem.* **2005**, *117*, 3780; e) H. Tokuyama, Y. Kaburagi, X. Chen, T. Fukuyama, *Synthesis* **2000**, 429.
[14] P. Siemsen, R. C. Livingston, F. Diederich, *Angew. Chem. Int. Ed.* **2000**, *39*, 2632; *Angew. Chem.* **2000**, *112*, 2740.
[15] a) R. Chinchilla, C. Najera, *Chem. Rev.* **2007**, *107*, 874; b) J.-H. Li, Y. Liang, Y.-X. Xie, *J. Org. Chem.* **2005**, *70*, 4393.
[16] The condensation reactions of **15** gave the starting material or the byproduct derived from **15** through loss of its ethyl carbamate group. The ethyl carbamate was also hydrolyzed during the saponification of **15**, intended to produce the carboxylic acid.
[17] The corresponding Pd/C-catalyzed hydrogenation of Boc-deprotected **12b** gave a 1:1 mixture of **17** and **18**.
[18] H.-C. Hsu, D.-R. Hou, *Tetrahedron Lett.* **2009**, *50*, 7169.

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