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Full Stereochemical Assignment and Synthesis of the Potent Anthelmintic Pyrrolobenzoxazine Natural Product CJ-12662

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The structure of the unusual anthelmintic pyrrolobenzoxazine terpenoid natural product CJ-12662 was established by X-ray crystallography and partial synthesis from 2-chloronitrobenzene. An unusual Meisenheimer-type rearrangement was used to provide the core pyrrolobenzoxazine heterocycle, and coupling of a tetracyclic pyrrolobenzoxazine lactone with the terpene alcohol was used to complete the synthesis of CJ-12662.

Introduction

During a search for novel anthelmintic and ectoparasiticidal compounds, we reported the isolation of a structurally novel natural product, CJ-12662 **1**, from the fermentation broth of *Aspergillus fischeri* var. *thermomutatus* ATCC 18618.[1] CJ-12662 **1** along with UK-88051 **2**,[2] a secondary metabolite produced by a fungus of the *Chrysosporium* species, and CJ-12663 **3**, a minor metabolite also isolated from *Aspergillus fischeri* var. *thermomutatus* ATCC 18618, belong to the unique class of terpenoid pyrrolobenzoxazine natural products (Figure 1). These alkaloids display excellent activities against insect pests, acari, and helminths including free-living nematodes and endo- and ectoparasites afflicting animals. The recent isolation and determination of the constitution of paeciloxazine,[3] a related pyrrolobenzoxazine alkaloid, prompted us to publish further details of our own research on this fascinating class of natural products. Herein we report the full structural elucidation of CJ-12662 **1** using a single-crystal X-ray structure determination. In addition, the structure was confirmed by a partial synthesis of the pyrrolobenzoxazine heterocycle from 2-chloronitrobenzene and its subsequent coupling with the terpene alcohol **4** derived from the selective degradation of the natural product **1**. Of particular note is the use of a double-oxidative cyclization of a tryptophan derivative in the first partial synthesis of CJ-12662 **1**. These results establish a convenient approach to pyrrolobenzoxazine derivatives for the optimization of structure−activity relationships.

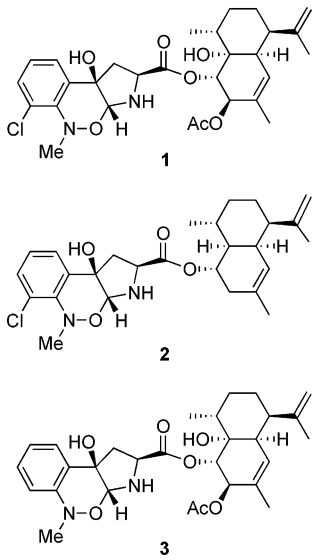

FIGURE 1. Pyrrolobenzoxazine natural products.

Results and Discussion

CJ-12662 **1**, isolated from the fermentation of specimens of *Aspergillus fischeri* var. *thermomutatus* ATCC 18618,[4] gave a 3:1 $(M + H)^+$ ion cluster at *m/z* 561, 563 in the LRLSIMS indicating that the molecule contained one chlorine atom. A HRLSIMS analysis of **1** showed that the mass of the $(M + H)^+$ cluster peak at *m/z* 561.239 was appropriate for a molecular formula of $C_{29}H_{37}ClN_2O_7$ (calcd 561.245) requiring 12 sites of unsaturation. Fortunately, CJ-12662 **1** was obtained as a crystalline solid thereby allowing a single-crystal structure determination (Figure 2). CJ-12662 **1** contains a pyrrolobenzoxazine carboxylic acid esterified with a sesquiterpene diol. The

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(1) Perry, D. A.; Maeda, H.; Tone, J. UK Pat. Appl. 2 240 100, 1991.
(2) Kojima, Y.; Yamauchi, N.; Kojima, N.; Bishop, B. F. Pat. Coop. Treaty WO 95/19363, 1995.
(3) Another terpenoid pyrrolobenzoxazine natural product has recently been isolated: Kanai, Y.; Fujimaki, T.; Kochi, S.; Konno, H.; Kanazawa, S.; Tokumasu, S. *J. Antibiot.* **2004**, *57*, 24−28.

(4) See ref 2 for the experimental procedure for the isolation of CJ-12662 **1**.

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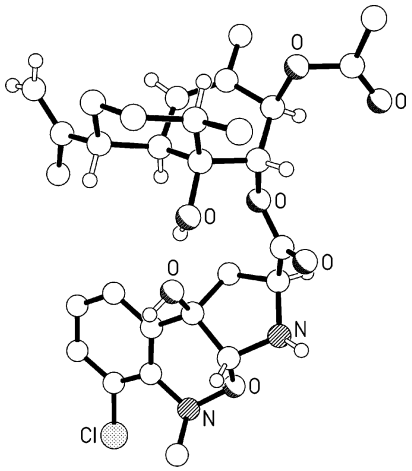
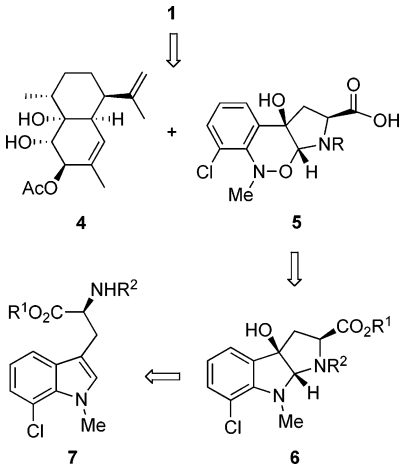


FIGURE 2. X-ray structure of CJ-12662 **1**.

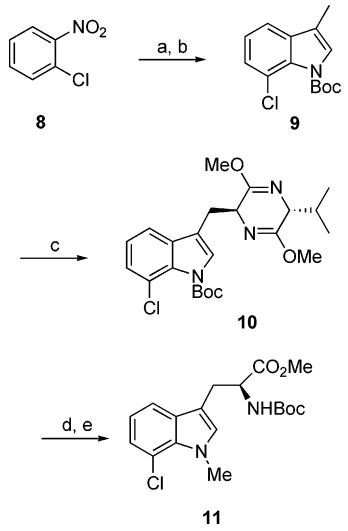
SCHEME 1. Retrosynthesis of CJ-12662 1



absolute stereochemistry of **1** was additionally established by the X-ray crystallographic structure determination.[5] To the best of our knowledge, the synthesis of a pyrrolobenzoxazine skeleton has not been previously reported. As a consequence, we sought to establish methodology for the synthesis of this unusual class of alkaloids including **1** using methods, which would be applicable for the preparation of analogues for biological evaluation.

We considered that the oxidation and subsequent rearrangement of a 3-hydroxypyrroloindole precursor should provide the pyrrolobenzoxazine system **5**. In turn, the key 3-hydroxypyrroloindole **6** should be available from the photooxygenation of a tryptophan derivative **7** (Scheme 1).[6] The synthesis of CJ-12662 **1** proceeded via 7-chloro-1-methyltryptophan **11** (Scheme 2). Bartoli reaction[7] of 1-chloro-2-nitrobenzene followed by subsequent Boc protection yielded indole **9**. This product was brominated regioselectively at the 3 position[8] and homologated using the Schöllkopf reagent derived from D-valine.[9,10] Only the desired *trans*-diastereoisomer **10** was obtained. Removal of the Boc group under thermal conditions and *N*-methylation gave the corresponding *N*-methylindole in a one-pot sequence.[11] Hydrolysis of the dihydropyrazine moiety under aqueous acidic conditions and Boc protection of the free amine provided the desired optically pure 7-chloro-1-methyltryptophan **11** in 84% yield.

SCHEME 2[a]



[a] Key: (a) prop-2-enylmagnesium bromide, −40 °C, THF (53%); (b) $(Boc)_2O$, DMAP, MeCN (86%); (c) NBS, AIBN, CCl_4, 80 °C; 2(*R*)-isopropyl-3−6-dimethoxy-2,5-dihydropyrazine, *n*-BuLi (1.1 equiv), −80 °C (71%); (d) xylenes, 160 °C; NaH, MeI, DMF, 0 °C (90%); (e) 2 M HCl/THF, 0−20 °C; $(Boc)_2O$, EtN^iPr_2, 1,4-dioxane, 0−20 °C (84%).

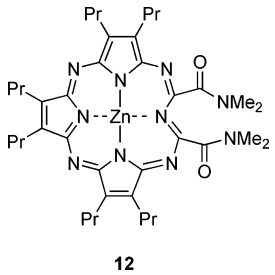


FIGURE 3. Secoporphyrazine **12**.

With tryptophan **11** in hand, formation of the 3-hydroxypyrroloindole moiety was carried out by irradiation of tryptophan **11** in the presence of the secoporphyrazine **12**, a potent singlet oxygen sensitizer ($\Phi_\Delta = 0.54$) (Figure 3).[12,13] Reduction of the intermediate 3-hydroperoxypyrroloindole yielded a separable mixture of diastereoiso-

(5) The absolute stereochemistry of **1** was determined by use of the Flack parameter [$x^+ = +0.02(3)$].

(6) (a) Nagawa, M.; Yokoyama, Y.; Kato, S.; Hino, T. *Tetrahedron* **1985**, *41*, 2125−2132. (b) Nagawa, M.; Kato, S.; Kataoka, S.; Kodato, S.; Watanabe, H.; Okajima, H.; Hino, T.; Wiktop, B. *Chem. Pharm. Bull.* **1981**, *29*, 1013−1026 and references therein.

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(9) Bull, S. D.; Davies, S. G.; Moss, W. O. *Tetrahedron: Asymmetry* **1998**, *9*, 321−327.

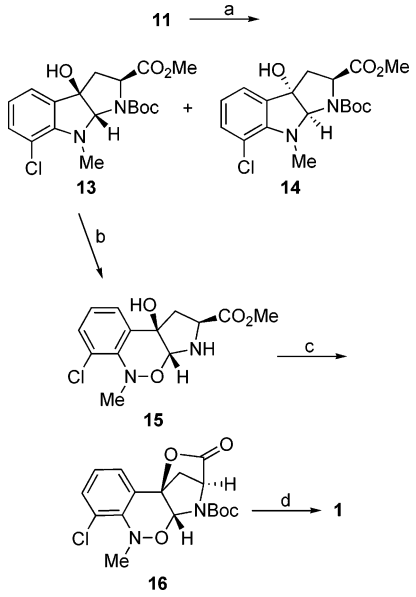
(10) Cook, J. M.; Tong, G.; Liu, R.; Yu, P.; Zhao, S.*J. Org. Chem.* **1997**, *62*, 9298−9304.

(11) Cook, J. M.; Zhao, S.; Liao, X. *Org. Lett*. **2002**, *4*, 687−690.

(12) (a) Garrido Montalban, A.; Lange, S. J.; Mani, N. S.; Williams, D. J.; White, A. J. P.; Barrett, A. G. M.; Hoffman, B. M. *J. Org. Chem.* **1997**, *62*, 9284−9289. (b) Trabanco, A. A.; Garrido Montalban, A.; Rumbles, G.; Barrett, A. G. M.; Hoffman, B. M. *Synlett* **2000**, 1010−1012.

(13) The rate of reaction with the high quantum yield photosensitizer **12** was approximately four times that using Rose Bengal.

SCHEME 3[a]



[a] Key: (a) O_2, **12** (cat.), $h\nu$, 500 W halogen lamp, MeOH, −30 °C; Me_2S, MeOH, 0 °C (58%); (b) *m*-CPBA, CH_2Cl_2, 0 °C; 1 M HCl/EtOAc, 20 °C (61%); (c) $(Boc)_2O$, DMAP, MeCN, 20 °C; 2 M NaOH/THF, 20 °C; EDCI, HOBT, EtN^iPr_2, CH_2Cl_2, 20 °C (79%); (d) terpene **4**, *t*-BuOK (cat.), CH_2Cl_2, 20 °C; 1 M HCl/Et_2O, 20 °C (57%).

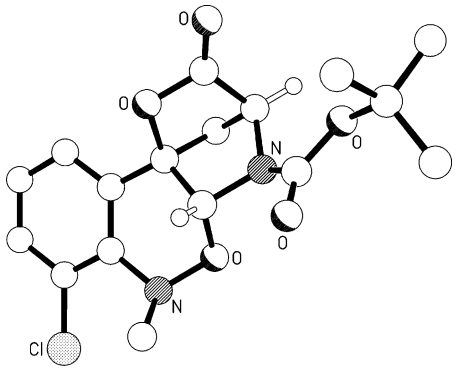


FIGURE 4. X-ray structure of **16**.

mers **13** and **14** (1:1) (Scheme 3). We were delighted to observe that oxidation of amine **13** followed by careful treatment under acidic conditions afforded pyrrolobenzoxazine **15** in 61% yield as a single diastereoisomer.[14] This unusual Meisenheimer-type rearrangement[15] provides convenient access to the pyrrolobenzoxazine moiety. To complete the synthesis of **1**, amino alcohol **15** was doubly Boc protected, saponified, and cyclized to afford pyrrolobenzoxazine **16** (79%). At this stage, a crystal structure of the key pyrrolobenzoxazine ring system was obtained (Figure 4), thereby confirming the insertion of the oxygen atom at the correct position and the absolute stereochemistry of the molecule. Finally, lactone **16** was coupled with terpene **4** by transacylation to afford CJ-12662 **1** in 57% yield as a single diastereoisomer after deprotection. All spectroscopic data of the synthetic compound (NMR, optical rotation,[16] mass, IR) were identical to those of the natural product.

Conclusion

The full structural assignment of a novel natural product CJ-12662 **1**, isolated from *Aspergillus fischeri* var. *thermomutatus* ATCC 18618, has been established by crystal structure analysis. The pyrrolobenzoxazine moiety was synthesized in a concise manner utilizing dye-sensitized photooxygenation of a tryptophan derivative and an unusual Meisenheimer-type rearrangement reaction. The synthetic pyrrolobenzoxazine was converted into CJ-12662 **1** using a transacylation protocol. Applications of the methodology to the synthesis of other pyrrolobenzoxazine alkaloids will be reported in due course.

Experimental Section

A full description of the scale-up fermentation and isolation of CJ-12662 **1** including its spectroscopic data is already published in patent format.[4]

(1*S*,2*R*,4a*S*,5*R*,8*R*,8a*R*)-1,8a-Dihydroxy-5-isopropenyl-3,8-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-2-yl Acetate 4. An isolated sample of CJ-12662 **1** (2.9 g), MeOH (20 mL), and Et_3N (300 μL) was allowed to stand for 3 h. Rotary evaporation and chromatography (hexanes/Et_2O 1:1) gave terpene **5** (1.34 g, 88%) as a white solid: mp 171−173 °C (from Et_2O); TLC (hexanes/Et_2O 1:1) R_f = 0.22; $[\alpha]^{22}_D$ −51.2 (*c* 1.00, $CHCl_3$); IR (film) 3442, 3318, 1731, 1639, 1450, 1367, 1238, 1143, 1018, 968, 885, 740 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 0.84 (d, 3 H, J = 6.7 Hz), 1.30−1.57 (m, 4 H), 1.62 (s, 3 H), 1.72 (s, 3 H), 1.92−1.96 (m, 1 H), 2.05 (s, 3 H), 2.51−2.54 (m, 1 H), 2.76−2.78 (m, 1 H), 3.14 (s, 1 H), 3.85 (dd, 1 H, J = 4.3, 1.6 Hz), 4.34 (d, 1 H, J = 4.3 Hz), 4.70 (s, 1 H), 4.93 (s, 1 H), 5.12 (s, 1 H), 5.38 (s, 1 H); ^{13}C NMR (125 MHz, acetone-d_6) δ 15.3, 20.2, 20.9, 22.6, 27.0, 31.4, 31.5, 39.4, 41.9, 72.0, 73.3, 76.2, 110.9, 127.8, 130.5, 148.7, 170.6; MS (CI) *m/z* 384 $(M + NH_4)^+$; HRMS (CI) *m/z* calcd for $C_{17}H_{30}NO_4$ $(M + NH_4)^+$ 312.2174, found $(M + NH_4)^+$ 312.2186. Further elution with Et_2O (100%) gave also pyrrolobenzoxazine **15** (1.49 g, 97%).

***tert*-Butyl 7-Chloro-3-methylindole-1-carboxylate 9.** Prop-2-enylmagnesium bromide in THF (100 mL, 50.0 mmol, 3.15 equiv) was added dropwise with stirring to 1-chloro-2-nitrobenzene (2.5 g, 15.9 mmol) in THF (100 mL) at −40 °C under argon. Stirring was continued for 1 h, after which time the reaction was quenched by the addition of aqueous HCl (10%, 30 mL) and immediately extracted with Et_2O (50 mL). The separated organic layer was dried (Na_2SO_4), concentrated, and chromatographed (hexanes/CH_2Cl_2 1:1) to afford 7-chloro-3-methylindole (1.4 g, 53%) as a white solid. Di-*tert*-butyl dicarbonate (2.23 g, 10.2 mmol, 1.2 equiv) and DMAP (60 mg, 0.49 mmol, 0.06 equiv) were added to 7-chloro-3-methylindole (1.4 g, 8.5 mmol) in MeCN (20 mL). The mixture was allowed to stand for 12 h and rotary evaporated. The residue was dissolved in Et_2O (50 mL) and washed with HCl in H_2O (1 M; 2 × 10 mL). The organic layer was dried (Na_2SO_4) and concentrated to afford a brown solid, which was recrystallized from hexanes to afford indole **9** (1.9 g, 86%) as a light yellow solid: mp 62−64 °C (from hexanes); TLC (hexanes/CH_2Cl_2 2:1) R_f = 0.38; IR (film) 1753, 1731, 1418, 1369, 1340, 1261, 1237, 1156, 1113, 1018, 849 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.67

(14) Synthetic ester **15** was identical (NMR, MS, IR, optical rotation) with an authentic sample prepared by chemical degradation of CJ-12662 **1**.

(15) (a) Nagawa, M.; Okajima, H.; Hino, T. *J. Am. Chem. Soc.* **1976**, *98*, 635−637. (b) Nagawa, M.; Yoshikawa, K.; Hino, T. *J. Am. Chem. Soc.* **1975**, *97*, 6496−6501. (c) Nagawa, M.; Kaneko, T.; Yoshikawa, K.; Hino, T. *J. Am. Chem. Soc.* **1974**, *96*, 624−625.

(16) The optical rotation of the natural product **1** was $[\alpha]^{22}_D$ −305.0, *c* 0.50, $CHCl_3$.

(s, 9 H), 2.26 (s, 3 H), 7.19−7.42 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.6, 28.0, 83.9, 115.9, 117.6, 120.6, 123.4, 126.4, 126.5, 132.4, 135.0, 149.0; MS (CI) *m/z* 283 $(M + NH_4)^+$; HRMS (CI) *m/z* calcd for $C_{14}H_{20}ClN_2O_2$ $(M + NH_4)^+$ 283.1213, found $(M + NH_4)^+$ 283.1206. Anal. Calcd for $C_{14}H_{16}ClNO_2$: C, 63.28; H, 6.07; N, 5.27. Found C, 63.27; H, 6.19; N, 5.20.

***tert*-Butyl 7-Chloro-3-(5*R*-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2*S*-ylmethyl)indole-1-carboxylate 10.** Indole **9** (7.3 g, 27.5 mmol) in CCl_4 (150 mL) was heated to reflux when an intimate mixture of recrystallized (H_2O) *N*-bromosuccinimide (5.9 g, 33.0 mmol, 1.2 equiv) and AIBN (290 mg, 1.8 mmol, 0.06 equiv) was added in three portions over 3 min. The mixture was heated to reflux for 20 min, when additional AIBN (150 mg, 0.91 mmol, 0.03 equiv) was added. The mixture was kept at reflux for 50 min and allowed to cool. The precipitated succinimide was filtered off and leached with hexane (4 × 10 mL). Rotary evaporation of the combined filtrates gave crude 3-(bromomethyl)indole (8.7 g, 92%) as a brown oil. The crude material was flash evaporated under reduced pressure from dry THF solution three times and used directly in the next step without further purification. *n*-BuLi (2.3M, 12.1 mL, 26.6 mmol, 1.1 equiv) was added dropwise with stirring to 2(*R*)-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine (5.1 g, 27.8 mmol, 1.1 equiv) in dry THF (100 mL) under nitrogen at −78 °C. After 30 min, crude 3-(bromomethyl)indole (8.7 g, 25.3 mmol) in THF (50 mL) was added dropwise, and the mixture was stirred at −78 °C for 4 days and allowed to slowly warm to room temperature. The solution was concentrated under reduced pressure and diluted with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL), and the combined organic layers were washed with brine (30 mL) and dried (Na_2SO_4). Rotary evaporation and chromatography (hexanes/EtOAc 4:1) gave indole **10** (8.7 g, 71%) as a yellow oil: TLC (hexanes/EtOAc 2:1) R_f = 0.74; $[\alpha]^{22}_D$ −178.0 (*c* 1.00, $CHCl_3$); IR (film) 1757, 1735, 1696, 1461, 1436, 1369, 1347, 1238, 1194, 1156, 1116, 1014, 843, 774, 762 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.63, 0.94 (2d, 6 H, J = 6.8 Hz), 1.62 (s, 9 H), 2.12−2.19 (m, 1 H), 3.14 (dd, 1 H, J = 14.5, 5.6 Hz), 3.20 (dd, 1 H, J = 14.5, 3.8 Hz), 3.54−3.56 (m, 1 H), 3.65 (s, 3 H), 3.67 (s, 3 H), 4.28−4.33 (m, 1 H), 7.10−7.14 (m, 1 H), 7.27 (d, 1 H, J = 7.2 Hz), 7.31 (s, 1 H), 7.49 (d, 1 H, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6, 18.9, 27.9, 29.1, 31.6, 52.2, 52.3, 55.9, 60.6, 83.8, 116.0, 118.2, 120.3, 123.0, 126.2, 127.8, 132.0, 134.9, 148.7, 162.4, 164.1; MS (CI) *m/z* 448 $(M + H)^+$; HRMS (CI) *m/z* calcd for $C_{23}H_{31}ClN_3O_4$ $(M + H)^+$ 448.2003, found $(M + H)^+$ 448.2002. Anal. Calcd for $C_{23}H_{30}ClN_3O_4$: C, 61.67; H, 6.75; N, 9.38. Found: C, 61.62; H, 6.64; N, 9.28.

Methyl (2*S*)-2-*tert*-Butoxycarbonylamino-3-(7-chloro-1-methyl-1*H*-indol-3-yl)propanoate 11. Carbamate **10** (5.6 g, 12.5 mmol) in xylenes (300 mL) was degassed and heated at reflux for 36 h. After rotary evaporation, the residue was flash evaporated under reduced pressure with dry THF three times and used directly in the next step without further purification. MeI (940 μL, 15.0 mmol, 1.2 equiv) was added to the crude product in dry DMF (100 mL) at 0 °C. NaH (360 mg, 15.0 mmol, 1.2 equiv) was added slowly, and the reaction mixture was stirred at 0 °C for 2 h. Cold H_2O (30 mL) and EtOAc (150 mL) were added sequentially, and the organic layer was washed with H_2O (4 × 50 mL) and dried (Na_2SO_4). Rotary evaporation and chromatography (hexanes/EtOAc 4:1) gave (3*S*,6*R*)-3-[(1-methyl-7-chloro-3-indolyl)methyl]-3,6-dihydro-6-isopropyl-2,5-dimethoxypyrazine (4.1 g) as a yellow oil, which was used directly without further purification. HCl in H_2O (2M; 8 mL) was added to an aliquot of the oil (1.0 g, 2.8 mmol) in THF (25 mL) at 0 °C. The mixture was stirred and allowed to warm to room temperature. After 1.5 h, the mixture was concentrated by evaporation under reduced pressure and the residue dissolved in 1,4-dioxane (25 mL) and cooled to 0 °C. Di-*tert*-butyl dicarbonate (1.3 g, 6.1 mmol, 2.2 equiv) and ^{i}Pr$_2$NEt (1.45 mL, 8.3 mmol, 3.0 equiv) were added, and the reaction mixture was allowed to warm to room temperature and stirred for 2 h. The solution was rotary evaporated and chromatographed (hexanes/EtOAc 4:1) to afford the tryptophan derivative **11** (850 mg, 84%) as a colorless oil: TLC (hexanes/EtOAc 2:1) R_f = 0.66; $[\alpha]^{22}_D$ +27.3 (*c* 1.00, $CHCl_3$); IR (film) 3406, 1744, 1713, 1490, 1456, 1366, 1166, 1077, 1059, 863, 780, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9 H), 3.17−3.28 (m, 2 H), 3.67 (s, 3 H), 4.08 (s, 3 H), 4.62 (dd, 1 H, J = 13.2, 5.4 Hz), 5.07 (d, 1 H, J = 7.8 Hz), 6.78 (s, 1 H), 6.94−6.98 (m, 1 H), 7.12 (d, 1 H, J = 7.2 Hz), 7.39 (d, 1 H, J = 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 28.3, 36.5, 52.2, 54.0, 79.8, 108.8, 117.0, 117.6, 119.8, 123.2, 130.1, 131.3, 132.1, 155.1, 172.5; MS (CI) *m/z* 367 $(M + H)^+$; HRMS (CI) *m/z* calcd for $C_{18}H_{24}ClN_2O_4$ $(M + H)^+$ 367.1425, found $(M + H)^+$ 367.1427. Anal. Calcd for $C_{18}H_{23}ClN_2O_4$: C, 58.93; H, 6.32; N, 7.64. Found: C, 58.74; H, 6.47; N, 7.41.

Methyl (2*S*,3a*R*,8a*S*)-7-Chloro-3a-hydroxy-8-methyl-3,3a,8,8a-tetrahydro-2*H*-pyrrolo[2,3-*b*]indole-1,2-dicarboxylate 13 and Methyl (2*S*,3a*S*,8a*R*)-7-Chloro-3a-hydroxy-8-methyl-3,3a,8,8a-tetrahydro-2*H*-pyrrolo[2,3-*b*]indole-1,2-dicarboxylate 14. Indole **11** (1.5 g, 4.1 mmol) and porphyrazine **12** (150 mg, 0.41 mmol, 0.05 equiv) in MeOH (300 mL) was irradiated at −30 °C (temperature of the reaction mixture) by a 500 W halogen lamp while a stream of oxygen was bubbled through the reaction vessel. After 90 min, Me_2S (10 mL) was added, and the reaction mixture was stirred for 2 h at −30 °C. Rotary evaporation and chromatography (CH_2Cl_2/EtOAc/Et_2O 15:1:1) gave alcohol **13** (463 mg, 30%) and alcohol **14** (446 mg, 28%) both as an orange oils. Alcohol **13**: TLC (CH_2Cl_2/EtOAc/Et_2O 8:1:1) R_f = 0.77; $[\alpha]^{22}_D$ −80.9 (*c* 1.00, $CHCl_3$); IR (film) 3441, 1756, 1708, 1606, 1472, 1368, 1200, 1164, 1050, 969, 784, 751 cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2$SO, 413 K) δ 1.45 (s, 9 H), 2.35 (dd, 1 H, J = 13.3, 5.6 Hz), 2.42 (dd, 1 H, J = 13.3, 8.3 Hz), 3.30 (s, 3 H), 3.69 (s, 3 H), 4.05−4.15 (m, 1 H), 5.08 (s, 1 H), 6.81 (t, 1 H, J = 7.5 Hz), 7.15−7.18 (m, 2 H); ^{13}C NMR (125 MHz, $(CD_3)_2$SO, 413 K) δ 27.3, 38.5, 41.3, 50.7, 58.9, 79.5, 83.9, 91.4, 115.1, 120.2, 121.0, 130.1, 135.7, 145.7, 153.3, 171.1; MS (CI) *m/z* 383 $(M + H)^+$; HRMS (CI) *m/z* calcd for $C_{18}H_{24}ClN_2O_5$ $(M + H)^+$ 383.1374, found $(M + H)^+$ 383.1376. Anal. Calcd for $C_{18}H_{23}ClN_2O_5$: C, 56.47; H, 6.06; N, 7.32. Found: C, 56.59; H, 5.93; N, 7.18. Alcohol **14**: TLC (CH_2Cl_2/EtOAc/Et_2O 8:1:1) R_f = 0.67; $[\alpha]^{22}_D$ +83.5 (*c* 1.00, $CHCl_3$); IR (film) 3418, 1739, 1706, 1681, 1606, 1475, 1393, 1368, 1310, 1164, 1121, 1051, 965, 751 cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2$SO, 373 K) δ 1.46 (s, 9 H), 2.23 (dd, 1 H, J = 13.1, 5.1 Hz), 2.57 (dd, 1 H, J = 13.1, 8.8 Hz), 3.27 (s, 3 H), 3.39 (s, 3 H), 4.58 (dd, 1 H, J = 8.8, 5.1 Hz), 5.08 (s, 1 H), 5.83 (s, 1 H), 6.69 (t, 1 H, J = 7.5 Hz), 7.07−7.10 (m, 2 H); ^{13}C NMR (125 MHz, $(CD_3)_2$SO, 373 K) δ 27.5, 36.0, 41.6, 50.9, 59.0, 79.5, 84.0, 90.6, 113.6, 119.1, 121.3, 130.4, 134.8, 145.1, 153.4, 170.8; MS (CI) *m/z* 383 $(M + H)^+$; HRMS (CI) *m/z* calcd for $C_{18}H_{24}ClN_2O_5$ $(M + H)^+$ 383.1374, found $(M + H)^+$ 383.1376. Anal. Calcd for $C_{18}H_{23}ClN_2O_5$: C, 56.47; H, 6.06; N, 7.32. Found: C, 56.54; H, 6.06; N, 7.23.

Methyl (2*S*,3a*R*,9b*R*)-6-Chloro-9b-hydroxy-5-methyl-1,2,3,3a,5,9b-hexahydro-4-oxa-3,5-diazacyclopenta[*a*]naphthalene-2-carboxylate 15. *m*-CPBA (61 mg, 0.33 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) was added dropwise with stirring to amine **13** (100 mg, 0.35 mmol) in CH_2Cl_2 (2 mL) at 0 °C. After 30 min, additional *m*-CPBA (61 mg, 0.35 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) was added dropwise and stirring continued at 0 °C for a further 30 min. The solution was diluted with CH_2Cl_2 (5 mL), washed with 10% aqueous Na_2CO_3, dried (Na_2SO_4), and rotary evaporated. HCl in EtOAc (1 M; 5 mL) was added with stirring to the residue. After 1 h, the solution was concentrated under reduced pressure, and saturated aqueous $NaHCO_3$ was added to pH 8. The mixture was extracted with CH_2Cl_2 (2 × 10 mL), and the organic layer was dried (Na_2SO_4). Rotary evaporation and chromatography (hexanes/EtOAc 1:1) gave ester **15** (64 mg, 61% yield) as a yellow oil: TLC (hexanes/EtOAc 1:1) R_f = 0.13; $[\alpha]^{22}_D$ +19.6 (*c* 1.00, $CHCl_3$); IR (film) 3381 (br), 1737, 1568, 1438, 1334, 1235, 1219, 1070, 1006, 934, 791, 759 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ

2.28 (dd, 1 H, J = 13.3, 9.3 Hz), 2.50 (d, 1 H, J = 13.3 Hz), 3.24 (s, 3 H), 3.71 (s, 3 H), 3.92−3.94 (m, 1 H, J = 9.3, 1.5 Hz), 5.23 (s, 1 H), 7.06 (t, 1 H, J = 7.8 Hz), 7.25 (dd, 1 H, J = 7.8, 1.5 Hz), 7.51 (dd, 1 H, J = 7.8, 1.5 Hz); ^{13}C NMR (125 MHz, acetone-d_6) δ 42.1, 42.5, 52.3, 58.6, 76.1, 86.2, 123.6, 125.3, 127.4, 129.8, 135.0, 145.0, 176.1; MS (CI) *m/z* 299 (M + H)$^+$; HRMS (CI) *m/z* calcd for $C_{13}H_{16}ClN_2O_4$ (M + H)$^+$ 299.0799, found (M + H)$^+$ 299.0800. Anal. Calcd for $C_{13}H_{15}ClN_2O_4$: C, 52.27; H, 5.06; N, 9.38. Found: C, 52.39; H, 5.00; N, 9.16.

Lactone 16. Di-*tert*-butyl dicarbonate (161 mg, 0.34 mmol, 2.2 equiv) and DMAP (4 mg, 0.07 mmol, 0.1 equiv) were added to amine **15** (100 mg, 0.34 mmol) in MeCN (3 mL). After 4 h, rotary evaporation gave a residue, which was dissolved in Et_2O (5 mL) and washed with aqueous HCl (0.1 M; 3 mL). The organic layer was dried (Na_2SO_4) and rotary evaporated. The residue was dissolved in EtOH (3 mL) and treated with aqueous NaOH (2 M; 2 mL). After standing overnight, the solution was neutralized with aqueous HCl (1 M). After concentration, the residue was dissolved in aqueous $NaHCO_3$ (10%; 3 mL) and washed with Et_2O (3 mL). The aqueous layer was acidified to pH 1 with aqueous HCl (1 M) and extracted with CH_2Cl_2 (3 × 5 mL), and the organic layer was dried (Na_2SO_4) and rotary evaporated. The crude residue was dissolved in CH_2Cl_2 (3 mL) and EDCI (64 mg, 0.34 mmol, 1.0 equiv), and HOBT (45 mg, 0.34 mmol, 1.0 equiv) and ^{i}PrNEt$_2$ (145 μL, 0.84 mmol, 2.5 equiv) were added. After 3 h, the solution was rotary evaporated. The residue was dissolved in Et_2O (10 mL) and washed successively with aqueous HCl (1 M; 5 mL), H_2O (5 mL), saturated aqueous $NaHCO_3$ (5 mL), H_2O (5 mL), and brine (5 mL). The organic layer was dried (Na_2SO_4), rotary evaporated, and chromatographed (hexanes/EtOAc 3:1) to afford lactone **16** (70 mg, 79%) as a crystalline solid: mp 155−157 °C (from Et_2O/hexanes 1:1); TLC (hexanes/EtOAc 2:1) R_f = 0.51; $[\alpha]^{22}_D$ −26.0 (*c* 0.50, $CHCl_3$); IR (film) 1815, 1722, 1439, 1370, 1289, 1192, 1117, 1070, 1021, 969, 902, 868, 785, 753 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 1.53 (s, 9 H), 2.42 (dd, 1 H, J = 11.0, 1.8 Hz), 2.62 (d, 1 H, J = 11.0 Hz), 3.49 (s, 3 H), 4.68 (s, 1 H), 5.49 (s, 1 H), 7.24 (t, 1 H, J = 7.8 Hz), 7.50 (dd, 1 H, J = 7.8, 1.5 Hz), 7.57 (dd, 1 H, J = 7.8, 1.5 Hz); ^{13}C NMR (75 MHz, acetone-d_6) δ 27.3, 42.1, 43.6, 58.1, 78.2, 81.9, 82.7, 123.0, 123.6, 125.0, 125.5, 131.5, 145.1, 170.3; MS (CI) *m/z* 384 (M + NH$_4$)$^+$; HRMS (CI) *m/z* calcd for $C_{17}H_{23}ClN_3O_5$ (M + NH$_4$)$^+$ 384.1326, found (M + NH$_4$)$^+$ 384.1323.

2*R*-Acetoxy-1*S*,2,4a*S*,5*R*,6,7,8*R*,8a*R*-octahydro-8a-hydroxy-3,8-dimethyl-5-(1-methylethenyl)-1-naphthalenyl-6-chloro-1,2,3,3a*R*,5,9b-hexahydroxy-9b*R*-hydroxy-5-methylpyrrolo[2,3-*c*][2,1]benzoxazine-2*S*-carboxylate 1. *t*-BuOK in THF (1 M; 10 μL, 0.01 mmol, 0.1 equiv) was added with stirring to lactone **16** (40 mg, 0.11 mmol) and terpene **4** (32 mg, 0.11 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL). After 1 h, the solution was rotary evaporated and HCl in Et_2O (2 M; 1 mL) added to the residue. The mixture was stirred 2 h and neutralized with ^{i}PrNEt$_2$ (500 μL). After concentration, the residue was chromatographed (hexanes/EtOAc 1:1) to afford synthetic **1** (26 mg, 57%) as a light yellow oil: TLC (hexanes/EtOAc 1:1) R_f = 0.20; $[\alpha]^{22}_D$ −292.1 (*c* 0.50, $CHCl_3$); IR (film) 3423, 1745, 1644, 1439, 1372, 1232, 1180, 1067, 1020, 992, 790, 758 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 0.92 (d, 3 H, J = 7.0 Hz), 1.35−1.57 (m, 4 H), 1.64 (s, 3 H), 1.89 (s, 3 H), 2.07−2.09 (m, 1 H), 2.10 (s, 3 H), 2.25−2.30 (m, 1 H), 2.61 (d, 1 H, J = 13.5 Hz), 2.67 (d, 1 H, J = 13.5 Hz), 2.81 (br, 1 H), 2.89−2.91 (m, 1 H), 3.25 (s, 3 H), 3.45−3.47 (m, 1 H), 4.03 (d, 1 H, J = 7.5 Hz), 4.75−4.78 (m, 1 H), 4.99−5.02 (m, 1 H), 5.15 (s, 1 H), 5.25 (d, 1 H,, J = 2.0 Hz), 5.30 (s, 1 H), 5.36 (d, 1 H, J = 2.0 Hz), 5.49 (s, 1 H), 7.09 (t, 1 H, J = 8.0 Hz), 7.27 (dd, 1 H, J = 8.0, 1.5 Hz), 7.50 (dd, 1 H, J = 8.0, 1.5 Hz); ^{13}C NMR (125 MHz, acetone-d_6) δ 16.4, 21.0, 21.8, 23.8, 27.9, 32.2, 32.6, 41.8, 42.7, 43.0, 43.1, 60.1, 73.9, 74.3, 75.8, 77.4, 86.5, 112.5, 124.8, 126.3, 128.2, 129.0, 131.1, 132.0, 135.5, 146.3, 149.1, 171.2, 175.4; MS (CI) *m/z* 561 (M + H)$^+$; HRMS (CI) *m/z* calcd for $C_{29}H_{38}ClN_2O_7$:(M + H)$^+$ 561.2368, found (M + H)$^+$ 561.2363. Anal. Calcd for $C_{29}H_{37}ClN_2O_7$: C, 62.08; H, 6.65; N, 4.99. Found: C, 61.94; H, 6.55; N, 4.91.

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Supporting Information Available: Structural data for all new compounds, as well as X-ray structure data for compound **1** and **16** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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