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A CONCISE SYNTHESIS OF THE PYRROLOQUINOLINE NUCLEUS OF THE MAKALUVAMINE ALKALOIDS

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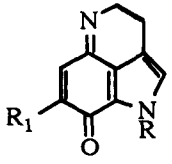
Abstract: A concise five step synthesis of the pyrroloquinoline related to makaluvamine, and discorhabdine from 1,2-dimethoxy-3,5-dinitrobenzene is developed.

The pyrrolo[4,3,2-de]quinolines constitute a group of natural compounds distributed in the parotid glands of the south American toad[1] and several marine alkaloids such as makaluvamine(A-F),[2] damirone,[3] batzellinec[4] and discorhabdine.



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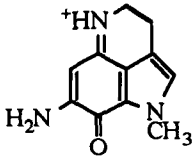
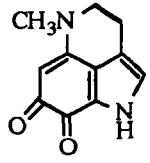
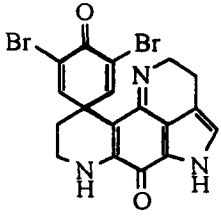


Makaluvamine A



Damirone B

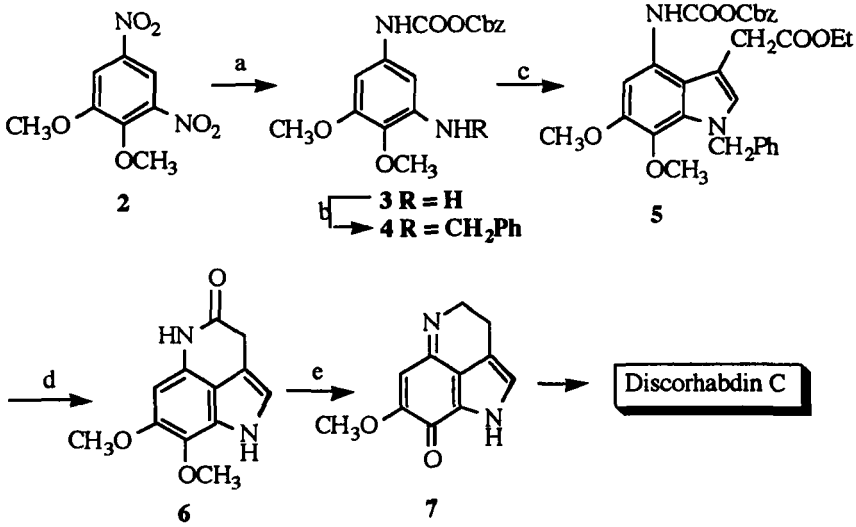


Discorhabdin C

These marine alkaloids exhibit potent *in vitro* cytotoxicity toward the human colon tumor cell-line HCT 116, show differential toxicity toward the topoisomerase II sensitive CHO cell line xrs-6, and inhibit topoisomerase II *in vitro*.[6] Efficient

total and partial synthesis of this class of compounds are synthetic challenges that have received much attention in recent years. Several groups have described the synthesis of the tricyclic system of this group and some related alkaloids.[7]

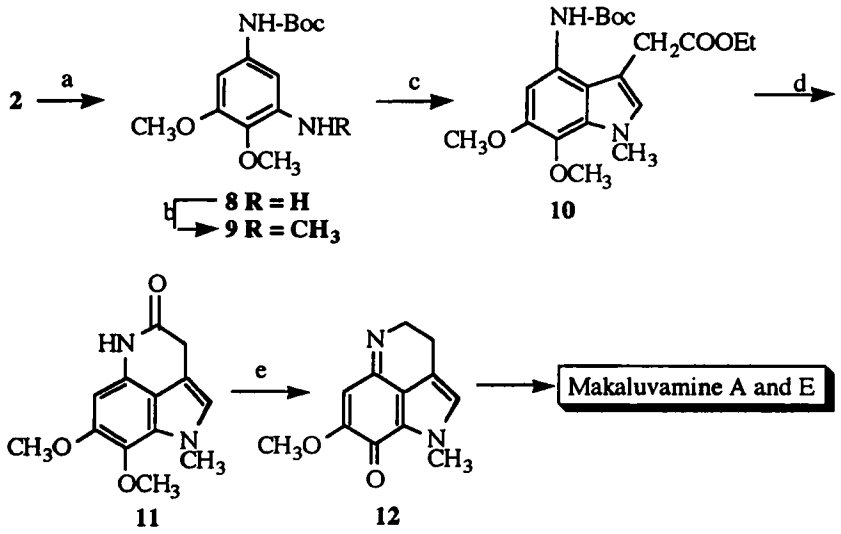
In a recent communication, we described the synthesis of pyrroloquinoline (**1**).[8] Using a different strategy, we now wish to report a practical five step regioselective synthesis of a key intermediate from the known 1,2-dimethoxy-3,5-dinitrobenzene (**2**).[9] This approach is more concise than previously reported syntheses.



Scheme I: a) H_2/Pd/C, benzyl chloroformate and triethylamine; b) PhCHO, $NaBH_3CN$; c) ethyl 4-chloroacetoacetate; d) H_2/Pd/black, 60% $HClO_4$, KOH, then EDCI; e) BH_3•SMe_2 then CAN.

This methodology involves the selective protection of 1,5-diamino-2,3-dimethoxybenzene prepared from hydrogenation of **2**. Thus hydrogenation of **2** over palladium on charcoal in methanol and then treatment with benzyl chloroformate or di-*tert*-butyl dicarbonate give **3** (scheme I) and **8** (scheme II) in 87% and 95% yield respectively. Treatment of **3** with benzaldehyde and sodium cyanoborohydride or **8** with dimethyl sulfate give **4** and **9** in 97% and 71% yield respectively. Reaction of **4** or **9** with ethyl chloroacetoacetate afforded indole **5** and

10 in 69% and 74% yield respectively. Hydrogenation of **5** over Pd-black under acidic conditions to remove benzyl and Cbz groups followed by alkaline hydrolysis afforded an unstable amino acid which was directly treated with 1-(3-dimethylaminopropyl)-3-ethylcarbo-diimide hydrochoride (EDCI) to yield lactam **6**



Scheme II: a) H_2/Pd/C, *tert*-butyl dicarbonate and NaOH; b) dimethyl sulfate and triethylamine; c) ethyl 4-chloroacetoacetate; d) HCl, KOH, then EDCI; e) BH_3•SMe_2 then CAN.

in 45% yield. Stepwise deprotection of **10** under standard conditions followed by ring closure in the presence of EDCI provided lactam **11** in 75% yield. Reduction of **6** and **11** with borane-methyl sulfide complex, followed by reaction with ceric ammonium nitrate under the conditions described in the literature[7d] afforded the pyrroloquinoline nucleus **7** and **12**, which are readily to converted to dicorhabdin C, makaluvamine A and E.[7]

Experimental

^{1}H-NMR spectra were recorded on Bruker AM-300 spectrometer. High resolution mass spectra were recorded on a Kratos AEI MS-9 mass spectrometer and reported as *m/z*. Analytical thin layer chromatography was performed on silica-

coated plastic plates (silica gel 60 F-254, Merck) and visualized under UV light. Preparative separations were performed by flash chromatography on silica gel (Merck, 70-230 or 230-400 mesh). Tetrahydrofuran was dried by distillation from sodium-benzophenone ketyl. Dimethylformamide and triethylamine were dried over molecular sieves (4A) before use. The above solvents were stored over molecular sieves (4A). All other solvents were used as received and were reagent grade where available.

1-Amino-2,3-dimethoxy-5-(benzyloxy)carbonylaminobenzene(3)

A solution of **2** (2.28 g, 10 mmol) in THF (50 mL) was hydrogenated over 10% pd/C (600 mg) at atmospheric pressure and then filtered. To the filtrate was added, dropwise at 0°C, benzyl chloroformate (1.88 g 11 mmol) and triethylamine(1.11 g, 11 mmol) over 30 min and then warmed up to room temperature. The reaction mixture was stirred overnight, concentrated, dissolved in 150 mL of ethyl acetate, washed (brine, water), dried (Na_2SO_4), concentrated. The residue was purified by flash chromatograph (22 mm, AcOEt:hexane = 1:1) to give an oil **3** (2.89 g, 87%). ^1H NMR ($CDCl_3$) δ 7.38–7.27 (m, 5H, aromatic-H), 6.75 (bs, 1H, NH). 6.48 (d, J = 2 Hz, 1H, aromatic-H), 6.37 (d, J = 2 Hz, 1H, aromatic-H), 5.15 (s, 2H, OCH_2), 3.81(bs, 2H, NH_2), 3.72 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3). HRMS, *m/z* (rel intensity) calcd. for $C_{16}H_{18}N_2O_4$ 302.1266, found 302.1259 (M^+, 100%).

1-Benzylamino-2,3-dimethoxy-5-(benzyloxy)carbonylaminobenzene(4).

To a solution of amine **3** (3.02 g, 10 mmol) in 50 ml THF was added benzaldehyde (1.17 g, 11 mmol) and a few drop of sulfuric acid. After refluxing 1 h at 50°C, $NaBH_3CN$ (0.94 g, 15 mmol) was added gradually. The mixture was stirred 4 h at 50°C and then overnight at room temperature, concentrated, dissolved in 150 mL ethyl acetate, washed (brine, water), dried (Na_2SO_4), concentrated to an oil. Purification by flash chromatograph (22 mm, AcOEt:hexane = 1:1) to give a pale yellow oil **4** (3.81g, 97%). ^1H NMR ($CDCl_3$) δ 7.39–7.21 (m, 10H, aromatic-H), 6.60 (bs, 1H, NH), 6.48 (d, J = 2 Hz, 1H, aromatic-H), 6.12 (d, J = 2 Hz, 1H, aromatic-H), 5.18 (s, 2H, OCH_2), 4.72 (bs, 1H, NH), 4.29 (d, J = 8 Hz, 2H, NCH_2), 3.79 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3). HRMS, *m/z* (rel intensity) calcd. for $C_{23}H_{24}N_2O_4$ 392.1736, found 392.1741 (M^+, 57%).

1-Benzyl-6,7-dimethoxy-3-ethoxycarbonylmethyl-4-(benzyloxy) carbonylaminoindole (5)

A mixture of **4** (3.92 g, 10 mmol) and ethyl 4-chloroacetoacetate (4.94 g, 30 mmol) dissolved in 50 mL of anhydrous ethanol containing 3A molecular sieves (3 g) was refluxed for 36 h. The reaction mixture was filtered, and the filtrate was evaporated, and then product was purified by flash chromotograph (22 mm, AcOEt:hexane = 1:1) to give **6** (3.46 g, 69%). ^{1}H NMR ($CDCl_3$) δ 8.39 (bs, 1H, NH), 7.00–7.45 (m, 11H, aromatic-H), 6.80 (s, 1H, aromatic-H), 5.50 (s, 2H, NCH_2), 5.23 (s, 2H, OCH_2), 4.17 (q, J = 7 Hz, 2H, CH_2CH_3), 3.89 (s, 3H, OCH_3), 3.72 (s, 2H, CH_2CO). 3.60 (s, 3H, OCH_3), 1.22 (t, J = 7 Hz, 3H, CH_2CH_3). HRMS, *m/z* (rel intensity) calcd. for $C_{29}H_{30}N_2O_6$ 502.2103, found 502.2107 (M^+, 78%).

7,8-Dimethoxy-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinolin-4-one (6)

To a solution of **5** (502 mg, 1 mmol) dissolved in acetic acid (6 mL) was added 120 mg Pd/black and 60% $HClO_4$ (1.2 mL). The resulting solution was allowed to stirred 1.5 h at rooom temperature under a hydrogen atmosphere, and then filtered. The filtrate was neutralized with aqueous $NaHCO_3$ and then extracted with ethyl acetate, dried (Na_2SO_4) and evaporated to yield an oil. To a solution of oil in EtOH (10 mL) was added 1N KOH solution (5 mL). The resulting solution was stirred at room temperature for 2 h, neutralized, concentrated to dryness. The residue was dissolved in DMF, 1-(3-dimethylaminopropyl)-3-ethylcarbo-diimide hydrochloride (EDCI) (230 mg, 1.2 mmol) was added. The mixture was stirred overnight at room temperature, and concentrated. Purification by flash chromatography by flash chromatography (22 mm, AcOEt:hexane = 1:1) provided the product **7** as pale yellow solid (104 mg, 45%). ^{1}H NMR ($CDCl_3$) δ 8.15 (bs, 1H, NH), 7.89 (bs, 1H, NH), 6.76 (d, J = 2 Hz, 1H, pyrrol-H), 6.16 (s, 1H, aromatic-H), 3.87 (d, J = 2 Hz, 1H, CH_2CO), 3.96 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3). HRMS, *m/z* (rel intensity) calcd. for $C_{12}H_{12}N_2O_3$ 232.0846 found 232.0852 (M^+, 100%).

1-Amino-2,3-dimethoxy-5-(*tert*-butoxy)carbonylaminobenzene (8)

Compound **8** was prepared in 95% yield from **2** (2.28g, 10 mmol) and di-*tert*-butyl dicarbonate (2.40 g, 10 mmol) in an a similar manner as described for **3**. ^{1}H NMR ($CDCl_3$) δ 6.44 (d, J = 2 Hz, 1H, aromatic-H), 6.40 (d, J = 2 Hz, 1H, aromatic-H), 6.31 (bs, 1H, NH), 3.81 (bs, 2H, NH), 3.80 (s, 3H, OCH_3), 3.77 (s, 3H,

OCH_3), 1.49 (s, 9H, $C(CH_3)_3$). HRMS, *m/z* (rel intensity) calcd. for $C_{13}H_{20}N_2O_4$ 268.1423 found 268.1419 (M^+, 47%).

1-Methylamino-2,3-dimethoxy-5-(*tert*-butoxy)carbonylaminobenzene (9)

To a solution of **8** (268 mg, 1 mmol) and triethylamine (111 mg, 1.1 mmol) in anhydrous ether (20 mL) was added, dropwise over 1 min period, dimethyl sulfate (139 mg, 1.1 mmol). After the mixture was refluxed for 2 h, and then concentrated. The residue was recrystallized from ether to give **9** (200 mg, 71%): mp 97°C; ^1H NMR ($CDCl_3$) δ 6.52 (d, J = 2 Hz, 1H, aromatic-H), 6.33 (bs, 1H, NH), 6.18 (d, J = 2 Hz, 1H, aromatic-H), 4.30 (bs, 1H, $NHCH_3$), 3.83 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 2.82 (d, J = 8 Hz, 3H, NCH_3), 1.48 (s, 9H, $C(CH_3)_3$). HRMS, *m/z* (rel intensity) calcd. for $C_{14}H_{22}N_2O_4$ 282.1579, found 282.1585 (M^+, 35%).

1-Methyl-6,7-dimethoxy-3-ethoxycarbonylmethyl-4-(*tert*-butoxy) carbonylaminoindole (10)

Compound **10** was prepared in 74 % yield from **9** (2.82 g, 10 mmol) and ethyl 4-chloroacetoacetate (4.94 g, 30 mmol) in a similar manner as described for **4**. ^1H NMR ($CDCl_3$) δ 8.31 (bs, 1H, NH), 7.20 (s, 1H, aromatic-H). 6.72 (s, 1H, aromatic-H), 4,17 (q, J = 7 Hz, 2H, CH_2CH_3), 3.89 (s, 3H, CH_3), 3.87 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 3.72 (s, 2H, CH_2CO), 1.52 (s, 9H, $C(CH_3)_3$), 1.28 (t, J = 7 Hz, 3H, CH_2CH_3). HRMS, *m/z* (rel intensity) calcd. for $C_{20}H_{28}N_2O_6$ 392.1947, found 392.1943 (M^+, 12%).

1-Methyl-7,8-dimethoxy-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinolin-4-one (11).

Compound **10** (392 mg, 1 mmol) was dissolved in a solution of dry HCl in methanol (15%, 20 mL). After 30 min, to the above solution was added, dropwise at 0°C, 5N KOH solution (2 mL). Following procedure is as same as that discribed above for **6** (185 mg, 75%). ^1H NMR ($CDCl_3$) δ 8.00 (bs, 1H, NH), 6.52 (d, J = 2 Hz, 1H, pyrrol-H), 6.15 (s, 1H, aromatic-H), 3.95 (d, J = 2 Hz, 1H, CH_2CO), 3.92 (s, 3H, CH_3), 3.90 (s, 3H, CH_3), 3.89 (s, 3H, CH_3). HRMS, *m/z* (rel intensity) calcd. for $C_{13}H_{14}N_2O_3$, 246.10044, found 246.1007 (M^+, 87%).

7-Methoxy-1,3,4,8-tetrahydropyrrolo[4,3,2-*de*]quinolin-8-one (7) and 7-methoxy-1-methyl-1,3,4,8-tetrahydropyrrolo[4,3,2-*de*]quinolin-8-one (12).

Compound **7** and **12** were prepared from **6** and **11** following the procedure reported.[7d] For **7**: yield: 53%; ^{1}H NMR ($CDCl_3$) δ 7.80 (bs, 1H, NH), 7.01 (s, 1H, pyrrol-H), 6.05 (s, 1H, aromatic-H), 4.14 (t, J = 8 Hz, 2H, CH_2N), 3.88 (s, 3H, CH_3), 2.88 (t, J = 8 Hz, 2H, CCH_2C). HRMS, *m/z* (rel intensity) calcd. for $C_{11}H_{10}N_2O_2$,202.0742, found 202.0747 (M^+, 32%). For **12**: yield: 57%; ^{1}H NMR ($CDCl_3$) δ 6.59 (s, 1H, pyrrol-H), 6.01 (s, 1H, aromatic-H), 4.11 (t, J = 8 Hz, 2H, CH_2N), 3.85 (s, 3H, CH_3), 3.78 (s, 3H, CH_3), 2.72 (t, J = 8 Hz, 2H, CCH_2C). HRMS, *m/z* (rel intensity) calcd. for $C_{12}H_{12}N_2O_2$,216.0898, found 216.0896 (M^+, 41%).

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References and Notes

1. Marki, F.; Robertson, A. V.; Witkop, B. *J. Am. Chem. Soc.* **1961**, *83*, 3341.
2. (a) Radisky, D. C.; Radisky, E. S.; Barrows, L. R.; Copp, B. R.; Kramer, R. A.; Ireland, C. M. *J. Am. Chem. Soc.* **1993**, *115*, 1632-1638.
3. Stierle, D. B.; Faulkner, D. J. *J. Nat. Prod.* **1991**, *54*, 1131.
4. (a) Sun, H. H.; Sakemi, S.; Burres, N.; McCarthy, P. *J. Org Chem.* **1990**, *55*, 4964. (b) Sakemi, S.; Sun, H. H.; Jefford, C. W.; Bernardinelli, G. *Tetrahedron Lett.* **1989**, *30*, 2517.
5. (a) Perry, N. B.; Blunt, J. W.; McCombs, J. D.; Munro, M. H. G. *J. Org. Chem.* **1986**, *51*, 5476. (b) Perry, N. B.; Blunt, J. W.; Munro, M. H. G. *Tetrahedron* **1988**, *44*, 1727. (c) Perry, N. B.; Blunt, J. W.; Munro, M. H. G.; Higa, T.; Sakai, R. *J. Org. Chem.* **1988**, *53*, 4127.
6. (a) Barrows, L. R; Radisky, D. C.; Copp, B. R.; Swaffar, D. S.; Kramer, R. A.; Warters, R. L.; Ireland, C. M. *Anti-Cancer Drug Design* **1993**, *8*, 333.

7. (a) Sadanandan, E. V.; Pillai, S. K.; Lakshmikantham, M. V.; Billimoria, A. D.; Culpepper, J. S.; Cava, M. P. *J. Org. Chem.* **1995**, *60*, 1800. (b) Sadanandan, E. V.; Cava, M. P. *Tetrahedron Lett.* **1993**, *34*, 2405. (c) White, J. D.; Yager, K. M.; Yakura, T. *J. Am. Chem. Soc.* **1994**, *116*, 1831. (c) Kita, Y.; Tohma, H.; Inagaki, M.; Hatanaka, K.; Yakura, T. *J. Am. Chem. Soc.* **1992**, *114*, 2175. (d) Tao, X. L.; Cheng, Ji-Fei; Nishiyama, S.; Yamamura, S. *Tetrahedron* **1994**, *50*, 2017. (e) Izawa, T.; Nishiyama, S.; Yamamura, S. *Tetrahedron* **1994**, *50*, 13593. (f) Balczewski, P.; Joule, J. A.; Estevez, C.; Alvarez, M. *J. Org. Chem.* **1994**, *59*, 4571.
8. Wang, H.; Ai-Said, N. H.; Lown, J. W. *Tetrahedron Lett.* **1994**, *35*, 4085.
9. (a) Pollecoff, F.; Robinson, R. *J. Chem. Soc.* **1918**, *113*, 645. (b) A simple method is from 1,2-dihydroxy-3,5-dinitrobenzene which was refluxed with dimethyl sulfate in acetone in the presence potassium carbonate.

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