Synthesis of 7,8-Dimethoxy-2-oxo-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline: A Key Intermediate en Route to Makaluvamines, Discorhabdin C and Other Marine Alkaloids of this Group via Vicarious Nucleophilic Substitution of Hydrogen

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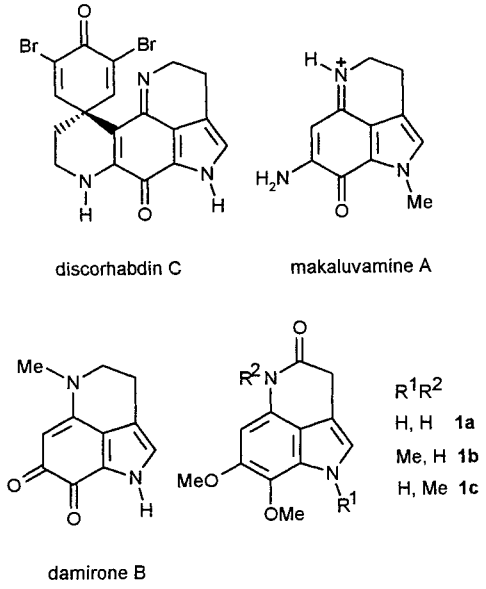
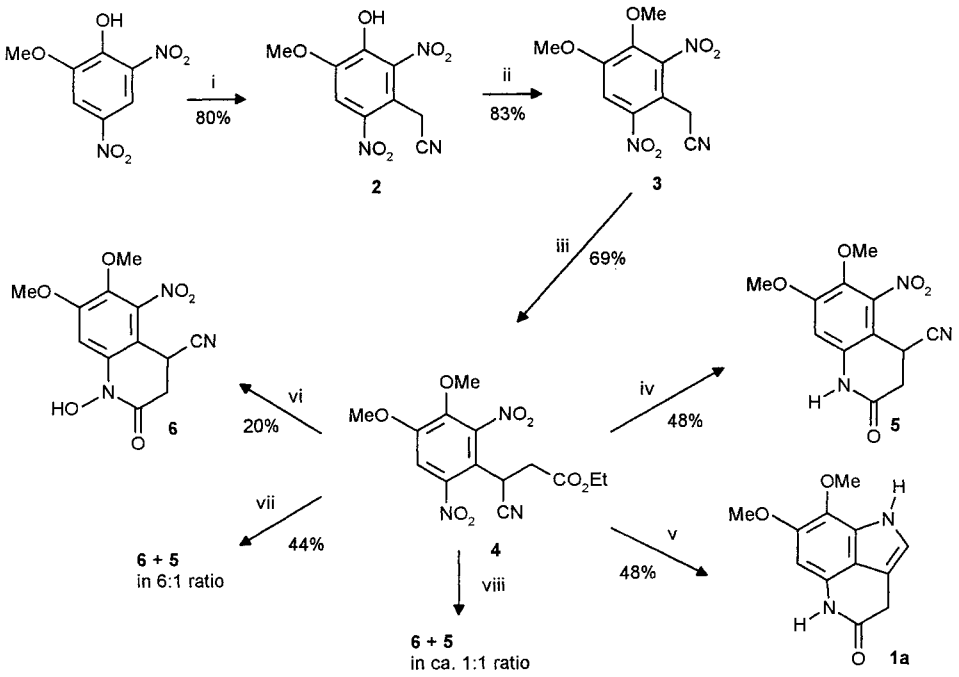
The title compound **1a**, a key intermediate in synthesis of an important group of alkaloids, is efficiently prepared via vicarious nucleophilic substitution of hydrogen followed by simple transformations.



Scheme 1

The tricyclic 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline ring system is a structural element common to the toad poison dehydrobufotenine[2] and several groups of marine alkaloids such as batzellines, isobatzellines, damirones, discorhabdins, makaluvamines, and the wakayin.[3] Some of these alkaloids exhibit potent biological activities including cytotoxic and topoisomerase II inhibition and their synthesis has recently received considerable interest.[3] Of the several synthetic approaches to these products developed so far, one proceeding through the key intermediates **1**[4] (Scheme 1) captured our attention, as we had already obtained similar compounds during our work on synthesis of *O*-methylnordehydrobufotenine.[5] The *N*-unsubstituted product **1a** has been already converted to makaluvamine D and discorhabdin C.[4a] However, in our opinion, this particular compound could be a much more versatile intermediate in a synthesis of marine alkaloids of this type. Depending on the ultimate target it could be subjected to an appropriate combination of reactions such as amide carbonyl group reduction, *N*(1)-methylation,[3,6] *N*(5)-methylation,[6] benzene nucleus chlorination, etc.[6] leading to natural products such as other makaluvamines, batzellines, isobatzellines, and damirones according to the procedures already described in the literature.



i: $PhOCH_2CN$, t-BuOK, DMF; ii: Me_2SO_4, $NaHCO_3$, acetone; iii: $BrCH_2CO_2Et$, K_2CO_3, MeCN; iv: H_2/($PdCl_2$,Fe), EtOH, AcOH, 40 min.; v: H_2/($PdCl_2$,Fe), EtOH, AcOH, 4 days; vi: Sn, HCl_{aq}, MeOH; vii: H_2/PtO_2 EtOH, AcOH; viii: H_2/Pd/C, EtOH, AcOH

Scheme 2

Here we report an efficient short synthesis of **1a** from simple and readily available starting materials using vicarious nucleophilic substitution of hydrogen[7] as a key step. We have already used similar a strategy in the synthesis of *O*-methylnordehydrobufotenine.[5] The reaction sequence is shown in Scheme 2.

2,4-Dinitroguaiacol, readily obtained via nitration of guaiacol, was subjected to the vicarious nucleophilic substitution of hydrogen with phenoxyacetonitrile in the presence of potassium butoxide in DMF to give a single product **2** containing the cyanomethyl substituent in position 3. This orientation, governed by the conjugation in the dinitrophenolate anion, is similar to that observed earlier in the VNS reaction with 2,4-dinitrophenol and other dinitrophenols.[8] Methylation of **2** with dimethyl sulfate in the presence of sodium bicarbonate gave the dimethoxy derivative **3**. The use of such a weak base was necessary; in the presence of a stronger base, e.g., sodium carbonate, a complex mixture of methylated products was formed. Compound **3** was then alkylated with ethyl bromoacetate in the presence of potassium carbonate to give cyanoester **4** which was subsequently subjected to a selective hydrogenation using $PdCl_2$/Fe catalyst.[9] We have already used this catalytic system for the selective reduction of one nitro group in a similar cyanoester.[5] Indeed, the reduction of **4** proceeded under these conditions with a sufficient selectivity. When it was arrested immediately after consumption of the substrate, TLC monitoring (ca. 40 min), the cyanotetrahydropyridine derivative **5** was isolated as the main product. Under these conditions the second nitro group was also reduced although substantially more slowly. Thus, when the reduction was carried out for ca. 4 days the desired final product **1a** was obtained in a reasonable yield of 49%.

Other methods of reduction listed in Scheme 2 failed to give the bicyclic product **1a** although this issue was not thoroughly studied. Thus, the sequence: VNS cyanomethylation of dinitroguaiacole, alkylation of the methylene group with ethyl bromoacetate, and the controlled selective consecutive reduction of the two nitro groups provides a short and effective route to **1a**, applicable for multigram synthesis, particularly taking into account that chromatographic purification was used essentially for removal of tars, not for separation from side products.

Melting points are uncorrected. ^{1}H NMR spectra were recorded on Varian Gemini (200 MHz). Chemical shifts are reported in ppm downfield from TMS as internal standard; coupling constants *J* are given in Hertz; assignments marked with an asterisk (*) may be interchanged; protons attached to cyclic systems are indicated by numbers (e.g., H-3) based on the numbering of the cyclic skeleton in the systematic name of the given compound; protons of side chains are indicated in a descriptive way (e.g., OCH_3). Mass spectra were recorded on AMD 604 spectrometer. IR spectra were taken with Perkin Elmer 1640 and only noteworthy absorptions are listed. Column chromatography was performed on silica gel 230–400 mesh (Merck). Organic extracts were dried with anhydrous $MgSO_4$. The following compounds were obtained according to the described procedures: 4-phenoxyacetonitrile[10] and 2,4-dinitroguaiacol.[11] Other reagents were commercially available. Compounds **1–6** gave satisfactory microanalyses: C ± 0.4, H ± 0.18, N ± 0.38. (exception: **5**, N–0.94).

(3-Hydroxy-4-methoxy-2,6-dinitrophenyl)acetonitrile (2):
To a solution of *t*-BuOK (41.7 g, 375 mmol) in DMF (250 mL) a solution of dinitroguaiacol (20.06 g, 93.7 mmol) and phenoxyacetonitrile (13.12 g, 98 mmol) in DMF (115 mL) was added dropwise at 0°C. The reaction mixture was stirred at 0°C for 40 min and then was poured into an ice-cold, dilute hydrochloric acid solution (1500 mL). The product was collected by filtration, washed with water (200 mL), and air-dried to give **2** as yellow crystals; yield: 18.85 g (80%); mp 197°C (dec.).

^{1}H NMR (acetone-d_6): δ = 4.05 (2H, s, $ArCH_2CN$), 4.11 (3H, s, $-OCH_3$), 7.98 (1H, s, H-5).

MS (EI): *m/z* (relative intensity, %) = 253 (M^+, 100), 236 (43), 223 (6), 218 (8), 208 (12), 190 (34), 160 (23), 147 (19), 134 (18), 118 (28), 106 (18).

(3,4-Dimethoxy-2,6-dinitrophenyl)acetonitrile (3):
To a solution of **2** (18.85 g, 75 mmol) and dimethyl sulfate (9.31 g, 75 mmol) in acetone (250 mL) $NaHCO_3$ (18.63 g, 0.22 mol) was added. The reaction mixture was refluxed with vigorous stirring for 9 h. Then another portion of dimethyl sulfate (0.47 g, 3.7 mmol, 5% excess) was added and reflux was continued for 8 h. After cooling, inorganic solids were filtered off and washed with acetone. The filtrate was evaporated. The residue was dissolved in CH_2Cl_2 (200 mL) and washed with a 10% solution of K_2CO_3 (150 mL) and with water (150 mL). The organic layer was dried and evaporated. The residue was recrystallized from isopropanol to give **3** as yellowish crystals: yield: 16.51 (83%); mp 136°C.

^{1}H NMR: δ = 3.89 (2H, s, $ArCH_2CN$), 4.05 (3H, s, OCH_3), 4.08 (3H, s, OCH_3), 7.89 (1H, s, H-5).

MS (EI): *m/z* (relative intensity, %) = 267 (M^+, 100), 250 (59), 233 (7), 219 (3), 205 (5), 189 (12), 176 (11), 160 (17), 148 (13), 133 (14), 115 (29), 102 (17).

Ethyl 3-Cyano-3-(3,4-dimethoxy-2,6-dinitrophenyl)propanoate (4):
To a solution of **3** (16.51 g, 61.8 mmol) and ethyl bromoacetate (10.84 g, 65 mmol) in acetonitrile (100 mL) anhydrous K_2CO_3 (17.11 g, 124 mmol) was added and the mixture was stirred vigorously under argon until **3** was consumed (5 h, TLC control). Inorganic solids were filtered off and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2 (200 mL) and washed with dilute hydrochloric acid solution (150 mL). The organic layer was dried and evaporated and the residue was passed through a short silica gel column (CH_2Cl_2). The crude product was recrystallized from isopropanol to give **4** as colorless crystals; yield: 14.50 g (69%); mp 103°C.

^{1}H NMR ($CDCl_3$): δ = 1.29 (3H, t, *J* = 7.1, $-OCH_2CH_3$), 2.92 (1H, dd, *J* = 17.4, *J* = 4.6), 3.47 (1H, dd, *J* = 17.4, *J* = 9.3, $-CH_2CO_2Et$), 4.03 (3H, s, OCH_3), 4.06 (3H, s, OCH_3), 4.22 (2H, q, *J* = 7.1, $-OCH_2CH_3$), 4.60 (1H, dd, *J* = 9.3, *J* = 4.6, >CHCN), 7.70 (1H, s, H-5).

MS (EI): *m/z* (relative intensity, %) = 353 (M^+, 1), 307 (49), 279 (63), 265 (30), 262 (27), 252 (100), 206 (66), 191 (12), 175 (15), 163 (12), 163 (11), 147 (7), 135 (10), 120 (7), 102 (8).

6,7-Dimethoxy-5-nitro-2-oxo-1,2,3,4-tetrahydroquinoline-4-carbonitrile (5):
A suspension of **4** (106 mg, 0.300 mmol) in a mixture of ethanol (2.5 mL) and acetic acid (0.5 mL) was heated until the solid dissolved, and the solution was allowed to cool, whereupon fine crystals of the substrate were deposited. Then, the catalyst [8 mg, prepared by grinding $PdCl_2$ (0.33 g) and iron powder (1.50 g) in a mortar] was added and the mixture was stirred under hydrogen until the substrate was consumed (40 min, TLC control). The catalyst was filtered off, the filtrate was evaporated, and the residue was purified by passing through a short silica gel column (hexane–ethyl acetate 1:1), to give **5** as yellow crystals; yield: 40 mg (48%); mp 210–212°C (dec., isopropanol).

^{1}H NMR (acetone-d_6): δ = 2.88 (1H, dd, *J* = 16.7, *J* = 2.3), 3.08 (1H, dd, *J* = 16.7, *J* = 6.4, H-3), 3.89 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 4.39 (1H, dd, *J* = 6.4, *J* = 2.3, H-4), 7.02 (1H, s, H-8), 9.73 (1H, br s, H-1).

IR (KBr): ν = 1372, 1540 (NO_2), 1714 (C=O), 2242 (CN), 3438 cm^{-1} (NH).

MS (EI): *m/z* (relative intensity, %) = 277 (M^+, 100), 262 (8), 245 (8), 232 (10), 216 (25), 200 (31), 190 (15186), 13 (170), 10 (158), 13 (153), 6 (130), 5 (116), 12 (103).

HRMS (EI) *m/e* calcd for $C_{12}H_{11}N_3O_5$ (M^+): 277.06987; found: 277.069659.

1-Hydroxy-6,7-dimethoxy-5-nitro-2-oxo-1,2,3,4-tetrahydroquinoline-4-carbonitrile (6):

To a suspension of **4** (2.034 g, 5.76 mmol) in methanol (20 mL) tin (1.438 g, 12 mmol) was added in small pieces, followed by concentrated hydrochloric acid (2 mL). The reaction mixture was stirred for 2.5 h and poured into water. The resulting suspension, containing the product and tin salts was extracted with several portions of ethyl acetate (15 mL, each). The combined organic extracts were dried and evaporated. The residue was purified by passing through a short silica gel column (Et_2O), to give **6** as yellow crystals; yield: 357 mg (20%); mp 199 °C (isopropanol).

^{1}H NMR (acetone-d_6): δ = 3.01 (1 H, dd, J = 16.8, J = 2.3), 3.23 (1 H, dd, J = 16.8, J = 6.3, H-3), 3.89 (3 H, s, OCH_3), 4.04 (3 H, s, OCH_3), 4.36 (1 H, dd, J = 6.4, J = 2.3, H-4), 7.34 (1 H, s, H-8), 9.95 (1 H, br s, H-1).

IR (KBr): ν = 1362, 1535 (NO_2), 1688 (C=O), 2249 (CN), 3105 cm^{-1} (OH).

MS (EI): *m/z* (relative intensity, %) = 293 (M^+, 100), 277 (24), 248 (10), 245 (9), 232 (20), 216 (25), 200 (12), 160 (8), 130 (6), 116 (8).

HRMS (EI): *m/e* calcd for $C_{12}H_{11}N_3O_6$ (M^+); 293.0647853 found: 293.064386.

Reduction of 4 on PtO_2:

To a suspension of **4** (106 mg, 0.300 mmol) in a mixture of ethanol (2.5 mL) and acetic acid (0.5 mL) (see pretreatment of the substrate in the preparation of **5**) platinium dioxide (5 mg) was added and the mixture was stirred under hydrogen until the substrate was consumed (20 min, TLC control). The catalyst was filtered off, the filtrate was evaporated and the residue was purified by passing through a short silica gel column (hexane–ethyl acetate, 1:1), to give a mixture of **6** and **5** in a 6:1 ratio as estimated on the basis of the ^{1}H NMR spectra; yield: 39 mg (44%).

7,8-Dimethoxy-2-oxo-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline (1a):

To a suspension of **4** (2.034 g, 5.76 mmol) in a mixture of ethanol (20 mL) and acetic acid (5 mL) the catalyst [360 mg, prepared by grinding $PdCl_2$ (0.33 g) and iron powder (1.50 g) in a mortar] was added and the mixture was stirred at 20 °C under hydrogen for 4 days, until only final product was present in the reaction mixture (TLC control, the spot of the product **1a** on the TLC plate turned yellow within minutes and then brown when left on air). The catalyst was filtered off, the filtrate was evaporated and the residue was purified by passing through a short silica gel column (CH_2Cl_2–Et_2O 1:1), to give **1a** as yellow crystals; yield: 688 mg (48%); mp 195 °C (dec).

The workup should be conducted immediately after stopping the reaction; we found 1 day delay to substantially decrease the yield of the product.

^{1}H NMR ($CDCl_3$): δ = 3.90 (3 H, s, OCH_3), 3.94 (3 H, s, OCH_3), 3.98 (2 H, d, J = 1.5, H-3), 6.18 (1 H, s, H-6), 6.79 (1 H, br d, J = 1.9, H-2), 7.82 (1 H, br s, H-5)*, 8.14 (1 H, br s, H-1)*.

IR (KBr): ν = 1527, 1618, 1651, 1683, 3398 cm^{-1} (NH).

MS (EI): *m/z* (relative intensity, %) = 232 (M^+, 93), 217 (100), 198 (3), 174 (17), 161 (6), 146 (10), 134 (6), 116 (6), 102 (6).

HRMS (EI): *m/e* calcd for $C_{12}H_{12}N_2O_3$ (M^+): 232.08479, found: 232.084657.

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