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A new synthesis of the phytotoxin porritoxin

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Abstract—A convenient synthesis of the phytotoxin porritoxin is described. Central to the approach employed is the formation of the isoindolinone template obtained via a directed lithiation/Parham cyclization process enabling the concomitant connection of an acetal appendage. Further conversion into the requisite hydroxyalkyl chain, selective deprotection, and O-prenylation complete the synthesis of the title compound.

1. Introduction

Porritoxin, as well as some other isoindolinone centered alkaloids, e.g., fumaridine,[1] fumaramidine,[2] nuevamine,[3] and piperolactam B,[4] belongs to this unique class of compounds whose structural assignments have been a subject of discussion and controversy. Initially this phytotoxin produced by the fungus *Alternaria porri* (Ellis) Ciferri, the causal fungus of black spot disease in stone-leek and onion was ascribed structure **1** characterized by a benzoxazocine skeleton.[5] However, probably shaken by the suggestion of Ayer and Miao who isolated stachybotramide **2** having an isoindole moiety[6] and then pointed out that the structure of porritoxin might be incorrect, the isolating group decided to launch a detailed structural reinvestigation. Finally persuasive data based upon detailed 2D NMR analysis ^{1}H–^{13}C and ^{1}H–^{15}N HMBC experiments convinced the authors to reassign their structure from **1** to **3** (Fig. 1).[7] Recently this revised structure was unambiguously confirmed by Kelly and Cornella[8] who reported the first total synthesis of the natural product. The marked advantages of their elegant synthesis lie mainly in the small number of steps and efficiency of the process. In this synthetic approach the key reaction is the formylation of the aromatic ring system by making use of iron pentacarbonyl then allowing the formation of the lactam unit by reductive amination and subsequent trans-amidification.

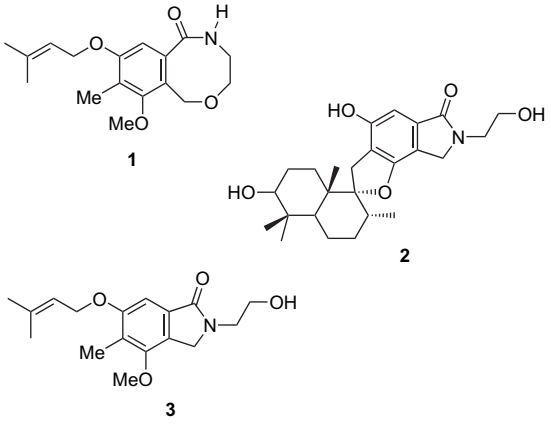

Figure 1.

2. Results and discussion

In this paper we wish to delineate an alternative synthesis of the title compound that relies upon our long standing experience in the field of isoindolinone chemistry.[9] Our synthetic tactic outlined in the retrosynthetic analysis shown in Scheme 1 hinges upon the Parham cyclization reaction of the aromatic carbamate **4** equipped with diverse and dense functionalities liable to secure the assembling of the rather congested isoindolinone template. Compound **4** could be in turn obtained by acylation of the secondary amine **6**. We also conjectured that the annulation process likely to give rise to **5** would allow the concomitant connection of an acetal appendage, which may serve as a handle for further conversion into the hydroxyalkyl chain present in the target

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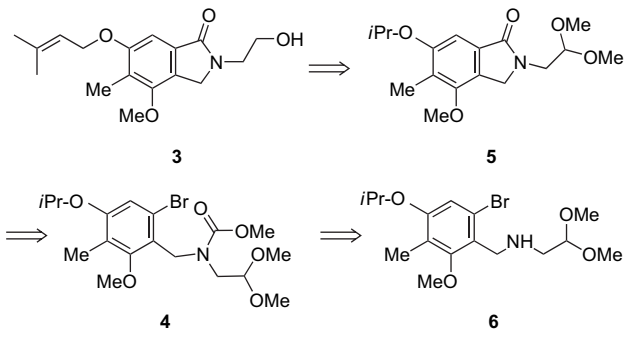
natural product. De-isopropylation followed by ultimate prenylation then should complete the total synthesis of the target compound.



Scheme 1.

The first facet of the synthesis was then the elaboration of the benzylamine derivative **6**. This compound was readily obtained as depicted in Scheme 2 by a reductive amination process involving the readily accessible benzaldehyde derivative **7** with aminoacetaldehyde dimethyl acetal. Acylation with methyl chloroformate proceeded uneventfully to deliver the carbamate **4**, a possible candidate for the planned Parham cyclization process. The Parham protocol hinges upon the trapping of an aromatic organometallic species with a suitable internal electrophile thereby providing the potential for direct access to an annulated compound.[10] Optimal conditions to ensure the requisite generation of the aryl metalled species derived from **4** by bromine–metal interconversion were then explored. For this purpose variations of the base, solvent, temperature profile, and incorporation of carbanion modifiers were all screened based upon literature precedents.[10] After various experimentation we found that upon adding a solution of carbamate **4** in THF to a solution of *n*-BuLi (3 equiv) and TMEDA (3 equiv) in THF at −78 °C for 30 min, the consumption of the parent compound was essentially complete and the desired annulated compound **5** was obtained with a very satisfactory yield (63%) upon immediate aqueous workup. Subsequent manipulation of the acetal residue by a two-step sequence provided the hydroxyalkylated isoindolinone **8** in fairly good yield. Regeneration of the 6-hydroxyphenolic function delivered the phenolic isoindolinone **9**, which can be regarded as an immediate precursor of the target alkaloid.[8] Indeed prenylation of **9** afforded **3** whose spectral data are in excellent agreement with those reported for natural porritoxin.[7]

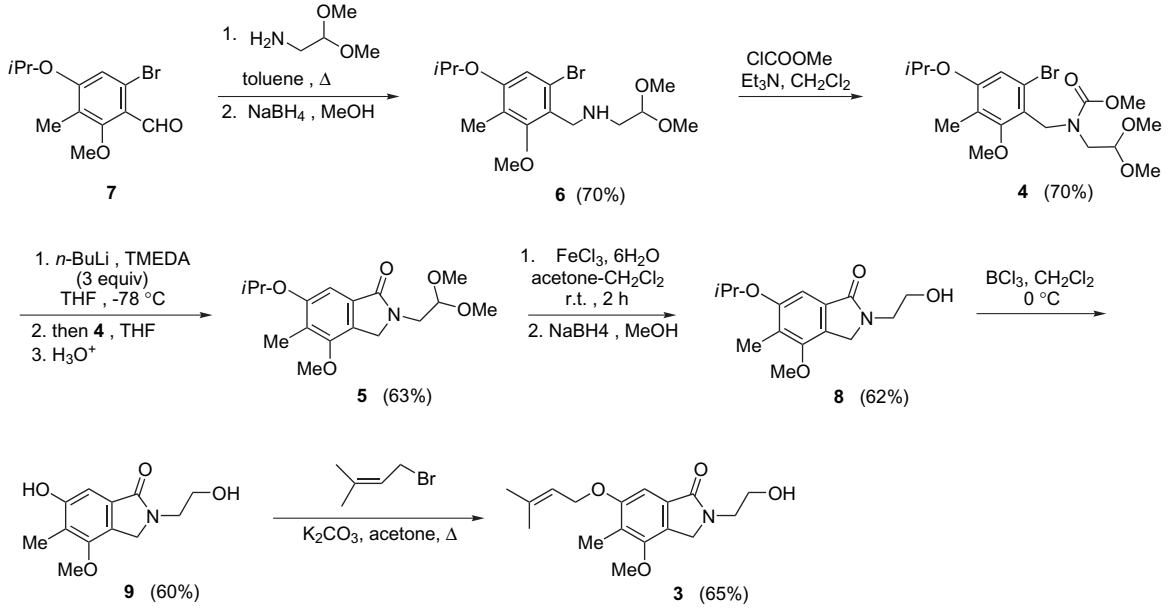
3. Conclusion

In conclusion we have defined a new synthetic route to natural product porritoxin. The key step of this approach made use of a directed lithiation/Parham cyclization process, which enabled the rapid construction of a highly functionalized isoindolinone. The concomitant incorporation of an acetal residue was used as a way to connect the requisite hydroxyethyl appendage. With this versatile synthetic route in hand, further studies will concentrate on exploring the potential of this approach for the elaboration of structurally modified biogenetic congeners.

4. Experimental

4.1. General

Tetrahydrofuran (THF) was pre-dried with anhydrous Na_2SO_4 and distilled over sodium benzophenone ketyl under Ar before use. DMF, CH_2Cl_2, NEt_3, and toluene were distilled from CaH_2. Dry glassware was obtained by oven-drying and assembly under dry Ar. The glassware was equipped with rubber septa and reagent transfer was performed by syringe techniques. For flash chromatography, Merck silica gel 60 (40–63 μm, 230–400 mesh ASTM) was used. The melting points were obtained on a Reichert–Thermopan apparatus and are not corrected. NMR spectra: Bruker AM 300



Scheme 2.

(300 and 75 MHz, for ^1H and ^{13}C), $CDCl_3$ as solvent, TMS as internal standard. Microanalyses were performed by the CNRS microanalysis center.

4.1.1. *N*-(6-Bromo-4-isopropoxy-2-methoxy-3-methylbenzyl)-*N*-(2,2-dimethoxyethyl)amine (6). A solution of benzaldehyde derivative **7**[9e] (2.10 g, 7.3 mmol) and 2,2-dimethoxyethylamine (0.77 g, 7.3 mmol) in toluene (50 mL) was refluxed for 3 h in a Dean–Stark apparatus. After evaporation of the solvent the crude oily imine (2.60 g) was dissolved in MeOH (50 mL) and $NaBH_4$ (0.53 g, 13.9 mmol) was added portionwise and the mixture was stirred for 2 h at room temperature. After addition of solid NH_4Cl and stirring for 30 min, the solution was concentrated under vacuum. The residue was dissolved in CH_2Cl_2 (50 mL), washed with water and brine, and dried (Na_2SO_4). Evaporation of the solvent left the amine **6** as a yellow oil, which was purified by column chromatography using ethyl acetate–NEt_3 (90:10) as eluent. Yield 1.91 g (70%); ^1H NMR (δ_H) 1.30 (d, J=6.1 Hz, 6H, 2×CH_3), 2.05 (s, 3H, CH_3), 2.71 (d, J=5.6 Hz, 2H, NCH_2), 3.31 (s, 6H, 2×OCH_3), 3.72 (s, 3H, OCH_3), 3.86 (s, 2H, $ArCH_2N$), 4.41–4.50 [m, 2H, $CHMe_2$+$CH(OMe_2)$], 6.81 (s, 1H, aromatic H) ppm; ^{13}C NMR (δ_C) 9.5, 22.1, 47.7, 50.1, 53.6, 61.3, 70.8, 103.7, 113.4, 120.7, 121.7, 125.0, 156.6, 158.6 ppm. Anal. Calcd for $C_{16}H_{26}BrNO_4$ (376.3): C, 51.07; H, 6.96; N, 3.72%. Found: C, 50.98; H, 7.09; N, 3.93%.

4.1.2. Methyl *N*-(6-bromo-4-isopropoxy-2-methoxy-3-methylbenzyl)-*N*-(2,2-dimethoxyethyl)carbamate (4). Methyl chloroformate (0.45 g, 4.8 mmol) was added dropwise to a stirred solution of amine **6** (1.40 g, 3.7 mmol) and NEt_3 (0.76 g, 7.5 mmol) in CH_2Cl_2 (50 mL) at 0 °C. Stirring was maintained for 3 h at room temperature. The mixture was washed with water and brine, and dried (Na_2SO_4). After evaporation of the solvent the oily residue was purified by column chromatography using ethyl acetate–hexanes (50:50) as eluent to furnish **4** as a colorless oil. Yield 1.13 g (70%); ^1H NMR (δ_H) 1.32 (d, J=6.1 Hz, 6H, 2×CH_3), 2.06 (s, 3H, CH_3), 3.12–3.23 (m, 2H, NCH_2), 3.32 (s, 6H, 2×OCH_3), 3.66 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 4.43–4.56 [m, 2H, $CHMe_2$+$CH(OMe_2)$], 4.67–4.72 (br s, 2H, $ArCH_2N$), 6.83 (s, 1H, aromatic H) ppm; ^{13}C NMR (δ_C) 9.6, 22.1, 45.9, 47.0, 52.7, 54.3, 61.0, 70.7, 102.4, 113.4, 120.8, 121.4, 122.2, 157.1, 159.6 ppm. Anal. Calcd for $C_{18}H_{28}BrNO_6$ (434.3): C, 49.78; H, 6.50; N, 3.22%. Found: C, 49.85; H, 6.38; N, 3.01%.

4.1.3. 2-(2,2-Dimethoxyethyl)-6-isopropoxy-4-methoxy-5-methyl-2,3-dihydro-1*H*-isoindol-1-one (5). A solution of *n*-BuLi (2 M in pentane, 3 mL, 6.0 mmol) and TMEDA (0.7 g, 6.0 mmol) in dry THF (5 mL) was carefully degassed by three freeze–thaw cycles and stirred at −78 °C under dry deoxygenated Ar. A solution of methyl carbamate derivative **4** (0.87 g, 2.0 mmol) in degassed THF (25 mL) was then added dropwise through a canula. The mixture was stirred for 30 min at −78 °C. After addition of aqueous satd NH_4Cl solution (5 mL) and Et_2O (25 mL), the aqueous layer was separated and extracted with Et_2O (25 mL). The organic layers were cumulated, dried (Na_2SO_4), and concentrated under vacuum. The crude oily residue was purified by column chromatography using ethyl acetate–hexanes–CH_2Cl_2 (40:40:20) as eluent to give **5** as a yellow oil. Yield 0.41 g (63%); ^1H NMR (δ_H) 1.30 (d, J=5.9 Hz, 6H, 2×CH_3), 2.12 (s, 3H, CH_3), 3.37 (s, 6H, 2×OCH_3), 3.66 (d, J=5.1 Hz, 2H, NCH_2), 3.81 (s, 3H, OCH_3), 4.47 (s, 2H, $ArCH_2N$), 4.50–4.60 [m, 2H, $CHMe_2$+$CH(OMe_2)$], 7.03 (s, 1H, aromatic H) ppm; ^{13}C NMR (δ_C) 9.6, 22.1, 44.4, 49.7, 54.4, 59.6, 70.6, 102.5, 102.9, 123.7, 123.8, 131.4, 153.5, 157.5, 168.8 ppm. Anal. Calcd for $C_{17}H_{25}NO_5$ (323.4): C, 63.14; H, 7.79; N, 4.33%. Found: C, 62.99; H, 7.98; N, 4.39%.

4.1.4. 2-(2-Hydroxyethyl)-6-isopropoxy-4-methoxy-5-methyl-2,3-dihydro-1*H*-isoindol-1-one (8). A solution of **5** (0.39 g, 1.2 mmol) and iron(III) chloride hexahydrate (0.92 g, 3.4 mmol) in a mixture of acetone–dichloromethane (1:4, 10 mL) was vigorously stirred over a period of 2 h at room temperature. The crude mixture was poured onto a aqueous satd NH_4Cl solution (5 mL), filtered on Celite, and extracted with CH_2Cl_2 (3×10 mL). The organic extracts were washed successively with water, brine, and dried over Na_2SO_4. The solvents were removed in vacuo then the crude solid residue was dissolved in MeOH (15 mL) and treated under stirring by portionwise addition of $NaBH_4$ (95 mg, 2.5 mmol). Stirring was maintained at room temperature for an additional 1 h. After concentration under vacuum, the residue was dissolved in CH_2Cl_2 (10 mL) and washed with aqueous satd NH_4Cl solution (10 mL). After drying (Na_2SO_4) the solvent was evaporated under vacuum to afford a solid residue, which was purified by flash column chromatography on silica using acetone–hexanes (80:20) as eluent. White crystals, yield 207 mg (62%); mp 113–114 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (d, J=6.0 Hz, 6H), 2.15 (s, 3H), 3.10–3.52 (br s, 1H), 3.73 (t, J=5.0 Hz, 2H), 3.84 (s, 3H), 3.90 (t, J=5.0 Hz, 2H), 4.52 (s, 2H), 4.58 (heptuplet, J=6.0 Hz, 1H), 7.04 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.0, 22.4, 46.6, 50.3, 60.0, 62.0, 71.0, 102.7, 123.8, 124.3, 131.8, 153.8, 157.9, 170.1 ppm. Anal. Calcd for $C_{15}H_{21}NO_4$ (279.3): C, 64.50; H, 7.58; N, 5.01%. Found: C, 64.59; H, 7.76; N, 4.83%.

4.1.5. 6-Hydroxy-2-(2-hydroxyethyl)-4-methoxy-5-methyl-2,3-dihydro-1*H*-isoindol-1-one (9). A solution of BCl_3 (1 M in CH_2Cl_2, 0.8 mL, 0.8 mmol) was added dropwise by syringe to a degassed solution of isoindolinone **8** (112 mg, 0.4 mmol) in CH_2Cl_2 (10 mL) at 0 °C under Ar. After stirring for 2 h at 0 °C, the reaction mixture was quenched with a few pieces of crushed ice. The aqueous phase was extracted with CH_2Cl_2 (3×10 mL) and Et_2O (3×10 mL). The organic solvents were combined and dried (Na_2SO_4). The solvents were removed in vacuum and the crude solid residue was finally recrystallized from toluene–ethanol to afford **7**. White crystals, yield 57 mg (60%); mp 176–178 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 2.1 (s, 3H), 3.53–3.67 (m, 4H), 4.61 (s, 2H), 6.87 (s, 1H), 9.81 (br s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 10.3, 45.6, 49.8, 59.1, 60.2, 61.8, 104.2, 120.0, 122.1, 132.8, 154.3, 157.5, 168.3 ppm. Anal. Calcd for $C_{12}H_{15}NO_4$ (237.3): C, 60.75; H, 6.37; N, 5.90. Found: C, 60.54; H, 6.19; N, 6.09.

4.1.6. Porritoxin (3). By prenylation of **9** (40 mg) following a reported procedure.[8] White crystals from hexane–toluene, yield 34 mg (65%); mp 115–116 °C (lit.[7] 115–116 °C). Analytical and spectral data matched those reported for the natural product.[7,8]

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