JOC*Note*

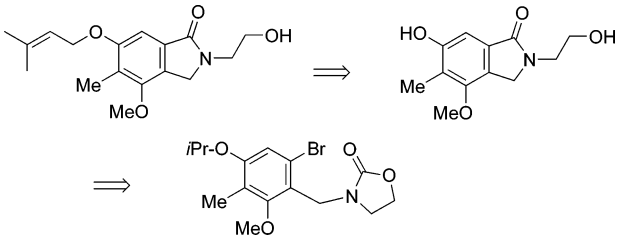
A New Total Synthesis of Porritoxin

Anne Moreau, Magali Lorion, Axel Couture,*
Eric Deniau, and Pierre Grandclaudon

Laboratoire de Chimie Organique Physique, UMR 8009 "Chimie Organique et Macromoléculaire", Université des Sciences et technologies de Lille, Bâtiment C3(2), F-59655 Villeneuve d'Ascq Cedex, France

axel.couture@univ-lille1.fr

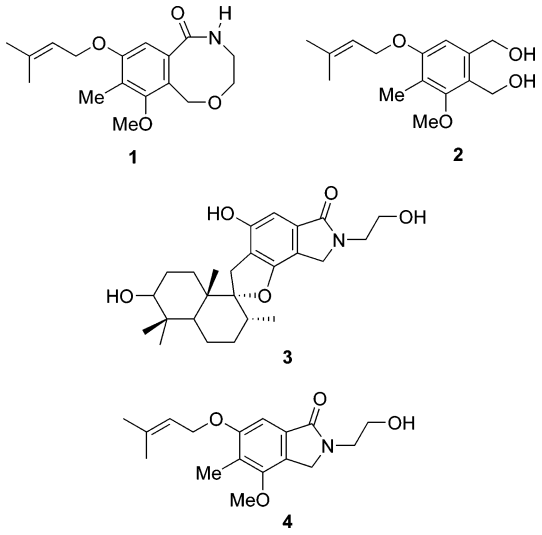
Received December 16, 2005



A concise and efficient total synthesis of the phytotoxin porritoxin is described. The key step of the synthesis is based upon a Parham cyclization methodology which enables the creation of the lactam unit embedded in the title compound framework with the concomitant formation of the tethered hydroxyakyl chain.

Porritoxin is a phytotoxin produced by the fungus *Alternaria porri* (Ellis) Ciferi responsible for black spot disease of commercially important plants such as stone-leek, lettuce, and onion.[1] This nonspecific toxin was isolated in 1992 from the stationary liquid cultures of the above-mentioned fungi and was initially assigned structure **1** possessing a unique benzoxazocine skeleton. Later, comparison of the ^{1}H and ^{13}C NMR spectra of the isolated product with zinniol (**2**) and also with the secondary metabolite stachybotramide (**3**) having an isoindolinone moiety led the isolating group to suspect an erroneous assignment. Finally, persuasive data mainly based upon extensive reinvestigation of the structure by detailed 2D NMR analysis including $^{1}H-^{13}C$ and $^{1}H-^{15}N$ HMBC experiments led to the revision of the structure of the natural product from **1** to **4**.[2]

Recently, Kelly et al. reported the first total synthesis of the revised structure **4** to confirm that porritoxin was not the originally assigned **1**.[3] Their elegant and skillful synthetic strategy hinges upon an *ortho*-lithiation/formylation with iron pentacarbonyl process leading to **5** (retrosynthetic Scheme 1, path a), a high-temperature annulation reaction giving rise to isoindolinone **6** and ultimately the selective mono-deprotection



of the 6-hydroxyphenolic function, thereby providing **7**, the immediate precursor of the target alkaloid **4**.

Herein, we wish to delineate a tactically and conceptually new synthetic approach to alkaloid porritoxin **4** that relies upon our long-standing experience in the field of isoindolinone chemistry.[4] Our strategy is based upon the exploitation of the Parham cyclization process for the creation of the five-membered lactam embedded in the isoindolinone framework of the targeted porritoxin. The protocol developed by Parham which hinges upon aromatic lithiation and subsequent reaction with an internal electrophile occupies a place of choice in the arsenal of synthetic tactics for the assembling of carbo- and heterocyclic systems.[5] However, applications of this concept to the elaboration of five-membered lactams are scarce,[6] and as far as we are aware, utilization of carbamates as internal electrophiles has been confined thus far to acyclic systems.[6a,7] We then reasoned that porritoxin **4** would be obtained by

* To whom correspondence should be addressed. Fax: +33 (0)3 20 33 63 09.

(1) Suemitsu, R.; Ohnishi, K.; Horiuchi, M.; Kitaguchi, A.; Odamura, K. *Phytochemistry* **1992**, *31*, 2325−2326.

(2) Horiuchi, M.; Maoka, T.; Iwase, N.; Ohnishi, K. *J. Nat. Prod.* **2002**, *65*, 1204−1205.

(3) Cornella, I.; Kelly, T. R. *J. Org. Chem.* **2004**, *69*, 2191−2193.

(4) (a) Hoarau, C.; Couture, A.; Cornet, H.; Deniau, E.; Grandclaudon, P. *J. Org. Chem.* **2001**, 66, 8064−8069. (b) Couture, A.; Deniau, E.; Grandclaudon, P.; Hoarau, C.; Rys, V. *Tetrahedron Lett.* **2002**, *43*, 2207−2210. (c) Moreau, A.; Couture, A.; Deniau, E.; Grandclaudon, P.; Lebrun, S. *Tetrahedron* **2004**, *60*, 6169−6176. (d) Moreau, A.; Couture, A.; Deniau, E.; Grandclaudon, P. *J. Org. Chem.* **2004**, *69*, 4527−4530. (e) Rys, V.; Couture, A.; Deniau, E.; Lebrun, S.; Grandclaudon, P. *Synlett* **2004**, 2233−2235. (f) Moreau, A.; Couture, A.; Deniau, E.; Grandclaudon, P. *Eur. J. Org. Chem.* **2005**, 3437−3442. (g) Deniau, E.; Enders, D.; Couture, A.; Grandclaudon, P. *Tetrahedron: Asymmetry* **2005**, *16*, 875−881.

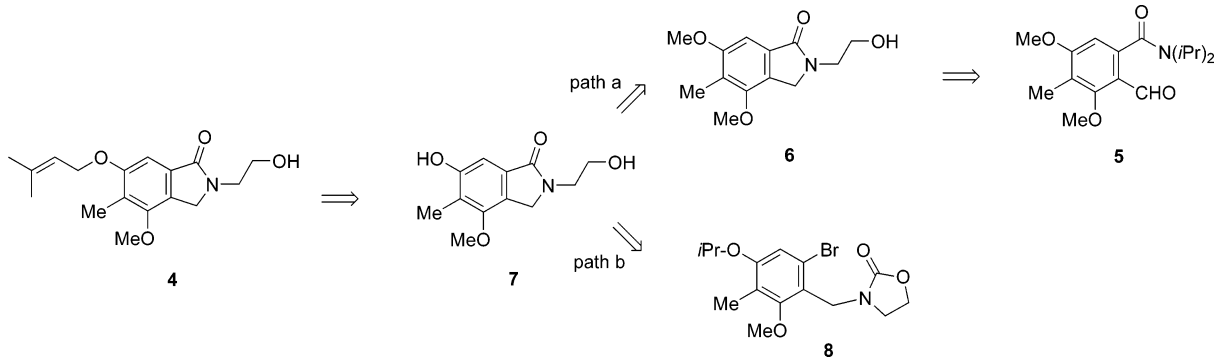
(5) Reviews: (a) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300−305. (b) Wakefield, B. J. *The Chemistry of Organolithium Compounds*, 2nd ed.; Pergamon: New York, 1990. (c) Gray, M.; Tinkl, M.; Snieckus, V. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Exeter, 1995; Vol. 11, pp 66−92. (d) Ardeo, A.; Collado, M. I.; Osante, I.; Ruiz, J.; Sotomayor, N.; Lete, E. In *Targets in Heterocyclic Systems*; Atanassi O., Spinelli, D., Eds.; Italian Society of Chemistry: Rome, 2001; Vol. 5, pp 393−418. (e) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Elsevier Science Ltd.: Oxford, 2002. (f) Mealy, M. J.; Bailey, W. F. *J. Organomet. Chem.* **2002**, *646*, 59−67. (g) Sotomayor, N.; Lete, E. *Curr. Org. Chem.*, **2003**, *7*, 275−300. (h) Nájera, C.; Sansano, J. M.; Yus, M. *Tetrahedron* **2003**, *59*, 9255−9303.

(6) (a) Carmen de la Fuente, M.; Dominguez, D. *Tetrahedron* **2004**, *60*, 10019−10028. (b) Giger, R. K. A. Swiss Pat. 1985, CH 648300; *Chem. Abstr.* **1985**, *103*, 71188. (c) Rys, V.; Couture, A.; Deniau, E.; Grandclaudon, P. *Eur. J. Org. Chem.* **2003**, 1231−1237.

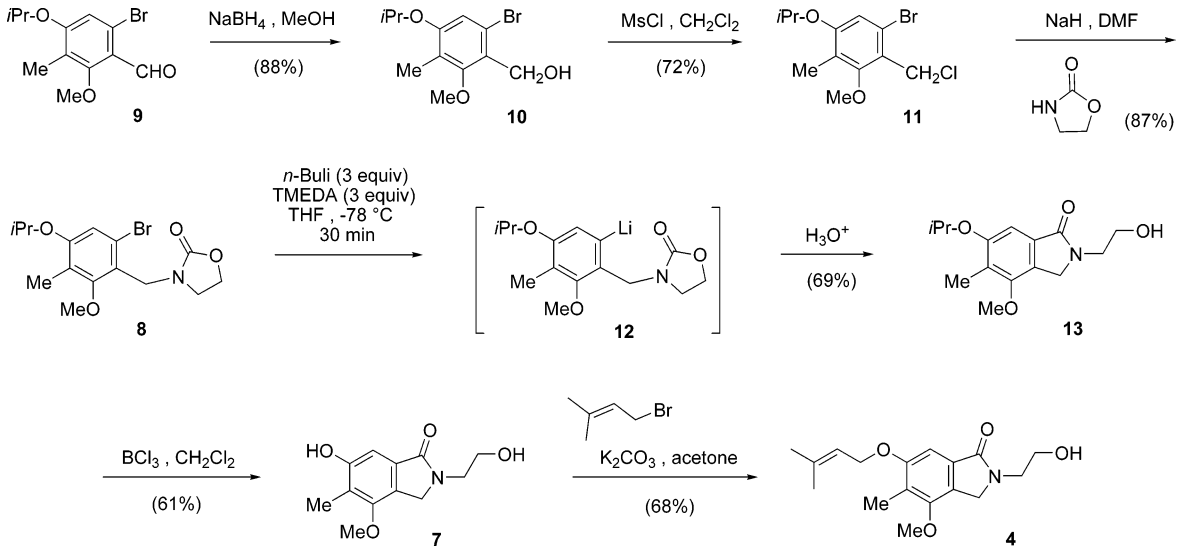
(7) Moreau, A.; Couture, A.; Deniau, E.; Grandclaudon, P.; Lebrun, S. *Org. Biomol. Chem.* **2005**, *3*, 2305−2309.

10.1021/jo052592f CCC: $33.50
Published on Web 03/04/2006

SCHEME 1



SCHEME 2



prenylation of **7**, and we then conjectured that this fused alkaloid would be conceivably assembled by a Parham-type cyclization of the *N*-bromobenzyl-substituted oxazolidinone **8** (retrosynthetic Scheme 1, path b) equipped with the diverse and dense functionalities present in the targeted compound. We also anticipated that interception of the aryllithiated species derived from **8** by the oxazolidinone ring system, i.e., a cyclic carbamate, would provide the potential for direct access to a protected version of the target **7** and the concomitant connection of the hydroxyalkyl chain.

Our investigation toward this synthetic approach started from the benzaldehyde derivative **9** equipped at this point of the synthesis with an isopropyl protecting group liable to survive the planned synthetic manipulations. Conversion of this starting material to one of the reaction partners required for the assembly of **8**, i.e., the rather congested benzyl chloride **11**, was achieved in two steps as shown in Scheme 2.

Thus, manipulation of the carboxaldehyde residue in **9** by reduction to the benzyl alcohol **10** was followed by complete and smooth conversion into the halogenated derivative **11** upon treatment with methanesulfonyl chloride (MsCl) in CH_2Cl_2.[8] The subsequent installation of the oxazolidinone unit was ensured by N-alkylation of 2-oxazolidinone with the benzyl chloride derivative **11**, and this simple operation delivered the cyclic carbamate precursor **8** in an excellent yield (Scheme 2). To ensure the optimal formation of the mandatory lithiated species **12**, variations of the solvent, base, temperature profile, and the inclusion of anion modifiers were all screened on the basis of precedents which have been shown to favor halogen/metal interconversion while sparing sensitive functionalities.[5] After considerable experimentations, we found that adding parent compound **8** to *n*-butyllithium (3 equiv) and TMEDA (3 equiv) in THF at −78 °C for 30 min led to complete consumption of the starting material and to isolation solely of the hydroxyalkyl chain tethered isoindolinone **13** in a fairly good yield. With this highly substituted isoindolinone **13** in hand, we were only a deprotection and a prenylation away from the target natural product. Thus, treatment of **13** with BCl_3 in CH_2Cl_2 under mild conditions triggered off the cleavage of the isopropyl protecting group. Finally O-prenylation in the sequel of the phenolic 6-OH group of **7**, the immediate precursor of porritoxin,[3] delivered the target final compound in an excellent yield. The spectral data and melting point of **4** were in excellent agreement with those published for porritoxin.[2,3]

In conclusion, we have completed a concise second total synthesis of the naturally occurring isoindolinone porritoxin. The advantages of the synthesis lie mainly in the experimental simplicity for the elaboration of the intermediates involved in the assembly of this alkaloid, the high efficiency, and above

(8) (a) van Oijen, A. H.; Huck, N. P. M.; Kruijtzer, J. A. W.; Erkelens, C.; van Boom, J. H.; Liskamp, R. M. J. *J. Org. Chem*. **1994**, *59*, 2399−2408. (b) Vieira, E.; Bingelli, A.; Breu, V.; Bur, D.; Fischli, W.; Güller, R.; Hirth, G.; Märki, H. P.; Müller, M.; Oefner, C.; Scalone, M.; Stadler, H.; Wilhelm, M.; Wostl, W. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 1397−1402.

all, the mildness of reaction conditions and the use of nonhazardous reagents. We also believe that this work provides a strong incentive for the elaboration of similar structurally modified naturally occurring alkaloids and their biogenetic congeners.

Experimental Section

(6-Bromo-4-isopropoxy-2-methoxy-3-methylphenyl)methanol (10). $NaBH_4$ (0.24 g, 6.3 mmol) was added portionwise to a stirred solution of **9** (1.52 g, 5.3 mmol) in MeOH (25 mL). Stirring was maintained at rt for an additional 1 h. After concentration under vacuum, the residue was dissolved in CH_2Cl_2 (20 mL) and washed with aqueous satd NH_4Cl solution (20 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 ethyl acetate/hexanes (30:70) as eluent: white crystals from hexane/toluene, 1.35 g (88%); mp 86−87 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (d, J = 6.1 Hz, 6H), 2.07 (s, 3H), 2.22 (br. s, 1H), 3.78 (s, 3H), 4.48 (hept, J = 6.1 Hz, 1H), 4.75 (s, 2H), 6.85 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.3, 22.1, 60.1, 61.9, 70.8, 113.3, 120.9, 121.7, 125.6, 157.3, 158.8. Anal. Calcd for $C_{12}H_{17}BrO_3$: C, 49.84; H, 5.93. Found: C, 50.01; H, 5.87.

6-Bromo-4-isopropoxy-2-methoxy-3-methylbenzyl Chloride (11). Methanesulfonyle chloride (MsCl, 0.80 g, 7.0 mmol) was added by syringe to a solution of the benzyl alcohol derivative **10** (1.33 g, 4.6 mmol) and Et_3N (0.71 g, 7.0 mmol) in CH_2Cl_2 (40 mL) at 0 °C. The solution was stirred overnight at rt, washed with aqueous satd $NaHCO_3$ solution and brine, and dried ($MgSO_4$). Evaporation of the solvent under vacuum afforded a yellow oil (1.02 g, 72%) which was used in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (d, J = 6.1 Hz, 6H), 2.07 (s, 3H), 3.83 (s, 3H), 4.47 (hept, J = 6.1 Hz, 1H), 4.78 (s, 2H), 6.87 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.5, 22.1, 41.8, 61.8, 70.8, 113.3, 120.8, 122.5, 122.8, 157.9, 158.7.

3-(6-Bromo-4-isopropoxy-2-methoxy-3-methylbenzyl)oxazolidin-2-one (8). A solution of oxazolidin-2-one (0.37 g, 4.25 mmol) in THF (10 mL) was added to a stirred suspension of NaH (0.12 g, 5.0 mmol) in THF (20 mL) under Ar. Once the addition was complete (ca. 30 min), the mixture was stirred for 1 h at rt. A solution of **11** (1.31 g, 4.25 mmol) in THF (10 mL) was then added dropwise, and the mixture was refluxed overnight. After cooling, water (20 mL) was added, and the mixture was extracted with Et_2O (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was evaporated under vacuum. The residue was purified by flash column chromatography on silica using ethyl acetate/hexanes (30:70) as eluent: white crystals from hexane/toluene, 1.02 g (67%); mp 63−64 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (d, J = 6.1 Hz, 6H), 2.07 (s, 3H), 3.35 (dd, J = 7.8 and 9.3 Hz, 2H), 3.71 (s, 3H), 4.22 (dd, J = 7.8 and 9.3 Hz, 2H), 4.48 (hept, J = 6.1 Hz, 1H), 4.58 (s, 2H), 6.85 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.9, 22.4, 43.1, 44.0, 61.5, 62.1, 71.1, 113.5, 120.1, 121.2, 122.6, 157.9, 158.3, 159.6. Anal. Calcd for $C_{15}H_{20}BrNO_4$: C, 50.29; H, 5.63; N, 3.91. Found: C, 50.50; H, 5.76; N, 4.03.

2-(2-Hydroxyethyl)-6-isopropoxy-4-methoxy-5-methyl-2,3-dihydro-1*H*-isoindol-1-one (13). A solution of *n*-BuLi (2 M in pentane, 2 mL, 4 mmol) and TMEDA (465 mg, 4 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 oxazolidinone **8** (0.47 g, 1.31 mmol) in degassed THF (15 mL) was then added dropwise through a cannula. The mixture was stirred for 30 min at −78 °C. Aqueous satd NH_4Cl solution (5 mL) was added, and after dilution with water (30 mL), the mixture was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried (Na_2SO_4), and the solvents were evaporated under vacuum to left **13** as a solid residue which was purified by flash column chromatography on silica using acetone/hexanes (80:20) as eluent: white crystals from hexane/toluene, 0.23 g (69%); mp 113−114 °C; ^{1}H 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 (hept, J = 6.0 Hz, 1H), 7.04 (s, 1H); ^{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. Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.59; H, 7.76; N, 4.83.

6-Hydroxy-2-(2-hydroxyethyl)-4-methoxy-5-methyl-2,3-dihydro-1*H*-isoindol-1-one (7). A solution of BCl_3 (1 M in CH_2Cl_2, 3.75 mL, 3.75 mmol) was added dropwise by syringe to a degassed solution of isoindolinone **13** (0.21 g, 0.75 mmol) in CH_2Cl_2 (15 mL) at 0 °C under Ar. After being stirred for 2 h at 0 °C, the reaction mixture was poured onto 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 under vacuum, and the crude solid residue was finally recrystallized from toluene−ethanol to afford **7**: white crystals; 108 mg (61%); mp 176−178 °C; ^{1}H 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); ^{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. Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.54; H, 6.19; N, 6.09.

Porritoxin (4). A stirred solution of **7** (90 mg, 0.38 mmol) and 1-bromo-3-methylbut-2-ene (69 mg, 0.46 mmol) in dry acetone (10 mL) was refluxed with K_2CO_3 (79 mg, 0.57 mmol) for 12 h. The mixture was filtered on Celite and concentrated under vacuum, and the solid residue was dissolved in Et_2O (15 mL). The cooled solution was washed with water, 10% NaOH solution (2 × 15 mL), and brine and dried (Na_2SO_4). The organic layer was evaporated under reduced pressure to afford the porritoxin **4**: white crystals from hexane/toluene, 111 mg (68%); mp 115−116 °C (lit.[2] mp 115−116 °C). Analytical and spectral data matched those reported for the natural product.[2,3]

Acknowledgment. We thank MENSR for financial support (grant to A. M. and M. L.) and Mélanie Dubois for technical assistance.

Supporting Information Available: General methods and analytical data for compounds **7**, **8**, **13**, and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO052592F