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Total Synthesis of Verruculogen and Fumitremorgin A Enabled by Ligand-controlled C–H Borylation

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Abstract

Verruculogen and fumitremorgin A are bioactive alkaloids that contain a unique eight-membered endoperoxide. Although related natural products such as fumitremorgins B and C have been previously synthesized, we report the first synthesis of the more complex, endoperoxide-containing members of this family. A concise route to verruculogen and fumitremorgin A relied not only on a hydroperoxide/indole hemiaminal cyclization, but also on the ability to access the seemingly simple starting material, 6-methoxytryptophan. An iridium-catalyzed C–H borylation/Chan–Lam procedure guided by an *N*-TIPS group enabled the conversion of a tryptophan derivative into a 6-methoxytryptophan derivative, proving to be a general way to functionalize the C6 position of an *N*,C3-disubstituted indole for the synthesis of indole-containing natural products and pharmaceuticals.

Graphical abstract

Fumitremorgin A (**1**, Figure 1)¹ and verruculogen (**2**)² stand alone as the only family of alkaloids that harbor an eight-membered endoperoxide.³ Indeed, of the five-, six- and eight-membered rings embedded in these hexacyclic alkaloids, the peroxide bridge is perhaps their most astounding feature. The juxtaposition of this classic oxidant with two nearby prenyl groups and a readily oxidizable 6-methoxyindole residue add to the allure of this 40-year-old unanswered synthetic puzzle. Aside from their exotic structure, these polycyclic tryptophan-based natural products were first identified due to their tremor-inducing activity in mice,^{1,2}

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Supporting Information. Experimental procedures and analytical data (¹H and ¹³C NMR, MS) for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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and the fumitremorgins display potent activity against multi-drug resistant (MDR) cancer cell lines⁴ and also against HIV by a similar mechanism.⁵ Although family members such as fumitremorgins B and C as well as verruculogen-TR2 have been previously synthesized,⁶ the more complex, en-doperoxide-containing compounds **1** and **2** have not yet been made. In this Communication, we present concise total syntheses of **1** and **2** that hinge upon a scalable solution to the synthesis of 6-substituted tryptophan and a diastereoselective peroxide-forming ring closure.

A suitable retrosynthetic precursor to fumitremorgin A (**1**) and verruculogen (**2**) is 6-methoxytryptophan methyl ester (**3**), which would ideally be derived from a chiral and inexpensive starting material, L-tryptophan methyl ester (Figure 1). To our surprise, a short, scalable, regiocontrolled route to **3** had not been reported. Given the sheer number of tryptamine-based alkaloids with C6 substitution, this is not such an esoteric problem.⁷ The only direct route to **3** from a tryptophan derivative involves a lead tetraacetate oxidation to afford a complex mixture of 5-, 6- and 7-oxytryptophans.^{6,8} Known routes to **3** or its derivatives either involve ring synthesis⁹ or C3-functionalization of 6-methoxyindole,^{10,11} which in turn is formed by ring synthesis^{11a,11c,12} (see summary of literature routes in the Supporting Information). To fill this gap in methodology, C–H functionalization logic¹³ was applied to the C6 problem.

The implicit challenge of a strategy seeking to modify only the C6–H bond is evident given the known propensity of indole to react preferentially at C2,¹⁴ C3,¹⁴ and C7.¹⁵ In fact, it could be argued that the C6 position is the most difficult position to directly functionalize on an indole, even when considering electrophilic aromatic substitution and directed *ortho*-metalation strategies.¹⁶ C–H borylation was selected as the method of choice to solve this problem given its demonstrated utility on tryptophan systems^{14b,15d} and recent reports showing ligand control of regioselectivity.¹⁷ Additionally, we postulated that a large blocking group on the indole nitrogen such as a TIPS group would be necessary to obtain the desired regioselectivity. Thus, Boc-L-Trp(TIPS)-OMe (**4**; Figure 2) was chosen as our starting point in order to shield the C2 and C7 positions from reacting.^{14a} Initially, reaction of **4** with B₂Pin₂ under catalytic [Ir(cod)Cl]₂ and dtbpy (**L1**) in octane^{14a} led to low reactivity (5% isolated yield) and low regioselectivity (2:1) of the desired C6-borylated tryptophan product **6** (Figure 2A, entry 1). Employing conditions developed for pyrrole-type heteroarenes,^{14b} which involve HBPIn under catalytic [Ir(cod)OMe]₂ and dtbpy (**L1**) in MTBE (specific solvent for tryptophan substrates), none of the desired C6-borylated product was obtained (entry 2). As such, optimization of reaction conditions was needed. In order to understand the effect of B₂Pin₂ versus HBPIn, entry 1 was repeated using HBPIn instead of B₂Pin₂ (entry 3), and entry 3 was repeated using B₂Pin₂ instead of HBPIn (entry 4), but neither of these conditions provided product. A solvent change from MTBE to a nonpolar solvent, hexanes,^{14b} gratifyingly resulted in 23% isolated yield of a 2:1 mixture of **6** and **5**, with 52% recovered **4** (entry 5). When both HBPIn and B₂Pin₂ were added,¹⁸ this led to an improved 47% isolated yield and 2.7:1 C6:C5 regioselectivity (entry 6). Judging that dtbpy (**L1**) has reached its limit in terms of regioselectivity, the ligand was changed. An immediate effect was observed when using tetramethylphenanthroline (Me₄phen; **L2**),¹⁹ whereby 64% isolated yield of a 3.8:1 mixture of **6** and **5** was obtained (entry 7). Eliminating HBPIn led to

lower yield (entry 8), whereas removing B₂Pin₂ was detrimental to the reaction (entry 9). Although a longer reaction time did not improve the reaction (entry 10), slightly higher temperatures led to 100% conversion (74% isolated yield) for the first time (entry 11). Using these optimized conditions of 5 mol% [Ir(cod)OMe]₂, 10 mol% ligand, 0.25 equiv. HBPIn, and 4.0 equiv. B₂Pin₂ in hexanes at 80 °C in a sealed tube for 24 h, a further ligand screen was conducted (entries 12–14). Out of these, phenanthroline (phen; **L3**) was the most effective, resulting in 77% isolated yield and 8.0:1 C6:C5 regioselectivity (entry 12). Since reduction of catalyst loading to 2 mol% slightly decreased the yield (entry 15), the conditions from entry 12 were retained.

Although this optimization was sufficient for the initial goal of generating 6-substituted tryptophans, a substrate screen was performed to examine the scope of *N*,C3-disubstituted indole substrates that can undergo C6–H borylation (Figure 2B). Re-screening ligands **L1**–**L3** for every substrate revealed that phen (**L3**) was indeed the best ligand for this transformation. Both C3-substituted and C2,C3-disubstituted indoles were viable substrates (**7**–**10**), however, sensitive functional groups such as a primary bromide (as in **12**) were not tolerated. Of note, reaction of desilylated **4** (i.e., Boc-*L*-Trp-OMe) only led to small amounts of C2- and C7-borylated products (not shown), indicating the importance of the TIPS group.^{15c,15d} As an extension of this indole reaction methodology, *N*-TIPS-carbazole (**13**) was reacted to give C2,C7-bis-borylated product, and C3-ethylated carbazole **14** provided C7-monoborylated product.

With this enabling method in hand, the total synthesis of fumitremorgin A (**1**) and verruculogen (**2**) from inexpensive *L*-tryptophan became a more realistic endeavor since decagram quantities of **3** were now accessible. This undertaking, however, was not without further challenges (Figure 3A).²⁰ Thus, a variety of dihydro- and tetrahydro-β-carbolines represented by the general structure **15** were subjected to oxidants in an attempt to realize a late-stage oxidation that mimics the biosynthetic pathway to **1** and **2**.²¹ In spite of these efforts, none of these reactions resulted in the endoperoxide **16**. Some of these reactions, however, encouragingly led to intermediates such as **17** and **18** that contain the required peroxide and cyclic motifs (Figure 3B). Studying these systems further, we eventually arrived at hydroperoxides **19a** and **19b**, whose NH and OOH groups can be cyclized onto 3-methyl-2-butenal (**20**) using BF₃•OEt₂ (Figure 3C). The presence of the eight-membered endoperoxide (as opposed to a seven-membered ether like **18**) and the diastereoselectivity of the hemiaminal stereocenter were confirmed by X-ray analysis of the starting material **19a** and the product **21a**. Notably, **21a/21b** contain the requisite motifs of the oxidizing peroxide bond and oxidizable π bonds present in alkaloids **1** and **2**.

This groundwork ultimately paved the way to the first total synthesis of fumitremorgin A (**1**) and verruculogen (**2**; Figure 3D). Commercially available Boc-*L*-Trp-OMe (**22**) was protected with TIPS-Cl to give the precursor for the Ir-catalyzed borylation, Boc-*L*-Trp(TIPS)-OMe (**4**). As described in Figure 2, **4** was borylated at the C6 position, then immediately subjected to Chan–Lam coupling²² with methanol in one pot to give **23** in 65% yield and with 8:1 C6:C5 selectivity. Deprotections with HCl and TBAF led to 6-methoxytryptophan methyl ester (**3**; not shown) in 91% yield from **23**. Pictet–Spengler

reaction with TBDPS-protected peroxy-aldehyde **24** (see the Supporting Information for its preparation from **20**) led to tricyclic peroxide **25** in 49% yield (2:1 d.r.). Coupling with *N*-Fmoc-L-prolyl chloride (**26**) then gave **27** in 87% yield. Late-stage dehydrogenation with $\text{ZrCl}_4/\text{PhNO}^{\text{9d}}$ proved essential as other oxidants such as DDQ failed in this transformation. Fmoc removal gave pentacycle **28** (69% yield over 2 steps), followed by a chemoselective dihydroxylation with OsO_4 to give **29** (79% yield).⁶ Treatment with TBAF allowed the removal of the TBDPS group, followed by the crucial endoperoxide-forming cyclization with aldehyde **20** to give verruculogen (**2**) in 30% yield over 2 steps. It is of note that this final annulation reaction was achieved with complete diastereoselectivity. Finally, prenylation of **2** using prenyl bromide, much like the biosynthetic pathway with prenyl pyrophosphate,²¹ led to fumitremorgin A (**1**) in 95% yield.

The longstanding challenge posed by the peroxide-containing alkaloids,²³ verruculogen (**2**) and fumitremorgin A (**1**), has thus been put to rest in 11 and 12 steps, respectively, starting from a commercially available tryptophan derivative. The enabling regioselective C–H borylation of the remote C6 position of tryptophan is a forceful reminder of the simplifying power of such disconnections.²⁴ One potential application of this work is the synthesis of valuable unnatural amino acids through C–H borylation and subsequent derivatization.^{15d} Lastly, this method was conducted on a variety of related indole systems and, not surprisingly, has already been field-tested on decagram scale at Novartis for incorporation into a medicinal chemistry program.²⁵

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Retrosynthetic analysis of fumitremorgin A (1) and verruculogen (2).

Figure 2.C–H borylation of indole derivatives for the synthesis of C6-substituted tryptophans. **A.**Optimization of the C–H borylation reaction on tryptophan derivative **4** in order to preferentially achieve C6-borylation. **B.** Substrate scope involving C3-substituted indoles as well as carbazoles.

^aReagents and conditions: (a) LiHMDS, TIPS-Cl, THF, -78 °C (89%); (b) Ir[(cod)OMe]₂ (5 mol %), phenanthroline (10 mol %), HBPIn (0.25 equiv), B₂Pin₂ (4.0 equiv), hexanes, 80 °C, 24 h; then Cu(OAc)₂, Et₃N, MeOH, O₂, 23 °C, 24 h (65%, 8:1 C6:C5); (c) 3 N HCl, MeOH, 60 °C; (d) 1 M TBAF, THF (91% over 2 steps); (e) **24**, 4 Å MS, CHCl₃, 0 °C, 1 h; then TFA (10 mol %), 0 °C, 24 h (49%, 2:1 dr desired:undesired); (f) **26**, CH₂Cl₂, sat. aq. NaHCO₃ (87%); (g) PhNO, ZrCl₄, CH₂Cl₂, 0 °C (76%); (h) Et₃NH, THF, 40 °C (91%); (i) OsO₄ (2.5% in ^tBuOH), *N*-methylmorpholine *N*-oxide (50% in H₂O), MeCN:acetone:H₂O (2:2:1) (79%); (j) 1 M TBAF, THF, AcOH, DMF, 0 °C; (k) **20**, 4 Å MS, BF₃·OEt₂, DCE, -20 °C (30% over 2 steps); (l) prenyl bromide, Bu₃SnO, Bu₄NI, DCE, 23 °C, 17 h (95%).

Figure 3.

Total synthesis of verruculogen (**2**) and fumitremorgin A (**1**). **A.** Failed attempts at directly oxidizing the indole core **15**. **B.** Isolated intermediates while attempting to forge the eight-membered endoperoxide. **C.** Successful eight-membered endoperoxide formation. **D.** First total synthesis of verruculogen (**2**) and fumitremorgin A (**1**) enabled by indole C6-borylation/oxidation and eight-membered endoperoxide closure.