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Communication

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Total Synthesis of Verruculogen and Fumitremorgin A Enabled by Ligand-Controlled C−H Borylation

Yu Feng,[‡] Dane Holte,[‡] Jochen Zoller, Shigenobu Umemiya, Leah R. Simke, and Phil S. Baran*

Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States

Supporting Information

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.

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] and the fumitremorgins display potent activity against multi-drug resistant (MDR) cancer cell lines[4] 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, endoperoxide-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, regio-controlled 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 involve either ring synthesis[9] or C3-functionalization of 6-methoxyindole,[10,11] which in turn is formed by ring synthesis[11a,c,12] (see summary of literature routes in the Supporting Information). To fill this gap in methodology, C−H functionalization logic[13] was applied to the C6 problem.

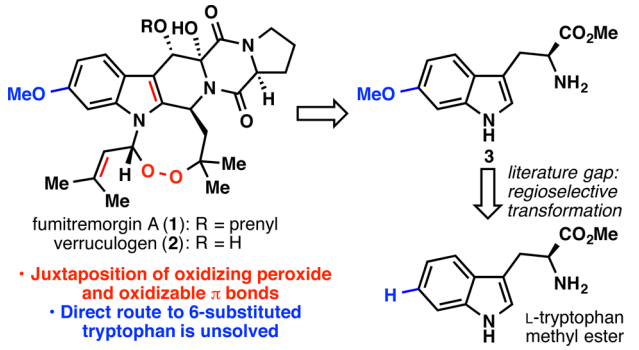

Figure 1. Retrosynthetic analysis of fumitremorgin A (**1**) and verruculogen (**2**).

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 B_2Pin_2 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,

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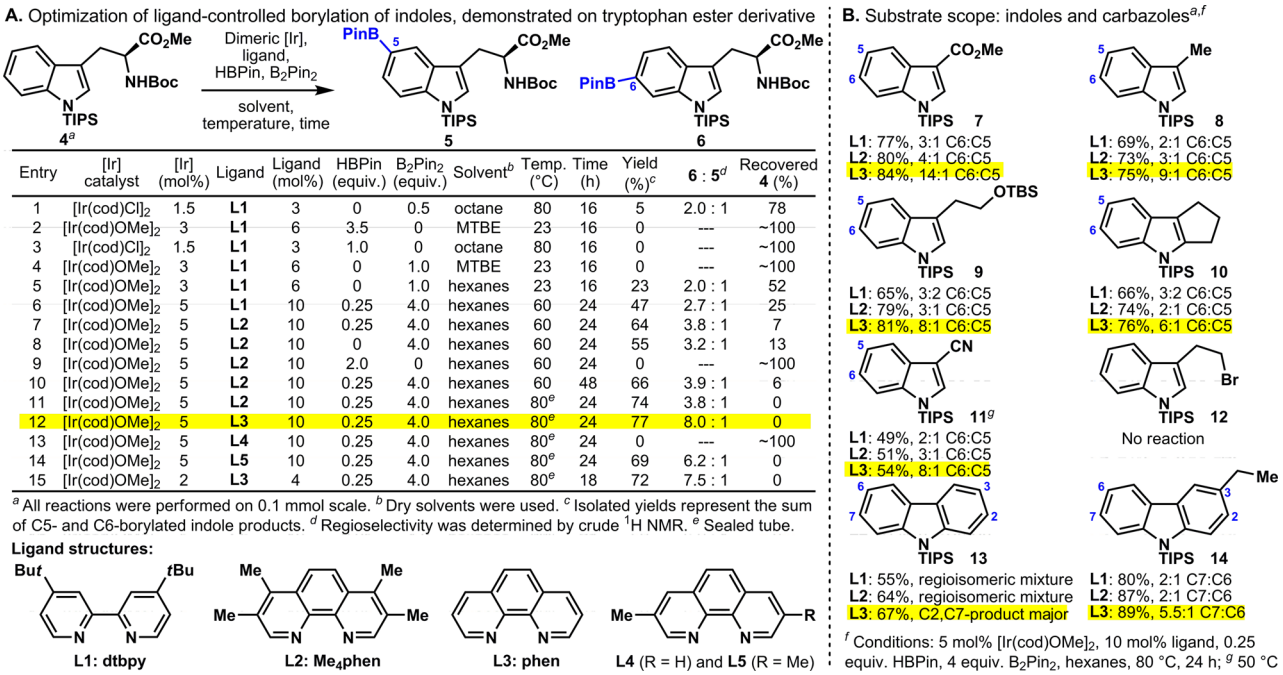

Entry	[Ir] catalyst	[Ir] (mol%)	Ligand	Ligand (mol%)	HBPin (equiv.)	B_2Pin_2 (equiv.)	Solvent[b]	Temp. (°C)	Time (h)	Yield (%)[c]	6 : 5[d]	Recovered 4 (%)
1	$[Ir(cod)Cl]_2$	1.5	L1	3	0	0.5	octane	80	16	5	2.0 : 1	78
2	$[Ir(cod)OMe]_2$	3	L1	6	3.5	0	MTBE	23	16	0	---	~100
3	$[Ir(cod)Cl]_2$	1.5	L1	3	1.0	0	octane	80	16	0	---	~100
4	$[Ir(cod)OMe]_2$	3	L1	6	0	1.0	MTBE	23	16	0	---	~100
5	$[Ir(cod)OMe]_2$	3	L1	6	0	1.0	hexanes	23	16	23	2.0 : 1	52
6	$[Ir(cod)OMe]_2$	5	L1	10	0.25	4.0	hexanes	60	24	47	2.7 : 1	25
7	$[Ir(cod)OMe]_2$	5	L2	10	0.25	4.0	hexanes	60	24	64	3.8 : 1	7
8	$[Ir(cod)OMe]_2$	5	L2	10	0	4.0	hexanes	60	24	55	3.2 : 1	13
9	$[Ir(cod)OMe]_2$	5	L2	10	2.0	0	hexanes	60	24	0	---	~100
10	$[Ir(cod)OMe]_2$	5	L2	10	0.25	4.0	hexanes	60	48	66	3.9 : 1	6
11	$[Ir(cod)OMe]_2$	5	L2	10	0.25	4.0	hexanes	80[e]	24	74	3.8 : 1	0
12	$[Ir(cod)OMe]_2$	5	L3	10	0.25	4.0	hexanes	80[e]	24	77	8.0 : 1	0
13	$[Ir(cod)OMe]_2$	5	L4	10	0.25	4.0	hexanes	80[e]	24	0	---	~100
14	$[Ir(cod)OMe]_2$	5	L5	10	0.25	4.0	hexanes	80[e]	24	69	6.2 : 1	0
15	$[Ir(cod)OMe]_2$	2	L3	4	0.25	4.0	hexanes	80[e]	18	72	7.5 : 1	0

[a] All reactions were performed on 0.1 mmol scale. [b] Dry solvents were used. [c] Isolated yields represent the sum of C5- and C6-borylated indole products. [d] Regioselectivity was determined by crude ^1H NMR. [e] Sealed tube.

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.

optimization of reaction conditions was needed. In order to understand the effect of B_2Pin_2 versus HBPin, entry 1 was repeated using HBPin instead of B_2Pin_2 (entry 3), and entry 2 was repeated using B_2Pin_2 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 B_2Pin_2 were added,[18] this led to an improved 47% isolated yield and 2.7:1 C6:C5 regioselectivity (entry 6). Once it was judged that dtbpy (**L1**) had reached its limit in terms of regioselectivity, the ligand was changed. An immediate effect was observed when using tetramethylphenanthroline (Me_4phen; **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 B_2Pin_2 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 of HBPin, and 4.0 equiv of B_2Pin_2 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). Rescreening 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**−**11**); 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) led to only small amounts of C2- and C7-borylated products (not shown), indicating the importance of the TIPS group.[15c,d] 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 $BF_3{\cdot}OEt_2$ (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** and **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 and then immediately subjected to Chan−Lam coupling[22] with methanol

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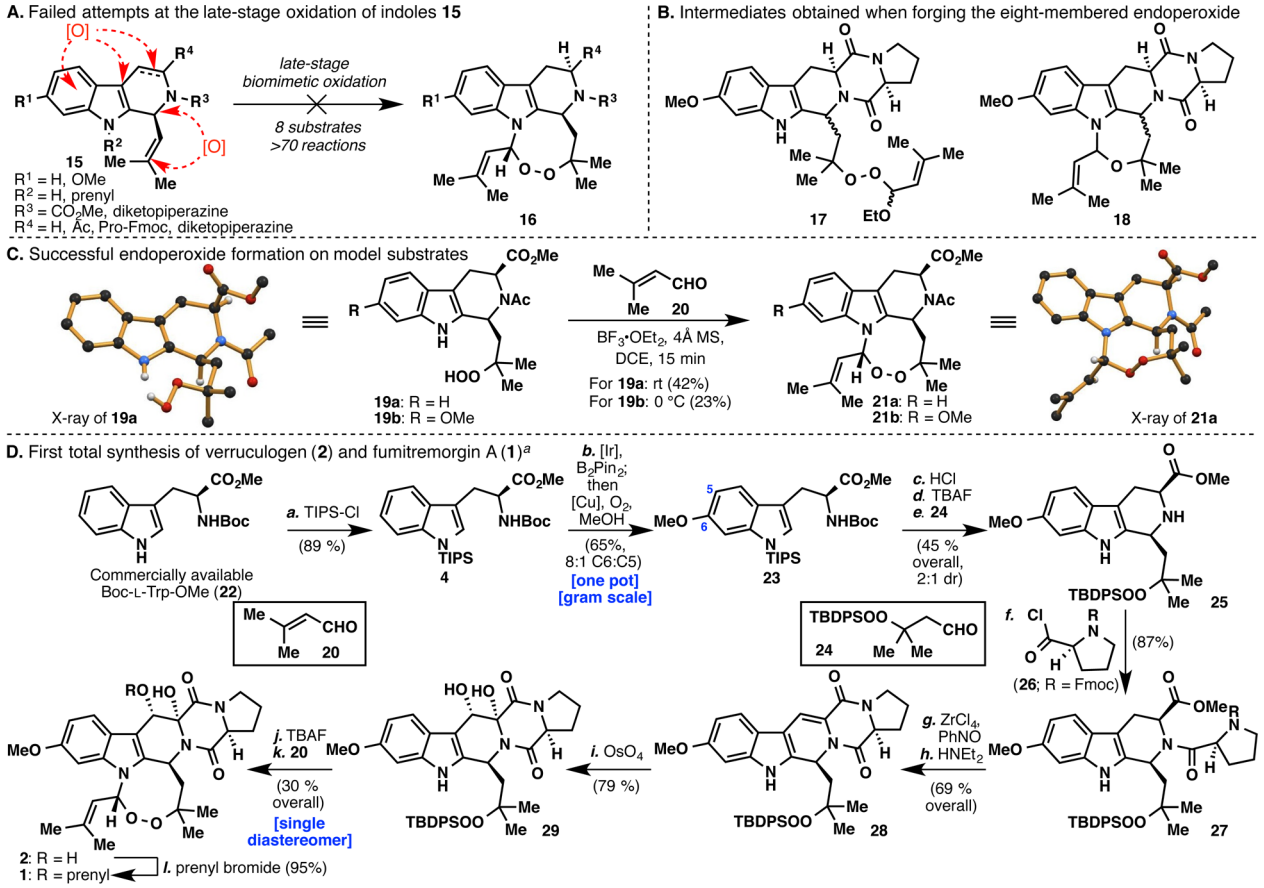

[a]Reagents and conditions: (a) LiHMDS, TIPS-Cl, THF, –78 °C (89%); (b) Ir[(cod)OMe]$_2$ (5 mol %), phenanthroline (10 mol%), HBPin (0.25 equiv), B_2Pin_2 (4.0 equiv), hexanes, 80 °C, 24 h; then Cu(OAc)$_2$, Et$_3$N, MeOH, O$_2$, 23 °C, 24 h (65%, 8:1 C6:C5); (c) 3 N HCl, MeOH, 60 °C; (d) 1 M TBAF, THF (91% over 2 steps); (e) **24**, 4Å MS, $CHCl_3$, 0 °C, 1 h; then TFA (10 mol%), 0 °C, 24 h (49%, 2:1 dr desired:undesired); (f) **26**, CH_2Cl_2, sat. aq. $NaHCO_3$ (87%); (g) PhNO, $ZrCl_4$, CH_2Cl_2, 0 °C (76%); (h) Et_2NH, THF, 40 °C (91%); (i) OsO_4 (2.5% in ^{t}BuOH), *N*-methylmorpholine *N*-oxide (50% in H_2O), MeCN:acetone:H_2O (2:2:1) (79%); (j) 1 M TBAF, THF, AcOH, DMF, 0 °C; (k) **20**, 4Å MS, BF_3•OEt_2, DCE, –20 °C (30% over 2 steps); (l) prenyl bromide, Bu_2SnO, Bu_4NI, 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) Intermediates isolated 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.

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 dr). Coupling with *N*-Fmoc-L-prolyl chloride (**26**) then gave **27** in 87% yield. Late-stage dehydrogenation with $ZrCl_4$/PhNO[9d] proved essential, as other oxidants such as DDQ failed in this transformation. Fmoc removal gave pentacycle **28** (69% yield over two 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 two 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 synthetic 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]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b07154.

^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

Experimental procedures and characterization data (PDF)

X-ray crystallographic data for **19** (CIF)

X-ray crystallographic data for **21** (CIF)

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AUTHOR INFORMATION

Corresponding Author

*pbaran@scripps.edu

Author Contributions

‡Y.F. and D.H. contributed equally to this paper.

Notes

The authors declare no competing financial interest.

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