Modular Total Synthesis of the 5/5-Spirocyclic Spiroindimicins

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Abstract. Total syntheses of the 5/5-spirocyclic indoline alkaloids spiroindimicins B, C, D, E, F, and G have been achieved via a modular approach. Our route features direct coupling of halogenated pyrrolemetal and isatin partners, Suzuki coupling to append the indole unit, Lewis acid-mediated spirocyclization, and divergent functionalization to various family members. These syntheses are concise (6–7 steps from commercial materials), scalable, and highly amenable to analogue synthesis. Further studies of the antiparasitic properties of this class have revealed promising activity against *T. brucei* for certain congeners. Together with our prior approach to 6/5-family members, our work constitutes a synthetic solution to all known spiroindimicin natural products.

Introduction:

The spiroindimicins (SPMs) are a small family of dimeric tryptophan alkaloids isolated from various marine *Streptomyces* species (**1**–**8**, Figure 1). Their structures are characterized, as their name might suggest, by a spirocyclic indoline or indolenine motif, around which additional pyrrole and indole rings are structured, with at least one chlorine atom present in the naturally occurring members.[1] Aside from representing rather unique topologies within the dimeric tryptophan alkaloids,[2] these natural products were found to display moderate cytotoxicity against several cancer cell lines.[1]

Our group has recently developed an approach to the spiroindimicins bearing a central 5/6-spirocyclic core, completing the first syntheses of spiroindimicin A (**1**) and its congener spiroindimicin H (**5**).[3] These syntheses relied on a key Pd-catalyzed spirocyclization to construct their core skeletons and small suite of analogues, screening of which revealed promising antiparasitic activity. In continuation of our interest in this family, we aimed to develop a concise route to the more prevalent 5/5-spirocyclic members (i.e., **2**–**4**, **6**–**8**), representing the remainder of the class.

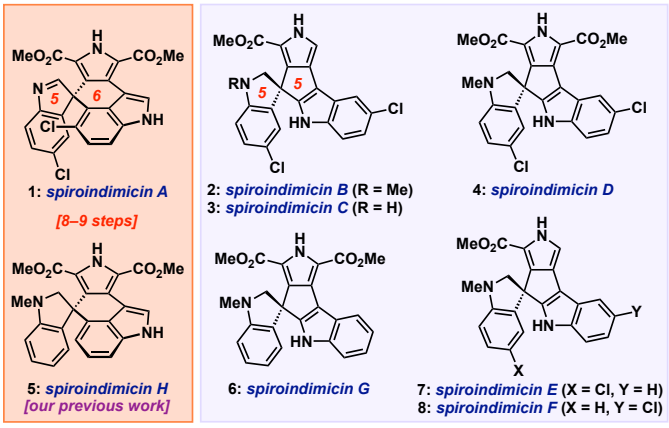


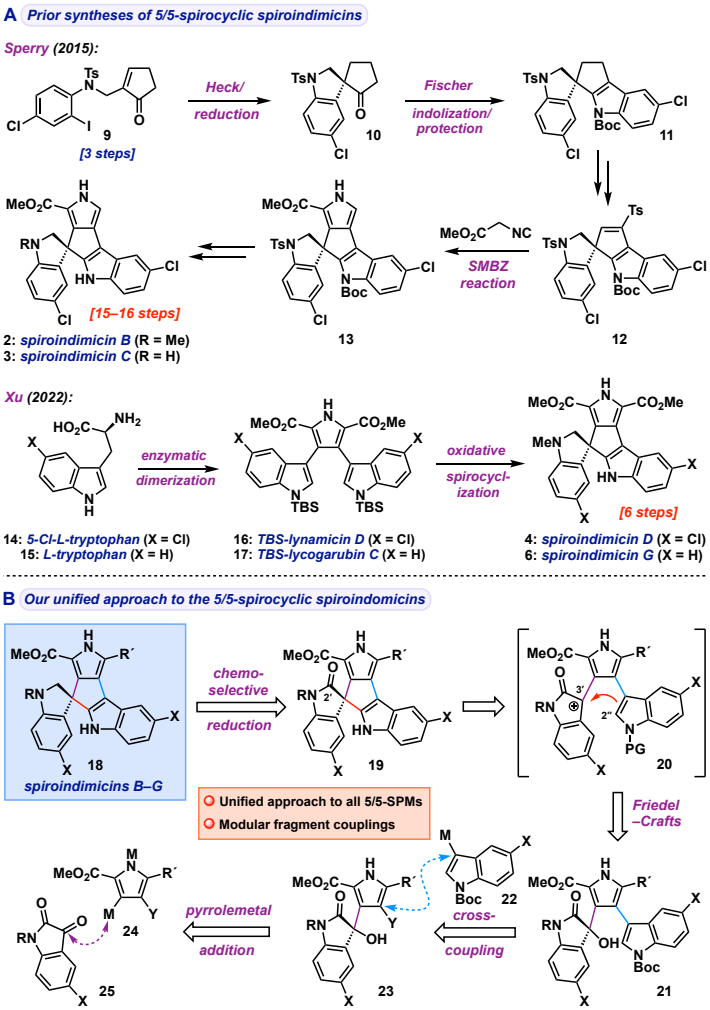
Figure 1. The spiroindimicin alkaloids.

To date, two total syntheses of the 5/5-spirocyclic spiroindimicins have been reported (Scheme 1A).[4] The first, by Sperry and Blair in 2015, provides access to racemic spiroindimicins B (**2**) and C (**3**) in 15–16 steps from commercial materials via early-stage construction of the spiroindoline via a Heck reaction, followed by installation of the remaining indole and pyrrole rings via Fisher indolization and Schöllkopf–Magnus–Barton–Zard (SMBZ) reaction, respectively.[5a] Very recently, Xu et al. have reported the biomimetic oxidative spirocyclization of *N*-protected versions of lynamicin D (**16**) and lycogarubin C (**17**), prepared via enzymatic dimerization of L-5-chlorotryptophan (**14**) or L-tryptophan (**15**), to arrive at short racemic syntheses of spiroindimicins D (**4**) and G (**6**, 6 steps from **14** or **15**), as well as the 6/5-spiroindimicins A (**1**) and H (**5**).[5b] Herein, we report our distinct approach to the 5/5-spiroindimicins via

the modular union of three functionalized fragments, and demonstrate its utility in the concise preparation of spiroindimicins B, C, D, E, F, and G.

Results and discussion:

Our strategy focused on providing flexibility for modular access to all known 5/5-spiroindimicin family members as well as later analogue preparation (Scheme 1B). We envisaged fragment couplings wherein each of the 3 heteroaromatic units might be easily varied, leading back to simple isatin (**25**), pyrrole (**24**), and indole (**22**) building blocks. Retrosynthetically, this led us to trace back generalized structure **18** to its C-2′-oxo analogue **19**, which in a forward sense would be transformed to the natural products through chemoselective reduction of the oxindole to indoline in the presence of the methyl ester(s). Spirocycle **19** was seen to arise through a Friedel–Crafts cyclization of C-2″ of the pendant indole ring onto a C-3′-cation formed via acid-mediated ionization of tertiary alcohol **21**, a step that was projected to be challenging due to the high degree of strain engendered in newly formed 5-membered ring containing 4 sp^2 carbon atoms. Triaryl compound **21**, which encompasses all 3 aromatic fragments of the natural products, might arise through two key C–C fragment couplings: a chemoselective Suzuki cross-coupling between indole boronate **22** and oxindole-pyrrole halide **23**, itself available through addition of highly functionalized pyrrolemetal species **24** to the ketone of isatin **25**.

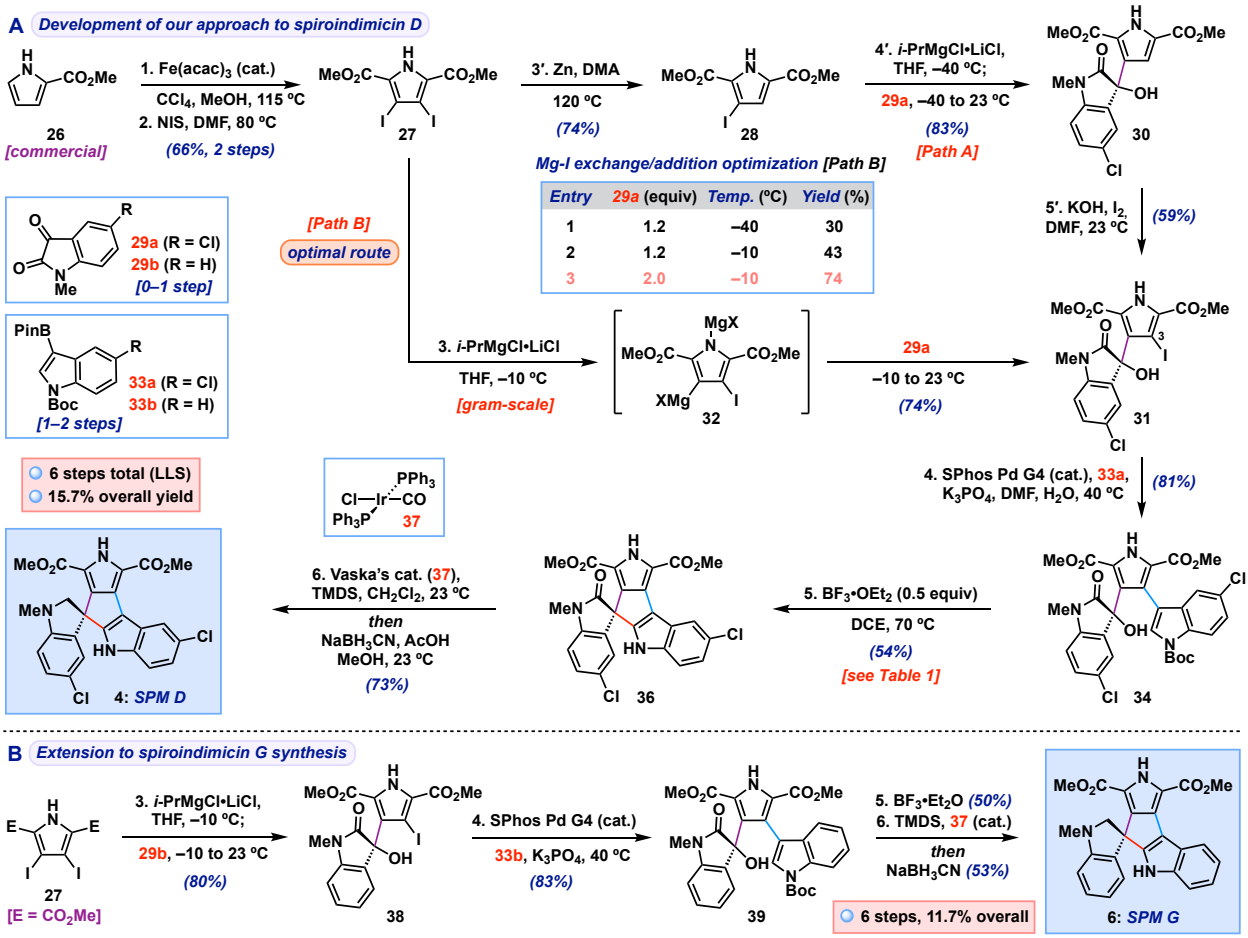


Scheme 1. (**A**) Prior total syntheses of 5/5-spirocyclic spiroindimicins. (**B**) Our modular approach to all 5/5-spiroindimicins.

We initiated our studies by targeting family members containing a pyrrole diester unit, namely spiroindimicins D (**4**) and G (**6**). Our synthesis began with the preparation of multigram quantities of pyrrole iodide **28** via a known[3,6] 3-step sequence from methyl 2-pyrrolecarboxylate (**26**), proceeding via diiodide **27** (Scheme 2A, Path A). Iodide **28** could be coupled with the indoline surrogate *N*-methyl 5-chloroisatin (**29a**)[7] via transformation into the corresponding Grignard reagent using Knochel's magnesium-halide exchange protocol[8] using *i*-PrMgCl•LiCl (2.2 equiv) at –40 °C, followed by addition of **29a**. In fact, this dianion-based protocol proved uniquely feasible versus low temperature lithium-halogen exchange with *n*-BuLi, presumably due to its greater functional group tolerance. The union of these two fragments delivered tertiary alcohol **30** in 83% yield. Iodination of the pyrrole moiety under basic conditions (KOH, I_2)[3] delivered iodide **31** bearing a suitable handle for installation of the remaining indole unit (59%).

Since the sequence outlined above involved an inelegant removal and reinstallation of a pyrrole iodide handle at C-3 (spiroindimicin numbering), we envisaged a more streamlined preparation of **31** via addition of a dianion equivalent derived from deprotonation and magnesium-iodide exchange of diiodide **27** (Scheme 2, Path B). If successful, this protocol would save two steps en route to **31**. Upon treatment of

27 with *i*-PrMgCl•LiCl under the same conditions employed for **28**, we were pleased to observe formation of iodide **31**, albeit in moderate yield (30%), without any competitive formation of deiodinated product **30**. Ultimately, screening efforts determined that by conducting the magnesium-iodine exchange at higher temperature (–10 °C), increasing the equivalents of isatin **29a** slightly (2 equiv), and azeotropically drying both partners beforehand, an improved yield of **31** (74%) could be achieved with similar results obtained on gram-scale.

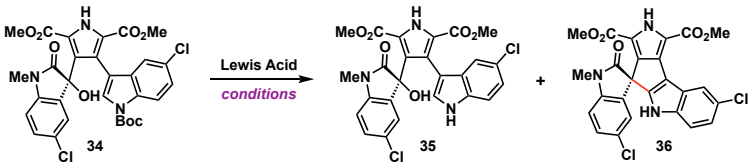


Scheme 2. (**A**) Development of a concise approach to spiroindimicin D (**4**); (**B**) Extension of the strategy to the deschloro variant, spiroindimicin G (**6**).

With reliable access to diaryl iodide **31**, we next focused on the attachment of the remaining indole ring via cross-coupling. Initial efforts based on Suzuki and Stille coupling protocols showed this to be a non-trivial task, with no product obtained under many standard conditions. A complicating factor was the limited solubility of iodide **31** in several typical solvents employed in the cross-couplings (e.g., THF, PhMe, 1,4-dioxane), especially when water was included in the Suzuki protocols. Eventually, after much experimentation (see Table S1), we found that by employing DMF/H_2O (20:1) as solvent with Buchwald's Pd SPhos G4[9] as the precatalyst and K_3PO_4 as base at 40 °C, we could obtain the desired Suzuki coupling product **34** (51%) with indole C-3 boronic acid ester **33a**[3] (1.8 equiv). Since **33a** suffers from competitive protodeborylation under the reaction conditions, increasing the amount of **33a** to 2.5 equivalents led to an optimal 81% yield of **34**, which it should be noted is formed as a 1:1 mixture of diastereomers due to the introduction of an axis of chirality in the coupling.

With all the requisite carbons of spiroindimicin D (**4**) now in place in **34**, a tandem *N*-Boc deprotection/spirocyclization to spiroindimicin oxindole **36** could be attempted under acidic conditions.

After screening many acidic systems, we found that Lewis acids were superior to Brønsted acid promoters, with generally a stoichiometric amount and heating being required to reach high conversion (Table 1, entries 1–7; see SI for full details). BF_3•OEt_2 emerged as the most effective Lewis acid, since this minimized the formation of de-Boc material **35**, though this had to be balanced with complicating decomposition of the product with prolonged reaction times. Ultimately, subjection to substoichiometric BF_3•OEt_2 (0.5 equiv) in DCE at 70 °C gave rapid conversion (20 min) to the desired spirocycle **36** in 58% NMR yield (entry 9). We found these conditions to translate reasonably well on preparative scale (albeit with higher BF_3•OEt_2 loading), affording **36** in 54% isolated yield, a result we deemed acceptable given the strained nature of the fused sp^2-rich cyclopentane being constructed.



Entry	Lewis Acid (equiv)	Solvent	Temp. (°C)	Time	35 (%)[a]	36 (%)[a]
1	$Sc(OTf)_3$ (1.0)	DCE	70	30 min	11	31
2	$In(OTf)_3$ (1.0)	DCE	70	1 h	19	22
3	$Cu(OTf)_2$ (1.0)	DCE	70	4 h	–	42
4	TMSOTf (1.0)	DCE	23	1 h	n.d.[b]	22
5	$Zn(OTf)_2$ (1.0)	DCE	85	24 h	83	11
6	$Ce(OTf)_3$ (1.0)	DCE	85	24 h	55	38
7	BF_3•OEt_2 (1.0)	DCE	70	30 min	–	43
8	BF_3•OEt_2 (1.0)	DCE	70	5 min	–	55
9	*BF_3•OEt_2 (0.5)*	*DCE*	*70*	*20 min*	–	*58*
10	BF_3•OEt_2 (1.0)	PhMe	70	24 min	12	54

[a]All reactions were carried out on 0.02 mmol scale; ^{1}H NMR yields with CH_2Br_2 as internal standard. [b]Not determined.

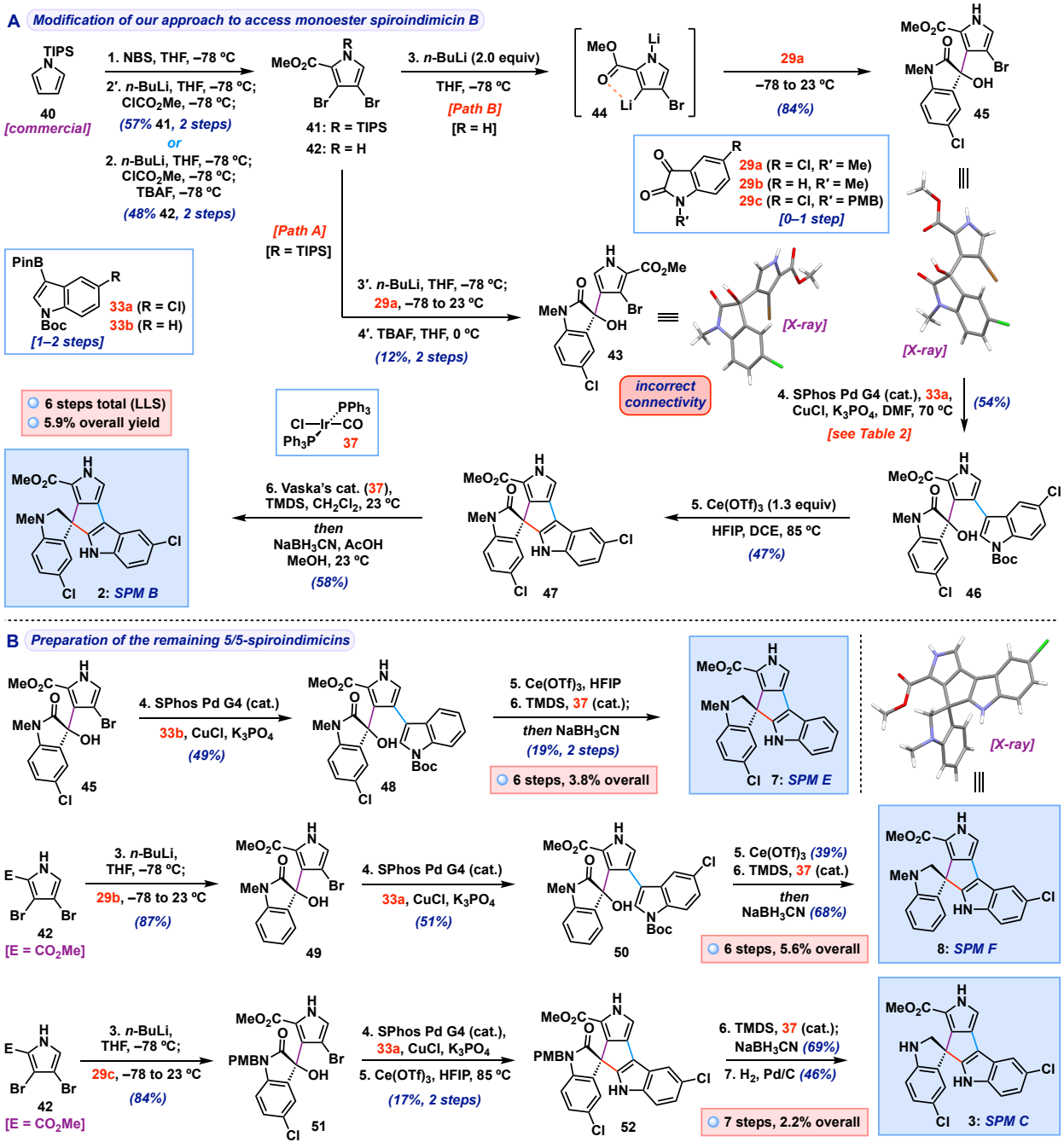
Table 1. Optimization of deprotection/spirocyclization to SPM oxindole **36**.

To access spiroindimicin D (**4**), a chemoselective reduction of the oxindole of **36** to an indoline in the presence of the two esters was required. After screening potential solutions, we found that the desired transformation could be achieved under Dixon's conditions,[10] involving Ir-catalyzed hydrosilylation to an intermediate *O*-silyl hemiaminal followed by its reduction with $NaBH_3CN$ in the same pot, affording spiroindimicin D (**4**) in 73% yield. Overall, our synthesis proceeds in 6 steps from commercial **26** (longest linear sequence) and 15.7% overall yield, with the synthesis proving scalable enough to provide >50 mg of **4** in a single pass.

Leveraging the modularity of our strategy, we could approach the synthesis of the closely related deschloro member spiroindimicin G[1c] (**6**, Scheme 2B). Applying the same sequence with minor modification, this time with *N*-methylisatin (**29b**) and indoleboronate **33b**, gave spiroindimicin G (**6**) also in 6 steps (11.7% overall yield).

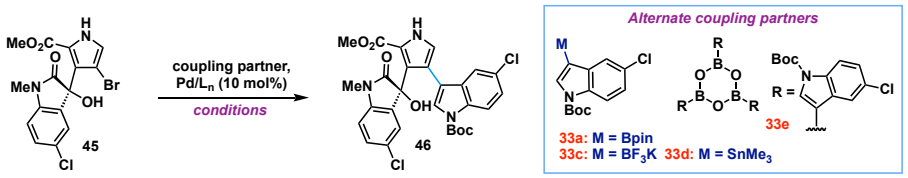
We next turned to the synthesis of spiroindimicins B, C, E, and F, all of which lack the C-2 methoxycarbonyl unit. Although in principle monodemethoxycarbonylation of SPM D (**4**) might provide access to these congeners, initial attempts along these lines were foiled by preferential hydrolysis of the incorrect ester. Thus, we instead sought to utilize our modular approach by incorporating a monoester variant of the initial halogenated pyrrolemetal fragment (**24**, R′ = H, Scheme 1B). Given existing literature precedent for the monolithiation[11] of known *N*-TIPS pyrroledibromide **41**,[12b] we began with its preparation (Scheme 3A). Commercial *N*-TIPS pyrrole was tribrominated with NBS to give an unstable tribromide that was taken forward without purification into the subsequent C-2 lithium-bromine exchange followed by trapping with methyl chloroformate.[12] This sequence gave monoester dibromide **41** in 57% over the 2 steps. Attempted lithiation at C-3, directed by the ester group, followed by addition of *N*-methyl 5-chloroisatin (**29a**) resulted in a moderate yield of an adduct that could be isolated in pure form after TIPS deprotection with TBAF (**43**, 12% over 2 steps; Path A). Although **43** appeared to have incorporated both fragments in the expected manner, the spectral data of this compound diverged from that of analogous adduct in the diester series, **31**. These concerns, coupled with the poor efficiency in its preparation, led us to consider reversing the order of the lithiation/coupling and deprotection steps (Path B). Ester **41** could therefore be deprotected to *N*-H pyrrole **42** with TBAF in good yield (80%, not shown); more step-economically, this TIPS-deprotection could be incorporated into the prior methoxycarbonylation step by simple introduction of TBAF to that reaction mixture in essentially the same overall yield (48% over 2 steps vs 46% over 3 steps). With **42** in hand, it could be engaged in our prior pyrrole dianion coupling by treatment with *n*-BuLi followed by introduction of **29a**, providing adduct **45** in 84% yield. Interestingly, the spectral data of **45**

differed from the adduct **43** from coupling of *N*-TIPS pyrrole dibromide **41** but were a better match with those obtained for diester adduct **31**. Ultimately, single crystal X-ray analysis confirmed the constitution of **45** as being that desired, allowing us to assign **43** as the constitutional isomer arising from attack of a 4-lithiopyrrole unit onto the isatin ketone, a fact later confirmed through its own crystal structure. While this outcome contrasts with the majority of studies on the lithiation/trapping of **41**,[11,12] we do note that Okano has demonstrated divergent regiochemical outcomes in a lithiation/borylation of a related pyrrole dibromide depending on the lithiation conditions employed.[13]



Scheme 3. (**A**) Synthetic entry to the monoester SPM, spiroindimicin B (**2**); (**B**) Modular preparation of spiroindimicins E (**7**), F (**8**), and C (**3**).

With gram-scale access to **45** secured, we were set to explore its Suzuki coupling with indole boronic acid ester **33a**. Unfortunately, hindered bromide **45** proved substantially less reactive than iodide **31** requiring significant experimentation to find a tractable coupling. A representative subset of our screening efforts is shown in Table 2 (for full details, see SI). Under the conditions previously optimal for **31**, we found that product **46** was formed in trace yield at best, even at higher temperatures (entry 1). Screening different coupling partners, including the corresponding 3-indolylstannane (**33d**), potassium trifluoroborate (**33c**), or boroxine (**33e**) yielded no significant improvement (entries 2–4).



Entry	Partner (equiv)	Catalyst	Additive (equiv)	Base (equiv)	Solvent[b]	Temp. (°C)	Time (h)	46 (%)[a]
1	33a (2.5)	SPhos Pd G4	–	K_3PO_4 (3.6)	DMF/H_2O	70	24	7
2	33c (2.5)	SPhos Pd G4	–	K_3PO_4 (3.6)	DMF/H_2O	70 to 90	36	–
3	33d (2.5)	$Pd(PPh_3)_4$	CuTc (1.5)	–	NMP	23 to 80	36	–
4	33e (0.9)	SPhos Pd G4	–	K_3PO_4 (3.6)	DMF/H_2O	70	24	10
5	33a (2.5)	SPhos Pd G4	CuCl (1.0)	K_3PO_4 (3.6)	DMF/H_2O	70	24	11
6	33a (2.5)	SPhos Pd G4	CuCl (1.0)	K_3PO_4 (3.6)	DMF	70	24	13
7	33a (2.5)	SPhos Pd G4	CuCl (2.5)	K_3PO_4 (3.6)	DMF	70	24	22
8	33e (0.9)	SPhos Pd G4	CuCl (2.5)	K_3PO_4 (3.6)	DMF	70	24	11
9	*33a (5.0)*	*SPhos Pd G4*	*CuCl (5.0)*	*K_3PO_4 (5.0)*	*DMF*	*70*	*24*	*44*
10	33a (5.0)	SPhos Pd G4	CuCl (2.5)	K_3PO_4 (5.0)	DMF	70	24	29
11	33a (2.5)	SPhos Pd G4	CuCl (5.0)	K_3PO_4 (3.6)	DMF	70	24	27

[a]All reactions were carried out on 0.035 mmol scale; ^{1}H NMR yield with CH_2Br_2 as internal standard. [b]For solvent mixtures the ratio was 20:1.

Other catalyst/ligands screened: $Pd(OAc)_2$/SPhos, $Pd(OAc)_2$/RuPhos, $Pd(OAc)_2$/dppf, SPhos Pd G4/SPhos, $Pd(dppf)Cl_2$, $Pd(dppf)Cl_2$/dppf, PEPPSI-IPr, XPhos Pd G2, XPhos Pd G2/XPhos, $(^tBu)_2PMe$ Pd G4, $NiCl_2$(dppp), $NiCl_2$(dppe)/dppe

Other Cu(I) source: CuI

Other bases screened: Cs_2CO_3, CsF, KO*t*-Bu

Table 2. Optimization of the construction of triaryl **46** via cross-coupling of bromide **45**.

Ultimately, the key factor in providing an efficient Suzuki coupling between **45** and **33a** proved to be the inclusion of a stoichiometric copper(I) additive as initially described by chemists at Merck.[14] In agreement with these authors, we also found stoichiometric CuCl to be superior in this regard and after minor adjustments to other parameters (entries 5–11) including increasing the equivalents of boronate partner **33a**, base, and CuCl, we were able to reproducibly generate coupled product **46** in 44% NMR yield (entry 9). On preparative scale we were able to obtain triaryl **46** in an improved 54% isolated yield under analogous conditions. Unfortunately, attempted deprotection/spirocyclization of monoester **46** under the prior BF_3-mediated conditions resulted in rapid decomposition even at lower temperatures. Thus, milder Lewis acidic conditions were required to effect this key C–C bond forming event in the monoester series; in the end, the use of $Ce(OTf)_3$ in a combination of HFIP and DCE at 85 °C was identified as optimal, providing spirocycle **47** in moderate yield (47%). Pleasingly, application of the prior oxindole reduction conditions delivered spiroindimicin B (**2**) in 58% yield, completing a 6-step total synthesis (5.6% overall yield).

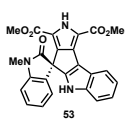
Again, as a testament to the modularity of our approach, the non-symmetrical monochlorinated compounds spiroindimicins E (**7**) and F (**8**) could be prepared simply by employing the appropriate deschloro isatin or indole boronic acid ester partners in the coupling sequence, followed by similar endgames (Scheme 3B). The successful execution of these sequences (6 steps, 3.8–5.6% overall yield) represents the first total syntheses of these family members. It is important to note that such non-symmetrical members would be challenging to selectively access via the biomimetic dimerization-based approach reported by Xu.[4b]

For the final 5/5-family member spiroindimicin C (**3**), which contains an *N*-H indoline, we prepared known isatin **29c**[15] containing a removable *N*-*p*-methoxybenzyl (PMB) group. Taking this compound through the same sequence of reactions of reactions, led to *N*-PMB spiroindimicin C (not shown). After screening a few deprotection conditions, we found that hydrogenolysis under acidic conditions (H_2, Pd/C, HCl, MeOH)[16] was able to provide the natural product **3** in 46% yield without affecting the aryl chloride units. Spiroindimicin C (**3**) was thus obtained in 7 steps from commercial **40** (2.2% overall yield). The spectral data for SPMs B, C, D, and G match well with those reported in the literature, while those for SPMs E and F show deviations in a few of signals in the ^{13}C NMR, which we attribute to a potential typographical

error.[17] We were additionally able to confirm the constitution of our synthetic spiroindimicin F (**8**) through single crystal X-ray analysis.

Given that our earlier synthetic studies in this alkaloid family had uncovered promising antiparasitic activity for the 6/5-spiroindimicins and their analogues,[3] we submitted our synthetic 5/5-spiroindimicins as well as their oxindole congeners to similar screening against *T. brucei*, *P. falciparum*, and *L. amazonensis*, exemplar causative agents for African trypanosomiasis, malaria, and leishmaniasis, respectively (Table 3). Our synthetic SPMs and analogues showed moderate antimalarial activity in these assays, with activities against *P. falciparum* falling in the EC_{50} = 2.9–13 μM range. While the 6/5-spiroindimicins had proven most potent against the trypanosomatid parasite *L. amazonensis* (e.g., SPM A (**1**): EC_{50} = 1.3 μM), the 5/5-spirocyclic members demonstrated reduced potency (EC_{50} = 6.7–9.9 μM). Interestingly, this activity appears to be largely confined to compounds containing basic amines (**2**–**8**, **55**), with only a single exception (**52**), suggesting that this motif may be important for efficacy in this parasite.

More promising activity was found for the present compounds against *T. brucei*, a parasite which causes the neglected tropical disease Human African trypanosomiasis (HAT; sleeping sickness), a source of significant disease burden in the developing world.[18] Here, a select number of compounds showed activities (EC_{50}) around (or even below) 1 μM with no significant cytotoxicity against HepG2 cells (a measure of selectivity). Namely, spiroindimicin G (**6**) and the PMB-protected spiroindimicin C (**55**) both showed high efficacy with minimal cytotoxicity against human HepG2 cells (**6**: EC_{50} = 0.65 μM, CC_{50} = >50 μM; **55**: EC_{50} = 1.2 μM, CC_{50} = >50 μM). These potencies, it should be noted, are comparable to acoziborole (EC_{50} = 0.6 μM), a leading Phase III candidate for the treatment of HAT.[19] Given the ease with which our synthetic platform can access these 5/5-spirocyclic compounds, we envisage being able to rapidly generate analogues of these initial leads to delve more deeply into their structure-activity relationships (SAR) against *T. brucei*.



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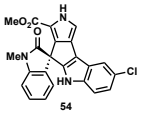

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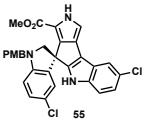

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Compound	Antiparasitic Activity			Selectivity
	T. brucei EC_{50} (μM)	*P. falciparum* 3D7 EC_{50} (μM)	*L. amazonensis* EC_{50} (μM)	HepG2 CC_{50} (μM)
2	3.0 ± 0.23	3.0 ± 0.20	8.0 ± 0.49	37 ± 4.3
3	13 ± 0.98	7.1 ± 0.58	>10	>50
4	3.4 ± 0.21	5.6 ± 0.22	7.7 ± 0.23	>50
6	0.65 ± 0.14	7.6 ± 0.47	8.1 ± 0.50	>50
7	4.4 ± 0.32	4.8 ± 0.51	9.3 ± 1.7	>50
8	4.0 ± 0.20	9.0 ± 0.97	9.9 ± 1.2	>50
36	4.5 ± 0.73	2.9 ± 0.64	>10	21 ± 1.8
47	11 ± 1.09	11 ± 0.67	>10	>50
52	1.5 ± 0.05	4.1 ± 0.10	6.7 ± 0.62	>50
53	7.6 ± 0.36	7.3 ± 0.52	>10	>50
54	14 ± 2.52	13 ± 0.88	>10	>50
55	1.2 ± 0.03	3.7 ± 0.35	>10	>50

[a]Data represent the mean EC_{50} ± standard error for 3 biological replicates. EC_{50} calculations for each biological replicate were based on data from technical triplicates.

Table 3. Antiparasitic screening of synthetic spiroindimicins and oxindole congeners.

Conclusion:

In summary, we have developed a modular synthetic approach to the 5/5-spirocyclic spiroindimicin alkaloids, allowing for the preparation of all 6 members of this subclass via highly concise synthetic sequences (6–7 steps) built upon ostensibly simple, but carefully choreographed fragment couplings. Taken together with our prior work towards the 5/6-spiroindimicins, these convergent total syntheses provide a synthetic blueprint to access *every member* of this intriguing alkaloid class as well as complex analogues. Our unified synthetic platform has enabled biological testing of the 5/5-spiroindimicins, demonstrating their antiparasitic properties for the first time and offering some preliminary SAR for the family. Their newfound availability, conferred by our synthesis, positions this class well for further biomedical exploration, including against African trypanosomiasis.

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Graphical Abstract: