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## Total synthesis of (+)-spiroindimicin A and congeners unveils their antiparasitic activity†

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The spiroindimicins are a unique class of chlorinated indole alkaloids characterized by three heteroaromatic rings structured around a congested spirocyclic stereocenter. Here, we report the first total synthesis of (+)-spiroindimicin A, which bears a challenging C-3'/C-5''-linked spiroindolenine. We detail our initial efforts to effect a biomimetic oxidative spirocyclization from its proposed natural precursor, lynamycin D, and describe how these studies shaped our final abiotic 9-step solution to this complex alkaloid built around a key Pd-catalyzed asymmetric spirocyclization. Scalable access to spiroindimicins A, H, and their congeners has enabled discovery of their activity against several parasites relevant to human health, providing potential starting points for new therapeutics for the neglected tropical diseases leishmaniasis and African sleeping sickness.

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## Introduction

Dimeric tryptophan natural products represent an important class of compounds that has grown significantly in recent decades and contains several medically important members like rebeccamycin (**1**) and staurosporine (**2**) (Fig. 1).<sup>1</sup> Among this broad class, the spiroindimicins constitute a unique subset of non-planar molecules isolated from marine Streptomyces. The inaugural members of this family, spiroindimicins A–D (**3–6**), were reported by Zhang and coworkers in 2012, followed by two monochlorinated members, spiroindimicins E and F (**7, 8**), described by Luzhetsky *et al.* in 2017.<sup>2a,b</sup> Two deschloro congeners, spiroindimicins G and H (**9, 10**), were also isolated by the Zhang group from a bacterial mutant with an inactivated halogenase gene.<sup>2c</sup> In the limited biological assays conducted thus far, the spiroindimicins displayed moderate cytotoxicity against several cancer cell lines (IC<sub>50</sub> = 9–44 μM).<sup>2a,c</sup>

Biosynthetically, the spiroindimicins are proposed to derive from the lynamicins, a previously isolated family of antibacterial alkaloids,<sup>3</sup> *via* a spirocyclization of C-3' of one indole unit onto either C-5'' or C-2'' of the neighboring indole fragment (Fig. 2, top; spiroindimicin numbering, used throughout). This process transforms one indole into a spiroindolenine or -indoline and creates the congested C-3' quaternary spirocenter. In line with this hypothesis, lynamicins A (**13**) and D (**12**) were

co-isolated with **3–6**, and further biosynthetic investigations by the Zhang group have shed light on their biogenesis as halogenated dimers of tryptophan and their viability as precursors to **3–6**.<sup>4,2c</sup> At present, however, the enzyme(s) responsible for their oxidative spirocyclization remain unelucidated.

In light of their appealing structures and preliminary bioactivities, it is unsurprising that the spiroindimicins have

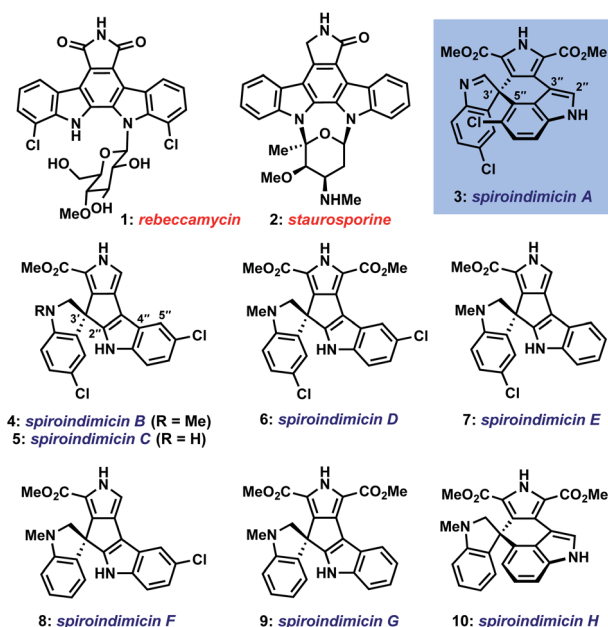


Fig. 1 Bioactive tryptophan dimers and the spiroindimicin family of alkaloids.

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attracted interest from the synthetic community.<sup>5</sup> One prior racemic synthesis of spiroindimicins B (4) and C (5) has been reported by Sperry and Blair (15–16 steps), centering upon early-stage construction of the spirocenter *via* an intramolecular Heck reaction, followed by stepwise introduction of the remaining heterocycles.<sup>6</sup> To the best of our knowledge, no synthetic studies toward either of the more challenging C-3'/C-5"-linked members, spiroindimicins A (3) and H (10), have been disclosed.

Herein, we describe the first total synthesis of (+)-spiroindimicin A (3) relying upon a short, gram-scale preparation of a triaryl precursor and its Pd-catalyzed asymmetric spirocyclization. We apply the developed strategy to the preparation of spiroindimicin H (10), lynamycins A and D (13, 12), and several structural analogues. Finally, with >100 mg of 3 in hand and a panel of congeners, we disclose their promising activity against the parasites *Trypanosoma brucei*, *Plasmodium falciparum*, and *Leishmania amazonensis*, causative agents of African trypanosomiasis (sleeping sickness), malaria, and leishmaniasis, respectively, diseases which constitute a serious and ongoing problem in the developing world.<sup>7</sup>

## Results and discussion

The main challenge associated with total synthesis of 3–10 arises in constructing their core quaternary spirocenters, especially in an enantiocontrolled fashion.<sup>8</sup> This challenge is amplified when targeting spiroindimicin A (3), as this entails linking C-3' of one indole unit to the less reactive C-5" position of the other indole ring (C-4 in indole nomenclature); in the case of the 4–9 the nucleophilic C-2" carbon is joined to this

position. Our approach to spiroindimicin A (3, SPM A) is outlined in Fig. 2 (bottom) and focused on two possible solutions to the challenging C-3' spirocenter, namely a biomimetic final C-3'/C-5" spirocyclization (shown in blue) of a lynamycin D-type precursor (14), or a non-natural C-3'/C-4 spirocyclization (shown in red) of an 'iso-lynamycin'-type compound (15). In both cases, the spirocyclization might be effected in either an oxidative sense (14, 15, X = H) or *via* a functional handle (X = I, Br, etc.). Control of the absolute stereochemistry in this key cyclization event remained a daunting prospect, however, given limited literature precedent. Precursors 14 and 15 should both be readily assembled *via* cross-coupling of appropriately functionalized heteroaryl fragments 16 and 17, themselves available *via* C–H functionalization of inexpensive indole and pyrrole starting materials.

Our initial efforts focused on the biomimetic approach wherein oxidative spirocyclization of lynamycin D (12) might deliver either SPM A (3) directly, or possibly a spiroindolenine precursor to SPM D (6). For this purpose, we required a short and scalable synthesis of lynamycin D (12). 12 has been prepared once before in 6 steps (longest linear sequence) by Sarli and Nikolakaki utilizing a Suzuki coupling-based assembly of its triaryl moiety.<sup>9</sup> Using their approach as inspiration, we were able to develop a shorter route to 12 leveraging the tools of C–H functionalization.<sup>10</sup> Thus, we could prepare pyrrole dibromide 18 *via* iron-catalyzed C–H methoxycarbonylation<sup>11</sup> of commercial ester 17, followed by dibromination (Scheme 1).<sup>12</sup>

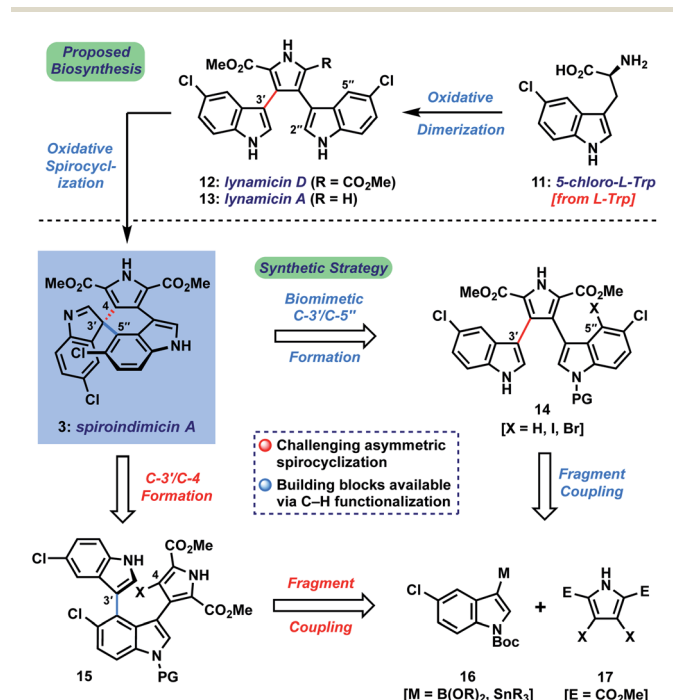
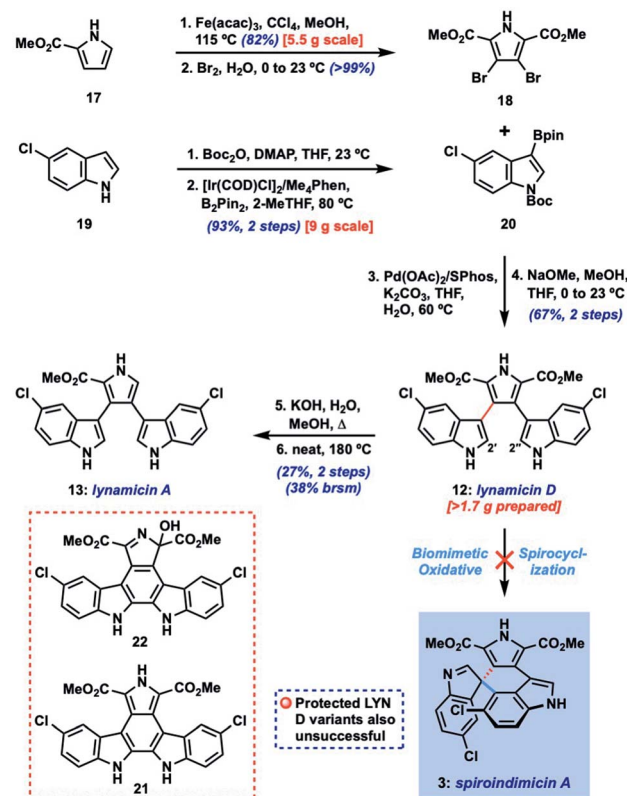


Fig. 2 Spiroindimicin biosynthesis from L-tryptophan and our synthetic approach to spiroindimicin A (3).



Scheme 1 Attempted biomimetic synthesis of spiroindimicin A (3) from lynamycin D (12).



For the other partner, we could advance 5-chloroindole (**19**) to C-3 boronic ester **20** through an efficient Ir-catalyzed C–H borylation sequence.<sup>13</sup> A high-yielding Suzuki coupling using Buchwald's SPhos ligand<sup>14</sup> and removal of the Boc protecting groups delivered lynamycin D (**12**, 4 steps LLS). Using this scalable route we have been able to prepare over 1.7 g of **12**, and additionally have achieved the first synthesis of lynamycin A (**13**) *via* a monohydrolysis/decarboxylation sequence.<sup>15</sup>

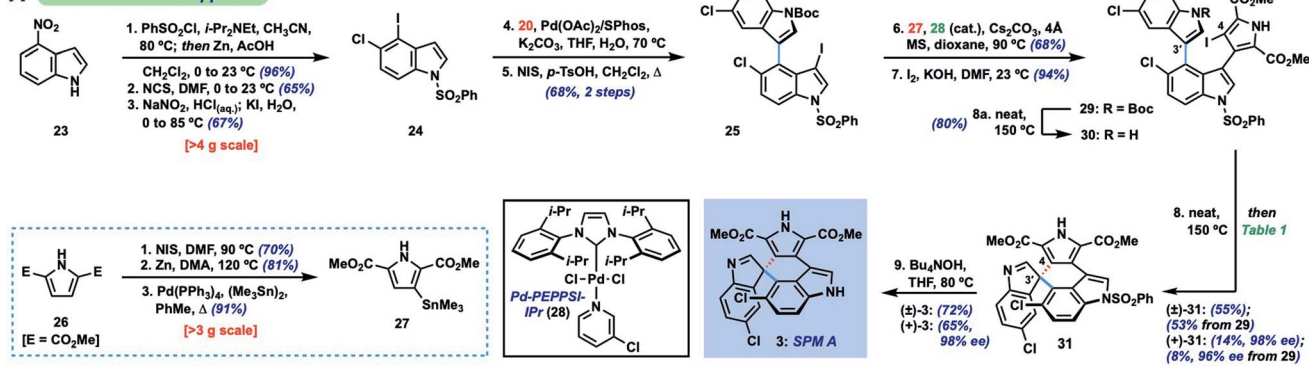
Unfortunately, despite extensive investigation we have been unable to achieve formation of C-5'' or C-2''-linked spiroindolenines from **12** under a range of oxidative conditions (reagent-based, electrochemical, photochemical; see ESI† for full details). Not surprisingly, 2',2''-linked indolocarbazole products such as **21** and **22** were often isolated.<sup>16</sup> Similarly, efforts to utilize electronically differentiated monoprotected variants of **12** (*e.g.*, **14**, PG = Ts, Ac, Boc, *cf.* Fig. 2) or use the pyrrole ester/acid to direct C-5'' functionalization also proved unsuccessful.

Given the challenge of achieving direct C-3'/C-5'' oxidative spirocyclization, we planned to prepare an analogue with a suitable functional handle to allow for regioselective spirocyclization. While we initially targeted a C-5''-functionalized variant of lynamycin D (*e.g.*, **14**, X = Br, I, *cf.* Fig. 2), preliminary efforts toward its assembly proved difficult. Our ultimate solution involved switching the order of bond formations to C-3', where we first aimed to install the more challenging C-3'/C-5'' bond in the form of an 'iso-lynamycin'-type precursor (**15**, Fig. 2). For this purpose, we prepared 4-iodoindole **24** in 3 steps on multigram scale from 4-nitroindole (**23**) by improving a known sequence (Scheme 2A).<sup>17</sup> The previously elusive C–C bond could then be formed *via* Suzuki coupling with boronic ester **20** in quantitative yield. Hereafter, indole C-3 iodination set the stage for a Stille coupling with pyrrole stannane **27**,

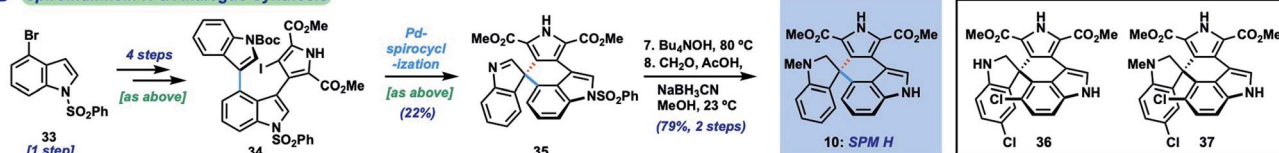
which was available from previously prepared **26** *via* stannylation of a known<sup>18</sup> monoiodide. The fragment coupling required significant optimization, however, with many common Stille conditions giving only low yields of the desired triaryl compound (not shown). Ultimately, we found that the use of Pd–NHC catalyst **28**<sup>19</sup> in the presence of Cs<sub>2</sub>CO<sub>3</sub> and 4 Å molecular sieves gave the desired product in a serviceable but scalable 68% yield. A final iodination<sup>20</sup> of the pyrrole ring and thermolytic Boc deprotection set the stage for the key spirocyclization, providing triaryl **30** which appears to exist as two separable atropisomers (*dr* ~3 : 1) that slowly interconvert at room temperature.

With hundred-milligram quantities of **30** in hand, we explored the racemic spirocyclization to **31** using Pd-catalyzed conditions developed by You as a starting point.<sup>21</sup> Although their optimal conditions ([Pd(allyl)Cl]<sub>2</sub>/PPh<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, PhMe, Δ) were unproductive, we did observe formation of C-2'-linked product **32** when employing Cs<sub>2</sub>CO<sub>3</sub> as base in the presence of several phosphine ligands (Table 1; see ESI† for details). This 7-membered product appears to arise through direct C-2' coupling rather than *via* C-3' to C-2' bond migration in desired spiroindolenine **31** based on control experiments with pure **31**.<sup>22</sup> Ultimately, we found that the ligand plays a crucial role in providing the desired connectivity, with NHC–Pd systems proving optimal: using Pd-PEPPSI-IPr (**28**)<sup>19</sup> as catalyst under otherwise identical conditions provided protected SPM A (**31**) in 55% yield (Table 1, entry 1). After screening over 40 chiral ligands (see ESI† for full details), we discovered that the use of chiral phosphoramidites provided the best balance between enantioselectivity and selectivity for **31** over **32** (entries 2–4). With optimal phosphoramidite **L3**,<sup>23</sup> enantioselectivity and especially yield were initially moderate (9%, 75% ee; entry 4) under our prior Cs<sub>2</sub>CO<sub>3</sub> conditions. Ultimately, extensive

### A Successful Abiotic Approach

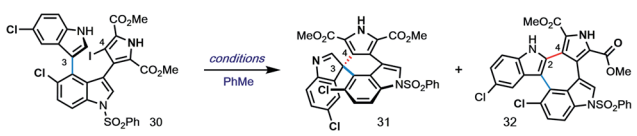


### B Spiroindimicin H & Analogue Synthesis

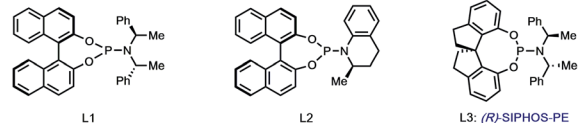


Scheme 2 (A) Revised approach to spiroindimicin A (**3**) *via* Pd-catalyzed spirocyclization; (B) synthesis of spiroindimicin H (**10**) and potentially undiscovered spiroindimicins.



Table 1 Optimization of Pd-catalyzed spirocyclization<sup>a</sup>


Entry	Pd/ligand	Base	T (°C)	31 : 32 <sup>b</sup>	Yield (%) <sup>c</sup>	ee <sup>d</sup>
1	Pd-PEPPSI-IPr	Cs <sub>2</sub> CO <sub>3</sub>	115	1.8 : 1	55	n/a
2	[Pd]/L1	Cs <sub>2</sub> CO <sub>3</sub>	90	1 : 1.1	11	-14
3	[Pd]/L2	Cs <sub>2</sub> CO <sub>3</sub>	90	1.7 : 1	14	4
4	[Pd]/L3	Cs <sub>2</sub> CO <sub>3</sub>	90	1 : 1.5	9	75
5	[Pd]/L3 <sup>e</sup>	Cs <sub>2</sub> CO <sub>3</sub> /Ag <sub>2</sub> CO <sub>3</sub> <sup>f</sup>	105	1 : 2	8	83
6	[Pd]/L3 <sup>e</sup>	Cs <sub>2</sub> CO <sub>3</sub> /Ag <sub>2</sub> CO <sub>3</sub> <sup>f</sup>	80	1 : 2.1	21	86
7	[Pd]/L3 <sup>g</sup>	Cs <sub>2</sub> CO <sub>3</sub> /Ag <sub>2</sub> CO <sub>3</sub> <sup>f</sup>	70	1 : 2.2	14	98
8	[Pd]/L1 <sup>e</sup>	Cs <sub>2</sub> CO <sub>3</sub> /Ag <sub>2</sub> CO <sub>3</sub> <sup>f</sup>	70	1 : 1.8	6	-53



<sup>a</sup> [Pd] = [Pd(allyl)Cl]<sub>2</sub>; standard conditions: Pd source (10 mol%), ligand (15 mol%), base (1.5 equiv.). <sup>b</sup> Determined by <sup>1</sup>H NMR analysis of the crude reaction mixture. <sup>c</sup> Yield of isolated **31**. <sup>d</sup> Determined by HPLC analysis. <sup>e</sup> [Pd]/ligand (30/45 mol%) prestirred in PhMe for 1 h. <sup>f</sup> 2.5 equiv. each. <sup>g</sup> [Pd]/ligand (40/60 mol%).

investigations involving systematic variation of reaction parameters showed that the combination of both Cs<sub>2</sub>CO<sub>3</sub> and Ag<sub>2</sub>CO<sub>3</sub> as base (2.5 equiv. each) and lowering of the temperature to 70 °C could effect spirocyclization in 14% yield and an excellent 98% ee (entry 7; see ESI<sup>†</sup>). Here, the modest yield of **31** is due to competitive formation of **32**, as well as proto-deiodination of **30**.<sup>24</sup> Intriguingly, we also found that work-up conditions had an impact on the enantiopurity of isolated **31** (see ESI<sup>†</sup> for details). Despite the moderate efficiency, to the best of our knowledge, this is the first report of a highly enantioselective arylative indole to spiroindolenine transformation, and the first use of such a reaction – racemic or asymmetric – in natural product synthesis.<sup>21,25,26</sup>

Additionally, we found that Boc deprotection and spirocyclization could be conducted as a one-pot procedure by simply subjecting the residue remaining after thermolysis to the spirocyclization conditions [(±)-**31** : 53%; (+)-**31** : 8%, 96% ee]. A final removal of the benzenesulfonyl group of **31** with Bu<sub>4</sub>NOH at 80 °C delivered spiroindimicin A [(±)-**3** : 72%; (+)-**3** : 65%], completing the first total synthesis of this target in 9 steps (longest linear sequence from commercial 4-nitroindole). Spectral data of our synthetic material matched those reported by Zhang and co-workers, and its chromatographic behavior was identical to an authentic sample (TLC; HPLC). The optical rotation was of the same sign and similar magnitude {[α]<sub>D</sub><sup>26</sup> = +64.0 (c = 0.05, MeOH) for 98% ee; lit.: [α]<sub>D</sub><sup>20</sup> = +46.49 (c = 0.15, MeOH)} confirming that we had prepared the natural enantiomer of **3**. Overall, our synthetic efforts have yielded over 100 mg of **3** to date.

Utilizing our developed strategy, we have also been able to complete the first synthesis of spiroindimicin H [(±)-**10**,

Scheme 2B] from 4-bromoindole (**33**). This material was similarly advanced to triaryl iodide **34**, which could be spirocyclized to **35** under our Pd-PEPPSI-IPr-catalyzed conditions in 22% yield. High-yielding indole deprotection (89%) and reductive methylation (89%) of the indolenine then completed the synthesis of **10** in 8 steps overall. Moreover, the dihydrospiroindimicin A congeners **36** and **37**, potentially as yet undiscovered natural products (cf. **4–10**), were prepared *via* similar indolenine reductions of spiroindimicin A (**3**).

Finally, with scalable access to spiroindimicin A (**3**) and a panel of related compounds, we have begun to explore their biological properties. Given that several tryptophan dimers, including staurosporine (**2**), have demonstrated antiparasitic activity,<sup>27</sup> preliminary testing was conducted against the parasites *Trypanosoma brucei*, *Plasmodium falciparum*, and *Leishmania amazonensis*,<sup>7</sup> revealing promising activity (Table 2). Specifically, SPM A (**3**) inhibits the growth of all three parasites (EC<sub>50</sub> = 1.3–11 μM), with the potencies of natural (*S*)-**3**, *ent*-(*R*)-**3**, and racemic **3** being similar, suggesting a non-protein-based target. SPM H (**10**) and SPM A derivatives **36** and **37** are also active, demonstrating similar or slightly improved potencies in some cases. Lynamycin-type compounds showed activity, with 2',2''-linked indolocarbazole **21** displaying the highest potency against *T. brucei* (EC<sub>50</sub> = 0.37 μM). Several compounds are also active against both multidrug-resistant (Dd2) and drug-sensitive (3D7) strains of *P. falciparum*. Importantly, in most cases the compounds did not display significant cytotoxicity against mammalian HepG2 and RAW 264.7 cells (a macrophage cell line) at 10 μM; when toxicity was observed, reasonable selectivity was maintained in several cases (e.g., for **21**, HepG2 vs. *T. brucei*: selectivity index ~12). The efficacy observed against *T.*



Table 2 Biological investigations of synthetic spiroindimicins, lynamincins, and analogues<sup>a</sup>

Compound	Antiparasitic activity				Selectivity	
	<i>T. brucei</i> EC <sub>50</sub> (μM)	<i>P. falciparum</i> 3D7 EC <sub>50</sub> (μM)	<i>P. falciparum</i> Dd2 EC <sub>50</sub> (μM)	<i>L. amazonensis</i> EC <sub>50</sub> (μM)	RAW CC <sub>50</sub> (μM)	HepG2 CC <sub>50</sub> (μM)
(±)-3	7.5 ± 1.1	2.8 ± 0.49	4.2 ± 0.11	1.4 ± 0.35	5.5 ± 0.41	10 ± 1.2
(S)-3	11 ± 1.2	3.9 ± 0.81	6.6 ± 0.12	1.3 ± 0.33	>10	>10
(R)-3	11 ± 1.2	4.8 ± 1.2	7.1 ± 0.33	5.3 ± 1.1	>10	>10
(±)-10	7.1 ± 1.2	n.t.	n.t.	4.5 ± 0.98	8.1 ± 0.38	>10
(±)-36	12 ± 1.1	4.4 ± 0.93	7.1 ± 0.83	6.3 ± 1.2	9.3 ± 0.67	>10
(±)-37	3.2 ± 0.64	3.7 ± 0.90	5.5 ± 0.51	6.0 ± 1.2	>10	>10
12	8.3 ± 1.0	>10	n.t.	>10	>10	>10
13	8.2 ± 0.45	>10	n.t.	8.9 ± 0.9	>10	>10
21	0.37 ± 0.073	0.79 ± 0.11	1.0 ± 0.030	4.5 ± 0.26	3.4 ± 1.1	4.6 ± 1.1

<sup>a</sup> Data represent the mean EC<sub>50</sub> ± standard error for 3 biological replicates. EC<sub>50</sub> calculations for each biological replicate were based on data from technical triplicates. n.t. = not tested.

*brucei* and *L. amazonensis* is noteworthy and comparable to that of existing therapeutics; for example, the approved leishmaniasis drug miltefosine displays an EC<sub>50</sub> = 1.2 μM against *L. amazonensis*.<sup>28,29</sup> Natural spiroindimicin A [(S)-3], in particular, may warrant further study against the neglected tropical disease leishmaniasis given its activity (EC<sub>50</sub> = 1.3 μM) and lack of significant cytotoxicity in RAW cells.

## Conclusions

In summary, we have reported the first total synthesis of (+)-spiroindimicin A (3). Our 9-step synthesis relies upon an efficient assembly of a triaryl scaffold with distinct connectivity to its natural precursor *via* cross-coupling, and a novel Pd-catalyzed asymmetric spirocyclization to construct the challenging C-3'/C-5''-linked spiroindolenine in high enantiopurity. We have also prepared spiroindimicin H and lynamincins A and D in a concise fashion and tested the conversion of the latter to the spiroindimicins through biomimetic oxidative spirocyclization. Although unproductive, these studies did inform our ultimately successful approach to 3 using an alternate triaryl fragment. With meaningful quantities of spiroindimicin A (3) and its congeners now available, we have begun to explore their biological activity more broadly. Studies to date have unveiled promising antiparasitic activity that may provide a starting point for developing compounds to treat leishmaniasis and African trypanosomiasis.<sup>28,29</sup>

## Author contributions

Z. Z. and M. W. S. conceived and executed the synthetic studies. S. R., L. I., and L. T. C. conducted the biological investigations under the supervision of M. A. P. and D. M. W., with high-throughput assistance provided by H. N., P. L. M., and B. A. P. M. W. S. composed the manuscript with input from all authors.

## Conflicts of interest

There are no conflicts to declare.

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