

# Biomimetic Total Syntheses of Flinderoles B and C

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**S** Supporting Information

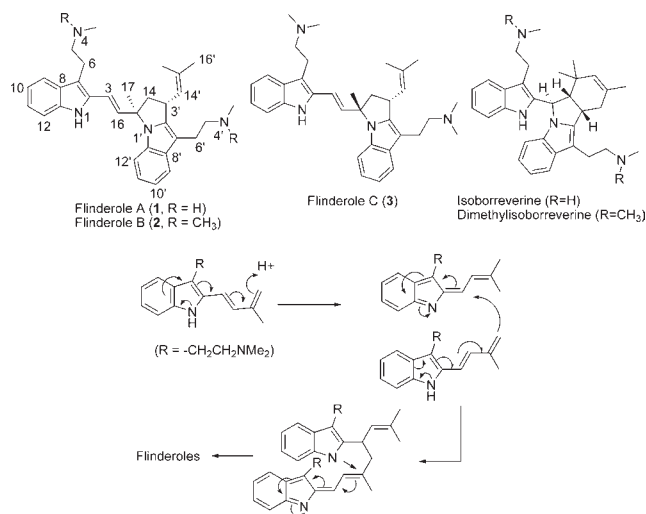
**ABSTRACT:** A simple and efficient biomimetic synthesis of pyrrolo[1,2-*a*]indoles using a highly stereo- and regioselective [3 + 2] reaction cascade was developed and then further applied in the first total synthesis of flinderoles B and C, which proceeded in 17.2% yield over the longest linear sequence of 11 steps.

Malaria chemotherapy is under continuous threat from the evolution and rise of multidrug resistance of *Plasmodium falciparum*.<sup>1</sup> To counter the threat of resistance, structurally and functionally novel antimalarial compounds with new mechanisms of action are needed. In 2009, flinderoles A–C (1–3, respectively; Scheme 1) were isolated through an initial antimalarial natural product extract screening program.<sup>2</sup> All of the flinderoles have shown impressive selective antimalarial activity against the *P. falciparum* parasite,<sup>2</sup> with flinderole C being most active ( $IC_{50} = 150$  nM), and flinderoles thus present new molecular scaffolds for antimalarial drug discovery. Flinderoles have a new skeleton that is rearranged relative to the known borreverine class of tryptamine isoprene-derived compounds borreverine, isoborreverine, and dimethylisoborreverine.<sup>3</sup> The dimeric structure of the flinderoles lends itself to a symmetrical retrosynthetic dissection through the center of the molecule. This dissection reveals monomeric tryptamine diene as a possible precursor—a scenario that might not be so dissimilar to their biosynthetic pathway (Scheme 1).

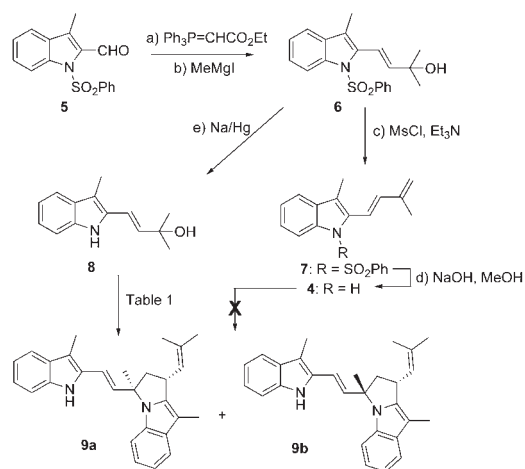
Our explorations to test this overall hypothesis began with the preparation of diene **4** from the known indole aldehyde **5** (Scheme 2) on a multigram scale. Treatment of indole aldehyde **5** with  $Ph_3P=CHCO_2Et$  followed by reaction of the resultant ester with  $MeMgBr$  generated the tertiary alcohol **6**. Mesylation of alcohol **6** and subsequent elimination yielded diene **7**, which gave the required diene **4** upon desulfonation using methanolic NaOH. To our surprise, diene **4** was found to polymerize with different Lewis acids under various reaction conditions employed, resulting in intractable mixtures. This could be explained by reasoning that the actual site of protonation in **4** is at C3 of the indole nucleus to produce a conjugated enamine, which could undergo cationic polymerization. At this juncture, it was reasoned that if diene **4** were generated in situ in sufficiently low concentration, it might undergo dimerization by a formal intermolecular [3 + 2] cycloaddition,<sup>5,6</sup> leading to the flinderole framework. On the basis of this hypothesis, the available alcohol **6** was desulfonated to obtain alcohol **8**. Various Lewis acids were screened for the proposed dimerization of **8**, and results are summarized in Table 1.

The reaction of alcohol **8** with TMSOTf furnished a complex mixture of products, and the dimers **9a** and **9b** were obtained in

## Scheme 1. Structures of Flinderoles A–C and the Proposed Biosynthetic Pathway



## Scheme 2. Exploration of the Biosynthetic Pathway<sup>4</sup>



<sup>4</sup> Conditions: (a)  $Ph_3P=CHCO_2Et$  (1.5 equiv),  $CH_2Cl_2$ , RT, 6 h, 95%; (b) MeI (7.0 equiv), Mg turnings (6.0 equiv),  $I_2$  (cat.),  $Et_2O$ , 0 °C to RT, 2 h, 81%; (c) MsCl (3.0 equiv),  $Et_3N$  (6.0 equiv), THF, 0 °C to reflux, 2 h, 82%; (d) NaOH (5.0 equiv), MeOH, 70 °C, 3 h, 75%; (e) Na/Hg (4.0 equiv),  $Na_2HPO_4$  (4.0 equiv), MeOH, RT, 1 h, 91%.

Received: December 29, 2010

Published: February 11, 2011

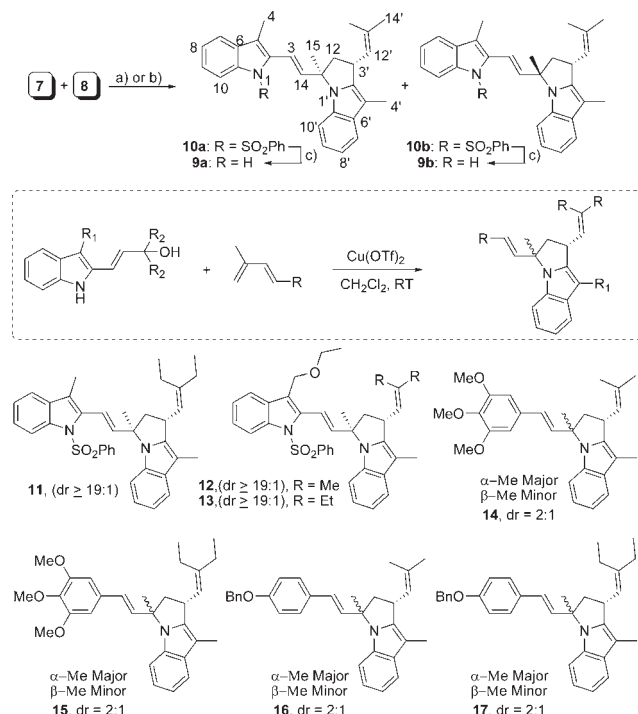
**Table 1. Invention and Optimization of the Dimerization Reaction of Alcohol 8<sup>a</sup>**

entry	Lewis acid	yield (%) <sup>b</sup>	dr (9a:9b) <sup>c</sup>
1	TMSOTf	10	1:1
2	Yb(OTf) <sub>3</sub>	25	1:1
3	Sc(OTf) <sub>3</sub>	25	1:1
4	BF <sub>3</sub> ·OEt <sub>2</sub>	38	3:2
5	Cu(OTf) <sub>2</sub>	46	2:1
6	TFA	35	3:2
7	Tf <sub>2</sub> O	0	N.A.

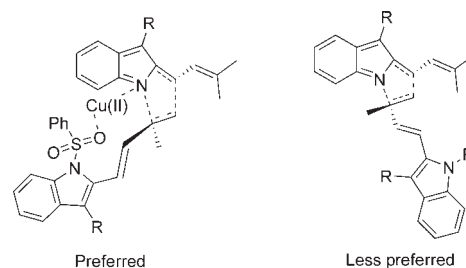
<sup>a</sup> All reactions were carried out on a 0.25 mmol scale in CH<sub>2</sub>Cl<sub>2</sub> as the solvent (0 °C to RT). <sup>b</sup> Isolated yield. <sup>c</sup> Determined by <sup>1</sup>H NMR analysis of the crude reaction mixture.

poor yield as 1:1 mixture of diastereomers (Table 1, entry 1). Similarly, Yb(OTf)<sub>3</sub> and Sc(OTf)<sub>3</sub> gave the desired adducts **9a** and **9b** in low yield (entries 2 and 3). BF<sub>3</sub>·OEt<sub>2</sub> was found to be a useful catalyst for effecting this transformation in a much cleaner manner, generating the products **9a** and **9b** in moderate yield and diastereoselectivity (entry 4). Even though Tf<sub>2</sub>O did not give any desired product, trifluoroacetic acid (TFA) did furnish the required products **9a** and **9b** in comparable yield (Table 1, entries 6 and 7). More interestingly Cu(OTf)<sub>2</sub> generated the flinderole frameworks **9a** and **9b** in much improved yield and diastereoselectivity (Table 1, entry 5). It is worth mentioning that no [4 + 2] cycloaddition product was observed even in trace amounts under these conditions. The dimers **9a** and **9b** could be separated by careful column chromatography, and their structures were established by spectroscopic analysis (<sup>1</sup>H and <sup>13</sup>C NMR, IR, HRMS) through comparison with flinderole spectral data.<sup>2</sup> Their relative stereochemistry was determined by rotational Overhauser effect spectroscopy (ROESY). Weak ROESY correlations between H3' and H14 and between 3H15 and H12' indicated that the C17 methyl group and the isobutene group must be on the same side of the five-membered ring in the major isomer **9a**.<sup>7</sup>

Scheme 3 describes the scope of this dimerization reaction. It was envisaged that the dimerization reaction would be more facile if the intermediate generated in situ from alcohol **8** were reacted with an olefin such as **7** bearing a sulfonyl group. It was anticipated that since the olefin would be preformed and the intermediate trapped immediately, the formation of polymerization products would be significantly reduced. Gratifyingly, when tertiary alcohol **8** and diene **7** were mixed together and treated with Cu(OTf)<sub>2</sub>, the dimers **10a** and **10b** were indeed obtained in excellent yield and diastereoselectivity (≥ 19:1). When BF<sub>3</sub>·OEt<sub>2</sub> was used as the catalyst, the diastereomeric ratio decreased to 2:1. The relative stereochemistry of **10a** and **10b** was determined by ROESY and nuclear Overhauser effect spectroscopy (NOESY) experiments. Although the reason for the excellent diastereoselectivity is not very clear at this moment, it was observed that excellent diastereoselectivity was obtained only when the -SO<sub>2</sub>Ph group was present and Cu(OTf)<sub>2</sub> was used as catalyst; thus, the diastereoselectivity could be rationalized in terms of a transition-state structure in which copper is coordinated to the -SO<sub>2</sub>Ph group of one indole unit and the nitrogen of the other unit. The approach of the olefin is endo, similar to the Diels-Alder reaction (Figure 1).<sup>8</sup> This transition-state structure reduces the unfavorable steric interaction present when the olefin approaches in exo mode. Removal of the benzenesulfonyl

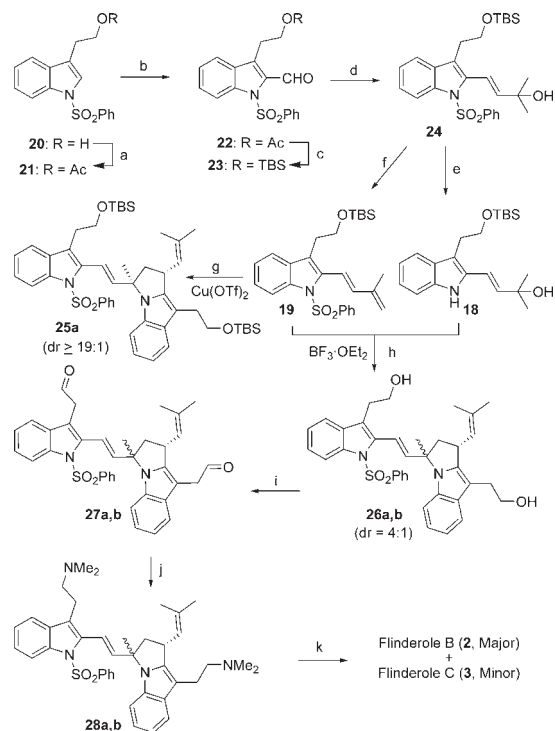
**Scheme 3. Intermolecular Cascade Reaction<sup>a</sup>**

<sup>a</sup> Conditions: (a) Cu(OTf)<sub>2</sub> (0.2 equiv), CH<sub>2</sub>Cl<sub>2</sub>, RT, 30 min, 95%; (b) BF<sub>3</sub>·OEt<sub>2</sub> (0.2 equiv), CH<sub>2</sub>Cl<sub>2</sub>, RT, 20 min, 92%; (c) Na/Hg (4.0 equiv), Na<sub>2</sub>HPO<sub>4</sub> (4.0 equiv), MeOH, RT, 1 h, 94%.

**Figure 1. Proposed stereochemical model for the [3 + 2] cycloaddition.**

protection could be readily accomplished using sodium amalgam, furnishing the dimers **9a** and **9b**, whose <sup>1</sup>H and <sup>13</sup>C NMR data were identical to those of the samples generated earlier. In order to expand the scope of the reaction, several diverse examples were carried out, as illustrated in Scheme 3. The reaction was found to work with equal efficiency when the tertiary alcohol had ethyl rather than methyl substitution (cf. adduct **11**). Similarly, having an ethoxymethyl substituent at C3 of the indole did not affect the yield or selectivity (cf. adducts **12** and **13**). It is noteworthy that not only indole derivatives but also even simple 1-phenyl-3-methylbutadiene derivatives reacted to give the corresponding highly substituted pyrrolo[1,2-*a*]indole derivatives in good yield, albeit with only modest selectivity.<sup>9</sup> These results encouraged us to proceed further to a biomimetic total synthesis of flinderoles.<sup>10</sup>

To access flinderoles B and C, indole tertiary alcohol **18** and indole diene **19** were identified as appropriate precursors for the key [3 + 2] cycloaddition reaction. The synthesis began with

Scheme 4. Total Synthesis of Flinderoles B (2) and C (3)<sup>a</sup>

<sup>a</sup> Conditions: (a) Ac<sub>2</sub>O (5.0 equiv), DMAP (0.2 equiv), pyridine (5.0 equiv), CH<sub>2</sub>Cl<sub>2</sub>, RT, 6 h, 91%; (b) dichloromethyl methyl ether (5.0 equiv), stannic chloride (5.0 equiv), CH<sub>2</sub>Cl<sub>2</sub>, -78 to -10 °C, 1 h, 80%; (c) (i) LiOH (5.0 equiv), H<sub>2</sub>O, THF, RT, 3 h; (ii) TBSCl (1.3 equiv), imidazole (1.5 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to RT, 6 h, 81% (over two steps); (d) (i) Ph<sub>3</sub>P=CHCO<sub>2</sub>Et (1.5 equiv), CH<sub>2</sub>Cl<sub>2</sub>, RT, 6 h, 91%; (ii) Mel (10 equiv), Mg turnings (9 equiv), I<sub>2</sub> (cat.), Et<sub>2</sub>O, 0 °C to RT, 2 h, 89%; (e) Na/Hg (4.0 equiv), Na<sub>2</sub>HPO<sub>4</sub> (4.0 equiv), MeOH, RT, 1 h, 97%; (f) MsCl (3.0 equiv), Et<sub>3</sub>N (6.0 equiv), THF, 0 °C to reflux, 2 h, 81%. (g) Cu(OTf)<sub>2</sub> (0.2 equiv), CH<sub>2</sub>Cl<sub>2</sub>, RT, 30 min, 62%; (h) BF<sub>3</sub>·OEt<sub>2</sub> (4.0 equiv), CH<sub>2</sub>Cl<sub>2</sub>, RT, 30 min, 78%; (i) IBX (6.0 equiv), EtOAc, reflux, 1 h, 84%; (j) NHMe<sub>2</sub> (4.0 equiv), NaCNBH<sub>3</sub> (4.0 equiv), AcOH (cat.), MeOH, RT, 12 h, 91%; (k) Na/Hg (4.0 equiv), Na<sub>2</sub>HPO<sub>4</sub> (4.0 equiv), MeOH, RT, 1 h, 2 (62%), 3 (15%).

known protected tryptophol **20**.<sup>11</sup> The primary hydroxyl group of **20** was acylated using acetic anhydride to furnish acetate **21**. Formylation of **21** using dichloromethyl methyl ether and stannic chloride gave acetate **22**. The acetyl protection in indole derivative **22** was changed to TBS protection following hydrolysis of acetate and reaction of the resultant alcohol with TBSCl to obtain TBS ether **23**. Wittig olefination of aldehyde **23** with Ph<sub>3</sub>P=CHCO<sub>2</sub>Et generated the unsaturated ester in 91% yield, which upon treatment with methylmagnesium iodide gave tertiary alcohol **24** in excellent yield. Dehydration of the hydroxyl group of **24** was achieved via its mesylate followed by elimination to furnish the requisite olefin **19**. On the other hand, deprotection of the phenylsulfonyl group in **24** using sodium amalgam gave the other coupling partner, alcohol **18** (Scheme 4). With gram quantities of tertiary alcohol **18** and diene **19** in hand, the stage was set for the key dimerization reaction for the synthesis of the flinderole skeleton.

To begin with, an equimolar mixture of tertiary alcohol **18** and diene **19** were treated with a catalytic amount of copper(II) triflate, which gratifyingly afforded the adduct **25a** in 62% yield

with excellent diastereoselectivity. Surprisingly, treatment of a mixture of **18** and **19** with excess BF<sub>3</sub>·OEt<sub>2</sub> not only gave the expected dimerization product but also deprotected both TBDMS groups, directly generating diols **26a** and **26b** in excellent overall yield, albeit with moderate diastereoselectivity (4:1). In line with the earlier observation, the major compound was found to be isomer **26a**, in which the methyl and isobutylene groups are cis to each other. The mixture of diols **26a** and **26b** was not separated at this stage, given the fact that both isomers would finally lead to the natural products, which could be separated in the last step. All of our attempts to convert **26a** and **26b** to the corresponding diamines via their mesylates or triflates failed to give the desired products. Finally, oxidation of the mixture of **26a** and **26b** using IBX followed by reductive amination of the resultant bisaldehydes **27a** and **27b** gave a mixture of amines **28a** and **28b** in 91% yield. Deprotection of the indole nitrogens of **28a** and **28b** followed by purification by preparative TLC delivered flinderoles B (**2**) and C (**3**), which were then treated individually with 0.005 M TFA in acetonitrile to get the corresponding TFA salts. The TFA salts of synthetic flinderoles B and C thus obtained possessed physical properties (IR, mass, <sup>1</sup>H and <sup>13</sup>C NMR data) identical to those reported in the literature.<sup>2</sup>

In summary, a highly stereo- and regioselective formal [3 + 2] cycloaddition reaction between a tertiary alcohol and an olefin has been developed for use in the synthesis of pyrrolo[1,2-*a*] indoles. The potential of this methodology has been amply demonstrated in the first total synthesis of the isomeric flinderoles B and C, which involves 11 steps in the longest linear sequence and gave an overall yield of 17.2%. The strategy is fairly general and is amenable to the synthesis of other natural products of this class as well as their analogues.

## ■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and spectral data for all of the compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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## ■ ACKNOWLEDGMENT

This paper is dedicated to Prof. A. Srikrishna. We thank Dr. C. V. Ramana and Dr. S. J. Gharpure for their valuable suggestions. We thank Dr. P. R. Rajmohan and team for recording NMR spectra. R.D.E. and A.R. thank CSIR, New Delhi, for the award of research fellowship. Financial support from NCL, Pune (Project MLP017726) and DST, New Delhi (Project GAP291026) is gratefully acknowledged.

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(7) For convenience, the numbering for compound **9a** follows that given for natural flinderoles.

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(9) For preparation of all of the starting materials, see the Supporting Information.

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