Organic LETTERS

Letter

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Biomimetic Synthesis of Moschamine-Related Indole Alkaloids via Iron-Catalyzed Selectively Oxidative Radical Coupling

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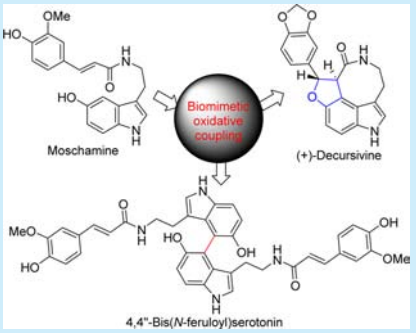
Supporting Information

ABSTRACT: An iron-catalyzed oxidative radical coupling reaction was developed to selectively construct indolofuran or bisphenolic indole cores, which exist in two types of moschamine-related indole alkaloids. Both (+)-decursivine and 4,4″-bis(*N*-feruloyl)serotonin were biomimetically synthesized by using coupling reactions. The proposed reassignment of the structure of montamine as 4,4″-bis(*N*-feruloyl)-serotonin was excluded.



(±)-Serotobenine (**1**), which has a unique tetracyclic skeleton that contains an indole, a furan, and an eight-membered lactam, was initially isolated from safflower seeds (*Carthamus tinctorius* L.) (Figure 1).[1] In 2002, (+)-decursivine (**2**) was isolated from the leaves and stems of *Rhaphidophora decursiva* Schott (Araceae), with IC_{50} values of 3.93 and 4.41 μg/mL against D6 and W2 clones of *Plasmodium falciparum*, respectively.[2] 4,4″-Bis(*N*-feruloyl)serotonin (**4**) was isolated from safflower oil cake (*Carthamus tinctorius* L.) and exhibited strong antioxidant activity.[3] 4,4″-Bis(*N*-feruloyl)serotonin (**4**) possesses a very rare type of bisphenolic indole alkaloid skeleton. Until now, only (+)-dispegatrine and blumeanine, which have similar skeletons, have been reported.[4]

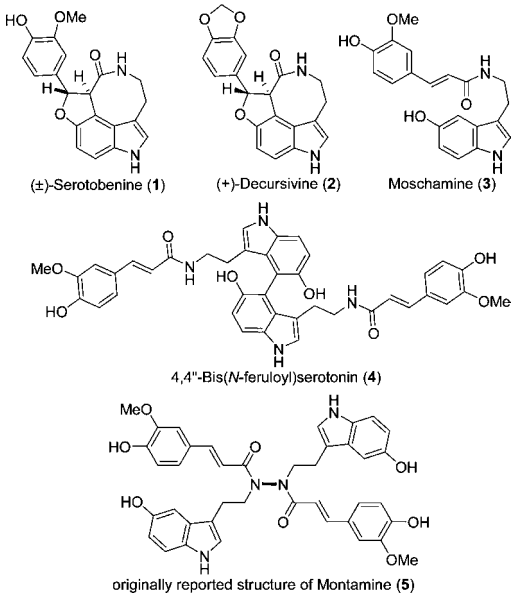


Figure 1. Structures of moschamine-related natural products.

Montamine (**5**) was isolated from seeds of the ornamental plant *Centaurea montana* and showed significant anticolon cancer activity in vitro (IC_{50} = 43.9 μM).[5] The structure of montamine (**5**) was originally assigned as a homodimer of moschamine (**3**) linked by an N−N′ bond on the serotonin side chain. A total synthesis of the reported structure by Sperry and co-workers showed this assignment to be incorrect. They proposed that montamine (**5**) was likely to be 4,4″-bis(*N*-feruloyl)serotonin (**4**) upon analysis of the spectroscopic data.[6] Unfortunately, they could not confirm this proposed structural reassignment of montamine (**5**) because the NMR data for these two natural products were reported in different solvents (CD_3OD and DMSO-d_6, respectively) and authentic samples of both the natural products necessary for a full spectroscopic comparison in the same NMR solvent were not available.

The unique structural features and potent biological activities of these natural products have drawn the attention of synthetic organic chemists. In 2007, Kerr reported the first total synthesis of (±)-decursivine (**2**) starting from a quinone monoamine in 18

Received: February 12, 2016
Published: March 7, 2016

DOI: 10.1021/acs.orglett.6b00417
Org. Lett. 2016, 18, 1474−1477

linear steps and 3% overall yield.[7] Mascal and Jia independently introduced the expedient synthesis of (±)-decursivine (**2**) via a Witkop photocyclization cascade sequence.[8] Jia also reported the total synthesis of (±)-serotobenine (**1**) and (±)-decursivine (**2**) by using a $Pd(OAc)_2$-mediated cascade sequence.[9] The asymmetric total synthesis of (+)-decursivine (**2**) was accomplished with PIDA-mediated intramolecular [3 + 2] cycloaddition.[10] Fukuyama reported the total synthesis of (−)-serotobenine (**1**) using a critical Rh-catalyzed C−H insertion reaction.[11] No reports were published on the synthesis of the 4,4″-bis(*N*-feruloyl)serotonin (**4**). Instead, another bisphenolic indole alkaloid, (+)-dispegatrine, was synthesized via a thallium(III)-mediated oxidative coupling.[12]

The biosynthetic pathway of these alkaloids has been a topic of intensive speculation and interest. The moschamine (**3**) was coisolated with serotobenine (**1**), and serotobenine (**1**) could be formed in vitro from moschamine (**4**) through enzymatic (horseradish peroxidase) oxidation.[1] Interestingly, moschamine (**3**) was also coisolated with its dimer, 4,4″-bis(*N*-feruloyl)-serotonin (**4**).[3] Moreover, the directly oxidative dimerization of phenols was proposed to involve the biosynthesis of a number of bisphenolic natural products.[13] Because of the structural similarities of serotobenine (**1**), decursivine (**2**), and 4,4″-bis(*N*-feruloyl)serotonin (**4**), it is possible that they could share a common biosynthetic pathway. Since oxidative coupling can directly construct carbon−carbon and carbon−heteroatom bonds between two nucleophiles in a single step without prefunctionalization, it has been a powerful method in the total syntheses of natural products in recent years.[12,14] Herein, we report the biomimetic total syntheses of moschamine-related indole alkaloids via oxidative radical coupling.

Although Sato reported that serotobenine could be generated through the nonenzymatic ($K_3Fe(CN)_6$) oxidation of moschamine by thin-layer chromatography (TLC) monitoring,[1] this nonenzymatic oxidation could not be repeated by Jia's group.[8c] Our initial efforts focused on the investigation to obtain decursivine (**2**) and 4,4″-bis(*N*-feruloyl)serotonin (**4**) through direct oxidation of the phenol of moschamine also failed. We hypothesized that, although the radical was generated under oxidative conditions, the radical was located in the O-position instead of delocalization to the C-position. For the coupling reactions to proceed, the radical should be delocalized to the C-position. Lei and Pappo reported the preparation of benzofurans by oxidative radical coupling of phenols with alkenes.[15] They discovered that $FeCl_3$ could promote phenol radical transfer from an O-radical to a C-radical by stabilizing the resonance structure of the radical. It is reported that the enzyme (horseradish peroxidase), which involved the biosynthesis of serotobenine (**1**), also contained an iron.[1] We proposed that the iron would also be critical in the oxidative radical coupling of 5-hydroxyindoles with alkenes by delocalization of the radical from the O-position to the C-position.

When $FeCl_3$ was used as a catalyst, and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) was used as an oxidant, the Ts-protected 5-hydroxyindole substrate **6a** was converted into both cross-coupling product **7a** and homocoupling product **8a** (Scheme 1).1 The Ns-protected substrate **6b** delivered only the cross-coupling/cyclization product **7b**. Instead, the substrates protected with weaker electron-withdrawing groups, such as Bz (**6c**) or Boc (**6d**), displayed selective generation of the homocoupling products **8c** and **8d** in 26% and 45% yields, respectively. Notably, the reaction with stoichiometric $FeCl_3$ but without DDQ did not afford any coupling products. These

Scheme 1. Oxidative Radical Coupling between 5-Hydroxyindoles and Styrene

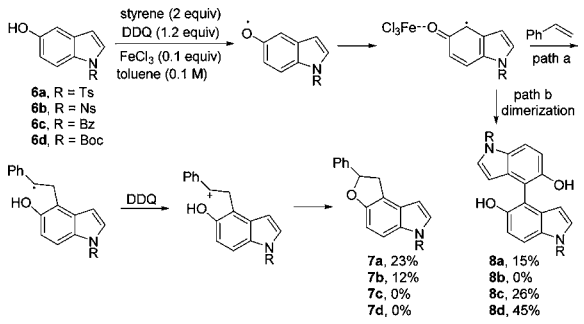
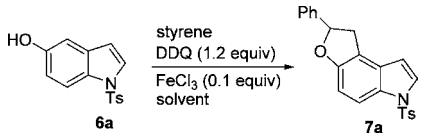


Table 1. Optimization of the Iron-Catalyzed Oxidative Coupling



entry	styrene (equiv)	solvent	conc (M)	time (h)	conv (%)	yield[b] (%)
1	2	toluene	0.1	24	100	30
2	2	CH_3CN	0.1	48	20[c]	13
3	2	DMF	0.1	48	0[c]	0
4	2	THF	0.1	48	10[c]	0
5	2	DCM	0.1	1.5	100	33
6	5	DCM	0.025	4	100	83
7[a]	10	DCM	0.025	4	100	92

[a]DDQ (0.1 M in DCM/toluene = 1/1) was added dropwise over 2 h. [b]Isolated yields by chromatography. [c]Incompleted conversion of starting materials.

results indicated that the radical was generated by oxidation with DDQ and that $FeCl_3$ acted as a radical-delocalized catalyst instead of an oxidative reagent.

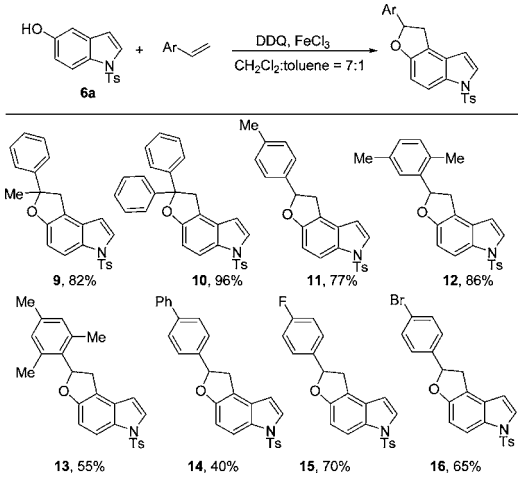
A series of solvents were screened to improve the chemoselectivity and increase the yield. The experimental results showed that DCM provided the fastest reaction rate and the best results (Table 1, entries 1−5). Further optimization of the reaction conditions revealed that the reaction was sensitive to both the reaction concentration and the amount of styrene. When the amount of styrene was increased to 10 equiv and the oxidant DDQ solution (0.1 M in DCM/toluene = 1/1) was added dropwise, the yield was elevated to 92% yield, and only the cross-coupling product **7a** was chemoselectively generated (Table 1, entry 7).

The scope of the iron-catalyzed oxidative cross-coupling/cyclization process was examined by varying the substituents on the double bond of styrene (Scheme 2). α-Methylstyrene and α-arylstyrene were suitable substrates and afforded the corresponding indolofuran products **9** and **10** in 82% and 96% yields, respectively. When the substrates were substituted with alkyl groups, the corresponding products were isolated in good to moderate yields (Scheme 2, **11**−**13**). The aryl-substituted styrene was subjected to reaction with **6a** and afforded product **14** in 40% yield. Notably, electron-withdrawing substituents, such as F and Br, were also tolerated in this transformation and afforded products **15** and **16** in 70% and 65% yields, respectively.

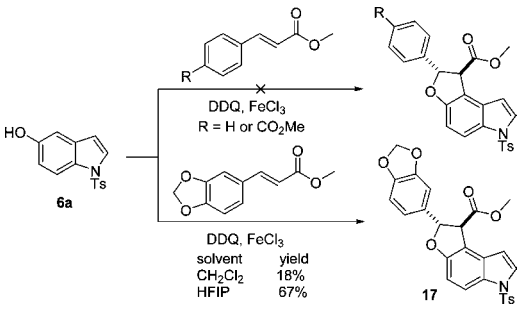
Because moschamine-related indole alkaloids have cinnamic acid moieties instead of styrene, we next turned our efforts to

DOI: 10.1021/acs.orglett.6b00417
Org. Lett. 2016, 18, 1474−1477

Scheme 2. Iron-Catalyzed Oxidative Coupling Reactions between 7a and Styrenes



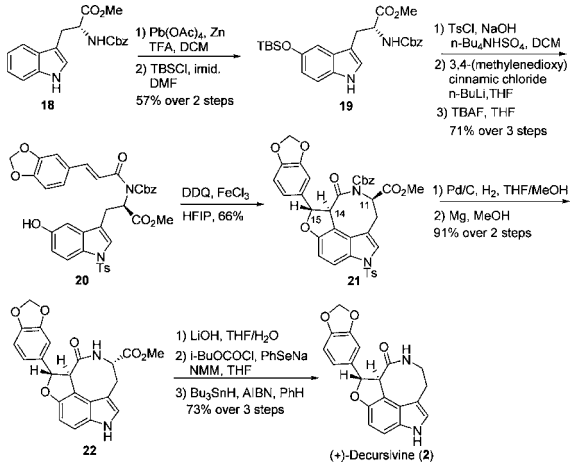
Scheme 3. Reactions between 7a and Cinnamic Acid Derivatives



evaluate cinnamic acid derivatives as partners for the iron-catalyzed oxidative radical reaction. However, methyl cinnamate or its *p*-methoxycarbonyl derivative failed to react with **6a** under the developed conditions (Scheme 3). We proposed that the radical addition reactivity of the double bonds in cinnamic acid derivatives were hindered by the substitution of the electron-withdrawing carbonyl group. Upon further analysis, we noted that in the natural products the aromatic nuclei of cinnamic acid derivatives always possess several oxygen substituents.[1,2,16] These oxygen substituents are therefore reasonably proposed to be vital for the cyclization process. Indeed, by employing methyl 3,4-(methylenedioxy)cinnamate as a partner, we observed that the reaction afforded the product **17** in 18% yield. The relative configuration of **17** was assigned as *anti* through analysis of its $^{3}J_{H\text{-}2/H\text{-}3}$ coupling constants.[15b] Pappo discovered that significant enhancement in the efficiency and selectivity of iron-catalyzed oxidative cross-coupling of phenols were achieved when fluoro alcohols were used as solvents.[17] We found that a substantial improvement was also achieved when hexafluoropropanol (HFIP) was used as the reaction solvent and the yield was increased to 67%.

After optimizing the iron-catalyzed oxidative radical coupling reaction conditions, we then sought to complete the biomimetic total syntheses of (+)-decursivine (**2**) and 4,4″-bis(*N*-feruloyl)-serotonin (**4**). The synthesis of (+)-decursivine commenced with the oxidation of D-tryptophan derivative **18** with Pb(OAc)$_4$[18] followed by protection of the hydroxyl group with a TBS group to afford the 5-hydroxytryptophan **19** (Scheme 4). After the N1 of indole **19** was protected with a Ts group, the 3,4-

Scheme 4. Total Synthesis of (+)-Decursivine (2)

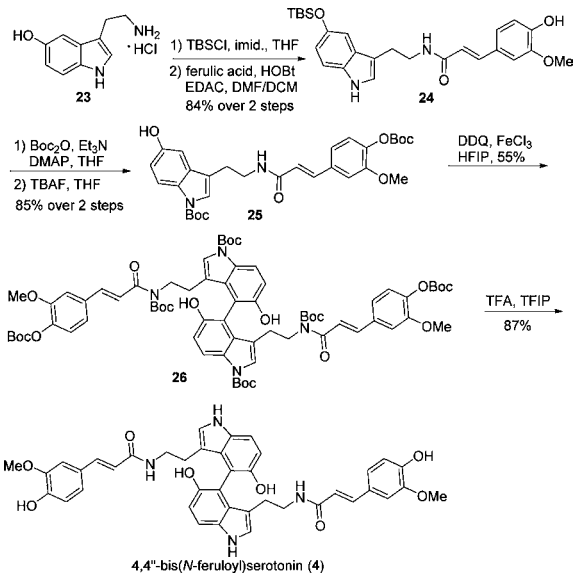


(methylenedioxy)cinnamic amide fragment was introduced with the corresponding acyl chloride. The silyl group was then removed by TBAF to afford compound **20** in 71% yield over the three steps. Initially, we conducted this iron-catalyzed biomimetic oxidative radical intramolecular cyclization reaction under typical reaction conditions (i.e., $FeCl_3$ 0.1 equiv, DDQ 1.2 equiv, HFIP 0.1 M) and observed that the desired cyclization product **21** could be obtained in low yield (28%). Careful examination of the reaction conditions revealed that the amount of $FeCl_3$ and the concentration of the reaction strongly influenced the reaction yield. The product **21** was obtained as a single diastereomer, and the yield was elevated to 66% when the substrate concentration was lowered to 0.01 M and the amount of $FeCl_3$ was increased to 0.5 equiv. Deprotecting the Cbz group under hydrogenolysis conditions and removing the Ts group under basic conditions produced **22** in 91% yield over two steps. The chirality of C11 was epimerized under the basic conditions used to deprotect the Ts group. Finally, removal of the methoxycarbonyl group following Li's procedures[10] afforded (+)-decursivine (**2**) in 73% yield over three steps. The spectroscopic data and the specific rotation ($[\alpha]_D^{20}$ = +262.2 (*c* = 0.02, MeOH); lit. $[\alpha]_D^{20}$ = +299.0 (*c* = 0.02, MeOH)) of synthetic (+)-decursivine (**2**) were in agreement with those of natural product.[2]

After completion of the total synthesis of (+)-decursivine (**2**) by oxidative cross-coupling, we then set out to synthesize 4,4″-bis(*N*-feruloyl)serotonin (**4**) under homocoupling conditions. Moreover, a comparison of the NMR spectra of synthetic 4,4″-bis(*N*-feruloyl)serotonin (**4**) with isolated montamine (**5**) using the same solvent (CD_3OD) would ascertain whether these two compounds possessed same structure. After serotonin **23** was protected with TBS, ferulic acid was introduced to afford the corresponding amide **24** in 84% yield over two steps (Scheme 5). To facilitate oxidative radical homocoupling, Boc protecting groups were installed on both the indole and amide positions. Removal of the TBS group by TBAF gave the compound **25** in 85% yield over two steps. The iron-catalyzed dimerization was carried out to smoothly afford the corresponding dimer product **26** in 55% yield. Finally, deprotection of four Boc groups with TFA delivered 4,4″-bis(*N*-feruloyl)serotonin (**4**) in 87% yield. The NMR data for synthetic 4,4″-bis(*N*-feruloyl)serotonin (**4**) in DMSO-d_6 were in good agreement with those reported in the literature (Supporting Information, Table S1).[3] We also performed the NMR characteristics of the synthetic 4,4″-bis(*N*-feruloyl)serotonin (**4**) in CD_3OD and compared the

DOI: 10.1021/acs.orglett.6b00417
Org. Lett. 2016, 18, 1474−1477

Scheme 5. Total Synthesis of 4,4″-Bis(*N*-feruloyl)serotonin (4)



spectra with those of montamine (**5**), which had also been recorded in CD_3OD (Supporting Information, Table S2). The results suggested that montamine (**5**) was not as the same structure of 4,4″-bis(*N*-feruloyl)serotonin (**4**) because both the ^1H NMR and ^{13}C NMR spectra displayed substantial differences.

In conclusion, inspired by the biosynthetic pathways of moschamine-related indole alkaloids, a selective homo- or cross-coupling reaction of 5-hydroxyindoles to access the bisphenolic indole and indolofuran cores has been established by an iron-catalyzed oxidative radical reaction under mild conditions. Using this bioinspired oxidative radical coupling, the highly efficient total synthesis of (+)-decursivine (**2**) and 4,4″-bis(*N*-feruloyl)-serotonin (**4**) was achieved. The suggested reassignment of montamine (**5**) as the same structure of 4,4″-bis(*N*-feruloyl)-serotonin (**4**) was excluded by comparison of the NMR spectra of montamine (**5**) and synthetic 4,4″-bis(*N*-feruloyl)serotonin (**4**) in the same solvent.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00417.

Experimental procedures and compound characterization (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by the National Natural Science Foundation of China (21272242 and 21302193), Yunnan High-End Technology Professionals Introduction Program (2010CI117), and Natural Science Foundation of Yunnan Province (2014FA008).

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DOI: 10.1021/acs.orglett.6b00417
Org. Lett. 2016, 18, 1474–1477