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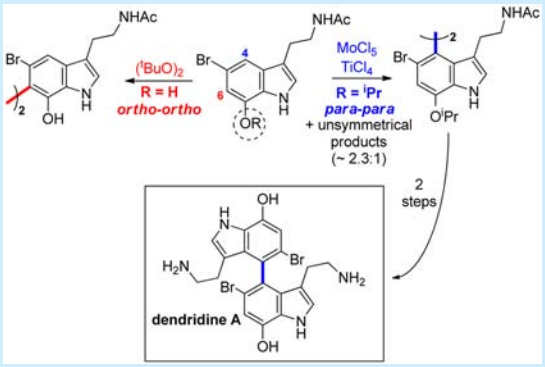
Biomimetic Synthesis of Dendridine A

Emily M. Boyd and Jonathan Sperry*

School of Chemical Sciences, University of Auckland, 23 Symonds Street, Auckland, New Zealand

Supporting Information

ABSTRACT: Biomimetic synthesis of the bisindole natural product dendridine A is reported. Although attempts to install the hindered biaryl bond by oxidative phenolic coupling of the 7-hydroxytryptamine **6** gave the undesired *ortho*−*ortho* product, a Scholl-type oxidative coupling of the 7-isopropoxytryptamine **9** with molybdenum pentachloride proceeded through the desired *para*−*para* pathway, installing the entire carbon framework of dendridine A.



Dendridine A (**1**),[1] dispegatrine (**2**),[2] and the antioxidant serotonin derivatives (**3**−**5**)[3] are the only alkaloids known to contain a 4,4′-bisindole bond[4] (Figure 1). Among this small subset of natural products, dendridine A is unique as the biaryl bond arises from a *para*−*para* oxidative phenolic coupling of the corresponding 7-hydroxyindole, whereas **2**−**5** all result from a 5-hydroxyindole undergoing *ortho*−*ortho* coupling.[5,6] The isolation paper does not report an optical rotation for **1**, but it cannot be ruled that its formation by oxidative coupling proceeds under enzymatic control, and hence **1** is enantioenriched.

A biomimetic synthesis of dendridine A (Scheme 1) would require executing a *para*−*para* oxidative phenolic coupling of monomeric 7-hydroxytryptamine (e.g., **6**), a challenging transformation due to the vacant C2 and C6 sites, which could result in *ortho*−*ortho* (6,6′) and *ortho*−*para* (4,6′) coupled products, reaction at the azole, and the formation of quinones, biaryl ethers, and oligomers.[7] Encouraging literature searches revealed that 7-hydroxyindole undergoes oxidative dimerization to give the 4,4′-dimer, albeit with the 3,4′-bisindole, trimeric, and tetrameric products.[8]

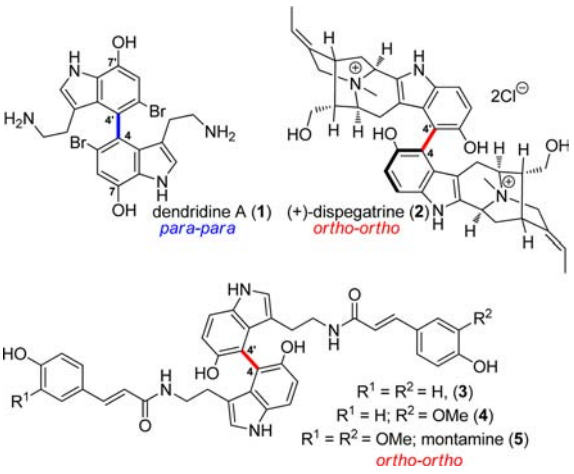
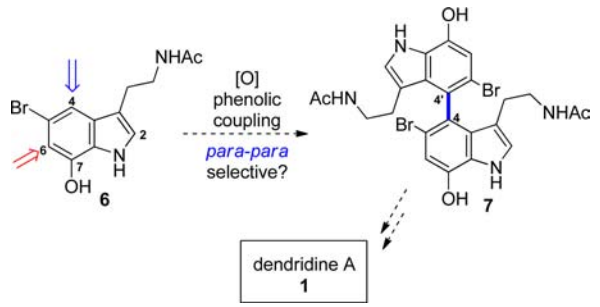


Figure 1. Natural products possessing a 4,4′-bisindole bond.

Scheme 1. Proposed Biomimetic Synthesis of Dendridine A (1)



Subjecting *hemi*-dendridine acetate **6**[9] to a battery of oxidants[7] known to effect the oxidative coupling of phenols, including $FeCl_3{\cdot}SiO_2$, Ag_2O, $Pb(OAc)_4$, $K_3[Fe(CN)_6]$, and $PhI(OAc)_2$, led to varying levels of degradation, with no dimeric products observed. However, exposing **6** to an excess of di-*tert*-butylperoxide in toluene heated to 130 °C in a sealed tube gave a single symmetrical dimer **8** (characterized as its tetraacetate **9**),[10] a result of *ortho*−*ortho* coupling (Scheme 2). In the absence of steric bias[11] or catalyst control,[12] the intermolecular oxidative radical coupling of phenols with vacant *ortho* and *para* sites generally favors the *ortho*−*ortho* pathway on stereoelectronic grounds, but even so, the absence of any *para*−*para* coupling was disappointing considering Nature likely employs

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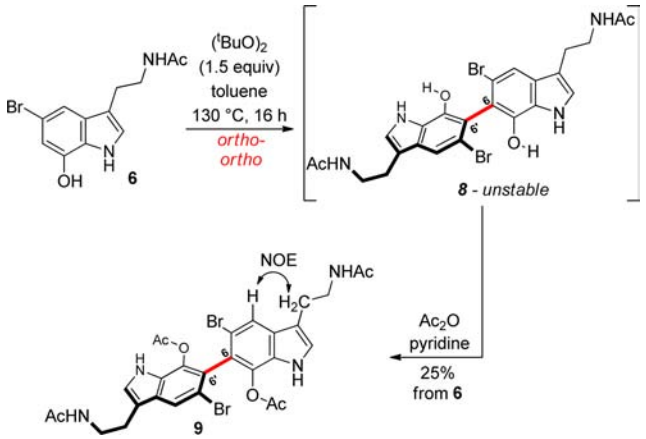
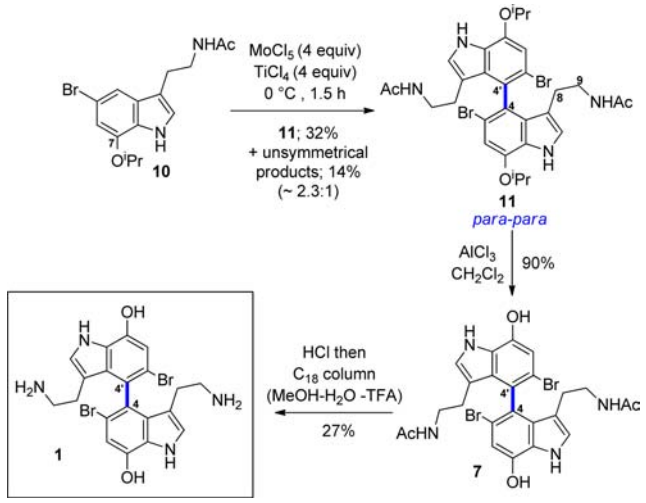
Scheme 2. Formation of the *ortho*−*ortho* Coupled Product



Scheme 3. Biomimetic Synthesis of Dendridine A (1)

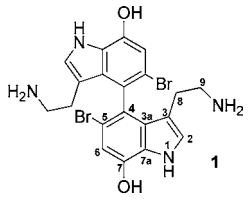


this strategy during the biosynthesis of dendridine A. An alternative approach was required.

The Scholl process[13] is an acid-catalyzed oxidative coupling that is widely used intramolecularly to access polycyclic aromatic hydrocarbons.[14] Intermolecular versions of this reaction are rare in natural product synthesis, although a recent total synthesis of P-(+)-dispegatrine (**2**) did employ a thallium(III)-mediated diastereoselective Scholl reaction to forge the bisindole bond.[15] Given that the outcome of a Scholl reaction mirrors that of electrophilic aromatic substitution reactions,[16] substrate **10**[17] was chosen with the aim that the 7-isopropoxy substituent[18] would direct dimerization to the *para* site (C4) while simultaneously restricting reaction at the *ortho* position (C6) on steric grounds. Subjecting **10** to several oxidative conditions[13] known to effect the dehydrogenative coupling of alkoxyarenes revealed that molybdenum pentachloride ($MoCl_5$) in the presence of the Lewis acid titanium tetrachloride (acting as a hydrogen chloride scavenger)[19] performed best, giving a ∼45% total yield of coupled products comprising 4,4′-bistryptamine **11** as the major component, with several other unsymmetrical compounds[20] (∼2.3:1 by ^{1}H NMR) (Scheme 3). Ongoing discussion infers that the Scholl reaction proceeds through two separate mechanistic pathways (radical cation or arenium cation) depending on the nature of the substrate and the oxidation conditions,[13d] but as the one-electron oxidant $MoCl_5$ is operating at 0 °C in this example, it is likely[13d] an initial single-electron transfer from **10** to $MoCl_5$[21] generates a radical cation that triggers the intermolecular C−C bond-forming event, the regioselectivity of which is effectively governed by the bulky isopropoxy group.

With the framework of dendridine A assembled, we set out to complete its total synthesis. Deisopropylation of **11** with aluminum trichloride gave **7** that upon acetamide hydrolysis gave a crude sample of dendridine A, which was subjected to the same final purification conditions used in the isolation report[1] to give pure dendridine A as its di-TFA salt. The NMR data for

Table 1. ^{1}H and ^{13}C NMR Data for Authentic and Synthetic 1 (Both as Their di-TFA Salts)



	dendridine A (**1**) (DMSO-d_6)		synthetic **1** (DMSO-d_6)	
carbon	δ_H (600 MHz)	δ_C (150 MHz)	δ_H (500 MHz)	δ_C (125 MHz)
1	11.17 (2 H, s)		11.22 (2 H, s)	
2	7.05 (2 H, s)	124.5	7.09 (2 H, s)	124.5
3		110.7		110.6
3a		128.0		127.9
4		122.7		122.6
5		115.0		114.9
6	6.81 (2 H, s)	108.9	6.82 (2 H, s)	108.8
7		143.9		143.8
7-OH	10.29 (2 H, s)		10.18 (2 H, s)	
7a		125.8		125.6
8	2.02 (4 H, t, *J* 7.0)	23.2	2.05 (4 H, t, *J* 6.8)	23.0
9	2.46 (4 H, m)	38.6	2.48−2.41 (4 H, m)	38.4
9-NH_2	7.51 (4 H, br s)		7.57 (4 H, br s)	

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synthetic **1** were in excellent agreement with the natural product (Table 1).[22]

In conclusion, a biomimetic synthesis of the alkaloid dendridine A has been achieved. Although the oxidative phenolic coupling of the 7-hydroxytryptamine **6** gave the undesired *ortho*−*ortho* product, a Scholl-type oxidative coupling of the corresponding 7-isopropoxytryptamine **9** gave the *para*−*para* coupled product **10**, which was readily converted to dendridine A. The success of $MoCl_5$ in forging the hindered bisindole bond in dendridine A under mild conditions hints at the potential utility of this reagent when considering intermolecular dehydrogenative couplings in natural products synthesis.[19,21]

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and NMR spectra of all novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: j.sperry@auckland.ac.nz.

Notes

The authors declare no competing financial interest.

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(10) The NMR data for **9** also did not match that of dendridine A tetraacetate; see ref 1.

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(17) 7-Isopropoxytryptamine **10** was prepared using the Fischer procedure described in ref 9. See Supporting Information.

(18) The 7-isopropoxytryptamine **9** was chosen as the isopropyl group is easier to dealkylate than its methyl counterpart (see ref 2c).

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(22) Synthetic **1** was treated with acetic anhydride in pyridine, and the spectroscopic data of the resulting tetra-acetate were in agreement with the tetra-acetate of the natural product. See Supporting Information.

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