Natural Product Synthesis

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Synthesis of Bis(indole) Alkaloids from *Arundo donax:* The Ynindole Diels–Alder Reaction, Conformational Chirality, and Absolute Stereochemistry**

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Abstract: *Bis(indole) alkaloids from Arundo donax were synthesized using the first ynindole Diels–Alder reaction. The alkaloids are chiral, having stable enantiomeric conformations with half-lives of racemization of $t_{1/2} = 4150–25100$ seconds at room temperature. Their absolute stereochemistry was determined using the exciton chirality method.*

In molecules lacking sp^3-hybridized stereogenic carbon atoms such as biaryls and cyclophanes, identification of chirality is not straightforward.[1,2] In such molecules, chirality means the molecules have relatively long half-lives of racemization.[3] In this context, chirality has been defined as those molecules which possess a half-life of 1000 seconds or longer.[4] Predicting half-lives of enantiomeric conformations of molecules using computational methods is not straightforward because small (1.4 kcal mol^{-1}) changes in the racemization barrier result in a change of an order of magnitude in the racemization half-life.[5] As a result, molecules lacking stereocenters could have unnoticed chirality. In such cases, chemical synthesis and experimental determination of the racemization half-life would be required to unambiguously demonstrate the presence of chirality. Described herein is such an investigation for a family of indole alkaloids.

Arundo donax is a grass native to Asia and it has been used in folk medicine since ancient times.[6] More recently, it has been used as the source of reeds for woodwind instruments, has been evaluated as a biofuel, and it can be an invasive species.[7] In 2002–2004 Khuzhaev and co-workers isolated six bis(indole) natural products (**1–6**; Figure 1) from the root ball of *A. donax*.[8,9] They display a 4-indoyl-indole molecular architecture, and as such, represent a unique class of bis(indole) natural products. Khuzhaev hypothesized that arundamine (**3**) is achiral based on computational analysis of C–N bond rotation.[10,11]

Despite Khuzhaev's hypothesis, we suspected the alkaloids from *A. donax* possess stable enantiomeric conformations. Tabulated ^{1}H NMR chemical shifts for the alkaloids reveal that the geminal methylene protons are chemical-shift inequivalent. This feature is diagnostic for racemization half-lives which are longer than the ^{1}H NMR timescale of approximately 0.001 to 0.1 seconds, and is not consistent with the barrier calculated by Khuzhaev.[11,12]

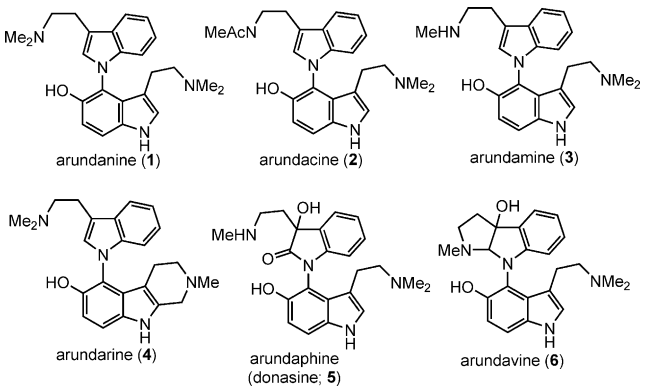
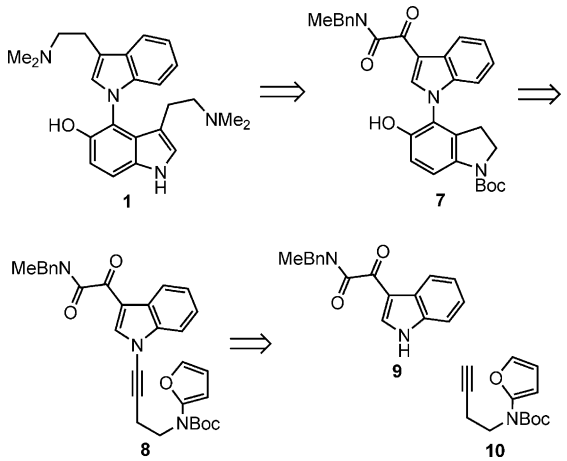


Figure 1. Bis(indole) alkaloids from *Arundo donax*.

The C–N biaryl axis of **1–4** is flanked by three non-hydrogen substituents, and such substitution patterns often lead to chirality in biphenyls.[1] Moreover, typical C–N bonds which connect azoles with phenyl rings are shorter (1.419–1.430 Å)[13] than C–C bonds in biphenyls (1.482–1.507 Å),[14] and would bring the large substituents closer, and could enhance steric effects.

We decided to prepare the *A. donax* alkaloids and measure their racemization half-lives. The alkaloids **1–4** could arise from the glyoxamide **7** (Scheme 1). We envisioned **7** as the product of a Diels–Alder cascade of **8**, which displays an amino-furan diene and an ynindole (*N*-alkynyl indole) dienophile. The intermediate **8** may arise from coupling of the



Scheme 1. Retrosynthetic analysis of the *A. donax* alkaloid. Boc = *tert*-butoxycarbonyl.

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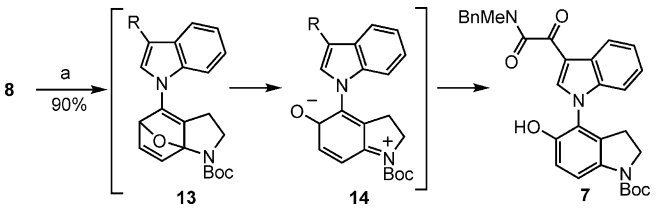
indole **9** and alkyne **10**. Notably, this strategy constructs the central C–N linkage prior to synthesis of the bis(indole) architecture. It was envisioned that the coupling of an indole NH and a terminal alkyne would be smoother than cross-coupling of two functionalized indole building blocks.

Amino-furan dienes have been used in Diels–Alder reactions,[15] but ynindoles are unknown as dienophiles. The lack of Diels–Alder reactivity of ynindoles could be attributed to a paucity of methods for their construction. Recently however, metal-catalyzed coupling of an indole with a bromoalkyne[16] or a propiolic acid[17] to form ynindoles was reported. In 2008, Stahl and co-workers reported a synthesis of an ynindole from 3-carbomethoxy indole (**11**) and a simple terminal alkyne.[18] All high-yielding ynindole formations use indoles substituted with electron-withdrawing groups. Possibly, the electron-withdrawing substituent renders the indole sufficiently acidic to be deprotonated under the reaction conditions.

Provided we could synthesize **8**, we considered whether or not it would undergo intramolecular Diels–Alder cycloaddition. The amino-furan functionality is known to be an electron-rich diene. We expected the alkyne to be electron poor based on the inductive electron-withdrawing ability of the indole. However, the electronic preference of ynindoles in Diels–Alder reactions was completely unknown. Nitrogen-substitued alkynes such as ynanimes are among the most electron-rich dienophiles.[19] However, the electron pair on the nitrogen atom of the ynidole participates in the aromaticity of the indole, and may not be available for resonance donation. Furthermore, the indole nitrogen lone pair would activate only one of two orthogonal π systems of the alkyne, thus leaving the remaining π bond for normal-electron-demand Diels–Alder cycloaddition. Such considerations offered a compelling reason to investigate the Diels–Alder reactivity of **8**.

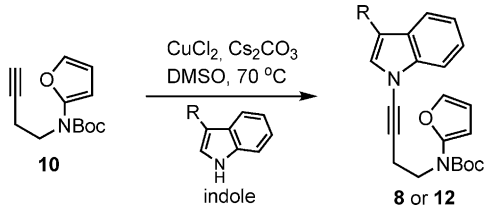
The alkyne **10** was prepared in four steps[20] from Boc-protected 2-aminofuran.[21] Coupling of **10** with **11** using copper in DMSO gave the ynindole **12** in good yield (Table 1). Indole or dimethyl tryptamine did not couple with **10**, presumably because they are not sufficiently acidic. We then coupled **10** with **9**, which is synthetically equivalent to dimethyl tryptamine and contains an electron-withdrawing substituent at the indole 3-position.

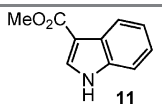
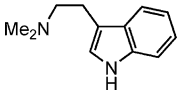
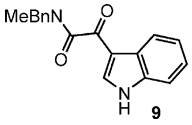
We evaluated the Diels–Alder reactivity of **8**. Gratifyingly, it underwent clean high-yielding cycloaddition to give the phenol **7** at mild temperatures (150 °C; Scheme 2). Presumably, the reaction proceeds via **13** which fragments to give the acyliminium ion **14**. Tautomerization then gives **7**. No intermediates were observed or isolated in the reaction.



Scheme 2. Reagents and conditions: a) 150 °C, toluene (sealed tube).

Table 1: Ynindole Diels–Alder substrates.



Entry	Indole	Product	Yield [%]
1		**12**	54
2		n.r.	0[a]
3		n.r.	0[a]
4		**8**	57

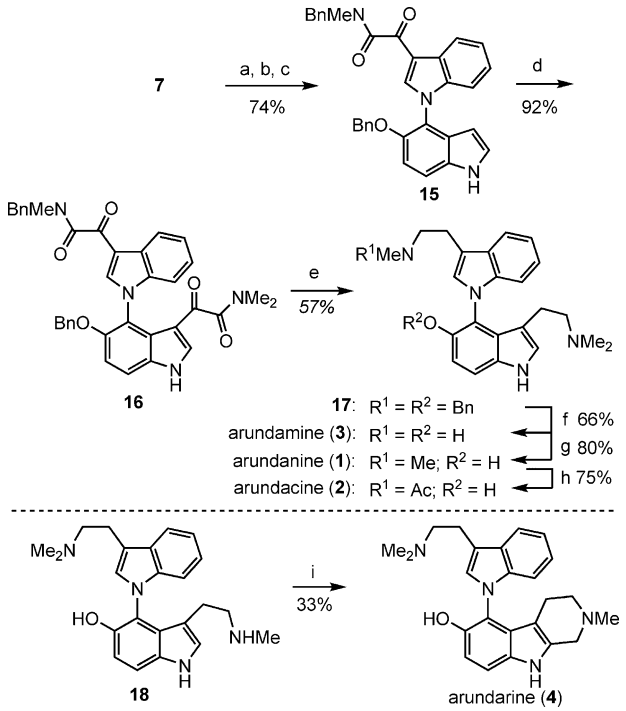
[a] Starting material was recovered unchanged. DMSO = dimethylsulfoxide, n.r. = no reaction.

Functional-group manipulations were used to complete the synthesis of the alkaloids (Scheme 3). The intermediate **7** was converted into the bis(indole) **15**. Acylation of **15** gave the bis(glyoxamide) **16**. Indole glyoxamides can be cleanly reduced to tryptamines using several hydride reducing agents such as $LiAlH_4$.[22] However, identifying reaction conditions for clean reduction of **16** was surprisingly difficult. After considerable experimentation, it was found that exhaustive reduction of **16** could be achieved with borane. The initial product of the reduction appears to be a boron complex,[23] which can be hydrolyzed to **17**. Hydrogenolysis of **17** in acetic acid removes the benzyl ether to give arundamine (**3**). Hydrogenolysis of **17** in methanol gave arudanine (**1**).[24,25] Acylation of arundamine gave arundacine (**2**). Arundarine (**4**) was formed by Pictet–Spengler reaction of the intermediate **18**.[20]

We then investigated the chiral properties of the alkaloids. Gratifyingly, **1**–**4** were cleanly resolved on chiral HPLC. Arundamine enantiomers (**3**) were separated for polarimetry and circular dichroic (CD) analysis. The dextrorotatory enantiomer, (+)-arundamine, was analyzed by CD spectroscopy (Figure 2). It exhibited a positive first Cotton effect and negative second Cotton effect ($\lambda = 234$ and 222 nm, respectively). The exciton chirality method[26,27] indicates this (+)-arundamine enantiomer possesses the a*R* absolute stereochemistry.

An enantiopure sample of (+)-arundamine underwent slow racemization at room temperature. The first-order rate constant was $k_{rac} = 1.67 \times 10^{-4}\ s^{-1}$, which corresponds to a half-life of $t_{1/2} = 4150$ s (1.15 h) and a free energy of activation for racemization of 23.3 kcal mol^{-1}.

The HPLC resolution, analysis of CD data, and measurement of racemization rate was conducted for the remaining



Scheme 3. Reagents and conditions: a) BnBr, K_2CO_3, DMF; b) TFA, CH_2Cl_2; c) MnO_2, acetone, 35 °C; d) 1. $(COCl)_2$, THF; 2. $HNMe_2$, H_2O; e) 1. BH_3·DMS, THF, reflux; 2. MeOH, reflux; f) H_2, Pd/C, AcOH; g) H_2, Pd/C, $(CH_2O)_n$, MeOH; h) Ac_2O, MeOH; i) $CH_2O_{(aq)}$, AcOH. DMF = *N*,*N*-dimethylformamide, DMS = dimethylsulfide, TFA = trifluoroacetic acid, THF = tetrahydrofuran.

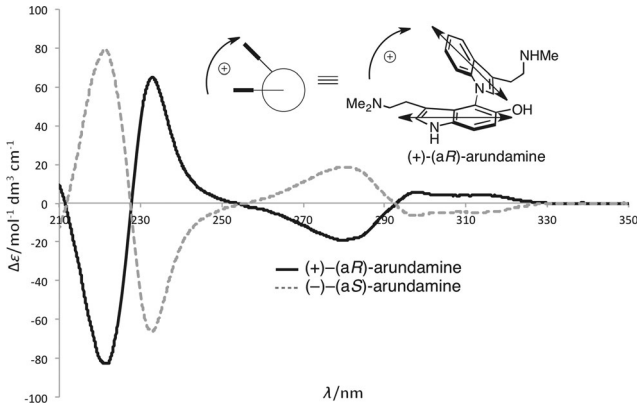


Figure 2. Absolute stereochemsitry of arundamine (**3**).

three alkaloids (Figure 3). Absolute configurations for the dextrorotatory enantiomers are shown, and were determined using the exciton chirality method. The free energies of activation for racemization, first-order rate constant for racemization, racemization half-lives, and the specific rotations are tabulated. The free energies of activation for racemization for the *A. donax* alkaloids are quite similar (23.3 to 24.3 kcal mol^{-1}), but the corresponding half-lives of racemization range from 4150 s (1.15 h) to 25100 s (6.97 h). These numbers highlight the difficulty in identifying molecular chirality in such molecules: small differences in racemization energies result in comparatively large differences in racemization half-life.

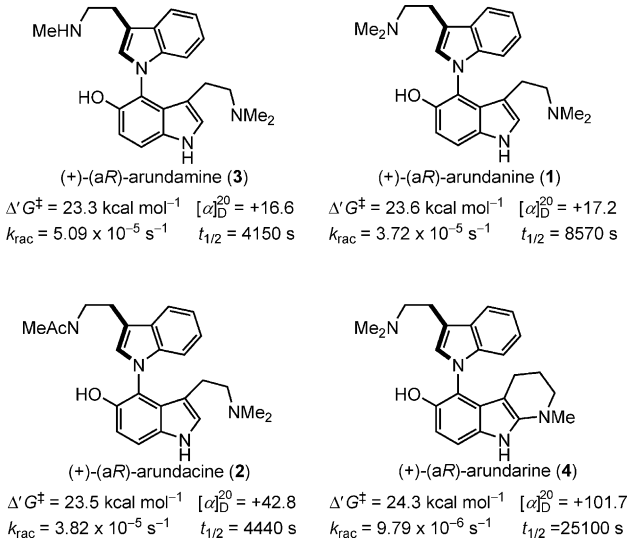


Figure 3. Racemization rates, specific rotations, and absolute configurations of the *A. donax* alkaloids.

In conclusion, the first synthesis of the *Arundo donax* alkaloids was accomplished using the first Diels–Alder reaction of the ynindole functional group. Synthetic material was used to determine the racemization half-life, free energy of activation for racemization, and absolute configuration of the molecules. The molecules are chiral, with half-lives of racemization at 25 °C of 4150–25100 seconds. Whether such molecules are biosynthesized in enantioenriched form or whether such molecules with modest racemization rates can be implicated in time-sensitive biological processes is the subject of our current research.

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