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One-Pot Dichotomous Construction of Inside-Azayohimban and Pro-Azayohimban Systems via an Enantioselective Organocatalytic Cascade; Their Use as a Model to Probe the (Aza-)Indole Local Solvent Environment

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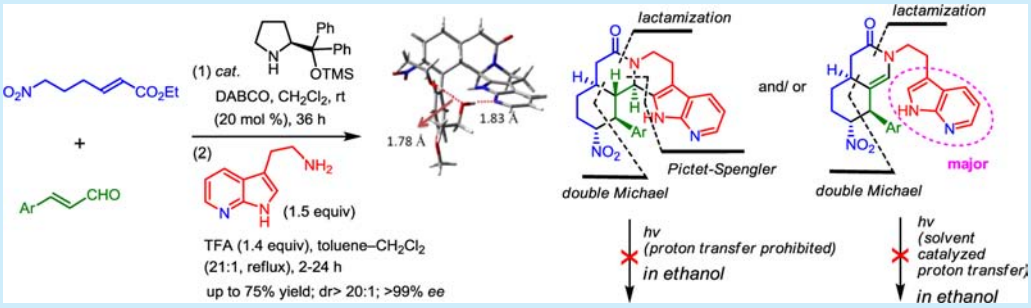
Supporting Information



ABSTRACT: A one-pot enantioselective synthesis of 7-azaindole-octahydroisoquinolin-3-one and an inside-aza-yohimbane system containing five contiguous stereogenic centers with high enantioselectivities (>99% *ee*) was achieved. The prepared highly functionalized polycyclic system provides a model for probing the solvent catalyzed proton transfer reaction and mimicking the local environment of the tryptophan moiety in proteins.

Quinolizidine alkaloids represent an important class of monoterpenoid-derived alkaloids with a wide spectrum of biological activities and have long attracted pharmacological and synthetic interests.[1] The yohimbane alkaloid, a characteristic pentacyclic indole alkaloid from the *Rubiaceae* family, and its related derivatives have been used as adrenergic blocking agents for Angina pectoris and arteriosclerosis, as well as for the treatment of impotency in patients with diabetic or vascular problems. Over the years, the related alkaloids have been extensively investigated for their pharmacology and chemistry. The biosynthesis of members of the yohimbane family[2] and the total synthesis[3] of the yohimbane-type alkaloids have been studied. Traditionally, *seco*-yohimbane lactam derivatives have been used for the synthesis of alloyohimbane and yohimbane via the Bischler−Napieralski reaction, Scheme 1.[4] Alternatively, the dodecahydrobenz[*a*]indolo[3,2-*h*]quinolizine, the so-called "inside yohimbane", with a variety of biological activities,[5] has emerged as a preeminent member of a related alkaloid category.

Because of the similarities in the structure of azaindole and indole, a derivative of 7-azaindole, namely, 7-azatryptophan, has been widely used to replace tryptophan in proteins of interest to probe the local polarity environment surrounding tryptophan residues.[6a,b] Further, in protic solvents such as alcohols (e.g., ethanol), 7-azaindole undergoes solvent-catalyzed proton transfer in the excited state.[6c−e] In a recent advancement, 2,7-diazaindole and, accordingly, its analogue 2,7-diazatryptophan[7] ((2,7-diaza)Trp, Scheme 2A) have been exploited to probe the water microsolvation surrounding the chromophore. In bulk water, 2,7-diazaindole or 2,7-diazaryptophan exist mainly as an N(1)-H form (∼98%) with a very minor portion (∼2%) as the N(2)-H isomer. Apparently, the population of the N(2)-H species is stabilized in bulk water, but not in microsolvated water. The latter is indicated by the negligible N(2)-H population when 2,7-diazatryptophan replaces tryptophan in various proteins. Under these conditions, only a few or a cluster of water molecules exist in proximity to the substituted 2,7-diazatryptophan residue, such that the N(1)-H isomer is the solely populated species.[7]

As for the N(1)-H species, upon electronic excitation and catalyzed by water molecules, proton transfer takes place from N(1)-H to N(7)-H, resulting in a characteristic N(7)-H tautomer emission with a maximum at ∼500 nm (for details, see Figure S3 in the Supporting Information). The replacement of a tryptophan by 2,7-diazatryptophan in a designated protein allows for the use of (2,7-diaza)Trp to detect the existence of water molecules, providing valuable information about the protein−water correlation and hence the protein functionality.[7,8]

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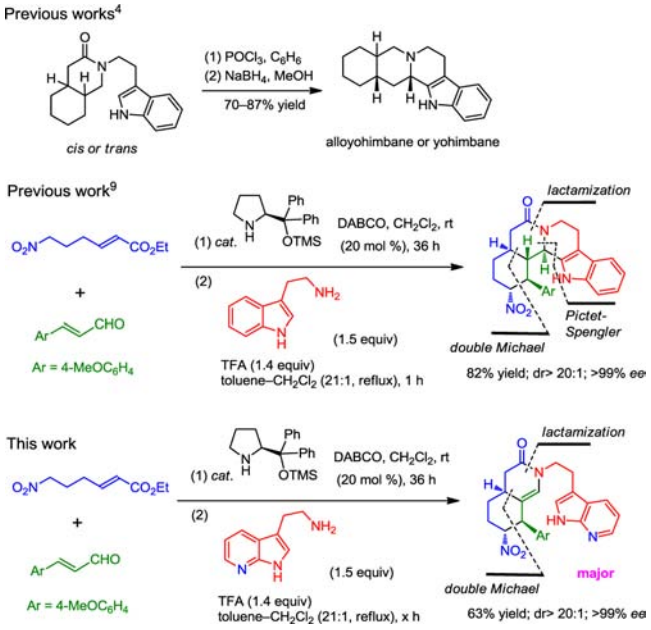
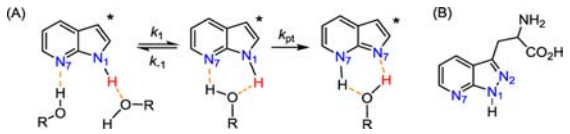
Scheme 1. Synthesis of Alloyohimbane, Yohimbane, and Inside-Yohimbane



Scheme 2[a]



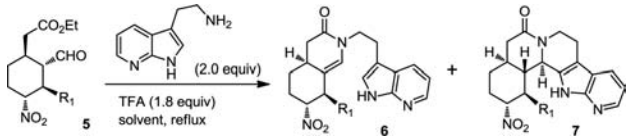
[a](A) The mechanism of solvent (alcohol) catalyzed excited-state proton-transfer reaction for 7-azaindole.[6e] (B) The structure of 2,7-diazatryptophan.[13]

The effect of the water microenvironment on proton transfer reactions is fundamentally important in the field of chemistry. Advances in this field will require the simulation of the environment at local sites within proteins, such that water-catalyzed proton transfer can be probed under conditions of a well characterized molecular structure. Inspired by Hong's recent accomplishment in a one-pot organocatalytic synthesis of both inside- and pro-yohimbane indole derivatives,[9] we proposed that, if a similar indole synthetic route can be applied to 7-azaindoles, the pro- versus inside-yohimbane 7-azaindole derivatives may serve as an ideal contrast model to represent sites with open access and restricted access, respectively, to the solvent molecules between the N(1)-H and N(7) sites. The inside-yohimbane 7-azaindole derivatives (e.g., **7**, vide supra) limit the number of solvent molecules accommodated; therefore, the associated dynamics of proton transfer in the excited state are expected to be altered accordingly.

In this proof-of-concept study, 7-azaindole instead of 2,7-diazaindole (or (2,7-aza)Trp) was selected to avoid the reaction complexity (vide infra). We then strategically designed and synthesized a series of 7-diazaindole derivatives using organocatalytic Michael/Michael/Pictet–Spengler-lactamization as the key step[10,11] (Scheme 1). To our surprise, with only subtle differences between 7-azaindole and indole, i.e., the N(7) versus C(7), the cascade reaction led to a very distinct outcome. Herein, we report this one-pot organocatalysis synthetic route to afford the *seco*-yohimbane derivatives, in which the inside-aza-yohimbane (pro-aza-yohimbane) product prohibits (allows) the proton transfer in polar protic media, e.g., alcohol solution, proving the key role of solvent molecules in the catalytic reaction. Detailed synthetic pathways, characterizations en route to the targeted compounds, and the associated photophysics are elaborated below.

At the outset of the study, reaction of cyclohexylcarbaldehyde **5a**, prepared from the double Michael reaction of nitro alkenoate **3** and cinnamaldehyde **4a** with 20 mol % of Jørgensen-Hayashi catalyst, DABCO,[12] and 2 equiv of 7-aza-tryptamine with 1.8 equiv of trifluoroacetic acid (TFA) in refluxing toluene for 2 h unexpectedly afforded 77% yield of **6a** as the predominant product (Table 1, entry 1). Notably, the reaction with 7-aza-tryptamine provided a different product, **6a**, with the tryptamine counterpart, where the pentacyclic benzindolo-quinolizine was obtained as the predominant product. Treatment of **5b** with 7-aza-tryptamine under the same reaction conditions for 5 h gave **6b** in 79% yield (Table 1, entry 2). In addition, the reaction with **5c**, with the *para*-methoxy phenyl substituent, gave rise to the formation of **6c** and **7c** in a ratio of 10:1 (Table 1, entry 3). A series of solvents was screened for the reaction, and the optimal yield of **7c** was obtained in 79% overall yield with a ratio of **6c**/**7c** = 3.5:1 for the reaction in CH_3CN (Table 1, entry 5). The same reaction in DMF or MeOH did not take place or gave low yields of **6c** with no observable **7c** (Table 1, entries 6 and 7). The structures of the adducts were assigned based on the X-ray analysis of a single crystal of (−)-**6a** and (−)-**7c** (Figure 1).

Table 1. Cyclization Reaction of 5[a]



entry	5	R_1	solvent	t (h)	yield[b] (%)	6/7[c]
1	**5a**	C_6H_5	toluene	2	77	>20:1
2	**5b**	4-$NO_2C_6H_4$	toluene	5	79	>20:1
3	**5c**	4-$MeOC_6H_4$	toluene	10	72	10:1
4[d]	**5c**	4-$MeOC_6H_4$	toluene	10	49	>20:1
5	**5c**	4-$MeOC_6H_4$	CH_3CN	10	79	3.5:1
6	**5c**	4-$MeOC_6H_4$	DMF	10	nr	na
7	**5c**	4-$MeOC_6H_4$	MeOH	22	20	>20:1

[a]Unless otherwise noted, the reactions were performed on a 0.1 mmol scale of **5**,7-aza-tryptamine (2.0 equiv) and TFA (1.8 equiv) at reflux temperature in the appropriate solvent. [b]Isolated yields of **6** and **7**. [c]Unless otherwise noted, diastereomeric ratio > 20:1, determined by ^{1}H NMR of the reaction mixture. [d]Reaction with CH_3COOH (1.8 equiv), instead of TFA. nr = no reaction. na = not available.

Later, the Michael–Michael and the subsequent lactamization or Pictet–Spengler lactamization reactions were achieved in a one-pot operation without the need to isolate the double Michael adducts **5a**. With these enhanced conditions in hand, the one-pot domino-reaction strategy was tested in the reaction with various

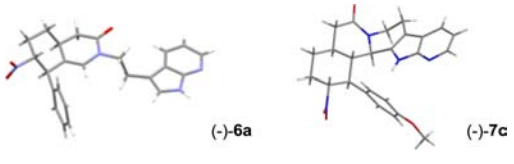


Figure 1. Stereoplots of the X-ray crystal structures of (−)-**6a** and (−)-**7c**: C, gray; O, red; N, blue.

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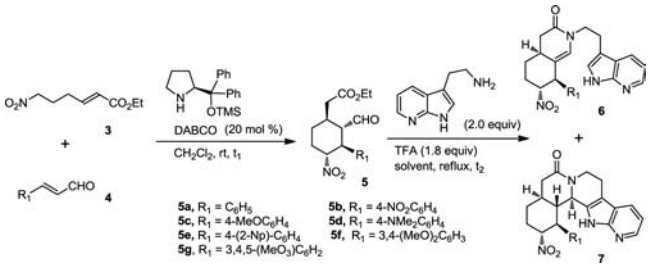
α,β-unsaturated aldehydes **4**, and the results were general, preferentially affording the *seco*-yohimbane lactam derivative **6** with high yields and stereoselectivities (Table 2). For example,

Table 2. Example of One-Pot Domino Reactions[a]



entry	5	solvent	t_1/t_2 (h)	yield[b] (%)[c]	6/7[c]	5 *ee* (%)[d]	6/7 *ee* (%)
1	**5a**	toluene	36/2	77	>20:1	99	99[e]/99[f]
2	**5b**	toluene	36/5	79	>20:1	99	99[f]/99[f]
3	**5c**	CH_3CN	40/10	78	3.5:1[g]	99	99[e]/99[f]
4	**5d**	CH_3CN	36/10	79	16.5:1	98	98[e]/99[f]
5	**5e**	CH_3CN	80/10	71	11.3:1	99	99[f]/99[f]
6	**5f**	CH_3CN	168/22	77	3.6:1	99	99[e]/99[f]
7	**5g**	CH_3CN	168/22	69	7.6:1	98	99[f]/99[f]

[a]Unless otherwise noted, the reactions were performed on a 0.2 N scale of **3** and **4** (1.2 equiv), using 20 mol % of the catalyst and DABCO at ambient temperature in CH_2Cl_2. After the complete formation of **5**, appropriate solvent was added into the reaction mixture (e.g., toluene: CH_2Cl_2 = 20:1), and the solution was heated to reflux. [b]Isolated yields of **6** and **7**. [c]Determined by ^{1}H NMR of the reaction mixture. [d]In a separate reaction, **5** was isolated, and the *ee* of **5** was determined by HPLC with Chiralpak IC. [e]Determined by HPLC with Chiralpak IA. [f]Determined by HPLC with Chiralpak IC. [g]When *i*-PrCN was used for the second step at refluxing condition for 24 h, ratio of **6c**/**7c** = 2.8:1 at 4 h, 1:1 at 8 h, and 1:2.7 at 22 h and maintained a similar ratio up to 36 h.

the one-pot operation was achieved via the addition of toluene in the reaction mixtures after the completion of the double Michael reaction of **3** and **4a** in CH_2Cl_2 (36 h), followed by treatment with 7-azatryptamine and TFA and heated to reflux in toluene for 2 h, affording 77% yield of **6a** with >99% *ee* (Table 2, entry 1). The same reaction conditions for **4b** and **4d**, the *para*-nitro and dimethylamino substituted cinnamaldehydes, gave similar yields of **6b** and **6d**, respectively, as well as chemoselectivity and stereoselectivity (Table 2, entries 2 and 4). However, the reactions with **4c**, **4f**, and **4g**, the methoxy substituted cinnamaldehydes, provided the product **6** with a substantial amount of pentacyclic product **7**. However, generally, the first-step double Michael reactions were completed in 2 days, but a prolonged reaction time was needed in the case with 3-naphthalen-2-yl-propenal (**4e**) and di- and trimethoxy cinnamaldehydes **4f** and **4g**, where the electron-donating groups on the benzene ring may impede the reaction (Table 2, entries 5–7).

In an effort to increase the selectivity of pentacyclic product **7**, we performed the reaction at a higher temperature by heating the crude **5** in *i*-PrCN to reflux. We observed a larger **7**:**6** ratio, and the **7**:**6** ratio was gradually increased as the reaction time was extended, albeit with slightly less yield. For example, the ratio of **6c**/**7c** was 2.8:1 at 4 h, 1:1 at 8 h, and 1:3 at 22 h; however, prolonged exposure of the reaction did not increase the **7c**/**6c** ratio, but resulted in the increased formation of complex side products (Table 2, footnote g). To explain the chemoselectivity and stereoselectivity of the reactions, a plausible mechanism is proposed (Scheme S1).[14]

As shown in Figure 1, the structures of **6a** and **7c** unveiled by X-ray analyses reveal a marked contrast in the orientation of the corresponding stereogenic center. The orientation of the 4-phenyl tether on **6a** is directed away from the 7-azaindole moiety, while **7c** displayed an inside-aza-yohimbane structure in which the rigid 4-methoxyphenyl group points toward the N(1)-H and N(7) sites of 7-azaindole, which may shield this structural motif from the surrounding solvent molecules. Accordingly, **6a** and **7c** may serve as a pair of model compounds to probe the local environment of the 7-azaindole moiety, mimicking that of the tryptophan moiety in proteins. Figure 2 shows the absorption

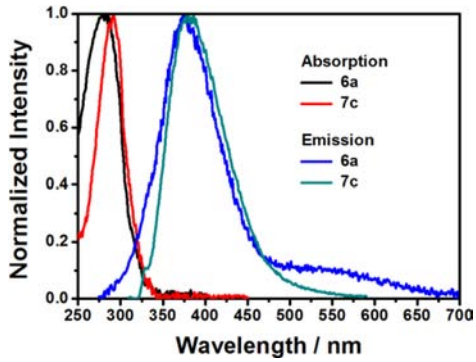


Figure 2. Absorption and emission spectra of **6a** and **7c** in ethanol. The concentration for **6a** and **7c** was prepared to be 2.2×10^{-5} and 2.5×10^{-5} M, respectively. The excitation wavelength: 275 nm for **6a** and 285 nm for **7c**.

and emission spectra of **6a** and **7c** in ethanol solution. Both **6a** and **7c** exhibited the lowest lying absorption band with the maximum at 280–290 nm, which is attributable to a $\pi\pi^*$ transition in nature. However, the emission behavior is drastically different between **6a** and **7c**, in which **6a** reveals dual emission bands maximized at 380 nm ($\tau_f \approx 230$ ps) and ~520 nm ($\tau_f \approx 1.5$ ns). This dual emission property is similar to that of parent 7-azaindole in ethanol. Upon electronic excitation in a protic solvent (i.e., ethanol), 7-azaindole undergoes a solvent-catalyzed proton transfer from the N(1)-H site to the N(7) site, resulting in both normal and proton-transfer tautomer emission.[6c−e] Due to the free access of the N(1)-H and N(7) sites to the ethanol molecules, **6a** should behave similarly to 7-azaidole, and hence, its dual emission consisting of normal and tautomer bands can be fully rationalized.

In stark contrast, **7c** exhibits only the normal emission band, with a maximum at 380 nm ($\tau_f \approx 1.1$ ns). The tautomer emission expected to be >450 nm is not resolvable. The result clearly indicates that the fused side chain in **7c** causes the shielding effect, which blocks the approach of the ethanol molecules around the N(1) and N(7)-H sites, prohibiting the ethanol-catalyzed proton transfer reaction in the excited state. Similar results are obtained for **6c** and **7a** pair of model compounds (see Figure S6 in Supporting Information). Further support for this viewpoint is given by a computational approach (PCM-B3LYP/6-31G(d), see SI for detail) in which we intended to add each of the N(1)-H and N(7) sites with one hydrogen-bonded ethanol molecule. The result shown in Figure S4 of Supporting Information indicates that after geometry optimization, one of the ethanol molecules originally attached at the N(1)-H site was out of the **7c** molecular framework, while the hydrogen bonded

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ethanols are retained at the designated two sites in **6a**. Therefore, in a qualitative manner, there is a deficit of solvent (ethanol) molecules surrounding the N(1)-H and N(7) sites in **7c**, such that the ethanol-catalyzed proton transfer in the excited state is prohibited. The geometries of the ground states were optimized by the density functional theory (DFT) methodology with a B3LYP hybrid function in combination with a integral equation formalism model (IEFPCM) in ethanol. The 6-31G(d) basis set was employed for all atoms. All calculations were carried out using the Gaussian 09 program.

In summary, we have reported a one-pot enantioselective synthesis of 7-azaindole-octahydroisoquinolin-3-one and an inside-aza-yohimbane system containing five contiguous stereogenic centers with high enantioselectivities (>99% *ee*) in an aim to probe the local 7-azaindole environment, particularly with respect to the surrounding solvent molecules. The structures and absolute configurations of products **6a** and **7c** have been confirmed by X-ray analyses, which showed that the stereogenic center is either away from or blocks the N(1)-H and N(7) sites of the 7-azaindole moiety. These compounds have been designated as pro-aza-yohimban (**6a**) and inside-aza-yohimbane (**7c**) derivatives. Catalyzed by the solvent molecules such as ethanol, **6a** undergoes an excited-state proton transfer reaction, resulting in a green tautomer emission (~520 nm). Conversely, the inside-aza-yohimbane in **7c** prevents the ethanol molecules from surrounding the N(1)-H and N(7) sites, inhibiting the proton transfer and tautomer formation. As a result, **6a** and **7c** can serve as a pair of contrasting models to mimic the local environment of the tryptophan moiety in proteins. Further work is underway to elaborate the synthetic applications of this procedure.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02949.

Experimental procedures and characterization data (PDF)
Compound (−)-**6a**(CIF)
Compound (−)-**7c**(CIF)

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Notes

The authors declare no competing financial interest.

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(13) In (A), the asterisk * symbolizes the electronically excited state. Also, only those alcohol molecules involved in the proton transfer are depicted. In reality, 7-azaindole is dissolved in bulk alcohol. In (B), the chirality of 2,7-diazatryptophan is not specified.

(14) See Scheme S1 in Supporting Information for details

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