Direct Access to (±)-10-Desbromoarborescidine A from Tryptamine and Pentan-1,5-diol

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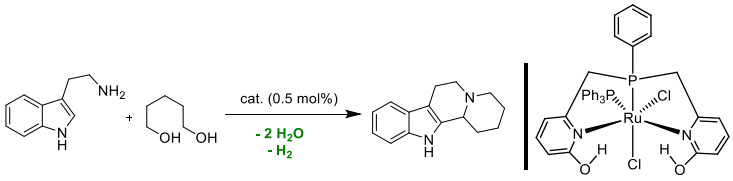
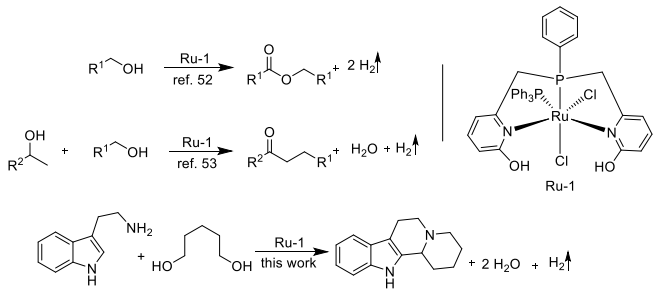


Trying to tame nature from saturated substrates with only one catalyst: The butterfly effect

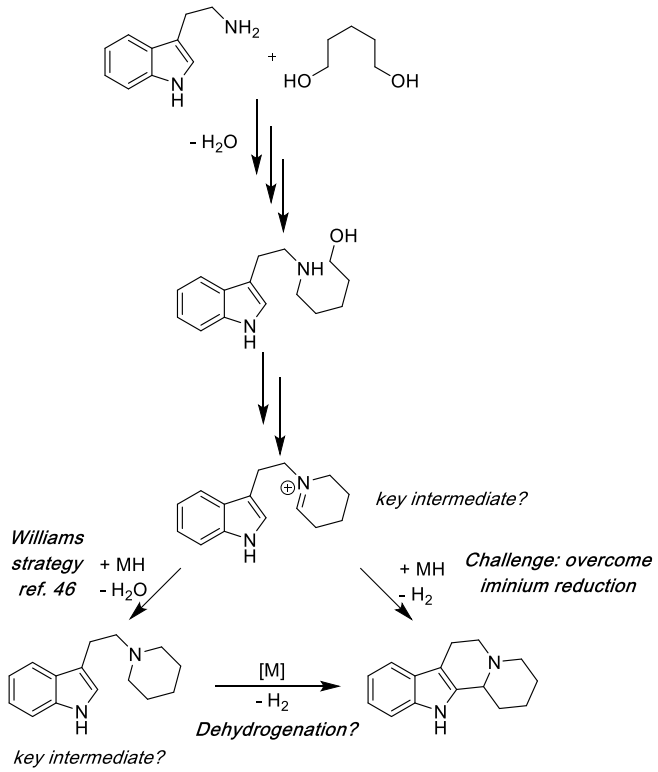
Abstract: A single step synthetic strategy for (±)10- Desbromoarborescidine A is described. Starting from tryptamine and pentan-1,5-diol, this acceptorless dehydrogenative condensation process is efficiently catalyzed by a ruthenium complex featuring proton-responsive phosphine pyridone ligand.

Indoloquinolizines and harmicines featuring a tetracyclic core structure constitute an important part of the attractive indole alkaloids family.[1-5] Owing to their structural diversity, these compounds display broad biological activities including opioid agonistic, blood pressure and antitumoral activities.[6-9] Isolated in 1966, (±)-10-desbromoarborescidine A represents the simplest indoloquinolizine alkaloid.[10] Reported in the early 50's, the pioneering syntheses of (±)-10-desbromoarborescidine A involve, amongst others, Fisher indole type synthesis of 1-ketoquinolizidine with phenylhydrazine.[11-13] In 1972, Gribble reported the synthesis of (±)-10-desbromoarborescidine A from tryptamine hydrochloride with glutaraldehyde by using sodium borohydride as a reducing agent with ten days of reaction time to prevent dimerization of the starting dialdehyde.[14-15] More recently, the same author reported an interesting condensation approach from tryptophan and 3,4-dihydro-2H-pyran.[16] These approaches lie on the transient formation of a keteniminium intermediate which undergoes condensation *via* the famous Pictet-Spengler condensation.[17] This latter transformation, became the method of choice for the synthesis of tetrahydro-β-carboline derivatives. Thus, other approaches to (±)-10-desbromoarborescidine A involving Pictet-Spengler condensation have been reported.[18-25] Alternative oxidative syntheses involve Polonovski type reactions.[26-28] Several enantioselective syntheses have also been reported. [29-38] However, these approaches suffer from one or more drawbacks like the requirement of specially designed starting materials, multi-step synthetic protocols, and generation of noxious wastes. Therefore, from a medicinal chemistry perspective, due to the promising biological activities of indoloquinolizines, a sustainable approach towards their synthesis involving minimum steps and wastes is highly desirable.

Hydrogen transfer processes ranging from borrowing hydrogen to acceptorless dehydrogenation represent sustainable strategies for the formation of carbon-carbon and carbon-heteroatom bonds.[39-42] These tandem transformations involve the activation of saturated substrates such as alcohols and amines through a formal dehydrogenation generating unsaturated reactive carbonyl or imine/ium intermediates acting as alkylating reagents. Depending on the catalytic species/reaction conditions, further reduction or liberation of molecular hydrogen can occur. These methodologies have been efficiently used for the construction of *N*-heterocycles from primary amines and diols.[41-46] In 2019, Yang, Ma, Tang, and coworkers reported the synthesis of tetrahydro-β-carboline from tryptamine and alcohol in the presence of methyl cinnamate acting as sacrificial hydrogen acceptor to ensure good conversion.[47] In 2005, Williams and coworkers, reported the *N*-alkylation of tryptamine with pentan-1,5-diols leading to the selective formation of *N*-heterocycles without formation of the indoloquinolizine Pictet-Spengler adduct.[46] Based on our recent contributions on tandem hydrogen transfer processes for the synthesis and functionalization of aza-heterocycles[48-51], we postulate that our recent **Ru-1** precatalyst (Scheme 1) would enable *N*-alkylation and be acidic enough to play the role of Pictet-Spengler surrogate to efficiently afford indoloquinolizine in one step generating hydrogen and water as the only side products of the transformation (Scheme 2).[52-53]



Scheme 1. Dehydrogenative couplings in the presence of **Ru-1** precatalyst.



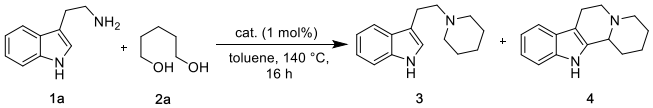
Scheme 2. Proposed metallo-catalyzed pathways to (±)-10-desbromoarborescidine A from diol and tryptamine.

Herein, we report the one step tunable formation of *N*-alkylated tryptamine derivatives and (±)-10-desbromoarborescidine A from tryptamine and pentan-1,5-diol through acceptorless dehydrogenative condensation.

Thus, we first evaluated the reaction of tryptamine **1a** and pentan-1,5-diol **2a** in toluene as solvent with various precatalysts (Table 1). Common ruthenium precursors such as $[Ru(p\text{-cymene})Cl_2]_2$, $[Ru_3(CO)_{12}]$ were found to be inactive with a **1a**/**2a** ratio of 1:1.3 (entries 1 and 3). Notably, $[RuCl_2(PPh_3)_3]$ bearing phosphine ligand was also inefficient (entry 2). We then focused our attention on iridium precursors. $[Ir(COD)Cl]_2$ precursor failed to afford any conversion (entry 6), confirming the previous findings of Williams who demonstrated the requirement of additional diphosphine ligand such as dppf to ensure *N*-alkylation of tryptamine with diols.[46] In contrast, the use of piano stool iridium precatalysts $[Cp^*IrCl_2]_2$ and $[Cp^*Ir(H_2O)_3(SO_4)]$ afforded up to 70% conversion (entries 4 and 5).[45] Analyses of these reactions revealed the formation of the *N*-alkylated adduct **3** as a major compound along with two side products. GC/MS analyses indicated the side formation of the (±)-10-desbromoarborescidine A (**4**) and the *N*-monoalkylated tryptamine**,** thus confirming our working hypothesis.[48] Astonishingly, our ruthenium precatalyst **Ru-1** containing phosphine-pyridone ligand under similar reaction conditions led to complete conversion of the tryptamine **1a** again with the major formation of the tricyclic product **3** along with **4** as the only side product in an interesting 7:3 ratio (entry 7).[52] It should be mentioned that under refluxing conditions, in the presence of precatalyst **Ru-**

1, product **3** can be selectively obtained with complete conversion and a 9:1 ratio (entry 8). Isolation of the product **3** was achieved by chromatography on alumina gel affording 80% isolated yield. Successful crystallization confirmed the tricyclic structure (Figure 1).

Table 1. Evaluation of precatalysts towards product distribution.



Entry[a]	Cat.	Ratio **3**/**4**[b]	conv. (%)[c]
1	$[Ru(p\text{-cymene})Cl_2]_2$	-	<1
2	$[RuCl_2(PPh_3)_3]$	99:1	2
3	$[Ru_3(CO)_{12}]$	-	0
4[d]	$[Cp^*IrCl_2]_2$	9:1	70
5[d]	$[Cp^*Ir(H_2O)_3(SO_4)]$	9:1	68
6	$[Ir(COD)Cl]_2$	-	0
7	**Ru-1**	7:3	100
8[e]	**Ru-1**	9:1	100(87;80)[c]

[a] Experimental conditions: all reactions were performed under an inert atmosphere of argon and carried out with tryptamine **1** (1 mmol), pentan-1,5-diol **2** (1.3 mmol), catalyst (1 mol% with respect to metal atom) in toluene (1 mL) for 16 h at 140°C.
[b] Ratio was determined by GC analysis on the crude reaction mixture.
[c] Conversions were determined by GC. First number in parentheses corresponds to the GC yield of the product **3** using tetradecane as internal standard and second to the isolated yield after column chromatography over alumina gel.
[d] 5-((2-(1H-indol-3-yl)ethyl)amino)pentan-1-ol side product was also detected during GC analysis.
[e] Reaction was performed under refluxing condition.

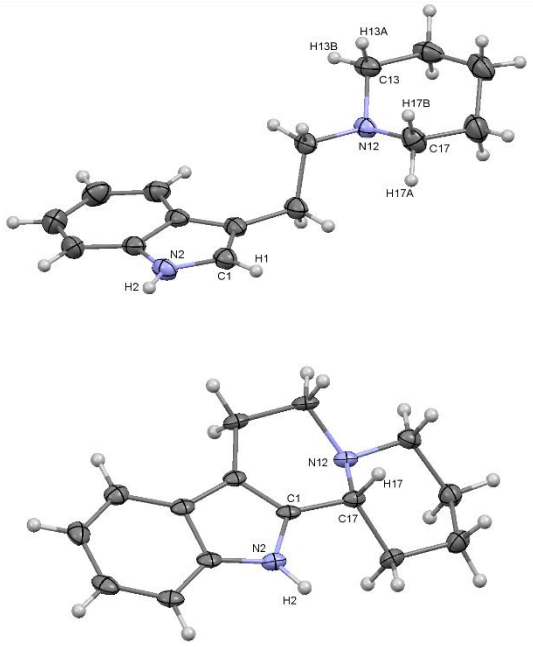
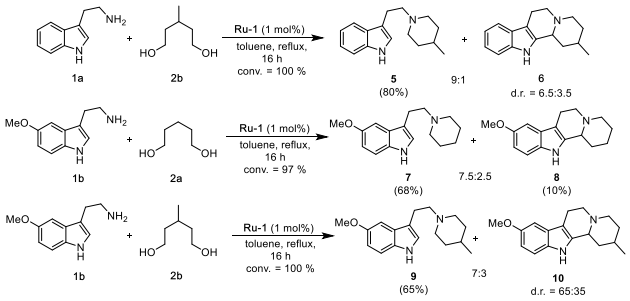


Figure 1. X-ray structures of isolated *N*-alkylated compound **3** and 10-Desbromoarborescidine **4**. CCDC 1965973, 1965972 contain the supplementary crystallographic data for compounds **3** and **4**, respectively.

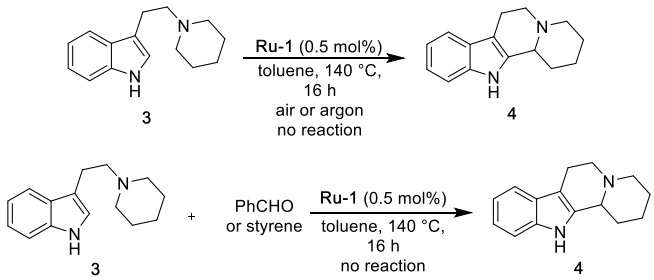
Under refluxing conditions, which are known to favor the formation of tricyclic adducts, we briefly examined the effect of the substituents toward product distribution (Scheme 3). Replacement of pentan-1,5-diol **2a** by 3-methylpentane-1,5-diol **2b** led to similar ratio and conversion and **5** was isolated in 80% isolated yield. As expected, the presence of the electron donating methoxy group in **1b** enhancing the nucleophilicity at position 2 of the indole nucleus resulted in the decrease of the selectivity and *N*-alkylated products **7** and **9** were obtained in 68% and 65% isolated yields, respectively. Noteworthy that for 3-methylpentane-1,5-diol **2b**, Indoloquinolizines **6** and **10** were observed as co-products with a 6.5:3.5 diastereoisomeric ratio.



Scheme 3. Effect of the substituents toward product distribution under refluxing conditions.

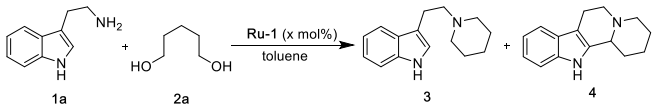
Having established the superior activity of **Ru-1**, we next turned our attention on the challenging selective formation of (±)-10-desbromoarborescidine A by modification of the reaction conditions (Table 2). The ratio of products **3** and **4** and conversion were greatly affected by the ratio of the reagents. In the presence of an excess of tryptamine **1a**, the reaction was inhibited, presumably due to the coordination of the nitrogen atoms to the catalyst (entries 1 and 2). However, up to 1:9 ratio in favor of the (±)-10-desbromoarborescidine A (**4**) was observed. Increasing the amount of diol **2** resulted in the increase of the reaction efficiency (entries 3 and 4). It should be noted that an excess of diols resulted in the selective formation of the compound **3** demonstrating that pentan-1,5-diol plays the role of both reagent and hydrogen donor generating lactone/polyesters along with hydrogen.[52,54-59] Interestingly, decrease of catalyst loading resulted in the selective formation of the (±)-10-desbromoarborescidine A (**4**) (entries 3 and 5). Similarly, increasing dilution favored the formation of the latter (entries 3,6 and 7). These results tend to demonstrate that the lifetime of the iminium intermediates is inversely proportional to the loading of precatalyst. Thus, low catalyst loading is required to preclude reduction of the iminium in order to favor the attack by the indole nucleus. Finally, at higher reaction temperature with a 1:1.2 reactant ratio, a ratio of 2:8 was obtained in favor of **4** produced in 65% GC yield (entry 10). The tedious separation of **3** and **4** over alumina gel resulted in a promising 45% isolated yield. Successful crystallization confirmed the tetracyclic structure (Figure 1).

One may argue that, the formation of (±)-10-desbromoarborescidine A (**4**) can also occur from the dehydrogenation/oxidation of uncyclized compound **3** as a formal monoamine oxidase/polonovski type reaction.[26] As demonstrated in Table 2, the ratio of **3**:**4** was not affected by reaction time (entries 12 and 13). Moreover, it should be pointed out that during the treatment of isolated **3** in the presence of various hydrogen acceptor or under air (±)-10-desbromoarborescidine A (**4**) was not detected even as traces (Scheme 4). Taken together, these results demonstrate that **4** arose from a Pictet-Spengler condensation on the last iminium intermediate (Figure 2).



Scheme 4. Attempts to convert tricyclic heterocycle **3** to indoloquinolizine **4**.

Table 2. Toward the selective formation of (±)-10-desbromoarborescidine A



Entry[a]	(mol %)	Ratio **1a**:**2a**	Conc.	T °C	Conv.[b]	Ratio **3**/**4**[c]
1	0.5	1:1	0.5	140	8	1:9
2	0.5	1.3:1	0.5	140	10	2:8
3	0.5	1:1.3	0.5	140	100	5:5
4	0.5	1:1.5	0.5	140	100	7:3
5	2	1:1.3	0.5	140	100	7:3
6	0.5	1:1.3	0.25	140	70	5:5
7	0.5	1:1.3	1	140	100	6.5:3.5
8	1	1:1.3	2.5	140	100	8:2
9	0.5	1:1.3	0.5	150	100	4:6
10	0.5	1:1.2	0.5	170	95(65;45)[b]	2:8
11	0.5	1:1.1	0.5	170	70	1:9
12[d]	0.5	1:1.3	1	140	100	6:4
13[e]	0.5	1:1.3	1	140	100	6:4

[a] Experimental conditions: all reactions were performed under an inert atmosphere of argon in a closed Schlenk tube in degassed dried toluene.

[b] Conversions were determined by GC. First number in parentheses corresponds to the GC yield of the product **4** using tetradecane as internal standard and second to the isolated yield after column chromatography over alumina gel.

[c] Ratio was determined by GC analysis on the crude reaction mixture.

[d] Reaction time 24 h.

[e] Reaction time 36 h.

In conclusion, it is now possible to access to (±)-10-desbromoarborescidine A (**4**) *via* a formal dehydrogenative dehydrative coupling of tryptamine and pentan-1,5-diol. To the best of our knowledge, this is the first *one-step* synthesis of (±)-10-desbromoarborescidine A. The lack of reactivity of **3** demonstrated the trapping of the iminium intermediate resulting from the second condensation and not the subsequent oxidation/dehydrogenation of **3**. Results also demonstrated that minor modification of the reaction conditions (ratio of reagents, concentration, catalyst loading, *etc*.) greatly affects the outcome of the reaction. Taken together, this strategy offers a powerful and promising way to repurpose the conventional syntheses of various indoloquinolizines and harmicine alkaloids. Current efforts are focused on the extension of this transformation with a second generation of precatalysts.

Acknowledgements

CEFIPRA/IFCPAR No. 5105-4 is gratefully acknowledged for the fellowships to A.R.S., G.L and the funding of this project. Prof. J. Cossy, Prof. P. C. J. Kamer, and Prof. F. Mongin are also thanked for their helpful comments.

Keywords: indoloquinolizine • green chemistry • natural products • homogeneous catalysis • hydrogen transfer

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