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Biomimetic Organocatalytic Approach to 4-Arylquinolizidine Alkaloids and Application in the Synthesis of (−)-Lasubine II and (+)-Subcosine II

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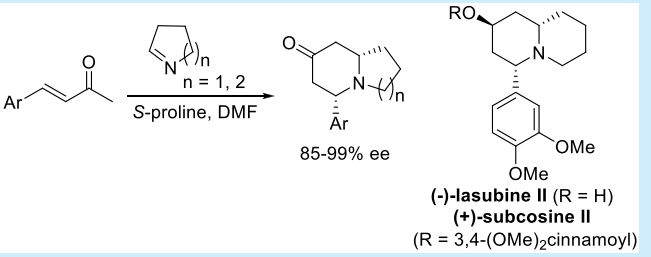
Supporting Information

ABSTRACT: An enantioselective, biomimetic organocatalytic synthesis of 4-arylquinolizidin-2-ones, key intermediates in the synthesis of several Lythraceae alkaloids, was developed. The methodology features *S*-proline-mediated Mannich/aza-Michael reactions of readily available arylideneacetones and Δ^1-piperideine. The total syntheses of (−)-lasubine II and (+)-subcosine II as well as the formal syntheses of structurally related Lythraceae alkaloids were achieved. The use of Δ^1-pyrroline in the Mannich/aza-Michael reaction provides enantiomerically enriched 5-arylindolizidin-7-ones, which are precursors to nonopiate antinociceptive agents.



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The Lythraceae plant family is a rich source of quinolizidine alkaloids (the Lythraceae alkaloids), representative examples of which are shown in Figure 1.

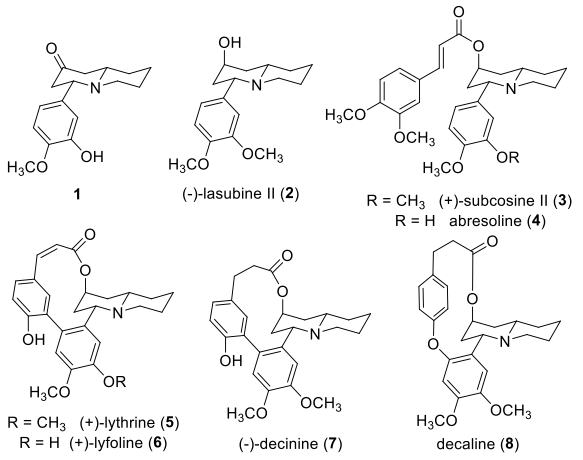

Figure 1. Selected naturally occurring *Lythraceae* alkaloids.

These alkaloids incorporate the quinolizidine ring system with an aryl substituent at C-4. A significant number of naturally occurring 4-arylquinolizidines have the *trans*-decalin-type structure in which the ring junction methine hydrogen and the aryl substituent are trans to each other. 4-Arylquinolizidin-2-one (**1**,[1] Figure 1), (−)-lasubine II (**2**),[2] (+)-subcosine II (**3**),[2] and (+)-abresoline (**4**)[3] are characteristic examples of this group. Further modification of the lasubine motif adds structural complexity to provide provide (+)-lythrine (**5**),[4] (+)-lyfoline (**6**),[6] (−)-decinine (**7**),[5] and decaline (**8**),[5] all of which are characterized by a 4-hydroxycinnamic acid derived macrolactone subunit that spans the 4-aryl substituent and the C2 hydroxy group.

The biosynthesis[7] of the Lythraceae alkaloids is known to involve Δ^1-piperideine and ring-oxygenated versions of (*E*)-3-oxo-5-phenylpent-4-enoic acid which are obtained from L-lysine and L-phenylalanine via the intermediacy of cadaverine and cinnamic acid, respectively, as shown in Figure 2. Mannich

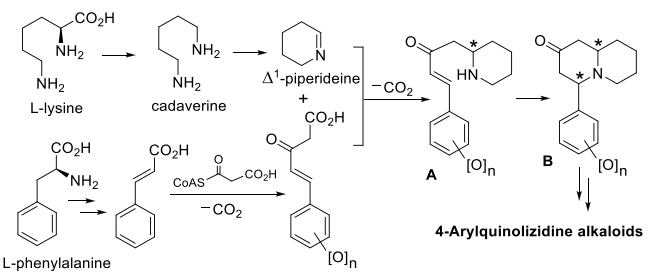

Figure 2. Biosynthesis of 4-arylquinolizidine alkaloids.

reaction of the phenylalanine-derived component and Δ^1-piperideine, followed by an intramolecular conjugate addition of the piperideine intermediate **A** (Figure 2), provides a quinolizidinone **B** which is the key biosynthetic precursor to the 4-arylquinolizidine alkaloids. Notably, one such quinolzidinone (**1**, Figure 1) and the alkaloids derived from it have been isolated from the same plant.[8]

Despite the simplicity of the biosynthetic route, none of the reported enantioselective syntheses of 4-arylquniolizidine alkaloids has adopted this strategy in the sense that they do

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not employ Δ^1-piperideine and a β-aryl enone derivative as the starting materials. Herein, we report preliminary results on a biomimetic enantioselective synthesis of (a) representative 4-arylquinolizidine alkaloids, (b) advanced intermediates to the macrolactone family of Lythraceae alkaloids, and (c) advanced intermediates to arylindolizidines with antinociceptive properties.

We reasoned that substituted piperidines similar to **B** (Figure 2) could probably be prepared by a biomimetic reaction of Δ^1-piperideine with aryl enones. Accordingly, our synthetic approach involves an enamine/iminium ion mediated organocatalytic Mannich–aza-Michael strategy that relies on readily available β-aryl enones and Δ^1-piperideine as the key components (Figure 3). Notably, although Δ^1-piperideine is

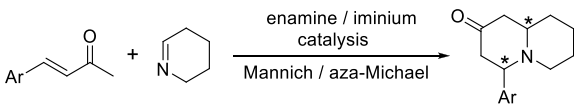


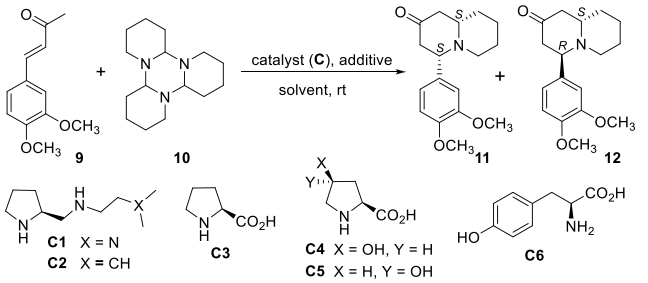
Figure 3. Organocatalytic strategy for the synthesis of 4-arylquinolizidin-2-ones.

easily prepared[9] from piperidine, it can be isolated only as the minor component in a mixture with tripiperideine since it trimerizes spontaneously. However, as shown by Bella,[9a] this trimer is a convenient source of Δ^1-piperideine which is generated by dissociation in solution. Nevertheless, only a few studies have examined the utility of Δ^1-piperideine in Mannich reactions with either acetone[9a] or functionalized nitroalkanes.[9b] Similarly, although reactions of enones with dihydro-β-carbolines are known,[9c,d] organocatalytic reactions of enones and Δ^1-piperideine are not reported.

We chose 3,4-dimethoxybenzylidene acetone (**9**) as the enone and a selection of pyrrolidine-based catalysts (**C1**–**C5**) and *S*-tyrosine (**C6**) for exploratory reactions with tripiperideine **10** (as a source Δ^1-piperideine). The results of these studies are summarized in Table 1.

The proline-derived triamine **C1**[10] and the diamine **C2**[10] were examined first, either with or without the use of an acid co-catalyst. Encouragingly, the 4-aryl quinolizidin-2-one **11**[11] was obtained from these reactions, albeit in low yield (20–26% yield). Notably, neither the diastereomeric 4-aryl quinolizidin-2-one **12** nor the amino enone (product of the Mannich reaction) could be detected in these reactions. The diamine **C2**, without an acid co-catalyst, provided a mixture of **11** and **12** (**11**:**12** = 0.6:1) in low yield (9%). The use of TsOH as a co-catalyst with **C2** was marginally beneficial, providing only **11** in 24% yield. Interestingly, the use of *S*-proline (**C3**) as the catalyst provided the best results (Table 1, entry 9), and **11** was obtained in 60% yield as a single diastereomer with 96% ee. Increasing the reaction time beyond 144 h is only marginally beneficial (yield of **11** after 240 h is 63%). Notably, the use of TsOH acid as a co-catalyst with proline was detrimental to the yield of the reaction (Table 1, entry 6). Having identified *S*-proline as the catalyst of choice in DMF, we conducted a brief solvent survey (Table 1, entries 10–16). With the exception of DMSO, the yield of **11** was adversely affected in all of the other solvents examined. Notably, the enantiomeric excess of **11** was uniformly high (96–99% ee), with methanol being the only exception (82% ee of **11**). However, the diastereoselectivity of the reaction was sensitive to the solvent used, and it was particularly low in acetonitrile, dichloromethane and chloroform (Table 1, entries 11, 13, and

Table 1. Mannich/Aza-Michael Reaction of 9 and 10



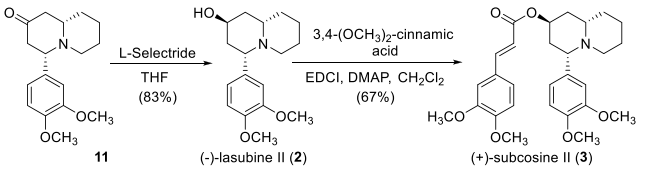
entry	cat[a]	acid[b]	solvent	time (h)	yield (%)	dr **11**/**12**	% ee[c] of **11**
1	C1		DMF	96	22	⩾99/1	19
2		TsOH		24	22	⩾99/1	8
3		TsOH		48	26	⩾99/1	7
4	C2		DMF	120	9	0.6:1	20
5		TsOH		120	24	⩾99/1	27
6	C3	TsOH	DMF	96	7	⩾99/1	96
7				43	35	⩾99/1	96
8				96	54	⩾99/1	96
9				144	60	⩾99/1	96
10			MeOH	144	15	⩾99/1	82
11			CH_3CN		22	2.6/1	>99
12			DMSO		58	⩾99/1	96
13			CH_2Cl_2		14	1/0.4	97
14			$CHCl_3$		31	0.7/1	96
15			THF				
16			toluene				
17	C4		DMF	48	2		
18		TsOH		96	7	⩾99/1	
19	C5		DMF	48			
20		TsOH		96	7	⩾99/1	
21	C6		DMF	48			
22		TsOH		96	10	⩾99/1	

[a]20 mol %. [b]20 mol %. [c]Chiral HPLC analysis.

14). Since there is no apparent correlation of the diastereoselectivity and the polarity of the solvent (high diastereoselectivity in methanol but low in acetonitrile), the reasons for this trend in diastereoselectivity are not evident at this time. Quinolizidinone **11** was obtained in very low yield when hydroxyprolines **C4** and **C5** or *S*-tyrosine (**C6**) were examined as catalysts.

It may be noted that *S*,*S*-**11** obtained in our studies is a direct precursor of the naturally occurring alkaloid (−)-lasubine II (**2**, Figure 1).[12] The stereoselective reduction of **11** provides (−)-lasubine II (**2**, 83%), and subsequent acylation of **2** with 3,4-dimethoxycinnamic acid generates (+)-subcosine II (**3**, 67%, Scheme 1).[13] To the best of our knowledge, these are the shortest reported syntheses of **2** (three steps) and **3** (four steps) from commercially available starting materials.

Scheme 1. Synthesis of (−)-Lasubine II and (+)-Subcosine II from 11



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As noted previously, other alkaloids share the 4-aryl quinolizidine unit present in **1** and **2** (Figure 1). Examples of such alkaloids include **4**, a structural variant of **2**, and also the alkaloids **5**–**8** (Figure 1) that incorporate a macrolactone moiety. The synthesis of these alkaloids has also been extensively investigated. A common theme in all of these syntheses[14−18] is the multistep construction of a suitable 4-arylquinolizidin-2-one (such as **11**) as the key starting material followed by reduction to the corresponding 4-aryl-2-hydroxyquinolizidine (such as **1**). Elaboration to the macrolactone-containing target is then achieved by linking the 4-aryl substituent and the hydroxy group with the appropriate carboxylic acid that is incorporated either directly or is constructed in the ring-closing step (Figure 4).

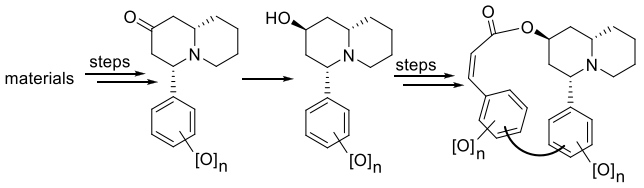


Figure 4. Reported synthetic strategies for alkaloids **5**–**8**.

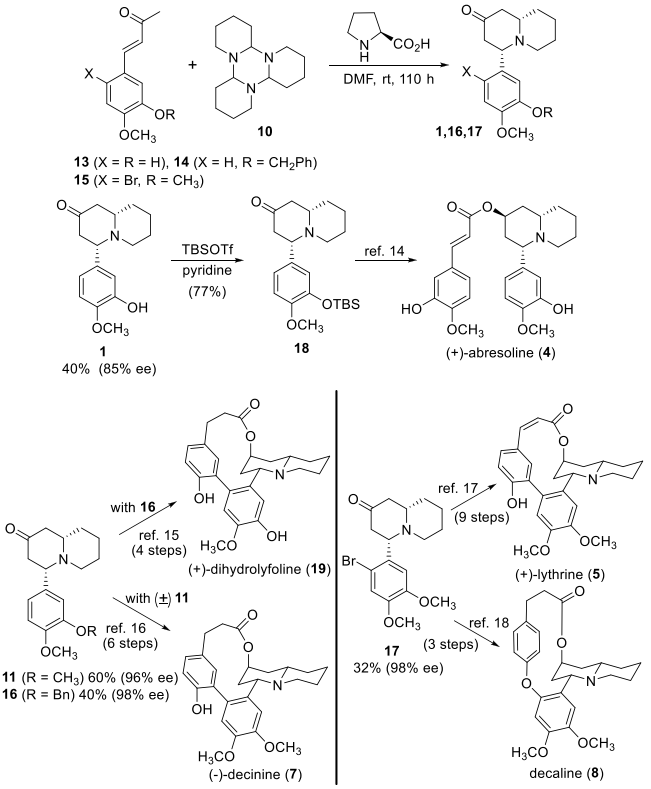
Clearly, syntheses of **5**–**8** that rely on a 4-arylindolizidin-2-one would benefit from a concise enantioselective synthesis of this starting material. The present synthesis of **11** is relevant in this context. We reasoned that the choice of a suitable enone would enable a single step synthesis of advanced intermediates to the Lythraceae alkaloids **5**–**8**. Accordingly, the reaction of enones **13**, **14**, and **15** with **10**, under the reaction conditions optimized for **11**, provided the 4-arylquinolizidinones **1** (40%, 85% ee), **16** (40%, 98% ee), and **17** (32%, 98% ee), respectively. Silylation of **1** provided **18** (77%, Scheme 2). Notably, the diastereomeric (4*S*,9a*R*) quinolizidinone product was not observed in any of these reactions. The conversion of **18** to (+)-abresoline (**4**),[14] **16** to (+)-dihydrolyfoline (**19**),[15] **11** to (−)-decinine (**7**, via **2**),[16] and **17** to lythrine (**5**)[17] and decalin (**8**)[18] is reported.

The present one-step syntheses of **11**, **16**, and **17** and the two-step synthesis of **18** compare favorably with the shortest multistep syntheses of these quinolizidinones reported to date (**11**: five steps from 2-pyrrolidone, 40% overall,[12e] or five steps from methyl 5-chloropenanoate, 30% overall;[12a] **16**: five steps from piperidine, 14.7% overall;[15] **17**: six steps from piperidine, 2% overall;[17] **18**: 12 steps from 3-(benzyloxy)-4-methoxybenzaldehyde, 14.8% overall[14]). In addition, with the exception of **18**, the reported syntheses require separation of the undesired diastereomeric 4-arylquinolizidin-2-one products that are invariably obtained and their subsequent isomerization to the diastereomers that are required for the natural product targets.

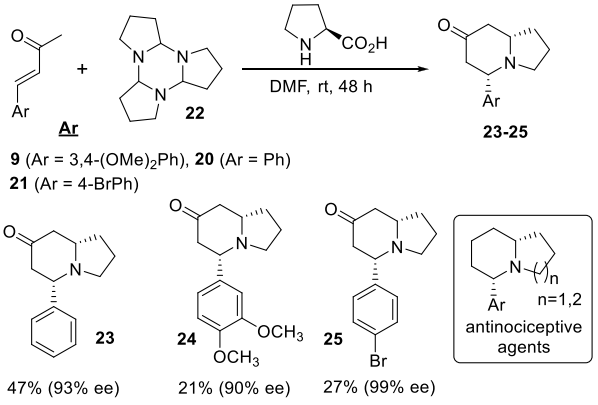
Preliminary results on the extension of this methodology to the synthesis of arylindolizidinones are promising, and the reaction of 1-pyrroline[19] with selected enones under proline catalysis provided 5-arylindolizidin-7-ones[20] with good enantioselectivity (Scheme 3). The reasons for the low yields observed in these reactions are not clear at this time. It may be noted that arylindolizidines and arylquinolizidines, which can be easily obtained by reduction of the corresponding indolizidinones and quinolizidinones,[21] are of interest as nonopiate antinociceptive agents.[21]

A plausible mechanism that explains the stereoselectivity of the Mannich−conjugate addition reaction and the sense of

Scheme 2. Synthesis of Advanced Intermediates to the Lythraceae Alkaloids 4−7



Scheme 3. Enantioselective Synthesis of 5-Arylindolizidin-7-ones



asymmetric induction is provided in Figure 5. Addition of the enamine derived from proline and the enone to the *re* face of the imine generates the iminium ion **D**. Intramolecular conjugate addition of the amine to the *si* face of the iminium ion generates the enamine **E**, which provides the observed (*S*,*S*) diastereomer of the 4-arylquinolizidin-2-one or the 5-arylindolizidin-7-one. The intramolecular aza-Michael reaction is also a component in other syntheses of 4-arylquinolizidine alkaloids.[12c,d,f,g,22] However, the diastereoselectivity of C−N bond formation in the other syntheses is low (dr for required diastereomer = 1.2:1,[12c] 7:1,[12e] and 0.7:1[12g]). In addition, opposite diastereoselectivity is observed when the aza-Michael reaction is mediated by a bifunctional catalyst (4*S*,9a*R* quinolizidinone is obtained)[22] and when *β*-alkyl enones,[9c,d]

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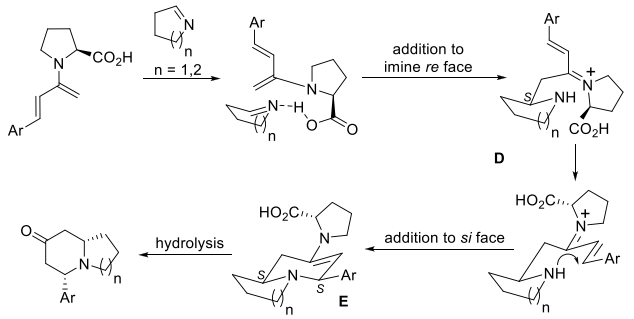

Figure 5. Proline-catalyzed Mannich/aza-Michael reaction of cyclic imines and arylideneacetones.

and enones with a β-aryl group lacking electron-rich substituents[9d] are employed.

While it is likely that formation of the C4 stereocenter in the 4-arylquinolizidinones is thermodynamically controlled, it should be mentioned that the diastereomer **12** was not observed at any time during the reaction of **9** and **10** under the optimized conditions. However, rapid equilibration of **E** and **D** via a retro-aza-Michael process, and the resultant conversion of **12** to **11** under thermodynamic control, cannot be ruled out.[23] A similar process may also be operative in the 5-arylindolizidinone synthesis.

In conclusion, we have developed a stereoselective biomimetic synthesis of (−)-lasubine II and (+)-subcosine II. The methodology also provides the shortest enantioselective route to several 4-arylquinolizidin-2-ones that are key intermediates in the synthesis of macrolactone-containing Lythraceae alkaloids. Current efforts focus on extension of the methodology to β-alkyl enones as well as 3-alkyl/aryl-but-2-enones and related ketones.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01840.

Experimental methods, spectroscopic data, and ^{1}H and ^{13}C data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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