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Asymmetric synthesis of (+)-abresoline

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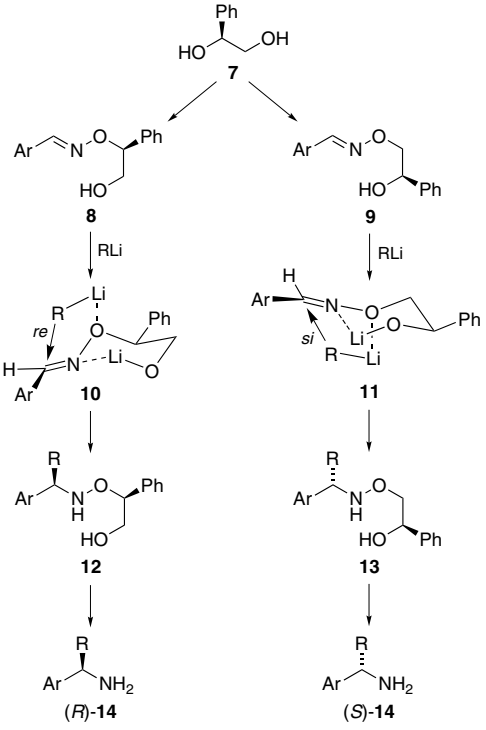
Abstract—The first asymmetric synthesis of (+)-abresoline has been achieved starting from the (*S*)-1-(aryl)homoallylic amine, which was prepared enantioselectively by the method based on allylation of the (*R*)-2′-(2-naphthyl)-bearing hydroxyoxime ether. This synthetic route employs the $TiCl_4$-induced intramolecular Mannich-type cyclization of the 1-azadiene-bearing ketal amine as the key steps to afford stereoselectively the *cis*-2,6-disubstituted piperidine, followed by CBr_4/PPh_3-induced dehydrocyclization for the elaboration of the amino alcohol to the *trans*-4-arylquinolizidine.

The 4-arylquinolizidin-2-ol (**1**)[1] and its ferulate abresoline (**2**),[2] both isolated from young seedlings of *Heimia salicifolia*,[1] are members of the arylquinolizidine class of lythraceae alkaloids.[3] This class of alkaloids including lasubine I (**3**) and II (**5**),[4] and their 3,4-dimethoxycinnamate esters subcosine I (**4**) and II (**6**)[4] have attracted increasing interest as synthetic targets, and numerous syntheses of these alkaloids in either racemic or enantiomerically pure form have been reported.[5–8] However, there have been no reports dealing with the asymmetric synthesis of abresoline, though its racemic syntheses have been reported.[5b,c]

Recently, we have reported[9] that the arylaldehyde oxime ethers **8** and **9** bearing (1′*S*)-2′-hydroxy-1′-phenylethyl and (2′*R*)-2′-hydroxy-2′-phenylethyl groups, respectively, as chiral auxiliaries both derived from (*R*)-1-phenyl-1,2-ethanediol (**7**) underwent nucleophilic addition of organolithium reagents to the *re*-and *si*-faces of the C=N bonds of six-membered chelation intermediates **10** and **11**, leading to the (*R*)- and (*S*)-adducts **12** and **13**, respectively (Scheme 1). After removal of the chiral auxiliary by reductive N–O bond cleavage, the EPC preparation of both enantiomers of primary 1-(aryl)alkylamine **14** has thus been established in an enantiodivergent fashion. On the basis of this hydroxyoxime ether-based protocol herein, we report the first enantioselective total synthesis of (+)-abresoline (**2**).

No description of the optical rotation data for the quinolizidol **1** and abresoline (**2**) has been given in the literature,[1,2] and their absolute stereochemistries have not been established but were assumed to have the configuration depicted in Figure 1 by analogy with the closely



Scheme 1. Enantiodivergent synthesis of 1-(aryl)alkylamines **14**.

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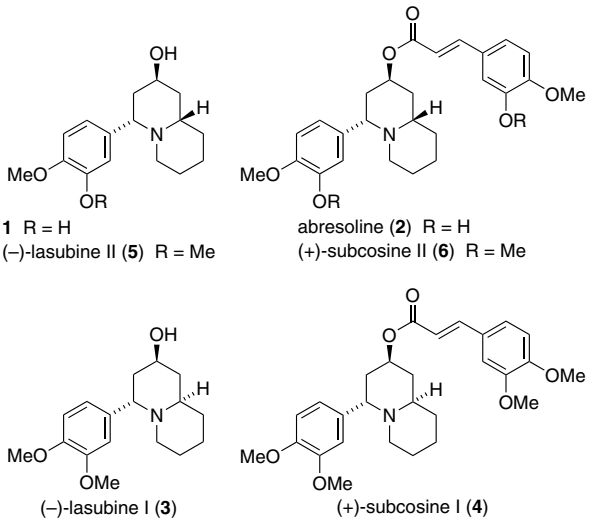
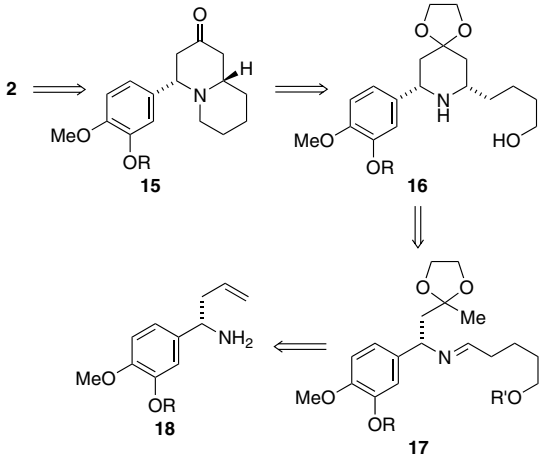


Figure 1. Structures of 4-arylquinolizidine alkaloids.



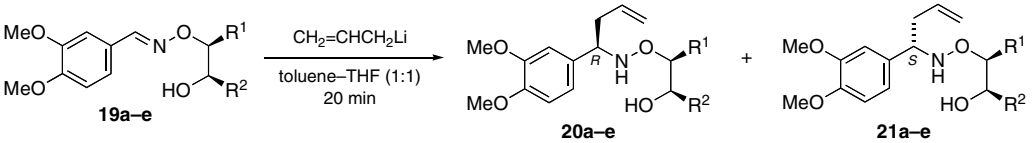
Scheme 2.

related lythraceae alkaloids, (−)-lasubine II (**5**) and (+)-subcosine II (**6**), both belonging to the *trans*-quinolizidine series. Thus, from the retrosynthetic analysis outlined in Scheme 2, we envisioned an enantioselective approach to **2** utilizing the 1-(aryl)homoallylic amine **18** with the *S* configuration as the starting material, which could be prepared by allylation of an appropriate hydroxyoxime ether. Subsequent elaboration of the (*S*)-imine **17** to the *cis*-2,6-disubstituted piperidine **16** by an intramolecular Mannich-type cyclization followed by intramolecular cyclization would provide the quinolizidinone **15** as a key precursor to abresoline (**2**).

On the basis of this analysis, our initial investigation focused on enantioselective synthesis of the 1-(aryl)homoallylic amines by nucleophilic addition of allyllithium to the hydroxyoxime ethers **19** prepared by condensation of veratraldehyde with the (*S*)-2-aryl aminooxy ethanol (for **19a** and **19b**) or the (*R*)-1-aryl aminooxy ethanol (for **19c–e**) according to our previous paper.[9] As can be seen in Table 1 (entry 1) upon treatment with allyllithium (5 equiv) in toluene–Et_2O (1:1) at 40 °C for 20 min, the allylation of the hydroxyoxime ether **19a** bearing a 1′-phenyl group was found to proceed to afford the (*R*)-allylated product **20a** (R^1 = Ph, R^2 = H) as a major isomer but with low diastereoselectivity of 2:1. When the hydroxyoxime ether **19b** bearing a 1′-(2-naphthyl) group was subjected to the same conditions, the allylation reaction proceeded but led to the loss of diastereoselectivity (**20b/21b** = 1:1, entry 2). Reversal of the diastereoselectivity in allylation was observed for **19c** incorporating the 2′-phenyl group, resulting in the allylated product **21c** (R^1 = H, R^2 = Ph) with the desired *S* configuration in a 2.5:1 diastereomeric ratio (entry 3). Use of the oxime ether **19d** bearing a 2′-(1-naphthyl) group also led to the (*S*)-adduct **21d** (R^1 = H, R^2 = 1-naphthyl) with low diastereoselectivity of 2:1 (entry 4), but a significant improvement in the diastereoselectivity (**21e/20e** = 5:1) was obtained upon using **19e** incorporating a 2′-(2-naphthyl) group (entry 5). In all cases, diastereomers were separable by column chromatography, and the absolute configuration of the major isomers was determined by N–O bond cleavage (Zn, AcOH) of the reaction products and comparison of the optical rotation of the obtained homoallylic amine with the reported data.[10]

It is interesting that the diastereoselectivity observed in the allylation is significantly lower (actually not stereoselective) for the 1′-(2-naphthyl)-bearing hydroxyoxime ether **19b** than for 2′-(2-naphthyl)-bearing hydroxyoxime ether **19e** since in our previous studies[9] we recog-

Table 1. Diastereoselective addition of allyllithium to hydroxyoxime ethers **19a–e**



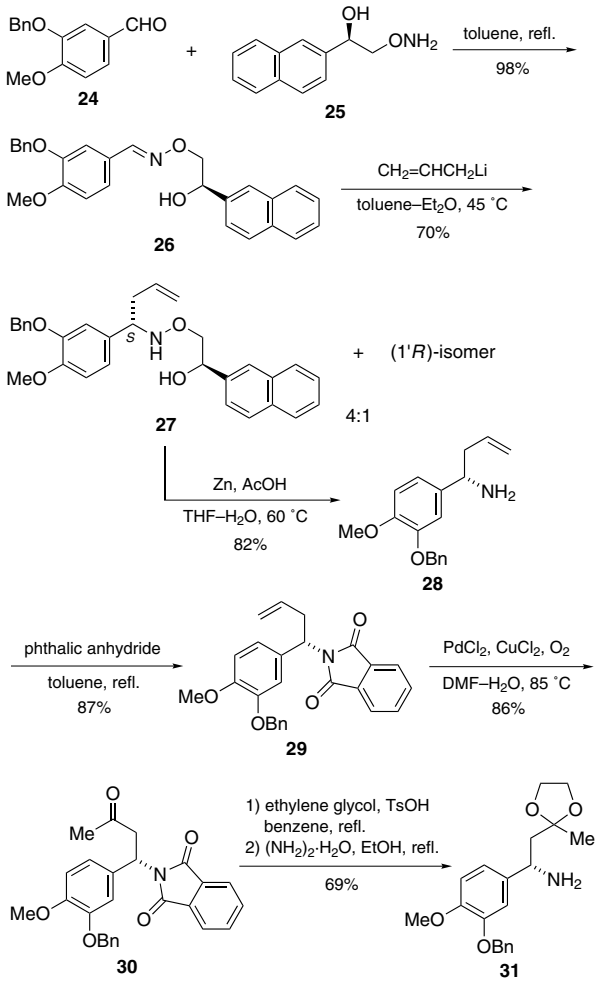
Entry	Substrate	R^1	R^2	Temperature (°C)	Yield[a] (%)	**20/21** Ratio[b]
1	**19a**	Ph	H	40	63	2:1
2	**19b**	2-Naphthyl	H	40	73	1:1
3	**19c**	H	Ph	45	70	1:2.5
4	**19d**	H	1-Naphthyl	45	77	1:2
5	**19e**	H	2-Naphthyl	45	75	1:5

[a] Isolated yield.
[b] Ratio determined by ^{1}H NMR spectroscopy on the crude products mixture.

nized that the diastereoselectivities of the nucleophilic additions of methyllithium and vinyllithium were generally higher for the 1′-phenyl-bearing hydroxyoxime ethers (**8** in Scheme 1) than for the 2′-phenyl-bearing hydroxyoxime ethers (**9** in Scheme 1). The low diastereoselectivity for **19b** can be rationalized by means of a six-membered chelate model **22** (Fig. 2), which constitutes a η^3-allyl-complex[11] with lithium coordination to the oxime ether oxygen atom in axial mode to avoid 1,3-allylic strain.[12] This transition state model **22** presents an unfavorable steric interaction between the allyl and the equatorially-oriented 2-naphthyl group, preventing the stereoselective formation of the expected (*R*)-allyl adduct **20b** (R^1 = 2-naphthyl, R^2 = H). In the allylation of **19e**, this interaction is avoided in the transition state **23**, leading to the preferential formation of the (*S*)-allyl adduct **21e** (R^1 = H, R^2 = 2-naphthyl).

Having established the protocol for the enantioselective preparation of the (*S*)-homoallylic amine **21e** via allylation of the oxime ether **19e** incorporating the 2′-(2-naphthyl) group, we sought to use this method for the synthesis of the (*S*)-homoallylic amine **28** required for the synthesis of abresoline (**2**). The requisite oxime ether **26** was prepared in 98% yield by condensation of *O*-benzylisovanilline (**24**) with the (*R*)-1-(2-naphthyl) aminooxy ethanol **25**. Treatment of **26** with allyllithium under the same conditions used for the allylation of **19e** (Table 1, entry 5) produced the (*S*)-adduct **27** as a major isomer in a 4:1 ratio and 70% combined yield (Scheme 3). Removal of the chiral auxiliary was carried out by reductive N–O bond cleavage with zinc and acetic acid to yield the (*S*)-homoallylic amine **28** with the chiral auxiliary ((1*R*)-1-naphthalen-2-ylethane-1,2-diol) being recovered. After protection of the amino group as the phthalimide, Wacker oxidation of the terminal alkene of **29** gave the methyl ketone **30**, which was then converted to the ketal amine **31** by the standard procedure involving acetalization followed by phthalimide cleavage.

Following the retrosynthetic analysis shown in Scheme 2, the attempted intramolecular Mannich-type cyclization[13] of the imine **17** (R = R′ = Bn), prepared



Scheme 3.

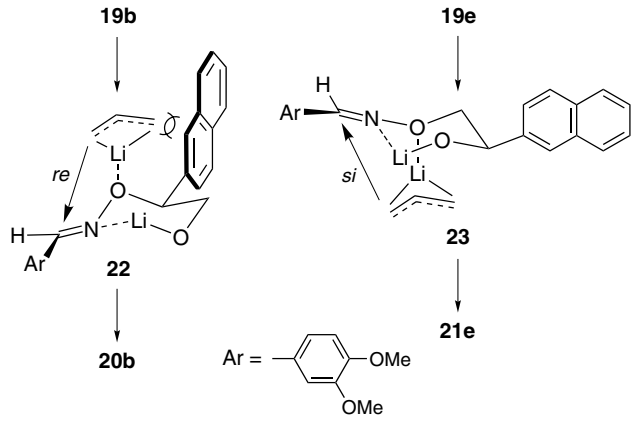
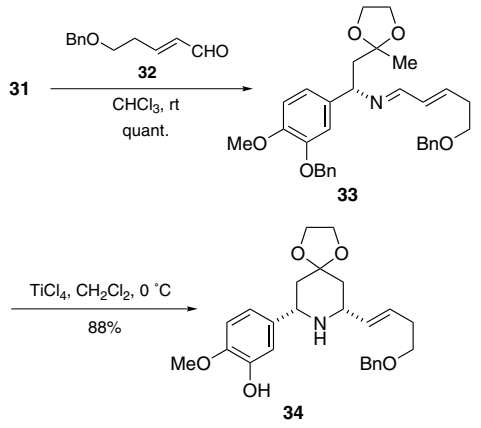


Figure 2.

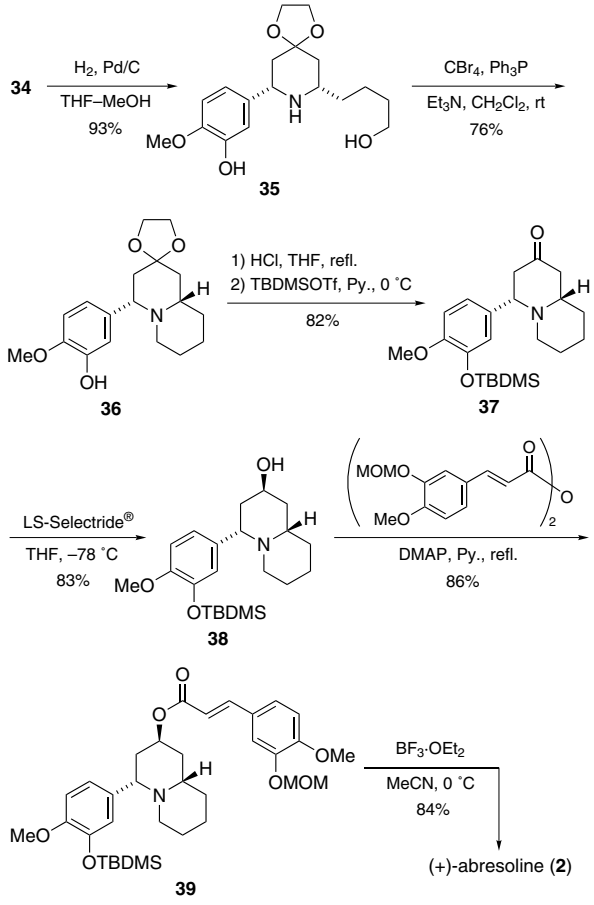
by condensation of the ketal amine **31** with 5-benzyloxypentanal, by acidic treatment (TsOH in benzene at reflux or $TiCl_4$ in CH_2Cl_2 at 0 °C) failed to yield the *cis*-2,6-disubstituted piperidine **16** (R = Bn) and instead gave rise to a complex mixture of products, possibly due to the instability of the iminium intermediate generated from **17** under the reaction conditions. We then sought to utilize the 1-azadiene **33** for the cyclization, in anticipating that its use in the acid-mediated Mannich-type cyclization would be effective in stabilizing the iminium intermediate by mesomeric effect of the olefinic double bond. Thus, the ketal amine **31** was condensed with 5-benzyloxypent-2-enal (**32**)[14] to give **33**. Upon treatment of **33** with $TiCl_4$ in CH_2Cl_2 at 0 °C, the intramolecular Mannich-type cyclization smoothly occurred[15] with accompanying selective cleavage of the phenolic benzyl ether that afforded the *cis*-2,6-disubstituted piperidine **34** in 88% yield as a single isomer (Scheme 4). The *cis* stereochemistry of **34** was confirmed by a NOESY interaction between H-2 and H-6 of the piperidine ring.

Catalytic hydrogenation of the olefin moiety of **34** with simultaneous cleavage of the benzyl ether afforded the amino alcohol **35**, which upon treatment with CBr_4 and



Scheme 4.

Ph_3P[16] in Et_3N/CH_2Cl_2 at room temperature dehydrocyclized to give the *trans*-quinolizidine **36** [IR ($CHCl_3$) Bohlmann bands, 2885–2778 cm^{-1}] in 76% yield (Scheme 5). Deketalization followed by silyl protection of the phenolic hydroxyl group gave the quinolizidin-2-one **37**, which was subjected to stereoselective reduction with LS-Selectride® to produce the quinolizidin-2-ol **38** as a single isomer. Conversion of **38** to the ferulate ester **39** (86%) was effected using MOM-protected ferulic anhydride in refluxed pyridine in the presence of 1 equiv of DMAP. Finally, simultaneous deprotection of the TBDMS and MOM ethers with $BF_3{\cdot}OEt_2$ in acetonitrile at 0 °C furnished (+)-abresoline (**2**) in 84% yield. Our synthetic sample of **3** was found to have $[\alpha]_D^{20}$ +91.1 (*c* 1.2, MeOH) and to be identical with natural abresoline[2] by IR, ^1H NMR, and mass spectra.



Scheme 5.

The first asymmetric synthesis of (+)-abresoline (**2**) has thus been achieved starting with the (*S*)-1-(aryl)homoallylic amine **28**, which was prepared enantioselectively by the method based on allylation of the (*R*)-2′-(2-naphthyl)-bearing hydroxyoxime ether **26**. This synthetic route employs as the key steps the $TiCl_4$-induced intramolecular Mannich-type cyclization of the 1-azadiene-bearing ketal **33** to afford the *cis*-2,6-disubstituted piperidine **34**, followed by CBr_4/PPh_3-induced dehydrocyclization for the elaboration of the amino alcohol **35** to the *trans*-4-arylquinolizidine **36**. Although the absolute configuration and the optical rotation of natural abresoline have not yet been determined (no literature data are available), since the optical rotation value for **2** was first obtained by the present synthesis, determination of the absolute configuration of abresoline will become possible by re-isolation of the natural product and optical rotation measurement.

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