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# General Strategy for the Synthesis of Antirhine Alkaloids: Divergent Total Syntheses of (±)-Antirhine, (±)-18,19-Dihydroantirhine, and Their 20-Epimers

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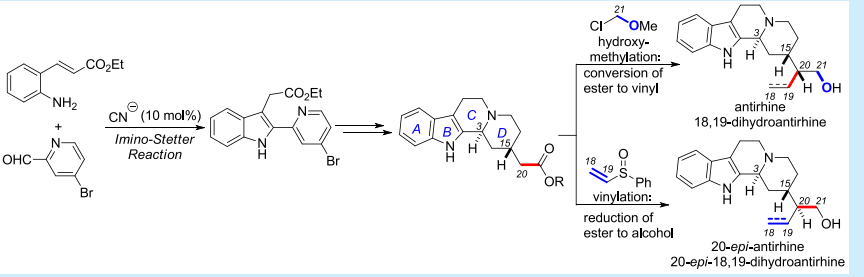


**ABSTRACT:** A general synthetic strategy for antirhine alkaloids was developed in this study. The cyanide-catalyzed imino-Stetter reaction of ethyl 2-aminocinnamate and 4-bromopyridine-2-carboxaldehyde afforded the corresponding indole-3-acetic acid derivative. Subsequent formation of the six-membered C ring followed by *trans*-selective installation of the two-carbon unit at C-15 provided rapid access to the key intermediate. Stereoselective installation of substituents at C-20 allowed the total syntheses of (±)-antirhine, (±)-18,19-dihydroantirhine, and their 20-epimers, all of the known natural products in the antirhine family.

Antirhine (**1**) and its congeners (**2**–**4**) comprise a small group within the indole monoterpene alkaloids possessing very unique structural features (Figure 1).[1,2] Unlike other indole monoterpene alkaloids bearing the indoloquinolizidine scaffold, the antirhine family has the C-18–C-19 vinyl (or ethyl) group connected to the side chain at C-20 rather than to the D ring at the carbon *meta* to the piperidine nitrogen (C-16). In addition, they possess a thermodynamically less stable *anti* relationship between the C-3 and C-15 stereocenters with a *cis* C–D ring junction. Moreover, as all of the C-20 epimers of these natural products are found in nature, additional structural diversity is imparted upon this family.

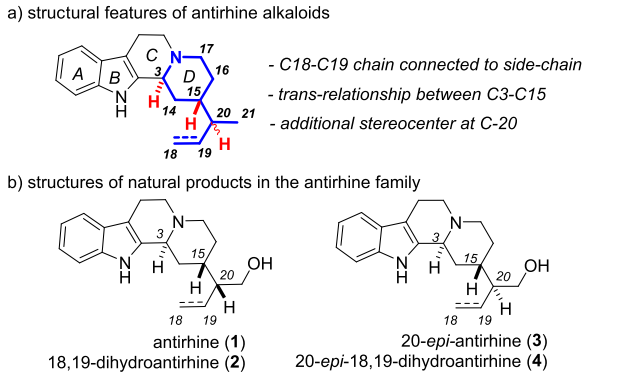


**Figure 1.** (a) Structural features of antirhine alkaloids. (b) Structures of antirhine (**1**), 18,19-dihydroantirhine (**2**), and their 20-Epimers (**3** and **4**).

The unique structural features of the antirhine family have attracted considerable attention from the synthetic chemists.[3,4] Conventionally, the natural product in the antirhine family has been synthesized from a specific starting material containing the key fragment with the desired stereochemistry at C-15 and C-20. Subsequent construction of the C and D rings with tryptamine provides the desired natural product. On the basis of these strategies, several total syntheses of antirhine and 18,19-dihydroantirhine have been reported.[3−5] Unfortunately, these conventional approaches have several limitations. First is the lack of generality applicable for both antirhine (**1**) and its congeners (**2**–**4**). Each of those previous syntheses was tailored for a specific target natural product from a starting material elaborated with specific substituents. To date there have been no examples of the divergent total synthesis of **1**–**4**. This is rather surprising in view of the fact that these natural products are derived biosynthetically from a common

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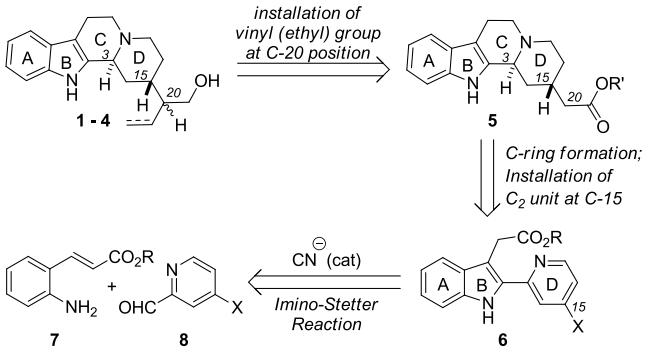
intermediate. Second is the lengthy synthetic sequence needed for the control of the C-15 and C-20 stereochemistry and/or installation of the additional functional groups during the construction of the C and D rings with tryptamine. Third is the difficulty in controlling the *trans* relationship between the C-3 and C-15 stereocenters due to the competing formation of a more stable *cis* product. To overcome these limitations, a general protocol allowing for the total synthesis of all of the products in this family from a common intermediate is highly desired.

Recently, our group reported a novel cyanide-catalyzed imino-Stetter reaction that provides rapid access to various synthetically useful 2-substituted indole-3-acetic acid derivatives[6,7] and also demonstrated their utility for the syntheses of indole alkaloid natural products.[8] As a part of our continuing efforts to use the cyanide-catalyzed imino-Stetter reaction in the total synthesis of indole alkaloids, we herein report a general synthetic strategy that allows the divergent total synthesis of (±)-antirhine (**1**), (±)-18,19-dihydroantirhine (**2**), (±)-20-*epi*-antirhine (**3**), and (±)-20-*epi*-18,19-dihydroantirhine (**4**).

Since all of the natural products in this family bear a tetracyclic indoloquinolizidine scaffold with a *trans* configuration at C-3 and C-15, they could be synthesized from the key intermediate through the stereocontrolled installation of the substituents at C-20. Based on this idea, our retrosynthetic analysis of **1**−**4** is depicted in Scheme 1. Natural products **1**−**4**

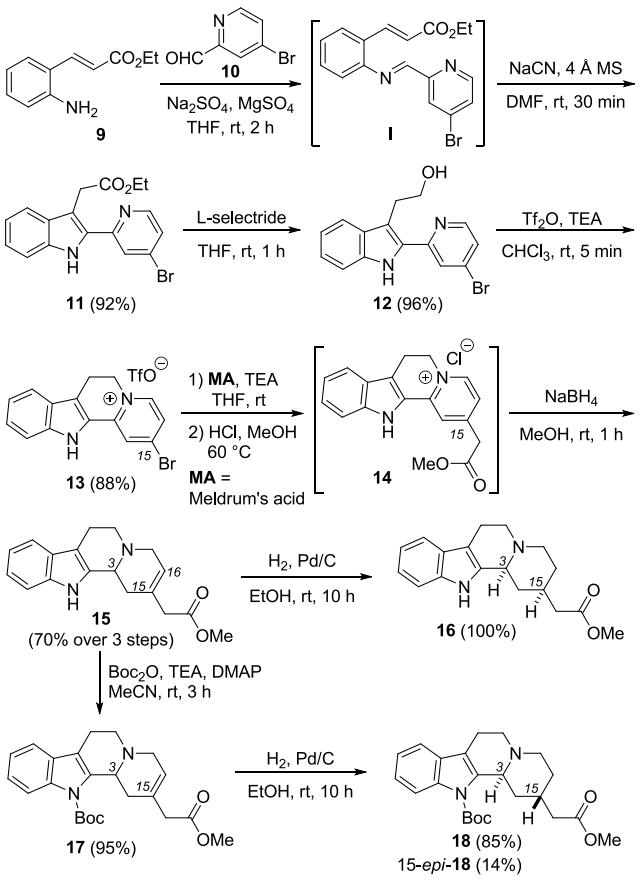
**Scheme 1. Retrosynthetic Analysis**




could be synthesized from indoloquinolizidine **5** through the stereoselective installation of a vinyl (ethyl) group at C-20. We expected that intermediate **5** could be prepared from 2-(2-pyridyl)indole-3-acetic acid **6** via formation of the C ring followed by the stereocontrolled installation of a 2-alkoxy-2-oxoethyl group at C-15. Indole **6** could be obtained from 2-aminocinnamic acid derivative **7** and pyridine-2-carboxaldehyde **8** via the cyanide-catalyzed imino-Stetter reaction.

Having identified a clear route to natural products **1**−**4**, we began the synthesis with the preparation of indoloquinolizidine **18** (Scheme 2). Toward this end, aldimine **I**, derived from ethyl 2-aminocinnamate (**9**) and 4-bromopyridine-2-carboxaldehyde (**10**), was submitted to the cyanide-catalyzed imino-Stetter reaction under the previously developed conditions.[6−8] Gratifyingly, the corresponding indole product **11** was obtained in 92% yield. Reduction of the ester moiety in **11** with L-Selectride followed by treatment of the resulting alcohol **12** with $Tf_2O$ provided dihydroindoloquinolizium salt **13** in 85% yield over the two steps.[8d]

**Scheme 2. Preparation of Key Intermediate 18**




We next sought to install the 2-alkoxy-2-oxoethyl group at C-15 using a suitable two-carbon nucleophile. When dihydroindoloquinolizium salt **13** was treated with Meldrum's acid in the presence of triethylamine (TEA), the desired product **14** bearing the 2-alkoxy-2-oxoethyl group at C-15 was obtained after thermolysis in methanol in the presence of HCl.[9] Subsequent reduction of the pyridinium ring in **14** with $NaBH_4$[10] at room temperature gave the corresponding indoloquinolizidine derivative **15** in 70% yield over three steps.

With compound **15** in hand, we turned our attention to the *trans*-selective hydrogenation of the C-15−C-16 double bond for the synthesis of key intermediate **18**. However, palladium-catalyzed hydrogenation of **15** resulted exclusively in the production of ester **16** with the *cis* configuration between the C-3 and C-15 stereocenters in quantitative yield. Previous studies indicated that masking the indole nitrogen with a sterically hindered bulky protecting group could change the facial selectivity during hydrogenation.[11] On the basis of that work, Boc-protected indoloquinolizidine **17** was prepared before submission to the catalytic hydrogenation conditions. To our delight, hydrogenation of **17** provided compound **18** with the desired *trans* configuration between the C-3 and C-15 stereocenters in 85% yield along with its *cis* isomer (~14% yield) following chromatographic separation.

Having successfully prepared key intermediate **18**, we investigated the installation of the C-20 vinyl group. Among various α-vinylation methods and conditions, we opted to use the protocol involving conjugate addition with vinyl sulfoxide and thermal elimination (Scheme 3).[12] When the enolate of ester **18**, generated by treatment with LiHMDS at −78 °C,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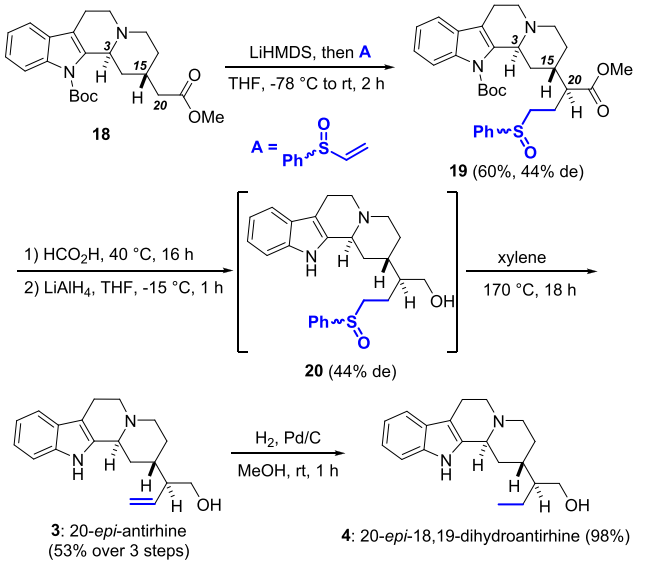
**Scheme 3. Total Syntheses of (±)-20-*epi*-Antirhine (3) and (±)-20-*epi*-18,19-Dihydroantirhine (4)**

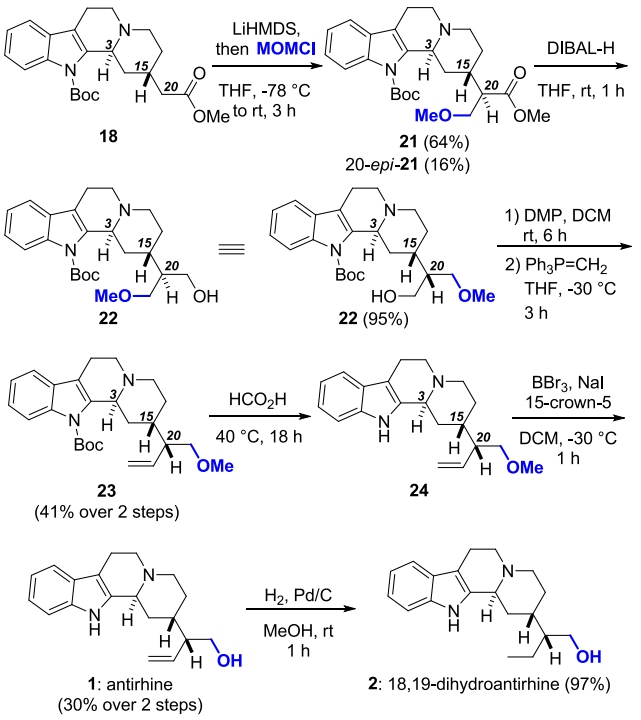



reacted with phenyl vinyl sulfoxide, the desired conjugate adduct **19** was obtained in moderate yield as a mixture of only two diastereomers.[13] Since compound **19** has two possible stereogenic centers (C-20 and the sulfur atom) and thus can have four possible diastereomers, we were not certain at this stage which stereogenic center affected the diastereoselectivity. We therefore chose to determine their stereochemistry after converting sulfoxide **19** into the known natural product(s) and comparing their spectroscopic data. Toward this end, the indole *N*-Boc group in **19** was removed with formic acid at 40 °C, and the methyl ester was reduced with $LiAlH_4$ to deliver alcohol **20** as a mixture of two diastereomers with a similar diastereomeric ratio as compound **19**. Surprisingly, the final thermal elimination of the sulfoxide group in alcohol **20** afforded the product as a single entity.[14] Since the spectroscopic data of the resulting homoallylic alcohol were identical to those of (±)-20-*epi*-antirhine (**3**),[1c] ester **19** was found to have the $\alpha$-H configuration at C-20. Its stereochemistry was further confirmed by comparing the spectroscopic data for the product of hydrogenation of the resulting homoallylic alcohol **3** with those of the reported (±)-20-*epi*-18,19-dihydroantirhine (**4**).[1b,4e] It should be noted that the diastereoselectivity at C-20 can be controlled during enolate alkylation, and the diastereomeric relationship in ester **19** can be attributed to the chirality of the sulfur atom. Furthermore, the electrophile approaches from the *Si* face to the enolate, predominantly leading to the formation of the $\alpha$-H isomer.

After obtaining the 20-epimers **3** and **4**, we continued with the synthesis of (±)-antirhine (**1**) and (±)-18,19-dihydroantirhine (**2**), which requires 20-$\beta$-H-selective installation of the vinyl (or ethyl) group at C-20 in ester **18**. In light of this, various alkylating partners and reaction conditions were explored. However, all of the efforts to reverse the stereochemical outcome of the alkylation reaction were fruitless. In most of these reactions, the electrophiles approached from the *Si* face of the enolate, leading to the 20-$\alpha$-H configuration as the major product. At this point, we decided to take advantage of the strong *Si* face selectivity observed in the C-20 alkylation reactions rather than trying to reverse it, envisioning that the introduction of a hydroxymethyl group at C-20 and the conversion of the ester group into the vinyl group would give (±)-antirhine (**1**) and (±)-18,19-dihydroantirhine (**2**).

On the basis of this hypothesis, we carried out the synthesis of (±)-antirhine (**1**) and (±)-18,19-dihydroantirhine (**2**) by following the route shown in Scheme 4. When submitted to

**Scheme 4. Total Synthesis of (±)-Antirhine (1) and (±)-18,19-Dihydroantirhine (2)**




the reaction with methoxymethyl (MOM) chloride, the enolate of **18** showed reasonable facial selectivity to give the desired 20-$\alpha$-H-isomer **21** in 64% yield along with its 20-epimer, 20-*epi*-**21** in 16% yield after column chromatography separation. Reduction of the ester moiety in **21** with DIBAL afforded the corresponding alcohol **22** in 95% yield. Dess–Martin oxidation of alcohol **22** afforded the corresponding aldehyde. However, this aldehyde was quite unstable and underwent rapid $\beta$-elimination to furnish the $\alpha,\beta$-unsaturated aldehyde during flash column chromatography.[15] To bypass this issue, we directly converted the resulting aldehyde to the corresponding double bond without isolating the aldehyde. The crude aldehyde product was directly submitted to the Wittig reaction at −30 °C without purification and provided homoallyl ether **23** in 41% overall yield.[16] Deprotection of the *N*-Boc group and demethylation under conditions developed by Yamada and co-workers[17] provided (±)-antirhine (**1**) in 30% yield. Saturation of the homoallylic double bond in **1** using palladium-catalyzed hydrogenation afforded (±)-18,19-dihydroantirhine (**2**). The spectroscopic data of **1** and **2** agreed with the reported values.[3,4]

To rationalize the strong *Si* face selectivity during the alkylation of the enolate derived from compound **18**, we proposed a possible transition state for the alkylation reaction of enolate **25** with electrophiles (Scheme 5a). The lithium cation in enolate **25** might interact with the tertiary nitrogen atom to form a rather rigid cyclic structure. In this cyclic structure, the *Re* face would be blocked by the bulky Boc group, and thus, the electrophile would approach from the *Si*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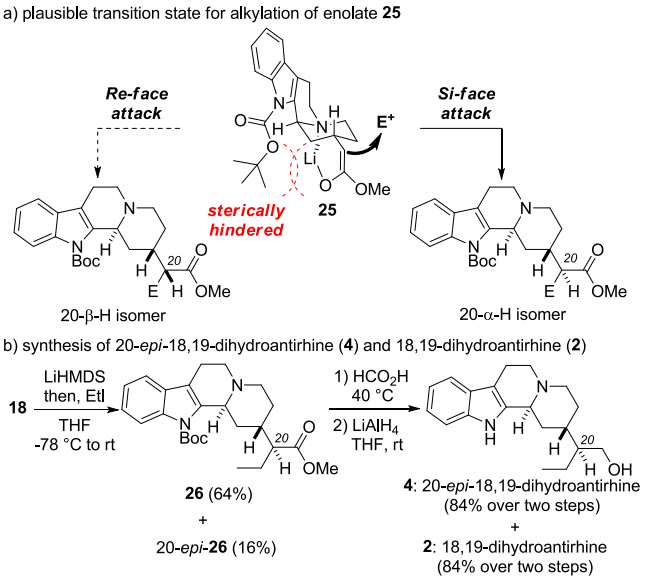
**Scheme 5. (a) Plausible Transition State for Alkylation of Enolate 25; (b) Synthesis of (±)-20-*epi*-18,19-Dihydroantirhine (4) and (±)-18,19-Dihydroantirhine (2)**




face, leading to the strong 20-α-H selectivity. To further prove this facial selectivity, we envisaged that (±)-20-*epi*-18,19-dihydroantirhine (**4**) could be prepared from compound **18** via ethylation of enolate **25** as long as the same facial selectivity was obtained (Scheme 5b). Treatment of enolate **25** with ethyl iodide provided the ethylated product **26** and its 20-epimer in 64% and 16% yield, respectively. Subsequent deprotection of the Boc group followed by reduction of the ester afforded **4** as the major product along with **2**.

In conclusion, we have developed a general strategy that allows the synthesis of the antirhine family of alkaloids, including (±)-antirhine (**1**), (±)-18,19-dihydroantirhine (**2**), and their 20-epimers. The key to the success is the cyanide-catalyzed imino-Stetter reaction to give indole-3-acetic acid derivatives bearing a pyridine ring at the 2-position. Subsequent construction of the piperidine C ring and *trans*-selective installation of the two-carbon unit at C-15 effectively delivered the key intermediate. Stereoselective alkylation at C-20 followed by functional group manipulations completed the total syntheses of (±)-antirhine, (±)-18,19-dihydroantirhine, and their 20-epimers.

This work continues to display the utility and versatility of our indole-3-acetic acid protocol via the cyanide-catalyzed imino-Stetter reaction. Furthermore, this method allowed us not only to access a unique molecule class but also to develop a previously unseen divergent synthesis that has clear potential for applications outside of this specific group.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00544.

Experimental details and full characterization data (PDF)

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### Author Contributions

§C.B. and E.P. contributed equally.


### Notes

The authors declare no competing financial interest.

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(15) The structure of the $\alpha,\beta$-unsaturated aldehyde was confirmed by $^{1}$H and $^{13}$C NMR spectroscopy and HRMS (see the Supporting Information).
(16) Controlling the reaction temperature during the Wittig reaction was very important to improve the yield of the desired product **23**. The reaction at temperatures above −30 °C generated a considerable amount of the $\alpha,\beta$-unsaturated aldehyde.
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