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# Enantio- and Diastereoselective Synthesis of 1,5-*syn*-(*Z*)-Amino Alcohols via Imine Double Allylboration: Synthesis of *trans*-1,2,3,6-Tetrahydropyridines and Total Synthesis of Andrachcine

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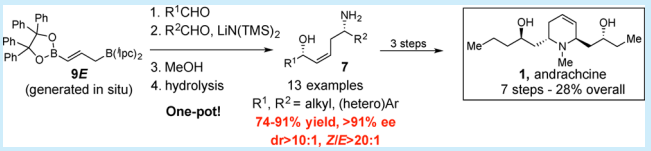
Supporting Information

**ABSTRACT:** A stereoselective synthesis of *trans*-1,2,3,6-tetrahydropyridines **8** is described. This synthesis proceeds via intramolecular Mistunobu reactions of 1,5-*syn*-(*Z*)-amino alcohols **7**, which were prepared by a highly diastereo- and enantioselective double-allylboration reaction of aldehyde **5** and silylimine **6**. The chiral bifunctional γ-borylallylborane **9*E*** was generated in situ by hydroboration of allene **3** with (diisopinocampheyl)borane **4**. This strategy was applied to the total synthesis of andrachcine **1**, thus establishing with certainty the absolute and relative configuration of the natural product.

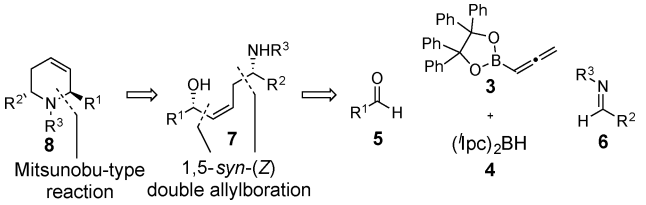



1,2,3,6-Tetrahydropyridines (THPs) are an important class of heterocycles that are substructures of numerous biologically active compounds.[1] This scaffold occurs in many alkaloid natural products[2] and has been used as intermediates in the synthesis of substituted piperidines[3] and iminosugars.[4] Consequently, numerous strategies for the stereoselective synthesis of 1,2,3,6-tetrahydropyridines and the corresponding piperidine derivatives have been described.[5] Of these, the *trans*-2,6-disubstituted 1,2,3,6-tetrahydropyridines are thermodynamically disfavored[6] owing to the pseudoaxial orientation of one of the two substituents α to the nitrogen atom. As such, this diastereomer must be accessed by using kinetically controlled reaction sequences. However, relatively few methods are available for the synthesis of enantiomerically enriched *trans*-1,2,3,6-tetrahydropyridines,[7] including iminium ion mediated vinylsilane[8] and allylsilane[9] cyclizations as well as ring-closing metathesis sequences.[10] Therefore, the development of new, highly stereochemically controlled syntheses of this ring system remains an important challenge.

Toward this goal, we envisioned that 2,6-disubstituted *trans*-1,2,3,6-tetrahydropyridines **8** could be formed by an intramolecular Mitsunobu cyclization of 1,5-*syn*-(*Z*)-amino alcohols **7**. The latter would be synthesized via the combination of an aldehyde **5**, an aldimine **6**, and a chiral γ-borylallylboronate generated in situ by hydroboration of allenylboronic ester **3** with (diisopinocampheyl)borane ($(^{l}Ipc)_2BH$)[11] **4** (Scheme 1).

During the past decade, our group has developed diastereo- and enantioselective double-allylboration strategies for the synthesis of substituted *syn*- and *anti*-1,5-pentenediols.[12] This powerful and convergent method has been successfully applied to the total synthesis of polypropionate natural products.[13] We anticipated that use of an imine as the electrophilic reaction partner in the second allylboration step would provide a highly selective route to 1,5-amino alcohols and would enable the scope of this method to be expanded to include the synthesis of alkaloid natural products. This concept is far from trivial since

**Scheme 1. Proposed Synthesis of *trans*-1,2,3,6-THPs**




stereoselective allylboration of imines[14] has proven to be challenging, although some diastereo- and enantioselective[15] methods have recently emerged.

We report herein the development of a highly diastereo- and enantioselective synthesis of 1,5-*syn*-(*Z*)-amino alcohols **7** and their conversion to enantioenriched *trans*-1,2,3,6-tetrahydropyridines **8** via an intramolecular Mistunobu-type reaction. This strategy was applied to the total synthesis and structure validation of andrachcine **1**, which had also previously been assigned the stereochemistry as presented in diastereoisomer **2** (Figure 1).[17]

Although few isolated syntheses of acyclic 1,5-*syn*-(*Z*)-amino alcohols have been reported,[18] a general and straightforward method to selectively form this motif is lacking in the literature.

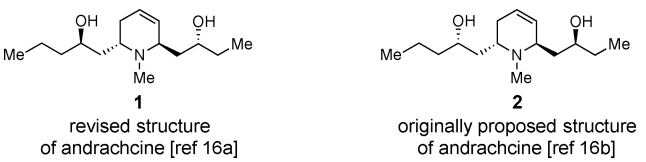



**Figure 1.** Two different structures of andrachcine reported in the literature.

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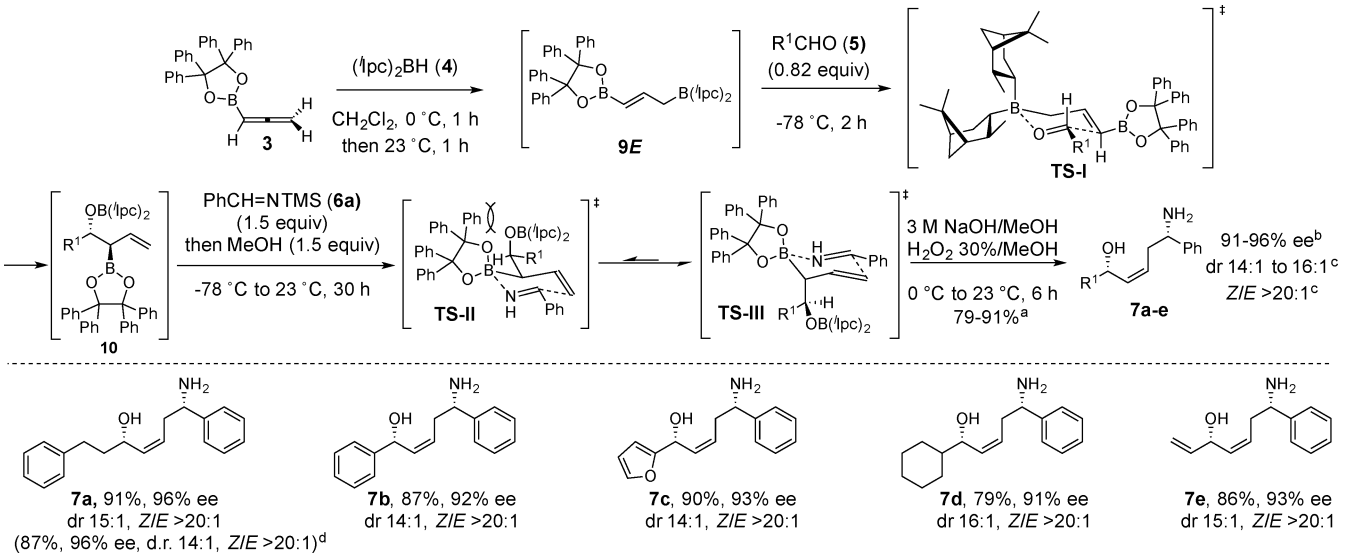
**Scheme 2. Diastereo- and Enantioselective Synthesis of 1,5-*syn*-(*Z*)-Amino Alcohols 7 from Silylimine 6a***

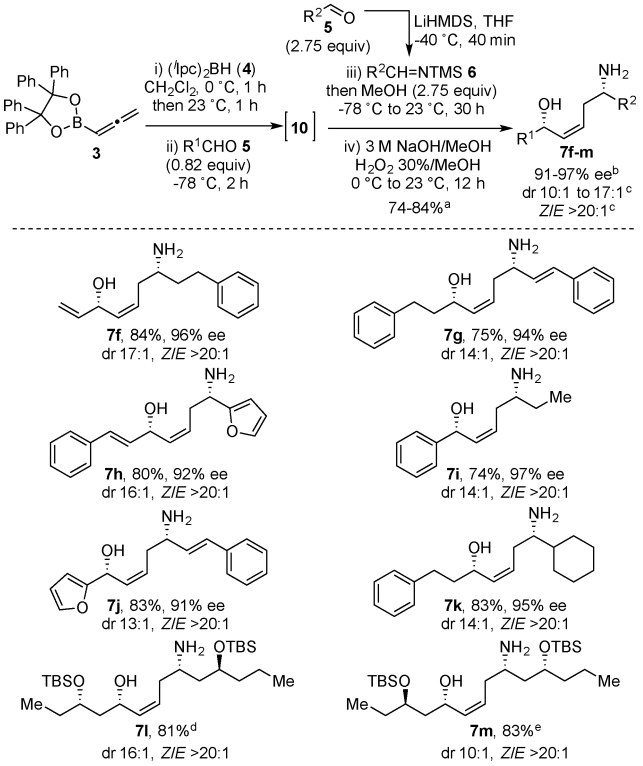



*Unless specified, all reactions were performed using 0.25 mmol of allene **3**. [a]Isolated yields of 1,5-*syn*-(*Z*)-amino alcohols **7** obtained after column chromatography. [b]Enantiomeric excess (% ee) and absolute configuration determined by using the Mosher ester/amide analysis.[16] [c]Diastereomer ratio (dr) determined by $^1$H NMR analysis after filtration through silica gel and broad fraction collection. [d]Reaction performed using 3.0 mmol of allene **3**.

Our initial efforts focused on the selection of imine **6** for use as the second electrophilic component of our previously established double-allylboration sequence (Scheme 2). Initial studies demonstrated that the second allylboration step, using in situ generated **10** as the allylborating agent, proved to be highly sensitive to steric hindrance, as *N*-tosyl imines, *N*-acyl imines, or *N*-(trimethylsilyl) imines proved to be unreactive under standard conditions (see the Supporting Information for details). We reasoned, as suggested originally by Brown,[15u] that the much smaller N−H imine would decrease nonbonded interactions and permit the second allylboration reaction to proceed via **TS-III**. Thus, the free N−H imine was generated in situ by methanolysis of the N−Si bond of **6a**.[15h,s,u] A representative set of 1,5-*syn*-(*Z*)-amino alcohols **7** was assembled from a panel of aldehydes **5** and (*E*)-*N*-(trimethylsilyl) benzylidene imine (**6a**). Thus, treatment of in situ generated **10**[12b,d,e] with 1.5 equiv of imine **6a** and 1.5 equiv of MeOH at −78 °C and then at room temperature for 30 h provided products **7a−e** in good to excellent yields (79−91%). These reactions proceeded with excellent diastereo- (dr 14:1−16:1) and enantioselectivity (91−96% ee), and the *Z*/*E* olefin ratio was >20:1 in all cases. This reaction sequence proved to be readily scalable as shown for **7a** (Scheme 2).

Encouraged by these results, we turned our attention to nonaromatic silylimines **6** in an effort to increase the scope of this double-allylboration procedure. Since aliphatic imines have the propensity to self-condense owing to facile imine−enamine equilibria,[19] we anticipated that in situ formation of silylimines **6** might prove to be a useful strategy (Scheme 3). This was accomplished by treating an aldehyde with LiHDMS in THF at −40 °C for 40 min (see the SI for additional efforts to optimize this reaction).[20] Ultimately, we determined that use of 2.75 equiv of aldehyde (as precursor of imine **6**) was necessary to achieve good yields of the double-allylboration products **7f−m** summarized in Scheme 3. However, the efficiency of this reaction sequence was still synthetically useful when 2.0 equiv

**Scheme 3. Synthesis of 7f−m by Double-Allylboration Reactions with in Situ Formation of *N*-Silylimines 6***




*Unless specified, all reactions were performed using 0.25 mmol of allene **3**. [a]Isolated yields of 1,5-*syn*-(*Z*)-amino alcohols **7** obtained after column chromatography. [b]Enantiomeric excess (% ee) and absolute configuration determined by using the Mosher ester/amide analysis.[18] [c]Diastereomer ratio (dr) determined by $^1$H NMR analysis after filtration through silica gel and broad fraction collection. [d]Reaction performed using 0.73 mmol of allene **3**. [e]Reaction performed using 3.0 mmol of allene **3**.



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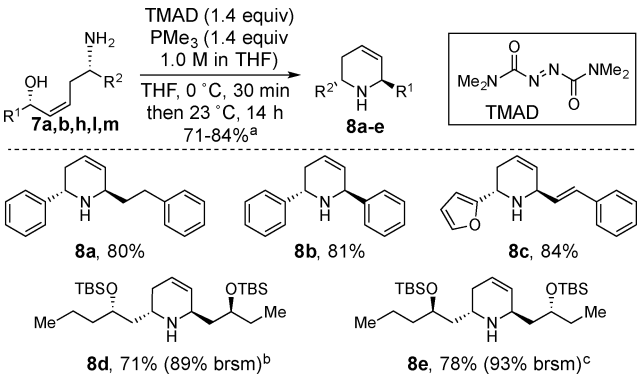
of the imine precursor aldehyde was used (see the SI for an optimization study).

As depicted in Scheme 3, a series of in situ generated silylimines **6** reacted with allylboronic ester intermediate **10** to give adducts **7f**–**m** in 74–85% yields and with high levels of diastereo- and enantioselectivity. Achiral aliphatic (for **7f**, **7i**, and **7k**), $\alpha,\beta$-unsaturated (**7g** and **7j**), and heteroaromatic (**7j**) imines were successfully generated and used in this double-allylboration sequence. In order to test the utility of the double allyboration in more complex synthetic contexts, we also examined this procedure in the double-asymmetric manifold.[21] As demonstrated by the formation of *syn*-1,5 amino alcohols **7l** and **7m**, imines generated in situ from sensitive chiral aldehydes were also successfully utilized.

We turned next to the intramolecular Mitsunobu reaction for the preparation of *trans*-1,2,3,6-tetrahydropyridines, **8**. Use of standard Mitsunobu conditions was not successful here.[22] Ultimately, we identified the combination of tetramethylazodicarboxamide (TMAD)[23] and trimethylphosphine as the best reagent combination. Mixing these two reagents in THF at 0 °C followed by addition of compounds **7** delivered the *trans*-1,2,3,6-tetrahydropyridines **8** in 71–84% yields (Scheme 4).

**Scheme 4. Stereospecific Cyclization of 7 to 8***



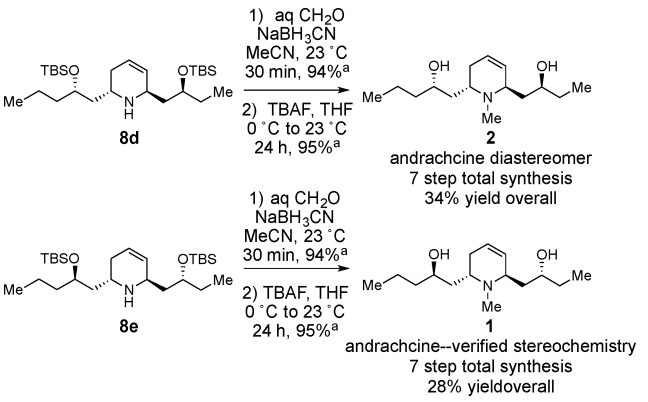

*Unless specified, all reactions were performed with 0.1 mmol of amino alcohol **7**. [a]Isolated yields of *trans*-1,2,3,6-THPs **8** obtained after column chromatography. [b]Reaction performed with 0.2 mmol of amino alcohol **7l**. [c]Reaction performed with 0.615 mmol of amino alcohol **7m**.

Chiral substrates **7l** and **7m** also underwent the reaction without complication, although these reactions proceeded more slowly and did not reach completion. The *trans*-tetrahydropyridine stereochemistry was confirmed by hydrogenation of **8a** followed by NOESY analysis of the resulting piperidine (see the SI).

The stimulation to develop this synthesis of *trans*-1,2,3,6-tetrahydropyridines was for its potential application to the total synthesis of alkaloid natural products. As a proof of concept, we selected andrachcine, a 2,6-disubstituted *trans*-1,2,3,6-tetrahydropyridine alkaloid first isolated in 1987 from the plant *Andrachne aspera* Spreng. (Euphorbiaceae) in Karachi, Pakistan. This plant is traditionally used in local medicine to improve eyesight, and the extracts from which andrachcine was islolated displayed antibacterial activity.[17b] Initially, andrachcine was reported to possess the stereochemistry represented in compound **2**[17b] (Figure 1), with both side-chain secondary alcohols assigned to have *S* absolute configuration. In 2000, Mill and Hootelé revised the structure of andrachcine to that depicted in structure **1**[17a] (Figure 1), in which both secondary alcohols have the *R* absolute configuration. We believed that our imine double allylboration reaction followed by Mitsunobu cyclization provided an efficient strategy to synthesize both **1** and **2** in order to confirm the stereochemistry of the natural product.

Thus, advanced precursors **8d** and **8e** were subjected to a two-step reductive amination and deprotection sequence, which completed the syntheses of **2** and **1**, respectively. In both cases, the *N*-methylation was achieved by treating the N–H tetrahydropyridine intermediates **8d** and **8e** with formaldehyde and $NaCNBH_3$. The two TBS ethers were subsequently deprotected by treatment with tetrabutylammonium fluoride (Scheme 5). The optical rotation as well as $^1H$ and $^{13}C$ NMR

**Scheme 5. Completion of the Total Synthesis of Andrachcine 1 and Its Diastereoisomer 2**




[a]Isolated by column chromatography.

data obtained for **1** were in complete agreement with the data reported for andrachcine.[16a] Therefore, we conclude that **1** represents the correct stereostructure of andrachcine.

In summary, we have developed a highly diastereo- and enantioselective synthesis of 1,5-*syn*-(*Z*)-amino alcohols **7** via double-allylboration reactions of silyl imines **6** (Schemes 2 and 3). The in situ formation of silyl imines **6** (Scheme 3) facilitated the use of both aromatic and aliphatic aldehyde imine precursors in this one-pot reaction sequence. Cyclization of the 1,5-*syn*-(*Z*)-amino alcohols **7** to *trans*-1,2,3,6-tetrahydropyridines **8** was achieved under mild conditions using TMAD and trimethylphosphine with complete inversion of configuration. Finally, we applied this imine double allylboration and Mitsunobu cyclization sequence to the total synthesis of andrachcine **1**, thus confirming its stereostructure as a whole. This work expands the utility of the double-allylboration reaction to include the synthesis of alkaloids and potentially scaffolds of use in drug discovery research. Further development of this double-allylboration strategy, as well as its application to other heterocycles and total synthesis of complex alkaloid natural products, will be reported in due course.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00995.

Experimental procedures (PDF)
Spectroscopic data for all new compounds (PDF)



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### Notes

The authors declare no competing financial interest.

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