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Synthesis of Lepadiformine Using a Hydroamination Transform

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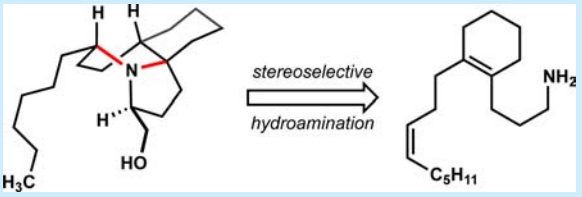
Supporting Information

ABSTRACT: Dissection of lepadiformine by a double hydroamination transform affords a simple achiral amino diene. This reaction is accomplished in the forward sense by amine-directed hydroboration and an oxidative alkyl shift to nitrogen, both of which occur with high stereoselectivity to generate three stereogenic centers and the lepadiformine skeleton.



Alkaloids are the only metabolite class not defined by structure, but by reactivity; i.e., the nitrogen atom must be capable of forming a salt with a mineral acid.[1] As a result, the class contains substantial biosynthetic and structural diversity, which prevents a unified synthesis strategy from predominating.[2] Broadly applied retrosynthetic transforms for C−N bond dissection include Mannich cascades, reductive amination or hydrogenation, cationic Ritter substitution,[3] and Hofmann−Löffler−Freytag transforms, among others. Alkene hydroamination, however, is an infrequently applied strategy, probably due to the poor chemoselectivity, stereoselectivity, predictability, oxygen sensitivity, or substrate breadth associated with current methods.

Nevertheless, dissection of an alkaloid scaffold into one or more prochiral alkenes and an amine can be very simplifying, especially if multiple stereocenters and rings are excised. Recently, we demonstrated that Vedejs' amine-directed hydroboration[4] combined with *in situ* amine oxidation effects the stereoselective hydroamination of polyunsaturated amines and is compatible with di-, tri-, and tetrasubstituted alkenes.[5] This polyhydroamination transform appeared to be applicable to a broad array of biosynthetically disparate alkaloids and seemed to substantially simplify the synthesis of lepadiformine (**1**).

Lepadiformine belongs to a class of tricyclic marine alkaloids first isolated in 1993 from ascidians of *Clavelina sp.*[6,7] Kibayashi reassigned the structure of **1** in the course of completing its first synthesis in 2000.[8] This reassignment highlighted one of the most challenging features of lepadiformine, the *trans*-1-azadecalin subunit of the A and B rings, which distorts the B-ring into a twist boat. Since the initial synthesis, a number of racemic as well as enantioselective syntheses have been reported.[9] Here, we report a concise, formal synthesis of (±)-lepadiformine utilizing a stereoselective hydroamination[5] reaction to form the tricyclic core.[10]

As shown in Figure 1, lepadiformine can be dissected via a stereoselective hydroamination transform to simple linear amine (**2**). However, it was unclear if our hydroamination reaction could be applied to **2** given the strain of the target (**1**), the apparent strain of the hydroboration transition state (**7**), and the strain of the two possible iodoamine-borate conformers required for C−N bond formation (**8** and **9**). The first option,

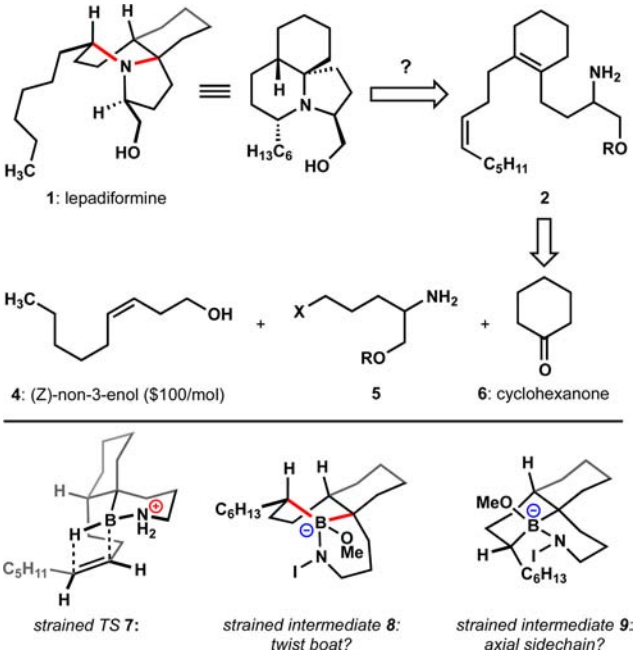


Figure 1. Application of a hydroamination transform to **1**.

8, would possess the twist-boat conformation of **1**, and the second, **9**, would possess two 1,3-diaxial interactions between the hexyl side chain and the bora-piperidine ring. Based on our previously developed stereochemical model,[5] we expected these diastereomers to predominate, but whether the intramolecular reactions were favored over bimolecular decomposition remained an outstanding question. Nevertheless, the aminodiene substrate could be easily procured for experimentation, a general benefit of these disconnections. We previously determined that *cis*-alkenes were superior to *trans*- for obtaining high stereoselectivity in these directed hydroborations.[5] Fortunately, *cis*-monounsaturated fatty alcohols are readily available at low cost, reflecting the abundance of *cis*-alkenes in

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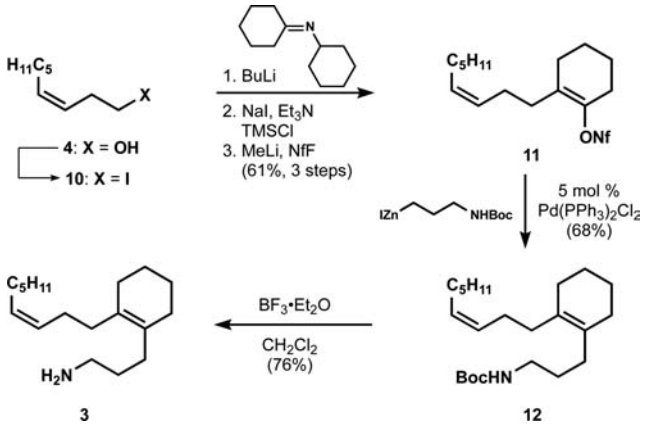
lipids. Thus, it seemed reasonable that aminodiene (**3**) could be divided into (*Z*)-non-3-enol (**4**) (ca. $100 per mol, Sigma-Aldrich), a derivative of which might be alkylated by cyclohexanone (Figure 1). Attachment of the aliphatic amine side chain could rely on cross-coupling technology.

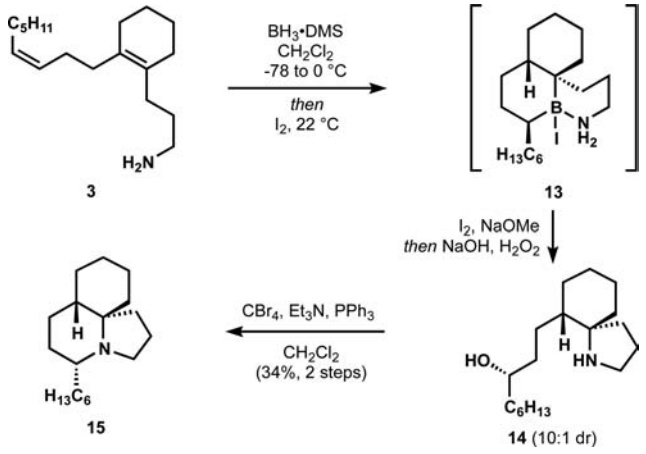
The test substrate for hydroamination, unsaturated amine **3**, was synthesized in six steps from commercially available alcohol **4** and cyclohexanone *N*-cyclohexylimine via (1) alkylation of iodide **10**, (2) thermodynamic silyl enol ether formation,[11] (3) nonaflation,[12] and then (4) coupling with *N*-Boc aminopropylzinc iodide (one step from commercial material) (Scheme 1).[13] Finally, deprotection with $BF_3{\cdot}Et_2O$ provided amine **3**.

Scheme 1. Synthesis of Hydroamination Precursor 3



Treatment of **3** with 1 equiv of $BH_3{\cdot}DMS$ followed by addition of 0.5 equiv of iodine over 1.5 h unfortunately showed minimal evidence of borinic amide **13** (Scheme 2) by LCMS.

Scheme 2. Stereoselective Cyclization of 3 to 15



As opposed to our previous hydroboration method, we eventually discovered that decreasing the addition time of iodine to a period of 1 min substantially increased yields of borinic amide **13**. Subsequent dilution of the reaction to 0.1 M followed by addition of 2 equiv of iodine and 4 equiv of sodium methoxide effected a 1,2-alkyl shift, and oxidative workup delivered amino alcohol **14** (10:1 dr by ^{1}H NMR analysis). So, it appears that the strain of transition state **7** is recompensed by the high potential energy of the ammonium borane, and the strain energy of possible intermediate **8** or **9** still allows the alkyl shift to predominate over competitive pathways such as oxidation to an imine.

It was unclear by NMR which diastereomer had been favored, so we derivatized **14** to the 3,5-dinitrobenzoyl ester and amide **16**. X-ray crystallographic analysis of **16** (Figure 2)

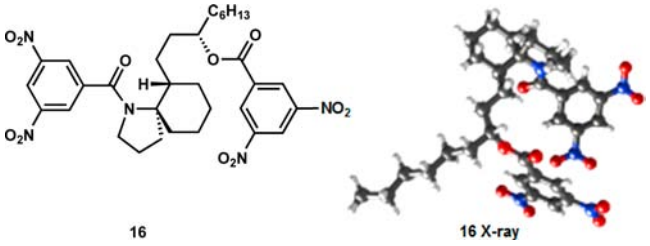


Figure 2. X-ray **16** proves the stereochemistry of **14**.

confirmed that the relative stereochemistry would lead to the correct *trans*-1-azadecalin by stereoinvertive ring closure of the C_2 alcohol. By following Kibayashi's protocol for cyclodehydration under Appel conditions (CBr_4, PPh_3, Et_3N),[14] the tricyclic core of lepadiformine (**15**) was produced in 34% yield and 10:1 dr from linear precursor **3**.

Only the appendage of the hydroxymethyl side chain remained to complete the synthesis of **1**. We initially looked to install the final C_{13} stereocenter via α-alkylation and trapping with a formaldehyde equivalent. It has been previously shown that coordination of tertiary amines by Lewis acids such as $BF_3{\cdot}Et_2O$ can facilitate α-deprotonation upon treatment with a strong base.[15] Using *N*-ethylpyrrolidine as a model system, we were able to apply this method to the synthesis of *N*-Et proline methyl ester (**17**, Figure 3). Unfortunately, these conditions failed to provide the desired α-alkylation product when applied to tricycle **15**.

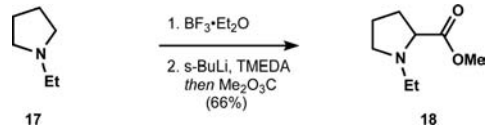
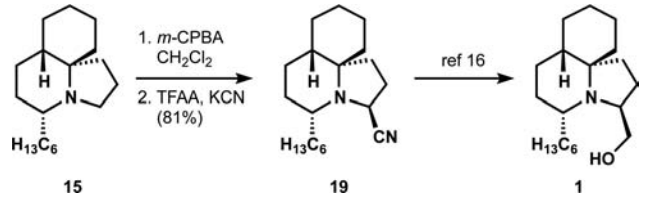


Figure 3. Pyrrolidine **17** is successfully carboxylated, but not tricycle **15**.

For the final steps of the synthesis, we instead employed reaction conditions analogous to those described by Rychnovsky[16] to convert tricycle **15** to the α-amino nitrile **19** (Scheme 3) by a modified Polonovski reaction. Interception of the Rychnovsky route at compound **19** completes the formal synthesis of **2**.

Because of the difficulties encountered in late stage hydroxymethylation, we did investigate installation of this group prior to the hydroamination sequence. Although *sec*-alkyl amines were competent to direct hydroboration, very little

Scheme 3. Formal Synthesis of (±)-1



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pyrrolidine was observed after oxidative alkyl migration. These lower yields were attributed to lower equilibrium values of N–B coordination due to substitution on the carbon adjacent to nitrogen.[17] This restricted coordination leads to significant amounts of imine products resulting from radical or polar elimination of the *N*-halo amines instead of the alkyl transfer.

Eventually we found that use of lower temperatures and significantly lengthened times for base addition increased the proportion of the alkyl shift product compared to the oxidation product (Figure 4), so we attempted incorporation of the hydroxymethyl side chain.[18]

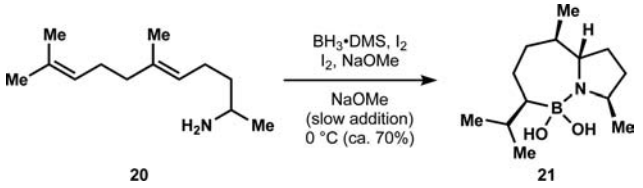

Figure 4. Hydroboration transform with α-substitution.

Coupling vinyl nonaflate **8** and enantiomerically pure organozinc reagents[19] (Figure 5) led to the synthesis of

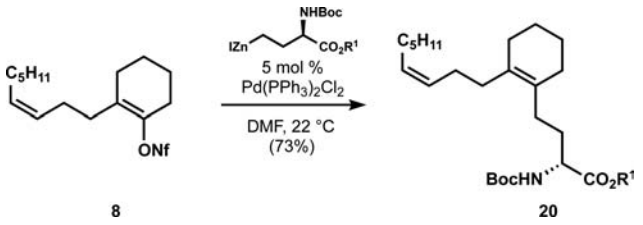

Figure 5. Appendage of chiral amino ester side chain.

amino esters **23** and **24** after *N*-Boc deprotection. Additionally, reduction of the *N*-Boc esters with $LiAlH_4$ followed by protection of the alcohol gave amino esters **25**–**30** (Figure 6).

After extensive screening of reaction conditions, we found that in all cases the reactions of **25**–**30** did not yield hydroboration products. We attributed this unreactivity to formation of coordinatively saturated and kinetically trapped

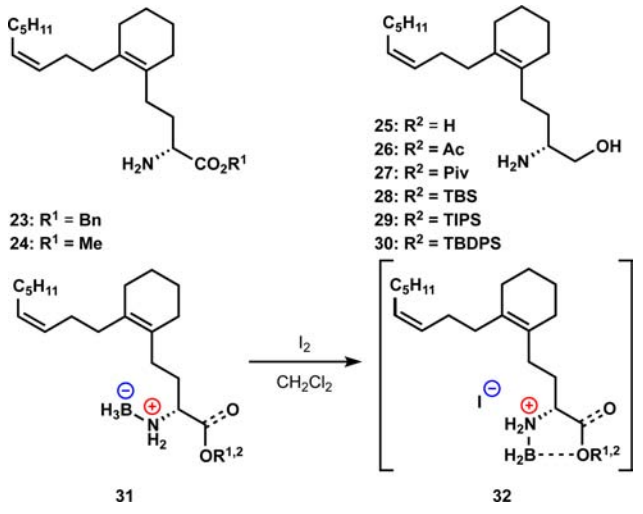

Figure 6. Amino esters, alcohols, and ethers fail to direct hydroboration due to capture of the open borane valence.

borane chelates. For example, we found **23** delivered the debenzylated carboxylic acid. Debenzylation and the absence of hydroboration were rationalized by formation of a chelated borane such as **32**, followed by removal of the benzyl group by the iodide counteranion. These observations should guide the use of directed hydroboration in the future.

In conclusion, we have completed a concise formal synthesis of (±)-lepadiformine from readily available achiral starting materials. At 10 steps and 9% overall yield to **19**, this route is comparable to but less efficient than Renaud's[9k] 10 step (15%) racemic synthesis, in addition to 7 step (11%), 15 step (11%), and 16 step (13%) syntheses by Lygo,[9v] Weinreb,[9m] and Funk,[9d] respectively.[20] Although many hurdles remain in the application of hydroamination to complex molecule synthesis, our work illustrates its potential to dramatically simplify the synthesis of alkaloids. Ideally, these hydroamination reactions will eventually put substantial amounts of molecular leads into the hands of biological screening centers and expand combinatorial libraries beyond polyaromatic scaffolds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02992.

Crystallographic data for compound **16** (CIF)
Experimental procedures, spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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(20) The efficiency of ref 14 cannot be evaluated because the synthesis of its noncommercial, nontrivial starting material, (5*E*,7*E*)-tetradeca-5,7-dien-1-ylmagnesium bromide, is not reported. Based on the 31% overall yield to (−)-**1** starting from this Grignard reagent, we suspect the efficiency may be among the highest of prior approaches, but cannot be certain.

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