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Total Synthesis of (±)-Calcaridine A and (±)-*epi*-Calcaridine A

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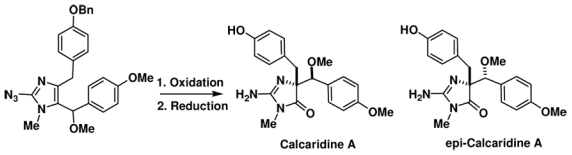
Abstract



The first total synthesis of the *Leucetta* alkaloid calcaridine A is described based on a biosynthetic postulate. Application of an oxidative rearrangement of a 4,5-disubstituted imidazole leads to the formation of both calcaridine A and *epi*-calcaridine A. An X-ray crystal structure determination on the latter has allowed the assignment of the relative configuration of the epimeric natural product and calcaridine A by extrapolation.

2-Aminoimidazole-containing alkaloids isolated from marine sponges have recently captured the attention of a number of synthetic groups, in particular several members of the oroidin family.[1–6] Other families of imidazole-containing alkaloids, including examples isolated from *Leucetta* sponges, have similarly attracted the attention of several groups.[7–9] Recently Crews and coworkers reported a series of structurally novel natural products **1–4** isolated from a Fijian marine sponge, *Leucetta* sp., some of which have modest anti-bacterial activity.[10, 11] Some concerns have been raised based on synthetic studies directed towards spiroleucettadine (**2**) with respect to the accuracy of the assigned structure.[12–14] This structural ambiguity notwithstanding, within each of these compounds a 2-aminoimidazole moiety and two benzyl moieties can be identified, although there are differences in the position of oxidation. There are obvious, if experimentally undefined, biosynthetic relationships between these molecules, and thus an approach to one may provide intermediates that can be used en route to other family members. In both the Crews reports,[11] and in a subsequent report by Watson and co-workers of an approach to the assigned structure of spiroleucettadine (**2**),[12] it is suggested that calcaridine A (**1**) and the other congeners **2–4** are derived from rearrangement and/or oxidation chemistry of naamine A[15–17] (14-desmethoxy **6**) or a closely related derivative.[10–12] This particular postulate led us to speculate that calcaridine A, at least, is formed by an oxidative rearrangement of an intermediate that we term 14-methoxynaamine A (**6**). Although **6** appears to be unknown in the literature at the present time, several years ago the *N*-substituted derivative, 14-methoxynaamidine A (**5**) was isolated from a *Leucetta* sp. sponge, and therefore it is tempting to speculate that **6** is a biosynthetic precursor to both (**1**) and (**5**).[18] In this communication, we describe the successful execution of a "biomimetically-inspired" approach to (±)-calcaridine A (**1**) which employs our recently discovered oxidative rearrangement of 4,5-disubstituted imidazoles to the corresponding 4,4-disubstituted-5-imidazolone.[19–21] Although calcaridine A may not be considered a complex and challenging natural product per se, it contains two vicinal stereocenters for which neither the absolute nor the relative

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stereochemistry were reported (our synthetic studies have led to the assignment of the relative stereochemistry). In addition, in the isolation reports no description of the biological activity of this natural product was provided and these endeavors should provide sufficient material to facilitate such an investigation.

We have for some time had an interest in the development of new methods and strategies for the construction of complex imidazole-containing natural products from simple imidazole derivatives, rather than de novo synthesis of the imidazole ring.[3] Towards this end, we have found that 4,5-disubstituted imidazoles on reaction with dimethyldioxirane or *N*-sulfonyloxaziridines undergo a rapid rearrangement to 5-imidazolones, or in some cases oxidative additions.[19, 21, 22] On the basis of these discoveries, we believed that these reactions might prove useful en route to the *Leucetta* alkaloids **1–4** depicted in Figure 1.[10, 11] However, prior to the work described herein, all of the reported examples are based on oxidation of tetrahydrobenzimidazole derivatives, therefore if the rearrangement reaction were to be employed in the present setting, this would suggest **6** as a precursor, constituting a new class of substrates for this chemistry (Figure 2). This rearrangement substrate would then be accessible from the corresponding 4,5- diiodoimidazole via a sequence of position selective metallation reactions, which based on our own work[22–24] and others[25–29] it is known that this can be executed in the order 5-, 4- and then 2-positions.

Our initial studies centered on the alkylation of diiodoimidazole **8** at the 5-position; this was attempted first by metallation (I → MgBr), transmetallation (MgBr → CuX) and then treatment with the appropriate benzyl bromide derivative.[26] Unfortunately, the desired product was not obtained in this case, but rather the imidazolium salt was isolated. It was subsequently determined that the required adduct could be prepared by reaction of the in situ generated 5-imidazolyl Grignard with Bn-protected benzaldehyde derivative **9** and ionic reduction of the hydroxyl moiety in **10** which provided **7** (Scheme 1).[8] Initial attempts to install the second benzylic substituent via similar metallation chemistry and reaction with anisaldehyde were unsuccessful. However metallation and reaction with *N*-methylformanilide gave the corresponding aldehyde **11** in good yield, which on reaction the Grignard reagent derived from bromoanisole provided the desired alcohol **12**. Methylation of **12** was readily accomplished on exposure of **11** to methanol in the presence of trifluoroacetic acid.

Introduction of the 2-amino group was carried out by C2-lithiation (*n*-BuLi) and reaction with TsN_3 (Scheme 2).[30] Simultaneous reduction of the azide and debenzylation was accomplished with $Pd(OH)_2$-C/H_2 providing the requisite rearrangement substrate **6** in good yield. We were delighted to discover that this substrate underwent oxidative rearrangement upon treatment with an *N*-sulfonyloxaziridine (**15**) in MeOH at 40 °C.[19, 31] The reaction proceeded in a modest 54% yield (unoptimized), but unfortunately produced the rearrangement products **1** and *epi*-**1** as 2:1 mixture of diastereomers based on ^{1}H NMR spectroscopy, favoring the epimeric natural product. This problem was exacerbated by virtue of the difficulty encountered during attempted chromatographic separation of the two diastereomers.[32]

As a result of the poor diastereoselectivity (and the subsequent purification issues), we decided to modify our approach by interchanging the locus of the two benzylic fragments with the idea that the presence of the chiral center closer to the 5-position, where the oxygen transfer occurs, should lead to improved diastereoselectivity. The construction of the requisite substrate again began from **8** by metallation and reaction with *N*-methylformanilide (Scheme 3), providing the aldehyde **16** in good yield. The aldehyde was converted to the ethylene ketal **17** and then metallation and treatment with the benzyl-protected benzaldehyde derivative **9** provided **18**. Alcohol **18** was deprotected with aqueous HCl and subjected to an ionic reduction of the doubly benzylic alcohol with Et_3SiH/TFA providing aldehyde **19**. A subsequent Grignard reaction with *p*-anisylmagnesium bromide gave alcohol **20**, which was then converted to the methyl

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ether **21** (NaH, MeI). Introduction of the azide via metallation at C2 and trapping with TsN_3 afforded **22** (Scheme 3).

Exposure of **22** to $Pd(OH)_2$-C/H_2 led to reduction of both the azide and the hydrogenolysis of the *O*-benzyl moiety, providing the key rearrangement substrate **23** (Scheme 4). Treatment of **23** with the *N*-sulfonyloxaziridine **15** also led to an oxidative rearrangement, providing a 1:1 mixture of calcaridine A (**1**) and *epi*-calcaridine A *epi*-(**1**). Although there was a small change in the diastereoselectivity in favor of the natural product, it was certainly not to the extent that we had hoped and expected. At this point, we decided to investigate whether rearrangement of a precursor, in particular **22**, might led to improved selectivities and facilitate separation of the epimeric imidazolones. We were delighted to discover that azide **21** underwent rearrangement on treatment with **15** to provide a 1:1 mixture of chromatographically separable imidazolones **24** and *epi*-**24**. At this point we did not know for certain which of the two azides possessed the appropriate relative stereochemistry for conversion to calcaridine A, although one had a strikingly similar NMR spectrum to **1**. Therefore, each of these rearrangement products was taken on individually through the next step which involved catalytic hydrogenation, one of which led cleanly to calcaridine A (**1**), and the other to *epi*-calcaridine A *epi*-(**1**). Synthetic and natural calcaridine A exhibited identical NMR data, however our synthetic material was isolated as a solid, whereas the natural material was isolated as an oil, presumably this reflects differences of scale, purity or perhaps the fact that the synthetic material is racemic.

During the characterization process it was noted that *epi*-calcaridine A *epi*-(**1**) formed nice crystals from MeOH-D_4, one of which was subjected to X-ray crystallography, which indicated a syn arrangement of the imidazolone nitrogen and the methoxy moiety.[33] The structure clearly confirms that the rearranged product has the correct connectivity expected from this sequence, and provides the relative configuration of the two chiral centers. This in turn allowed the assignment of the relative configuration of calcaridine A (**1**) as indicated in Scheme 4.

The present report constitutes the first description of a total synthesis of the *Leucetta* alkaloid calcaridine A which employs an oxidative rearrangement of a polysubstituted imidazole. These are the first examples of rearrangements involving substrates other than a tetrahydrobenzimidazole-type derivative. While these experiments do not prove that calcaridine A is formed biosynthetically via an oxidative rearrangement of 14-methoxynaamine A, they do demonstrate that it is a *feasible* pathway. Although chemically the rearrangement exhibits poor diastereoselectivity, an enzyme-mediated process might be expected to proceed with substantially higher levels of selectivity. In addition to the total synthesis, we have determined the relative stereochemistry of the natural product through X-ray crystallography of the epimeric congener. Present efforts are directed toward improving the diastereoselectivity, developing an asymmetric synthesis and investigating the biological activity of this natural product and its epimer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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31. Attempts to conduct the rearrangement with DMDO were unsuccessful leading to the formation of complex reaction mixtures
32. It was subsequently determined that the diastereomers could be separated by fractional recrystallization by seeding the mixture with the non-naturally occurring diastereomer
33. For details of this determination, see Supplementary Information

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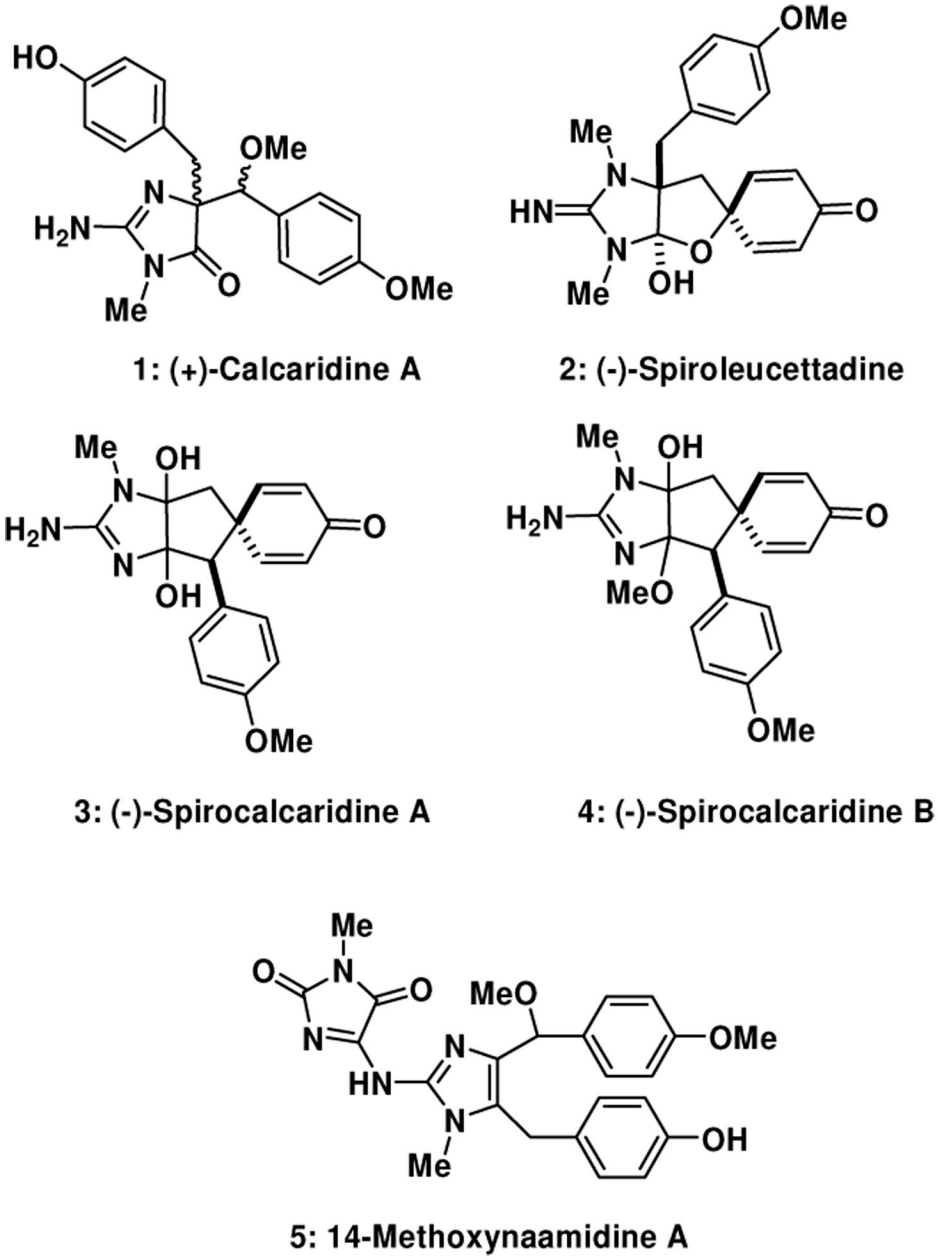

Figure 1.
Selected *Leucetta* alkaloids

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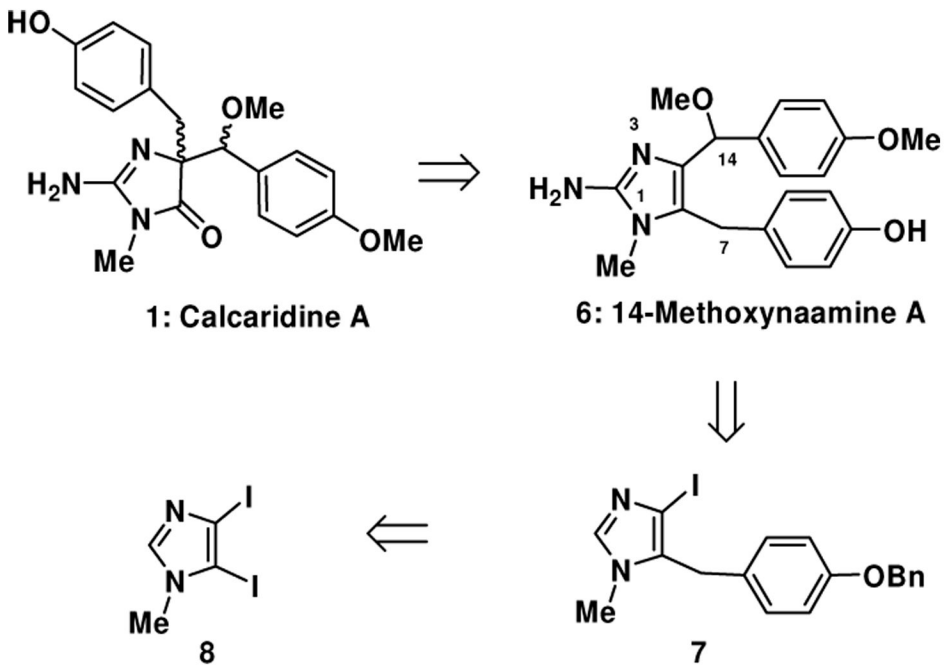

Figure 2.
Retrosynthetic analysis of Calcaridine A

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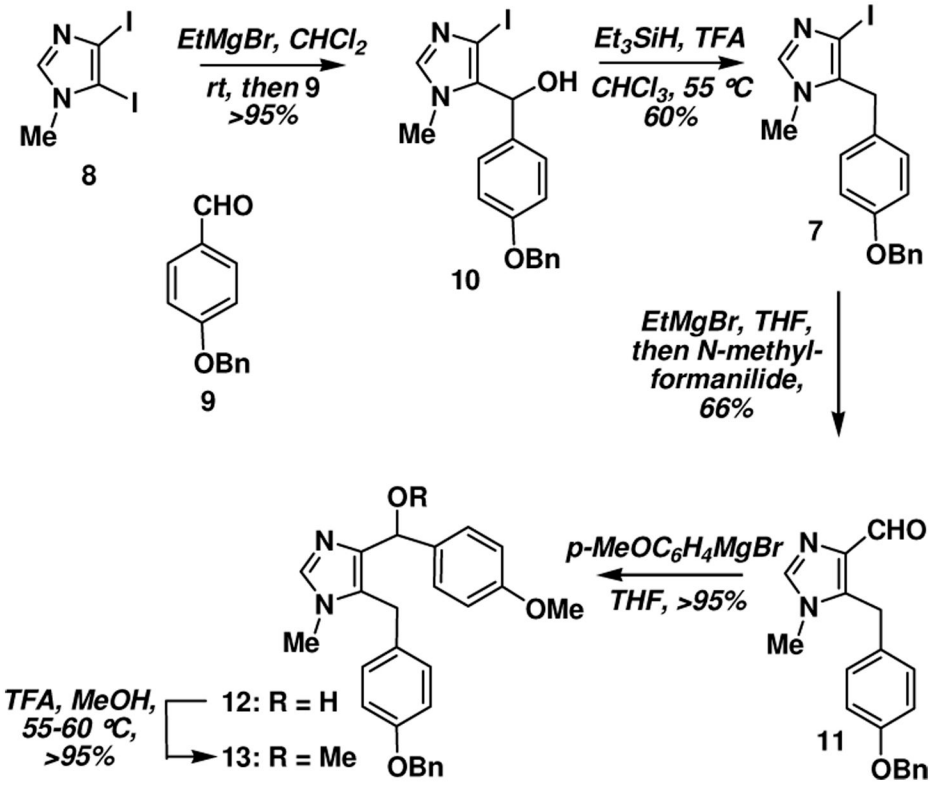

Scheme 1.

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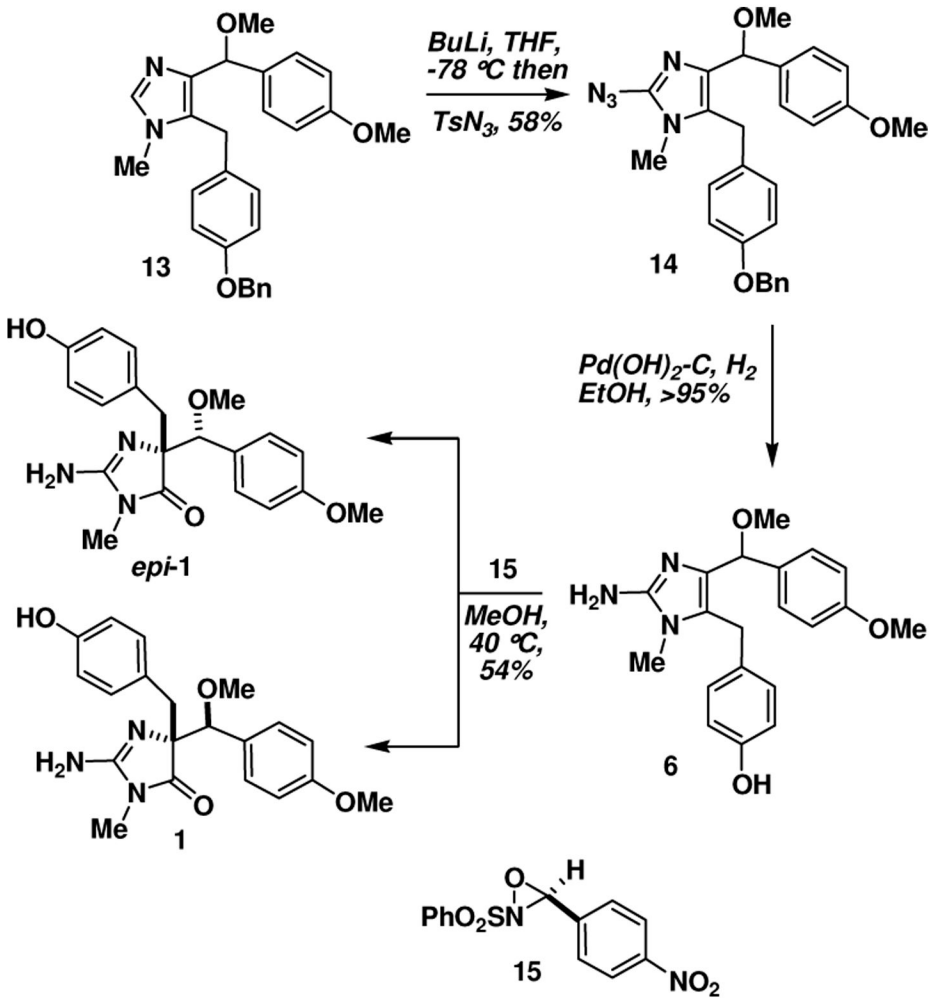
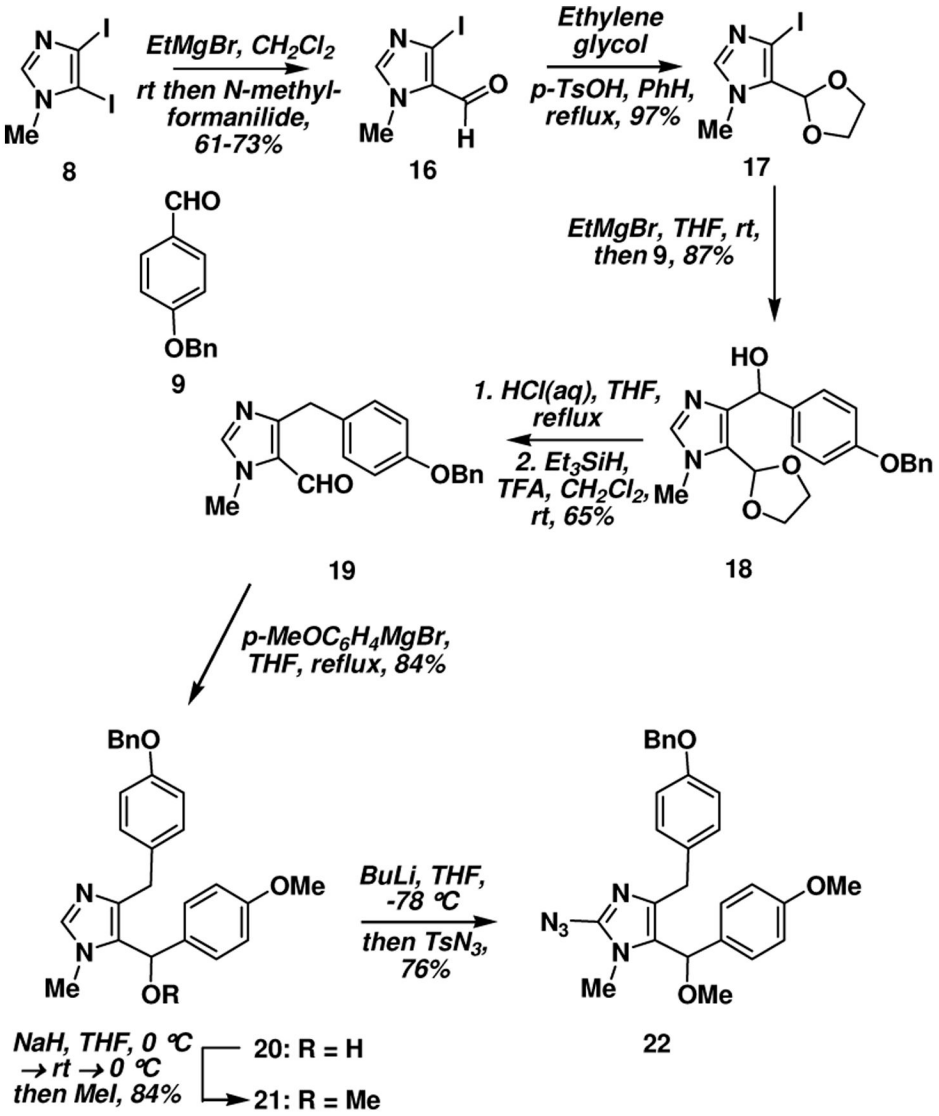


Scheme 2.



Scheme 3.

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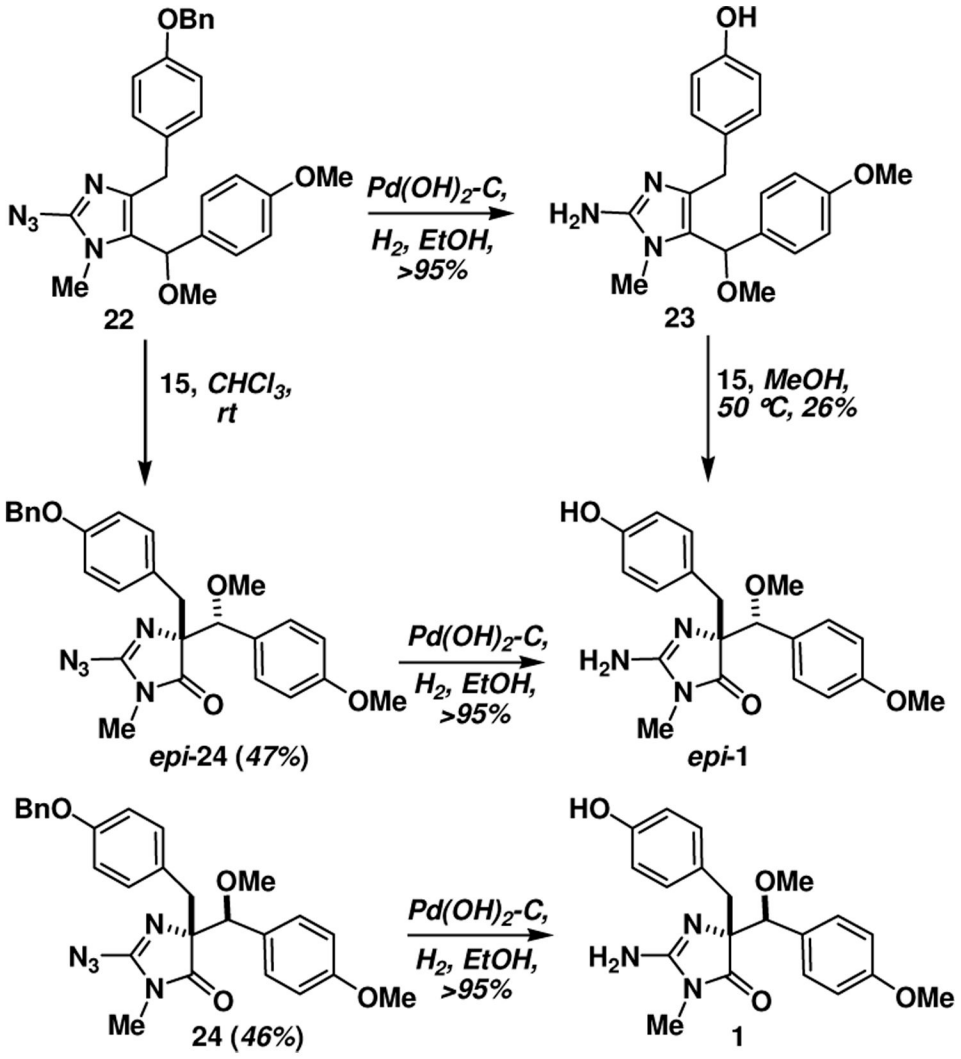

Scheme 4.