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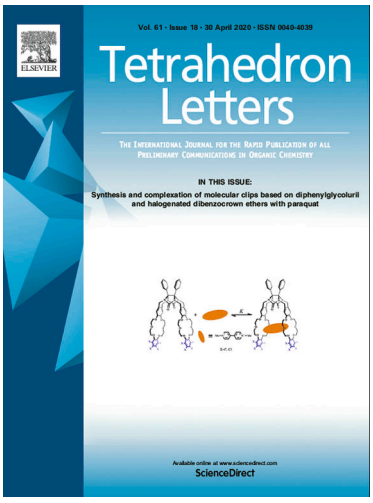

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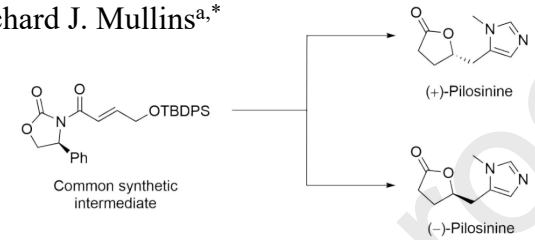

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Total Synthesis of (+)-Pilosinine via a Stereodivergent Conjugate Addition Strategy

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ABSTRACT

In recent work, asymmetric conjugate addition reactions to chiral 4-phenyl-*N*-enoyl-1,3-oxazolidinones have been shown to give different stereochemical outcomes depending on the conditions employed. Through the application of stereodivergent reaction conditions, the total synthesis of (+)-pilosinine and the formal synthesis of ( )-pilosinine has been completed from a single enantiomer of the 1,3-oxazolidinone auxiliary.

Introduction

The Michael addition, also known as a 1,4-conjugate addition, is a powerful reaction between a nucleophile and an α,β-unsaturated carbonyl yielding β-substitution.[1,2] Among many C C bond forming reactions, the use of 1,3-oxazolidinones as chiral auxiliaries has found great utility in stereocontrolled conjugate addition reactions. In particular, the use of nonracemic 4-phenyl-1,3-oxazolidinone, pioneered by Hruby and colleagues[3-7], has enabled highly diastereoselective conjugate additions of organocopper reagents for the synthesis of several natural products.[8-17] Mechanistically, the stereocontrol in these reactions presumably results from initial formation of a metal chelate (a and d). This chelate, with restricted rotation, positions the 4-phenyl group such that attack of the nucleophilic organocopper species is directed to a single face (e/f over b/c) (**Figure 1**).

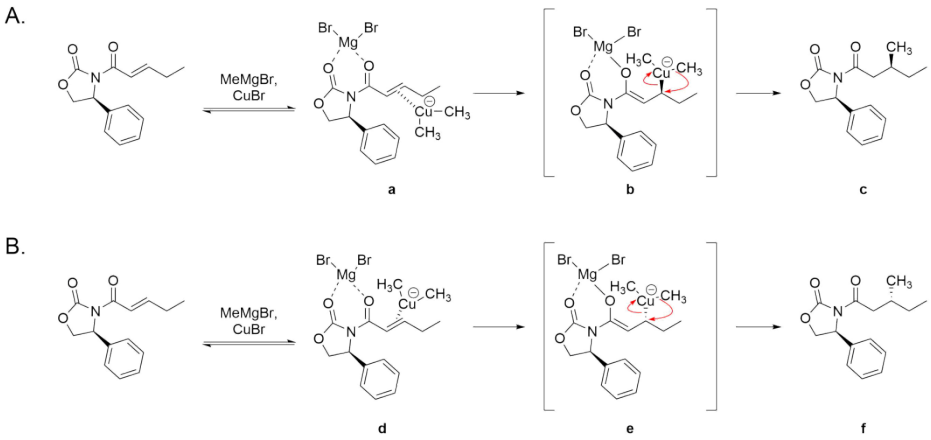


Figure 1. In organocopper conjugate addition, the methyl group adds opposite the bulky phenyl group, favoring path B over path A.

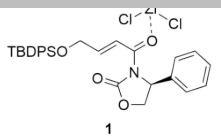
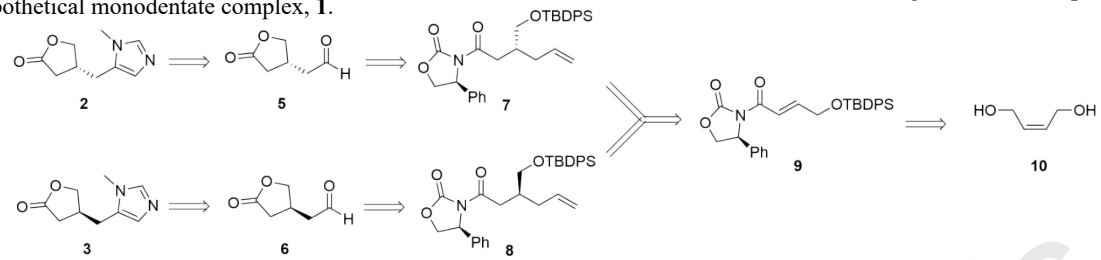


Figure 2. Hypothetical monodentate complex, **1**.



Scheme 1. Retrosynthetic analysis of (+)- and ( )-pilosinine.

In 2003, Williams and Mullins described the asymmetric conjugate addition of allyl- and crotylstannanes to Lewis acid precomplexed nonracemic α,β-unsaturated *N*-enoyl-1,3-oxazolidinones.[18] These studies revealed a curious reversal in stereochemical outcome when compared to the well-known conjugate additions of organocopper reagents to these same systems. While one could imagine that this reversal of selectivity arises from monodentate chelation to give complex **1**, unpublished work has provided little concrete evidence of any mechanistic pathway (**Figure 2**). Regardless, the conjugate addition of allyl- and crotylstannanes[19] and silanes[20] has since been utilized in the synthesis of several natural products.

The stereocontrol of chiral auxiliaries is indisputable. However, one limitation is that each enantiomeric substrate typically yields only one diastereomeric product. For example, if the opposite stereocenter is desired, a synthetic route would need to be altered utilizing the opposite enantiomer of the chiral auxiliary. The stereodivergence exhibited by reaction of nonracemic α,β-unsaturated *N*-enoyl-1,3-oxazolidinones with organocopper or allylstannane reagents provides the opportunity to produce enantiomeric products from a single substrate. This work highlights the potential of these complementary methods in the total synthesis of (+)-pilosinine (**2**) and the formal syntheses of ( )-pilosinine (**3**) and (+)-pilocarpine (**4**) (**Figure 3**).

Pilocarpine (**4**) was isolated from the plant species *Pilocarpus jaborandi* in 1875.[21] Since its discovery, it has been used as a common treatment for glaucoma by reducing intraocular pressure.[22,23] In recent years, research has evaluated the use of pilocarpine as a method for early detection of Alzheimer's through the observation of corneal constriction.[24] Due to its medicinal

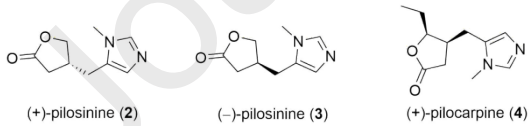


Figure 3. Structures of (+)-, ( )-pilosinine, and (+)-pilocarpine.

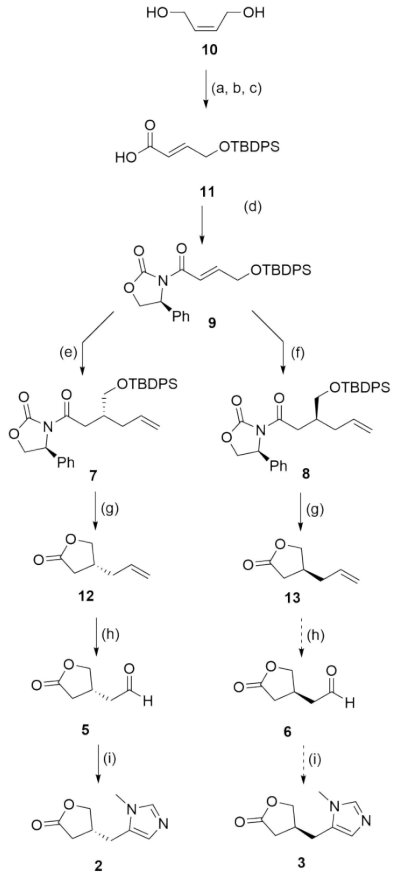
application, pilocarpine has drawn the attention of various groups as a promising target for total synthesis, with notable syntheses from the Rapoport, Büchi, Lu, and Davies groups.[25-30] In particular, the imidazole formation in the Büchi synthesis inspired the final step in the synthesis described herein.

This project sought to address two shortcomings of previous syntheses: 1) to develop a concise, enantioselective route to both enantiomers from a common starting material and 2) to fully characterize (+)-pilosinine using spectroscopic methods, which to our surprise has yet to be disclosed. As described above, we sought to leverage the stereodivergence enabled by the choice of key stereocenter in the natural product. Starting with (*S*)-*N*-enoyl-4-phenyl-1,3-oxazolidinone, the use of allylstannane and a Lewis acid would deliver (+)-pilosinine, while the use of an organocopper reagent would ultimately deliver ( )-pilosinine. Formation of the imidazole ring in a final step was chosen to hopefully increase the overall yield of (+)-pilosinine (**2**) compared to previous synthetic efforts.

Results and Discussion

Retrosynthetically, (+)-pilosinine (**2**) and ( )-pilosinine (**3**) can be formed by a cycloaddition-elimination reaction with the homopilosinic aldehydes **5** and **6** (**Scheme 1**). These aldehydes can be envisioned through lactonization of **7** and **8** mediated by silyl deprotection and followed by ozonolysis. The key intermediates **7** and **8** can both be formed via the stereodivergent conjugate addition reactions of **9**. Finally, **9** is prepared via a three step sequence beginning with the commercially available diol **10**.

In the forward direction (**Scheme 2**), *cis*-2-butene-1,4-diol undergoes monoprotection with *tert*-butyldiphenylsilyl chloride to afford (*Z*)-4-((*tert*-butyldiphenylsilyl)oxy)but-2-en-1-ol in 64% yield. Monoprotection was assured by employing *n*BuLi (1 equiv)



Scheme 2. Stereodivergent synthesis of ( )- and (+)-pilosinine. *Reagents and conditions*: (a) *n*-BuLi, TBDPSCl, THF, 0°C; (b) SO_3-pyridine, Et_3N, DMSO, DCM, 25°C 3h; (c) NaO_2Cl, NaH_2PO_4, 2-methyl-2-butene, acetone, 25°C, 18 h; (d) Et_3N and PivCl then LiCl, (*S*)-(+)-4-phenyl-2-oxazolidinone, THF, 18h; (e) $ZrCl_4$, allyltributyltin, DCM, 78°C to 20°C, 18h; (f) CuBr·DMS, allymagnesium bromide, THF, 78°C to 20°C, 18h; (g) TBAF, THF, 25°C, 18h; (h) O_3/PPh_3, DCM, 25°C, 18h; (i) CH_3NH_2, K_2CO_3, THF, 40°C, 18h followed by Et_3N, TosMIC, 25°C, 7 days.

in THF to deprotonate the diol. Subsequent two-step oxidation of the monoprotected alcohol provides carboxylic acid **11** in 88% yield. Activation of **11** sets the stage for nucleophilic addition of (*S*)-(+)-4-phenyl-2-oxazolidinone to furnish the oxazolidinone **9** in 95% yield.

At this point in the synthesis, the two enantiomers diverge in the conjugate addition step. To access (+)-pilosinine, **9** undergoes an asymmetric 1,4-conjugate addition with allylstannane in the presence of zirconium chloride to give **7** in 90% yield and 10:1 d.r. (**Scheme 2**). Deprotection of **7** with TBAF resulted in intramolecular ring closure to afford lactone **12** in 98% yield. Lactone **12** is then subjected to ozonoylsis to provide the homopilosinic aldehyde **5** in 99% yield. Finally, **5** is treated with methylamine in the presence of potassium carbonate to form the precursor imine *in situ*, followed by imidazole formation upon treatment with TosMIC to furnish (+)-pilosinine (**2**) in 55% yield.

Alternatively, to access ( )-pilosinine, **9** is subjected to allylmagnesium bromide in the presence of copper (I) bromide-dimethyl sulfide complex to deliver **8** (**Scheme 2**) as the major diastereomer (confirmed by ^{1}H NMR) in 79% yield. Deprotection of **8** with TBAF once again resulted in intramolecular ring closure to afford lactone **13** in 95% yield. Based on the reactions described above for the synthesis of (+)-pilosinine, the preparation of lactone **13** represents a formal synthesis of ( )-pilosinine.

Conclusion

In conclusion, using stereodivergent conjugate addition reactions, we have completed the total synthesis of (+)-pilosinine in 7 steps and 26% overall yield, and by extension, a formal synthesis of ( )-pilosinine. This work conclusively demonstrates the ability to utilize the reversal of selectivity observed in allylstannane conjugate addition reactions for synthesis of enantiomeric products using a single chiral auxiliary. Furthermore, this approach enables access to different stereoisomers without altering the overall synthetic route and permits the expeditious production of analogs from a common precursor**.**

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Supplementary Material

Supplementary material for this article, including experimental design and spectral analysis, can be found online at <insert link>.

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☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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a Stereodivergent Conjugate Addition Strategy

- Chiral auxiliary controlled 1,4-conjugate addition of an allylstannane
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- Divergent stereochemical outcomes from the same chiral auxiliary
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