Pure & Appl. Chem., Vol. 69, No. 3, pp. 477–481, 1997.
Printed in Great Britain.

Asymmetric synthesis and synthetic utility of 2,3-dihydro-4-pyridones

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Abstract: Nucleophilic addition of organometallics to chiral 1-acylpyridinium salts occurs with high diastereoselectivity to give *N*-acyl-2,3-dihydro-4-pyridones, which are useful building blocks for the asymmetric synthesis of various alkaloids. The synthetic utility of these heterocycles lies in the ease of preparation and substitution. Our recent efforts at exploring the scope of this chemistry and its application towards the enantioselective synthesis of various alkaloids are described.

Dihydropyridones of the type **1** are interesting heterocycles and attractive building blocks for alkaloid synthesis (Fig. 1). The enone moiety within **1** can be utilized as a Michael acceptor (1), or 1,2-addition to the enone carbonyl can be effected by choosing the proper conditions (2). The C-5 position of the heterocycle is susceptible to electrophilic substitution (3a), and alkylation at C-3 can be carried out via the enolate (3b). Due to $A^{(1,3)}$ strain, the C-2 substituent of **1** is forced axial, providing a conformational bias in the molecule (4). This conformational bias can be used to control the stereochemical outcome of 1,2- and 1,4-additions to the enone as well as alkylations at C-3. In addition to these synthetically useful properties, *N*-acyldihydropyridones **1** are readily prepared in one step by the addition of organometallics to 1-acyl salts of 4-methoxypyridine (1a). We have reported that dihydropyridones **1** are useful intermediates for the stereoselective preparation of several racemic alkaloids (5). Recently, we enhanced

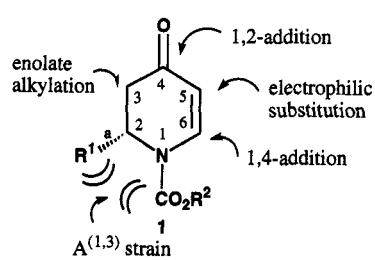
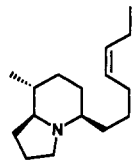


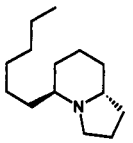
Fig. 1 The versatile *N*-Acyl-2,3-dihydro-4-pyridones

the scope of this chemistry by describing a method for preparing heterocycles **1** enantiomerically pure by the addition of Grignard reagents (6) or metallo enolates (7) to homochiral 1-acylpyridinium salts. This asymmetric modification has been useful for the enantioselective preparation of various alkaloids (6).

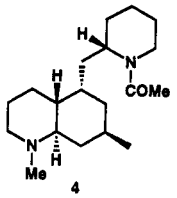
We now report our latest efforts at expanding the scope of the synthetic utility of homochiral heterocycles **1**. Concise asymmetric syntheses of (-)-indolizidine 235B **2**, and indolizidine 209D **3**, and progress towards (-)-phlegmarine **4** are discussed.



2
(-)-indolizidine 235B



3
(+)-indolizidine 209D

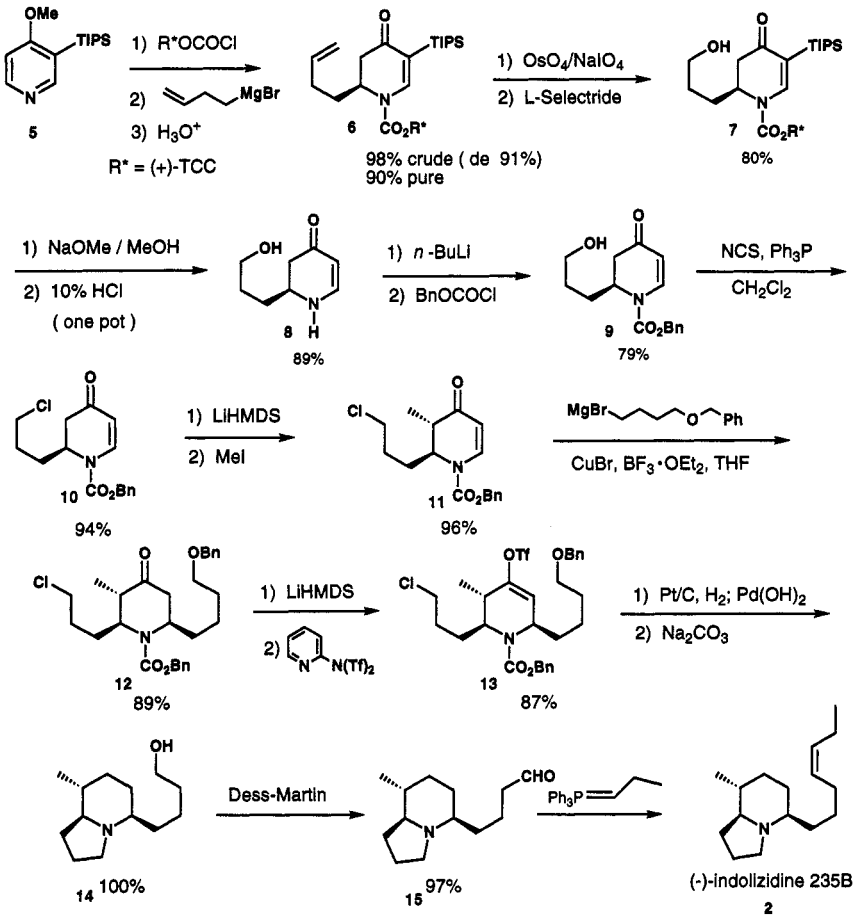


4
(-)-N_α-acetyl-N_β-methyl-phlegmarine

Synthesis of (-)-Indolizidine 235B

The utility of enantiopure dihydropyridones **1** as chiral building blocks is exhibited in a highly stereocontrolled synthesis of (-)-indolizidine 235B, an alkaloid extracted from the skins of neotropical poison-dart frogs (8). The key steps of the synthesis shown in Scheme 1 are the asymmetric formation of dihydropyridone **6** in high de, the stereoselective incorporation of the C-3 methyl group of **11**, formation of the last stereocenter at C-6 of **12** through a highly stereocontrolled 1,4-addition reaction, and the one-pot conversion of vinyl triflate **13** to indolizidine **14** in quantitative yield. This eleven-step asymmetric synthesis of **2** is the shortest and most stereoselective to date (8).

Scheme 1

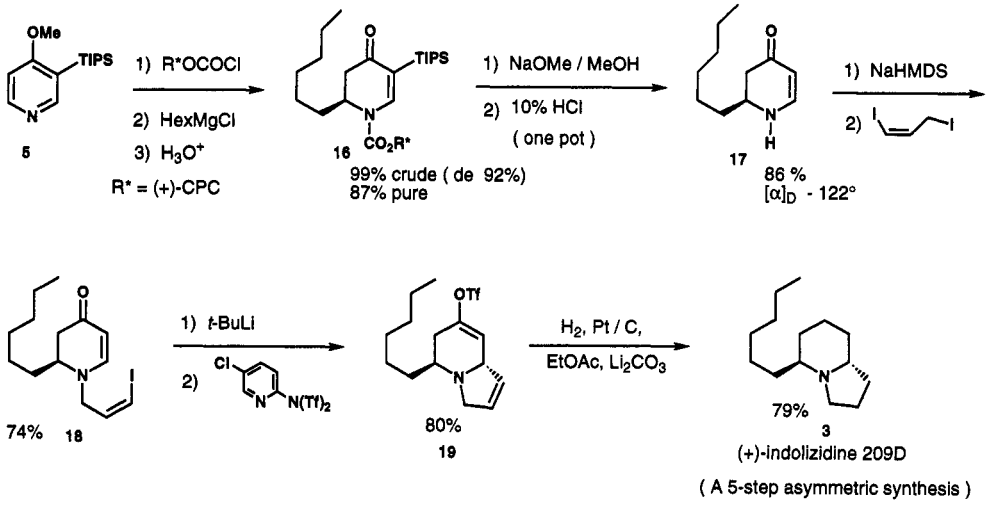


Synthesis of (+)-Indolizidine 209D

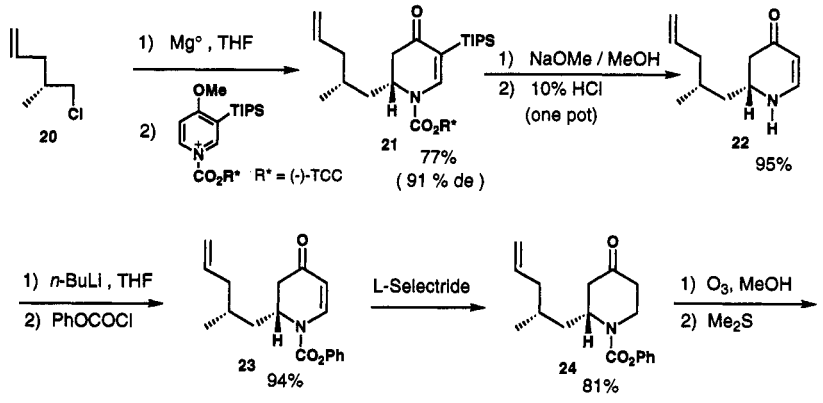
A related poison-dart frog alkaloid, indolizidine 209D **3**, was synthesized in an asymmetric fashion using only five synthetic steps as shown in Scheme 2. The dihydropyridone **16** was prepared in high yield

using our chiral 1-acylpyridinium salt chemistry (6). Removal of the chiral auxiliary (95% recovery) and the C-5 TIPS group gave **17** via a one-pot reaction. Alkylation of the deprotonated **17** with (Z)-1,3-diiodopropene provided vinyl iodide **18.** Addition of *tert*-butyllithium effected lithium-halogen exchange and subsequent anionic cyclization. The intermediate ketone enolate was trapped with *N*-(5-chloro-2-pyridyl)triflimide (9) to give a high yield of vinyl triflate **19.** The anionic cyclization occurred with complete trans stereoselectivity. Catalytic hydrogenation of **19** completed the highly stereocontrolled, 5-step, asymmetric synthesis of (+)-indolizidine 209D **3.** The overall yield was 35%.

Scheme 2

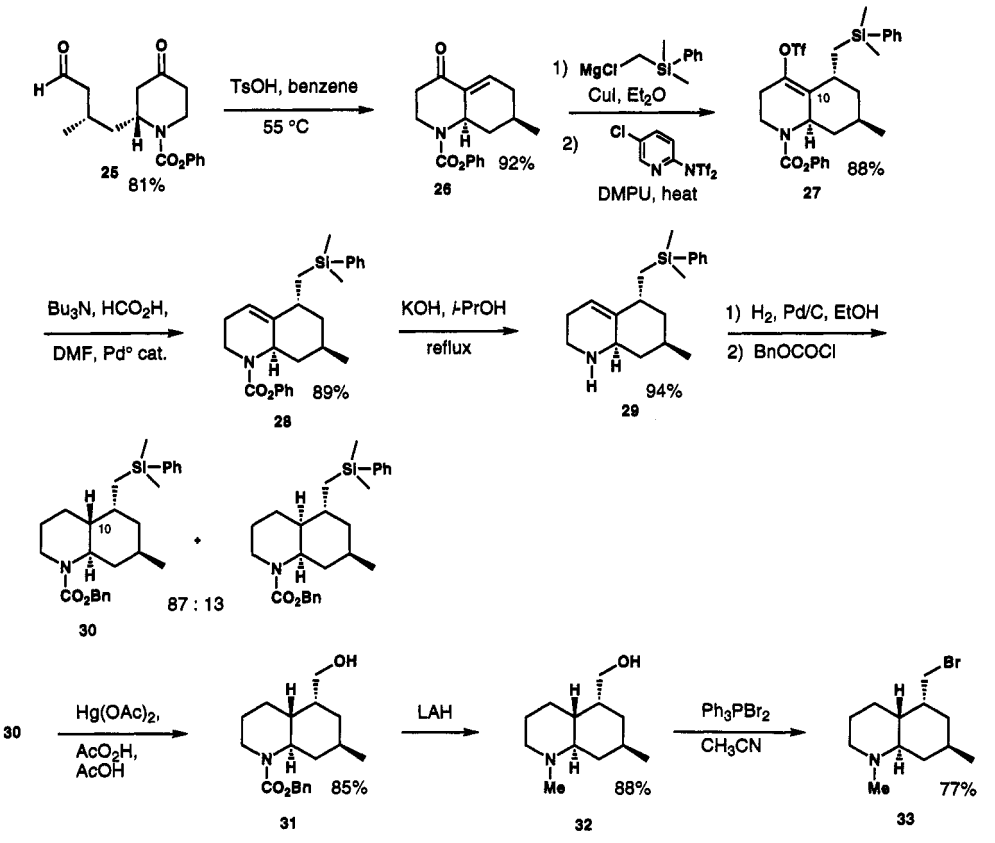


Scheme 3



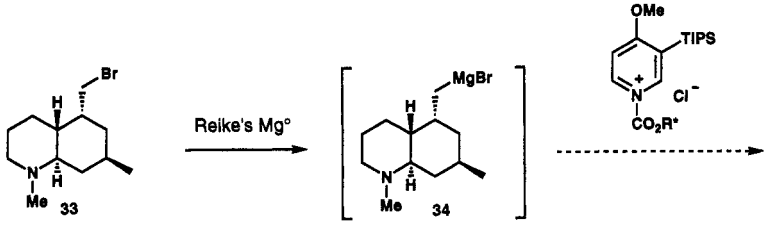
Progress Towards the Asymmetric Synthesis of Phlegmarine 4

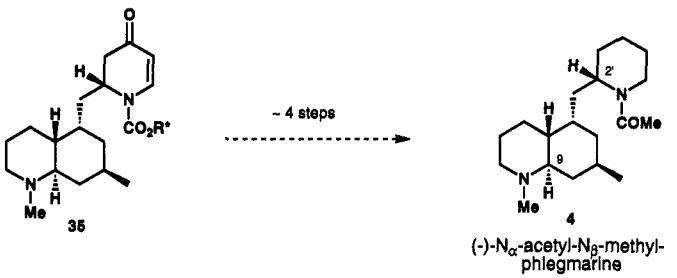
Phlegmarine **4** is a *Lycopodium* alkaloid isolated from *Lycopodium clavatum* by Nyembo and co-workers (10). The relative stereochemistry of **4** was defined by MacLean's racemic synthesis (11). Using a 2,3-dihydro-4-pyridone as a chiral building block, we have made considerable progress towards the first asymmetric synthesis of a phlegmarine alkaloid. The molecule was attractive as a target as the two stereogenic centers at C-9 and C-2' could both potentially be introduced using our chiral 1-acylpyridinium salt chemistry. Our progress towards **4** is outlined in Scheme 3.



The starting enantiopure dihydropyridone **23** was prepared in three steps from homochiral alkyl chloride **20.** Selective 1,4-reduction of the enone was carried out using L-Selectride® to give ketone **24.** Oxidative cleavage of the terminal alkene gave aldehyde **25,** which on acid-catalyzed cyclization afforded enone **26** in high yield. A copper-mediated 1,4-addition of (dimethylphenylsilyl)methylmagnesium chloride to **26** gave the desired enolate *in situ,* which was trapped as the vinyl triflate **27** (12). The stereochemistry at C-10 was to be set via catalytic hydrogenation. The stereochemical outcome of this reduction was very dependent on conformational and substituent effects. Good results were obtained by converting **27** to amine **29,** then reducing the olefin stereoselectively to provide carbamate **30.** The key intermediate **33** was prepared from **30** in high yield through a three-step process. The anticipated finale is depicted in Scheme **4,** and efforts following this approach are ongoing in our laboratories.

Scheme 4





ACKNOWLEDGEMENTS

We are grateful to the National Institutes of Health (GM 34442) for support of this research. The author wishes to express sincere appreciation to his former graduate students, postdoctoral associates and undergraduates for their dedication, friendship and contributions to this work.

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