Synthesis of (+)-Kuraramine

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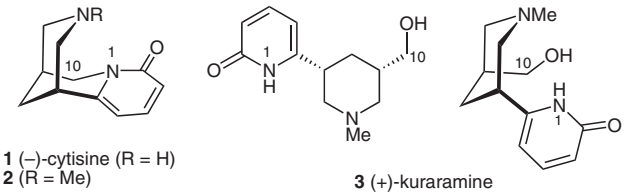
Abstract: The first synthesis of (+)-kuraramine via oxidative cleavage of (–)-*N*-methylcytisine is reported. An alternative but unsuccessful approach to (+)-kuraramine is also described based on extending an intramolecular enolate addition protocol that had previously been applied successfully to cytisine.

Key words: cytisine, kuraramine, alkaloids

The lupin alkaloids constitute an important class of pharmacologically active quinolizidine and piperidine-based molecules, the best known of which is (–)-cytisine (**1**, Figure 1)[1] which is an important partial agonist at neuronal nicotinic acetylcholine receptors.[2,3]



1 (–)-cytisine (R = H)
2 (R = Me)

3 (+)-kuraramine

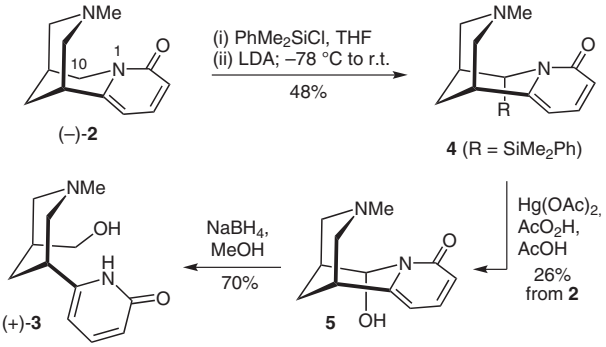
Figure 1

N-Methylcytisine (**2**, and other N-substituted variants) are also known,[4] as are simple monocyclic piperidines such as (+)-kuraramine (**3**), which was isolated by Murakoshi and co-workers from *Sophora flavescens*.[5] The structural (and possible biosynthetic) relationship between **2** and **3**, which involves cleavage of the N(1)–C(10) linkage of **2**, is illustrated above.

The synthesis of (–)-kuraramine (the unnatural enantiomer) was reported recently by Honda,[6] and although the strategy used also provided access to the corresponding *trans* diastereomer [(–)-isokuraramine], these *cis*/*trans* isomers were not available selectively. In this paper we describe two approaches to (+)-kuraramine, one of which represents a biomimetic approach and the other, which represents an extension of our earlier strategy for lupin alkaloids, failed to give **3**, but demonstrates further the scope and limitations of this earlier work.

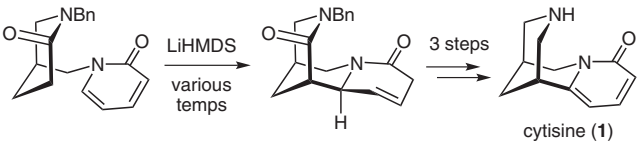
N-Methylcytisine (**2**) provides an obvious precursor to **3** and key to utilizing this substrate as a precursor is the ability to functionalize **2** at C(10) in such a way that allows cleavage of N(1)–C(10). Rouden[7] has shown that *N*-acylcytisine derivatives undergo a N-to-C isomerization in a process that is proposed to involve lithiation at C(10) and acyl-group transfer from nitrogen. This chemistry has been extended to provide a general method for the regio- and diastereoselective C(10) functionalization of cytisine and this, in turn, has provided novel pharmacologically interesting cytisine derivatives.[8]

The synthesis of (+)-kuraramine (**3**) from (–)-*N*-methylcytisine (**2**) is shown in Scheme 1. In situ silylation of **2** was achieved by lithiation (using LDA) in the presence of $PhMe_2SiCl$ to give the silylated adduct **4** in 48% yield as a single diastereomer. ^1H NMR studies (NOE and *J* values)[9] indicated the C(10) stereochemistry shown in Scheme 1, which is consistent with that described by Rouden and corresponds to the thermodynamically more stable orientation at C(10). Fleming–Tamao oxidation[10] of **4** followed by reduction of carbinol **5**[11] gave (+)-**3** {$[\alpha]_D^{20}$ +9.5 (*c* 2.1, EtOH); lit.[5] $[\alpha]_D^{29}$ +8.4 (*c* 0.52, EtOH)} in 18% overall yield from **2**.



Scheme 1 Synthesis (+)-kuraramine (**3**) from (–)-*N*-methylcytisine (**2**)

A second approach to (+)-kuraramine (**3**) has also been evaluated, and this is based on the intramolecular 1,6-addition of a lactam enolate to a pyridone. This has been successfully applied to the synthesis of cytisine (**1**, Scheme 2) as well as cytisine analogues and other lupin alkaloids.[12]



Scheme 2 Lactam enolate approach to cytisine (**1**)[12]

Application of this enolate-addition strategy to kuraramine is outlined in Scheme 3, and we targeted an

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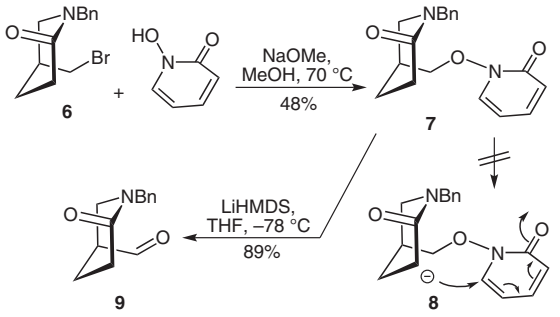
intermediate based on *N*-hydroxypyridone. O-Alkylation of *N*-hydroxypyridone with the piperidinone bromide **6** gave lactam **7**. Exposure of this intermediate to the enolization and cyclization conditions that had been developed for cytisine (**1**) failed to give the desired adduct; see reaction pathway illustrated with enolate **8**. Instead a clean fragmentation was observed to give aldehyde **9**[13] in 89% yield.

This chemistry is interesting in terms of its relationship to the transformations shown in Scheme 1 and the earlier work of Rouden[7,8a] and others[14] involving (presumably) carbonyl-directed metalation of an *N*-alkyl pyridone. This directing effect is powerful but the cyclization pathway outlined within structure **8** also involves formation of a seven-membered ring, which represents a larger ring than we had previously achieved with this cyclization protocol. In that sense, a feasible explanation is that (as might be expected) lactam enolization does occur but the desired ring closure (see **8**) is slow compared to (feasibly intramolecular) proton abstraction associated with the lactam enolate derived from **7** which triggers the elimination step that provides aldehyde **9**.



Scheme 3 Lactam enolate addition approach to (+)-kuraramine (**3**)

In summary, the first synthesis of (+)-kuraramine (**3**) has been accomplished via a biomimetic transformation of *N*-methylcytisine (**2**).[15] The ability to cleave *N*-methylcytisine (and the same chemistry works as efficiently with *N*-benzylcytisine) opens an entry to a range of substituted piperidines in a stereocontrolled fashion, that are, based on earlier work in this area, not trivial to access.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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References and Notes

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(9) For silane **4**, the key NMR signals [^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.34 (1 H, d, *J* = 1.0 Hz, H10) and ^{13}C NMR (126 MHz, $CDCl_3$): δ = 54.2 (C10)] showed the presence of a single diastereomer. The small coupling constant (*J* = 1.0 Hz) suggested an equatorial–equatorial coupling between H9 and H10. The equatorial assignment of H10 was further supported by NOE data: irradiation of H10 showed enhancements of H9, H11 and $SiCH_3$, while irradiation of $H8_{ax}$ and $H8_{eq}$ showed no enhancement associated with H10.
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(15) Supporting Information (as a pdf) is available with this paper and contains full experimental details of all compounds reported and copies of spectra, including NOE experiments.