Fully Substituted Carbon Centers by Diastereoselective Spirocyclization: Stereoselective Synthesis of (+)-Lepadiformine C

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Abstract: Reductive lithiation of *N*-Boc α-amino nitriles generated α-amino alkyllithium reagents with unexpected selectivity. The intermediate radical prefers to align with the nitrogen lone pair, and this interaction leads to an $A_{1,3}$-strain effect that biases the conformation of the radical. In cyclohexane rings with α-substituents the net effect is an inversion of configuration on reductive lithiation. In the presence of a tethered electrophile the alkyllithium cyclizes to produce a spiro compound, again with inversion of configuration. The overall result is retention of configuration in the cyclization reaction. The same overall selectivity is found with α-oxygen alkyllithium cyclizations, but in this case both steps proceed with retention. The difference can be explained by careful consideration of the intermediate geometries. The α-amino spirocyclization was utilized in a concise and stereoselective synthesis of lepadiformine C.

Stereoselective construction of fully substituted carbon atoms is a challenge that is often at the heart of a successful complex natural product synthesis. Several years ago we reported a synthesis of spirocycles that was based on stereoselective generation of alkyllithium reagents arising from anomeric stabilization of radical intermediates.[1,2] Herein we describe studies on the generation of α-hetero alkyllithium reagents where classic anomeric stabilization is not relevant, but that still show highly stereoselective transformations. This new stereoselective strategy leads to fully substituted carbon atoms and is illustrated with a concise synthesis of lepadiformine C.[3]

Reduction of *N*-protected α-amino nitriles with Freeman's reagent (LiDBB)[4] is an effective strategy to generate tertiary α-amino alkyllithium reagents.[5] An *N*-alkyl 2-cyano piperidine generally leads to the alkyllithium with high selectivity, but when the nitrogen atom is protected as a Boc carbamate the alkyllithium is produced as a 1.5:1 mixture of isomers.[6] The reductive lithiation of *N*-Boc piperidine **1** in Scheme 1 was investigated to probe the reactivity of the Boc-protected α-amino alkyllithium reagent. Although the lithiation is not stereoselective, both alkyllithium isomers cyclize effectively at −78 °C to produce the bicycle **2** in excellent yield. These tertiary *N*-Boc α-amino alkyllithium reagents are expected to be conformationally stable at −78 °C, with inversion barriers of ca. 20 kcal/mol.[7] This experiment demonstrated that tertiary *N*-Boc alkyllithium reagents may cyclize with retention (SE$_{ret}$) or inversion (SE$_{inv}$) and that suitably constrained systems can produce single isomers in high yields.[8,9]

The spirocyclizations of nitriles **3** and **5** were highly stereoselective. Both cyclizations proceed with overall retention at the fully substituted center,[10] and the heteroatom ends up in the equatorial position. The rationale for the selectivity is not obvious, but the transformation could be useful in synthesis.

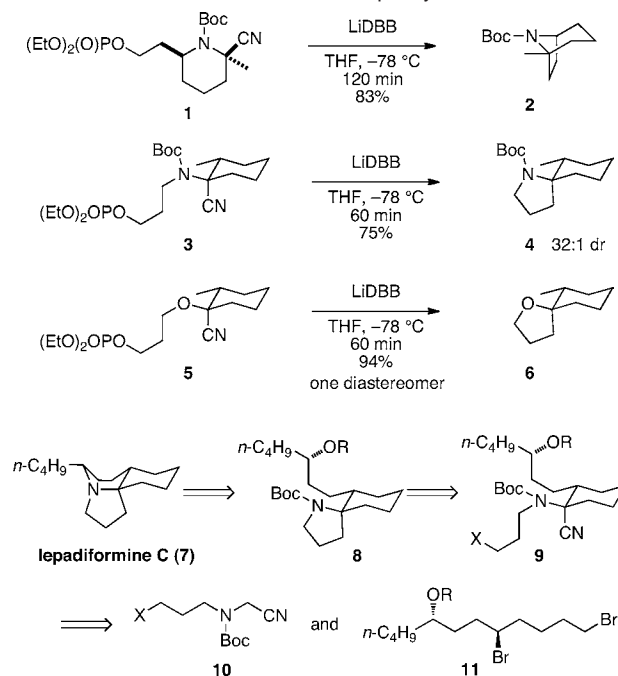**Scheme 1.** Stereoselective Reductive Spirocyclizations

Figure 1. Synthetic analysis of lepadiformine C.

Lepadiformine C is an alkaloid isolated from the tunicate *Clavelina moluccensis* along with lepadiformine B.[3] These alkaloids have an effect on the cardiovascular system and block the cardiac inward rectifying K$^+$ channel. Lepadiformine C is the simplest of the alkaloids in this class[11] and appears to be a suitable synthetic target for the spirocyclization reaction described above. Our synthetic analysis is shown in Figure 1. Reductive lithiation and cyclization of nitrile **9** would generate the spirocycle **8**. Compound **9** could arise from a Strecker reaction of the corresponding cyclohexanone, but preliminary investigation suggested that the equilibrium was unfavorable.[12] A more interesting approach would generate the cyclohexane ring by sequential alkylation[2a,d,13] of amino nitrile **10** with a dibromide **11**. This strategy rapidly introduces all three rings from acyclic precursors.

The synthesis of lepadiformine C is presented in Scheme 2. The known optically pure alcohol **12**[14,15] was coupled with 5-((*tert*-butyldimethylsilyl)oxy)pentanal (**13**) and oxidized to generate ketone **14**. Enantioselective reduction of the propargyl ketone using Noyori's method,[15] hydrogenation, deprotection, and bromination produced the dibromide **16** in good overall yield. The assembly of the ring system began with alkylation of amino nitrile **17** with dibromide **16**. The two reagents were combined and treated with an LDA solution in portions until no more of the monoalkylated product was visible by TLC analysis. Cyclohexane **18** was isolated

Scheme 2. Synthesis of Lepadiformine C

Scheme 3. Stereoselective Reductive Lithiation and Protonation Control Experiments
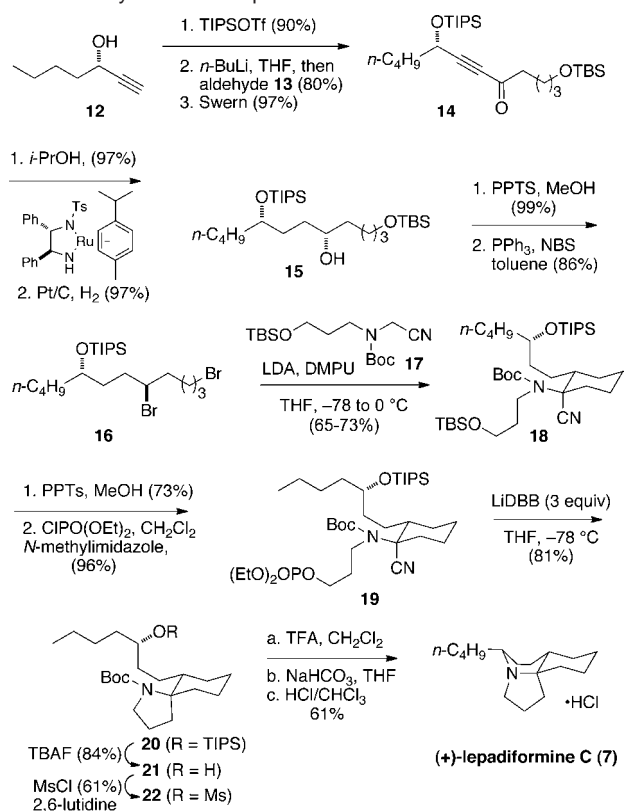
as a single isomer with the nitrile in the axial position.[16] The TBS ether was exchanged for a diethylphosphate leaving group, and subsequent reduction of phosphate **19** with Freeman's reagent (LiDBB)[4] produced the cyclic product as a single isomer in excellent yield. Deprotection of the TIPS group led to the crystalline alcohol **21**, and X-ray analysis confirmed the expected relative configuration of the stereogenic centers.[17] The synthesis was completed by converting the alcohol to a mesylate and removing the Boc group.[18] Upon neutralization, the amine cyclized to form the final ring of lepadiformine C, which was isolated as its hydrochloride salt. The characterization data (¹H and ¹³C NMR, HRMS, optical rotation, IR) for lepadiformine C matched that reported for the natural product.[3a] The synthesis features a rapid and stereoselective assembly of the tricyclic structure from acyclic dibromide **16** and amino nitrile **17**.

The origin of the selectivity in the reductive lithiation and cyclization of nitriles **3**, **5**, and **19** was explored (Scheme 3). All of the alkyllithium intermediates are expected to be configurationally stable under the reaction conditions.[7] The configuration of the alkyllithium intermediates was assessed by protonation, which is assumed to proceed with retention of configuration.[7b] Reductive lithiation and protonation of TBS ether **18** gave the cis disubstituted cyclohexane **26**.[19] The lithiation proceeds with an unanticipated inversion of configuration. One explanation is that the initially formed radical intermediate **23** is stabilized by interaction with the nitrogen electrons, and the resulting steric crowding of the equatorial R′ group generates a conformational isomerization to produce radical **24**.[20] Further reduction of radical **24** would produce alkyllithium **25**, which upon protonation would lead to carbamate **26**. The lithiation of nitrile **19** presumably follows the same course, with intermediate alkyllithium **27** arising from inversion of configuration. The subsequent cyclization of **27** also proceeds with clean inversion of configuration to produce spirocycle **20**. The
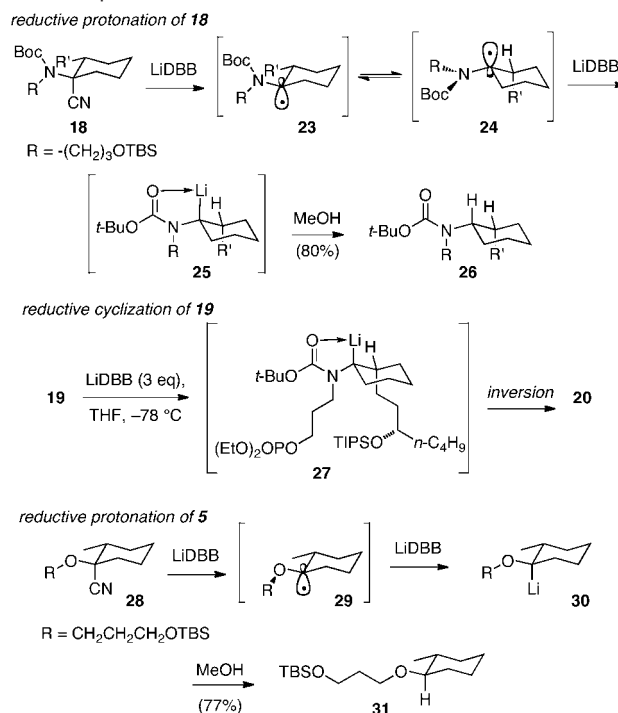
efficient cyclization of nitrile **1** to bicycle **2** demonstrates that these N-Boc alkyllithium reagents may cyclize efficiently with either retention[21] or inversion[7] of configuration. Coordination of the Boc nitrogen to the lithium atom in **27** would restrict the conformation, and the phosphate is well positioned to react from the back of the alkyllithium in an SE_{inv} pathway. The spirocyclization is highly stereoselective and proceeds through an unanticipated double inversion sequence.

The cyclization of nitrile **5** to spirocycle **6** shows the same sense of selectivity, but the underlying sequence diverges. In this case reductive lithiation of the corresponding TBS ether **28**, followed by protonation, proceeds with retention of configuration.[19,22] Presumably the axial radical **29** is stabilized by the lone pairs on the adjacent oxygen, with the alkyl substituent adopting a gauche alignment reminiscent of an exoanomeric effect. Cyclization also takes place with retention of configuration[1,23] in the reaction with nitrile **5**. The oxygen and N-Boc substrates present an interesting contrast, where superficially similar selectivities result from stereochemically complementary intermediates.

These stereoselective spirocyclization reactions provide an interesting new tool for assembling fully substituted carbon centers. In the case of lepadiformine C, the nitrile in substrate **17** facilitates two alkylation reactions followed by a stereoselective reductive lithiation and cyclization. Thus all the carbon−carbon bonds in the most highly substituted atom were assembled late in the synthesis in an effective but unconventional strategy.

Supporting Information Available: Experimental procedures for all compounds, X-ray analysis of compound **21**. and configuration assignments for compound **26** and **31** are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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