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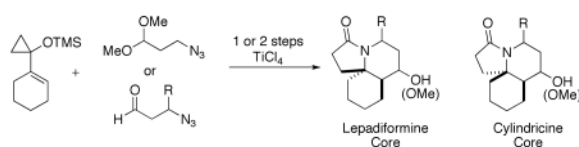
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A Tandem Prins/Schmidt Reaction Approach to Marine Alkaloids: Formal and Total Syntheses of Lepadiformines A and C

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Abstract



The tricyclic core of the cyclindricine or lepadiformine families of alkaloid natural products was assembled via a Prins addition/intramolecular Schmidt rearrangement under Lewis acid conditions. Both single-pot and two-stage variations of this process were examined, with particular attention to the stereochemical outcome of the processes. This technology has been applied to a formal total synthesis of lepadiformine A and a total synthesis of lepadiformine C.

The ocean is a fertile source of natural products, many of which are valuable due to their biological properties. The genus *Clavelina* has proven no exception, yielding a number of alkaloids that have attracted substantial synthetic interest over the past decade. Two such families are the lepadiformines and the cyclindricines (Figure 1). The cyclindricines are a large family of tricyclic compounds that were isolated by the Blackman group from *Clavelina cylindrica* found off of the coast of Tasmania.¹ At about the same time, the structurally related lepadiformines were isolated from several different species by Biard and coworkers.² Despite only a few reports of biological activity (e.g., lepadiformines A and B are inwardly rectifying K⁺ channel blockers^{2,3} and some of the cyclindricines have modest cytotoxicity¹) the members of both families have attracted a great deal of attention due to their intricate tricyclic structures.⁴ In this letter, we describe a synthetic method that allows rapid access to the tricyclic ring systems embodied by these alkaloids, a formal total synthesis of lepadiformine A,⁵ and the first total synthesis of lepadiformine C.³

One retrosynthetic analysis of cyclindricine C would entail the late-stage installation of the hydroxymethyl substituent via a lactam intermediate, a maneuver that had been utilized by the Renaud group's total synthesis of lepadiformine A (Scheme 1).⁶ Going further, one could gain access to this lactam via an intramolecular Schmidt reaction on a [5.3]spirocyclic ketone such as that shown. Although the lepadiformines lack the oxygenation associated with cyclindricine C (Figure 1), incorporating an appropriately protected alcohol at this stage of the synthesis would enable, in principle, access to analogs of both classes by deoxygenation or oxidation as appropriate. However, the preparation of the necessary [5.3]spirocyclic keto azide precursor still constitutes a considerable synthetic challenge.

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Supporting Information **Available**. Experimental procedures, characterization data, and ¹H and ¹³C NMR spectra for new compounds.

One attractive solution would be to employ the Prins-like reactivity of 1-silyloxy-1-alkylcyclopropanes introduced by Trost⁷ and later exploited by Cha's group⁸ as shown in Scheme 2. In this chemistry, cyclopropane **4**^{8,9} was treated with an acetal in the presence of Lewis acid. Conversion of the acetal to a reactive oxonium ion and attachment of **4** yields a cyclopropyl cation that undergoes ring expansion to afford a mixture of three spirocyclobutanone diastereomers, of which **5a** was predominant. Not only would this approach afford a concise entry into the appropriately functionalized ring system, but the use of Lewis acid in the key step suggested that incorporation of an azide into the starting acetal (or its equivalent) might lead directly into a subsequent Schmidt-styled ring expansion of the cyclobutanone adduct to achieve the 5,6,6-tricyclic lactam.^{10,11}

The concept was initially tested by treating **4** with azide-containing acetal **6**, which yielded three spirocyclobutanone diastereomers **7a**, **7b**, and **7c** in high combined yield (Scheme 3). The structure of the major product **7a** was based on the structure of **5a** as determined by Cha and via X-ray crystallography.^{8b} The structures of the minor products **7b** and **7c** were determined by subsequent conversion of the ketones to the corresponding lactams via intramolecular Schmidt rearrangement. Thus, treatment of **7b** with TiCl₄ cleanly afforded lactam **8b** in excellent yield, the stereochemistry of which was determined by NMR spectroscopy (see Supporting Information for details of stereochemical assignments). The stereochemistry of **7c** was obtained by chemical correlation of **8c** with alcohol **14** as prepared below. We also sought conditions by which reaction of **4** and **6** would lead directly to **8** in a single pot, but the best overall yield obtained was considerably less than that of the two-step version (35% for **4** + **6** → **8** (mixture)).

Although aldehydes were not previously reported as partners in this Prins reaction variant, we chose to examine them in the present instance, in part to avoid using a methyl ether as a protecting group.¹² Thus, reacting aldehyde **12** with **4** under optimized conditions for a one-pot sequence yielded two products, cyclobutanone **13** and lactam **14**, as single diastereomers (Scheme 5). Separate submission of **13** to a variety of Lewis acid conditions did not result in lactam formation. However, acetylation of the free hydroxyl group of **13** and subsequent treatment with TiCl₄ did generate the desired lactam **17** in high yield over the two steps. Compound **16** was also isolated from the acetylation procedure.

A crystal structure of **14** confirmed the relative stereochemistry shown, which maps onto that of the cylindricines (i.e., containing a *cis*-azadecalin ring system). The relative stereochemistry for **17** was determined by NMR and matched the core of the lepadiformines with a *trans*-azadecalin ring structure. It is interesting that the reaction pathways seem to diverge depending on the relative stereochemistry between the azide-containing side chain and the emerging cyclobutanone ring (Scheme 6). Thus, the intermediate in which the cyclobutanone carbonyl group is *cis* to the azide connector readily affords lactam **14** under these reaction conditions. In contrast, the recovery of the ketone **13** from the reaction suggests that this isomeric species is unable to undergo an intramolecular Schmidt reaction in the presence of the free alcohol group (in contrast to the successful reaction with acetylated **15**). We suggest that *in situ* hemiketal formation – the likelihood of which is supported by the isolation of **16** from the acetylation reaction shown in Scheme 5 – as one possible explanation for this divergent behavior.

The reactions of β -substituted azidoaldehydes **18** and **19** behaved analogously to **12** (Scheme 7). Thus, these reactions afforded a single diastereomer of cyclobutanone (**20** or **21**) along with three diastereomers of lactams **22a–c** or **23a–c**, respectively (ratios estimated by ¹³C NMR of the crude reaction mixture). In all isomers, the relative stereochemistry of the emerging alcohol from the Prins addition is *syn* (C-4 and C-5, cylindricine numbering imposed¹). Interestingly, unexpectedly high 1,3-*syn* ratios were observed between C-2 and C-4 (ca. 11:1 for **20** + **22a**

+ **22c**)/**22b** and 7:1 for (**21** + **23a** + **23c**)/**23b**), suggesting a reasonable level of diastereofacial selectivity in additions to aldehydes **18** and **19**.

Several of the compounds so prepared were used to gain entry into the alkaloids that inspired these studies in the first place, beginning with a formal synthesis of lepadiformine A. Thus spirocyclobutanone **20** was acetylated and then treated with TiCl_4 to afford lactam **25** in excellent yield (Scheme 8). Deprotection of the hydroxyl group, xanthate formation, and Barton–McCombie dehydroxylation¹³ furnished lactam **28**, which is a common intermediate to Renaud's synthesis of lepadiformine A.⁶

Similarly, the total synthesis of lepadiformine C (**2**) was achieved from **21** as shown in Scheme 9. Analogous acetylation, intramolecular Schmidt reaction, and Barton–McCombie dehydroxylation followed by amide reduction and amine protonation yielded lepadiformine C, **2**.

In conclusion, we have developed a route to the tricyclic cores of the cylindricine and lepadiformine families using several variations of a tandem Prins/Schmidt sequence. Using this chemistry, we achieved a formal synthesis of lepadiformine A (corresponding to 12 steps and 8% overall yield) and the first total synthesis of lepadiformine C (9 total steps and 10% overall yield). Additional work on this and related domino reaction sequences involving the intramolecular Schmidt reaction is underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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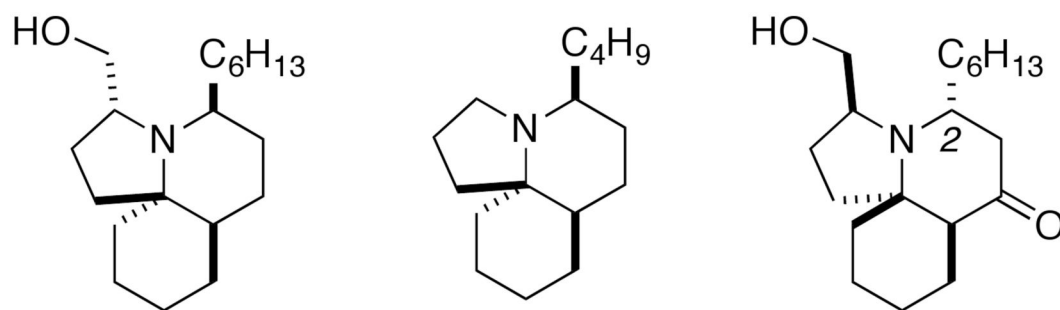
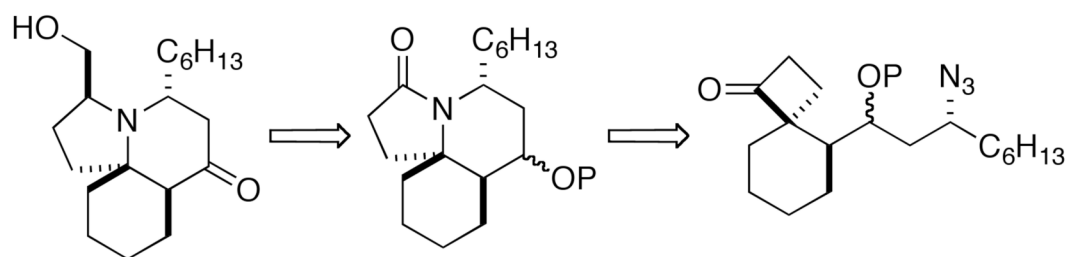
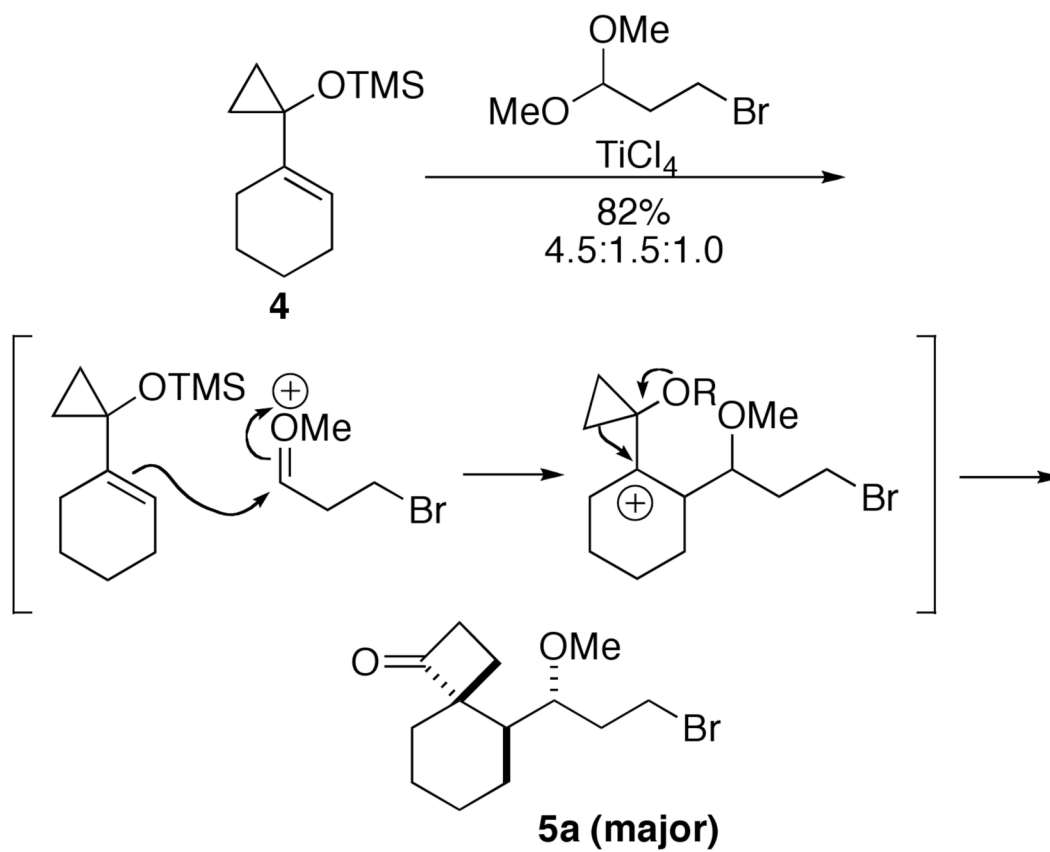


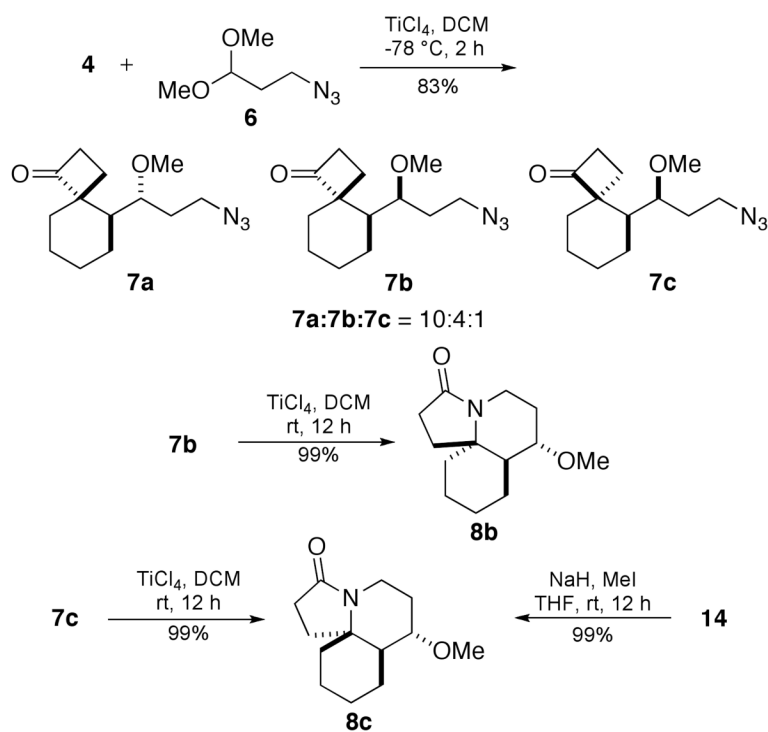
Figure 1.
Representative Structures from the Genus *Clavelina*



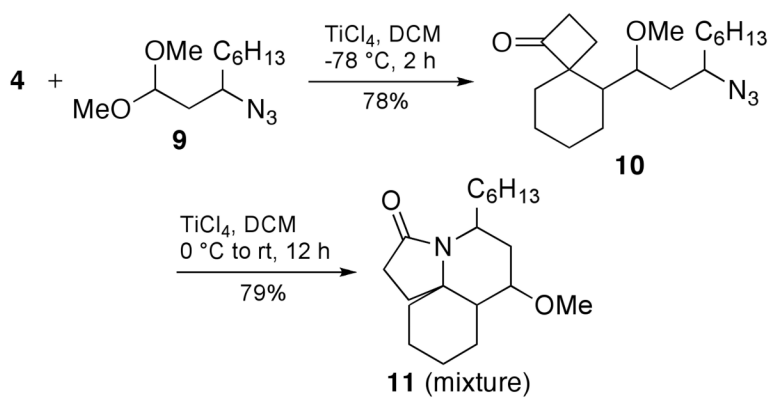
Scheme 1.
Retrosynthetic Analysis of Cylandricine C



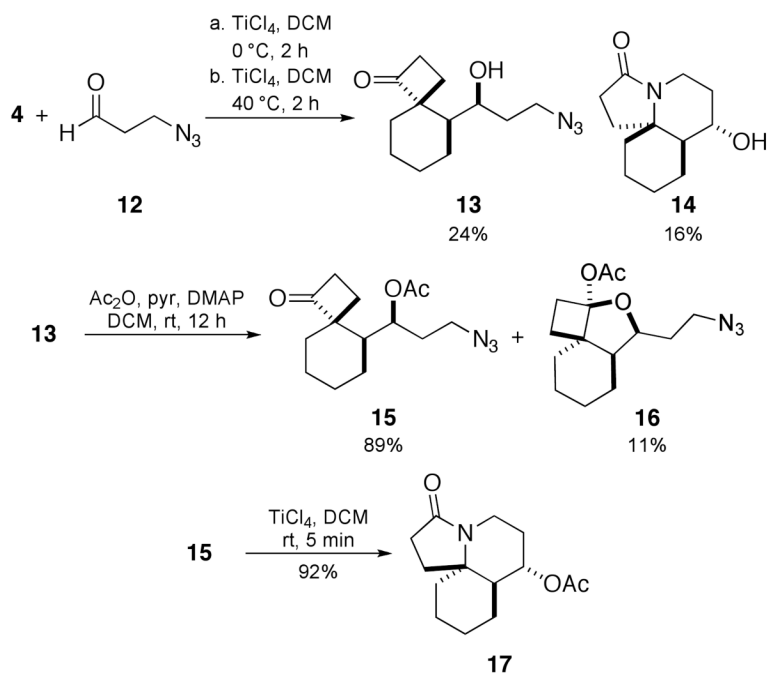
Scheme 2.
Prins Precedent^{8b}



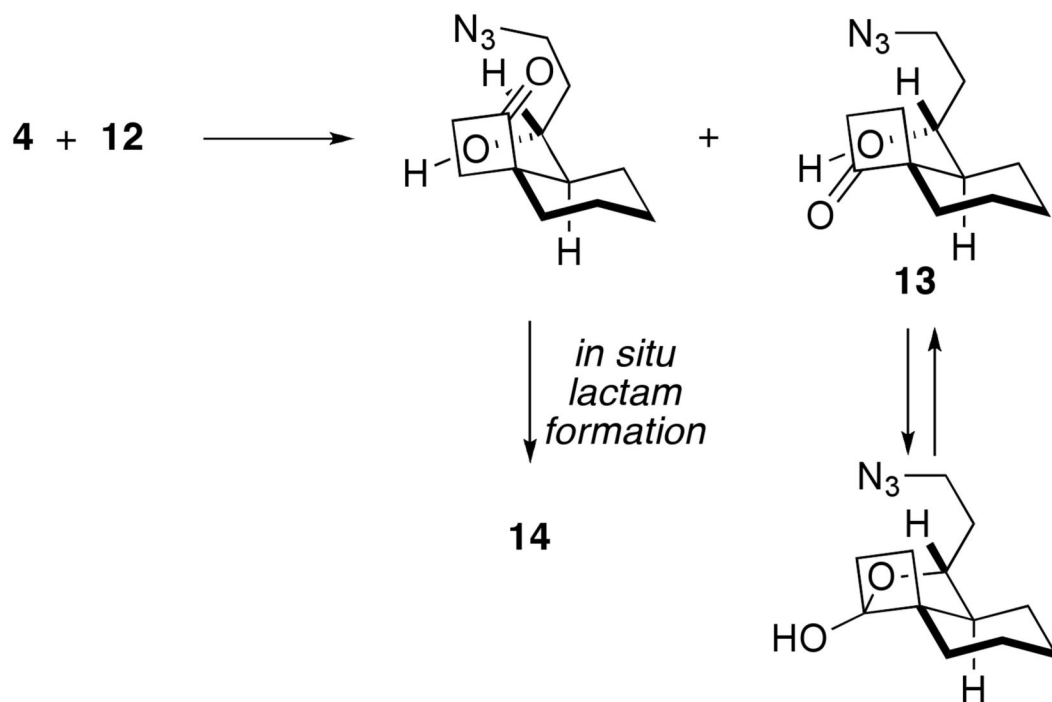
Scheme 3.
Two-Step Prins/Schmidt Reaction Sequence



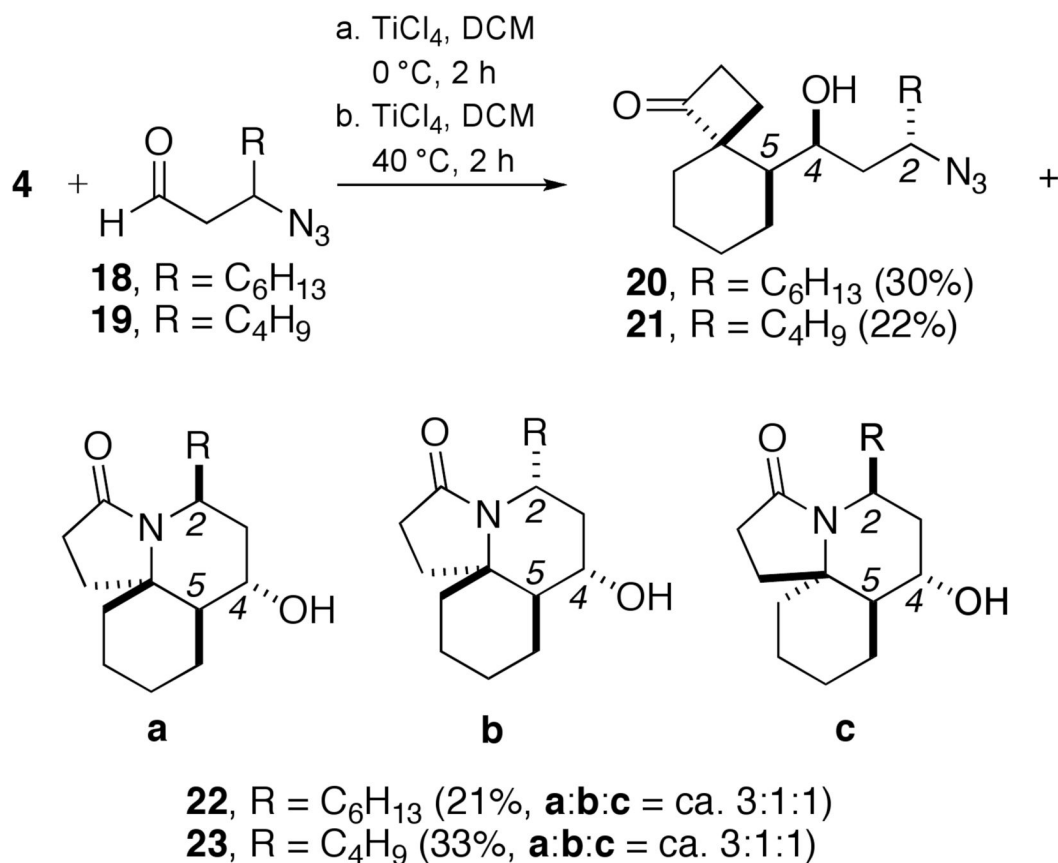
Scheme 4.
Reaction of **4** and a β -Substituted Azidoacetal

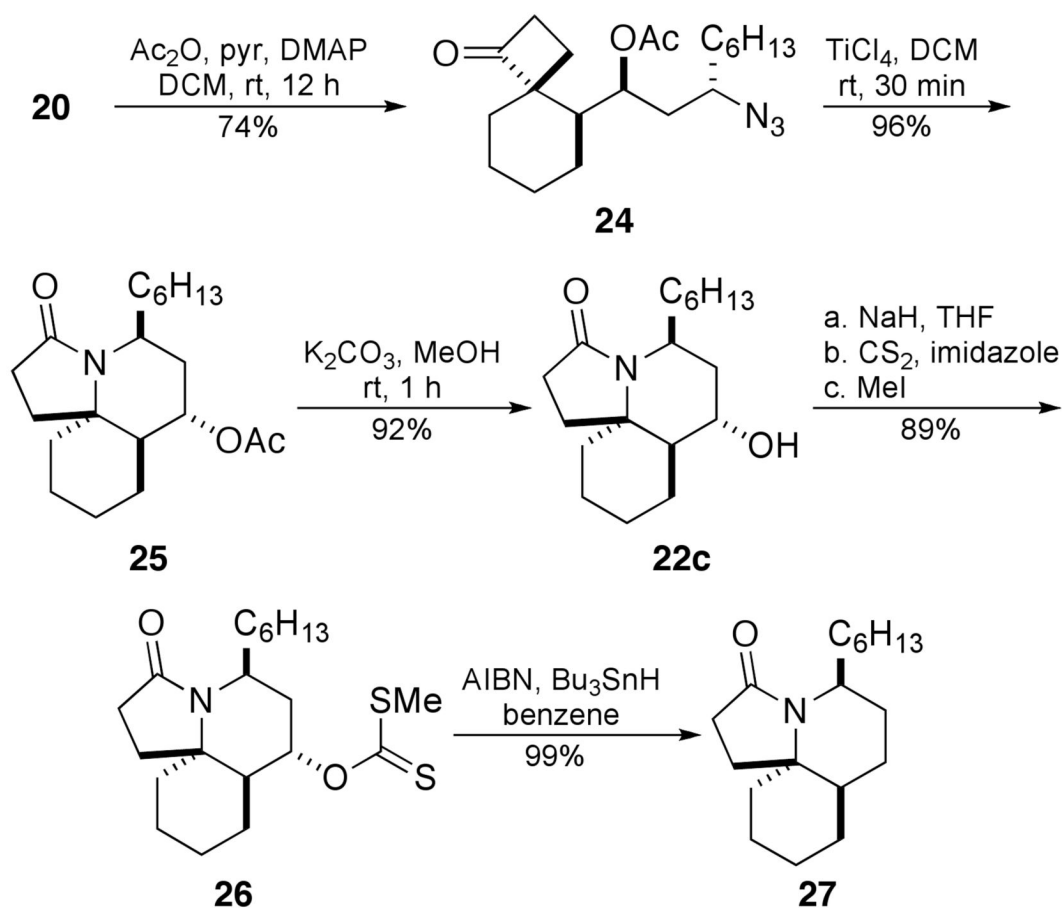


Scheme 5.
Tandem Prins/Schmidt Reaction with 3-Azidopropanal

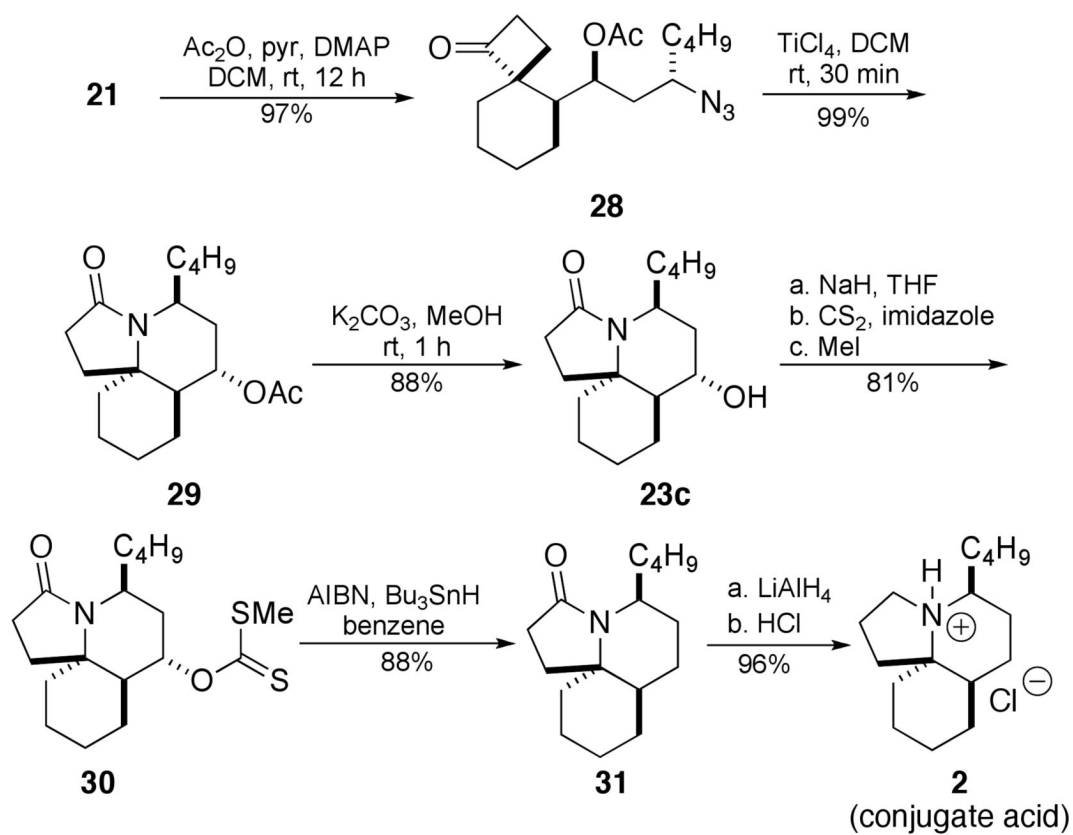


Scheme 6.
Stereochemical Effect on Reaction Products From the Tandem Reaction of **4** and **12**

**Scheme 7.**Tandem Prins/Schmidt Reaction with β -Substituted Azidoaldehydes



Scheme 8.
Formal Synthesis of Lepadiformine A



Scheme 9.
Total Synthesis of Lepadiformine C