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Divergent Cycloaddition and Ring-Closing Metathesis Approaches to Indolizidine and Pyrrolo[1,2-*a*]azepine Skeletons from a Chiral Precursor: An Expeditious Route to (–)-8-*epi*-Swainsonine Triacetate

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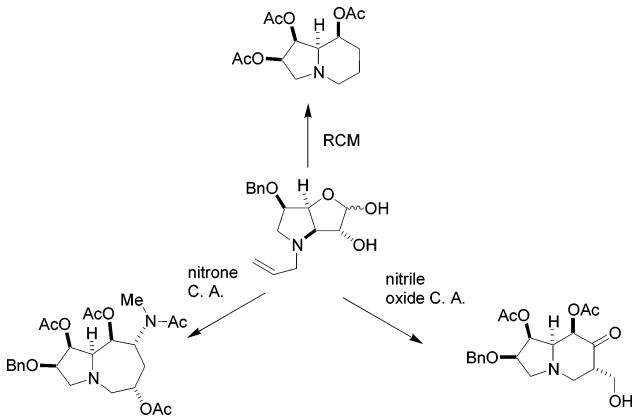
ABSTRACT



A divergent strategy for the synthesis of diverse azabicyclic ring systems has been developed in which a chiral *N*-allylpyrrolidine derivative, obtained from a carbohydrate precursor was converted to (–)-8-*epi*-swainsonine triacetate by RCM and to a pyrrolo[1,2-*a*]azepine derivative and a 3-hydroxymethyl-substituted indolizidine by *N*-allylcarbohydrate nitrone and nitrile oxide cycloadditions.

The indolizidine and the pyrrolo[1,2-*a*]azepine skeleta are present in a large number of naturally occurring azabicyclic compounds.[1,2] The well-known potent glycosidase inhibitors castanospermine and swainsonine incorporate the indolizidine nucleus **A** (Scheme 1), whereas the *Stemona* alkaloids, many of which have diverse physiological properties, incorporate the pyrrolo[1,2-*a*]azepine nucleus **C** (Scheme 1). The biological activity of these compounds, coupled with their complex structural features, have led to the development of a large number of synthetic routes to these and similar skeleta.[3] Even so, the development of new expeditious approaches that are capable of furnishing these molecules in enantiomerically pure form from a common precursor remains a worthwhile task because of the obvious advantages of using the same starting material for multiple targets. *N*- and *O*-alkenylcarbohydrate nitrone and nitrile oxide cycloadditions have provided efficient and operationally simple

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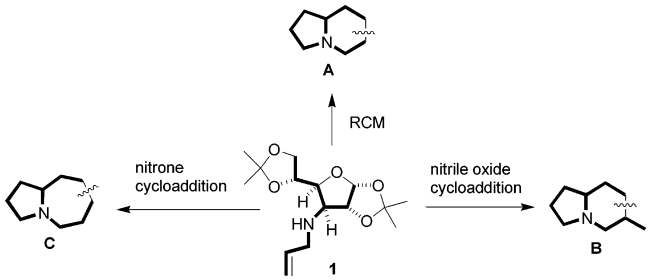
Scheme 1. Divergent Approaches to Indolizidine and Pyrrolo[1,2-*a*]azepine Ring Systems from a Common Precursor



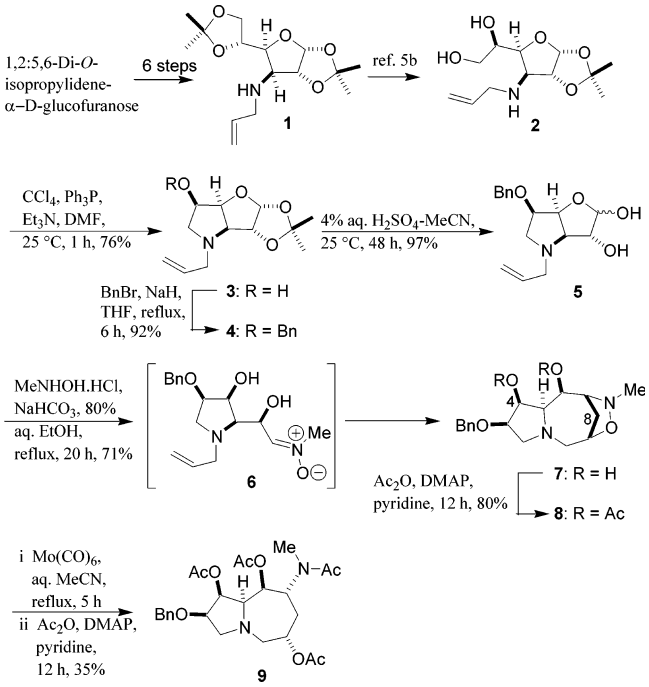
routes to many enantiopure cyclic amines and ether derivatives.[4] In this regard, we recently reported the formation of various six- and seven-membered nitrogen heterocycles by the cycloaddition of nitrones generated from *N*-allyl carbohydrate derivatives.[5] We envisaged our application of the aforementioned cycloadditions, as well as ring-closing metathesis, to a common precursor might lead to some of the azabicyclic skeleta depicted in Scheme 1.

An interesting feature of this scheme is that the **B** and **C** skeleta retain all the carbon atoms of the precursor molecule **1**, while skeleton **A** contains one carbon atom less than is present in **1**. We report herein the realization of the approach shown in Scheme 1.

Diol **2**, which was obtained from the *N*-allylcarbohydrate derivative **1** by a known procedure (Scheme 2),[5b] cyclized in the presence of CCl_4 and Ph_3P to give the *O*-benzyl derivative **4** via the pyrrolidine derivative **3** in 70% overall yield. Removal of the 1,2-isopropylidene group with 4% aqueous H_2SO_4−CH_3CN at 25 °C afforded the furanoside-fused pyrrolidine **5** as a 2:1 anomeric mixture in 97% yield. The furanoside **5** proved to be a versatile precursor for the synthesis of all three skeleta **A**, **B** and **C** via diverse functionalization procedures. Furanosides or pyranosides similar to **5** having free anomeric positions as well as off-template alkenyl moieties have been directly converted to nitrones in situ by reaction with secondary hydroxylamines.[6]

Accordingly **5** on treatment with *N*-methylhydroxylamine hydrochloride in the presence of $NaHCO_3$ in aqueous ethanol at reflux for 20 h gave exclusively the bridged isoxazolidine **7** (71%) via the nitrone **6** (Scheme 2). The bridged nature

Scheme 2. Synthesis of the Pyrrolo[1,2-*a*]azepine **9** by Nitrone Cycloaddition



of the isoxazolidine was easily established from the ^1H and ^{13}C NMR spectra, which exhibited the bridge $-CH_2-$ protons as two sets of doublets and the $-CH_2-$ carbon atom as a high field signal. Additional support for the structure of **7** was secured by mass spectral, COSY, HSQC, and HMBC analysis. The stereochemistry of the bridge methylene in **7** was established by NOESY analysis. The observed NOE between 4-OH and one of the H-8 protons indicated the assigned stereochemistry of **7**. The formation of bridged isoxazolidine **7** from the nitrone **6** is in agreement with the previously reported cycloaddition of *N*-allylcarbohydrate derivatives.[5] Cleavage of the isoxazolidine ring in the diacetyl derivative **8** with a view to exposing the pyrrolo[1,2-*a*]-azepine skeleton incorporated within the structure proved problematic, and the usual methods such as treatment with Zn−AcOH or transfer hydrogenation in the presence of cyclohexene and Pd−C were unsuccessful, with an intractable mixture of products being obtained. Finally treatment with $Mo(CO)_6$ in aq MeCN, followed by acetylation, afforded the azabicyclic derivative **9** in 35% yield after purification by HPLC.[7] The ^1H and ^{13}C NMR spectra of **9** were rather complex due to the restricted rotation of the tertiary amide

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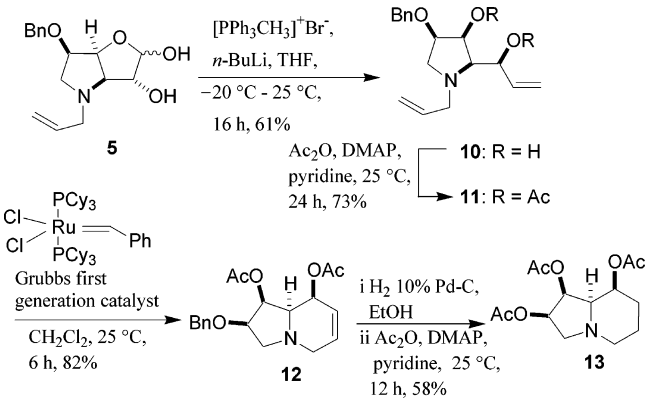
group. This was indicated by the ^{1}H NMR spectra obtained at higher temperatures and the resulting shift of some of the NMR signals.

In a separate route, Wittig reaction of the furanoside intermediate **5** led to the diene intermediate **10** in 61% yield (Scheme 3).[8] The diacetate **11** prepared from **10** smoothly

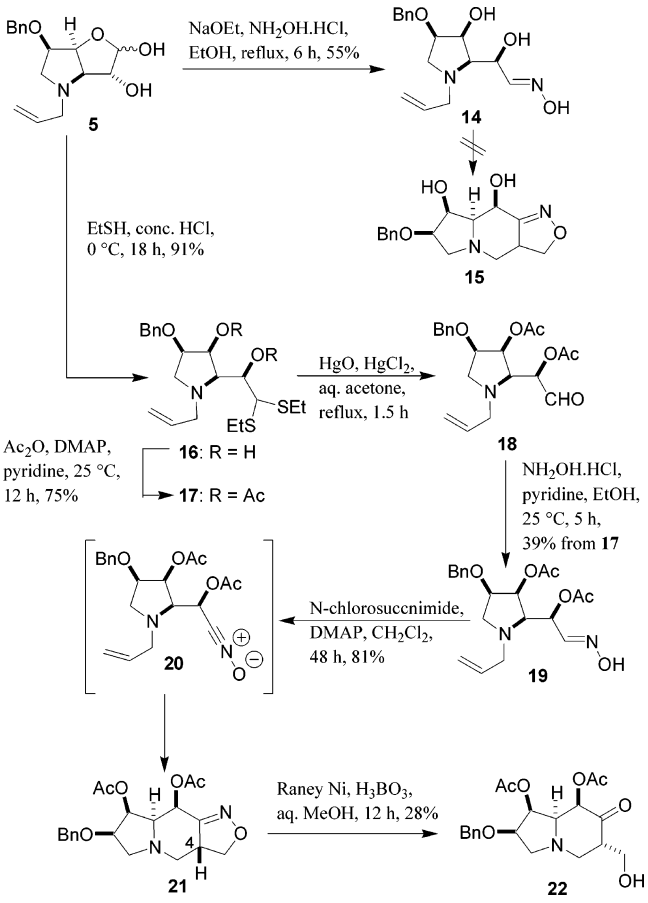
Scheme 3. Synthesis of (−)-8-*epi*-Swainsonine Triacetate by RCM



underwent ring-closing metathesis using the Grubbs' first-generation catalyst to provide the indolizidine derivative **12** in 82% yield. The ^{1}H NMR spectrum of **12** in $CDCl_3$ exhibited broad peaks for most of the protons indicating the presence of two or more equilibrating conformers. The appearance of the peaks in the ^{1}H NMR spectrum obtained in $C_2D_2Cl_4$ changed with increasing temperature, and the spectrum at 75 °C was found to be a better resolved one and was fully consistent with the structure of **12**. Hydrogenation of **12** in EtOH, in the presence of 10% Pd−C, followed by acetylation led to a 58% yield of (−)-8-*epi*-swainsonine triacetate (**13**). The melting point, optical rotation, ^{1}H and ^{13}C NMR, IR, and mass spectra of **13** were in agreement with those reported earlier.[3f,9]

The successful cycloaddition of the nitrone derived from **5** suggested the possibility of the cycloaddition of the corresponding nitrile oxide. This was expected to lead to an isoxazoline fused to a six-membered ring, in contrast to the seven-membered ring observed for the nitrone **6**. Attempted preparation of the oxime **14** and its conversion to the nitrile oxide followed by *in situ* cycloaddition to **15** proved unsuccessful (Scheme 4). Treatment of the crude **14** with *N*-chlorosuccinimide led to the formation of an intractable mixture of products. Consequently, a more circuitous route was developed in order to access the ring system of **15**. The furanoside **5** was treated with ethanethiol in the presence of concd HCl to afford the diethyldithioacetal **16**, acetylation of which gave the diacetate **17** in 68% overall yield (Scheme 4). Cleavage of the dithioacetal moiety in **17** was difficult,

Scheme 4. Synthesis of 3-Hydroxymethyl-Substituted Indolizidine **22** by Nitrile Oxide Cycloaddition



and after several attempts it was achieved by treatment with $HgCl_2$−HgO in acetone.[10] The aldehyde **18** thus obtained was immediately converted to the oxime **19** in 39% overall yield by treatment with NH_2OH. The nitrile oxide **20** generated from **19** by reaction with *N*-chlorosuccinimide underwent in situ cycloaddition to give the isoxazoline **21** in 81% yield. The structure of **21** was secured by mass and NMR spectral analysis (including HSQC, COSY and NOESY). The observed NOE between H-4 and the benzyl protons led to the assigned stereochemistry of the newly formed chiral center. Reductive cleavage of the isoxazoline **21** by hydrogenation in the presence of Raney nickel and boric acid produced the indolizidine derivative **22** (28%). The mass spectra and the ^{1}H and ^{13}C NMR spectra were fully consistent with the assigned structure. An important structural feature of **22** is that it represents a 3-hydroxymethyl substituted indolizidine nucleus, which is expected to be a potentially useful precursor of analogues of castanospermine and swainsonine. The common intermediate **5** has thus served as a precursor of all three skeletal structures **A**, **B,** and **C** represented in Scheme 1. Interestingly, the azabicyclic derivatives **8** and **11**, which were directly prepared from **5** could also be synthesized from the aldehyde intermediate

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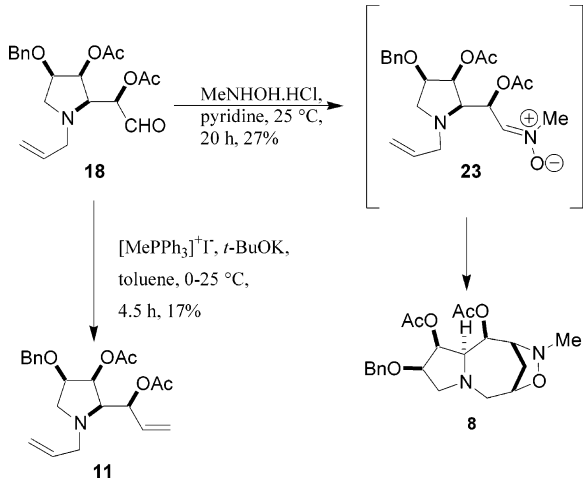
Scheme 5. Alternative Syntheses of **8** and **11** Using the Precursor **18**



18 according to Scheme 5. The nitrone **23** generated from **18** by treatment with MeNHOH·HCl and pyridine smoothly gave the isoxazolidine **8** in 27% yield. In contrast, the Wittig reaction of **18** was found to be unexpectedly difficult, and isolation of the bis-olefinic intermediate **11** (17%), the RCM of which has already been described, proved particularly troublesome.

In conclusion, the above work described the conversion of a carbohydrate derivative to the chiral *N*-allyl pyrrolidine derivatives **5** and **18**, which served as the common precursors of two differently substituted indolizidine and a multisubstituted pyrrolo[1,2-*a*]azepine skeleta.[11] The strategy is expected to be important for the synthesis of skeletally diverse complex azabicyclic systems, and work along this line is in progress.

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Supporting Information Available: Experimental procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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