Approach to the hyacinthacines: first non-chiral pool synthesis of (+)-hyacinthacine A_1†

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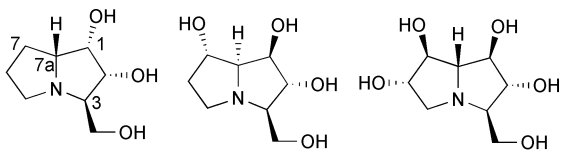
The first non-chiral pool total synthesis of (+)-hyacinthacine A_1 is described. This synthesis is based on an effective [2 + 2] cycloaddition of dichloroketene to a Stericol®-based enol ether, a diastereoselective dihydroxylation, and an efficient Tamao–Fleming oxidation.

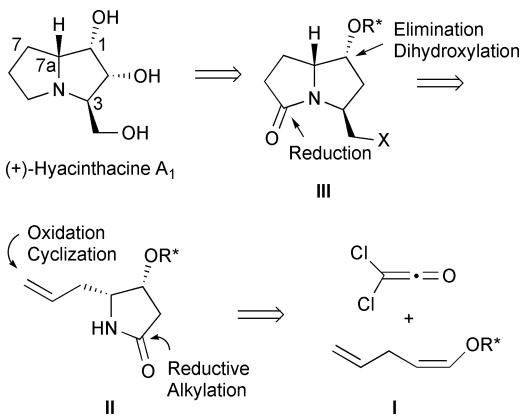
Glycosidases and glycotransferases are enzymes that catalyze the degradation and the biosynthesis of oligosaccharides and glycoconjugates (glycoproteines, glycolipids), which are involved in a large array of biological phenomena. Inhibitors of these enzymes can be considered as potential candidates for the treatment of a variety human diseases, such as diabetes, cancers, malaria, and viral infections.[1] Iminosugars, structurally related to carbohydrates, are among the most promising of the inhibitors,[1,2] and within this group, the polyhydroxylated pyrrolizidines are of particular interest because of their selectivity, as well as the challenges associated with their stereoselective synthesis.[3]

Over the past few years, we have been studying the asymmetric synthesis of alkaloids through the use of diastereoselective dichloroketene–chiral enol ether cycloaddition.[4] This methodology has been applied to the synthesis of naturally occurring pyrrolidines,[5] indolizidines,[6] and, recently, pyrrolizidines.[7] Amphorogynines A and D,[7a] two members of a new class of C-1,C-6-substituted pyrrolizidines, and retronecine,[7b] a necine base (C-1,C-7-substituted pyrrolizidine), have thus been efficiently prepared. Another important pyrrolizidine class, exemplified by hyacinthacine A_1 (**1**),[8,9] alexine (**2**),[10] and casuarine (**3**),[11] is characterized by the presence of a hydroxymethyl group at C-3.[12] The first non-chiral pool total synthesis of (+)-hyacinthacine A_1 is now reported, which serves to underscore both the flexibility and efficiency of our pyrrolizidine approach.



Hyacinthacine A_1 was isolated in low yield (5 mg kg^{-1}) from the bulbs of *Muscari armeniacum* (Hyacinthaceae) and found to exhibit selective inhibitory activity toward rat intestinal lactase (IC_{50} value of 4.4 μM).[8] To the best of our knowledge, only three syntheses of this alkaloid have so far been reported in the literature, one racemic[13] and two from chiral pool material.[12d]

It was planned that hyacinthacine A_1 would derive from the protected pyrrolizidinone **III** by installation of the hydroxyl functions and lactam reduction (Scheme 1). This pyrrolizidinone, in turn, was seen as arising from lactam **II** by stereoselective reductive alkylation with a latent hydroxymethyl group, followed by oxidation and cyclization. Lactams of the general type **II** had already been prepared in our group by stereoselective cycloaddition of dichloroketene to chiral enol ethers **I**, Beckmann ring expansion, and dechlorination.[6c,7]



Scheme 1 Retrosynthesis of (+)-hyacinthacine A_1.

The synthesis began from (*S*)-(−)-Stericol®, a broadly effective chiral auxiliary,[14,15] which was converted into the known[7] lactam **5** in 57% overall yield (Scheme 2).[16] This was transformed into the hemiaminal derivative **7** *via* imide **6** in 71% yield by successive treatment with Boc anhydride, Super Hydride®, and *p*-toluenesulfonic acid in methanol in preparation for the introduction of a hydroxymethyl equivalent. Initial attempts to achieve this end through the reaction of **7** with a variety of hydroxymethylcuprate derivatives (from $ROCH_2Li$; R = Bn, *p*-$MeOC_6H_4CH_2$, *tert*-Bu, TBDMS)[17] under different reaction conditions provided at best only low yields of the desired adduct. Fortunately, however, magnesio-(dimethylphenylsilylmethyl)cuprate[18] reacted with **7** in the presence of boron trifluoride etherate[19] in 7:1 ether–dimethyl sulfide to give a 6:1 mixture of difficult to separate pyrrolidines (major isomer **8** shown) in 96% yield (in ether alone, the diastereoselectivity was 3:1). The diastereomeric ratios and the stereochemical assignments were established by careful analysis of high-field ^1H NMR spectra recorded at 85 °C.

With a surrogate hydroxymethyl group now in place, the pyrrolidine derivatives were transformed into esters **9** by hydroboration,

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† Electronic supplementary information (ESI) available: Characterization data for compounds **1**, **6–12**, **15**, **16** and NMR spectra for compounds **1**, **6**, **8–12**, **15**, **16**. See DOI: 10.1039/b800445e

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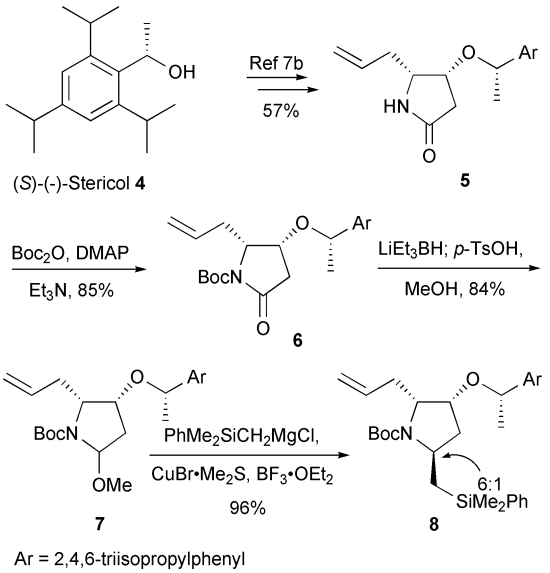
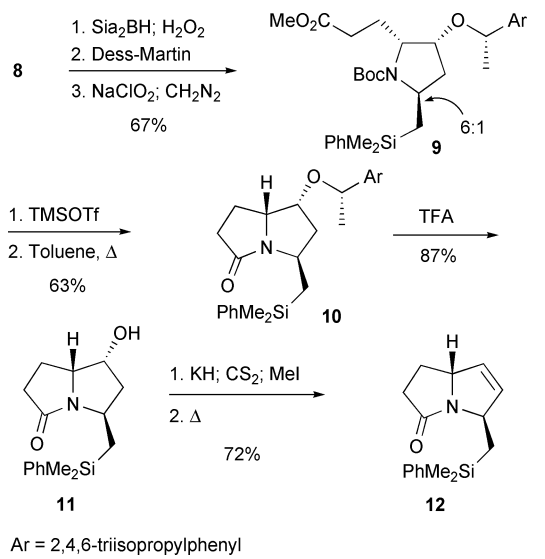


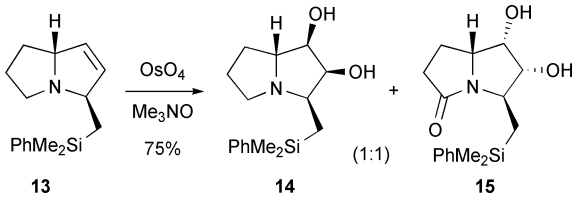
Scheme 2 Preparation of silane **8**.

oxidation,[20,21] and esterification (Scheme 3). Conveniently, on heating in toluene the free amines, obtained selectively from **9** with TMSOTf,[22] only the major diastereomer cyclized, to provide pyrrolizidinone **10** in 63% yield (2 steps). This fortuitous event can most likely be ascribed to the significant steric interactions that would be encountered in going from the minor pyrrolidine to the diastereomeric pyrrolizidinone. The chiral auxiliary was next cleaved with trifluoroacetic acid to provide pyrrolizidinol **11**, which could best be converted into olefin **12** by pyrolysis of the corresponding methyl xanthate[23] under published conditions.[24]



Scheme 3 Preparation of pyrrolizidinone **12**.

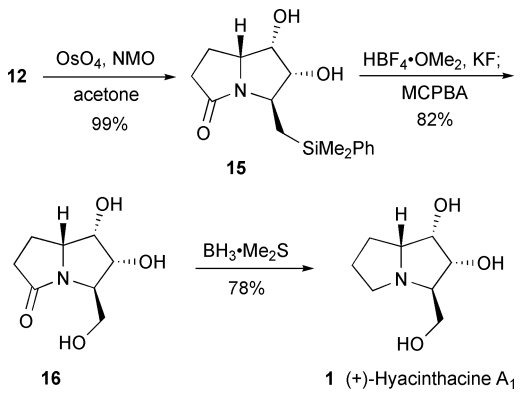
Efforts to stereoselectively introduce vicinal hydroxyl groups proved interesting. In initial studies conducted with the pyrrolizidine **13**[25] (Scheme 4), it had been found that catalytic osmium tetroxide-mediated dihydroxylation with trimethylamine *N*-oxide as the co-oxidant produced an equimolar mixture of *cis* diols, which to our surprise was composed of the undesired β,β-diol **14** and the desired α,α-diol, the latter, however, as the over-oxidized



Scheme 4 Initial studies conducted with pyrrolizidine **13**.

lactam **15**.[26] Since several modifications of the experimental conditions did not fundamentally alter these disappointing results, the above preparation of lactam **12** was conceived with the expectation now that this considerably flatter bicycle would provide a highly satisfactory stereochemical outcome.

Much to our delight, dihydroxylation of pyrrolidinone **12** under similar conditions indeed proved highly stereoselective: the desired diol **15** was formed *exclusively* in 99% yield (Scheme 5). The primary hydroxyl group was next unmasked in **15** through a Tamao–Fleming oxidation,[27] which proceeded smoothly to afford triol **16** in 82% yield. Completion of the synthesis was achieved through borane reduction of **16** to give in 78% yield hyacinthacine A_1 ($[a]_D^{21}$ +43.9 (*c* 0.29, H_2O)), which provided spectral data in perfect agreement with those of the naturally derived product ($[a]_D$ +38.2 (*c* 0.23, H_2O)).[8,28]



Scheme 5 Completion of the synthesis of (+)-hyacinthacine A_1.

In conclusion, we have demonstrated through this efficient synthesis of (+)-hyacinthacine A_1 (6.5% overall yield) that the dichloroketene–chiral enol ether cycloaddition approach to natural products can provide a stereocontrolled entry to another important class of pyrrolizidines. Application of this novel methodology for the preparation of more complex hyacinthacines is currently under investigation.

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