Nonchiral-Pool Synthesis of (+)-Hyacinthacine B_1

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To the memory of an excellent alkaloid chemist, Dr. Christian Marazano.

Abstract: The first nonchiral-pool total synthesis of (+)-hyacinthacine B_1 has been achieved. The synthesis uses as key steps an efficient [2+2] cycloaddition of dichloroketene to a chiral enol ether, two diastereoselective Bruylants-like alkylations, and an effective double Tamao–Fleming oxidation.

Key words: stereoselective synthesis, natural products, azasugars, cycloadditions, double Tamao–Fleming oxidation

The discovery of biologically active compounds with unusual mechanisms of action is important for confronting the serious problem of multidrug resistance. Iminosugars[1] effectively inhibit α-glycosidases, enzymes that are involved in a large array of biological phenomena, and thus are of potential use for the treatment of a variety human diseases, inter alia, diabetes, cancers, malaria, and viral infections.[2] Among the naturally occurring iminosugars, the rapidly expanding class of polyhydroxylated pyrrolizidines[3] has attracted significant attention because of the selective inhibitory activity associated with several of the alkaloids.[1]

The hyacinthacines, a recently discovered pyrrolizidine subgroup characterized by C-3 hydroxymethyl substitution, are divided into hyacinthacines A, B, and C based on the number of hydroxyl and hydroxymethyl groups on the second ring (cf. **1**–**3**, Figure 1).[4] Most reported synthetic efforts toward these compounds have focused on the relatively simple hyacinthacine A series and have either yielded the racemic product or used chiral-pool starting material or enzymatic techniques to obtain the natural product.[5] Very recently, we reported[6] the first nonchiral-pool synthesis of hyacinthacine A_1 through the use of diastereoselective dichloroketene–chiral enol ether cycloaddition,[7] a methodology previously applied for the preparation of a variety of other alkaloids.[8–10] As an extension of this work, we now describe the first nonchiral-pool preparation of hyacinthacine B_1, a pyrrolizidine characterized by the presence of synthetically challenging hydroxymethyls at C-3 and C-5 and five stereocenters. Isolated in low yield (12 mg/kg) by Asano and co-workers from immature fruits and stalks of bluebells (*Hyacinthoides nonscripta*), this alkaloid has been shown to be a selective inhibitor of β-glucosidase, β-galactosidase, and β-mannosidase.[11,12]

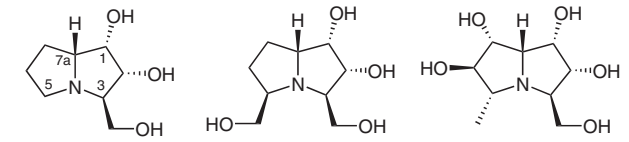
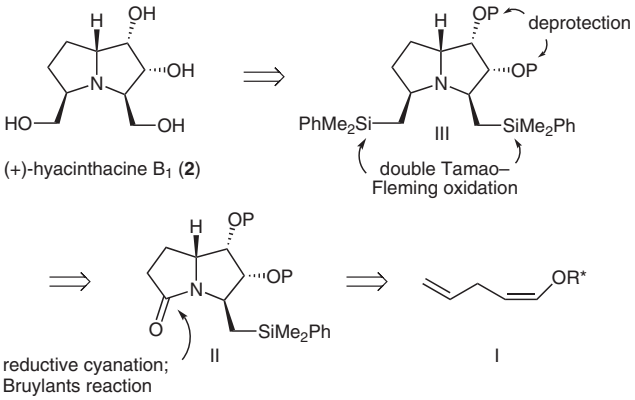


Figure 1 Examples of the three classes of hyacinthacines

We planned that hyacinthacine B_1 would be secured from the disilylated derivative **III** by an unusual double Tamao–Fleming oxidation that would engender the two hydroxymethyl units in a single step (Scheme 1). We hoped that the C-5 silylmethyl substituent in **III** might be introduced through a stereoselective Bruylants reaction of the aminonitrile obtained by reductive cyanation of pyrrolizidinone **II**. Pyrrolizidinone **II** (P = H) had earlier been prepared from enol ether **I** (R*OH = Stericol®).[6]



Scheme 1 Retrosynthesis of (+)-hyacinthacine B_1

The synthesis of hyacinthacine B_1 thus started from the commercially available chiral auxiliary (*S*)-(–)-Stericol® **4**[13] (Scheme 2). This inductor allowed the preparation of pyrrolizidinone **6**, via lactam **5**[10b,14] in a highly stereoselective manner, the key diastereoselective steps being: a [2+2] cycloaddition of dichloroketene to a Stericol-derived enol ether, a Bruylants-like addition of the silylmethyl substituent, and an *endo*-selective dihydroxylation.[6]

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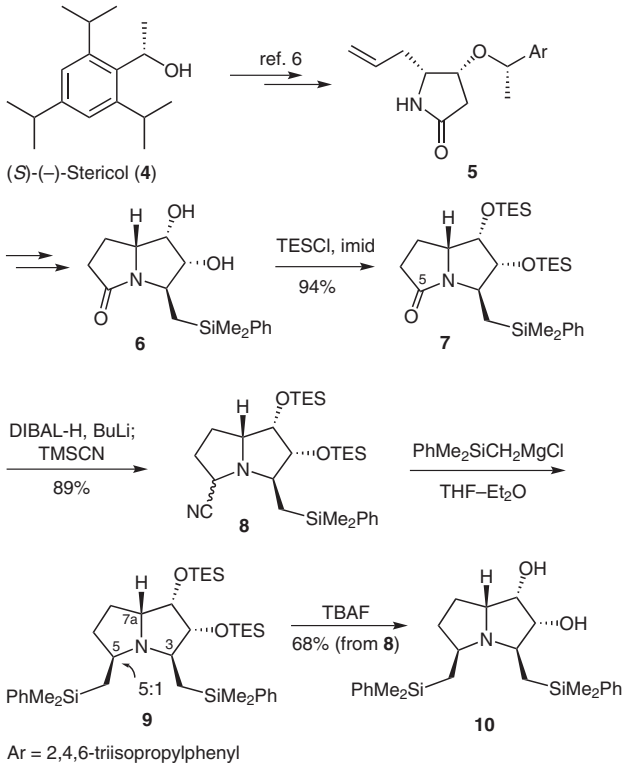
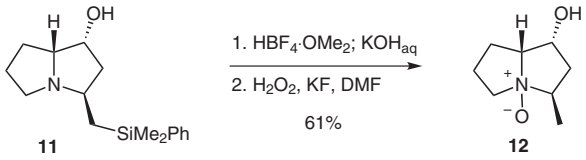
Triethylsilyl groups were chosen for protection of the C-1 and C-2 hydroxyl functions in **6** as they appeared to offer the best balance between easy of introduction/removal and steric hindrance, which was expected to influence the stereoselectivity of the upcoming Bruylants[15] C-5 alkylation. Triethylsilylation of **6** proceeded smoothly with triethylsilyl chloride in presence of imidazole to produce lactam **7** (Scheme 2). The conversion of this lactam into the corresponding aminonitrile[16] in preparation for the Bruylants reaction proved, though, problematic. Reductive cyanation with the often used DIBAL-H/KCN system[17] led invariably to significant amounts of over-reduced material, while the use of Schwartz's reagent with TMSCN[18] led primarily to recovered starting material. Fortunately, though, the DIBAL-H–*n*-BuLi ate complex[19] smoothly produced the desired hemiaminal, which, following treatment in situ with TMSCN, gave in 89% yield a 1.6:1 mixture of the epimeric aminonitriles **8**.



Scheme 2 Preparation of bissilane **10**

The mixture of aminonitriles reacted with dimethylphenylsilylmethylmagnesium chloride in diethyl ether–THF at room temperature to afford a 5:1 epimeric mixture of alkylated pyrrolizidines **9**. A sample of the major isomer, separated with difficulty by silica gel chromatography, provided ^{1}H NMR data in agreement with the depicted structure. Particularly diagnostic was the strong NOE (10%) between the C-3 and C-5 hydrogens. The TES groups were next removed from **9** by treatment with TBAF, and the resultant mixture could now be easily separated by chromatography to give diol **10** in 68% overall yield from **8**. As further support for the stereochemical assignments, the minor diol was resilylated to provide the pure minor pyrrolizidine **9**, which showed no significant NOE between the hydrogens at C-3 and C-5, but one (1%) between those at C-5 and C-7a.

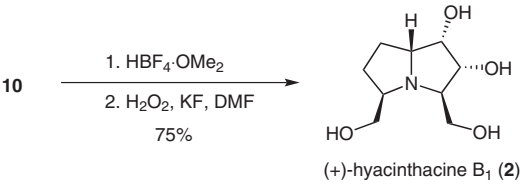
Several different procedures have been developed for silane oxidation,[20] and some of them have been successfully used with a potentially oxidizable amino group in the substrate.[21] In a model study carried out using pyrrolizidine **11**, a lack of reactivity was observed under the basic conditions developed by Smitrovich and Woerpel;[21a] in contrast, the expected silanol was formed with tetrafluoroboric acid followed by a basic workup,[21c] but the subsequent oxidation with hydrogen peroxide in the presence of potassium fluoride gave, disappointingly, only the protodesilylated *N*-oxide derivative **12** (Scheme 3).



Scheme 3 Attempted Tamao–Fleming oxidation

It was hoped, however, that by eliminating the basic workup, thereby leaving the nitrogen atom protonated, a better result might be obtained in this Tamao–Fleming oxidation. To our considerable satisfaction, removal of volatiles after treatment of pyrrolizidine **11** with tetrafluoroboric acid and then oxidation of the protonated silyl fluoride intermediate, indeed produced the corresponding diol, without significant formation of the *N*-oxide.

With this encouraging model-system result in hand, the double Tamao–Fleming oxidation of **10** was next investigated. While double Tamao–Fleming oxidations are relatively few in the literature,[22] a recent example reported by Somfai and co-workers[22g] in their synthesis of (+)-alexine allowed a degree of optimism. Under acidic conditions [$Hg(OTf)_2$, AcOOH, AcOH], they were able to obtain a 2:1 mixture of the expected diol and its *N*-oxide in 62% combined yield. Much to our delight, by applying the Tamao–Fleming protocol that had been successful in our model system, **10** underwent clean double oxidation to afford hyacinthacine B_1 in 75% yield, without discernible *N*-oxide formation (Scheme 4). The synthetically derived natural product {$[\alpha]_D$ +40} so obtained was spectroscopically and chromatographically indistinguishable from a sample of the naturally derived material {$[\alpha]_D$ +41.3[11]}.[23]



Scheme 4 Completion of the synthesis of (+)-hyacinthacine B_1

In summary, (+)-hyacinthacine B_1 has been efficiently prepared (4.4% overall yield) in enantiopure form through an asymmetric cycloaddition approach. This approach, which does not rely on chiral-pool substrates, is highly flexible and should be useful for the synthesis of yet other hyacinthacines.

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

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