Synthetic studies on vincorine: access to the 3a,8a-dialkyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole skeleton†

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Synthetic studies on vincorine are described; the conversion of 3-aminoethyl-3-alkyloxindoles to 3a,8a-dialkyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indoles has been achieved through an addition–cyclization sequence, and a fully functionalized key intermediate was constructed with this method.

Vincorine (**1**) is an alkaloid isolated from *Vinca minor* L, which possesses a characteristic bicyclic framework fused with 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole skeleton **A** (Fig. 1).[1] With related compounds such as echitamine (**2**) and ceylanine (**3**), vincorine (**1**) forms a subgroup within the akuammiline alkaloids.[2] Although these alkaloids are known to exhibit a broad range of important bioactivities, including anticancer activity, synthetic studies have been extremely limited,[3] and only one total synthesis has been reported.[4] Additionally, two total syntheses of minfiensine (**4**), a *Strychnos* alkaloid, which has a related molecular framework, have been reported: the first total synthesis by Overman *et al*. in 2005,[5] and the second by Qin *et al*. in 2008.[6]

Our synthetic plan is summarized in Fig. 2. Disconnection of the C15–C20 bond gives cyclohexene derivative **5**, with a vinylic bromide on the side chain. The conversion of **5** to **1** may be accomplished through an intramolecular conjugate addition or Heck reaction. Opening of the cyclohexene ring and removal of the *N*-butenyl chain results in compound **6**, which has the 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole framework. This framework, the so-called physostigmine skeleton, is frequently observed in biologically active compounds such as acetylcholinesterase inhibitors, and a variety of derivatives have been synthesized.[7] However, the synthesis of compounds doubly alkylated at the 5,5-ring junction (C3a and C8a on structure **A**, see Fig. 1) such as **6** has rarely been studied.[8,9] We thought that it might be interesting to develop a synthetic route for this class of compounds, not only for the total synthesis but also to provide dialkyl analogues of physostigmine-type compounds for further medicinal studies.

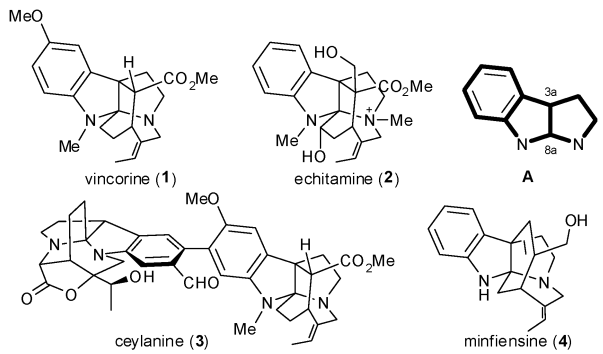


Fig. 1 Vincorine (**1**) and related compounds.

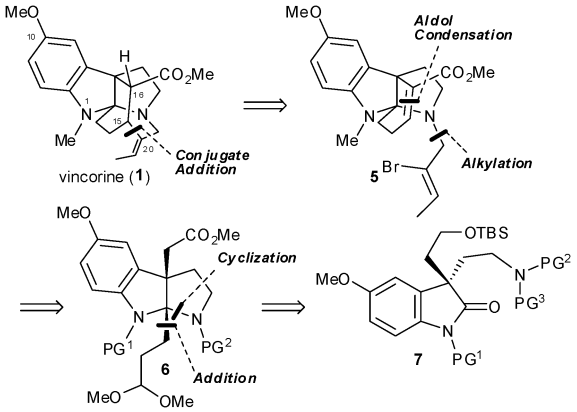
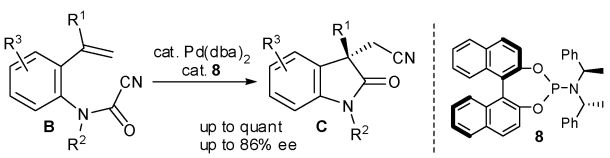


Fig. 2 Synthetic plan for vincorine (**1**).

We constructed the hexahydropyrroloindole skeleton from 3,3-disubstituted oxindoles such as **7**, since we have developed a method to synthesize a variety of 3,3-disubstituted oxindoles in an enantioselective manner (Scheme 1).[10] We found that when alkenylcyanoformamide **B** was treated with a catalytic amount of palladium in the presence of Feringa's optically active phosphoramidite **8**,[11] enantioselective cyanoamidation took place to give optically active 3,3-disubstituted oxindole **C**. Our plan provides general access to a variety of optically active 3a,8a-dialkyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indoles.

For the construction of hexahydropyrroloindole **6**, addition of an organometallic reagent to the amide carbonyl of oxindole **7** followed by formation of an *N*,*N*-acetal was planned (see Fig. 2). The success of this transformation relies on the proper selection of the protecting groups of compound



Scheme 1 Synthesis of 3,3-disubstituted oxindoles through enantioselective cyanoamidation.

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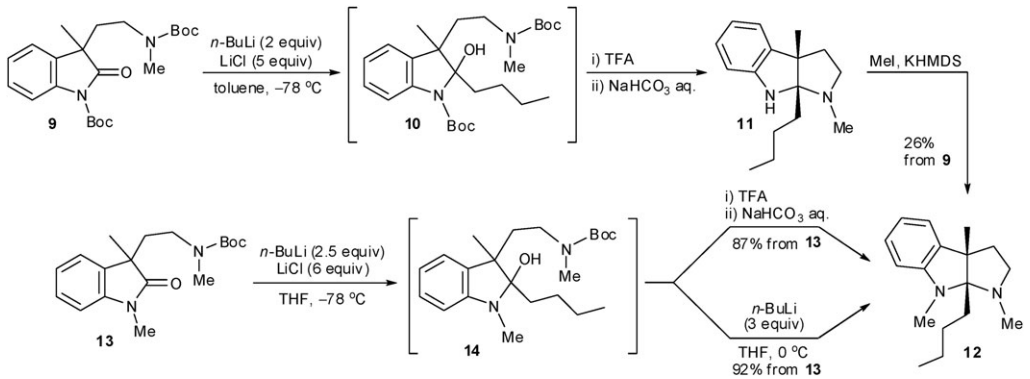
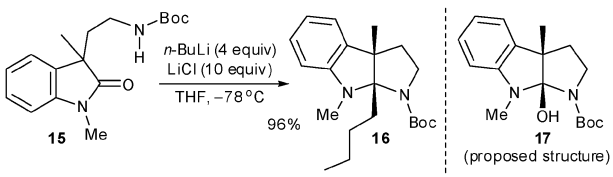


Scheme 2 Formation of hexahydropyrroloindoles through an addition–deprotection–cyclization sequence.

7: PG^1 on the oxindole nitrogen may control the reactivity of the oxindole carbonyl towards organometallic reagents; PG^2 and PG^3 on the amine nitrogen of the side chain are expected to keep the amino group inactive during the addition reaction, and later on, to allow the formation of the *N*,*N*-acetal through cleavage of one of these protecting groups. To our surprise, even though there have been numerous synthetic studies on oxindoles, the addition of organometallic reagents to oxindole carbonyls has rarely been reported.[12]

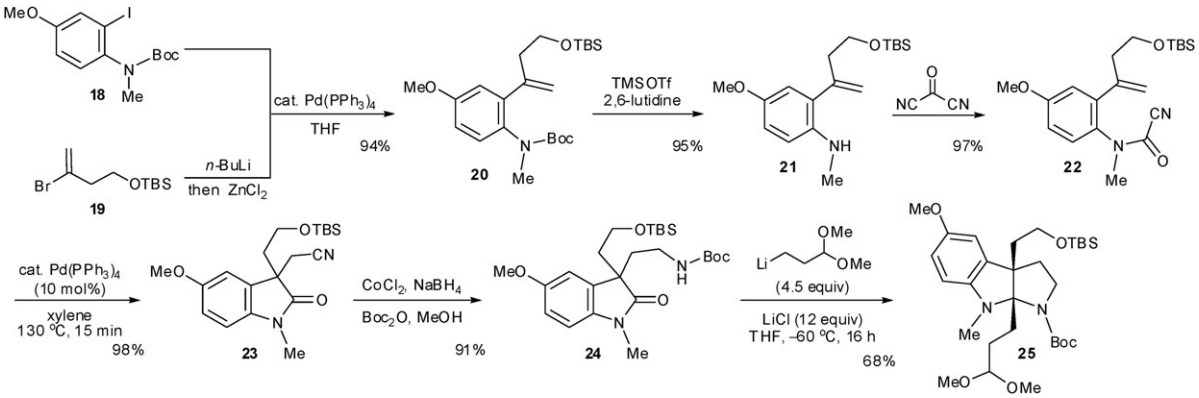
To study the formation of dialkylhexahydropyrroloindole, two 3-methyl-3-(*N*-methylaminoethyl)oxindoles, **9** and **13**, were synthesized (Scheme 2). An *N*-Boc group was placed on the side chain of both compounds; this is cleaved after the addition reaction to allow *N*,*N*-acetal formation. On the other hand, compounds **9** and **13** have different groups on the oxindole nitrogen: **9** has a Boc group and **13** has a methyl. Initially, compound **9** was treated with organometallic reagents under several different conditions. In many cases, the starting material was consumed smoothly at −78 °C. However, besides the desired addition to the oxindole carbonyl, cleavage of the Boc group placed on the oxindole was often observed. We considered that these results arose from the unusual reactivity of both reactive sites: the reactivity of the amido carbonyl is reduced due to high steric hindrance, and the reactivity of the Boc carbonyl is increased because of relatively weaker electron donation from the aniline nitrogen. After several attempts, it was found that the desired addition occurred predominantly when alkyllithium reagents such as *n*-BuLi were used in the presence of excess LiCl in toluene. After the reaction, the mixture containing addition product **10** was subjected to TFA treatment followed by methylation. As a result, the desired hexahydropyrroloindole **12** was isolated; however, the yield was only 26%. We next subjected oxindole **13** with the methyl group on the oxindole nitrogen to the sequence of reactions. Owning to the low reactivity of the amide carbonyl, **13** was inert to organomagnesium reagents. However, alkyllithium reagents were effective: when oxindole **13** was treated with *n*-BuLi and LiCl, the addition took place smoothly.[13] Aqueous work-up followed by TFA treatment and neutralization gave hexahydropyrroloindole **12** in 87% yield. We also found an alternative one-pot method for the cyclization. After the completion of the addition reaction at −78 °C, the reaction mixture was warmed to 0 °C and a further 3 equiv. of *n*-BuLi were added. A spot-to-spot conversion, presumably from **14** to **12**, was observed by TLC within several minutes. Normal aqueous work-up gave cyclized product **12** in 92% yield. Although the reaction mechanism is not clear, the one-pot method should be useful, especially for substrates bearing acid-sensitive groups.



Scheme 3 Reaction of oxindole **15** possessing an acidic hydrogen.

Encouraged by these results, we attempted the conversion of oxindole **15**, which has an acidic hydrogen on its side chain, to hexahydropyrroloindole **16** (Scheme 3). In some cases, the lithium amide generated on the side chain attacked the oxindole carbonyl intramolecularly before the attack of the alkyllithium reagents. A compound likely to be hemiaminal **17** was isolated, and isomerization to the original oxindole **15** was observed. We found the use of excess lithium reagent can overcome this problem by enhancing the rate of the attack of the lithium reagent. Finally, hexahydropyrroloindole **16** was isolated in 96% yield through the reaction with *n*-BuLi (4 equiv.) and LiCl (10 equiv.), followed by normal aqueous work-up.

With methods to construct dialkylhexahydropyrroloindoles in hand, we studied the synthesis of vincorine (**1**) (Scheme 4). We constructed the hexahydropyrroloindole intermediate using the method used for the synthesis of compound **16**. Precursor **24** for the addition–cyclization sequence was synthesized by Negishi coupling and cyanoamidation. First, iodoanisidine **18** was coupled with the zinc reagent generated from vinyl bromide **19**[14] to afford styrene **20** in 94% yield. Then, **20** was converted to aniline **21** through selective removal of the *N*-Boc group by Ohfune's conditions.[15] The resulting aniline, **21**, was treated with carbonyl cyanide[16] to give cyanoformamide **22**. The racemic cyanoamidation was carried out with a catalytic amount of $Pd(PPh_3)_4$ in xylene at 130 °C, which resulted in giving oxindole **23** in 98% yield.[17] The reduction of the cyano group of oxindole **23** required several attempts. When reductants such as DIBAL-H or Red-Al were used, a mixture of unidentified materials was obtained. When the reagent combination of $NaBH_4$ with $CoCl_2$[18] was applied,



Scheme 4 Synthesis of fully functionalized key intermediate **25**.

the reduction of the cyano group took place, but the isolated yield of the resulting amine was moderate. Finally, the reaction was performed with $NaBH_4$ and $CoCl_2$ in the presence of $(Boc)_2O$, which allowed the isolation of carbamate **24** in 91% yield. With compound **24** in hand, its conversion to hexahydropyrroloindole was examined. 3,3-Dimethoxypropyllithium (4.5 equiv.) was added to a solution of compound **24** and LiCl in THF at −78 °C. The reaction was very slow at −78 °C, which is likely to be due to the increased steric hindrance compared with oxindole **15**. Since some undesired side reactions took place when the reaction mixture was warmed to above −40 °C, the mixture was kept at −60 °C for 16 h. At the end, we were pleased to isolate the desired hexahydropyrroloindole **25** in 68% yield. Compound **25** has distinct functional groups, such as TBS ether, dimethyl acetal and a Boc-protected amine, which are necessary for the total synthesis of vincorine (**1**).

In summary, we have developed a concise method of synthesizing hexahydropyrrolo[2,3-*b*]indole frameworks that are doubly alkylated at the ring junction. When this method is combined with enantioselective cyanoamidation, a variety of optically active dialkylhexahydropyrroloindoles are expected to be available. This method was also applied to construct the fully functionalized key intermediate **25** for the total synthesis of vincorine (**1**). Further studies towards the total synthesis are ongoing in our lab.

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