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Asymmetric Synthesis of (+)-Isofebrifugine and (−)-Sedacryptine from a Common Chiral Nonracemic Building Block

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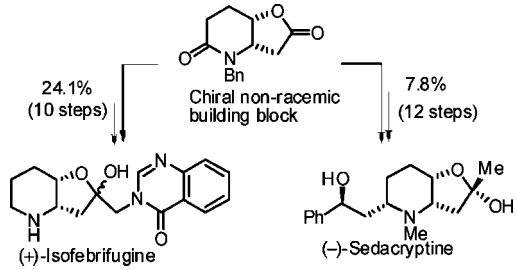
ABSTRACT



The stereoselective syntheses of 2-substituted and 2,6-disubstituted 3-hydroxypiperidine alkaloids, (+)-isofebrifugine and (−)-sedacryptine, from a common, functionalized nonracemic bicyclic building block are achieved, demonstrating the flexibilty of the approach.

Piperidine alkaloids have diverse structures with interesting stereochemistries and are widespread in nature.[1] A subgroup of these alkaloids possessing the 3-hydroxypiperidine moiety as their core structure, exemplified by **1**−**5** (Figure 1), are also frequently found in nature. Many of these alkaloids show a wide range of biological activities[1a,c,2] which have potential applications in medicine and in the design of new drugs.[3] These attributes have stimulated intense efforts directed at the development of synthetic approaches and methods[4] for use in the synthesis of piperidine intermediates enroute to alkaloids. In spite of the advancements achieved to date, versatile and stereoselective routes are still highly desired.

We recently reported[5] the synthesis of the functionalized chiral nonracemic intermediate **6** (Figure 1) and described its use in the synthesis of an indolizidine alkaloid. The cis-bicyclic structure also provides a stereochemical bias for

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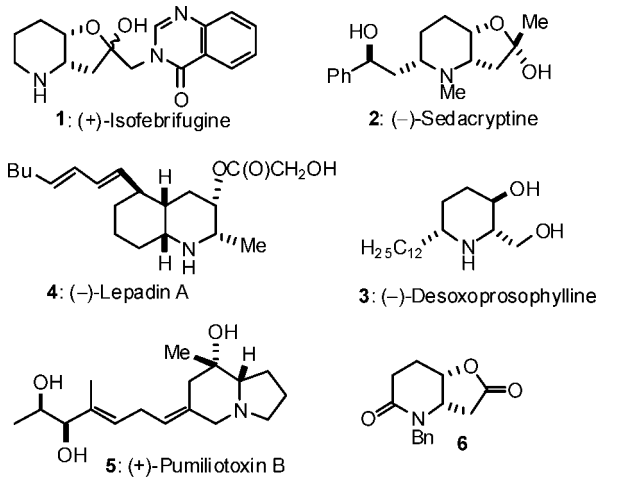
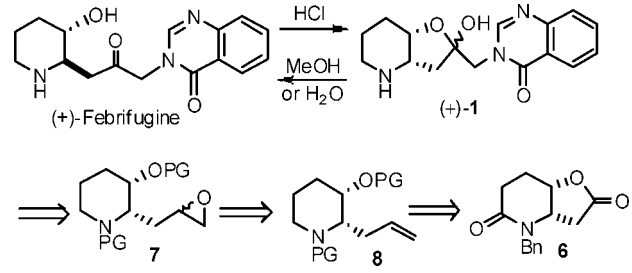


Figure 1. Representative 3-hydroxypiperidine alkaloids and building block **6**.

reactions that are carried out on **6** facilitating the stereoselective installation of substituents on the bicycle. In connection with this work, we now report the enantioselective syntheses of (+)-isofebrifugine (**1**) and (−)-sedacryptine (**2**) starting from **6**. The successful syntheses of **1** and **2** highlight the utility of **6** as a nonracemic building block[6] and demonstrate the flexibility of the approach which provides ready access to both 2-substituted and 2,6-disubstituted 3-hydroxypiperidine alkaloids.[7]

(+)-Isofebrifugine (**1**) and (+)-febrifugine (Scheme 1) are two antimalarial compounds isolated from the roots of the

Scheme 1. Retrosynthesis of (+)-Isofebrifugine (**1**)



Chinese herbal plant *Dichroa febrifuga* Lour. and related hydrangea plants.[8] There is renewed interest in these two alkaloids and their synthetic analogues due to the increasing resistance of the malarial parasite toward quinine and synthetic antimalarial drugs such as chloroquine.[9] From a chemical standpoint, these two compounds show an interesting interconversion; it was found that (+)-febrifugine was converted[10a] to (+)-**1** by heating the former compound in refluxing aqueous HCl, whereas (+)-**1** was converted to (+)-febrifugine when it was refluxed in methanol[10a] (or water[10b]). On the basis of the ease of conversion of (+)-isofebrifugine to (+)-febrifugine, we chose the former as our synthetic target. There have been two racemic[11a,b] and six asymmetric syntheses[10a,b,11c−f] of (+)-**1** to date; our approach is fundamentally different from those reported.

The retrosynthesis of (+)-**1** is shown in Scheme 1. The epoxide unit in **7** will serve as an hydroxyethyl carbocation equivalent to permit its coupling to 4-quinazolinone and installation of the secondary alcohol unit that is destined to be a ketone carbonyl function. Compound **7** will be derived from the alkene **8**, which in turn will be prepared from building block **6**.

The synthesis began with the chemoselective reduction[5] of the lactone carbonyl in **6** with RedAl to obtain the lactol **9** in 94% yield (Scheme 2). Wittig olefination of **9** followed by protection of the secondary alcohol as the methoxymethyl ether gave lactam **10**. Reduction of the lactam carbonyl with

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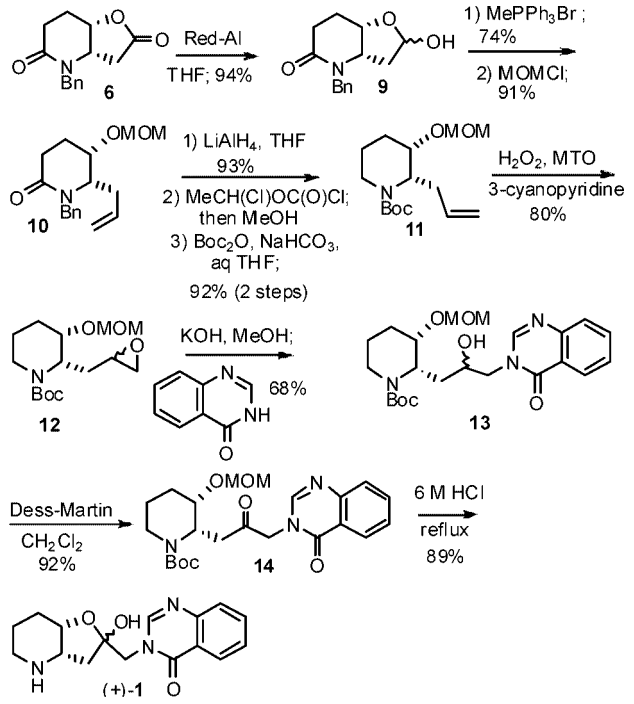
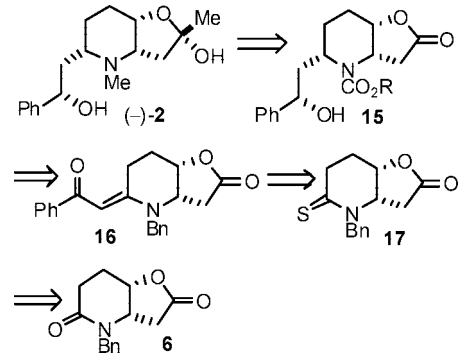
Scheme 2. Synthesis of (+)-Isofebrifugine



$LiAlH_4$ gave the piperidine intermediate in 93% yield. Acylative *N*-debenzylation using α-chloroethyl chloroformate[12] followed by *N*-carbamoylation using Boc_2O gave the alkene intermediate **11** in an overall yield of 92%. The epoxidation of the terminal double bond in **11** turned out not to be trivial. Epoxidation using *m*-CPBA was unproductive, and starting **11** was recovered (86%); *m*-CPBA oxidation in the presence of K_2CO_3[13] led to a low yield (38%) of the desired epoxide **12**, and 50% of **11** was recovered. The use of DCC/H_2O_2[14] gave no epoxide **12** and a low recovery (56%) of alkene **11**. Gratifyingly, it was found that $MeReO_3$ (MTO)-catalyzed epoxidation using H_2O_2 as co-oxidant in the presence of 3-cyanopyridine[15] was efficient and yielded the desired epoxide **12** in 80% yield and as an inseparable mixture of diastereomers. Base-mediated coupling of **12** with 4-quinazolinone[16] yielded a diastereomeric mixture of the secondary alcohol **13**. The stereochemistry of the carbinol center was inconsequential to the synthesis as it will be converted to a ketone carbonyl in **14**. This was accomplished in 92% yield by oxidation using Dess−Martin periodinane.[17] Acid hydrolysis of **14** effected deprotection of the hydroxyl and amino groups to furnish (+)-isofebrifugine (**1**). Our synthetic (+)-**1** showed $[\alpha]^{22}_D = +120.8$ (*c* 0.30, $CHCl_3$) [lit.[10b] $[\alpha]^{22}_D = +124.3$ (*c* 0.50, $CHCl_3$), lit.[11c] $[\alpha]^{23}_D = +123$ (*c* 0.30, $CHCl_3$), lit.[11e] $[\alpha]^{23}_D = +128.9$ (*c*, 0.31, $CHCl_3$)], and its ^1H and ^{13}C NMR data are in accord with literature data.[10a,11e,f]

The use of building block **6** in the synthesis of (−)-sedacryptine (**2**), a 2,6-disubstituted 3-hydroxypiperidine alkaloid, was next pursued. Sedacryptine is a minor alkaloid that was isolated, along with sedinine, from *Sedum acre*.[18] Its structure was solved by X-ray crystallographic analysis. Since its isolation, there have been four reported syntheses,[19] two of which described the asymmetric synthesis of sedacryptine. Our retrosynthesis of (−)-sedacryptine is shown in Scheme 3.

Scheme 3. Retrosynthesis of (−)-Sedacryptine (**2**)



The intermediate **15** is derived from the vinylogous amide **16**, which in turn is to be assembled from the thiolactam **17**, using the Eschenmoser sulfide contraction method.[20] Thiolactam **17** is to be prepared from **6** via chemoselective thionation of the lactam carbonyl group.

Thus, treatment of **6** with Lawesson's reagent[21] proceeded efficiently (Scheme 4) to give the corresponding thiolactam **17** in excellent yield. Alkylation of **17** with phenacyl bromide followed by Ph_3P gave the vinylogous amide **16** in 67% yield. We found that the use of 1-methylpiperidine[22] as the base was beneficial because, with Et_3N, the yield of **16** was 52%.

Hydrogenation of **16** catalyzed by Adams' catalyst gave a 98% yield of the phenyl ketone as a 90:10 ratio of diastereomers **18a**,**b**. The major diastereomer was assigned structure **18a** on the basis that hydrogenation would preferentially occur from the less hindered convex side of the bicycle. The stereochemistry of the phenylacetonyl side chain in **18a** was confirmed after installation of the side-chain benzylic carbinol stereocenter (cf. **15**, vide infra).

Subsequent *N*-debenzylation of **18a** under catalytic transfer hydrogenation using Pearlman's catalyst gave the corresponding piperidine intermediate, which was not purified but was immediately reacted with methyl chloroformate to furnish **19** in 63% yield over two steps. Reduction of the

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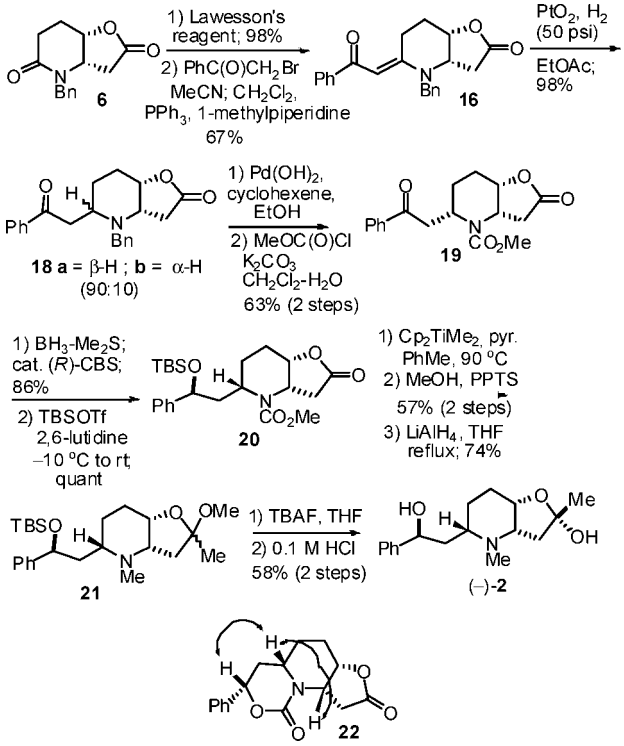
Scheme 4. Synthesis of (−)-Sedacryptine



ketone group in **19** with $BH_3{\cdot}SMe_2$ catalyzed by (*R*)-2MeCBS[23] gave a high yield of the corresponding alcohol **15** (R = Me; Scheme 3) with the desired *S*-configuration at the carbinol center. The epimeric alcohol was not detected.

The assigned stereochemistries of the benzylic carbinol center in **15** (R = Me) and of the phenylacetonyl side chain in **18a** were established by 1D NOESY experiment on the cyclic carbamate **22**.

Protection of the secondary alcohol in **15** (R = Me) was accomplished in high yield using *t*-$BuMe_2SiOTf$ to give **20**. Methylenation of the γ-lactone carbonyl using Petasis' reagent[24] proceeded chemoselectively to give the corresponding cyclic methylidene ether, which was not purified but treated immediately with dry methanol in the presence of a catalytic amounts of PPTS. The resultant cyclic ketal was obtained in a respectable 57% overall yield. Reduction of the carbamate group of the cyclic ketal with $LiAlH_4$ gave the *N*-methylpiperidine derivative **21** (74%).

Desilylation of **21** followed by hydrolysis of the cyclic ketal in refluxing aqueous 0.1 M HCl gave sedacryptine (**2**). We found it useful to let a methanolic solution of **2** to stand at rt for 36 h before purification and recrystallization from cyclohexane.[19d] Synthetic (−)-**2** showed $[\alpha]^{25}_D = -13.5$ (*c* 0.74, $CHCl_3$); for (+)-sedacryptine:[19d] $[\alpha]^{20}_D = +14$ (*c* 0.54, $CHCl_3$). Its spectroscopic data agreed with reported[19a,d] literature values.

In summary, we have demonstrated the versatility of the nonracemic building block **6** in the asymmetric synthesis of two structurally different 3-hydroxypiperidine alklaoids, (+)-isofebrifugine and (−)-sedacryptine. The use of **6** provides flexibility in our approach. Further studies in the use of **6** in alklaoid synthesis are continuing.

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Supporting Information Available: Experimental procedures and data for the preparation of **10**−**14**, (+)-**1**, **16**−**21**, (−)-**2**, and **22**, NMR data for compounds **10**−**14**, (+)-**1**, **16**, **18a**,**b**, **19**−**22**, and (−)-**2**, and 1D NOESY spectra for **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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