

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

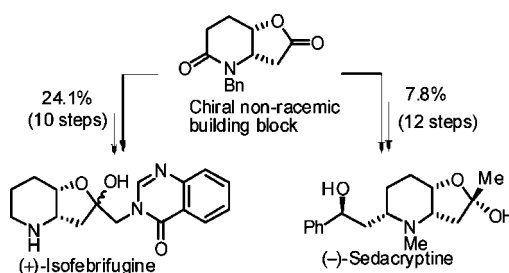
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ABSTRACT



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 flexibility 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 methods⁴ 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 reported⁵ 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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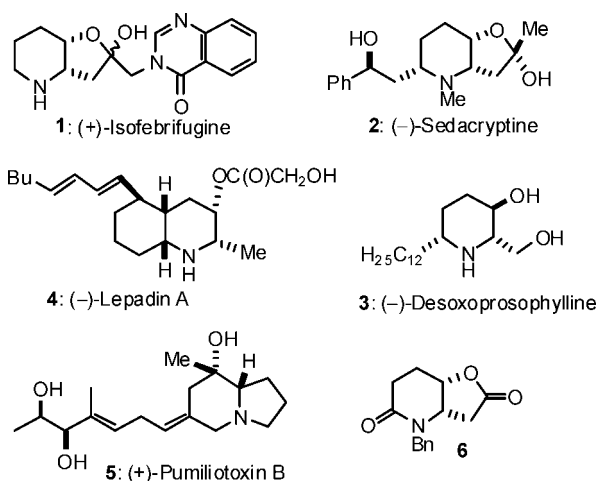


Figure 1. Representative 3-hydroxypiperidine alkaloids and building block **6**.

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 block⁶ and demonstrate the flexibility of the approach which provides ready access to both 2-substituted and 2,6-disubstituted 3-hydroxypiperidine alkaloids.⁷

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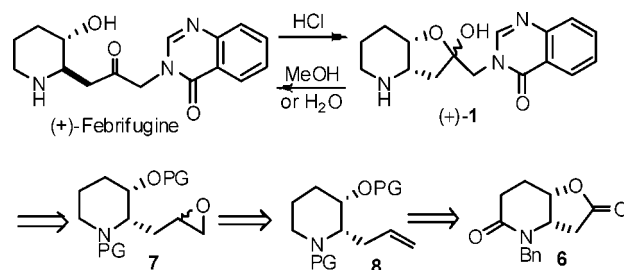
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(+)-Isofebrifugine (**1**) and (+)-febrifugine (Scheme 1) are two antimalarial compounds isolated from the roots of the

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 reduction⁵ 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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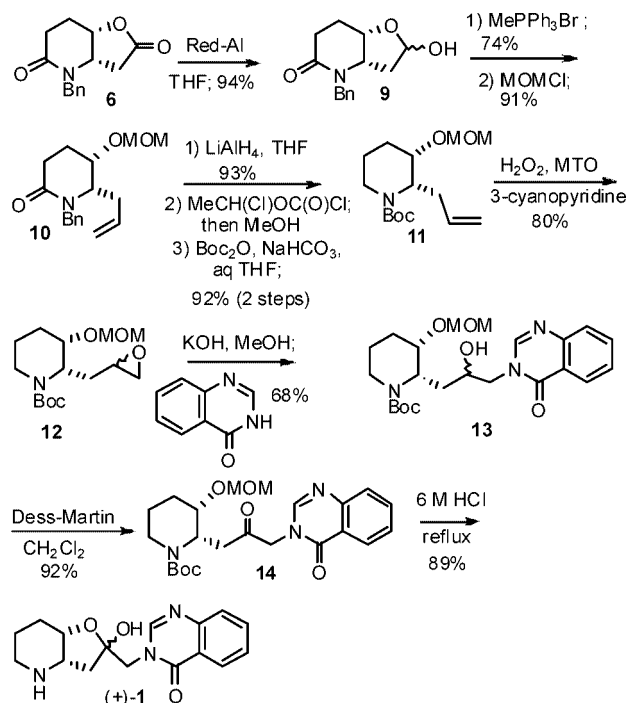
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Scheme 2. Synthesis of (+)-Isofebrifugine

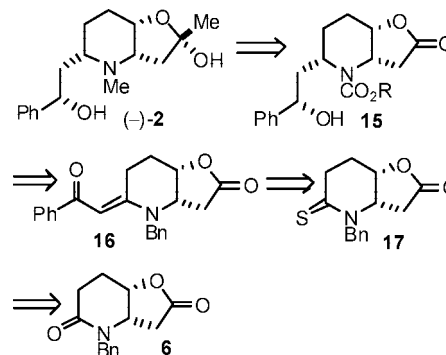


LiAlH₄ gave the piperidine intermediate in 93% yield. Acylative *N*-debenzylation using α -chloroethyl chloroformate¹² followed by *N*-carbamoylation using Boc₂O gave the alkene intermediate **11** in an overall yield of 92%. The epoxidation of the terminal double bond in **11** turned out not to be trivial. Epoxidation using *m*-CPBA was unproductive, and starting **11** was recovered (86%); *m*-CPBA oxidation in the presence of K₂CO₃¹³ led to a low yield (38%) of the desired epoxide **12**, and 50% of **11** was recovered. The use of DCC/H₂O₂¹⁴ gave no epoxide **12** and a low recovery (56%) of alkene **11**. Gratifyingly, it was found that MeReO₃ (MTO)-catalyzed epoxidation using H₂O₂ as co-oxidant in the presence of 3-cyanopyridine¹⁵ 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-quinazolinone¹⁶ 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 $[\alpha]^{22}_{\text{D}} = +120.8$ (*c* 0.30, CHCl₃) [lit.^{10b} $[\alpha]^{22}_{\text{D}} = +124.3$ (*c* 0.50, CHCl₃), lit.^{11c} $[\alpha]^{23}_{\text{D}} = +123$ (*c* 0.30, CHCl₃), lit.^{11e} $[\alpha]^{23}_{\text{D}} = +128.9$ (*c*, 0.31, CHCl₃)], and its ¹H and ¹³C 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 vinyllogous 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 reagent²¹ proceeded efficiently (Scheme 4) to give the corresponding thiolactam **17** in excellent yield. Alkylation of **17** with phenacyl bromide followed by Ph₃P gave the vinyllogous amide **16** in 67% yield. We found that the use of 1-methylpiperidine²² as the base was beneficial because, with Et₃N, 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 phenylacetyl 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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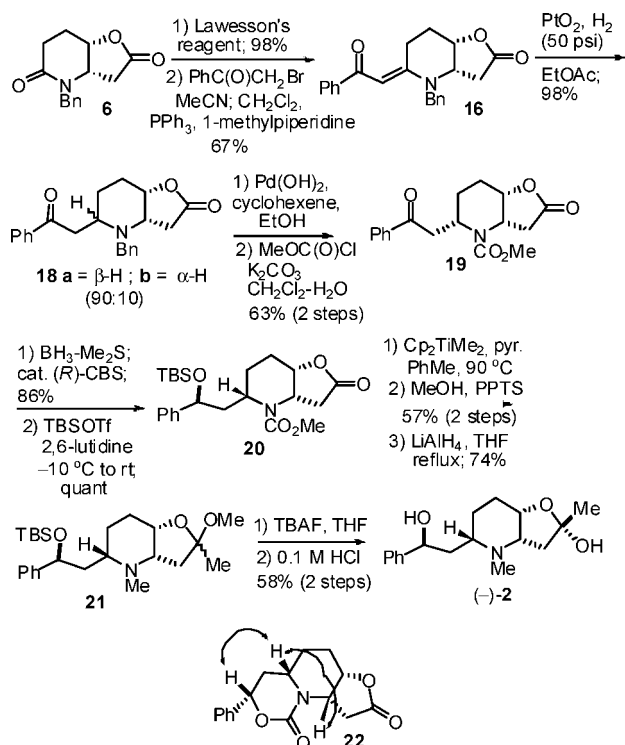
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Scheme 4. Synthesis of (–)-Sedacryptine



ketone group in **19** with BH₃·SMe₂ catalyzed by (*R*)-2MeCBS²³ 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 phenylacetyl 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*-BuMe₂SiOTf to give **20**. Methylenation of the γ-lactone carbonyl using Petasis' reagent²⁴ proceeded chemoselectively to give the corresponding cyclic methylenide 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 LiAlH₄ 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 [α]_D²⁵ = –13.5 (*c* 0.74, CHCl₃); for (+)-sedacryptine:^{19d} [α]_D²⁰ = +14 (*c* 0.54, CHCl₃). 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 alkaloids, (+)-isofebrifugine and (–)-sedacryptine. The use of **6** provides flexibility in our approach. Further studies in the use of **6** in alkaloid synthesis are continuing.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council, Canada, and the University of Regina for financial support.

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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