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# Radicamines A and B: Synthesis and Revision of the Absolute Configuration

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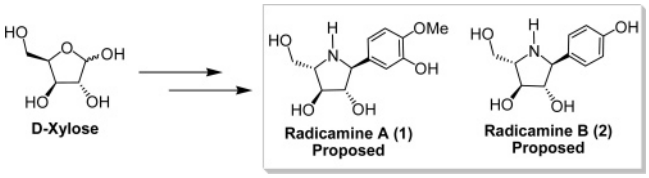
## ABSTRACT




**Starting from D-xylose, enantioselective syntheses of 1 and 2, the proposed structures for radicamines A and B, were accomplished. Both $^{1}H$ and $^{13}C$ NMR spectra of 1 and 2 were identical with those of the natural products, but the optical rotation measurements identified that 1 and 2 were actually the enantiomers of the natural radicamines A and B, respectively.**

Polyhydroxylated alkaloids (or iminosugars)[1] have been extensively studied over the past three decades owing to their remarkable biological properties and their potential as pharmaceuticals.[2] Polyhydroxylated pyrrolidines carrying an aromatic substituent on the iminosugar ring are a rare class of alkaloids found in nature. (−)-Codonopsinine **3** and (−)-codonopsine **6**[3] are the first two examples in this unusual category (Figure 1). These two alkaloids were later found to exhibit hypotensive pharmacological activity with no effect on the central nervous symtem in animal tests; thus, much effort has been devoted to synthetic studies on **3** and **6**.[4] In 2001, two new aromatic pyrrolidine alkaloids, radicamines A and B, were isolated by Kusano and co-workers[5] from *Lobelia chinensis* LOUR (Campanulaceae), a plant distributed widely throughout China, Korea, and Japan. The relative stereochemistry of these two compounds was proposed on the basis of the extensive spectroscopic data. The absolute configuration of the pyrrolidine moiety of radicamine A was determined to be (2*S*,3*S*,4*S*,5*S*) by the comparison of the positive $[\alpha]_D$ value of *N*-methylradicamine A {$[\alpha]_D$ +6.3 (*c* = 0.80, MeOH)} with that of (+)-codonopsinine **4** {$[\alpha]_D$ +12.5 (*c* = 2.55, MeOH)}, and by a similar method, the (2*S*,3*S*,4*S*,5*S*)-configuration was assigned for radicamine B. The benzoate chirality method[5a] was also claimed to support the propsed absolute configurations above.

Both radicamines and codonopsinine can be regarded as DMDP derivatives which usually possess a (2*R*,3*R*,4*R*,5*R*)-pyrrolidine moiety.[6] Thus, the proposed absolute configuration of the radicamines is opposite to that of the naturally occurring DMDP derivatives. We considered it worthwhile establishing whether this might be another case of mis-

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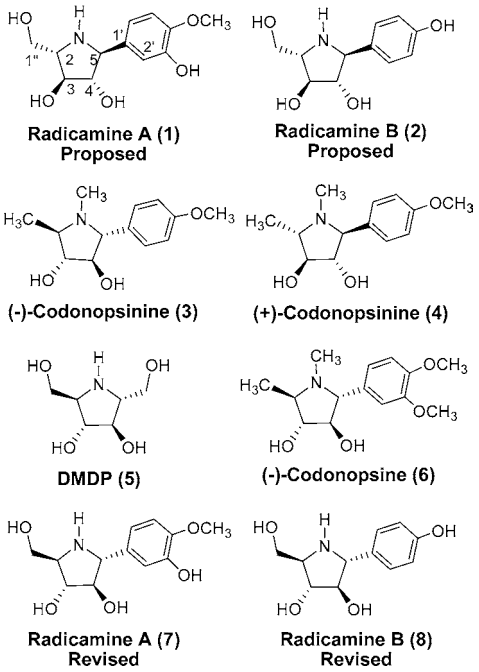
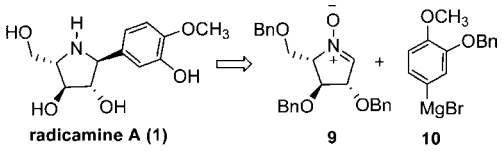



**Figure 1.** Radicamines and related natural compouds.

assigned natural products.[7] Furthermore, radicamines exhibit potent inhibitory activity against α-glucosidase.[5a] These two alkaloids and their derivatives might possess interesting biological activities and potential in pharmaceutical applications. Therefore, we became interested in the synthesis of radicamines A and B. In this paper, we report our convergent syntheses of the proposed structures for radicamines A and B, **1** and **2**, repectively, as well as revision of the absolute configuration of the natural products (Scheme 1).

**Scheme 1.** Retrosynthesis of Radimcamine A (**1**)

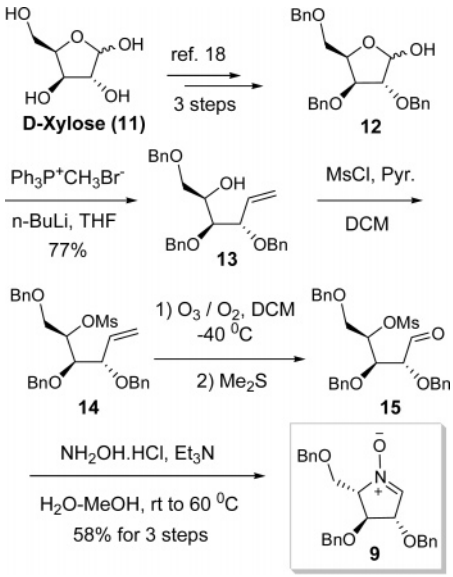



The chemical synthesis of polyhydroxylated pyrrolidines is extensively developed and well-documented in the literature.[8] Our synthetic strategy for **1** (Scheme 1) was based on the highly diastereoselective addition of organometallic reagents such as **10** to the polyhydroxylated cyclic nitrone **9**, tactics first reported by Coates[9] and further explored by many other groups such as that of Goti,[10] Petrini,[11] Merino,[12] Trombini,[13] and so on.

Nitrones are a versatile class of intermediates in organic synthesis, especially as 1,3-dipoles in cycloaddition reactions.[14] In addition, the carbon atom of the nitrone system is electrophilic enough to react with a variety of nucleophiles, including Grignard reagents. Recent developments of novel chemistry of nitrones has greatly extended their applications in organic synthesis.[15] For the synthesis of polyhydroxylated pyrrolidine alkaloids, introduction of substituents through addition of a nucleophile to a polydroxylated cyclic nitrone is potentially powerful approach.

Our concise synthesis relied on the practical preparation of the cyclic nitrone **9**[16] from D-xylose (Scheme 2).

**Scheme 2.** Preparation of Cyclic Nitrone **14**




Inspired by the reported methods,[17] we designed a synthetic route for the synthesis of **9**. The partially protected

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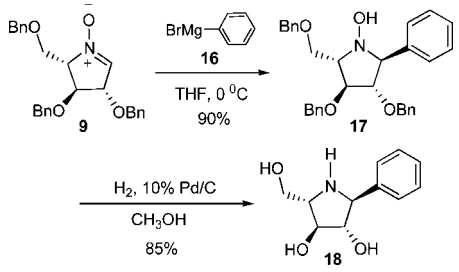
sugar **12**[18] derived from D-xylose was treated with methylenetriphenylphosphorane[19] to give the alkene **13**, and the resulting secondary alcohol was transformed to *O*-mesylate **14**. After ozonolysis of the terminal alkene, the aldehyde **15** with a leaving group was obtained. Treatment of the 4-mesylate−aldehyde **15** with hydroxylamine under basic conditions produced the cyclic nitrone **9** possibly through the formation of a geminal bis(hydroxylamino) sugar, then cyclization and subsequent elimination of the second hydroxylamine unit.[20] During nitrone formation, although pyridine was inefficient as a base, triethylamine, diethylamine, sodium bicarbonate, and sodium carbonate all work well for mediating this process. This synthetic approach possesses obvious merits in that (1) one-pot reactions can be effected from **13** to the final product **9** and (2) the sequence is capable of multigram scale synthesis.

We next investigated the model addition of phenylmagnesium bromide **16** to nitrone **9**. Thus, treatment of **9** with phenylmagnesium bromide **16** afforded the desired product, the benzyl-protected *N*-hydroxylpyrrolidine **17**, in 90% isolated yield. The gratifyingly high stereoselectivity might be ascribed to a Felkin−Anh transition-state model which could be invoked.[21] Catalytic hydrogenation of **17** furnished coumpound **18**, 4′-deoxyradicamine B, in 85% isolated yield.[22] The configuration of the newly created stereocenter was confirmed to be (*S*) through the strong nOe effects between C(4)-H and C(2′,6′)-H in the 600 MHz $^1$H NMR spectrum of **18**.

Following the successful model reaction, we turned our attention to the synthesis of radicamine A. According to our retrosynthesis (Scheme 1), Grignard reagent **10** was required. Starting with guaiacol, we revised the preparation of substituted phenyl bromide **23**[23] as depicted in Scheme 3. Guaiacol was treated with benzoyl chloride in aqueous sodium hydroxide to give the benzoate **20**. The electron-withdrawing property of benzoyl group leads to the regio-

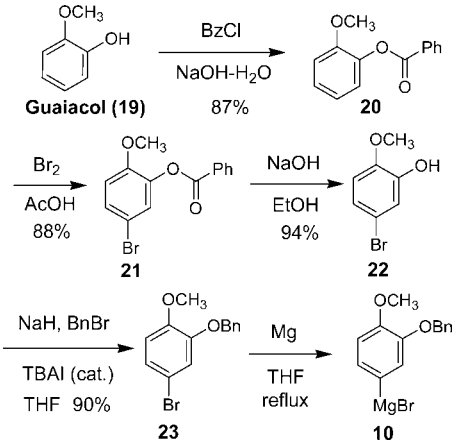
**Scheme 3.** Synthesis of 4′-Deoxyradicamine B (**18**)




selective bromination of benzene at the para position of the methoxyl group using AcOH as solvent.[24] Debenzoylation of **21** was unsuccessful with potassium carbonate in EtOH. However, the phenol hydroxyl group was released easily after treatment of **21** with sodium hydroxide in EtOH, followed by bubbling in carbon dioxide. The benzylation of 4-bromoguaiacol **22** was accomplished to afford the desired bromide **23** according to the reported procedures.[25]

Unlike phenylmagnesium bromide, the preparation of Grinard reagent **10** required heating the bromide **23** and magnesium turnings in refluxing THF for 1−3 h (Scheme 4). Similarly, reaction of the Grignard reagent **10** with nitrone

**Scheme 4.** Preparation of Grignard Reagent **10**




**9** in THF afforded the desired benzyl-protected *N*-hydroxylpyrrolidine **24** in 89% isolated yield. After catalytic hydrogenation of **24**, compound **1** was readily obtained in 87% isolated yield (Scheme 5).

The 600 MHz NOESY spectrum ($D_2O$) supported the assigned stereochemistry based on the strong NOE effects seen between the C(4)-H and C(2′)-H as well as between the C(5)-H and C(6′)-H. $^1$H and $^{13}$C NMR spectra of compound **1** were identical with those reported for the natural

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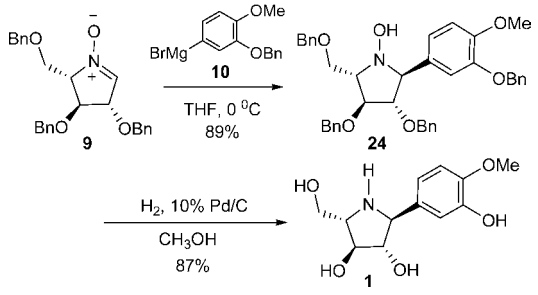
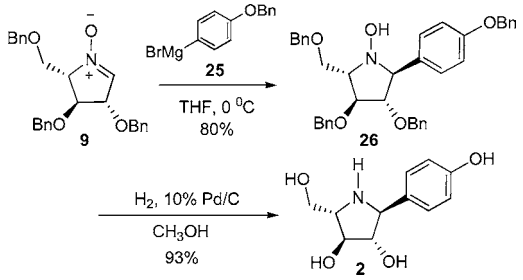
**Scheme 5.** Synthesis of Radicamine A (**1**)




**Scheme 6.** Synthesis of Radicamine B (**2**)




radicamine A. However, the optical rotation of compound **1** {$[\alpha]_D$ −44.4 ($c$ = 0.45, $H_2O$)} was opposite to that of the natural product {$[\alpha]_D$ +43.7 ($c$ = 0.13, $H_2O$)}. Therefore, it can be concluded that compound **1**, the proposed structure for radicamine A, is actually the enantiomer of natural radicamine A. The correct structure of the natural radicamine A is **7** which is of (2*R*,3*R*,4*R*,5*R*)-configuration.

Through similiar synthetic procedures to those above, the reaction of nitrone **9** with 4-benzyloxyphenylmagnesium bromide **25**[26] afforded compound **26** in 80% isolated yield. Catalytic hydrogenation of **26** produced compound **2** in 93% isolated yield (Scheme 6). The 600 MHz 1D and 2D NMR spectra confirmed the stereochemistry of compound **2**. $^1$H and $^{13}$C NMR spectra of compound **2** were identical to those reported for the natural radicamine B. However, the optical rotation of **2** {$[\alpha]^{30}_D$ −72.7 ($c$ = 0.17, $H_2O$)} was opposite to that of the natural radicamine B {li.t[5a] $[\alpha]_D$ +72.0 (c = 0.10, $H_2O$)}, indicating that compound **2** is actually the enantiomer of natural radicamine B. The correct structure of radicamine B is **8** which is also of (2*R*,3*R*,4*R*,5*R*) configuration.

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In summary, we have achieved a pratical preparation of D-xylose-derived cyclic nitrone **9** and accomplished the total synthesis of compounds **1** and **2**, the proposed structures for radicamines A and B, respectively. On the basis of comparison of the optical rotation of **1** and **2** with those of the natural products, the absolute configuration of the two alkaloids was revised to (2*R*,3*R*,4*R*,5*R*) configuration.

For the total synthesis of the natural products **7** and **8**, we are currently working on the synthesis of the enantiomer of the polyhydrohydroxylated cyclic nitrone **9** starting from D-arabinose and will report our results in due course.

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**Supporting Information Available:** Experimental procedures, characterization data, and $^1$H NMR and $^{13}$C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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