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Total synthesis of (−)-radicamine B

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Abstract—The synthesis of a chiral cyclic nitrone with L-*arabino* configuration and its application in the total synthesis of radicamine B is reported. An agreement in the spectral data with natural radicamine B but specific rotation with an opposite sign warranted a revision of the absolute configuration of radicamine B.

Radicamines A **1** and B **2**,[1] two new pyrrolidine alkaloids were isolated as inhibitors of α-glucosidase[2] from the plant *Lobelia chinensis* Lour., a herb that is used as a diuretic, an antidote, a hemostat and as a carcinostatic agent for stomach cancer in Chinese folk medicine. The structures and relative stereochemistry of both these compounds (Fig. 1) were determined on the basis of extensive NMR studies. However, the absolute configuration of these compounds was assigned by comparing the specific rotation with the natural codonopsinine **3** and with its antipode **4**. Due to its remarkable biological properties we have undertaken the synthesis of radicamine B. Herein, we describe the total synthesis of radicamine B with the proposed absolute configuration.

The facial selective addition of a suitable aryl Grignard to the L-*arabino* configured cyclic nitrone **5** (Fig. 1) forms the key approach of our intended synthesis of **2**.[3] Synthesis of the key nitrone **5** was envisaged from L-arabinose.[4] Very recently, Yu et al. reported (**5** was made from D-xylose) a similar strategy for the synthesis of radicamines A and B and revised the absolute configuration of both.[5]

Our initial efforts on the synthesis of **2** were focused on the preparation of cyclic nitrone **5** with control of the relative configuration of the three contiguous stereocenters, as shown in Scheme 1, based on the reported synthesis of *ent*-**5** from D-arabinose by Vogel and co-workers.[4b]

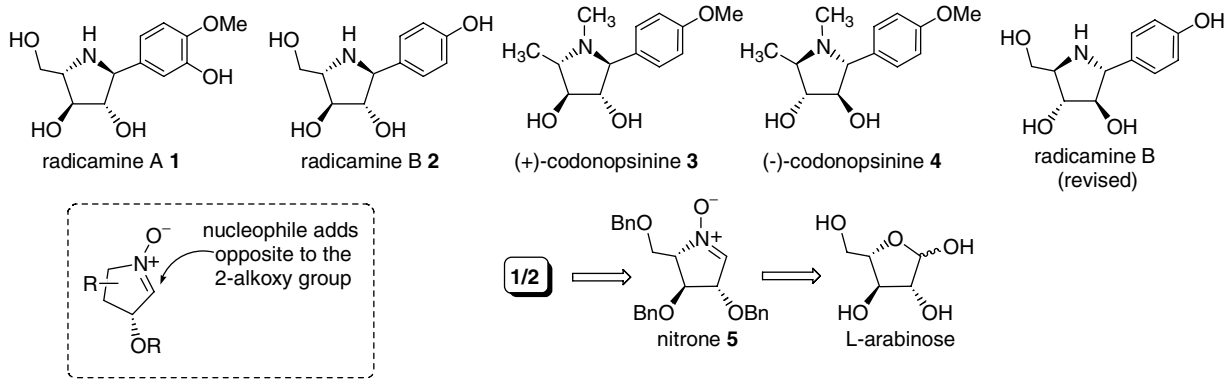

Figure 1. Radicamines and their retrosynthetic analysis.

Keywords: Polyhydroxy pyrrolidine alkaloids; Radicamine B; Codonopsinine; Cyclic nitrone; Grignard addition.
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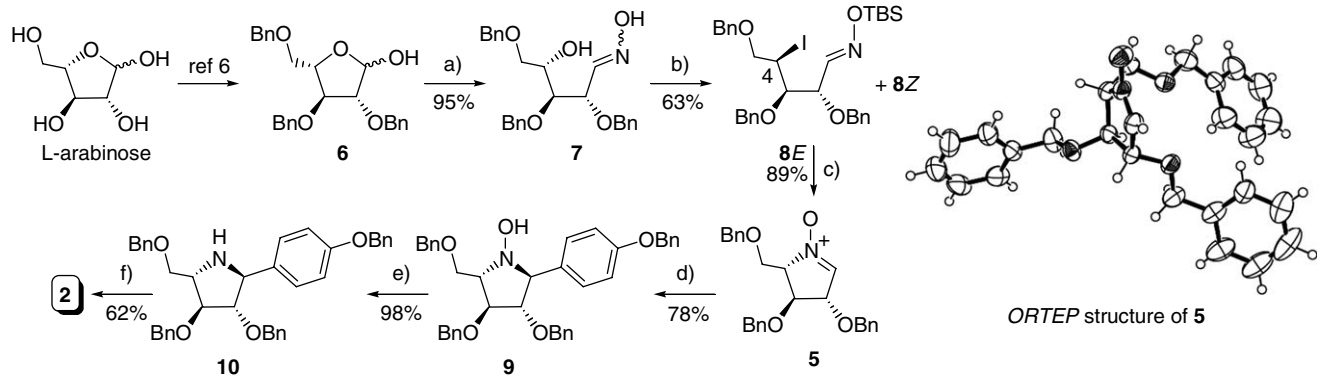

Scheme 1. Reagents and conditions: (a) $NH_2OH{\cdot}HCl$, $NaHCO_3$, EtOH, reflux, 2 h; (b) i. TBDMSCl, pyridine, rt, 36 h; ii. I_2, TPP, imidazole, toluene, reflux, 3 h; (c) TBAF, toluene, reflux, 3 h; (d) 4-benzyloxyphenyl MgBr, Et_2O–THF (1:2), −78 °C, 2 h; (e) Zn, aq NH_4Cl, reflux, 3 h; (f) H_2, $PdCl_2$, EtOH, rt, 20 h.

The 2,3,5-tri-*O*-benzyl-L-arabinose **6** was prepared from L-arabinose (48% overall yield) using the reported procedure.[6] The reaction of lactol **6** with hydroxylamine hydrochloride afforded an inseparable mixture (7:3) of *E*/*Z*-oximes **7**. Selective *O*-silylation with TBDMSCl in dry pyridine, followed by iodination with inversion of the configuration at C(4) led to the isolation of a mixture of *E*/*Z*-oxime derivatives **8**. After chromatographic separation, desilylation of the major isomer **8***E* with concomitant intramolecular nucleophilic displacement was attempted with anhydrous TBAF in toluene under reflux and the required nitrone **5** was obtained as a crystalline solid. The spectral and analytical data of **5** were in agreement with the reported data of *ent*-**5**. A single crystal X-ray structural analysis of **5** confirmed the structure (Scheme 1).[7]

The reaction of cyclic nitrone **5** with *p*-benzyloxyphenylmagnesium bromide was executed in Et_2O–THF at −78 °C.[3b] The reaction was highly diastereo-selective and afforded *N*-hydroxypyrrolidine derivative **9** in 78% yield. The spectral and analytical data of **9** were in agreement with the proposed structure. Reductive N–O bond cleavage using Zn in aq NH_4Cl gave the pyrrolidine derivative **10**. Finally, hydrogenolysis of **10** with H_2 over $PdCl_2$ in ethanol gave **2** in 62% yield. The relative stereochemistry of **2** was confirmed from ^1H–^1H coupling constants, COSY and NOESY spectra. Although, the spectral data of synthetic **2** had minor deviations (chemical shifts) from the reported data of the natural product, which was expected due to the exceptional chelating ability of these polyhydroxy pyrrolidine compounds with a metal or proton,[8] the optical rotation however, of **2** ($[\alpha]_D^{25}$ −69 (*c* 0.2, H_2O) {lit.[1] $[\alpha]_D^{25}$ +72 (*c* 0.1, H_2O)}),[9] was similar in magnitude but opposite in sign. This confirmed the revision[5] in the absolute configuration of radicamine B.

In conclusion, a concise synthesis of unnatural (−)-radicamine B is described herein from L-arabinose (10 steps, in an overall yield of 12%) which confirms the revised absolute configuration of naturally occurring radicamine B as (2*R*,3*R*,4*R*,5*R*).

Acknowledgements

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Supplementary data

NMR spectra of compounds **2**, **5**, and **9**, and crystallographic data for **5** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.07.120.

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7. The crystallographic data of compound **5** have been deposited with the Cambridge Crystallographic Data Centre as deposition No. CCDC 611018. Copies of the data can be obtained, free of charge, on application to the

CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk].
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9. Spectral data of compound **2**: $[\alpha]_D^{25}$ −69 (*c* 0.2, H_2O); lit.[1] $[\alpha]_D^{25}$ +72 (*c* 0.1, H_2O); ^1H NMR (500 MHz, $CDCl_3$): δ 3.68–3.70 (m, 1H), 3.96 (dd, $J = 12.5$, 5.8 Hz, 1H), 4.01 (dd, $J = 12.5$, 3.9 Hz, 1H), 4.23 (t, $J = 7.8$ Hz, 1H), 4.43 (d, $J = 10.1$ Hz, 1H), 4.51 (dd, $J = 10.1$, 7.8 Hz, 1H), 7.05 (d, $J = 8.2$ Hz, 2H), 7.49 (d, $J = 8.2$ Hz, 2H). ^{13}C NMR (125 MHz): 58.5 (t), 61.4 (d), 62.7 (d), 73.9 (d), 77.6 (d), 115.9 (d), 123.8 (s), 129.8 (d), 156.7 (s). ESI-MS *m*/*z*: 226.53 ($[M+1]^+$). Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22%. Found C, 58.40; H, 7.02; N, 6.32%.