JOC Note

Short, Stereoselective Synthesis of the Naturally Occurring Pyrrolidine Radicamine B and a Formal Synthesis of Nectrisine

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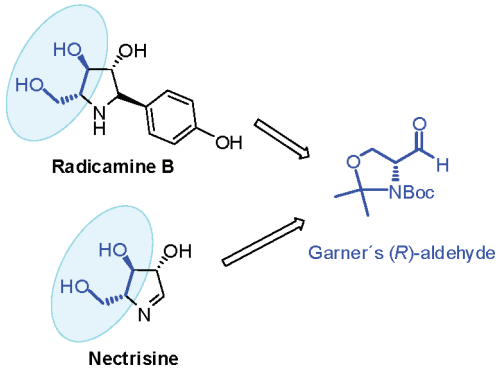
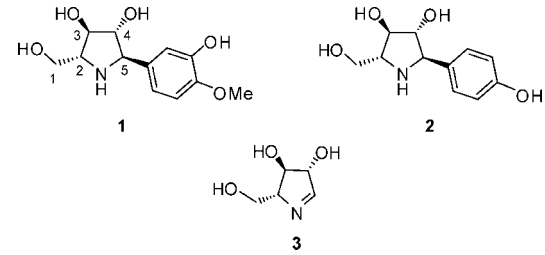


A short, stereoselective synthesis of the naturally occurring pyrrolidine radicamine B is reported. Garner's (*R*)-aldehyde, prepared from D-serine, was the chiral starting material. The pyrrolidine ring was stereoselectively created in a very efficient way through a five-step, one-pot transformation. In addition, an intermediate of this synthesis was transformed into an intermediate of a previously published synthesis of the potent α-glucosidase inhibitor nectrisine.

The polyhydroxylated alkaloids (iminosugars) radicamines A (**1**) and B (**2**) are two compounds belonging to the ample group of the naturally occurring pyrrolidines.[1] Members of this compound class are known to exhibit a broad range of biological activities.[1d,2] Compounds **1** and **2** were isolated a few years ago by Kusano and co-workers from *Lobelia chinensis* Lour. (Campanulaceae), a plant used in Chinese folk medicine as a diuretic, a hemostat, and a carcinostatic agent for stomach cancer.[3] Both compounds were found to exhibit inhibitory activity on α-glucosidase.[4] A strong inhibitory ability on α-glucosidase and other glycosidases has also been found for the Δ^1-dehydropyrrolidine nectrisine **3**, initially isolated as immunomodulator FR-900483 from a strain of the fungus *Nectria lucida*.[5] The frequent association of this type of biological property with useful pharmacological applications has led to a significant synthetic effort on members of this compound class.[6]



Seven syntheses of nectrisine have been reported, including one of the non-natural enantiomer.[7,8] Various commercially

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(8) Analogues and surrogates of nectrisine with a similar pharmacological profile have also been prepared. See: (a) Tschamber, T.; Gessier, F.; Neuburger, M.; Gurcha, S. S.; Besra, G. S.; Streith, J. *Eur. J. Org. Chem.* **2003**, 2792–2798. (b) Tschamber, T.; Gessier, F.; Dubost, E.; Newsome, J.; Tarnus, C.; Kohler, J.; Neuburger, M.; Streith, J. *Bioorg. Med. Chem.* **2003**, *11*, 3559–3568.

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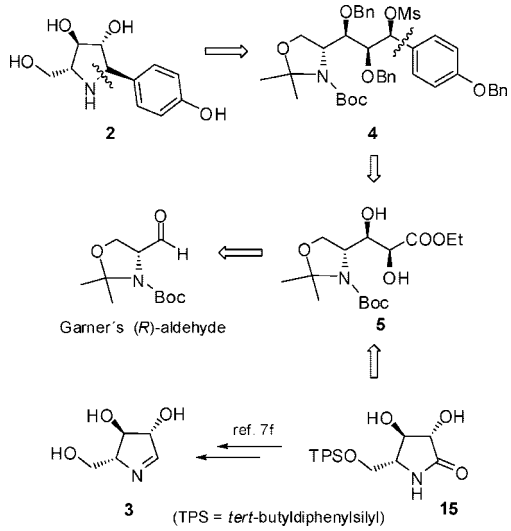
available products (sugar derivatives, diethyl tartrate, D-serine) were the chiral starting materials. Furthermore, four previous syntheses of radicamine B (**2**) have very recently been reported, one of the natural compound itself and three of its enantiomer.[7g,9] These syntheses, which are almost identical and show only marginal differences, used five-carbon sugars as starting materials and relied on the same synthetic concept with a cyclic nitrone as a key intermediate. Stereoselective addition of an arylmetal reagent to the C=N bond of the nitrone was a key step in all cases.[7g,9]

We now present an efficient synthesis of **2**, performed according to a different concept shown as a retrosynthetic plan in Scheme 1. Thus, **2** should be available from mesylate **4** with pyrrolidine ring formation via intramolecular nucleophilic substitution. Compound **4** should be prepared from dihydroxy ester **5**, to be obtained in turn from Garner′s (*R*)-aldehyde via olefination and dihydroxylation. In addition, compound **5** should be amenable to an easy conversion into an intermediate of a previous synthesis of nectrisine (compound **15**, see Scheme 4).[7f] This would thus amount to a formal synthesis of this natural compound.

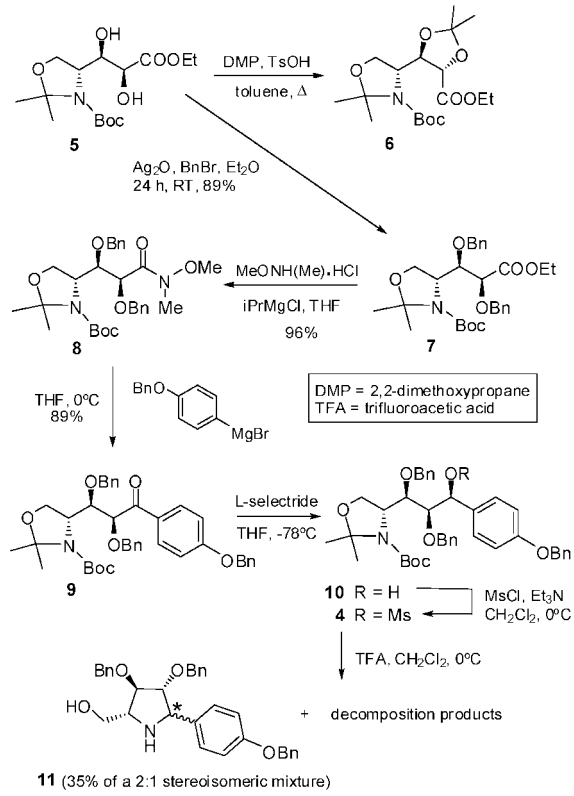
SCHEME 1. Retrosynthetic Analysis of Radicamine B (2)



This retrosynthetic concept for pyrrolidine **2** was put into practice as depicted in Scheme 2. The known dihydroxy ester **5** was prepared in two steps and 83% overall yield from Garner′s (*R*)-aldehyde[10] by means of a modification of the procedure described for the preparation of the enantiomer.[11] In order to unambiguously confirm the stereostructure of **5**, we converted it into the crystalline acetonide **6**.[11] An X-ray diffraction analysis of **6** secured its relative as well as its absolute configuration.

Benzylation of the hydroxyl groups in diol **5** with benzyl bromide and silver oxide[12] gave **7**, which was then converted

SCHEME 2. Attempt at a Stereoselective Synthesis of Radicamine B



into Weinreb amide **8**.[13,14] Treatment of **8** with the Grignard reagent *p*-benzyloxyphenyl magnesium bromide[15] afforded ketone **9**, which was then stereoselectively reduced with L-selectride to alcohol **10** (obtained as an 87:13 mixture of diastereoisomers).[16] Mesylation of **10** furnished **4**, which was then subjected in crude form to acidic conditions. These were intended to cause initial cleavage of the acetonide and Boc groups[17] followed by intramolecular nucleophilic displacement of the mesyl group with closure of the pyrrolidine ring.[18] However, the only result was the formation of a ca. 2:1 mixture

(9) (a) Yu, C.-Y.; Huang, M.-H. *Org. Lett.* **2006**, *8*, 3021–3024. (b) Gurjar, M. K.; Borhade, R. G.; Puranik, V. G.; Ramana, C. V. *Tetrahedron Lett.* **2006**, *47*, 6979–6981. (c) Merino, P.; Delso, I.; Tejero, T.; Cardona, F.; Goti, A. *Synlett* **2007**, 2651–2654. (d) Liu, C.; Gao, J.; Yang, G.; Wightman, R. H.; Jiang, S. *Lett. Org. Chem.* **2007**, *4*, 556–558.

(10) Prepared from D-serine according to: Campbell, A. D.; Raynham, T. M.; Taylor, R. J. K. *Synthesis* **1998**, 1707–1709. For a review on Garner's aldehyde, see: Liang, X.; Andersch, J.; Bols, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2136–2157.

(11) Dondoni, A.; Merino, P.; Perrone, D. *Tetrahedron* **1993**, *49*, 2939–2956. Our modification consisted in carrying out the dihydroxylation by means of the Sharpless asymmetric procedure. In this way, the overall yield of **5** from Garner′s (*R*)-aldehyde was improved from ca. 50 to 83% (see Experimental Section).

(12) For examples of O-benzylation with this method, see: (a) Mislow, K.; O'Brien, R. E.; Schaefer, H. *J. Am. Chem. Soc.* **1962**, *84*, 1940–1944. (b) Takai, K.; Heathcock, C. H. *J. Org. Chem.* **1985**, *50*, 3247–3251. (c) Marshall, J. A.; Seletsky, B. M.; Luke, G. P. *J. Org. Chem.* **1994**, *59*, 3413–3420. (d) Chen, M.-D.; He, M.-Z.; Zhou, X.; Huang, L.-Q.; Ruan, Y.-P.; Huang, P.-Q. *Tetrahedron* **2005**, *61*, 1335–1344. (e) Yokokawa, F.; Inaizumia, A.; Shioiri, T. *Tetrahedron* **2005**, *61*, 1459–1480.

(13) For reviews on Weinreb amides, see: (a) Mentzel, M.; Hoffmann, H. M. R. *J. Prakt. Chem.* **1997**, *339*, 517–524. (b) Singh, J.; Satyamurthi, N.; Aidhen, I. S. *J. Prakt. Chem.* **2000**, *342*, 340–347. (c) Khlestkin, V. K.; Mazhukin, D. G. *Curr. Org. Chem.* **2003**, *7*, 967–993.

(14) The conditions used for the preparation of Weinreb amide **8** were taken from: Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U. H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461–5464.

(15) Kamada, A.; Sasaki, A.; Kitazawa, N.; Okabe, T.; Nara, K.; Hamaoka, S.; Araki, S.; Hagiwara, H. *Chem. Pharm. Bull* **2004**, *52*, 79–88. The Grignard reagent has now become commercially available.

(16) The stereochemical course of the reduction of **9** was assumed to be as depicted in Scheme 2 upon reliance on the results in the reduction of a ketone closely related to **9** (with an alkyl residue instead of the aryl group), where the configuration of the alcohol was secured by means of X-ray diffraction (unpublished results).

(17) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York, 1999; pp 518−525.

(18) For some recent examples of pyrrolidine ring closure via intramolecular nucleophilic displacement, see for example: (a) Yoda, H.; Asai, F.; Takabe, K. *Synlett* **2000**, 1001–1003. (b) Merino, P.; Franco, S.; Lafuente, D.; Merchán, F.; Revuelta, J.; Tejero, T. *Eur. J. Org. Chem.* **2003**, 2877–2881. (c) Chandrasekhar, S.; Chandrasekhar, G.; Vijeender, K.; Sarma, G. D. *Tetrahedron: Asymmetry* **2006**, *17*, 2864–2869.

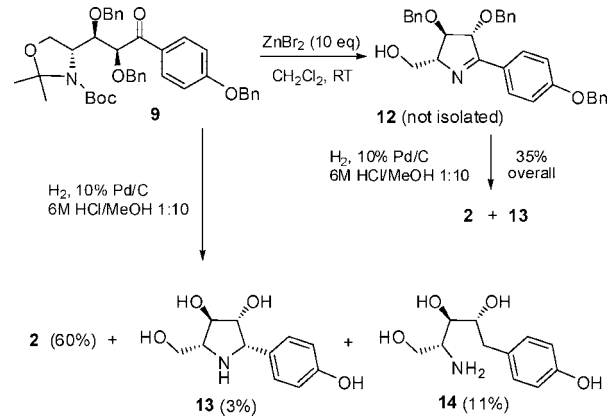
of stereoisomeric pyrrolidines **11** in low yield, accompanied by extensive decomposition. This was attributed to the marked instability of mesylate **4**. Most likely, its benzylic nature caused a marked tendency to react via a S_N1 mechanism with formation of an unstable carbocation and subsequent loss of stereochemical control.[19] We then tried other conditions for mesylation (−20 °C) and other sulfonylating reagents such as TsCl, NsCl, or $ClCH_2SO_2Cl$[20] but without success. Either decomposition or no reaction at all was the only result observed.

In view of these failures in creating the C−N bond by means of an intramolecular displacement, we modified our synthetic concept and decided to form the pyrrolidine ring through reduction of the C=N bond in a cyclic imine. Thus, treatment of ketone **9** with anhydrous $ZnBr_2$ in dry CH_2Cl_2 caused Boc and acetonide cleavage[21] with formation of the unstable imine **12**, which was not isolated (Scheme 3). When crude **12** was stirred under a H_2 atmosphere in an acidic medium with a palladium catalyst,[22] it only furnished in low overall yield a mixture of radicamine B (**2**) and pyrrolidine **13**, the non-natural epimer of **2** at C-5.[23,24] Attempts at reduction of **12** with $NaCNBH_3$ only caused decomposition.[6k,25] The instability of imine **12** suggested that it should be generated and reduced in situ in an one-pot procedure.[26] Indeed, when ketone **9** was stirred under H_2 in the same conditions as above, the desired **2** was formed as the major compound (ca. 60% yield), together with small amounts of **13** (3%) and the primary amine **14** (11%), a hydrogenolysis product of **2** and/or **13**.[24] It is worth noting here that **2** is formed in a one-pot manner through of a sequence of five steps (the precise order is not known): hydrogenolytic cleavage of the three benzyl groups, acidic cleavage of the Boc and the acetonide groups, intramolecular imine formation, and reduction of the imine C=N bond.

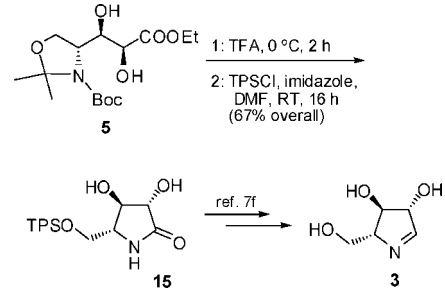
As commented above, dihydroxy ester **5** could be readily converted into an intermediate of a previous synthesis of nectrisine.[7f] Acid treatment of **5** caused cleavage of the Boc and acetonide groups, followed by in situ spontaneous formation of the lactam ring. This gave a crude triol which was then subjected to selective silylation of the primary alcohol group to yield pyrrolidinone **15** in 67% overall yield (eight steps and 47% yield from D-serine). Since **15** was a late intermediate in Hulme's synthesis of **3**,[7f,27] this constitutes a formal synthesis of this natural compound.

In summary, we have performed an efficient, stereoselective synthesis of the glycosidase inhibitor radicamine B **2** in six steps and 38% overall yield from Garner's (*R*)-aldehyde. This corresponds to 10 steps and 32% overall yield from the commercially available D-serine.[10] This result is markedly better

SCHEME 3. Stereoselective Synthesis of Radicamine B (2)



SCHEME 4. Formal Synthesis of Nectrisine 3



in terms of overall yield[28] than those reported in the previous syntheses of either **2** or its enantiomer.[7g,9] Furthermore, we have used an intermediate of this synthesis to perform a formal synthesis of the glycosidase inhibitor nectrisine **3**.

Experimental Section

General experimental features are described in the Supporting Information.

***tert*-Butyl (4*R*)-4-[(1*R*,2*S*)-1,2-bis(benzyloxy)-3-(4-benzyloxyphenyl)-3-oxopropyl]-2,2-dimethyloxazolidine-3-carboxylate (9).** 4-Benzyloxyphenylmagnesium bromide was generated from the corresponding bromide according to the reported procedure.[15] Weinreb amide **8** (400 mg, ca. 0.75 mmol) was dissolved under N_2 in dry THF (4 mL) and treated dropwise at 0 °C with the aforementioned Grignard reagent (3 mmol, 4 equiv). The reaction mixture was then stirred for 1 h at the same temperature. Workup (extraction with Et_2O) and column chromatography of the oily residue on silica gel (hexanes−EtOAc, 9:1) provided **9** (436 mg, 89%): oil; $[\alpha]_D$ −3 (*c* 1.5, $CHCl_3$); ^1H NMR (500 MHz, DMSO-d_6, 70 °C) δ 8.02 (2H, d, J = 8.8 Hz), 7.50−7.20 (14H, br m), 7.10 (3H, m), 5.22 (2H, s), 4.76 (1H, br d, J = 4 Hz), 4.50−4.45 (4H, br m), 4.38 (1H, br d, J = 11.2 Hz), 4.15 (1H, dd, J = 8.7, 3.6 Hz), 3.92 (1H, br s), 3.89 (1H, br t, J = 8 Hz), 1.41 (12H, s), 1.40 (3H, s); ^{13}C NMR (125 MHz, DMSO-d_6, 70 °C) δ 208.8*, 162.2, 151.5*, 137.4, 137.3, 136.2, 128.7, 92.9, 79.3 (C), 130.8 (x2), 128.1 (x2), 127.9 (x2), 127.6 (x3), 127.5 (x3), 127.3 (x2), 127.2 (x2), 114.4 (x2), 127.0, 84.2, 78.8*, 58.6* (CH), 74.1, 71.8, 69.4, 62.8 (CH_2), 27.8 (x3), 25.6*, 23.9* (starred signals are low and broad); IR ν_{max} 1690 (br, C=O) cm^{-1}; HR FAB MS *m*/*z* 652.3281 (M + H^+). Calcd for $C_{40}H_{46}NO_7$, 652.3274.

***tert*-Butyl (4*R*)-4-[(1*R*,2*R*,3*S*)-1,2-bis(benzyloxy)-3-(4-benzyloxyphenyl)-3-hydroxypropyl]-2,2-dimethyloxazolidine-3-carboxylate (10).** A solution of ketone **9** (195 mg, 0.3 mmol) in dry

(19) This idea was suggested by the fact that acidic treatment of alcohol **10** under similar conditions as **4** (TFA, 1 h, 0 °C) also gave a 2:1 mixture of pyrrolidines **11**, together with extensive decomposition.

(20) Shimizu, T.; Ohzeki, T.; Hiramoto, K.; Hori, N.; Nakata, T. *Synthesis* **1999**, 1373–1385.

(21) Ribes, C.; Falomir, E.; Murga, J. *Tetrahedron* **2006**, *62*, 1239–1244.

(22) (a) Card, P. J.; Hitz, W. D. *J. Org. Chem.* **1985**, *50*, 891–893. (b) Takayama, S.; Martin, R.; Wu, J.; Laslo, K.; Siuzdak, G.; Wong, C.-H. *J. Am. Chem. Soc.* **1997**, *119*, 8146–8151. (c) Espelt, L.; Parella, T.; Bujons, J.; Solans, C.; Joglar, J.; Delgado, A.; Clapés, P. *Chem.—Eur. J.* **2003**, *9*, 4887–4899.

(23) Mixtures of **2** and **13** (5-epi-radicamine B) of variable composition were obtained, with the undesired **13** being always the major compound.

(24) For a synthesis of **13**, see: Zhou, X.; Liu, W.-J.; Ye, J.-L.; Huang, P.-Q. *Tetrahedron* **2007**, *63*, 6346–6357.

(25) Wong, C.-H.; Provencher, L.; Jung, S.-H.; Wang, Y.-F.; Chen, L.; Wang, R.; Steensma, D. H. *J. Org. Chem.* **1995**, *60*, 1492–1501.

(26) For a similar situation, see for example: Yu, D.-S.; Xu, W.-X.; Liu, L.-X.; Huang, P.-Q. *Synlett* **2008**, 1189–1192.

(27) Hulme, A. N.; Montgomery, C. H.; Henderson, D. K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1837–1841.

(28) The syntheses reported in ref 7g, 9 involve reaction sequences of 9−11 steps from D-xylose, L-xylose, or L-arabinose as the starting materials. Overall yields were in the range from 8 to 17%.

THF (2 mL/mmol) was cooled under N_2 to −78 °C and treated dropwise with a 1 M solution of L-selectride in THF (0.6 mL, 0.6 mmol). The mixture was stirred for 3 h at the same temperature and then quenched through addition of 10% aq NaOH (0.7 mL) and 30% H_2O_2 (0.45 mL). Further stirring for 20 min at 0 °C and workup (extraction with Et_2O) gave an oily residue which was chromatographed on silica gel (hexanes−EtOAc, 9:1). This yielded alcohol **10** as an 87:13 mixture of diastereoisomers (determined by ^{1}H NMR) (174 mg, 89%), which could not be separated. This mixture was used in the mesylation step.

(2*R*,3*R*,4*R*,5*R*,*S*)-3,4-Bis(benzyloxy)-5-(4-benzyloxyphenyl)-2-hydroxymethylpyrrolidine (11). The mixture of diastereoisomeric alcohols **10** from above was dissolved under N_2 in dry CH_2Cl_2 (2 mL), cooled to 0 °C, and treated with MsCl (40 μL, ca. 0.5 mmol), Et_3N (140 μL, 1 mmol), and DMAP (3 mg, 0.025 mmol). The mixture was stirred at 0 °C for 1 h. Workup (extraction with CH_2Cl_2) gave an oily residue which was dissolved at 0 °C in dry CH_2Cl_2 (1 mL), treated with trifluoroacetic acid (1 mL), and stirred at the same temperature for 1 h. The volatiles were then removed under reduced pressure, and the oily residue was dissolved in MeOH and treated with aqueous ammonia until basic pH. Evaporation to dryness gave an oily residue which was then chromatographed on silica gel (CH_2Cl_2−MeOH, 19:1). This yielded a 2:1 mixture of diastereoisomers **11** (46 mg, 35%) identified by hydrogenolytic conversion to a mixture of **2** and **13** (identified in turn through their ^{1}H and ^{13}C NMR spectra).[7g,9,24]

(2*R*,3*R*,4*R*,5*R*)-2-(Hydroxymethyl)-5-(4-hydroxyphenyl)pyrrolidine-3,4-diol, Radicamine B (2). Ten percent palladium on carbon (Degussa-type E101 NE/W, 180 mg) was suspended in MeOH (5 mL) and stirred under an H_2 atmosphere for 5 min. Ketone **9** (195 mg, 0.3 mmol) was dissolved in MeOH (20 mL) and mixed with 6 M aqueous HCl (2 mL). The mixture was then added via syringe to the catalyst suspension, which was then stirred for 16 h at room temperature and ambient pressure. Filtration through Celite and removal of all volatiles under reduced pressure gave a residue which was dissolved in MeOH (10 mL) and treated dropwise with 33% aq NH_3 until basic pH. Removal of the solvent under reduced pressure gave a residue which was put on the top of a ion-exchange resin column (Dowex 50W × 4 200−400, preacidified with 0.5 M HCl). Elution with water (50 mL) and then 1 M aq NH_3 (15 mL), followed by removal of the volatiles of the latter fraction under reduced pressure, gave a brownish residue which was subjected to column chromatography on silica gel ($CHCl_3$−MeOH−aq NH_3, gradient from 95:4:1 to 70:29:1). This yielded a mixture of **2**, **13**, and **14** (50 mg, 74% overall), which could not be separated by means of standard chromatography. Final purification took place with the aid of HPLC (LiChroCART 250−10, elution with MeCN/H_2O 60:40, 2 mL/min). This gave **2** (40 mg, 60%), **13** (2 mg, 3%), and **14** (7 mg, 11%).

2: oil; $[\alpha]_D$ +73.6 (*c* 0.1, H_2O), lit.[3a] $[\alpha]_D$ +72 (*c* 0.1, H_2O); ^{1}H NMR (500 MHz, D_2O) δ 7.38 (2H, apparent d, J = 8.6 Hz), 6.98 (2H, apparent d, J = 8.6 Hz), 4.18 (1H, dd, J = 9, 7.5 Hz), 4.03 (1H, t, J = 7.5 Hz), 4.00 (1H, br d, J = 9 Hz), 3.84 (1H, dd, J = 11.5, 4.5 Hz), 3.77 (1H, dd, J = 11.5, 6.5 Hz), 3.34 (1H, ddd, J = 7.5, 6.5, 4.5 Hz); ^{13}C NMR (125 MHz, D_2O) δ 158.5, 133.2 (C), 131.8 (x2), 118.6 (x2), 84.3, 79.8, 66.1, 64.4 (CH), 64.8 (CH_2).

Radicamine B (2) and 5-*epi*-Radicamine B (13) via Imine 12. Ketone **9** (195 mg, 0.3 mmol) was dissolved in dry CH_2Cl_2 (3 mL) and treated with anhydrous $ZnBr_2$ (675 mg, 3 mmol). The mixture was then stirred for 20 min at room temperature. Quenching was performed by means of addition of saturated aq EDTA (15 mL). Extraction with CH_2Cl_2 (3 × 15 mL), drying of the organic layer on anhyd Na_2SO_4, and removal of all volatiles under reduced pressure gave an oily residue containing **12** which was used directly in the next reaction. Hydrogenation was performed under the same conditions as above. The column chromatography on silica gel afforded a ca. 2:1 mixture of **13** and **2** (24 mg, 35% overall).

(3*S*,4*R*,5*R*)-5-(*tert*-Butyldiphenylsilyloxymethyl)-3,4-dihydroxypyrrolidin-2-one (15). An ice-cooled solution of dihydroxy ester **5** (67 mg, 0.2 mmol) in CH_2Cl_2 (1 mL) was treated with trifluoroacetic acid (1 mL). The mixture was then stirred for 2 h at 0 °C. Removal of all volatiles under reduced pressure gave a residue which was dissolved in dry DMF (2 mL) and treated under N_2 with *tert*-butyldiphenylsilyl chloride (57 μL, 0.22 mmol) and imidazole (30 mg, 0.45 mmol). The mixture was then stirred for 16 h at room temperature. Workup (extraction with Et_2O) and column chromatography on silica gel (EtOAc) provided **15** (51 mg, 67%): oil; $[\alpha]_D$ +10.3 (*c* 0.9, $CHCl_3$), lit.[27] $[\alpha]_D$ +11.5 (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65−7.60 (4H, m), 7.45−7.35 (6H, br m), 6.20 (1H, s, NH), 4.90 (1H, br s, OH), 4.28 (1H, d, J = 7.5 Hz), 3.99 (1H, t, J = 7.5 Hz), 3.90 (1H, br s, OH), 3.89 (1H, dd, J = 10.5, 3 Hz), 3.62 (1H, dd, J = 10.5, 7.5 Hz), 3.52 (1H, td, J = 7.5, 3 Hz), 1.05 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 132.8, 132.7, 19.2 (C), 135.5, 135.4, 130.1, 130.0, 127.9 (x6), 76.4, 75.9, 58.2 (CH), 64.5 (CH_2), 26.9 (x3) (CH_3); IR ν_{max} 3300 (br, OH), 1708 (C=O) cm^{-1}.

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Supporting Information Available: Description of general and experimental features. Graphical ^{1}H and ^{13}C NMR spectra of compounds **2**, **5**, **6**, **7**, **8**, **9**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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