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A concise and divergent approach to radicamine B and hyacinthacine A_3 based on a step-economic transformation

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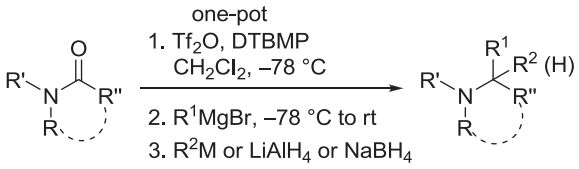
ABSTRACT

Based on our recently developed step-economic methodology of reductive alkylation of lactams/amides, we have developed a two-step synthesis of azasugar radicamine B (**2a**) and a four-step synthesis of azasugar hyacinthacine A_3 (**5**) from the common chiral building block **12**. Hantzsch ester (HEH) was used as a milder hydride donor in the one-pot stereoselective reductive alkylation of lactam **12**. The Wacker oxidation of fully substituted pyrrolidine derivative 2,5-*trans*-**17** led to the synthesis of hyacinthacine A_3 (**5**). Compound 2,5-*trans*-**17** could also serve as a plausible key intermediate for the synthesis of broussonetine sub-class of azasugars.

1. Introduction

Efficiency is the major goal in contemporary organic synthesis.[1] Step-economic organic synthesis is a useful tactic for this goal.[2] In this context, we have recently developed some step-economic organic transformations that allowed one-pot access to target molecules,[3–5] one such example being the one-pot sequential reductive alkylation of lactams/amides with Grignard and organolithium reagents or hydrides (Scheme 1).[3]



Scheme 1. One-pot sequential reductive alkylation of lactams/amides.

Polyhydroxylated alkaloids (or azasugars) have been extensively studied over the past three decades owing to the remarkable biological properties and the potential as pharmaceuticals.[6] For example, radicamines A (**1a**) and B (**2a**, Fig. 1), isolated from *Lobelia chinensis* Lour (Campanulaceae), show α-glucosidase inhibitory activity.[7] Codonopsinol (**3**),[8c] a new codonopsine related alkaloid recently isolated from the aerial parts of *Codonopsis clematidea*,[8a] also shows inhibitory activity against the α-glucosidase of yeast and bacillus *Bacillus stearothermophilus lyoph*.[8b] Interestingly, the unnatural analogues **1b** and **2b** show better inhibitory activities against α-glucosidases than radicamines A (**1a**) and B (**2a**).[8b] Hyacinthacines [e.g., A_2 (**4**) and A_3 (**5**)], a group of pyrrolizidine azasugars[9] isolated from the bulbs of *Muscari armeniacum* (Hyacinthaceae), show interesting inhibitory activities against a variety of glycosidases. Broussonetines, a sub-class of pyrrolidine azasugars [e.g., broussonetines C, D, M, O, P (**6**, **7**, **8**, **9**, **10**)] isolated from the plant species *Broussonetia kazinoki* Siebold (Moraceae),[10] exhibit stronger inhibitory activity against some glycosidases than standard azasugars.

As a continuation of our longstanding interest in the asymmetric synthesis of bioactive alkaloids and azasugars,[11] we have developed an approach to the asymmetric syntheses of 5-*epi*-radicamine B (**13**)[11f] and hyacinthacine A_3 (**5**)[9d] starting from tartarimide **11** (Scheme 2). This approach, however, have some shortcomings, such as the multi-step transformations from pyrrolidin-2-one **12** to 5-*epi*-radicamine B (**13**)[11f] and hyacinthacine A_3 (**5**), and the failure to access to the natural product of the former. Consequently, it is necessary to develop a concise and versatile synthetic route to these two alkaloids. We now report the efficient and divergent syntheses of azasugars radicamine B (**2a**) and hyacinthacine A_3 (**5**) by applying the above-mentioned step-economic method of reductive alkylation of lactams/amides (Scheme 1).[3]

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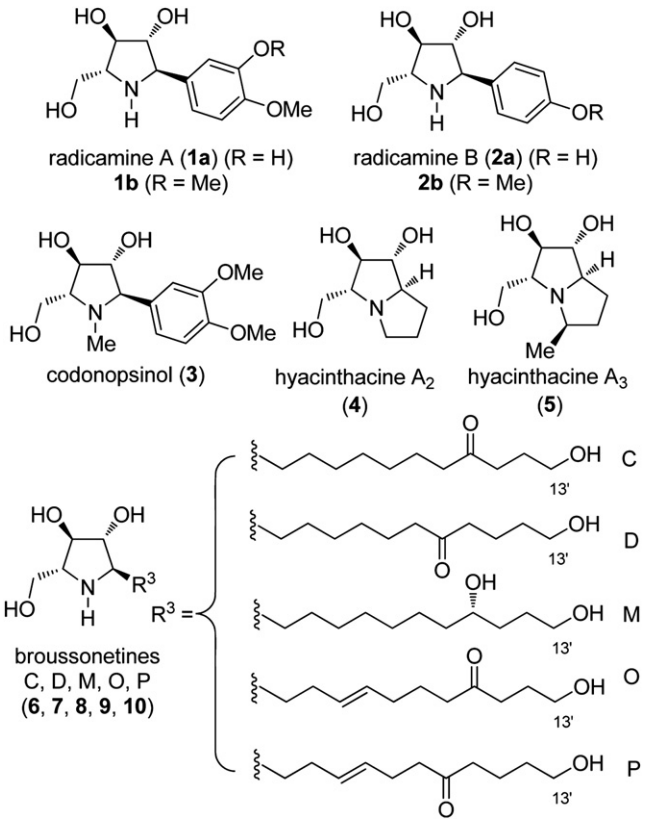
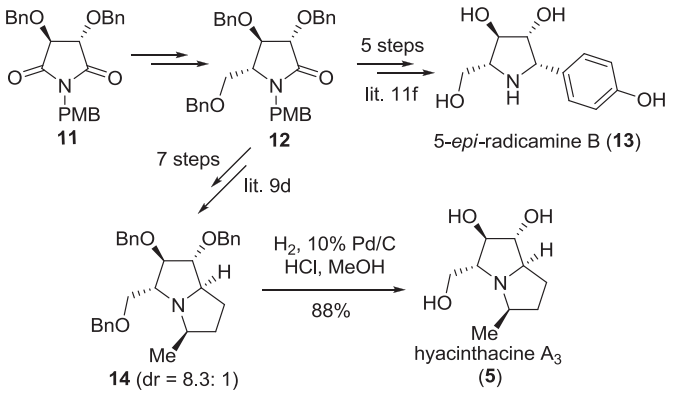


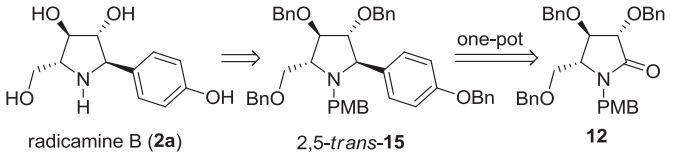
Fig. 1. Structures of some bioactive polyhydroxylated pyrrolidines and azasugars.



Scheme 2. Our previous syntheses of 5-*epi*-radicamine B and hyacinthacine A_3.

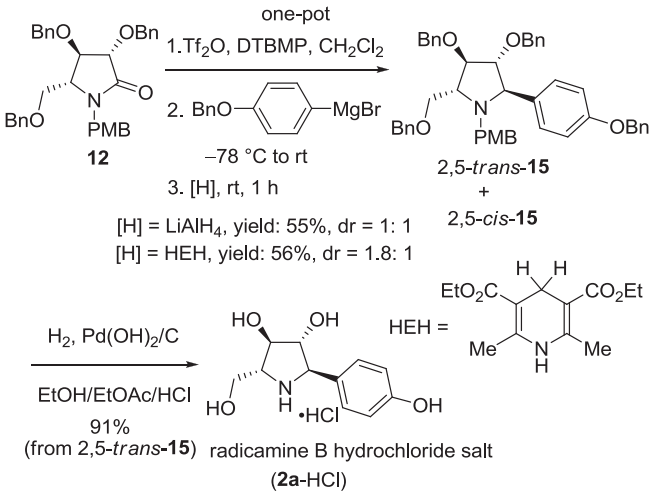
2. Results and discussion

We first undertook the synthesis of radicamine B (**2a**). Thanks to the nice work of Yu and Huang,[7c] the absolute configurations of radicamines A (**1a**) and B (**2a**) have been revised as shown in Fig. 1. Our retrosynthetic analysis of radicamine B (**2a**) is depicted in Scheme 3. For the rapid transformation of lactam **12** to 2,5-*trans*-pyrrolidine **15**, the one-pot reductive alkylation procedure[3b] was envisioned. The challenge in this transformation is the stereochemical control regarding the highly substituted ring system.



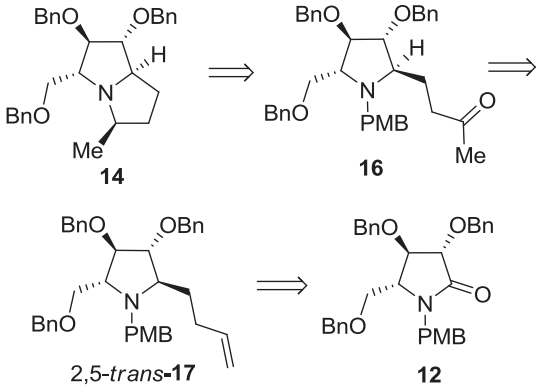
Scheme 3. Retrosynthetic analysis of radicamine B.

The synthesis started with the one-pot reductive alkylation of the known chiral building block **12**[3b] that was easily accessible from D-tartaric acid.[5,11f,12] Successive treatment of the CH_2Cl_2 solution of lactam **12** (1.0 equiv) and DTBMP (1.2 equiv) with 1.2 equiv of Tf_2O (−78 °C, 45 min), 1.0 equiv of 4-(benzyloxy)phenylmagnesium bromide in THF (rt, 1 h), and 3.0 equiv of $LiAlH_4$ (rt, 1 h), afforded the desired reductive alkylation product 2,5-*trans*-**15** and 2,5-*cis*-**15** in 55% yield. However, the diastereoselectivity was very low (dr=1:1, Scheme 4). To improve stereoselectivity, Hantzsch ester (HEH), a milder hydride donor,[13] was exploited. Indeed, the diastereoselectivity was improved to 1.8:1 in favor of diastereomer 2,5-*trans*-**15** with a combined yield of 56%. The stereochemistry of the major diastereomer was ultimately confirmed by conversion into radicamine B (**2a**). Compared with the previous four-step synthesis, this one step transformation is remarkably efficient, although both the yield and the diastereoselectivity were modest.[11f] Deprotection of 2,5-*trans*-**15** under catalytic hydrogenolytic conditions [H_2, 1 atm, 20% $Pd(OH)_2$/C, EtOH/EtOAc/HCl, rt, 15 h] gave the hydrochloride salt of radicamine B (**2a**·HCl) {$[\alpha]_D^{20}$ +79 (*c* 0.25, H_2O); lit.[7e] $[\alpha]_D^{25}$ +81 (*c* 0.25, H_2O)} in 91% yield. The ^1H and ^{13}C NMR spectral data of our synthetic product are in good agreement with those reported.[7e]



Scheme 4. Improved synthesis of radicamine B.

We next turned our attention to the synthesis of hyacinthacine A_3 (**5**) (Scheme 5). As depicted in Scheme 5, our retrosynthetic analysis started with the protected form of hyacinthacine A_3 (**14**), which could be directly converted into hyacinthacine A_3 (**5**) by deprotection.[9d] Pyrrolizidine **14** could be accessed from pyrrolidino ketone **16** via a stereoselective one-pot transformation reported in the literature.[9d] Ketone **16** was envisioned to be formed by the Wacker oxidation[14] of olefin 2,5-*trans*-**17**. However, this conversion appeared challenging, due to the strong Lewis basicity and good chelating capacity of the amino group in 2,5-*trans*-**17**. The failure in the Wacker oxidation of amino-containing olefins such as **18** (Fig. 2)[15] has been reported. The presence of amino group also causes troubles in other transition metal-catalyzed reactions such as olefin metathesis reactions.[16] Nevertheless, successful Wacker oxidation reaction[17] and olefin metathesis reactions[16]of amino-containing compounds have also been reported. For example, the olefin metathesis of compound **19** gave the desired product in high yield.[18]



Scheme 5. Retrosynthetic analysis of pyrrolizidine **14**.

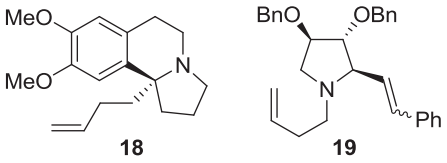
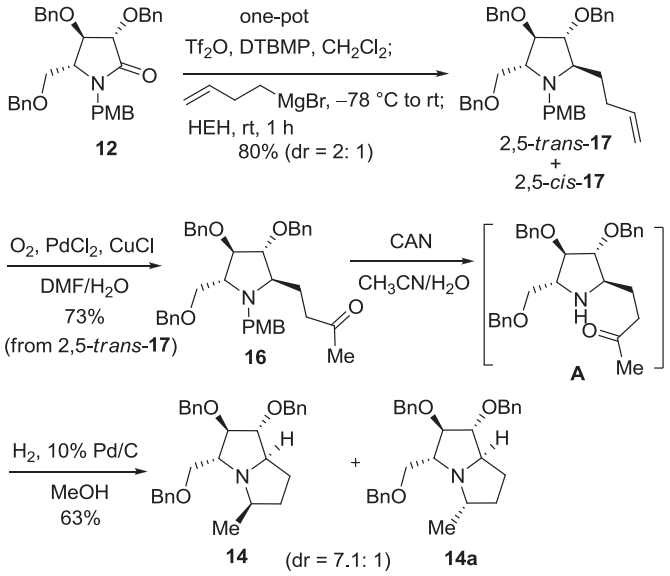


Fig. 2. Two substrates tested for the Wacker oxidation and the olefin metathesis reaction, respectively.

The synthesis started with the one-pot reductive alkylation of the known chiral building block **12**, which was treated successively with Tf_2O/DTBMP, but-3-enylmagnesium bromide, and HEH to afford a mixture of separable diastereomers 2,5-*trans*-**17** and 2,5-*cis*-**17** in a ratio of 2:1 with 80% combined yield (Scheme 6). The stereochemistry of the major diastereomer was confirmed by conversion into compound **14**. To our delight, 2,5-*trans*-pyrrolidine **17** was converted to methyl ketone **16** in 73% yield under modified Wacker oxidation conditions [O_2 (1 atm), $PdCl_2$ (0.5 equiv), CuCl (1.1 equiv), DMF/H_2O (v/v=3:1), rt],[17] in which the amount of $PdCl_2$ was increased from the commonly used 0.1 equiv[14] to 0.5 equiv.[17a] The success of this reaction might be ascribed to the steric hindrance in 2,5-*trans*-pyrrolidine **17**, which prevented the amino group coordination to the palladium catalyst. In fact, the steric hindrance also facilitated the Wacker oxidation of other amino-containing compounds.[17]

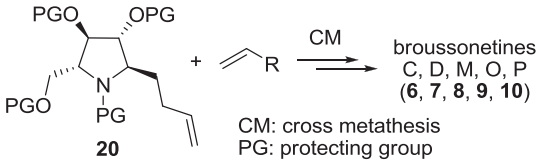


Scheme 6. Improved synthesis of (+)-hyacinthacine A_3.

Compound **16** was then treated with ceric ammonium nitrite (CAN) in a mixed solvent (MeCN/H_2O=3:1) to give the presumed free amine **A**, which without purification was subjected to catalytic hydrogenation conditions (H_2, 10% Pd/C, MeOH, rt, 12 h) to produce pyrrolizidine **14** {$[\alpha]_D^{20}$ −1.0 (*c* 1.0, $CHCl_3$); lit.[9d] $[\alpha]_D^{20}$ −0.95 (*c* 2.0, $CHCl_3$)} and its diastereomer **14a** (dr=7.1:1) in a combined yield of 63%. It is worth noting that, although a one-pot transformation of **16** to hyacinthacine A_3 (**5**) was possible, stopping the reaction at the stage of **14** is advantageous because two diastereomers **14** and **14a** are easily separated. Thus, starting from pyrrolidinone **12**, a three-step synthesis of *O*-benzylated pyrrolizidine **14** was achieved with an overall yield of 22%. This approach is four steps shorter than the previous route[9d] (seven steps, 21% overall yield). Final deprotection of pyrrolizidine **14** to complete the synthesis of hyacinthacine A_3 (**5**) has been described.[9d]

3. Conclusion

To conclude, by applying the method of one-pot reductive alkylation of lactams/amides, we have developed a two-step synthesis of natural radicamine B (**2a**) and five-step synthesis of hyacinthacine A_3 (**5**) from pyrrolidin-2-one **12**. The approach to hyacinthacine A_3 (**5**) is especially effective compared with the previous eight-step route.[9d] Moreover, since compound **20** has been designed and used by Marco and co-workers as a common intermediate in the total synthesis of broussonetines C, D, M, O, P (**6**, **7**, **8**, **9**, and **10**) (Scheme 7),[10h,i] the reductive alkylation product 2,5-*trans*-**17** would serve as a valuable intermediate for the syntheses of this class of natural products.



Scheme 7. Marco' general approach to broussonetines C, D, M, O, and P.

4. Experimental section

4.1. General methods

Infrared spectra were measured a Nicolet Avatar 360 FT-IR spectrometer using film KBr pellet techniques. ^1H and ^{13}C NMR data were acquired with spectrometer Bruker AMX 400 MHz. Chemical shifts (δ) are expressed downfield from TMS. Mass spectra were recorded by Bruke Dalton Esquire 3000 Plus, HRFABMS spectra were recorded on a Bruker APEX-FTMS apparatus. Tetrahydrofuran (THF) was distilled prior to use from sodium benzophenone ketyl. Methylene chloride (CH_2Cl_2) was distilled over calcium hydride under N_2. Silica gel (zhifu, 300–400 mesh) from Yantai silica gel factory (China) was used for column chromatography. Both of the Grignard reagents were titrated immediately before use.[19]

*4.1.1. (2R,3R,4R,5R)-1-(4-Methoxybenzyl)-3,4-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-5-(benzyloxymethyl)pyrrolidine (2,5-trans-**15**).* Tf_2O (79 μL, 0.47 mmol) was added dropwise to a cooled (−78 °C) solution of lactam **12** (210 mg, 0.39 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (96 mg, 0.47 mmol) in CH_2Cl_2 and the resultant mixture was stirred at −78 °C for 45 min. A solution of freshly prepared 4-(benzyloxy)phenylmagnesium bromide (0.52 M, 0.75 mL, 0.39 mmol) in THF was added dropwise to the resultant mixture. The mixture was allowed to warm slowly to room temperature and stirred for 1 h. Then the mixture was cooled

to −78 °C, and Hantzsch ester (HEH) (147 mg, 0.59 mmol) was added in one portion. The mixture was allowed to warm slowly to room temperature and stirred for 1 h. The mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: CH_2Cl_2/hexane=1:2) to afford compound 2,5-*trans*-**15** (100 mg, yield: 36%) and its diastereomer 2,5-*cis*-**15** (55 mg, yield: 20%) (combined yield: 56%, dr=1.8:1). Compound 2,5-*trans*-**15**: colorless oil; $[\alpha]_D^{20}$ +6.2 (*c* 0.6, $CHCl_3$); IR (film): 3062, 3030, 2918, 2851, 1610, 1510, 1454, 1245, 736, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.36 (ddd, *J*=6.5, 6.2, 3.4 Hz, 1H, H-2), 3.38 (d, *J*=14.5 Hz, 1H, NCH_2), 3.53 (dd, *J*=9.4, 3.4 Hz, 1H, H-6), 3.55 (d, *J*=14.5 Hz, 1H, NCH_2), 3.60 (dd, *J*=9.4, 6.2 Hz, 1H, H-6), 3.77 (s, 3H, OCH_3), 4.01 (dd, *J*=6.6, 3.2 Hz, 1H, H-4), 4.03 (d, *J*=6.6 Hz, 1H, H-5), 4.16 (dd, *J*=6.5, 3.2 Hz, 1H, H-3), 4.32 (d, *J*=11.7 Hz, 1H, OCH_2Ph), 4.36 (d, *J*=11.7 Hz, 1H, OCH_2Ph), 4.45 (d, *J*=12.0 Hz, 1H, OCH_2Ph), 4.48 (d, *J*=11.8 Hz, 1H, OCH_2Ph), 4.49 (d, *J*=12.0 Hz, 1H, OCH_2Ph), 4.54 (d, *J*=11.8 Hz, 1H, OCH_2Ph), 5.06 (s, 2H, OCH_2Ph), 6.77 (d, *J*=8.5 Hz, 2H, Ar−H), 6.94 (d, *J*=8.5 Hz, 2H, Ar−H), 7.08−7.48 (m, 24H, Ar−H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 49.4, 55.2, 62.0, 67.9, 70.0, 70.9, 71.6, 72.0, 73.3, 85.1, 91.5, 113.6 (2C), 114.8 (2C), 127.3, 127.4 (3C), 127.5, 127.6 (2C), 127.7 (2C), 127.8 (2C), 127.9, 128.1 (2C), 128.2 (2C), 128.3 (2C), 128.5 (2C), 128.9 (2C), 129.2 (2C), 131.4, 134.2, 137.2, 138.3, 138.3, 138.5, 158.3, 158.3 ppm; MS (ESI) *m/z* 706 ($M+H^+$, 100%); HRESIMS calcd for $[C_{47}H_{48}NO_5]^+$ ($M+H^+$): 706.3527; found: 706.3521. Compound 2,5-*cis*-**15**: colorless oil; $[\alpha]_D^{20}$ +3.4 (*c* 1.0, $CHCl_3$); IR (film): 3061, 3031, 2916, 2849, 1609, 1510, 1453, 1108, 735, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.32 (ddd, *J*=6.9, 6.8, 4.3 Hz, 1H, H-2), 3.44 (d, *J*=14.6 Hz, 1H, NCH_2), 3.47 (dd, *J*=9.4, 4.3 Hz, 1H, H-6), 3.55 (d, *J*=6.5 Hz, 1H, H-5), 3.72 (dd, *J*=9.4, 6.8 Hz, 1H, H-6), 3.77 (s, 3H, OCH_3), 3.80 (d, *J*=14.6 Hz, 1H, NCH_2), 3.81 (dd, *J*=6.5, 4.4 Hz, 1H, H-4), 3.98 (dd, *J*=6.9, 4.4 Hz, 1H, H-3), 4.28 (d, *J*=11.7 Hz, 1H, OCH_2Ph), 4.33 (d, *J*=11.7 Hz, 1H, OCH_2Ph), 4.40 (d, *J*=12.0 Hz, 1H, OCH_2Ph), 4.45 (d, *J*=12.0 Hz, 1H, OCH_2Ph), 4.53 (d, *J*=11.9 Hz, 1H, OCH_2Ph), 4.59 (d, *J*=11.9 Hz, 1H, OCH_2Ph), 5.07 (s, 2H, OCH_2Ph), 6.75 (d, *J*=8.6 Hz, 2H, Ar−H), 6.94 (d, *J*=8.6 Hz, 2H, Ar−H), 7.06 (d, *J*=8.6 Hz, 4H, Ar−H), 7.18−7.47 (m, 20H, Ar−H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 54.2, 55.2, 62.9, 70.0, 70.1, 70.4, 72.1, 72.3, 73.3, 82.8, 89.3, 113.3 (2C), 114.7 (2C), 127.3, 127.4 (2C), 127.5 (2C), 127.5 (3C), 127.6 (4C), 127.9, 128.2 (2C), 128.2 (3C), 128.5 (2C), 129.3 (2C), 129.7, 130.6 (2C), 134.2, 137.2, 138.2, 138.6, 138.7, 158.2, 158.5 ppm; MS (ESI) *m/z* 706 ($M+H^+$, 100%); HRESIMS calcd for $[C_{47}H_{48}NO_5]^+$ ($M+H^+$): 706.3527; found: 706.3538.

*4.1.2. (2R,3R,4R,5R)-3,4-Dihydroxy-2-(hydroxymethyl)-5-(4-hydroxyphenyl) pyrrolidine (radicamine B) hydrochloride salt (**2a**).* Compound 2,5-*trans*-**15** (60 mg, 0.08 mmol) was dissolved in EtOAc (1 mL) containing concentrated HCl (0.1 mL, 16.7 mmol) and then 20% $Pd(OH)_2/C$ (30 mg) was added. The mixture was stirred under a hydrogen atmosphere (1 atm, balloon) at room temperature for 15 h. After the catalyst was filtered off, the filtrate was concentrated under reduced pressure, affording radicamine B hydrochloride salt **2a** (20 mg, yield: 91%) as a white solid. Mp >145 °C (dec) [lit.[7g] mp >150 °C (dec)]; $[\alpha]_D^{20}$ +79 (*c* 0.25, H_2O) {lit.[7e] $[\alpha]_D^{25}$ +81 (*c* 0.25, H_2O)}; IR (film): 3329, 2933, 1618, 1513, 1254, 832 cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 3.57 (ddd, *J*=7.8, 5.7, 3.9 Hz, 1H, H-2), 3.81 (dd, *J*=12.6, 5.7 Hz, 1H, H-6), 3.86 (dd, *J*=12.6, 3.9 Hz, 1H, H-6), 4.08 (dd, *J*=7.8, 7.5 Hz, 1H, H-3), 4.31 (d, *J*=10.1 Hz, 1H, H-5), 4.38 (dd, *J*=10.1, 7.5 Hz, 1H, H-4), 6.86 (d, *J*=8.3 Hz, 2H, Ar−H), 7.32 (d, *J*=8.3 Hz, 2H, Ar−H) ppm; ^{13}C NMR (100 MHz, D_2O): δ 58.2, 61.6, 62.8, 73.6, 77.1, 116.2, 122.9, 130.2, 157.1 ppm; MS (ESI) *m/z* 226 ($M-Cl^-$, 100%); HRESIMS calcd for $[C_{11}H_{16}NO_4]^+$ ($M-Cl^-$): 226.1074; found: 226.1079.

*4.1.3. (2R,3R,4R,5R)-1-(4-Methoxybenzyl)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-(but-3-enyl) pyrrolidine (2,5-trans-**17**).* Tf_2O (75 μL, 0.45 mmol) was added dropwise to a cooled (−78 °C) solution of lactam **12** (200 mg, 0.37 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (91 mg, 0.45 mmol) in CH_2Cl_2 and the resultant mixture was stirred at −78 °C for 45 min. A solution of freshly prepared but-3-enylmagnesium bromide (0.29 M, 1.28 mL, 0.37 mmol) in THF was added dropwise to the resultant mixture. The mixture was allowed to warm slowly to room temperature and stirred for 1 h. Then the mixture was cooled to −78 °C, and Hantzsch ester (HEH) (140 mg, 0.56 mmol) was added in one portion. After being stirred for 1 h, the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/hexane=1:10) to afford compound 2,5-*trans*-**17** (115 mg, yield: 53%) and its diastereomer 2,5-*cis*-**17** (58 mg, yield: 27%). Compound 2,5-*trans*-**17**: colorless oil; $[\alpha]_D^{20}$ +25.5 (*c* 1.0, $CHCl_3$); IR (film): 2924, 2857, 1610, 1510, 1496, 1453, 1246, 1099, 1028, 735, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.50−1.60 (m, 1H, H-6), 1.70−1.80 (m, 1H, H-6), 1.88−1.98 (m, 1H, H-7), 2.02−2.13 (m, 1H, H-7), 3.04 (ddd, *J*=8.9, 4.0, 3.6 Hz, 1H, H-5), 3.22 (ddd, *J*=7.0, 4.5, 2.3 Hz, 1H, H-2), 3.50 (dd, *J*=9.5, 7.0 Hz, 1H, H-10), 3.57 (dd, *J*=9.5, 4.5 Hz, 1H, H-10), 3.59 (d, *J*=13.9 Hz, 1H, NCH_2), 3.79 (dd, *J*=3.6, 2.3 Hz, 1H, H-4), 3.80 (s, 3H, OCH_3), 3.89 (d, *J*=13.9 Hz, 1H, NCH_2), 3.96 (app. t, *J*=2.3 Hz, 1H, H-3), 4.45−4.50 (m, 5H, OCH_2), 4.57 (d, *J*=12.0 Hz, 1H, OCH_2), 4.86−4.98 (m, 2H, $=CH_2$), 5.73 (ddt, *J*=17.1, 10.3, 6.8 Hz, 1H, =CH), 6.81−6.84 (m, 2H, Ar−H), 7.24−7.32 (m, 17H, Ar−H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.7, 29.5, 50.5, 55.3, 64.2, 64.5, 69.0, 71.3, 71.4, 73.2, 85.8, 87.2, 113.6, 114.3, 127.5, 127.5, 127.5, 127.6 (2C), 127.8 (2C), 127.9 (2C), 128.3 (4C), 128.3 (2C), 129.2 (2C), 130.5 (2C), 138.4, 138.5, 138.5, 138.7, 158.5 ppm; MS (ESI) *m/z* 578 ($M+H^+$, 100%); HRESIMS calcd for $[C_{38}H_{43}NO_4]^+$: 578.3265; found: 578.3275. Compound 2,5-*cis*-**17**: a colorless oil; $[\alpha]_D^{20}$ −25.0 (*c* 1.0, $CHCl_3$); IR (film): 2918, 2856, 1610, 1511, 1453, 1248, 1098, 1028, 736, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.56−1.68 (m, 1H, H-6), 1.76−1.86 (m, 1H, H-6), 1.86−1.93 (m, 2H, H-7), 2.95 (ddd, *J*=9.6, 8.5, 4.5 Hz, 1H, H-5), 3.07−3.10 (m, 1H, H-2), 3.10 (dd, *J*=8.9, 4.4 Hz, 1H, H-10), 3.30 (app. t, *J*=8.9 Hz, 1H, H-10), 3.62 (d, *J*=13.6 Hz, 1H, NCH_2), 3.76 (dd, *J*=6.9, 4.5 Hz, 1H, H-4), 3.82 (s, 3H, OCH_3), 3.88−3.90 (m, 1H, H-3), 3.92 (d, *J*=13.6 Hz, 1H, NCH_2), 4.24 (d, *J*=12.0 Hz, 1H, OCH_2), 4.26 (d, *J*=12.1 Hz, 1H, OCH_2), 4.39 (d, *J*=12.1 Hz, 1H, OCH_2), 4.46 (d, *J*=12.0 Hz, 1H, OCH_2), 4.48 (d, *J*=12.2 Hz, 1H, OCH_2), 4.57 (d, *J*=12.2 Hz, 1H, OCH_2), 4.90−4.98 (m, 2H, $=CH_2$), 5.78 (ddt, *J*=16.8, 10.3, 6.5 Hz, 1H, =CH), 6.78−6.83 (m, 2H, Ar−H), 7.26−7.36 (m, 17H, Ar−H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.2, 30.7, 55.2, 57.5, 65.9, 68.5, 70.7, 71.3, 72.0, 72.9, 81.9, 82.4, 113.5, 114.2, 127.4 (2C), 127.5 (2C), 127.6 (4C), 128.0 (2C), 128.2 (2C), 128.3 (2C), 128.3 (2C), 130.5 (2C), 131.1, 138.2, 138.6, 138.6, 138.9, 158.7 ppm; MS (ESI) *m/z* 578 ($M+H^+$, 100%); HRESIMS calcd for $[C_{38}H_{43}NO_4]^+$ ($M+H^+$): 578.3265; found: 548.3267.

*4.1.4. 4-((2R,3R,4R,5R)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)-1-(4-methoxybenzyl)pyrrolidin-2-yl)butan-2-one (**16**).* To a solution of olefin 2,5-*trans*-**17** (49 mg, 0.085 mmol) in DMF (1.5 mL) and H_2O (0.5 mL) were added CuCl (9.3 mg, 0.094 mmol) and $PdCl_2$ (7.5 mg, 0.043 mmol) and the resulting suspension was stirred under an oxygen atmosphere (1 atm, balloon) at room temperature for 6 h. The insoluble materials were removed by filtration, and washed with CH_2Cl_2. The filtrate was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/hexane=1:5) to give **16** (37 mg, yield: 73%) as a colorless oil. $[\alpha]_D^{20}$ +12.0 (*c* 1.0, $CHCl_3$); IR (film): 2921, 2851, 1712, 1610, 1511, 1453, 1364, 1246, 1097, 1028, 737, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.68−1.77 (m, 1H, H-6), 1.92−1.98 (m, 1H, H-6), 2.00 (s, 3H, CH_3), 2.30 (ddd, *J*=17.5, 9.3, 6.0 Hz, 1H, H-7), 2.42 (ddd, *J*=17.5, 9.5, 5.5 Hz, 1H, H-7), 3.02 (ddd, *J*=7.3, 4.8, 4.4 Hz, 1H, H-5), 3.25 (m, 1H, H-2), 3.49 (dd, *J*=9.2, 7.3 Hz, 1H, H-10), 3.56

(dd, J=9.2, 4.4 Hz, 1H, H-10), 3.59 (d, J=14.1 Hz, 1H, NCH_2), 3.70 (dd, J=4.8, 1.9 Hz, 1H, H-4), 3.79 (s, 3H, OCH_3), 3.83 (d, J=14.1 Hz, 1H, NCH_2), 3.98 (app. t, J=1.9 Hz, 1H, H-3), 4.38–4.46 (m, 4H, OCH_2), 4.49 (d, J=11.9 Hz, 1H, OCH_2), 4.53 (d, J=12.0 Hz, 1H, OCH_2), 6.83 (d, J=8.5 Hz, 2H, Ar–H), 7.21 (d, J=8.5 Hz, 2H, Ar–H), 7.25–7.34 (m, 15H, Ar–H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.9, 29.7, 29.8, 38.8, 50.2, 55.3, 63.6, 64.5, 68.1, 71.3, 73.3, 85.2, 87.3, 113.7 (2C), 127.5, 127.6, 127.6 (3C), 127.9 (3C), 128.3 (4C), 128.3 (3C), 129.2 (2C), 131.4, 138.3, 138.3, 138.4, 158.5, 208.6 ppm; MS (ESI) m/z 594 ($M+H^+$, 100%); HRESIMS calcd for $[C_{38}H_{43}NO_5]^+$ ($M+H^+$): 594.3214; found: 594.3211.

*4.1.5. (3R,4R,6R,7R,7aR)-6,7-Bis(benzyloxy)-5-(benzyloxymethyl)-3-methyl-hexahydro-1H-pyrrolizine (**14**).* To a solution of **16** (160 mg, 0.27 mmol) in MeCN (30 mL) and H_2O (10 mL) was added ceric ammonium nitrate (2.96 g, 2.60 mmol) at 0 °C. After stirring at the same temperature for 1 h, the mixture was allowed to warm to room temperature and stirred for 16 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (30 mL) and the resulting mixture was extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was used in the next step without further purification. The residue was dissolved in MeOH (5 mL) and was hydrogenated in the presence of Pd/C (10% Pd, 16 mg) under a hydrogen atmosphere (1 atm, balloon) for 12 h. The resulting mixture was filtered and washed with MeOH, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/hexane=1:1) to afford compound **14** (68 mg, yield: 55%) and its diastereomer **14a** (10 mg, yield: 8%). Compound **14**: colorless oil; $[\alpha]_D^{20}$ −1.0 (c 1.0, $CHCl_3$) {lit.[9d] $[\alpha]_D^{20}$ −0.95 (c 1.0 $CHCl_3$)}; IR (film): 2963, 2857, 1601, 1451, 1360, 1259, 1070 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (d, J=6.7 Hz, 3H, CH_3), 1.32–1.47 (m, 1H, H-2), 1.56–1.67 (m, 1H, H-1), 1.68–1.83 (m, 2H, H-1, H-2), 3.11–3.27 (m, 2H, H-3, H-5), 3.37–3.43 (m, 2H, H-8), 3.45–3.52 (m, 1H, H-7a), 3.68 (t, J=4.0 Hz, 1H, H-7), 3.98 (t, J=4.0 Hz, 1H, H-6), 4.37–4.52 (m, 6H, OCH_2), 7.12–7.26 (m, 15H, Ar–H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.3, 29.2, 32.6, 57.7, 61.0, 68.8, 71.5, 71.9, 73.2, 73.2, 86.9, 88.2, 127.5, 127.5, 127.5, 127.6 (2C), 127.7 (2C), 127.7 (2C), 128.3 (2C), 128.3 (2C), 128.3 (2C), 138.4, 138.6 (2C) ppm; MS (ESI) m/z 458 ($M+H^+$, 100%); HRESIMS calcd for $[C_{30}H_{35}NO_3]^+$ ($M+H^+$): 458.2690; found: 458.2708. Compound **14a**: colorless oil; $[\alpha]_D^{20}$ +5.2 (c 0.75, $CHCl_3$). IR (film): 2958, 2842, 1611, 1432, 1354, 1263, 1052 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (d, J=6.3 Hz, 3H, CH_3), 1.33–1.46 (m, 1H, H-2), 1.57–1.68 (m, 1H, H-1), 1.85–1.94 (m, 1H, H-2), 1.99 (m, 1H, H-1), 2.92–3.00 (m, 1H, H-3), 3.01–3.09 (m, 1H, H-5), 3.43–3.48 (m, 2H, H-8), 3.48–3.57 (m, 1H, H-7a), 3.78 (t, J=4.0 Hz, 1H, H-7), 4.04 (t, J=4.0 Hz, 1H, H-6), 4.43 (d, J=11.9 Hz, 1H, OCH_2), 4.46–4.50 (m, 3H, OCH_2), 4.49 (d, J=11.8 Hz, 1H, OCH_2), 4.54 (d, J=11.8 Hz, 1H, OCH_2), 7.12–7.31 (m, 15H, Ar–H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.8, 29.7, 32.0, 62.5, 68.1, 68.5, 71.7, 72.2, 72.2, 73.3, 87.0, 89.5, 127.4, 127.4, 127.6, 127.6 (2C), 127.7 (2C), 127.7 (2C), 128.2 (2C), 128.3 (2C), 128.3 (2C), 138.4, 138.5 (2C) ppm; MS (ESI) m/z 458 ($M+H^+$, 100%); HRESIMS calcd for $[C_{30}H_{35}NO_3]^+$ ($M+H^+$): 458.2690; found: 458.2707.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2012.01.085. These data include MOL files and InChiKeys of the most important compounds described in this article.

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