Tetrahedron Letters 52 (2011) 4885-4887

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet



Stereoselective synthesis of (+)-radicamine B

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ARTICLE INFO

Article history: Received 1 June 2011 Revised 6 July 2011 Accepted 11 July 2011 Available online 19 July 2011

Keywords: Pyrrolidine alkaloids Radicamines Sharpless asymmetric epoxidation HWE olefination

ABSTRACT

A simple and efficient stereoselective synthesis of naturally occurring pyrrolidine alkaloid, radicamine B has been accomplished in 13 steps from the commercially available starting materials with an overall yield of 9.75%. The synthesis utilizes Sharpless asymmetric epoxidation and Horner–Wadsworth–Emmons (HWE) olefination as key steps.

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Nitrogen-containing heterocycles are widespread in medicinal chemistry due to the fact that many natural, synthetic, and biologically active compounds share this common architectural feature.¹Among them, polyhydroxy pyrrolidine alkaloidal (imino sugars) framework represents one of the major classes of alkaloids, which exhibits remarkable biological properties, such as potential inhibition of glycosidases,² antiviral agents,³ and acaricides.⁴ Radicamine A and B are important groups of naturally occurring polyhydroxylated pyrrolidine alkaloids isolated by Kusano and co-workers from Lobelia Chinensis (Campanulaceae), which are commonly used as a Chinese folk medicine for the treatment of a wide range of human diseases including α -glucosidase inhibitory activity, antidiuretic, and anticarcinostatic properties for stomach cancer.⁵ From a structural point of view, radicamine B that possesses aromatic substituent on the iminosugar ring is a rare class of alkaloids found in nature. The structures and relative stereochemistry of both these compounds (Fig. 1) were determined on the basis of extensive NMR studies while the absolute configuration of these compounds was assigned by comparing the specific rotation with the natural codonopsinine (**5**).⁵ Because of their fascinating structural features and interesting biological properties, radicamines have solicited considerable interest among organic chemists.

As a consequence of the central role played by this pyrrolidine ring system, numerous methods have been devised for the asymmetric synthesis. There are currently three total syntheses of radicamine B accomplished by five groups.⁶ Besides, some formal syntheses and related synthetic studies of radicamines have also been reported.⁷ In 2006, the total synthesis of radicamine B (**4**) was attained by Yu et al., and revised the exact stereochemistry of this compound through extensive studies. These reported syntheses are almost identical and show only marginal differences, which were relied on the same synthetic strategy with a cyclic nitrone as a key intermediate derived from five-carbon sugar or amino acid.^{6,7}

As continuation of our research program directed toward the expedient synthesis of alkaloids from cheap and readily available starting materials,⁸ we have initiated a program aiming for developing an efficient strategy for the stereoselective synthesis of radicamine B. The realization of this goal and an application to the efficient synthesis of radicamine B (1) are presented herein. Our approach to the synthesis of radicamine B is based upon the Sharpless asymmetric epoxidation as the key asymmetry inducing reaction,



Figure 1. Representative examples of pyrrolidine.



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Scheme 1. Retrosynthetic analysis of radicamine B.

starting from commercially and cheaply available *p*-hydroxybenzaldehyde (**12**) in 13 steps with an overall yield of 9.75%.

As shown retrosynthetically in Scheme 1, synthesis of radicamine B (**4**) was envisaged based on the construction of key intermediate **8** by Sharpless asymmetric epoxidation of **9**, which could be obtained through two carbon Wittig olefination reaction of aldehyde generated from **10**. The preparation of **10** was proposed from **11** by performing regioselective SN^2 opening of epoxide with NaN₃. The chiral synthon **11** could be prepared from *p*-hydroxybenzaldhyde from the reported procedure. This short and versatile synthetic approach should also provide access to potentially active substituted pyrrolidine derivatives at the C-2 position. More importantly, we have successfully implemented a strategy that minimizes protecting group manipulation in a unique fashion, a common and unavoidable practice in synthesis of alkaloids.

Based on the above mentioned plan, synthesis of (+) radicamine B(4) was initiated with commercially available *p*-hydroxybenzaldehyde **12**, which was converted into its *p*-tosyl cinnamyl alcohol **13** in three steps by following the literature procedure.⁹ Sharpless asymmetric epoxidation of **13** with (+)-DET furnished **11** in 98% yield⁹ with excellent enantioselectivity of 99.5% ee (determined by chiral HPLC).¹⁰ Regioselective ring opening of epoxide **11** at benzylic position with NaN₃ (1.6 equiv) in the presence of NH₄Cl (0.3 equiv) overnight stirring at 55 °C in THF, water (2:1 ratio) to yield azido diol **14** (77%)¹¹ and this was further confirmed by chopping reaction with NaIO₄.

Reduction of azide functionality in **14** using PPh₃ in THF, water (1:1 ratio) to amine,¹² followed by addition of Boc anhydride afforded Boc-protected amine in good yield, in which diol functionality was protected with benzaldehyde dimethylacetal to using the catalytic amount of *p*-TSA in DCM¹³ to give **15**. Ring opening of hemi acetal in **15** with DIBAL-H (4 equiv) yielded primary alcohol **10**. The resultant benzyl ether 10 was subjected to IBX oxidation followed by Horner–Wadsworth–Emmons olefination to yield α , β unsaturated ester **16**¹⁴ with excellent *E*-selectivity. Further, *E*-selectivity of **16** was confirmed by the large coupling constant (J = 16 Hz) in the ¹H NMR spectrum. Upon reduction of α , β -unsaturated ester 16 with DIBAL-H in DCM at 0 °C for 1 h yielded corresponding allylalcohol 9 in 90% yield. Finally, Sharpless asymmetric epoxidation of resultant allyl alcohol 9 with (+)-DIPT in the presence of cumene hydrogen peroxide acquired key intermediate 8 in excellent yield (90%) with 99.2% ee (Scheme 2).15,16

With the successful synthesis of key fragment **8** in hand, we turned our attention to the synthesis of radicamine B. Thus, deprotection of tosyl group in compound **8** using K₂CO₃ in refluxing methanol yielded **17**, which was further treated with Pd/C, under H₂ atmosphere in methanol to get **7** in good yield.¹⁷ Finally, removal of Boc-group with TFA in DCM at 0 °C followed by treatment with satd NaHCO₃ smoothly yielded alkaloid (+) radicamine B in good yield (Scheme 3).^{18,19} Spectroscopic data and optical rotation $[\alpha]_D^{25}$ +70.6 (*c*, 0.2, H₂O)] of (+) radicamine B(**4**) were in full agreement with reported literature^{5a} and all the intermediate



Scheme 2. Synthesis of key intermediate 8. Reagents and conditions: (a) TsCl, Et₃N, DCM, 0 °C to rt, 1 h, 98%; (b) Ph₃P OEt benzene, rt, 6 h, 96%; (c) DIBAL-H, DCM, 0 °C to

rt, 1.5 h, 90%; (d) (+)-DET, Ti(*i*-prO)₄, TBHP, 4 Å molecular sieves, DCM, -20 °C, 3 h, 98%; (e) NaN₃, NH₄Cl, THF-water (2:1), 55 °C, overnight, 77%; (f) (i) PPh₃, THF-water (1:1), rt, 1 h, then (Boc)₂O, satd NaHCO₃, 6 h, 97%; (ii) benzaldehyde dimethyl acetal, DCM, cat. PTSA, 4 h, 75%; (g) DIBAL-H, DCM, 0 °C to rt, 3 h, 80%; (h) (i) IBX, DMSO, THF, rt, 3 h; (ii) (OEt)₂PO(CH₂COOEt), NaH, THF, 0 °C to rt, 6 h, 90% (over two steps); (i) DIBAL-H, DCM, 0 °C to rt, 1.5 h, 90%; (j) (+)-DIPT, Ti(*i*-pro)₄, CHP, 4 Å molecular sieves, DCM, -20 °C, 12 h, 90%.



Scheme 3. Synthesis of (+) radicamine B (4). Reagents and conditions: (k) K₂CO₃, MeOH, reflux, 1 h, 95%; (l) Pd/C, H₂ balloon, MeOH, overnight, 90%; (m) TFA, DCM, 0 °C, 30 min then solid NaHCO₃, 30 h, 40%.

compounds were well characterized by the ¹H NMR, ¹³C NMR, Mass and IR spectroscopic techniques.²⁰

In conclusion, we have developed an efficient, linear synthetic protocol for synthesis of polyhydroxy pyrrolidine alkaloid, (+)-radicamine B (**4**) using Sharpless epoxidation and HWE olefination as key steps. This general synthetic route demonstrates its versatility toward the synthesis of highly functionalized pyrrolidine and also paves the way for the structurally related analogues. On the basis of the route described herein, further work toward preparation of the library of polyhydroxy pyrrolidine alkaloids for biological analysis is in progress in our laboratory.

Acknowledgments

The authors gratefully acknowledge the keen interest shown by Dr. J. S. Yadav, Director, IICT, Hyderabad. R.S.C.K. and B.P. thank CSIR and UGC, New Delhi for financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.07.035.

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- 19. Experimental procedure for the synthesis (+)- radicamine B (4): To a stirred solution of the compound 7 (0.2 g, 0.61 mmol) in 2 mL DCM at 0 °C was added TFA (1 mL) drop wise and allowed to stir at the same temparature for 30 min. After completion of the reaction (by TLC analysis), solvent and excess TFA were removed in high vacuum. 10 mL of dry DCM was added to the reaction mixture at 0 °C under nitrogen atmosphere. Reaction was quenched with solid NaHCO₃ and stirred at room temperature for 30 h. The reaction mixture was filtered and washed with DCM (10 × 2 mL), the organic layer was separated and evaporated under reduced pressure to afford the crude product which was purified by column chromatography on neutral alumina using chloroform-MeOH (6:4) as a eluent to afford target compound **4** in 40% (0.05 g) yield.
- Spectral data of selected compounds; Compound 7: pale yellow sticky liquid; $[\alpha]_D^{25}$ +40.4 (*c* 1, CH₃OH); ¹H NMR (300 MHz CDCl₃ + CD₃OD): δ 7.13–7.03 (d, 20 2H, J = 8.4 Hz), 6.77-6.72(d, 2H, J = 8.3 Hz), 4.93-4.83 (br s, 1H), 4.34-3.98 (m, 1H), 3.77–3.34 (m, 4H), 2.90–2.72 (m, 1H), 1.41–1.38 (s, 9H); ¹³C NMR (300 MHz CDCl₃ + CD₃OD): δ 156.5, 156.3, 130.5, 128.4, 115.8, 80.0, 77.2, 66.8, 60.8, 60.2, 59.2, 28.3; FABMS: *m/z* 348 [M+Na]⁺; IR (KBr): cm⁻¹. 3345, 2925, 2854, 1689, 1614, 1514, 1368, 1248, 1167, 1043. Compound **8**: pale yellow sticky liquid; $[\alpha]_D^{25}$ –15.8 (c 1, CHCl_3); $^1\mathrm{H}$ NMR (300 MHz CDCl_3): δ 7.77–7.57 (d, 2H, J = 8.3 Hz), 7.41–6.99 (m, 9H), 6.99–6.74 (d, 2H, J = 8.3 Hz), 5.68–5.40 (br d, 1H), 4.87-4.60 (br s, 1H), 4.51-4.39 (s, 2H), 3.82-3.46 (m, 3H), 3.27-3.19 (d, 1H, J = 10.5 Hz), 3.03–2.77 (m, 1H), 2.47–2.41 (s, 3H), 1.46–1.37 (s, 9H); ¹³C NMR (75 MHz, CDCl₃): δ 154.9, 149.2, 144.9, 137.1, 236.5, 132.8, 129.7, 128.7,128.6, 128.4, 128.1, 127.9, 122.4, 77.4, 73.9, 68.4, 62.7, 61.2, 60.6, 28.4, 21.7; FABMS: *m/z* 592 [M+Na]*; IR (KBr): cm⁻¹; 3407, 2925, 2853, 1702, 1598, 1501, 1370, 1177, 1155, 866, 749. Compound **10**: pale yellow liquid; $[\alpha]_D^2$ -12.5 (c 1, CHCl₃); ¹H NMR (300 MHz CDCl₃): δ 7.69-7.65 (d, 2H, J = 8.12 Hz), 7.32–7.13 (m, 9H), 6.90–6.86 (d, 2H, J = 8.12 Hz), 5.79–5.72 (br d, 1H), 4.77– 4.70 (br s, 1H), 4.43-4.41 (s, 2H), 4.01–3.93 (m, 1H), 3.36–3.28 (m, 1H), 3.19–3.10 (m, 1H), 2.45–2.42 (s, 3H), 1.41–1.37 (s, 9H); ¹³C NMR (75 MHz, CDCl₃): δ 155.2, 148.2, 144.9, 138.1, 137.2, 132.7, 129.6, 128.5, 127.9, 127.6, 122.2, 79.6, 76.9, 73.5, 71.0, 56.6, 28.4, 21.7; FABMS:*m/z* 550 [M+Na]⁺; IR (KBr): cm⁻¹; 3409, 2923, 2853, 1700, 1598, 1501, 1370, 1198, 1177, 867,750; Compound 14: Pale yellow oily liquid; [α]₀²⁵ –32.8 (*c*1, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 7.71–7.67 (d, 2H, J = 8.3 Hz), 7.32–7.23 (m, 4H), 7.01–6.97 (d, 2H, J = 8.4 Hz), 4.52–4.48 (m, 1H), 3.77–3.46 (m, 3H), 2.47–2.44 (s, 3H); ¹³C NMR (75 MHz, 1.27 MHz), 1.27 MHz, 1.2 CDCl₃): 8 149.5, 145.4, 135.4, 132.7, 129.9, 129.2, 128.5, 122.2, 74.0, 66.1, 62.7, 21.8; FABMS: *m/z* 386 [M+Na]⁺; IR (KBr): cm⁻¹; 3360, 2921, 2851, 2105, 1598, 1502, 1373, 1198, 1178, 867