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Stereoselective total synthesis of alkaloid caulophyllumine B using iterative olefin cross-metathesis protocol

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ABSTRACT

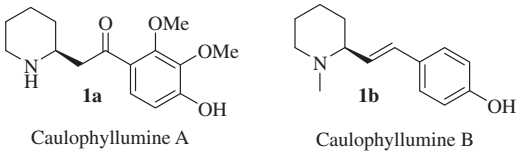
Herein we report the first total synthesis of alkaloid caulophyllumine B in 14 steps by an iterative olefin cross-metathesis strategy from L-glutamic acid.

Caulophyllumine A and B (Fig. 1) are the two new piperidine alkaloids isolated by Ali and Khan[1a] from Blue Cohosh, *Caulophyllum thalictroides* (L.) Michx (Berberidaceae), an indigenous perennial plant found in north-eastern North America. It is a well known dietary supplement used for regulation of the menstrual cycle and to ease childbirth and painful cramps. Native Americans used this plant for various ailments like rheumatism, dropsy, colic, sore throat, cramp, epilepsy, hysterics, and inflammation of the uterus.[1b] Among the isolated alkaloids, caulophyllumine B inhibited major drug metabolizing cytochrome P450 (CYP450) enzymes showed strong inhibition of CYP 2C19, 3A4, 2D6, and 1A2 enzymes to various extents (IC_{50}: 2.5–50 μM).[2]

Caulophyllumine B (**1b**) attracted our attention primarily due to the interest we harbor in the synthesis of piperidine-based natural products.[3] Additionally, caulophyllumine B has impressive biological profile as well as the presence of a rare 2-vinyl-piperidine moiety as part of the structure. The above mentioned features led us to undertake its synthesis. Toward the synthesis of **1b**, we envisaged that olefin cross-metathesis could be the key reaction in assembling the piperidine skeleton. In fact, herein we propose to perform two cross-metathesis reactions; the first one to access the crucial intermediate (*S*)-2-vinyl-*N*-Boc-piperidine **3** and the other one during the coupling of **3** with commercially available 4-acetoxy styrene (Aldrich) en route the target compound. Thus in essence the retrosynthetic strategy (Scheme 1) proposed is as follows: **1b** could be obtained by the exhaustive reduction of **2** wherein the Boc group manifests into a 'methyl' group with the simultaneous deblocking of the acetyl group in one-pot. The advanced intermediate **2** in turn could be realized from the cross-metathesis reaction of **3** and 4-acetoxy styrene. Though piperidine derivative **3** was synthesized previously,[4] herein we propose a strategically different route to access it from naturally occurring L-glutamic acid as starting material involving an olefin cross-metathesis protocol. It is pertinent to mention that (*S*)-2-vinyl-*N*-Boc-piperidine **3** is a key building block in the synthesis of natural products like epilupinine and (−)-aloperine.[4]

Accordingly, synthesis of **1b** commenced with the known[5] *N*-Boc-allyloxazolidine **5** (Scheme 2). Thus, compound **5** was accessed by a modified literature route from L-glutamic acid and the structure was confirmed by comparing its analytical data with reported values.

After having the *N*-Boc-allyloxazolidine **5** in hand, Grubbs catalyst assisted cross-metathesis[6] reaction of **5** (1.0 equiv) with its olefin partner, methyl acrylate {2.5 equiv; G-II (8 mol %)/CH_2Cl_2/6 h} was conducted to afford α,β-unsaturated ester (**4**, 80%)[7] as an exclusive *E*-isomer (Scheme 2). Compound **4** was characterized by its spectroscopic data, for instance, the ^1H NMR spectrum revealed a peak at δ 5.85 ppm (J = 15.8 Hz) indicating the *trans*-geometry of the olefin and the optical rotation value was found



Caulophyllumine A Caulophyllumine B

Figure 1. New alkaloids from blue cohosh.

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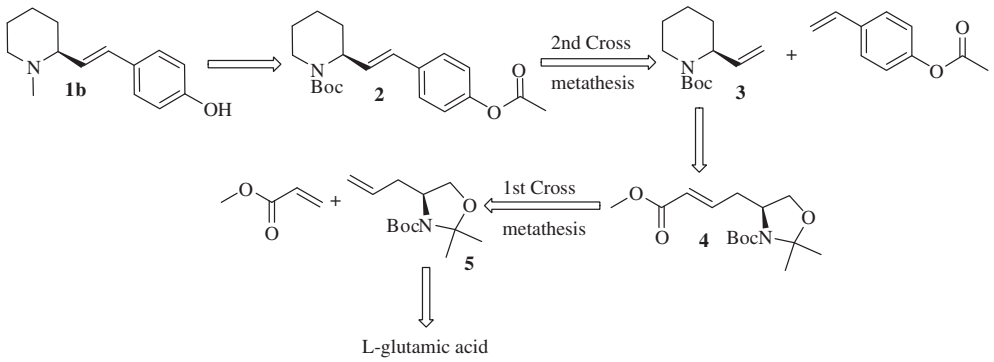
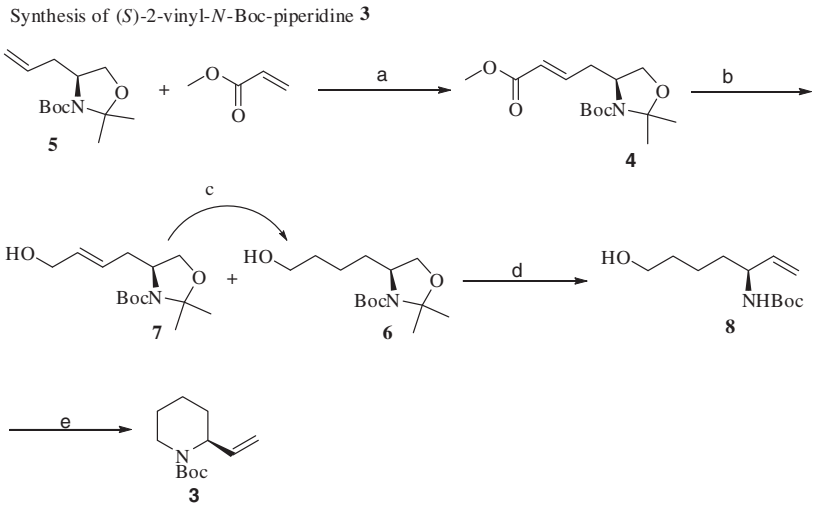


Scheme 1. Retrosynthetic analysis of caulophyllumine B.

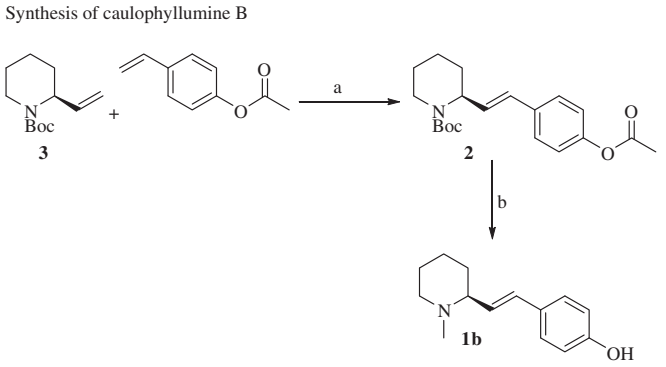


Scheme 2. Reagents and conditions: (a) G-II (8 mol %), rt, 6 h, 80%; (b) (i) $LiAlH_4$, THF, 0 °C to rt, 2.5 h, (compound **6**, 32%, compound **7**, 51%); (c) Pd/C, H_2, EtOAc, 4 h, 78%; (d) (i) TBDPSCl, imidazole, CH_2Cl_2, rt, 2 h, 94%; (ii) $CuCl_2{\cdot}2H_2O$, CH_3CN, rt, 0.5 h, 89%; (iii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1.5 h; (iv) $Ph_3P^+CH_3I^-$, KO^tBu, THF, −5 °C, 6 h, then aldehyde, rt, 2 h, 83% over two steps; (v) TBAF, THF, rt, 1.5 h, 88%; (e) (i) MsCl, Et_3 N, CH_2Cl_2, rt, 0.5 h; (ii) KO^tBu, THF, 0 °C to rt, 4 h (for two steps overall yield 93%).

to be $[\alpha]_D^{25}$ +25.3 (*c* 0.85, $CHCl_3$). Incidentally, an enantiomer of **4** was reported in the literature[7] {$[\alpha]_D^{25}$ −27.9 (*c* 1.15, $CHCl_3$)}.

Further, the *trans*-α,β-unsaturated ester (**4**) on reduction with LAH resulted in a chromatographically separable mixture of saturated alcohol **6** (32%) and unsaturated alcohol **7** (51%).[7b] After separation of this mixture into individual components, compound **7** was hydrogenated (Pd-C/H_2/rt/EtOAc/78%) to furnish an additional crop of saturated alcohol **6**. Later, the pooled alcohol **6** was protected as its silyl ether (TBDPSCl/imidazole/CH_2Cl_2/rt/2 h/94%), which on acetonide group deprotection[8] ($CuCl_2{\cdot}2H_2O$/CH_3CN/rt/89%) gave the corresponding primary alcohol that was oxidized under Swern conditions and the ensuing aldehyde was exposed to a Wittig olefination reaction ($Ph_3P^+CH_3I^-$/KO^tBu/THF/−5 °C to rt/8 h, 83%). It furnished an olefin without any epimerization as ascertained at a later stage of the synthesis of **3** by comparing the specific rotation values. Next, the silyl group was deblocked (TBAF/THF/rt/1.5 h) to afford the corresponding primary alcohol **8** (88%). Further, alcohol **8** was converted into its corresponding mesylate (MsCl/Et_3N/CH_2Cl_2/rt), which on immediate base induced intramolecular S_N2 reaction (KO^tBu/THF/0 °C to rt) furnished (*S*)-2-vinyl-*N*-Boc-piperidine **3** (93% over two steps, Scheme 2). Compound **3** was characterized by comparing its spectral data with the reported values.[4,9]

During the crucial cross-metathesis reaction (Scheme 3), 2.5-folds of 4-acetoxy styrene was reacted with 1.0 fold of (*S*)-2-vinyl-*N*-Boc-piperidine **3** {G-II (10 mol %)/CH_2Cl_2/rt/1.5 h} to afford the (*E*)-olefin **2** (76%) as the major product albeit a small amount



Scheme 3. Reagents and conditions: (a) G-II (10 mol %), CH_2Cl_2, rt, 1.5 h, 76%; (b) $LiAlH_4$, THF, reflux, 3 h, 68%.

of homo dimer of 4-acetoxy styrene (10%) was also observed as a separable mixture. (*E*)-Olefin **2** was characterized by its spectroscopic data, wherein the ^1H NMR spectrum displayed the olefinic protons at δ 6.33 ppm (*J* = 16.2 Hz) and at δ 6.09 ppm (*J* = 16.2 Hz) indicating the *trans* disposition of the olefinic protons. (*E*)-Olefin **2** on reaction with LAH in THF at reflux resulted in the one-pot deprotection of the acetyl group as well as the transformation of Boc group into the methyl functionality to furnish the natural product caulophyllumine B **1b** (68%) as a brown powder. The spectral data matched with the reported values.[1,9]

In conclusion, a method for the synthesis of (*S*)-2-vinyl-*N*-Boc-piperidine **3**, a versatile intermediate in the synthesis of piperidine based natural products was accomplished and its use was exemplified in the first stereoselective total synthesis of caulophyllumine B (**1b**) via an iterative olefin cross-metathesis reaction. The combinatorial advantage of this synthetic strategy lies in the second cross-metathesis wherein various styrenes/designed olefins could be coupled for generating a diverse library of compounds.[10]

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References and notes

1. (a) Ali, Z.; Khan, I. A. *Phytochemistry* **2008**, *69*, 1037–1042; (b) Jhoo, J.; Sang, S.; He, K.; Cheng, X.; Zhu, N.; Stark, R. E.; Zheng, Q. Y.; Rosen, R. T.; Ho, C. T. *J. Agric. Food. Chem.* **2001**, *49*, 5969–5974.
2. Madgula, V. L. M.; Ali, Z.; Smillie, T.; Khan, I. A.; Walker, L. A.; Khan, S. I. *Planta Med.* **2009**, *75*, 329–332.
3. (a) Radha Krishna, P.; Srishailam, A. *Tetrahedron Lett.* **2007**, *48*, 6924–6927; (b) Radha Krishna, P.; Dayaker, G. *Tetrahedron Lett.* **2007**, *48*, 7279–7282; (c) Radha Krishna, P.; Lopinti, K. *Synlett* **2007**, 1742–1744; (d) Radha Krishna, P.; Reddy, P. S. *J. Comb. Chem.* **2008**, *10*, 426–435.
4. (a) Cheng, G.; Wang, X.; Su, D.; Liu, H.; Liu, F.; Hu, Y. *J. Org. Chem.* **2010**, *75*, 1911–1916; (b) Yamouchi, S.; Omi, Y. *Biosci. Biotechnol. Biochem.* **2005**, *69*, 1589–1594; (c) Lim, S. H.; Ma, S.; Beak, P. *J. Org. Chem.* **2001**, *66*, 9056–9062; (d) Hassner, A.; Mourya, R.; Padwa, A. *J. Org. Chem.* **1991**, *56*, 2775–2781.
5. Dondoni, A.; Giovannini, P. P.; Perrone, D. *J. Org. Chem.* **2005**, *70*, 5508–5518.
6. (a) Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3171–3174; (b) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117–7140; (c) Nolen, E. G.; Kurish, A. J.; Wong, K. A.; Orlando, M. D. *Tetrahedron Lett.* **2003**, *44*, 2449–2453.
7. (a) Blackburn, L.; Wei, X.; Taylor, R. J. K. *Chem. Commun.* **1999**, 1337–1338; (b) Kawate, T.; Fukuta, N.; Nishida, A.; Nakagawa, M. *Chem. Pharm. Bull.* **1997**, *45*, 2116–2118.
8. Chandrasekhar, M.; Chandra, K. L.; Singh, V. K. *J. Org. Chem.* **2003**, *63*, 4039–4045.
9. *Spectral data for selected compounds. Compound* **5***:* Colorless liquid; (two rotamers). $[\alpha]_D^{25}$ +19.8 (*c* 0.85, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.73 (br s, 1H), 5.12–5.16 (m, 2H), 3.95–3.75 (m, 3H), 2.59–2.43 (m, 1H), 2.30–2.20 (m, 1H), 1.60–1.47 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.5, 134.6, 117.7, 96.1, 93.9, 66.4, 66.1, 56.9, 38.1, 37.1, 28.5, 27.5, 26.7, 24.6, 23.3; ESI-MS (*m*/*z*): 242 $[M+H]^+$, 264 $[M+Na]^+$; HRMS (*m*/*z*) calcd for: $C_{13}H_{23}NO_3Na$ 264.1575 $[M+Na]^+$, found 264.1574. *Compound* **4***:* Colorless liquid; (two rotamers). $[\alpha]_D^{25}$ +25.3 (*c* 0.63, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.86 (ddd, *J* = 7.9, 14.3 Hz, 1H), 5.85 (d, *J* = 15.9 Hz, 1H), 3.72–3.68 (m, 4H), 2.70–2.39 (m, 2H), 1.55 (d, *J* = 15.9 Hz, 2H), 1.55–1.46 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 159.0, 137.4, 135.7, 130.7, 129.9, 129.2, 118.8, 117.9, 113.6, 81.7, 77.9, 76.8, 72.8, 71.5, 70.1, 55.2, 41.2, 35.8, 35.1, 31.7, 29.1, 25.1, 22.4; ESI-MS (*m*/*z*): 300 $[M+H]^+$, 322 $[M+Na]^+$. *Compound* **6***:* Colorless syrup; (two rotamers). $[\alpha]_D^{25}$ +24.3 (*c* 0.74, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 3.92–3.61 (m, 5H), 1.71–1.25 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.2, 151.3, 96.2, 66.7, 64.8, 62.0, 57.5, 52.5, 33.5, 32.4, 31.1, 28.6, 27.7, 26.0, 24.6, 23.3, 22.6, 22.1; ESI-MS (*m*/*z*): 274 $[M+H]^+$, 296 $[M+Na]^+$; HRMS (*m*/*z*) calcd for: $C_{14}H_{27}NO_4Na$, 296.1837 $[M+Na]^+$, found (*m*/*z*): 296.1845. *Compound* **8***:* Colorless thick liquid; $[\alpha]_D^{25}$ +2.3 (*c* 0.74, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.82–5.68 (m, 1H), 5.1 (tq, *J* = 1.2, 17.2 Hz, 2H), 4.38 (d, *J* = 7.7 Hz, 1H), 4.1 (d, *J* = 6.8 Hz, 1H), 3.62 (t, *J* = 5.8 Hz, 2H), 1.65–1.38 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.5, 139.0, 114.5, 79.4, 62.6, 52.5, 34.9, 32.5, 28.5, 21.9; ESI-MS (*m*/*z*): 230 $[M+H]^+$, 252 $[M+Na]^+$. *Compound* **3***:* Colorless liquid; $[\alpha]_D^{25}$ −38.2 (*c* 1.25, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.73 (ddd, *J* = 4.1, 10.6, 17.4 Hz, 1H), 5.16 (ddd, *J* = 1.5, 2.3, 10.6 Hz, 1H), 5.03 (ddd, *J* = 1.9, 2.3, 17.4 Hz, 1H), 4.75 (br s, 1H), 3.92 (br d, *J* = 13.5 Hz, 1H), 2.80 (dt, *J* = 2.6, 12.8 Hz, 1H), 1.74–1.54 (m, 4H), 1.52–1.40 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.3, 136.8, 115.4, 79.2, 52.4, 39.6, 28.9, 28.4, 25.5, 19.4; ESI-MS (*m*/*z*): 212 $[M+H]^+$, 234 $[M+Na]^+$. *Compound* **2***:* Colorless syrup; $[\alpha]_D^{25}$ −34.2 (*c* 0.25, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.34 (d, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 8.3 Hz, 2H), 6.33 (dd, *J* = 1.1, 16.6 Hz, 1H), 6.09 (dd, *J* = 4.5, 15.8 Hz, 1H), 4.92 (br s, 1H), 3.97 (d, *J* = 13.6 Hz, 1H), 2.87 (t, *J* = 12.8 Hz, 1H), 2.27 (s, 3H), 1.80–1.62 (m, 3H), 1.47 (s, 9H), 1.25 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 155.4, 149.9, 134.9, 129.7, 129.1, 127.2, 121.7, 79.6, 52.2, 39.9, 29.6, 28.5, 25.5, 21.1, 19.7; ESI-MS (*m*/*z*): 346 $[M+H]^+$, 368 $[M+Na]^+$; HRMS (*m*/*z*) calcd for: $C_{20}H_{27}NO_4Na$ 368.1837 $[M+Na]^+$, found 368.1855. *Compound* **1b***:* Brown powder; $[\alpha]_D^{25}$ −8.5 (*c* 0.27, MeOH); ^1H NMR (300 MHz, $CDCl_3$): δ 7.17 (d, *J* = 8.3 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 6.43 (d, *J* = 15.9 Hz, 1H), 5.95 (dd, *J* = 9.0, 15.9 Hz, 1H), 3.12 (br d, *J* = 11.0 Hz, 1H), 2.67 (ddd, *J* = 4.9, 9.1, 13.2 Hz, 1H), 2.37 (s, 3H), 2.22 (ddd, *J* = 4.2, 11.3, 15.1 Hz 1H), 1.84–1.60 (m, 5H), 1.43–1.22 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.1, 132.2, 128.2, 127.8, 127.3, 116.2, 68.5, 56.4, 43.5, 32.5, 24.9, 23.6; ESI-MS (*m*/*z*): 218 $[M+H]^+$; HRMS (*m*/*z*) calcd for: $C_{14}H_{20}NO$ 218.1544 $[M+H]^+$, found 218.1541.
10. The authors are thankful to the referee for asking us to bring out this importance.