Asymmetric Synthesis of (–)-6-*epi*-Centrolobine

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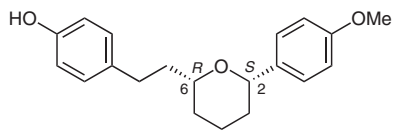
Abstract: A stereoselective total synthesis of (–)-6-*epi*-centrolobine, an unnatural analogue of (–)-centrolobine, starting from readily available tri-*O*-acetyl-D-glucal has been described for the first time. The key steps involved in this synthetic approach are stereoselective C-glycosidation, dehydroxylation and Wittig reaction. The target molecule was achieved in nine steps with 49% overall yield.

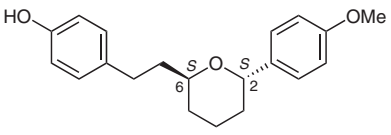
Key words: centrolobine, tri-*O*-acetyl-D-glucal, C-glycosidation, dehydroxylation, Wittig reaction

(–)-Centrolobine (**1**) is a natural product obtained from the Amazon forest, isolated from the heartwood of *Centrolobium robustum* and from the stem of *Brosinium potabile*.[1] Centrolobine is known to exhibit anti-leishmanial activity against Leishmania amazonesis prosmatigotes.[2] The absolute configuration of this natural product was determined in 2002 by Colobert et al. via asymmetric total synthesis.[3] Due to the biological importance and relatively simple structure of (–)-centrolobine, it makes a perfect target for synthetic organic chemists and its enantioselective synthesis has been achieved by various groups,[4] including ours.[5] After the synthesis of (–)-centrolobine (**1**), we turned our attention to the synthesis of its analogues, unnatural derivatives, which can be used to study structure–activity relationships (SARs), with the anticipation of obtaining better biological activity. Towards this aim, herein we report the asymmetric synthesis of (–)-6-*epi*-centrolobine (**2**; Figure 1), a non-natural analogue.

From a retrosynthetic perspective, we envisioned 2, 6-*trans*-disubstituted dihydropyran **4** as a precursor, which would lead to **2** through a Wittig reaction with **3** followed by a hydrogenation reaction. We postulated that this precursor **4** could be accessed by a palladium-catalyzed stereoselective C-glycosidation of tri-*O*-acetyl-D-glucal **5** followed by dehydroxylation as key reactions (Scheme 1).

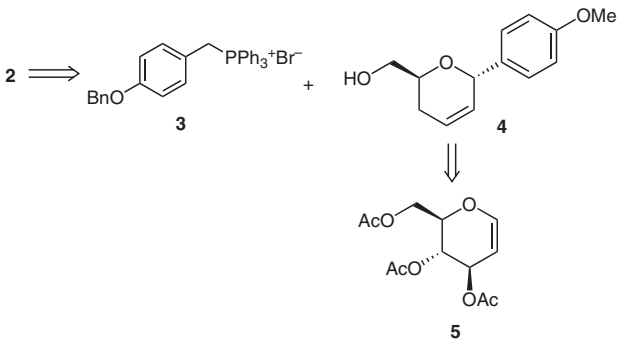


(–)-centrolobine **1**



(–)-6-*epi*-centrolobine **2**

Figure 1 Structures of (–)-centrolobine and its 6-epimer



Scheme 1 Retrosynthetic approach to (–)-6-*epi*-centrolobine

Thus, *C*-aryl pseudoglycal **7** was prepared by the stereoselective C-glycosidation of tri-*O*-acetyl-D-glucal (**5**) with 4-methoxyphenylboronic acid (**6**) in the presence of $Pd(OAc)_2$ in 78% yield (Scheme 2).[6] Next, deacetylation of compound **7** was carried out using potassium carbonate to afford the diol **8** in 96% yield. The primary hydroxyl group of diol **8** was selectively protected as its *tert*-butyldimethylsilyl (TBDMS) ether **9** using imidazole and TBDMSCl in 91% yield. Dehydroxylation of the secondary hydroxyl group of compound **9** was achieved via tosylation of the hydroxyl group using *p*-tolunesulfonyl chloride/pyridine followed by the treatment with lithium aluminum hydride to give **10** (88% yield, two steps). At this stage, the TBDMS protection in **10** was removed by tetrabutylamonium fluoride (TBAF) to reveal the primary alcohol **4** in 97% yield. The alcohol **4** was oxidized using Dess–Martin periodinane into the aldehyde, which was then subjected to a Wittig olefination with 4-benzyloxybenzyl triphenylphosphonium bromide (**3**), which was prepared using a known procedure.[7,4b] In the presence of *n*-butyllithium in tetrahydrofuran, compound **11** was obtained as a mixture of *E*/*Z* isomers (3:2) in 87% yield (two steps). Finally, one-pot deprotection of the benzyl ether and reduction of two double-bonds in compound **11** (mixture of *E*/*Z*, 3:2) using hydrogenation in the presence of PtO_2 (98% yield), completed the total synthesis of (–)-6-*epi*-centrolobine (**2**). This unnatural analogue of (–)-centrolobine was fully characterized by IR, HRMS, ^1H and ^{13}C NMR spectral data.

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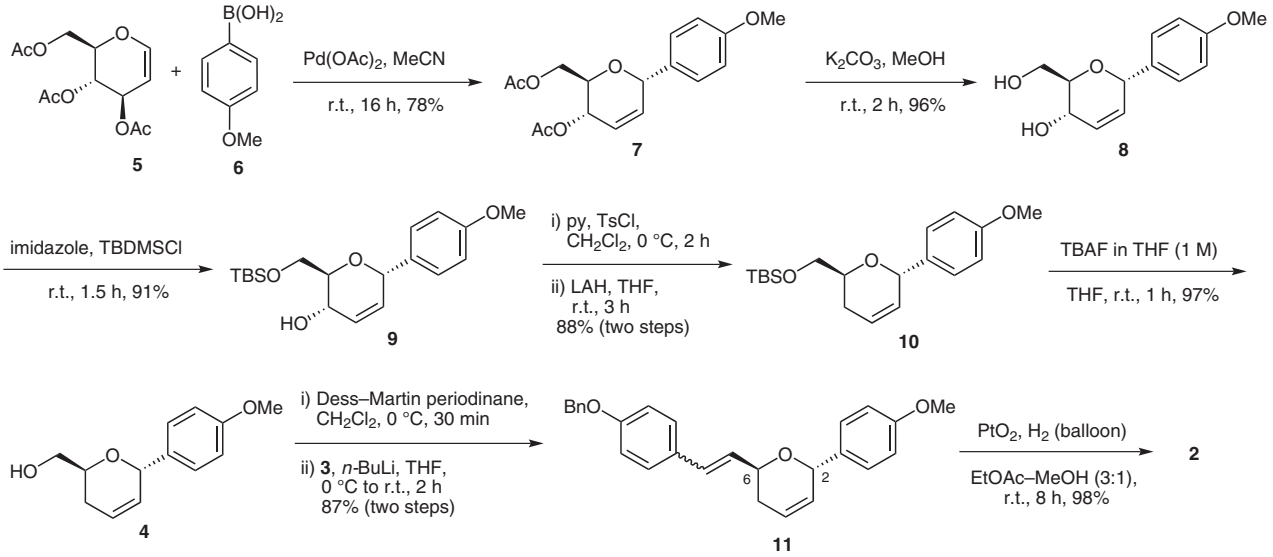

Scheme 2

The synthesis of other analogues of (–)-centrolobine including its aza-analogue using different synthetic approaches is in progress. Upon completion of the synthesis, all these analogues will be tested for anti-leishmanial activity by comparison with the natural centrolobine and the results will be published later.

In conclusion, we have successfully achieved the asymmetric total synthesis of (–)-6-*epi*-centrolobine from commercially available tri-*O*-acetyl-D-glual in nine steps with 49% overall yield.

All solvents and reagents were purified by standard techniques. Crude products were purified by column chromatography on silica gel (60–120 mesh). IR spectra were recorded on a Perkin–Elmer 683 spectrometer. Optical rotations were obtained on Jasco Dip 360 digital polarimeter. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Gemini 200 and Brucker Avance 300. Chemical shifts are reported in parts per million (ppm) with respect to internal TMS. Coupling constants (*J*) are quoted in Hz. Mass spectra were recorded on CEC-21-11013 or Fannigan Mat 1210 double focusing mass spectrometers operating with a direct inlet system or LC/MSD Trap SL (Agilent Technologies).

(2*S*,5*S*,6*R*)-6-(Acetoxymethyl)-2-(4-methoxyphenyl)-5,6-dihydro-2*H*-pyran-5-yl Acetate (7)

To a mixture of the tri-*O*-acetyl-D-glucal (**5**; 0.5 g, 1.83 mmol) and 4-methoxyphenylboronic acid (**6**; 0.56 g, 3.67 mmol) in MeCN (5 mL) was added $Pd(OAc)_2$ (0.046 g, 0.18 mmol). The resulting suspension was stirred at r.t. for 16 h. After this time, the reaction mixture was diluted with CH_2Cl_2 (15 mL) and filtered through a pad of silica gel. The filtrate was concentrated and subjected to column chromatography (EtOAc–hexanes, 1:4) to afford **7**.

Yield: 0.67 g (78%); white solid; mp 39–41 °C; $[\alpha]_D^{25}$ –6.2 (*c* 1.1, $CHCl_3$).

IR (neat): 3008, 2929, 1739, 1606, 1510, 1370, 1259, 1033, 817 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.3 Hz, 2 H), 6.85 (d, *J* = 8.3 Hz, 2 H), 6.15–6.1 (m, 1 H), 5.98–5.92 (m, 1 H), 5.28–5.21 (m, 2 H), 4.24–4.17 (m, 1 H), 4.05–3.99 (m, 1 H), 3.8 (s, 3 H), 3.76–3.7 (m, 1 H), 2.08 (s, 3 H), 2.05 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.7, 170.3, 159.5, 131.6, 130.7, 129.3 (2 × C), 124.9, 113.7 (2 × C), 73.7, 68.8, 65.0, 62.8, 55.1, 20.9, 20.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{20}O_6Na$: 343.1157; found: 343.1159.

(2*S*,5*S*,6*R*)-6-(Hydroxymethyl)-2-(4-methoxyphenyl)-5,6-dihydro-2*H*-pyran-5-ol (8)

To a solution of **7** (0.35 g, 1.09 mmol) in MeOH (10 mL), was added K_2CO_3 (0.45 g, 3.28 mmol) at 27 °C and the reaction was stirred for 2 h. Upon completion (reaction monitored by TLC), the solvent was removed in vacuo, H_2O (10 mL) was added and the residue was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The residue obtained was purified by silica gel column chromatography (EtOAc–hexanes, 3:2) to afford **8**.

Yield: 0.46 g (96%); white solid; mp 85–86 °C; $[\alpha]_D^{25}$ –88.4 (*c* 1.3, $CHCl_3$).

IR (neat): 3305, 3038, 2879, 1610, 1511, 1242, 1174, 1067, 1024, 823 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 8.5 Hz, 2 H), 6.84 (d, *J* = 8.5 Hz, 2 H), 6.0 (s, 2 H), 5.17 (s, 1 H), 4.28–4.16 (m, 1 H), 3.79 (s, 3 H), 3.68 (t, *J* = 4.6 Hz, 2 H), 3.37–3.32 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.4, 131.3, 130.2, 129.7 (2 × C), 128.8, 113.8 (2 × C), 73.7, 72.4, 63.5, 62.4, 55.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{16}O_4Na$: 259.0946; found: 259.0944.

(2*S*,5*S*,6*R*)-6-[(*tert*-Butyldimethylsilyloxy)methyl]-2-(4-methoxyphenyl)-5,6-dihydro-2*H*-pyran-5-ol (9)

To a solution of diol **8** (0.5 g, 2.11 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 °C was added imidazole (0.29 g, 4.2 mmol) followed by TBDMSCl (0.32 g, 2.11 mmol) in anhydrous CH_2Cl_2 (5 mL) and the reaction was allowed to warm to r.t. After stirring for 1.5 h, the reaction mixture was diluted with H_2O (10 mL), the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10mL). The combined organic layer was washed with brine (15 mL), dried over Na_2SO_4 and concentrated to dryness. Purification of the residue by silica gel column chromatography (EtOAc–hexanes, 7%) gave **9**.

Yield: 0.67 g (91%); viscous liquid; $[\alpha]_D^{25}$ –58.0 (*c* 1, $CHCl_3$).

IR (neat): 3443, 2926, 2855, 1609, 1510, 1249, 1081, 778 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 9.0 Hz, 2 H), 6.76 (d, *J* = 9.0 Hz, 2 H), 5.9 (s, 2 H), 5.06 (s, 1 H), 4.1 (d, *J* = 6.7 Hz, 1 H), 3.71 (s, 3 H), 3.71–3.67 (m, 1 H), 3.64–3.57 (m, 1 H), 3.33–3.25 (m, 1 H), 2.93 (br s, 1 H), 0.82 (s, 9 H), 0.01 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.6, 131.6, 129.8 (2 × C), 129.5, 128.7, 113.8 (2 × C), 73.7, 70.9, 67.4, 66.0, 55.4, 26.0 (3 × C), 18.3, –5.3, –5.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{30}O_4NaSi$: 373.1811; found: 373.1823.

(2*S*,6*S*)-6-[(*tert*-Butyldimethylsilyloxy)methyl]-2-(4-methoxyphenyl)-5,6-dihydro-2*H*-pyran (10)

To a solution of compound **9** (0.25 g, 0.71 mmol) in CH_2Cl_2 (5 mL) was added pyridine (0.18 mL, 2.2 mmol), PTSA (0.17 g, 0.9 mmol) and a catalytic amount of DMAP at 0 °C, and the reaction was stirred for 2 h at the same temperature. After the reaction was complete (monitored by TLC), the reaction mixture was diluted with CH_2Cl_2 (5 mL), washed with aq sat. $CuSO_4$ (2 × 5 mL), brine (5 mL), dried over Na_2SO_4 and concentrated to dryness. The residue was passed through a silica gel pad (EtOAc–hexanes, 1:9), to obtain the corresponding tosylated compound (~0.36 g), which was immediately used in the next step.

To a suspension of LAH (0.077 g, 2.01 mmol) in anhydrous THF (5 mL) at 0 °C was added the above obtained tosylated compound (0.36 g, 0.67 mmol) in THF (5 mL) and the reaction was stirred at r.t. for 3 h. After the reaction was complete (monitored by TLC), the mixture was quenched with moistened Na_2SO_4 (50 mg) at 0 °C and stirring was continued for 3 h. The white colored salts were filtered on a sintered-glass funnel and the residue was rinsed with H_2O (20 mL), EtOAc (3 × 10 mL). The organic layer was separated and washed with brine (15 mL), dried over Na_2SO_4 and concentrated on rotary evaporator. The residue obtained was purified by silica gel column chromatography (EtOAc–hexanes, 1:4) to yield **10**.

Yield: 0.198 g (88%); viscous oil; $[\alpha]_D^{25}$ –132.5 (*c* 1.4, $CHCl_3$).

IR (neat): 2928, 2856, 1604, 1512, 1252, 1106, 838 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.3 Hz, 2 H), 6.78 (d, *J* = 8.3 Hz, 2 H), 6.0–5.9 (m, 2 H), 5.14 (s, 1 H), 3.77 (s, 3 H), 3.76–3.67 (m, 1 H), 3.64–3.47 (m, 2 H), 2.26–2.18 (m, 1 H), 2.04–1.99 (m, 1 H), 0.85 (s, 9 H), 0.01 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 133.3, 129.4 (2 × C), 127.9, 125.4, 113.6 (2 × C), 73.6, 68.2, 66.3, 55.3, 27.5, 26.0 (3 × C), 18.4, –5.2 (2 × C).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{30}O_4NaSi$: 357.1861; found: 357.1874.

(2*S*,6*S*)-6-(Hydroxymethyl)-2-(4-methoxyphenyl)-5,6-dihydro-2*H*-pyran (4)

To a solution of *tert*-butyldimethylsilyl ether **10** (0.5 g, 1.49 mmol) in THF (7 mL) was added TBAF (0.52 mL, 1.79 mmol, 1M in THF) at r.t., and the mixture was stirred for 1 h. The reaction mixture was quenched with aq sat. NH_4Cl (10 mL), diluted with H_2O (10 mL) and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4 and evaporated in vacuo to give the crude product, which was purified by silica gel column chromatography (EtOAc-hexanes, 1:3) to obtain **4**.

Yield: 0.33 g (97.5%); white solid; mp 41–43 °C; $[\alpha]_D^{25}$ –149.9 (*c* 1.1, $CHCl_3$).

IR (neat): 3420, 2924, 1610, 1511, 1245,1032, 827 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.3 Hz, 2 H), 6.83 (d, *J* = 9.0 Hz, 2 H), 6.08–5.91 (m, 2 H), 5.19 (s, 1 H), 3.79 (s, 3 H), 3.76–3.68 (m, 1 H), 3.64–3.45 (m, 2 H), 1.96–1.86 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.4, 132.8, 129.6 (2 × C), 127.6, 125.4, 113.8 (2 × C), 73.8, 67.7, 65.5, 55.4, 26.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{16}O_3Na$: 243.0997; found: 243.1000.

(2*S*,6*S*)-6-[4-(Benzyloxy)styryl]-2-(4-methoxyphenyl)-5,6-dihydro-2*H*-pyran (11)

To a solution of alcohol **4** (0.1 g, 0.45 mmol) under a nitrogen atmosphere was added anhydrous CH_2Cl_2 (5 mL) and Dess–Martin periodinane (0.19 g, 0.45 mmol) at 0 °C and the reaction was stirred at the same temperature for 30 min. The reaction mixture was quenched with aq sat. $Na_2S_2O_3$ (10 mL), the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4 and evaporated in vacuo to obtain the crude product, which was used for the next step without purification.

To a solution of phosphonium salt **3** (1.24 g, 2.29 mmol) in THF (5 mL) at 0 °C was added *n*-BuLi (1.07 mL, 1.72 mmol, 1.6 M in hexanes). The solution turned orange-red and was stirred for 20 min at 0 °C. To this, a solution of the above prepared aldehyde (0.25 g, 1.15 mmol) in THF (5 mL) was added and the reaction mixture was stirred for 30 min at 0 °C. After the reaction was complete (monitored by TLC), the mixture was quenched with aq sat. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4 and concentrated to dryness. Purification of the residue by silica gel column chromatography (EtOAc–hexanes, 3%) gave **11**.

Yield: 0.39 g (87.3%); a 2:3 mixture of *E*/*Z* isomers.

IR (neat): 3448, 2922, 2852, 1605, 1509, 1244, 1174, 1032, 838, 739 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.21 (m, 9 H), 6.92–6.76 (m, 4 H), 6.51 (d, *J* = 9.0 Hz, 1 H), 6.43 (d, *J* = 11.3 Hz, 1 H), 6.11–5.86 (m, 2 H), 5.24 (s, 1 H), 5.04 (s, 1 H), 4.95 (s, 1 H), 4.51–4.41 (m, 1 H), 3.81 (s, 3 H), 2.23–2.14 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.6, 159.3, 158.5, 157.9, 137.1, 133.4, 133.1, 132.9, 130.5, 130.4, 130.2, 130.0, 129.5, 128.7, 128.1, 127.9, 127.8, 127.6, 125.5, 125.3, 115.0, 114, 4, 113.9, 113.8, 74.0, 73.7, 70.2, 69.9, 68.4, 64.1, 55.5, 31.5, 30.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{26}O_3Na$: 421.1779; found: 421.1795.

(2*S*,6*S*)-6-[4-(Hydroxy)phenethyl]-2-(4-methoxyphenyl)-tetrahydro-2*H*-pyran (2)

To a solution of compound **11** (0.03 g, 0.07 mmol) in a mixture of EtOAc–MeOH (3:1, 3 mL) was added a catalytic amount of PtO_2 and the mixture was kept under a H_2 atmosphere (balloon) for 8 h at 27 °C. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through a pad of celite and concentrated to dryness. Purification of the residue by silica gel column chromatography (EtOAc–hexanes, 1:5) afforded the desired product **2**.

Yield: 0.22 g (98%); $[\alpha]_D^{25}$ –1.4 (*c* 0.4, $CHCl_3$).

IR (neat): 3441, 2923, 2853, 1613, 1512, 1244, 1033, 760 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.7 Hz, 2 H), 7.02 (d, *J* = 8.4 Hz, 2 H), 6.86 (d, *J* = 9.0 Hz, 2 H), 6.69 (d, *J* = 8.4 Hz, 2 H), 4.97 (br s, 1 H), 4.78 (t, *J* = 5.4 Hz, 1 H), 3.78 (s, 3 H), 3.76–3.72 (m, 1 H), 2.76–2.66 (m, 1 H), 2.57–2.47 (m, 1 H), 1.88–1.82 (m, 2 H), 1.75–1.57 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.8, 153.8, 134.7, 134.5, 129.6 (2 × C), 128.0 (2 × C), 115.3 (2 × C), 113.9 (2 × C), 72.0, 71.4, 55.5, 35.4, 31.5, 30.3, 30.1, 19.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{24}O_3Na$: 335.1623; found: 335.1634.

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(7) 4-Benzyloxybenzyl triphenylphosphonium bromide was prepared in two steps from commercially available *p*-benzyloxybenzyl alcohol using a known protocol, see ref. 4b.