Tetrahedron: *Asymmetry* 21 (2010) 103–105

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

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

Synthesis of a diarylheptanoid, (+)-centrolobine

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ARTICLE INFO

Article history:
Received 19 November 2009
Accepted 11 January 2010
Available online 1 February 2010

ABSTRACT

A chiron approach for the total synthesis of (+)-centrolobine has been described from the commercially available aldehyde **3** employing an acid-catalyzed stereoselective formation of tetrahydropyran ring as the key step. The desired molecule was accomplished in eight steps with 62% overall yield.

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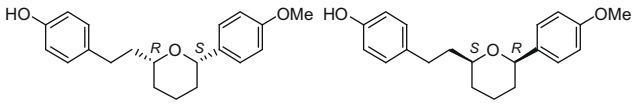
1. Introduction

Diarylheptanoid natural products containing a tetrahydropyran (THP) ring have received considerable attention due to their wide range of biological activities.[1–3] The centrolobine family is one of the diarylheptanoids with a 2,6-disubstituted tetrahydropyran ring isolated from centrolobium species (Leguminasae). The heart wood of *Centrolobium robustum* was found to contain (−)-centrolobine **1** while the other species *Centrolobium tomentosum* was found to contain (+)-centrolobine **2** (Fig. 1).[2] Furthermore, centrolobine and related natural products have been found to exhibit anti-inflammatory and anti-bacterial as well as anti-leishmanial activities.[2c,3] Among the centrolobine family members, (−)-centrolobine has received significant attention from synthetic organic chemists after the determination of its absolute configuration by Solladie et al. via the first asymmetric total synthesis.[4a] Since then, a variety of approaches have been reported towards the synthesis of **1** in both racemic and optically active forms.[4b–t] However, to date there is only one report in the literature describing the formal synthesis of (+)-centrolobine[5a] and recently one total synthesis has been reported[5b] while the present work was in progress. In continuation of our interest on the synthesis of diarylheptanoids,[4k,6] in particular the synthesis of centrolobine analogues, we herein report the stereoselective synthesis of (+)-centrolobine.



(-)-Centrolobine (**1**) (+)-Centrolobine (**2**)

Figure 1. Structures of (−)-centrolobine and (+)-centrolobine.

2. Results and discussion

Our synthesis of (+)-centrolobine (Scheme 1) started from the commercially available (*R*)-1,4-dioxaspiro[4,5]-decane-2-carboxaldehyde **3**. Wittig-olefination of aldehyde **3** with known 3-(benzyloxy)-propyl) triphenylphosphonium bromide **4**[7] in the presence of *n*BuLi in THF provided compound **5** in 89% yield (*E*/*Z* ratio 5:95). Hydrogenation of compound **5** in methanol under 10% Pd/C catalysis at room temperature gave alcohol **6** in 98% yield. Next, oxidation of alcohol **6** to aldehyde (IBX, DMSO, THF, 1 h) followed by Grignard reaction with 4-methoxyphenyl magnesium bromide, derived from **7**, afforded benzylic alcohol **8** in 89% yield over two steps. Now the stage was set for the key stereoselective cyclization to obtain 2,6-disubstituted tetrahydropyran. The treatment of compound **8** with camphorsulfonic acid in methanol at room temperature gave the desired tetrahydropyran **9** within 30 min (92%), through the deprotection of the ketal followed by intramolecular cyclization of the 1,5-diol.[8] The exclusive formation of *cis*-2,6-disubstituted tetrahydropyran **9** was confirmed by NOE studies.[9] Alcohol **9** was oxidized using Dess–Martin periodinane into the aldehyde, which was then subjected to a Wittig-olefination with 4-benzyloxybenzyl triphenylphosphonium bromide **10**, (prepared using a literature procedure)[4c] in the presence of *n*BuLi in THF. The above-mentioned reaction gave compound **11** in 90% yield (over two steps) as a mixture of *E*/*Z* isomers (3:1). Finally, the reduction of the olefin functionality and deprotection of the benzyl ether in compound **11** were accomplished in a one-pot reaction using hydrogenation in the presence of PtO_2 in EtOAc/MeOH (3:1), which completed the total synthesis of (+)-centrolobine (**2**). The spectroscopic data (IR, ^1H and ^{13}C NMR) of the obtained (+)-centrolobine (**2**) were identical and the specific rotation observed for **2**, $[\alpha]_D^{27} = +94.7$ (*c* 0.1, MeOH), was comparable to that reported for the natural product {lit: $[\alpha]_D^{25} = +97.5$ (*c* 0.1, MeOH)}.[2c]

3. Conclusions

In conclusion, an efficient total synthesis of (+)-centrolobine **2** has been demonstrated via a chiron approach. The target molecule

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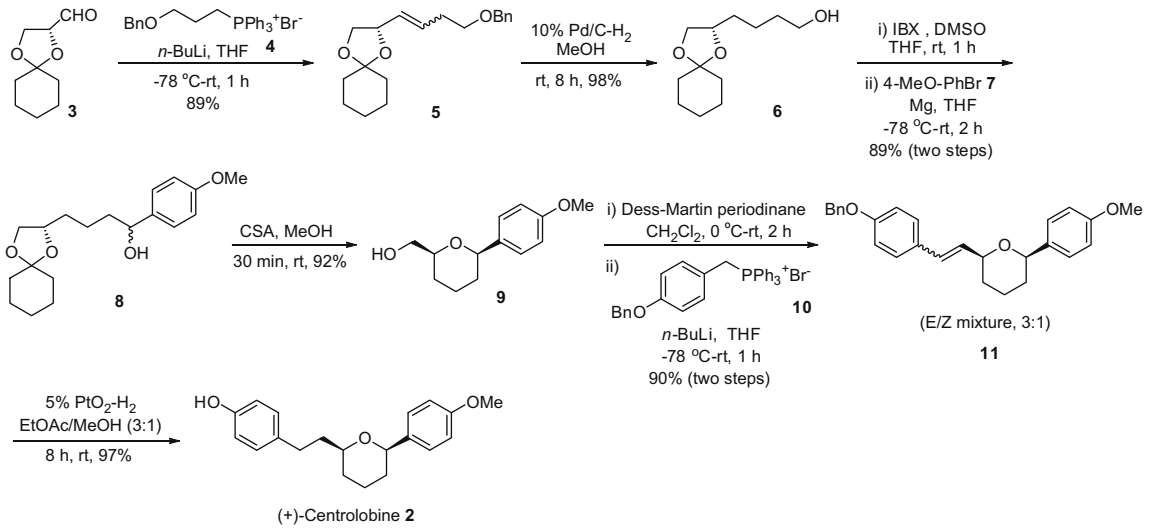
doi:10.1016/j.tetasy.2010.01.002



Scheme 1. Synthesis of (+)-centrolobine.

was accomplished in eight steps with 62% overall yield, which is significant. The synthetic route is new and unique which would also lead to the synthesis of (−)-centrolobine (starting from the other isomer of aldehyde **3**) as well as other analogues.

4. Experimental section

4.1. General

All solvents and reagents were purified by standard techniques. Crude products were purified by column chromatography on silica gel of 60–120 mesh. IR spectra are recorded on a Perkin–Elmer 683 spectrometer. Optical rotations were obtained on a Perkin–Elmer digital polarimeter. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Brucker Avance 300. Chemical shifts were reported in parts per million (ppm) with respect to internal TMS. Coupling constants (J) are quoted in Hz. Mass spectra were obtained on an Agilent Technologies LC/MSD Trap SL.

4.1.1. 4.1.1.(*S*)-2-(4-(Benzyloxy)but-1-enyl)-1,4-dioxaspiro[4.5]-decane 5

To a solution of (3-benzyloxy)-propyl) triphenylphosphonium bromide **4** (0.40 g, 0.82 mmol) in THF (10 mL) at −78 °C was added *n*BuLi (0.28 mL of a 2.5 M solution in hexanes, 0.71 mmol). The reaction mixture was allowed to warm up to 0 °C for 30 min, where the solution turned orange-red. Next, it was cooled to −78 °C and to this, a solution of aldehyde **3** (0.1 g, 0.59 mmol) in THF (5 mL) was added. It was stirred for 30 min at room temperature. After completion of the reaction (monitored by TLC), it was quenched with aqueous saturated NH_4Cl (10 mL) and the organic layer was separated. The aqueous layer was 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. The residue was purified by silica gel column chromatography (4% of EtOAc in hexanes) to give compound **5** (0.158 g) in 89% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.20 (m, 5H), 5.69–5.58 (m, 1H), 5.53–5.43 (m, 1H), 4.84–4.74 (m, 1H), 4.48 (s, 2H), 4.02–3.95 (m, 1H), 3.53–3.38 (m, 3H), 2.42 (q, J = 6.8, 13.9 Hz, 2H), 1.65–1.55 (m, 8H), 1.44–1.35 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.2, 130.5, 129.4, 128.3, 127.5, 109.6, 72.9, 71.5, 69.4, 69.0, 36.3, 35.4, 28.4, 25.1, 23.9, 23.8; IR (neat): ν 3402, 2935, 2859, 1726, 1162, 1101, 1042, 929, 739 cm^{-1}; HRMS (ESI): m/z [M+Na]$^+$ calcd for $C_{19}H_{26}O_3Na$: 325.1779; found: 325.1794.

4.1.2. (*S*)-4-(1,4-Dioxaspiro[4.5]decan-2-yl)butan-1-ol 6

To a solution of compound **5** (0.2 g, 0.66 mmol) in methanol (2 mL) was added a catalytic amount of 10% Pd/C and the mixture was kept under a H_2 atmosphere (balloon) for 8 h at room temperature. After the reaction was complete (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 (25% of EtOAc in hexanes) afforded the product **6** (0.139 g) in 98% yield. $[\alpha]_D^{26} = +2.6$ (c 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.14–3.99 (m, 2H), 3.69–3.62 (m, 2H), 3.55–3.47 (m, 1H), 1.71–1.33 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 109.2, 75.5, 69.0, 62.6, 36.5, 35.2, 33.3, 32.5, 25.1, 23.9, 23.8, 22.0; IR (neat): ν 3420, 2935, 2860, 1631, 1384, 1105, 1037, 931, 758 cm^{-1}; HRMS (ESI): m/z [M+Na]$^+$ calcd for $C_{12}H_{22}O_3Na$: 237.1466; found: 237.1473.

4.1.3. (*S*)-1-(4-Methoxyphenyl)-4-(1,4-dioxaspiro[4.5]decan-2-yl)butan-1-ol 8

To a solution of iodoxybenzoic acid (0.39 g, 1.4 mmol) in DMSO (1 mL), was added a solution of alcohol **6** (0.2 g, 0.93 mmol) dropwise in THF (15 mL). The reaction mixture was stirred at room temperature for 1 h. After the completion of reaction (monitored by TLC), ether (5 mL) was added to the reaction mixture and the resulting solid materials were filtered through a sintered funnel. The resulting filtrate was washed with saturated $NaHCO_3$ solution (10 mL) and the organic layer was separated. The aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated in vacuo to afford the aldehyde, which was used as such without purification.

To a solution of Mg turnings (0.056 g, 2.35 mmol) in anhydrous THF (5 mL) was slowly added dropwise the bromo compound **7** (0.23 mL, 1.88 mmol) at room temperature. After the formation of the Grignard reagent, the reaction mixture was cooled to −78 °C. The above-mentioned crude aldehyde (0.2 g, 0.94 mmol) in THF (15 mL) was added and stirred for 2 h. After completion of the reaction (monitored by TLC), it was quenched with saturated NH_4Cl (15 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 10 mL) and 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 (18% of EtOAc in hexanes) gave the benzylic alcohol **8** (0.269 g) in 89% yield (for two steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21 (d, J = 8.3 Hz, 2H), 6.82 (d, J = 9.1 Hz,

2H), 4.62–4.55 (m, 1H), 4.05–3.92 (m, 2H), 3.79 (s, 3H), 3.47–3.39 (m, 1H), 1.87–1.31 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.9, 136.8, 127.0, 113.7, 109.1, 75.5, 73.9, 69.0, 55.2, 38.8, 36.5, 35.2, 33.5, 25.1, 23.9, 23.8, 22.2; IR (neat): ν 3425, 2930, 2857, 1611, 1511, 1245, 1102, 1034, 930, 830 cm^{-1}; HRMS (ESI): m/z [M+Na]$^+$ calcd for $C_{19}H_{28}O_4Na$: 343.1885; found: 343.1886.

4.1.4. ((2*R*,6*S*)-2-(4-Methoxyphenyl)tetrahydro-2*H*-pyran-2-yl)methanol 9

To a solution of benzylic alcohol **8** (0.05 g, 0.15 mmol) in methanol (8 mL) was added a catalytic amount of camphorsulfonic acid at room temperature. The reaction mixture was stirred at the same temperature for 30 min. After the disappearance of the starting material (monitored by TLC), solid $NaHCO_3$ (catalytic amount) was added to the reaction mixture, then it was filtered and concentrated to dryness. Purification of the residue by silica gel column chromatography (21% of EtOAc in hexanes) gave alcohol **9** (0.032 g) in 92% yield. $[\alpha]_D^{26} = +53.8$ (c 1.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.23 (d, J = 9.1 Hz, 2H), 6.83 (d, J = 9.1 Hz, 2H), 4.36–4.29 (m, 1H), 3.79 (s, 3H), 3.67–3.45 (m, 3H), 2.20–2.09 (br s, 1H), 2.02–1.92 (m, 1H), 1.84–1.23 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.8, 135.1, 127.2, 113.6, 79.3, 78.6, 66.2, 55.2, 33.4, 26.8, 23.4; IR (neat): ν 3442, 2933, 2855, 1612, 1514, 1246, 1080, 1036, 829, 765, 546 cm^{-1}. HRMS (ESI): m/z [M+Na]$^+$ calcd for $C_{13}H_{18}O_3Na$: 245.1153; found: 245.1151.

4.1.5. (2*R*,6*S*)-2-(4-(Benzyloxy)styryl)-2-(4-methoxyphenyl)-tetrahydro-2*H*-pyran 11

To a solution of alcohol **9** (0.2 g, 0.9 mmol) in anhydrous CH_2Cl_2 (10 mL) under a nitrogen atmosphere was added Dess–Martin periodinane (0.57 g, 1.35 mmol) at 0 °C and the reaction mixture was stirred at ambient temperature for 2 h. Then, the reaction was quenched with aqueous saturated $Na_2S_2O_3$ (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 aldehyde, which was used as such for the next step without purification.

To a solution of 4-benzylyoxybenzyl triphenylphosphonium bromide **10** (1.22 g, 2.27 mmol) in THF (20 mL) at 0 °C was slowly added dropwise *n*BuLi (0.72 mL of a 2.5 M solution in hexanes, 1.8 mmol). After 30 min (orange-red solution formed), the above-mentioned aldehyde (0.2 g, 0.91 mmol) in THF (10 mL) was added dropwise at 0 °C and the stirring continued for 30 min. The reaction was quenched with aqueous saturated NH_4Cl (15 mL), the organic layer was separated and the aqueous layer was 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 (4% of EtOAc in hexanes) gave **11** (0.33 g) as a *E*/*Z* mixture (3:1) in 90% yield over two steps. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54–7.23 (m, 8H), 7.20 (d, J = 9.1 Hz, 1H), 6.89 (d, J = 9.1 Hz, 2H), 6.81 (d, J = 8.3 Hz, 2H), 6.55–6.40 (m, 1H), 6.15–6.04 and 5.66–5.56 (m, 1H), 5.04 (d, J = 5.3 Hz, 2H), 4.42–4.28 (m, 2H), 3.78 (s, 3H), 2.04–1.90 (m, 1H), 1.86–1.45 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.8, 157.9, 136.8, 135.4, 132.2, 132.1, 131.4, 130.7, 130.1, 129.8, 129.1, 128.9, 128.5, 128.3, 127.9, 127.5, 127.4, 114.7, 113.6, 79.5, 78.9, 78.8, 74.8, 69.9, 55.2, 33.3, 31.7, 31.5, 24.0, 23.8; IR (KBr): ν 3418, 2929, 2855, 1608, 1511, 1251, 1176, 1032, 832, 740, 710 cm^{-1}; HRMS (ESI): m/z [M+Na]$^+$ calcd for $C_{27}H_{28}O_3Na$: 423.1936; found: 423.1954.

4.1.6. (+)-Centrolobine 2

To a solution of compound **11** (0.05 g, 0.12 mmol) in a mixture of ethyl acetate/methanol (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 room temperature. After the reaction was complete (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 (14% EtOAc in hexanes) afforded the desired product **2** (0.038 g) in 97% yield. $[\alpha]_D^{27} = +94.7$ (c 0.1, MeOH), ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 (d, J = 7.0 Hz, 2H), 7.02 (d, J = 8.3 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 6.69 (d, J = 8.5 Hz, 2H), 4.65–4.52 (br s, 1H), 4.31–4.22 (m, 1H), 3.79 (s, 3H), 3.49–3.34 (m, 1H), 2.79–2.57 (m, 2H), 2.0–1.41 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.6, 153.4, 135.8, 134.6, 129.5, 127.0, 115.0, 113.5, 79.0, 77.1, 55.2, 38.2, 33.2, 31.2, 30.7, 24.0; IR (neat): ν 3444, 2936, 1737, 1642, 1434, 1373, 1239, 1045, 756, 666, 487 cm^{-1}; HRMS (ESI): m/z [M+Na]$^+$ calcd for $C_{20}H_{24}O_3Na$: 335.1623; found: 335.1640.

Acknowledgements

The authors thank DST, New Delhi for financial assistance and CSIR, New Delhi for research fellowship to P.P.M.

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8. The selective formation of **9** may be explained by the addition of a chiral hydroxy group on to benzylic cation, which is in conjugation with 4-methoxyphenyl ring. A similar cyclization was used for the synthesis of centrolobine.[2b,4s]
9. NOE experiments have been carried out on compound **9** and the enhancement is shown below.