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Stereoselective formal synthesis of (−)-centrolobine

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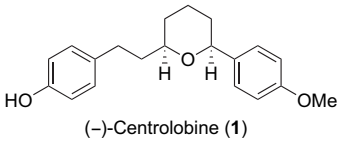
Abstract—Stereoselective formal synthesis of (−)-centrolobine was achieved from naturally occurring L-(+)-tartaric acid, employing a facile $FeCl_3$ mediated stereoselective formation of a tetrahydropyran as the key step.

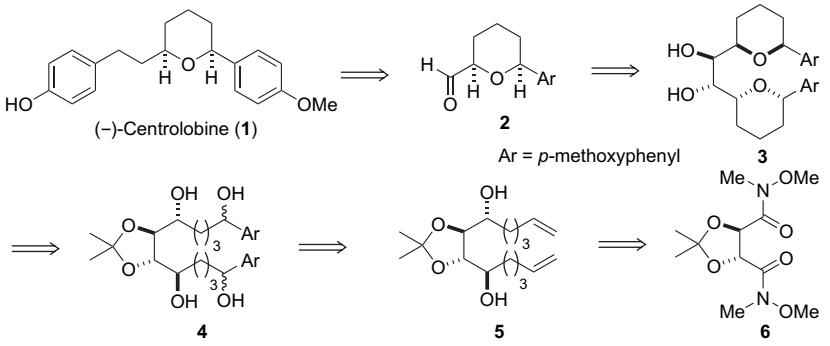
1. Introduction

Tetrahydropyrans, tetrahydrofurans, and oxepanes are ubiquitous structural sub-units present in a number of bio-active natural products such as Annonaceae acetogenins,[1] ionophores,[2] etc. Centrolobine **1**, a diarylheptanoid natural product, containing a *cis*-2,6-disubstituted tetrahydropyran, was isolated from the heart wood of *Centrolobium robustum* and from the stem of *Brosimum potabile* in the Amazon Forest.[3] Centrolobine was shown to be antileishmanial agent against *Leishmania amazonensis* promastigotes.[4] Although the structure of centrolobine was confirmed by racemic synthesis in 1964,[3a] absolute configuration of centrolobine was confirmed only recently, in 2002 through an enantioselective synthesis by Solladie et al.[5a,c] The bio-activity associated with centrolobine and related tetrahydropyran containing natural products, resulted in the enantioselective synthesis of (−)-centrolobine by different groups in recent years.[5] Herein, we report an efficient stereoselective synthesis of (−)-centrolobine based on Lewis acid mediated cyclization of a 1,5-diol to form a tetrahydropyran.



2. Results and discussion

Continuing efforts from our group in the stereoselective synthesis of natural products from chiral pool L-(+)-tartaric acid culminated in the syntheses of several bio-active pheromones[6] and styryl lactones.[7] Key approach in our methodology is the enantioselective synthesis of α-hydroxy aldehydes, which serves as excellent building blocks for a number of natural products. As shown in the retrosynthesis (Scheme 1), we envisaged the synthesis of centrolobine **1** through the known intermediate aldehyde **2**. Synthesis of the aldehyde **2** was anticipated from the 1,2-diol **3**. Stereoselective iron(III) chloride mediated cyclization of a 1,5-diol **4** was considered



Scheme 1. Retrosynthesis of (−)-centrolobine (**1**).

Keywords: (−)-Centrolobine; Stereoselective reduction; $FeCl_3$; Tartaric acid.
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for the tetrahydropyran unit formation. 1,5-Diol **4** can be obtained from the elaboration of C_2-symmetric diol **5**, the synthesis of which has already been established in our laboratory from the bis-Weinreb amide **6** derived from L-(+)-tartaric acid.

The synthetic sequence for the pivotal 1,5-diol **4** commenced with the controlled addition of 4-pentenylmagnesium bromide to the bis-Weinreb amide **6**, furnishing the 1,4-diketone **7** in excellent yield. Under conditions optimized by us for the reduction of such diketones,[8] stereoselective reduction of 1,4-diketone **7** with L-Selectride afforded the 1,4-diol **5** as a single diastereomer in 94% yield. Protection of the 1,4-diol **5** as the corresponding bis-silylether utilizing standard conditions resulted in the bis-silylether **8** in 94% yield. Ozonolysis of the terminal olefins in **8** furnished the bis-aldehyde, which without further purification, was subjected to the Grignard reaction with *p*-methoxyphenylmagnesium bromide to yield **9** as mixture of diastereomers at the benzylic position in 90% combined yield for two steps (Scheme 2). Since Lewis acid mediated cyclization of a 1,5-diol involving a benzylic carbocation was envisaged, no effort was made to separate the diastereomers. Deprotection of the silyl ethers in **9** with tetrabutylammonium fluoride afforded the 1,5-diol **4** in 89% yield.

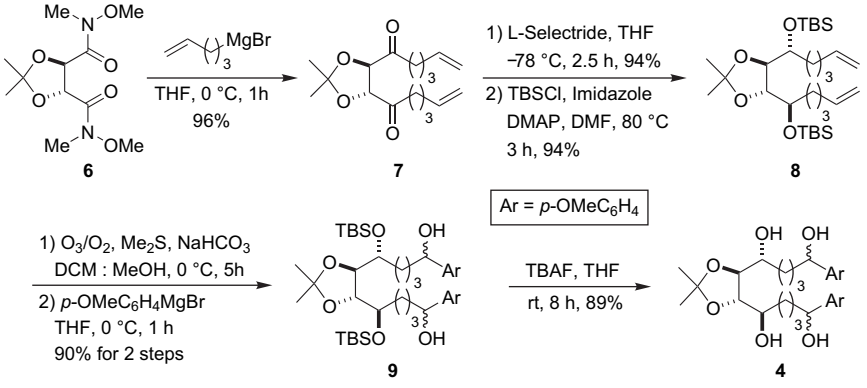
Reaction of 1,5-diol **4** with $FeCl_3$ furnished a separable mixture of tetrahydropyrans **3** and **3a** in 70% and 10%, respectively, formed through the cyclization of 1,5-diol with concomitant deprotection of the acetonide.[9] The major C_2-symmetric diastereomer **3** on treatment with $Pb(OAc)_4$ cleanly furnished the tetrahydropyran aldehyde **2**.[10] Since the conversion of aldehyde **4** to (−)-centrolobine **1** through Wittig olefination followed by hydrogenation has already been reported in the literature, the present sequence constitutes a formal synthesis of (−)-centrolobine (Scheme 3).

In summary, a formal approach for the stereoselective synthesis of (−)-centrolobine was achieved from the bis-Weinreb amide derived from L-(+)-tartaric acid. The tetrahydropyran framework in (−)-centrolobine was accomplished through a facile $FeCl_3$ mediated cyclization of a 1,5-diol.

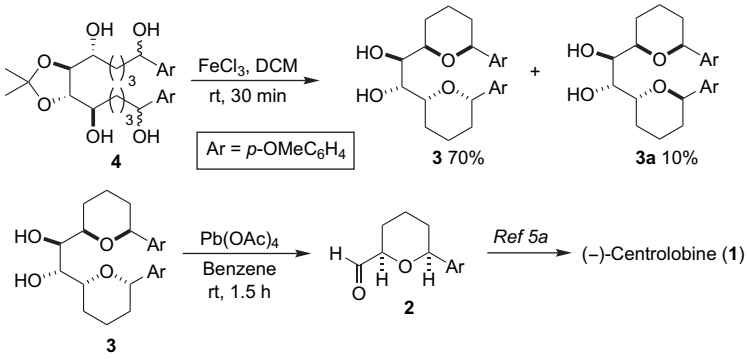
3. Experimental

3.1. General procedures

Column chromatography was performed on silica gel, Acme grade 100–200 mesh. TLC plates were visualized either with UV, in an iodine chamber, or with phosphomolybdic acid spray, unless noted otherwise. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification. THF was freshly distilled over Na-benzophenone ketyl. Melting points were uncorrected. Unless stated otherwise, all the reactions were performed under an inert atmosphere. Optical rotations were measured on a JASCO DIP-370 digital polarimeter at 25 °C. IR spectra were recorded on a Jasco FTIR 410 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on JNM λ-300 spectrometer. The chemical shifts and coupling constants are reported in the standard fashion with reference



Scheme 2. Synthesis of key inetermediate 1,5-diol **4**.



Scheme 3. Synthesis of (−)-centrolobine (**1**).

to either an internal tetramethylsilane (for ^1H) or the central line (77.1 ppm) of $CDCl_3$ (for ^{13}C). NMR samples were prepared in $CDCl_3$. High-resolution mass spectra were recorded on a Micromass Q-TOF micro mass spectrometer using an electron spray ionization mode.

3.1.1. Preparation of (4*R*,5*R*)-4,5-bis(hex-5-enoyl)-2,2-dimethyl-1,3-dioxolane (7). In an oven dried two necked 50-mL round-bottom flask equipped with a magnetic stir bar and an argon inlet was placed the bis-Weinreb amide (**6**) (0.5 g, 1.8 mmol) dissolved in THF (6 mL). This was cooled to 0 °C and a THF solution of 4-pentenylmagnesium bromide (7 mL of a 1 M solution in THF, 7 mmol) was added dropwise under argon. The reaction mixture was stirred for 1 h, quenched with satd NH_4Cl (3 mL), poured into water (10 mL), and extracted with ether (3×10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The residue obtained after the evaporation of solvent was purified by column chromatography using ethylacetate/petroleum ether (1:9) as an eluent to yield **7** as colorless oil in 96% (0.51 g). $[\alpha]_D$ +11.6 (*c* 1.2, $CHCl_3$); IR (neat): 2937, 1725, 1455, 1375, 1259, 1153, 995, 914, 860 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.77 (ddt, *J*=17.1, 10.2, 6.6 Hz, 2H), 5.06–4.96 (m, 4H), 4.55 (s, 2H), 2.75–2.56 (m, 4H), 2.12–2.05 (m, 4H), 1.77–1.67 (m, 4H), 1.42 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.4, 137.8, 115.3, 112.4, 81.4, 38.2, 32.9, 26.1, 22.1; HRMS for $C_{17}H_{26}O_4$+Na calcd 317.1729; found 317.1742.

3.1.2. Preparation of (4*S*,5*S*)-4,5-bis((*R*)-1-hydroxyhex-5-enyl)-2,2-dimethyl-1,3-dioxolane (5). To a solution of **7** (0.4 g, 1.36 mmol) in THF (4 mL) at −78 °C was added L-Selectride (5 mL of a 1 M solution in THF, 5 mmol) dropwise over 10 min, under argon. The reaction mixture was stirred for 2.5 h. After the reaction was complete (TLC), it was quenched with 2 M NaOH (5 mL) and then H_2O_2 (30% w/v in water, 2.5 mL) was added at the same temperature and stirred for 3 h at room temperature. (H_2O_2 treatment is necessary to remove residual boron impurities resulting from Selectride). The reaction mixture was filtered through a short pad of Celite and the Celite pad was washed with ether (20 mL). Combined ethereal layers were washed with brine and dried (Na_2SO_4). Residue obtained after evaporation of solvent was purified by column chromatography using ethylacetate/petroleum ether (3:7) as an eluent to yield **5** in 94% (0.38 g) as colorless oil. $[\alpha]_D$ −7.5 (*c* 1.1, $CHCl_3$); IR (neat): 3446, 2985, 2861, 1457, 1415, 1380, 1240, 1166, 1072, 993, 883 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.81 (ddt, *J*=16.8, 10.2, 6.6 Hz, 2H), 5.05–4.94 (m, 4H), 3.90 (s, 2H), 3.50 (br s, 2H), 2.12–2.01 (m, 4H), 1.71–1.36 (m, 8H), 1.42 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 114.8, 109.3, 79.9, 69.9, 34.3, 33.5, 27.3, 24.9; HRMS for $C_{17}H_{30}O_4$+Na calcd 321.2042; found 321.2043.

3.1.3. Preparation of (4*S*,5*S*)-4,5-bis((*R*)-1-(*tert*-butyldimethylsilyloxy)-hex-5-enyl)-2,2-dimethyl-1,3-dioxolane (8). To a solution of **5** (0.35 g, 1.17 mmol) in DMF (3.5 mL) were added imidazole (0.36 g, 5.3 mmol), DMAP (0.020 g, 0.1 mmol), and TBDMSCl (0.53 g, 3.5 mmol) at room temperature. The reaction mixture was kept at 80 °C and stirred at the same temperature for 2 h. After the reaction was completed (indicated by TLC), it was cooled to room temperature and poured into water (15 mL) and extracted with ether (3×10 mL). The combined ethereal extracts were washed with brine and dried over Na_2SO_4. Evaporation of solvent followed by column chromatography of the resultant residue using ethylacetate/petroleum ether (1:9) as an eluent yielded **8** as colorless oil in 94% (0.58 g). $[\alpha]_D$ −13.8 (*c* 1.8, $CHCl_3$); IR (neat): 2931, 2858, 1462, 1376, 1253, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.80 (ddt, *J*=17.4, 10.2, 6.6 Hz, 2H), 5.05–4.93 (m, 4H), 3.95 (s, 2H), 3.61 (m, 2H), 2.14–1.98 (m, 4H), 1.72–1.63 (m, 2H), 1.55–1.36 (m, 6H), 1.39 (s, 6H), 0.90 (s, 18H), 0.07 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 114.6, 108.7, 79.1, 72.2, 33.8, 33.7, 27.3, 26.0, 24.9, 18.3, −4.1, −4.2; HRMS for $C_{29}H_{58}O_4Si_2$+Na calcd 549.3771; found 549.3760.

3.1.4. Preparation of (4*S*,5*S*)-4,5-bis((1*R*)-1-(*tert*-butyldimethylsilyloxy)-5-hydroxy-5-(4-methoxyphenyl)pentyl)-2,2-dimethyl-1,3-dioxolane (9). Ozone was bubbled through a pre-cooled (−78 °C) solution of **8** (0.5 g, 0.95 mmol) in DCM/MeOH (4:1, 12.5 mL) containing solid $NaHCO_3$ (10 mg) till the pale blue color persisted. Excess ozone was flushed off with oxygen and Me_2S (0.8 mL) was added and stirred for 4.5 h at 0 °C. The reaction mixture was concentrated under reduced pressure, filtered through a short pad of Celite and the Celite pad was washed with ether (20 mL). The ethereal layers were combined and evaporation of solvent afforded the crude bis-aldehyde, which was subjected to Grignard reaction without further purification.

The bis-aldehyde obtained above was dissolved in THF (5 mL) under argon. This was cooled to 0 °C and a THF solution of *p*-methoxyphenylmagnesium bromide (3.5 mL, 1 M solution in THF, 3.5 mmol) was added dropwise over a period of 5 min. The reaction mixture was stirred for 1 h at the same temperature. After the reaction was complete as indicated by TLC, it was quenched with satd NH_4Cl (3 mL), poured into water (15 mL), and extracted with ether (3×10 mL). The combined ethereal extracts were washed with brine and dried (Na_2SO_4). The residue obtained after evaporation of solvent was purified by column chromatography using ethylacetate/petroleum ether (1:3) as an eluent to yield **9** as colorless oil in 90% (0.64 g). IR (neat): 3407, 2929, 2856, 1612, 1511, 1461, 1247, 1035, 833, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J*=8.4 Hz, 4H), 6.85 (d, *J*=8.4 Hz, 4H), 4.62–4.55 (m, 2H), 3.92–3.84 (m, 2H), 3.78 (s, 6H), 3.72–3.54 (m, 2H), 2.31 (br s, 2H), 1.80–1.20 (m, 12H), 1.37 (s, 3H), 1.36 (s, 3H), 0.86 (br s, 18H), 0.04 (br s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 136.8, 128.6, 127.7, 127.1, 127.0, 113.9, 113.8, 108.7, 79.0, 74.1, 74.0, 72.2, 72.1, 65.0, 55.2, 39.0, 34.0, 27.3, 27.2, 25.9, 22.1, 22.0, 18.2, −4.2; HRMS for $C_{40}H_{70}O_8Si_2$+Na calcd 769.4507; found 769.4503.

3.1.5. Preparation of (4*S*,5*S*)-4,5-bis((1*R*)-1,5-dihydroxy-5-(4-methoxyphenyl)pentyl)-2,2-dimethyl-1,3-dioxolane (4). To a solution of **9** (0.5 g, 0.67 mmol) dissolved in dry THF (7 mL) was added TBAF (1.05 g, 4 mmol) at 0 °C under argon. It was slowly allowed to warm to room temperature over a period of 30 min. After stirring for 8 h at room temperature, it was poured into water (10 mL) and extracted with ethylacetate (3×10 mL). Combined ethylacetate extracts

were washed with brine (15 mL) and dried over Na_2SO_4. Evaporation of solvent followed by column chromatography of the resultant residue using ethylacetate/petroleum ether (9:1) as an eluent yielded **4** in 89% (0.31 g) as colorless oil. IR (neat): 3403, 2935, 1611, 1512, 1246, 1174, 1033, 832 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, J=8.4 Hz, 4H), 6.82 (d, J=8.4 Hz, 4H), 4.57–4.51 (m, 2H), 3.84 (br s, 2H), 3.75 (s, 6H), 3.48–3.43 (m, 2H), 3.30–3.00 (br s, 4H), 1.81–1.20 (m, 12H), 1.36 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 136.9, 126.9, 113.6, 108.9, 79.6, 73.6, 73.5, 69.8, 69.7, 60.3, 55.0, 49.2, 38.6, 38.5, 34.0, 33.8, 27.1, 22.0, 20.8, 14.0; HRMS for $C_{29}H_{42}O_8$+Na calcd 541.2777; found 541.2764.

3.1.6. Preparation of (1*R*,2*R*)-1,2-bis((2*R*,6*S*)-tetrahydro-6-(4-methoxyphenyl)-2*H*-pyran-2-yl)ethane-1,2-diol (3). In an oven dried single necked 10-mL round-bottom flask was placed **4** (0.2 g, 0.45 mmol) dissolved in dry DCM (3 mL) under argon. $FeCl_3$ (72 mg, 0.45 mmol) was added at room temperature and the reaction mixture was stirred for 30 min. After the reaction was complete (as indicated by TLC), it was diluted with ether (20 mL) and washed with satd $NaHCO_3$ (3 times), brine (10 mL), and dried over Na_2SO_4. Residue obtained after evaporation of solvent was purified by column chromatography using ethylacetate/petroleum ether (1:1) as an eluent to yield **3** in 70% (0.12 g) along with **3a** in 10% (0.017 g) yield. Physical and spectral data of the major isomer **3**. $[\alpha]_D$ −74.0 (c 1.5, $CHCl_3$); IR (neat): 3477, 2937, 2842, 1513, 1245, 1176, 1078, 1031, 811 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J=8.7 Hz, 4H), 6.86 (d, J=8.7 Hz, 4H), 4.40–4.34 (m, 2H), 3.85–3.66 (m, 4H), 3.79 (s, 3H), 3.13 (br s, 2H), 1.20–1.94 (m, 2H), 1.83–1.37 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 135.2, 127.1, 113.6, 79.9, 79.7, 73.5, 55.2, 33.4, 26.5, 23.5; Anal. calcd for: C, 70.56; H, 7.74. Found: C, 70.61; H, 7.98.

3.1.7. Preparation of (2*S*,6*R*)-2-(4-methoxyphenyl)-6-formyltetrahydropyran (2). To a solution of 1,2-diol (**3**) (0.1 g, 0.22 mmol) in benzene (3 mL) at room temperature was added $Pb(OAc)_4$ (0.2 g, 0.4 mmol) under argon. The reaction mixture was stirred for 1.5 h at the same temperature. After the reaction was completed (TLC), it was filtered through short pad of Celite, the Celite pad was washed with dichloromethane (15 mL) and dried over Na_2SO_4. Evaporation of solvent under reduced pressure afforded **2** as colorless oil in quantitative yield (99 mg). $[\alpha]_D$ −9.1 (c 3.4, $CHCl_3$); lit.[5c] $[\alpha]_D$ −6 (c 0.874, $CHCl_3$); IR (neat): 2932, 2855, 1737, 1612, 1517, 1441, 1369, 1030, 812, 768 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.70 (s, 1H), 7.32 (d, J=8.7 Hz, 2H), 6.90 (d, J=8.7 Hz, 2H), 4.44–4.39 (m, 1H), 4.01–3.94 (m, 1H), 3.80 (s, 3H), 2.12–1.39 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.2, 159.0, 134.3, 127.2, 113.7, 82.1, 79.6, 55.2, 33.0, 25.9, 23.2.

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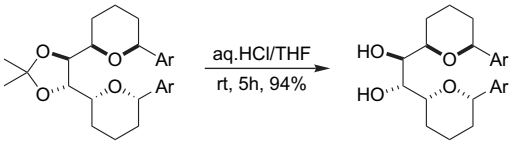
9. Although, $FeCl_3$ mediated cyclization of 1,4-diols to the corresponding THF ethers is known in the literature (Sharma, G. V. M.; Kumar, K. R.; Sreenivas, P.; Krishna, P. R.; Chorghade, M. S. *Tetrahedron: Asymmetry* **2002**, *13*, 687–690), to the best of our knowledge formation of tetrahydropyrans by similar cyclization is not addressed. Formation of the tetrahydropyran **3b** in 17% yield was also observed, which on further reaction with aq HCl furnished **3**.



3b **3**

10. Stereochemistry as well as enantiopurity of the aldehyde **2** were further confirmed by reduction to the corresponding alcohol ($[\alpha]_D$ −53 (c 1.3, $CHCl_3$), lit.[5c] $[\alpha]_D$ −53 (c 0.806, $CHCl_3$)), the spectral data of which is consistent with that reported in literature.