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A chiron approach to (1*R*,2*R*,5*S*,7*S*)-2-hydroxy-*exo*-brevicomin: a component of the volatiles produced by the male mountain pine beetle, *Dendroctonus ponderosae*☆

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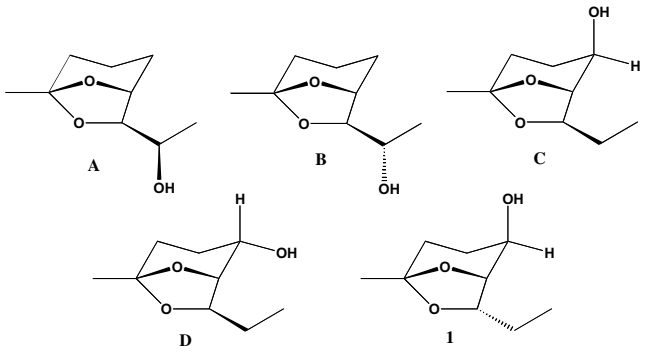
Abstract—A chiron approach for the synthesis of (1*R*,2*R*,5*S*,7*S*)-2-hydroxy-*exo*-brevicomin **1**, a component of the volatiles obtained from male mountain pine beetles, *Dendroctonus ponderosae* has been achieved. Our synthesis started with commercially available D-ribose and involves a Wittig olefination, an acid catalyzed one pot hydrogenation and the internal acetalization as key steps.

1. Introduction

In 1996 Francke et al.[1] identified several new oxygenated derivatives of 6,8-dioxabicyclo[3.2.1]octane in the head space volatiles obtained from the male mountain pine beetle, *Dendroctonus ponderosae*, which are destructive pests causing damage to coniferous forests in the northern hemisphere. These compounds are mainly stereoisomers of 7-ethyl-5-methyl-6,8-dioxabicyclo-[3.2.1]octan-2-ol and 1-(5-methyl-6,8-dioxabicyclo-[3.2.1]octyl)-ethanol such as **A**–**D** and **1**.



2. Results and discussion

Previously we have reported an asymmetric synthesis of **A** and **B** including the formal synthesis of (+)-*exo*-brevicomin starting from α-picoline[2] and a chiron approach to the synthesis of **C** starting from D-mannitol.[3] With these successful achievements and in continuation of our interest in the synthesis of other family members, herein we report a chiron approach to the synthesis of **1**. Francke et al. reported its first synthesis based on a kinetic resolution using a Sharpless asymmetric epoxidation.[1] Herein we report the synthesis of **1** starting from D-ribose as depicted in Scheme 1.

2,3-*O*-Isopropylidene-D-ribose **2** was prepared according to the literature procedure.[4] The primary hydroxyl group in acetonide **2** was protected as silyl ether using TBDMSCl, imidazole to give **3** (89%). This was subjected to Wittig reaction with methylene triphenylphosphorane to give olefin **4** (82%), which upon benzylation with benzyl bromide gave **5** (62%). Compound **5** was desilylated using 1 M TBAF solution in THF to yield **6** (78%). The primary hydroxyl functionality in **6** was oxidized to the aldehyde using TEMPO conditions, which was subsequently treated with $Ph_3PCHCOCH_3$ to give **7** (60% overall yield for two steps) as a mixture of *cis*:*trans*-isomers (1:9 by ^1H NMR). Hydrogenation of **7** in the presence of a catalytic amount of Pd–C and aqueous HCl in MeOH gave target **1** (40%) directly. The physical and spectral data of compound **1** are in

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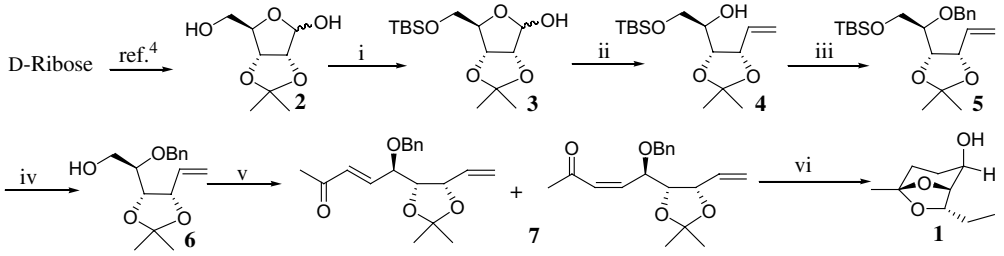

Scheme 1. Reagents and conditions: (i) TBDMSCl, imidazole, DCM, rt, 89%; (ii) Ph_3PCH_2I, KO^{t}Bu, THF, −78 °C, 82%; (iii) NaH, benzyl bromide, THF, 62%; (iv) 1 M TBAF, THF, 78%; (v) (a) TEMPO, NaOCl, toluene, ethyl acetate, water; (b) $Ph_3PCHCOCH_3$, DCM, 60% (for two steps); (vi) H_2–Pd–C and catalytic aq HCl, MeOH, 40%.

good agreement with the reported values.[1] The final step was carried out as per the procedure reported by us earlier in the synthesis of **C**, in which hydrogenation, debenzylation, acetonide deprotection, and internal acetalization takes place in one step.[3]

3. Conclusion

In summary we have demonstrated a chiron approach for the synthesis of **1** starting from D-ribose involving simple and standard transformations.

4. Experimental

TLC was performed on Merck Kiesel gel 60, F254 plates (layer thickness 0.25 mm). Column chromatography was performed on silica gel (60–120 mesh) using ethyl acetate and hexane mixture as eluent. Melting points were determined on a Fisher John's melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer RX-1 FT-IR system. ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded on a Varian Gemini-200 MHz spectrometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on Bruker Avance-300 MHz spectrometer. Optical rotations were measured with Horiba-SEPA-300 digital polarimeter. The EI mass spectra were recorded on GC–MS system (Agilent Technologies, CA) equipped with agilent 6890 GC and 5973 GC mass selective detector. Accurate mass measurement for sodiated molecular ions **2**–**7** generated under electrospray ionization conditions was performed on Quattro LC mass spectrometer (Micromass, UK). Accurate mass for the molecular ion of compound **1** was measured using VG-Autospec M mass spectrometer, (Micromass, UK) under electron ionization conditions at 20 eV.

4.1. 2,3-*O*-Isopropylidene-5-(*tert*-butyldimethylsilyl)-D-ribose 3

To a stirred solution of **2** (3.50 g, 18.4 mmol) in dry DCM (50 mL) was added imidazole (3.13 g, 44.0 mmol) and *tert*-butyldimethylsilylchloride (3.22 g, 21.4 mmol) at room temperature and the mixture stirred for 3 h. The solvent was removed and the residue partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate, 70:30) to give **3** (5 g, 89%) as colorless oil (9:1 anomeric mixture). IR ν_{max} (film): 2943, 2863, 2357, 1466, 1376, 1254, 1213, 1156, 1074, 997, 838, 776; ^{1}H NMR (400 MHz, $CDCl_3$) for major isomer: δ 5.20 (d, 1H, J = 11.9 Hz), 4.63 (d, 1H, J = 6.3 Hz), 4.43 (d, 1H, J = 6.3 Hz), 4.38 (d, 1H, J = 11.1 Hz), 4.27 (m, 1H), 3.78–3.72 (m, 2H), 1.46 (s, 3H), 1.30 (s, 3H), 0.94 (s, 9H), 0.14 (s, 6H); EIMS = 289 (M^+−15), accurate mass calcd for $[M+Na]^+$ ($C_{14}H_{28}O_5Na$): 327.1603. Found: 327.1608.

4.2. (1*R*,4′*R*,5′*S*)-(−)-1-(2′,2′-Dimethyl-5′-vinyl-1′,3′-dioxolan-4′-yl)-2-(*tert*-butyldimethylsilyloxy)-1(*R*)-ethan-1-ol 4

To a mixture of methyl triphenylphosphonium iodide (7.170 g, 17.74 mmol) and potassium *tert*-butoxide (1.66 g, 14.8 mmol) was added dry THF (100 mL) and stirred at room temperature under N_2 for 4 h. Stirring was stopped and the solid allowed to settle. The clear supernatant orange-yellow liquid was then cannulated into the solution of compound **3** (0.90 g, 2.96 mmol) in dry THF (10 mL) at −78 °C. The reaction mixture was then slowly allowed to attain room temperature. After 3 h the reaction mixture was quenched with crushed ice and diluted with ethyl acetate. The organic portion was separated and dried over anhydrous Na_2SO_4, filtered, and evaporated. The resulting syrup was purified by silica gel column chromatography (hexane/ethyl acetate, 85:15) to give **4** (0.73 g, 82%) as a pale yellow syrup, $[\alpha]_D^{29.6}$ = −3.2 (c 0.69, $CHCl_3$); IR ν_{max} (film): 3562, 2929, 2858, 1465, 1374, 1254, 1217, 1167, 1063, 1009, 927, 840, 780; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.99 (ddd, 1H, J = 6.0, 10.5, 17.0 Hz), 5.38 (td, 1H, J = 1.5, 17.0 Hz), 5.23 (td, 1H, J = 1.5, 10.5 Hz), 4.64 (t, 1H, J = 6.0 Hz), 3.98 (dd, 1H, J = 6.7, 9.8 Hz), 3.77 (dd, 1H, J = 3.0, 9.8 Hz), 3.71–3.52 (m, 2H), 2.34 (d, 1H, J = 6.0 Hz), 1.44 (s, 3H), 1.33 (s, 3H), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, proton decoupled): δ 134.21, 117.46, 108.74, 78.81, 77.43, 69.38, 64.38, 27.82, 25.37, 25.42, 18.32, −4.7; EIMS = 287 (M^+−15), accurate mass calcd for $[M+Na]^+$ ($C_{15}H_{30}O_4SiNa$): 325.1811. Found: 325.1814.

4.3. (1′*R*,4*R*,5*S*)-(−)-4-[2′-(*tert*-Butyldimethylsilyloxy)-1′-(benzyloxy)-ethyl]-2,2-dimethyl-5-vinyl-1,3-dioxolane 5

To a stirred solution of sodium hydride (94.0 mg, 60% wt in mineral oil, 2.35 mmol) in dry THF (2 mL) was

added alcohol **4** (0.60 g, 2.0 mmol) dissolved in dry THF (3 mL) at 0 °C. After 20 min, benzyl bromide (0.26 mL, 2.19 mmol) was added and stirring continued for 2 h at room temperature. The reaction was quenched by the addition of a saturated solution of NH_4Cl (5 mL) and extracted with ethyl acetate. The organic extracts were washed with water, brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the crude product by column chromatography (hexane/ethyl acetate, 95:5) afforded benzyl ether **5** (0.48 g, 62%) as a pale yellow liquid, $[\alpha]_D^{29.6} = -22.8$ (*c* 0.69, $CHCl_3$); IR ν_{max} (film): 3031, 2987, 2931, 2886, 2857, 1728, 1496, 1459, 1377, 1254, 1216, 1093, 1033, 1003, 926, 838, 778, 739; ^1H NMR (300 MHz, $CDCl_3$): δ 7.33–7.17 (m, 5H), 5.89 (ddd, 1H, $J = 6.3$, 10.2, 17.3 Hz), 5.32 (td, 1H, $J = 1.5$, 17.3 Hz), 5.17 (td, 1H, $J = 1.5$, 11.0 Hz), 4.79 (d, 1H, $J = 11.0$ Hz), 4.64 (t, 1H, $J = 6.3$ Hz), 4.41 (d, 1H, $J = 11.0$ Hz), 4.15 (dd, 1H, $J = 6.3$, 8.6 Hz), 3.96 (dd, 1H, $J = 2.3$, 11.0 Hz), 3.73 (dd, 1H, $J = 5.5$, 11.0 Hz), 3.45 (ddd, 1H, $J = 2.3$, 5.5, 8.6 Hz), 1.45 (s, 3H), 1.33 (s, 3H), 0.91 (s, 9H), 0.06 (s, 6H); EIMS = 377 (M^+-15), accurate mass calcd for $[M+Na]^+$ ($C_{22}H_{36}O_4SiNa$): 415.2280. Found: 415.2293.

4.4. (2*R*,4′*R*,5′*S*)-(−)-2-(Benzyloxy)-2-[2′,2′-dimethyl-5′-vinyl-1′,3′-dioxolan-4′-yl]-ethan-1-ol 6

To an ice-cooled solution of **5** (0.40 g, 1.02 mmol) in dry THF (5 mL) was added a 1 M solution of TBAF (2.0 mL, 2.0 mmol) and stirred for 2 h at room temperature. After completion of the reaction, water was added to the reaction mixture and THF was removed under vacuum. Then the aqueous layer was extracted with ethyl acetate and washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuum. The residue was purified by column chromatography (hexane/ethyl acetate, 80:20) to give **6** (0.22 g, 78%) as a colorless oil, $[\alpha]_D^{29.6} = -30.5$ (*c* 0.55, $CHCl_3$); IR ν_{max} (film): 3473, 2988, 2931, 1457, 1378, 1250, 1216, 1166, 1071, 926, 874, 742; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37–7.26 (m, 5H), 5.92 (ddd, 1H, $J = 5.9$, 10.4, 17.0 Hz), 5.41 (td, 1H, $J = 1.4$, 17.0 Hz), 5.24 (td, 1H, $J = 1.4$, 10.4 Hz), 4.73 (t, 1H, $J = 5.9$ Hz), 4.59 (d, 1H, $J = 11.1$ Hz), 4.45 (d, 1H, $J = 11.1$ Hz), 4.26 (dd, 1H, $J = 5.9$, 8.1 Hz), 3.90–3.73 (m, 2H), 3.47 (m, 1H), 1.95 (br dd, 1H, $J = 2.2$, 9.6 Hz), 1.5 (s, 3H), 1.4 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, proton decoupled): δ 137.84, 133.83, 128.46, 127.86, 127.73, 117.21, 108.73, 78.51, 77.60, 77.43, 71.36, 61.42, 27.70, 25.25; EIMS = 263 (M^+-15), accurate mass calcd for $[M+Na]^+$ ($C_{16}H_{22}O_4Na$): 301.1415. Found: 301.1427.

4.5. (5*R*,4′*R*,5′*S*)-5-[5′-Vinyl-2′,2′-dimethyl-1′,3′-dioxolan-4′-yl]-5-benzyloxy-*E* or *Z*-3-penten-2-one 7

To a stirred solution of **6** (0.19 g, 0.68 mmol) in ethyl acetate/toluene mixture (1:1, 2 mL) were added sodium bromide (0.07 g, 0.68 mmol), water (0.3 mL) and TEMPO free radical (2.0 mg, 0.013 mmol) at 0 °C simultaneously. $NaHCO_3$ (0.16 g, 1.91 mmol) dissolved in NaOCl solution (1.3 mL, 0.69 mmol, 4% aqueous solution) was added slowly to the above reaction mixture at 0 °C. After completion of the reaction the resultant aldehyde was washed with an aqueous solution of KI (5 mg), 10% $KHSO_4$ (2 mL) and 10% hypo (2 mL) followed by water. The organic layer was separated and concentrated to give the aldehyde (0.15 g) as a light yellow color oil, which was taken to next step without any purification.

To the crude aldehyde in dry DCM (5 mL), was added $Ph_3PCHCOCH_3$ (0.25 g, 0.79 mmol) dissolved in dry DCM (2 mL) slowly at 0 °C. After the addition, the reaction mixture was brought to room temperature and stirred for a further 2 h and quenched with water. The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated. Purification by column chromatography (hexane/ethyl acetate, 93:7) afforded **7** (0.13 g, 60% for two steps) as a clear oil (1:9 *cis*:*trans*-diastereomeric mixture, by ^1H NMR). IR ν_{max} (film): 2986, 2925, 2861, 2361, 1683, 1633, 1495, 1455, 1419, 1370, 1254, 1216, 1167, 1074, 986, 928, 873, 743; ^1H NMR for major isomer (300 MHz, $CDCl_3$): δ 7.35–7.21 (m, 5H), 6.68 (dd, 1H, $J = 6.0$, 16.6 Hz), 6.23 (d, 1H, $J = 16.6$ Hz), 5.88 (m, 1H), 5.39 (td, 1H, $J = 1.5$, 17.3 Hz), 5.20 (td, 1H, $J = 1.5$, 10.5 Hz), 4.71 (t, 1H, $J = 6.0$ Hz), 4.44 (d, 1H, 10.5 Hz), 4.26 (d, 1H, 10.5 Hz), 4.08 (dd, 1H, $J = 6.0$, 8.3 Hz), 3.91 (dd, 1H, $J = 6.7$, 8.3 Hz), 2.28 (s, 3H), 1.46 (s, 3H), 1.33 (s, 3H); EIMS = 301 (M^+-15), accurate mass calcd for $[M+Na]^+$ ($C_{19}H_{24}O_4Na$): 339.1572. Found: 339.1571.

4.6. (1*R*,2*R*,5*S*,7*S*)-2-Hydroxy-*exo*-brevicomin 1

To a solution of compound **7** (0.10 g, 0.32 mmol) in MeOH (2 mL) were added catalytic amounts of Pd–C and aqueous HCl. The reaction mixture was stirred under hydrogen atmosphere for overnight, filtered, and the filtrate neutralized with solid $NaHCO_3$ after which the volatiles were removed under vacuum. The resultant residue was partitioned between ethyl acetate and water. The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated to give the crude product, which was purified on column chromatography (hexane/ethyl acetate 75:25) to get the pure compound **1** (0.022 g, 40%) as colorless oil (97.99% pure by GC analysis). $[\alpha]_D^{26} = +91.3$ (*c* 0.4, $CHCl_3$); ^1H NMR (300 MHz, C_6D_6): δ 3.95 (m, 1H), 3.81 (ddd, 1H, $J = 4.2$, 5.9, 8.0 Hz), 3.39 (m, 1H), 2.15 (br s, 1H), 1.92–1.75 (m, 1H), 1.60–1.26 (m, 4H), 1.40 (s, 3H), 1.07 (m, 1H), 0.75 (t, 3H, $J = 7.6$ Hz); ^{13}C NMR (75 MHz, C_6D_6, proton decoupled): δ 107.24, 81.12, 80.11, 63.91, 31.53, 26.41, 24.98, 21.61, 11.07; HR-EIMS calcd for ($C_9H_{16}O_3$): 172.1099. Found: 172.1092.

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