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Enantiospecific synthesis of (−)-2-hydroxy-*exo*-brevicomin

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Abstract—An enantiospecific synthesis of (−)-2-hydroxy-*exo*-brevicomin was achieved from L-(+)-tartaric acid in high yield. The key step involves a very highly diastereoselective reduction of a keto Weinreb amide.

1. Introduction

Alkylated 6,8-dioxabicyclo[3.2.1]octanes are prominent bicylic acetals obtained from several species of the western pine beetle species *Dendroctonus brevicomis*. Amongst the head space volatiles obtained from these species, brevicomin **1** and frontalin **2** were some of the earliest to be identified.[1] Francke et al. have systematically investigated the volatiles produced by the *Dendroctonus ponderosae* and identified *exo*-isobrevicomin **3** and a series of stereoisomers of hydroxy brevicomin **4**–**6** (Fig. 1).[2] Brevicomins play a major role in the communication system of the bark beetle species. With the proven importance of single enantiomer compounds in the inhibition of pheromone response,[3] there has been a sustained interest in the synthesis of these pheromones in their enantiomerically pure form (Fig. 1).

Although the synthesis of *exo*-brevicomin and frontalin has been extensively studied, their hydroxy analogues syntheses have rarely been addressed in the literature. There have been a handful of reports of the synthesis of hydroxy-*exo*-brevicomin,[4] and two reports for the synthesis of 2-hydroxy-*exo*-brevicomin reported by Mori et al.[5] and List et al.[6] A recent report of the synthesis of 2-hydroxy-*endo*-brevicomin has also surfaced in the literature.[7] Our efforts in the synthesis of bioactive compounds from chiral pool resulted in the synthesis of *exo*-brevicomin and hydroxy-*exo*-brevicomin.[8] Herein, we report the synthesis of 2-hydroxy-*exo*-brevicomin from naturally abundant L-(+)-tartaric acid.

2. Results and discussion

We envisaged that the triol precursor **14**, for 2-hydroxy-*exo*-brevicomin could be obtained by the deoxygenation of ketone **10**. Ketone **10** can be obtained by a sequential

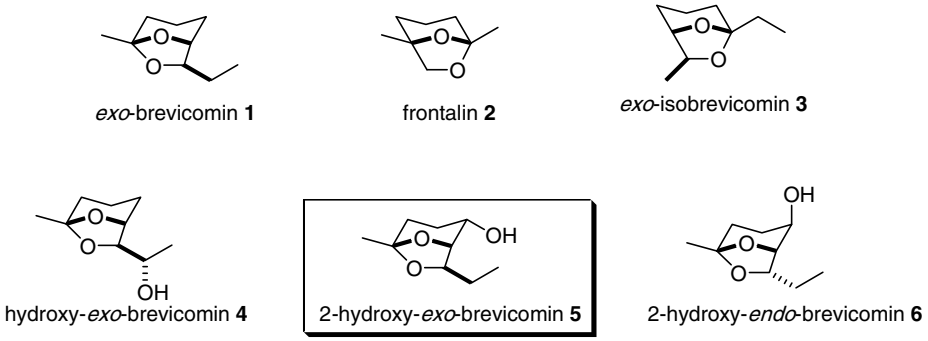

Figure 1. 6,8-Dioxabicyclo[3.2.1]octanes isolated from several species of western pine beetle.

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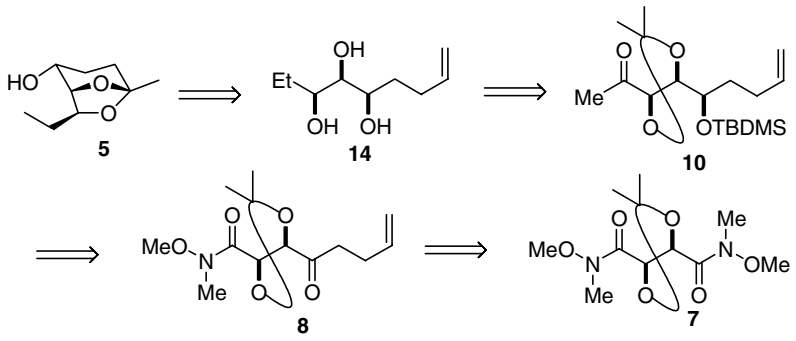
Grignard addition and stereoselective reduction from the bis-Weinreb amide **7** derived from tartaric acid (Scheme 1).

Our synthetic sequence started from the protected bis-Weinreb amide[9] **7**, which upon controlled addition of 3-butenylmagnesium bromide resulted in the formation of keto Weinreb amide **8** in 90% yield. Stereoselective reduction of the keto group in **8** with L-Selectride resulted in a single diastereomer of the product alcohol, which was protected as the *tert*-butyl dimethylsilyl ether **9** in 79% combined yield. Addition of MeMgCl to silyloxy Weinreb amide **9** afforded ketone **10** in 98% yield. Reduction of the keto group in **10** was accomplished with $NaBH_4$ to yield alcohol **11** as an equal mixture of diastereomers. Since the resultant alcohol had to be deoxygenated the mixture of alcohols was not separated and was converted to the xanthate **12** under standard conditions in 94% yield. Reaction of xanthate with tributyltin hydride under Barton–McCombie conditions,[10] afforded **13**,[11] which is a protected form of triol **14**. Compound **13** was used as such and then subjected to Wacker oxidation[12] with $PdCl_2$ under an oxygen atmosphere in DMF.

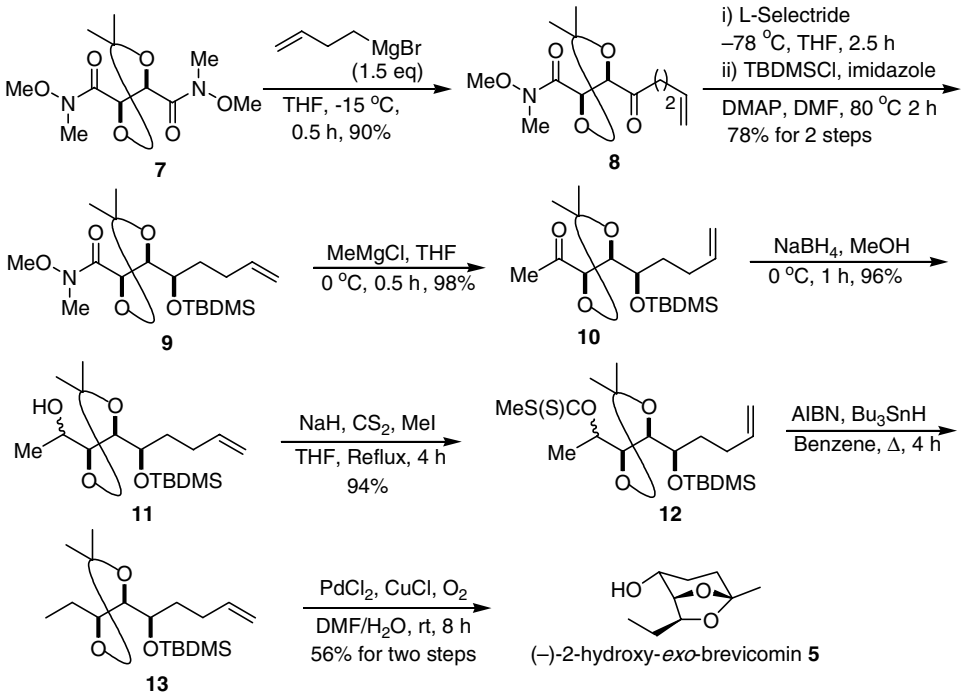
This resulted in the formation of 2-hydroxy-*exo*-brevicomin via the formation of the ketone and simultaneous deprotection of the silyl and acetonide group followed by intramolecular ketalization (Scheme 2). The synthetic sample $[\alpha]_D = -32$ (*c* 0.5, $CHCl_3$) {lit.[5] $[\alpha]_D = +33.3$ (*c* 1.94, $CHCl_3$) for the (+)-enantiomer} exhibited spectral data identical to that of the authentic sample.

3. Conclusion

In conclusion, a high yielding synthesis of 2-hydroxy-*exo*-brevicomin in 35% overall yield starting from the bis-Weinreb amide of tartaric acid was accomplished. The synthetic transformations are highly stereoselective and are opera-



Scheme 1. Retrosynthesis for the synthesis of 2-hydroxy-*exo*-brevicomin.



Scheme 2. Synthesis of (−)-2-hydroxy-*exo*-brevicmoin **5**.

tionally simple. Further applications of this strategy in the synthesis of all regio isomers of hydroxy brevicomin are currently in progress.

4. Experimental

4.1. Preparation of (+)-(4*R*,5*R*)-5-(pent-4-enoyl)-*N*-methoxy-*N*,2,2-trimethyl-1,3-dioxolane-4-carboxamide 8

In an oven dried two neck 50 mL round-bottomed flask, equipped with magnetic stirrer bar and argon inlet was placed the bis-Weinreb amide **7** (0.5 g, 1.8 mmol) dissolved in 6 mL of THF. The reaction mixture was cooled to −15 °C and a THF solution of 3-butenyl magnesium bromide (3 mL of 1 M solution in THF, 3 mmol) was added dropwise under an argon atmosphere. The reaction mixture was stirred for 30 min, quenched with saturated NH_4Cl (3 mL) and extracted with ether (2 × 15 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 to yield **8** as a colorless oil in 90% (0.44 g). $[\alpha]_D = +4.4$ (*c* 3.6, $CHCl_3$); IR (neat): 3079, 2987, 1720, 1670, 1457, 1442, 1382, 1157, 1081, 995 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.82 (ddt, $J = 16.8$, 10.5, 6.3 Hz, 1H), 5.10–4.87 (m, 3H), 4.83 (d, $J = 4.5$ Hz, 1H), 3.71 (s, 3H), 3.24 (s, 3H), 2.90–2.63 (m, 2H), 2.42–2.25 (m, 2H), 1.49 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.4, 169.6, 136.7, 115.3, 112.7, 82.1, 73.8, 61.6, 38.3, 32.4, 26.9, 26.6, 26.1. HRMS for $C_{13}H_{21}NO_5$+Na calcd 294.1317; found 294.1309.

4.2. Preparation of (4*R*,5*R*)-5-((*R*)-1-*tert*-butyldimethylsilyloxypent-4-enyl)-*N*-methoxy-*N*,2,2-trimethyl-1,3-dioxolane-4-carboxamide 9

To a solution of **8** (0.42 g, 1.5 mmol) in 4 mL of THF at −78 °C was added L-Selectride (3 mL of 1 M solution in THF, 3 mmol) dropwise over 10 min, under an argon atmosphere. The reaction mixture was stirred for 2.5 h, quenched with water (3 mL) and extracted with ether (2 × 15 mL). The combined ethereal layers were washed with brine and dried over Na_2SO_4. The residue obtained after evaporation of the solvent was filtered through a short silica pad and evaporated to yield the crude product, which was used as such for the next step.

To a solution of the crude product (obtained above) in 3 mL of DMF was added imidazole (0.19 g, 2.8 mmol), DMAP (0.02 g, 0.15 mmol), and TBDMSCl (0.31 g, 2.1 mmol). The reaction mixture was kept at 80 °C and stirred at the same temperature for 2 h. After TLC indicated completion of the reaction, it was quenched with water and extracted with ether. The combined ether layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography of the crude residue afforded **9** as a colorless oil in 78% (0.47 g) yield. $[\alpha]_D = -9.5$ (*c* 2.1, $CHCl_3$); IR (Neat): 3079, 2952, 1673, 1471, 1382, 1213, 1072, 993 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.74 (ddt, $J = 17.4$, 10.2, 6.6 Hz, 1H), 5.01–4.84 (m, 2H), 4.64 (br s, 1H), 4.54–4.46 (m, 1H), 3.77 (dt, $J = 7.8$, 4.8 Hz, 1H), 3.68 (s, 3H), 3.14 (s, 3H), 2.20–1.94 (m, 2H), 1.69–1.53 (m, 1H), 1.52–1.36 (m, 1H), 1.38 (s, 3H), 1.36 (s, 3H), 0.80 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 138.4, 114.6, 111.0, 80.0, 72.3, 71.5, 61.8, 31.9, 29.8, 26.9, 26.2, 25.8, 25.6, 18.1, −3.6, −4.5. HRMS for $C_{19}H_{37}NO_5Si$+H calcd 388.2519; found 388.2517.

4.3. Preparation of (4*R*,5*R*)-5-((*R*)-1-*tert*-butyldimethylsilyloxypent-4-enyl)-4-acetyl-2,2-dimethyl-1,3-dioxolane 10

To a solution of **9** (0.45 g, 1.2 mmol) in 5 mL of THF at 0 °C was added MeMgCl (0.5 mL, 1.5 mmol, 3 M solution in THF) portionwise. The reaction mixture was stirred for 30 min, and poured into saturated NH_4Cl solution. It was then extracted with ether (2 × 15 mL) and the ether layer washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure. Residue obtained after evaporation of solvent was subjected to column chromatography to yield **10** as a colorless oil in 98% (0.39 g). $[\alpha]_D = +12.7$ (*c* 1.1, $CHCl_3$); IR (neat): 2954, 2857, 1720, 1473, 1255, 1095, 912, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.79 (ddt, $J = 16.8$, 10.5, 6.6 Hz, 1H), 5.06–4.91 (m, 2H), 4.26 (d, $J = 6.9$ Hz, 1H), 4.07 (dd, $J = 6.9$, 3.9 Hz, 1H), 3.78 (td, $J = 6.3$, 3.9 Hz, 1H), 2.27 (s, 3H), 2.19–2.02 (m, 2H), 1.81–1.66 (m, 1H), 1.63–1.50 (m, 1H), 1.44 (s, 3H), 1.37 (s, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.7, 138.3, 114.7, 110.5, 81.3, 79.8, 71.3, 32.7, 29.6, 26.7, 26.6, 26.3, 25.9, 18.1, −4.3, −4.4. HRMS for $C_{18}H_{34}O_4Si$+Na calcd 365.2124; found 365.2081.

4.4. Preparation of (4*S*,5*R*)-5-((*R*)-1-*tert*-butyldimethylsilyloxypent-4-enyl)-4-(1-hydroxy ethyl)-2,2-dimethyl-1,3-dioxolane 11

To a solution of **10** (0.35 g, 1.0 mmol) in 5 mL of MeOH at 0 °C was added $NaBH_4$ (0.08 g, 2 mmol) under an argon atmosphere. The reaction mixture was stirred for 1 h at the same temperature. It was then poured into water and extracted with ether. The ethereal layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated. The residue thus obtained was subjected to column chromatography to yield **11** in 96% (0.34 g) as a colorless oil, which is an inseparable mixture of diastereoisomers. IR (neat): 3461, 2956, 2856, 1463, 1253, 1076, 836, 775 cm^{-1}; ^1H NMR (mixture of diastereomers) (300 MHz, $CDCl_3$) δ 5.80 (ddt, $J = 17.1$, 10.8, 6.3 Hz, 1H), 5.08–4.93 (m, 2H), 3.94 (dd, $J = 7.5$, 3.6 Hz, 1H), 3.85 (dd, $J = 7.8$, 3.6 Hz, 1H), 3.80–3.68 (m, 2H), 2.26–2.03 (m, 2H), 1.89–1.70 (m, 1H), 1.68–1.46 (m, 1H), 1.40–1.35 (m, 6H), 1.27–1.20 (m, 3H), 0.93–0.86 (m, 9H), 0.15–0.66 (m, 6H); ^{13}C NMR for mixture of diastereoisomers (75 MHz, $CDCl_3$) δ 138.2, 138.0, 114.9, 114.7, 108.7, 108.1, 82.4, 80.3, 80.1, 79.0, 71.4, 71.3, 68.1, 66.8, 32.4, 31.8, 30.4, 29.9, 27.3, 27.2, 27.0, 26.9, 25.9, 25.8, 20.3, 19.3, 18.1, −4.2, −4.3, −4.5, −4.6.

4.5. Preparation of (4*S*,5*R*)-5-((*R*)-1-*tert*-butyldimethylsilyloxypent-4-enyl)-4-(1-S-methyl carbonodithioxy ethyl)-2,2-dimethyl-1,3-dioxolane 12

To a solution of **11** (0.3 g, 0.9 mmol) in 3 mL of THF was added NaH (0.07 g of 60% suspension in mineral oil,

1.8 mmol) at room temperature portionwise under an argon atmosphere. It was then refluxed for 1 h and to the resultant suspension thus obtained was added CS_2 (0.16 mL, 2.7 mmol) at the same temperature and stirred for 45 min. After stirring for further 45 min, MeI (0.17 mL, 2.7 mmol) was added at the same temperature and stirred for 2.5 h. After the reaction was complete (as indicated by TLC), it was cautiously quenched with water and extracted with ether. The organic layer was washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure. Column chromatography of the crude product afforded **12** as pale yellow oil in 94% (0.36 g) yield as a mixture of diastereomers, which was used as such for the next step. IR (neat): 2927, 1253, 1218, 1062, 912, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.80–5.63 (m, 2H), 4.98–4.84 (m, 2H), 4.13–3.99 (m, 1H), 3.84–3.73 (m, 1H), 3.70–3.60 (m, 1H), 2.49 (s, 3H), 2.11–1.90 (m, 2H), 1.76–1.15 (m, 11H), 0.85–0.80 (m, 9H), 0.03–0.02 (m, 6H).

4.6. Preparation of (−)-2-hydroxy-*exo*-brevicomin

To a solution of **12** (0.1 g, 0.22 mmol) in 2 mL of benzene under reflux was added a solution of AIBN (6 mg, 0.022 mmol) and Bu_3SnH (0.3 mL, 1 mmol) in benzene (1 mL), under an argon atmosphere. On completion of the reaction as indicated by TLC (~4 h), it was cooled to room temperature, cautiously quenched by addition of 1% aq NH_3 solution. It was then extracted with ether and the ether layer washed with 1% aq NH_3, brine, dried over Na_2SO_4. Evaporation of solvent followed by short path column chromatography of the crude residue yielded **13**, which was contaminated with tin impurities and was used without further purification in the next step.

A mixture of $PdCl_2$ (0.006 g, 0.03 mmol, 7 mol %) and CuCl (0.2 g, 2.2 mmol) in 6 mL of DMF and 1.5 mL of water was stirred under an O_2 atmosphere at room temperature for 1.5 h. To this reaction mixture a solution of **13** (obtained above) in minimum amount of DMF was added at rt. It was then stirred for 6.5 h under oxygen atmosphere at room temperature, quenched with 3 N HCl and extracted with ether. The combined ether layers were washed with brine, and dried over Na_2SO_4. Evaporation of solvent followed by column chromatography of the residue yielded (−)-2-hydroxy-*exo*-brevicomin (20 mg, 56%) as a highly volatile colorless oil. $[\alpha]_D = -32$ (*c* 0.5, $CHCl_3$) lit.[5] $[\alpha]_D = +33.3$ (*c* 1.94, $CHCl_3$) for the (+)-isomer; ^1H NMR (300 MHz, C_6D_6) δ 4.15 (t, $J = 6.3$ Hz, 1H), 3.76 (br s, 1H), 3.62–3.53 (m, 1H), 1.68–0.84 (m, 6H), 1.44 (s, 3H), 0.90 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 106.9, 80.5, 77.2, 66.3, 34.9, 28.3, 26.7, 23.9, 9.7.

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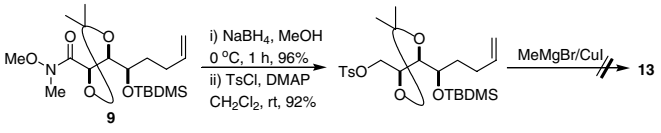
11. Attempts to arrive at **13** from **9** through the tosylate route failed to yield the product.



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