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Asymmetric syntheses of (1*R*,1′*R*,5′*R*,7′*R*) and (1*S*,1′*R*,5′*R*,7′*R*)-1-hydroxy-*exo*-brevicomin and a formal synthesis of (+)-*exo*-brevicomin ☆

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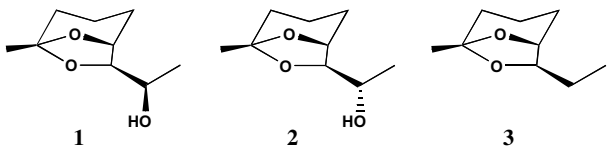
Abstract—Asymmetric syntheses of (1*R*,1′*R*,5′*R*,7′*R*) and (1*S*,1′*R*,5′*R*,7′*R*)-1-hydroxy-*exo*-brevicomins **1** and **2**, volatiles of the male mountain pine beetle, and a formal synthesis of (+)-*exo*-brevicomin **3**, a component of the attracting pheromone system of several bark beetles have been achieved. The key steps are Birch reduction of commercially available α-picoline, selective Wittig olefination, and Sharpless asymmetric dihydroxylation.

The 6,8-dioxabicyclo[3.2.1]octane skeleton is a common structural subunit in the pheromones of a variety of bark beetle species. In 1989, Prestwich[1] discovered oxygenated 6,8-dioxabicyclo[3.2.1]octane derivatives in volatiles produced by bark beetles and in 1996, Francke[2] et al. identified two diastereomers **1** and **2** along with some other derivatives in the volatiles of the males of the mountain pine beetle, *Dendroctonus brevicomis.* Among various alkyl derivatives, (+)-*exo*-brevicomin **3** (7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane) a component of several bark beetle species belonging to the genera *Dendrectonus* and *Dryocoetes*[3] is a well known synthetic target (Fig. 1).

To date, two syntheses[2,4] have been reported for (+)-1-hydroxy-*exo*- brevicomins **1** and **2** applying kinetic resolution by Sharpless asymmetric epoxidation and Sharpless asymmetric dihydroxylation, respectively.



1 **2** **3**

Figure 1.

Barbas III and his co-workers[5] synthesized enantiomers of **1** and **2**, that is (−)-hydroxy brevicomins via enantioselective C–C bond formation using the aldolase antibody 38C2 catalyst. A number of syntheses[6,7] have been reported and reviewed in the literature for compound **3**. Most of the synthetic strategies for the above targets involved organometallic reagents and protection, deprotection protocols to construct the required carbon skeleton. Owing to the commercial potential of these pheromones and for the preparation of more active analogues, their efficient synthesis demands great attention. Herein we report a short and common strategy for the enantioselective total syntheses of (+)-(1*R*)-1-hydroxy-*exo*-brevicomin **1**, (+)-(1*S*)-1-hydroxy-*exo*-brevicomin **2**, and (+)-*exo*-brevicomin **3**, starting from easily available α-picoline **4**.

Our synthesis involved Birch reduction of α-picoline **4** and Wittig olefination as key steps. Earlier, a Birch reduction strategy was utilized in our laboratory for the synthesis of biologically active compounds.[8] Birch reduction of pyridine and substituted pyridines is known to give dihydro compounds, which on hydrolysis afford 1,5-diketo products.[9] These 1,5-diketo compounds can undergo intramolecular cyclization to give aldolized products. Birch, Shaw, and Danishefsky used this strategy efficiently in targeted natural product syntheses.[10] Similarly α-picoline gave cyclohexenone via 5-oxohexanal **6** (not isolated),[11] which showed that α-picoline could be used as a 5-oxohexanal equivalent, a key fragment in our synthesis.

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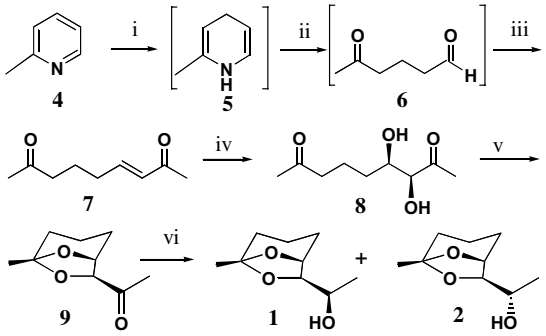
The synthesis commenced with the Birch reduction of α-picoline **4** with Na (3 equiv) in liq. NH_3 containing EtOH (10 equiv) using the known procedure.[11] The residue containing dihydro-α-picoline **5**, obtained upon evaporation of the ammonia, was treated with 4 N HCl to afford 5-oxohexanal **6**. Chemoselective Wittig olefination on crude **6** with $PPh_3CHCOCH_3$ in DCM gave the required carbon skeleton **7** with *trans* stereoselectivity in 38% overall yield from α-picoline (average yield for each step is 71%). The resulting α,β-unsaturated ketone **7** was subjected to asymmetric dihydroxylation with AD-mix-β® under Sharpless conditions[12] affording compound **8**, which upon treatment with catalytic *p*-TSA in DCM gave cyclized product **9**. The cyclized compound **9** was reduced with different reducing agents to give diastereomers **1** and **2** (see Table 1), which were separated by column chromatography. The physical and spectral data of these compounds were in good agreement with the reported values[2,4,13] (Scheme 1).

Similarly, when 5-oxohexanol **6** was treated with Ph_3PCHCO_2Et, compound **10** was formed in 26% overall yield (average yield for each step is 65%). This when subjected to Sharpless asymmetric dihydroxylation using AD-mix-β® gave **11**, which upon cyclization with catalytic *p*-TSA in DCM afforded **12** in good yield. Cyclized ester **12** on reduction with $LiBH_4$ gave alcohol **13**, the spectral data for which matched with the reported values.[13,14]Compound **13** has been converted to (+)-*exo*-brevicomin **3** in two steps,[14] providing a formal synthesis of target molecule **3** (Scheme 2).

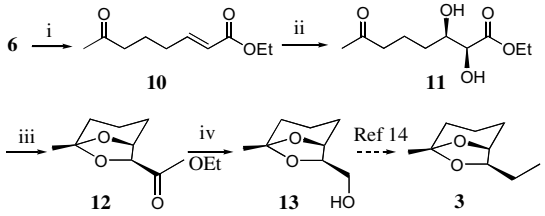
Table 1

	Solvents and temperature	Yield (%)	**1**[a]	**2**[a]
LAH	THF, 0 °C	86	32	68
$NaBH_4$	MeOH, 0 °C	92	36	64
$Zn(BH_4)_2$	THF, 0 °C	84	25	75
K-Selectride	Toluene, −78 °C	79	22	78
DIBAL-H	THF, 0 °C	92	20	80

[a] Calculated from NMR.



Scheme 1. Reagents and conditions: (i) Na in liq. NH_3·EtoH; (ii) 4 N HCl; (iii) $Ph_3PCHCOCH_3$, DCM, 3 h (overall yield for three steps 35%); (iv) AD mix-β, *t*-BuOH/H_2O, 1:1, 3 h, 0 °C; (v) catalyst *p*-TSA, DCM, 54% (for two steps from **7**); (vi) see Table 1.



Scheme 2. Reagents and conditions: (i) $Ph_3PCHCOOEt$, DCM 30 min (overall yield for three steps 25%); (ii) AD mix-β, *t*-BuOH/H_2O, 1:1, 3 h, 0 °C; (iii) catalytic *p*-TSA, DCM, 56% (for two steps from **10**); (iv) LiCl, $NaBH_4$, EtOH, THF, 77%.

In earlier approaches for the synthesis of (+)-*exo*-brevicomin **3** employing Sharpless asymmetric dihydroxylation, Weigel and Turpin[15], and Soderquest and Rane[16] observed that the remote ketone functionality lowers the enantiomeric excess in asymmetric dihydroxylation of the isolated double bond. However in the case of **8** and **11** good enantiomeric excess was observed in the AD reaction.[17] In this instance, the presence of a keto or ester functionality in conjugation with the olefin might have minimized the interference of the remote ketone. It is also well known that α,β-unsaturated esters/carbonyl compounds give diols with good enantiomeric excess in the AD reaction.

In conclusion, we have developed a short approach for the synthesis of (1*R*,1′*R*,5′*R*,7′*R*)-(+)-hydroxy-*exo*-brevicomin **1**, (1*S*,1′*R*,5*R*,7′*R*)-(+)-1-hydroxy-*exo*-brevicomin **2**, and (+)-*exo*-brevicomin **3** starting from cheaply available α-picoline.

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13. Spectral data for selected compounds: Compound **9**: $[\alpha]_D^{24.8} = -49.86$ (*c* 1.23, $CHCl_3$); IR ($CHCl_3$ cm^{-1}): 2962, 1718, 1382, 1349, 1220, 1015, and 1049; ^1H NMR (300 MHz, $CDCl_3$): δ 1.52 (s, 3H), 1.56–1.88 (m, 6H), 2.22 (s, 3H), 4.18 (s, 1H), 4.45 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.89, 109.90, 84.24, 79.28, 34.61, 27.89, 26.95, 24.37, 17.07; EI-MS *m/z*: 170 (M^+), 155, 141, 127, 99, 81, 69, 43.
Compound **1**: Low melting solid {lit.[2] 29 °C}; $[\alpha]_D^{25.4} = +54.12$ (*c* 1.82, $CHCl_3$) {lit.[2] $[\alpha]_D^{21} = +56.7$ (*c* 0.8, $CHCl_3$), lit.[4] $[\alpha]_D^{26} = +55.2$ (*c* 0.82, $CHCl_3$)}; IR ($CHCl_3$ cm^{-1}): 3470, 2941, 2853, 1741, 1460, 1380, 1165, 1102, 1087, 1026, 1005, and 827; ^1H NMR (500 MHz, CD_3CN): δ 1.10 (d, 3H, $J = 6.4$ Hz), 1.31 (s, 3H), 1.45 (m, 1H), 1.52–1.61 (m, 3H), 1.68–1.76 (m, 1H), 1.78–1.88 (m, 1H), 2.60–2.68 (br s, 1H), 3.42 (m, 1H), 3.65 (d, 1H, $J = 7.1$ Hz), 4.35 (br s 1H). ^{13}C NMR (125 MHz, CD_3CN): δ 17.97, 19.74, 25.09, 28.54, 35.57, 69.15, 76.91, 84.56, 108.52.
Compound **2**: Colorless oil $[\alpha]_D^{25.9} = +63.38$ (*c* 2.95, $CHCl_3$) {lit.[4] $[\alpha]_D^{21} = +61.3$ (*c* 1.18, $CHCl_3$)}; IR ($CHCl_3$ cm^{-1}): 3472, 2938, 1450, 1384, 1237, 1173, 1115, 1040, 1010, 930, 883, 851, and 773; ^1H NMR (500 MHz, CD_3CN): δ 1.01 (d, 3H, $J = 6.3$ Hz), 1.35 (s, 3H), 1.42–1.48 (m, 1H), 1.53–1.63 (m, 3H), 1.67–1.75 (m, 1H), 1.79–1.89 (m, 1H), 2.72 (d, 1H, $J = 3.3$ Hz), 3.52 (m, 1H, $J = 3.3$, 6.3 Hz), 3.75 (d, 1H, $J = 6.3$ Hz); 4.22 (br s, 1H); ^{13}C NMR (125 MHz, CD_3CN): δ 17.91, 18.65, 25.10, 28.48, 35.56, 69.46, 76.80, 84.38, 108.75; EI-MS *m/z*: 172 (M^+), 127, 112, 97, 81, 69, 55, 43.
Compound **12**: $[\alpha]_D^{26.1} = +35.75$ (*c* 1.1, $CHCl_3$); IR (neat cm^{-1}): 2980, 2940, 1750, 1715, 1375, 1295, 1175, 1150, 1095, 1050, 1035, 1000, and 825; ^1H NMR (200 MHz, $CDCl_3$): δ 1.33 (t, 3H $J = 7.4$ Hz), 1.54 (s, 3H), 1.60–1.95 (m, 6H), 4.23 (q, 2H, $J = 7.4$ Hz), 4.43 (s, 1H), 4.61 (br s, 1H) ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.51, 109.87, 79.07, 77.42, 65.05, 34.33, 27.58, 24.07, 16.96, 14.04; FAB-MS *m/z*: 201 (M^+ +1), 154, 137, 107, 97, 83, 69, 55.
Compound **13**: Colorless oil $[\alpha]_D^{25.9} = +50.25$ (*c* 1.3, $CHCl_3$) {lit.[13] $[\alpha]_D^{27} = 53.7 \pm 2$ (*c* 0.94, $CHCl_3$)}; IR (neat cm^{-1}): 3200, 1450, 1180, and 760; ^1H NMR (200 MHz, $CDCl_3$): δ 1.40 (s, 3H), 1.42–1.85 (m, 6H), 3.50 (d, 2H, $J = 6$ Hz), 4.07 (t, 1H, $J = 6$ Hz), 4.23 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 108.34, 79.53, 76.51, 64.91, 34.69, 27.53, 24.87, 17.05; FAB-MS *m/z*: 159 (M^+ +1), 147, 136, 109, 95, 81, 73, 55.
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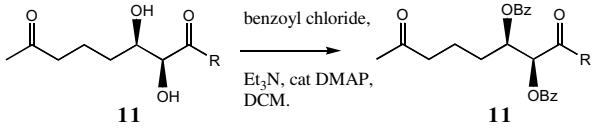
17. Enantiomeric purities of **8** and **11** were estimated to be 90.1% ee and >97% ee, respectively, by HPLC analysis of the corresponding dibenzoates **8a** $\{[\alpha]_D^{26.5} = +73.67$ (*c* 1.19, $CHCl_3$)$\}$ and **11a** $\{[\alpha]_D^{26.6} = +71.44$ (*c* 1.43, $CHCl_3$)$\}$ using a Chiracel OD-H column. (For **8a** 10% *i*-propanol/*n*-hexane, flow rate 0.5 mL/min, $\lambda = 254$ nm; for **11a** 7% *i*-propanol/*n*-hexane, flow rate 0.5 mL/min, $\lambda = 254$ nm.)



11 **11**

8 R = CH_3 **8a** R = CH_3

11 R = OEt **11a** R = OEt