Communications

A Facile Total Synthesis of (-)-Frontalin, (-)-*endo*-Brevicomin and (-)-*exo*-Brevicomin through $PtCl_4$ Catalyzed Hydroalkoxylation Reaction

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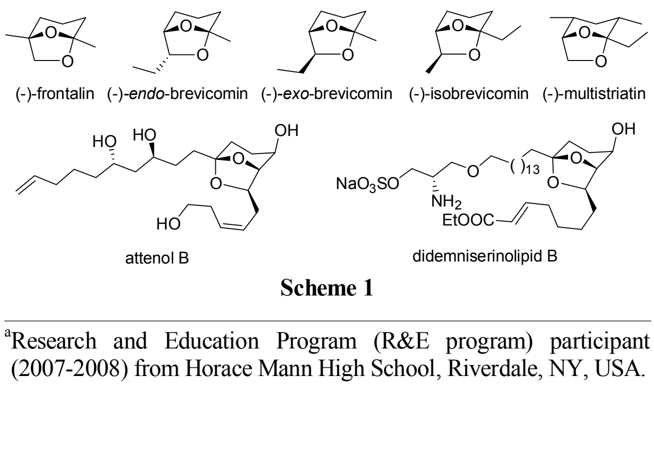
6,8-Dioxabicyclo[3.2.1]octane is a core structure of many natural products possessing various biological activities with wide structural diversity, and thus is considered one of privileged structures (Scheme 1).[1] Among these natural products, relatively simple derivatives such as frontalin and brevicomins are not only major bioactive component of the aggregation pheromones of beetles[2] but also long sought pheromones in mammalians as they are secreted by elephants.[3] While these pheromones exhibit biological activity only as a single enantiomer in beetles,[4] the same pheromones secreted by elephants with varying ratio of enantiomers depending on elephant's age and musth show different sexual behavior and aggressions.[5] While various synthetic route to the total synthesis of frontalin[2] and brevicomins[6] have been reported, we became interested in devising a versatile and efficient synthetic route to these pheromones and their analogs with varying enantiomeric ratio for future study on structure activity relationship and e.r. activity relationship.

Recent progress in transition metal catalyzed hydroalkoxylation reaction of alkynes[7] prompted us to envision a facile and versatile synthetic route to frontalin, brevicomins and their analogs in *enantio*-controlled manner. The synthetic plan is depicted in the Scheme 2. Starting from 5-hexynol, hex-1-en-5-yne system **1** with various substitution pattern can be readily prepared. Dihydroxylation of **1** would set up the required stereochemistry for enantiomerically differentiated diol **2** and $PtCl_4$ catalyzed hydroalkoxylation reaction of **2** would produce the intended bicyclic products **3**.

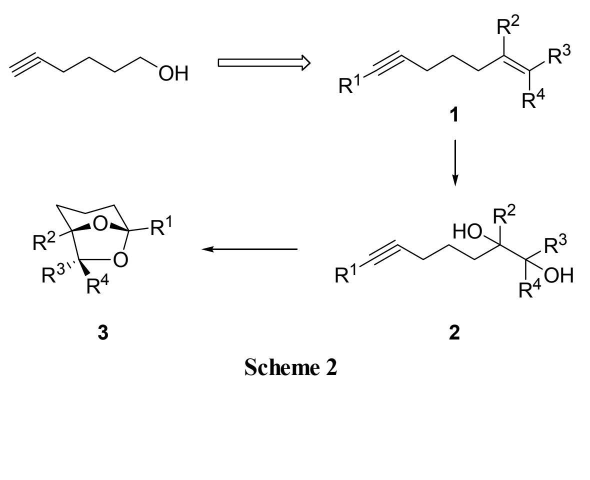
The synthesis started with silylation of the terminal alkyne of 5-hexynol. Though the protection of the terminal alkyne was not necessary, the terminal alkyne was silylated to suppress the volatility of the synthetic intermediates. Oxidation of the alcohol produced the aldehyde **5** and this aldehyde served as the branching point of the total synthesis of frontalin and brevicomin. For the synthesis of frontalin, methyl anion was added to the aldehyde and the resulting alcohol was oxidized to the corresponding ketone **6** in 62% yield for two steps. Wittig olefination reaction of **6** furnished all the carbon atoms required for frontalin in 89% yield. Asymmetric dihydroxylation[8] of the olefin of **7** produced the diol **8** in 92% yield with 68% e.e.[9] Direct hydroalkoxylation reaction of silylated alkynediol **8** with $PtCl_4$ did not proceed at all. The hydroalkoxylation reaction of **8** after desilylation reaction proceeded smoothly to produce (-)-frontalin.[10]

For the total synthesis of brevicomins, Wittig olefination reaction of the aldehyde **5** followed by the Sharpless asymmetric dihydroxylation produced 4:1 ratio of *anti*-diol **9** and *syn*-diol **10** in 49% yield with 20.9% e.e. and > 99% e.e. respectively. *Anti*-diol **9** was subjected to the $PtCl_4$ catalyzed hydroalkoxylation after desilylation reaction to produce (-)-*endo*-brevicomin in 72% yield and *syn*-diol **10** produced (-)-*exo*-brevicomin in 37% yield through the same reaction sequence.

Versatility of the current synthetic route can be extended to

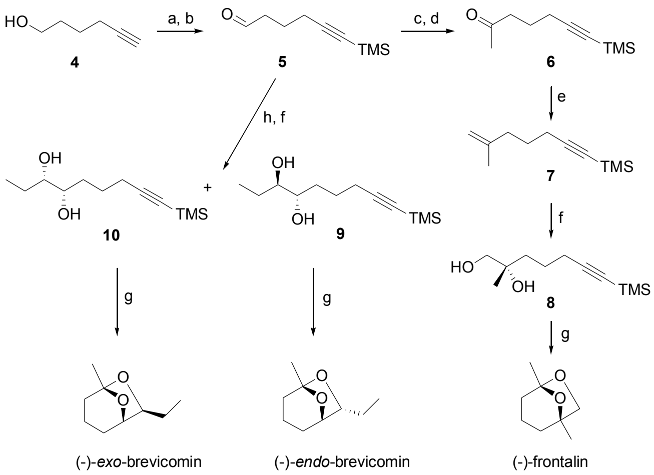


Scheme 1



Scheme 2

[a]Research and Education Program (R&E program) participant (2007-2008) from Horace Mann High School, Riverdale, NY, USA.



Scheme 3. Reagents and conditions: (a) EtMgBr, TMSCl/THF, 93%; (b) PCC/CH_2Cl_2, 69%; (c) MeMgBr/Et_2O, 70%; (d) PCC/CH_2Cl_2, 89%; (e) Ph_3PCH_3Br, *t*-BuOK/PhH, 89%; (f) AD-mix-α, *t*-BuOH, H_2O, 0 °C, 8hr, 92% for **8**, 99% for **9** and **10**; (g) TBAF, THF, 0 °C, 30 min; $PtCl_4$(5 mol%), THF, rt, 3 hr, 91% for frontalin, 72% for endo-brevicomin, 37% for exo-brevicomin (h) *n*-$PrPPh_3Br$, *n*-BuLi, THF, 12 hr, 49%.

Table 1. Temperature effect on enantioselectivity

Temperature	0 °C	23 °C	40 °C	60 °C
e.e.	68	44	27	15

the synthesis of frontalin with varying enantiomeric ratio as it can simulate the enantiomeric ratio of frontalin produced by elephant and pine bark beetle. While pine bark beetles produce frontalin with high enantiomeric purity, elephants produce frontalin with low enantiomeric purity or as racemic form. The enantiomeric ratio of synthetic frontalin could be controlled at the asymmetric dihydroxylation step without using different asymmetric catalyst for dihydroxylation reaction as the reaction temperature alters the enantiomeric ratio during the asymmetric dihydroxylation reaction.[11] Temperature effect during the asymmetric dihydroxylation on the enantiomeric ratio of frontalin was summarized in the Table 1. As expected, lower temperature produced higher enantiomeric ratio and higher temperature produced lower enantiomeric ratio of frontalin.

This temperature effect on the asymmetric dihydroxylation reaction that is leading to the enantiomeric ratio of frontalin might have a relevance to the enantiomeric ratios observed in nature as elephants produce frontalin with low enantiomeric ratio their at 37 °C of their body temperature[12] and beetles produce frontalin with high enantiomeric ratio at 7 °C.[13]

In summary, a versatile and efficient synthetic route to pheromones with 6,8-dioxabicyclo[3.2.1]octane structure was developed as frontalin was synthesized in 7 steps with 30% overall yield and brevicomins were synthesized in 6 steps with 15% overall yield. The enantiomeric ratios of these pheromones were also controlled by applying asymmetric dihydroxylation reaction with varying temperature conditions. Thus, the current synthetic route will be readily applied to the synthesis of various analogs of these pheromones and to study the effect of enantiomeric ratios of these pheromones in communications among beetles and elephants.

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9. The e.e. value was determined by chiral HPLC (Chiralcel AD-H, 1 mL/min, 2% *i*-PrOH/hexane) after benzoylation of the diols **8**, **9** and **10**.
10. Representative reaction conditions for the hydroalkoxylation reaction: To a stirred solution of **8** (119.5 mg, 0.56 mmol) in dry THF (2 mL) was added TBAF (570 μL, 1.0 M in THF, 0.57 mmol) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C, and then filtered through a silica pad, and concentrated under reduced pressure. The resulting crude was used next step without further purification. To a stirred solution of crude alkynediol in dry THF (5 mL) was added $PtCl_4$ (3.77 mg, 0.011 mmol) at room temperature. The reaction mixture was stirred for 3 hr at room temperature, and then concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate/hexane = 1/50 to 1/10) to give (-)-frontalin (72 mg, 91% in 2steps) as a colorless oil. $[\alpha]^{22}_{D}$ = -20.7 (c = 0.9, diethyl ether) ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (2H, d, *J* = 6.7 Hz), 3.43 (2H, dd, *J* = 6.7 Hz, 1.6 Hz), 1.84 (1H, m), 1.65-1.47 (5H, m), 1.41 (3H, s), 1.30 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$)) δ 108.1, 80.0, 74.2, 34.5, 33.9, 24.7, 23.1, 18.0.
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