Chiral Synthesis of Natural (+)-*endo*-Brevicomin with Enzymatic Reaction from L-Tartaric Acid

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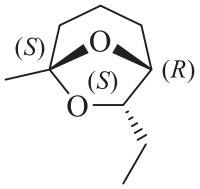
Dendroctonus brevicomis is a serious damaging pest to pine forest of the southwestern United States, west coast of North America and also Norway spruce.[1] Use of pheromone is a safer way to control pest than that of insecticides. It has several features such as being active at very low concentration, non-toxic, and species-specific. Accordingly, synthesis of insect pheromones has been important. (+)-*endo*-Brevicomin (**1**), structurally known as (1*R*,5*S*,7*S*)-7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane, is the aggregation pheromone of bark beetles, ***D. brevicomis*** (Figure 1).[2] But, (−)-*endo*-Brevicomin significantly reduces the response of beetles.[3] Because of interesting biological activities of brevicomins, various synthetic approaches have been reported.[1,4–10]

The chiral epoxide (2*S*,3*R*)- or (2*R*,3*S*)-3,4-epoxy-1,2-*O*-isoproplidenebutane-1,2-diol (**11**) has four carbon-skeleton and two stereochemically defined chiral centers at C-2 and C-3, and has been utilized as an enantiomerically enriched synthetic starting material. A biologically active substance such as bestatin and pheromone could be synthesized from this C-4 synthon. Synthesis of (2*S*,3*R*)-3,4-epoxy-1,2-*O*-isopropylidenebutane-1,2-diol **11** from L-ascorbic acid and D-isoascorbic acid was reported.[11] (2*R*,3*R*)-Tartaric acid (**2**) is a chiral pool material of the C-4 skeleton and easy to get in nature. Several methods of synthesis of *exo*-brevicomin had been reported using L-(+)-tartaric acid **2**.[12,13] However, *endo*-brevicomin has not been reported.[14] This research described that synthesis of (2*S*,3*R*)-3,4-epoxy-1,2-*O*-isopropylidenebutane-1,2-diol **11** via enzyme-mediated regioselective hydrolysis and inversion of one stereogenic center of the two chiral centers from L-tartaric acid **2**. It also described synthesis of optically selective (+)-*endo*-brevicomin.

We established a route to 11 which is useful chiral intermediate in nine steps from (2*R*,3*R*)-**2** as shown in Scheme 1. First, carboxyl groups were esterified to give **3**. Diethyl-L-(+)-tartrate **3** was synthesized by acid-catalyzed esterification of starting material L-(+)-tartaric acid **2** in EtOH in 88% yield. Acetalization of diethyl-L-(+)-tartrate **3** with 2,2-dimethoxypropane furnished protected form **4** in 88% yield. The diester **4** was reduced to diol **5** by using LAH in 89% yield. Treating diol **5** with butyric anhydride in pyridine provided dibutanoate **6** in a high yield (96%). Lipase TOYOBO (LIP-301) which have been found optimizing selective hydrolysis was applied to provide mono-hydroxy ester **7** in 90% yield.[15,16] Deprotection of acetonide in eight was carried out under as mild conditions as 15% AcOH to provide triol **8** in 82% yield. To protect the 1,2-hydroxy groups of triol, 1,2-acetonide protection was conducted by using *p*-TsOH in acetone in 64% yield. It appeared higher yield in low temperature than room temperature. The free hydroxy group of alcohol **9** was conducted mesylation with MsCl and triethylamine as base furnished the mesylate **10** in 97% yield.

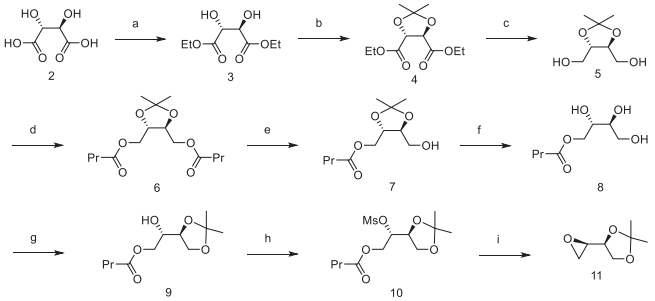
For inversion of chiral center, epoxide ring formation of mesylate **10** using KOH in MeOH finally obtained (2*S*,3*R*)-3,4-epoxy-1,2-O-isopropylidenebutane-1,2-diol **11** as a key chiral building block in 90% yield. Stereochemical configuration of **11** was identified from the comparison of the optical rotation value with a reported one.[17]

Our synthetic strategy to synthesize (+)-*endo*-brevicomin **1** from (2*S*,3*R*)-3,4-epoxy-1,2-*O*-isopropylidenebutane-1,2-diol **11** is shown in Scheme 2. To add the carbon frame, Grignard reaction with Li_2CuCl_4 of epoxide **11** with C_4H_7MgBr provided alcohol **12** in 60% yield. Acetonide was hydrolyzed in acidic condition to provide triol **13** in 97% yield. The triol **13** was converted into monotosylate **14** with *p*-TsCl in the presence of pyridine and triethylamine in 61% yield. Methylation of tosylate **14** with methylmagnesium bromide in Et_2O afforded diol **15** in 70% yield. Finally, Wacker oxidation[18] of diol **15**

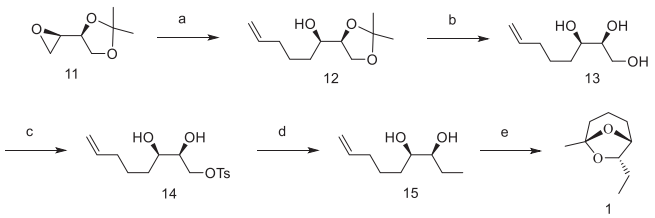


(+)-*endo*-brevicomin **1**

Figure 1. Structure of the (+)-*endo*-brevicomin **1**.



Scheme 1. Synthesis of (2*S*,3*R*)-3,4-epoxy-1,2-O-isopropylidenebutane-1,2-diol **11**. (a) H_2SO_4, EtOH, 88%; (b) 2,-2-dimethoxypropane, *p*-TsOH, benzene, 88%; (c) LAH, Et_2O, 89%; (d) $Pr(CO)_2O$, DMAP, pyridine, 96%; (e) TOYOBO lipase, pH 6.4 phosphate buffer, 90%; (f) 15% AcOH, 82%; (g) *p*-TsOH, acetone, 64%; (h) MsCl, TEA, CH_2Cl_2, 97%; (i) KOH, MeOH, H_2O, 90%.



Scheme 2. Synthesis of (+)-endo-brevicomin **1**. (a) C_4H_7MgBr, Li_2CuCl_4, THF, 60%; (b) HCl, MeOH, 97%; (c) *p*-TsCl, pyridine, TEA, CH_2Cl_2, 61%; (d) $(CH_3)_2CuLi$, Et_2O, 70%; (e) $PdCl_2$, $CuCl_2$, 1,2-dimethoxyethane, 62%.

employing $PdCl_2$ and $CuCl_2$ as catalyst in 1,2-dimethoxyethane successfully obtained (+)-*endo*-brevicomin **1** in 62% yield, $[\alpha]_D^{25}$= +78.8 (c = 1.0, Et_2O). The spectral data of **1** was identified from the comparison of the optical rotation value with a reported data.[5,9] For more detailed synthesis methods to the supporting information Appendix S1.

In summary, we achieved a facile synthesis of (+)-*endo*-brevicomin **1** in 14 steps including enzyme-mediated selective monohydrolysis, alkylation and Wacker oxidation from L-(+)-tartaric acid **2**. The epoxide **11** has been used important chiral building block to synthesize biologically active substance. Using this, we expect this simple optically selective synthetic approach to insect pheromone to be useful in insect pheromone trap industry.

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Supporting Information. Additional supporting information may be found online in the Supporting Information section at the end of the article.

References

1. K. Mori, Y.-B. Seu, *Tetrahedron* **1985**, *41*, 3429.
2. R. M. Silverstein, R. G. Brownlee, T. E. Bellas, D. L. Wood, L. E. Browne, *Science* **1968**, *159*, 889.
3. J. P. Vité, R. F. Billings, C. W. Ware, K. Mori, *Naturwissenschaften* **1985**, *72*, 99.
4. B. Oehlschlager, D. Johnston, *Am. Chem. Soc.* **1987**, *52*, 940.
5. R. A. Fernandes, P. Kattanguru, V. Bethi, *RSC Adv.* **2014**, *4*, 14507.
6. S.-G. Kim, T.-H. Park, B. J. Kim, *Tetrahedron Lett.* **2006**, *47*, 6369.
7. K. Mori, *Biosci. Biotechnol. Biochem.* **2011**, *75*, 976.
8. P. Pal, A. K. Shaw, *Tetrahedron* **2011**, *67*, 4036.
9. S. Singh, P. J. Guiry, *J. Org. Chem.* **2009**, *74*, 5758.
10. S. D. Burke, N. Müller, C. M. Beaudry, *Org. Lett.* **1999**, *1*, 1827.
11. Y. Le Merrer, C. Gravier-Pelletier, J. Dumas, J. C. Depezay, *Tetrahedron Lett.* **1990**, *31*, 1003.
12. K. Mori, *Tetrahedron* **1974**, *30*, 4223.
13. K. R. Prasad, P. Anbarasan, *Tetrahedron Asymmetry* **2005**, *16*, 3951.
14. L. Ann, *Chem.* **1988**, *12*, 1135.
15. Y.-B. Seu, T.-K. Lim, C.-J. Kim, S.-C. Kang, *Tetrahedron Asymmetry* **1995**, *6*, 3009.
16. W. H. Lee, I. H. Bae, B. M. Kim, Y.-B. Seu, *Bull. Kor. Chem. Soc.* **2016**, *37*, 1910.
17. M. Pottie, J. Van der Eycken, M. Vandewalle, H. Röper, *Tetrahedron Asymmetry* **1991**, *2*, 329.
18. K. Machiya, I. Ichimoto, M. Kirihata, H. Ueda, *Agric. Biol. Chem.* **1985**, *49*, 643.

