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A novel and stereospecific synthesis of (+)-*exo*-brevicomin☆

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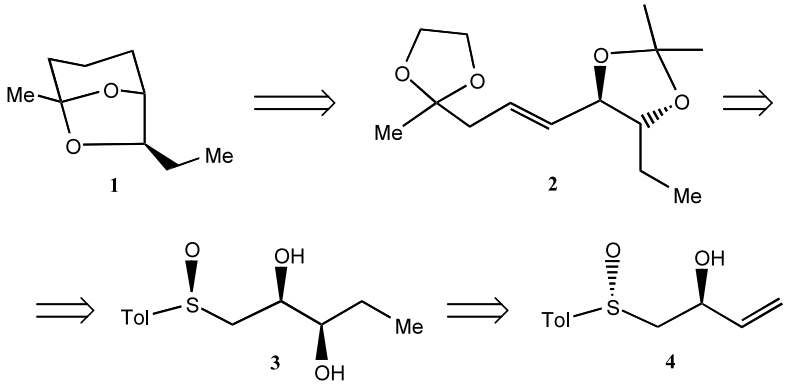
Abstract—A novel and stereospecific synthesis of (+)-*exo*-brevicomin is disclosed. The key step of the reaction sequence employs the sulfinyl moiety as an intramolecular nucleophile to functionalize an alkene π-complexed to a bromonium ion.

exo-Brevicomin[1] **1** is an aggregation pheromone produced by *Dendroctonus brevicomis*, the western pine beetle, which is a principal pest in the timber regions on the western coast of North America. The pheromone attracts other beetles of the same species to the host tree which is inoculated with a pathogenic fungus leading to the tree's death. *exo*-Brevicomin was first synthesized in racemic form[2] and since then several syntheses of the racemic substance as well as the optically active isomers have been reported,[3] perhaps more as a test for the efficacy and versatility of new synthetic strategies. In spite of the large number of reported syntheses, they are not satisfactory in terms of the simplicity of the process and the enantiomeric and/or diastereomeric excess of the products. The design of a highly successful strategy still remains a synthetic challenge. We have been interested in the regio- and stereoselective heterofunctionalization of olefins by 1,2/1,3-asymmetric induction using the sulfinyl moiety as an internal nucleophile.[4] We illustrate the potential of this methodology by the stereospecific synthesis of (+)-*exo*-brevicomin using a straightforward sequence of reactions. Our approach to (+)-**1** is illustrated retrosynthetically in Scheme 1.

We envisioned that **1** would be obtained from the diketal **2** by reduction followed by ketal exchange and that **2** would be derived from the diol **3** which in turn would be derived from olefin **4**.

The synthesis began with the allyl alcohol **4**[5] which was transformed into the bromohydrin **5** regio- and stereospecifically.[5] Treatment of **5** with dimethylcuprite afforded diol **3** cleanly in 72% yield. Subjecting diol **3** to treatment with 2,2-dimethoxypropane in the presence of catalytic amounts of camphor-10-sulfonic acid afforded the acetonide **6**. Subjecting **6** to rearrangement



Scheme 1.

Keywords: *exo*-brevicomin; sulfinyl moiety; internal nucleophile.
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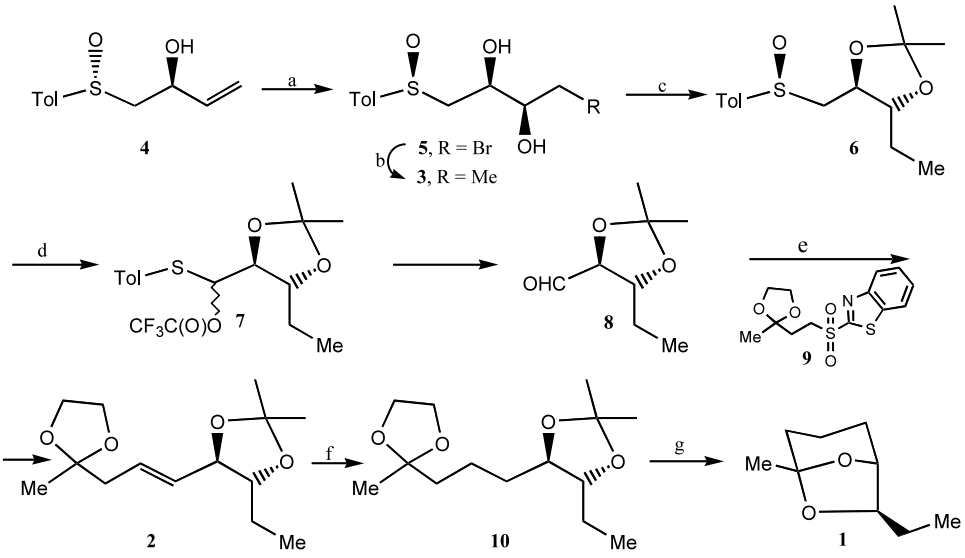
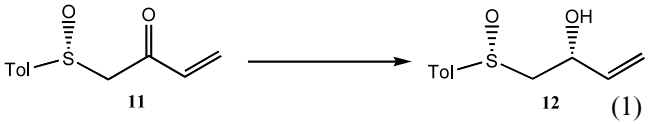


Scheme 2. *Reaction conditions*: (a) NBS, H_2O, toluene, rt, 30 min, 81%; (b) Me_2CuLi, THF, −78°C to rt, 2 h, 72%; (c) 2,2-DMP, cat. CSA, acetone, rt, 1 h, 92%; (d) TFAA, Et_3N, CH_2Cl_2, 0°C, 15 min, then aq. $NaHCO_3$, 0°C–rt, 15 min, 64% overall yield; (e) LiHMDS, THF, −78°C to rt, 3 h, 68%; (f) Pt/C, H_2, EtOAc, 4 h, rt, 91%; (g) PTSA, CH_2Cl_2, rt, 88%.

under Pummerer reaction conditions[6] with trifluoroacetic anhydride in the presence of Et_3N afforded intermediate **7** which without isolation was subjected to hydrolysis by treatment with aq. saturated $NaHCO_3$ to yield the aldehyde **8**. Condensation of **8** with the sulfone **9**[7] using the modified Julia olefination conditions[8] afforded the *trans* olefin **2** as the only isolated product. Reduction of the double-bond by treatment with Pt/C under an atmosphere of hydrogen in ethyl acetate as the solvent yielded diketal **10** (Scheme 2).

Treatment of **10** with catalytic amounts of *p*-toluenesulfonic acid[9] in dichloromethane as the solvent afforded (+)-*exo*-brevicomin **1** with physical characteristics in excellent agreement with those reported in the literature.[3]

The diastereomeric allyl alcohol **12**,[10] differing from **4** at the carbon bearing the hydroxy group was prepared by reduction (>95% d.e.) of the β-ketosulfoxide **11**[5] using DIBAH/$ZnCl_2$ (Eq. (1)).[11] Following the same sequence of reactions as detailed above, (−)-*exo*-brevicomin can be elaborated from **12**.



(1)

In summary, we have disclosed herein an efficient, stereospecific synthesis of (+)-*exo*-brevicomin. The key steps of the reaction sequence include diastereoselective reduction of β-ketosulfoxide **11** to yield allyl alcohol **4** or **12** (>95% d.e.) and use of the sulfinyl moiety as the internal nucleophile for the regio- and stereospecific functionalization of the alkene.

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10. **12**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.55 (d, $J=8.0$ Hz, 2H), 7.32 (d, $J=8.0$ Hz, 2H), 5.83 (ddd, $J=17.0$, 11.0, 5.70 Hz, 1H), 5.37 (d, $J=17.0$ Hz, 1H), 5.29 (d, $J=11.0$ Hz, 1H), 4.81 (m, 1H), 3.71 (s, 1H), 2.97 (dd, $J=13.7$, 10.3 Hz, 1H), 2.80 (dd, $J=13.7$, 2.7 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.9, 140.4, 138.3, 130.1, 124.1, 116.1, 69.5, 62.5, 21.5. $[\alpha]_D^{25}=180.5$ (*c* 0.76, $CHCl_3$).
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