Total Synthesis of the Ubiquitin-Activating Enzyme Inhibitor (+)-Panepophenanthrin

In 2002, the first natural product inhibitor of ubiquitin activating enzyme, panepophenanthrin (**1**), was isolated from the mushroom strain *Panus rudis* Fr. IFO8994.[1] In 2003, we completed the first total synthesis of (+)-panepophenanthrin utilizing a highly stereoselective Diels-Alder dimerization of an epoxyquinol dienol monomer.[2] Our retrosynthetic route for panepophenanthrin is depicted in **Figure 1. Epoxyquinol 1** may be derived from hemiacetal formation of hydroxy ketone precursor **2.** The propensity for epoxyquinol derivatives to form both hydrates and hemiacetals by reaction of water and alcohols with the electrophilic carbonyl has been documented. Open-form precursor **2** may be derived from *exo*-Diels Alder dimerization[3] of epoxyquinol monomer **3**, the conjugated diene isomer of the natural product panepoxydon **4**. Reports by Shotwell *et al* have documented the facile rearrangement of **4** to conjugated isomers such as **3** under mildly acidic conditions.[4] Epoxyquinol diene monomer **3** may be derived from transformations of chiral, nonracemic epoxy ketone **5**, including a Heck-type coupling to install the dienol. Compound **5** may be prepared in either antipode using tartrate-mediated asymmetric nucleophilic epoxidation of a quinone monoketal precursor.

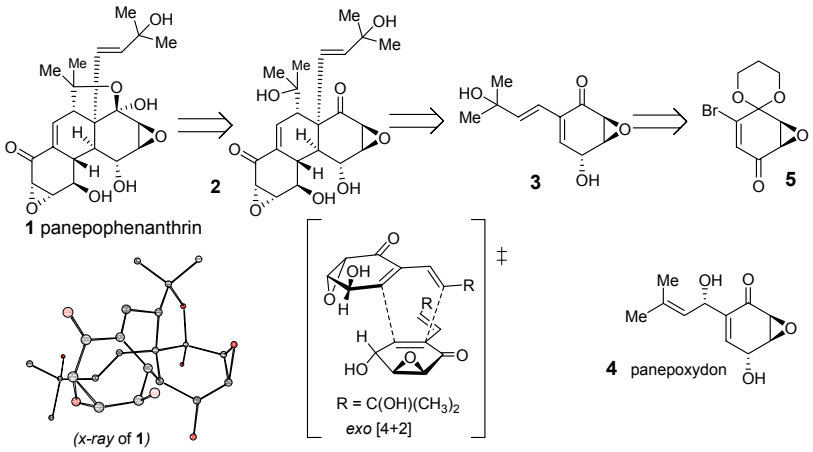
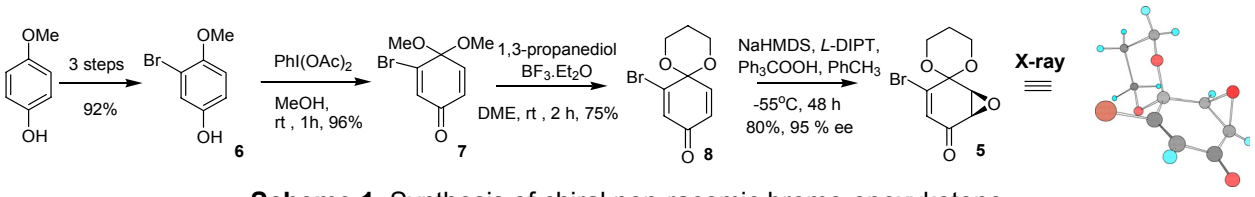


Figure 1. Retrosynthetic analysis for panepophenanthrin

The synthesis was initiated by hypervalent iodine oxidation of the readily available bromide **6** to afford dimethoxyketal **7** (**Scheme 1**). Transketalization of **7** with 1, 3-propanediol using Pirrung's conditions[5] afforded 1, 3-dioxane **8** which was found to be a suitable substrate for nucleophilic epoxidation. Tartrate-mediated nucleophilic epoxidation of **8** using NaHMDS as base cleanly produced epoxy ketone **5** (80 % yield, 95 % ee). The absolute stereochemistry of **5** was confirmed by single X-ray crystal structure analysis.

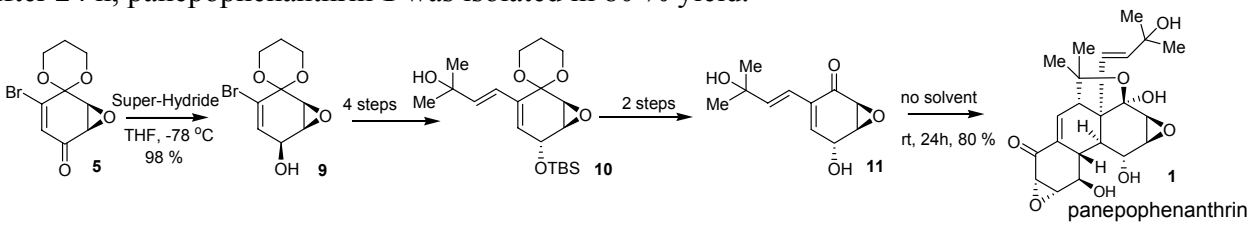
References Cited

[1] Sekizawa, R.; Ikeno, S.; Nakamura, H.; Naganawa, H.; Matsui, S.; Iinuma, H.; Takeuchi, T. *J. Nat. Prod.* **2002**, *65*, 1491.
[2] Lei, X.; Johnson, R. P.; Porco, J. A., Jr. *Angew. Chem. Int. Ed*. **2003**, *42*, 3913; *Angew. Chem*. **2003**, *115*, 4043.
[3] Spino, C.; Pesant, M.; Dory, Y. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 3262
[4] Shotwell, J. B.; Hu, S.; Medina, E.; Abe, M.; Cole, R.; Crews, C. M.; Wood, J. L. *Tetrahedron Lett*. **2000**, *41*, 9639.
[5] Pirrung, M. C.; Nunn, D. S. *Tetrahedron Lett*. **1992**, *33*, 6591.



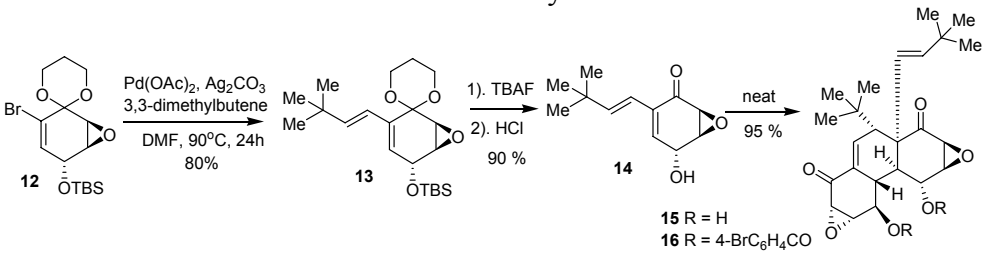
Scheme 1. Synthesis of chiral non-racemic bromo-epoxyketone

Advancement of **5** to the natural product panepophenanthrin **1** is shown in **Scheme 2**. Super-Hydride reduction of **5** cleanly afforded the *syn*-epoxy alcohol **9**, which was subsequently converted to dienol monomer **11** through six steps in overall good yield. Interestingly, Diels-Alder dimerization of **11** proceeded when the monomer was allowed to stand at 25 °C without solvent. After 24 h, panepophenanthrin **1** was isolated in 80 % yield.



Scheme 2.Total synthesis of panepophenanthrin

To further probe the role of the tertiary hydroxyl group in Diels-Alder dimerization of **11**, we prepared an epoxyquinol monomer lacking this functionality (**Scheme 3**). Heck-type coupling of **12** with 3,3-dimethylbutene afforded **13** (80%). Treatment of **13** with TBAF followed by 0.2 M HCl produced monomer **14** in 90 % yield. Epoxyquinol **14** was cleanly dimerized to **15** (neat, 24 h). Regio- and stereo-chemistry of **15** was confirmed by single x-ray crystal structure analysis of bis-*para*-bromobenzoate **16**. Production of dimer **15** confirms that that tertiary alcohol of monomer **11** is not essential for successful Diels-Alder dimerization. These studies support our proposal that the Diels-Alder dimerization occurs first and is followed by hemiacetal formation.



Scheme 3.Synthesis of new dimer **15**