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Total Synthesis of Panepophenanthrin

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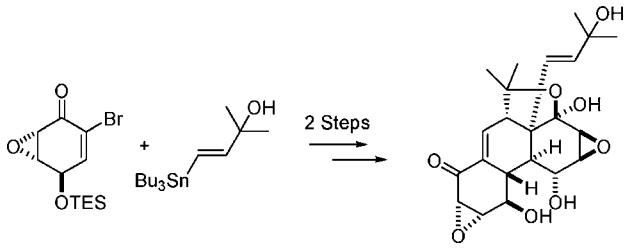
ABSTRACT



The biomimetic synthesis of the racemic dimer panepophenanthrin was achieved in good yield employing a tandem reaction sequence.

Panepophenanthrin **1** is a newly discovered inhibitor of the ubiquitin-proteosome pathway (UPP), whose unique molecular structure has been fully elucidated by spectroscopic and X-ray crystallographic techniques (Figure 1).[1] This naturally occurring substance was isolated in 2002 by Sekizawa et al, from the fermented broth of the mushroom strain *Panus rudus* IFO8994.

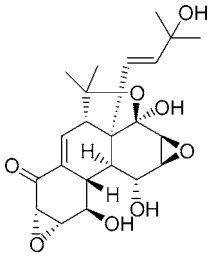


Figure 1. Panepophenanthrin **1**.

Panepophenanthrin **1** is the first example of an inhibitor of the ubiquitin-activating enzyme (E1), which is indispensable for the ubiquitin-proteasome pathway. Thus, **1** is of great biological significance and could provide insight for further investigations into ubiquitin functions that are linked to serious disease.[2]

Panepophenanthrin's unprecedented molecular architecture is characterized by its densely substituted tetracyclic core, containing 11 contiguous stereocenters, two of which are quaternary. Its novel structural features and sensitive functionalities, coupled with its important biological activity, make panepophenanthrin **1** an attractive target for total synthesis. Herein we wish to report a facile total synthesis of this unusual natural product in its racemic form.

Scheme 1 depicts, in a retrosynthetic format, the overall biomimetic strategy employed in our total synthesis of **1**. Thus, a retro Diels−Alder reaction reveals the hemiketal **2**, which can be further disconnected to give 2 equiv of the known conjugated diene **3**.[3] Disconnection of **3** realized the known compounds, vinyl stannane **4** and vinyl bromide (bromoxone) **5**, as key intermediates.

Central to the success of this strategy was to ensure strict diastereocontrol of the Diels−Alder reaction, which we envisaged would be imposed on the system by initial hemiketal formation to **2**. Such a strategy should secure rapid and straightforward access to the natural product **1**.

The present synthesis began with the preparation of fragment **4** using a palladium-catalyzed hydrostannation of 2-methyl-3-butyn-2-ol, which furnished vinyl stannane **4** with

(1) Sekizawa, R.; Ikeno, S.; Nakamura, H.; Naganawa, H.; Matsui, S.; Iinuma, H.; Takeuchi, T. *J. Nat. Prod.* **2002**, *65*, 1491.

(2) Swinney, D. C. *Drug Discovery Today* **2001**, *6*, 244.

(3) Shotwell, J. B.; Hu, S.; Medina, E.; Abe, M.; Cole, R.; Crews, C. M.; Wood, J. L. *Tetrahedron Lett.* **2000**, *41*, 9639.

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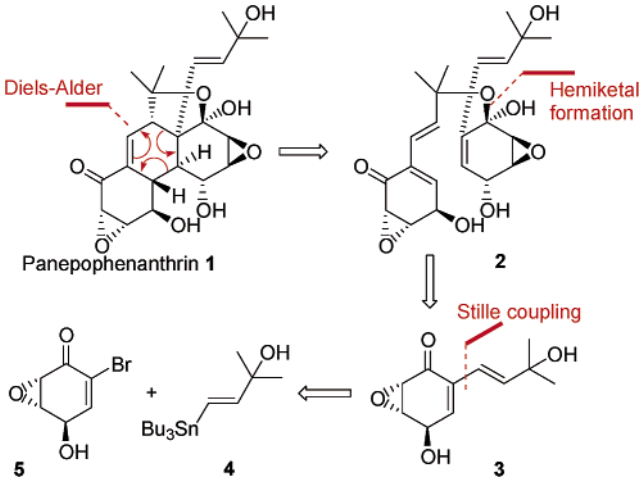
Scheme 1. Retrosynthetic Analysis of **1**



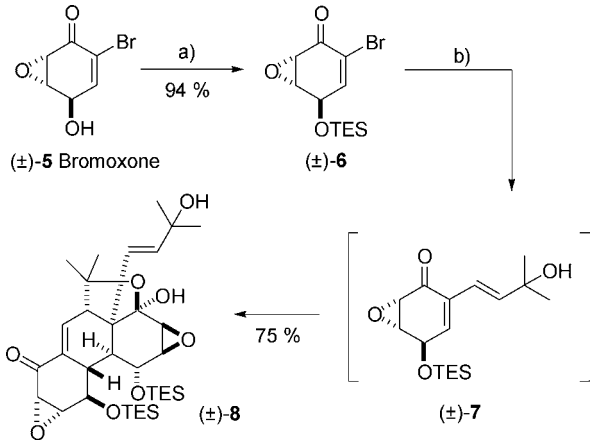
total regio- and stereoselectivity.[4] For our study, we chose to prepare bromoxone **5** in racemic form, although the enantiomerically pure material is readily obtained by enzymatic resolution.[5] Therefore, (±)-**5** was efficiently obtained in five steps from benzoquinone in accordance with the literature procedure.[5]

At this point, the stage was set to attempt the Stille coupling of fragments **4** and (±)-**5**; however, it was subsequently found that protection of the free hydroxyl group of bromoxone (±)-**5** was required to permit efficient Stille cross-coupling. Thus, TES protection of the secondary alcohol gave silyl ether (±)-**6** in 94% yield, which smoothly coupled with **4** using modified Stille conditions[6] to give a separable mixture of the TES-protected monomer (±)-**7** and TES-protected dimer (±)-**8**. However, (±)-**7** was found to be unstable and dimerized completely upon standing overnight to give (±)-**8** as a single diastereoisomer in 75% overall yield from (±)-**6** (Scheme 2).

Finally, deprotection of the TES ether (±)-**8** with NH_4F in methanol gave panepophenanthrin (±)-**1** in 85% yield (Scheme 3). The ^1H NMR, ^{13}C NMR, and mass spectral data obtained for the synthetic material are in agreement with those reported for the naturally occurring compound.[1]

(4) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857.
(5) (a) Adelt, S.; Pletenburg, O.; Stricker, R.; Reiser, G.; Altenbach, H.; Vogel, G. *J. Med. Chem.* **1999**, *42*, 1262. (b) Block, O.; Klein, G.; Altenbach, H.; Brauer, D. J. *J. Org. Chem.* **2000**, *65*, 716.
(6) Li, C.; Bardhan, S.; Pace, E.; Liang, M.; Gilmore, T.; Porco, J. *Org. Lett.* **2002**, *4*, 3267.

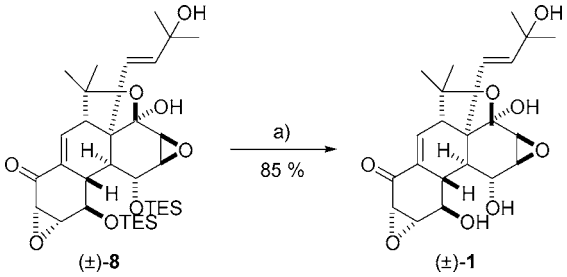
Scheme 2[a]



[a] Reagents and conditions: (a) TESCl, 2,6-lutidine, DMAP, CH_2Cl_2, 0°C to rt. (b) **4**, $Pd_2(dba)_3$, $AsPh_3$, 110°C, toluene.

In conclusion, the synthetic challenges presented by the title compound have been successfully met by employing a tandem reaction sequence. The key intramolecular Diels–Alder reaction was found to be rather efficient in terms of stereo- and regiochemical control, thus demonstrating the power of this biomimetic approach.

Scheme 3[a]



[a] Reagents and conditions: (a) NH_4F, MeOH, rt.

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Supporting Information Available: Experimental procedures and NMR data for compounds **7**, **8**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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