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C–H Functionalization-Enabled 11-Step Semisynthesis of (–)-Veragranine A and Characterization of Synthetic Analogs in Osteoarthritis-related Pain Treatment

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Synthesis and Medicinal Chemistry of Veragranine Alkaloids

Category

Innovative Drug
Discovery and
Development

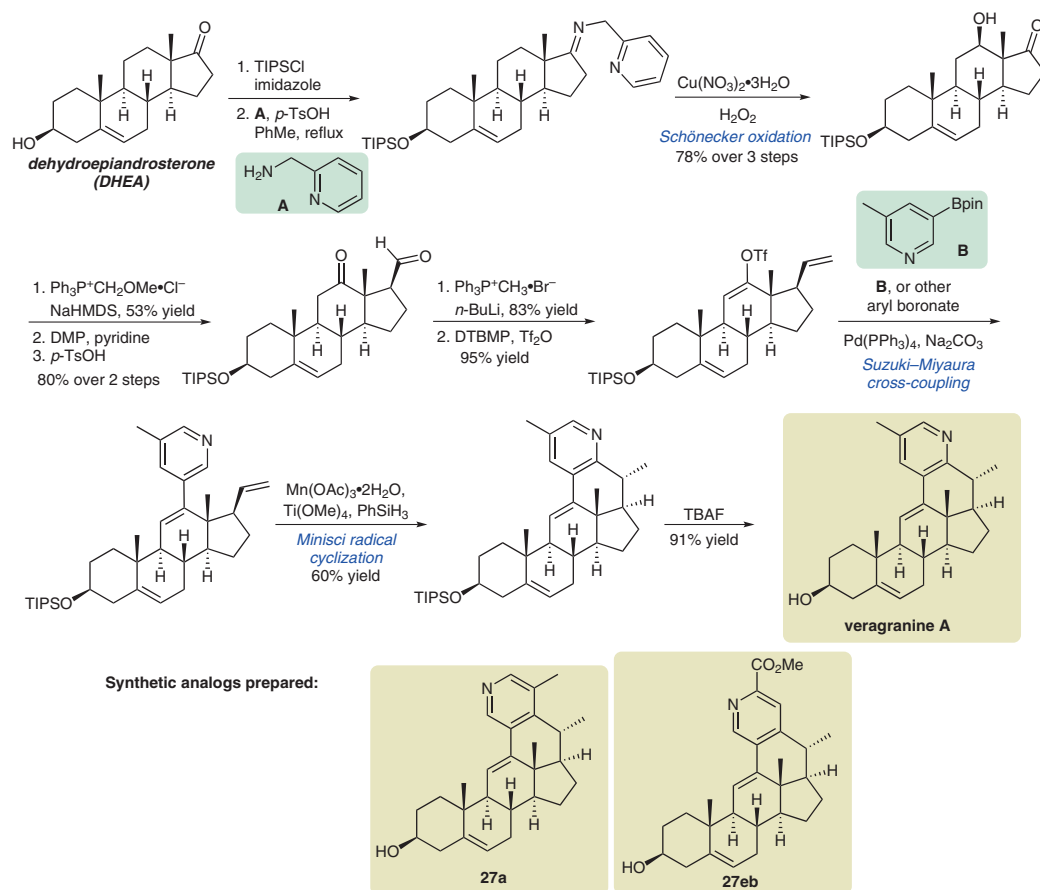
Key words

veragranine

voltage-gated
calcium channel

Minisci cyclization

Synfact
of the
Month



Significance: The veragranine alkaloids are a class of steroidal natural products isolated in 2022 from *Veratrum grandiflorum*, a flowering plant with a history of use in traditional medicine. Veragranine A has been shown to possess analgesic properties, likely due to its ability to block voltage-gated calcium channels ($\text{Ca}_v2.2 \text{ IC}_{50} = 45.76 \pm 1.14$). Khanna, Dai, and co-workers report the first laboratory preparation of veragranine A through a semisynthesis from commercially available dehydroepiandrosterone (DHEA). Additionally, the authors report the synthesis of a number of unnatural F-ring analogs, several of which possess similar analgesic activity to veragranine A.

Comment: Veragranine A was accessed in eleven steps from the commercially available steroid dehydroepiandrosterone (DHEA). Key steps include a *Schönecker oxidation* to functionalize the C12 position, a Suzuki–Miyaura cross-coupling reaction to install the pyridine F ring, and a Minisci-type radical cyclization to form the E ring. Use of different aryl boronates in the cross-coupling reaction allowed for the preparation of a small library of compounds. Two of these synthetic analogues, **27a** and **27eb**, demonstrated *in vivo* efficacy as calcium channel blockers.

SYNFACTS Contributors: Dirk Trauner, Daniel W. Zuschlag
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