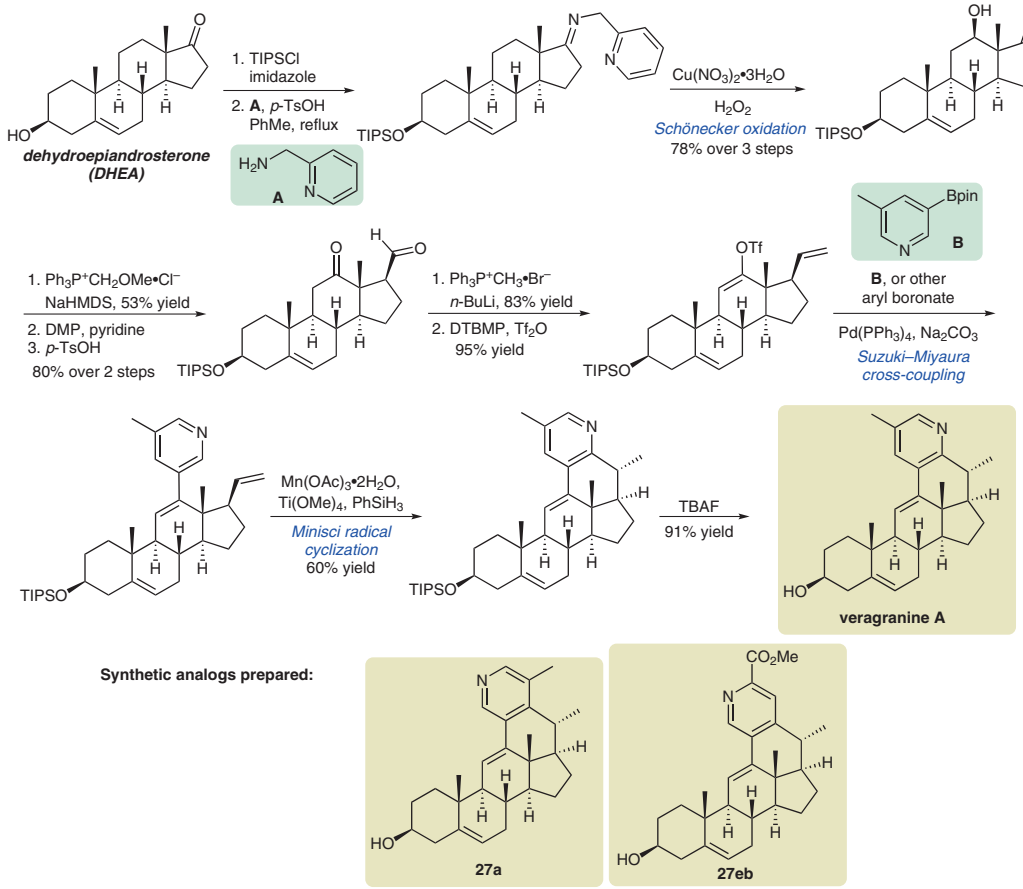
D. MA, P. DURAN, R. AL-AHMAD, S. HESTEHAVE, M. JOA, O. ALSBIEI, E. J. RODRÍGUEZ-PALMA, Y. LI, S. WANG, R. KHANNA, M. DAI* (UNIVERSITY OF FLORIDA, GAINESVILLE AND EMORY UNIVERSITY, ATLANTA, USA)

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

J. Am. Chem. Soc. **2024**, *146*, 16698–16705, DOI: 10.1021/jacs.4c04025.

Synthesis and Medicinal Chemistry of Veragranine Alkaloids



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 ($Ca_v2.2$ IC_{50} = 45.76 ± 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
Synfacts 2024, 20(09), 0979 Published online: 16.08.2024
DOI: 10.1055/s-0043-1775291; **Reg-No.:** T08524SF

Category

Innovative Drug Discovery and Development

Key words

veragranine

voltage-gated calcium channel

Minisci cyclization

Synfact of the Month