(+)-resiniferatoxin**daphnane
diterpenoid****[5+2]-oxidopyrylium
cycloaddition****zirconocene-
mediated cyclization****Achmatowicz
reaction****orthoester
formation**Synfact
ClassicP. A. WENDER*, C. D. JESUDASON, H. NAKAHIRA, N. TAMURA, A. L. TEBBE, Y. UENO
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The First Synthesis of a Daphnane Diterpene: The Enantiocontrolled Total Synthesis of (+)-Resiniferatoxin

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The First Total Synthesis of (+)-Resiniferatoxin

Significance: In 1997, Wender and co-workers reported the first total synthesis of (+)-resiniferatoxin, a daphnane diterpenoid isolated from spurge *Euphorbia resinifera*. Mediated by TRPV1, it exhibits analgesic potencies 10³ to 10⁵ greater than capsaicin. It also has a score of 16 billion on the Scoville scale.

Comment: In their seminal work, the authors employed a [5+2]-oxidopyrylium cycloaddition to generate a [6,7]-scaffold. **C** was further elaborated by Cp₂ZrBu₂-mediated cyclization and reductive iodoether fragmentation en route to the target, which was completed in a total of 45 steps.

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