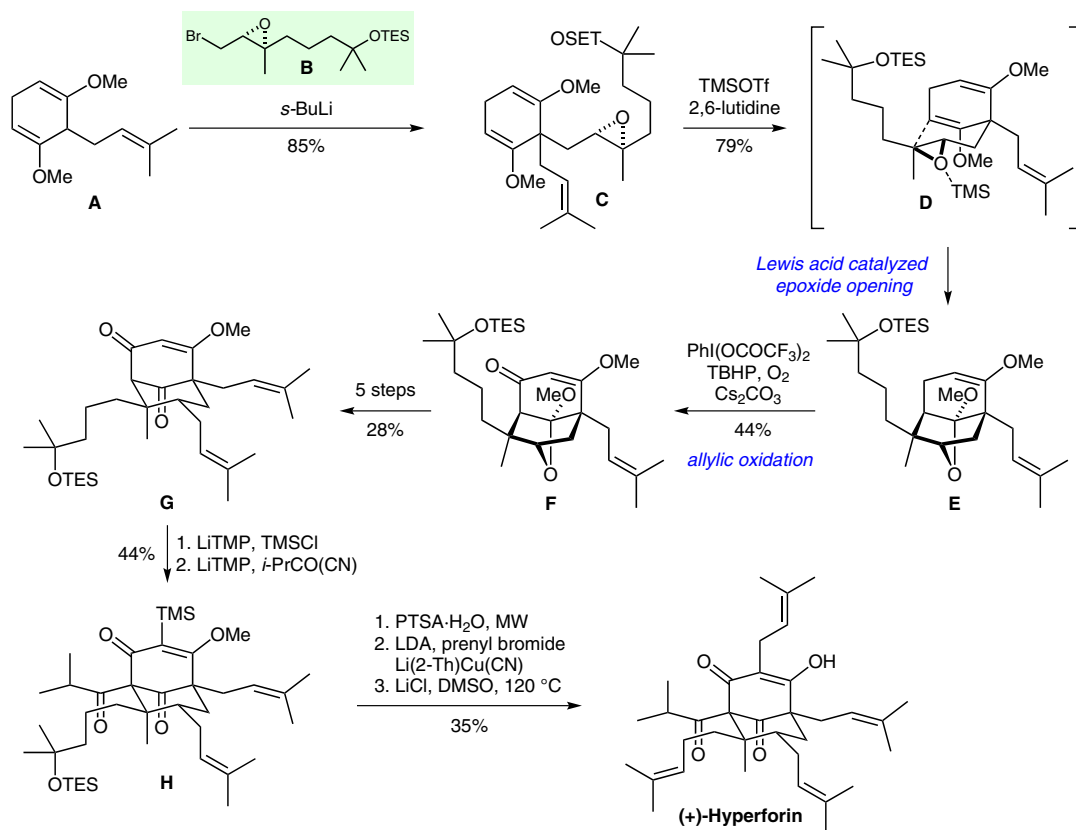


B. A. SPARLING, D. C. MOEBIUS, M. D. SHAIR* (HARVARD UNIVERSITY, CAMBRIDGE, USA)

Enantioselective Total Synthesis of Hyperforin

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Total Synthesis of (+)-Hyperforin



Significance: Hyperforin, a constituent of *St. John's wort*, is a member of the polycyclic poly-prenylated acylphloroglucinol natural product family. Its well-studied antidepressant activity, along with the structural complexity, renders it an attractive target for total synthesis. To date, only one total synthesis has been reported with an overall length of 51 steps (*Angew. Chem. Int. Ed.* **2010**, *49*, 1103; *Synfacts* **2010**, 510). This synthesis by Shair and co-workers is significantly shorter, utilizing an epoxide-opening cyclization to set four stereocenters in one step, thus affording (+)-hyperforin in only 18 steps.

Comment: Intramolecular Lewis acid mediated opening of epoxide **C** by only one of the diastereotopic enol ethers furnished the key bicyclo-[3.3.1]nonane core as the methyl ketal **E**. In this impressive display of stereocontrol, four stereocenters, including two quaternary ones, were set in good yield from an enantiopure epoxide. The subsequent allylic oxidation proceeded in a highly chemoselective fashion to furnish ketone **F** which was then transformed into (+)-hyperforin in ten further steps.

SYNFACTS Contributors: Erick M. Carreira, Simon Breitler
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