Category

Innovative Drug Discovery and Development

Key words

total synthesis

neurotrophic natural products

structure–activity relationship

quaternary center-guided synthesis

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Total Synthesis of (±)-Jiadifenin and Studies Directed to Understanding Its SAR: Probing Mechanistic and Stereochemical Issues in Palladium-Mediated Allylation of Enolate-Like Structures

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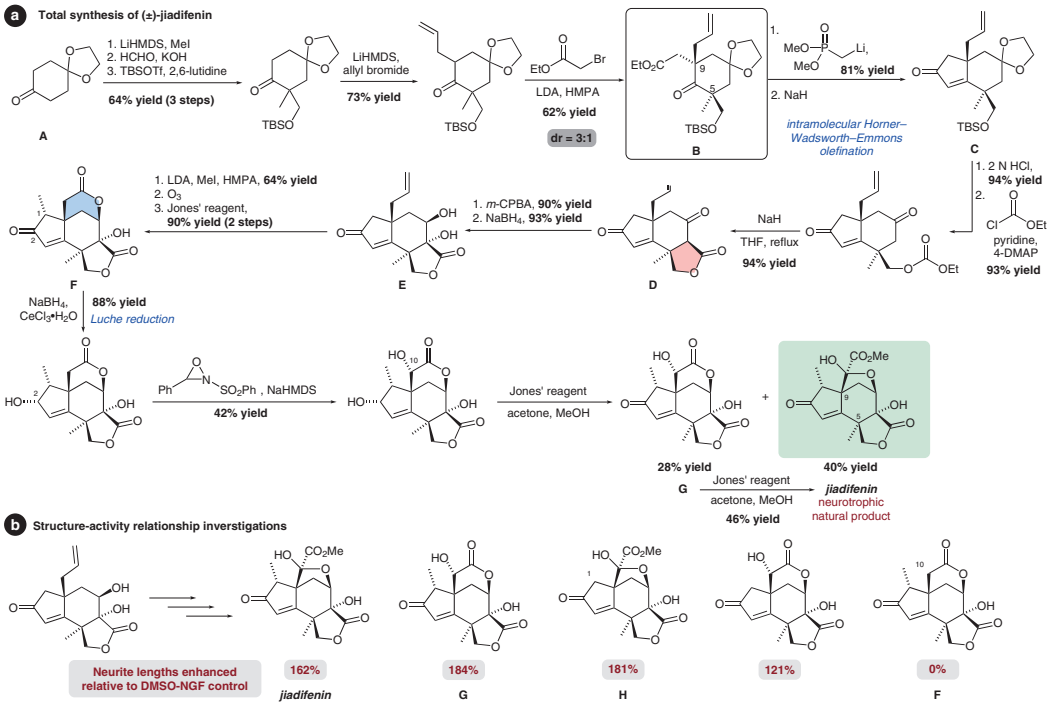
Total Synthesis and SAR Studies of the Neurotrophic Sesquiterpenoid Jiadifenin



Significance: The natural product jiadifenin belongs to the family of the *Illicium* sequiterpenoids, which have attracted a considerable amount of attention due to their potent neurotrophic properties. Following their 2004 publication on the first total synthesis of jiadifenin (*J. Am. Chem. Soc.* **2004**, *126*, 14358), the Danishefsky group published an extended study including investigations on the structure–activity relationship of the neurotrophic sesquiterpenoid, as well as the development of a more efficient route to a core intermediate via palladium-mediated allylation. This works not only is a landmark in organic synthesis that demonstrated the capability of the science at the time to efficiently assemble highly oxidized, complex structures, but also allowed for a first insight into which structural features of the *Illicium* sesquiterpenoids are crucial for the natural products to exert their neurotrophic activity. This work is therefore one of the cornerstones of research on these natural products.

Comment: The Danishefsky group's synthesis evolves around the early construction of the central six-membered carbocycle of jiadifenin with the two crucial C5 and C9 quaternary centers (**a**). Starting from **A**, a series of alkylations and an aldol reaction with formaldehyde lead to core intermediate **B**, featuring these structural elements. The functionality surrounding the quaternary centers was subsequently used to guide the construction of the remaining rings of the natural product. Key reactions are an intramolecular HWE olefination to build up cyclopentenone **C**, an intramolecular α-acylation to form γ-lactone **D**, and construction of the δ-lactone ring in **F** via oxidative double-bond cleavage. Further redox transformations completed the synthesis of jiadifenin and its direct precursor **G**. The route allowed access to a set of related structures (**b**). Evaluation of their bioactivity showed that **G** and demethyl-jiadifenin **H** were more potent than the natural product itself.

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