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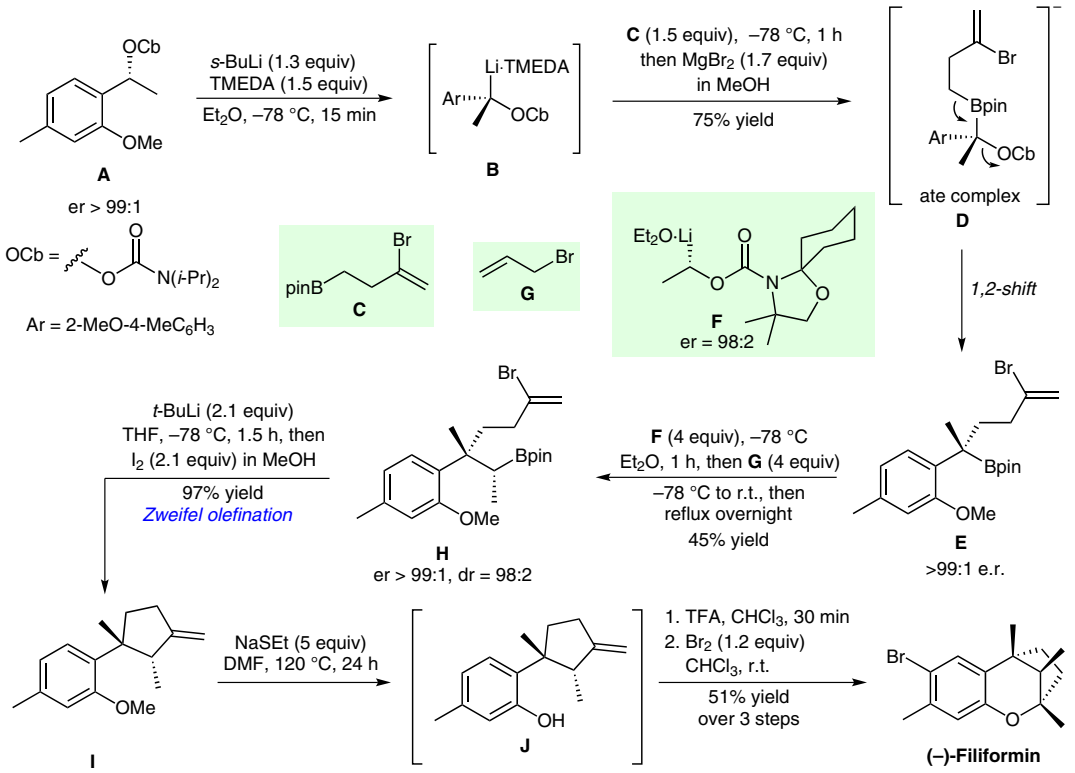
Stereocontrolled Synthesis of Adjacent Acyclic Quaternary-Tertiary Motifs: Application to a Concise Total Synthesis of (–)-Filiformin

Angew. Chem. Int. Ed. **2014**, *53*, 5552–5555.

Total Synthesis of (–)-Filiformin



Significance: Aggarwal and co-workers report an enantioselective synthesis of the sesquiterpene natural product filiformin. Their elegant strategy relies on the lithiation–borylation methodology specifically developed by the group to install the vicinal quaternary and tertiary stereocenters with full control of absolute and relative stereochemistry. The work underscores the power of the lithiation–borylation methodology in asymmetric synthesis and has resulted in the shortest enantioselective synthesis of filiformin reported to date.

Comment: Lithiation of carbamate **A** gives chiral carbenoid **B**, which is reacted with boronic ester **C** to give ate complex **D**. 1,2-Metallate rearrangement of **D** then affords homologated product **E**. A second homologation, this time using chiral carbenoid **F** and tertiary boronic ester **E**, gives **H** with essentially perfect enantio- and diastereoselectivity. Key to the success of this challenging homologation is the use of diamine-free carbenoid **F** and the addition of allylbromide **G** to quench any benzylic carbanion formed during the 1,2-rearrangement. An intramolecular Zweifel-type olefination furnishes cyclopentene **I** in excellent yield. Cleavage of the aryl methyl ether, acid-catalyzed cyclization, and bromination complete the synthesis of the natural product.

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Synfacts 2014, 10(7), 0667 Published online: 16.06.2014
DOI: 10.1055/s-0033-1339161; **Reg-No.:** C03314SF

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Category

Synthesis of Natural Products and Potential Drugs

Key words

filiformin

quaternary stereocenter

stereodivergence

acyclic stereocontrol

Zweifel olefination

lithiation–borylation

chiral carbenoids

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