Total Synthesis of Neurotrophic Factor 11-O-debenzoyltashironin

Neurotrophic factors are responsible for the growth, maintenance and survival of neurons. They may be key in treating neurodegenerative diseases such as Alzheimer’s and Parkinson’s. However, human neurotrophic factors suffer problems of pharmacokinetics and bioavailability when used as a drug. Nonpeptidyl small molecule neurotrophic factor mimetics have the potential of avoiding these pitfalls. While they still feature neurotrophic activity, they may also be orally bioavailable, blood-brain barrier permeable, and more specific in their target receptor activation. This technology presents the total synthesis of one such small molecule, 11-O-debenzoyltashironin. Naturally obtained from the methanol extract of the pericarps of Illicium merrillianum, an Asian plant related to star anise, 11-O-debenzoyltashironin promotes neurite outgrowth in fetal rat cortical neurons at concentrations as low as 0.1 - 10 μM. Because of the extremely low yield of 11-O-debenzoyltashironin from natural sources, its total synthesis is essential to proceed with further biological studies.

Method for the total synthesis of nonpeptidyl small molecule

11-O-debenzoyltashironin is a tetracyclic sesquiterpene consisting of a [2,2,2]-bicyclic core, a cyclopentane ring, and a five-membered acetal. It has two tertiary methyl groups, one secondary methyl group, two hydroxyl groups, a ketone group, and six stereogenic bridgehead centers anchoring the faces together. The key substrate, transformed from commercially available vanillyl alcohol, can be either a tetrasubstituted enol ether to yield all four rings or a terminal alkyn to yield the bicyclic core and cyclopentane ring. If only those three rings are formed, then the 5-membered acetal is closed afterwards.

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Applications:
• Further biological studies
• Neutrotrophic activity
• Growing neurons from stem cells
Advantages:

• First total synthesis
• Synthesized from commercially available molecules
• No isolation from plants necessary

Patent information:

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Related Publications:

• Cook SP, Polara A, Danishefsky SJ. “The Total Synthesis of (+/-)-11-O-Debenzoyltashironin” JACS, 2006;128:16440-16441.

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