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Enantioselective Synthesis of (–)-Jiadifenin, a Potent Neurotrophic Modulator

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Abstract

The first enantioselective synthesis of (–)-jiadifenin (**1**), a potent neurite outgrowth promoter isolated from *Illicium* species, is described. The synthetic strategy builds upon bicyclic motif **6** that represents the AB ring of the natural product and proceeds in 19 steps and 1.1% overall yield. Key to our approach is a Mn(III)-mediated oxidation reaction of A ring that, following a regio- and diastereoselective α -hydroxylation and methylation sequence, produces the desired functionalities of (–)-jiadifenin. The effect of synthetic **1** in NGF-mediated neurite outgrowth was also measured in PC-12 cells.

Nerve growth factor (NGF) and related members of the neurotrophin family of proteins are essential for the survival and differentiation of sensory and sympathetic neurons.¹ Studies over past decades have demonstrated the great therapeutic potential in using NGF to prevent, slow down, or even reverse the progression of neurodegenerative disorders, including Alzheimer's and Parkinson's disease.² Like many polypeptides, NGF is rapidly degraded in the body and is incapable of crossing the blood-brain barrier. Its poor pharmacokinetic profile has prompted the scientific community to explore alternative therapeutic strategies based on small molecules that can mimic neurotrophins, promote their biosynthesis or regulate their cellular signaling.

In 2002, Fukuyama and co-workers reported the isolation of a novel seco-prezizaane-type sesquiterpene, jiadifenin (**1**) (Figure 1), from *Illicium jiadifengpi*.³ Initial evaluation of its biological profile showed that **1** promotes significant neurite outgrowth in primary cultures of fetal rat cortical neurons in concentrations as low as 0.1 μ M. More recently, from the same plant species the Fukuyama group isolated jiadifenolide (**2**), another structurally related and more potent neurotrophic agent.⁴ Their complex fused-ring system, along with

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Supporting Information Available: Experimental procedures and characterization data of key intermediates. This material is available free of charge via the Internet at <http://pubs.acs.org>.

their significant therapeutic potential, provide very intriguing and challenging targets. Synthetic studies toward these compounds⁵ culminated a racemic synthesis of jiadifenin by the Danishefsky group.⁶ These efforts also allowed preliminary SAR studies that highlighted clearly the medicinal value of this family of small molecules.

We have recently reported the first enantioselective synthesis of jiadifenolide (**2**).⁷ Our strategy offers the opportunity to diversify our chemistry towards other members of this family. Herein, we report the first enantioselective synthesis of jiadifenin (**1**).

Scheme 1 illustrates the retrosynthetic analysis towards (–)-jiadifenin. The target molecule was envisioned to ultimately arise from oxidation and hemiacetalization of **3**. A sequential diastereoselective C-10 α -hydroxylation and C-1 methylation could be used to install the desired functional groups on the jiadifenin framework. Moreover, the A ring of **3** was projected to arise from selective manipulation at the C-1 and C-2 centers of motif **4**. In turn, **4** could be formed from tricyclic structure **5**,⁷ via a sequence that includes oxidative cleavage of the terminal alkene, regio- and diastereoselective epoxide formation and acid-induced “6-exo-tet” epoxide opening thus constructing the D ring lactone. Access to **5** would be accomplished from “Hajos-Parrish-like”^{7, 8} diketone **6**,⁹ via a sequential Stiles carboxylation¹⁰ and installation of the quaternary methyl moiety, followed by a Pd(0)-mediated carbomethoxylation¹¹ and TFA-assisted C ring formation. Lastly, diketone **6** would be produced via an asymmetric Robinson annulation¹² using compounds **7** and **8** as starting materials.

The synthetic effort departed from lactone **4** that was enantioselectively and efficiently synthesized from diketone **6** in 13 steps with a 15% overall yield (> 90% ee¹³, Scheme 2). With an abundant amount of **4** in hand (> 3 grams), the elimination of C-1 hydroxyl moiety became the first challenge. Various trials of the C-1 alcohol deoxygenation under standard or modified Barton-McCombie conditions¹⁴ proved unsuccessful. Moreover, mesylation of **4** followed by treatment with a variety of bases failed to produce the corresponding alkene **9**. The dehydration proceeded smoothly using Martin sulfurane¹⁵ and the derived crude diene **9** was hydrogenated selectively at the C-1-C-2 centers with H₂(1 atm)/Pd/C to produce compound **10** (72% yield over 2 steps).

The ensuing allylic oxidation at the C-2 position of **10** proved to be difficult, presumably due to the sensitive 6-membered lactone moiety. Several standard or modified conditions were evaluated, including SeO₂,¹⁶ CrO₃/TBHP,¹⁷ PDC/TBHP,¹⁸ PhI(OAc)₂/TBHP,¹⁹ Pd(O₂CCF₃)₂/BQ²⁰ and Rh₂(cap)₄/TBHP,²¹ but none of them could yield a satisfactory result. Gratifyingly, Mn(III) acetate/TBHP^{22,23} produced traces of **11** after 72 hours at ambient temperature. To avoid side reactions and accelerate the desired transformation, the reaction temperature was then raised to 40 °C, which significantly improved the yield to 65% and shortened the reaction time to 16 hours. With **11** in hand, we attempted to methylate the C-1 center. We hypothesized that this reaction would install the methyl group α - to the enone in a chemoselective fashion. To our surprise, lithiation (LDA) and methylation of **11** with 1.2 equiv of MeI afforded the C-10 methylated adduct **12**. The C-1 position could be methylated only upon excess amount of MeI, producing the dimethylated product **13** together with **12**. The structures of compounds **12** and **13** were unambiguously confirmed via single crystal X ray analysis (Scheme 2).²⁴ Other related alkylation attempts gave us similar or worse results.

Based on these observations, it became obvious that the C-10 center is more sterically accessible than the C-1 position. Thus, an alternative sequence for the A-ring functionalization was developed. Treating **11** with NaHMDS and quenching of the C-11 enolate with Davis oxaziridine²⁵ (1 equiv) produced α -hydroxylated lactone **14** as a single

diastereomer in 61% yield. Alkylation of **14** with LDA/MeI/HMPA furnished the desired C-1 methylated product **3** with the desired stereochemistry. Without extensive purification, alcohol **3** was oxidized and rearranged under Jones conditions⁶ giving rise, after methanolic work up, to (–)-jiadifenin (**1**) as the major product in 45% yield (C-10 anomeric mixture, major anomer : minor anomer $\approx$ 2.5 : 1). Synthetic jiadifenin was found to have identical spectroscopic and analytical properties (¹H-NMR, ¹³C-NMR, HRMS) and similar optical rotation values (measured: $[\alpha]^{24}_{\text{D}} -123.8$ (c 0.17, EtOH), literature³: $[\alpha]^{22}_{\text{D}} -152.9$ (c 0.24, EtOH)).

Validation of the biological profile of synthetic (–)-jiadifenin (**1**) with regard to the stimulation of NGF-mediated neurite outgrowth was carried out using a PC-12 cellular assay.^{6a,26} As shown in Figure 2, a significant increase of neuronal differentiation could be observed upon 72 hours of incubation with NGF (50 ng/mL) and **1** (0.3 and 0.5 μM). Specifically, jiadifenin at 0.3 μM induced 21% of neurite bearing cells compared to 12% found in the control containing only NGF and DMSO (Figure 3A). A 28% of neurite bearing cells was observed at 0.5 μM of **1** (Figure 3A). In terms of total neurite outgrowth, the neurite lengths enhanced by **1**, at 0.3 μM and 0.5 μM , were 148% ($p < 0.001$) and 172% ($p < 0.001$) respectively, compared to the DMSO+NGF control (Figure 3B). It should be noted that no neurite outgrowth was observed in the absence of NGF,²⁷ in agreement with previous findings.^{6a}

In summary, we describe here an efficient and enantioselective approach to (–)-jiadifenin (**1**), a potent promoter of neurite outgrowth. This approach departs from readily available diketone **6** and proceeds in 19 steps and 1.1% overall yield. In addition, we have shown that synthetic jiadifenin induces significant neurite outgrowth in PC-12 cells in the presence of NGF. Along these lines, our strategy paves the way for the synthesis of several natural products of this family²⁸ and designed analogs thereof that could shine light into the unexplored biological mode of action of these compounds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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1: jiadifenin

2: jiadifenolide

Figure 1.
Structures of jiadifenin (1) and jiadifenolide (2)

Figure 2. Images of neurons after 72 hours treatment with (A) DMSO (1% v/v) + NGF (50 ng/mL), (B) compound **1** (0.3 μ M) + DMSO + NGF, and (C) compound **1** (0.5 μ M) + DMSO + NGF.

Figure 3.

NGF-enhancement in the PC-12 assay for 72 hours. **(A)** Percentage of cells with longer processes than two cell body lengths; and **(B)** total neurite outgrowth length. Values are reported as means $\pm$ SE of triplicate experiments: * $P < 0.03$, ** $P < 0.01$, *** $P < 0.001$.

Scheme 1.
Retrosynthetic analysis of (-)-jiadifenin

Scheme 2.
Synthesis of **11**

Scheme 3.
Completion of the synthesis of (-)-jiadifenin