Abstract: As a potent neurotrophic agent, the sesquiterpenoid jiadifenolide represents a valuable small-molecule lead for the potential therapeutic treatment of neurodegenerative diseases. A stereocontrolled total synthesis of this densely functionalized natural product is reported, central to which is an adventurous samarium-mediated cyclization reaction to establish the tricyclic core and the adjacent C5 and C6 quaternary stereocenters.

Jiadifenolide (1, Scheme 1) is an architecturally complex sesquiterpenoid first isolated from the pericarps of the Chinese plant *Illicium jiadifenpi* by Fukuyama and co-workers in 2009. Preliminary biological investigation revealed potent neurotrophic activity, promoting neurite outgrowth in primary cultured rat cortical neurons at concentrations as low as 10 nM. Given the important regulatory role of neurotrophins in the central nervous system, jiadifenolide represents a valuable small-molecule lead for the potential therapeutic treatment of neurodegenerative conditions such as Alzheimer’s disease. Its low natural abundance (1.5 mg kg⁻¹ plant material) makes total synthesis of particular importance for the preparation of sufficient quantities for further biological evaluation and to enable access to a range of analogues for structure–activity relationship (SAR) profiling.

Our interest in jiadifenolide derives not only from its potent bioactivity, but also from its complex *seco*-prezizaane skeleton, placing it amongst the *Illicium* family of sesquiterpenoids, which has garnered substantial synthetic attention. Jiadifenolide’s intricate and densely functionalized caged pentacyclic structure (1) comprises four rings emanating from a central, highly substituted B-ring cyclohexane. This poses particular synthetic challenges, most notably the controlled introduction of five contiguous quaternary stereocenters, which we aimed to address as part of a concise and efficient total synthesis, following that first reported by Theodorakis in 2011 and most recently by Sorensen (2014).

Our conceptually unique synthetic solution sought to forge the central B-ring from a functionalized A,C-ring precursor. As outlined retrosynthetically in Scheme 1, we envisaged late-stage unveiling the D- and E-rings through oxidation of the C13-pendant vinyl group of ABC-tricycle 2. A critical transformation would thus be the reductive cyclization of keto-butenolide 3 to establish the central B-ring and the adjacent C5 and C6 quaternary stereocenters in a single operation. Cyclization substrate 3 would be prepared through aldol coupling of butenolide 5 with aldehyde 4. Notably, a single C5 stereocenter would template for all remaining stereochemistry under substrate-based control.

The preparation of aldehyde 4 commenced with Luche reduction of cyclopentenone 6 (Scheme 2). The ensuing allylic alcohol then underwent hydroxy-directed epoxidation with m-CPBA and TBS protection to deliver epoxide 7 in 65% yield over the three steps. The C2 methyl-bearing stereocenter was then established through Lewis-acid mediated rearrangement of 7 to selectively deliver the 2,5-syn-configured cyclopentanone 8 (78%, 19:1 d.r.). Horner–Wadsworth–Emmons (HWE) homologation of 8 (73%, >19:1 E,Z) followed by reduction and acylation of 10 then smoothly delivered allylic acetate 11 in readiness for an Ireland–Claisen rearrangement to install the key C13 quaternary stereocenter.

In the event, heating the corresponding TBS ketene acetal (LDA, TBSCI) in anhydrous benzene led...
to the selective (10:1 d.r.) formation of a mixture of rearranged products arising from preferential reaction at the less hindered alkene z-face. This material was subjected directly to reduction with LiAlH₄ to deliver alcohol 12 in 63% yield from 11. Finally, hydrolysis of the TBS ether and double oxidation under Swern conditions gave the targeted aldehyde 4 in 74% yield (13% overall from 6).

Initial approaches at appending the C-ring butenolide through addition of 3-metallated furyl derivatives to 4 all met with failure, with optimally only trace amounts of adducts observed. By contrast (Scheme 3), it was found that addition of 3-chloroperoxybenzoic acid, DMAP = N,N-dimethyl-4-aminopyridine.

Figure 1. a) X-ray crystal structure of alcohol 17. b) Possible samarium-chelate transition structure leading to 16.

TES ethers 15 and 11-epi-15 as alternative substrates, which were chromatographically separable. Now, gratifyingly, it was found that addition of 15 to a freshly prepared solution of SmI₂ (ca. 6 equiv) in THF and heating to 65°C led to the generation of a single cycladduct (51%), identified as 16 on the basis of NMR and computational analysis. More rigorous structural proof was subsequently obtained through X-ray crystallographic analysis of alcohol 17, formed upon acid-mediated desilylation of 16 (Figure 1a).

Subsequent oxidation with PCC then delivered the targeted ABC-ketone 2 (81%) along with diol 18 (11%), containing the requisite oxygenation at C10. Attempts to encourage complete oxidation to 18 were unsuccessful however.

The desired stereochemical outcome of the SmI₂-mediated reductive cyclization reaction of 15 is consistent with a chelated boat-type transition structure such as 19 (Figure 1b), in which the C11 substituent is equatorially disposed.

This may explain the failure of the epimeric C11
TMS ether (natural configuration, pseudo-axially disposed) to undergo analogous cyclization, attesting, along with failed substrates 13 and 14, to the challenge of this adventurous transformation.

With the requisite carbon skeleton of jiadifenolide secured, completion of the total synthesis was accomplished through controlled oxygenation at C10, C11, C14, and C15, with attendant cyclization to form the D-rings (Scheme 4). Accordingly, chemoselective dihydroxylation (OsO4, NMO) of the TMS-enol ether of 2 (TMSOTf, Et3N), cleanly provided the C10 tertiary alcohol (18, 99%). This was then utilized to set the adjacent C11 alcohol stereocenter through hydroxy-directed reduction with Me3NBH(OAc)2 (87%, >19:1 d.r.).[22] TES protection proved necessary to facilitate the subsequent unveiling of the D-rings (20, 96%). In the event, pyridine-accelerated dihydroxylation of the C13-pendant alkene of 20 provided a diol which then underwent smooth oxidative lactonization upon treatment with TPAP, NMO to form the E-ring (84%).[23] Finally, desilylation occurred with oxidative lactonization upon treatment with TPAP, NMO to scaffold for further biological evaluation and analogue asymmetric.[24] Work to prepare quantities of this valuable methyl-cyclopenten-1-ol should thus render this approach a single C5 alcohol stereocenter. Starting from known ([S]-3-methyl-cyclopenten-1-ol) should thus render this approach asymmetric.[25] Work to prepare quantities of this valuable scaffold for further biological evaluation and analogue synthesis[26] will be reported in due course.

Scheme 4. Total synthesis of jiadifenolide (1). Reagents and conditions: a) TMSOTf, Et3N, THF, −78 °C; b) OsO4, NMO, tBuOH/H2O, RT; 99% over 2 steps; c) Me3NBH(OAc)2, AcOH, MeCN, −20°C, 87%, >19:1 d.r.; d) TESCI, imid, DMF, RT, 96%; e) OsO4, NMO, py, tBuOH/H2O, RT; f) TPAP, NMO, 4 Å MS, CH2Cl2, RT, 84% over 2 steps; g) HF-py, THF, RT, 86%. NMO = N-methylmorpholine-N-oxide, TMS = trimethylsilyl, TPAP = tetrapropylammonium peruthenate.

In summary, we have completed the total synthesis of the neurotrophic agent jiadifenolide in 2.3% yield over 23 steps, including provision of synthetic (-)-jadifenolide (1, 86%), which exhibited spectral characteristics (1H/13C NMR, IR, HRMS) identical in all respects to that reported for the natural sample.[5]

In conclusion, we have completed the total synthesis of the neurotrophic agent jiadifenolide in 2.3% yield over 23 steps, showcasing a pivotal SmI2-mediated reductive cyclization reaction to establish the tricyclic core. Notably, the synthesis demonstrates a high degree of solely substrate-based stereocontrol to establish this densely functionalized structure, wherein the full relative configuration is templated for by a single C5 alcohol stereocenter. Starting from known (S)-3-methyl-cyclopenten-1-ol should thus render this approach asymmetric.[25] Work to prepare quantities of this valuable scaffold for further biological evaluation and analogue synthesis[26] will be reported in due course.

Keywords: cyclization · neurological agents · samarium · terpenoids · total synthesis


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[19] CCDC 993662 (17) and 993663 (2) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.


[21] Alternative chelated transition structures leading to the trans-A,B-fused product are expected to be of significantly higher energy due to incurred ring strain and steric interaction with the C13 vinyl group.

