Enantioselective Total Synthesis of (−)-Jiadifenolide**

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Neurotrophic factors (neurotrophins) are a family of proteins that regulate nervous system development and maintain adult nervous system plasticity and structural integrity.[3] Their ability to exhibit neuroprotective properties explains the interest they have received in the context of acute nervous system injury or for the treatment of chronic neurodegenerative diseases. Unfortunately, as a result of their chemical structure, these proteins cannot persist in the body for an extended period and also cannot cross the brain–blood barrier. In contrast, small molecules that are able to mimic extended period and also cannot cross the brain–blood barrier. In contrast, small molecules that are able to mimic neurotrophic factors, or to induce neurotrophic factor bioavailability, possess a distinct pharmacological advantage and have received in the context of acute nervous system plasticity and structural integrity.[1] Their ability to exhibit neuroprotective properties explains the interest they have received in the context of acute nervous system injury or for the treatment of chronic neurodegenerative diseases. Unfortunately, as a result of their chemical structure, these compounds belong to a family of species with potent neuropharmacological activities.

In the search of new small molecules with neurotrophic modulatory properties, Fukuyama and co-workers isolated three novel pentacyclic sesquiterpenoids, (-)-jiadifenolide (1) and jiadifenoxolanes A (2) and B (3) from the pericarps of *Illicium jiadifengpi* (Figure 1).[3] Among them, 1 and 2 have shown potent activities in promoting neurite outgrowth in primary cultured rat cortical neurons at concentrations as low as 10 nm and 1 μm, respectively. From the standpoint of the chemical structure, these compounds belong to a family of caged seco-prezizaanes that also includes neomajucin (4),[4] anisatin (5),[5] and jiadifenin (6).[6] The combination of a challenging caged-like motif and intriguing biological properties has invited the development of efficient strategies toward their chemical syntheses[7,8] culminating in a racemic synthesis of 6 by the Danishefsky group.[9] Herein, we report the first total synthesis of (–)-jiadifenolide (1), one of the most structurally challenging and biologically potent caged seco-prezizaanes. Our strategy proceeds in an enantioselective manner and can be used to explore and enhance the biological and pharmacological activities of this family.

Scheme 1 highlights the overall retrosynthetic strategy toward (–)-jiadifenolide (1). Key to the synthesis was a remarkable oxidative conversion of the lactone 9 into tetracyclic motif 8 that installed the desired E ring. In the forward direction, compound 8 could be further functionalized on the A ring to produce 7 and, after C10 oxidation and hemiacetalization, could give rise to 1. In contrast, the carbon framework of 9 can be traced to the tricyclic motif 10. Further disconnection across the C ring of 10 suggests the Hajos–Parrish-like diketone 11 as an appropriate synthetic precursor that is available in high enantiomeric purity.[10,11]

Our synthetic approach began with the commercially available diketone 12 that was converted into compound 13[12] in two steps and 63% yield (Scheme 2). The D-prolinamide/PPTS-catalyzed[12] and optimized asymmetric aldol condensation of 13 produced the optically enriched diketone 11 in 74% yield (> 90% ee). Regio- and stereoselective reduction of the more electrophilic C1-carbonyl group of 11 and subsequent selective silylation of the resulting alcohol using NH4NO3/TBSCl conditions[11d,13] produced compound 14 (2 steps, 92% yield). Conversion of 14 into 15 was accomplished through a sequence of two steps: a) carboxylation of the C5 enolate with magnesium methyl carbonate[14] and subsequent trapping of the resulting carboxylic acid with Meerwein’s salt (Et3OBF4),[15] and b) formation of the extended TMS-enolate[16] with subsequent methylation under TBAF/MeI conditions. This sequence of reactions constructed the C5 quaternary center to deliver a single isomer.

**Figure 1.** Representative structures of natural products from *Illicium* species with potent neuropharmacological activities.
 Synthesis of ABC ring. Reagents and conditions: a) o-prolinamide (30 mol%), PPTS (30 mol%), MeCN, 40°C, 14 days, 74% (> 90% ee); b) NaBH₄, (0.25 equiv), EtOH, 0°C, 1 h; c) TBSOTf, NH₄NO₃, DMF, RT, 12 h, 92% for 2 steps; d) MMC, DMF, 130°C, 3 h, then Et₂O·BF₃·2·i-Pr·NEt, CH₂Cl₂, 0°C, 5 min; e) TMSOTf, 2.6-lutidine, CH₂Cl₂, 0°C to RT, 1 h; then TBAF (1.0 equiv), Mel, THF, −78°C to RT, 3 h, 43% for 2 steps; f) LiAlH₄, THF, 0°C to RT, 1 h; g) TBSCI, 1(M) equiv), imidazole, CH₂Cl₂, 0°C, 30 min; h) IBX, DMDSO, 80°C, 1 h, 85% for 3 steps; i) KHMDS, PhNTf₂, THF, −78°C, 1 h; j) CO (1 atm), (FtD(PPh₃)₃)₂ (1 mol%), MeOH, DMF, Et₃N, 50°C, 2 h, then TFA, CH₂Cl₂, RT, 5 h, 69% for 2 steps. DMF = N,N-dimethylformamide, DMDSO = dimethyl sulfoxide, HMDS = hexamethyldisilazane, IBX = 2-iodoxybenzoic acid, MMC = magnesium methlyl carbonate, PPTS = pyridinium p-toluenesulfonate, TBAF = tetra-n-butylammonium fluoride, TFA = trifluoroacetic acid, THF = tetrahydrofuran, TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl.

Scheme 2. Synthesis of ABC ring. Reagents and conditions: a) o-prolinamide (30 mol%), PPTS (30 mol%), MeCN, 40°C, 14 days, 74% (> 90% ee); b) NaBH₄, (0.25 equiv), EtOH, 0°C, 1 h; c) TBSOTf, NH₄NO₃, DMF, RT, 12 h, 92% for 2 steps; d) MMC, DMF, 130°C, 3 h, then Et₂O·BF₃·2·i-Pr·NEt, CH₂Cl₂, 0°C, 5 min; e) TMSOTf, 2.6-lutidine, CH₂Cl₂, 0°C to RT, 1 h; then TBAF (1.0 equiv), Mel, THF, −78°C to RT, 3 h, 43% for 2 steps; f) LiAlH₄, THF, 0°C to RT, 1 h; g) TBSCI, 1(M) equiv), imidazole, CH₂Cl₂, 0°C, 30 min; h) IBX, DMDSO, 80°C, 1 h, 85% for 3 steps; i) KHMDS, PhNTf₂, THF, −78°C, 1 h; j) CO (1 atm), (FtD(PPh₃)₃)₂ (1 mol%), MeOH, DMF, Et₃N, 50°C, 2 h, then TFA, CH₂Cl₂, RT, 5 h, 69% for 2 steps. DMF = N,N-dimethylformamide, DMDSO = dimethyl sulfoxide, HMDS = hexamethyldisilazane, IBX = 2-iodoxybenzoic acid, MMC = magnesium methlyl carbonate, PPTS = pyridinium p-toluenesulfonate, TBAF = tetra-n-butylammonium fluoride, TFA = trifluoroacetic acid, THF = tetrahydrofuran, TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl.

in 43% overall yield. Global reduction of 15 with subsequent selective silylation of the primary alcohol and oxidation of the C6 secondary alcohol formed 16 in 85% yield. The C6-carbonyl group of 16 was then converted into the corresponding vinyl triflate that untraveled Pt⁴-catalyzed carbomethylation.⁹ TFA-mediated desilylation, and lactonization to form lactone 10 (69% for 2 steps).

The next task was to install the desired C6-C7 trans-diol functionality on the tricyclic motif 10. Along these lines, 10 was treated with NaOH/H₂O₂ to selectively and quantitatively produce epoxide 17 (Scheme 3). We projected that a Ru⁴⁺-based direct oxidative cleavage of the terminal alkene into the corresponding carboxylic acid would trigger a “6-exo-tet” epoxide opening⁵⁰ to furnish the desired lactone 9 in one pot. However, under all reaction conditions explored, this reaction led to decomposition of the starting material. Instead, we were pleased to find out that a stepwise sequence can achieve the desired conversion. The optimized approach involves oxidative cleavage of the terminal alkene to form the corresponding aldehyde under OsO₄ (cat.)/NaI0₄ conditions and subsequent Jones oxidation⁵¹ to produce the C11 carboxylic acid. Gratifyingly, these conditions triggered the desired “6-exo-tet” epoxide opening to produce lactone 9 in 70% overall yield. The structure of lactone 9 was unambiguously confirmed by single-crystal X-ray analysis.⁵² Notably, this compound represents the core structure of several natural products of the Illicium species and can be readily produced in multigram scale.

With compound 9 in hand, we sought to introduce a hydroxyl group at C4. To this end, removal of the C1 silyl ether produced compound 18. Epoxidation of the C3-C4 double bond, and subsequent treatment of the resulting epoxide with Dess–Martin periodinane gave rise to lactone 8 which contained the desired E ring (38%) for 2 steps. The structure of 8 was also confirmed by single-crystal X-ray analysis (Scheme 3).⁵³⁵⁴

A reasonable scenario for the remarkable conversion of 18 into 8 is presented in Scheme 4. Treatment of 18 with mCPBA produced epoxide 1 as a single isomer. We postulate that this epoxidation was promoted by the C1 homoallylic alcohol and occurred from the β face of the A ring of 18.⁵⁵ DMP treatment of 1 induces oxidation of the C1-hydroxy group to yield ketone II and generate acid in situ. The latter could further induce formation of the C2-C3 enone with concomitant generation of the C4 tertiary alcohol, which is axial and in close proximity to the C11-carbonyl group, thus triggering the desired trans lactonization. The driving force of this rearrangement may be due to the formation of a thermodynamically favored five-membered ring lactone.

With enone 8 in hand, we then focused on the final modification of the A ring (Scheme 5). The C2-C3 double
bond of 8 was hydrogenated under standard Pd/C-catalyzed conditions, and the C7 secondary alcohol was silylated using TESOTf to afford 19 (90% overall yield). Various methyleneation approaches were attempted to install the missing C15-carbon atom at C1. All these efforts (Wittig reaction, titanium[23] or zinc-based[23] reagents) were unsuccessful, presumably because of the steric hindrance of the C1-carbonyl group. Gratifyingly, an alternative strategy based on a Pd-mediated cross-coupling method was used to install the desired C15-carbon atom. To this end, selective conversion of the C1-carbonyl group of 19 into the corresponding vinyl triflate and subsequent treatment with excess AlMe3 under palladium catalysis[24] furnished compound 7 in 57% yield. Eventually, the C1–C2 double bond of 7 was selectively hydrogenated from the α face under 90 bar of H2 using PdO2 as the catalyst to form the corresponding C1–C15 equatorial methyl group. The remaining functionalization at C10 was performed using conditions employed by the Danishefsky group toward the synthesis of jiadifenin.[9] An α-hydroxylation using NaHMDS and the Davis oxaziridine[25] produced the α-hydroxy lactone 20 as a single isomer. Without extensive purification, compound 20 was oxidized under Jones conditions and concomitant desilylation of the C7 silyl ether to produce (–)-jiadifenolide (1, 33% over 3 steps). The synthetic material, thus obtained, possessed identical spectral and analytical properties to those reported for the natural product.[3] The absolute stereochemistry of 1 was confirmed by copper-radiation X-ray analysis,[24] which was in agreement with the original assignment.[3]

In conclusion, we have accomplished the first total synthesis of (–)-jiadifenolide in 1.5% overall yield (25 steps in total) from the commercially available cyclopentanone 1,3-dione (12). Key to the strategy is an acid-induced cascade reaction[26] that forms the E ring lactone of 1. The C and A rings of 1 were produced through a Pd-catalyzed carboxylic esterification and a Pd-mediated methylation, respectively. The overall approach is enantioselective, efficient, and suitable for scale-up. Importantly, the tetracyclic lactone 9 can be readily available and represents a significant scaffold for the synthesis of related natural products and analogues. Synthesis and methodological biological evaluation of such molecules could lead to the identification of more potent and selective neurotrophic molecules for medicinal applications.

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[20] CCDC 807620 (9), 807621 (8), and 807950 (1) 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.


