Natural Products

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Enantioselective Total Synthesis of (−)-Jiadifenolide**

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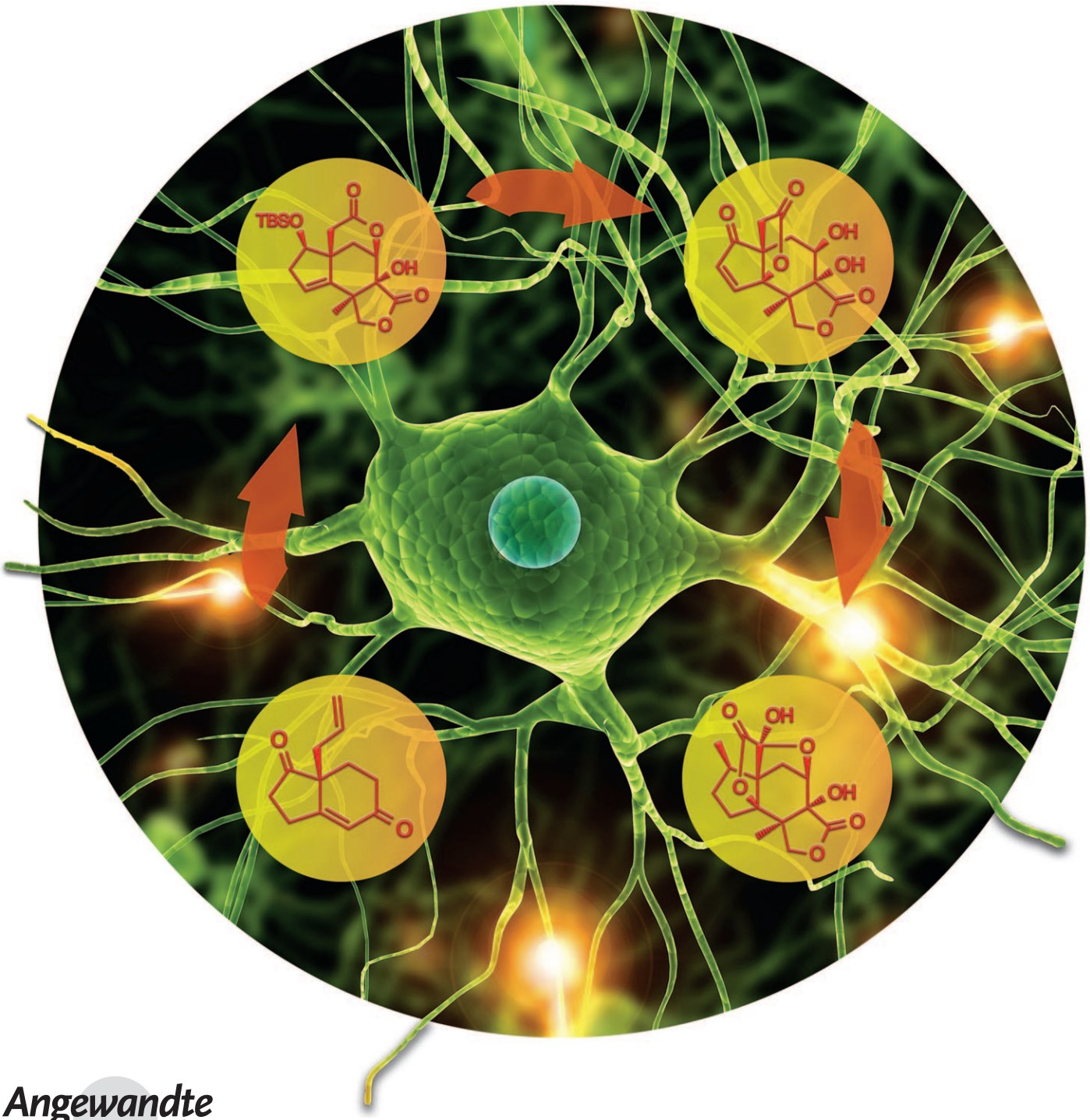


Neurotrophic factors (neurotrophins) are a family of proteins that regulate nervous system development and maintain adult nervous system plasticity and structural integrity.[1] Their ability to exhibit neuroprotective properties explains the interest they have received in the context of acute nervous system injury or for the treatment of chronic neurodegenerative diseases. Unfortunately, as a result of their chemical structure, these 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 neurotrophic factors, or to induce neurotrophic factor biosynthesis, possess a distinct pharmacological advantage and provide an attractive starting point for the development of medicines against various neurodegenerative disorders, including Alzheimer's and Parkinson's disease.[1,2]

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

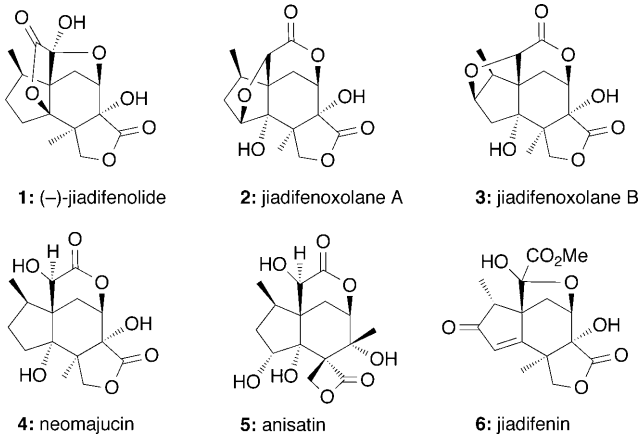
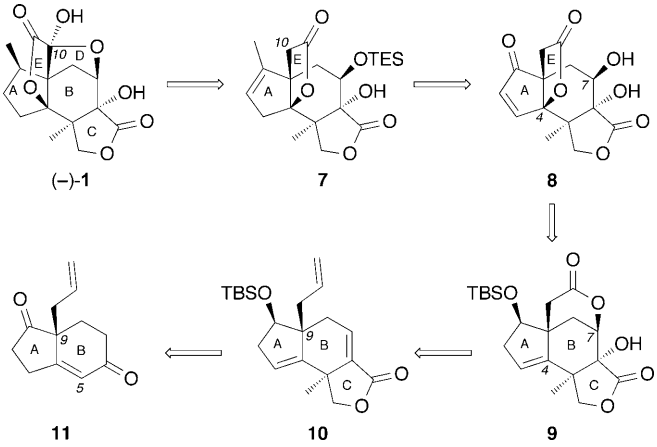


Figure 1. Representative structures of natural products from *Illicium* species with potent neuropharmacological activities.

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



Scheme 1. Retrosynthetic strategy toward **1**. TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl.

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[10c] 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[12c] 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 NH_4NO_3/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 ($Et_3O^+BF_4^-$);[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

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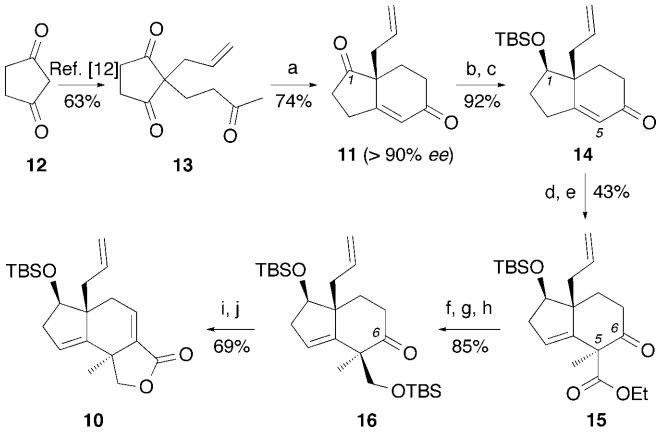
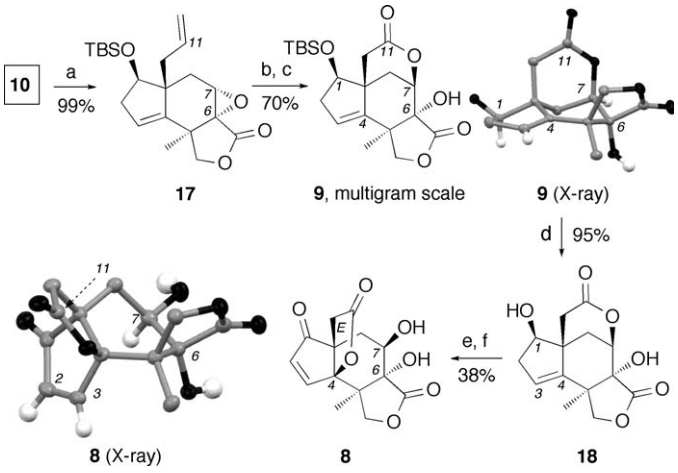


Scheme 2. Synthesis of ABC ring. Reagents and conditions: a) D-prolinamide (30 mol%), PPTS (30 mol%), MeCN, 40°C, 14 days, 74% (>90% *ee*); b) $NaBH_4$ (0.25 equiv), EtOH, 0°C, 1 h; c) TBSCl, NH_4NO_3, DMF, RT, 12 h, 92% for 2 steps; d) MMC, DMF, 130°C, 3 h, then $Et_3O^+BF_4^-$, *i*Pr_2NEt, CH_2Cl_2, 0°C, 5 min; e) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0°C to RT, 1 h; then TBAF (1.0 equiv), MeI, THF, −78°C to RT, 3 h, 43% for 2 steps; f) $LiAlH_4$, THF, 0°C to RT, 1 h; g) TBSCl (1.0 equiv), imidazole, CH_2Cl_2, 0°C, 30 min; h) IBX, DMSO, 80°C, 1 h, 85% for 3 steps; i) KHMDS, $PhNTf_2$, THF, −78°C, 1 h; j) CO (1 atm), $[Pd(PPh_3)_4]$ (1 mol%), MeOH, DMF, Et_3N, 50°C, 2 h, then TFA, CH_2Cl_2, RT, 5 h, 69% for 2 steps. DMF = *N*,*N*′-dimethylformamide, DMSO = dimethyl sulfoxide, HMDS = hexamethyldisilazane, IBX = 2-iodoxybenzoic acid, MMC = magnesium methyl 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 underwent Pd^0-catalyzed carbomethoxylation,[17] TFA-mediated desilylation, and lactonization to form lactone **10** (69% for 2 steps).

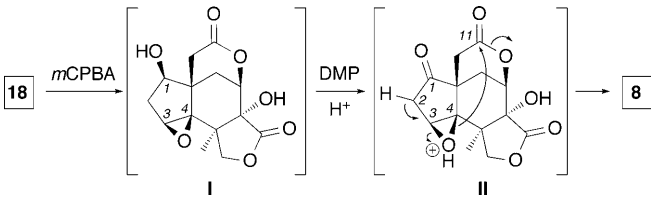
The next task was to install the desired C6–C7 *trans*-diol functionality on the tricyclic motif **10**. Along these lines, **10** was treated with $NaOH/H_2O_2$ to selectively and quantitatively produce epoxide **17** (Scheme 3). We projected that a Ru^{III}-based[18] direct oxidative cleavage of the terminal alkene into the corresponding carboxylic acid would trigger a "6-*exo*-tet" epoxide opening[19] 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 OsO_4 (cat.)/$NaIO_4$ conditions and subsequent Jones oxidation[9] 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.[20] Notably, this compound represents the core structure of several natural products of the *Illicium* species and can be readily produced in multigram scale.



Scheme 3. Synthesis of E ring. Reagents and conditions: a) H_2O_2, 3 M NaOH, THF, 0°C to RT, 5 h, 99%; b) OsO_4 (1 mol%), $NaIO_4$, 1,4-dioxane, H_2O, RT, 12 h; c) Jones reagent, acetone, 0°C, 30 min, 70% for 2 steps; d) TBAF, THF, RT, 30 min, 95%; e) *m*CPBA, THF, 50°C, 3 h; f) Dess–Martin periodinane, acetone, RT, 2 h, 38% for 2 steps. *m*CPBA = 3-chloroperbenzoic acid, Jones reagent = CrO_3 in diluted H_2SO_4. Some hydrogen atoms and the TBS group of compound **9** were omitted for clarity.

With compound **9** in hand, we sought to introduce a hydroxy 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).[20]

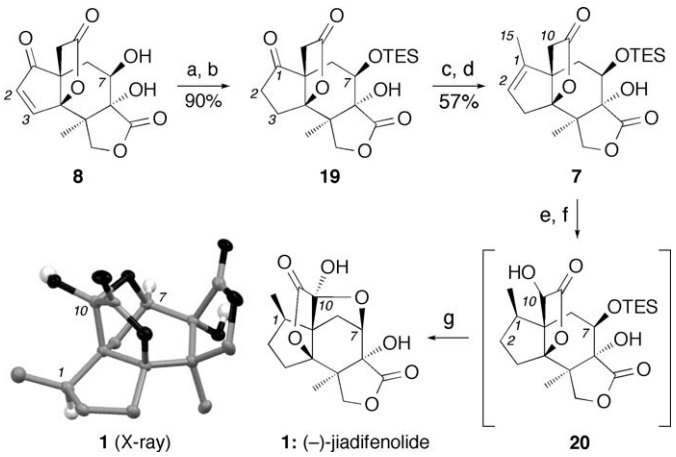
A reasonable scenario for the remarkable conversion of **18** into **8** is presented in Scheme 4. Treatment of **18** with *m*CPBA produced epoxide **I** as a single isomer. We postulate



Scheme 4. Plausible mechanistic scenario for the conversion of **18** into **8**.

that this epoxidation was promoted by the C1 homoallylic alcohol and occurred from the β face of the A ring of **18**.[21] DMP treatment of **I** 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 translactonization. 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



Scheme 5. Completion of the synthesis. Reagents and conditions: a) H_2 (6 atm), 10% Pd/C (5 mol%), MeOH, RT, 24 h; b) TESOTf, 2,6-lutidine, THF, 0°C to RT, 30 min, 90% for 2 steps; c) KHMDS, Comins reagent, THF, −78°C, 1.5 h; d) $AlMe_3$, $[Pd(PPh_3)_4]$ (50 mol%), THF, RT, 2 h, 57% for 2 steps; e) H_2 (90 atm), PtO_2 (20 mol%), MeOH, RT, 24 h; f) NaHMDS, (±)-*trans*-2-(phenylsulfonyl)-3-phenyloxaziridine, THF, −78°C to RT, 1.5 h; g) Jones reagent, acetone, 0°C, 15 min, 33% for 3 steps. Comins reagent = *N*-(5-chloro-2-pyridyl)triflimide, HMDS = hexamethyldisilazane, TES = triethylsilyl, Tf = trifluoromethanesulfonyl. Some hydrogen atoms were omitted for clarity.

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 methylenation approaches were attempted to install the missing C15-carbon atom at C1. All these efforts (Wittig reaction, titanium-[22] 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^0-mediated cross-coupling method installed 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 $AlMe_3$ 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 H_2 using PtO_2 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 spectroscopic and analytical properties to those reported for the natural product.[3] The absolute stereochemistry of **1** was confirmed by copper-radiation X-ray analysis,[20] 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 cyclopentane 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^0-catalyzed carbomethoxylation and a Pd^0-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 methodical biological evaluation of such molecules could lead to the identification of more potent and selective neurotrophic molecules for medicinal applications.

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